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(54) **Titre : CONJUGAISON SPECIFIQUE POUR UN CONJUGUE ANTICORPS-MEDICAMENT**
(54) **Title: SPECIFIC CONJUGATION FOR AN ANTIBODY-DRUG CONJUGATE**

(57) **Abrégé/Abstract:**
Provided herein is a process for preparing a homogeneous conjugate of an antibody or antibody-like protein via linkage of cysteine sites between heavy-light chains in the IgG antibody or antibody-like protein. Provided herein also are methods of making the conjugates in a specific manner comprising either generation of specific thiols of an antibody or antibody-like protein agent, followed by reaction with drug/linker complexes, or generation of specific thiols of an antibody or antibody-like protein agent and conjugation of a synthetic linker-drug assembly with the thiols simultaneously in one pot reaction, to provide conjugates with over 75%, in most cases more than 80%of payloads linked at the specific cysteine sites between heavy-light chains of the IgG antibody or antibody-like protein. It also relates to methods of using the homogeneous conjugate in targeted prophylaxis or treatment of cancer, infection and immunological disorders.

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Abstract:

Provided herein is a process for preparing a homogeneous conjugate of an antibody or antibody-like protein via linkage of cysteine sites between heavy-light chains in the IgG antibody or antibody-like protein. Provided herein also are methods of making the conjugates in a specific manner comprising either generation of specific thiols of an antibody or antibody-like protein agent, followed by reaction with drug/linker complexes, or generation of specific thiols of an antibody or antibody-like protein agent and conjugation of a synthetic linker-drug assembly with the thiols simultaneously in one pot reaction, to provide conjugates with over 75%, in most cases more than 80%of payloads linked at the specific cysteine sites between heavy-light chains of the IgG antibody or antibody-like protein. It also relates to methods of using the homogeneous conjugate in targeted prophylaxis or treatment of cancer, infection and immunological disorders.

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SPECIFIC CONJUGATION FOR AN ANTIBODY-DRUG CONJUGATE

DESCRIPTION

INFORMATION OF PRIORITY

The present application claims the benefit of PCT/CN2021/128453 (WO/2022/078524), filed on November 3rd, 2021, which is incorporated herein by reference entirely. This application is also claims the benefit of PCT/CN2022/123901, filed on October 8, 2022, which is incorporated herein by reference entirely. Thus, the present application claims the benefit of both PCT/CN2021/128453 and PCT/CN2022/123901.

FIELD OF THE INVENTION

The present invention relates to a process for preparing a homogeneous conjugate of an antibody via linkage of certain sulphurs of cysteine sites in the antibody. The present invention also relates to methods of making the conjugates in a specific manner comprising either generation of specific thiols of an antibody or antibody-like protein agent, followed by reaction with drug/linker complexes, or generation of specific thiols of an antibody or antibody-like protein agent and conjugation of a synthetic linker-drug assembly to the protein molecule simultaneously in one pot reaction. It also relates to methods of using the homogeneous conjugate in targeted prophylaxis or treatment of cancer, infection and immunological disorders.

BACKGROUND OF THE INVENTION

Nowadays, the pace of ADC development is accelerating, with the number of the clinical trials having more than tripled over the past 5 years and 9 of 14 marketed ADCs were approved by US FDA in last 3 years, underscoring the enthusiasm for this transformative approach to cancer treatment. The conjugation of payload and antibody via a linker is a critical aspect that defines ADC quality, safety, efficacy and the overall success (M. Acchione, H. Kwon, et al, 2012, mAbs 4:3, 362-372; M. J. Birrer, K. N. Moore, et al, 2019, J. National Cancer Inst., 111(6), 538-549). A report published by US FDA indicated that for most ADCs currently in clinical development, dose-limiting toxicities (DLT) appear to be unrelated to the targeted antigen, but driven by the payload/linker complexes (H. Saber and J. K. Leighton, Regulatory Toxicology and Pharmacology 71 (2015) 444–452); It also known that ADC linkers and the conjugation sites play critical roles in an ADCs' stability during preparation and storage, as well extent of systemic toxicity in the blood circulation in vivo (J. R. McCombs and S. C. Owen, 2015, AAPS Journal 17, 339–351).

Thus research and development into ADC chemistry and design are now expanding the scopes of the linker-payload compartments and conjugate chemistry to address the challenge of dose-limiting toxicities (DLT) of ADCs toward target diseases (Lambert, J. M. 2016, Ther. Deliv. 7, 279-82; Zhao, R. Y. et al, 2011, J. Med. Chem. 54, 3606-23). Nowadays, one of the extensive R&D effort for broader therapeutic windows (TW) of ADCs is to establish novel reliable methods for site-specific ADC conjugation, which seem to have longer circulation half-life, higher efficacy, potentially decreased off-target toxicity, and a narrow range of in vivo pharmacokinetic (PK) properties of ADCs as well as better batch-to-batch consistency in ADC production (Hussain, A. F., et al, Pharmaceuticals (Basel), 2021, 14(4), 343; Sadiki, A., et al, Antib Ther. 2020, 3(4), 271-284; Wolska-Washer, A.; Robak, T., Drug Saf, 2019, 42(2), 295-314; Tsuchikama, K., An, Z., Protein Cell. 2018, 9(1), 33-46; Thomas, A. et al, Lancet Oncol. 2016, 17(6), e254-e262; Strop, P., et al 2013 Chem. Biol. 20, 161−67; Wakankar, A. mAbs, 2011, 3, 161–172; Zhao, R. Y. et al, 2011, J. Med. Chem. 54, 3606-23).

There are several approaches developed in recent years for the site selective ADC preparation (Panowski, S, 2014, mAbs 6, 34). They include incorporation of unpaired cysteines, e.g. engineered reactive cysteine residues, called THIOMAB from Genentech (Junutula, J. R., et al 2010 Clin. Cancer Res. 16, 4769; Junutula, J. R., et al 2008 Nat Biotechnol. 26, 925-32; US Patents 8, 309, 300; 7, 855, 275; 7, 521, 541; 7, 723, 485, WO2008/141044), genetically introduced glutamine tag with Streptoverticillium mobaraense transglutaminase (mTG) (Strop, P., Bioconjugate Chem., 2014, 25, 855–862; Strop, P., et al., 2013, Chem. Biol. 20, 161–167; US Patent 8, 871, 908 for Rinat-Pfizer) or with Microbial transglutaminase (MTGase) (Dennler, P., et al, 2014, Bioconjug. Chem. 25, 569–578. US pat appl 20130189287 for Innate Pharma; US Pat 7, 893, 019 for Bio-Ker S.r.l. (IT)), incorporation of thiolfucose (Okeley, N. M., et al 2013 Bioconjugate Chem. 24, 1650), incorporation of unnatural amino acids through mutagenesis (Axup, J.Y., et al., 2012, Proc. Natl. Acad. Sci. 109, 16101–16106; Zimmerman, E.S., et al., 2014, Bioconjug. Chem. 25, 351–361; Wu, P., et al, 2009 Proc. Natl. Acad. Sci. 106, 3000-5; Rabuka, D., et al, 2012 Nat. Protoc. 7, 1052−67; US Pattent 8, 778, 631, and US Pat Appl. 20100184135, WO2010/081110 for Sutro Biopharma; WO2006/069246, 2007/059312, US Patents 7, 332, 571, 7, 696, 312, and 7, 638, 299 for Ambrx; WO2007/130453, US patents 7, 632, 492 and 7, 829, 659 for Allozyne), incorporation of selenocysteine into antibodies (Hofer, T., et al 2009, Biochemistry 48, 12047–12057; US Patent 8, 916, 159 for US National Cancer Institute), Conversion of cysteines located in the CXPXR consensus sequence to formylglycine (FGly) with formylglycine generating enzyme (FGE) (Drake, P.M., et al., 2014, Bioconjug. Chem. 25, 1331–1341; Carrico, I. S. et al 7, 985, 783; 8, 097, 701; 8, 349, 910, and US Pat Appl 20140141025, 20100210543 for Redwood Bioscience); via glycoengineeringly

introduction of sialic acid with the use of galactosyl- and sialytransferases (Zhou, Q., et al 2014, Bioconjug.Chem., 25, 510-520, US9,580,511/US Pat Appl 20140294867 for Sanofi-Genzyme); the incorporation of a cyclopropene derivative of lysine, followed by Diels-Alder cycloaddition with tetrazine derivatives to yield 1, 4-dihydropyridazines in conjugation (Oller-Salvia, B. et al, 2018 Angew Chem Int Ed Engl, 57, 2831-2834). However, the above methods are required antibody-engineering processes and reoptimization of cell culture conditions, often suffer from low protein expression, low conjugation yields, or are limited to specific conjugation sites. Therefore, some simple homogeneous conjugation methods were practically studied through rebridging the reduced inter chain disulfide bonds of a native antibody, such as, using bromo or dibromo-maleimides, called next generation maleimides (NGMs) (Schumacher, F.F., et al 2014, Org. Biomol. Chem. 12, 7261–69; UCL Cancer Institute), or using dibromopyri-dazinediones (A. Maruani, et al, Nat. Commun., 2015, 6, 6645; M. T. Lee, et al, Chem. Sci., 2017, 8, 2056), or applying bis-alkylating reagents via a three-carbon bridge (Badescu, G., et al., 2014, Bioconjug. Chem. 25, 1124–36; WO2013/190272, WO2014/064424 for PolyTherics Ltd), or via arylenedipropiolonitrile (ADPN) molecule (Koniev, O., et al, 2018 MedChemComm. 2018, 9, 827-830). Recently, Coumans et al used 2-(diphenylphosphino)-benzenesulfonic acid (diPPBS) as the reducing agent that only reduced the engineered cysteines without harming the interchain disulfides in an antibody for preparation of ADCs (R. G. E. Coumans, et al, Bioconjugate Chem. 2020, 31, 2136−2146). Wuxi Biologics Co., applied Zn^{2+} ions ($ZnCl_2$ salt in a buffer) for selected control the cystine reduction in an antibody, followed by reaction with a payload containing maleimide linker to improve homogeneity in production of ADCs (PCT/CN2020/075162). However, as most of antibodies are stored in a phosphate based buffer, e. g. called PBS buffer, Zn cation may swiftly precipitate in a phosphate buffer to form zinc phosphate, since the solubility constant of zinc phosphate is about 9.1×10^{-33} at neutral or base pH conditions (Martin, R. Bruce. "Solubility and Solubility Products (J. Chem. Educ. 1998, 75, 1179-1181 and J. Chem. Educ. 1998, 75, 1182-1185) "J. Chem. Educ. 2000, 77, 1558; Dupuis, V., et al, 1992, Biomaterials, 13 (7), 467-470; https://www.chm.uri.edu/weuler/chm112/refmater/KspTable.html). Therefore, when using $ZnCl_2$ in the reduction of an antibody, the amount of phosphate anions and the pH of the buffers have to be precisely controlled to avoid formation of the precipitate of zinc phosphate.

We have disclosed several conjugation methods of rebridging a pair of thiols of the reduced inter chain disulfide bonds of a native antibody, such as using bromo maleimide and dibromomaleimide linkers (WO2014/009774), 2, 3-disubstituted succinic /2-monosubstituted / 2, 3-disubstituted fumaric or maleic linkers (WO2015/155753, WO2016/596228), acetylenedicarboxylic linkers (WO2015/151080, WO2016/596228), hydrazine linkers (WO2015/151081), acryloyl or

propiolyl linkers (WO2018/086139), bis-linker (WO2018185526), and 2, 3-diaminosuccinyl linker (WO2020/073345). In this patent application, we extend the scopes of our earlier patent application in production of more homogeneous conjugates via selective control reduction of interchains of disulfide bonds of an antibody follow by or simultaneous conjugation under coordinative help by a zinc amino complex / chelate. Zinc amino complexes have more advantages over $ZnCl_2$ in coordination of reduction of disulfide bond in an antibody. First, zinc amino complexes are much bulkier than $ZnCl_2$ and can be more 3-D space selectively inserted in certain positions (e. g. more specifically in the positions of the disulfide bonds between heavy-light chains of an IgG1 antibody); Second, zinc amino complexes are more stable in a water based solution, for instance, the stability constant of zinc ammonia complex ion is 2.9×10^9 (https://chempedia. info/info/stability_constants/), which in turn, slow the precipitation in a neutral pH phosphate buffer. More importantly, by uses of zinc amino complexes to stoichiometrically control reduction of the disulfur bonds between the light chain and heavy chain of an IgG antibody without hurting the disulfide bonds between the heavy-heavy chains (in the hinge region) of the antibody, a bis-alkylation of the two geometrically adjacent thiols with a linker, particularly with a bis-linker can be well specifically achieved. In a word, the conjugation strategy of this invention has robust manufacturability to yield highly homogeneous ADCs without antibody engineering and can successfully tackle an important shortcoming in current ADC preparation methods, in particular for bridge-linkage of di-thiol conjugation of an antibody. This conjugation strategy can be applied directly to other antibody likes of proteins. The resulting homogeneous ADCs demonstrate improved pharmacokinetics, superior efficacy, and reduced toxicity in vivo compared to analogous conventional heterogeneous ADCs.

SUMMARY OF THE INVENTION

The present invention provides conjugation process with improved homogeneity of an antibody conjugate, or antibody-like protein conjugate, in particular, an antibody –drug conjugate (ADC), wherein over 75% of payloads (drugs) are specifically conjugated to the disulfide bond sites between heavy-light chains of an antibody.

The homogenous conjugation process comprises the following three key steps:

(a) incubating an antibody-like protein, in particular, an IgG antibody in the presence of an effective amount of transition metal cation-amino chelate/complex ($Zn(NR_1R_2R_3)_{m1}^{2+}$) and a reductant (e.g. Tris(2-carboxyethyl)phosphine (TCEP)) in a buffer system (e. g. PBS, Mes, Bis-Tris, Bis-Tris Propane, Pipes, Aces, Mopso, Bes, Mops, Hepes, Tes, Pipps, Dipso, Tapso, Heppso, Tris-up, Tris-HCl, Tricine, Hepps, Gly-Gly, Bicine, Taps, Hepee, Acetates, Histidine, Citrates, MES, or Borates, etc.) to selectively reduce interchain disulfide bonds within the antibody, or antibody-like protein to generate thiols;

(b). introducing an effective amount of linker or payload/linker complex/assembly bearing thiol reactive groups (e.g., a drug containing maleimide terminal) to react with the thiol groups resulted from step (a); and

(c). optionally adding an effective amount of oxidant (e. g. dehydroascorbic acid (DHAA)) to re-oxidize unreacted thiol groups, or adding a thiol reactive compound (e.g. N-ethyl maleimide (NEM) or N-ethyl-maleimide-3-sulfonate) to quench the unreacted thiols in the protein, and then purifying the resulted conjugates;

(d). the step (c) can be optionally replaced by: adding an effective amount of cystine to quench the excessive conjugation linker or linker/payload complex containing thiol reactive groups (e. g. maleimide); and simultaneously or sequentially adding an azido compound (e. g. 4-(azidomethyl)-benzoic acid) or a disulfide compound (e. g. cystine) to quench the unreacted reductant (e. g. TCEP or Tris(hydroxypropyl)phosphine). The addition of cystine to quench the unreacted reductant (e. g. TCEP) can form a cysteine which can simultaneously quench the excessive conjugation linker or linker/payload complex containing thiol reactive groups (e. g. maleimide).

wherein R_1, R_2 and R_3 in the formula of $Zn(NR_1R_2R_3)_{m1}^{2+}$ are independently selected from C_1-C_8 of alkyl; C_2-C_8 of heteroalkyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 of aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; m1 is selected from 1, 2, 3, 4, 5, 6, 7 or 8; Proferably m1 is 1, 2, 3 or 4.

In addition, $(NR_1R_2R_3)_{m1}$ can be form a dimer, trimer, tetramer, pentamer, or hexamer wherein these polymers are covalently linked among N, R_1, R_2 and R_3; and N, R_1, R_2 or R_3 themselves or together can form heterocyclic, carbocyclic, diheterocyclic, or dicarbocyclic rings.

The Zinc cation-amino chelate/complex, $Zn(NR_1R_2R_3)_{m1}^{2+}$, used in step (a) is 0.01 mM — 1.0mM in concentration, or 0.5 ~ 20 equivalents in moles of the protein, and it can be added to the reaction solution with a water-soluble organic solvent, selected from, ethanol, methanol, propanol, propandiol, DMA, DMF, DMSO, THF, CH_3CN.

The reductant is an organic phosphine, preferably selected from Tris(2-carboxyethyl)-phosphine (TECP) or Tris(hydroxypropyl)phosphine and its use in the reaction solution is 0.02 mM — 1.0mM in concentration, or 1.0 – 20 equivalents in moles of the protein. The oxidant to be added in step (c) may be DHAA, Fe^{3+}, I_2, Cu^{2+}, Mn^{3+}, MnO_2, or a mixture of Fe^{3+}/I^- or DHAA/Fe^{3+}. The oxidant used in the reaction solution is 0.02 mM – 1.0 mM in concentration, or 0.2 -100 equivalents in moles of the protein. The optimum pH in the conjugation reaction is typically between about 5.0 to 8.0, and preferably, about 5.5 to 7.5. The optimum temperature in the conjugation reaction is typically between about - 5 to about 40 °C, and preferably, about 0 to

37 °C; more preferably about 2 to 8 °C; further preferably about 2 to 6 °C. The optimum time of the conjugation reaction is typically between about 15 min to about 48 hours and preferably, about 30 min to overnight (10 ~ 16 h), more preferably about 2 h ~ 6 h. The optimal reaction conditions (e. g. pH, temeperature, buffer, concentrations of the reactants) of course are depended upon specifically an antibody-like protein, a payload/linker complex, a reductant and/or $Zn(NR_1R_2R_3)_{m1}^{2+}$ used.

The antibody or antibody-like protein in the conjugation process can be any types of antibodies or proteins as long as they have two or more disulfide bonds in the protein for differentiation of reduction. And the payload/linker complex may be any types or formats as long as it has a thiol reactive group.

In a word, the ADCs prepared by the process of the present application have more than 70% (and many of them can be over 85%) of payloads conjugated in the Fab region of an antibody, in contrast to the conventional process wherein around 40% of the payloads are in the Fab region of an antibody. The advantages of the application along with the improved conjugation process for homogeneity of ADCs will become more apparent from the following detailed description of several embodiments, experimentals and figures.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows the general synthesis of components of a bis-linker.

Fig. 2 shows the synthesis of a camptothecin analog and its conjugate containing a bis-conjugate linker.

Fig. 3 shows the synthesis of a camptothecin analog containing a bis-conjugate linker.

Fig. 4 shows the synthesis of a camptothecin analog containing a bis-conjugate linker.

Fig. 5 shows the general synthesis of components of a bis-linker.

Fig. 6 shows the synthesis of a camptothecin analog containing a bis-conjugate linker.

Fig. 7 shows the synthesis of a camptothecin analog containing a bis-conjugate linker.

Fig. 8 shows the synthesis of a camptothecin analog containing a bis-conjugate linker.

Fig. 9 shows the general synthesis of components of a bis-linker.

Fig. 10 shows the synthesis of a camptothecin analog containing a bis-conjugate linker.

Fig. 11 shows the synthesis of a tubulysin B analog containing a bis-conjugate linker.

Fig. 12 shows the synthesis of a tubulysin B analog containing a bis-conjugate linker.

Fig. 13 shows the synthesis of a tubulysin B analog containing a bis-conjugate linker.

Fig. 14 shows the synthesis of a tubulysin B analog containing a bis-conjugate linker.

Fig. 15 shows the synthesis of a tubulysin B analog containing a bis-conjugate linker.

Fig. 16 shows the synthesis of a tubulysin B analog containing a bis-conjugate linker.

Fig. 17 shows the synthesis of components of a tubulysin B analogs.

Fig. 18 shows the synthesis of a tubulysin B analog containing a bis-conjugate linker.

Fig. 19 shows the synthesis of a tubulysin B analog containing a bis-conjugate linker.

Fig. 20 shows the synthesis of a camptothecin analog containing a bis-conjugate linker.

Fig. 21 shows the synthesis of a camptothecin analog containing a bis-conjugate linker.

Fig. 22 shows the synthesis of a camptothecin analog and its conjugate containing a bis-conjugate linker.

Fig. 23 shows the synthesis of a camptothecin analog containing a bis-conjugate linker.

Fig. 24 shows the synthesis of a camptothecin analog containing a bis-conjugate linker.

Fig. 25 shows the synthesis of a camptothecin analog containing a bis-conjugate linker and components of amanitin analogs.

Fig. 26 shows the synthesis of a conjugate of an amanitin containing a bis-conjugate linker.

Fig. 27 shows the synthesis of a conjugate of an amanitin containing a bis-conjugate linker.

Fig. 28 shows the synthesis of a conjugate of an amanitin containing a bis-conjugate linker.

Fig. 29 shows the synthesis of a conjugate of an amanitin containing a bis-conjugate linker.

Fig. 30 shows the synthesis of a conjugate of a tubulysin B analog containing a linker.

Fig. 31 shows the synthesis of a conjugate of a tubulysin B analog containing a linker.

Fig. 32 shows the synthesis of a conjugate of a tubulysin B analog containing a linker.

Fig. 33 shows the synthesis of a conjugate of a tubulysin B analog containing a bis-linker.

Fig. 34 shows the synthesis of a conjugate of a tubulysin B analog containing a bis-linker.

Fig. 35 shows the synthesis of a conjugate of a tubulysin B analog containing a bis-linker.

Fig. 36 shows the synthesis of a conjugate of a tubulysin B analog containing a bis-linker.

Fig. 37 shows the synthesis of a conjugate of a tubulysin B analog containing a bis-linker.

Fig. 38 shows the synthesis of a conjugate of a camptothecin analog containing a linker.

Fig. 39 shows the synthesis of a conjugate of a camptothecin analog containing a bis-linker.

Fig. 40 shows the synthesis of a conjugate of a camptothecin analog containing a linker.

Fig. 41 shows the synthesis of a conjugate of a camptothecin analog containing a linker.

Fig. 42 shows the synthesis of a conjugate of a camptothecin analog containing a linker.

Fig. 43 shows the synthesis of a conjugate of a camptothecin analog containing a linker.

Fig. 44 shows the synthesis of a conjugate of a camptothecin analog containing a linker.

Fig. 45 shows the synthesis of a conjugate of a camptothecin analog containing a linker.

Fig. 46 shows the synthesis of a conjugate of a camptothecin analog containing a linker.

Fig. 47 shows the synthesis of a conjugate of a camptothecin analog containing a linker.

Fig. 48 shows the synthesis of a conjugate of an amanitin containing a linker.

Fig. 49 shows the synthesis of a PBD dimer containing a bis-linker.

Fig. 50 shows the synthesis of a conjugate of a camptothecin analog containing a bis-linker.

Fig. 51 shows the synthesis of a camptothecin analog containing a bis-linker.

Fig. 52 shows the synthesis of a conjugate of a camptothecin analog containing a bis-linker.

Fig. 53 shows the synthesis of a conjugate of a camptothecin analog containing a bis-linker.

Fig. 54 shows the synthesis of a conjugate of a camptothecin analog containing a bis-linker.

Fig. 55 shows the synthesis of a conjugate of a camptothecin analog containing a bis-linker.

Fig. 56 shows the synthesis of a conjugate of a camptothecin analog containing a linker.

Fig. 57 shows the synthesis of a conjugate of a camptothecin analog containing a bis-linker.

Fig. 58 shows middle-level characterization of BCMA-Tubulysin B analog ADC (C-390) after N-deglycosylation and reduction. (a) rpHPLC chromatogram of ADC fragments obtained after deglycosylation and DTT reduction. Light chains (LC) with zero or one drug molecule attached (L0 and L1), (b) heavy chains with zero, one, two, or three drug molecules attached (H0, H1, H2 and H3). It demonstrated that the drug was mainly (>85%) conjugated at Fab region.

Fig. 59 shows the Percentage of Drug Loaded Peptides of a BCMA ADC (C-390). (a): LC Peptide [GEC] with zero or one drug molecule attached (D0 and D1); (b): HC Peptide [SCDK] at the arm with zero or one drug molecule attached (D0 and D1); (c): HC Peptide [THTCPPCPAPELLGGPSVFLFPPKPK] at the hinge with zero, one or two drug molecules attached (D0, D1 and D2).

Fig. 60 shows middle-level characterization of a conjugate of Trop2-C608 ADC after reduction. Light chains (LC) with zero or one drug molecule attached (L0 and L1), and heavy chains with zero, one, two, or three drug molecules attached (H0, H1, H2 and H3). It demonstrated that the drug was mainly (>85%) conjugated at Fab region.

Fig. 61 shows middle-level characterization of bridged cysteine conjugations (a conjugate of Muc-1-C606) after reduction. Light chains(LC), heavy chain(HC) and cysteine-bridged HC and LC with one drug molecule (LC+HC+LP). It demonstrated that the drug was mainly (>85%) conjugated at Fab region.

Fig. 62 shows middle-level characterization of bridged cysteine conjugations (a conjugate of Muc-1-C72) after reduction. Light chains(LC), heavy chain(HC) and cysteine-bridged HC and LC with one drug molecule (LC+HC+LP). It demonstrated that the drug was mainly (>85%) conjugated at Fab region.

Fig. 63 shows middle-level characterization of bridged cysteine conjugations (a conjugate of Muc-1-C45) after reduction. Light chains(LC), heavy chain(HC) and cysteine-bridged HC and LC with one drug molecule (LC+HC+LP).

Fig. 64 shows middle-level characterization of bridged cysteine conjugations (a conjugate of Trop2-C140) after reduction. Light chains(LC), heavy chain(HC) and cysteine-bridged HC and LC with one drug molecule (LC+HC+LP).

Fig. 65 shows change in tumor volume in a NCI-H929 cell xenograft mouse model of multiple myeloma in response to a serial of single dose (3 mg/Kg) treatment with BCMA (hu5D2) ADCs (C-68a, C-115, C-192, C-202, C-221, C-290, C-306, C-385, C-390, C-399, C-402, C-417), in comparison to BCMA-mcMMAF(belantamab-mcMMAF) and PBS buffer (the control).The figure indicates that all the 13 conjugates had antitumor activity, and the orders of the antitumor activity are: C-385 < C-306 < C-290 < C-68a < C-115 < BCMA-mcMMAF< C-192 < C-202 < C-399 < C-390 < C-417 < C-402 < C-221.

Fig. 66 shows change in tumor volume in a JJN-3 cell xenograft mouse model of multiple myeloma in response to a serial of single dose (5 mg/Kg) treatment with hu5D2-ADC in comparison to belantamab-mcMMAF and PBS buffer (the control). The figure indicates that all the 9 conjugates had antitumor activity, and the orders of the antitumor activity are: Paclitaxel < C-385 < belantamab-mcMMAF < C-195 < C-137 < C-181b < C-126 < C-83 < C-277 < C-258.

Fig. 67 shows change in tumor volume in NCI-H929 cell xenograft mouse model of multiple myeloma in response to a serial of single dose (2 mg/Kg) treatment with hu5D2-ADC in comparison to belantamab-mcMMAF and PBS buffer (the control). The figure indicates that all the 7 conjugates had antitumor activity, and the orders of the antitumor activity are: belantamab-mcMMAF < C-406 < C-396 < C-399 < C-400 < C-221b < C-402.

Figure 68 shows the comparison of the anti-tumor effect of B7H3 antibody conjugate of C-550, C-570-T (with traditional conjugation at DAR =4.0), C-543, C-595, C-570-H (with homogeneous conjugation of this invention), C-581, C-582, C-560, C-562, and C-561, at dose of 6 mg/Kg, single injection, along with Paclitaxel at dose of 15 mg/Kg, QWx3, against Calu-6 cells. The figure indicates that all the 10 conjugates had better antitumor activity than paclitaxel. And the conjugate C-570 prepared with the method of this invention had better in vivo activity than that prepared by the regular method.

Figure 69 shows the comparison of the anti-tumor effect of Muc1 antibody conjugate of C-553, C-484, C-490, C-450, C-432-T (with traditional conjugation at DAR =4.0), C-501, C-519, C-432-H (with homogeneous conjugation of this invention), C-417, and C-560, at dose of 6 mg/Kg, single injection, along with Paclitaxel at dose of 15 mg/Kg, QWx3, against Calu-6 cells. The figure indicates that all the 10 conjugates had better antitumor activity than paclitaxel. And the conjugate C-432 prepared with the method of this invention had better in vivo activity than that prepared by the regular method.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

"Alkyl" refers to an aliphatic hydrocarbon group or univalent groups derived from alkane by removal of one or two hydrogen atoms from carbon atoms. It may be straight or branched having C_1-C_8 (1 to 8 carbon atoms) in the chain. "Branched" means that one or more lower C numbers of alkyl groups such as methyl, ethyl or propyl are attached to a linear alkyl chain. Exemplary alkyl groups include methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *n*-pentyl, 3-pentyl, octyl, nonyl, decyl, cyclopentyl, cyclohexyl, 2, 2-dimethylbutyl, 2, 3-dimethylbutyl, 2, 2-dimethylpentyl, 2, 3-dimethylpentyl, 3, 3-dimethylpentyl, 2, 3, 4-trimethylpentyl, 3-methyl-hexyl, 2, 2-dimethylhexyl, 2, 4-dimethylhexyl, 2, 5-dimethylhexyl, 3, 5-dimethylhexyl, 2, 4-dimethylpentyl, 2-methylheptyl, 3-methylheptyl, *n*-heptyl, isoheptyl, *n*-octyl, and isooctyl. A C_1-C_8 alkyl group can be unsubstituted or substituted with one or more groups including, but not limited to, -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), -aryl, -C(O)R', -OC(O)R', -C(O)OR', -C(O)NH_2, -C(O)NHR', -C(O)$N(R')_2$, -NHC(O)R', -SR', -$S(O)_2$R', -S(O)R', -OH, -halogen, -N_3, -NH_2, -NH(R'), -$N(R')_2$ and -CN; where each R' is independently selected from -C_1-C_8 alkyl and aryl.

"Halogen" refers to fluorine, chlorine, bromine or iodine atom; preferably fluorine and chlorine atom.

"Heteroalkyl" refers to C_2-C_8 alkyl in which one to four carbon atoms are independently replaced with a heteroatom from the group consisting of O, S and N.

"Carbocycle" refers to a saturated or unsaturated ring having 3 to 8 carbon atoms as a monocycle or 7 to 13 carbon atoms as a bicycle. Monocyclic carbocycles have 3 to 6 ring atoms, more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, arranged as a bicycle [4, 5], [5, 5], [5, 6] or [6, 6] system, or 9 or 10 ring atoms arranged as a bicycle [5, 6] or [6, 6] system. Representative C_3-C_8 carbocycles include, but are not limited to, -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclopentadienyl, -cyclohexyl, -cyclohexenyl, -1, 3-cyclohexadienyl, -1, 4-cyclohexadienyl, -cycloheptyl, -1, 3-cycloheptadienyl, -1, 3, 5-cycloheptatrienyl, -cyclooctyl, and -cyclooctadienyl.

A "C_3-C_8 carbocycle" refers to a 3-, 4-, 5-, 6-, 7- or 8-membered saturated or unsaturated nonaromatic carbocyclic ring. A C_3-C_8 carbocycle group can be unsubstituted or substituted with one or more groups including, but not limited to, -C_1-C_8 alkyl, -O-(C_1-C_8 alkyl), -aryl, -C(O)R', -OC(O)R', -C(O)OR', -C(O)NH_2, -C(O)NHR', -C(O)$N(R')_2$, -NHC(O)R', -SR', -S(O)R', -$S(O)_2$R', -OH, -halogen, -N_3, -NH_2, -NH(R'), -$N(R')_2$ and -CN; where each R' is independently selected from -C_1-C_8 alkyl and aryl.

"Alkenyl" refers to an aliphatic hydrocarbon group containing a carbon-carbon double bond

which may be straight or branched having 2 to 8 carbon atoms in the chain. Exemplary alkenyl groups include ethenyl, propenyl, n-butenyl, i-butenyl, 3-methylbut-2-enyl, n-pentenyl, hexylenyl, heptenyl, octenyl.

"Alkynyl" refers to an aliphatic hydrocarbon group containing a carbon-carbon triple bond which may be straight or branched having 2 to 8 carbon atoms in the chain. Exemplary alkynyl groups include ethynyl, propynyl, *n*-butynyl, 2-butynyl, 3-methylbutynyl, 5-pentynyl, *n*-pentynyl, hexylynyl, heptynyl, and octynyl.

"Alkylene" refers to a saturated, branched or straight chain or cyclic hydrocarbon radical of 1-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. Typical alkylene radicals include, but are not limited to: methylene (-CH_2-), 1, 2-ethyl (-CH_2CH_2-), 1, 3-propyl (-$CH_2CH_2CH_2$-), 1, 4-butyl (-$CH_2CH_2CH_2CH_2$-), and the like.

"Alkenylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. Typical alkenylene radicals include, but are not limited to: 1, 2-ethylene (-CH=CH-).

"Alkynylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne. Typical alkynylene radicals include, but are not limited to: acetylene, propargyl and 4-pentynyl.

"Aryl" or Ar refers to an aromatic or hetero aromatic group, composed of one or several rings, comprising three to fourteen carbon atoms, preferentially six to ten carbon atoms. The term of "hetero aromatic group" refers one or several carbons on aromatic group, preferentially one, two, three or four carbon atoms are replaced by O, N, Si, Se, P or S, preferentially by O, S, and N. The term aryl or Ar also refers to an aromatic group, wherein one or several H atoms are replaced independently by -R', -halogen, -OR', or -SR', -NR'R'', -N=NR', -N=R', -NR'R'', -NO_2, -S(O)R', -$S(O)_2$R', -$S(O)_2$OR', -$OS(O)_2$OR', -PR'R'', -P(O)R'R'', -P(OR')(OR''), -P(O)(OR')(OR'') or -OP(O)(OR')(OR'') wherein R', R'' are independently H, alkyl, alkenyl, alkynyl, heteroalkyl, aryl, arylalkyl, carbonyl, or pharmaceutical salts.

"Heterocycle" refers to a ring system in which one to four of the ring carbon atoms are independently replaced with a heteroatom from the group of O, N, S, Se, B, Si and P. Preferable heteroatoms are O, N and S. Heterocycles are also described in The Handbook of Chemistry and Physics, 78th Edition, CRC Press, Inc., 1997-1998, p. 225 to 226, the disclosure of which is hereby incorporated by reference. Preferred nonaromatic heterocyclic include epoxy, aziridinyl, thiiranyl,

pyrrolidinyl, pyrazolidinyl, imidazolidinyl, oxiranyl, tetrahydrofuranyl, dioxolanyl, tetrahydropyranyl, dioxanyl, dioxolanyl, piperidyl, piperazinyl, morpholinyl, pyranyl, imidazolinyl, pyrrolinyl, pyrazolinyl, thiazolidinyl, tetrahydrothiopyranyl, dithianyl, thiomorpholinyl, dihydropyranyl, tetrahydropyranyl, dihydropyranyl, tetrahydropyridyl, dihydropyridyl, tetrahydropyrimidinyl, dihydrothiopyranyl, azepanyl, as well as the fused systems resulting from the condensation with a phenyl group.

The term "heteroaryl" or aromatic heterocycles refers to a 3 to 14, preferably 5 to 10 membered aromatic hetero, mono-, bi-, or multi-cyclic ring. Examples include pyrrolyl, pyridyl, pyrazolyl, thienyl, pyrimidinyl, pyrazinyl, tetrazolyl, indolyl, quinolinyl, purinyl, imidazolyl, thienyl, thiazolyl, benzothiazolyl, furanyl, benzofuranyl, 1, 2, 4-thiadiazolyl, isothiazolyl, triazolyl, tetrazolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, carbazolyl, benzimidazolyl, isoxazolyl, pyridyl-*N*-oxide, as well as the fused systems resulting from the condensation with a phenyl group.

"Alkyl", "cycloalkyl", "alkenyl", "alkynyl", "aryl", "heteroaryl", "heterocyclic" and the like refer also to the corresponding "alkylene", "cycloalkylene", "alkenylene", "alkynylene", "arylene", "heteroarylene", "heterocyclene" and the likes which are formed by the removal of two hydrogen atoms.

"Arylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, benzyl, 2-phenylethan-1-yl, 2-phenylethen-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, 2-naphthylethen-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like.

"Heteroarylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with a heteroaryl radical. Examples of heteroarylalkyl groups are 2-benzimidazolylmethyl, 2-furylethyl.

Examples of a "hydroxyl protecting group" include, methoxymethyl ether, 2-methoxyethoxy-methyl ether, tetrahydropyranyl ether, benzyl ether, *p*-methoxybenzyl ether, trimethylsilyl ether, triethylsilyl ether, triisopropylsilyl ether, *t*-butyldimethylsilyl ether, triphenylmethylsilyl ether, acetate ester, substituted acetate esters, pivaloate, benzoate, methanesulfonate and *p*-toluenesulfonate.

"Leaving group" refers to a functional group that can be substituted by another functional group. Such leaving groups are well known in the art, and examples include, a halide (e.g., chloride, bromide, and iodide), methanesulfonyl (mesyl), *p*-toluenesulfonyl (tosyl), trifluoro-methylsulfonyl (triflate), and trifluoromethylsulfonate. A preferred leaving group is selected from nitrophenol; N-hydroxysuccinimide (NHS); phenol; dinitrophenol; pentafluorophenol; tetrafluorophenol; difluorophenol; monofluorophenol; pentachlorophenol; triflate; imidazole; dichlorophenol; tetrachlorophenol; 1-hydroxybenzotriazole; tosylate; mesylate; 2-ethyl-5-phenylisoxazolium-3′-

sulfonate, anhydrides formed its self, or formed with the other anhydride, e.g. acetyl anhydride, formyl anhydride; or an intermediate molecule generated with a condensation reagent for peptide coupling reactions or for Mitsunobu reactions.

The following abbreviations may be used herein and have the indicated definitions: Boc, tert-butoxy carbonyl; BroP, bromotrispyrrolidinophosphonium hexafluorophosphate; CDI, 1, 1'-carbonyldiimidazole; DCC, dicyclohexylcarbodiimide; DCE, dichloroethane; DCM, dichloromethane; DIAD, diisopropylazodicarboxylate; DIBAL-H, diisobutyl-aluminium hydride; DIPEA, diisopropylethylamine; DEPC, diethyl phosphorocyanidate; DMA, N, N-dimethyl acetamide; DMAP, 4-(N, N-dimethylamino)pyridine; DMF, N, N-dimethylformamide; DMSO, dimethylsulfoxide; DTT, dithiothreitol; EDC, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; ESI-MS, electrospray mass spectrometry; HATU, O-(7-azabenzotriazol-1-yl)-N, N, N', N'-tetramethyluronium hexafluorophosphate; HOBt, 1-hydroxybenzotriazole; HPLC, high pressure liquid chromatography; NHS, N-Hydroxysuc-cinimide; MMP, 4-methylmorpholine; PAB, p-aminobenzyl; PBS, phosphate-buffered saline (pH 7.0~7.5); PEG, polyethylene glycol; SEC, size-exclusion chromatography; TCEP, tris(2-carboxyethyl)phosphine; TFA, trifluoroacetic acid; THF, tetrahydrofuran; Val, valine.

The "amino acid(s)" can be natural and/or unnatural amino acids, preferably alpha-amino acids. Natural amino acids are those encoded by the genetic code, which are alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tyrosine. tryptophan and valine. The unnatural amino acids are derived forms of proteinogenic amino acids. Examples include hydroxyproline, lanthionine, 2-aminoisobutyric acid, dehydroalanine, gamma-aminobutyric acid (the neurotransmitter), ornithine, citrulline, beta alanine (3-aminopropanoic acid), gamma-carboxyglutamate, selenocysteine (present in many noneukaryotes as well as most eukaryotes, but not coded directly by DNA), pyrrolysine (found only in some archaea and one bacterium), N-formylmethionine (which is often the initial amino acid of proteins in bacteria, mitochondria, and chloroplasts), 5-hydroxytryptophan, L-dihydroxyphenylalanine, triiodothyronine, L-3, 4-dihydroxyphenylalanine (DOPA), and O-phosphoserine. The term amino acid also includes amino acid analogs and mimetics. Analogs are compounds having the same general $H_2N(R)CHCO_2H$ structure of a natural amino acid, except that the R group is not one found among the natural amino acids. Examples of analogs include homoserine, norleucine, methionine-sulfoxide, and methionine methyl sulfonium. Preferably, an amino acid mimetic is a compound that has a structure different from the general chemical structure of an alpha-amino acid but functions in a manner similar to one. The term "unnatural amino acid" is intended to represent the "D" stereochemical form, the natural

amino acids being of the "L" form. When 1~8 amino acids are used in this patent application, amino acid sequence is then preferably a cleavage recognition sequence for a protease. Many cleavage recognition sequences are known in the art. See, e.g., Matayoshi et al. Science 247: 954 (1990); Dunn et al. Meth. Enzymol. 241: 254 (1994); Seidah et al. Meth. Enzymol. 244: 175 (1994); Thornberry, Meth. Enzymol. 244: 615 (1994); Weber et al. Meth. Enzymol. 244: 595 (1994); Smith et al. Meth. Enzymol. 244: 412 (1994); and Bouvier et al. Meth. Enzymol. 248: 614 (1995); the disclosures of which are incorporated herein by reference. In particular, the sequence is selected from the group consisting of Val-Cit, Ala-Val, Val-Ala-Val, Lys-Lys, Ala-Asn-Val, Val-Leu-Lys, Ala-Ala-Ala, Gly-Gly-Phe-Gly, Ala-Arg, Val-Arg, Phe-Arg, Ala-Cit, Phe-Cit, Cit-Cit, Val-Lys, Ala-Ala-Asn, Lys, Cit, Ser, and Glu.

"Pharmaceutically" or "pharmaceutically acceptable" refer to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate.

"Pharmaceutically acceptable solvate" or "solvate" refer to an association of one or more solvent molecules and a disclosed compound. Examples of solvents that form pharmaceutically acceptable solvates include, but are not limited to, water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid and ethanolamine.

"Pharmaceutically acceptable excipient" includes any carriers, diluents, adjuvants, or vehicles, such as preserving or antioxidant agents, fillers, disintegrating agents, wetting agents, emulsifying agents, suspending agents, solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions as suitable therapeutic combinations.

As used herein, "pharmaceutical salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, tartaric, citric, methanesulfonic, benzenesulfonic, glucuronic, glutamic, benzoic, salicylic, toluenesulfonic, oxalic, fumaric, maleic, lactic and the like.

Further addition salts include ammonium salts such as tromethamine, meglumine, epolamine, etc., metal salts such as sodium, potassium, calcium, zinc or magnesium.

The pharmaceutical salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared via reaction the free acidic or basic forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two. Generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Administering" or "administration" refers to any mode of transferring, delivering, introducing or transporting a pharmaceutical drug or other agent to a subject. Such modes include oral administration, topical contact, intravenous, intraperitoneal, intramuscular, intralesional, intranasal, subcutaneous or intrathecal administration. Also contemplated by the present invention is utilization of a device or instrument in administering an agent. Such device may utilize active or passive transport and may be slow-release or fast-release delivery device.

The abbreviations of biological buffers and their chemical names are listed below:

ACES (N-(2-Acetamido)-2-aminoethanesulfonic acid) is used to buffer at pH = 6.1 - 7.5 (pKa = 6.88)

ADA (N-(2-Acetamido)iminodiacetic acid, N-(Carbamoylmethyl)iminodiacetic acid) is useful to buffer at pH = 6.0 - 7.2 (pKa = 6.65).

AMPD (2-amino-2-methyl-1, 3-propanediol)) is a useful buffer at pH = 7.8 - 9.7.

AMPSO (N-(1, 1-Dimethyl-2-hydroxyethyl)-3-amino-2-hydroxypropanesulfonic acid).

BES (N, N-Bis(2-hydroxyethyl)-2-aminoethanesulfonic acid).

Bicine (N, N-Bis(2-hydroxyethyl)glycine], Bis(2-hydroxyethyl)amino-tris(hydroxymethyl) methane) is used to buffer at pH = 5.8 - 7.2 (pKa = 8.35).

BisTris (Bis-(2-Hydroxyethyl)amino-tris(Hydroxymethyl)Methane).

BisTris propane (1, 3-Bis[tris(hydroxymethyl)methylamino]propane).

DIPSO (N, N-Bis(2-hydroxyethyl)-3-amino-2-hydroxypropanesulfonic acid) is used to buffer at pH = 7.0 - 8.2.

Gly-Gly (Diglycine; Glycyl-glycine) is used to buffer at pH = 7.5 - 8.9 (pKa = 8.30).

HEBPS (N-(2-Hydroxyethyl)piperazine-N′-(4-butanesulfonic acid)) is an homolog of HEPES and EPPS with higher pKa (pKa= 8.30), used to buffer at pH = 7.6 - 9.0

HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid ; 2-morpholinoethanesulfonic acid;

2-(4-morpholino)ethanesulphonic acid; 2-(N-morpholino)ethanesulfonic acid; morpholine-4-ethanesulfonic acid hydrate) is widely used to buffer at pH = 6.8 - 8.2; pKa at 20°C: 7.45 - 7.65)

HEPPS or EPPS (3-[4-(2-Hydroxyethyl)-1-piperazinyl]propanesulfonic acid hydrate; 4-(2-Hydroxyethyl)piperazine-1-(2-hydroxypropanesulfonic acid) Hydrate) is used as a buffering agent at pH 7.3-8.7 (pKa= 8.00/piperazine ring).

HEPPSO (4-(2-Hydroxyethyl)piperazine-1-(2-hydroxypropanesulfonic acid) hydrate).

MES (2-(N-morpholino)ethanesulfonic acid, monohydrate) is used as buffering agent at pH = 5.2 - 7.1 (pKa = 6.16).

MOBS (4-Morpholinebutanesulfonic acid; 3-(N-Morpholino)butanesulfonic acid hemisodium salt) is an homolog of MES and MOPS with higher pKa/ It is used to buffer solution at pH = 6.9 - 8.3 (pKa = 7.6).

MOPS (4-Morpholinepropanesulfonic acid Sodium salt).

MOPSO (β-Hydroxy-4-morpholinepropanesulfonic acid, 3-Morpholino-2-hydroxypropanesulfonic acid).

PIPES (Piperazine-1, 4-bis(2-ethanesulfonic acid) is used to buffer at pH 6.1-7.5 (pKa = 6.80).

POPSO (Piperazine-1, 4-bis(2-hydroxypropanesulfonic acid) dihydrate).

TAPS ([(2-Hydroxy-1, 1-bis(hydroxymethyl)ethyl)amino]-1-propanesulfonic acid).

TAPSO (2-Hydroxy-3-[tris(hydroxymethyl)methylamino]-1-propanesulfonic acid).

TES (2-[(2-Hydroxy-1, 1-bis(hydroxymethyl)ethyl)amino]ethanesulfonic acid).

Tricine (Piperazine-N, N'-bis[2-Hydroxypropanesulfonic Acid)] is used to buffer at pH = 7.4 - 8.8 (pKa = 8.16).

The term "antibody" is used herein in the broadest sense and encompasses various antibody structures, including but not limited to monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), and antibody fragments so long as they exhibit the desired antigen-binding activity and fusion proteins comprising an antibody, and any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site. An antibody includes an antibody of any class, such as IgG, IgA, or IgM (or sub-class thereof), and the antibody need not be of any particular class. Depending on the antibody amino acid sequence of the constant region of its heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2. The heavy-chain constant regions that correspond to the different classes of immunoglobulins are called alpha, delta, epsilon, gamma, and my, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

An "antibody fragment" refers to a molecule other than an intact antibody that comprises a portion of an intact antibody and that binds the antigen to which the intact antibody binds. Examples of antibody fragments include but are not limited to Fv, Fab, Fab', Fab'-SH, F(ab')2; diabodies; linear antibodies; single-chain antibody molecules (e.g. scFv); and multispecific antibodies formed from antibody fragments.

A "humanized" antibody refers to a chimeric antibody comprising amino acid residues from non-human HVRs and amino acid residues from human FRs. In certain embodiments, a humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the HVRs (e.g., CDRs) correspond to those of a non-human antibody, and all or substantially all of the FRs correspond to those of a human antibody. A humanized antibody optionally may comprise at least a portion of an antibody constant region derived from a human antibody. A "humanized form" of an antibody, e.g., a non-human antibody, refers to an antibody that has undergone humanization.

The term "variable region" or "variable domain" refers to the domain of an antibody heavy or light chain that is involved in binding the antibody to antigen. The variable domains of the heavy chain and light chain (VH and VL, respectively) of a native antibody generally have similar structures, with each domain comprising four conserved framework regions (FRs) and three hypervariable regions (HVRs). (See, e.g., Kindt et al. Kuby Immunology, 6th ed., W.H. Freeman and Co., page 91 (2007).) A single VH or VL domain may be sufficient to confer antigen-binding specificity. Furthermore, antibodies that bind a particular antigen may be isolated using a VH or VL domain from an antibody that binds the antigen to screen a library of complementary VL or VH domains, respectively. See, e.g., Portolano et al., J. Immunol. 150: 880-887 (1993); Clarkson et al., Nature 352: 624-628 (1991).

As used herein, "monoclonal antibody" refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to polyclonal antibody preparations, which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method first described by Kohler and Milstein, Nature 256:495, 1975, or may be made by

recombinant DNA methods such as described in U.S. Pat. No. 4, 816, 567. The monoclonal antibodies may also be isolated from phage libraries generated using the techniques described in McCafferty et al., Nature 348:552-554, 1990, for example.

As used herein, "humanized" antibody refers to forms of non-human (e.g. murine) antibodies that are chimeric immunoglobulins, immunoglobulin chains, or fragments thereof (such as Fv, Fab, Fab', F(ab')2 or other antigen binding subsequences of antibodies) that contain minimal sequence derived from non-human immunoglobulin. Preferably, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementarity determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, the humanized antibody may comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences, but are included to further refine and optimize antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region or domain (Fc), typically that of a human immunoglobulin. Preferred are antibodies having Fc regions modified as described in WO 99/58572. Other forms of humanized antibodies have one or more CDRs (CDR L1, CDR L2, CDR L3, CDR H1, CDR H2, or CDR H3) which are altered with respect to the original antibody, which are also termed one or more CDRs "derived from" one or more CDRs from the original antibody.

As used herein, "human antibody" means an antibody having an amino acid sequence corresponding to that of an antibody produced by a human and/or which has been made using any of the techniques for making human antibodies known to those skilled in the art or disclosed herein. This definition of a human antibody includes antibodies comprising at least one human heavy chain polypeptide or at least one human light chain polypeptide. One such example is an antibody comprising murine light chain and human heavy chain polypeptides. Human antibodies can be produced using various techniques known in the art. In one embodiment, the human antibody is selected from a phage library, where that phage library expresses human antibodies (Vaughan et al., Nature Biotechnology, 14:309-314, 1996; Sheets et al., Proc. Natl. Acad. Sci. (USA) 95:6157-6162, 1998; Hoogenboom and Winter, J. Mol. Biol., 227:381, 1991; Marks et al., J. Mol. Biol., 222:581, 1991). Human antibodies can also be made by immunization of animals into which human

immunoglobulin loci have been transgenically introduced in place of the endogenous loci, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. This approach is described in U.S. Pat. Nos. 5, 545, 807; 5, 545, 806; 5, 569, 825; 5, 625, 126; 5, 633, 425; and 5, 661, 016. Alternatively, the human antibody may be prepared by immortalizing human B lymphocytes that produce an antibody directed against a target antigen (such B lymphocytes may be recovered from an individual or from single cell cloning of the cDNA, or may have been immunized in vitro). See, e.g., Cole et al. Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77, 1985; Boerner et al., J. Immunol., 147 (1):86-95, 1991; and U.S. Pat. No. 5, 750, 373.

The term "chimeric antibody" is intended to refer to antibodies in which the variable region sequences are derived from one species and the constant region sequences are derived from another species, such as an antibody in which the variable region sequences are derived from a mouse antibody and the constant region sequences are derived from a human antibody.

The terms "polypeptide", "oligopeptide", "peptide" and "protein" are used interchangeably herein to refer to chains of amino acids of any length, preferably, relatively short (e.g., 10-100 amino acids). The chain may be linear or branched, it may comprise modified amino acids, and/or may be interrupted by non-amino acids. The terms also encompass an amino acid chain that has been modified naturally or by intervention; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification, such as conjugation with a labeling component. Also included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), as well as other modifications known in the art. It is understood that the polypeptides can occur as single chains or associated chains.

A "monovalent antibody" comprises one antigen binding site per molecule (e.g., IgG or Fab). In some instances, a monovalent antibody can have more than one antigen binding sites, but the binding sites are from different antigens.

A "monospecific antibody" comprises two identical antigen binding sites per molecule (e.g. IgG) such that the two binding sites bind identical epitope on the antigen. Thus, they compete with each other on binding to one antigen molecule. Most antibodies found in nature are monospecific. In some instances, a monospecific antibody can also be a monovalent antibody (e.g. Fab).

A "bivalent antibody" comprises two antigen binding sites per molecule (e.g., IgG). In some instances, the two binding sites have the same antigen specificities. However, bivalent antibodies may be bispecific.

A "bispecific" or "dual-specific" is a hybrid antibody having two different antigen binding sites. The two antigen binding sites of a bispecific antibody bind to two different epitopes, which may

reside on the same or different protein targets.

A "bifunctional" is antibody is an antibody having identical antigen binding sites (i.e., identical amino acid sequences) in the two arms but each binding site can recognize two different antigens.

A "heteromultimer", "heteromultimeric complex", or "heteromultimeric polypeptide" is a molecule comprising at least a first polypeptide and a second polypeptide, wherein the second polypeptide differs in amino acid sequence from the first polypeptide by at least one amino acid residue. The heteromultimer can comprise a "heterodimer" formed by the first and second polypeptide or can form higher order tertiary structures where polypeptides in addition to the first and second polypeptide are present.

A "heterodimer", "heterodimeric protein", "heterodimeric complex", or "heteromultimeric polypeptide" is a molecule comprising a first polypeptide and a second polypeptide, wherein the second polypeptide differs in amino acid sequence from the first polypeptide by at least one amino acid residue.

The "hinge region", "hinge sequence", and variations thereof, as used herein, includes the meaning known in the art, which is illustrated in, for example, Janeway et al., ImmunoBiology: the immune system in health and disease, (Elsevier Science Ltd., NY) (4th ed., 1999); Bloom et al., Protein Science (1997), 6:407-415; Humphreys et al., J. Immunol. Methods (1997), 209:193-202.

The "immunoglobulin-like hinge region", "immunoglobulin-like hinge sequence, " and variations thereof, as used herein, refer to the hinge region and hinge sequence of an immunoglobulin-like or an antibody-like molecule (e.g., immunoadhesins). In some embodiments, the immunoglobulin-like hinge region can be from or derived from any IgG1, IgG2, IgG3, or IgG4 subtype, or from IgA, IgE, IgD or IgM, including chimeric forms thereof, e.g., a chimeric IgG1/2 hinge region.

The term "immune effector cell" or "effector cell" as used herein refers to a cell within the natural repertoire of cells in the human immune system which can be activated to affect the viability of a target cell. The viability of a target cell can include cell survival, proliferation, and/or ability to interact with other cells.

Antibodies of the invention can be produced using techniques well known in the art, e.g., recombinant technologies, phage display technologies, synthetic technologies or combinations of such technologies or other technologies readily known in the art (see, for example, Jayasena, S. D., Clin. Chem., 45: 1628-50, 1999 and Fellouse, F. A., et al, J. Mol. Biol., 373(4): 924-40, 2007).

The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents a cellular function and/or causes cell death or destruction. Cytotoxic agents include, but are not limited to, radioactive isotopes (e.g., At211, I131, I125, Y90, In111, Re186, Re188, Sm153, Bi212, P32,

Pb212, Zr89, F18, and radioactive isotopes of Lu, e.g. Lu177); chemotherapeutic agents or drugs (e.g., tubulysin, maytansin, auristatin, DNA minor groove binders (such as PBD dimers), ducarmysin, topoisomerase I or II inhibitor, RNA polymerase inhibitors, DNA alkylators, methotrexate, adriamicin, vinca alkaloids (vincristine, vinblastine, etoposide), doxorubicin, melphalan, mitomycin C, chlorambucil, daunorubicin or other intercalating agents); growth inhibitory agents; enzymes and fragments thereof such as nucleolytic enzymes; antibiotics; toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof; and the various antitumor or anticancer agents disclosed throughout the application.

"Linker" refers to a chemical moiety comprising a covalent bond or a chain of atoms that covalently attaches an antibody to a drug moiety. In various embodiments, linkers include a divalent radical such as an alkyldiyl, an aryldiyl, a heteroaryldiyl, moieties such as: --$(CR_2)_nO(CR_2)$ n--, repeating units of alkyloxy (e.g. polyethylenoxy, PEG, polymethyleneoxy) and alkylamino (e.g. polyethyleneamino); and diacid ester and amides including succinate, succinamide, diglycolate, malonate, and caproamide. In various embodiments, linkers can comprise one or more amino acid residues, such as valine, phenylalanine, lysine, and homolysine.

The words "comprise", "comprising", "include", "including" and "includes" when used in this specification and claims are intended to specify the presence of stated features, integers, components, or steps, but they do not preclude the presence or addition of one or more other features, integers, components, steps, or groups thereof. The novel conjugates disclosed herein use the bridge linkers. Examples of some suitable linkers and their synthesis are shown in the examples 1- 468 below of the specification.

THE CONJUGATION PROCESS OF THE PRESENT INVENTION

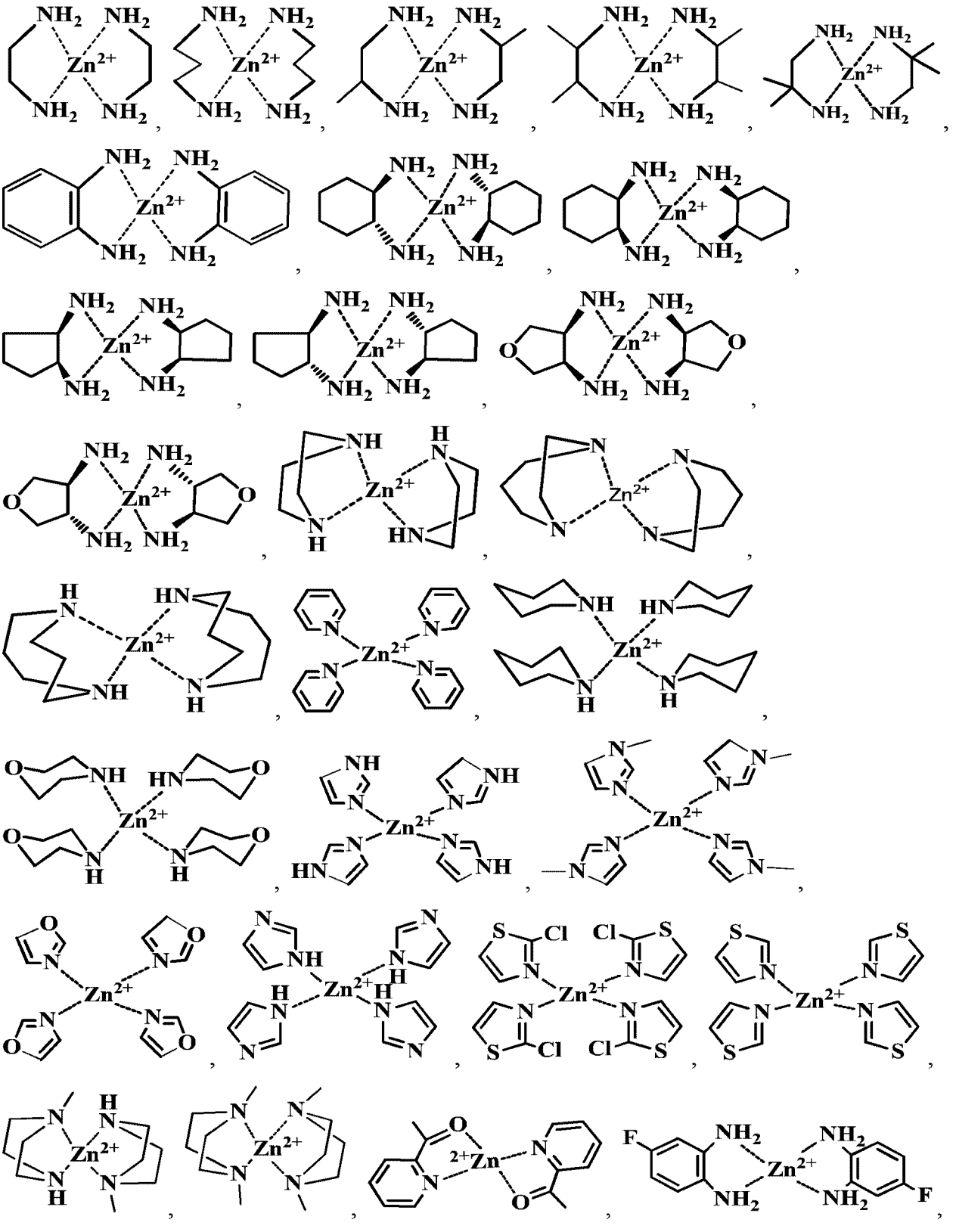
As disclosed above, the key factor of the invention in the conjugation process is the transition zinc cation-amino complex, $Zn(NR_1R_2R_3)_{m1}^{2+}$, which coordinate the selective reduction of certain chain of disulfide bonds of biomolecule. Preferably the certain inter-chain disulfide bonds in an antibody. Previous study by LC-MS indicated that inter chain disulfide bonds of IgG antibodies are more susceptible to reduction than intra chain disulfide bonds, and the disulfide bonds between the light chain and heavy chain were more susceptible than disulfide bonds between the two heavy chains. The upper disulfide bond of the two inter heavy chain disulfide bonds of IgG antibodies was more susceptible than the lower one. Furthermore, disulfide bonds in the CH2 domain were the most susceptible to reduction. Disulfide bonds in VL, CL, VH, and CH1 domains had similar and moderate susceptibility, while disulfide bonds in the CH3 domain were the least susceptible to reduction (Liu, H, et al Anal. Chem., 2010, *82*, 5219–5226). The using of $ZnCl_2$ salt at low

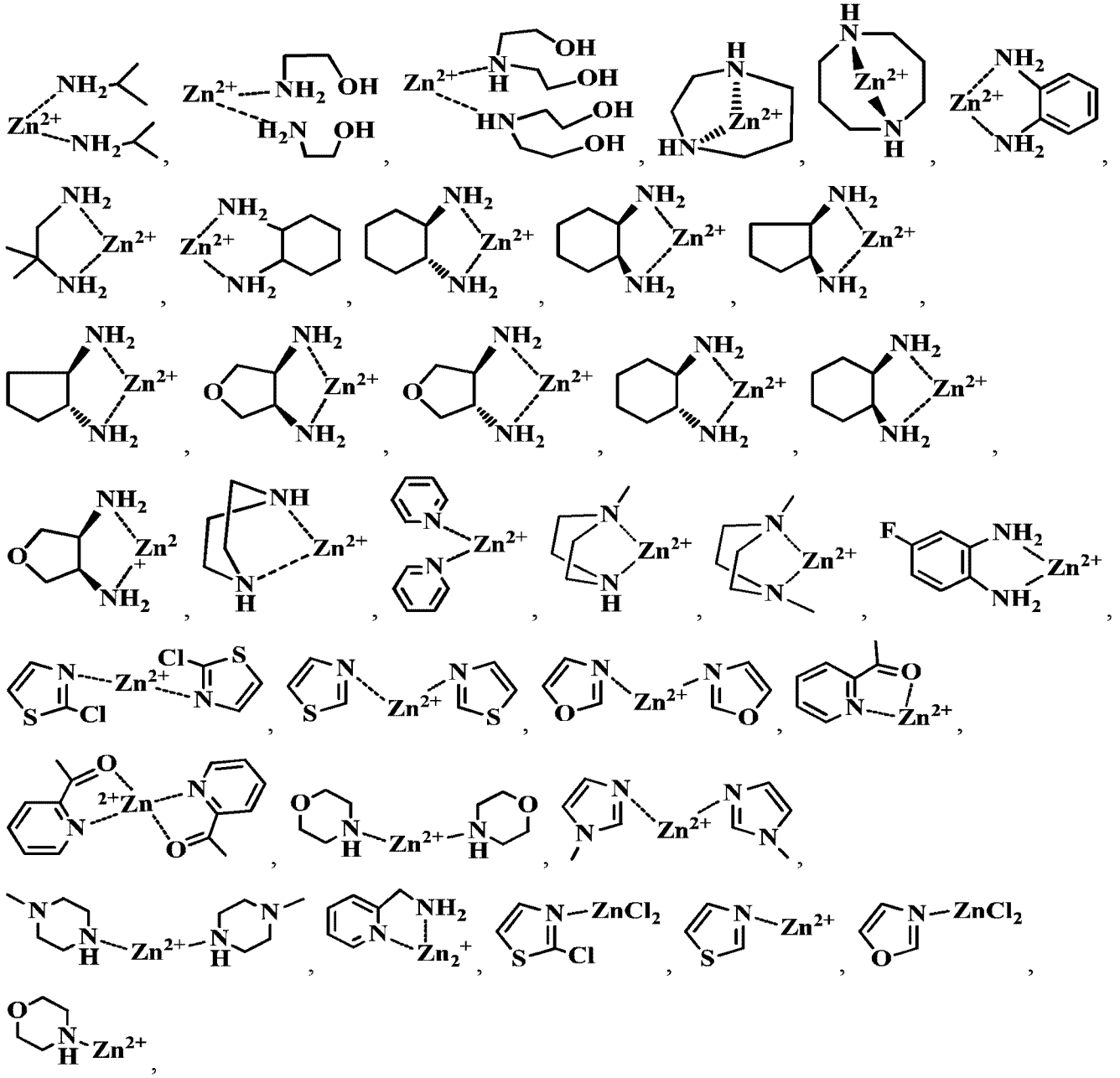
temperatures of 2 ~ 8 °C in coordination the reduction of the disulfide bonds of a IgG antibody of the invention WO2020164561 made practically possible of the distinguishable reduction above. Here, the transition zinc cation-amino complex, $Zn(NR_1R_2R_3)_{m1}^{2+}$, which is used in the conjugation process of the invention, is much bulky, not only can coordinate the disulfide reduction, but also stereoscopically hinders the reductant (such as TCEP) to access to disulfide bonds between the two heavy chains of an IgG antibody, thus results in much better selective reduction and following by conjugation with a drug/linker complex.

The transition Zinc cation-amino chelate/complex, $Zn(NR_1R_2R_3)_{m1}^{2+}$, wherein R_1, R_2 and R_3 are independently selected from C_1-C_8 of alkyl; C_2-C_8 of heteroalkyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 of aryl, Ar-alkyl, heteroaryl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; m1 is selected from 1, 2, 3, 4, 5, 6, 7, or 8; In preference, M is selected from Zn^{2+}, m_1 is selected from 1, 2, 3, or 4, and m_1 is more preferably 2.

In addition, $(NR_1R_2R_3)_{m1}$ can form a dimer, trimer, tetramer, pentamer, or hexamer wherein these polymers are covalently linked among N, R_1, R_2 and R_3; and N, R_1, R_2 and/or R_3 themselves can form heterocyclic, carbocyclic, diheterocyclic, or dicarbocyclic rings.

The preferred $Zn(NR_1R_2R_3)_{m1}^{2+}$ are exampled as following: $Zn(NH_2CH_3)_2^{2+}$, $Zn(NH_2CH_2CH_3)_2^{2+}$, $Zn(NH_2CH_2CH_2CH_3)_2^{2+}$, $Zn(NH_2CH(CH_3)_2)_2^{2+}$, $Zn(NH_2C(CH_3)_3)_2^{2+}$, $Zn(NH_2CH_2C(CH_3)_3)_2^{2+}$, $Zn(NH(CH_3)_2)_2^{2+}$, $Zn(NH(CH_2CH_3)_2)_2^{2+}$, $Zn(NH(CH(CH_3)_2)_2)_2^{2+}$, $Zn(NH(C(CH_3)_3)_2)_2^{2+}$, $Zn(NH(CH(CH_2CH_3)_2)_2)_2^{2+}$, $Zn(NH(CH_2C(CH_3)_3)_2)_2^{2+}$, $Zn(NH(CH_2C(CH_2CH_3)_3)_2)_2^{2+}$, $Zn(NH(CH_2CH_2C(CH_3)_3)_2)_2^{2+}$, $Zn(NH_2CH_2CH_2OH)_2^{2+}$, $Zn(NH(CH_2CH_2OH)_2)_2^{2+}$, $Zn(N(CH_2CH_2OH)_3)_2^{2+}$, $Zn(NH_2CH_2COOH)_2^{2+}$, $Zn(NH_2CH_2CONH_2)_2^{2+}$, $Zn(NH_2CH_2COOCH_3)_2^{2+}$, $Zn(NH_2CH_2COOCH_2CH_3)_2^{2+}$, $Zn(NH_2CH_2COOC(CH_3)_3)_2^{2+}$, $Zn(NH_2CH_2COOCH(CH_3)_2)_2^{2+}$, $Zn(NH_2CH_2CH_2COOH)_2^{2+}$, $Zn(NH(CH_2COOH)_2)_2^{2+}$, $Zn(N(CH_2CH_2COOH)_3)_2^{2+}$, $Zn(NH_2CH_3)_4^{2+}$, $Zn(NH_2CH_2CH_3)_4^{2+}$, $Zn(NH_2CH_2CH_2CH_3)_4^{2+}$, $Zn(NH_2CH(CH_3)_2)_4^{2+}$, $Zn(NH_2C(CH_3)_3)_4^{2+}$, $Zn(NH_2CH_2C(CH_3)_3)_4^{2+}$, $Zn(NH(CH_3)_2)_4^{2+}$, $Zn(NH(CH_2CH_3)_2)_4^{2+}$, $Zn(NH(CH(CH_3)_2)_2)_4^{2+}$, $Zn(NH(C(CH_3)_3)_2)_4^{2+}$, $Zn(NH(CH(CH_2CH_3)_2)_2)_4^{2+}$, $Zn(NH(CH_2C(CH_3)_3)_2)_4^{2+}$, $Zn(NH(CH_2C(CH_2CH_3)_3)_2)_4^{2+}$, $Zn(NH(CH_2CH_2C(CH_3)_3)_2)_4^{2+}$, $Zn(NH_2CH_2CH_2OH)_4^{2+}$, $Zn(NH(CH_2CH_2OH)_2)_4^{2+}$, $Zn(N(CH_2CH_2OH)_3)_4^{2+}$, $Zn(NH_2CH_2COOH)_4^{2+}$, $Zn(NH_2CH_2CONH_2)_4^{2+}$, $Zn(NH_2CH_2COOCH_3)_4^{2+}$, $Zn(NH_2CH_2COOCH_2CH_3)_4^{2+}$, $Zn(NH_2CH_2COOC(CH_3)_3)_4^{2+}$, $Zn(NH_2CH_2COOCH(CH_3)_2)_4^{2+}$, $Zn(NH_2CH_2CH_2COOH)_4^{2+}$, $Zn(NH(CH_2COOH)_2)_4^{2+}$, $Zn(N(CH_2CH_2COOH)_3)_4^{2+}$,





All the complex cations above can be formed with an anion, selected from, but not limited, Cl^-, Br^-, I^-, SO_4^{2-}, HSO_4^-, NO_3^-, PO_4^{3-}, HPO_4^{2-}, $H_2PO_4^-$, CO_3^{2-}, HCO_3^-, $HCOO^-$, CH_3COO^-, F_3CCOO^-, Cl_3CCOO^-, FCH_2COO^-, $ClCH_2COO^-$, F_2CHCOO^-, Cl_2CHCOO^-, BF_4^-, SO_3^{2-}, HSO_3^-, CH_3SO^{3-}, $C_6H_5CH_2SO^{3-}$, $C_6H_5SO^{3-}$, $C_6H_5COO^-$, $C_6H_5CH_2COO^-$, $C_6F_5O^-$, $C_6H_4(OH)COO^-$, $C_6H_2F_3O^-$, $C_6H_4(NO_2)O^-$, $C_6H_2(NO_2)_3O^-$, etc.

The zinc cation-amino complex in the reaction solution are 0.5 ~ 20 equivalents of the antibody, preferably 1.0 -5.0 equivalents of the antibody, more preferably 1.5 -3.0 equivalents of the antibody. The transition metal cation-amino complex can be added to the reaction solution

with a water- miscible organic solvent, selected from, but not limited, ethanol, methanol, propanol, propandiol, DMA, DMF, DMSO, THF, or CH_3CN.

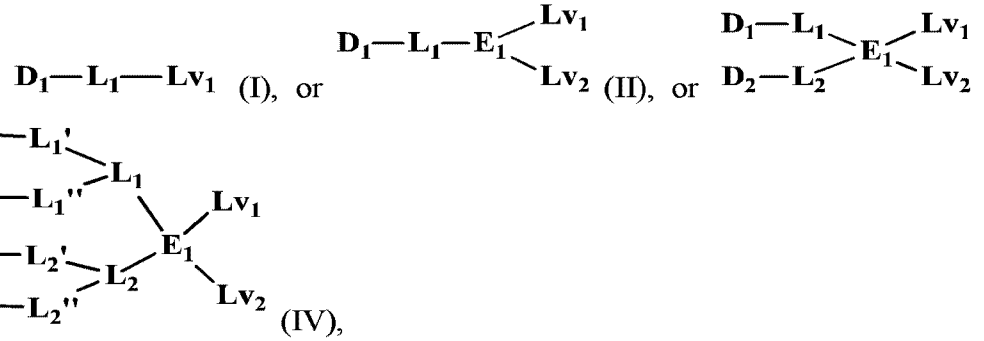
The reductant used in the reaction solution with the transition metal cation-amino complex is selected from Tris(2-carboxyethyl)phosphine (TCEP), ($P(CH_2CH_2COOH)_3$). It can be other reductants, such as Tris(hydroxypropyl)-phosphine ($P(CH_2CH_2CH_2OH)_3$), $P(CH_2CH_3)_3$, $P(CH_2CH_2CH_3)_3$, $P(CH_2CH_2\text{-}CH_2CH_3)_3$, $P(CH(CH_3)_2)_3$, $P(CH_2CH{=}CH_2)_3$, $P(CH_2CH_2CN)_3$, $P(CH(CH_3)_2)_2(CH_2CH_2NH_2)$, $P(CH_2CH_2CONH_2)_3$, $P(CH_2CH_2CONHCH_3)_3$, $P(CH_2CH_2CH_2NHCOCH_3)_3$, $NaB(CN)H_3$, $(C_6H_{11})_2P(CH_2)_4P(C_6H_{11})_2$, $(C_6H_{11})_2P(CH_2)_3P\text{-}(C_6H_{11})_2$, Dicyclohexyl(ethyl)phosphine, Bis[2-(di-*tert*-butylphosphino)ethyl]amine, Tricyclohexylphosphine, 1, 2-Ethanediylbis[dicyclohexyl]-phosphine, Bis[2-(dicyclohexylphosphino)ethyl]amine, Tris[2-(diphenylphosphino)ethyl]-phosphine ($[(C_6H_5)_2PCH_2CH_2]_3P$), triphenylphosphine, sulfonylated triphenylphosphines (2-(diphenylphosphino)benzenesulfonic acid (diPPBS), 3-(diphenylphosphino)benzenesulfonic acid, 4-(diphenylphosphino)benzenesulfonic acid, 3, 3', 3''-phosphinetriyltribenzenesulfonic acid). Preferably the reductant is selected from TECP or $P(CH_2CH_2CH_2OH)_3$, and more preferably the reductant is selected from TECP. And the concentration of the reductant in the reaction solution may be 0.04 mM – 0.4 mM, or 1.0 - 10.0 equivalents of antibody used in the reaction. Preferably the reductant is used at 2.0 - 4.0 equivalents of an antibody.

The optimum buffer for conduction of the selective reduction is selected from, but not limited, PBS, Mes, Bis-Tris, Bis-Tris Propane, Pipes, Aces, Mopso, Bes, Mops, Hepes, Tes, Pipps, Dipso, Tapso, Heppso, Tris-up, Tris-HCl, Tricine, Hepps, Gly-Gly, Bicine, Taps, Hepee, Acetates, Histidine, Citrates, MES, Borates, or combinations two, three or four buffer components from above. And the pH of the buffer is selected 4.0 -9.0, preferred 5.0 -7.5, more preferred 5.5 -7.5. The concentration of the buffer in the reaction is 0.02 – 1.0 M, preferably 20 – 200 mM, more preferably 20 – 100 mM. And up to 30% of water mixable (miscible) organic solvents, selected from DMA, DMF, ethanol, methanol, acetone, acetonitrile, THF, isopropanol, dioxane, propylene glycol, or ethylene diol can be added as the co-solvent in water based buffer solution;

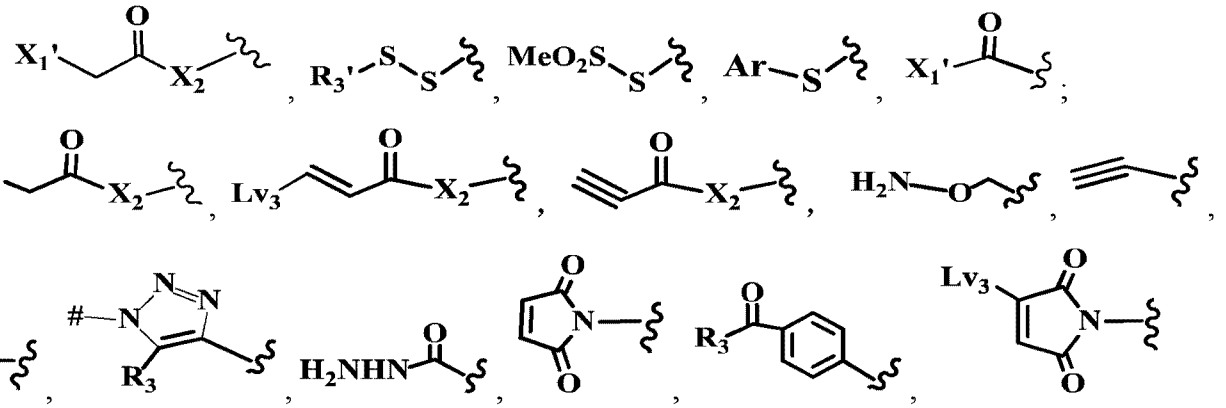
The optimum temperature for the reduction reaction is typically controlled between about -5 and 40 °C, and the reaction time is 15 minutes to 48 hours. But it is well-understandable in the field of protein conjugation that the reaction time and temperature can be determined by those skilled in the art based on the specific protein, in particular, the antibody to be conjugated. For example a preferable reduction reaction can be controlled at a temperature typically between about - 5 to about 40 °C, and preferably, about 0 to 37 °C; more preferably

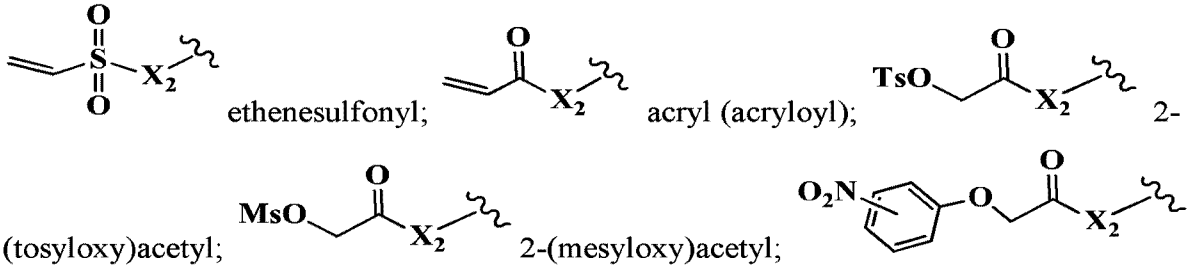
about 2 to 8 °C, and more precisely 4 ± 2 °C. The process of the conjugation is 15 min to 12 hours, and more preferably at a temperature between about 2 and 8 °C, and the process time is about 30 min to 15 hours (overnight).

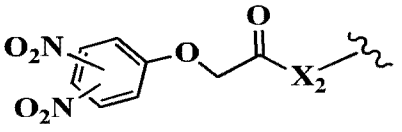
During the reduction, or after the reduction, a Drug/linker complex/assembly is directly added to the solution of the reduction reaction for conjugation. The Drug/linker complex/assembly, having a formula (I) or (II) represented as:

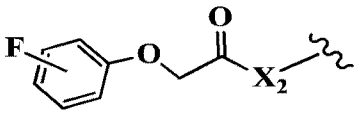
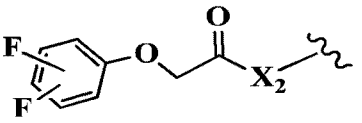
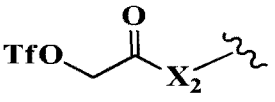

(I), or (II), or (III), or (IV),

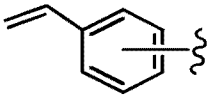
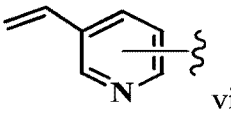
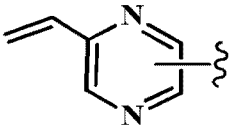
wherein: Lv_1 and Lv_2 are a thiol reaction group, and are independently or jointly selected from:

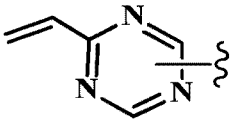
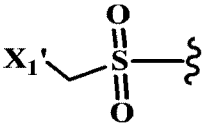

monosubstituted maleimide; disubstituted maleimide; monosubstituted succinimide; disubstituted succinimide; -CHO aldehyde;

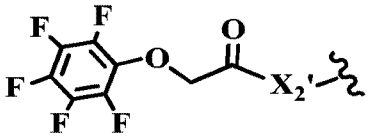
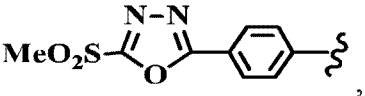

ethenesulfonyl; acryl (acryloyl); 2-(tosyloxy)acetyl; 2-(mesyloxy)acetyl; 2-

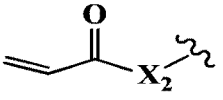
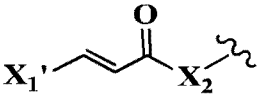
(nitrophenoxy)acetyl;  2-(dinitrophenoxy)acetyl;

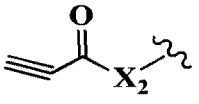
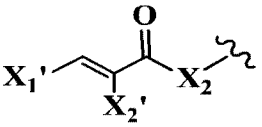
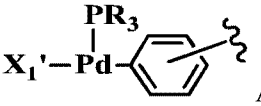
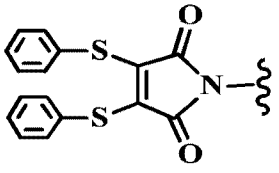
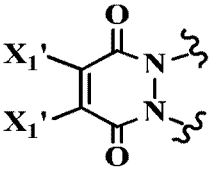
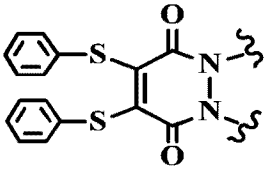
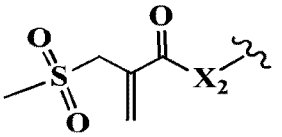
 2-(fluorophenoxy)-acetyl;  2-(difluorophenoxy)-acetyl;  2-(((trifluoromethyl)-sulfonyl)oxy)acetyl;

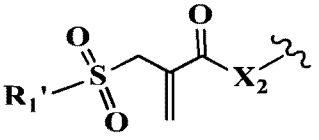
 styrene,  vinylpyridine,  vinylpyrazine,

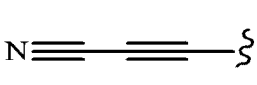
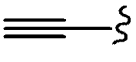
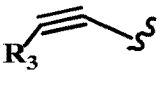
 vinyl-1, 3, 5-triazine,  substituted methylsulfonyl,

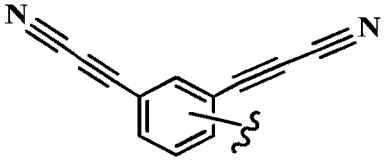
 2-(pentafluorophenoxy)acetyl;  ,

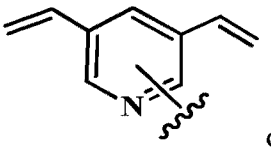
methylsulfonephenyloxadiazole (ODA);  acryl,  halo acryl,

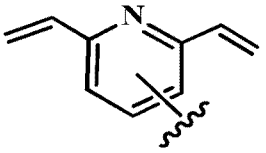
 propiol,  2, 3-dihaloacryl,  Aryl-palladium complex,  bis(phenylsulfanyl)-maleimides,  bis-halide-pyridazinediones,  bis-phenylsulfanyl-pyridazinedione, 

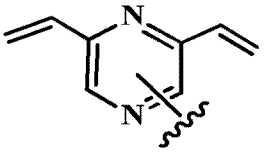
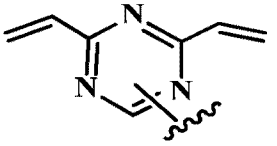
2-((methylsulfonyl)methyl)acryl,  2-((alkyl or aryl-sulfonyl)methyl)acryl,

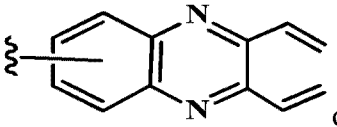
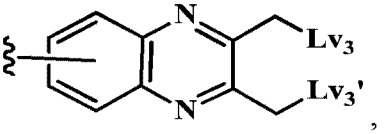
 cyanoethynyl,  ethynyl;  alkynyl,

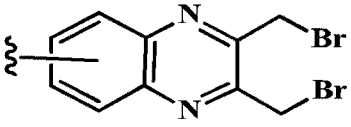
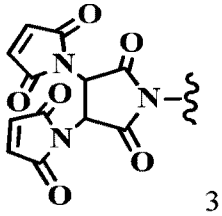


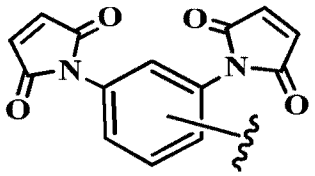
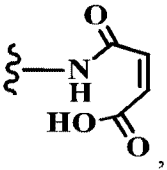
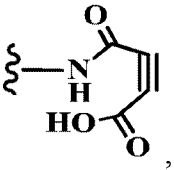
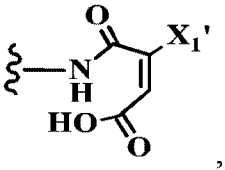
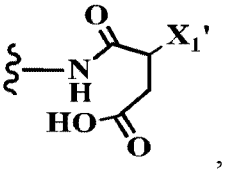
arylenedipropiolonitrile (ADPN),  or

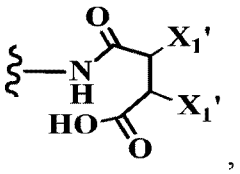
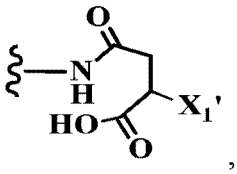
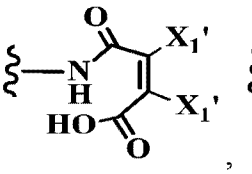
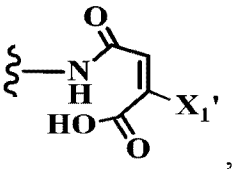
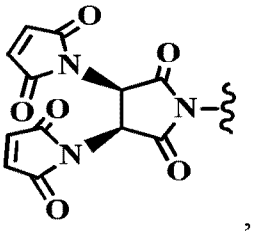


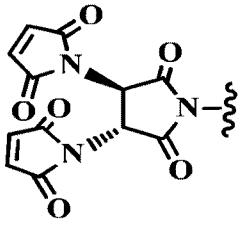
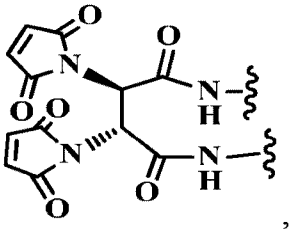
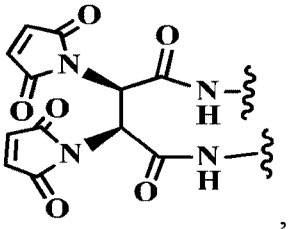
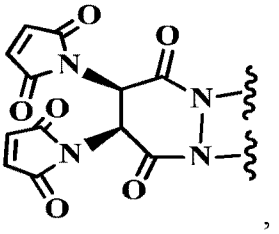
divinylpyridine,  divinylpyrazine, 

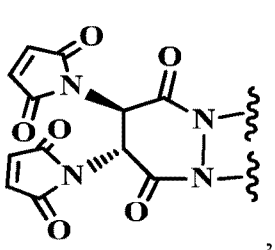
divinyltriazine,  divinylquinoxaline,  ,

 , or  3, 4-bis(maleimido)-2, 5-dioxopyrrolidine,

 ,  ,  ,  , ,  ,

 ,  ,  ,  ,  ,

 ,  ,  ,  ,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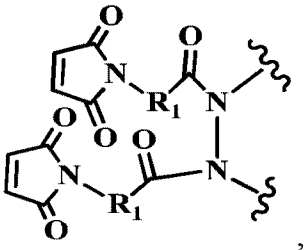
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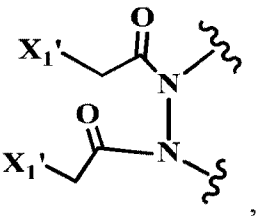
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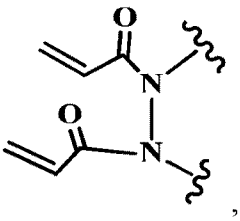
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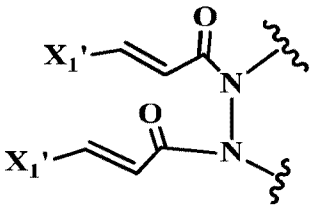
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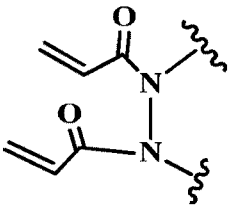
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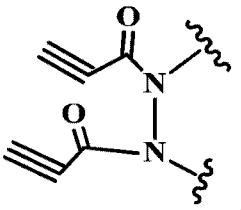
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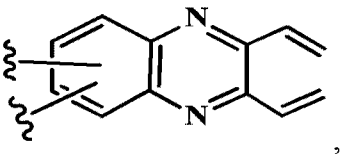
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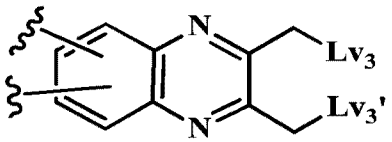
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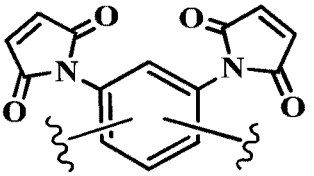
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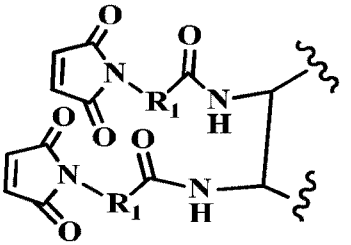
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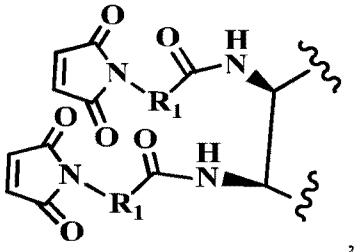
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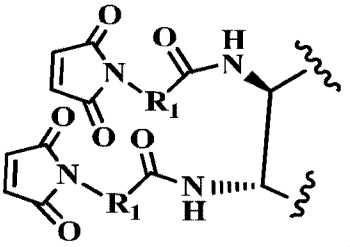
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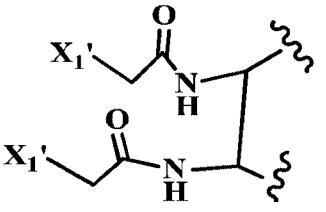
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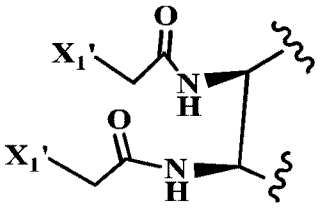
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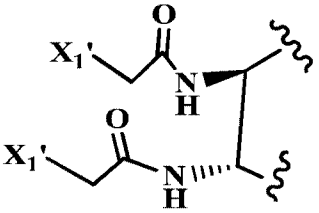
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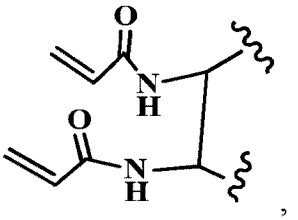
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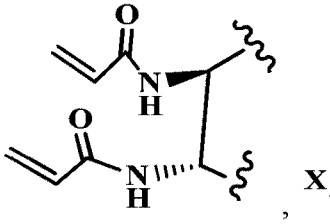
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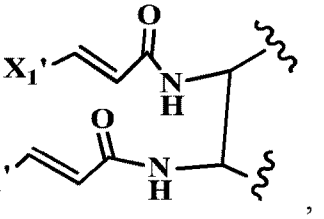
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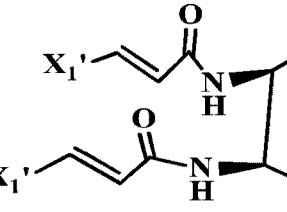
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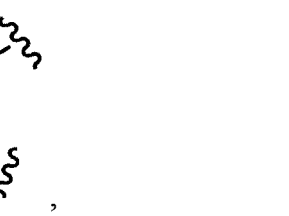
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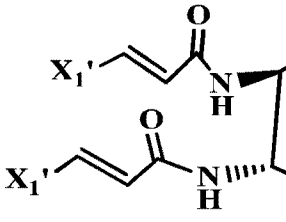
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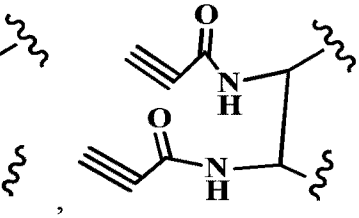
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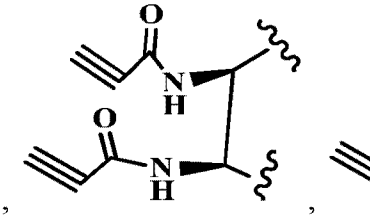
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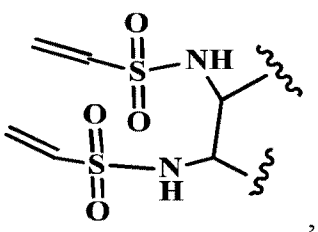
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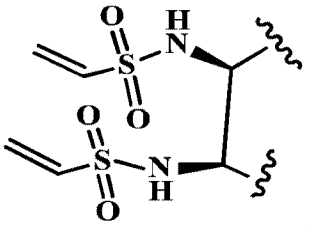
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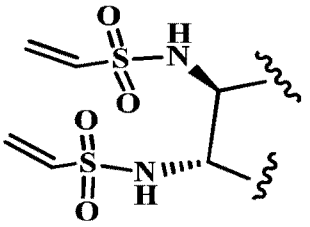
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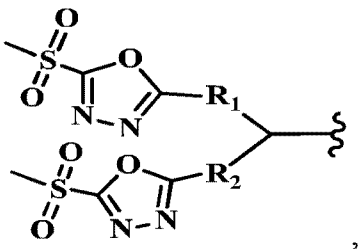
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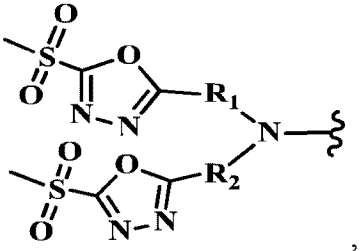
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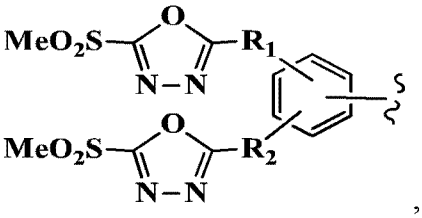
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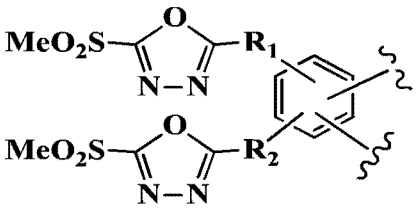
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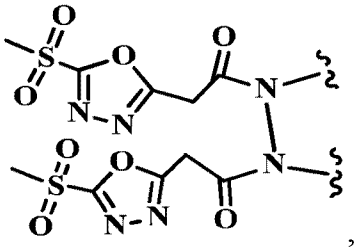
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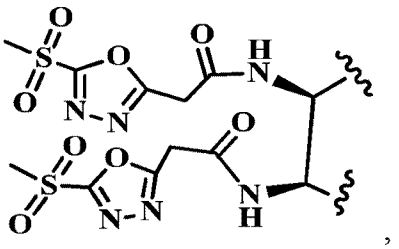
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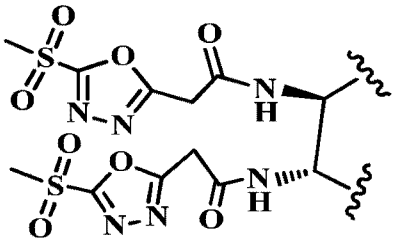
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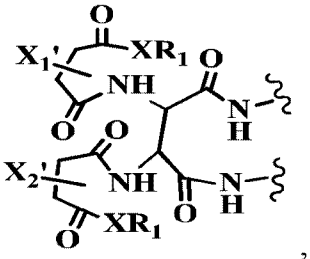
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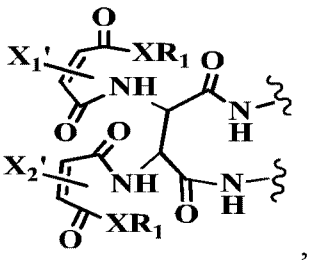
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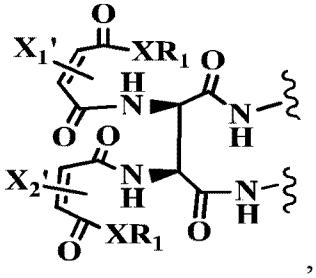
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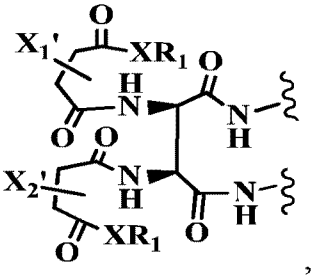
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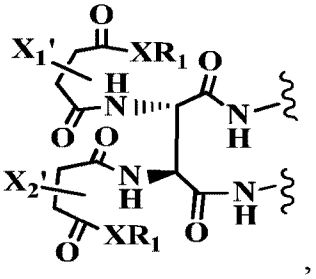
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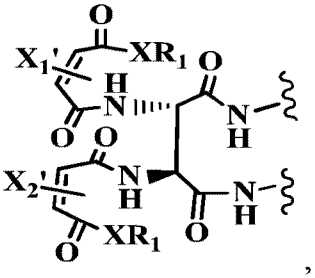
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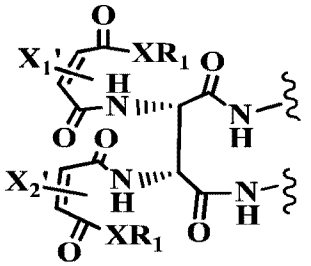
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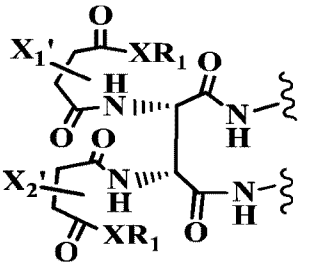
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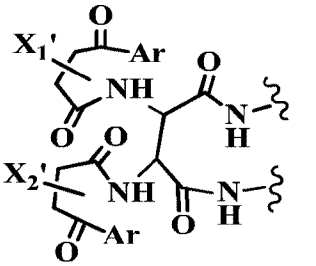
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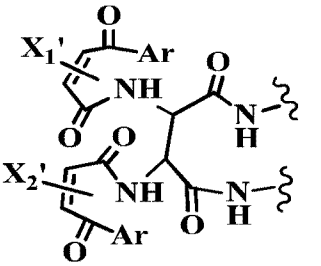
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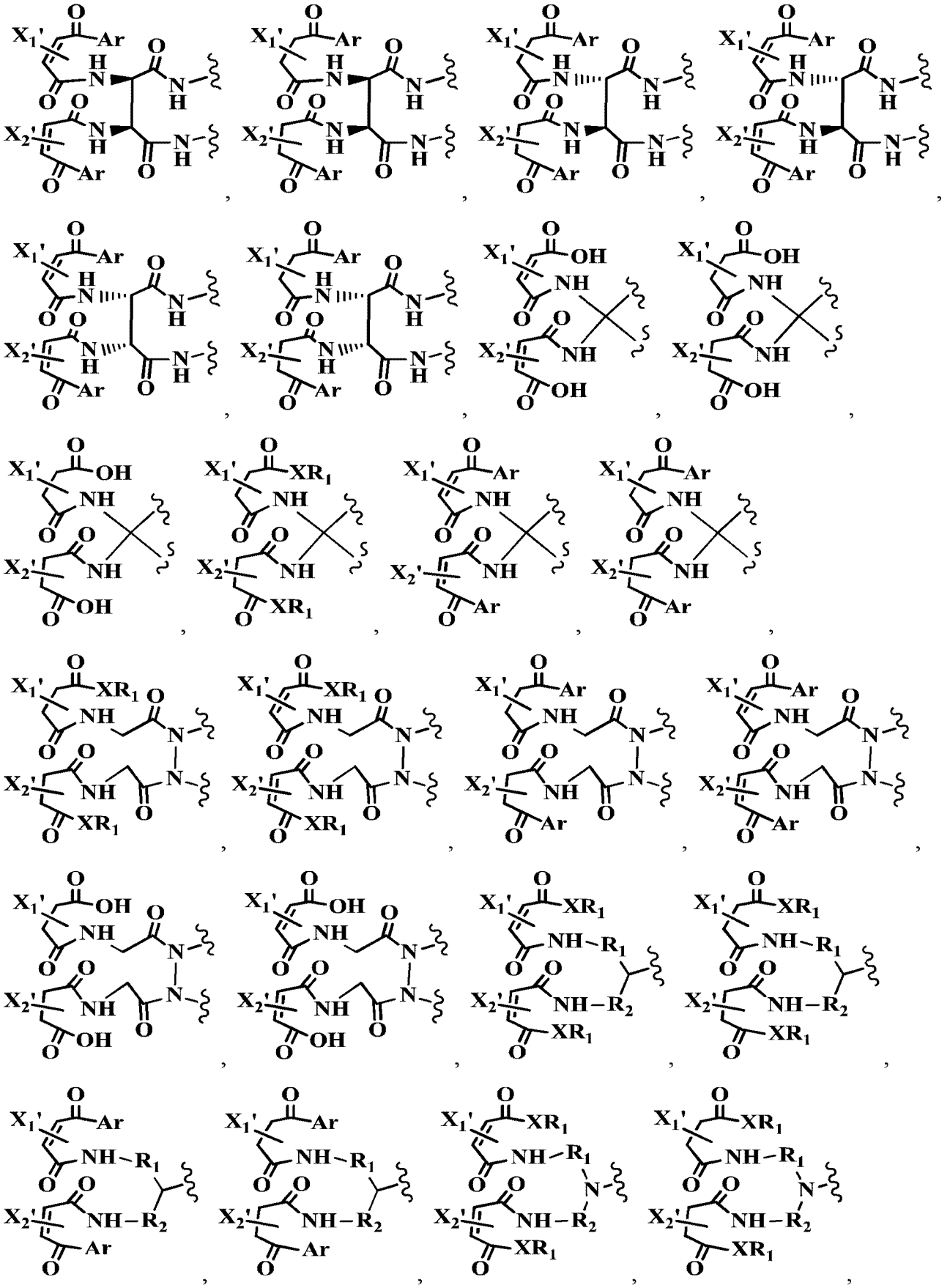
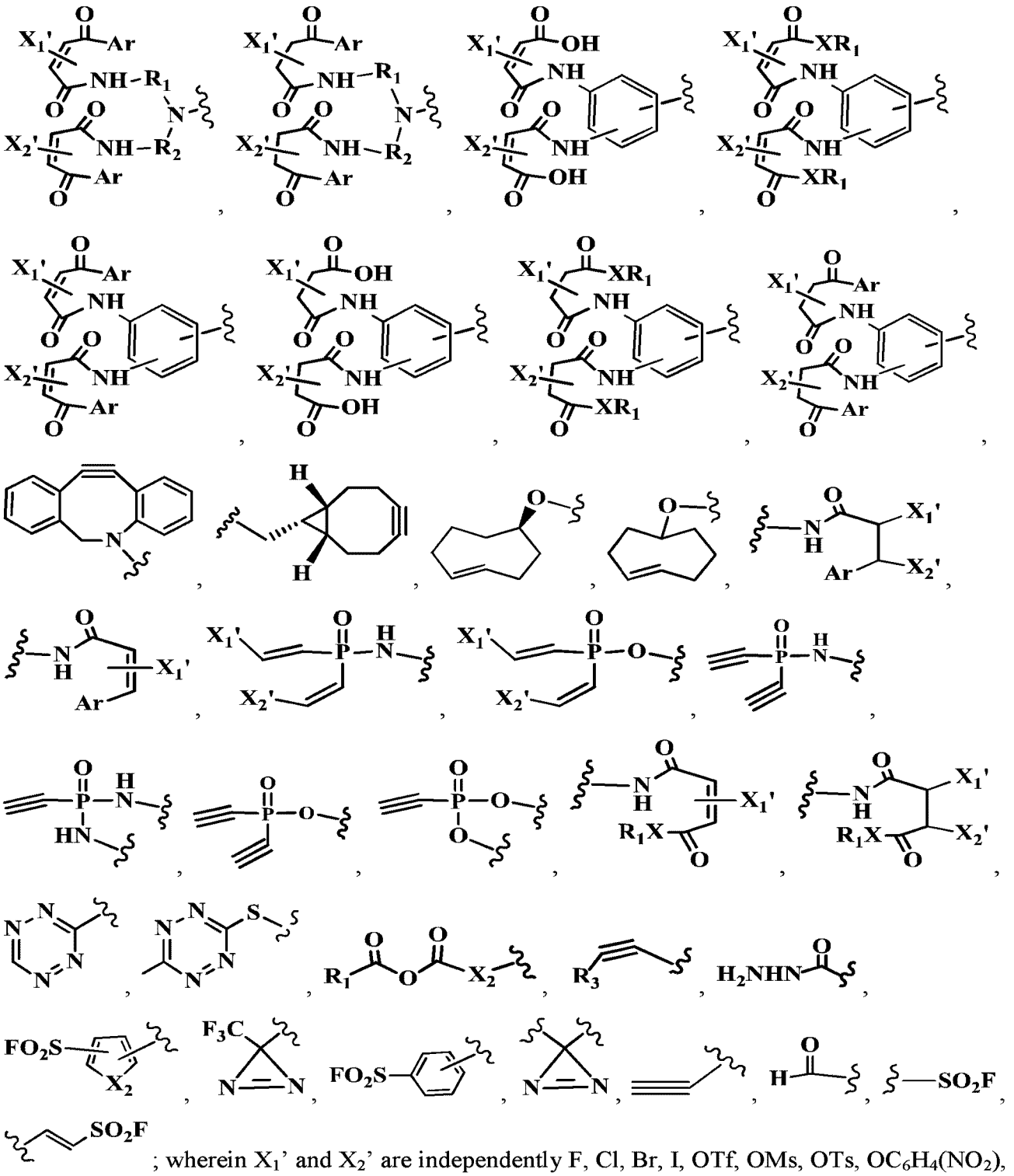
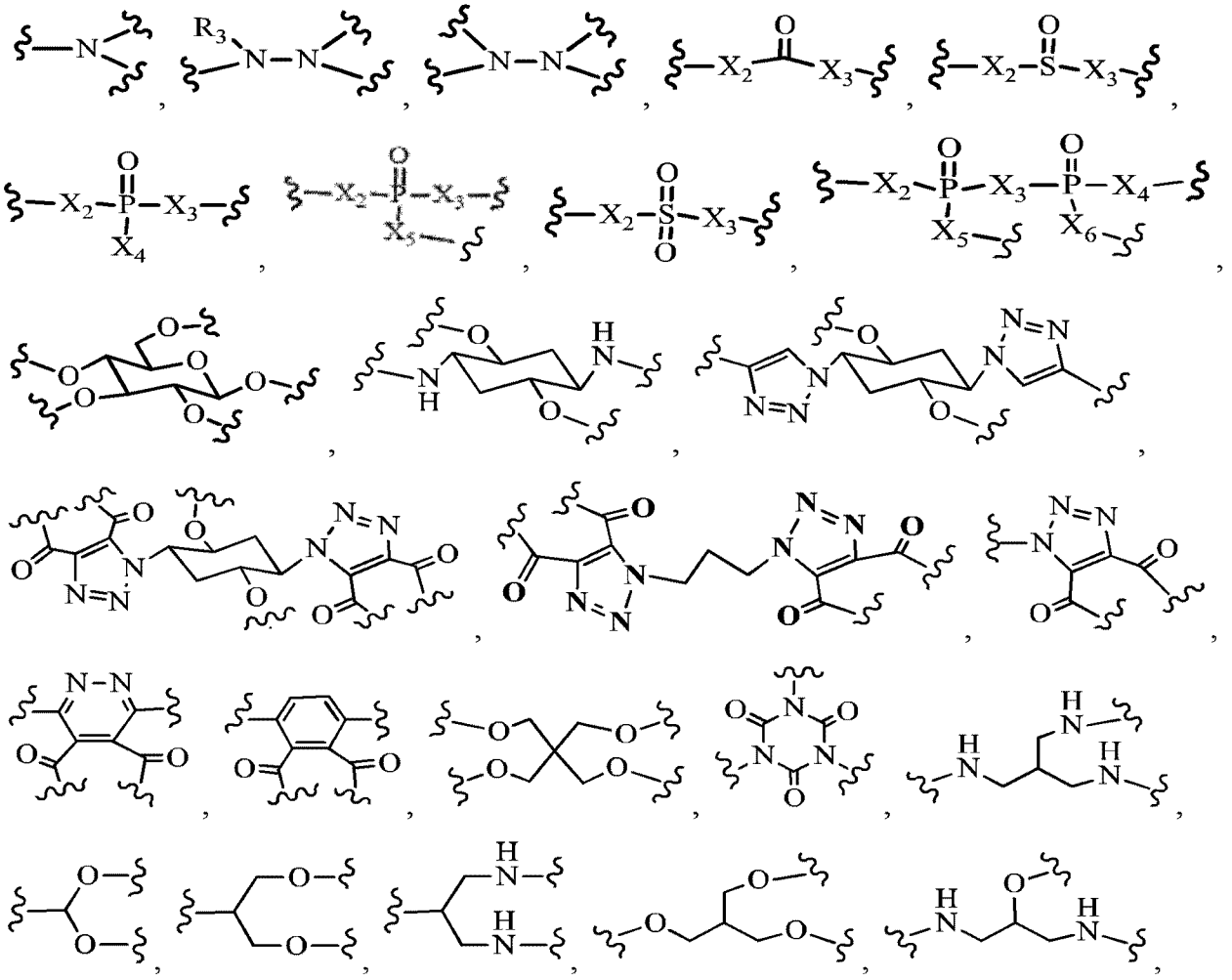


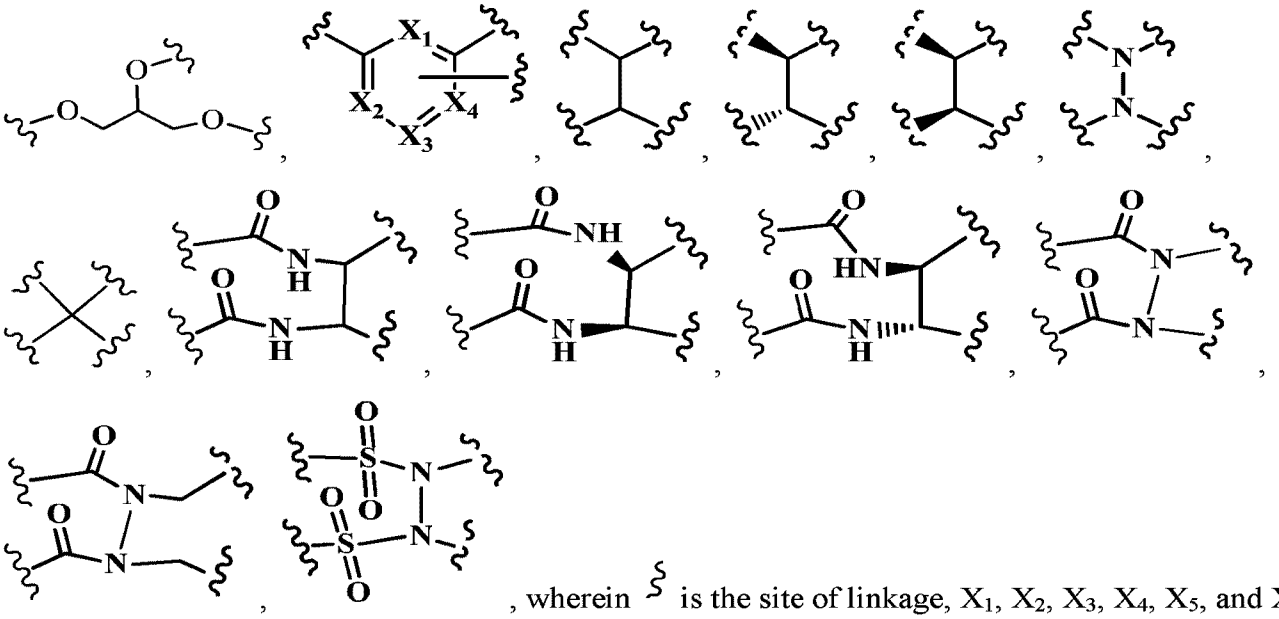


; wherein X_1' and X_2' are independently F, Cl, Br, I, OTf, OMs, OTs, $OC_6H_4(NO_2)$, $OC_6H_3(NO_2)_2$, OC_6F_5, OC_6HF_4, $OC_6H_2F_3$, or Lv_3; X_2 is O, NH, $N(R_1)$, or CH_2; R_3 and R_5 are independently H, R_1, aromatic, heteroaromatic, or aromatic group wherein one or several H atoms are replaced independently by $-R_1$, -halogen, $-OR_1$, $-SR_1$, $-NR_1R_2$, $-NO_2$, $-S(O)R_1$, $-S(O)_2R_1$, or $-COOR_1$; Lv_3 and Lv_3' are independently a leaving group selected from F, Cl, Br, I, nitrophenoxyl; N-hydroxysuccinimide (NHS); phenoxyl; benzenethiol, dinitrophenoxyl; pentafluorophenoxyl;

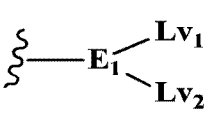
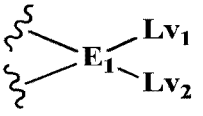
tetrafluorophenoxyl; difluorophenoxyl; monofluorophenoxyl; pentachlorophenoxyl; triflate; imidazole; dichlorophenoxyl; tetrachlorophenoxyl; 1-hydroxybenzotriazole; tosylate; mesylate; 2-ethyl-5-phenylisoxazolium-3′-sulfonate, anhydrides formed its self, or formed with the other anhydride, e.g. acetyl anhydride, formyl anhydride; or an intermediate molecule generated with a condensation reagent for peptide coupling reactions or for Mitsunobu reactions;

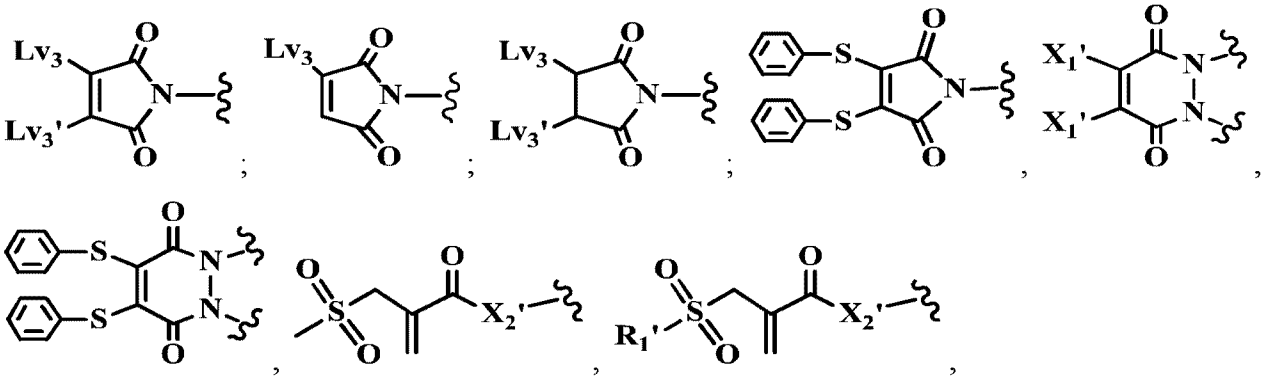
E_1 is a joint group that link two thiol reactive groups of Lv_1 and Lv_2. E_1 is selected from CH, CH_2, NH, NHNH, $N(R_3)$, $N(R_3)N(R_{3'})$, N=N, N-N, P, P(=O), S, Si, C_2-C_8 of alkyl, heteroalkyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 of aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; a peptide containing1~4 units of aminoacids, preferably selected from aspartic acid, glutamic acid, arginine, histidine, lysine, serine, threonine, asparagine, glutamine, cysteine, selenocysteine, tyrosine, phenylalanine, glycine, proline, tryptophan, alanine; or one of the following structures:

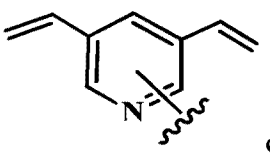
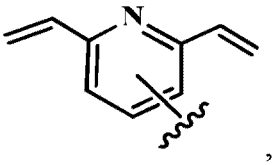


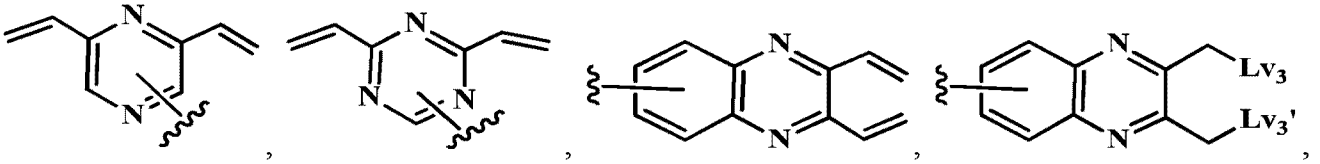


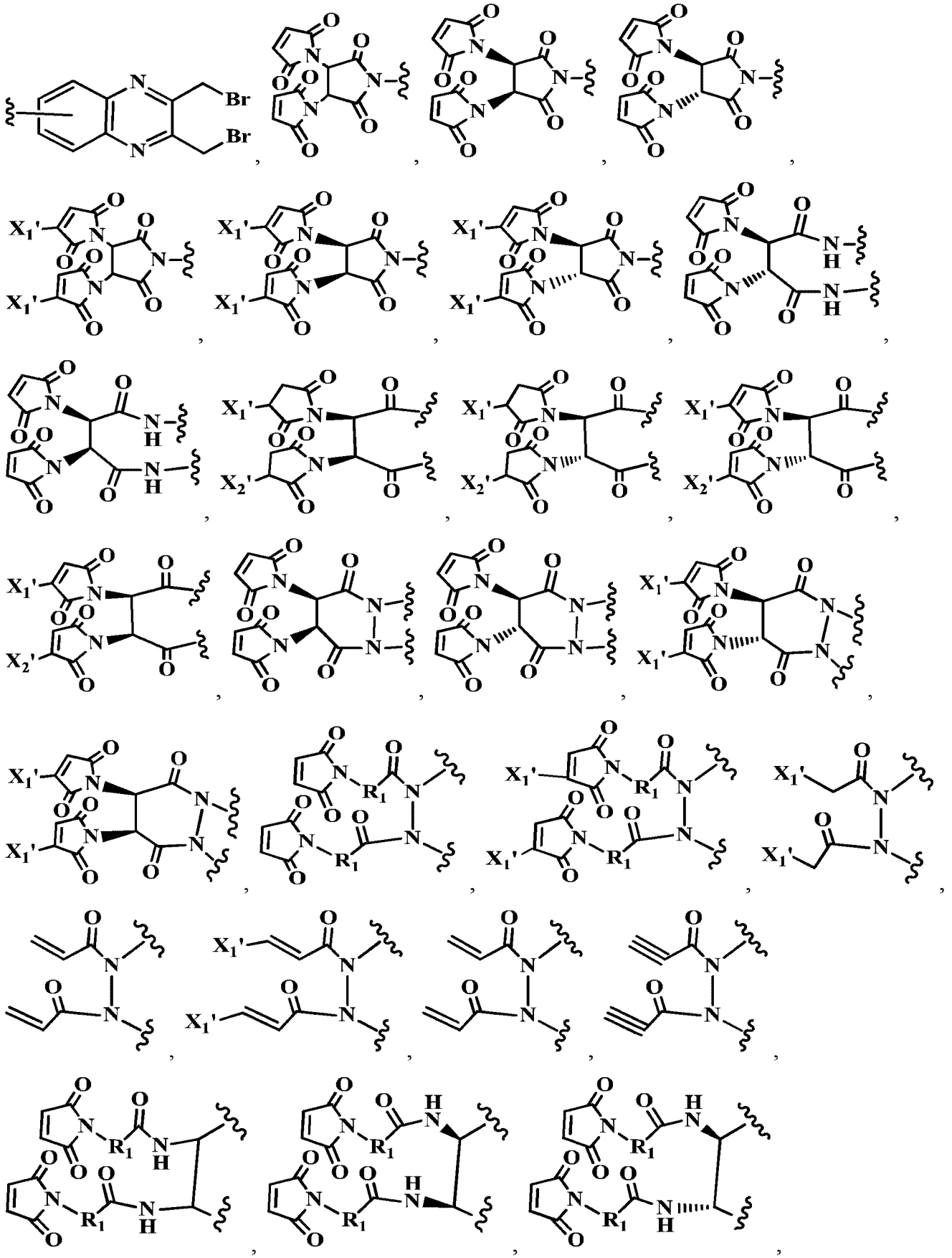
, wherein is the site of linkage, X_1, X_2, X_3, X_4, X_5, and X_6 are independently selected from O, NH, S, N(R_3), CH_2; R_3 is C_1-C_6 alkyl.

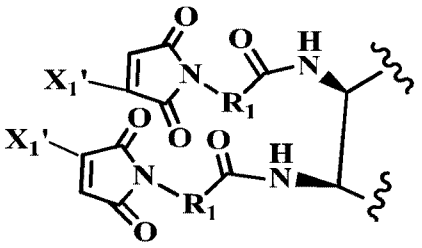
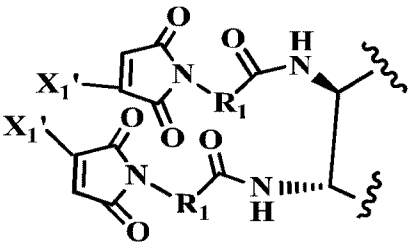
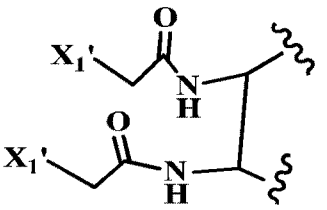
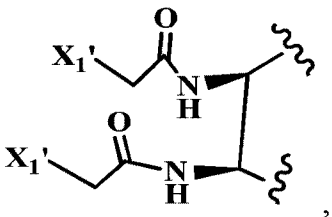
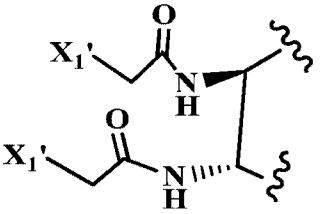
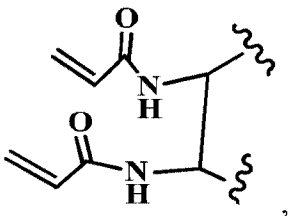
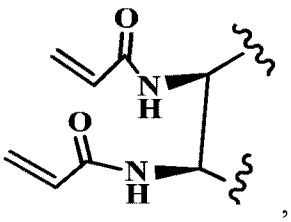
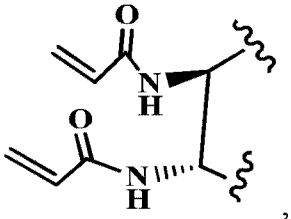
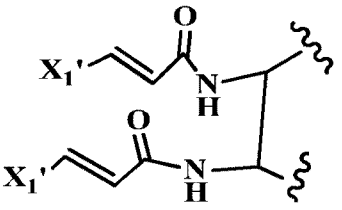
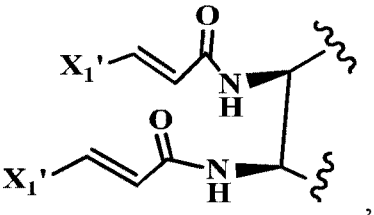
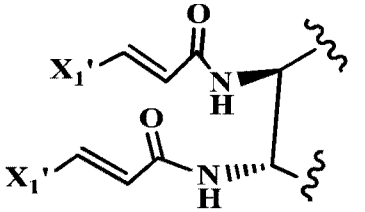
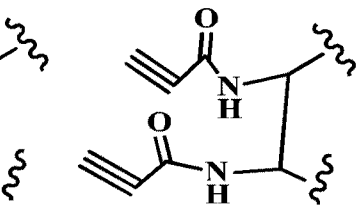
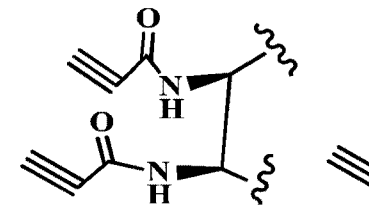
In the formula (II), formula (III) and formula (IV) wherein  and  can be selected from:

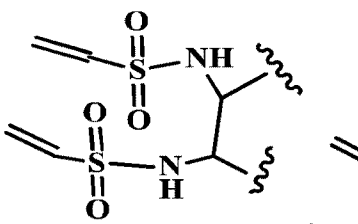
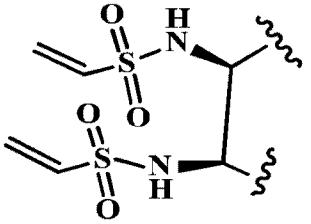
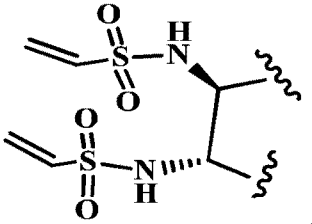
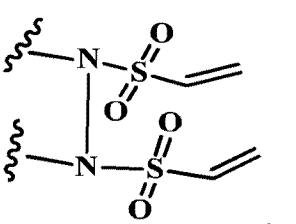
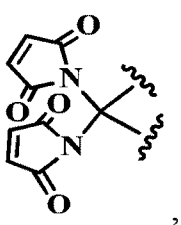
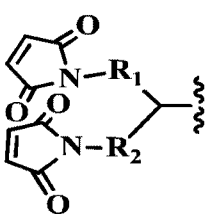
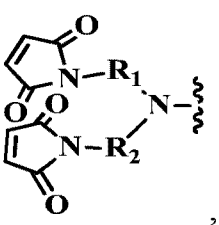
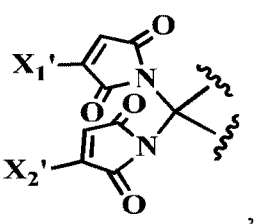
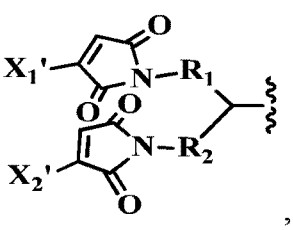
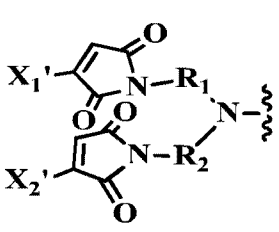
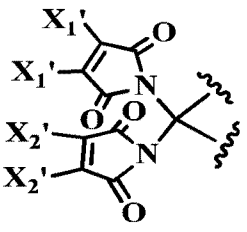
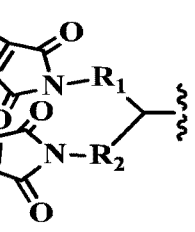
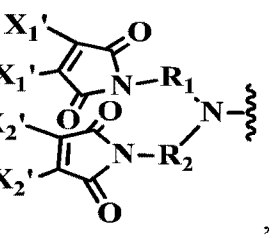


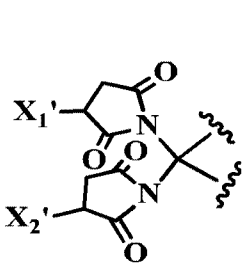
(ADPN),  or  ,



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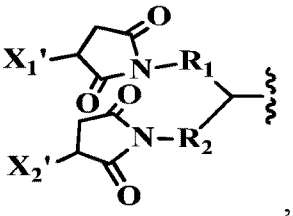
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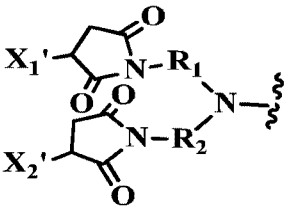
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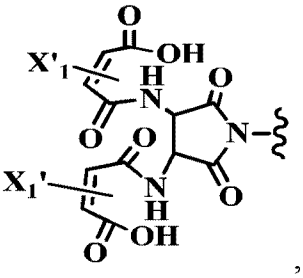
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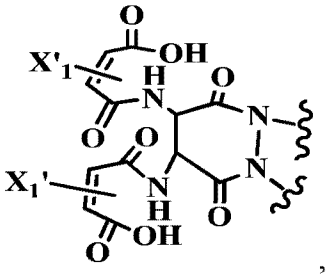
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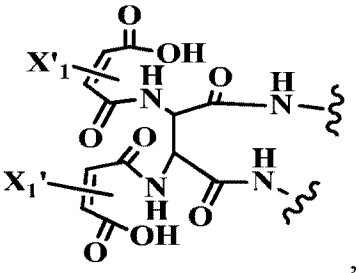
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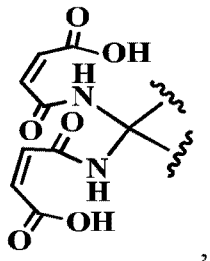
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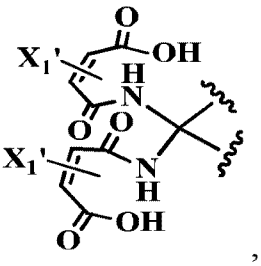
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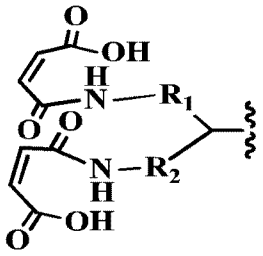
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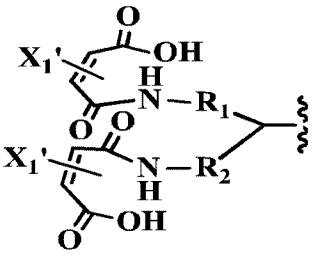
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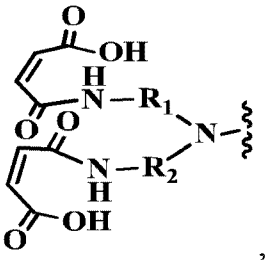
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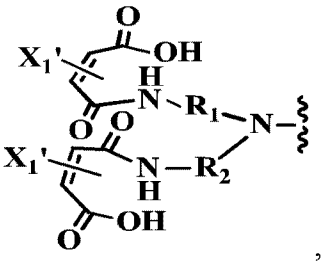
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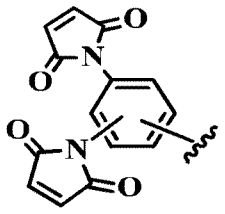
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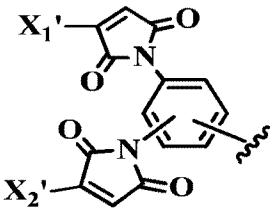
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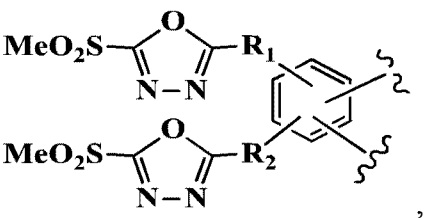
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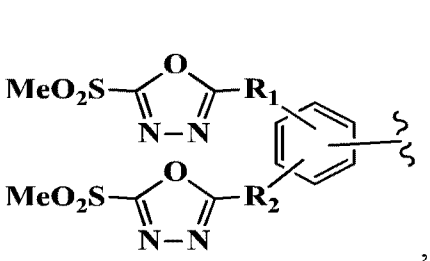
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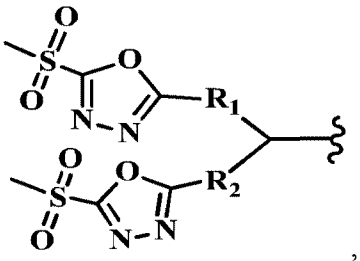
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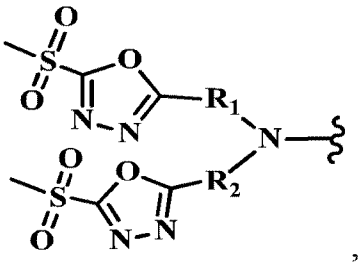
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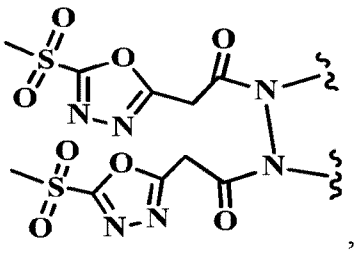
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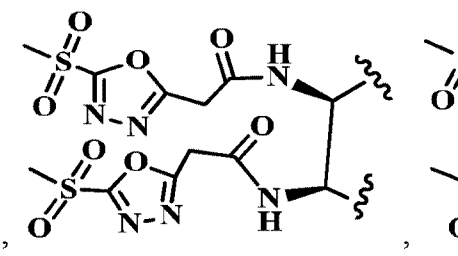
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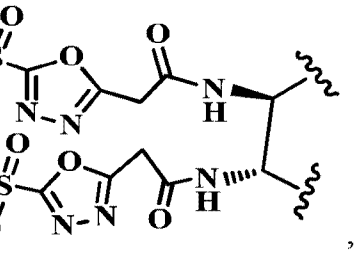
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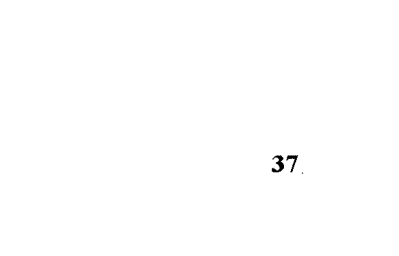
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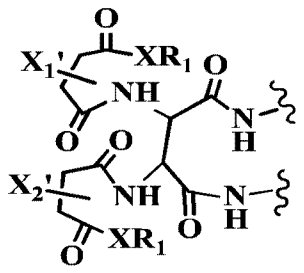
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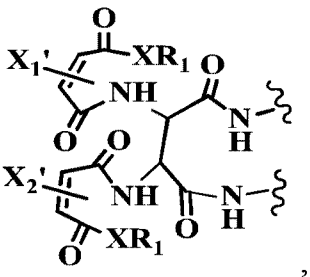
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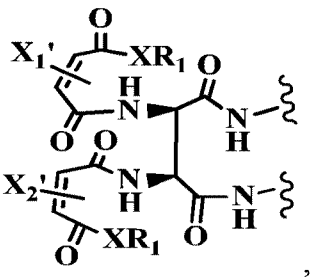
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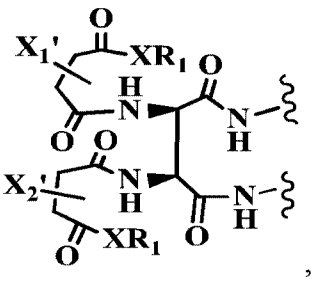
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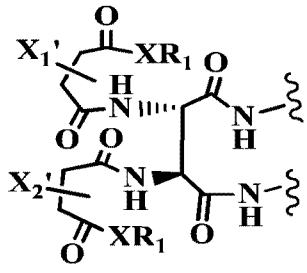
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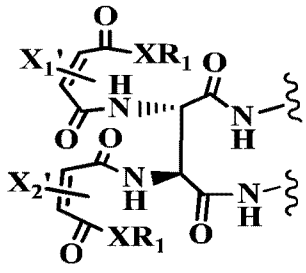
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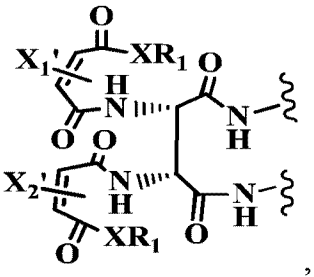
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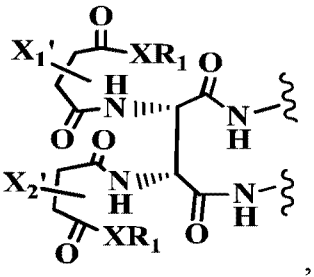
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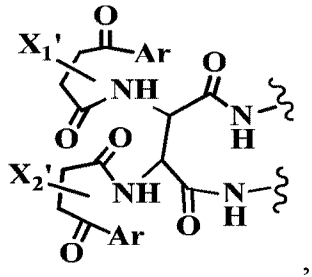
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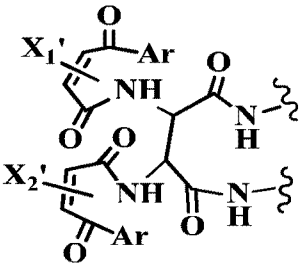
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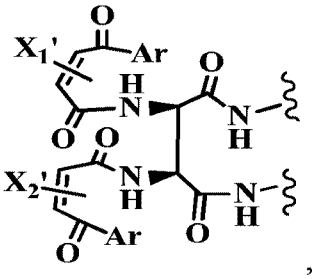
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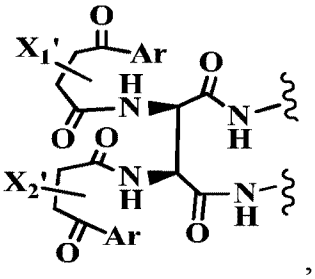
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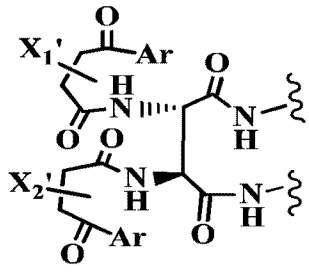
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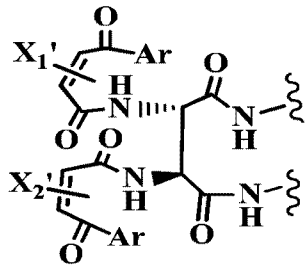
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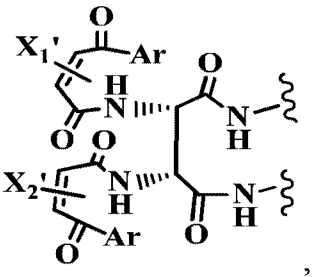
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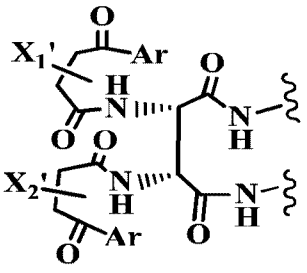
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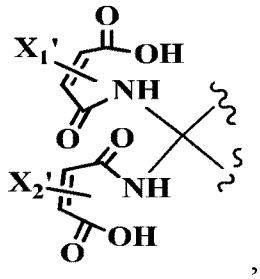
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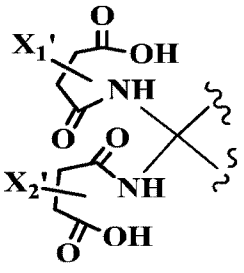
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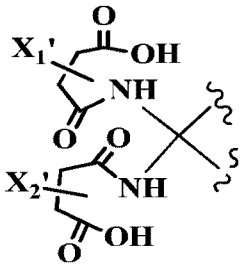
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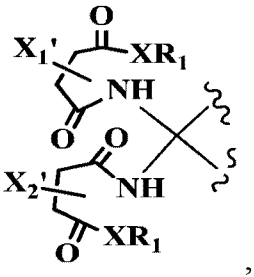
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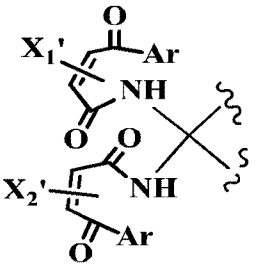
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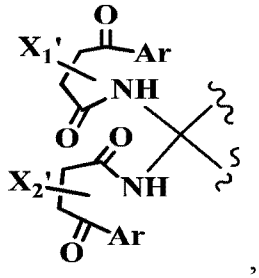
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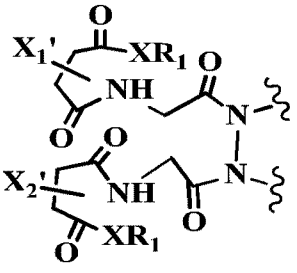
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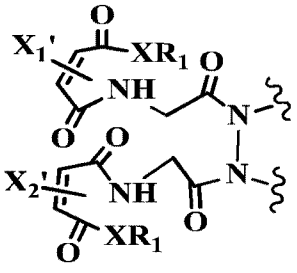
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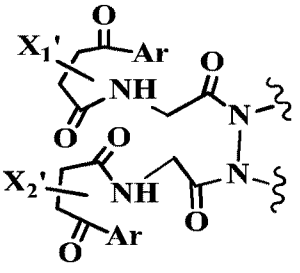
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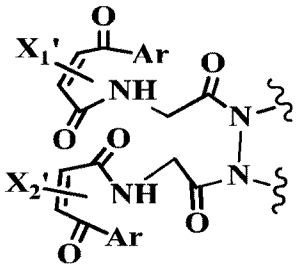
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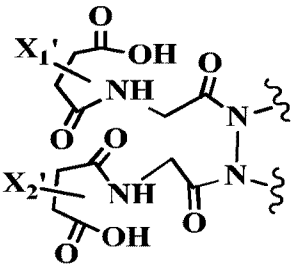
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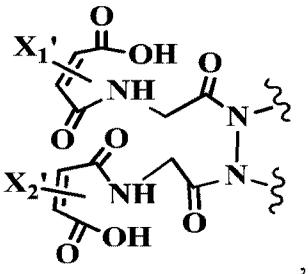
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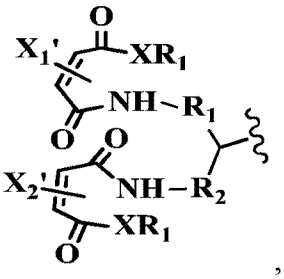
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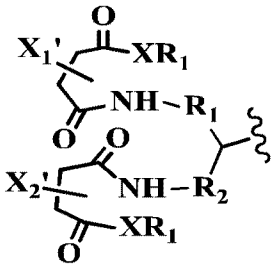
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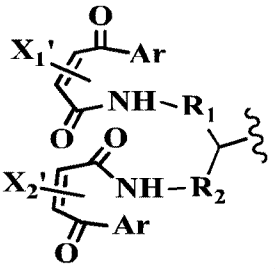
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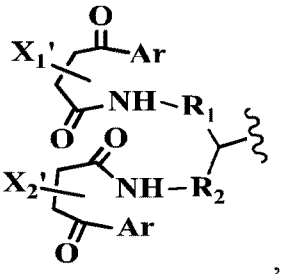
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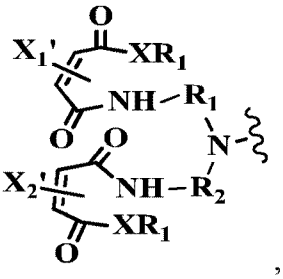
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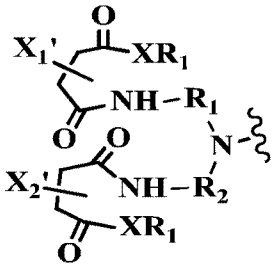
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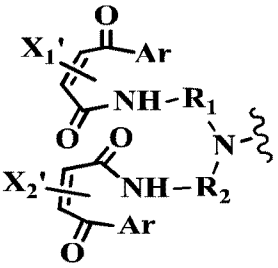
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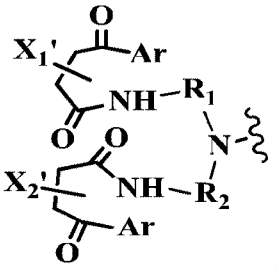
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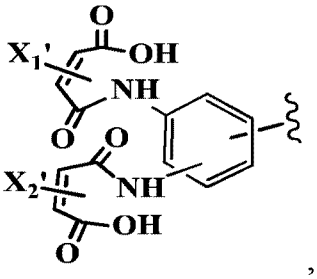
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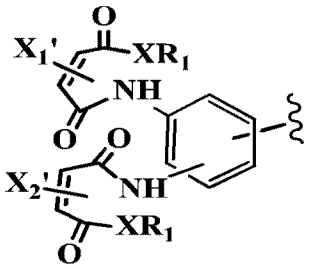
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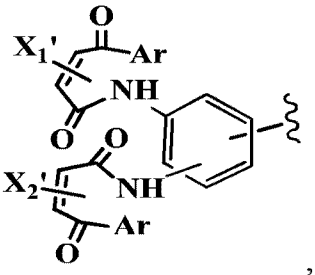
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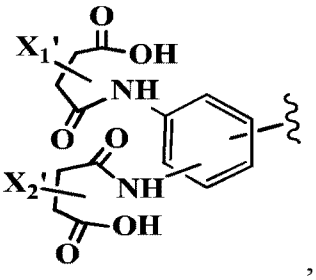
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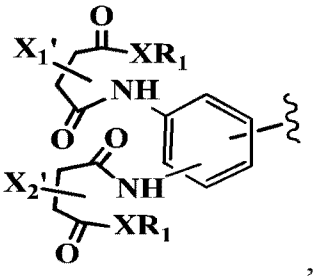
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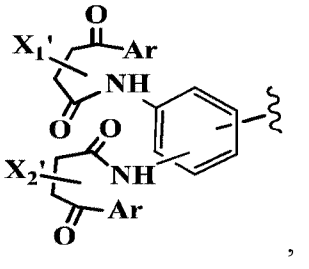
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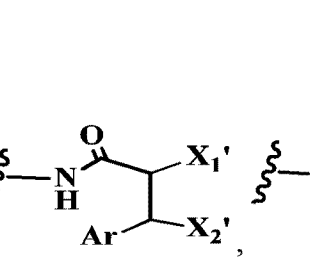
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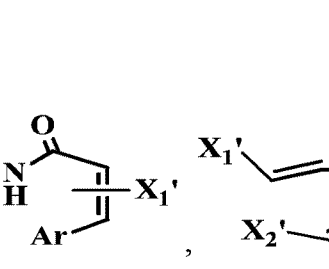
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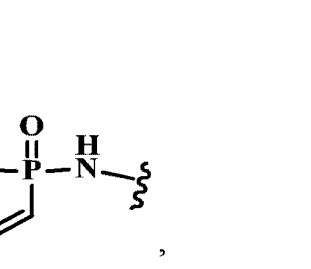
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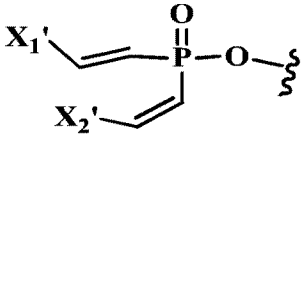
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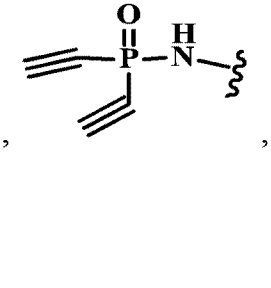
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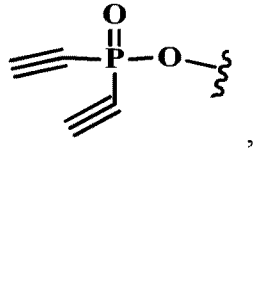
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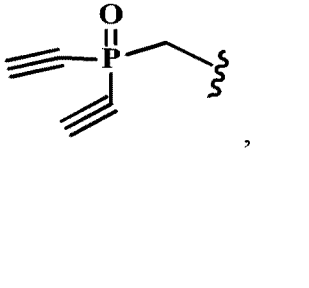
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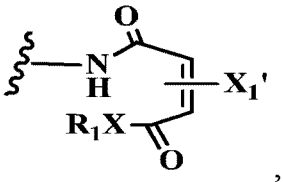
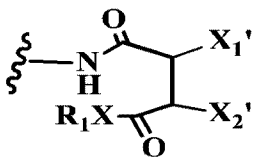
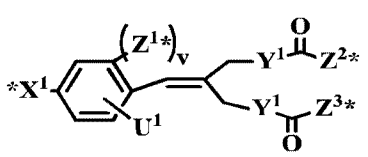
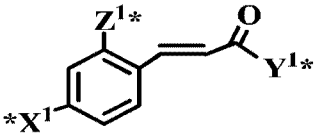
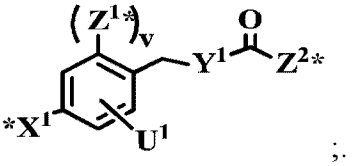



wherein Lv_3, Lv_3', X_1' and X_2'are described above; the connecting bond "—" in the middle of the two atoms means it can link either one of the two atoms;

Wherein L_1 and L_2 are, the same or different, independently selected from O, NH, S, NHNH, $N(R_3)$, $N(R_3)N(R_3')$, polyethyleneoxy unit of formula $(OCH_2CH_2)_pOR_3$, or $(OCH_2CH(CH_3))_pOR_3$, or $NH(CH_2CH_2O)_pR_3$, or $NH(CH_2CH(CH_3)O)_pR_3$, or $N[(CH_2CH_2O)_pR_3][(CH_2CH_2O)_{p'}R_3']$, or $(OCH_2CH_2)_pCOOR_3$, or $CH_2CH_2(OCH_2CH_2)_pCOOR_3$, wherein p and p' are independently an integer selected from 0 to about 1000, or combination thereof; C_1-C_8 of alkyl; C_2-C_8 of heteroalkyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 of aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; Wherein R_3 and R_3' are independently H; C_1-C_8 of alkyl; C_2-C_8 of heteroalkyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 of aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; or 1-8 carbon atoms of esters, ether, amide or aminoalkylcarboxyl; or 1~8 natural or unnatural amino acids or peptides described in the definition; or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$ or $(OCH_2CH(CH_3))_p$, wherein p is an integer from 0 to about 1000, or combination above thereof.

Wherein L_1 or L_2 may contain a self-immolative or a non-self-immolative component, peptidyl units, a hydrazone bond, a disulfide, an ester, an oxime, an amide, or a thioether bond. The self-immolative unit includes, but is not limited to, aromatic compounds that are electronically similar to the para-aminobenzylcarbamoyl (PAB) groups such as 2-aminoimidazol-5-methanol derivatives, heterocyclic PAB analogs, beta-glucuronide, and ortho or para-aminobenzylacetals.

Preferably, the self-immolative linker component has one of the following structures:


; 
; 
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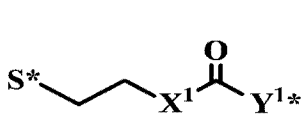
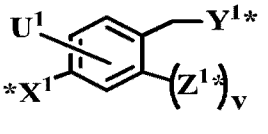
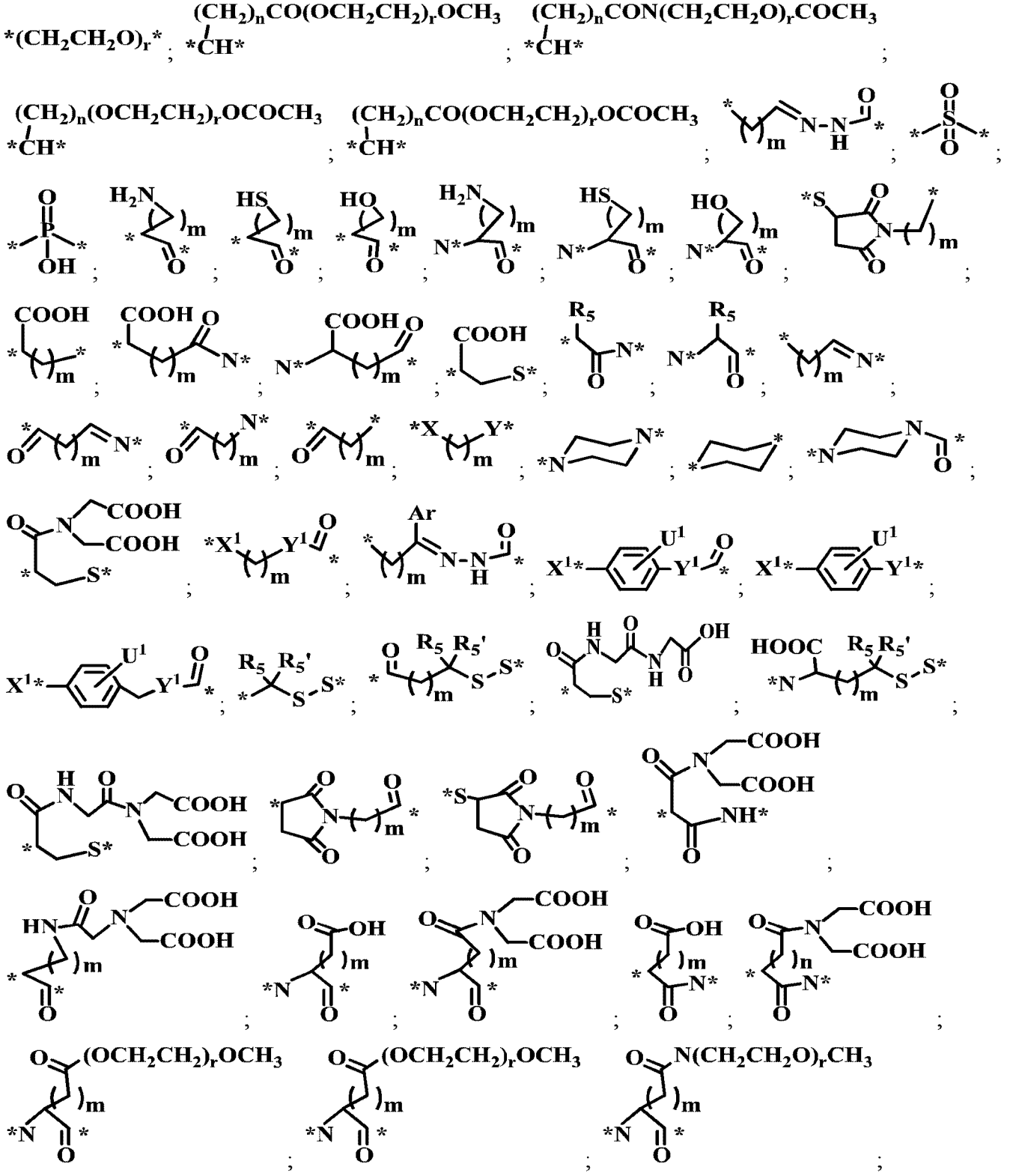
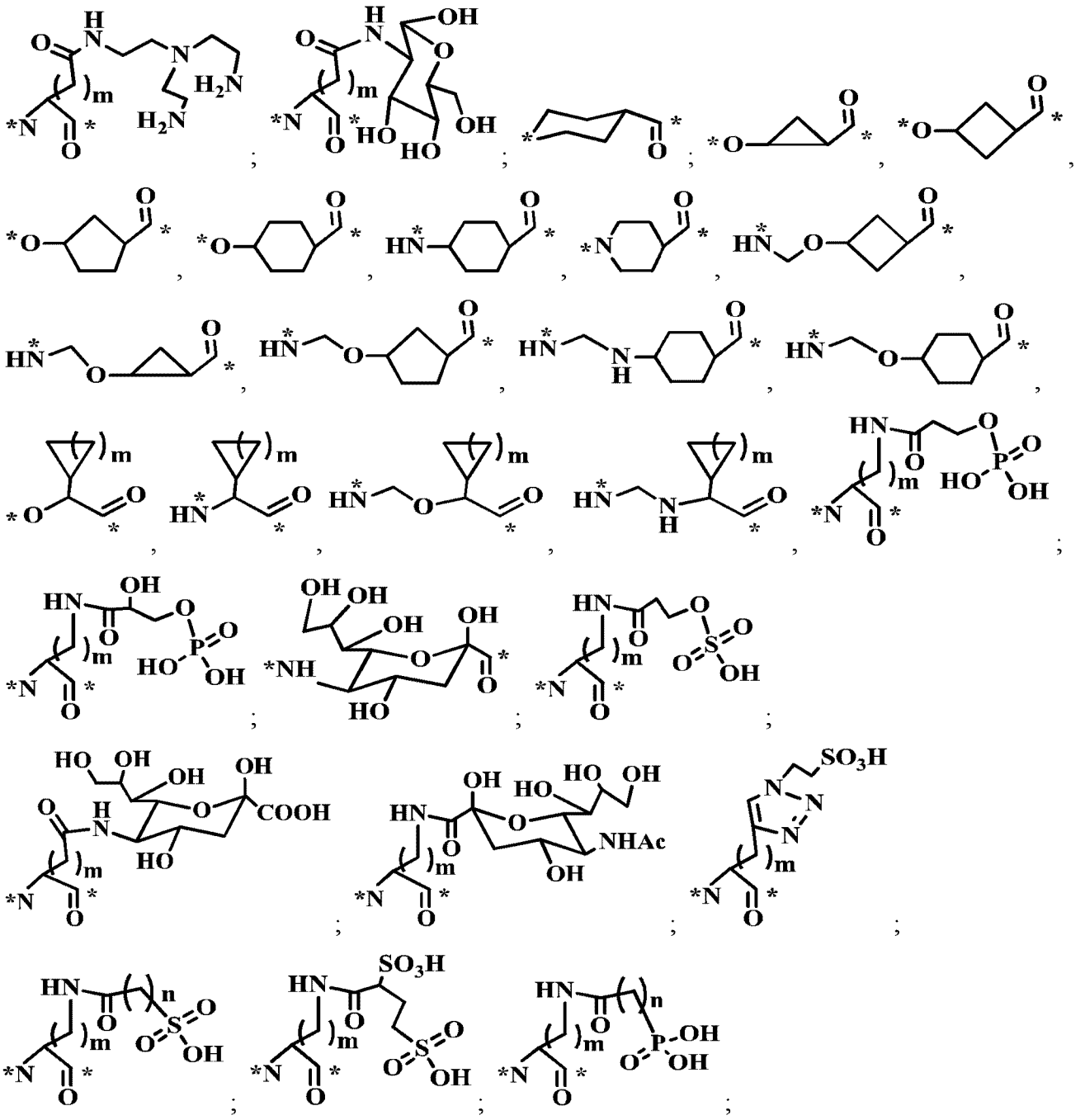

; or 

wherein the (*) atom is the point of attachment of additional spacer or releasable linker units, or the cytotoxic agent, and/or the binding molecule (CBA); X^1, Y^1, Z^2 and Z^3 are independently NH, O, or S; Z^1 is independently H, NH, O or S; v is 0 or 1; U^1 is independently H, OH, C_1~C_6 alkyl, $(OCH_2CH_2)_nF$, Cl, Br, I, OR_5, SR_5, NR_5R_5', $N{=}NR_5$, $N{=}R_5$, NR_5R_5', NO_2, SOR_5R_5', SO_2R_5, SO_3R_5, OSO_3R_5, PR_5R_5', POR_5R_5', $PO_2R_5R_5'$, $OPO(OR_5)(OR_5')$, or $OCH_2PO(OR_5(OR_5')$ wherein R_5 and R_5'

are as defined above; preferably R_5 and R_5' are independently selected from H, C_1~C_8 alkyl; C_2~C_8 alkenyl, alkynyl, heteroalkyl; C_3~C_8 aryl, heterocyclic, carbocyclic, cycloalkyl, heterocycloalkyl, heteroaralkyl, alkylcarbonyl; or pharmaceutical cation salts.

The non-self-immolative linker component is one of the following structures:





Wherein the (*) atom is the point of attachment of additional spacer R_1 or releasable linkers, the cytotoxic agents, and/or the binding molecules; X^1, Y^1, U^1, R_1, R_5, R_5' are defined as above; r is 0~100; m and n are 0~6 independently.

More preferably, L_1 or L_2 may be composed of one or more linker components of 6-maleimidocaproyl ("MC"), maleimidopropanoyl ("MP"), valine-citrulline ("val-cit" or "vc"), alanine-phenylalanine ("ala-phe" or "af"), p-aminobenzyloxycarbonyl ("PAB"), 4-thiopentanoate ("SPP"), 4-(N-maleimidomethyl)cyclohexane-1 carboxylate ("MCC"), (4-acetyl)amino-benzoate

("SIAB"), 4-thio-butyrate (SPDB), 4-thio-2-hydroxysulfonyl-butyrate (2-Sulfo-SPDB), or natural or unnatural peptides having 1~8 natural or unnatural amino acid unites.

Further preferably, L_1 or L_2 may be a releasable linker. The term releasable linker refers to a linker that includes at least one bond that can be broken under physiological conditions, such as a pH-labile, acid-labile, base-labile, oxidatively labile, metabolically labile, biochemically labile, or enzyme-labile bond. It is appreciated that such physiological conditions resulting in bond breaking do not necessarily include a biological or metabolic process, and instead may include a standard chemical reaction, such as a hydrolysis or substitution reaction, for example, an endosome having a lower pH than cytosolic pH, and/or disulfide bond exchange reaction with an intracellular thiol, such as a millimolar range of abundant of glutathione inside the malignant cells.

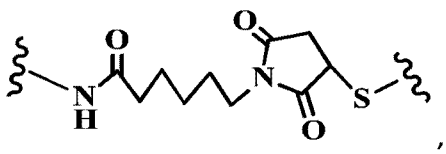
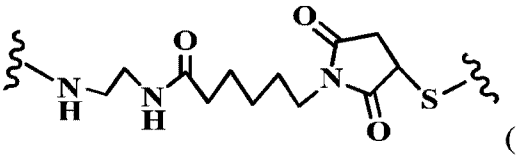
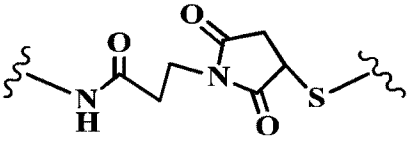
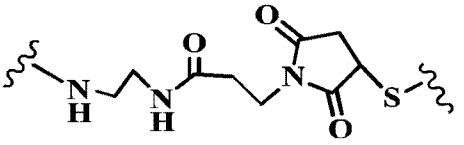
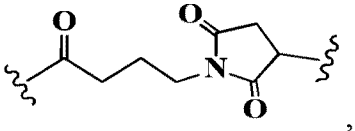
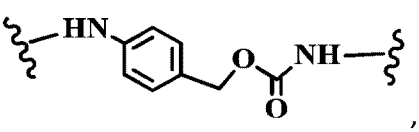
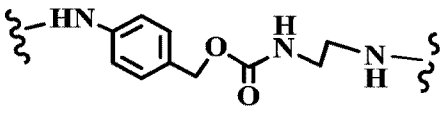
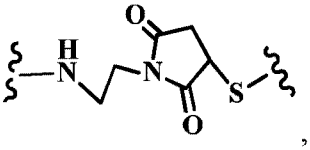
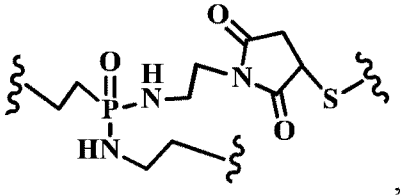
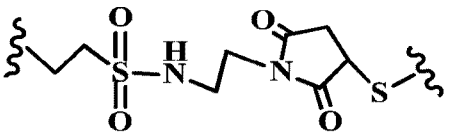
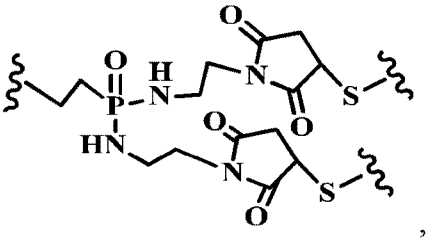
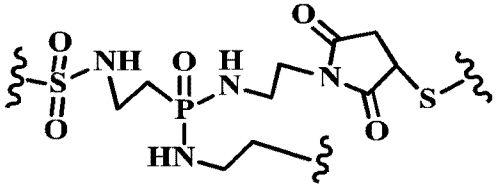
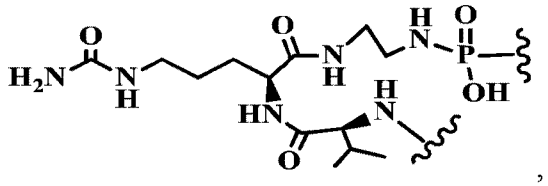
Examples of the releasable linkers (L, L_1, L_1', L_2 or L_2') include, but not limited:

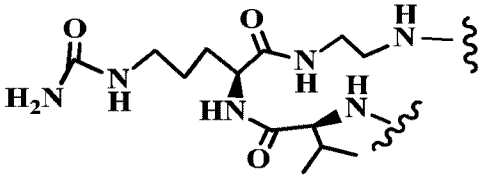
-$(CR_5R_6)_m$(Aa)r$(CR_7R_8)_n(OCH_2CH_2)_t$-, -$(CR_5R_6)_m(CR_7R_8)_n$(Aa)$_r(OCH_2CH_2)_t$-, -(Aa)$_r(CR_5R_6)_m$-$(CR_7R_8)_n(OCH_2CH_2)_t$-, -$(CR_5R_6)_m(CR_7R_8)_n(OCH_2CH_2)_r(Aa)_t$-, -$(CR_5R_6)_m(CR_7{=}CR_8)(CR_9R_{10})_n(Aa)_t$-$(OCH_2CH_2)_r$-, -$(CR_5R_6)_m(NR_{11}CO)(Aa)_t(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -$(CR_5R_6)_m(Aa)_t(NR_{11}CO)$-$(CR_9R_{10})_n(OCH_2CH_2)_r$-, -$(CR_5R_6)_m(OCO)(Aa)_t(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -$(CR_5R_6)_m(OCNR_7)(Aa)_t$-$(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -$(CR_5R_6)_m(CO)(Aa)_t$-$(CR_9R_{10})_n(OCH_2CH_2)_r$-, -$(CR_5R_6)_m(NR_{11}CO)(Aa)_t$-$(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -$(CR_5R_6)_m$-$(OCO)(Aa)_t(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -$(CR_5R_6)_m(OCNR_7)(Aa)_t$-$(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -$(CR_5R_6)_m(CO)(Aa)_t(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -$(CR_5R_6)_m$-phenyl-CO-(Aa)$_t(CR_7R_8)_n$-, -$(CR_5R_6)_m$-furyl-CO(Aa)$_t(CR_7R_8)_n$-, -$(CR_5R_6)_m$-oxazolyl-CO(Aa)$_t(CR_7R_8)_n$-, -$(CR_5R_6)_m$thiazolyl-CO-(Aa)$_t$(C$CR_7R_8)_n$-, -$(CR_5R_6)_t$-thienyl-CO-$(CR_7R_8)_n$-, -$(CR_5R_6)_t$-imidazolyl-CO-$(CR_7R_8)_n$-, -$(CR_5R_6)_t$-morpholino-CO(Aa)$_t$-$(CR_7R_8)_n$-, -$(CR_5R_6)_t$piperazino-CO(Aa)$_t(CR_7R_8)_n$-, -$(CR_5R_6)_t$-N-methyl-piperazin-CO(Aa)$_t$-$(CR_7R_8)_n$-, -$(CR_5R)_m$-(Aa)$_t$phenyl-, -$(CR_5R_6)_m$-(Aa)$_t$furyl-, -$(CR_5R_6)_m$-oxazolyl(Aa)$_t$-, -$(CR_5R_6)_m$-thiazolyl(Aa)$_t$-, -$(CR_5R_6)_m$-thienyl-(Aa)$_t$-, -$(CR_5R_6)_m$-imidazolyl(Aa)$_t$-, -(C $R_5R_6)_m$-morpholino-(Aa)$_t$-, -$(CR_5R_6)_m$-piperazino-(Aa)$_t$-, -$(CR_5R_6)_m$N-methylpiperazino-(Aa)$_t$-, -K$(CR_5R_6)_m$(Aa)r$(CR_7R_8)_n(OCH_2CH_2)_t$-, -K$(CR_5R_6)_m$-$(CR_7R_8)_n$-(Aa)$_r(OCH_2CH_2)_t$-, -K(Aa)$_r(CR_5R_6)_m$-$(CR_7R_8)_n(OCH_2CH_2)_t$-, -K$(CR_5R_6)_m(CR_7R_8)_n$-$(OCH_2CH_2)_r$(Aa)$_t$-, -K$(CR_5R_6)_m(CR_7{=}CR_8)(CR_9R_{10})_n$-(Aa)$_t(OCH_2CH_2)_r$-, -K$(CR_5R_6)_m$-$(NR_{11}CO)(Aa)_t(CR_9R_{10})_n(OCH_2CH_2)_r$-, -K$(CR_5R_6)_m(Aa)_t(NR_{11}CO)$-$(CR_9R_{10})_n(OCH_2$-$CH_2)_r$-, -K$(CR_5R_6)_m(OCO)(Aa)_t(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -K$(CR_5R_6)_m(OCNR_7)(Aa)_t$-$(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -K$(CR_5R_6)_m(CO)(Aa)_t$-$(CR_9R_{10})_n(OCH_2CH_2)_r$-, -K$(CR_5R_6)_m(NR_{11}CO)$-(Aa)$_t$-$(CR_9R_{10})_n(OCH_2CH_2)_r$-, -K$(CR_5R_6)_m$-$(OCO)(Aa)_t(CR_9R_{10})_n(OCH_2CH_2)_r$-, -K$(CR_5R_6)_m(OCNR_7)$-(Aa)$_t(CR_9R_{10})_n(OCH_2CH_2)_r$-, -K$(CR_5R_6)_m(CO)(Aa)_t(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -K$(CR_5R_6)_m$-phenyl-CO-(Aa)$_t(CR_7R_8)_n$-, -K-$(CR_5R_6)_m$-furyl-CO(Aa)$_t$-$(CR_7R_8)_n$-, -K$(CR_5R_6)_m$-oxazolyl-CO-(Aa)$_t(CR_7R_8)_n$-, -K$(CR_5R_6)_m$thiazolyl-CO(Aa)$_t$-$(CR_7R_8)_n$-, -K$(CR_5R_6)_t$-thienyl-CO$(CR_7R_8)_n$-, -K-

$(CR_5R_6)_t$imidazolyl-CO-$(CR_7R_8)_n$-, -$K(CR_5R_6)_t$morpholino-CO$(Aa)_t(CR_7R_8)_n$-, -$K(CR_5R_6)_t$-piperazino-CO$(Aa)_t$-$(CR_7R_8)_n$-, -$K(CR_5R_6)_t$-N-methylpiperazinCO$(Aa)_t(CR_7R_8)_n$-, -$K(CR_5R)_m(Aa)_t$-phenyl, -K-$(CR_5R_6)_m$-$(Aa)_t$furyl-, -$K(CR_5R_6)_m$-oxazolyl$(Aa)_t$-, -$K(CR_5R_6)_m$-thiazolyl$(Aa)_t$-, -K-$(CR_5R_6)_m$-thienyl-$(Aa)_t$-, -$K(CR_5R_6)_m$-imidazolyl$(Aa)_t$-, -$K(CR_5R_6)_m$-morpholino$(Aa)_t$-, -$K(CR_5R_6)_m$-piperazino-$(Aa)_t$G, -$K(CR_5R_6)_m$N-methylpiperazino-$(Aa)_t$-;

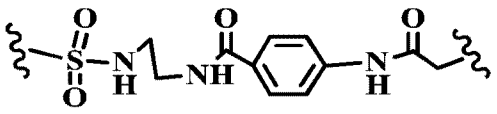
werein m, Aa, m, n, R_3, R_4, and R_5 are described above; t and r are 0 – 100 independently; R_6, R_7, and R_8 are independently chosen from H; halide; C_1~C_8 of alkyl, aryl, alkenyl, alkynyl, ether, ester, amine or amide, which optionally substituted by one or more halide, CN, NR_1R_2, CF_3, OR_1, Aryl, heterocycle, $S(O)R_1$, SO_2R_1, $-CO_2H$, $-SO_3H$, $-OR_1$, $-CO_2R_1$, -$CONR_1$, $-PO_2R_1R_2$, $-PO_3H$ or $P(O)R_1R_2R_3$; K is NR_1, -SS-, -C(=O)-, -C(=O)NH-, -C(=O)O-, -C=NH-O-, -C=N-NH-, -C(=O)NH-NH-, O, S, Se, B or C_3-C_6 heteroaromatic group.

Example structures of the components of the linker L_1 and L_2 may contain:



(containing MC, 6-maleimidocaproyl),


(MP, maleimidopropanoyl),



(PAB, p-aminobenzyloxycarbonyl),









(containing valine-citrulline (VC)),



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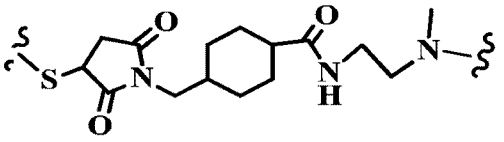
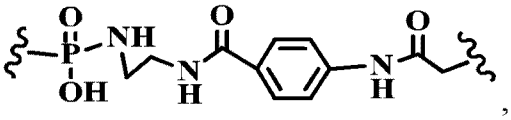


(MCC, 4-(N-maleimidomethyl)cyclohexane-1 carboxylate),



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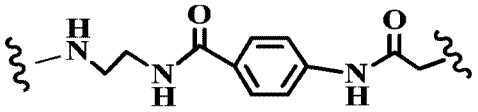
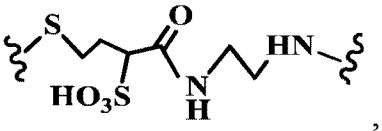


((4-acetyl)aminobenzoate),



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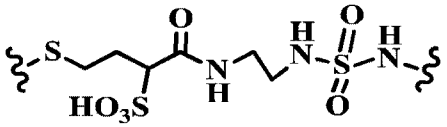
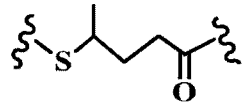
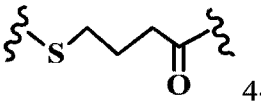


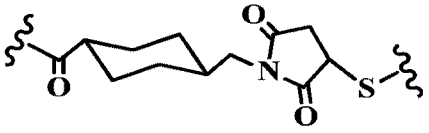
(4-thio-2-hydroxysulfonyl-butyrate, 2-sulfo-SPDB), (PAB),



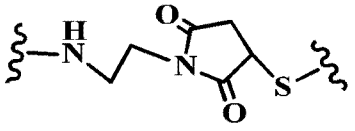
4-thio-pentanoate (SPP),



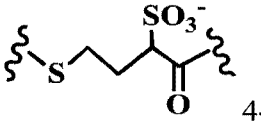
4-thio-butyrate (SPDB),



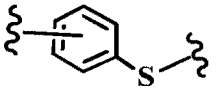
4-(N-maleimidomethyl)cyclo-hexane-1-carboxylate (MCC),



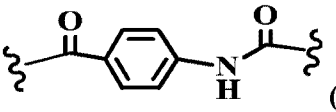
maleimidoethyl (ME),



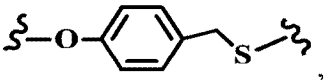
4-thio-2-hydroxysulfonyl-butyrate (2-Sulfo-SPDB),



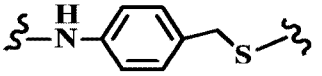
aryl-thiol (PhSS),



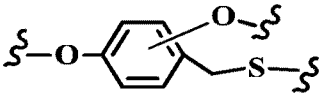
(4-acetyl)amino-benzoate (SIAB),



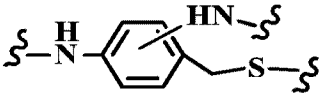
, oxylbenzylthio,



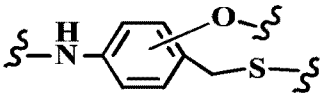
aminobenzylthio,



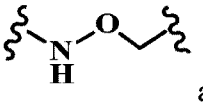
dioxylbenzylthio,



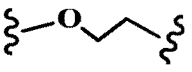
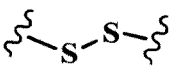
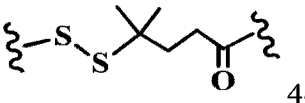
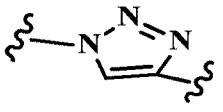
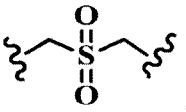
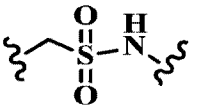
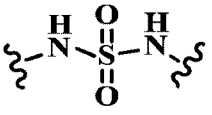
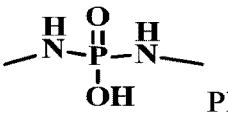
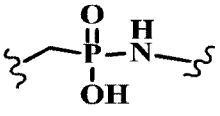
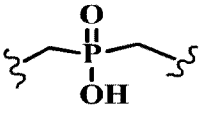
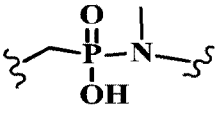
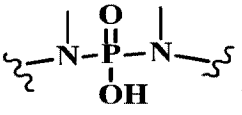
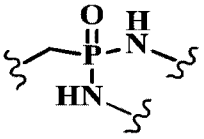
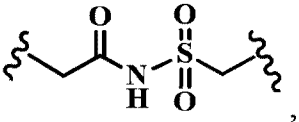
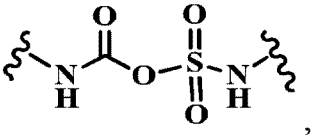
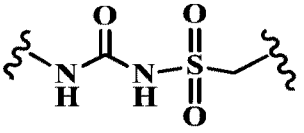
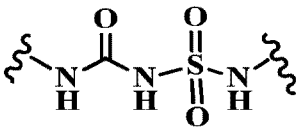
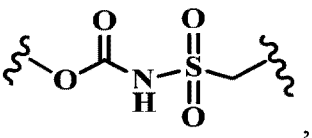
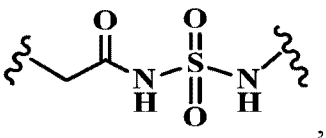
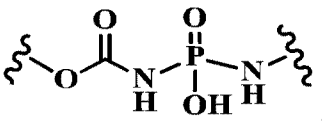
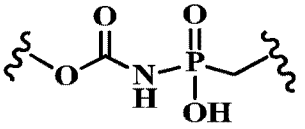
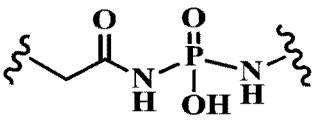
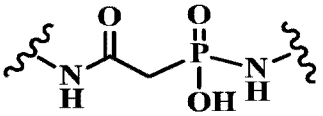
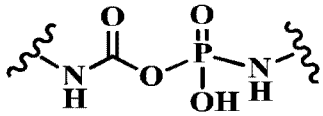
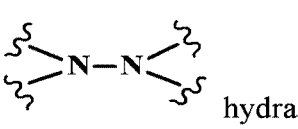
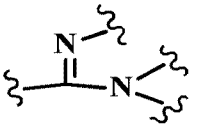
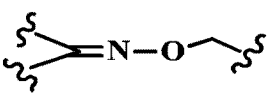
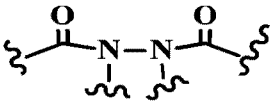
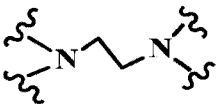
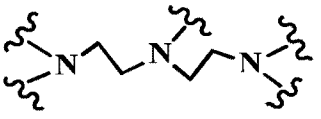
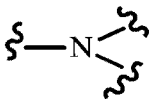
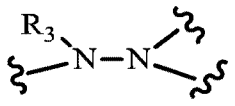
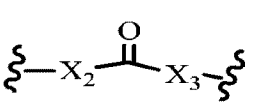
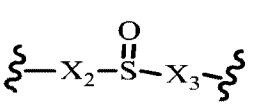
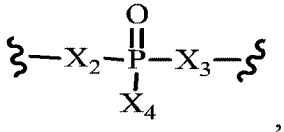
diaminobenzylthio,

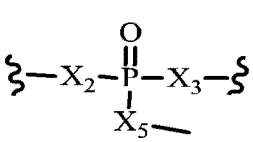


amino-oxylbenzylthio,



alkoxy amino

(AOA),  ethyleneoxy(EO),  dithio,  4-methyl-4-dithio-pentanoic (MPDP),  triazole,  alkylsulfonyl,  alkylsulfonamide,  sulfon-bisamide,  Phosphondiamide,  alkylphosphonamide,  phosphinic acid,  N-methylphosphonamidic acid,  N, N'-dimethylphosphonamidic acid,  N, N'-dimethylphosphondiamide,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  hydrazine,  acetimidamide,  oxime,  acetylacetohydrazide,  aminoethyl-amine,  aminoethyl-aminoethyl-amine,  ,  ,  ,  ,  ,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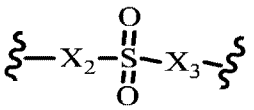
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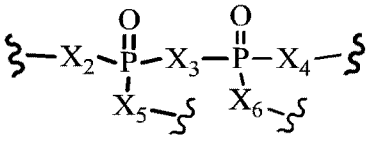
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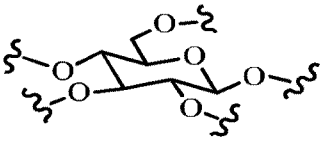
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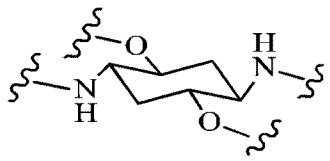
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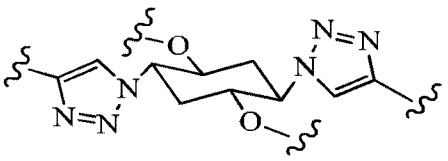
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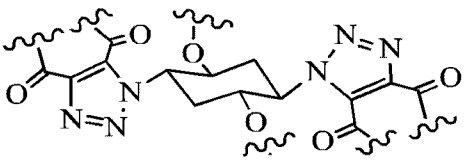
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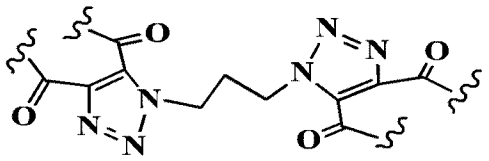
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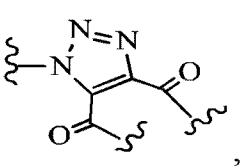
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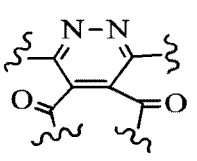
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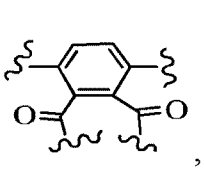
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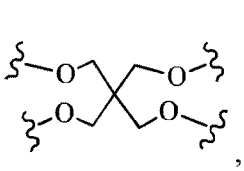
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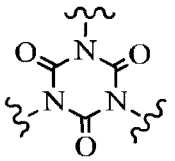
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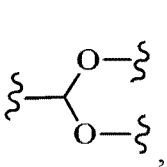
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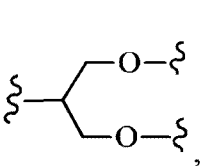
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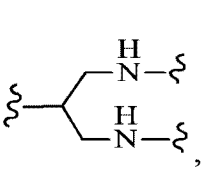
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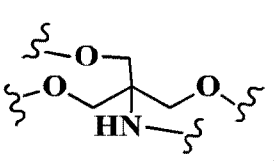
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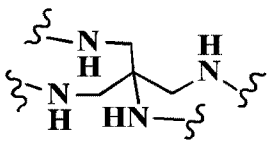
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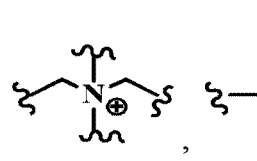
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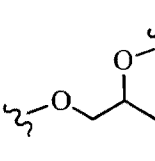
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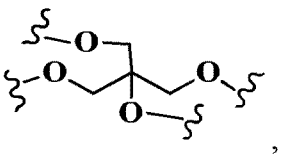
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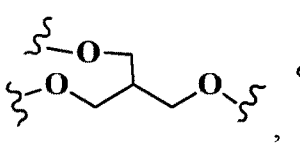
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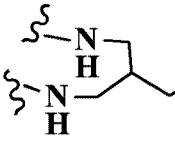
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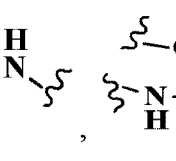
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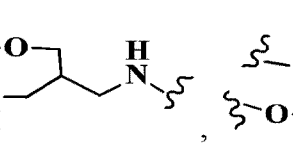
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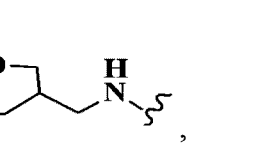
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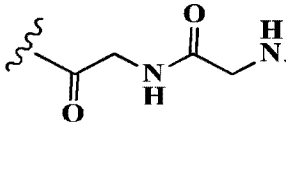
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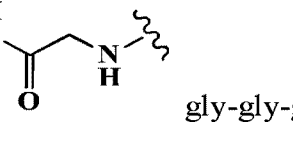
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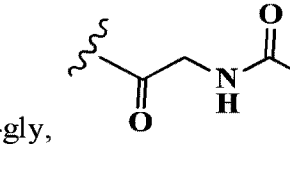
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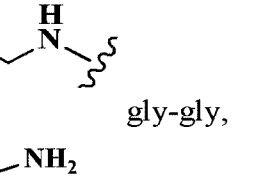
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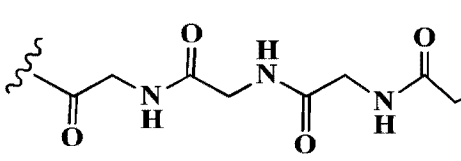
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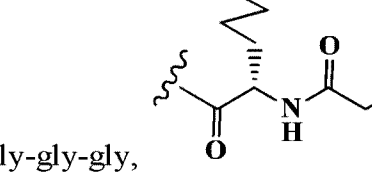
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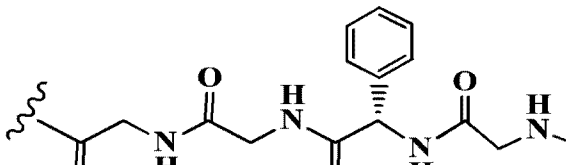
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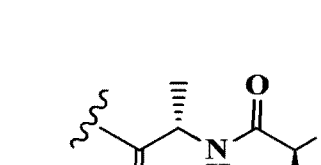
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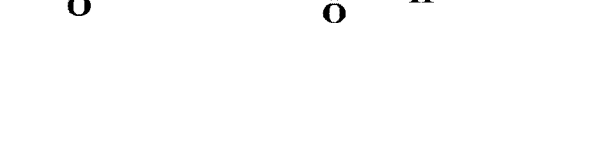
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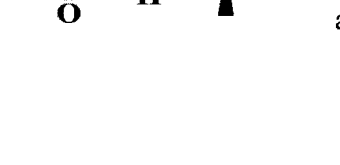
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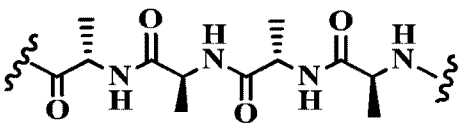
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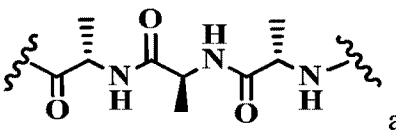
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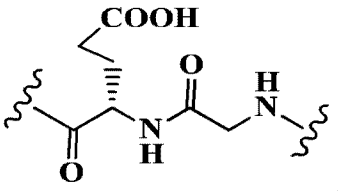
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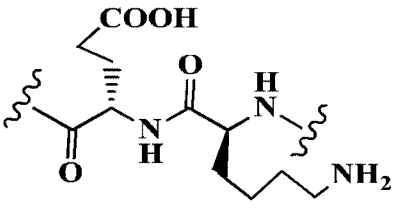
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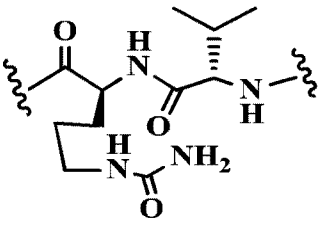
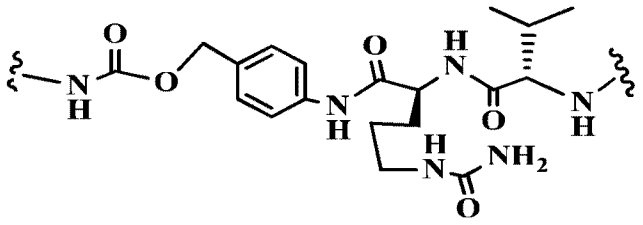
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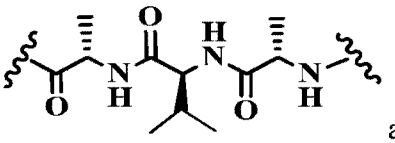
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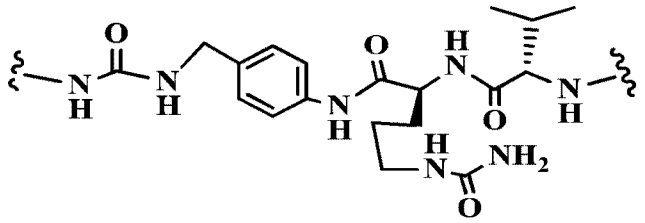
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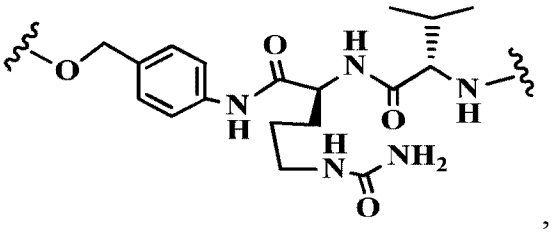
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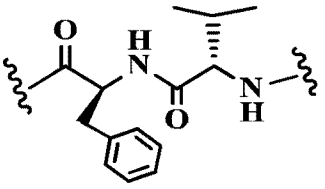
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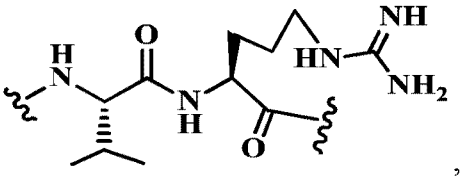
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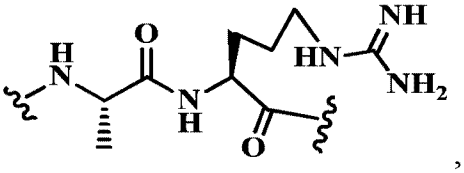
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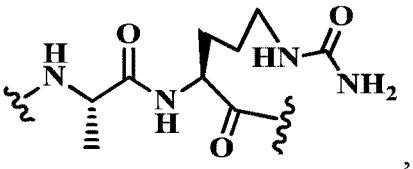
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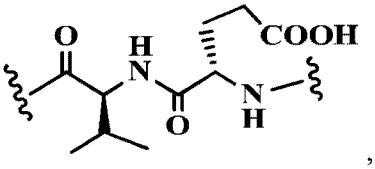
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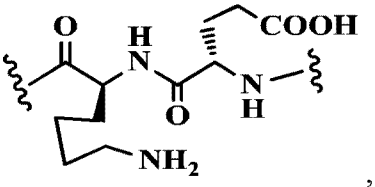
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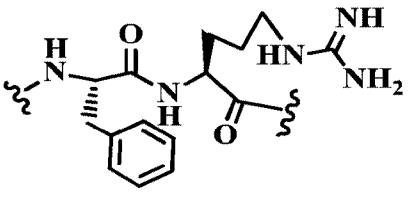
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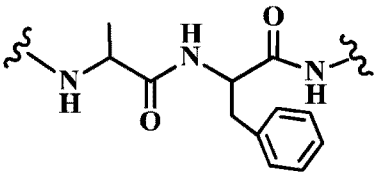
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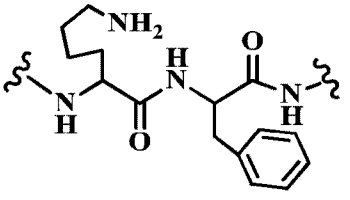
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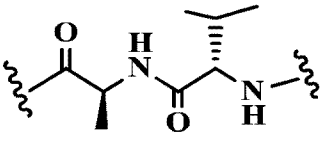
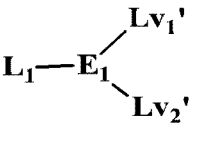
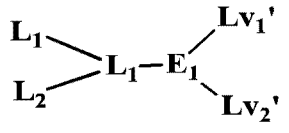
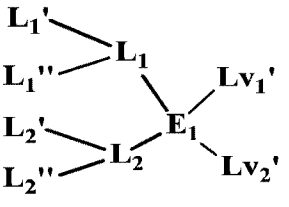
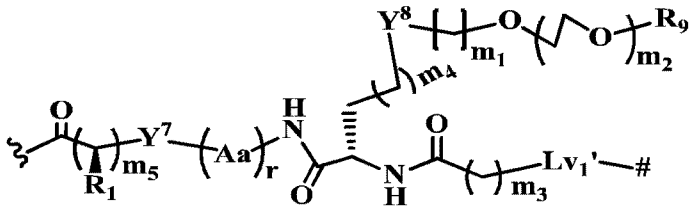

, (lys-phe), or a combination above thereof; wherein is the site of linkage; X_2, X_3, X_4, X_5, or X_6, are independently selected from NH; NHNH; $N(R_{12})$; $N(R_{12})N(R_{12'})$; O; S; C_1-C_6 of alkyl; C_2-C_6 of heteroalkyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 of aryl, Ar-alkyl,

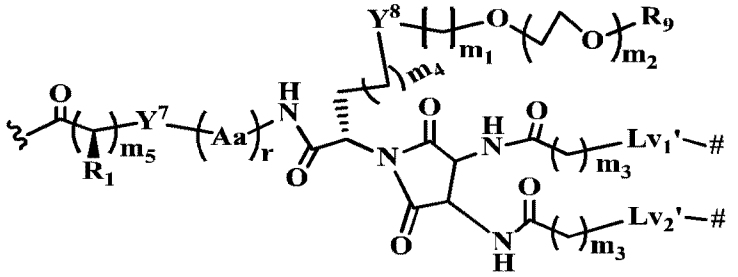
heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; CH_2OR_{12}, CH_2SR_{12}, CH_2NHR_{12}, or 1~8 amino acids; wherein R_{12} and $R_{12'}$ are independently H;C_1-C_8 of alkyl; C_2-C_8 of hetero-alkyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 of aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; or 1-8 carbon atoms of esters, ether, or amide; or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$ or $(OCH_2CH(CH_3))_p$, wherein p is an integer from 0 to about 100.

In addition, L_1, L_2, X_1, X_2, X_3, $X_{1'}$, $X_{2'}$ and $X_{3'}$ can be independently absent.

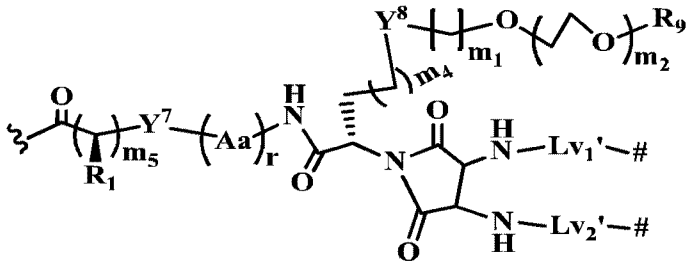
In other embodiments, the conjugate of formula (VI), (VII), (VIII) or (IX), wherein the components of in formula (VI),  in formula (VII),  in formula (VIII), and  in formula (IX), are preferably selected from the following structures accordingly:



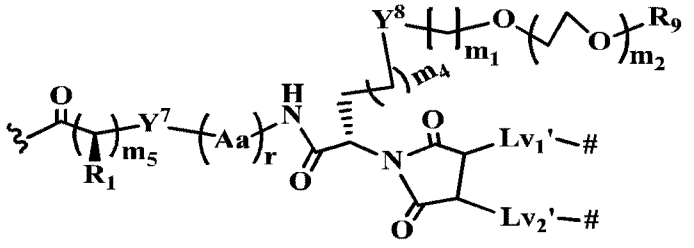
(I-a),



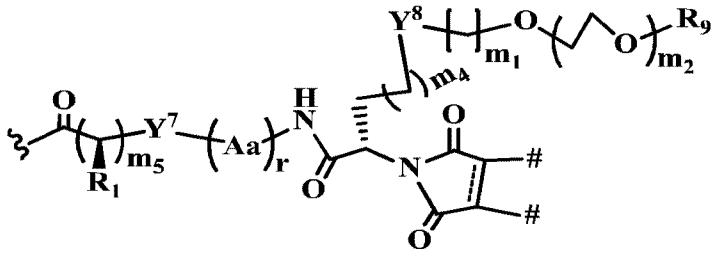
(I-b),



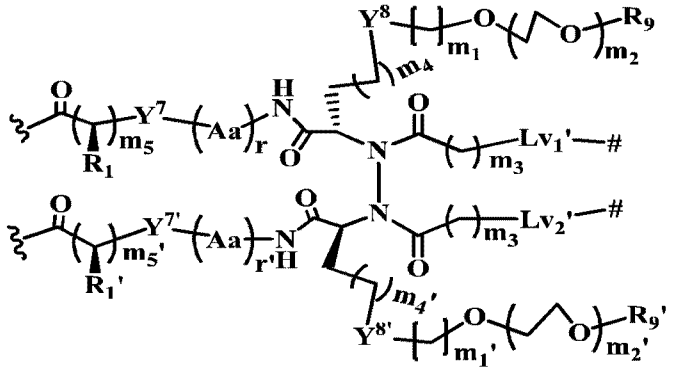
(I-c),



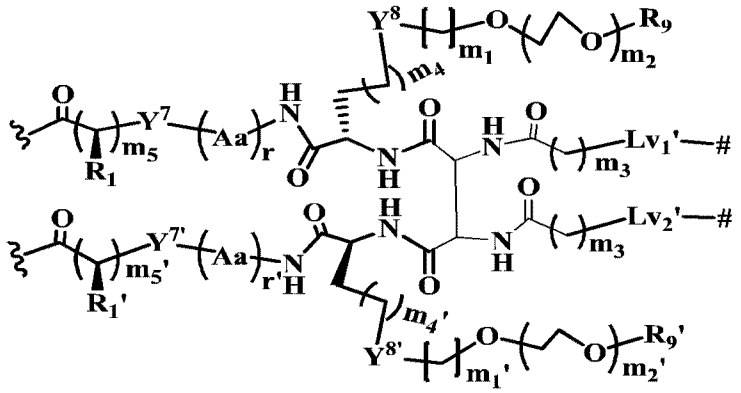
(I-d),



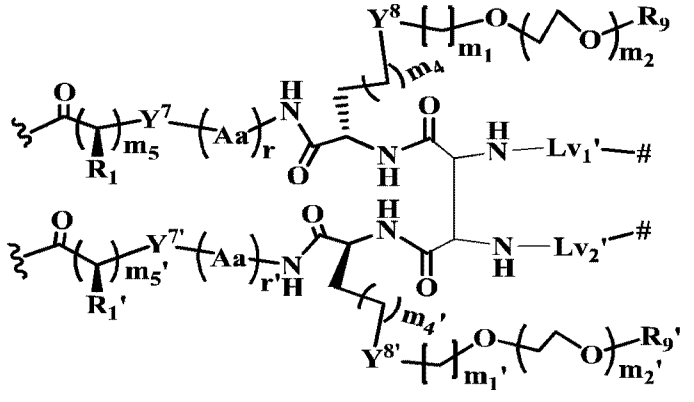
(I-e),



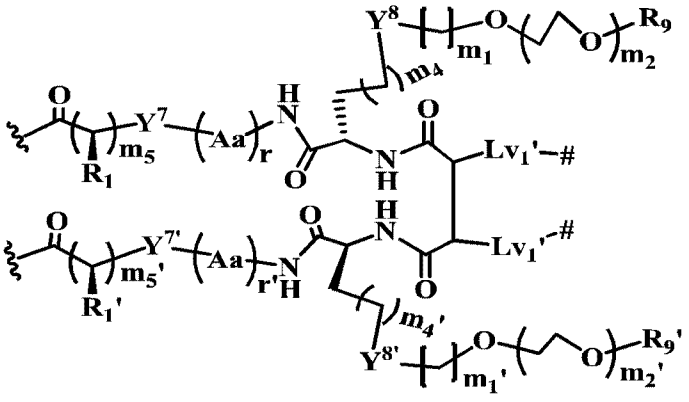
(I-f),



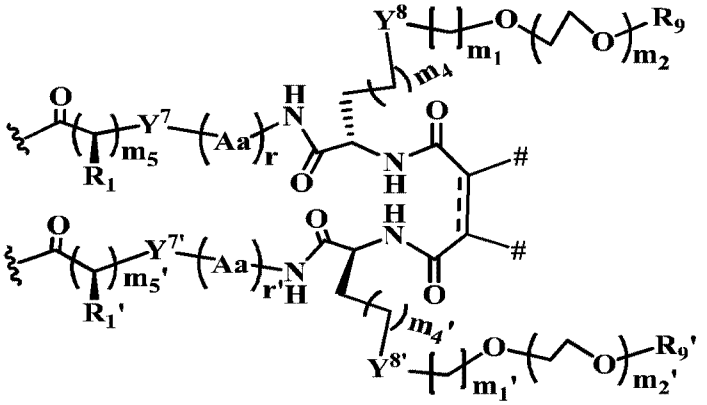
(I-g),



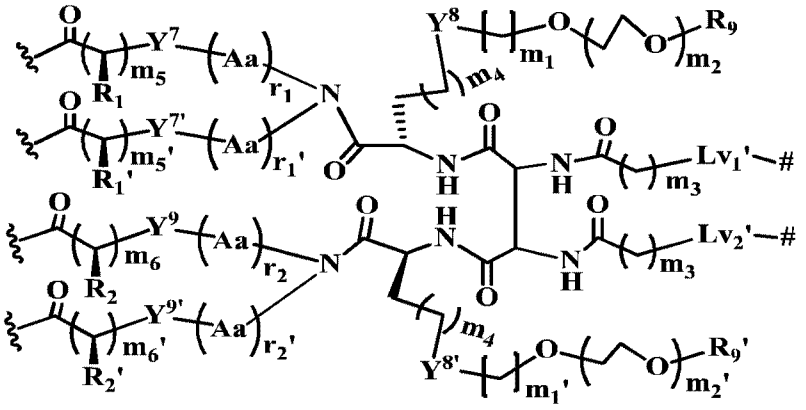
(I-h),



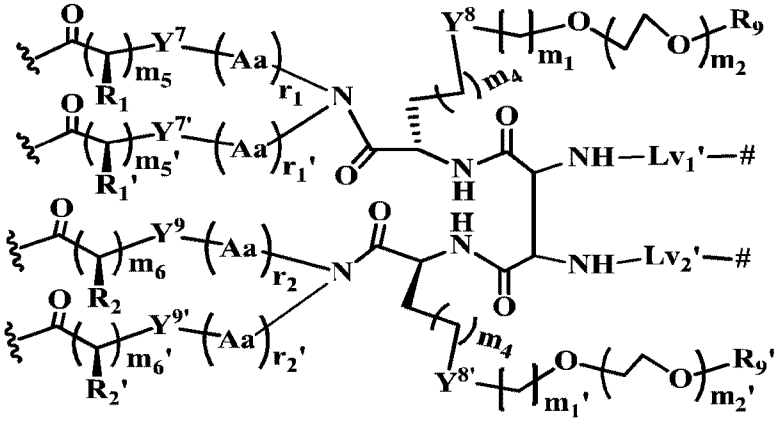
(I-i),



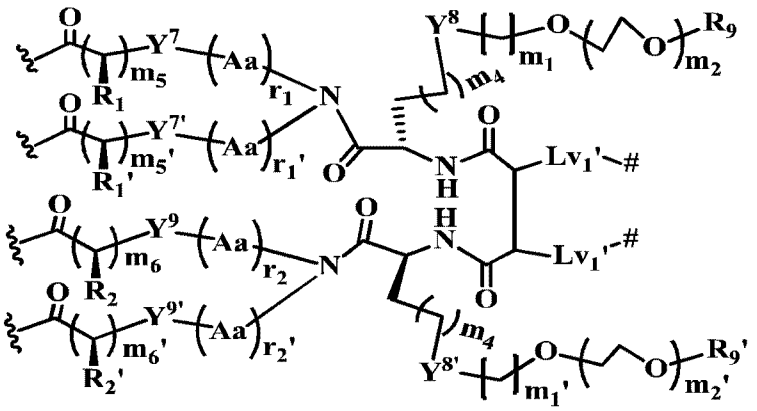
(I-j),



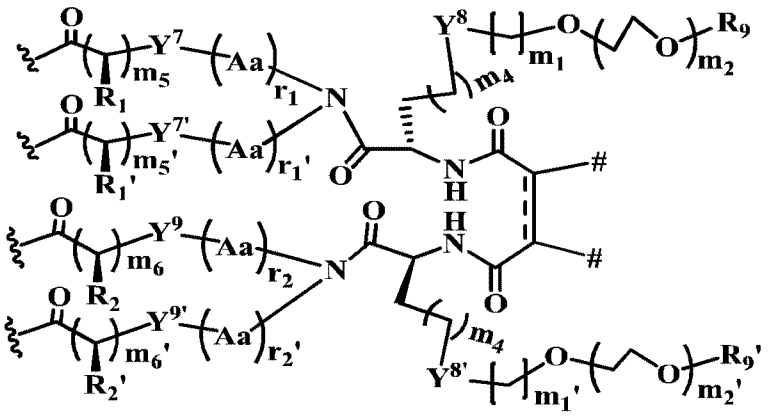
(I-k),



(I-l),



(I-m),



(I-n),

Wherein " ξ " is a site that links a drug or a site of linker L_1, L_1', L_2, or L_2'; "#" is a site that links a S (thiol), O (phenol), NH (amino), CHO (aldehyde), C(=O) (ketone), C(O)(NH) (amide) and C(O)(OH) (carboxylate) of an antibody; Aa is L-or D- natural or unnatural amino acids;

Wherein R_1, R_1', R_2, and R_2' are independently selected from H, C_1-C_8 alkyl, OH, CH_2OH, CH_2CH_2OH, NH_2, SH, SCH_3, CH_2COOH, CH_2CH_2COOH, $CH_2CH_2CH_2CH_2NH_2$, C_6H_5, $CH_2C_6H_5$, $CH_2C_6H_4OH$, $CH(OH)CH_3$, $CH_2C(O)NH_2$, $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2NHC(=NH)NH_2$;

Wherein r, r_1, r_1', r_2, and r_2' are independently selected from is 0-12; when r is not 0, $(Aa)_r$ is the same or different amino acids or peptide units;

Wherein m_1 and m_1' are independently 1 - 18; m_2 and m_2' are independently 1-100; m_3 and m_3' are independently 1 - 8; m_4 and m_4' are independently 0 - 8; m_5 and m_5' are independently 1 - 8;

Wherein Y^7 and $Y^{7'}$ are independently NH, OCH_2NH, NHC(=O), NHNH, C(=O)NH, N(R_1), SO_2, P(O)(OH), $NHS(O)_2$, $NHS(O)_2NH$, $NHS(O)_2NHC(O)$, $NHS(O)_2NHC(O)O$, $NHS(O)_2NHC(O)NH$, NHP(O)(OH), NHP(O)(OH)NH, OP(O)(OH)O, NHP(O)(OH)O, OP(O)(OH)NH, S, O, OP(O)(OH)OP(O)(OH)NH, NHP(O)(OH)OP(O)(OH)NH, NHP(O)(OH)OP(O)(OH)O, OCH_2CH_2O, OCH_2CH_2NH,

$N(CH_2CH_2)_2N$, NHC_6H_4NH, CH_2;

Y^8 and $Y^{8'}$ are independently NHC(=O), $NHS(O_2)$, NH(SO), $NHS(O_2)NH$, NHP(O)(OH)NH or C(O)NH;

Y^9 and $Y^{9'}$ are independently H, $(O=)CR_1$, $(O=)CNHR_1$, R_1COOH, $R_1(COCH_2NH)_{m2}H$, $R_1(Aa)_r$ or $R_1(COCH_2NCH_3)_{m2}H$, wherein R_1 is defined above;

In other embodiments, D, D_1, D_2, D_3, and D_4 are independently a cytotoxic drug, or a therapeutic drug, or an immunotherapeutical protein, or a function molecule for enhancement of binding or stabilization of the cell-binding protein agent, or a cell-surface receptor binding ligand, such as an antibody or an antibody fragment, or siRNA or DNA molecule.

The cytotoxic drug is selected from, but not limited to:

1). Chemotherapeutic agents: a). Alkylating agents: such as Nitrogen mustards: chlorambucil, chlornaphazine, cyclophosphamide, dacarbazine, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, mannomustine, mitobronitol, melphalan, mitolactol, pipobroman, novembichin, phenesterine, prednimustine, thiotepa, trofosfamide, uracil mustard; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); Duocarmycin (including the synthetic analogues, KW-2189 and CBI-TMI); Benzodiazepine dimers (e.g., dimmers of pyrrolobenzodiazepine (PBD) or tomaymycin, indolinobenzodiazepines, imidazobenzothiadiazepines, or oxazolidino-benzodiazepines); Nitrosoureas: (carmustine, lomustine, chlorozotocin, fotemustine, nimustine, ranimustine); Alkylsulphonates: (busulfan, treosulfan, improsulfan and piposulfan); Triazenes: (dacarbazine); Platinum containing compounds: (carboplatin, cisplatin, oxaliplatin); aziridines, such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemel-amine, trietylenephosphoramide, triethylenethio-phosphaoramide and trimethylolomel-amine]; b). Plant Alkaloids: such as Vinca alkaloids: (vincristine, vinblastine, vindesine, vinorelbine, navelbin); Taxoids: (paclitaxel, docetaxol) and their analogs, Maytansinoids (DM1, DM2, DM3, DM4, DM5, DM21, maytansine and ansamitocins) and their analogs, cryptophycins (particularly cryptophycin 1 and cryptophycin 8); epothilones, eleutherobin, discodermo-lide, bryostatins, dolostatins, auristatins, tubulysins, cephalostatins; pancratistatin; a sarcodictyin; spongistatin; c). DNA Topoisomerase Inhibitors: such as [Epipodophyllins: (9-aminocamptothecin, camptothecin, crisnatol, daunomycin, etoposide, etoposide phosphate, irinotecan, mitoxantrone, novantrone, retinoic acids (retinols), teniposide, topotecan, 9-nitrocamptothecin (RFS 2000)); mitomycins: (mitomycin C)]; d). Anti-metabolites: such as {[Anti-folate: DHFR inhibitors: (methotrexate, trimetrexate, denopterin, pteropterin, aminopterin (4-aminopteroic acid) or the other folic acid analogues); IMP dehydrogenase Inhibitors: (mycophenolic acid, tiazofurin, ribavirin, EICAR); Ribonucleotide

reductase Inhibitors: (hydroxyurea, deferoxamine)]; [Pyrimidine analogs: Uracil analogs: (ancitabine, azacitidine, 6-azauridine, capecitabine (Xeloda), carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, 5-Fluorouracil, floxuridine, ratitrexed (Tomudex)); Cytosine analogs: (cytarabine, cytosine arabinoside, fludarabine); Purine analogs: (azathioprine, fludarabine, mercaptopurine, thiamiprine, thioguanine)]; folic acid replenisher, such as frolinic acid}; e). Hormonal therapies: such as {Receptor antagonists: [Anti-estrogen: (megestrol, raloxifene, tamoxifen); LHRH agonists: (goscrclin, leuprolide acetate); Anti-androgens: (bicalutamide, flutamide, calusterone, dromostanolone propionate, epitiostanol, goserelin, leuprolide, mepitiostane, nilutamide, testolactone, trilostane and other androgens inhibitors)]; Retinoids/Deltoids: [Vitamin D3 analogs: (CB 1093, EB 1089 KH 1060, cholecalciferol, ergocalciferol); Photodynamic therapies: (verteporfin, phthalocyanine, photosensitizer Pc4, demethoxy-hypocrellin A); Cytokines: (Interferon-alpha, Interferon-gamma, tumor necrosis factor (TNFs), human proteins containing a TNF domain)]}; f). Kinase inhibitors, such as BIBW 2992 (anti-EGFR/Erb2), imatinib, gefitinib, pegaptanib, sorafenib, dasatinib, sunitinib, erlotinib, nilotinib, lapatinib, axitinib, pazopanib. vandetanib, E7080 (anti-VEGFR2), mubritinib, ponatinib (AP24534), bafetinib (INNO-406), bosutinib (SKI-606), cabozantinib, vismodegib, iniparib, ruxolitinib, CYT387, axitinib, tivozanib, sorafenib, bevacizumab, cetuximab, Trastuzumab, Ranibizumab, Panitumumab, ispinesib; g). antibiotics, such as the enediyne antibiotics (e.g. calicheamicins, especially calicheamicin $\gamma 1$, $\delta 1$, $\alpha 1$ and $\beta 1$, see, e.g., *J. Med. Chem.*, 39 (11), 2103–2117 (1996), Angew Chem Intl. Ed. Engl. 33:183-186 (1994); dynemicin, including dynemicin A and deoxydynemicin; esperamicin, kedarcidin, C-1027, maduropeptin, as well as neocarzinostatin chromophore and related chromoprotein enediyne antiobiotic chromomophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin; chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, nitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; f). Others: such as Polyketides (acetogenins), especially bullatacin and bullatacinone; gemcitabine, epoxomicins (e. g. carfilzomib), bortezomib, thalidomide, lenalidomide, pomalidomide, tosedostat, zybrestat, PLX4032, STA-9090, Stimuvax, allovectin-7, Xegeva, Provenge, Yervoy, Isoprenylation inhibitors (such as Lovastatin), Dopaminergic neurotoxins (such as 1-methyl-4-phenylpyridinium ion), Cell cycle inhibitors (such as staurosporine), Actinomycins (such as Actinomycin D, dactinomycin), Bleomycins (such as bleomycin A2, bleomycin B2, peplomycin), Anthracyclines (such as daunorubicin, doxorubicin (adriamycin), idarubicin, epirubicin,

pirarubicin, zorubicin, mtoxantrone, MDR inhibitors (such as verapamil), Ca^{2+}ATPase inhibitors (such as thapsigargin), Histone deacetylase inhibitors (Vorinostat, Romidepsin, Panobinostat, Valproic acid, Mocetinostat (MGCD0103), Belinostat, PCI-24781, Entinostat, SB939, Resminostat, Givinostat, AR-42, CUDC-101, sulforaphane, Trichostatin A); Thapsigargin, Celecoxib, glitazones, epigallocatechin gallate, Disulfiram, Salinosporamide A.; Anti-adrenals, such as aminoglutethimide, mitotane, trilostane; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; arabinoside, bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; eflornithine (DFMO), elfomithine; elliptinium acetate, etoglucid; gallium nitrate; gacytosine, hydroxyurea; ibandronate, lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine, razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2, 2', 2''-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verrucarin A, roridin A and anguidine); urethane, siRNA, antisense drugs, and a nucleolytic enzyme.

2). An anti-autoimmune disease agent includes, but is not limited to, cyclosporine, cyclosporine A, aminocaproic acid, azathioprine, bromocriptine, chlorambucil, chloroquine, cyclophosphamide, corticosteroids (e.g. amcinonide, betamethasone, budesonide, hydrocortisone, flunisolide, fluticasone propionate, fluocortolone danazol, dexamethasone, Triamcinolone acetonide, beclometasone dipropionate), DHEA, enanercept, hydroxychloroquine, infliximab, meloxicam, methotrexate, mofetil, mycophenylate, prednisone, sirolimus, tacrolimus.

3). An anti-infectious disease agent includes, but is not limited to, a). Aminoglycosides: amikacin, astromicin, gentamicin (netilmicin, sisomicin, isepamicin), hygromycin B, kanamycin (amikacin, arbekacin, bekanamycin, dibekacin, tobramycin), neomycin (framycetin, paromomycin, ribostamycin), netilmicin, spectinomycin, streptomycin, tobramycin, verdamicin; b). Amphenicols: azidamfenicol, chloramphenicol, florfenicol, thiamphenicol; c). Ansamycins: geldanamycin, herbimycin; d). Carbapenems: biapenem, doripenem, ertapenem, imipenem/cilastatin, meropenem, panipenem; e). Cephems: carbacephem (loracarbef), cefacetrile, cefaclor, cefradine, cefadroxil, cefalonium, cefaloridine, cefalotin or cefalothin, cefalexin, cefaloglycin, cefamandole, cefapirin, cefatrizine, cefazaflur, cefazedone, cefazolin, cefbuperazone, cefcapene, cefdaloxime, cefepime, cefminox, cefoxitin, cefprozil, cefroxadine, ceftezole, cefuroxime, cefixime, cefdinir, cefditoren, cefepime, cefetamet, cefmenoxime, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotiam, cefozopran, cephalexin, cefpimizole, cefpiramide, cefpirome, cefpodoxime, cefprozil, cefquinome, cefsulodin, ceftazidime, cefteram, ceftibuten, ceftiolene, ceftizoxime, ceftobiprole, ceftriaxone, cefuroxime, cefuzonam, cephamycin (cefoxitin, cefotetan, cefmetazole), oxacephem (flomoxef, latamoxef); f). Glycopeptides: bleomycin, vancomycin (oritavancin, telavancin),

teicoplanin (dalbavancin), ramoplanin; g). Glycylcyclines: e. g. tigecycline; g). β-Lactamase inhibitors: penam (sulbactam, tazobactam), clavam (clavulanic acid); i). Lincosamides: clindamycin, lincomycin; j). Lipopeptides: daptomycin, A54145, calcium-dependent antibiotics (CDA); k). Macrolides: azithromycin, cethromycin, clarithromycin, dirithromycin, erythromycin, flurithromycin, josamycin, ketolide (telithromycin, cethromycin), midecamycin, miocamycin, oleandomycin, rifamycins (rifampicin, rifampin, rifabutin, rifapentine), rokitamycin, roxithromycin, spectinomycin, spiramycin, tacrolimus (FK506), troleandomycin, telithromycin; l). Monobactams: aztreonam, tigemonam; m). Oxazolidinones: linezolid; n). Penicillins: amoxicillin, ampicillin (pivampicillin, hetacillin, bacampicillin, metampicillin, talampicillin), azidocillin, azlocillin, benzylpenicillin, benzathine benzylpenicillin, benzathine phenoxymethyl-penicillin, clometocillin, procaine benzylpenicillin, carbenicillin (carindacillin), cloxacillin, dicloxacillin, epicillin, flucloxacillin, mecillinam (pivmecillinam), mezlocillin, meticillin, nafcillin, oxacillin, penamecillin, penicillin, pheneticillin, phenoxymethylpenicillin, piperacillin, propicillin, sulbenicillin, temocillin, ticarcillin; o). Polypeptides: bacitracin, colistin, polymyxin B; p). Quinolones: alatrofloxacin, balofloxacin, ciprofloxacin, clinafloxacin, danofloxacin, difloxacin, enoxacin, enrofloxacin, floxin, garenoxacin, gatifloxacin, gemifloxacin, grepafloxacin, kano trovafloxacin, levofloxacin, lomefloxacin, marbofloxacin, moxifloxacin, nadifloxacin, norfloxacin, orbifloxacin, ofloxacin, pefloxacin, trovafloxacin, grepafloxacin, sitafloxacin, sparfloxacin, temafloxacin, tosufloxacin, trovafloxacin; q). Streptogramins: pristinamycin, quinupristin/dalfopristin); r). Sulfonamides: mafenide, prontosil, sulfacetamide, sulfamethizole, sulfanilimide, sulfasalazine, sulfisoxazole, trimethoprim, trimethoprim-sulfamethoxazole (co-trimoxazole); s). Steroid antibacterials: e.g. fusidic acid; t). Tetracyclines: doxycycline, chlortetracycline, clomocycline, demeclocycline, lymecycline, meclocycline, metacycline, minocycline, oxytetracycline, penimepicycline, rolitetracycline, tetracycline, glycylcyclines (e.g. tigecycline); u). Other types of antibiotics: annonacin, arsphenamine, bactoprenol inhibitors (Bacitracin), DADAL/AR inhibitors (cycloserine), dictyostatin, discodermolide, eleutherobin, epothilone, ethambutol, etoposide, faropenem, fusidic acid, furazolidone, isoniazid, laulimalide, metronidazole, mupirocin, mycolactone, NAM synthesis inhibitors (e. g. fosfomycin), nitrofurantoin, paclitaxel, platensimycin, pyrazinamide, quinupristin/dalfopristin, rifampicin (rifampin), tazobactam tinidazole, uvaricin;

4). Anti-viral drugs: a). Entry/fusion inhibitors: aplaviroc, maraviroc, vicriviroc, gp41 (enfuvirtide), PRO 140, CD4 (ibalizumab); b). Integrase inhibitors: raltegravir, elvitegravir, globoidnan A; c). Maturation inhibitors: bevirimat, vivecon; d). Neuraminidase inhibitors: oseltamivir, zanamivir, peramivir; e). Nucleosides &nucleotides: abacavir, aciclovir, adefovir, amdoxovir, apricitabine, brivudine, cidofovir, clevudine, dexelvucitabine, didanosine (ddI),

elvucitabine, emtricitabine (FTC), entecavir, famciclovir, fluorouracil (5-FU), 3'-fluoro-substituted 2', 3'-dideoxynucleoside analogues (e.g. 3'-fluoro-2', 3'-dideoxythymidine (FLT) and 3'-fluoro-2', 3'-dideoxyguanosine (FLG), fomivirsen, ganciclovir, idoxuridine, lamivudine (3TC), l-nucleosides (e.g. β-l-thymidine and β-l-2'-deoxycytidine), penciclovir, racivir, ribavirin, stampidine, stavudine (d4T), taribavirin (viramidine), telbivudine, tenofovir, trifluridine valaciclovir, valganciclovir, zalcitabine (ddC), zidovudine (AZT); f). Non-nucleosides: amantadine, ateviridine, capravirine, diarylpyrimidines (etravirine, rilpivirine), delavirdine, docosanol, emivirine, efavirenz, foscarnet (phosphonoformic acid), imiquimod, interferon alfa, loviride, lodenosine, methisazone, nevirapine, NOV-205, peginterferon alfa, podophyllotoxin, rifampicin, rimantadine, resiquimod (R-848), tromantadine; g). Protease inhibitors: amprenavir, atazanavir, boceprevir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, pleconaril, ritonavir, saquinavir, telaprevir (VX-950), tipranavir; h). Other types of anti-virus drugs: abzyme, arbidol, calanolide a, ceragenin, cyanovirin-n, diarylpyrimidines, epigallocatechin gallate (EGCG), foscarnet, griffithsin, taribavirin (viramidine), hydroxyurea, KP-1461, miltefosine, pleconaril, portmanteau inhibitors, ribavirin, seliciclib.

5). The drugs used for conjugates via a bridge linker of the present invention also include radioisotopes. Examples of radioisotopes (radionuclides) are ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{32}P, ^{35}S, ^{64}Cu, ^{68}Ga, ^{86}Y, ^{99}Tc, ^{111}In, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{133}Xe, ^{177}Lu, ^{211}At, or ^{213}Bi. Radioisotope labeled antibodies are useful in receptor targeted imaging experiments or can be for targeted treatment such as with the antibody-drug conjugates of the invention (Wu et al (2005) Nature Biotechnology 23(9): 1137-46). The cell binding molecules, e.g. an antibody can be labeled with ligand reagents through the bridge linkers of the present patent that bind, chelate or otherwise complex a radioisotope metal, using the techniques described in Current Protocols in Immunology, Volumes 1 and 2, Coligen et al, Ed. Wiley-Interscience, New York, Pubs. (1991). Chelating ligands which may complex a metal ion include DOTA, DOTP, DOTMA, DTPA and TETA (Macrocyclics, Dallas, Tex. USA).

6). The pharmaceutically acceptable salts, acids or derivatives of any of the above drugs.

In another embodiment, the drug D can be a chromophore molecule, for which the conjugate can be used for detection, monitoring, or study the interaction of the cell binding molecule with a target cell. Chromophore molecules are a compound that have the ability to absorb a kind of light, such as UV light, florescent light, IR light, near IR light, visual light; A chromatophore molecule includes a class or subclass of xanthophores, erythrophores, iridophores, leucophores, melanophores, and cyanophores; a class or subclass of fluorophore molecules which are fluorescent chemical compounds re-emitting light upon light; a class or subclass of visual phototransduction molecules; a class or subclass of photophore molecules; a class or subclass of luminescence molecules; and a class or subclass of luciferin compounds.

The chromophore molecule can be selected from, but not limited, non-protein organic fluorophores, such as: Xanthene derivatives (fluorescein, rhodamine, Oregon green, eosin, and Texas red); Cyanine derivatives: (cyanine, indocarbocyanine, oxacarbocyanine, thiacarbocyanine, and merocyanine); Squaraine derivatives and ring-substituted squaraines, including Seta, SeTau, and Square dyes; Naphthalene derivatives (dansyl and prodan derivatives); Coumarin derivatives; Oxadiazole derivatives (pyridyloxazole, nitrobenzoxadiazole and benzoxadiazole); Anthracene derivatives (anthraquinones, including DRAQ5, DRAQ7 and CyTRAK Orange); Pyrene derivatives (cascade blue, etc); Oxazine derivatives (Nile red, Nile blue, cresyl violet, oxazine 170 etc). Acridine derivatives (proflavin, acridine orange, acridine yellow etc). Arylmethine derivatives (auramine, crystal violet, malachite green). Tetrapyrrole derivatives (porphin, phthalocyanine, bilirubin).

Or a chromophore molecule can be selected from any analogs and derivatives of the following fluorophore compounds: CF dye (Biotium), DRAQ and CyTRAK probes (BioStatus), BODIPY (Invitrogen), Alexa Fluor (Invitrogen), DyLight Fluor (Thermo Scientific, Pierce), Atto and Tracy (Sigma Aldrich), FluoProbes (Interchim), Abberior Dyes (Abberior), DY and MegaStokes Dyes (Dyomics), Sulfo Cy dyes (Cyandye), HiLyte Fluor (AnaSpec), Seta, SeTau and Square Dyes (SETA BioMedicals), Quasar and Cal Fluor dyes (Biosearch Technologies), SureLight Dyes (APC, RPEPerCP, Phycobilisomes)(Columbia Biosciences), APC, APCXL, RPE, BPE (Phyco-Biotech).

Examples of the widely used fluorophore compounds which are reactive or conjugatable with the linkers of the invention are: Allophycocyanin (APC), Aminocoumarin, APC-Cy7 conjugates, BODIPY-FL, Cascade Blue, Cy2, Cy3, Cy3.5, Cy3B, Cy5, Cy5.5, Cy7, Fluorescein, FluorX, Hydroxycoumarin, IR-783, Lissamine Rhodamine B, Lucifer yellow, Methoxycoumarin, NBD, Pacific Blue, Pacific Orange, PE-Cy5 conjugates, PE-Cy7 conjugates, PerCP, R-Phycoerythrin (PE), Red 613, Seta-555-Azide, Seta-555-DBCO, Seta-555-NHS, Seta-580-NHS, Seta-680-NHS, Seta-780-NHS, Seta-APC-780, Seta-PerCP-680, Seta-R-PE-670, SeTau-380-NHS, SeTau-405-Maleimide, SeTau-405-NHS, SeTau-425-NHS, SeTau-647-NHS, Texas Red, TRITC, TruRed, X-Rhodamine.

The fluorophore compounds that can be linked to the linkers of the invention for study of nucleic acids or proteins are selected from the following compounds or their derivatives: 7-AAD (7-aminoactinomycin D, CG-selective), Acridine Orange, Chromomycin A3, CyTRAK Orange (Biostatus, red excitation dark), DAPI, DRAQ5, DRAQ7, Ethidium Bromide, Hoechst33258, Hoechst33342, LDS 751, Mithramycin, PropidiumIodide (PI), SYTOX Blue, SYTOX Green, SYTOX Orange, Thiazole Orange, TO-PRO: Cyanine Monomer, TOTO-1, TO-PRO-1, TOTO-3, TO-PRO-3, YOSeta-1, YOYO-1. The fluorophore compounds that can be linked to the linkers of the invention for study cells are selected from the following compounds or their derivatives: DCFH

(2'7'Dichorodihydro-fluorescein, oxidized form), DHR (Dihydrorhodamine 123, oxidized form, light catalyzes oxidation), Fluo-3 (AM ester. pH > 6), Fluo-4 (AM ester. pH 7.2), Indo-1 (AM ester, low/high calcium (Ca2+)), and SNARF (pH 6/9). The preferred fluorophore compounds that can be linked to the linkers of the invention for study proteins/antibodies are selected from the following compounds or their derivatives: Allophycocyanin (APC), AmCyan1 (tetramer, Clontech), AsRed2 (tetramer, Clontech), Azami Green (monomer, MBL), Azurite, B-phycoerythrin (BPE), Cerulean, CyPet, DsRed monomer (Clontech), DsRed2 ("RFP", Clontech), EBFP, EBFP2, ECFP, EGFP (weak dimer, Clontech), Emerald (weak dimer, Invitrogen), EYFP (weak dimer, Clontech), GFP (S65A mutation), GFP (S65C mutation), GFP (S65L mutation), GFP (S65T mutation), GFP (Y66F mutation), GFP (Y66H mutation), GFP (Y66W mutation), GFPuv, HcRed1, J-Red, Katusha, Kusabira Orange (monomer, MBL), mCFP, mCherry, mCitrine, Midoriishi Cyan (dimer, MBL), mKate (TagFP635, monomer, Evrogen), mKeima-Red (monomer, MBL), mKO, mOrange, mPlum, mRaspberry, mRFP1 (monomer, Tsien lab), mStrawberry, mTFP1, mTurquoise2, P3 (phycobilisome complex), Peridinin Chlorophyll (PerCP), R-phycoerythrin(RPE), T-Sapphire, TagCFP (dimer, Evrogen), TagGFP (dimer, Evrogen), TagRFP (dimer, Evrogen), TagYFP (dimer, Evrogen), tdTomato (tandem dimer), Topaz, TurboFP602 (dimer, Evrogen), TurboFP635 (dimer, Evrogen), TurboGFP (dimer, Evrogen), TurboRFP (dimer, Evrogen), TurboYFP (dimer, Evrogen), Venus, Wild Type GFP, YPet, ZsGreen1 (tetramer, Clontech), ZsYellow1 (tetramer, Clontech).

In another embodiment, the drug D can be polyalkylene glycols that are used for extending the half-life of the cell-binding antibody, or antibody-like protein molecule when administered to a mammal. Polyalkylene glycols include, but are not limited to, poly(ethylene glycols) (PEGs), poly(propylene glycol) and copolymers of ethylene oxide and propylene oxide; particularly preferred are PEGs, and more particularly preferred are monofunctionally activated hydroxyPEGs (e.g., hydroxyl PEGs activated at a single terminus, including reactive esters of hydroxyPEG-monocarboxylic acids, hydroxyPEG-monoaldehydes, hydroxyPEG-monoamines, hydroxyPEG-monohydrazides, hydroxyPEG-monocarbazates, hydroxyl PEG-monoiodoacetamides, hydroxyl PEG-monomaleimides, hydroxyl PEG-monoorthopyridyl disulfides, hydroxyPEG-monooximes, hydroxyPEG-monophenyl carbonates, hydroxyl PEG-monophenyl glyoxals, hydroxyl PEG-monothiazolidine-2-thiones, hydroxyl PEG-monothioesters, hydroxyl PEG-monothiols, hydroxyl PEG-monotriazines and hydroxyl PEG-monovinylsulfones).

In certain such embodiments, the polyalkylene glycol has a molecular weight of from about 10 Daltons to about 200 kDa, preferably about 88 Da to about 40 kDa; two branches each with a molecular weight of about 88 Da to about 40 kDa; and more preferably two branches, each of about 88 Da to about 20 kDa. In one particular embodiment, the polyalkylene glycol is poly(ethylene)

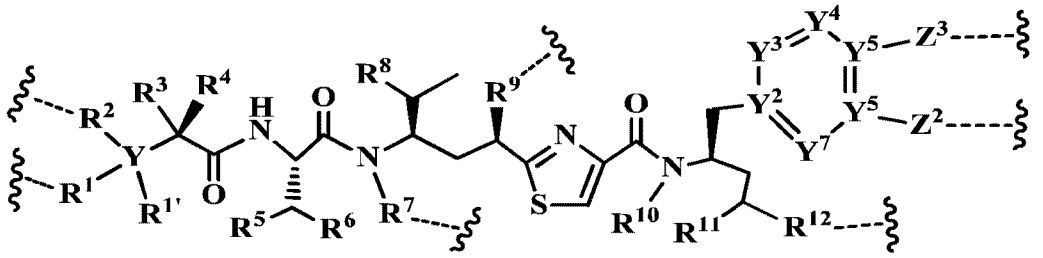
glycol and has a molecular weight of about 10 kDa; about 20 kDa, or about 40 kDa. In specific embodiments, the PEG is a PEG 10 kDa (linear or branched), a PEG 20 kDa (linear or branched), or a PEG 40 kDa (linear or branched). A number of US patents have disclosed the preparation of linear or branched "non-antigenic" PEG polymers and derivatives or conjugates thereof, e.g., U.S. Pat. Nos. 5, 428, 128; 5, 621, 039; 5, 622, 986; 5, 643, 575; 5, 728, 560; 5, 730, 990; 5, 738, 846; 5, 811, 076; 5, 824, 701; 5, 840, 900; 5, 880, 131; 5, 900, 402; 5, 902, 588; 5, 919, 455; 5, 951, 974; 5, 965, 119; 5, 965, 566; 5, 969, 040; 5, 981, 709; 6, 011, 042; 6, 042, 822; 6, 113, 906; 6, 127, 355; 6, 132, 713; 6, 177, 087, and 6, 180, 095.

In yet another embodiment, D is more preferably a potent cytotoxic agent, selected from a tubulysin and its analogs, a maytansinoid and its analogs, a taxanoid (taxane) and its analogs, a CC-1065 and its analogs, a daunorubicin or doxorubicin and its analogs, an amatoxin and its analogs, a benzodiazepine dimer (e.g., dimers of pyrrolobenzodiazepine (PBD), tomaymycin, anthramycin, indolinobenzodiazepines, imidazobenzothiadiazepines, or oxazolidinobenzo-diazepines) and their analogs, a calicheamicin and the enediyne antibiotic and their analogs, an actinomycin and its analogs, an azaserine and its analogs, a bleomycin and its analogs, an epirubicin and its analogs, a tamoxifen and its analogs, an idarubicin and its analogs, a dolastatin and its analogs, an auristatin (including monomethyl auristatin E (MMAE), MMAF, auristatin PYE, auristatin TP, Auristatins 2-AQ, 6-AQ, EB (AEB), and EFP (AEFP)) and its analogs, a combretastatin, a duocarmycin and its analogs, a camptothecin, a geldanamycin and its analogs, a methotrexate and its analogs, a thiotepa and its analogs, a vindesine and its analogs, a vincristine and its analogs, a hemiasterlin and its analogs, a nazumamide and its analogs, a spliceostatin, a pladienolide, a microginin and its analogs, a radiosumin and its analogs, an alterobactin and its analogs, a microsclerodermin and its analogs, a theonellamide and its analogs, an esperamicin and its analogs, PNU-159682 and its analogs, a protein kinase inhibitor, a MEK inhibitor, a KSP inhibitor, a nicotinamide phosphoribosyltransferase (NAMPT) inhibitor, a topoisomerase I or II inhibitor, an immunotoxin, and stereoisomers, isosteres, analogs, or derivatives above thereof.

Tubulysin and its analogs are well known in the art and can be isolated from natural sources according to known methods or prepared synthetically according to known methods (e. g. Balasubramanian, R., et al. J. Med. Chem., 2009, 52, 238–40; Wipf, P., et al. Org. Lett., 2004, 6, 4057–60; Pando, O., et al. J. Am. Chem. Soc., 2011, 133, 7692–5; Reddy, J. A., et al. Mol. Pharmaceutics, 2009, 6, 1518–25; Raghavan, B., et al. J. Med. Chem., 2008, 51, 1530–33; Patterson, A. W., et al. J. Org. Chem., 2008, 73, 4362–9; Pando, O., et al. Org. Lett., 2009, 11 (24), 5567–9; Wipf, P., et al. Org. Lett., 2007, 9 (8), 1605–7; Friestad, G. K., Org. Lett., 2004, 6, 3249–52; Peltier, H. M., et al. J. Am. Chem. Soc., 2006, 128, 16018–9; Chandrasekhar, S., et al J. Org. Chem., 2009,

74, 9531–4; Liu, Y., et al. Mol. Pharmaceutics, 2012, 9, 168–75; Friestad, G. K., et al. Org. Lett., 2009, 11, 1095–8; Kubicek, K., et al., Angew Chem Int Ed Engl, 2010.49: 4809-12; Chai, Y., et al., Chem Biol, 2010, 17: 296-309; Ullrich, A., et al., Angew Chem Int Ed Engl, 2009, 48, 4422-5; Sani, M., et al. Angew Chem Int Ed Engl, 2007, 46, 3526-9; Domling, A., et al., Angew Chem Int Ed Engl, 2006, 45, 7235-9; Patent applications: Zanda, M., et al, Can. Pat. Appl. CA 2710693 (2011); Chai, Y., et al. Eur. Pat. Appl. 2174947 (2010), WO 2010034724; Leamon, C. et al, WO2010033733, WO 2009002993; Ellman, J., et al, PCT WO2009134279; WO 2009012958, US appl. 20110263650, 20110021568; Matschiner, G., et al, WO2009095447; Vlahov, I., et al, WO2009055562, WO 2008112873; Low, P., et al, WO2009026177; Richter, W., WO2008138561; Kjems, J., et al, WO 2008125116; Davis, M.; et al, WO2008076333; Diener, J.; et al, U.S. Pat.Appl. 20070041901, WO2006096754; Matschiner, G., et al, WO2006056464; Vaghefi, F., et al, WO2006033913; Doemling, A., Ger. Offen. DE102004030227, WO2004005327, WO2004005326, WO2004005269; Stanton, M., et al, U.S. Pat. Appl. Publ. 20040249130; Hoefle, G., et al, Ger. Offen. DE10254439, DE10241152, DE10008089; Leung, D., et al, WO2002077036; Reichenbach, H., et al, Ger. Offen. DE19638870; Wolfgang, R., US20120129779; Chen, H., US appl. 20110027274. The preferred structures of tubulysins for conjugation of cell binding molecules through process of the present patent application are described in the patent application of PCT/IB2012/053554.

Tubulysin analog having the following formula (V):



(V)

or a pharmaceutically acceptable salt, hydrates, or hydrated salt; or a polymorphic crystalline structure; or an optical isomer, racemate, diastereomer or enantiomer thereof,

wherein ∿∿ is a linkage site that either one or two of them can link to L_1 and/or L_2 independently; when two of " ∿∿ " link to both L_1 and L_2, R^1 and R^2, or Z^2 and Z^3 are preferably the dual linkage sites;

wherein R^1, $R^{1'}$, R^2, R^3, and R^4 are independently H, C_1~C_8 alkyl; C_2~C_8 heteroalkyl, or heterocyclic; C_3~C_8 aryl, Ar-alkyl, cycloalkyl, alkylcycloalkyl, heterocycloalkyl, heteroalkylcycloalkyl, carbocyclic, or alkylcarbonyl; or R^1R^2, R^1R^3, R^2R^3, R^3R^4, or R^5R^6 form a 3~7 membered carbocyclic, cycloalkyl, heterocyclic, heterocycloalkyl, aromatic or heteroaromatic ring system; R^1 and R^2 can be independently absent when they link to L_1 or L_2 independently or simultaneously, Y^1 is N or CH;

wherein R^5, R^6, R^8, R^{10} and R^{11} are independently H, or C_1~C_4 alkyl or heteroalkyl;

wherein R^7 is independently H, R^{14}, $-R^{14}C(=O)X^1R^{15}$; or $-R^{14}X^1R^{15}$; X^1 is O, S, S-S, NH, CH_2 or NR^{14};

wherein R^9 is selected from H, OH, =O, $-OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)NHR^{14}$, $-OC(=O)NR^{14}R^{15}$, $OP(=O)(OR^{14})_2$, $-OC(=O)NR^{14}R^{15}$, or $OR^{14}OP(=O)(OR^{15})_2$; when R^9 links L_1 or L_2, R^9 is , -O-, -OC(=O)NH- or $-OC(=O)N(R^{14})-$;

wherein R^{11} is independently H, R^{14}, $-R^{14}C(=O)R^{15}$, $-R^{14}C(=O)X^2R^{15}$, wherein X^2 is -O-, -S-, -NH-, or $-N(R^{14})-$;

wherein R^{12} is -COOH, -COSH, $-CONH_2$, $CONHNH_2$, $CONHNHR^{15}$, $-CONH(R^{15})$, $-COOR^{15}$, $-R^{15}COR^{16}$, $-R^{15}COOR^{16}$, $-R^{15}C(O)NH_2$, $-R^{15}C(O)NHR^{16}$, $-COSR^{15}$, $R^{15}S(=O)_2R^{16}$, $-R^{15}P(=O)(OR^{17})_2$, $-R^{15}OP(=O)(OR^{17})_2$, $-COOCH_2OP(=O)(OR^{17})_2$, $-COX^2SO_2R^{17}$, $-COOR^{15}X^2R^{16}$, tetrazole, imidazole, or triazole, where X^2 is -O-, -S-, -NH-, $-N(R^{15})-$, $-O-R^{15}-$, $-S-R^{15}-$, CH_2 or $-NHR^{15}-$; when R^{12} links L_1 or L_2, R^{12} is $-C(O)O-$, $-C(O)NH-$, $-C(=O)NHS(O)_2R^{15}-$ or $-C(=O)N(R^{15})-$;

$R^{13}$and R^{14} are independently C_1~C_8 alkyl, heteroalkyl; C_2-C_8 of alkenyl, alkynyl, heteroalkyl, heterocycloalkyl; C_3-C_8 of aryl, Ar-alkyl;

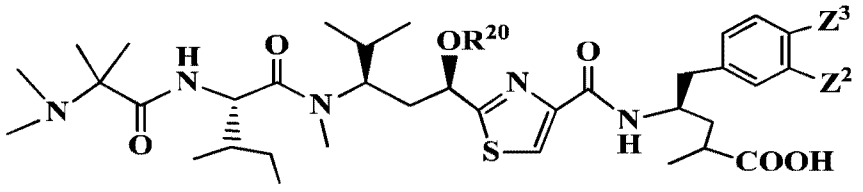
Z^2 and Z^3 are independently H, O, S, NH, $N(R^{15})$, NHNH, -OH, -SH, $-NH_2$, NH, $NHNH_2$, $-NH(R^{15})$, $-OR^{15}$, CO, $-COX^2$, $-COX^2R^{16}$, R^{17}, F, Cl, Br, I, SR^{16}, $NR^{16}R^{17}$, $N=NR^{16}$, $N=R^{16}$, NO_2, $SOR^{16}R^{17}$, SO_2R^{16}, SO_3R^{16}, OSO_3R^{16}, $PR^{16}R^{17}$, $POR^{16}R^{17}$, $PO_2R^{16}R^{17}$, $OP(O)(OR^{17})_2$, $OCH_2OP(O)(OR^{17})_2$, $OC(O)R^{17}$, $OC(O)OP(O)(OR^{17})_2$, $PO(OR^{16})(OR^{17})$, $OP(O)(OR^{17})OP(O)(OR^{17})_2$, $OC(O)NHR^{17}$;-O-(C_4-C_{12} glycoside), -N-(C_4-C_{12} glycoside); C_1~C_8 alkyl, heteroalkyl; C_2-C_8 of alkenyl, alkynyl, heteroalkyl, heterocycloalkyl; C_3-C_8 of aryl, Ar-alkyl, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl, or 2- 8 carbon atoms of esters, ether, or amide; or peptides containing 1-8 amino acids $(NH(Aa)_{1\sim8}$, or $CO(Aa)_{1\sim8}$ (which are respectively N-terminal or C-terminal 1 - 8 the same or different amino acids)), or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$ or $(OCH_2CH(CH_3))_p$, wherein p is an integer from 0 to about 1000, or combination of above groups thereof; X^2 is O, S, S-S, NH, CH_2, OH, SH, NH_2, CHR^{15} or NR^{15};

R^{15}, R^{16} and R^{17} are independently H, C_1~C_8 alkyl, heteroalkyl; C_2-C_8 of alkenyl, alkynyl, heteroalkyl, heterocycloalkyl; C_3-C_8 of aryl, Ar-alkyl, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl, alkylcarbonyl, or Na^+, K^+, Cs^+, Li^+, Ca^{2+}, Mg^+, Zn^{2+}, $N^+(R^1)(R^2)(R^3)(R^4)$, $HN^+(C_2H_5OH)_3$ salt;

Y^1 and Y^2 are independently N or CH; q is 0 or 1; when q=0, Y^3 does not exist, Y^4, Y^5, Y^6 and Y^7 are independently CH, N, NH, O, S, or N (R1), thus Y^2, Y^4, Y^5, Y^6 and Y^7form a heteroaromatic ring of furan, pyrrole thiophene, thiazole, oxazole and imidazole, pyrazole, triazole, tetrazole, thiadiazole; when q=1, Y^3, Y^4, Y^5, Y^6 and Y^7 are independently CH or N, thus Y^2, Y^3, Y^4, Y^5, Y^6

and Y^7 form aromatic ring of benzene, pyridine, pyridazine, pyrimidine, pyrazine, triazine, tetrazine, pentazine;

Examples of the structures of the tubulysin analogs are shown below:



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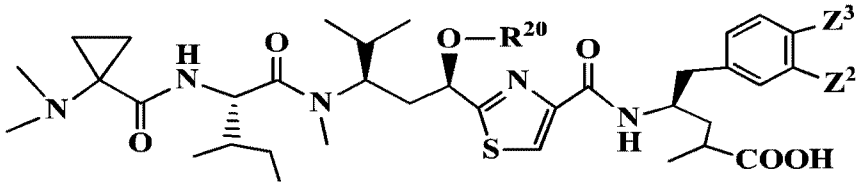

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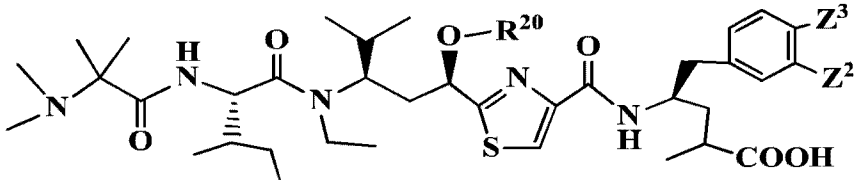

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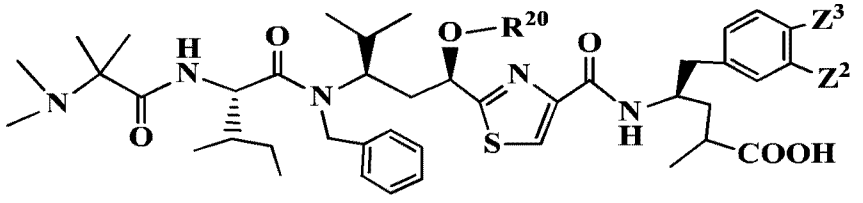

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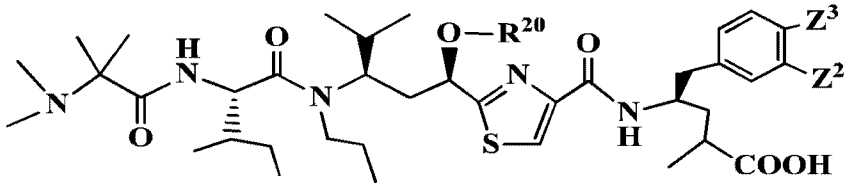

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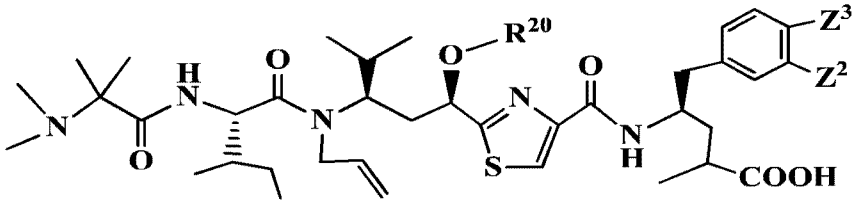

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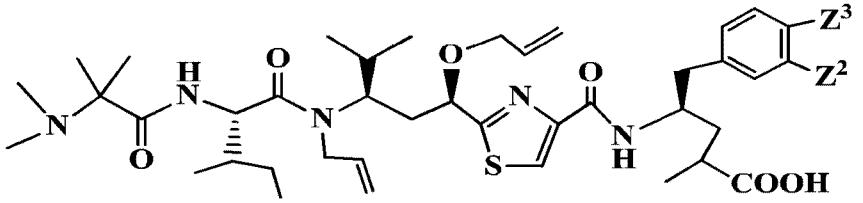

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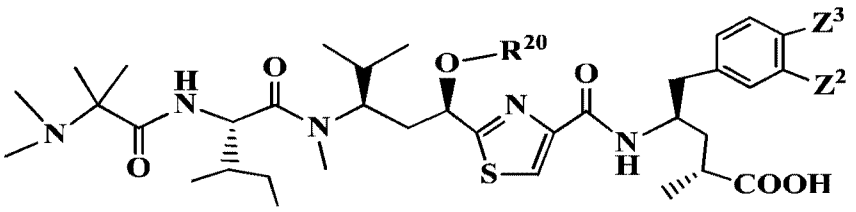
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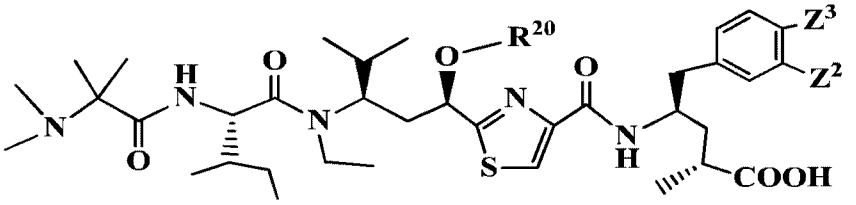
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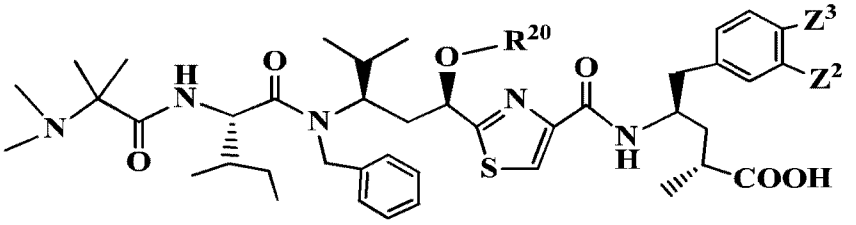
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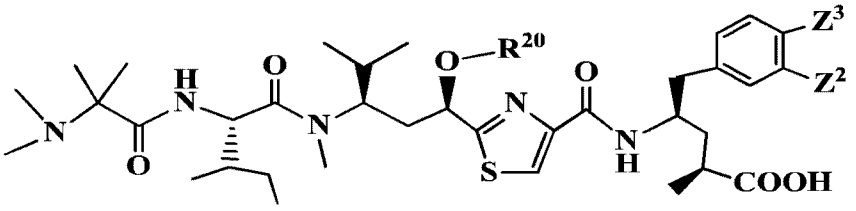
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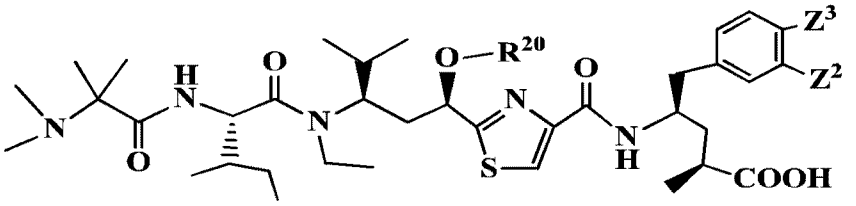
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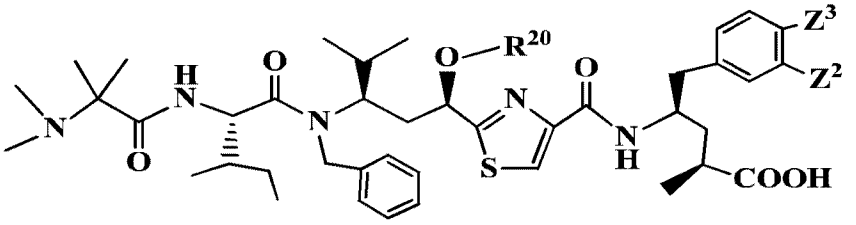
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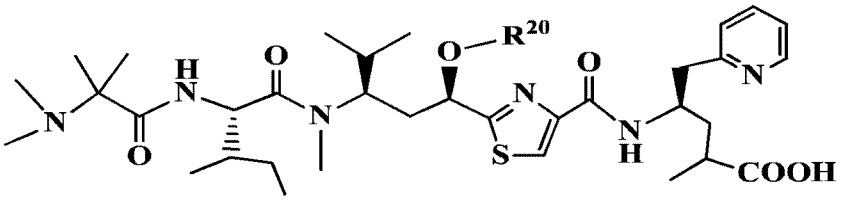
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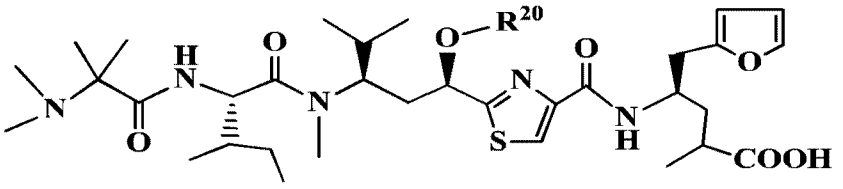
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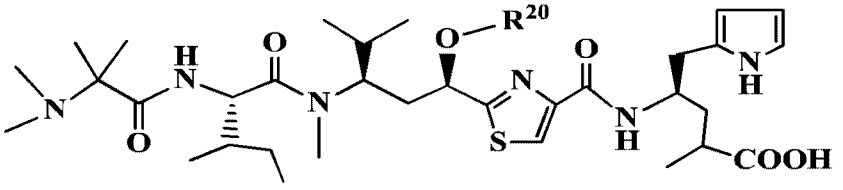
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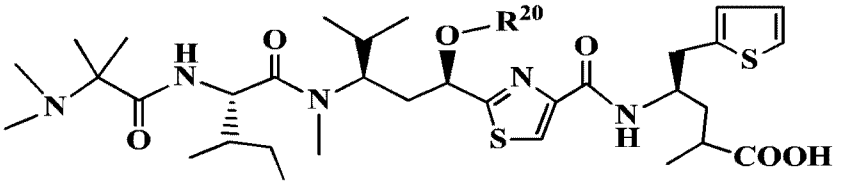
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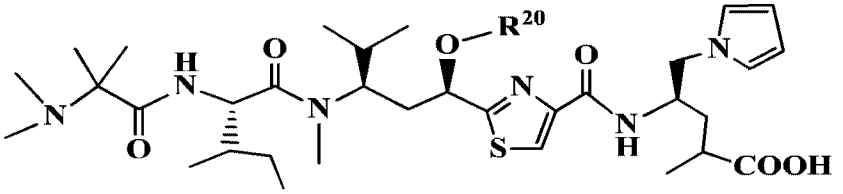
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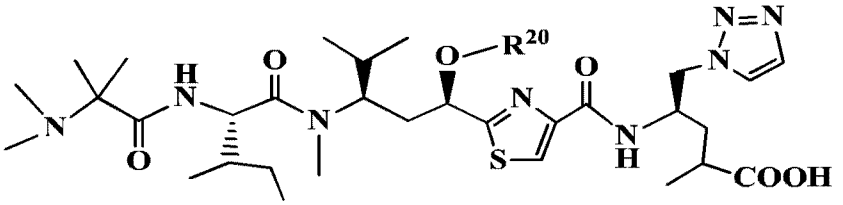
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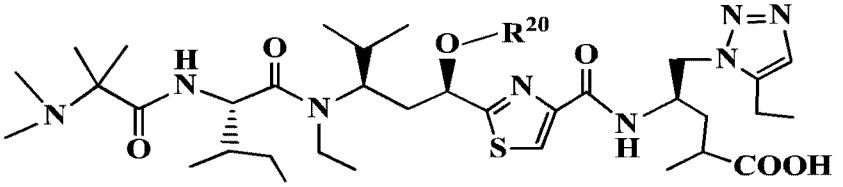
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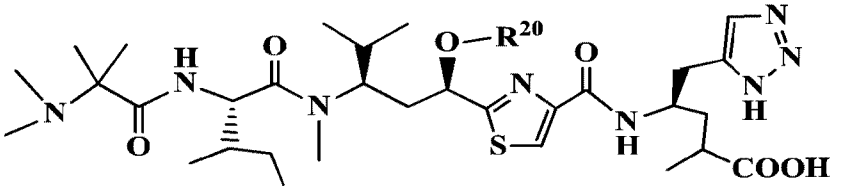
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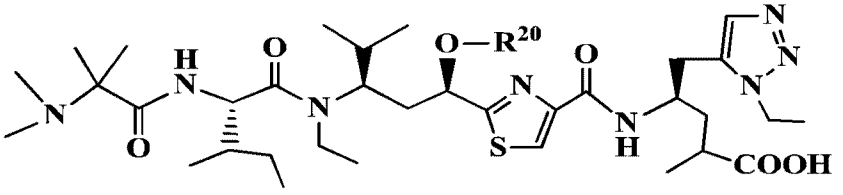
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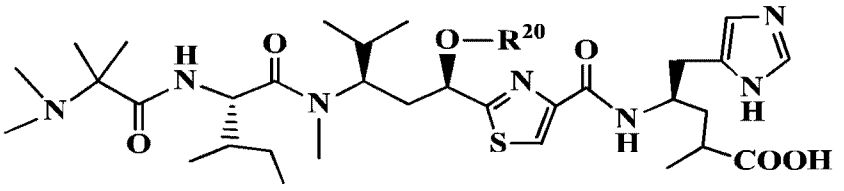
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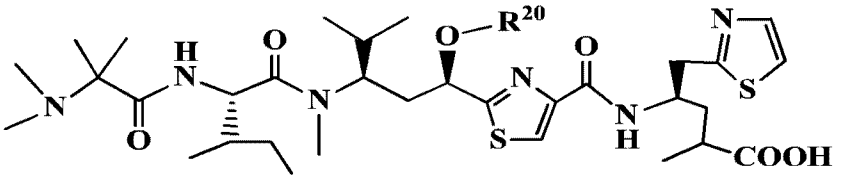
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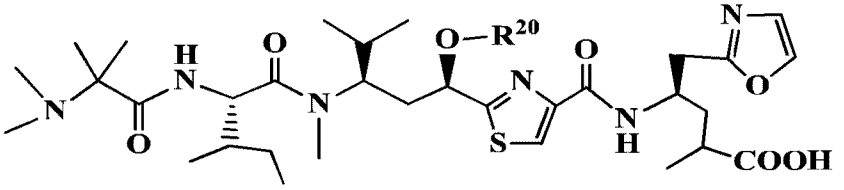
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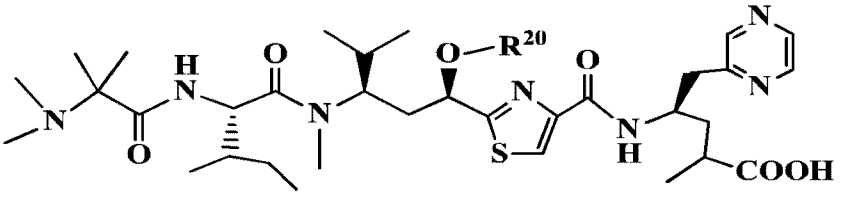
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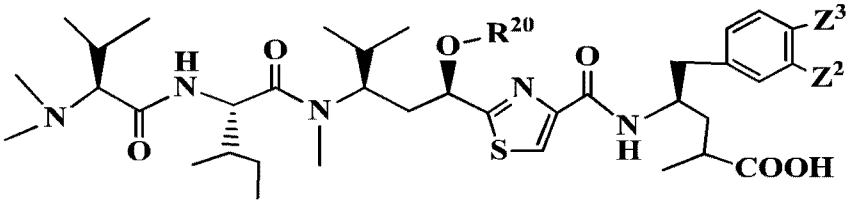
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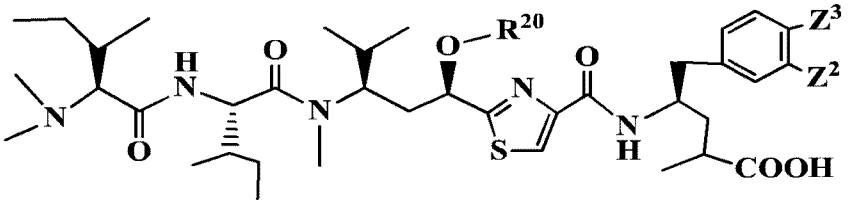
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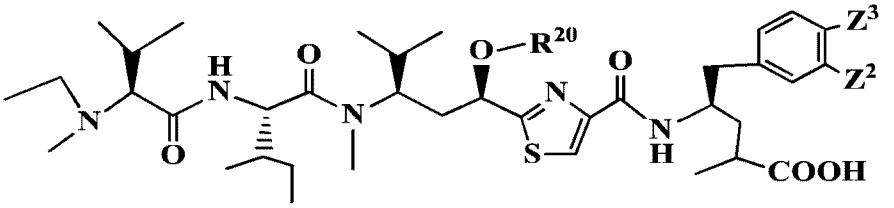
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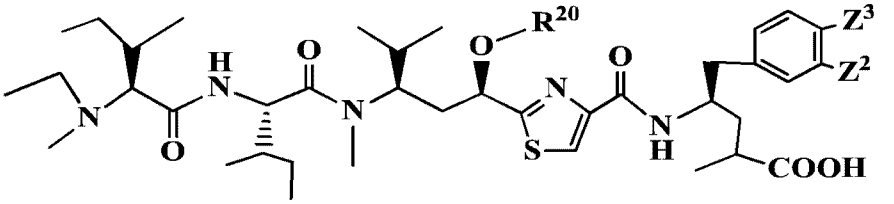
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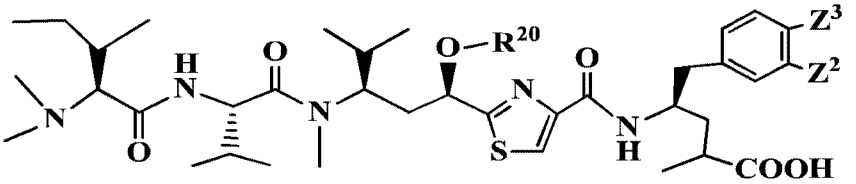
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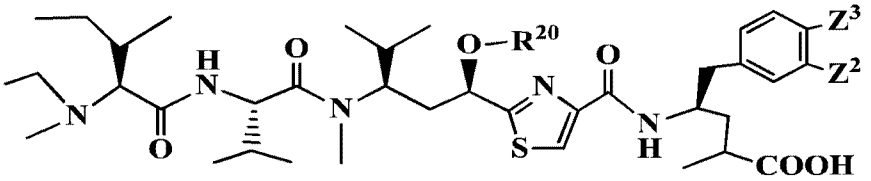
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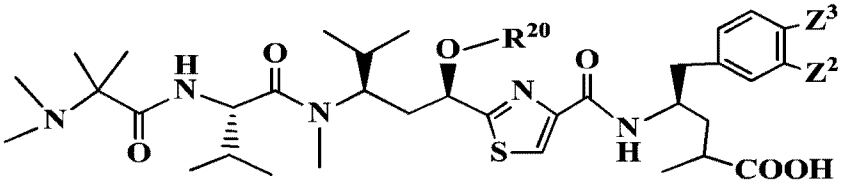
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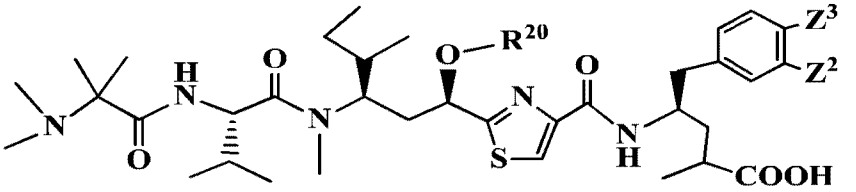
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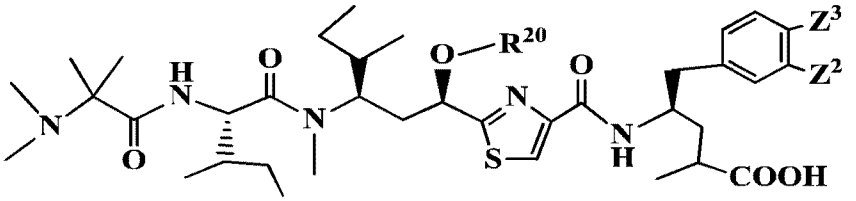
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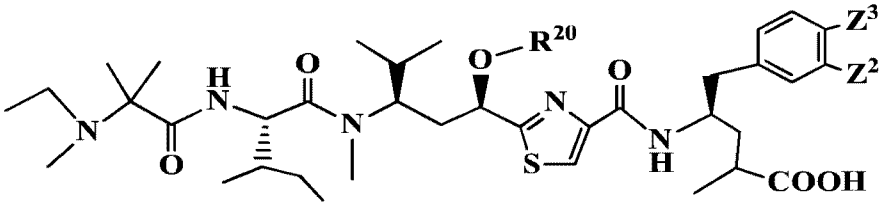
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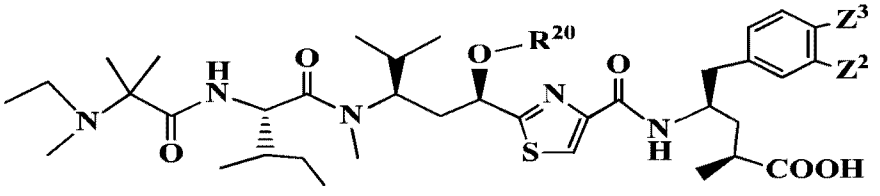
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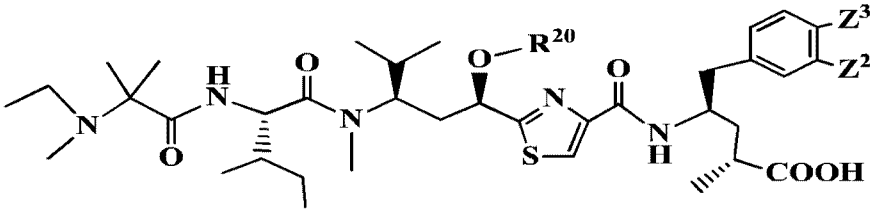
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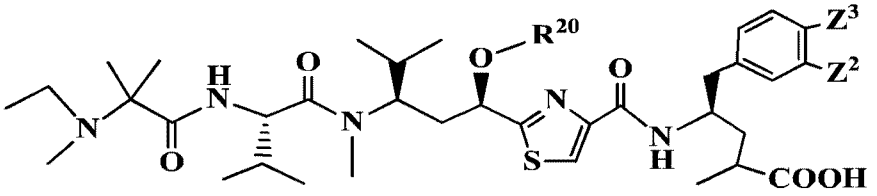
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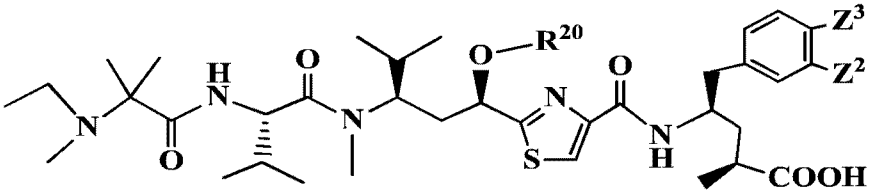
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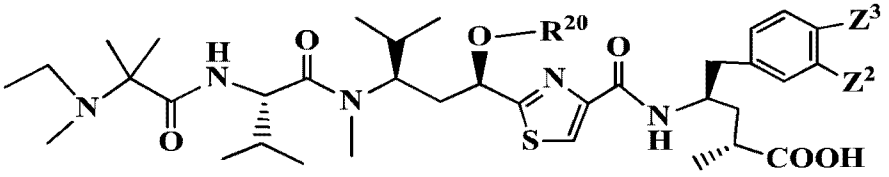
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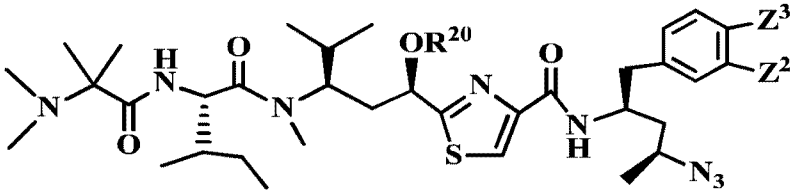
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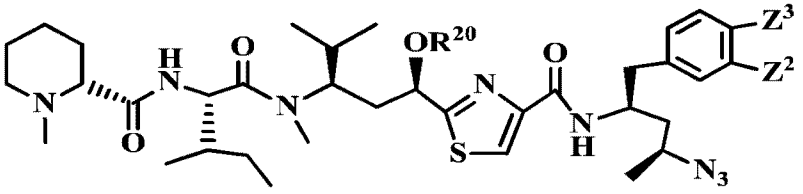
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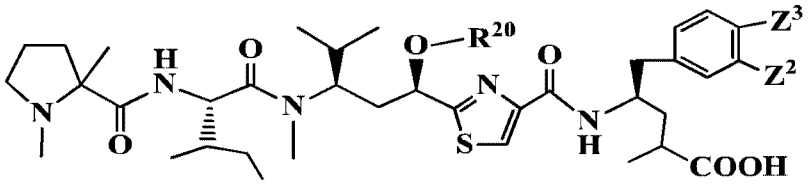
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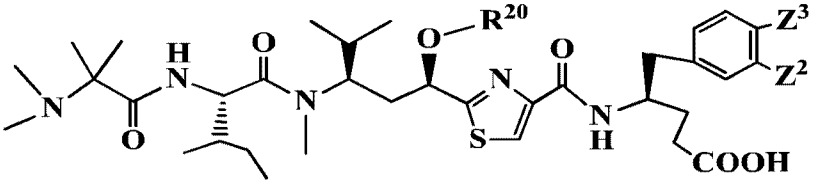
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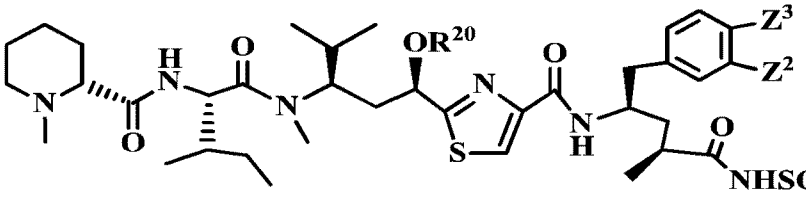
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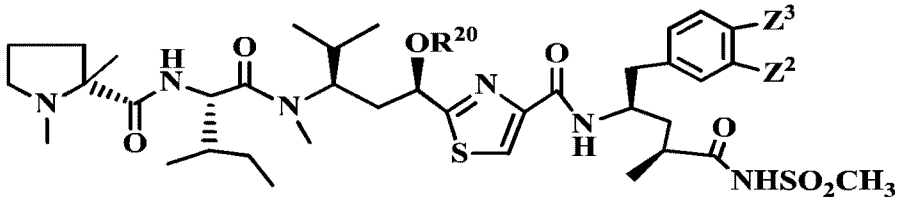
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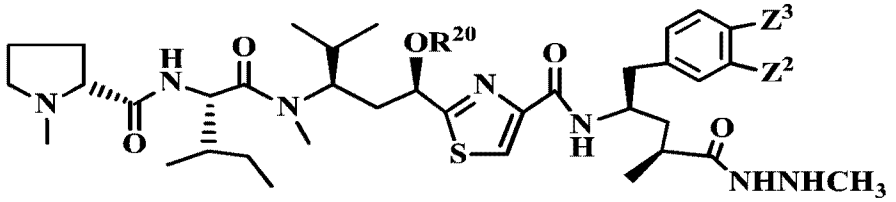
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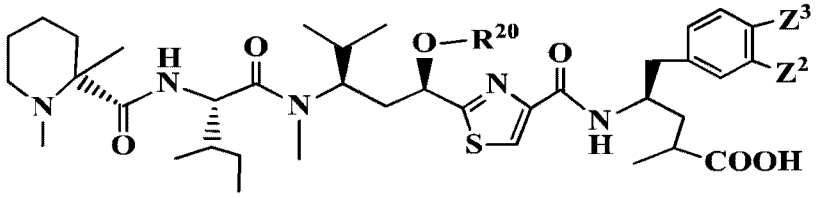
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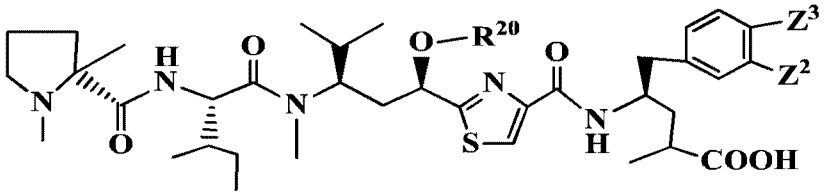
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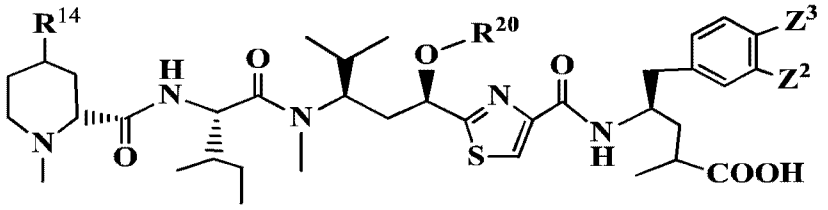
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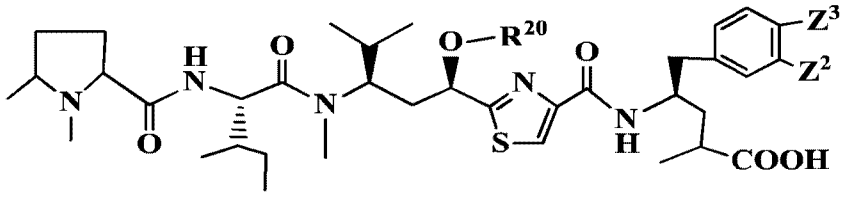
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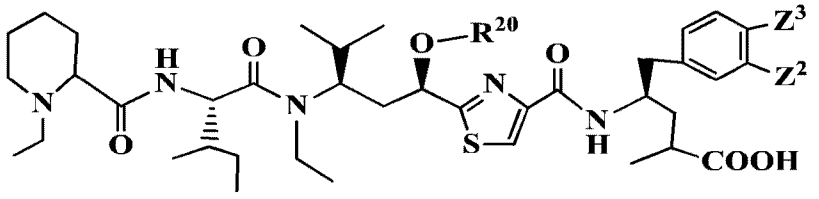
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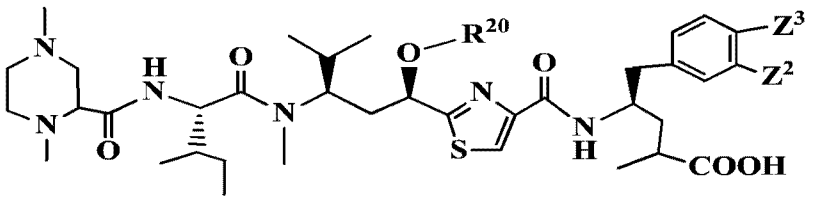
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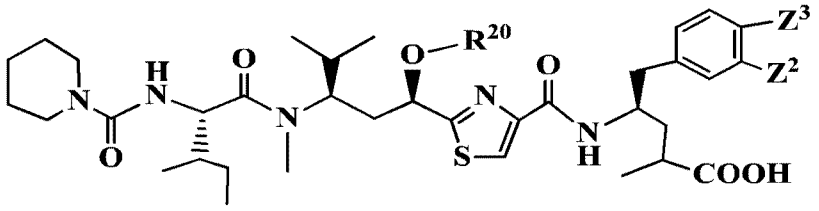
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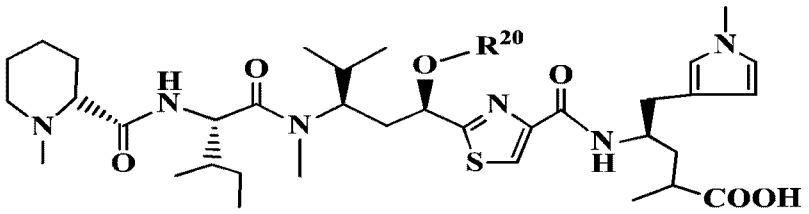
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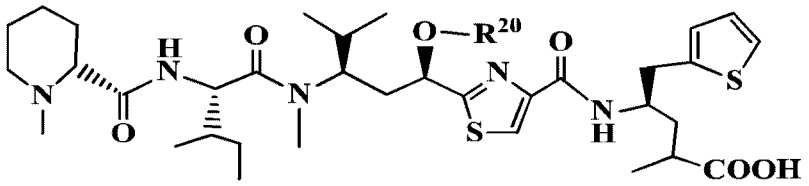
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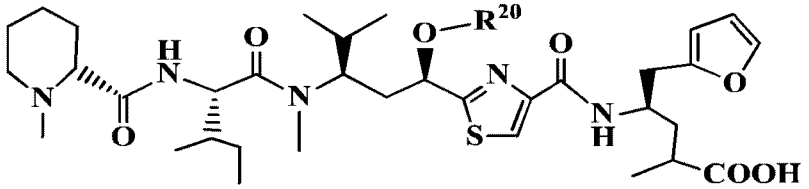
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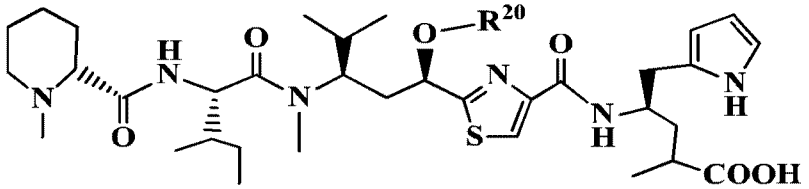
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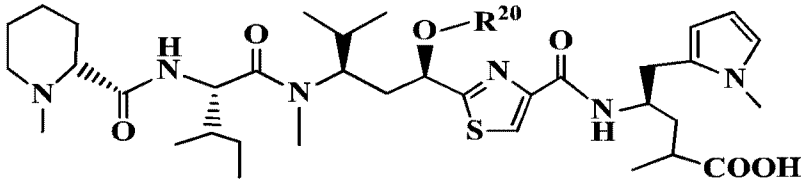
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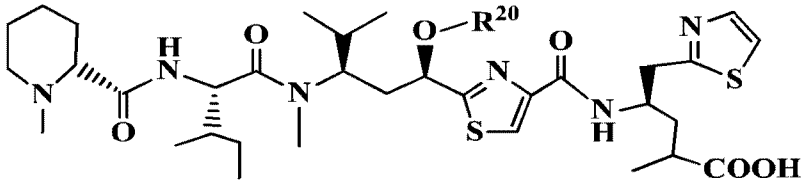
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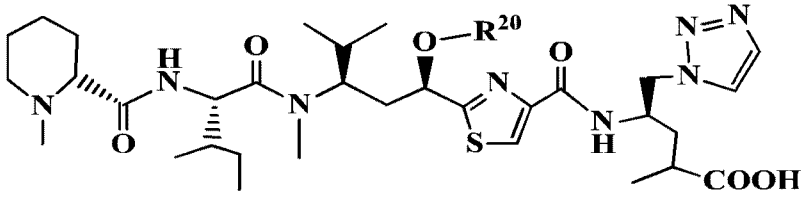
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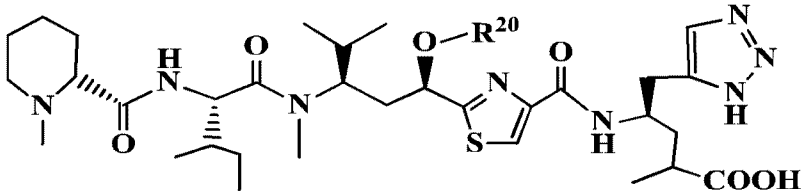
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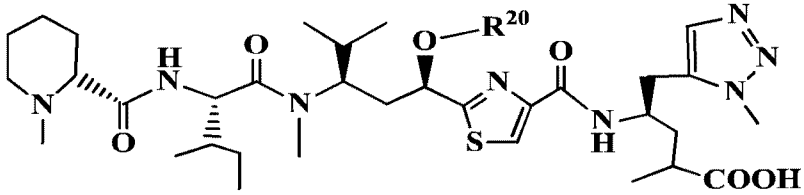
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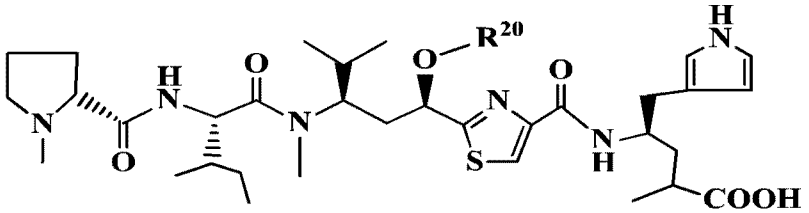
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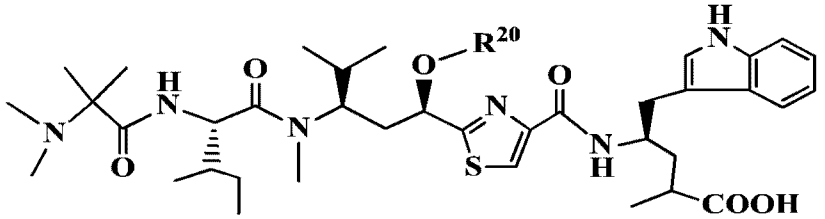
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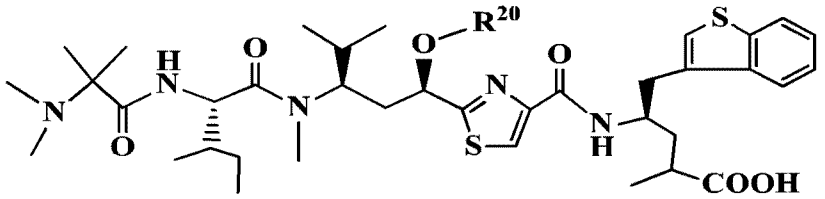
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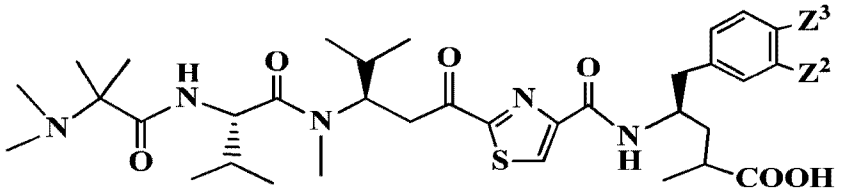
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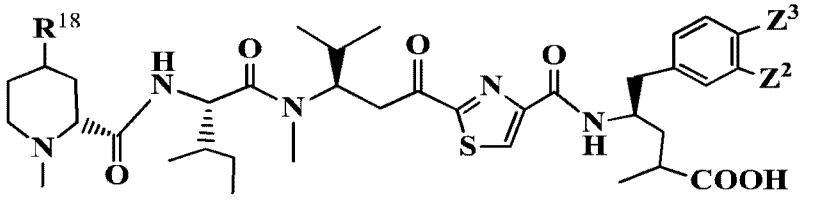
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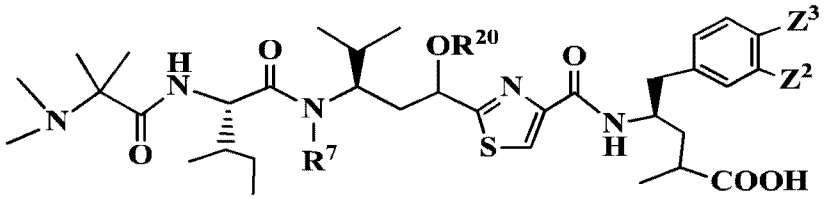
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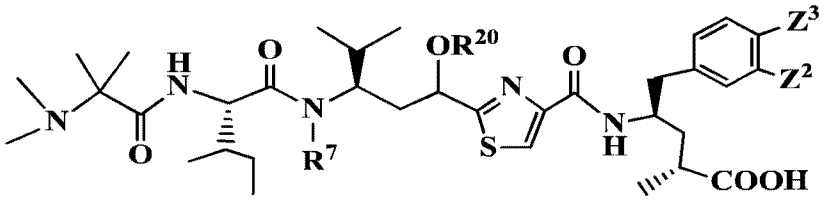
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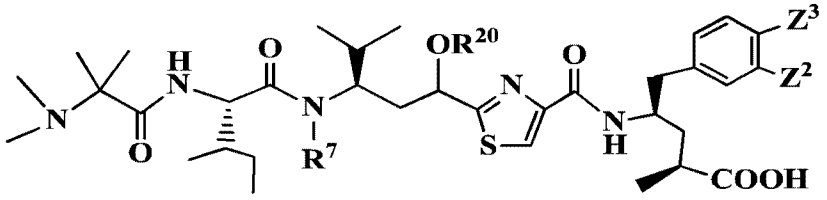
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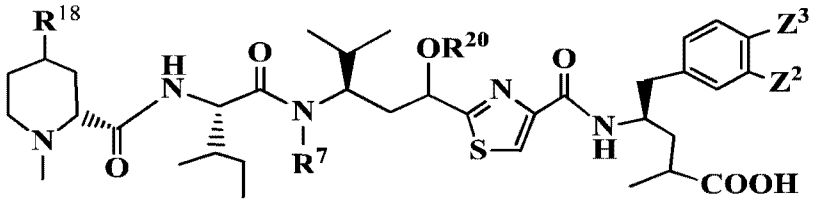
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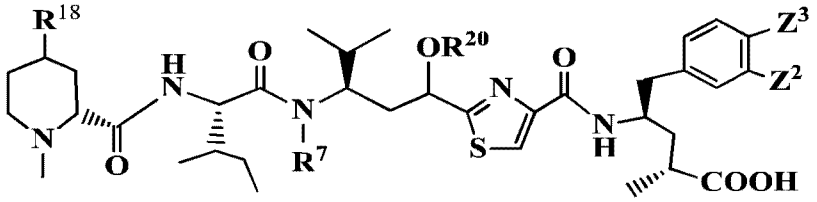
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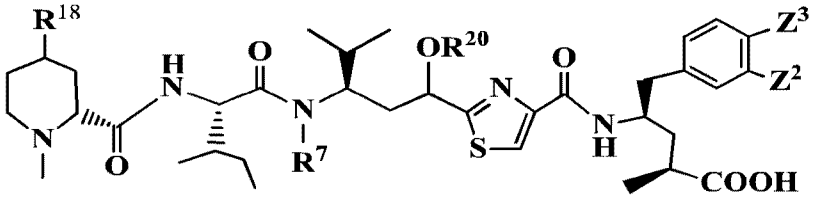
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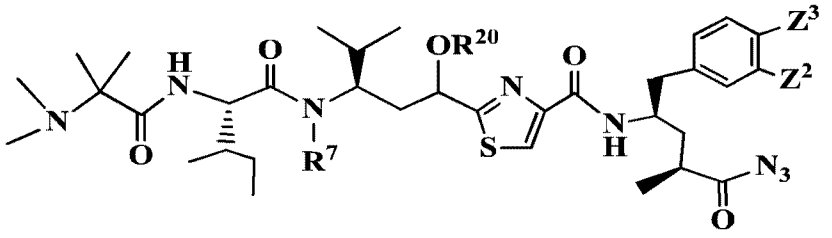

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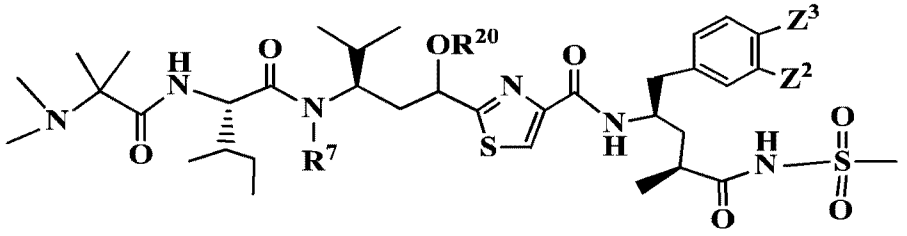

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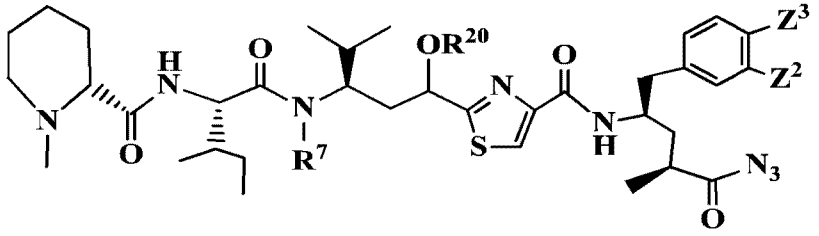

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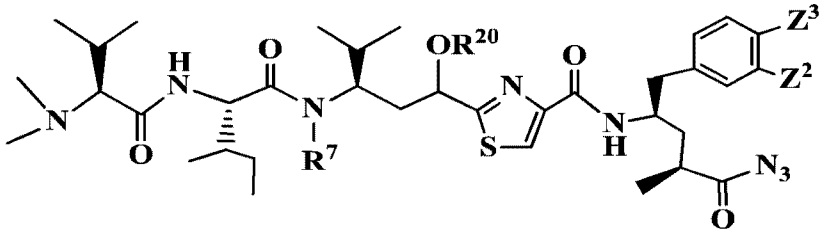

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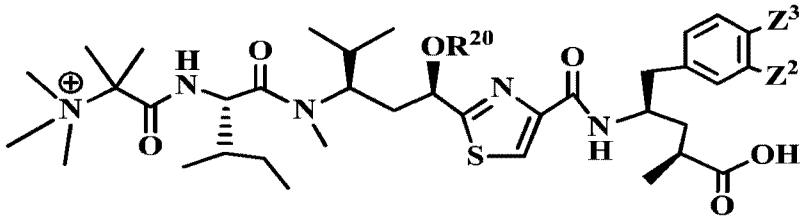

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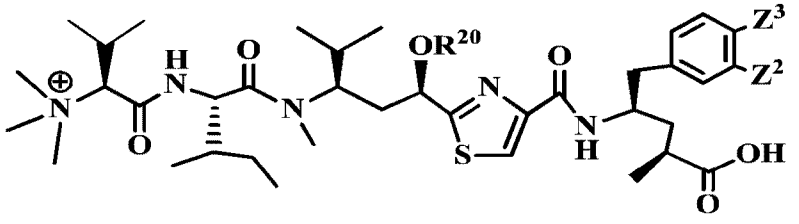

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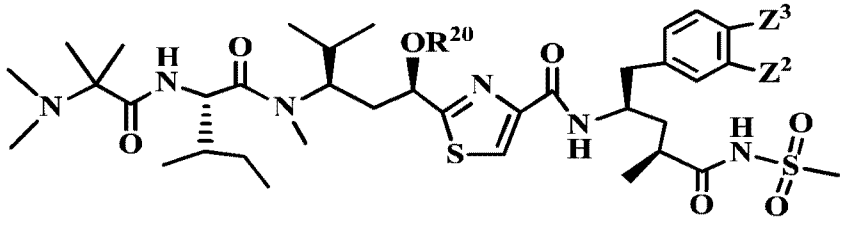

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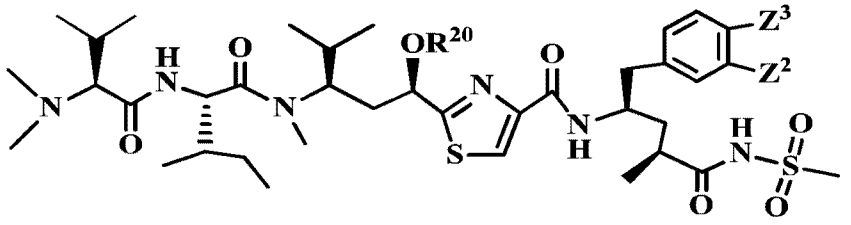
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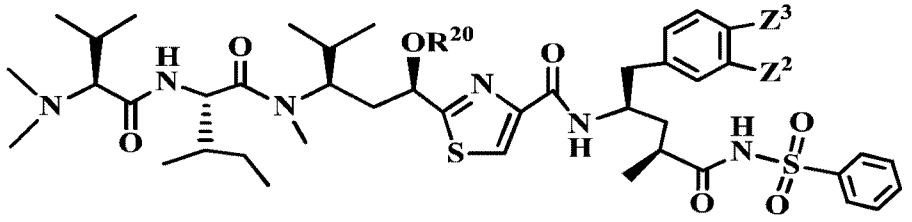
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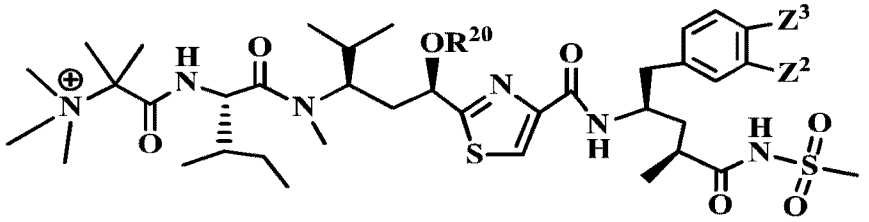
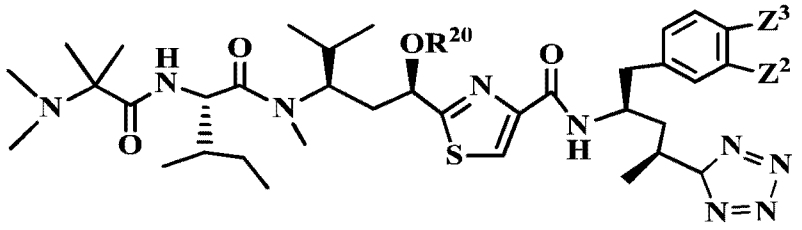
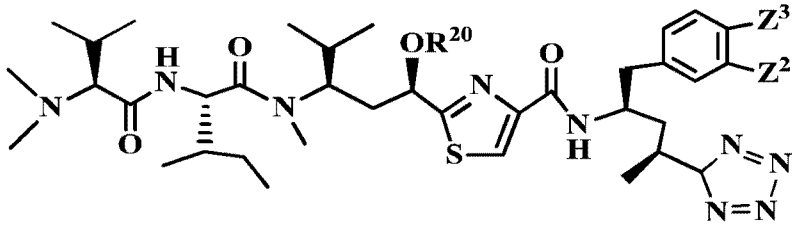
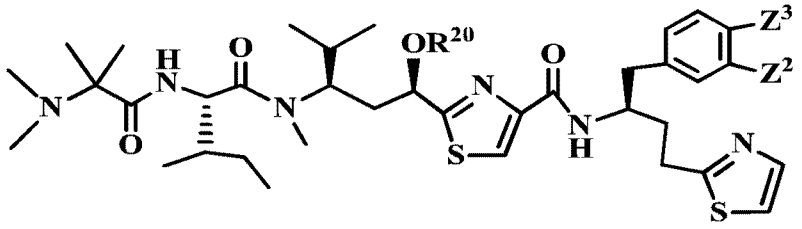
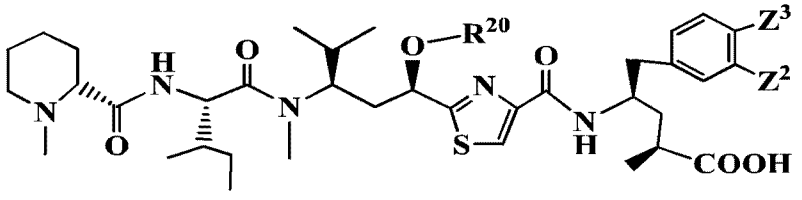
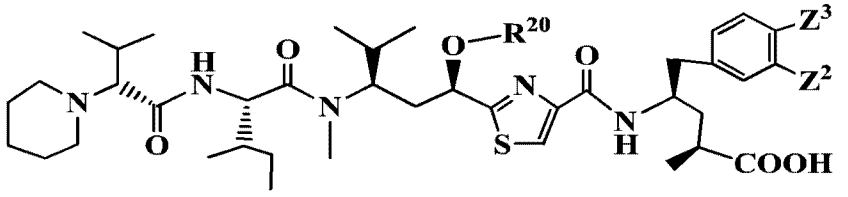

V-85,

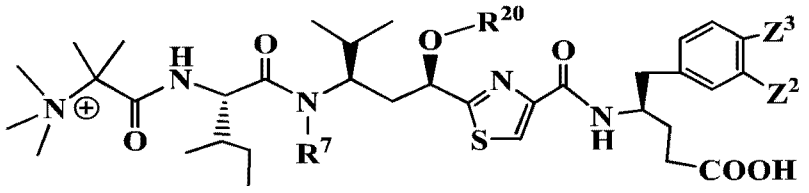

V-86,

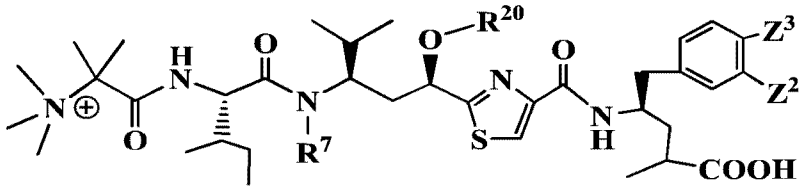

V-87,

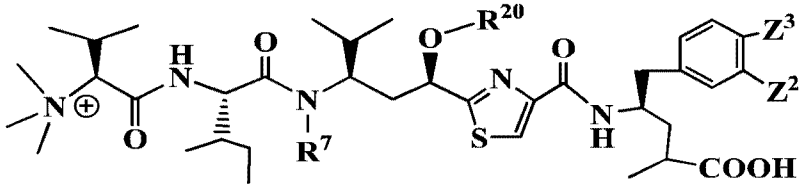

V-88,

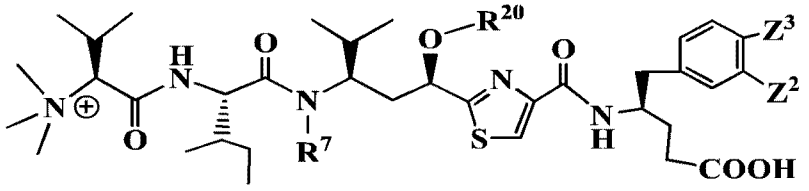

V-89,


V-90,


V-91,


V-92,

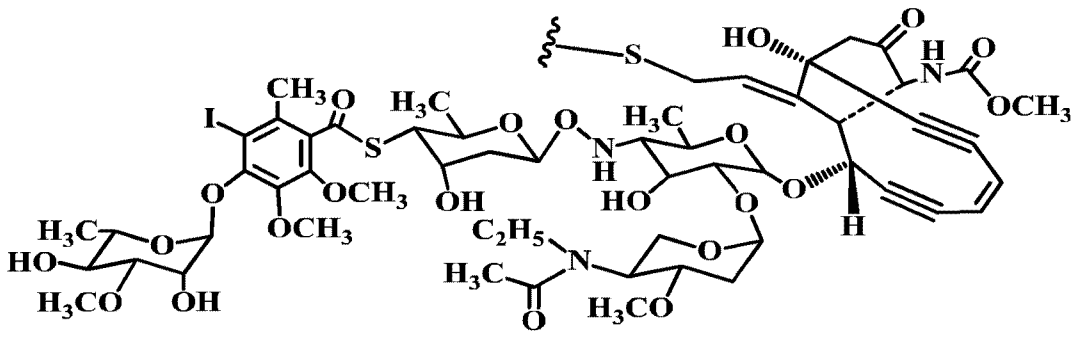

V-93,


V-94,

wherein R^{20} is H; C_1-C_8 of linear or branched alkyl or heteroalkyl; C_2-C_8 of linear or branched alkenyl, alkynyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 linear or branched of aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; carbonate (-$C(O)OR^{17}$), carbamate (-$C(O)NR^{17}R^{18}$); or 1-8 carbon atoms of carboxylate, esters, ether, or amide; or 1~8 amino acids; or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$ or $(OCH_2CH(CH_3))_p$, wherein p is an integer from 0 to about 1000; or R^{20} is absent and the oxygen forms a ketone, or combination above thereof; $Z^3$and Z^3 are independently H, OH, NH_2, O, NH, COOH, COO, C(O), C(O), C(O)NH, $C(O)NH_2$, R^{18}, $OCH_2OP(O)(OR^{18})_2$, $OC(O)OP(O)(OR^{18})_2$, $OPO(OR^{18})_2$, $NHPO(OR^{18})_2$, $OP(O)(OR^{18})OP(O)(OR^{18})_2$, $OC(O)R^{18}$, $OC(O)NHR^{18}$, $OSO_2(OR^{18})$, O-(C_4-C_{12}-glycoside), of linear or branched alkyl or heteroalkyl; C_2-C_8 of linear or branched alkenyl, alkynyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 linear or branched of aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; carbonate (-$C(O)OR^{17}$), carbamate (-$C(O)NR^{17}R^{18}$); $R^{17}$and R^{18} are independently H, linear or branched alkyl or heteroalkyl;

C_2-C_8 of linear or branched alkenyl, alkynyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 linear or branched of aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; carbonate (-C(O)OR^{17}), carbamate (-C(O)$NR^{17}R^{18}$); $R^{19}$is H, OH, NH_2, $OSO_2(OR^{18})$, $XCH_2OP(O)(OR^{18})_2$, $XPO(OR^{18})_2$, XC(O)OP(O)$(OR^{18})_2$, XC(O)R^{18}, XC(O)NHR^{18}, C_1~C_8 alkyl or carboxylate; C_2~C_8 alkenyl, alkynyl, alkylcycloalkyl, heterocycloalkyl; C_3~C_8 aryl or alkylcarbonyl; or pharmaceutical salts; X is O, S, NH, NHNH, or CH_2; R^7 is H, R^{14}, -$R^{14}C(=O)X^1R^{15}$; or -$R^{14}X^1R^{15}$; X^1 is O, S, S-S, NH, CH_2 or NR^{14}, wherein R^{14} and R^{15} are independently C_1~C_8 alkyl, heteroalkyl; C_2-C_8 of alkenyl, alkynyl, heteroalkyl, heterocycloalkyl; C_3-C_8 of aryl, Ar-alkyl; wherein the linkage sites, " ∿∿ " in formula IV-01- IV-94 are the same indication according to formula (IV).

Calicheamicins and their related enediyne antibiotics that are described in: Nicolaou, K. C. et al, Science 1992, 256, 1172-1178; Proc. Natl. Acad. Sci USA. 1993, 90, 5881-8), U.S. Patent Nos. 4, 970, 198; 5, 053, 394; 5, 108, 912; 5, 264, 586; 5, 384, 412; 5, 606, 040; 5, 712, 374; 5, 714, 586; 5, 739, 116; 5, 770, 701; 5, 770, 710; 5, 773, 001; 5, 877, 296; 6, 015, 562; 6, 124, 310; 8, 153, 768. Exemplary enediynes include, but are not limited to, calicheamicin, esperamicin, uncialamicin, dynemicin, and their derivatives. The structure of calicheamicins is preferred the following formula:

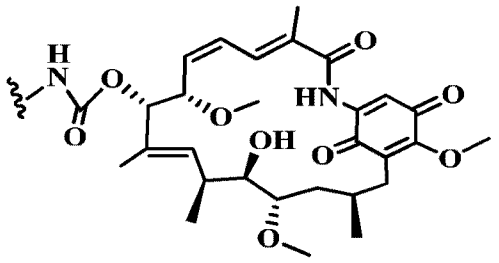


(Ia),

or an isotope of a chemical element, or a pharmaceutically acceptable salt, hydrates, or hydrated salt; or a polymorphic crystalline structure; or an optical isomer, racemate, diastereomer or enantiomer thereof,

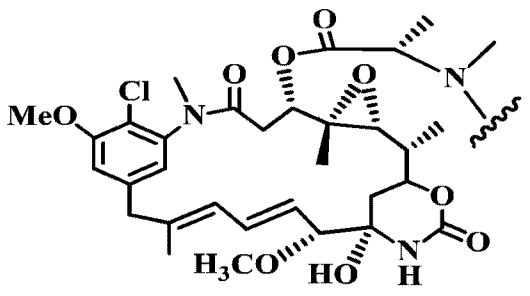
wherein ∿∿ is the site linked to L_1 or L_2;

Geldanamycins are benzoquinone ansamycin antibiotic that bind to Hsp90 (Heat Shock Protein 90) and have been used antitumor drugs. Exemplary geldanamycins include, but are not limited to, 17-AAG (17-N-Allylamino-17-Demethoxygeldanamycin) and 17-DMAG (17-dimethylamino-ethylamino-17-demethoxygeldanamycin). One of the geldanamycins structures is shown below:



wherein ~~~ is the site linked to L_1 or L_2.

Maytansines or their derivatives maytansinoids inhibit cell proliferation by inhibiting the mcirotubules formation during mitosis through inhibition of polymerization of tubulin. See Remillard et al., Science 189:1002-1005 (1975). Exemplary maytansines and maytansinoids include, but are not limited to, mertansines (DM1, DM4), maytansinol and its derivatives as well as ansamitocin. Maytansinoids are described in U.S. Patent Nos. 4, 256, 746, 4, 361, 650, 4, 307, 016, 4, 294, 757, 4, 294, 757, 4, 371, 533, 4, 424, 219, 4, 331, 598, 4, 450, 254, 4, 364, 866, 4, 313, 946, 4, 315, 929 4, 362, 663, 4, 322, 348, 4, 371, 533, 4, 424, 219, 5, 208, 020, 5, 416, 064, 5, 208, 020; 5, 416, 064; 6, 333.410; 6, 441, 163; 6, 716, 821, 7, 276, 497, 7, 301, 019, 7, 303, 749, 7, 368, 565, 7, 411, 063, 7, 851, 432, and 8, 163, 888. The structure of maytansinoids is preferred the following formula:



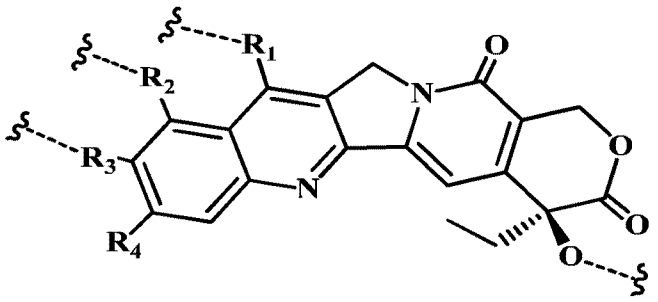
(Ib),

wherein ~~~ is the site linked to L_1 or L_2.

A camptothecin (CPTs) and its derivatives, which are topoisomerase inhibitors to prevent DNA re-ligation and therefore to causes DNA damage resulting in apoptosis, are described in: Shang, X. F. et al, Med Res Rev. 2018, 38(3):775-828; Botella, P. and Rivero-Buceta, E. J Control Release. 2017, 247: 28-54; Martino, E. et al, Bioorg Med Chem Lett. 2017, 27(4):701-707; Lu, A., et al, Acta Pharmacol Sin 2007, 28(2): 307–314. It includes SN-38, Topotecan, Irinotecan (CPT-11), Silatecan (DB-67, AR-67), Cositecan (BNP-1350), Etirinotecan, Exatecan, Lurtotecan, Gimatecan (ST1481), Belotecan (CKD-602), Rubitecan and several others (Shang, X. F. et al, Med Res Rev. 2018, 38(3):775-828). So far three CPT analogues, topotecan, irinotecan, and belotecan, have been approved and are used in cancer chemotherapy (Palakurthi, S., Expert Opin Drug Deliv. 2015;12(12):1911-21; Shang, X. F. et al, Med Res Rev. 2018, 38(3):775-828) and both SN-38 and Exatecan have been successfully used as payloads for ADC conjugates in the clinical trials (Ocean, A. J. et al, Cancer. 2017, 123(19): 3843-3854; Starodub, A. N., et al, Clin Cancer Res. 2015, 21(17):

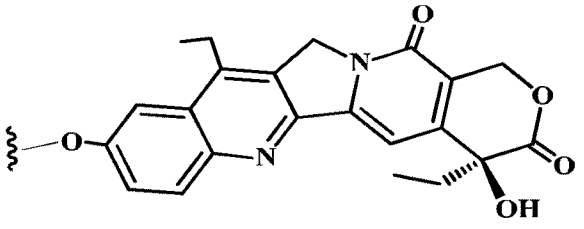
3870-8; Cardillo, T. M., et al, Bioconjug Chem. 2015, 26(5): 919-31; Ogitani, Y. et al, Bioorg Med Chem Lett. 2016, 26(20): 5069-5072; Takegawa, N. et al, Int J Cancer. 2017 Oct 15;141(8):1682-1689. US patents 7, 591, 994; 7, 999, 083, 8, 080, 250, 8, 268, 317; US patent applications 20130090458, 20140099258, 20150297748, 20160279259).

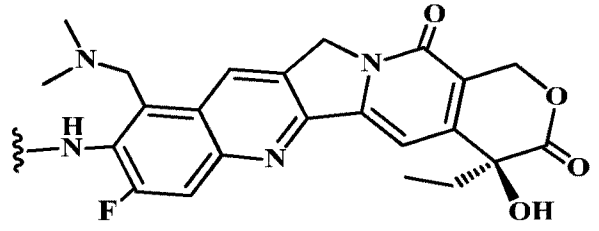
The structure of Camptothecin (CPT) is illustrated below formula:

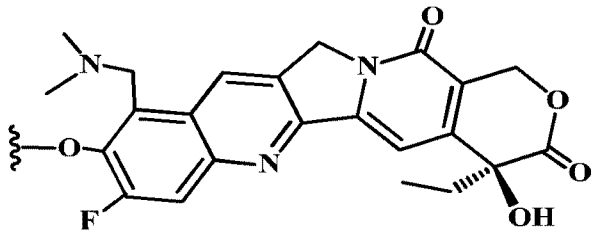

(Ic)

or an isotope of one or more chemical elements, or pharmaceutically acceptable salts, hydrates, or hydrated salts; or the polymorphic crystalline structures of these compounds; or the optical isomers, racemates, diastereomers or enantiomers; wherein R_1, R_2 and R_4 are independently selected from H, F, Cl, Br, CN, NO_2, C_1~C_8 alkyl; O-C_1~C_8 alkyl; NH-C_1~C_8 alkyl; C_2-C_8 of heteroalkyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 of aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; or 2-8 carbon atoms of esters, ether, amide, carbonate, urea, or carbamate; R_3 is H, OH, NH_2, C_1~C_8 alkyl; O-C_1~C_8 alkyl; NH-C_1~C_8 alkyl; C_2-C_8 of heteroalkyl, alkylcycloalkyl, heterocycloalkyl; or 2-8 carbon atoms of esters, ether, amide, carbonate, urea, or carbamate; or R_1R_2, R_2R_3 and R_3R_4 independently form a 5~7 membered carbocyclic, heterocyclic, heterocycloalkyl, aromatic or heteroaromatic ring system; ∿∿ is the site in the molecule that can be linked to L_1 or L_2.

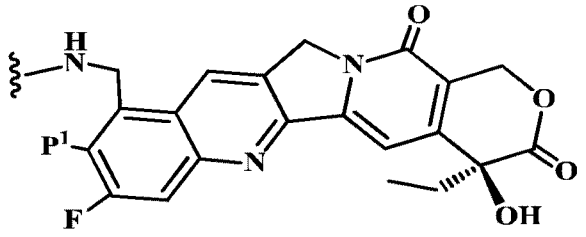
The structures of camptothecins are preferred the following formula:


(Ic-01), SN-38,

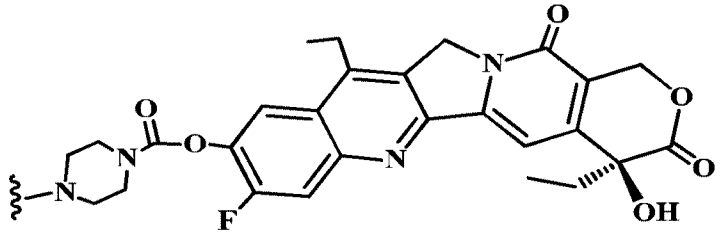

(Ic-02)



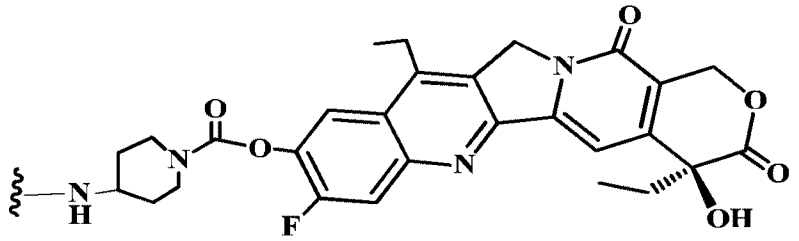
(Ic-03), Topotecan analog,



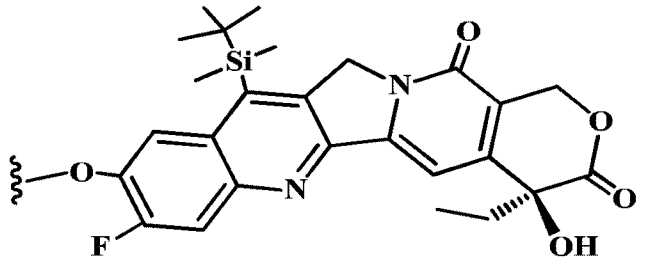
(Ic-04),



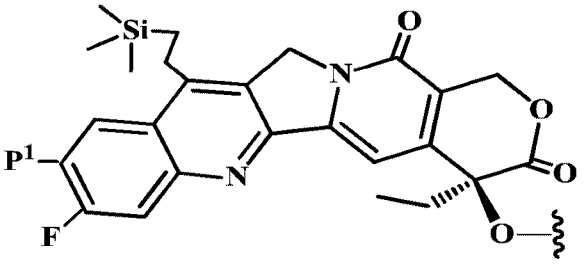
(Ic-05), Irinotecan analog,



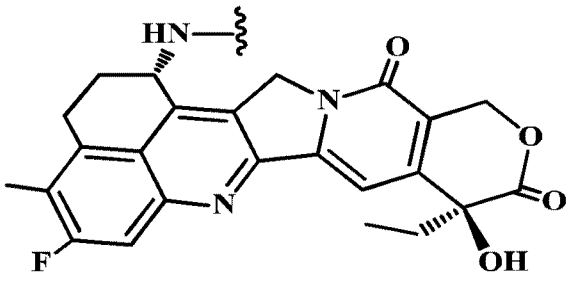
(Ic-06), Irinotecan analog,



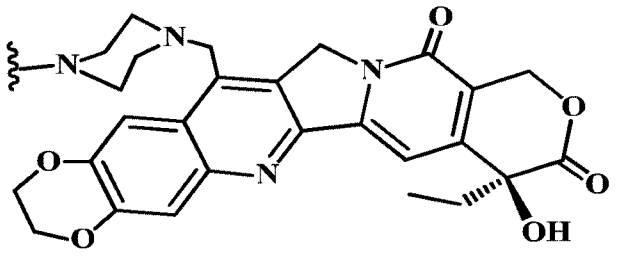
(Ic-07), Silatecan analog,



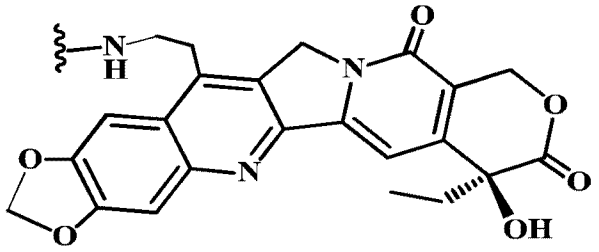
(Ic-08), Cositecan, analog



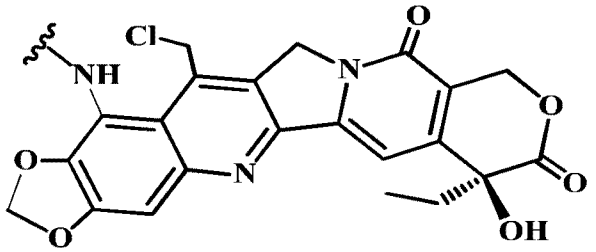
(Ic-09), Exatecan,



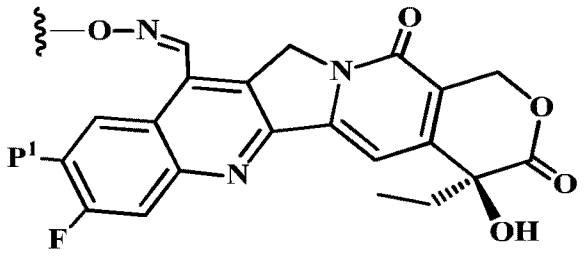
(Ic-10), Lurtotecan,



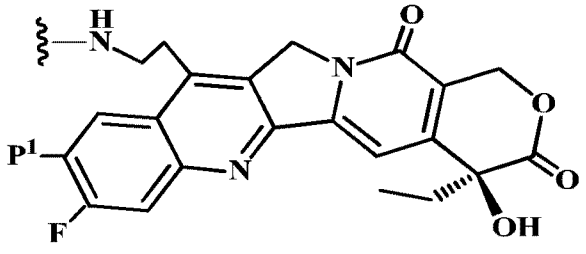
(Ic-11),



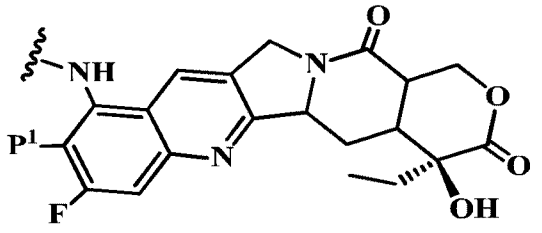
(Ic-12), GI-149893 analog,



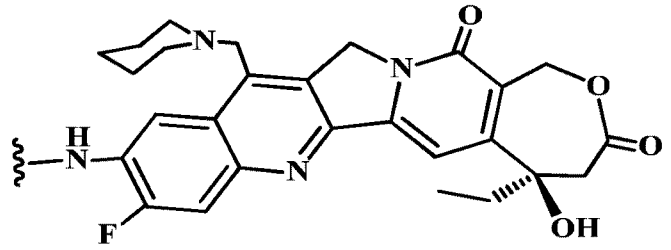
(Ic-13), Gimatecan analog,



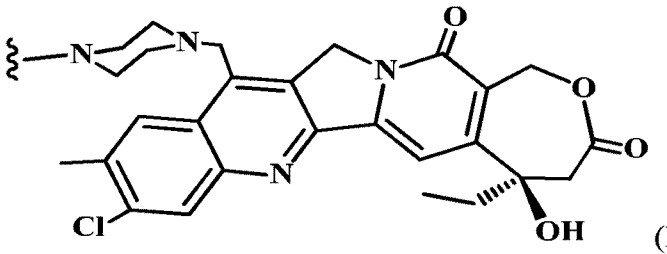
(Ic-14), Belotecan analog,



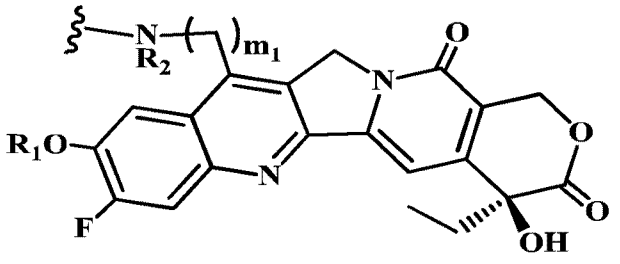
(Ic-15), Rubitecan or IDEC-132 analog, ,



(Ic-16), BN-80927 analog,



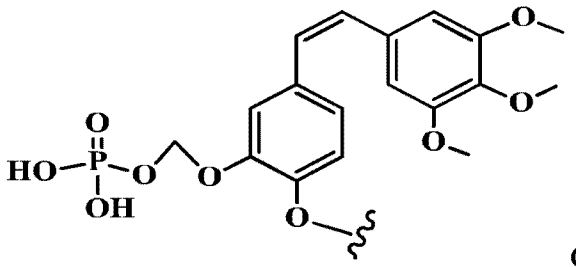
(Ic-17), BN-80927 analog,



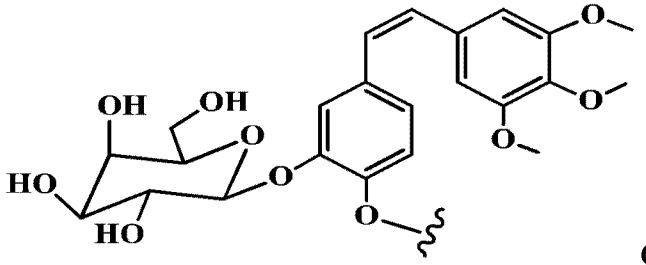
(Ic-18),

or an isotope of one or more chemical elements, or pharmaceutically acceptable salts, hydrates, or hydrated salts; or the polymorphic crystalline structures of these compounds; or the optical isomers, racemates, diastereomers or enantiomers; wherein ~~~ is the site linked to L_1, L_1', L_2 or L_2'; P^1 is H, OH, NH_2, COOH, $C(O)NH_2$, $OCH_2OP(O)(OR^{18})_2$, $OC(O)OP(O)(OR^{18})_2$, $OPO(OR^{18})_2$, $NHPO(OR^{18})_2$, $OC(O)R^{18}$, $OP(O)(OR^{18})OP(O)(OR^{18})_2$, $OC(O)NHR^{18}$, $OC(O)N(C_2H_4)_2NCH_3$, $OSO_2(OR^{18})$, O-(C_4-C_{12}-glycoside), $OC(O)N(C_2H_4)_2CH_2N(C_2H_4)_2CH_3$, O-($C_1$-$C_8$ of linear or branched alkyl), C_1-C_8 of linear or branched alkyl or heteroalkyl; C_2-C_8 of linear or branched alkenyl, alkynyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 linear or branched of aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; carbonate (-$C(O)OR^{17}$), carbamate (-$C(O)NR^{17}R^{18}$); $R^{17}$and R^{18} are independently H, linear or branched alkyl or heteroalkyl; C_2-C_8 of linear or branched alkenyl, alkynyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 linear or branched of aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl;

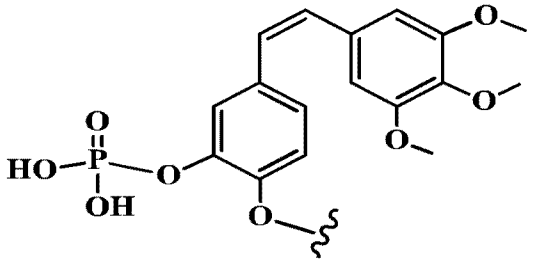
Combretastatins are natural phenols with vascular disruption properties in tumors. Exemplary combretastatins and their derivatives include, but are not limited to, combretastatin A-4 (CA-4), CA4-βGals, CA-4PD, CA4-NPs and ombrabulin.



CA-01

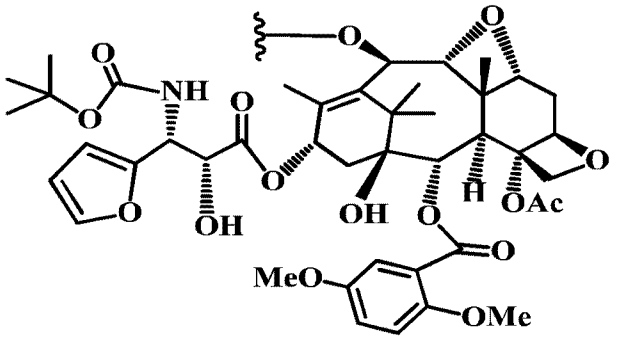


CA-02 (CA4-βGal),

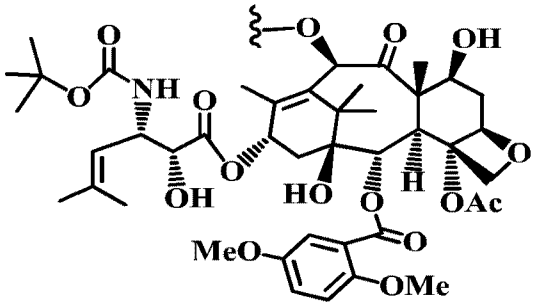


CA-03,

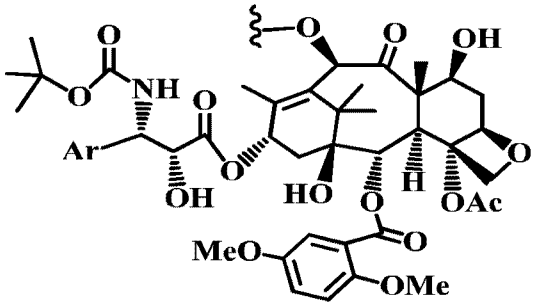
~~~ is a site in the molecule that can be linked to L_1, L_1', L_2 or L_2';

Taxanes, which includes Paclitaxel (Taxol), a cytotoxic natural product, and docetaxel (Taxotere), a semi-synthetic derivative, and their analogs which are preferred for conjugation are exampled in: K C. Nicolaou et al., J. Am. Chem. Soc. 117, 2409-20, (1995); Ojima et al, J. Med. Chem. 39:3889-3896 (1996); 40:267-78 (1997); 45, 5620-3 (2002); Ojima et al., Proc. Natl. Acad. Sci., 96:4256-61 (1999); Kim et al., Bull. Korean Chem. Soc., 20, 1389-90 (1999); Miller, et al. J. Med. Chem., 47, 4802-5 (2004); U.S. Patent No. 5, 475, 011 5, 728, 849, 5, 811, 452; 6, 340, 701; 6, 372, 738; 6, 391, 913, 6.436, 931; 6, 589, 979; 6, 596, 757; 6, 706, 708; 7, 008, 942; 7, 186, 851; 7, 217, 819; 7, 276, 499; 7, 598, 290; and 7, 667, 054. The structures of taxanes are preferred the following formula:
~~~



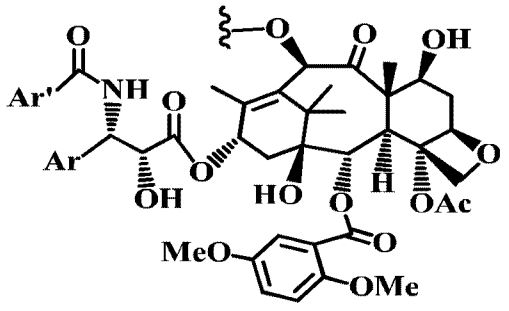
(Id-01),



(Id-02),



(Id-03),

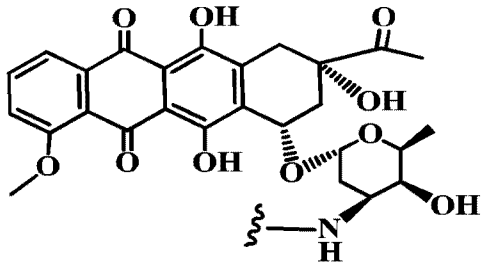


(Id-04),

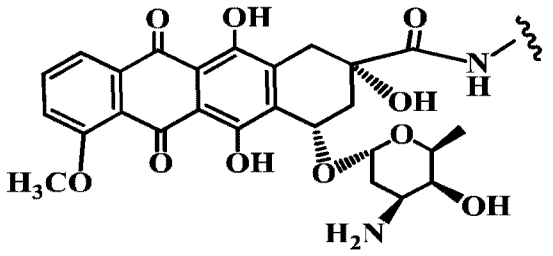
wherein ~~~ is the site linked to L_1 or L_2; Ar and Ar' are independently aryl or heteroaryl.

Anthracyclines are mammalian DNA topoisomerases II inhibitors that are able to stabilize enzyme-DNA complexes wherein DNA strands are cut and covalently linked to the antibody-like protein. These anticancer agents maintain a prominent role in treating many forms of solid tumors and acute leukemias during the last several decades. However, anthracyclines cause cardiovascular morbidity and mortality (Sagi, J. C., et al, Pharmacogenomics. 2016, 17(9), 1075-87; McGowan, J. V., et al, Cardiovasc Drugs Ther. 2017, 31(1), 63-75). Thus, to enhance specific activity of such molecules while reducing the cardiotoxicity, researchers actively are using the conjugation of

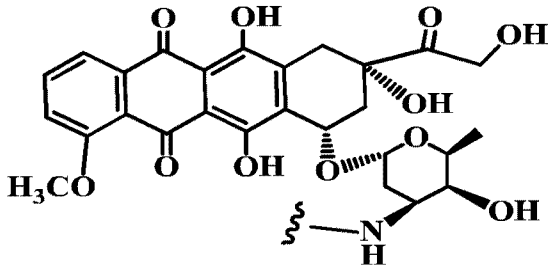
anthracyclines to a cell-binding antibody, or antibody-like protein molecule as a general approach for improving the therapeutic index of these drugs, (Mollaev, M. et al, Int J Pharm. 2018 Dec 29. pii: S0378-5173(18) 30991-8; Rossin, R., et al, Bioconjug Chem. 2016, 27(7):1697-706; Dal Corso, A., et al, J Control Release. 2017, 264:211-218). Exemplary anthracyclines include, but are not limited to, daunorubicin, doxorubicin (i.e., adriamycin), epirubicin, idarubicin, valrubicin, and mitoxantrone. The structures of anthracyclines used for the present application are preferred the following formula:



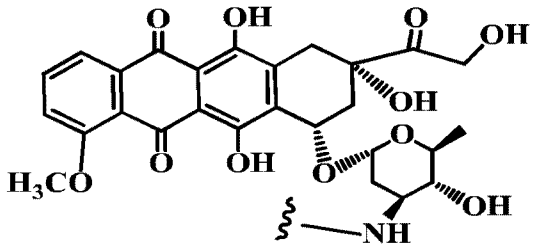
(Ie-01), Daunorubicin analog,



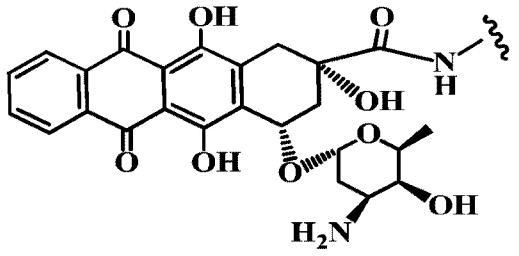
(Ie-02), Daunorubicin analog,



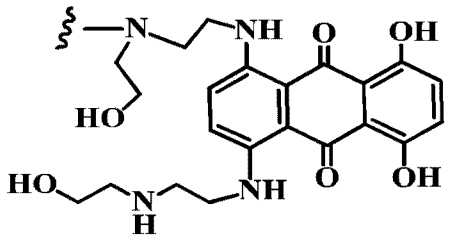
(Ie-03), Doxorubicin analog,



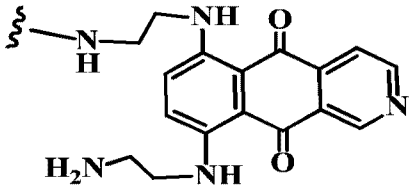
(Ie-04), Epirubicin analog,



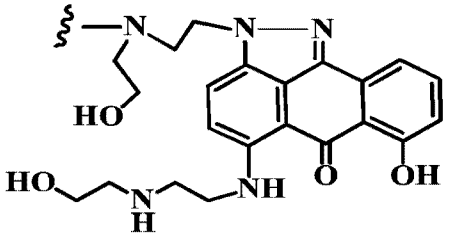
(Ie-05), Idarubicin analog,



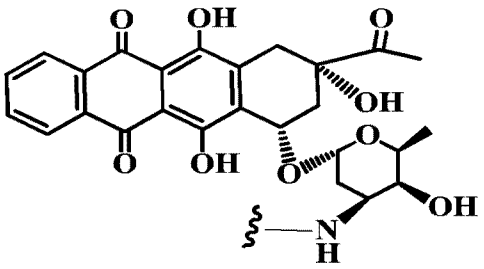
(Ie-06), Mitoxantrone analog,



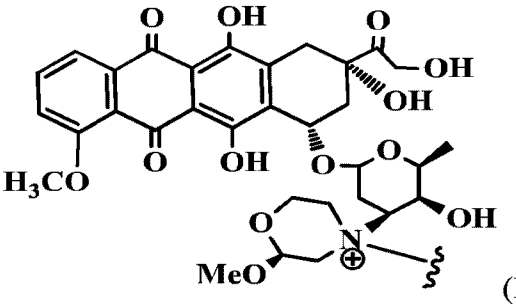
(Ie-07), Pixantrone analog,



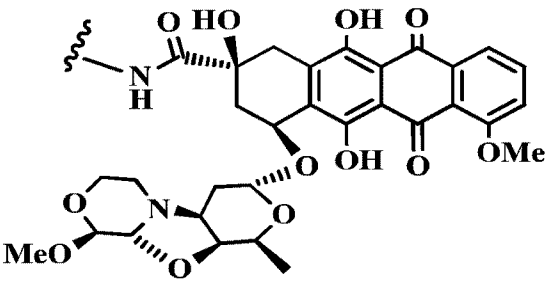
(Ie-08), Losoxantrone analog,



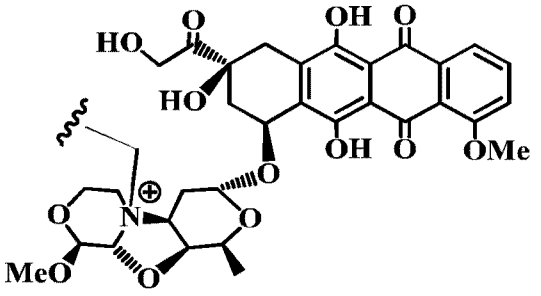
(Ie-09), analog,



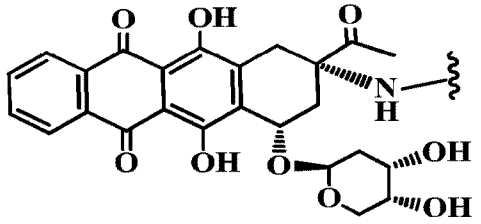
(Ie-10),



(Ie-11),



(Ie-12),

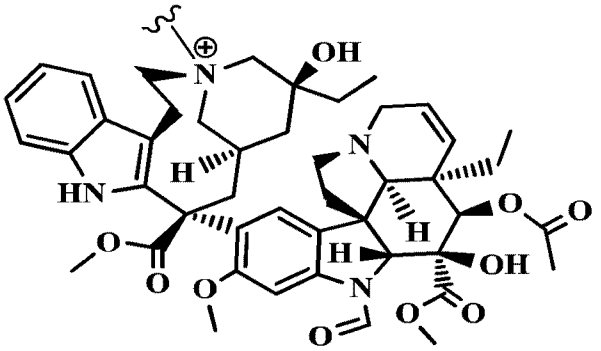


(Ie-13), Amrubicin analog.

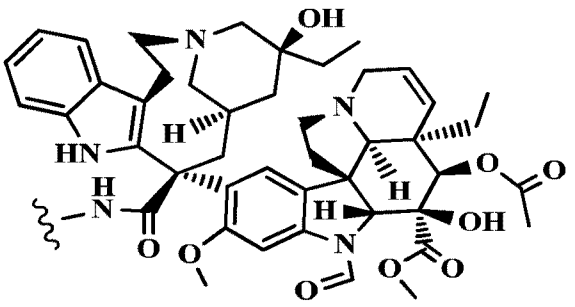
wherein ~~~ is the site that links to L_1 or L_2.

Vinca alkaloids are a set of anti-mitotic and anti-microtubule alkaloid agents that work by inhibiting the ability of cancer cells to divide. Vinca alkaloids include vinblastine, vincristine,

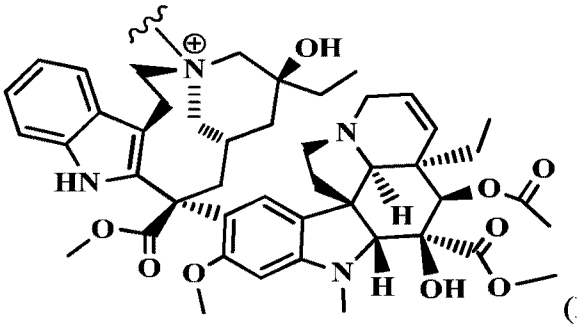
vindesine, leurosine, vinorelbine, catharanthine, vindoline, vincaminol, vineridine, minovincine, methoxyminovincine, minovincinine, vincadifformine, desoxyvincaminol, vincamajine, vincamine, vinpocetine, and vinburnine. The structures of vinca alkaloids are preferred vinblastine, vincristine having the following formula:



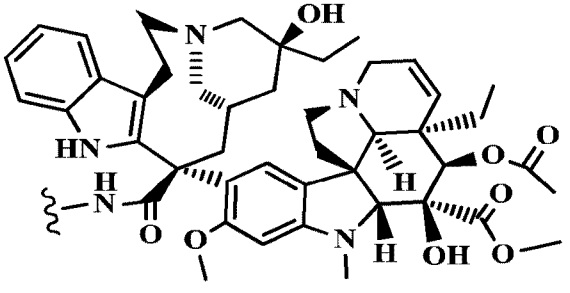
(If-01), vincristine (leurocristine),



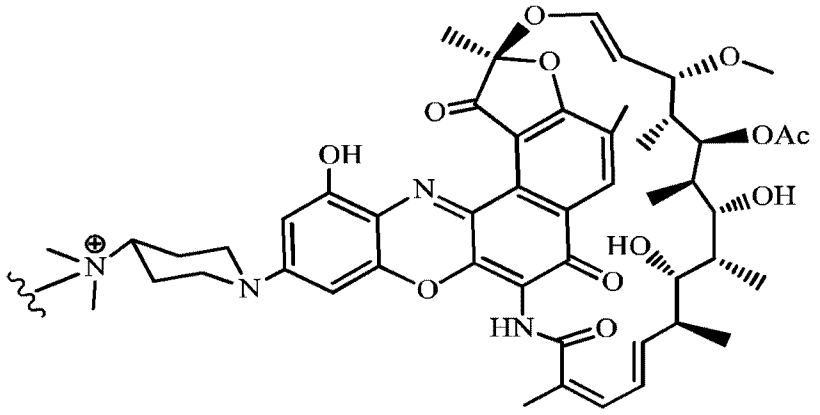
(If-02), vincristine (leurocristine),



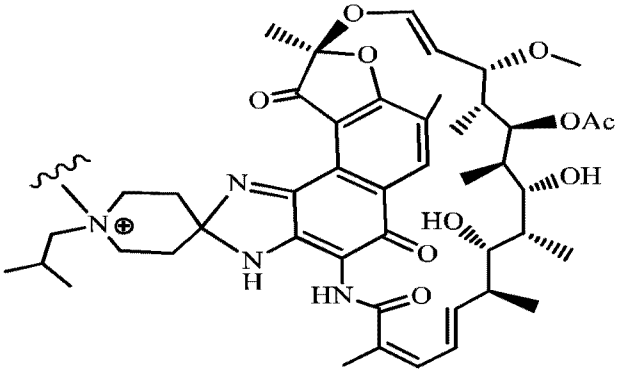
(If-03), vinblastine,



(If-04), vinblastine;



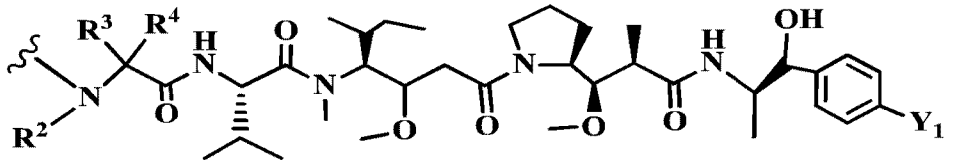
(If-05), Rifabutin analog,



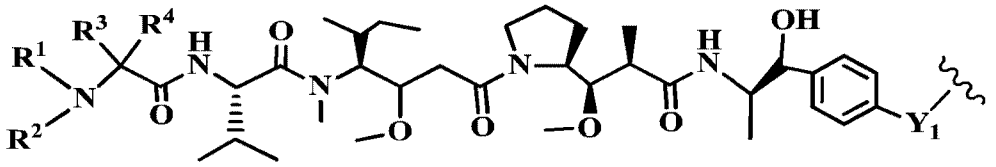
(If-06), rifabutin analog,

~~~ is a site in the molecule that can be linked to L_1, L_1', L_2 or L_2';

Dolastatins and their peptidic analogs and derivatives, auristatins, are highly potent antimitotic agents that have been shown to have anticancer and antifungal activity. See, e.g., U.S. Pat. No. 5, 663, 149 and Pettit et al., Antimicrob. Agents Chemother. 42:2961-2965, 1998. Exemplary dolastatins and auristatins include, but are not limited to, dolastatin 10, auristatin E (AE), auristatin EB (AEB), auristatin EFP (AEFP), MMAD (Monomethyl Auristatin D or monomethyl dolastatin 10), MMAF (Monomethyl Auristatin F or N-methylvaline-valine-dolaisoleuine-dolaproine-phenylalanine), MMAE (Monomethyl Auristatin E or N-methylvaline-valine-dolaisoleuine-dolaproine-norephedrine), 5-benzoylvaleric acid-AE ester (AEVB), Auristatin F phenylene diamine (AFP) and other novel auristatins. The auristatins are described in Int. J. Oncol. 15: 367-72 (1999); Molecular Cancer Therapeutics, vol. 3, No. 8, pp. 921-32 (2004); U.S. Application Nos. 11134826, 20060074008, 2006022925. U.S. Patent Nos. 4414205, 4753894, 4764368, 4816444, 4879278, 4943628, 4978744, 5122368, 5165923, 5169774, 5286637, 5410024, 5521284, 5530097, 5554725, 5585089, 5599902, 5629197, 5635483, 5654399, 5663149, 5665860, 5708146, 5714586, 5741892, 5767236, 5767237, 5780588, 5821337, 5840699, 5965537, 6004934, 6033876, 6034065, 6048720, 6054297, 6054561, 6124431, 6143721, 6162930, 6214345, 6239104, 6323315, 6342219, 6342221, 6407213, 6569834, 6620911, 6639055, 6884869, 6913748, 7090843, 7091186, 7097840, 7098305, 7098308, 7498298, 7375078, 7462352, 7553816, 7659241, 7662387, 7745394, 7754681, 7829531,
~~~

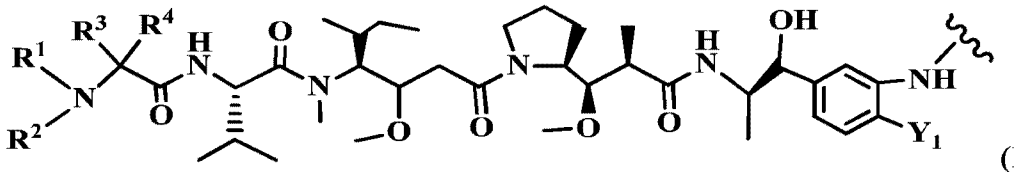
7837980, 7837995, 7902338, 7964566, 7964567, 7851437, 7994135. The structures of auristatin analogs are preferred the following formula (Ih-01), (Ih-02), (Ih-03), (Ih-04), (Ih-05), (Ih-06), (Ih-07), (Ih-08), (Ih-09), (Ih-10), and (Ih-11):



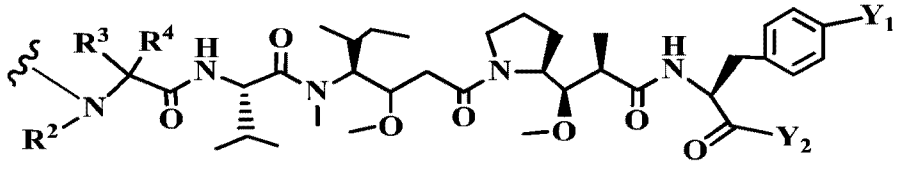
(Ih-01),



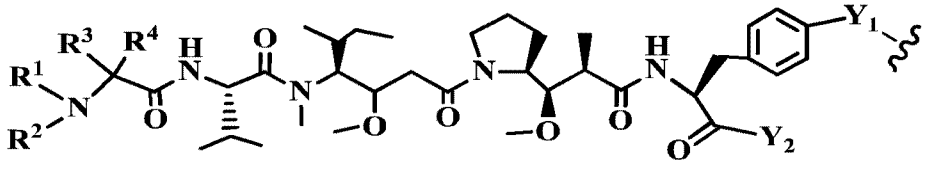
(Ih-02),



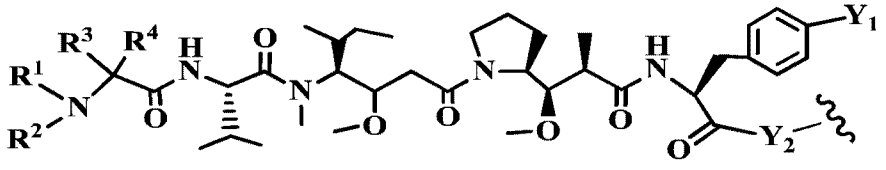
(Ih-03),



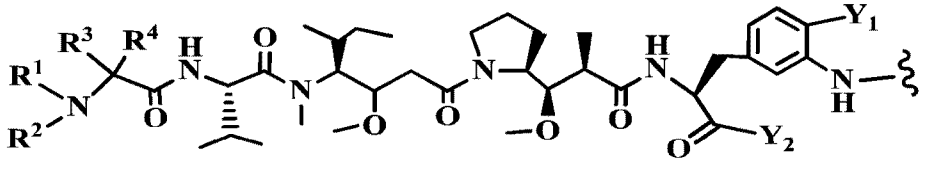
(Ih-04),



(Ih-05),



(Ih-06),



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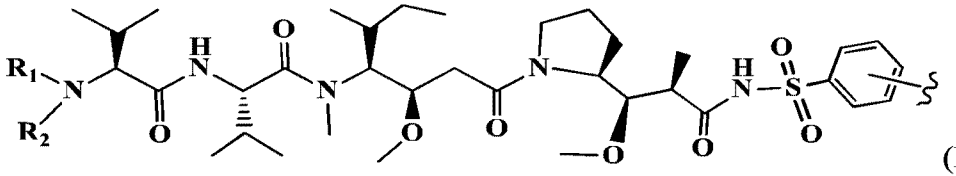
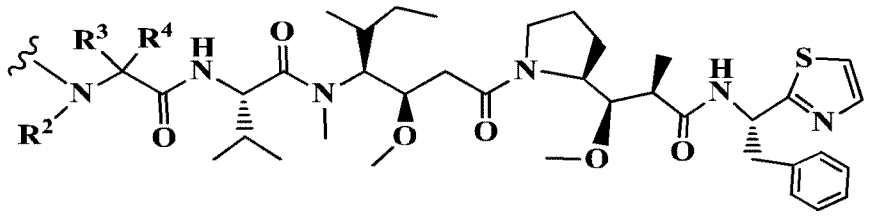


(Ih-08)



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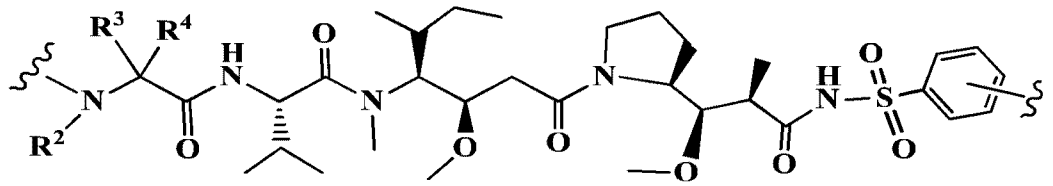

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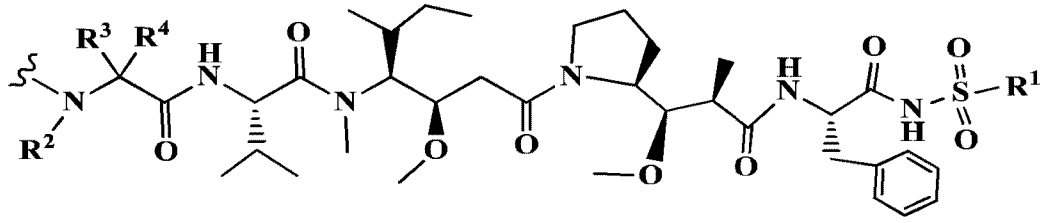

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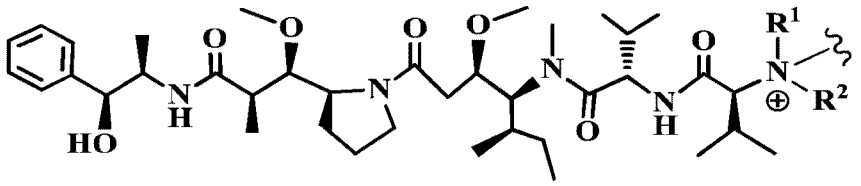

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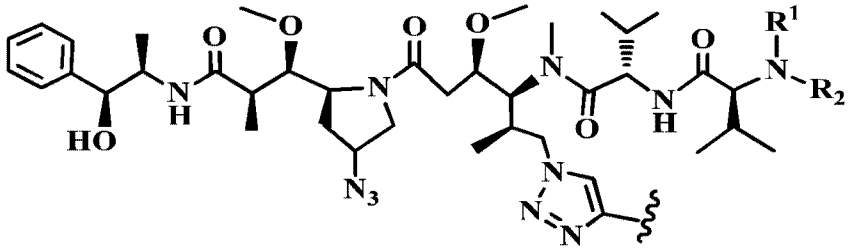
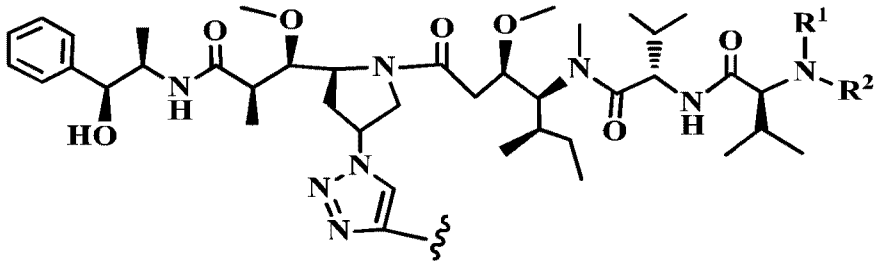
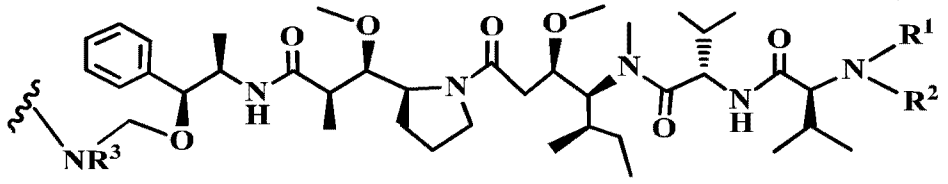


(Ih-13),



(Ih-14),



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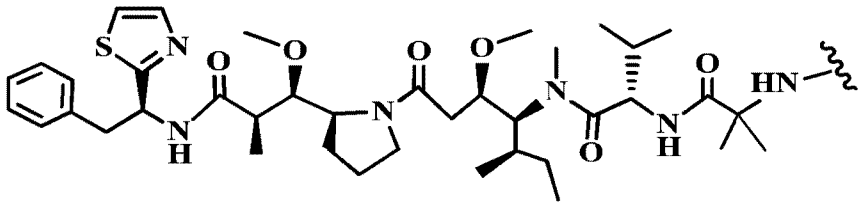

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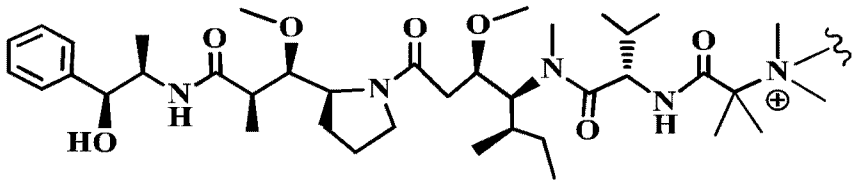
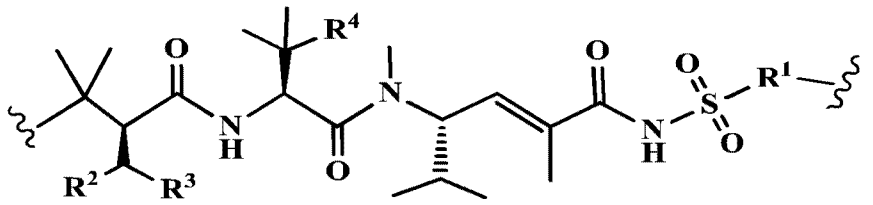


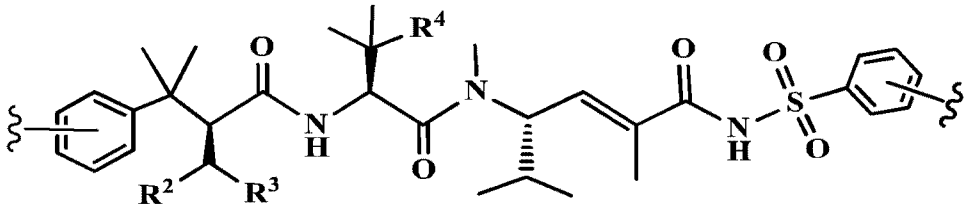
(Ih-17),

or an isotope of one or more chemical elements, or pharmaceutically acceptable salts, hydrates, or hydrated salts; or the polymorphic crystalline structures of these compounds; or the optical isomers, racemates, diastereomers or enantiomers; wherein R^1, R^2, R^3, R^4 and R^5 are independently H; C_1-C_8 linear or branched alkyl, aryl, heteroaryl, heteroalkyl, alkylcycloalkyl, ester, ether, amide, amines, heterocycloalkyl, or acyloxylamines; or peptides containing 1-8 aminoacids, or polyethyleneoxy unit having formula $(OCH_2CH_2)_p$ or $(OCH_2CH(CH_3))_p$, wherein p is an integer from 1 to about 1000. The two Rs: R^1R^2, R^2R^3, R^1R^3 or R^3R^4 together can form 3~8 member cyclic ring of alkyl, aryl, heteroaryl, heteroalkyl, or alkylcycloalkyl group; Y_1 and Y_2 are independently O, NH, NHNH, NR_5, S, C(O)O, C(O)NH, OC(O)NH, OC(O)O, NHC(O)NH, NHC(O)S, $OC(O)N(R_1)$, $N(R_1)C(O)N(R_2)$, C(O)NHNHC(O) and $C(O)NR_1$ when linked to the connecting site " ∿∿ " (that links to L_1 and/or L_2 independently); or OH, NH_2, $NHNH_2$, NHR_5, SH, C(O)OH, $C(O)NH_2$, $OC(O)NH_2$, OC(O)OH, $NHC(O)NH_2$, NHC(O)SH, $OC(O)NH(R_1)$, $N(R_1)C(O)NH(R_2)$, C(O)NHNHC(O)OH and $C(O)NHR_1$ when not linked to the connecting site " ∿∿ "; R_{12} is OH, NH_2, NHR_1, $NHNH_2$, NHNHCOOH, O-R_1-COOH, NH-R_1-COOH, NH-$(Aa)_n$COOH, $O(CH_2CH_2O)_pCH_2CH_2OH$, $O(CH_2CH_2O)_pCH_2CH_2NH_2$, $NH(CH_2CH_2O)_pCH_2CH_2NH_2$, NR_1R_1', NHOH, $NHOR_1$, $O(CH_2CH_2O)_pCH_2CH_2COOH$, $NH(CH_2CH_2O)_pCH_2CH_2COOH$, NH-Ar-COOH, NH-Ar-$NH_2$, $O(CH_2CH_2O)_pCH_2CH_2NH$-SO_3H, $NH(CH_2CH_2O)_pCH_2CH_2NHSO_3H$, R_1-$NHSO_3H$, NH-R_1-$NHSO_3H$, $O(CH_2CH_2O)_pCH_2$-$CH_2NHPO_3H_2$, $NH(CH_2CH_2O)_pCH_2CH_2NHPO_3H_2$, OR_1, R_1-$NHPO_3H_2$, R_1-OPO_3H_2, $O(CH_2CH_2O)_pCH_2CH_2OPO_3H_2$, OR_1-$NHPO_3H_2$, NH-R_1-$NHPO_3H_2$, $NH(CH_2CH_2NH)_pCH_2$-CH_2NH_2, $NH(CH_2CH_2S)_pCH_2CH_2NH_2$, $NH(CH_2CH_2NH)_pCH_2CH_2OH$, $NH(CH_2CH_2S)_pCH_2$-CH_2OH, NH-R_1-NH_2, or $NH(CH_2CH_2O)_pCH_2CH_2NHPO_3H_2$, wherein Aa is 1-8 the same or different aminoacids; p is 1 -1000; R_1, R_2, R_3, R_4, R_5, R_5', Z_1, Z_2, and n are defined the same above.

Hemiasterlin and its analogues (e.g., HTI-286) bind to the tubulin, disrupt normal microtubule dynamics, and, at stoichiometric amounts, depolymerize microtubules. The structure of maytansinoids is preferred the following formula:



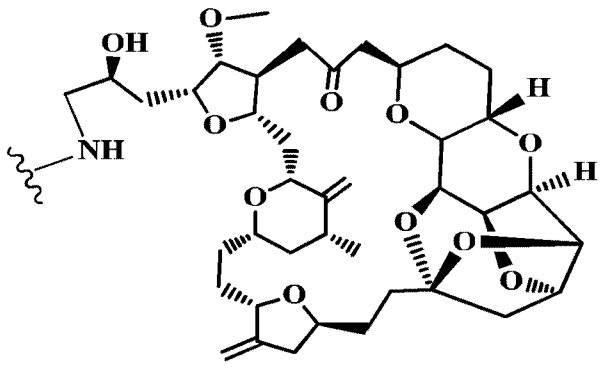
(Hs-01)



(Hs-02)

wherein wherein R^1, R^2, R^3, R^4 and R^5 are independently H; C_1-C_8 linear or branched alkyl, aryl, heteroaryl, heteroalkyl, alkylcycloalkyl, ester, ether, amide, amines, heterocycloalkyl, or acyloxylamines; or peptides containing 1-8 aminoacids, or polyethyleneoxy unit having formula $(OCH_2CH_2)_p$ or $(OCH_2CH(CH_3))_p$, wherein p is an integer from 1 to about 5000; In addition, R^2R^3 can form 3~8 member cyclic ring of alkyl, aryl, heteroaryl, heteroalkyl, or alkylcycloalkyl group.

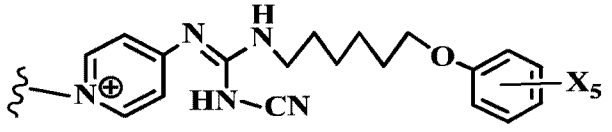
Eribulin which is binding predominantly to a small number of high affinity sites at the plus ends of existing microtubules has both cytotoxic and non-cytotoxic mechanisms of action. Its cytotoxic effects are related to its antimitotic activities, wherein apoptosis of cancer cells is induced following prolonged and irreversible mitotic blockade (Kuznetsov, G. et al, Cancer Research. 2004, 64 (16): 5760–6.; Towle, M. J, et al, Cancer Research. 2010, 71 (2): 496–505). In addition to its cytotoxic, antimitotic-based mechanisms, preclinical studies in human breast cancer models have shown that eribulin also exerts complex effects on the biology of surviving cancer cells and residual tumors that appear unrelated to its antimitotic effects. Eribulin has been approved by US FDA for the treatment of metastatic breast cancer who have received at least two prior chemotherapy regimens for late-stage disease, including both anthracycline- and taxane-based chemotherapies, as well as for the treatment of liposarcoma (a specific type of soft tissue sarcoma) that cannot be removed by surgery (unresectable) or is advanced (metastatic). Eribulin has been used as payload for ADC conjugates (US20170252458). The structure of Eribulin is preferred the following formula, Eb01:

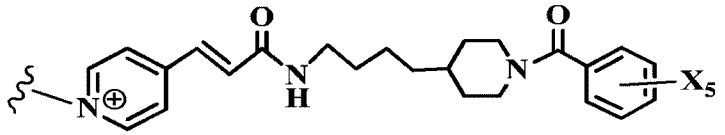


Eb01,

~~~ is a linkage site that links to L_1, L_1', L_2 and/or L_2' independently;

An Inhibitor of nicotinamide phosphoribosyltransferases (NAMPT) can be an interesting ADC payload due to their unique mechanisms of high potent activity (Sampath D, et al, Pharmacol Ther **2015**; 151, 16-31). NAMPT regulates nicotinamide adenine dinucleotide (NAD) levels in cells wherein NAD plays as an essential redox cofactor to support energy and anabolic metabolism. NAD has several essential roles in metabolism. It acts as a coenzyme in redox reactions, as a donor of ADP-ribose moieties in ADP-ribosylation reactions, as a precursor of the second messenger molecule cyclic ADP-ribose, as well as acting as a substrate for bacterial DNA ligases and a group of enzymes called sirtuins that use NAD^+ to remove acetyl groups from proteins. In addition to these metabolic functions, NAD^+ emerges as an adenine nucleotide that can be released from cells spontaneously and by regulated mechanisms (Smyth L. M, et al, J. Biol. Chem. 2004, 279 (47), 48893–903; Billington R. A, et al, Mol Med. 2006, 12, 324–7), and can therefore have important extracellular roles (Billington R. A, et al, Mol Med. 2006, 12, 324–7). When inhibitors of NAMPT present, NAD levels decline below the level needed for metabolism resulting in energy crisis and therefore cell death. So far, clinical NAMPT inhibitor candidates FK-866, CHS-828, and GMX-1777 advanced to clinical trials but each encountered dose-limiting toxicities prior to any objective responses (Holen K., et al, Invest New Drugs 2008, 26, 45-51; Hovstadius, P., et al, Clin Cancer Res 2002, 8, 2843-50; Pishvaian, M. J., et al, J Clin Oncol 2009, 27, 3581). Thus using ADCs for targeting delivery of NAMPT inhibitors might circumvent the systemic toxicities to achieve much broader therapeutic index. The structures of NAMPT inhibitors are preferred the following formula, NP01, NP02, NP03, NP04, NP05, NP06, NP07, NP08, and NP09:


NP01,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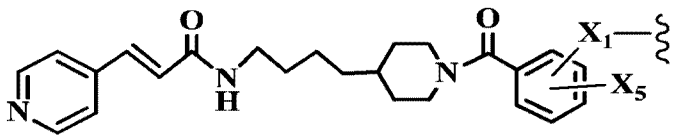
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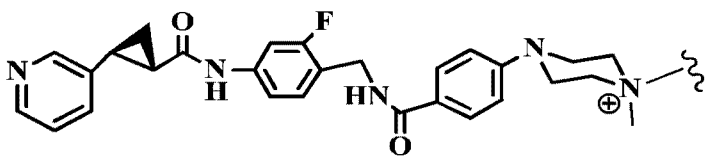
NP04,
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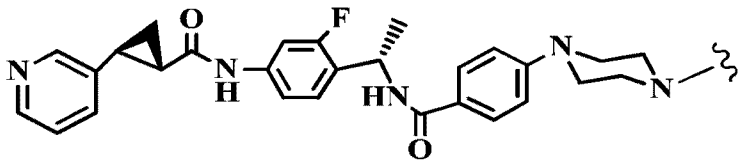

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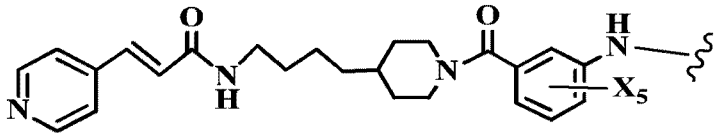
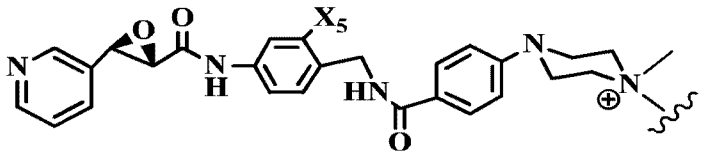


NP06,

NP07,

NP08,

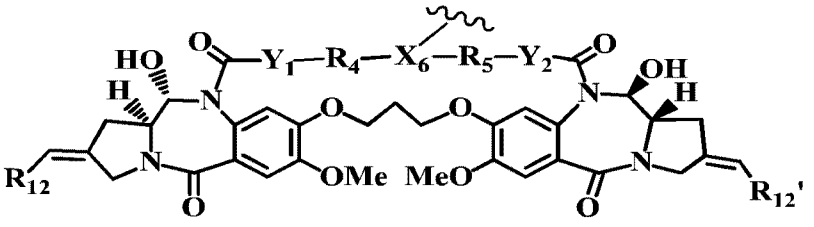


NP09,

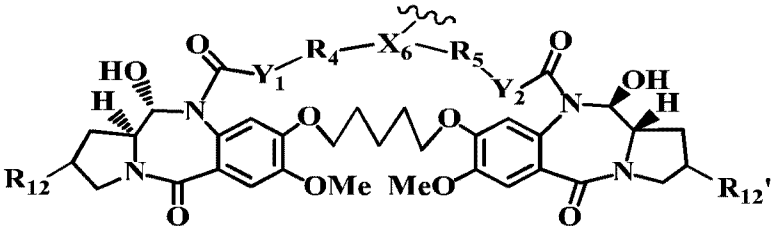
or an isotope of one or more chemical elements, or pharmaceutically acceptable salts, hydrates, or hydrated salts; or the polymorphic crystalline structures of these compounds; or the optical isomers, racemates, diastereomers or enantiomers; wherein " ∿∿ " is the same above; X_5 is F, Cl, Br, I, OH, OR_1, R_1, OPO_3H_2, OSO_3H, NHR_1, $OCOR_1$, $NHCOR_1$, wherein R_1 is defined the same above, and is preferred H, C_1-C_8 linear or branched alkyl.

A benzodiazepine dimer and its analogs: (e. g. a dimer of pyrrolobenzodiazepine (PBD) or (tomaymycin), a dimer of indolinobenzodiazepine (IGN), a dimer of imidazobenzothiadiazepine, or a dimer of oxazolidinobenzodiazepines) are anti-tumor agents that contain one or more immine functional groups, or their equivalents, that bind to duplex DNA. PBD and IGN molecules are based on the natural product athramycin, and interact with DNA in a sequence-selective manner, with a preference for purine-guanine-purine sequences. The preferred benzodiazepine dimers according to the present invention are exampled in: US Patent Nos. 8, 163, 736; 8, 153, 627; 8, 034, 808; 7, 834, 005; 7, 741, 319; 7, 704, 924; 7, 691, 848; 7, 678, 787; 7, 612, 062; 7, 608, 615; 7, 557, 099; 7, 528, 128; 7, 528, 126; 7, 511, 032; 7, 429, 658; 7, 407, 951; 7, 326, 700; 7, 312, 210; 7, 265, 105; 7, 202, 239; 7, 189, 710; 7, 173, 026; 7, 109, 193; 7, 067, 511; 7, 064, 120; 7, 056, 913; 7, 049, 311; 7, 022, 699; 7, 015, 215; 6, 979, 684; 6, 951, 853; 6, 884, 799; 6, 800, 622; 6, 747, 144; 6, 660, 856; 6, 608, 192; 6, 562, 806; 6, 977, 254; 6, 951, 853; 6, 909, 006; 6, 344, 451; 5, 880, 122; 4, 935, 362; 4, 764, 616; 4, 761, 412; 4, 723, 007; 4, 723, 003; 4, 683, 230; 4, 663, 453; 4, 508, 647; 4, 464, 467; 4, 427,

587; 4, 000, 304; US patent appl. 20100203007, 20100316656, 20030195196. Examples of the structures of the conjugate of the antibody- benzodiazepine dimers are illustrated below PB01, PB02, PB03, PB04, PB05, PB06, PB07, PB08, PB09, PB10, PB11, PB12, PB13, PB14, PB15, PB16, PB17, PB18, PB19, PB20, PB21, PB22, PB23, PB24, PB25, PB26, PB27 and PB28:



PB01,



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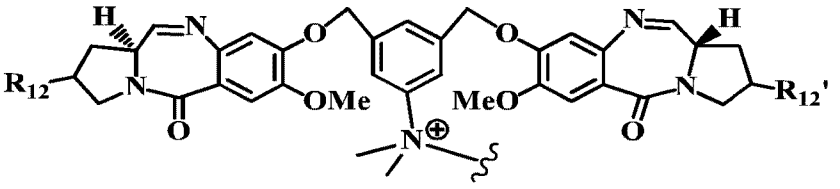

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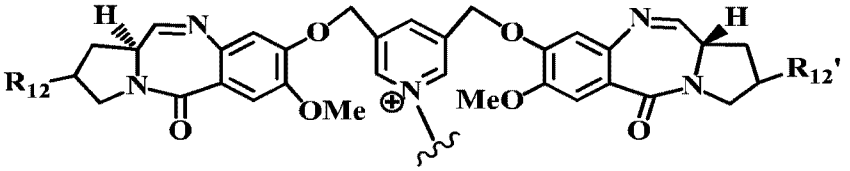

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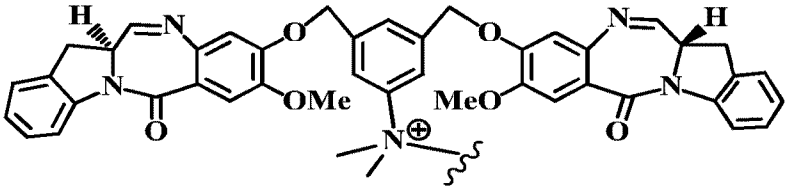

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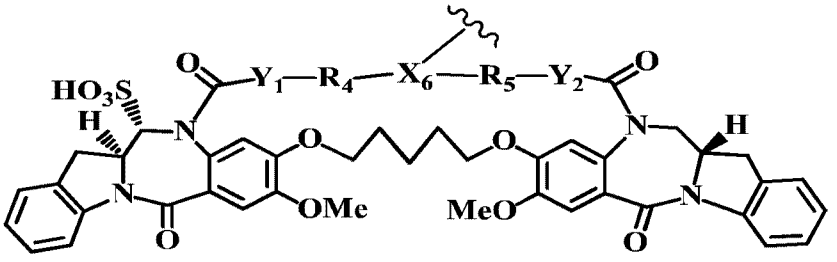

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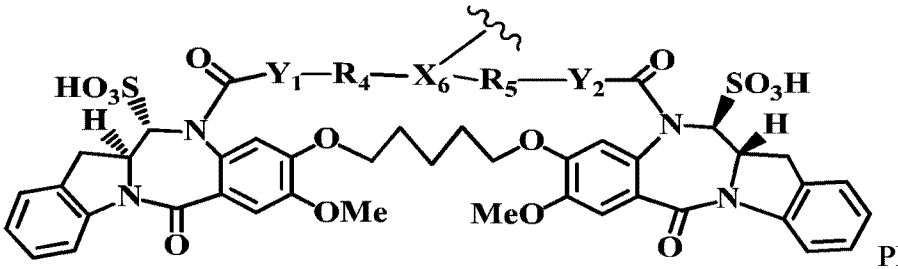
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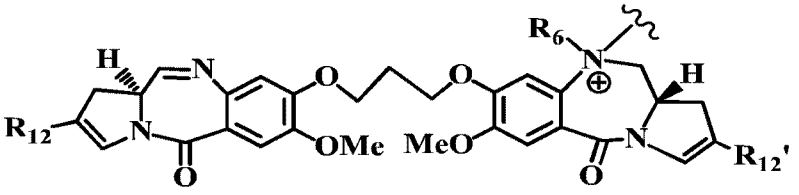
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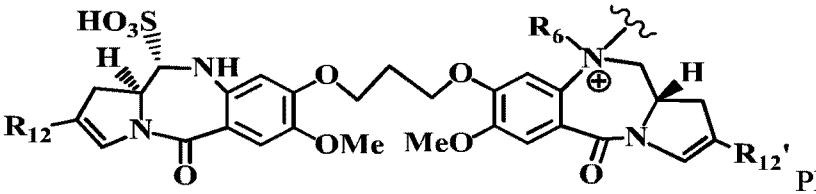
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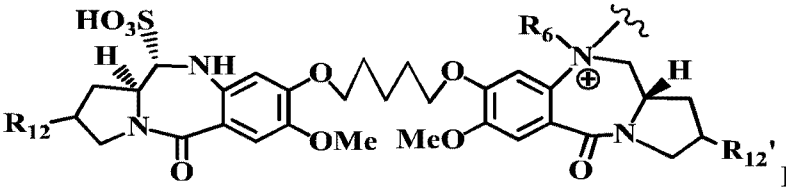
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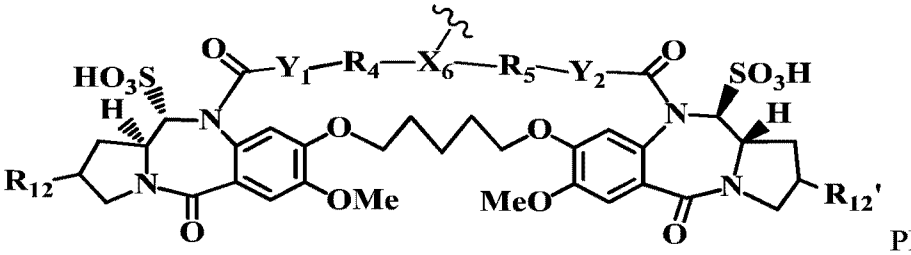
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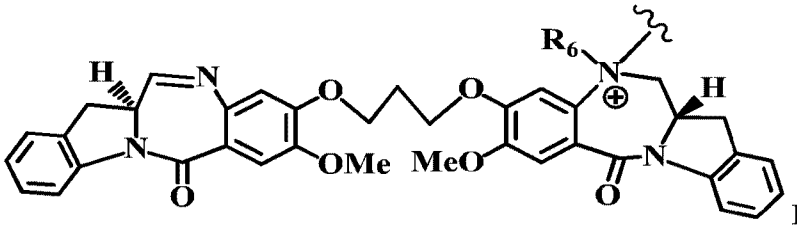
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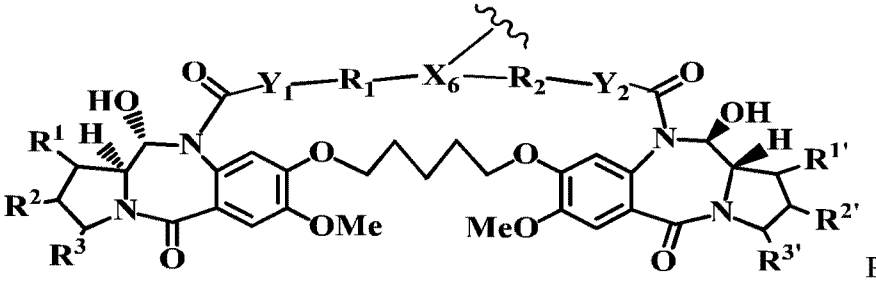
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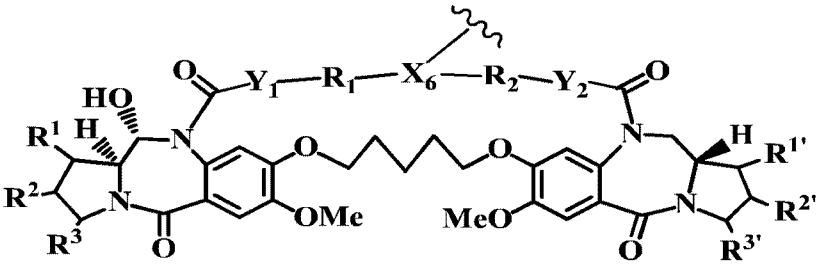
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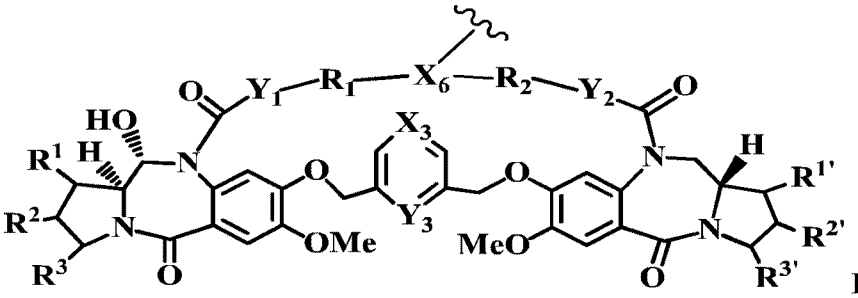
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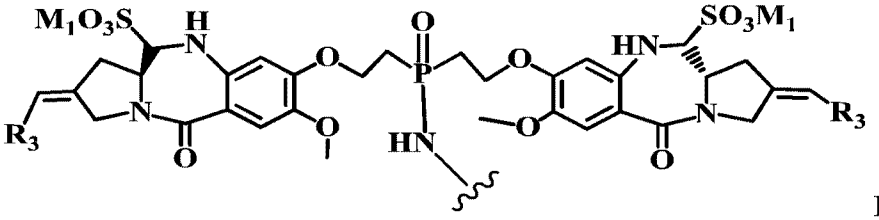
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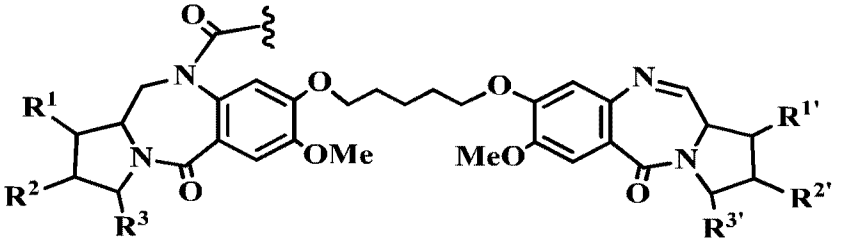
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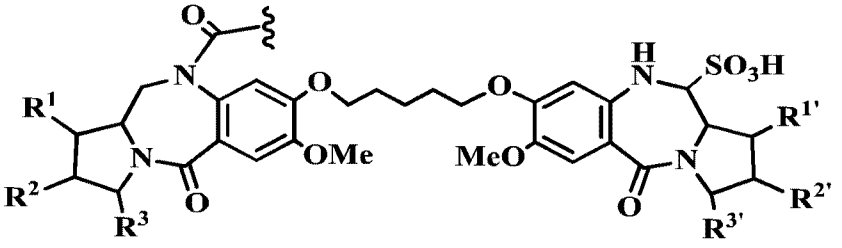
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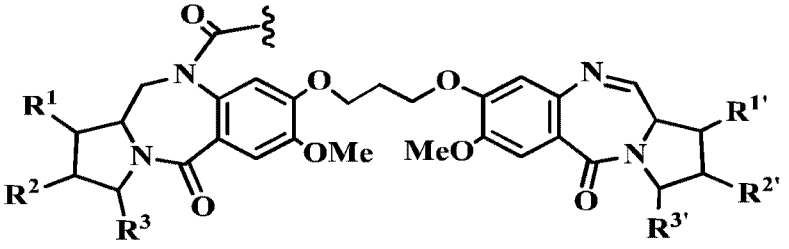
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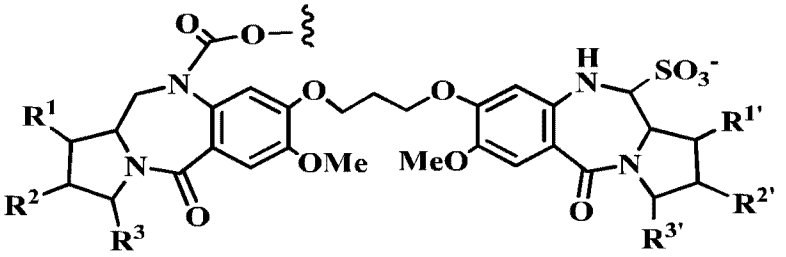

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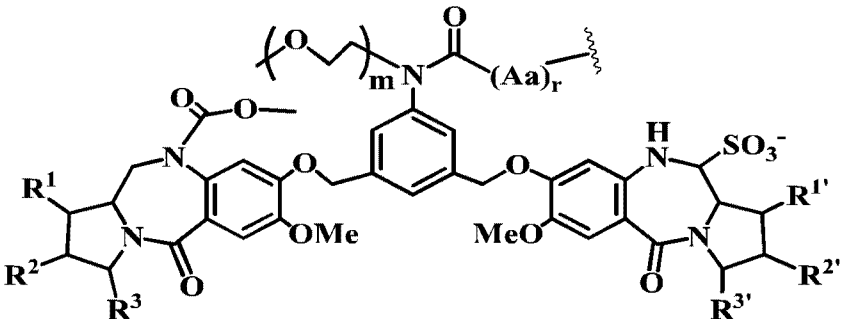

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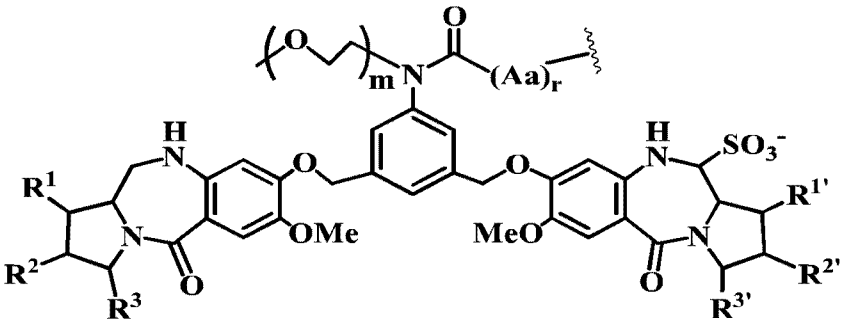

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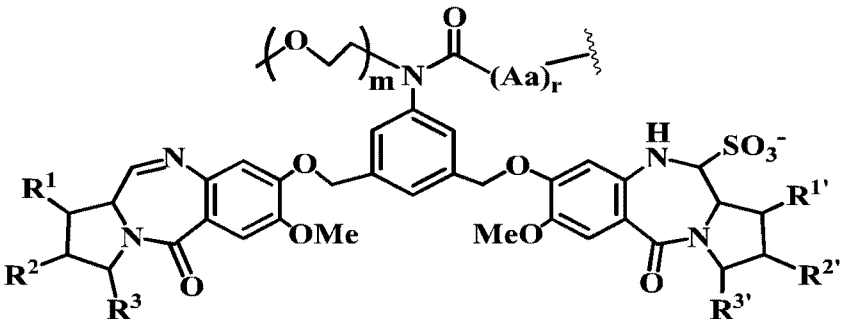

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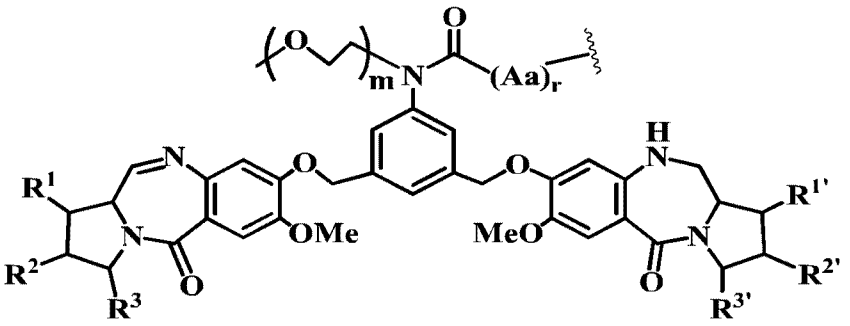

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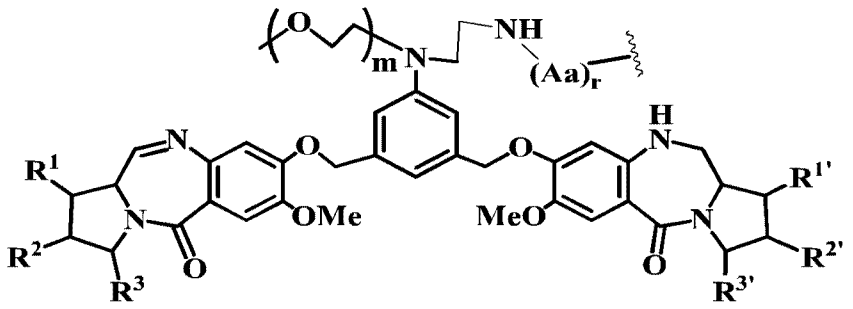
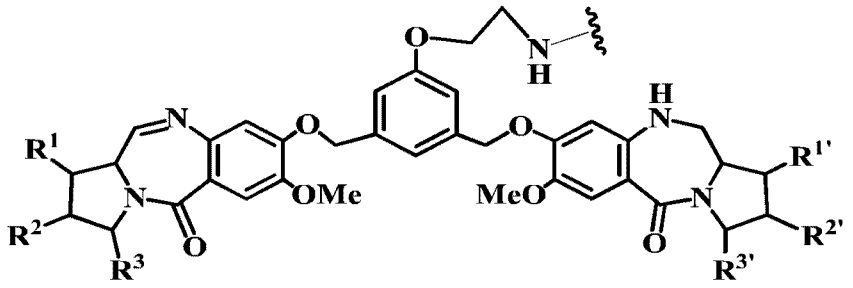
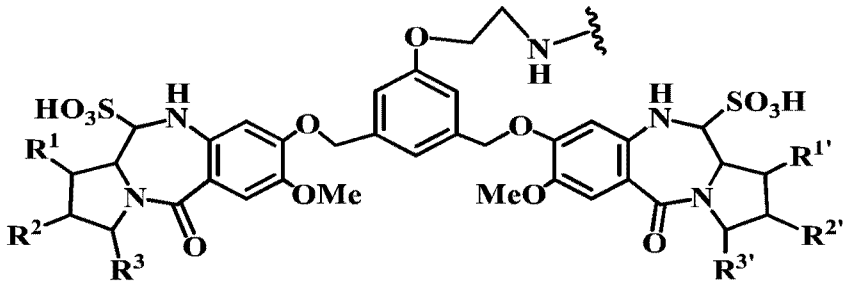
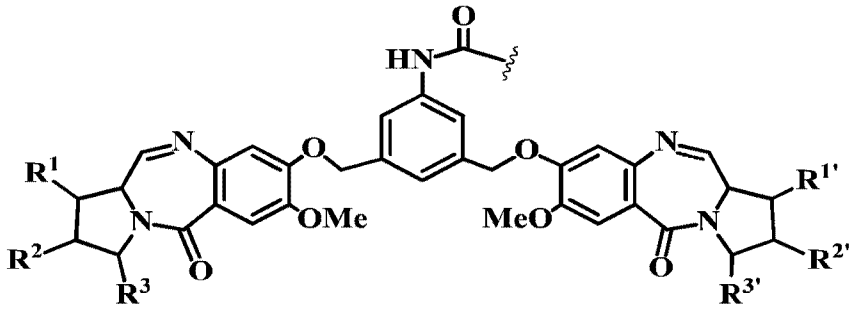

PB25,


PB26,


PB27,

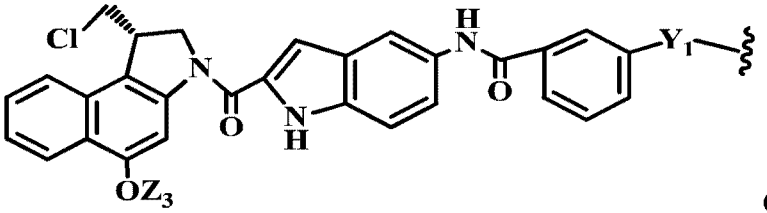

PB28,

or an isotope of one or more chemical elements, or pharmaceutically acceptable salts, hydrates, or hydrated salts; or the polymorphic crystalline structures of these compounds; or the optical isomers, racemates, diastereomers or enantiomers; wherein X_1, X_2, Y_1, Y_2, Z_1, Z_2, and n are defined the same above; Preferably X_1, X_2, Y_1 and Y_2 are independently O, N, NH, NHNH, NR_5, S, C(O)O, C(O)NH, OC(O)NH, OC(O)O, NHC(O)NH, NHC(O)S, OC(O)N(R_1), N(R_1)C(O)N(R_1), CH, C(O)NHNHC(O) and C(O)NR_1; R^1, R^2, R^3, $R^{1'}$, $R^{2'}$, and $R^{3'}$ are independently H; F; Cl; =O; =S; OH; SH; C_1-C_8 linear or branched alkyl, aryl, alkenyl, heteroaryl, heteroalkyl, alkylcycloalkyl, ester ($COOR_5$ or –$OC(O)R_5$), ether (OR_5), amide ($CONR_5$), carbamate ($OCONR_5$), amines (NHR_5, NR_5R_5'), heterocycloalkyl, or acyloxylamines (-C(O)NHOH, -$ONHC(O)R_5$); or peptides containing

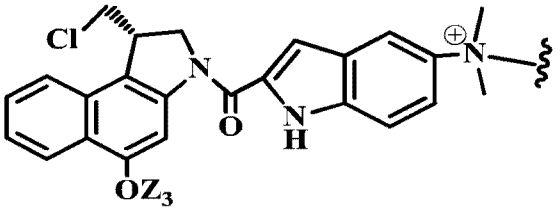
1-20 natural or unnatural aminoacids, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$ or $(OCH_2CH(CH_3))_p$, wherein p is an integer from 1 to about 5000. The two Rs: R^1R^2, R^2R^3, R^1R^3, $R^{1'}R^{2'}$, $R^{2'}R^{3'}$, or $R^{1'}R^{3'}$ can independently form 3~8 member cyclic ring of alkyl, aryl, heteroaryl, heteroalkyl, or alkylcycloalkyl group; X_3 and Y_3 are independently N, NH, CH_2 or CR_5, or one of X_3 and Y_3 can be absent; wherein R_1, and R_2 are C_1-C_8 linear or branched alkyl, heteroalkyl; C_3-C_8 aryl, heteroaryl, alkylcycloalkyl, acyloxyl, alkylaryl, alkylaryloxyl, alkylarylamino, alkylarylthiol; or 1-6 the same or different sequence of amino acid/peptides (Ar)r, r =1 -6; wherein R_4, R_5, R_5', R_6, R_{12} and R_{12}' are independently H, OH, NH_2, $NH(CH_3)$, $NHNH_2$, COOH, SH, OZ_3, SZ_3, F, Cl, or C_1-C_8 linear or branched alkyl, aryl, heteroaryl, heteroalkyl, alkylcycloalkyl, acyloxylamines; Z_3 is H, $OP(O)(OM_1)(OM_2)$, $OCH_2OP(O)(OM_1)(OM_2)$, OSO_3M_1, or O-glycoside (glucoside, galactoside, mannoside, glucuronoside/glucuronide, alloside, fructoside, etc.), NH-glycoside, S-glycoside or CH_2-glycoside; M_1 and M_2 are independently H, Na, K, Ca, Mg, NH_4, $NR_1R_2R_3$; X_6 is CH, N, P(O)NH, $P(O)NR_1$, CHC(O)NH, C_3-C_8 aryl, heteroaryl, alkylcycloalkyl, acyloxyl, alkylaryl, alkylaryloxyl, alkylarylamino, or an Aa (amino acid, is preferably selected from Lys, Phe, Asp, Glu, Ser, Thr, His, Cys, Tyr, Trp, Gln, Asn, Arg); "⎓" is either single bond or double bond; " ∿∿ " is defined the same above.

An CC-1065 analog and doucarmycin analogs are also preferred to be used for a conjugate of the present process invention. The examples of the CC-1065 analogues and doucarmycin analogs as well as their synthesis are described in: e.g. Warpehoski, et al, J. Med. Chem. 31:590-603 (1988); D. Boger et al., J. Org. Chem; 66; 6654-61, 2001; U. S. Patent Nos: 4169888, 4391904, 4671958, 4816567, 4912227, 4923990, 4952394, 4975278, 4978757, 4994578, 5037993, 5070092, 5084468, 5101038, 5117006, 5137877, 5138059, 5147786, 5187186, 5223409, 5225539, 5288514, 5324483, 5332740, 5332837, 5334528, 5403484, 5427908, 5475092, 5495009, 5530101, 5545806, 5547667, 5569825, 5571698, 5573922, 5580717, 5585089, 5585499, 5587161, 5595499, 5606017, 5622929, 5625126, 5629430, 5633425, 5641780, 5660829, 5661016, 5686237, 5693762, 5703080, 5712374, 5714586, 5739116, 5739350, 5770429, 5773001, 5773435, 5786377 5786486, 5789650, 5814318, 5846545, 5874299, 5877296, 5877397, 5885793, 5939598, 5962216, 5969108, 5985908, 6060608, 6066742, 6075181, 6103236, 6114598, 6130237, 6132722, 6143901, 6150584, 6162963, 6172197, 6180370, 6194612, 6214345, 6262271, 6281354, 6310209, 6329497, 6342480, 6486326, 6512101, 6521404, 6534660, 6544731, 6548530, 6555313, 6555693, 6566336, 6, 586, 618, 6593081, 6630579, 6, 756, 397, 6759509, 6762179, 6884869, 6897034, 6946455, 7, 049, 316, 7087600, 7091186, 7115573, 7129261, 7214663, 7223837, 7304032, 7329507, 7, 329, 760, 7, 388, 026, 7, 655, 660, 7, 655, 661, 7, 906, 545, and 8, 012, 978. Examples of the structures of the conjugate of the

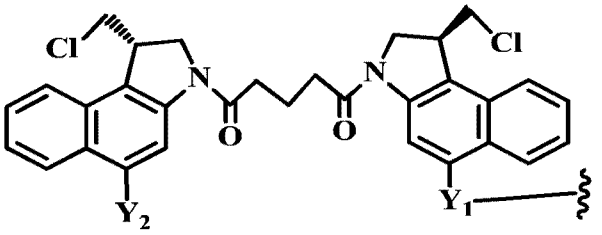
antibody-CC-1065 analogs via the linker of the patent are illustrated below CC01, CC02, CC03, CC04, CC05, CC06 and CC07:



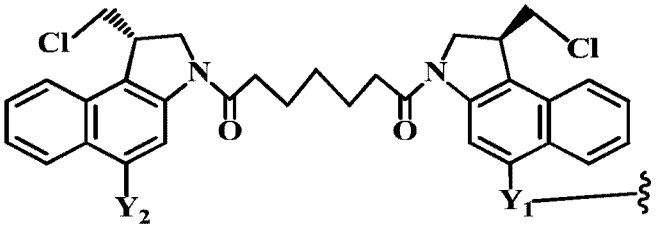
CC01,



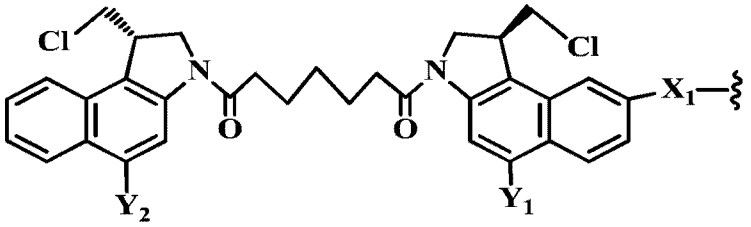
CC02,



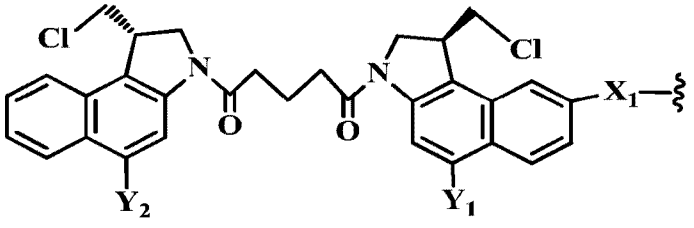
CC03,



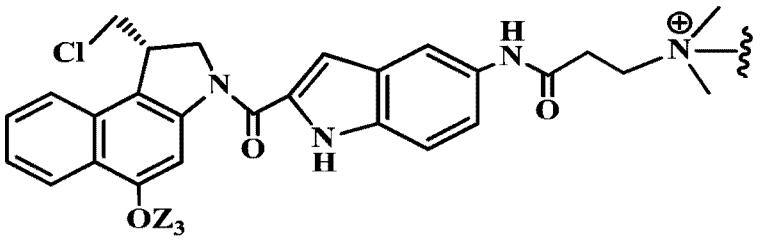
CC04,



CC05,



CC06,

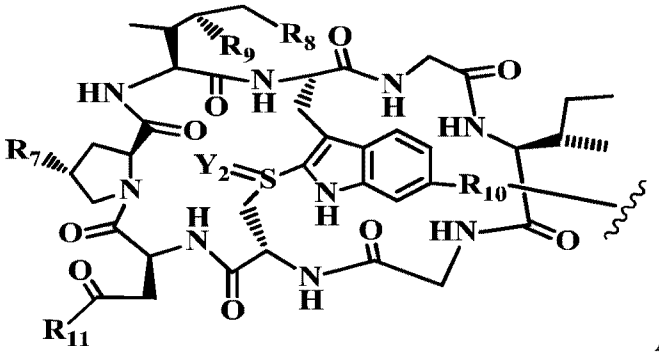


CC07,

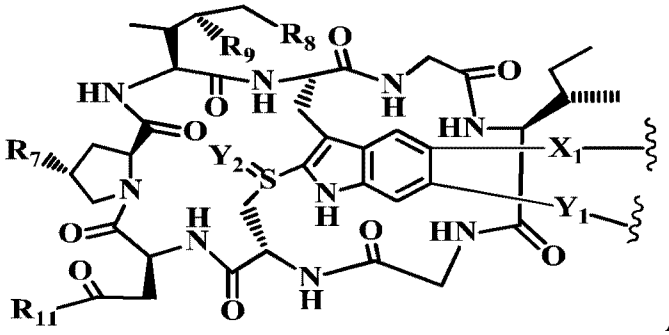
wherein X_1, X_2, Y_1 and Y_2 are independently O, NH, NHNH, NR_5, S, C(O)O, C(O)NH, OC(O)NH, OC(O)O, NHC(O)NH, NHC(O)S, $OC(O)N(R_1)$, $N(R_1)C(O)N(R_2)$, C(O)NHNHC(O) and $C(O)NR_1$ when linked to the connecting site " ∿∿ "; or OH, NH_2, $NHNH_2$, NHR_1, SH, C(O)OH, $C(O)NH_2$, $OC(O)NH_2$, OC(O)OH, $NHC(O)NH_2$, NHC(O)SH, $OC(O)NH(R_1)$, $N(R_1)C(O)NH(R_2)$, C(O)NHNHC(O)OH and $C(O)NHR_1$ when not linked to the connecting site " ∿∿ "; Z_3 is H, $PO(OM_1)(OM_2)$, SO_3M_1, $CH_2PO(OM_1)(OM_2)$, $CH_3N(CH_2CH_2)_2NC(O)$-, $O(CH_2CH_2)_2NC(O)$-, R_1, or glycoside; wherein R_1, R_2, R_3, M_1, M_2, and n are defined the same above;

An amatoxin and its analogs which are a subgroup of at least ten toxic compounds originally found in several genera of poisonous mushrooms, most notably Amanita phalloides and several other mushroom species, are also preferred for conjugation of the present patent. These ten amatoxins, named α-Amanitin, β-Amanitin, γ-Amanitin, ε-Amanitin, Amanullin, Amanullinic acid, Amaninamide, Amanin, Proamanullin, are rigid bicyclic peptides that are synthesized as 35-amino-acid proproteins, from which the final eight amino acids are cleaved by a prolyl oligopeptidase (Litten, W. 1975 Scientific American232 (3): 90–101; H. E. Hallen, et al 2007 Proc. Nat. Aca. Sci. USA 104, 19097–101; K. Baumann, et al, 1993 Biochemistry 32 (15): 4043–50; Karlson-Stiber C, Persson H. 2003, Toxicon 42 (4): 339–49; Horgen, P. A. et al. 1978 Arch. Microbio. 118 (3): 317–9). Amatoxins kill cells by inhibiting RNA polymerase II (Pol II), shutting down gene transcription and protein biosynthesis (Brodner, O. G. and Wieland, T. 1976 *Biochemistry*, 15(16): 3480–4; Fiume, L., Curr Probl Clin Biochem, 1977, 7: 23-8; Karlson-Stiber C, Persson H. 2003, Toxicon 42(4): 339–49; Chafin, D. R., Guo, H. & Price, D. H. 1995 J. Biol. Chem. 270 (32): 19114–19; Wieland (1983) Int. J. Pept. Protein Res. 22(3): 257-76.). Amatoxins can be produced from collected Amanita phalloides mushrooms (Yocum, R. R. 1978 Biochemistry 17(18): 3786-9; Zhang, P. et al, 2005, FEMS Microbiol. Lett.252(2), 223-8), or from fermentation using a basidiomycete (Muraoka, S. and Shinozawa T., 2000 J. Biosci. Bioeng. 89(1): 73-6) or from fermentation using A. fissa (Guo, X. W., et al, 2006 Wei Sheng Wu Xue Bao 46(3): 373-8), or from culturing Galerina fasciculata or Galerina helvoliceps, a strain belonging to the genus (WO/1990/009799, JP11137291). However, the yields from these isolation and fermentation were quite low (less than 5 mg/L culture). Several preparations of amatoxins and their analogs have been reported in the past three decades (W. E. Savige, A. Fontana, Chem. Commun. 1976, 600–1; Zanotti, G., et al, Int J Pept Protein Res, 1981.

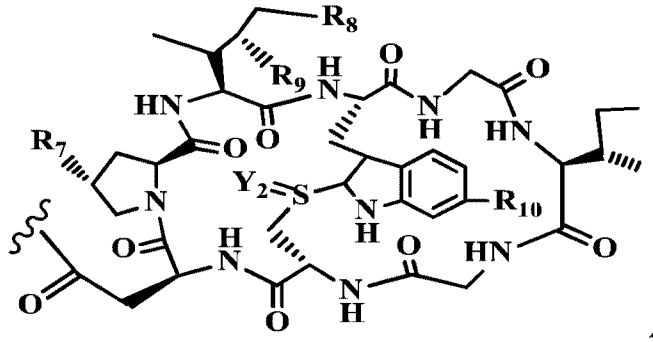
18(2): 162-8; Wieland, T., et al, Eur. J. Biochem. 1981, 117, 161–4; P. A. Bartlett, et al, Tetrahedron Lett. 1982, 23, 619–22; Zanotti, G., et al., Biochim Biophys Acta, 1986. 870(3): 454-62; Zanotti, G., et al., Int. J. Peptide Protein Res. 1987, 30, 323–9; Zanotti, G., et al., Int. J. Peptide Protein Res. 1987, 30, 450–9; Zanotti, G., et al., Int J Pept Protein Res, 1988. 32(1): 9-20; G. Zanotti, T. et al, Int. J. Peptide Protein Res. 1989, 34, 222–8; Zanotti, G., et al., Int J Pept Protein Res, 1990. 35(3): 263-70; Mullersman, J. E. and J. F. Preston, 3rd, Int J Pept Protein Res, 1991. 37(6): 544-51; Mullersman, J.E., et al, Int J Pept Protein Res, 1991. 38(5): 409-16; Zanotti, G., et al, Int J Pept Protein Res, 1992. 40(6): 551-8; Schmitt, W. et al, J. Am. Chem. Soc. 1996, 118, 4380–7; Anderson, M.O., et al, J. Org. Chem., 2005, 70(12): 4578-84; J. P. May, et al, J. Org. Chem. 2005, 70, 8424–30; F. Brueckner, P. Cramer, Nat. Struct. Mol. Biol. 2008, 15, 811–8; J. P. May, D. M. Perrin, Chem. Eur. J. 2008, 14, 3404–9; J. P. May, et al, Chem. Eur. J. 2008, 14, 3410–17; Q. Wang, et al, Eur. J. Org. Chem. 2002, 834–9; May, J. P. and D. M. Perrin, Biopolymers, 2007. 88(5): 714-24; May, J. P., et al., Chemistry, 2008. 14(11): 3410-7; S. De Lamo Marin, et al, Eur. J. Org. Chem. 2010, 3985–9; Pousse, G., et al., Org Lett, 2010. 12(16): 3582-5; Luo, H., et al., Chem Biol, 2014. 21(12): 1610-7; Zhao, L., et al., Chembiochem, 2015. 16(10): 1420-5) and most of these preparations were by partial synthesis. Because of their extreme potency and unique mechanism of cytotoxicity, amatoxins have been used as payloads for conjugations (Fiume, L., Lancet, 1969. 2 (7625): 853-4; Barbanti-Brodano, G. and L. Fiume, Nat New Biol, 1973. 243(130): 281-3; Bonetti, E., M. et al, Arch Toxicol, 1976. 35(1): p. 69-73; Davis, M. T., Preston, J. F. Science 1981, 213, 1385–1388; Preston, J.F., et al, Arch Biochem Biophys, 1981. 209(1): 63-71; H. Faulstich, et al, Biochemistry 1981, 20, 6498–504; Barak, L.S., et al., Proc Natl Acad Sci U S A, 1981. 78(5): 3034-8; Faulstich, H. and L. Fiume, Methods Enzymol, 1985. 112: 225-37; Zhelev, Z., A. et al, Toxicon, 1987. 25(9): 981-7; Khalacheva, K., et al, Eksp Med Morfol, 1990. 29(3): 26-30; U. Bermbach, H. Faulstich, Biochemistry 1990, 29, 6839–45; Mullersman, J. E. and J. F. Preston, Int. J. Peptide Protein Res. 1991, 37, 544–51; Mullersman, J.E. and J.F. Preston, Biochem Cell Biol, 1991. 69(7): 418-27; J. Anderl, H. Echner, H. Faulstich, Beilstein J. Org. Chem. 2012, 8, 2072–84; Moldenhauer, G., et al, J. Natl. Cancer Inst. 2012, 104, 622–34; A. Moshnikova, et al; Biochemistry 2013, 52, 1171–8; Zhao, L., et al., Chembiochem, 2015. 16(10): 1420-5; Zhou, B., et al., Biosens Bioelectron, 2015. 68: 189-96; WO2014/043403, US20150218220, EP 1661584). We have been working on the conjugation of amatoxins for a while. Examples of the structures of the amatoxins used for the present application are preferred the following structures of Am01, Am02, Am03 and Am04:



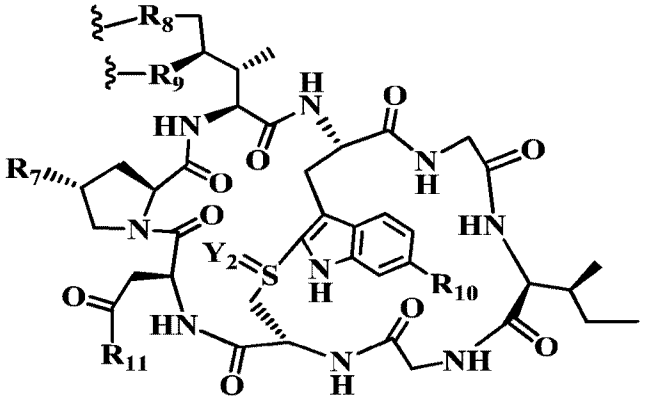
Am01,



Am02,



Am03,

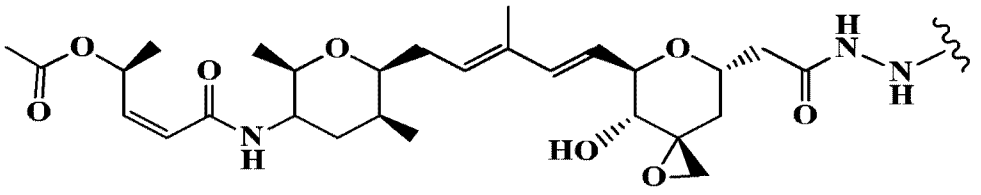


Am04

or an isotope of one or more chemical elements, or pharmaceutically acceptable salts, hydrates, or hydrated salts; or the polymorphic crystalline structures of these compounds; or the optical isomers, racemates, diastereomers or enantiomers; wherein X_1, and Y_1 are independently O, NH, NHNH, NR_5, S, C(O)O, C(O)NH, OC(O)NH, OC(O)O, NHC(O)NH, NHC(O)S, OC(O)N(R_1), N(R_1)C(O)N(R_1), CH_2, CHNH, CH_2O, C(O)NHNHC(O) and C(O)NR_1; R_7, R_8, and R_9 are

independently H, OH, OR_1, NH_2, NHR_1, C_1-C_6 alkyl, or absent; Y_2 is O, O_2, NR_1, NH, or absent; R_{10} is CH_2, O, NH, NR_1, NHC(O), NHC(O)NH, NHC(O)O, OC(O)O, C(O), OC(O), OC(O)(NR_1), (NR_1)C(O)(NR_1), C(O)R_1 or absent; R_{11} is OH, NH_2, NHR_1, $NHNH_2$, NHNHCOOH, O-R_1-COOH, NH-R_1-COOH, NH-$(Aa)_r$COOH, $O(CH_2CH_2O)_pCH_2CH_2OH$, $O(CH_2CH_2O)_pCH_2CH_2NH_2$, $NH(CH_2CH_2O)_pCH_2CH_2NH_2$, NR_1R_2, $O(CH_2CH_2O)_pCH_2CH_2$-COOH, $NH(CH_2CH_2O)_pCH_2CH_2COOH$, NH-Ar-COOH, NH-Ar-$NH_2$, $O(CH_2CH_2O)_pCH_2CH_2$-$NHSO_3H$, $NH(CH_2CH_2O)_pCH_2CH_2NHSO_3H$, R_1-$NHSO_3H$, NH-R_1-$NHSO_3H$, $O(CH_2CH_2O)_p$-$CH_2CH_2NHPO_3H_2$, $NH(CH_2CH_2O)_pCH_2CH_2NHPO_3H_2$, OR_1, R_1-$NHPO_3H_2$, R_1-OPO_3H_2, $O(CH_2CH_2O)_pCH_2CH_2OPO_3H_2$, OR_1-$NHPO_3H_2$, NH-R_1-$NHPO_3H_2$, or $NH(CH_2CH_2O)_pCH_2$-$CH_2NHPO_3H_2$, wherein $(Aa)_r$ is 1-8 aminoacids; n and m_1 are independently 1-20; p is 1 -5000; R_1, R_2 and Ar, are the same defined through out the application; " ∿∿ " is defined the same above.

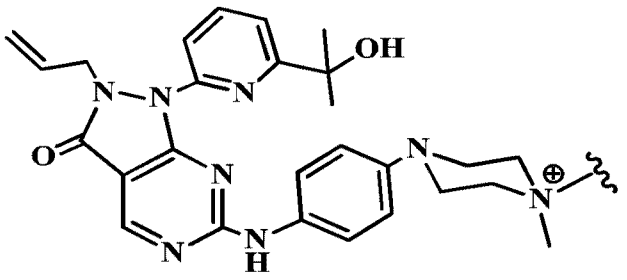
Spliceostatins and pladienolides are anti-tumor compounds which inhibit splicing and interacts with spliceosome, SF3b. Examples of spliceostatins include, but are not limited to, spliceostatin A, FR901464, and (2S, 3Z)-5-{[(2R, 3R, 5S, 6S)-6-{(2E, 4E)-5-[(3R, 4R, 5R, 7S)-7-(2-hydrazinyl-2-oxoethyl)-4-hydroxy-1, 6-dioxaspiro[2.5]oct-5-yl]-3-methylpenta-2, 4-dien-1-y-1}-2, 5-dimethyltetrahydro-2H-pyran-3-yl]amino}-5-oxopent-3-en-2-yl acetate having the core structure:



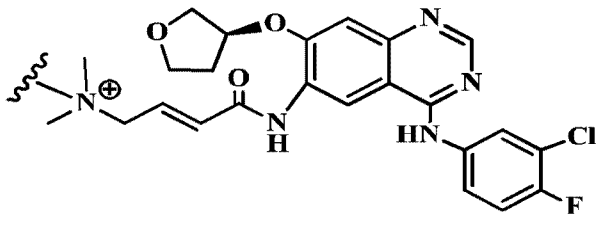
(Sp-01),

Examples of pladienolides include, but are not limited to, Pladienolide B, Pladienolide D, and E7107.

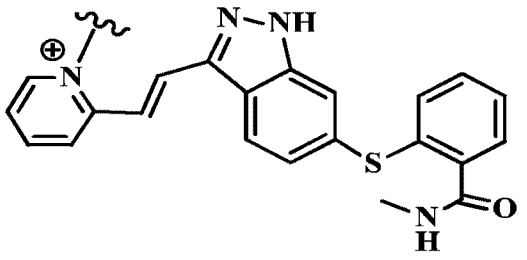
Protein kinase inhibitors that block the action of an enzyme to add a phosphate (PO_4) group to serine, threonine, or tyrosine amino acids on an antibody-like protein, and can modulate the protein function. The protein kinase inhibitors can be used to treat diseases due to hyperactive protein kinases (including mutant or overexpressed kinases) in cancer or to modulate cell functions to overcome other disease drivers. The structures of protein kinase inhibitors are preferred to selected from Adavosertib, Afatinib, Axitinib, Bafetinib, Bosutinib, Cobimetinib, Crizotinib, Cabozantinib, Dasatinib, Entrectinib, Erdafitinib, Erlotinib, Erlotinib, Fostamatinib, Gefitinib, Ibrutinib, Imatinib, Lapatinib, Lenvatinib, Mubritinib, Nilotinib, Pazopanib, Pegaptanib, Ponatinib, Rebastinib, Regorafenib, Ruxolitinib, Sorafenib, Sunitinib, SU6656, Tofacitinib, Vandetanib, Vemurafenib, Entrectinib, Palbociclib, Ribociclib, Abemaciclib, Dacomitinib, Neratinib, Rociletinib (CO-1686), Osimertinib, AZD3759, Nazartinib (EGF816), having the following formula, PK01 ~ PK40:



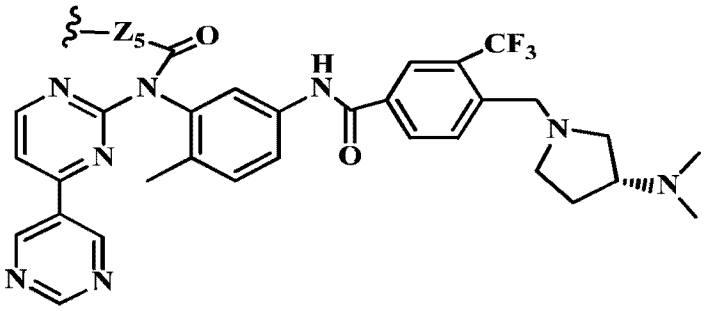
PK01, Adavosertib,



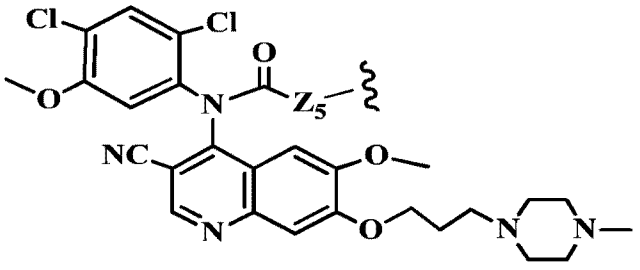
PK02, Afatinib,



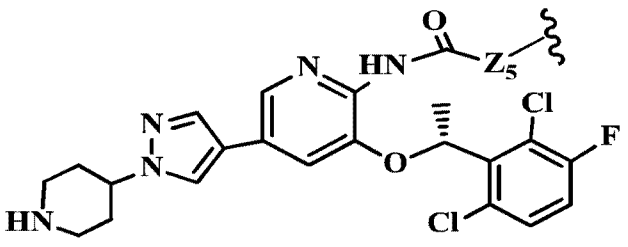
PK03, Axitinib,



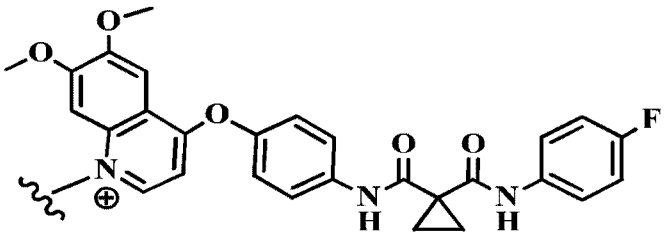
PK04, Bafetinib



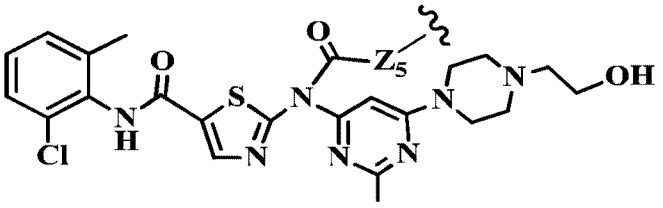
PK05, Bosutinib,



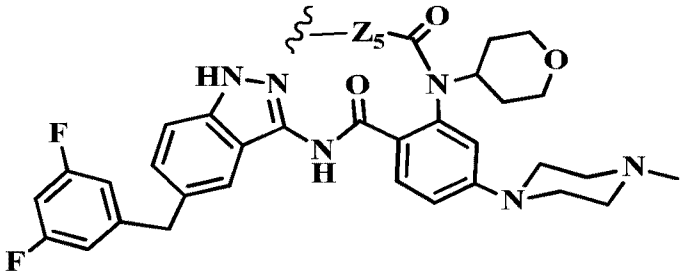
PK06, Crizotinib,



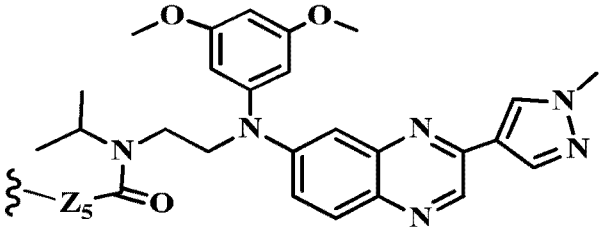
PK07, Cabozantinib,



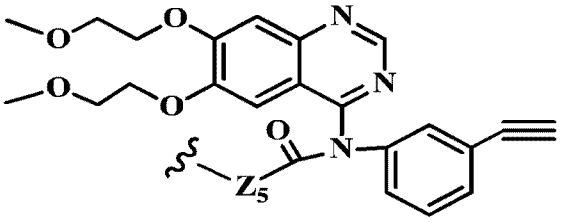
PK08, Dasatinib,



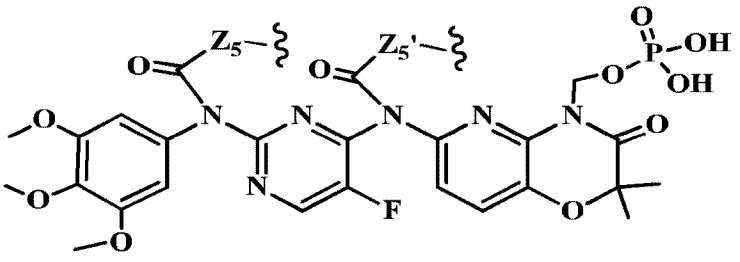
PK09, Entrectinib,



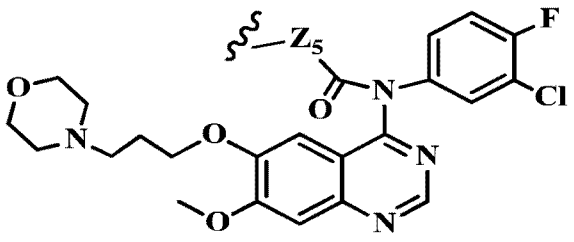
PK10, Erdafitinib,



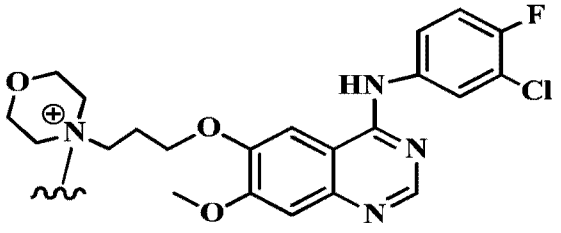
PK11, Erlotinib,



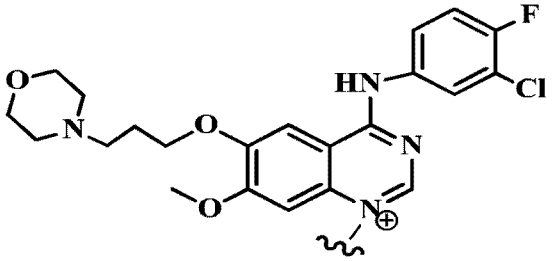
PK12, Fostamatinib,



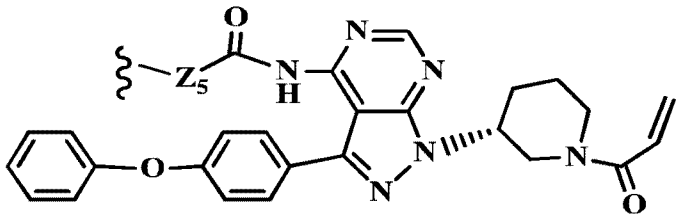
PK13, Gefitinib,



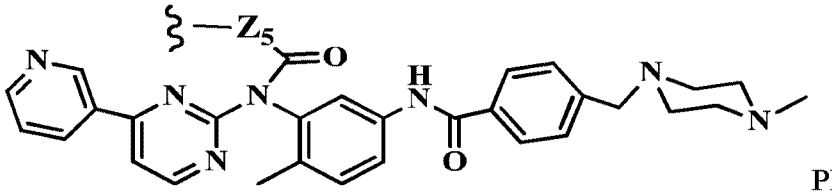
PK14, Gefitinib,



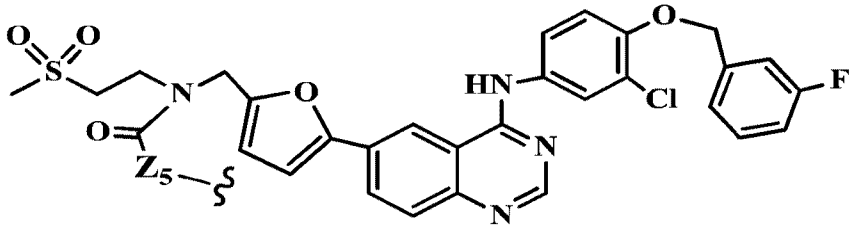
PK15, Gefitinib,



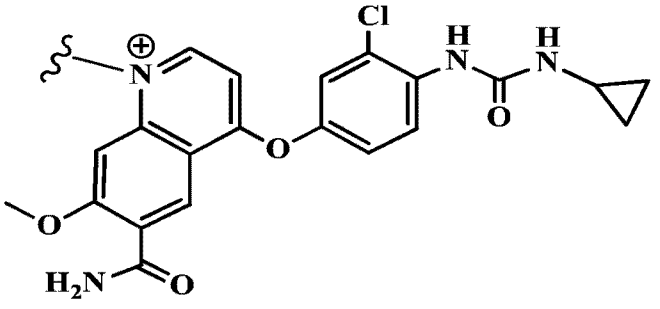
PK16, Ibrutinib,



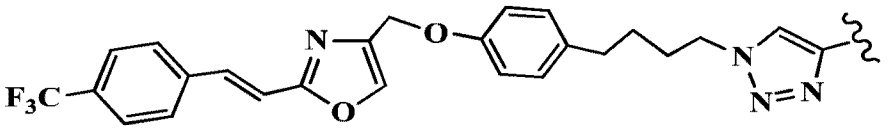
PK17, Imatinib,



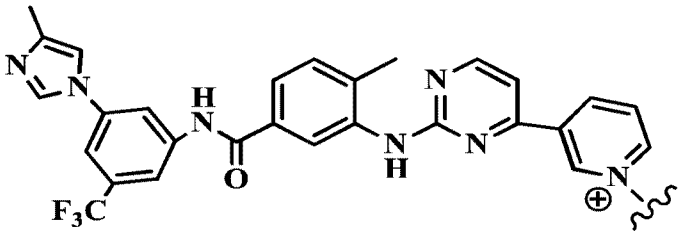
PK18, Lapatinib,



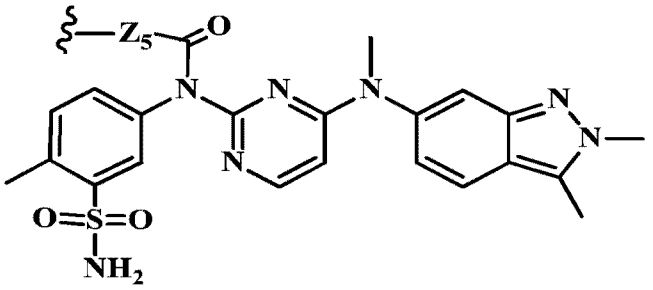
PK19, Lenvatinib,



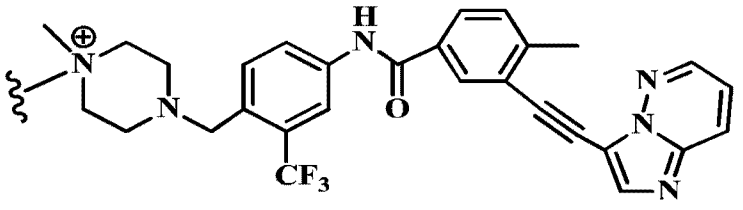
PK20, Mubritinib,



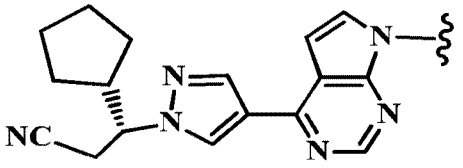
PK21, Nilotinib,



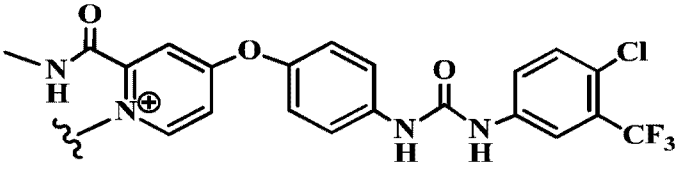
PK22, Pazopanib,



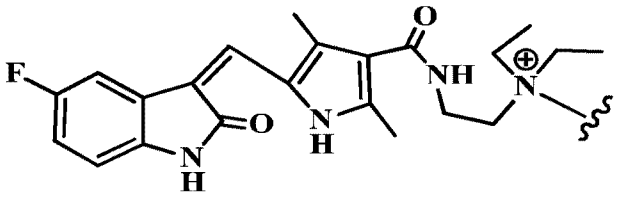
PK23, Ponatinib,



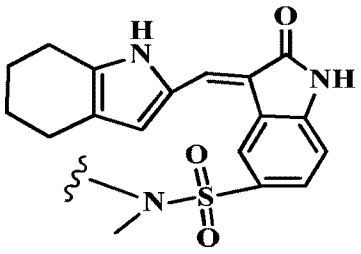
PK24, Ruxolitinib,



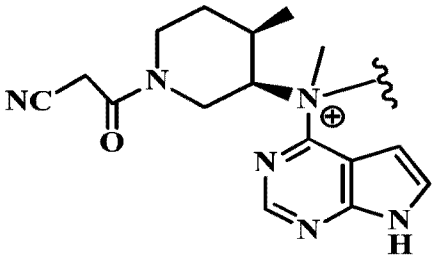
PK25, Sorafenib,



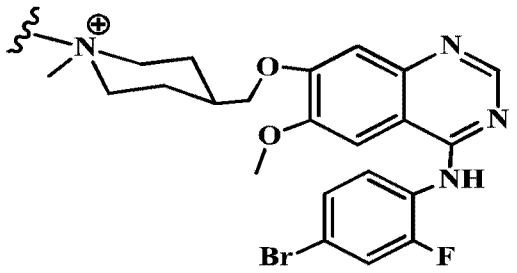
PK26, Sunitinib,



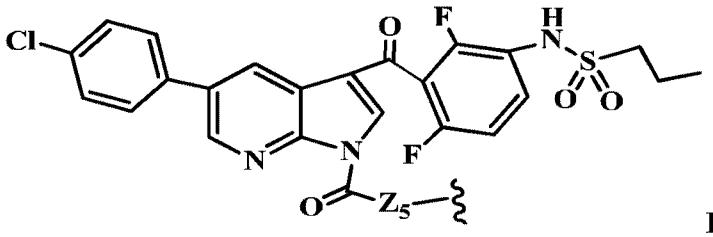
PK27, SU6656,



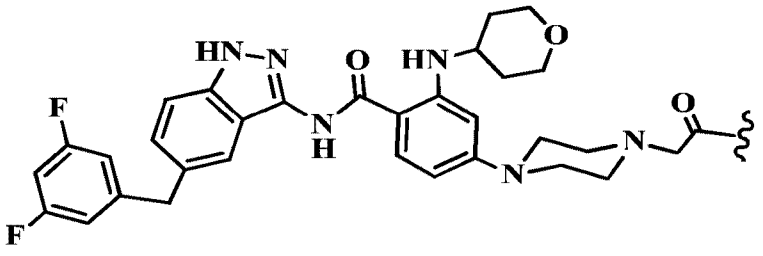
PK28, Tofacitinib,



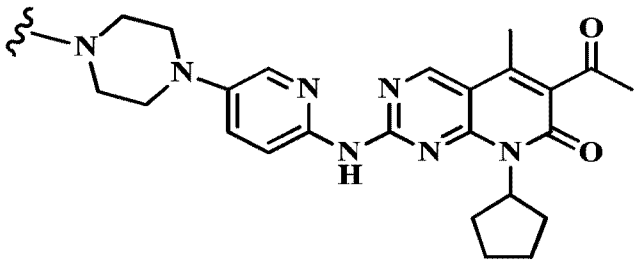
PK29, Vandetanib,



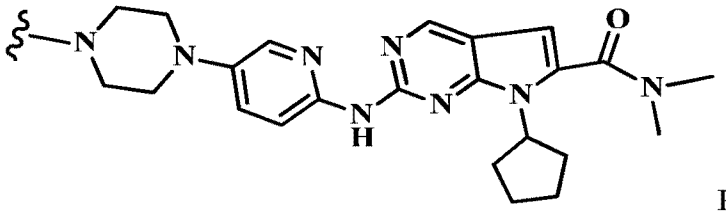
PK30, Vemurafenib;



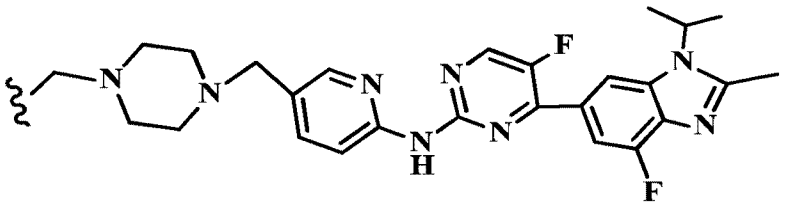
PK 31, Entrectinib;



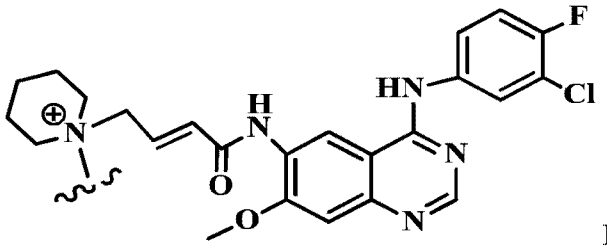
PK-32, Palbociclib analog,



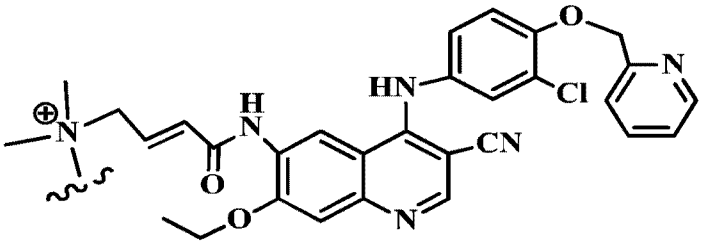
PK-33, Ribociclib,



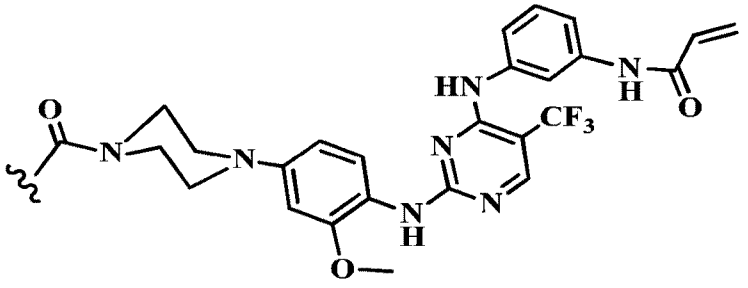
PK-34, Abemaciclib,



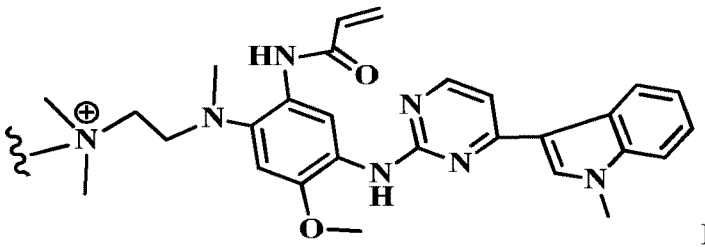
PK-35, Dacomitinib,



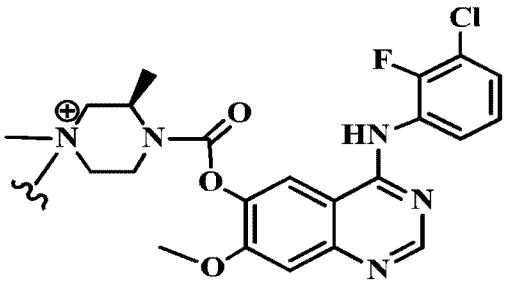
PK-36, Neratinib,



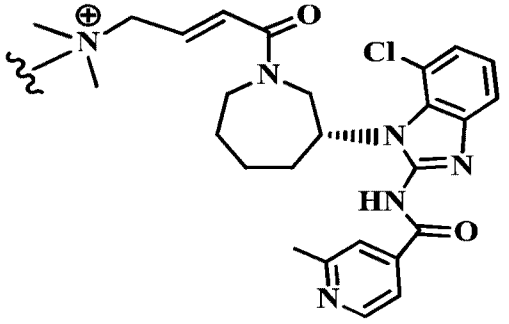
PK-37, Rociletinib (CO-1686),



PK-38, Osimertinib,



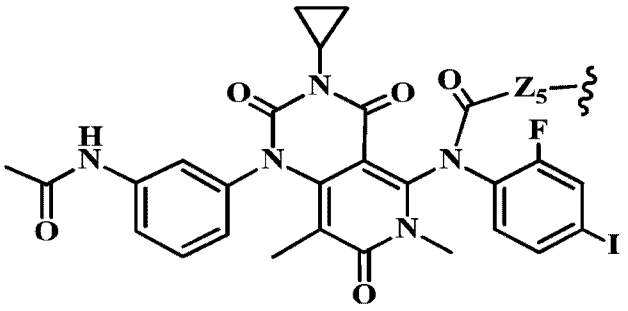
PK-39, AZD3759,



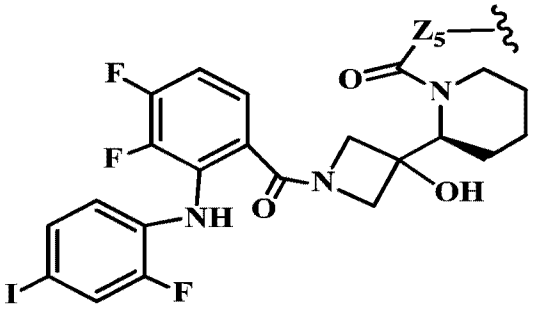
PK-40, Nazartinib (EGF816),

wherein Z_5 and Z_5' are independently selected from O, NH, NHNH, NR_5, S, C(O)O, C(O)NH, OC(O)NH, OC(O)O, NHC(O)O, NHC(O)NH, NHC(O)S, OC(O)N(R_1), N(R_1)C(O)N(R_2), C(O)NHNHC(O) and C(O)NR_1; " ∿∿∿ " is defined the same above.

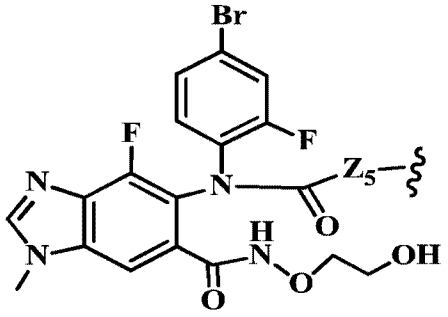
A MEK inhibitor inhibits the mitogen-activated protein kinases MEK1 and/or MEK2 which is often overactive in some cancers. MEK inhibitors are especially used for treatment of BRAF-mutated melanoma, and KRAS/BRAF mutated colorectal cancer, breast cancer, and non-small cell lung cancer (NSCLC). MEK inhibitors are selected from PD0325901, selumetinib (AZD6244), cobimetinib (XL518), refametinib, trametinib (GSK1120212), pimasertib, Binimetinib (MEK162), AZD8330, RO4987655, RO5126766, WX-554, E6201, GDC-0623, PD-325901 and TAK-733. The preferred MEK inhibitors are selected from Trametinib (GSK1120212), Cobimetinib (XL518), Binimetinib (MEK162), selumetinib having the following formula:



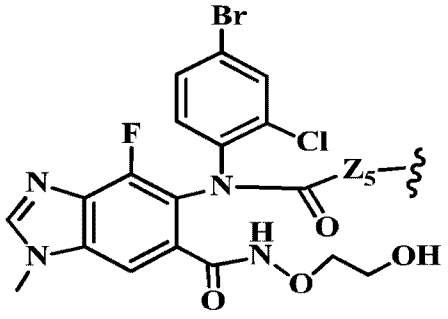
MEK01, Trametinib,



MEK02, Cobimetinib,



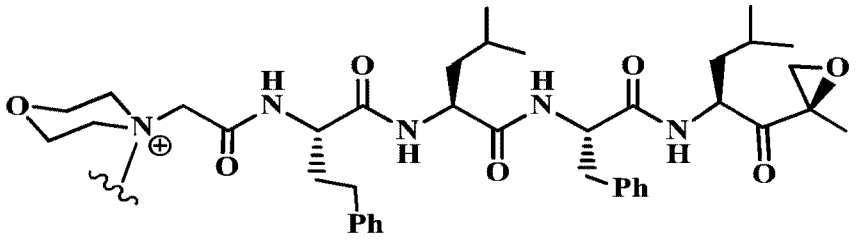
MEK03, Binimetinib,



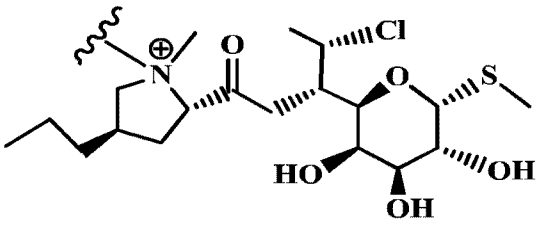
MEK04, selumetinib,

wherein Z_5 is selected from O, NH, NHNH, NR_5, S, C(O)O, C(O)NH, OC(O)NH, OC(O)O, NHC(O)O, NHC(O)NH, NHC(O)S, OC(O)N(R_1), N(R_1)C(O)N(R_2), C(O)NHNHC(O) and C(O)NR_1; R_1 and R_2 are the same as defined above.

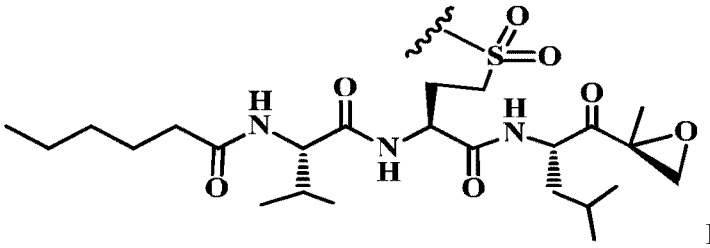
A proteinase inhibitor that are used as a payload is preferably selected from: Carfilzomib, Clindamycin, Retapamulin, Indibulin, as shown in the following structures:



PI01, Carfilzomib,



PI02, Clindamycin,



PI03, Carmaphycin analog,

An immunotoxin herein is a macromolecular drug which is usually a cytotoxic protein derived from a bacterial or plant protein, such as Diphtheria toxin (DT), Cholera toxin (CT), Trichosanthin (TCS), Dianthin, Pseudomonas exotoxin A (ETA′), Erythrogenic toxins, Diphtheria toxin, AB toxins, Type III exotoxins, etc. It also can be a highly toxic bacterial pore-forming protoxin that requires proteolytic processing for activation. An example of this protoxin is proaerolysin and its genetically modified form, topsalysin. Topsalysin is a modified recombinant protein that has been engineered to be selectively activated by an enzyme in the prostate, leading to localized cell death and tissue disruption without damaging neighboring tissue and nerves; An immunotoxin herein is preferably conjugated via the process of the application through an amino acid having free amino, thiol or carboxyl acid group; and more preferably through N-terminal amino acid.

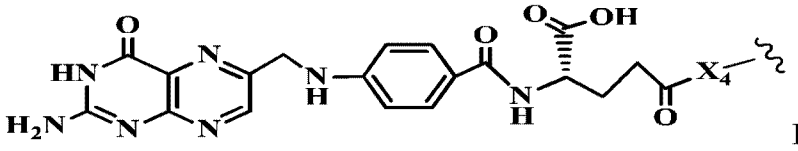
In addition, a certain cell-binding ligand or cell receptor agonist, a cell stimulating molecule or intracellular signalling molecule can be as a drug D conjugated via the process of the invention.

A cell-binding ligand or receptor agonist selected from: Folate derivatives; Glutamic acid urea derivatives; Somatostatin and its analogs (selected from the group consisting of octreotide (Sandostatin) and lanreotide (Somatuline)); Aromatic sulfonamides; Pituitary adenylate cyclase activating peptides (PACAP) (PAC1); Vasoactive intestinal peptides (VIP/PACAP) (VPAC1, VPAC2); Melanocyte-stimulating hormones (α-MSH); Cholecystokinins (CCK) /gastrin receptor agonists; Bombesins (selected from the group consisting of Pyr-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2)/gastrin-releasing peptide (GRP); Neurotensin receptor ligands (NTR1,

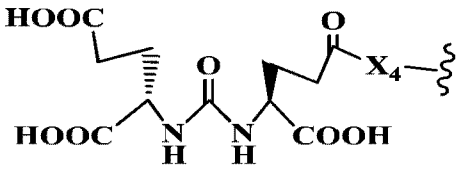
NTR2, NTR3); Substance P (NK1 receptor) ligands; Neuropeptide Y (Y1–Y6); Homing Peptides include RGD (Arg-Gly-Asp), NGR (Asn-Gly-Arg), the dimeric and multimeric cyclic RGD peptides (selected from cRGDfV), TAASGVRSMH and LTLRWVGLMS (Chondroitin sulfate proteoglycan NG2 receptor ligands) and F3 peptides; Cell Penetrating Peptides (CPPs); Peptide Hormones, selected from the group consisting of luteinizing hormone-releasing hormone (LHRH) agonists and antagonists, and gonadotropin-releasing hormone (GnRH) agonist, acts by targeting follicle stimulating hormone (FSH) and luteinizing hormone (LH), as well as testosterone production, selected from the group consisting of buserelin (Pyr-His-Trp-Ser-Tyr-D-Ser(OtBu)-Leu-Arg-Pro-NHEt), Gonadorelin (Pyr-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2), Goserelin (Pyr-His-Trp-Ser-Tyr-D-Ser(OtBu)-Leu-Arg-Pro-AzGly-NH_2), Histrelin (Pyr-His-Trp-Ser-Tyr-D-His(N-benzyl)-Leu-Arg-Pro-NHEt), leuprolide (Pyr-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-NHEt), Nafarelin (Pyr-His-Trp-Ser-Tyr-2Nal-Leu-Arg-Pro-Gly-NH_2), Triptorelin (Pyr-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH_2), Nafarelin, Deslorelin, Abarelix (Ac-D-2Nal-D-4-chloroPhe-D-3-(3-pyridyl)Ala-Ser-(N-Me)Tyr-D-Asn-Leu-isopropylLys-Pro-DAla-NH_2), Cetrorelix (Ac-D-2Nal-D-4-chloroPhe-D-3-(3-pyridyl)Ala-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH_2), Degarelix (Ac-D-2Nal-D-4-chloroPhe-D-3-(3-pyridyl)Ala-Ser-4-aminoPhe(L-hydroorotyl)-D-4-aminoPhe(carba-moyl)-Leu-isopropylLys-Pro-D-Ala-NH_2), and Ganirelix (Ac-D-2Nal-D-4-chloroPhe-D-3-(3-pyridyl)Ala-Ser-Tyr-D-(N9, N10-diethyl)-homoArg-Leu-(N9, N10-diethyl)-homoArg-Pro-D-Ala-NH_2); Pattern Recognition Receptor (PRRs), selected from the group consisting of Toll-like receptors' (TLRs) ligands, C-type lectins and Nodlike Receptors' (NLRs) ligands; Calcitonin receptor agonists; integrin receptors' and their receptor subtypes' (selected from the group consisting of$\alpha_V\beta_1$, $\alpha_V\beta_3$, $\alpha_V\beta_5$, $\alpha_V\beta_6$, $\alpha_6\beta_4$, $\alpha_7\beta_1$, $\alpha_L\beta_2$, $\alpha_{IIb}\beta_3$) agonists (selected from the group consisting of GRGDSPK, cyclo(RGDfV) (L1) and its derives [cyclo(-N(Me)R-GDfV), cyclo(R-Sar-DfV), cyclo(RG-N(Me)D-fV), cyclo(RGD-N(Me)f-V), cyclo(RGDf-N(Me)V-)(Cilengitide)]; Anticalin (a derivative of Lipocalins); Adnectins (10th FN3 (Fibronectin)); Designed Ankyrin Repeat Proteins (DARPins); Avimers; EGF receptors, or VEGF receptors' agonists;

A cell-binding molecule/ligand or a cell receptor agonist selected from the following: LB01 (Folate), LB02 (PMSA ligand), LB03 (PMSA ligand), LB04 (PMSA ligand), LB05 (Somatostatin), LB06 (Somatostatin), LB07 (Octreotide, a Somatostatin analog), LB08 (Lanreotide, a Somatostatin analog), LB09 (Vapreotide (Sanvar) , a Somatostatin analog), LB10 (CAIX ligand), LB11 (CAIX ligand), LB12 (Gastrin releasing peptide receptor (GRPr), MBA), LB13 (luteinizing hormone-releasing hormone (LH-RH) ligand and GnRH), LB14 (luteinizing hormone-releasing hormone (LH-RH) and GnRH ligand), LB15 (GnRH antagonist, Abarelix), LB16 (cobalamin, vitamin B12 analog), LB17 (cobalamin, vitamin B12 analog), LB18 (for $\alpha_v\beta_3$ integrin receptor, cyclic RGD

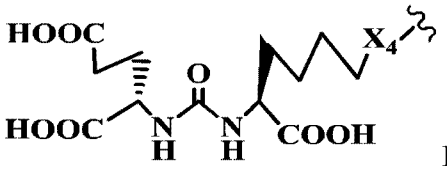
pentapeptide), LB19 (hetero-bivalent peptide ligand for VEGF receptor), LB20 (Neuromedin B), LB21 (bombesin for a G-protein coupled receptor), LB22 (TLR_2 for a Toll-like receptor,), LB23 (for an androgen receptor), LB24 (Cilengitide/cyclo(-RGDfV-) for an α_v integrin receptor, LB23 (Fludrocortisone), LB25 (Rifabutin analog), LB26 (Rifabutin analog), LB27 (Rifabutin analog), LB28 (Fludrocortisone), LB29 (Dexamethasone), LB30 (fluticasone propionate), LB31 (Beclometasone dipropionate), LB32 (Triamcinolone acetonide), LB33 (Prednisone), LB34 (Prednisolone), LB35 (Methylprednisolone), LB36 (Betamethasone), LB37 (Irinotecan analog), LB38 (Crizotinib analog), LB39 (Bortezomib analog), LB40 (Carfilzomib analog), LB41 (Carfilzomib analog), LB42 (Leuprolide analog), LB43 (Triptorelin analog), LB44 (Clindamycin), LB45 (Liraglutide analog), LB46 (Semaglutide analog), LB47 (Retapamulin analog), LB48 (Indibulin analog), LB49 (Vinblastine analog), LB50 (Lixisenatide analog), LB51 (Osimertinib analog), LB52 (a nucleoside analog), LB53 (Erlotinib analog) or LB54 (Lapatinib analog) which are shown in the following structures:



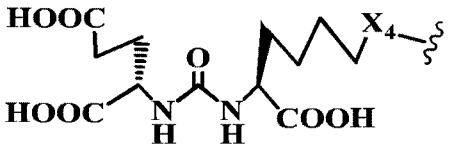
LB01 (Folate),



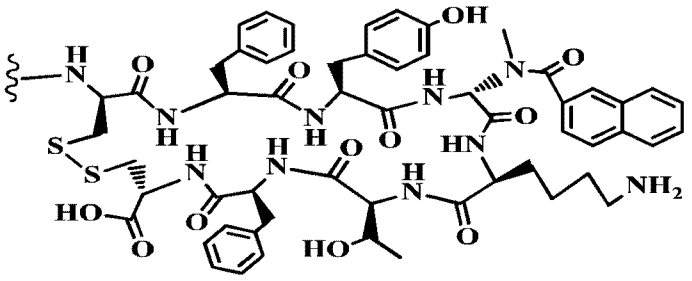
LB02 (PMSA ligand conjugate),



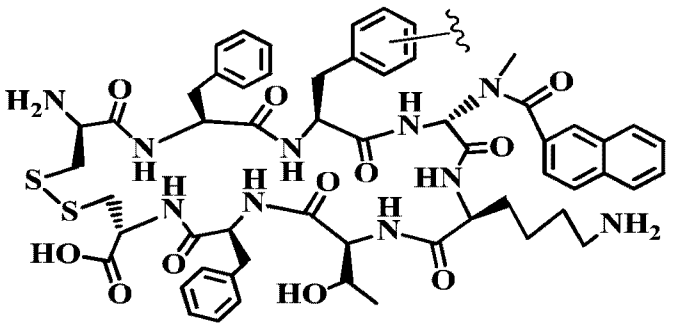
LB03 (PMSA ligand),



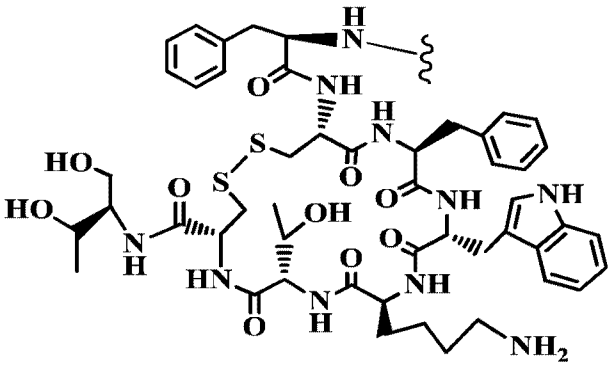
LB04 (PMSA ligand),



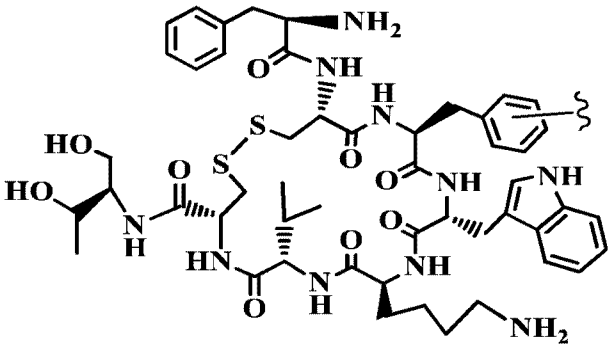
LB05 (Somatostatin),



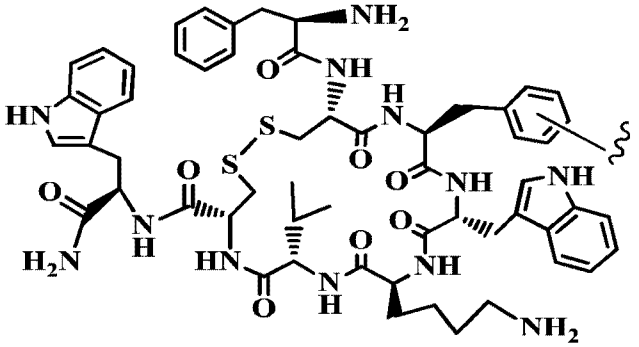
LB06 (Somatostatin),



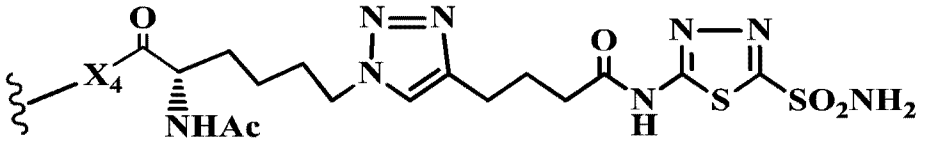
LB07 (Octreotide, a Somatostatin analog),



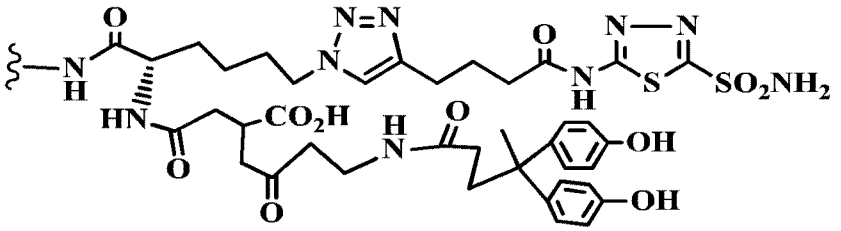
LB08 (Lanreotide, a Somatostatin analog),



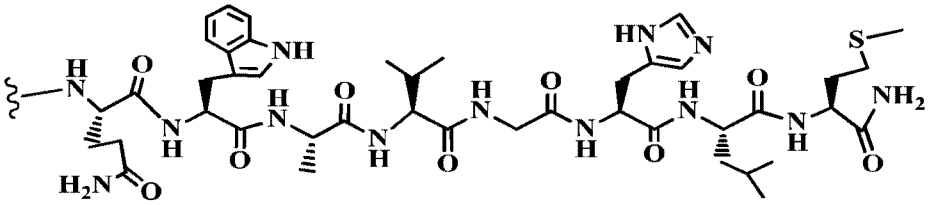
LB09 (Vapreotide (Sanvar), a Somatostatin analog),



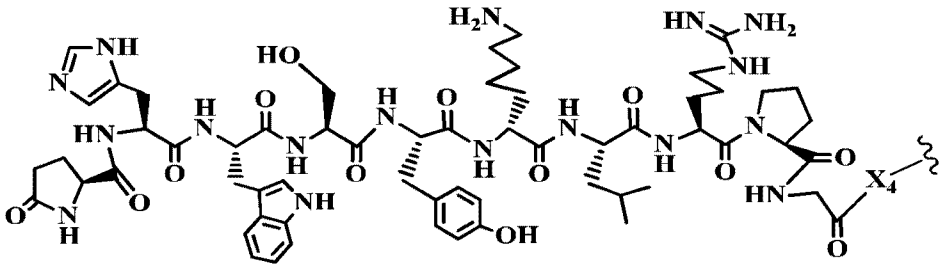
LB10 (CAIX ligand),



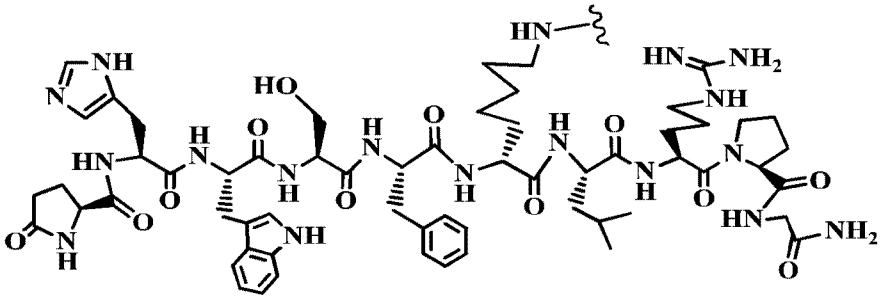
LB11 (CAIX ligand),



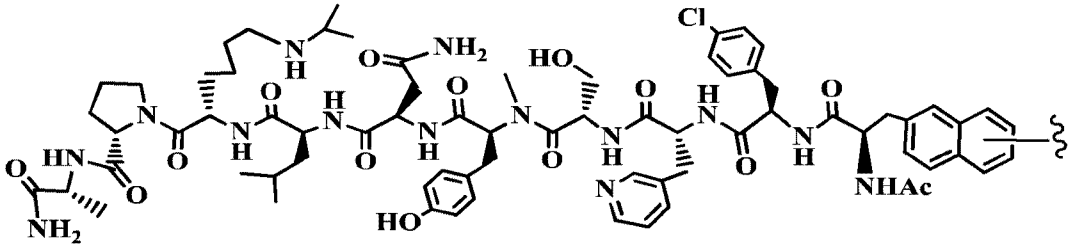
LB12 (Gastrin releasing peptide receptor (GRPr), MBA),



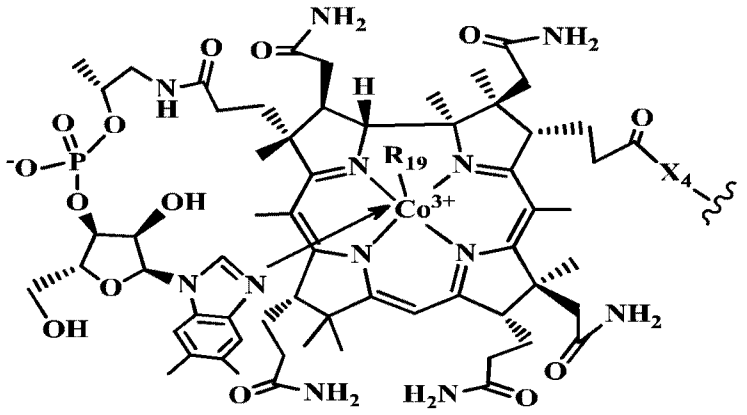
LB13 (luteinizing hormone-releasing hormone (LH-RH) ligand and GnRH),



LB14 (luteinizing hormone-releasing hormone (LH-RH) and GnRH ligand),

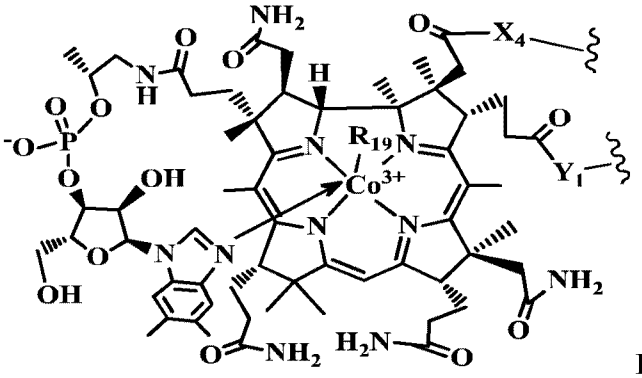


LB15 (GnRH antagonist, Abarelix),

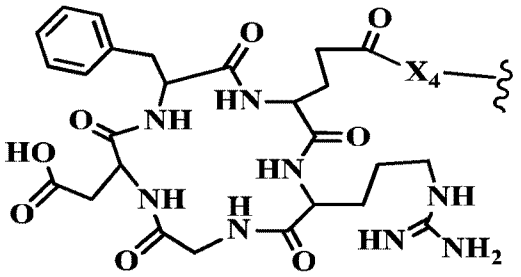


R_{19} is 5'deoxyadenosyl, Me, OH, CN;

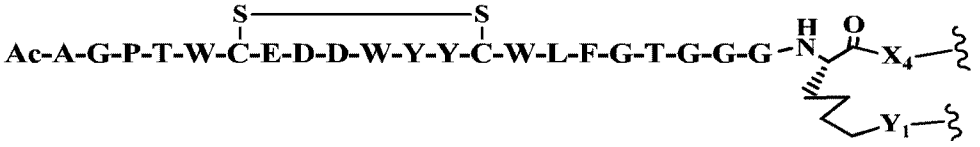
LB16 (cobalamin, vitamin B12 analog),



R_{19} is 5'deoxyadenosyl, Me, OH, CN; LB17 (cobalamin, vitamin B12 analog),

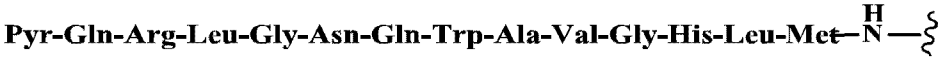


LB18 (for $\alpha_v\beta_3$ integrin receptor, cyclic RGD pentapeptide),

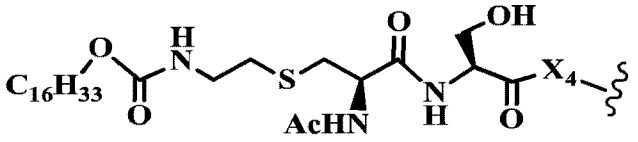


LB19 (hetero-bivalent peptide ligand conjugate for VEGF receptor),

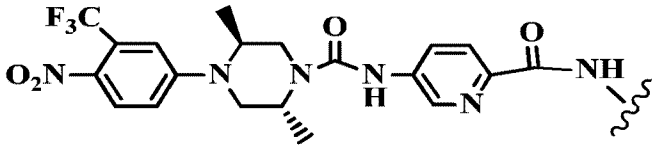
LB20 (Neuromedin B),



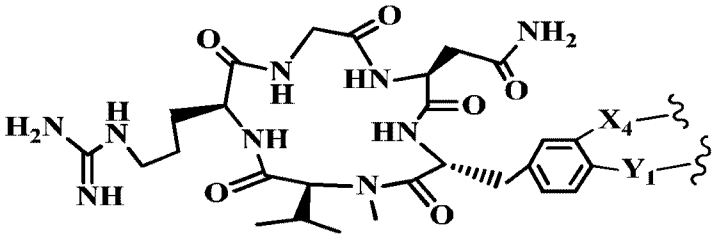
LB21 (bombesin conjugate for a G-protein coupled receptor),



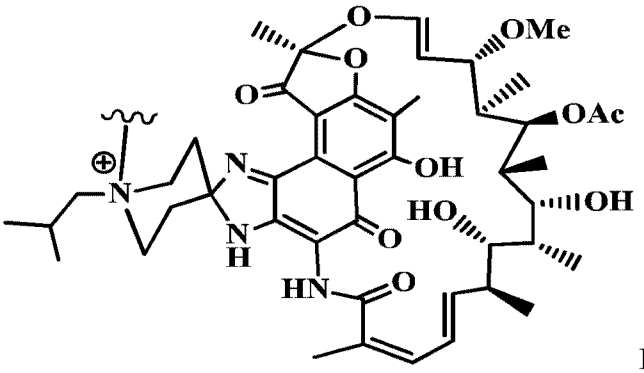
LB22 (TLR_2 conjugate for a Toll-like receptor),



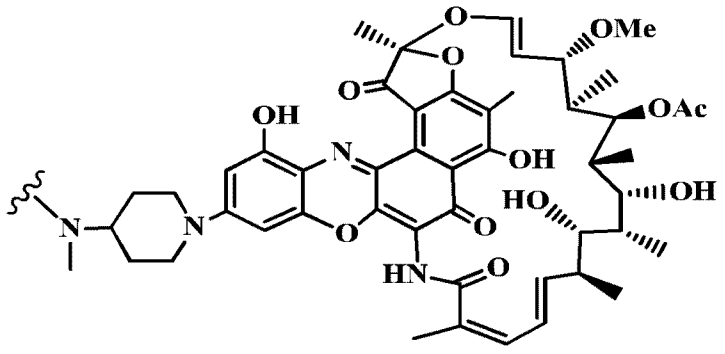
LB23 (an androgen receptor),



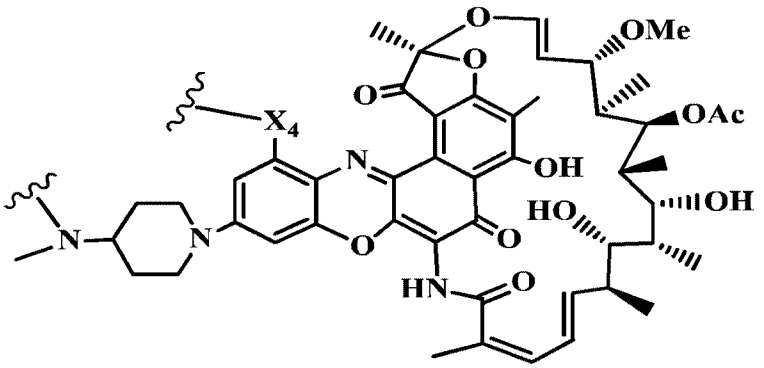
LB24 (Cilengitide/cyclo(-RGDfV-) conjugate for an α_v integrin receptor)



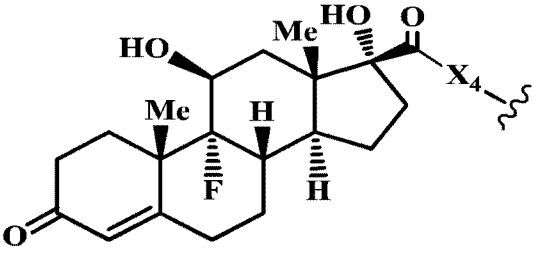
LB25 (Rifabutin analog),



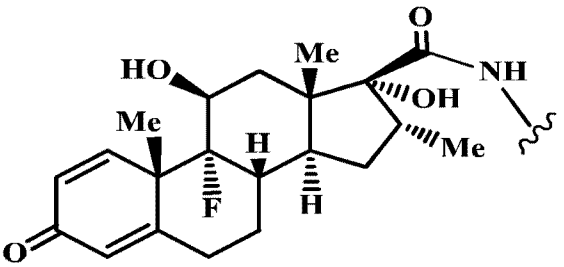
LB26 (Rifabutin analog),



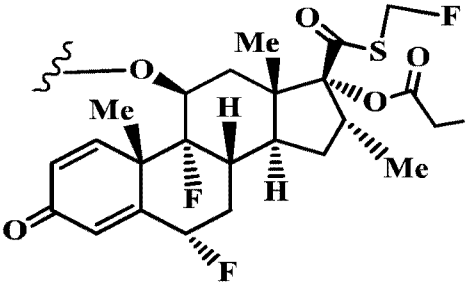
LB27 (Rifabutin analog),



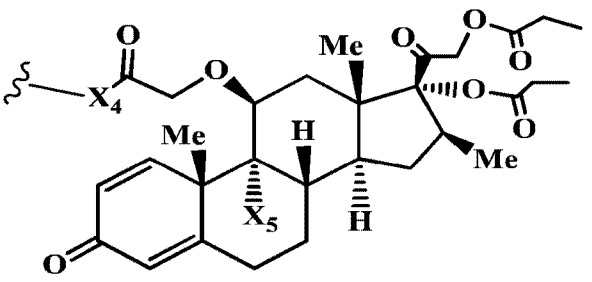
LB28 (Fludrocortisone),



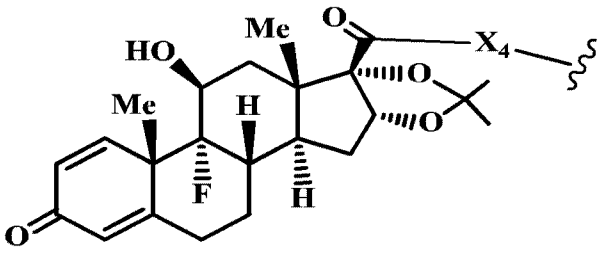
LB29 (Dexamethasone),



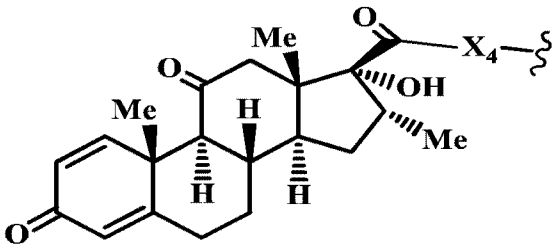
LB30 (fluticasone propionate),



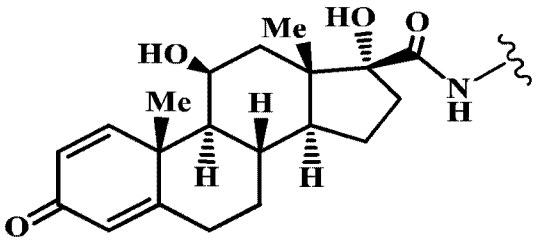
LB31 (Beclometasone dipropionate),



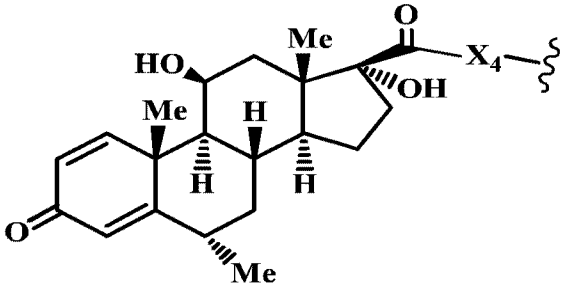
LB32 (Triamcinolone acetonide),



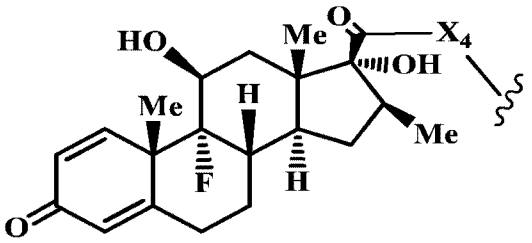
LB33 (Prednisone),



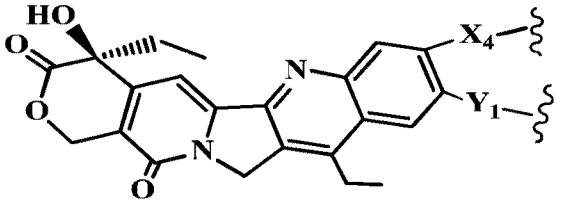
LB34 (Prednisolone),



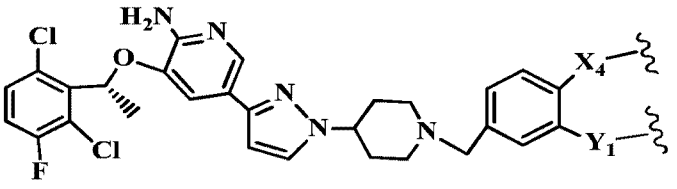
LB35 (Methylprednisolone),



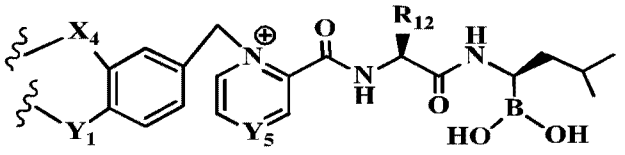
LB36 (Betamethasone),



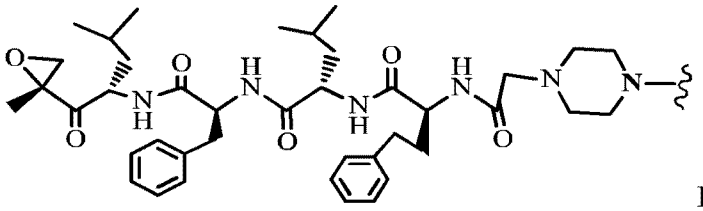
LB37 (Irinotecan analog),



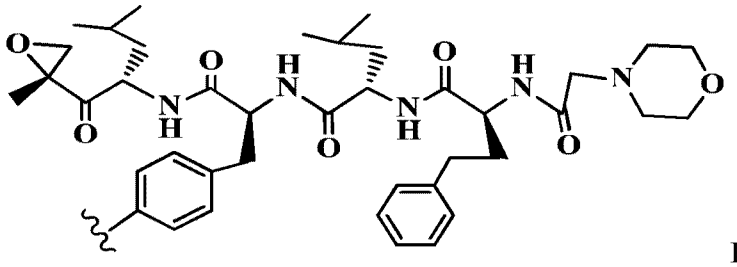
LB38 (Crizotinib analog),



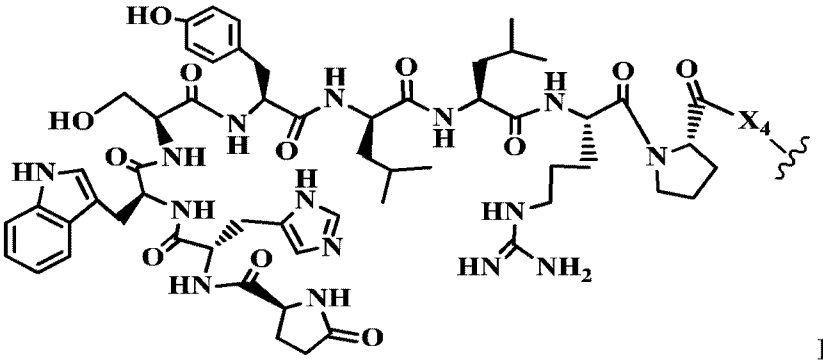
LB39 (Bortezomib analog), wherein Y_5, is N, CH, C(Cl), $C(CH_3)$, or $C(COOR_1)$; R_{12} is H, C_1-C_6 Alkyl, C_3-C_8 Ar;



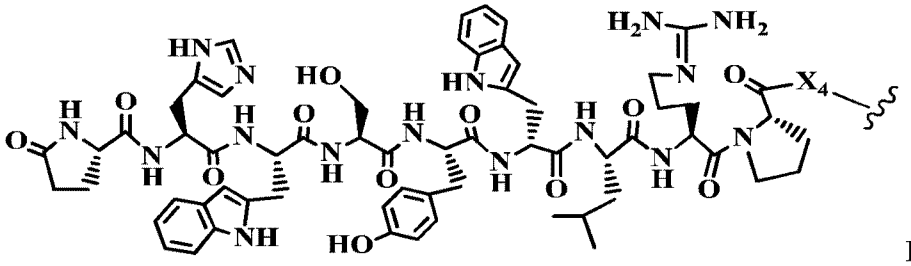
LB40 (Carfilzomib analog),



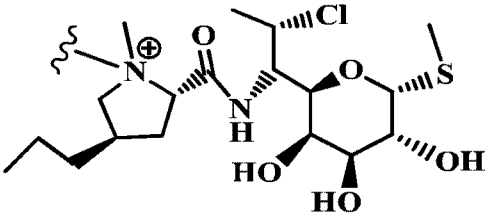
LB41 (Carfilzomib analog),



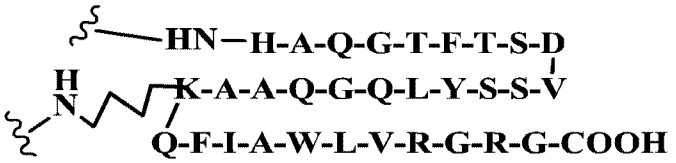
LB42 (Leuprolide analog),



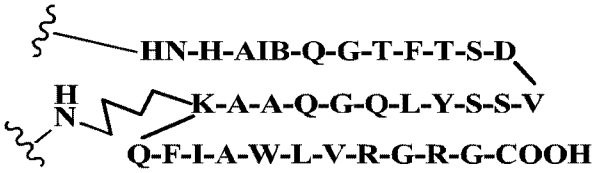
LB43 (Triptorelin analog),



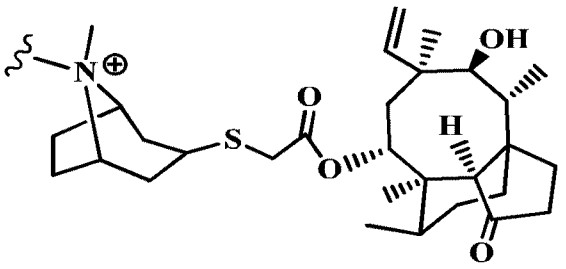
LB44 (Clindamycin),



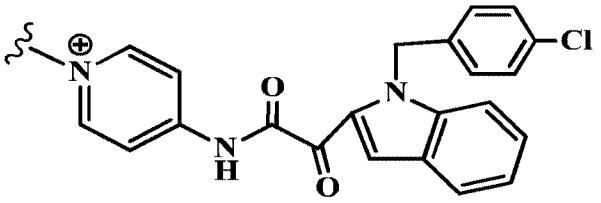
LB45 (Liraglutide analog),



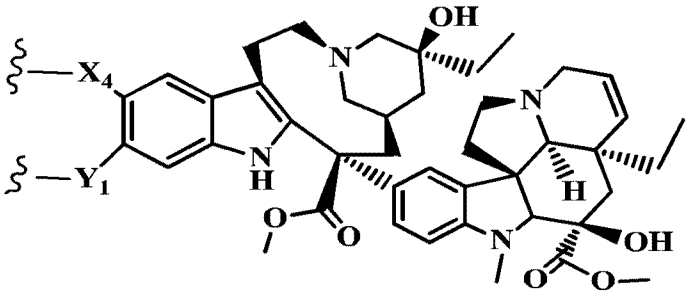
LB46 (Semaglutide analog),



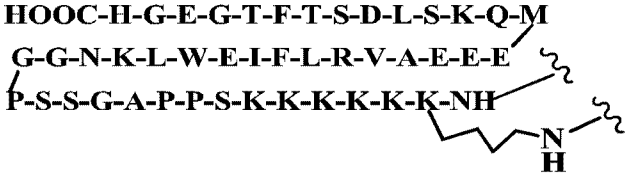
LB47 (Retapamulin analog),



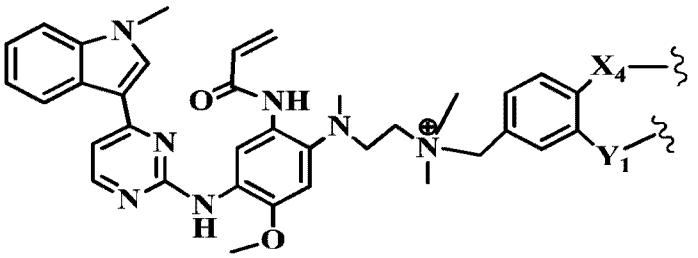
LB48 (Indibulin analog),



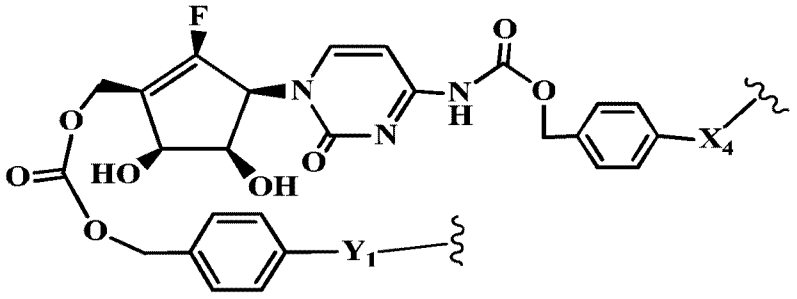
LB49 (Vinblastine analog),



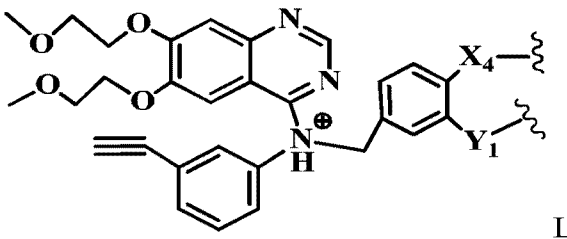
LB50 (Lixisenatide analog),



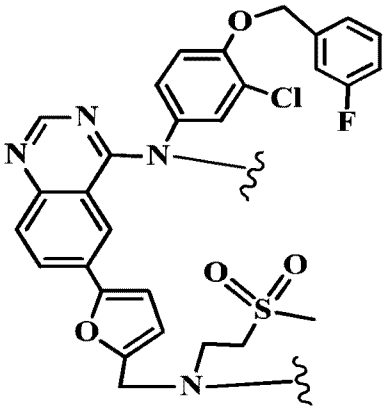
LB51 (Osimertinib analog),



LB52 (a nucleoside analog),



LB53 (Erlotinib analog),



LB54 (Lapatinib analog);

Wherein X_4, and Y_1 are independently O, NH, NHNH, NR_1, S, C(O)O, C(O)NH, OC(O)NH, OC(O)O, NHC(O)NH, NHC(O)S, OC(O)N(R_1), N(R_1)C(O)N(R_1), CH_2, C(O)NHNHC(O) and C(O)NR_1; R_1, R_2 and Ar, are defined the same above.

In certain embodiments, one, two or more DNA, RNA, mRNA, small interfering RNA (siRNA), microRNA (miRNA), and PIWI interacting RNAs (piRNA) can be as a drug D conjugated via the process of the invention:

, SI01,

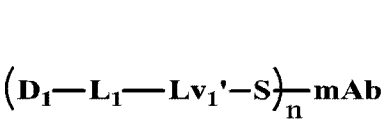
, SI02;

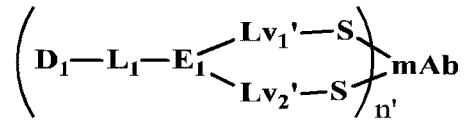
wherein " ∿∿ " is the site to link the side chain linker of the present patent; is single or double strands of DNA, RNA, mRNA, siRNA, miRNA, or piRNA; X_1,and Y are independently O, NH, NHNH, NR_1, S, C(O)O, C(O)NH, OC(O)NH, OC(O)O, NHC(O)NH, NHC(O)S, $OC(O)N(R_1)$, $N(R_1)C(O)N(R_1)$, CH_2, C(O)NHNHC(O) and $C(O)NR_1$; R_1, and R_2 are defined the same above.

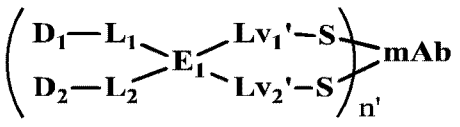
In certain embodiments, the oxidant which can be added in step (c) (after the step of the conjugation reaction) in the process of invention is preferably selected from dehydroascorbic acid (DHAA) to re-oxidize unreacted thiol groups, thus leading to restore the disulfide linkage in the antibody or antibody-like protein for having longer half-life. The concentration of the oxidant in the reaction solution may be 0.01 mM - 1.0 mM.

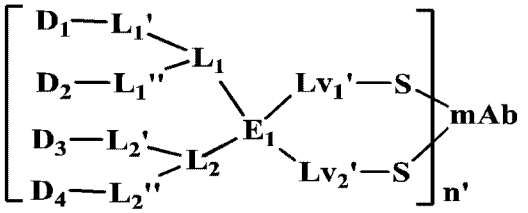
Instead of addition of DHAA in the process of invention, an excess amount of disulfide compound, such as cystine can be added in the step (c) to replace DHAA. Thus the disulfide compound can be reduced by the excess reductant, such as TCEP in step (b), to form a thiol compound, which simultaneously reacts to the excessive conjugation linker or linker/payload complex containing thiol reactive groups (e. g. maleimide), and following by removing of the generated thiol-succinimide linker/payload complex by chromatography.

In some embodiments, under conjugation process of the present invention to introduce specific thiols in an antibody or antibody-like protein (preferably mainly at the sites of disulfide bonds between heavy-light chain), then the thiols simultaneously or sequentially in conjugation process react to formula (I), (II), (III) or (IV) independently to the antibody or antibody-like protein to form a conjugate of formula (VI), (VII), (VIII) or (IX) accordingly as represented below:


(VI),

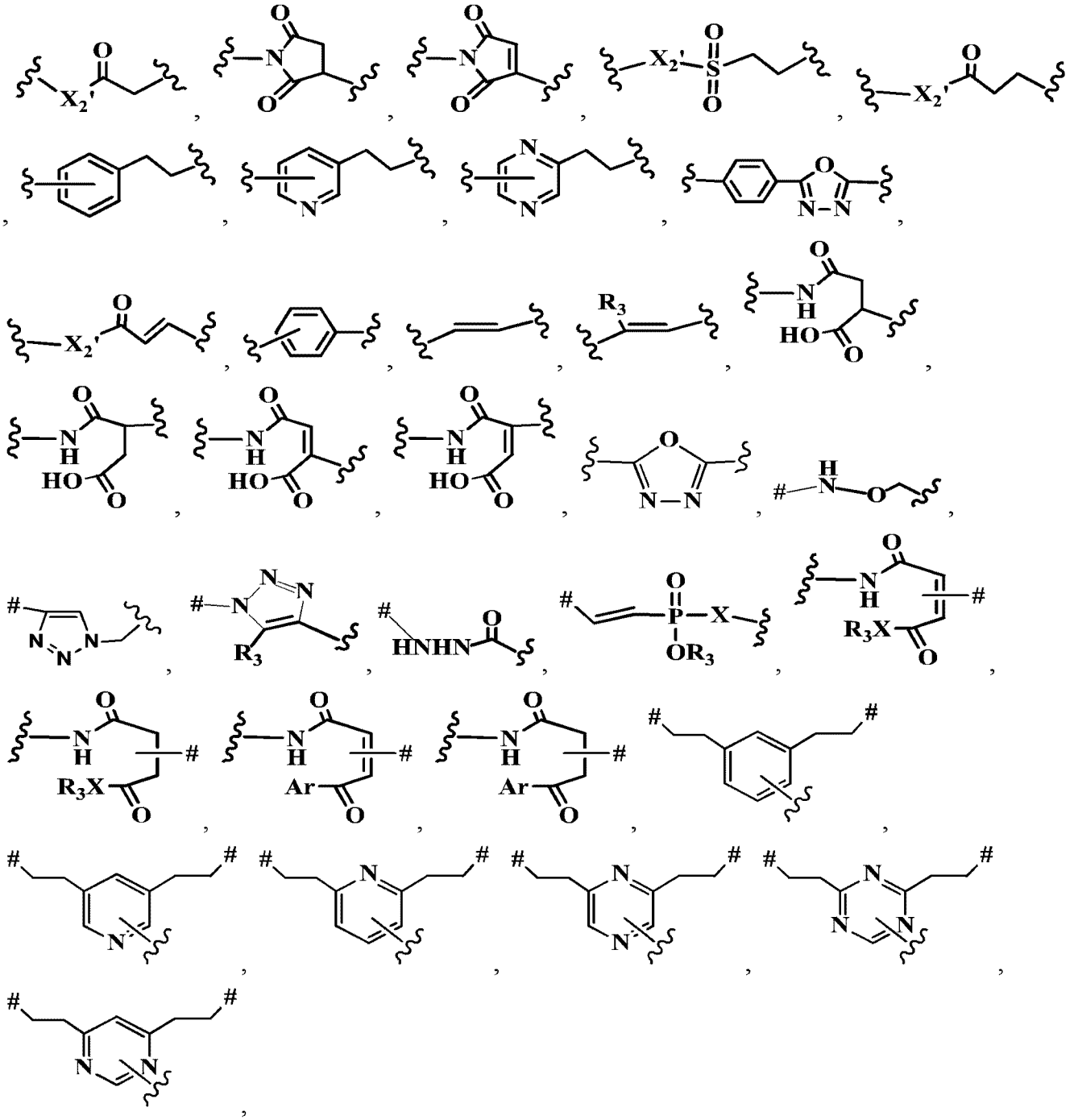

(VII),


(VIII),

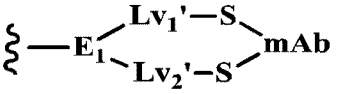
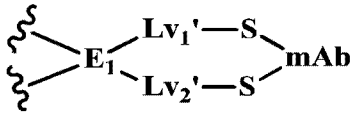

(IX),

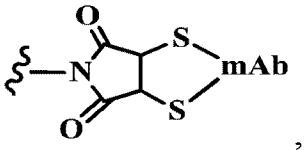
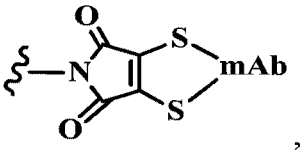
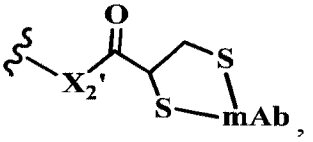
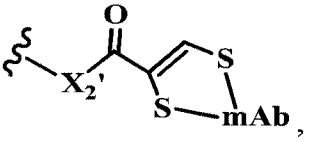
wherein n is 1 – 20; n' is 1-10; preferably n is 1 -8 and n' is 1 - 4; more preferably n is 2 -4 and n' is 1 - 2; D_1, D_2, L_1, L_2, and E_1 are described the same above; S (sulfur) is generated from the reduction of disulfide bonds in the antibody-like protein (e.g. antibody) under process of the

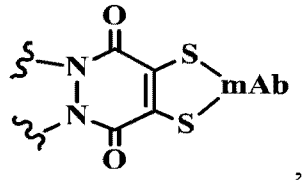
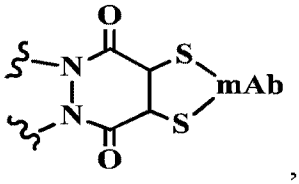
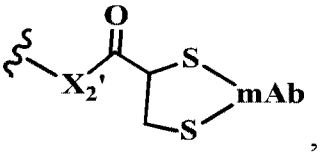
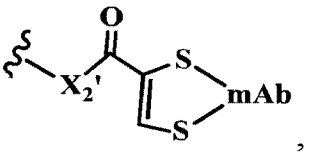
invention; mAb is an antibody-like protein; Wherein Lv_1' and Lv_2' are independently the resulting groups that a thiol in mAb reacted with Lv_1 and Lv_2, whose structures described above. Wherein Lv_1' and Lv_2' are independently having the following structures:

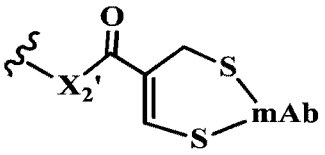
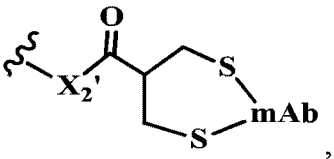
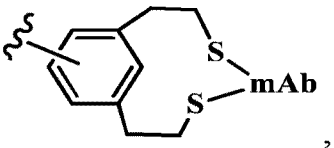


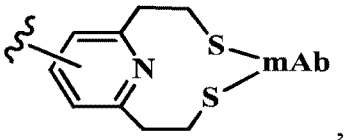
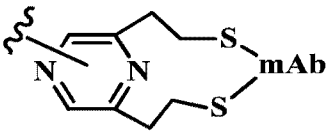
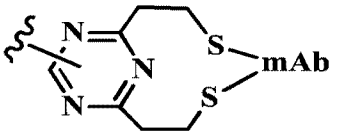
wherein Ar, X_2' and R_3 are defined the same previously.

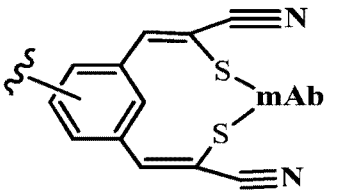
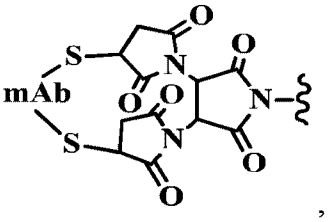
In the formula (VII), (VII) and (IX) wherein the fragments of,  and  can independently be selected from:

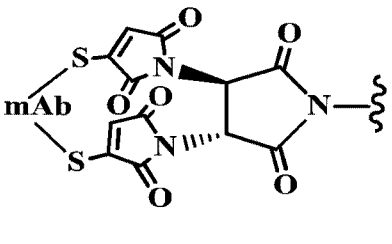
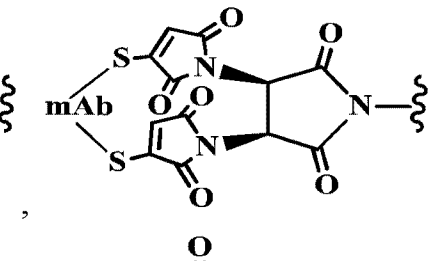
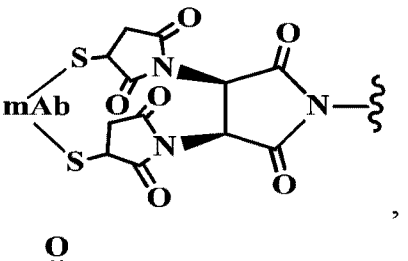
 ,  ,  ,  ,

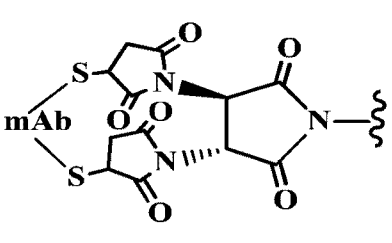
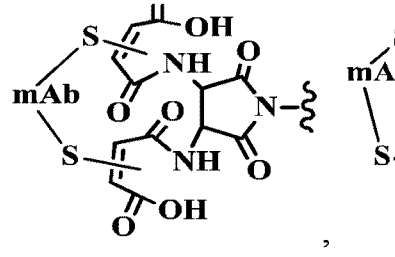
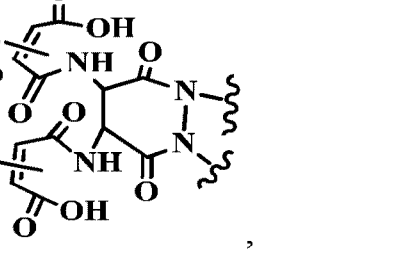
 ,  ,  ,  ,

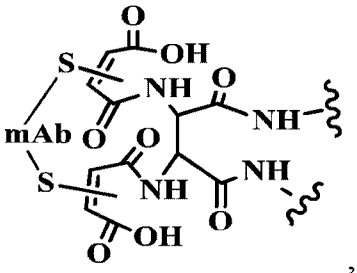
 ,  ,  ,

 ,  ,  ,

 ,  , ,

 ,  ,  ,

 ,  ,  ,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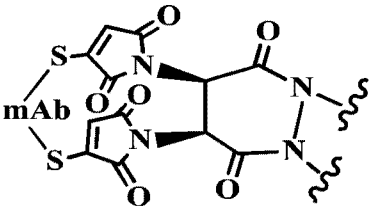
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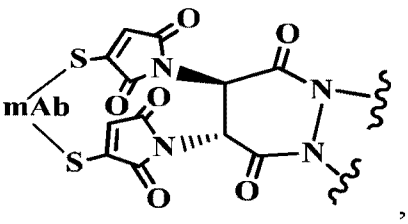
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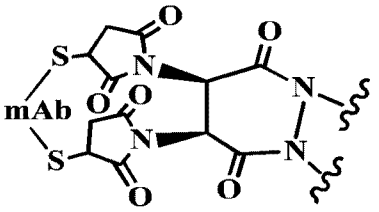
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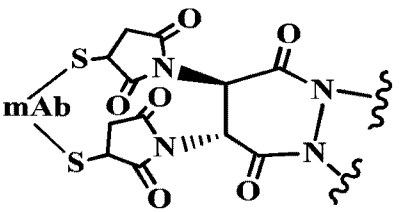
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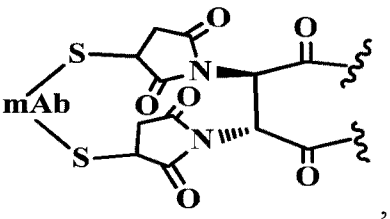
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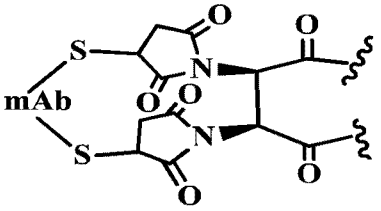
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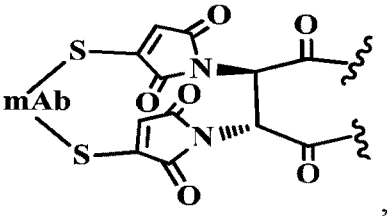
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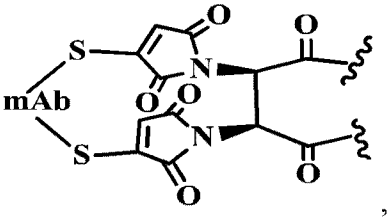
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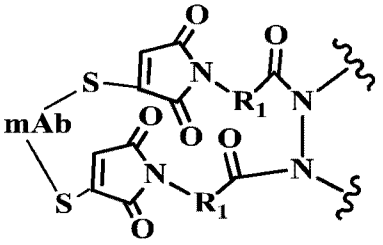
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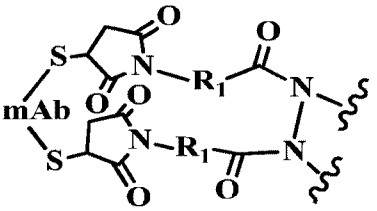
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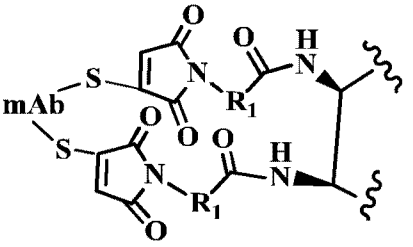
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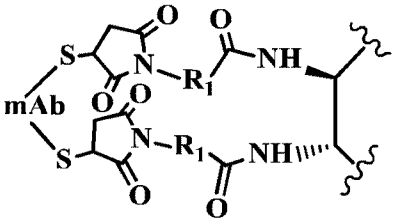
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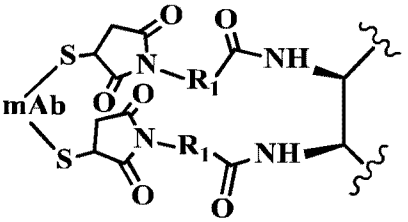
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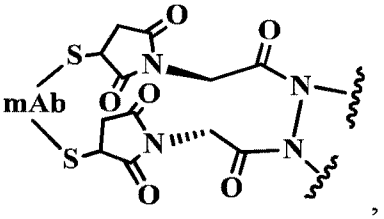
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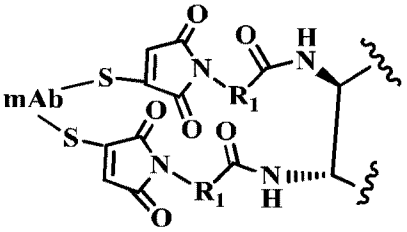
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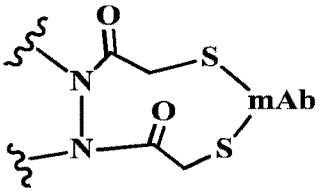
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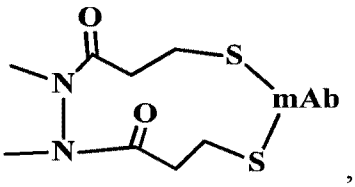
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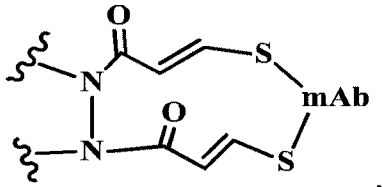
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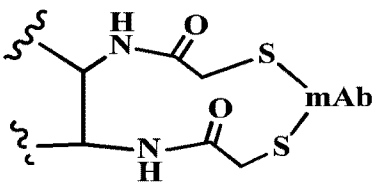
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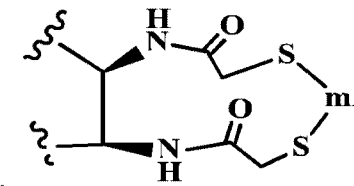
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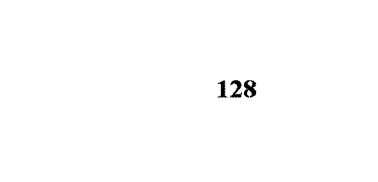
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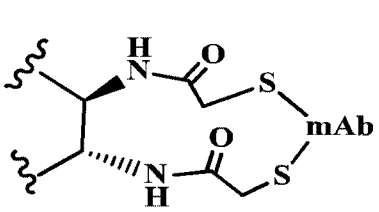
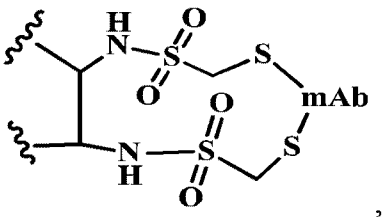
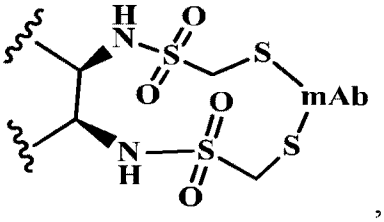
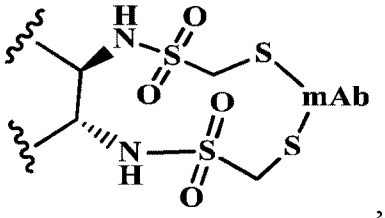
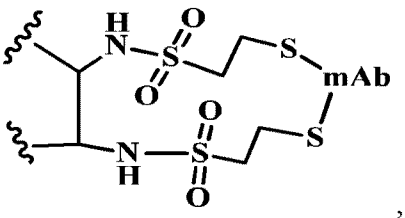
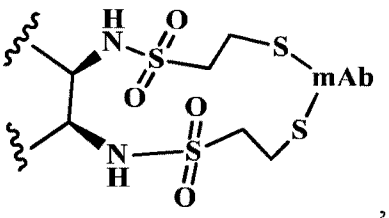
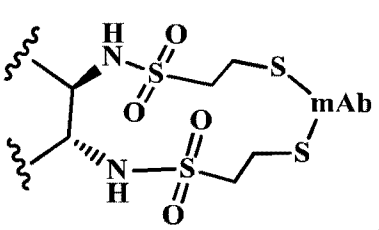
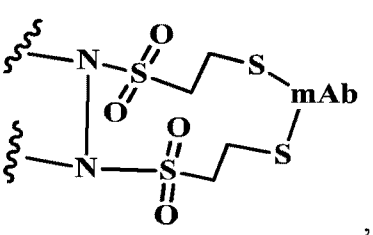
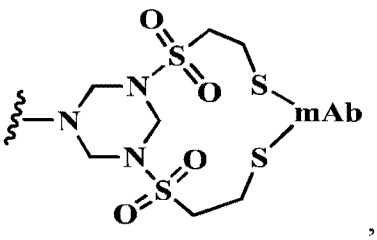
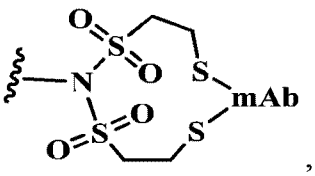
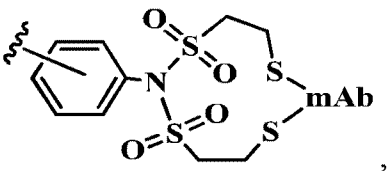
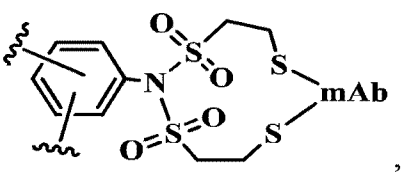
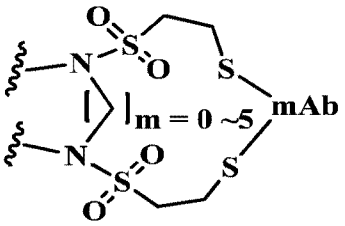
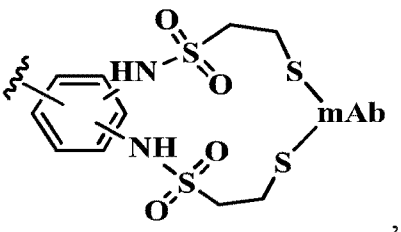
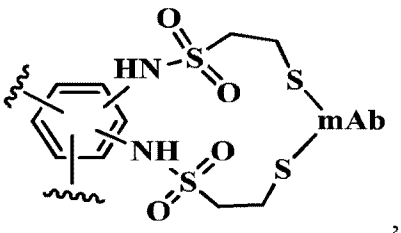
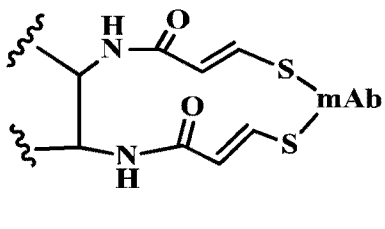
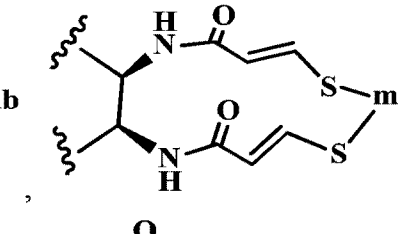
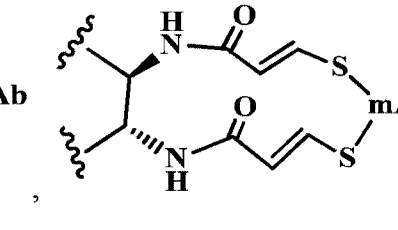
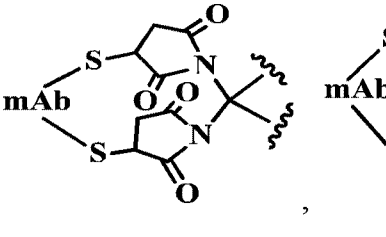
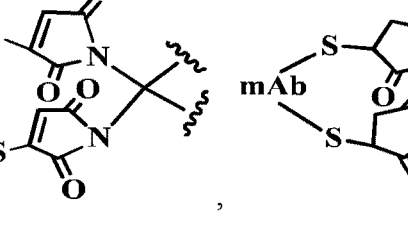
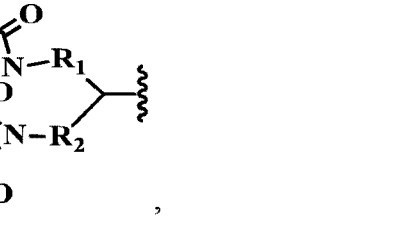
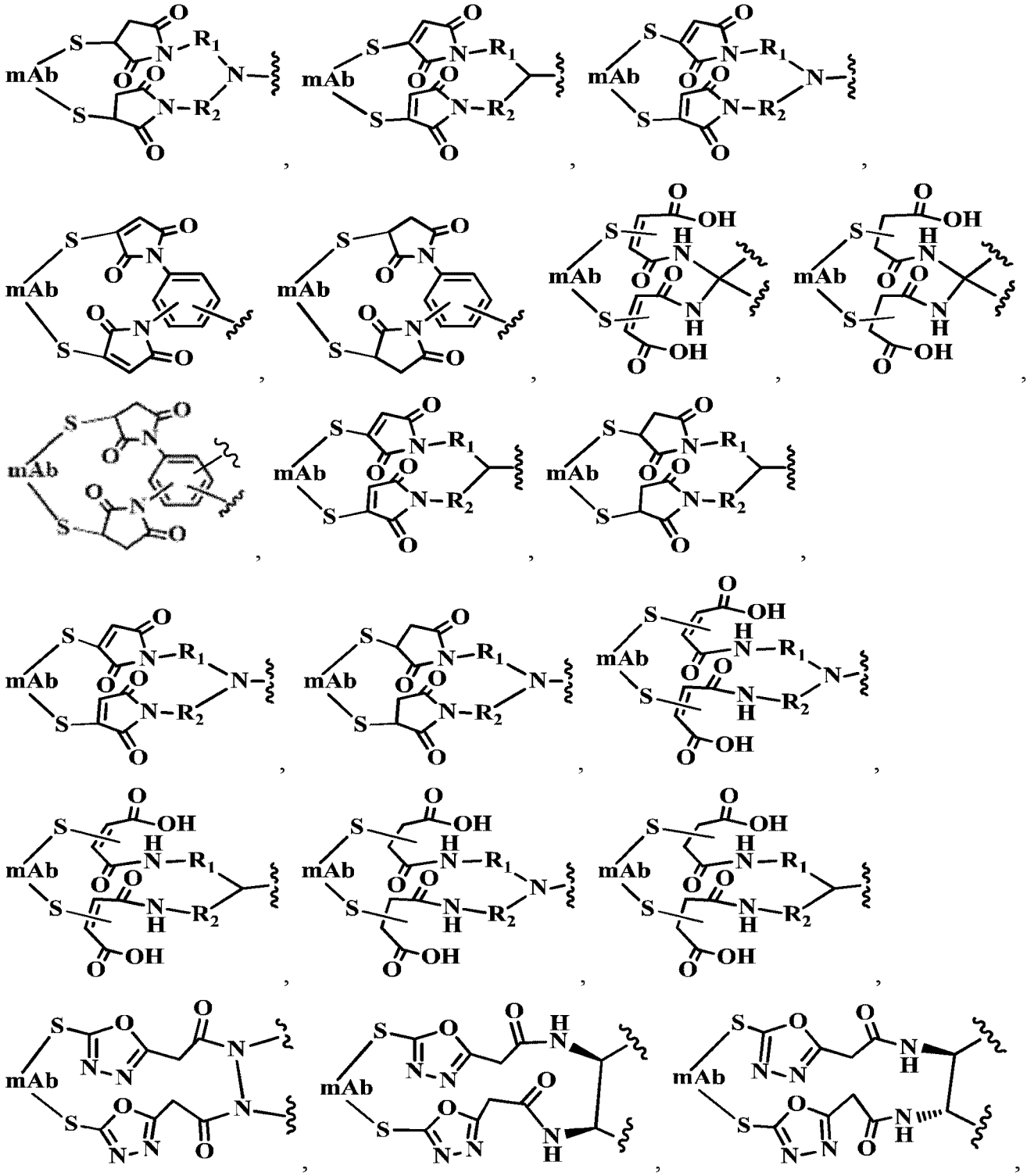
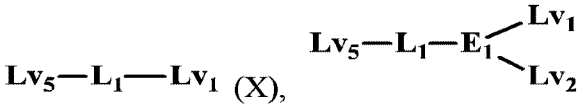
























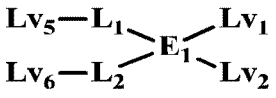
wherein R_1, R_2, X_2 are defined the same above; mAb is an antibody-like protein, preferably an antibody. Preferably, the conjugates are specifically linked to the tiols between heavy-light chains of the antibody when an antibody-like protein is specifically an antibody.

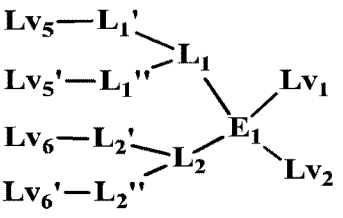
In other embodiments, under process of the present patent invention, wherein a linker having formula (X), (XI), (XII) or (XIII) illustrated below can react first to the selectively reduced thiols in

the antibody or antibody-like protein (e. g. typically thiols between heavy-light chain when the antibody or antibody-like protein is IgG antibody) independently, followed by condensation with a cytotoxic drug or cytotoxic drug/linker complex to form the conjugates of formula (VI), (VII), (VIII) or (IX) as shown above:

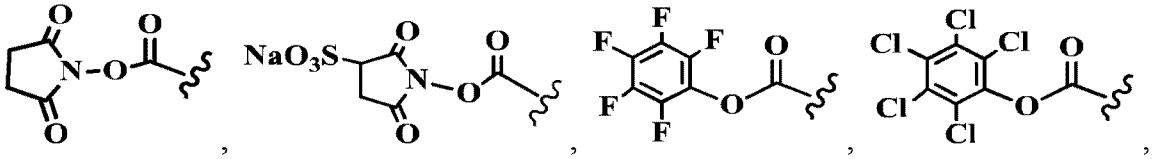

(X),

(XI),


(XII),


(XIII),

Wherein L_1, L_1', L_2, L_2', E_1, Lv_1, and Lv_2 are defined the same above for Formula (VI), (VII) (VIII) and (IX); wherein Lv_5 and Lv_6 are independently selected from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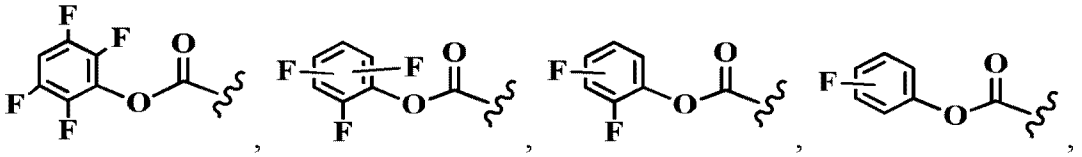
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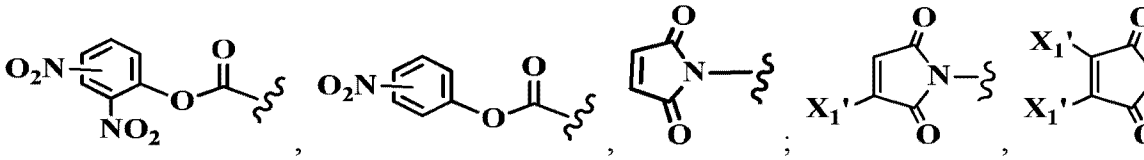
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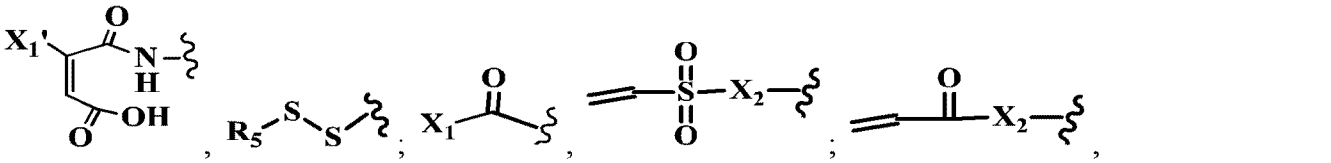
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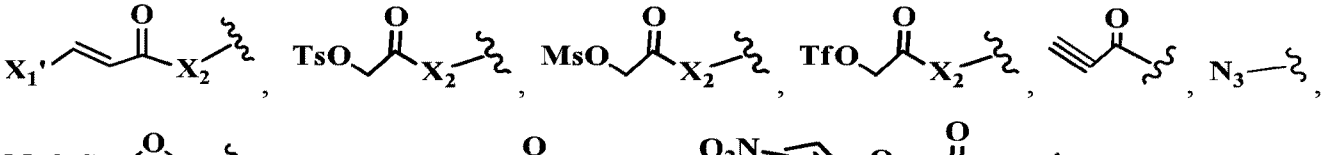
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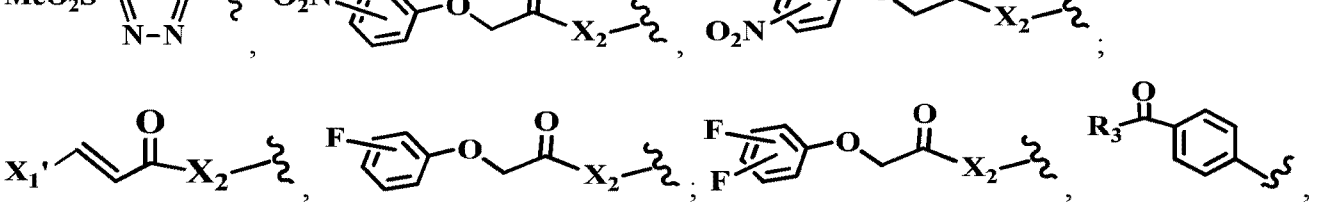
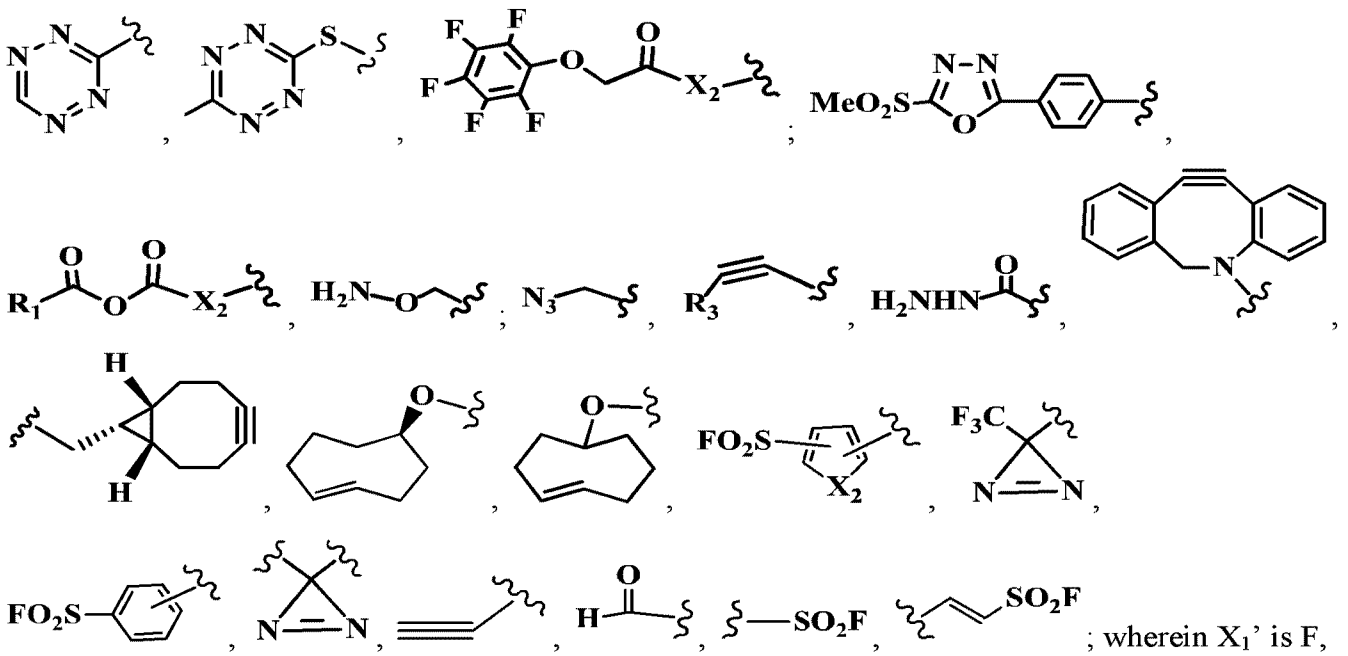
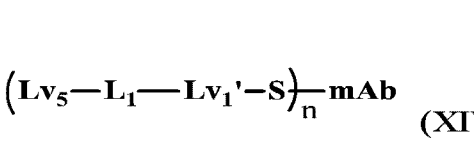
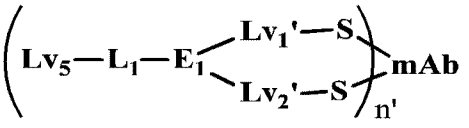


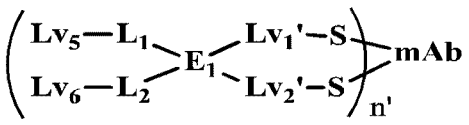


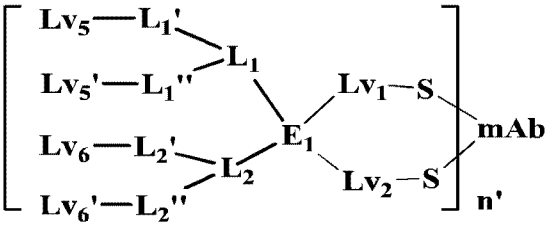
; wherein X_1' is F, Cl, Br, I, OTs (tosylate), OTf (triflate), OMs (mesylate), $OC_6H_4(NO_2)$, $OC_6H_3(NO_2)_2$, OC_6F_5, OC_6HF_4, or Lv_3; X_2' is O, NH, $N(R_1)$, or CH_2; R_3 and R_5 are independently H, R_1, aromatic, heteroaromatic, or aromatic group wherein one or several H atoms are replaced independently by -R_1, -halogen, -OR_1, -SR_1, -NR_1R_2, - NO_2, -$S(O)R_1$, -$S(O)_2R_1$, or -$COOR_1$; Lv_3 and Lv_3' are independently a leaving group selected from F, Cl, Br, I, nitrophenoxyl; N-hydroxysuccinimide (NHS); phenoxyl; benzenethiol, dinitrophenoxyl; pentafluorophenoxyl; tetrafluorophenoxyl; difluorophenoxyl; monofluorophenoxyl; pentachlorophenoxyl; triflate; imidazole; dichlorophenoxyl; tetrachlorophenoxyl; 1-hydroxybenzotriazole; tosylate; mesylate; 2-ethyl-5-phenylisoxazolium-3′-sulfonate, anhydrides formed its self, or formed with the other anhydride, e.g. acetyl anhydride, formyl anhydride; or an intermediate molecule generated with a condensation reagent for peptide coupling reactions or for Mitsunobu reactions; wherein the function groups Lv_5 and/or Lv_6 can be also reacted with a thiol in a cytotoxic drug as long as the reaction are at least one fold faster or slower than the reaction between Lv_1 or Lv_2 and a thiol in an antibody-like protein, in particular, in an antibody.

In other embodiments, under process of the present patent invention introducing specific thiols in the antibody-like protein, typically generating thiols between heavy-light chain when the antibody or antibody-like protein is IgG antibody, then the thiols simultaneously or sequentially in the conjugation process react to the linker of formula (X), (XI), (XII), or (XIII) illustrated above to form the antibody/linker complex molecule of formula (XIV), (XV), (XVI) or (XVII) below, following by reaction with a cytotoxic drug D_1 or D_2 independently to form the conjugate of formula (V), (VI), (VII) or (VIII).


(XIV),


(XV),


(XVI),


(XVII),

wherein Lv_5, Lv_6, L_1, L_2, L_1', L_2', E_1, Lv_1' Lv_2', mAb, n and n' are described the same above.

In further embodiments, under process of the present patent invention, wherein the linker of formula (X), (XI), (XII) or (XIII) illustrated above can react first with a cytotoxic drug to form the cytotoxic drug/linker complex molecule of formula (I), (II), (III) or (IV), follow by reaction with the reduced thiols in the antibody or antibody-like protein independently to form the conjugate of formula (VI), (VII), (VIII) or (IX) under process of this invention. The first step condensation reaction of the formula (X), (XI), (XII) or (XIII) to a cytotoxic drug can be in a separated pot, and the resulted cytotoxic drug/linker complex molecules of formula (I), (II), (III) or (IV) can be optionally purified by a chromatography, extraction or precipitation before for conjugation to the reduced thiols in the antibody-like protein. The first step of specific reduction of disulfide bonds in an antibody-like protein and conjugation reaction with formula (I), (II), (III) or (IV) are preferred in the same pot without separation of intermediates.

To distinguish the reactions between Lv_5 and/or Lv_6 to a cytotoxic drug, and Lv_1 and/or Lv_2 to a thiol in an antibody-like protein, each step of the reactions for the linker of formula (X), (XI), (XII) or (XIII) can be conducted at different conditions in the same or different reaction pots. For instance, a drug containing an amino group can undergo condensation with a carboxylic acid group in the linker in the present of a condensation regent, e. g. EDC, TBTU or BroP, to give a modified drug/linker complex of Formula (I), (II), (III) or (IV) bearing amide bonds. This condensation reaction can be performed at physiological buffer solution wherein the carboxylic acid group at one terminal of the linker of formula (X), (XI), (XII) or (XIII) is activated to be N-hydroxysuccinimidyl (NHS), pentfluorophenyl, dinitrophenyl ester, or carboxylic acid chloride group, etc, which can react to a drug bearing an amino group to provide drug/linker complex of Formula (I), (II), (III) or (IV), then subsequently or simultaneously undergo the conjugation to thiols of an antibody-like protein according to the process of the present application to form the conjugate of formula (VI), (VII), (VIII) or (IX). In another practice, the linker of formula (X), (XI), (XII) or (XIII) bearing both a thiol reactive group (e. g. maleimido, vinylsulfonyl, haloacetyl, acrylic, substituted propiolic) at one terminal and a drug reactive group (e. g. hydoxylsuccinimidyl (NHS), pentfluorophenyl, dinitrophenyl ester, amino, alkyloxylamino or clickable chemistry group (e. g. azide, alkyne,

dibenzocyclooctyne, BCN ((1*R*, 8*S*, 9*s*)-bicyclo[6.1.0]non-4-yn-9-ylmethanol)) at the other terminal can undergo undergo the conjugation to thiols of an antibody-like protein (preferably an antibody) according to the process of the present application in a buffer solution at pH 4.5 -7.5, 2 °C – 40 °C (preferably 2 °C -8 °C) with or without addition of 0~30% of water mixable (miscible) organic solvents to form the antibody-linker conjugate of formula (XIV), (XV), (XVI) or (XVII) independently. Then a drug bearing a reactive group which are matched to the reactive group in the antibody-linker conjugate of formula (XIV), (XV), (XVI) or (XVII) accordingly can be subsequently or simultaneously added to the reaction solution to provide the conjugate of formula (VI), (VII), (VIII) or (IX). In the second step reaction, the antibody-linker conjugate of formula (XIV), (XV), (XVI) or (XVII) can be optionally purified before proceeding the condensation with a drug, and the condensation condition of the second step can be adjusted, e. g. the pH is adjusted to 6.5 – 8.0, and/or temperature is adjusted to 20 -45 °C.

In other embodiments, during the process of the conjugation of this invention, prior to conjugating with a drug, the antibody can be modified through attachment of a heterobifunctional cross linker of formula (XIV), (XV), (XVI) or (XVII), such as with linkers of Amine-to-Sulfhydryl (succinimidyl (NHS) ester/maleimide, NHS ester/ pyridyldithiol, NHS esters/ haloacetyl), diazirine (SDA)–to-Sulfhydryl, Azide-to-Sulfhydryl, Alkyne-to-Sulfhydryl, Sulfhydryl-to-Carbohydrate (Maleimide/Hydrazide, Pyridyldithiol /Hydrazide, haloacetyl /Hydrazide), Hydroxyl-to-Sulfhydryl (Isocyanate/Maleimide), Sulfhydryl-to-DNA (Maleimide/ Psoralen, Pyridyldithiol / Psoralen, haloacetyl/Psoralen), Sulfhydryl-to-Carboxyl (Carbodiimide).

The reactive group of a drug/cytotoxic agent that reacting to a modified an antibody-linker conjugate of formula (XIV), (XV), (XVI) or (XVII) to give the final conjugate can be in different ways accordingly. For example, the conjugate linked via disulfide bonds is achieved via the first step, a linker of formula (X), (XI), (XII) or (XIII) is conjugated to the antibody at 2 °C - 8 °C, pH 4.5 – 6.0, according to the present invention of reduction and conjugation of an antibody, following by a disulfide exchange between a drug containing a free thiol group and the disulfide bond ((e. g. pyridyldithio moiety) in the linker attached to the modified antibody at pH 6.5 – 8.0, at 20 °C - 40 °C. Before the addition of the drug containing a free thiol for conjugation, the excess reduction agent (e. g. TCEP, or tri(3-hydroxylpropyl)phosphine) is preferably removed from the reaction pot. Synthesis of the conjugates linked via thioether is achieved by first reaction of a linker containing both thiol reactive terminals of maleimido or haloacetyl or ethylsulfonyl or substituted propiolic group to the thiols in an antibody which are reduced by the process of the present patent application at 2 °C - 8 °C, pH 4.5 – 6.0 to give the antibody-linker conjugate of formula (XIV), (XV), (XVI) or (XVII), following by reaction of a drug containing a thiol at pH 6.5 – 8.0, at 20 °C - 40 °C to provide the conjugate of formula (VI), (VII), (VIII) or (IX). If the same pH and/or temeperature conditions are

chosen for the two step reactions for thioether linked conjugates, the over four times equivalents of the linker containing dual terminal thiol reactive are used for the conjugation. It should be noted that the preferred methods of synthesis of the disulfide or thiol-ether linked conjugates are through the first chemical synthesis the drug-linker complex having disulfide or thiol-ether bonds of the formula (I), (II), (III) or (IV), following by reaction with the thiols in the protein (antibody) according the process of the invention. Synthesis of conjugates bearing an acid labile hydrazone linkage can be achieved by reaction of a carbonyl group with the hydrazide moiety in the linker, by methods known in the art (see, for example, P. Hamann et al., Cancer Res. 53, 3336-34, 1993; B. Laguzza et al., J. Med. Chem., 32; 548-55, 1959; P. Trail et al., Cancer Res., 57; 100-5, 1997). Synthesis of conjugates bearing triazole linkage can be achieved by reaction of a 1-yne group of the drug with the azido moiety in the linker, through the click chemistry (Huisgen cycloaddition) (Lutz, J-F. et al, 2008, Adv. Drug Del. Rev. 60, 958–70; Sletten, E. M. et al, 2011, AccChem. Research 44, 666–76). Synthesis of the conjugates linked via oxime is achieved by reaction of a modified antibody-like protein containing a ketone or aldehyde and a drug containing oxyamine group. A drug bearing a hydroxyl group or a thiol group can be reacted with a modified linker of Formula (XIV), (XV), (XVI) or (XVII), bearing a halogen, particularly the alpha halide of carboxylates, in the presence of a mild base, e.g. pH 8.0 ~ 9.5, to give a modified drug/linker complex bearing an ether or thiol ether linkage of Formula (I), (II), (III) or (IV). A drug containing a hydroxyl group can be condensed with a linker of Formula (XIV), (XV), (XVI) or (XVII) bearing a carboxyl group, in the presence of a dehydrating agent, such as EDC or DCC, to give ester linkage, then the subject drug/linker complex undergoes the conjugation with an antibody-like protein under the process of the present invention. A drug containing an amino group can condensate with a carboxyl ester of NHS, imidazole, nitrophenoxyl; N-hydroxysuccinimide (NHS); methylsufonylphenoxyl; dinitrophenoxyl; pentafluorophenoxyl; tetrafluorophenoxyl; difluorophenoxyl; monofluorophenoxyl; pentachlorophenoxyl; triflate; imidazole; dichlorophenoxyl;tetrachlorophenoxyl;1-hydroxybenzotriazole; tosylate; mesylate; 2-ethyl-5-phenylisoxazolium-3′-sulfonate on the antibody-linker of Formula (XIV), (XV), (XVI) or (XVII) to give a conjugate via amide bond linkage of Formula (VI), (VII), (VII) or (IX). For a linker of formula (X), (XI), (XII) or (XIII) which contains both different thiol reactive terminals (e. g. one end is maleimido group(s) and the other end is vinyl sulfonyl group(s)), then the conjugation can be proceeded at different pHs or temperatures or with a catalyst to differentiate the one terminal reaction with a thiol group of a drug or of an antibody from another end of terminal reaction. In the case of both one end is maleimido group(s) and the other end is vinyl sulfonyl group(s)), the reaction (Michael addition) of a thiol group of a drug or of an antibody with a maleimido group can be proceeded at pH below 5.5 (normally at pH 4.5 ~ 7.0) of a buffer solution,

at low temperature (2 ~ 15 °C), and in a short time (30 min ~ 2 hrs.), but the reaction (Michael addition) of a thiol group of a drug or of an antibody with a vinyl sulfonyl group has to be proceeded at pH over 7.0 (normally at pH 7.0 ~ 8.5) of a buffer solution, at high temperature (20 ~ 37 °C), and for at least 8 hrs. Thus, a thiol group of a drug or of an antibody can first react to a maleimido group in a linker of formula (X), (XI), (XII) or (XIII), at low pH (e. g. below 6) for less than 2 hrs., following by addition of a thiol reduced antibody (containing a thiol) or a drug containing a thiol to react a vinyl sulfonyl group at the other end of the linker complex at higher pH (e. g. 7.5).

In further embodiments, under process of the present patent invention, the resulted conjugates of formula (VI), (VI)), (VIII) or (IX) are over 75% linked to the cysteine sites between heavy-light chains of an antibody, and are less than 15% linked to the cysteine sites between heavy-heavy chains (hinge region) of an antibody. Typically, for formula (VI) or (VII), when drug/antibody ratio (DAR) is set to be 4, the distributions in percentage of the numbers of drugs in the antibody are: D0 <1%, D2<10%, D4>75%, D6<10%, D8<10%; for formula (VIII) or (IX), when drug/antibody ratio (DAR) is set to be 8, the distributions in percentage of the numbers of drugs in the antibody are: D0 <1%, D1<10%, D2>75%, D3<10%, D4<10%.

The resulted conjugate may be purified by standard biochemical means, such as gel filtration on a Sephadex G25 or Sephacryl S300 column, adsorption chromatography, ion (cation or anion) exchange chromatography or by dialysis (ultrafiltration or hyperfiltration (UF) and diafiltration (DF)). In some cases, a small size molecule of antibody-like protein (e.g. < 10 KD) conjugated with a small molecular drugs can be purified by chromatography such as by HPLC, medium pressure column chromatography or ion exchange chromatography.

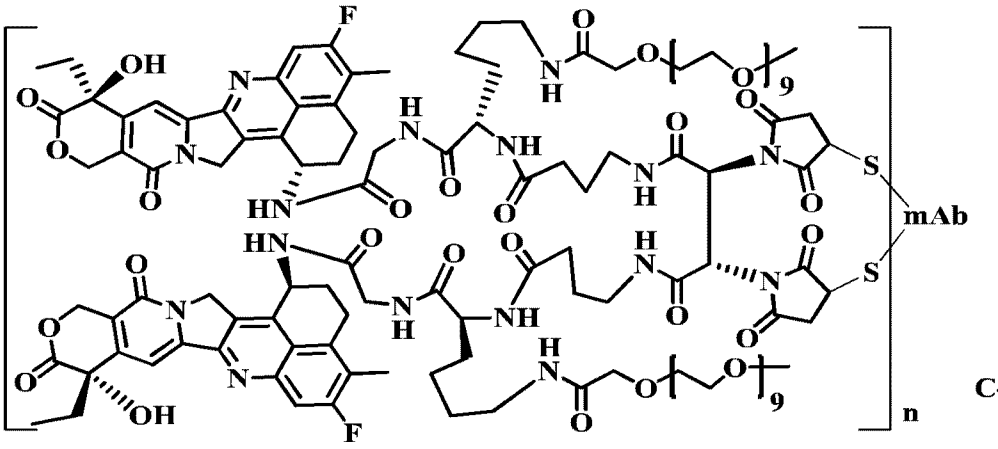
In general, the conjugate of Formula (VI), (VII), (VIII) or (IX) is preferably generated from a drug/linker complex of Formula (I), (II), (III) or (VI), as in a one pot reaction. When a thiol reduced from an antibody protein reacts a thiol reactive group in the terminal of drug/linker complex of Formula (I), (II), (III) or (IV), the Ellman reagent can be optionally used to monitor the efficient reduction of the disulfide bonds and conjugation of the tiols through measurement of the numbers of the free thiols during the reactions. A UV spectrometry at wavelength of range 190-390 nm, preferably at 240-380 nm, more preferably at 240-330 nm is preferred to be used in assisting the reaction (via monitoring the conjugation). The conjugation reaction can be thus measured or conducted in a quartz cell or Pyrex flask in temperature control environment. The drug/protein (antibody) ratios (DAR) of the conjugates can also be measured by UV at wavelength of range 240-380 nm via calculation of the concentrations of the drug and the protein, by Hydrophobic Interaction Chromatography (HIC-HPLC) via measurement of the integration areas of each drug/protein fragment, by Capilary electrophoresis (CE), and/or by LC-MS or LC-MS/MS or CE-MS (the

combination of liquid chromatography (LC) or CE with mass spectrometry (MS) via measurement of both the integration areas of LC or CE and Peak intensity of MS for each drug/protein fragment). It is also noted in the conjugation process of the present invention, when a drug or a drug/linker complex is not well soluble in a water based buffer solution, up to 30% of water mixable (miscible) organic solvents, such as DMA, DMF, ethanol, methanol, acetone, acetonitrile, THF, isopropanol, dioxane, propylene glycol, or ethylene diol can be added as the co-solvent in water based buffer solution.

The aqueous solutions for the modification of the antibody-like protein are buffered between pH 4 and 9, preferably between 6.0 and 7.5 and can contain any non-nucleophilic buffer salts useful for these pH ranges. Typical buffers include phosphate, acetate, triethanolamine HCl, HEPES, and MOPS buffers, which can contain additional components, such as cyclodextrins, sucrose and salts, for examples, NaCl and KCl. Other biological buffers that are used for the conjugation process are listed in the definition section. The progress of the reaction can be monitored by measuring the decrease in the absorption at a certain UV wavelength, such as at 254 nm, or increase in the absorption at a certain UV wavelength, such as 280 nm, or the other appropriate wavelength. After the reaction is complete, isolation of the modified cell-binding antibody-like protein agent can be performed in a routine way, using for example gel filtration chromatography, or adsorptive chromatography.

When disulfide exchange reaction is used for modification of an antibody-like protein, the extent of the modification can be assessed by measuring the absorbance of the nitropyridine thione, dinitropyridine dithione, pyridine thione, carboxylamidopyridine dithione and dicarboxyl-amidopyridine dithione group released via UV spectra. For the conjugation without a chromophore group, the modification or conjugation reaction can be monitored by LC-MS, preferably by UPLC-QTOF mass spectrometry, or Capilary electrophoresis–mass spectrometry(CE-MS). The linker compounds have diverse functional groups that can react with drugs, preferably cytotoxic agents that possess a suitable substituent. For examples, the modified antibody-like protein bearing an amino or hydroxyl substituent can react with drugs bearing an N-hydroxysuccinimide (NHS) ester, the modified antibody-like protein bearing a thiol substituent can react with drugs bearing a maleimido or haloacetyl group. Additionally, the modified antibody-like protein bearing a carbonyl (ketone or aldehyde) substituent can react with drugs bearing a hydrazide or an alkoxyamine. One skilled in the art can readily determine which linker to use based on the known reactivity of the available functional group on the linkers.

In certain embodiments, examples of preferred conjugates of formula (VI), (VII), (VIII) and (IX) which can be constructed under the process of the invention are illustrated below:



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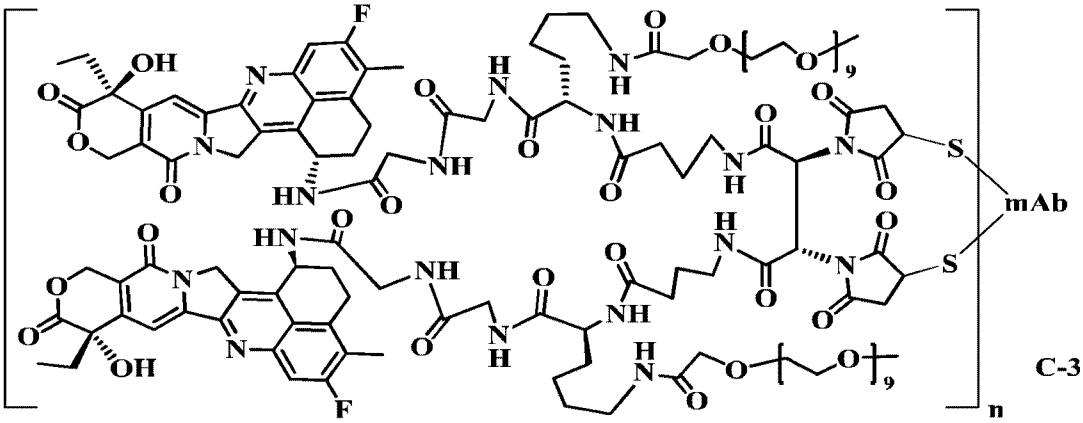

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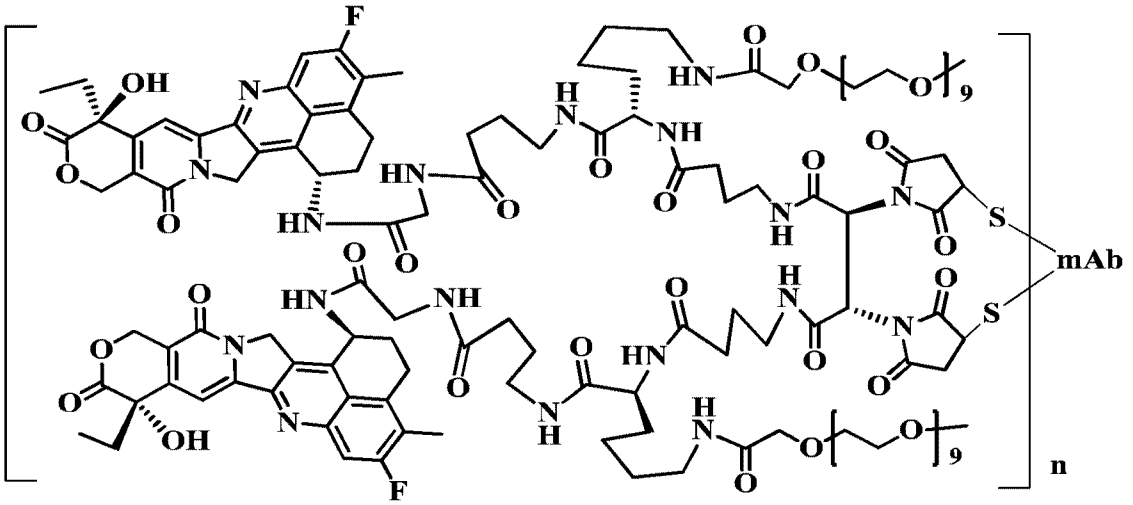

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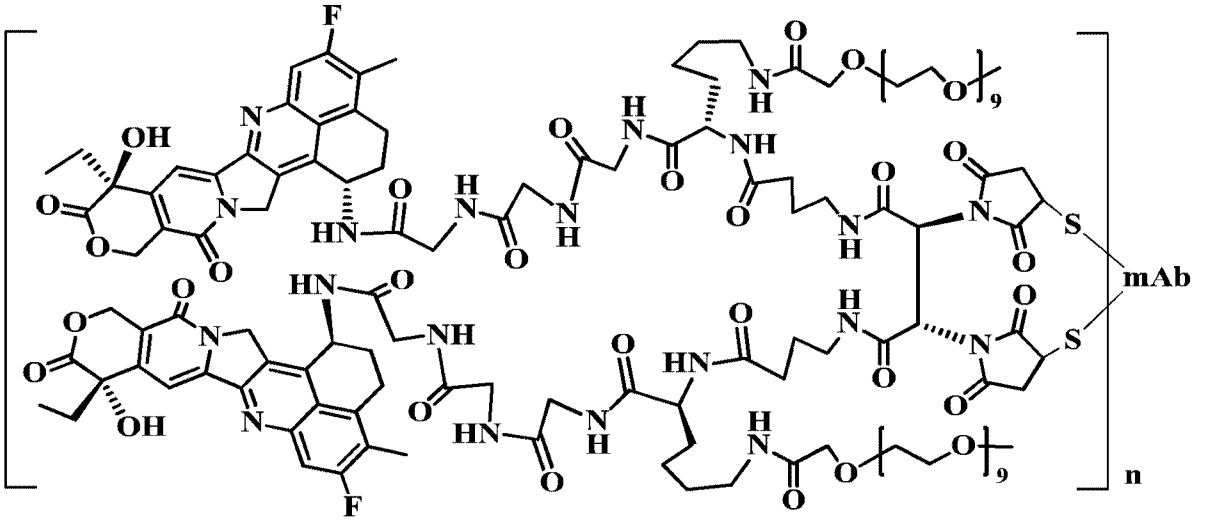

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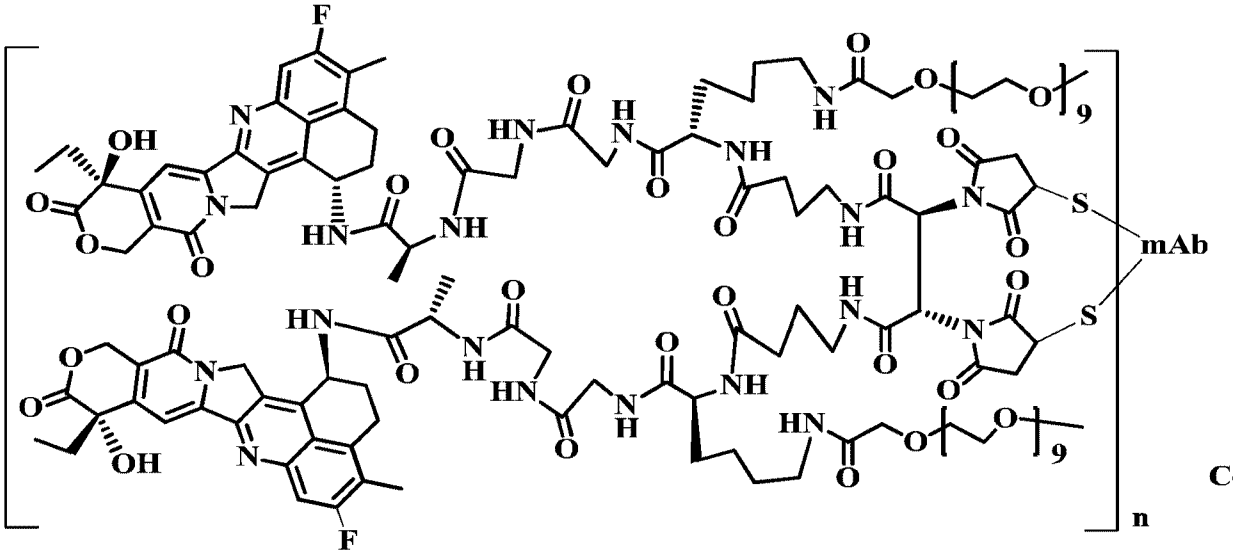

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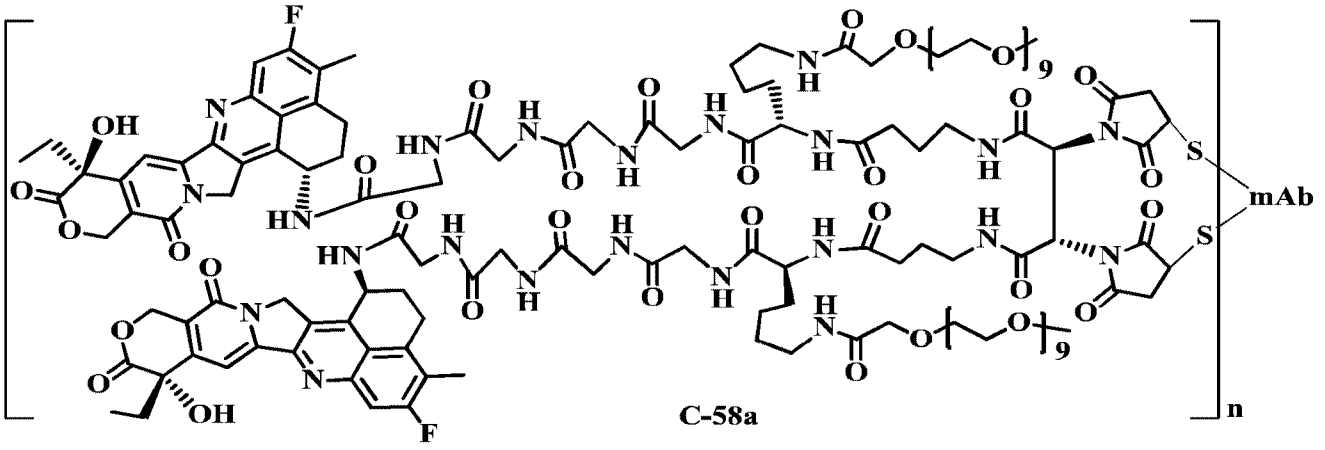

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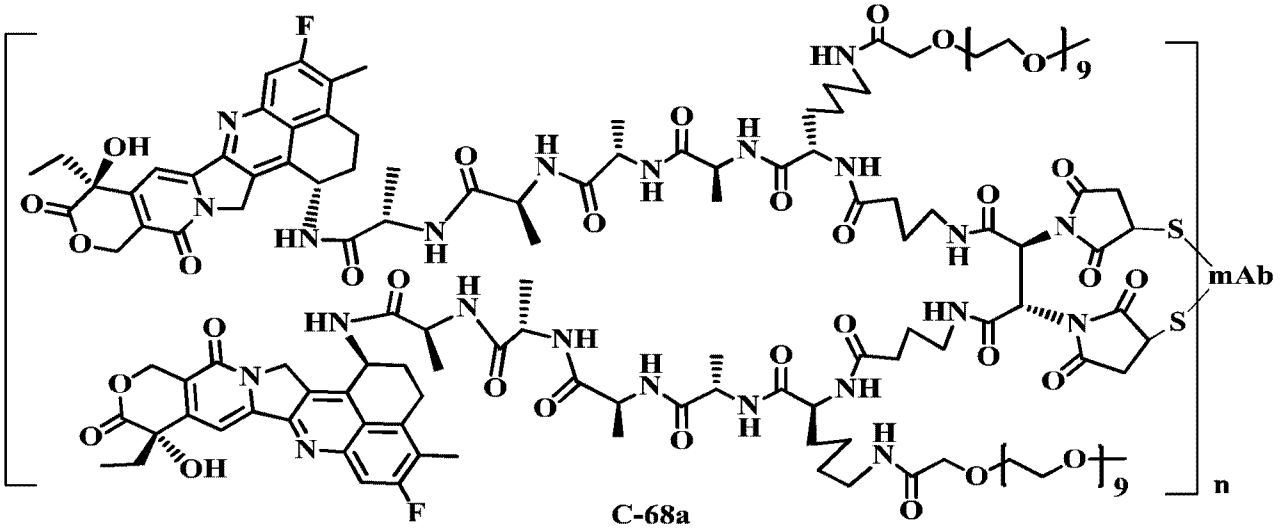

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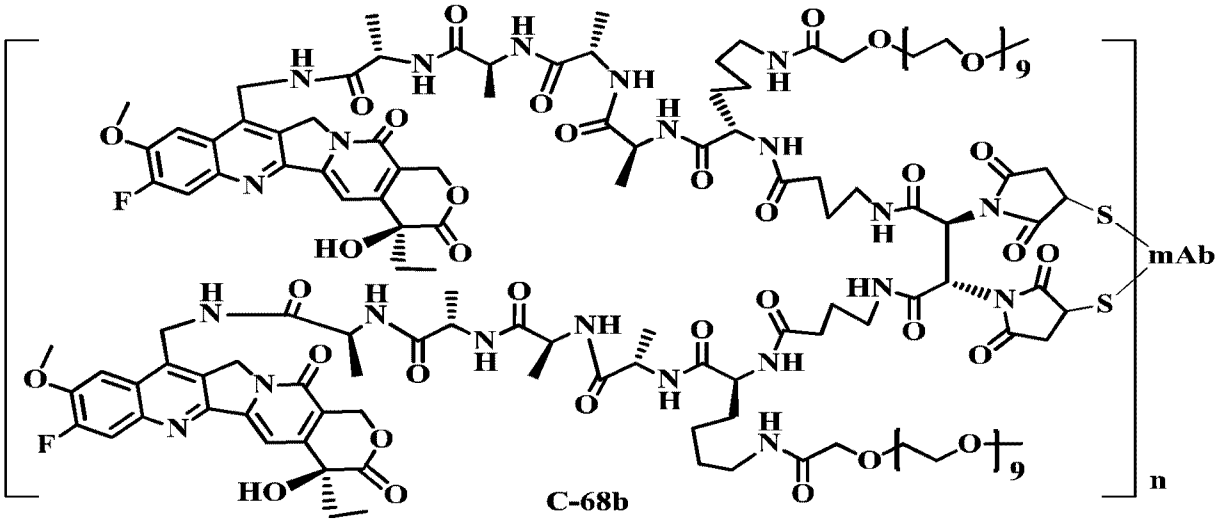

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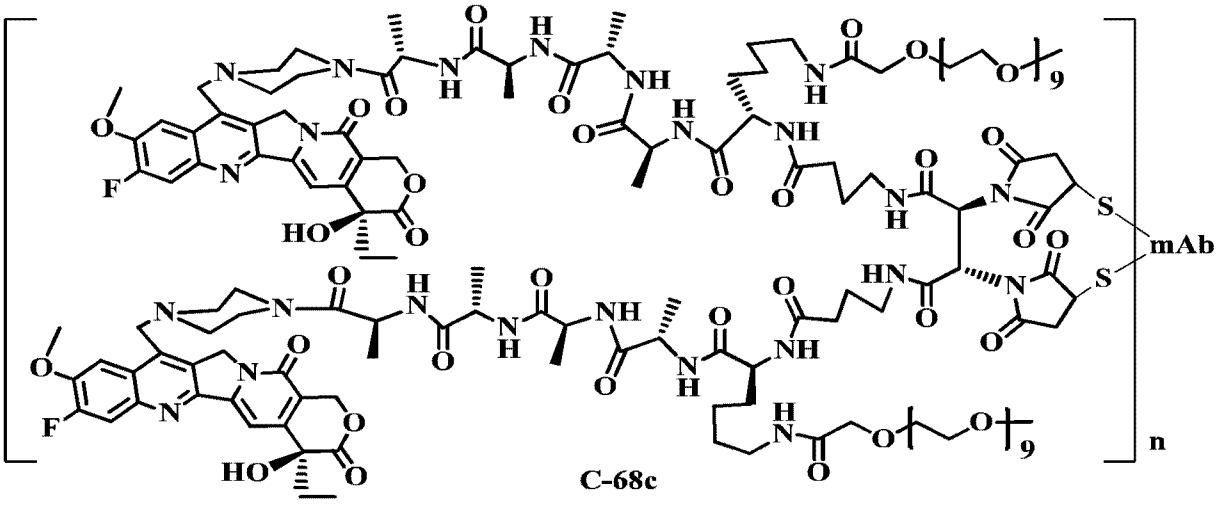

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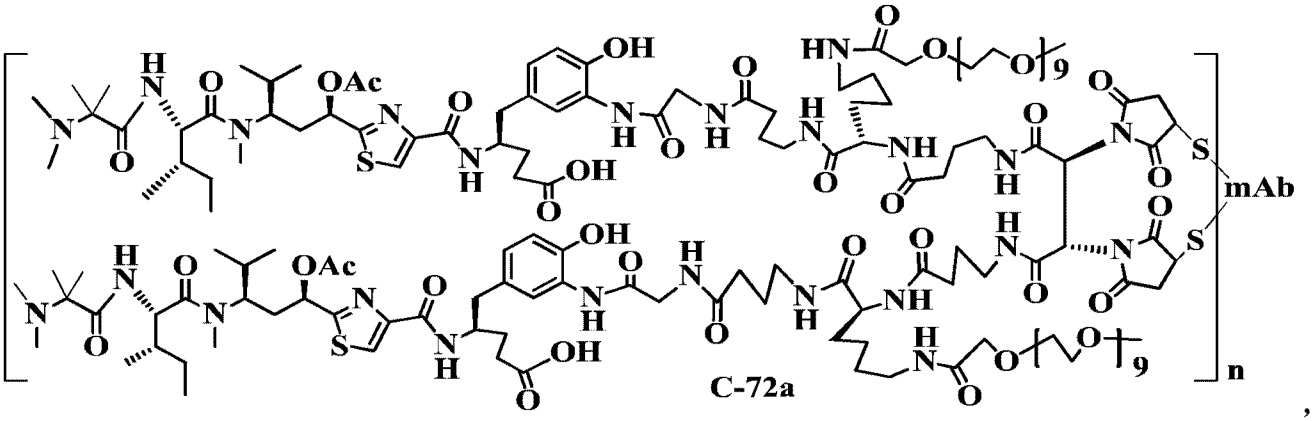

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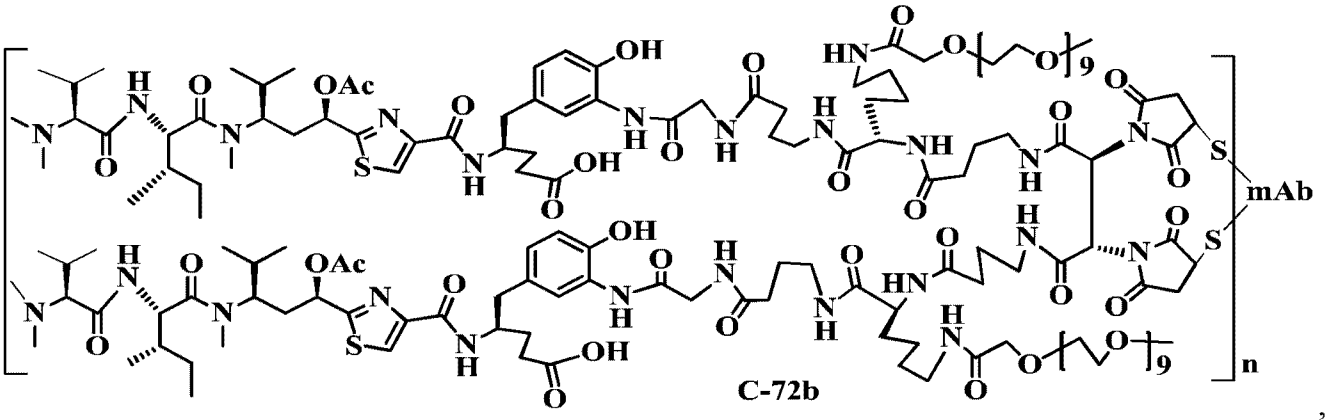

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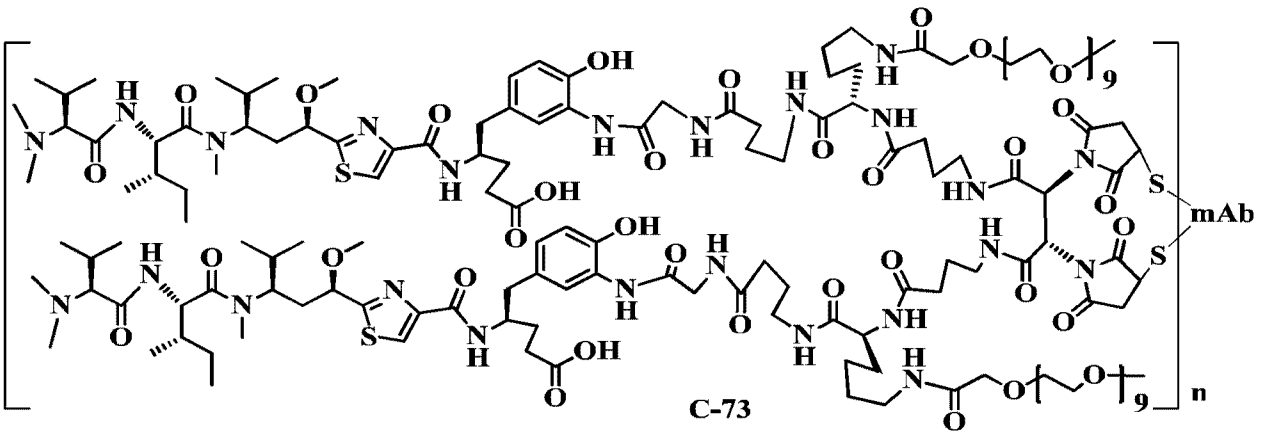

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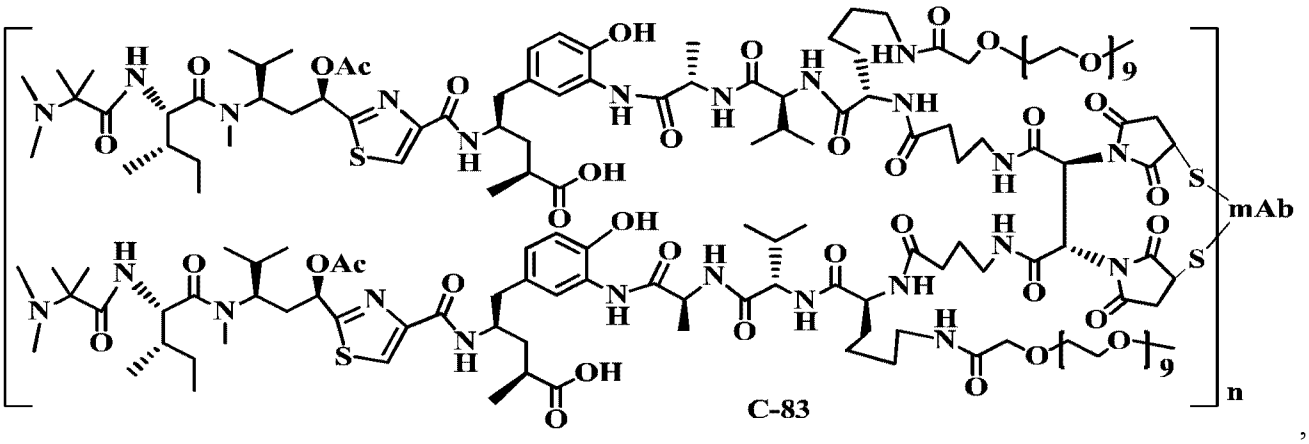

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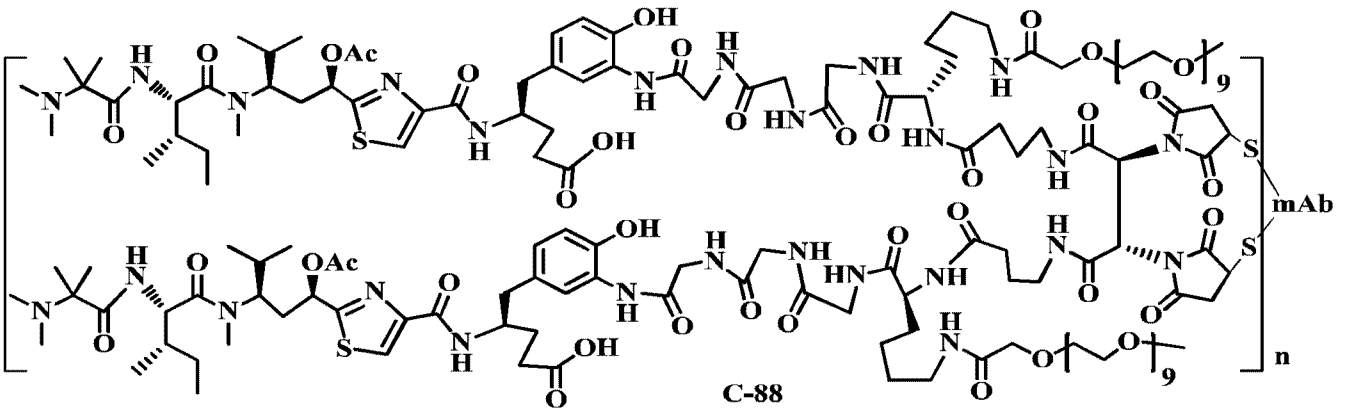

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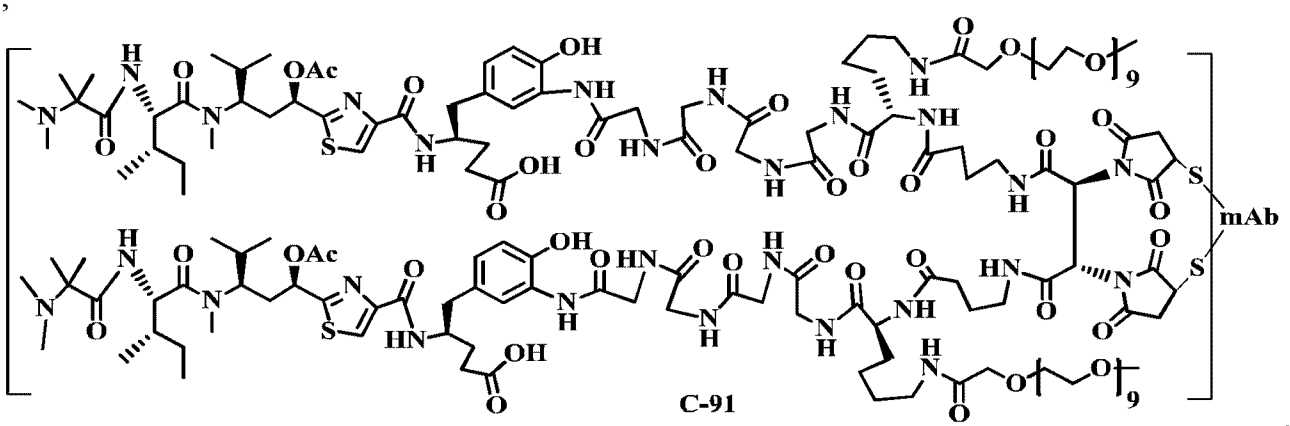

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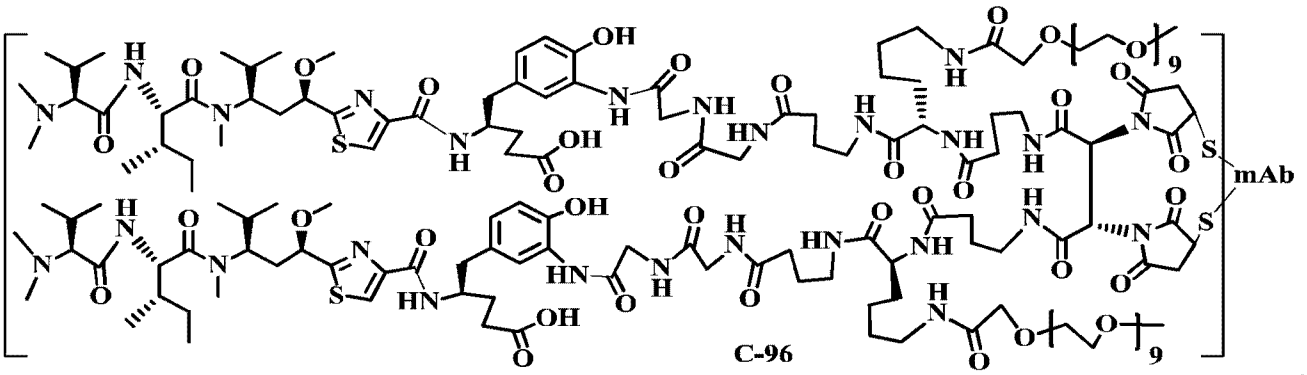

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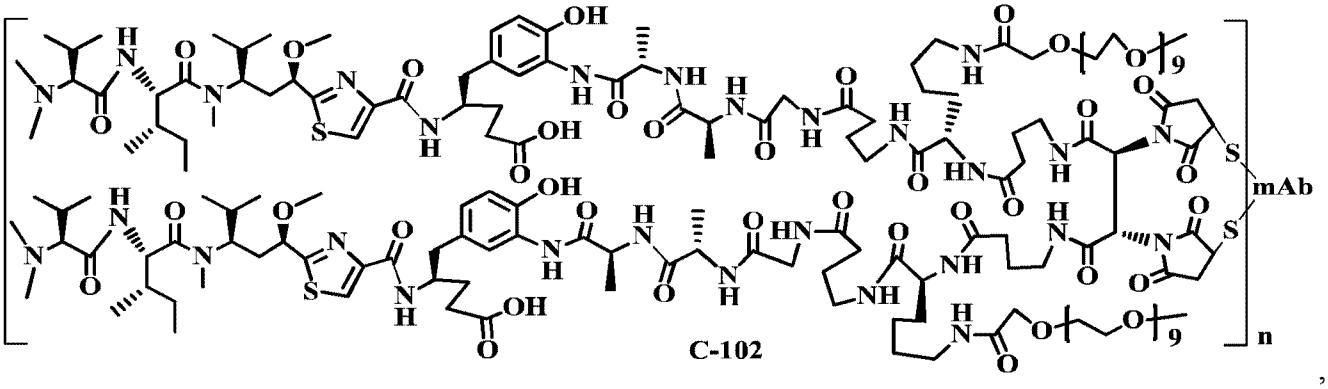

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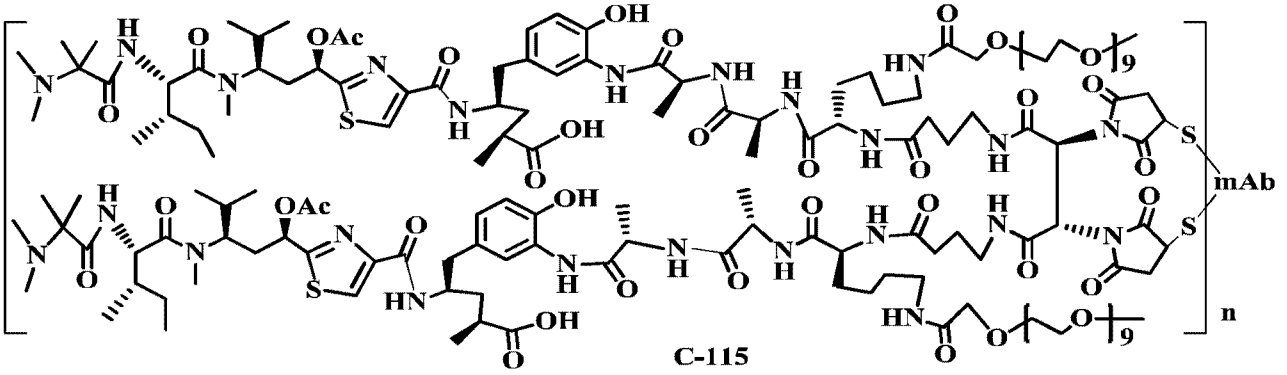

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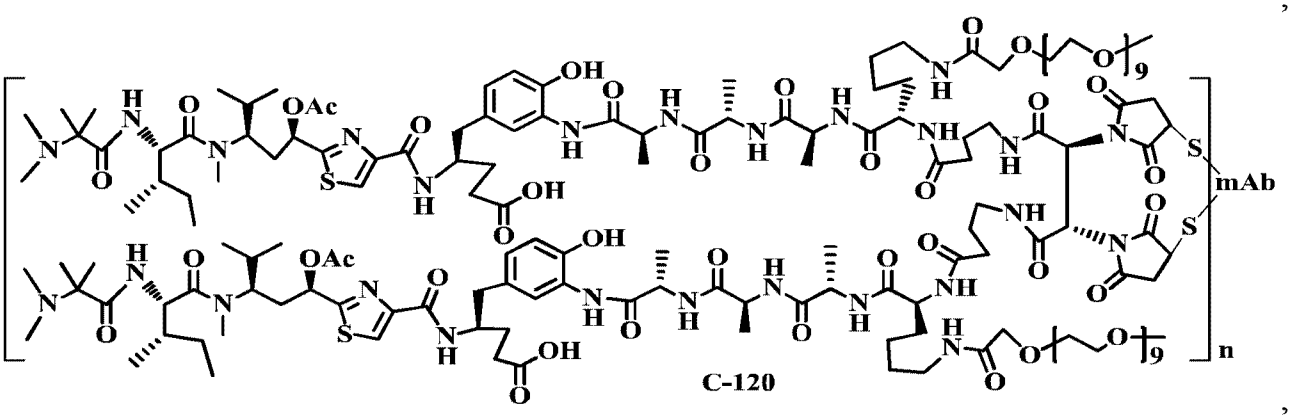

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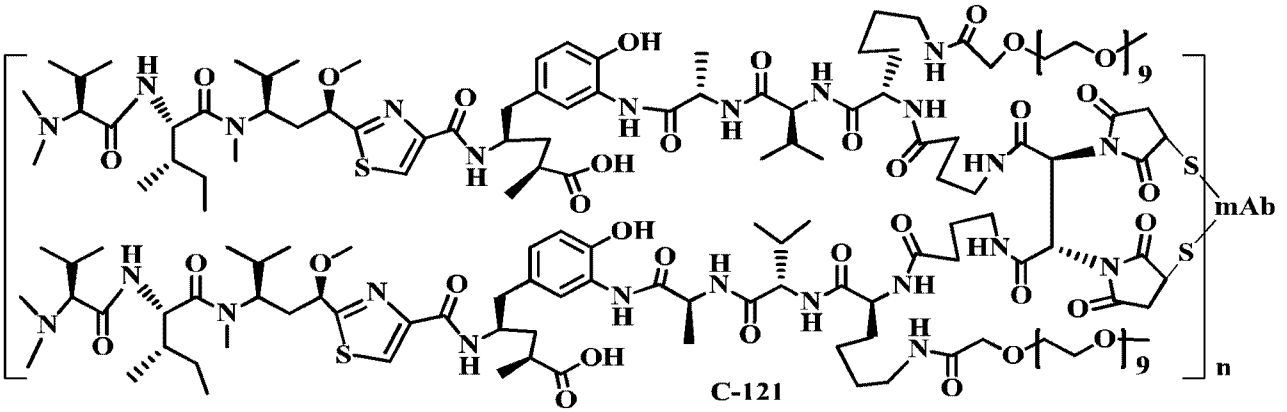

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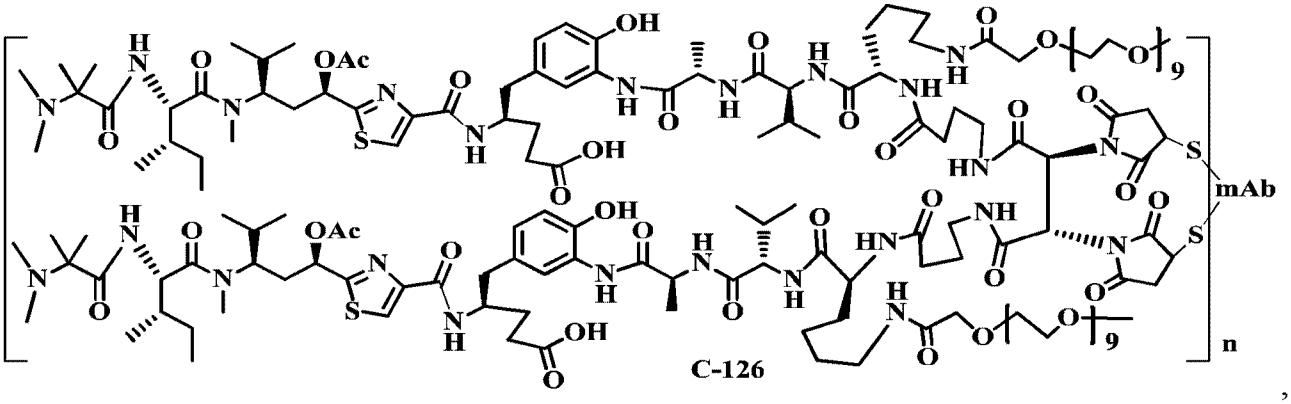

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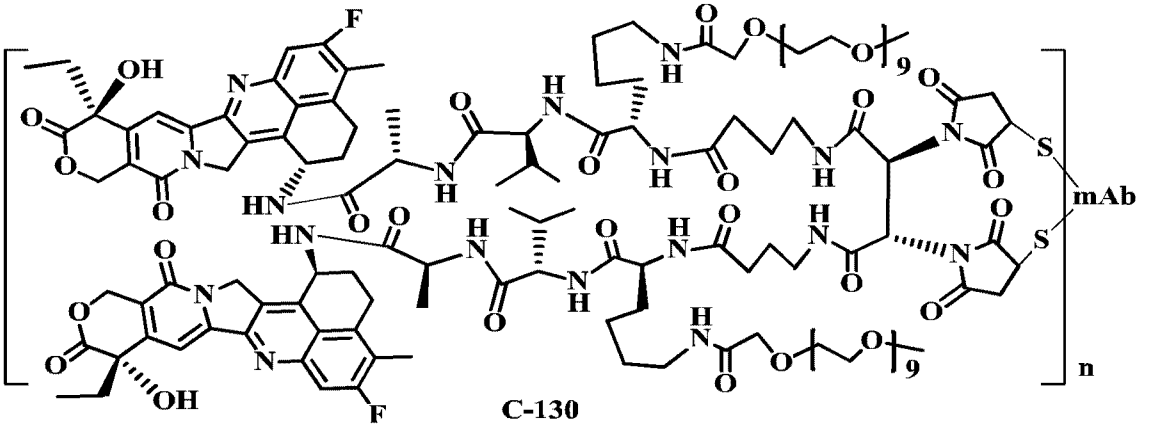

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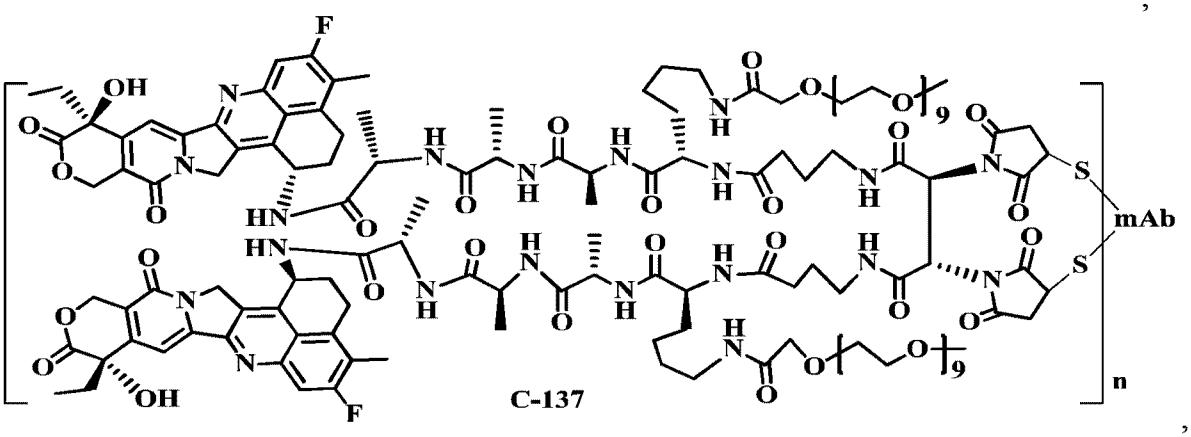

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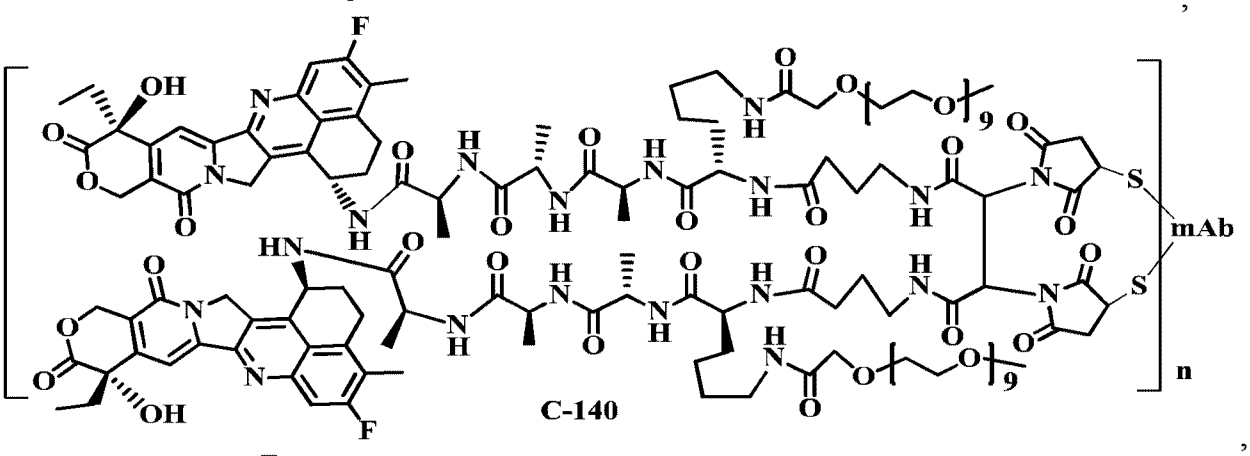

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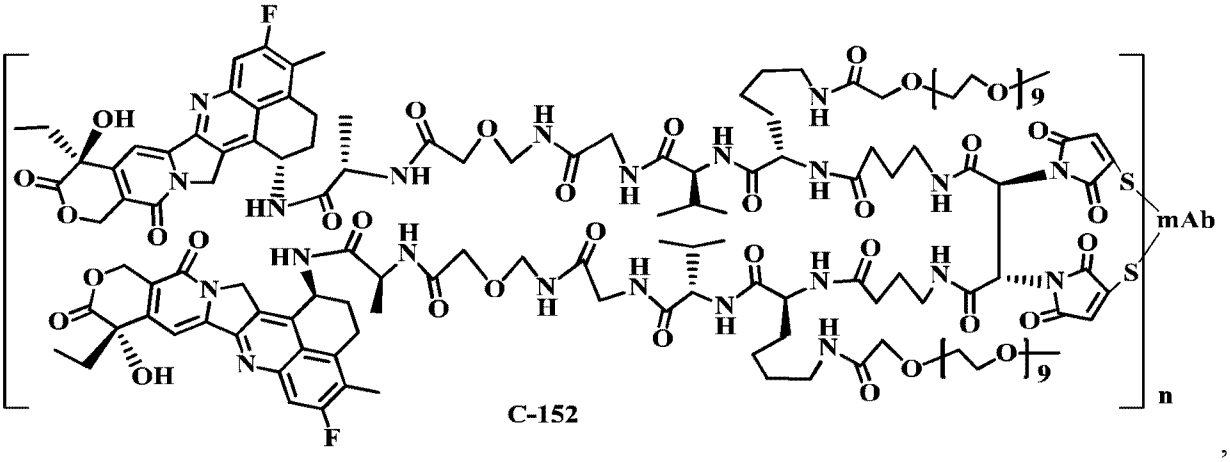

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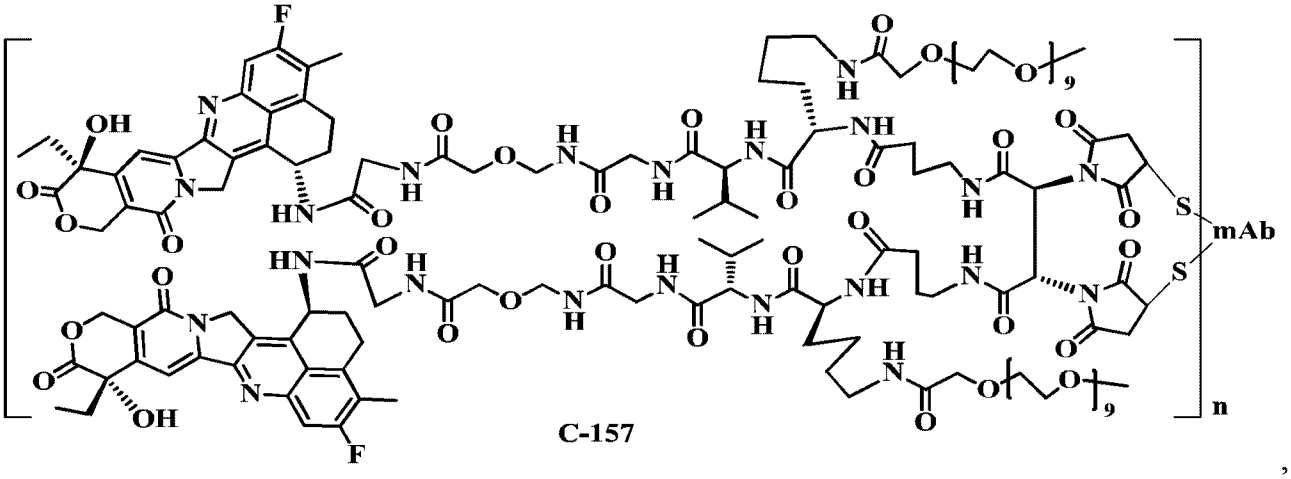

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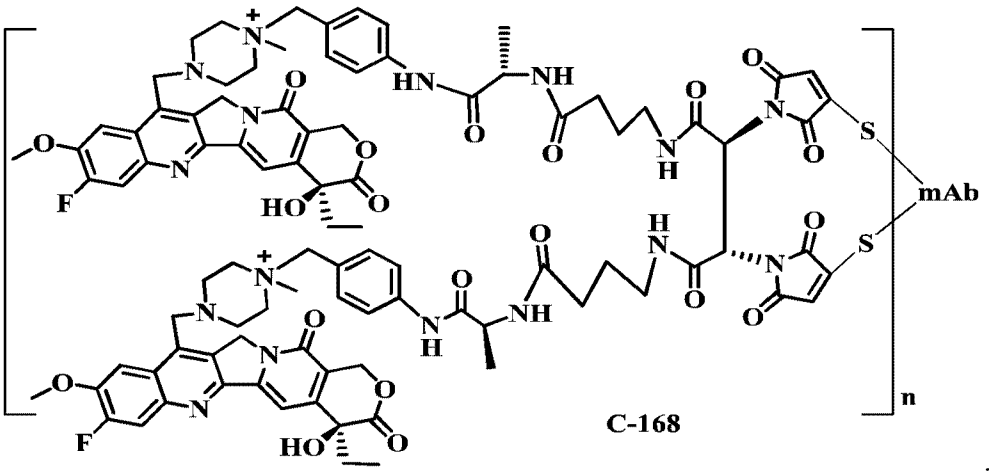

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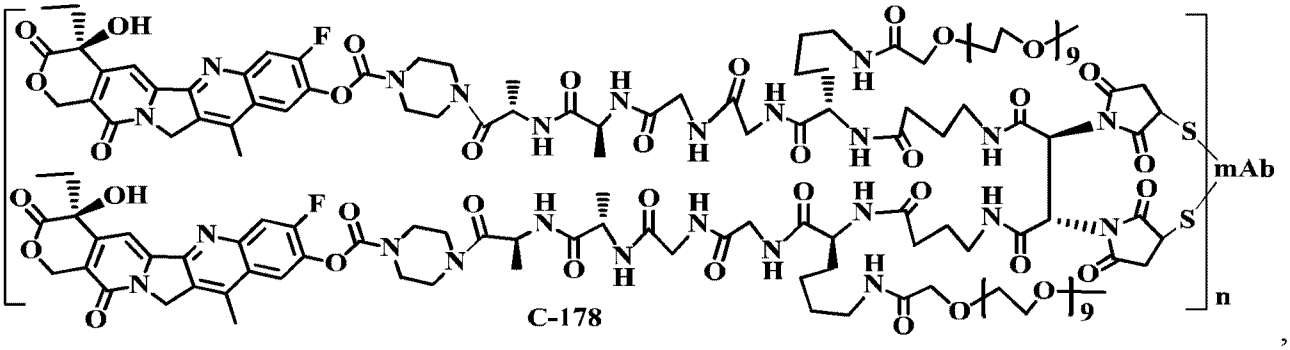
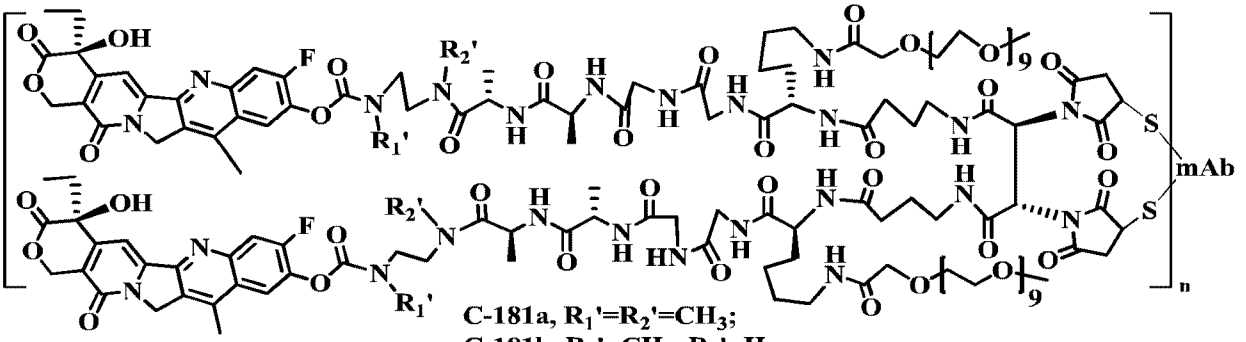
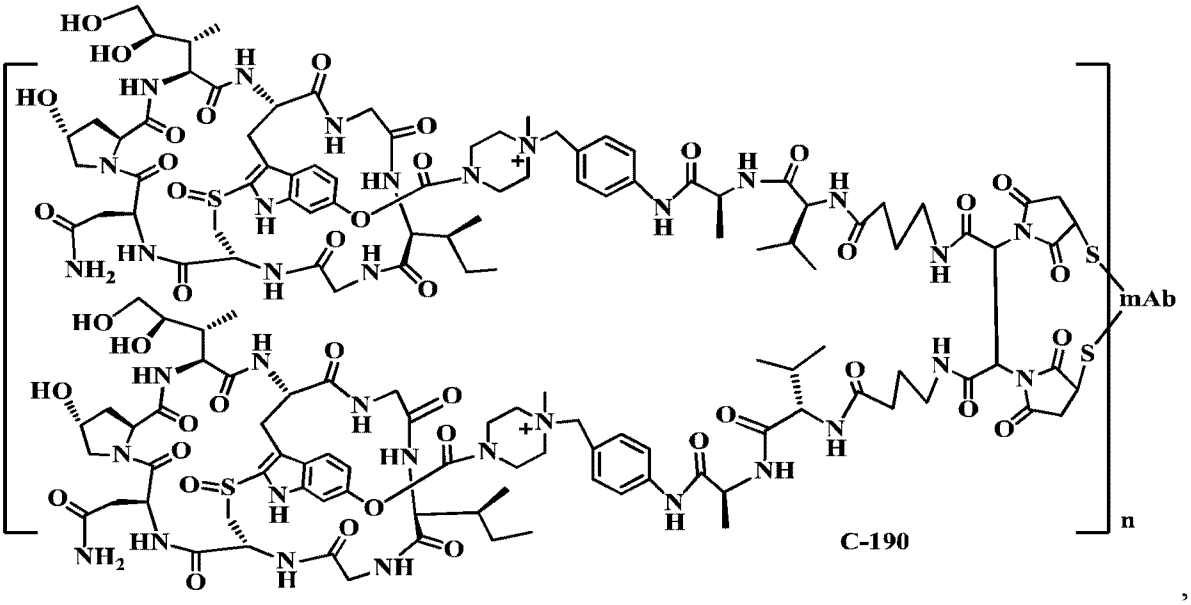


C-178



C-181a, $R_1'=R_2'=CH_3$;
C-181b, $R_1'=CH_3$, $R_2'=H$;
C-181c, $R_1'=H$, $R_2'=CH_3$;
C-181d, $R_1'=R_2'=H$;



C-190

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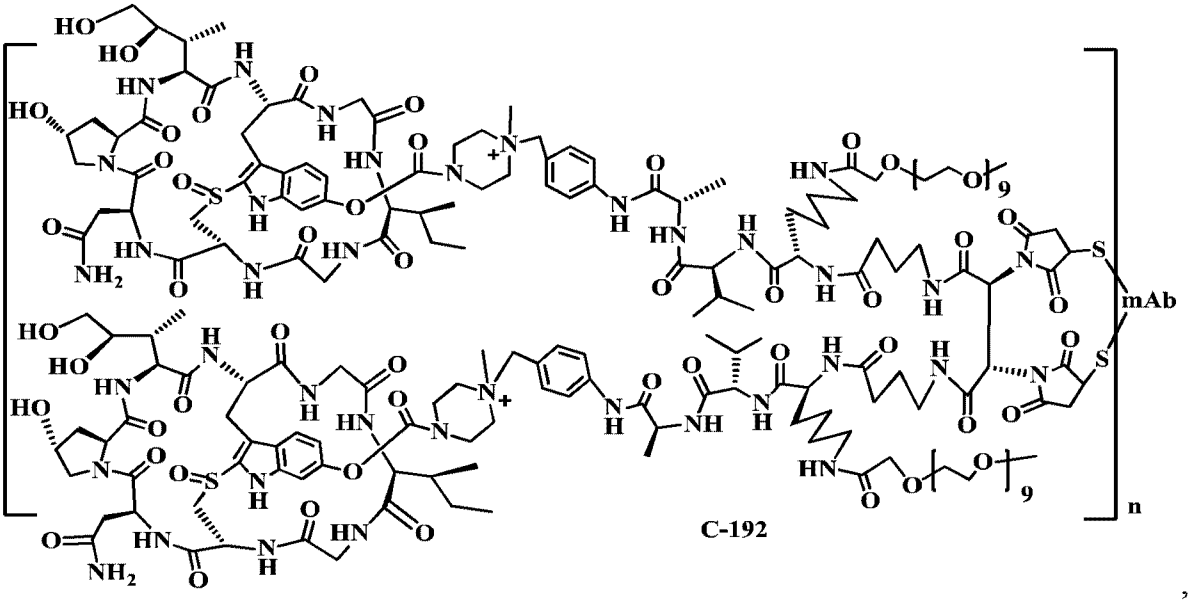

C-192

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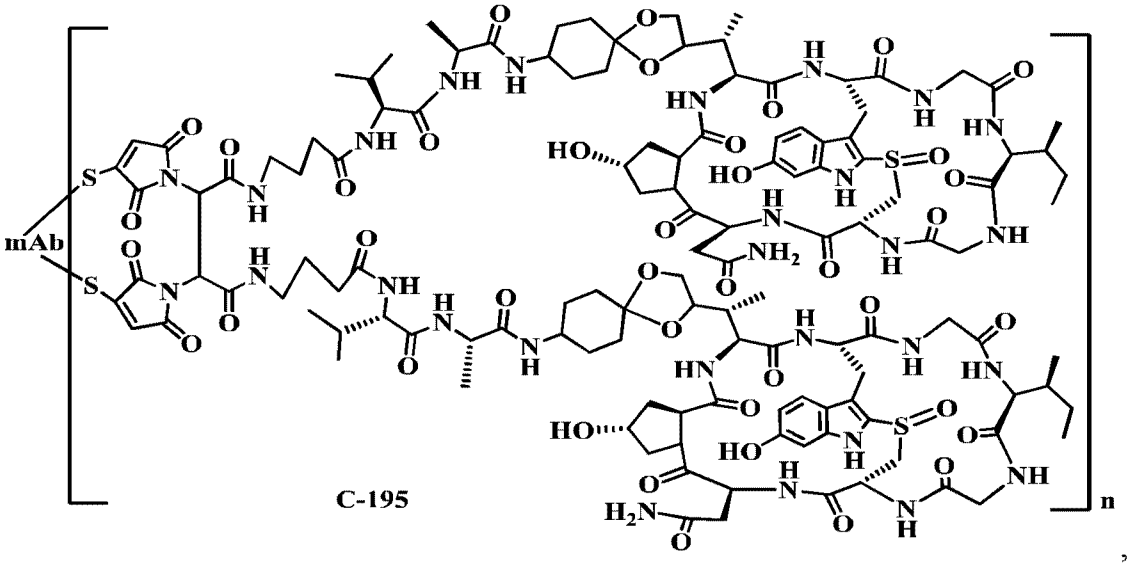

C-195

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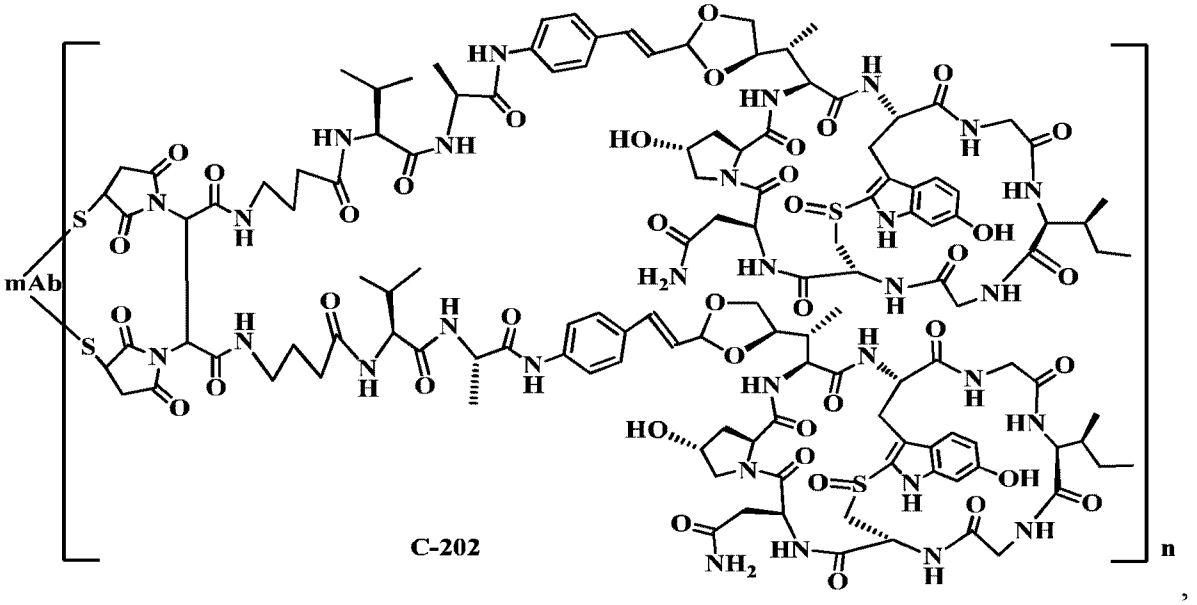
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C-202
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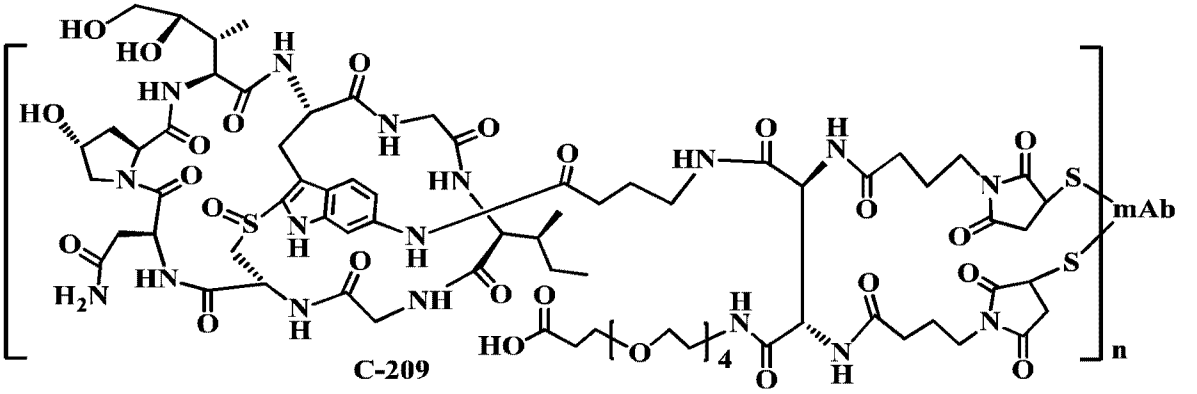
C-209
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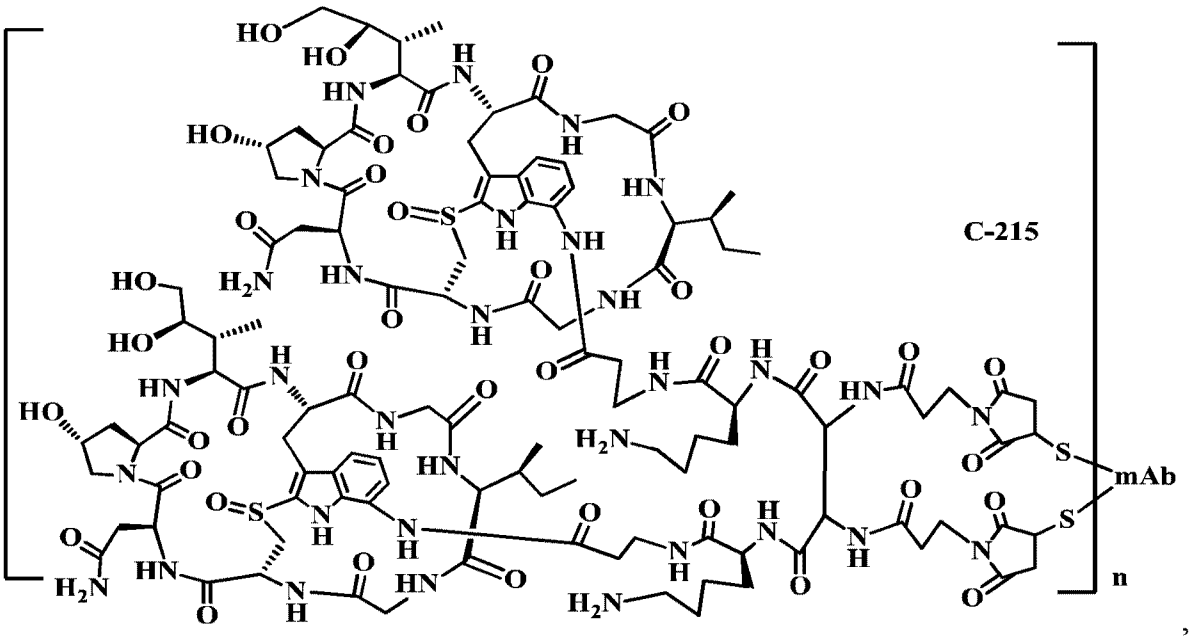
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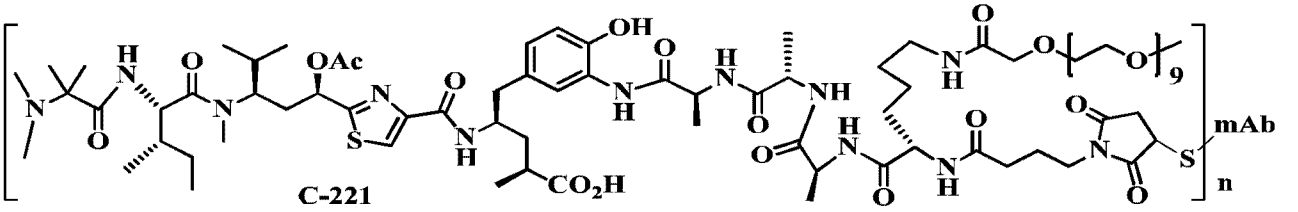
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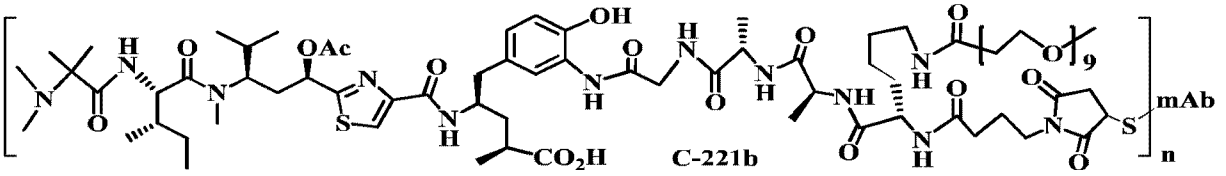
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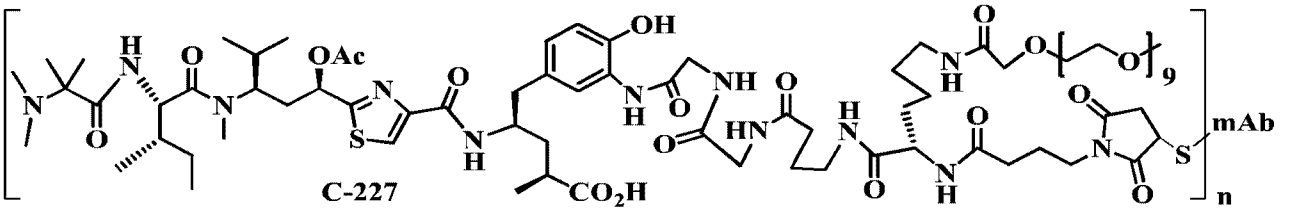
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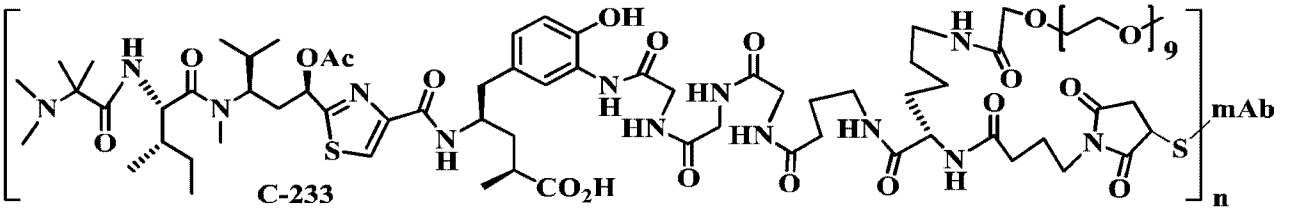
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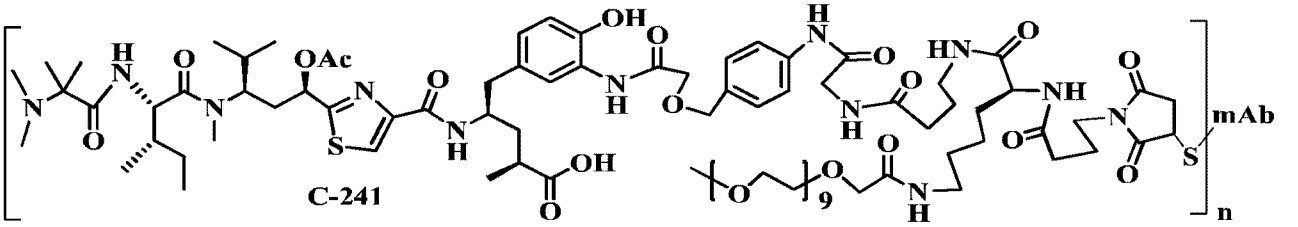
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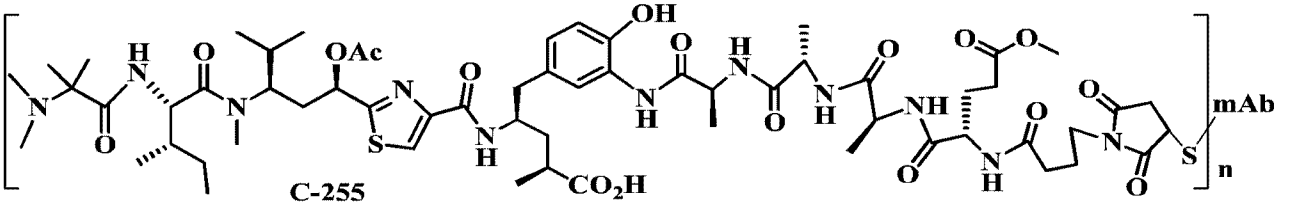
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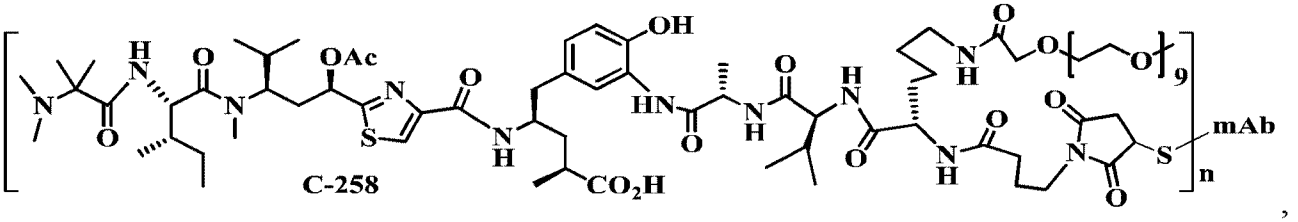
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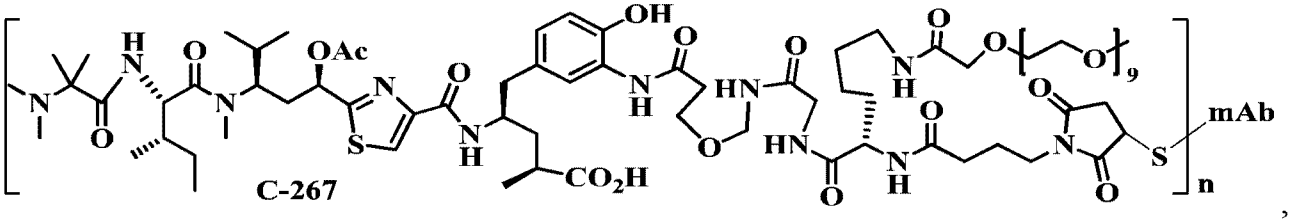
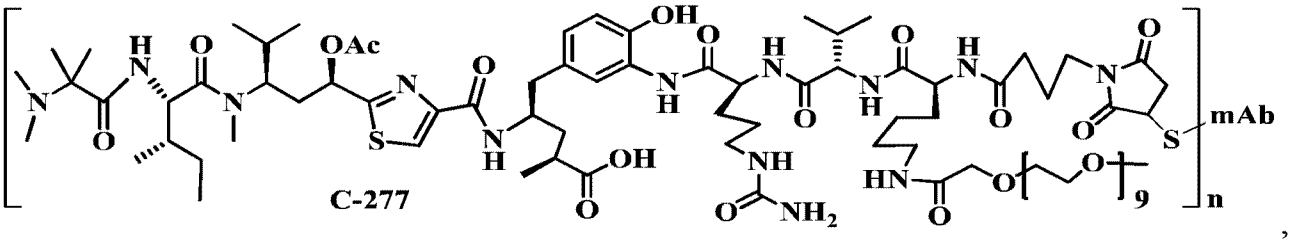

C-267,


C-277
mAb
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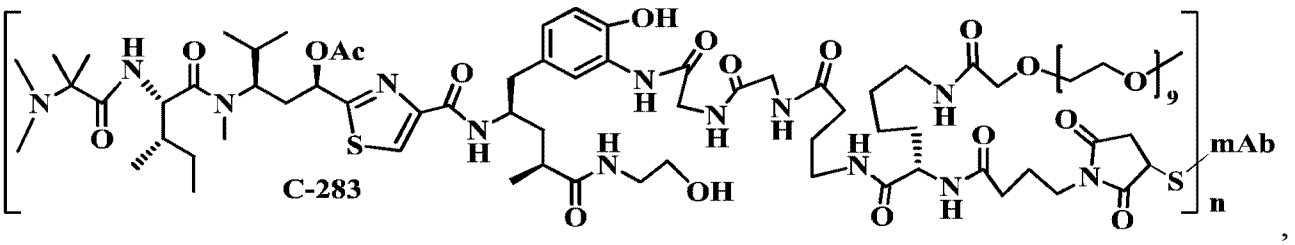
C-283
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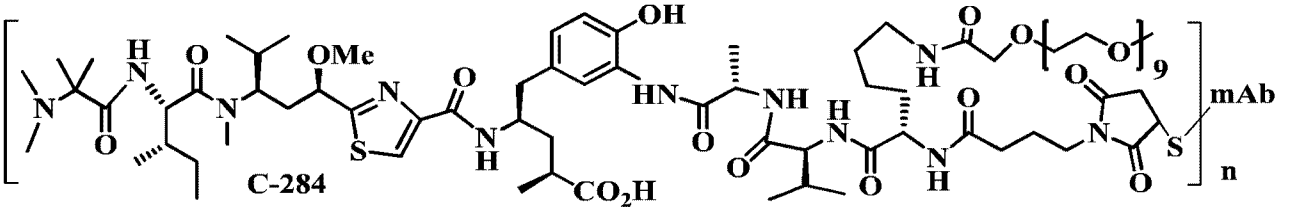
C-284
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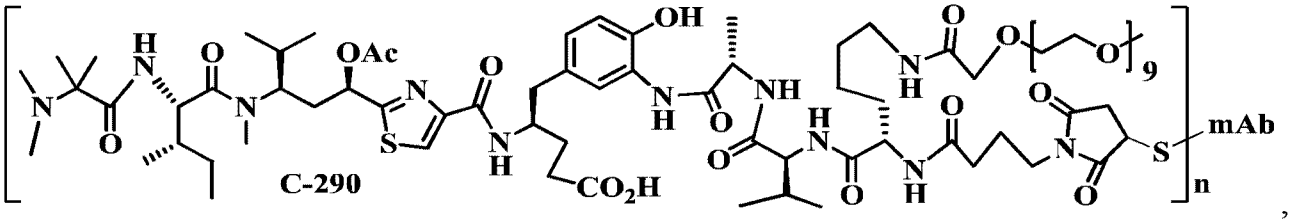
C-290
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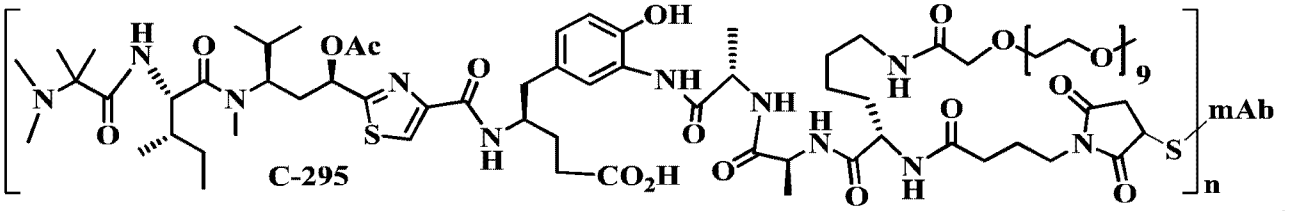
C-295
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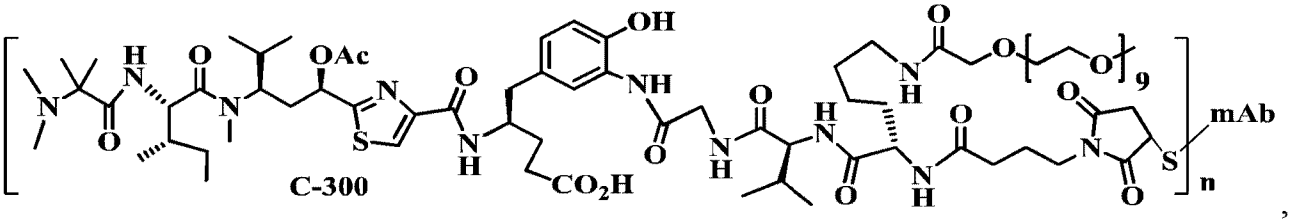
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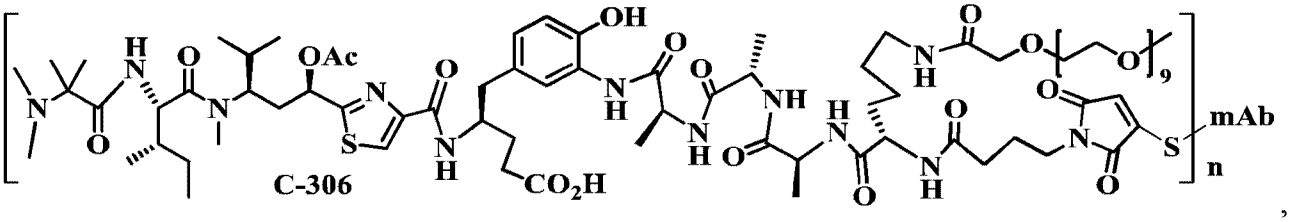
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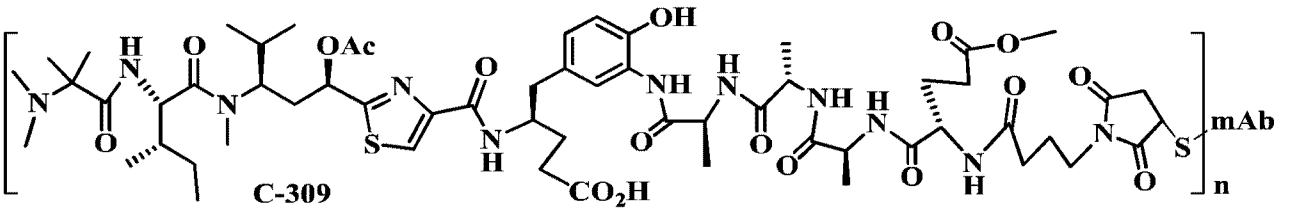
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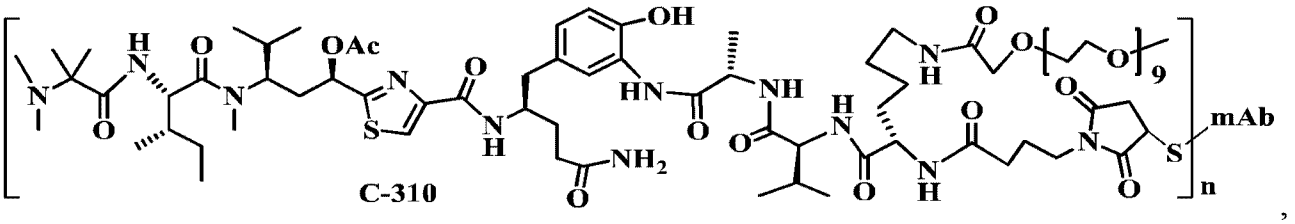
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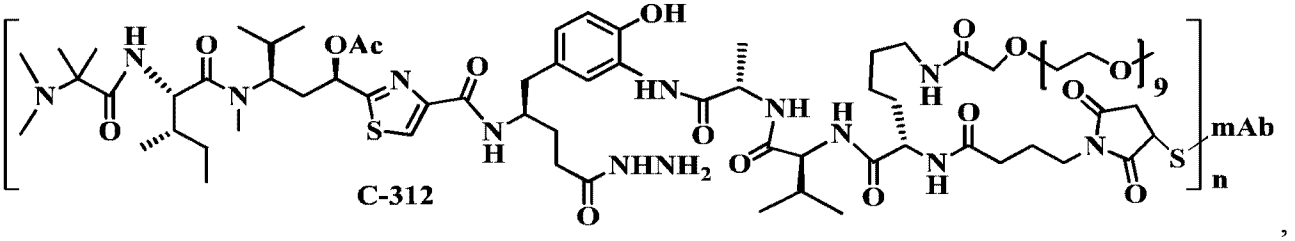
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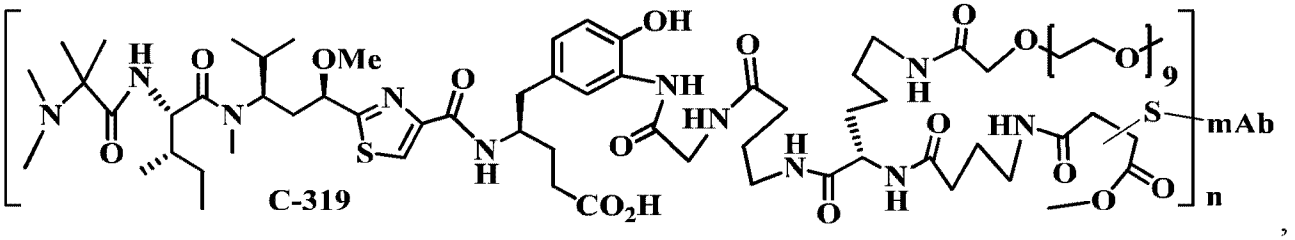
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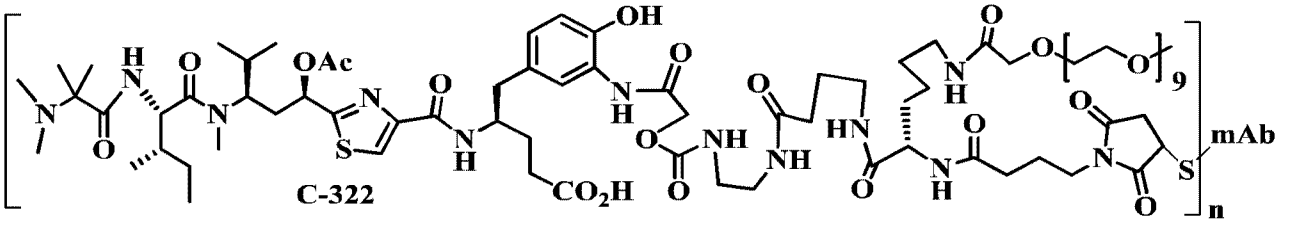
C-322
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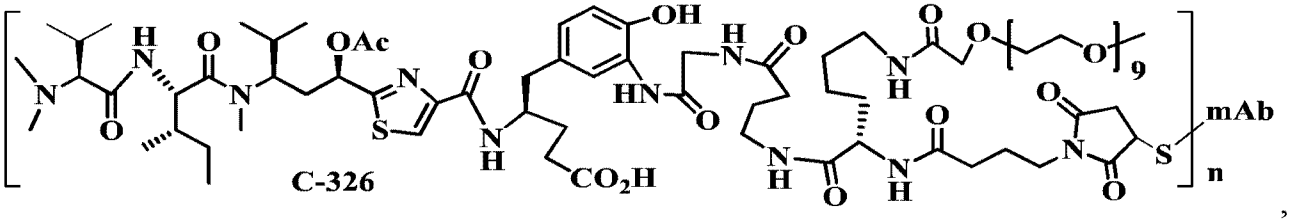
C-326
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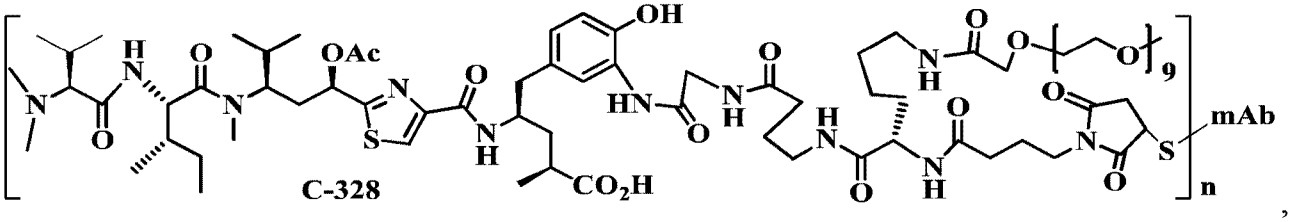
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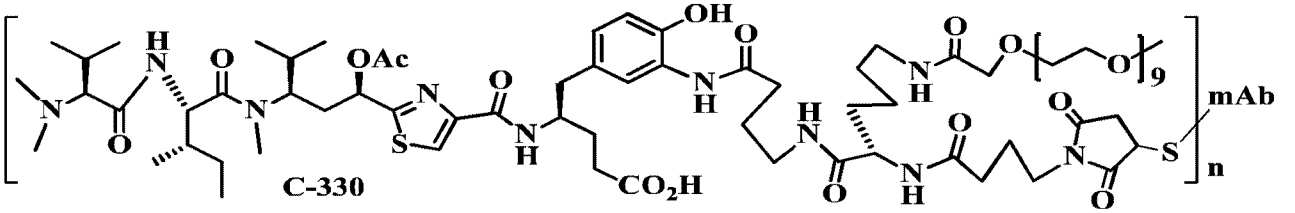
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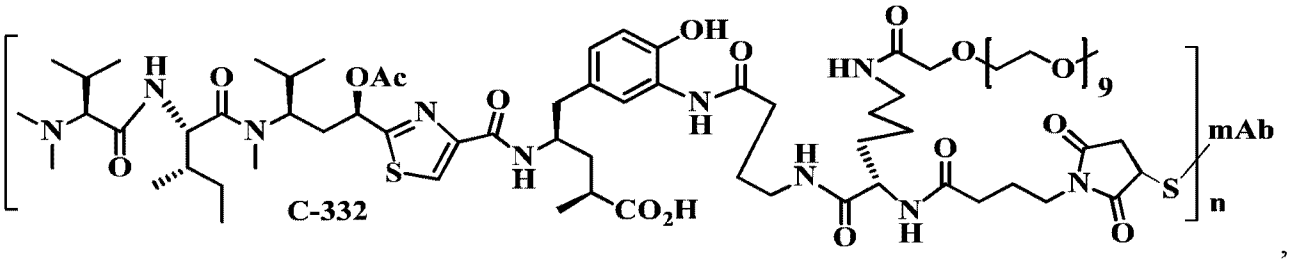
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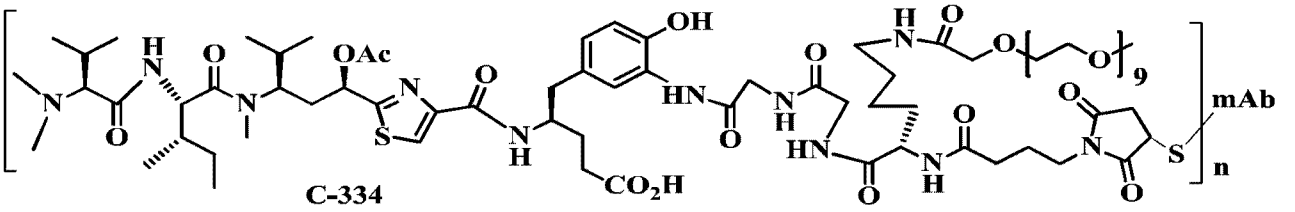
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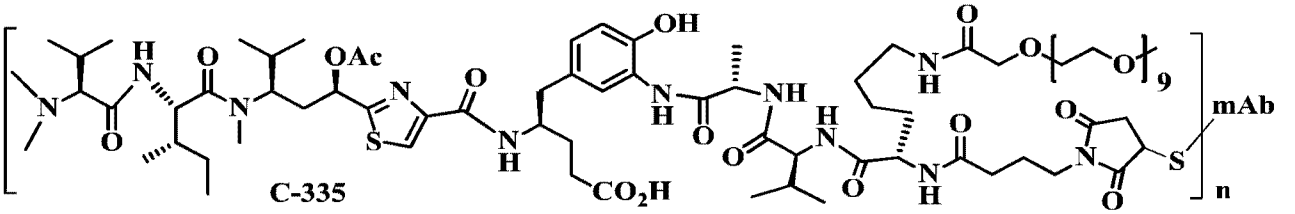
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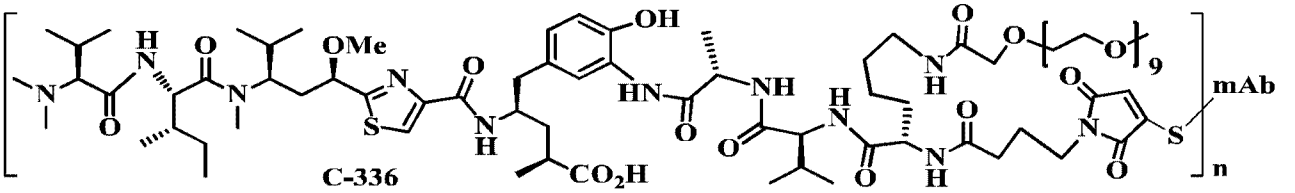
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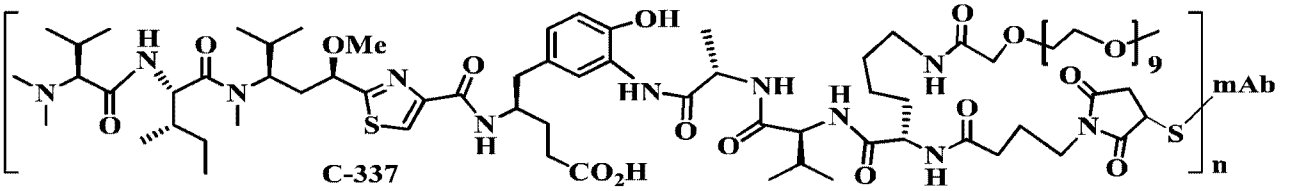
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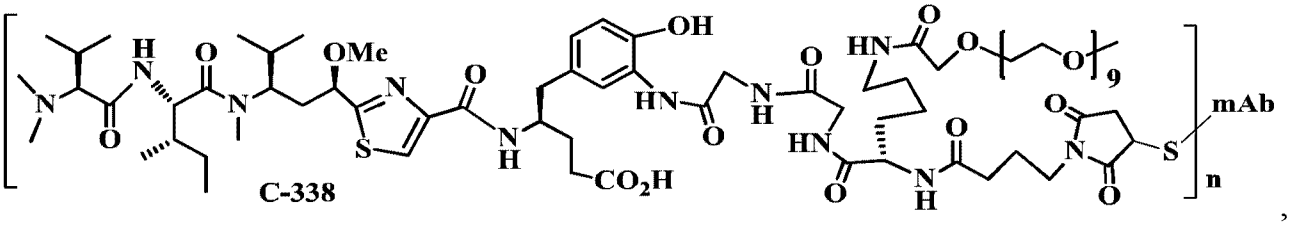
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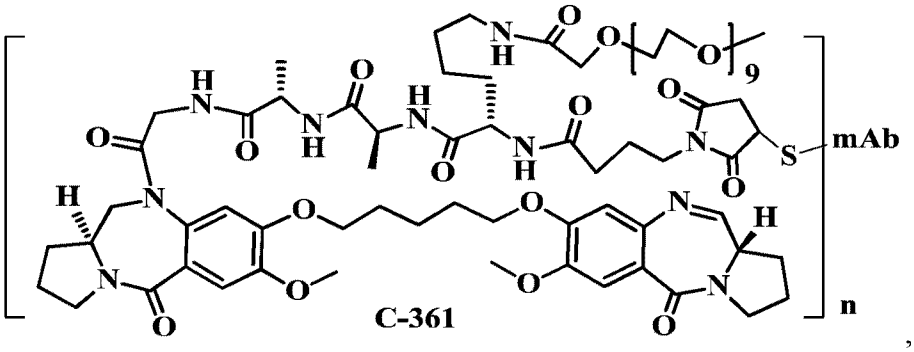

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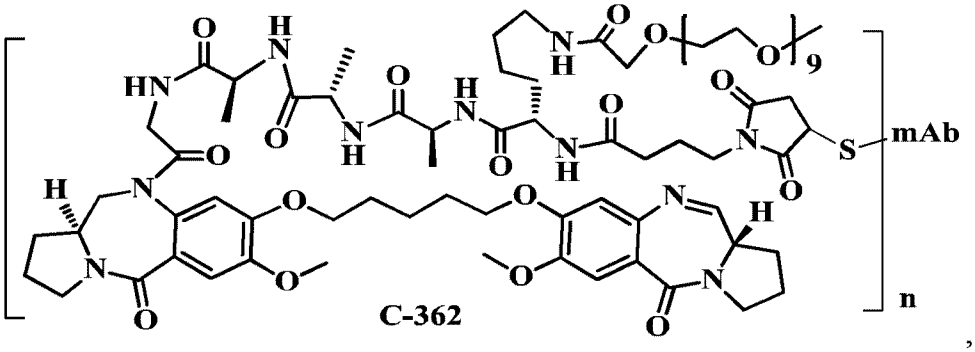

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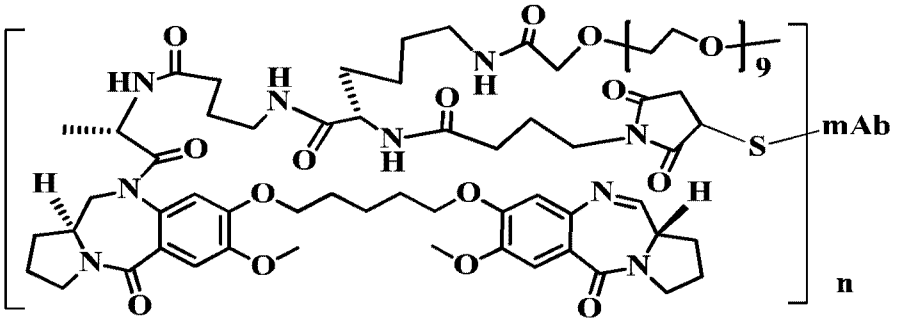

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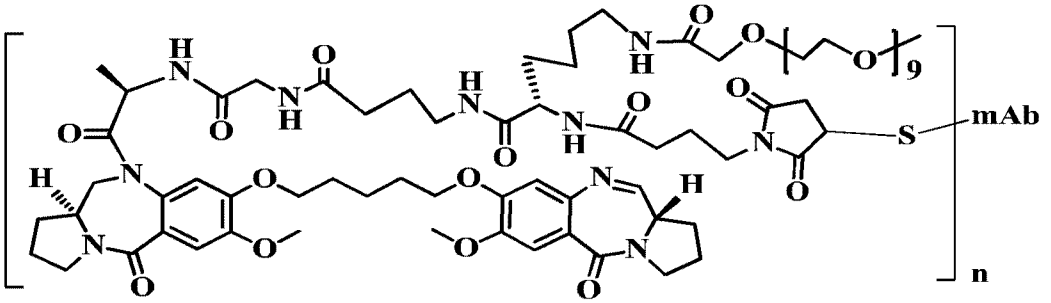

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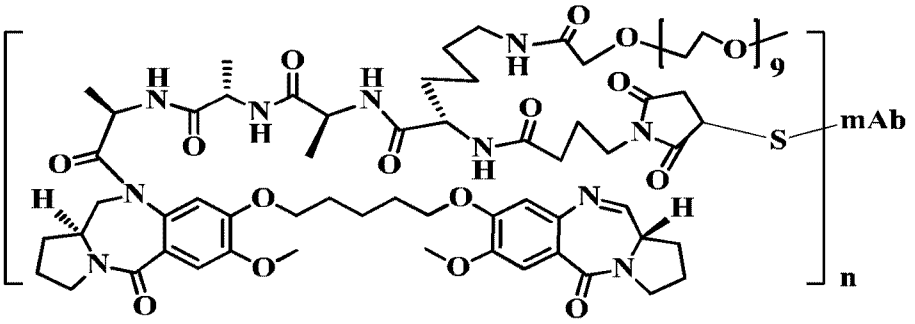

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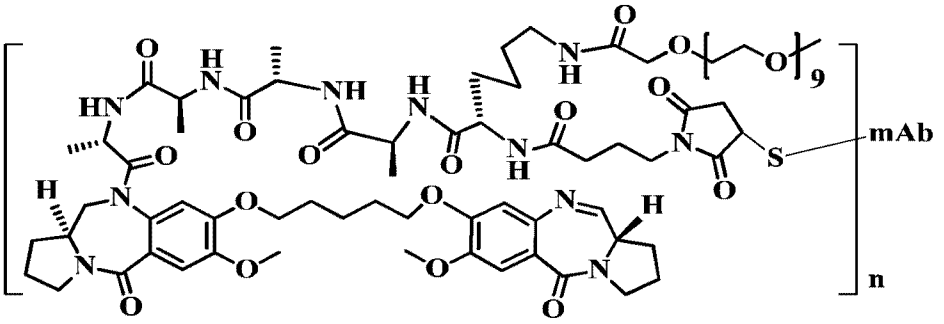

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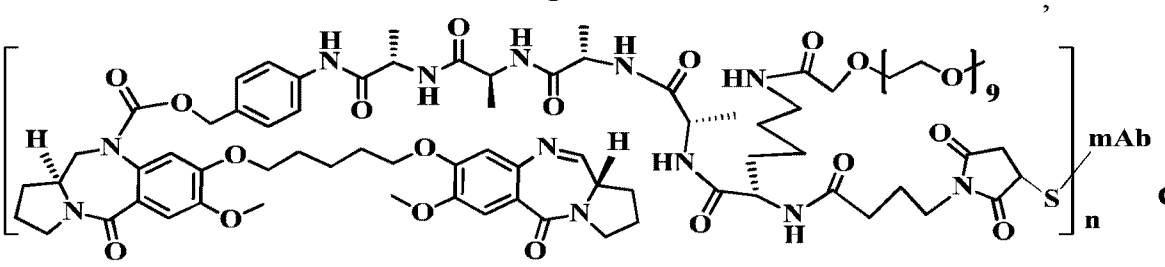

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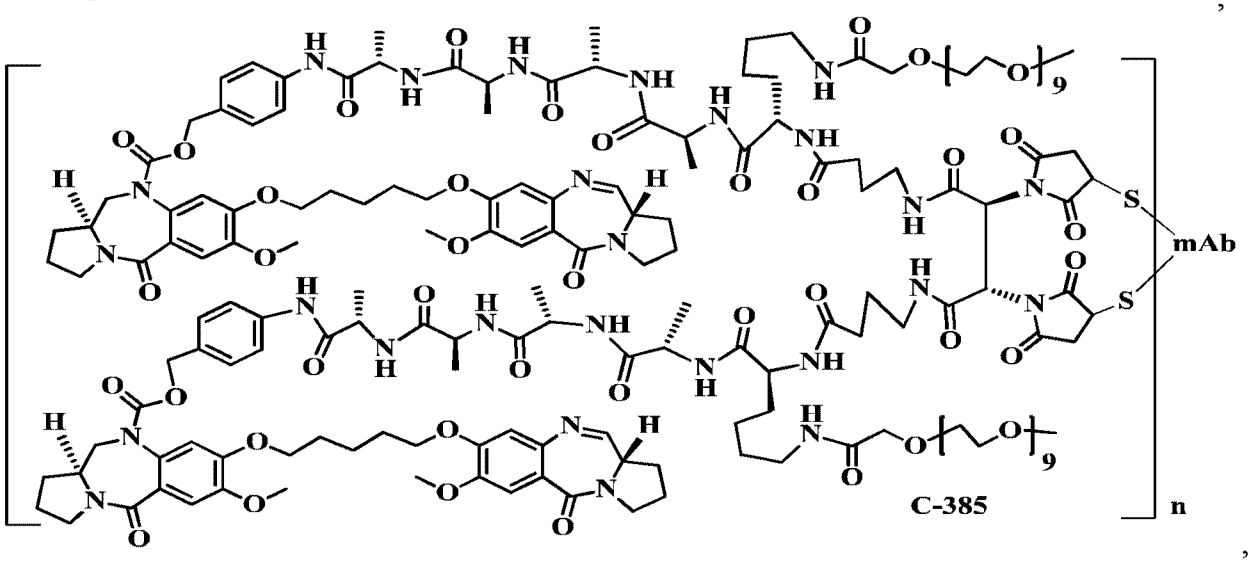

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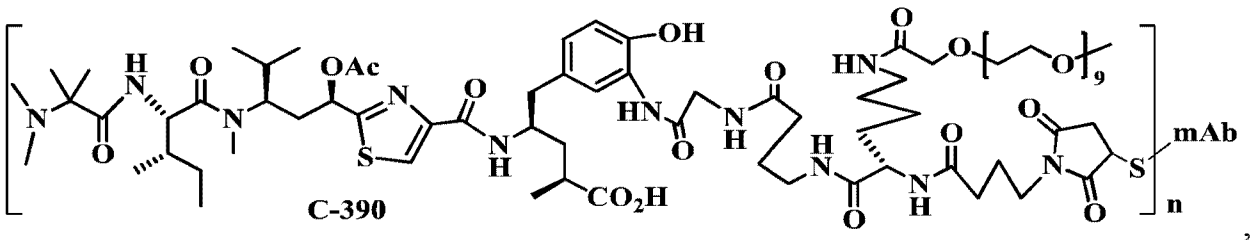

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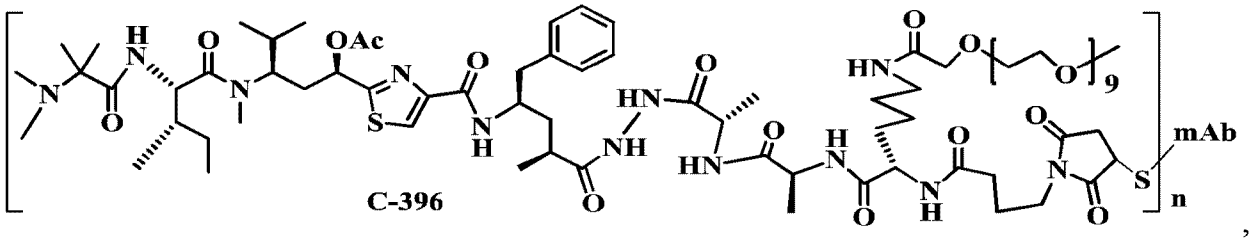

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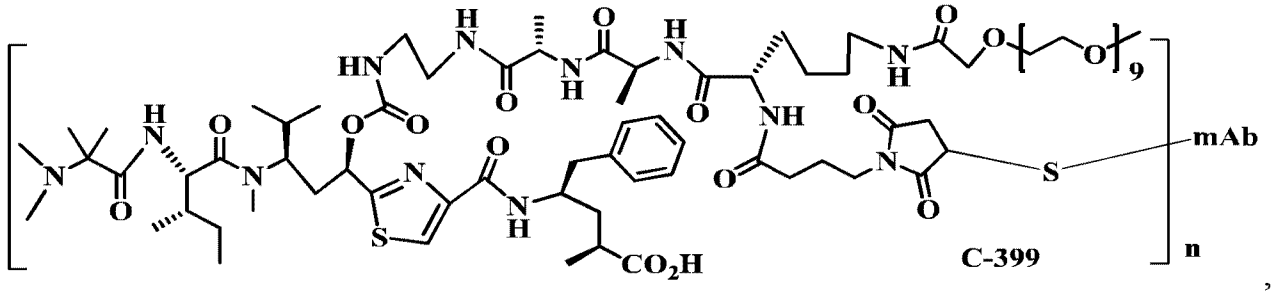
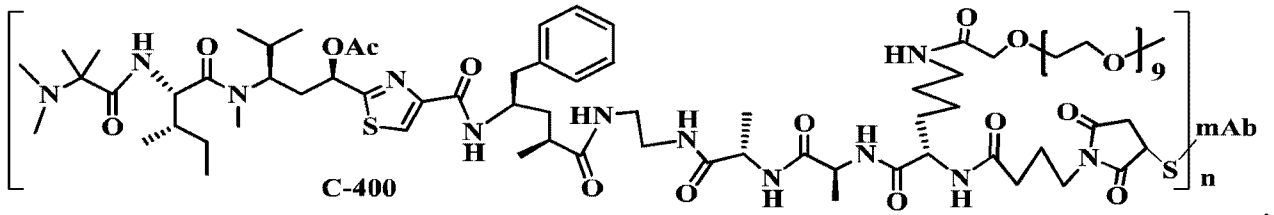
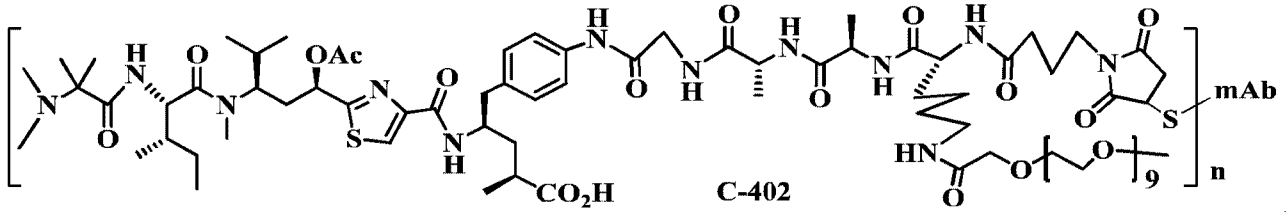


C-399 ,



C-400 ,



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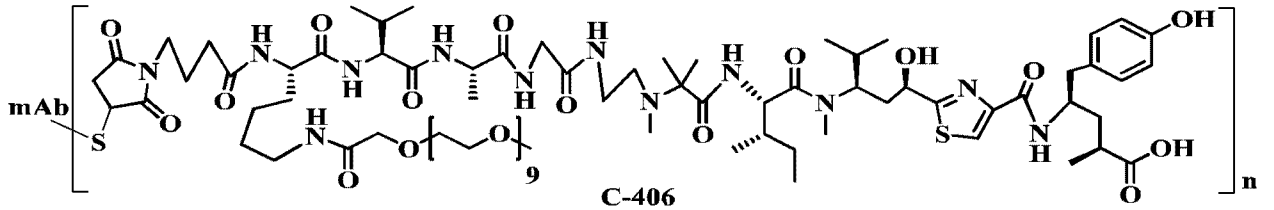
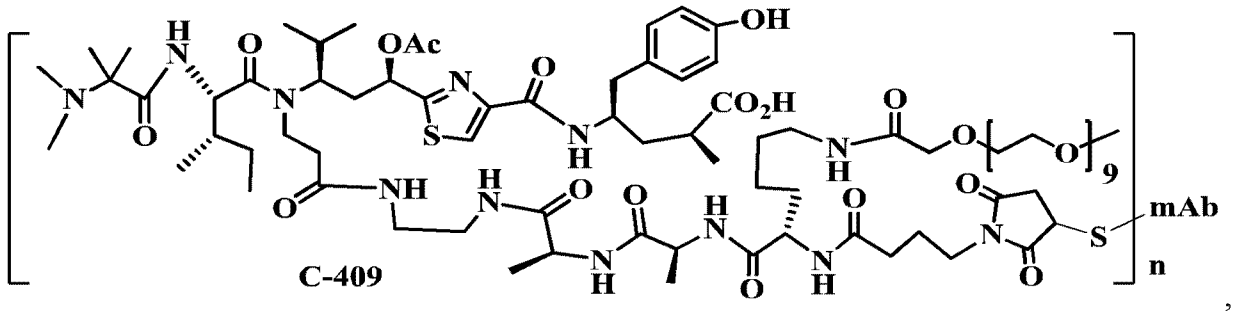
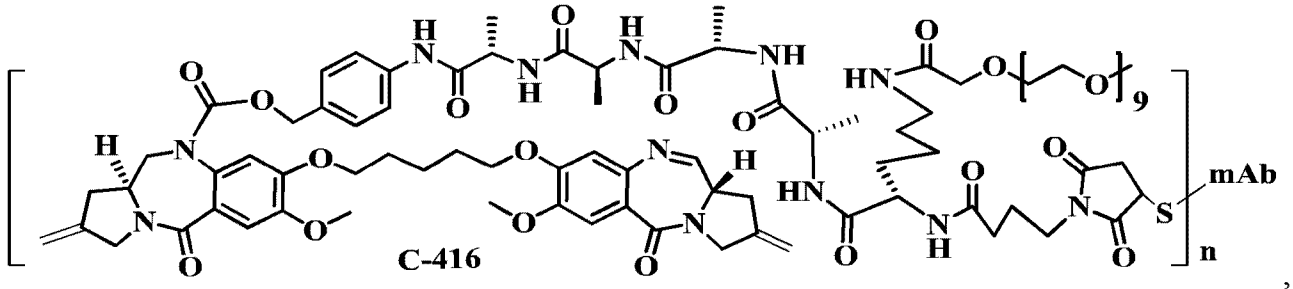


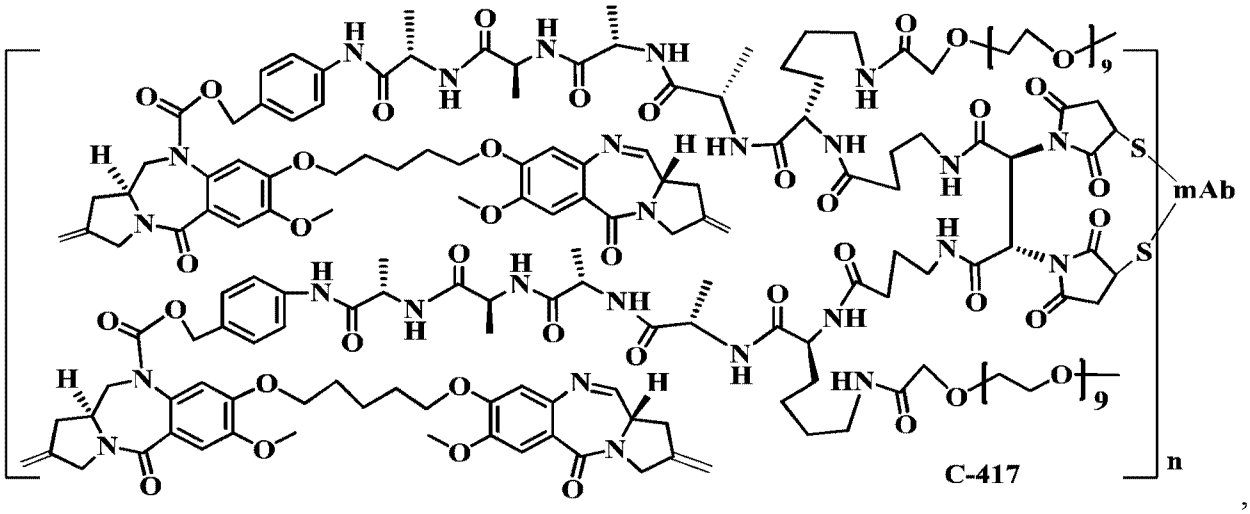
C-406 ,



C-409 ,



C-416 ,


C-417
mAb
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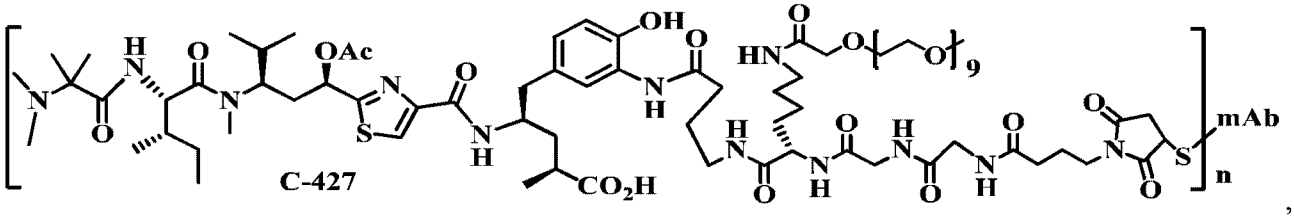
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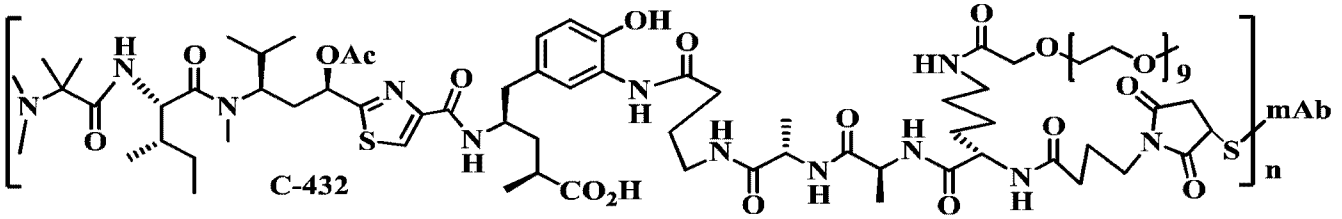
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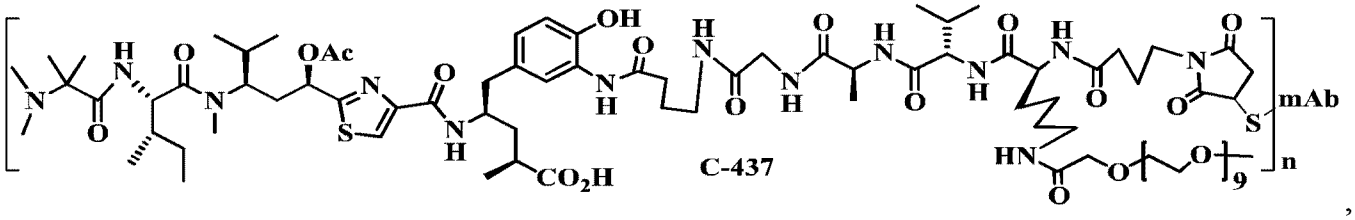
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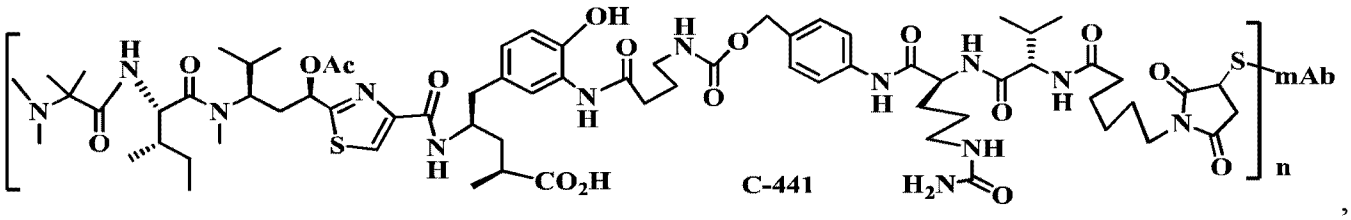
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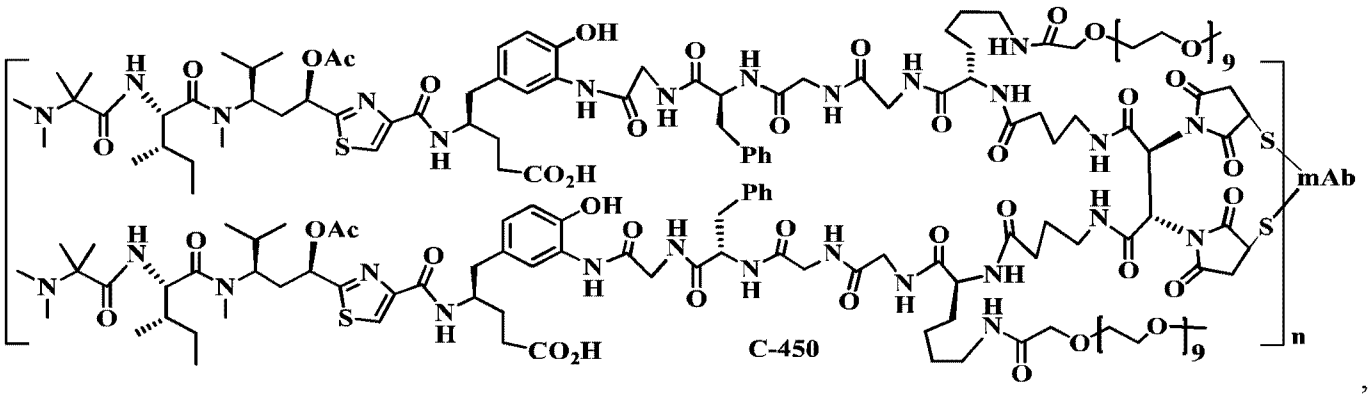
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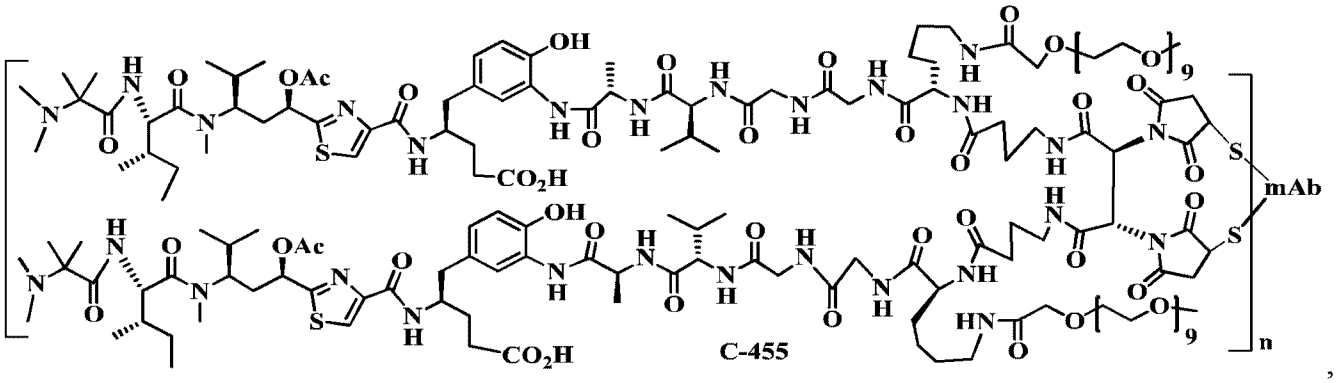
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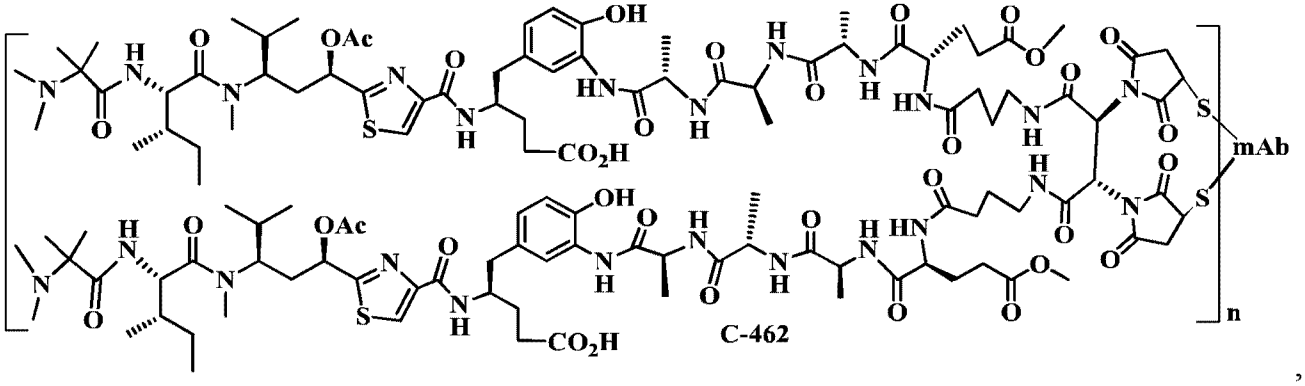
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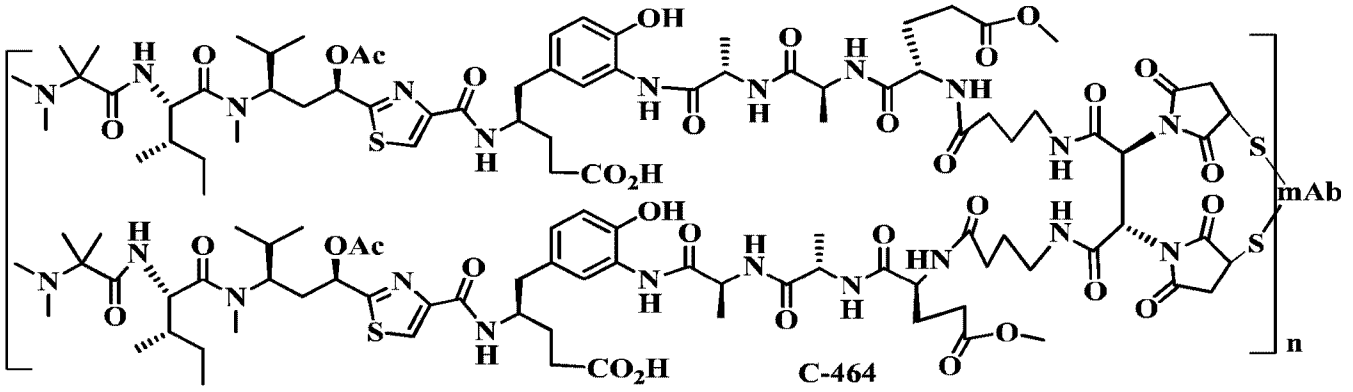
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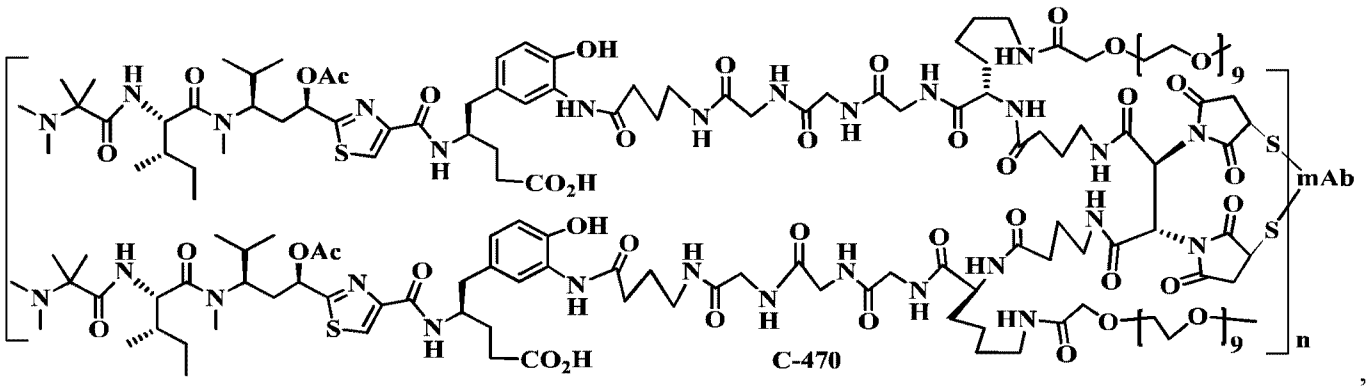

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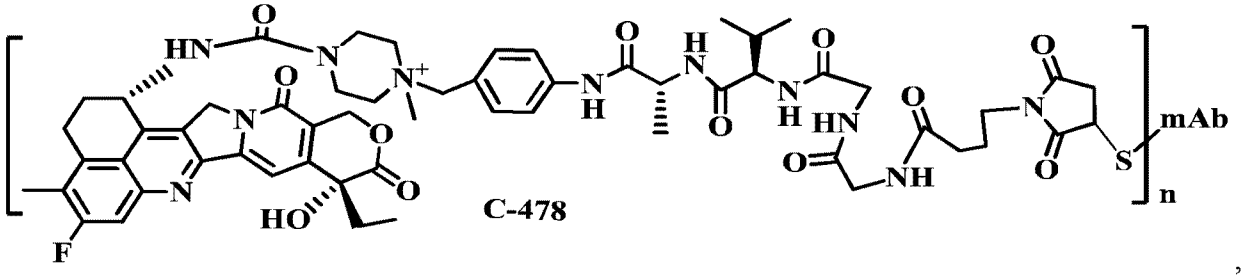

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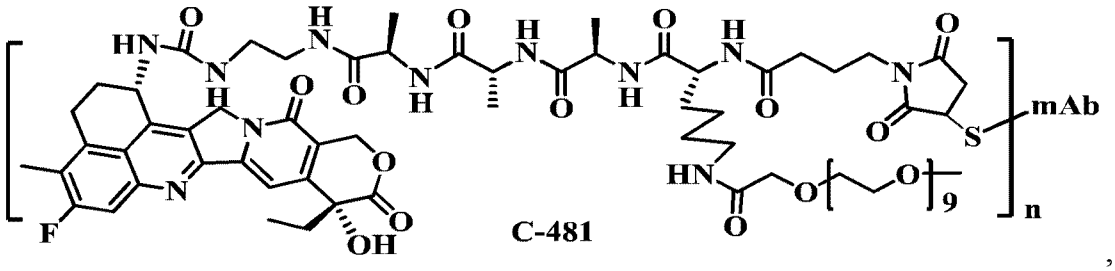

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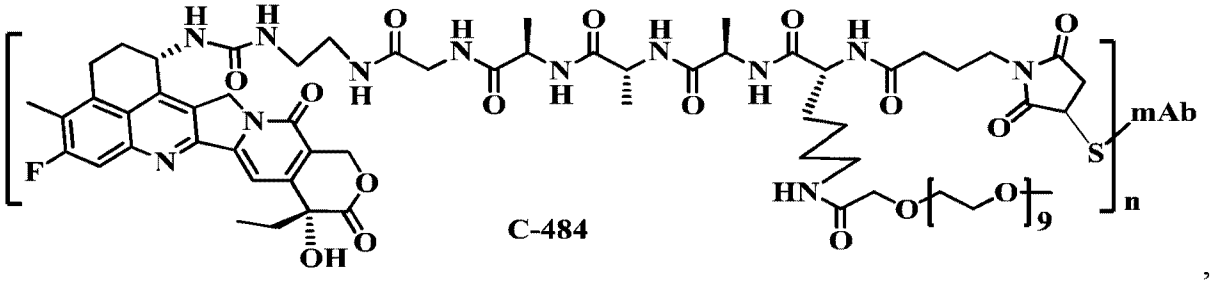

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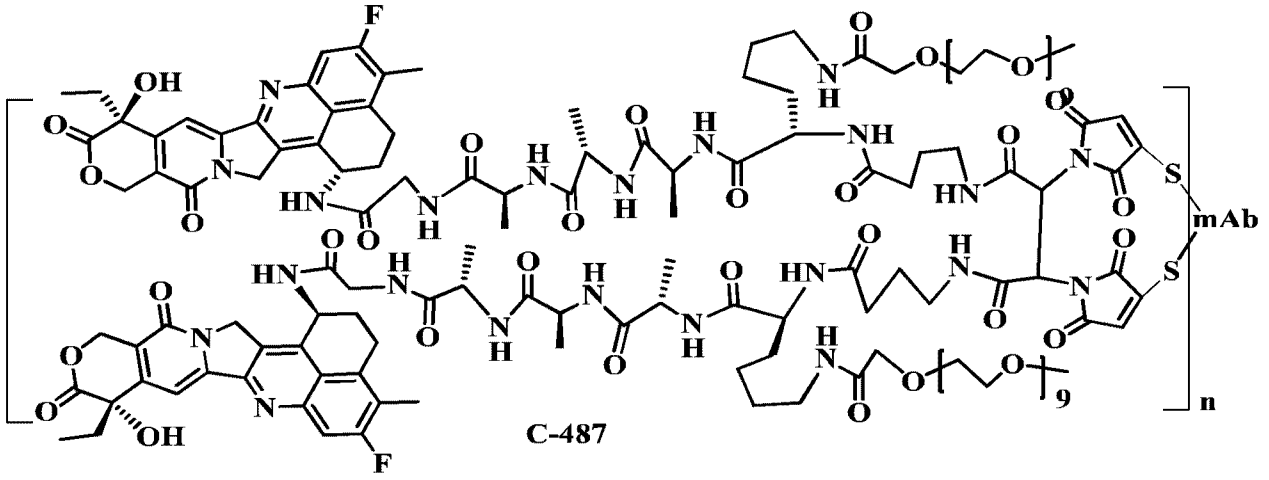

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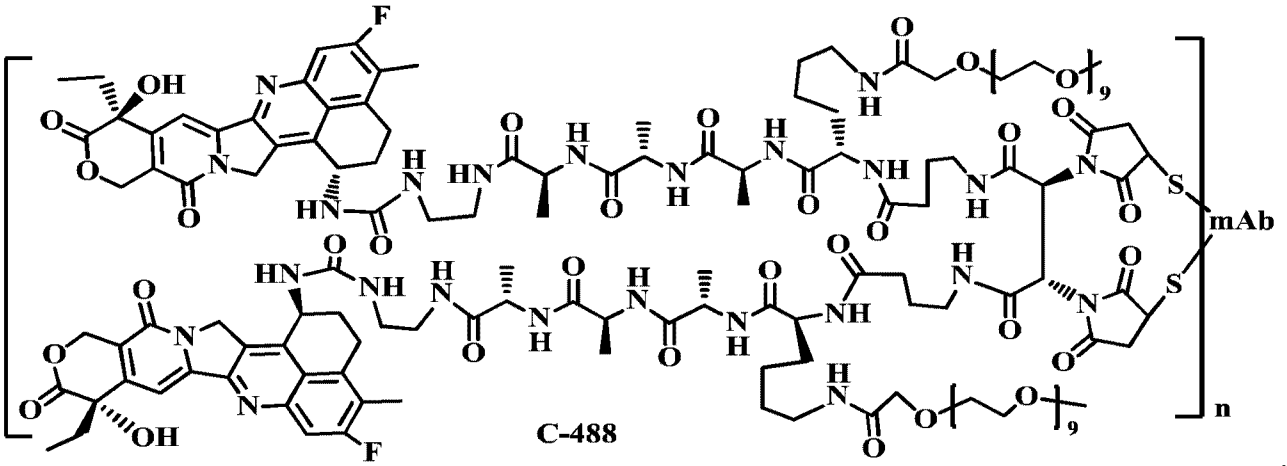
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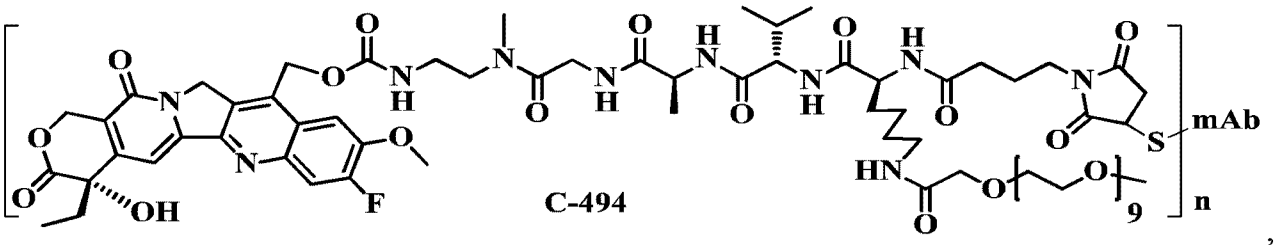
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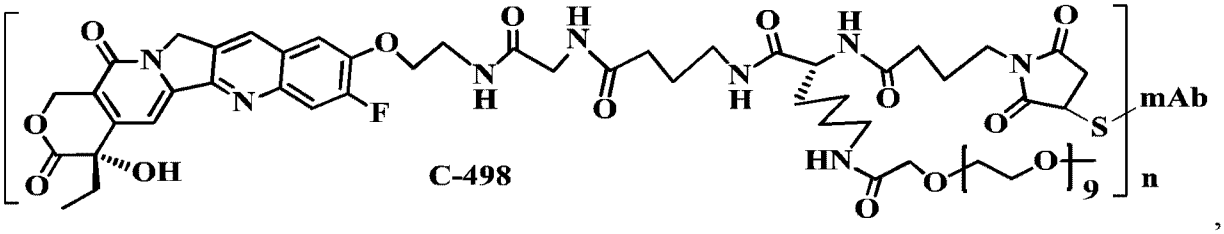
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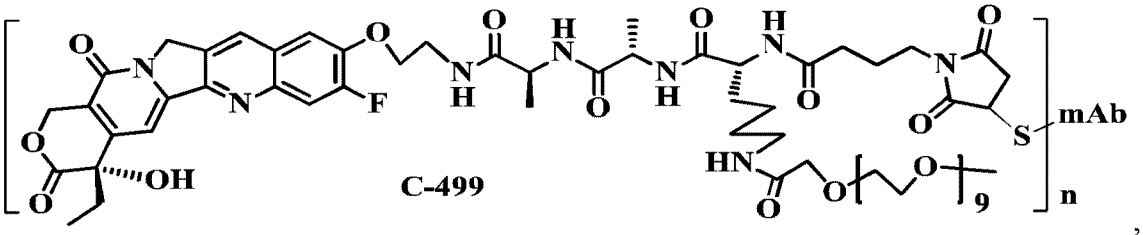
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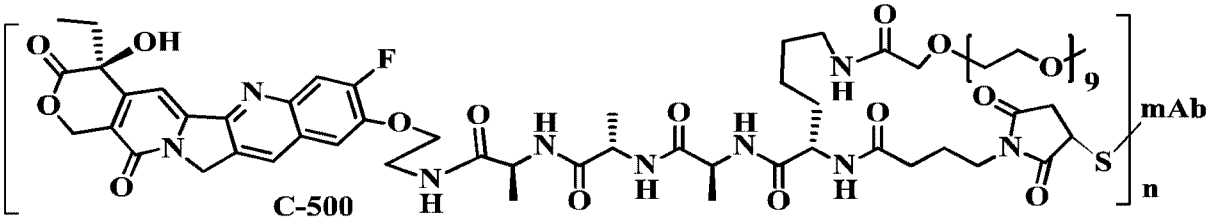
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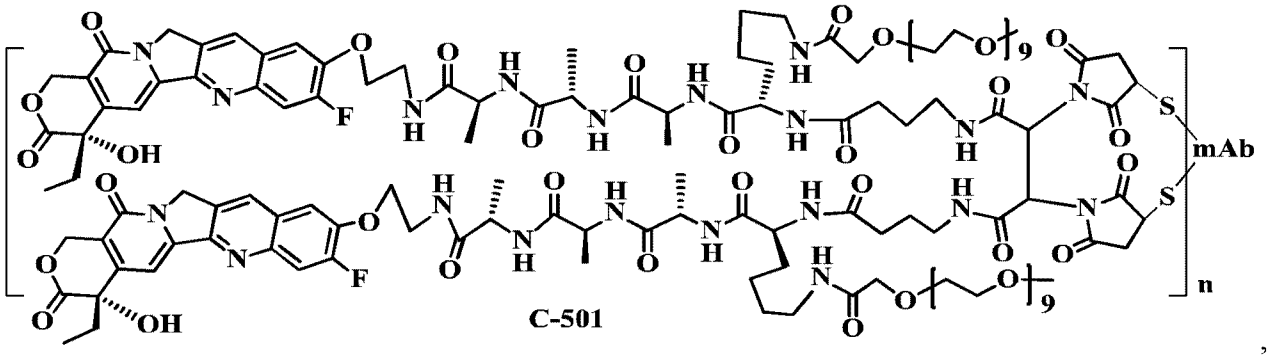

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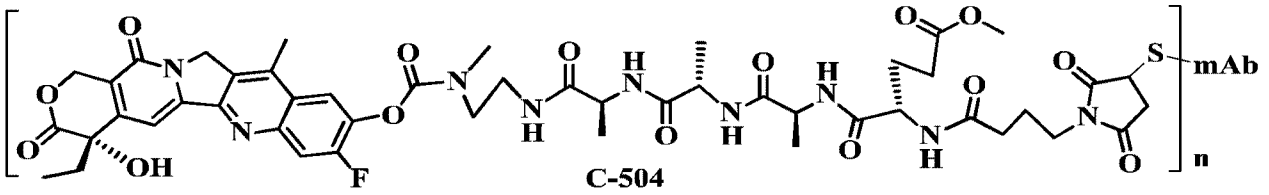

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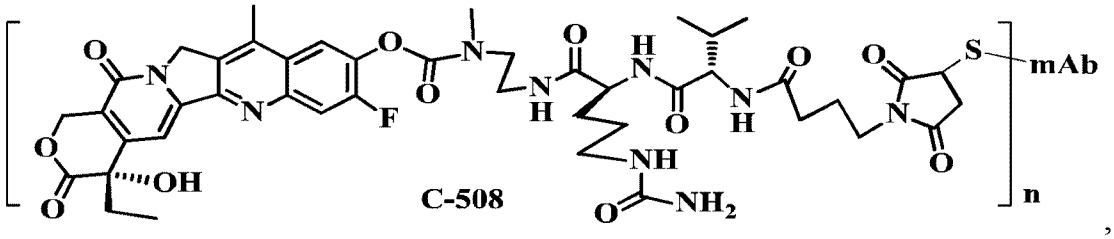

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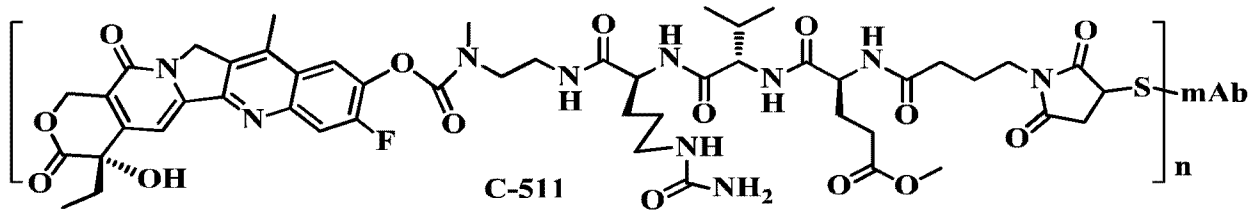

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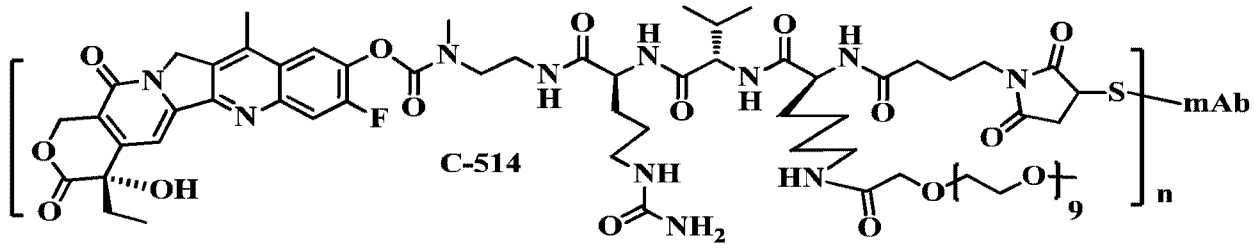

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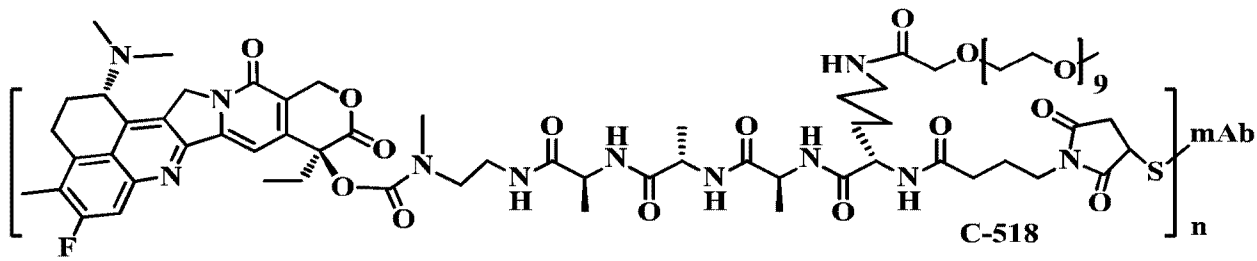

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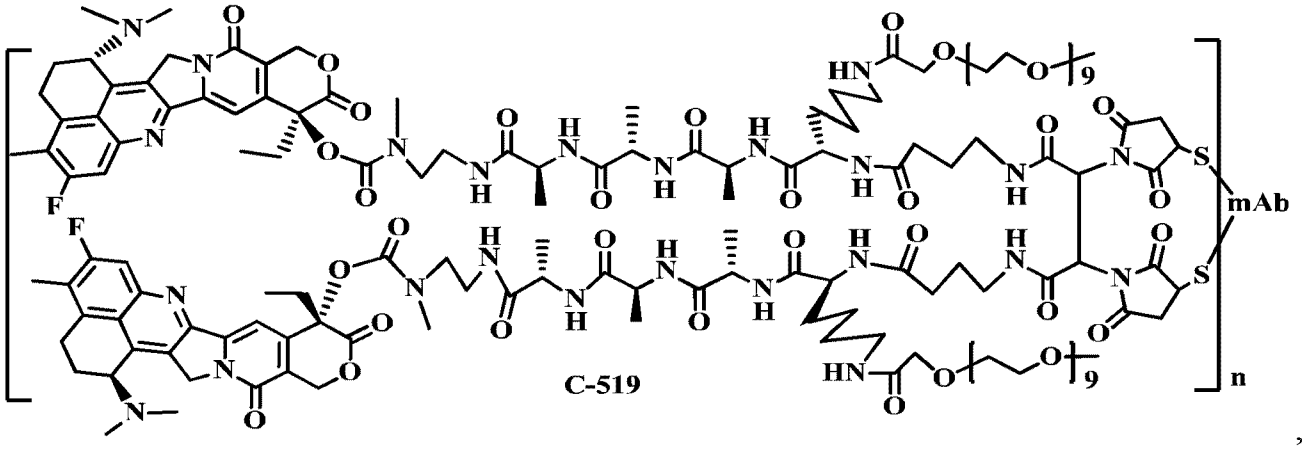
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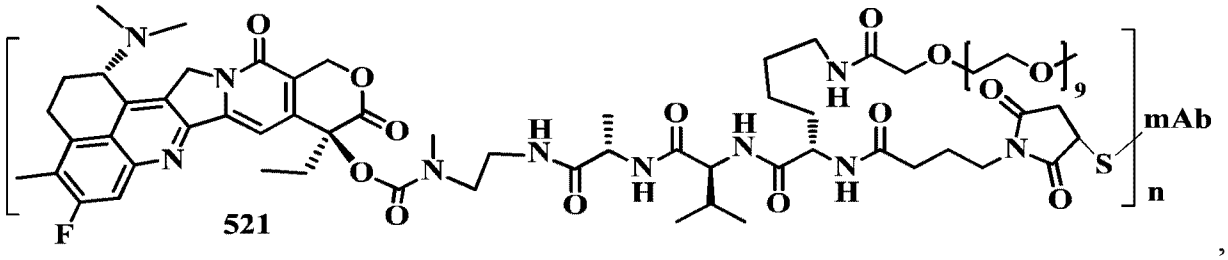
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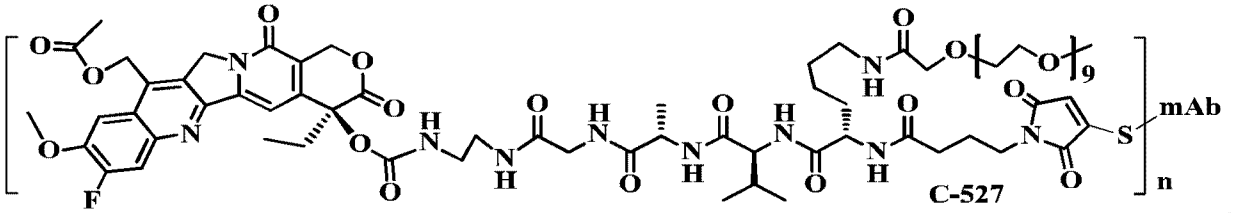
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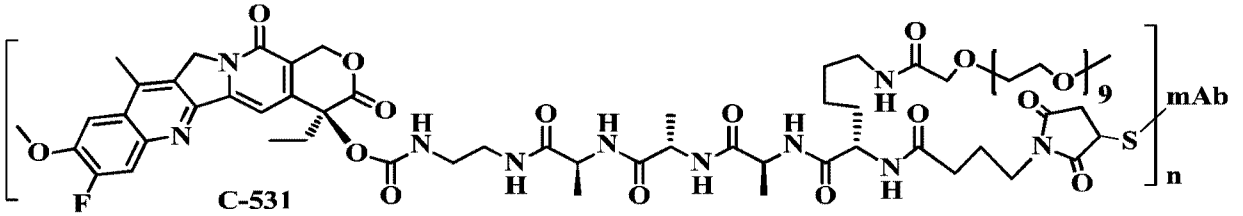
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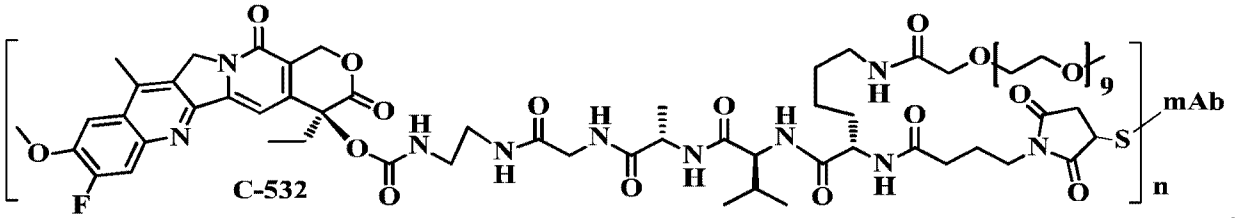
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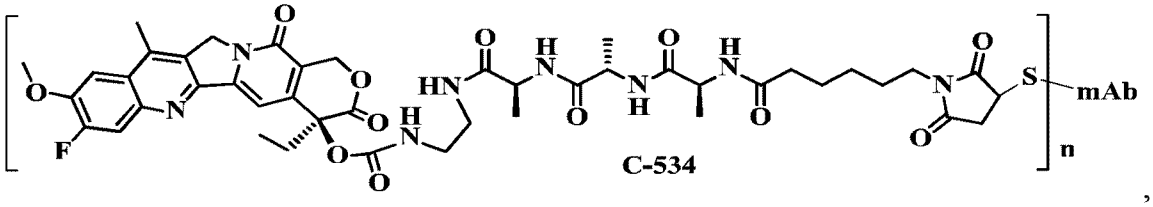
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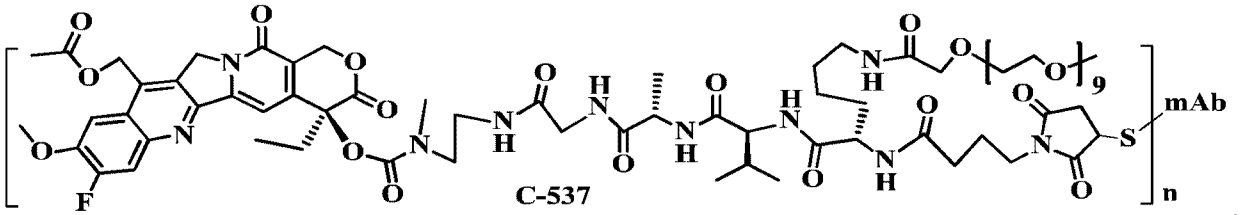
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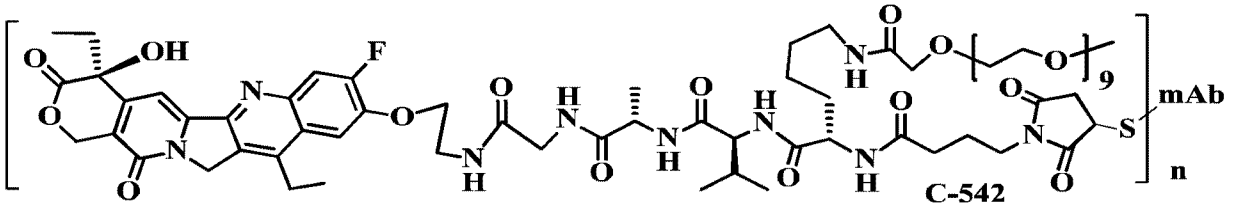
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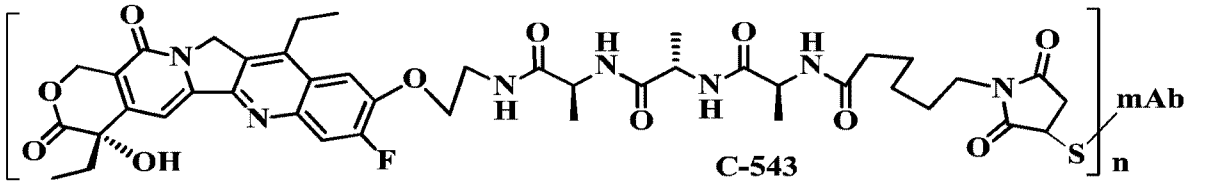
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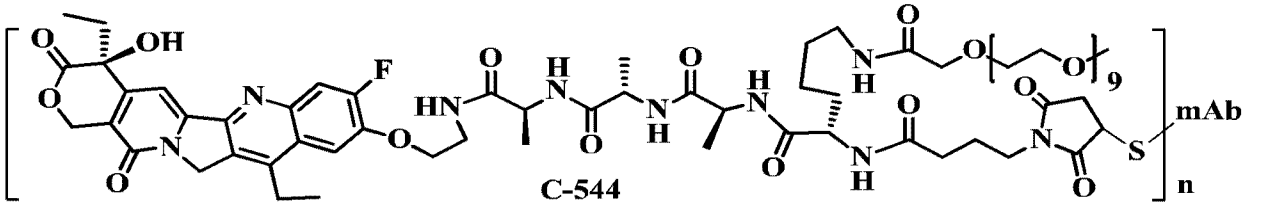
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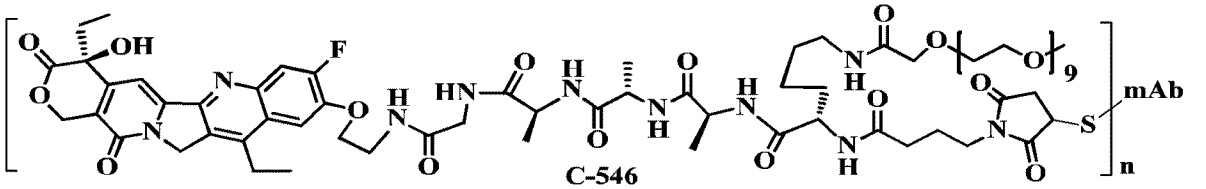
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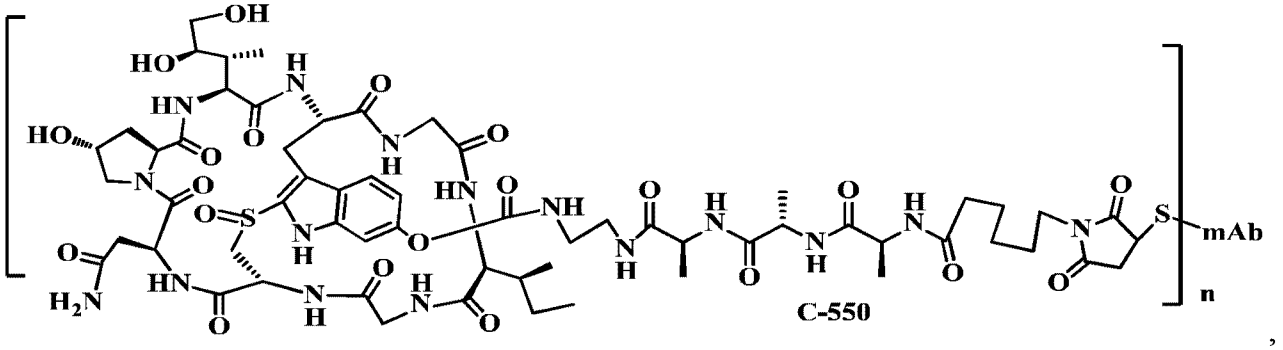
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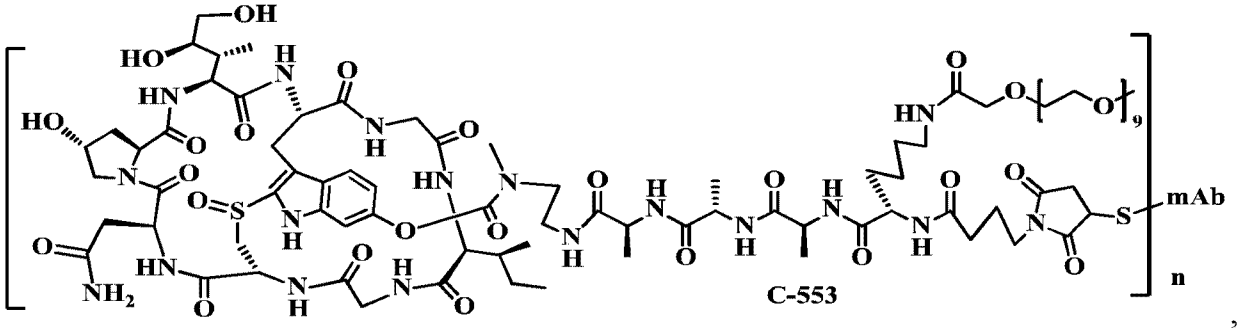
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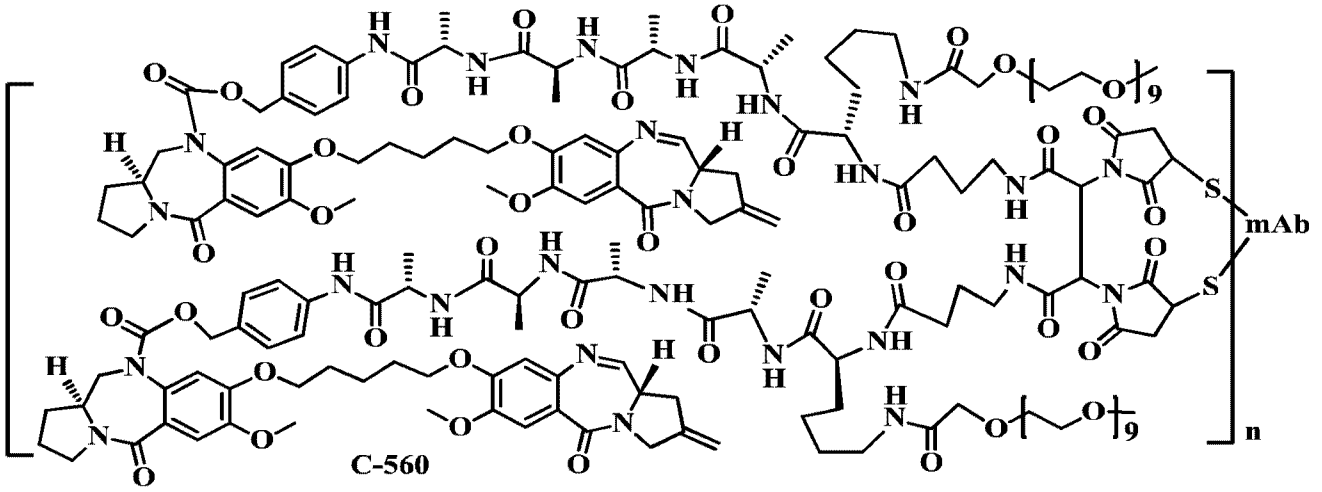

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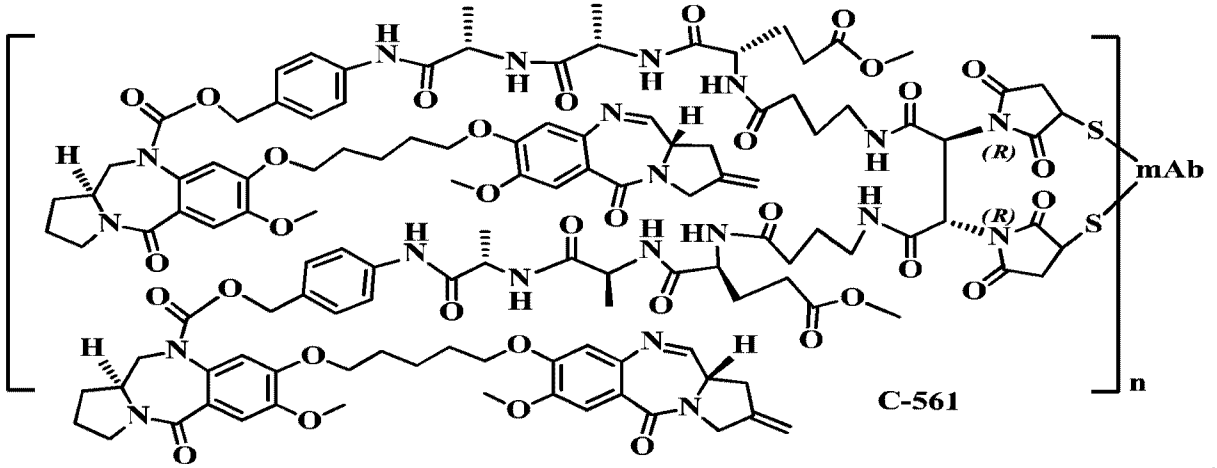

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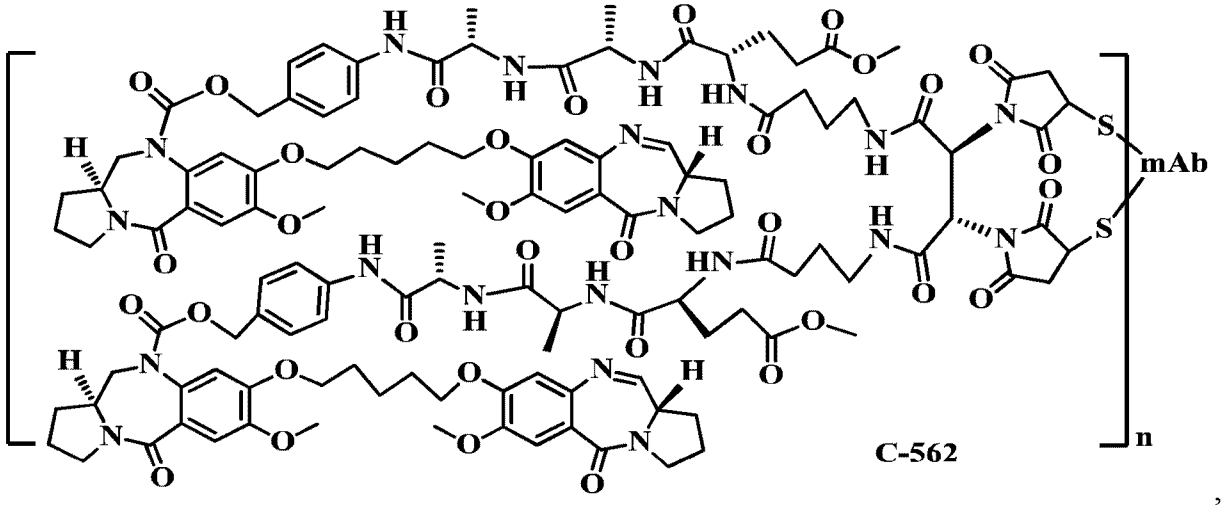

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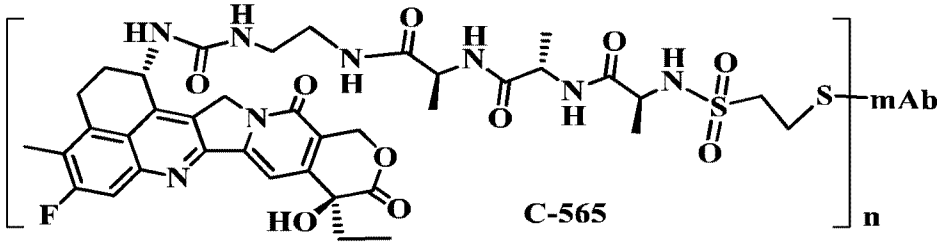

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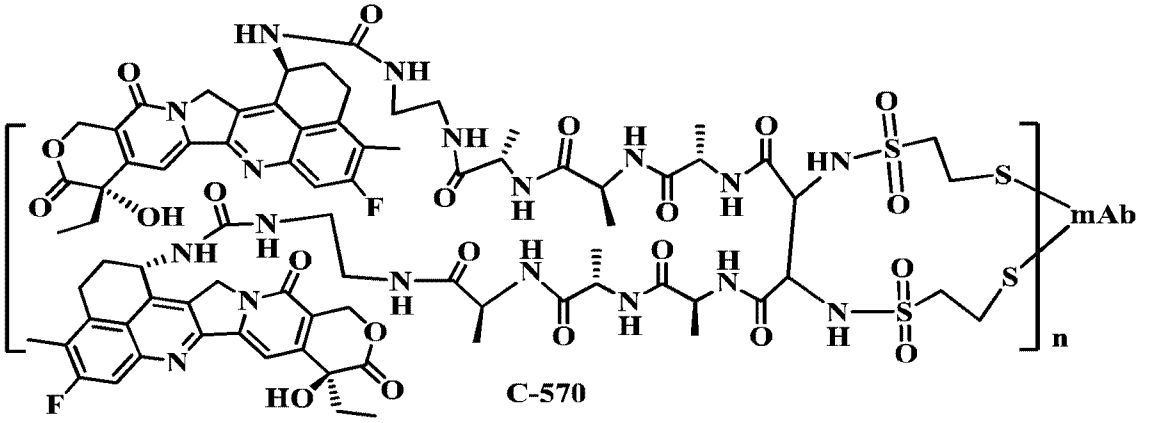
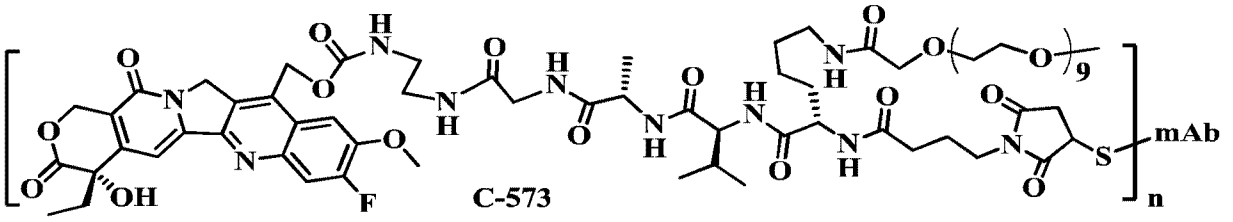


C-570



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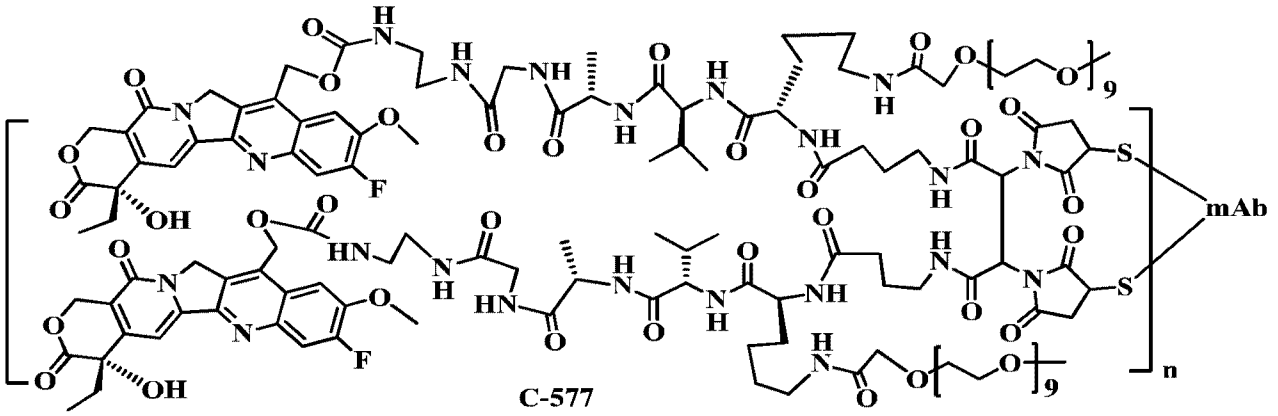

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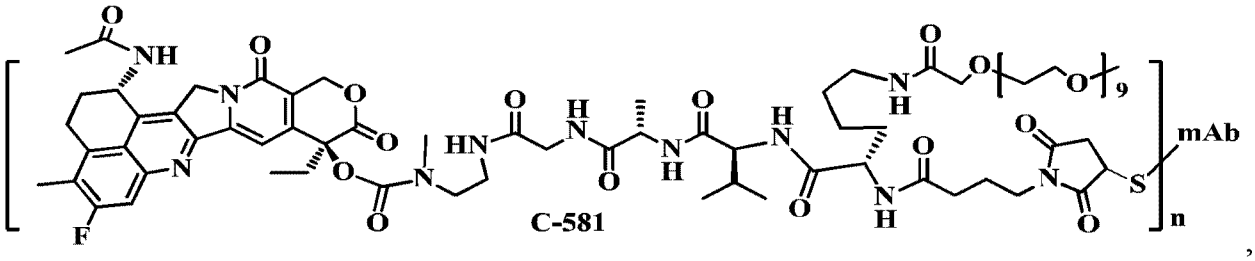

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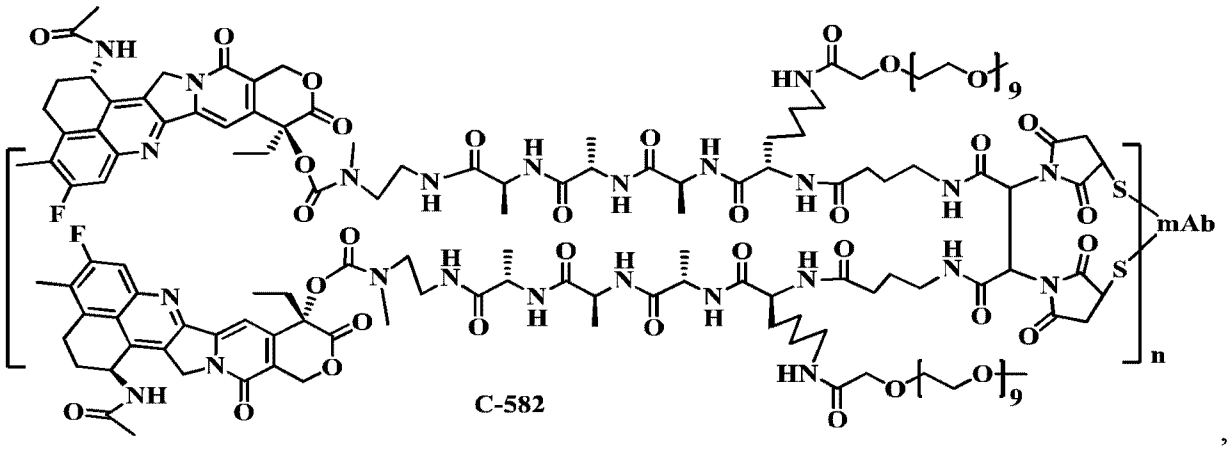

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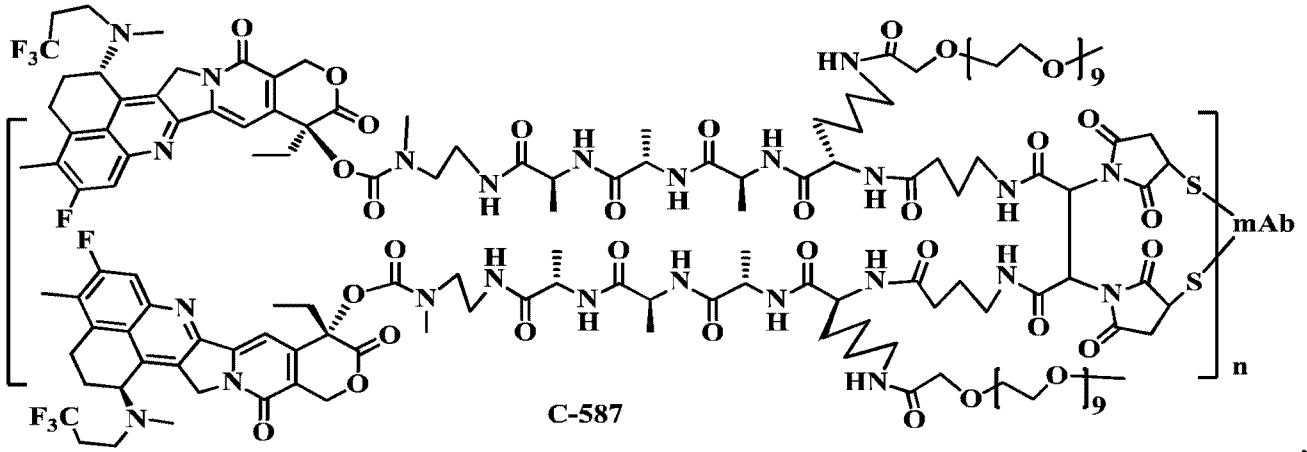

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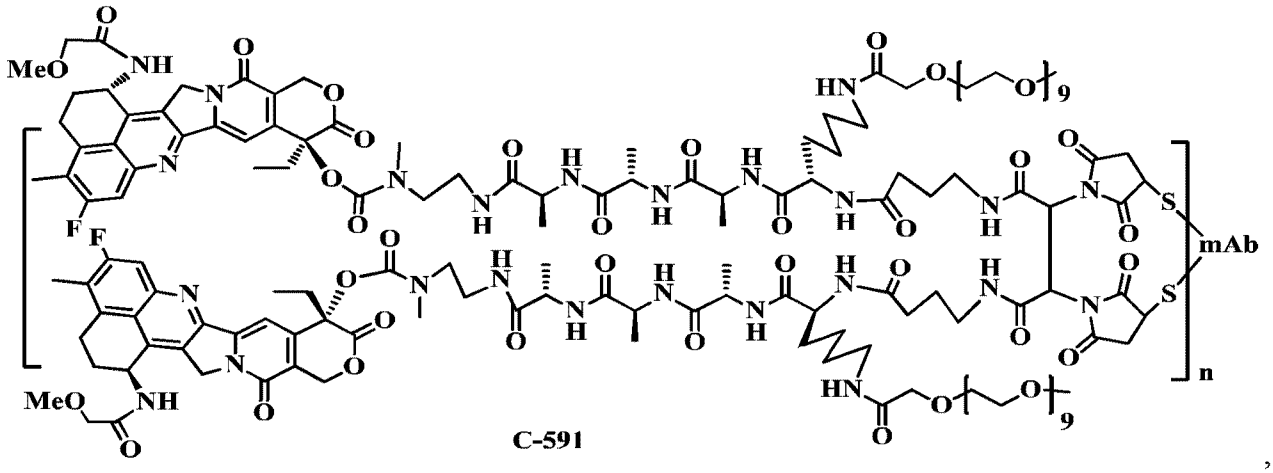

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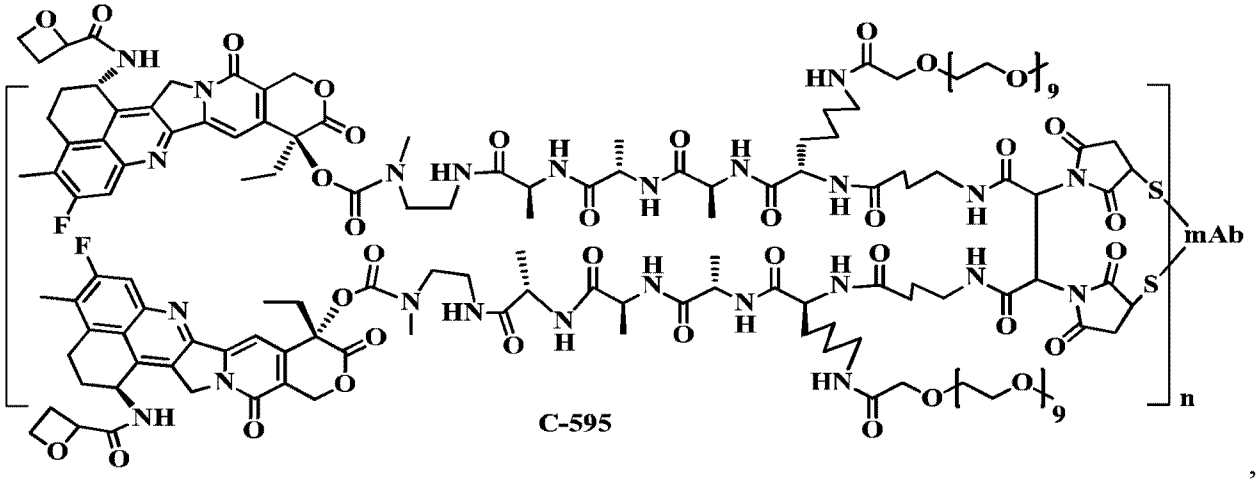

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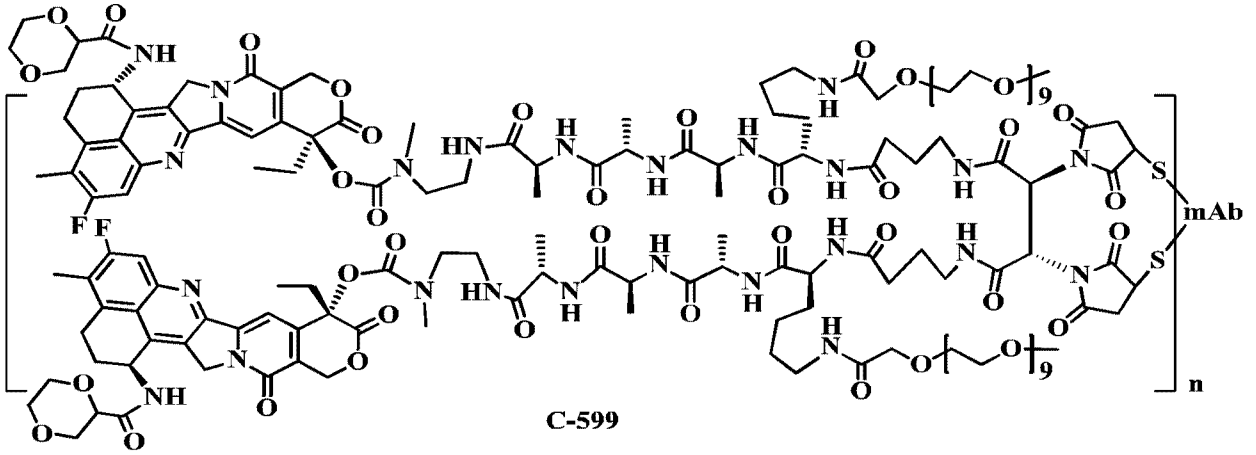

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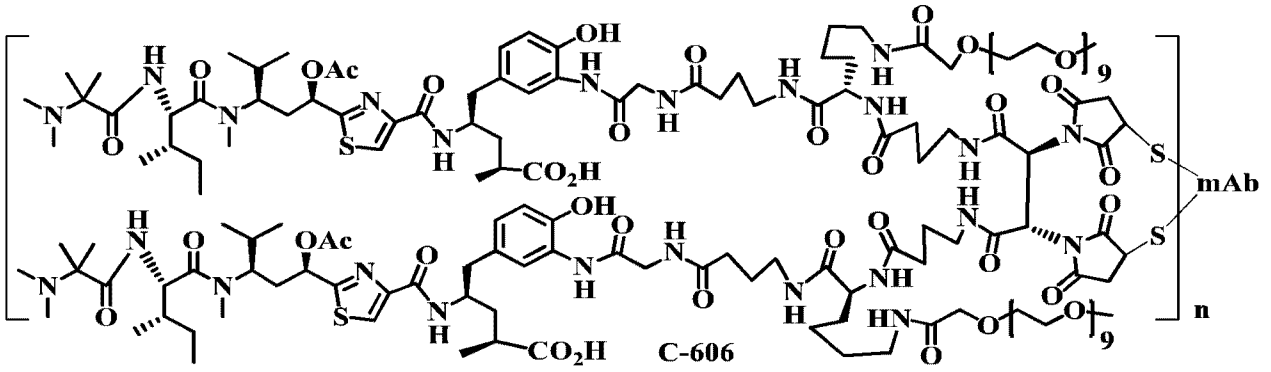

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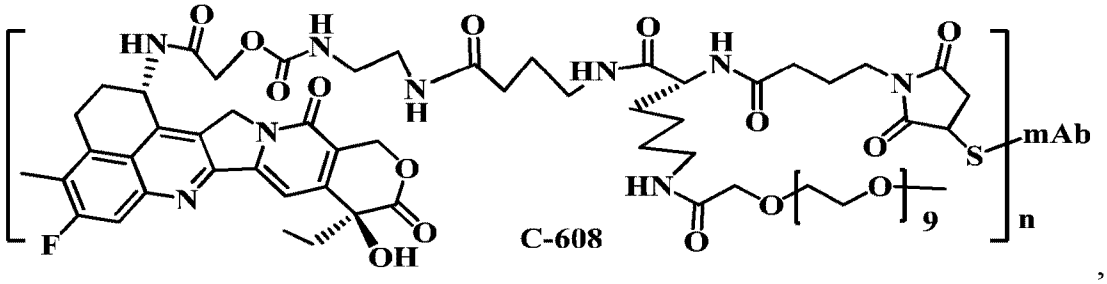

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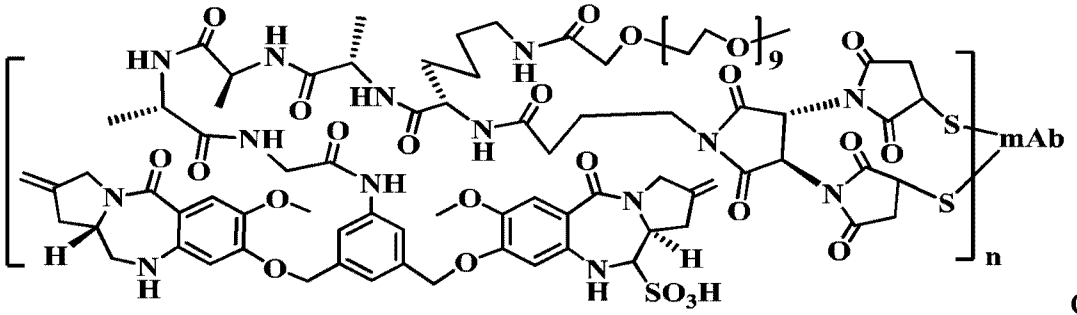

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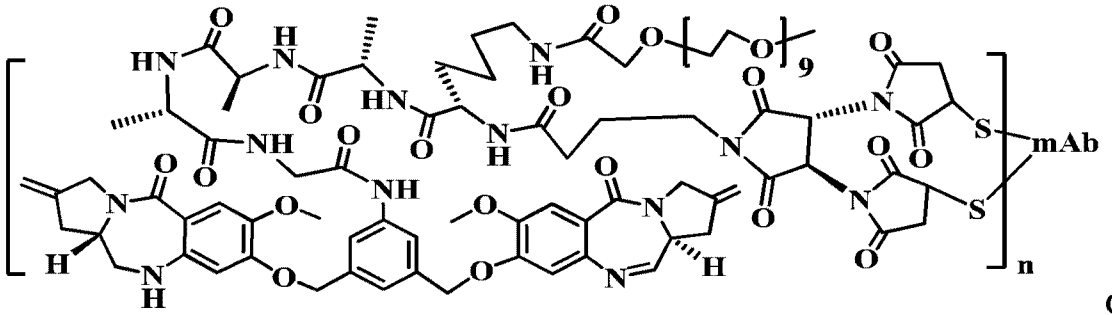

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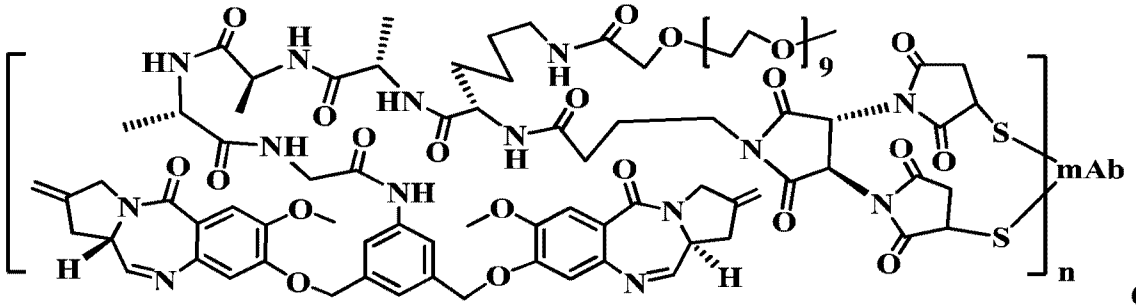

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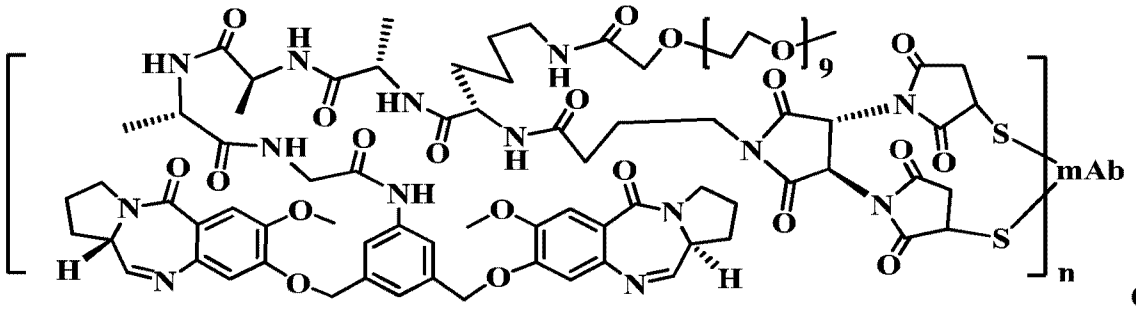

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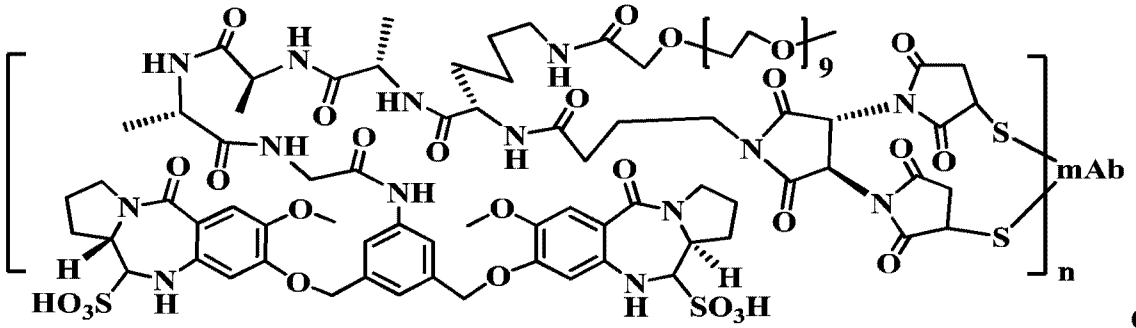

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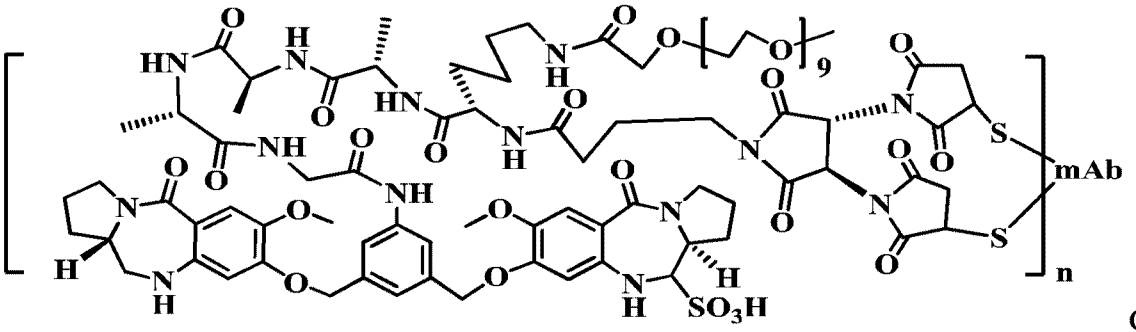

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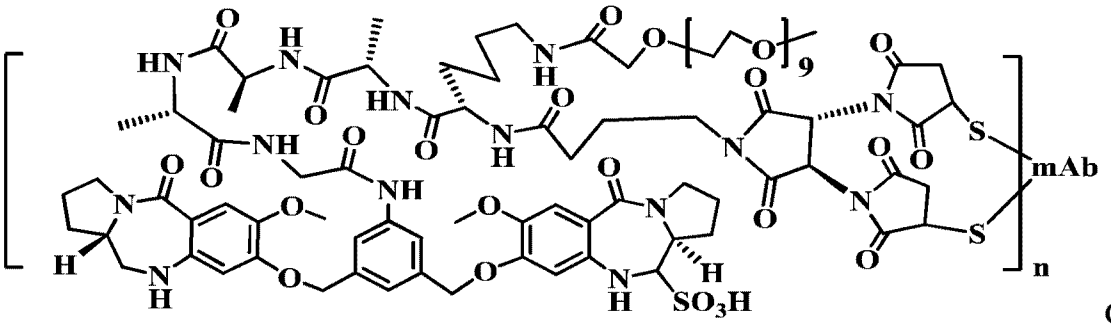

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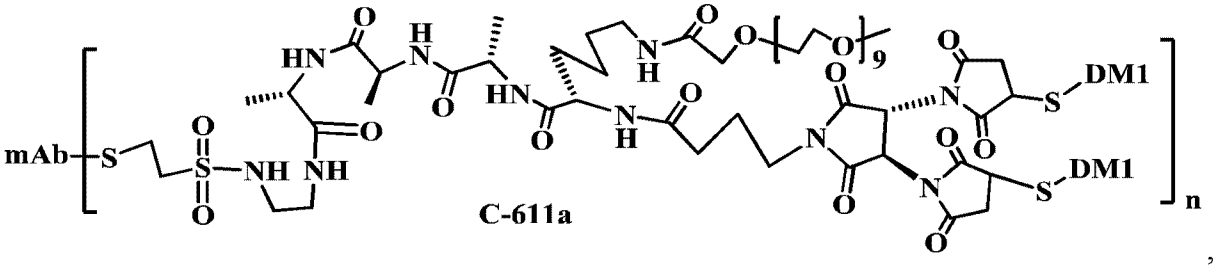

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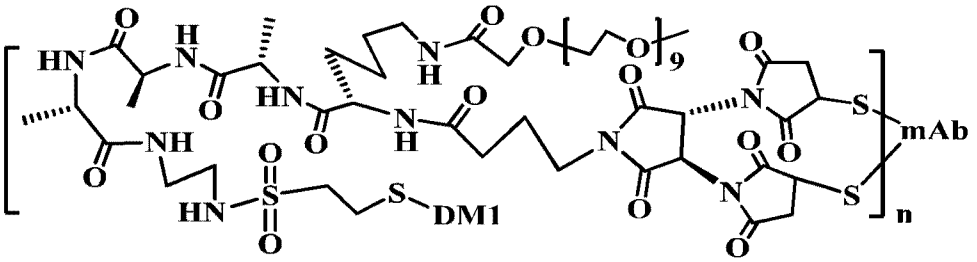

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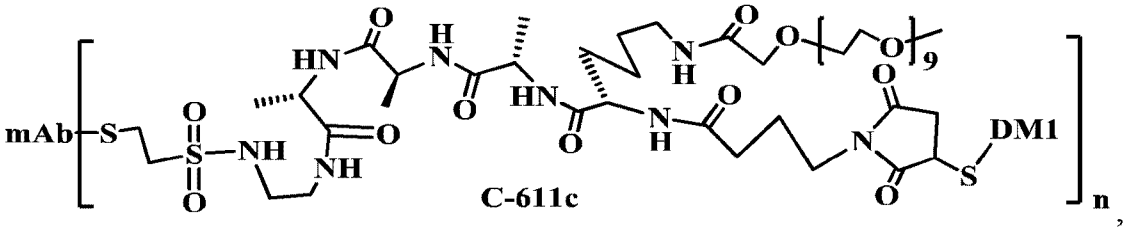

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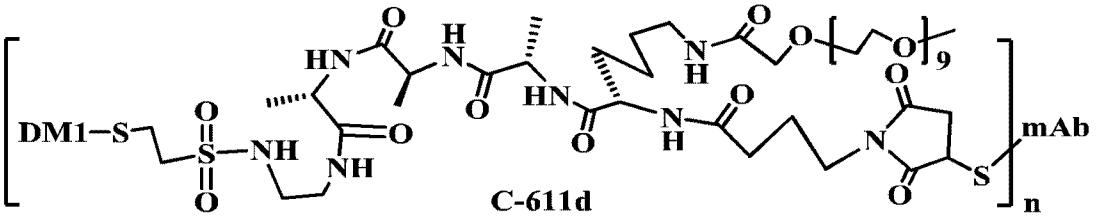

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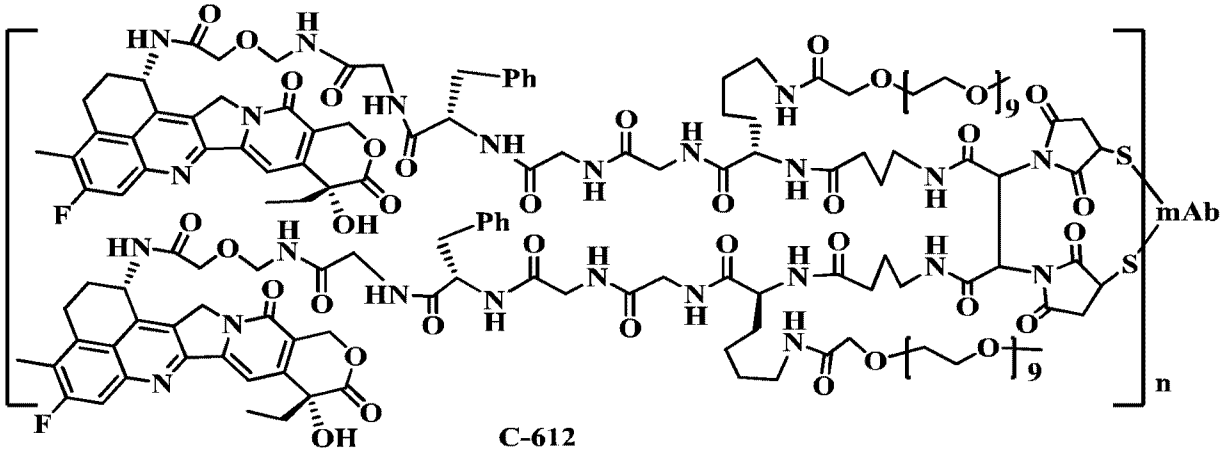

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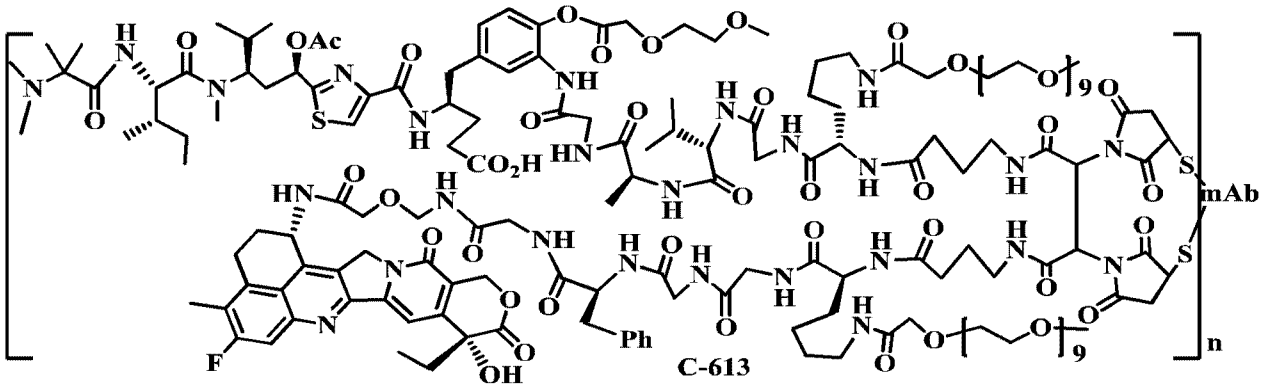

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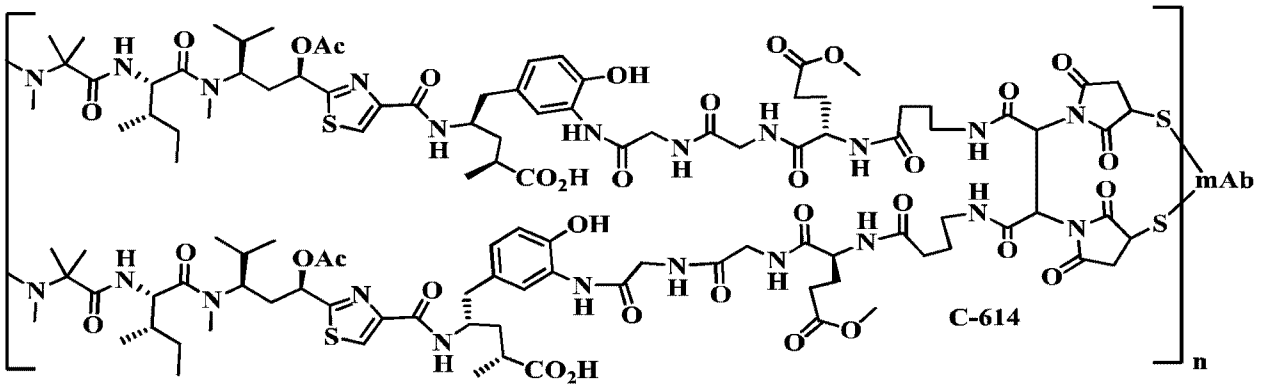

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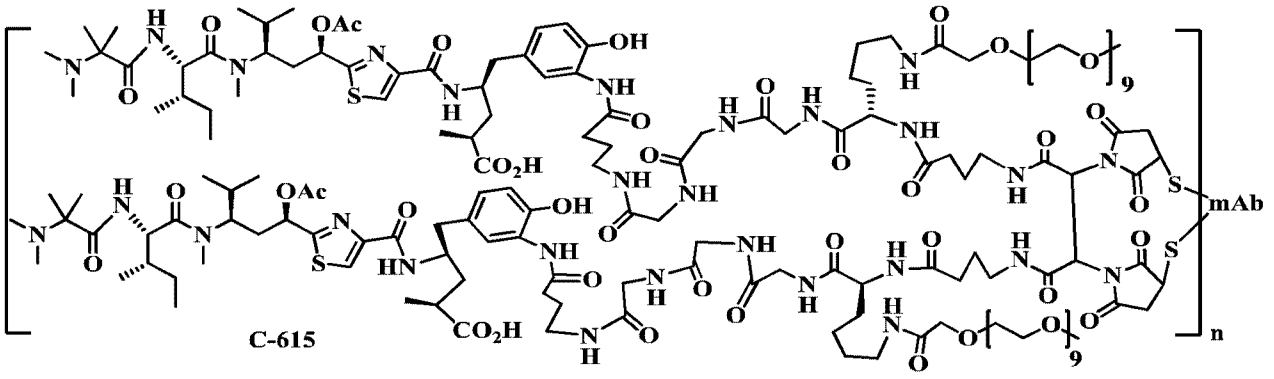

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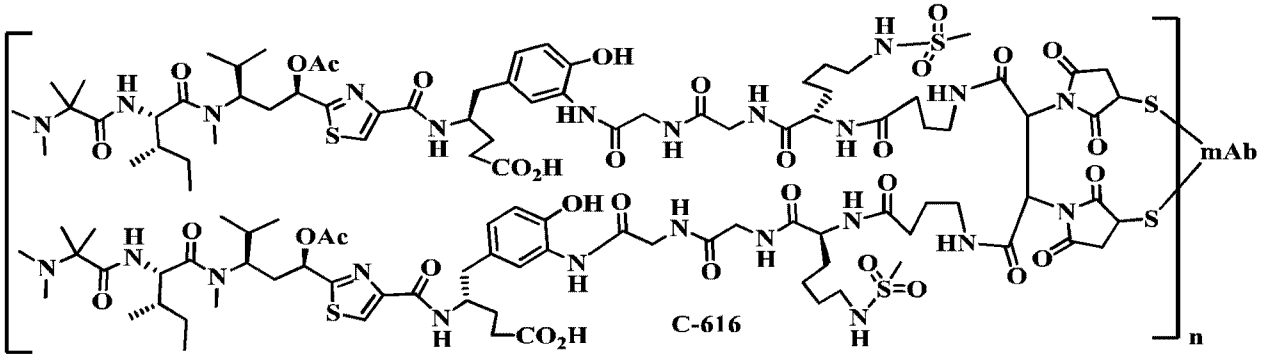

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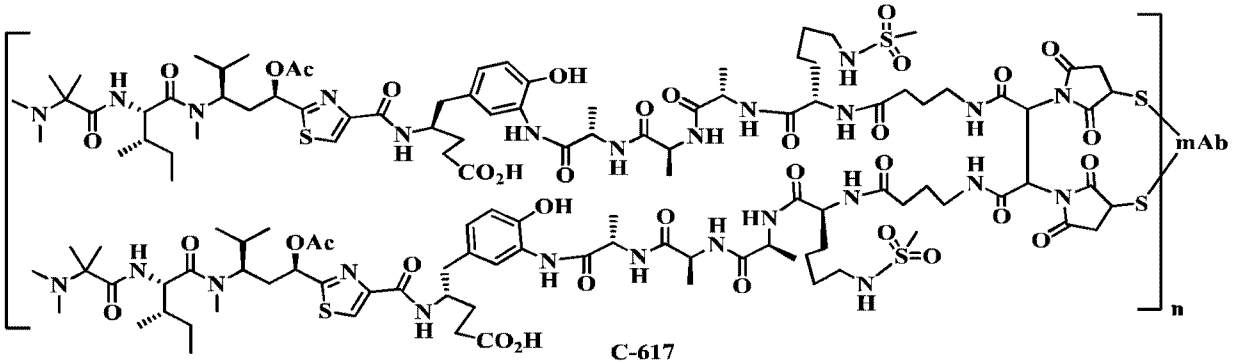

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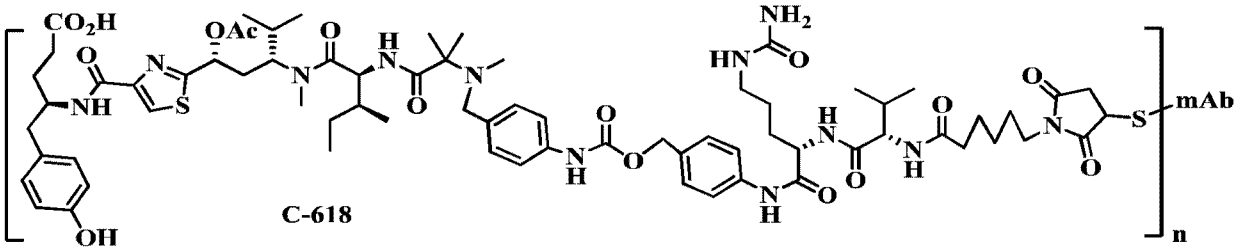

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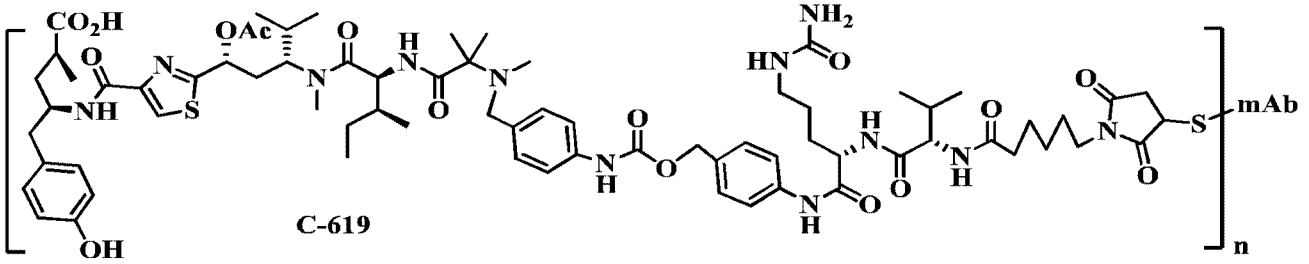

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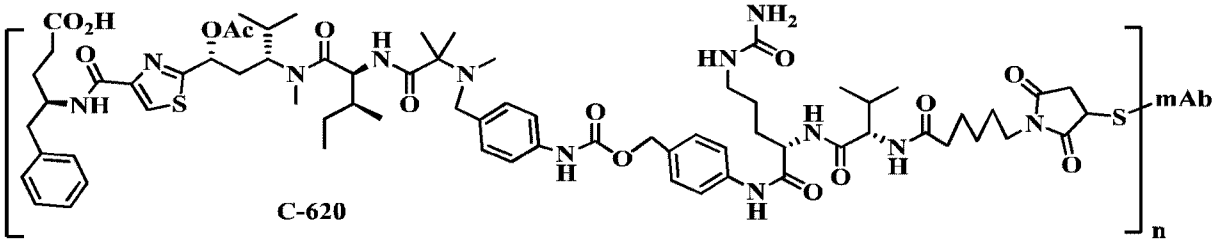

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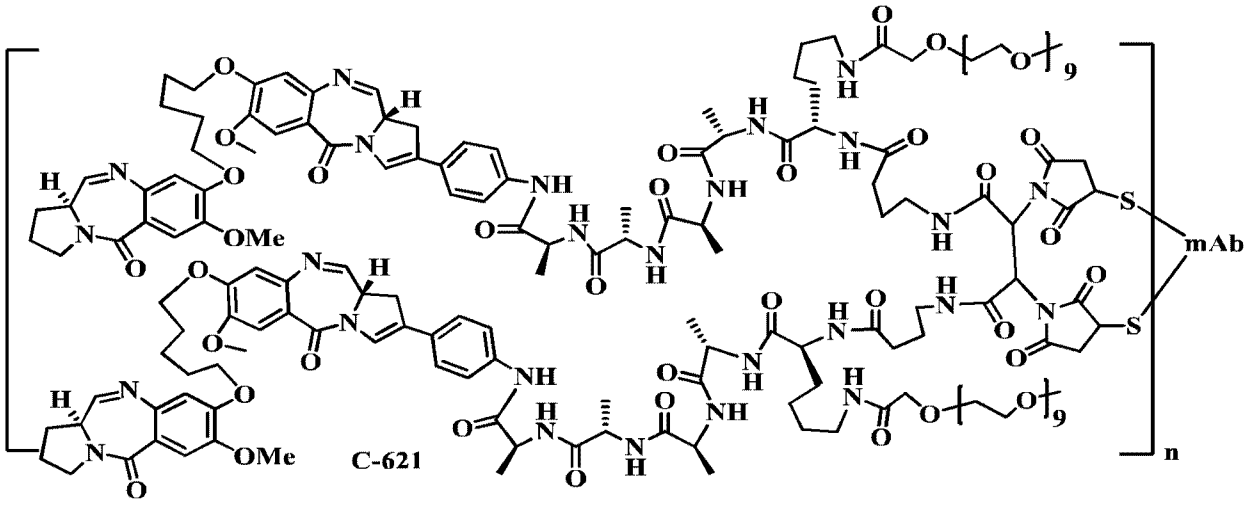

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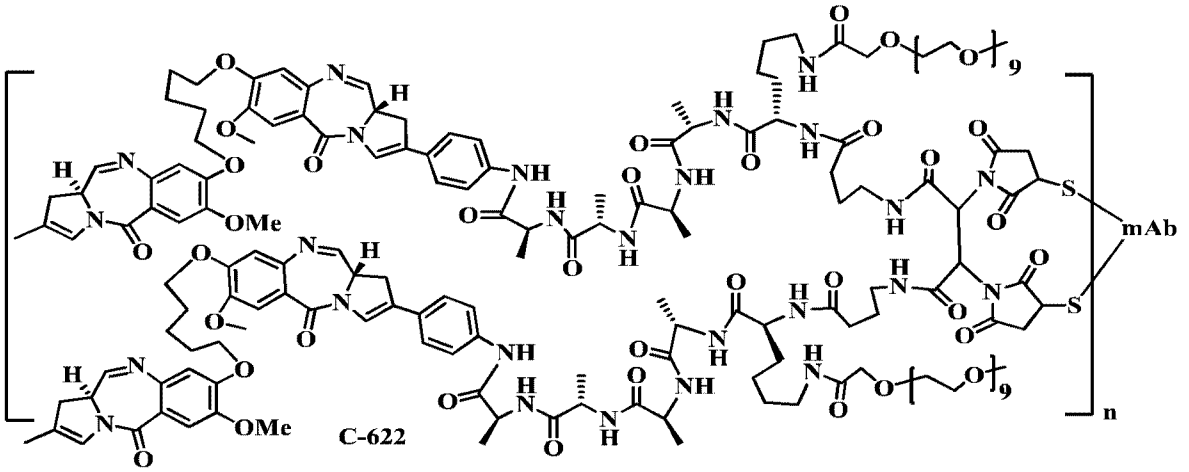

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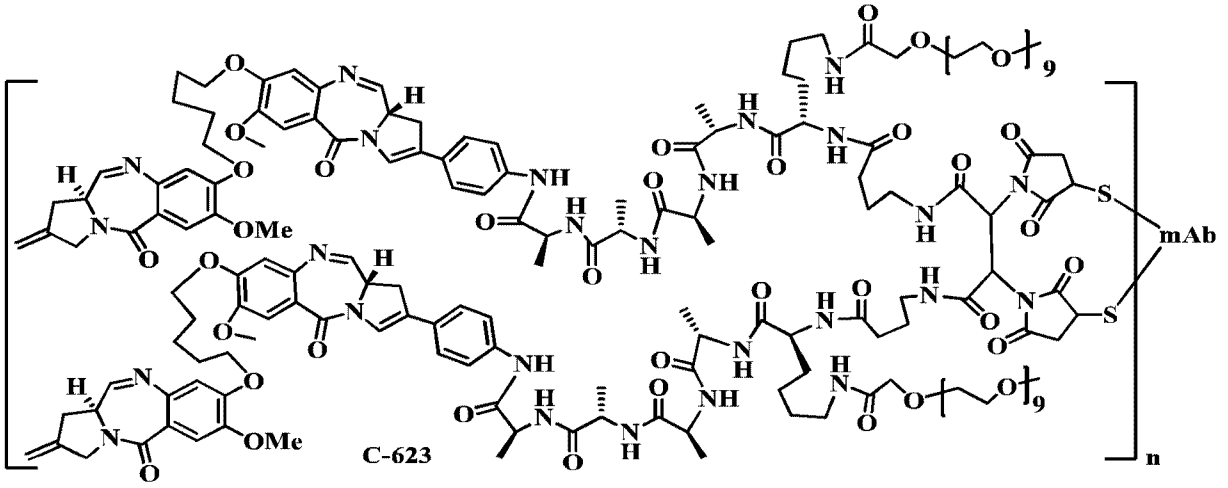

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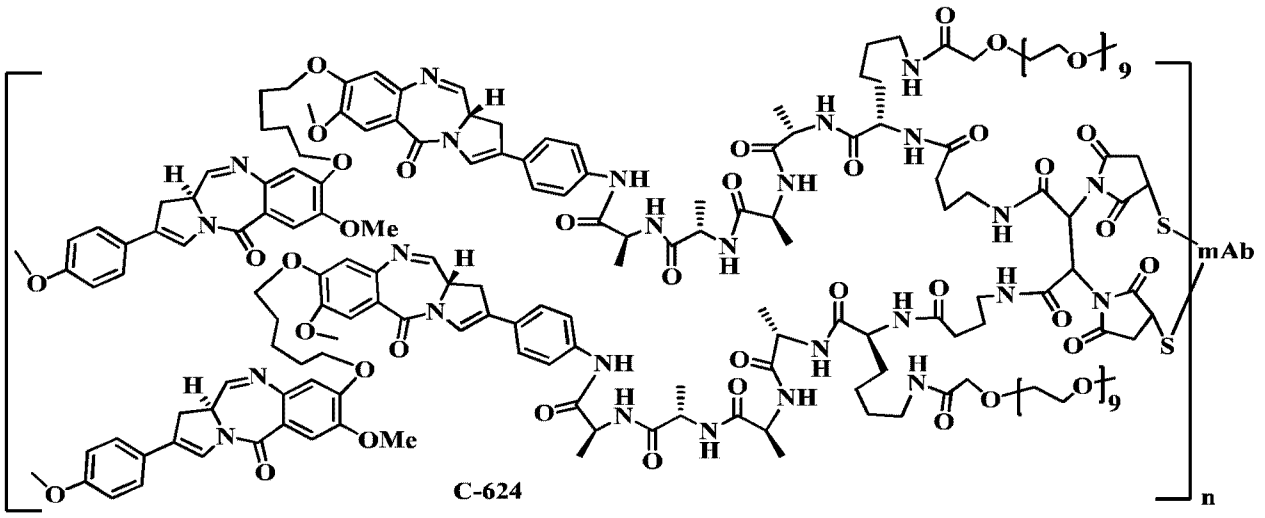

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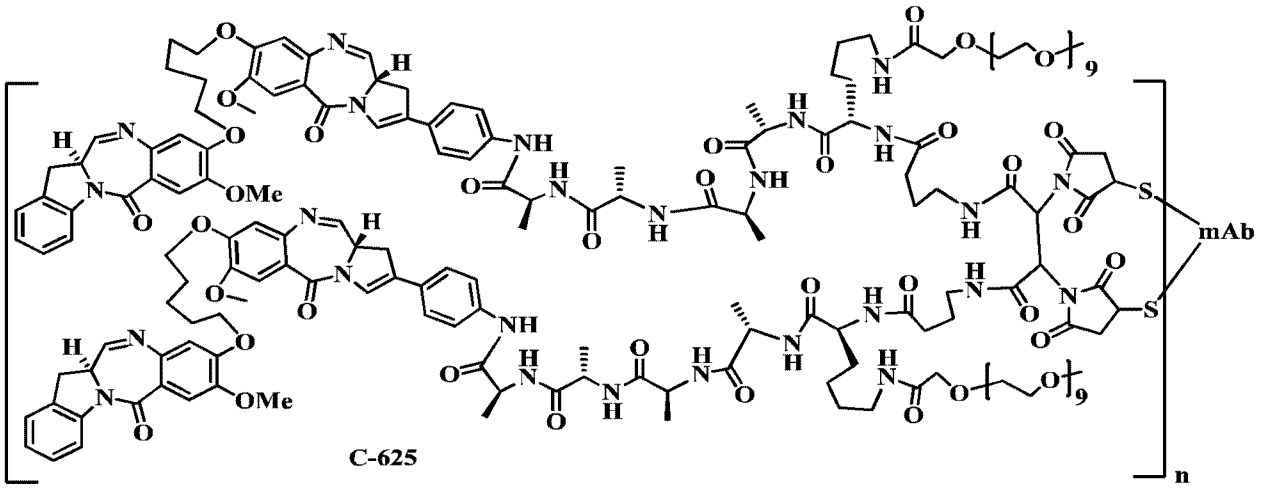

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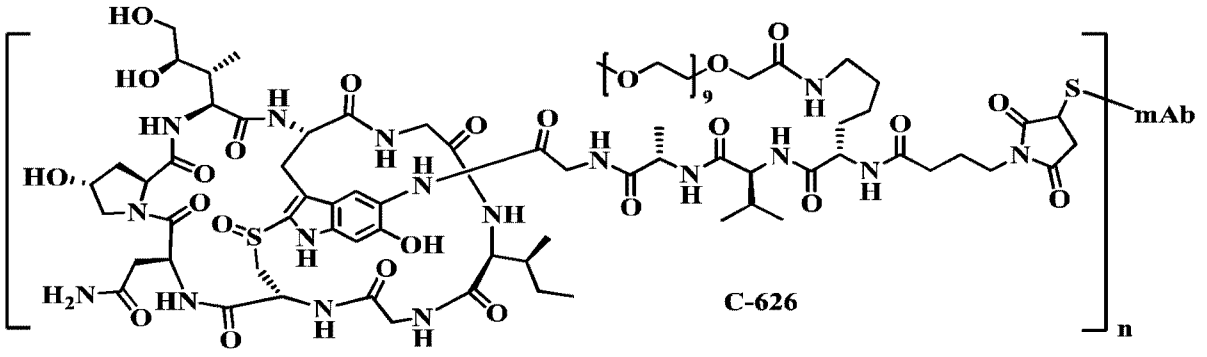

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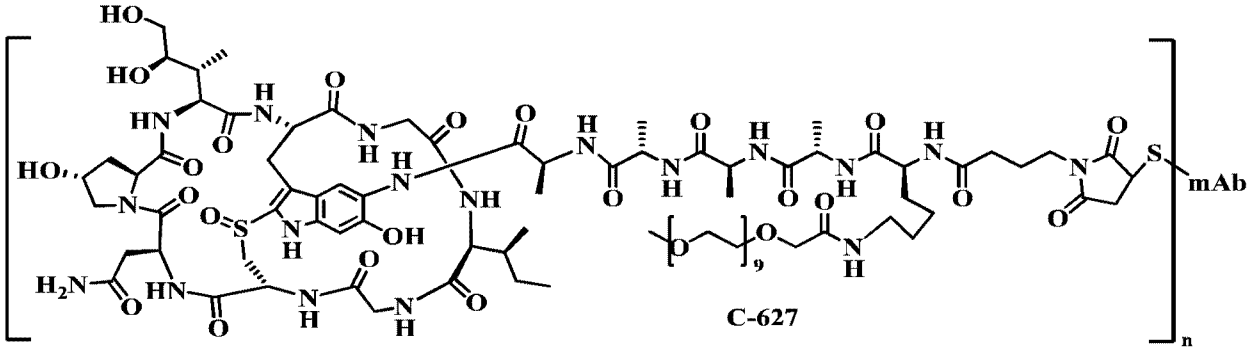

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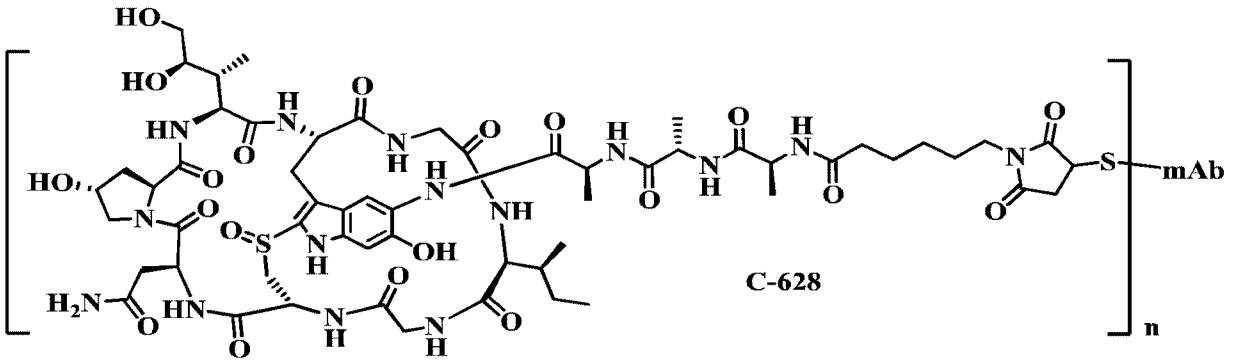

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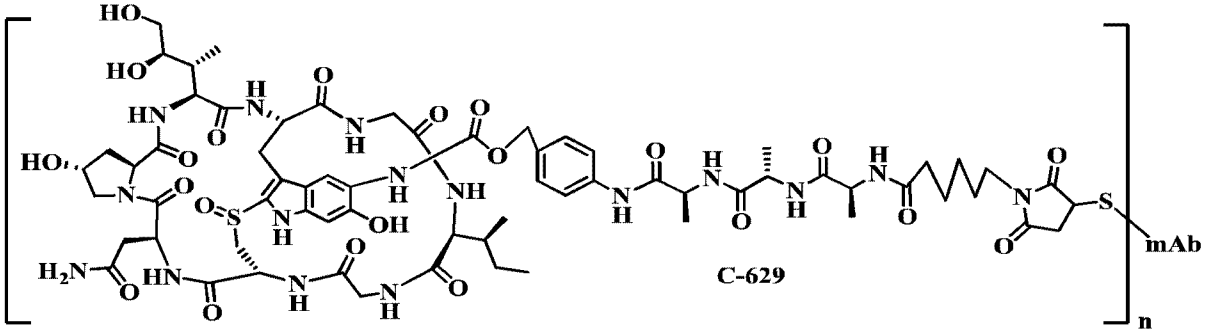

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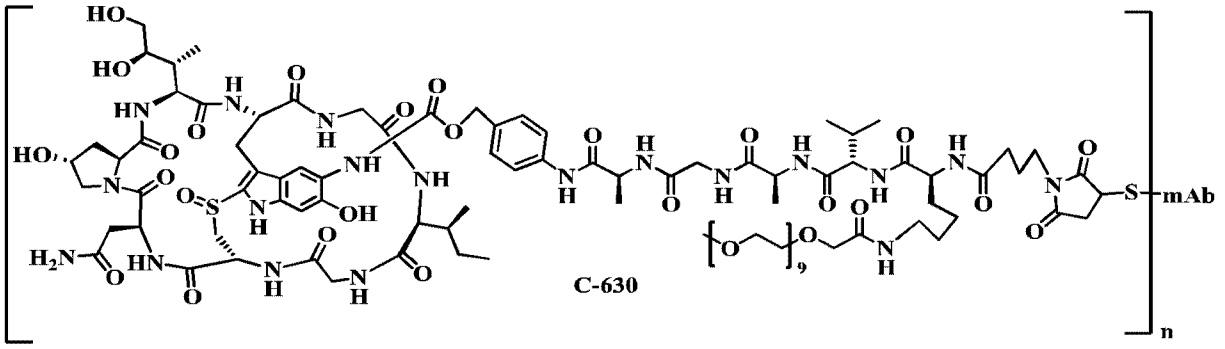

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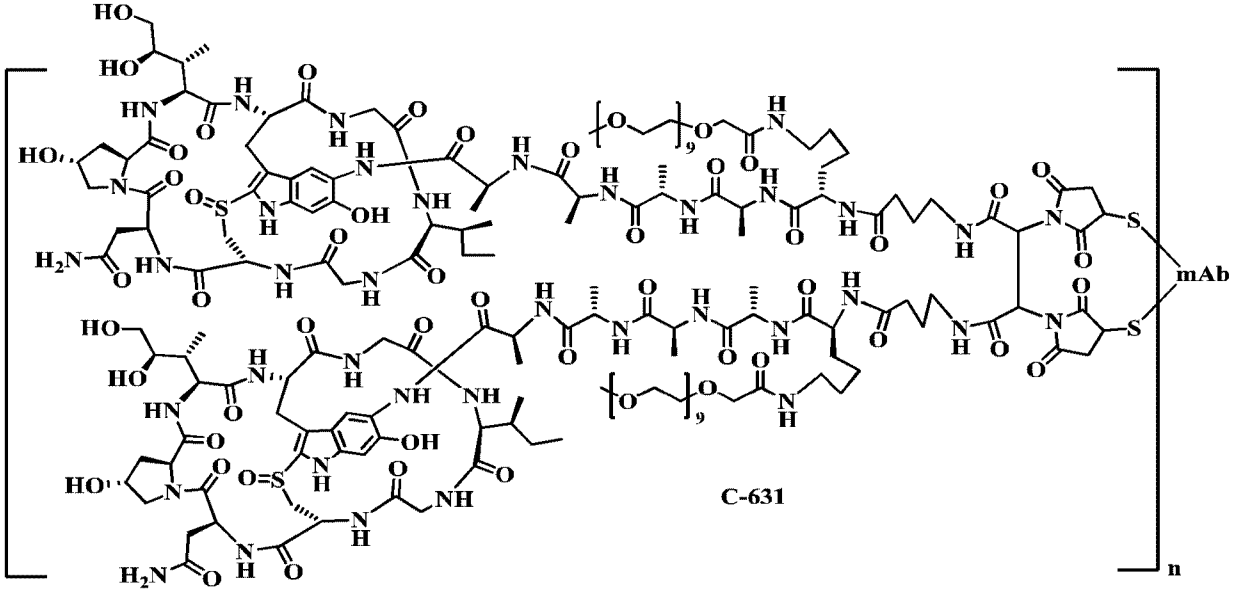

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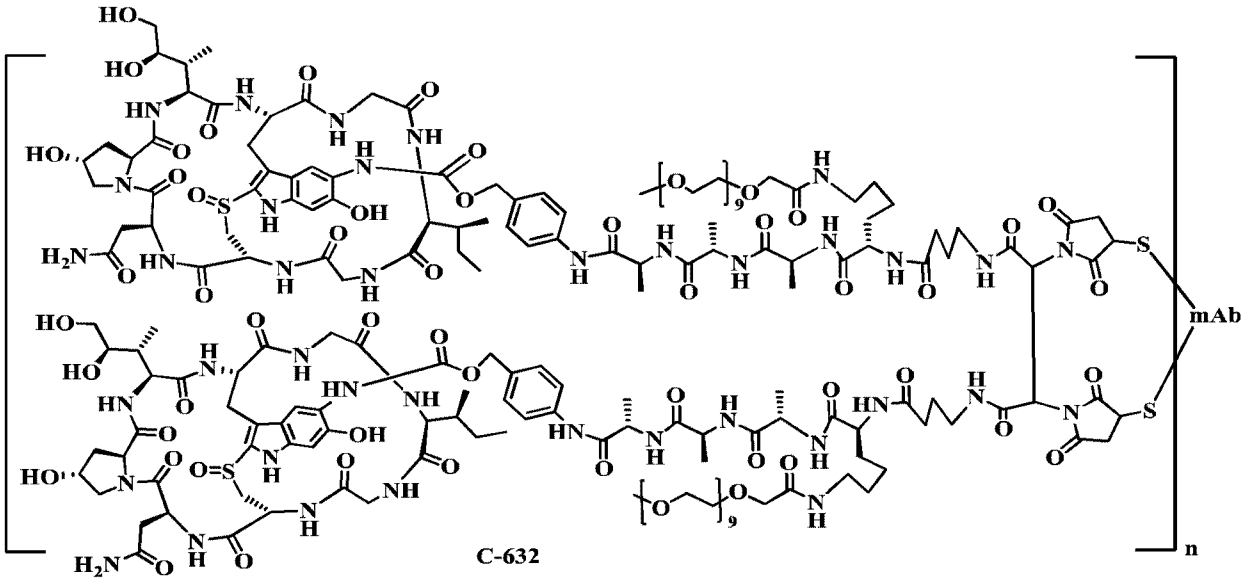

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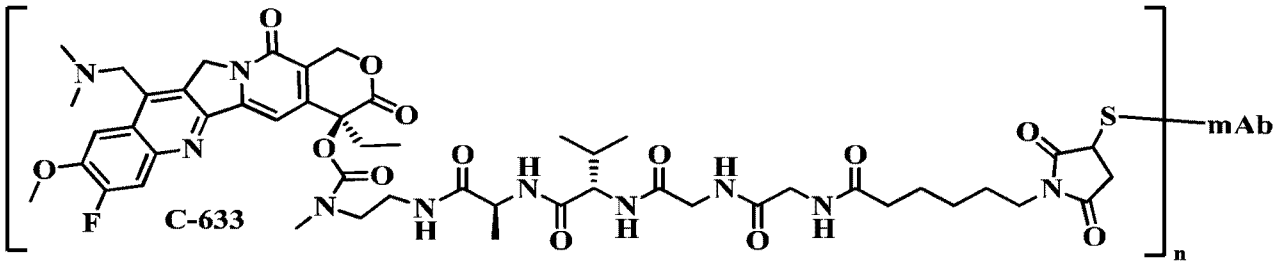

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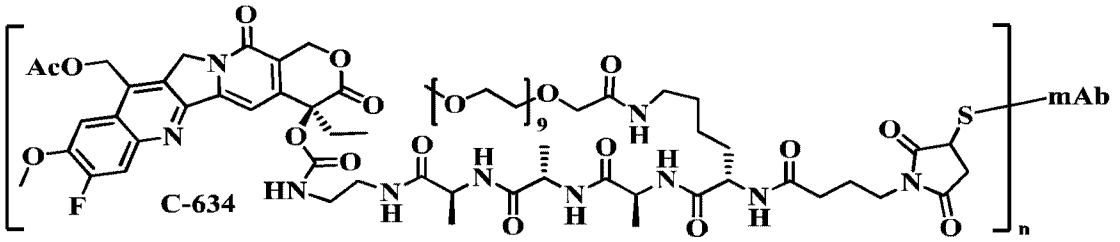

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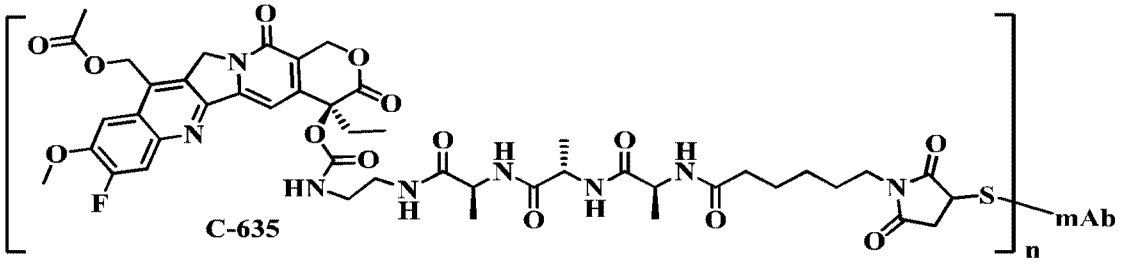

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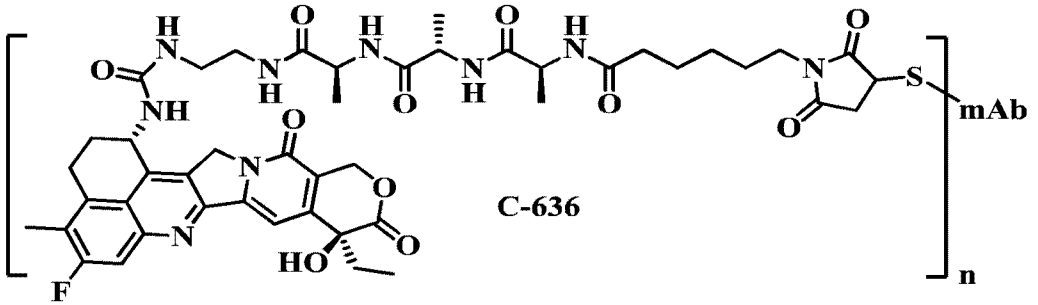

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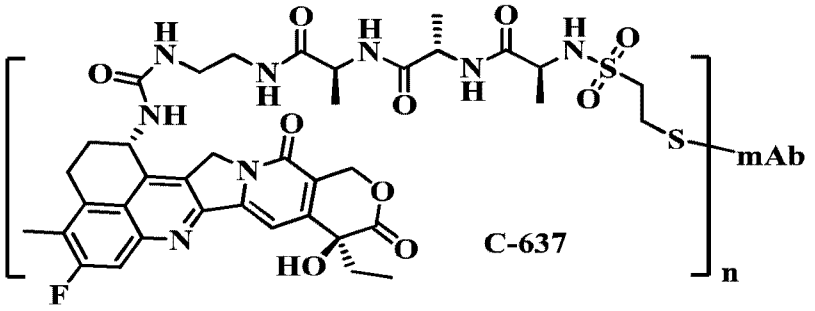
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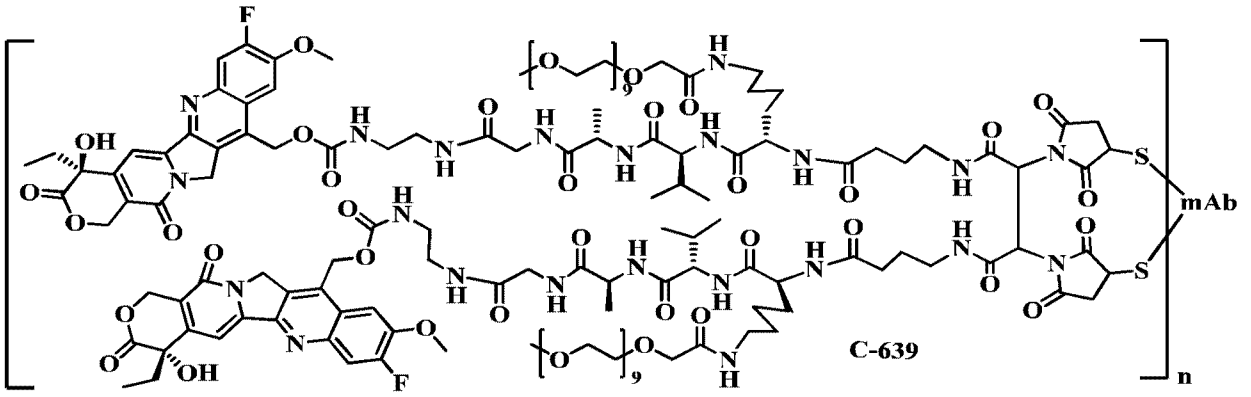
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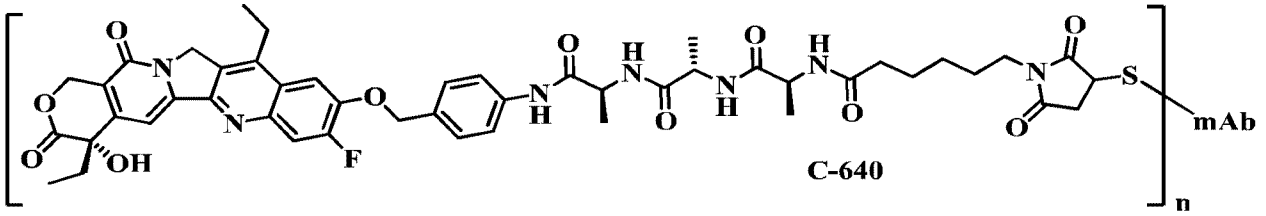
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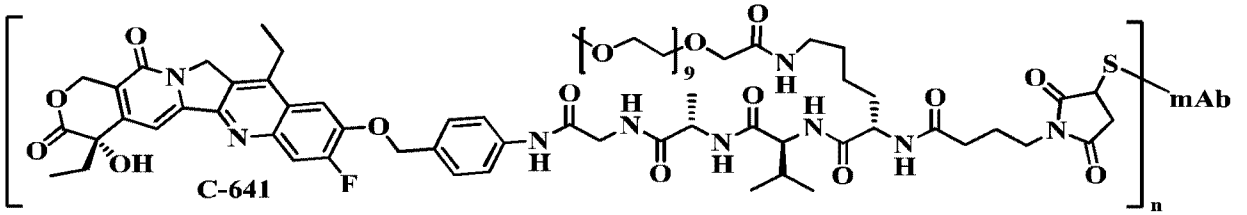
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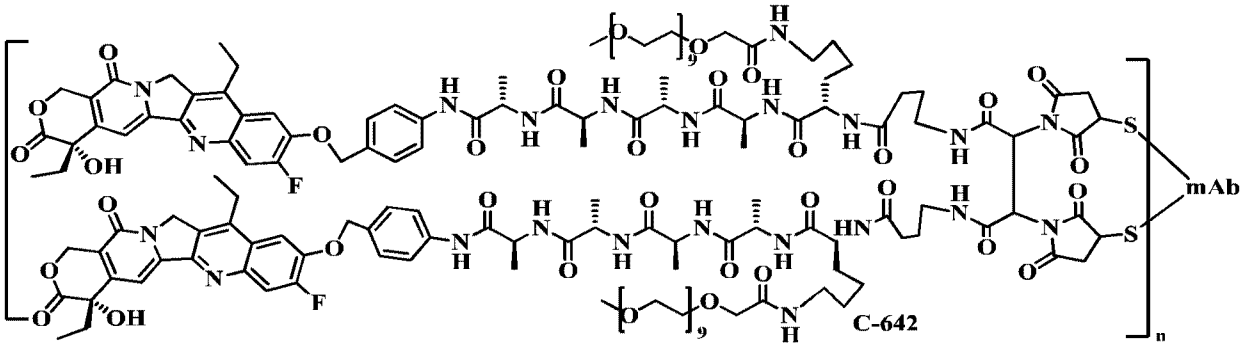
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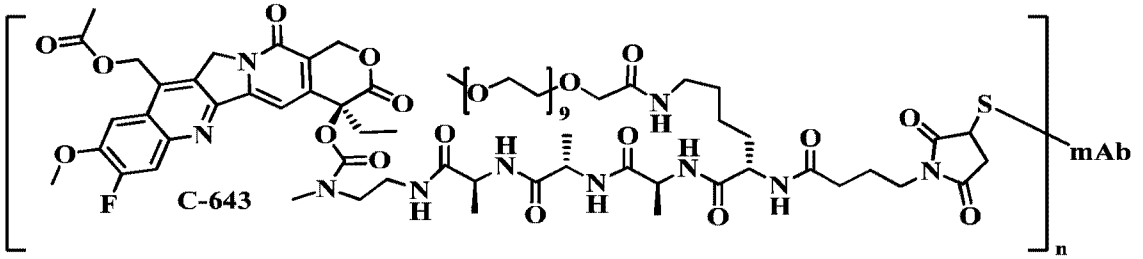
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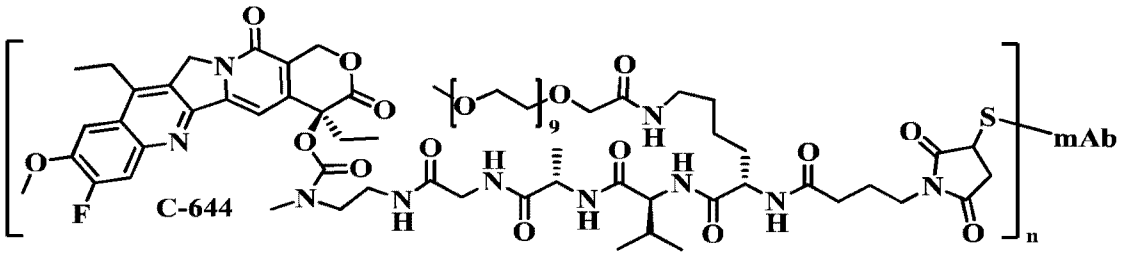
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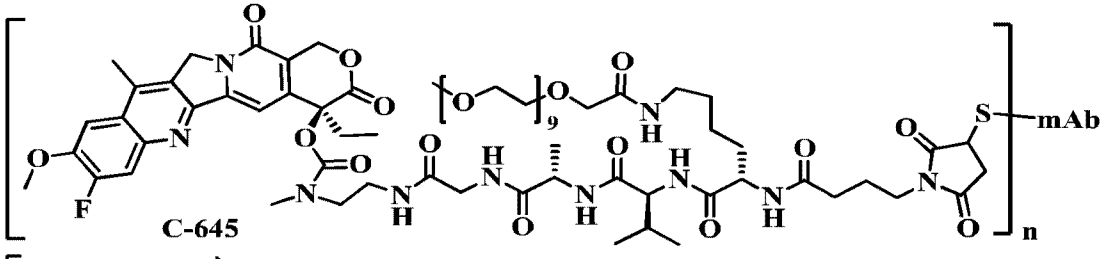
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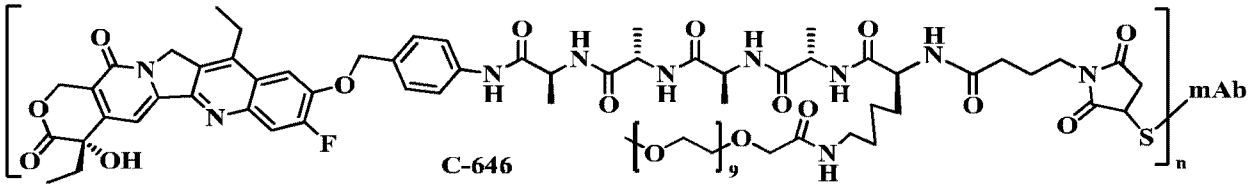
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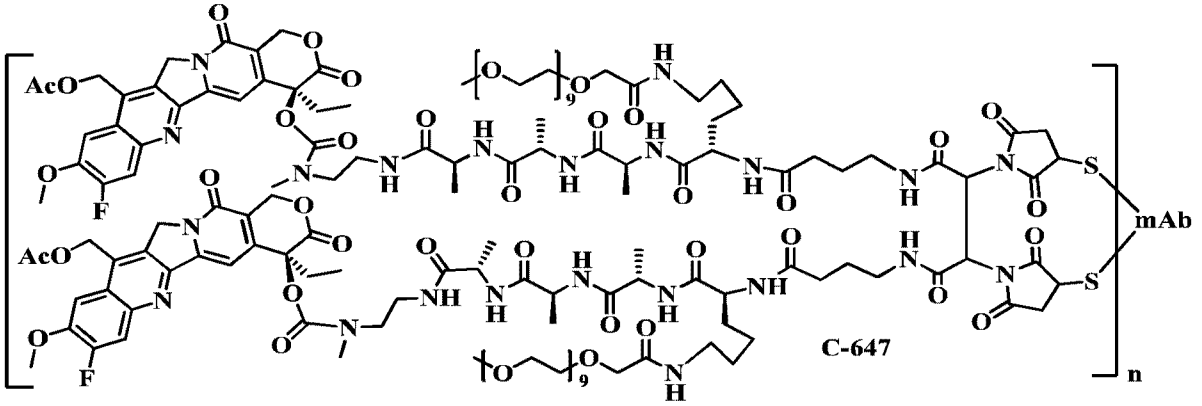
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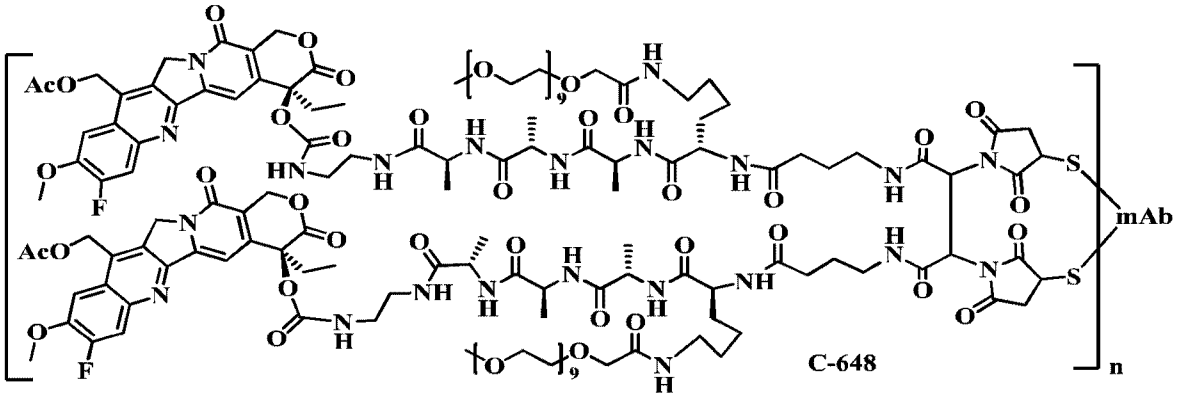
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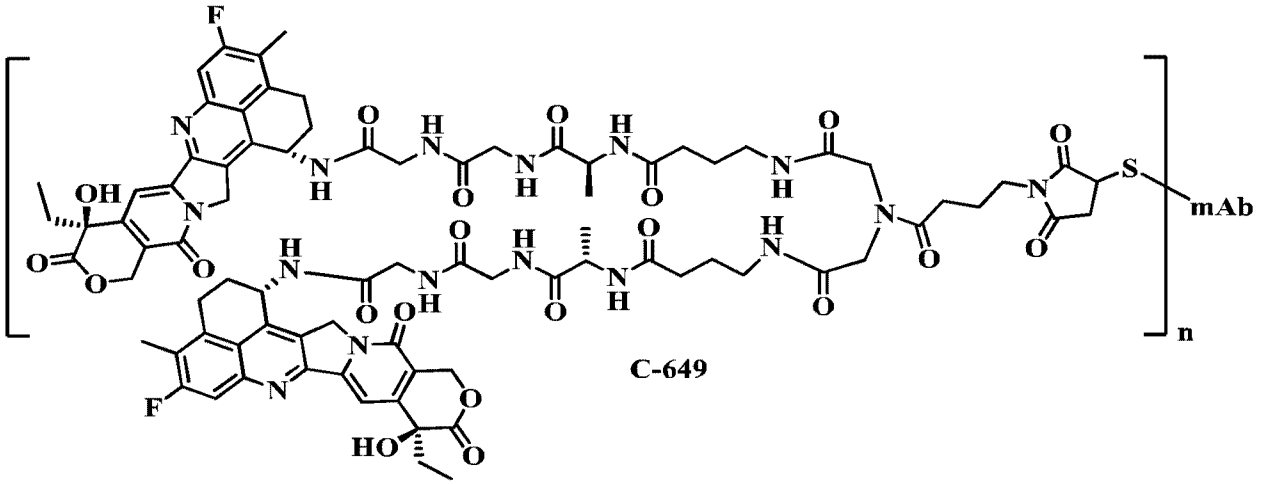

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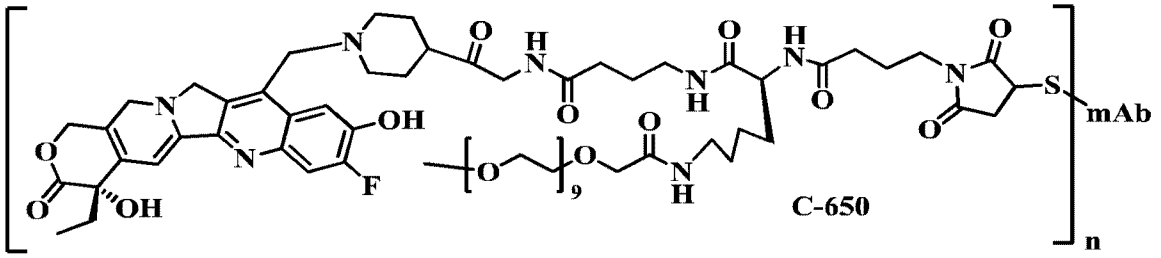

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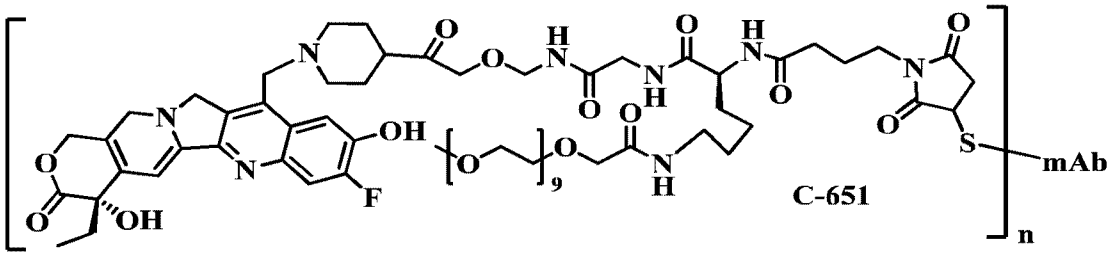

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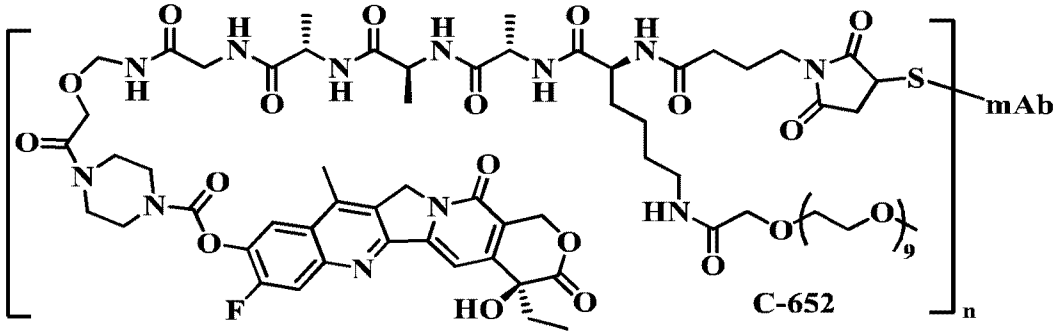

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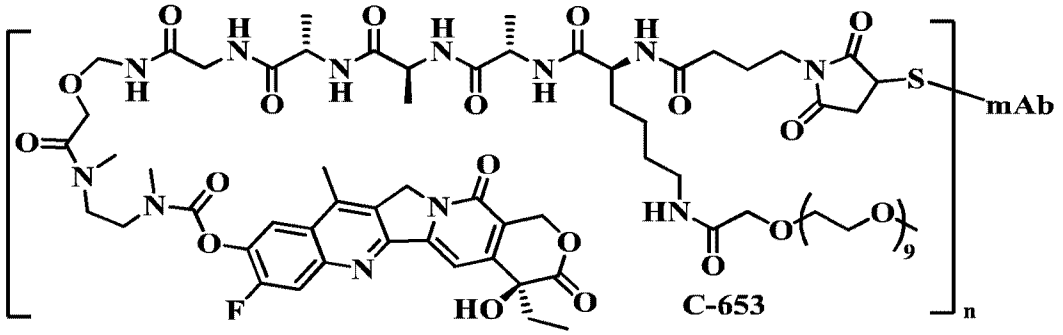

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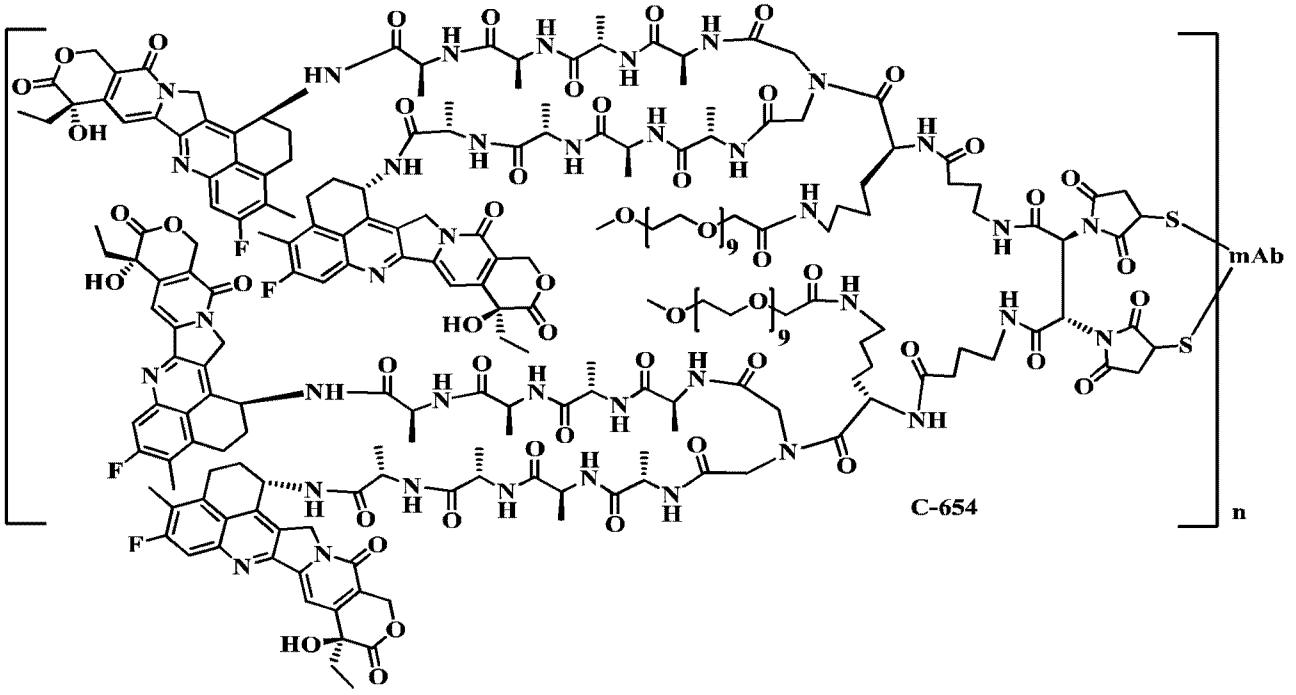

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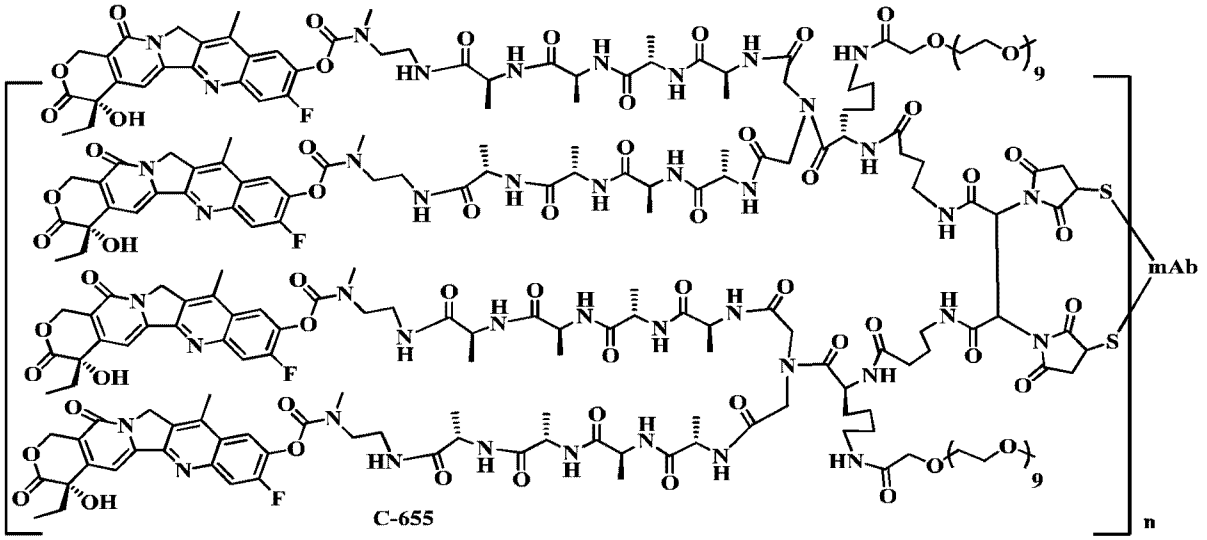

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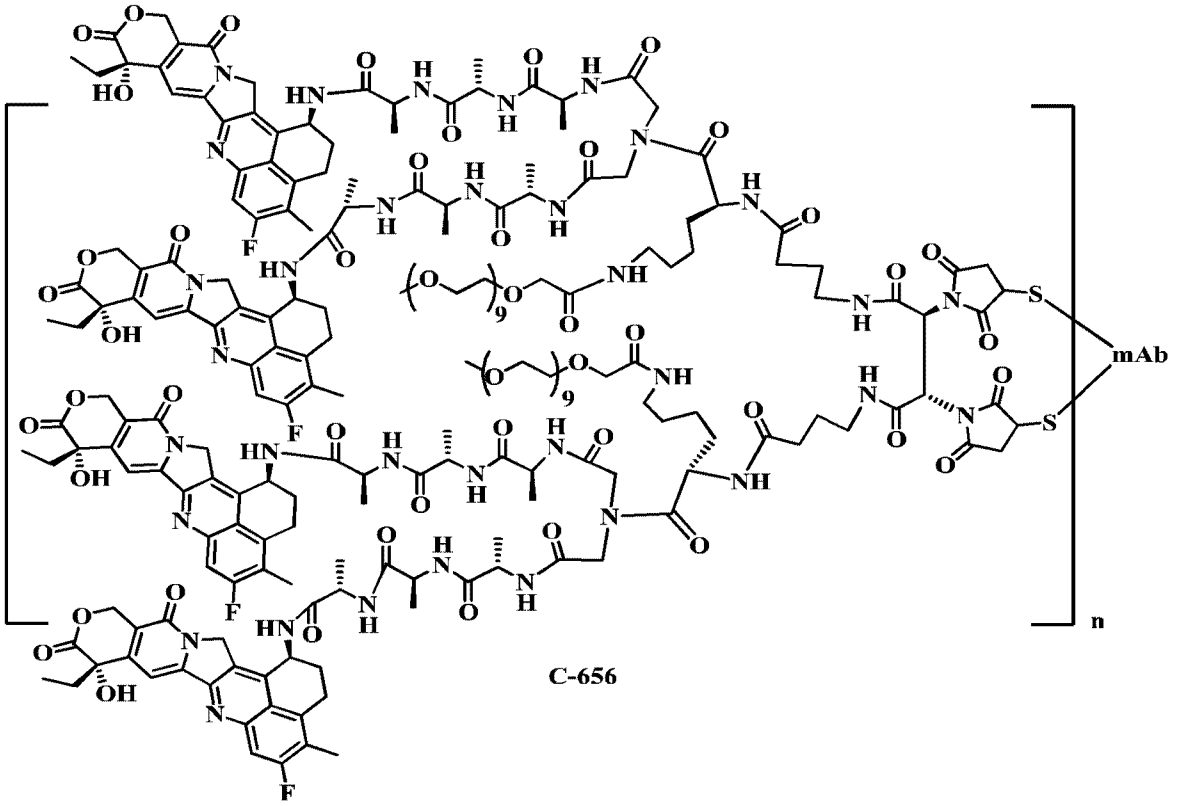

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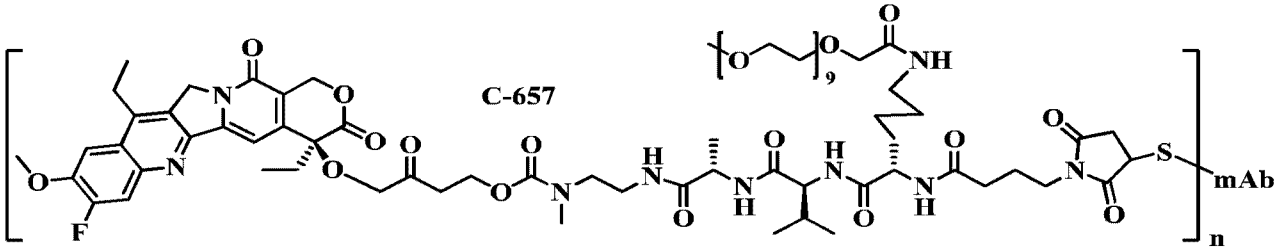

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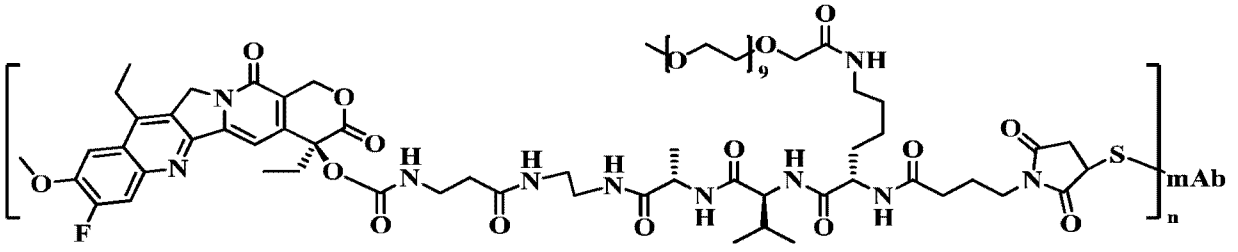
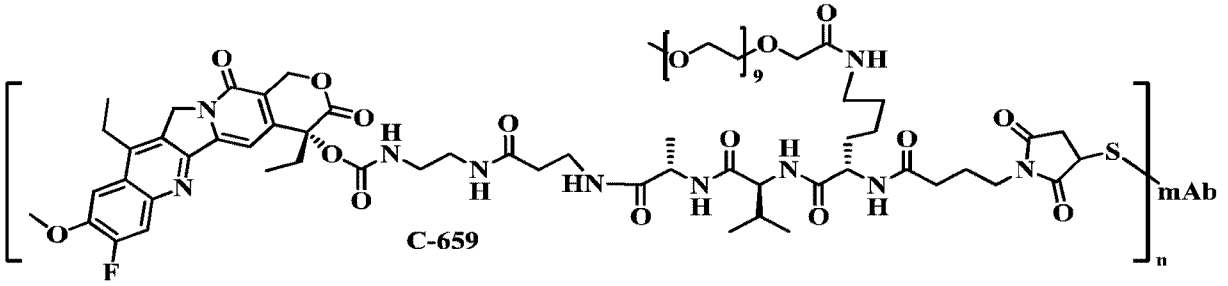


C-658



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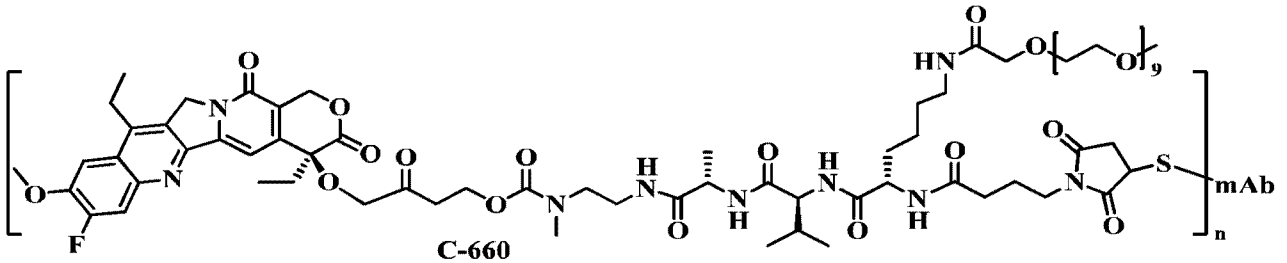

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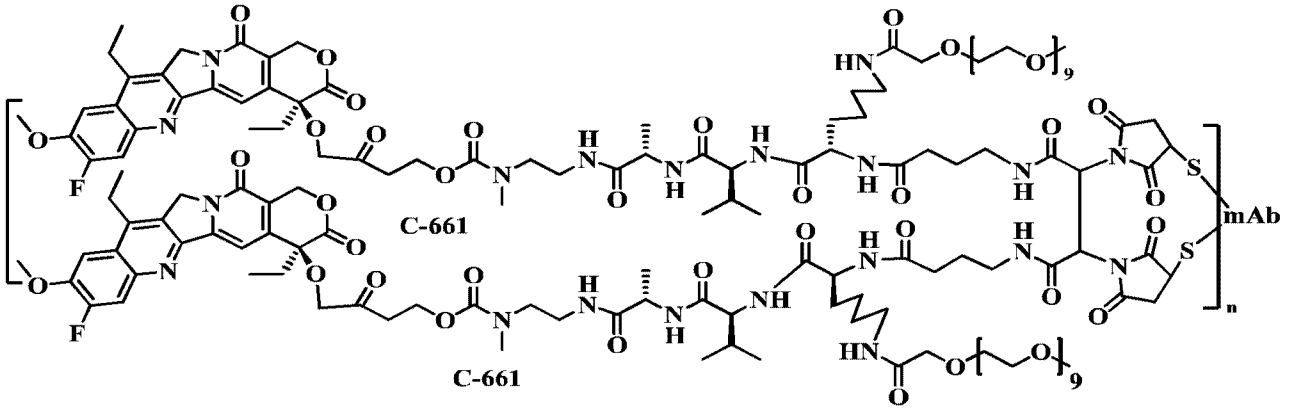

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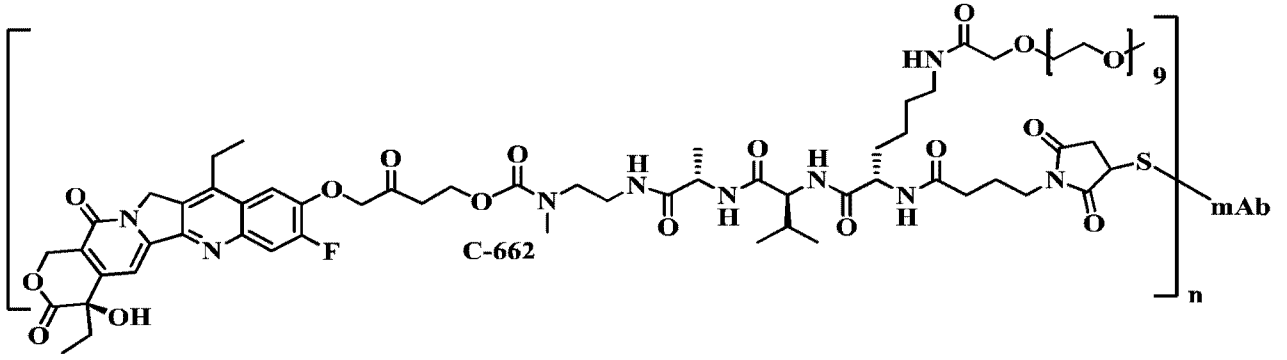

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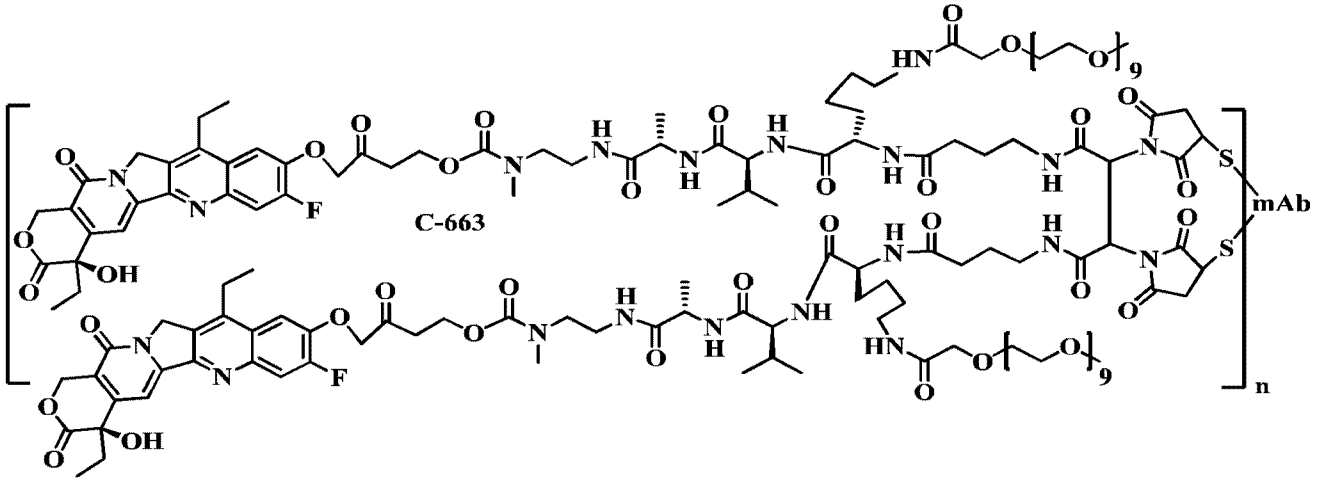

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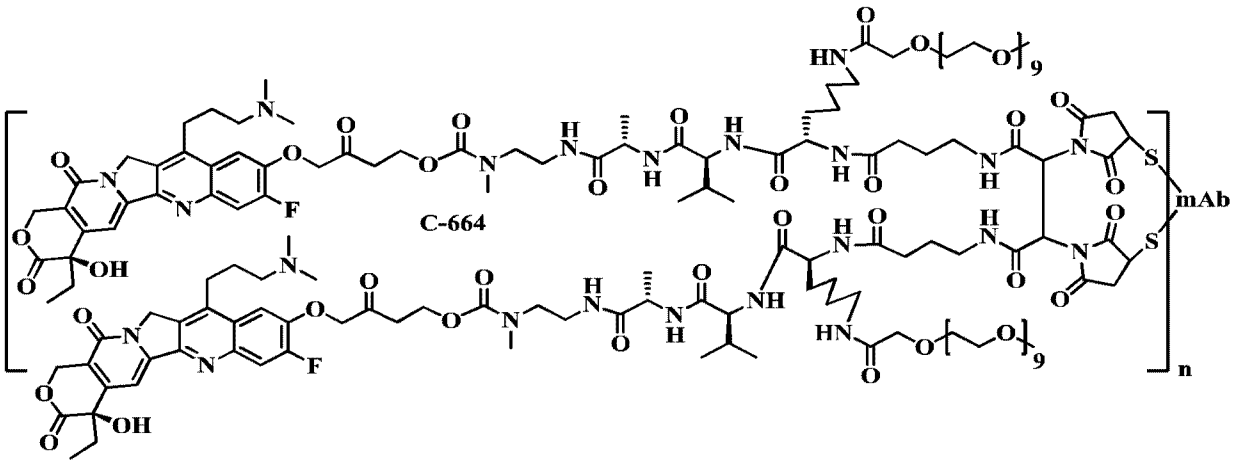
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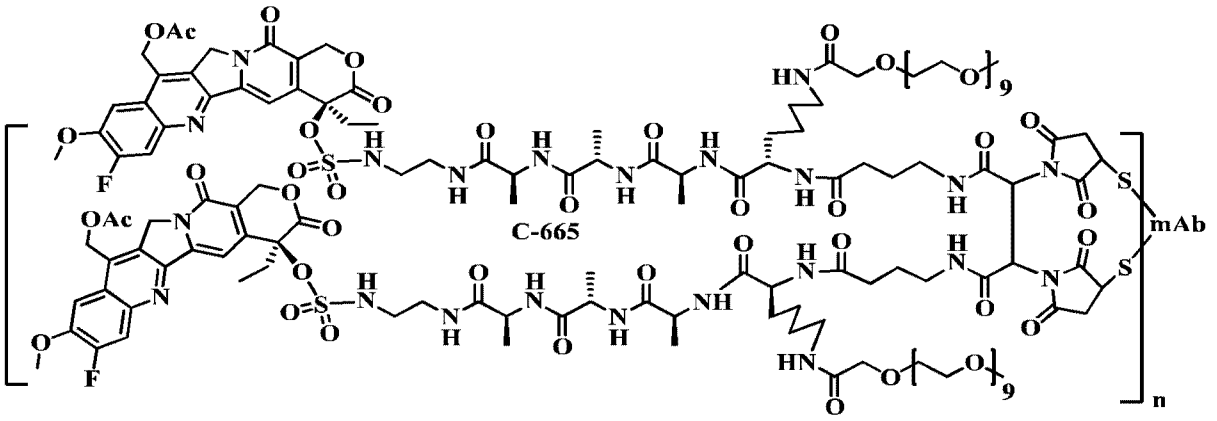
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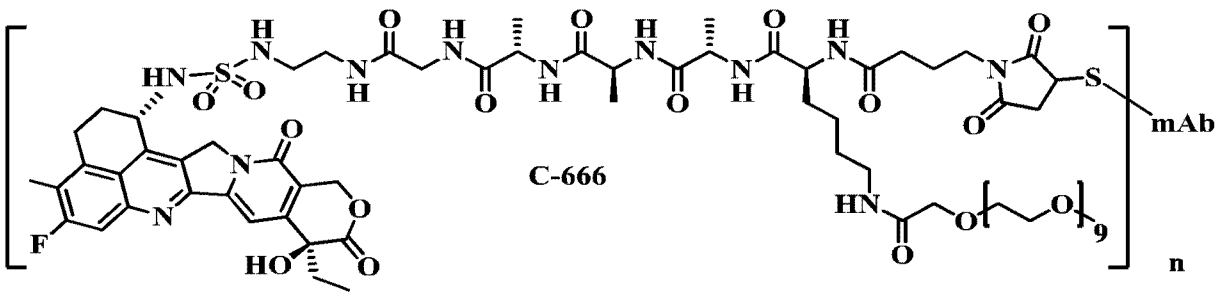
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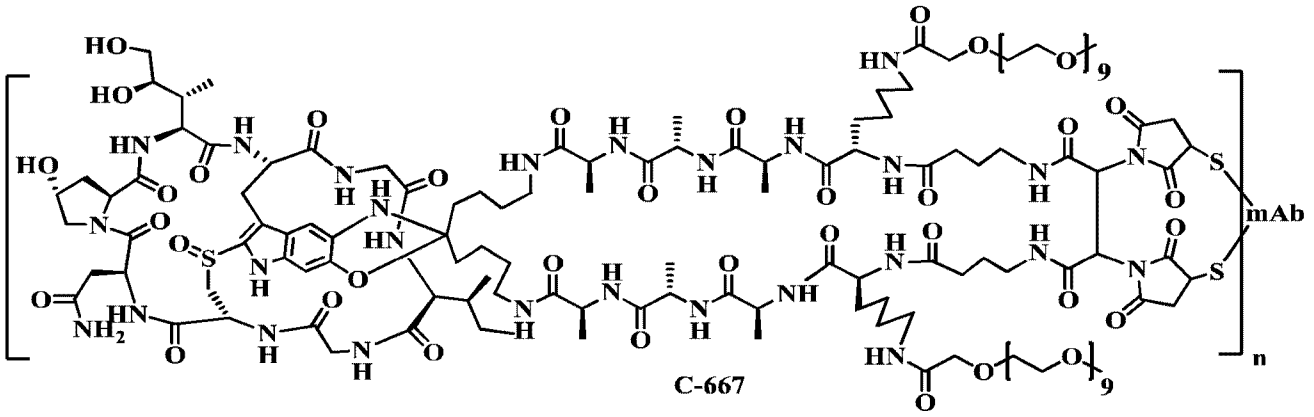
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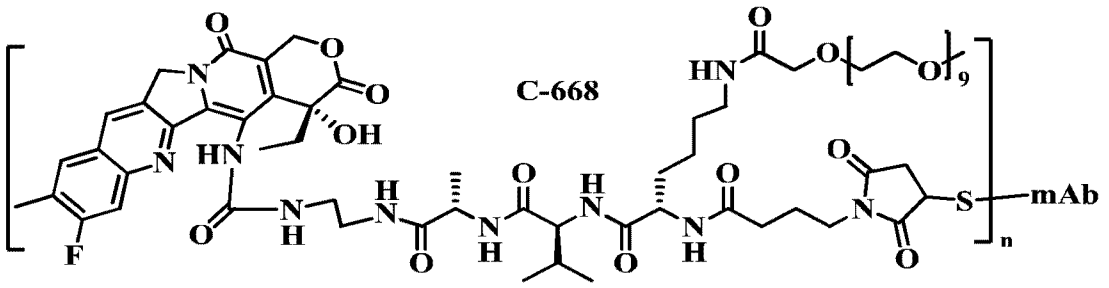

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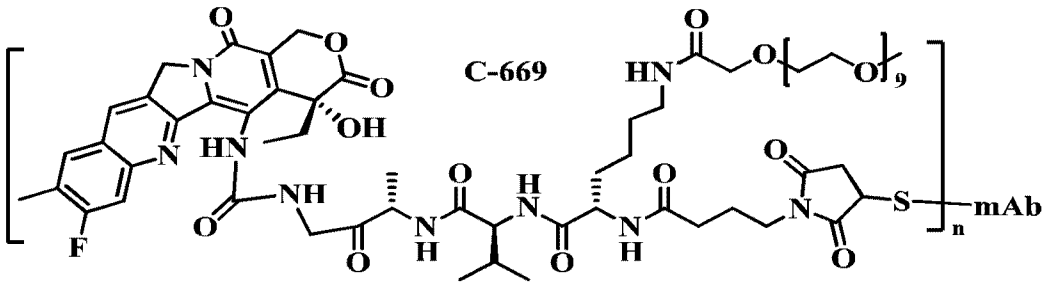

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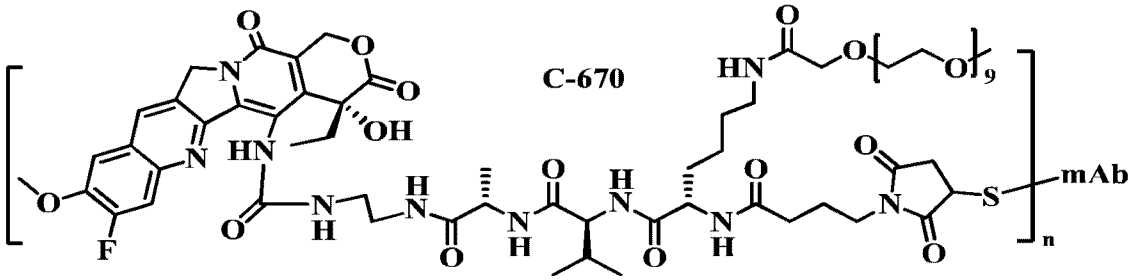

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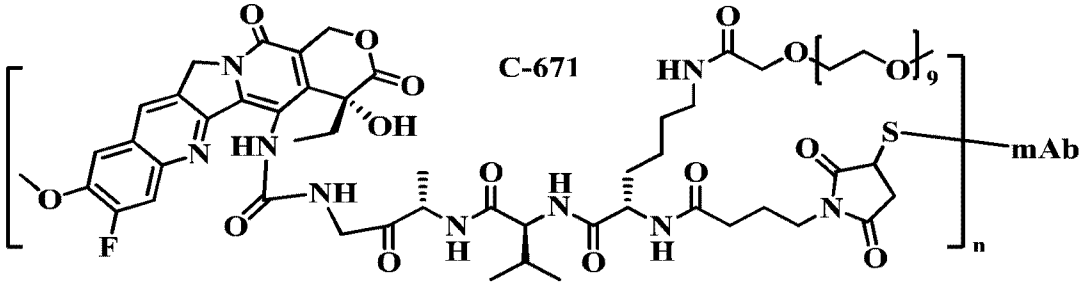

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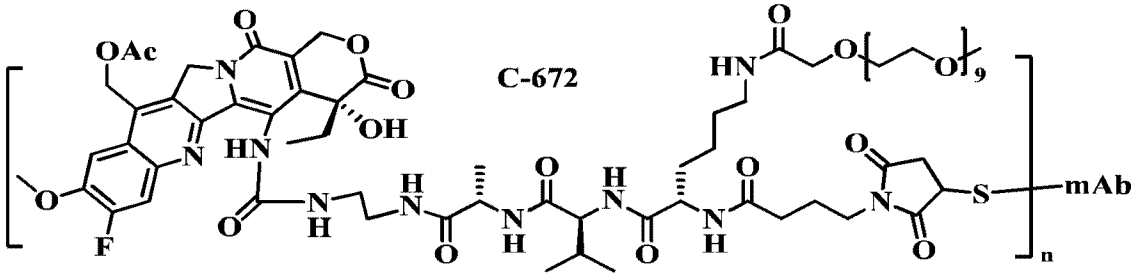

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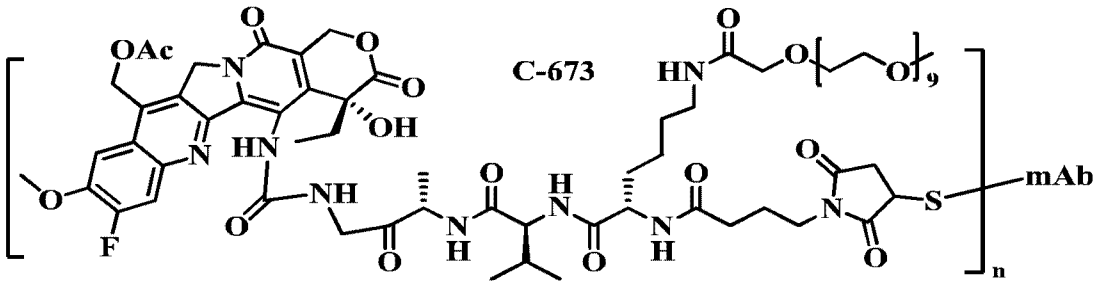
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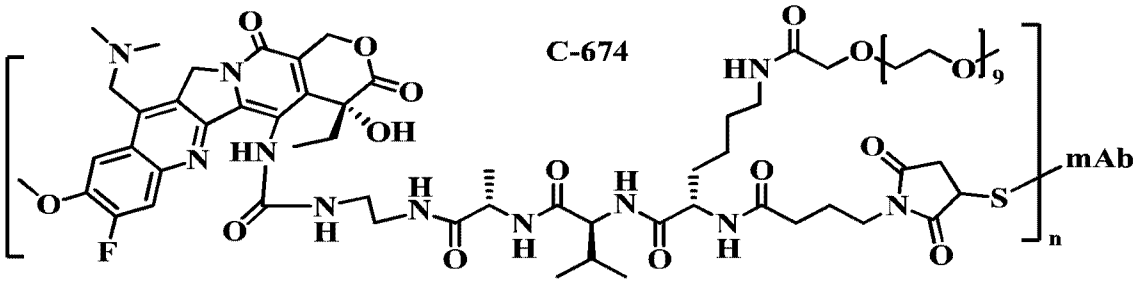
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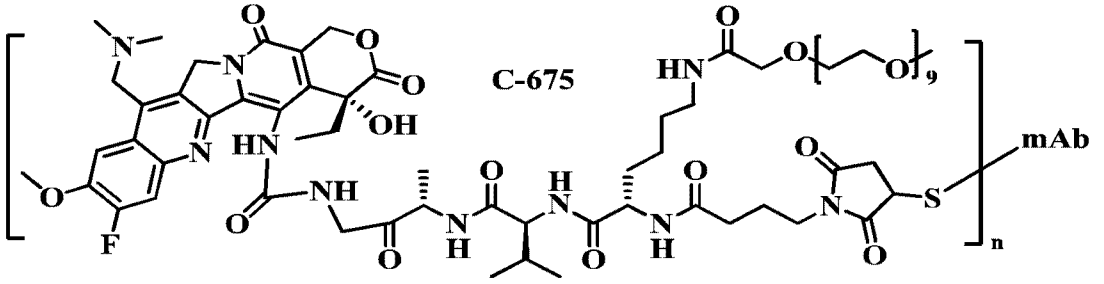
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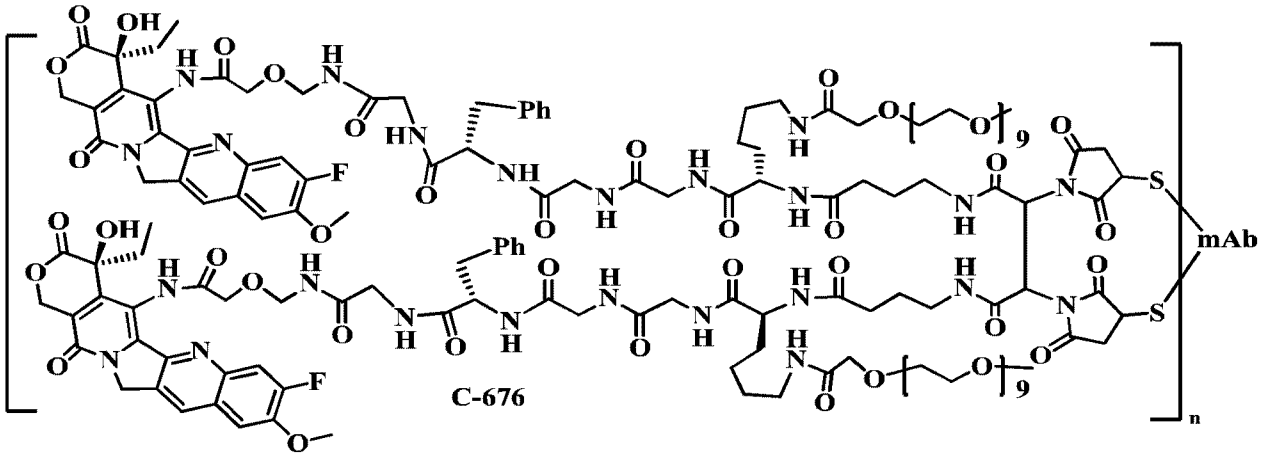
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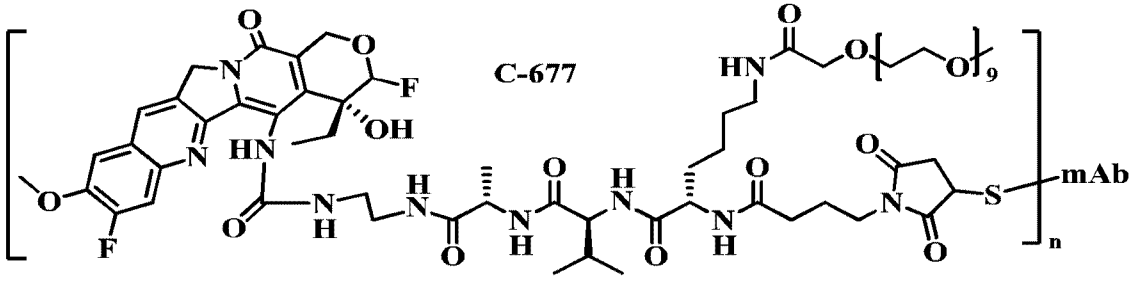
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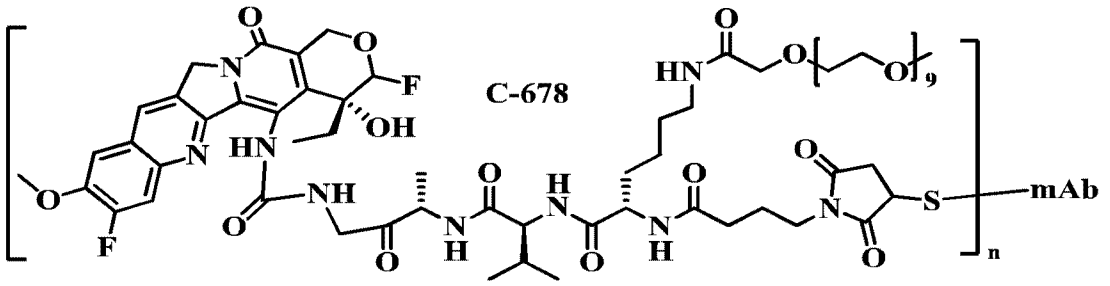
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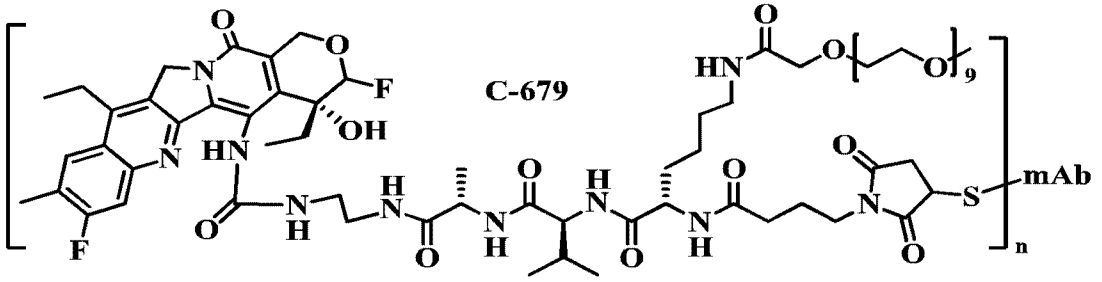
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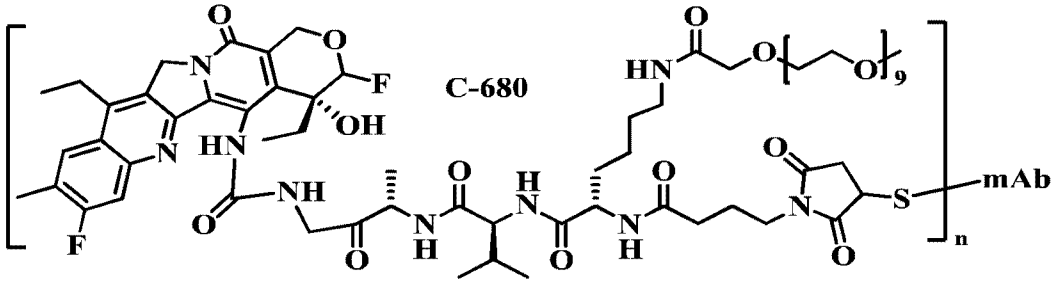
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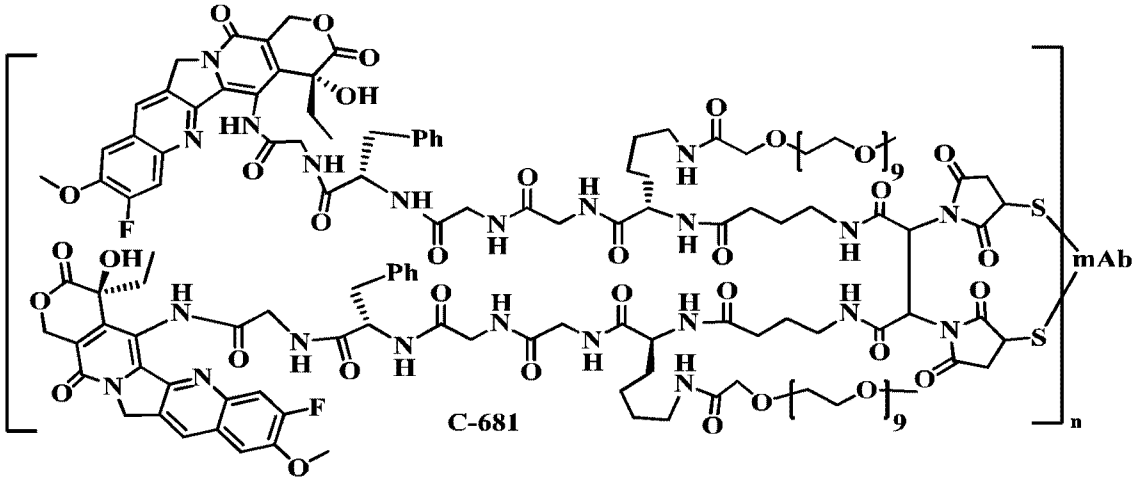
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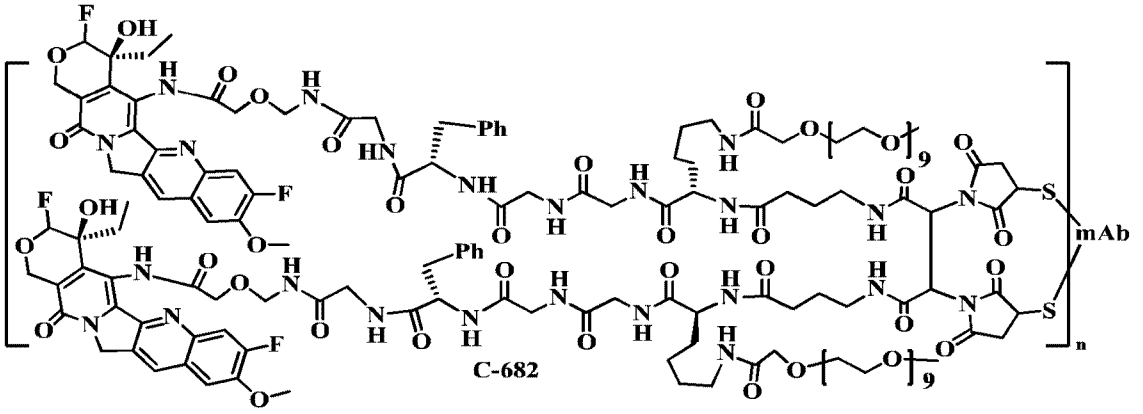
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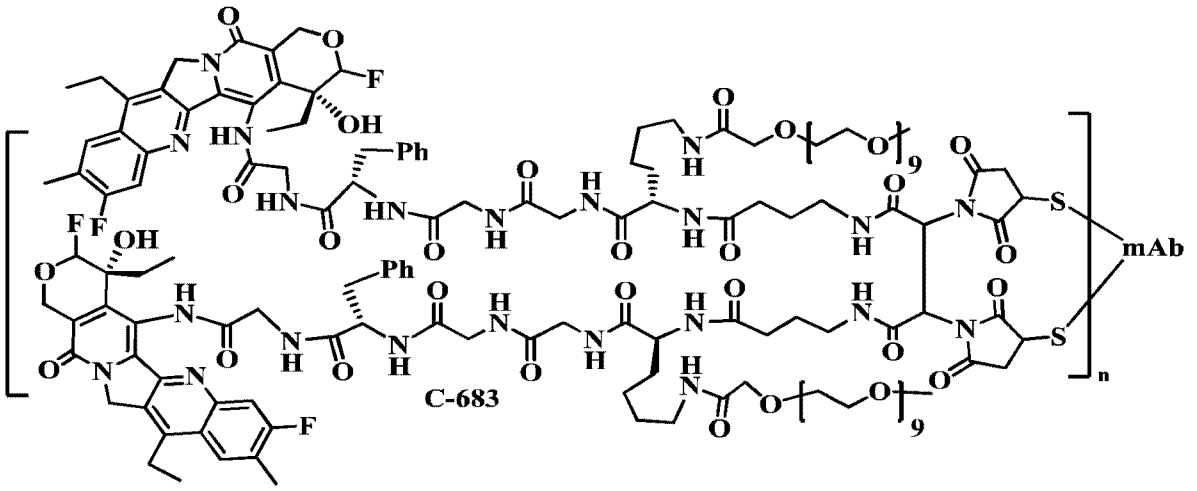
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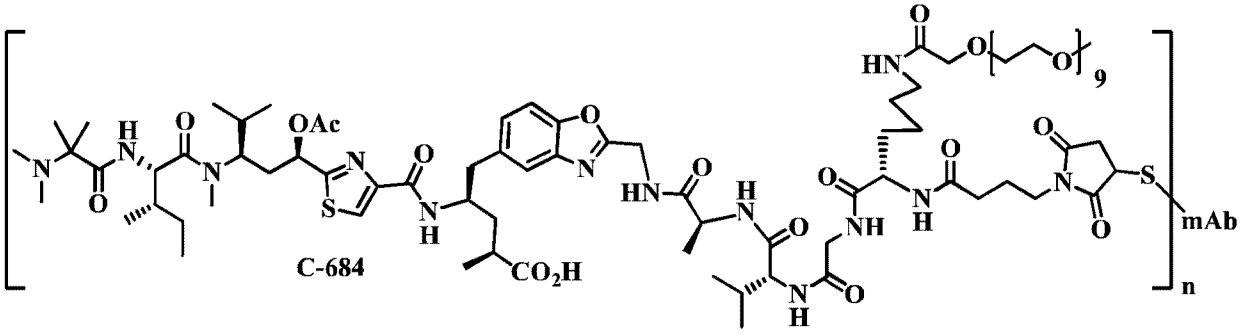
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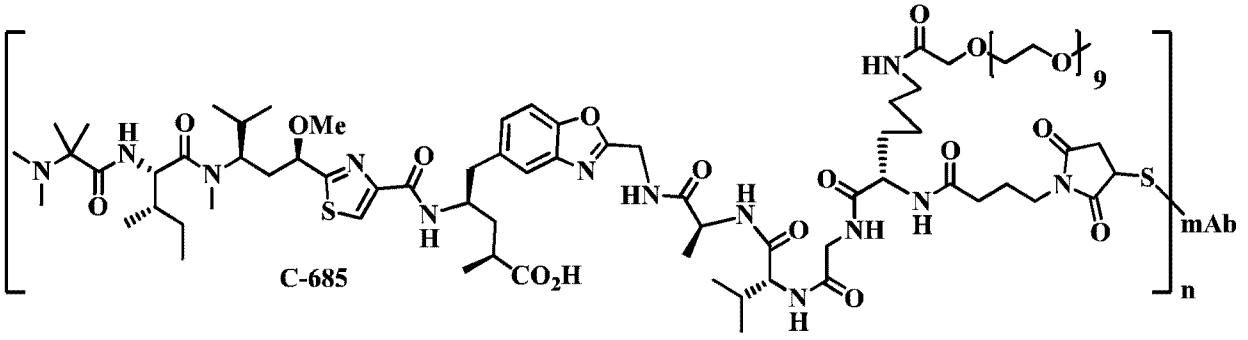
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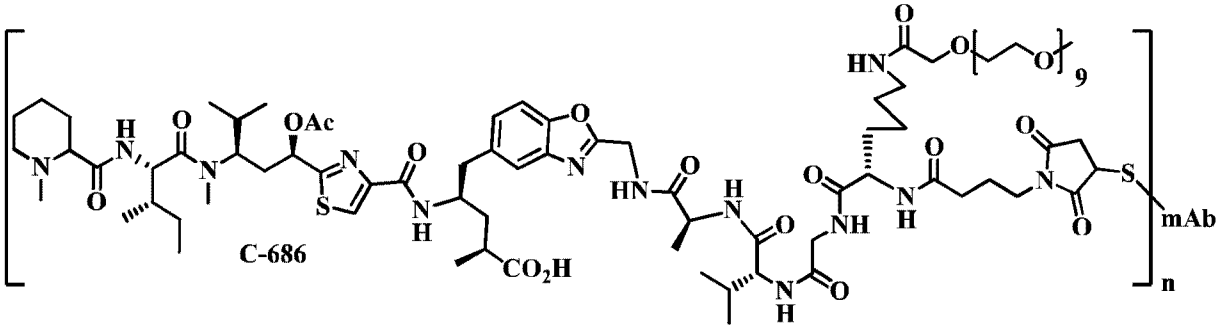
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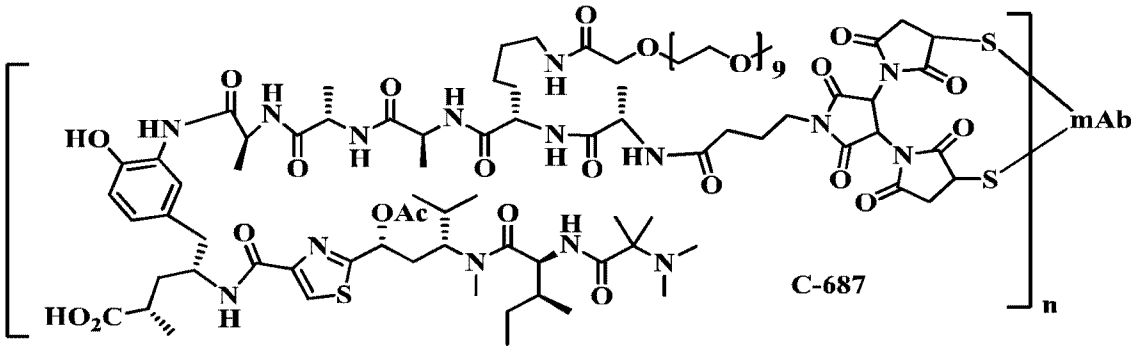
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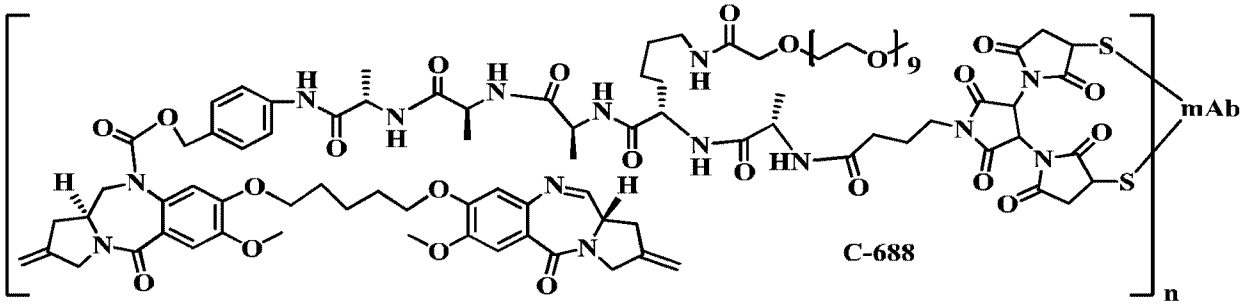
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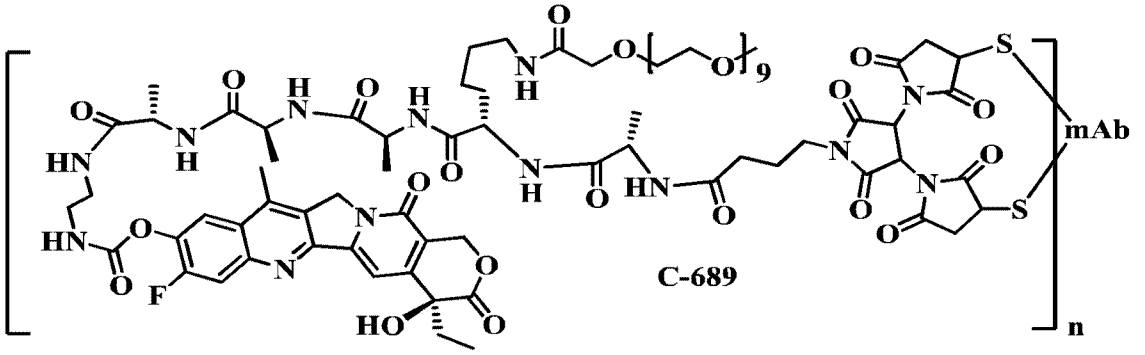
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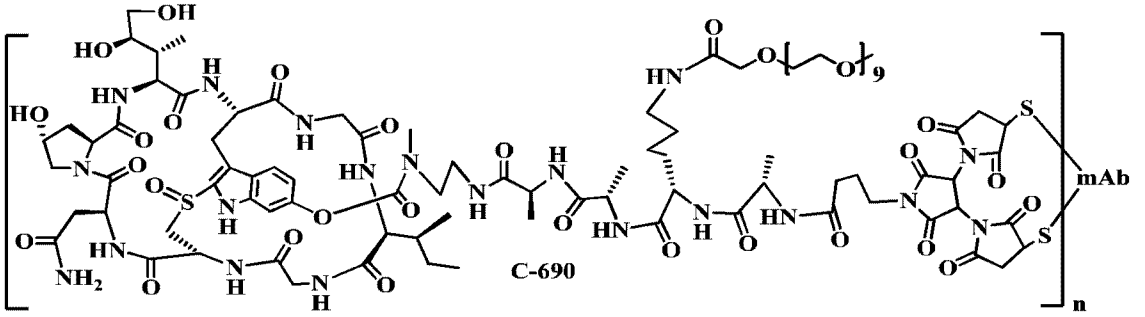
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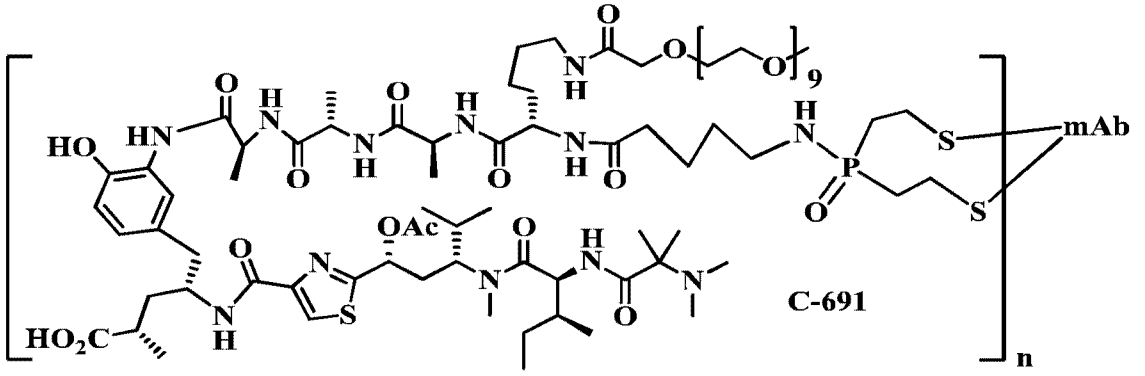
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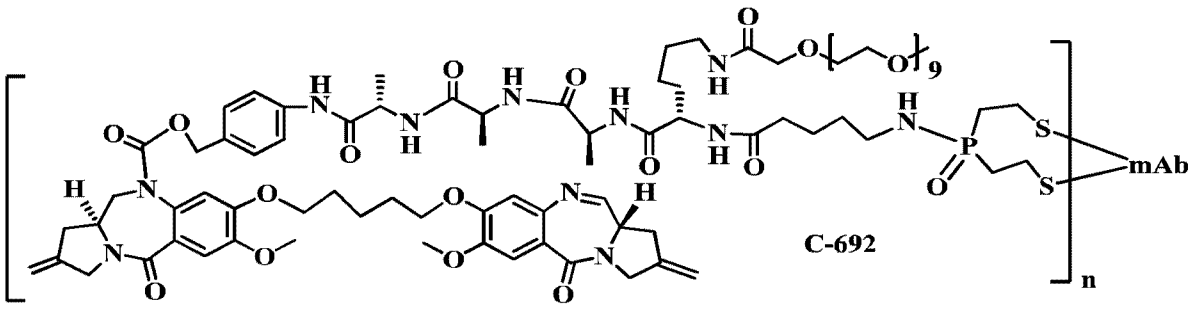

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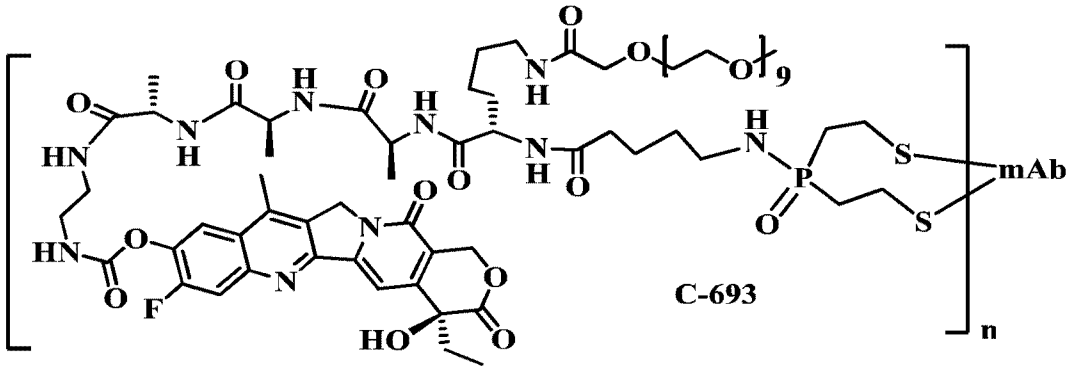

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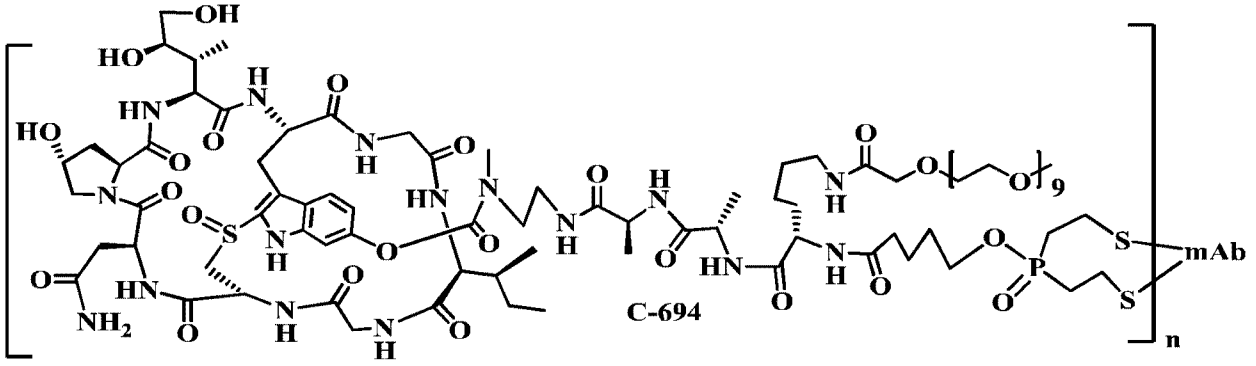

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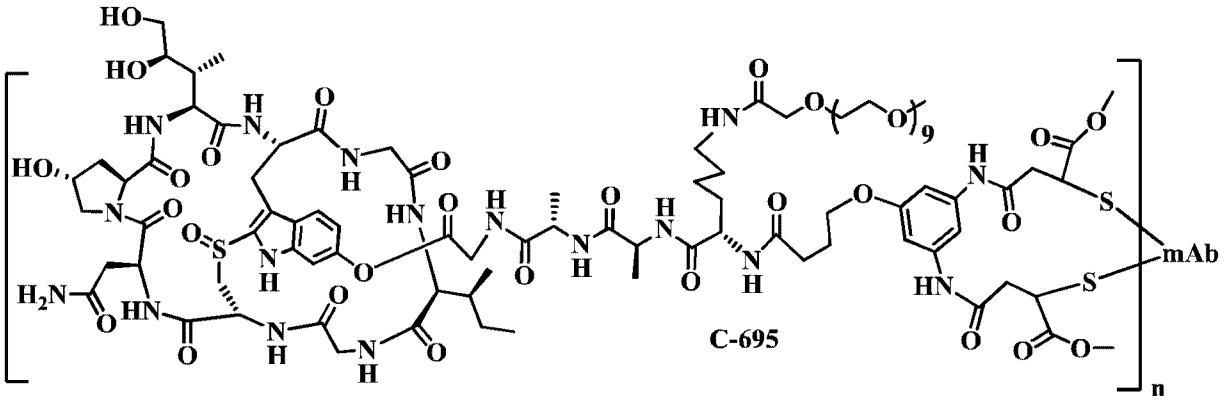

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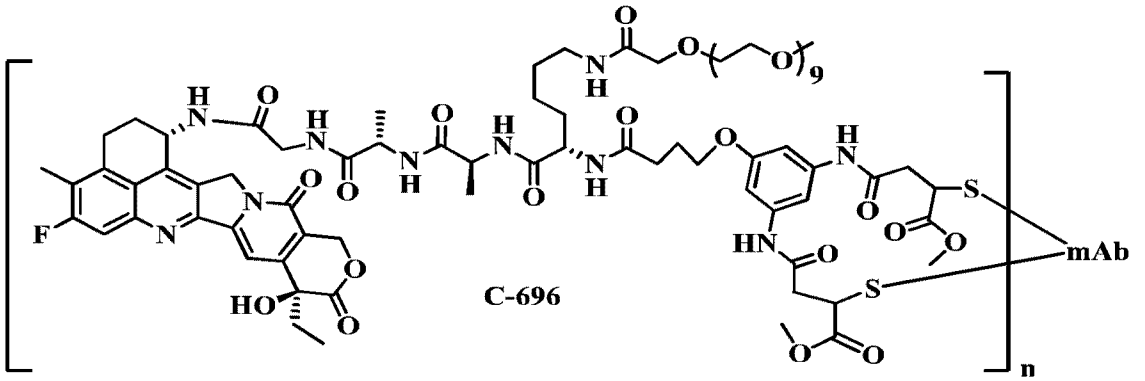
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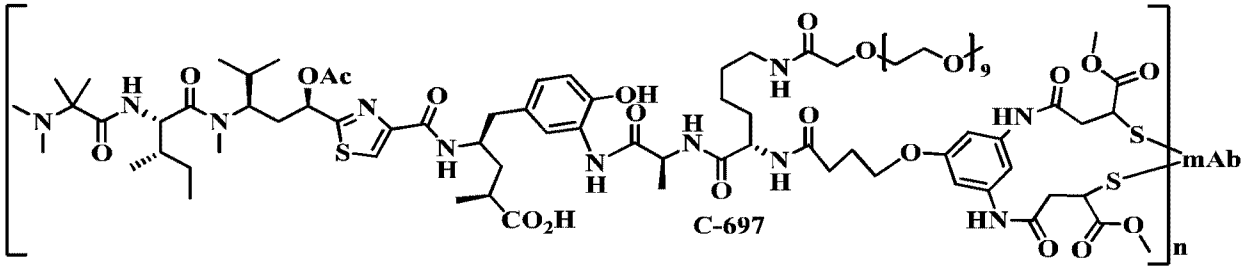
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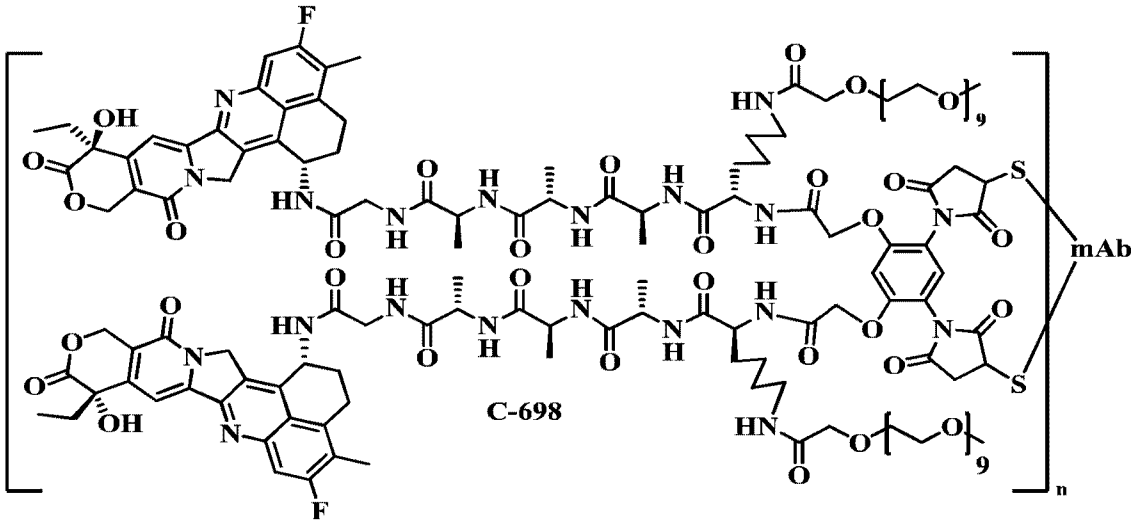
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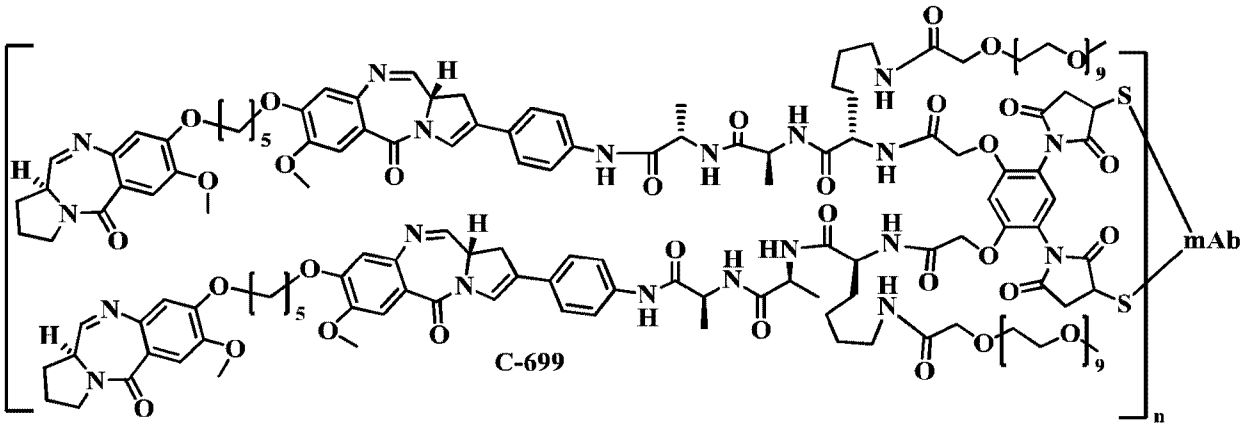
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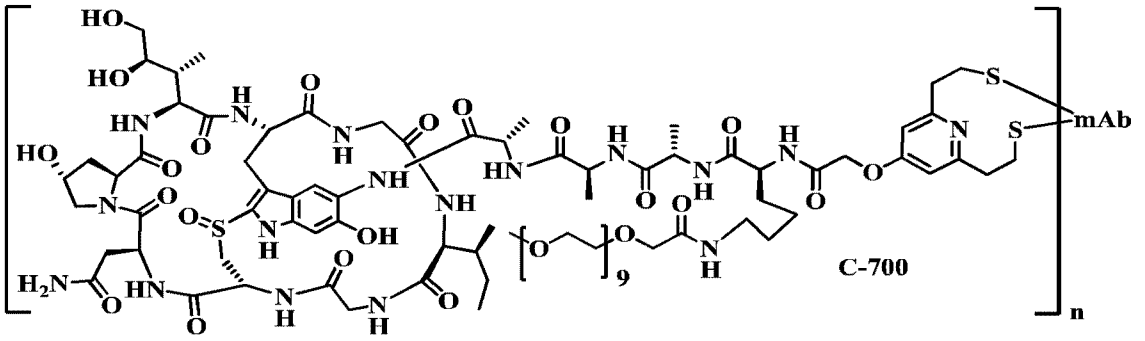
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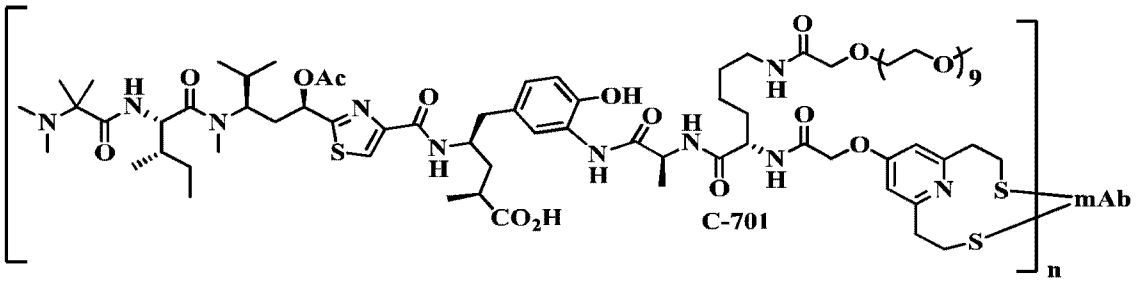
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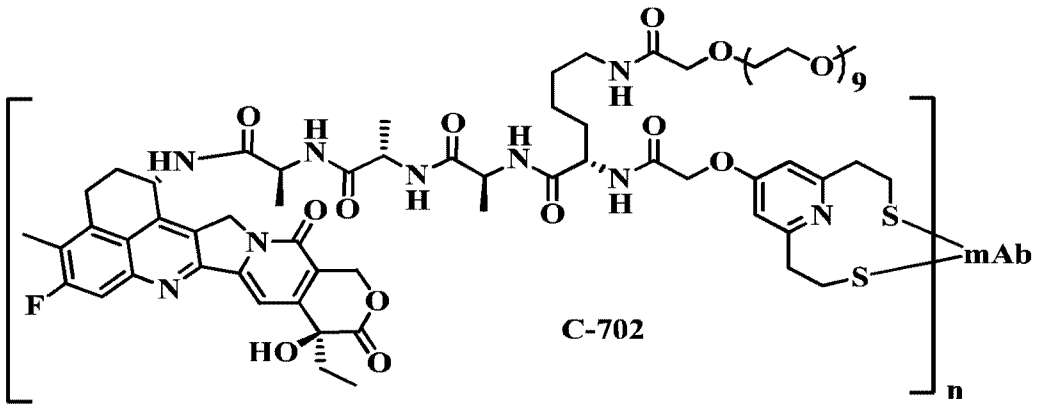
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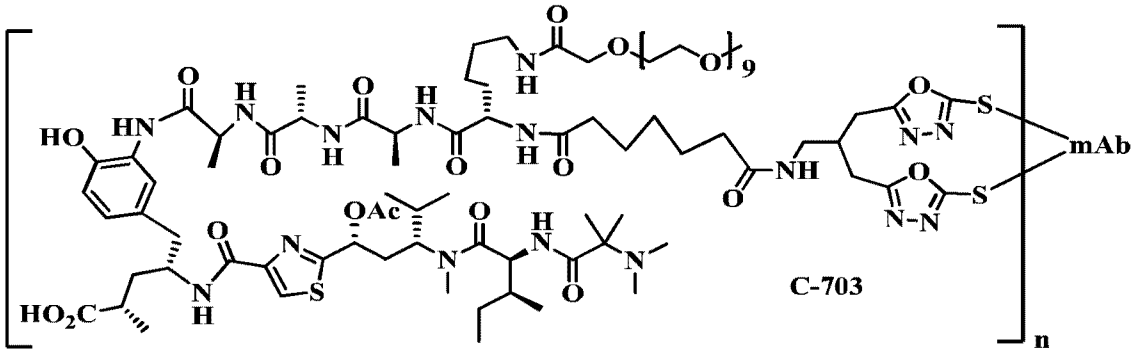
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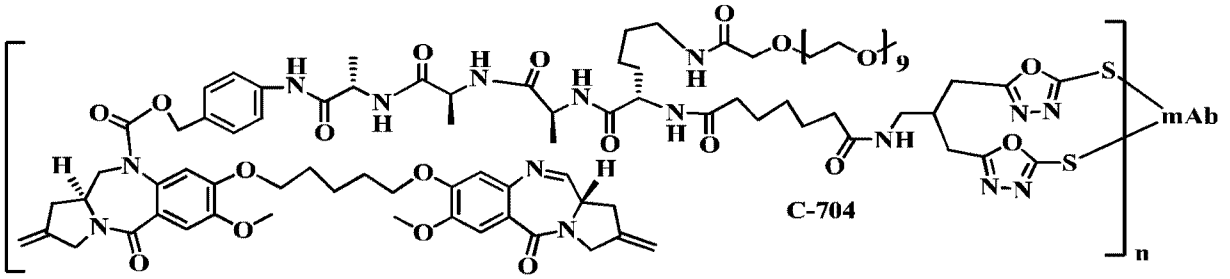
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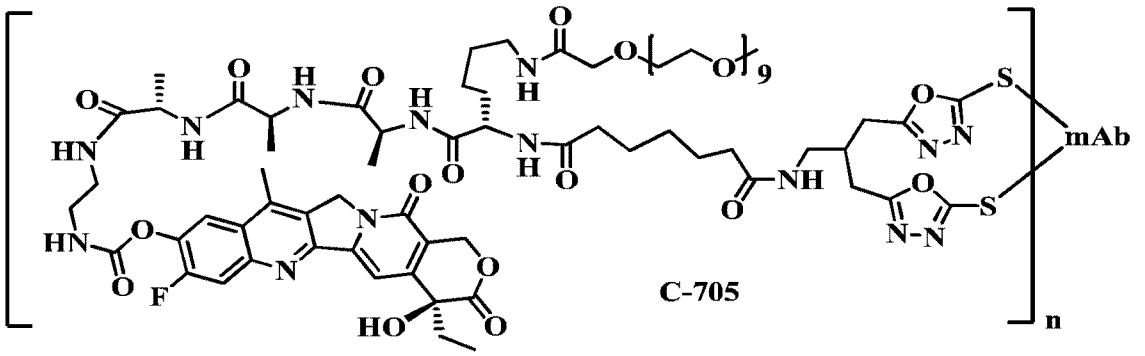

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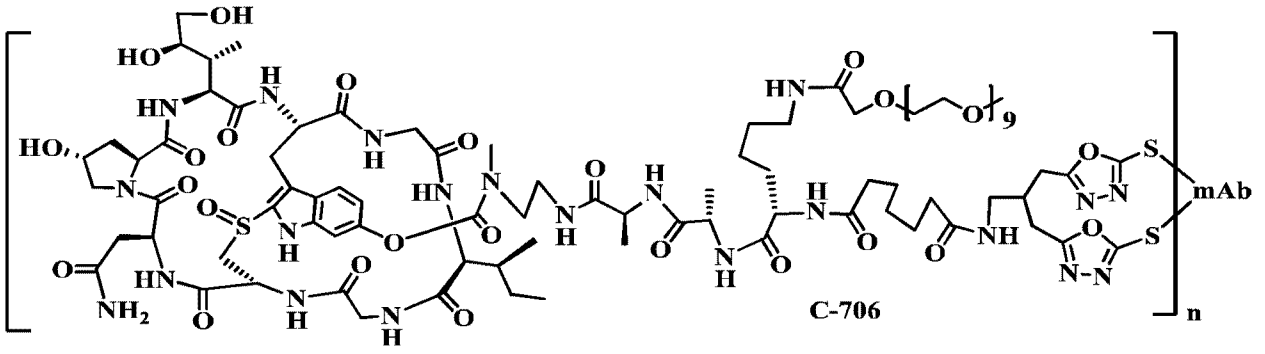
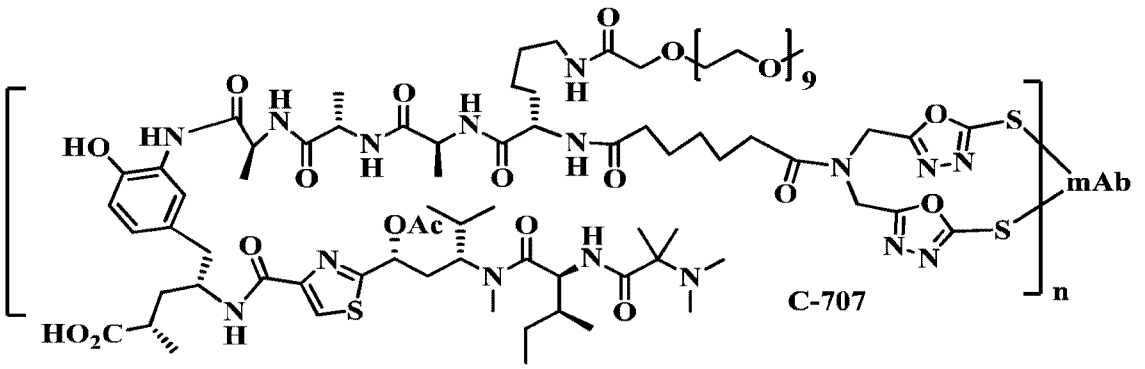
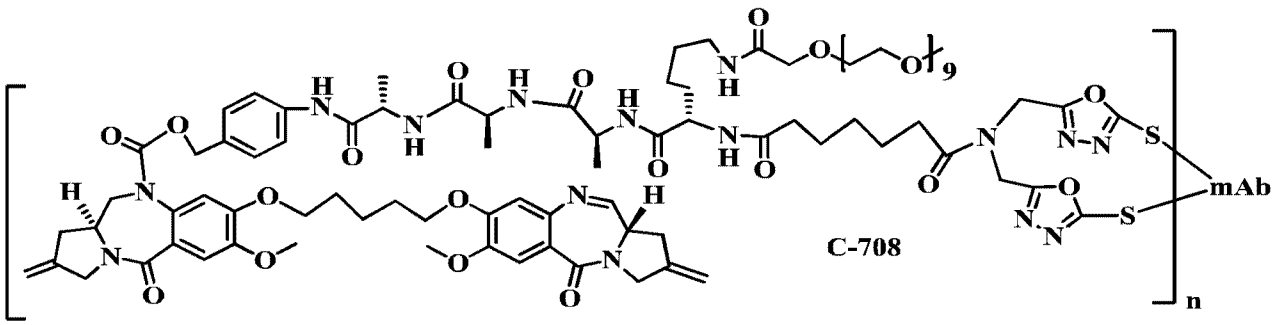


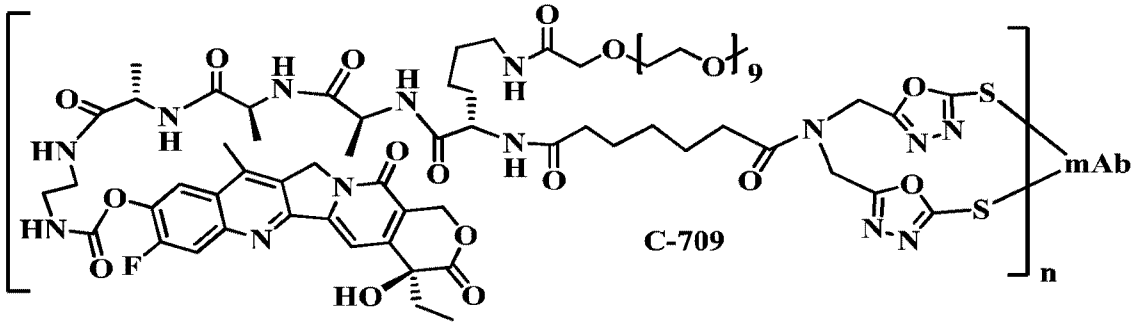
C-706



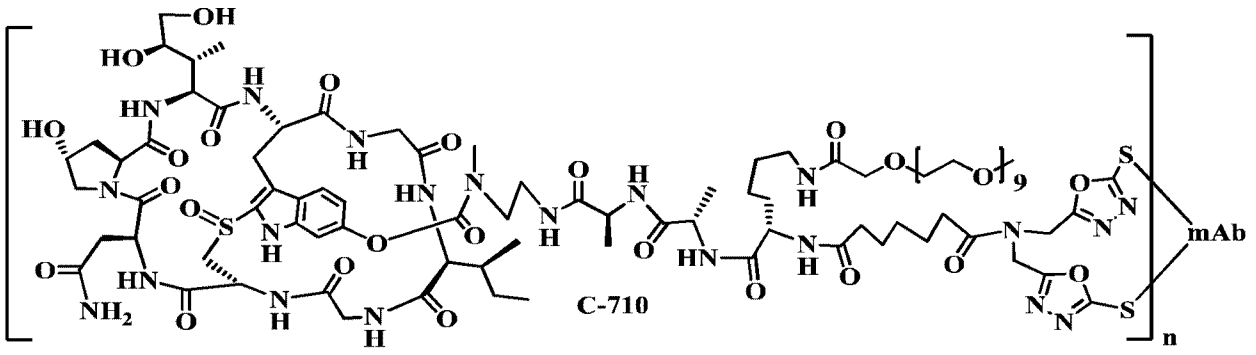
C-707



C-708

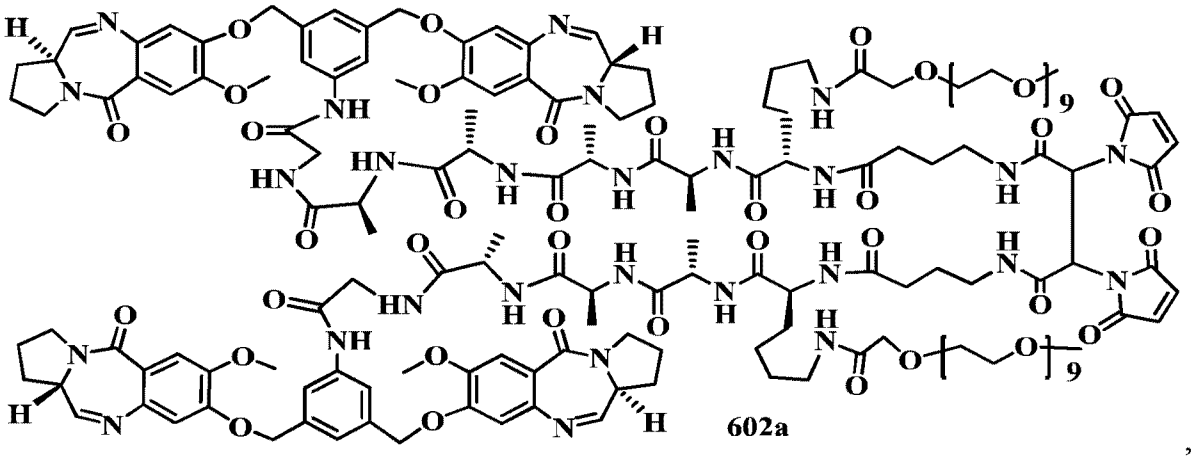


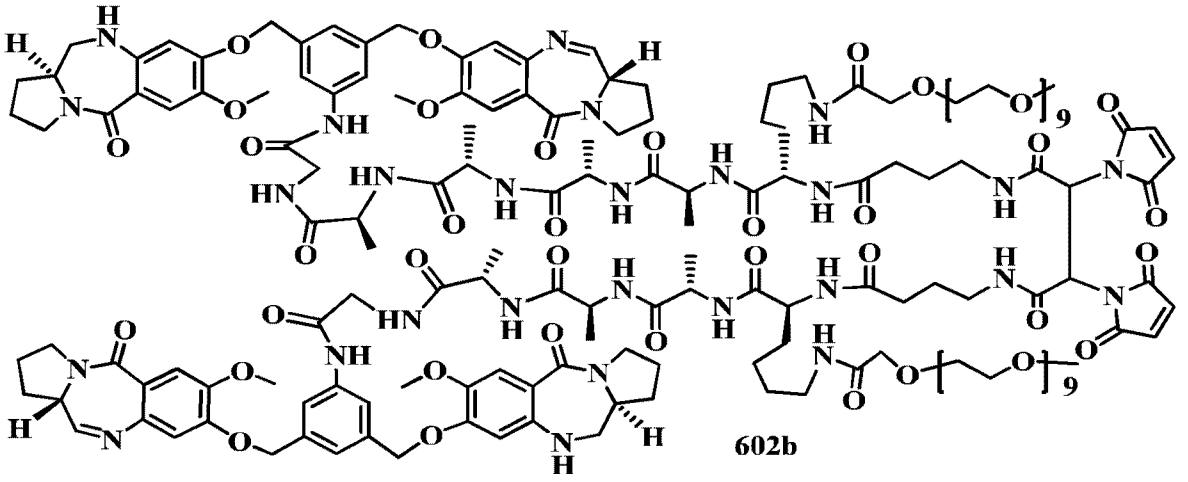
C-709



or one or more isotope of chemical elements, pharmaceutically acceptable salts, hydrates, or hydrated salts; or the polymorphic crystalline structures of these compounds; or the optical isomers, racemates, diastereomers or enantiomers; wherein n is 1 -10.

In other certain embodiments, examples of preferred drug/linker complex of formula (I), (II), (III) and (IV) which can be used under the process of the invention to achieve over 75% of the total drugs linked to the sites of cysteines between heavy-light chains (Fabs) of an antibody are illustrated in the sections of Figures and Examples as compounds of 25, 30, 36, 45, 51, 58a, 68a, 68b, 68c, 72a, 72b, 73, 83, 88, 91, 96, 102, 115, 120, 121, 126, 130, 137, 140, 152, 157, 168, 178, 181a, 181b, 181c, 181d, 190, 192, 195, 202, 209, 215, 221, 221b, 227, 233, 241, 255, 267, 277, 283, 284, 290, 300, 306, 309, 310, 312, 319, 322, 326, 328, 330, 332, 334, 335, 336, 337, 338, 361, 362, 372, 373, 374, 375, 384, 385, 390, 396, 399, 400, 402, 406, 409, 416, 417, 427, 432, 437, 441, 450, 455, 462, 464, 470, 478, 481, 484, 487, 488, 494, 498, 499, 500, 501, 504, 508, 511, 514, 518, 519, 521, 527, 531, 532, 534, 537, 542, 543, 544, 546, 550, 553, 560, 561, 562, 565, 570, 573, 577, 581, 582, 587, 591, 595, 599. The other examples of preferred drug/linker complex of formula (I), (II), (III) and (IV) are shown below:





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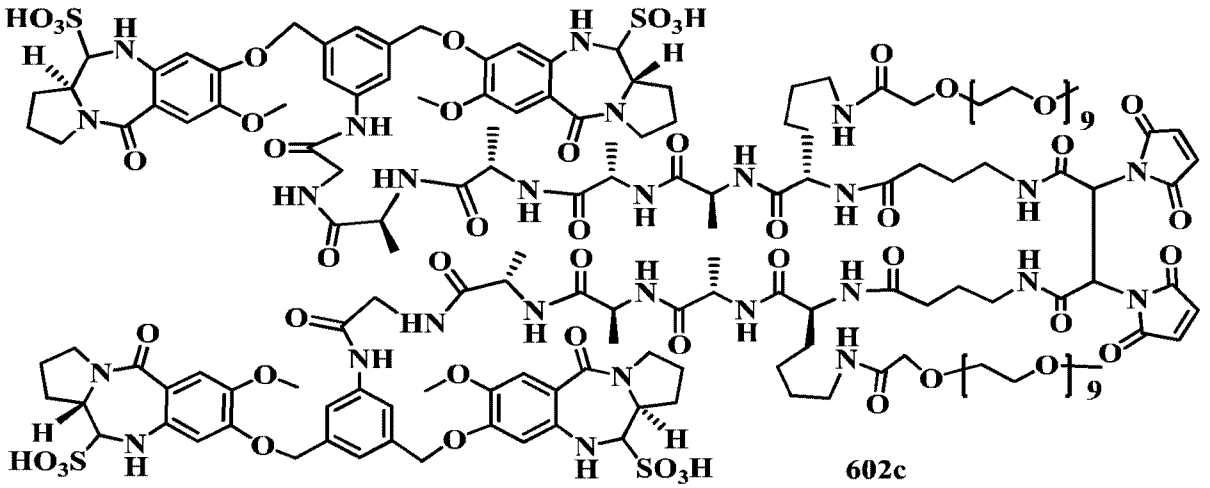

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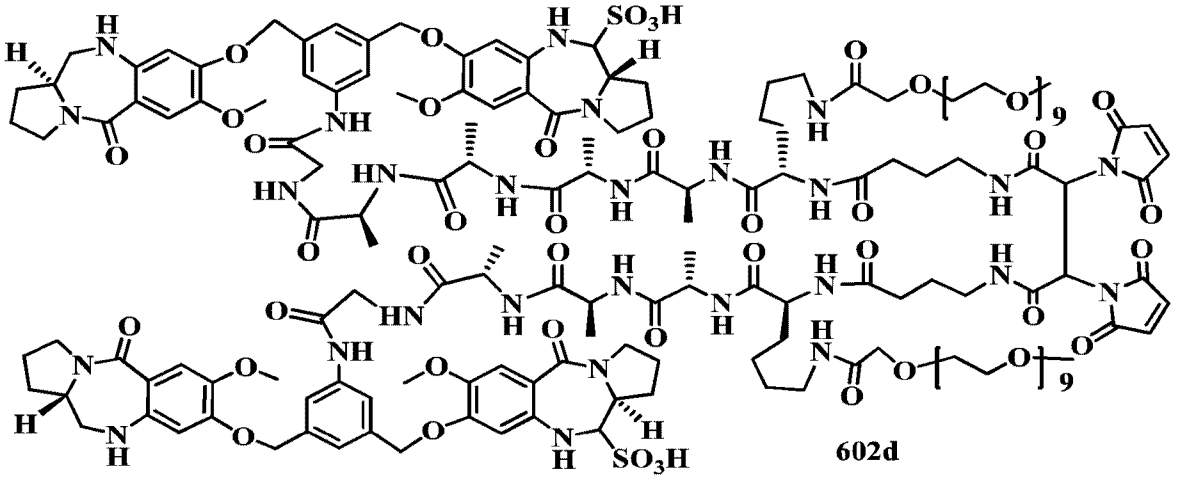

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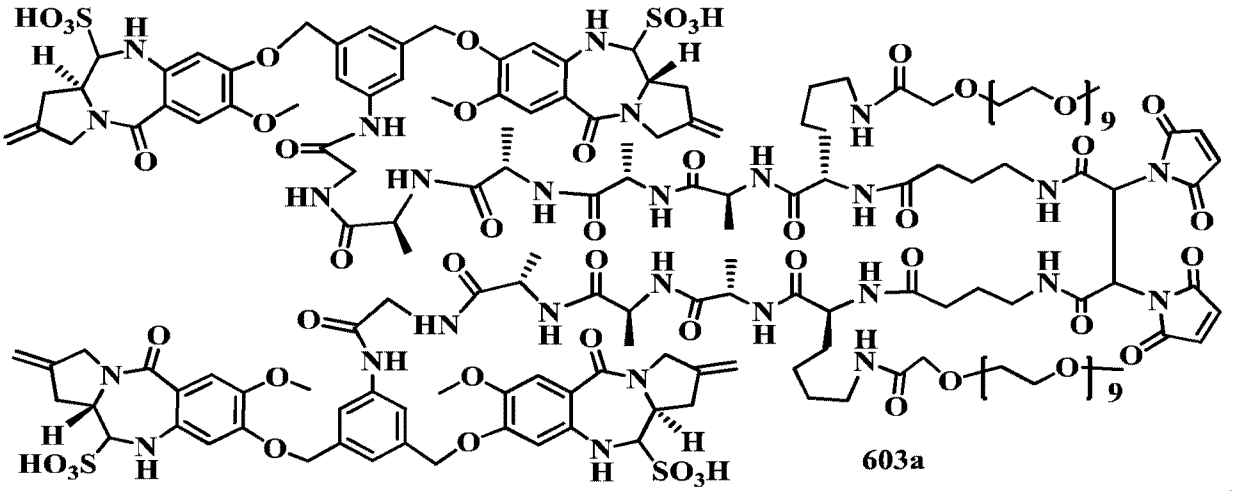

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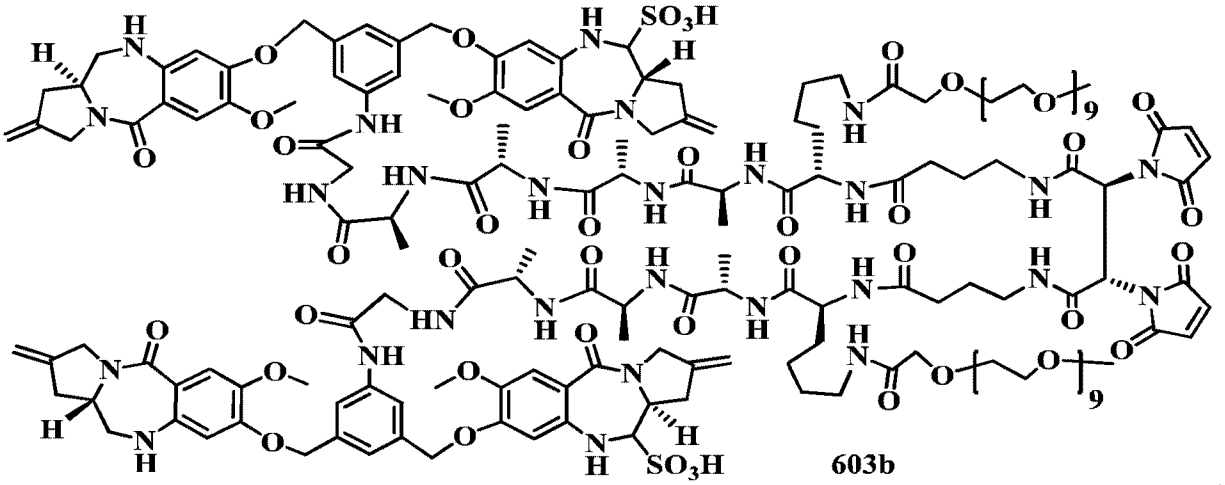

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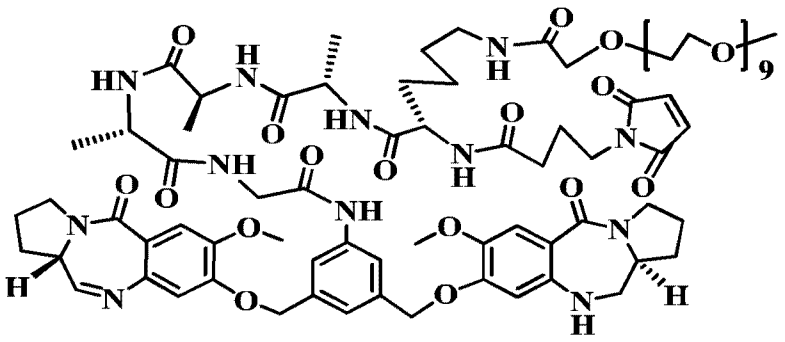

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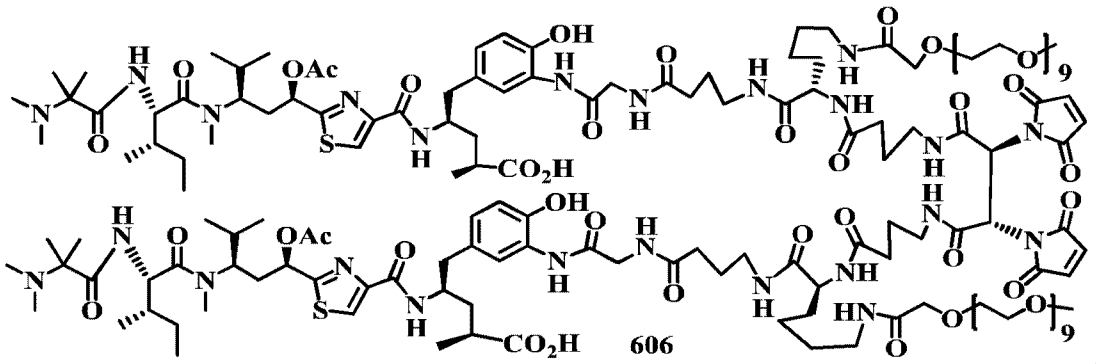

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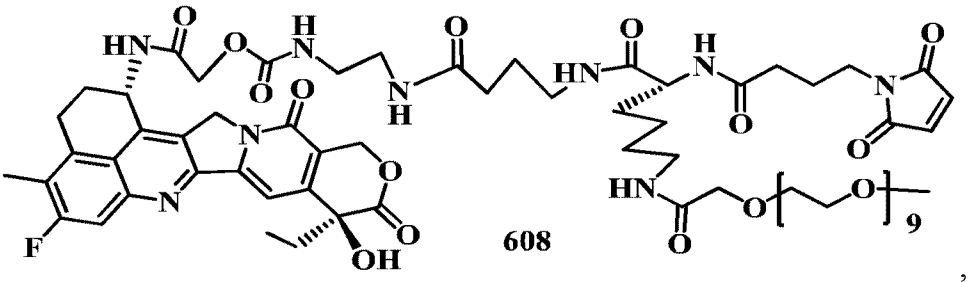

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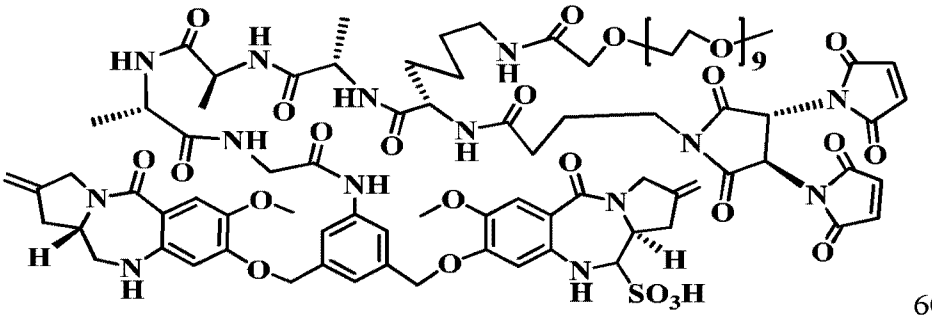

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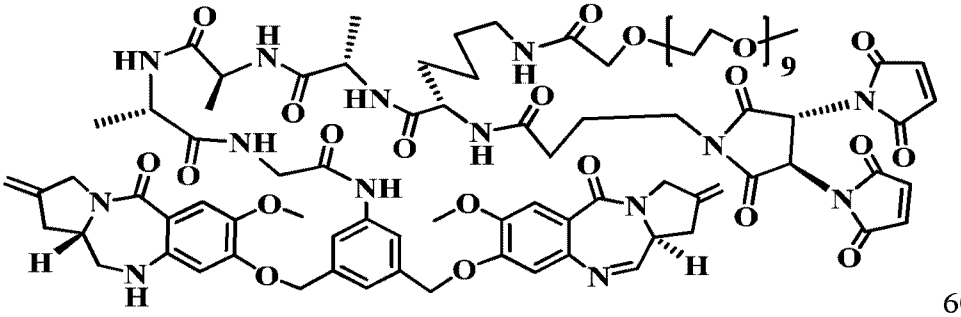

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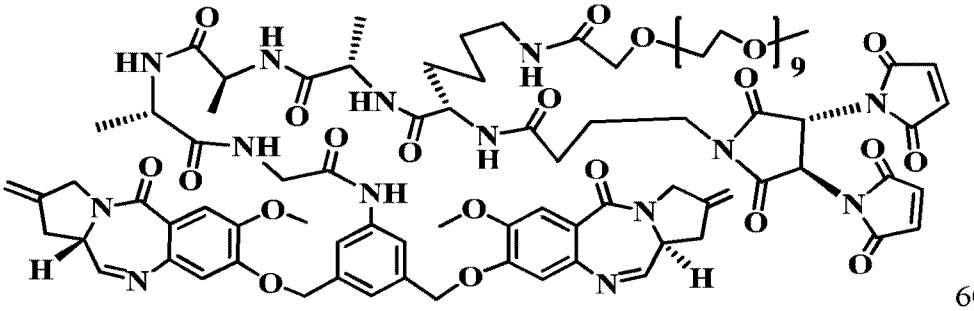

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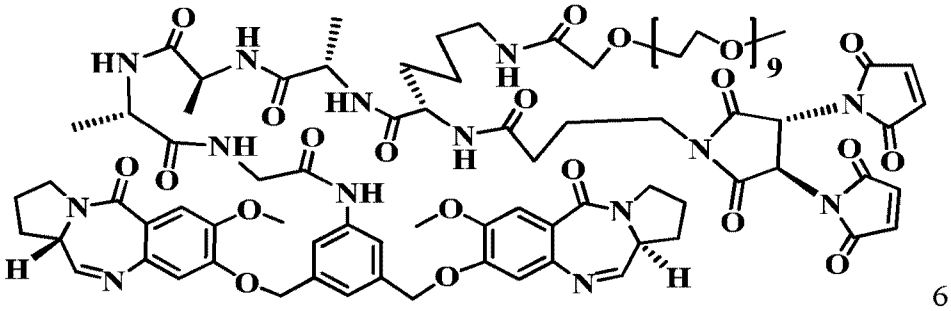

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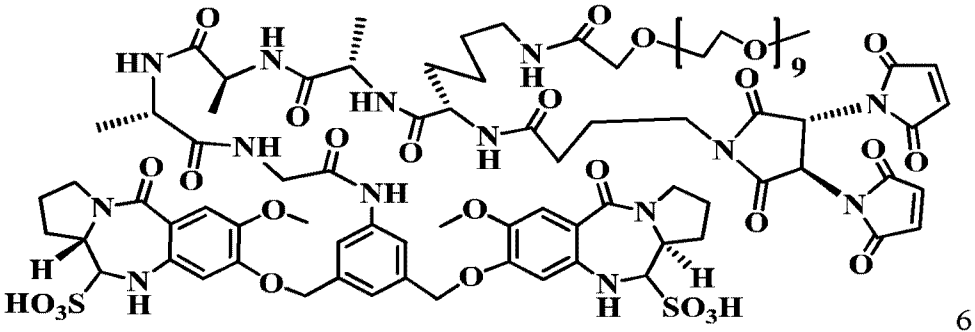

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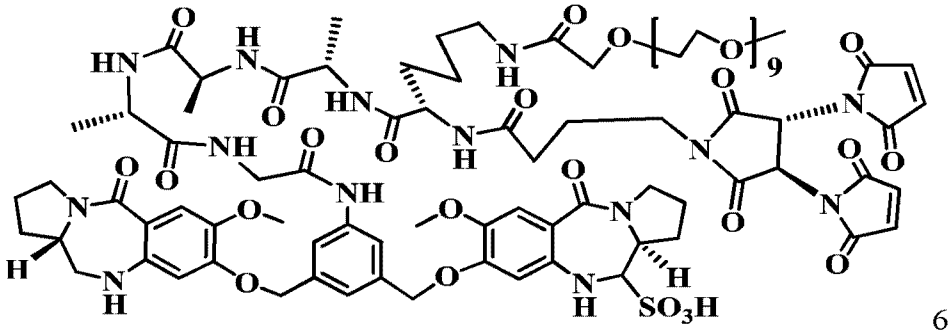

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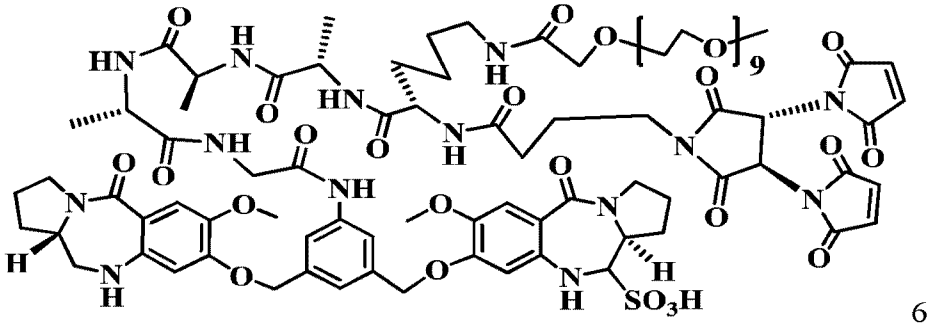

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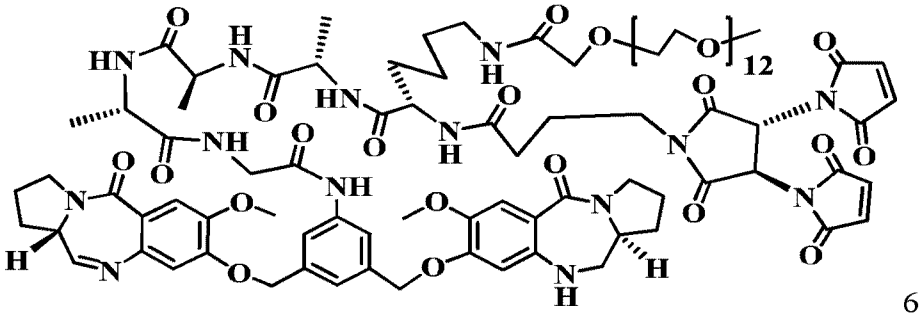

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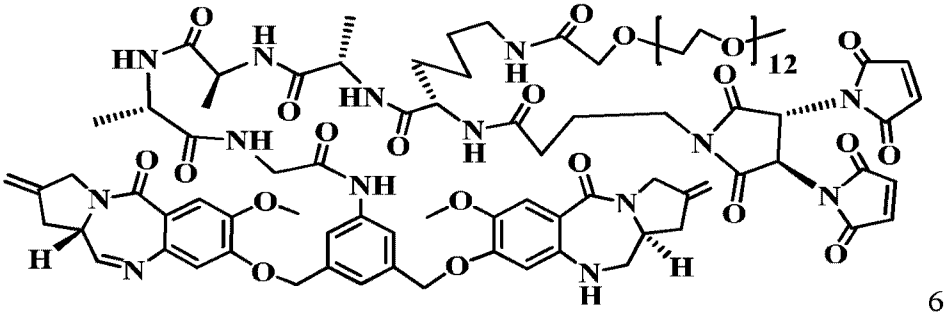

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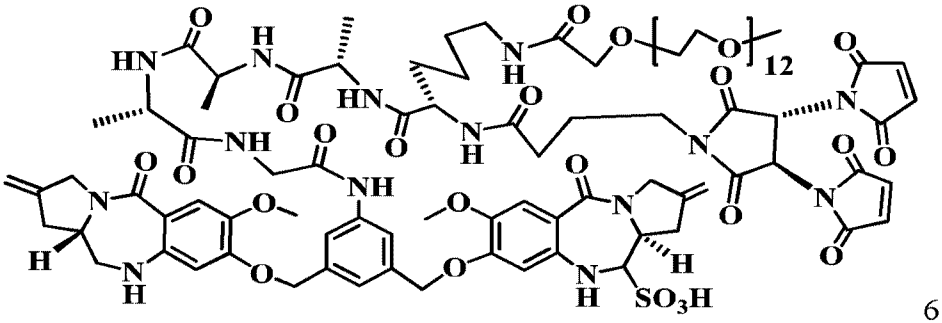

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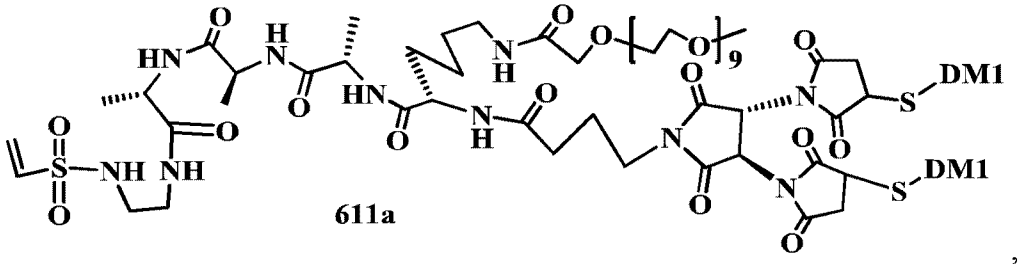

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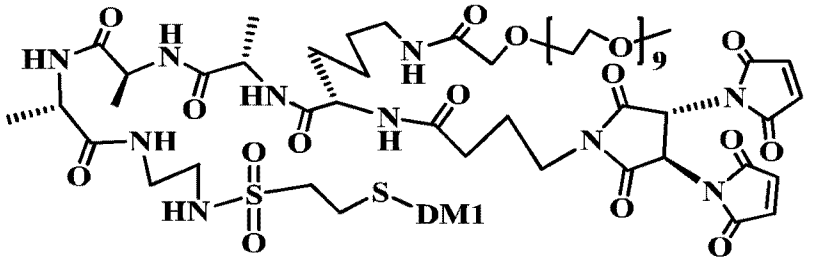

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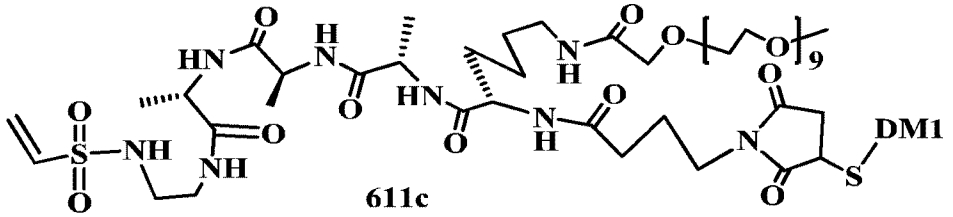

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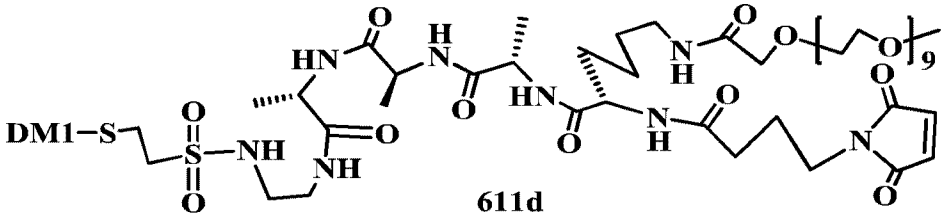

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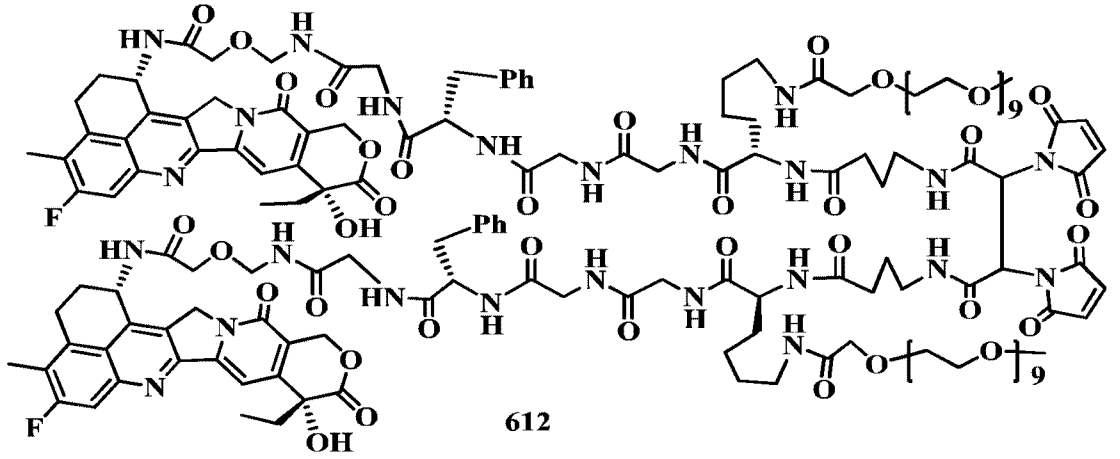

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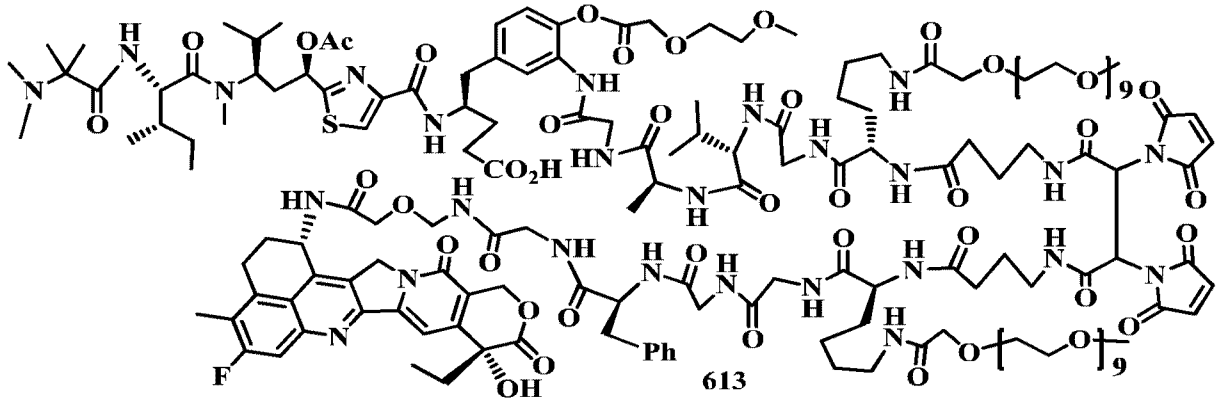

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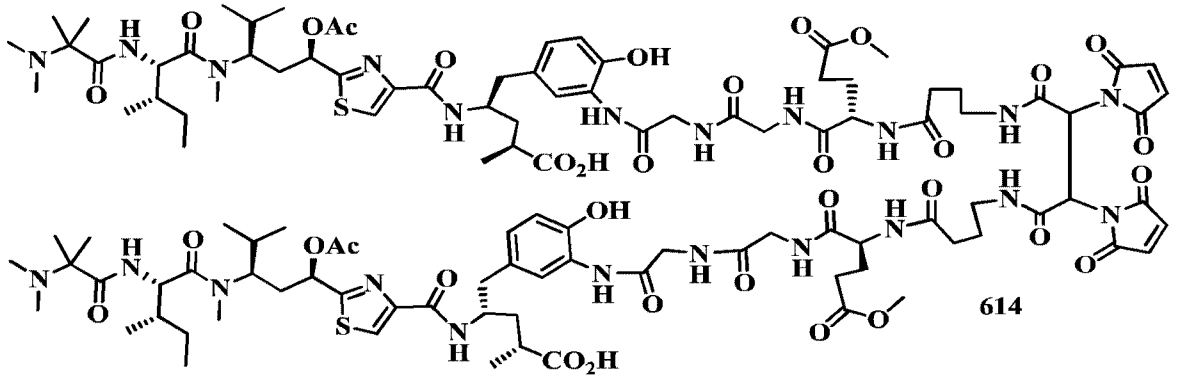

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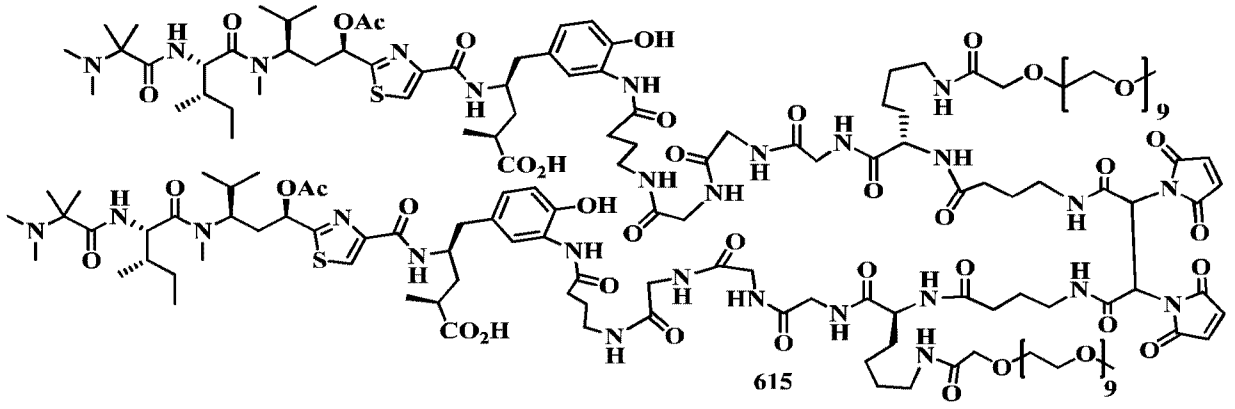

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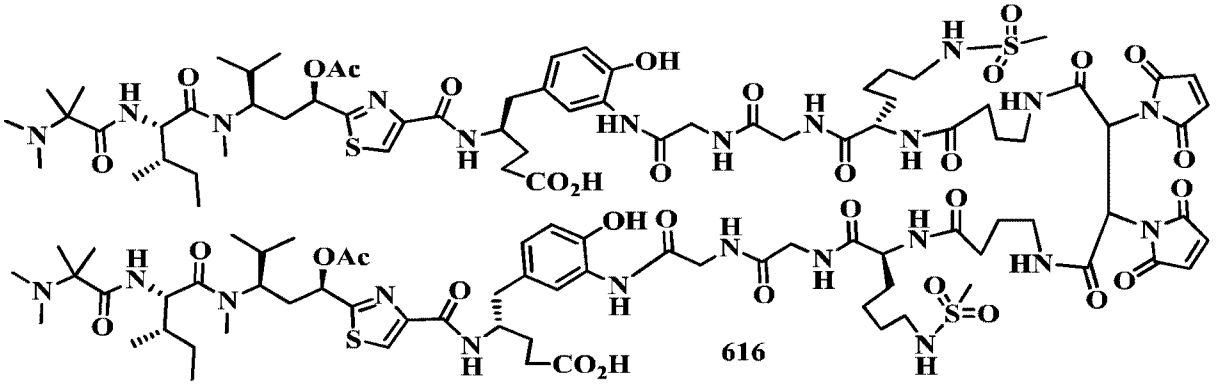

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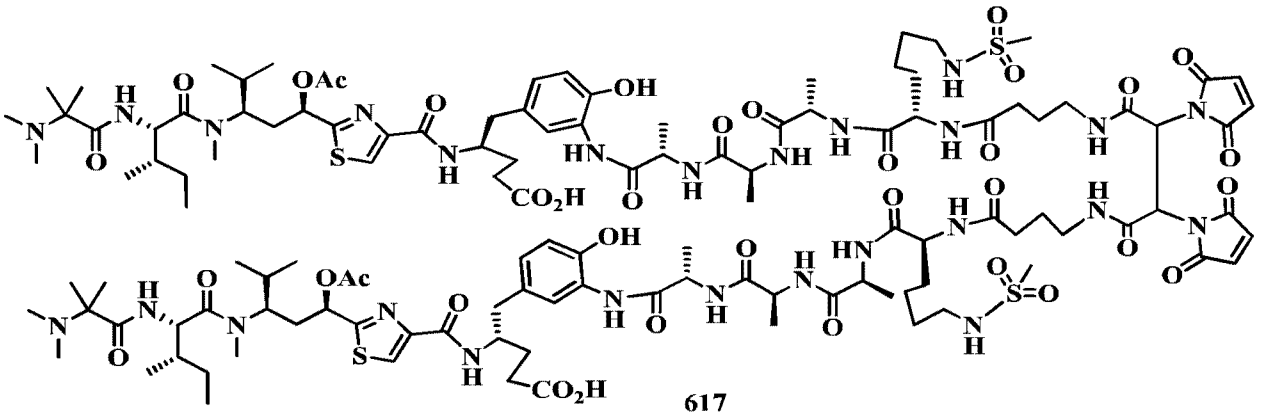

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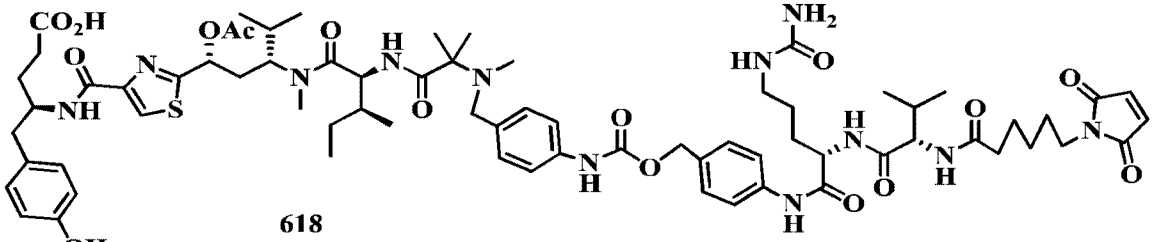

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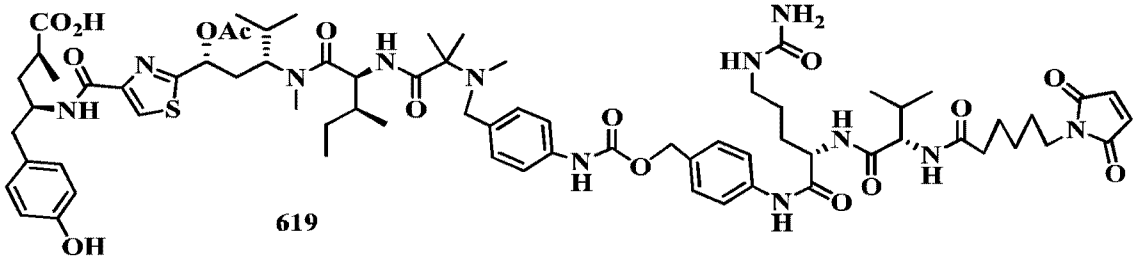

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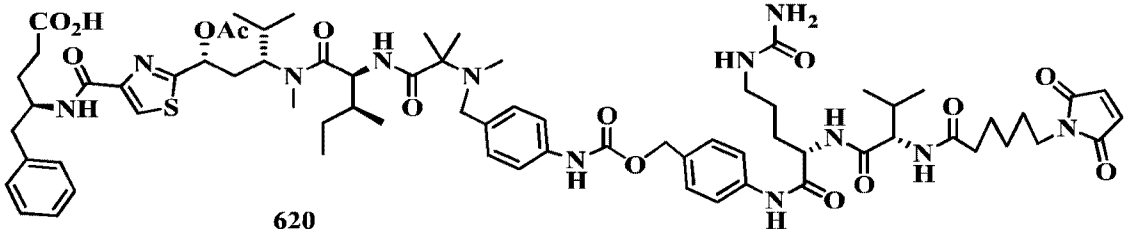

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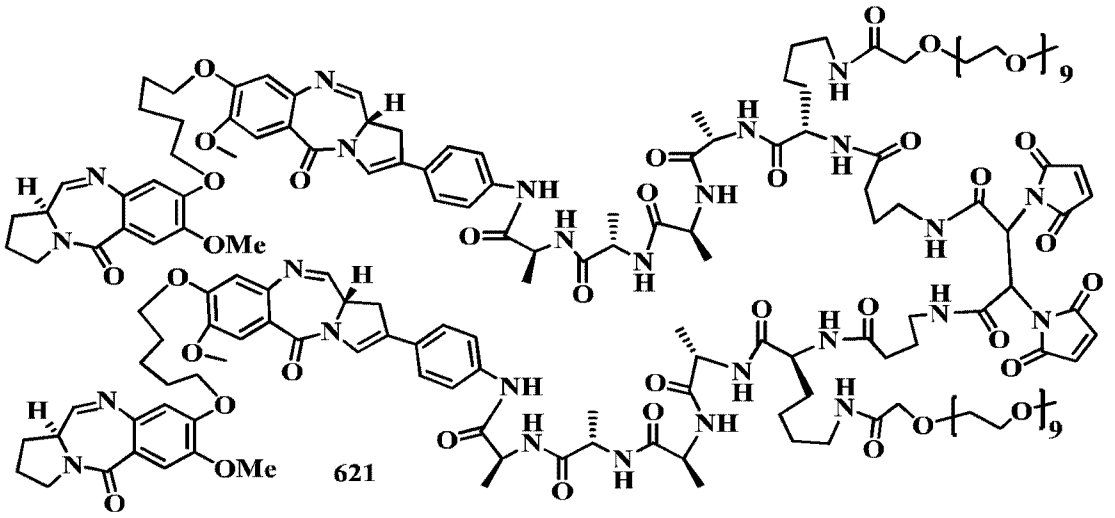

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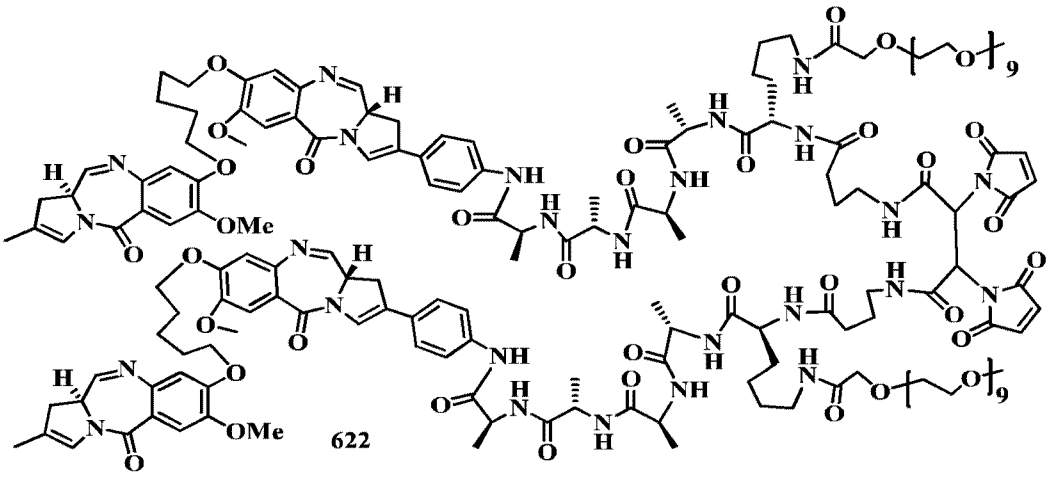

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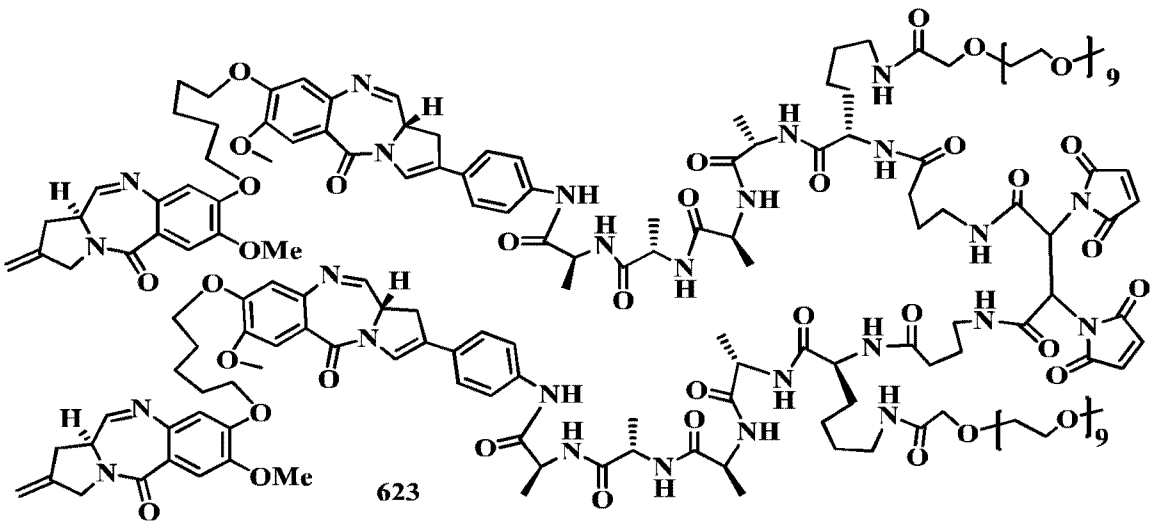

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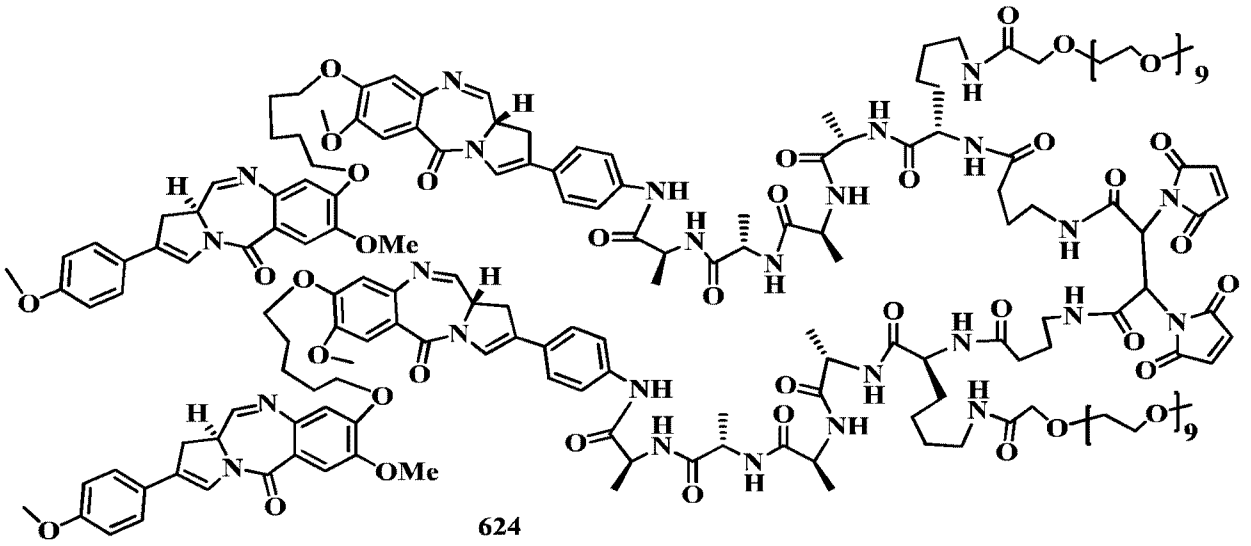

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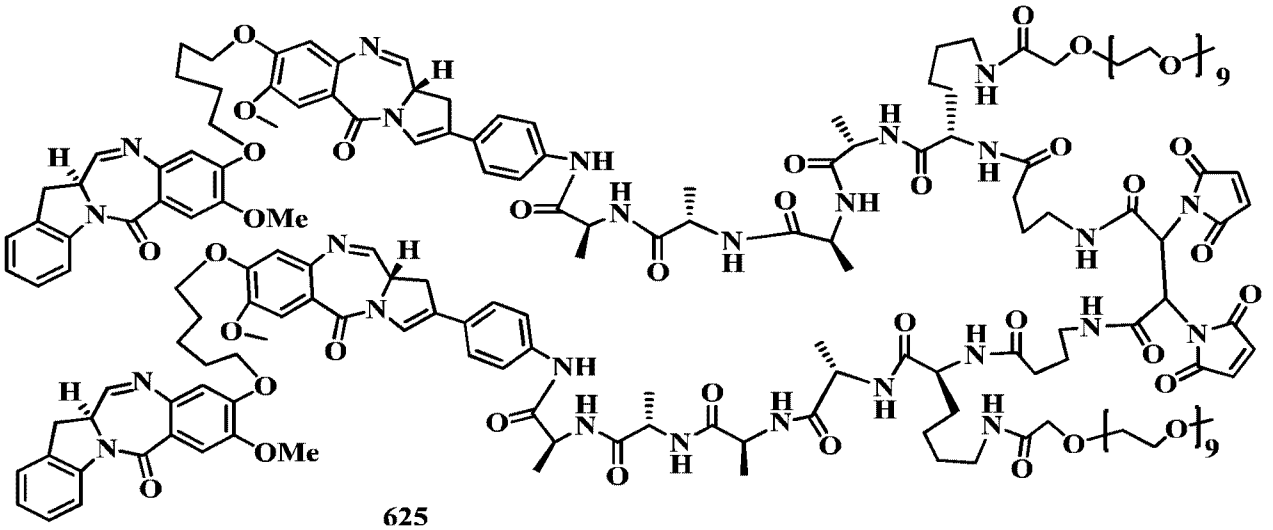

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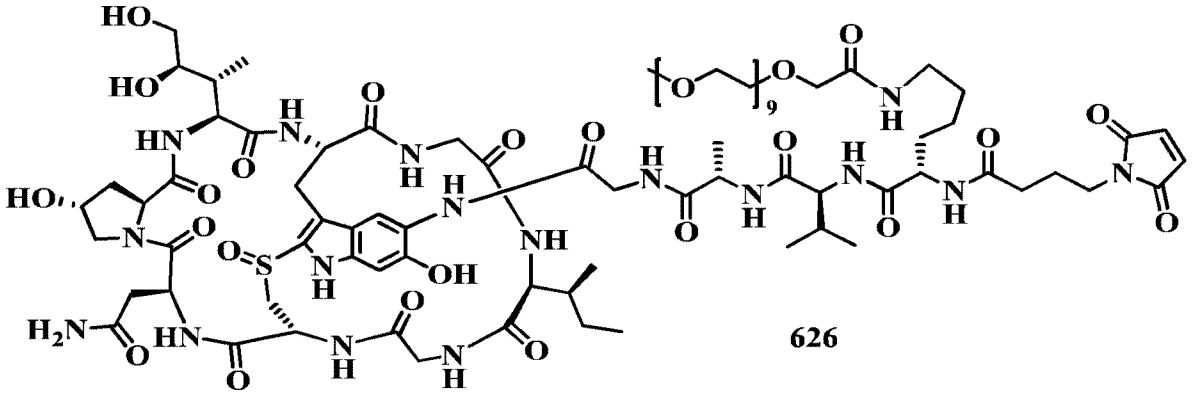

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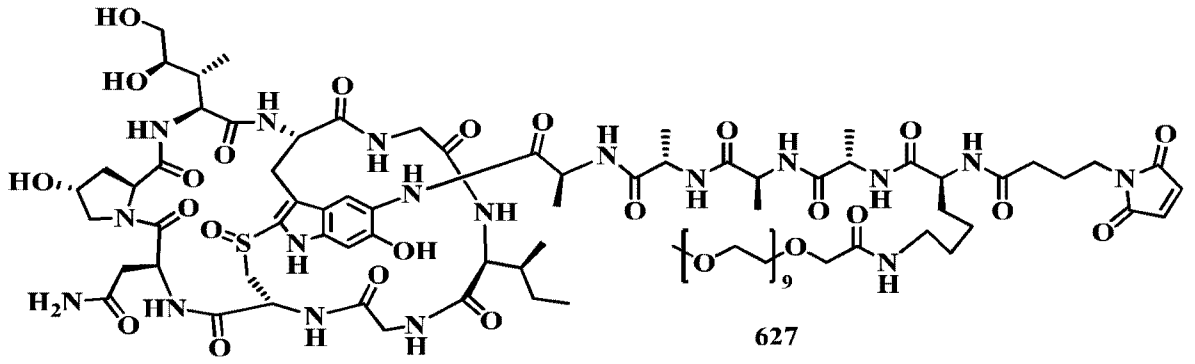

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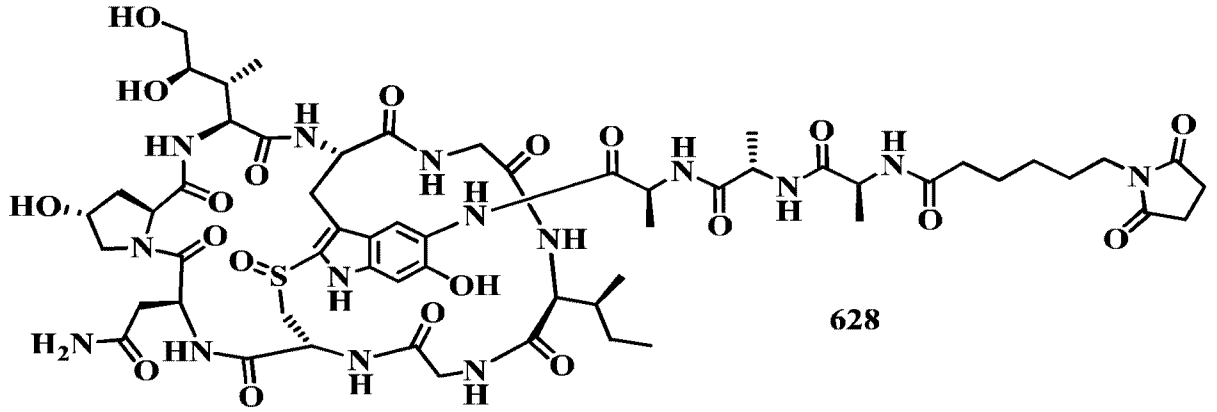

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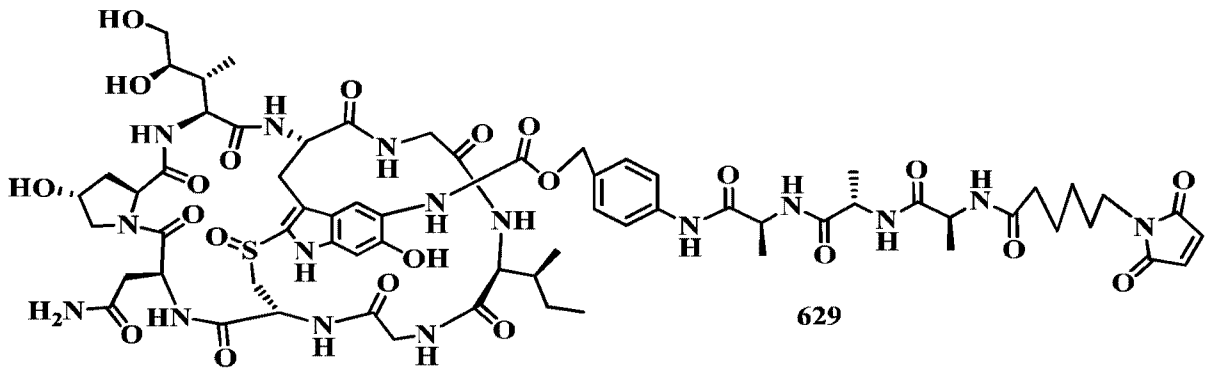

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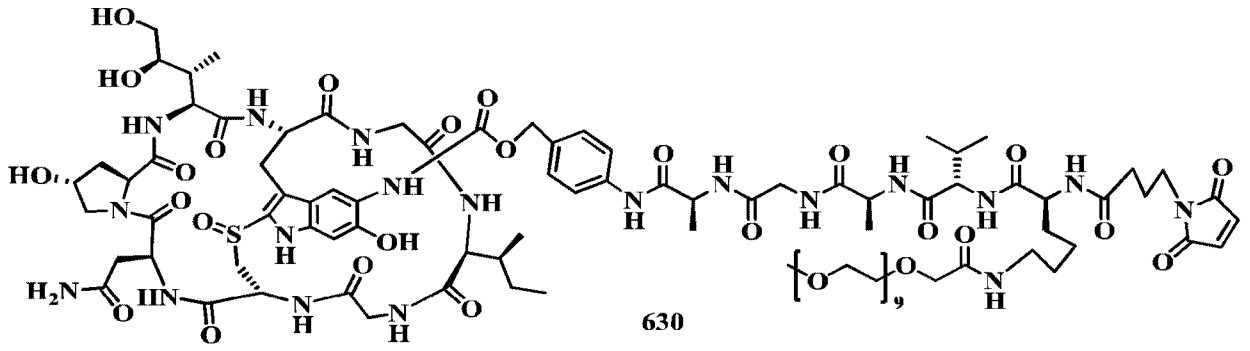

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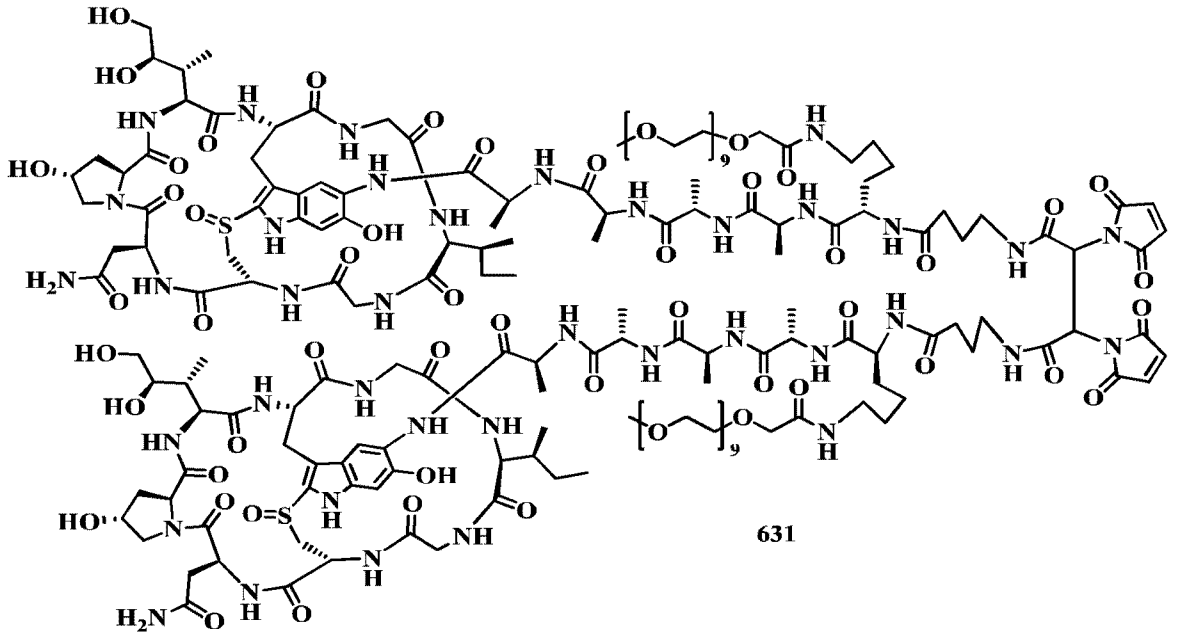

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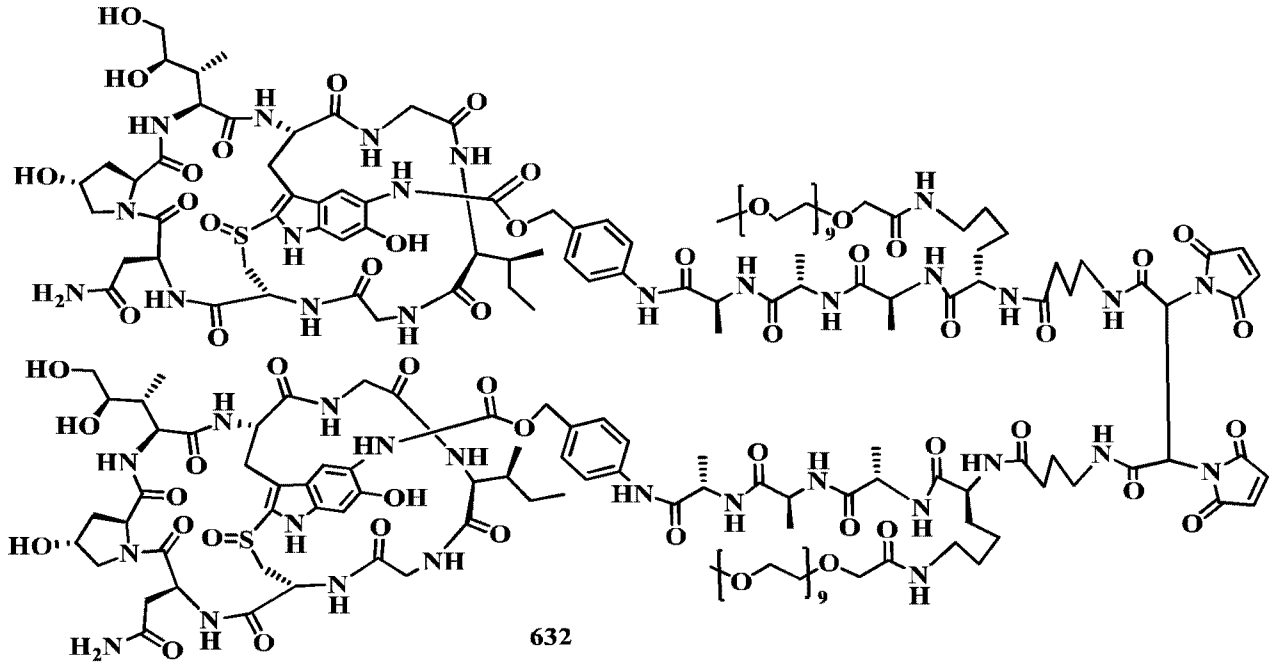

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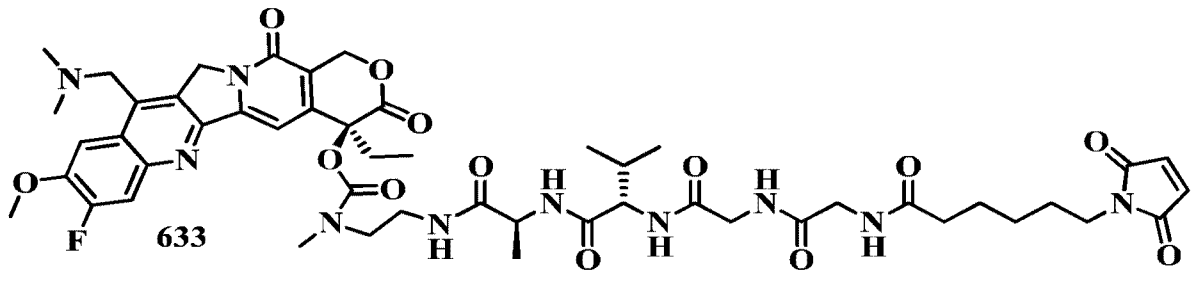

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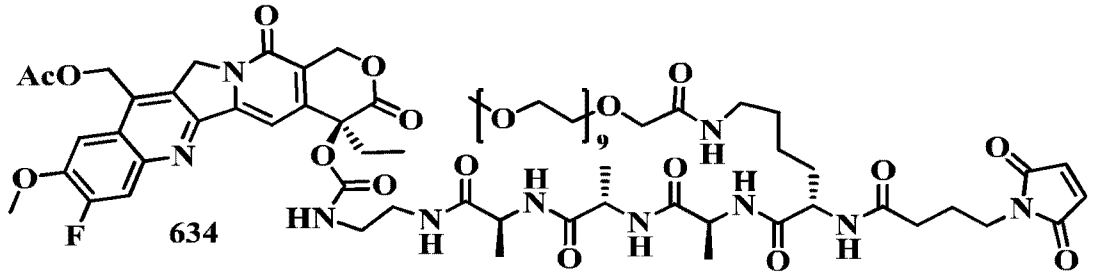

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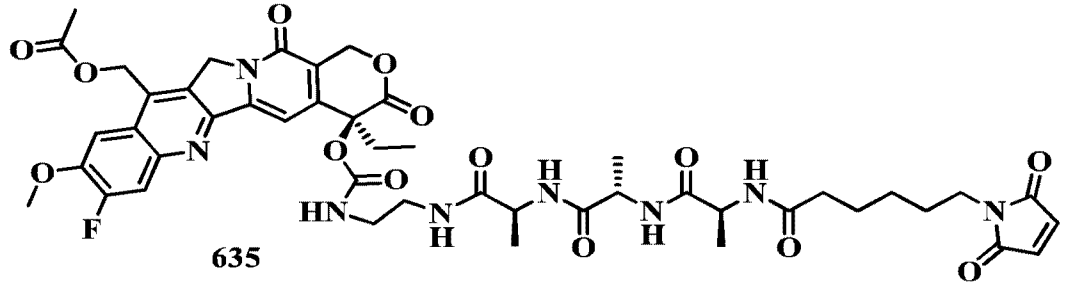

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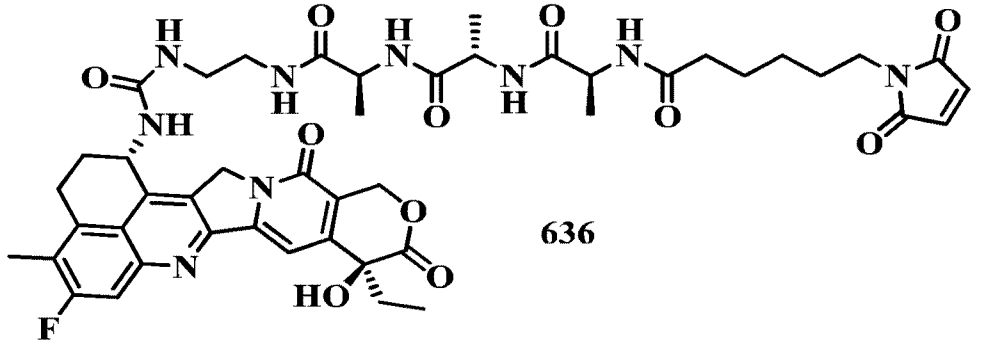

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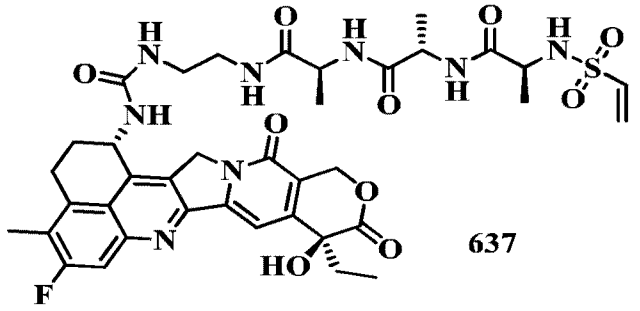

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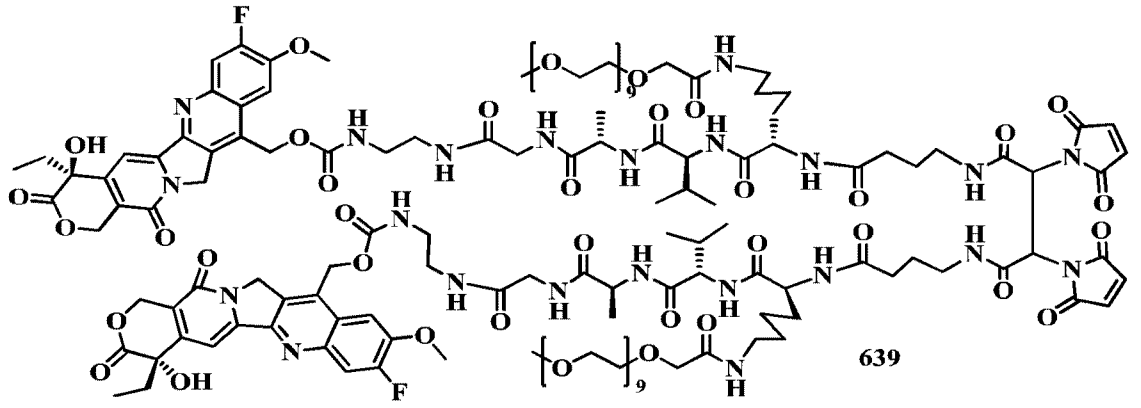

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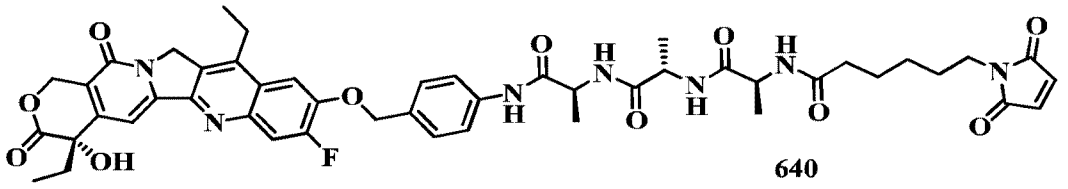

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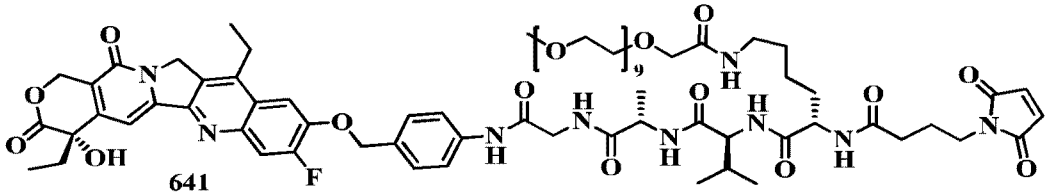

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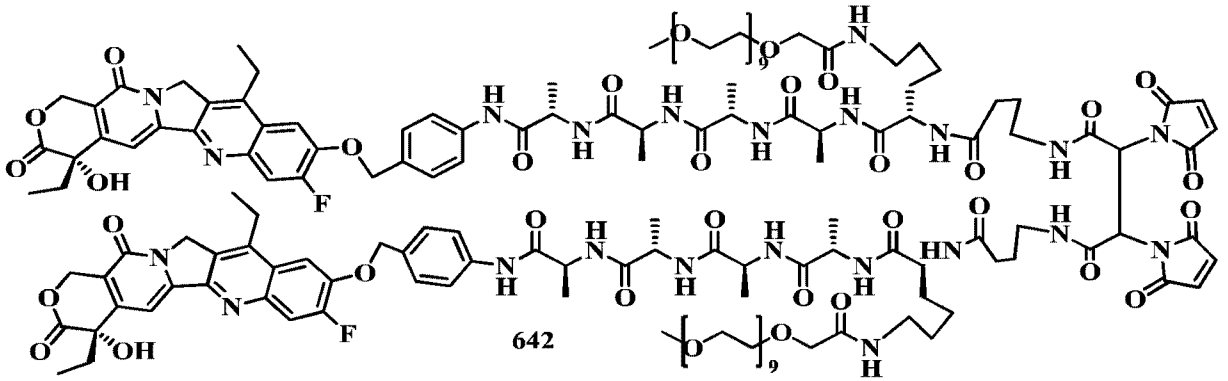

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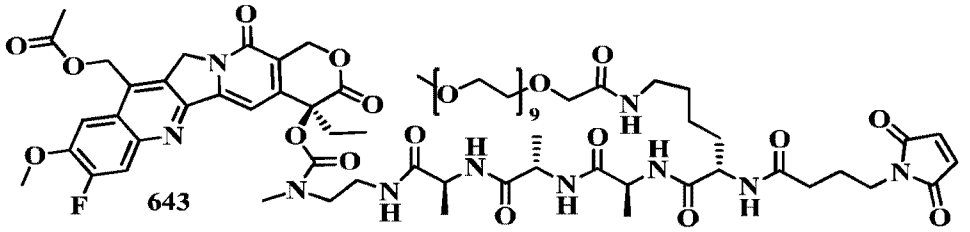

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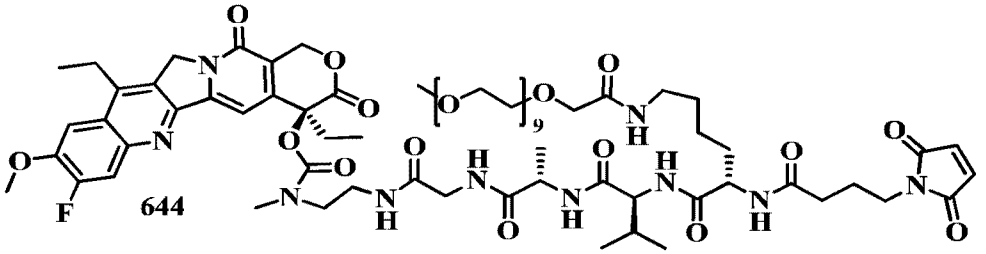

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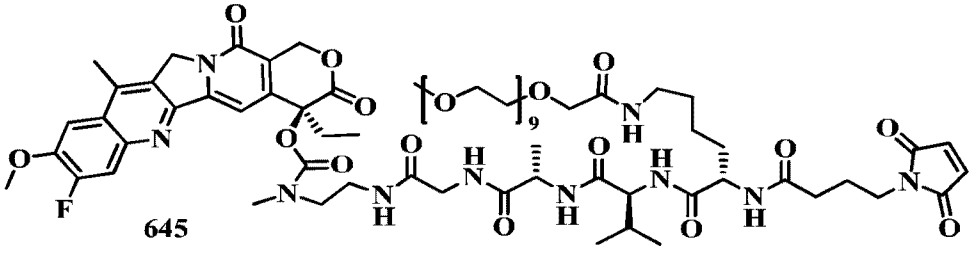

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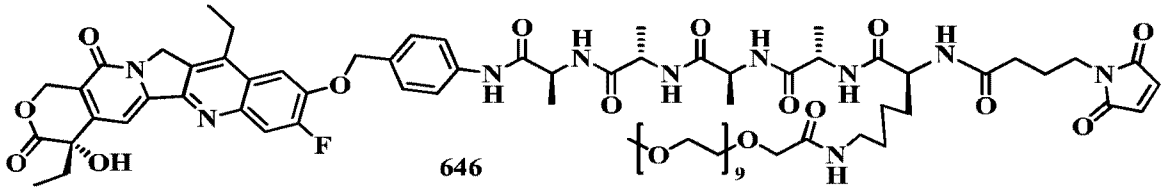

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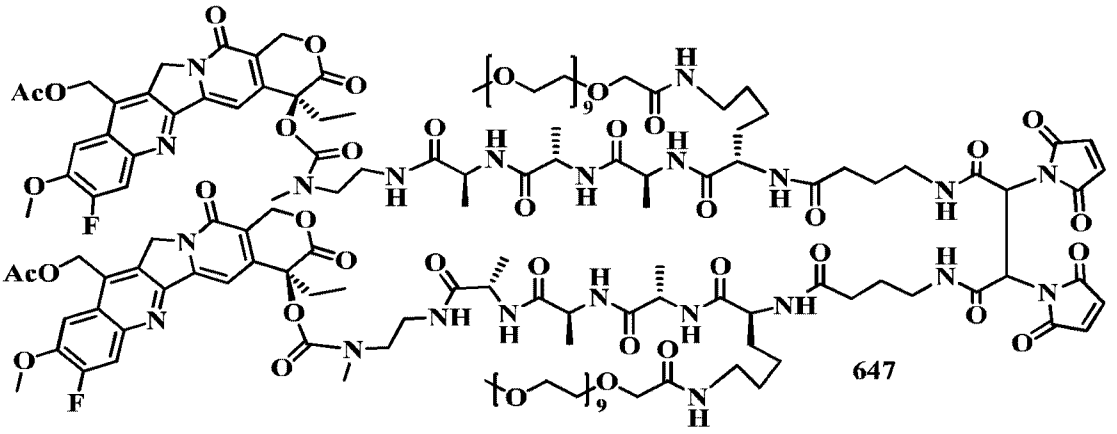

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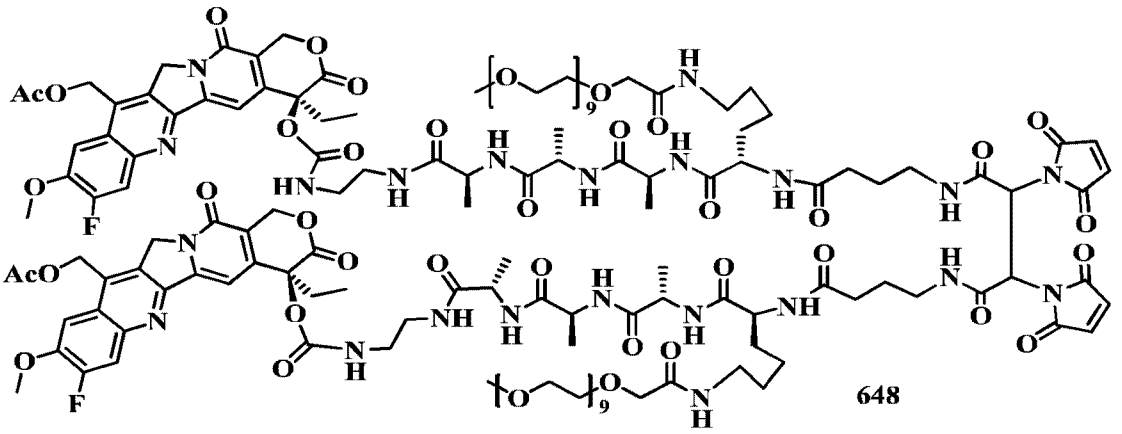

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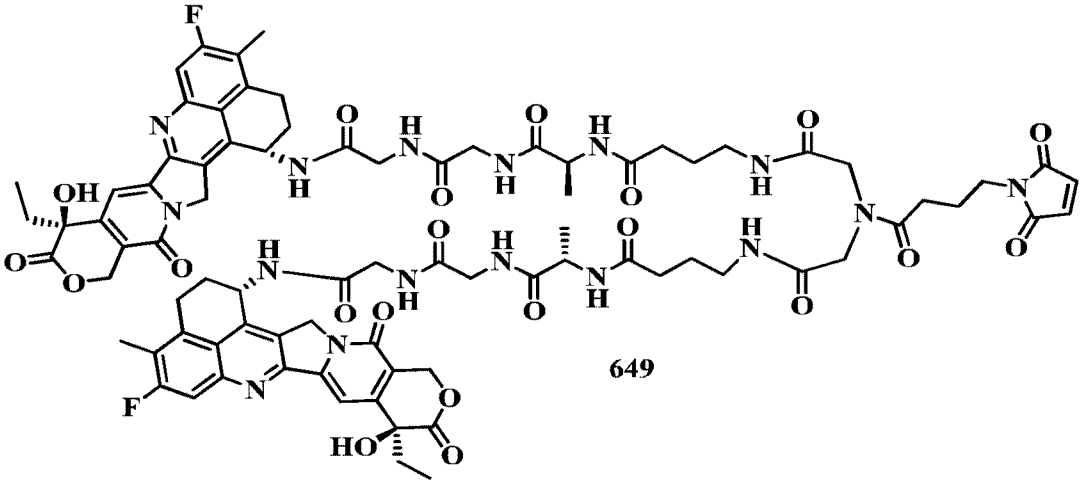

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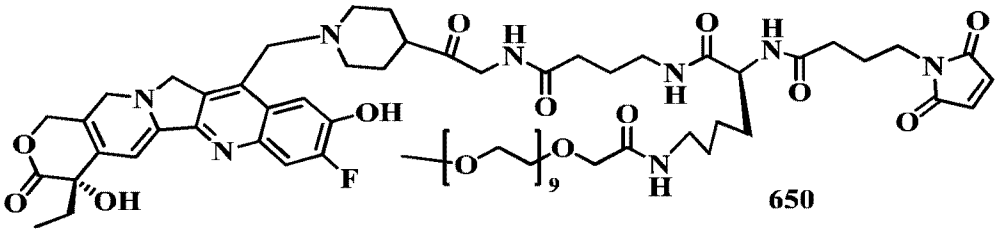

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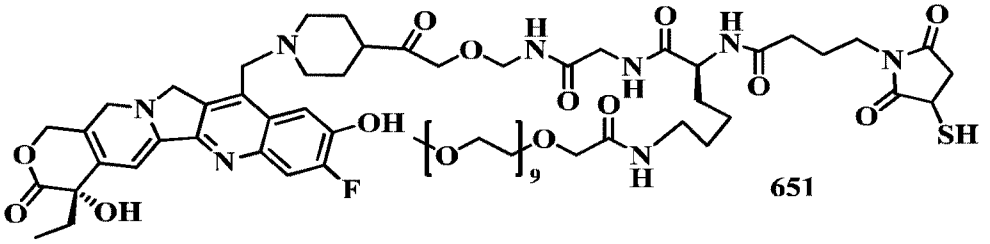

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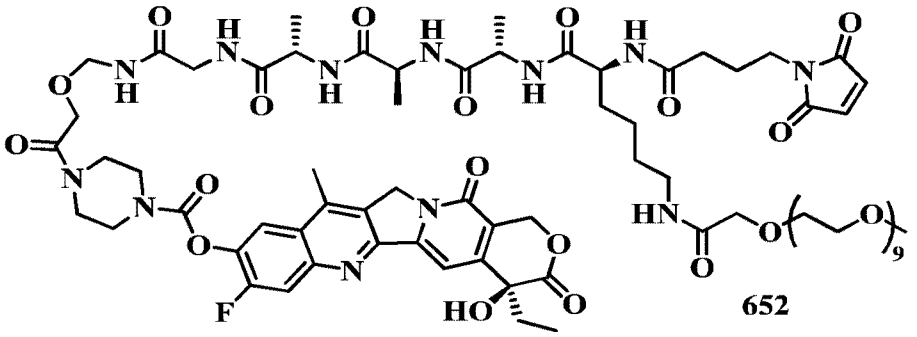

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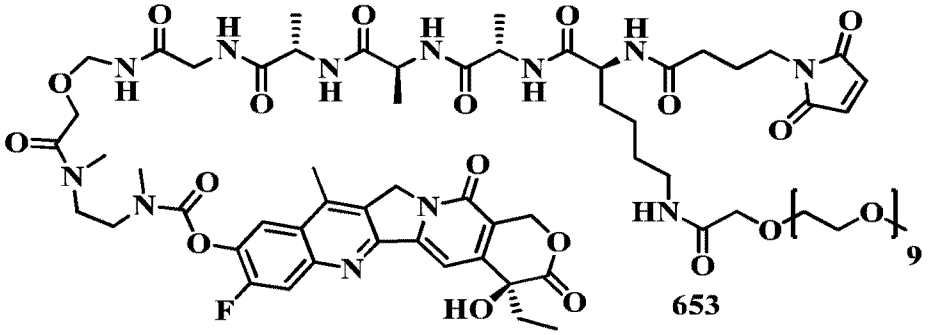

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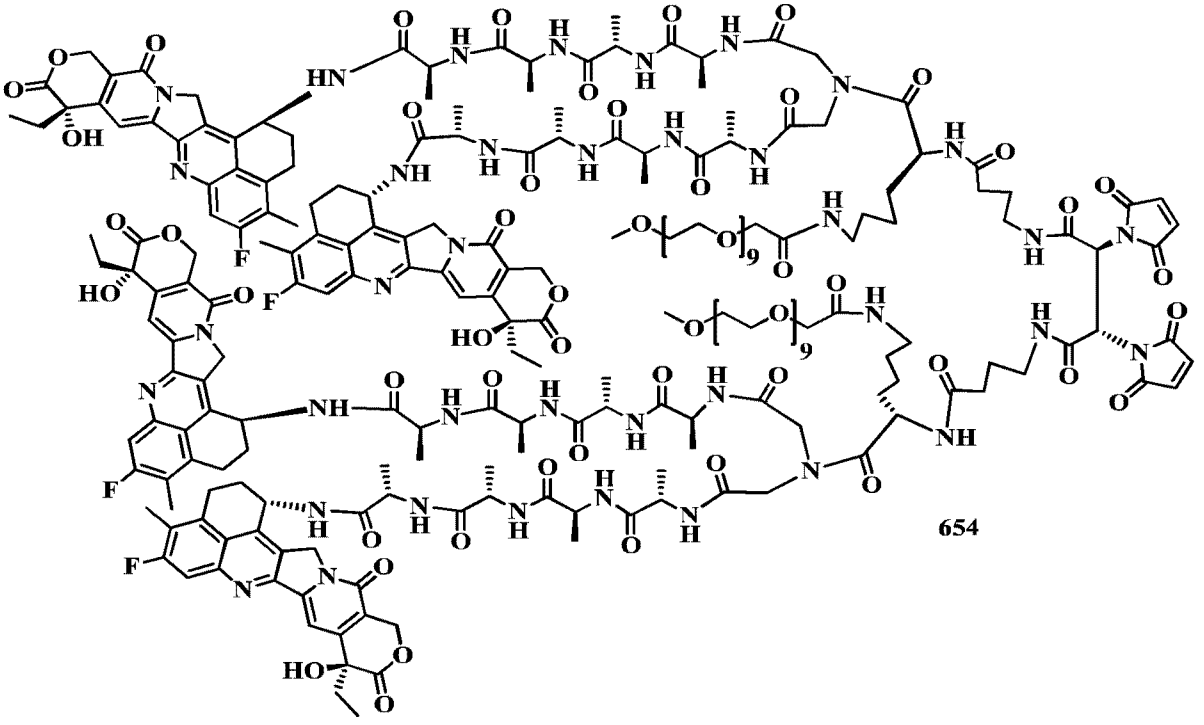

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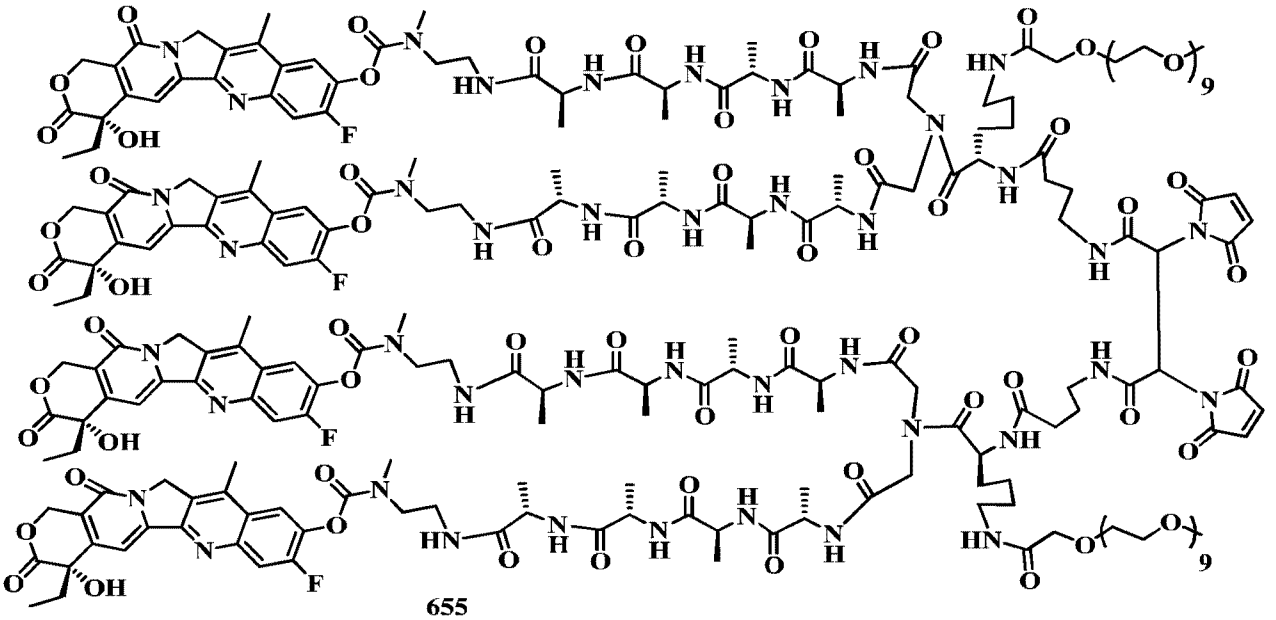

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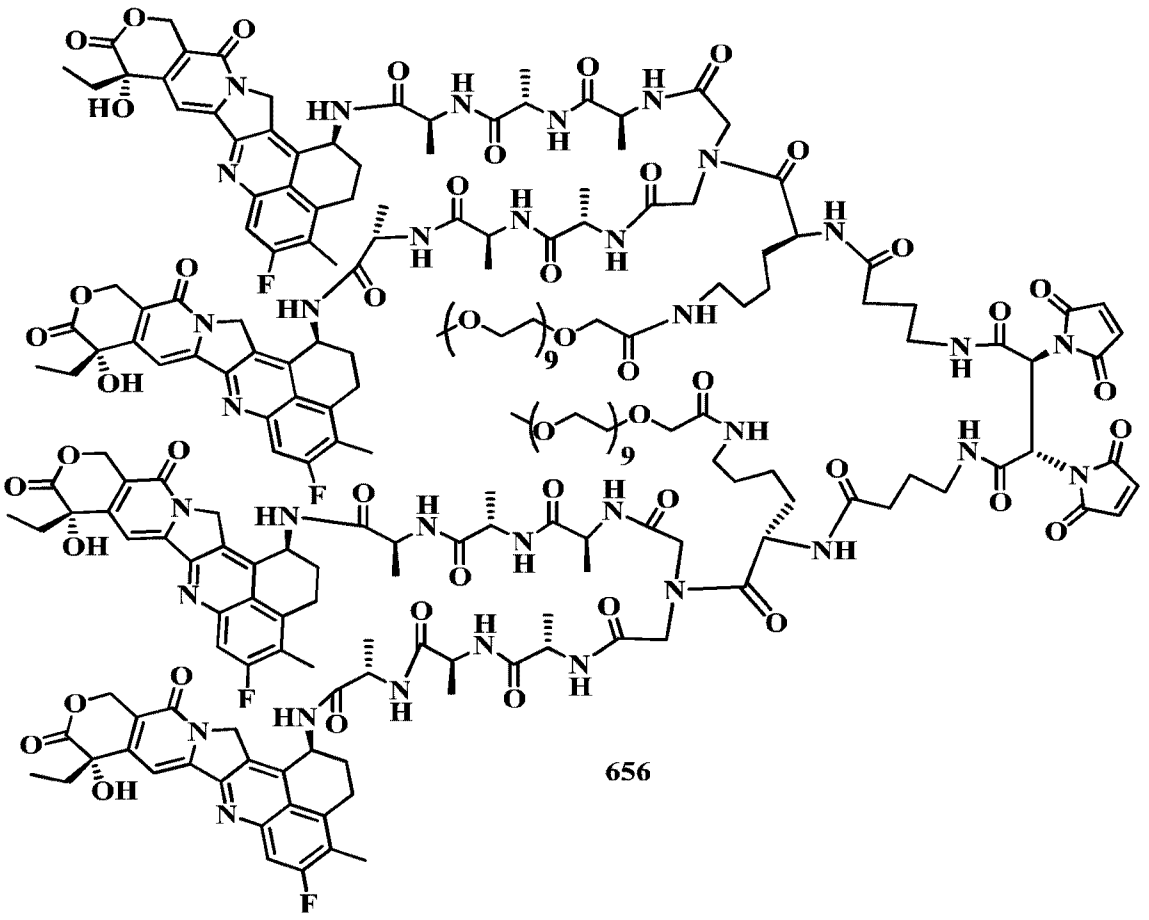

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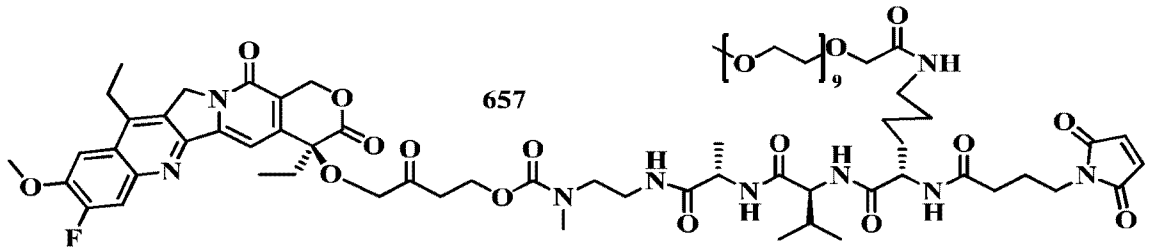

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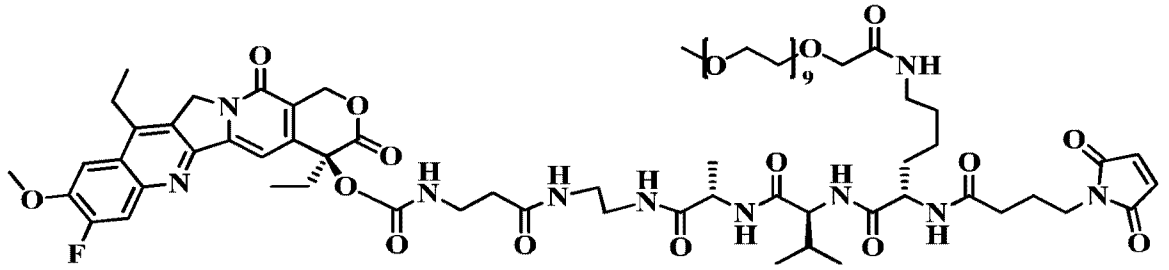

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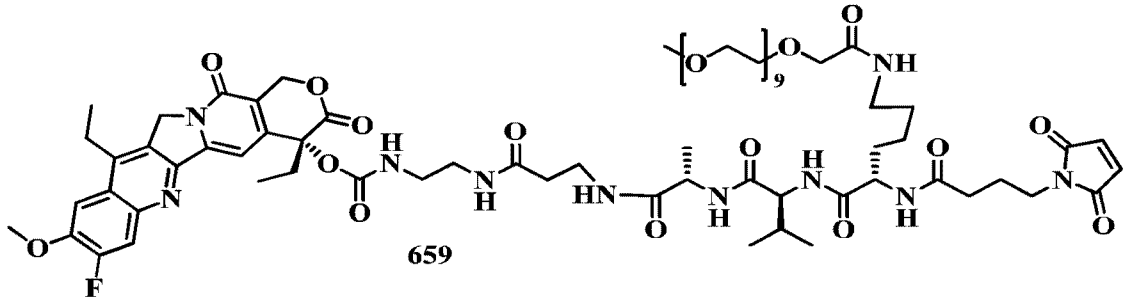

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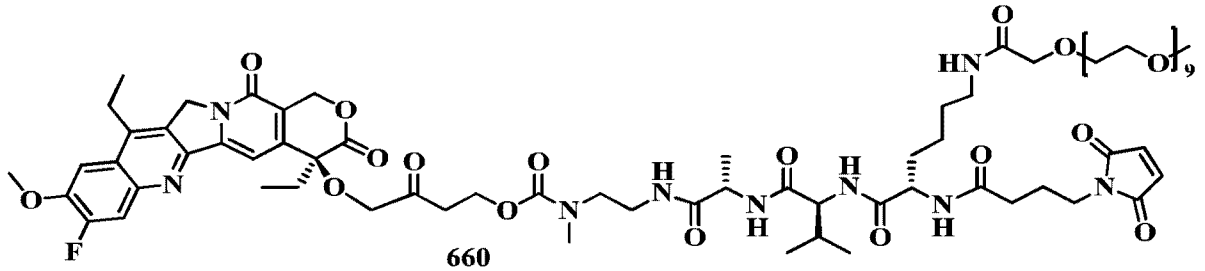

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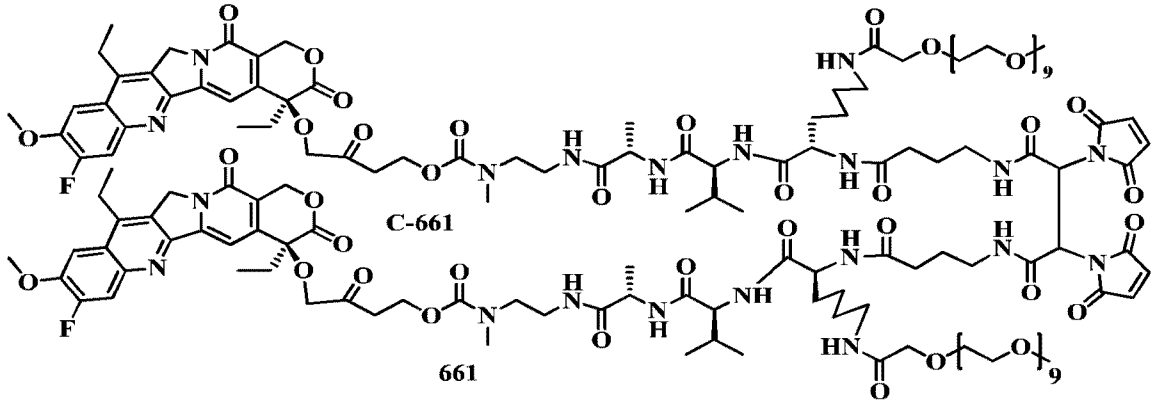

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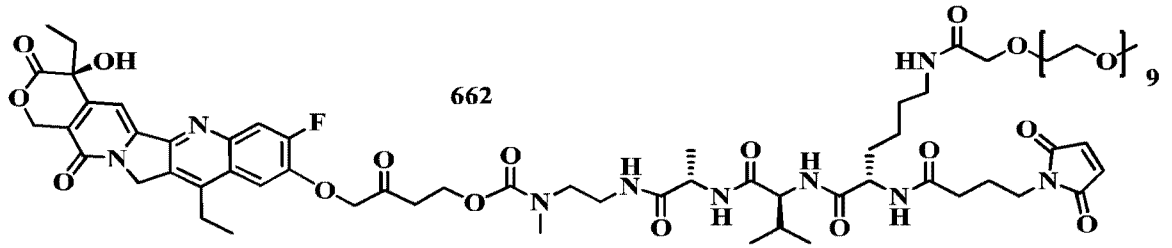

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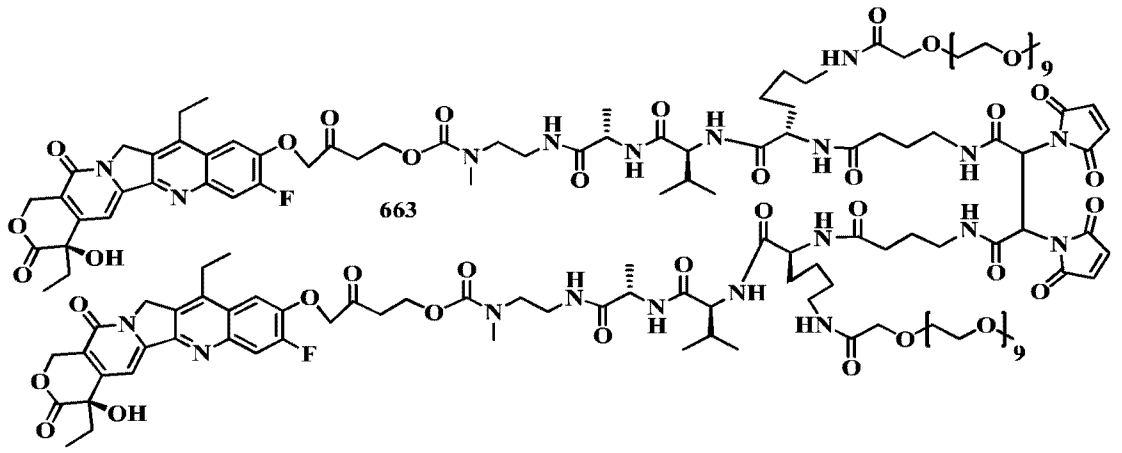

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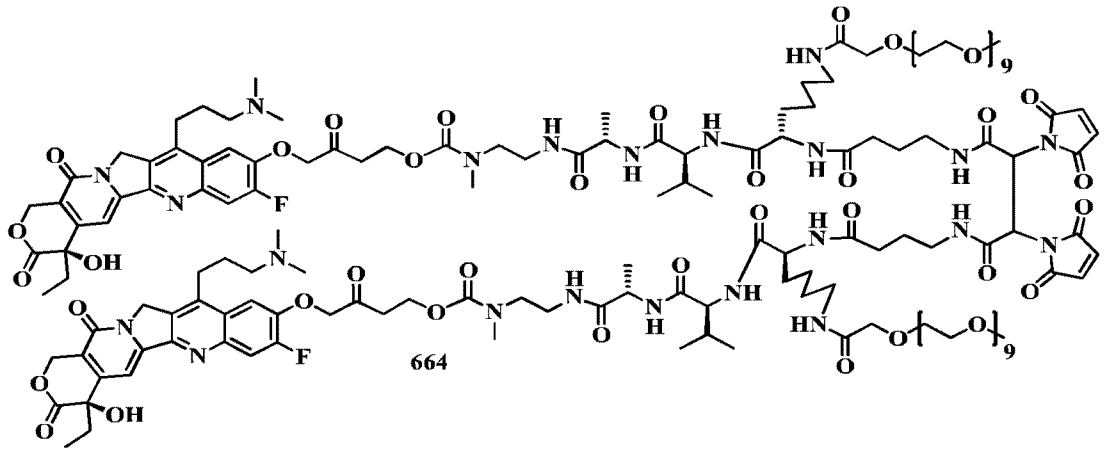

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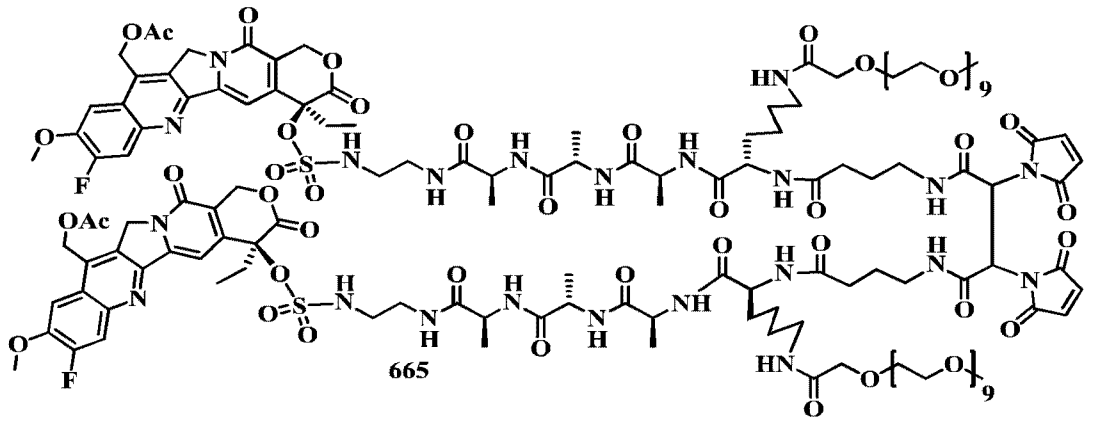

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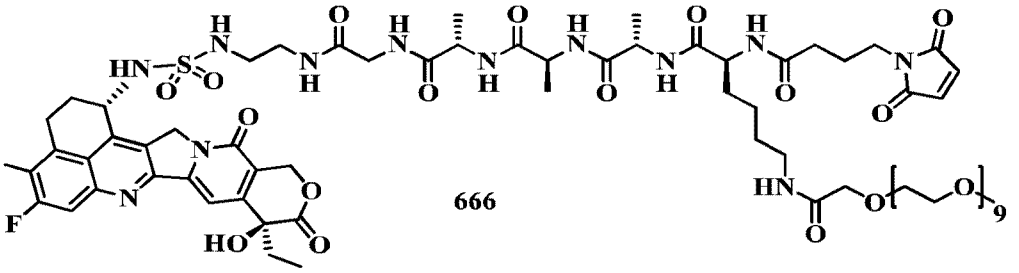

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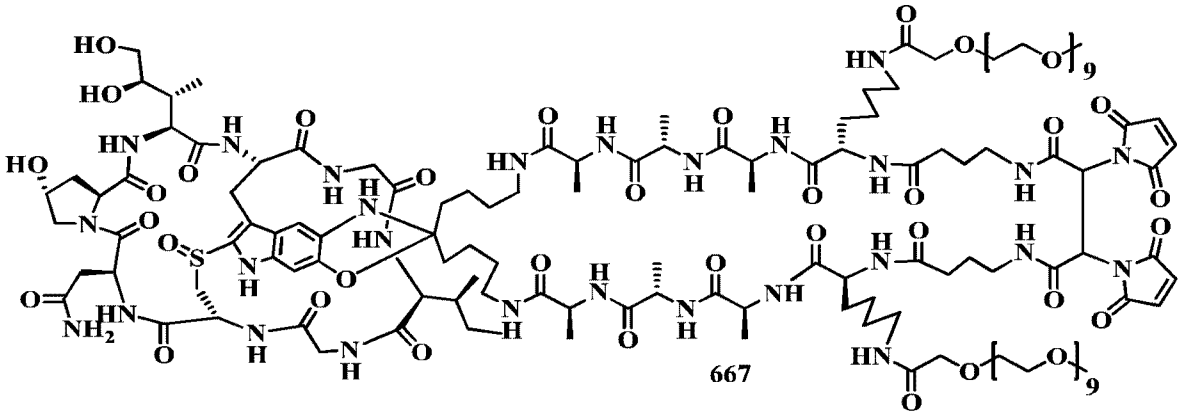

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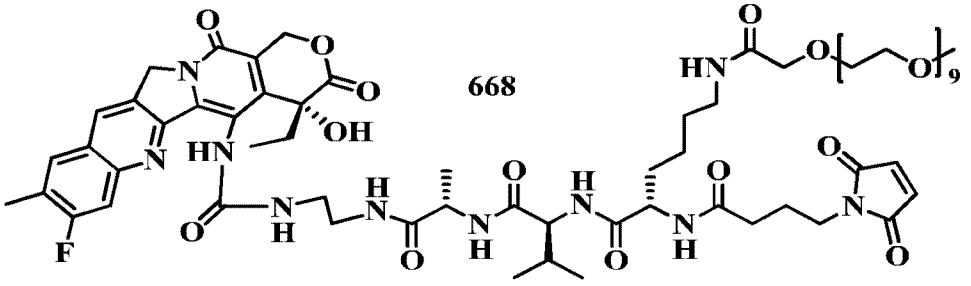

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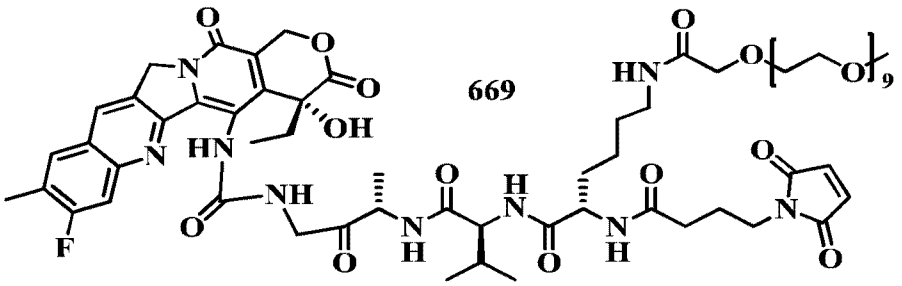

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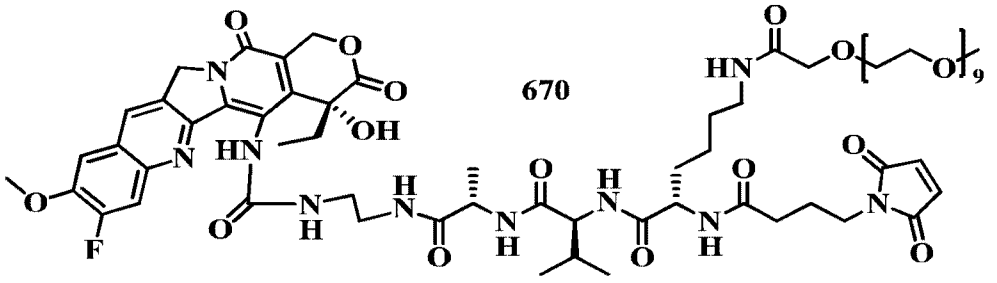

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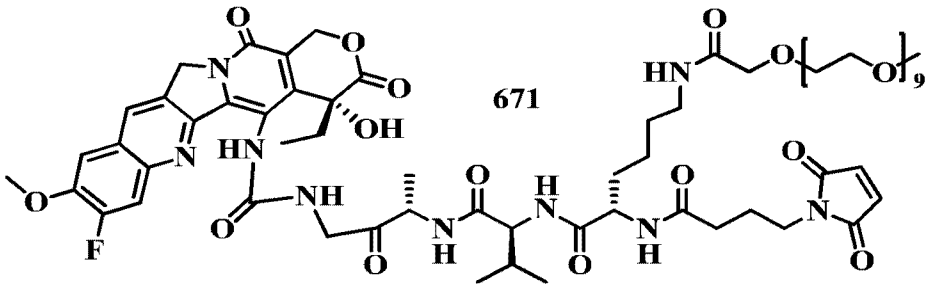

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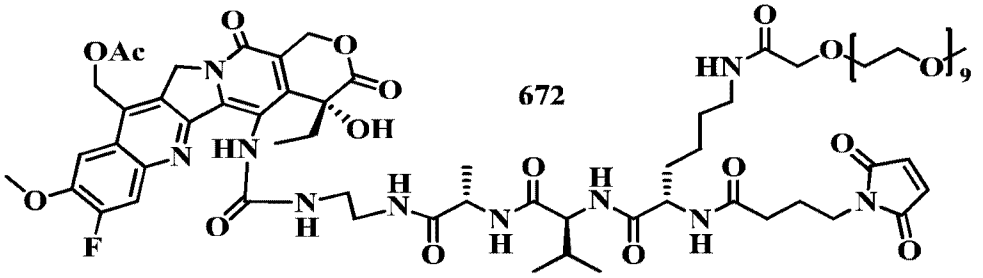

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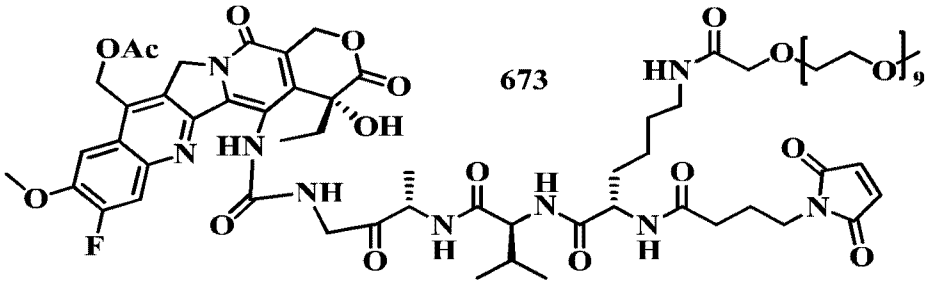

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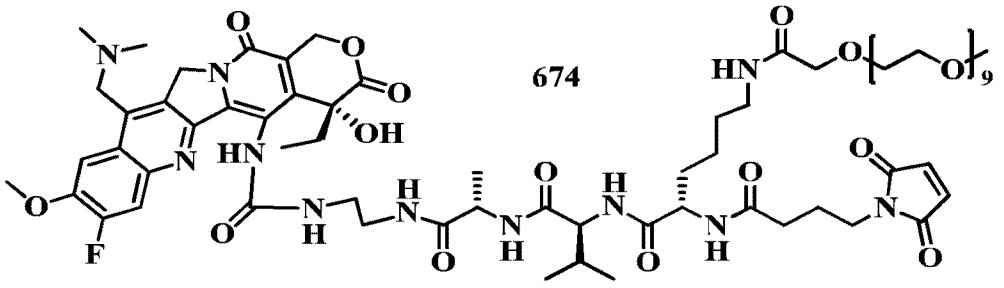

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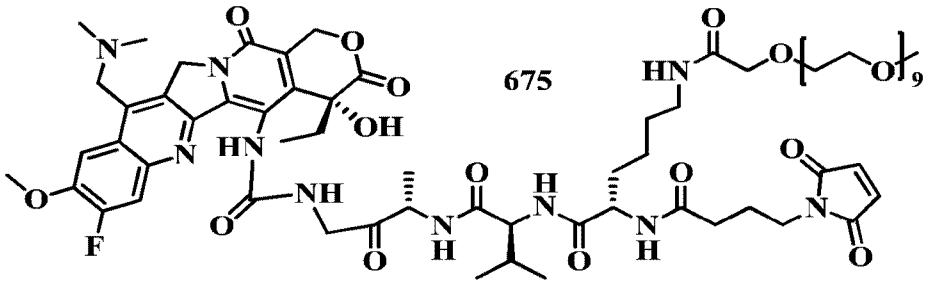

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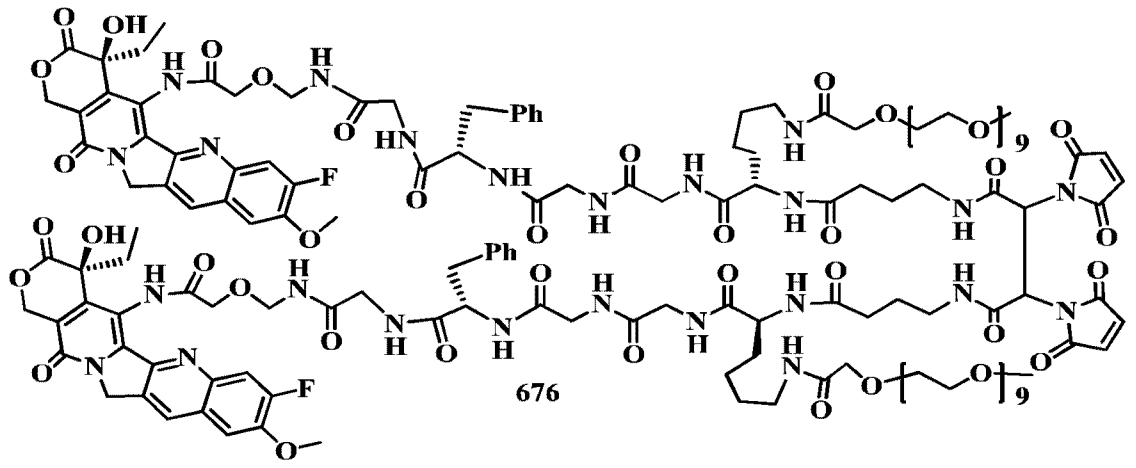

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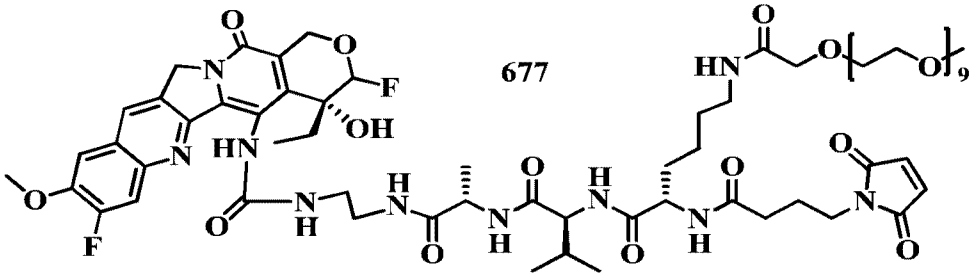

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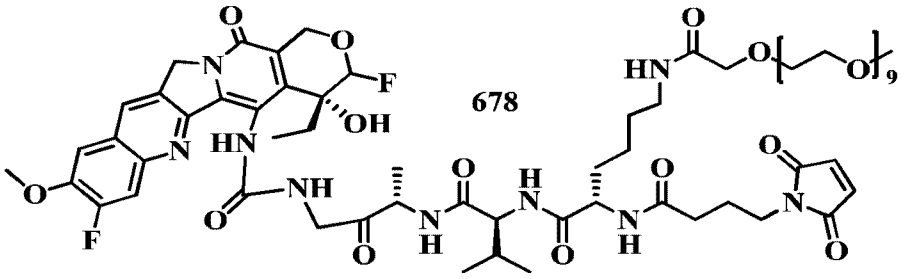

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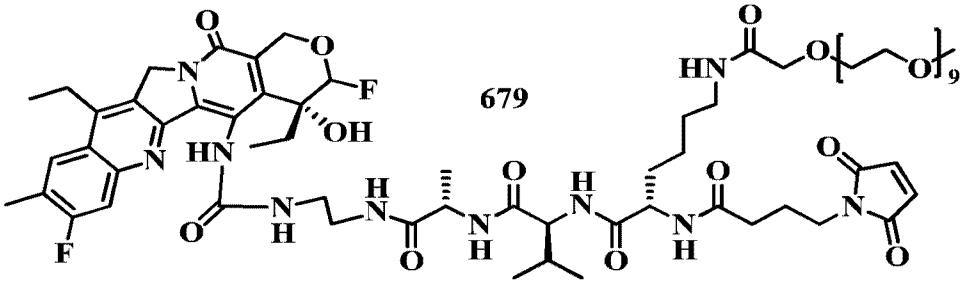

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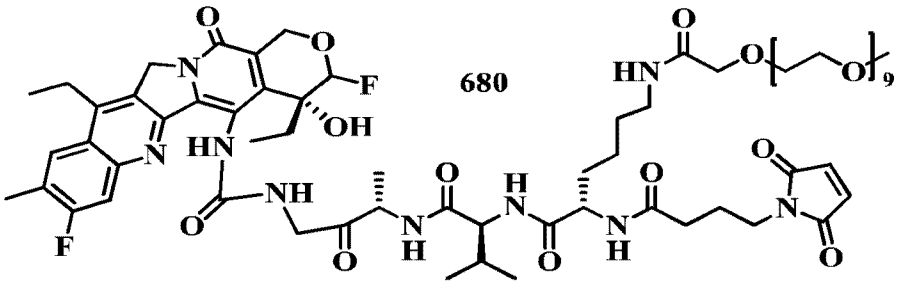

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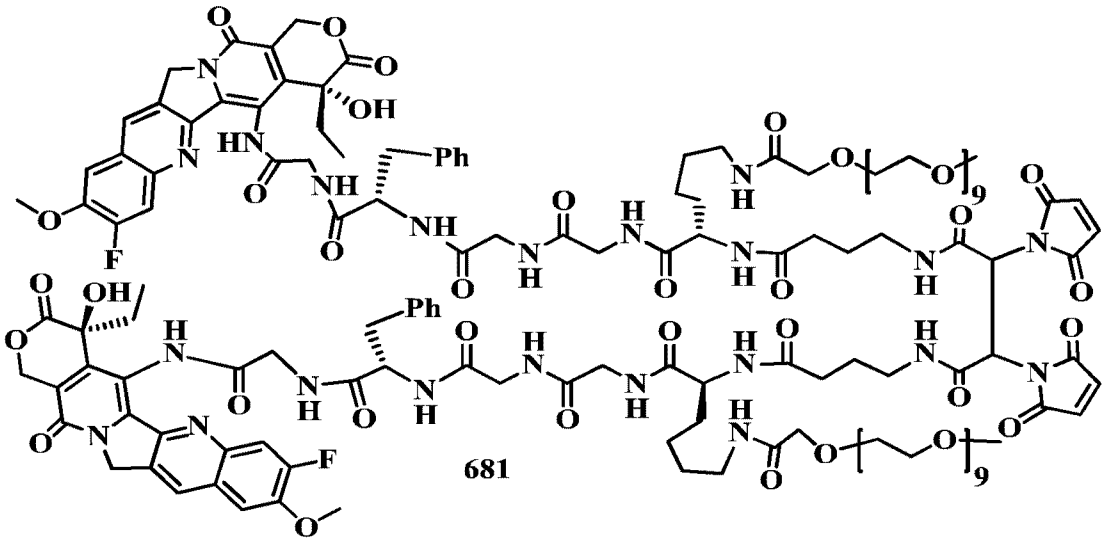

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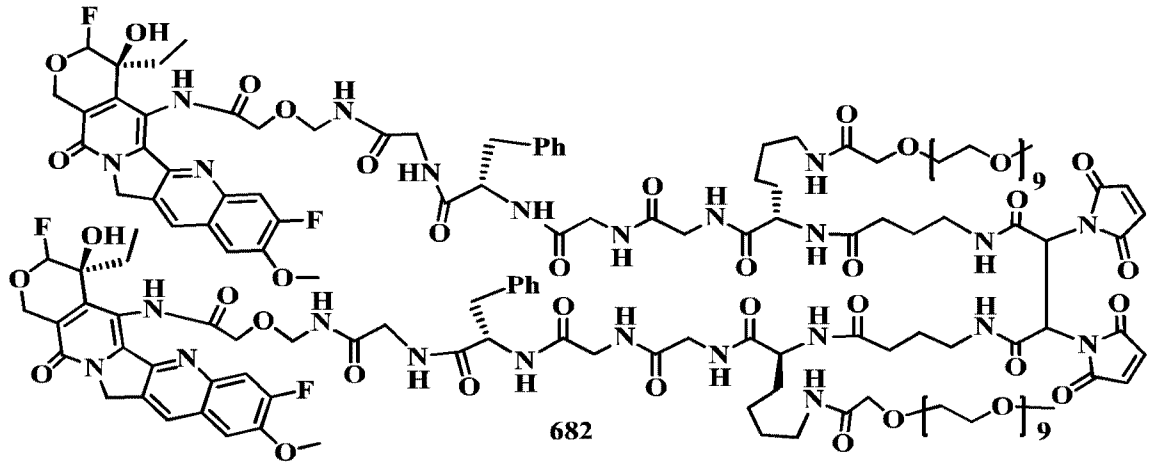

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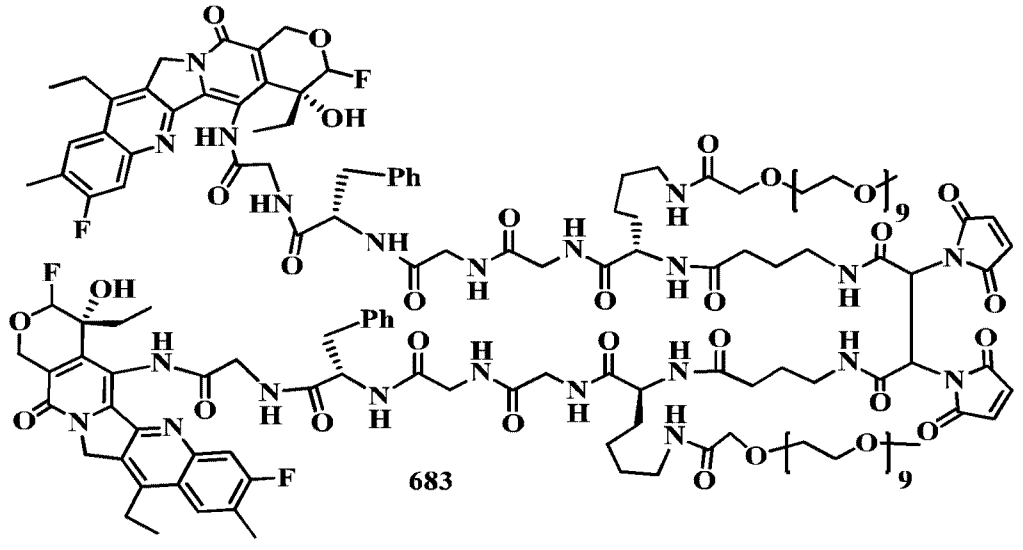

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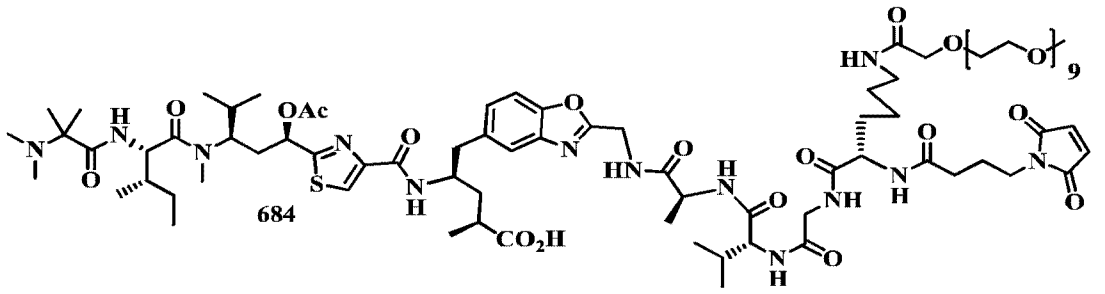

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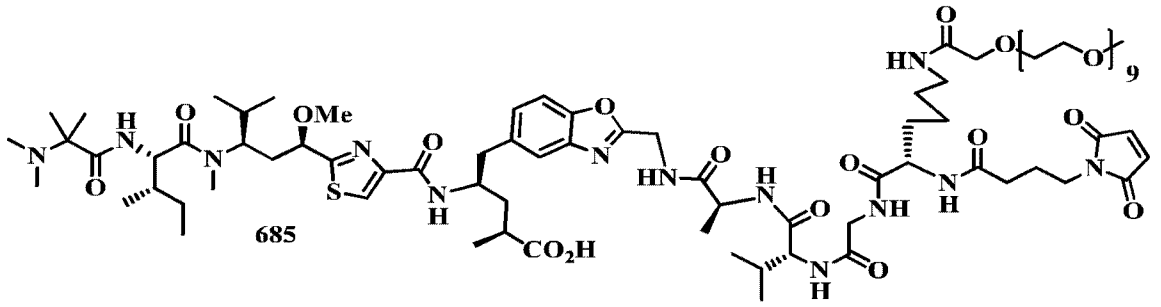

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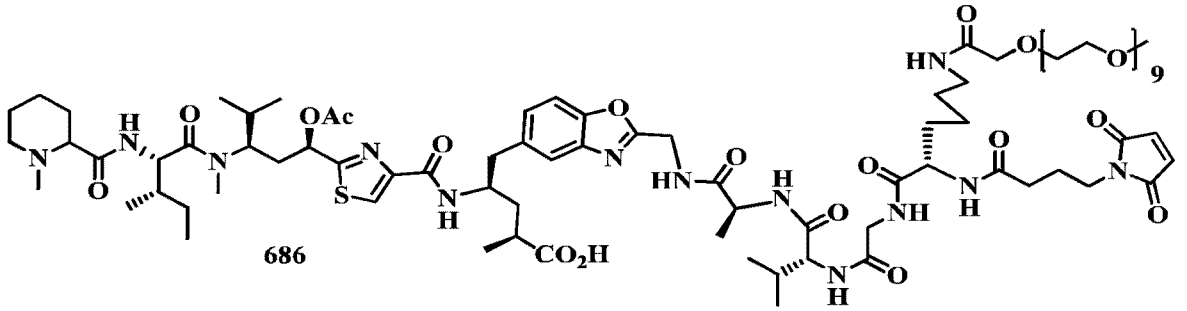

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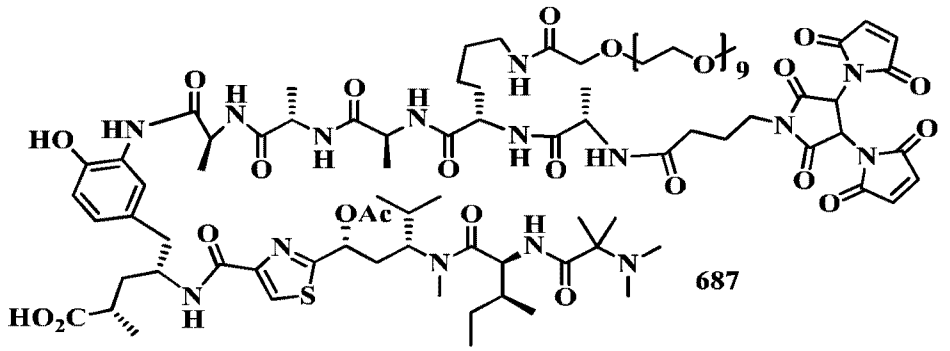

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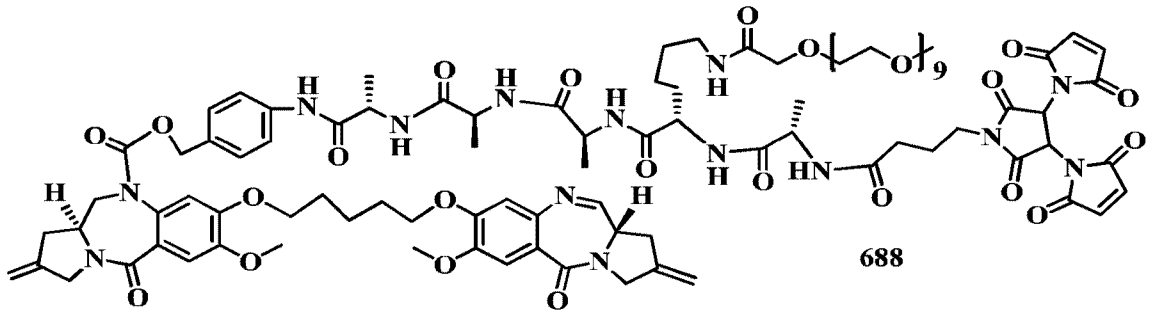

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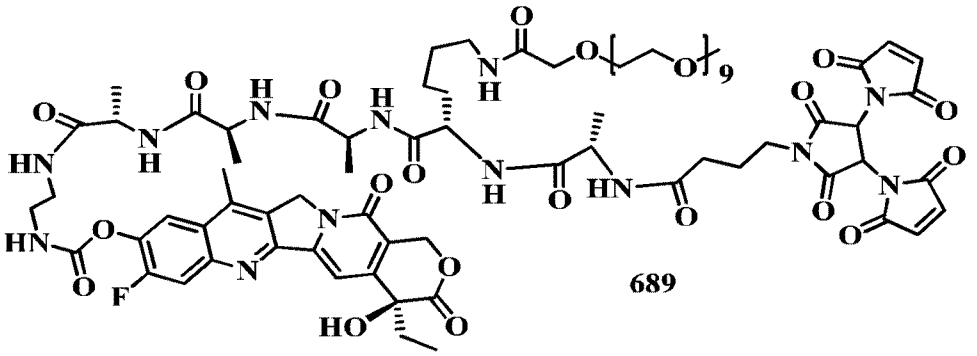

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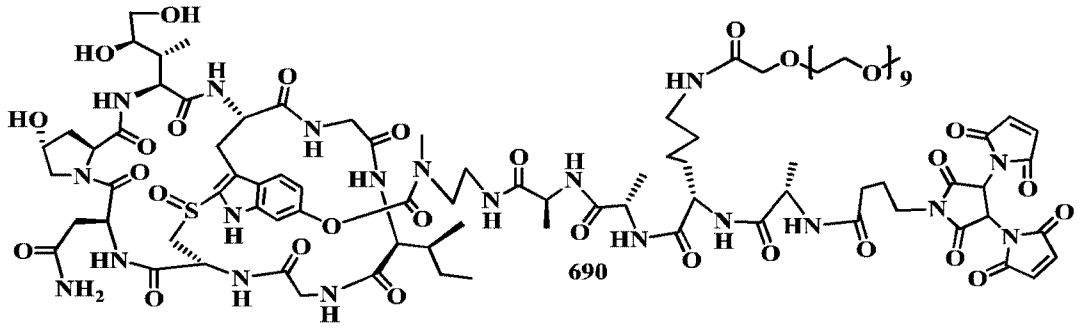

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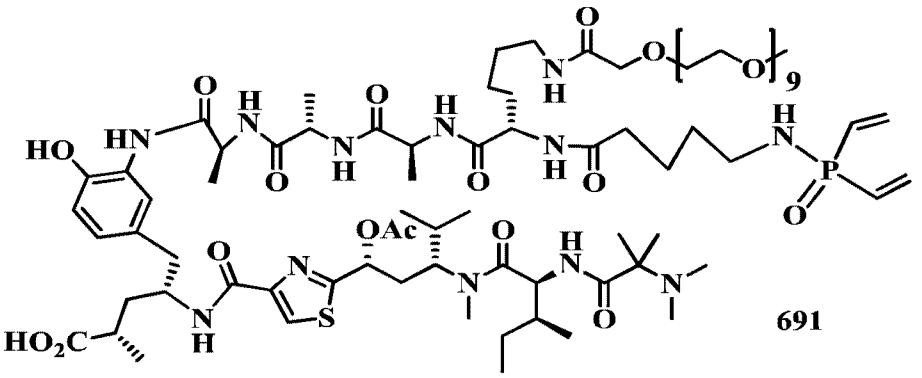

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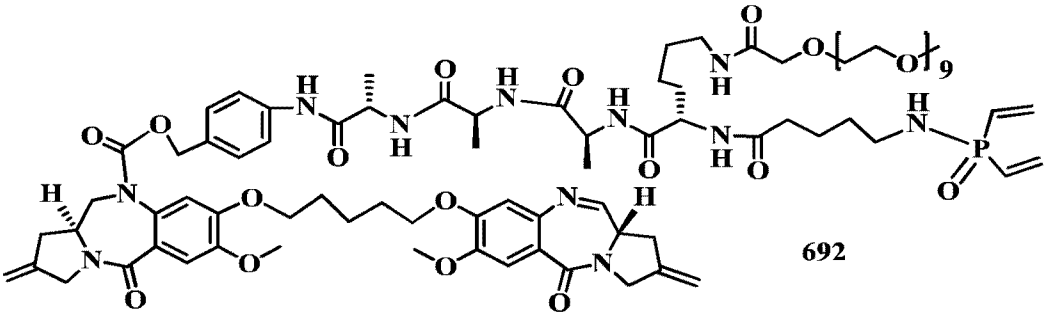

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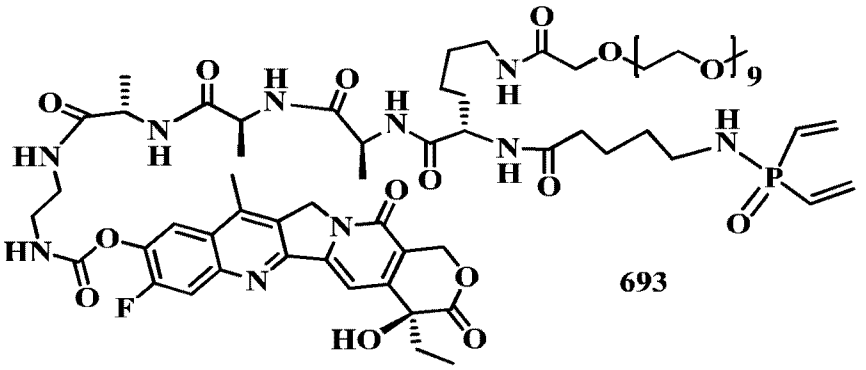

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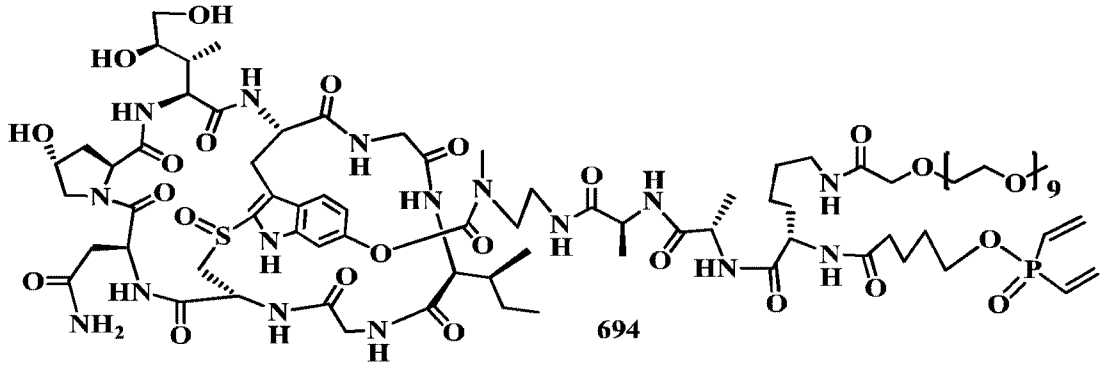

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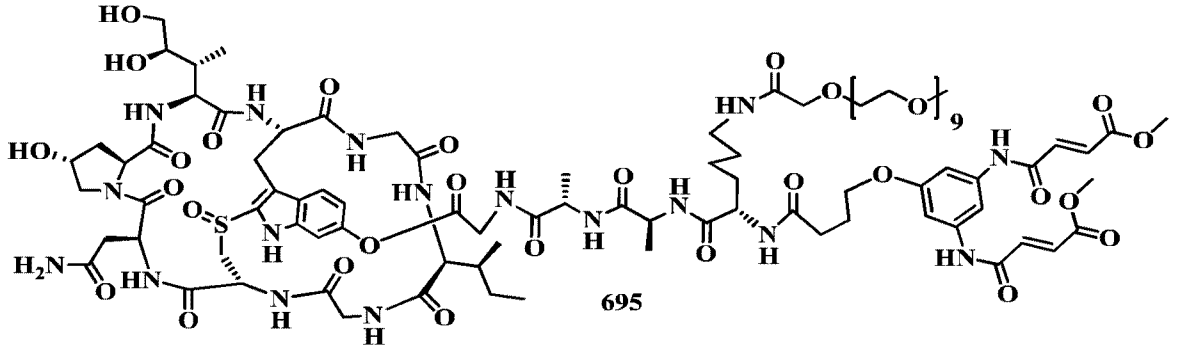

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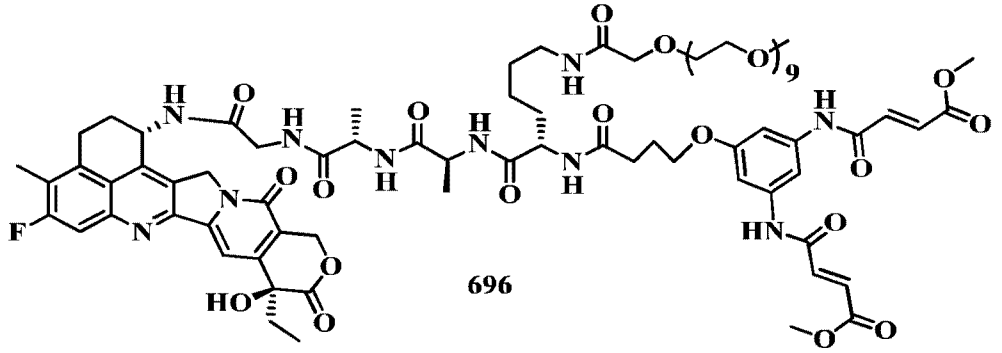

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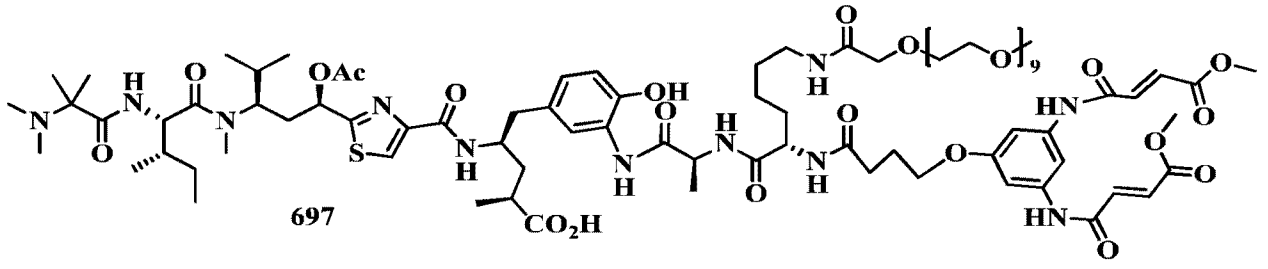

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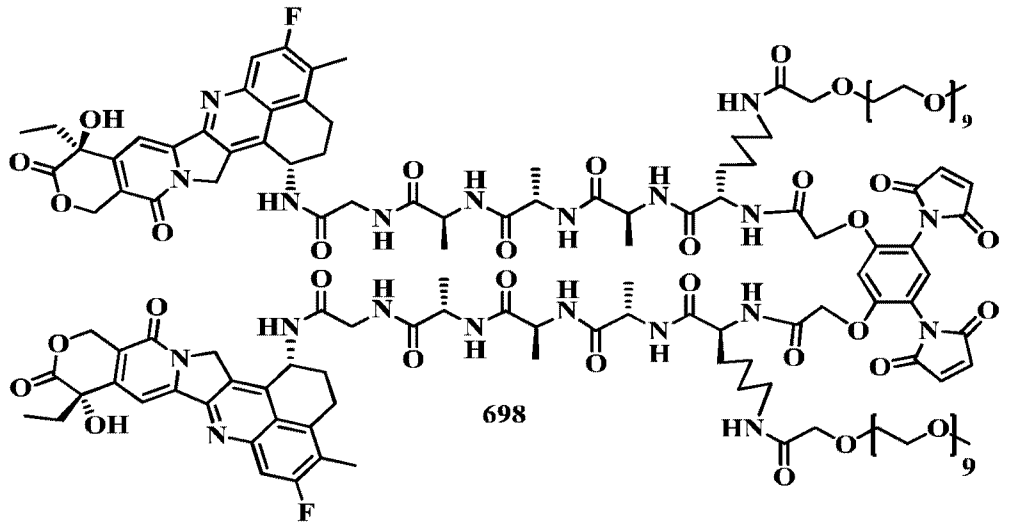

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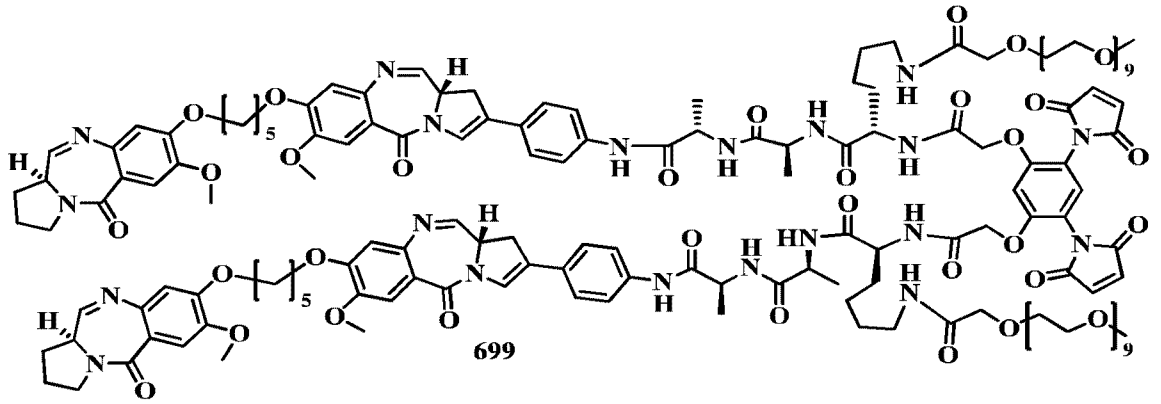

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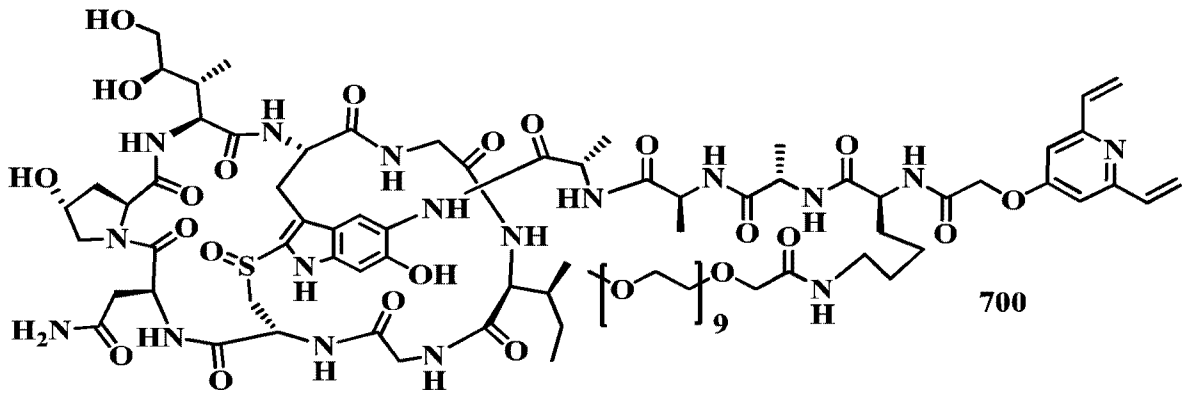

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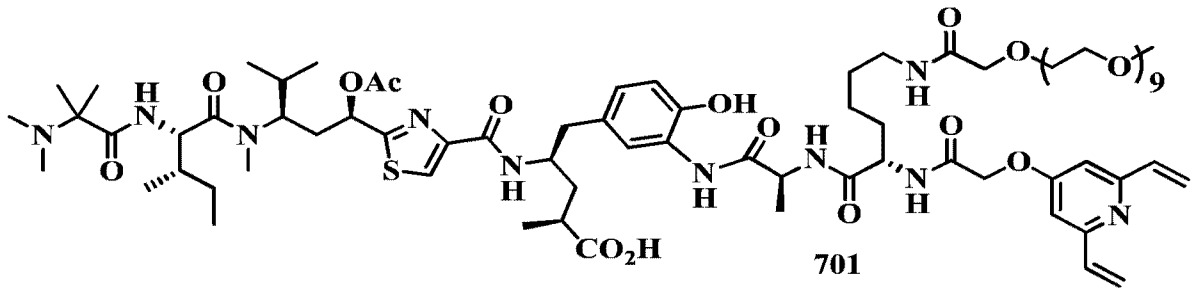

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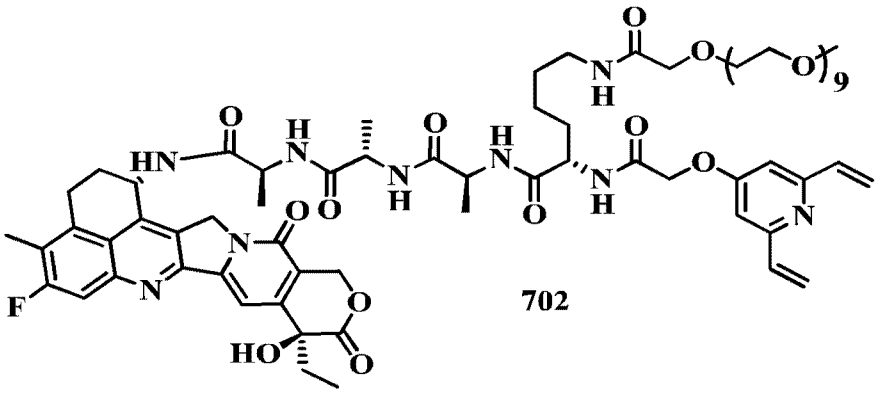

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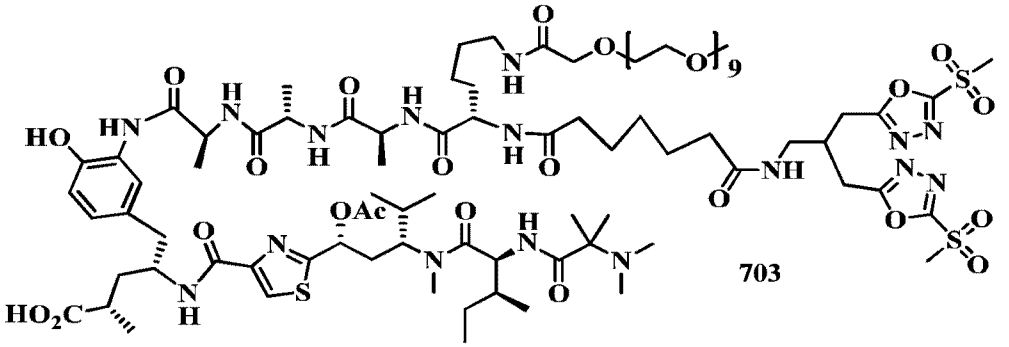

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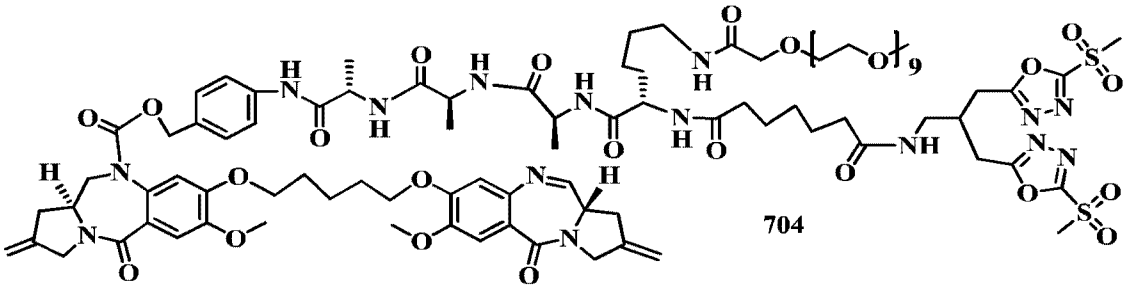

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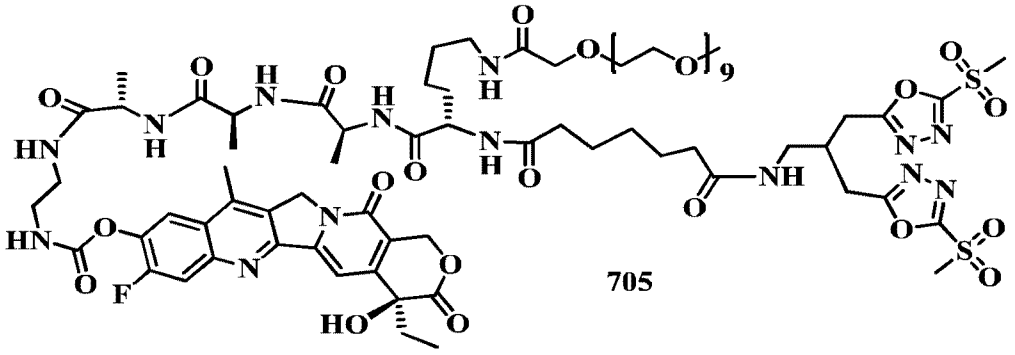

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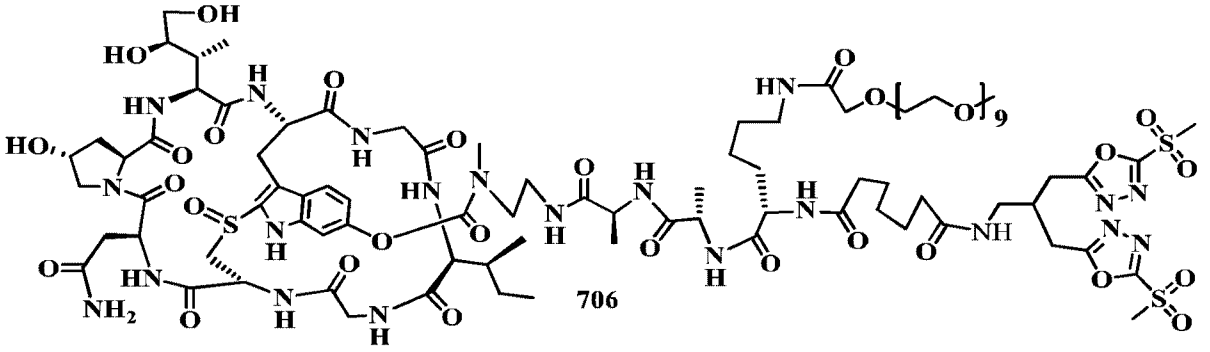

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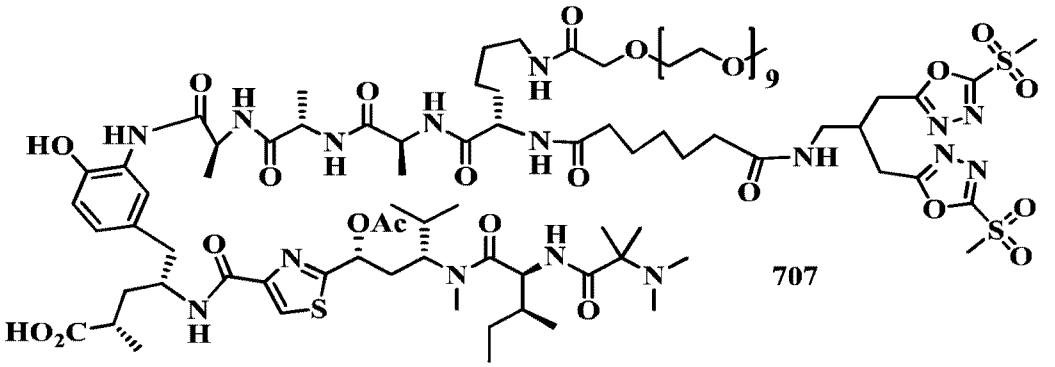

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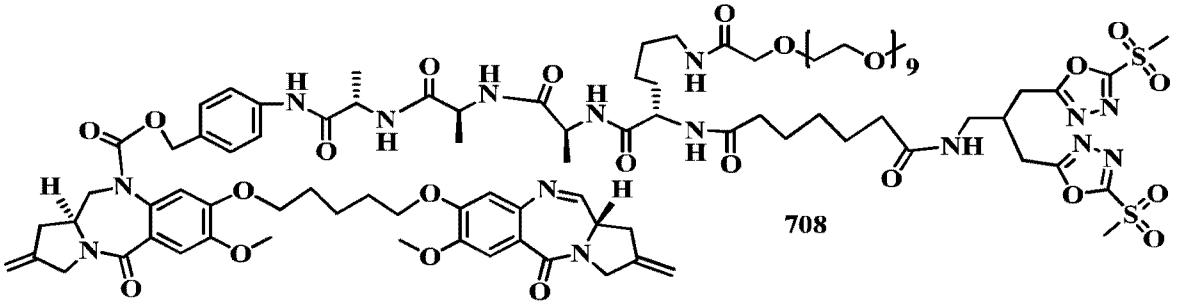

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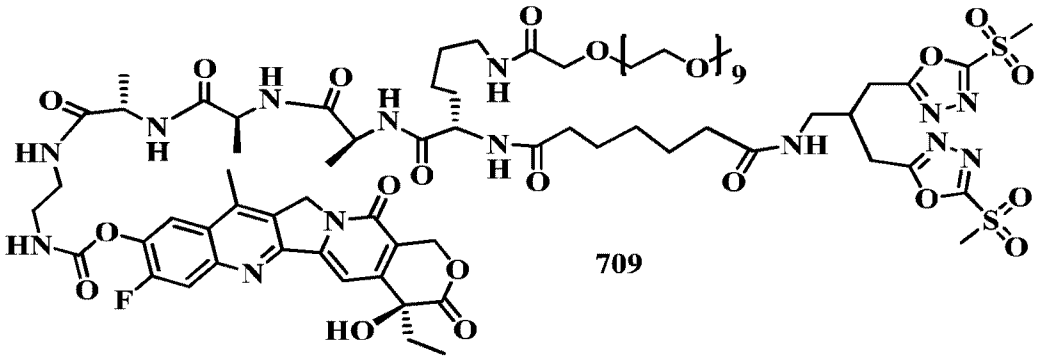

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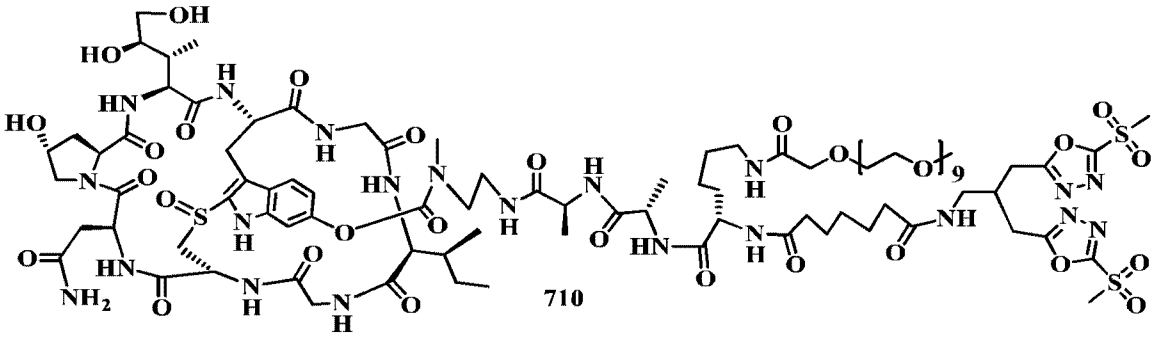
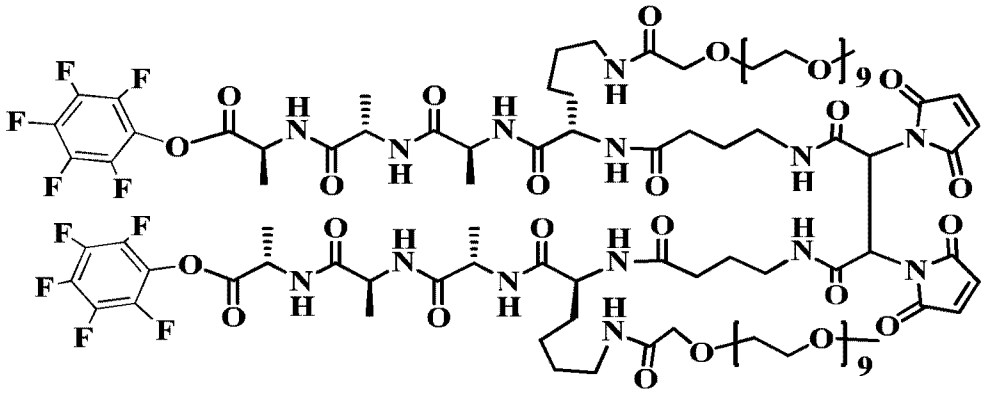


710

or a derivative with one or more isotopes, a pharmaceutically acceptable salt, hydrate, or hydrated salt thereof; or a polymorphic crystalline structure thereof; or an optical isomer, racemate, diastereomer or enantiomer thereof; wherein n is 1 -10.

In further embodiments, examples of linker molecules of formula (X), (XI), (XII), or (XIII) are demonstrated below as:



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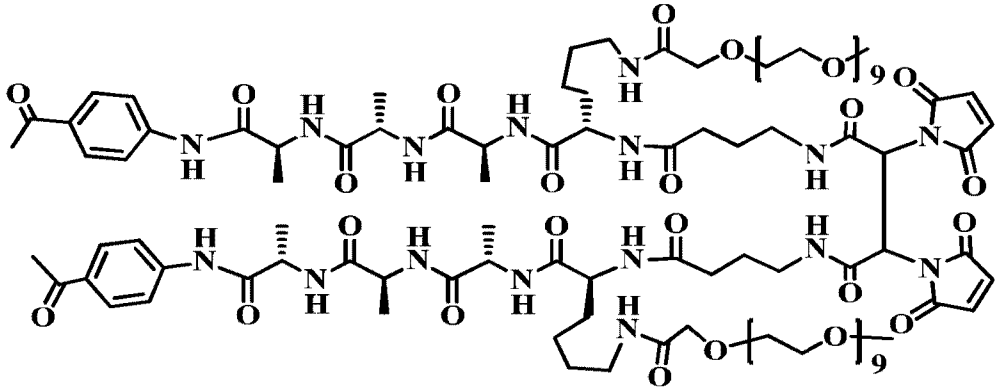

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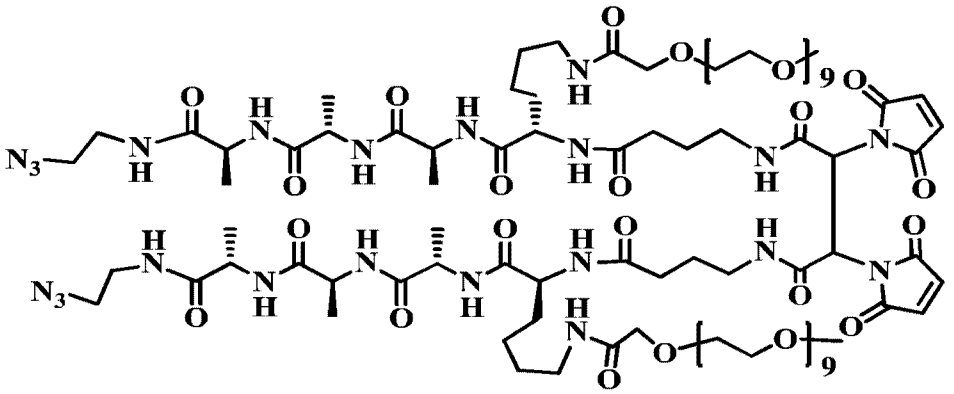

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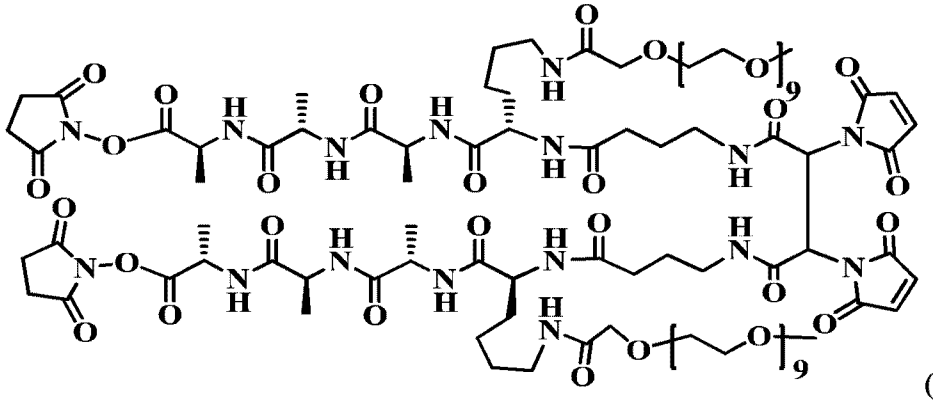

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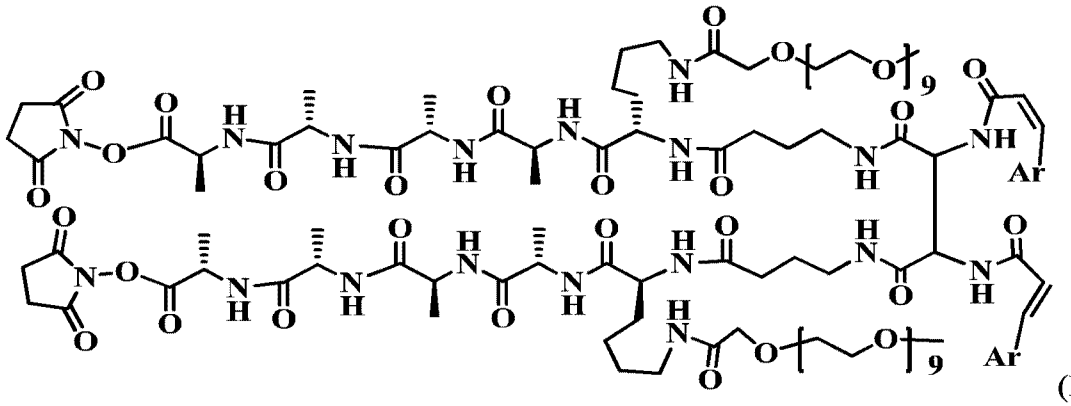

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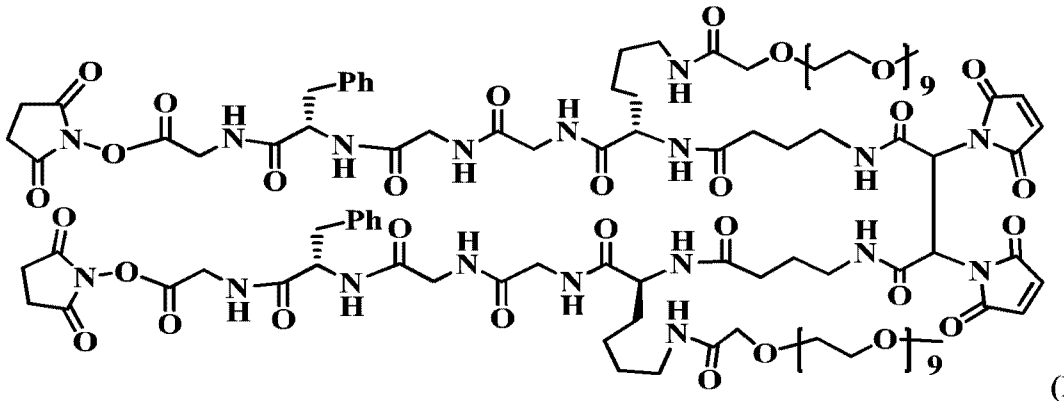
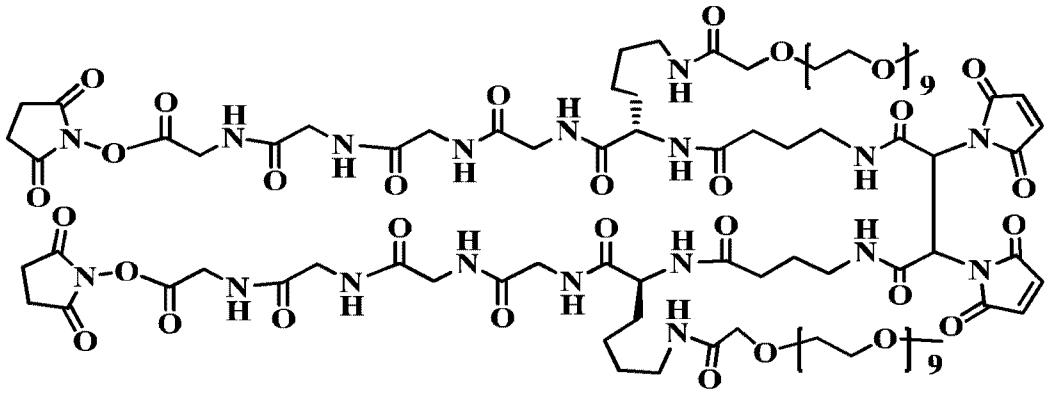


(XII-06),



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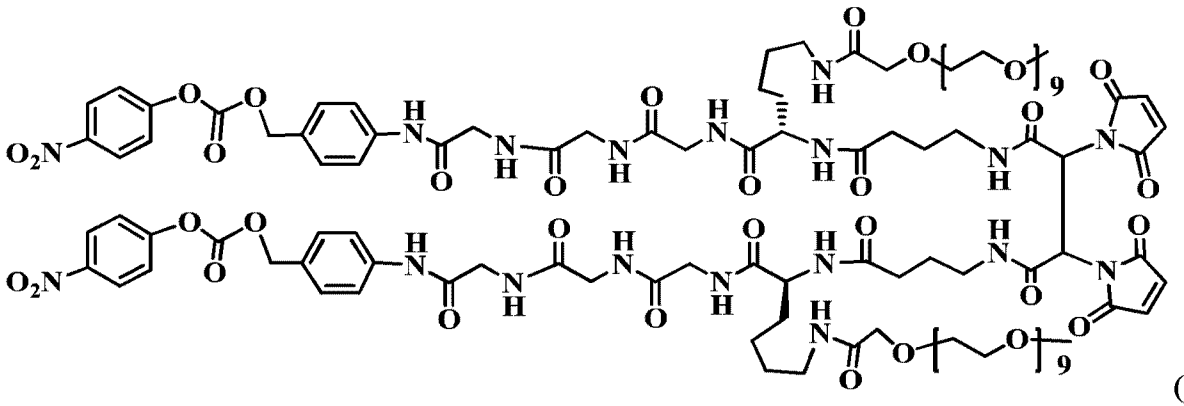

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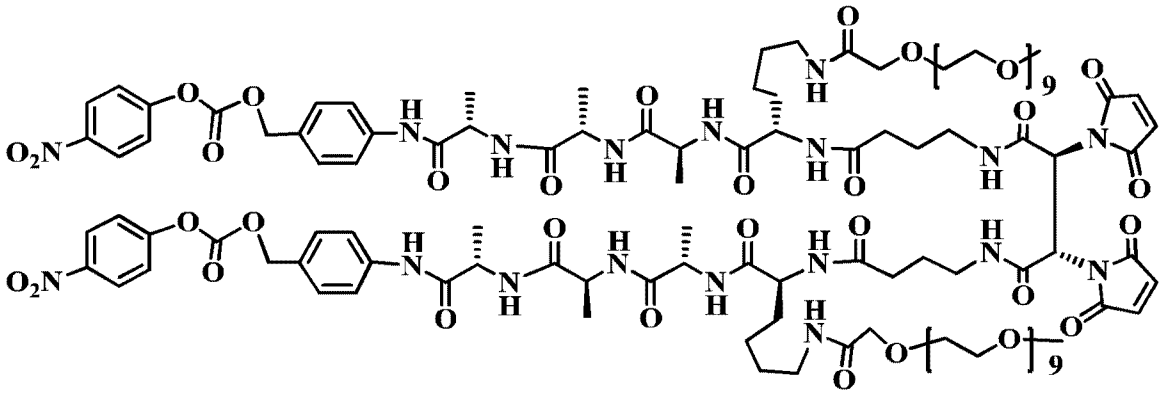

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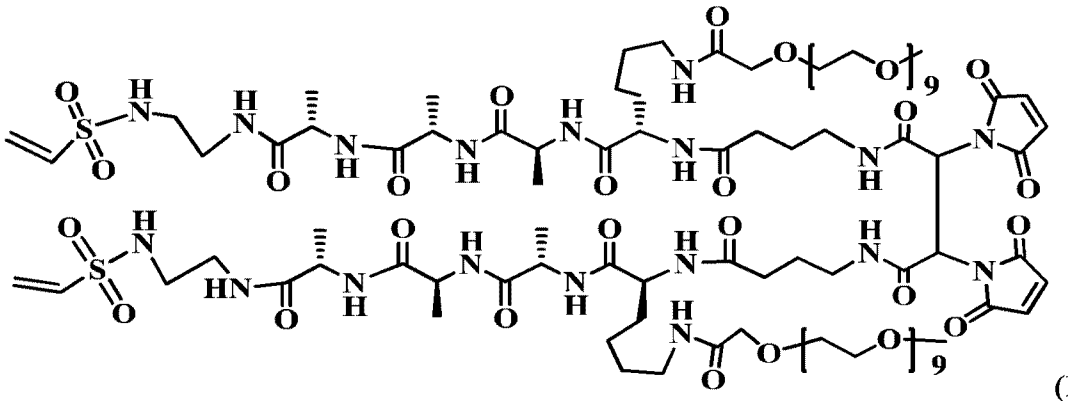

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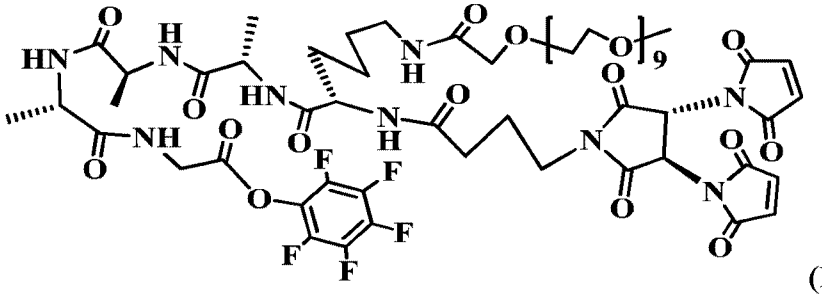
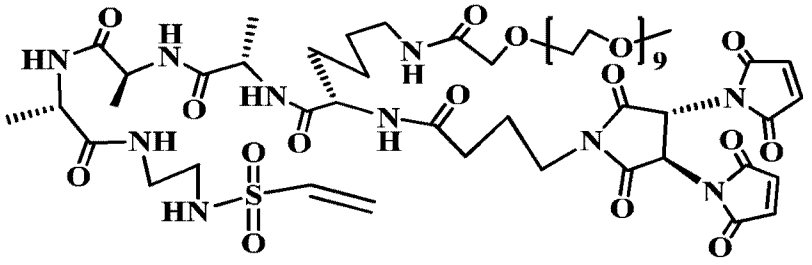
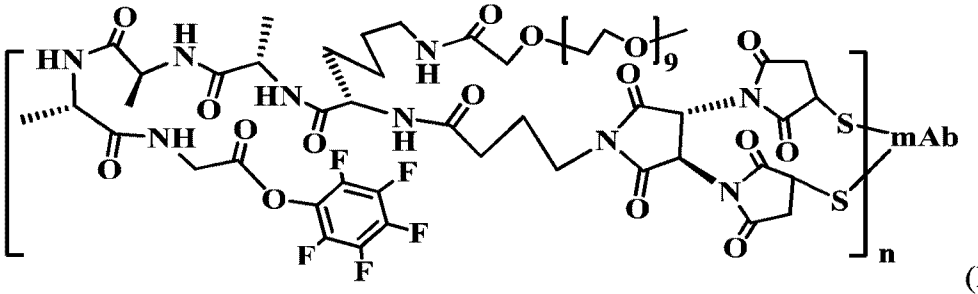


(XI-01),

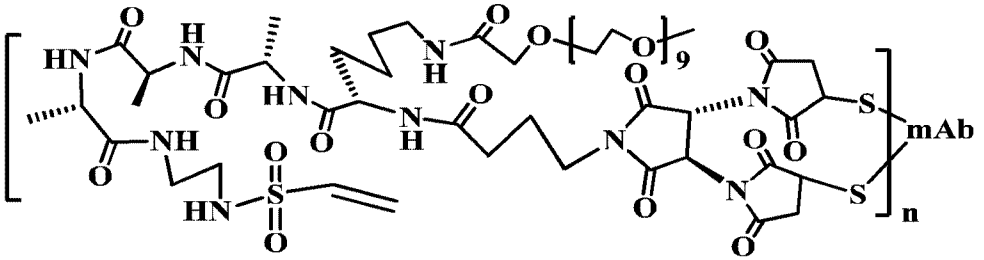


(XI-02).

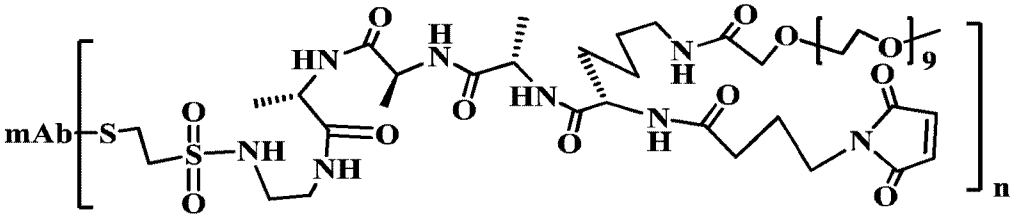
In further embodiments, examples of linker molecules of formula (XIV), (XV), (XVI) or (XVII) a are demonstrated below as:



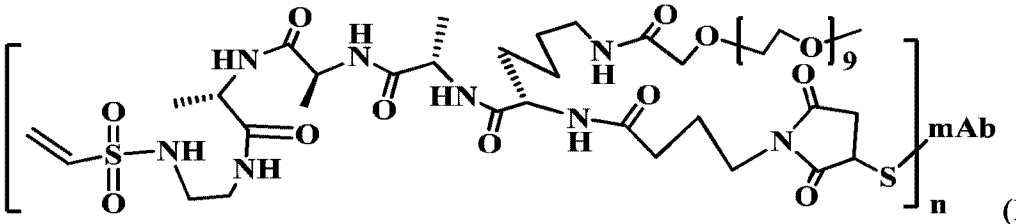
(XV-01),



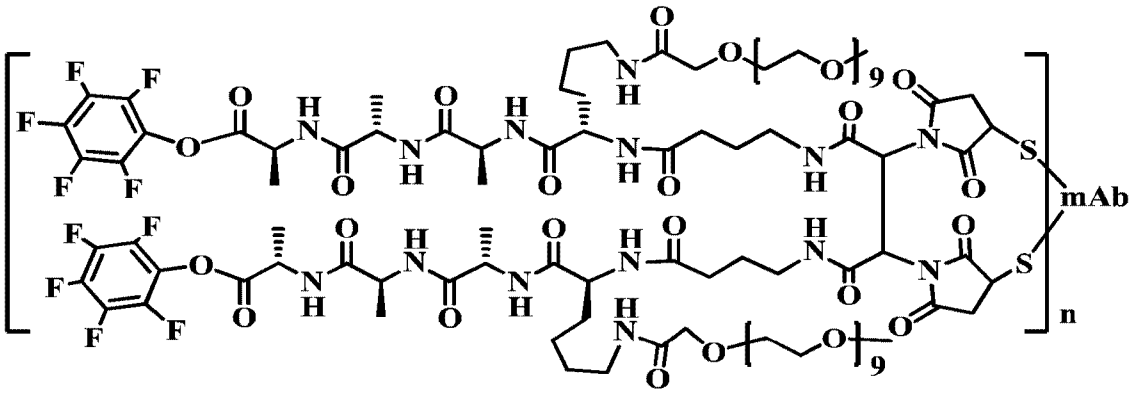
(XV-02),



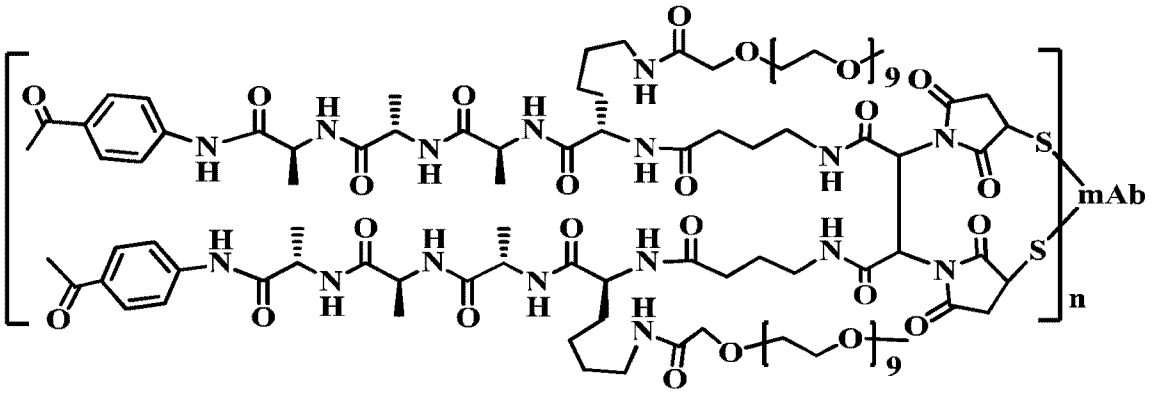
(XIV-01),



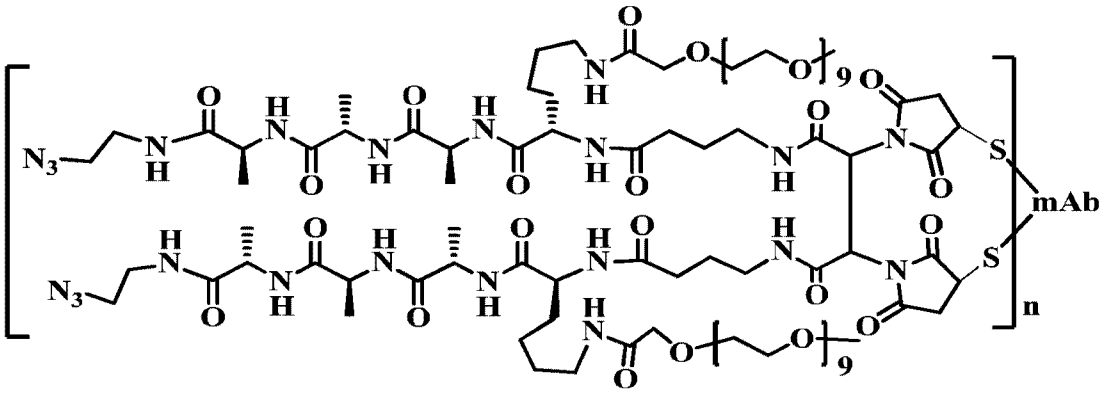
(XIV-02),



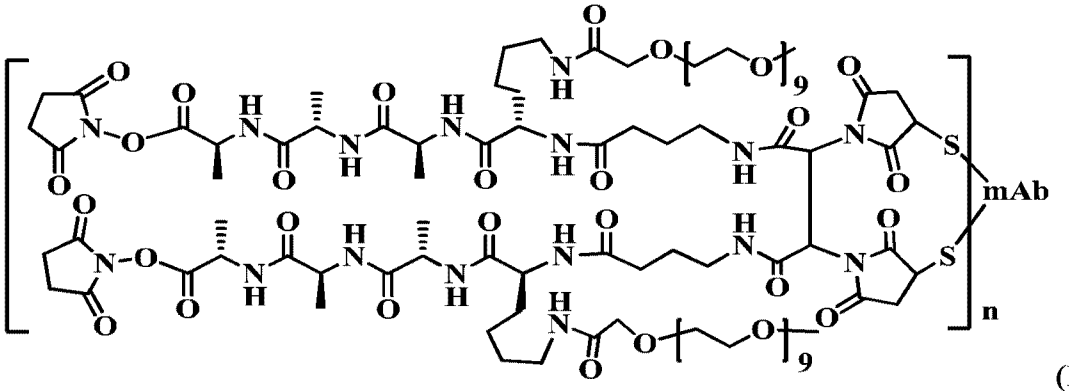
(XVI-01),



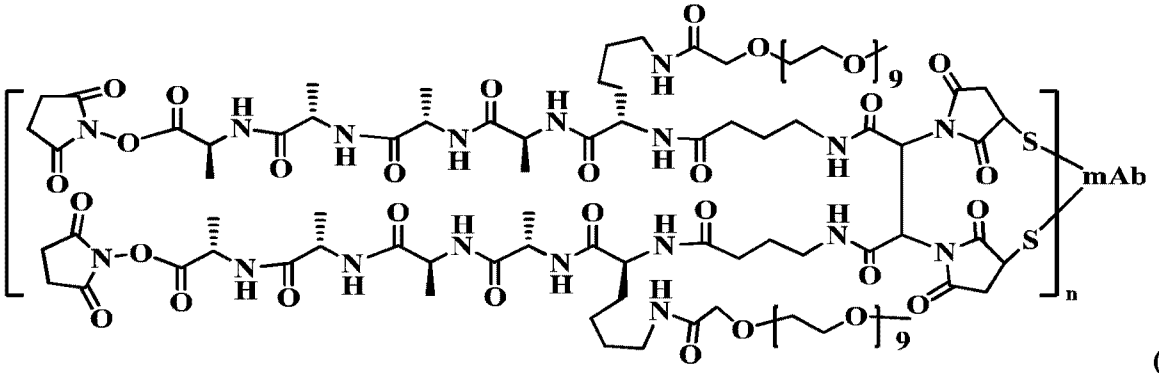
(XVI-02),



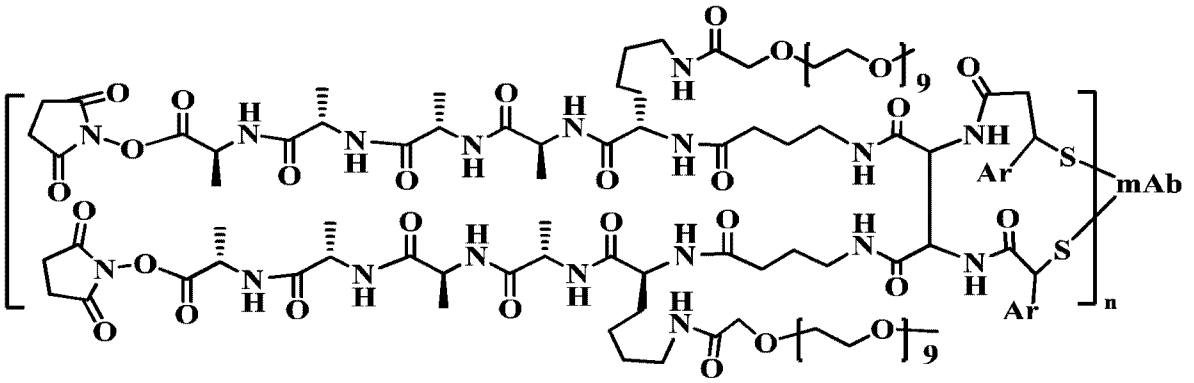
(XVI-03),



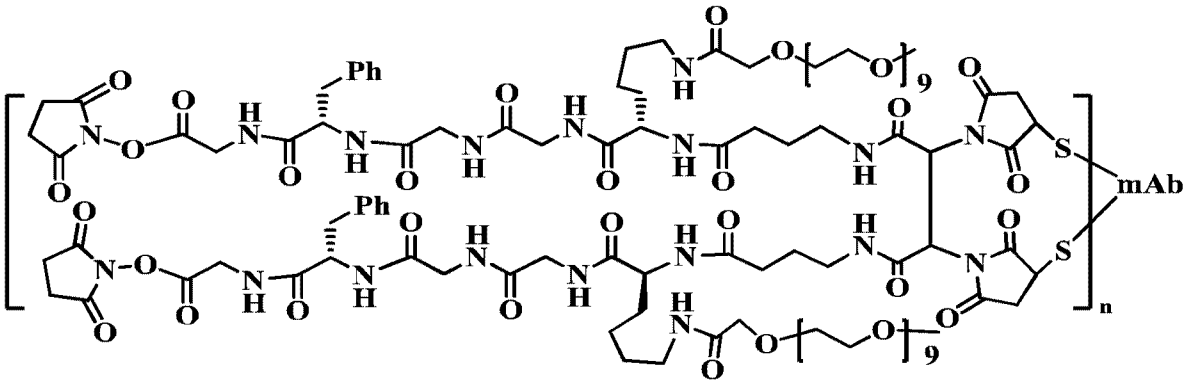
(XVI-04),



(XVI-05)



(XVI-06),



(XVI-07).

Many of the structures of the linker compounds of formula (X), (XI), (XII), (XIII), (XIV), (XV), (XVI) or (XVII) have been incorporated in the synthesis in the sections of Examples and Figures. One skilled in the art of conjugation of drugs/cytotoxic agents will readily understand that each of the linker compounds described or incorporated in the conjugates of examples of formula (VI), (VII), (VIII) or (IX) herein can be modified in such a manner for swift conjugation. The skilled artisan will also understand that many of linker compounds which are well known in art can be used in place of the linker compounds described herein for homogeneous conjugation of antibodies with this invention.

THE ANTIBODY

The antibody (mAb) used for the conjugation process is preferred a cell-binding antibody or antibody-like protein molecule that binds to, complexes with, or reacts with a moiety of a cell population sought to be therapeutically or otherwise biologically modified.

For convenience in this section and elsewhere, "antibody" should be understood to include "antibody-like protein and peptide" except where the context requires otherwise. Suitable antibody-like proteins which may be present in the conjugates of the invention include for example peptides, polypeptides, antibodies, antibody fragments, enzymes, cytokines, chemokines, receptors, blood factors, peptide hormones, toxin, transcription antibody-like proteins, or multimeric antibody-like proteins, wherein they have interchain disulfide bonds structurally.

Enzymes include carbohydrate-specific enzymes, proteolytic enzymes and the like, for example the oxidoreductases, transferases, hydrolases, lyases, isomerases and ligases disclosed by U.S. Pat. No. 4, 179, 337. Specific enzymes of interest include asparaginase, arginase, adenosine deaminase, superoxide dismutase, catalase, chymotrypsin, lipase, uricase, bilirubin oxidase, glucose oxidase, glucuronidase, galactosidase, glucocerbrosidase, and glutaminase.

Blood antibody-like proteins include albumin, transferrin, Factor VII, Factor VIII or Factor IX, von Willebrand factor, insulin, ACTH, glucagen, somatostatin, somatotropins, thymosin, parathyroid hormone, pigmentary hormones, somatomedins, erythropoietin, luteinizing hormone, hypothalamic releasing factors, antidiuretic hormones, prolactin, interleukins, interferons, for example IFN-α. or IFN-β, colony stimulating factors, haemoglobin, cytokines, antibodies, antibody fragments, chorionicgonadotropin, follicle-stimulating hormone, thyroid stimulating hormone and tissue plasminogen activator.

Other antibody-like proteins of interest are allergen antibody-like proteins disclosed by Dreborg et al Crit. Rev. Therap. Drug Carrier Syst. (1990) 6 315-365 as having reduced allergenicity when conjugated with a polymer such as poly(alkylene oxide) and consequently are suitable for use as tolerance inducers. Among the allergens disclosed are Ragweed antigen E, honeybee venom, mite allergen and the like.

Glycopolypeptides such as immunoglobulins, ovalbumin, lipase, glucocerebrosidase, lectins, tissue plasminogen activator and glycosylated interleukins, interferons and colony stimulating factors are of interest, as are immunoglobulins such as IgG, IgE, IgM, IgA, IgD and fragments thereof. Of particular interest are receptor and ligand binding antibody-like proteins and antibodies and antibody fragments which are used in clinical medicine for diagnostic and therapeutic purposes.

The antibody herein is preferred (A): the group consisting of an antibody, a antibody-like protein molecule, probody, nanobody, peptides, an antibody coating on polymeric micelle, an antibody-liposome, a lipoprotein-based drug carrier, an antibody coating on nano-particle, an antibody-dendrimer, and a particle said above coated or linked with an antibody-like protein (antibody), or a combination of said above thereof;

(B): an antibody, full-length antibodies (polyclonal antibodies, monoclonal antibodies, dimers, multimers, multispecific antibodies (e.g., bispecific antibody, trispecific antibody, or tetraspecific antibody); single chain antibodies; an antibody fragment that binds to the target cell, a monoclonal antibody, a single chain monoclonal antibody, a monoclonal antibody fragment that binds the target cell, a chimeric antibody, a chimeric antibody fragment that binds to the target cell, a domain antibody, a domain antibody fragment that binds to the target cell, a resurfaced antibody, a resurfaced single chain antibody, or a resurfaced antibody fragment that binds to the target cell, a

humanized antibody or a resurfaced antibody, a humanized single chain antibody, or a humanized antibody fragment that binds to the target cell, anti-idiotypic (anti-Id) antibodies, CDR's, diabody, triabody, tetrabody, miniantibody, a probody, a probody fragment, small immune antibody-like proteins (SIP), a lymphokine antibody-like protein, a hormone type antibody-like protein, a growth factor antibody-like protein, a colony stimulating factor antibody-like protein, a nutrient-transport antibody-like protein, large molecular weight antibody-like proteins, fusion antibody-like proteins, a kinase inhibitor antibody-like protein, gene-targeting antibody-like protein, antibody-like protein coated on nanoparticles or polymers modified with antibodies or large molecular weight antibody-like proteins;

The fragments of antibodies include Fab, Fab', $F(ab')_2$, F_v, [Parham, J. Immunol. 131, 2895-902 (1983)], fragments produced by a Fab expression library, and epitope-binding fragments of any of the above which immuno-specifically bind to cancer cell antigens, viral antigens, microbial antigens or an antibody-like protein generated by the immune system that is capable of recognizing, binding to a specific antigen or exhibiting the desired biological activity (Miller et al (2003) J. of Immunology 170: 4854-61); interferons (such as type I, II, III); peptides; lymphokines such as IL-2, IL-3, IL-4, IL-5, IL-6, IL-10, GM-CSF, interferon-gamma (IFN-γ); hormones such as insulin, TRH (thyrotropin releasing hormones), MSH (melanocyte-stimulating hormone), steroid hormones, such as androgens and estrogens, melanocyte-stimulating hormone (MSH); growth factors and colony-stimulating factors such as epidermal growth factors (EGF), granulocyte-macrophage colony-stimulating factor (GM-CSF), transforming growth factors (TGF), such as TGFα, TGFβ, insulin and insulin like growth factors (IGF-I, IGF-II) G-CSF, M-CSF and GM-CSF [Burgess, Immunology Today, 5, 155-8 (1984)]; vaccinia growth factors (VGF); fibroblast growth factors (FGFs); smaller molecular weight antibody-like proteins, poly-peptide, peptides and peptide hormones, such as bombesin, gastrin, gastrin-releasing peptide; platelet-derived growth factors; interleukin and cytokines, such as interleukin-2 (IL-2), interleukin-6 (IL-6), leukemia inhibitory factors, granulocyte-macrophage colony-stimulating factor (GM-CSF); vitamins, such as folate; apoproteins and glycoproteins, such as transferrin [O'Keefe et al, 260 J. Biol. Chem. 932-7 (1985)]; sugar-binding proteins or lipoproteins, such as lectins; cell nutrient-transport molecules; and small molecular inhibitors, such as prostate-specific membrane antigen (PSMA) inhibitors and small molecular tyrosine kinase inhibitors (TKI), non-peptides or any other cell binding molecule or substance, such as bioactive polymers (Dhar, et al, Proc. Natl. Acad. Sci. 2008, 105, 17356-61); bioactive dendrimers (Lee, et al, Nat. Biotechnol. 2005, 23, 1517-26; Almutairi, et al; Proc. Natl. Acad. Sci. 2009, 106, 685-90); nanoparticles (Liong, et al, ACS Nano, 2008, 2, 1309-12; Medarova, et al, Nat. Med. 2007, 13, 372-7; Javier, et al, Bioconjugate Chem. 2008, 19, 1309-12); liposomes

(Medinai, et al, Curr. Phar. Des. 2004, 10, 2981-9); viral capsides (Flenniken, et al, Viruses Nanotechnol. 2009, 327, 71-93).

In general, a monoclonal antibody is preferred as a cell-surface binding agent if an appropriate one is available. And the antibody may be murine, human, humanized, chimeric, or derived from other species.

Production of antibodies used in the present invention involves in vivo or in vitro procedures or combinations thereof. Methods for producing polyclonal anti-receptor peptide antibodies are well-known in the art, such as in U.S. Pat. No. 4, 493, 795 (to Nestor et al). A monoclonal antibody is typically made by fusing myeloma cells with the spleen cells from a mouse that has been immunized with the desired antigen (Köhler, G.; Milstein, C. (1975). Nature 256: 495-7). The detailed procedures are described in "Antibodies--A Laboratory Manual", Harlow and Lane, eds., Cold Spring Harbor Laboratory Press, New York (1988), which is incorporated herein by reference. Particularly monoclonal antibodies are produced by immunizing mice, rats, hamsters or any other mammal with the antigen of interest such as the intact target cell, antigens isolated from the target cell, whole virus, attenuated whole virus, and viral proteins. Splenocytes are typically fused with myeloma cells using polyethylene glycol (PEG) 6000. Fused hybrids are selected by their sensitivity to HAT (hypoxanthine-aminopterin-thymine). Hybridomas producing a monoclonal antibody useful in practicing this invention are identified by their ability to immunoreact specified receptors or inhibit receptor activity on target cells.

A monoclonal antibody used in the present invention can be produced by initiating a monoclonal hybridoma culture comprising a nutrient medium containing a hybridoma that secretes antibody molecules of the appropriate antigen specificity. The culture is maintained under conditions and for a time period sufficient for the hybridoma to secrete the antibody molecules into the medium. The antibody-containing medium is then collected. The antibody molecules can then be further isolated by well-known techniques, such as using protein-A affinity chromatography; anion, cation, hydrophobic, or size exclusive chromatographies (particularly by affinity for the specific antigen after protein A, and sizing column chromatography); centrifugation, differential solubility, or by any other standard technique for the purification of proteins.

Media useful for the preparation of these compositions are both well-known in the art and commercially available and include synthetic culture media. An exemplary synthetic medium is Dulbecco's minimal essential medium (DMEM; Dulbecco et al., Virol. 8, 396 (1959)) supplemented with 4.5 gm/l glucose, 0~20 mM glutamine, 0~20% fetal calf serum, several ppm amount of heavy metals, such as Cu, Mn, Fe, or Zn, etc, or/and the other heavy metals added in their salt forms, and with an anti-foaming agent, such as polyoxyethylene-polyoxypropylene block copolymer.

In addition, antibody-producing cell lines can also be created by techniques other than fusion, such as direct transformation of B lymphocytes with oncogenic DNA, or transfection with an oncovirus, such as Epstein-Barr virus (EBV, also called human herpesvirus 4 (HHV-4)) or Kaposi's sarcoma-associated herpesvirus (KSHV). See, U.S. Pat. Nos. 4, 341, 761; 4, 399, 121; 4, 427, 783; 4, 444, 887; 4, 451, 570; 4, 466, 917; 4, 472, 500; 4, 491, 632; 4, 493, 890. A monoclonal antibody may also be produced via an anti-receptor peptide or peptides containing the carboxyl terminal as described well-known in the art. See Niman et al., Proc. Natl. Acad. Sci. USA, 80: 4949-53 (1983); Geysen et al., Proc. Natl. Acad. Sci. USA, 82: 178-82 (1985); Lei et al. Biochemistry 34(20): 6675-88, (1995). Typically, the anti-receptor peptide or a peptide analog is used either alone or conjugated to an immunogenic carrier, as the immunogen for producing anti-receptor peptide monoclonal antibodies.

There are also a number of other well-known techniques for making monoclonal antibodies as binding molecules in this invention. Particularly useful are methods of making fully human antibodies. One method is phage display technology which can be used to select a range of human antibodies binding specifically to the antigen using methods of affinity enrichment. Phage display has been thoroughly described in the literature and the construction and screening of phage display libraries are well known in the art, see, e.g., Dente et al, Gene. 148(1):7-13 (1994); Little et al, Biotechnol Adv. 12(3): 539-55 (1994); Clackson et al., Nature 352: 264-8 (1991); Huse et al., Science 246: 1275-81 (1989).

Monoclonal antibodies derived by hybridoma technique from another species than human, such as mouse, can be humanized to avoid human anti-mouse antibodies when infused into humans. Among the more common methods of humanization of antibodies are complementarity-determining region grafting and resurfacing. These methods have been extensively described, see e.g. U.S. Pat. Nos. 5, 859, 205 and 6, 797, 492; Liu et al, Immunol Rev. 222: 9-27 (2008); Almagro et al, Front Biosci. 13: 1619-33 (2008); Lazar et al, Mol Immunol. 44(8): 1986-98 (2007); Li et al, Proc. Natl. Acad. Sci. U S A. 103(10): 3557-62 (2006) each incorporated herein by reference. Fully human antibodies can also be prepared by immunizing transgenic mice, rabbits, monkeys, or other mammals, carrying large portions of the human immunoglobulin heavy and light chains, with an immunogen. Examples of such mice are: the Xenomouse. (Abgenix/Amgen), the HuMAb-Mouse (Medarex/BMS), the VelociMouse (Regeneron), see also U.S. Pat. Nos. 6, 596, 541, 6, 207, 418, 6, 150, 584, 6, 111, 166, 6, 075, 181, 5, 922, 545, 5, 661, 016, 5, 545, 806, 5, 436, 149 and 5, 569, 825. In human therapy, murine variable regions and human constant regions can also be fused to construct called "chimeric antibodies" that are considerably less immunogenic in man than murine mAbs (Kipriyanov et al, Mol Biotechnol. 26: 39-60 (2004); Houdebine, Curr Opin Biotechnol. 13:

625-9 (2002) each incorporated herein by reference). In addition, site-directed mutagenesis in the variable region of an antibody can result in an antibody with higher affinity and specificity for its antigen (Brannigan et al, Nat Rev Mol Cell Biol. 3: 964-70, (2002)); Adams et al, J Immunol Methods. 231: 249-60 (1999)) and exchanging constant regions of a mAb can improve its ability to mediate effector functions of binding and cytotoxicity.

Antibodies immunospecific for a malignant cell antigen can also be obtained commercially or produced by any method known to one of skill in the art such as, e.g., chemical synthesis or recombinant expression techniques. The nucleotide sequence encoding antibodies immune-specific for a malignant cell antigen can be obtained commercially, e.g., from the GenBank database or a database like it, the literature publications, or by routine cloning and sequencing.

Apart from an antibody, an antibody like peptide or protein that bind/block/target or in some other way interact with the epitopes or corresponding receptors on a targeted cell can be used as a binding molecule. These antibody like peptides or proteins could be any random peptide or proteins that have an affinity for the epitopes or corresponding receptors and they don't necessarily have to be of the immune-globulin family. These peptides can be isolated by similar techniques as for phage display antibodies (Szardenings, J Recept Signal Transduct Res. 2003, 23(4): 307-49). The use of peptides from such random peptide libraries can be similar to antibodies and antibody fragments. The binding molecules of antibody like peptides or proteins may be conjugated on or linked to a large molecules or materials, such as, but is not limited, an albumin, a polymer, a liposome, a nano particle, a dendrimer, as long as such attachment permits the peptide or protein to retain its antigen binding specificity.

Examples of antibodies used for conjugation of drugs of this prevention for treating cancer, autoimmune disease, and/or infectious disease include, but are not limited to, 3F8 (anti-GD2), Abagovomab (anti CA-125), Abciximab (anti CD41 (integrin alpha-IIb), Adalimumab (anti-TNF-α), Adecatumumab (anti-EpCAM, CD326), Afelimomab (anti-TNF-α); Afutuzumab (anti-CD20), Alacizumab pegol (anti-VEGFR2), ALD518 (anti-IL-6), Alemtuzumab (Campath, MabCampath, anti- CD52), Altumomab (anti-CEA), Anatumomab (anti-TAG-72), Anrukinzumab (IMA-638, anti-IL-13), Apolizumab (anti-HLA-DR), Arcitumomab (anti-CEA), Aselizumab (anti-L-selectin (CD62L), Atlizumab (tocilizumab, Actemra, RoActemra, anti-IL-6 receptor), Atorolimumab (anti-Rhesus factor), Bapineuzumab (anti-beta amyloid), Basiliximab (Simulect, antiCD25 (α chain of IL-2 receptor), Bavituximab (anti-phosphatidylserine), Bectumomab (LymphoScan, anti-CD22), Belimumab (Benlysta, LymphoStat-B, anti-BAFF), Benralizumab (anti-CD125), Bertilimumab (anti-CCL11 (eotaxin-1)), Besilesomab (Scintimun, anti-CEA-related antigen), Bevacizumab (Avastin, anti-VEGF-A), Biciromab (FibriScint, anti-fibrin II beta chain), Bivatuzumab (anti-CD44

v6), Blinatumomab (BiTE, anti-CD19), Brentuximab (cAC10, anti-CD30 TNFRSF8), Briakinumab (anti-IL-12, IL-23) Canakinumab (Ilaris, anti-IL-1), Cantuzumab (C242, anti-CanAg), Capromab, Catumaxomab (Removab, anti-EpCAM, anti-CD3), CC49 (anti-TAG-72), Cedelizumab (anti-CD4), Certolizumab pegol (Cimzia anti-TNF-α), Cetuximab (Erbitux, IMC-C225, anti-EGFR), Citatuzumab bogatox (anti-EpCAM), Cixutumumab (anti-IGF-1), Clenoliximab (anti-CD4), Clivatuzumab (anti-MUC1), Conatumumab (anti-TRAIL-R2), CR6261 (anti-Influenza A hemagglutinin), Dacetuzumab (anti-CD40), Daclizumab (Zenapax, anti-CD25 (α chain of IL-2 receptor)), Daratumumab (anti-CD38 (cyclic ADP ribose hydrolase), Denosumab (Prolia, anti-RANKL), Detumomab (anti-B-lymphoma cell), Dorlimomab, Dorlixizumab, Ecromeximab (anti-GD3 ganglioside), Eculizumab (Soliris, anti-C5), Edobacomab (anti-endotoxin), Edrecolomab (Panorex, MAb17-1A, anti-EpCAM), Efalizumab (Raptiva, anti-LFA-1 (CD11a), Efungumab (Mycograb, anti-Hsp90), Elotuzumab (anti-SLAMF7), Elsilimomab (anti-IL-6), Enlimomab pegol (anti-ICAM-1 (CD54)), Epitumomab (anti-episialin), Epratuzumab (anti-CD22), Erlizumab (anti-ITGB2 (CD18)), Ertumaxomab (Rexomun, anti-HER2/neu, CD3), Etaracizumab (Abegrin, anti-integrin $\alpha_v\beta_3$), Exbivirumab (anti-hepatitis B surface antigen), Fanolesomab (NeutroSpec, anti-CD15), Faralimomab (anti-interferon receptor), Farletuzumab (anti-folate receptor 1), Felvizumab (anti-respiratory syncytial virus), Fezakinumab (anti-IL-22), Figitumumab (anti-IGF-1 receptor), Fontolizumab (anti-IFN-γ), Foravirumab (anti-rabies virus glycoprotein), Fresolimumab (anti-TGF-β), Galiximab (anti-CD80), Gantenerumab (anti- beta amyloid), Gavilimomab (anti-CD147 (basigin)), Gemtuzumab (anti-CD33), Girentuximab (anti-carbonic anhydrase 9), Glembatumumab (CR011, anti-GPNMB), Golimumab (Simponi, anti-TNF-α), Gomiliximab (anti-CD23 (IgE receptor)), Ibalizumab (anti-CD4), Ibritumomab (anti-CD20), Igovomab (Indimacis-125, anti-CA-125), Imciromab (Myoscint, anti-cardiac myosin), Infliximab (Remicade, anti-TNF-α), Intetumumab (anti-CD51), Inolimomab (anti-CD25 (α chain of IL-2 receptor)), Inotuzumab (anti-CD22), Ipilimumab (anti-CD152), Iratumumab (anti- CD30 (TNFRSF8)), Keliximab (anti-CD4), Labetuzumab (CEA-Cide, anti-CEA), Lebrikizumab (anti- IL-13), Lemalesomab (anti-NCA-90 (granulocyte antigen)), Lerdelimumab (anti-TGF beta 2), Lexatumumab (anti-TRAIL-R2), Libivirumab (anti-hepatitis B surface antigen), Lintuzumab (anti-CD33), Lucatumumab (anti-CD40), Lumiliximab (anti- CD23 (IgE receptor), Mapatumumab (anti-TRAIL-R1), Maslimomab (anti- T-cell receptor), Matuzumab (anti-EGFR), Mepolizumab (Bosatria, anti-IL-5), Metelimumab (anti-TGF beta 1), Milatuzumab (anti-CD74), Minretumomab (anti-TAG-72), Mitumomab (BEC-2, anti-GD3 ganglioside), Morolimumab (anti-Rhesus factor), Motavizumab (Numax, anti-respiratory syncytial virus), Muromonab-CD3 (Orthoclone OKT3, anti-CD3), Nacolomab (anti-C242), Naptumomab (anti-5T4), Natalizumab (Tysabri, anti-integrin α_4), Nebacumab (anti-endotoxin),

Necitumumab (anti-EGFR), Nerelimomab (anti-TNF-α), Nimotuzumab (Theracim, Theraloc, anti-EGFR), Nofetumomab, Ocrelizumab (anti-CD20), Odulimomab (Afolimomab, anti-LFA-1 (CD11a)), Ofatumumab (Arzerra, anti-CD20), Olaratumab (anti-PDGF-R α), Omalizumab (Xolair, anti-IgE Fc region), Oportuzumab (anti-EpCAM), Oregovomab (OvaRex, anti-CA-125), Otelixizumab (anti-CD3), Pagibaximab (anti-lipoteichoic acid), Palivizumab (Synagis, Abbosynagis, anti-respiratory syncytial virus), Panitumumab (Vectibix, ABX-EGF, anti-EGFR), Panobacumab (anti- Pseudomonas aeruginosa), Pascolizumab (anti-IL-4), Pemtumomab (Theragyn, anti-MUC1), Pertuzumab (Omnitarg, 2C4, anti-HER2/neu), Pexelizumab (anti-C5), Pintumomab (anti-adenocarcinoma antigen), Priliximab (anti-CD4), Pritumumab (anti-vimentin), PRO 140 (anti-CCR5), Racotumomab (1E10, anti-(N-glycolylneuraminic acid (NeuGc, NGNA)-gangliosides GM3)), Rafivirumab (anti-rabies virus glycoprotein), Ramucirumab (anti-VEGFR2), Ranibizumab (Lucentis, anti-VEGF-A), Raxibacumab (anti-anthrax toxin, protective antigen), Regavirumab (anti-cytomegalovirus glycoprotein B), Reslizumab (anti-IL-5), Rilotumumab (anti-HGF), Rituximab (MabThera, Rituxanmab, anti-CD20), Robatumumab (anti-IGF-1 receptor), Rontalizumab (anti-IFN-α), Rovelizumab (LeukArrest, anti-CD11, CD18), Ruplizumab (Antova, anti-CD154 (CD40L)), Satumomab (anti-TAG-72), Sevirumab (anti-cytomegalovirus), Sibrotuzumab (anti-FAP), Sifalimumab (anti-IFN-α), Siltuximab (anti-IL-6), Siplizumab (anti-CD2), (Smart) MI95 (anti-CD33), Solanezumab (anti-beta amyloid), Sonepcizumab (anti-sphingosine-1-phosphate), Sontuzumab (anti-episialin), Stamulumab (anti-myostatin), Sulesomab (LeukoScan, (anti-NCA-90 (granulocyte antigen), Tacatuzumab (anti-alpha-fetoprotein), Tadocizumab (anti-integrin $\alpha_{IIb}\beta_3$), Talizumab (anti-IgE), Tanezumab (anti-NGF), Taplitumomab (anti-CD19), Tefibazumab (Aurexis, (anti-clumping factor A), Telimomab, Tenatumomab (anti-tenascin C), Teneliximab (anti-CD40), Teplizumab (anti-CD3), TGN1412 (anti-CD28), Ticilimumab (Tremelimumab, (anti-CTLA-4), Tigatuzumab (anti-TRAIL-R2), TNX-650 (anti-IL-13), Tocilizumab (Atlizumab, Actemra, RoActemra, (anti-IL-6 receptor), Toralizumab (anti-CD154 (CD40L)), Tositumomab (anti-CD20), Trastuzumab (Herceptin, (anti-HER2/neu), Tremelimumab (anti-CTLA-4), Tucotuzumab celmoleukin (anti-EpCAM), Tuvirumab (anti-hepatitis B virus), Urtoxazumab (anti- Escherichia coli), Ustekinumab (Stelara, anti-IL-12, IL-23), Vapaliximab (anti-AOC3 (VAP-1)), Vedolizumab, (anti-integrin $\alpha_4\beta_7$), Veltuzumab (anti-CD20), Vepalimomab (anti-AOC3 (VAP-1), Visilizumab (Nuvion, anti-CD3), Vitaxin (anti-vascular integrin avb3), Volociximab (anti-integrin $\alpha_5\beta_1$), Votumumab (HumaSPECT, anti-tumor antigen CTAA16.88), Zalutumumab (HuMax-EGFr, (anti-EGFR), Zanolimumab (HuMax-CD4, anti-CD4), Ziralimumab (anti-CD147 (basigin)), Zolimomab (anti-CD5), Etanercept (Enbrel®), Alefacept (Amevive®), Abatacept (Orencia®), Rilonacept (Arcalyst), 14F7 [anti-IRP-2 (Iron Regulatory Protein 2)], 14G2a (anti-GD2 ganglioside, from Nat.

Cancer Inst. for melanoma and solid tumors), J591 (anti-PSMA, Weill Cornell Medical School for prostate cancers), 225.28S [anti-HMW-MAA (High molecular weight-melanoma-associated antigen), Sorin Radiofarmaci S.R.L. (Milan, Italy) for melanoma], COL-1 (anti-CEACAM3, CGM1, from Nat. Cancer Inst. USA for colorectal and gastric cancers), CYT-356 (Oncoltad®, for prostate cancers), HNK20 (OraVax Inc. for respiratory syncytial virus), ImmuRAIT (from Immunomedics for NHL), Lym-1 (anti-HLA-DR10, Peregrine Pharm. for Cancers), MAK-195F [anti-TNF (tumor necrosis factor; TNFA, TNF-alpha; TNFSF2), from Abbott / Knoll for Sepsis toxic shock], MEDI-500 [T10B9, anti-CD3, TRαβ (T cell receptor alpha/beta), complex, from MedImmune Inc for Graft-versus-host disease], RING SCAN [anti-TAG 72 (tumour associated glycoprotein 72), from Neoprobe Corp. for Breast, Colon and Rectal cancers], Avicidin (anti-EPCAM (epithelial cell adhesion molecule), anti-TACSTD1 (Tumor-associated calcium signal transducer 1), anti-GA733-2 (gastrointestinal tumor-associated protein 2), anti-EGP-2 (epithelial glycoprotein 2); anti-KSA; KS1/4 antigen; M4S; tumor antigen 17-1A; CD326, from NeoRx Corp. for Colon, Ovarian, Prostate cancers and NHL]; LymphoCide (Immunomedics, NJ), Smart ID10 (Protein Design Labs), Oncolym (Techniclone Inc, CA), Allomune (BioTransplant, CA), anti-VEGF (Genentech, CA); CEAcide (Immunomedics, NJ), IMC-1C11 (ImClone, NJ) and Cetuximab (ImClone, NJ) .

Other antibodies as cell binding molecules/ligands include, but are not limited to, are antibodies against the following antigens: Aminopeptidase N (CD13), Annexin A1, B7-H3 (CD276, various cancers), CA125 (ovarian), CA15-3 (carcinomas), CA19-9 (carcinomas), L6 (carcinomas), Lewis Y (carcinomas), Lewis X (carcinomas), alpha fetoprotein (carcinomas), CA242 (colorectal), placental alkaline phosphatase (carcinomas), prostate specific antigen (prostate), prostatic acid phosphatase (prostate), epidermal growth factor (carcinomas), CD2 (Hodgkin's disease, NHL lymphoma, multiple myeloma), CD3 epsilon (T cell lymphoma, lung, breast, gastric, ovarian cancers, autoimmune diseases, malignant ascites), CD19 (B cell malignancies), CD20 (non-Hodgkin's lymphoma), CD22 (leukemia, lymphoma, multiple myeloma, SLE), CD30 (Hodgkin's lymphoma), CD33 (leukemia, autoimmune diseases), CD38 (multiple myeloma), CD40 (lymphoma, multiple myeloma, leukemia (CLL)), CD51 (Metastatic melanoma, sarcoma), CD52 (leukemia), CD56 (small cell lung cancers, ovarian cancer, Merkel cell carcinoma, and the liquid tumor, multiple myeloma), CD66e (cancers), CD70 (metastatic renal cell carcinoma and non-Hodgkin lymphoma), CD74 (multiple myeloma), CD80 (lymphoma), CD98 (cancers), mucin (carcinomas), CD221 (solid tumors), CD227 (breast, ovarian cancers), CD262 (NSCLC and other cancers), CD309 (ovarian cancers), CD326 (solid tumors), CEACAM3 (colorectal, gastric cancers), CEACAM5 (carcinoembryonic antigen; CEA, CD66e) (breast, colorectal and lung cancers), DLL3 or DLL4 (delta-like-3 or delta-like-4), EGFR (Epidermal Growth Factor Receptor, various cancers), CTLA4

(melanoma), CXCR4 (CD184, Heme-oncology, solid tumors), Endoglin (CD105, solid tumors), EPCAM (epithelial cell adhesion molecule, bladder, head, neck, colon, NHL prostate, and ovarian cancers), ERBB2 (Epidermal Growth Factor Receptor 2; lung, breast, prostate cancers), FCGR1 (autoimmune diseases), FOLR (folate receptor, ovarian cancers), GD2 ganglioside (cancers), G-28 (a cell surface antigen glyvolipid, melanoma), GD3 idiotype (cancers), Heat shock proteins (cancers), HER1 (lung, stomach cancers), HER2 (breast, lung and ovarian cancers), HLA-DR10 (NHL), HLA-DRB (NHL, B cell leukemia), human chorionic gonadotropin (carcinoma), IGF1R (insulin-like growth factor 1 receptor, solid tumors, blood cancers), IL-2 receptor (interleukin 2 receptor, T-cell leukemia and lymphomas), IL-6R (interleukin 6 receptor, multiple myeloma, RA, Castleman's disease, IL6 dependent tumors), Integrins (αvβ3, α5β1, α6β4, αIIβ3, α5β5, αvβ5, for various cancers), MAGE-1 (carcinomas), MAGE-2 (carcinomas), MAGE-3 (carcinomas), MAGE 4 (carcinomas), anti-transferrin receptor (carcinomas), p97 (melanoma), MS4A1 (membrane-spanning 4-domains subfamily A member 1, Non-Hodgkin's B cell lymphoma, leukemia), MUC1 or MUC1-KLH (breast, ovarian, cervix, bronchus and gastrointestinal cancer), MUC16 (CA125) (Ovarian cancers), CEA (colorectal), gp100 (melanoma), MART1 (melanoma), MPG (melanoma), MS4A1 (membrane-spanning 4-domains subfamily A, small cell lung cancers, NHL), Nucleolin, Neu oncogene product (carcinomas), P21 (carcinomas), Paratope of anti-(N-glycolylneuraminic acid, Breast, Melanoma cancers), PLAP-like testicular alkaline phosphatase (ovarian, testicular cancers), PSMA (prostate tumors), PSA (prostate), ROBO4, TAG 72 (tumour associated glycoprotein 72, AML, gastric, colorectal, ovarian cancers), T cell transmembrane protein (cancers), Tie (CD202b), TNFRSF10B (tumor necrosis factor receptor superfamily member 10B, cancers), TNFRSF13B (tumor necrosis factor receptor superfamily member 13B, multiple myeloma, NHL, other cancers, RA and SLE), TPBG (trophoblast glycoprotein, Renal cell carcinoma), TRAIL-R1 (Tumor necrosis apoprosis Inducing ligand Receptor 1, lymphoma, NHL, colorectal, lung cancers), VCAM-1 (CD106, Melanoma), VEGF, VEGF-A, VEGF-2 (CD309) (various cancers). Some other tumor associated antigens recognized by antibodies have been reviewed (Gerber, et al, mAbs 1:3, 247-53 (2009); Novellino et al, Cancer Immunol Immunother. 54(3), 187-207 (2005). Franke, et al, Cancer Biother Radiopharm. 2000, 15, 459-76).

The antibody-like protein, more preferred an IgG antibody that is able to against tumor cells, virus infected cells, microorganism infected cells, parasite infected cells, autoimmune disease cells, activated tumor cells, myeloid cells, activated T-cells, an affecting B cells, or melanocytes. More specifically the antibody is able to against abnormal cells expressing any one of the following antigens or receptors: CD1, CD1a, CD1b, CD1c, CD1d, CD1e, CD2, CD3, CD3d, CD3e, CD3g, CD4, CD5, CD6, CD7, CD8, CD8a, CD8b, CD9, CD10, CD11a, CD11b, CD11c, CD11d, CD12w,

CD14, CD15, CD16, CD16a, CD16b, CDw17, CD18, CD19, CD20, CD21, CD22, CD23, CD24, CD25, CD26, CD27, CD28, CD29, CD30, CD31, CD32, CD32a, CD32b, CD33, CD34, CD35, CD36, CD37, CD38, CD39, CD40, CD41, CD42, CD42a, CD42b, CD42c, CD42d, CD43, CD44, CD45, CD46, CD47, CD48, CD49b, CD49c, CD49c, CD49d, CD49f, CD50, CD51, CD52, CD53, CD54, CD55, CD56, CD57, CD58, CD59, CD60, CD60a, CD60b, CD60c, CD61, CD62E, CD62L, CD62P, CD63, CD64, CD65, CD65s, CD66, CD66a, CD66b, CD66c, CD66d, CD66e, CD66f, CD67, CD68, CD69, CD70, CD71, CD72, CD73, CD74, CD75, CD75s, CD76, CD77, CD78, CD79, CD79a, CD79b, CD80, CD81, CD82, CD83, CD84, CD85, CD85a, CD85b, CD85c, CD85d, CD85e, CD85f, CD85g, CD85g, CD85i, CD85j, CD85k, CD85m, CD86, CD87, CD88, CD89, CD90, CD91, CD92, CD93, CD94, CD95, CD96, CD97, CD98, CD99, CD100, CD101, CD102, CD103, CD104, CD105, CD106, CD107, CD107a, CD107b, CD108, CD109, CD110, CD111, CD112, CD113, CD114, CD115, CD116, CD117, CD118, CD119, CD120, CD120a, CD120b, CD121, CD121a, CD121b, CD122, CD123, CD123a, CD124, CD125, CD126, CD127, CD128, CD129, CD130, CD131, CD132, CD133, CD134, CD135, CD136, CD137, CD138, CD139, CD140, CD140a, CD140b, CD141, CD142, CD143, CD144, CD145, CDw145, CD146, CD147, CD148, CD149, CD150, CD151, CD152, CD153, CD154, CD155, CD156, CD156a, CD156b, CD156c, CD156d, CD157, CD158, CD158a, CD158b1, CD158b2, CD158c, CD158d, CD158e1, CD158e2, CD158f2, CD158g, CD158h, CD158i, CD158j, CD158k, CD159, CD159a, CD159b, CD159c, CD160, CD161, CD162, CD163, CD164, CD165, CD166, CD167, CD167a, CD167b, CD168, CD169, CD170, CD171, CD172, CD172a, CD172b, CD172g, CD173, CD174, CD175, CD175s, CD176, CD177, CD178, CD179, CD179a, CD179b, CD180, CD181, CD182, CD183, CD184, CD185, CD186, CDw186, CD187, CD188, CD189, CD190, CD191, CD192, CD193, CD194, CD195, CD196, CD197, CD198, CD199, CDw198, CDw199, CD200, CD201, CD202, CD202（a, b）, CD203, CD203c, CD204, CD205, CD206, CD207, CD208, CD209, CD210, CDw210a, CDw210b, CD211, CD212, CD213, CD213a1, CD213a2, CD214, CD215, CD216, CD217, CD218, CD218a, CD218, CD21b9, CD220, CD221, CD222, CD223, CD224, CD225, CD226, CD227, CD228, CD229, CD230, CD231, CD232, CD233, CD234, CD235, CD235a, CD235b, CD236, CD237, CD238, CD239, CD240, CD240ce, CD240d, CD241, CD242, CD243, CD244, CD245, CD246, CD247, CD248, CD249, CD250, CD251, CD252, CD253, CD254, CD255, CD256, CD257, CD258, CD259, CD260, CD261, CD262, CD263, CD264, CD265, CD266, CD267, CD268, CD269, CD270, CD271, CD272, CD273, CD274, CD275, CD276, CD277, CD278, CD279, CD281, CD282, CD283, CD284, CD285, CD286, CD287, CD288, CD289, CD290, CD291, CD292, CD293, CD294, CD295, CD296, CD297, CD298, CD299, CD300, CD300a, CD300b, CD300c, CD301, CD302, CD303, CD304, CD305, CD306, CD307, CD307a, CD307b, CD307c, CD307d, CD307e, CD307f, CD308, CD309,

CD310, CD311, CD312, CD313, CD314, CD315, CD316, CD317, CD318, CD319, CD320, CD321, CD322, CD323, CD324, CD325, CD326, CD327, CD328, CD329, CD330, CD331, CD332, CD333, CD334, CD335, CD336, CD337, CD338, CD339, CD340, CD341, CD342, CD343, CD344, CD345, CD346, CD347, CD348, CD349, CD350, CD351, CD352, CD353, CD354, CD355, CD356, CD357, CD358, CD359, CD360, CD361, CD362, CD363, CD364, CD365, CD366, CD367, CD368, CD369, CD370, CD371, CD372, CD373, CD374, CD375, CD376, CD377, CD378, CD379, CD381, CD382, CD383, CD384, CD385, CD386, CD387, CD388, CD389, CRIPTO, CRIPTO, CR, CR1, CRGF, CRIPTO, CXCR5, LY64, TDGF1, 4-1BB, APO2, ASLG659, BMPR1B, 4-1BB, 5AC, 5T4 (Trophoblastic glycoprotein, TPBG, 5T4, Wnt-Activated Inhibitory Factor 1 or WAIF1), Adenocarcinoma antigen, AGS-5, AGS-22M6, Activin receptor-like kinase 1, AFP, AKAP-4, ALK, Alpha integrin, Alpha v beta6, Amino-peptidase N, Amyloid beta, Androgen receptor, Angiopoietin 2, Angiopoietin 3, Annexin A1, Anthrax toxin protective antigen, Anti-transferrin receptor, AOC3 (VAP-1), B7-H3, Bacillus anthracis anthrax, BAFF (B-cell activating factor), BCMA, B-lymphoma cell, bcr-abl, Bombesin, BORIS, C5, C242 antigen, CA125 (carbohydrate antigen 125, MUC16), CA-IX (or CAIX, carbonic anhydrase 9), CALLA, CanAg, Canis lupus familiaris IL31, Carbonic anhydrase IX, Cardiac myosin, CCL11(C-C motif chemokine 11), CCR4 (C-C chemokine receptor type 4), CCR5, CD3E (epsilon), CEA (Carcinoembryonic antigen), CEACAM3, CEACAM5 (carcino-embryonic antigen), CFD (Factor D), Ch4D5, Cholecystokinin 2 (CCK2R), CLDN18 (Claudin-18), Clumping factor A, cMet, CRIPTO, FCSF1R (Colony stimulating factor 1 receptor), CSF2 (colony stimulating factor 2, Granulocyte-macrophage colony-stimulating factor (GM-CSF)), CSP4, CTLA4 (cytotoxic T-lymphocyte-associated protein 4), CTAA16.88 tumor antigen, CXCR4, C-X-C chemokine receptor type 4, cyclic ADP ribose hydrolase, Cyclin B1, CYP1B1, Cytomegalovirus, Cytomegalovirus glycoprotein B, Dabigatran, DLL3 (delta-like-ligand 3), DLL4 (delta-like-ligand 4), DPP4 (Dipeptidyl-peptidase 4), DR5 (Death receptor 5), E. coli shiga toxin type-1, E. coli shiga toxin type-2, ED-B, EGFL7 (EGF-like domain-containing protein 7), EGFR, EGFRII, EGFRvIII, Endoglin, Endothelin B receptor, Endotoxin, EpCAM (epithelial cell adhesion molecule), EphA2, Episialin, ERBB2 (Epidermal Growth Factor Receptor 2), ERBB3, ERG (TMPRSS2 ETS fusion gene), Escherichia coli, ETV6-AML, FAP (Fibroblast activation protein alpha), FCGR1, alpha-Fetoprotein, Fibrin II, beta chain, Fibronectin extra domain-B, FOLR (folate receptor), Folate receptor alpha, Folate hydrolase, Fos-related antigen 1F protein of respiratory syncytial virus, Frizzled receptor, Fucosyl GM1, GD2 ganglioside, G-28 (a cell surface antigen glyvolipid), GD3 idiotype, GloboH, Glypican 3, N-glycolylneuraminic acid, GM3, GMCSF receptor α-chain, Growth differentiation factor 8, GP100, GPNMB (Trans-membrane glycoprotein NMB), GUCY2C (Guanylate cyclase 2C, guanylyl cyclase C(GC-C), intestinal Guanylate cyclase,

Guanylate cyclase-C receptor, Heat-stable enterotoxin receptor (hSTAR)), Heat shock proteins, Hemagglutinin, Hepatitis B surface antigen, Hepatitis B virus, HER1 (human epidermal growth factor receptor 1), HER2, HER2/neu, HER3 (ERBB-3), IgG4, HGF/SF (Hepatocyte growth factor/scatter factor), HHGFR, HIV-1, Histone complex, HLA-DR (human leukocyte antigen), HLA-DR10, HLA-DRB , HMWMAA, Human chorionic gonadotropin, HNGF, Human scatter factor receptor kinase, HPV E6/E7, Hsp90, hTERT, ICAM-1 (Intercellular Adhesion Molecule 1), Idiotype, IGF1R (IGF-1, insulin-like growth factor 1 receptor), IGHE, IFN-γ, Influenza hemagglutinin, IgE, IgE Fc region, IGHE, interleukins (comprising IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-6R, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, IL-17, IL-17A, IL-18, IL-19, IL-20, IL-21, IL-22, IL-23, IL-27, or IL-28), IL31RA, ILGF2 (Insulin-like growth factor 2), Integrins (α4, $\alpha_{IIb}\beta_3$, αvβ3, $\alpha_4\beta_7$, α5β1, α6β4, α7β7, αIIβ3, α5β5, αvβ5), Interferon gamma-induced protein, ITGA2, ITGB2, KIR2D, Kappa Ig, LCK, Le, Legumain, Lewis-Y antigen, LFA-1 (Lymphocyte function-associated antigen 1, CD11a), LHRH, LINGO-1, Lipoteichoic acid, LIV1A, LMP2, LTA, MAD-CT-1, MAD-CT-2, MAGE-1, MAGE-2, MAGE-3, MAGE A1, MAGE A3, MAGE 4, MART1, MCP-1, MIF (Macrophage migration inhibitory factor, or glycosylation-inhibiting factor (GIF)), MS4A1 (membrane-spanning 4-domains subfamily A member 1), B7H3, B7H4, MSLN (mesothelin), MUC1(Mucin 1, cell surface associated (MUC1) or polymorphic epithelial mucin (PEM)), MUC1-KLH, MUC16 (CA125), MCP1(monocyte chemotactic protein 1), MelanA/MART1, ML-IAP, MPG, MS4A1 (membrane-spanning 4-domains subfamily A), MYCN, Myelin-associated glycoprotein, Myostatin, NA17, NARP-1, NCA-90 (granulocyte antigen), Nectin-4 (ASG-22ME), NGF, Neural apoptosis-regulated proteinase 1, NOGO-A, Notch receptor, Nucleolin, Neu oncogene product, NY-BR-1, NY-ESO-1, OX-40, OxLDL (Oxidized low-density lipoprotein), OY-TES1, P21, p53 nonmutant, P97, Page4, PAP, Paratope of anti-(N-glycolylneuraminic acid), PAX3, PAX5, PCSK9, PDCD1 (PD-1, Programmed cell death protein 1), PDGF-Rα (Alpha-type platelet-derived growth factor receptor), PDGFR-β, PDL-1, PLAC1, PLAP-like testicular alkaline phosphatase, Platelet-derived growth factor receptor beta, Phosphate-sodium co-transporter, PMEL 17, Polysialic acid, Proteinase3 (PR1), Prostatic carcinoma, PS (Phosphatidylserine), Prostatic carcinoma cells, Pseudomonas aeruginosa, PSMA, PSA, PSCA, Rabies virus glycoprotein, RHD (Rh polypeptide 1 (RhPI)), Rhesus factor, RANKL, RhoC, Ras mutant, RGS5, ROBO4, Respiratory syncytial virus, RON, ROR1, Sarcoma translocation breakpoints, SART3, Sclerostin, SLAMF7 (SLAM family member 7), Selectin P, SDC1 (Syndecan 1), sLe(a), Somatomedin C, SIP (Sphingosine-1-phosphate), Somatostatin, Sperm protein 17, SSX2, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), STEAP2, STn, TAG-72 (tumor associated glycoprotein 72), Survivin, T-cell receptor, T cell transmembrane protein, TEM1 (Tumor endothelial marker 1), TENB2, Tenascin C (TN-C),

TGF-α, TGF-β (Transforming growth factor beta), TGF-β1, TGF-β2 (Transforming growth factor-beta 2), Tie (CD202b), Tie2, TIM-1 (CDX-014), Tn, TNF, TNF-α, TNFRSF8, TNFRSF10B (tumor necrosis factor receptor superfamily member 10B), TNFRSF-13B (tumor necrosis factor receptor superfamily member 13B), TPBG (trophoblast glycoprotein), TRAIL-R1 (Tumor necrosis apoptosis Inducing ligand Receptor 1), TRAILR2 (Death receptor 5 (DR5)), tumor-associated calcium signal transducer 2, tumor specific glycosylation of MUC1, TWEAK receptor, TYRP1(glycoprotein 75), TRP-1 (Trop1), TRP-2 (Trop2), Tyrosinase, VCAM-1, VEGF, VEGF-A, VEGF-2, VEGFR-1, VEGFR2, or vimentin, WT1, XAGE 1, or cells expressing any insulin growth factor receptors, or any epidermal growth factor receptors.

Many of tumor-associated antigens (TAA) or tumor cell receptors are known in the art, and can be prepared for use in generating antibodies using methods and information which are well known in the art. In attempts to discover effective cellular targets for cancer diagnosis and therapy, researchers have sought to identify transmembrane or otherwise tumor-associated polypeptides or glycoproteins that are specifically expressed on the surface of one or more particular type(s) of cancer cell as compared to on one or more normal non-cancerous cell(s). Often, such tumor-associated polypeptides are more abundantly expressed on the surface of the cancer cells as compared to on the surface of the non-cancerous cells. The identification of such tumor-associated cell surface antigen polypeptides has given rise to the ability to specifically target cancer cells for destruction via the ADCs of this application. Examples of the TAA and cognate antibodies with their known in art are:

(1) BMPR1B (Bone Morphogenetic Protein Receptor-Type IB):

Nucleotide: Genbank accession no. NM_001203; Genbank version no. NM_001203.2 GI:169790809. Polypeptide: Genbank accession no. NP_001194; Genbank version no. NP_001194.1 GI:4502431.

Cross-References: Attisano L, et al, Cell. 75(4):671-80 (1993); ten Dijke, P., et al Science 264 (5155): 101-104 (1994), Ide H., et al, Oncogene 14 (11):1377-1382 (1997); WO2004/063362 (Claim 2); WO2003/042661 (Claim 12); US2003/134790-A1 (Page 38-39); WO2002/102235 (Claim 13; Page 296); WO2003/055443 (Page 91-92); WO2002/99122 (Example 2; Page 528-530); WO2003/029421 (Claim 6); WO2003/024392 (Claim 2; FIG. 112); WO2002/98358 (Claim 1; Page 183); WO2002/54940 (Page 100-101); WO2002/59377 (Page 349-350); WO2002/30268 (Claim 27; Page 376); 15 WO2001/48204 (Example; FIG. 4); NP_001194 bone morphogenetic protein receptor, type IB/pid=NP_001194.1; MIM:603248; AY065994

(2) E16 (LAT1, SLC7A5):

Nucleotide: Genbank accession no. NM_003486; Genbank version no. NM_003486.5 GI:71979931. Polypeptide: Genbank accession no. NP_003477; Genbank version no. NP_003477.4 GI:71979932.

Cross References: Prasad, P. D. et al, *Biochem. Biophys. Res. Commun.* 255 (2), 283-288 (1999), Mastroberardino, L., et al, *Nature* 395 (6699):288-291 (1998), Pfeiffer R, et al, EMBO J. 18(1):49-57 (1999); Gaugitsch, H. W., et al, *J. Biol. Chem.* 267 (16):11267-11273 (1992); WO2004/048938 (Example 2); WO2004/032842 (Example IV); WO2003/042661 (Claim 12); WO2003/016475 (Claim 1); WO2002/78524 (Example 2); WO2002/99074 (Claim 19; Page 127-129); WO2002/86443 (Claim 27; Pages 222, 393); WO2003/003906 (Claim 10; Page 293); WO2002/64798 (Claim 33; Page 93-95); WO2000/14228 (Claim 5; Page 133-136); US2003/224454 (FIG. 3); 25 WO2003/025138 (Claim 12; Page 150); NP_003477 solute carrier family 7 (cationic amino acid transporter, y+system), member 5/pid=NP_003477.3—*Homo sapiens*; MIM:600182; NM_015923.

(3) STEAP1 (Six Transmembrane Epithelial Antigen of Prostate):

Nucleotide: Genbank accession no. NM_012449; Genbank version no. NM_012449.2 GI:22027487. Polypeptide: Genbank accession no. NP_036581; Genbank version no. NP_036581.1 GI:9558759.

Cross References: Tang, D. et al, *Cancer Res.* 61 (15), 5857-5860 (2001); Hubert, R. S., et al, *Proc. Natl. Acad. Sci. U.S.A.* 96 (25):14523-14528 (1999); WO2004/065577 (Claim 6); WO2004/027049 (FIG. 1L); EP1394274 (Example 11); WO2004/016225 (Claim 2); WO2003/042661 (Claim 12); US2003/157089 (Example 5); US2003/185830 (Example 5); US2003/064397 (FIG. 2); WO2002/89747 (Example 5; Page 618-619); WO2003/022995 (Example 9; FIG. 13A, 35 Example 53; Page 173, Example 2; FIG. 2A); six transmembrane epithelial antigen of the prostate; MIM:604415.

(4) 0772P (CA125, MUC16):

Nucleotide: Genbank accession no. AF361486; Genbank version no. AF361486.3 GI:34501466. Polypeptide: Genbank accession no. AAK74120; Genbank version no. AAK74120.3 GI:34501467.

Cross References: Yin, B. W., Lloyd, K. O. *J. Biol. Chem.* 276 (29): 27371-5 (2001); Bouanène H, Miled A. Bull Cancer. 96(5):597-601 (2009); Felder M, et al, Mol Cancer. 2014, 13:129; WO2004/045553 (Claim 14); WO2002/92836 (Claim 6; FIG. 12); WO2002/83866 (Claim 15; Page 116-121); US2003/124140 (Example 16); GI:34501467;

(5) MPF (MPF, MSLN, SMR, Megakaryocyte Potentiating Factor, Mesothelin):

Nucleotide: Genbank accession no. NM_005823; Genbank version no. NM_005823.5 GI:293651528. Polypeptide: Genbank accession no. NP_005814; Genbank version no. NP_005814.2 GI:53988378.

Cross References: Hassan R, et al, Clin Cancer Res. 10(12 Pt 1):3937-42(2004), Yamaguchi, N., et al *Biol. Chem.* 269 (2), 805-808 (1994), Scholler, N., *et al, Proc. Natl. Acad. Sci. U.S.A.* 96 (20):11531-11536 (1999), Chang, K., Pastan, I., *Proc. Natl. Acad. Sci. U.S.A.* 93 (1):136-140 (1996), Kojima T., et al, *J. Biol. Chem.* 270 (37):21984-21990 (1995); WO2003/101283 (Claim 14); (WO2002/102235 (Claim 13; Page 287-288); WO2002/101075 (Claim 4; Page 308-309); WO2002/71928 (Page 320-321); WO94/10312 (Page 52-57); IM:601051.

(6) Napi3b (NAPI-3B, NPTIIb, SLC34A2, Solute Carrier Family 34 (Sodium Phosphate), Member 2, Type II Sodium-Dependent Phosphate Transporter 3b)

Nucleotide: Genbank accession no. NM_006424; Genbank version no. NM_006424.2 GI:110611905. Polypeptide: Genbank accession no. NP_006415; Genbank version no. NP_006415.2 GI:110611906.

Cross References: Hiroko Segawa, et al, *J. Biol. Chem.* 277 (22):19665-19672 (2002), Xu H, et al, *Genomics* 62 (2):281-284 (1999), Feild, J. A., et al *Biochem. Biophys. Res. Commun.* 258 (3):578-582(1999); WO2004/022778 (Claim 2); EP1394274 (Example 11); WO2002/102235 (Claim 13; Page 326); EP0875569 (Claim 1; Page 17-19); WO2001/57188 (Claim 20; Page 329); WO2004/032842 (Example IV); WO2001/75177 (Claim 24; Page 139-140); MIM:604217.

(7) Sema 5b (FLJ10372, KIAA1445, Mm.42015, SEMA5B, SEMAG, Semaphorin 5b Hlog, 25 Sema Domain, Seven Thrombospondin Repeats (Type 1 and Type 1-Like), Transmembrane Domain™ and Short Cytoplasmic Domain, (Semaphorin) 5B)

Nucleotide: Genbank accession no. AB040878; Genbank version no. AB040878.1 GI:7959148. Polypeptide: Genbank accession no. BAA95969; Genbank version no. BAA95969.1 GI:7959149.

Cross References: Nagase T., et al *DNA Res.* 7 (2):143-150 (2000); WO2004/000997 (Claim 1); WO2003/003984 (Claim 1); WO2002/06339 (Claim 1; Page 50); WO2001/88133 (Claim 1; Page 41-43, 48-58); WO2003/054152 (Claim 20); WO2003/101400 (Claim 11); Accession: 30 Q9P283; Genew; HGNC:10737.

(8) PSCA hlg (2700050C12Rik, C530008016Rik, RIKEN cDNA 2700050C12, RIKEN cDNA 2700050C12 gene):

Nucleotide: Genbank accession no. AY358628; Genbank version no. AY358628.1 GI:37182377. Polypeptide: Genbank accession no. AAQ88991; Genbank version no. AAQ88991.1 GI:37182378.

Cross References: Ross et al *Cancer Res.* 62:2546-2553(2002); US2003/129192 (Claim 2); US2004/044180 (Claim 12); US2004/044179 (Claim 11); US2003/096961 (Claim 11); US2003/232056 (Example 5); WO2003/105758 16 (Claim 12); US2003/206918 (Example 5); EP1347046 (Claim 1); WO2003/025148 (Claim 20); GI:37182378.

(9) ETBR (Endothelin Type B Receptor)

Nucleotide: Genbank accession no. AY275463; Genbank version no. AY275463.1 GI:30526094. Polypeptide: Genbank accession no. AAP32295; Genbank version no. AAP32295.1 GI:30526095.

Cross References: Nakamuta M., et al *Biochem. Biophys. Res. Commun.* 177, 34-39(1991); Ogawa Y., et al *Biochem. Biophys. Res. Commun.* 178, 248-255(1991); Arai H., et al *Jpn. Circ. J.* 56, 1303-1307(1992); Arai H., et al *J. Biol. Chem.* 268, 3463-3470(1993); Sakamoto A., Yanagisawa M., et al *Biochem. Biophys. Res. Commun.* 178, 656-663(1991); Elshourbagy N. A., et al *J. Biol. Chem.* 268, 3873-3879(1993); Haendler B., et al *J. Cardiovasc. Pharmacol.* 20, S1-S4(1992); Tsutsumi M., et al *Gene* 228, 43-49(1999); Strausberg R. L., et al *Proc. Natl. Acad. Sci. U.S.A.* 99, 16899-16903(2002); Bourgeois C., et al *J. Clin. Endocrinol. Metab.* 82, 3116-3123(1997); Okamoto Y., et al *Biol. Chem.* 272, 21589-21596(1997); Verheij J. B., et al *Am. J. Med. Genet.* 108, 223-225(2002); Hofstra R. M. W., et al *Eur. J. Hum. Genet.* 5, 180-185(1997); Puffenberger E. G., et al *Cell* 79, 1257-1266(1994); Attie T., et al, *Hum. Mol. Genet.* 4, 2407-2409(1995); Auricchio A., et al *Hum. Mol. Genet.* 5:351-354(1996); Amiel J., et al *Hum. Mol. Genet.* 5, 355-357(1996); Hofstra R. M. W., et al *Nat. Genet.* 12, 445-447(1996); Svensson P. J., et al *Hum. Genet.* 103, 145-148(1998); Fuchs S., et al *Mol. Med.* 7, 115-124(2001); Pingault V., et al *Hum. Genet.* 111, 198-206(2002); WO2004/045516 (Claim 1); WO2004/048938 (Example 2); WO2004/040000 (Claim 151); WO2003/087768 (Claim 1); 20 WO2003/016475 (Claim 1); WO2003/016475 (Claim 1); WO2002/61087 (FIG. 1); WO2003/016494 (FIG. 6); WO2003/025138 (Claim 12; Page 144); WO2001/98351 (Claim 1; Page 124-125); EP0522868 (Claim 8; FIG. 2); WO2001/77172 (Claim 1; Page 297-299); US2003/109676; U.S. Pat. No. 6,518,404 (FIG. 3); U.S. Pat. No. 5,773,223 (Claim 1a; Col 31-34); WO2004/001004.

(10) MSG783 (RNF124, Hypothetical Protein FLJ20315)

Nucleotide: Genbank accession no. NM_017763; Genbank version no. NM_017763.4 GI:167830482. Polypeptide: Genbank accession no. NP_060233; Genbank version no. NP_060233.3 GI:56711322.

Cross References: WO2003/104275 (Claim 1); WO2004/046342 (Example 2); WO2003/042661 (Claim 12); WO2003/083074 (Claim 14; Page 61); WO2003/018621 (Claim 1); WO2003/024392 (Claim 2; FIG. 93); WO2001/66689 (Example 6); LocusID:54894.

(11) STEAP2 (HGNC_8639, IPCA-1, PCANAP1, STAMP1, STEAP2, STMP, Prostate Cancer Associated Gene 1, Prostate Cancer Associated Protein 1, Six Transmembrane Epithelial Antigen of Prostate 2, Six Transmembrane Prostate Protein)

Nucleotide: Genbank accession no. AF455138; Genbank version no. AF455138.1 GI:22655487. Polypeptide: Genbank accession no. AAN04080; Genbank version no. AAN04080.1 GI:22655488.

Cross References: Porkka, K P., et al, Lab. Invest. 82 (11):1573-1582 (2002); WO2003/087306; US2003/064397 (Claim 1; FIG. 1); WO2002/72596 (Claim 13; Page 54-55); WO2001/72962 (Claim 1; FIG. 4B); WO2003/104270 (Claim 11); WO2003/104270 (Claim 16); US2004/005598 (Claim 22); WO2003/042661 (Claim 12); US2003/060612 (Claim 12; FIG. 10); WO2002/26822 (Claim 23; FIG. 2); WO2002/16429 (Claim 12; FIG. 10); GI:22655488.

(12) TrpM4 (BR22450, FLJ20041, TRPM4, TRPM4B, Transient Receptor Potential Cation 5 Channel, Subfamily M, Member 4)

Nucleotide: Genbank accession no. NM_017636; Genbank version no. NM_017636.3 GI:304766649. Polypeptide: Genbank accession no. NP_060106; Genbank version no. NP_060106.2 GI:21314671.

Cross References: Xu, X. Z., et al *Proc. Natl. Acad. Sci. U.S.A.* 98 (19):10692-10697 (2001), Launay P., et al *Cell* 109 (3):397-407 (2002), Nilius B., et al *J. Biol. Chem.* 278 (33):30813-30820 (2003); US2003/143557 (Claim 4); WO2000/40614 (Claim 14; Page 100-103); WO2002/10382 (Claim 1; FIG. 9A); WO2003/042661 (Claim 12); WO2002/30268 (Claim 27; Page 391); US2003/219806 (Claim 4); WO2001/62794 (Claim 14; FIG. 1A-D); MIM:606936.

(13) CRIPTO (CR, CR1, CRGF, CRIPTO, TDGF1, Teratocarcinoma-Derived Growth Factor)

Nucleotide: Genbank accession no. NM_003212; Genbank version no. NM_003212.3 GI:292494881. Polypeptide: Genbank accession no. NP_003203; Genbank version no. NP_003203.1 GI:4507425.

Cross References: Ciccodicola, A., et al *EMBO J.* 8 (7):1987-1991 (1989), Dono R., et al, *Am. J. Hum. Genet.* 49 (3):555-565 (1991); US2003/224411 (Claim 1); WO2003/083041 (Example 1); WO2003/034984 (Claim 12); WO2002/88170 (Claim 2; Page 52-53); WO2003/024392 (Claim 2; FIG. 58); WO2002/16413 (Claim 1; Page 94-95, 105); WO2002/22808 (Claim 2; FIG. 1); U.S. Pat. No. 5,854,399 (Example 2; Col 17-18); U.S. Pat. No. 5,792,616 (FIG. 2); MIM:187395.

(14) CD21 (CR2 (Complement Receptor 2) or C3DR (C3d/Epstein Barr Virus Receptor) or Hs. 73792)

Nucleotide: Genbank accession no M26004; Genbank version no. M26004.1 GI:181939. Polypeptide: Genbank accession no. AAA35786; Genbank version no. AAA35786.1 GI:181940.

Cross References: Fujisaku et al *J. Biol. Chem.* 264 (4):2118-2125(1989); Weis J. J., et al *J. Exp. Med.* 167, 1047-1066(1988); Moore M., et al *Proc. Natl. Acad. Sci. U.S.A.* 84, 9194-9198(1987); Barel M., et al *Mol. Immunol.* 35, 1025-1031(1998); Weis J. J., et al *Proc. Natl. Acad. Sci. U.S.A.* 83, 5639-5643(1986); Sinha S. K., et al *J. Immunol.* 150, 5311-5320(1993); WO2004/045520 (Example 4); US2004/005538 (Example 1); WO2003/062401 (Claim 9); WO2004/045520 (Example 4); WO91/02536 (FIGS. 9.1-9.9); WO2004/020595 (Claim 1); Accession: P20023; Q13866; Q14212; EMBL; M26004; AAA35786.1.

(15) CD79b (CD79B, CD793, IGb (Immunoglobulin-Associated Beta), B29)

Nucleotide: Genbank accession no NM_000626; Genbank version no. NM_000626.2 GI:90193589. Polypeptide: Genbank accession no. NP_000617; Genbank version no. NP_000617.1 GI:11038674.

Cross References: Gordon MS., et al *Proc. Natl. Acad. Sci. U.S.A.* 100 (7):4126-4131 (2003), *Cragg MS., et al Blood* 100 (9):3068-3076 (2002), Muller et al *Eur. J. Immunol.* 22 (6):1621-1625(1992); WO2004/016225 (claim 2, FIG. 140); WO2003/087768, US2004/101874 (claim 1, page 102); WO2003/062401 (claim 9); WO2002/78524 (Example 2); US2002/150573 (claim 35 5, page 15); U.S. Pat. No. 5,644,033; WO2003/048202 (claim 1, pages 306 and 309); WO 99/58658, U.S. Pat. No. 6,534,482 (claim 13, FIG. 17A/B); WO2000/55351 (claim 11, pages 1145-1146); MIM:147245

(16) FcRH2 (IFGP4, IRTA4, SPAP1A (SH2 Domain Containing Phosphatase Anchor Protein 5 La), SPAP1B, SPAP1C)

Nucleotide: Genbank accession no NM_030764; Genbank version no. NM_030764.3 GI:227430280. Polypeptide: Genbank accession no. NP_110391; Genbank version no. NP_110391.2 GI:19923629.

Cross References: AY358130); Clark HF., et al *Genome Res.* 13 (10):2265-2270 (2003), Guselnikov SV., et al *Immunogenetics* 54 (2):87-95 (2002), Miller I., et al *Blood* 99 (8):2662-2669 (2002), Davis RS., et al *Proc. Natl. Acad. Sci. U.S.A.* 98 (17):9772-9777 (2001), Xu, M. J., et al *Biochem. Biophys. Res. Commun.* 280 (3):768-775(2001); WO2004/016225 (Claim 2); WO2003/077836; WO2001/38490 (Claim 5; FIG. 18D-1-18D-2); WO2003/097803 (Claim 12); 10 WO2003/089624 (Claim 25); MIM:606509.

(17) HER2 (ErbB2):

Nucleotide: Genbank accession no M11730; Genbank version no. M11730.1 GI:183986. Polypeptide: Genbank accession no. AAA75493; Genbank version no. AAA75493.1 GI:306840.

Cross References: Coussens L., et al *Science* 230(4730):1132-1139(1985); Yamamoto T., et al *Nature* 319, 230-234(1986); Semba K., et al *Proc. Natl. Acad. Sci. U.S.A.* 82, 6497-6501(1985);

Swiercz J. M., et al *J. Cell Biol.* 165, 869-880(2004); Kuhns J. J., et al *J. Biol. Chem.* 274, 36422-36427(1999); Cho H.-S., et al *Nature* 421, 756-760(2003); Ehsani A., et al *Genomics* 15, 426-429(1993); WO2004/048938 (Example 2); WO2004/027049 (FIG. 11); WO2004/009622; WO2003/081210; WO2003/089904 (Claim 9); WO2003/016475 (Claim 1); US2003/118592; WO2003/008537 (Claim 1); WO2003/055439 (Claim 29; FIG. 1A-B); WO2003/025228 (Claim 37; FIG. 5C); 20 WO2002/22636 (Example 13; Page 95-107); WO2002/12341 (Claim 68; FIG. 7); WO2002/13847 (Page 71-74); WO2002/14503 (Page 114-117); WO2001/53463 (Claim 2; Page 41-46); WO2001/41787 (Page 15); WO2000/44899 (Claim 52; FIG. 7); WO2000/20579 (Claim 3; FIG. 2); U.S. Pat. No. 5,869,445 (Claim 3; Col 31-38); WO9630514 (Claim 2; Page 56-61); EP1439393 (Claim 7); WO2004/043361 (Claim 7); WO2004/022709; WO2001/00244 25 (Example 3; FIG. 4); Accession: P04626; EMBL; M11767; AAA35808.1. EMBL; M11761; AAA35808.1

Antibodies: Abbott: US20110177095, For example, an antibody comprising CDRs having overall at least 80% sequence identity to CDRs having amino acid sequences of SEQ ID NO:3 (CDR-H1), SEQ ID NO:4 (CDR-H2), SEQ ID NO:5 (CDR-H3), SEQ ID NO:104 and/or SEQ ID NO:6 (CDR-L1), SEQ ID NO:7 (CDR-L2), and SEQ ID NO:8 (CDR-L3), wherein the anti-HER2 antibody or anti-HER2 binding fragment has reduced immunogenicity as compared to an antibody having a VH of SEQ ID NO:1 and a VL of SEQ ID NO:2.

Biogen: US20100119511； For example, ATCC accession numbers: PTA-10355, PTA-10356, PTA-10357, PTA-10358

For example, a purified antibody molecule that binds to HER2 comprising all six CDR's from an antibody selected from the group consisting of BIIB71F10 (SEQ ID NOs:11, 13), B11B69A09 (SEQ ID NOs:15, 17); BIIB67F10 (SEQ ID NOs:19, 21); BIIB67F11 (SEQ ID NOs:23, 25), BIIB66A12 (SEQ ID NOs:27, 29), BIIB66C01 (SEQ ID NOs:31, 33), BIIB65C10 (SEQ ID NOs:35, 37), BIIB65H09 (SEQ ID NOs:39, 41) and B11B65B03 (SEQ ID NOs:43, 45), or CDRs which are identical or which have no more than two alterations from said CDRs.

Herceptin (Genentech): U.S. Pat. No. 6,054,297; ATCC accession no. CRL-10463 (Genentech);

Pertuzumab (Genentech): US20110117097. For example, see SEQ IDs No. 15&16, SEQ IDs No. 17&18, SEQ IDs No. 23&24 & ATCC accession numbers HB-12215, HB-12216, CRL 10463, HB-12697. US20090285837, US20090202546. For example, ATCC accession numbers: HB-12215, HB-12216, CRL 10463, HB-12698. US20060088523. For example, ATCC accession numbers: HB-12215, HB-12216. For example, an antibody comprising the variable light and variable heavy amino acid sequences in SEQ ID Nos. 3 and 4, respectively. For example, an antibody comprising a light chain amino acid sequence selected from SEQ ID No. 15 and 23, and a heavy chain amino acid sequence selected from SEQ ID No. 16 and 24 US20060018899. For example, ATCC accession

numbers: (7C2) HB-12215, (7F3) HB-12216, (4D5) CRL-10463, (2C4) HB-12697. For example, an antibody comprising the amino acid sequence in SEQ ID No. 23, or a deamidated and/or oxidized variant thereof. US2011/0159014. For example, an antibody having a light chain variable domain comprising the hypervariable regions of SEQ ID NO: 1". For example, an antibody having a heavy chain variable domain comprising the hypervariable regions of SEQ ID NO: 2. US20090187007

Glycotope: TrasGEX antibody http://www.glycotope.com/pipeline. For example, see International Joint Cancer Institute and Shanghai Hospital Cancer Cent: HMTI-Fc Ab—Gao J., et al *BMB Rep.*; 42(10):636-41(2009).

Symphogen: US20110217305, Union Stem Cell &Gene Engineering, China—Liu HQ., et al *Xi Bao Yu Fen Zi Mian YiXue Za Zhi.*; 26(5):456-8(2010).

(18) NCA (CEACAM6):

Nucleotide: Genbank accession no M18728; Genbank version no. M18728.1 GI:189084. Polypeptide: Genbank accession no. AAA59907; Genbank version no. AAA59907.1 GI:189085.

Cross References: Barnett T., et al *Genomics* 3, 59-66(1988); Tawaragi Y., et al *Biochem. Biophys. Res. Commun.* 150, 89-96(1988); Strausberg R. L., et al *Proc. Natl. Acad. Sci. U.S.A.* 99:16899-16903(2002); WO2004/063709; EP1439393 (Claim 7); WO2004/044178 (Example 4); WO2004/031238; WO2003/042661 (Claim 12); WO2002/78524 (Example 2); WO2002/86443 (Claim 27; Page 427); WO2002/60317 (Claim 2); Accession: P40199; Q14920; EMBL; M29541; AAA59915.1. EMBL; M18728.

(19) MDP (DPEP1):

Nucleotide: Genbank accession no BC017023; Genbank version no. BC017023.1 GI:16877538. Polypeptide: Genbank accession no. AAH17023; Genbank version no. AAH17023.1 GI:16877539.

Cross References: Strausberg RL., et al *Proc. Natl. Acad. Sci. U.S.A.* 99 (26):16899-16903 (2002); WO2003/016475 (Claim 1); WO2002/64798 (Claim 33; Page 85-87); JP05003790 (FIG. 6-8); WO99/46284 (FIG. 9); MIM:179780.

(20) IL20R-Alpha (IL20Ra, ZCYTOR7):

Nucleotide: Genbank accession no AF184971; Genbank version no. AF184971.1 GI:6013324. Polypeptide: Genbank accession no. AAF01320; Genbank version no. AAF01320.1 GI:6013325.

Cross References: Clark H. F., et al *Genome Res.* 13, 2265-2270(2003); Mungall A. J., et al *Nature* 425, 805-811(2003); Blumberg H., et al *Cell* 104, 9-19(2001); Dumoutier L., et al *J. Immunol.* 167, 3545-3549(2001); Parrish-Novak J., et al *J. Biol. Chem.* 277, 47517-47523(2002); Pletnev S., et al 10 *Biochemistry* 42:12617-12624 (2003); Sheikh F., et al *J. Immunol.* 172, 2006-2010(2004); EP1394274 (Example 11); US2004/005320 (Example 5); WO2003/029262 (Page 74-75); WO2003/002717 (Claim 2; Page 63); WO2002/22153 (Page 45-47); US2002/042366 (Page 20-

21); WO2001/46261 (Page 57-59); WO2001/46232 (Page 63-65); WO98/37193 (Claim 1; Page 55-59); Accession: Q9UHF4; Q6UWA9; Q96SH8; EMBL; AF184971; AAF01320.1.

(21) Brevican (BCAN, BEHAB):

Nucleotide: Genbank accession no AF229053; Genbank version no. AF229053.1 GI:10798902. Polypeptide: Genbank accession no. AAG23135. Genbank version no. AAG23135.1 GI:10798903.

Cross References: Gary S. C., et al *Gene* 256, 139-147(2000); Clark H. F., et al *Genome Res.* 13, 2265-2270(2003); Strausberg R. L., et al *Proc. Natl. Acad. Sci. U.S.A.* 99, 16899-16903(2002); US2003/186372 (Claim 11); US2003/186373 (Claim 11); US2003/119131 (Claim 1; FIG. 52); US2003/119122 (Claim 1; FIG. 52); US2003/119126 (Claim 1); US2003/119121 (Claim 1; FIG. 52); US2003/119129 (Claim 1); US2003/119130 (Claim 1); US2003/119128 (Claim 1; FIG. 52); US2003/119125 (Claim 1); WO2003/016475 (Claim 1); WO2002/02634 (Claim 1)

(22) EphB2R (DRT, ERK, Hek5, EPHT3, Tyro5):

Nucleotide: Genbank accession no NM_004442; Genbank version no. NM_004442.6 GI:111118979. Polypeptide: Genbank accession no. NP_004433; Genbank version no. NP_004433.2 GI:21396504.

Cross References: Chan, J. and Watt, V. M., Oncogene 6 (6), 1057-1061 (1991), Fox GM., et al, Oncogene 10 (5):897-905 (1995), Flanagan JG., et al, Annu. Rev. Neurosci. 21:309-345 (1998), Wilkinson DG, Int. Rev. Cytol. 196:177-244 (2000); WO2003042661 (Claim 12); WO200053216 (Claim 1; Page 41); WO2004065576 (Claim 1); WO2004020583 (Claim 9); WO2003004529 (Page 128-132); WO200053216 (Claim 1; Page 42); MIM:600997.

(23) ASLG659 (B7h):

Nucleotide: Genbank accession no. AX092328; Genbank version no. AX092328.1 GI:13444478.

Cross References: US2004/0101899 (Claim 2); WO2003104399 (Claim 11); WO2004000221 (FIG. 3); US2003/165504 (Claim 1); US2003/124140 (Example 2); US2003/065143 (FIG. 60); WO2002/102235 (Claim 13; Page 299); US2003/091580 (Example 2); WO2002/10187 (Claim 6; FIG. 10); WO2001/94641 (Claim 12; FIG. 7b); WO2002/02624 (Claim 13; FIG. 1A-1B); US2002/034749 (Claim 54; Page 45-46); WO2002/06317 (Example 2; Page 320-321, Claim 34; Page 321-322); WO2002/71928 (Page 468-469); WO2002/02587 (Example 1; FIG. 1); WO2001/40269 (Example 3; Pages 190-192); WO2000/36107 (Example 2; Page 205-207); WO2004/053079 (Claim 12); WO2003/004989 (Claim 1); WO2002/71928 (Page 233-234, 452-453); WO 01/16318.

(24) PSCA (Prostate Stem Cell Antigen Precursor):

Nucleotide: Genbank accession no AJ297436; Genbank version no. AJ297436.1 GI:9367211. Polypeptide: Genbank accession no. CAB97347; Genbank version no. CAB97347.1 GI:9367212.

Cross References: Reiter R. E., et al *Proc. Natl. Acad. Sci. U.S.A.* 95, 1735-1740(1998); Gu Z., et al *Oncogene* 19, 1288-1296(2000)*; Bahrenberg G., et al, Biochem. Biophys. Res. Commun.* 275(3):783-788(2000); WO2004/022709; EP1394274 (Example 11); US2004/018553 (Claim 17); WO2003/008537 (Claim 1); WO2002/81646 (Claim 1; Page 164); WO2003/003906 (Claim 10; Page 288); WO2001/40309 (Example 1; FIG. 17); US2001/055751 (Example 1; FIG. 1 b); WO2000/32752 (Claim 18; FIG. 1); WO98/51805 (Claim 17; Page 97); WO98/51824 (Claim 10; Page 94); WO98/40403 (Claim 2; FIG. 1B); Accession: 043653; EMBL; AF043498; AAC39607.1

(25) GEDA:

Nucleotide: Genbank accession no AY260763; Genbank version no. AY260763.1 GI:30102448. Polypeptide: Genbank accession no. AAP14954; Genbank version no. AAP14954.1 GI:30102449.

Cross References: AP14954 lipoma HMGIC fusion-partnerlike protein/pid=AAP14954.1—*Homo sapiens* (human); WO2003/054152 (Claim 20); WO2003/000842 (Claim 1); WO2003/023013 (Example 3, Claim 20); US2003/194704 (Claim 45); GI:30102449.

(26) BAFF-R (B Cell-Activating Factor Receptor, BLyS Receptor 3, BR3):

Nucleotide: Genbank accession no AF116456; Genbank version no. AF116456.1 GI:4585274. Polypeptide: Genbank accession no. AAD25356; Genbank version no. AAD25356.1 GI:4585275.

Cross References: BAFF receptor/pid=NP_443177.1—*Homo sapiens*: Thompson, J. S., et al *Science* 293 (5537), 2108-2111 (2001); WO2004/058309; WO2004/011611; WO2003/045422 (Example; Page 32-33); WO2003/014294 (Claim 35; FIG. 6B); WO2003/035846 (Claim 70; Page 615-616); WO2002/94852 (Col 136-137); WO2002/38766 (Claim 3; Page 133); WO2002/24909 (Example 3; FIG. 3); MIM:606269; NP_443177.1; NM_052945_1; AF132600

(27) CD22 (B-Cell Receptor CD22-B Isoform, BL-CAM, Lyb-8, Lyb8, SIGLEC-2, FLJ22814):

Nucleotide: Genbank accession no AK026467; Genbank version no. AK026467.1 GI:10439337. Polypeptide: Genbank accession no. BAB15489; Genbank version no. BAB15489.1 G1:10439338.

Cross References: Wilson et al *J. Exp. Med.* 173:137-146(1991); WO2003/072036 (Claim 1; FIG. 1); IM:107266; NP_001762.1; NM_001771_1.

(27A) Cd22 (Cd22 Molecule):

Nucleotide: Genbank accession no X52785; Genbank version no. X52785.1 G1:29778. Polypeptide: Genbank accession no. CAA36988; Genbank version no. CAA36988.1 G1:29779.

Cross References: Stamenkovic I. et al., *Nature* 345 (6270), 74-77 (1990).

Other Information: Official Symbol: CD22; Other Aliases: SIGLEC-2, SIGLEC2 Other Designations: B-cell receptor CD22; B-lymphocyte cell adhesion molecule; BL-CAM; CD22 antigen; T-cell surface antigen Leu-14; sialic acid binding Ig-like lectin 2; sialic acid-binding Ig-like lectin 2

Antibodies: G5/44 (Inotuzumab): DiJoseph J F., et al *Cancer Immunol Immunother.*54(1):11-24(2005). Epratuzumab—Goldenberg DM., et al *Expert Rev Anticancer Ther.* 6(10): 1341-53(2006).

(28) CD79a (CD79A, CD79alpha), Immunoglobulin-Associated Alpha, a B Cell-Specific Protein that Covalently Interacts with Ig Beta (CD79B) and Forms a Complex on the Surface with Ig M 35 Molecules, Transduces a Signal Involved in B-Cell Differentiation), Pl: 4.84, MW: 25028 Tm: 2 [P] Gene Chromosome: 19q13.2):

Nucleotide: Genbank accession no NM_001783; Genbank version no. NM_001783.3 GI:90193587. Polypeptide: Genbank accession no. NP_001774; Genbank version no. NP_001774.1 GI:4502685.

Cross References: WO2003/088808, US2003/0228319; WO2003/062401 (claim 9); US2002/150573 (claim 4, pages 13-14); WO99/58658 (claim 13, FIG. 16); WO92/07574 (FIG. 1); U.S. Pat. No. 5,644,033; Ha et al *J. Immunol.* 148(5):1526-1531 (1992); Müller et al *Eur. J. Immunol.* 22:1621-1625(1992); Hashimoto et al *Immunogenetics* 40(4):287-295 (1994); Preud'homme et al Clin. Exp. 5 *Immunol.* 90(1):141-146(1992); Yu et al *J. Immunol.* 148(2) 633-637(1992); Sakaguchi et al *EMBO J.* 7(11):3457-3464(1988).

(29) CXCR5 (Burkitt's Lymphoma Receptor 1, a G Protein-Coupled Receptor that is Activated by the CXCL13 Chemokine, Functions in Lymphocyte Migration and Humoral Defense, Plays a 10 Role in HIV-2 Infection and Perhaps Development of AIDS, Lymphoma, Myeloma, and Leukemia); 372 Aa, Pl: 8.54 MW: 41959 TM: 7 [P] Gene Chromosome: 11q23.3:

Nucleotide: Genbank accession no NM_001716; Genbank version no. NM_001716.4 GI:342307092. Polypeptide: Genbank accession no. NP_001707; Genbank version no. NP_001707.1 GI:4502415.

Cross References: WO2004/040000; WO2004/015426; US2003/105292 (Example 2); U.S. Pat. No. 6,555,339 (Example 2); WO2002/61087 (FIG. 1); WO2001/57188 (Claim 20, page 269); WO2001/72830 (pages 12-13); WO2000/22129 (Example 1, pages 152-153, Example 2, pages 254-256); WO99/28468 (claim 1, page 38); U.S. Pat. No. 5,440,021 (Example 2, col 49-52); WO94/28931 (pages 56-58); WO92/17497 (claim 7, FIG. 5); Dobner et al *Eur. J. Immunol.* 22:2795-2799(1992); Barella et al *Biochem. J.* 309:773-779(1995).

(30) HLA-DOB (Beta Subunit of MHC Class II Molecule (La Antigen) that Binds Peptides and 20 Presents them to CD4+T Lymphocytes); 273 Aa, Pl: 6.56, MW: 30820. TM: 1 [P] Gene Chromosome: 6p21.3):

Nucleotide: Genbank accession no NM_002120; Genbank version no. NM_002120.3 GI:118402587. Polypeptide: Genbank accession no. NP_002111; Genbank version no. NP_002111.1 GI:4504403.

Cross References: Tonnelle C., et al *EMBO J.* 4(11):2839-2847 (1985); Jonsson AK., et al *Immunogenetics* 29(6):411-413 (1989); Beck S., et al *J. Mol. Biol.* 228:433-441 (1992); Strausberg RL., et al *Proc. Natl. Acad. Sci USA* 99:16899-16903(2002); Servenius B., et al *J. Biol. Chem.* 262:8759-8766 (1987); Beck S., et al *J. Mol. Biol.* 255:1-13(1996); Naruse TK., et al *Tissue Antigens* 59:512-519 (2002); WO99/58658 (claim 13, FIG. 15); U.S. Pat. No. 6,153,408 (Col 35-38); U.S. Pat. No. 5,976,551 (col 168-170); U.S. Pat. No. 6,011,146 (col 145-146); Kasahara M., et al *Immunogenetics* 30(1):66-68(1989); Larhammar D., et al *J. Biol. Chem.* 260(26):14111-14119(1985).

(31) P2X5 (Purinergic Receptor P2X Ligand-Gated Ion Channel 5, an Ion Channel Gated by Extracellular ATP, May be Involved in Synaptic Transmission and Neurogenesis, Deficiency May Contribute to the Pathophysiology of Idiopathic Detrusor Instability); 422 Aa), Pl: 7.63, MW: 47206 TM: 1 [P] Gene Chromosome: 17p13.3):

Nucleotide: Genbank accession no NM_002561; Genbank version no. NM_002561.3 GI:325197202. Polypeptide: Genbank accession no. NP_002552; Genbank version no. NP_002552.2 GI:28416933.

Cross References: Le KT., et al *FEBS Lett.* 418(1-2):195-199(1997); WO2004/047749; WO2003/072035 (claim 10); Touchman JW., et al *Genome Res.* 10:165-173(2000); WO2002/22660 (claim 20); WO2003/093444 (claim 1); WO2003/087768 (claim 1); WO2003/029277 (page 82)

(32) CD72 (B-Cell Differentiation Antigen CD72, Lyb-2); 359 Aa, Pl: 8.66, MW: 40225, TM: 1 5 [P] Gene Chromosome: 9p13.3):

Nucleotide: Genbank accession no NM_001782; Genbank version no. NM_001782.2 GI:194018444. Polypeptide: Genbank accession no. NP_001773; Genbank version no. NP_001773.1 GI:4502683.

Cross References: WO2004042346 (claim 65); WO2003/026493 (pages 51-52, 57-58); WO2000/75655 (pages 105-106); Von Hoegen et al *J. Immunol.* 144(12):4870-4877 (1990); Strausberg RL et al *Proc. Natl. Acad. Sci USA* 99:16899-16903(2002).

(33) LY64 (Lymphocyte Antigen 64 (RP105), Type I Membrane Protein of the Leucine Rich Repeat (LRR) Family, Regulates B-Cell Activation and Apoptosis, Loss of Function is Associated

with Increased Disease Activity in Patients with Systemic Lupus Erythematosis); 661 Aa, pl: 6.20, MW: 74147 TM: 1 [P] Gene Chromosome: 5q12):

Nucleotide: Genbank accession no NM_005582; Genbank version no. NM_005582.2 GI:167555126. Polypeptide: Genbank accession no. NP_005573; Genbank version no. NP_005573.2 GI:167555127.

Cross References: US2002/193567; WO97/07198 (claim 11, pages 39-42); Miura Y et al *Genomics* 38(3):299-304(1996); Miura Y et al *Blood* 92:2815-2822(1998); WO2003/083047; WO97/44452 (claim 8, pages 57-61); WO2000/12130 (pages 24-26).

(34) FcRH1 (Fc Receptor-Like Protein 1, a Putative Receptor for the Immunoglobulin Fc Domain that Contains C2 Type Ig-Like and ITAM Domains, May have a Role in B-Lymphocyte 20 Differentiation); 429 Aa, Pl: 5.28, MW: 46925 TM: 1 [P] Gene Chromosome: 1q21-1q22)

Nucleotide: Genbank accession no NM_052938; Genbank version no. NM_052938.4 GI:226958543. Polypeptide: Genbank accession no. NP_443170; Genbank version no. NP_443170.1 GI:16418419.

Cross References: WO2003/077836; WO2001/38490 (claim 6, FIG. 18E-1-18-E-2); Davis RS et al *Proc. Natl. Acad. Sci USA* 98(17):9772-9777(2001); WO2003/089624 (claim 8); EP1347046 (claim 1); WO2003/089624 (claim 7).

(35) IRTA2 (Immunoglobulin Superfamily Receptor Translocation Associated 2, a Putative Immunoreceptor with Possible Roles in B Cell Development and Lymphomagenesis; Deregulation of the Gene by Translocation Occurs in Some B Cell Malignancies); 977 Aa, pl: 6.88, MW: 106468, TM: 1 [P] Gene Chromosome: 1q21):

Nucleotide: Genbank accession no AF343662; Genbank version no. AF343662.1 GI:13591709. Polypeptide: Genbank accession no. AAK31325; Genbank version no. AAK31325.1 GI:13591710.

Cross References: AF343663, AF343664, AF343665, AF369794, AF397453, AK090423, AK090475, AL834187, AY358085; Mouse: AK089756, AY158090, AY506558; NP_112571.1; WO2003/024392 (claim 2, FIG. 97); Nakayama Y et al *Biochem. Biophys. Res. Commun.* 277(1):124-127(2000); WO2003/077836; WO2001/38490 (claim 3, FIG. 18B-1-18B-2).

(36) TENB2 (TMEFF2, Tomoregulin, TPEF, HPP1, TR, Putative Transmembrane 35 Proteoglycan, Related to the EGF/Heregulin Family of Growth Factors and Follistatin); 374 Aa):

Nucleotide: Genbank accession no AF179274; Genbank version no. AF179274.2 GI:12280939. Polypeptide: Genbank accession no. AAD55776; Genbank version no. AAD55776.2 GI:12280940.

Cross References: NCBI Accession: AAD55776, AAF91397, AAG49451, NCBI RefSeq: NP_057276; NCBI Gene: 23671; OMIM: 605734; SwissProt Q9UIK5; AY358907, CAF85723, CQ782436; WO2004/074320; JP2004113151; WO2003/042661; WO2003/009814; EP1295944

(pages 69-70); WO2002/30268 (page 329); WO2001/90304; US2004/249130; US2004/022727; WO2004/063355; US2004/197325; US2003/232350; US2004/005563; US2003/124579; Horie M et al *Genomics* 67:146-152(2000); Uchida T et al *Biochem. Biophys. Res. Commun.* 266:593-602(1999); Liang G et al *Cancer Res.* 60:4907-12 (2000); Glynne-Jones E et al *Int J Cancer*; 94(2):178-84(2001).

(37) PSMA-FOLH1 (Folate Hydrolase (Prostate-Specific Membrane Antigen) 1):

Nucleotide: Genbank accession no M99487; Genbank version no. M99487.1 G1:190663. Polypeptide: Genbank accession no. AAA60209; Genbank version no. AAA60209.1 GI:190664.

Cross References: Israeli R. S., et al *Cancer Res.* 53 (2), 227-230 (1993)

Other Information: Official Symbol: FOLH1; Other Aliases: GIG27, FGCP, FOLH, GCP2, GCPII, NAALAD1, NAALAdase, PSM, PSMA, mGCP; Other Designations: N-acetylated alpha-linked acidic dipeptidase 1; N-acetylated-alpha-linked acidic dipeptidase I; NAALADase I; cell growth-inhibiting gene 27 protein; folylpoly-gamma-glutamate carboxypeptidase; glutamate carboxylase II; glutamate carboxypeptidase 2; glutamate carboxypeptidase II; membrane glutamate carboxypeptidase; prostate specific membrane antigen variant F; pteroylpoly-gamma-glutamate carboxypeptidase.

Antibodies: U.S. Pat. No. 7,666,425; Antibodies produces by Hybridomas having the following ATCC references: ATCC accession No. HB-12101, ATCC accession No. HB-12109, ATCC accession No. HB-12127 and ATCC accession No. HB-12126.

Proscan: a monoclonal antibody selected from the group consisting of 8H12, 3E11, 17G1, 29B4, 30C1 and 20F2 (U.S. Pat. No. 7,811,564; Moffett S., et al Hybridoma (Larchmt) 26(6):363-72(2007)).

Cytogen: monoclonal antibodies 7E11-C5 (ATCC accession No. HB 10494) and 9H10-A4 (ATCC accession No. HB11430)—U.S. Pat. No. 5,763,202.

GlycoMimetics: NUH2—ATCC accession No. HB 9762 (U.S. Pat. No. 7,135,301).

Human Genome Science: HPRAJ70—ATCC accession No. 97131 (U.S. Pat. No. 6,824,993); Amino acid sequence encoded by the cDNA clone (HPRAJ70) deposited as American Type Culture Collection ("ATCC") Deposit No. 97131.

Medarex: Anti-PSMA antibodies that lack fucosyl residues—U.S. Pat. No. 7,875,278.

Mouse anti-PSMA antibodies include the 3F5.4G6, 3D7.1.1, 4E10-1.14, 3E11, 4D8, 3E6, 3C9, 2C7, 1G3, 3C4, 3C6, 4D4, 1G9, 5C8B9, 3G6, 4C8B9, and monoclonal antibodies. Hybridomas secreting 3F5.4G6, 3D7.1.1, 4E10-1.14, 3E11, 4D8, 3E6, 3C9, 2C7, 1G3, 3C4, 3C6, 4D4, 1G9, 5C8B9, 3G6 or 4C8B9 have been publicly deposited and are described in U.S. Pat. No. 6,159,508. Relevant hybridomas have been publicly deposited and are described in U.S. Pat. No. 6,107,090.

Moreover, humanized anti-PSMA antibodies, including a humanized version of J591, are described in further detail in PCT Publication WO 02/098897.

Other mouse anti-human PSMA antibodies have been described in the art, such as mAb 107-1A4 (Wang, S. et al. Int. J. Cancer 92:871-876 (2001)) and mAb 2C9 (Kato, K. et al. Int. J. Urol. 10:439-444 (2003)).

Examples of human anti-PSMA monoclonal antibodies include the 4A3, 7F12, 8C12, 8A11, 16F9, 2A10, 2C6, 2F5 and 1C3 antibodies, isolated and structurally characterized as originally described in PCT Publications WO 01/09192 and WO 03/064606 and in U.S. Provisional Application Ser. No. 60/654,125, entitled "Human Monoclonal Antibodies to Prostate Specific Membrane Antigen (PSMA)", filed on Feb. 18, 2005. The V.sub.H amino acid sequences of 4A3, 7F12, 8C12, 8A11, 16F9, 2A10, 2C6, 2F5 and 1C3 are shown in SEQ ID NOs: 1-9, respectively. The V.sub.L amino acid sequences of 4A3, 7F12, 8C12, 8A11, 16F9, 2A10, 2C6, 2F5 and 1C3 are shown in SEQ ID NOs: 10-18, respectively.

Other human anti-PSMA antibodies include the antibodies disclosed in PCT Publication WO 03/034903 and US Application No. 2004/0033229.

NW Biotherapeutics: A hybridoma cell line selected from the group consisting of 3F5.4G6 having ATCC accession number HB12060, 3D7-1.1. having ATCC accession number HB12309, 4E10-1.14 having ATCC accession number HB12310, 3E11 (ATCC HB12488), 4D8 (ATCC HB12487), 3E6 (ATCC HB12486), 3C9 (ATCC HB12484), 2C7 (ATCC HB12490), 1G3 (ATCC HB12489), 3C4 (ATCC HB12494), 3C6 (ATCC HB12491), 4D4 (ATCC HB12493), 1G9 (ATCC HB12495), 5C8B9 (ATCC HB12492) and 3G6 (ATCC HB12485)—see U.S. Pat. No. 6,150,508.

PSMA Development Company/Progenics/Cytogen—Seattle Genetics: mAb 3.9, produced by the hybridoma deposited under ATCC Accession No. PTA-3258 or mAb 10.3, produced by the hybridoma deposited under ATCC Accession No. PTA-3347—U.S. Pat. No. 7,850,971.

PSMA Development Company—Compositions of PSMA antibodies (US 20080286284, Table 1) This application is a divisional of U.S. patent application Ser. No. 10/395,894, filed on Mar. 21, 2003 (U.S. Pat. No. 7,850,971).

University Hospital Freiburg, Germany—mAbs 3/A12, 3/E7, and 3/F11 (Wolf P., et al *Prostate.*; 70(5):562-9 (2010)).

(38) SST (Somatostatin Receptor; Note that there are 5 Subtypes):

(38.1) SSTR2 (Somatostatin Receptor 2):

Nucleotide: Genbank accession no NM_001050; Genbank version no. NM_001050.2 GI:44890054. Polypeptide: Genbank accession no. NP_001041; Genbank version no. NP_001041.1 GI:4557859.

Cross References: Yamada Y., et al Proc. Natl. Acad. Sci. U.S.A. 89 (1), 251-255 (1992); Susini C., et al Ann Oncol. 17(12):1733-42(2006)

Other Information: Official Symbol: SSTR2; Other Designations: SRIF-1; SS2R; somatostatin receptor type 2.

(38.2) SSTR5 (Somatostatin Receptor 5):

Nucleotide: Genbank accession no D16827; Genbank version no. D16827.1 GI:487683. Polypeptide: Genbank accession no. BAA04107; Genbank version no. BAA04107.1 GI:487684.

Cross References: Yamada, Y., et al *Biochem. Biophys. Res. Commun.* 195 (2), 844-852 (1993).

Other Information: Official Symbol: SSTR5; Other Aliases: SS-5-R; Other Designations: Somatostatin receptor subtype 5; somatostatin receptor type 5.

(38.3) SSTR1; (38.4) SSTR3; (38.5) SSTR4; AvB6—Both Subunits (39+40).

(39) ITGAV (Integrin, Alpha V:

Nucleotide: Genbank accession no M14648 J02826 M18365; Genbank version no. M14648.1 GI:340306. Polypeptide: Genbank accession no. AAA36808; Genbank version no. AAA36808.1 GI:340307.

Cross References: Suzuki S., et al *Proc. Natl. Acad. Sci. U.S.A.* 83 (22), 8614-8618 (1986).

Other Information: Official Symbol: ITGAV; Other Aliases: CD51, MSK8, VNRA, VTNR

Other Designations: antigen identified by monoclonal antibody L230; integrin alpha-V; integrin alphaVbeta3; integrin, alpha V (vitronectin receptor, alpha polypeptide, antigen CD51); vitronectin receptor subunit alpha.

(40) ITGB6 (Integrin, Beta 6):

Nucleotide: Genbank accession no NM_000888; Genbank version no. NM_000888.3 GI:9966771. Polypeptide: Genbank accession no. NP_000879; Genbank version no. NP_000879.2 GI:9625002.

Cross References: Sheppard D. J., et al *Biol. Chem.* 265 (20), 11502-11507 (1990)

Other Information: Official Symbol: ITGB6; Other Designations: integrin beta-6.

Antibodies:

Biogen: U.S. Pat. No. 7,943,742—Hybridoma clones 6.3G9 and 6.8G6 were deposited with the ATCC, accession numbers ATCC PTA-3649 and -3645, respectively.

Biogen: U.S. Pat. No. 7,465,449—In some embodiments, the antibody comprises the same heavy and light chain polypeptide sequences as an antibody produced by hybridoma 6.1A8, 6.3G9, 6.8G6, 6.2B1, 6.2B10, 6.2A1, 6.2E5, 7.1G10, 7.7G5, or 7.1C5.

Centocor (J&J): U.S. Pat. Nos. 7,550,142; 7,163,681. For example in U.S. Pat. No. 7,550,142—an antibody having human heavy chain and human light chain variable regions comprising the amino acid sequences shown in SEQ ID NO: 7 and SEQ ID NO: 8.

Seattle Genetics: 15H3 (Ryan M C., et al Cancer Res Apr. 15, 2012; 72(8 Supplement): 4630).

(41) CEACAM5 (Carcinoembryonic Antigen-Related Cell Adhesion Molecule 5):

Nucleotide: Genbank accession no M17303; Genbank version no. M17303.1 GI:178676.

Polypeptide: Genbank accession no. AAB59513; Genbank version no. AAB59513.1 G1:178677.

Cross References: Beauchemin N., et al *Mol. Cell. Biol.* 7 (9), 3221-3230 (1987).

Other Information: Official Symbol: CEACAM5; Other Aliases: CD66e, CEA;

Other Designations: meconium antigen 100.

Antibodies:

AstraZeneca-MedImmune: US 20100330103; US20080057063;

US20020142359. For example an antibody having complementarity determining regions (CDRs) with the following sequences: heavy chain; CDR1—DNYMH, CDR2—WIDPENGDTE YAPKFRG, CDR3—LIYAGYLAMD Y; and light chain CDR1—SASSSVTYMH, CDR2—STSNLAS, CDR3—QQRSTYPLT. [0218] Hybridoma 806.077 deposited as European Collection of Cell Cultures (ECACC) deposit no. 96022936.

Research Corporation Technologies, Inc.: U.S. Pat. No. 5,047,507.

Bayer Corporation: U.S. Pat. No. 6,013,772.

BioAlliance: U.S. Pat. Nos. 7,982,017; 7,674,605; U.S. Pat. No. 7,674,605 an antibody comprising the heavy chain variable region sequence from the amino acid sequence of SEQ ID NO: 1, and the light chain variable region sequence from the amino acid sequence of SEQ ID NO:2. an antibody comprising the heavy chain variable region sequence from the amino acid sequence of SEQ ID NO:5, and the light chain variable region sequence from the amino acid sequence of SEQ ID NO:6.

Celltech Therapeutics Limited: U.S. Pat. No. 5,877,293.

The Dow Chemical Company: U.S. Pat. Nos. 5,472,693; 6,417,337; 6,333,405; U.S. Pat. No. 5,472,693—for example, ATCC No. CRL-11215; U.S. Pat. No. 6,417,337—for example, ATCC CRL-12208; U.S. Pat. No. 6,333,405—for example, ATCC CRL-12208.

Immunomedics, Inc: U.S. Pat. Nos. 7,534,431; 7,230,084; 7,300,644; 6,730,300; US20110189085; an antibody having CDRs of the light chain variable region comprise: CDR1 comprises KASQDVGTSVA (SEQ ID NO: 20); CDR2 comprises WTSTRHT (SEQ ID NO: 21); and CDR3 comprises QQYSLYRS (SEQ ID NO: 22); and the CDRs of the heavy chain variable region of said anti-CEA antibody comprise: CDR1 comprises TYWMS (SEQ ID NO: 23); CDR2

comprises EIHPDSSTINYAPSLKD (SEQ ID NO: 24); and CDR3 comprises LYFGFPWFAY (SEQ ID NO: 25). US20100221175; US20090092598; US20070202044; US20110064653; US20090185974; US20080069775.

(42) MET (Met Proto-Oncogene; Hepatocyte Growth Factor Receptor):

Nucleotide: Genbank accession no M35073; Genbank version no. M35073.1 GI:187553. Polypeptide: Genbank accession no. AAA59589; Genbank version no. AAA59589.1 GI:553531.

Cross References: Dean M., et al *Nature* 318 (6044), 385-388 (1985).

Other Information: Official Symbol: MET; Other Aliases: AUTS9, HGFR, RCCP2, c-Met.

Other Designations: HGF receptor; HGF/SF receptor; SF receptor; hepatocyte growth factor receptor; met proto-oncogene tyrosine kinase; proto-oncogene c-Met; scatter factor receptor; tyrosine-protein kinase Met.

Antibodies:

Abgenix/Pfizer: US20100040629, For example, the antibody produced by hybridoma 13.3.2 having American Type Culture Collection (ATCC) accession number PTA-5026; the antibody produced by hybridoma 9.1.2 having ATCC accession number PTA-5027; the antibody produced by hybridoma 8.70.2 having ATCC accession number PTA-5028; or the antibody produced by hybridoma 6.90.3 having ATCC accession number PTA-5029.

Amgen/Pfizer: US20050054019, For example, an antibody comprising a heavy chain having the amino acid sequences set forth in SEQ ID NO: 2 where X2 is glutamate and X4 is serine and a light chain having the amino acid sequence set forth in SEQ ID NO: 4 where X8 is alanine, without the signal sequences; an antibody comprising a heavy chain having the amino acid sequences set forth in SEQ ID NO: 6 and a light chain having the amino acid sequence set forth in SEQ ID NO: 8, without the signal sequences; an antibody comprising a heavy chain having the amino acid sequences set forth in SEQ ID NO: 10 and a light chain having the amino acid sequence set forth in SEQ ID NO: 12, without the signal sequences; or an antibody comprising a heavy chain having the amino acid sequences set forth in SEQ ID NO: 14 and a light chain having the amino acid sequence set forth in SEQ ID NO: 16, without the signal sequences.

Agouron Pharmaceuticals (Now Pfizer): US20060035907.

Eli Lilly: US20100129369.

Genentech: U.S. Pat. No. 5,686,292; US20100028337; US20100016241; US20070129301; US20070098707; US20070092520, US20060270594; US20060134104; US20060035278; US20050233960; US20050037431; U.S. Pat. No. 5,686,292—for example, ATCC HB-11894 and ATCC HB-11895; US 20100016241—for example, ATCC HB-11894 (hybridoma 1A3.3.13) or HB-11895 (hybridoma 5D5.11.6).

National Defense Medical Center, Taiwan: Lu R M., et al Biomaterials. 2011 April; 32(12):3265-74.

Novartis: US20090175860.

For example, an antibody comprising the sequences of CDR1, CDR2 and CDR3 of heavy chain 4687, wherein the sequences of CDR1, CDR2, and CDR3 of heavy chain 4687 are residues 26-35, 50-65, and 98-102, respectively, of SEQ ID NO: 58; and the sequences of CDR1, CDR2, and CDR3 of light chain 5097, wherein the sequences of CDR1, CDR2, and CDR3 of light chain 5097 are residues 24-39,55-61, and 94-100 of SEQ ID NO: 37.

Pharmacia Corporation: US20040166544.

Pierre Fabre: US20110239316, US20110097262, US20100115639.

Sumsung: US 20110129481—for example a monoclonal antibody produced from a hybridoma cell having accession number KCLRF-BP-00219 or accession number of KCLRF-BP-00223.

Samsung: US 20110104176—for example an antibody produced by a hybridoma cell having Accession Number: KCLRF-BP-00220.

University of Turin Medical School: DN-30 Pacchiana G., et al *J Biol Chem.*; 285(46):36149-57(2010).

Van Andel Research Institute: Jiao Y., et al *Mol Biotechnol.*; 31(1):41-54(2005).

(43) MUC1 (Mucin 1, Cell Surface Associated):

Nucleotide: Genbank accession no J05581; Genbank version no. J05581.1 GI:188869. Polypeptide: Genbank accession no. AAA59876; Genbank version no. AAA59876.1 G1:188870.

Cross References: Gendler S. J., et al *J. Biol. Chem.* 265 (25), 15286-15293 (1990)

Other Information: Official Symbol: MUC1; Other Aliases: RP11-263K19.2, CD227, EMA, H23AG, KL-6, MAM6, MUC-1, MUC-1/SEC, MUC-1/X, MUC1/ZD, PEM, PEMT, PUM.

Other Designations: DF3 antigen; H23 antigen; breast carcinoma-associated antigen DF3; carcinoma-associated mucin; episialin; krebs von den Lungen-6; mucin 1, transmembrane; mucin-1; peanut-reactive urinary mucin; polymorphic epithelial mucin; tumor associated epithelial mucin; tumor-associated epithelial membrane antigen; tumor-associated mucin.

Antibodies:

AltaRex—Quest Pharma Tech: U.S. Pat. No. 6,716,966—for example an Alt-1 antibody produced by the hybridoma ATCC No PTA-975.

AltaRex—Quest Pharma Tech: U.S. Pat. No. 7,147,850.

CRT: 5E5—Sorensen AL., et al *Glycobiology*. 16(2) 96-107(2006); HMFG2—Burchell J., et al *Cancer Res.*, 47, 5476-5482 (1987); see WO2015/159076

Glycotope GT-MAB: GT-MAB 2.5-GEX (Website: http://www.glycotope.com/pipeline/pankomab-gex)

Immunogen: U.S. Pat. No. 7,202,346. For example, antibody MJ-170: hybridoma cell line MJ-170 ATCC accession no. PTA-5286Monoclonal antibody MJ-171: hybridoma cell line MJ-171 ATCC accession no. PTA-5287; monoclonal antibody MJ-172: hybridoma cell line MJ-172 ATCC accession no. PTA-5288; or monoclonal antibody MJ-173: hybridoma cell line MJ-173 ATCC accession no. PTA-5302.

Immunomedics: U.S. Pat. No. 6,653,104.

Ramot Tel Aviv Uni: U.S. Pat. No. 7,897,351.

Regents Uni. CA: U.S. Pat. No. 7,183,388; US20040005647; US20030077676.

Roche GlycArt: U.S. Pat. No. 8,021,856.

Russian National Cancer Research Center: Imuteran—Ivanov P K., et al *Biotechnol J.*; 2(7):863-70(2007).

Technische Univ Braunschweig: (IIB6, HT186-B7, HT186-D11, HT186-G2, HT200-3A-C1, HT220-M-D1, HT220-M-G8)—Thie H., et al *PLoS One.*; 6(1):e15921(2011).

(44) CA9 (Carbonic Anhydrase IX):

Nucleotide: Genbank accession no. X66839; Genbank version no. X66839.1 GI:1000701. Polypeptide: Genbank accession no. CAA47315; Genbank version no. CAA47315.1 G1:1000702.

Cross References: Pastorek J., et al *Oncogene* 9 (10), 2877-2888 (1994).

Other Information: Official Symbol: CA9; Other Aliases: CAIX, MN;

Other Designations: CA-IX; P54/58N; RCC-associated antigen G250; RCC-associated protein G250; carbonate dehydratase IX; carbonic anhydrase 9; carbonic dehydratase; membrane antigen MN; pMW1; renal cell carcinoma-associated antigen G250.

Antibodies:

Abgenix/Amgen: US20040018198.

Affibody: Anti-CAIX Affibody molecules (http://www.affibody.com/en/Product-Portfolio/Pipeline/).

Bayer: U.S. Pat. No. 7,462,696.

Bayer/Morphosys: 3ee9 mAb—Petrul H M., et al *Mol Cancer Ther.*; 11(2):340-9(2012)

Harvard Medical School: Antibodies G10, G36, G37, G39, G45, G57, G106, G119, G6, G27, G40 and G125. Xu C., et al *PLoS One.*; 5(3): e9625(2010).

Institute of Virology, Slovak Academy of Sciences (Bayer)—U.S. Pat. No. 5,955,075. For example, M75—ATCC Accession No. HB 11128 or MN12—ATCC Accession No. HB 11647.

Institute of Virology, Slovak Academy of Sciences: U.S. Pat. No. 7,816,493. For example the M75 monoclonal antibody that is secreted from the hybridoma VU-M75, which was deposited at the American Type Culture Collection under ATCC No. HB 11128; or the V/10 monoclonal antibody secreted from the hybridoma V/10-VU, which was deposited at the International Depository Authority of the Belgian Coordinated Collection of Microorganisms (BCCM) at the Laboratorium voor Moleculaire Bioloqie-Plasmidencollectie (LMBP) at the Universeit Gent in Gent, Belgium, under Accession No. LMBP 6009CB.

Institute of Virology, Slovak Academy of Sciences US20080177046; US20080176310; US20080176258; US20050031623.

Novartis: US20090252738.

Wilex: U.S. Pat. No. 7,691,375—for example the antibody produced by the hybridoma cell line DSM ASC 2526.

Wilex: US20110123537; Rencarex: Kennett R H., et al *Curr Opin Mol Ther.*; 5(1):70-5(2003).

Xencor: US20090162382.

(45) EGFRvIII (Epidermal Growth Factor Receptor (EGFR), Transcript Variant 3):

Nucleotide: Genbank accession no. NM_201283; Genbank version no. NM_201283.1 G1:41327733. Polypeptide: Genbank accession no. NP_958440; Genbank version no. NP_958440.1 G1:41327734.

Cross-References: Batra SK., et al *Cell Growth Differ.*; 6(10):1251-1259(1995).

Antibodies: U.S. Pat. Nos. 7,628,986 and 7,736,644 (Amgen) For example, a heavy chain variable region amino acid sequence selected from the group consisting of SEQ ID NO: 142 and variants & a light chain variable region amino acid sequence selected from the group consisting of: SEQ ID NO: 144 and variants.

US20100111979 (Amgen); For example, an antibody comprising a heavy chain amino acid sequence comprising: CDR1 consisting of a sequence selected from the group consisting of the amino acid sequences for the CDR1 region of antibodies 13.1.2 (SEQ ID NO: 138), 131 (SEQ ID NO: 2), 170 (SEQ ID NO: 4), 150 (SEQ ID NO: 5), 095 (SEQ ID NO: 7), 250 (SEQ ID NO: 9), 139 (SEQ ID NO: 10), 211 (SEQ ID NO: 12), 124 (SEQ ID NO: 13), 318 (SEQ ID NO: 15), 342 (SEQ ID NO: 16), and 333 (SEQ ID NO: 17); CDR2 consisting of a sequence selected from the group consisting of the amino acid sequences for the CDR2 region of antibodies 13.1.2 (SEQ ID NO: 138), 131 (SEQ ID NO: 2), 170 (SEQ ID NO: 4), 150 (SEQ ID NO: 5), 095 (SEQ ID NO: 7), 250 (SEQ ID NO: 9), 139 (SEQ ID NO: 10), 211 (SEQ ID NO: 12), 124 (SEQ ID NO: 13), 318 (SEQ ID NO: 15), 342 (SEQ ID NO: 16), and 333 (SEQ ID NO: 17); and CDR3 consisting of a sequence selected from the group consisting of the amino acid sequences for the CDR3 region of antibodies 13.1.2

(SEQ ID NO: 138), 131 (SEQ ID NO: 2), 170 (SEQ ID NO: 4), 150 (SEQ ID NO: 5), 095 (SEQ ID NO: 7), 250 (SEQ ID NO: 9), 139 (SEQ ID NO: 10), 211 (SEQ ID NO: 12), 124 (SEQ ID NO: 13), 318 (SEQ ID NO: 15), 342 (SEQ ID NO: 16), and 333 (SEQ ID NO: 17).

US20090240038 (Amgen): For example, an antibody having at least one of the heavy or light chain polypeptides comprises an amino acid sequence that is at least 90% identical to the amino acid sequence selected from the group consisting of: SEQ ID NO: 2, SEQ ID NO: 19, SEQ ID NO: 142, SEQ ID NO: 144, and any combination thereof.

US20090175887 (Amgen): For example, an antibody having a heavy chain amino acid sequence selected from the group consisting of the heavy chain amino acid sequence of antibody 13.1.2 (SEQ ID NO: 138), 131 (SEQ ID NO: 2), 170 (SEQ ID NO: 4), 150 (SEQ ID NO: 5), 095 (SEQ ID NO: 7), 250 (SEQ ID NO: 9), 139 (SEQ ID NO: 10), 211 (SEQ ID NO: 12), 124 (SEQ ID NO: 13), 318 (SEQ ID NO: 15), 342 (SEQ ID NO: 16), and 333 (SEQ ID NO: 17).

US20090156790 (Amgen): For example, antibody having heavy chain polypeptide and a light chain polypeptide, wherein at least one of the heavy or light chain polypeptides comprises an amino acid sequence that is at least 90% identical to the amino acid sequence selected from the group consisting of: SEQ ID NO: 2, SEQ ID NO: 19, SEQ ID NO: 142, SEQ ID NO: 144, and any combination thereof.

US20090155282, US20050059087 and US20050053608 (Amgen): For example, an antibody heavy chain amino acid sequence selected from the group consisting of the heavy chain amino acid sequence of antibody 13.1.2 (SEQ ID NO: 138), 131 (SEQ ID NO: 2), 170 (SEQ ID NO: 4), 150 (SEQ ID NO: 5), 095 (SEQ ID NO: 7), 250 (SEQ ID NO: 9), 139 (SEQ ID NO: 10), 211 (SEQ ID NO: 12), 124 (SEQ ID NO: 13), 318 (SEQ ID NO: 15), 342 (SEQ ID NO: 16), and 333 (SEQ ID NO: 17).

MR1-1 (U.S. Pat. No. 7,129,332; Duke): For example, a variant antibody having the sequence of SEQ ID NO.18 with the substitutions S98P-T99Y in the CDR3 VH, and F92W in CDR3 VL.

L8A4, H10, Y10 (Wikstrand CJ., et al *Cancer Res.*; 55(14):3140-8(1995); Duke).

US20090311803 (Harvard University): For example, SEQ ID NO:9 for antibody heavy chain variable region, and SEQ ID NO: 3 for light chain variable region amino acid sequences

US20070274991 (EMD72000, also known as matuzumab; Harvard University) For example, SEQ ID NOs: 3 & 9 for light chain and heavy chain respectively.

U.S. Pat. No. 6,129,915 (Schering) For example, SEQ. ID NOs: 1, 2, 3, 4, 5 and 6.

mAb CH12—Wang H., et al *FASEB J.*; 26(1):73-80(2012) (Shanghai Cancer Institute).

RAbDMvIII—Gupta P., et al *BMC Biotechnol.*; 10:72 (2010)(Stanford University Medical Center).

mAb Ua30—Ohman L., et al Tumour Biol.; 23(2):61-9 (2002) (Uppsala University).

Han DG., et al *Nan Fang Yi Ke Da Xue Xue Bao.*; 30(1):25-9(2010) (Xi'an Jiaotong University).

(46) Cd33 (Cd33 Molecule):

Nucleotide: Genbank accession no. M_23197; Genbank version no. NM_23197.1 G1:180097. Polypeptide: Genbank accession no. AAA51948; Genbank version no. AAA51948.1 G1:188098.

Cross-References: Simmons D., et al *J. Immunol.* 141 (8), 2797-2800 (1988). CD33, a member of the sialic acid binding, immunoglobulin-like lectin family, is a 67-kDa glycosylated transmembrane protein. CD33 is expressed on most myeloid and monocytic leukemia cells in addition to committed myelomonocytic and erythroid progenitor cells. It is not seen on the earliest pluripotent stem cells, mature granulocytes, lymphoid cells, or nonhematopoietic cells (Sabbath et al., (1985) J. Clin. Invest. 75:756-56; Andrews et al., (1986) Blood 68: 1030-5). CD33 contains two tyrosine residues on its cytoplasmic tail, each of which is followed by hydrophobic residues similar to the immunoreceptor tyrosine-based inhibitory motif (ITIM) seen in many inhibitory receptors.

Other Information: Official Symbol: CD33; Other Aliases: SIGLEC-3, SIGLEC3, p67.

Other Designations: CD33 antigen (gp67); gp67; myeloid cell surface antigen CD33; sialic acid binding Ig-like lectin 3; sialic acid-binding Ig-like lectin.

Antibodies: H195 (Lintuzumab)—Raza A., et al *Leuk Lymphoma.*; 50(8):1336-44 (2009); U.S. Pat. No. 6,759,045 (Seattle Genetics/Immunomedics).

mAb OKT9: Sutherland, D. R. et al. *Proc Natl Acad Sci USA* 78(7): 4515-4519 (1981), Schneider C., et al *J Biol Chem* 257(14), 8516-8522 (1982).

mAb E6: Hoogenboom, H. R., et al *J Immunol* 144(8), 3211-3217 (1990).

U.S. Pat. No. 6,590,088 (Human Genome Sciences) For example, SEQ ID NOs: 1 and 2 and ATCC accession no. 97521.

U.S. Pat. No. 7,557,189 (Immunogen) For example, an antibody or fragment thereof comprising a heavy chain variable region which comprises three CDRs having the amino acid sequences of SEQ ID NOs:1-3 and a light chain variable region comprising three CDRs having the amino acid sequences of SEQ ID NOs:4-6.

(47) Cd19 (Cd19 Molecule):

Nucleotide: Genbank accession no. NM_001178098; Genbank version no. NM_001178098.1 G1:296010920. Polypeptide: Genbank accession no. NP_001171569; Genbank version no. NP_001171569.1 G1:296010921.

Cross-References: Tedder T F., et al J. Immunol. 143 (2): 712-7 (1989)

Other Information: Official Symbol: CD19; Other Aliases: B4, CVID3.

Other Designations: B-lymphocyte antigen CD19; B-lymphocyte surface antigen B4; T-cell surface antigen Leu-12; differentiation antigen CD19.

Antibodies

Immunogen: HuB4—Al-Katib A M., et al *Clin Cancer Res.*; 15(12):4038-45(2009).

4G7: Kügler M., et al *Protein Eng Des Sel.*; 22(3):135-47(2009).

For example, sequences in FIG. 3 of Knappik, A. et al. *J Mol Biol.*; 296(1):57-86(2000).

AstraZeneca/MedImmune: MEDI-551—Herbst R., et al *J Pharmacol Exp Ther.*; 335(1):213-22(2010).

Glenmark Pharmaceuticals: GBR-401—Hou S., et al Mol Cancer Ther (Meeting Abstract Supplement) C164(2011).

U.S. Pat. No. 7,109,304 (Immunomedics): For example, an antibody comprising the sequence of hA19Vk (SEQ ID NO:7) and the sequence of hA19VH (SEQ ID NO:10).

U.S. Pat. No. 7,902,338 (Immunomedics): For example, an antibody or antigen-binding fragment thereof that comprises the light chain complementarity determining region CDR sequences CDR1 of SEQ ID NO: 16 (KASQSVDYDGDSYLN); CDR2 of SEQ ID NO: 17 (DASNLVS); and CDR3 of SEQ ID NO: 18 (QQSTEDPWT) and the heavy chain CDR sequences CDR1 of SEQ ID NO: 19 (SYWMN); CDR2 of SEQ ID NO: 20 (QIWPGDGDTNYNGKFKG) and CDR3 of SEQ ID NO: 21 (RETTTVGRYYYAMDY) and also comprises human antibody framework (FR) and constant region sequences with one or more framework region amino acid residues substituted from the corresponding framework region sequences of the parent murine antibody, and wherein said substituted FR residues comprise the substitution of serine for phenylalanine at Kabat residue 91 of the heavy chain variable region.

Medarex: MDX-1342—Cardarelli P M., et al *Cancer Immunol Immunother.*; 59(2):257-65(2010).

MorphoSys/Xencor: MOR-208/XmAb-5574—Zalevsky J., et al *Blood.*; 113(16):3735-43(2009)

U.S. Pat. No. 7,968,687 (Seattle Genetics) An antibody or antigen-binding fragment comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO:9 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 24.

4G7 chim—Lang P., et al Blood.; 103(10):3982-5(2004) (University of Tübingen) For example, FIG. 6 and SEQ ID No: 80 of US20120082664.

Zhejiang University School of Medicine: 2E8—Zhang J., et al J Drug Target.; 18(9):675-8(2010).

(48) IL2RA (Interleukin 2 Receptor, Alpha); NCBI Reference Sequence: NM_000417.2):

Nucleotide: Genbank accession no. NM_000417; Genbank version no. NM_000417.2 GI:269973860. Polypeptide: Genbank accession no. NP_000408; Genbank version no. NP_000408.1 G1:4557667.

Cross-References: Kuziel W. A., et al *J. Invest. Dermatol.* 94 (6 SUPPL), 27S-32S (1990)

Other Information: Official Symbol: IL2RA; Other Aliases: RP11-536K7.1, CD25, IDDM10, IL2R, TCGFR; Other Designations: FIL-2 receptor subunit alpha; IL-2-RA; IL-2R subunit alpha; IL2-RA; TAC antigen; interleukin-2 receptor subunit alpha; p55.

Antibodies: U.S. Pat. No. 6,383,487 (Novartis/UCL: Baxilisimab [Simulect]) U.S. Pat. No. 6,521,230 (Novartis/UCL: Baxilisimab [Simulect]) For example, an antibody having an antigen binding site comprises at least one domain which comprises CDR1 having the amino acid sequence in SEQ. ID. NO: 7, CDR2 having the amino acid sequence in SEQ. ID. NO: 8, and CDR3 chaving the amino acid sequence in SEQ. ID. NO: 9; or said CDR1, CDR2 and CDR3 taken in sequence as a whole comprise an amino acid sequence which is at least 90% identical to SEQ. ID. NOs: 7, 8 and 9 taken in sequence as a whole.

Daclizumab—Rech A J., et al *Ann N Y Acad Sci.*; 1174:99-106(2009) (Roche).

(49) AXL (AXL Receptor Tyrosine Kinase):

Nucleotide: Genbank accession no. M76125; Genbank version no. M76125.1 G1:292869. Polypeptide: Genbank accession no. AAA61243; Genbank version no. AAA61243.1 G1:29870.

Cross-References: O'Bryan J. P., et al *Mol. Cell. Biol.* 11 (10), 5016-5031 (1991); Bergsagel P. L., et al *J. Immunol.* 148 (2), 590-596 (1992).

Other Information: Official Symbol: AXL; Other Aliases: JTK11, UFO.

Other Designations: AXL oncogene; AXL transforming sequence/gene; oncogene AXL; tyrosine-protein kinase receptor UFO.

Antibodies: YW327.6S2—Ye X., et al *Oncogene.*; 29(38):5254-64(2010). (Genentech); BergenBio: BGB324 (http://www.bergenbio.com/BGB324).

(50) CD30—TNFRSF8 (Tumor Necrosis Factor Receptor Superfamily, Member 8):

Nucleotide: Genbank accession no. M83554; Genbank version no. M83554.1 G1:180095. Polypeptide: Genbank accession no. AAA51947; Genbank version no. AAA51947.1 G1:180096.

Cross-References: Durkop H., et al *Cell* 68 (3), 421-427 (1992).

Other Information: Official Symbol: TNFRSF8; Other Aliases: CD30, D1S166E, Ki-1

Other Designations: CD30L receptor; Ki-1 antigen; cytokine receptor CD30; lymphocyte activation antigen CD30; tumor necrosis factor receptor superfamily member 8.

(51) BCMA (B-Cell Maturation Antigen)—TNFRSF17 (Tumor Necrosis Factor Receptor Superfamily, Member 17):

Nucleotide: Genbank accession no. Z29574; Genbank version no. Z29574.1 GI:471244. Polypeptide: Genbank accession no. CAA82690; Genbank version no. CAA82690.1 GI:471245.

Cross-References: Laabi Y., et al Nucleic Acids Res. 22 (7), 1147-1154 (1994).

Other Information: Official Symbol: TNFRSF17; Other Aliases: BCM, BCMA, CD269.

Other Designations: B cell maturation antigen; B-cell maturation factor; B-cell maturation protein; tumor necrosis factor receptor superfamily member 17.

(52) CT Ags—CTA (Cancer Testis Antigens):

Cross-References: Fratta E., et al. *Mol Oncol.*; 5(2):164-82(2011); Lim S H., et al Am J Blood Res.; 2(1):29-35(2012).

(53) CD174 (Lewis Y)—FUT3 (Fucosyltransferase 3 (Galactoside 3(4)-L-Fucosyltransferase, Lewis Blood Group):

Nucleotide: Genbank accession no. NM000149; Genbank version no. NM000149.3 GI:148277008. Polypeptide: Genbank accession no. NP_000140; Genbank version no. NP_000140.1 G1:4503809.

Cross-References: Kukowska-Latallo, J. F., et al *Genes Dev.* 4 (8), 1288-1303 (1990).

Other Information: Official Symbol: FUT3; Other Aliases: CD174, FT3B, FucT-III, LE, Les

Other Designations: Lewis FT; alpha-(1,3/1,4)-fucosyltransferase; blood group Lewis alpha-4-fucosyltransferase; fucosyltransferase III; galactoside 3(4)-L-fucosyltransferase.

(54) CLEC14A (C-Type Lectin Domain Family 14, Member a; Genbank Accession No. NM175060):

Nucleotide: Genbank accession no. NM175060; Genbank version no. NM175060.2 G1:371123930. Polypeptide: Genbank accession no. NP_778230; Genbank version no. NP_778230.1 G1:28269707.

Other Information: Official Symbol: CLEC14A; Other Aliases: UNQ236/PRO269, C14orf27, CEG1, EGFR-5.

Other Designations: C-type lectin domain family 14 member A; CIECT and EGF-like domain containing protein; epidermal growth factor receptor 5.

(55) GRP78—HSPA5 (Heat Shock 70 kDa Protein 5 (Glucose-Regulated Protein, 78 kDa):

Nucleotide: Genbank accession no. NM005347; Genbank version no. NM005347.4 G1:305855105. Polypeptide: Genbank accession no. NP_005338; Genbank version no. NP_005338.1 GI:16507237.

Cross-References: Ting J., et al DNA 7 (4), 275-286 (1988).

Other Information: Official Symbol: HSPA5; Other Aliases: BIP, GRP78, MIF2.

Other Designations: 78 kDa glucose-regulated protein; endoplasmic reticulum lumenal Ca(2+)-binding protein grp78; immunoglobulin heavy chain-binding protein.

(56) Cd70 (Cd70 Molecule) L08096:

Nucleotide: Genbank accession no. L08096; Genbank version no. L08096.1 GI:307127. Polypeptide: Genbank accession no. AAA36175; Genbank version no. AAA36175.1 GI:307128.

Cross-References: Goodwin R. G., et al *Cell* 73 (3), 447-456 (1993).

Other Information: Official Symbol: CD70; Other Aliases: CD27L, CD27LG, TNFSF7.

Other Designations: CD27 ligand; CD27-L; CD70 antigen; Ki-24 antigen; surface antigen CD70; tumor necrosis factor (ligand) superfamily, member 7; tumor necrosis factor ligand superfamily member 7.

Antibodies: MDX-1411 against CD70 (Medarex) h1F6 (Oflazoglu, E., et al, Clin Cancer Res.; 14(19):6171-80(2008); (Seattle Genetics) For example, see US20060083736 SEQ ID NOs: 1, 2, 11 and 12 and FIG. 1.

(57) Stem Cell Specific Antigens: For Example: 5T4 (see entry (63) below) ; CD25 (see entry (48) above); CD32 . Polypeptide: Genbank accession no. ABK42161; Genbank version no. ABK42161.1 GI:117616286; LGR5/GPR49. Nucleotide: Genbank accession no. NM_003667; Genbank version no. NM_003667.2 G1:24475886. Polypeptide: Genbank accession no. NP_003658; Genbank version no. NP_003658.1 G1:4504379. Prominin/CD133. Nucleotide: Genbank accession no. NM_006017; Genbank version no. NM_006017.2 G1:224994187. Polypeptide: Genbank accession no. NP_006008; Genbank version no. NP_006008.1 G1:5174387.

(58) ASG-5:

Cross-References: (Smith L. M., et. al *AACR* 2010 *Annual Meeting* (abstract #2590); Gudas J. M., et. al. *AACR* 2010 *Annual Meeting* (abstract #4393).

Antibodies Anti-AGS-5 Antibody: M6.131 (Smith, L. M., et. al *AACR* 2010 *Annual Meeting* (abstract #2590)).

(59) ENPP3 (Ectonucleotide Pyrophosphatase/Phosphodiesterase 3):

Nucleotide: Genbank accession no. AF005632; Genbank version no. AF005632.2 G1:4432589. Polypeptide: Genbank accession no. AAC51813; Genbank version no. AAC51813.1 G1:2465540.

Cross-References: Jin-Hua P., et al *Genomics* 45 (2), 412-415 (1997).

Other Information: Official Symbol: ENPP3; Other Aliases: RP5-988G15.3, B10, CD203c, NPP3, PD-IBETA, PDNP3.

Other Designations: E-NPP 3; dJ1005H11.3 (phosphodiesterase I/nucleotide pyrophos-phatase 3); dJ914N13.3 (phosphodiesterase I/nucleotide pyrophosphatase 3); ectonucleotide

pyrophosphatase/phosphodiesterase family member 3; gp130RB13-6; phosphodiesterase I beta; phosphodiesterase I/nucleotide pyrophosphatase 3; phosphodiesterase-1 beta.

(60) PRR4 (Proline Rich 4 (Lacrimal)):

Nucleotide: Genbank accession no. NM_007244; Genbank version no. NM_007244.2 G1:154448885. Polypeptide: Genbank accession no. NP_009175; Genbank version no. NP_009175.2 G1:154448886.

Cross-References: Dickinson D. P., et al *Invest. Ophthalmol. Vis. Sci.* 36 (10), 2020-2031 (1995).

Other Information: Official Symbol: PRR4; Other Aliases: LPRP, PROL4.

Other Designations: lacrimal proline-rich protein; nasopharyngeal carcinoma-associated proline-rich protein 4; proline-rich polypeptide 4; proline-rich protein 4.

(61) GCC—GUCY2C (Guanylate Cyclase 2C (Heat Stable Enterotoxin Receptor):

Nucleotide: Genbank accession no. NM_004963; Genbank version no. NM_004963.3 G1:222080082. Polypeptide: Genbank accession no. NP_004954; Genbank version no. NP_004954.2 G1:222080083.

Cross-References: De Sauvage F. J., et al *J. Biol. Chem.* 266 (27), 17912-17918 (1991); Singh S., et al *Biochem. Biophys. Res. Commun.* 179 (3), 1455-1463 (1991).

Other Information: Official Symbol: GUCY2C; Other Aliases: DIAR6, GUC2C, MUCIL, STAR.

Other Designations: GC-C; STA receptor; guanylyl cyclase C; hSTAR; heat-stable enterotoxin receptor; intestinal guanylate cyclase.

(62) Liv-1—SLC39A6 (Solute Carrier Family 39 (Zinc Transporter), Member 6):

Nucleotide: Genbank accession no. U41060; Genbank version no. U41060.2 GI:12711792. Polypeptide: Genbank accession no. AAA96258; Genbank version no. AAA96258.2 GI:12711793.

Cross-References: Taylor KM., et al *Biochim Biophys Acta.*; 1611(1-2):16-30(2003).

Other Information: Official Symbol: SLC39A6; Other Aliases: LIV-1.

Other Designations: LIV-1 protein, estrogen regulated; ZIP-6; estrogen-regulated protein LIV-1; solute carrier family 39 (metal ion transporter), member 6; solute carrier family 39 member 6; zinc transporter ZIP6; zrt- and Irt-like protein 6.

(63) 5T4, Trophoblast Glycoprotein, TPBG—TPBG (Trophoblast Glycoprotein):

Nucleotide: Genbank accession no. AJ012159; Genbank version no. AJ012159.1 GI:3805946. Polypeptide: Genbank accession no. CAA09930; Genbank version no. CAA09930.1 GI:3805947.

Cross-References: King K. W., et al *Biochim. Biophys. Acta* 1445 (3), 257-270 (1999).

DEMANDE OU BREVET VOLUMINEUX

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CECI EST LE TOME 1 DE 3
CONTENANT LES PAGES 1 À 264

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JUMBO APPLICATIONS/PATENTS

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NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

CLAIMS

What is claimed is:

1. A homogenous conjugation process comprises the following steps:

(a) incubating an antibody or antibody-like protein in the presence of an effective amount of a Zinc-amino chelate/complex ($Zn(NR_1R_2R_3)_{m1}^{2+}$) chelate and a reductant, in a water based buffer system to selectively reduce inter-chain disulfide bonds within the antibody or antibody-like protein to generate thiol groups;

(b) introducing an effective amount of a linker or drug/linker complex bearing thiol reactive groups to react with the thiol groups resulted from step (a);

(c) optionally adding an effective amount of an oxidant to re-oxidize unreacted thiol groups; or adding a quenching agent to cap unreacted thiol groups; and

(d) purifying resulted conjugate;

wherein the optional step (c) can be replaced by: adding an effective amount of cysteine, or a relative disulfide compound, or an azido compound to quench unreacted reductant, while generating cysteine or a thiol compound from reduction of the cystine or a disulfide compound to quench excessive conjugation linker or drug/linker complex containing a thiol reactive group, or an effective amount of cysteine or relative thiol compound can be added to quench excessive linker or linker/payload complex molecule;

wherein R_1, R_2 and R_3 are independently a C_1-C_8 alkyl; C_2-C_8 heteroalkyl, alkylcycloalkyl, or heterocycloalkyl; C_3-C_8 aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, or heteroaryl; m1 is 1, 2, 3, 4, 5, 6, 7 or 8; or N, R_1, R_2 and/or R_3 themselve can form a heterocyclic, carbocyclic, diheterocyclic, or dicarbocyclic ring; and $(NR_1R_2R_3)_{m1}$ can form a dimer, trimer, tetramer, pentamer, or hexamer wherein these polymers are covalently linked by N, R_1, R_2 and/or R_3; the zinc-amino chelate/complex, $Zn(NR_1R_2R_3)_{m1}^{2-}$, used in step (a) is 0.01 mM-1.0 mM in concentration, or 0.5-20 equivalents in moles of the protein;

wherein the reductant is an organic phosphine reductant and used at 1.0 – 20 equivalents in moles of the protein;

wherein the oxidant in step (c) is DHAA, Fe^{3+}, I_2, Cu^{2+}, Mn^{3+}, MnO_2, or a mixture of Fe^{3+}/I^-, the oxidant used in a reaction solution of step (c) is 0.02 mM—1.0 mM in concentration, or 1-100 equivalents in moles of the protein;

wherein a pH in a conjugation reaction of step (b) is between about 5.0 to 8.0;

wherein the reaction solution of step (a) comprises up to 30% of a water mixable (miscible) organic solvent selected from DMA, DMF, ethanol, methanol, acetone, acetonitrile, THF,

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isopropanol, dioxane, propylene glycol, or ethylene diol as a co-solvent in the water based buffer system;

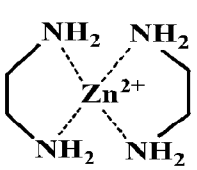
wherein a temperature in the conjugation reaction of step (b) is between about -5 °C to 40 °C; a reaction time of step (b) is between about 15 min to about 48 hours;

wherein the resulted conjugate is purified by gel filtration on a Sephadex G25 or Sephacryl S300 column, adsorption chromatography, ion (cation or anion) exchange chromatography or by dialysis (ultrafiltration or hyperfiltration (UF) and/or diafiltration (DF);

wherein a drug/antibody like protein (antibody) ratio (DAR) of the conjugate is measured by UV at wavelength of range 240-380 nm, by hydrophobic interaction chromatography (HIC-HPLC), Capilary electrophoresis (CE), LC-MS, CE-MS, or LC-MS/MS.

2. The process according to Claim 1, wherein

(a) the zinc cation-amino chelate is selected from the group consisting of $Zn(NH_2CH_3)_2^{2+}$, $Zn(NH_2CH_2CH_3)_2^{2+}$, $Zn(NH_2CH_2CH_2CH_3)_2^{2+}$, $Zn(NH_2CH(CH_3)_2)_2^{2+}$, $Zn(NH_2C(CH_3)_3)_2^{2+}$, $Zn(NH_2CH_2C(CH_3)_3)_2^{2+}$, $Zn(NH(CH_3)_2)_2^{2+}$, $Zn(NH(CH_2CH_3)_2)_2^{2+}$, $Zn(NH(CH(CH_3)_2)_2)_2^{2+}$, $Zn(NH(C(CH_3)_3)_2)_2^{2+}$, $Zn(NH(CH(CH_2CH_3)_2)_2)_2^{2+}$, $Zn(NH(CH_2C(CH_3)_3)_2)_2^{2+}$, $Zn(NH(CH_2C(CH_2CH_3)_3)_2)_2^{2+}$, $Zn(NH(CH_2CH_2C(CH_3)_3)_2)_2^{2+}$, $Zn(NH_2CH_2CH_2OH)_2^{2+}$, $Zn(NH(CH_2CH_2OH)_2)_2^{2+}$, $Zn(N(CH_2CH_2OH)_3)_2^{2+}$, $Zn(NH_2CH_2COOH)_2^{2-}$, $Zn(NH_2CH_2CONH_2)_2^{2+}$, $Zn(NH_2CH_2COOCH_3)_2^{2+}$, $Zn(NH_2CH_2COOCH_2CH_3)_2^{2+}$, $Zn(NH_2CH_2COOC(CH_3)_3)_2^{2+}$, $Zn(NH_2CH_2COOCH(CH_3)_2)_2^{2+}$, $Zn(NH_2CH_2CH_2COOH)_2^{2+}$, $Zn(NH(CH_2COOH)_2)_2^{2+}$, $Zn(N(CH_2CH_2COOH)_3)_2^{2+}$, $Zn(NH_2CH_3)_4^{2+}$, $Zn(NH_2CH_2CH_3)_4^{2+}$, $Zn(NH_2CH_2CH_2CH_3)_4^{2+}$, $Zn(NH_2CH(CH_3)_2)_4^{2+}$, $Zn(NH_2C(CH_3)_3)_4^{2+}$, $Zn(NH_2CH_2C(CH_3)_3)_4^{2+}$, $Zn(NH(CH_3)_2)_4^{2+}$, $Zn(NH(CH_2CH_3)_2)_4^{2+}$, $Zn(NH(CH(CH_3)_2)_2)_4^{2+}$, $Zn(NH(C(CH_3)_3)_2)_4^{2+}$, $Zn(NH(CH(CH_2CH_3)_2)_2)_4^{2+}$, $Zn(NH(CH_2C(CH_3)_3)_2)_4^{2+}$, $Zn(NH(CH_2C(CH_2CH_3)_3)_2)_4^{2+}$, $Zn(NH(CH_2CH_2C(CH_3)_3)_2)_4^{2+}$, $Zn(NH_2CH_2CH_2OH)_4^{2+}$, $Zn(NH(CH_2CH_2OH)_2)_4^{2+}$, $Zn(N(CH_2CH_2OH)_3)_4^{2+}$, $Zn(NH_2CH_2COOH)_4^{2+}$, $Zn(NH_2CH_2CONH_2)_4^{2+}$, $Zn(NH_2CH_2COOCH_3)_4^{2+}$, $Zn(NH_2CH_2COOCH_2CH_3)_4^{2+}$, $Zn(NH_2CH_2COOC(CH_3)_3)_4^{2+}$, $Zn(NH_2CH_2COOCH(CH_3)_2)_4^{2+}$, $Zn(NH_2CH_2CH_2COOH)_4^{2+}$, $Zn(NH(CH_2COOH)_2)_4^{2-}$, $Zn(N(CH_2CH_2COOH)_3)_4^{2+}$,



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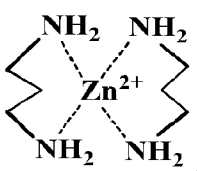

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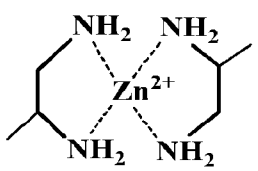

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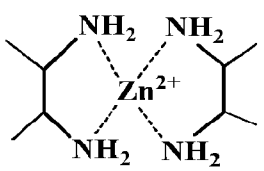

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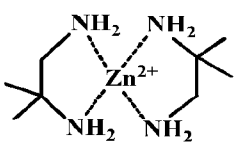

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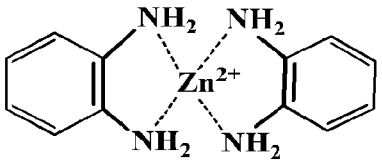
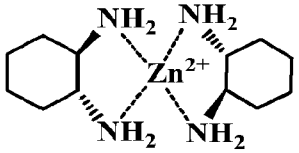
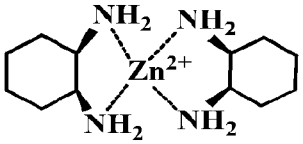
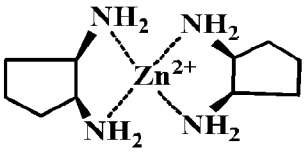
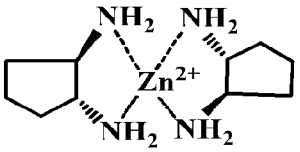
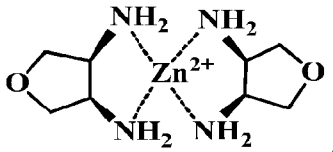
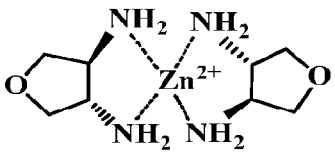
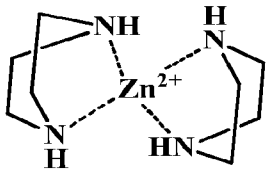
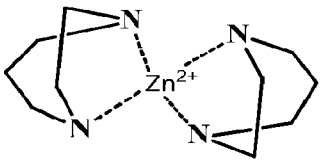
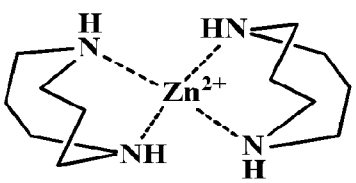
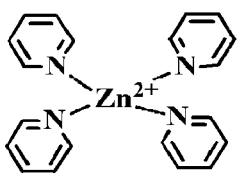
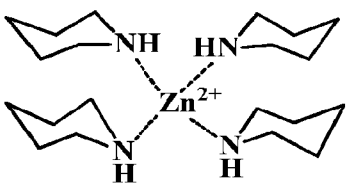
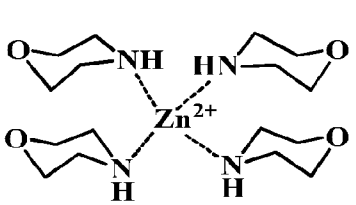
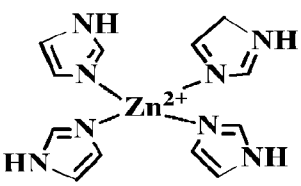
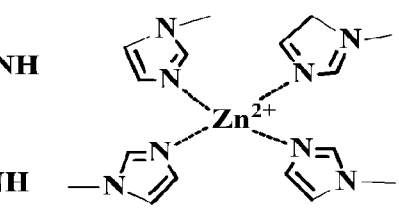
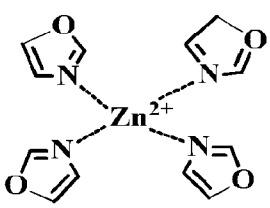
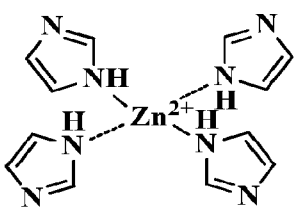
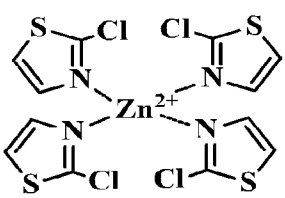
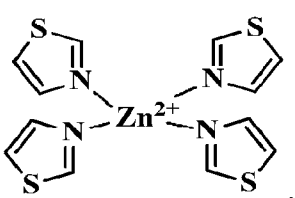
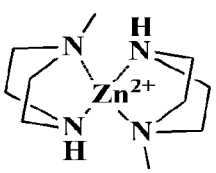
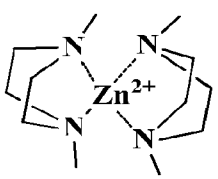
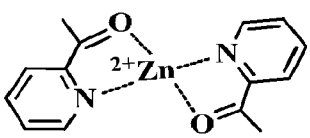
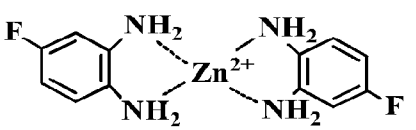
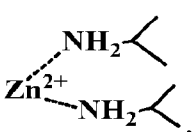
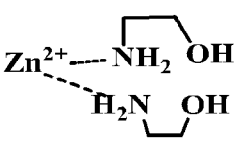
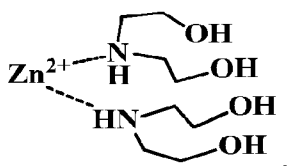
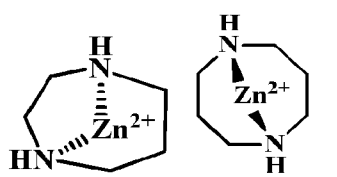

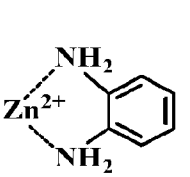

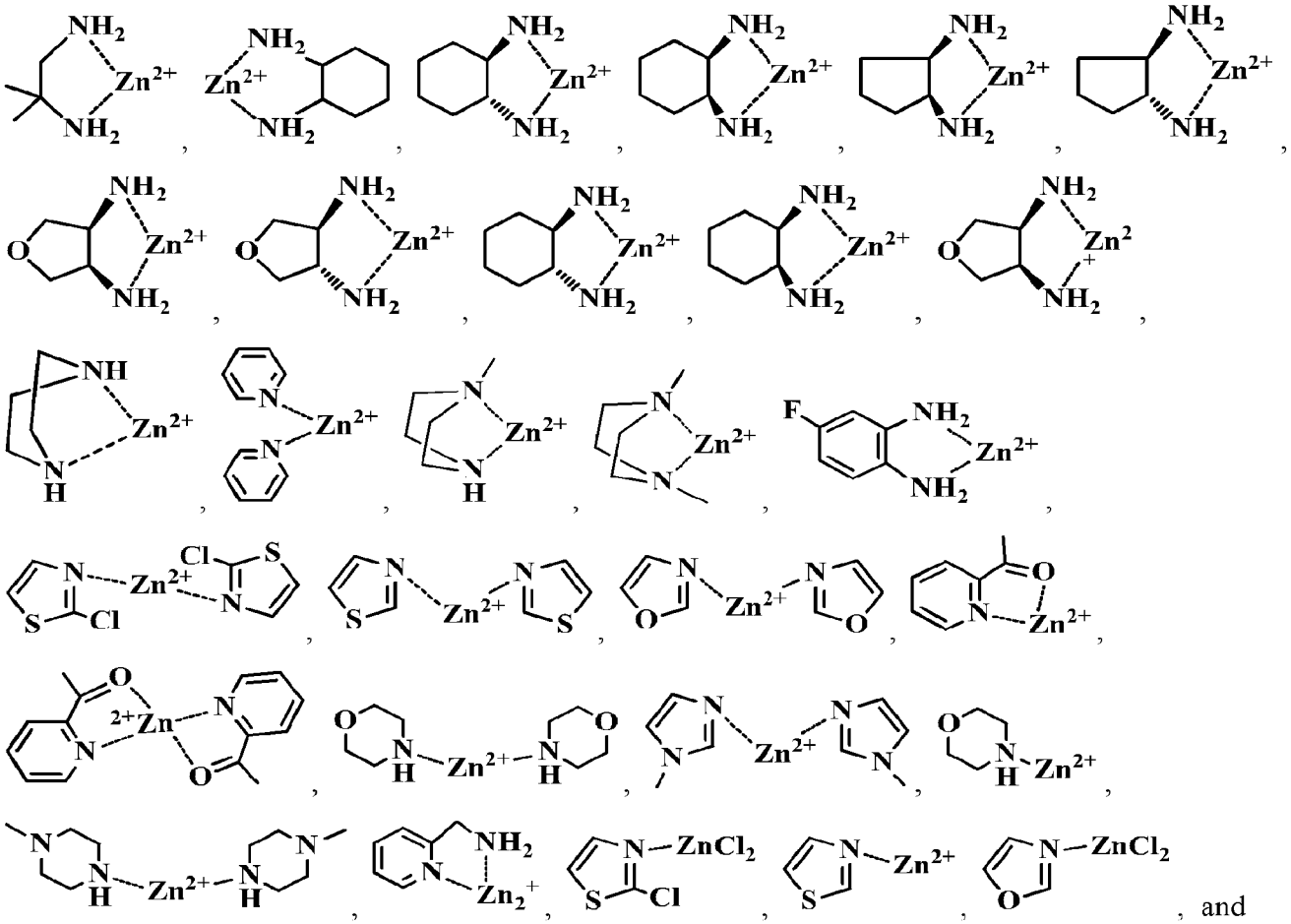

, and

a salt formed from any of the above cations with an anion which is selected from the group consisting of Cl^-, Br^-, I^-, SO_4^{2-}, HSO_4^-, NO_3^-, PO_4^{3-}, HPO_4^{2-}, $H_2PO_4^-$, CO_3^{2-}, HCO_3^-, $HCOO^-$, CH_3COO^-, F_3CCOO^-, Cl_3CCOO^-, FCH_2COO^-, $ClCH_2COO^-$, F_2CHCOO^-, Cl_2CHCOO^-, BF_4^-, SO_3^{2-}, HSO_3^-, CH_3SO^{3-}, $C_6H_5CH_2SO^{3-}$, $C_6H_5SO^{3-}$, $C_6H_5COO^-$, $C_6H_5CH_2COO^-$, $C_6F_5O^-$, $C_6H_4(OH)COO^-$, $C_6H_2F_3O^-$, $C_6H_4(NO_2)O^-$, and $C_6H_2(NO_2)_3O^-$;

wherein the zinc-amino complex in the reaction solution of step (a) are 0.5 -20 equivalents in moles of the protein, and is added with a water- miscible organic solvent, selected from ethanol, methanol, propanol, propandiol, DMA, DMF, DMSO, THF, or CH_3CN.

(b). wherein the organic phosphine reductant is selected from the group consisting of Tris(2-carboxycthyl)phosphinc (TCEP) ($P(CH_2CH_2COOH)_3$), Tris(hydroxypropyl)phosphinc ($P(CH_2CH_2CH_2OH)_3$), and the reductant used in the reaction solution of step (A) is 2.0 - 4.0 equivalents in moles of the protein.

(c). wherein the buffer system comprises PBS, Mes, Bis-Tris, Bis-Tris Propane, Pipes, Aces, Mopso, Bes, Mops, Hepes, Tes, Pipps, Dipso, Tapso, Heppso, Tris-up, Tris-HCl, Tricine, Hepps, Gly-Gly, Bicine, Taps, Hepee, Acetate, Histidine, Citrate, MES, Borate, or a combination

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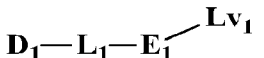
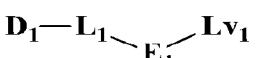
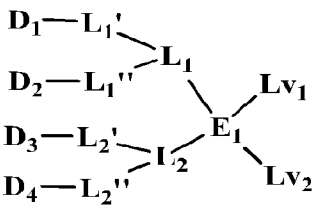
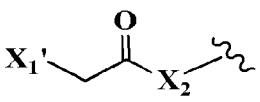
of two, three or four buffer components from above; a pH of the buffer system is 4.0 -9.0; a concentration of the buffer in the reaction solution of step (A) is 0.02 – 1.0 M.

3. The process according to Claim 1, wherein the drug/linker complex has a formula (I), (II), (III) or (IV):

(I), or

(II), or

(III), or

(IV),

wherein: Lv_1 and Lv_2 are a thiol reaction group, and are independently or jointly selected from: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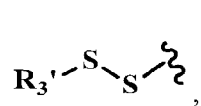
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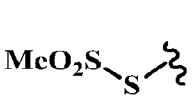
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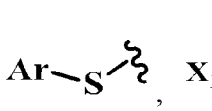
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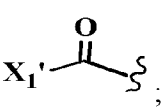
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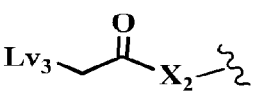
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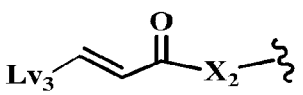
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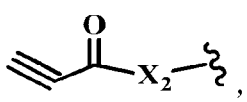
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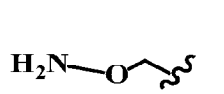
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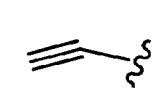
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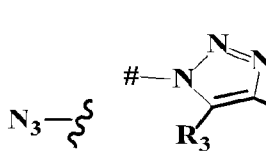
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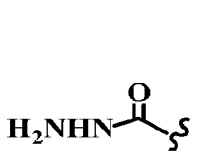
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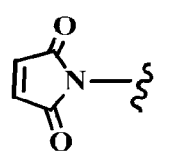
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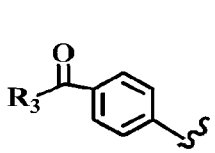
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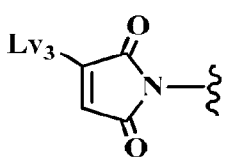
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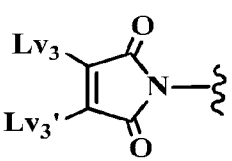
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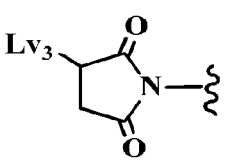
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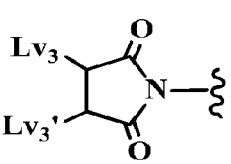
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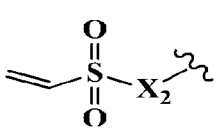

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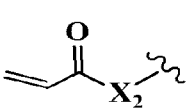
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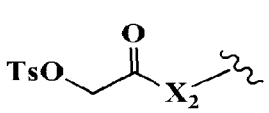
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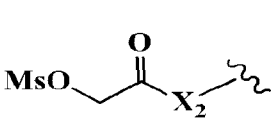
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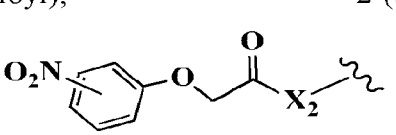
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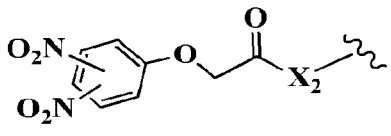
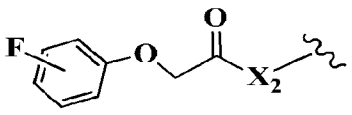
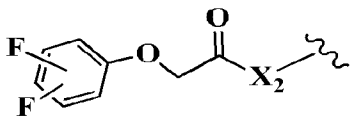
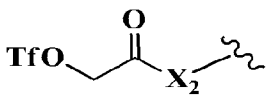
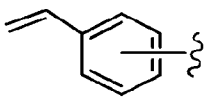
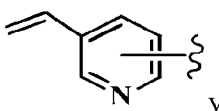
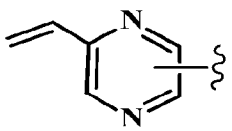
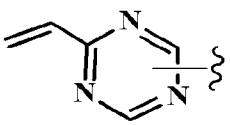
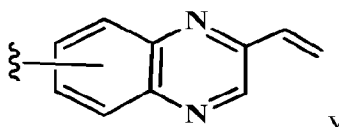
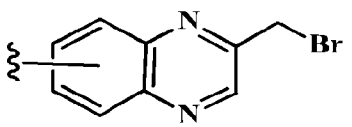
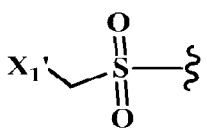
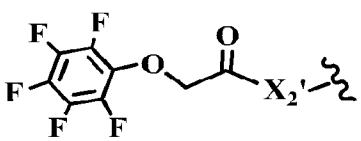
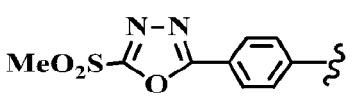
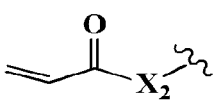
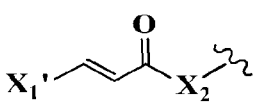
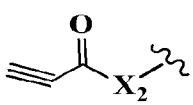
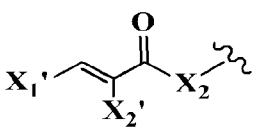
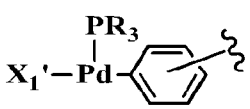
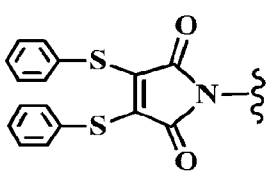
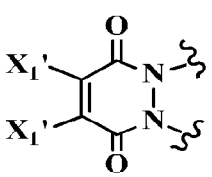
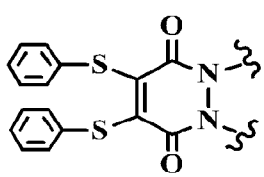
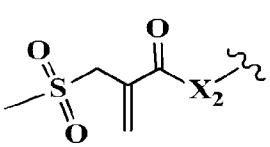
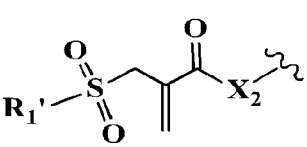
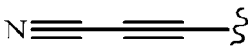
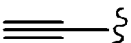
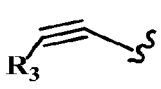

2-(dinitrophenoxy)acetyl;  2-(fluorophenoxy)-acetyl;  2-(difluorophenoxy)-acetyl;  2-(((trifluoromethyl)-sulfonyl)oxy)acetyl;  styrene,  vinylpyridine,  vinylpyrazine,  vinyl-1, 3, 5-triazine,  vinylquinoxaline,  ,  substituted methylsulfonyl,  2-(pentafluorophenoxy)acetyl;  , methylsulfonephenyloxadiazole (ODA);  acryl,  halo acryl,  propiol,  2, 3-dihaloacryl,  Aryl-palladium complex,  bis(phenylsulfanyl)-maleimides,  bis-halide-pyridazinediones,  bis-phenylsulfanyl-pyridazinedione,  2-((methylsulfonyl)methyl)acryl,  2-((alkyl or aryl-sulfonyl)methyl)acryl,  cyanoethynyl,  ethynyl;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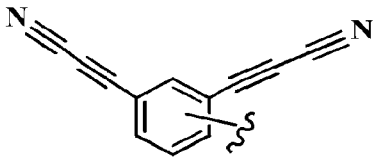
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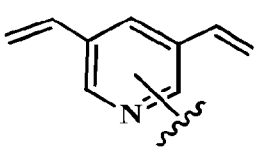
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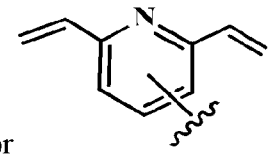
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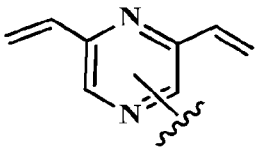
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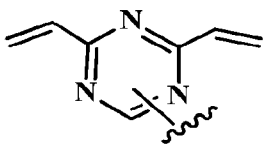
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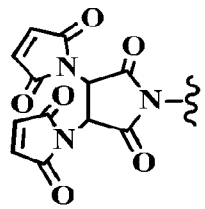
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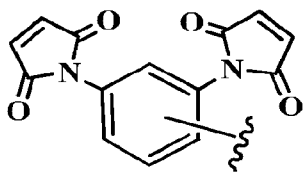
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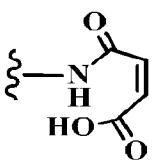
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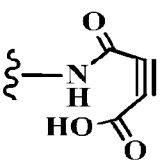
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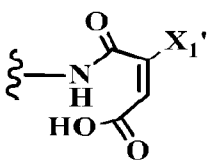
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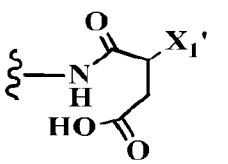
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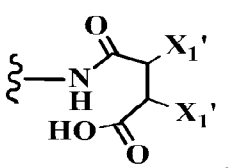
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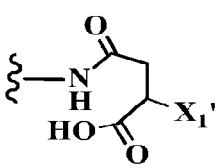
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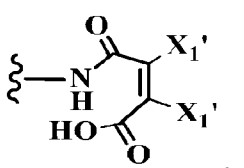
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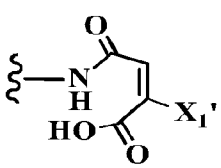
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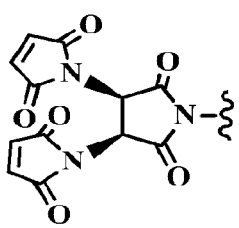
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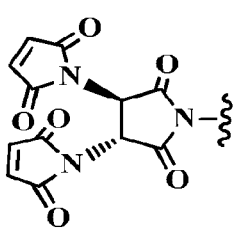
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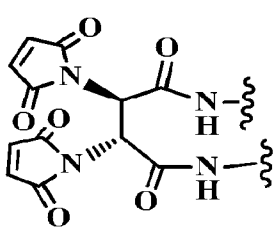
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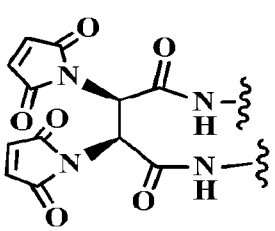
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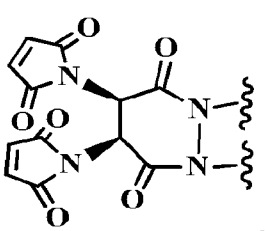
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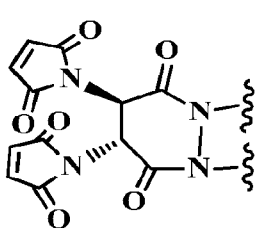
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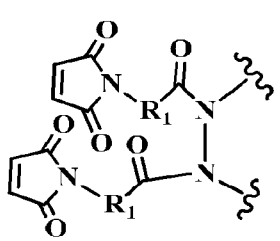
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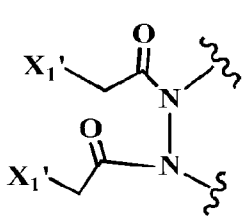
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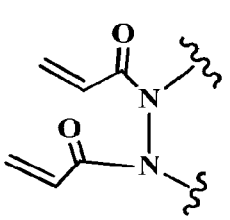
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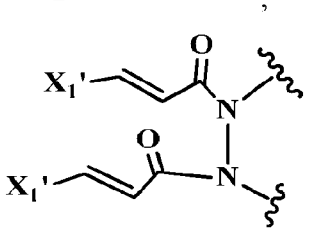
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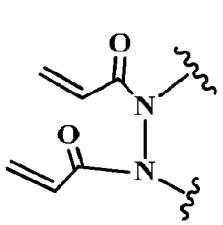
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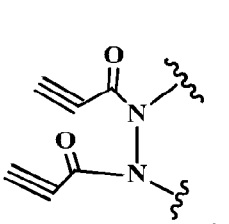
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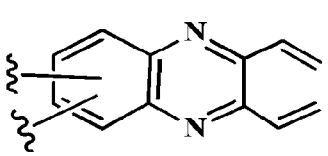
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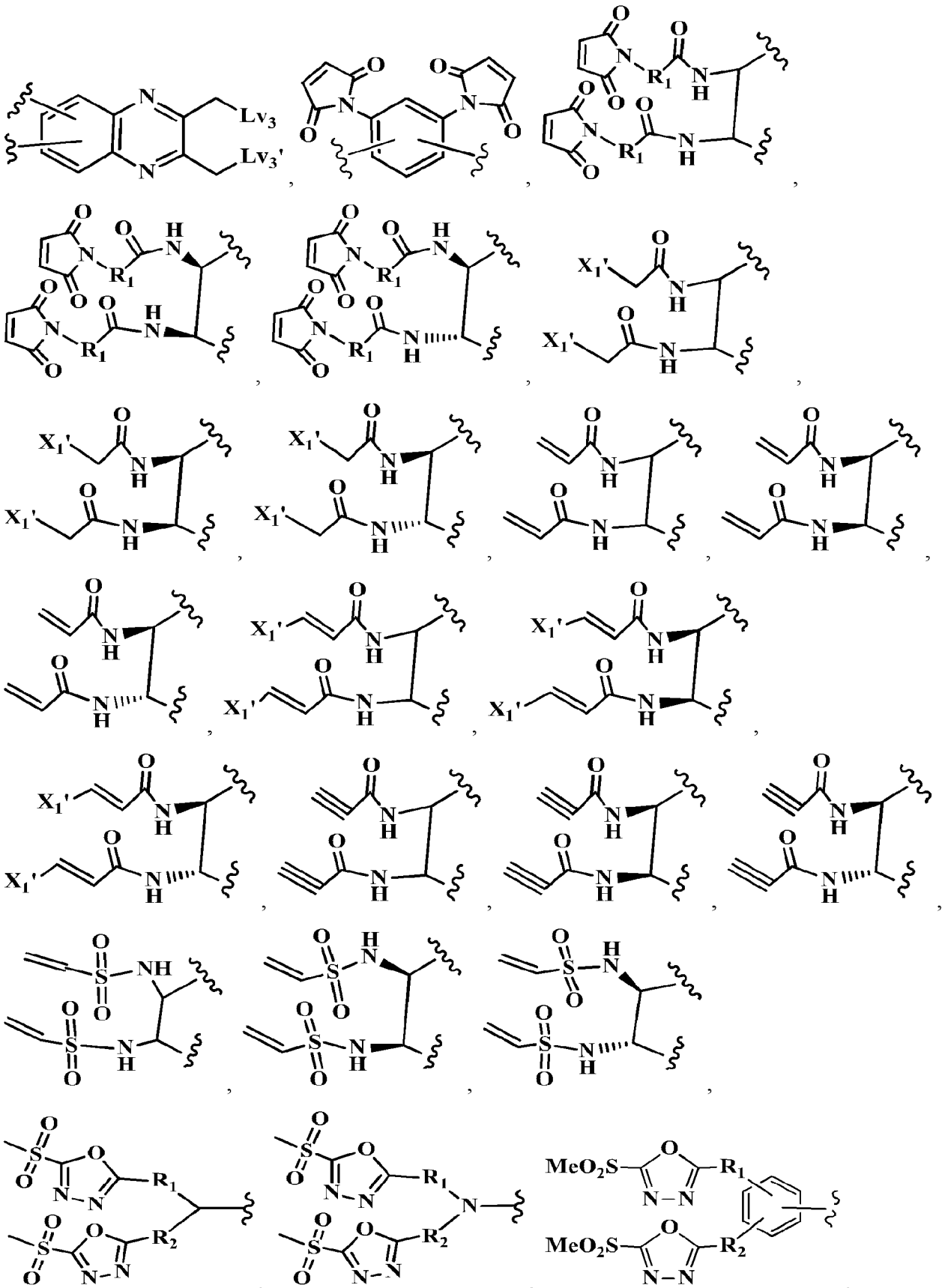

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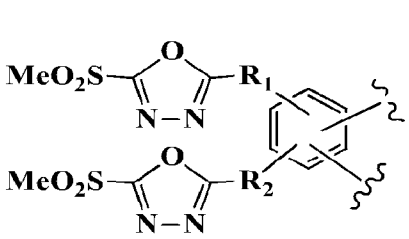
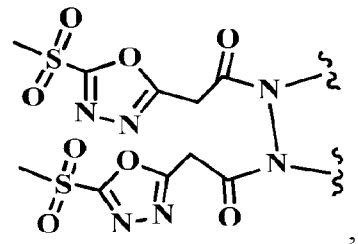
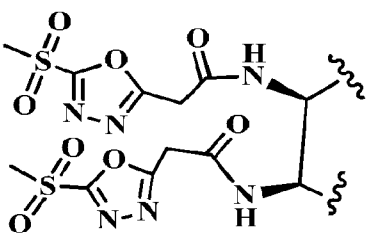
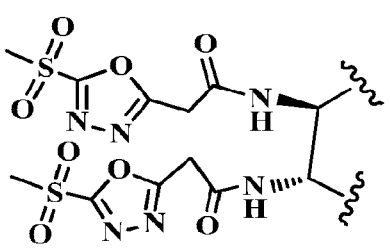
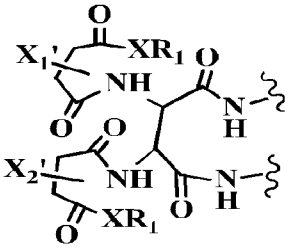
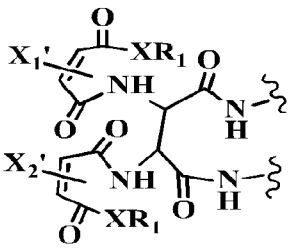
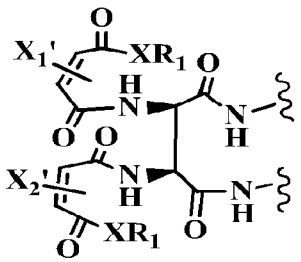
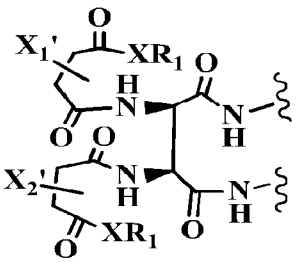
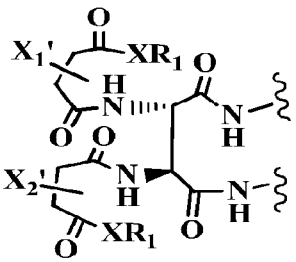
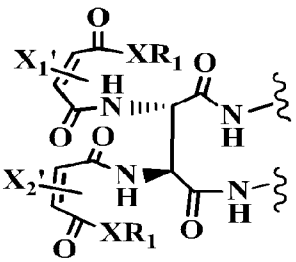
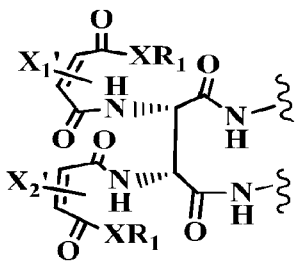
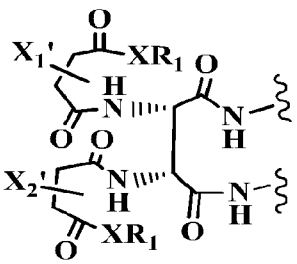
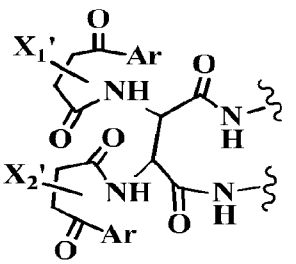
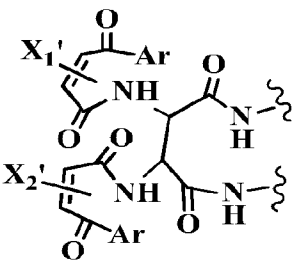
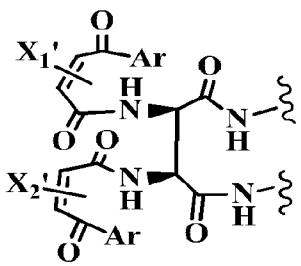
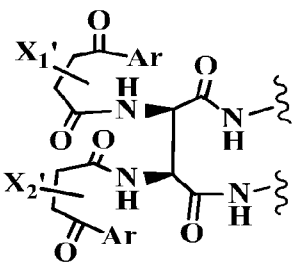
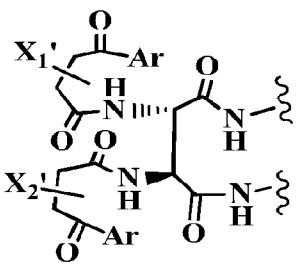
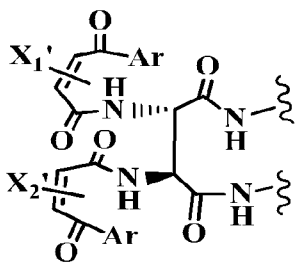
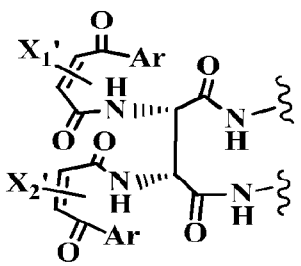
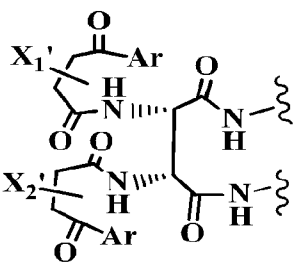
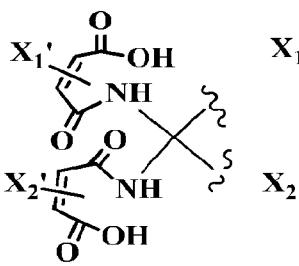
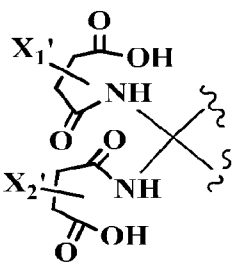

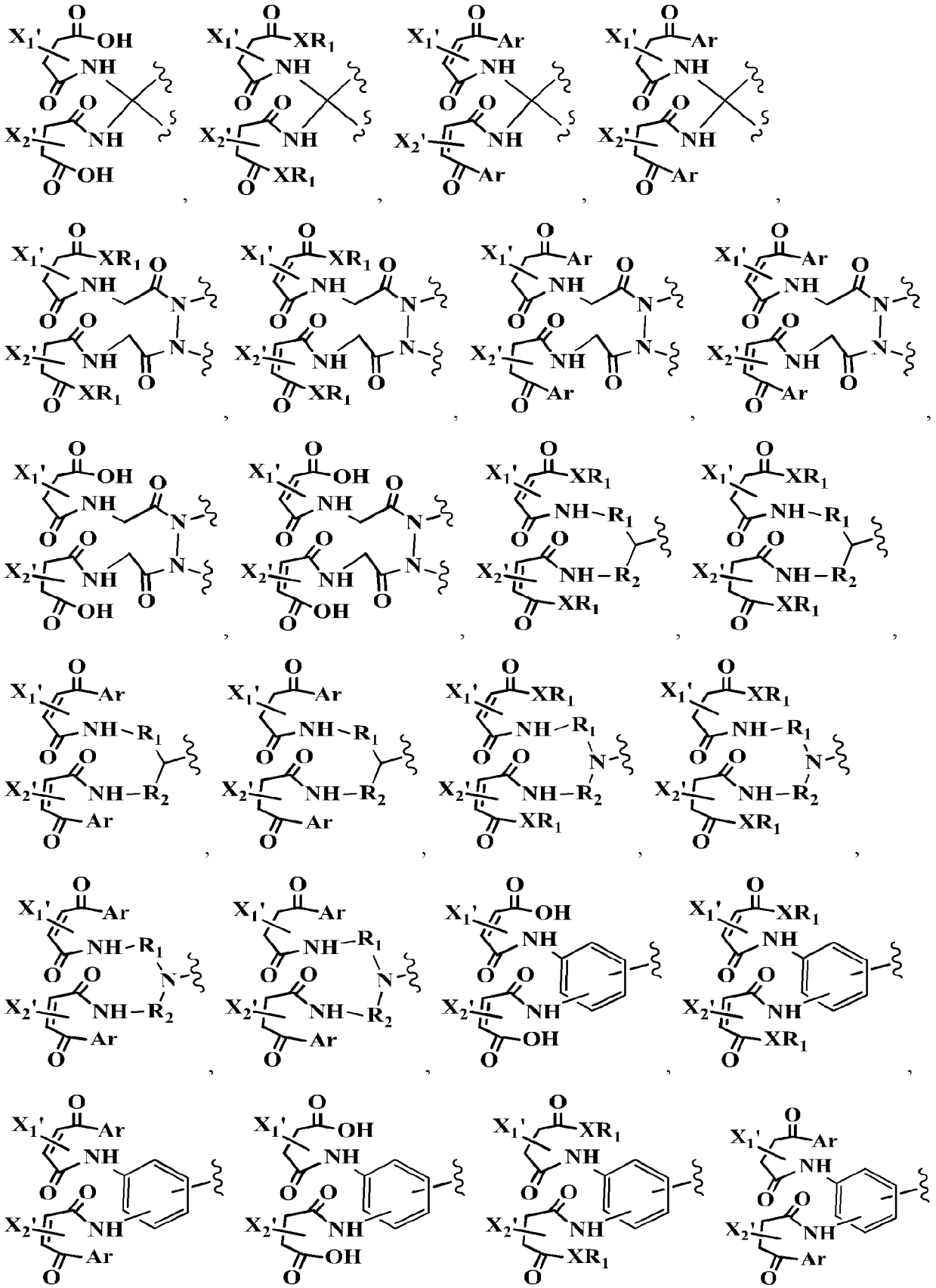

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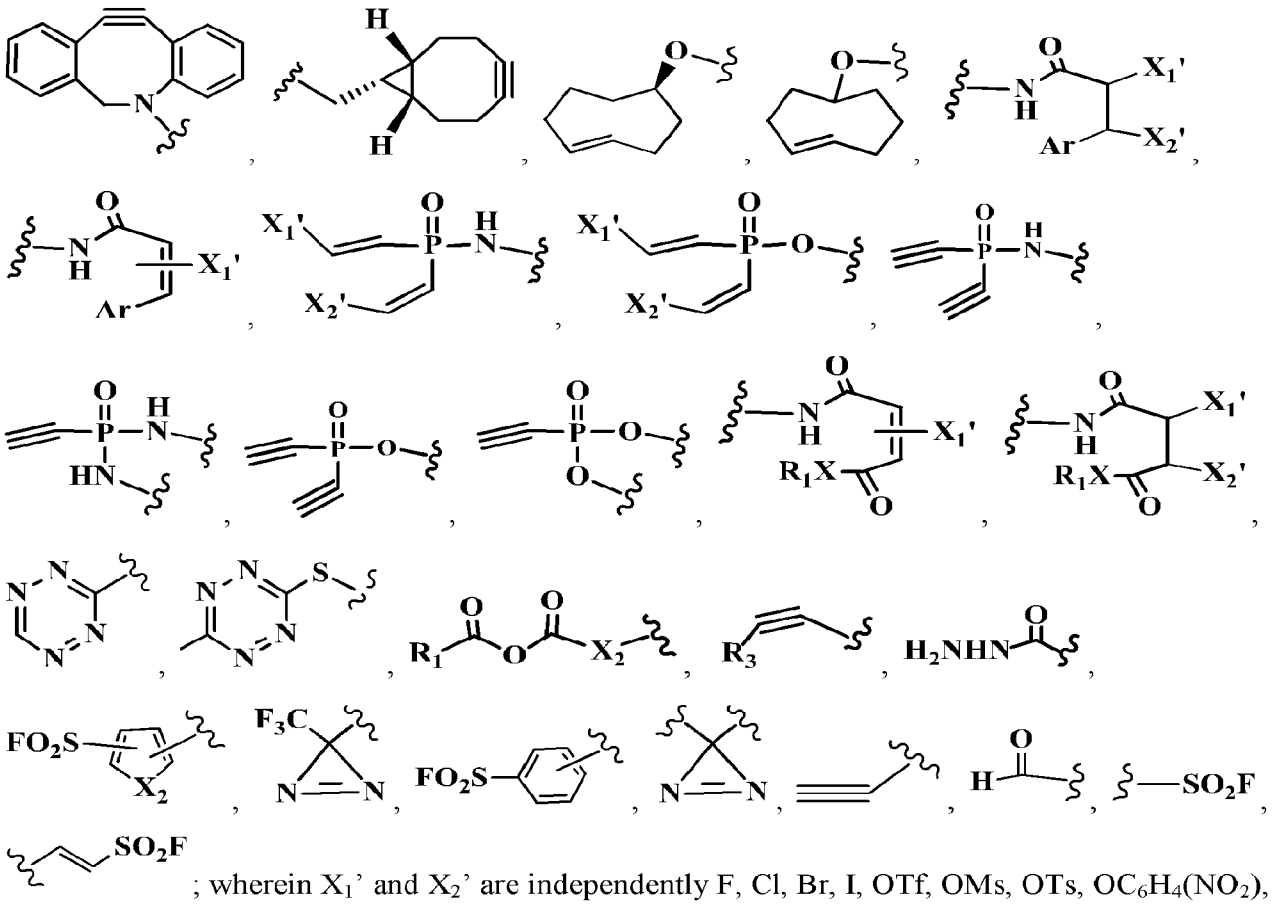

; wherein X_1' and X_2' are independently F, Cl, Br, I, OTf, OMs, OTs, $OC_6H_4(NO_2)$, $OC_6H_3(NO_2)_2$, OC_6F_5, OC_6HF_4, $OC_6H_2F_3$, or Lv_3; X_2 is O, NH, $N(R_1)$, or CH_2; R_3 and R_5 are independently H, R_1, aromatic, heteroaromatic, or aromatic group wherein one or several H atoms are replaced independently by -R_1, -halogen, -OR_1, -SR_1, -NR_1R_2, - NO_2, -$S(O)R_1$, -$S(O)_2R_1$, or -$COOR_1$; Lv_3 and Lv_3' are independently a leaving group selected from F, Cl, Br, I, nitrophenoxyl; N-hydroxysuccinimide (NHS); phenoxyl; benzenethiol, dinitrophenoxyl; pentafluorophenoxyl; tetrafluorophenoxyl; difluorophenoxyl; monofluorophenoxyl; pentachlorophenoxyl; triflate; imidazole; dichlorophenoxyl; tetrachlorophenoxyl; 1-hydroxybenzotriazole; tosylate; mesylate; 2-ethyl-5-phenylisoxazolium-3′-sulfonate, anhydrides formed its self, or formed with the other anhydride, e.g. acetyl anhydride, formyl anhydride; or an intermediate molecule generated with a condensation reagent for peptide coupling reactions or for Mitsunobu reactions;

Wherein E_1 is a joint group that link two thiol reactive groups of Lv_1 and Lv_2. E_1 is selected from CH, CH_2, NH, NHNH, $N(R_3)$, $N(R_3)N(R_{3'})$, N=N, N-N, P, P(=O), S, Si, C_2-C_8 of alkyl, heteroalkyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 of aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; a peptide containing1~4 units of aminoacids, preferably selected from aspatic acid, glutamic acid, arginine, histidine, lysine, serine, threonine,

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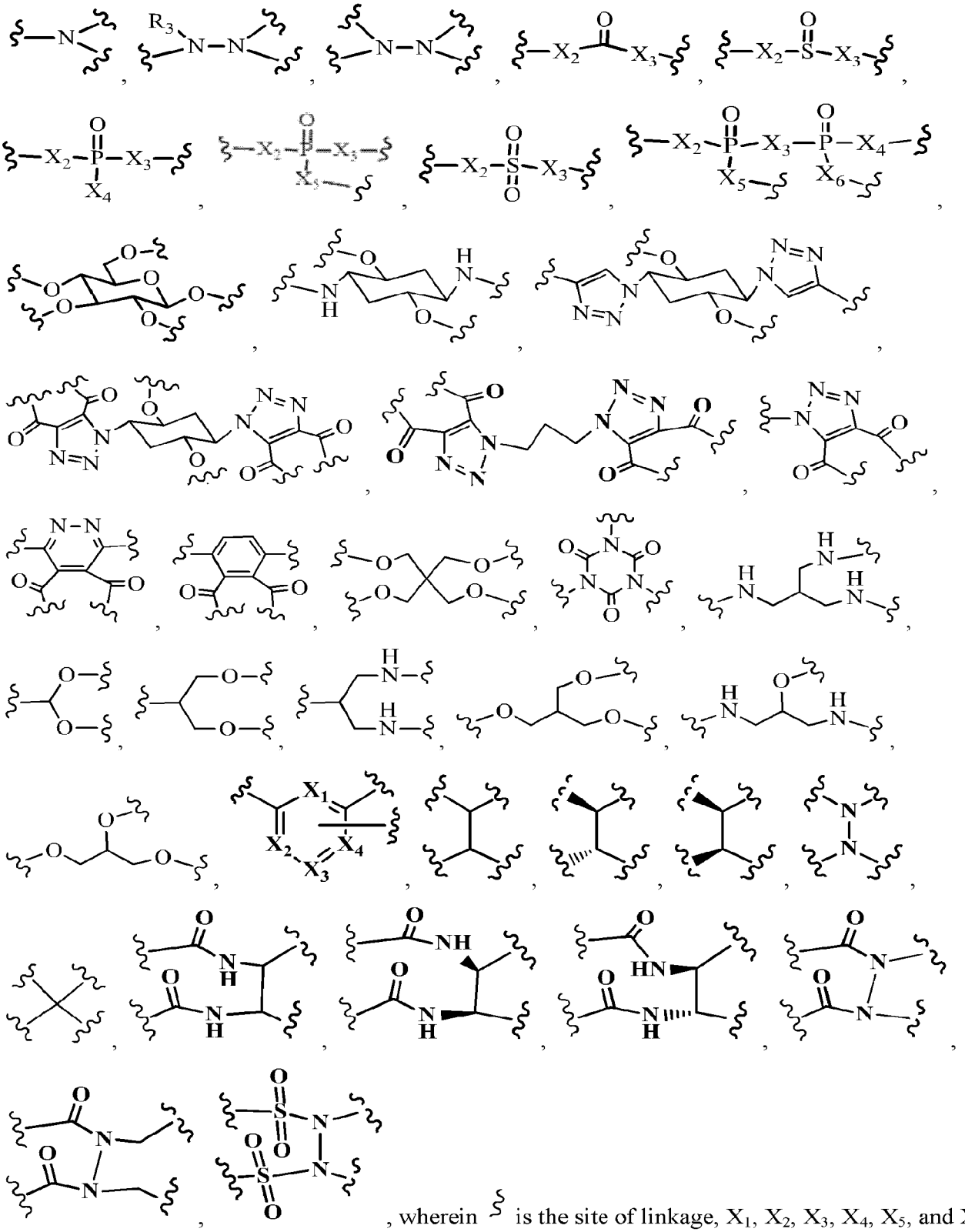
asparagine, glutamine, cysteine, selenocysteine, tyrosine, phenylalanine, glycine, proline, tryptophan, alanine; or one of the following structures:



, wherein ~ is the site of linkage, X_1, X_2, X_3, X_4, X_5, and X_6 are independently selected from O, NH, S, N(R_3), CH_2; R_3 is C_1-C_6 alkyl.

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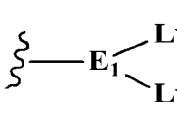
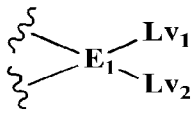
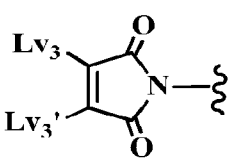
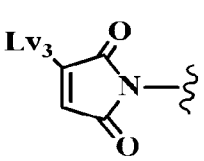
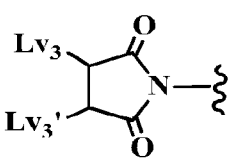
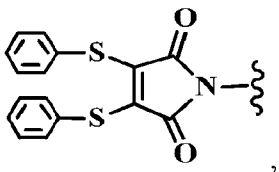
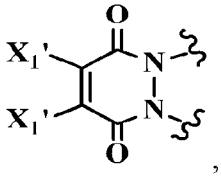
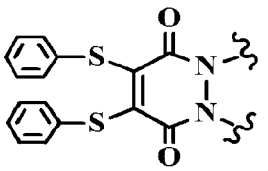
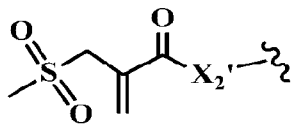
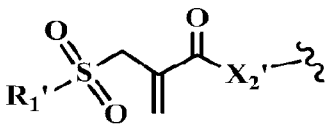
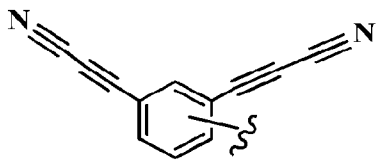
In the formula (II), formula (III) and formula (IV) wherein  and  can be selected from:

 ;
 ;
 ;
 ,
 ,
 ,
 ,
 ,

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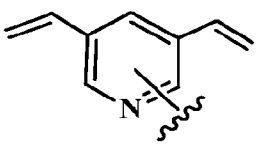
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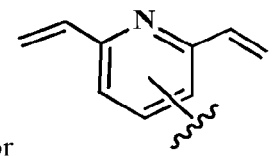
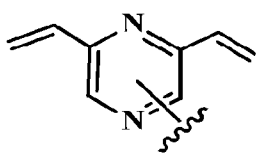
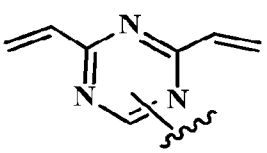
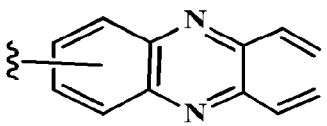
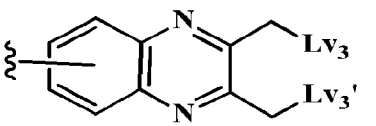
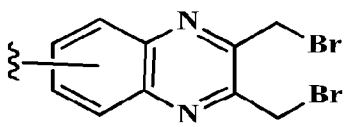
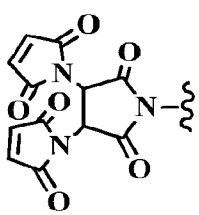
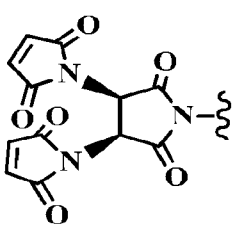
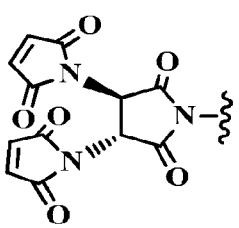
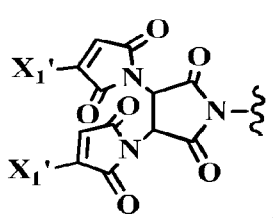
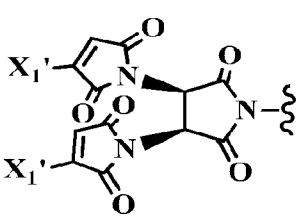
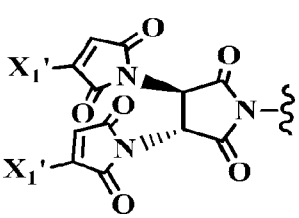
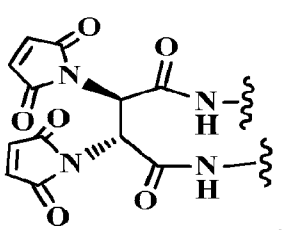
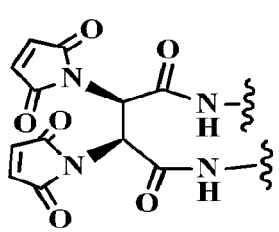
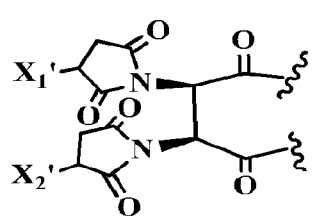
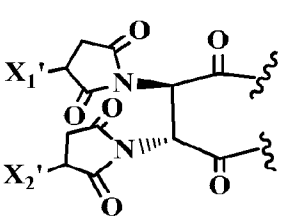
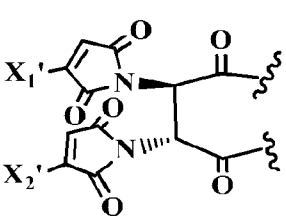
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,

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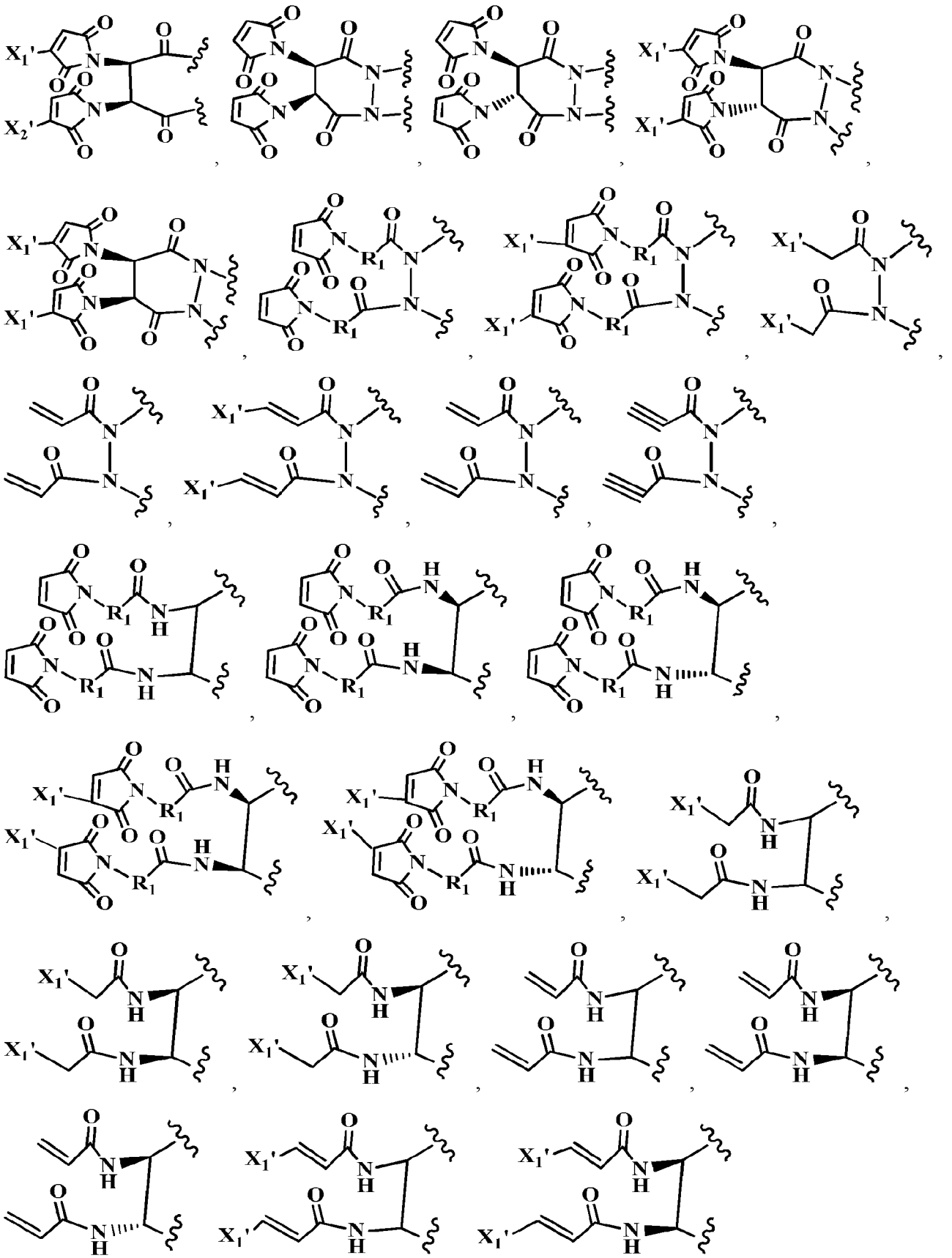

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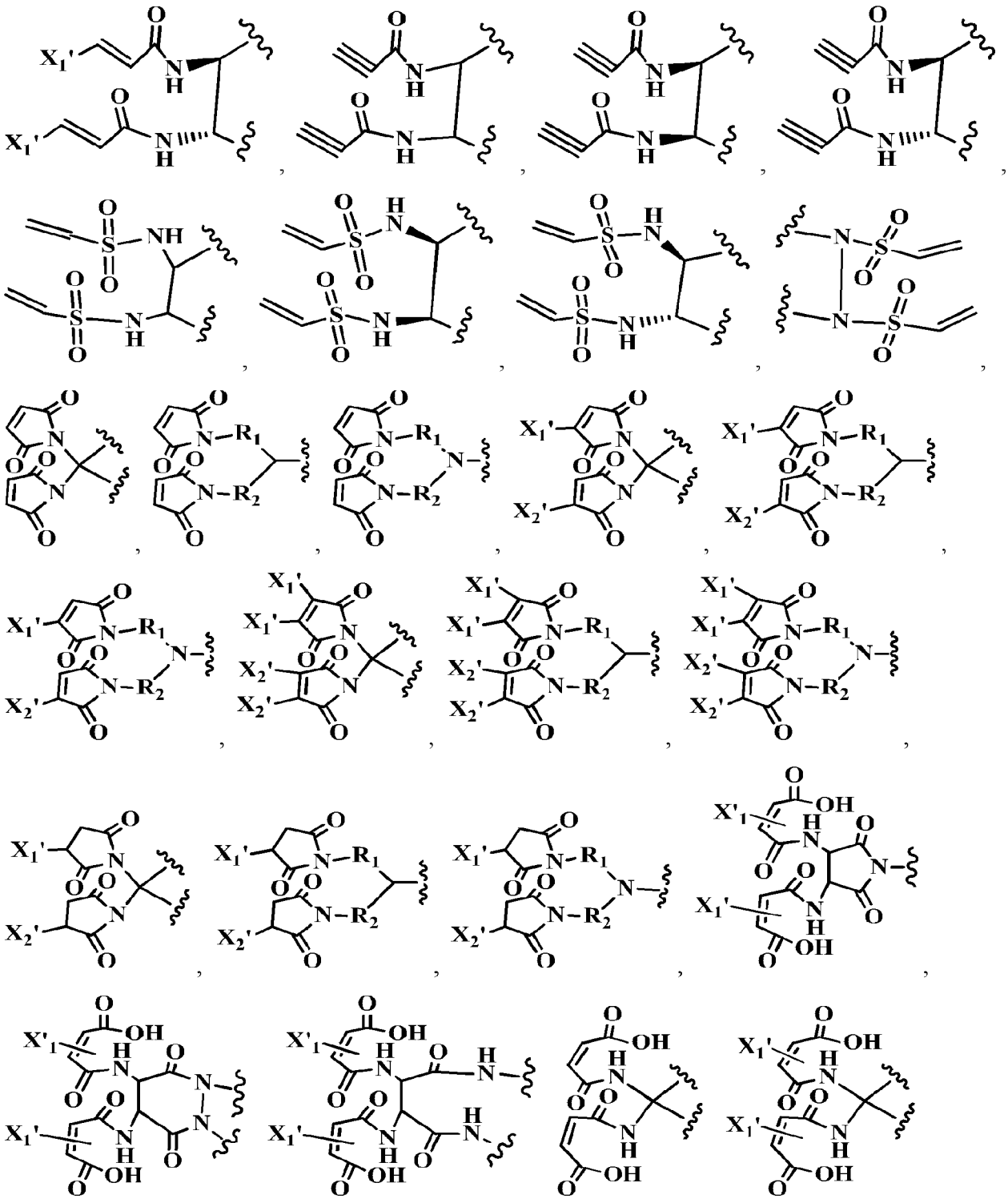

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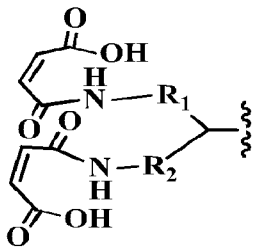
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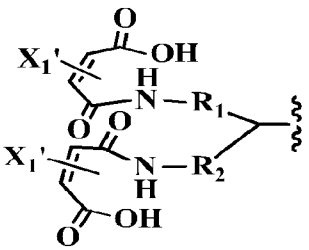
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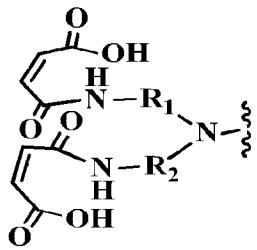
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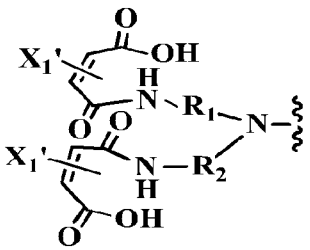
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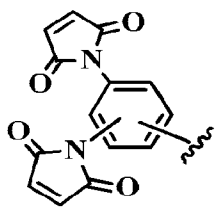
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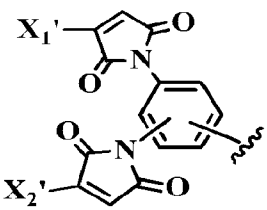
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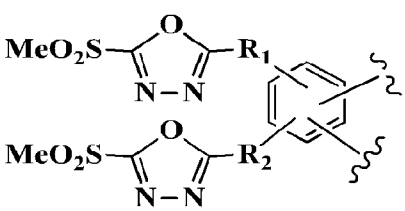
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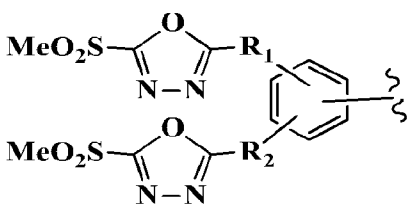
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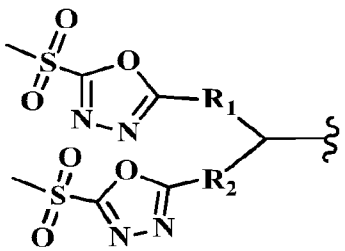
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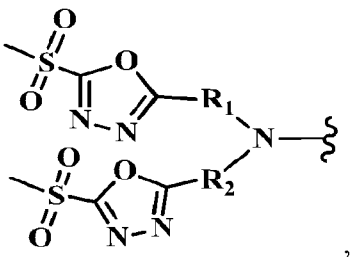
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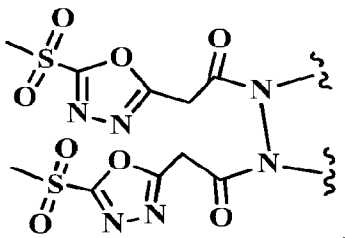
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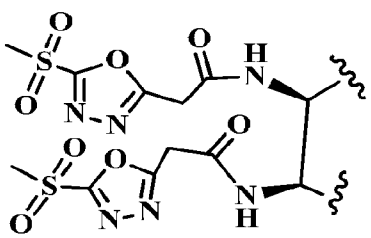
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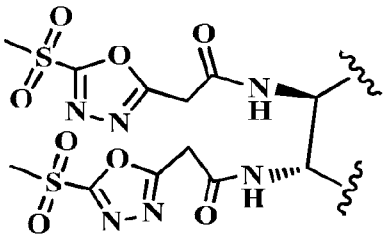
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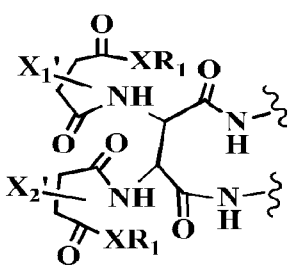
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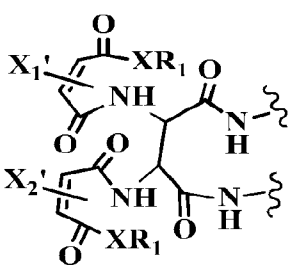
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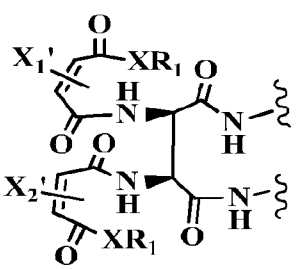
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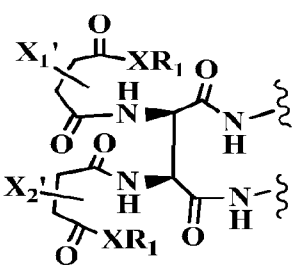
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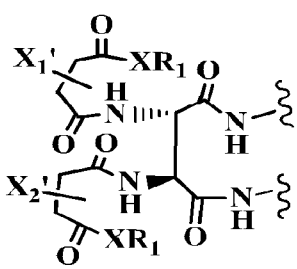
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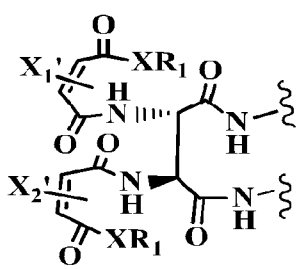
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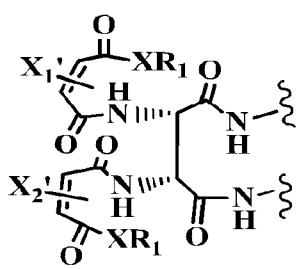
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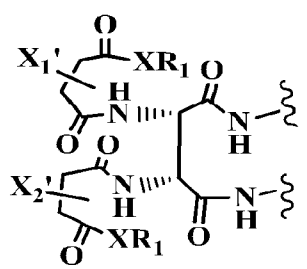
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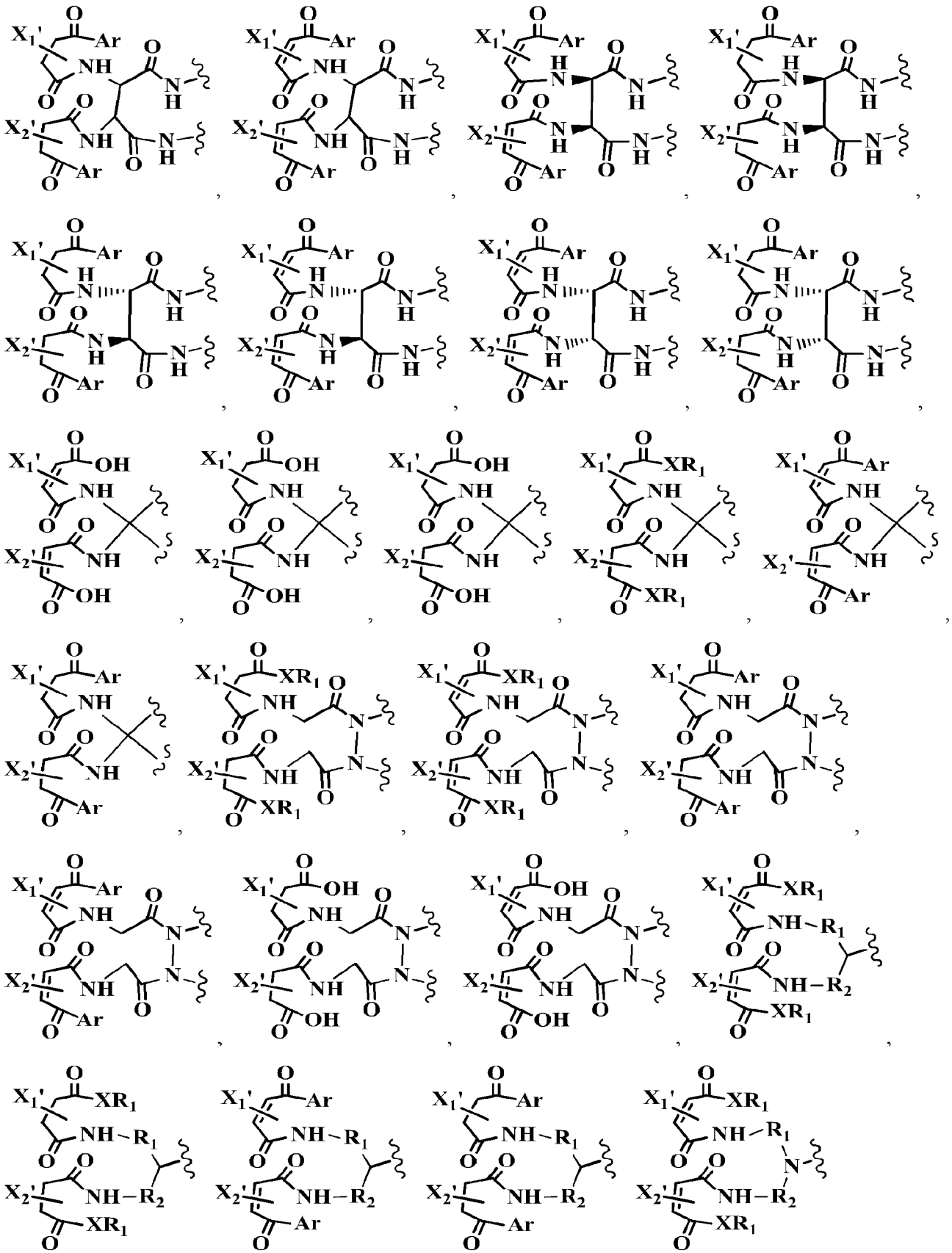

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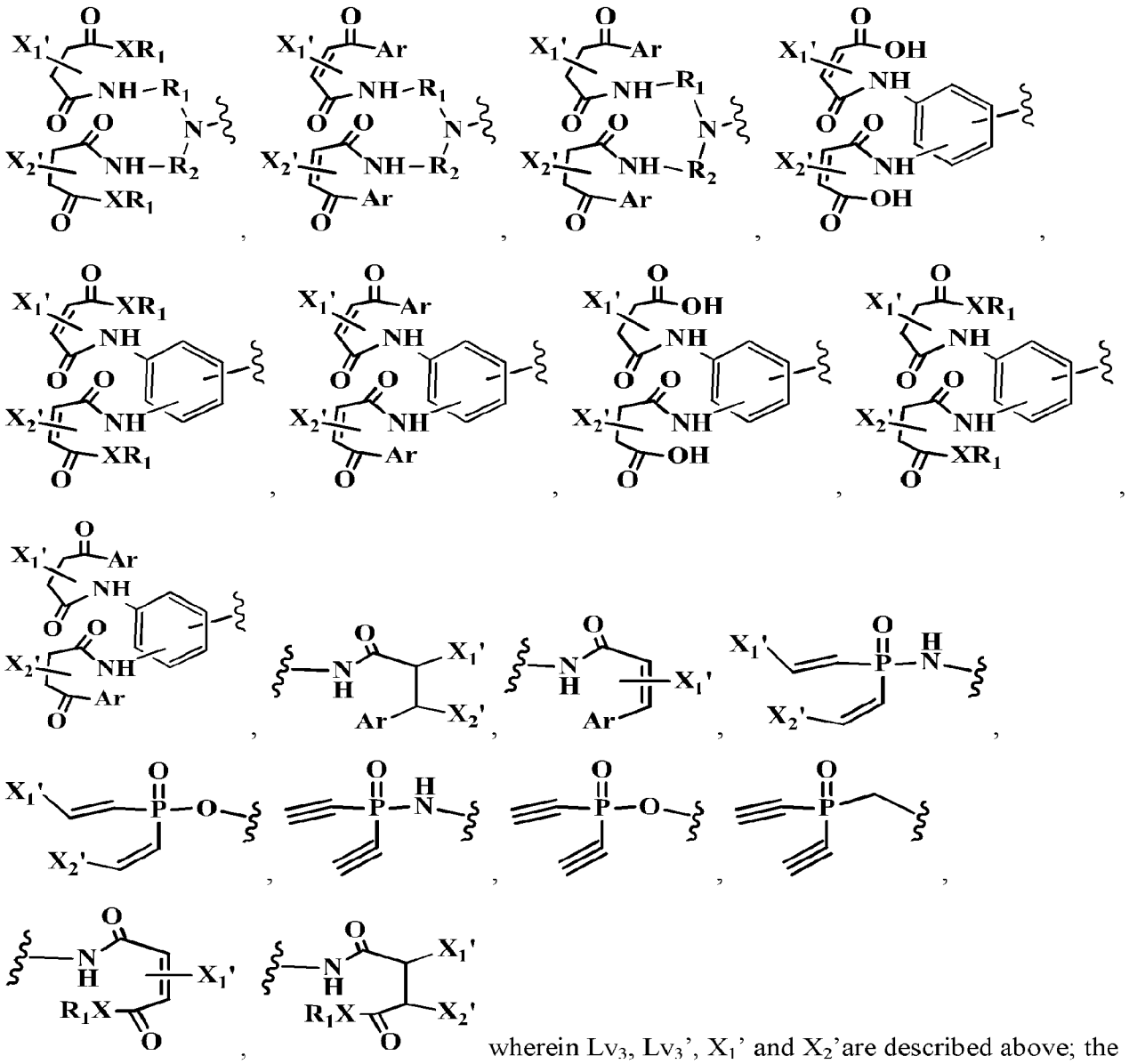

wherein Lv_3, Lv_3', X_1' and X_2'are described above; the conneting bond " — " in the middle of the two atoms means it can link either one of the two atoms;

Wherein L_1, L_2, L_1' and L_2 ' are, the same or different, independently selected from O, NH, S, NHNH, $N(R_3)$, $N(R_3)N(R_3')$, polyethyleneoxy unit of formula $(OCH_2CH_2)_pOR_3$, or $(OCH_2CH(CH_3))_pOR_3$, or $NH(CH_2CH_2O)_pR_3$, or $NH(CH_2CH(CH_3)O)_pR_3$, or $N[(CH_2CH_2O)_pR_3][(CH_2CH_2O)_{p'}R_3']$, or $(OCH_2CH_2)_pCOOR_3$, or $CH_2CH_2(OCH_2CH_2)_pCOOR_3$, wherein p and p' are independently an integer selected from 0 to about 1000, or combination thereof; C_1-C_8 of alkyl; C_2-C_8 of heteroalkyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 of aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; Wherein R_3 and R_3' are independently H; C_1-C_8 of alkyl; C_2-C_8 of heteroalkyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 of aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; or 1-8 carbon atoms of esters, ether, amide or aminoalkylcarboxyl; or 1~8 natural or unnatural amino acids or

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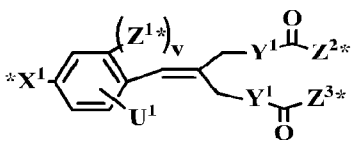
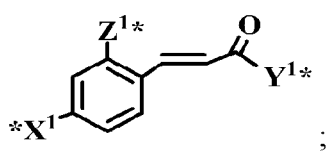
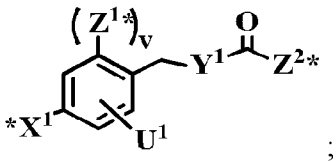
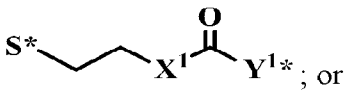
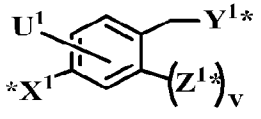
peptides described in the definition; or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$ or $(OCH_2CH(CH_3))_p$, wherein p is an integer from 0 to about 1000, or combination above thereof.

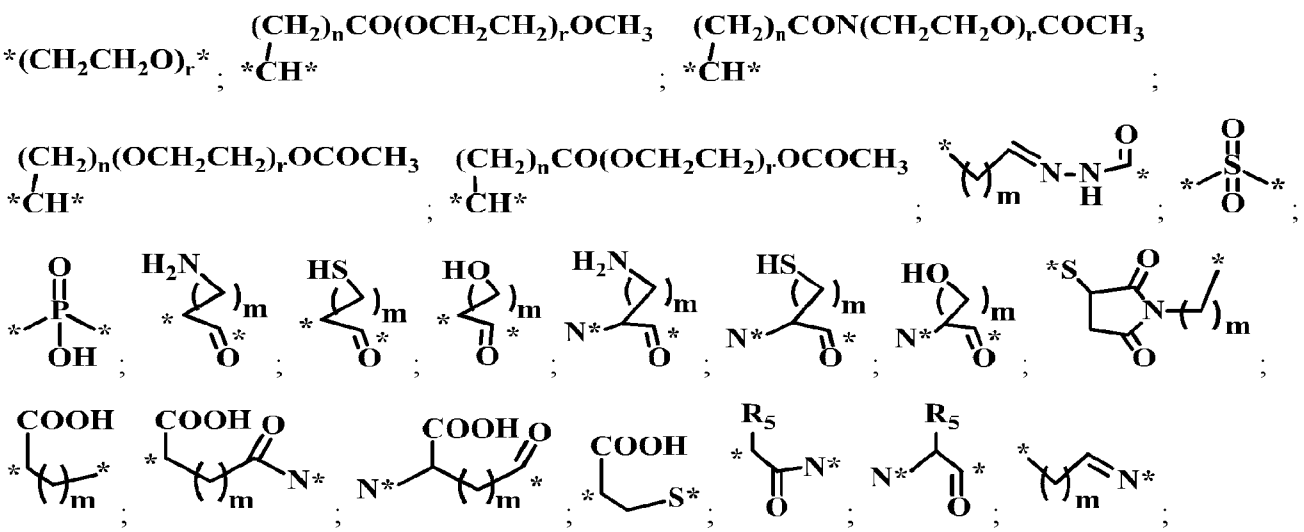
Wherein L_1, L_1', L_2, or L_2', may contain a self-immolative or a non-self-immolative component, peptidyl units, a hydrazone bond, a disulfide, an ester, an oxime, an amide, or a thioether bond. The self-immolative unit includes, but is not limited to, aromatic compounds that are electronically similar to the para-aminobenzylcarbamoyl (PAB) groups such as 2-aminoimidazol-5-methanol derivatives, heterocyclic PAB analogs, beta-glucuronide, and ortho or para-aminobenzylacetals.

Wherein the self-immolative linker component has one of the following structures:

wherein the (*) atom is the point of attachment of additional spacer or releasable linker units, or the cytotoxic agent, and/or the binding molecule (CBA); X^1, Y^1, Z^2 and Z^3 are independently NH, O, or S; Z^1 is independently H, NH, O or S; v is 0 or 1; U^1 is independently H, OH, C_1~C_6 alkyl, $(OCH_2CH_2)_nF$, Cl, Br, I, OR_5, SR_5, NR_5R_5', N=NR_5, N=R_5, NR_5R_5', NO_2, SOR_5R_5', SO_2R_5, SO_3R_5, OSO_3R_5, PR_5R_5', POR_5R_5', $PO_2R_5R_5$', $OPO(OR_5)(OR_5')$, or $OCH_2PO(OR_5(OR_5')$ wherein R_5 and R_5' are as defined above; preferably R_5 and R_5' are independently selected from H, C_1~C_8 alkyl; C_2~C_8 alkenyl, alkynyl, heteroalkyl; C_3~C_8 aryl, heterocyclic, carbocyclic, cycloalkyl, heterocycloalkyl, heteroaralkyl, alkylcarbonyl; or pharmaceutical cation salts.

Wherein the non-self-immolative linker component is one of the following structures:



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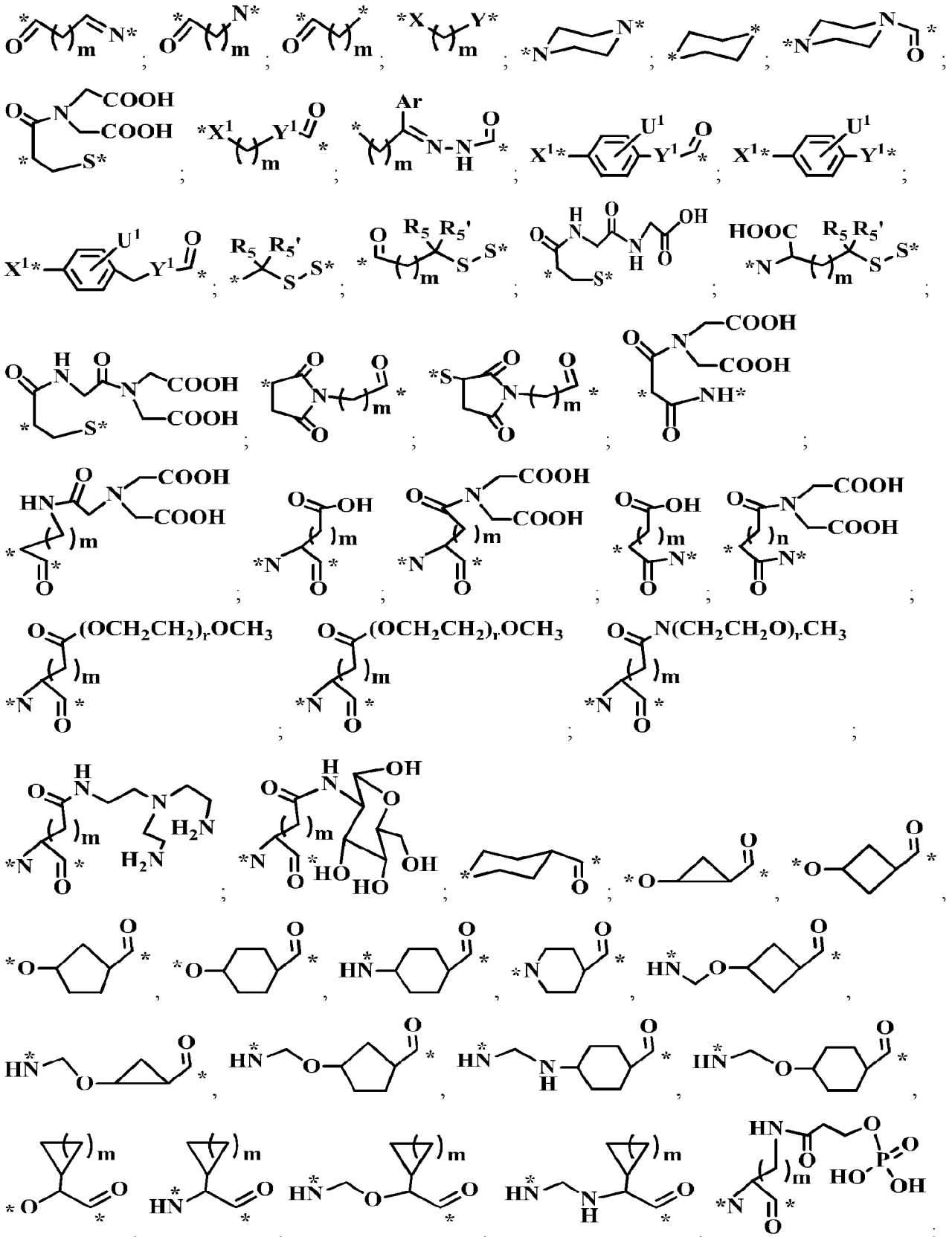

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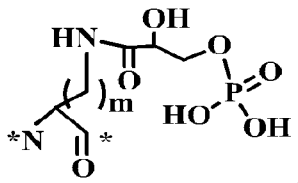
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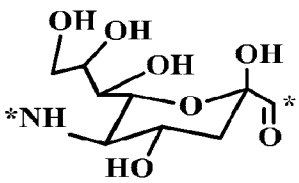
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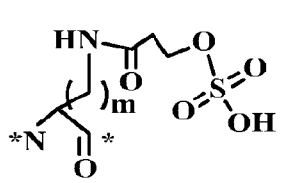
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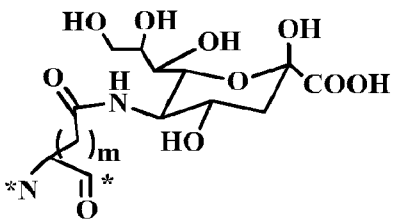
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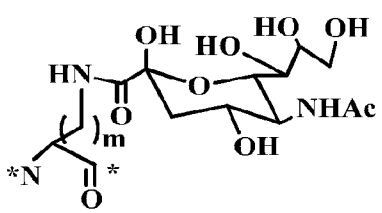
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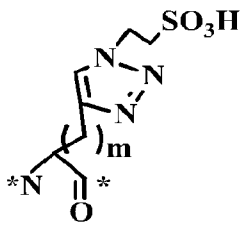
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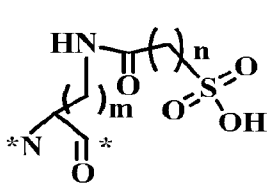
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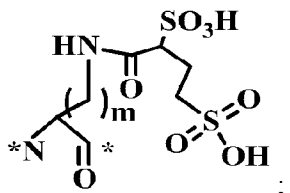
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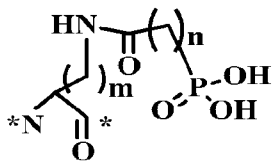
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Wherein the (*) atom is the point of attachment of additional spacer R_1 or releasable linkers, the cytotoxic agents, and/or the binding molecules; X^1, Y^1, U^1, R_1, R_5, R_5' are defined as above; r is 0~100; m and n are 0~6 independently.

wherein L_1, L_1', L_2, or L_2' may be a releasable linker and comprises one of the following structures:

-$(CR_5R_6)_m(Aa)r(CR_7R_8)_n(OCH_2CH_2)_t$-, -$(CR_5R_6)_m(CR_7R_8)_n(Aa)_r(OCH_2CH_2)_t$-, -$(Aa)_r(CR_5R_6)_m$-$(CR_7R_8)_n(OCH_2CH_2)_t$-, -$(CR_5R_6)_m(CR_7R_8)_n(OCH_2CH_2)_r(Aa)_t$-, -$(CR_5R_6)_m(CR_7{=}CR_8)(CR_9R_{10})_n(Aa)_t$-$(OCH_2CH_2)_r$-, -$(CR_5R_6)_m(NR_{11}CO)(Aa)_t(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -$(CR_5R_6)_m(Aa)_t(NR_{11}CO)$-$(CR_9R_{10})_n(OCH_2CH_2)_r$-, -$(CR_5R_6)_m(OCO)(Aa)_t(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -$(CR_5R_6)_m(OCNR_7)(Aa)_t$-$(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -$(CR_5R_6)_m(CO)(Aa)_t$-$(CR_9R_{10})_n(OCH_2CH_2)_r$-, -$(CR_5R_6)_m(NR_{11}CO)(Aa)_t$-$(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -$(CR_5R_6)_m$-$(OCO)(Aa)_t(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -$(CR_5R_6)_m(OCNR_7)(Aa)_t$-$(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -$(CR_5R_6)_m(CO)(Aa)_t(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -$(CR_5R_6)_m$-phenyl-CO-$(Aa)_t(CR_7R_8)_n$-, -$(CR_5R_6)_m$-furyl-CO$(Aa)_t(CR_7R_8)_n$-, -$(CR_5R_6)_m$-oxazolyl-CO$(Aa)_t(CR_7R_8)_n$-, -$(CR_5R_6)_m$thiazolyl-CO-$(Aa)_t(CCR_7R_8)_n$-, -$(CR_5R_6)_t$-thienyl-CO-$(CR_7R_8)_n$-, -$(CR_5R_6)_t$-imidazolyl-CO-$(CR_7R_8)_n$-, -$(CR_5R_6)_t$-morpholino-CO$(Aa)_t$-$(CR_7R_8)_n$-, -$(CR_5R_6)_t$piperazino-CO$(Aa)_t(CR_7R_8)_n$-, -$(CR_5R_6)_t$-N-methyl-piperazin-CO$(Aa)_t$-$(CR_7R_8)_n$-, -$(CR_5R)_m$-$(Aa)_t$phenyl-, -$(CR_5R_6)_m$-$(Aa)_t$furyl-, -$(CR_5R_6)_m$-oxazolyl$(Aa)_t$-, -$(CR_5R_6)_m$-thiazolyl$(Aa)_t$-, -$(CR_5R_6)_m$-thienyl-$(Aa)_t$-, -$(CR_5R_6)_m$-imidazolyl$(Aa)_t$-, -(C $R_5R_6)_m$-morpholino-$(Aa)_t$-, -$(CR_5R_6)_m$-piperazino-$(Aa)_t$-, -$(CR_5R_6)_m$-N-methylpiperazino-$(Aa)_t$-, -K$(CR_5R_6)_m(Aa)r(CR_7R_8)_n(OCH_2CH_2)_t$-, -K$(CR_5R_6)_m$-$(CR_7R_8)_n$-$(Aa)_r(OCH_2CH_2)_t$-, -K$(Aa)_r(CR_5R_6)_m$-$(CR_7R_8)_n(OCH_2CH_2)_t$-, -K$(CR_5R_6)_m(CR_7R_8)_n$-$(OCH_2CH_2)_r(Aa)_t$-, -K$(CR_5R_6)_m(CR_7{=}CR_8)(CR_9R_{10})_n$-$(Aa)_t(OCH_2CH_2)_r$-, -K$(CR_5R_6)_m$-

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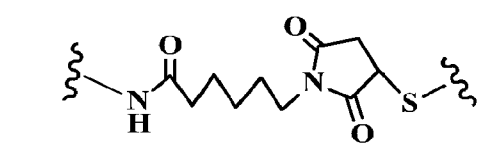
$(NR_{11}CO)(Aa)_t(CR_9R_{10})_n(OCH_2CH_2)_r$-, -$K(CR_5R_6)_m(Aa)_t(NR_{11}CO)$-$(CR_9R_{10})_n(OCH_2$-$CH_2)_r$-, -$K(CR_5R_6)_m(OCO)(Aa)_t(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -$K(CR_5R_6)_m(OCNR_7)(Aa)_t$-$(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -$K(CR_5R_6)_m(CO)(Aa)_t$-$(CR_9R_{10})_n(OCH_2CH_2)_r$-, -$K(CR_5R_6)_m(NR_{11}CO)$-$(Aa)_t$-$(CR_9R_{10})_n(OCH_2CH_2)_r$-, -$K(CR_5R_6)_m$-$(OCO)(Aa)_t(CR_9R_{10})_n(OCH_2CH_2)_r$-, -$K(CR_5R_6)_m(OCNR_7)$-$(Aa)_t(CR_9R_{10})_n(OCH_2CH_2)_r$-, -$K(CR_5R_6)_m(CO)(Aa)_t(CR_9R_{10})_n$-$(OCH_2CH_2)_r$-, -$K(CR_5R_6)_m$-phenyl-CO-$(Aa)_t(CR_7R_8)_n$-, -K-$(CR_5R_6)_m$-furyl-CO$(Aa)_t$-$(CR_7R_8)_n$-, -$K(CR_5R_6)_m$-oxazolyl-CO-$(Aa)_t(CR_7R_8)_n$-, -$K(CR_5R_6)_m$thiazolyl-CO$(Aa)_t$-$(CR_7R_8)_n$-, -$K(CR_5R_6)_t$-thienyl-CO$(CR_7R_8)_n$-, -K-$(CR_5R_6)_t$imidazolyl-CO-$(CR_7R_8)_n$-, -$K(CR_5R_6)_t$morpholino-CO$(Aa)_t(CR_7R_8)_n$-, -$K(CR_5R_6)_t$-piperazino-CO$(Aa)_t$-$(CR_7R_8)_n$-, -$K(CR_5R_6)_t$-N-methylpiperazinCO$(Aa)_t(CR_7R_8)_n$-, -$K(CR_5R)_m(Aa)_t$-phenyl, -K-$(CR_5R_6)_m$-$(Aa)_t$furyl-, -$K(CR_5R_6)_m$-oxazolyl$(Aa)_t$-, -$K(CR_5R_6)_m$-thiazolyl$(Aa)_t$-, -K-$(CR_5R_6)_m$-thienyl-$(Aa)_t$-, -$K(CR_5R_6)_m$-imidazolyl$(Aa)_t$-, -$K(CR_5R_6)_m$-morpholino$(Aa)_t$-, -$K(CR_5R_6)_m$-piperazino-$(Aa)_t$G, -$K(CR_5R_6)_m$N-methylpiperazino-$(Aa)_t$-;

werein m, Aa, m, n, R_3, R_4, and R_5 are described above; t and r are 0 – 100 independently; R_6, R_7, and R_8 are independently chosen from H; halide; C_1~C_8 of alkyl, aryl, alkenyl, alkynyl, ether, ester, amine or amide, which optionally substituted by one or more halide, CN, NR_1R_2, CF_3, OR_1, Aryl, heterocycle, $S(O)R_1$, SO_2R_1, $-CO_2H$, $-SO_3H$, $-OR_1$, $-CO_2R_1$, $-CONR_1$, $-PO_2R_1R_2$, $-PO_3H$ or $P(O)R_1R_2R_3$; K is NR_1, -SS-, -C(=O)-, -C(=O)NH-, -C(=O)O-, -C=NH-O-, -C=N-NH-, -C(=O)NH-NH-, O, S, Se, B or C_3-C_6 heteroaromatic group.

Wherein the structures of the components of the linker L_1, L_1', L_2, or L_2', may contain: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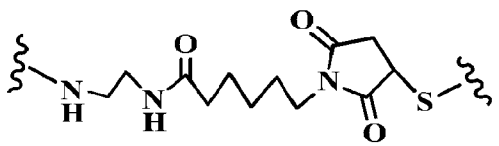
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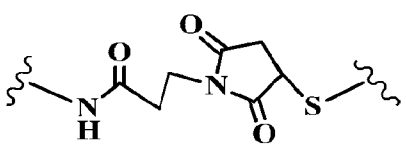
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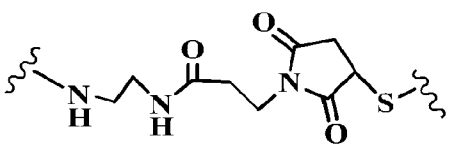
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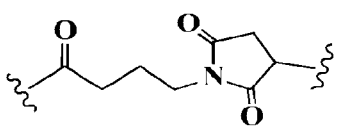
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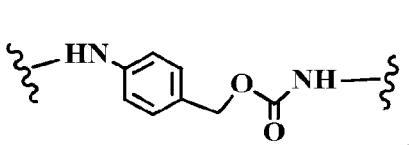
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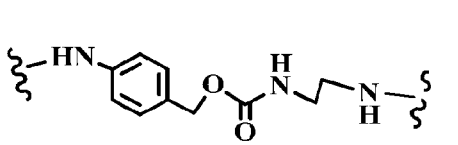
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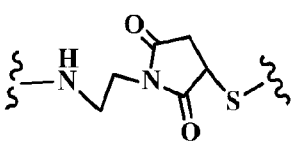
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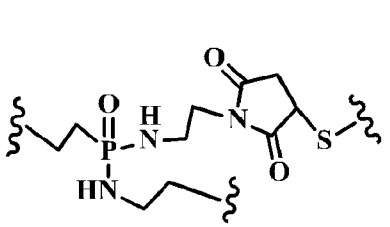
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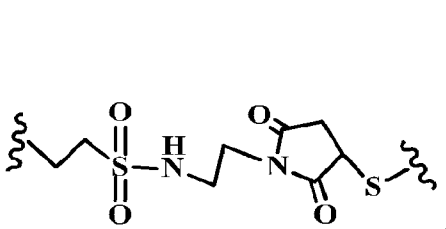
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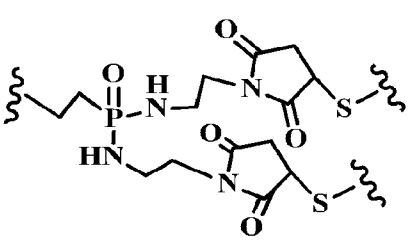
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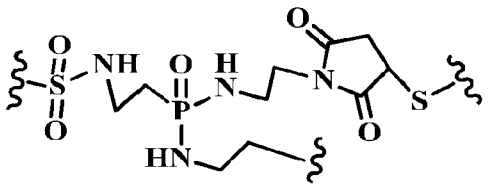
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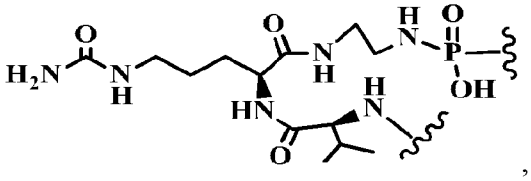
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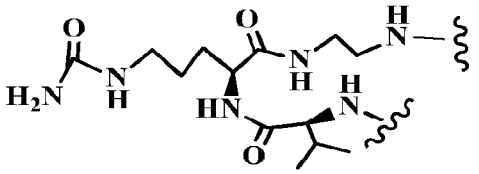
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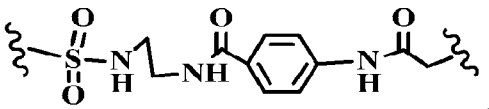
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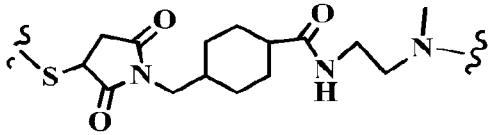
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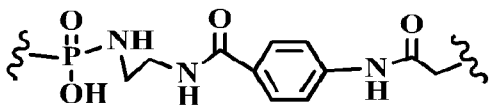
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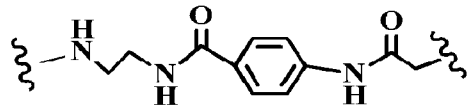
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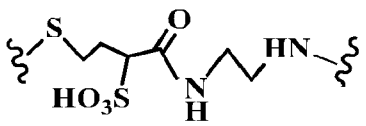
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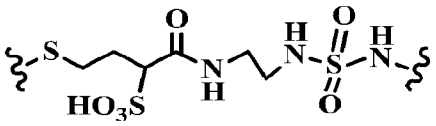
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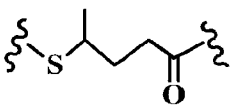
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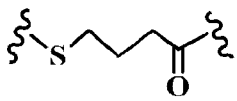
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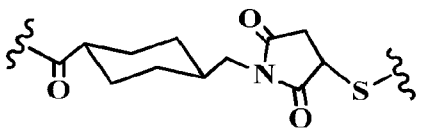
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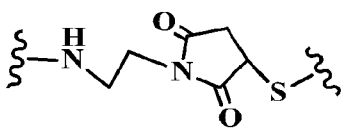
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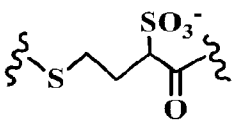
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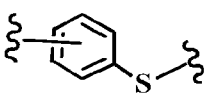
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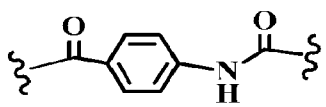
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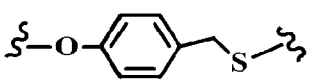
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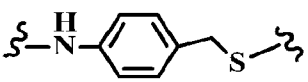
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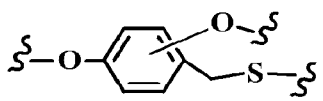
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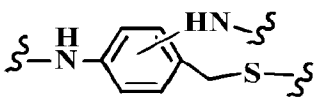
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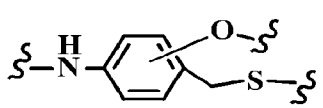
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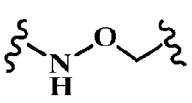
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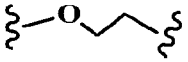
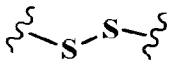
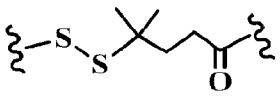
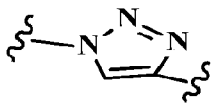
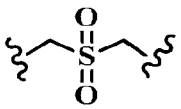
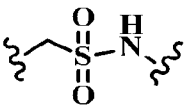
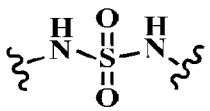
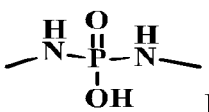
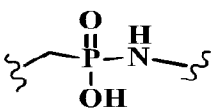
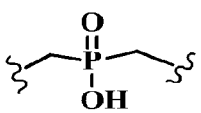
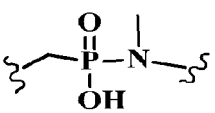
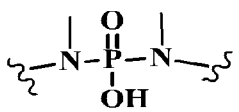
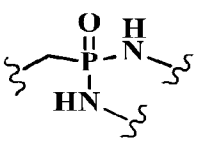


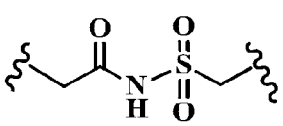
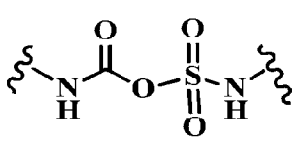
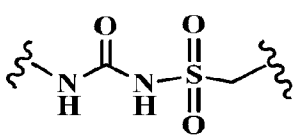
ethyleneoxy(EO),  dithio,  4-methyl-4-dithio-pentanoic (MPDP),

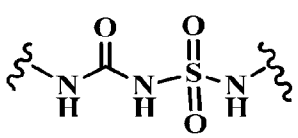
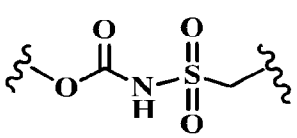
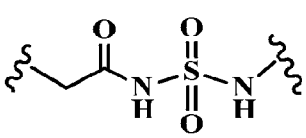
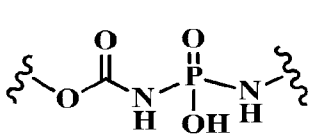
 triazole,  alkylsulfonyl,  alkylsulfonamide,

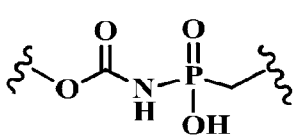
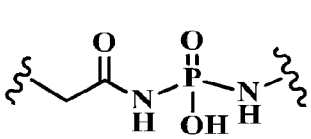
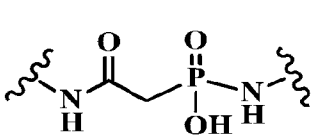
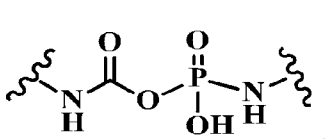
 sulfon-bisamide,  Phosphondiamide,  alkylphosphona-

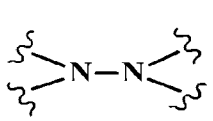
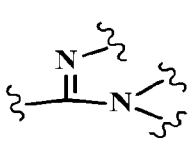
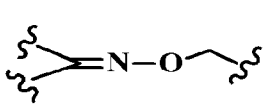
mide,  phosphinic acid,  N-methylphosphonamidic acid,

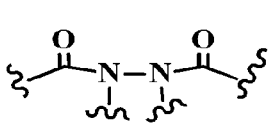
 N, N'-dimethylphosphonamidic acid,  N, N'-

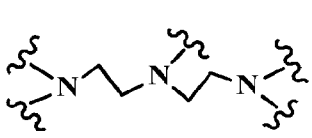
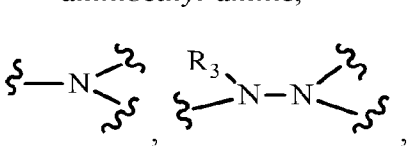
dimethylphosphondiamide,  ,  ,  ,

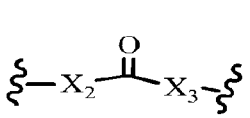
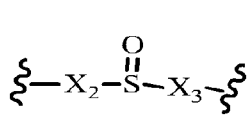
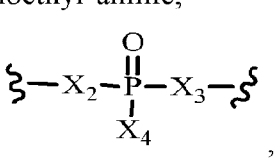
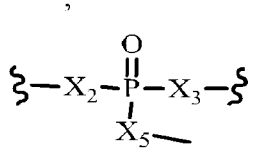
 ,  ,  ,  ,

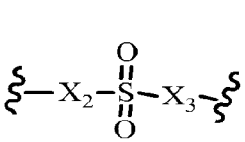
 ,  ,  ,  ,

 hydrazine,  acetimidamide,  oxime,

 acetylacetohydrazide, aminoethyl-amine,

 aminoethyl-aminoethyl-amine,  ,

 ,  ,  ,  ,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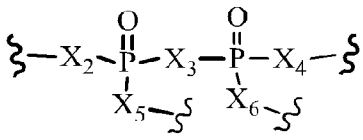
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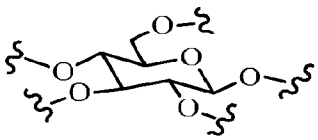
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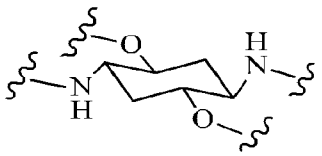
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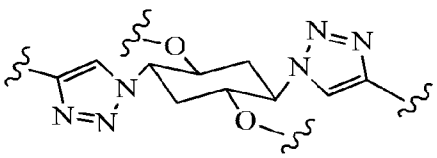
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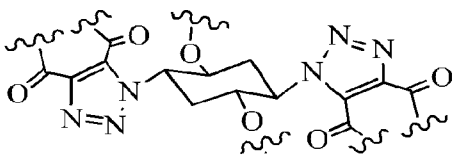
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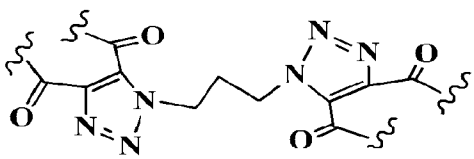
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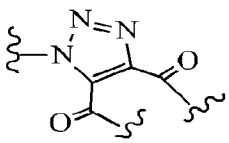
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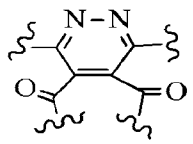
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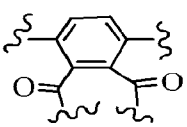
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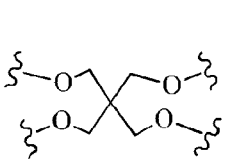
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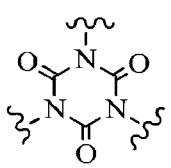
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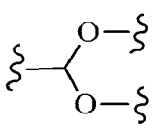
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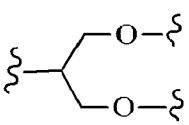
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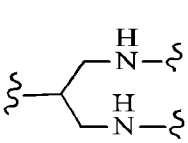
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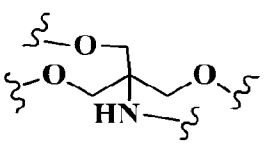
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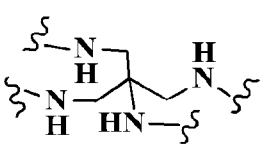
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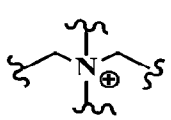
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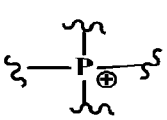
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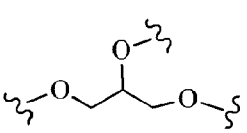
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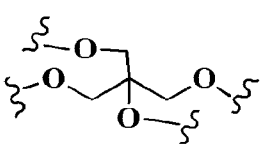
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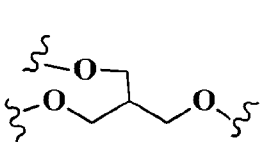
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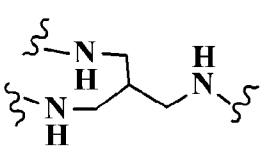
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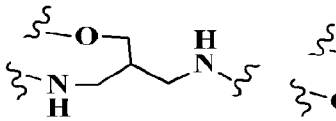
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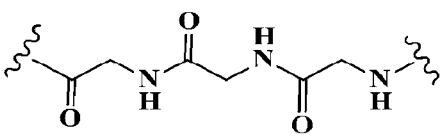
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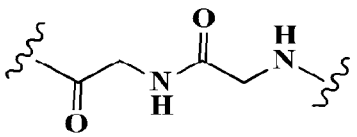
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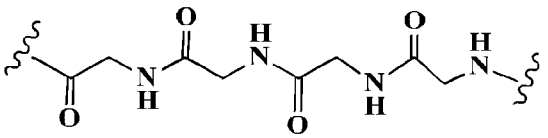
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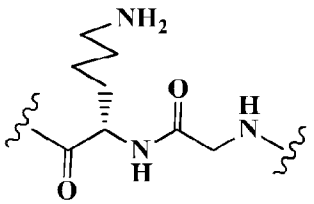
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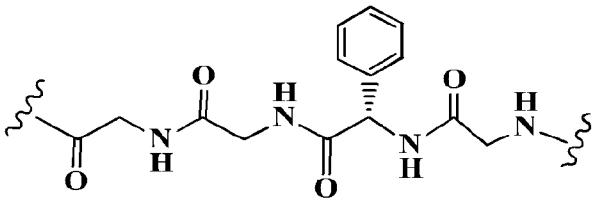
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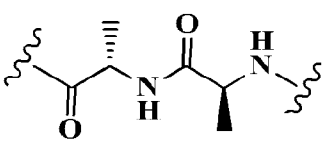
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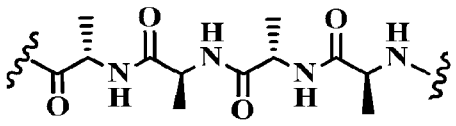
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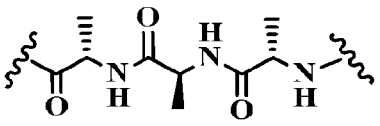
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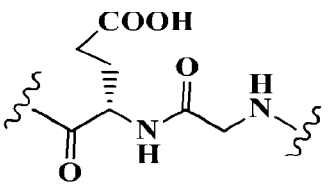
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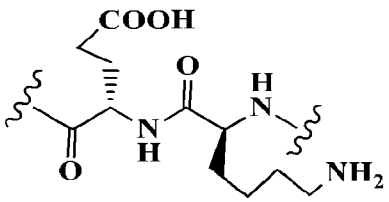
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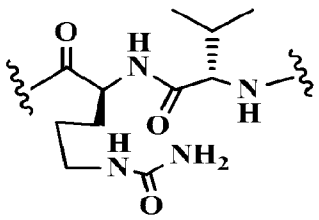
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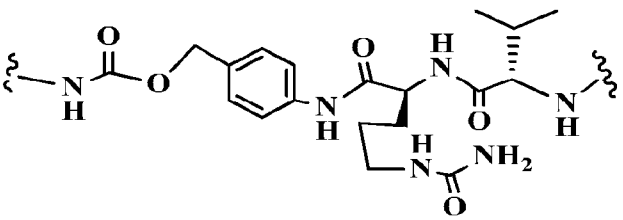
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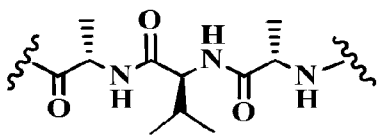
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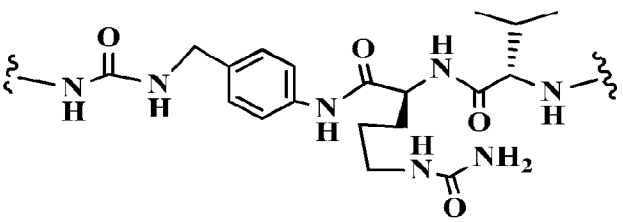
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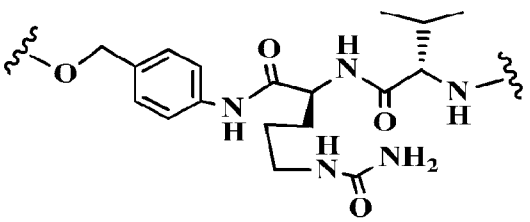
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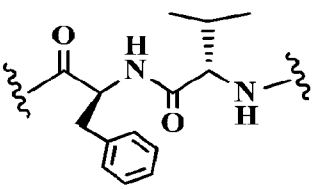
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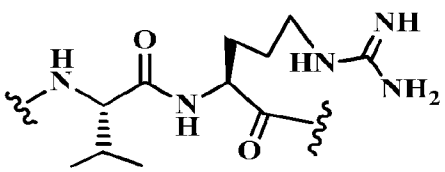
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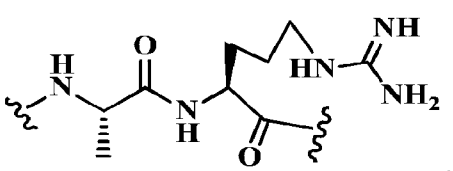
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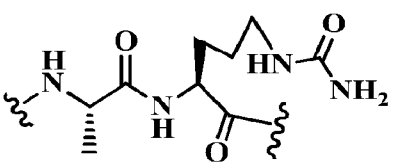
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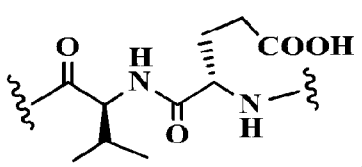
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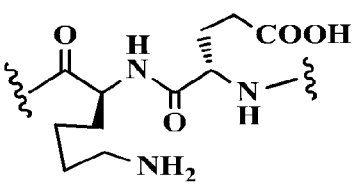
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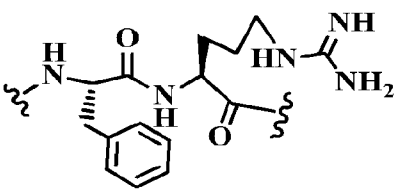
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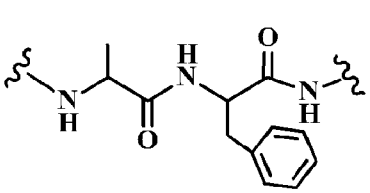
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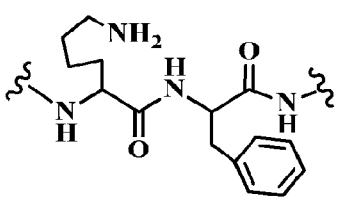
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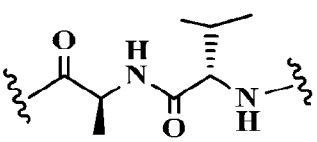
, (lys-phe), or a combination above thereof; wherein is the site of linkage; X_2, X_3, X_4, X_5, or X_6, are independently selected from NH; NHNH; N(R_{12}); N(R_{12})N($R_{12'}$); O; S; C_1-C_6 of alkyl; C_2-C_6 of heteroalkyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 of aryl, Ar-alkyl, heterocyclic,

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carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; CH_2OR_{12}, CH_2SR_{12}, CH_2NHR_{12}, or 1~8 amino acids; wherein R_{12} and $R_{12'}$ are independently H;C_1-C_8 of alkyl; C_2-C_8 of hetero-alkyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 of aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; or 1-8 carbon atoms of esters, ether, or amide; or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$ or $(OCH_2CH(CH_3))_p$, wherein p is an integer from 0 to about 100.

In addition, L_1, L_2, L_1, L_1', L_2', X_1, X_2, X_3, X_1', X_2' and X_3' can be independently absent.

wherein D_1 and D_2 are a cytotoxic drug, or a therapeutic drug, an immunotherapeutical short antibody-like protein, a function molecule for enhancement of binding or stabilization of the cell-binding antibody-like protein agent, a cell-surface receptor binding ligand, an antibody fragment, siRNA or DNA molecule, and are selected from:

1) Chemotherapeutic agents:

a) Alkylating agents: nitrogen mustards: chlorambucil, chlornaphazine, cyclophosphamide, dacarbazine, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, mannomustine, mitobronitol, melphalan, mitolactol, pipobroman, novembichin, phenesterine, prednimustine, thiotepa, trofosfamide, uracil mustard; CC-1065 (including its synthetic analogues adozelesin, carzelesin and bizelesin); Duocarmycin (including the synthetic analogues, KW-2189 and CBI-TMI); Benzodiazepine dimers (including dimers of pyrrolobenzodiazepine (PBD) or tomaymycin, indolinobenzodiazepines, imidazobenzothiadiazepines, or oxazolidino-benzodiazepines); Nitrosoureas: (carmustine, lomustine, chlorozotocin, fotemustine, nimustine, ranimustine); Alkylsulphonates: (busulfan, treosulfan, improsulfan and piposulfan); Triazenes: (dacarbazine); Platinum containing compounds: (carboplatin, cisplatin, oxaliplatin); aziridines: benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemel-amine, trietylenephosphoramide, triethylenethio-phosphaoramide and trimethylolomel-amine];

b) Plant Alkaloids: Vinca alkaloids: (vincristine, vinblastine, vindesine, vinorelbine, navelbin); Taxoids: (paclitaxel, docetaxol) and their analogs, Maytansinoids (DM1, DM2, DM3, DM4, DM5, DM21, maytansine and ansamitocins) and their analogs, cryptophycins (particularly cryptophycin 1 and cryptophycin 8); epothilones, eleutherobin, discodermo-lide, bryostatins, dolostatins, auristatins, tubulysins, cephalostatins; pancratistatin; a sarcodictyin; spongistatin;

c) DNA Topoisomerase Inhibitors: Epipodophyllins: (9-aminocamptothecin, camptothecin, crisnatol, daunomycin, etoposide, etoposide phosphate, irinotecan, mitoxantrone, novantrone, retinoic acids (retinols), teniposide, topotecan, 9-nitrocamptothecin (RFS 2000)); mitomycins: (mitomycin C);

d) Anti-metabolites: [Anti-folate: DHFR inhibitors: (methotrexate, trimetrexate, denopterin, pteropterin, aminopterin (4-aminopteroic acid) or the other folic acid analogues); IMP dehydroge-

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nase Inhibitors: (mycophenolic acid, tiazofurin, ribavirin, EICAR); Ribonucleotide reductase Inhibitors: (hydroxyurea, deferoxamine)]; [Pyrimidine analogs: Uracil analogs: (ancitabine, azacitidine, 6-azauridine, capecitabine (Xeloda), carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, 5-Fluorouracil, floxuridine, ratitrexed (Tomudex)); Cytosine analogs: (cytarabine, cytosine arabinoside, fludarabine); Purine analogs: (azathioprine, fludarabine, mercaptopurine, thiamiprine, thioguanine)]; folic acid replenisher, frolinic acid;

e) Hormonal therapies: Receptor antagonists: [Anti-estrogen: (megestrol, raloxifene, tamoxifen); LHRH agonists: (goscrclin, leuprolide acetate); Anti-androgens: (bicalutamide, flutamide, calusterone, dromostanolone propionate, epitiostanol, goserelin, leuprolide, mepitiostane, nilutamide, testolactone, trilostane and other androgens inhibitors)]; Retinoids/Deltoids: [Vitamin D3 analogs: (CB 1093, EB 1089 KH 1060, cholecalciferol, ergocalciferol); Photodynamic therapies: (verteporfin, phthalocyanine, photosensitizer Pc4, demethoxy-hypocrellin A); Cytokines: (Interferon-alpha, Interferon-gamma, tumor necrosis factor (TNFs), human antibody-like proteins containing a TNF domain)];

f) Kinase inhibitors: BIBW 2992 (anti-EGFR/Erb2), imatinib, gefitinib, pegaptanib, sorafenib, dasatinib, sunitinib, erlotinib, nilotinib, lapatinib, axitinib, pazopanib. vandetanib, E7080 (anti-VEGFR2), mubritinib, ponatinib (AP24534), bafetinib (INNO-406), bosutinib (SKI-606), cabozantinib, vismodegib, iniparib, ruxolitinib, CYT387, axitinib, tivozanib, sorafenib, bevacizumab, cetuximab, Trastuzumab, Ranibizumab, Panitumumab, ispinesib; g). antibiotics, such as the enediyne antibiotics: calicheamicins:calicheamicin $\gamma 1$, $\delta 1$, $\alpha 1$ and $\beta 1$; dynemicin: dynemicin A and deoxydynemicin; esperamicin, kedarcidin, C-1027, maduropeptin, neocarzinostatin chromophore and related chromoprotein enediyne antiobiotic chromomophores, aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin; chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, nitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin;

f) Polyketides (acetogenins): bullatacin and bullatacinone; gemcitabine, epoxomicins, bortezomib, thalidomide, lenalidomide, pomalidomide, tosedostat, zybrestat, PLX4032, STA-9090, Stimuvax, allovectin-7, Xegeva, Provenge, Yervoy, Isoprenylation inhibitors: Lovastatin, Dopaminergic neurotoxins: 1-methyl-4-phenylpyridinium ion, Cell cycle inhibitors: staurosporine, Actinomycins: Actinomycin D, dactinomycin, Bleomycins: bleomycin A2, bleomycin B2, peplomycin, Anthracyclines: daunorubicin, doxorubicin (adriamycin), idarubicin, epirubicin, pirarubicin, zorubicin, mtoxantrone, MDR inhibitors: verapamil, Ca^{2+}ATPase inhibitors: thapsigargin, Histone deacetylase

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inhibitors: Vorinostat, Romidepsin, Panobinostat, Valproic acid, Mocetinostat (MGCD0103), Belinostat, PCI-24781, Entinostat, SB939, Resminostat, Givinostat, AR-42, CUDC-101, sulforaphane, Trichostatin A; Thapsigargin, Celecoxib, glitazones, epigallocatechin gallate, Disulfiram, Salinosporamide A.; Anti-adrenals: aminoglutethimide, mitotane, trilostane; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; arabinoside, bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; eflornithine (DFMO), elfomithine; elliptinium acetate, etoglucid; gallium nitrate; gacytosine, hydroxyurea; ibandronate, lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine, razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2, 2', 2"-trichlorotriethylamine; trichothecenes: T-2 toxin, verrucarin A, roridin A and anguidine; urethane, siRNA, antisense drugs, and a nucleolytic enzyme;

2) An anti-autoimmune disease agent selected from the group consisting of cyclosporine, cyclosporine A, aminocaproic acid, azathioprine, bromocriptine, chlorambucil, chloroquine, cyclophosphamide, corticosteroids: amcinonide, betamethasone, budesonide, hydrocortisone, flunisolide, fluticasone propionate, fluocortolone danazol, dexamethasone, Triamcinolone acetonide, beclometasone dipropionate, DHEA, enanercept, hydroxychloroquine, infliximab, meloxicam, methotrexate, mofetil, mycophenylate, prednisone, sirolimus, and tacrolimus.

3) An anti-infectious disease agent:

a) Aminoglycosides: amikacin, astromicin, gentamicin (netilmicin, sisomicin, isepamicin), hygromycin B, kanamycin (amikacin, arbekacin, bekanamycin, dibekacin, tobramycin), neomycin (framycetin, paromomycin, ribostamycin), netilmicin, spectinomycin, streptomycin, tobramycin, verdamicin;

b) Amphenicols: azidamfenicol, chloramphenicol, florfenicol, thiamphenicol;

c) Ansamycins: geldanamycin, herbimycin;

d) Carbapenems: biapenem, doripenem, ertapenem, imipenem/cilastatin, meropenem, panipenem;

e) Cephems: carbacephem (loracarbef), cefacetrile, cefaclor, cefradine, cefadroxil, cefalonium, cefaloridine, cefalotin or cefalothin, cefalexin, cefaloglycin, cefamandole, cefapirin, cefatrizine, cefazaflur, cefazedone, cefazolin, cefbuperazone, cefcapene, cefdaloxime, cefepime, cefminox, cefoxitin, cefprozil, cefroxadine, ceftezole, cefuroxime, cefixime, cefdinir, cefditoren, cefepime, cefetamet, cefmenoxime, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotiam, cefozopran, cephalexin, cefpimizole, cefpiramide, cefpirome, cefpodoxime, cefprozil, cefquinome, cefsulodin, ceftazidime, cefteram, ceftibuten, ceftiolene, ceftizoxime, ceftobiprole, ceftriaxone, cefuroxime, cefuzonam, cephamycin (cefoxitin, cefotetan, cefmetazole), oxacephem (flomoxef, latamoxef);

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f) Glycopeptides: bleomycin, vancomycin (oritavancin, telavancin), teicoplanin (dalbavancin), ramoplanin;

g) Glycylcyclines;

h). β-Lactamase inhibitors: penam (sulbactam, tazobactam), clavam (clavulanic acid);

i). Lincosamides: clindamycin, lincomycin;

j) Lipopeptides: daptomycin, A54145, calcium-dependent antibiotics (CDA);

k) Macrolides: azithromycin, cethromycin, clarithromycin, dirithromycin, erythromycin, flurithromycin, josamycin, ketolide (telithromycin, cethromycin), midecamycin, miocamycin, oleandomycin, rifamycins (rifampicin, rifampin, rifabutin, rifapentine), rokitamycin, roxithromycin, spectinomycin, spiramycin, tacrolimus (FK506), troleandomycin, telithromycin;

l) Monobactams: aztreonam, tigemonam;

m) Oxazolidinones: linezolid;

n) Penicillins: amoxicillin, ampicillin (pivampicillin, hetacillin, bacampicillin, metampicillin, talampicillin), azidocillin, azlocillin, benzylpenicillin, benzathine benzylpenicillin, benzathine phenoxymethyl-penicillin, clometocillin, procaine benzylpenicillin, carbenicillin (carindacillin), cloxacillin, dicloxacillin, epicillin, flucloxacillin, mecillinam (pivmecillinam), mezlocillin, meticillin, nafcillin, oxacillin, penamecillin, penicillin, pheneticillin, phenoxymethylpenicillin, piperacillin, propicillin, sulbenicillin, temocillin, ticarcillin;

o) Polypeptides: bacitracin, colistin, polymyxin B;

p) Quinolones: alatrofloxacin, balofloxacin, ciprofloxacin, clinafloxacin, danofloxacin, difloxacin, enoxacin, enrofloxacin, floxin, garenoxacin, gatifloxacin, gemifloxacin, grepafloxacin, kano trovafloxacin, levofloxacin, lomefloxacin, marbofloxacin, moxifloxacin, nadifloxacin, norfloxacin, orbifloxacin, ofloxacin, pefloxacin, trovafloxacin, grepafloxacin, sitafloxacin, sparfloxacin, temafloxacin, tosufloxacin, trovafloxacin;

q) Streptogramins: pristinamycin, quinupristin/dalfopristin);

r) Sulfonamides: mafenide, prontosil, sulfacetamide, sulfamethizole, sulfanilimide, sulfasalazine, sulfisoxazole, trimethoprim, trimethoprim-sulfamethoxazole (co-trimoxazole);

s) Steroid antibacterials;

t) Tetracyclines: doxycycline, chlortetracycline, clomocycline, demeclocycline, lymecycline, meclocycline, metacycline, minocycline, oxytetracycline, penimepicycline, rolitetracycline, tetracycline, glycylcyclines;

u) antibiotics: annonacin, arsphenamine, bactoprenol inhibitors (Bacitracin), DADAL/AR inhibitors (cycloserine), dictyostatin, discodermolide, eleutherobin, epothilone, ethambutol, etoposide, faropenem, fusidic acid, furazolidone, isoniazid, laulimalide, metronidazole, mupirocin, mycolac-

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tone, NAM synthesis inhibitors: fosfomycin, nitrofurantoin, paclitaxel, platensimycin, pyrazinamide, quinupristin/dalfopristin, rifampicin (rifampin), tazobactam tinidazole, uvaricin;

4) Anti-viral drugs:

a) Entry/fusion inhibitors: aplaviroc, maraviroc, vicriviroc, gp41 (enfuvirtide), PRO 140, CD4 (ibalizumab);

b) Integrase inhibitors: raltegravir, elvitegravir, globoidnan A;

c) Maturation inhibitors: bevirimat, vivecon;

d) Neuraminidase inhibitors: oseltamivir, zanamivir, peramivir;

e). Nucleosides &nucleotides: abacavir, aciclovir, adefovir, amdoxovir, apricitabine, brivudine, cidofovir, clevudine, dexelvucitabine, didanosine (ddI), elvucitabine, emtricitabine (FTC), entecavir, famciclovir, fluorouracil (5-FU), 3'-fluoro-substituted 2',3'-dideoxynucleoside analogues (3'-fluoro-2', 3'-dideoxythymidine (FLT) and 3'-fluoro-2', 3'-dideoxyguanosine (FLG), fomivirsen, ganciclovir, idoxuridine, lamivudine (3TC), l-nucleosides (β-l-thymidine and β-l-2'-deoxycytidine), penciclovir, racivir, ribavirin, stampidine, stavudine (d4T), taribavirin (viramidine), telbivudine, tenofovir, trifluridine valaciclovir, valganciclovir, zalcitabine (ddC), zidovudine (AZT);

f) Non-nucleosides: amantadine, ateviridine, capravirine, diarylpyrimidines (etravirine, rilpivirine), delavirdine, docosanol, emivirine, efavirenz, foscarnet (phosphonoformic acid), imiquimod, interferon alfa, loviride, lodenosine, methisazone, nevirapine, NOV-205, peginterferon alfa, podophyllotoxin, rifampicin, rimantadine, resiquimod (R-848), tromantadine;

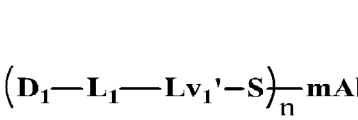
g) Protease inhibitors: amprenavir, atazanavir, boceprevir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, pleconaril, ritonavir, saquinavir, telaprevir (VX-950), tipranavir;

h) anti-virus drugs: abzyme, arbidol, calanolide a, ceragenin, cyanovirin-n, diarylpyrimidines, epigallocatechin gallate (EGCG), foscarnet, griffithsin, taribavirin (viramidine), hydroxyurea, KP-1461, miltefosine, pleconaril, portmanteau inhibitors, ribavirin, seliciclib;

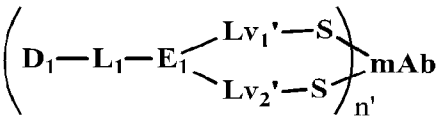
5) radioisotopes (radionuclides): ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{32}P, ^{35}S, ^{64}Cu, ^{68}Ga, ^{86}Y, ^{99}Tc, ^{111}In, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{133}Xe, ^{177}Lu, ^{211}At, and ^{213}Bi;

6) a pharmaceutically acceptable salt, acid or derivative of any of the above drugs.

4. The process according to Claim 1, a conjugate of formula (VI), (VII), (VIII) or (IX) as represented below is generated from the rection wherein the reduced thiol groups in the antibody or antibody-like protein in step (a) simultaneously or sequentially react with the drug/linker complex of formula (I), (II), (III) or (IV) accordingly:



(VI),



(VII),

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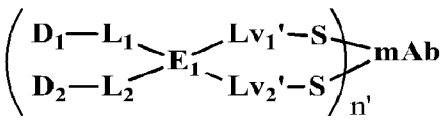
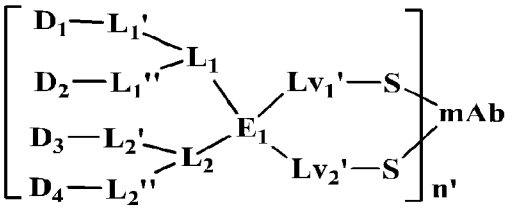


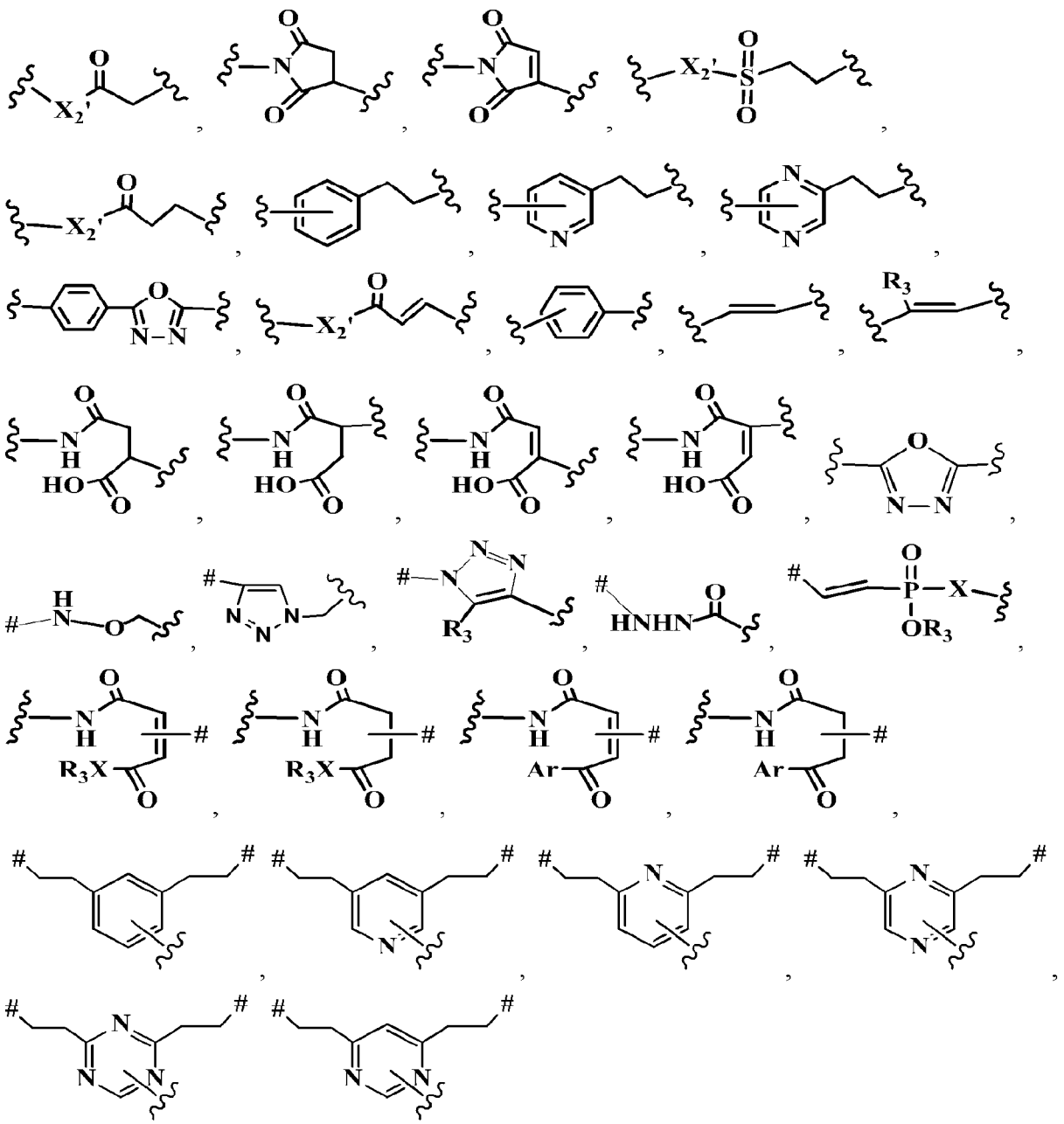
(VIII),



(IX),

wherein n is 1 – 20; n' is 1-10; D_1, D_2, L_1, L_1', L_2, L_2', and E_1 are the same as described in claim 3; S (sulfur) is generated from the reduction of disulfide bonds in the antibody or antibody-like protein; mAb is the antibody or antibody-like protein;

wherein Lv_1' and Lv_2' independently have one of the following structures:



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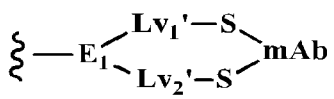
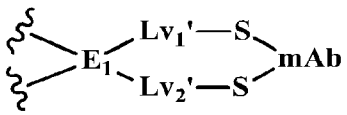
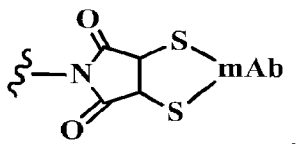
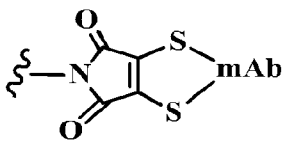
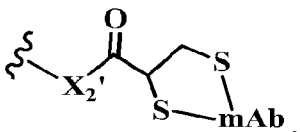
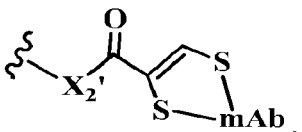
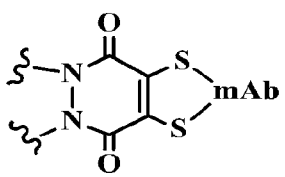
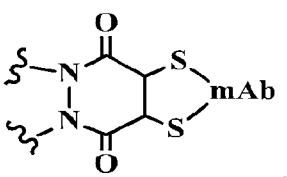
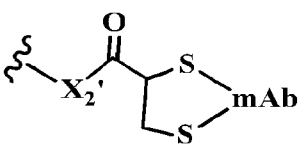
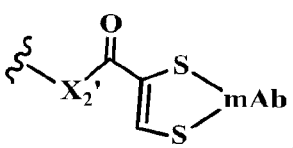
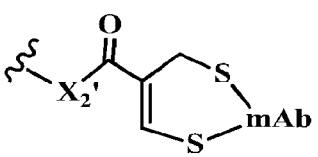
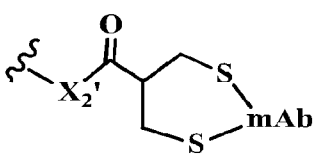
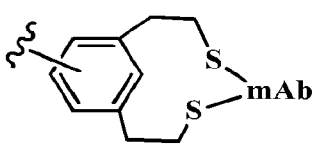
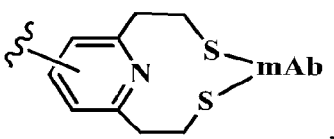
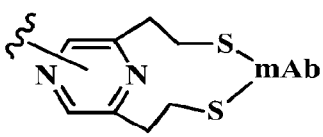
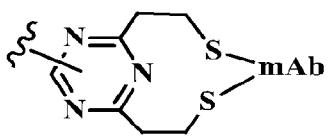
wherein Ar, X_2' and R_3 are defined the same as in Claim 3;

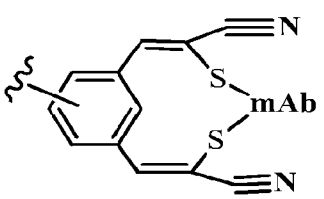
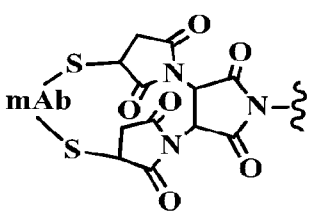
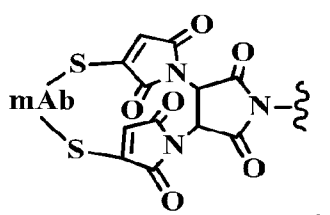
wherein in the formula (VII), (VII) and (IX), the fragments of,  and  are independently selected from:

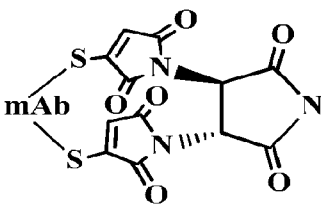
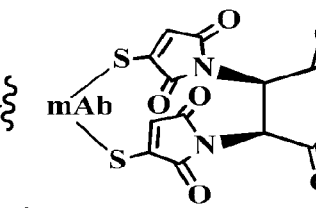
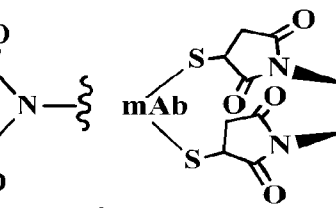
 ,  ,  ,  ,

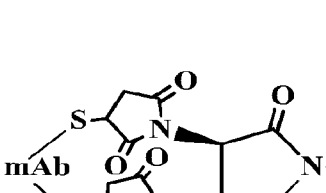
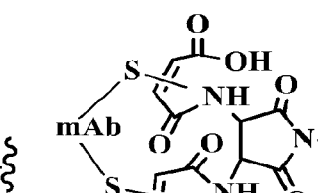
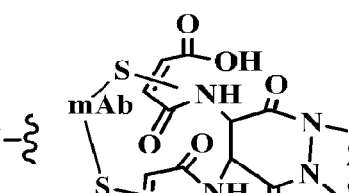
 ,  ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

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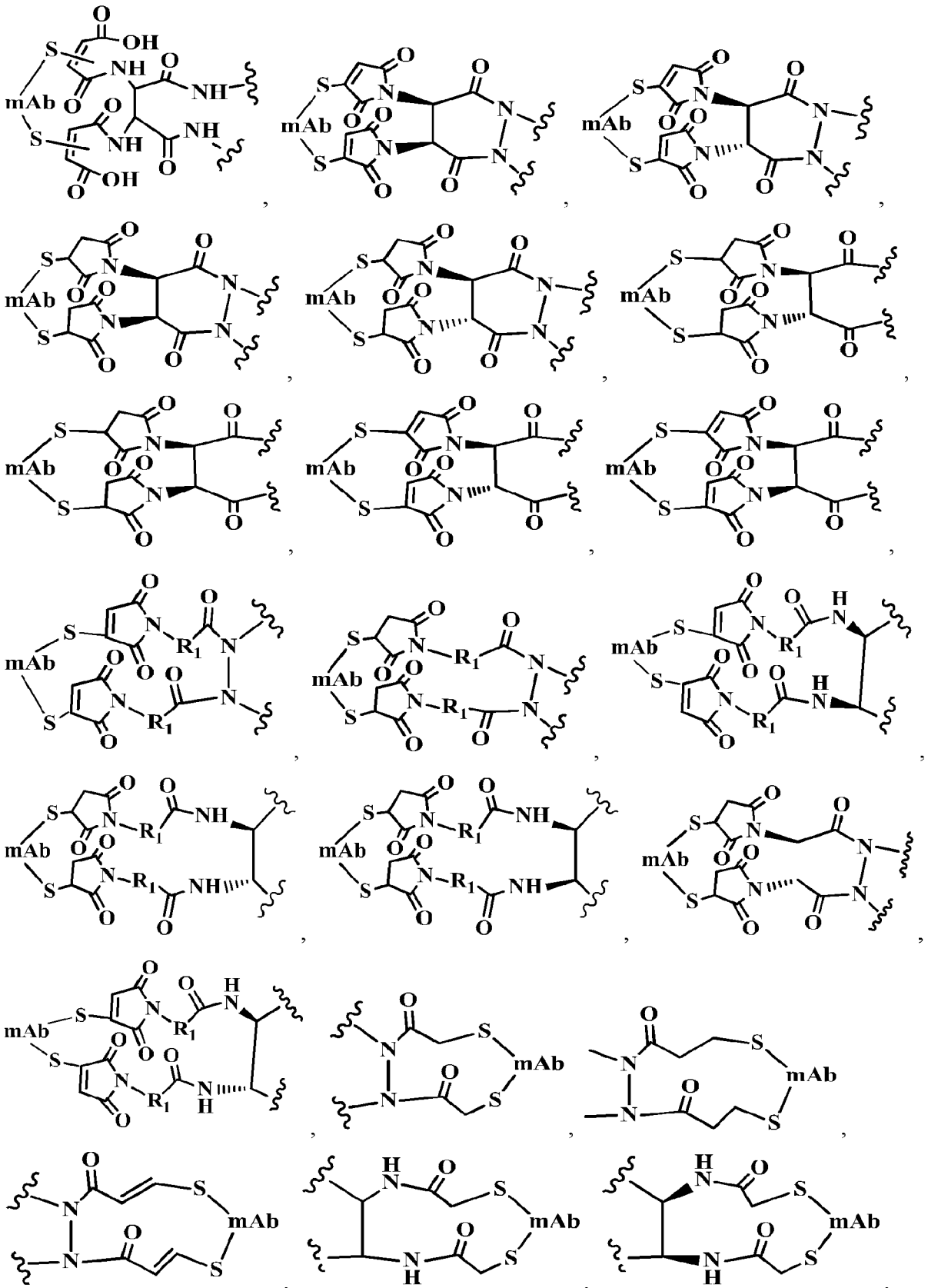

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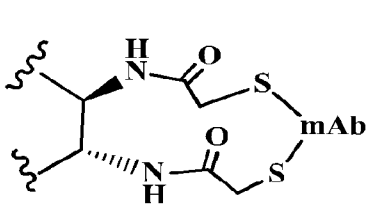
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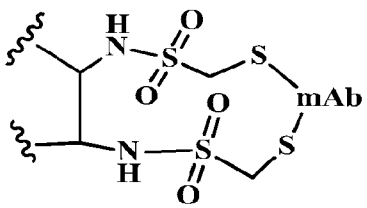
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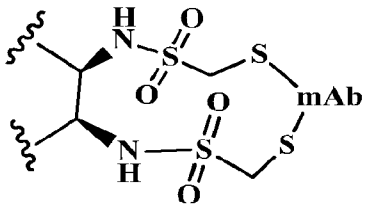
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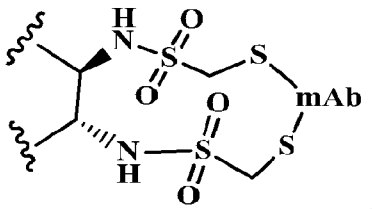
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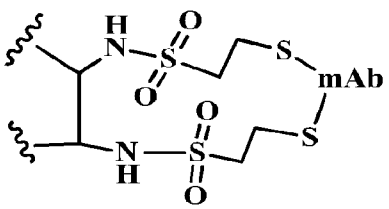
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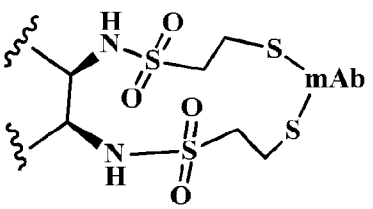
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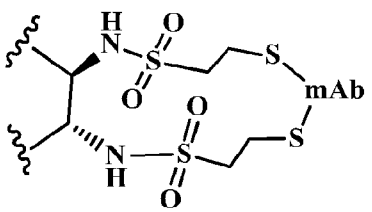
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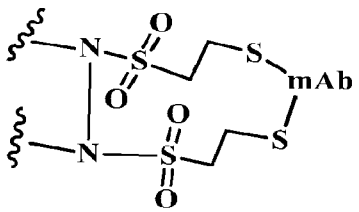
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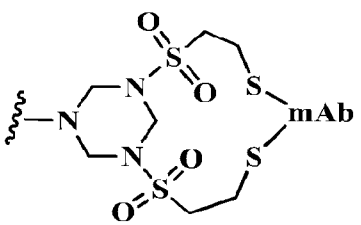
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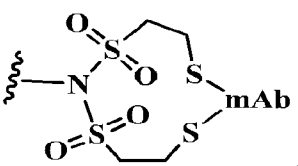
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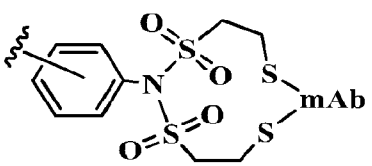
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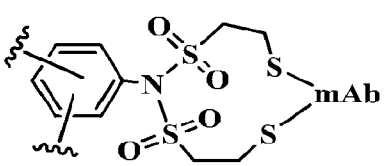
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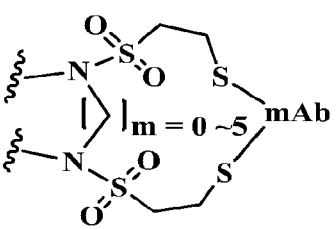
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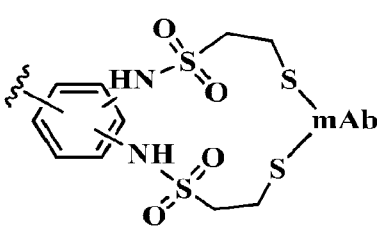
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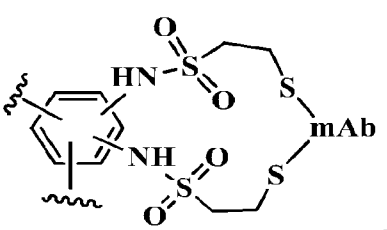
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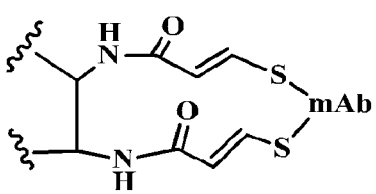
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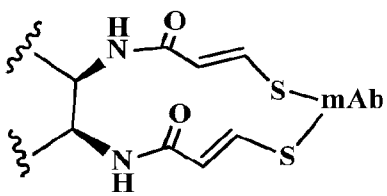
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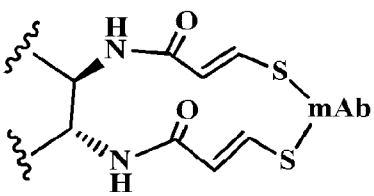
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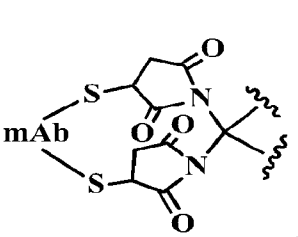
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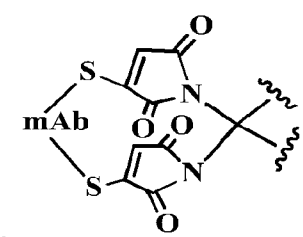
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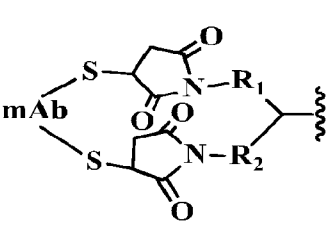
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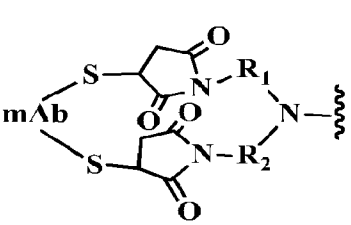
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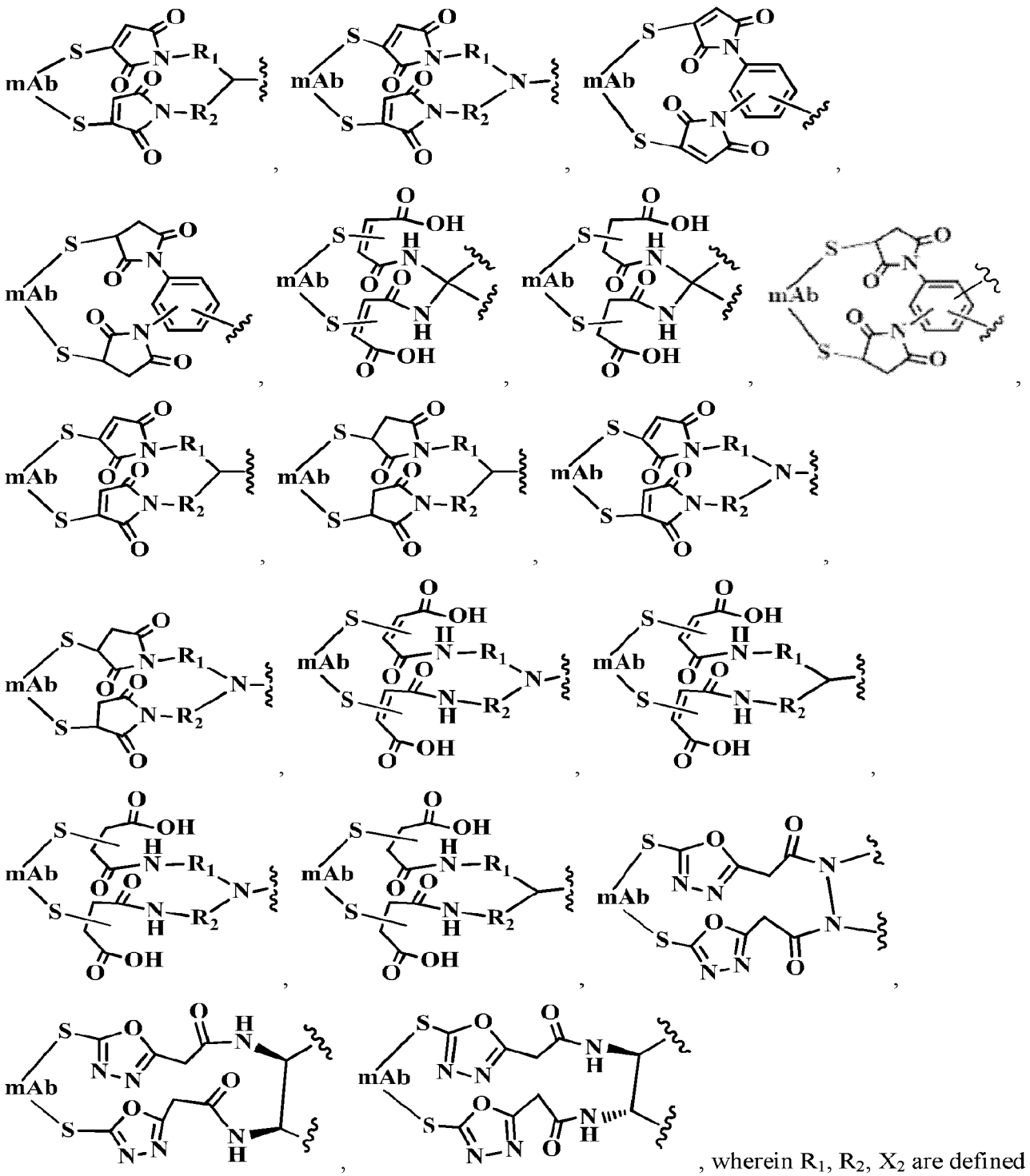
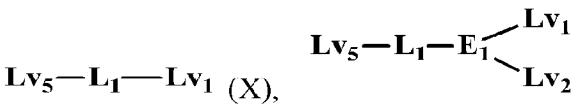


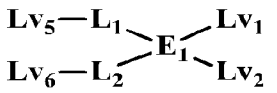
, wherein R_1, R_2, X_2 are defined the same above; mAb is an antibody.

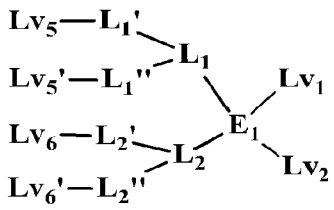
5. The process according to Claim 1, wherein the thiol groups in the antibody or antibody-like protein generated in step (a) simultaneously or sequentially react with a condensation compound

having structural formula (X), (XI), (XII) or (XIII) as illustrated below and with a drug, D_1 and/or D_2 independently, to form the conjugate of formula (VI), (VII), (VIII) or (IX):

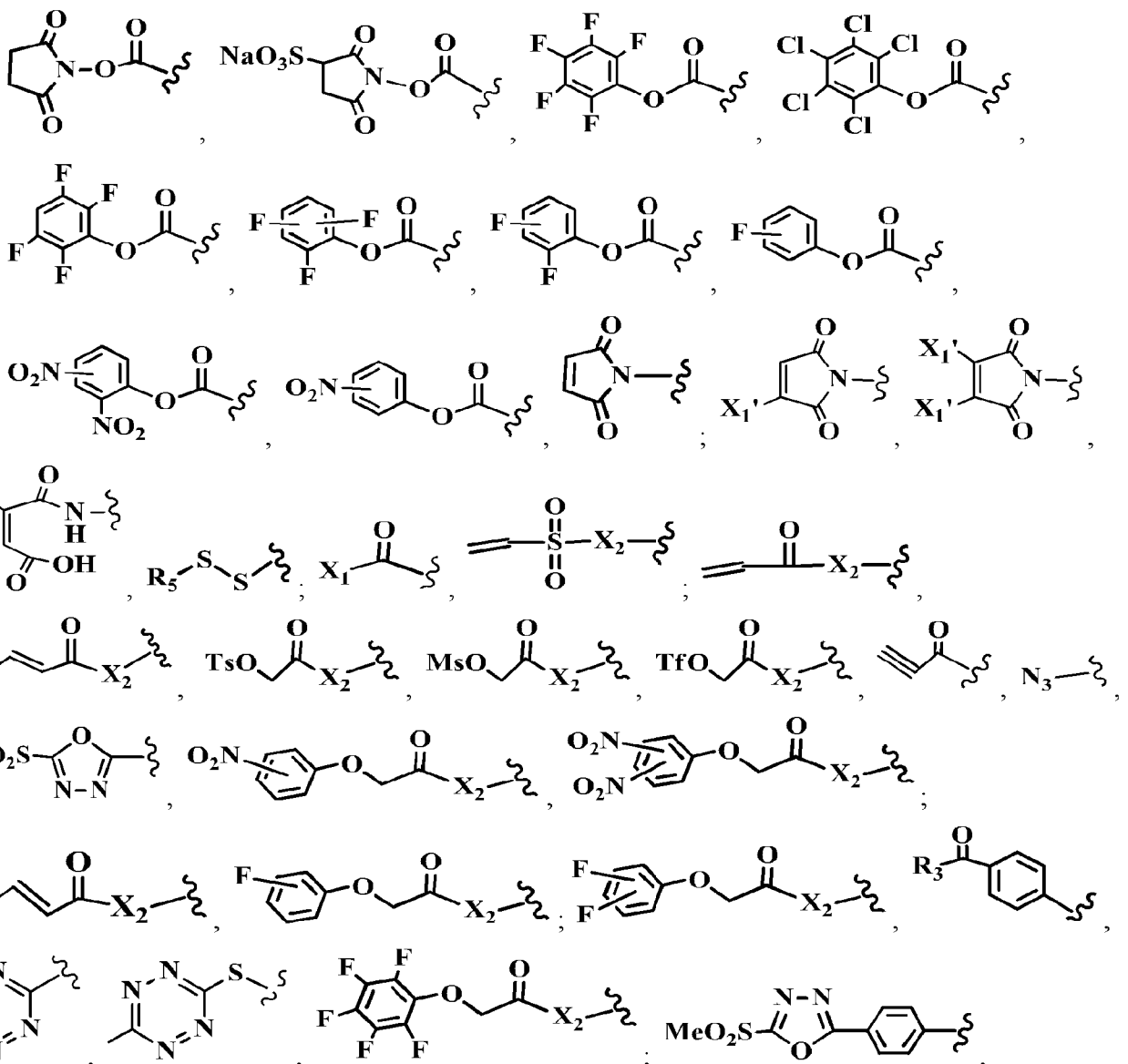

(X),

(XI),


(XII),


(XIII),

Wherein L_1, L_1', L_2, L_2', E_1, Lv_1, and Lv_2 are defined the same above in Claim 3; wherein Lv_5 and Lv_6 are independently selected from



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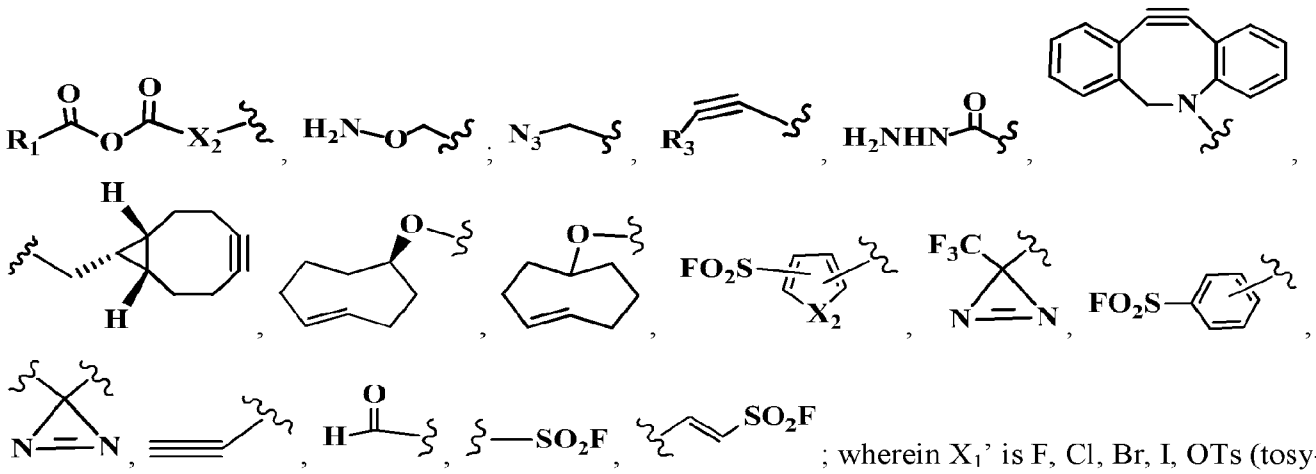
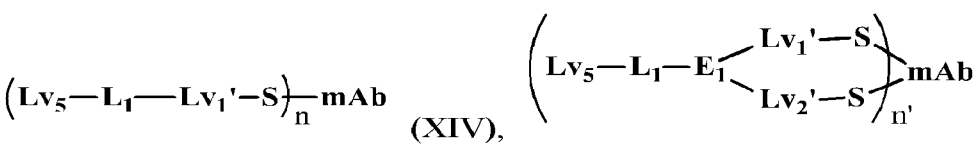


; wherein X_1' is F, Cl, Br, I, OTs (tosylate), OTf (triflate), OMs (mesylate), $OC_6H_4(NO_2)$, $OC_6H_3(NO_2)_2$, OC_6F_5, OC_6HF_4, or Lv_3; X_2' is O, NH, $N(R_1)$, or CH_2; R_3 and R_5 are independently H, R_1, aromatic, heteroaromatic, or aromatic group wherein one or several H atoms are replaced independently by $-R_1$, -halogen, $-OR_1$, $-SR_1$, $-NR_1R_2$, $-NO_2$, $-S(O)R_1$, $-S(O)_2R_1$, or $-COOR_1$; Lv_3 and Lv_3' are independently a leaving group selected from F, Cl, Br, I, nitrophenoxyl; N-hydroxysuccinimide (NHS); phenoxyl; benzenethiol, dinitrophenoxyl; pentafluorophenoxyl; tetrafluorophenoxyl; difluorophenoxyl; monofluorophenoxyl; pentachlorophenoxyl; triflate; imidazole; dichlorophenoxyl; tetrachlorophenoxyl; 1-hydroxybenzotriazole; tosylate; mesylate; 2-ethyl-5-phenylisoxazolium-3'-sulfonate, anhydrides formed its self, or formed with the other anhydride, e.g. acetyl anhydride, formyl anhydride; or an intermediate molecule generated with a condensation reagent for peptide coupling reactions or for Mitsunobu reactions; wherein the fuction groups Lv_5 and/or Lv_6 can be also reacted with a thiol in a cytotoxic drug as long as the reaction are at least one fold faster or slower than the reaction between Lv_1 or Lv_2 and a thiol in an antibody-like protein, in particular, in an antibody.

wherein Lv_5 and/or Lv_6 can be also reactive with a thiol in a cytotoxic drug as long as the reaction are at least one fold faster or slower than the reaction between Lv_1 or Lv_2 and the thiol groups in the antibody.

6. The process according to Claims 4 and 5, an antibody/linker complex molecule of formula (XIV), (XV), (XVI) or (XVII) illustrated below, is generated from a reaction of the reduced thiol groups in the antibody or antibody-like protein with formula (X), (XI), (XII), or (XIII) accordingly, and followed by reaction with the drug independently to form the conjugate of formula (VI), (VII), (VIII) or (IX).



(XIV), (XV),

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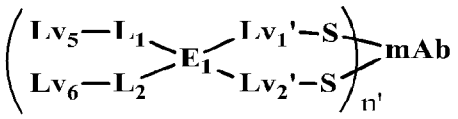
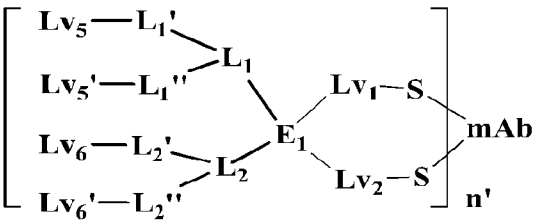
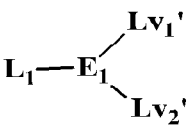
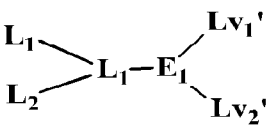
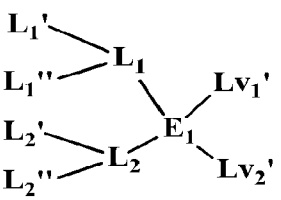


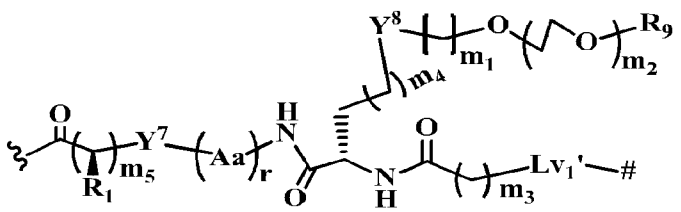
(XVI),



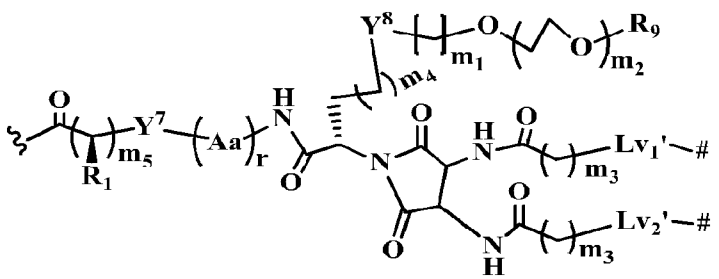
(XVII),

wherein Lv_5, Lv_6, L_1, L_2, L_1', L_2', E_1, Lv_1' Lv_2', mAb, n and n' are described are the same in claims 3 and 7.

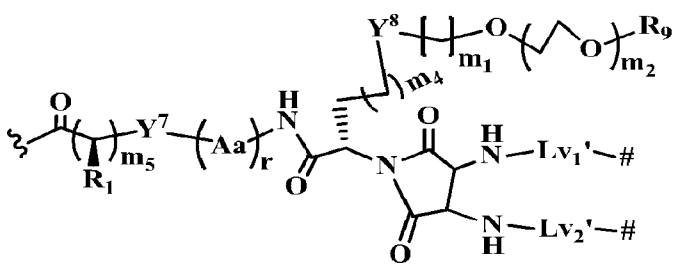
7. The conjugate of formula (VI), (VII), (VIII) or (IX) according to Claim 4, wherein the components of $L_1—E_1—Lv_1'$ in formula (VI),  in formula (VII),  in formula (VIII), and  in formula (IX), are selected from the following structures accordingly:



(I-a),



(I-b),



(I-c),

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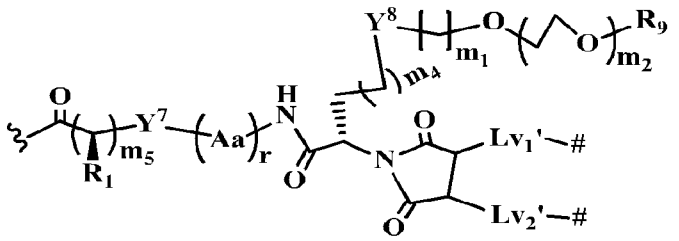
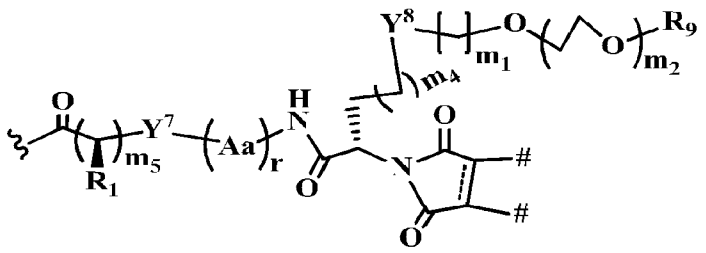
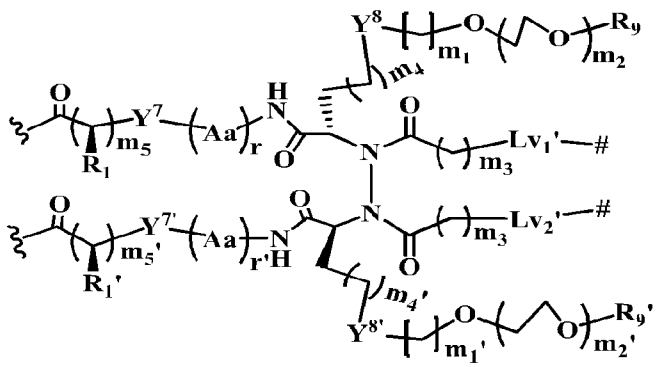


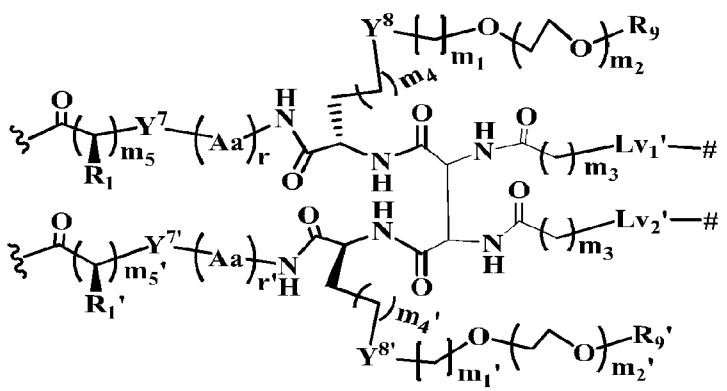
(I-d),



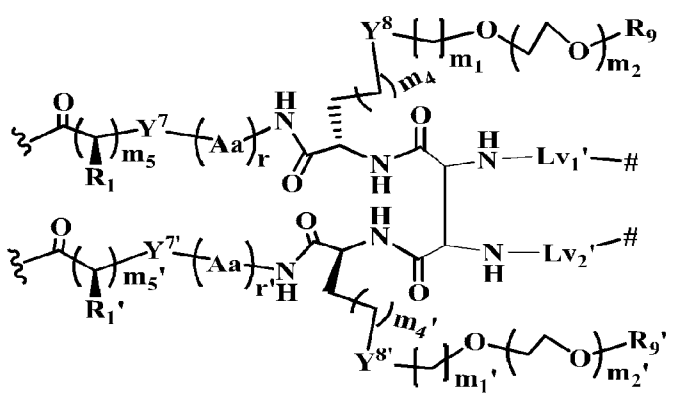
(I-e),



(I-f),



(I-g),



(I-h),

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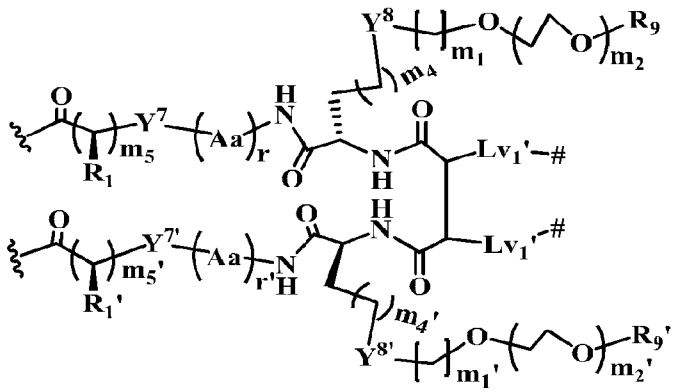
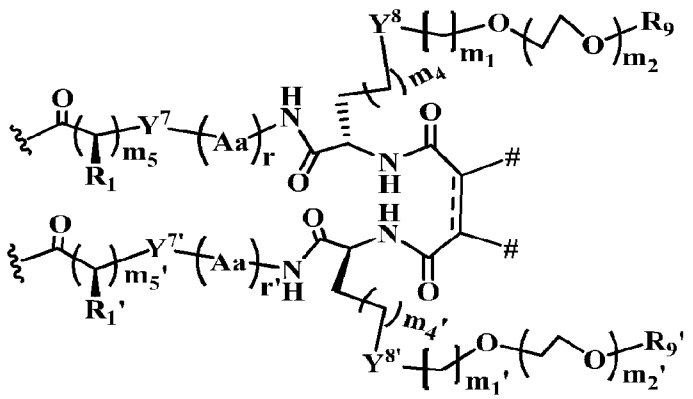
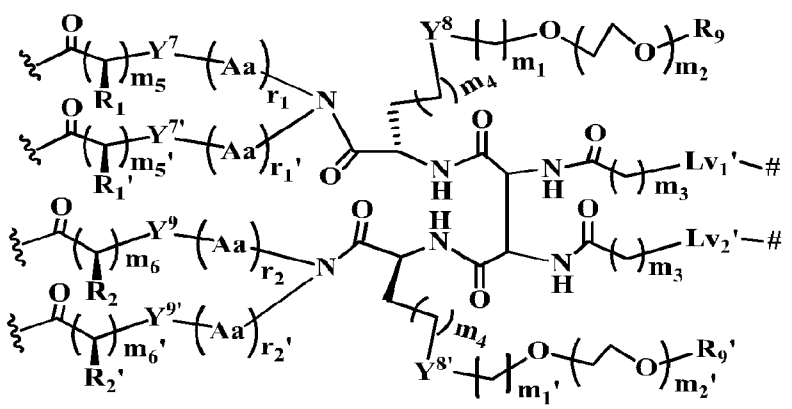


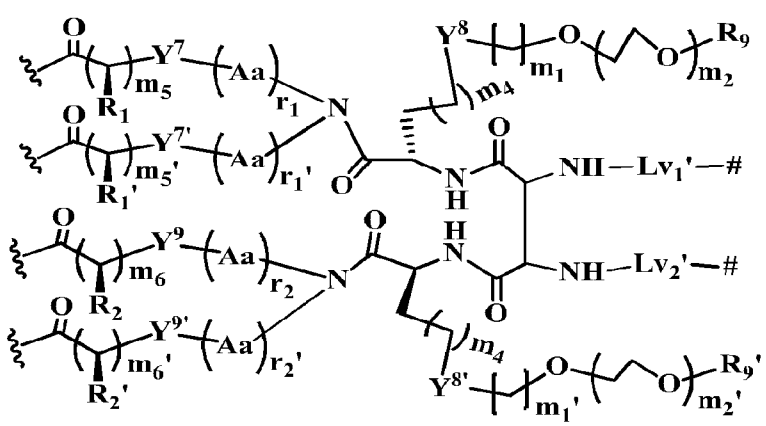
(I-i),



(I-j),



(I-k),



(I-l),

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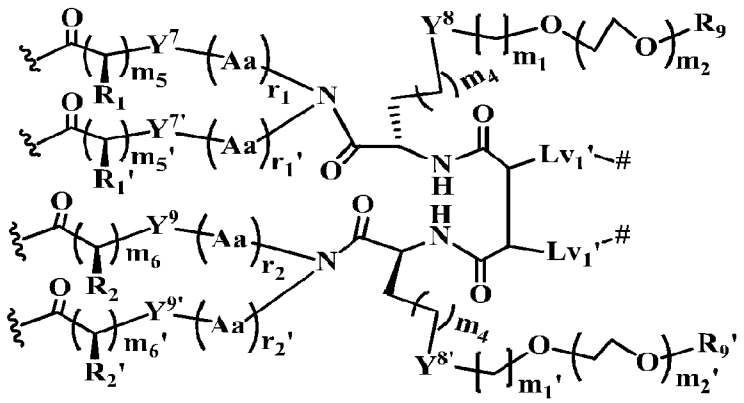
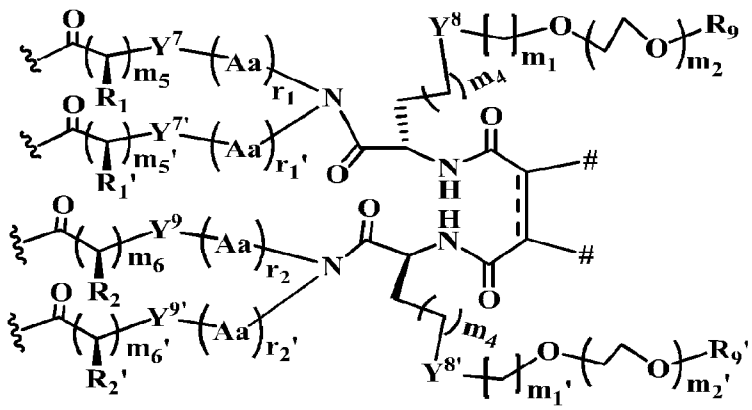


(I-m),



(I-n),

Wherein "$\sim$" is a site that links a drug or a site of linker L_1, L_1', L_2, or L_2'; "#" is a site that links a S (thiol) of an antibody; Aa is L-or D- natural or unnatural amino acids;

Wherein R_1, R_1', R_2, and R_2' are independently selected from H, C_1-C_8 alkyl, OH, CH_2OH, CH_2CH_2OH, NH_2, SH, SCH_3, CH_2COOH, CH_2CH_2COOH, $CH_2CH_2CH_2CH_2NH_2$, C_6H_5, $CH_2C_6H_5$, $CH_2C_6H_4OH$, $CH(OH)CH_3$, $CH_2C(O)NH_2$, $CH_2CH_2C(O)NH_2$, $CH_2CH_2CH_2NHC(=NH)NH_2$;

Wherein r, r_1, r_1', r_2, and r_2' are independently selected from is 0-12; when r is not 0, $(Aa)_r$ is the same or different amino acids or peptide units;

Wherein m_1 and m_1' are independently 1 - 18; m_2 and m_2' are independently 1-100; m_3 and m_3' are independently 1 - 8; m_4 and m_4' are independently 0 - 8; m_5 and m_5' are independently 1 - 8;

Wherein Y^7 and $Y^{7'}$ are independently NH, OCH_2NH, NHC(=O), NHNH, C(=O)NH, $N(R_1)$, SO_2, P(O)(OH), $NHS(O)_2$, $NHS(O)_2NH$, $NHS(O)_2NHC(O)$, $NHS(O)_2NHC(O)O$, $NHS(O)_2NHC(O)NH$, NHP(O)(OH), NHP(O)(OH)NH, OP(O)(OH)O, NHP(O)(OH)O, OP(O)(OH)NH, S, O, OP(O)(OH)OP(O)(OH)NH, NHP(O)(OH)OP(O)(OH)NH, NHP(O)(OH)OP(O)(OH)O, OCH_2CH_2O, OCH_2CH_2NH, $N(CH_2CH_2)_2N$, NHC_6H_4NH, CH_2;

Y^8 and $Y^{8'}$ are independently NHC(=O), $NHS(O_2)$, NH(SO), $NHS(O_2)NH$,

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NHP(O)(OH)NH or C(O)NH;

Y^9 and $Y^{9'}$ are independently H, (O=)CR_1, (O=)$CNHR_1$, R_1COOH, $R_1(COCH_2NH)_{m2}H$, $R_1(Aa)_r$ or $R_1(COCH_2NCH_3)_{m2}H$, wherein R_1 is defined above.

8. The process according to Claim 4, wherein the drug D_1, D_2, D_3 and D_4 are a chromophore molecule that is capable of absorbing UV light, florescent light, IR light, near IR light, or visual light; a chromatophore molecule of a class or subclass of xanthophores, erythrophores, iridophores, leucophores, melanophores, and cyanophores; a class or subclass of fluorophore molecules which are fluorescent chemical compounds re-emitting light upon light; a class or subclass of visual phototransduction molecules; a class or subclass of photophore molecules; a class or subclass of luminescence molecules; or a class or subclass of luciferin compounds;

the chromophore molecule is selected from, non-protein organic fluorophores: Xanthene derivatives (including fluorescein, rhodamine, Oregon green, eosin, and Texas red); Cyanine derivatives: (including cyanine, indocarbocyanine, oxacarbocyanine, thiacarbocyanine, and merocyanine); Squaraine derivatives and ring-substituted squaraines, including Seta, SeTau, and Square dyes; Naphthalene derivatives (including dansyl and prodan derivatives); Coumarin derivatives; Oxadiazole derivatives (pyridyloxazole, nitrobenzoxadiazole and benzoxadiazole); Anthracene derivatives (anthraquinones, including DRAQ5, DRAQ7 and CyTRAK Orange); Pyrene derivatives (including cascade blue); Oxazine derivatives (including Nile red, Nile blue, cresyl violet, oxazine 170); Acridine derivatives (including proflavin, acridine orange, acridine yellow); Arylmethine derivatives (including auramine, crystal violet, malachite green); Tetrapyrrole derivatives (including porphin, phthalocyanine, bilirubin);

the chromophore molecule can be also selected from analogs and derivatives of the following fluorophore compounds: CF dye, DRAQ and CyTRAK probes, BODIPY, Alexa Fluor, DyLight Fluor, Atto and Tracy, FluoProbes, Abberior Dyes, DY and MegaStokes Dyes, Sulfo Cy dyes, Hi-Lyte Fluor, Seta, SeTau and Square Dyes, Quasar and Cal Fluor dyes, SureLight Dyes (APC, RPEPerCP, Phycobilisomes), APC, APCXL, RPE, BPE, Allophycocyanin (APC), Aminocoumarin, APC-Cy7 conjugates, BODIPY-FL, Cascade Blue, Cy2, Cy3, Cy3.5, Cy3B, Cy5, Cy5.5, Cy7, Fluorescein, FluorX, Hydroxycoumarin, IR-783, Lissamine Rhodamine B, Lucifer yellow, Methoxycoumarin, NBD, Pacific Blue, Pacific Orange, PE-Cy5 conjugates, PE-Cy7 conjugates, PerCP, R-Phycoerythrin (PE), Red 613, Seta-555-Azide, Seta-555-DBCO, Seta-555-NHS, Seta-580-NHS, Seta-680-NHS, Seta-780-NHS, Seta-APC-780, Seta-PerCP-680, Seta-R-PE-670, SeTau-380-NHS, SeTau-405-Maleimide, SeTau-405-NHS, SeTau-425-NHS, SeTau-647-NHS, Texas Red, TRITC, TruRed, X-Rhodamine, 7-AAD (7-aminoactinomycin D, CG-selective), Acridine

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Orange, Chromomycin A3, CyTRAK Orange (Biostatus, red excitation dark), DAPI, DRAQ5, DRAQ7, Ethidium Bromide, Hoechst33258, Hoechst33342, LDS 751, Mithramycin, PropidiumIodide (PI), SYTOX Blue, SYTOX Green, SYTOX Orange, Thiazole Orange, TO-PRO: Cyanine Monomer, TOTO-1, TO-PRO-1, TOTO-3, TO-PRO-3, YOSeta-1, YOYO-1, DCFH (2',7'-Dichorodihydro-fluorescein, oxidized form), DHR (Dihydrorhodamine 123, oxidized form, light catalyzes oxidation), Fluo-3 (AM ester. pH > 6), Fluo-4 (AM ester. pH 7.2), Indo-1 (AM ester, low/high calcium (Ca^{2+})), and SNARF (pH 6/9).

9. The process according to Claim 3 or 4, wherein the drug D_1, D_2, D_3 and D_4 are independently a polyalkylene glycol selected from poly(ethylene glycols) (PEGs), poly(propylene glycol) and copolymers of ethylene oxide and propylene oxide; the polyalkylene glycol has a molecular weight of from about 10 Daltons to about 200 kDa.

10. The process according to Claim 3 or 4, wherein the drug D_1, D_2, D_3 and D_4 are selected from a tubulysin and its analogs, a maytansinoid and its analogs, a taxanoid (taxane) and its analogs, a CC-1065 and its analogs, a daunorubicin or doxorubicin and its analogs, an amatoxin and its analogs, a benzodiazepine dimer (including dimers of pyrrolobenzodiazepine (PBD), tomaymycin, anthramycin, indolinobenzodiazepines, imidazobenzothiadiazepines, or oxazolidinobenzodiazepines) and their analogs, a calicheamicin or an enediyne antibiotic and its analogs, an actinomycin and its analogs, an azaserine and its analogs, a bleomycin and its analogs, an epirubicin and its analogs, a tamoxifen and its analogs, an idarubicin and its analogs, a dolastatin and its analogs, an auristatin (including monomethyl auristatin E (MMAE), MMAF, auristatin PYE, auristatin TP, Auristatins 2-AQ, 6-AQ, EB (AEB), and EFP (AEFP)) and its analogs, a combretastatin, a duocarmycin and its analogs, a camptothecin and its analogs, a geldanamycin and its analogs, a methotrexate and its analogs, a thiotepa and its analogs, a vindesine and its analogs, a vincristine and its analogs, a hemiasterlin and its analogs, a nazumamide and its analogs, a spliceostatin, a pladienolide, a microginin and its analogs, a radiosumin and its analogs, an alterobactin and its analogs, a microsclerodermin and its analogs, a theonellamide and its analogs, an esperamicin and its analogs, PNU-159682 and its analogs, a protein kinase inhibitor, a MEK inhibitor, a KSP inhibitor, a nicotinamide phosphoribosyltransferase (NAMPT) inhibitor, an immunotoxin, a cell receptor agonist, a cell stimulating molecule or intracellular signalling molecule, one, two or more DNA, RNA, mRNA, small interfering RNA (siRNA), microRNA (miRNA), and PIWI interacting RNAs (piRNA), and stereoisomers, isosteres, analogs, or derivatives thereof;

wherein:

(a) Tubulysin and its analogs have the following formula (V):

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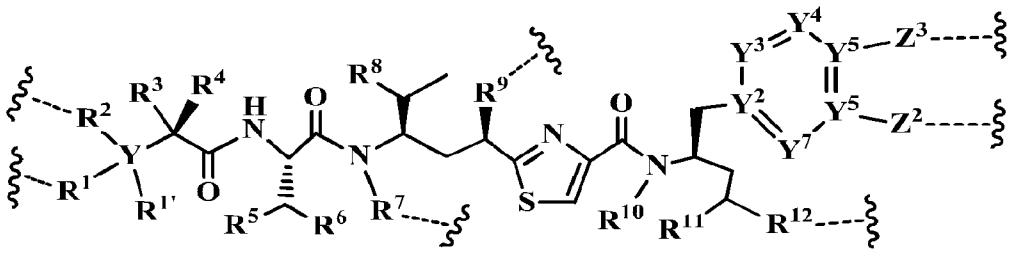

((V)

or a derivative with one or more isotopes; or a pharmaceutically acceptable salt, hydrate, or hydrated salt thereof; or a polymorphic crystalline structure thereof; or an optical isomer, racemate, diastereomer or enantiomer thereof,

wherein ~~ is a linkage site that either one or two of them can link to L_1 and/or L_2 independently; when two of " ~~ " link to both L_1 and L_2, R^1 and R^2, or Z^2 and Z^3 are preferably the dual linkage sites;

wherein R^1, $R^{1'}$, R^2, R^3, and R^4 are independently H, C_1~C_8 alkyl; C_2~C_8 heteroalkyl, or heterocyclic; C_3~C_8 aryl, Ar-alkyl, cycloalkyl, alkylcycloalkyl, heterocycloalkyl, heteroalkylcycloalkyl, carbocyclic, or alkylcarbonyl; or R^1R^2, R^1R^3, R^2R^3, R^3R^4, or R^5R^6 form a 3~7 membered carbocyclic, cycloalkyl, heterocyclic, heterocycloalkyl, aromatic or heteroaromatic ring system; R^1 and R^2 can be independently absent when they link to L_1 or L_2 independently or simultaneously, Y^1 is N or CH;

wherein R^5, R^6, R^8, R^{10} and R^{11} are independently H, or C_1~C_4 alkyl or heteroalkyl;

wherein R^7 is independently H, R^{14}, $-R^{14}C(=O)X^1R^{15}$; or $-R^{14}X^1R^{15}$; X^1 is O, S, S-S, NH, CH_2 or NR^{14};

wherein R^9 is selected from H, OH, =O, $-OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)NHR^{14}$, $-OC(=O)NR^{14}R^{15}$, $OP(=O)(OR^{14})_2$, $-OC(=O)NR^{14}R^{15}$, or $OR^{14}OP(=O)(OR^{15})_2$; when R^9 links L_1 or L_2, R^9 is , -O-, -OC(=O)NH- or $-OC(=O)N(R^{14})$-;

wherein R^{11} is independently H, R^{14}, $-R^{14}C(=O)R^{15}$, $-R^{14}C(=O)X^2R^{15}$, wherein X^2 is -O-, -S-, -NH-, or $-N(R^{14})$-;

wherein R^{12} is -COOH, -COSH, $-CONH_2$, $CONHNH_2$, $CONHNHR^{15}$, $-CONH(R^{15})$, $-COOR^{15}$, $-R^{15}COR^{16}$, $-R^{15}COOR^{16}$, $-R^{15}C(O)NH_2$, $-R^{15}C(O)NHR^{16}$, $-COSR^{15}$, $R^{15}S(=O)_2R^{16}$, $-R^{15}P(=O)(OR^{17})_2$, $-R^{15}OP(=O)(OR^{17})_2$, $-COOCH_2OP(=O)(OR^{17})_2$, $-COX^2SO_2R^{17}$, $-COOR^{15}X^2R^{16}$, tetrazole, imidazole, or triazole, where X^2 is -O-, -S-, -NH-, $-N(R^{15})$-, $-O-R^{15}$-, $-S-R^{15}$-, CH_2 or $-NHR^{15}$-; when R^{12} links L_1 or L_2, R^{12} is $-C(O)O$-, $-C(O)NH$-, $-C(=O)NHS(O)_2R^{15}$- or $-C(=O)N(R^{15})$-;

R^{13} and R^{14} are independently C_1~C_8 alkyl, heteroalkyl; C_2-C_8 of alkenyl, alkynyl, heteroalkyl, heterocycloalkyl; C_3-C_8 of aryl, Ar-alkyl;

Z^2 and Z^3 are independently H, O, S, NH, $N(R^{15})$, NHNH, -OH, -SH, $-NH_2$, NH, $NHNH_2$, $-NH(R^{15})$, $-OR^{15}$, CO, $-COX^2$, $-COX^2R^{16}$, R^{17}, F, Cl, Br, I, SR^{16}, $NR^{16}R^{17}$, $N=NR^{16}$, $N=R^{16}$, NO_2, $SOR^{16}R^{17}$, SO_2R^{16}, SO_3R^{16}, OSO_3R^{16}, $PR^{16}R^{17}$, $POR^{16}R^{17}$, $PO_2R^{16}R^{17}$, $OP(O)(OR^{17})_2$,

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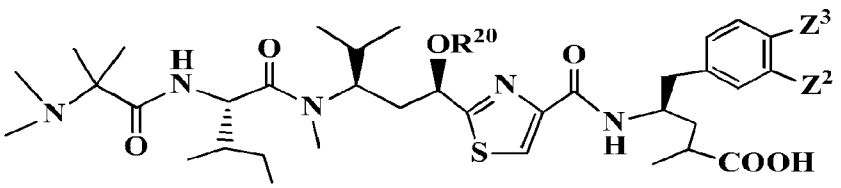
$OCH_2OP(O)(OR^{17})_2$, $OC(O)R^{17}$, $OC(O)OP(O)(OR^{17})_2$, $PO(OR^{16})(OR^{17})$, $OP(O)(OR^{17})OP(O)(OR^{17})_2$, $OC(O)NHR^{17}$;-O-(C_4-C_{12} glycoside), -N-(C_4-C_{12} glycoside); C_1~C_8 alkyl, heteroalkyl; C_2-C_8 of alkenyl, alkynyl, heteroalkyl, heterocycloalkyl; C_3-C_8 of aryl, Ar-alkyl, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl, or 2- 8 carbon atoms of esters, ether, or amide; or peptides containing 1-8 amino acids $(NH(Aa)_{1\sim8}$, or $CO(Aa)_{1\sim8}$ (which are respectively N-terminal or C-terminal 1 - 8 the same or different amino acids)), or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$ or $(OCH_2CH(CH_3))_p$, wherein p is an integer from 0 to about 1000, or combination of above groups thereof; X^2 is O, S, S-S, NH, CH_2, OH, SH, NH_2, CHR^{15} or NR^{15};

R^{15}, R^{16} and R^{17} are independently H, C_1~C_8 alkyl, heteroalkyl; C_2-C_8 of alkenyl, alkynyl, heteroalkyl, heterocycloalkyl; C_3-C_8 of aryl, Ar-alkyl, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl, alkylcarbonyl, or Na^+, K^+, Cs^+, Li^+, Ca^{2+}, Mg^+, Zn^{2+}, $N^+(R^1)(R^2)(R^3)(R^4)$, $HN^+(C_2H_5OH)_3$ salt;

Y^1 and Y^2 are independently N or CH; q is 0 or 1; when q=0, Y^3 does not exist, Y^4, Y^5, Y^6 and Y^7 are independently CH, N, NH, O, S, or N (R1), thus Y^2, Y^4, Y^5, Y^6 and Y^7form a heteroaromatic ring of furan, pyrrole thiophene, thiazole, oxazole and imidazole, pyrazole, triazole, tetrazole, thiadiazole; when q=1, Y^3, Y^4, Y^5, Y^6 and Y^7 are independently CH or N, thus Y^2, Y^3, Y^4, Y^5, Y^6 and Y^7 form aromatic ring of benzene, pyridine, pyridazine, pyrimidine, pyrazine, triazine, tetrazine, pentazine;

Wherein the tubulysin analogs have the structures shown below:



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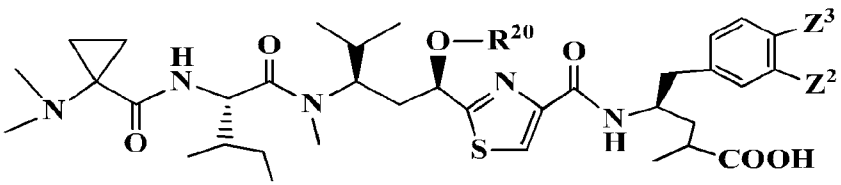

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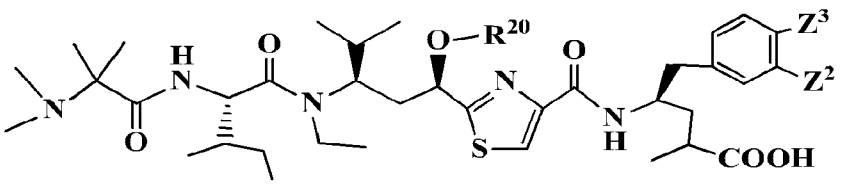

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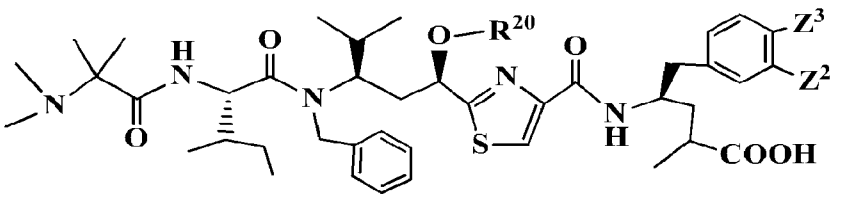

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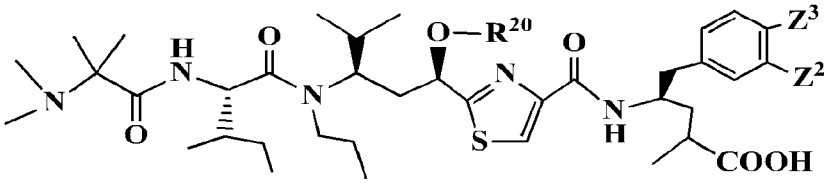
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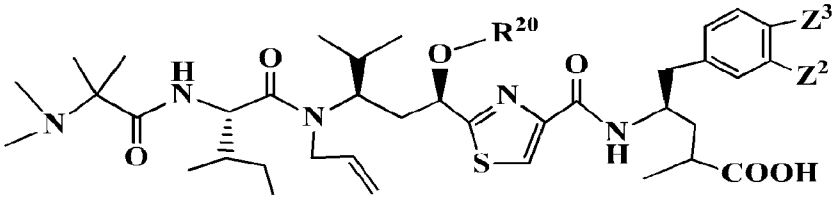
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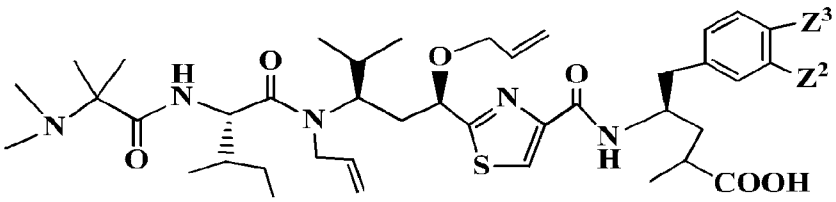
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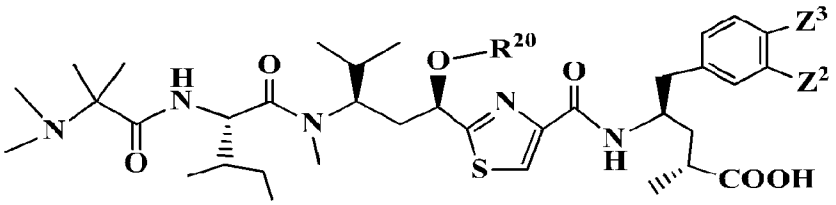
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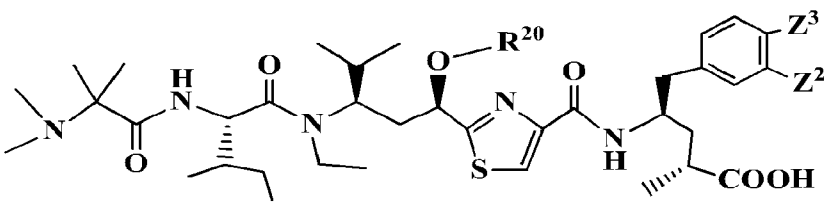
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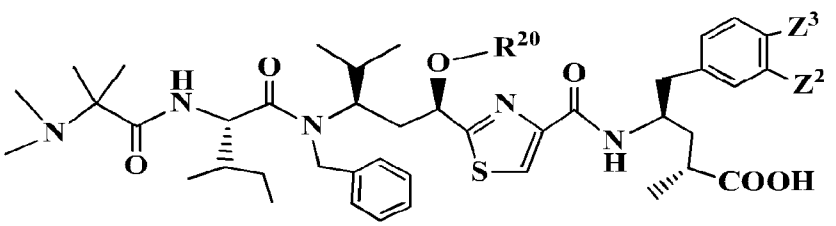
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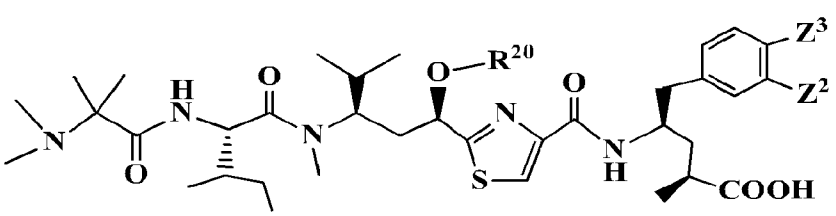
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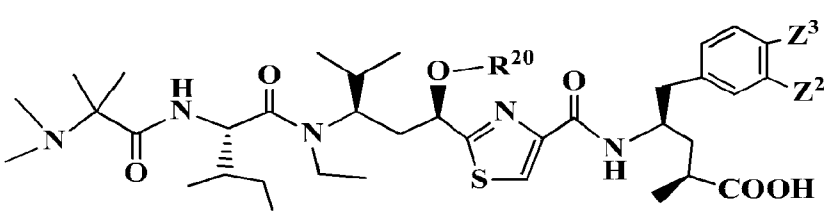
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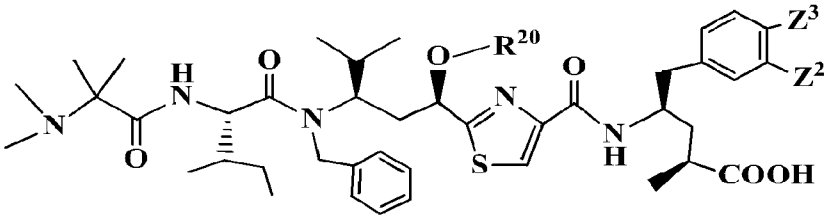
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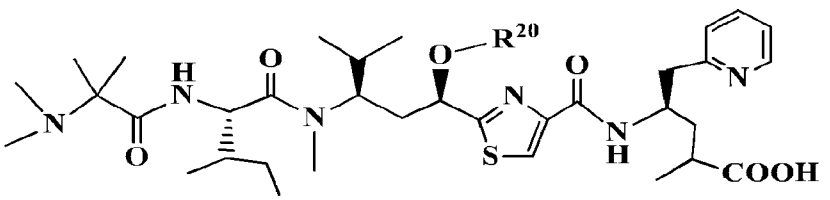
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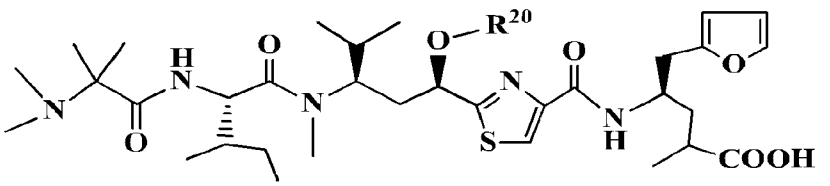
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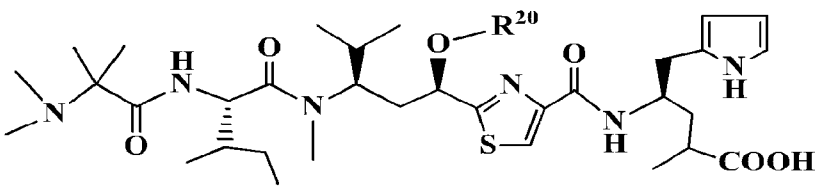
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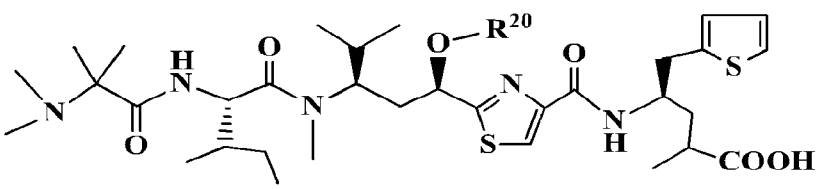
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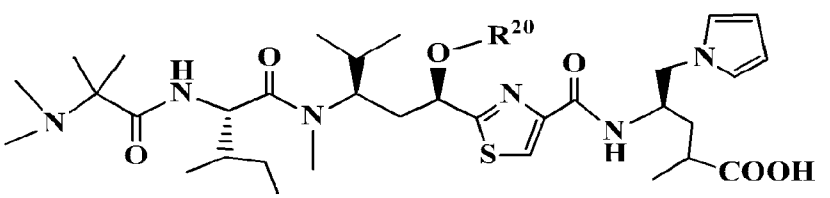
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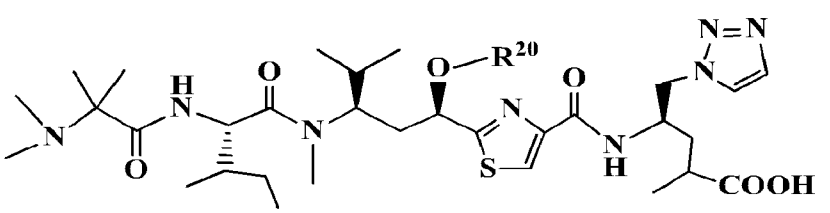
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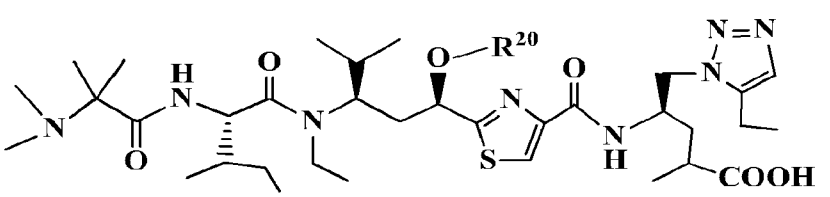
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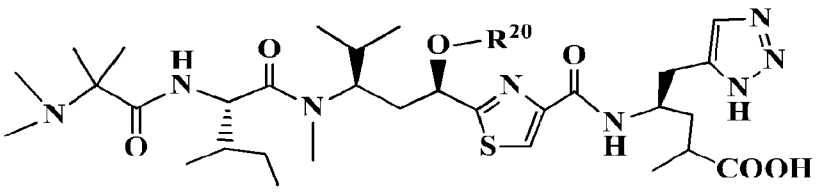
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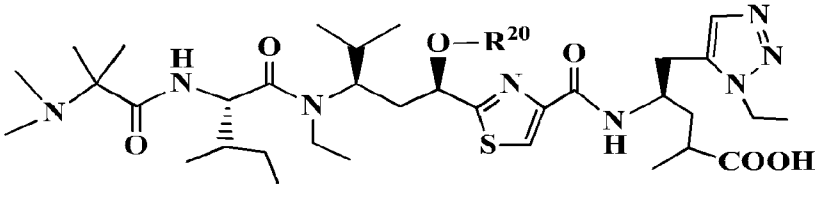
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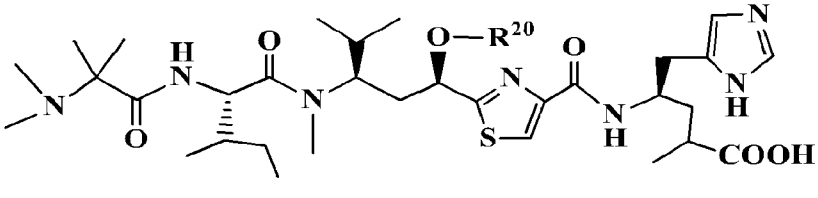
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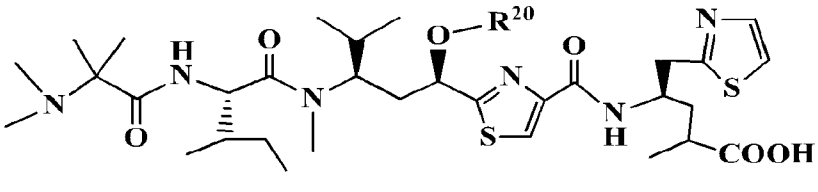
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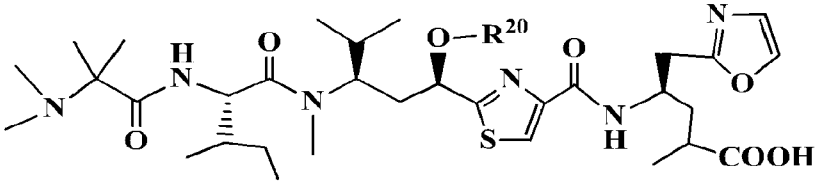
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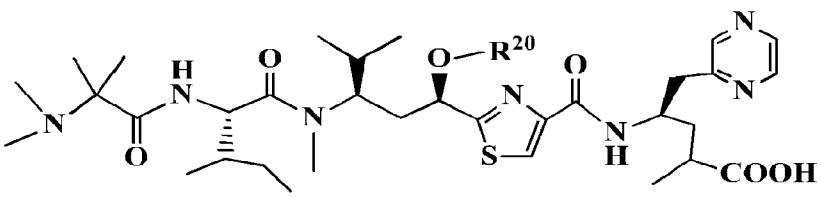
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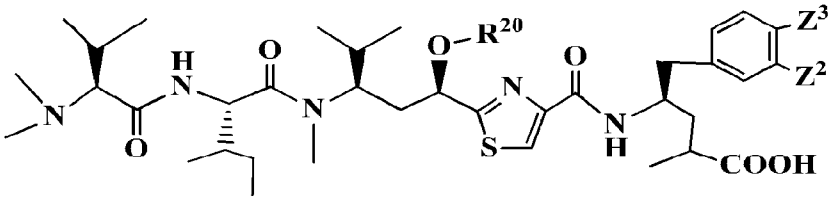
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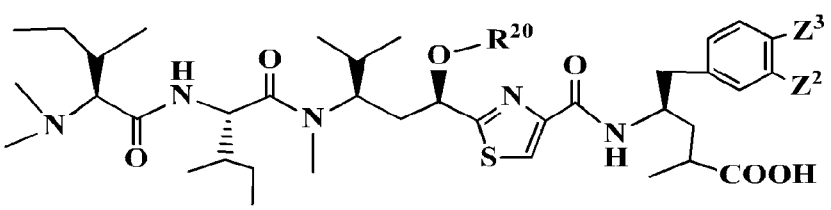
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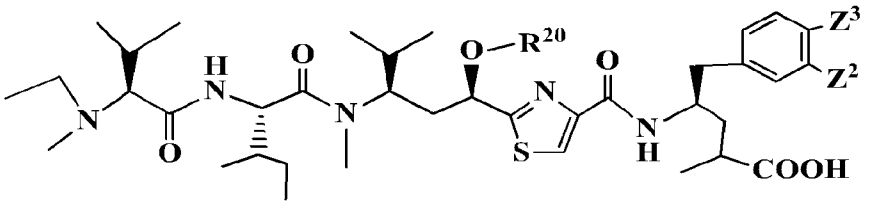
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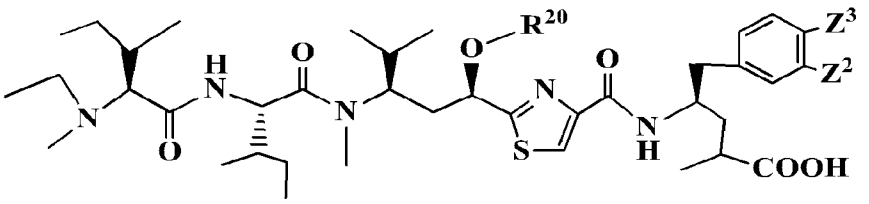
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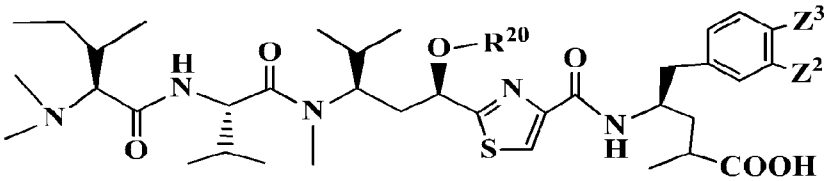
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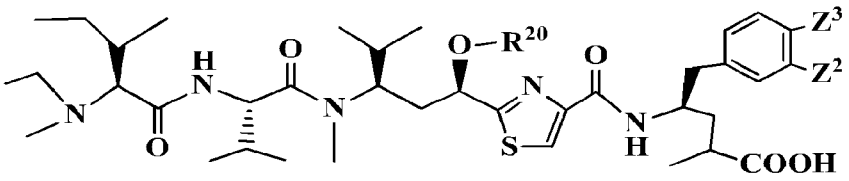
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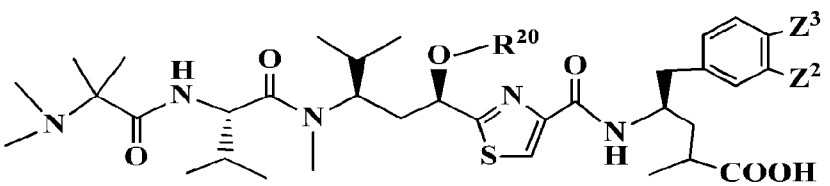
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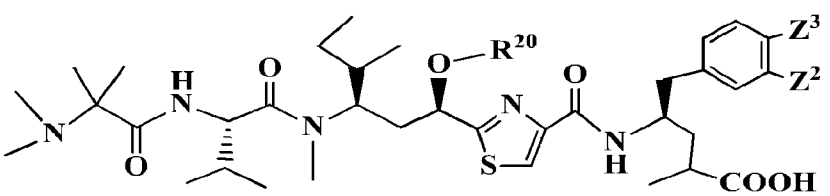
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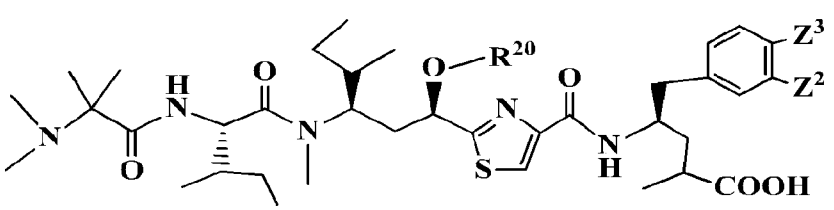
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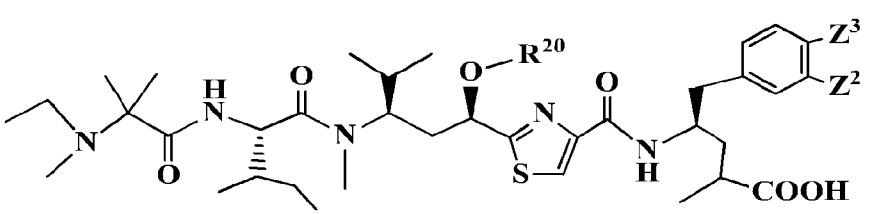
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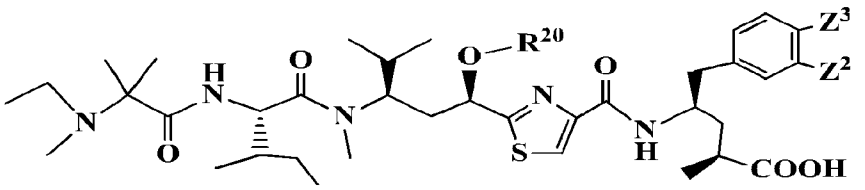
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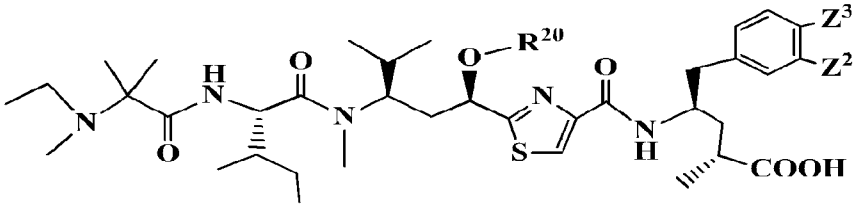
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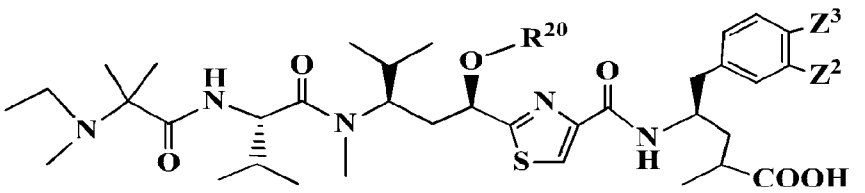
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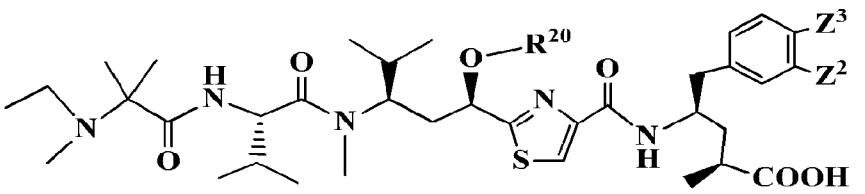
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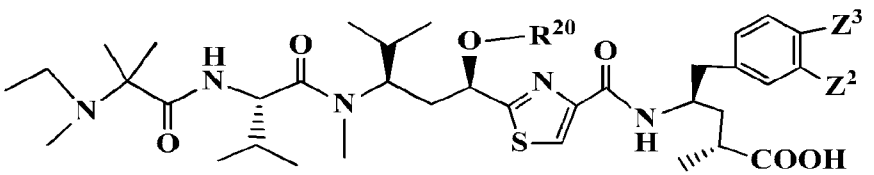
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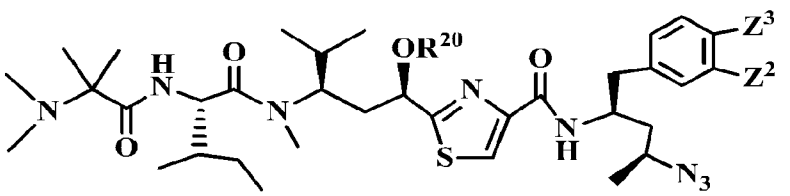
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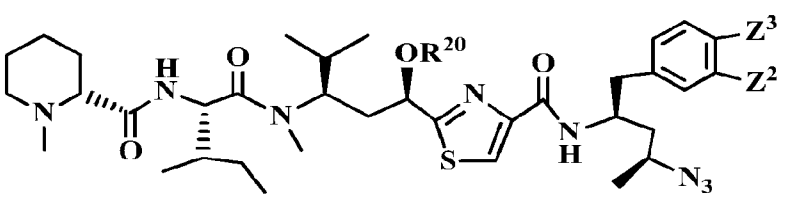
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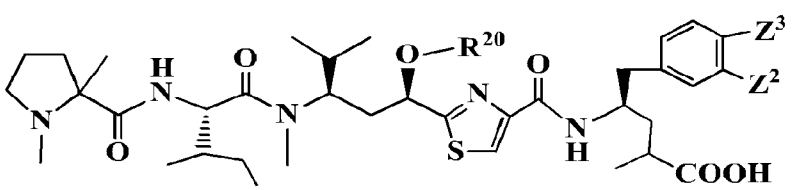
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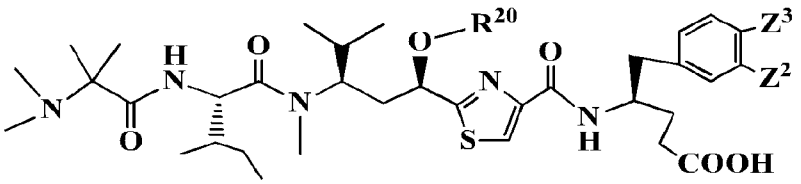
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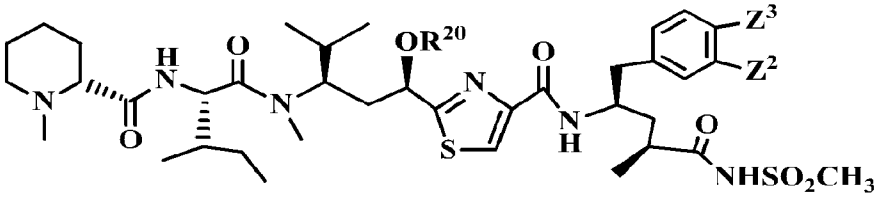
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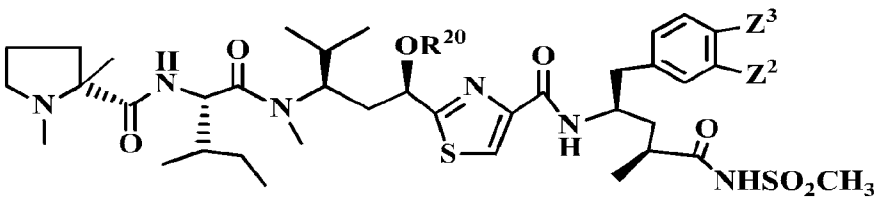
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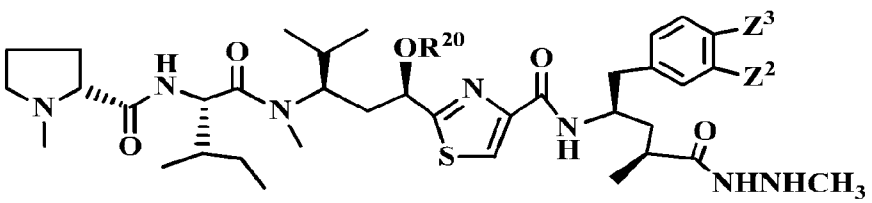
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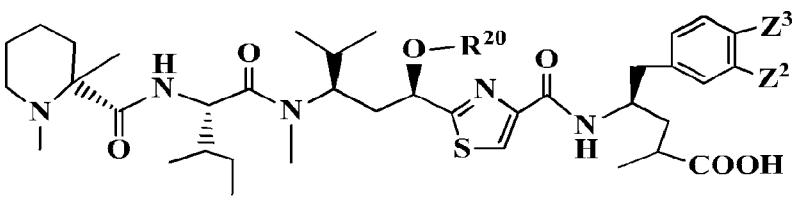
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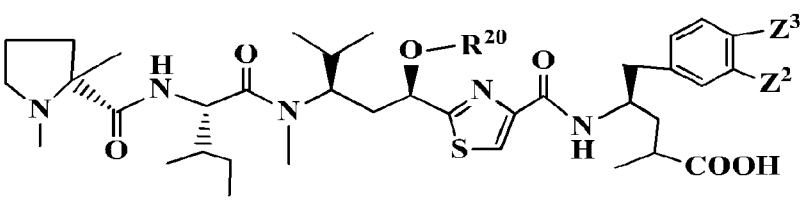
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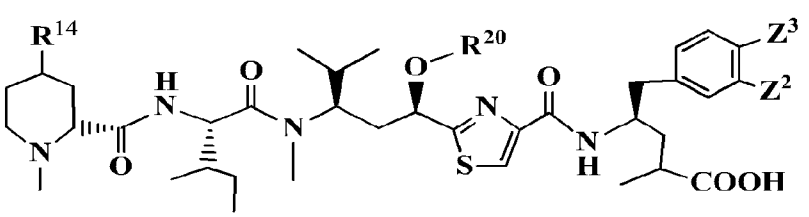
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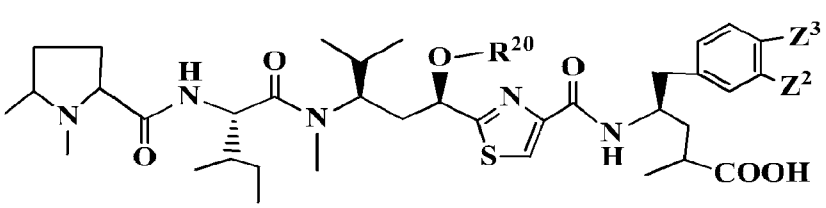
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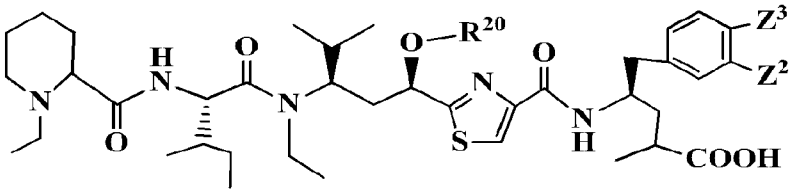
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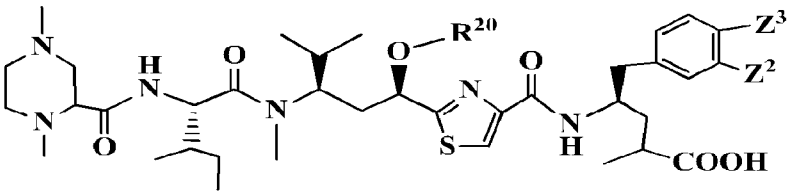
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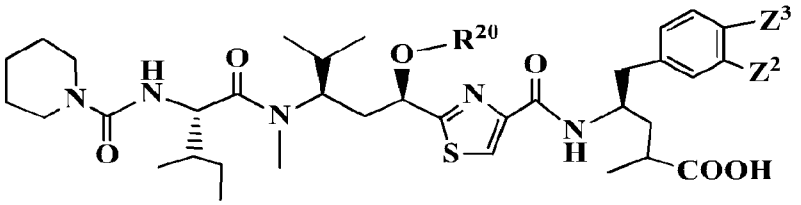
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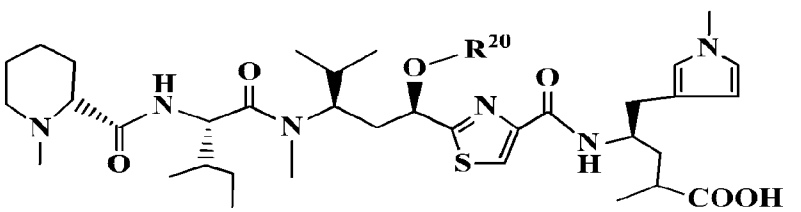
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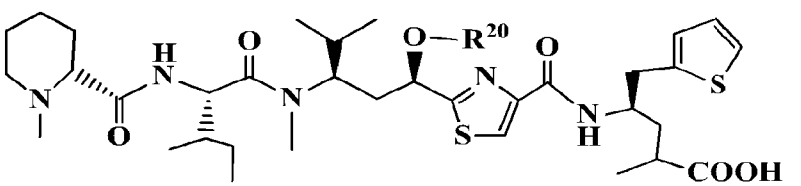
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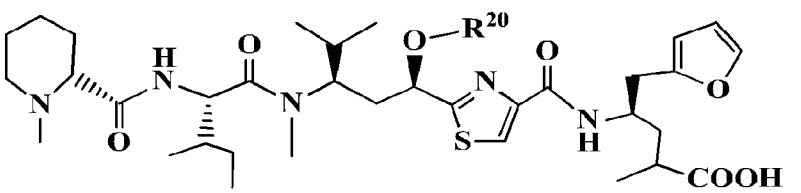
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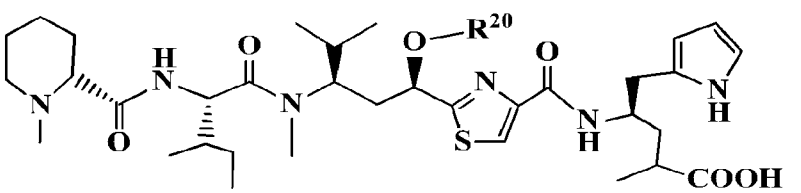
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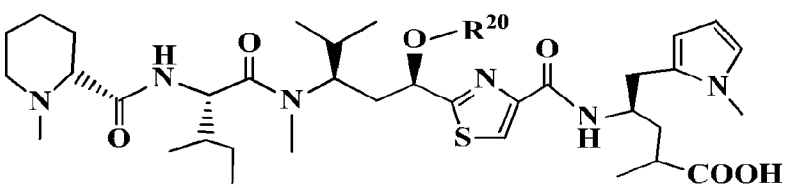
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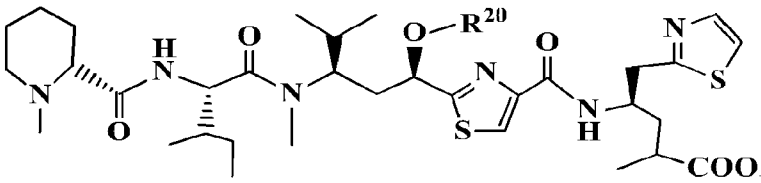
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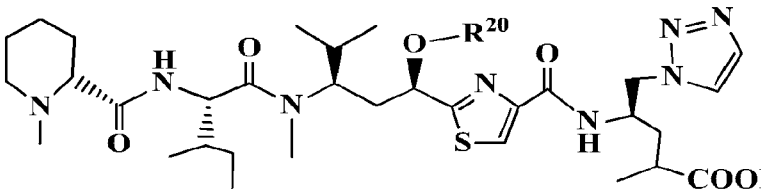
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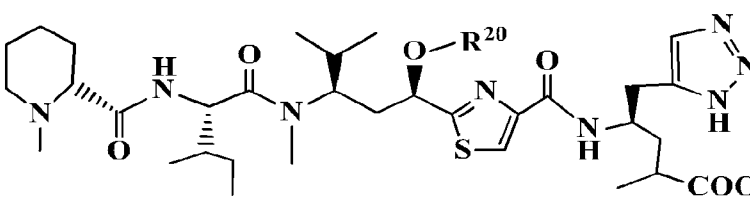
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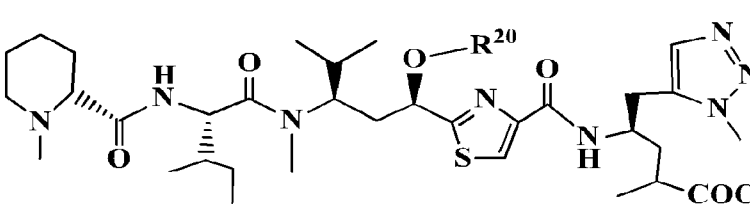
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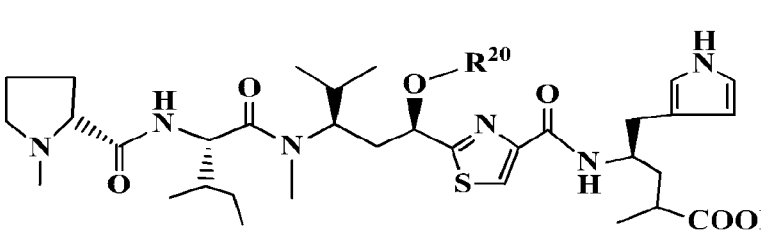
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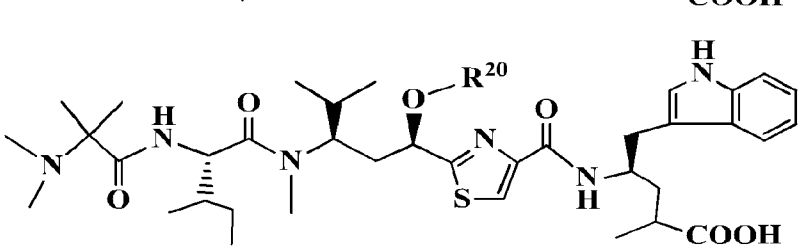
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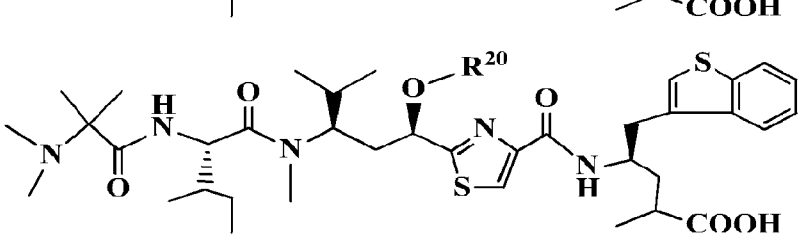
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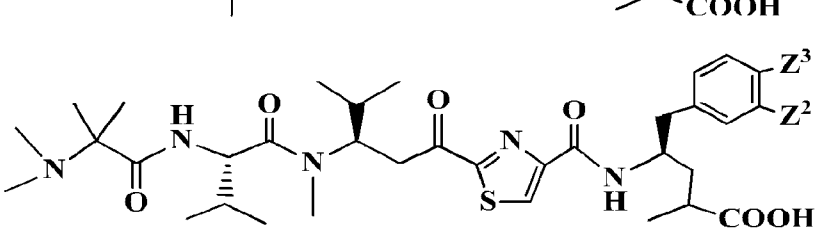
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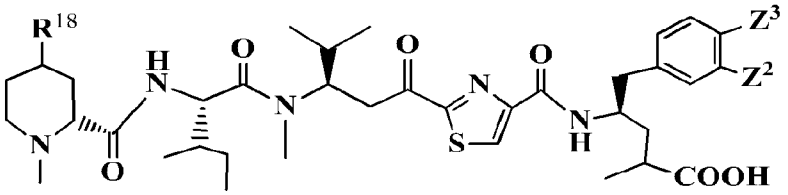
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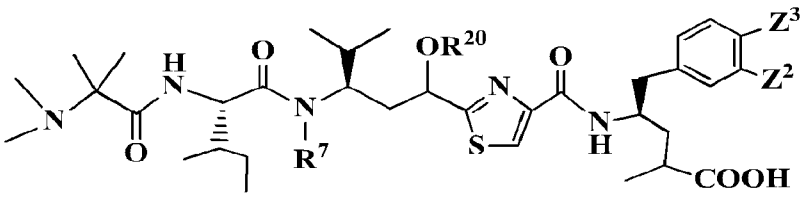
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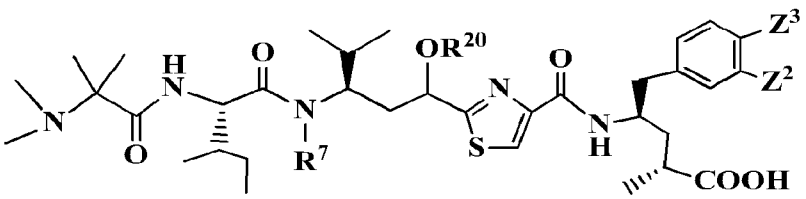
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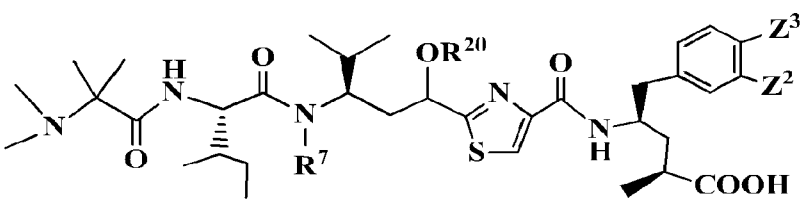
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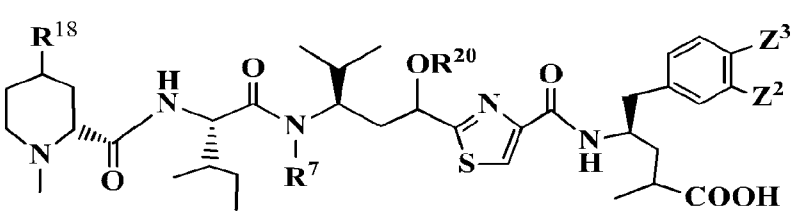
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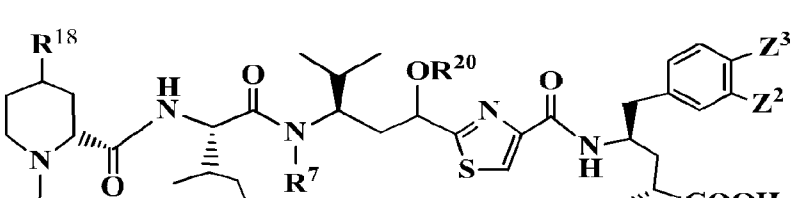
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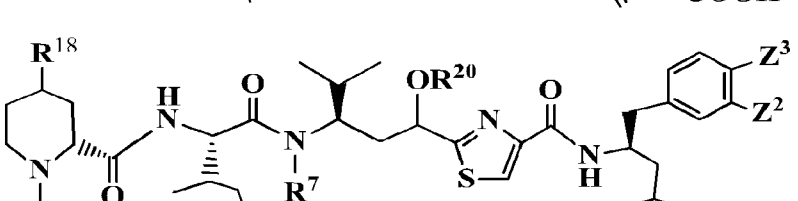
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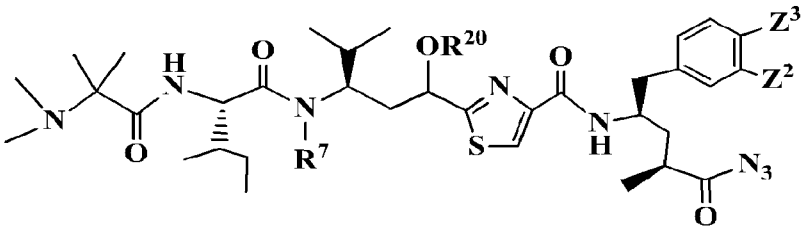

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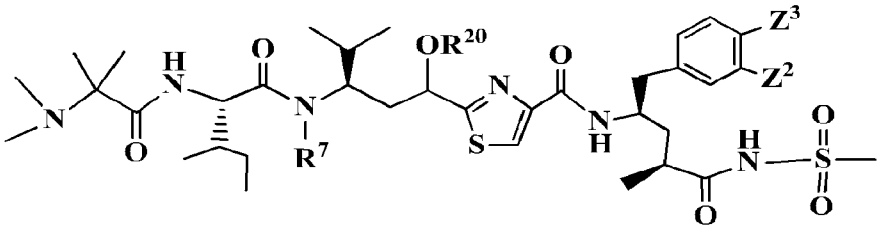

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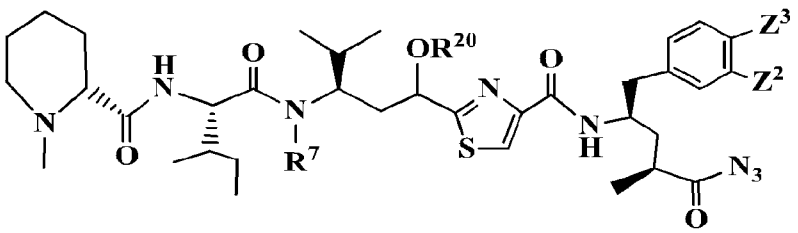

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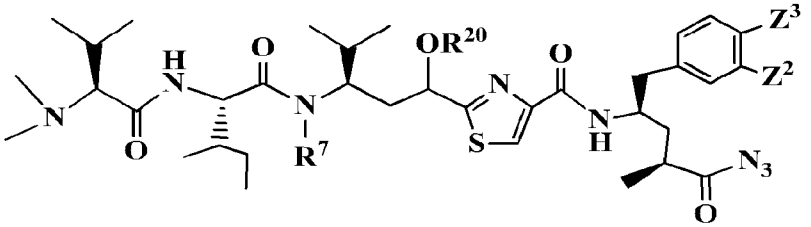

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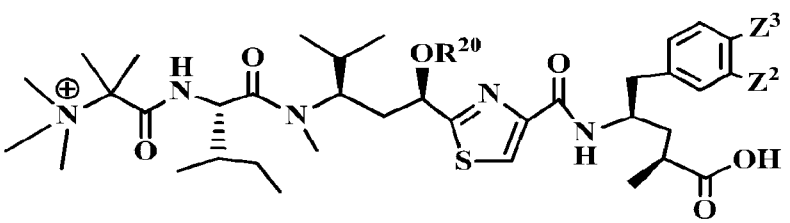

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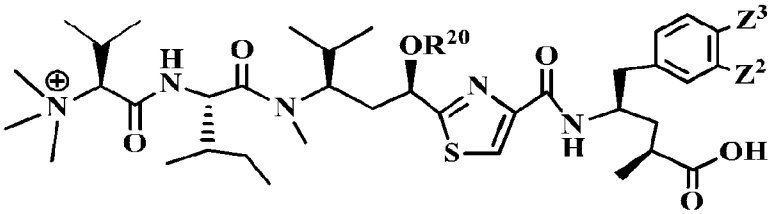

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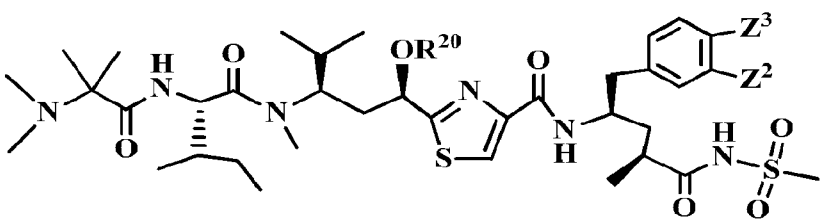

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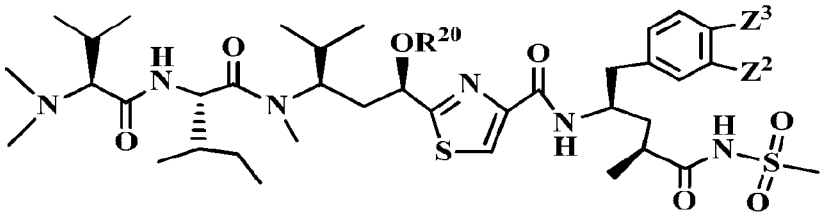
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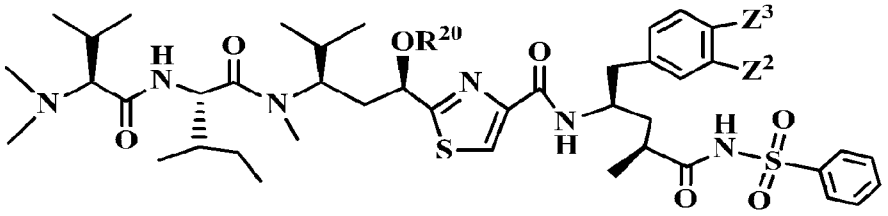
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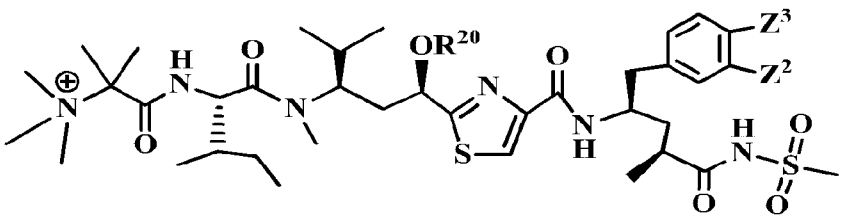
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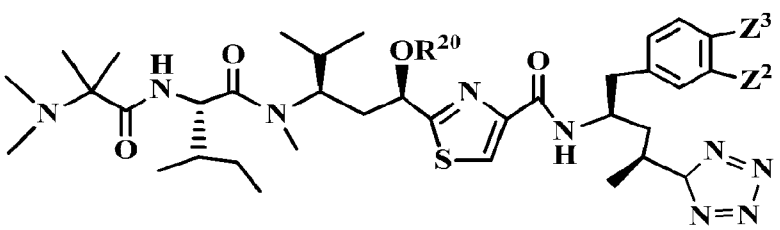
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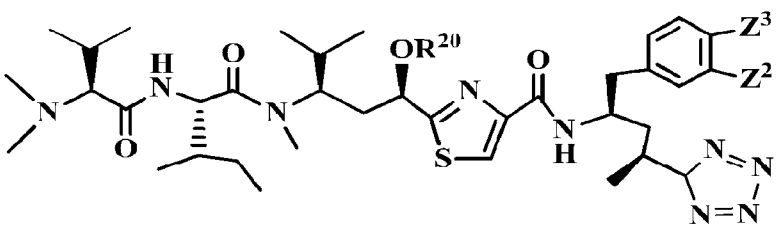
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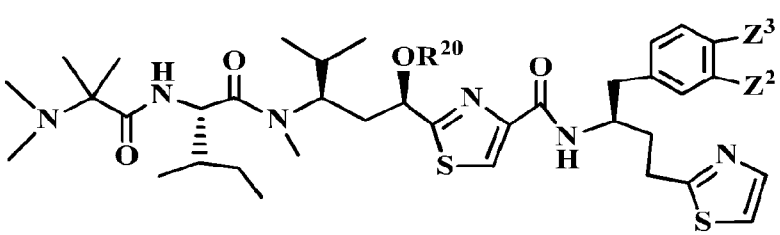
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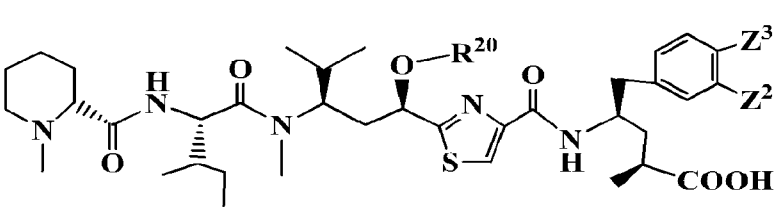
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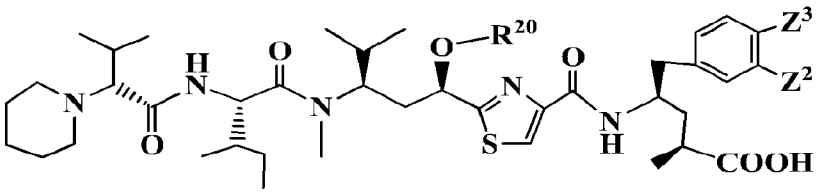
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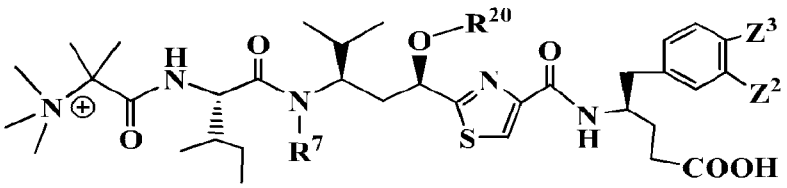
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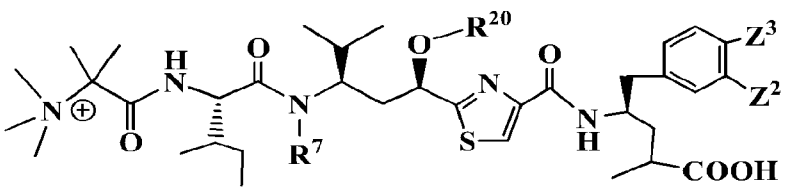
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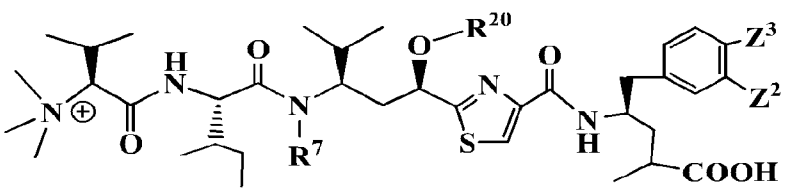
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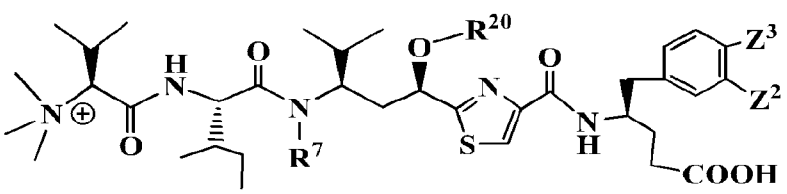
V-94,

wherein R^{20} is H; C_1-C_8 of linear or branched alkyl or heteroalkyl; C_2-C_8 of linear or branched alkenyl, alkynyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 linear or branched of aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; carbonate (-$C(O)OR^{17}$), carbamate (-$C(O)NR^{17}R^{18}$); or 1-8 carbon atoms of carboxylate, esters, ether, or amide; or 1~8 amino acids; or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$ or $(OCH_2CH(CH_3))_p$, wherein p is an integer from 0 to about 1000; or R^{20} is absent and the oxygene forms a ketone, or combination above thereof; $Z^3$and Z^3 are independently H, OH, NH_2, O, NH, COOH, COO, C(O), C(O), C(O)NH, $C(O)NH_2$, R^{18}, $OCH_2OP(O)(OR^{18})_2$, $OC(O)OP(O)(OR^{18})_2$, $OPO(OR^{18})_2$, $NHPO(OR^{18})_2$, $OP(O)(OR^{18})OP(O)(OR^{18})_2$, $OC(O)R^{18}$, $OC(O)NHR^{18}$, $OSO_2(OR^{18})$, O-(C_4-C_{12}-glycoside), of linear or branched alkyl or heteroalkyl; C_2-C_8 of linear or branched alkenyl, alkynyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 linear or branched of aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; carbonate (-$C(O)OR^{17}$), carbamate (-$C(O)NR^{17}R^{18}$); $R^{17}$and R^{18} are independently H, linear or branched alkyl or heteroalkyl; C_2-C_8 of linear or branched alkenyl, alkynyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 linear or branched of

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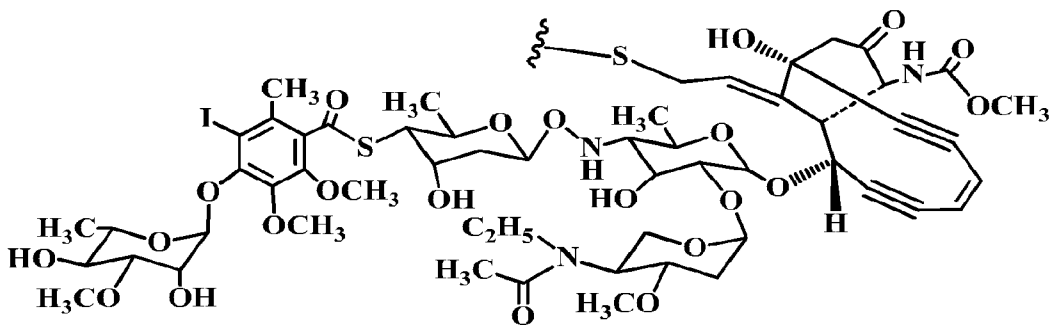
aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; carbonate (-C(O)OR^{17}), carbamate (-C(O)NR^{17}R^{18}); R^{19}is H, OH, NH_2, $OSO_2(OR^{18})$, $XCH_2OP(O)(OR^{18})_2$, $XPO(OR^{18})_2$, $XC(O)OP(O)(OR^{18})_2$, $XC(O)R^{18}$, $XC(O)NHR^{18}$, C_1~C_8 alkyl or carboylate; C_2~C_8 alkenyl, alkynyl, alkylcycloalkyl, heterocycloalkyl; C_3~C_8 aryl or alkylcarbonyl; or pharmaceutical salts; X isO, S, NH, NHNH, or CH_2; R^7 is H, R^{14}, -R^{14}C(=O)X^{1}R^{15}; or -R^{14}X^{1}R^{15}; X^1 is O, S, S-S, NH, CH_2 or NR^{14}, wherein R^{14} and R^{15} are independently C_1~C_8 alkyl, heteroalkyl; C_2-C_8 of alkenyl, alkynyl, heteroalkyl, heterocycloalkyl; C_3-C_8 of aryl, Ar-alkyl; wherein the linkage sites, " ∿∿ " in formula IV-01- IV-94 are the same indication according to Claim 4;

(b) the calicheamicins and their related enediyne antibiotics have the following formula:

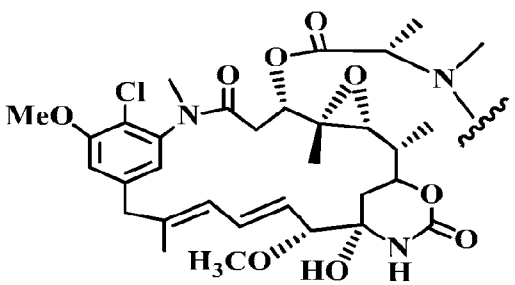


(Ia),

or a derivative with one or more isotopes, or a pharmaceutically acceptable salt, hydrate, or hydrated salt thereof; or a polymorphic crystalline structure thereof; or an optical isomer, racemate, diastereomer or enantiomer thereof,

wherein ∿∿ is a site linked to L_1 or L_2;

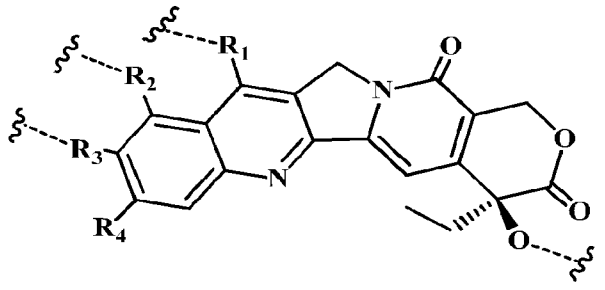
(c) the Maytansines or their derivatives maytansinoids have the following formula:



(Ib),

wherein ∿∿ is a site linked to L_1 or L_2;

(d) the camptothecin (CPTs) and its derivatives have the following formula:

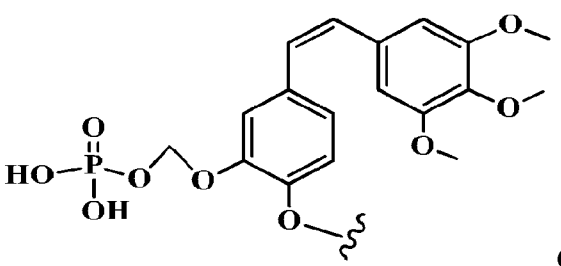


(Ic)

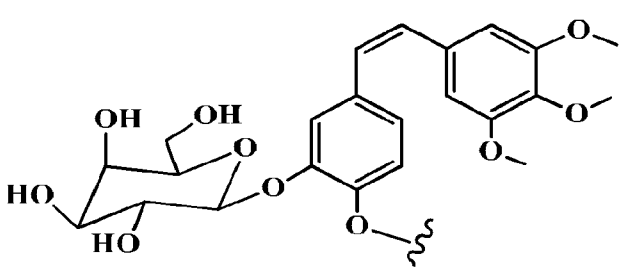
or an isotope of one or more chemical elements, or a pharmaceutically acceptable salt, hydrate, or hydrated salt thereof; or a polymorphic crystalline structure thereof; or an optical isomer, racemate, diastereomer or enantiomer thereof;

wherein R_1, R_2 and R_4 are independently selected from H, F, Cl, Br, CN, NO_2, C_1~C_8 alkyl; O-C_1~C_8 alkyl; NH-C_1~C_8 alkyl; C_2-C_8 of heteroalkyl, alkylcycloalkyl, heterocycloalkyl; C_3-C_8 of aryl, Ar-alkyl, heterocyclic, carbocyclic, cycloalkyl, heteroalkylcycloalkyl, alkylcarbonyl, heteroaryl; or 2-8 carbon atoms of esters, ether, amide, carbonate, urea, or carbamate; R_3 is H, OH, NH_2, C_1~C_8 alkyl; O-C_1~C_8 alkyl; NH-C_1~C_8 alkyl; C_2-C_8 of heteroalkyl, alkylcycloalkyl, heterocycloalkyl; or 2-8 carbon atoms of esters, ether, amide, carbonate, urea, or carbamate; or R_1R_2, R_2R_3 and R_3R_4 independently form a 5~7 membered carbocyclic, heterocyclic, heterocycloalkyl, aromatic or heteroaromatic ring system; ~~~ is the site in the molecule that can be linked to L_1, L_1', L_2 or L_2'.

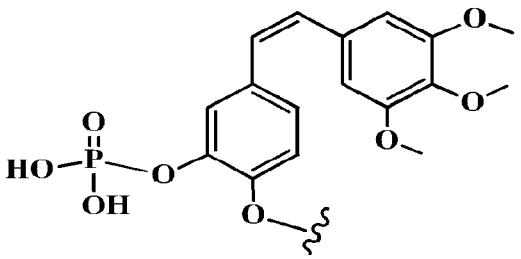
(e) the Combretastatins have the following formula:



CA-01,



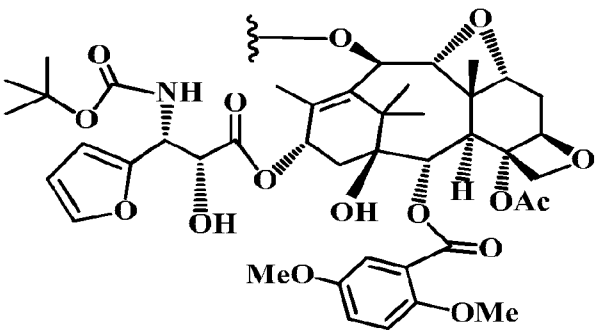
CA-02 (CA4-βGal),



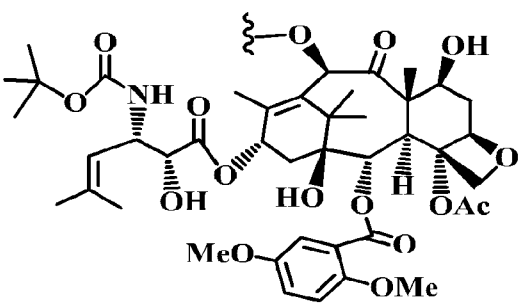
CA-03,

~~~ is a site in the molecule that can be linked to L_1, L_1', L_2 or L_2';

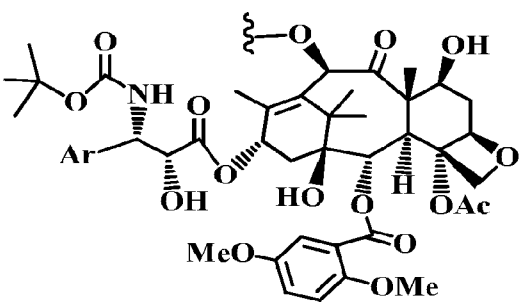
(f) the Taxanes have the following formula:



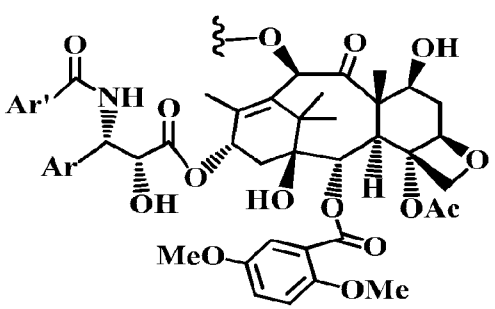
(Id-01),



(Id-02),



(Id-03),



(Id-04),

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~~~
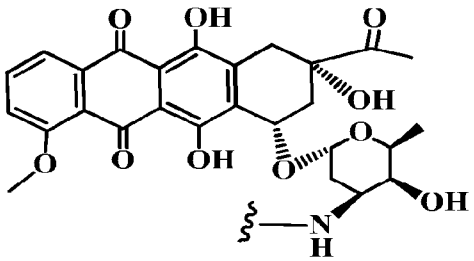
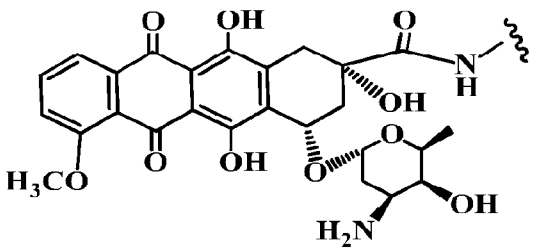

Wherein ~~~ is a site in the molecule that can be linked to L_1, L_1', L_2 or L_2'; Ar and Ar' are independently aryl or heteroaryl;

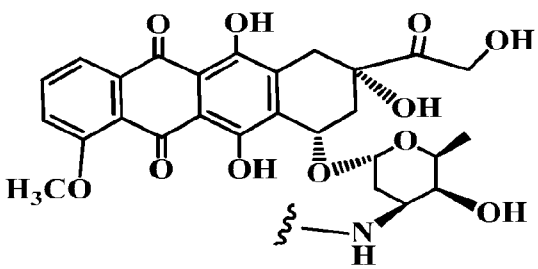
(g) the anthracyclines have the following formula:



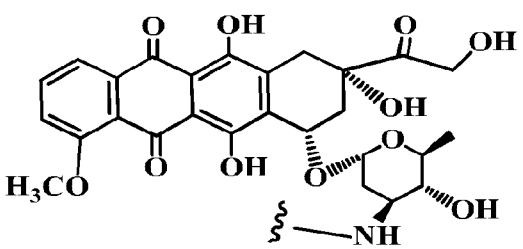
(Ie-01), Daunorubicin analog,



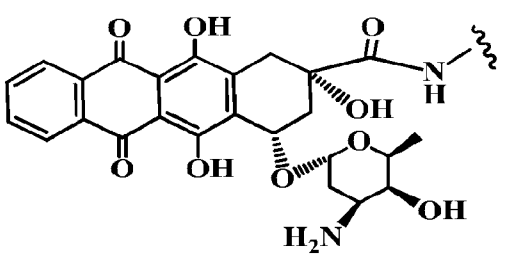
(Ie-02), Daunorubicin analog,



(Ie-03), Doxorubicin analog,



(Ie-04), Epirubicin analog,



(Ie-05), Idarubicin analog,

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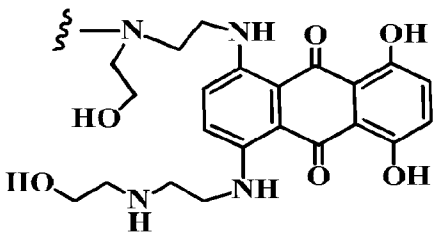
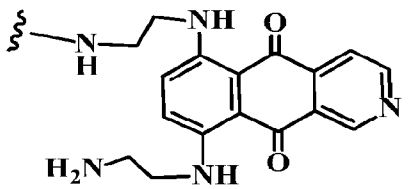
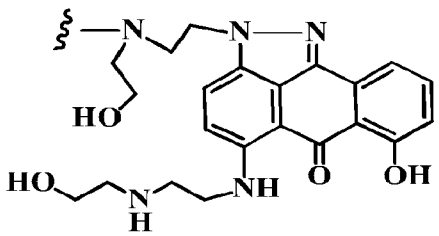


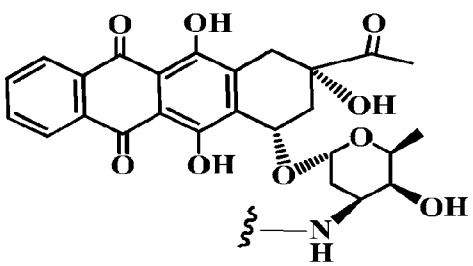
(Ie-06), Mitoxantrone analog,



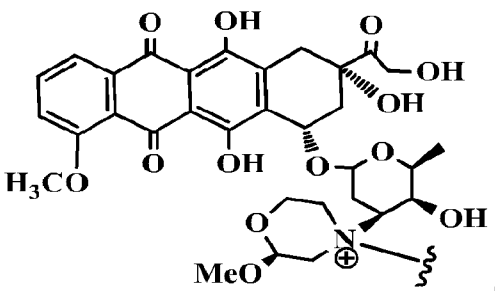
(Ie-07), Pixantrone analog,



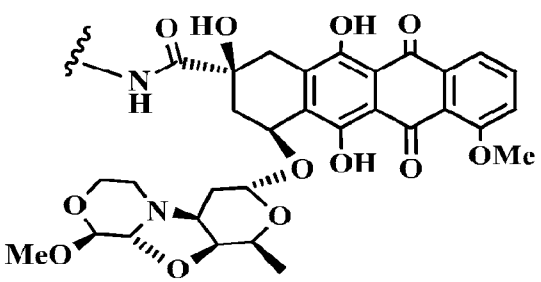
(Ie-08), Losoxantrone analog,



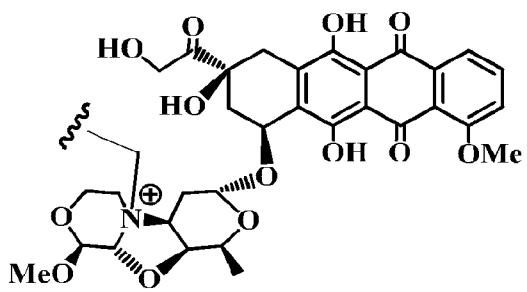
(Ie-09),



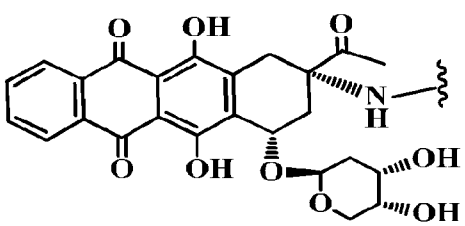
(Ie-10),



(Ie-11),



(Ie-12),

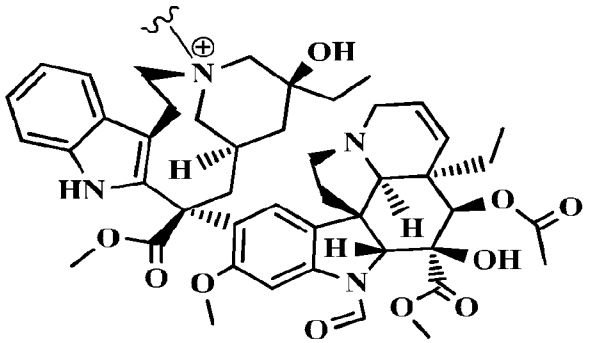


(Ie-13), Amrubicin analog,

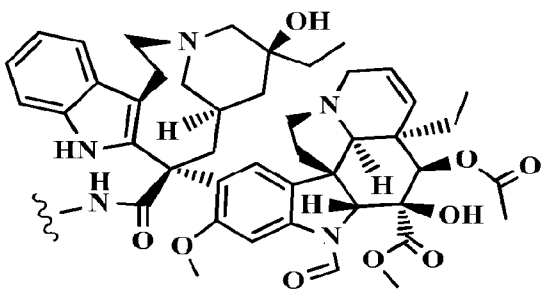
Wherein ~~~ is a site in the molecule that can be linked to L_1, L_1', L_2 and/or L_2';

(h) the Vinca alkaloids are selected from vinblastine, vincristine, vindesine, leurosine, vinorelbine, catharanthine, vindoline, vincaminol, vineridine, minovincine, methoxyminovincine,

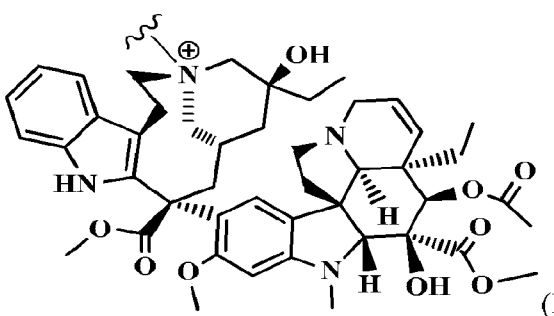
minovincinine, vincadifformine, desoxyvincaminol, vincamajine, vincamine, vinpocetine, and vinburnine and have the following formula:



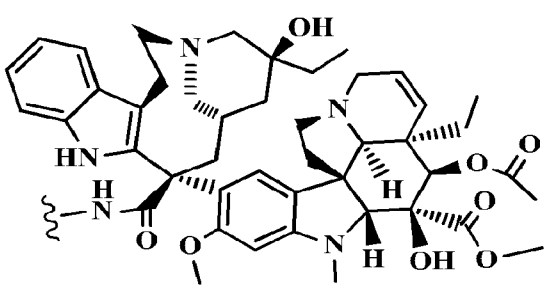
(If-01), vincristine (leurocristine),



(If-02), vincristine (leurocristine),



(If-03), vinblastine,



(If-04), vinblastine;

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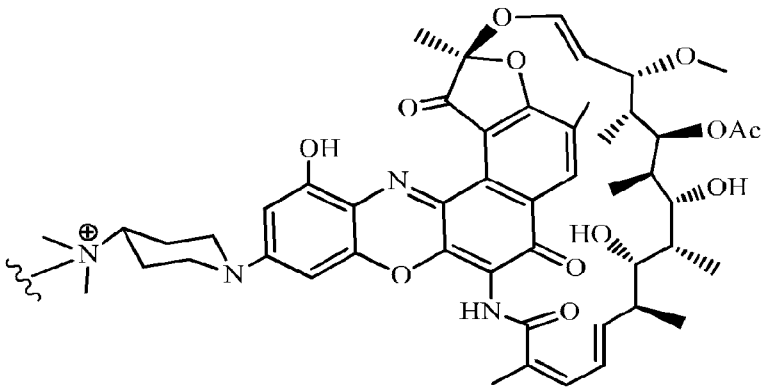
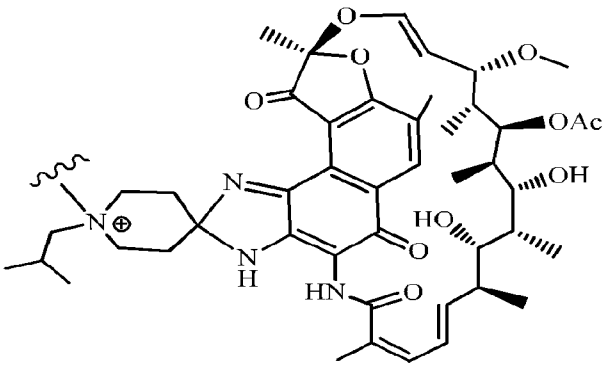


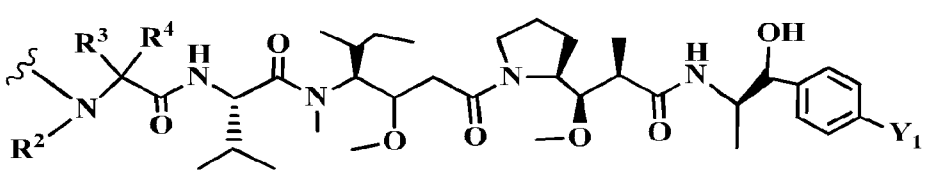
(If-05), Rifabutin analog,



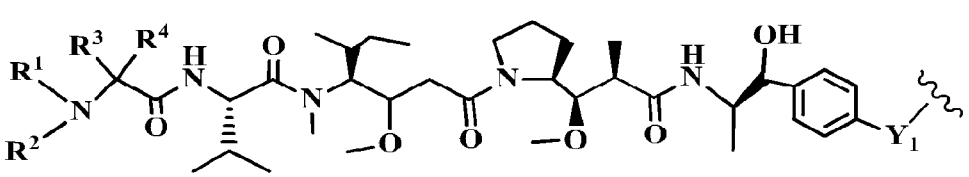
(If-06), rifabutin analog,

wherein ∿∿ is a site linked to L_1, L_1', L_2 and/or L_2';

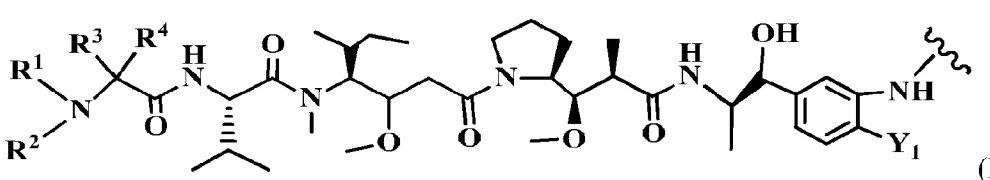
(i) the Dolastatins and their peptidic analogs and derivatives are selected from dolastatin 10, auristatin E (AE), auristatin EB (AEB), auristatin EFP (AEFP), MMAD (Monomethyl Auristatin D or monomethyl dolastatin 10), MMAF (Monomethyl Auristatin F or N-methylvaline-valine-dolaisoleuine-dolaproine-phenylalanine), MMAE (Monomethyl Auristatin E or N-methylvaline-valine-dolaisoleuine-dolaproine-norephedrine), 5-benzoylvaleric acid-AE ester (AEVB), Auristatin F phenylene diamine (AFP) and have the following formula:



(Ih-01),



(Ih-02),



(Ih-03),

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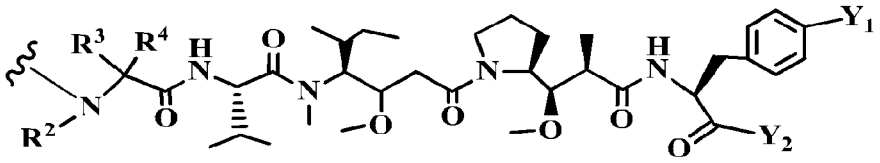

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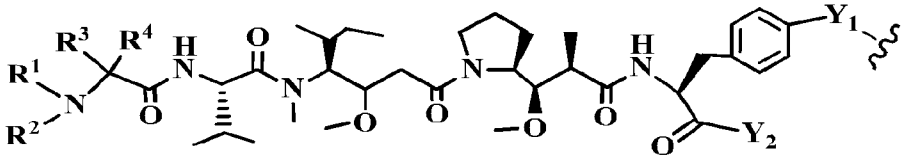
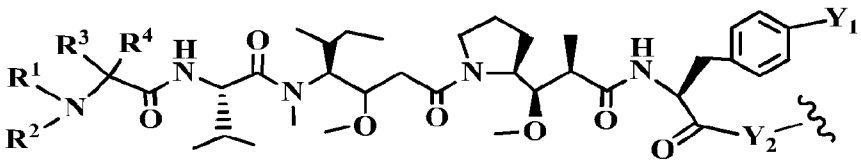
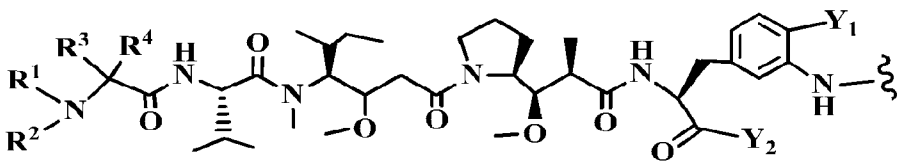


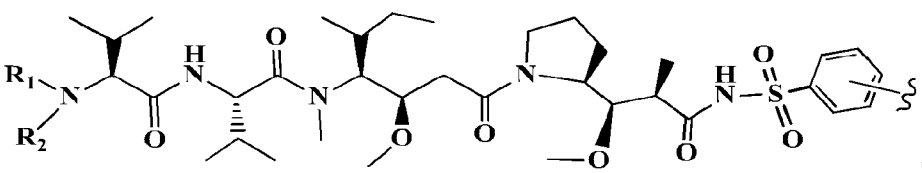
(Ih-05),



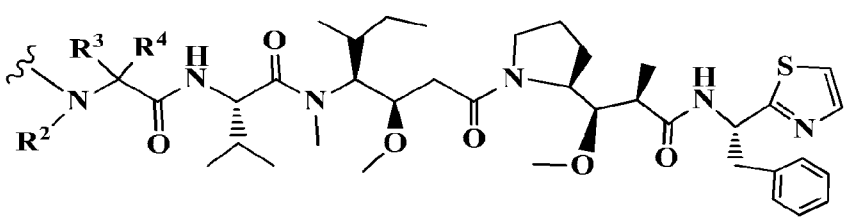
(Ih-06),



(Ih-07),



(Ih-08)



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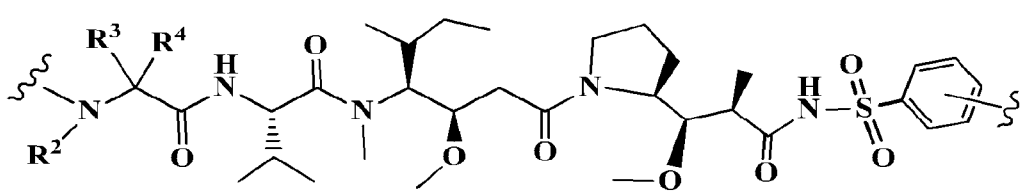

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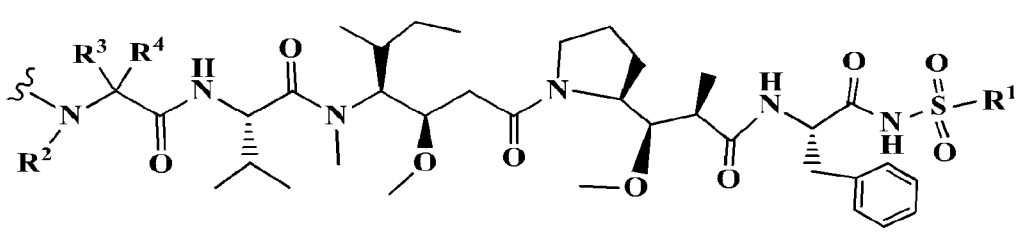

(Ih-11),

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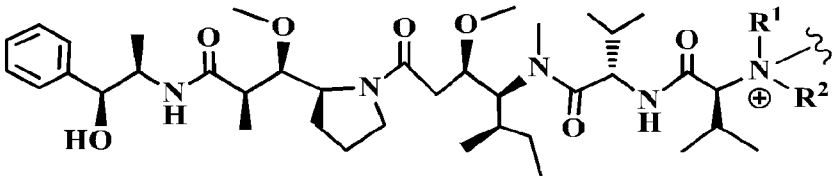
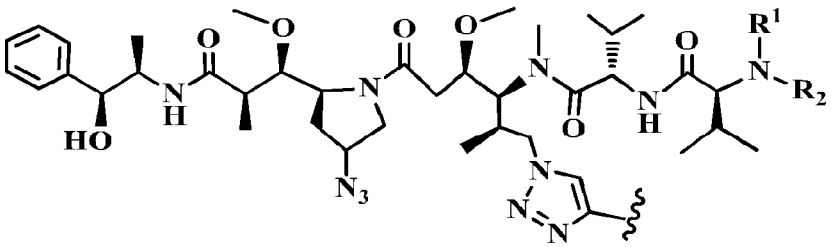
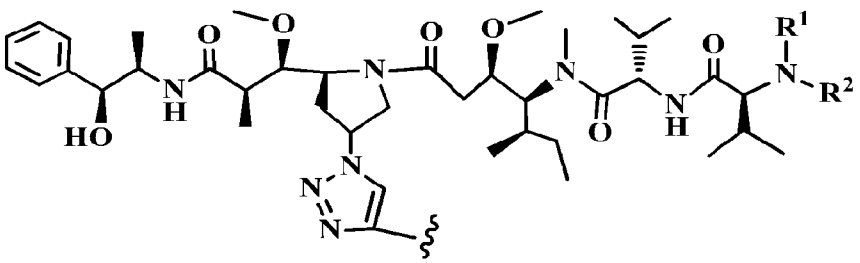


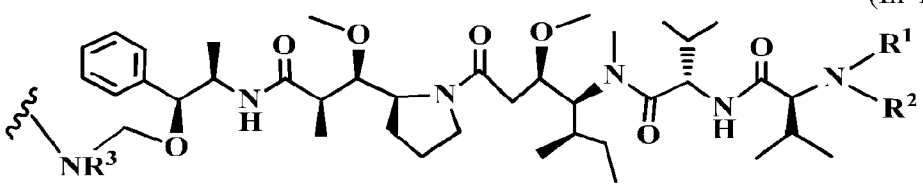
(Ih-12),



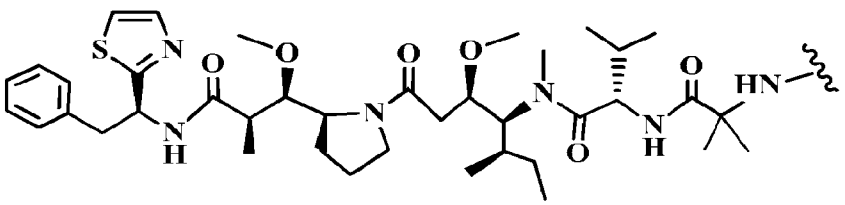
(Ih-13),



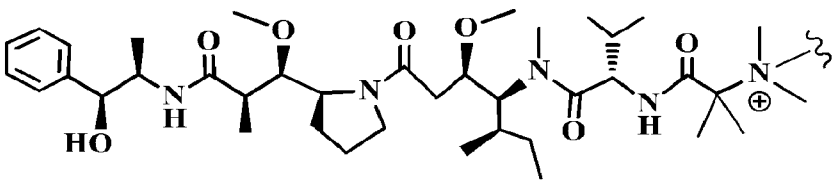
(Ih-14),



(Ih-15),



(Ih-16),



(Ih-17),

or a derivative with one or more isotopes; or a pharmaceutically acceptable salt, hydrate, or hydrated salt thereof; or a polymorphic crystalline structure thereof; or an optical isomer, racemate, diastereomer or enantiomer thereof;

wherein R^1, R^2, R^3, R^4 and R^5 are independently H; C_1-C_8 linear or branched alkyl, aryl, heteroaryl, heteroalkyl, alkylcycloalkyl, ester, ether, amide, amines, heterocycloalkyl, or acyloxylamines; or peptides containing 1-8 aminoacids, or polyethyleneoxy unit having formula $(OCH_2CH_2)_p$ or $(OCH_2CH(CH_3))_p$, wherein p is an integer from 1 to about 1000. The two Rs: R^1R^2, R^2R^3, R^1R^3 or R^3R^4 together can form 3~8 member cyclic ring of alkyl, aryl, heteroaryl, heteroalkyl, or alkylcycloalkyl group; Y_1 and Y_2 are independently O, NH, NHNH, NR_5, S, C(O)O,

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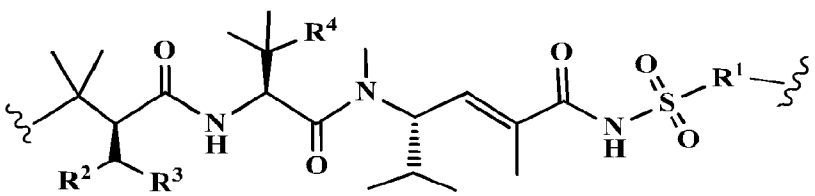
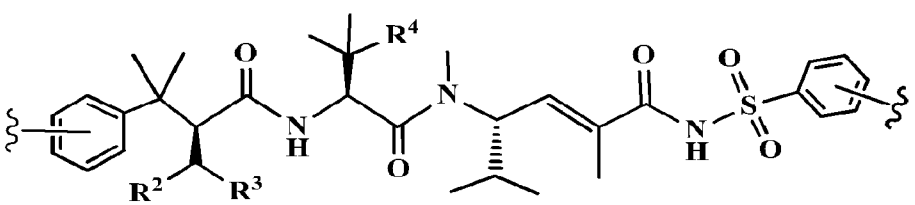
C(O)NH, OC(O)NH, OC(O)O, NHC(O)NH, NHC(O)S, $OC(O)N(R_1)$, $N(R_1)C(O)N(R_2)$, C(O)NHNHC(O) and $C(O)NR_1$ when linked to the connecting site " ∿∿ " (that links to L_1, L_1', L_2 and/or L_2' independently); or OH, NH_2, $NHNH_2$, NHR_5, SH, C(O)OH, $C(O)NH_2$, $OC(O)NH_2$, OC(O)OH, $NHC(O)NH_2$, NHC(O)SH, $OC(O)NH(R_1)$, $N(R_1)C(O)NH(R_2)$, C(O)NHNHC(O)OH and $C(O)NHR_1$ when not linked to the connecting site " ∿∿ "; R_{12} is OH, NH_2, NHR_1, $NHNH_2$, NHNHCOOH, O-R_1-COOH, NH-R_1-COOH, NH-$(Aa)_n$COOH, $O(CH_2CH_2O)_pCH_2CH_2OH$, $O(CH_2CH_2O)_pCH_2CH_2NH_2$, $NH(CH_2CH_2O)_pCH_2CH_2NH_2$, NR_1R_1', NHOH, $NHOR_1$, $O(CH_2CH_2O)_pCH_2CH_2COOH$, $NH(CH_2CH_2O)_pCH_2CH_2COOH$, NH-Ar-COOH, NH-Ar-$NH_2$, $O(CH_2CH_2O)_pCH_2CH_2NH$-SO_3H, $NH(CH_2CH_2O)_pCH_2CH_2NHSO_3H$, R_1-$NHSO_3H$, NH-R_1-$NHSO_3H$, $O(CH_2CH_2O)_pCH_2$-$CH_2NHPO_3H_2$, $NH(CH_2CH_2O)_pCH_2CH_2NHPO_3H_2$, OR_1, R_1-$NHPO_3H_2$, R_1-OPO_3H_2, $O(CH_2CH_2O)_pCH_2CH_2OPO_3H_2$, OR_1-$NHPO_3H_2$, NH-R_1-$NHPO_3H_2$, $NH(CH_2CH_2NH)_pCH_2$-CH_2NH_2, $NH(CH_2CH_2S)_pCH_2CH_2NH_2$, $NH(CH_2CH_2NH)_pCH_2CH_2OH$, $NH(CH_2CH_2S)_pCH_2$-CH_2OH, NH-R_1-NH_2, or $NH(CH_2CH_2O)_pCH_2CH_2NHPO_3H_2$, wherein Aa is 1-8 the same or different aminoacids; p is 1 -1000; R_1, R_2, R_3, R_4, R_5, R_5', Z_1, Z_2, and n are defined the same above.;

(j) the Hemiasterlin and its analogues have the following formula:



(Hs-01)



(Hs-02)

wherein R^1, R^2, R^3, R^4 and R^5 are independently H; C_1-C_8 linear or branched alkyl, aryl, heteroaryl, heteroalkyl, alkylcycloalkyl, ester, ether, amide, amine, heterocycloalkyl, or acyloxylamine; or peptide containing 1-8 aminoacids, or polyethyleneoxy unit having formula $(OCH_2CH_2)_p$ or $(OCH_2CH(CH_3))_p$, wherein p is an integer from 1 to about 5000; the R^2 and R^3 can form 3-8 member cyclic ring of alkyl, aryl, heteroaryl, heteroalkyl, or alkylcycloalkyl group;

(k) the Eribulin has the following formula:

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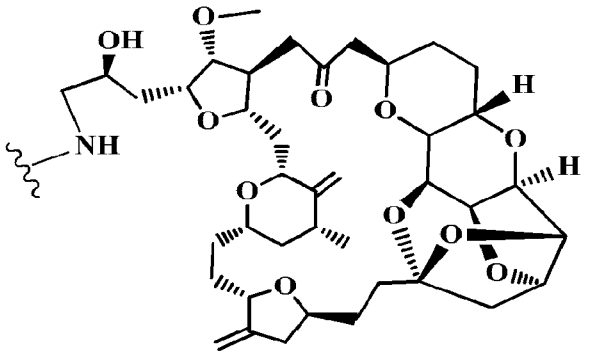
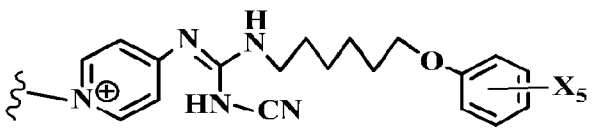


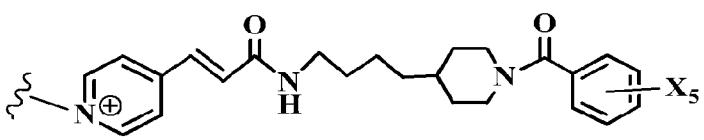
Eb01,

wherein ~~~ is a linkage site that links to L_1, L_1', L_2 and/or L_2' independently;

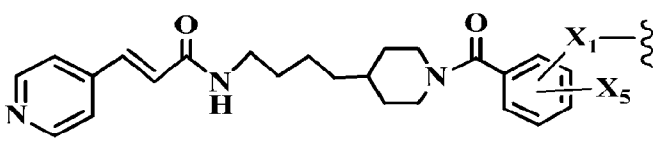
(l) the Inhibitor of nicotinamide phosphoribosyltransferases (NAMPT) have the following formula, NP01, NP02, NP03, NP04, NP05, NP06, NP07, NP08, and NP09:



NP01,



NP02,



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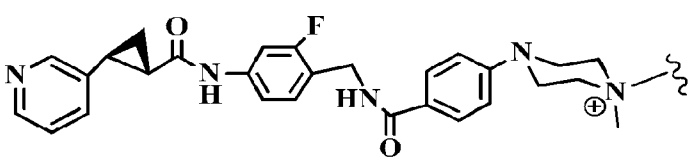

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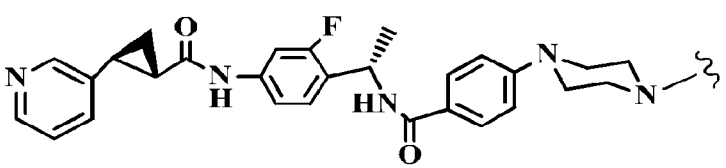

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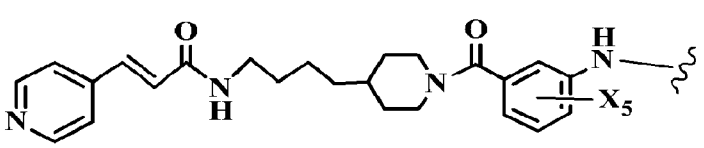

NP06,

NP07,

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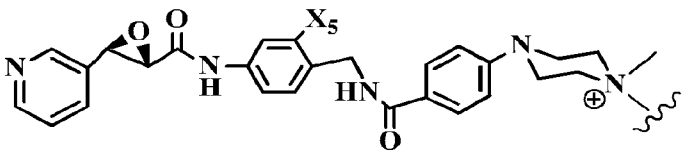
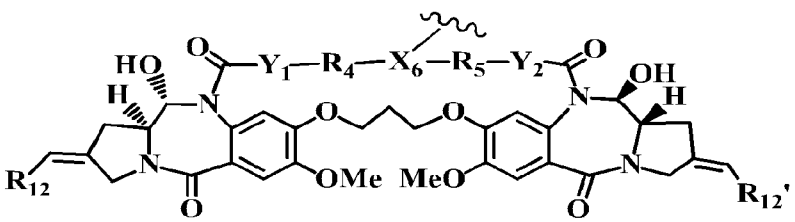
NP08,



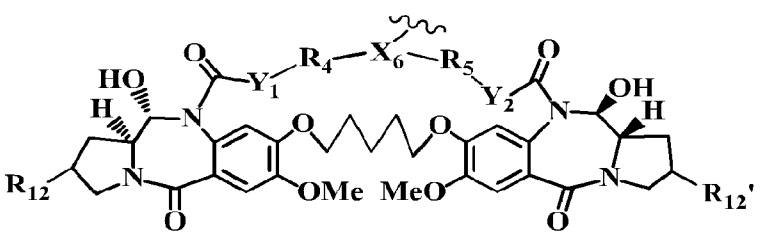
NP09,

or a derivative with one or more isotopes, or a pharmaceutically acceptable sals, hydrate, or hydrated salt thereof; or a polymorphic crystalline structure thereof; or an optical isomer, racemate, diastereomer or enantiomer thereof; wherein " ∿∿ " is the same above; X_5 is F, Cl, Br, I, OH, OR_1, R_1, OPO_3H_2, OSO_3H, NHR_1, $OCOR_1$, or $NHCOR_1$;

(m) the benzodiazepine dimer and its analogs have the following formulae, PB01, PB02, PB03, PB04, PB05, PB06, PB07, PB08, PB09, PB10, PB11, PB12, PB13, PB14, PB15, PB16, PB17, PB18, PB19, PB20, PB21, PB22, PB23, PB24, PB25, PB26, PB27 and PB28:



PB01,



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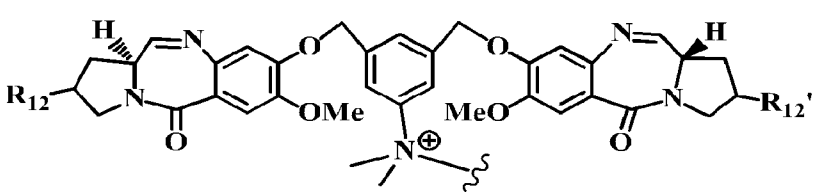

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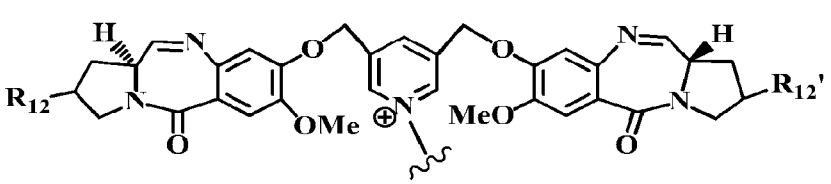

PB04,

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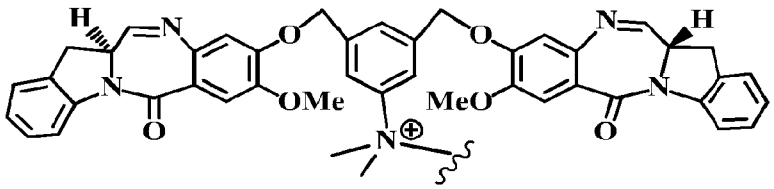

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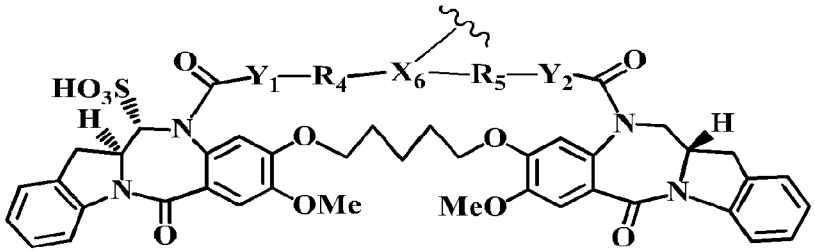

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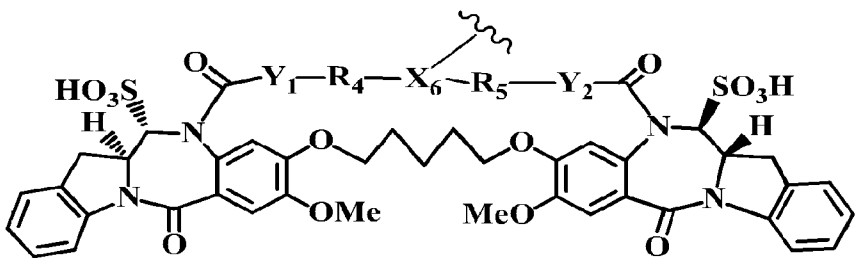

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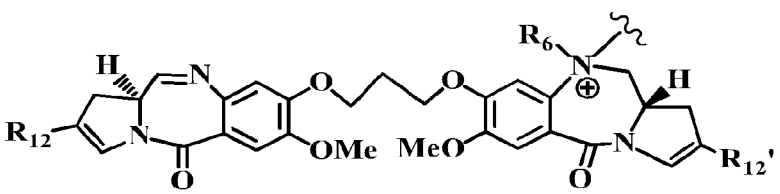

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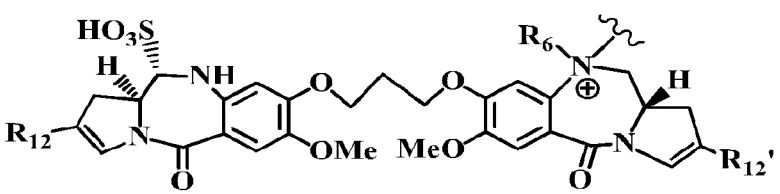

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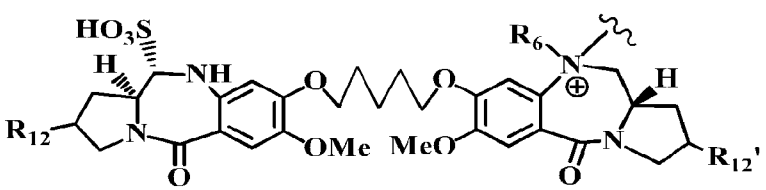

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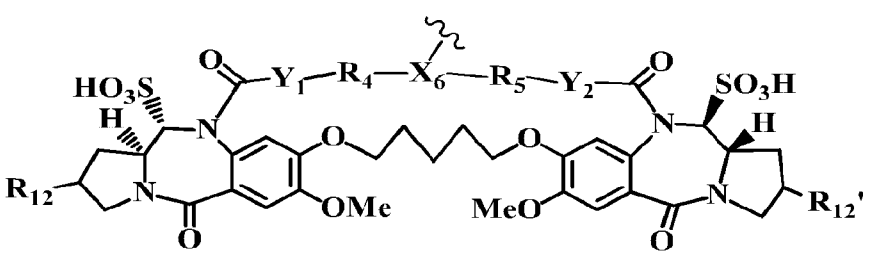

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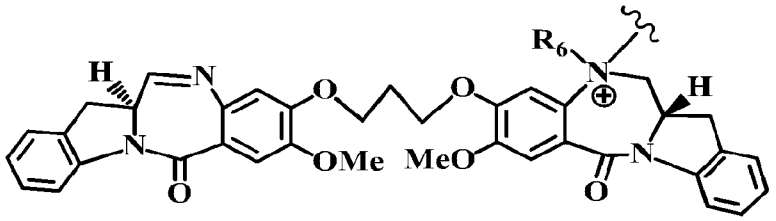
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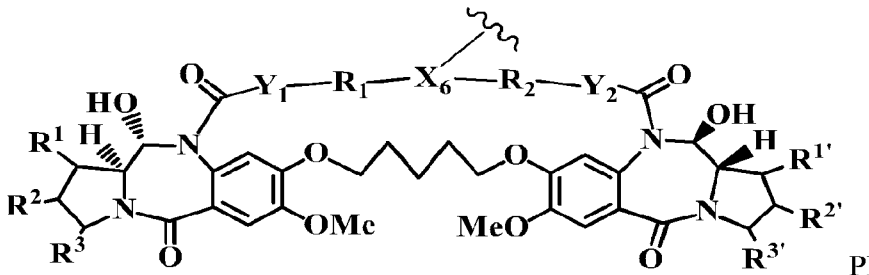
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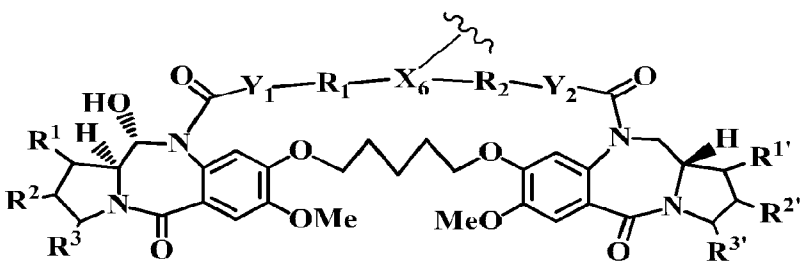
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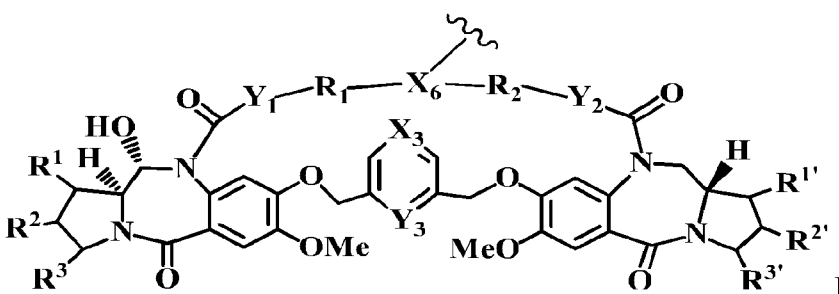
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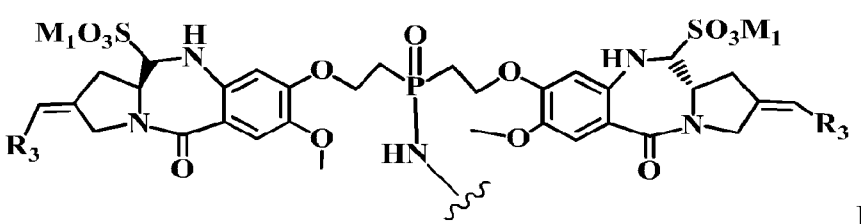
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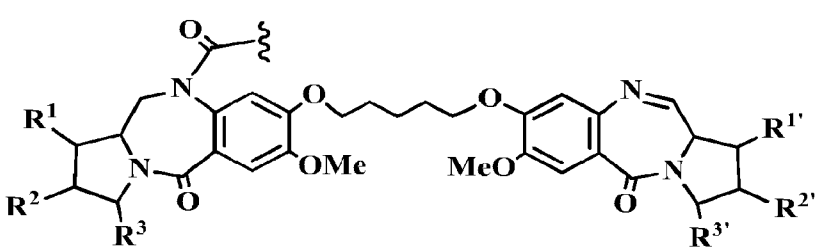
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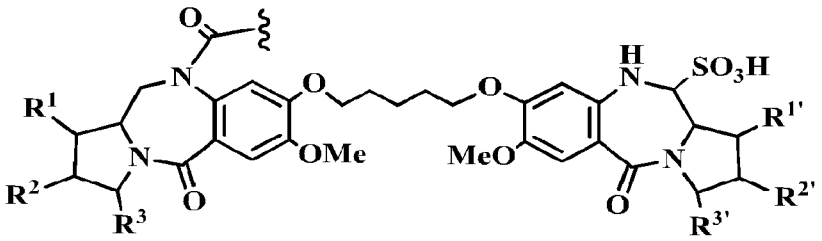
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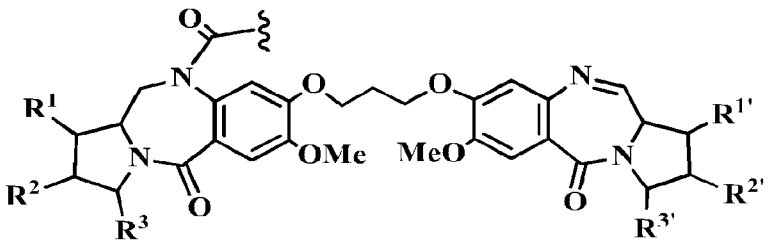
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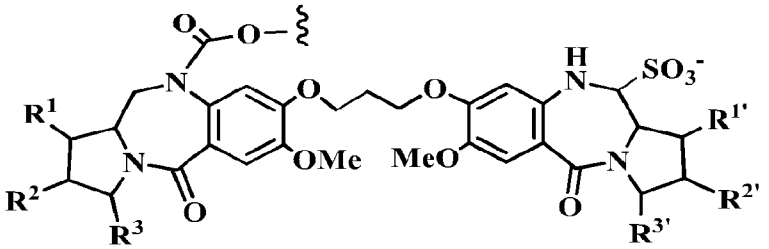
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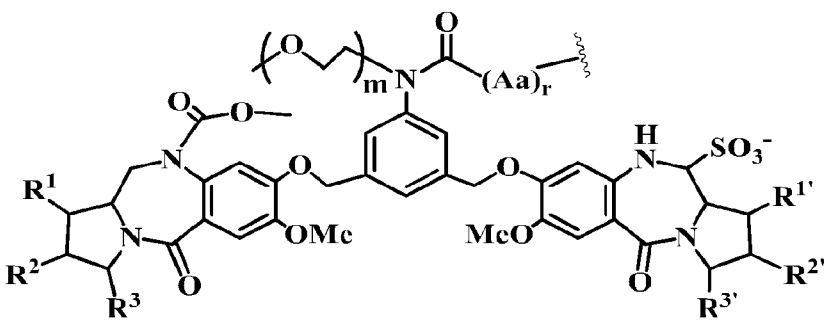
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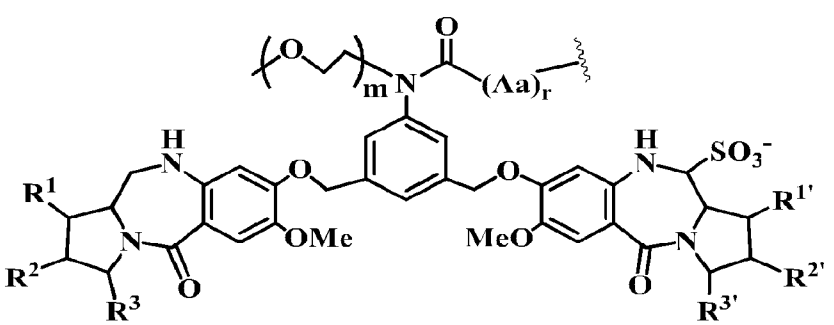
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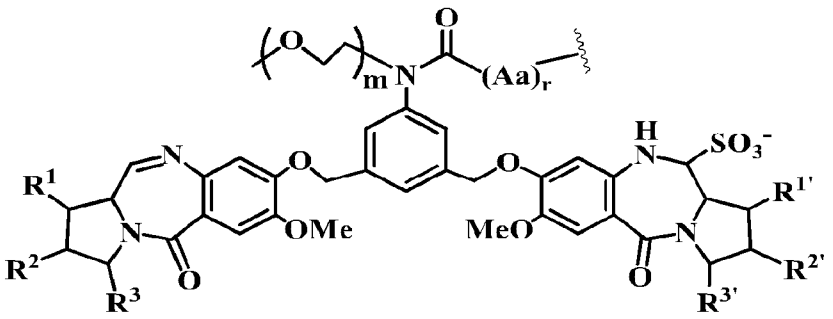
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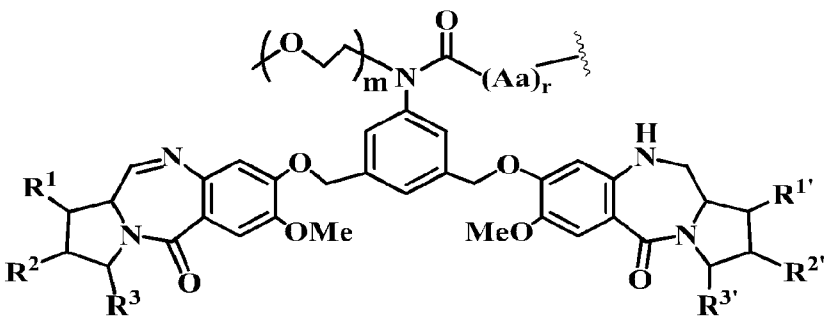
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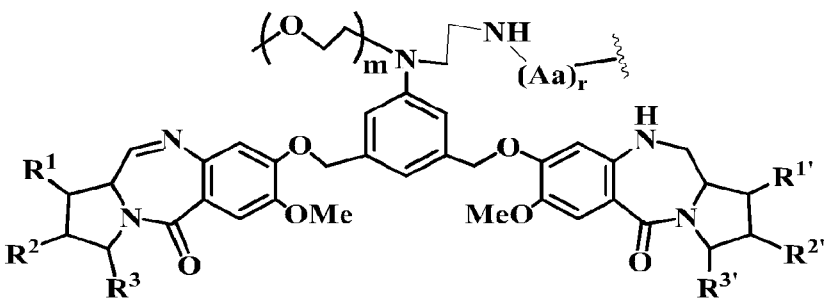
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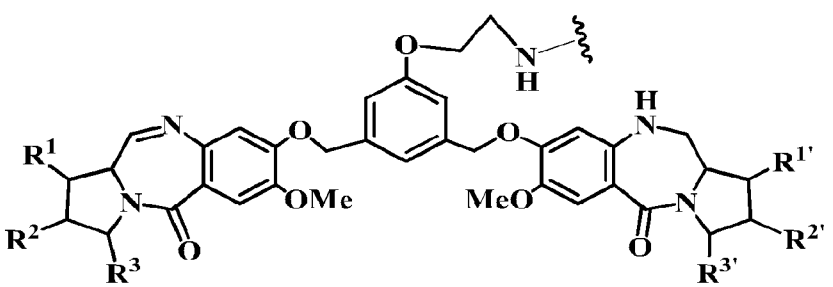
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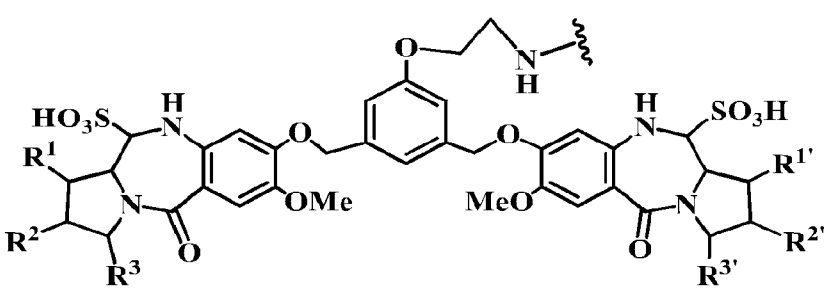
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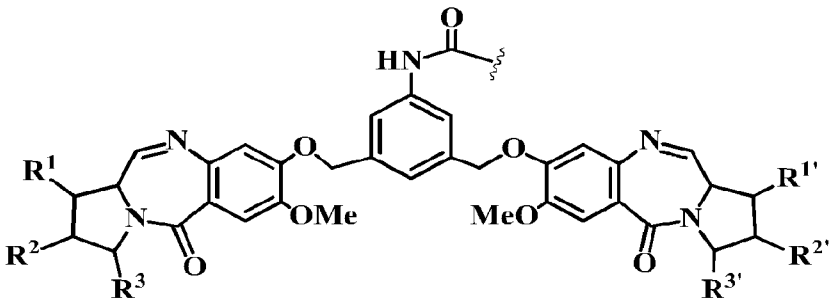

PB28,

or an isotope of one or more chemical elements, or pharmaceutically acceptable salts, hydrates, or hydrated salts; or the polymorphic crystalline structures of these compounds; or the optical isomers, racemates, diastereomers or enantiomers; wherein X_1, X_2, Y_1, Y_2, Z_1, Z_2, and n are defined the same above; Preferabably X_1, X_2, Y_1 and Y_2 are independently O, N, NH, NHNH, NR_5, S, C(O)O, C(O)NH, OC(O)NH, OC(O)O, NHC(O)NH, NHC(O)S, OC(O)N(R_1), N(R_1)C(O)N(R_1), CH, C(O)NHNHC(O) and C(O)NR_1; R^1, R^2, R^3, $R^{1'}$, $R^{2'}$, and $R^{3'}$ are independently H; F; Cl; =O; =S; OH; SH; C_1-C_8 linear or branched alkyl, aryl, alkenyl, heteroaryl, heteroalkyl, alkylcycloalkyl, ester ($COOR_5$ or –$OC(O)R_5$), ether (OR_5), amide ($CONR_5$), carbamate ($OCONR_5$), amines (NHR_5, NR_5R_5'), heterocycloalkyl, or acyloxylamines (-C(O)NHOH, -ONHC(O)R_5); or peptides containing 1-20 natural or unnatural aminoacids, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$ or $(OCH_2CH(CH_3))_p$, wherein p is an integer from 1 to about 5000. The two Rs: R^1R^2, R^2R^3, R^1R^3, $R^{1'}R^{2'}$, $R^{2'}R^{3'}$, or $R^{1'}R^{3'}$ can independently form 3~8 member cyclic ring of alkyl, aryl, heteroaryl, heteroalkyl, or alkylcycloalkyl group; X_3 and Y_3 are independently N, NH, CH_2 or CR_5, or one of X_3 and Y_3 can be absent; wherein R_1, and R_2 are C_1-C_8 linear or branched alkyl, heteroalkyl; C_3-C_8 aryl, heteroaryl, alkylcycloalkyl, acyloxyl, alkylaryl, alkylaryloxyl, alkylarylamino, alkylarylthiol; or 1-6 the same or different sequence of aminao acid/peptides (Ar)r, r =1 -6; wherein R_4, R_5, R_5', R_6, R_{12} and R_{12}' are independently H, OH, NH_2, $NH(CH_3)$, $NHNH_2$, COOH, SH, OZ_3, SZ_3, F, Cl, or C_1-C_8 linear or branched alkyl, aryl, heteroaryl, heteroalkyl, alkylcycloalkyl, acyloxylamines; Z_3 is H, $OP(O)(OM_1)(OM_2)$, $OCH_2OP(O)(OM_1)(OM_2)$, OSO_3M_1, or O-glycoside (glucoside, galactoside, mannoside, glucuronoside/glucuronide, alloside, fructoside, etc.), NH-glycoside, S-glycoside or CH_2-glycoside; M_1 and M_2 are independently H, Na, K, Ca, Mg, NH_4, $NR_1R_2R_3$; X_6 is CH, N, P(O)NH, P(O)NR_1, CHC(O)NH, C_3-C_8 aryl, heteroaryl, alkylcycloalkyl, acyloxyl, alkylaryl, alkylaryloxyl, alkylarylamino, or an Aa (amino acid, is preferably selected from Lys, Phe, Asp, Glu, Ser, Thr, His, Cys, Tyr, Trp, Gln, Asn, Arg); " ┈┈ " is either single bond or double bond; " ∿∿ " is defined the same above;

(n) the CC-1065 analog and doucarmycin analogs have the following formula, CC01, CC02, CC03, CC04, CC05, CC06 and CC07:

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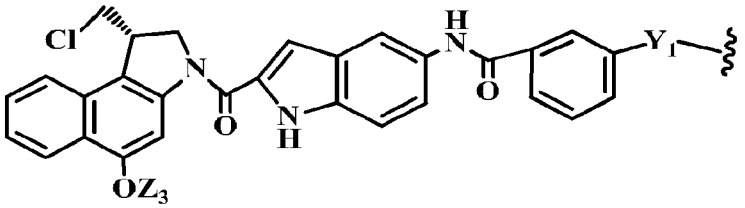
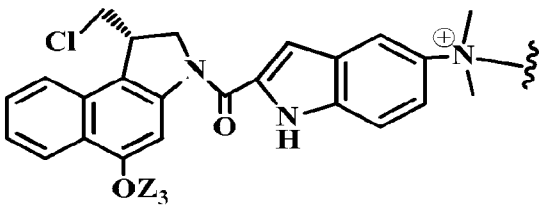
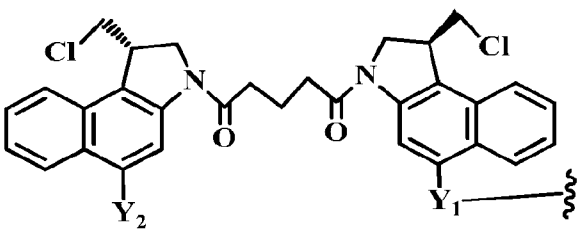


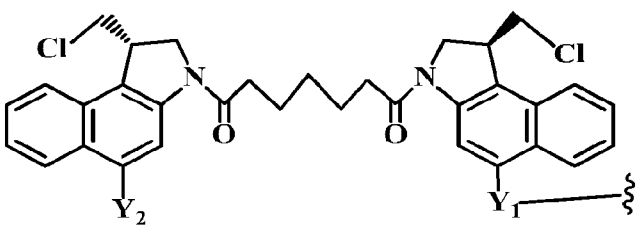
CC01,



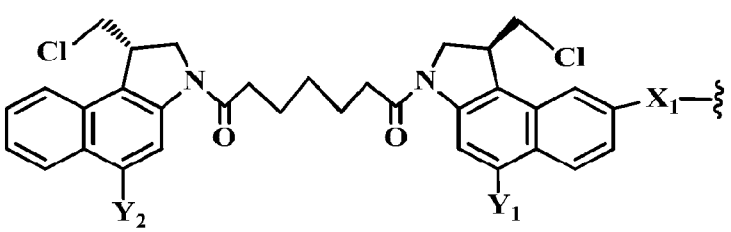
CC02,



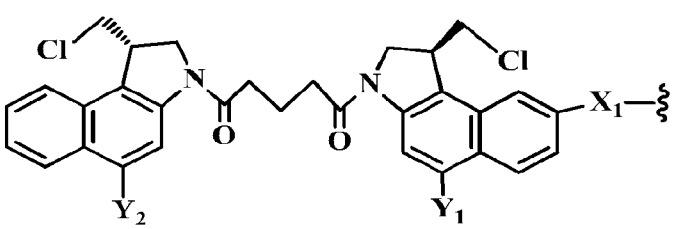
CC03,



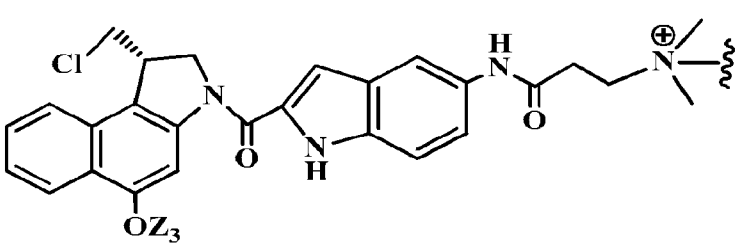
CC04,



CC05,



CC06,



CC07,

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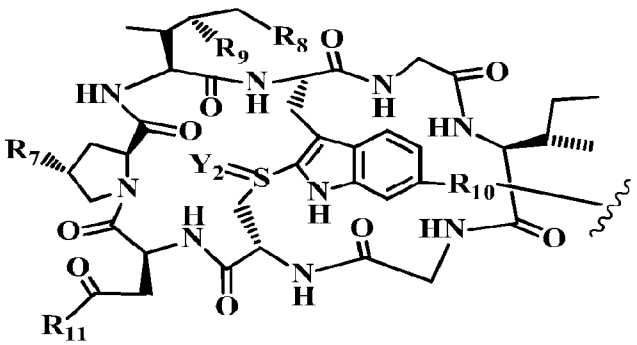
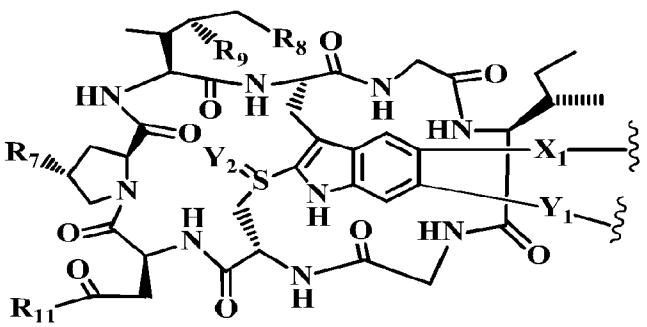
wherein X_1, X_2, Y_1 and Y_2 are independently O, NH, NHNH, NR_5, S, C(O)O, C(O)NH, OC(O)NH, OC(O)O, NHC(O)NH, NHC(O)S, OC(O)N(R_1), N(R_1)C(O)N(R_2), C(O)NHNHC(O) or C(O)NR_1 when linked to a connecting site " ∿∿ "; or OH, NH_2, $NHNH_2$, NHR_1, SH, C(O)OH, C(O)NH_2, OC(O)NH_2, OC(O)OH, NHC(O)NH_2, NHC(O)SH, OC(O)NH(R_1), N(R_1)C(O)NH(R_2), C(O)NHNHC(O)OH or C(O)NHR_1 when not linked to the connecting site " ∿∿ "; Z_3 is H, $PO(OM_1)(OM_2)$, SO_3M_1, $CH_2PO(OM_1)(OM_2)$, $CH_3N(CH_2CH_2)_2NC(O)$-, $O(CH_2CH_2)_2NC(O)$-, R_1, or glycoside; wherein R_1, R_2, R_3, M_1, M_2, and n are the same as defined above;

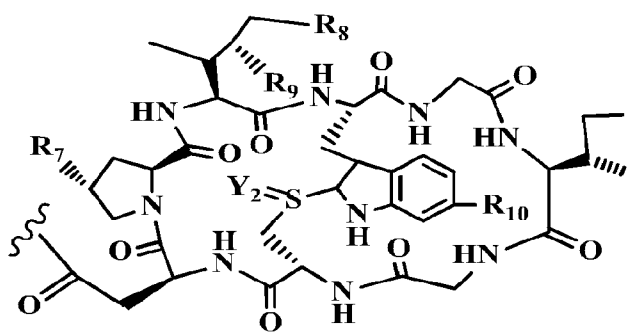
(o) the amatoxin and its analogs have the following formula, Am01, Am02, Am03 and Am04:



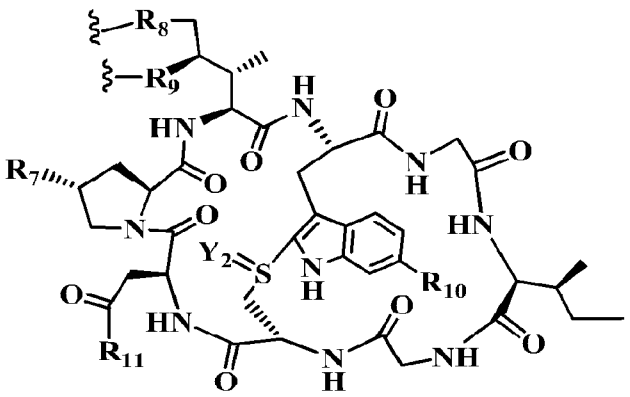
Am01,



Am02,



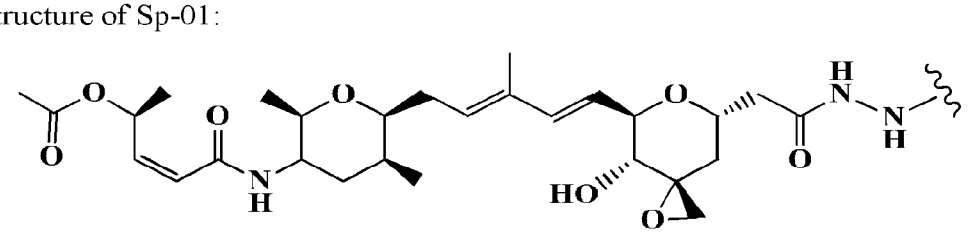
Am03,



Am04

or an isotope of one or more chemical elements, or pharmaceutically acceptable salts, hydrates, or hydrated salts; or the polymorphic crystalline structures of these compounds; or the optical isomers, racemates, diastereomers or enantiomers; wherein X_1, and Y_1 are independently O, NH, NHNH, NR_5, S, C(O)O, C(O)NH, OC(O)NH, OC(O)O, NHC(O)NH, NHC(O)S, $OC(O)N(R_1)$, $N(R_1)C(O)N(R_1)$, CH_2, CHNH, CH_2O, C(O)NHNHC(O) and $C(O)NR_1$; R_7, R_8, and R_9 are independently H, OH, OR_1, NH_2, NHR_1, C_1-C_6 alkyl, or absent; Y_2 is O, O_2, NR_1, NH, or absent; R_{10} is CH_2, O, NH, NR_1, NHC(O), NHC(O)NH, NHC(O)O, OC(O)O, C(O), OC(O), $OC(O)(NR_1)$, $(NR_1)C(O)(NR_1)$, $C(O)R_1$ or absent; R_{11} is OH, NH_2, NHR_1, $NHNH_2$, NHNHCOOH, O-R_1-COOH, NH-R_1-COOH, NH-$(Aa)_r$COOH, $O(CH_2CH_2O)_pCH_2CH_2OH$, $O(CH_2CH_2O)_pCH_2CH_2NH_2$, $NH(CH_2CH_2O)_pCH_2CH_2NH_2$, NR_1R_2, $O(CH_2CH_2O)_pCH_2CH_2$-COOH, $NH(CH_2CH_2O)_pCH_2CH_2COOH$, NH-Ar-COOH, NH-Ar-$NH_2$, $O(CH_2CH_2O)_pCH_2CH_2$-$NHSO_3H$, $NH(CH_2CH_2O)_pCH_2CH_2NHSO_3H$, R_1-$NHSO_3H$, NH-R_1-$NHSO_3H$, $O(CH_2CH_2O)_p$-$CH_2CH_2NHPO_3H_2$, $NH(CH_2CH_2O)_pCH_2CH_2NHPO_3H_2$, OR_1, R_1-$NHPO_3H_2$, R_1-OPO_3H_2, $O(CH_2CH_2O)_pCH_2CH_2OPO_3H_2$, OR_1-$NHPO_3H_2$, NH-R_1-$NHPO_3H_2$, or $NH(CH_2CH_2O)_pCH_2$-$CH_2NHPO_3H_2$, wherein $(Aa)_r$ is 1-8 aminoacids; n and m_1 are independently 1-20; p is 1 -5000; R_1, R_2 and Ar, are the same defined through out the application; " ∿∿ " is defined the same above;

(p) the Spliceostatins and pladienolides are spliceostatin A, FR901464, and (2S, 3Z)-5-{[(2R, 3R, 5S, 6S)-6-{(2E, 4E)-5-[(3R, 4R, 5R, 7S)-7-(2-hydrazinyl-2-oxoethyl)-4-hydroxy-1, 6-dioxaspiro[2.5]oct-5-yl]-3-methylpenta-2, 4-dien-1-y- 1}-2,5-dimethyltetrahydro-2H-pyran-3-yl]amino}-5-oxopent-3-en-2-yl acetate, Pladienolide B, Pladienolide D, and E7107 having a core structure of Sp-01:



(Sp-01),

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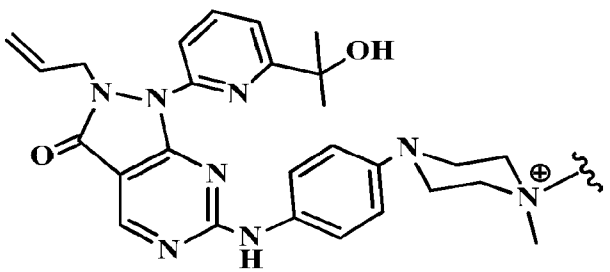
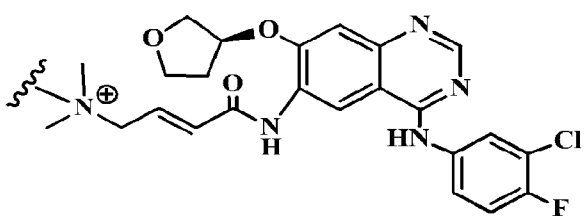
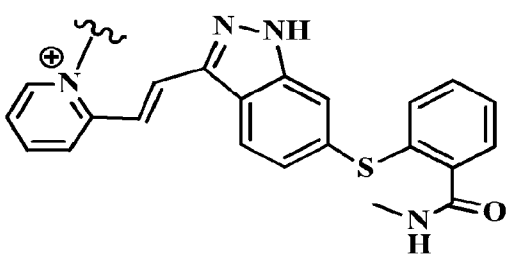
(q) the protein kinase inhibitors are selected from Adavosertib, Afatinib, Axitinib, Bafetinib, Bosutinib, Cobimetinib, Crizotinib, Cabozantinib, Dasatinib, Entrectinib, Erdafitinib, Erlotinib, Erlotinib, Fostamatinib, Gefitinib, Ibrutinib, Imatinib, Lapatinib, Lenvatinib, Mubritinib, Nilotinib, Pazopanib, Pegaptanib, Ponatinib, Rebastinib, Regorafenib, Ruxolitinib, Sorafenib, Sunitinib, SU6656, Tofacitinib, Vandetanib, Vemurafenib, Entrectinib, Palbociclib, Ribociclib, Abemaciclib, Dacomitinib, Neratinib, Rociletinib (CO-1686), Osimertinib, AZD3759, and Nazartinib (EGF816), having the following formula, PK01 - PK40:



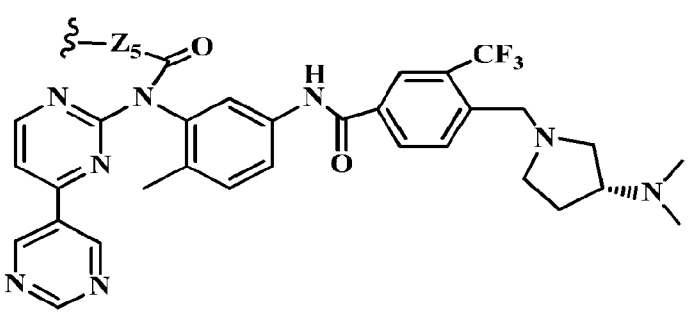
PK01, Adavosertib,



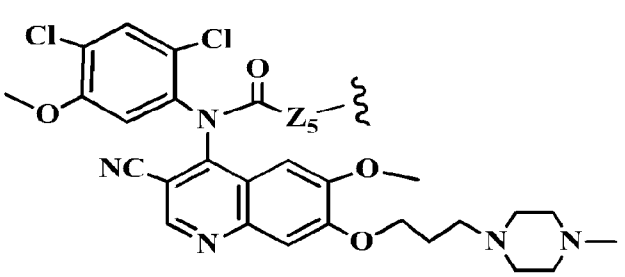
PK02, Afatinib,



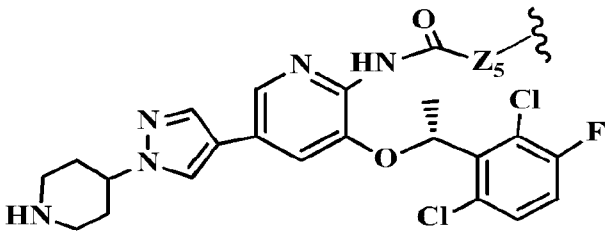
PK03, Axitinib,



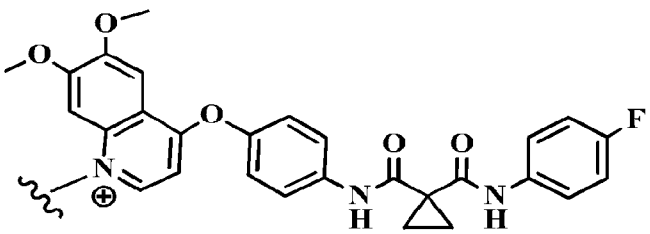
PK04, Bafetinib



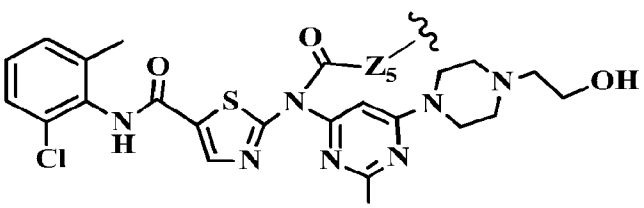
PK05, Bosutinib,



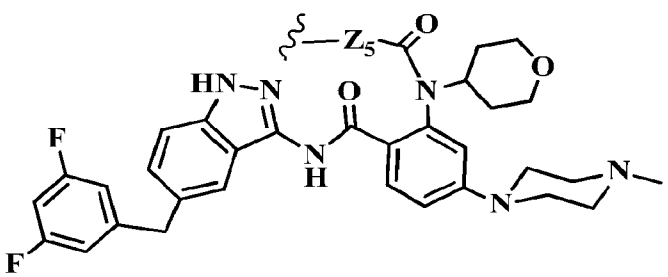
PK06, Crizotinib,



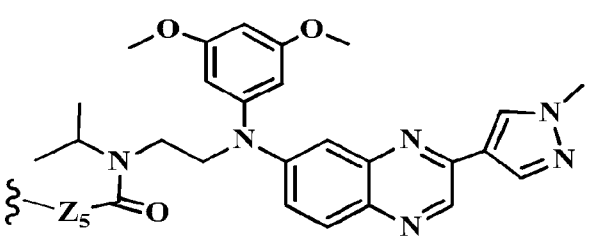
PK07, Cabozantinib,



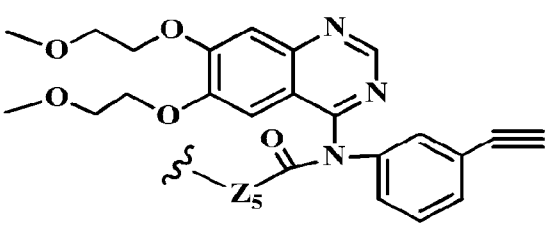
PK08, Dasatinib,



PK09, Entrectinib,



PK10, Erdafitinib,



PK11, Erlotinib,

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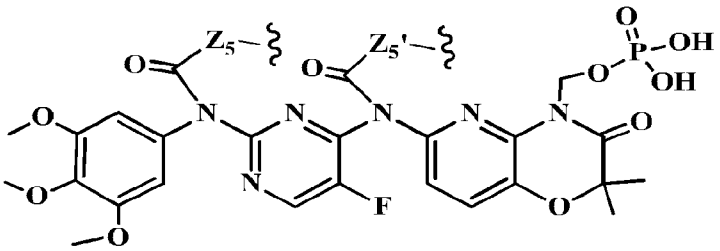
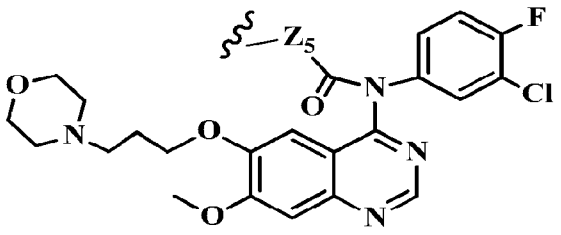
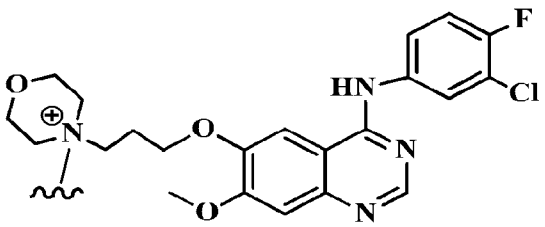


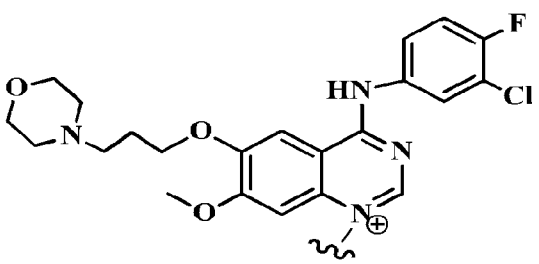
PK12, Fostamatinib,



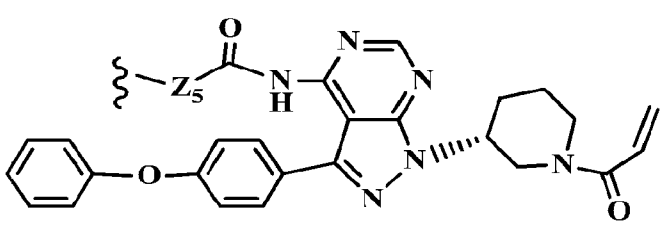
PK13, Gefitinib,



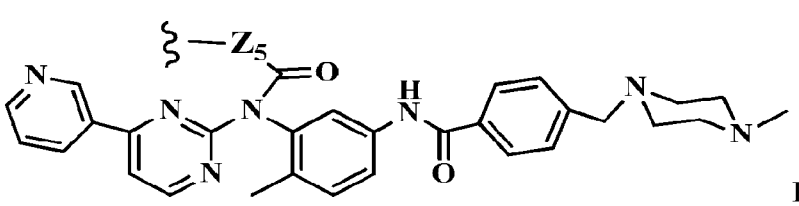
PK14, Gefitinib,



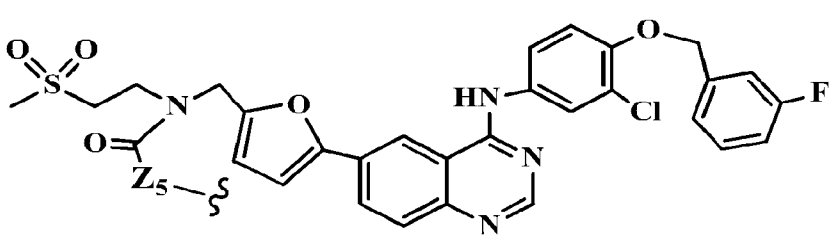
PK15, Gefitinib,



PK16, Ibrutinib,



PK17, Imatinib,



PK18, Lapatinib,

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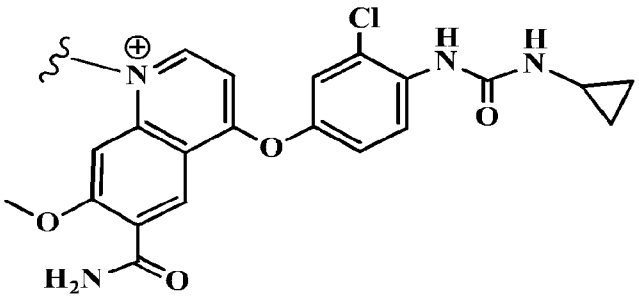
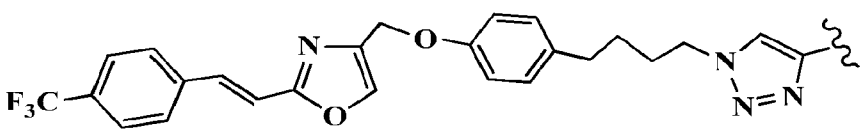
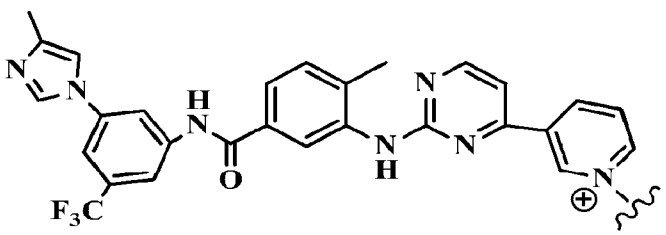


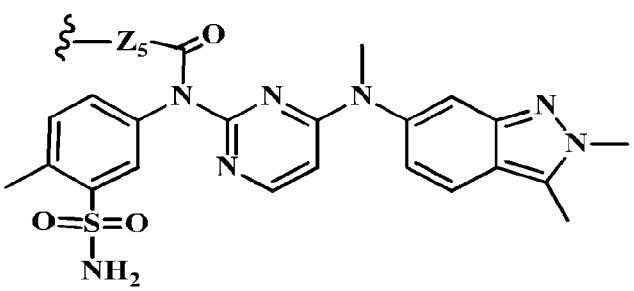
PK19, Lenvatinib,



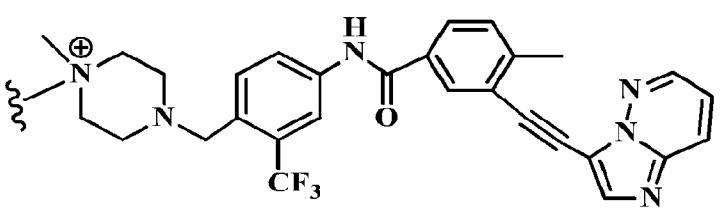
PK20, Mubritinib,



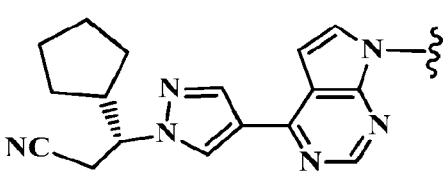
PK21, Nilotinib,



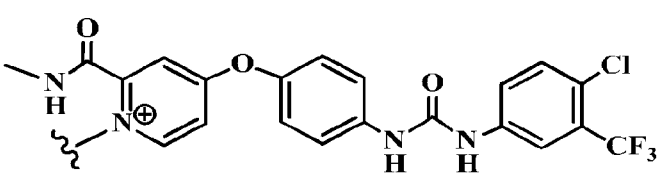
PK22, Pazopanib,



PK23, Ponatinib,



PK24, Ruxolitinib,



PK25, Sorafenib,

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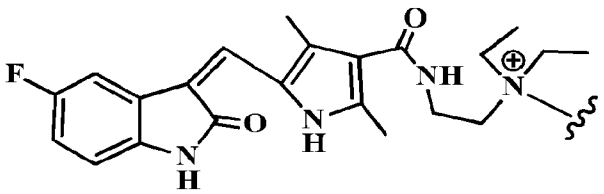
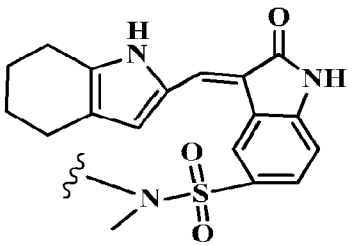
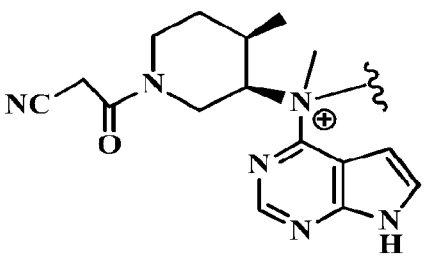


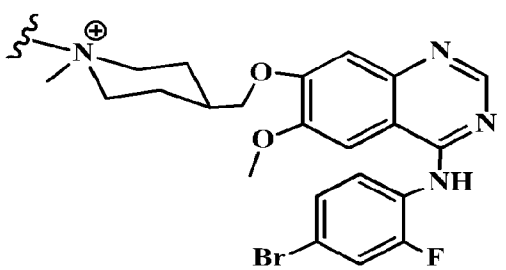
PK26, Sunitinib,



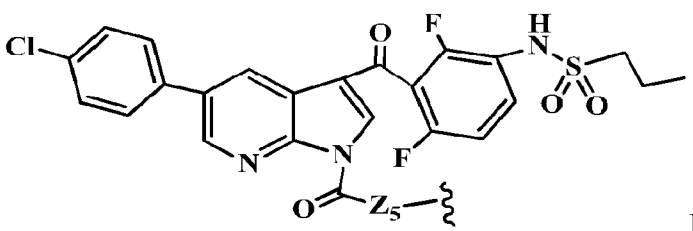
PK27, SU6656,



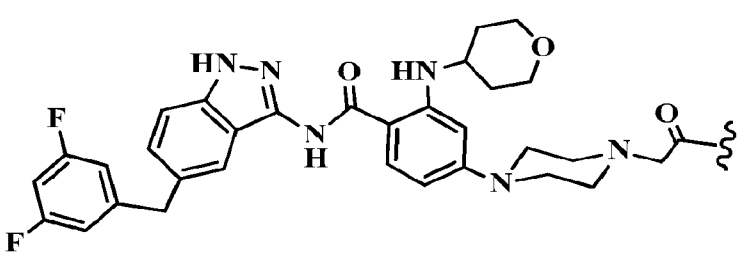
PK28, Tofacitinib,



PK29, Vandetanib,



PK30, Vemurafenib;



PK 31, Entrectinib;

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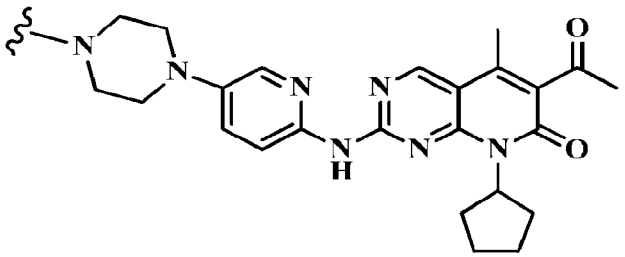
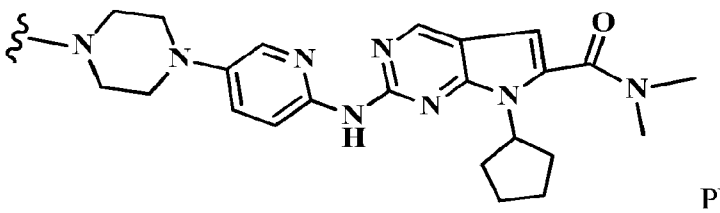
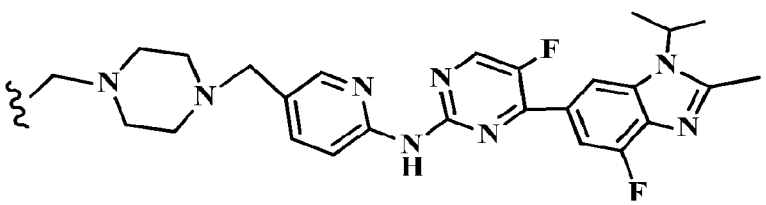


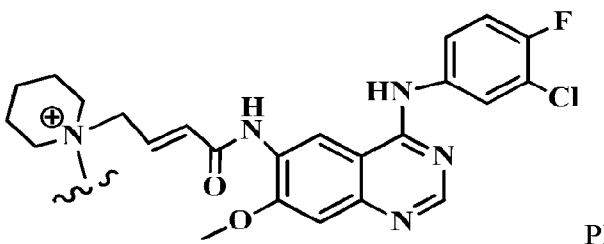
PK-32, Palbociclib,



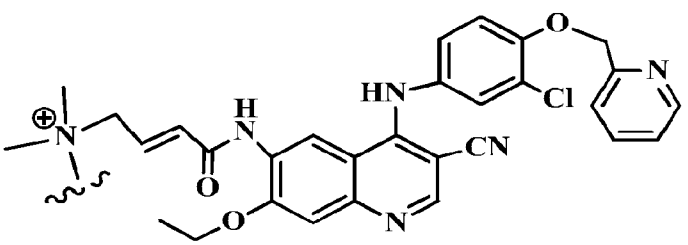
PK-33, Ribociclib,



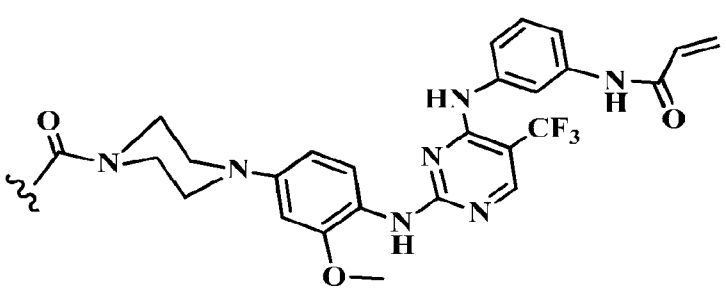
PK-34, Abemaciclib,



PK-35, Dacomitinib,



PK-36, Neratinib,



PK-37, Rociletinib (CO-1686),

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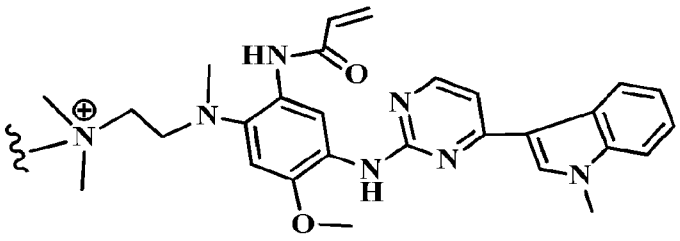
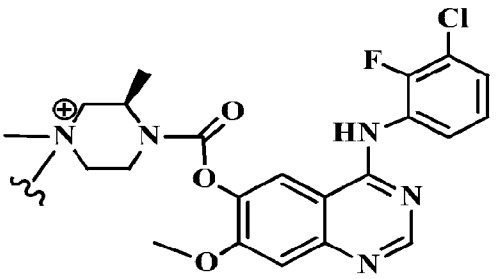
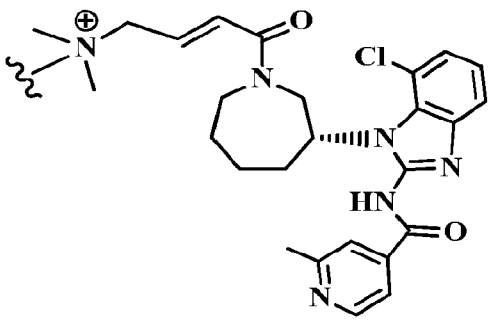


PK-38, Osimertinib,



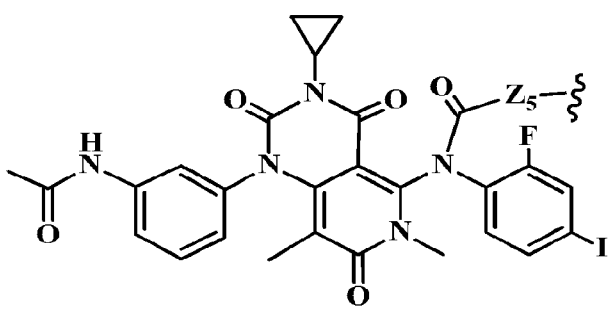
PK-39, AZD3759,



PK-40, Nazartinib (EGF816),

wherein Z_5 and Z_5' are indepently O, NH, NHNH, NR_5, S, C(O)O, C(O)NH, OC(O)NH, OC(O)O, NHC(O)O, NHC(O)NH, NHC(O)S, OC(O)N(R_1), N(R_1)C(O)N(R_2), C(O)NHNHC(O) or C(O)NR_1; R_1, R_2 and Ar, are defined the same above;

(r) the MEK inhibitors are selected from PD0325901, selumetinib (AZD6244), cobimetinib (XL518), refametinib, trametinib (GSK1120212), pimasertib, Binimetinib (MEK162), AZD8330, RO4987655, RO5126766, WX-554, E6201, GDC-0623, PD-325901 and TAK-733, and have the following formula:



MEK01, Trametinib,

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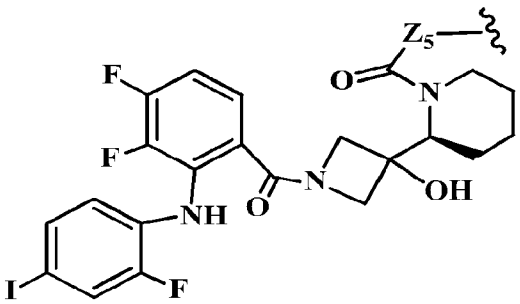
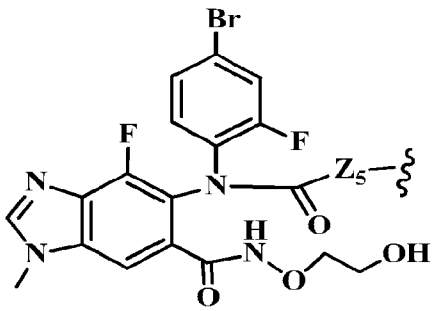
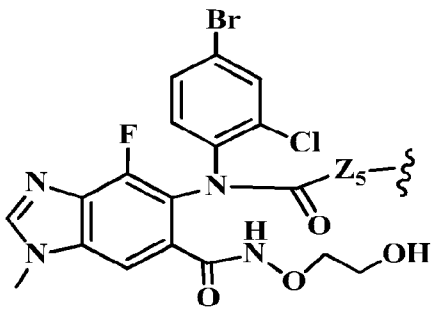


MEK02, Cobimetinib,



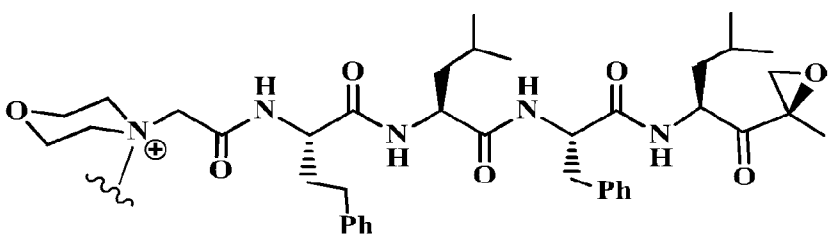
MEK03, Binimetinib,



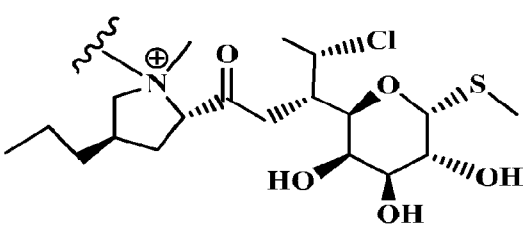
MEK04, selumetinib,

wherein Z_5 is selected from O, NH, NHNH, NR_5, S, C(O)O, C(O)NH, OC(O)NH, OC(O)O, NHC(O)O, NHC(O)NH, NHC(O)S, $OC(O)N(R_1)$, $N(R_1)C(O)N(R_2)$, C(O)NHNHC(O) and $C(O)NR_1$; R_1 and R_2 are the same as defined above;

(s) the proteinase inhibitors are selected from Carfilzomib, Clindamycin, Retapamulin, Indibulin, having the following formulae:



PI01, Carfilzomib,



PI02, Clindamycin,

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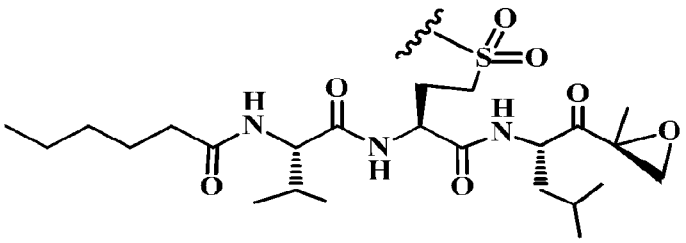
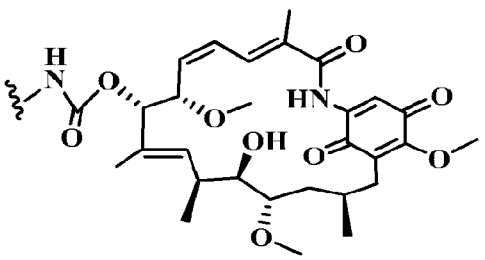


PI03, Carmaphycin analog;

(t) the geldanamycins or their derivatives have the following formula:



(t1), wherein ∿∿∿ is a site defined above;

(u) the immunotoxin are selected from Diphtheria toxin (DT), Cholera toxin (CT), Trichosanthin (TCS), Dianthin, Pseudomonas exotoxin A (ETA), Erythrogenic toxins, Diphtheria toxin, AB toxins, Type III exotoxins, proaerolysin, and topsalysin;

(v) the cell receptor agonist or stimulating molecule are selected from: Folate derivatives; Glutamic acid urea derivatives; Somatostatin and its analogs (selected from the group consisting of octreotide (Sandostatin) and lanreotide (Somatuline)); Aromatic sulfonamides; Pituitary adenylate cyclase activating peptides (PACAP) (PAC1); Vasoactive intestinal peptides (VIP/PACAP) (VPAC1, VPAC2); Melanocyte-stimulating hormones (α-MSH); Cholecystokinins (CCK) /gastrin receptor agonists; Bombesins (selected from the group consisting of Pyr-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2)/gastrin-releasing peptide (GRP); Neurotensin receptor ligands (NTR1, NTR2, NTR3); Substance P (NK1 receptor) ligands; Neuropeptide Y (Y1–Y6); Homing Peptides include RGD (Arg-Gly-Asp), NGR (Asn-Gly-Arg), the dimeric and multimeric cyclic RGD peptides (selected from cRGDfV), TAASGVRSMH and LTLRWVGLMS (Chondroitin sulfate proteoglycan NG2 receptor ligands) and F3 peptides; Cell Penetrating Peptides (CPPs); Peptide Hormones selected from the group consisting of luteinizing hormone-releasing hormone (LHRH) agonists and antagonists, and gonadotropin-releasing hormone (GnRH) agonist selected from the group consisting of buserelin (Pyr-His-Trp-Ser-Tyr-D-Ser(OtBu)-Leu-Arg-Pro-NHEt), Gonadorelin (Pyr-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2), Goserelin (Pyr-His-Trp-Ser-Tyr-D-Ser(OtBu)-Leu-Arg-Pro-AzGly-NH_2), Histrelin (Pyr-His-Trp-Ser-Tyr-D-His(N-benzyl)-Leu-Arg-Pro-NHEt), leuprolide (Pyr-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-NHEt), Nafarelin (Pyr-His-Trp-Ser-Tyr-2Nal-Leu-Arg-Pro-Gly-NH_2), Triptorelin (Pyr-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH_2), Nafarelin, Deslorelin, Abarelix (Ac-D-2Nal-D-4-chloroPhe-D-3-(3-pyridyl)Ala-Ser-(N-Me)Tyr-D-Asn-Leu-isopropylLys-Pro-DAla-NH_2), Cetro-

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relix (Ac-D-2Nal-D-4-chloroPhe-D-3-(3-pyridyl)Ala-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH_2), Degarelix (Ac-D-2Nal-D-4-chloroPhe-D-3-(3-pyridyl)Ala-Ser-4-aminoPhe(L-hydroorotyl)-D-4-aminoPhe(carba-moyl)-Leu-isopropylLys-Pro-D-Ala-NH_2), and Ganirelix (Ac-D-2Nal-D-4-chloroPhe-D-3-(3-pyridyl)Ala-Ser-Tyr-D-(N9, N10-diethyl)-homoArg-Leu-(N9, N10-diethyl)-homoArg-Pro-D-Ala-NH_2); Pattern Recognition Receptor (PRRs), selected from the group consisting of Toll-like receptors' (TLRs) ligands, C-type lectins and Nodlike Receptors' (NLRs) ligands; Calcitonin receptor agonists; integrin receptors' and their receptor subtypes' (selected from the group consisting of$\alpha_V\beta_1$, $\alpha_V\beta_3$, $\alpha_V\beta_5$, $\alpha_V\beta_6$, $\alpha_6\beta_4$, $\alpha_7\beta_1$, $\alpha_L\beta_2$, $\alpha_{IIb}\beta_3$) agonists (selected from the group consisting of GRGDSPK, cyclo(RGDfV) (L1) and its derives [cyclo(-N(Me)R-GDfV), cyclo(R-Sar-DfV), cyclo(RG-N(Me)D-fV), cyclo(RGD-N(Me)f-V), cyclo(RGDf-N(Me)V-)(Cilengitide)]; Anticalin (a derivative of Lipocalins); Adnectins (10th FN3 (Fibronectin)); Designed Ankyrin Repeat Proteins (DARPins); Avimers; EGF receptors, or VEGF receptors' agonists;

the cell receptor agonist is selected from the following: LB01 (Folate), LB02 (PMSA ligand), LB03 (PMSA ligand), LB04 (PMSA ligand), LB05 (Somatostatin), LB06 (Somatostatin), LB07 (Octreotide, a Somatostatin analog), LB08 (Lanreotide, a Somatostatin analog), LB09 (Vapreotide (Sanvar), a Somatostatin analog), LB10 (CAIX ligand), LB11 (CAIX ligand), LB12 (Gastrin releasing peptide receptor (GRPr), MBA), LB13 (luteinizing hormone-releasing hormone (LH-RH) ligand and GnRH), LB14 (luteinizing hormone-releasing hormone (LH-RH) and GnRH ligand), LB15 (GnRH antagonist, Abarelix), LB16 (cobalamin, vitamin B12 analog), LB17 (cobalamin, vitamin B12 analog), LB18 (for $\alpha_v\beta_3$ integrin receptor, cyclic RGD pentapeptide), LB19 (heterobivalent peptide ligand for VEGF receptor), LB20 (Neuromedin B), LB21 (bombesin for a G-protein coupled receptor), LB22 (TLR_2 for a Toll-like receptor,), LB23 (for an androgen receptor), LB24 (Cilengitide/cyclo(-RGDfV-) for an α_v integrin receptor, LB23 (Fludrocortisone), LB25 (Rifabutin analog), LB26 (Rifabutin analog), LB27 (Rifabutin analog), LB28 (Fludrocortisone), LB29 (Dexamethasone), LB30 (fluticasone propionate), LB31 (Beclometasone dipropionate), LB32 (Triamcinolone acetonide), LB33 (Prednisone), LB34 (Prednisolone), LB35 (Methylprednisolone), LB36 (Betamethasone), LB37 (Irinotecan analog), LB38 (Crizotinib analog), LB39 (Bortezomib analog), LB40 (Carfilzomib analog), LB41 (Carfilzomib analog), LB42 (Leuprolide analog), LB43 (Triptorelin analog), LB44 (Clindamycin), LB45 (Liraglutide analog), LB46 (Semaglutide analog), LB47 (Retapamulin analog), LB48 (Indibulin analog), LB49 (Vinblastine analog), LB50 (Lixisenatide analog), LB51 (Osimertinib analog), LB52 (a nucleoside analog), LB53 (Erlotinib analog) or LB54 (Lapatinib analog) having following structures:

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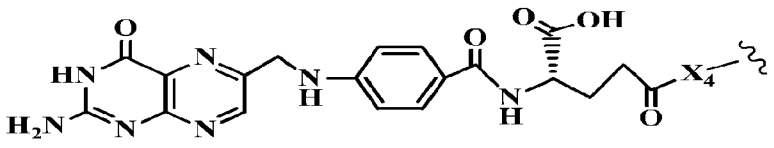
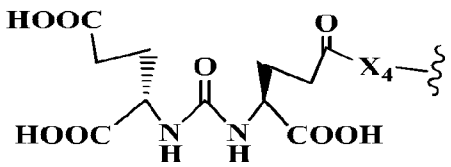
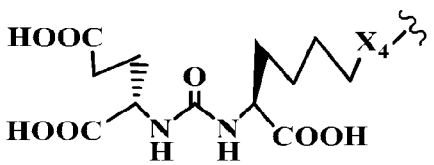


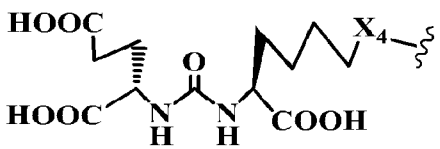
LB01 (Folate conjugate),



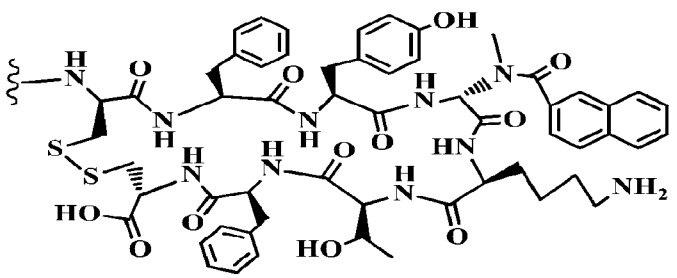
LB02 (PMSA ligand conjugate),



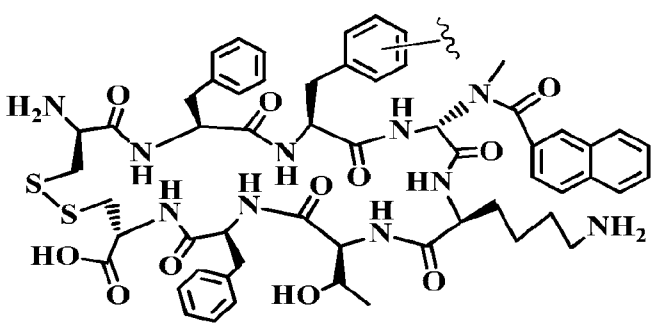
LB03 (PMSA ligand conjugate),



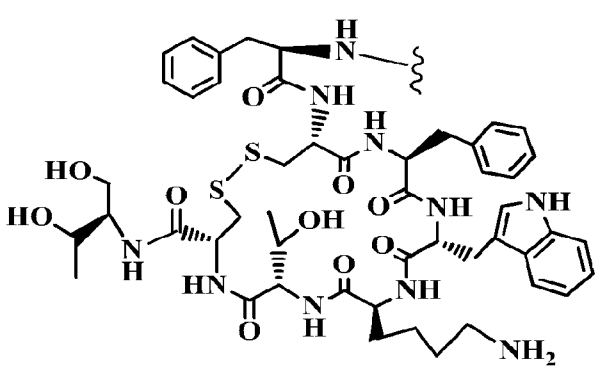
LB04 (PMSA ligand),



LB05 (Somatostatin),



LB06 (Somatostatin),



LB07 (Octreotide, a Somatostatin analog),

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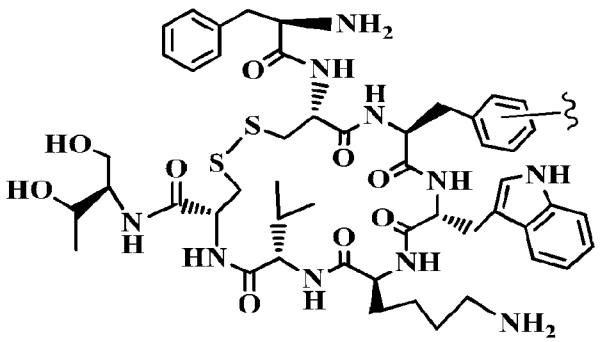
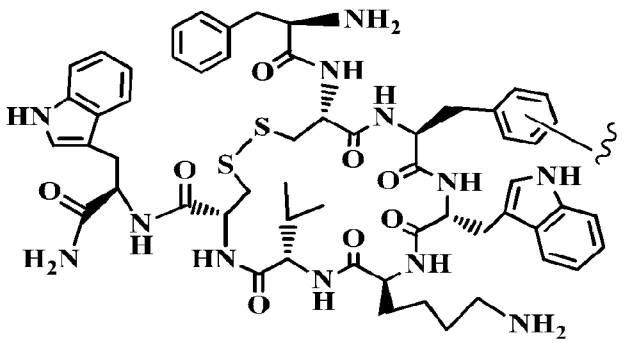
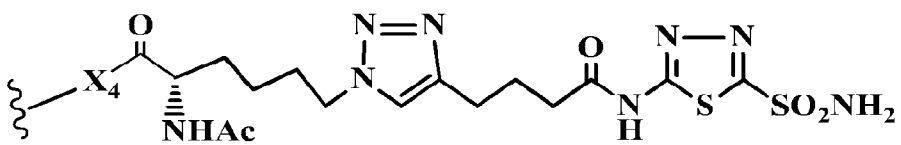


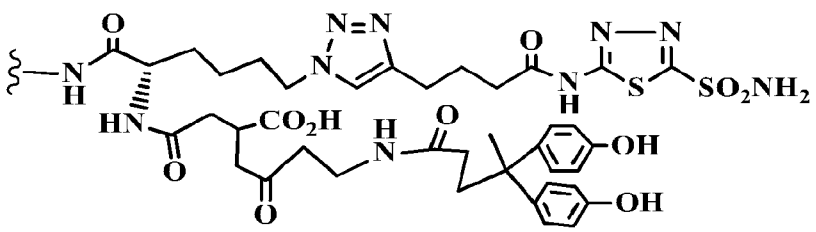
LB08 (Lanreotide, a Somatostatin analog),



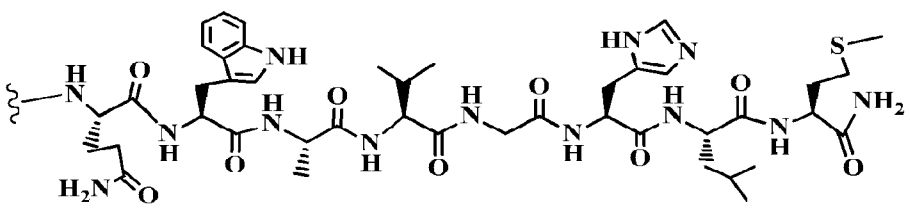
LB09 (Vapreotide (Sanvar), a Somatostatin analog),



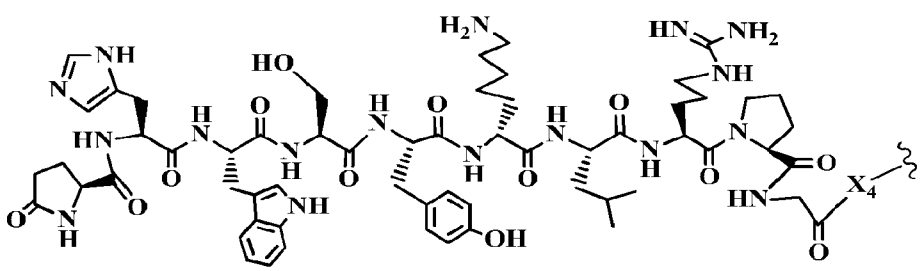
LB10 (CAIX ligand),



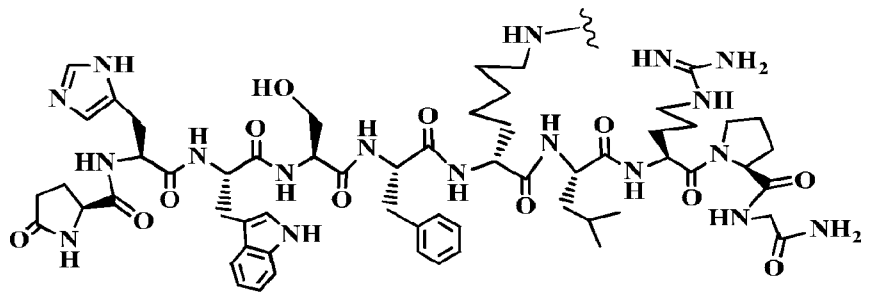
LB11 (CAIX ligand),



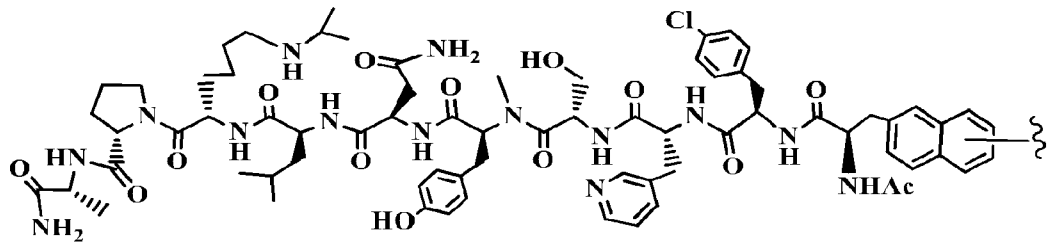
LB12 (Gastrin releasing peptide receptor (GRPr), MBA),



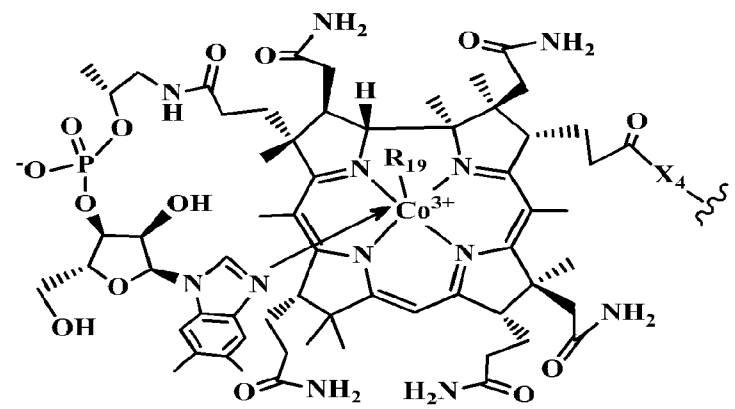
LB13 (luteinizing hormone-releasing hormone (LH-RH) ligand and GnRH),



LB14 (luteinizing hormone-releasing hormone (LH-RH) and GnRH ligand),

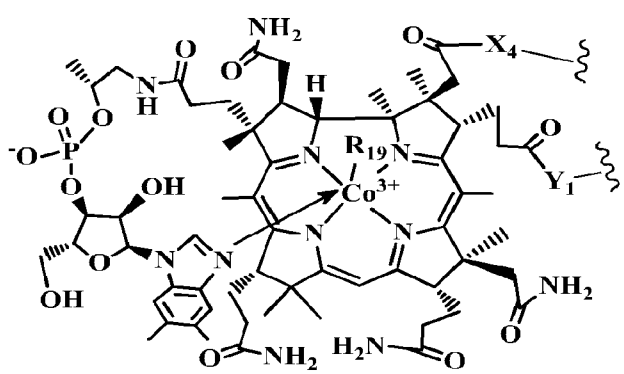


LB15 (GnRH antagonist, Abarelix),



R_{19} is 5'deoxyadenosyl, Me, OH, or CN;

LB16 (cobalamin, vitamin B12 analog),



R_{19} is 5'deoxyadenosyl, Me, OH, or CN; LB17 (cobalamin, vitamin B12 analog),

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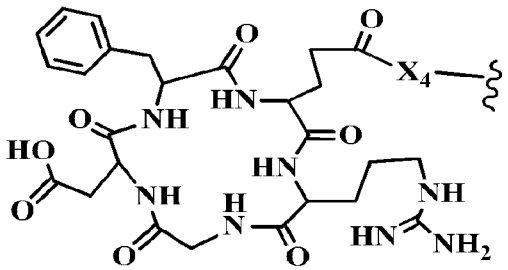
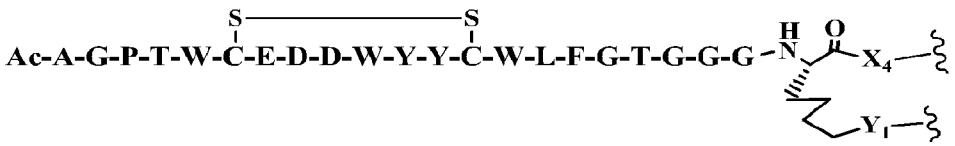
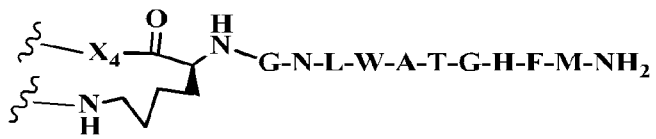


LB18 (for $\alpha_v\beta_3$ integrin receptor, cyclic RGD pentapeptide),

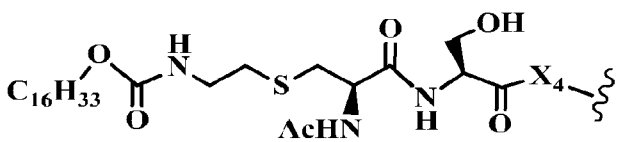


LB19 (hetero-bivalent peptide ligand conjugate for VEGF receptor),

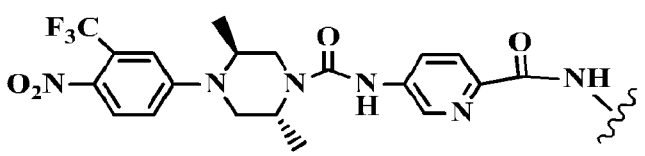


LB20 (Neuromedin B),

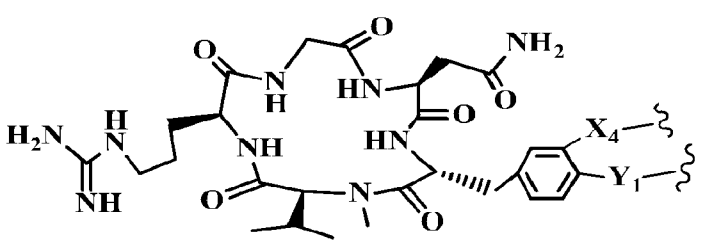
LB21 (bombesin conjugate for a G-protein coupled receptor),



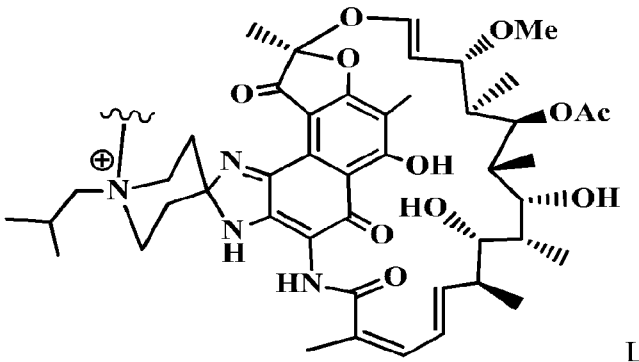
LB22 (TLR_2 conjugate for a Toll-like receptor),



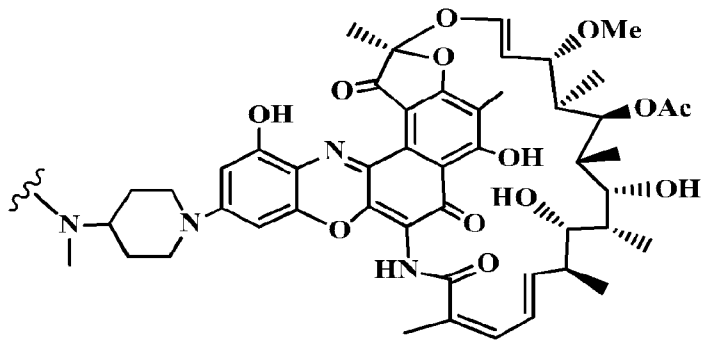
LB23 (an androgen receptor),



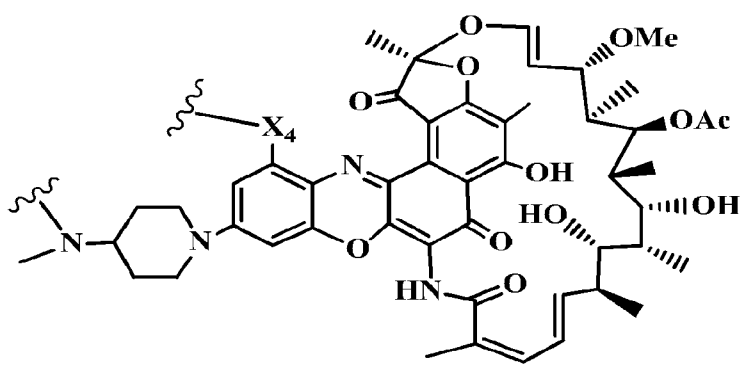
LB24 (Cilengitide/cyclo(-RGDfV-) conjugate for an α_v integrin receptor)



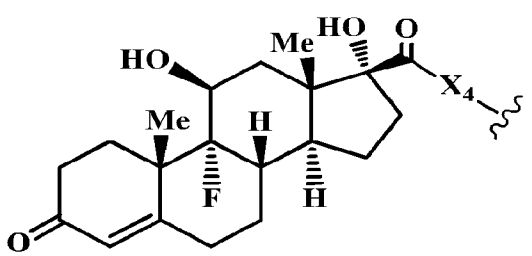
LB25 (Rifabutin analog),



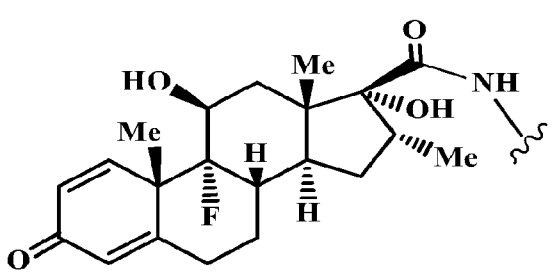
LB26 (Rifabutin analog),



LB27 (Rifabutin analog),



LB28 (Fludrocortisone),



LB29 (Dexamethasone),

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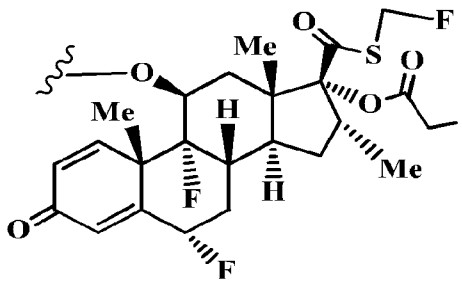
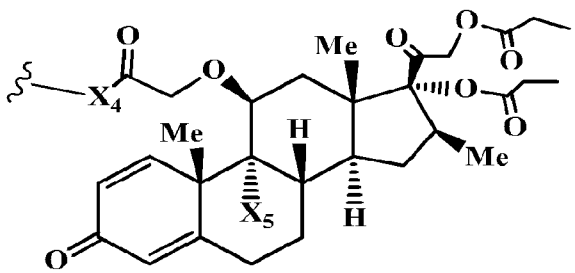
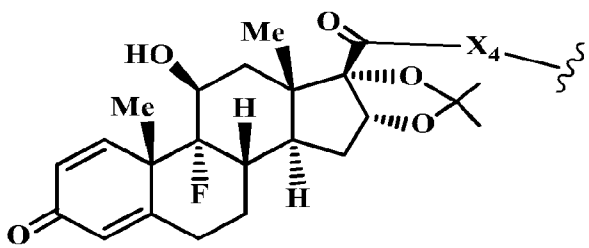


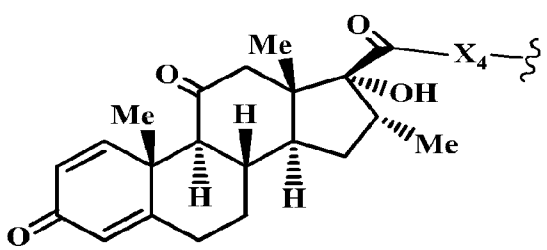
LB30 (fluticasone propionate),



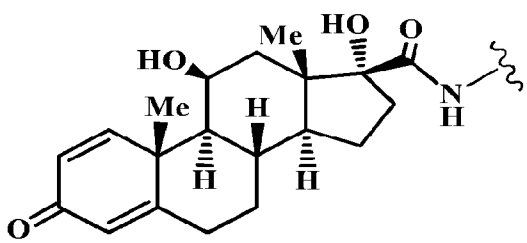
LB31 (Beclometasone dipropionate),



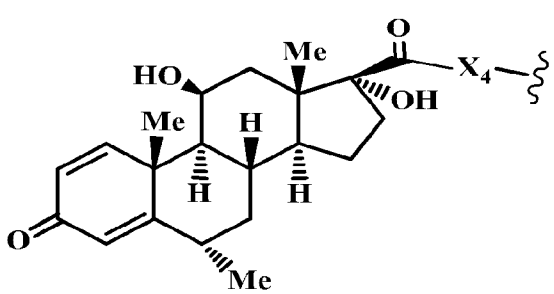
LB32 (Triamcinolone acetonide),



LB33 (Prednisone),



LB34 (Prednisolone),



LB35 (Methylprednisolone),

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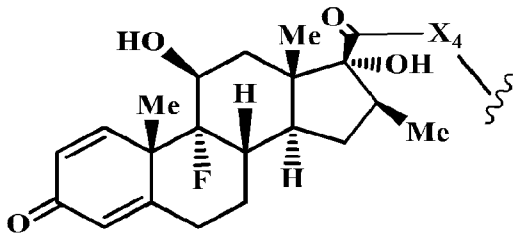
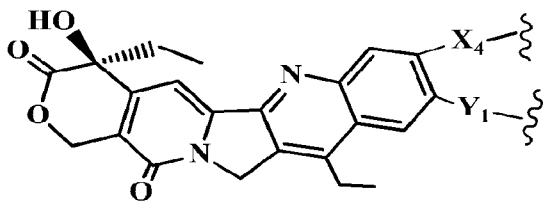
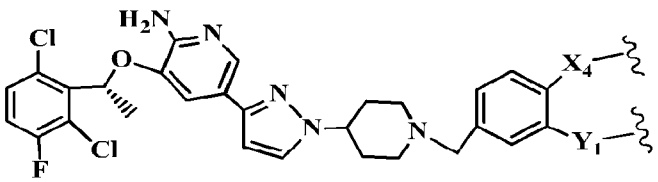


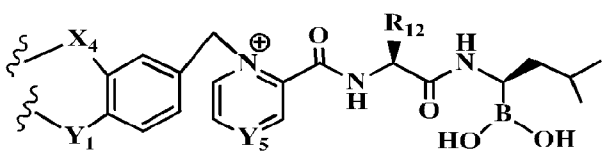
LB36 (Betamethasone),



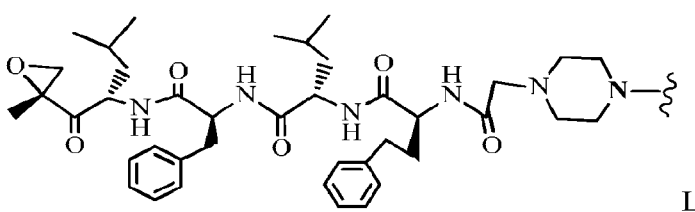
LB37 (Irinotecan analog),



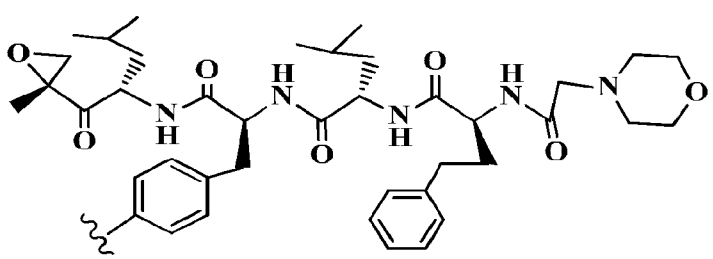
LB38 (Crizotinib analog),



LB39 (Bortezomib analog), wherein Y_5, is N, CH, C(Cl), $C(CH_3)$, or $C(COOR_1)$; R_{12} is H, C_1-C_6 Alkyl, or C_3-C_8 Ar;



LB40 (Carfilzomib analog),



LB41 (Carfilzomib analog),

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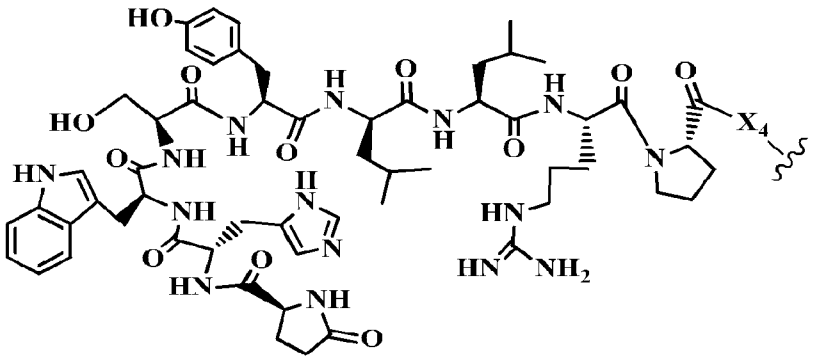
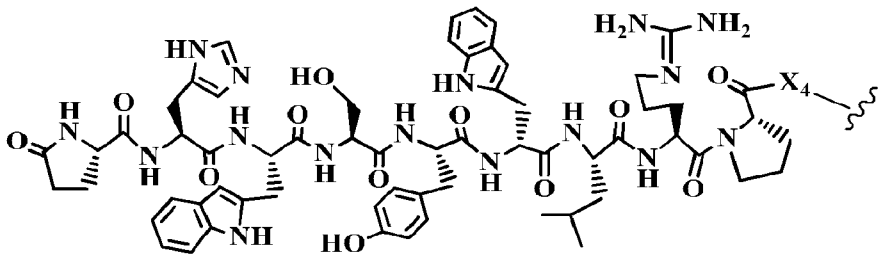
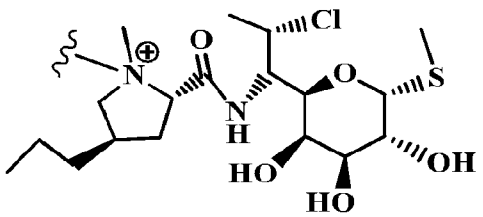


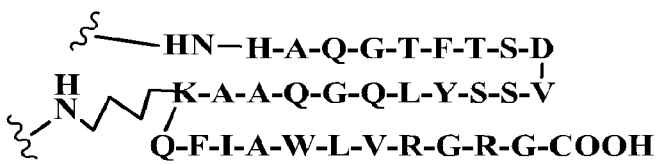
LB42 (Leuprolide analog),



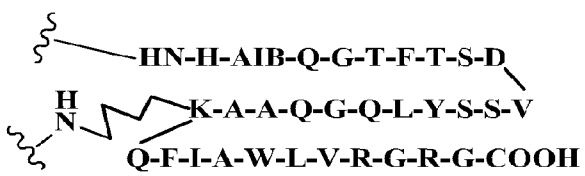
LB43 (Triptorelin analog),



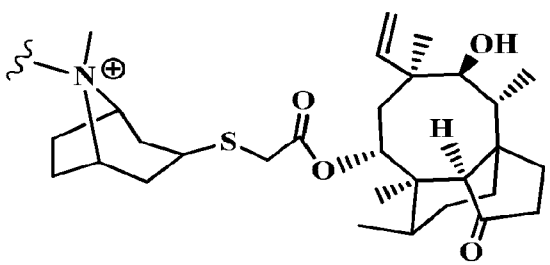
LB44 (Clindamycin),



LB45 (Liraglutide analog),



LB46 (Semaglutide analog),



LB47 (Retapamulin analog),

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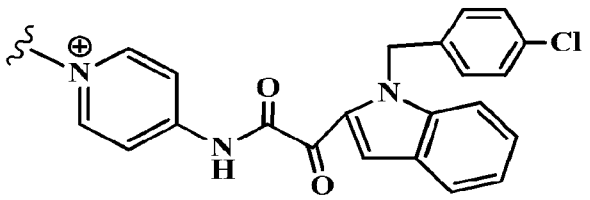
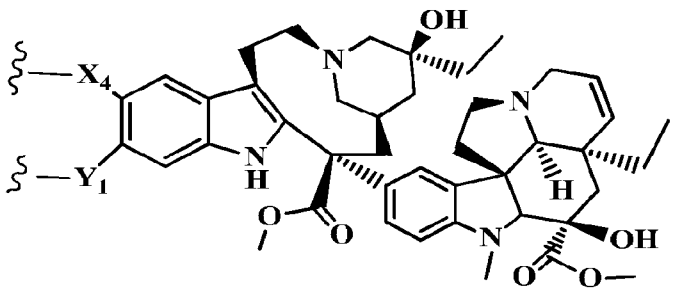
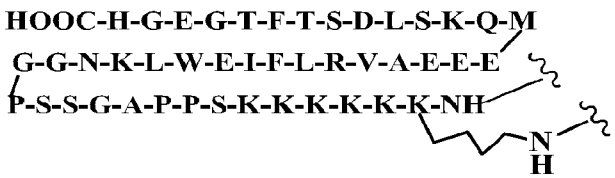


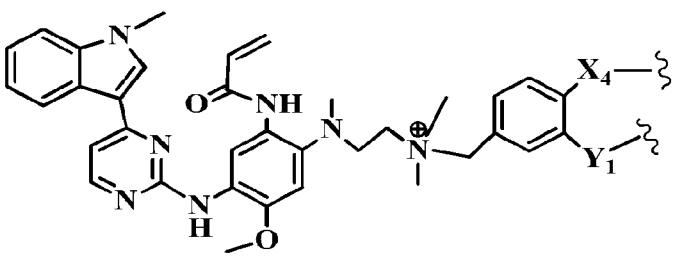
LB48 (Indibulin analog),



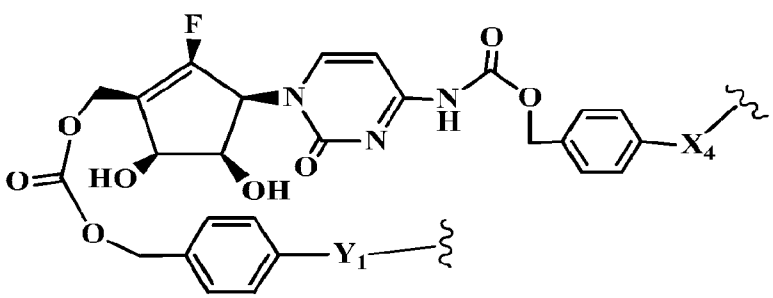
LB49 (Vinblastine analog),



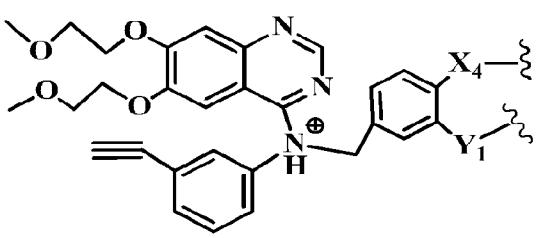
LB50 (Lixisenatide analog),



LB51 (Osimertinib analog),



LB52 (a nucleoside analog),



LB53 (Erlotinib analog),

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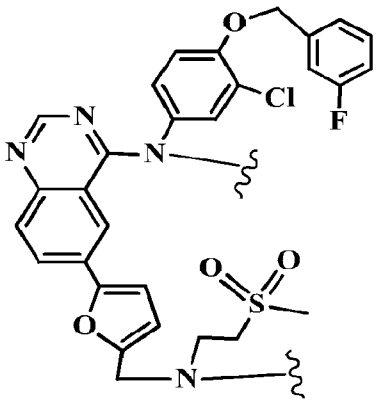


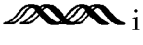
LB54 (Lapatinib analog);

wherein X_4, and Y_1 are independently O, NH, NHNH, NR_1, S, C(O)O, C(O)NH, OC(O)NH, OC(O)O, NHC(O)NH, NHC(O)S, $OC(O)N(R_1)$, $N(R_1)C(O)N(R_1)$, CH_2, C(O)NHNHC(O) or $C(O)NR_1$; R_1, and R_2 are defined the same above;

(w) the one, two or more DNA, RNA, mRNA, small interfering RNA (siRNA), micro-RNA (miRNA), and PIWI interacting RNAs (piRNA) have a structure of:

, SI01, or

, SI02;

wherein " ∿∿ " is a site to link the side chain linker;  is single or double strands of DNA, RNA, mRNA, siRNA, miRNA, or piRNA; X_1, and Y are independently O, NH, NHNH, NR_1, S, C(O)O, C(O)NH, OC(O)NH, OC(O)O, NHC(O)NH, NHC(O)S, $OC(O)N(R_1)$, $N(R_1)C(O)N(R_1)$, CH_2, C(O)NHNHC(O) or $C(O)NR_1$; R_1, and R_2 are defined the same above.

11. The process according to Claim 1, or 3, or 4, wherein the antibody or antibody-like protein is selected from:

(A): the group consisting of probody, nanobody, peptides, a polymeric micelle, a liposome, a lipoprotein-based drug carrier, a nano-particle drug carrier, a dendrimer, and a molecule or a particle said above coating or linking with a cell-binding ligand, or a combination of two or more of the above;

(B): the group consisting of a full-length antibody (polyclonal antibody, monoclonal antibody, antibody dimer, antibody multimer), multispecific antibody (selected from, bispecific antibody, trispecific antibody, or tetraspecific antibody); a single chain antibody, an antibody fragment that binds to the target cell, a monoclonal antibody, a single chain monoclonal antibody, a monoclonal antibody fragment that binds the target cell, a chimeric antibody, a chimeric antibody

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fragment that binds to the target cell, a domain antibody, a domain antibody fragment that binds to the target cell, a resurfaced antibody, a resurfaced single chain antibody, or a resurfaced antibody fragment that binds to the target cell, a humanized antibody or a resurfaced antibody, a humanized single chain antibody, or a humanized antibody fragment that binds to the target cell, anti-idiotypic (anti-Id) antibodies, CDR's, diabody, triabody, tetrabody, miniantibody, a probody, a probody fragment, small immune antibody-like proteins (SIP), a lymphokine antibody-like protein, a hormone antibody-like protein, a growth factor antibody-like protein, a colony stimulating factor antibody-like protein,, a nutrient-transport antibody-like protein, large molecular weight antibody-like proteins, fusion antibody-like proteins, kinase inhibition antibody-like protein, gene-targeting antibody-like protein, antibody-like protein coated on nanoparticles or polymers modified with antibodies or large molecular weight antibody-like proteins; or

(C): the group consisting of an IgG antibody that is able to bind against tumor cells, virus infected cells, microorganism infected cells, parasite infected cells, autoimmune disease cells, activated tumor cells, myeloid cells, activated T-cells, an affecting B cells, or melanocytes, or abnormal cells expressing any one of the following antigens or receptors: CD1, CD1a, CD1b, CD1c, CD1d, CD1e, CD2, CD3, CD3d, CD3e, CD3g, CD4, CD5, CD6, CD7, CD8, CD8a, CD8b, CD9, CD10, CD11a, CD11b, CD11c, CD11d, CD12w, CD14, CD15, CD16, CD16a, CD16b, CDw17, CD18, CD19, CD20, CD21, CD22, CD23, CD24, CD25, CD26, CD27, CD28, CD29, CD30, CD31, CD32, CD32a, CD32b, CD33, CD34, CD35, CD36, CD37, CD38, CD39, CD40, CD41, CD42, CD42a, CD42b, CD42c, CD42d, CD43, CD44, CD45, CD46, CD47, CD48, CD49b, CD49c, CD49c, CD49d, CD49f, CD50, CD51, CD52, CD53, CD54, CD55, CD56, CD57, CD58, CD59, CD60, CD60a, CD60b, CD60c, CD61, CD62E, CD62L, CD62P, CD63, CD64, CD65, CD65s, CD66, CD66a, CD66b, CD66c, CD66d, CD66e, CD66f, CD67, CD68, CD69, CD70, CD71, CD72, CD73, CD74, CD75, CD75s, CD76, CD77, CD78, CD79, CD79a, CD79b, CD80, CD81, CD82, CD83, CD84, CD85, CD85a, CD85b, CD85c, CD85d, CD85e, CD85f, CD85g, CD85g, CD85i, CD85j, CD85k, CD85m, CD86, CD87, CD88, CD89, CD90, CD91, CD92, CD93, CD94, CD95, CD96, CD97, CD98, CD99, CD100, CD101, CD102, CD103, CD104, CD105, CD106, CD107, CD107a, CD107b, CD108, CD109, CD110, CD111, CD112, CD113, CD114, CD115, CD116, CD117, CD118, CD119, CD120, CD120a, CD120b, CD121, CD121a, CD121b, CD122, CD123, CD123a, CD124, CD125, CD126, CD127, CD128, CD129, CD130, CD131, CD132, CD133, CD134, CD135, CD136, CD137, CD138, CD139, CD140, CD140a, CD140b, CD141, CD142, CD143, CD144, CD145, CDw145, CD146, CD147, CD148, CD149, CD150, CD151, CD152, CD153, CD154, CD155, CD156, CD156a, CD156b, CD156c, CD156d, CD157, CD158, CD158a, CD158b1, CD158b2, CD158c, CD158d, CD158e1, CD158e2, CD158f2, CD158g, CD158h, CD158i, CD158j, CD158k, CD159, CD159a, CD159b, CD159c, CD160, CD161, CD162, CD163, CD164, CD165, CD166, CD167, CD167a,

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CD167b, CD168, CD169, CD170, CD171, CD172, CD172a, CD172b, CD172g, CD173, CD174, CD175, CD175s, CD176, CD177, CD178, CD179, CD179a, CD179b, CD180, CD181, CD182, CD183, CD184, CD185, CD186, CDw186, CD187, CD188, CD189, CD190, CD191, CD192, CD193, CD194, CD195, CD196, CD197, CD198, CD199, CDw198, CDw199, CD200, CD201, CD202, CD202（a, b）, CD203, CD203c, CD204, CD205, CD206, CD207, CD208, CD209, CD210, CDw210a, CDw210b, CD211, CD212, CD213, CD213a1, CD213a2, CD214, CD215, CD216, CD217, CD218, CD218a, CD218, CD21b9, CD220, CD221, CD222, CD223, CD224, CD225, CD226, CD227, CD228, CD229, CD230, CD231, CD232, CD233, CD234, CD235, CD235a, CD235b, CD236, CD237, CD238, CD239, CD240, CD240ce, CD240d, CD241, CD242, CD243, CD244, CD245, CD246, CD247, CD248, CD249, CD250, CD251, CD252, CD253, CD254, CD255, CD256, CD257, CD258, CD259, CD260, CD261, CD262, CD263, CD264, CD265, CD266, CD267, CD268, CD269, CD270, CD271, CD272, CD273, CD274, CD275, CD276, CD277, CD278, CD279, CD281, CD282, CD283, CD284, CD285, CD286, CD287, CD288, CD289, CD290, CD291, CD292, CD293, CD294, CD295, CD296, CD297, CD298, CD299, CD300, CD300a, CD300b, CD300c, CD301, CD302, CD303, CD304, CD305, CD306, CD307, CD307a, CD307b, CD307c, CD307d, CD307e, CD307f, CD308, CD309, CD310, CD311, CD312, CD313, CD314, CD315, CD316, CD317, CD318, CD319, CD320, CD321, CD322, CD323, CD324, CD325, CD326, CD327, CD328, CD329, CD330, CD331, CD332, CD333, CD334, CD335, CD336, CD337, CD338, CD339, CD340, CD341, CD342, CD343, CD344, CD345, CD346, CD347, CD348, CD349, CD350, CD351, CD352, CD353, CD354, CD355, CD356, CD357, CD358, CD359, CD360, CD361, CD362, CD363, CD364, CD365, CD366, CD367, CD368, CD369, CD370, CD371, CD372, CD373, CD374, CD375, CD376, CD377, CD378, CD379, CD381, CD382, CD383, CD384, CD385, CD386, CD387, CD388, CD389, CRIPTO, CRIPTO, CR, CR1, CRGF, CRIPTO, CXCR5, LY64, TDGF1, 4-1BB, APO2, ASLG659, BMPR1B, 4-1BB, 5AC, 5T4 (Trophoblastic glycoprotein, TPBG, 5T4, Wnt-Activated Inhibitory Factor 1 or WAIF1), Adenocarcinoma antigen, AGS-5, AGS-22M6, Activin receptor-like kinase 1, AFP, AKAP-4, ALK, Alpha integrin, Alpha v beta6, Amino-peptidase N, Amyloid beta, Androgen receptor, Angiopoietin 2, Angiopoietin 3, Annexin A1, Anthrax toxin protective antigen, Anti-transferrin receptor, AOC3 (VAP-1), B7-H3, Bacillus anthracis anthrax, BAFF (B-cell activating factor), BCMA, B-lymphoma cell, bcr-abl, Bombesin, BORIS, C5, C242 antigen, CA125 (carbohydrate antigen 125, MUC16), CA-IX (or CAIX, carbonic anhydrase 9), CALLA, CanAg, Canis lupus familiaris IL31, Carbonic anhydrase IX, Cardiac myosin, CCL11(C-C motif chemokine 11), CCR4 (C-C chemokine receptor type 4), CCR5, CD3E (epsilon), CEA (Carcinoembryonic antigen), CEA-CAM3, CEACAM5 (carcino-embryonic antigen), CFD (Factor D), Ch4D5, Cholecystokinin 2 (CCK2R), CLDN18 (Claudin-18), Clumping factor A, cMet, CRIPTO, FCSF1R (Colony stimulating

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factor 1 receptor), CSF2 (colony stimulating factor 2, Granulocyte-macrophage colony-stimulating factor (GM-CSF)), CSP4, CTLA4 (cytotoxic T-lymphocyte-associated protein 4), CTAA16.88 tumor antigen, CXCR4, C-X-C chemokine receptor type 4, cyclic ADP ribose hydrolase, Cyclin B1, CYP1B1, Cytomegalovirus, Cytomegalovirus glycoprotein B, Dabigatran, DLL3 (delta-like-ligand 3), DLL4 (delta-like-ligand 4), DPP4 (Dipeptidyl-peptidase 4), DR5 (Death receptor 5), E. coli shiga toxin type-1, E. coli shiga toxin type-2, ED-B, EGFL7 (EGF-like domain-containing protein 7), EGFR, EGFRII, EGFRvIII, Endoglin, Endothelin B receptor, Endotoxin, EpCAM (epithelial cell adhesion molecule), EphA2, Episialin, ERBB2 (Epidermal Growth Factor Receptor 2), ERBB3, ERG (TMPRSS2 ETS fusion gene), Escherichia coli, ETV6-AML, FAP (Fibroblast activation protein alpha), FCGR1, alpha-Fetoprotein, Fibrin II, beta chain, Fibronectin extra domain-B, FOLR (folate receptor), Folate receptor alpha, Folate hydrolase, Fos-related antigen 1F protein of respiratory syncytial virus, Frizzled receptor, Fucosyl GM1, GD2 ganglioside, G-28 (a cell surface antigen glyvolipid), GD3 idiotype, GloboH, Glypican 3, N-glycolylneuraminic acid, GM3, GMCSF receptor α-chain, Growth differentiation factor 8, GP100, GPNMB (Trans-membrane glycoprotein NMB), GUCY2C (Guanylate cyclase 2C, guanylyl cyclase C(GC-C), intestinal Guanylate cyclase, Guanylate cyclase-C receptor, Heat-stable enterotoxin receptor (hSTAR)), Heat shock proteins, Hemagglutinin, Hepatitis B surface antigen, Hepatitis B virus, HER1 (human epidermal growth factor receptor 1), HER2, HER2/neu, HER3 (ERBB-3), IgG4, HGF/SF (Hepatocyte growth factor/scatter factor), HHGFR, HIV-1, Histone complex, HLA-DR (human leukocyte antigen), HLA-DR10, HLA-DRB , HMWMAA, Human chorionic gonadotropin, HNGF, Human scatter factor receptor kinase, HPV E6/E7, Hsp90, hTERT, ICAM-1 (Intercellular Adhesion Molecule 1), Idiotype, IGF1R (IGF-1, insulin-like growth factor 1 receptor), IGHE, IFN-γ, Influenza hemagglutinin, IgE, IgE Fc region, IGHE, interleukins (comprising IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-6R, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, IL-17, IL-17A, IL-18, IL-19, IL-20, IL-21, IL-22, IL-23, IL-27, or IL-28), IL31RA, ILGF2 (Insulin-like growth factor 2), Integrins (α4, $\alpha_{IIb}\beta_3$, αvβ3, $\alpha_4\beta_7$, α5β1, α6β4, α7β7, αIIβ3, α5β5, αvβ5), Interferon gamma-induced protein, ITGA2, ITGB2, KIR2D, Kappa Ig, LCK, Le, Legumain, Lewis-Y antigen, LFA-1 (Lymphocyte function-associated antigen 1, CD11a), LHRH, LINGO-1, Lipoteichoic acid, LIV1A, LMP2, LTA, MAD-CT-1, MAD-CT-2, MAGE-1, MAGE-2, MAGE-3, MAGE A1, MAGE A3, MAGE 4, MART1, MCP-1, MIF (Macrophage migration inhibitory factor, or glycosylation-inhibiting factor (GIF)), MS4A1 (membrane-spanning 4-domains subfamily A member 1), B7H3, B7H4, MSLN (mesothelin), MUC1(Mucin 1, cell surface associated (MUC1) or polymorphic epithelial mucin (PEM)), MUC1-KLH, MUC16 (CA125), MCP1(monocyte chemotactic protein 1), MelanA/MART1, ML-IAP, MPG, MS4A1 (membrane-spanning 4-domains subfamily A), MYCN, Myelin-associated glycoprotein, Myostatin, NA17, NARP-1, NCA-90 (granu-

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locyte antigen), Nectin-4 (ASG-22ME), NGF, Neural apoptosis-regulated proteinase 1, NOGO-A, Notch receptor, Nucleolin, Neu oncogene product, NY-BR-1, NY-ESO-1, OX-40, OxLDL (Oxidized low-density lipoprotein), OY-TES1, P21, p53 nonmutant, P97, Page4, PAP, Paratope of anti-(N-glycolylneuraminic acid), PAX3, PAX5, PCSK9, PDCD1 (PD-1, Programmed cell death protein 1), PDGF-Rα (Alpha-type platelet-derived growth factor receptor), PDGFR-β, PDL-1, PLAC1, PLAP-like testicular alkaline phosphatase, Platelet-derived growth factor receptor beta, Phosphate-sodium co-transporter, PMEL 17, Polysialic acid, Proteinase3 (PR1), Prostatic carcinoma, PS (Phosphatidyl-serine), Prostatic carcinoma cells, Pseudomonas aeruginosa, PSMA, PSA, PSCA, Rabies virus glycoprotein, RHD (Rh polypeptide 1 (RhPI)), Rhesus factor, RANKL, RhoC, Ras mutant, RGS5, ROBO4, Respiratory syncytial virus, RON, ROR1, Sarcoma translocation breakpoints, SART3, Sclerostin, SLAMF7 (SLAM family member 7), Selectin P, SDC1 (Syndecan 1), sLe(a), Somatome-din C, SIP (Sphingosine-1-phosphate), Somatostatin, Sperm protein 17, SSX2, STEAP1 (six-transmembrane epithelial antigen of the prostate 1), STEAP2, STn, TAG-72 (tumor associated gly-coprotein 72), Survivin, T-cell receptor, T cell transmembrane protein, TEM1 (Tumor endothelial marker 1), TENB2, Tenascin C (TN-C), TGF-α, TGF-β (Transforming growth factor beta), TGF-β1, TGF-β2 (Transforming growth factor-beta 2), Tie (CD202b), Tie2, TIM-1 (CDX-014), Tn, TNF, TNF-α, TNFRSF8, TNFRSF10B (tumor necrosis factor receptor superfamily member 10B), TNFRSF-13B (tumor necrosis factor receptor superfamily member 13B), TPBG (trophoblast glyco-protein), TRAIL-R1 (Tumor necrosis apoptosis Inducing ligand Receptor 1), TRAILR2 (Death receptor 5 (DR5)), tumor-associated calcium signal transducer 2, tumor specific glycosylation of MUC1, TWEAK receptor, TYRP1(glycoprotein 75), TRP-1 (Trop1), TRP-2 (Trop2), Tyrosinase, VCAM-1, VEGF, VEGF-A, VEGF-2, VEGFR-1, VEGFR2, or vimentin, WT1, XAGE 1, or cells expressing any insulin growth factor receptors, or any epidermal growth factor receptors.

12. The process according to Claim 4, wherein the conjugate, in which the drugs are mainly conjugated to sites of disulfide bond between heavy-light chains (Fab) of an antibody has one of the structures of C-25, C-30, C-36, C-45, C-51, C-58a, C-68a, C-68b, C-68c, C-72a, C-72b, C-73, C-83, C-88, C-91, C-96, C-102, C-115, C-120, C-121, C-126, C-130, C-137, C-140, C-152 C-157, C-168, C-178, C-181a, C-181b, C-181c, C-181d, C-190, C-192 C-195, C-202, C-209, C-215, C-221, C-221b, C-227, C-233, C-241, C-255, C-258, C-267, C-277, C-283, C-284, C-290, C-295, C-300, C-306, C-309, C-310, C-312, C319, C-322, C-326, C-328, C-330, C-334, C-335, C-336, C-337, C-338, C-361, C-362, C-372, C-373, C-374, C-375, C-384, C-385, C-390, C-396, C-399, C-400, C-402, C-406, C-409, C-416, C-417, C-427, C-432, C-437, C-441, C-450, C-455, C-462, C-464, C-470, C-478, C-481, C-484, C-487, C-488, C-494, C-498, C-499, C-500, C-501, C-504, C-508, C-511, C-514, C-518, C-519, C-521, C-527, C-531, C-532, C-537, C-542, C-543, C-544, C-546, C-550, C-553, C-560, C-561,

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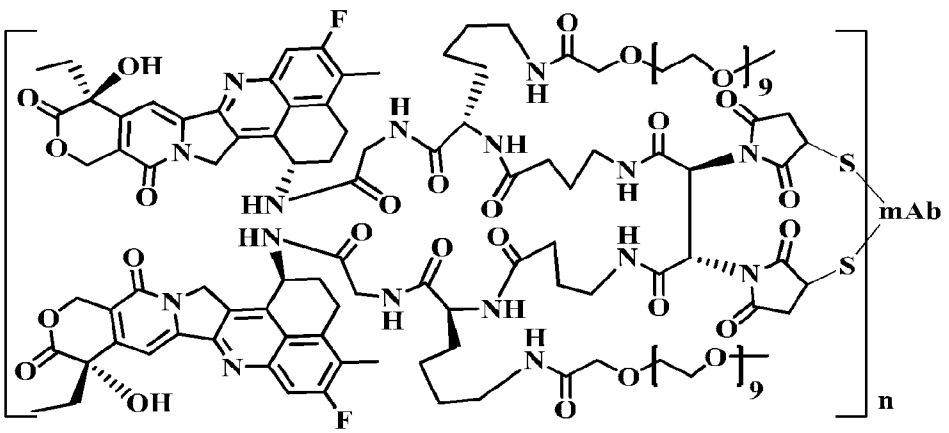
C-562, C-565, C-570, C-573, C-577, C-581, C-582, C-587, C-591, C-595, C-599, C-602a, C-602b, C-602c, C-602d, C-603a, C-603b, C-604, C-606, C-608, C-609a, C-609b, C-609c, C-610a, C-610b, C-610c, C-610d, C-610e, C-610f, C-610g, C-611a, C-611b, C-611c, C-611d, C-612, C-613, C-614, C-615, C-616, C-617, C-618, C-619, C-620, C-621, C-622, C-623, C-624, C-625, C-626, C-627, C-628, C-629, C-630, C-631, C-632, C-633, C-634, C-635, C-636, C-637, C-639, C-640, C-641, C-642, C-643, C-644, C-645, C-646, C-647, C-648, C-649, C-650, C-651, C-652, C-653, C-654, C-655, C-656, C-657, C-658, C-659, C-660, C-661, C-662, C-663, C-664, C-665, C-666, C-667, C-668, C-669, C-670, C-671, C-672, C-673, C-674, C-675, C-676, C-677, C-678, C-679, C-680, C-681, C-682, C-683, C-684, C-685, C-686, C-687, C-688, C-689, C-690, C-691, C-692, C-693, C-694, C-695, C-696, C-697, C-698, C-699, C-700, C-701, C-702, C-703, C-704, C-705, C-706, C-707, C-708, C-709, C-710, as illustrated below:



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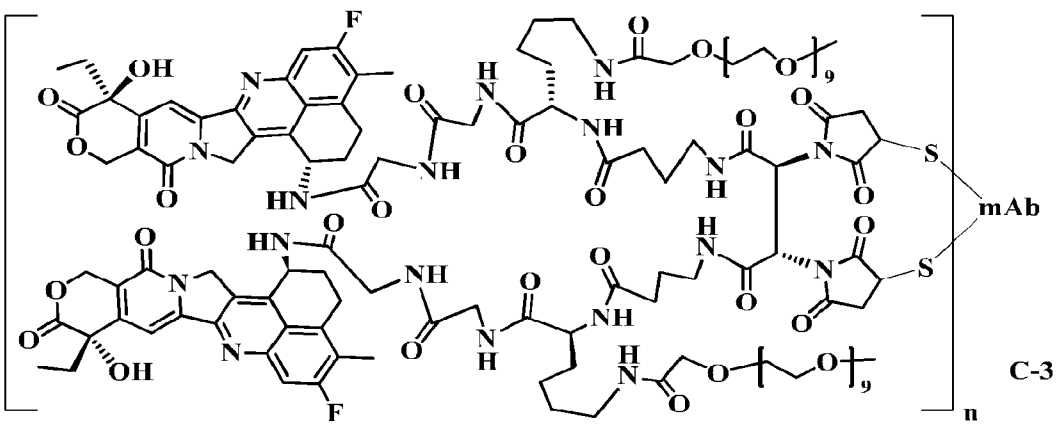

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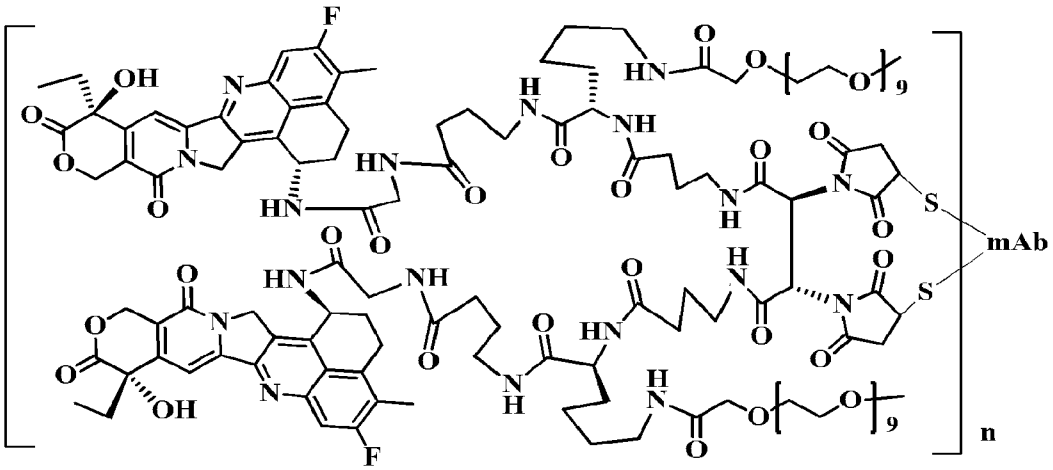

C-36

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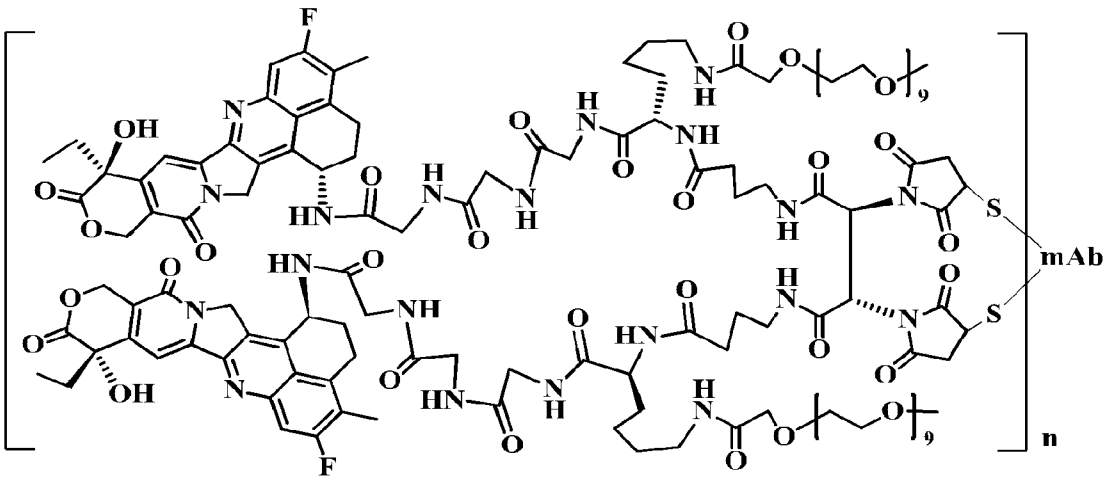

C-45

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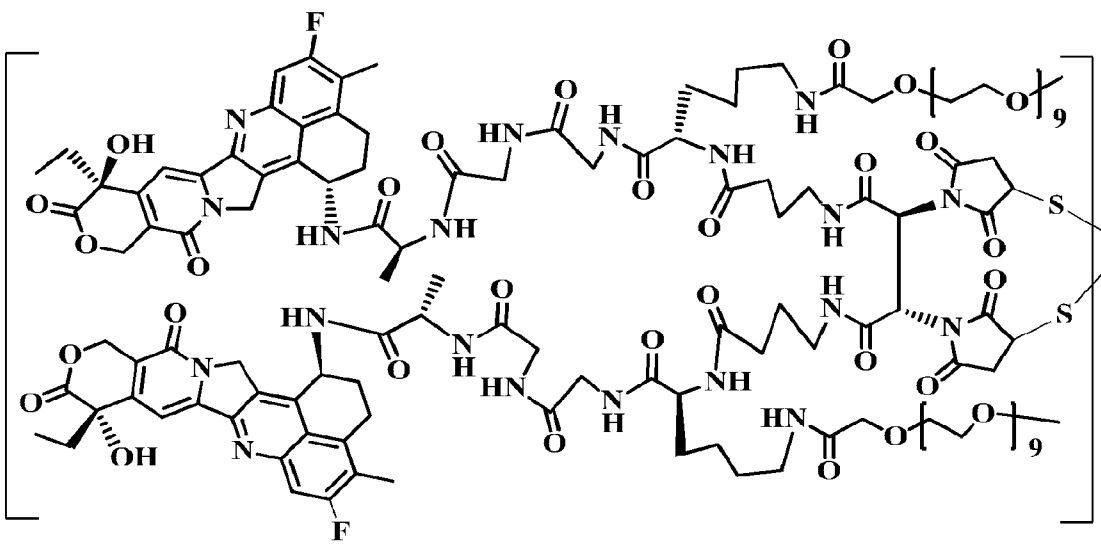

C-51

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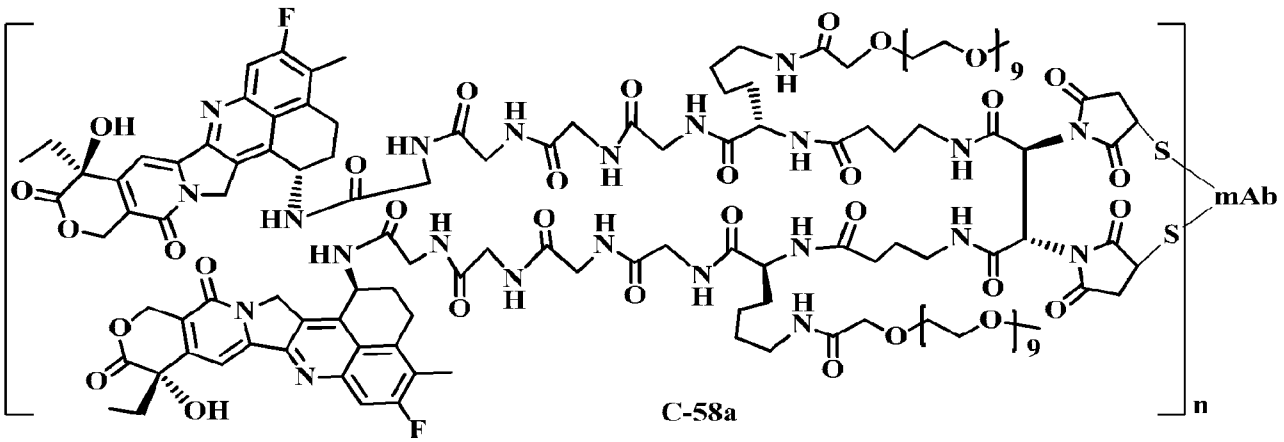
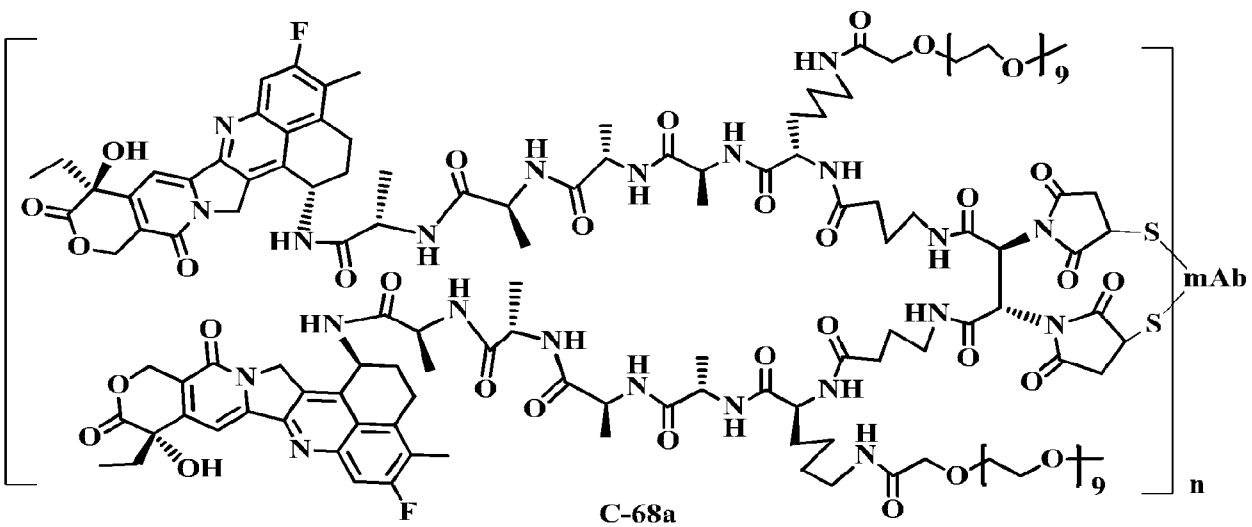
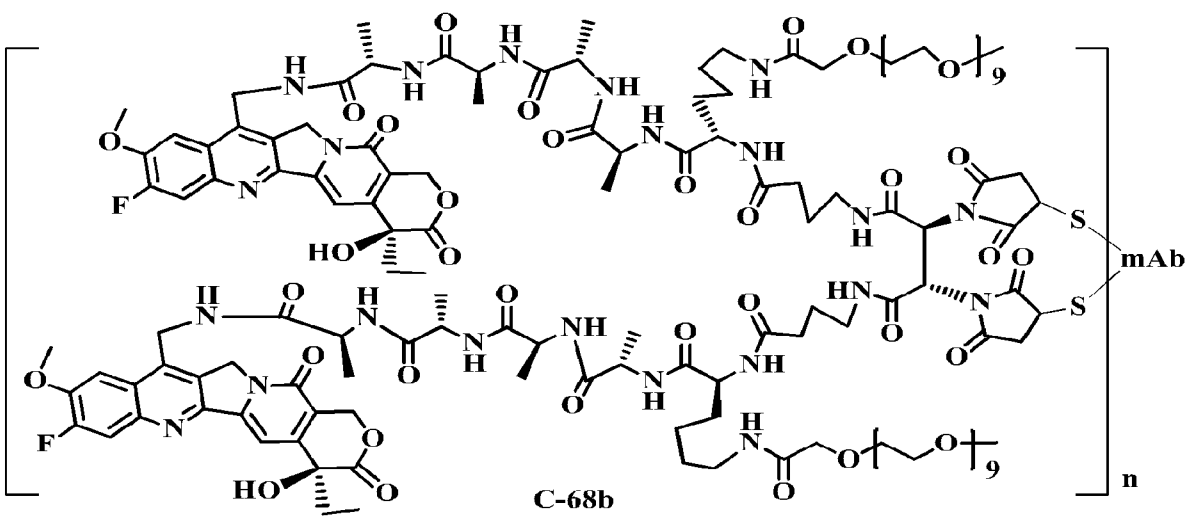


C-58a ,



C-68a



C-68b

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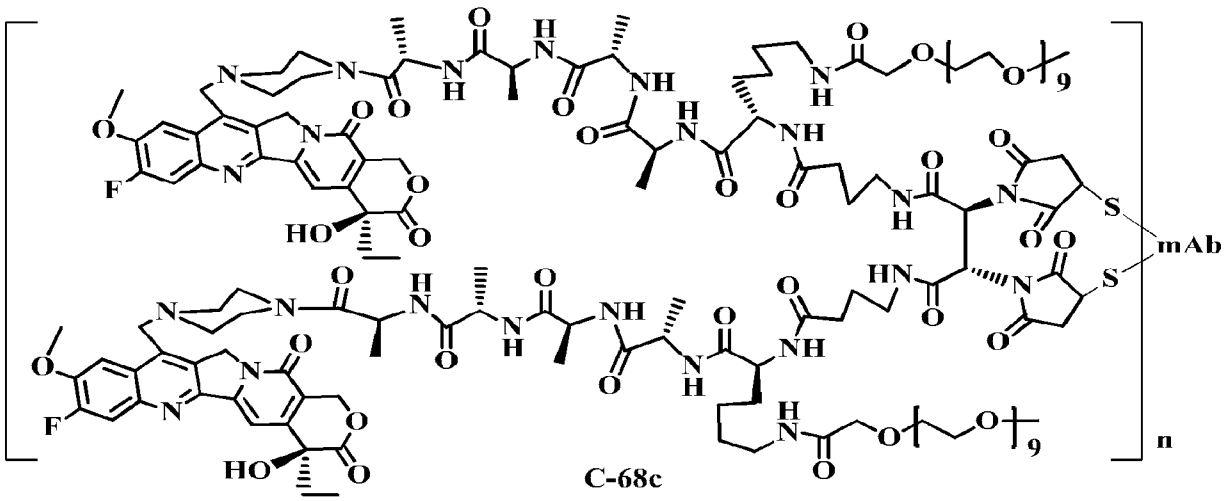

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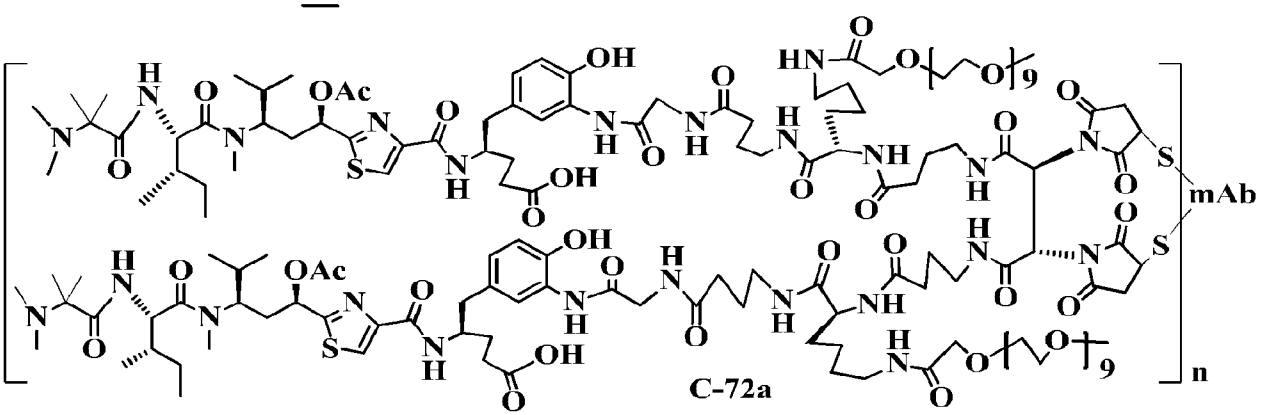
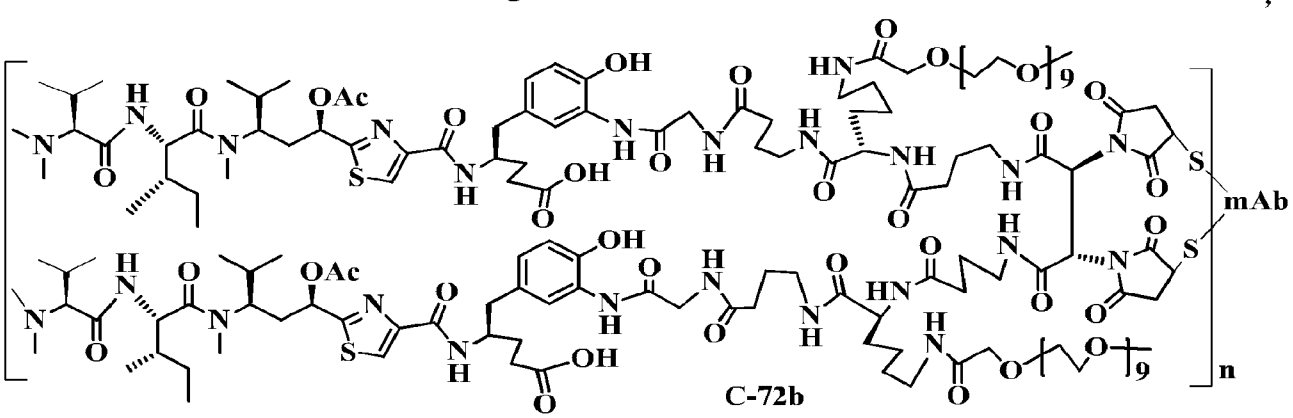


C-72a ,



C-72b ,

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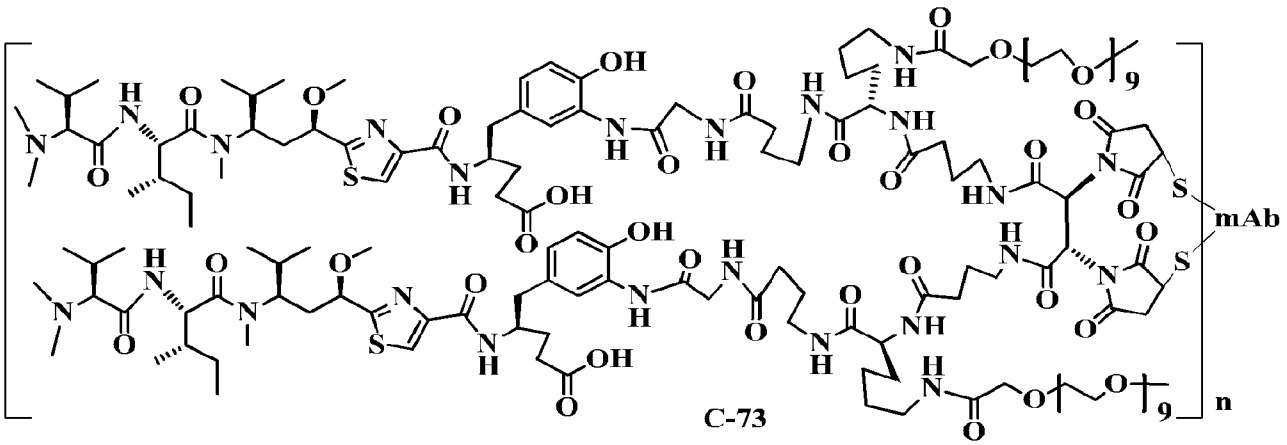

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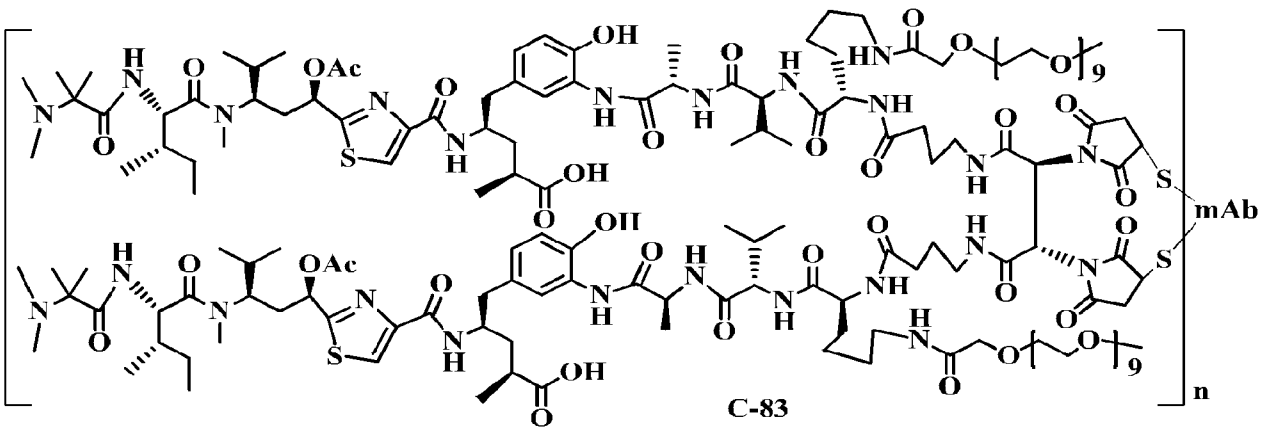

C-83

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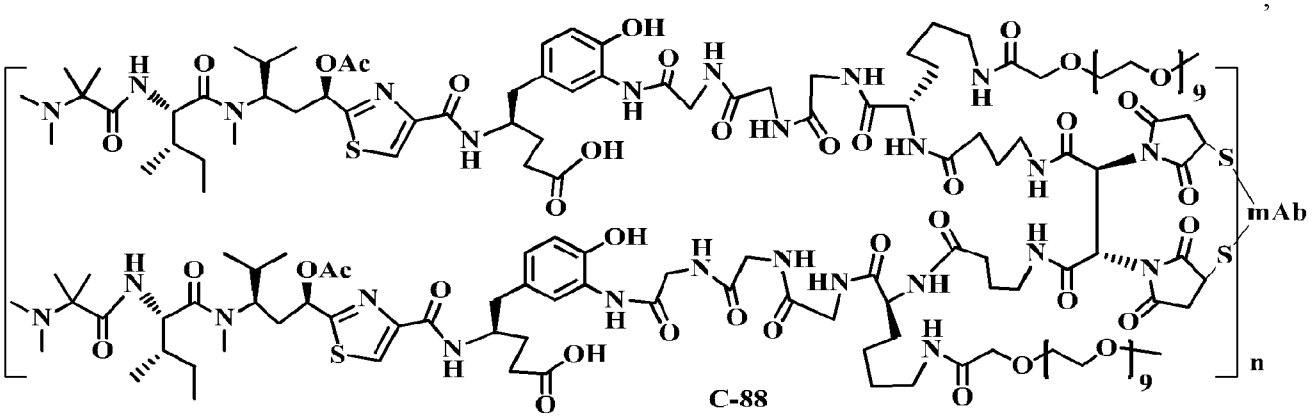

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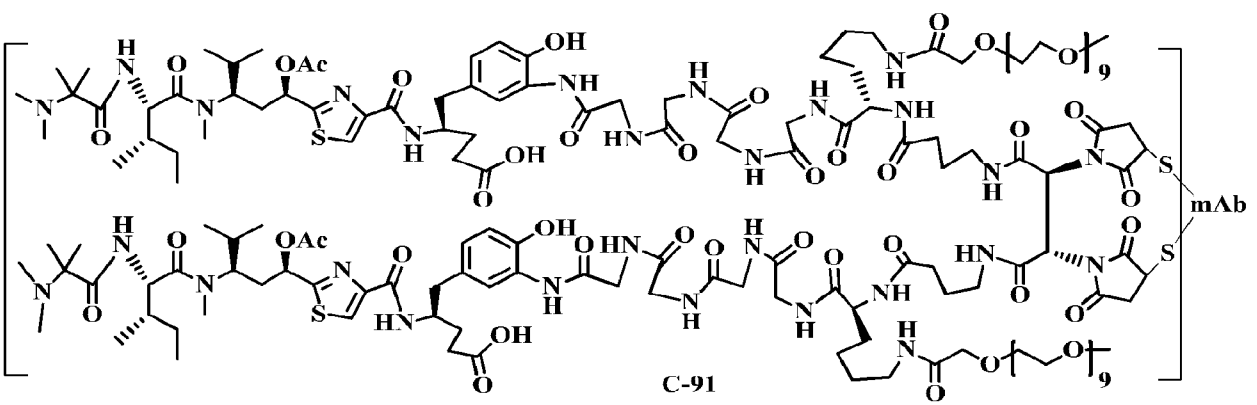

C-91

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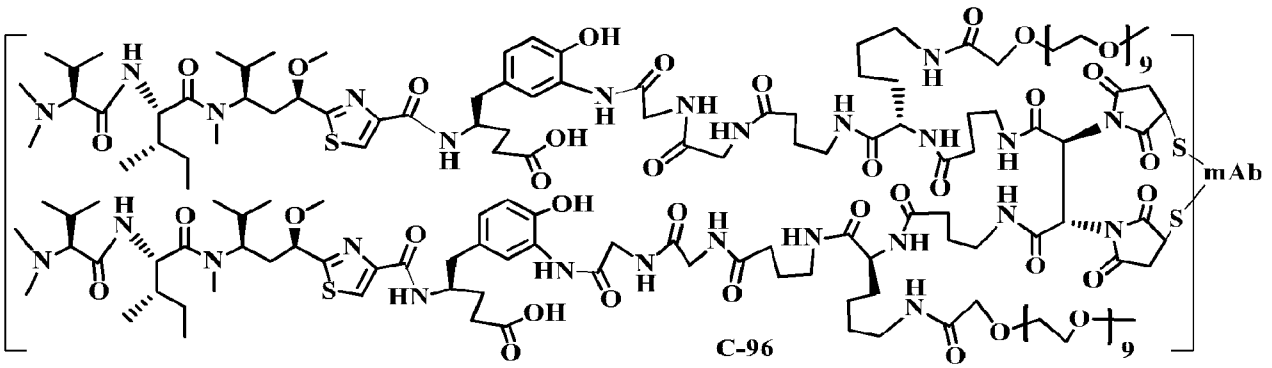
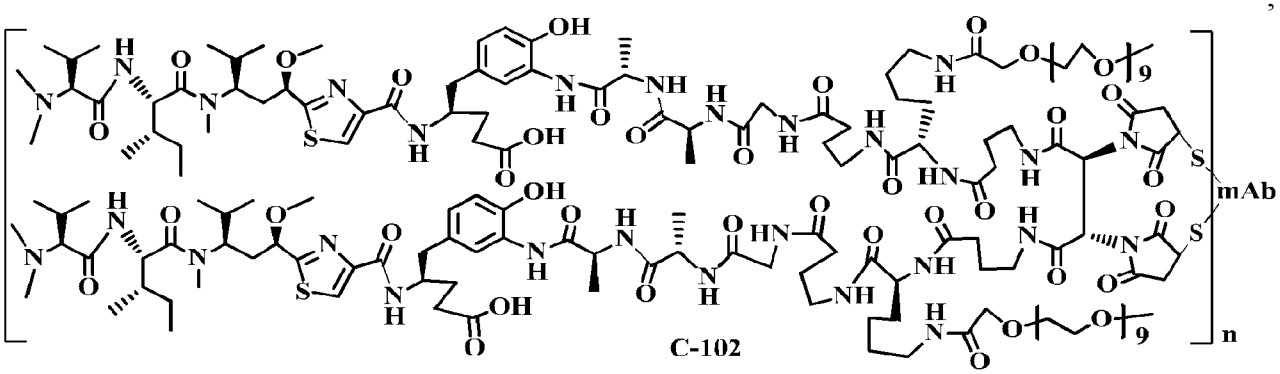
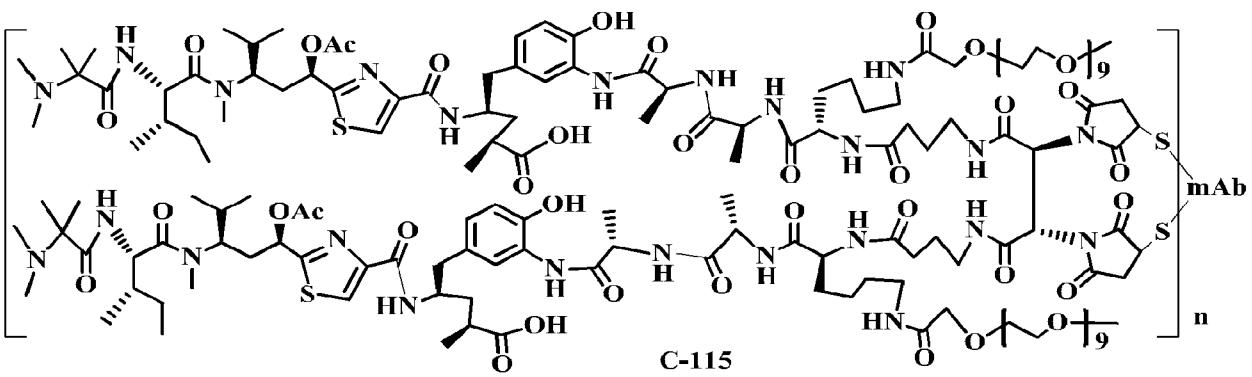


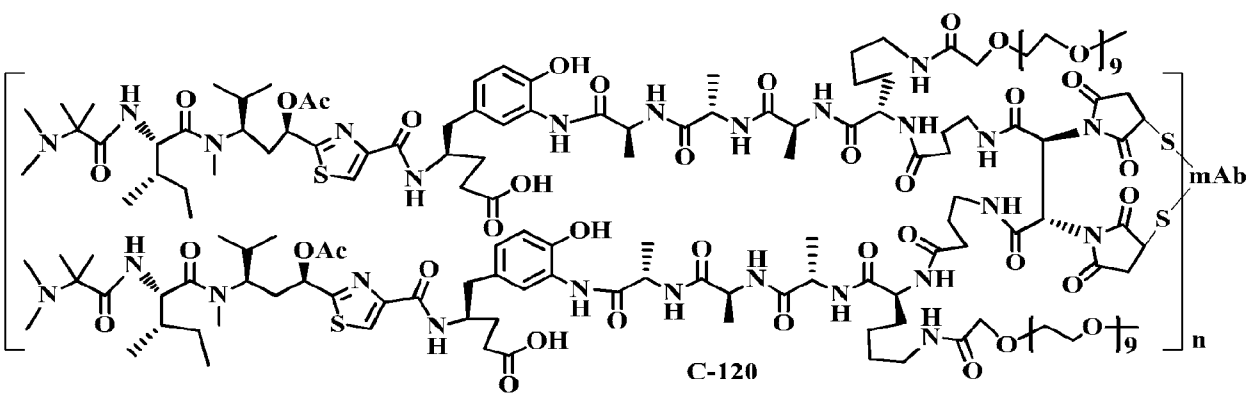
C-96 ,



C-102 ,



C-115 ,



C-120 ,

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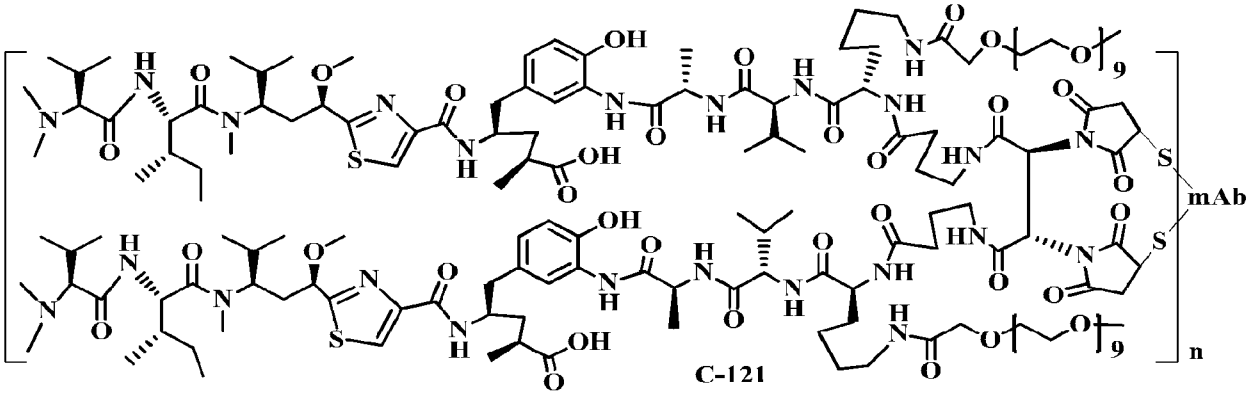

C-121

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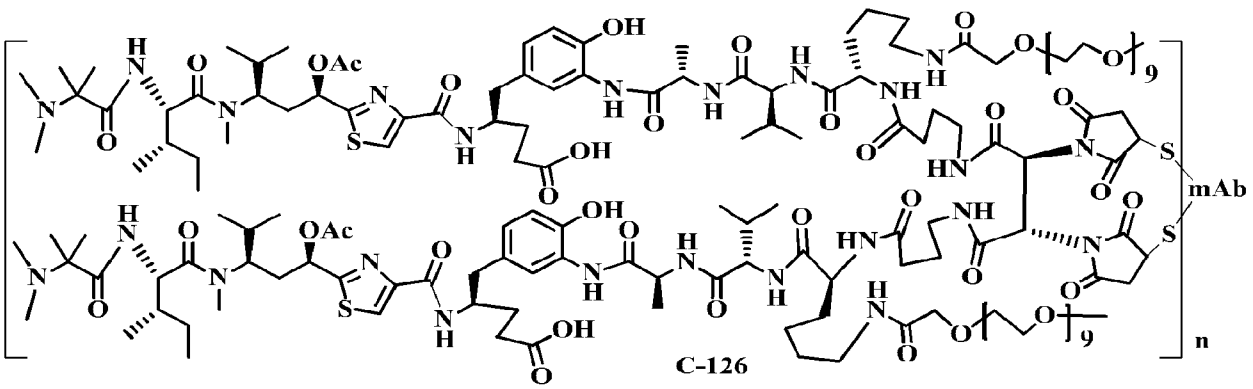

C-126

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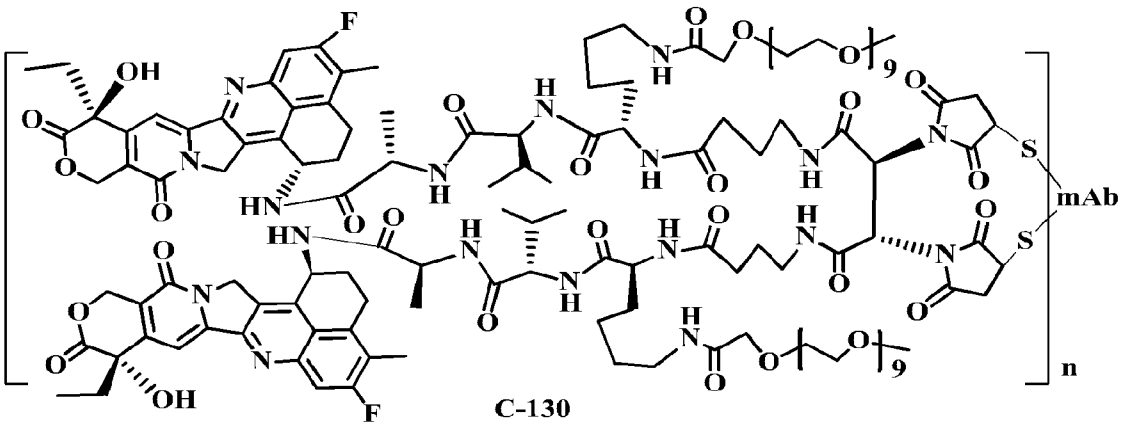

C-130

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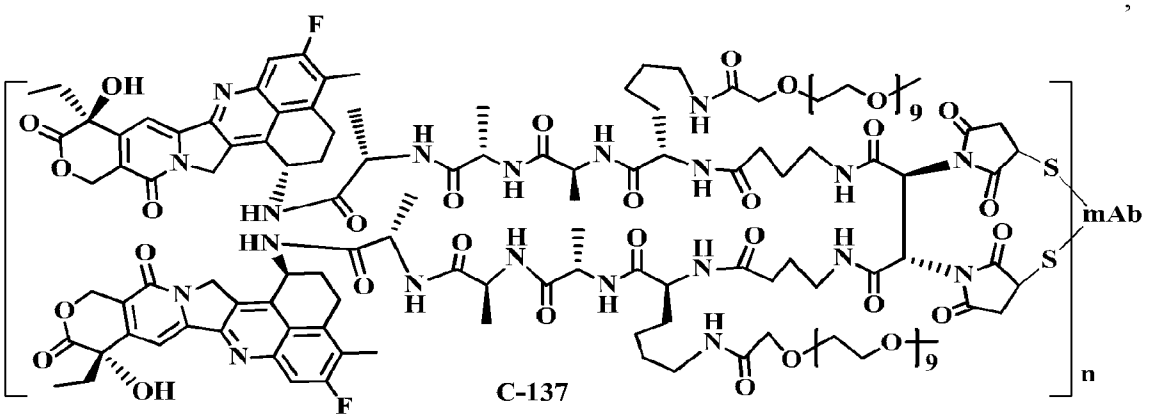

C-137

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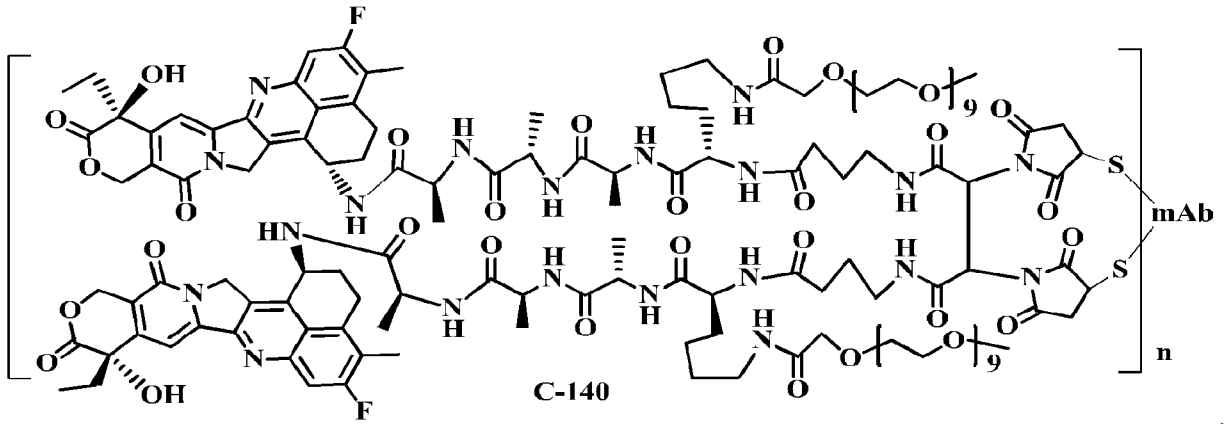
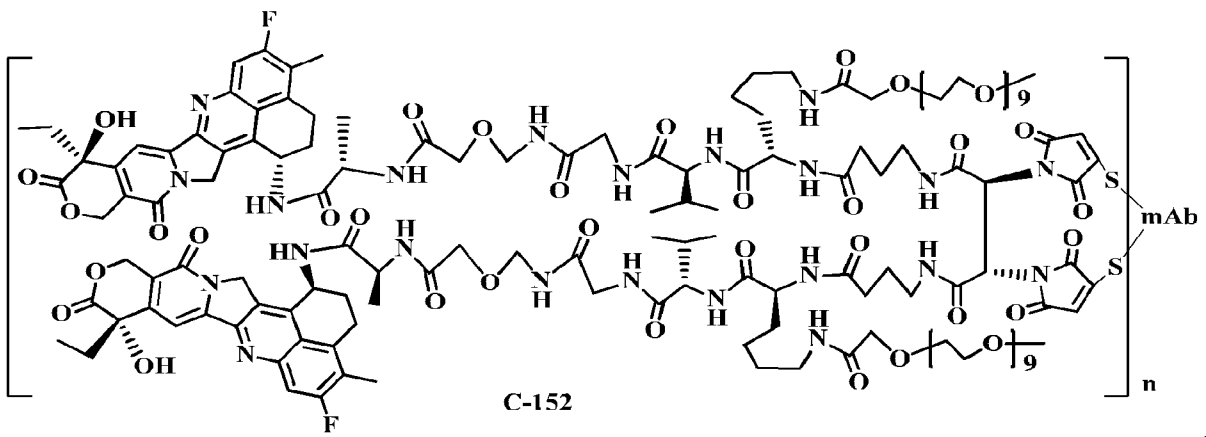
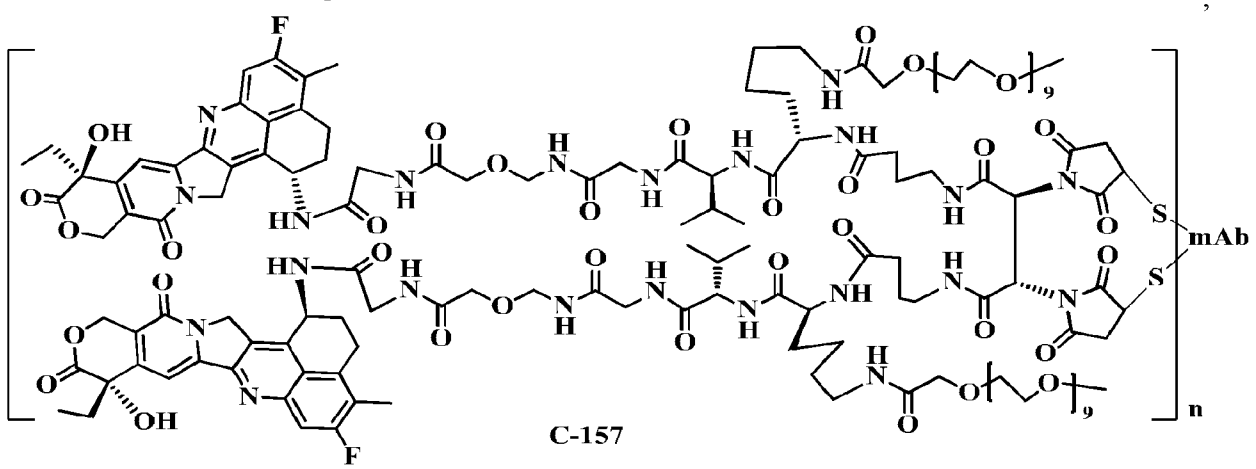


C-140 ,



C-152 ,



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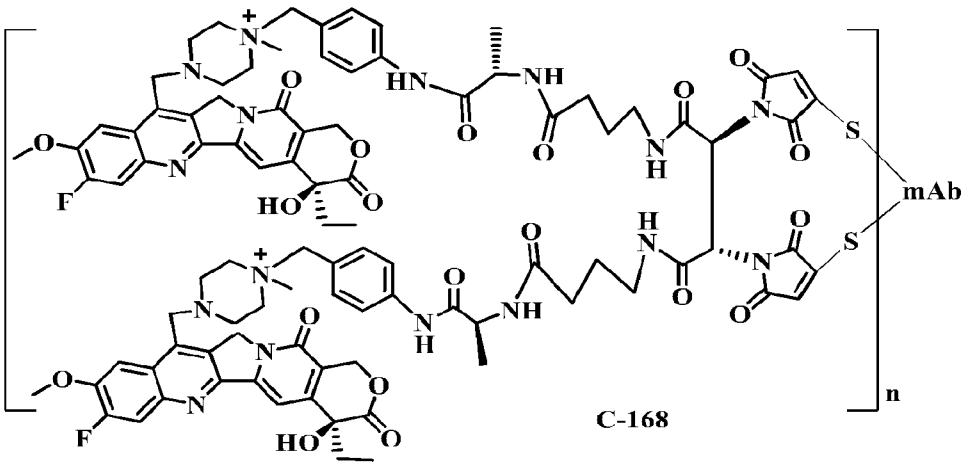
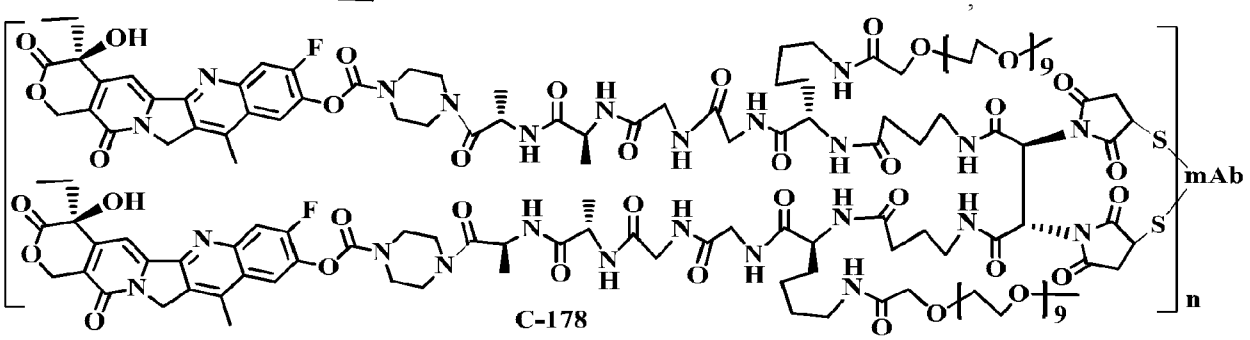
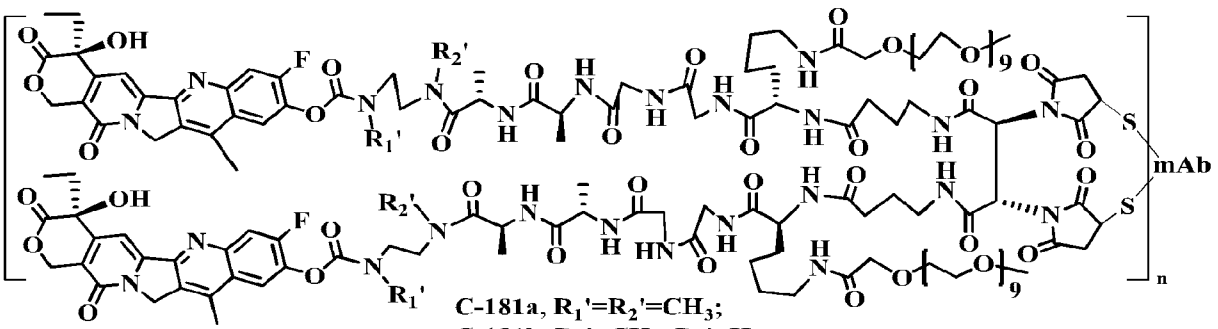
CA 03236754 2024-4-30



C-168



C-178



C-181a, $R_1'=R_2'=CH_3$;
C-181b, $R_1'=CH_3$, $R_2'=H$;
C-181c, $R_1'=H$, $R_2'=CH_3$;
C-181d, $R_1'=R_2'=H$;

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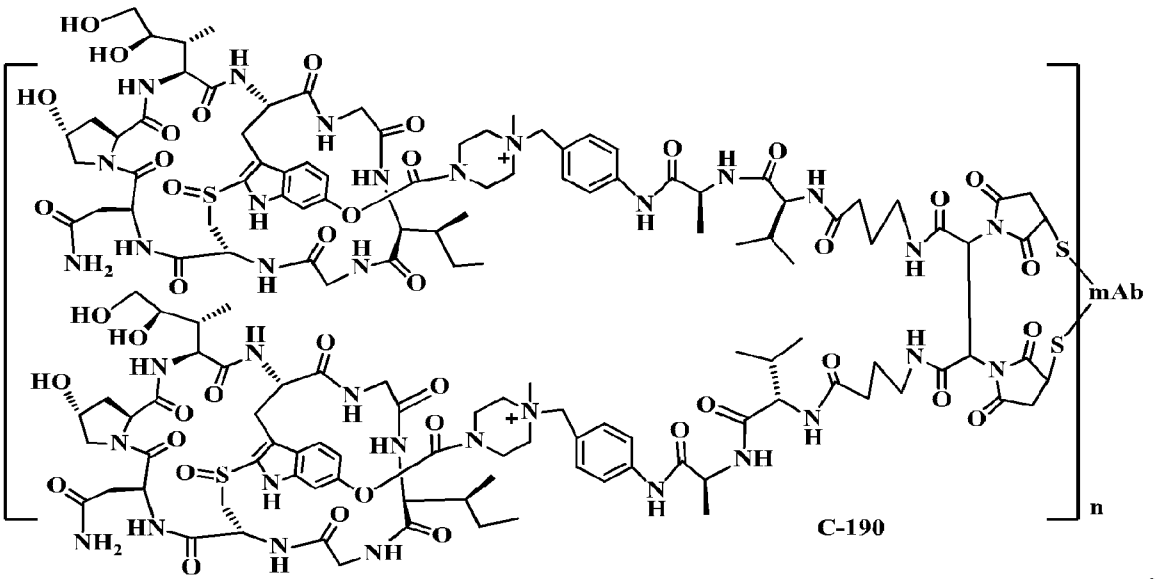

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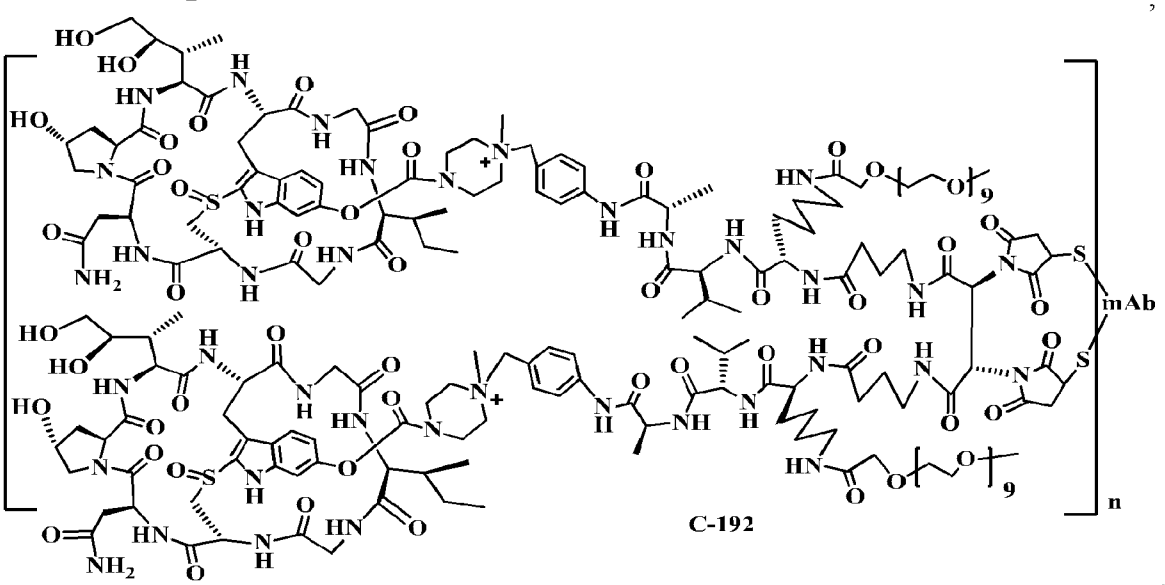

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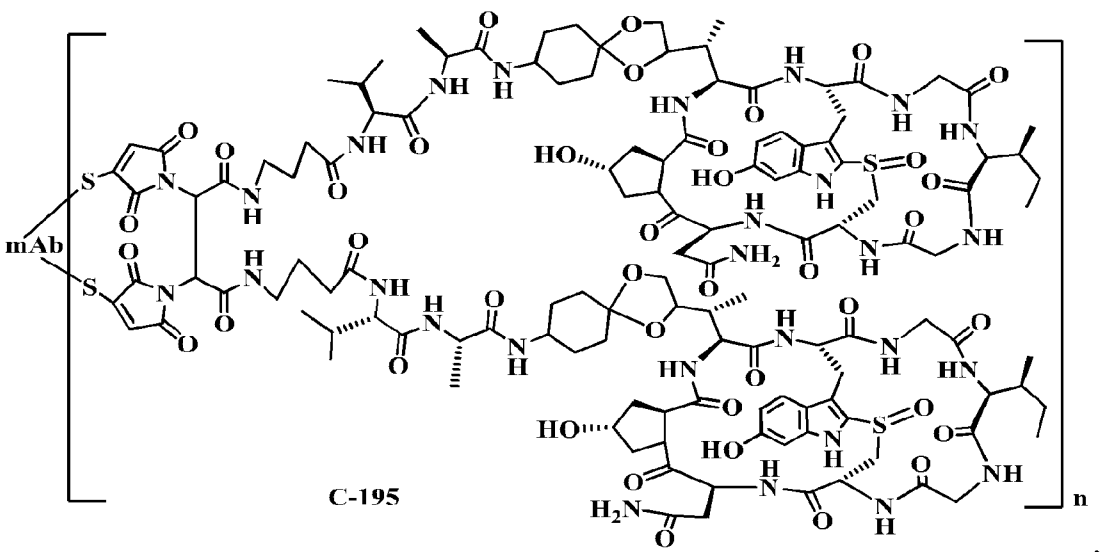

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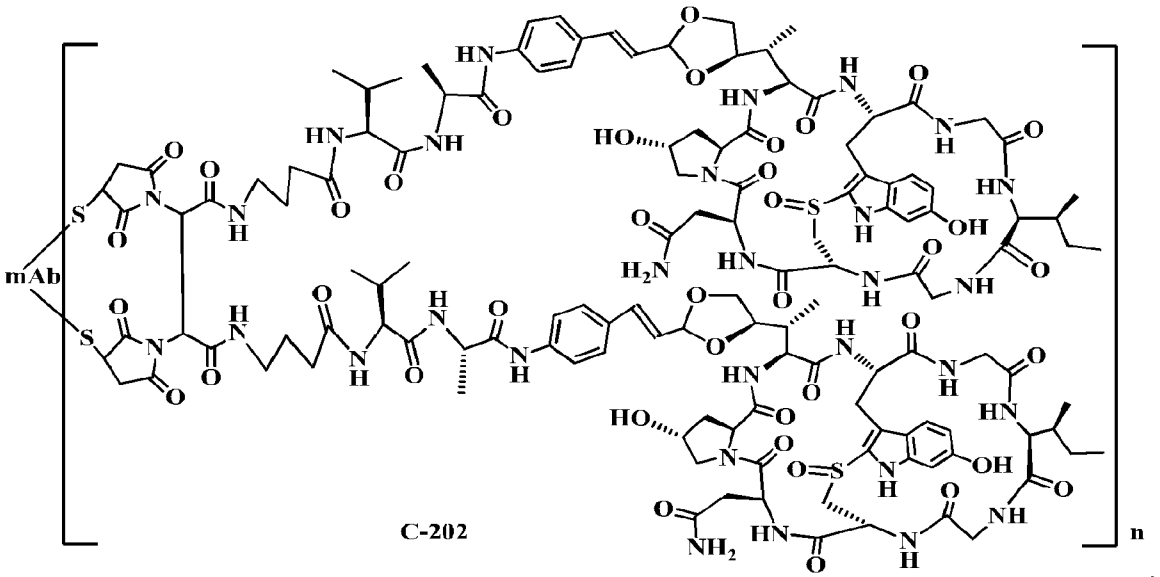
mAb
C-202
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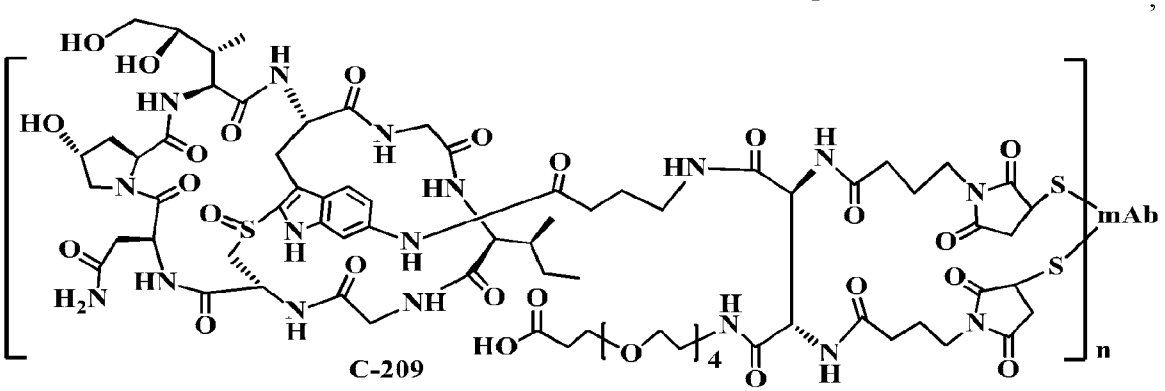
C-209
mAb
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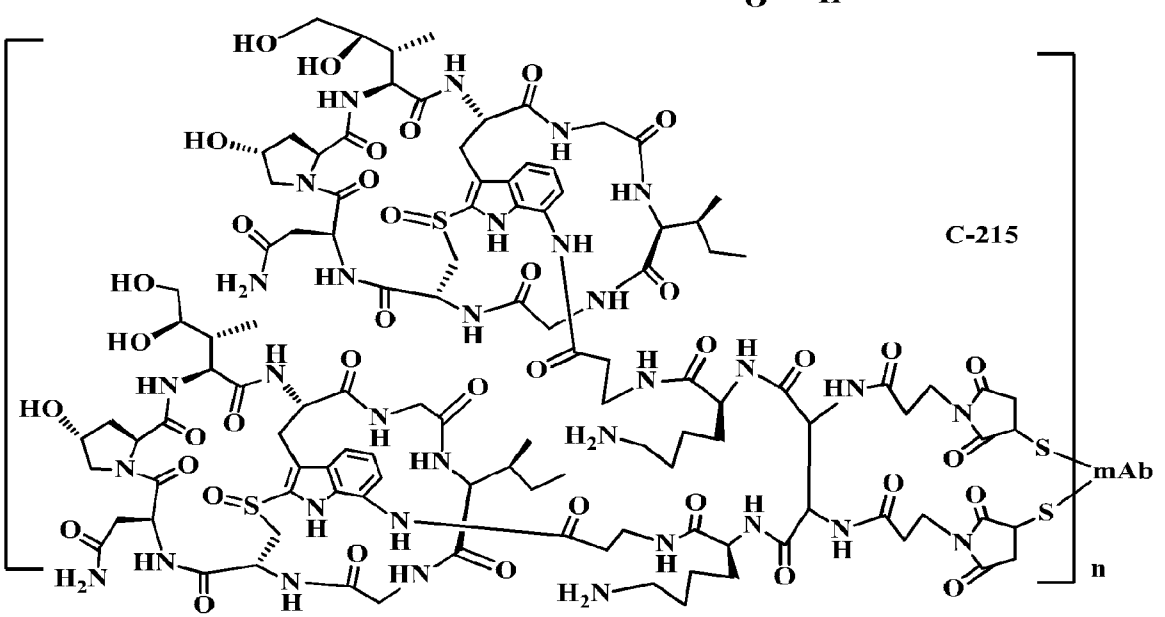
C-215
mAb
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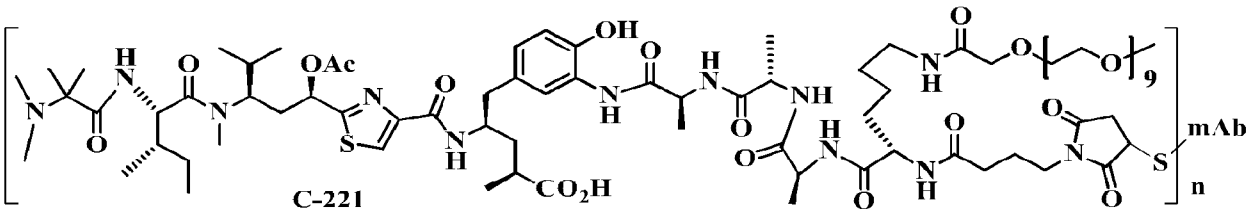
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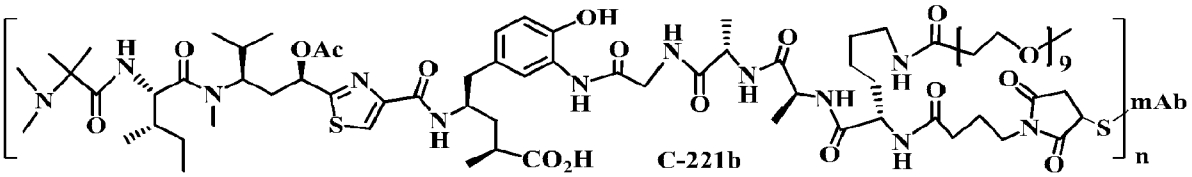
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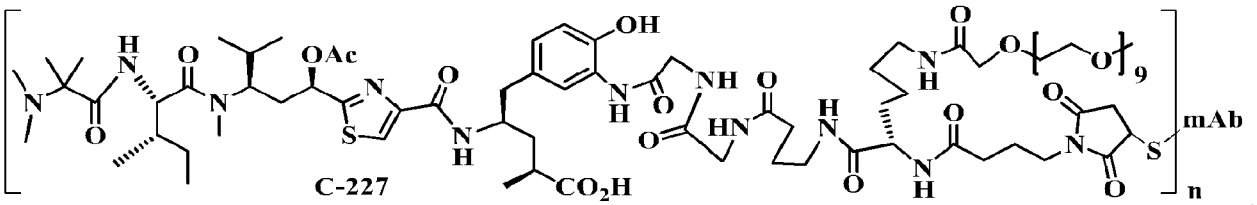
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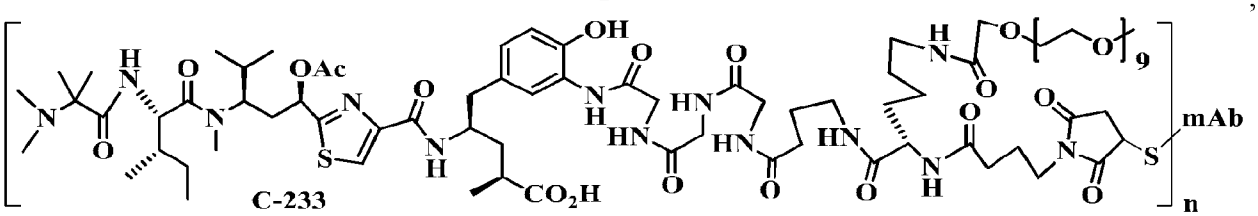
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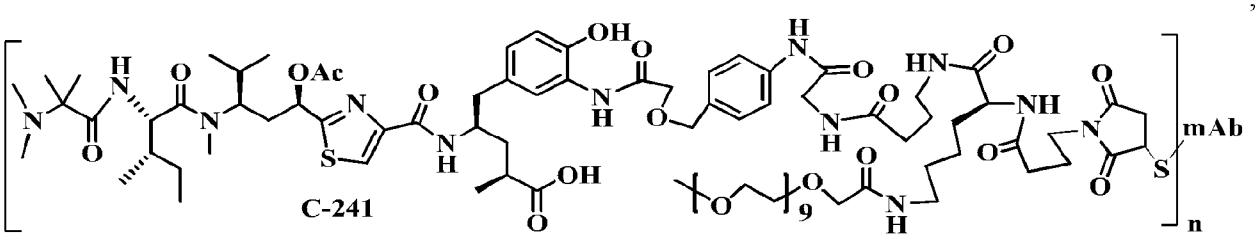
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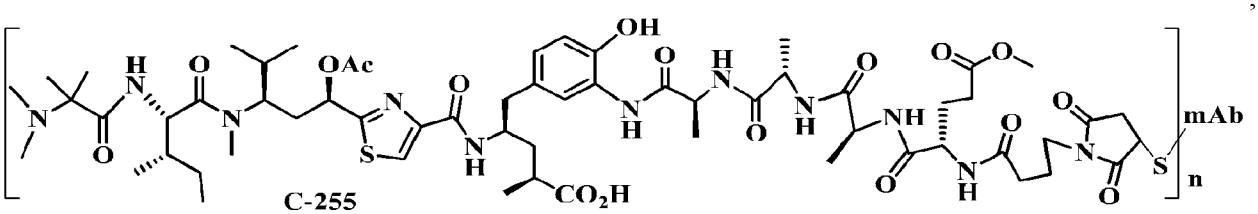
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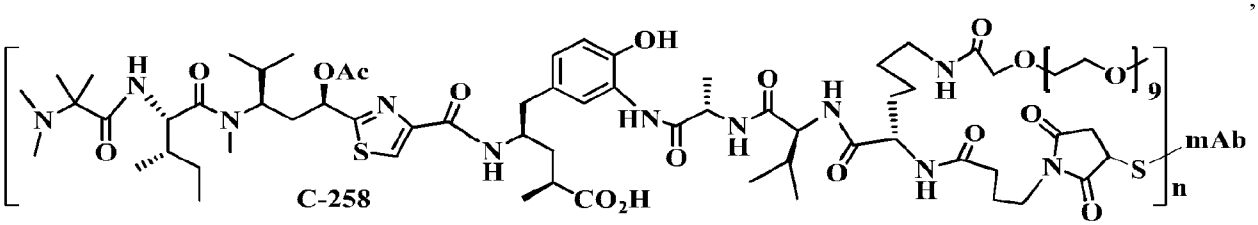
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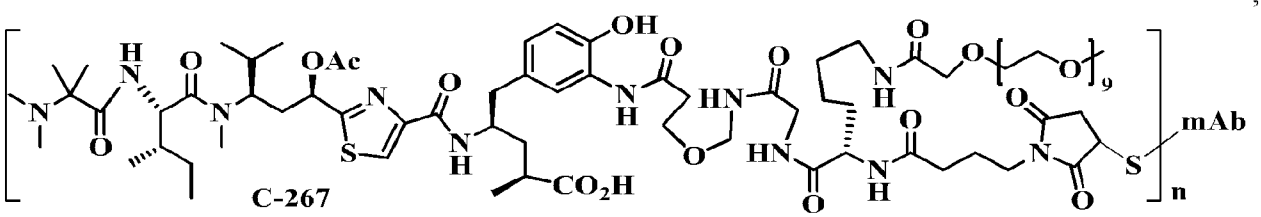
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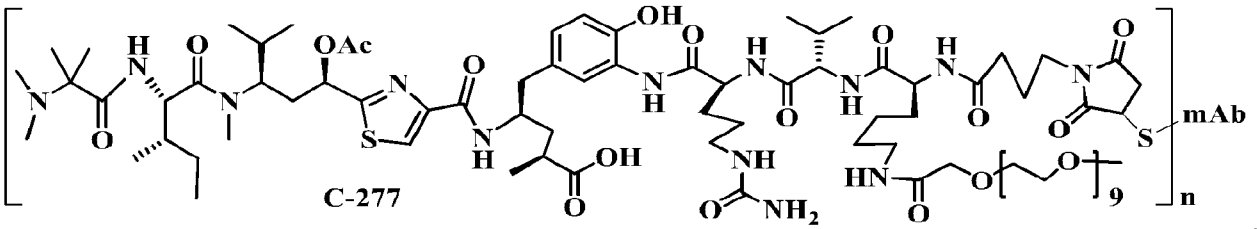
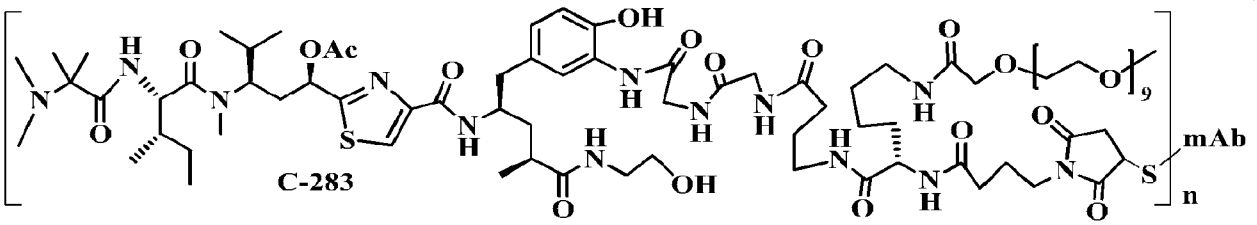
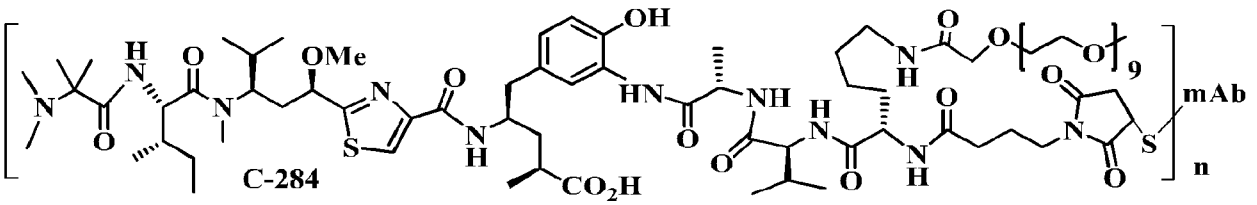


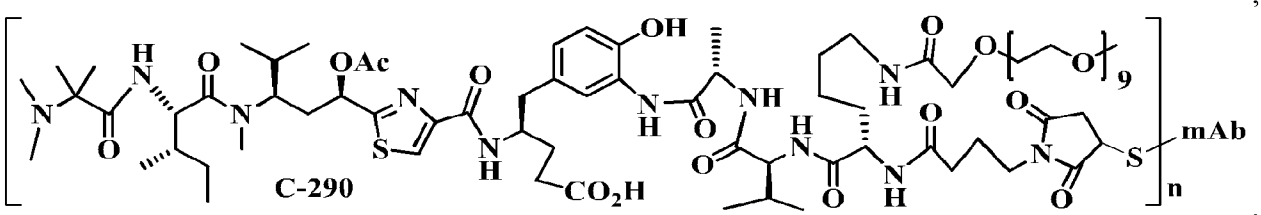
C-277 ,



C-283 ,



C-284 ,



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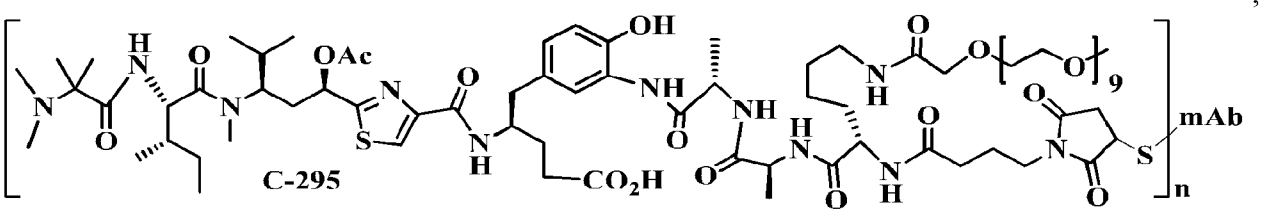

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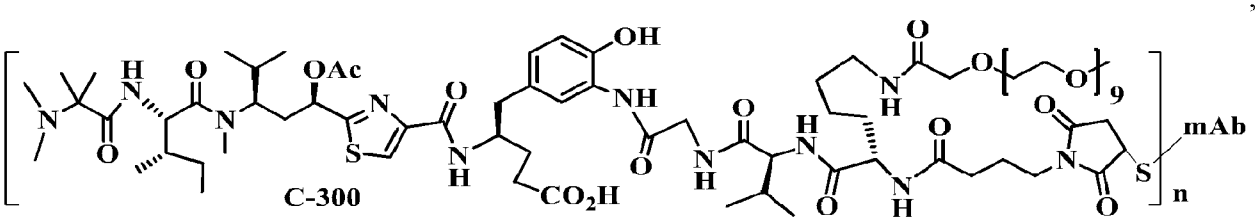
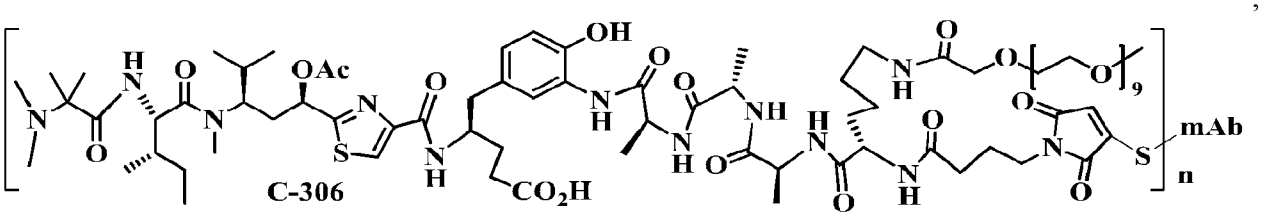


C-300 ,



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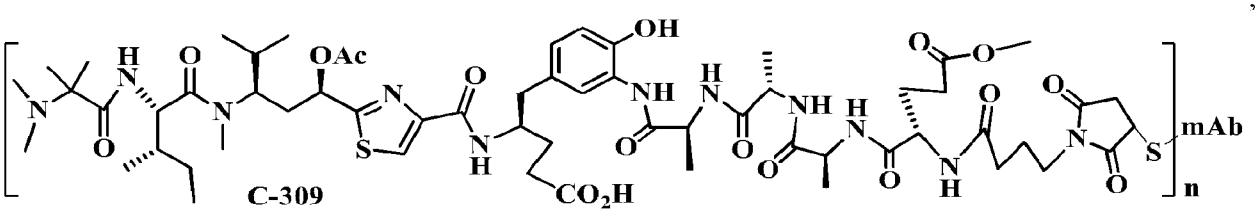
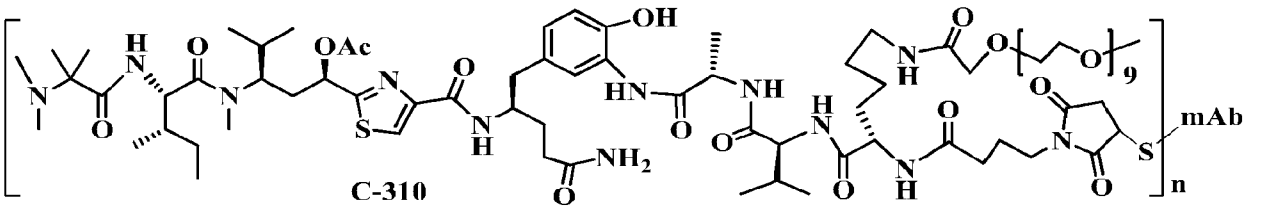
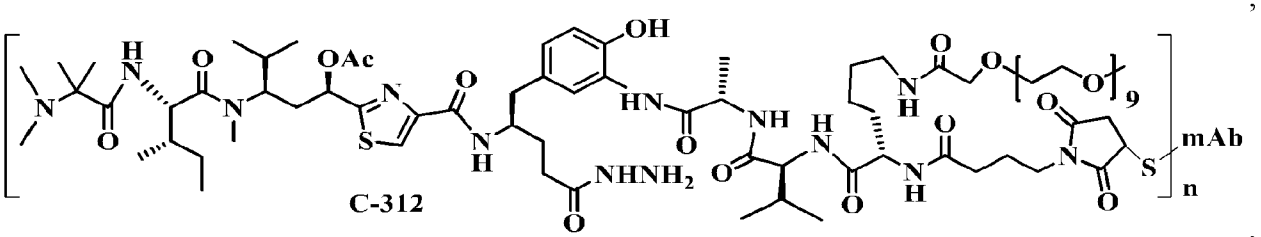


C-309 ,

CA 03236754 2024-4-30



C-310 ,



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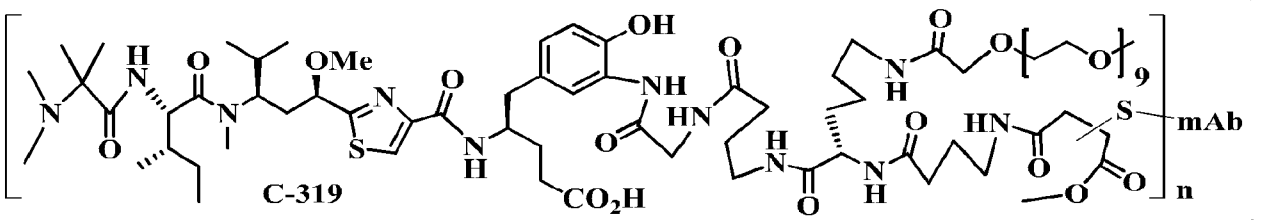
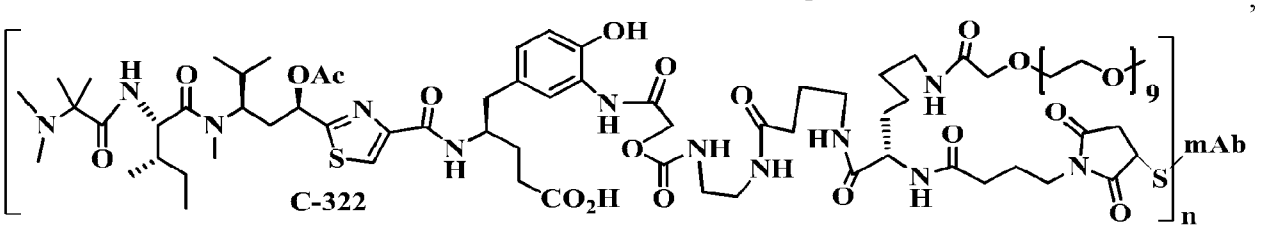
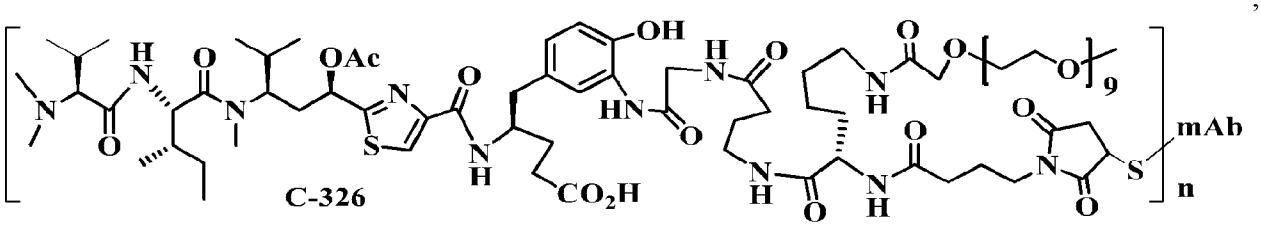


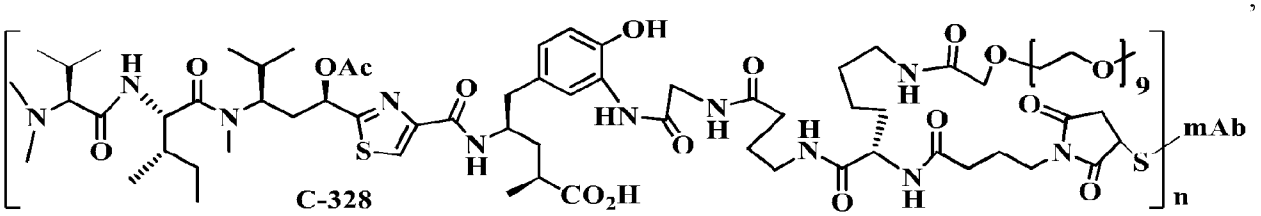
C-319 ,



C-322 ,



C-326 ,



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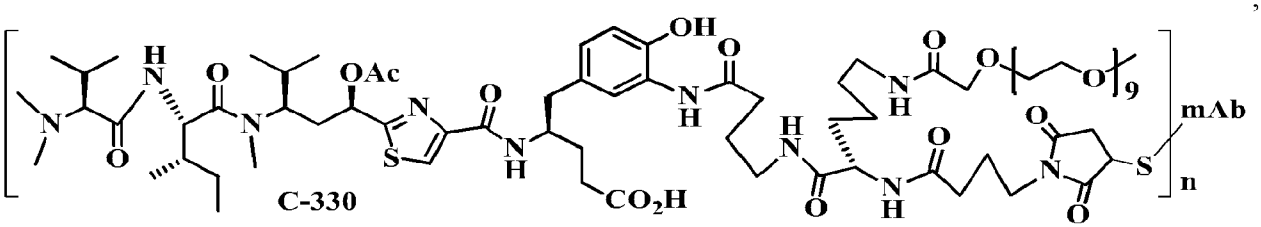

C-330 ,

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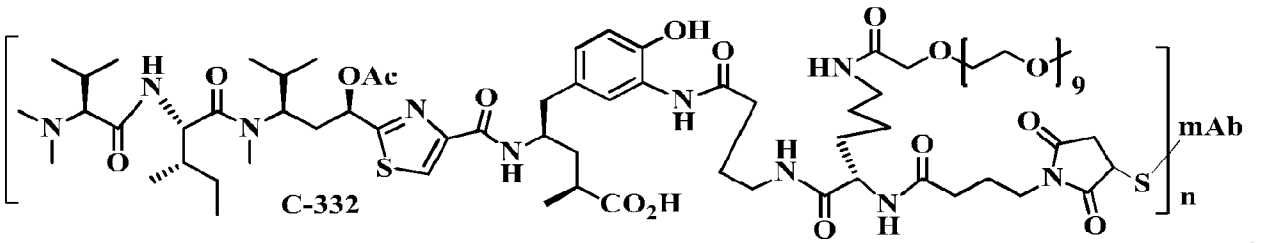

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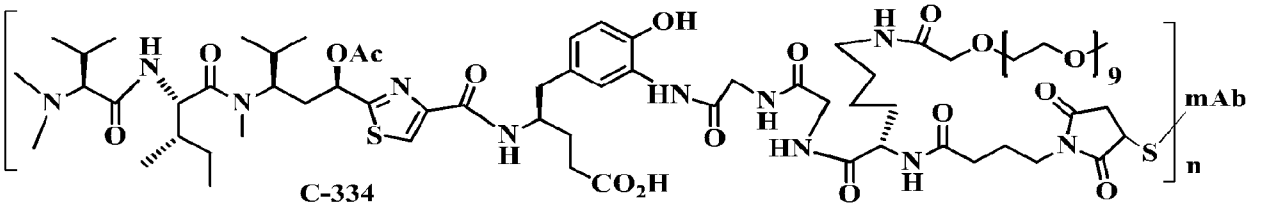

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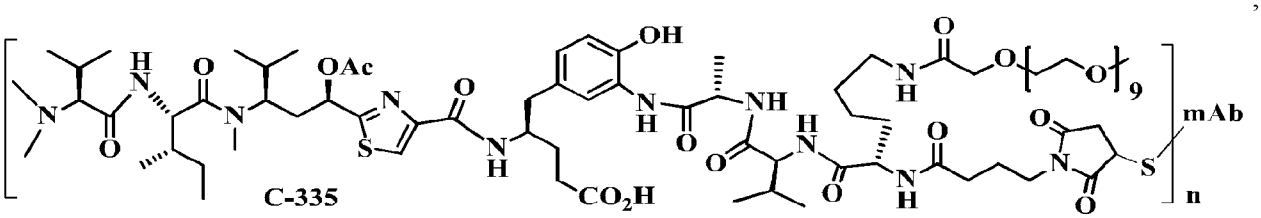

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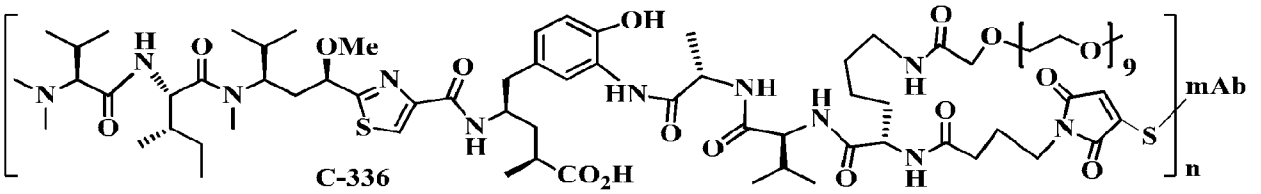

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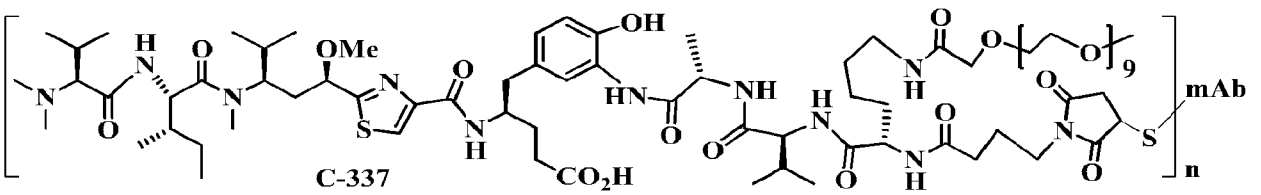

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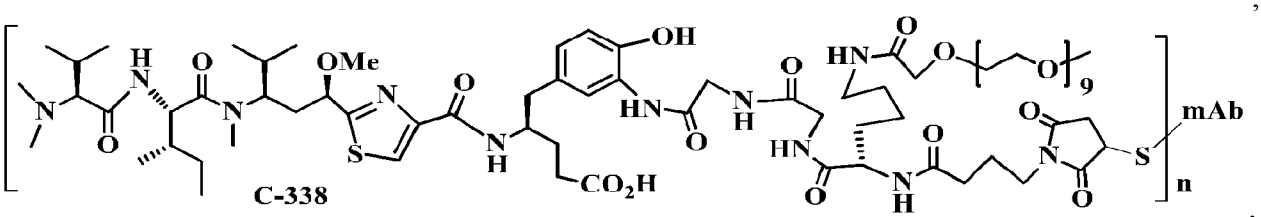

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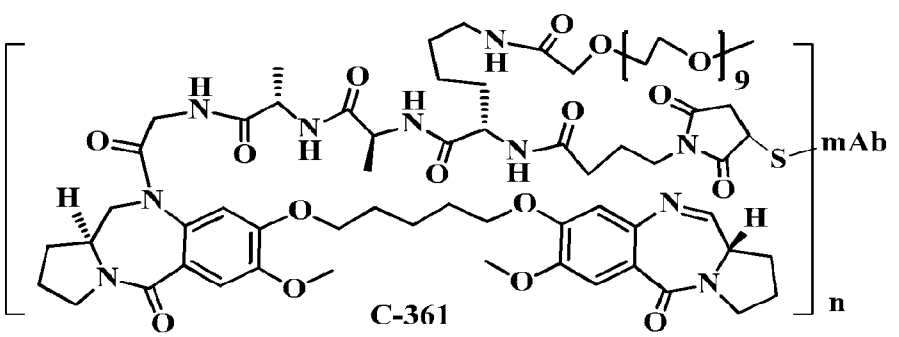

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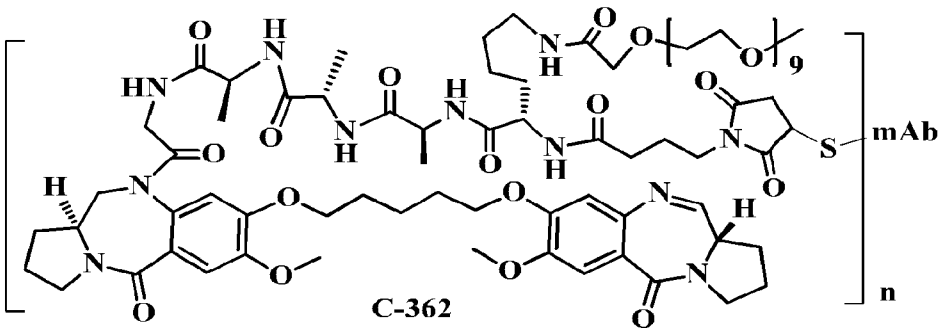
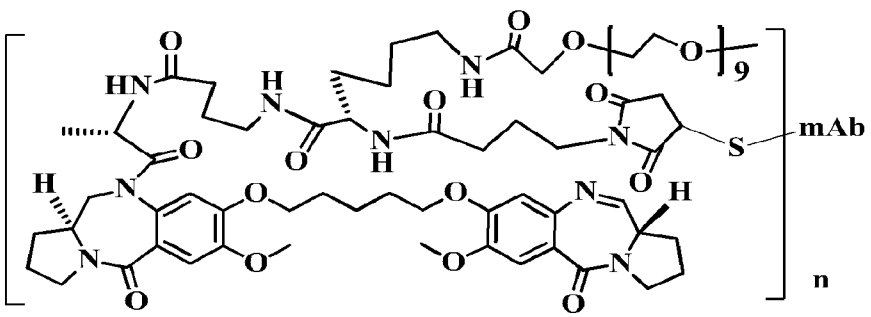
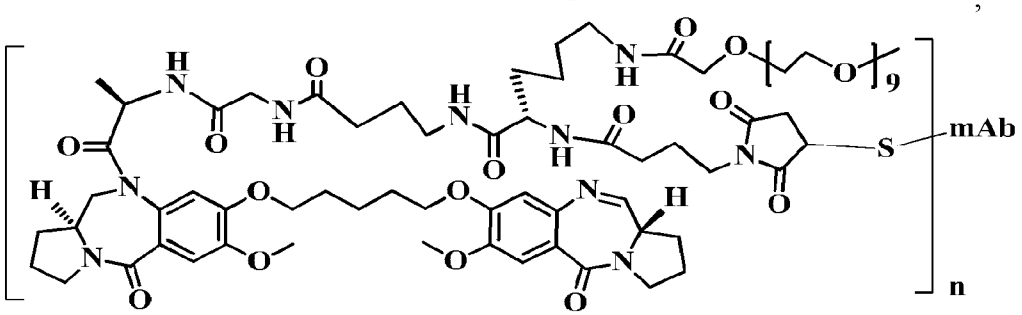


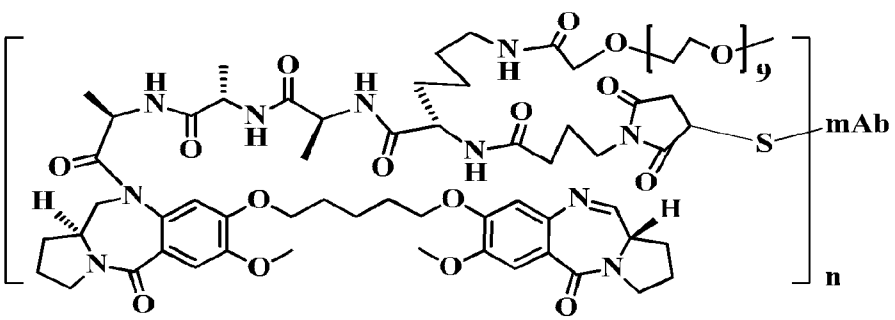
C-362 ,



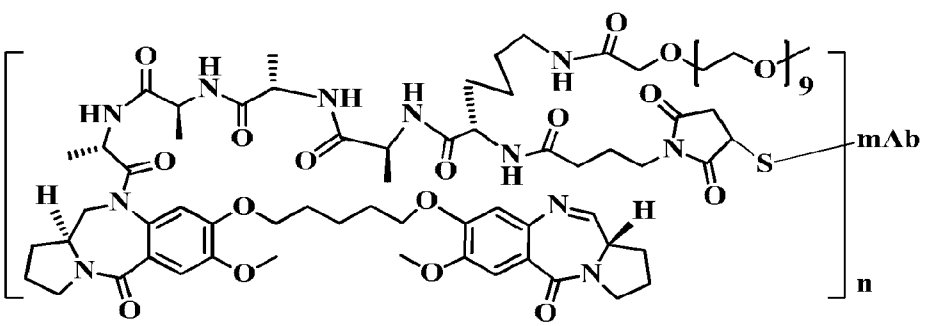
C-372 ,



C-373 ,

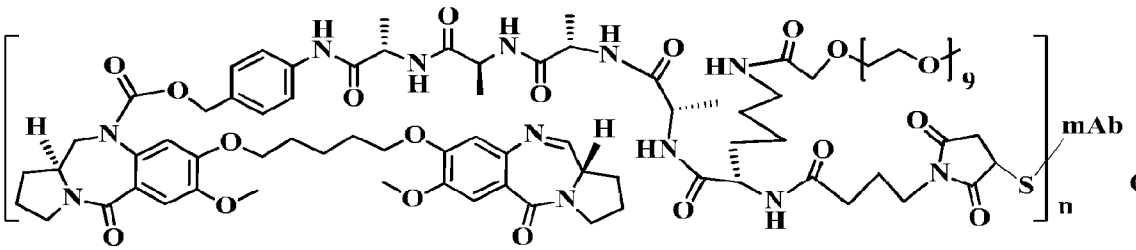


C-374 ,



C-375 ,

CA 03236754 2024-4-30



C-384

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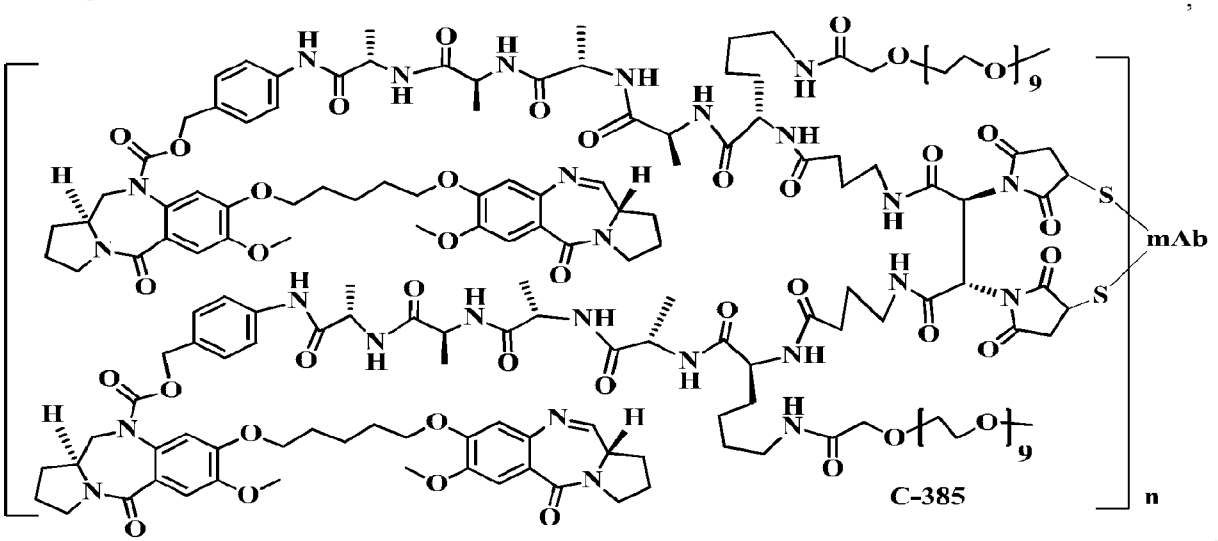

C-385

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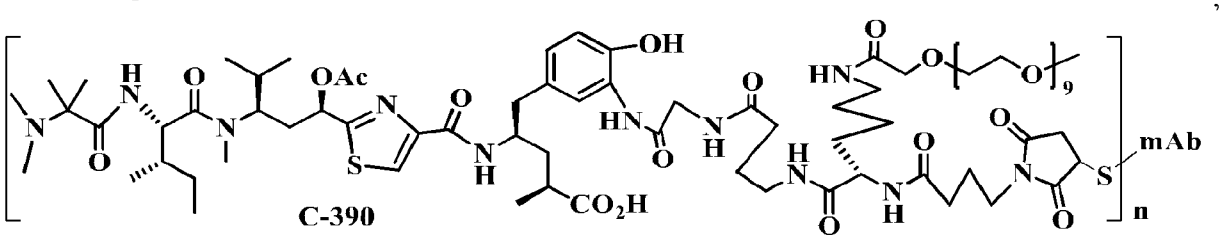

C-390

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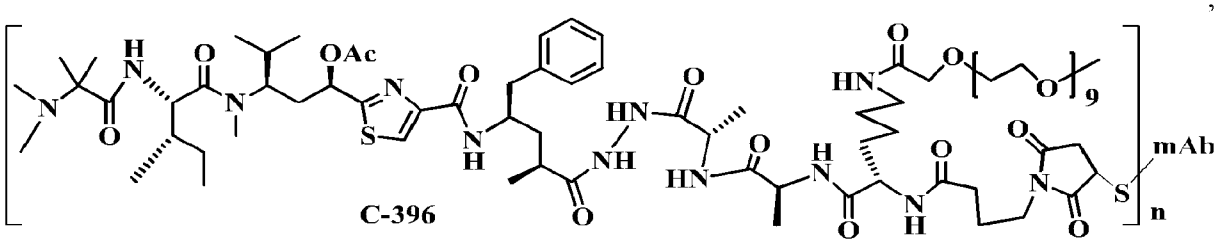

C-396

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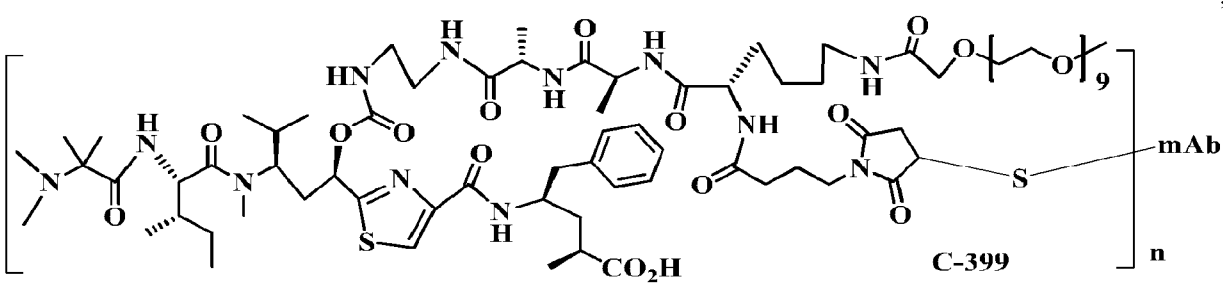

C-399

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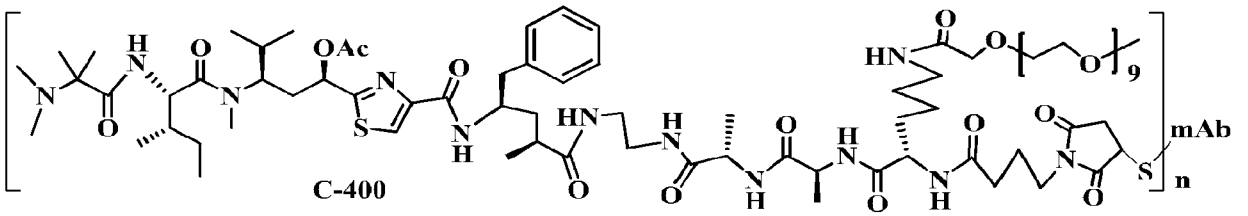

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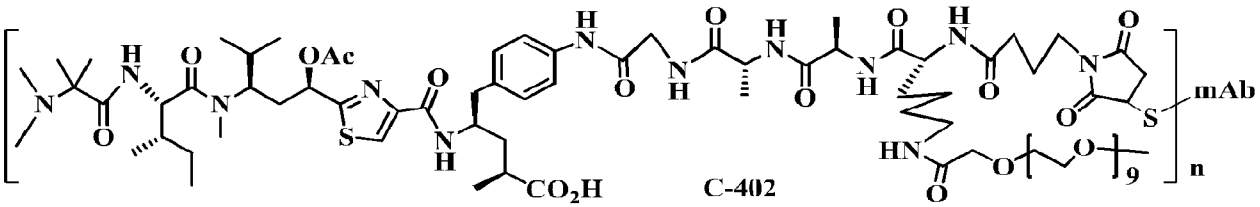

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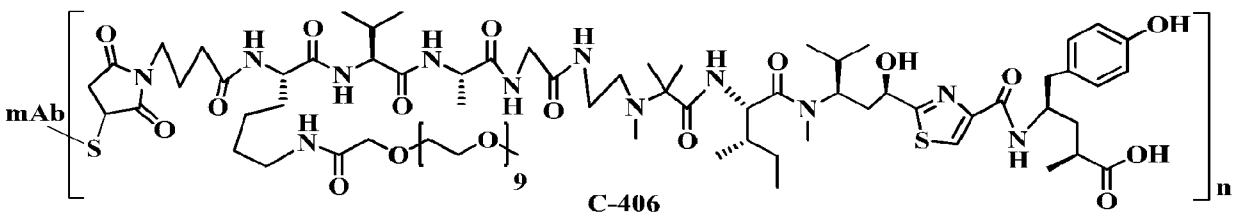

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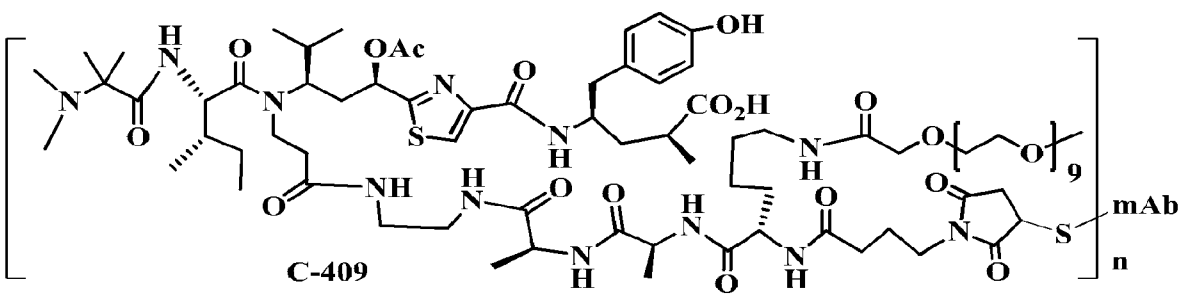

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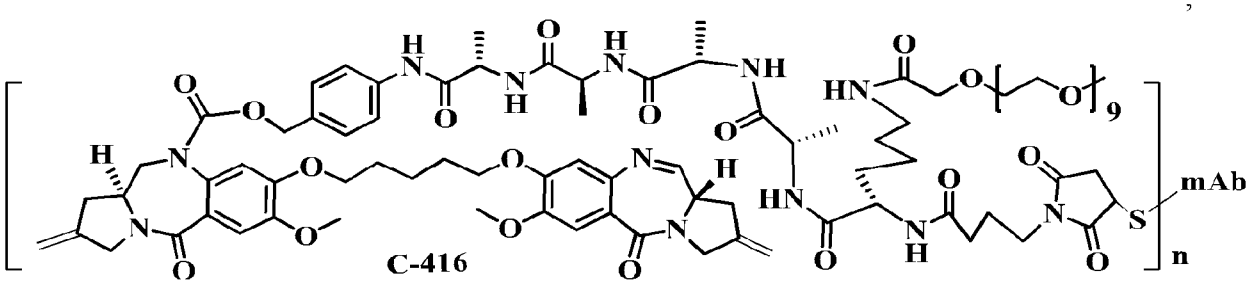

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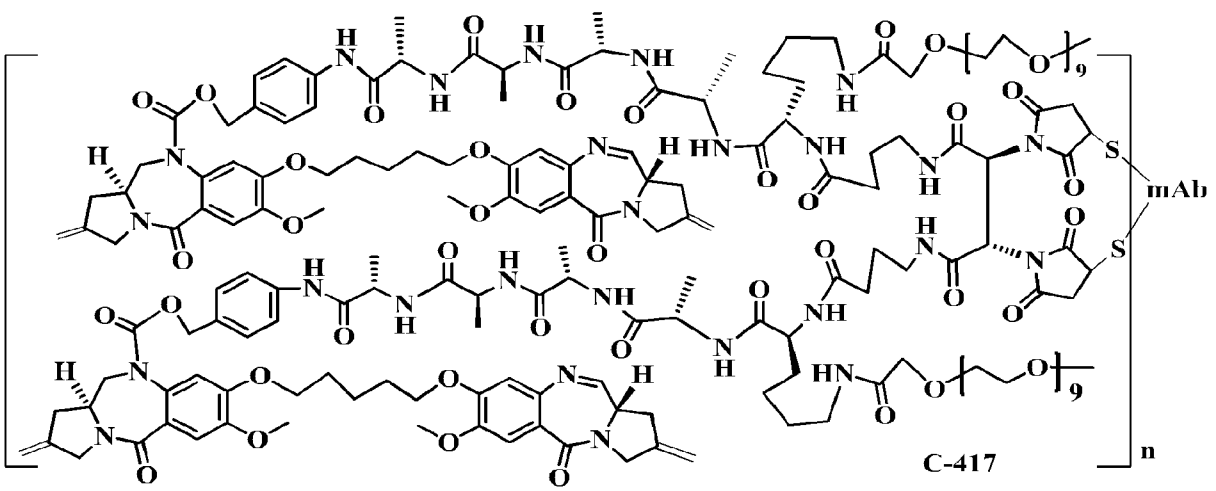

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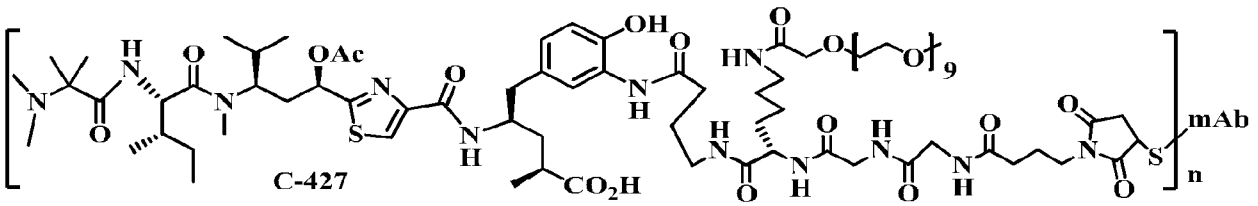

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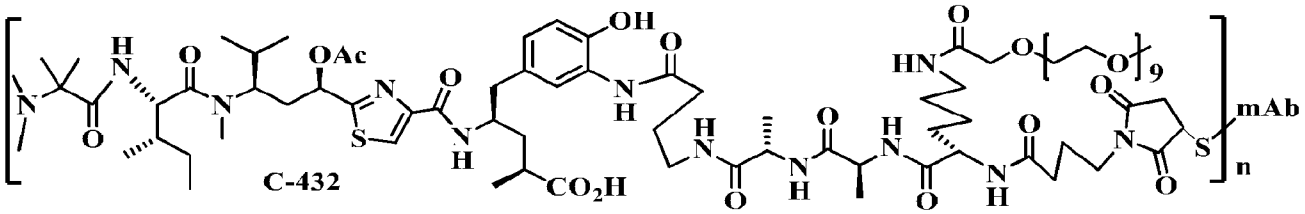

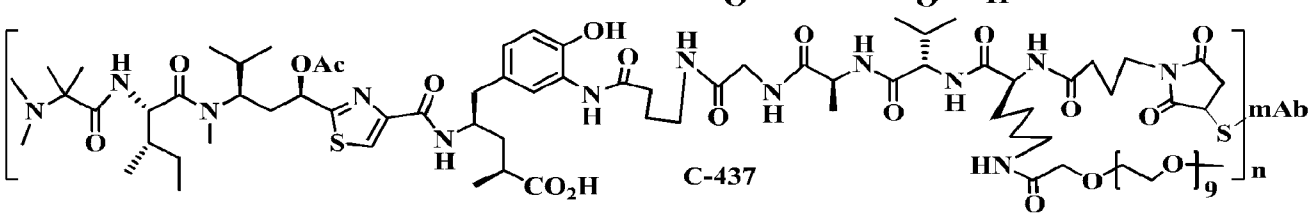

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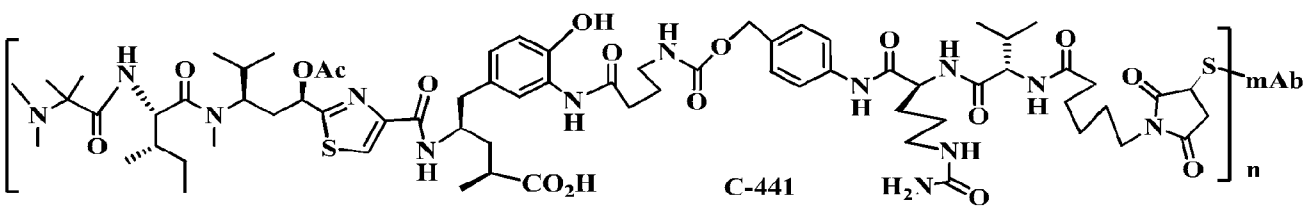

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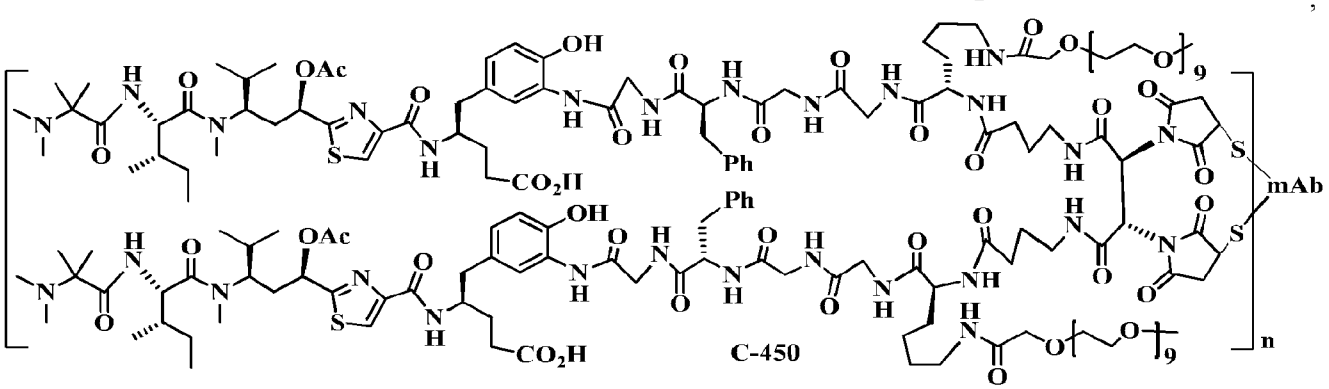

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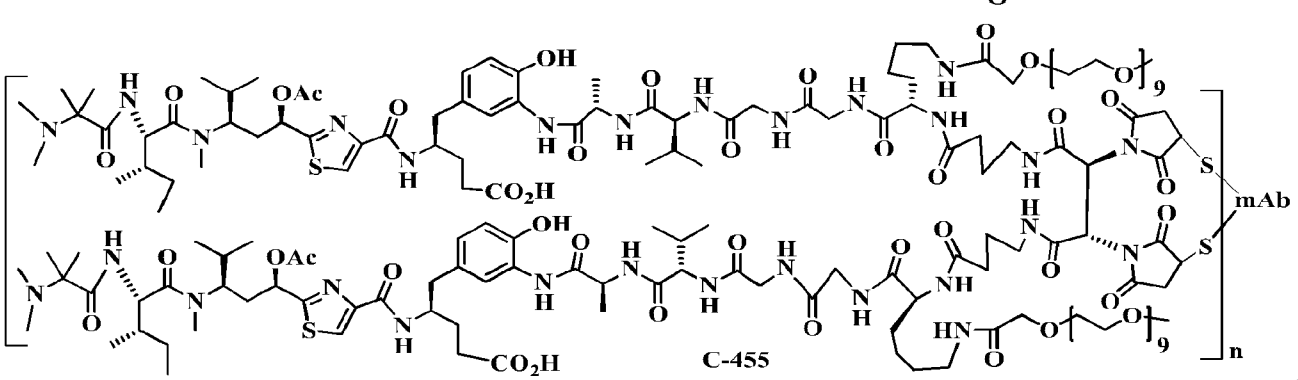

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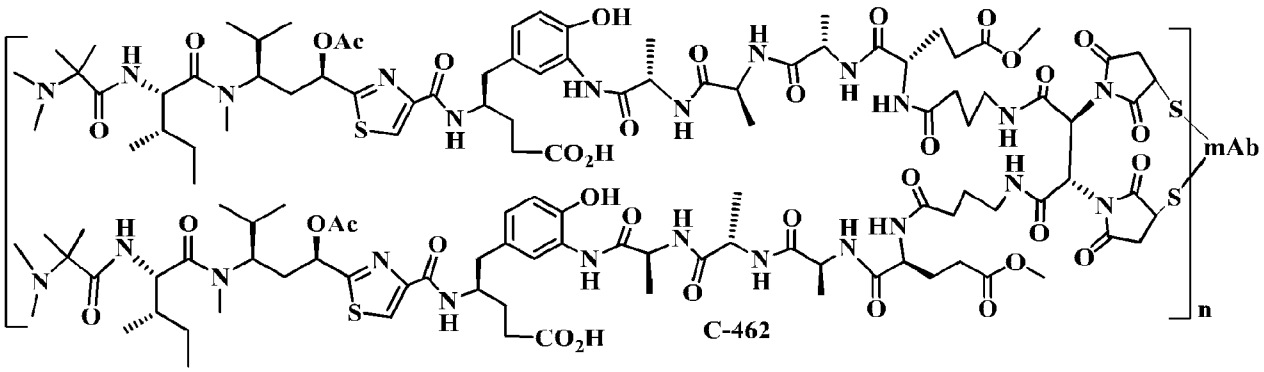

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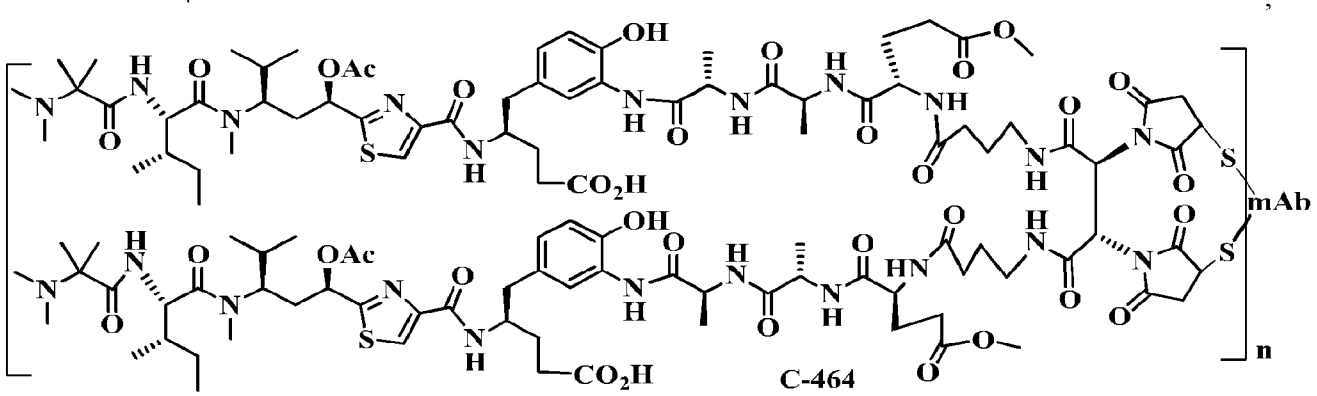

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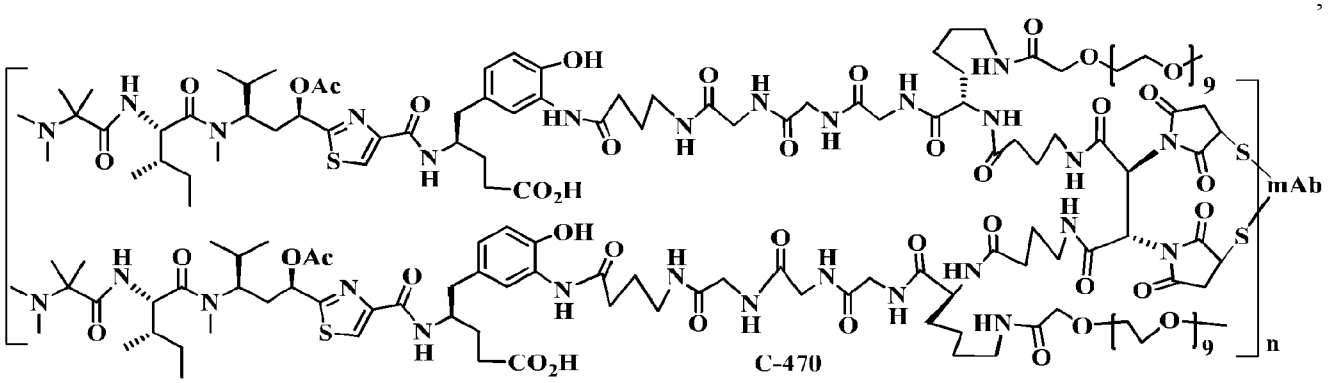
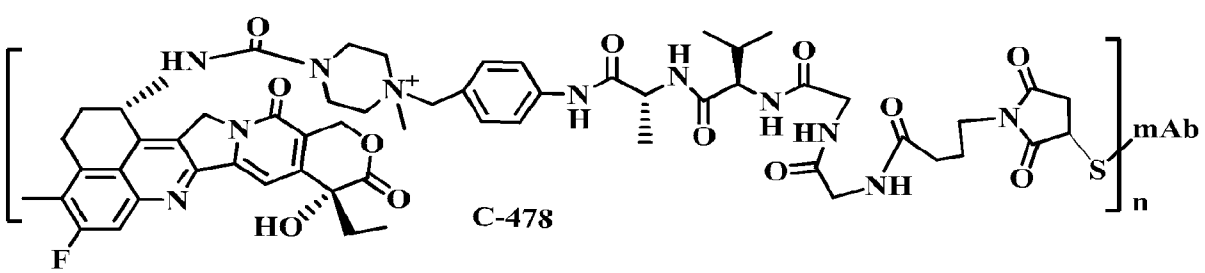


C-470



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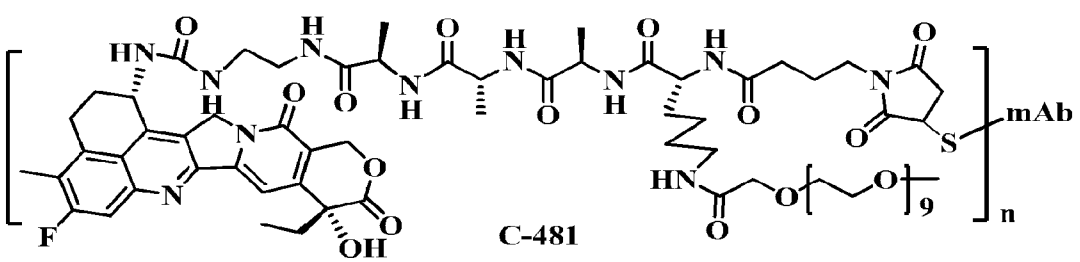

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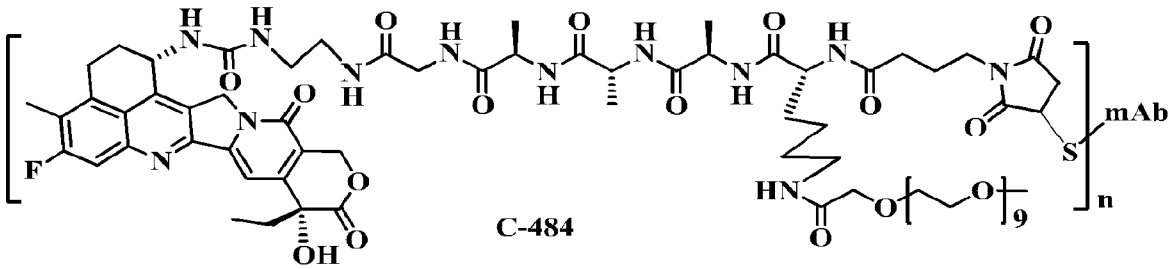

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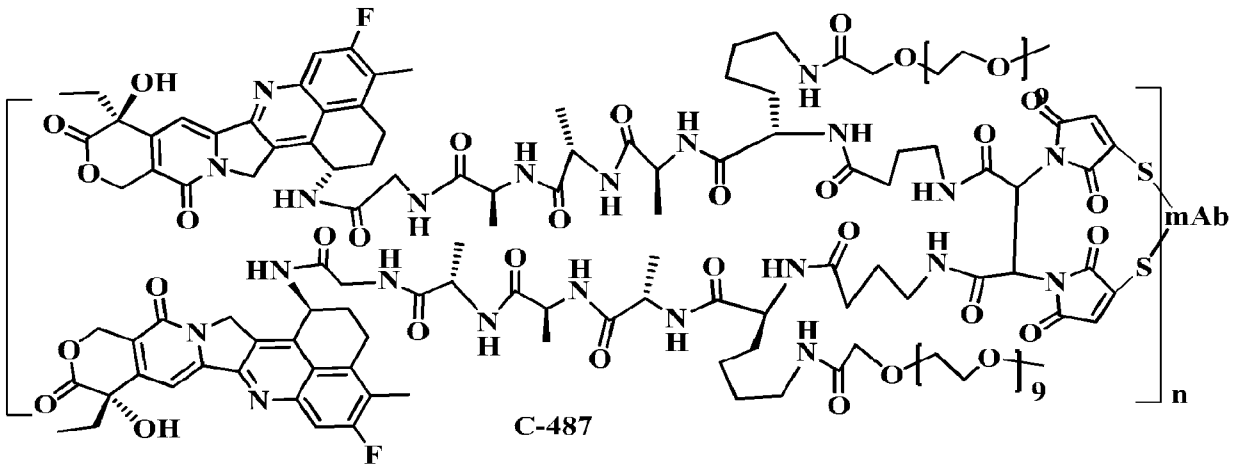

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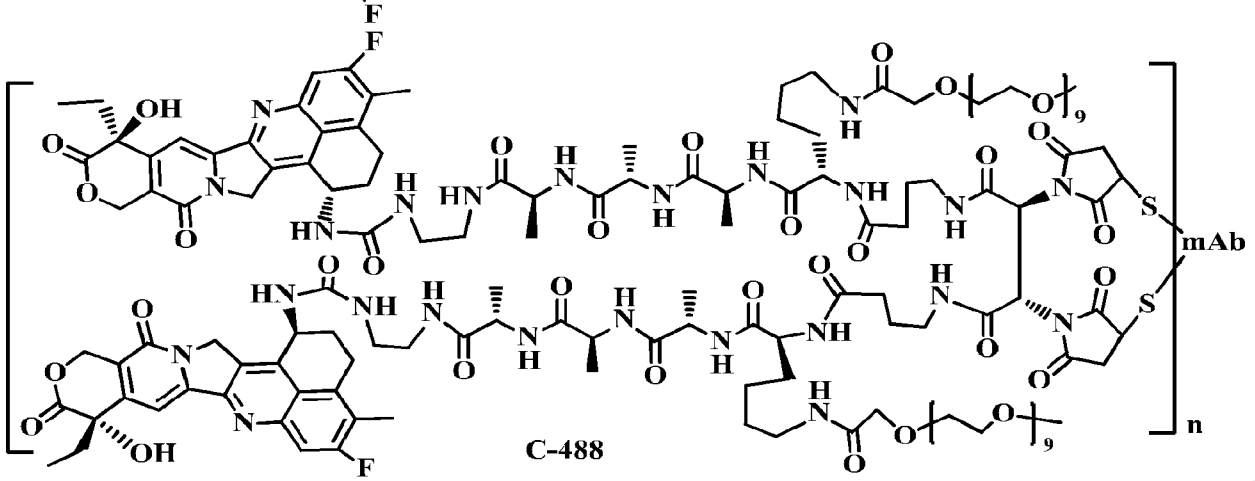

C-488

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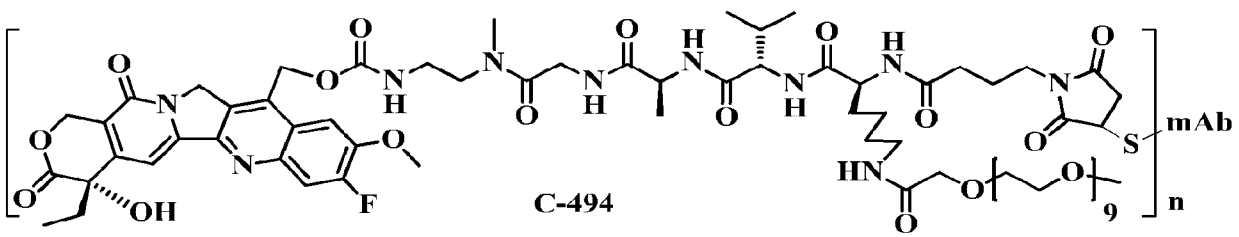

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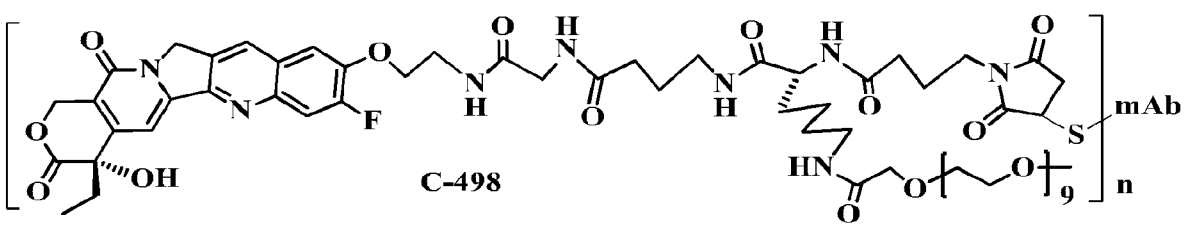

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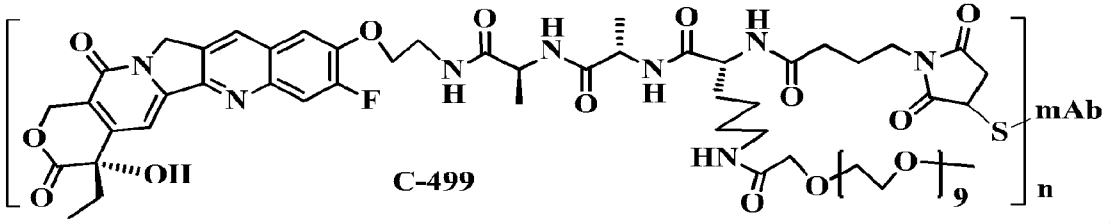

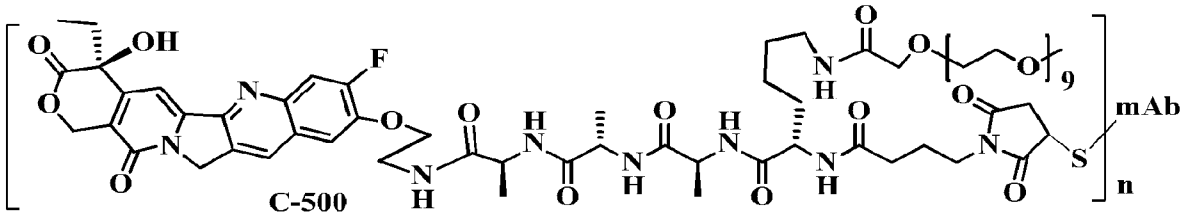

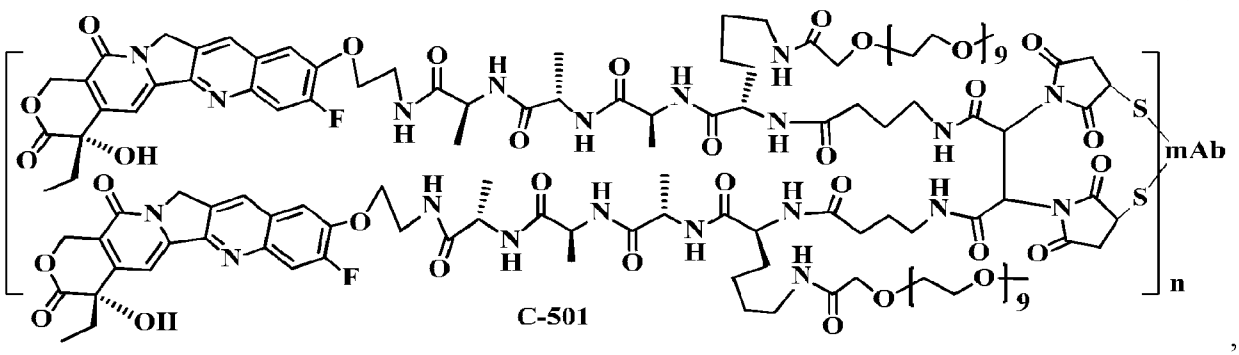

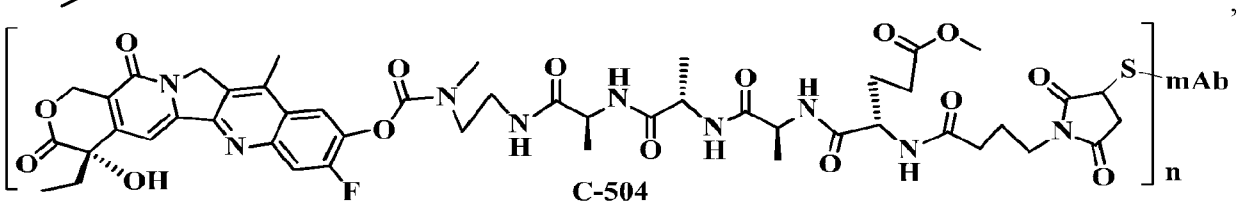

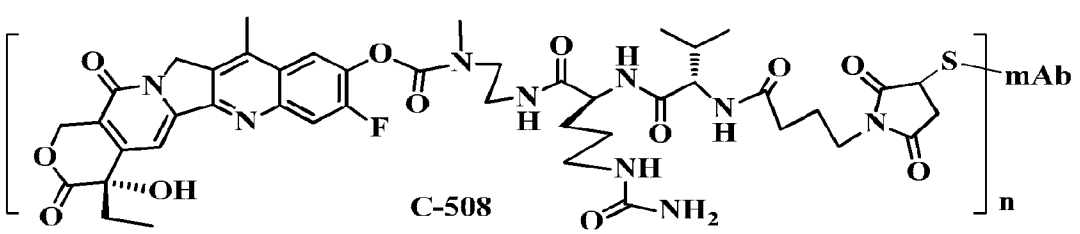

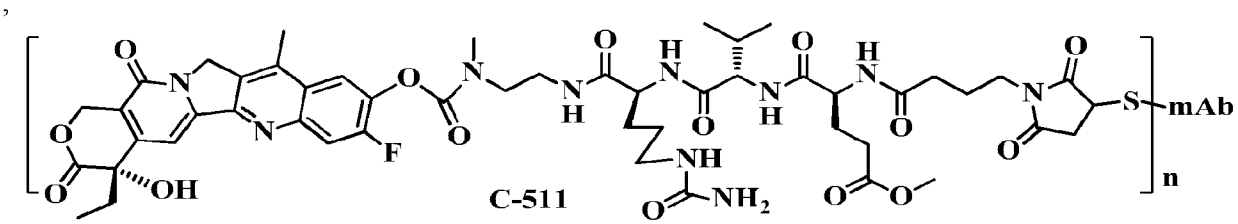

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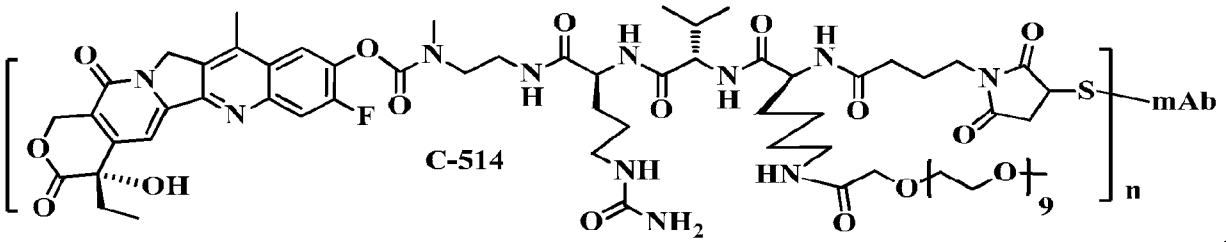

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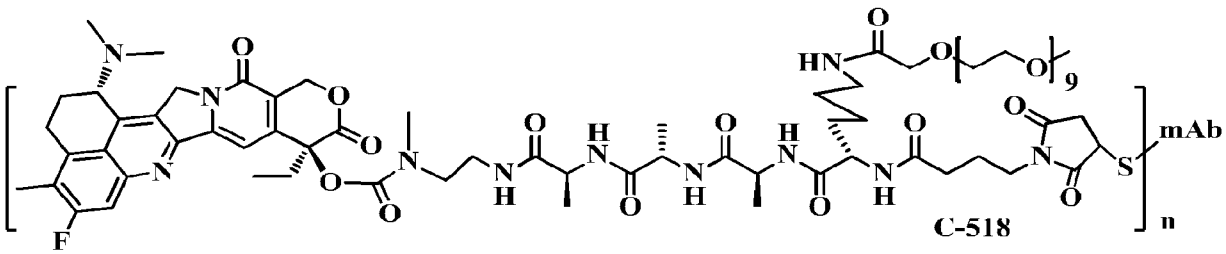

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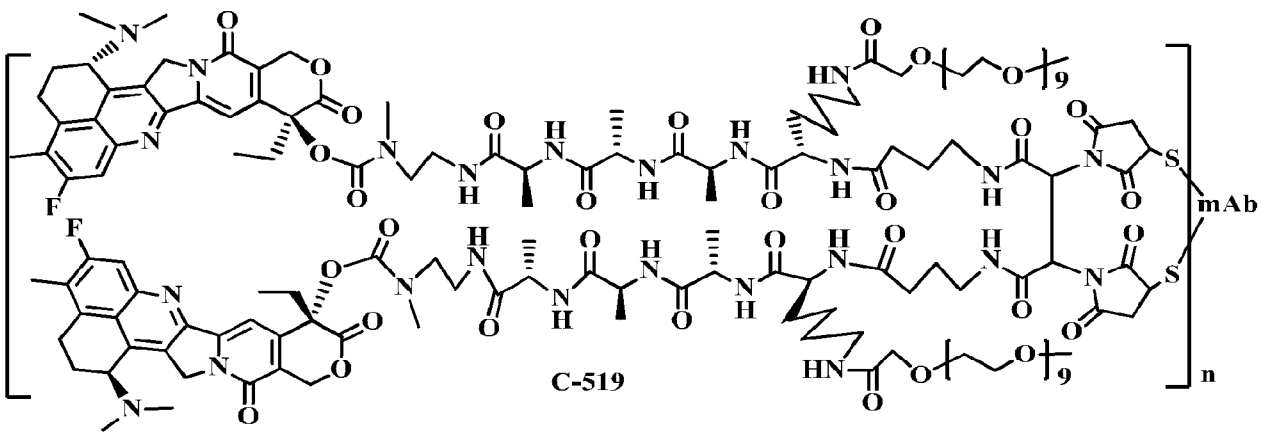

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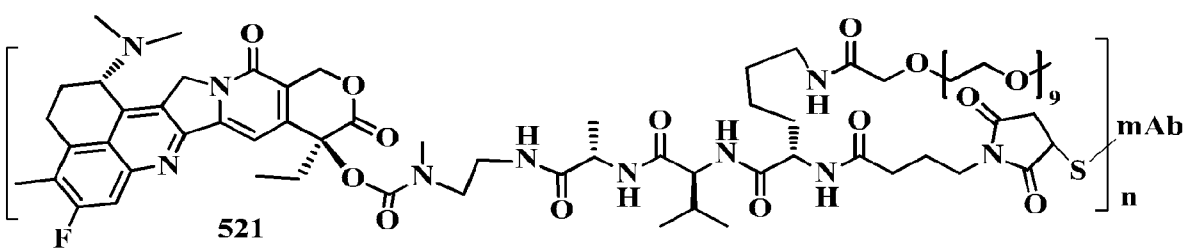

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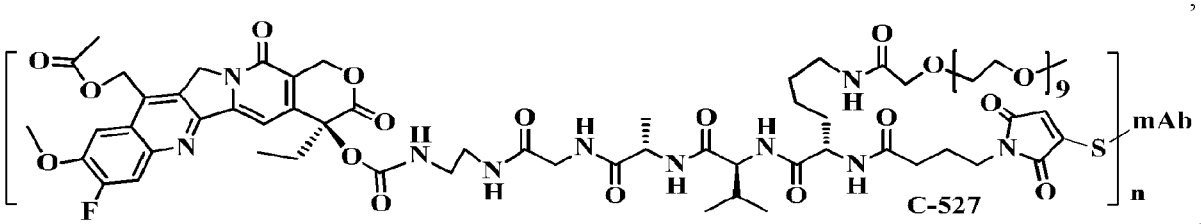

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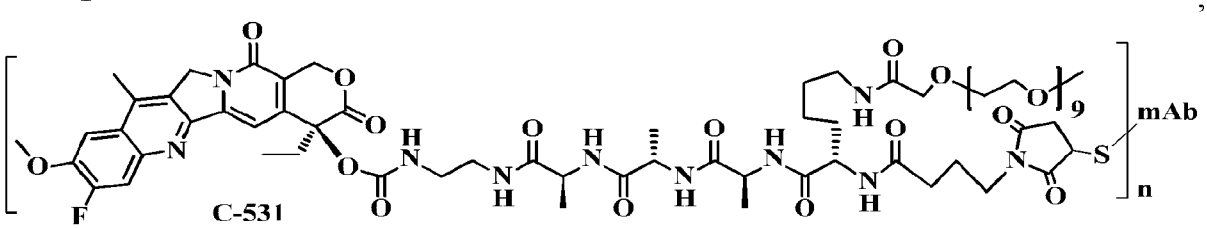

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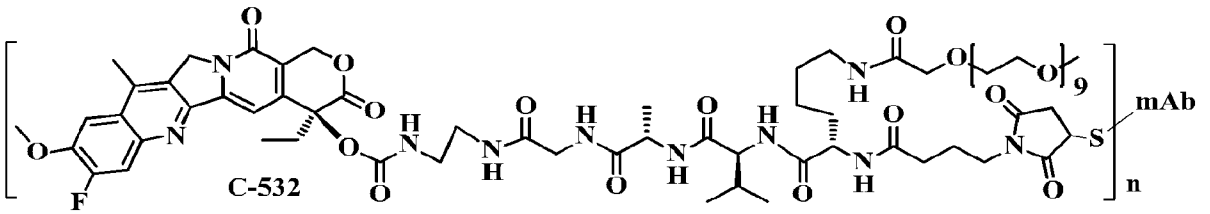
CA 03236754 2024-4-30



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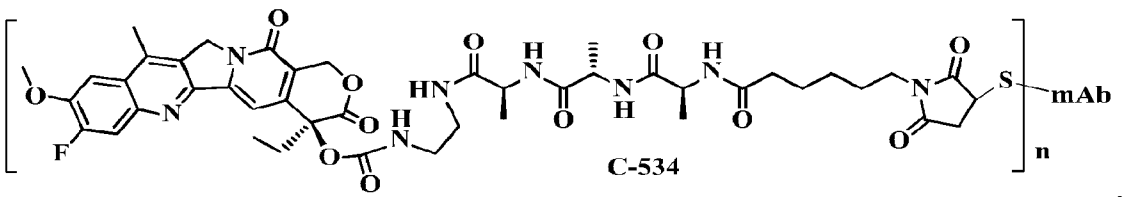

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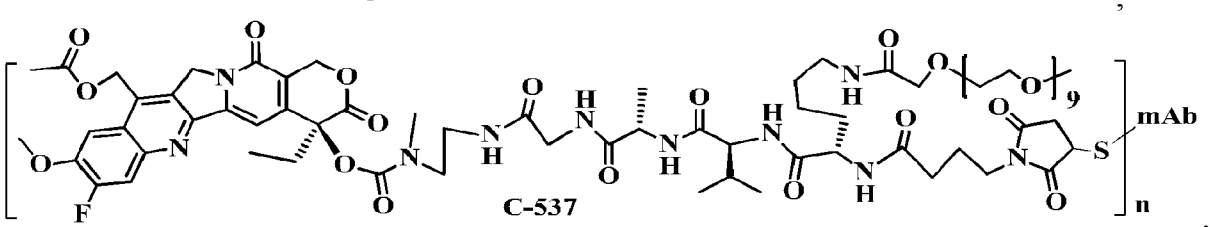

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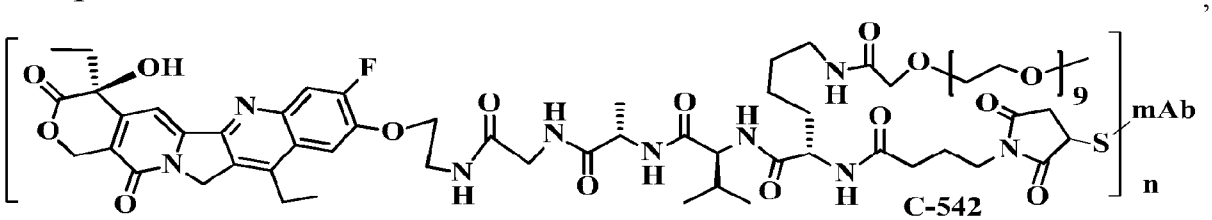

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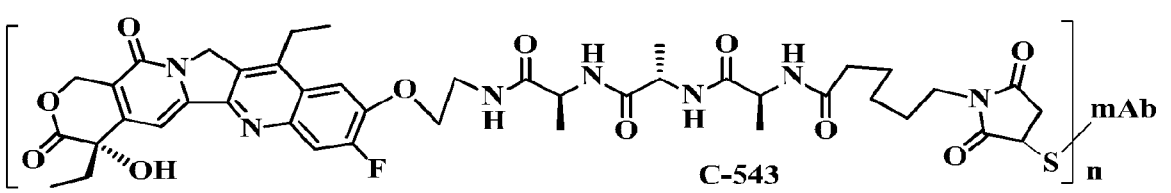

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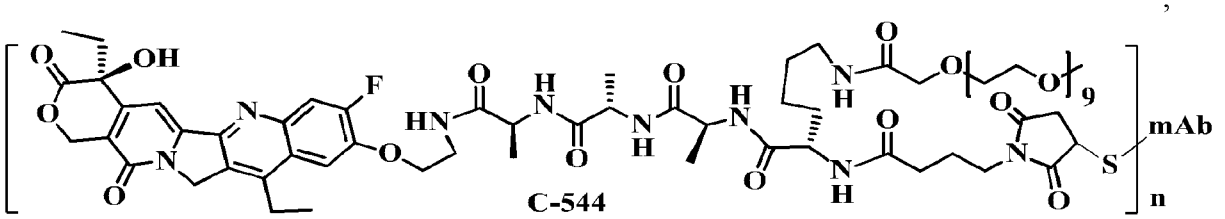

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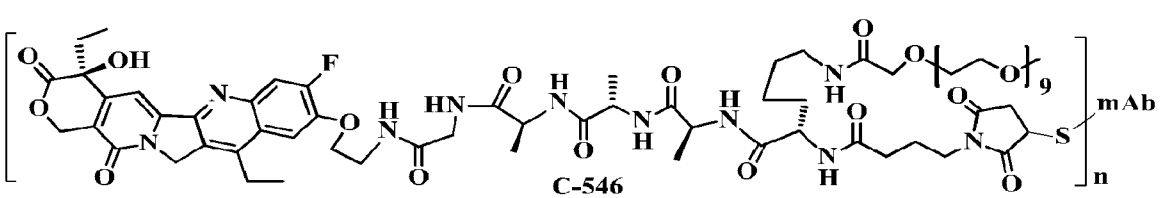

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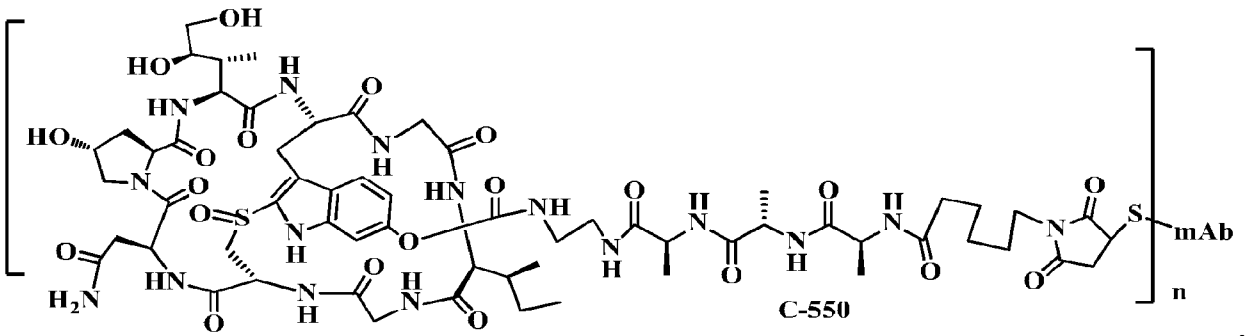

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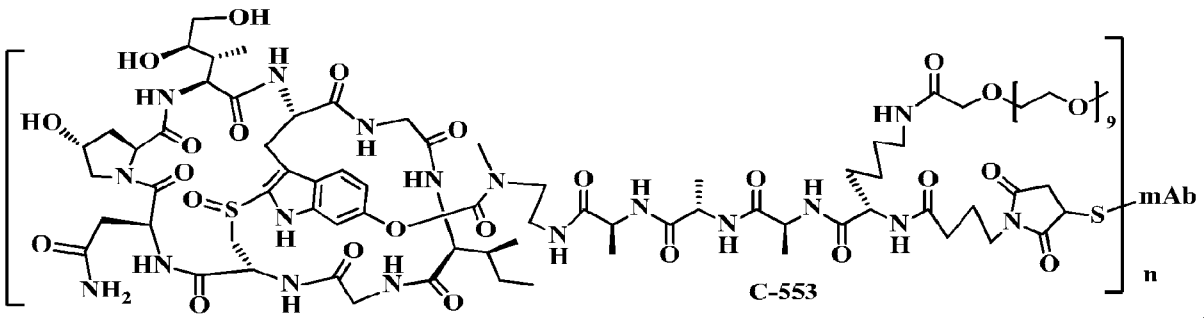

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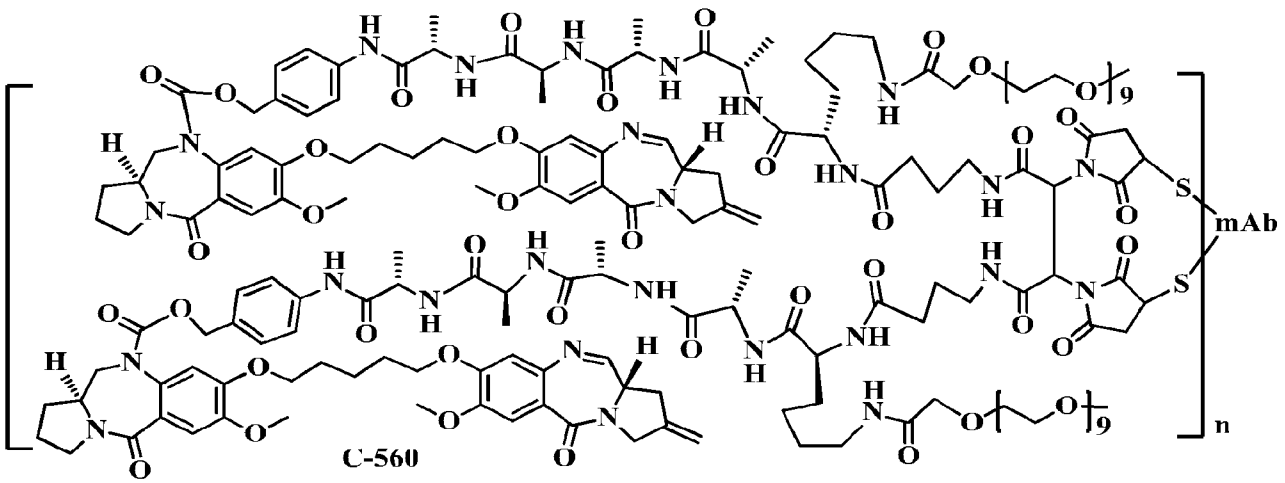

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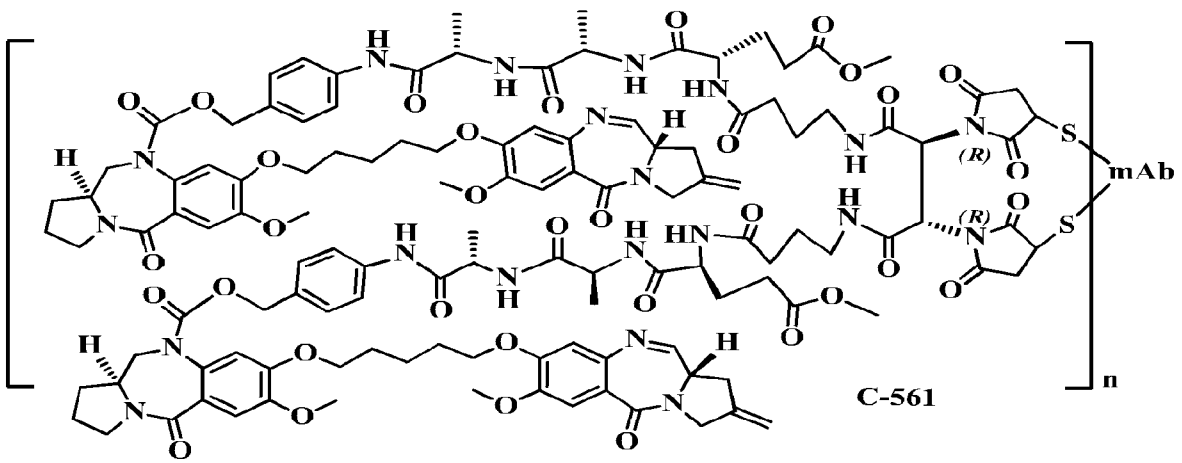

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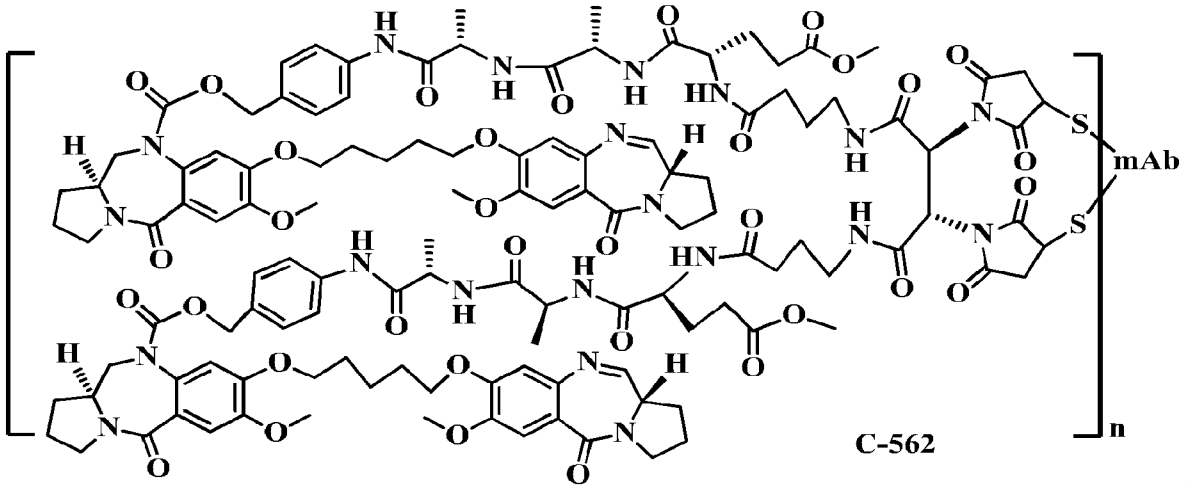

C-562

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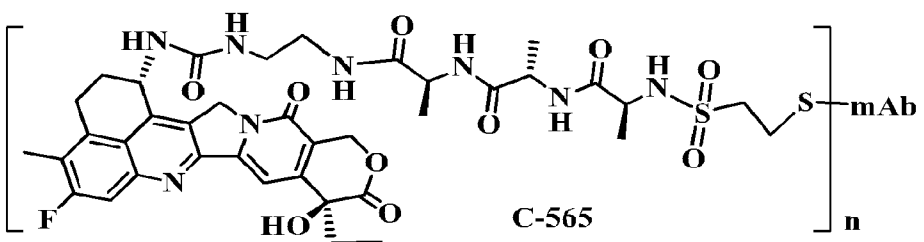

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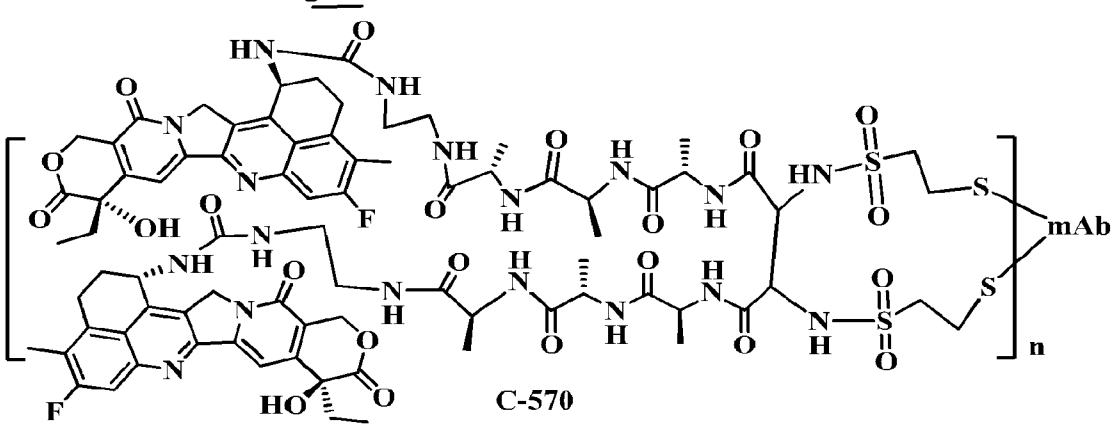

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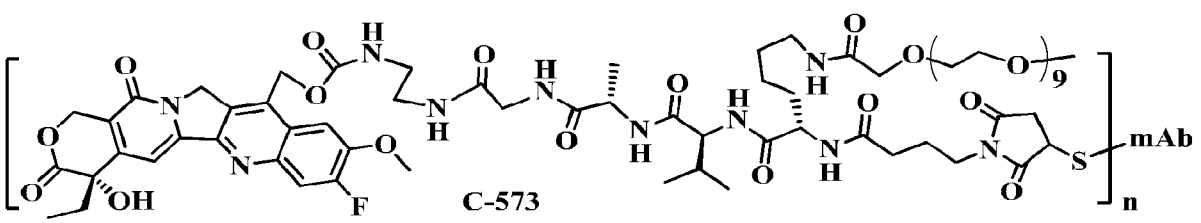

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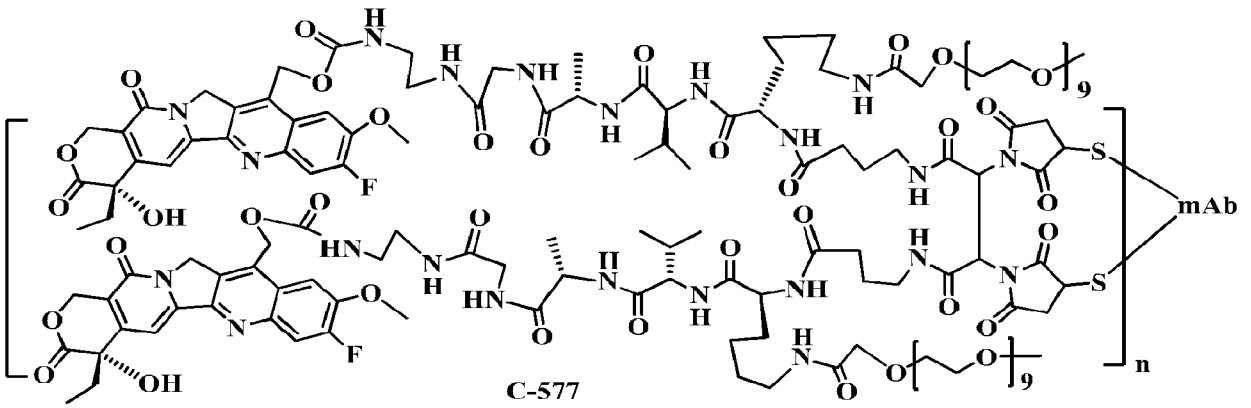
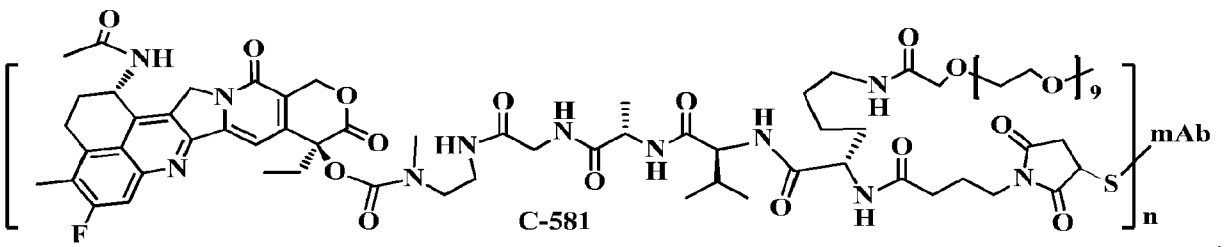


C-577



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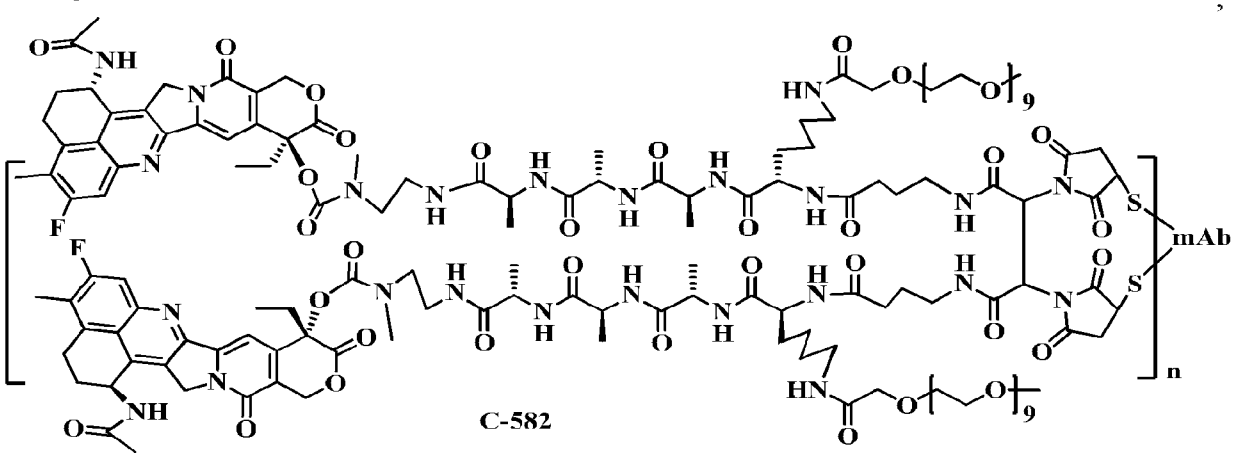

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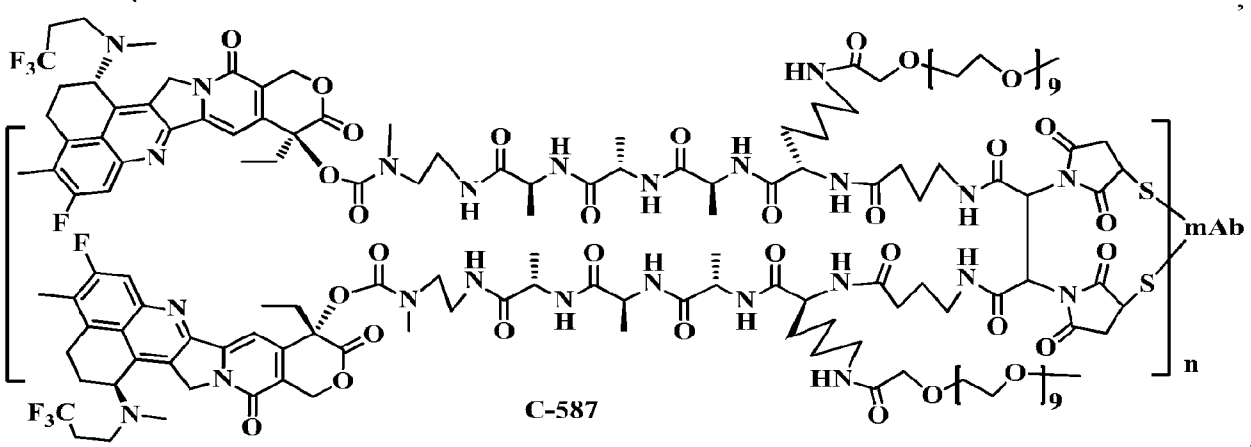

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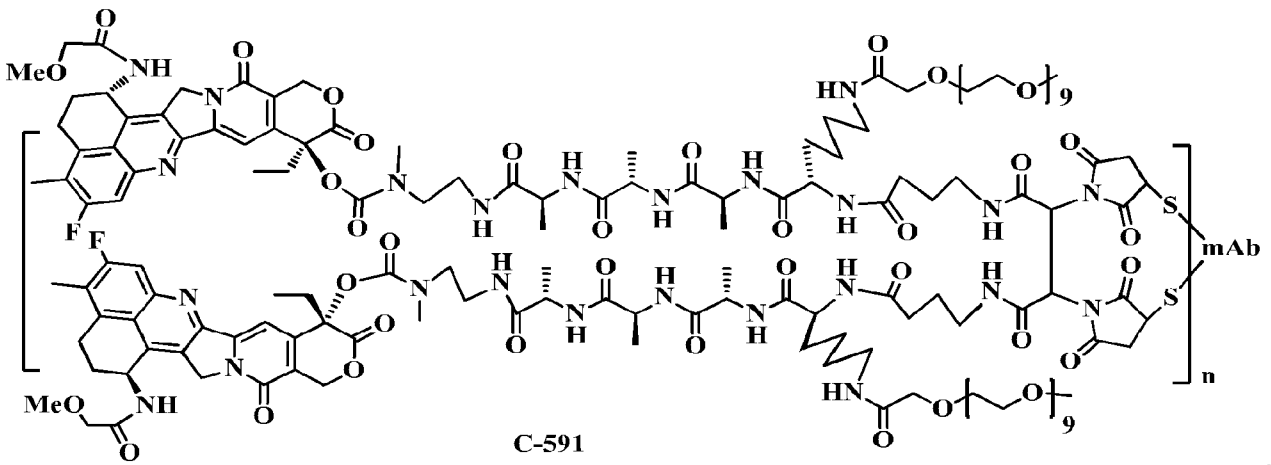
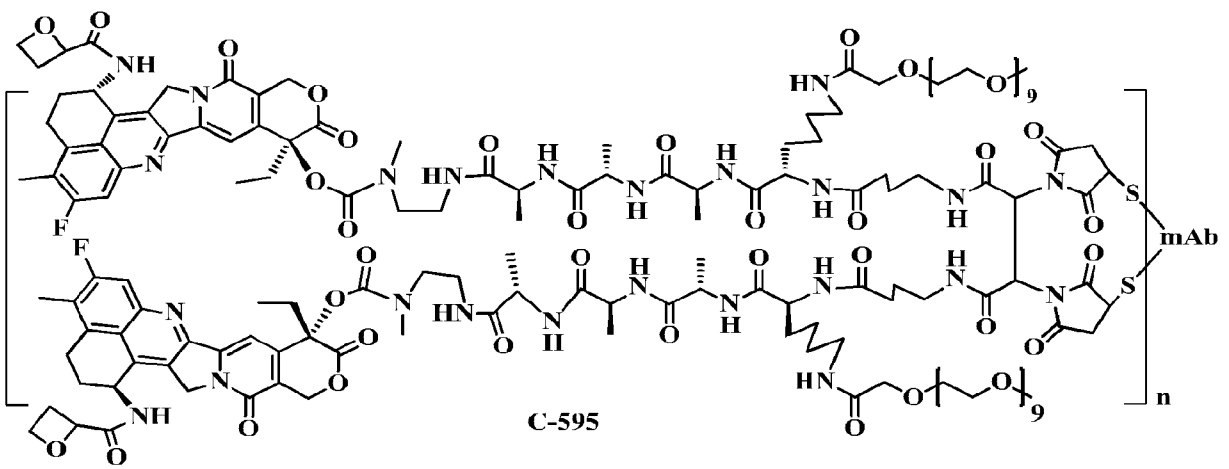


C-591



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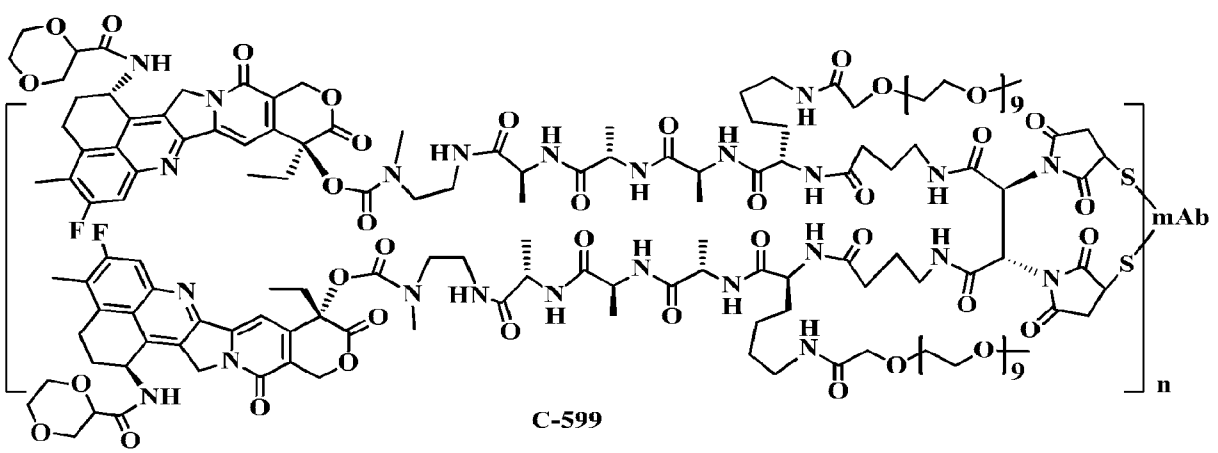

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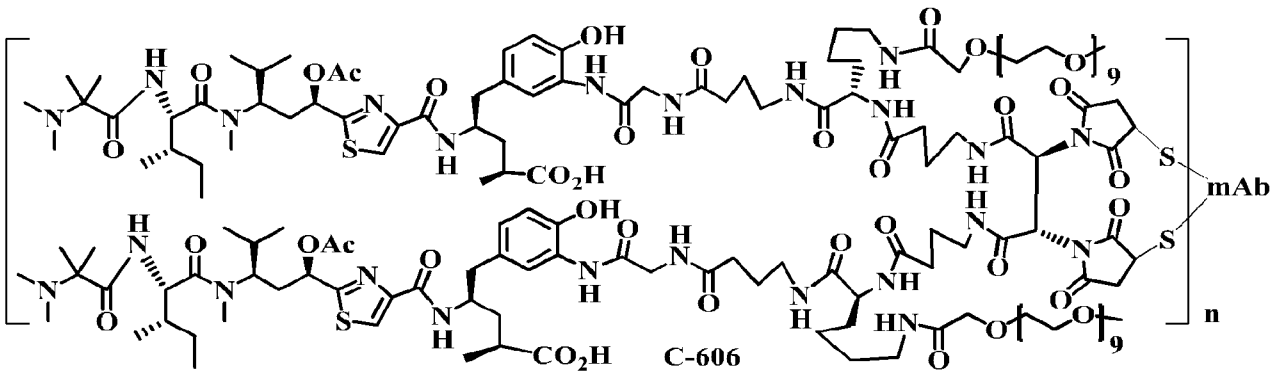

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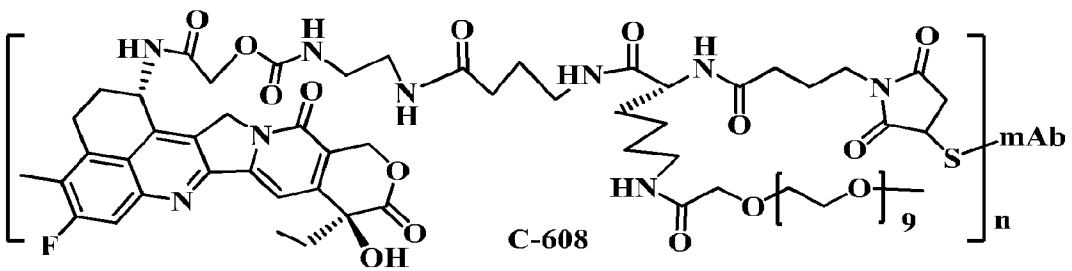

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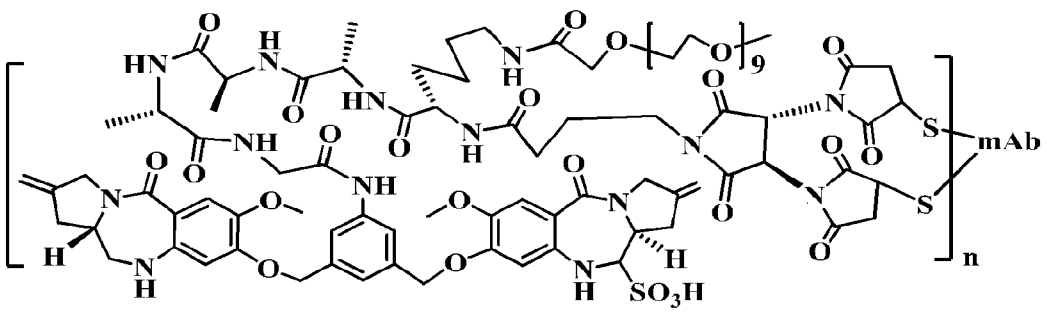

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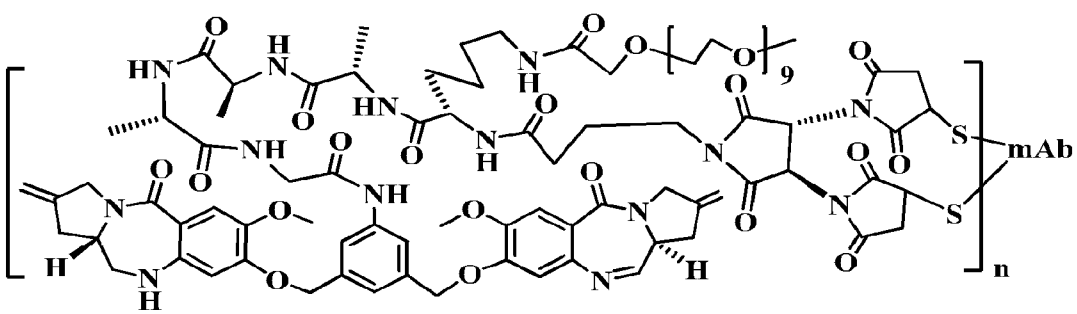

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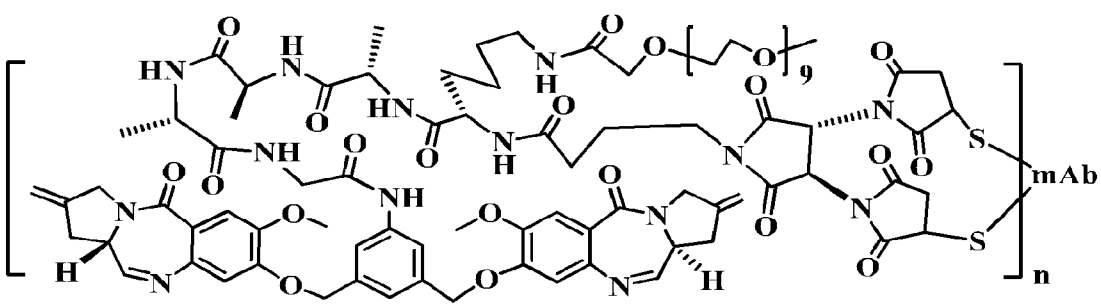

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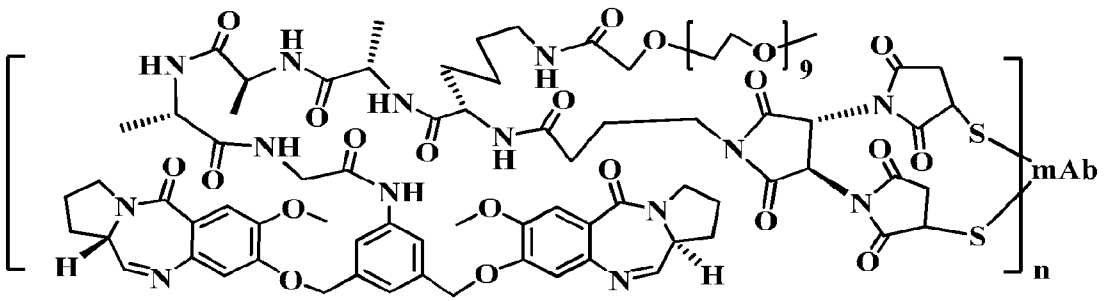

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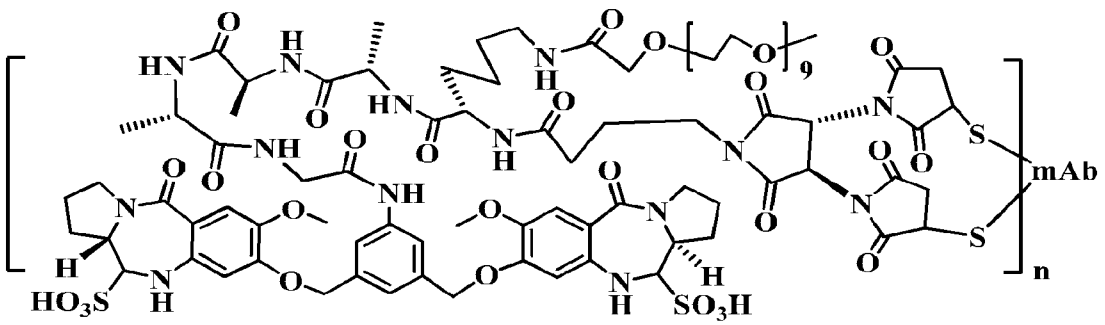

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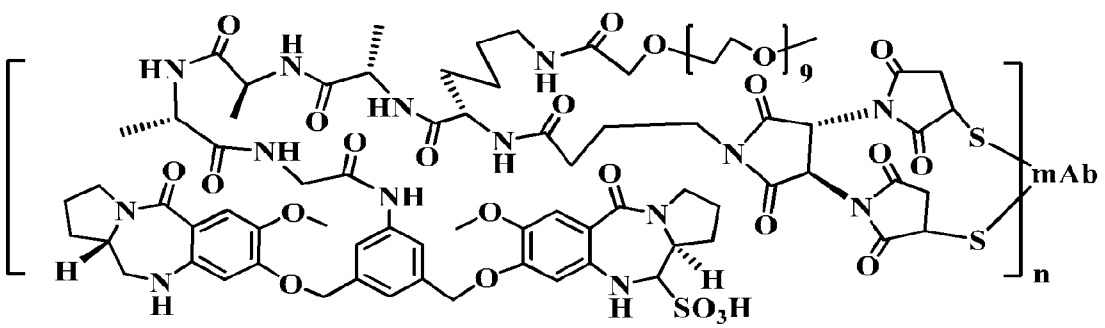

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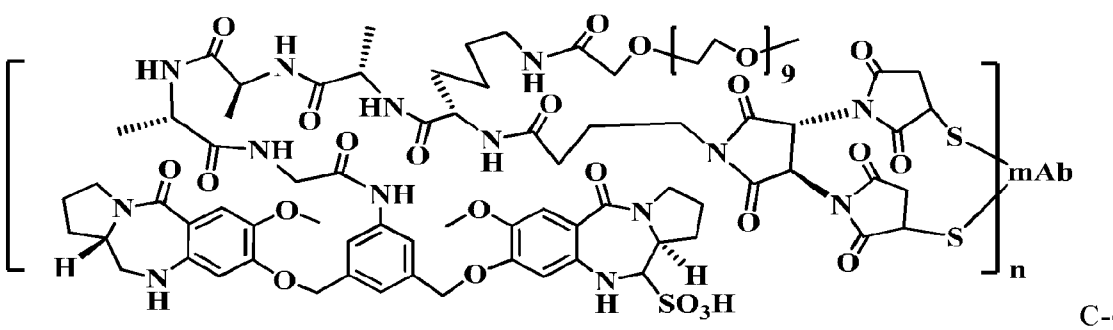

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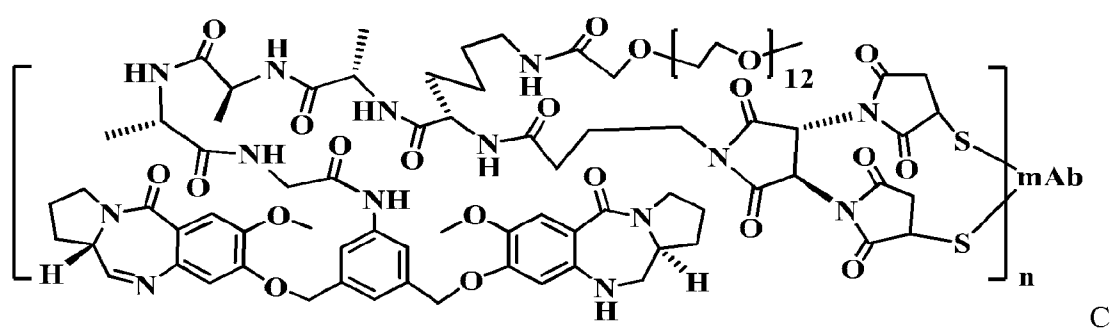

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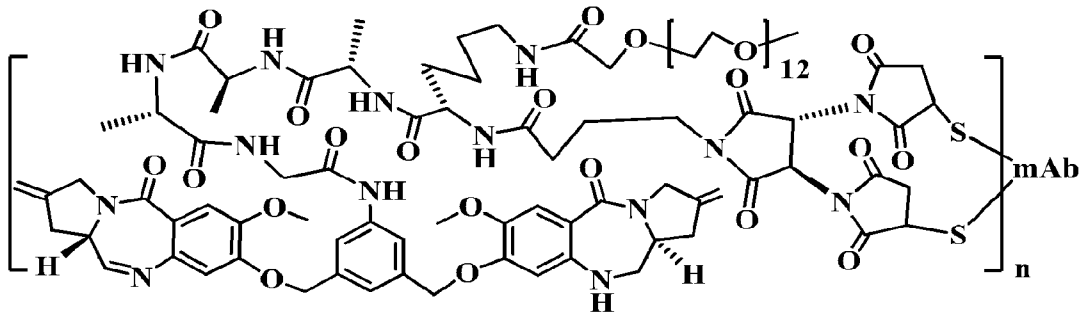

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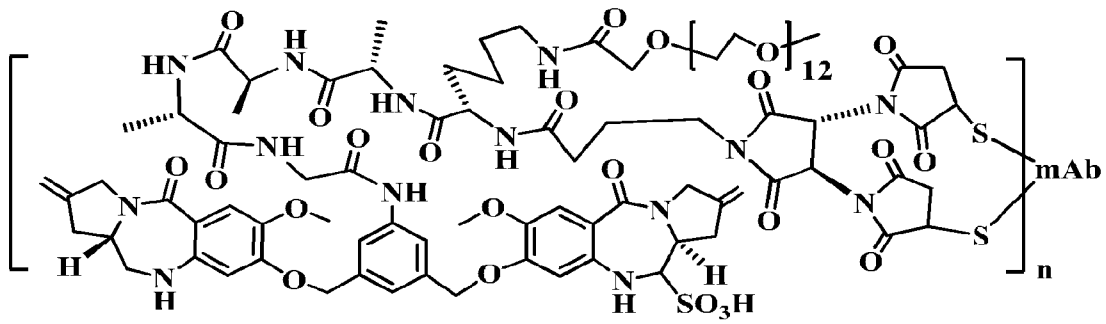

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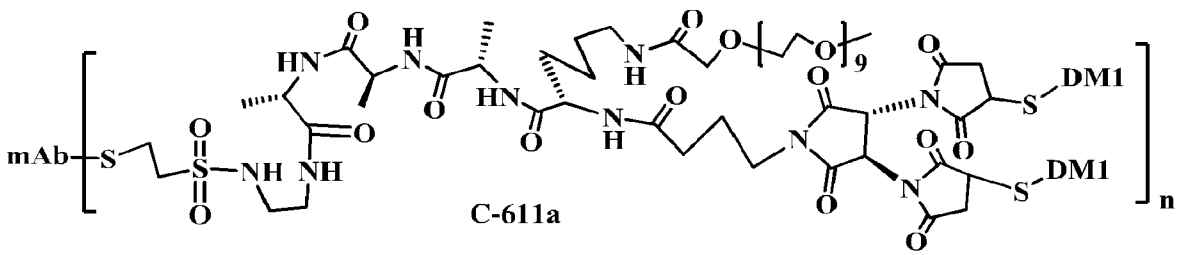

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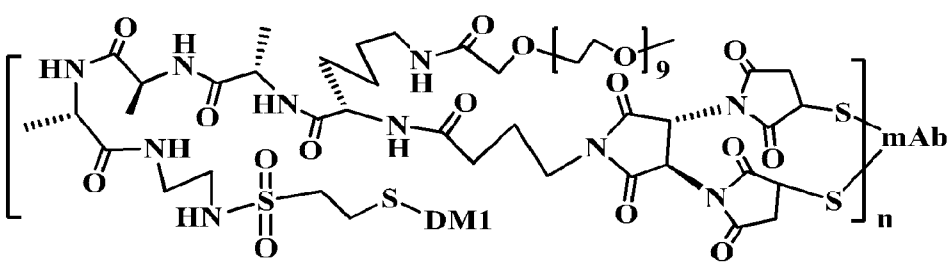

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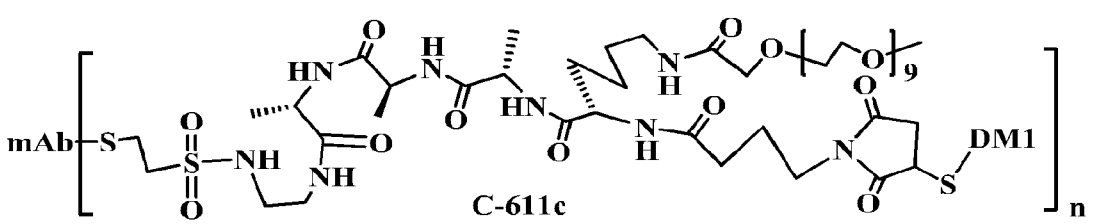

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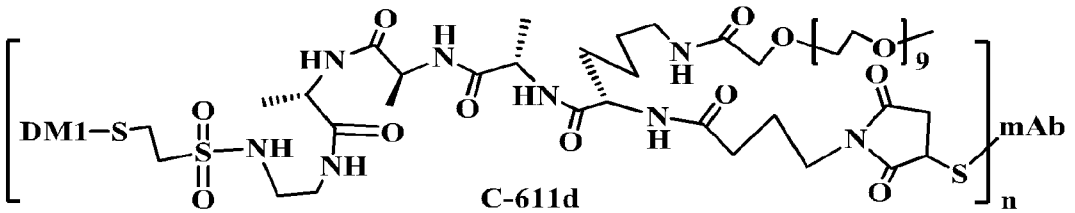
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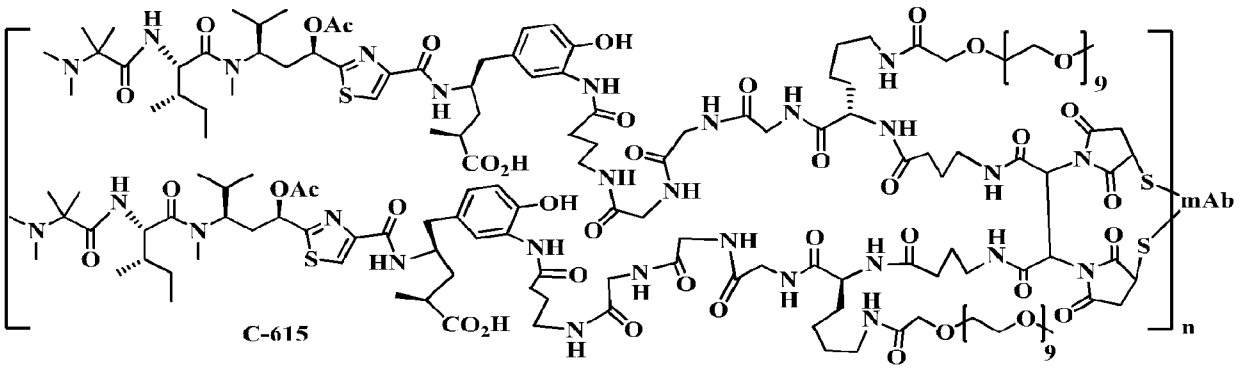

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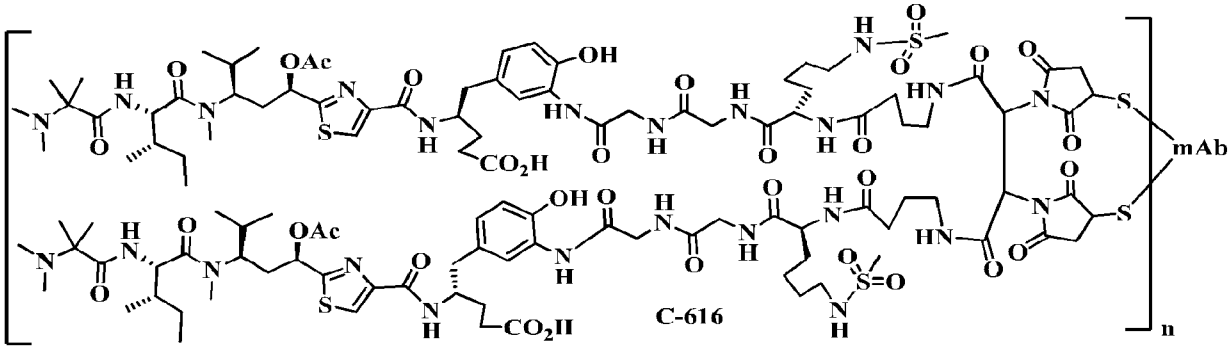

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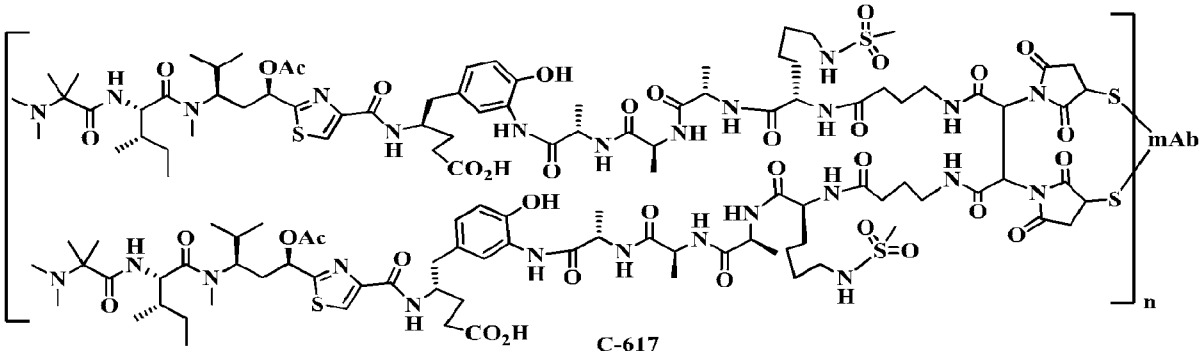

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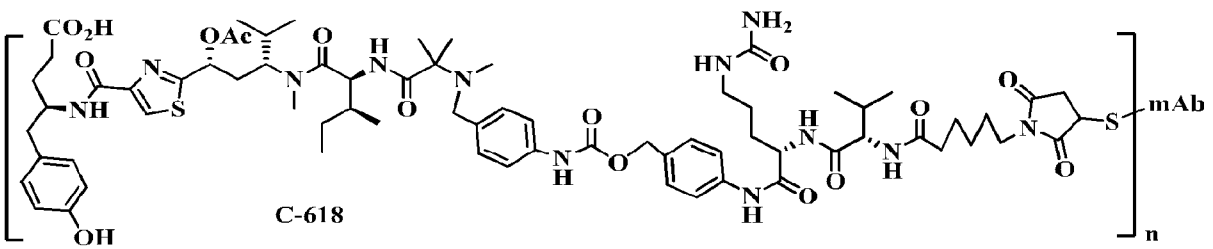

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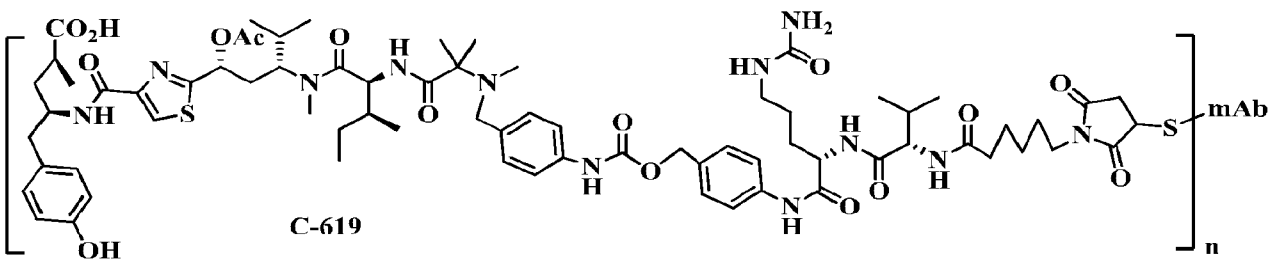

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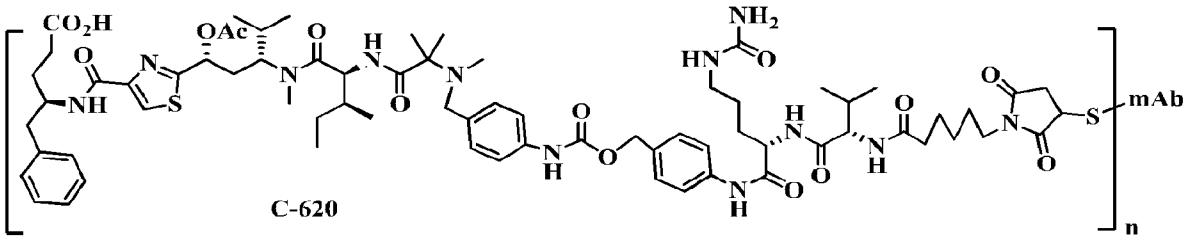

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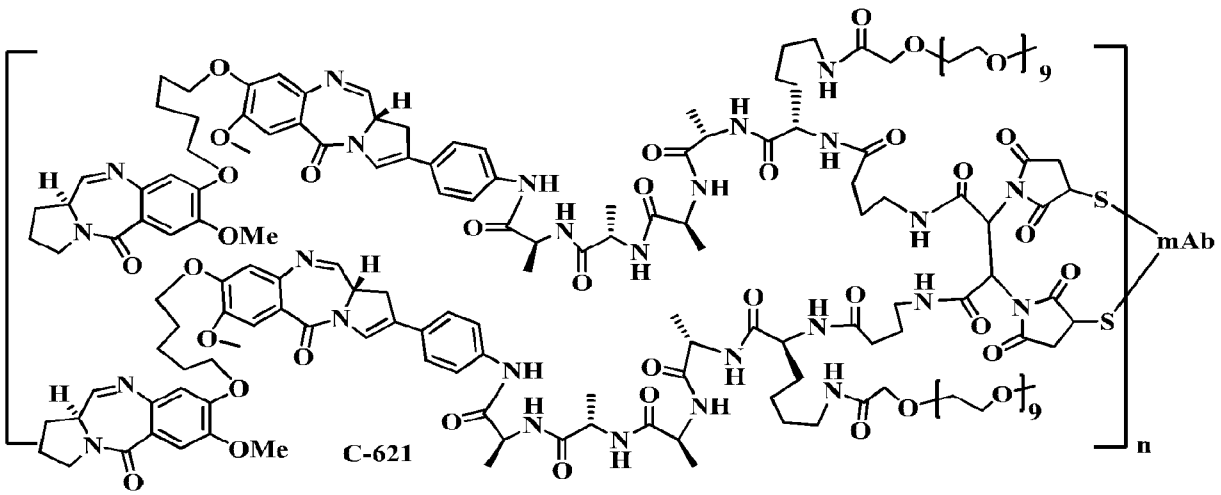

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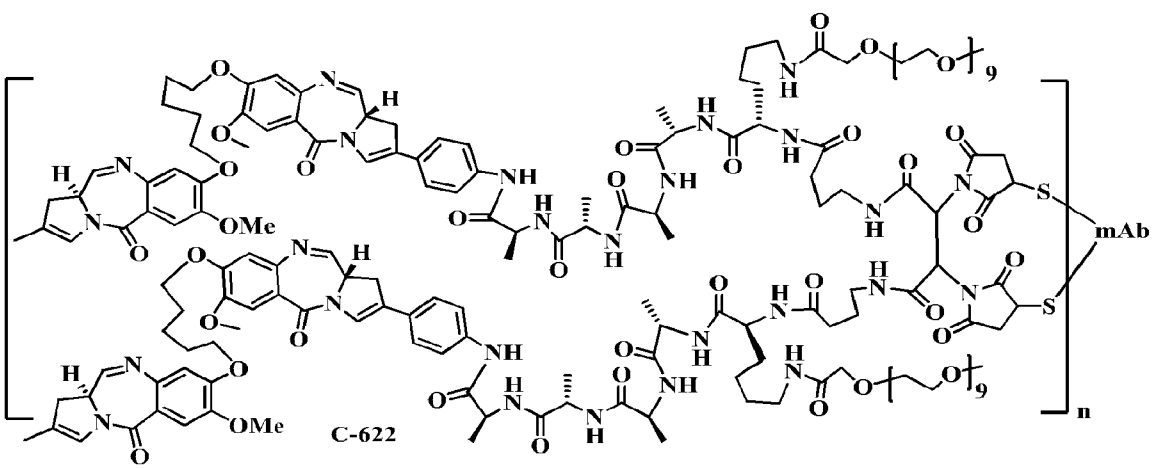

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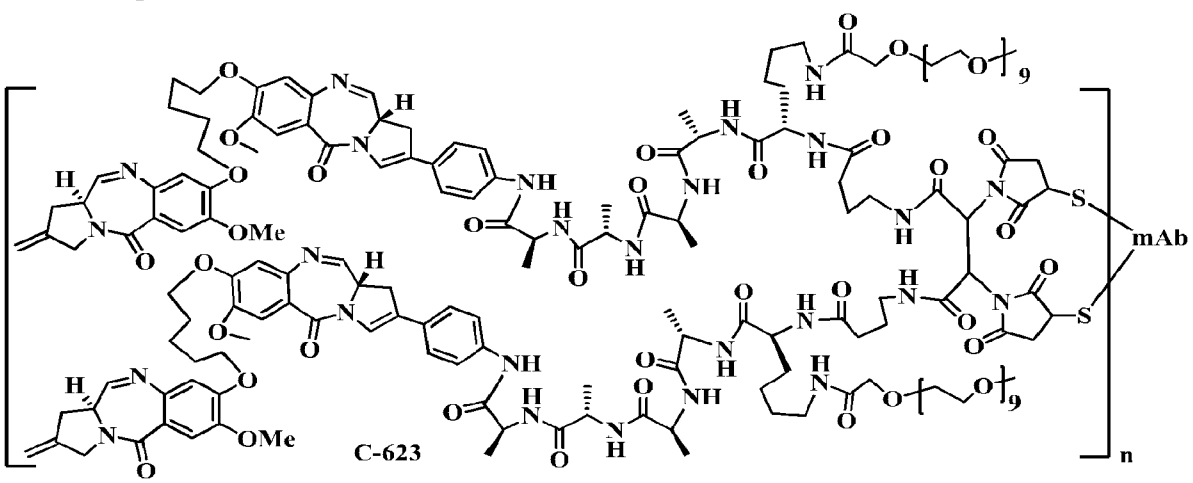

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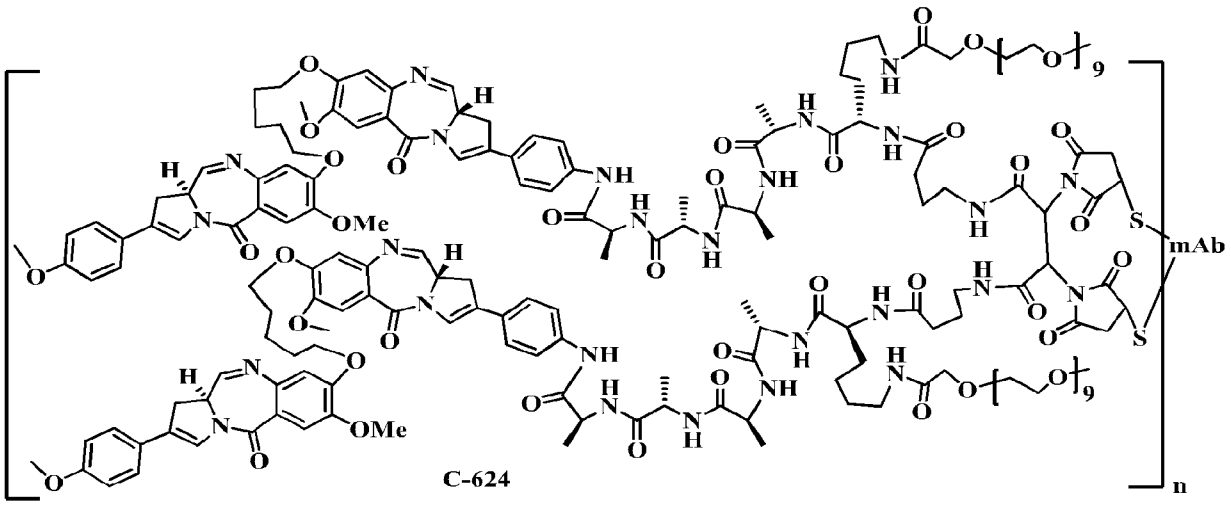

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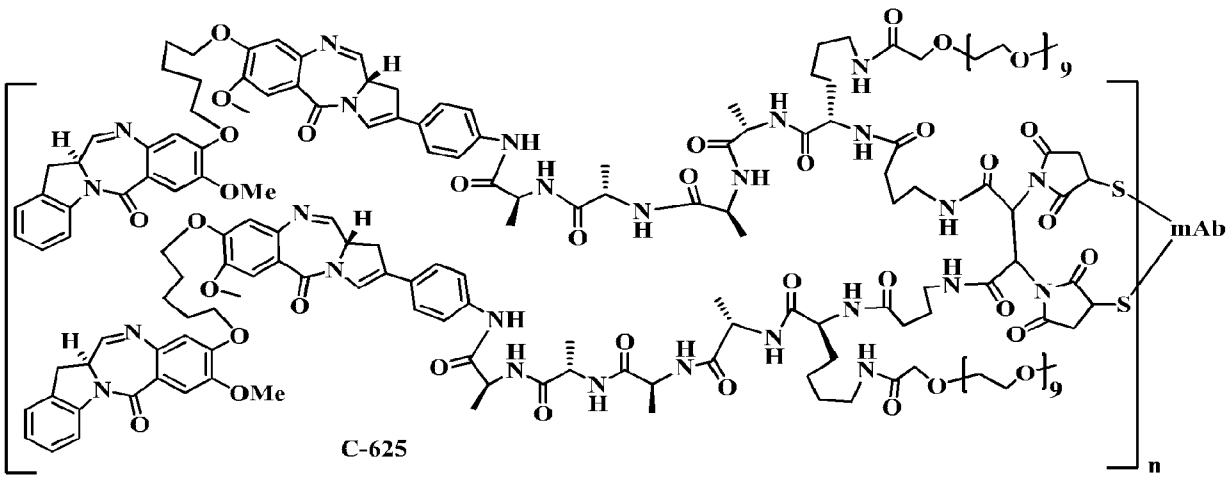

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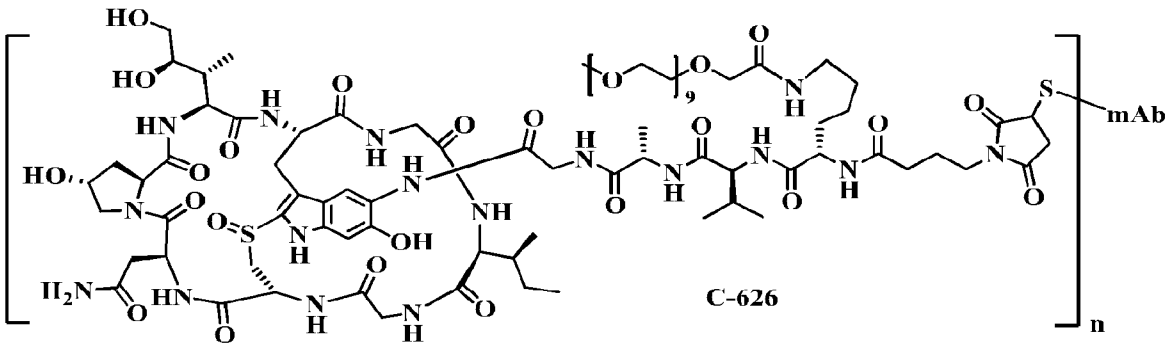

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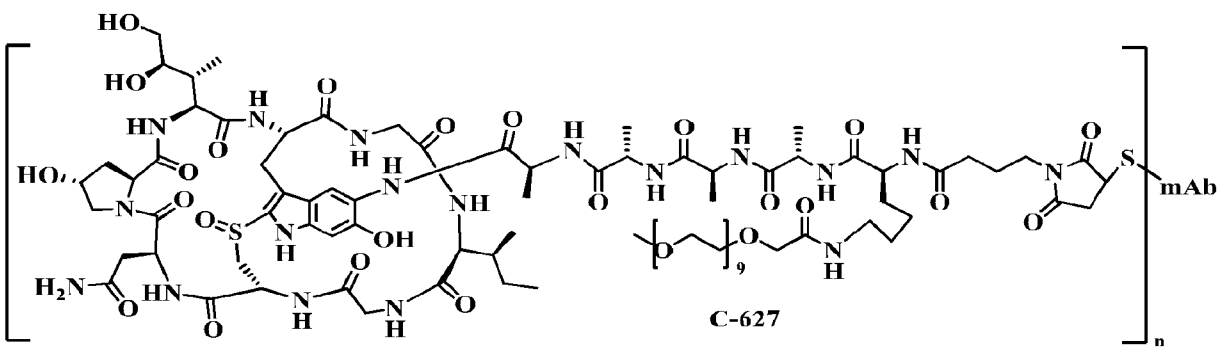

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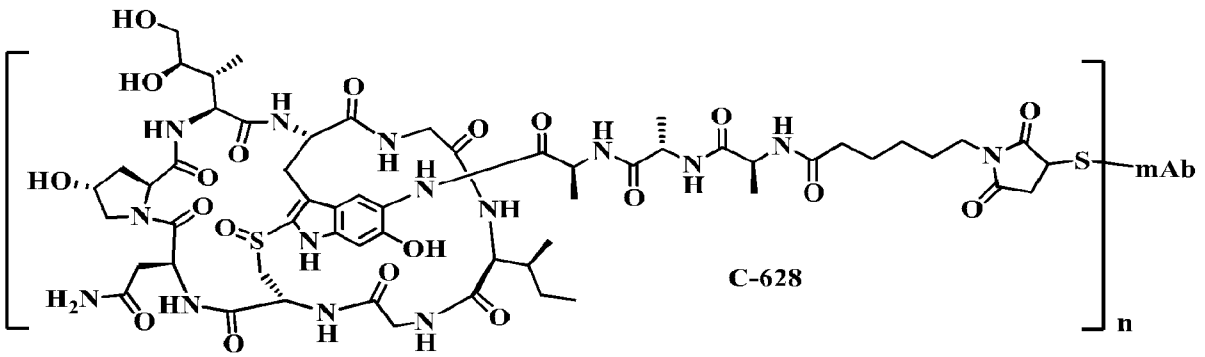

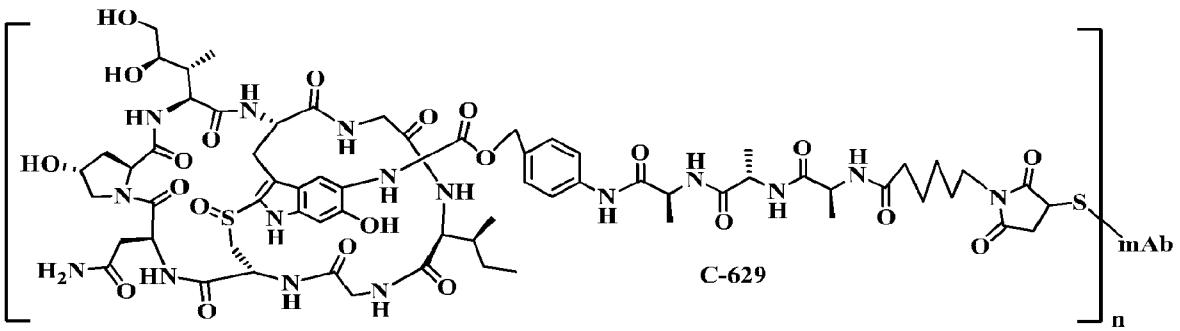

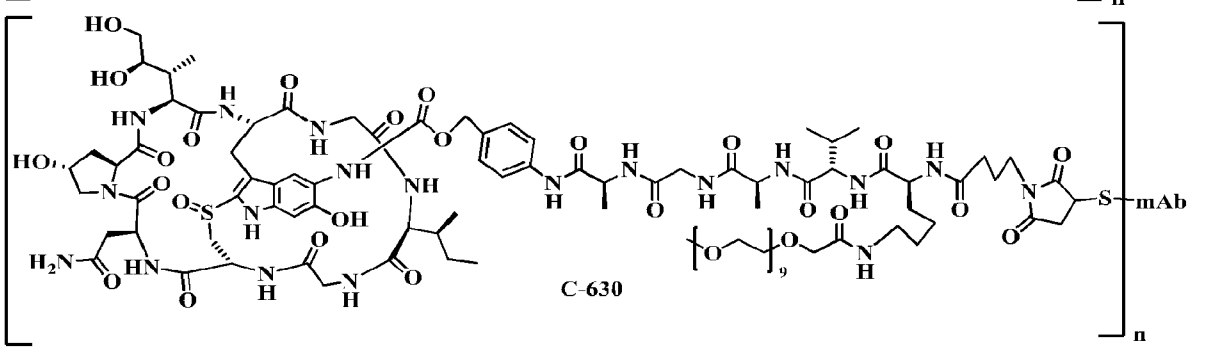

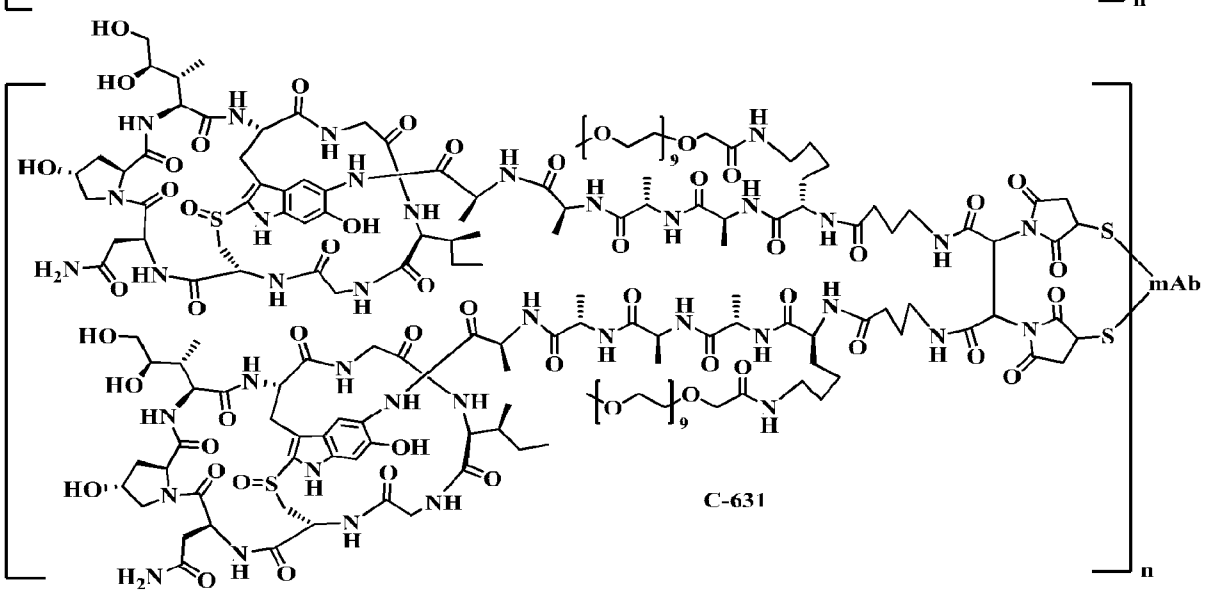

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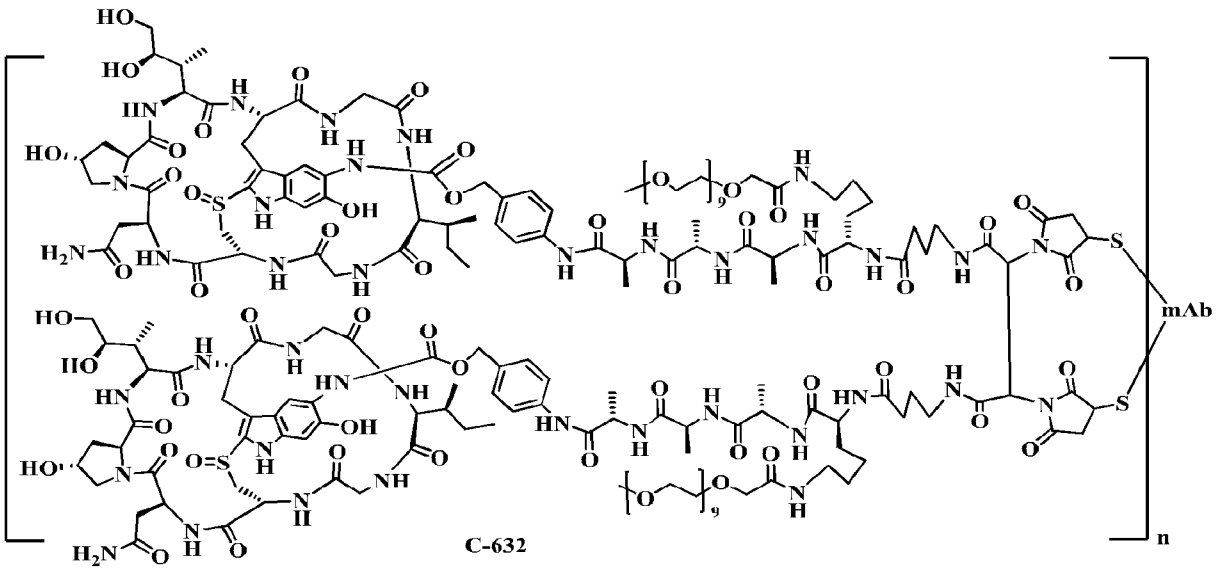

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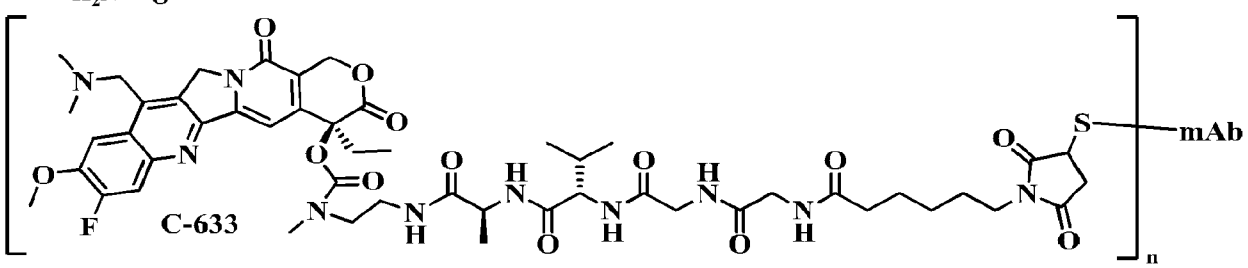

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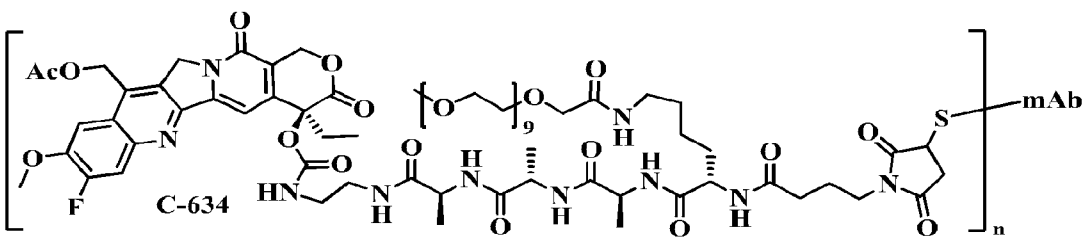

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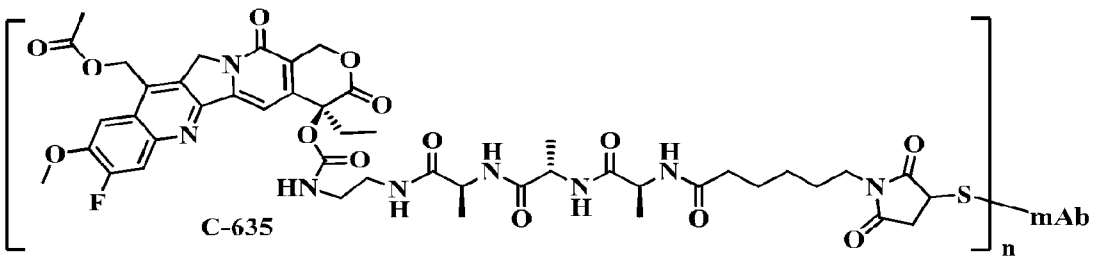

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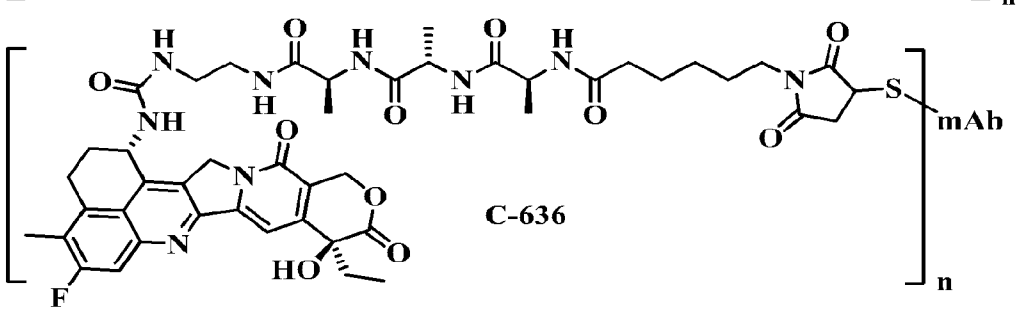

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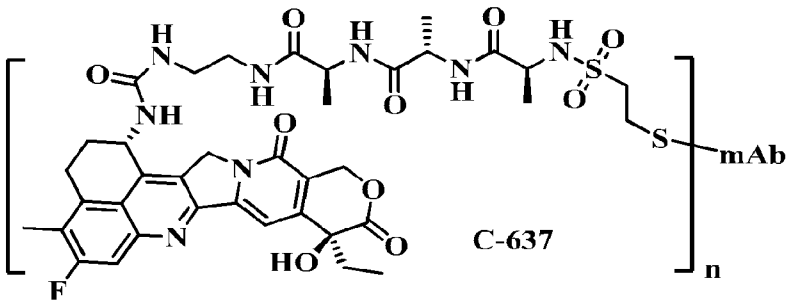

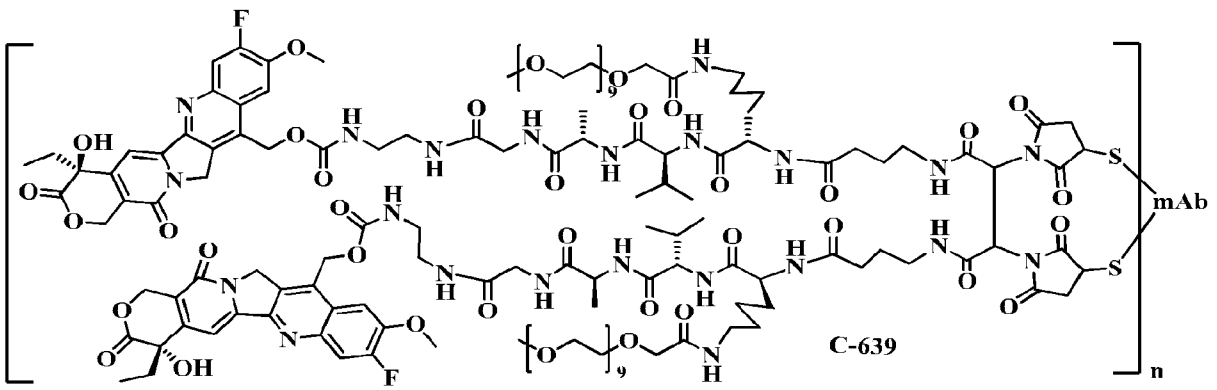

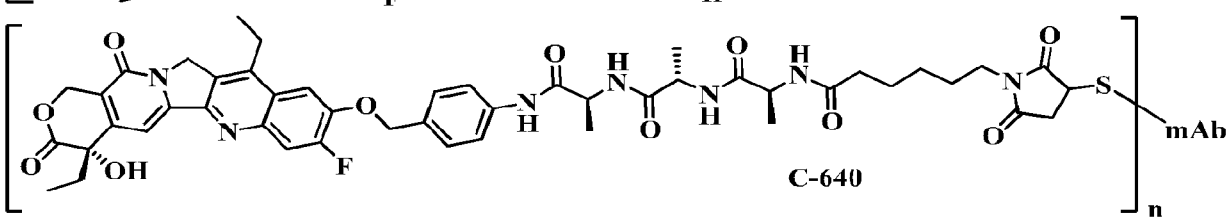

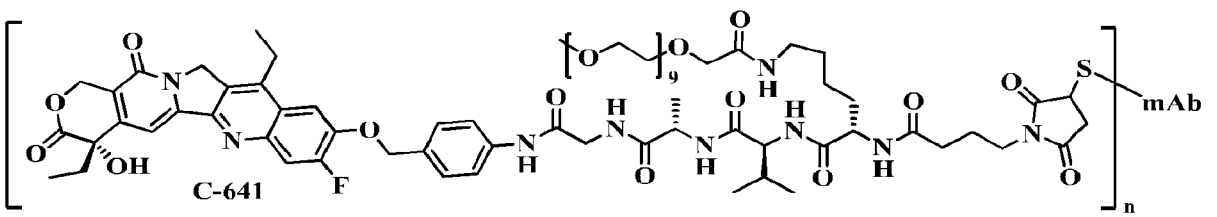

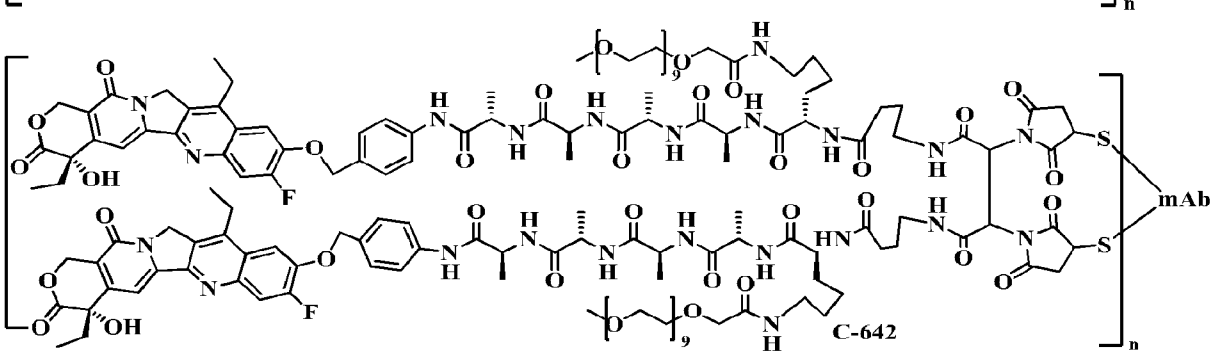

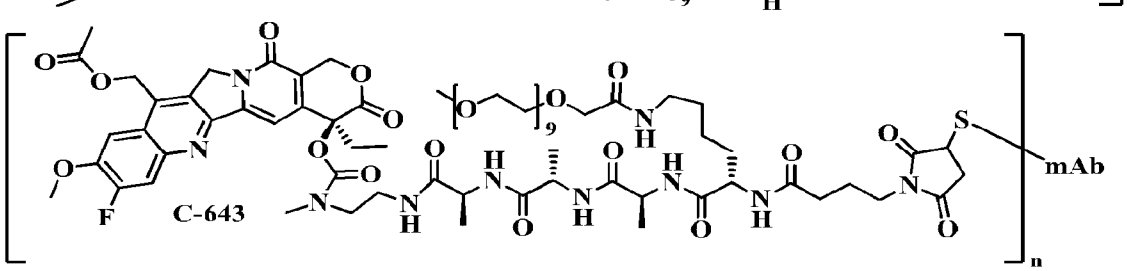

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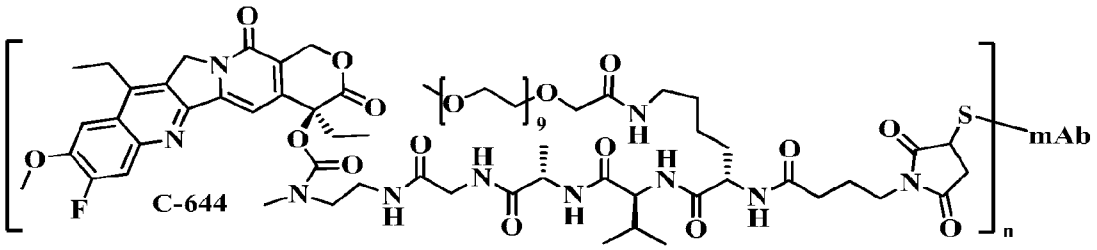

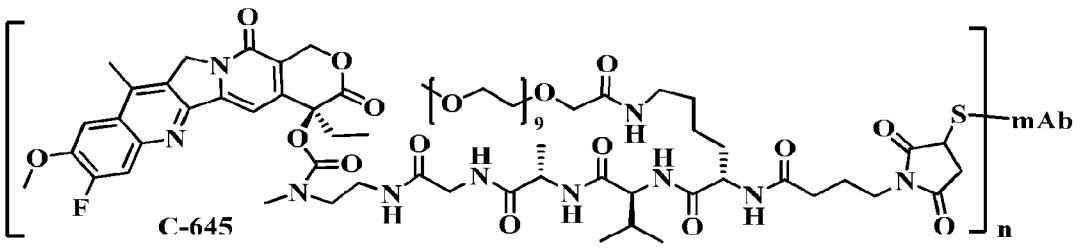

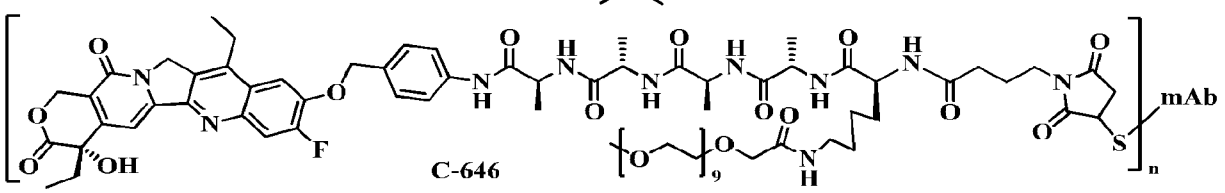

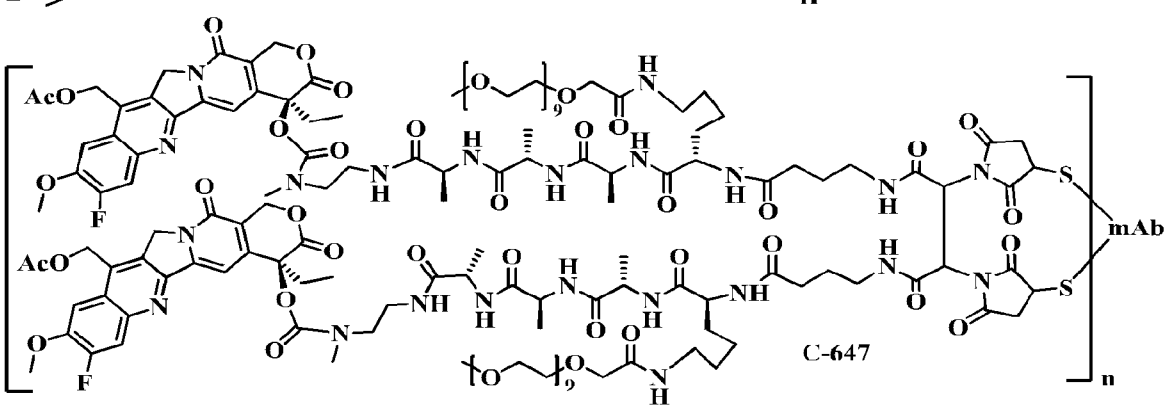

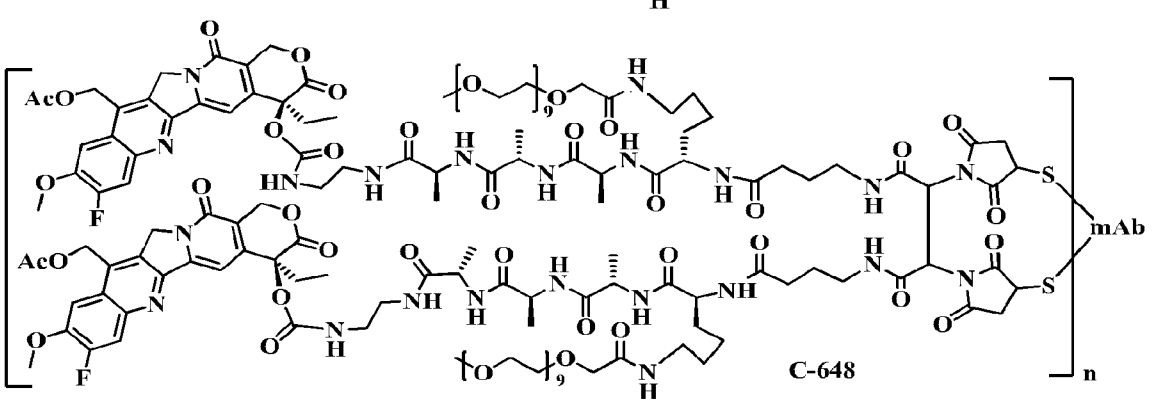

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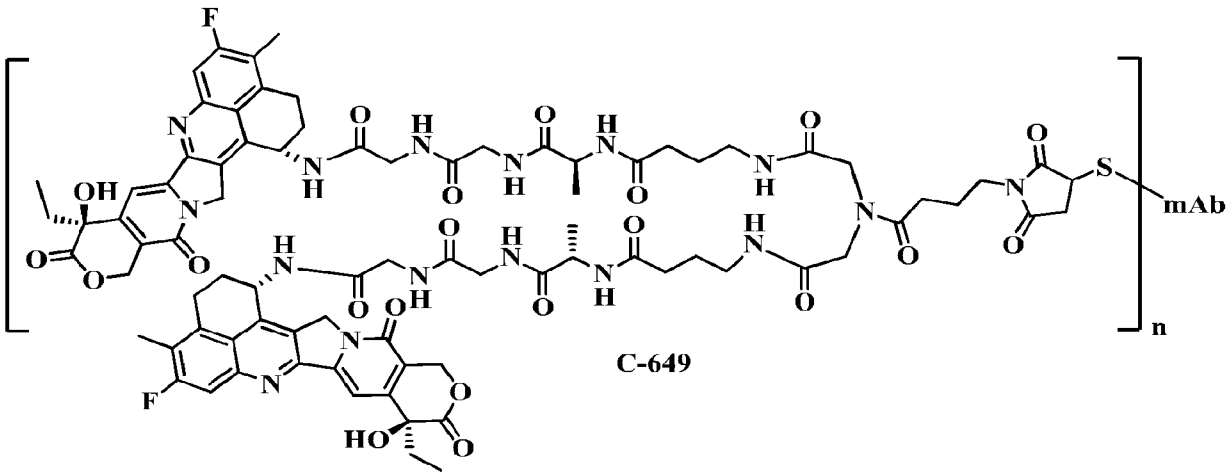

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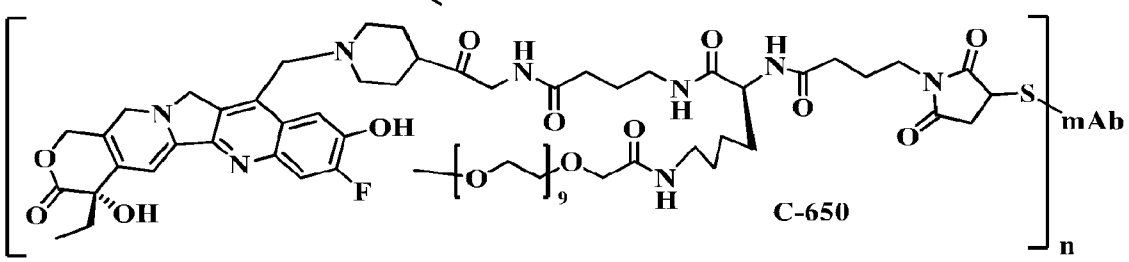

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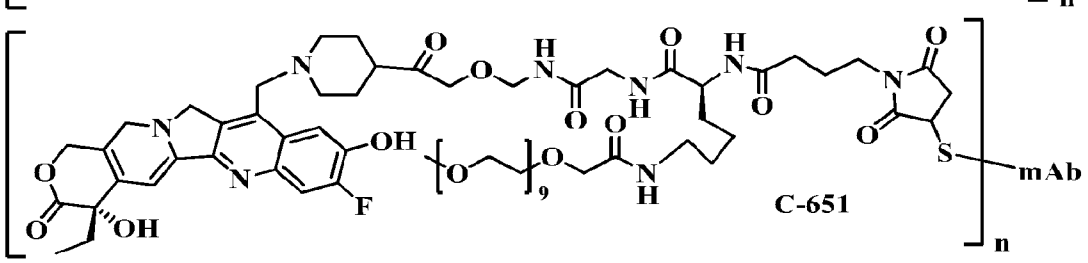

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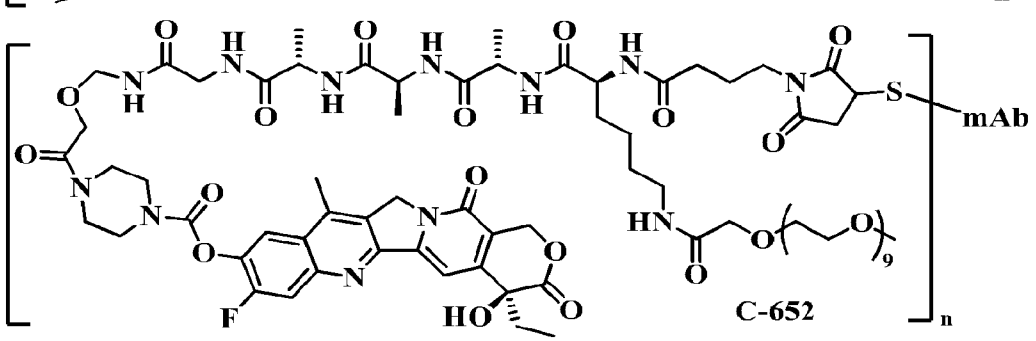

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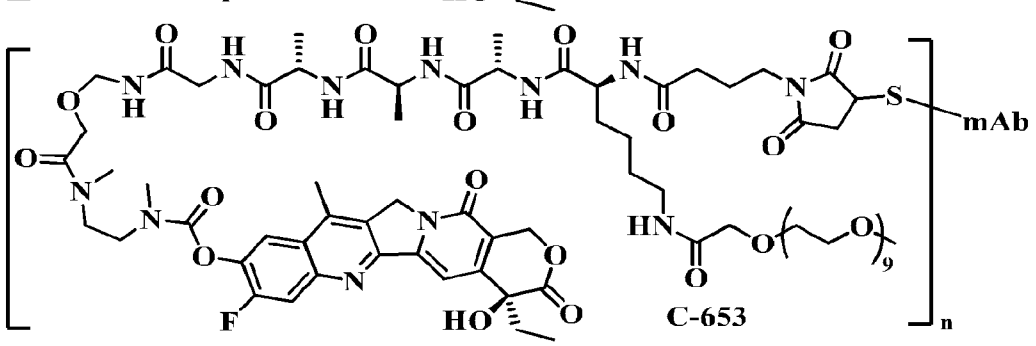

C-653

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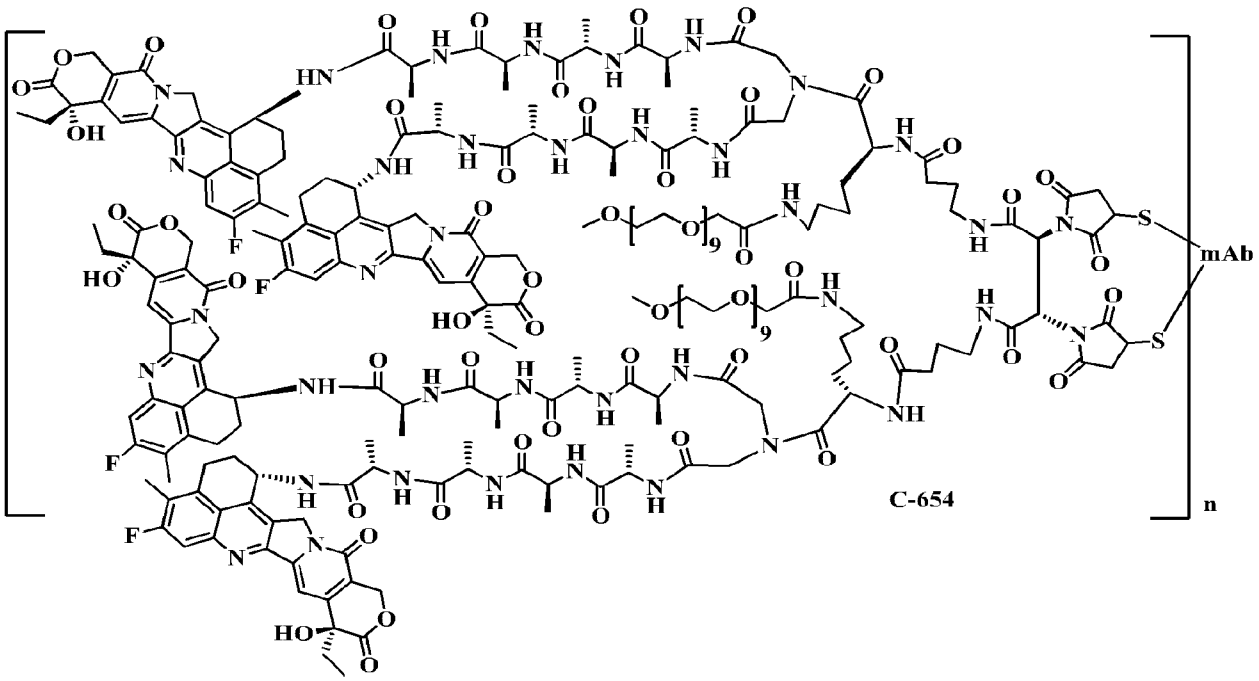
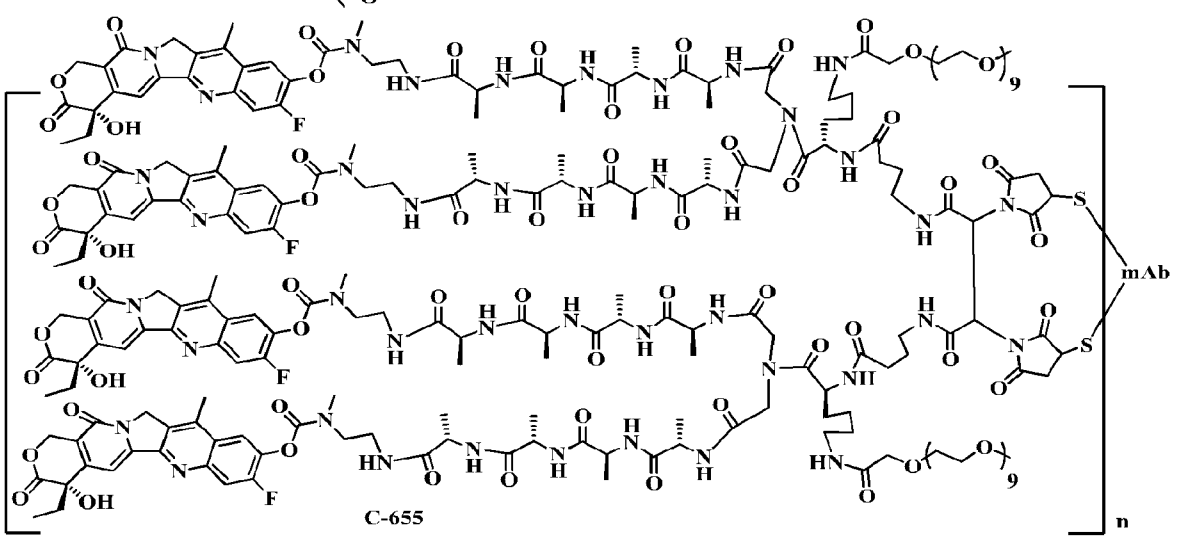
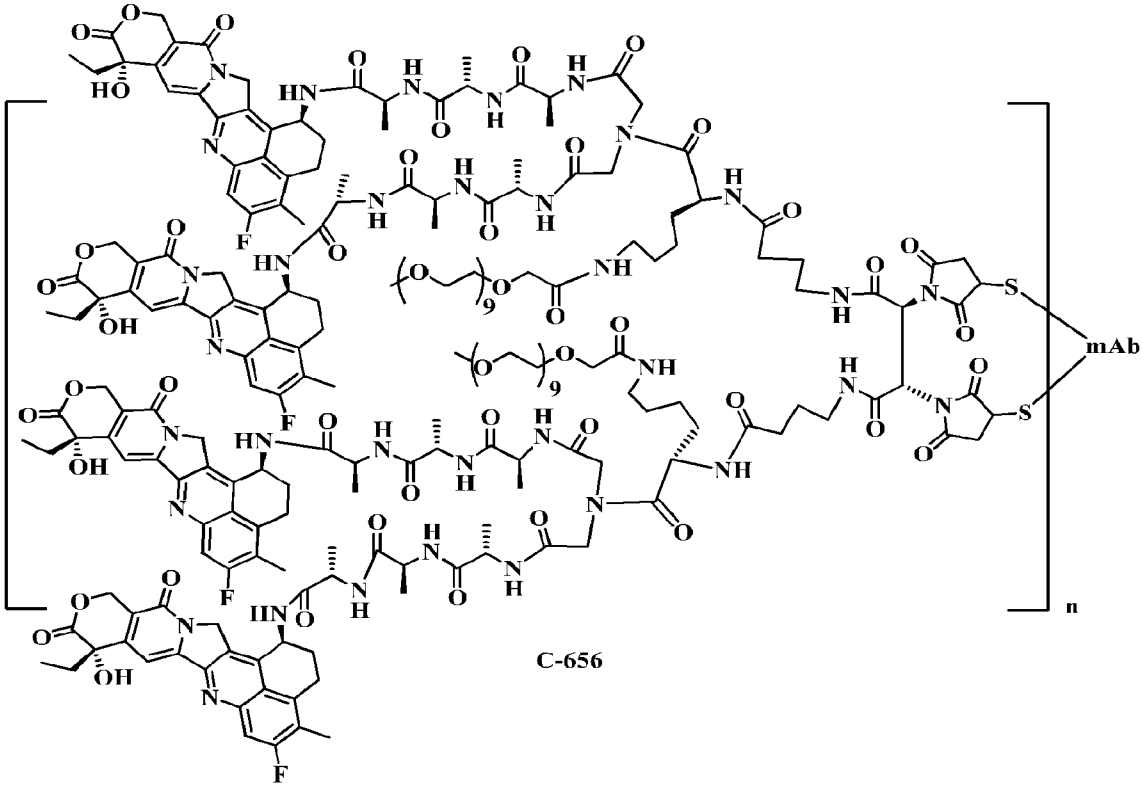


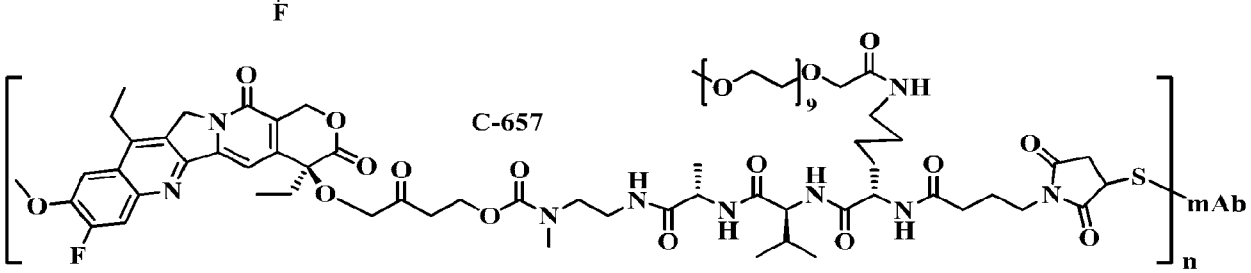
C-654



C-655



C-656



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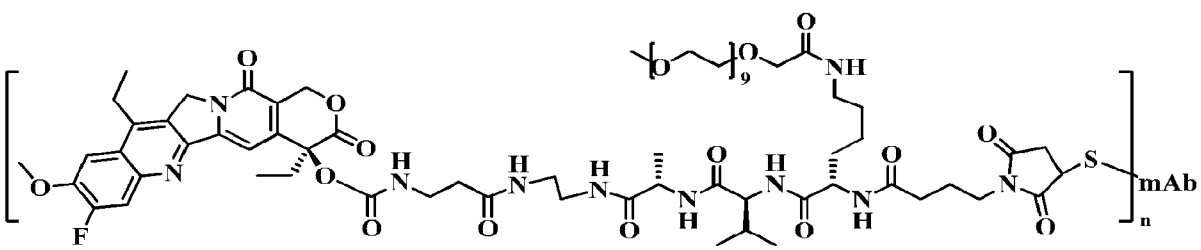

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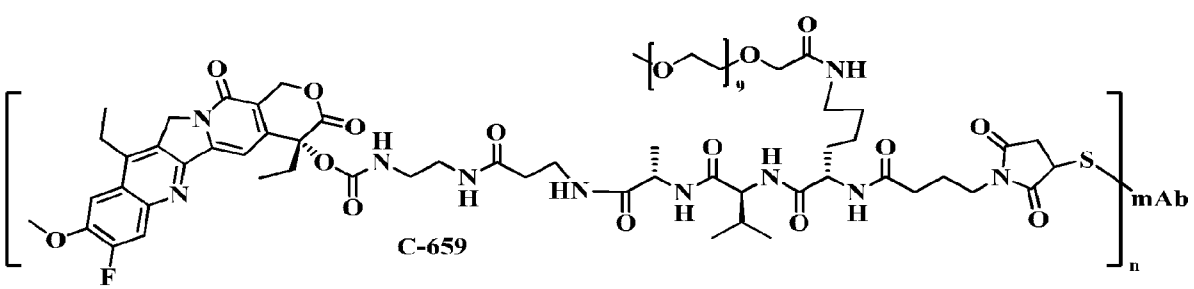

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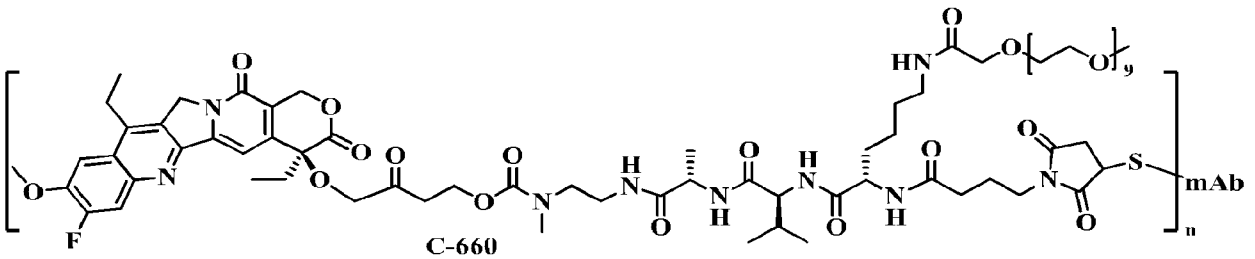
CA 03236754 2024-4-30



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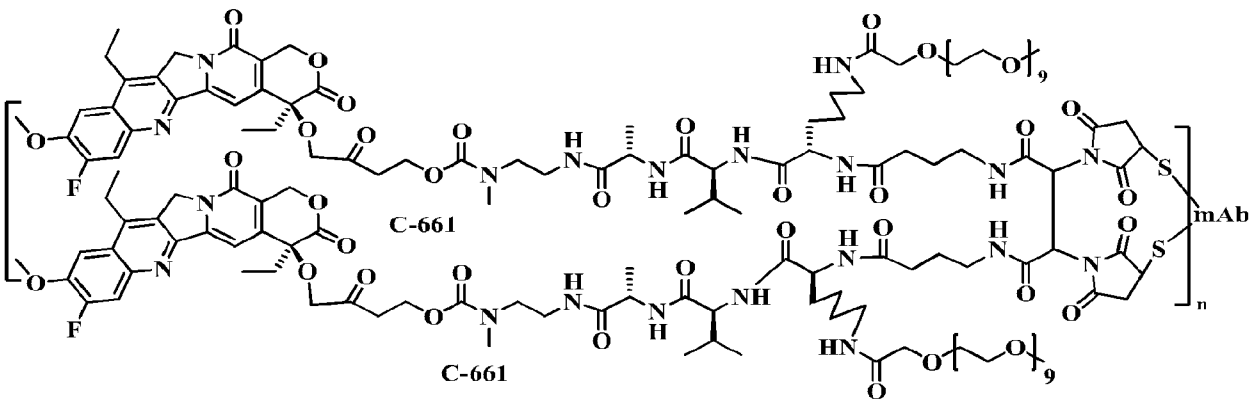

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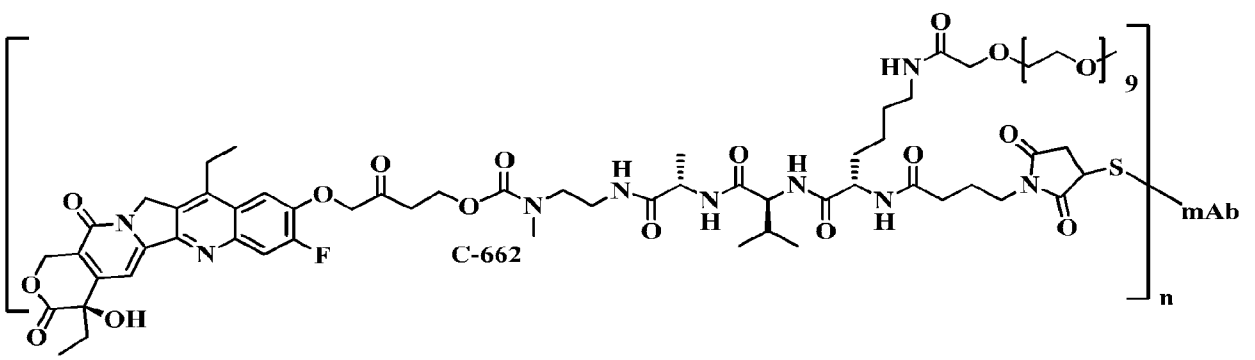

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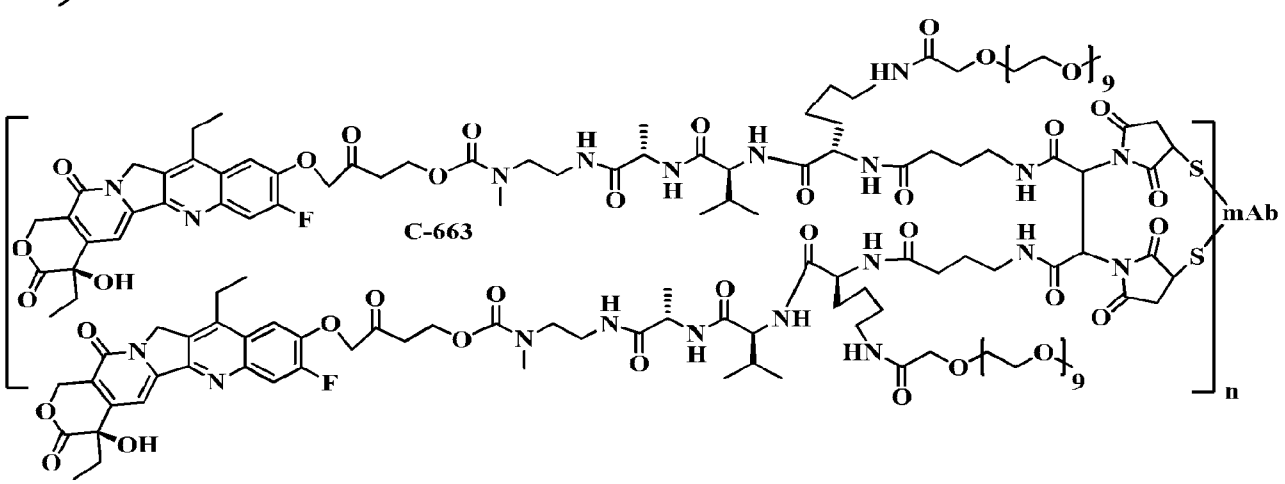

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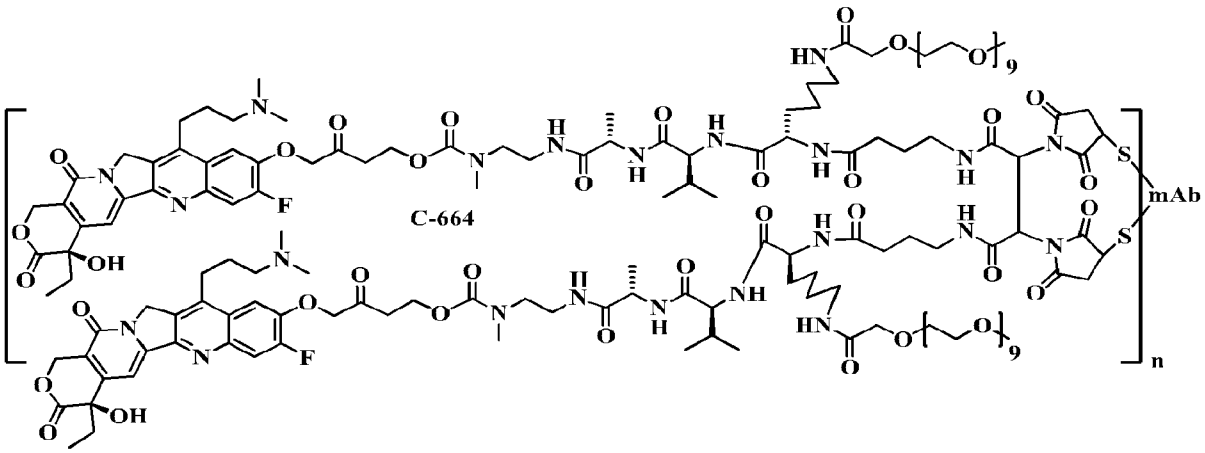
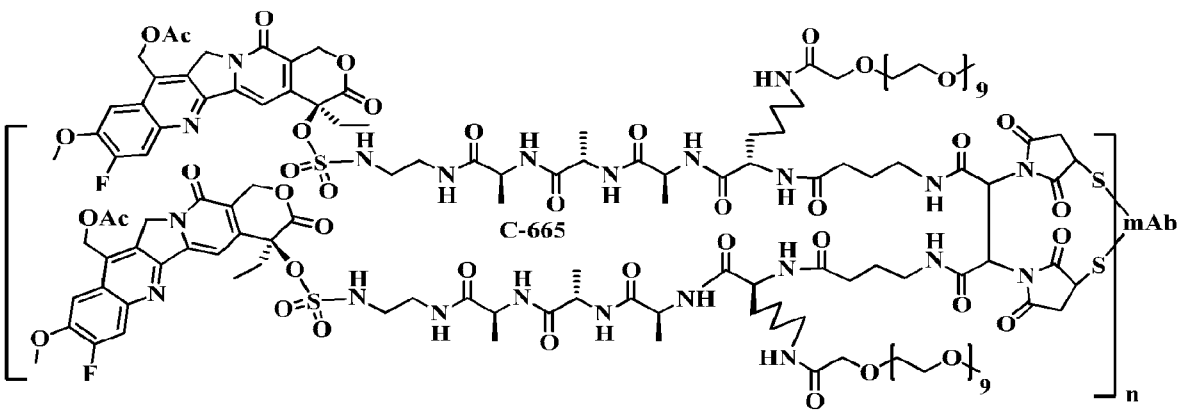
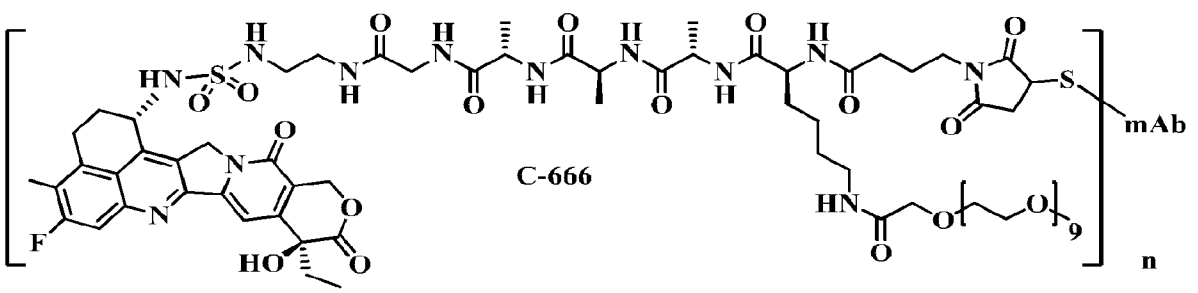
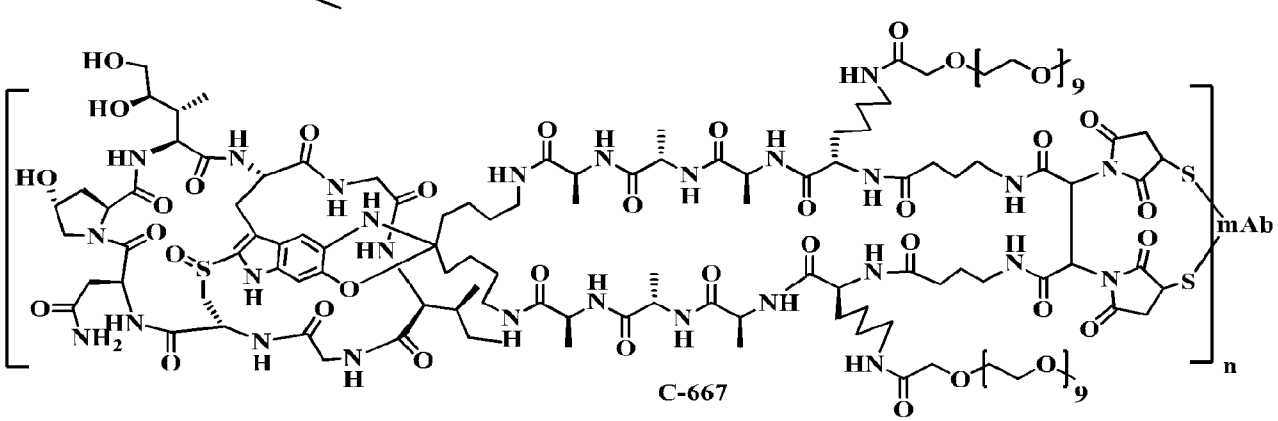
CA 03236754 2024-4-30









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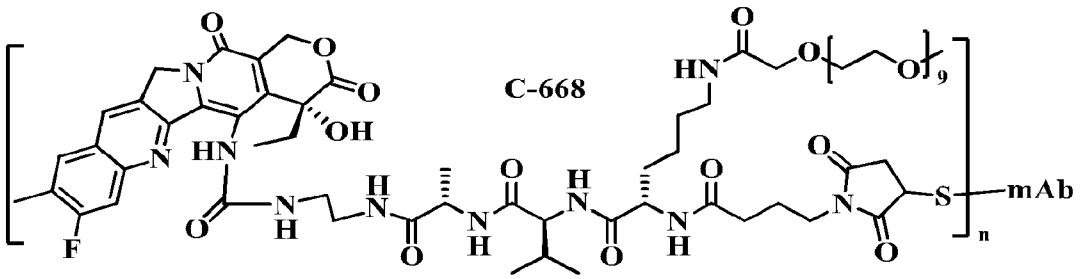
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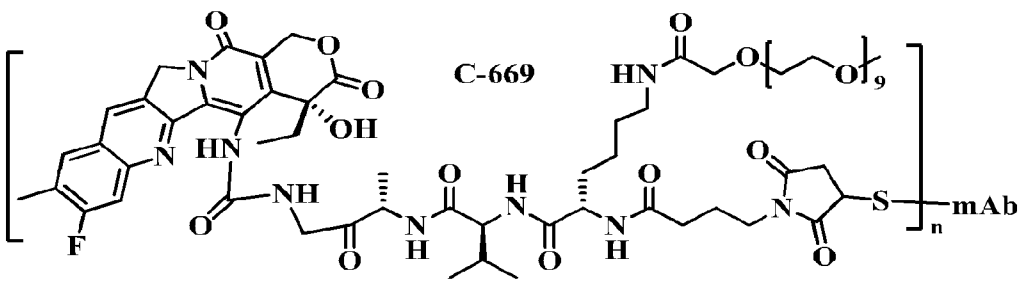
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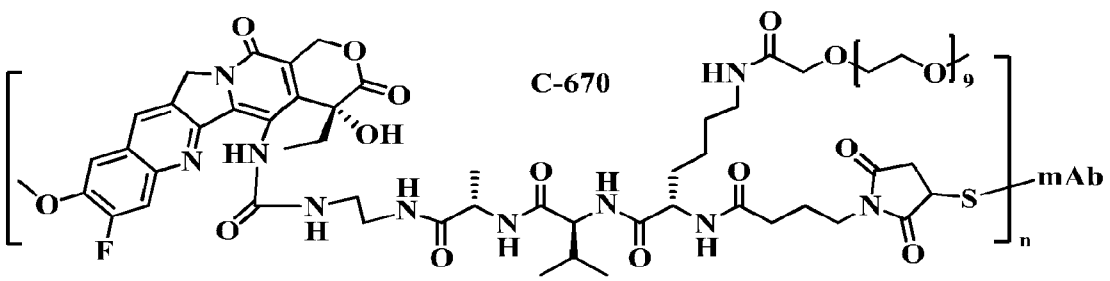
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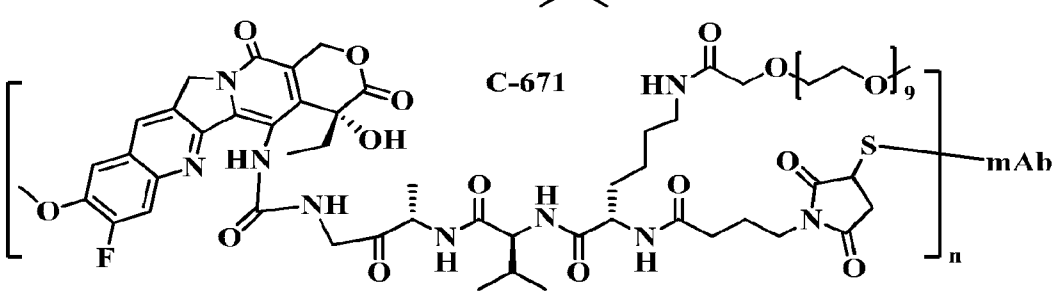
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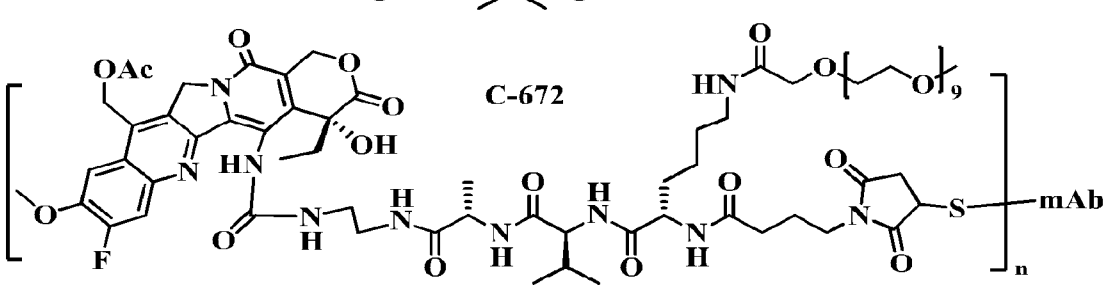
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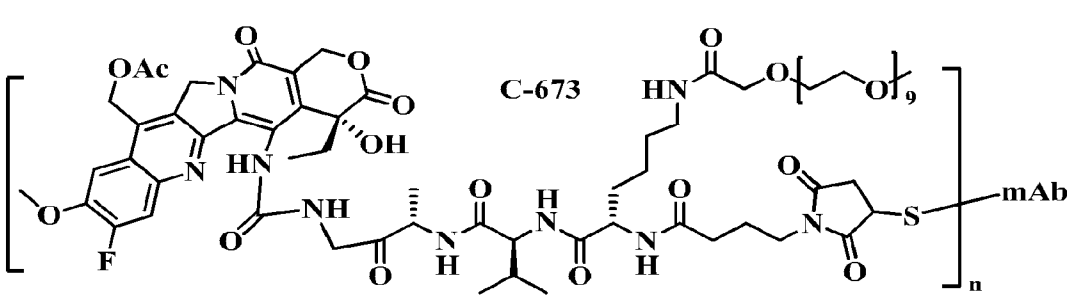
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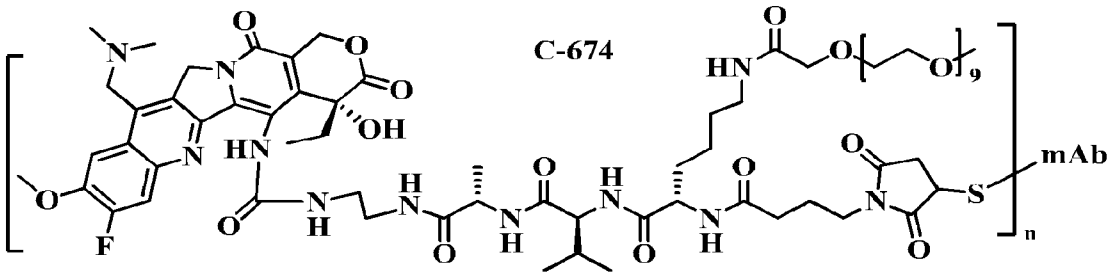
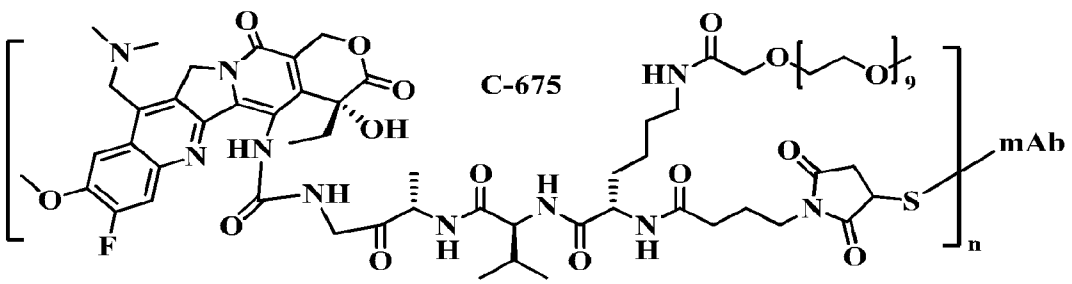
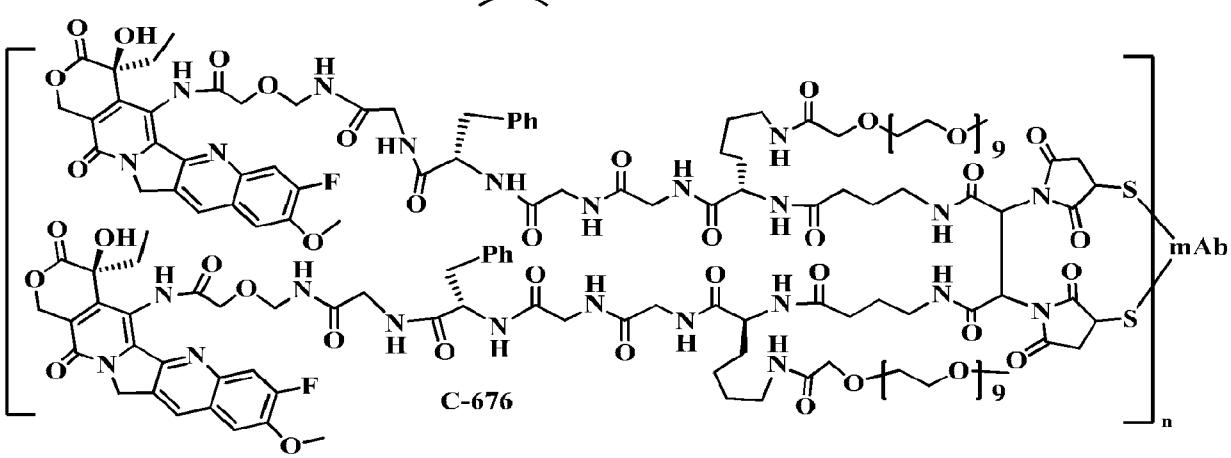
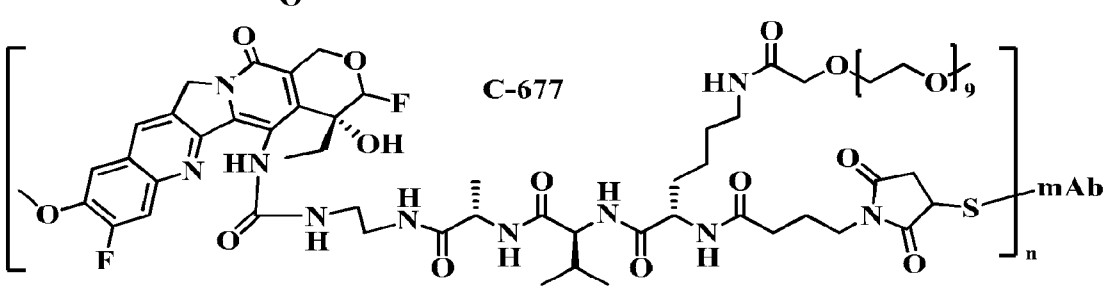
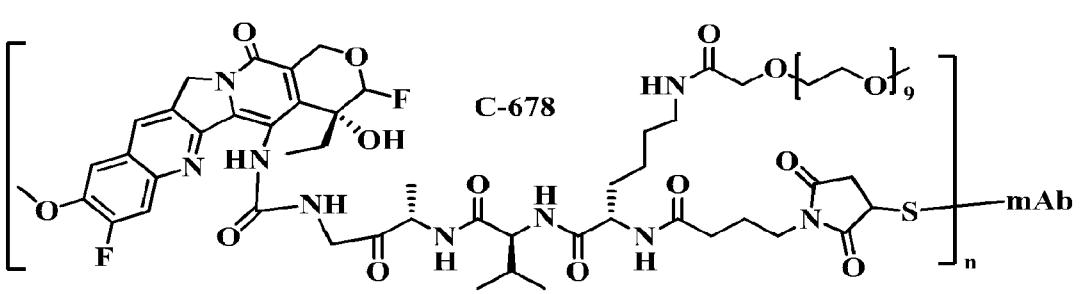


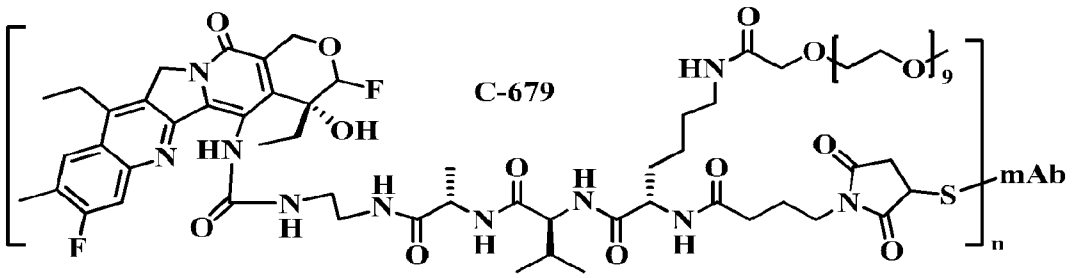


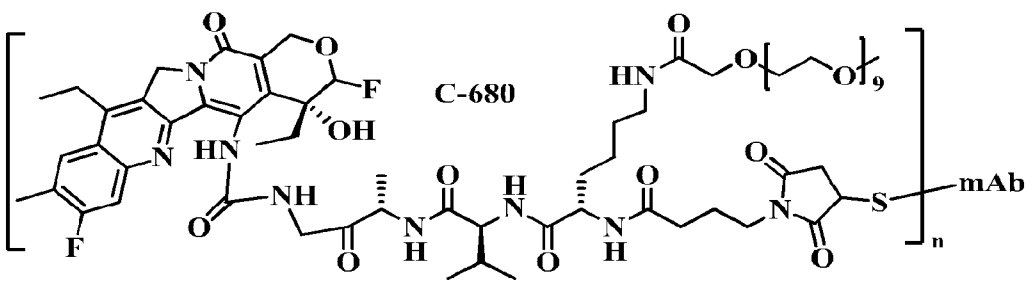


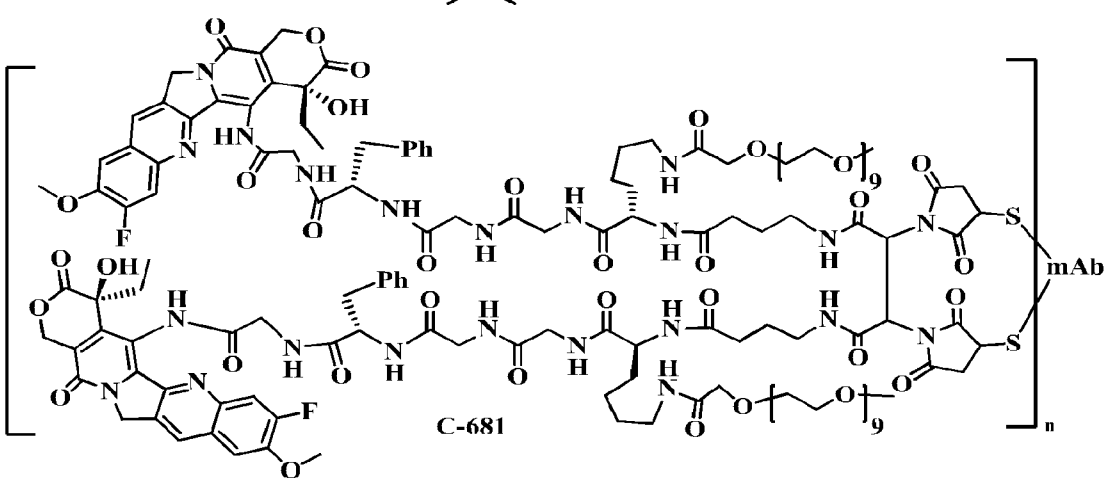


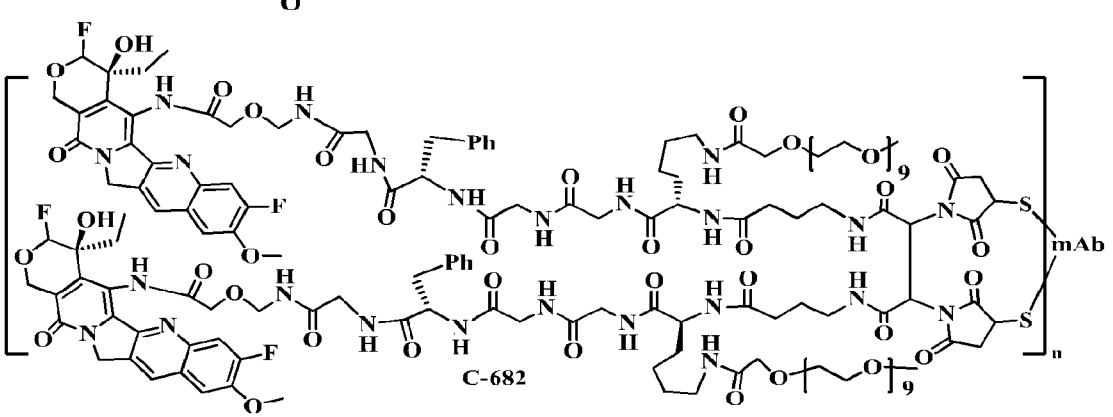


CA 03236754 2024-4-30

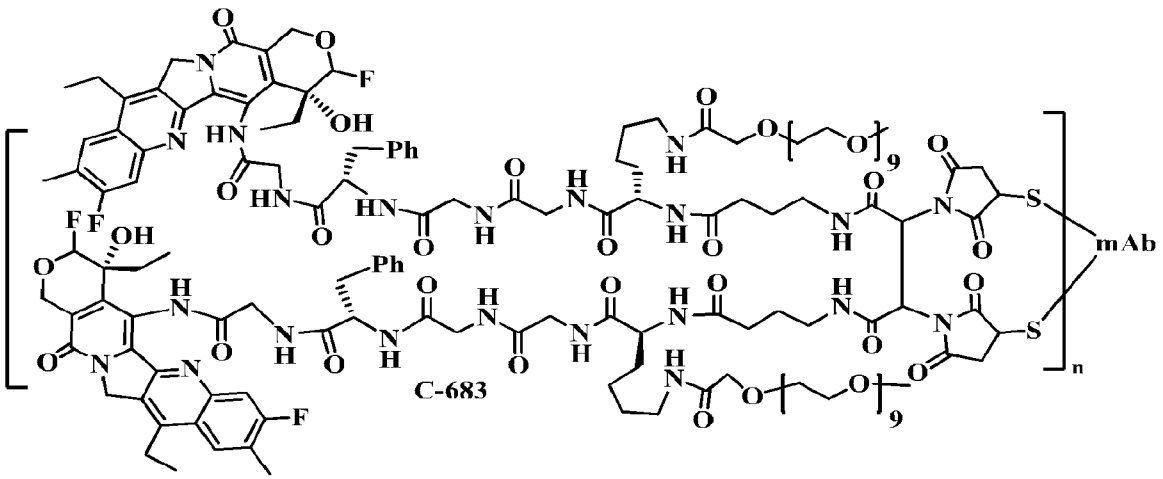








CA 03236754 2024-4-30



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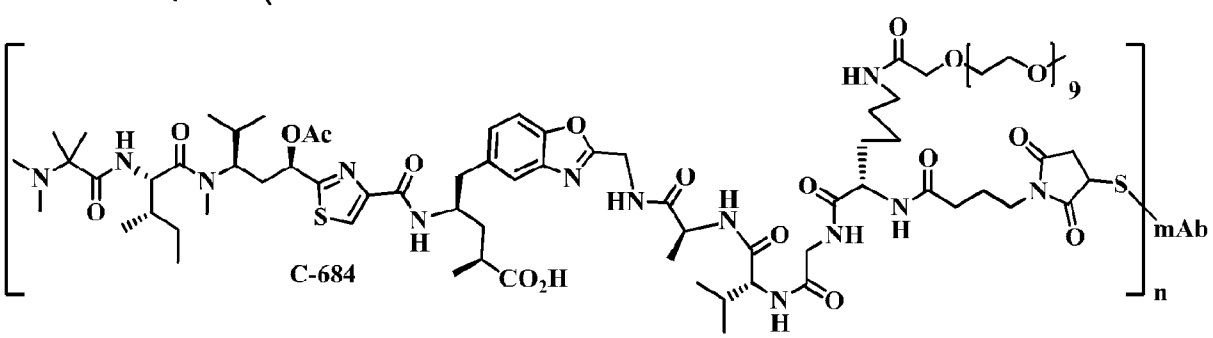

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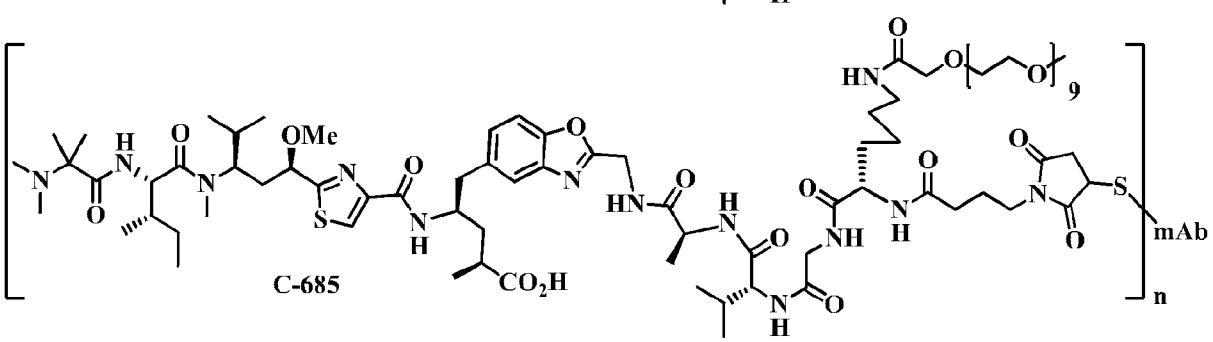

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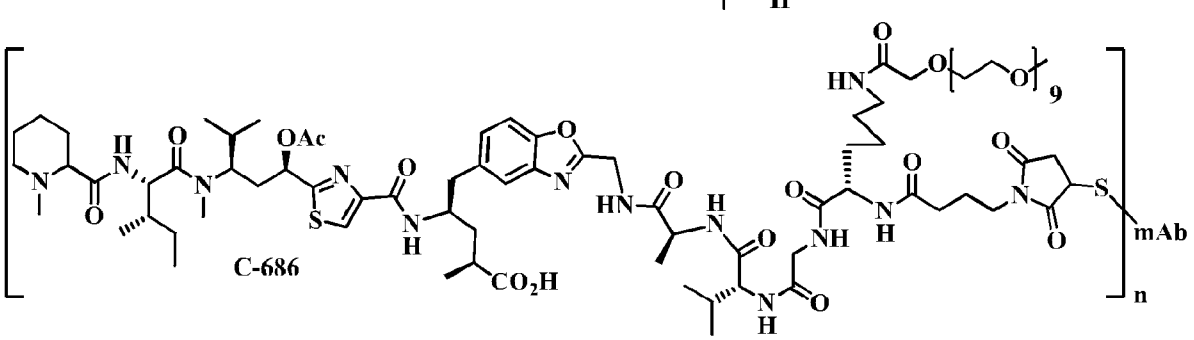

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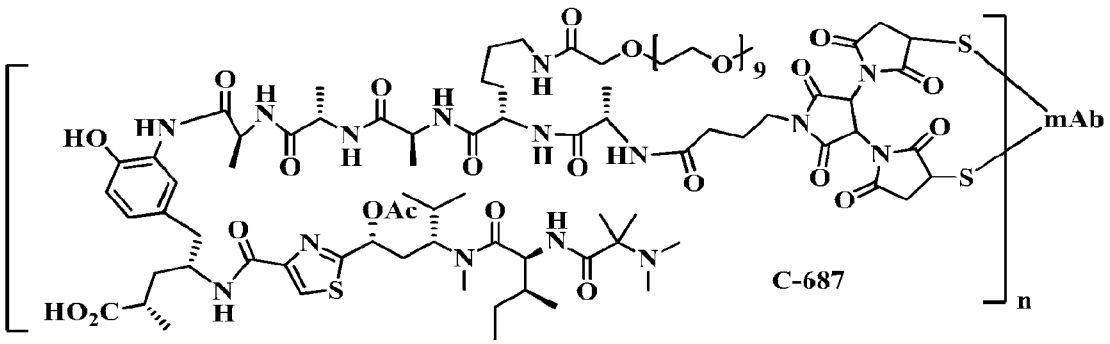

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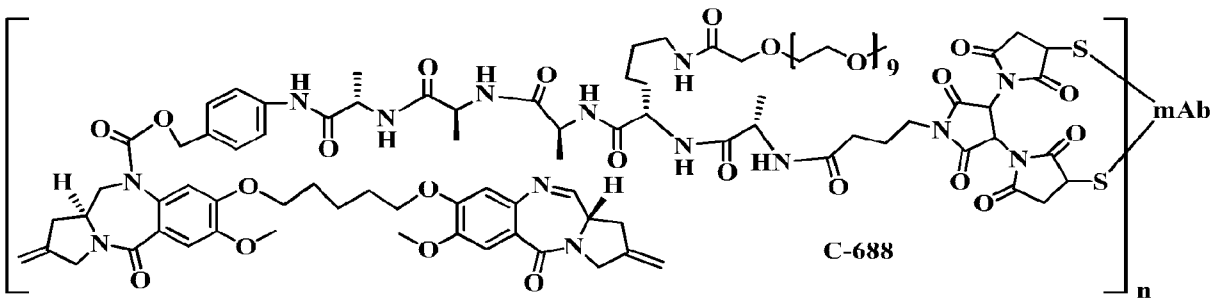

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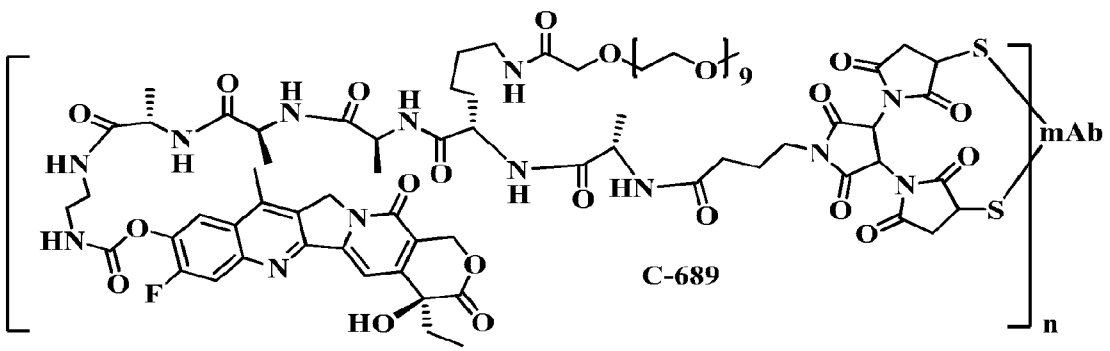

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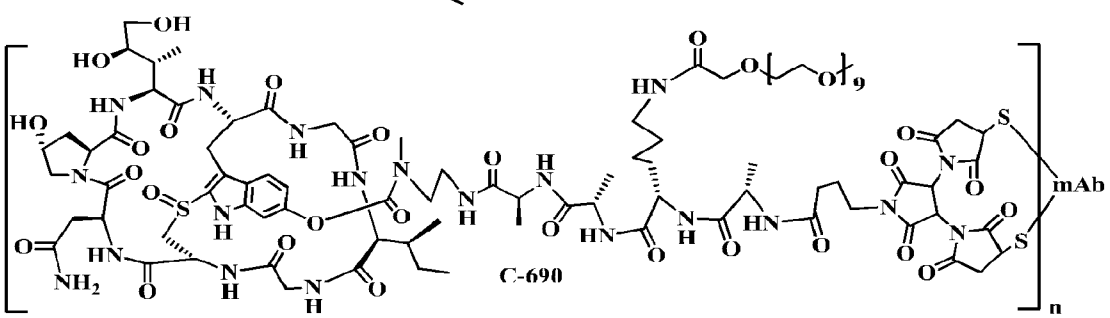

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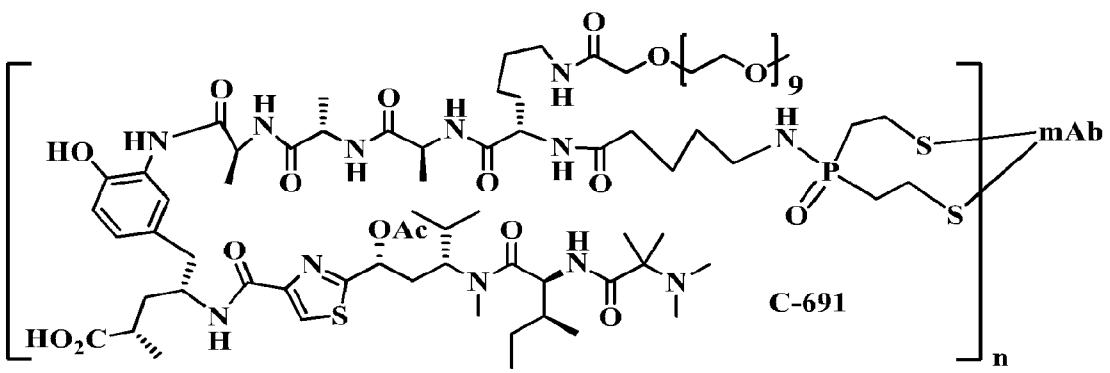

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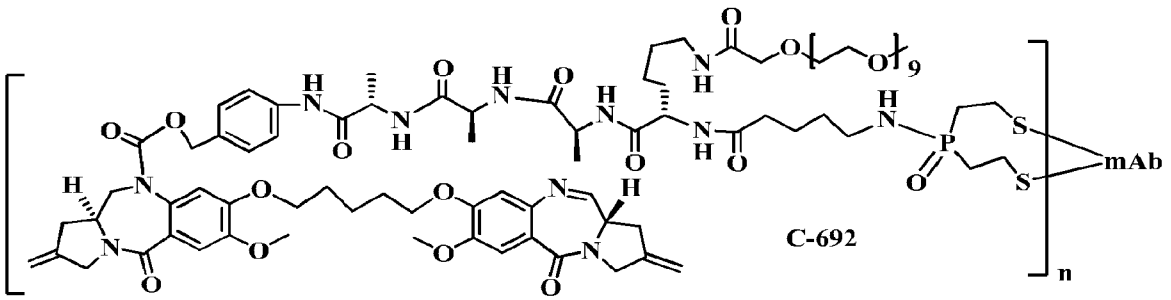

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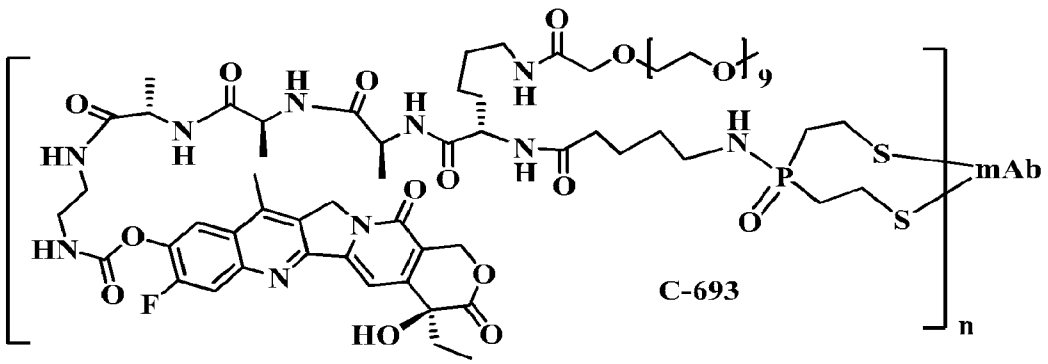

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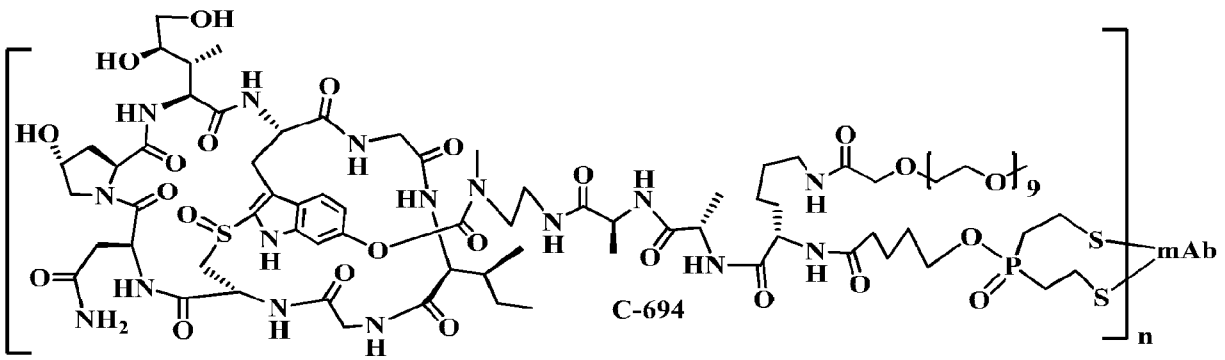

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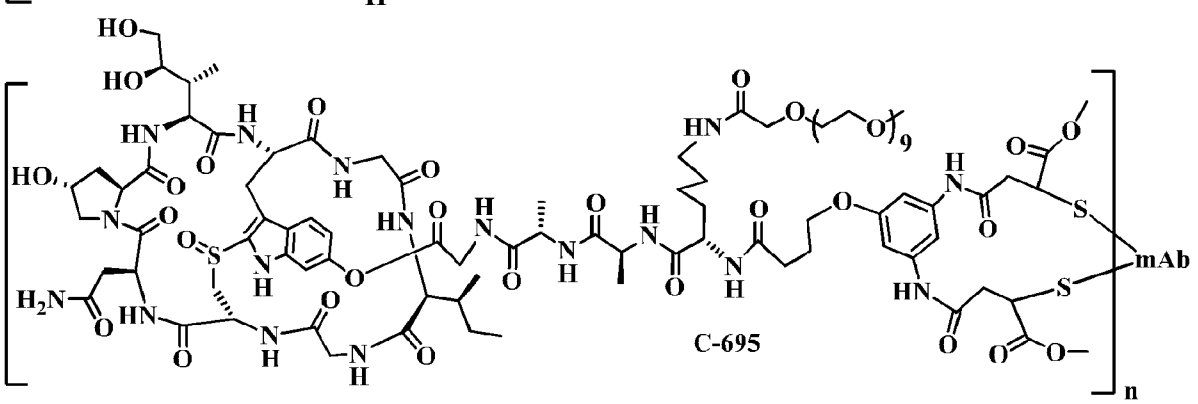

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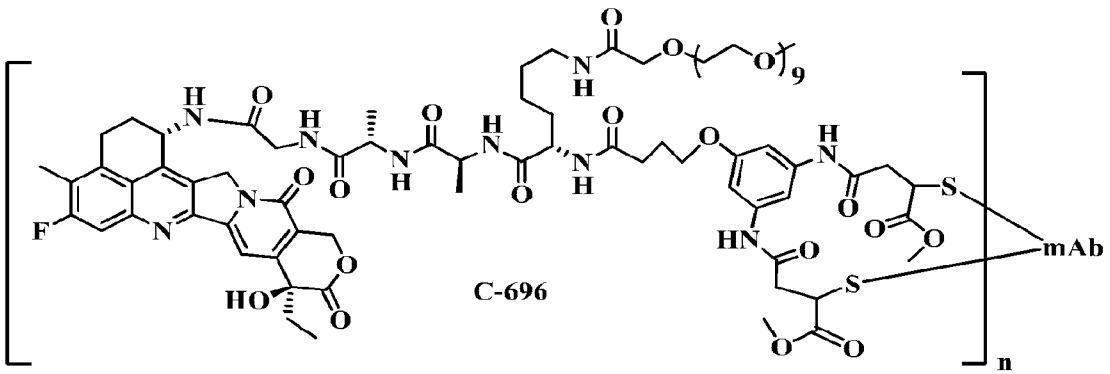

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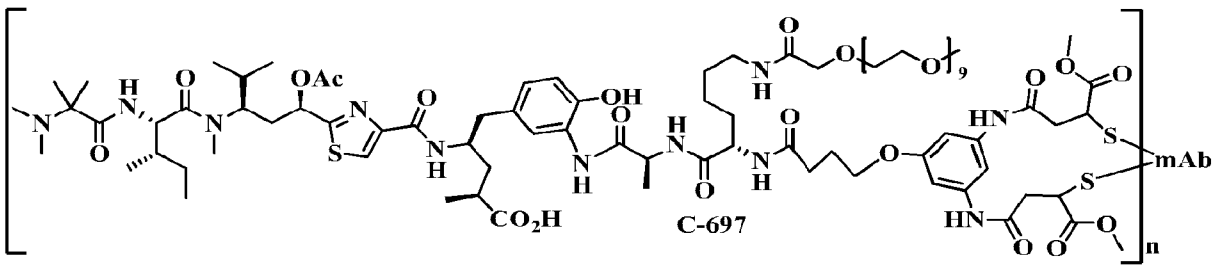

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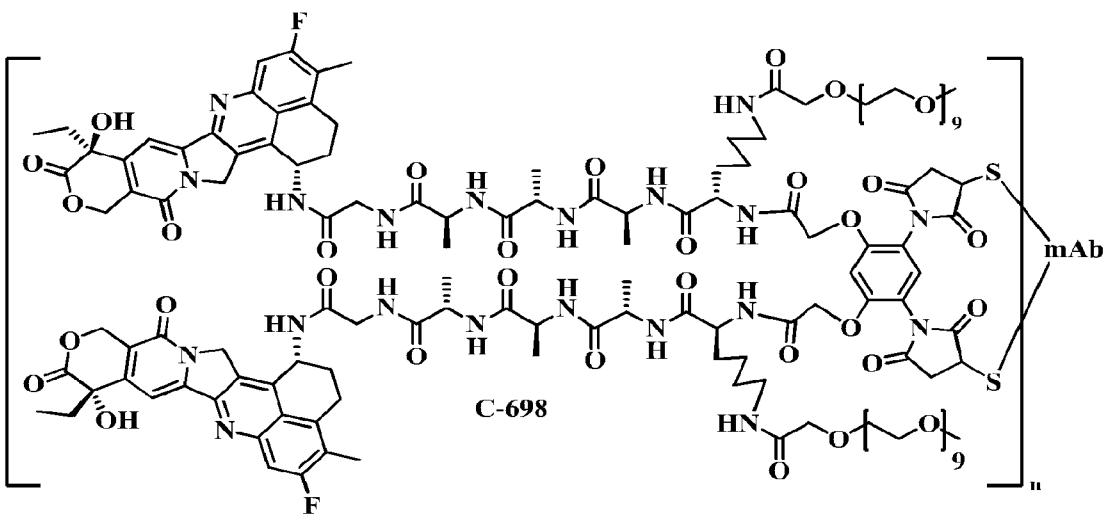

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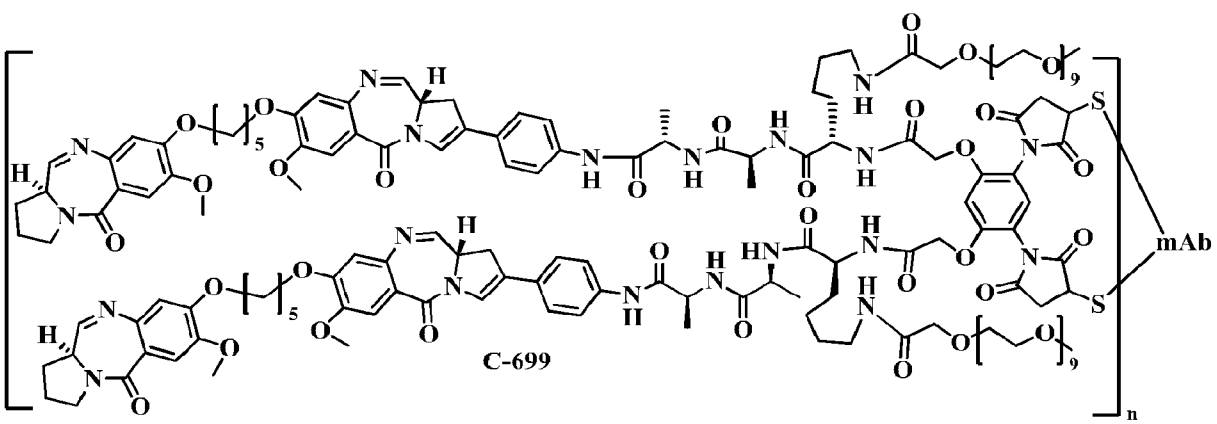

C-699

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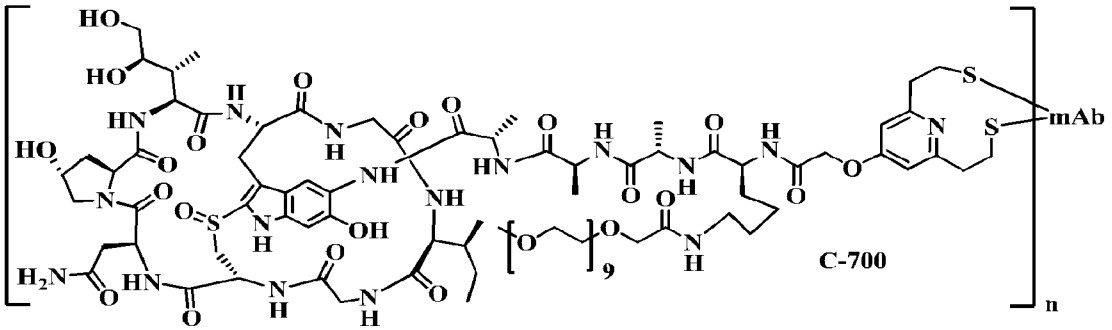
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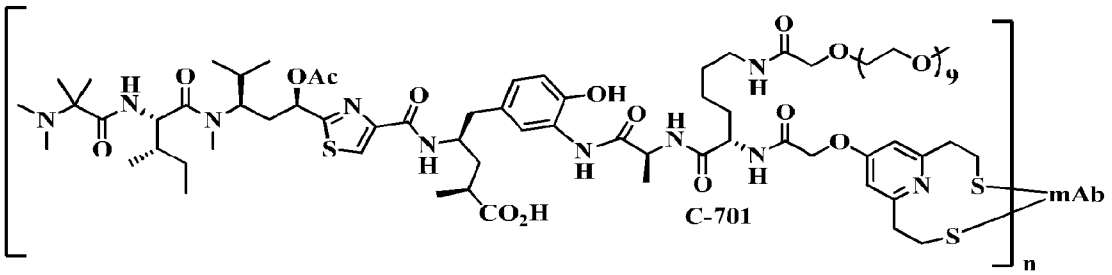
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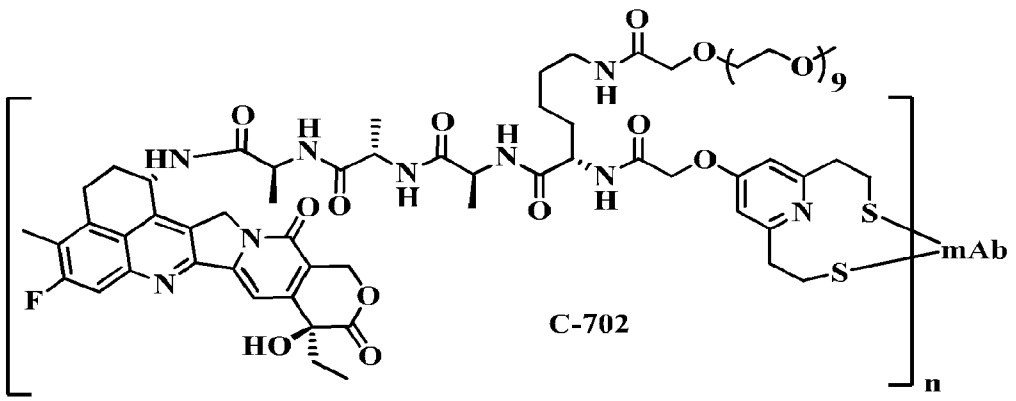
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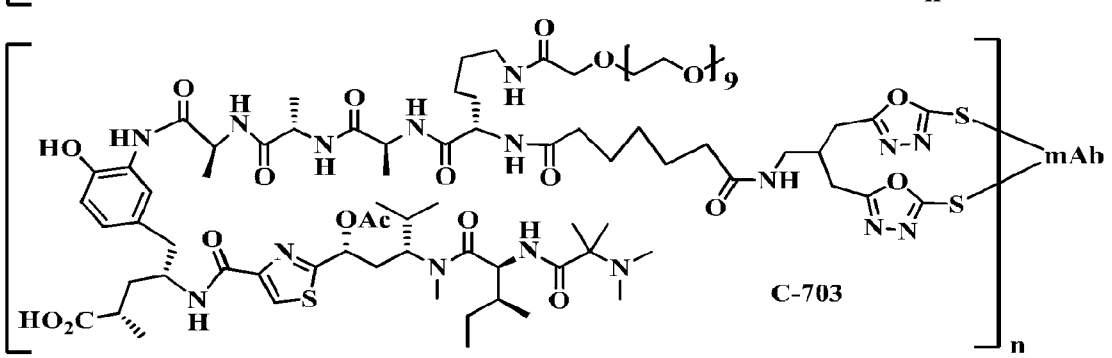
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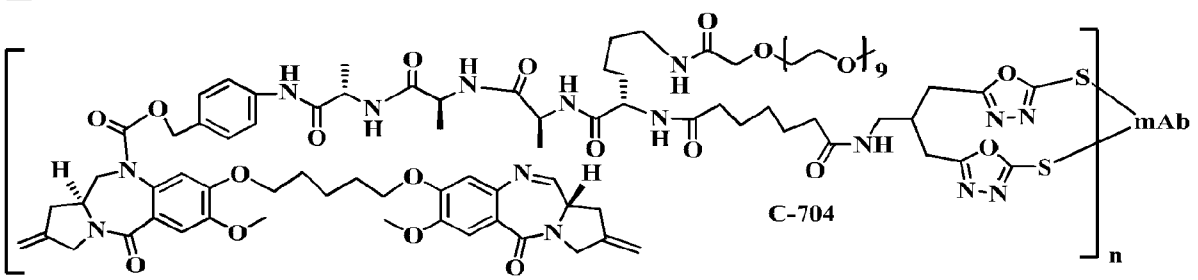
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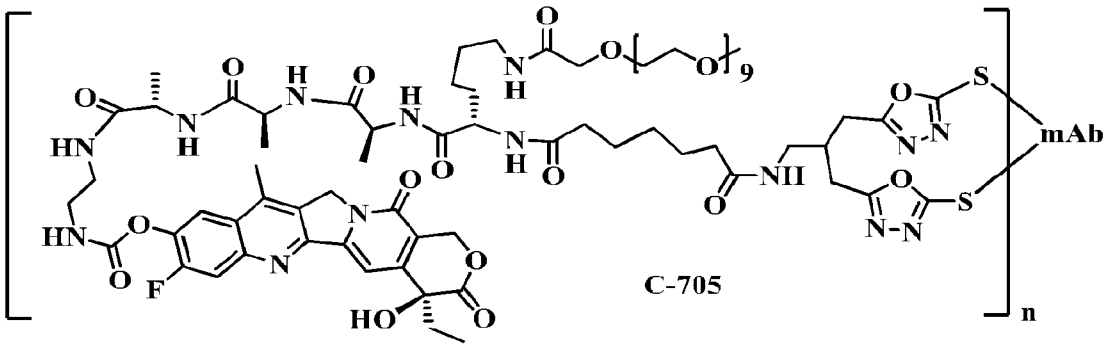

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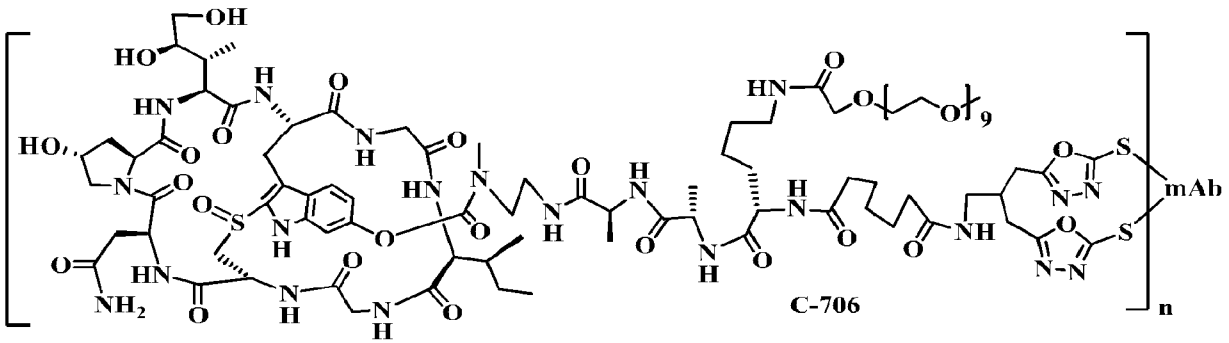

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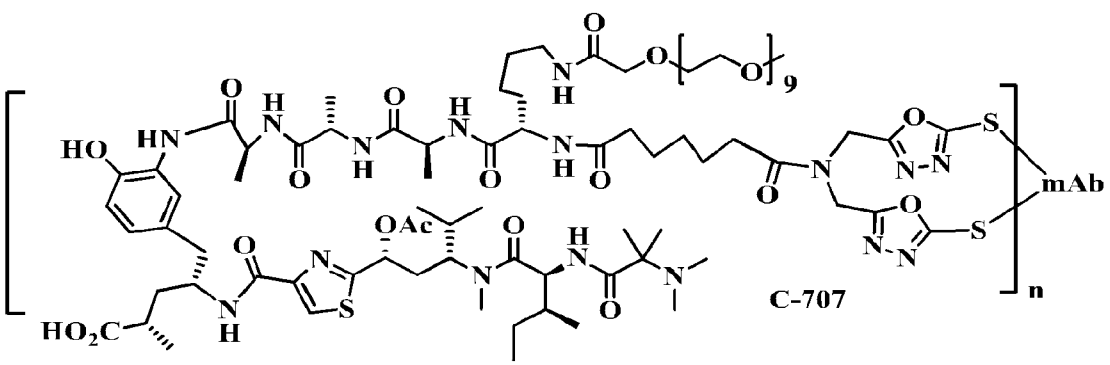

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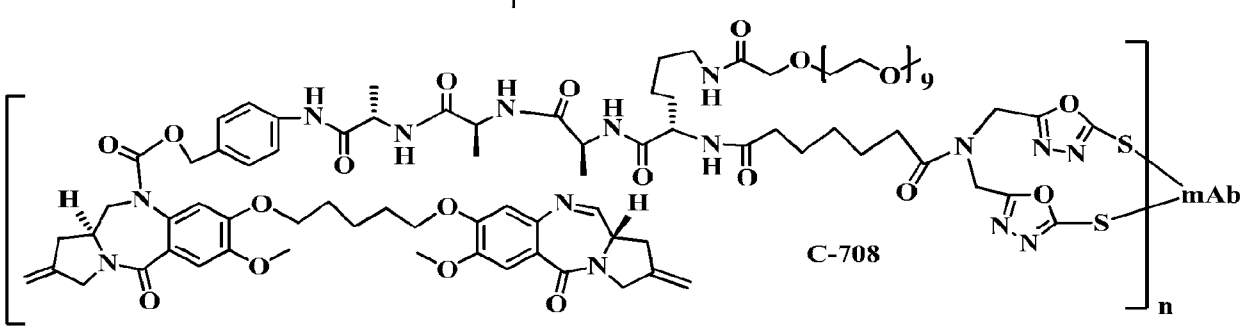
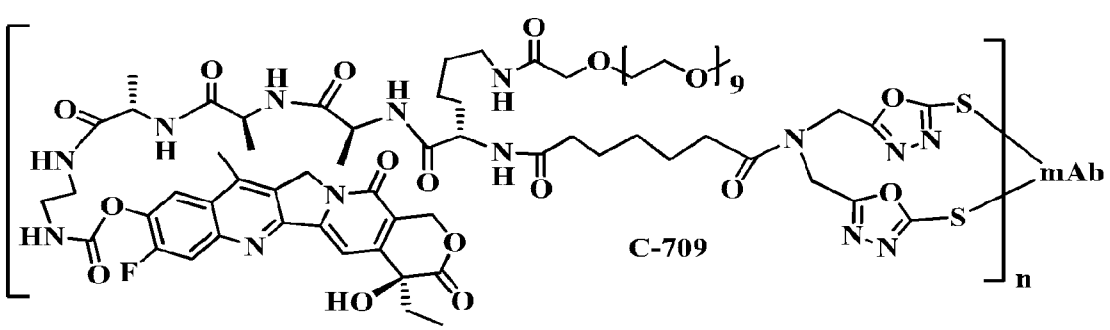
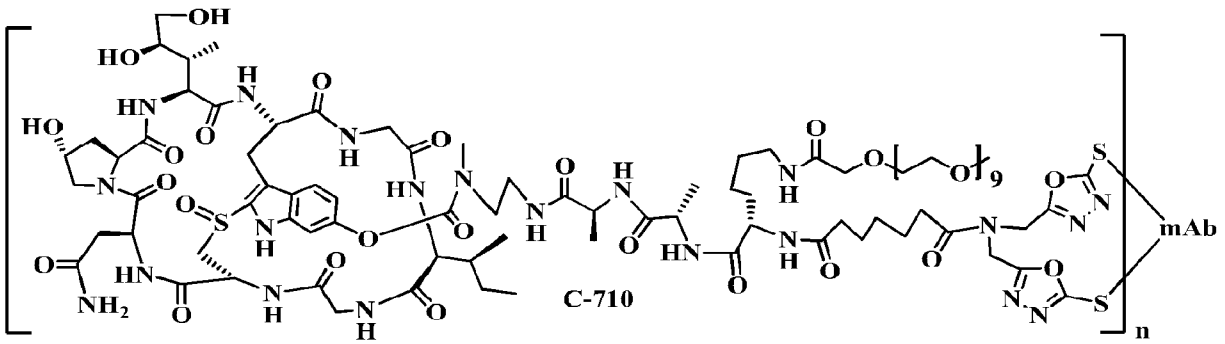


C-708

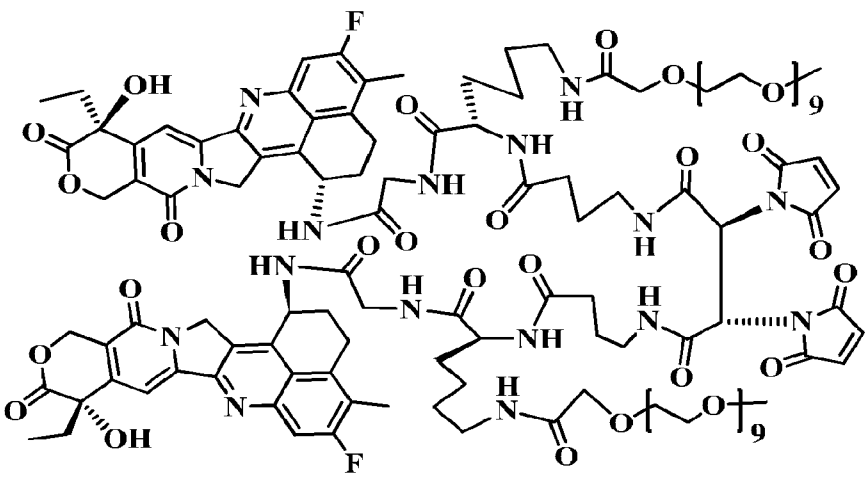


C-709



or one or more isotope of chemical elements, pharmaceutically acceptable salts, hydrates, or hydrated salts; or the polymorphic crystalline structures of these compounds; or the optical isomers, racemates, diastereomers or enantiomers; wherein n is 1 -10, mAb is an antibody or antibody-like protein.

13. The process according to claim 3, wherein the drug/linker complex , has one of the structures of below:



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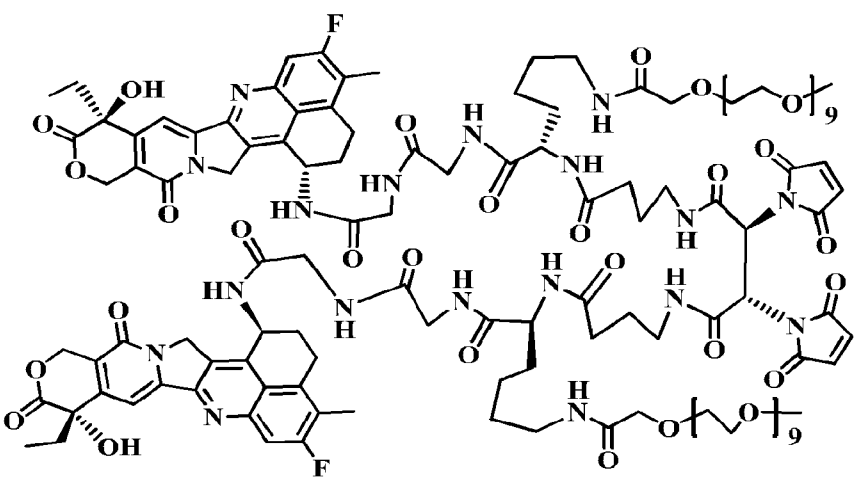

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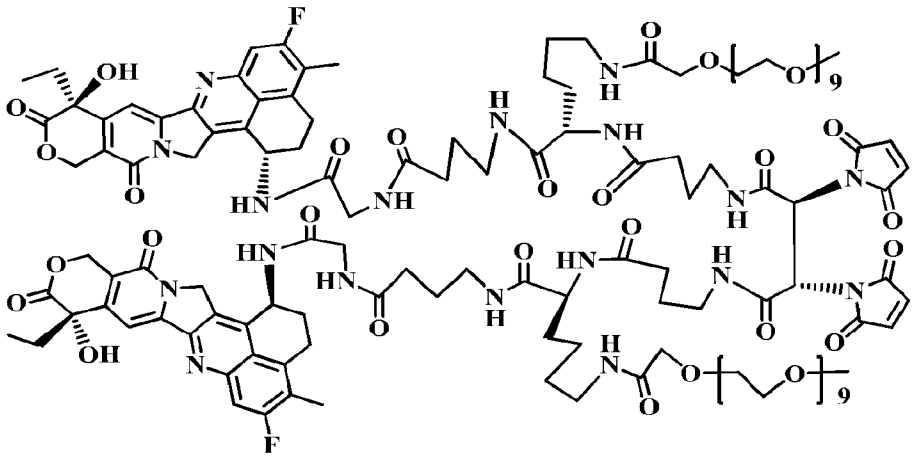

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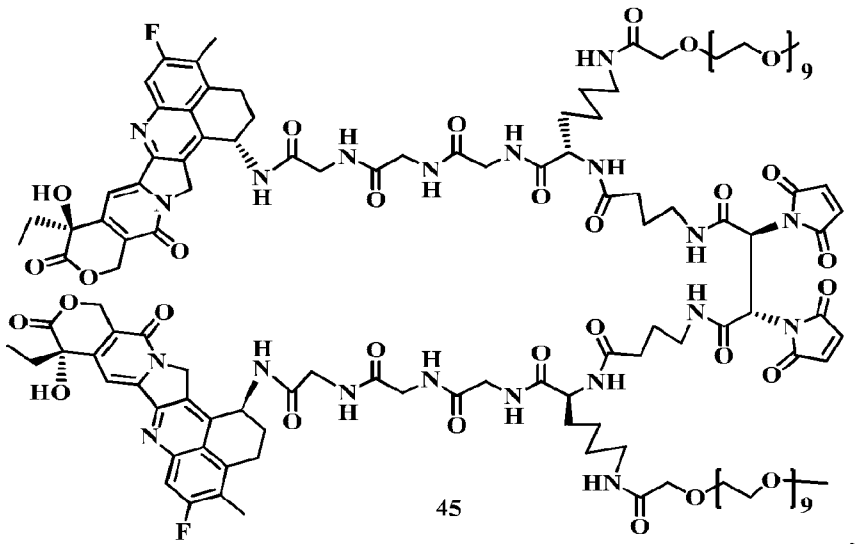

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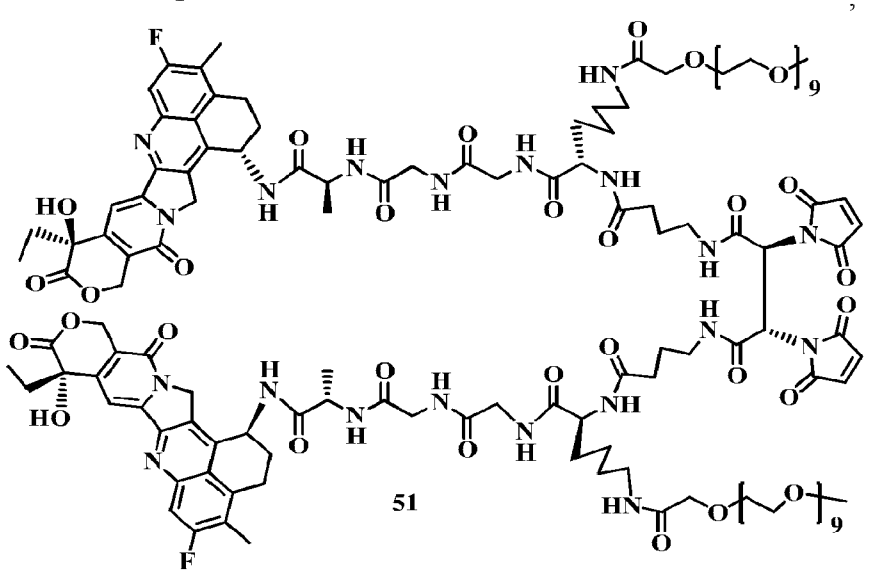

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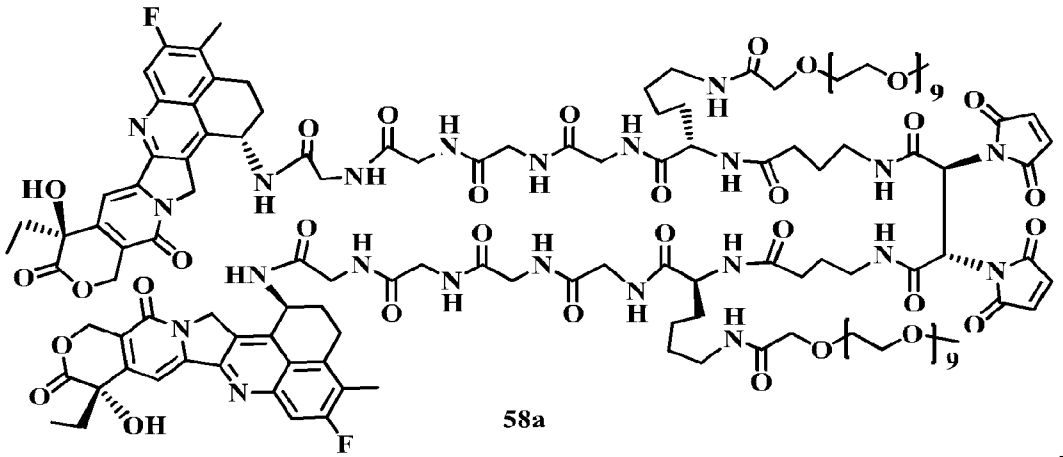

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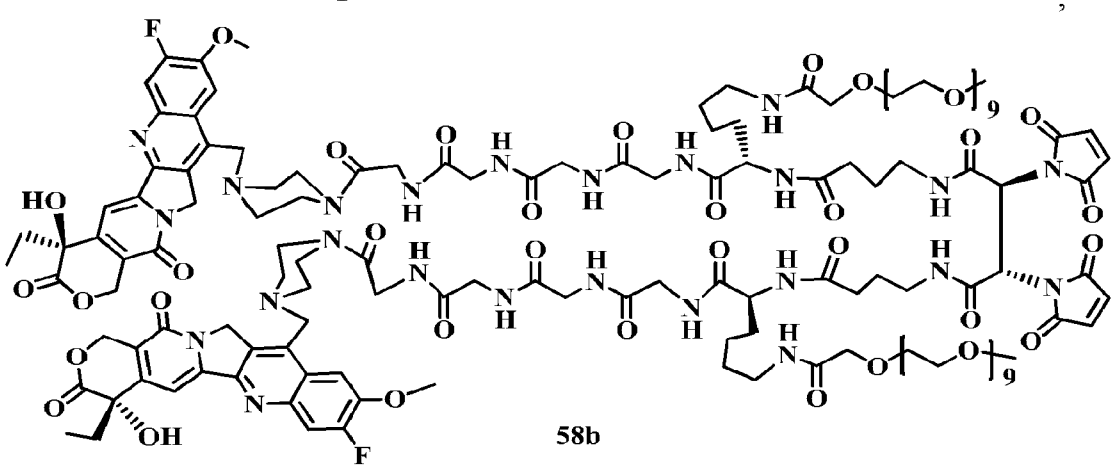

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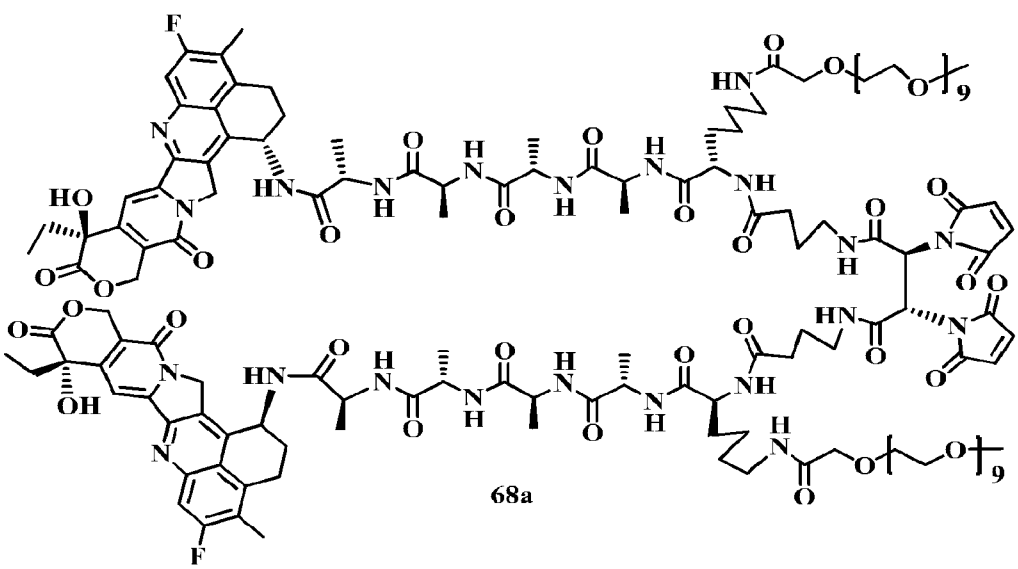

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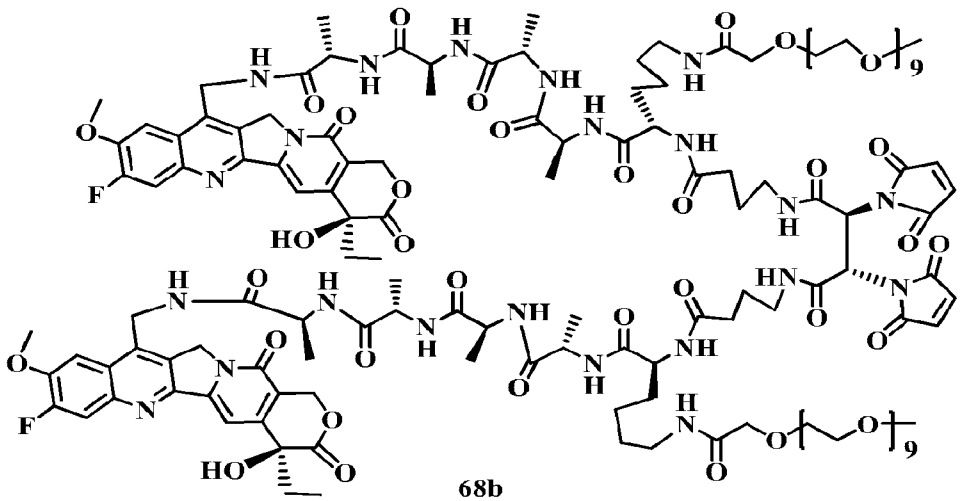

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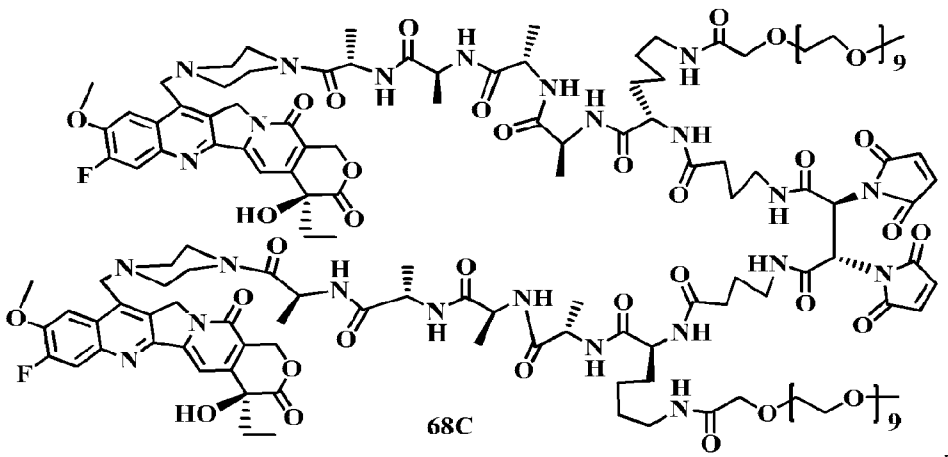

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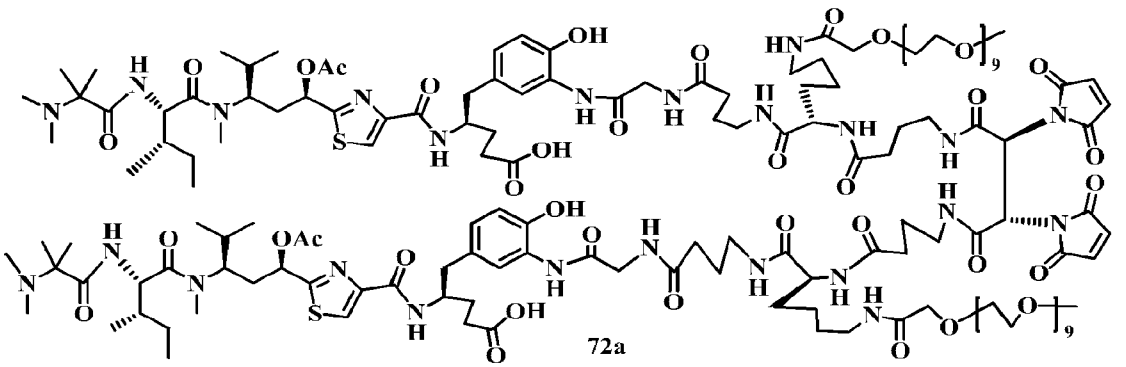

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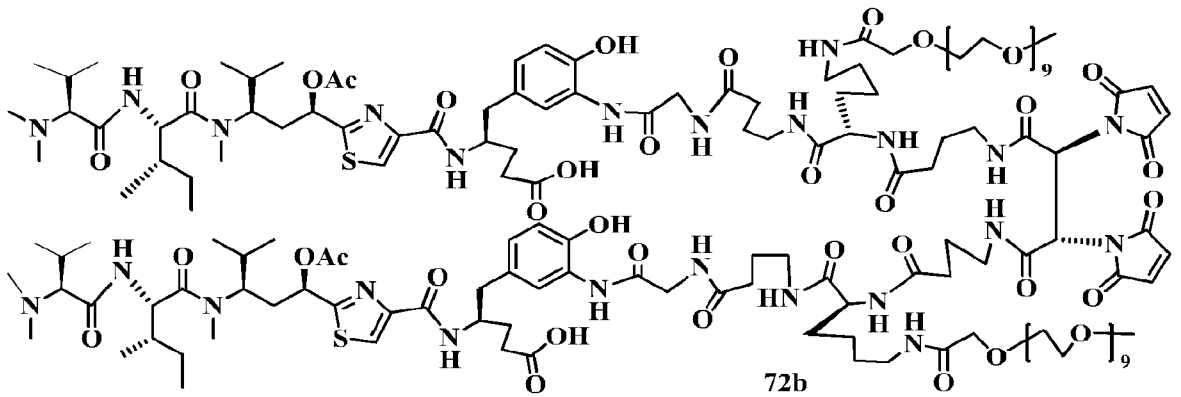

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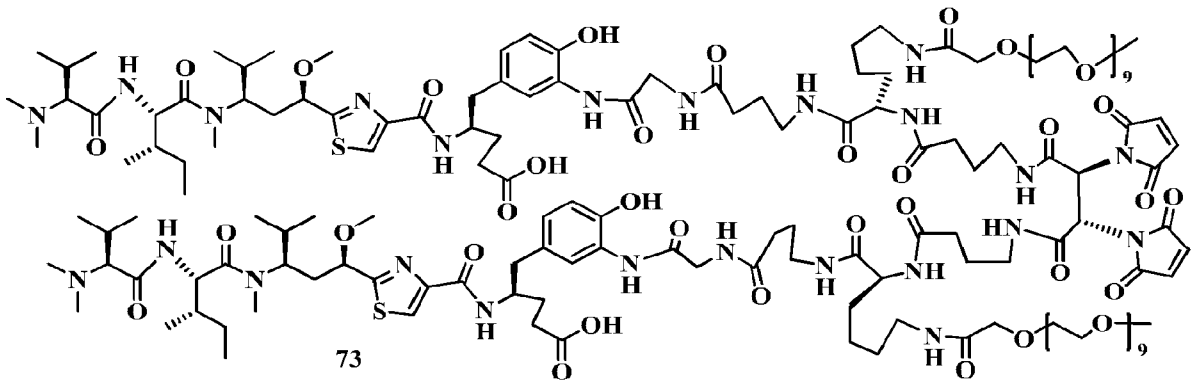

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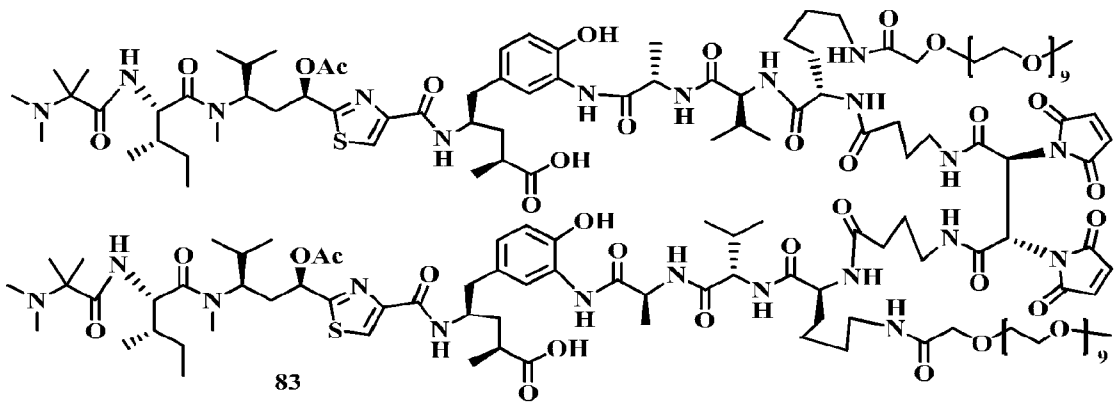

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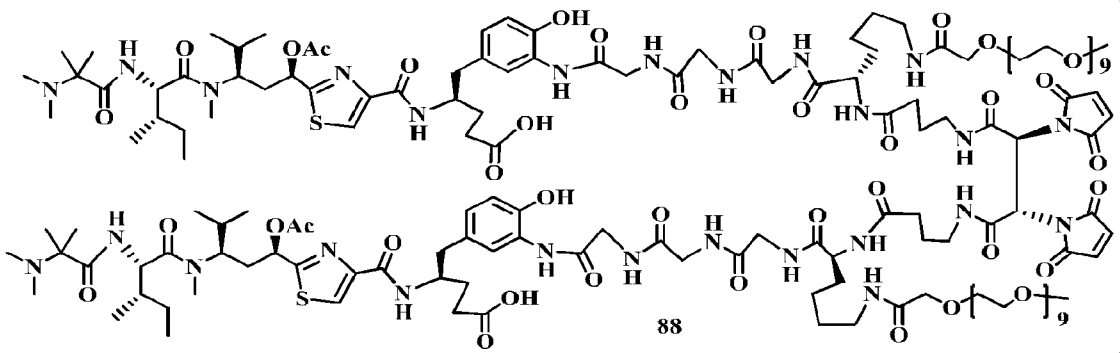

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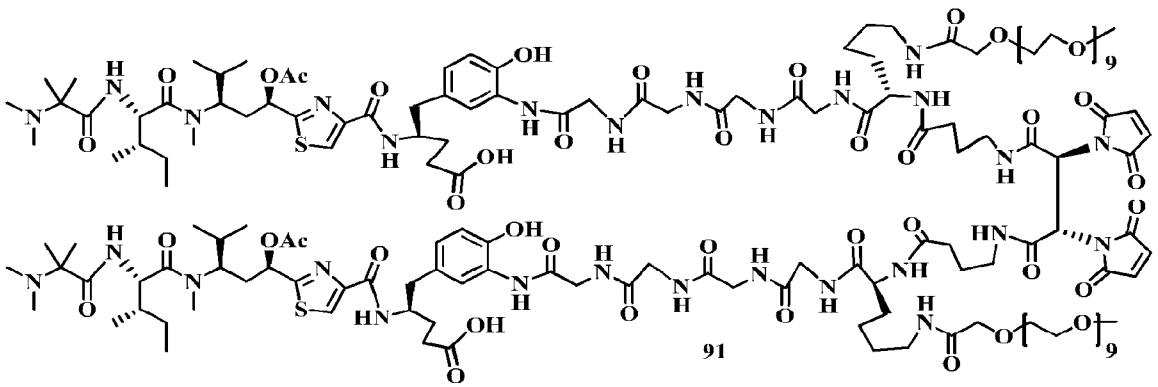

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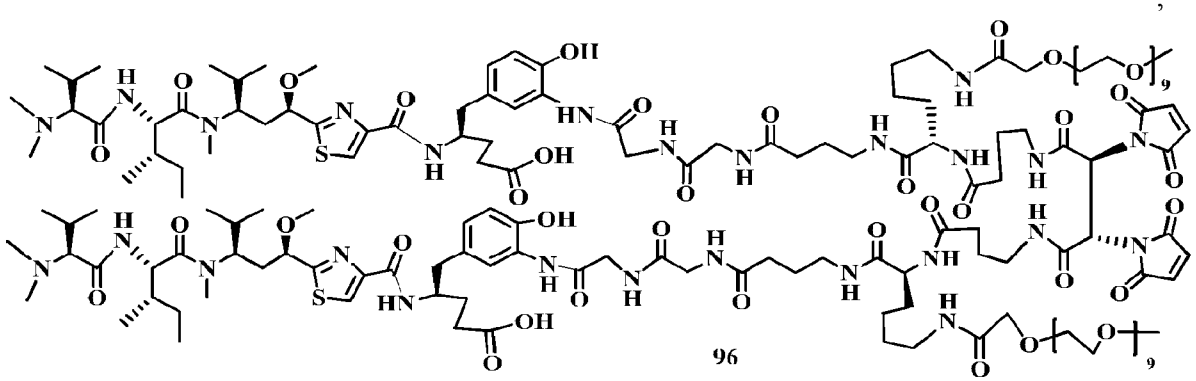

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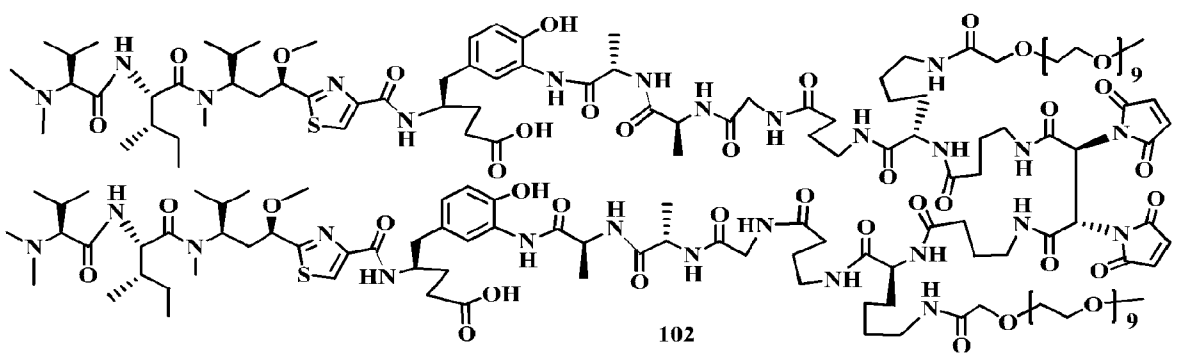

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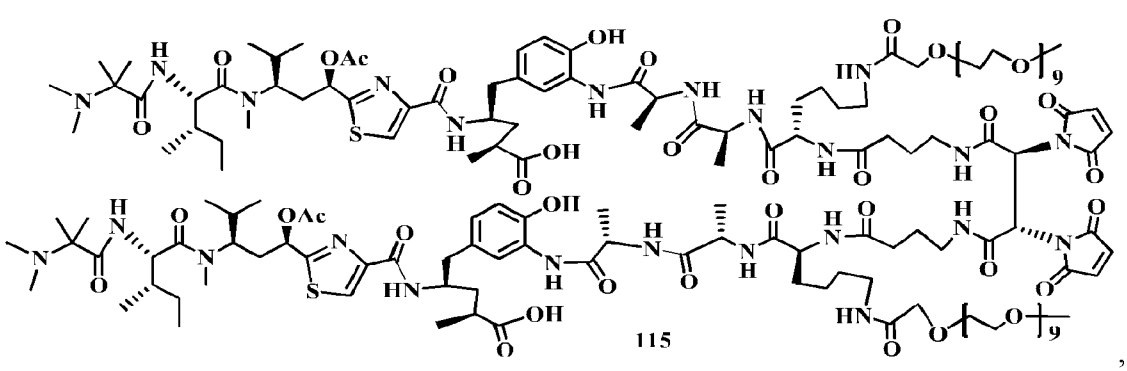

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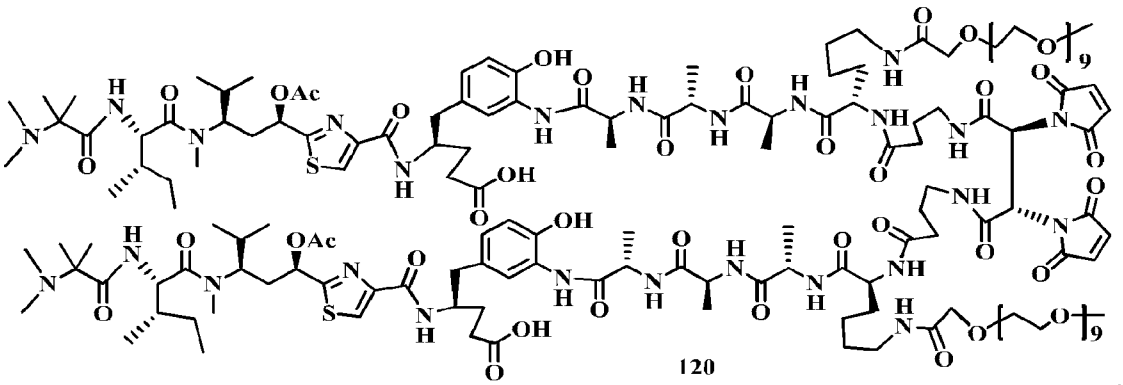

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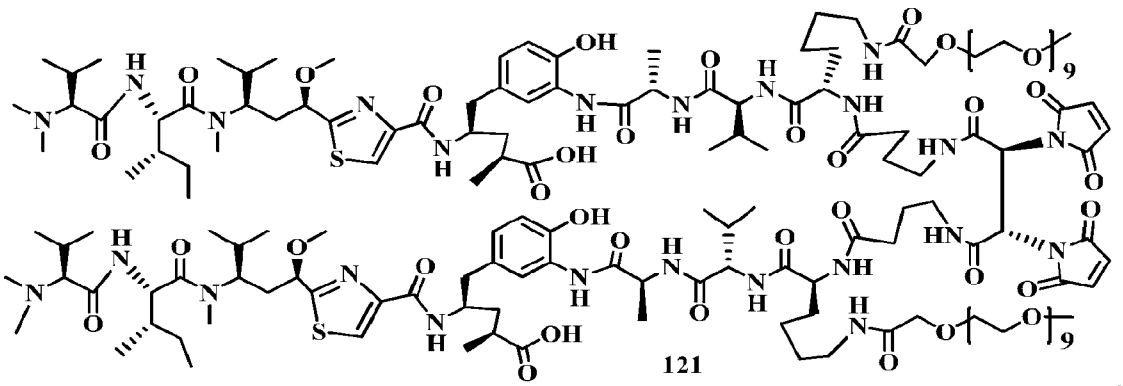

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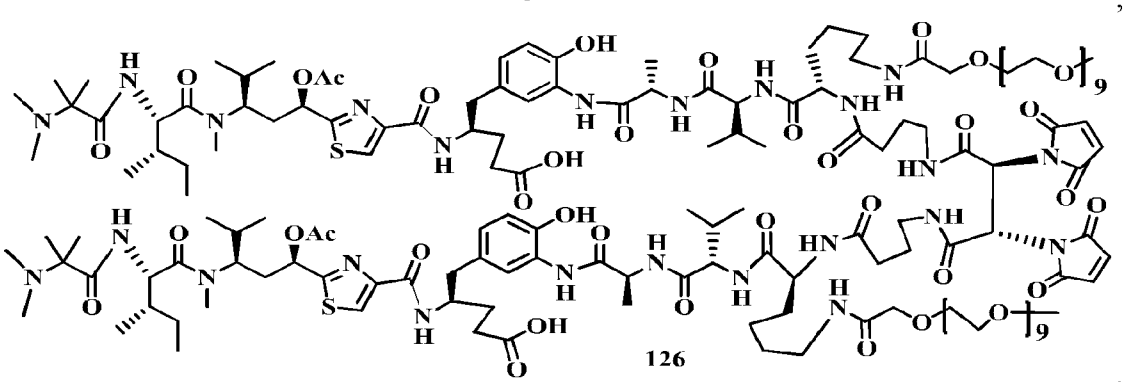

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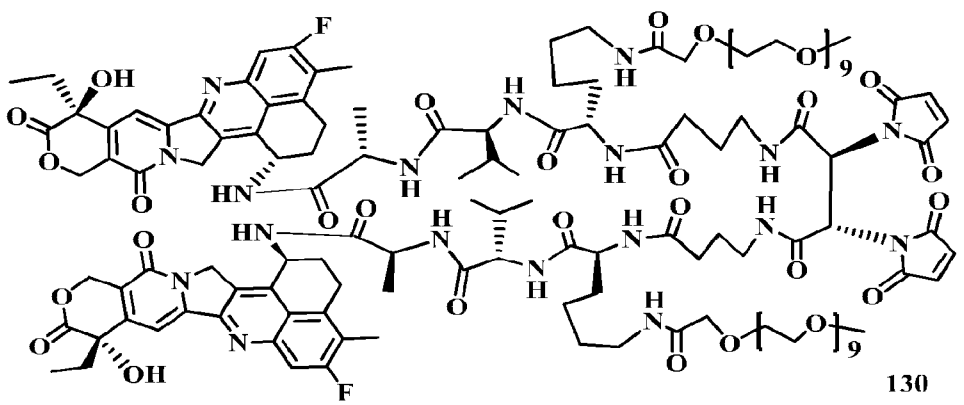

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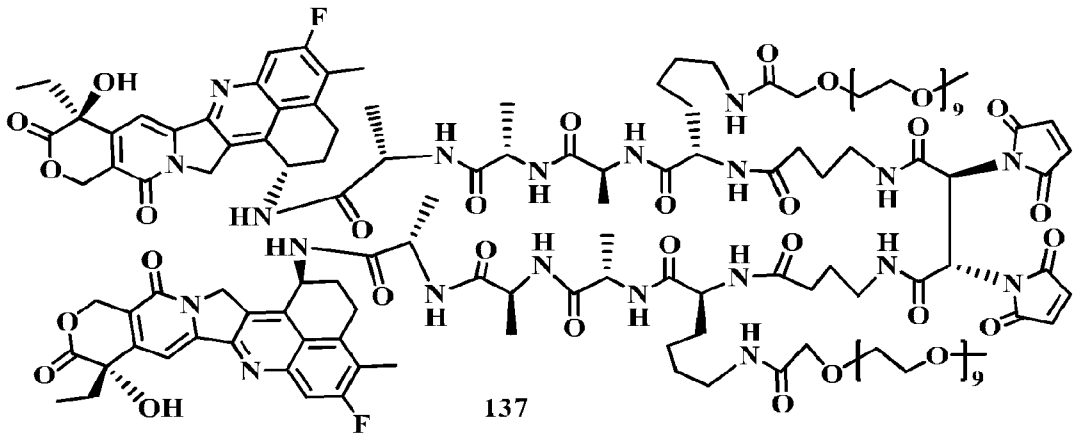

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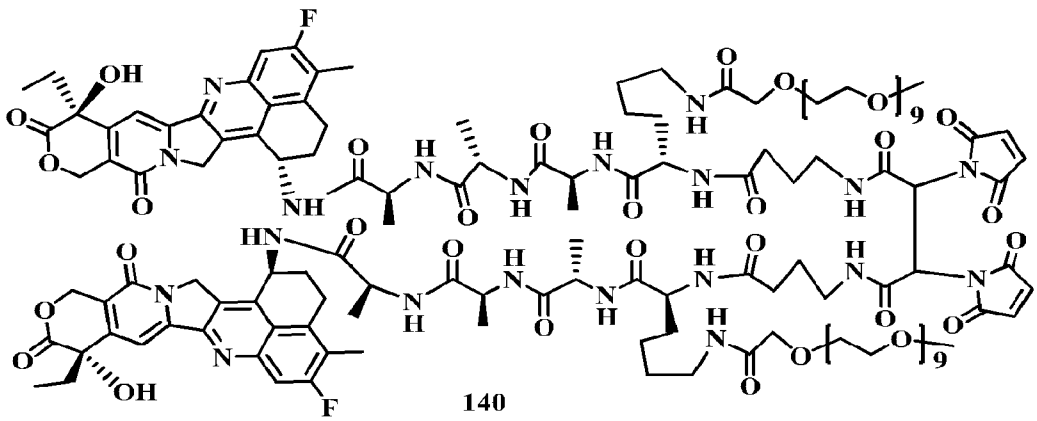

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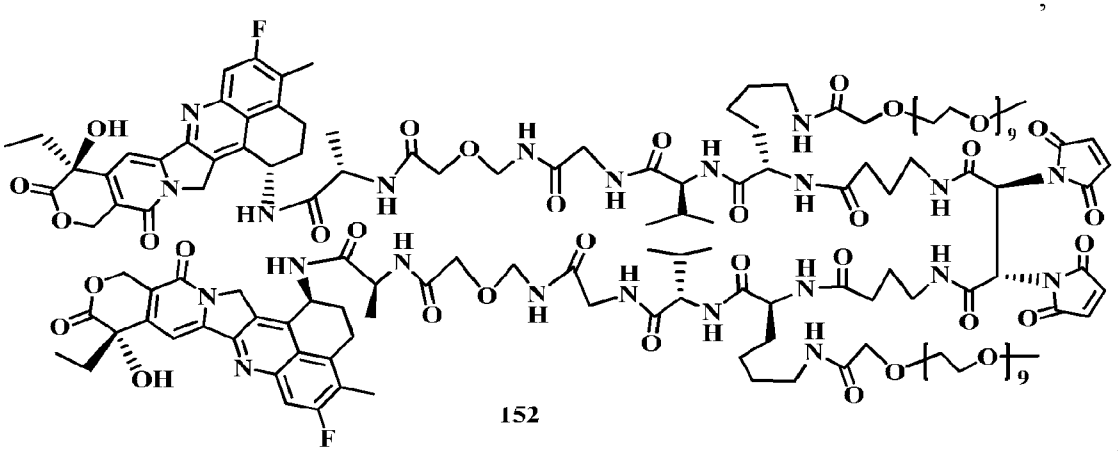

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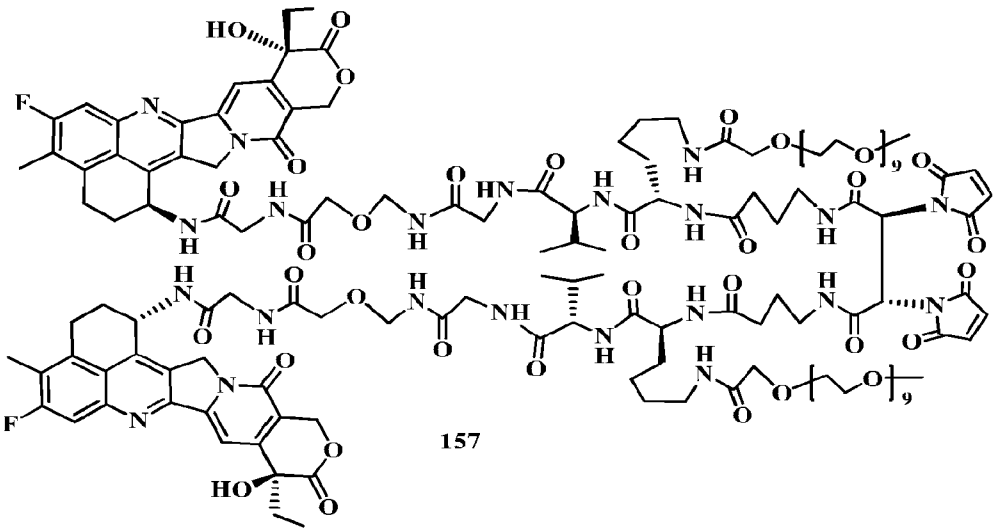

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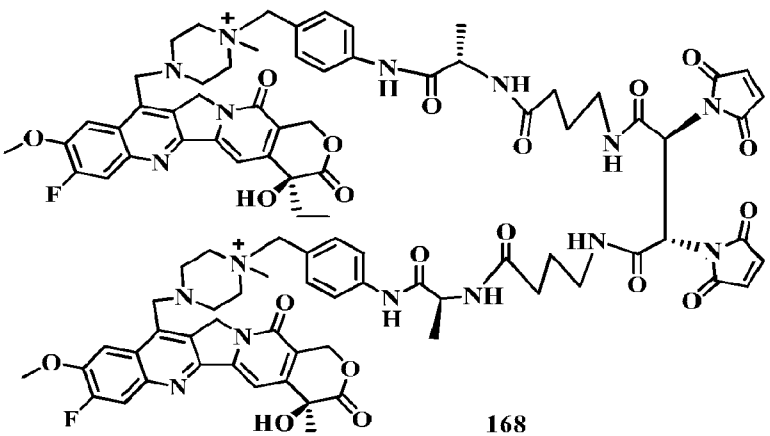

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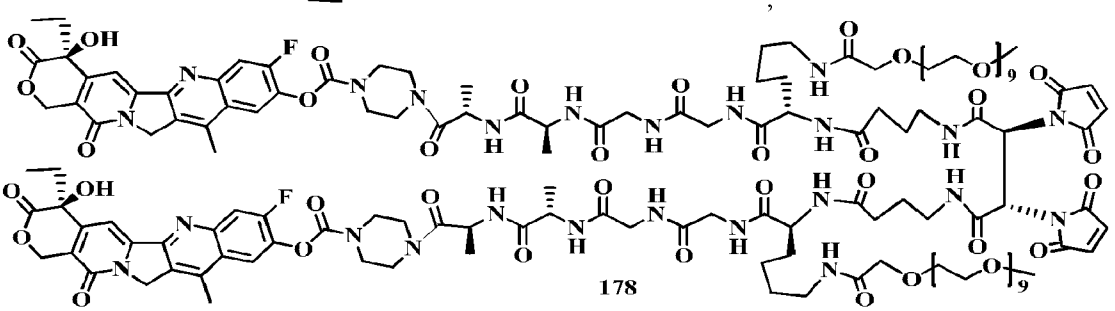

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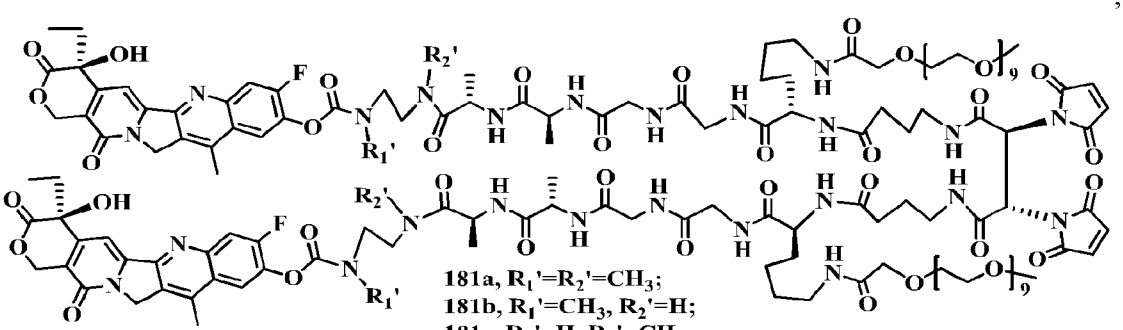

181

181a, $R_1'=R_2'=CH_3$;
181b, $R_1'=CH_3$, $R_2'=H$;
181c, $R_1'=H$, $R_2'=CH_3$;
181d, $R_1'=R_2'=H$;

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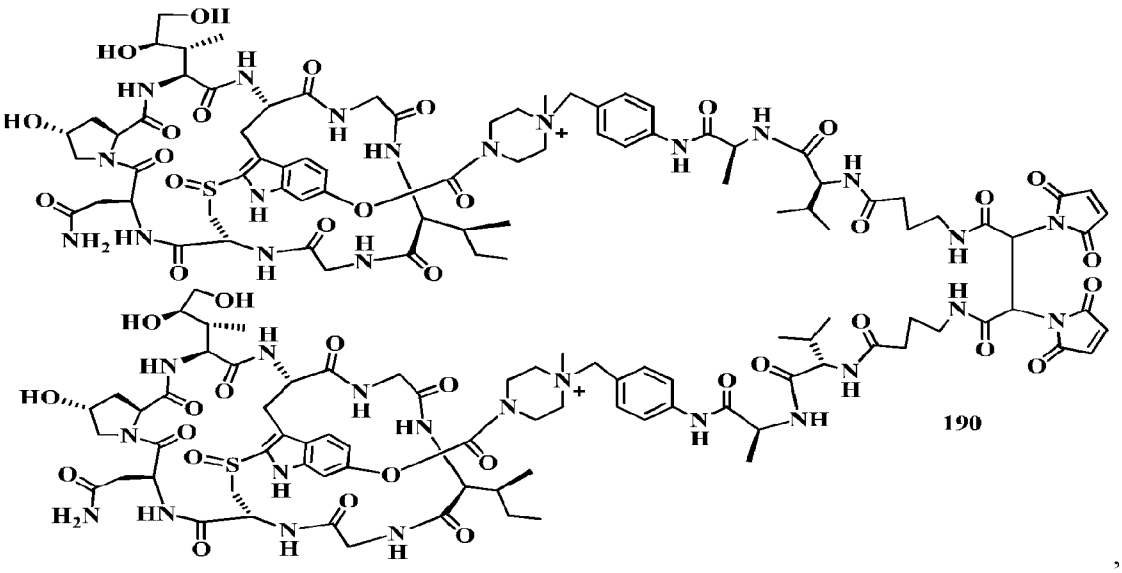

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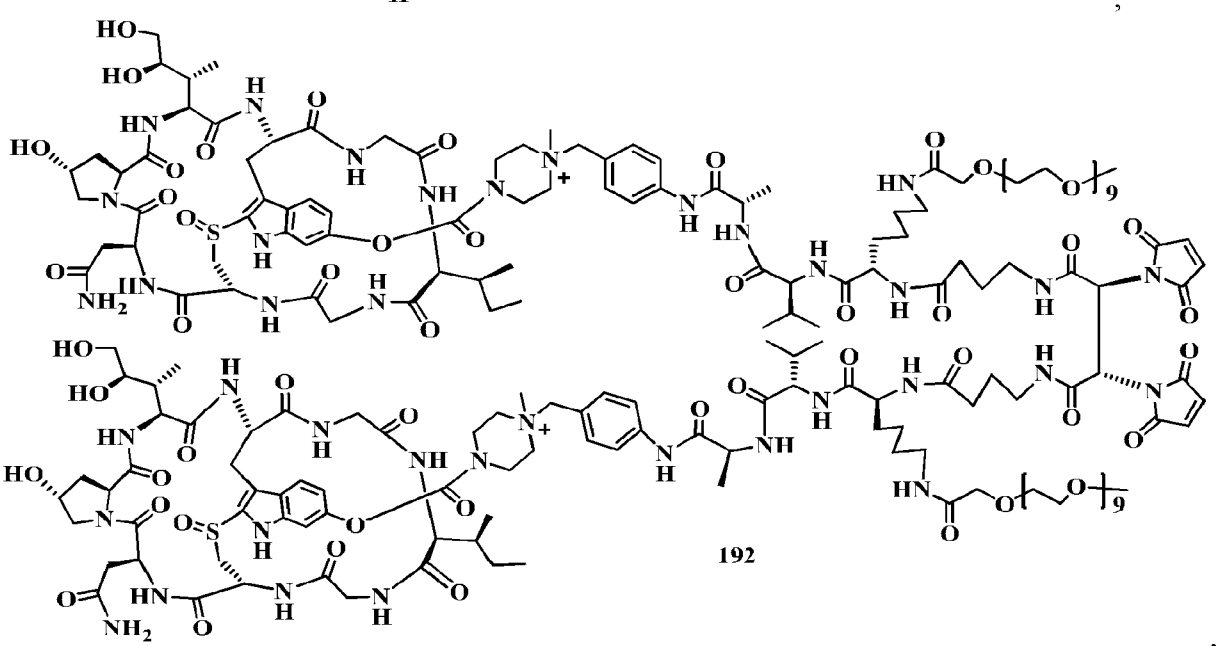

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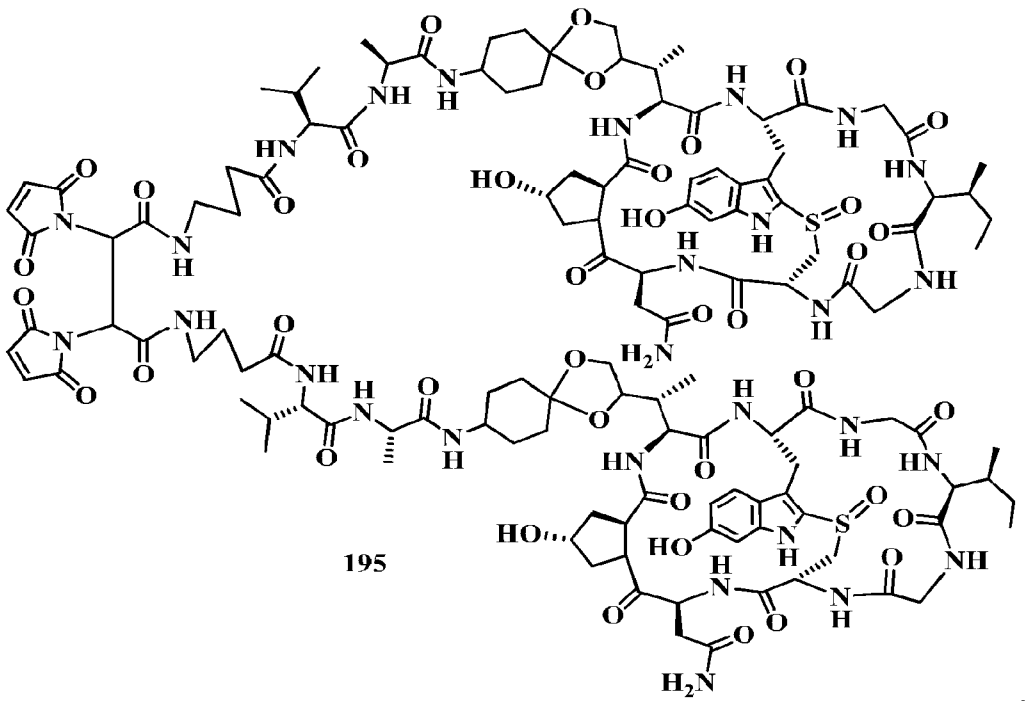

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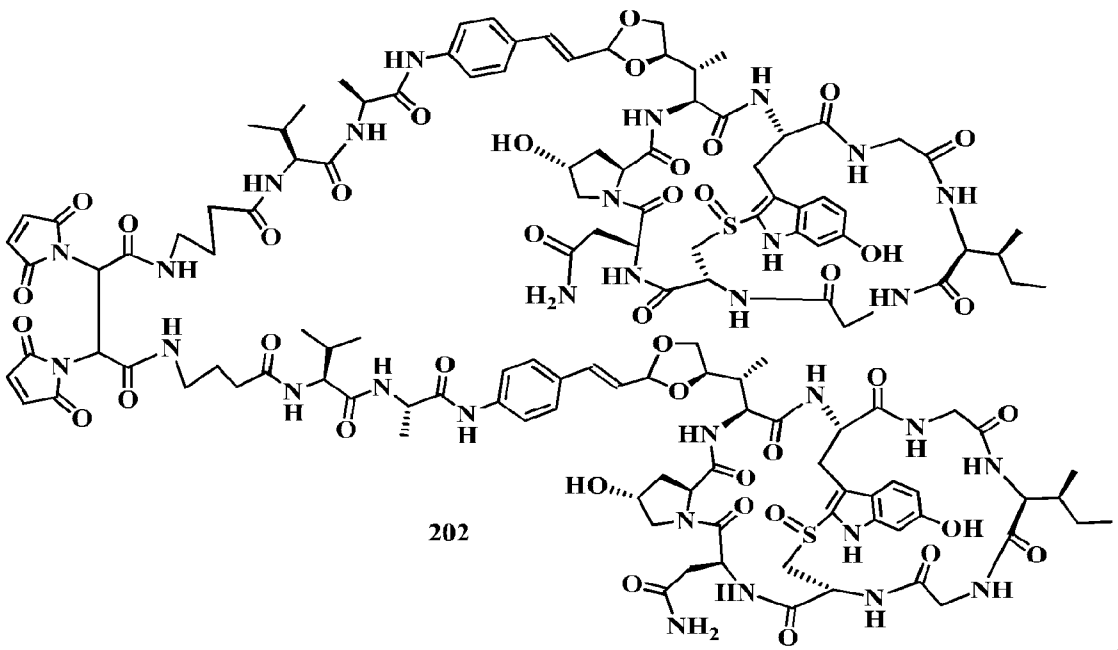

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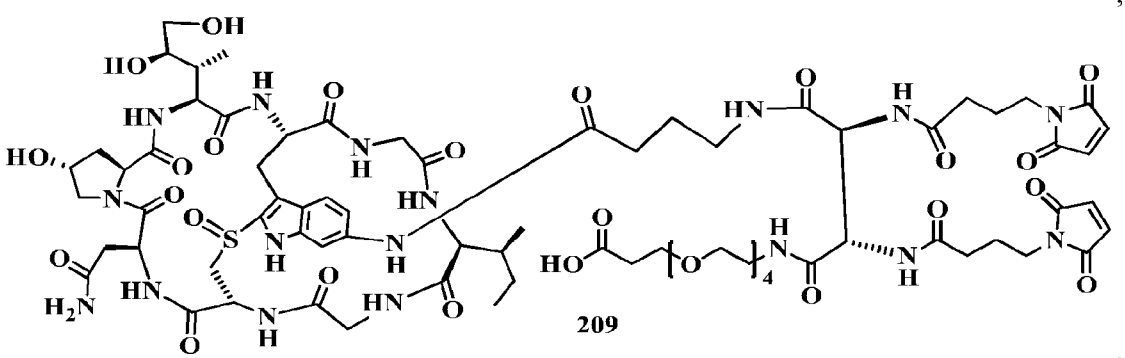

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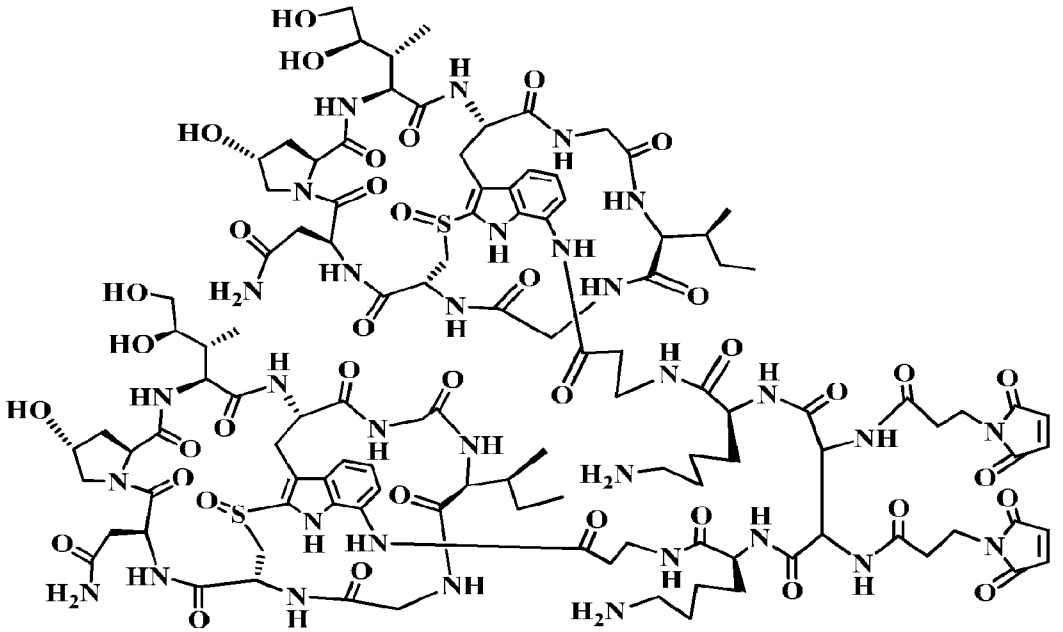

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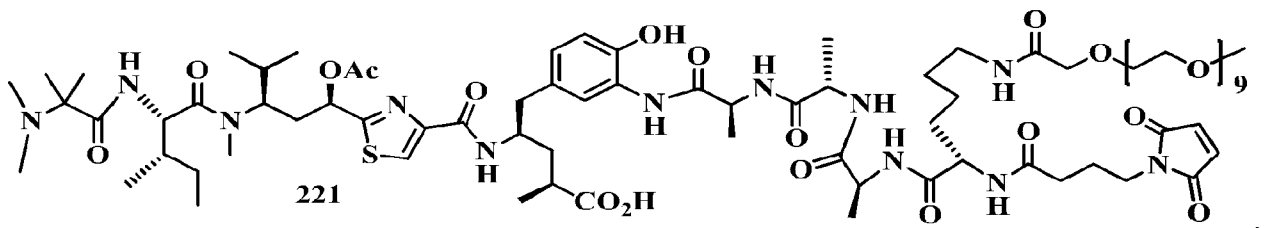

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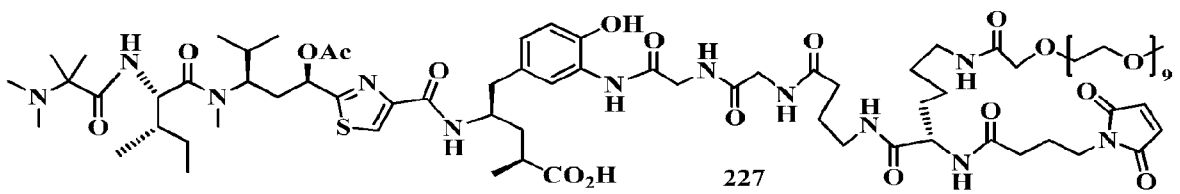

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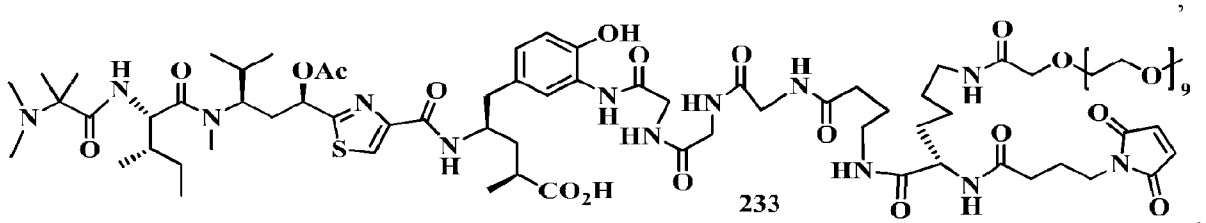

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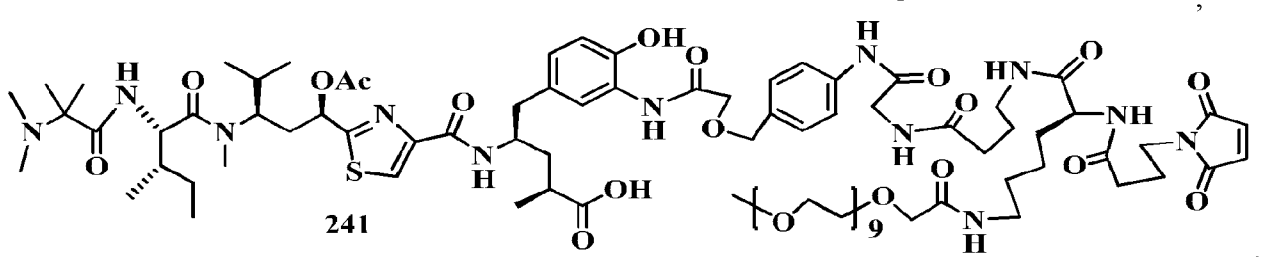

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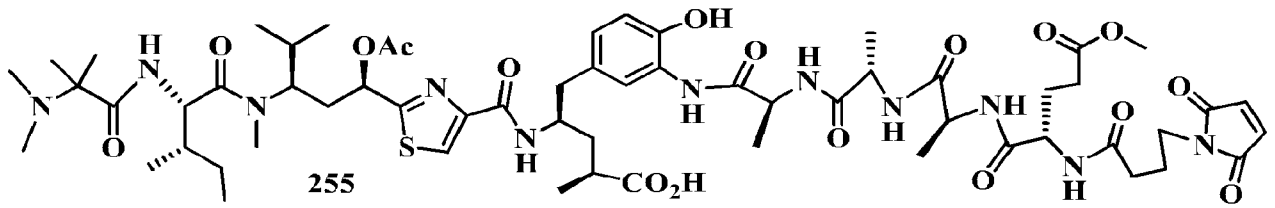

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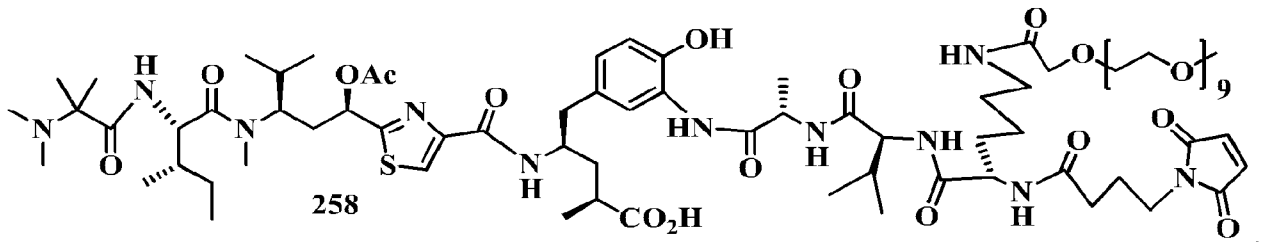

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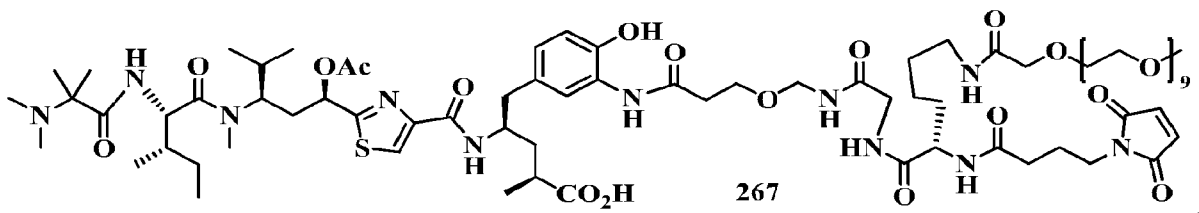

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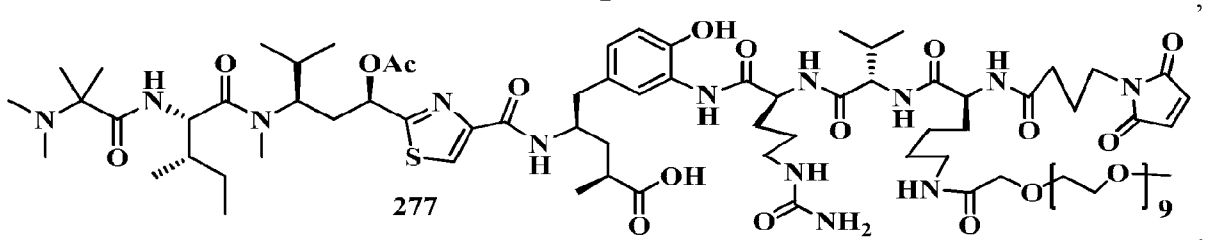

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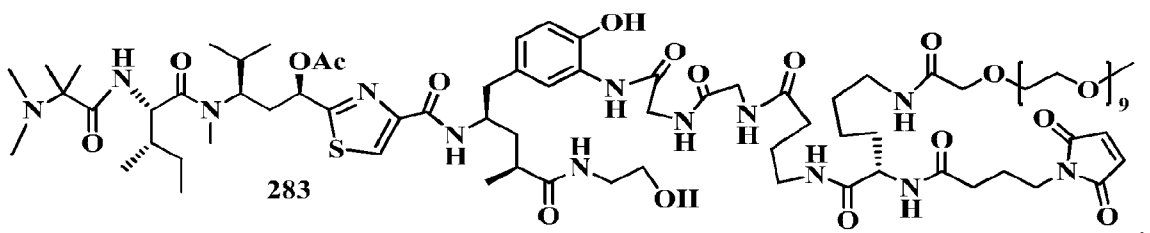

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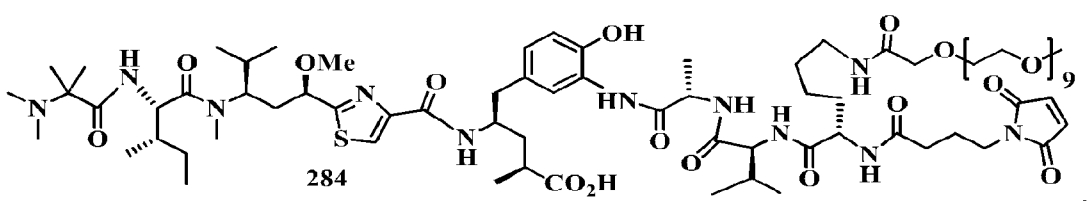

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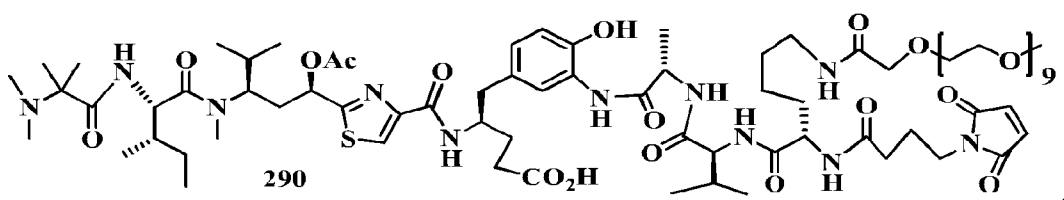

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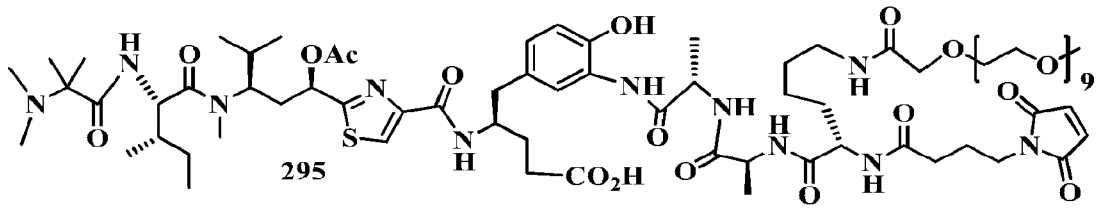

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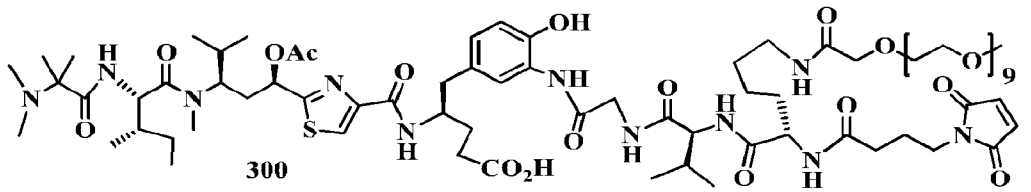

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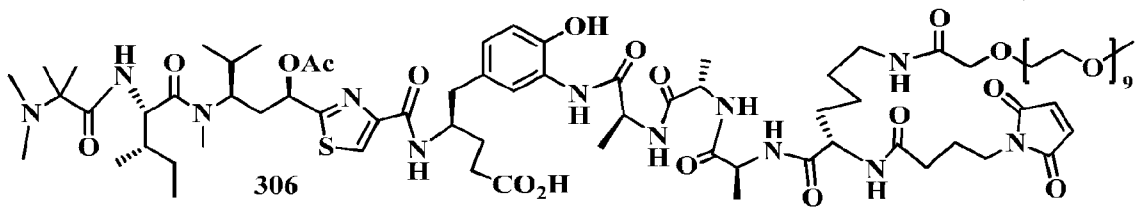

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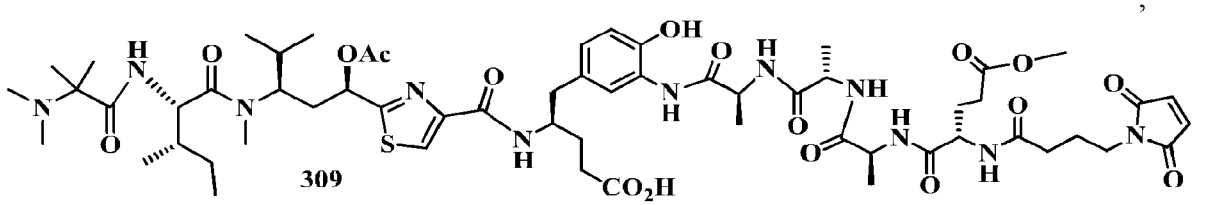

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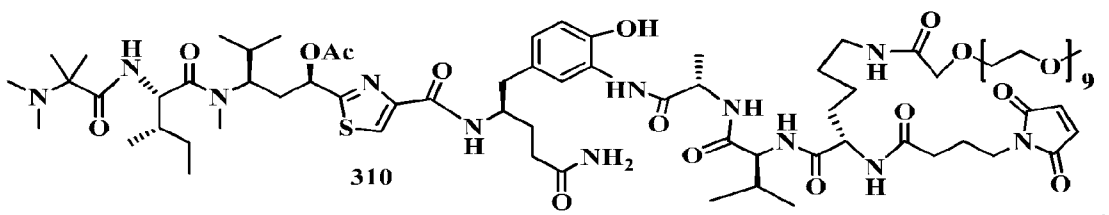

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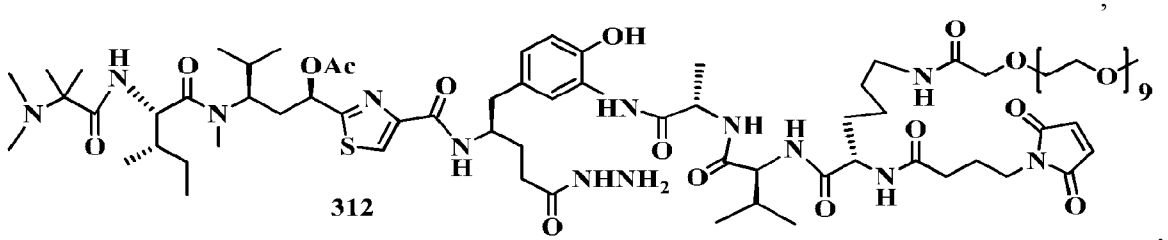

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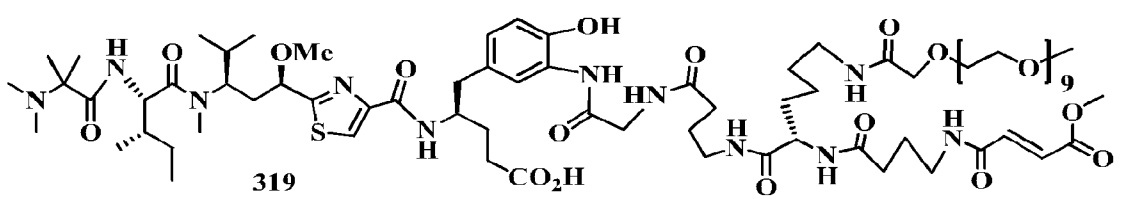

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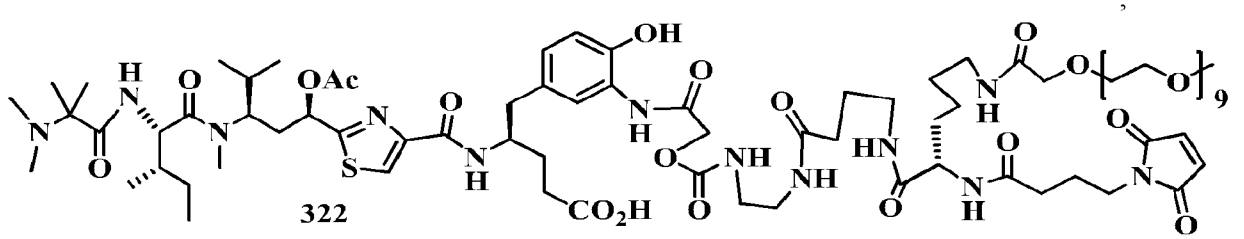

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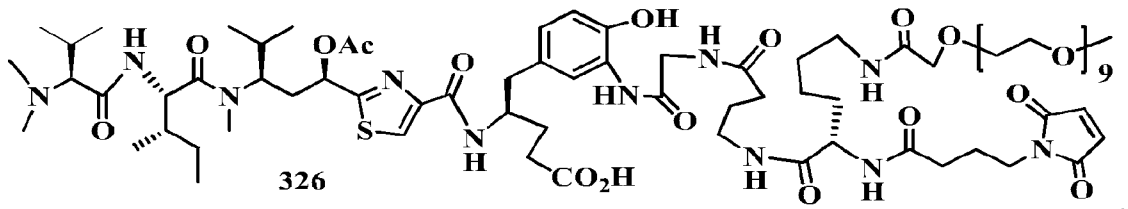

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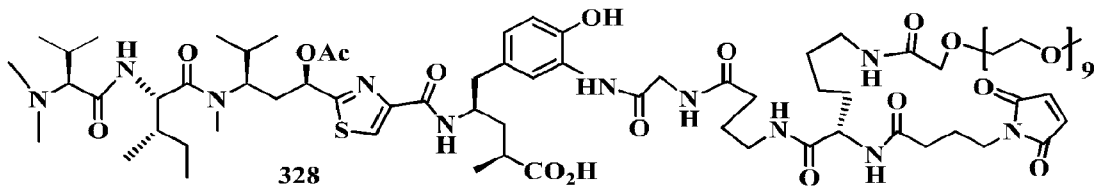

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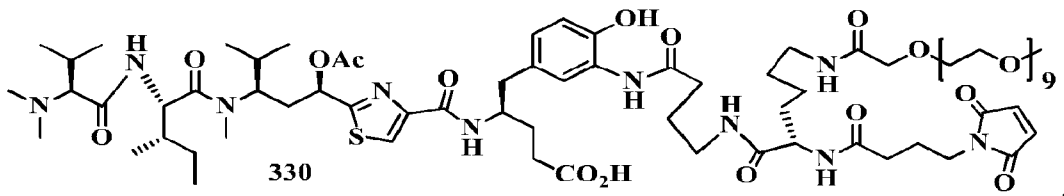

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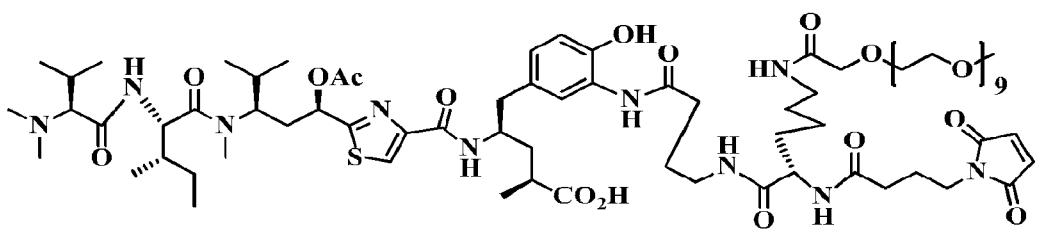

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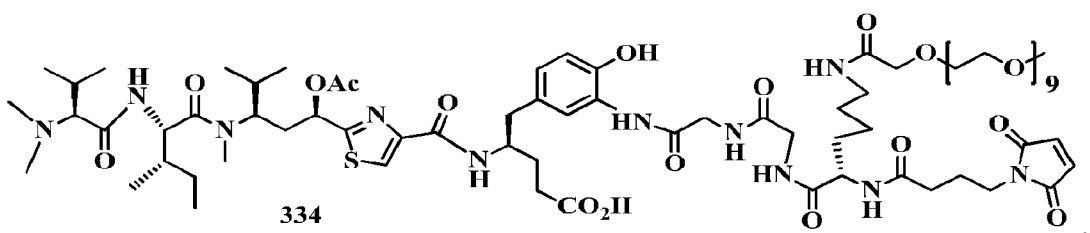

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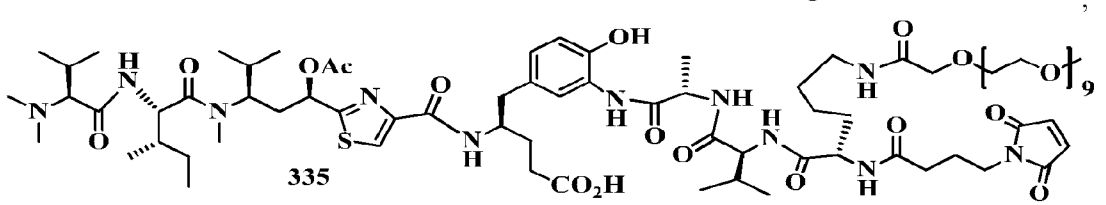

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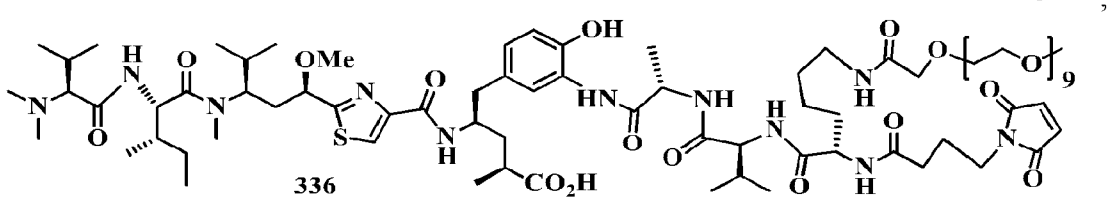

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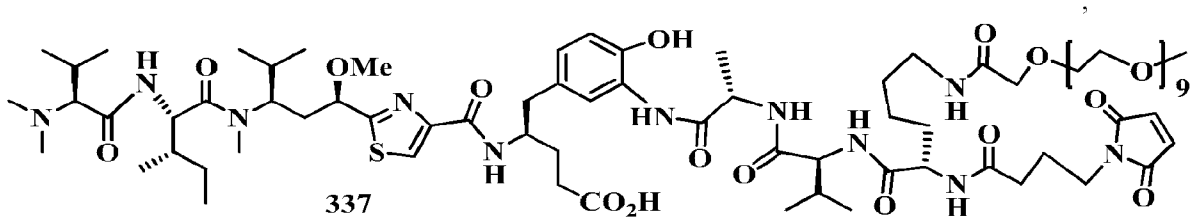

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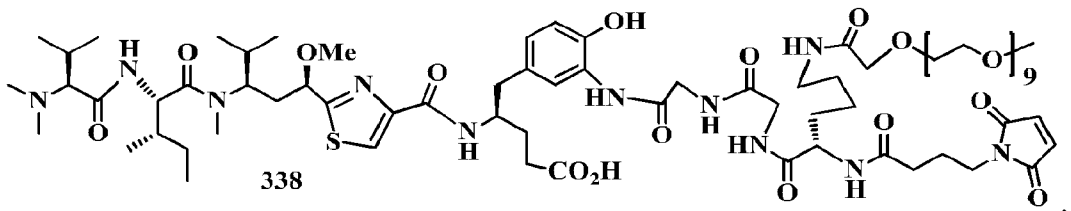

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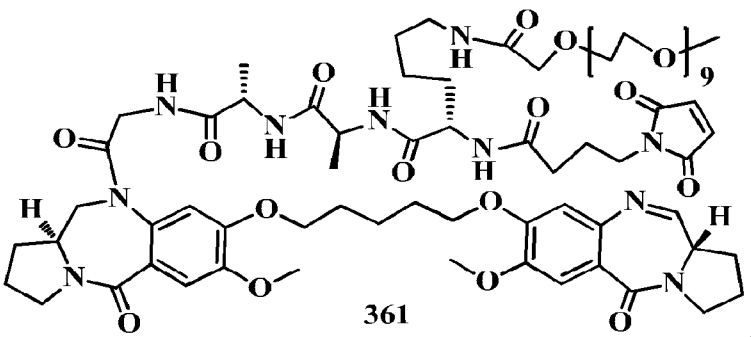

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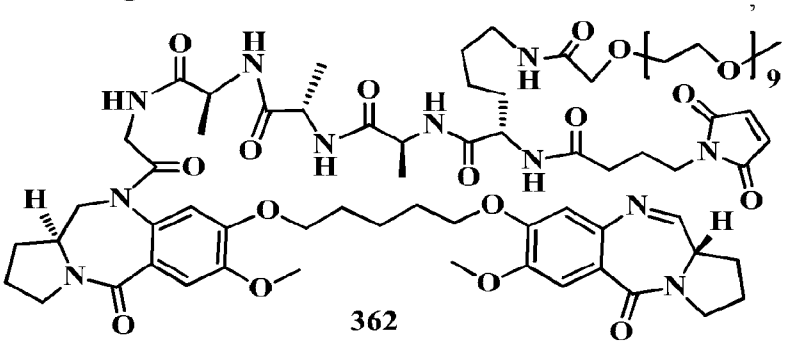

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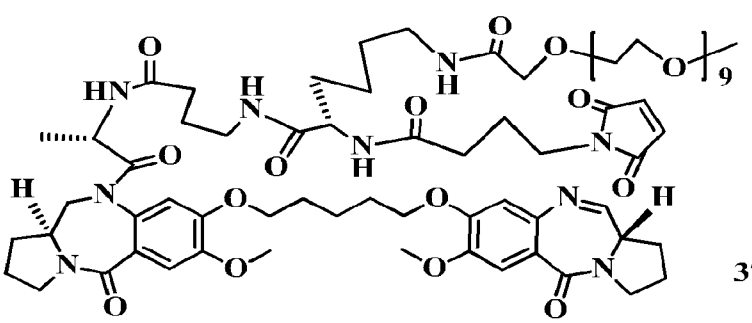

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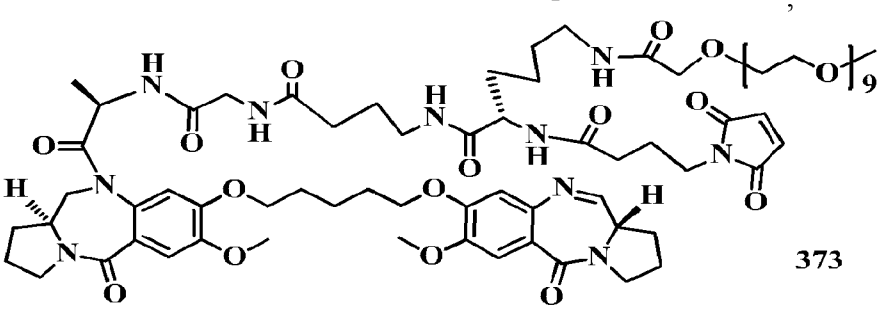

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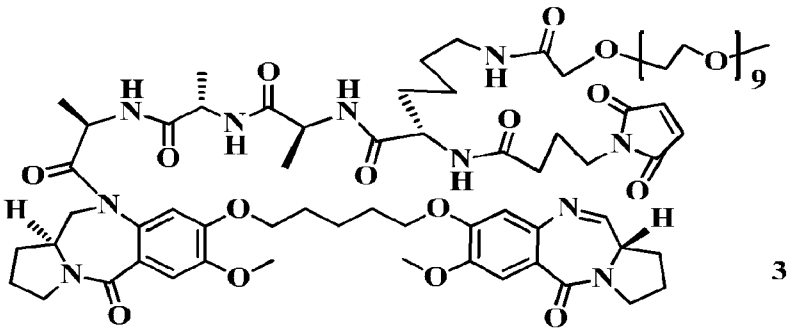

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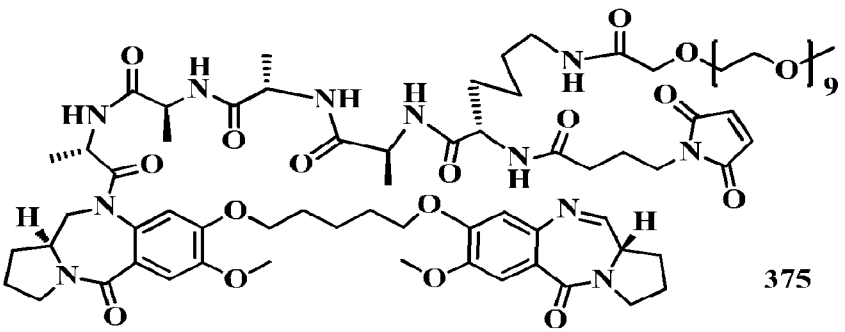

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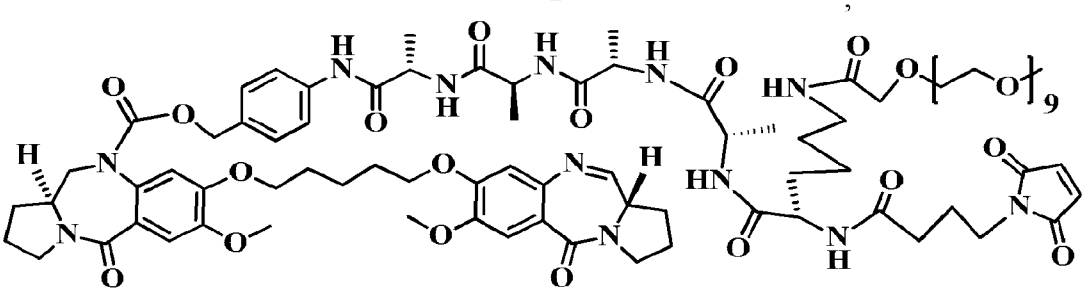

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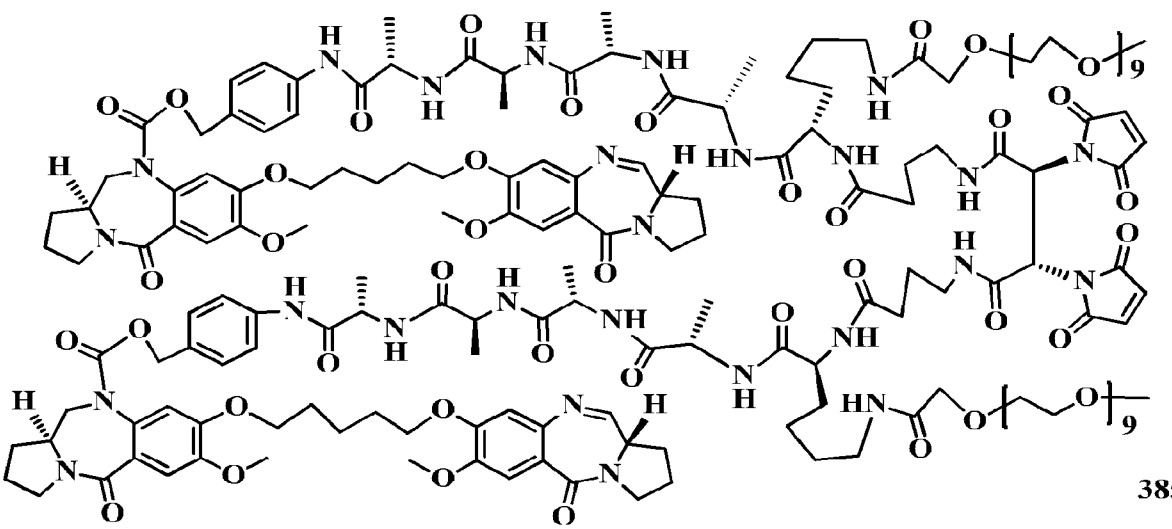

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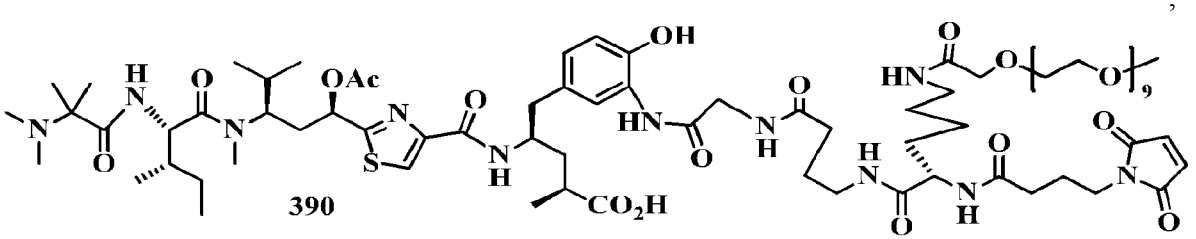

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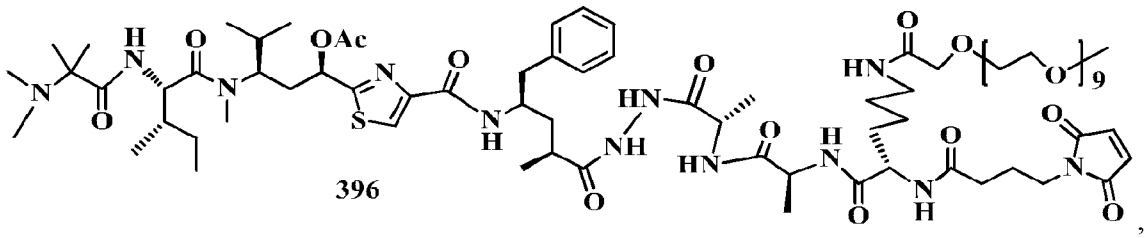

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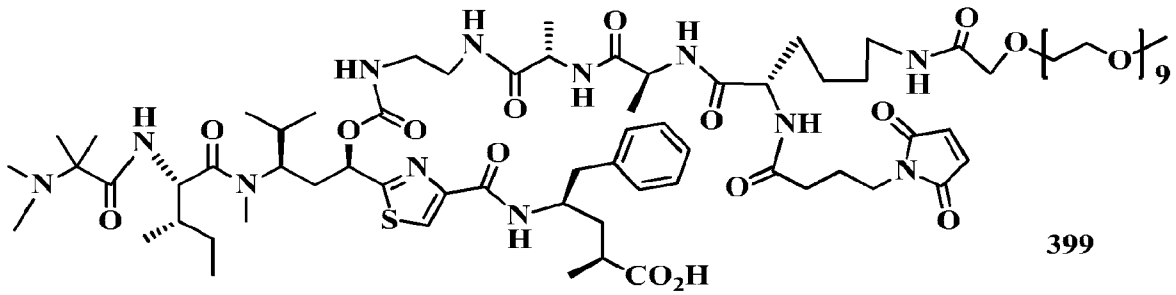

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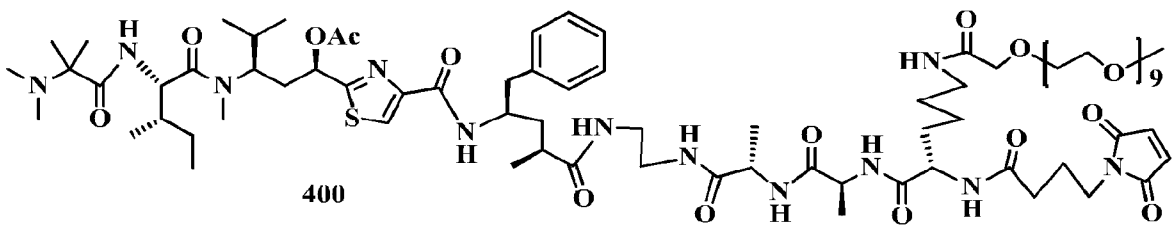

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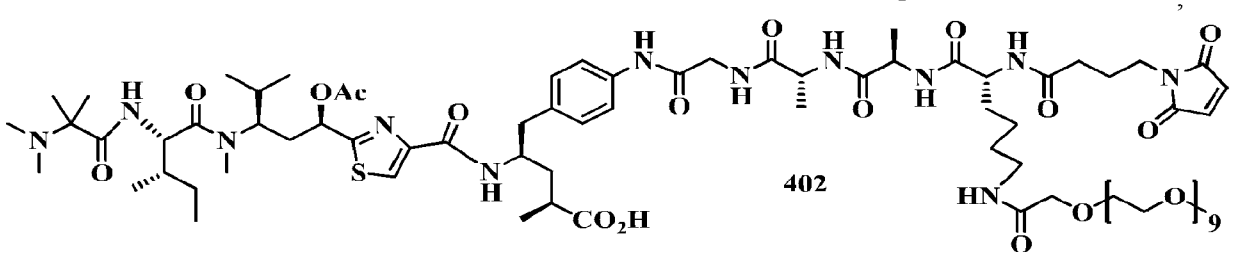

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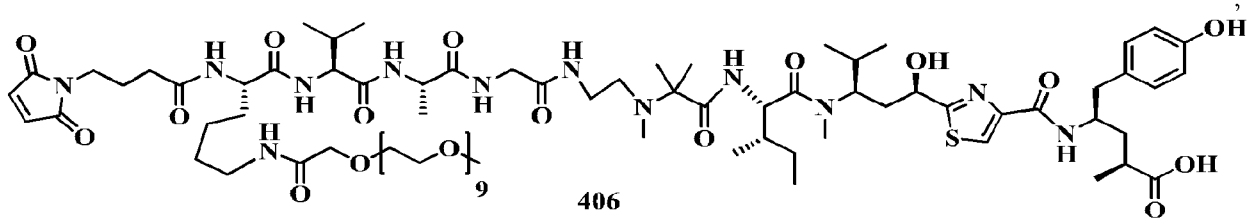

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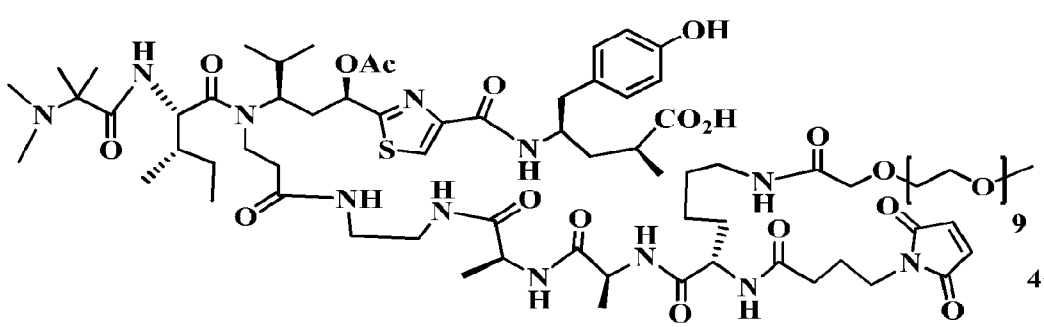

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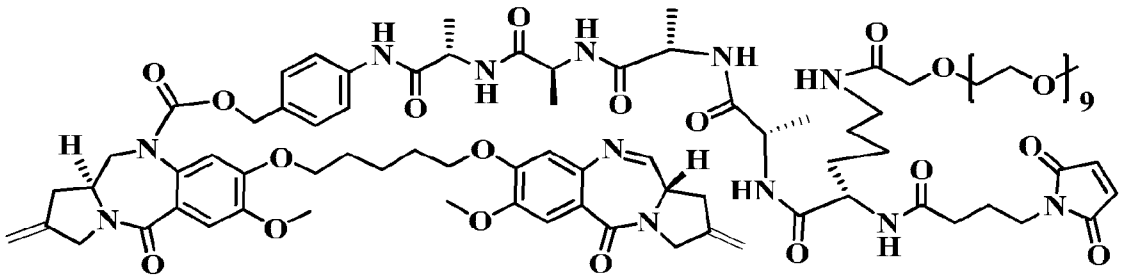

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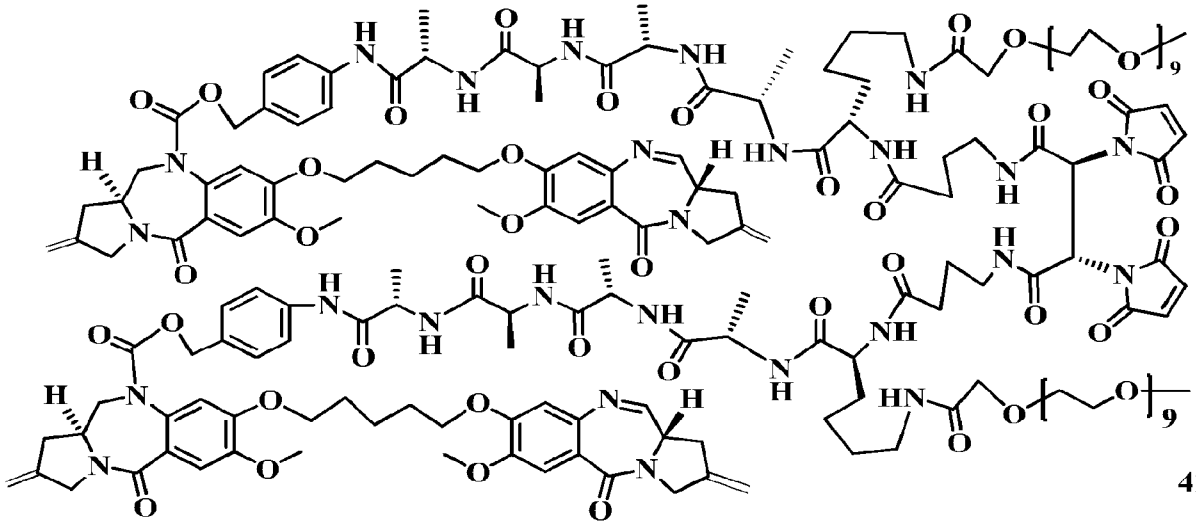

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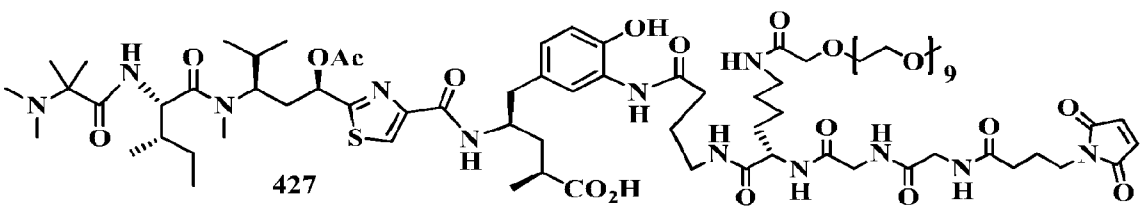

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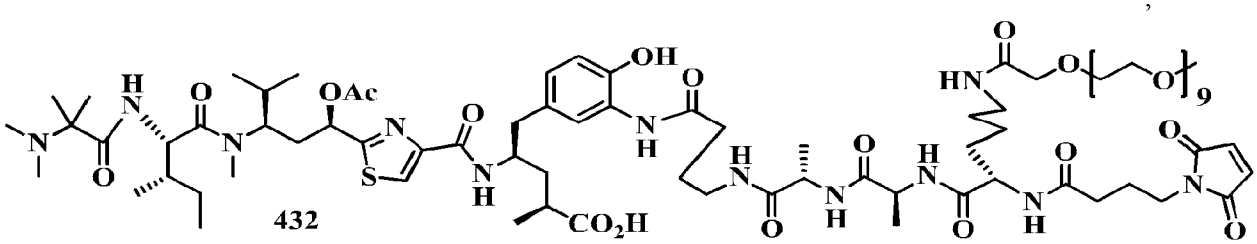

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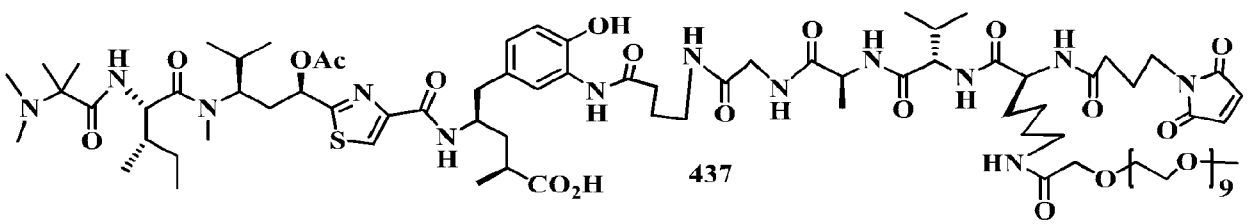

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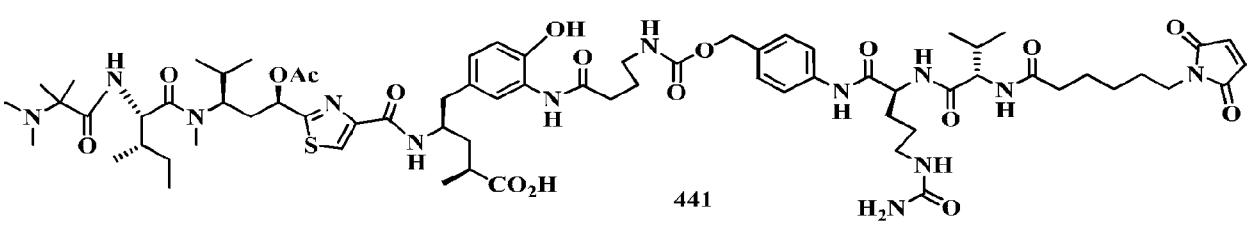

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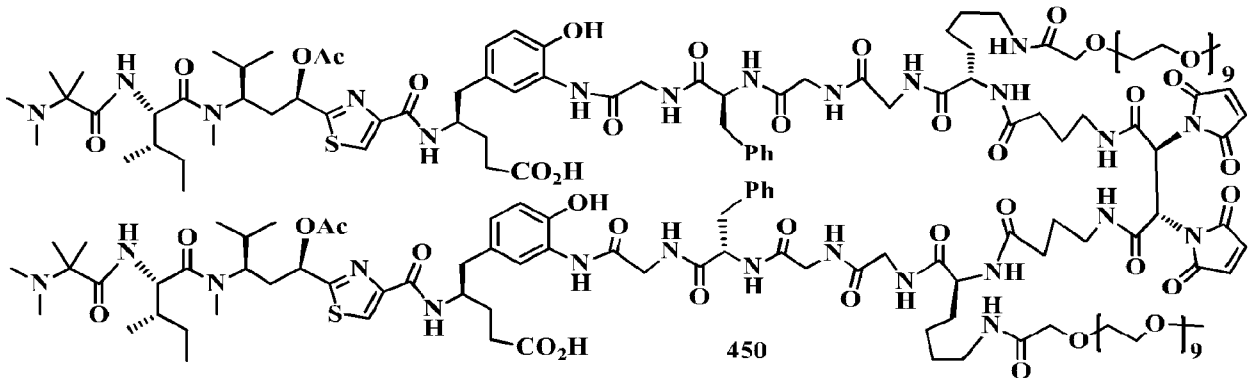

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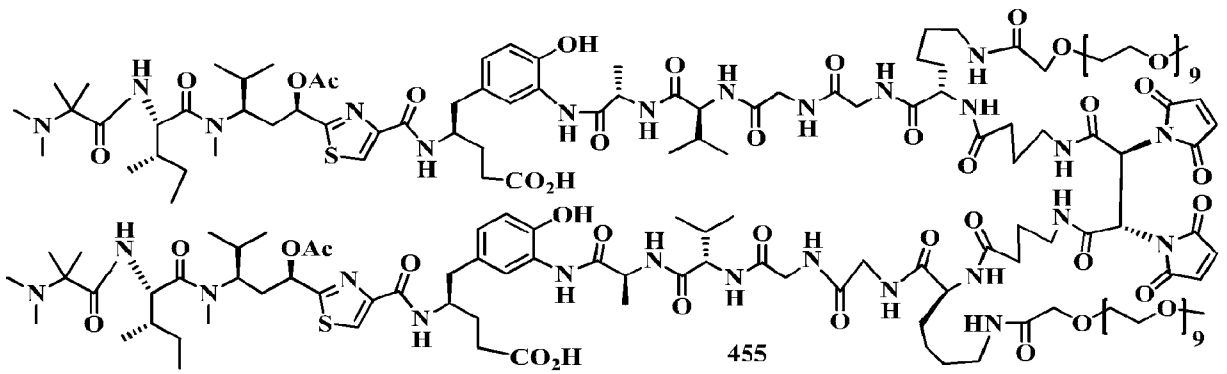

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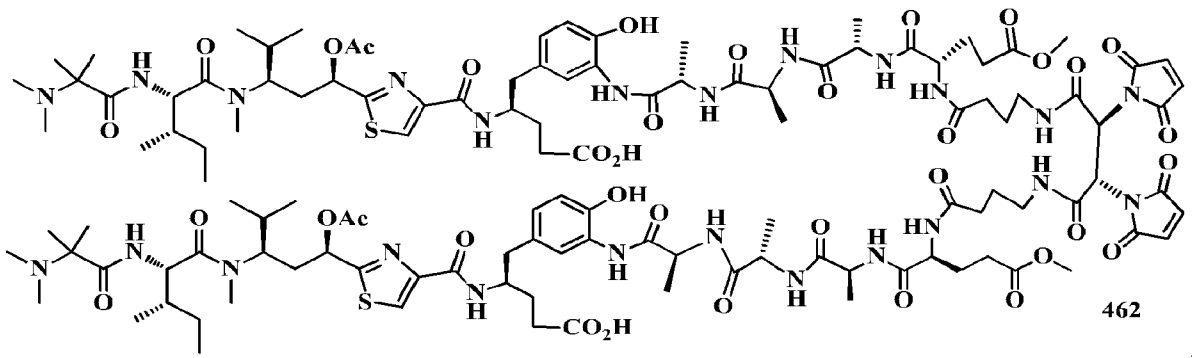

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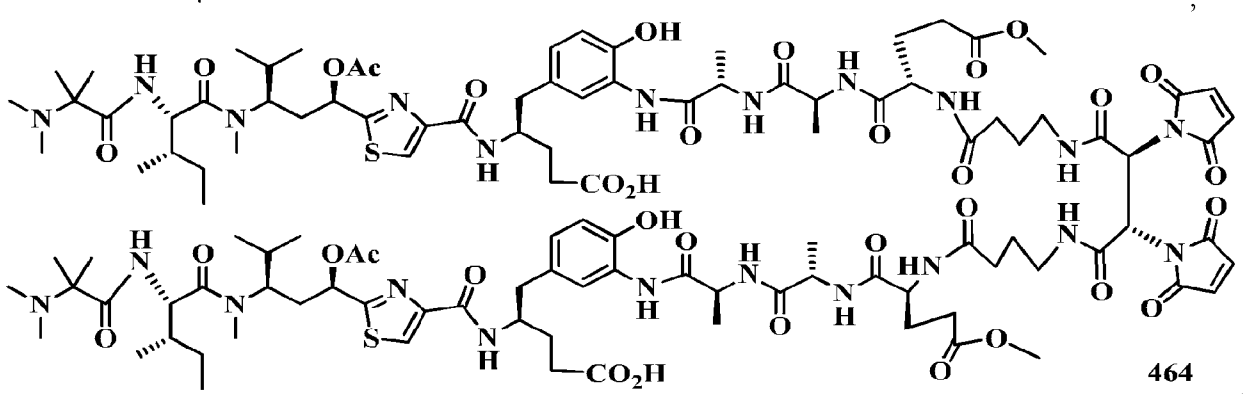

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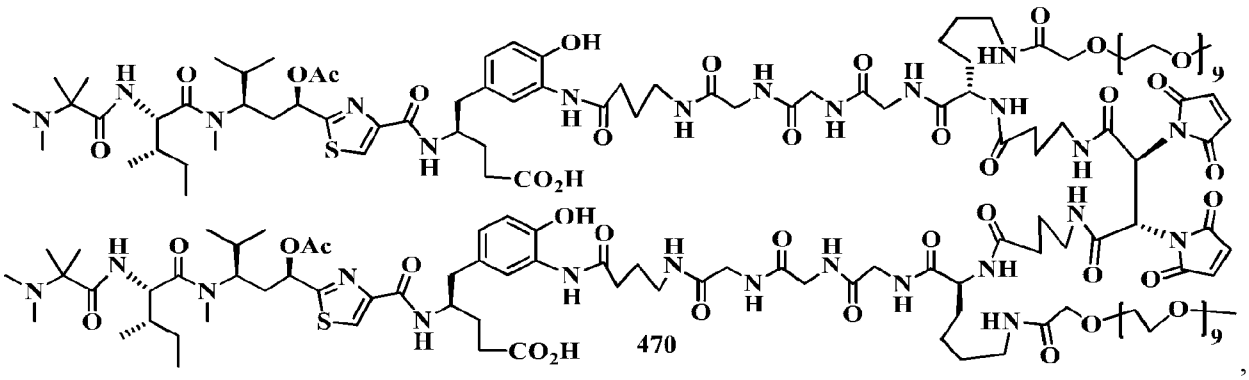

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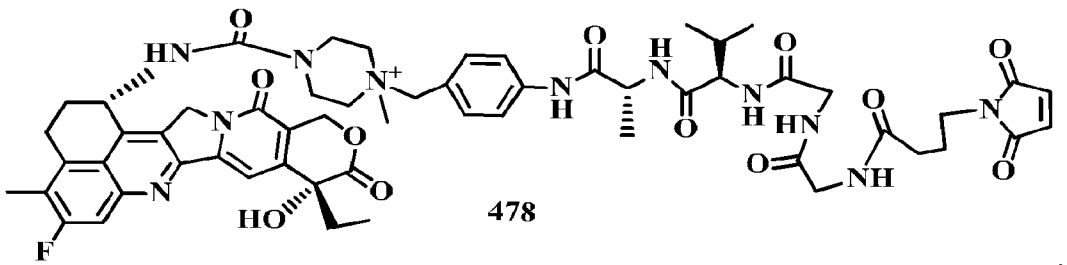

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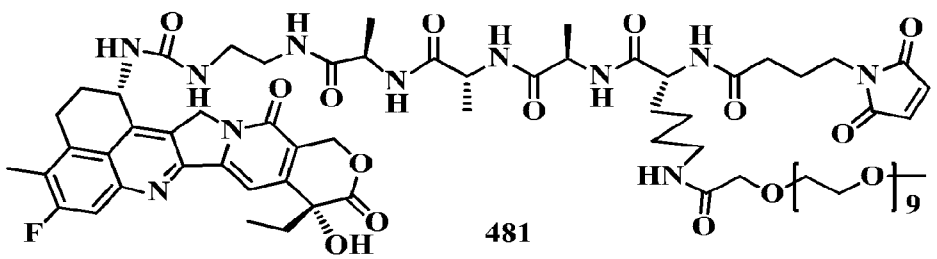

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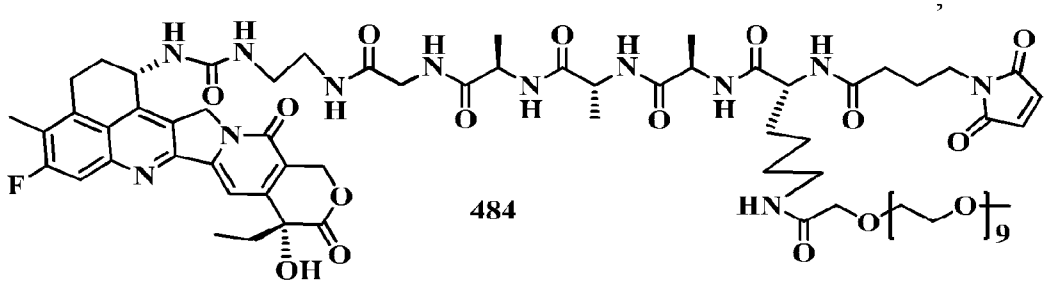

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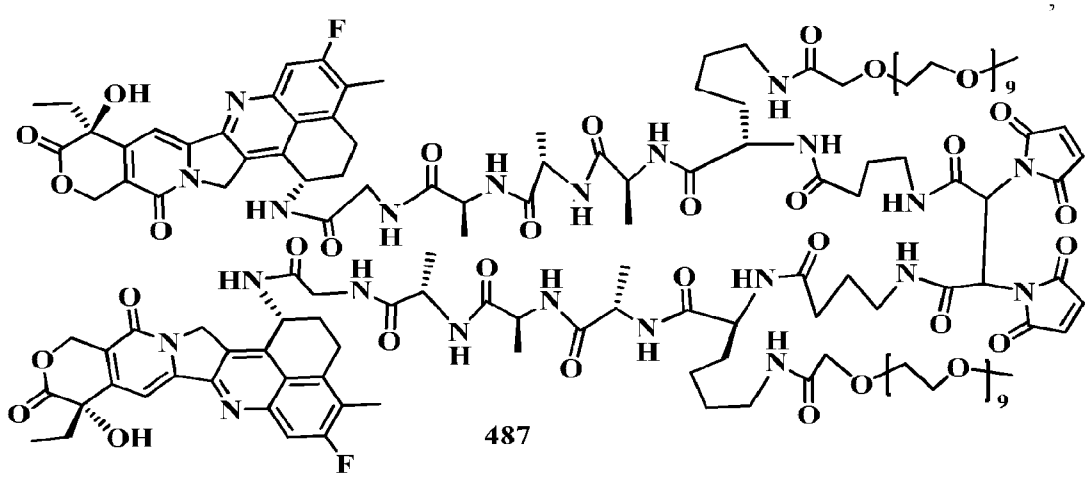

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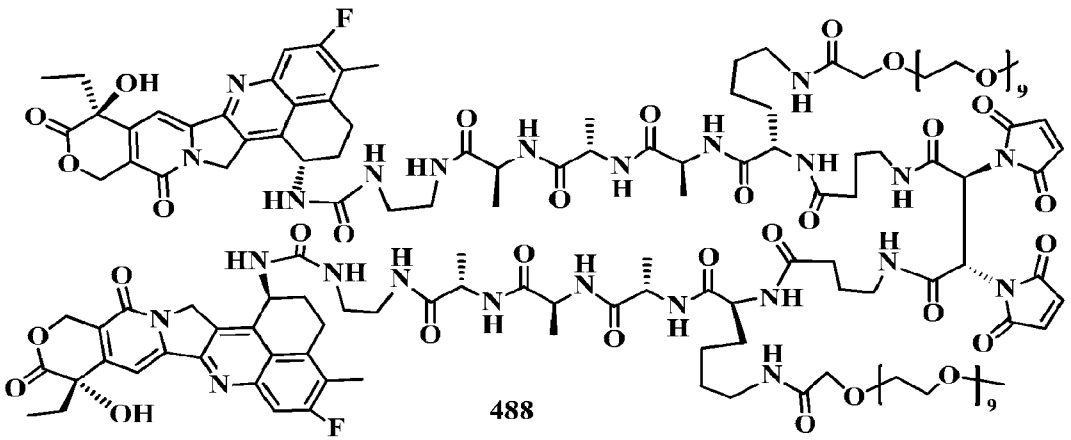

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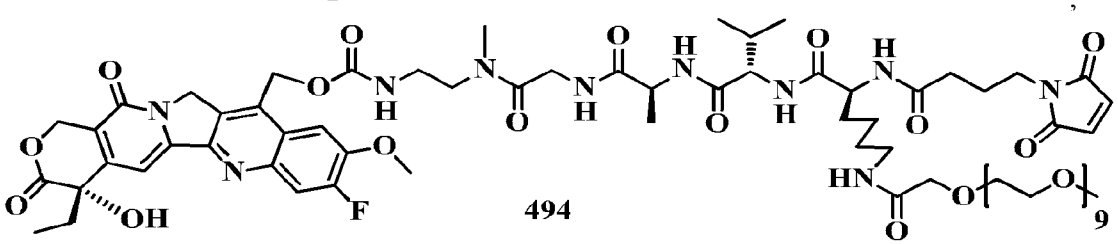

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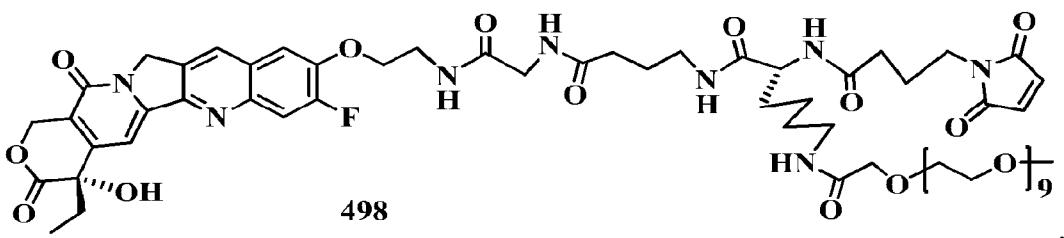

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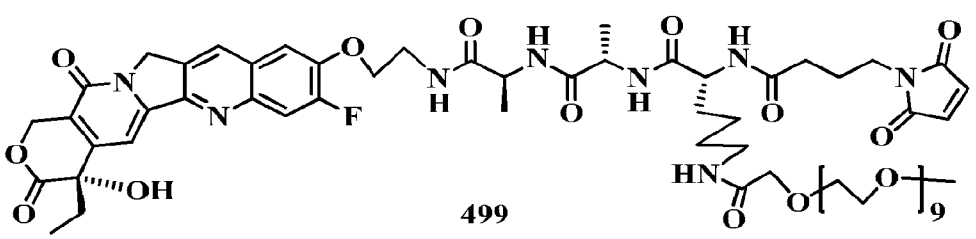

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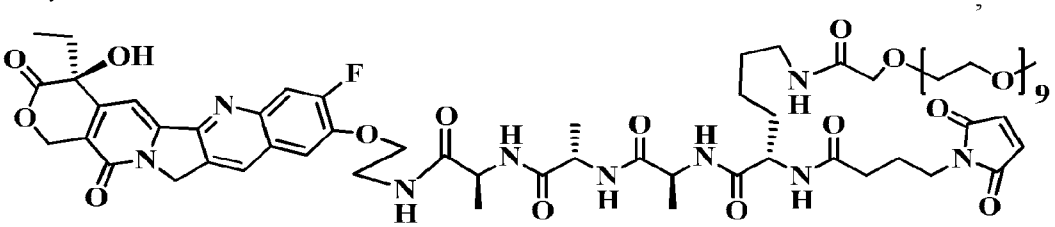

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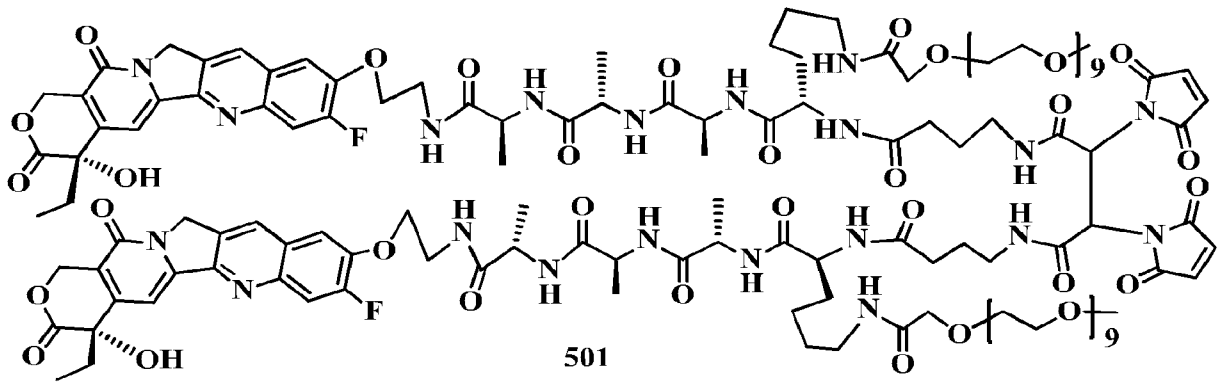

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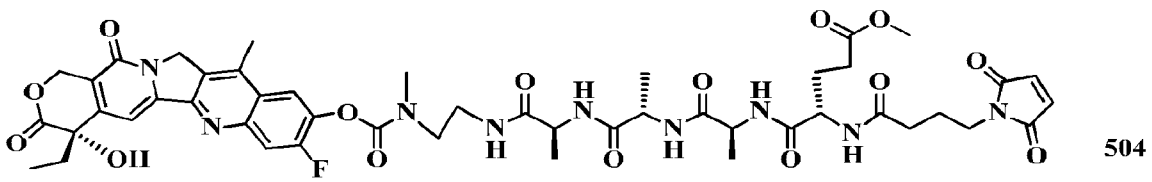

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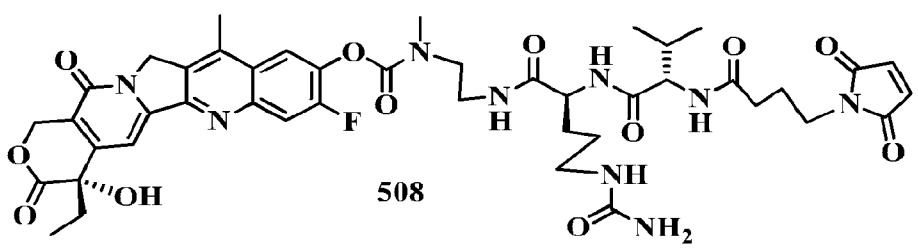

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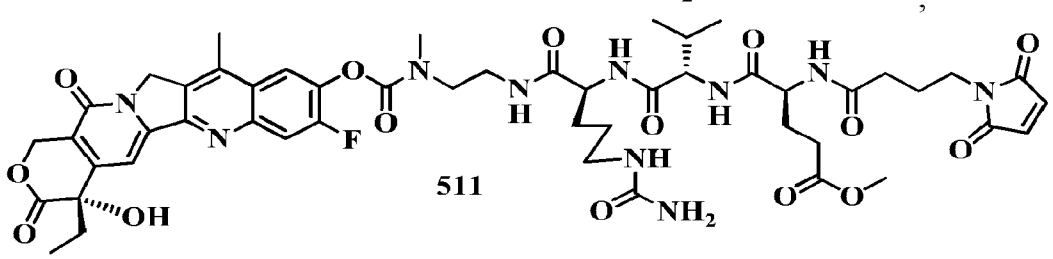

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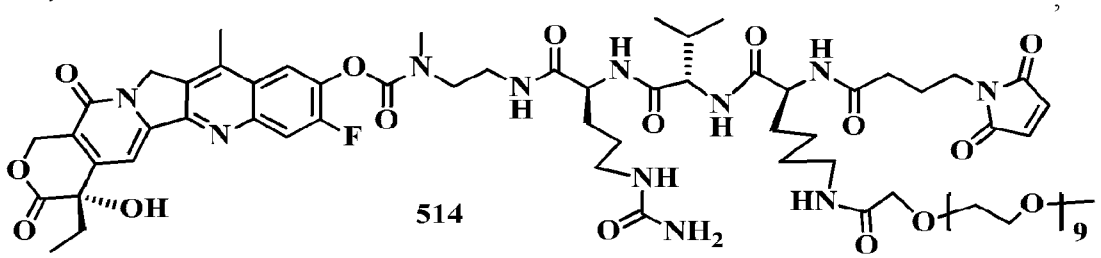

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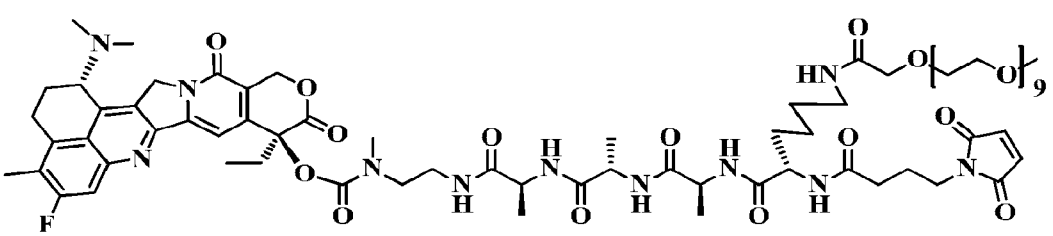

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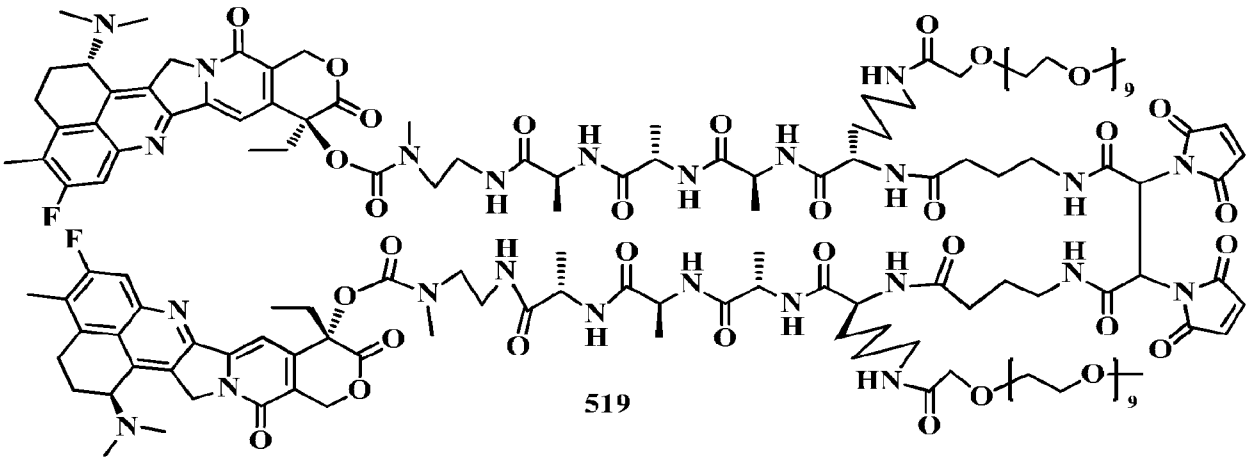

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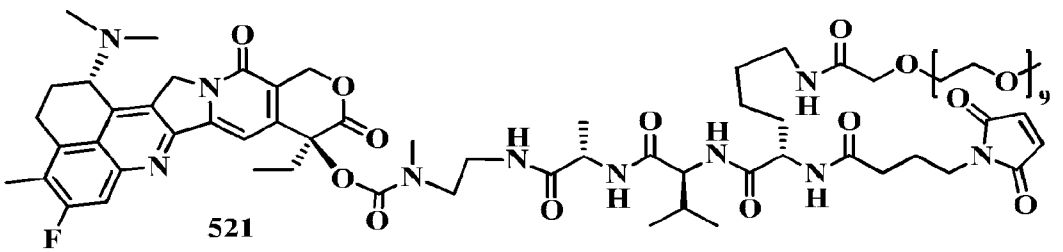

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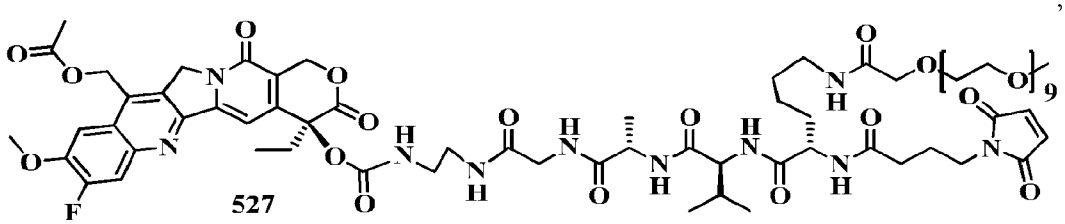

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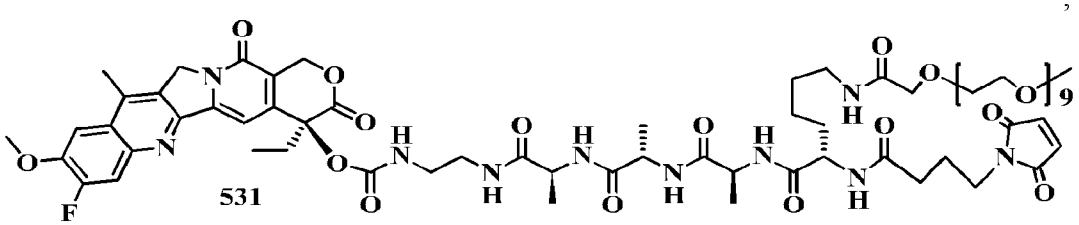

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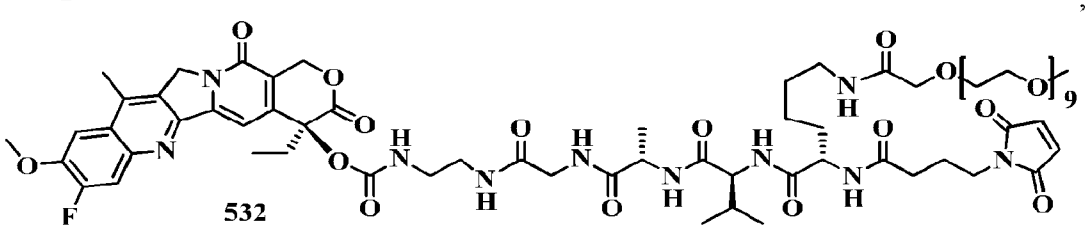

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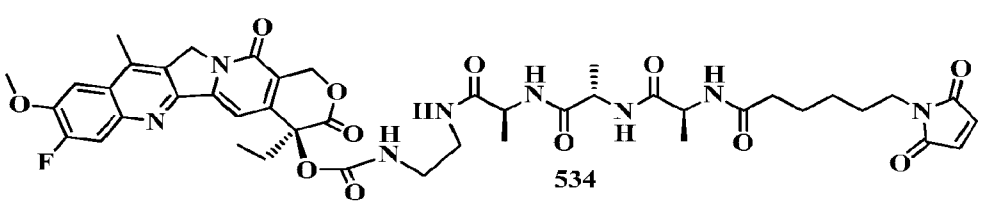

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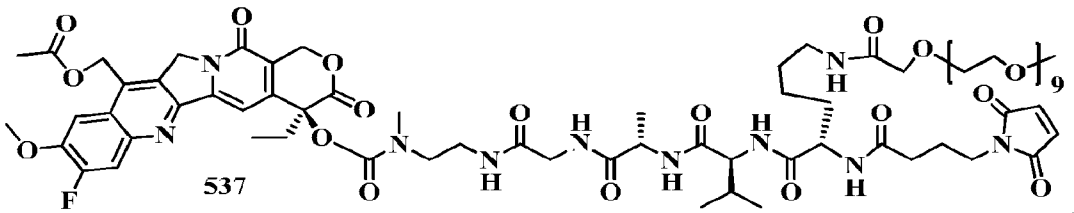
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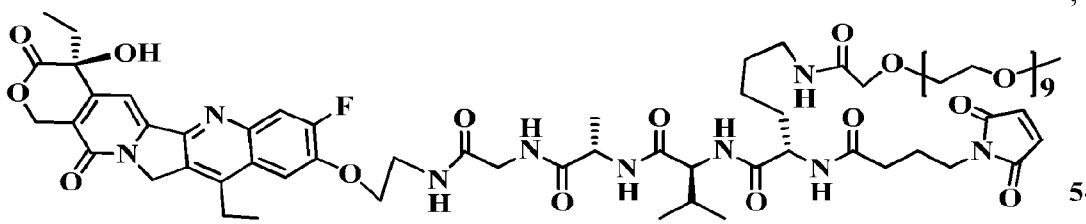
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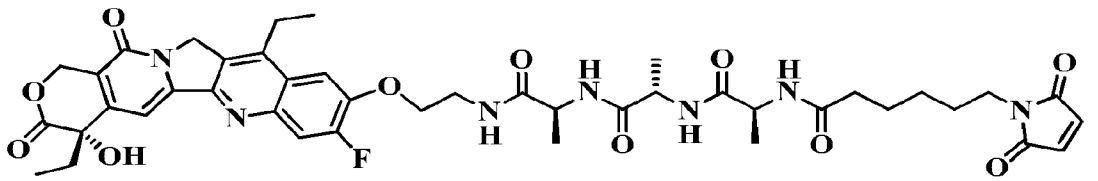
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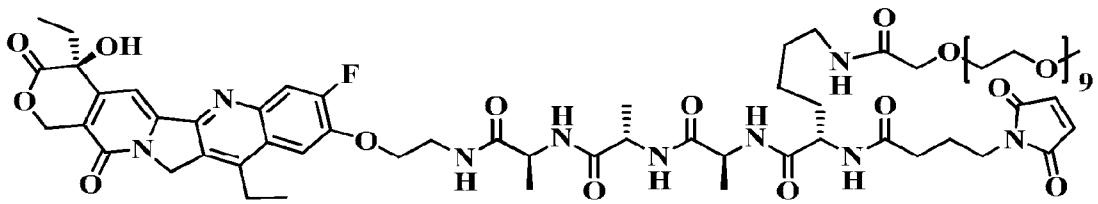
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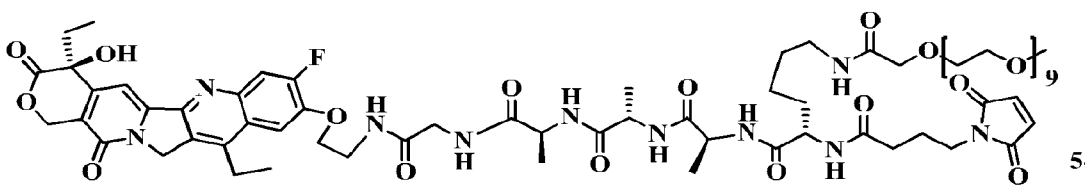
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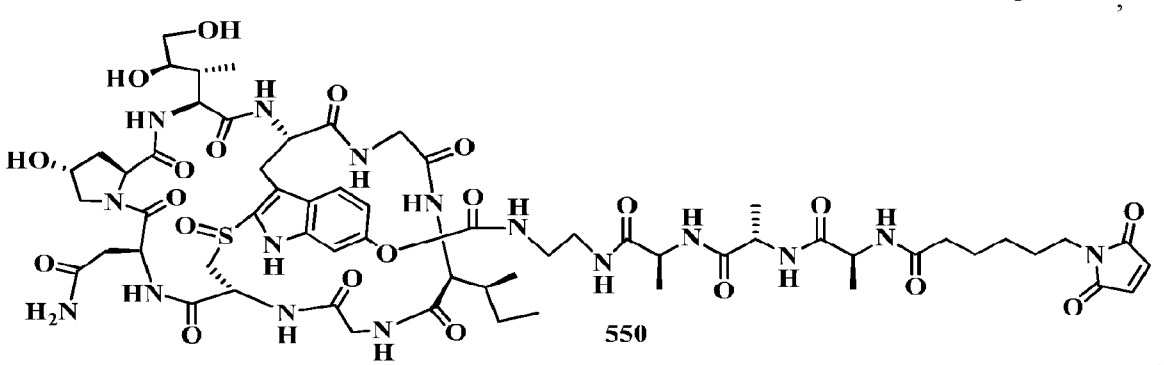
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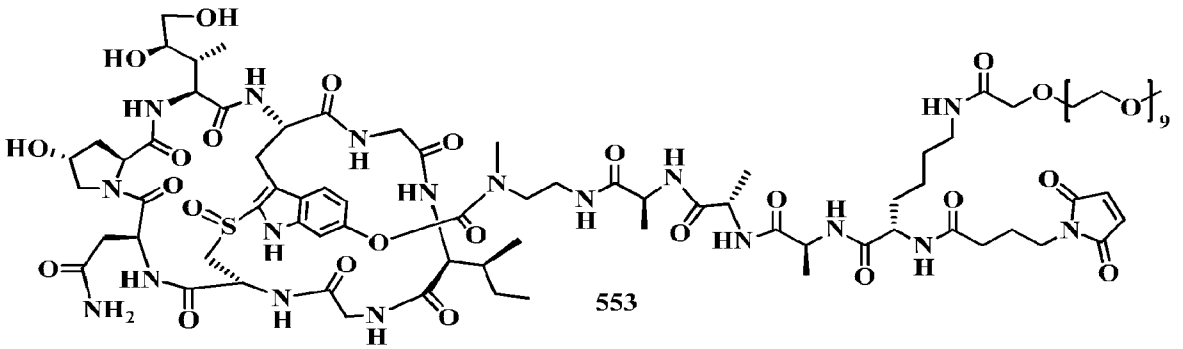

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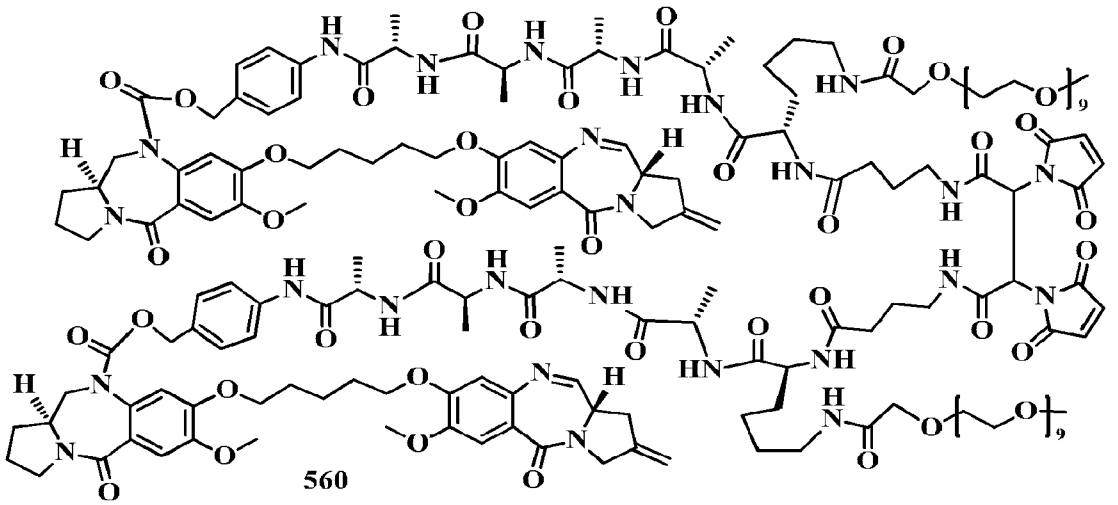

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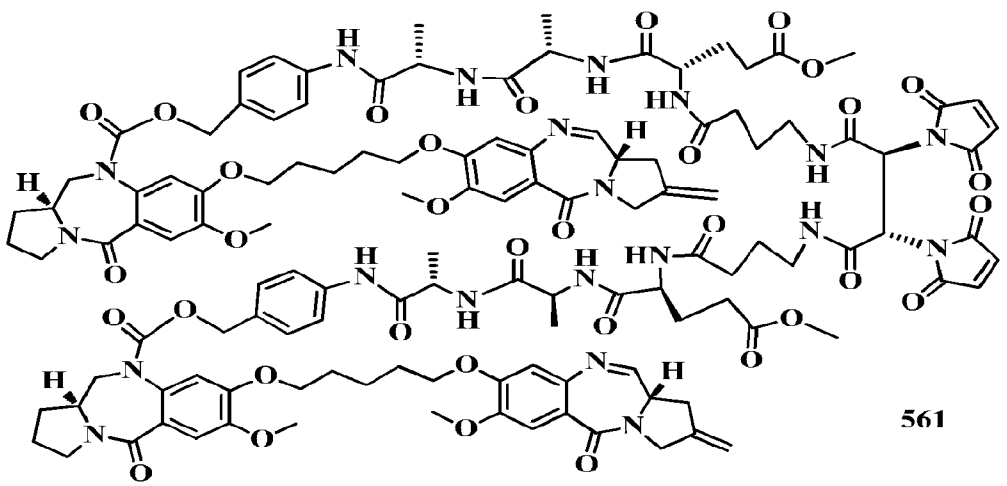

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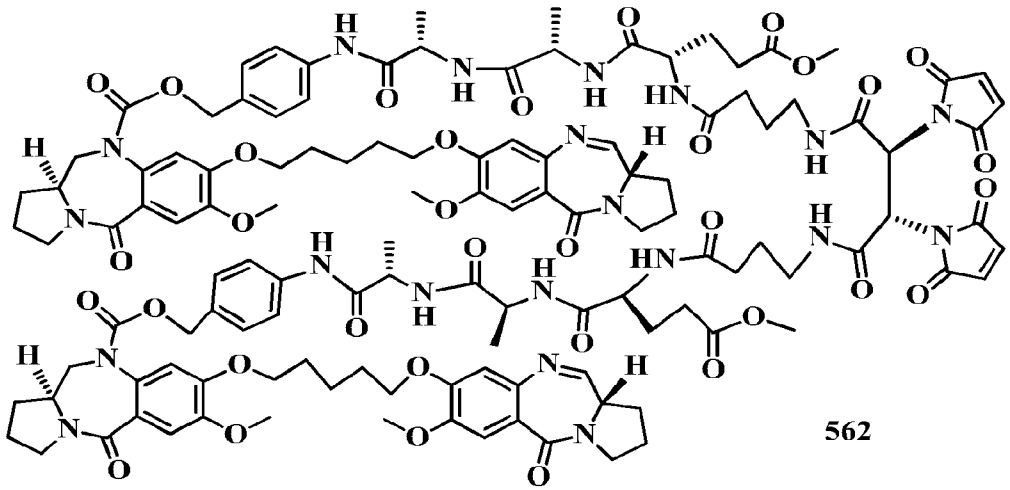

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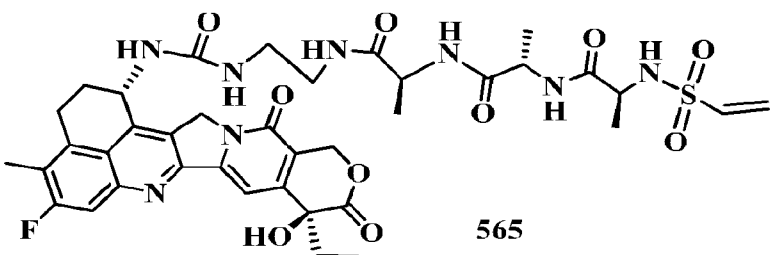

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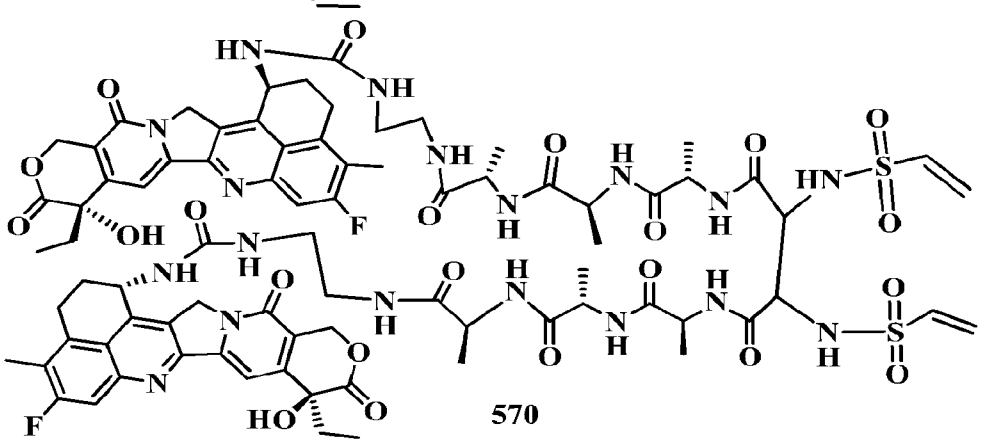

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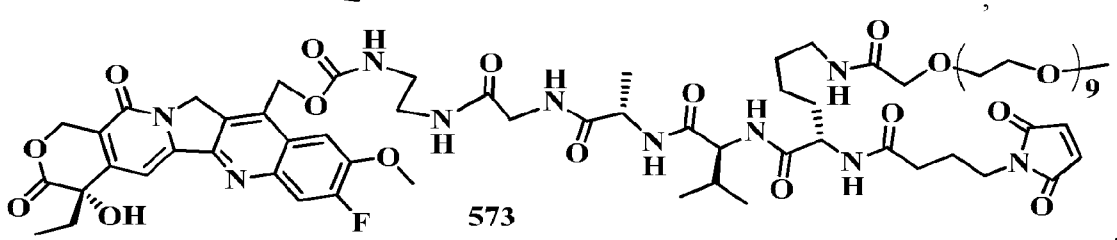

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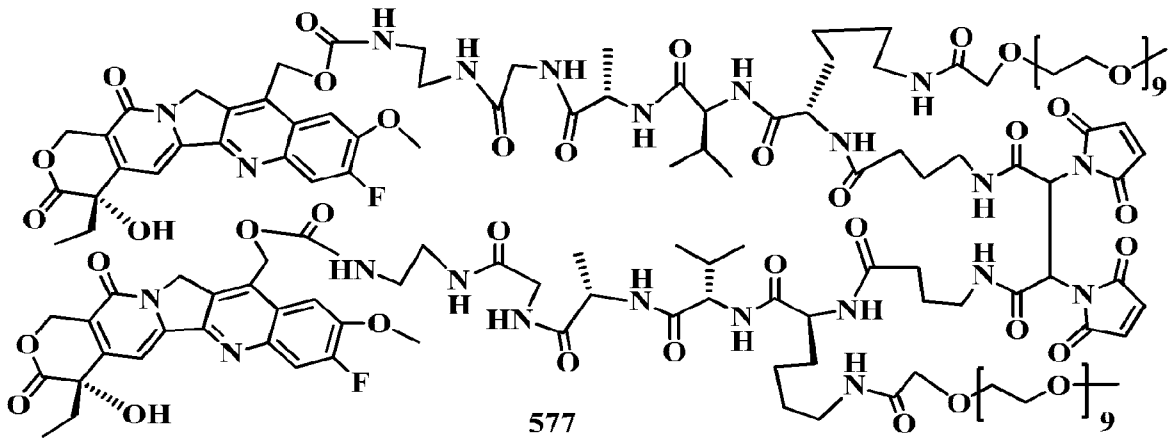

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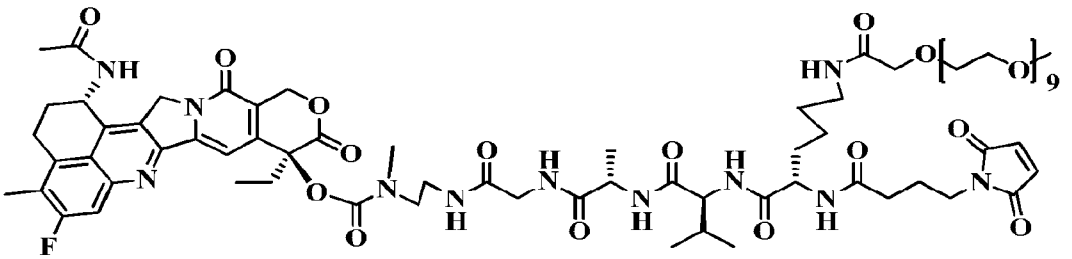

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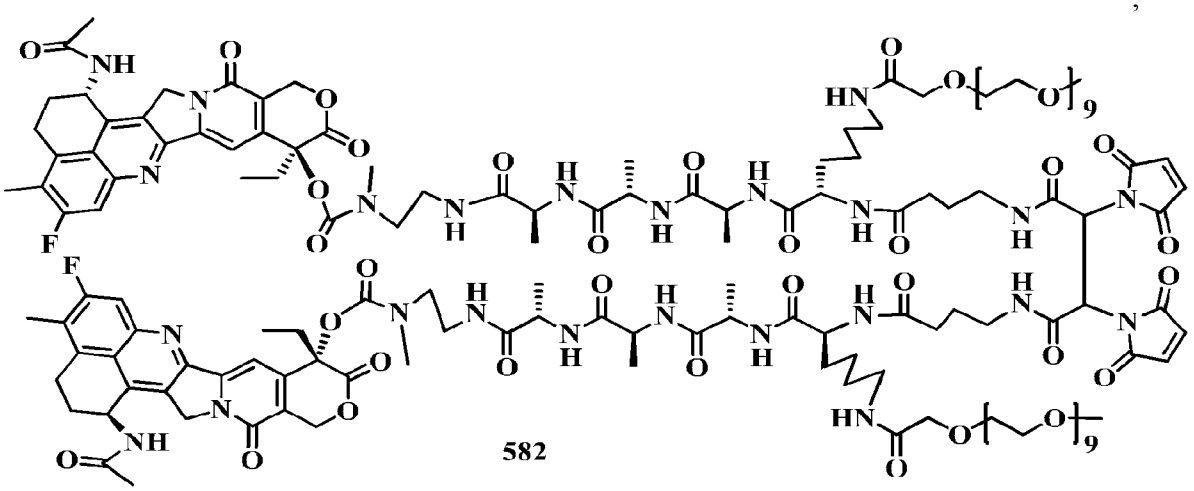

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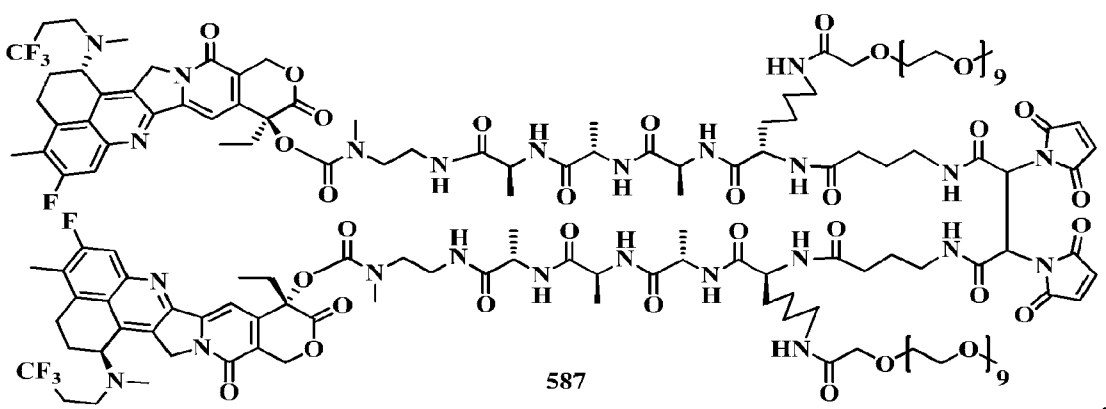

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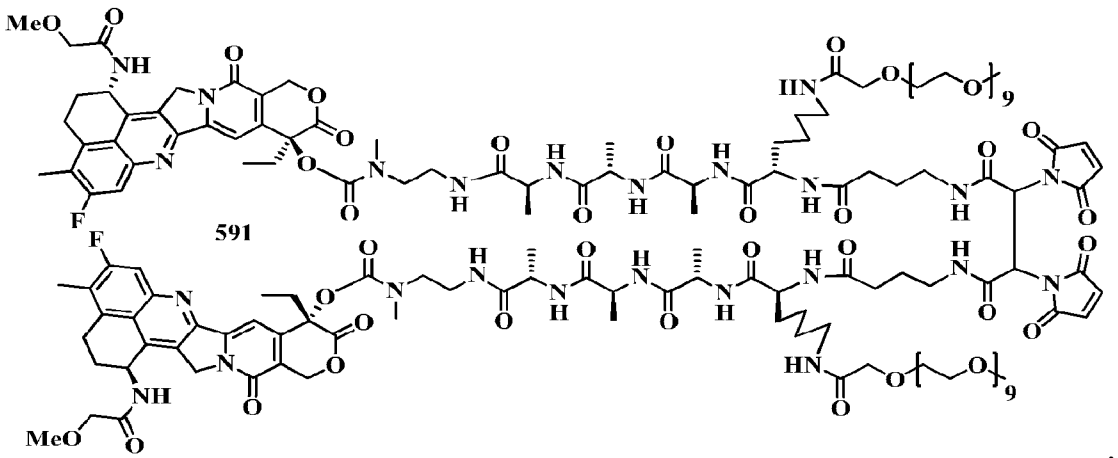

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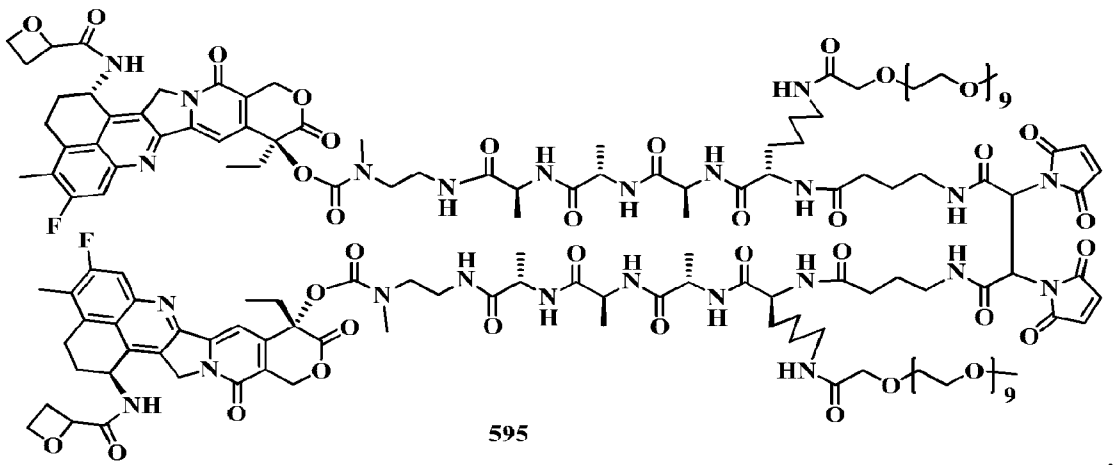

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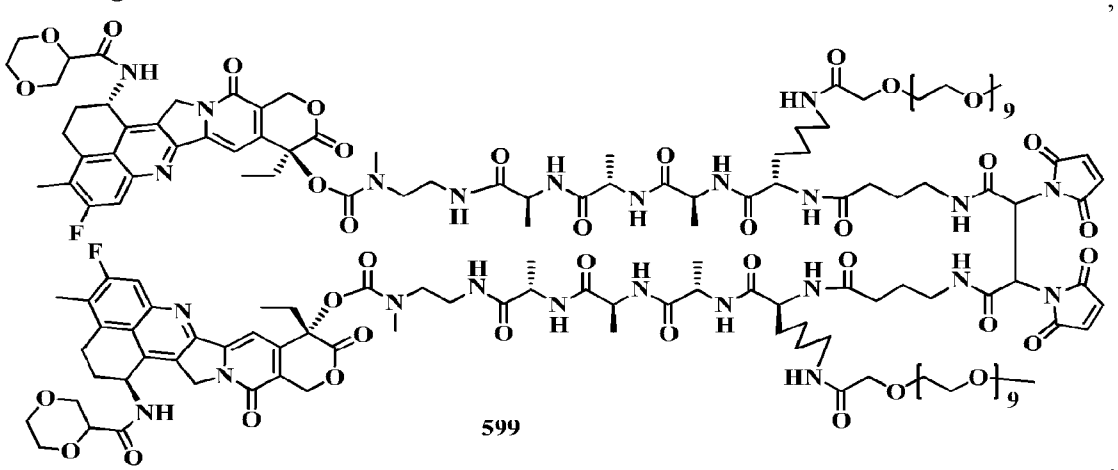

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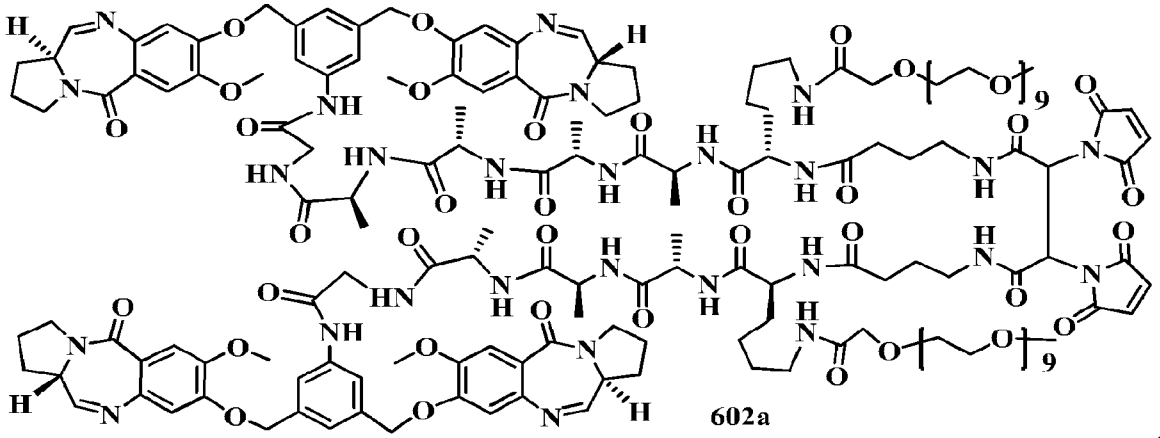

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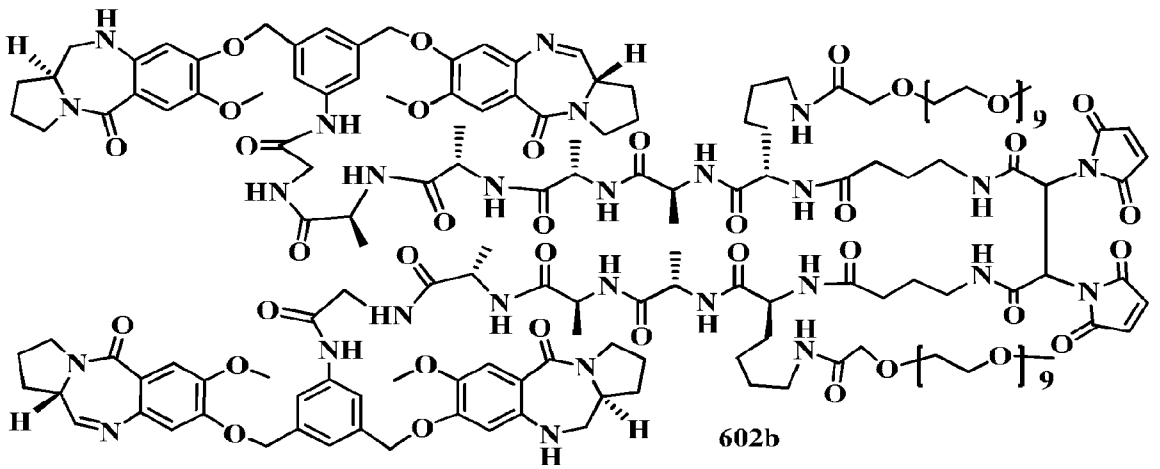

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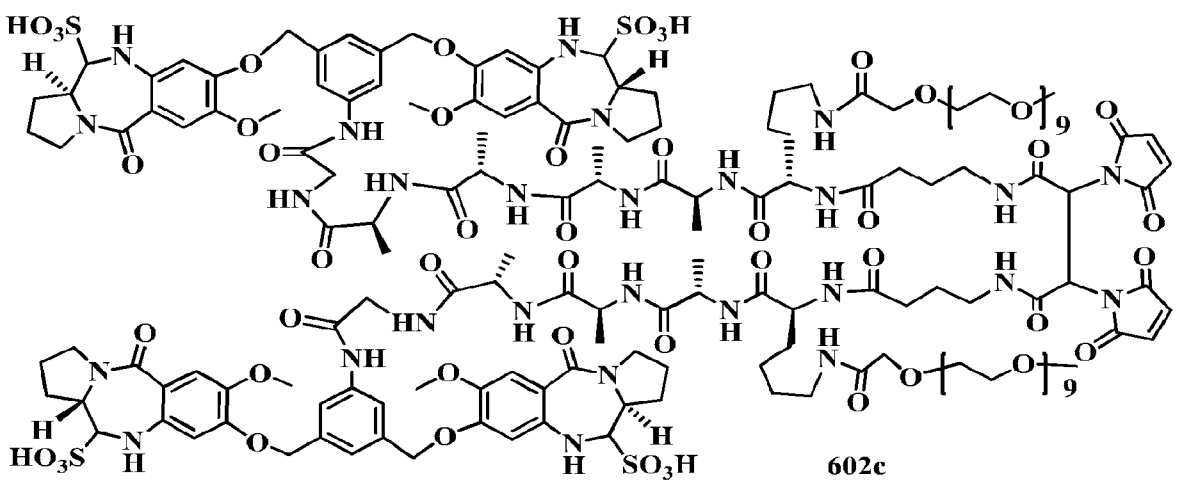

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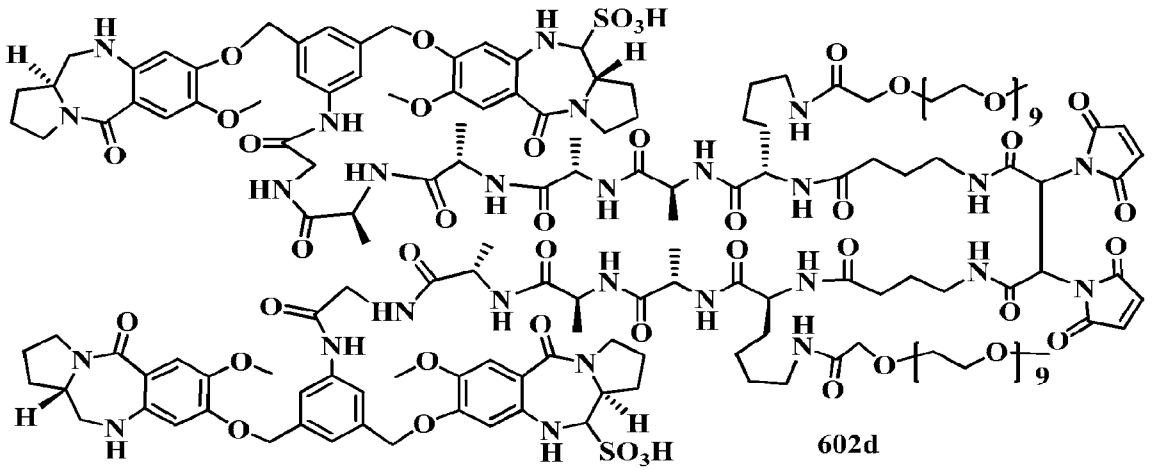

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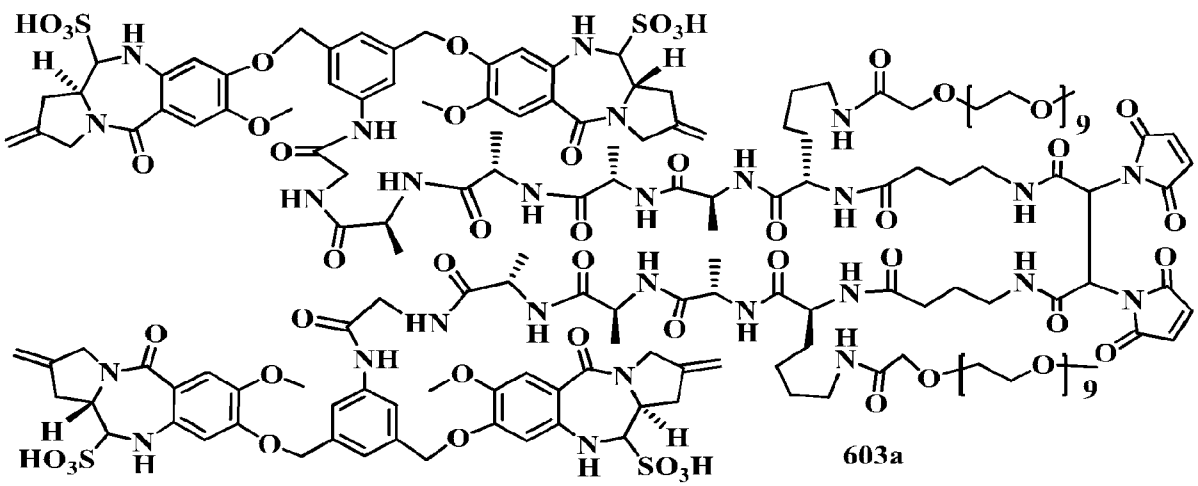

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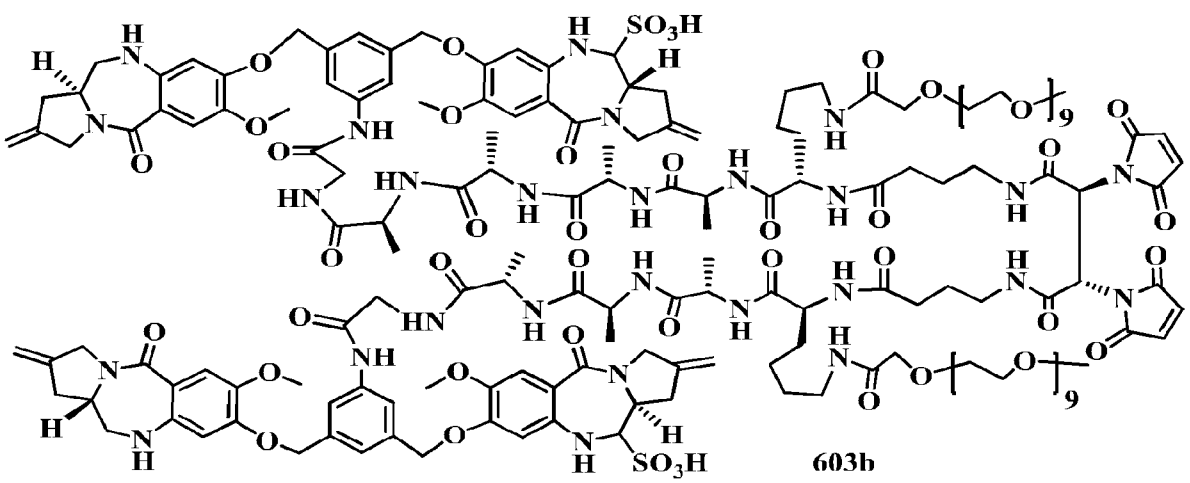

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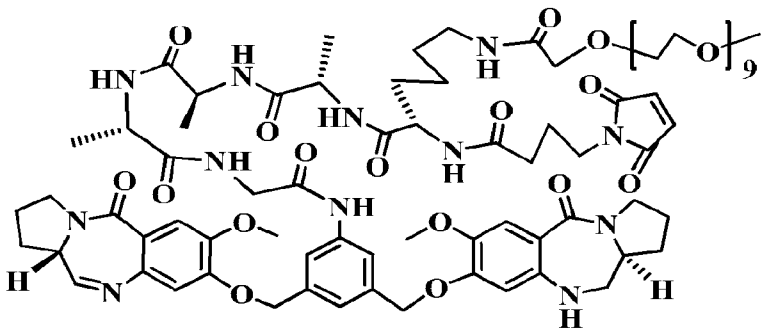

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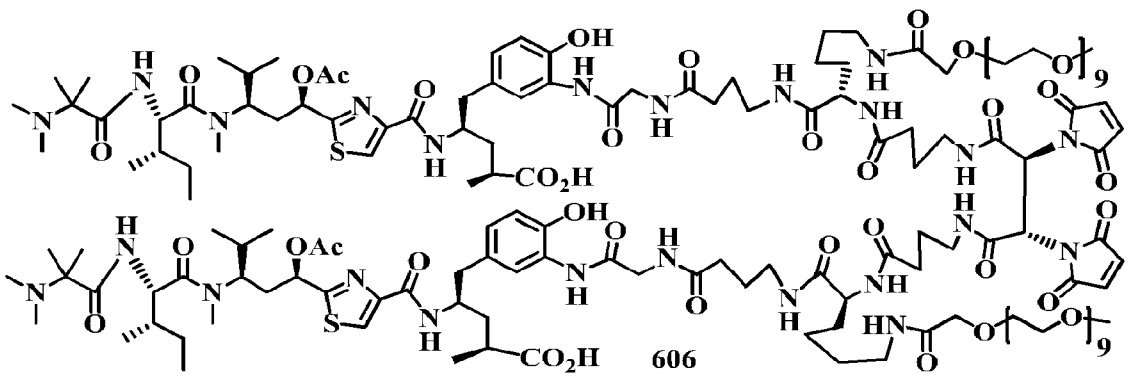

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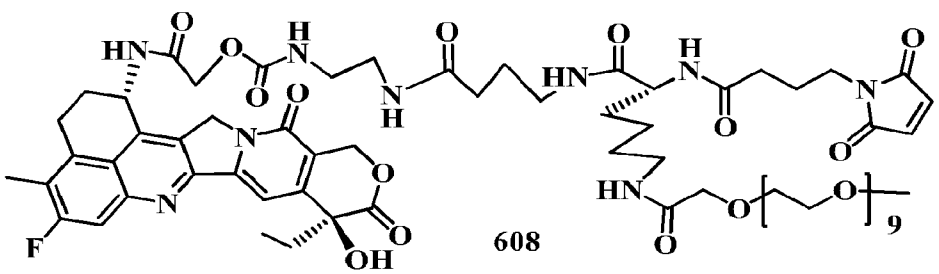

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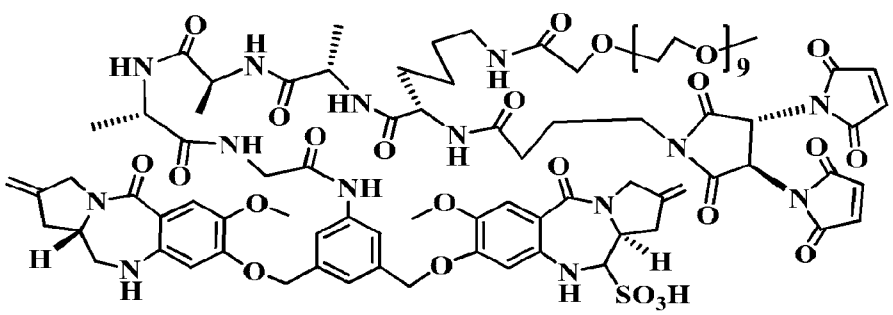

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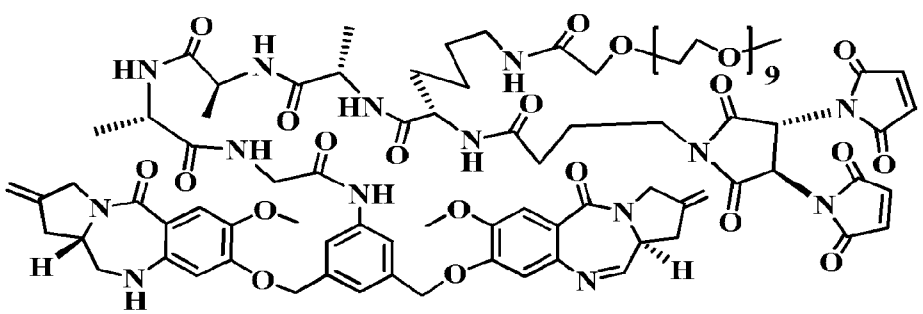

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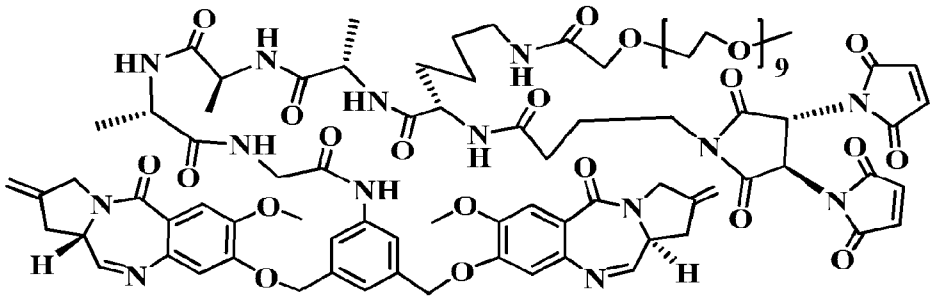

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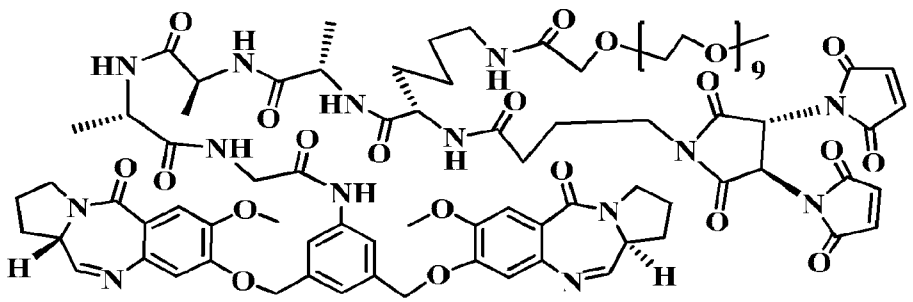

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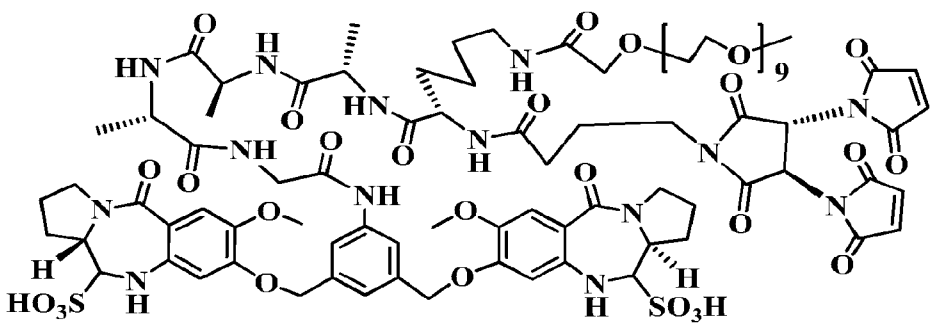

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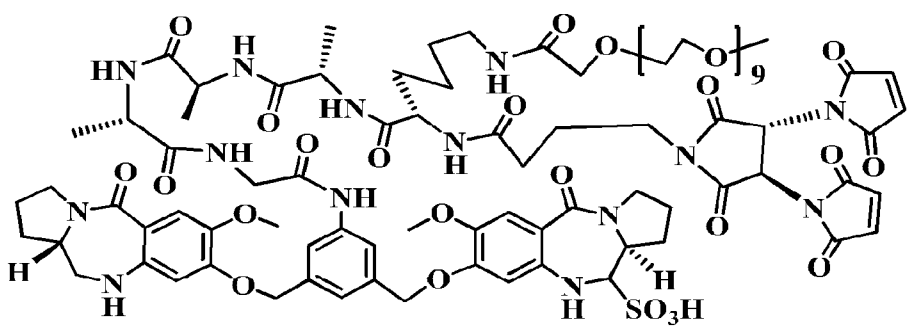

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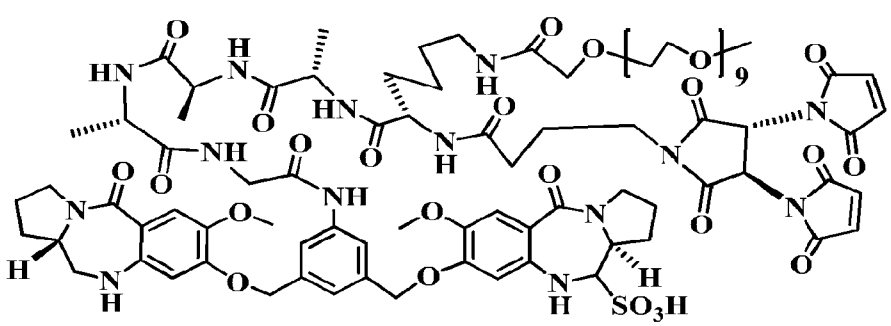

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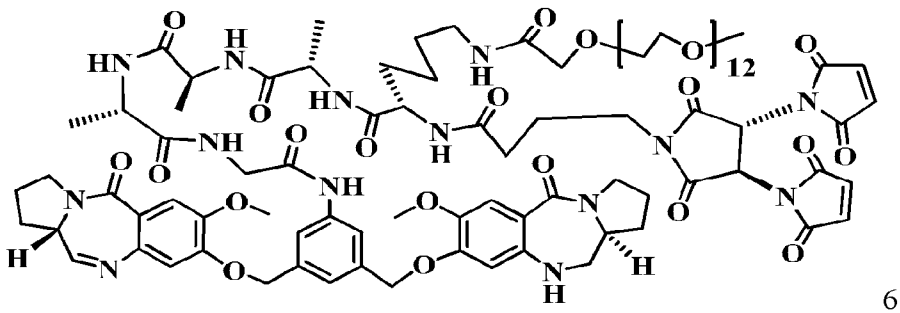

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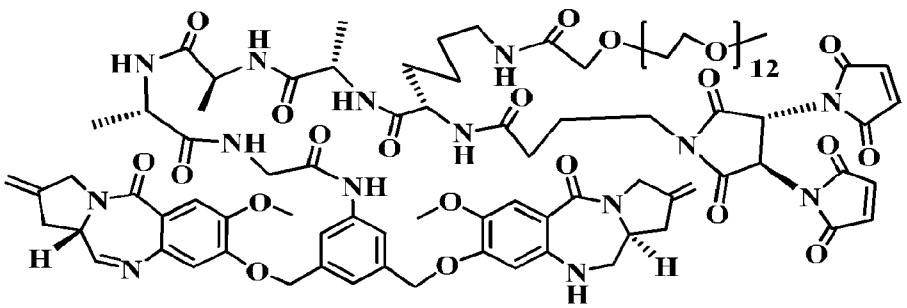

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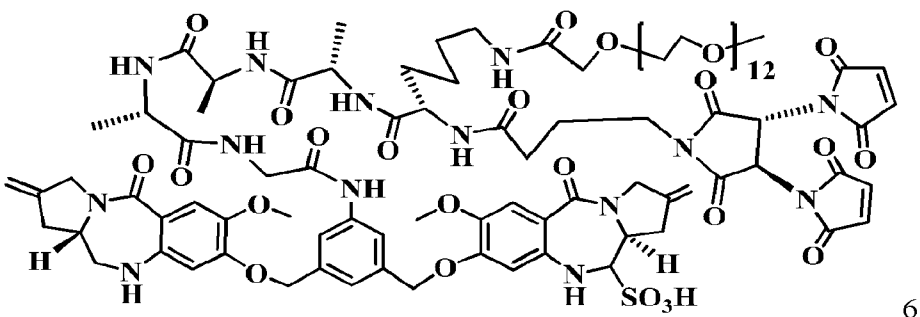

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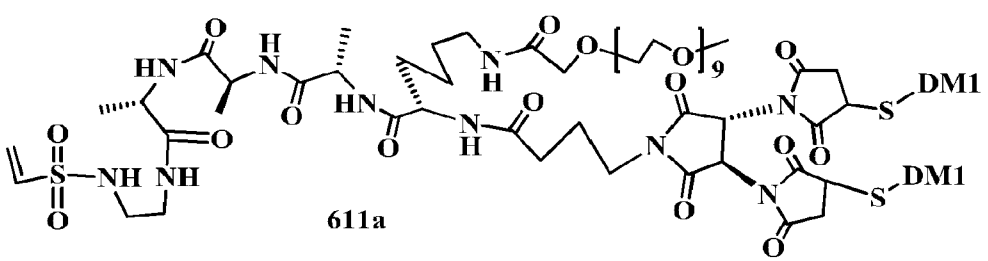

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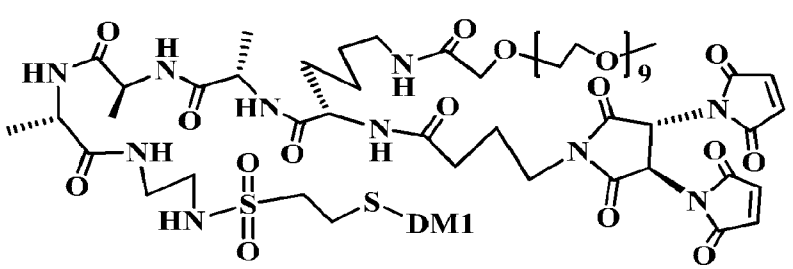

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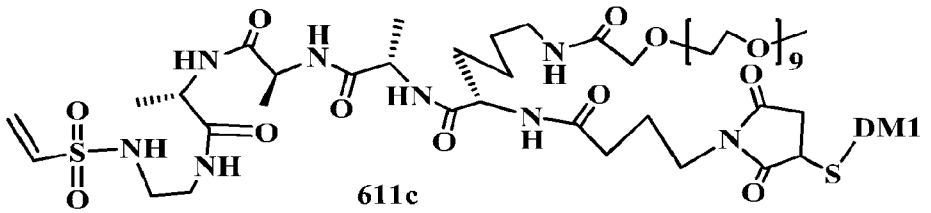

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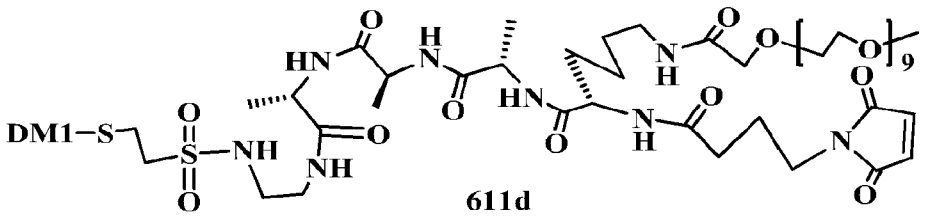

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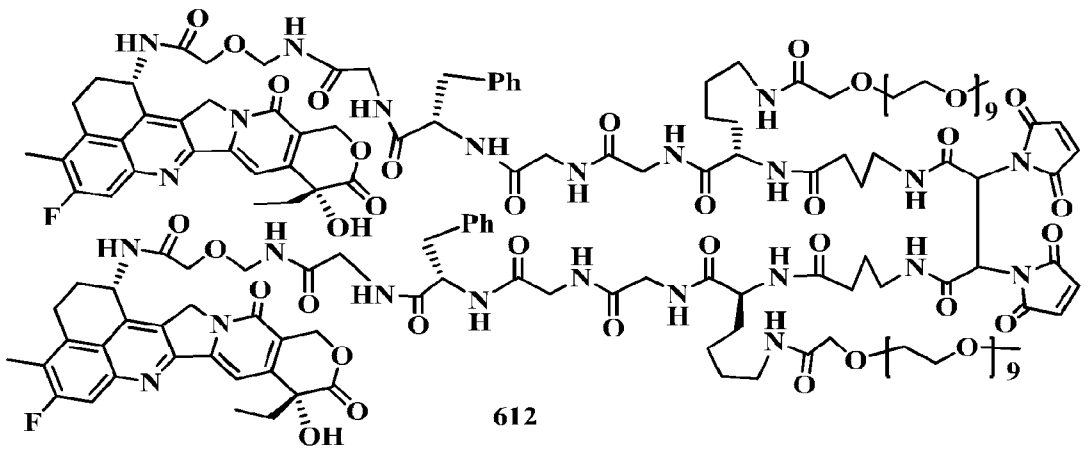

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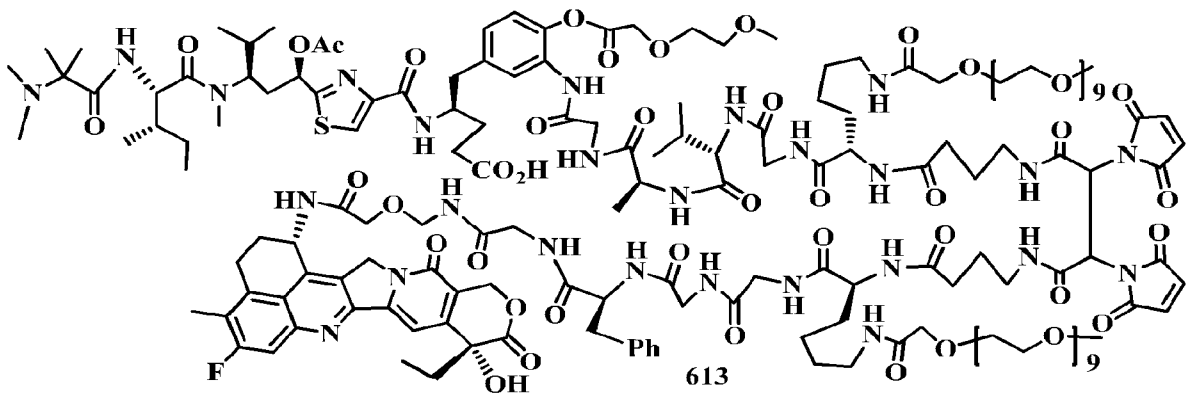

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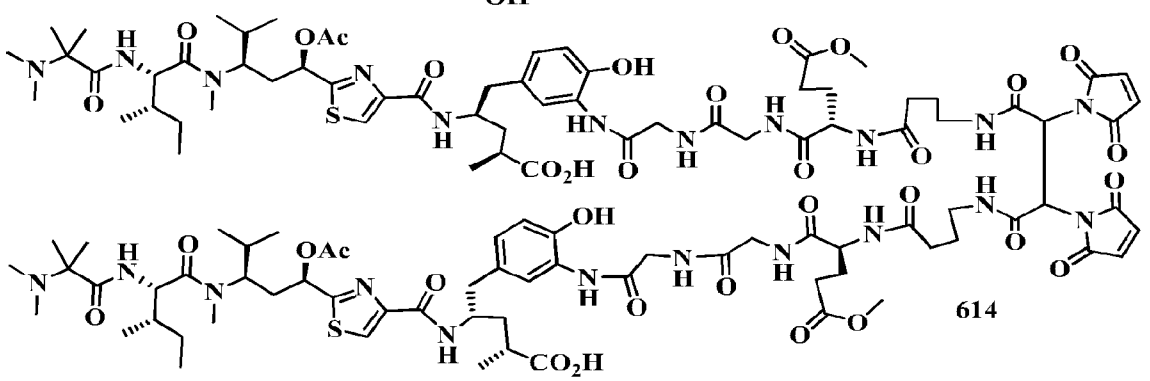

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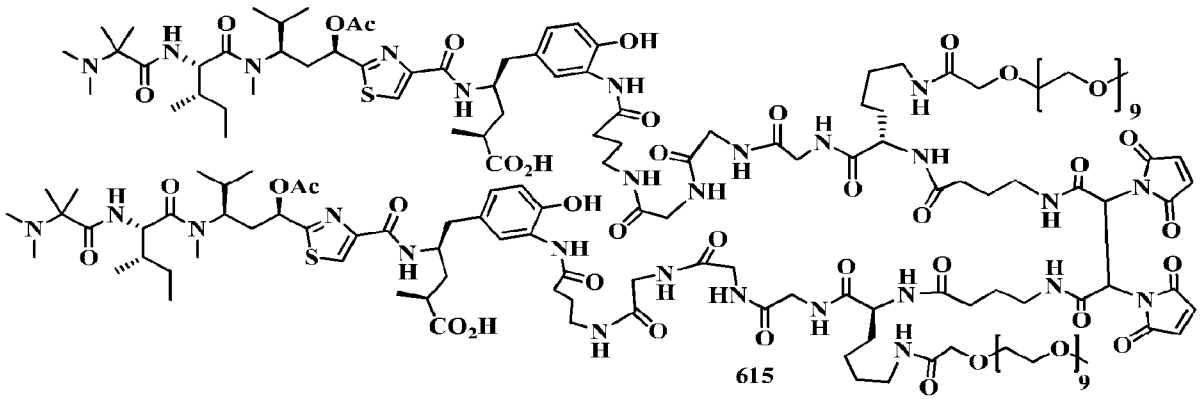

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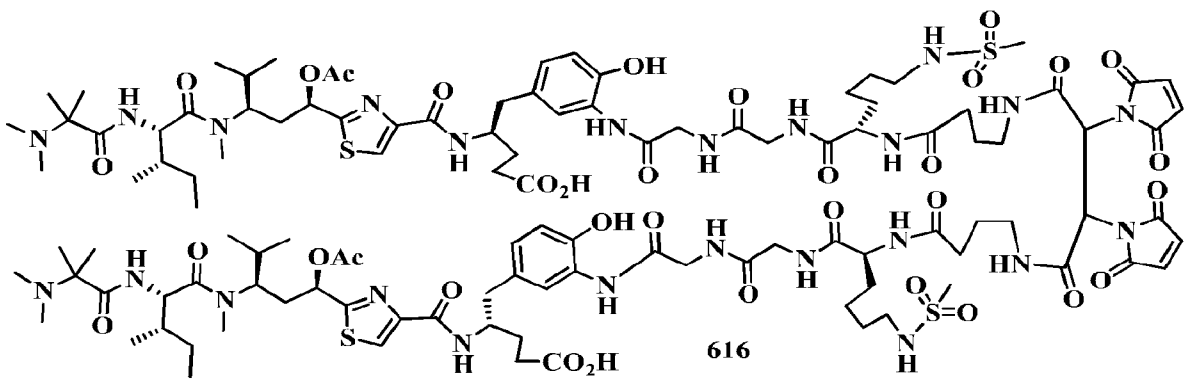

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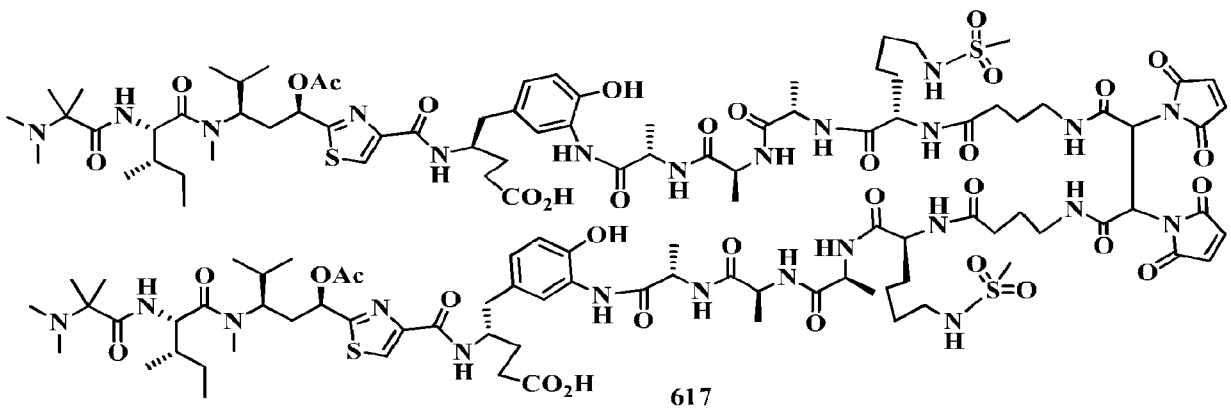

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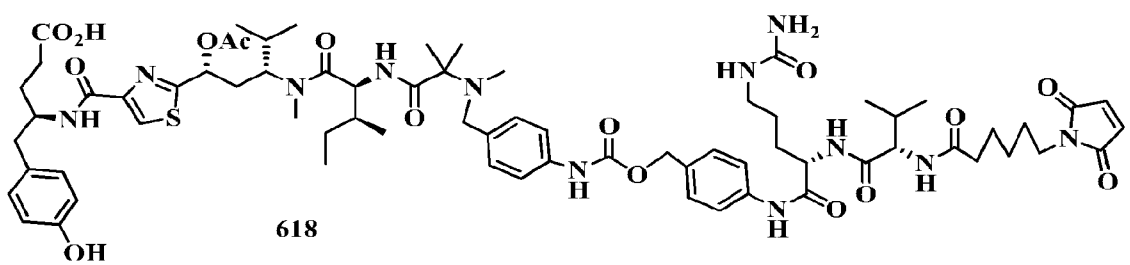

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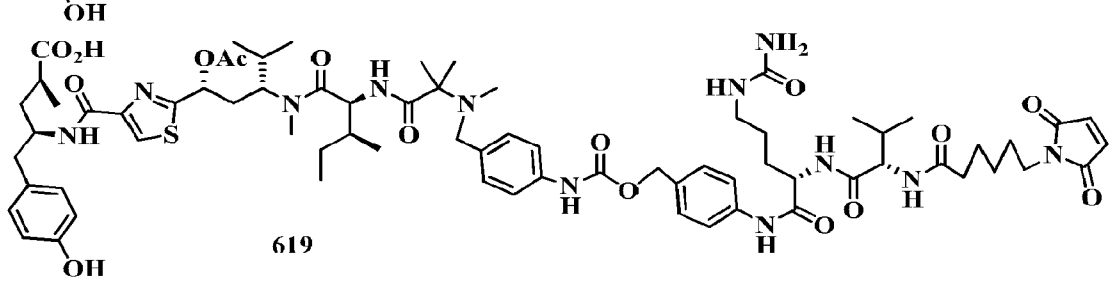

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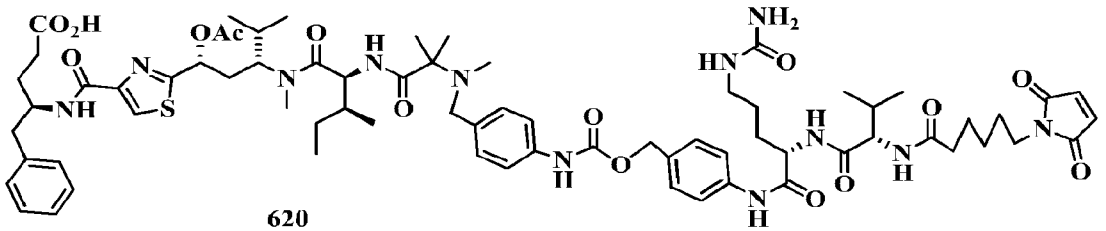

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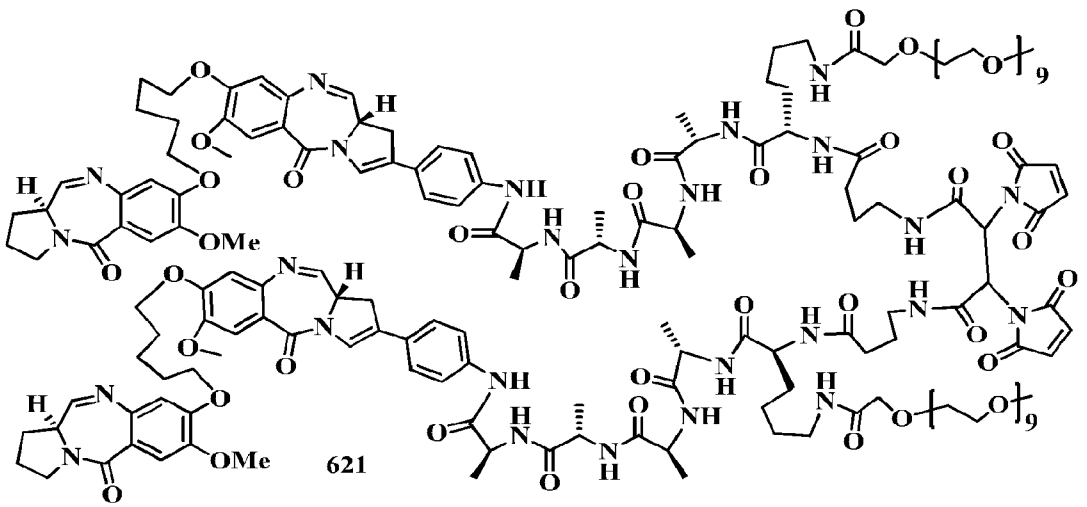

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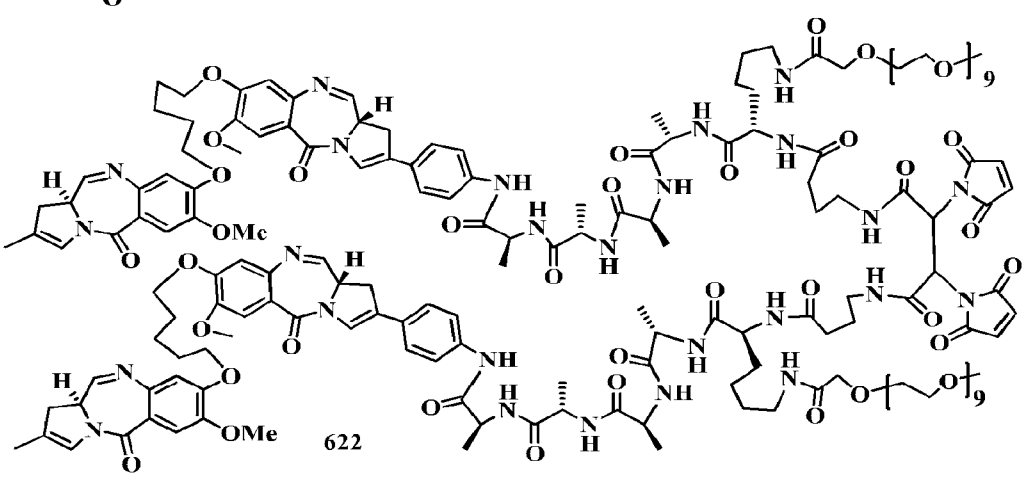

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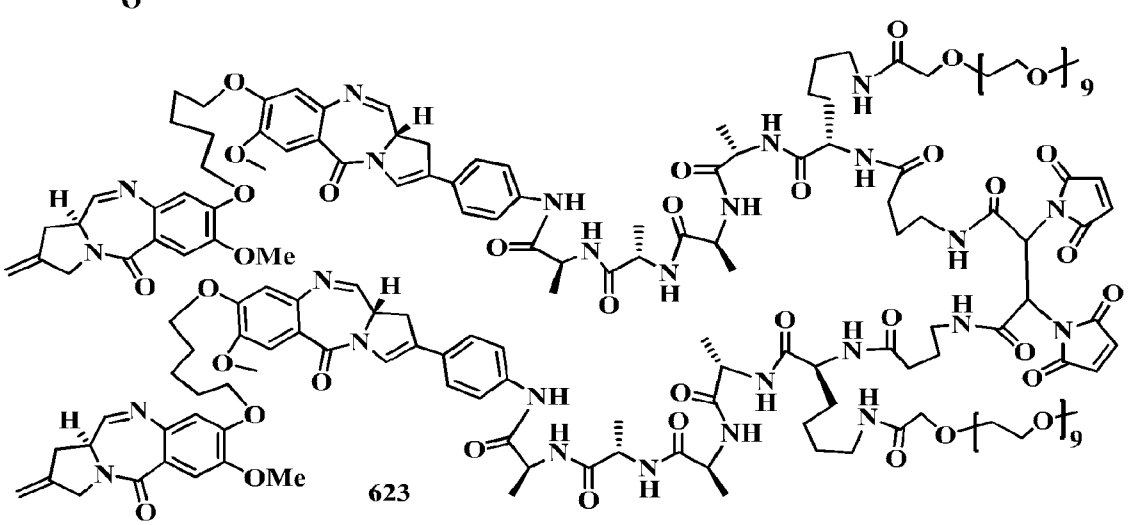

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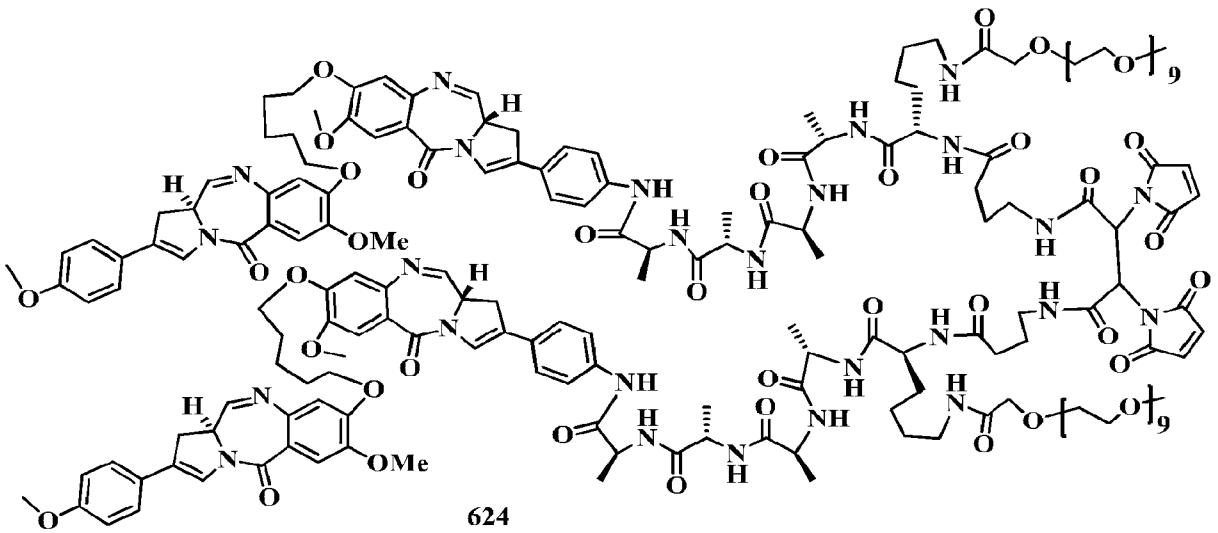

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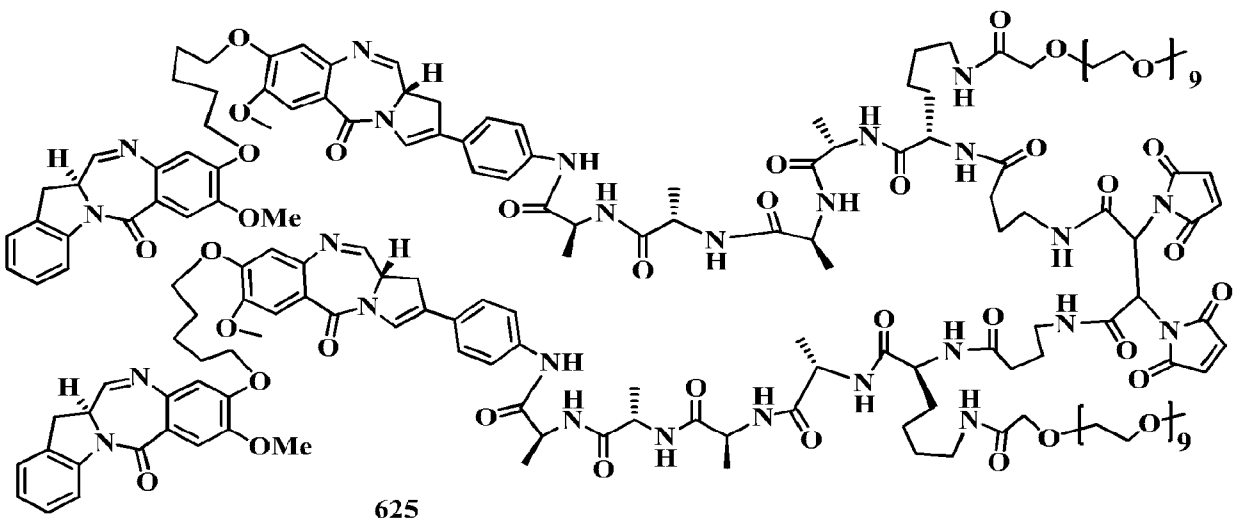

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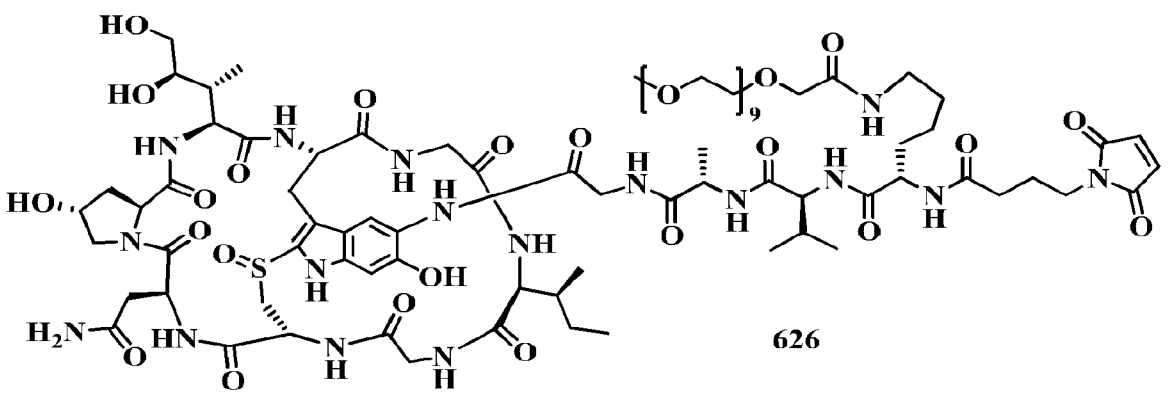

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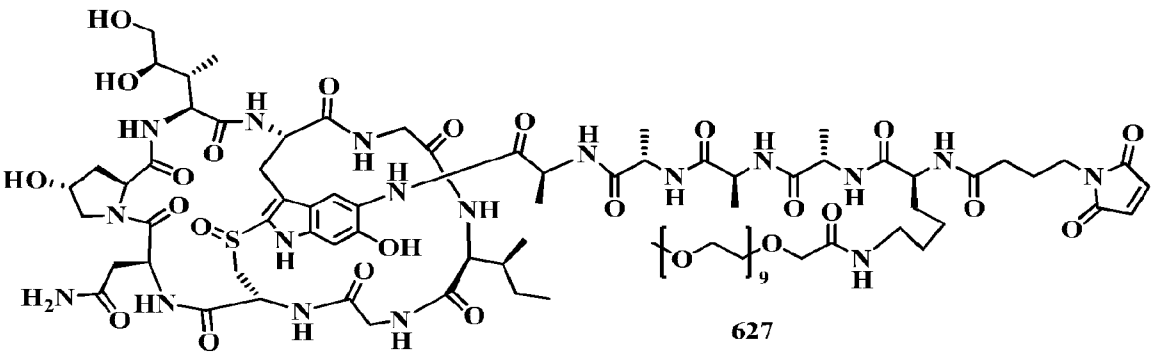

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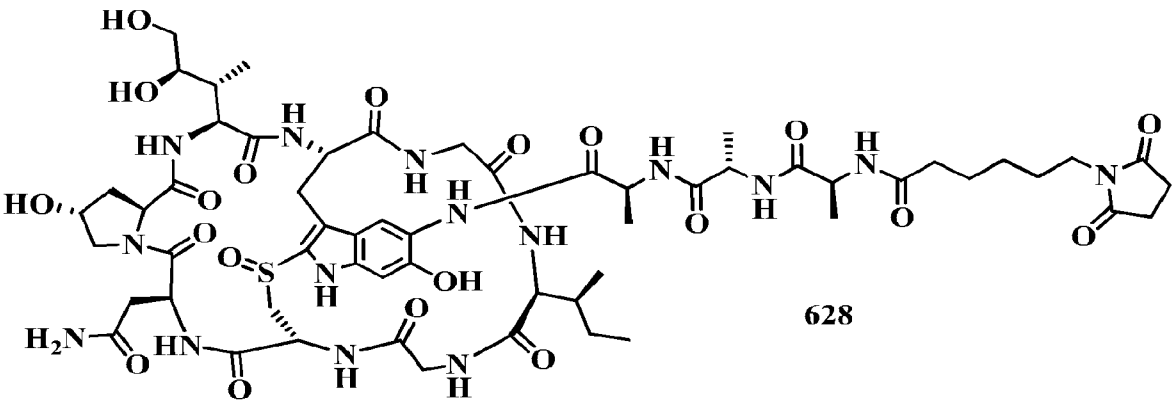

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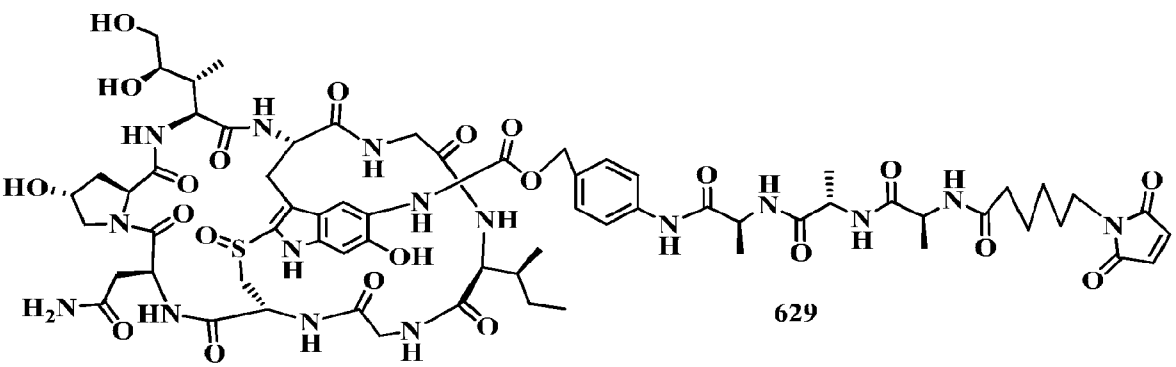

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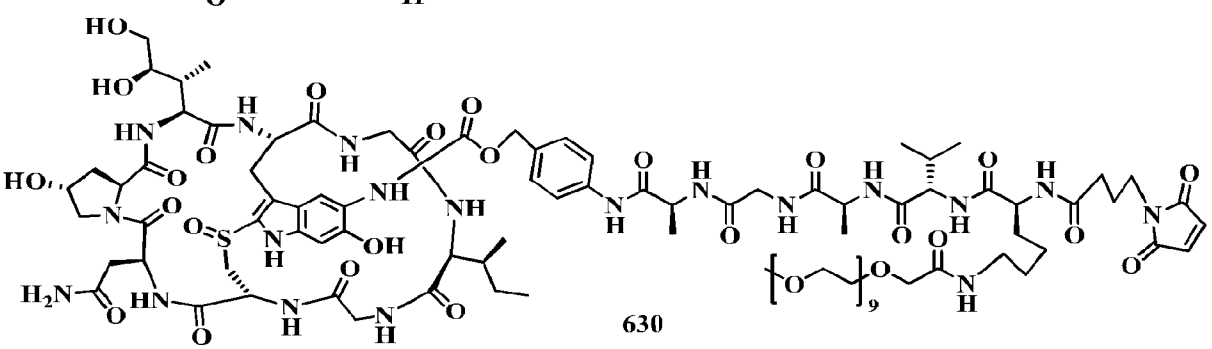

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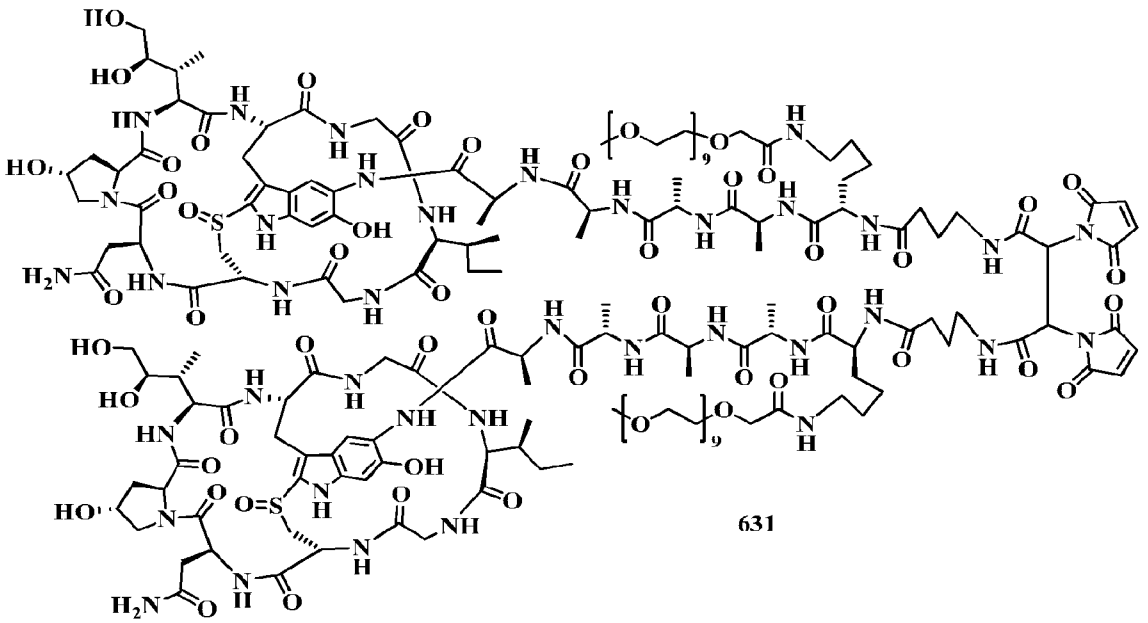

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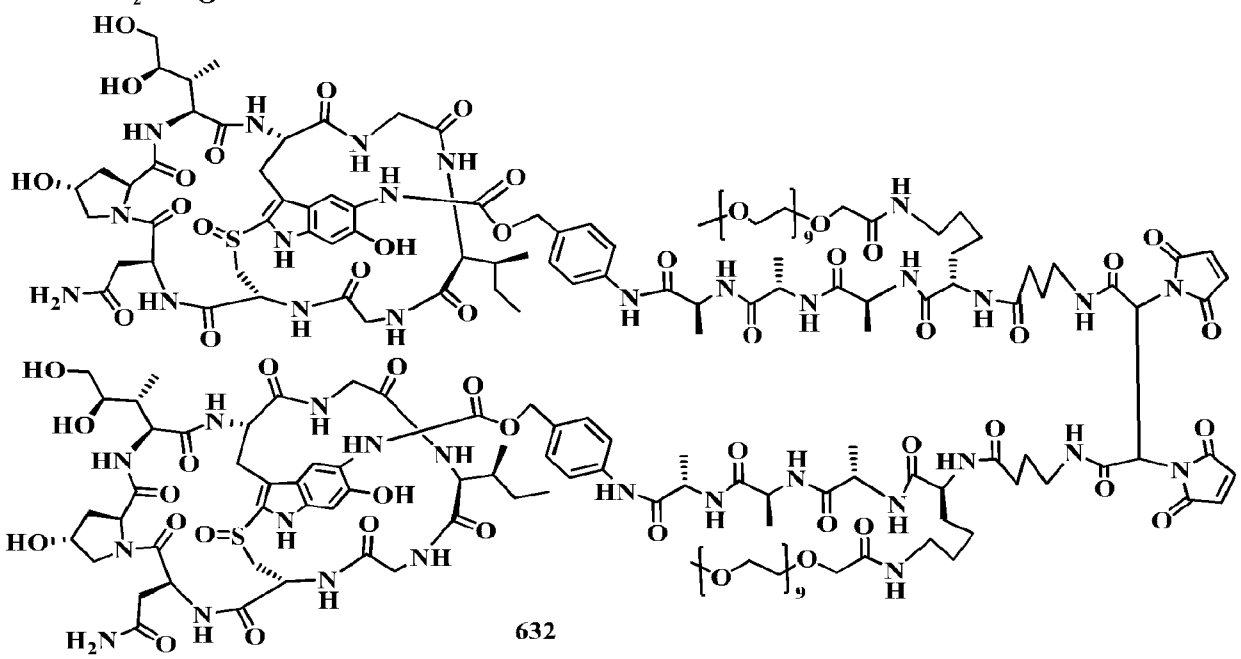

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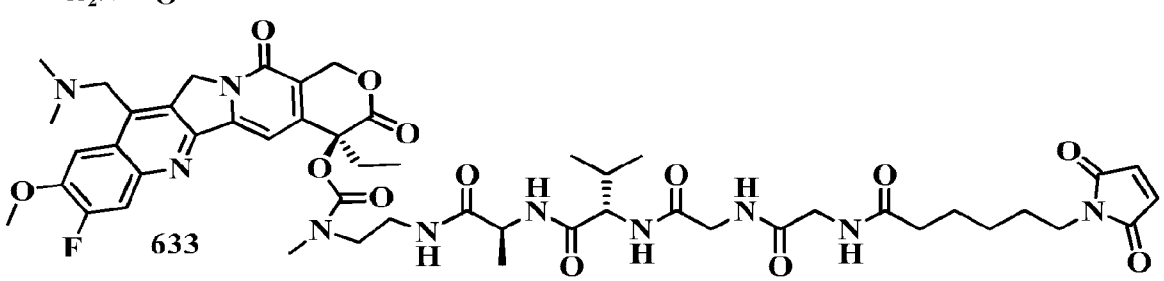

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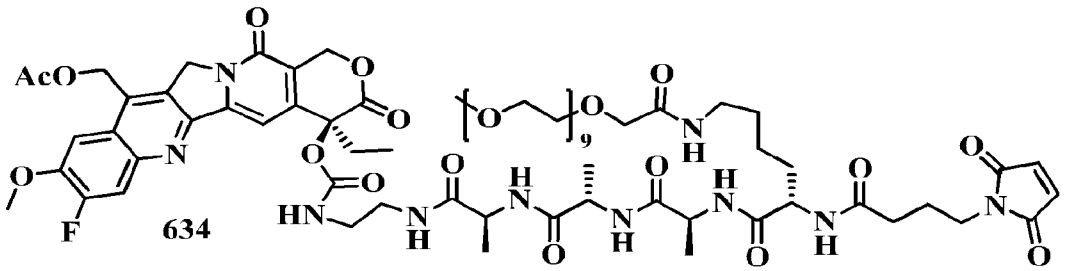

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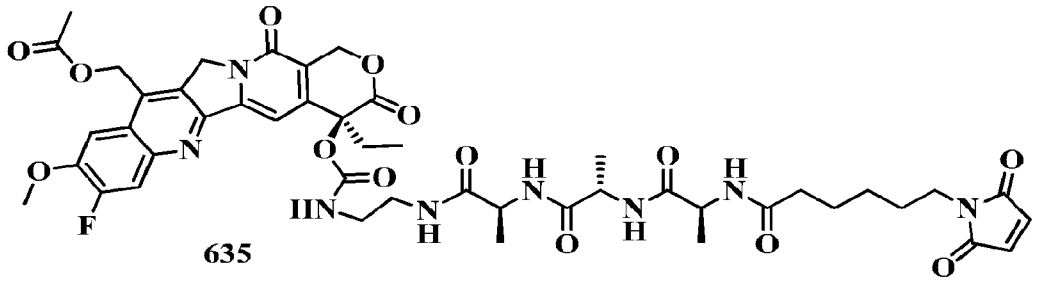

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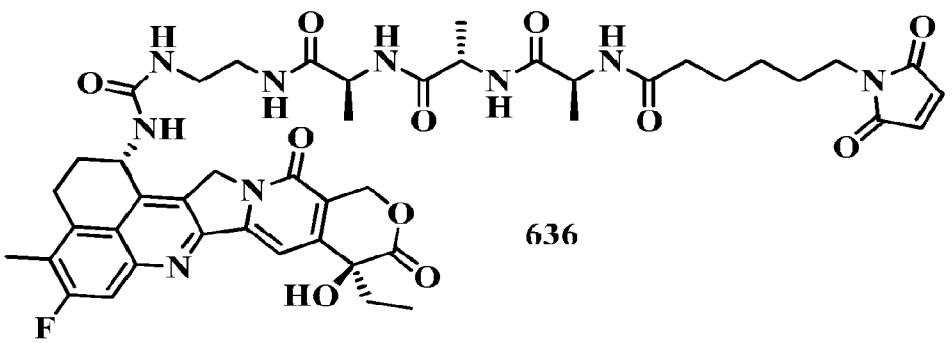

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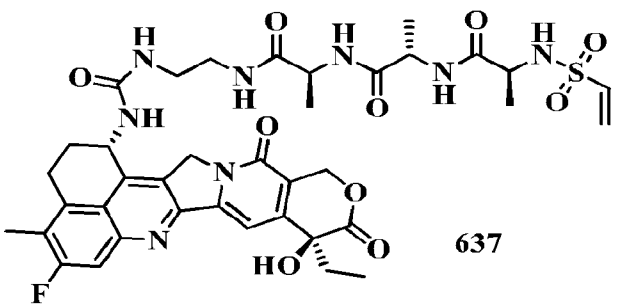

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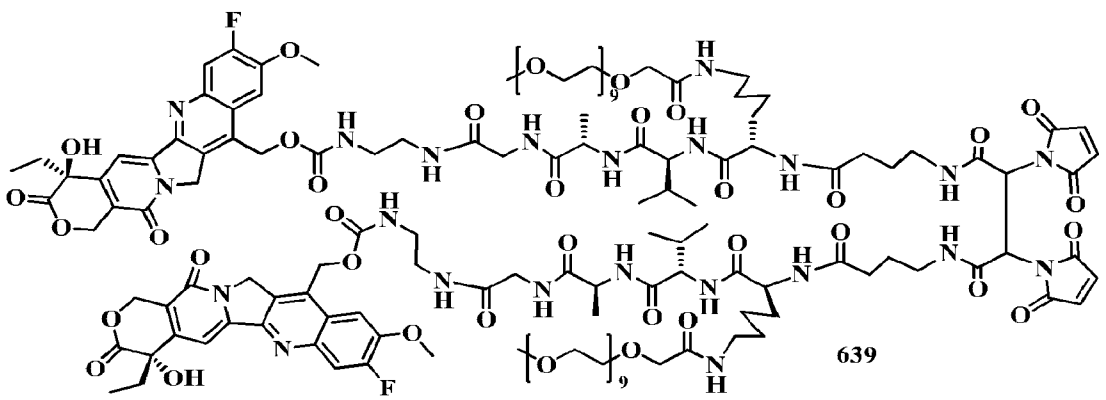

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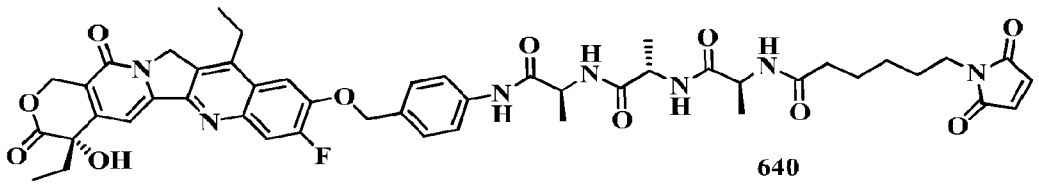

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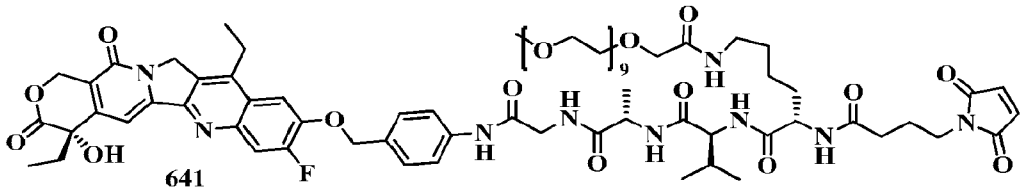

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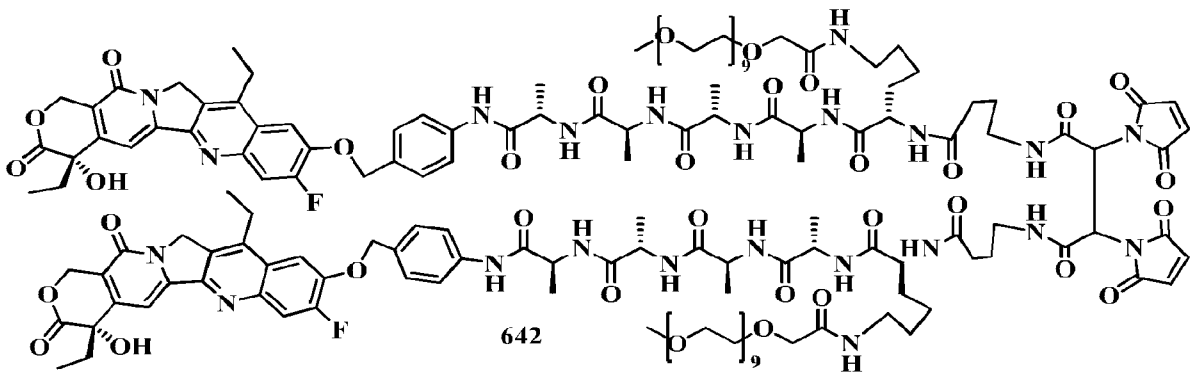

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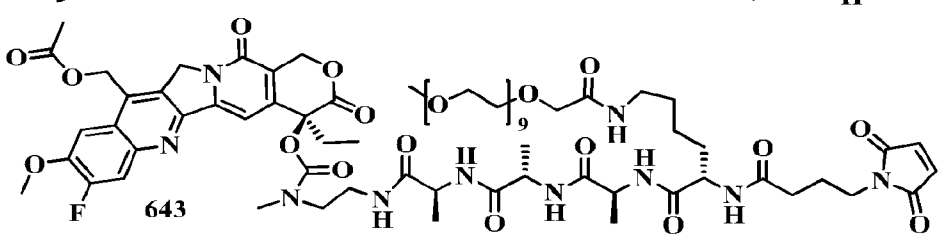

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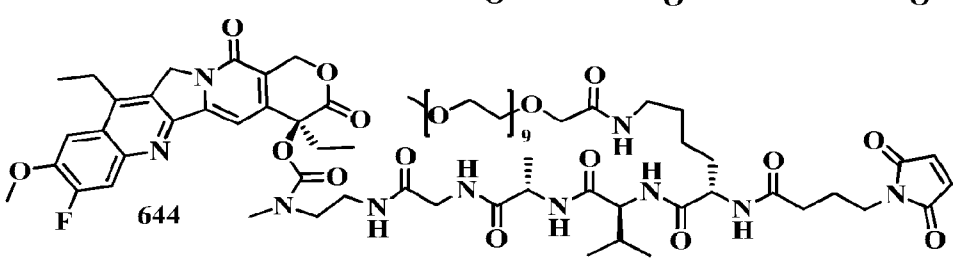

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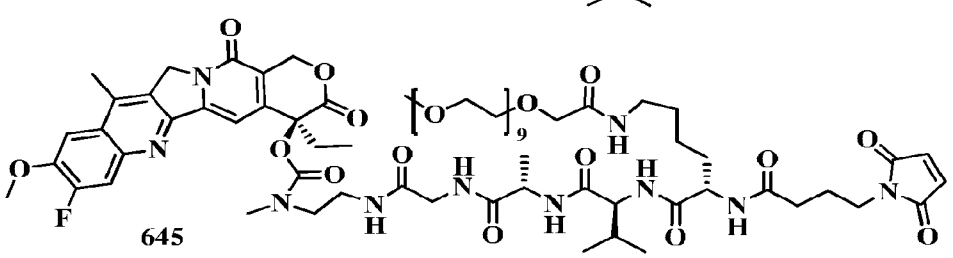

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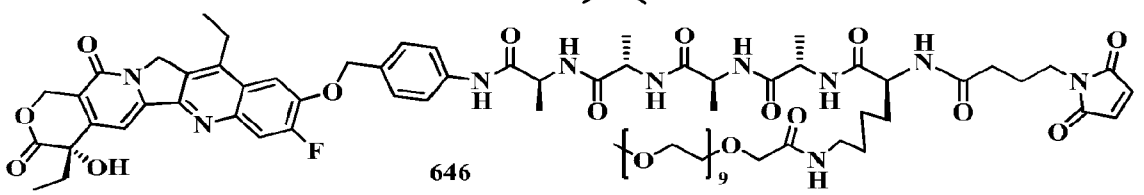

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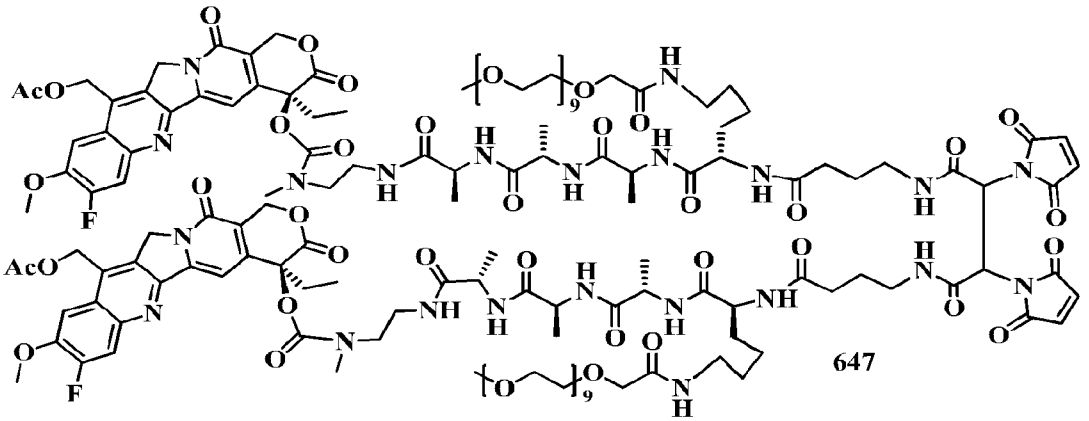

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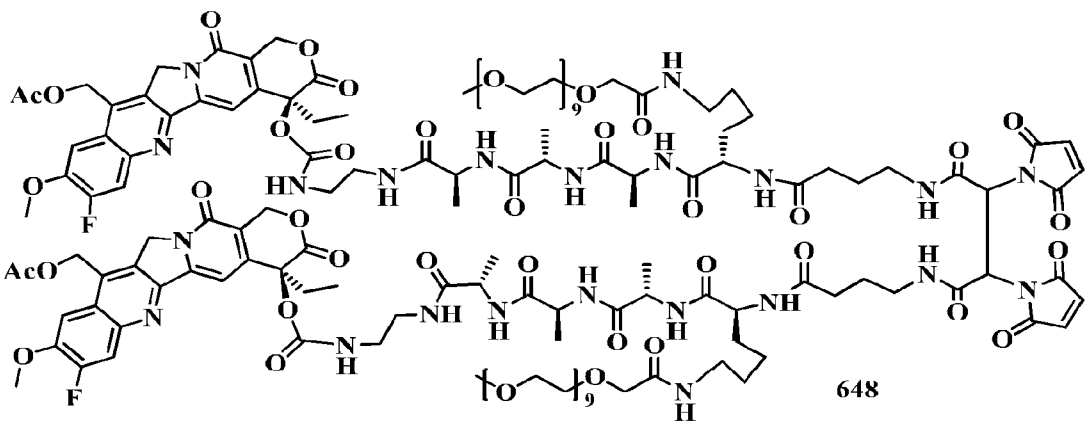

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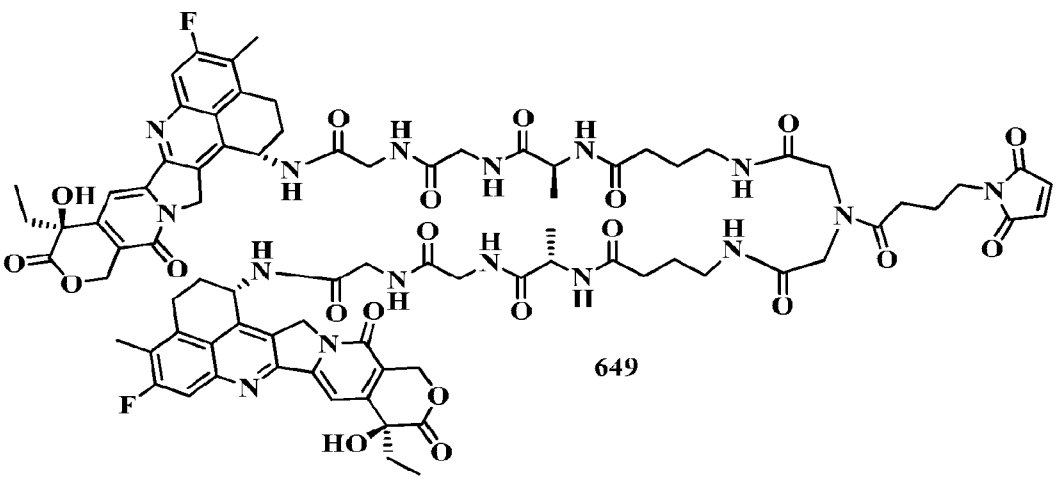

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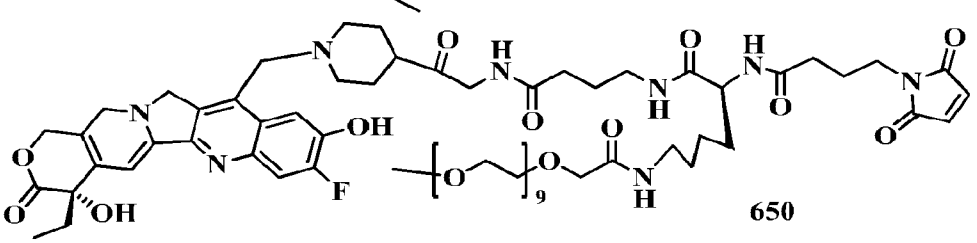

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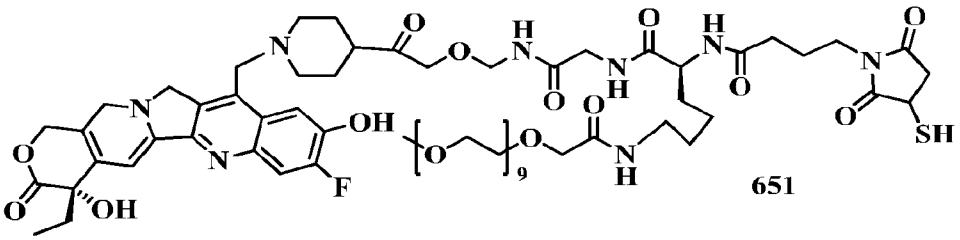

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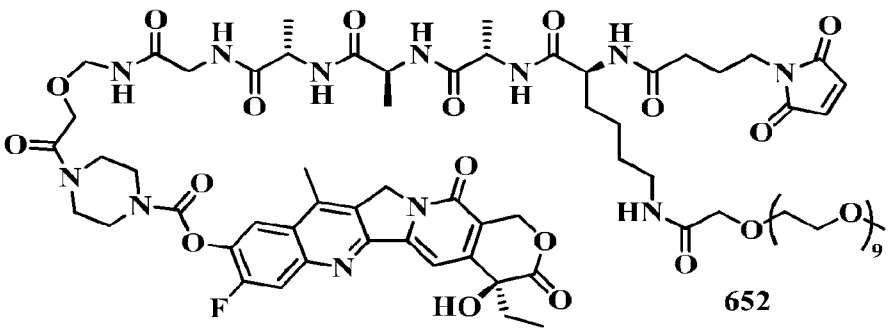

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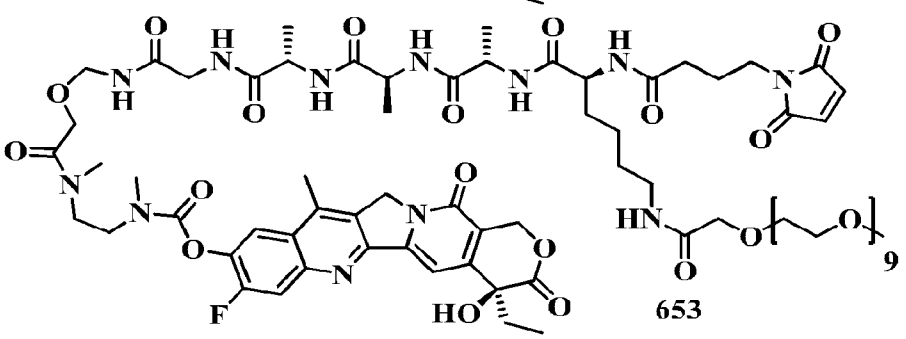

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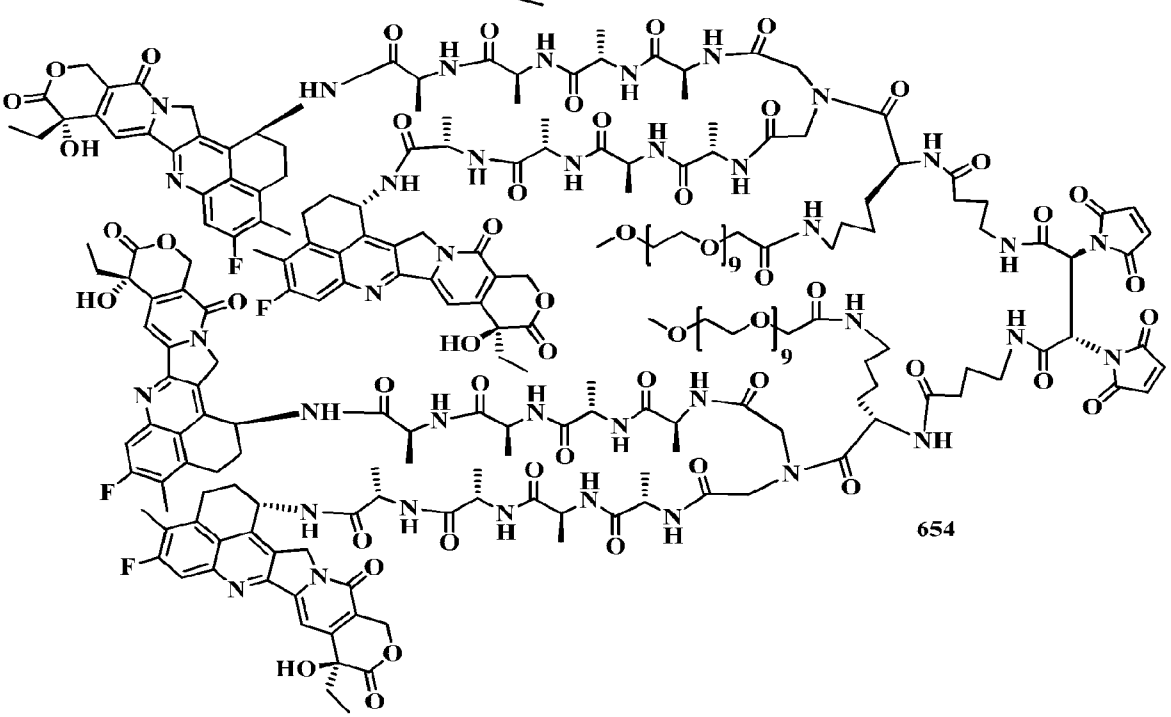

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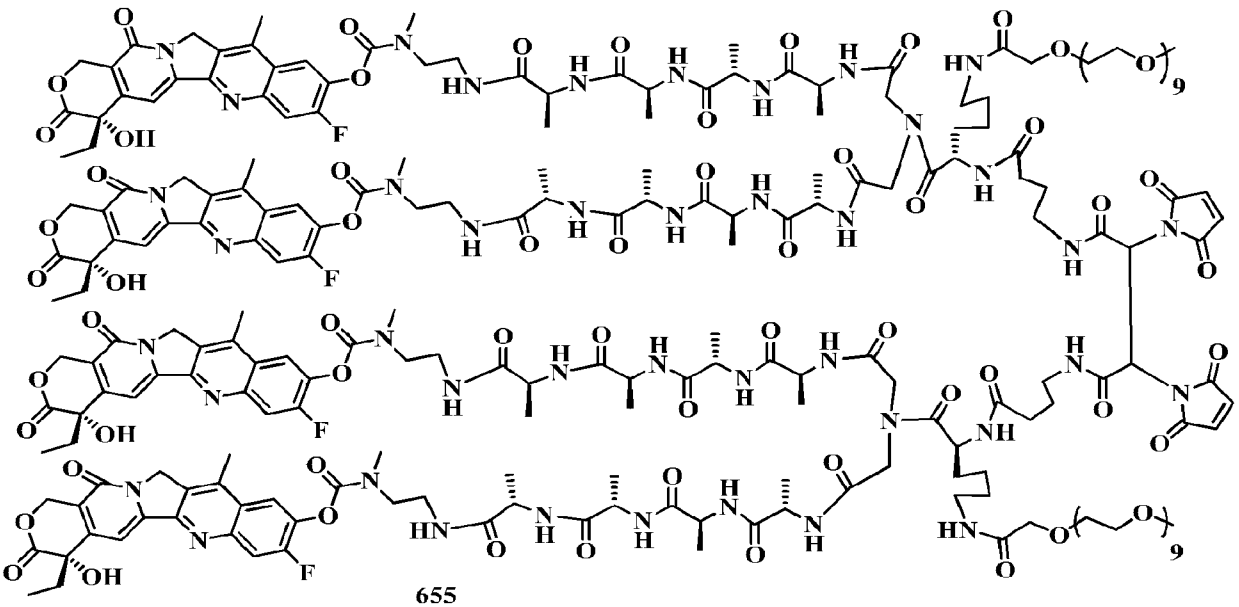

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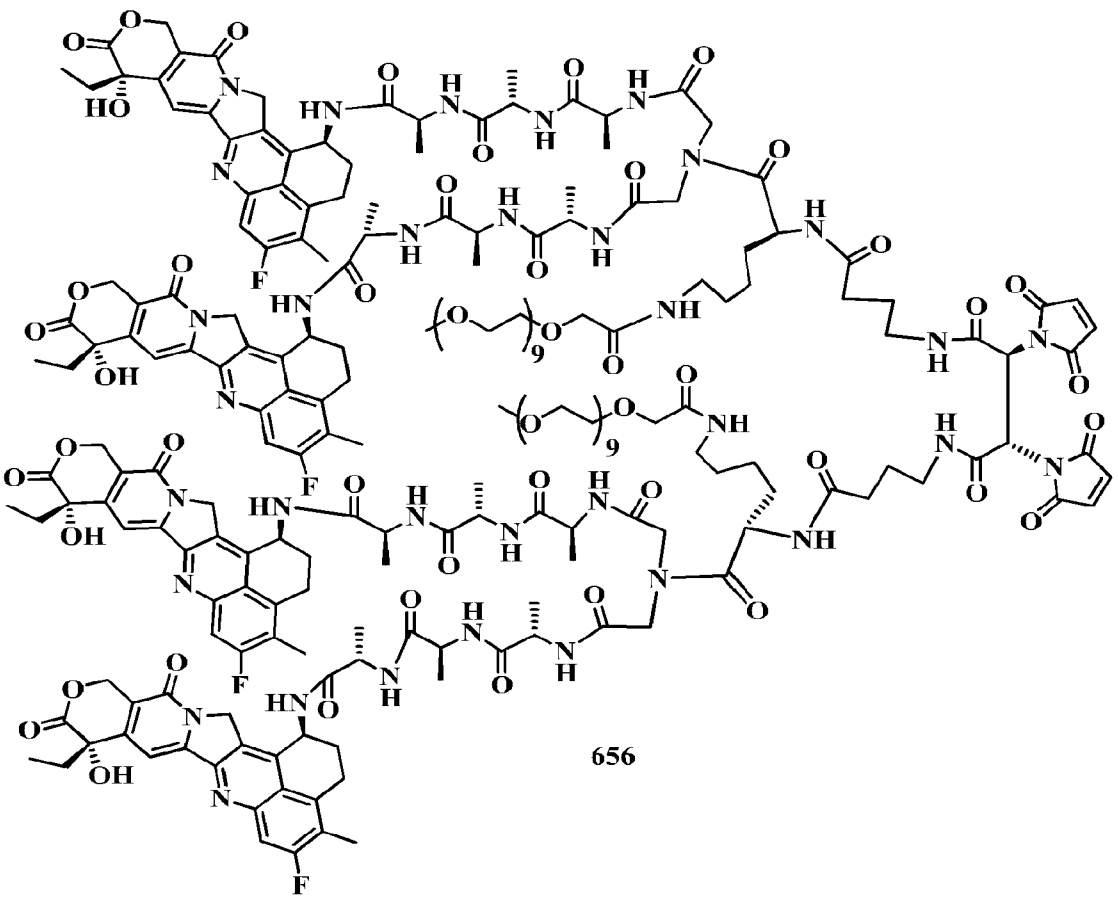

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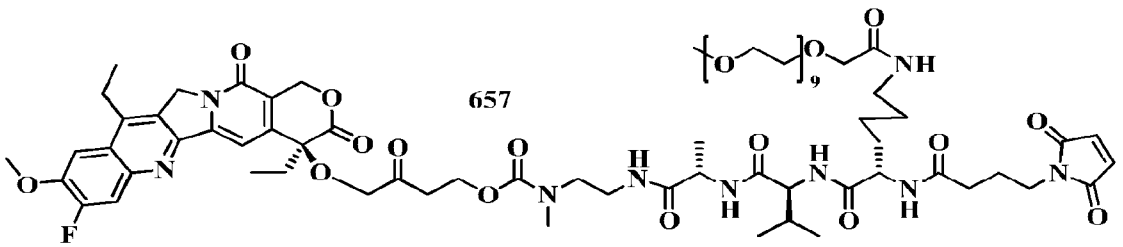

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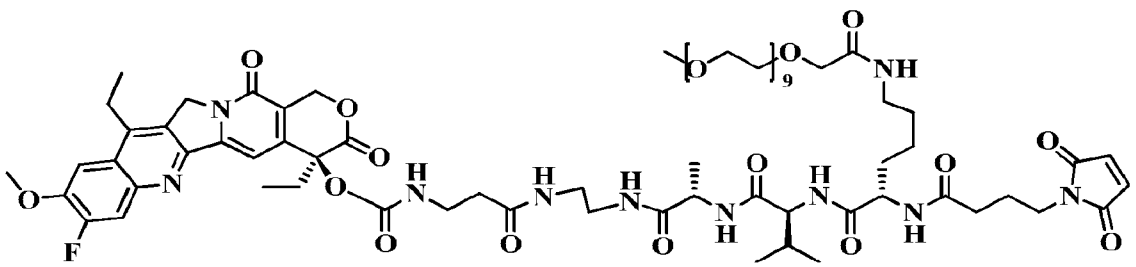

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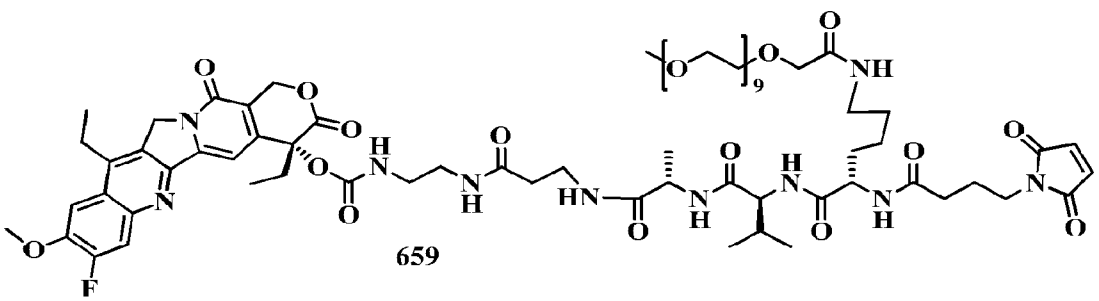

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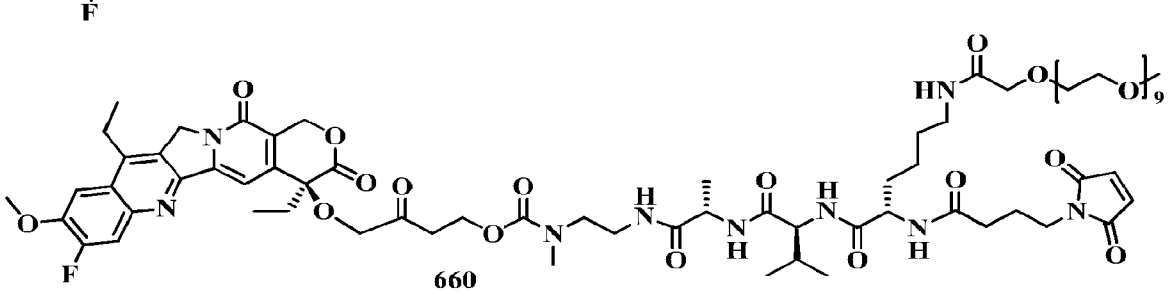

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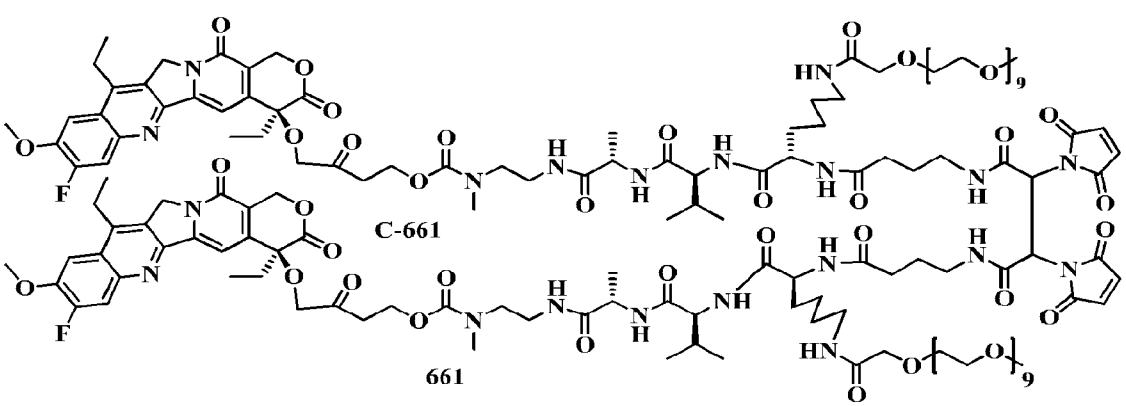

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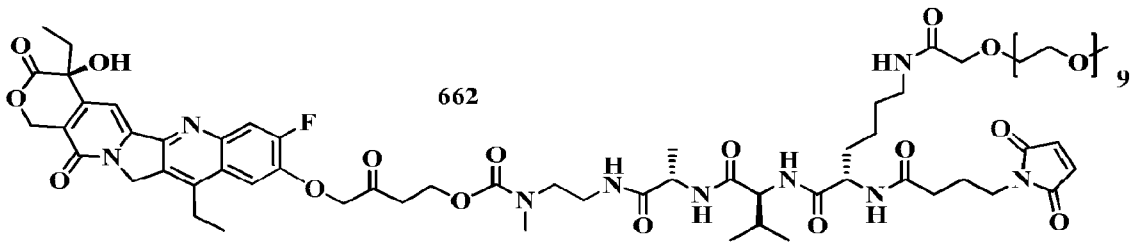

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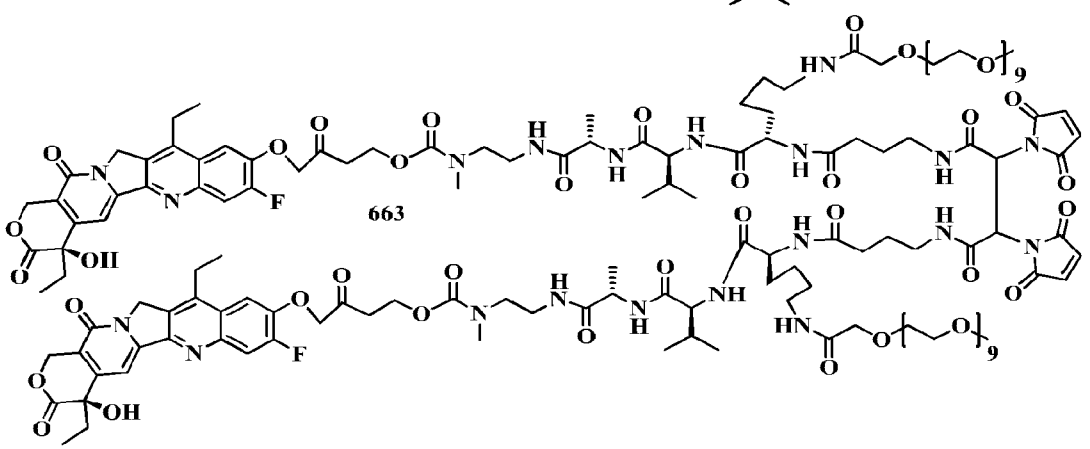

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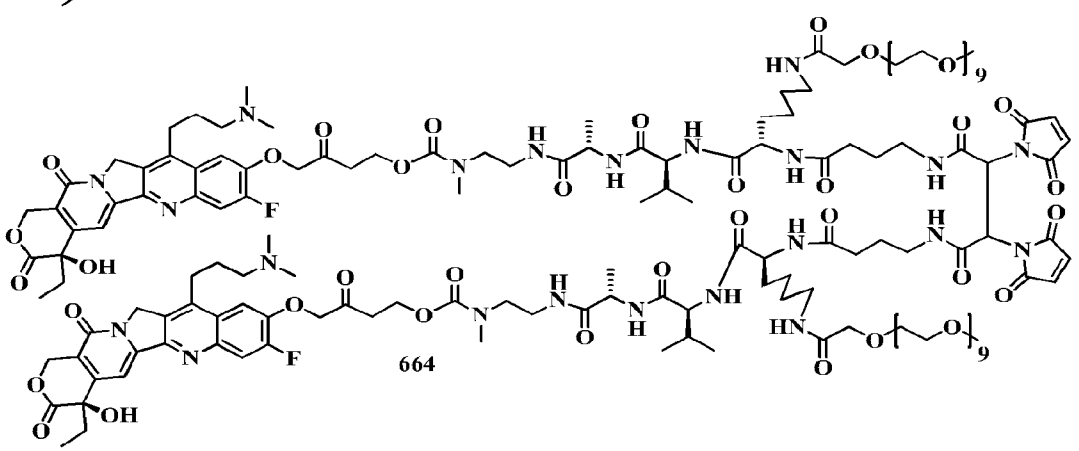

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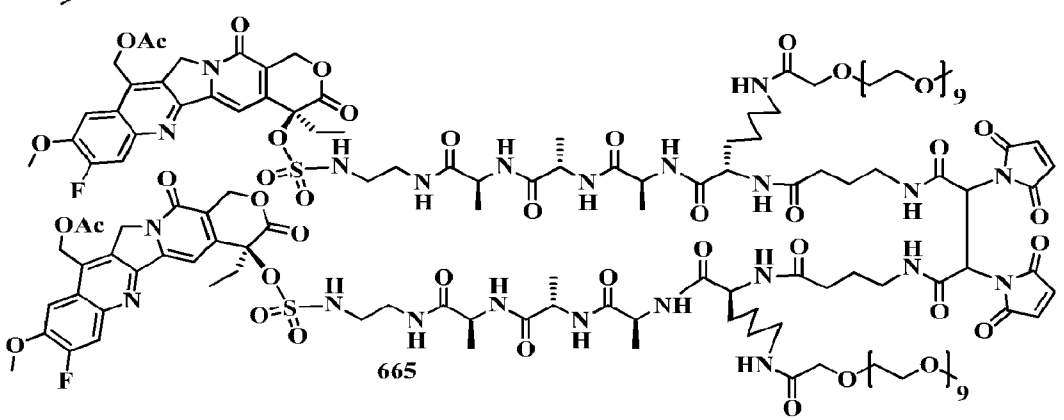

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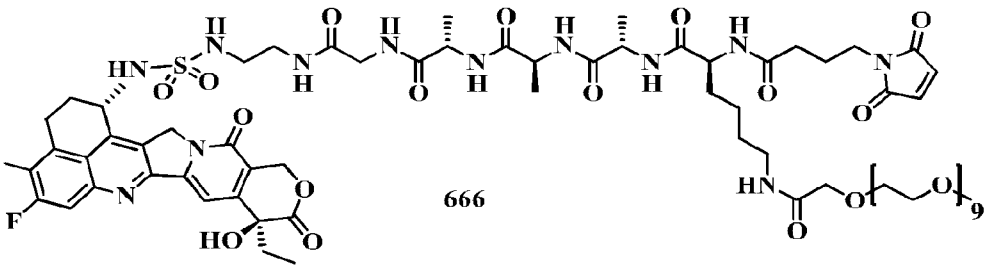

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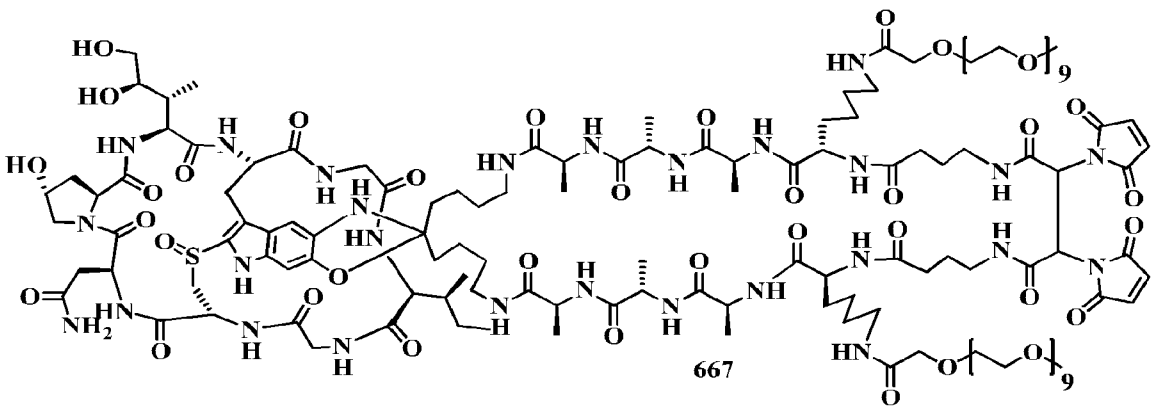

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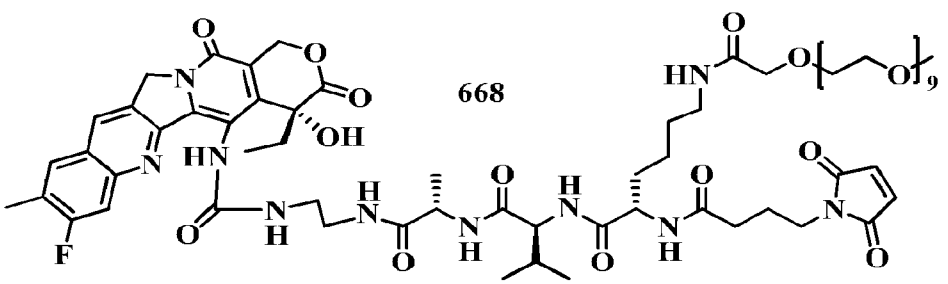

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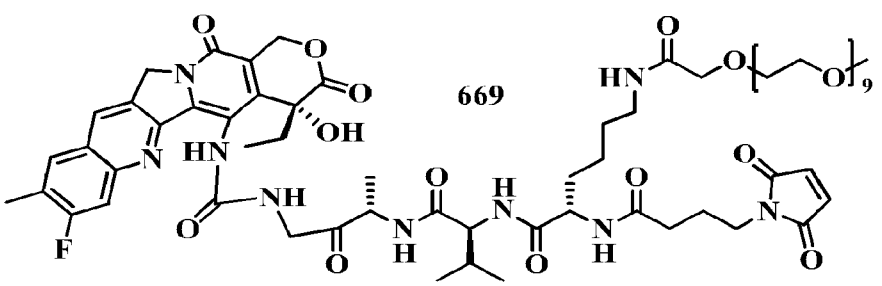

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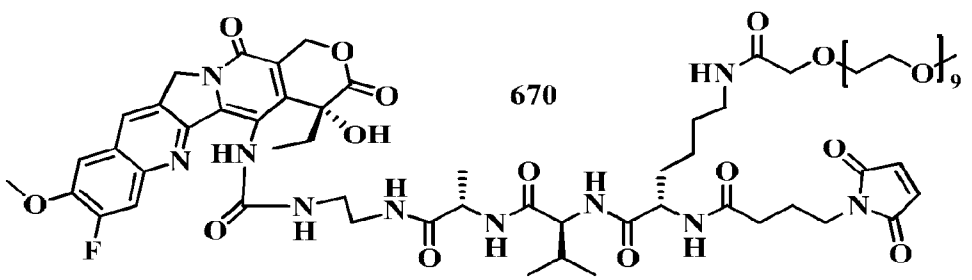

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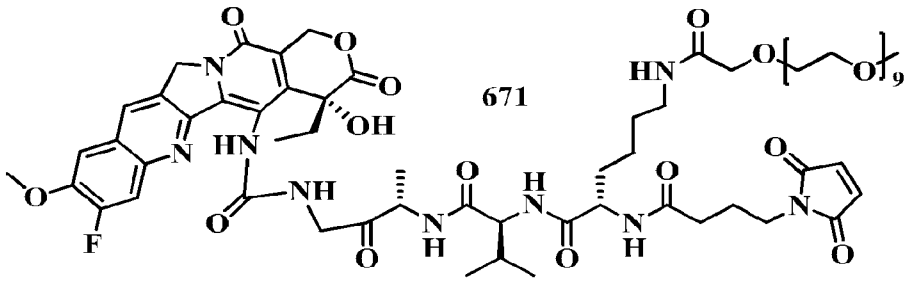

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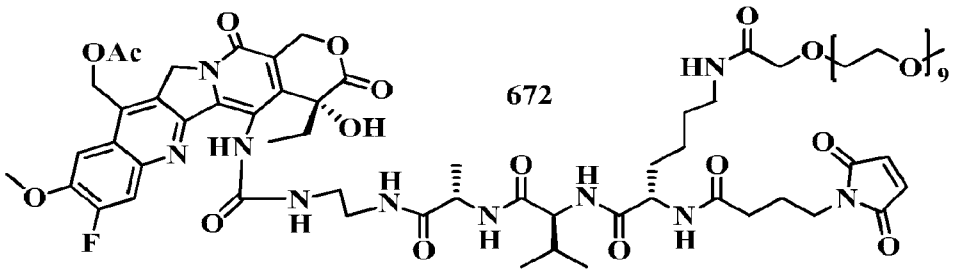

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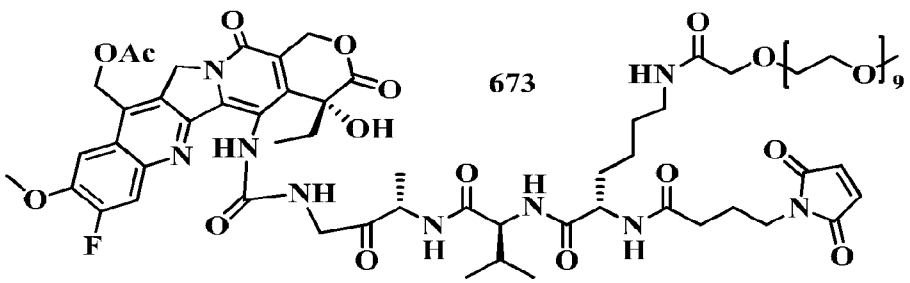

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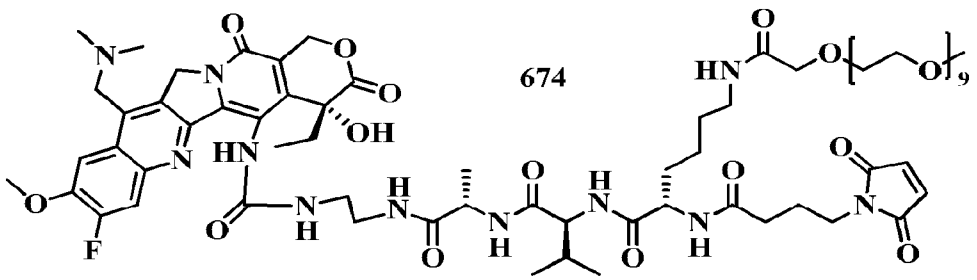

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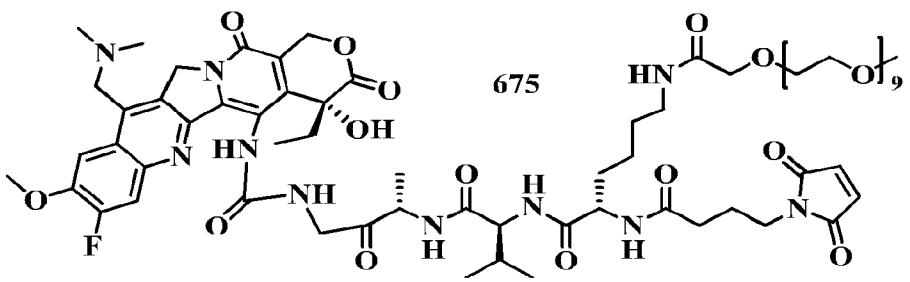

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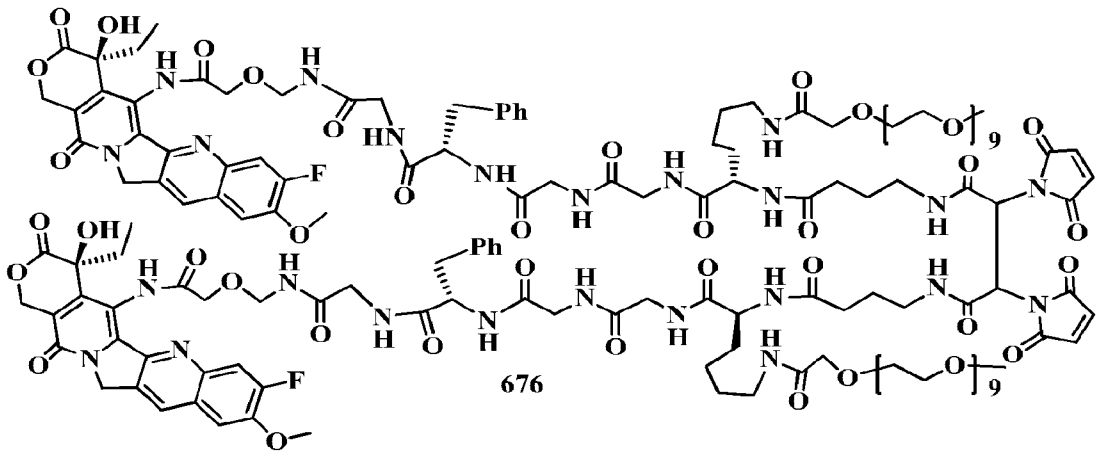

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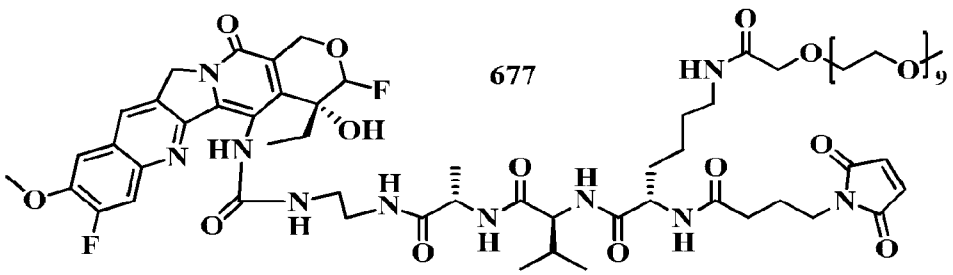

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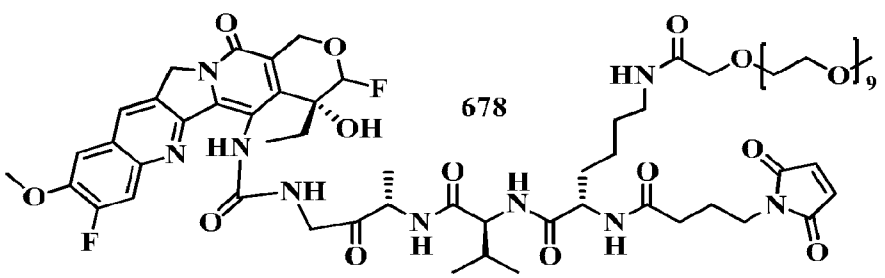

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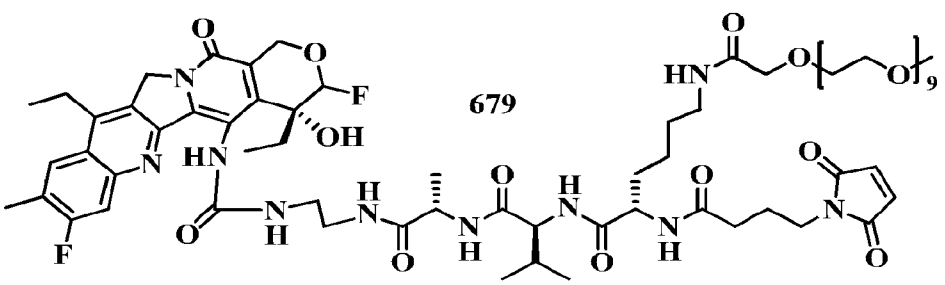

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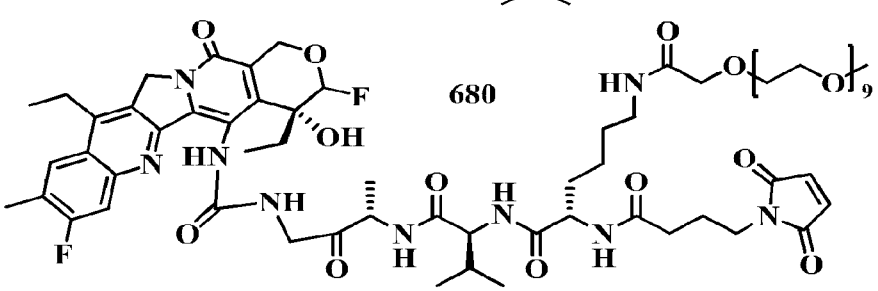

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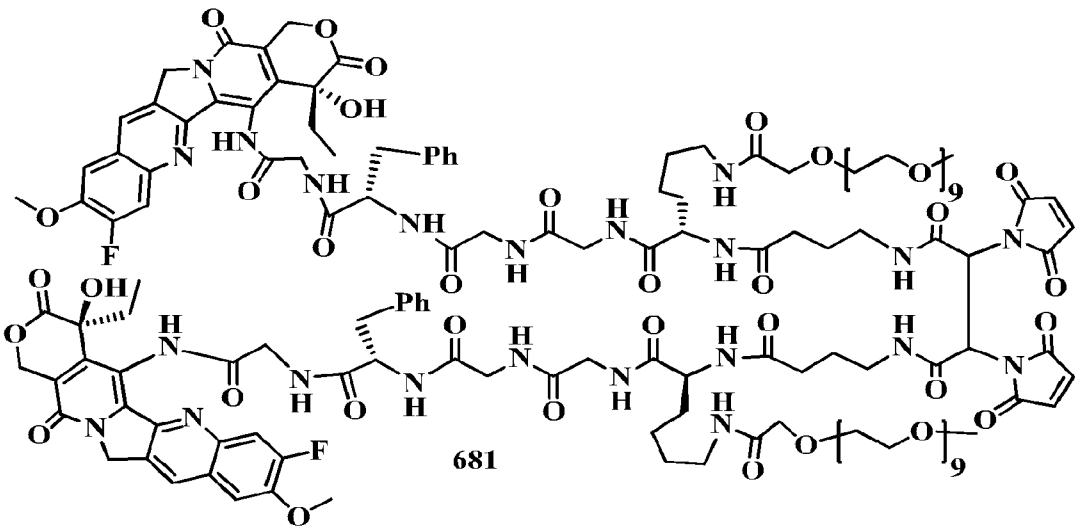

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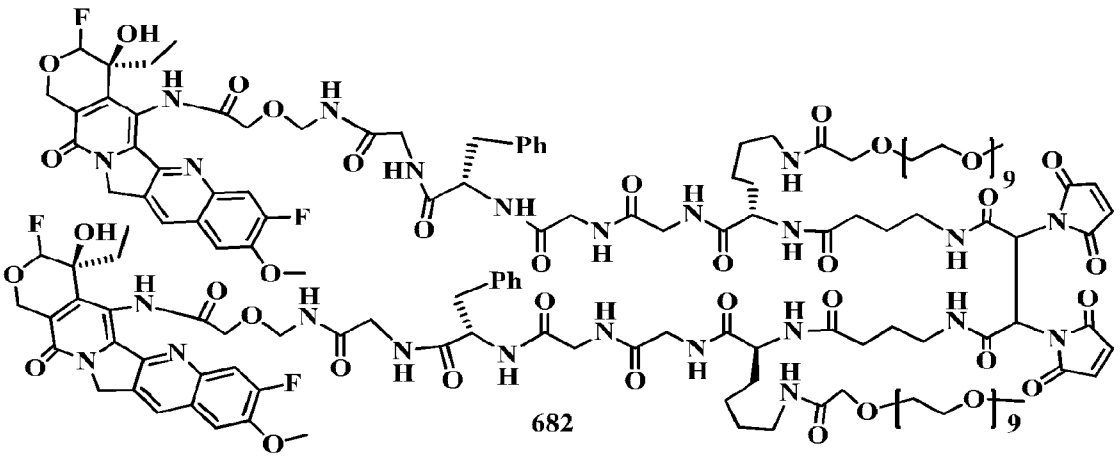

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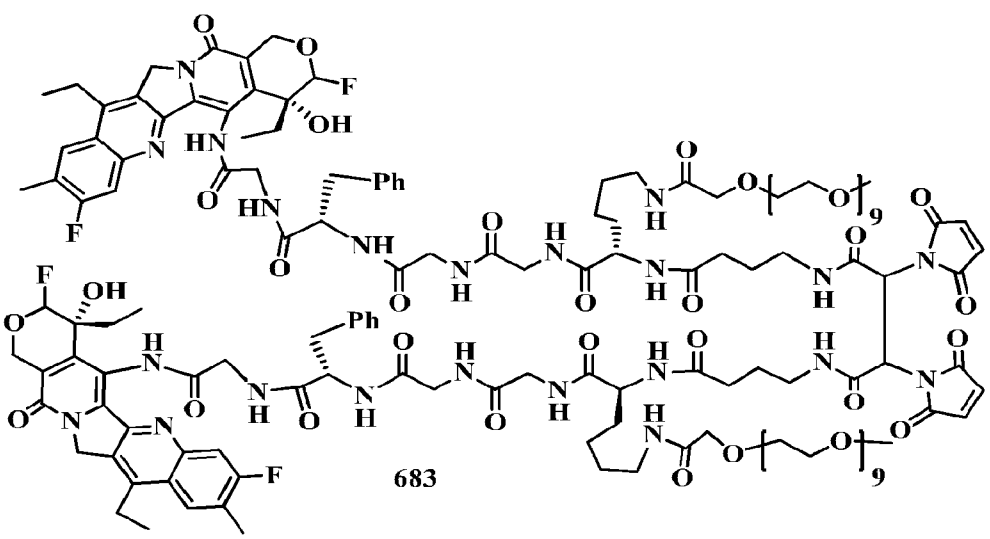

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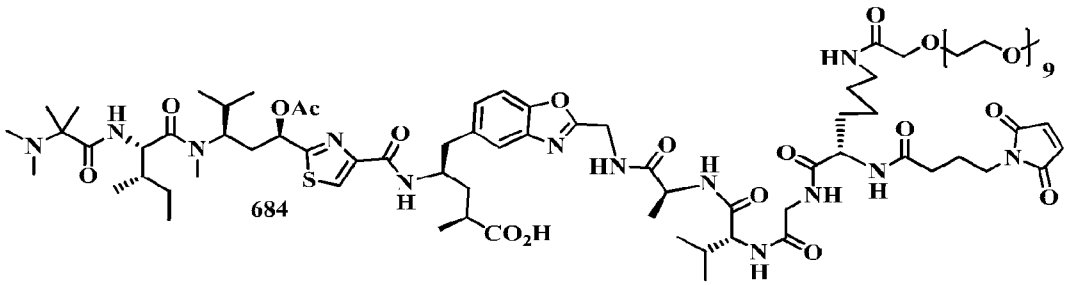

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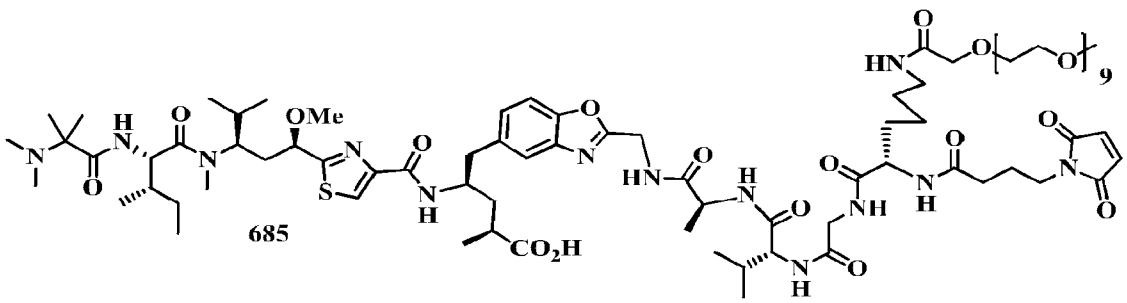

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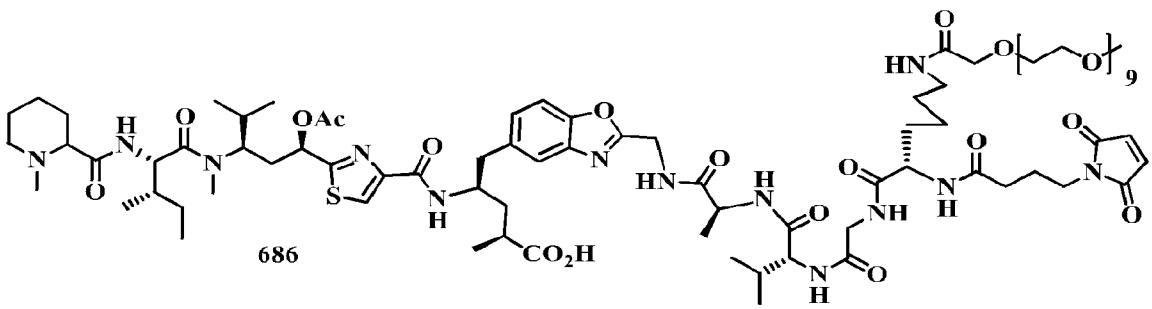

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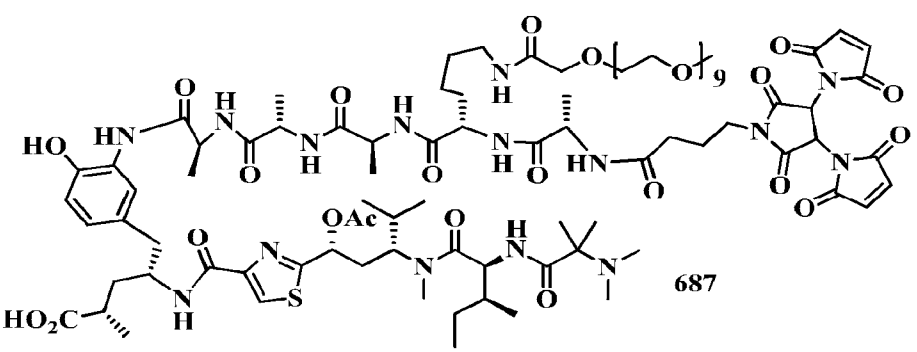

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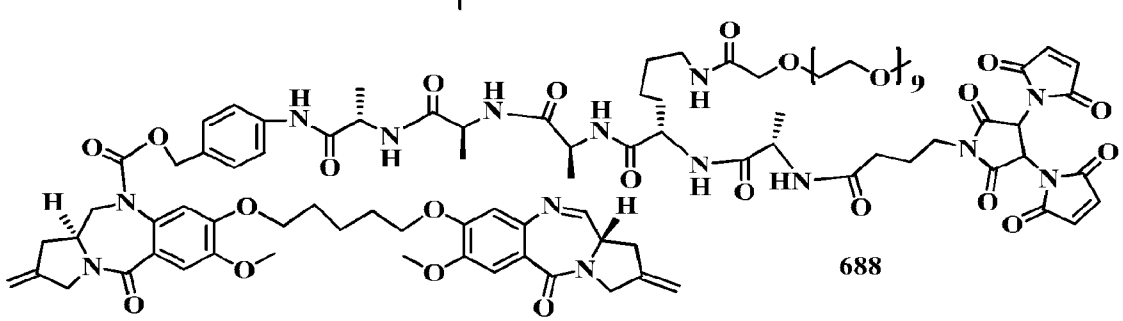

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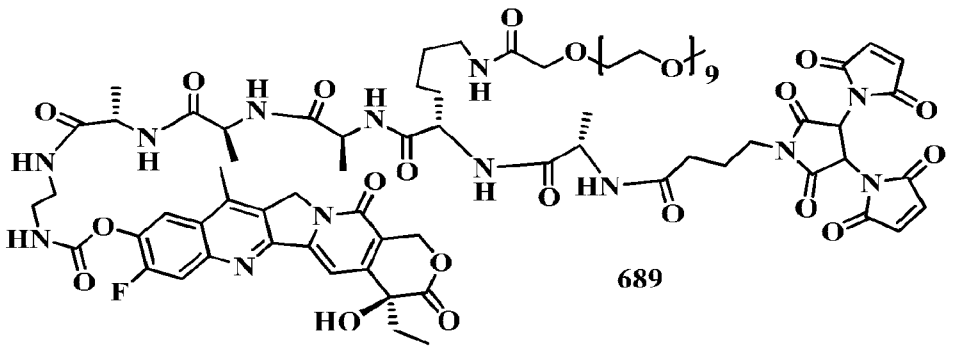

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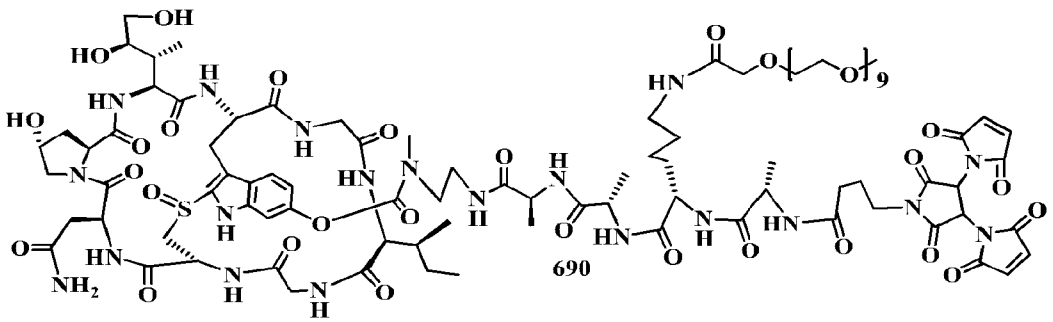

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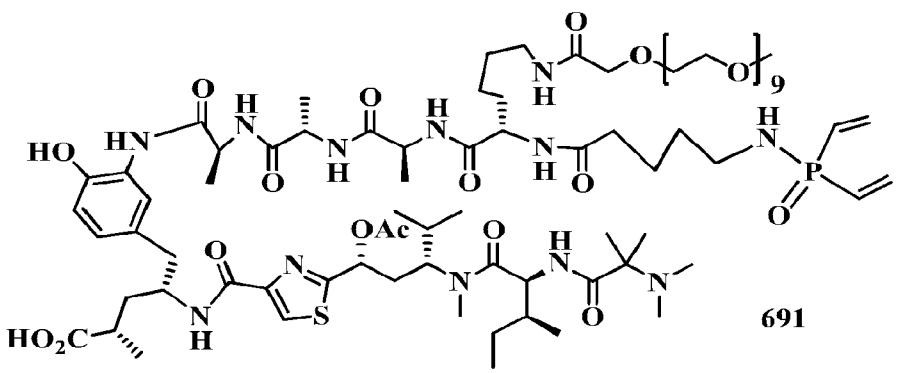

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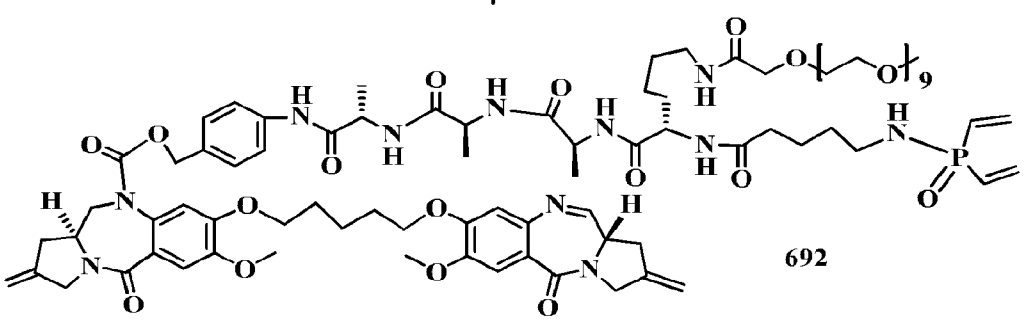

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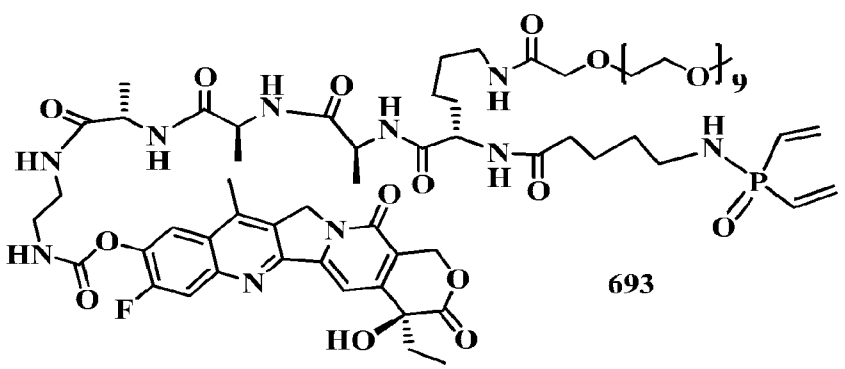

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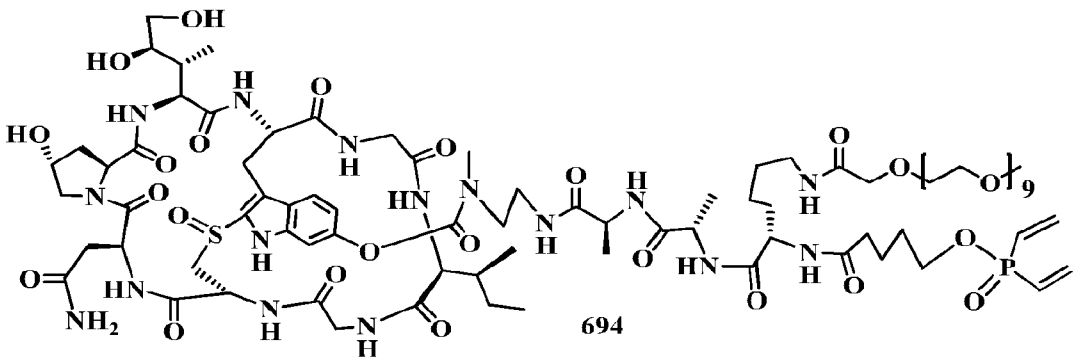

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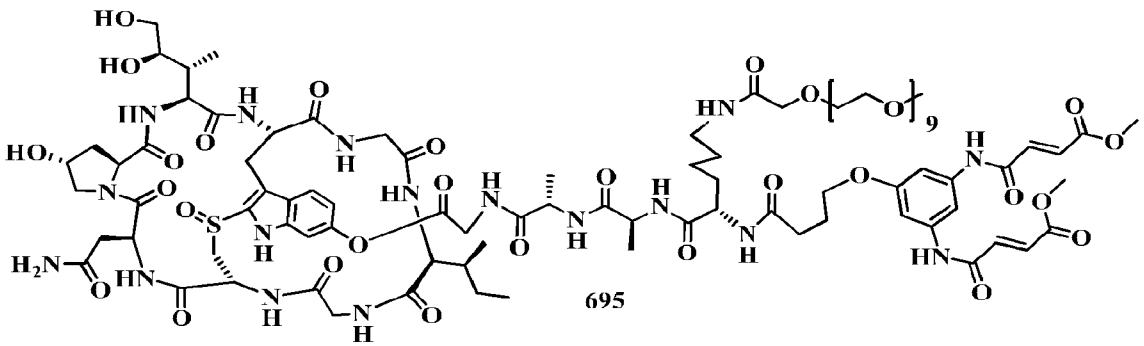

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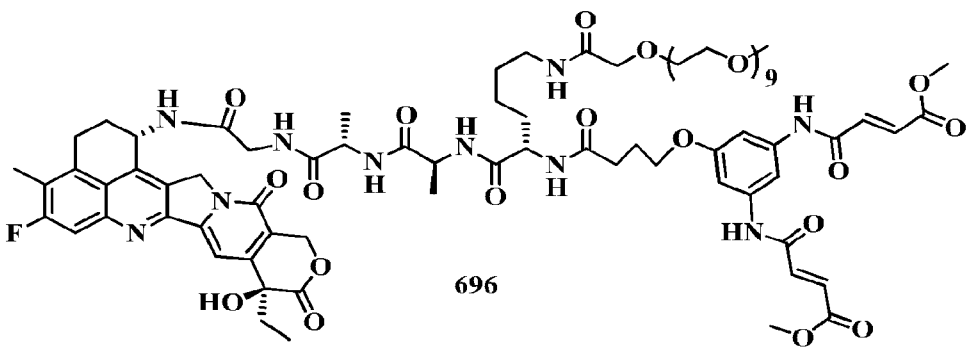

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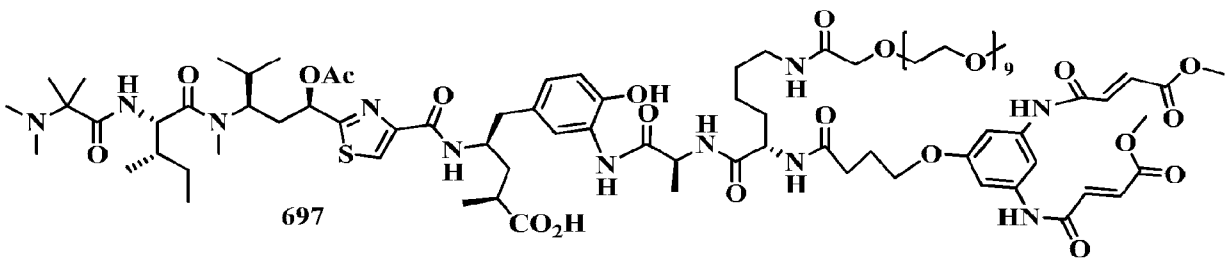

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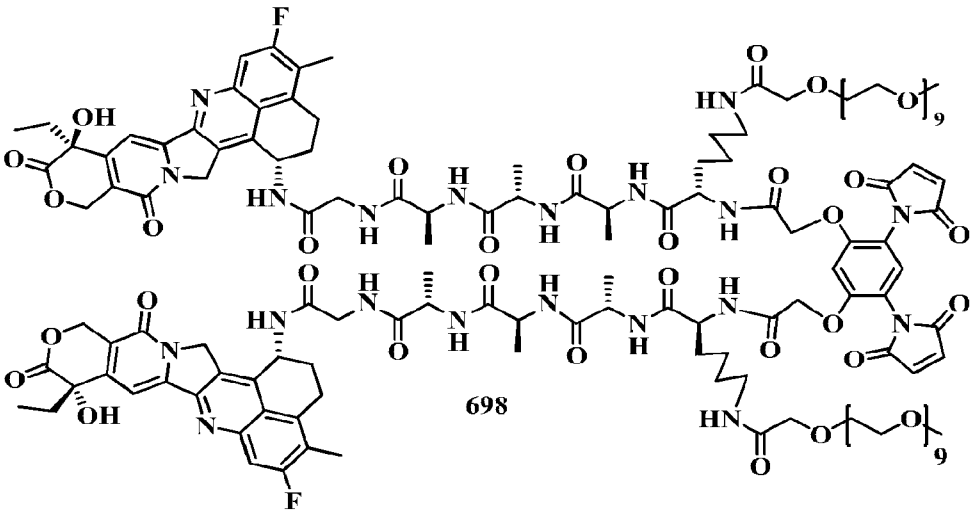

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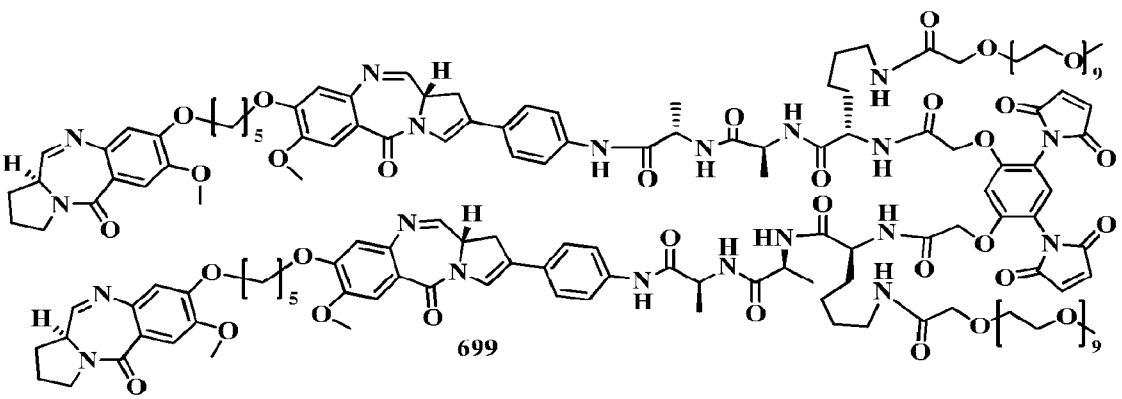

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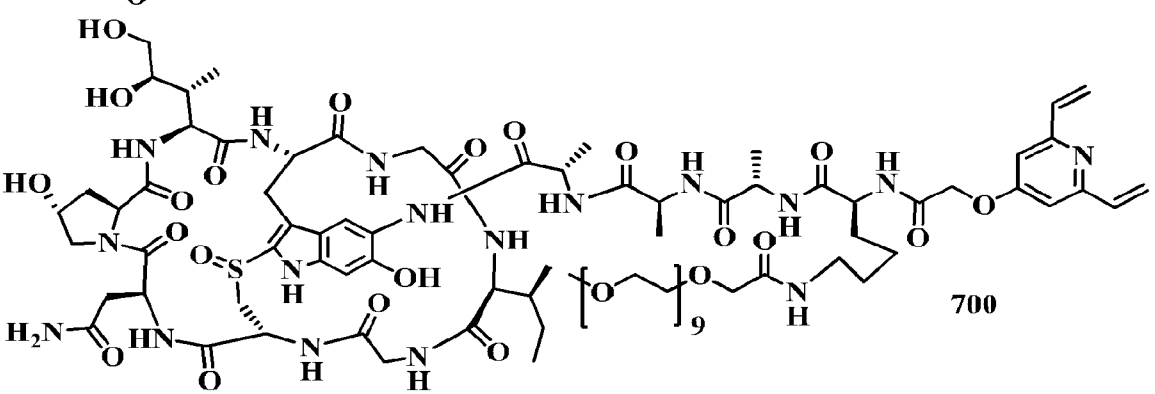

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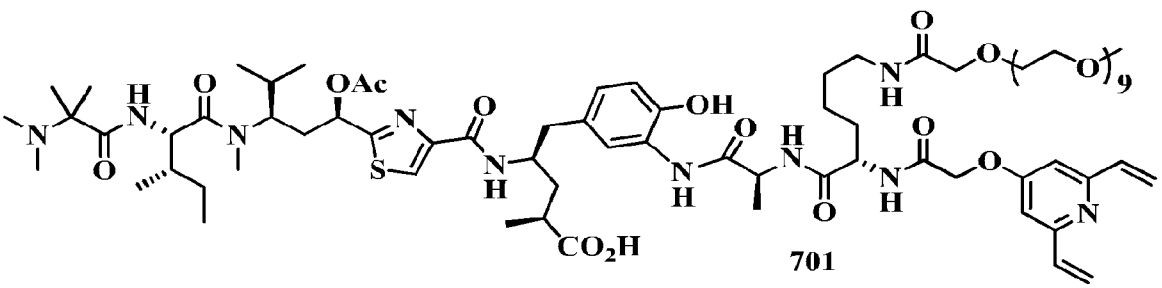

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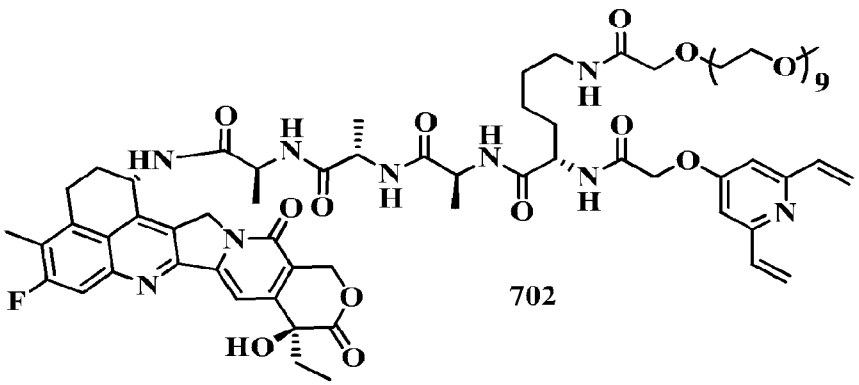

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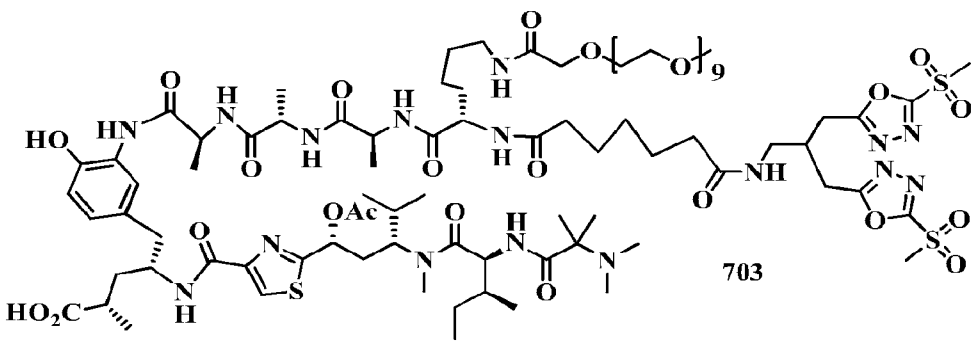

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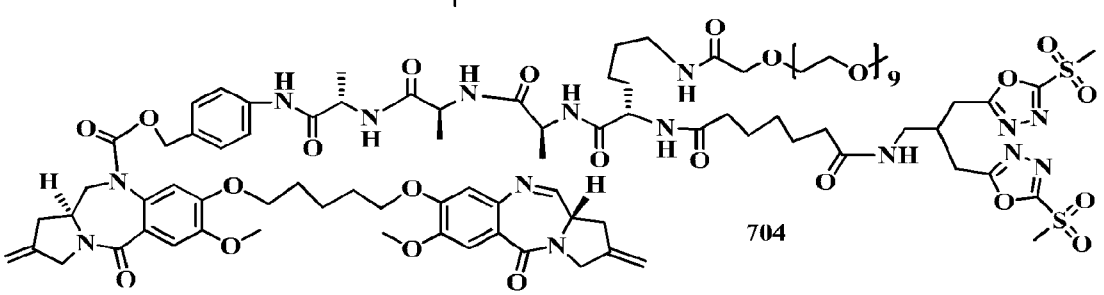

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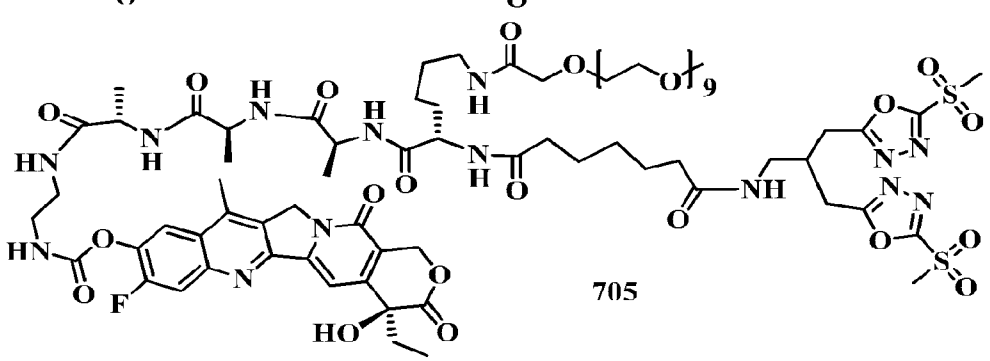

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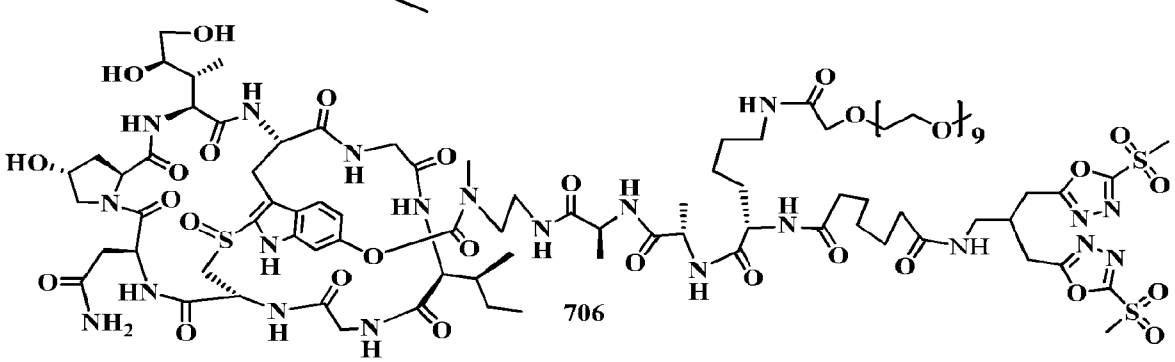

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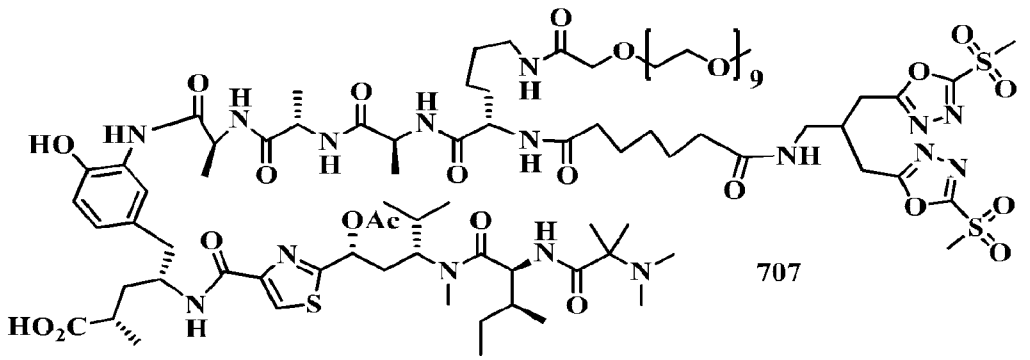

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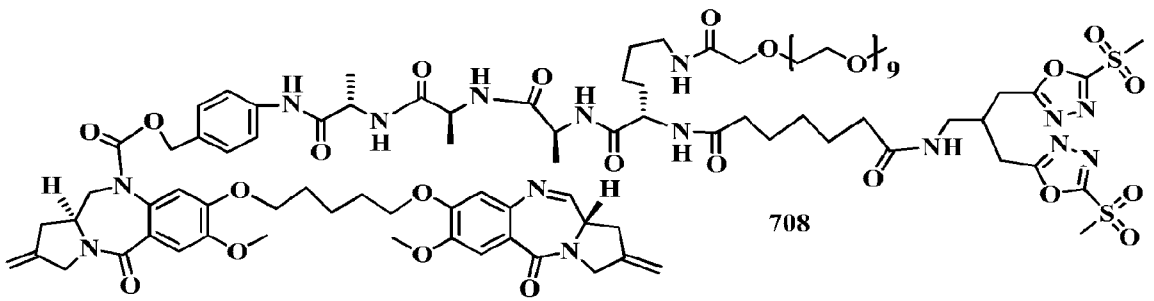

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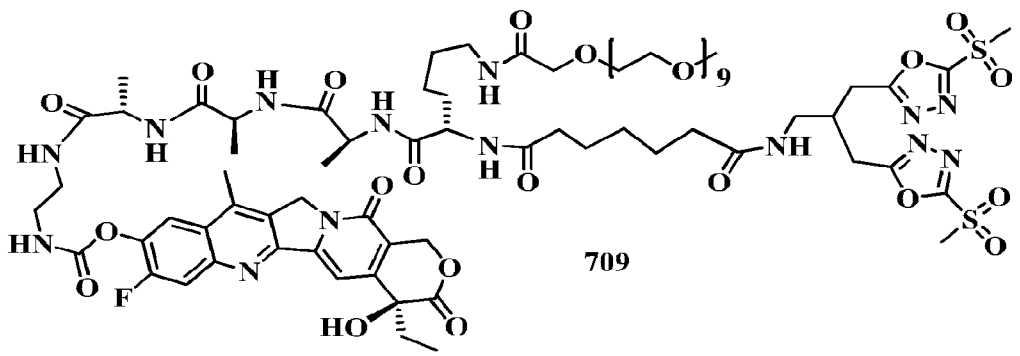

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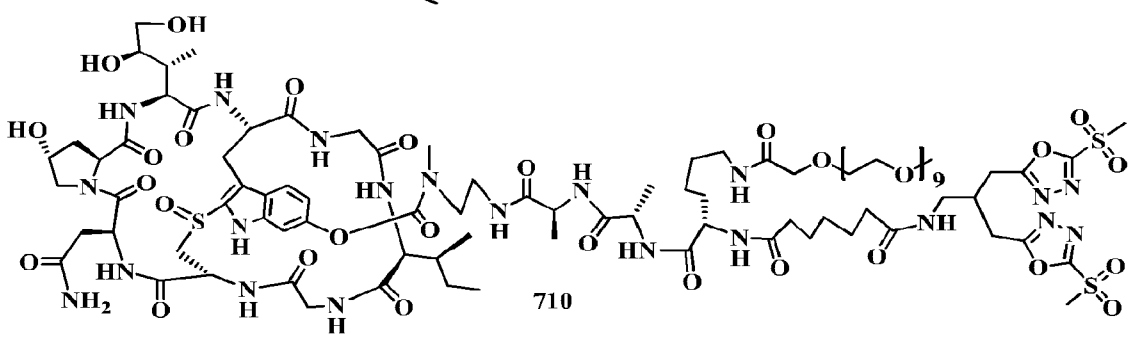

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or a derivative with one or more isotopes, a pharmaceutically acceptable salt, hydrate, or hydrated salt thereof; or a polymorphic crystalline structure thereof; or an optical isomer, racemate, diastereomer or enantiomer thereof; wherein n is 1 -10.

14. The process according to Claim 11, wherein the tumor cell is selected from the group consisting of lymphoma cells, myeloma cells, renal cells, breast cancer cells, prostate cancer cells,

ovarian cancer cells, colorectal cancer cells, gastric cancer cells, squamous cancer cells, small-cell lung cancer cells, none small-cell lung cancer cells, testicular cancer cells, malignant cells, and cells that grow and divide at an unregulated, quickened pace to cause cancers.

15. A pharmaceutical composition comprising a therapeutically effective amount of the conjugate of Claim **4, 12** or **20,** and a pharmaceutically acceptable salt, carrier, diluent, or excipient therefor, or a combination of two or more of the conjugates, for treatment or prevention of a cancer, or an autoimmune disease, or an infectious disease.

16. The pharmaceutical composition according to Claim **15**, which is either in a liquid formula or in a formulated lyophilized solid/powder, comprising by weight of: 0.01%-99% of one or more of the conjugates of Claim **4, 12** or **20**; 0.0%-20.0% of one or more polyols; 0.0%-2.0% of one or more surfactants; 0.0%-5.0% of one or more preservatives; 0.0%-30% of one or more amino acids; 0.0%-5.0% of one or more antioxidants; 0.0%-0.3% of one or more metal chelating agents; 0.0%-30.0% of one or more buffer salts for adjusting pH of the composition to pH 4.5 - 7.5; and 0.0%-30.0% of one or more isotonic agents for adjusting osmotic pressure between from about 250 to 350 mOsm when being reconstituted for administration to a patient;

wherein the polyol is selected from the group consisting of fructose, mannose, maltose, lactose, arabinose, xylose, ribose, rhamnose, galactose, glucose, sucrose, trehalose, sorbose, melezitose, raffinose, mannitol, xylitol, erythritol, maltitol, lactitol, erythritol, threitol, sorbitol, glycerol, or L-gluconate and metallic salts thereof;

wherein the surfactant is selected from the group consisting of polysorbate 20, polysorbate 40, polysorbate 65, polysorbate 80, polysorbate 81, or polysorbate 85, poloxamer, poly(ethylene oxide)-poly(propylene oxide), polyethylene-polypropylene, Triton; sodium dodecyl sulfate (SDS), sodium laurel sulfate; sodium octyl glycoside; lauryl-, myristyl-, linoleyl-, or stearyl-sulfobetaine; lauryl-, myristyl-, linoleyl- or stearyl-sarcosine; linoleyl-, myristyl-, or cetyl-betaine; lauroamidopropyl-, cocamidopropyl-, linoleamidopropyl-, myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-betaine (lauroamidopropyl); myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-dimethylamine; sodium methyl cocoyl-, or disodium methyl oleyl-taurate; dodecyl betaine, dodecyl dimethylamine oxide, cocamidopropyl betaine and coco ampho glycinate; or isostearyl ethylimidonium ethosulfate; polyethyl glycol, polypropyl glycol, and copolymers of ethylene and propylene glycol;

wherein the preservative is selected from the group consisting of benzyl alcohol, octadecyldimethylbenzyl ammonium chloride, hexamethonium chloride, benzalkonium chloride, benzetho-

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nium chloride, phenol, butyl and benzyl alcohol, alkyl parabens such as methyl or propyl paraben, catechol, resorcinol, cyclohexanol, 3-pentanol, and m-cresol;

wherein the amino acid is selected from the group consisting of arginine, cystine, glycine, lysine, histidine, ornithine, isoleucine, leucine, alanine, glycine glutamic acid and aspartic acid;

wherein the antioxidant is selected from ascorbic acid, glutathione, cystine or and methionine;

wherein the chelating agent is EDTA or EGTA;

wherein the buffer salt is selected from the group consisting of sodium, potassium, ammonium, or trihydroxyethylamino salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid or phthalic acid; Tris or tromethamine hydrochloride, phosphate or sulfate; and arginine, glycine, glycylglycine, or histidine with anionic acetate, chloride, phosphate, sulfate, or succinate salt;

wherein the tonicity agent is selected from the group consisting of mannitol, sorbitol, sodium acetate, potassium chloride, sodium phosphate, potassium phosphate, trisodium citrate, and sodium chloride.

17. The pharmaceutical composition according to Claim 15, which is packed in a vial, bottle, pre-filled syringe, or pre-filled auto-injector syringe, in a form of a liquid or lyophilized solid.

18. A method for synergistical treatment or prevention of a cancer, an autoimmune disease, or an infectious disease, comprising administering the pharmaceutical composition according to Claim 15 concurrently with a synergistic agent of a chemotherapeutic agent, a radiation therapy agent, an immunotherapy agent, an autoimmune disorder agent, an anti-infectious agents or another conjugate.

19. The method according to Claim **18**, wherein the synergistic agentis one or more selected from the following drugs: Abatacept, Abiraterone acetate, Abraxane, Acetaminophen/hydrocodone, Acalabrutinib, aducanumab, Adalimumab, ADXS31-142, ADXS-HER2, Afatinib dimaleate, Aldesleukin, Alectinib, Alemtuzumab, Alitretinoin, ado-trastuzumab emtansine, Amphetamine/ dextroamphetamine, Anastrozole, Aripiprazole, anthracyclines, Aripiprazole, Atazanavir, Atezolizumab, Atorvastatin, Avelumab, Axicabtagene ciloleucel, Axitinib, Belinostat, BCG Live, Bevacizumab, Bexarotene, Blinatumomab, Bortezomib, Bosutinib, Brentuximab vedotin, Brigatinib, Budesonide, Budesonide/formoterol, Buprenorphine, Cabazitaxel, Cabozantinib, Capmatinib, Capecitabine, Carfilzomib, chimeric antigen receptor-engineered T (CAR-T) cells, Celecoxib, Ceritinib, Cetuximab, Chidamide, Ciclosporin, Cinacalcet, Crizotinib, Cobimetinib, Cosentyx, Crizotinib, CTL019, Dabigatran, Dabrafenib, Dacarbazine, Daclizumab, Dacomotinib, Daptomycin, Daratumumab, Darbepoe-

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tin alfa, Darunavir, Dasatinib, Denileukin diftitox, Denosumab, Depakote, Dexlansoprazole, Dexmethylphenidate, Dexamethasone, Dinutuximab, Doxycycline, Duloxetine, Duvelisib, Durvalumab, Elotuzumab, Emtricitabine/ Rilpivirine/Tenofovir, Disoproxil fumarate, Emtricitbine/tenofovir/efavirenz, Enoxaparin, Ensartinib, Enzalutamide, Epoetin alfa, erlotinib, Esomeprazole, Eszopiclone, Etanercept, Everolimus, Exemestane, Everolimus, Exenatide ER, Ezetimibe, Ezetimibe/simvastatin, Fenofibrate, Filgrastim, Fingolimod, Fluticasone propionate, Fluticasone/salmeterol, Fulvestrant, Gazyva, Gefitinib, Glatiramer, Goserelin acetate, Icotinib, Imatinib, Ibritumomab tiuxetan, Ibrutinib, Idelalisib, Ifosfamide, Infliximab, Imiquimod, ImmuCyst, Immuno BCG, Iniparib, Insulin aspart, Insulin detemir, Insulin glargine, Insulin lispro, Interferon alfa, Interferon alfa-1b, Interferon alfa-2a, Interferon alfa-2b, Interferon beta, Interferon beta 1a, Interferon beta 1b, Interferon gamma-1a, Iapatinib, Ipilimumab, Ipratropium bromide/salbutamol, Ixazomib, Kanuma, Lanreotide acetate, Lenalidomide, Lenaliomide, Lenvatinib mesylate, Letrozole, Levothyroxine, Levothyroxine, Lidocaine, Linezolid, Liraglutide, Lisdexamfetamine, LN-144, Lorlatinib, Memantine, Methylphenidate, Metoprolol, Mekinist, Mericitabine/Rilpivirine/ Tenofovir, Modafinil, Mometasone, Mycidac-C, Necitumumab, neratinib, Nilotinib, Niraparib, Nivolumab, Ofatumumab, Obinutuzumab, Olaparib, Olmesartan, Olmesartan/ hydrochlorothiazide, Omalizumab, Omega-3 fatty acid ethyl esters, Oncorine, Oseltamivir, Osimertinib, Oxycodone, Palbociclib, Palivizumab, Panitumumab, Panobinostat, Pazopanib, Pembrolizumab, PD-1 antibody, PD-L1 antibody, Pemetrexed, Pertuzumab, Pneumococcal conjugate vaccine, Pomalidomide, Poziotinib, Pregabalin, ProscaVax, Propranolol, Quetiapine, Rabeprazole, Radium 223 chloride, Raloxifene, Raltegravir, Ramucirumab, Ranibizumab, Regorafenib, Rituximab, Rivaroxaban, Romidepsin, Rosuvastatin, Ruxolitinib phosphate, Salbutamol, Savolitinib, Semaglutide, Sevelamer, Sildenafil, Siltuximab, Sipuleucel-T, Sitagliptin, Sitagliptin/metformin, Solifenacin, Solanezumab, Sonidegib, Sorafenib, Sunitinib, Tacrolimus, Tacrimus, Tadalafil, Tamoxifen, Tafinlar, Talimogene laherparepvec, Talazoparib, Telaprevir, Talazoparib, Temozolomide, Temsirolimus, Tenofovir/emtricitabine, Tenofovir disoproxil fumarate, Testosterone gel, Thalidomide, TICE BCG, Tiotropium bromide, Tisagenlecleucel, Toremifene, Trametinib, Trastuzumab, Trastuzumab deruxtecan, Trabectedin (ecteinascidin 743), Trametinib, Tremelimumab, Trifluridine/tipiracil, Tretinoin, Uro-BCG, Ustekinumab, Valsartan, Veliparib, Vandetanib, Vemurafenib, Venetoclax, Vorinostat, Ziv-aflibercept, Zostavax, and an analog, derivative, a pharmaceutically acceptable salt thereof, carrier, diluent or excipient thereof or a combination of two or more of the above compounds.

20. The conjugate of Claim **4,** or **12**, having in vitro, in vivo or ex vivo cell killing activity.

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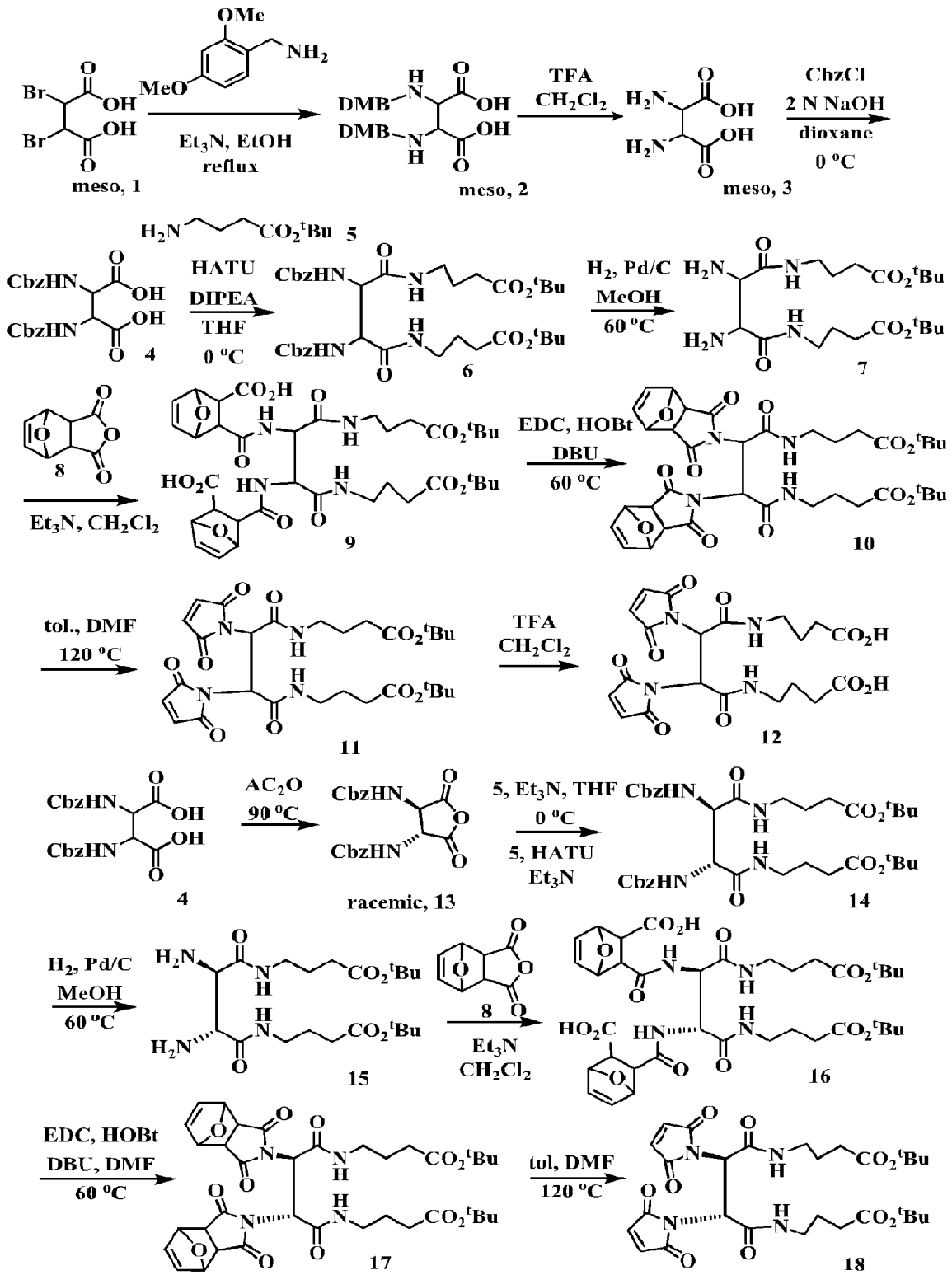

Fig. 1

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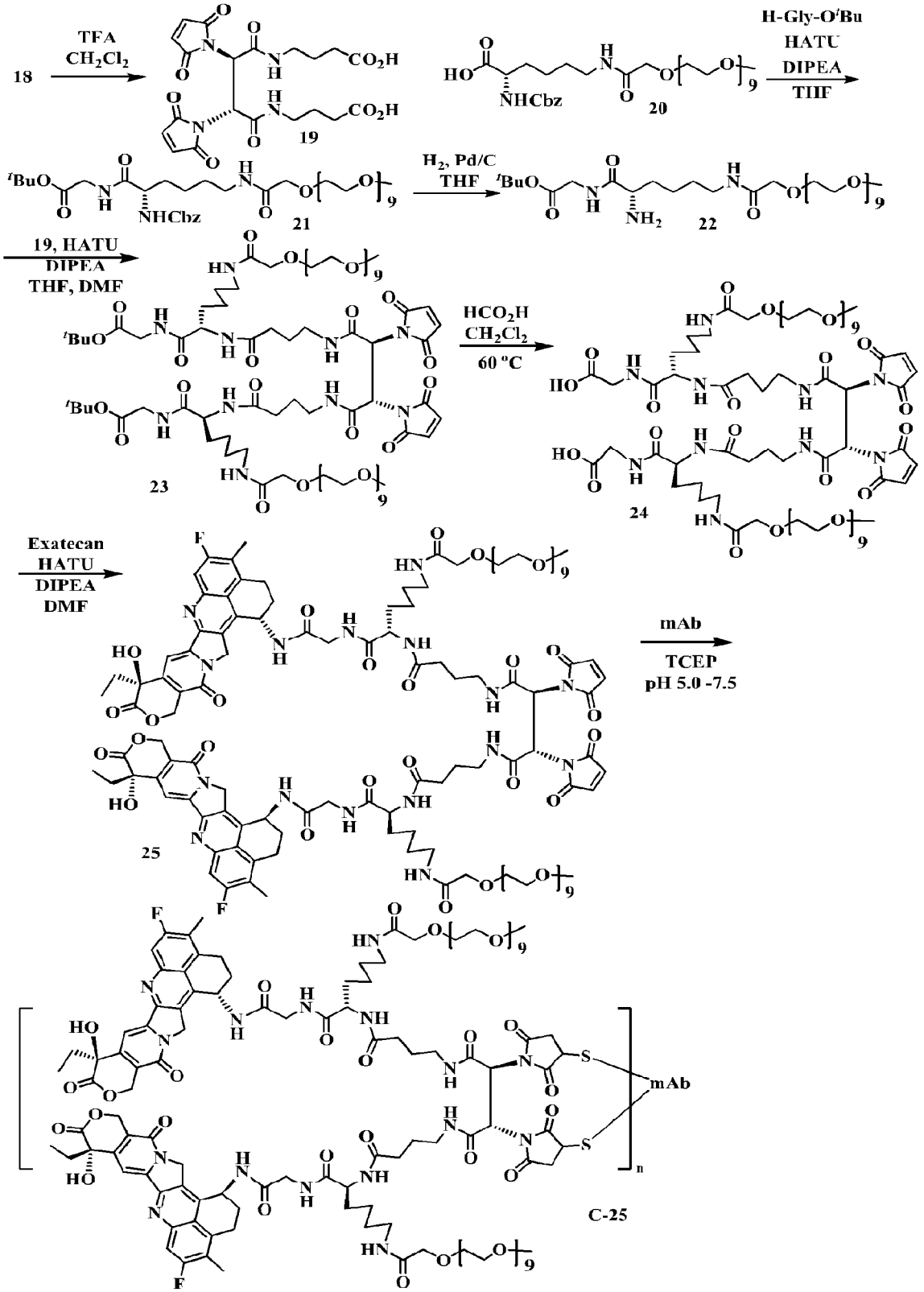

Fig. 2.

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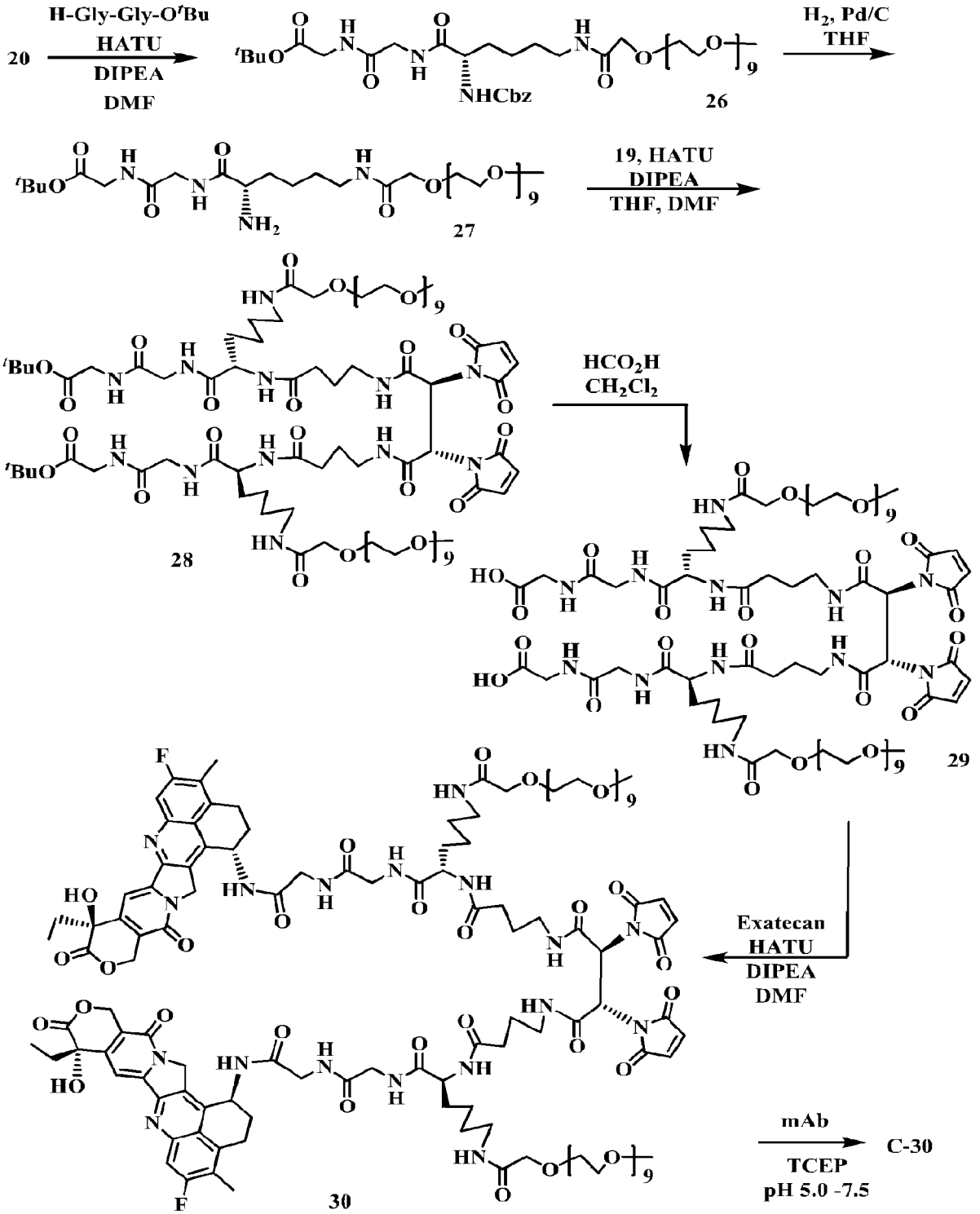

Fig. 3

CA 03236754 2024-4-30

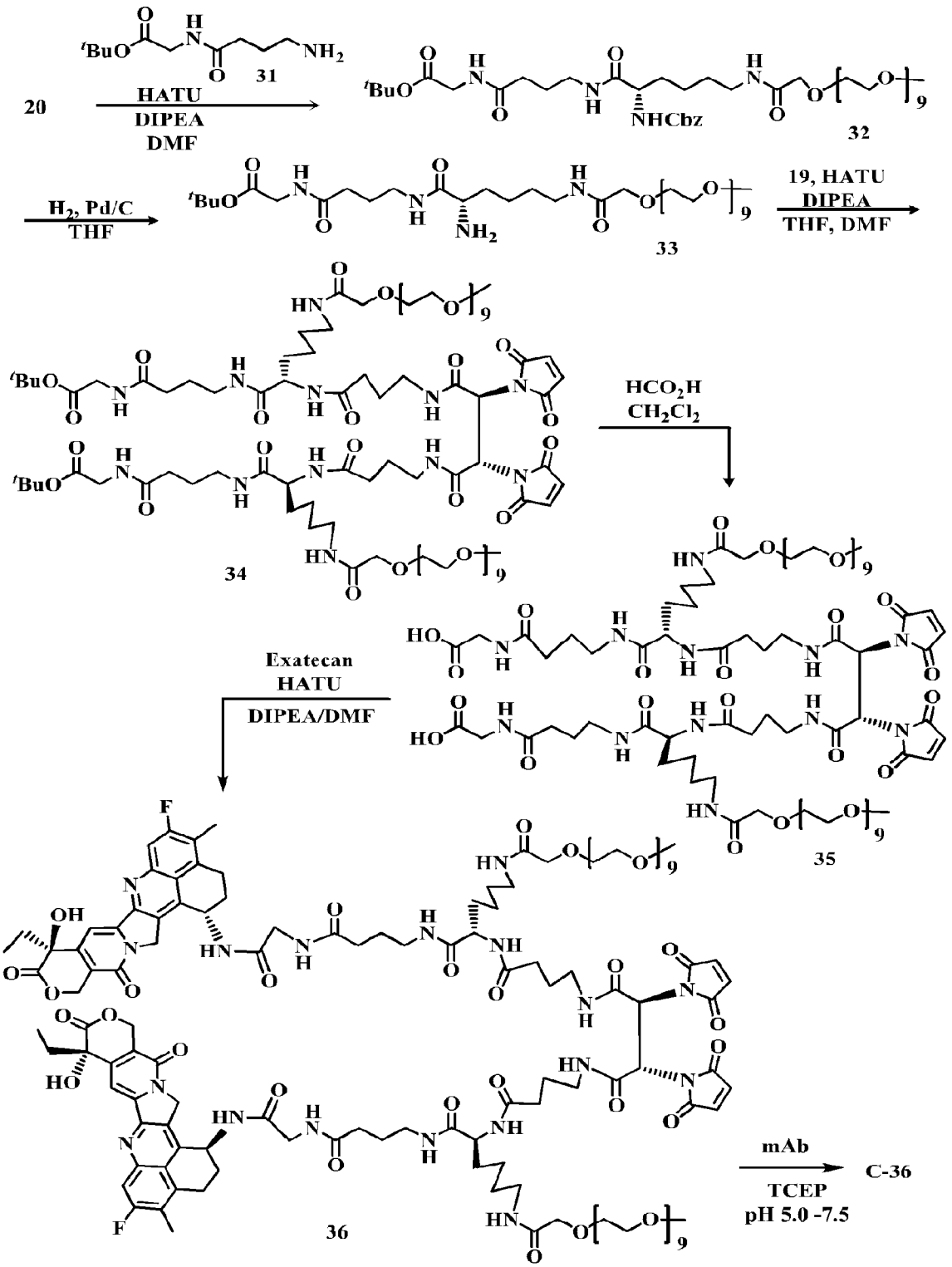

Fig. 4

CA 03236754 2024-4-30

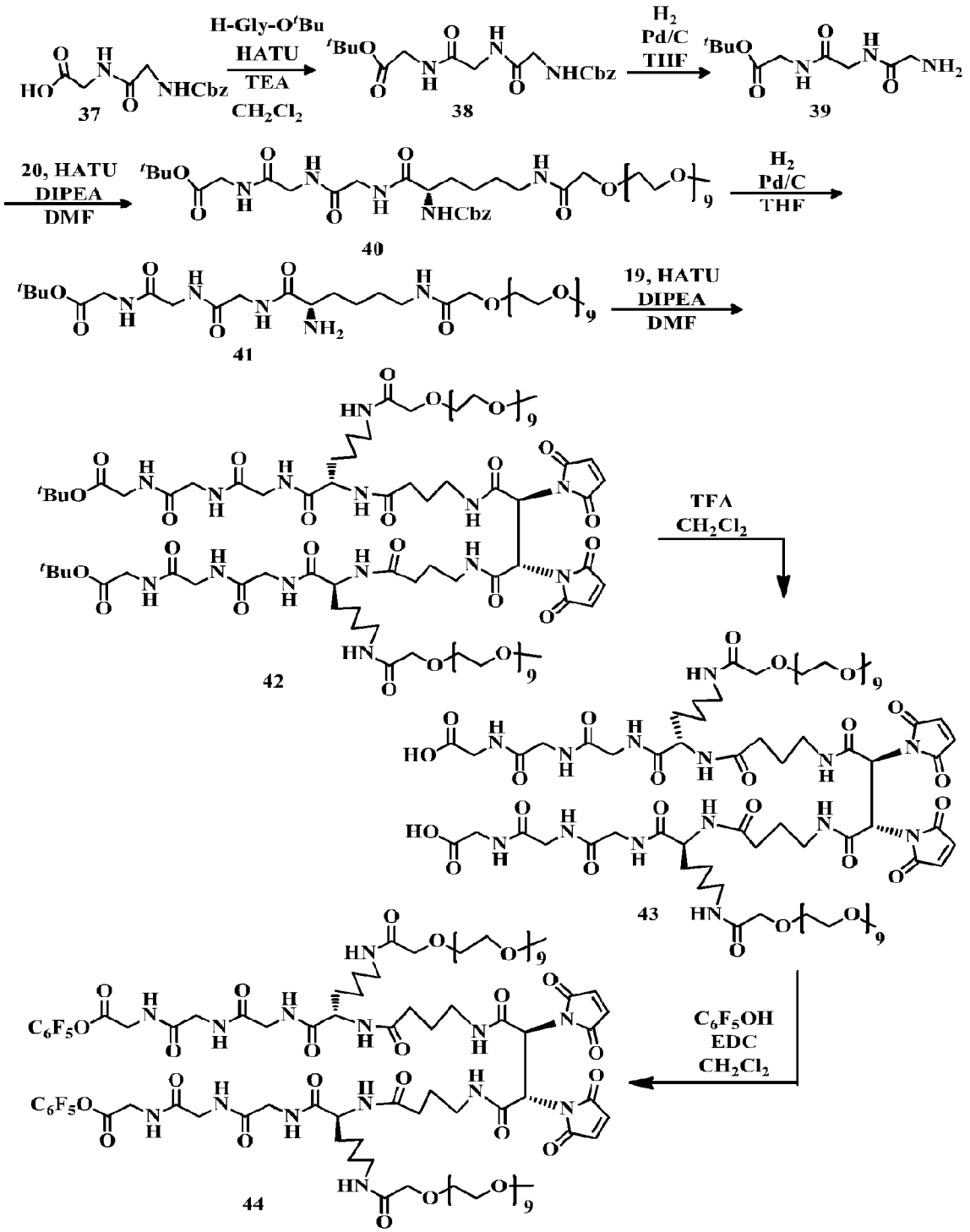

Fig. 5

CA 03236754 2024-4-30

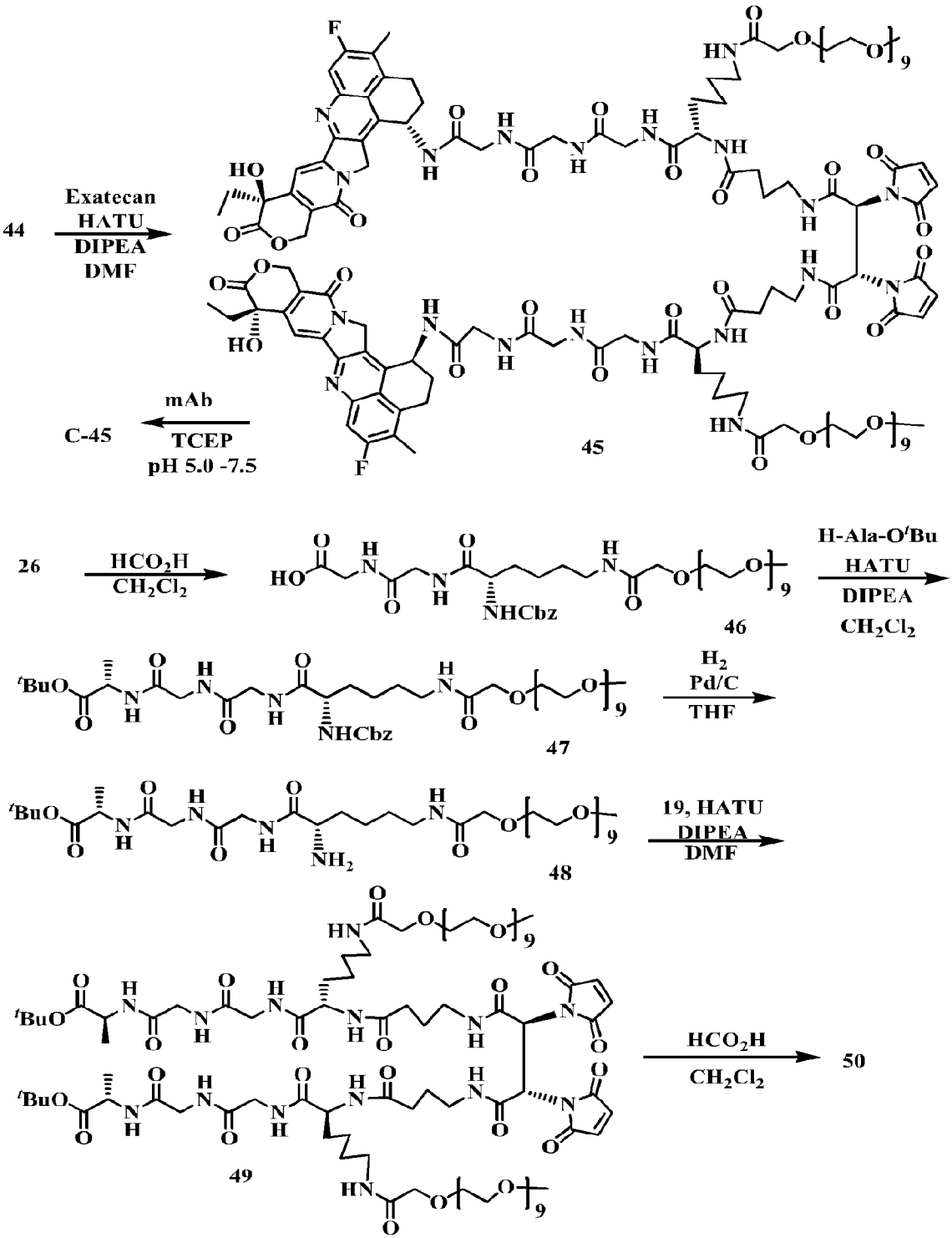

Fig. 6

CA 03236754 2024-4-30

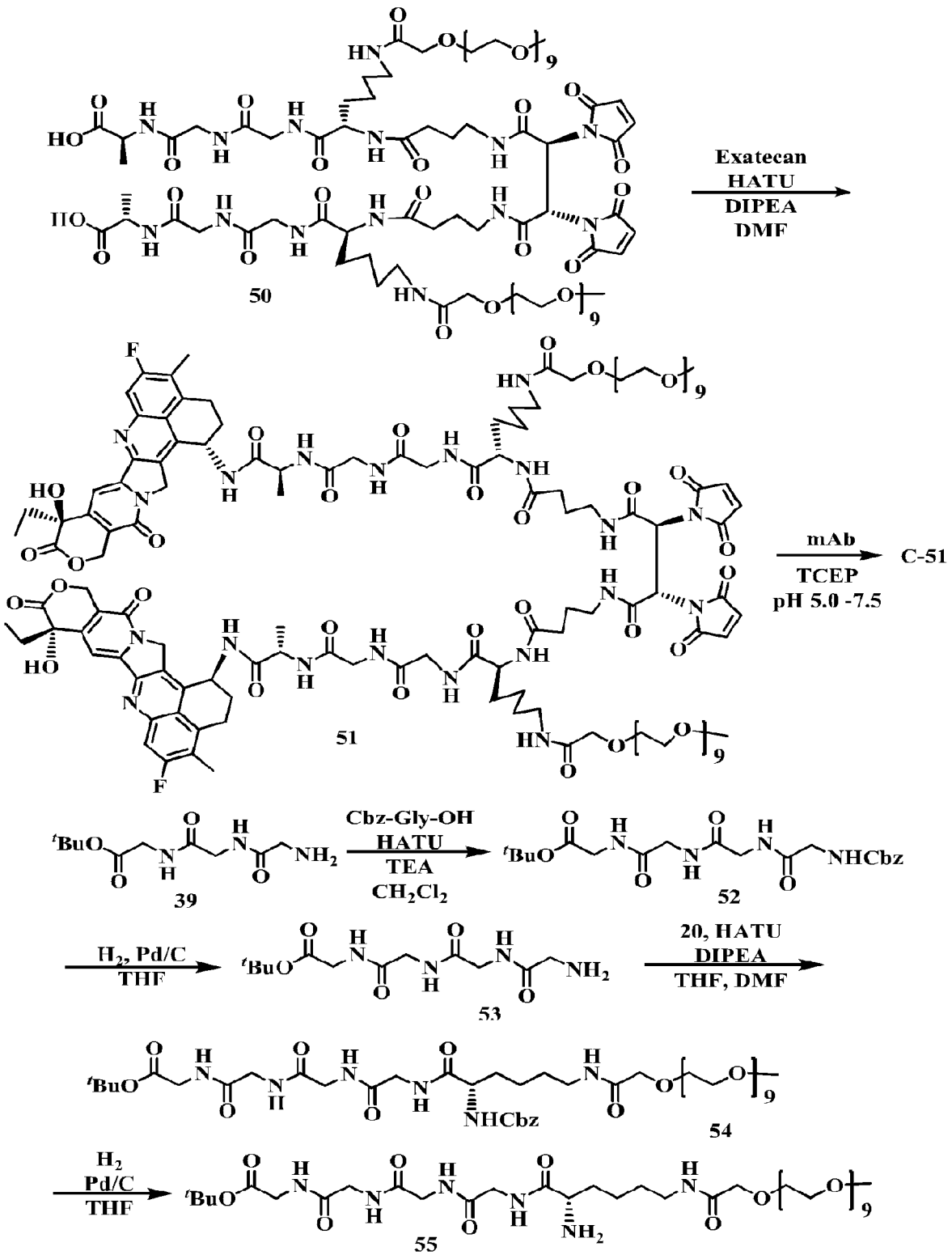

Fig. 7

CA 03236754 2024-4-30

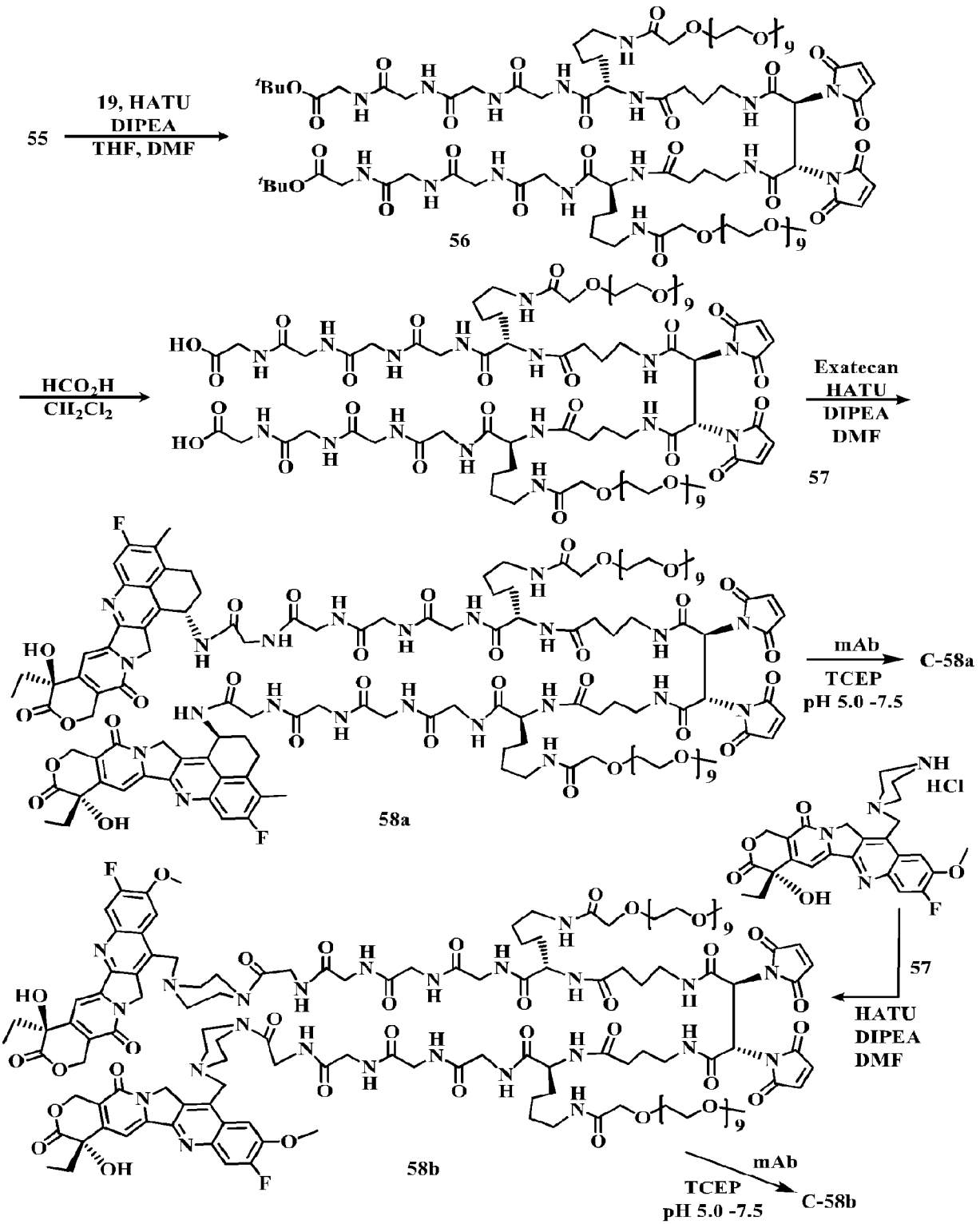

Fig. 8

CA 03236754 2024-4-30

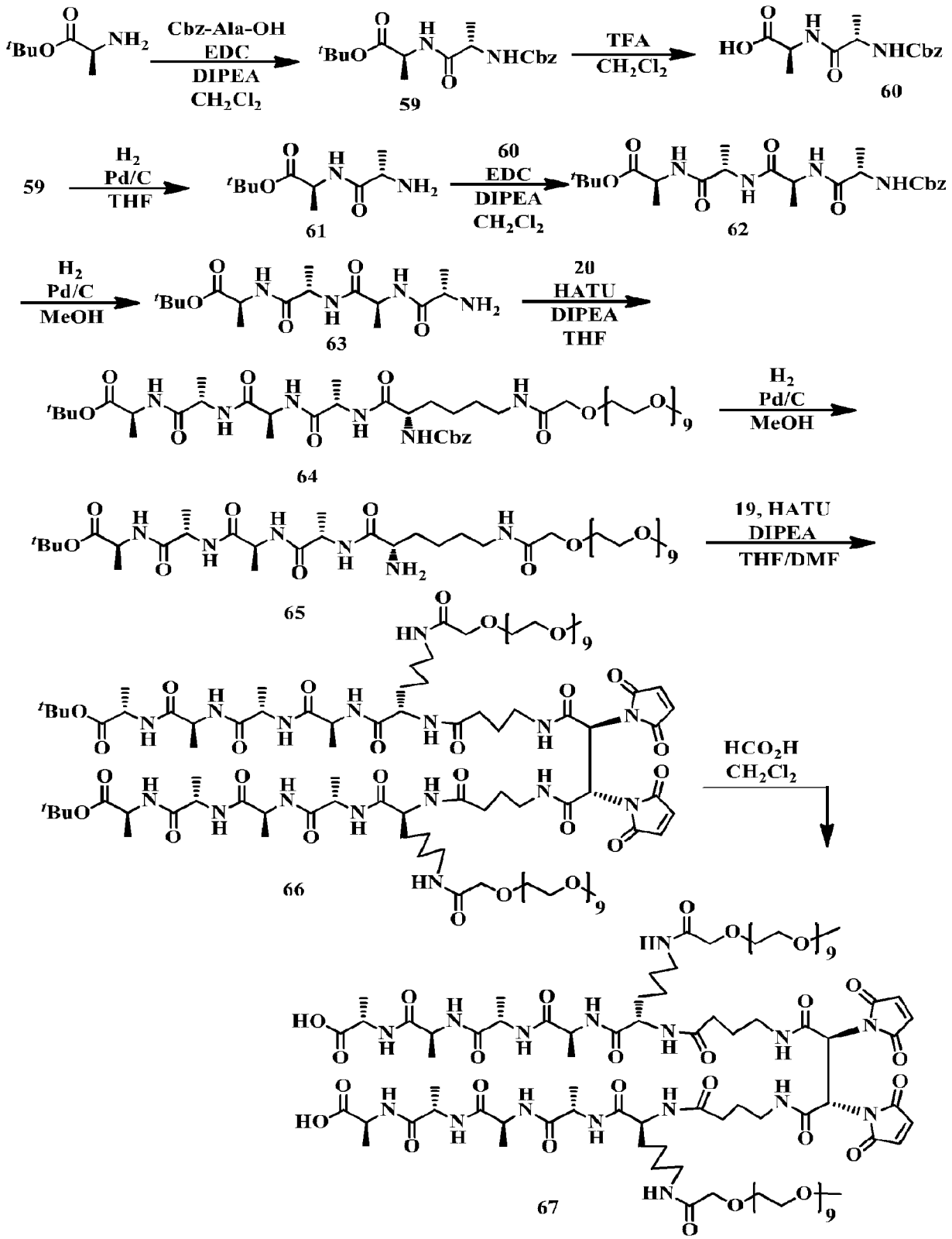

Fig. 9

CA 03236754 2024-4-30

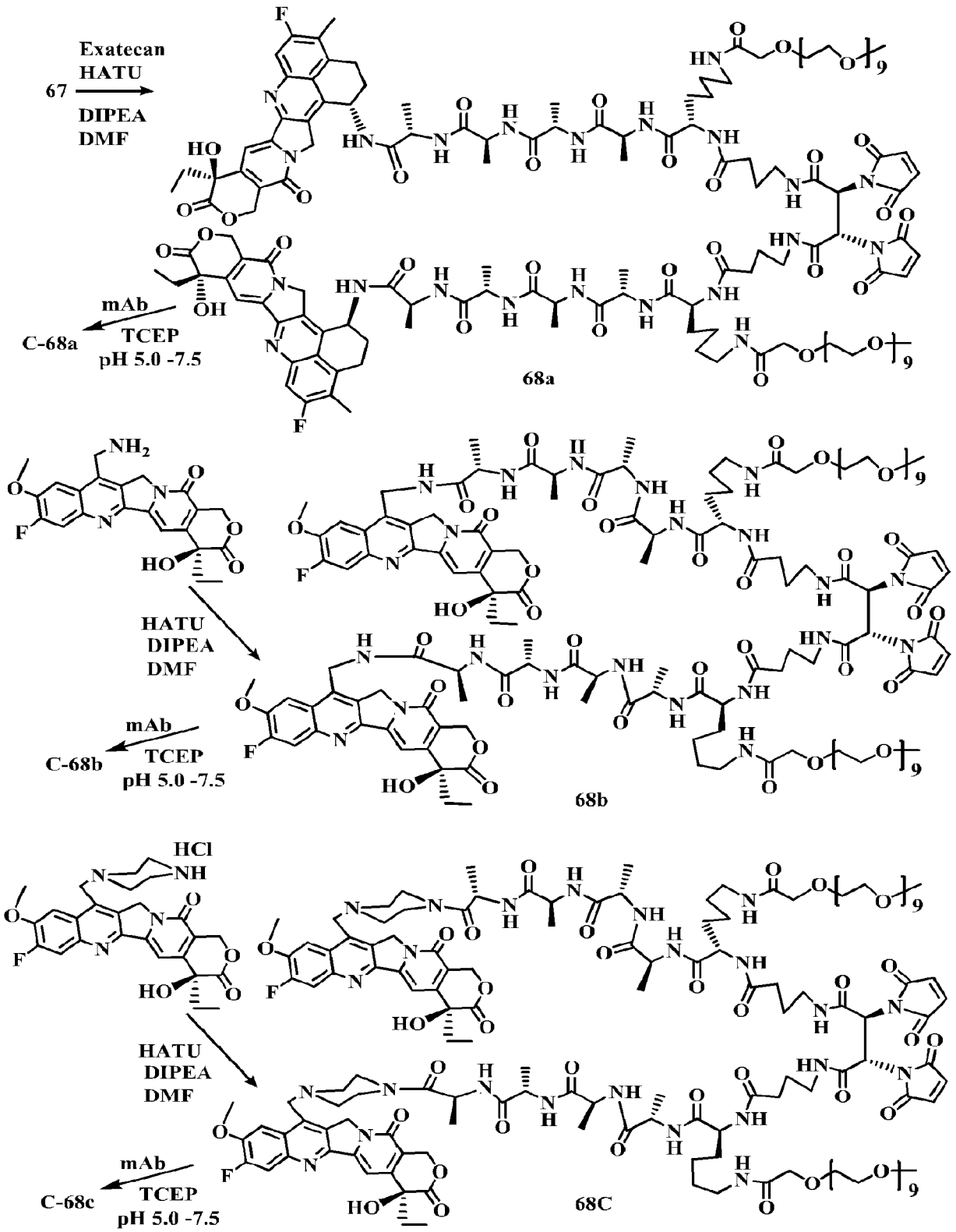

Fig. 10

CA 03236754 2024-4-30

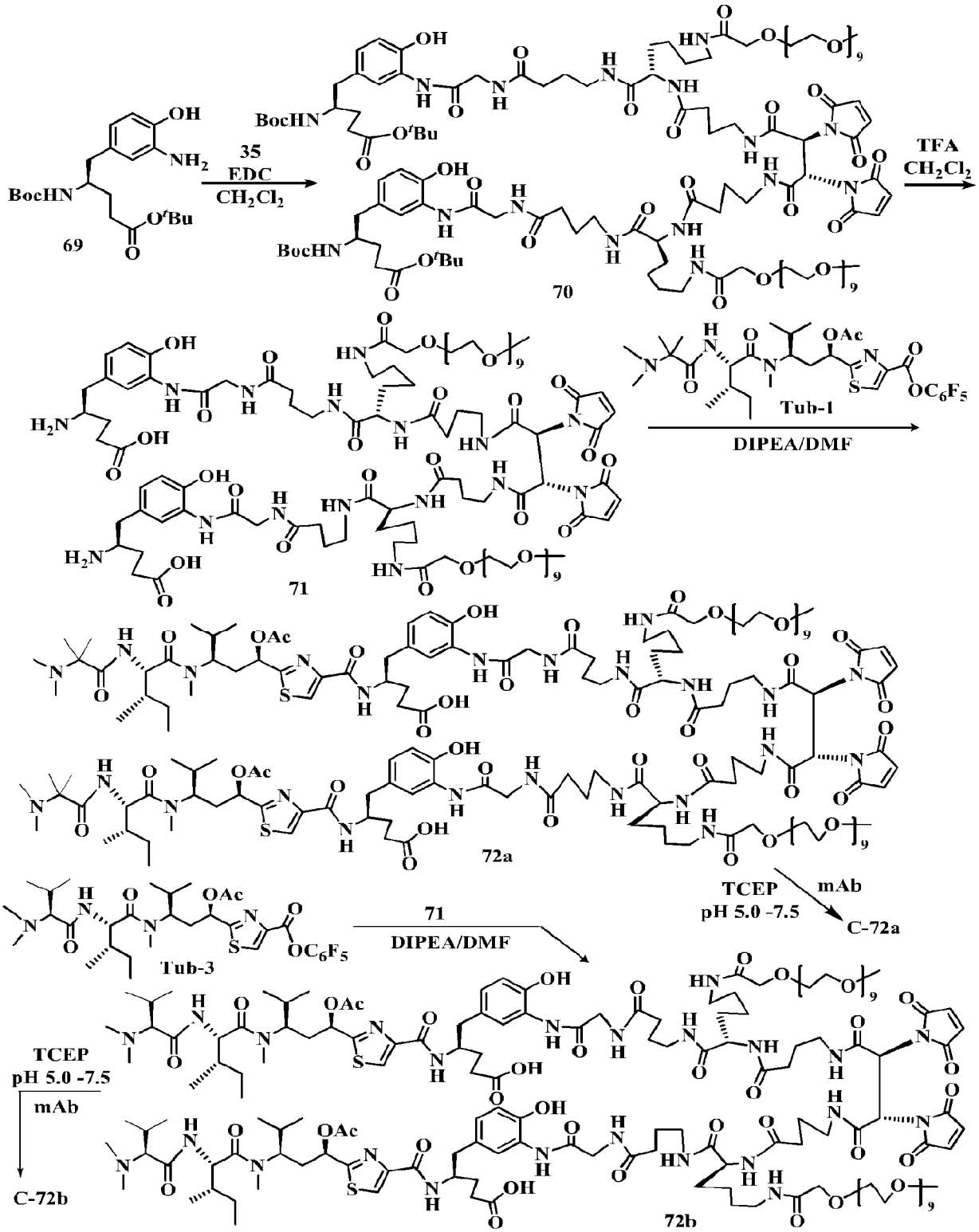

Fig. 11

CA 03236754 2024-4-30

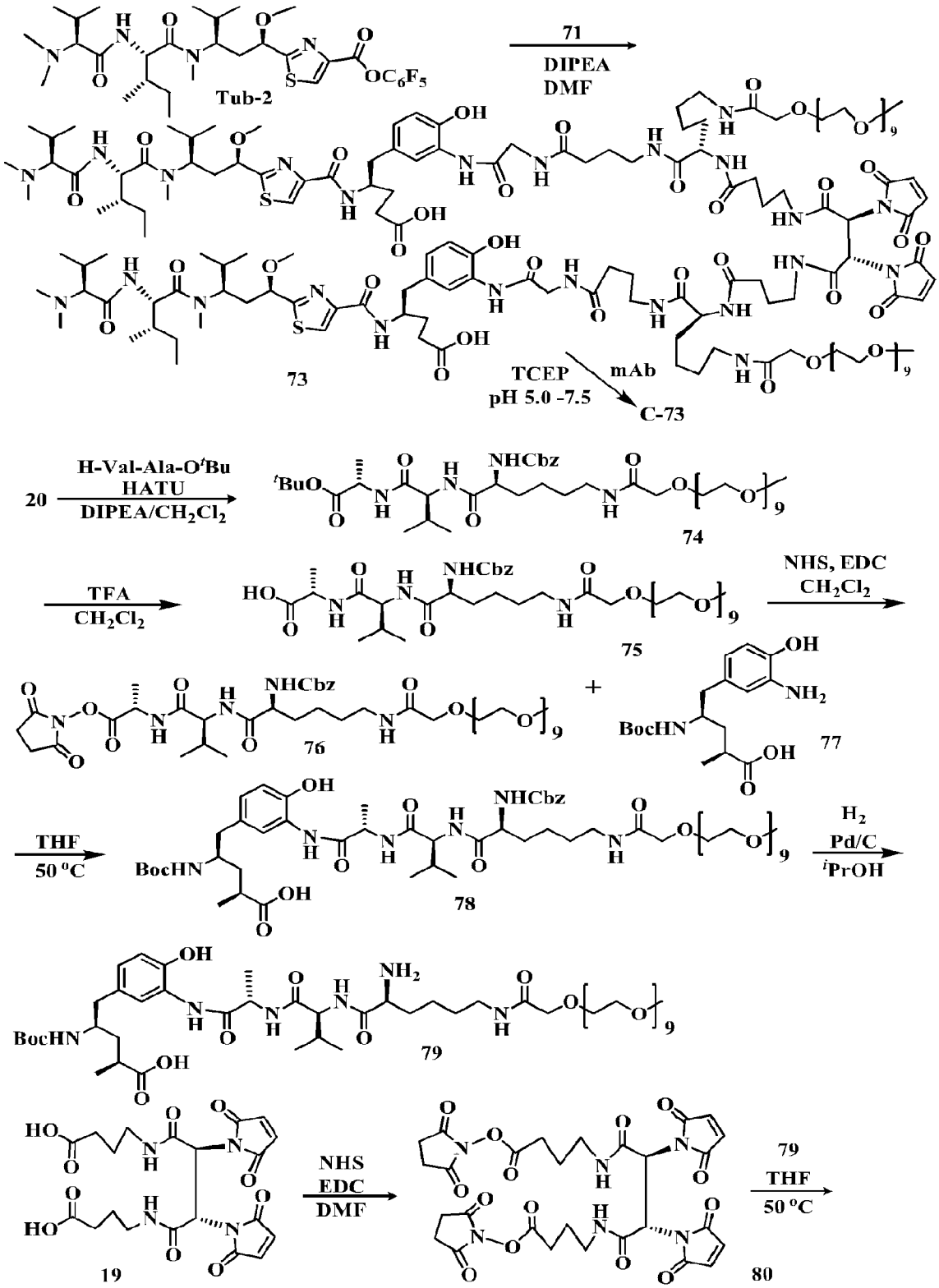

Fig. 12

CA 03236754 2024-4-30

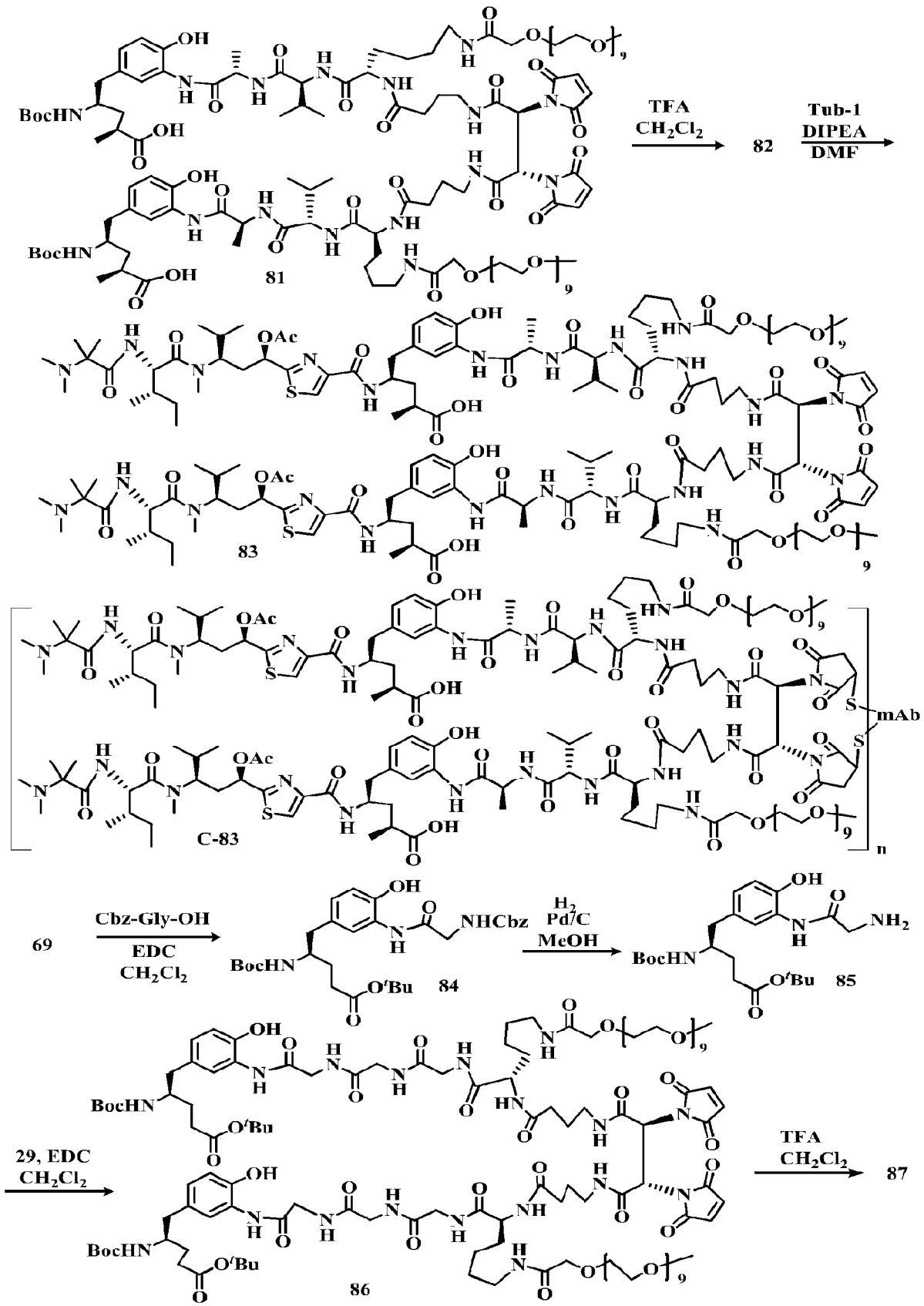

Fig. 13

CA 03236754 2024-4-30

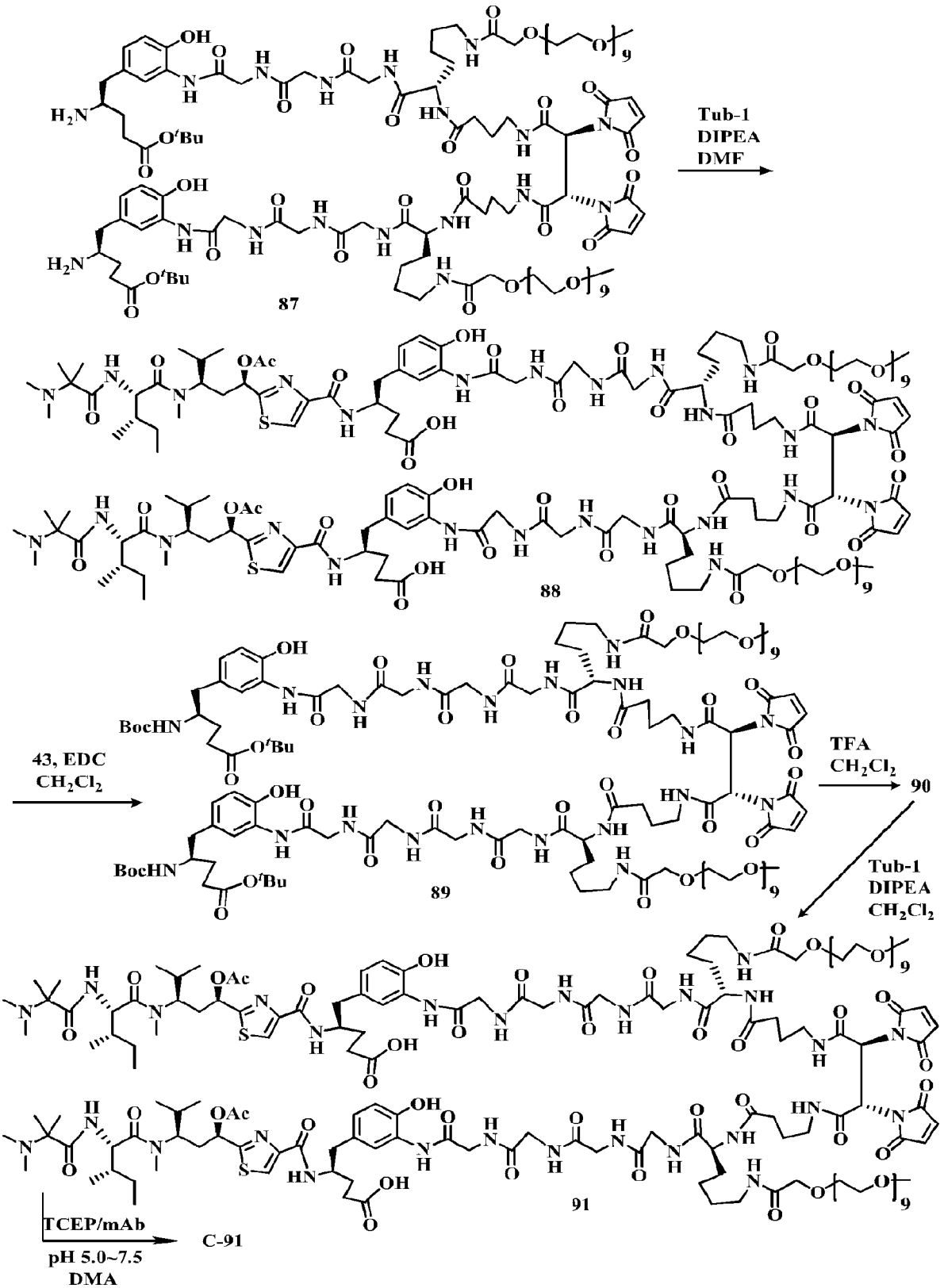

Fig. 14

CA 03236754 2024-4-30

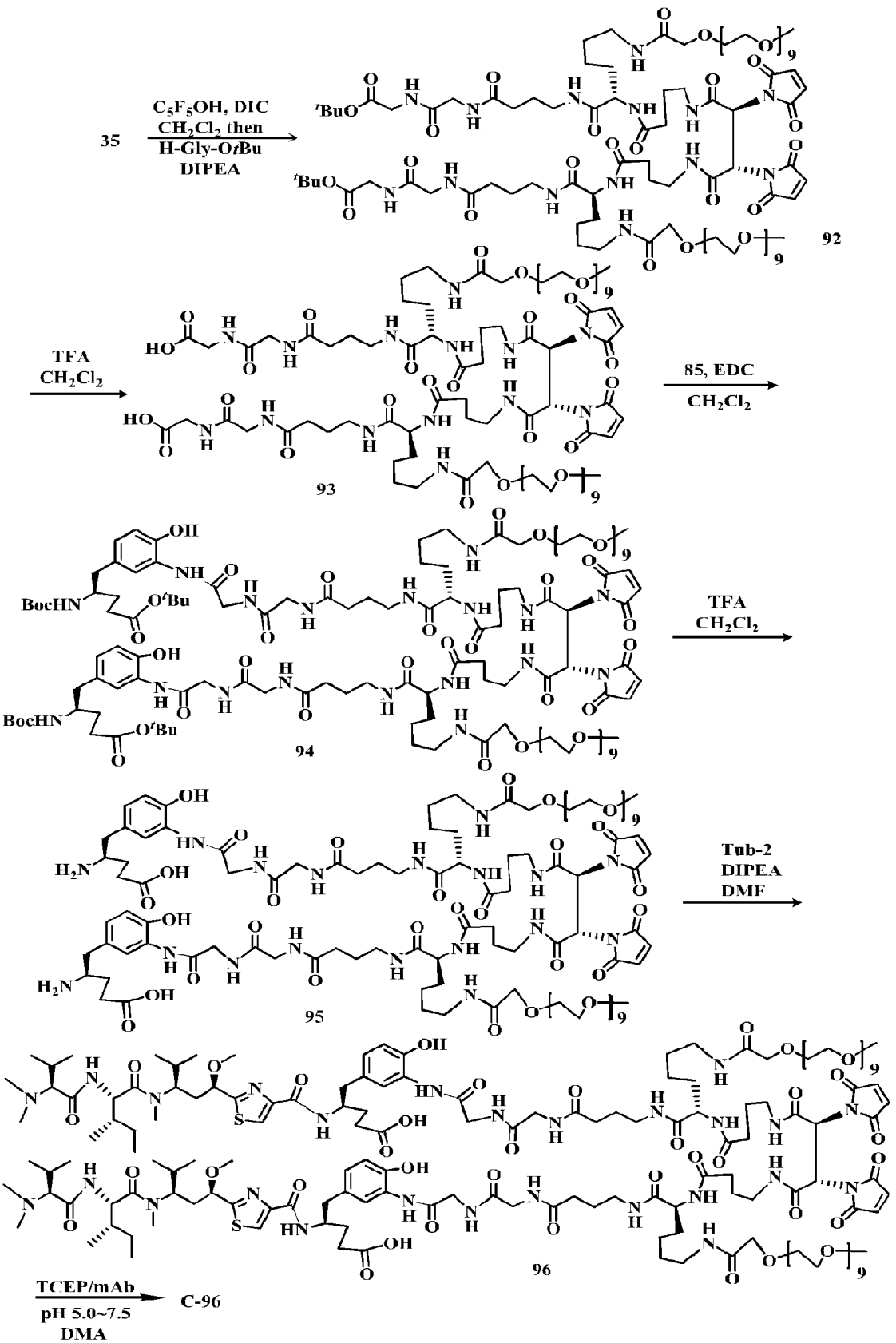

Fig. 15

CA 03236754 2024-4-30

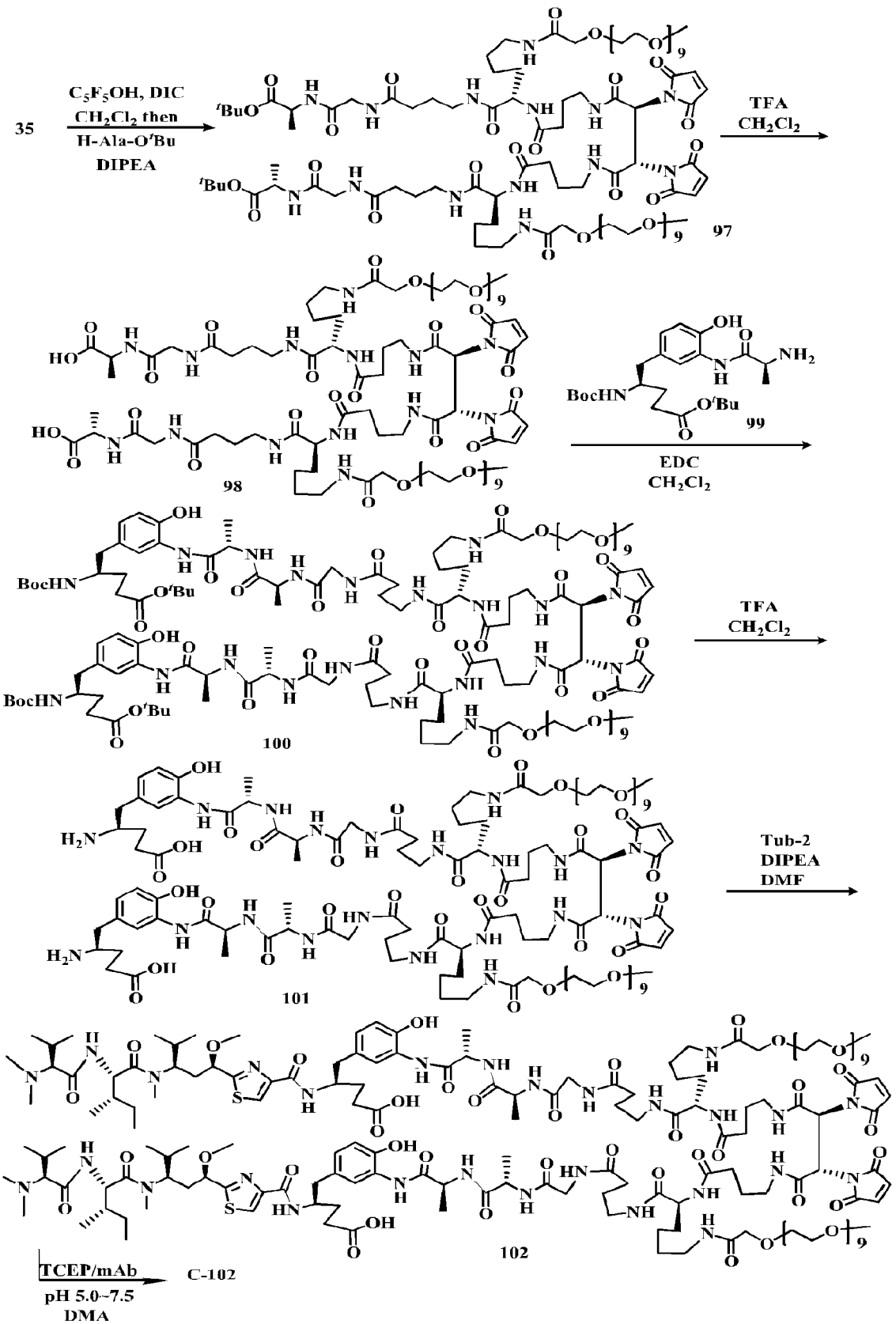

Fig. 16

CA 03236754 2024-4-30

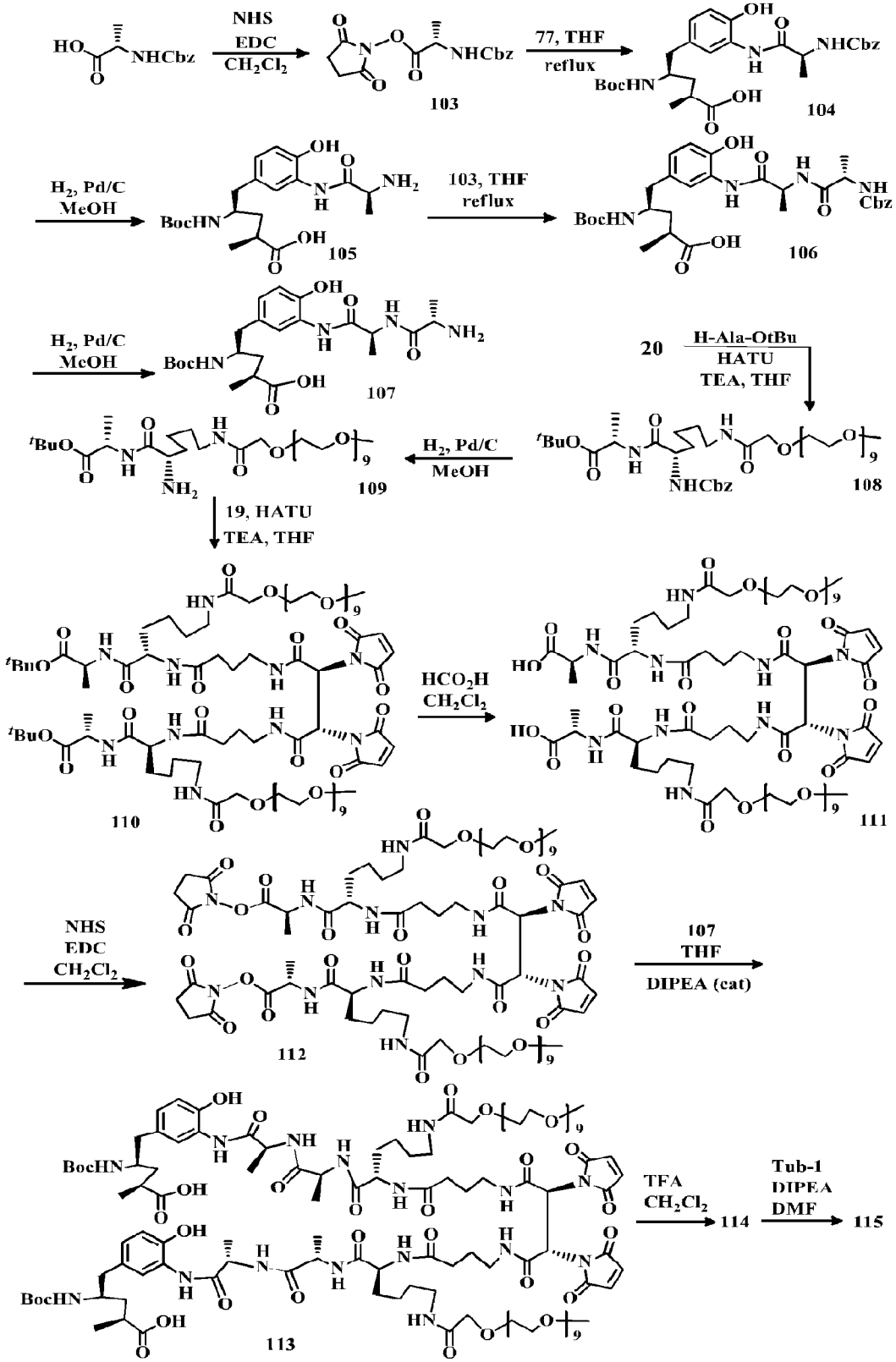

Fig 17.

CA 03236754 2024-4-30

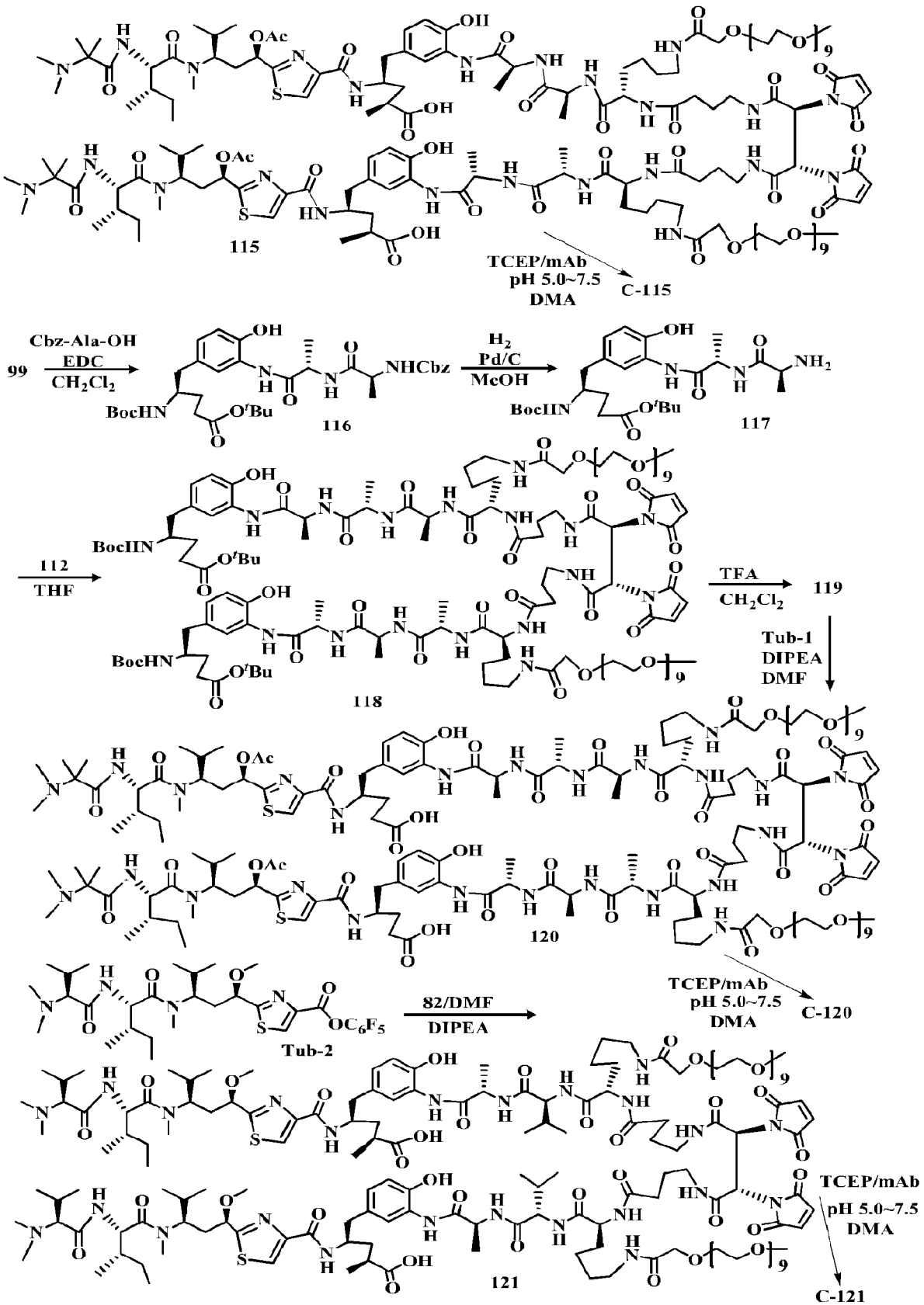

Fig. 18

CA 03236754 2024-4-30

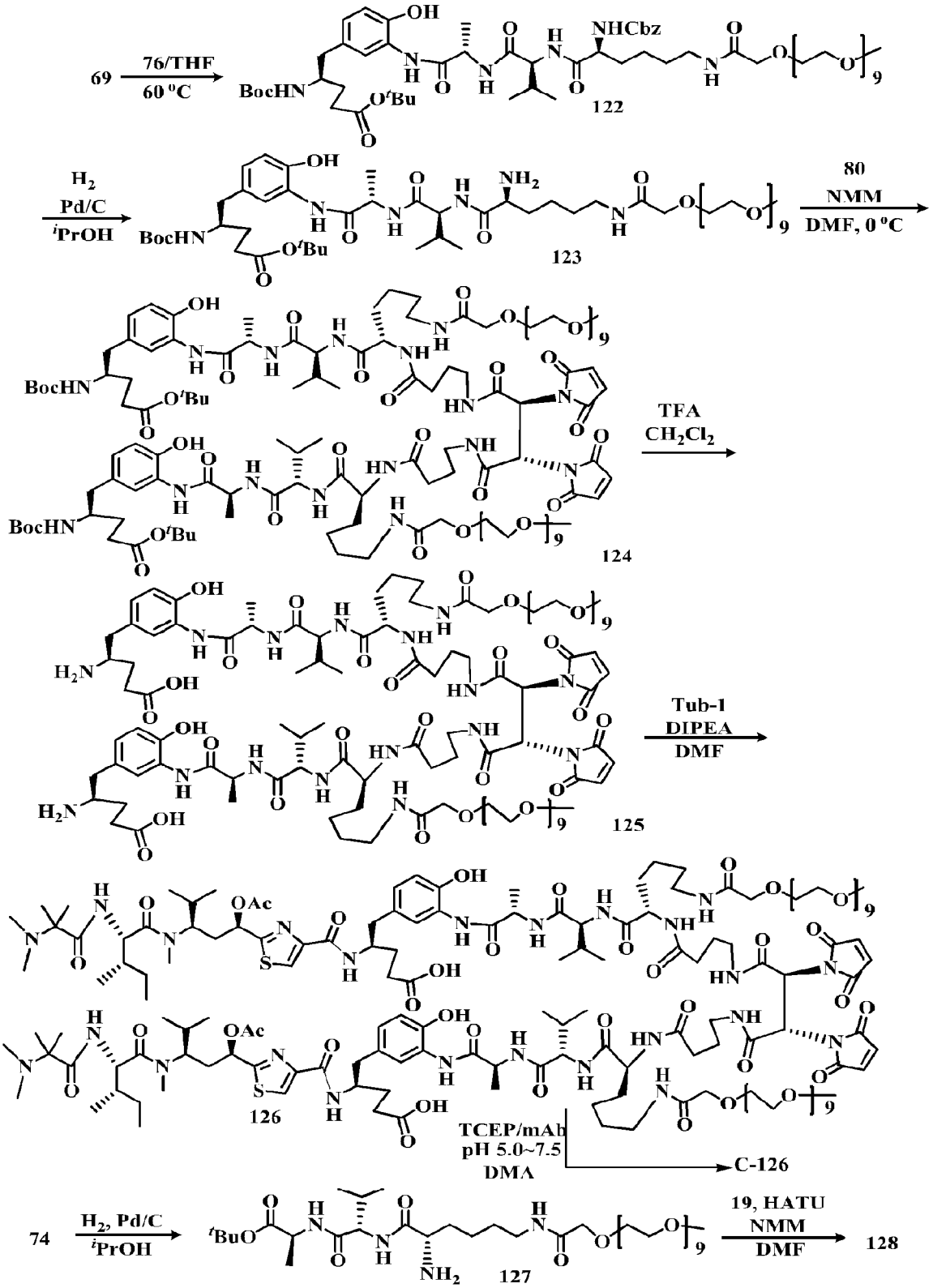

Fig. 19

CA 03236754 2024-4-30

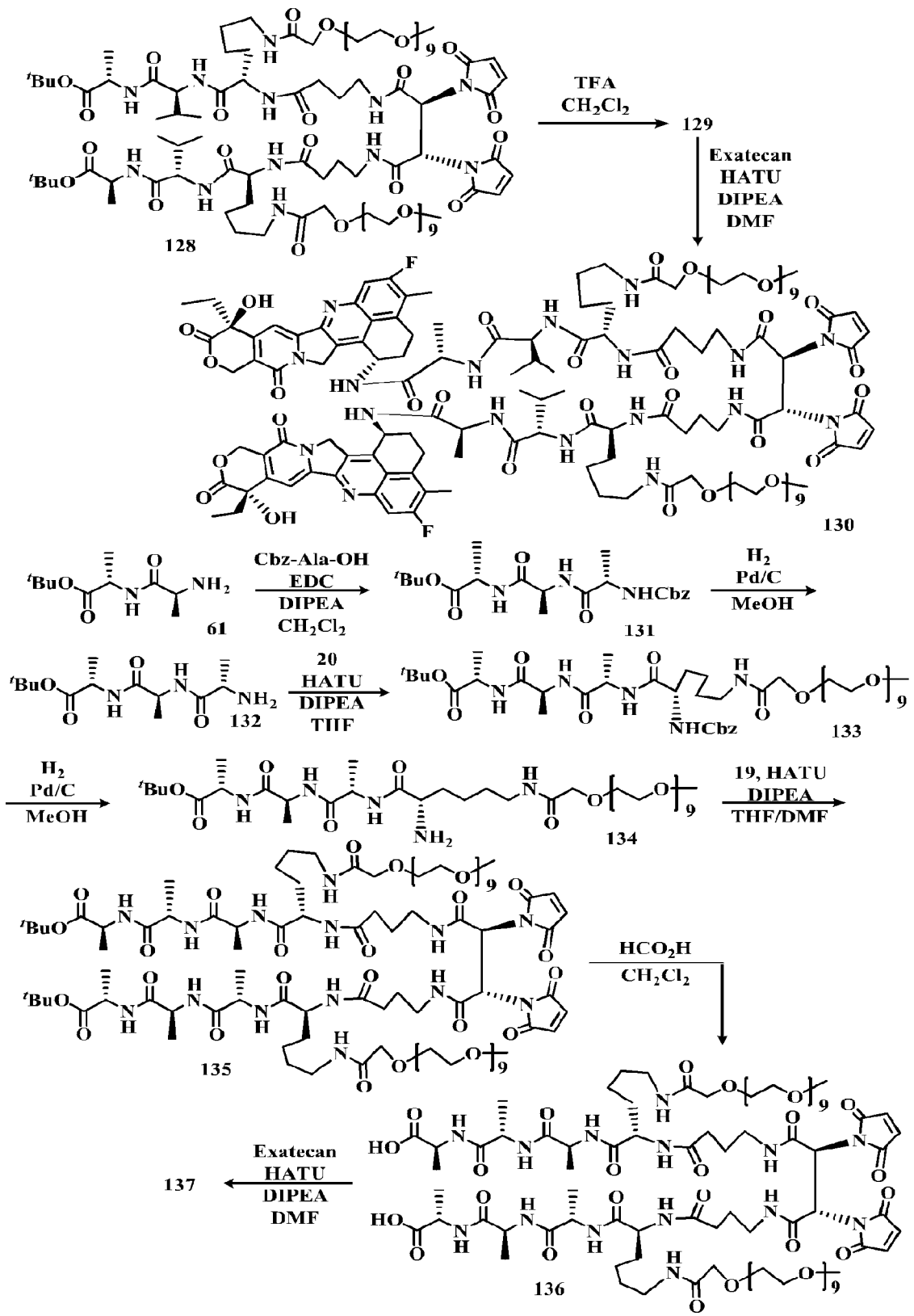

Fig. 20

CA 03236754 2024-4-30

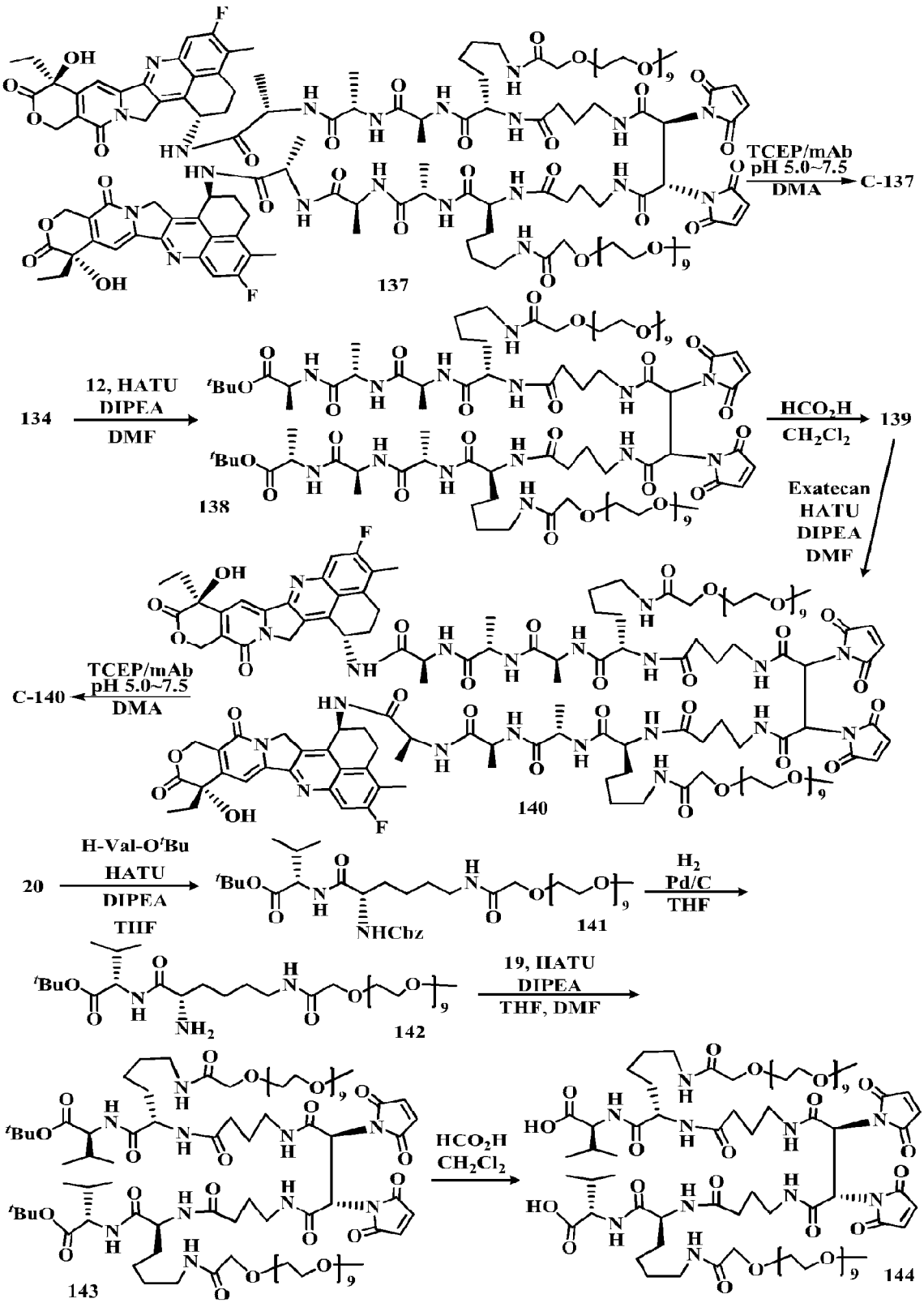

Fig. 21

CA 03236754 2024-4-30

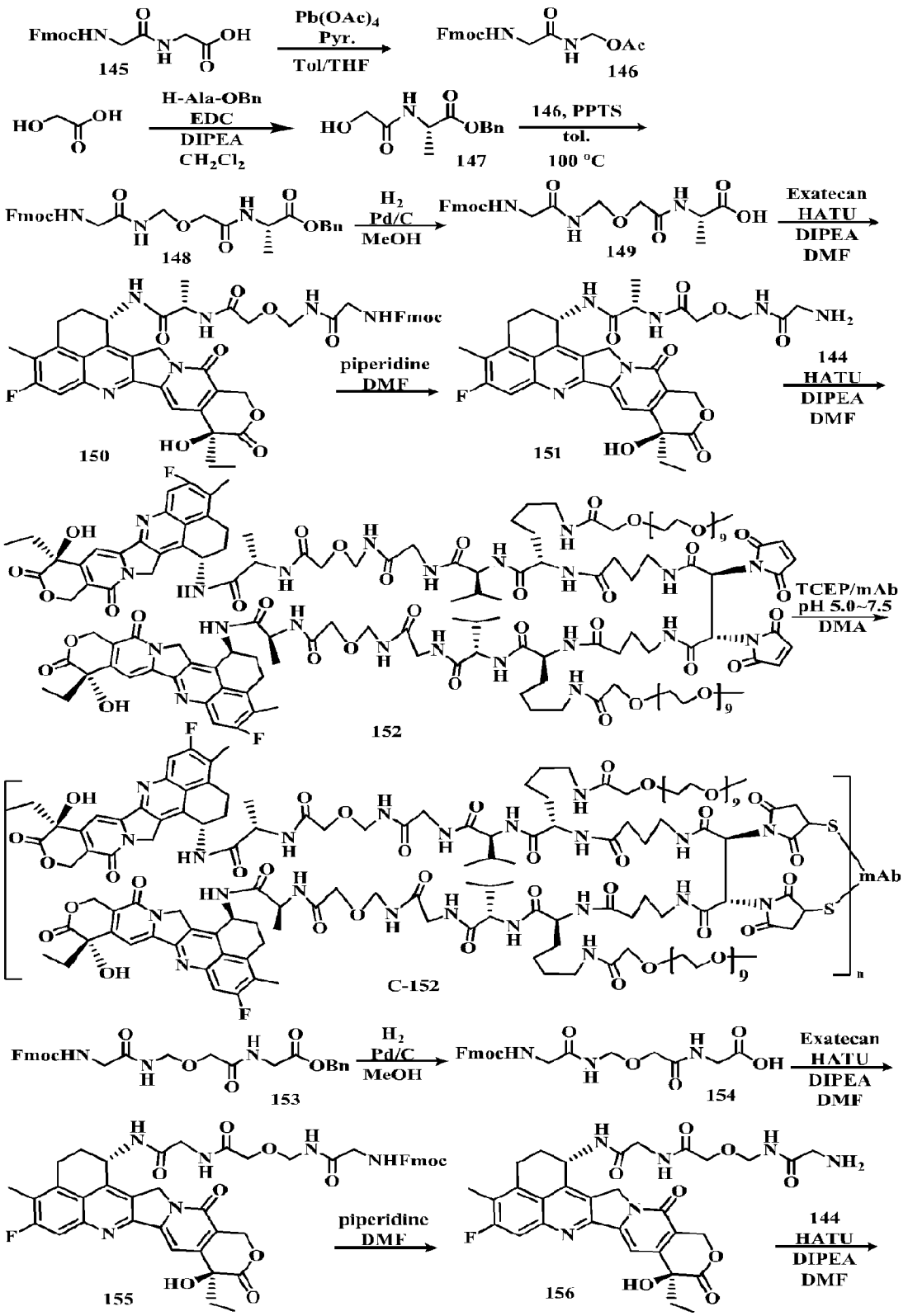

Fig. 22

CA 03236754 2024-4-30

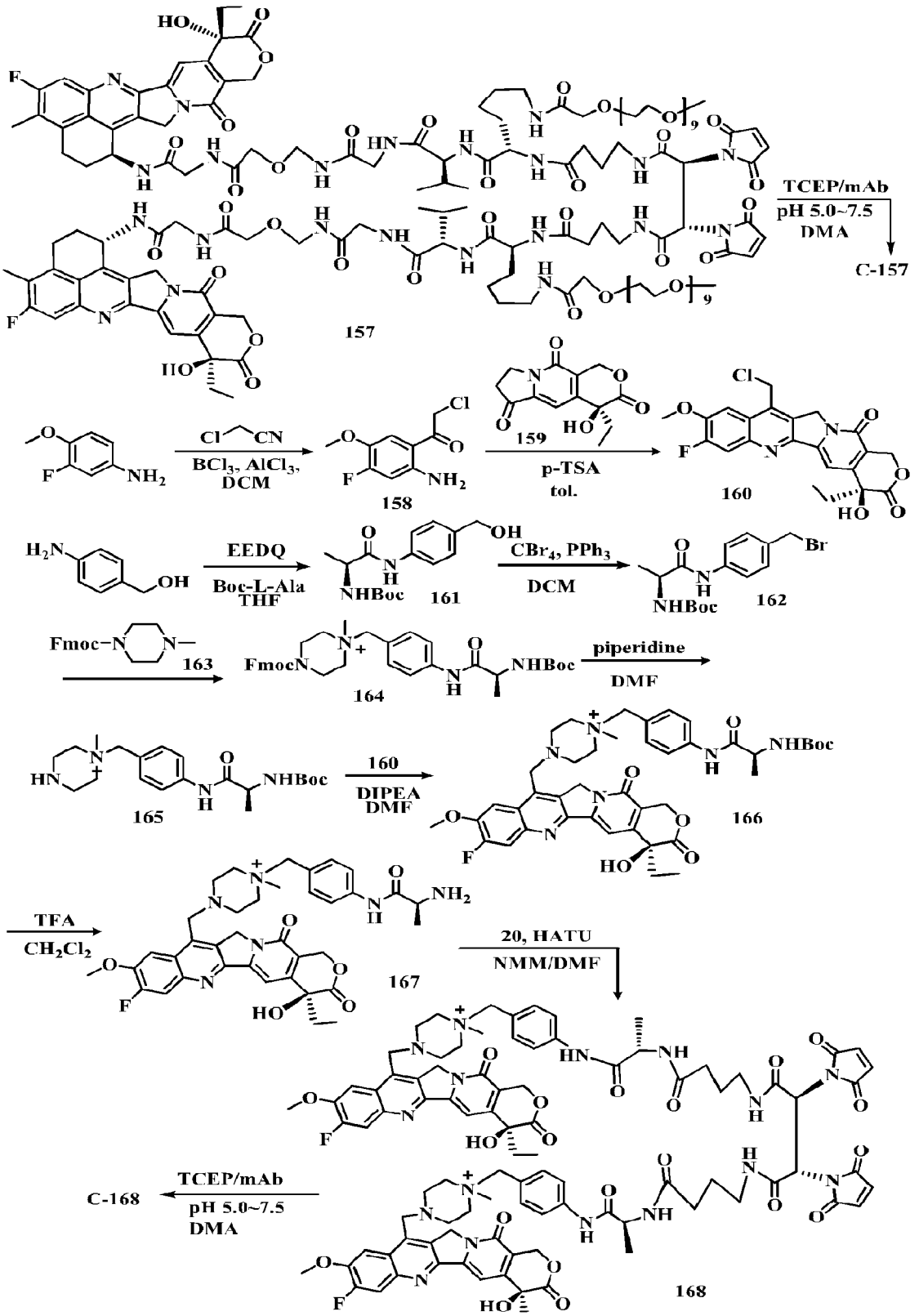

Fig. 23

CA 03236754 2024-4-30

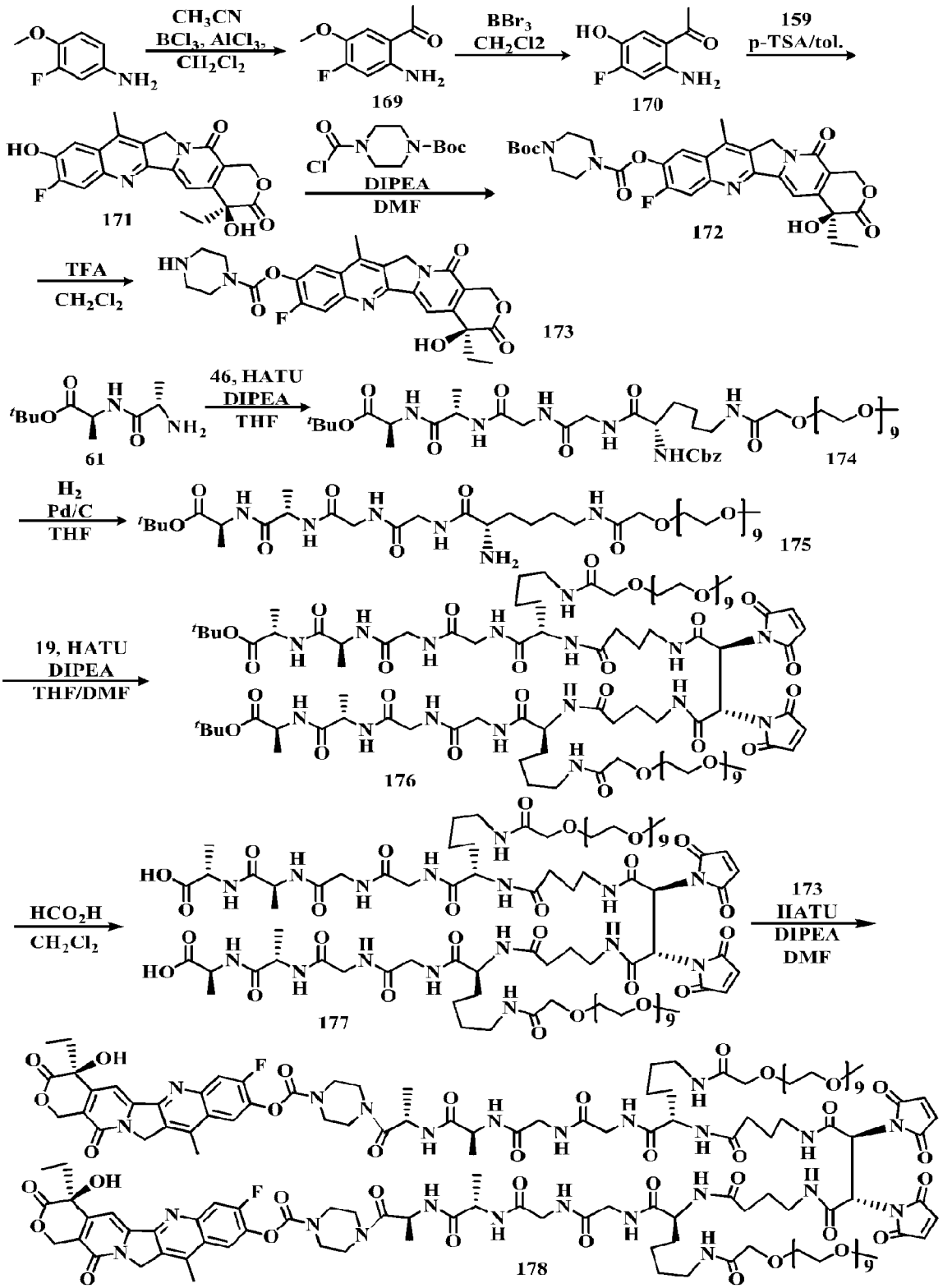

Fig. 24

CA 03236754 2024-4-30

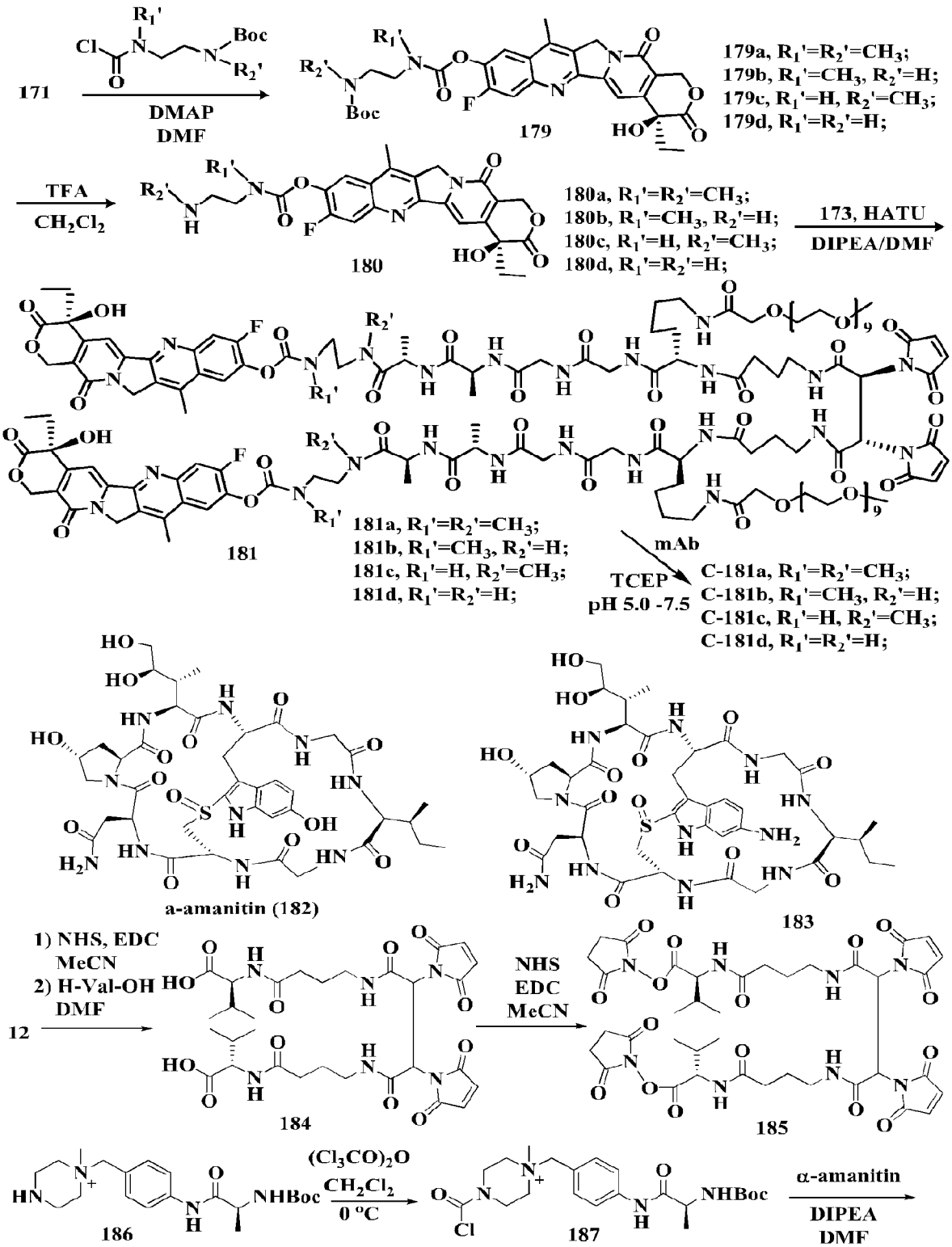

Fig. 25

CA 03236754 2024-4-30

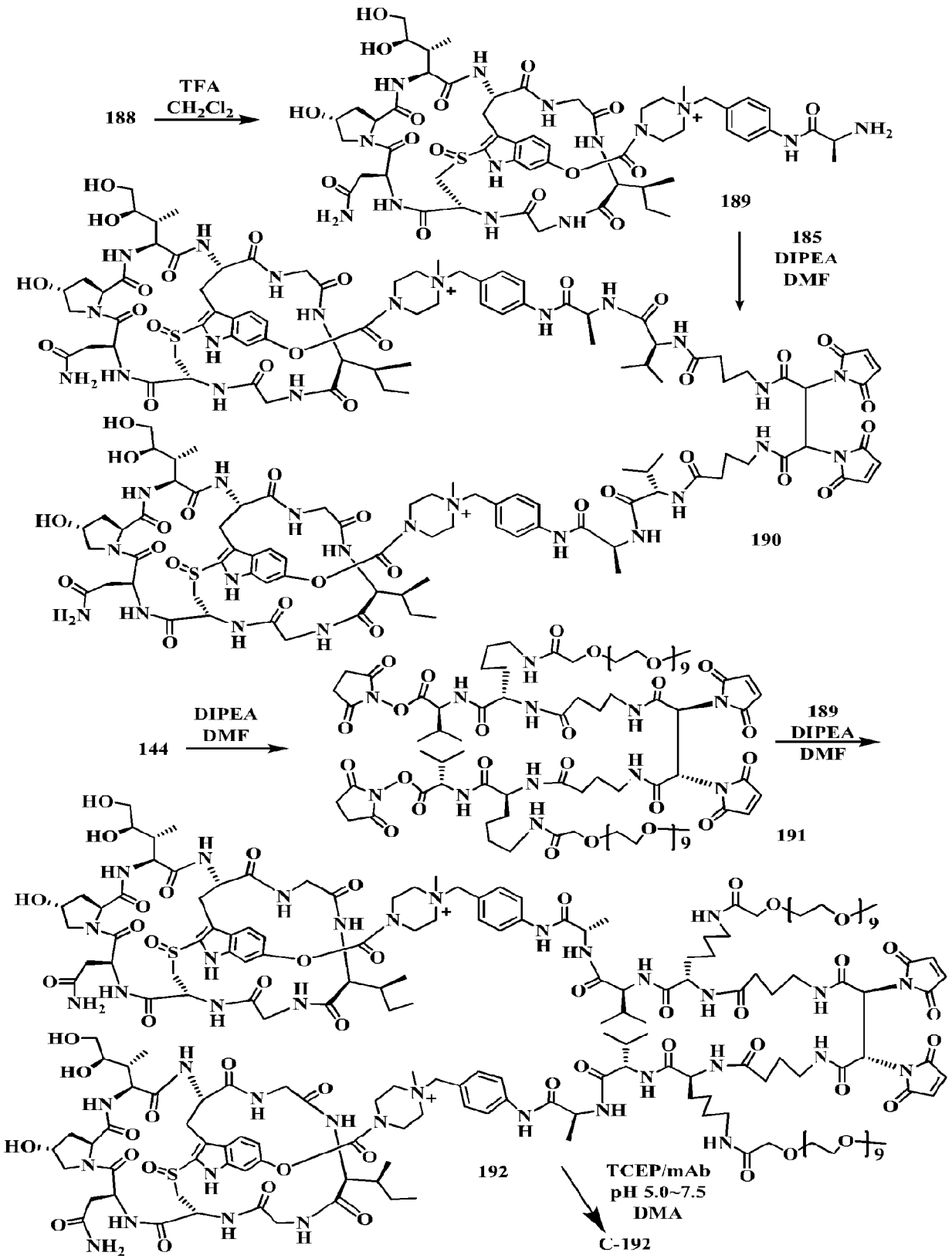

Fig. 26

CA 03236754 2024-4-30

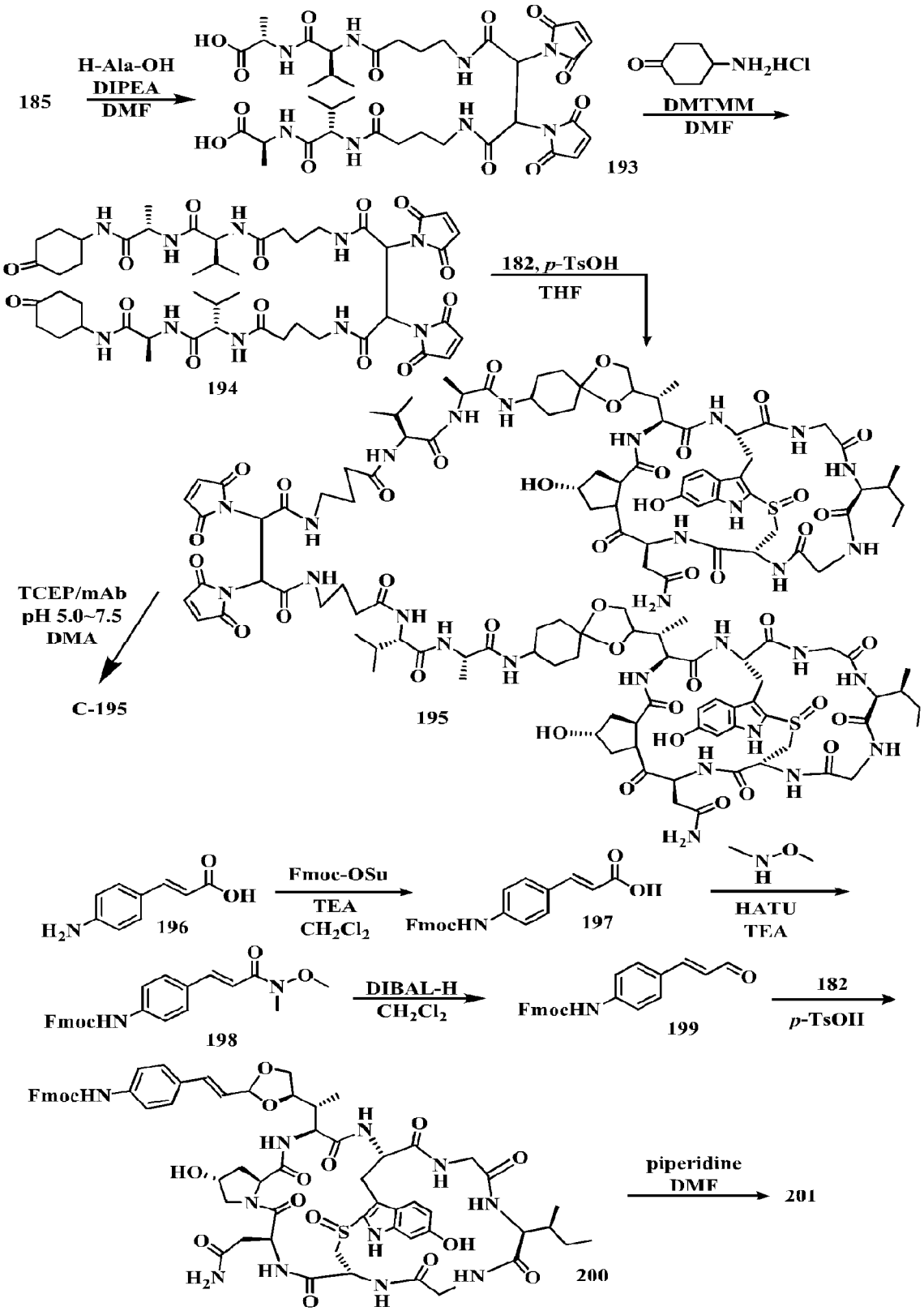

Fig. 27

CA 03236754 2024-4-30

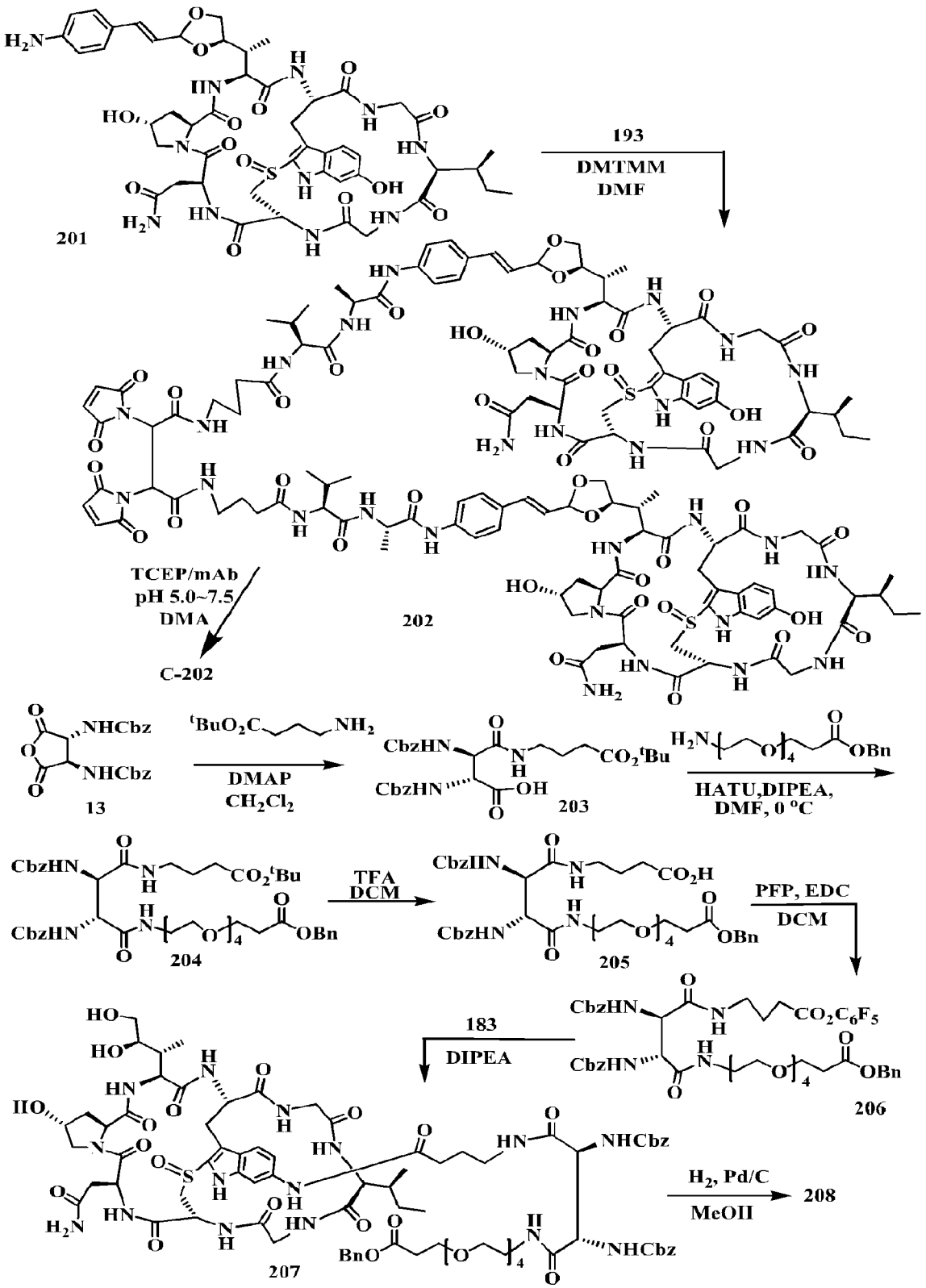

Fig. 28

CA 03236754 2024-4-30

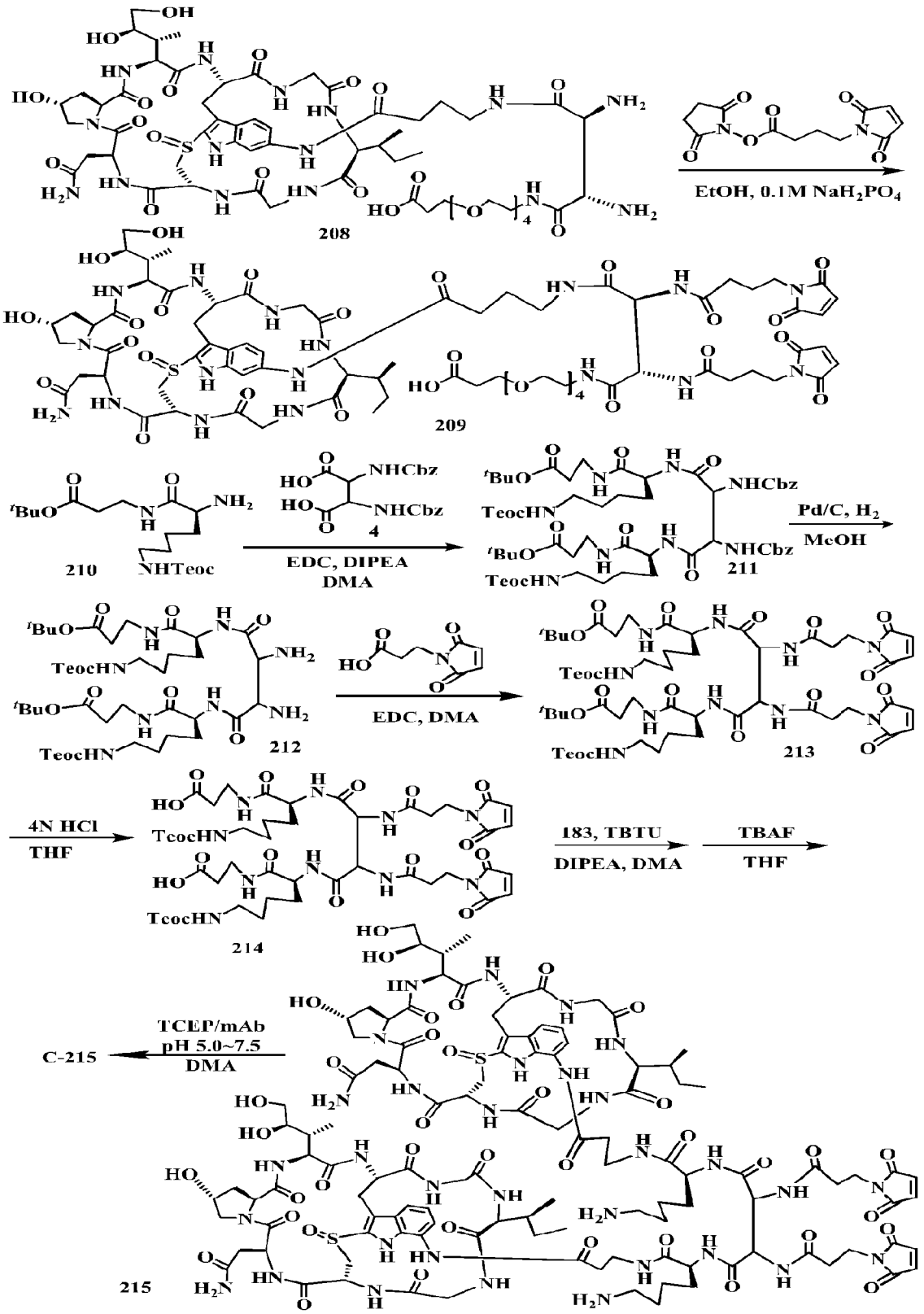

Fig. 29

CA 03236754 2024-4-30

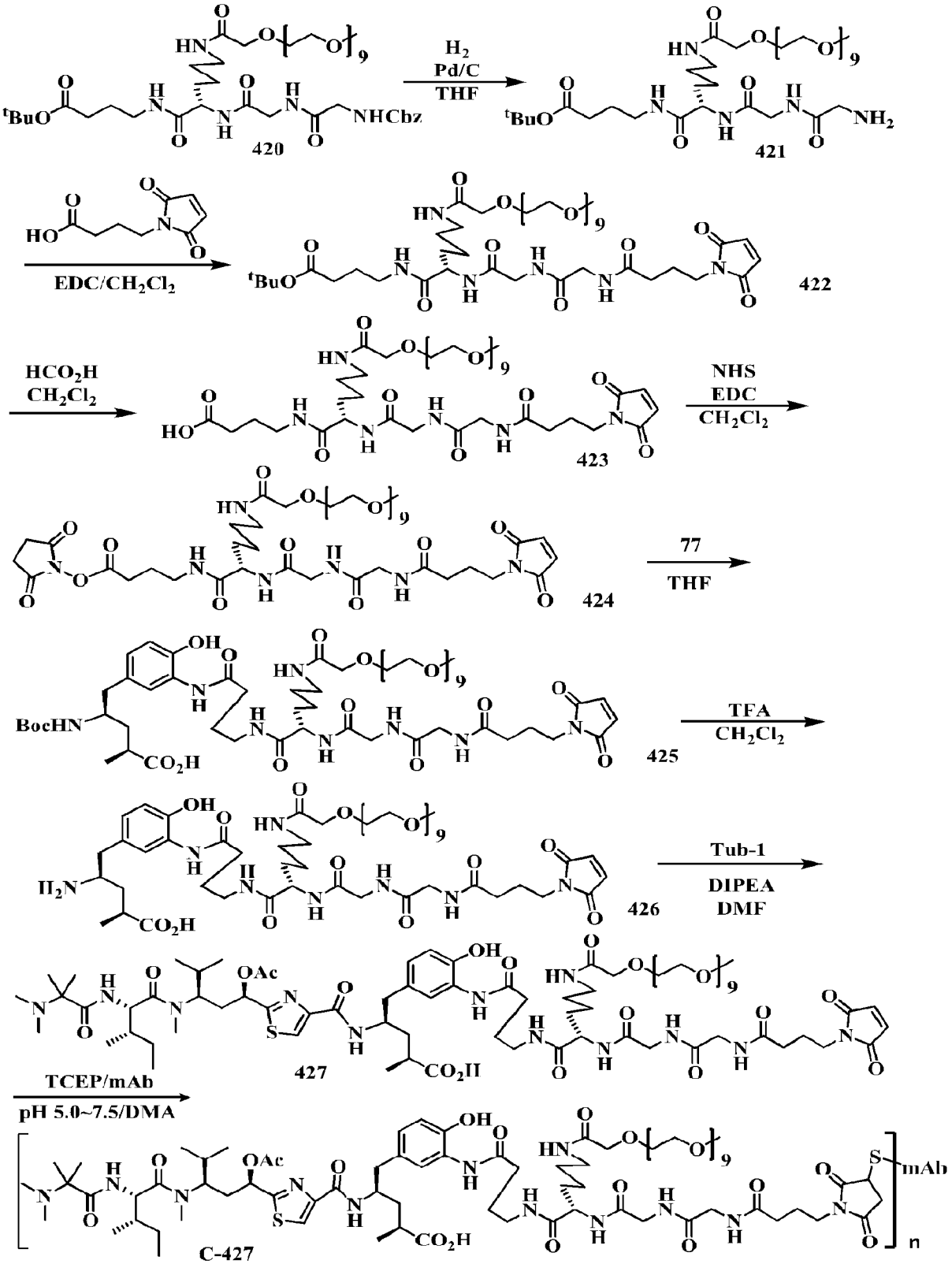

Fig. 30

CA 03236754 2024-4-30

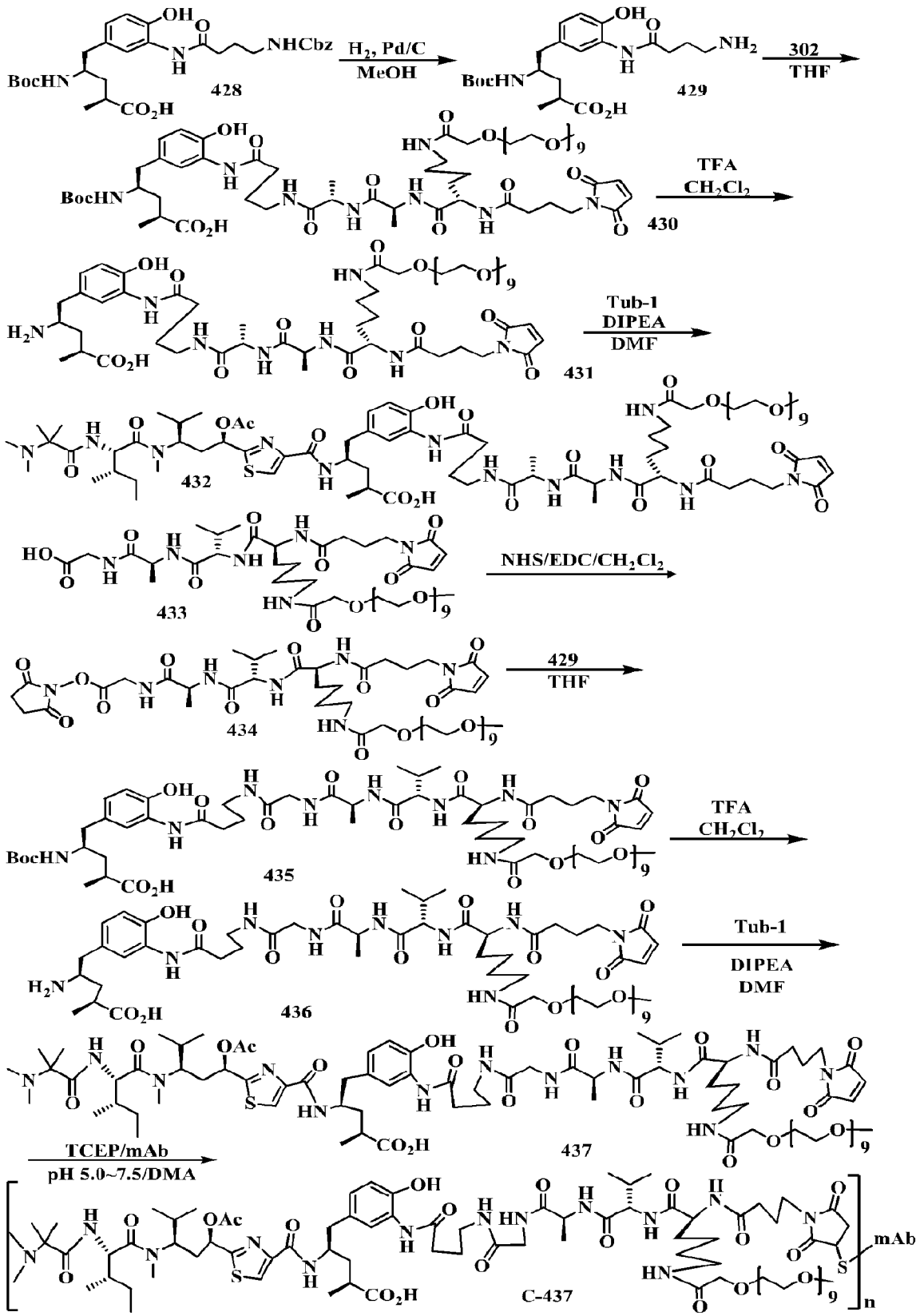

Fig. 31

CA 03236754 2024-4-30

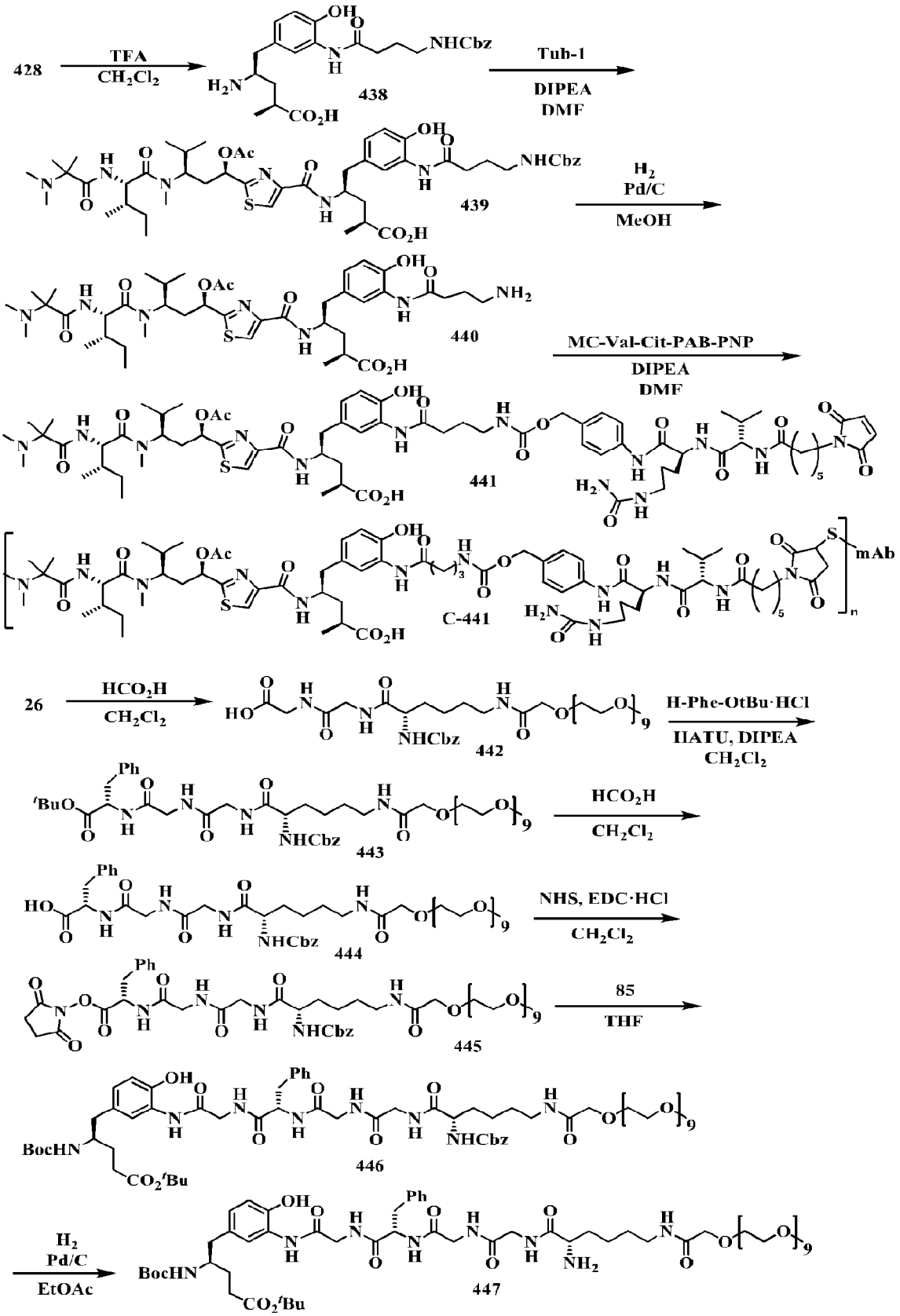

Fig. 32

CA 03236754 2024-4-30

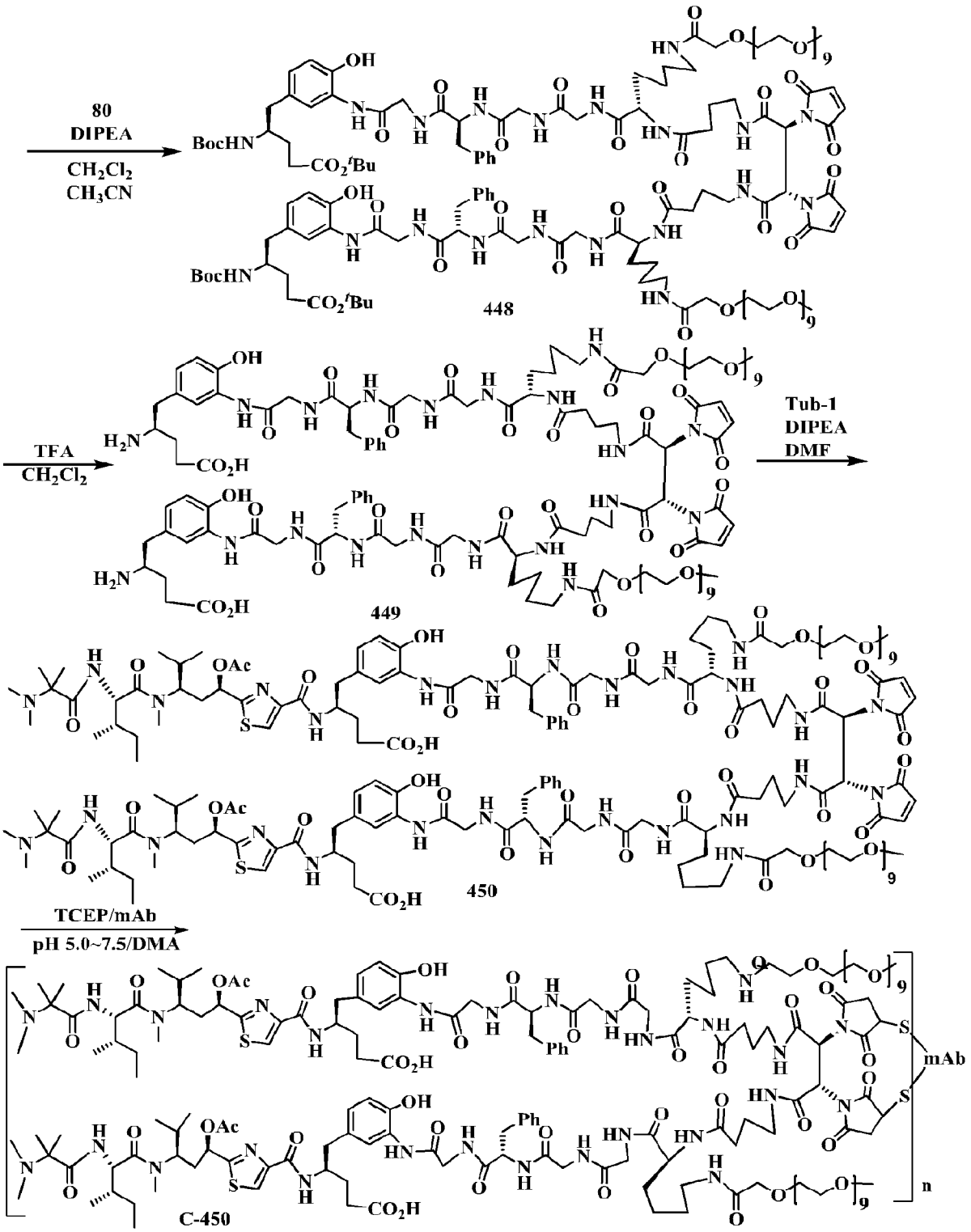

Fig. 33

CA 03236754 2024-4-30

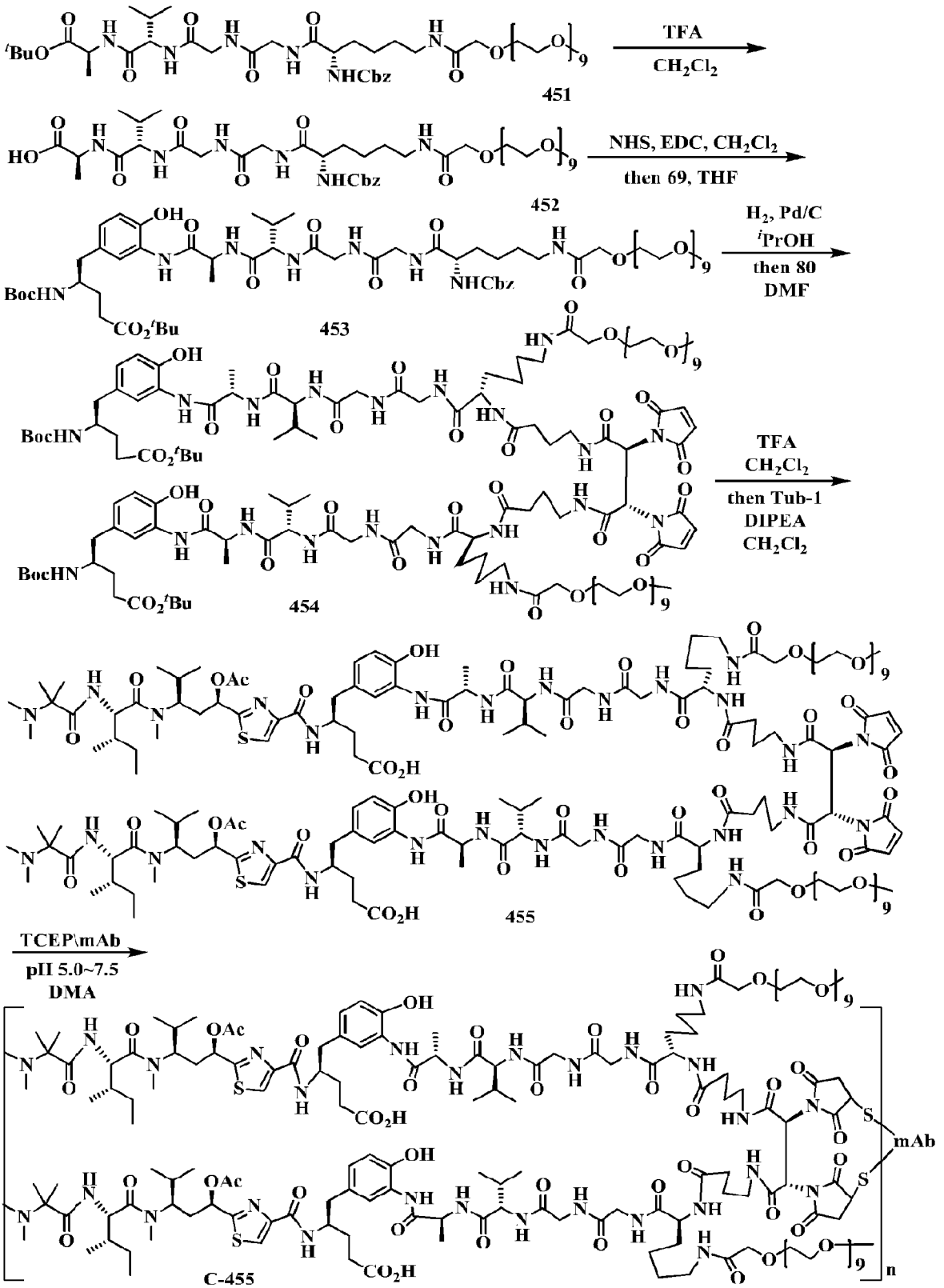

Fig. 34

CA 03236754 2024-4-30

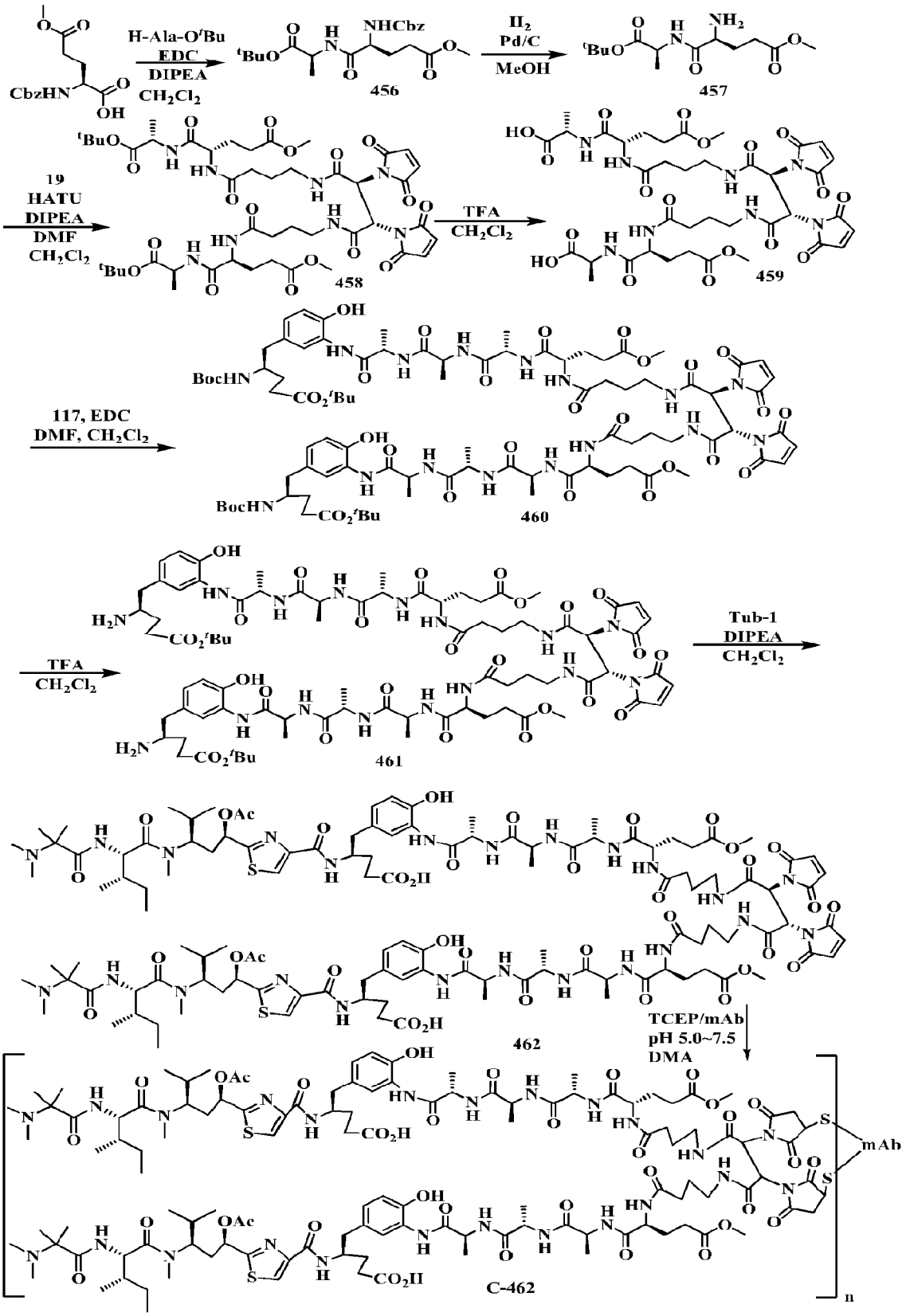

Fig. 35

CA 03236754 2024-4-30

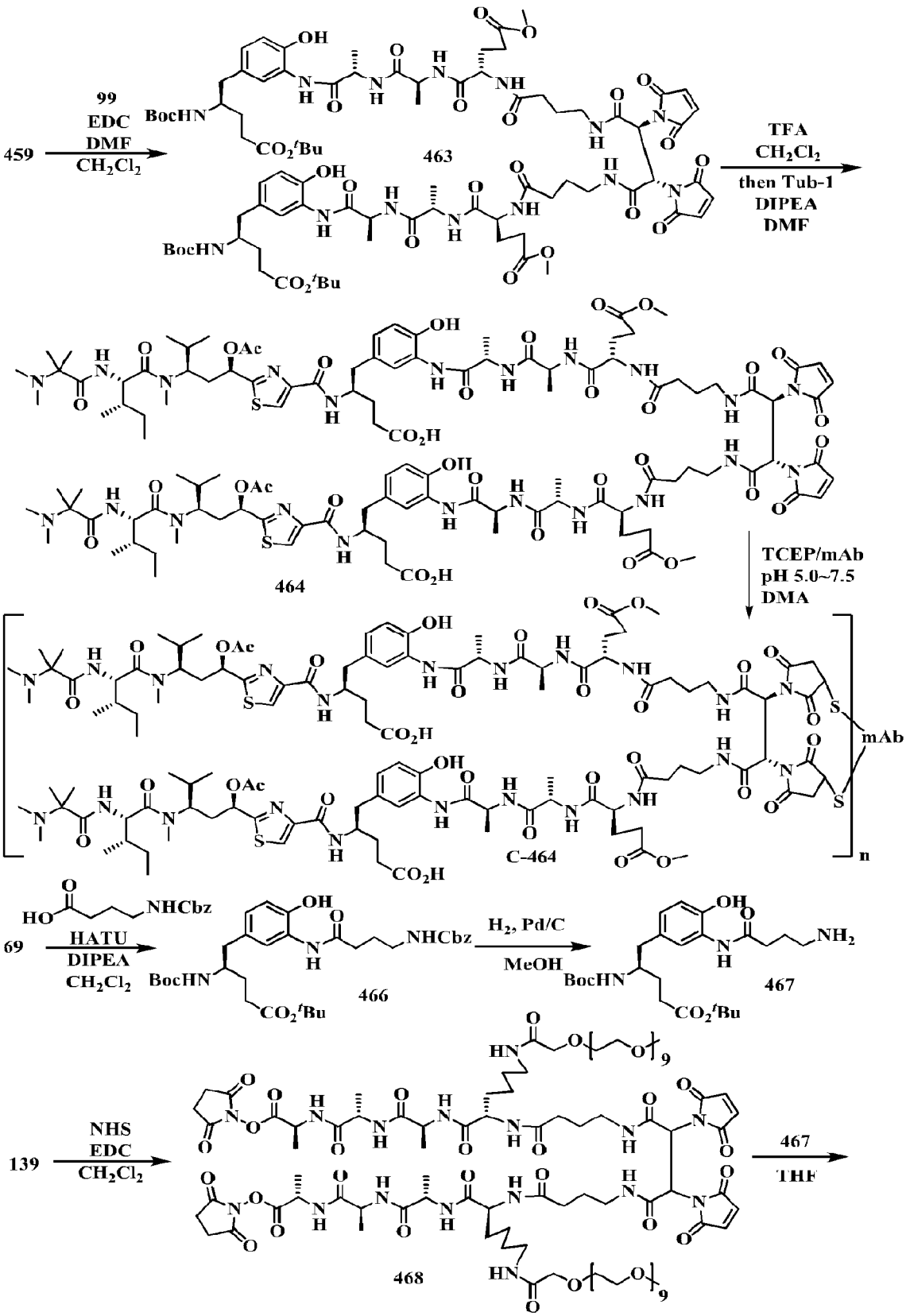

Fig. 36

CA 03236754 2024-4-30

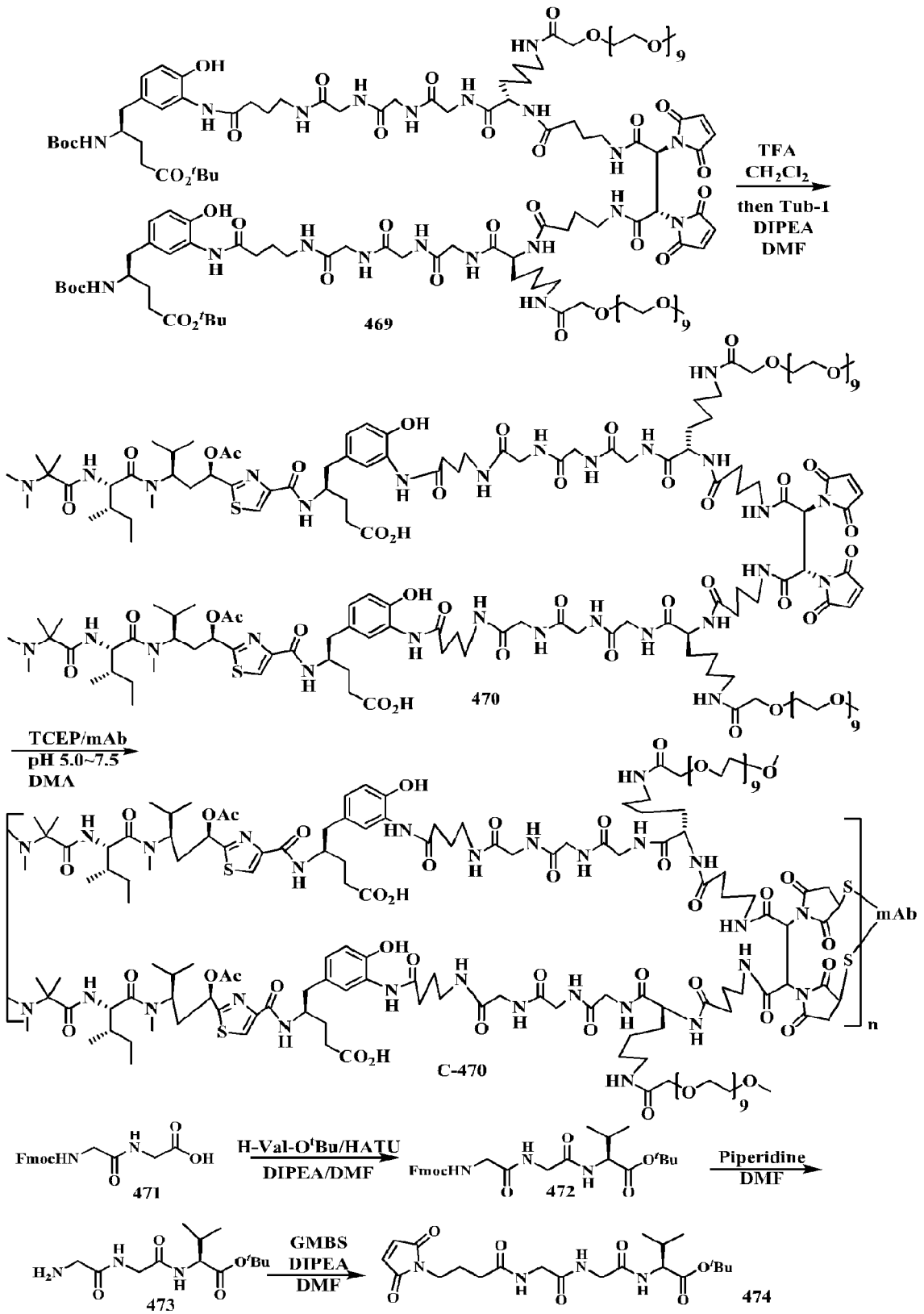

Fig. 37

CA 03236754 2024-4-30

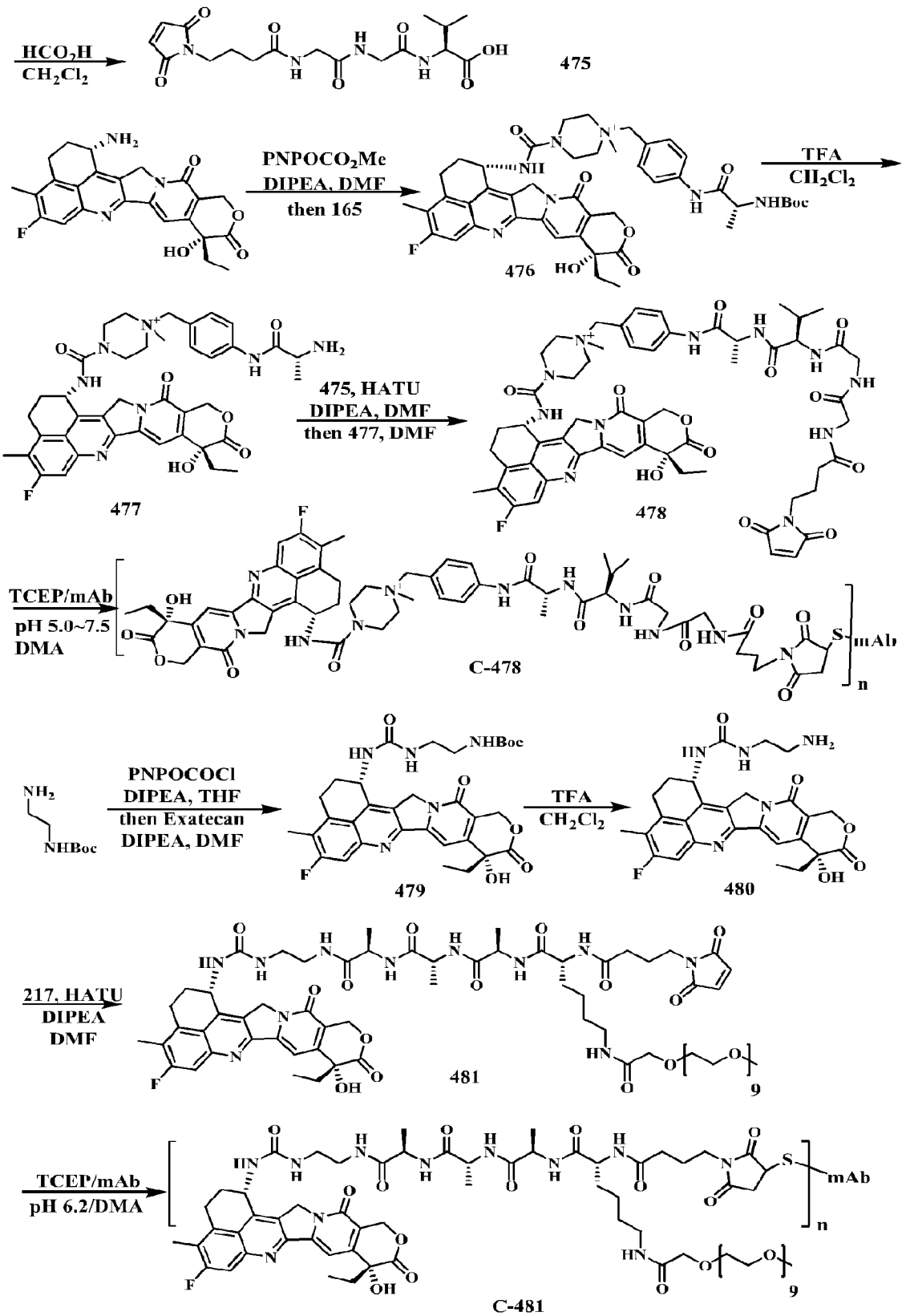

Fig. 38

CA 03236754 2024-4-30

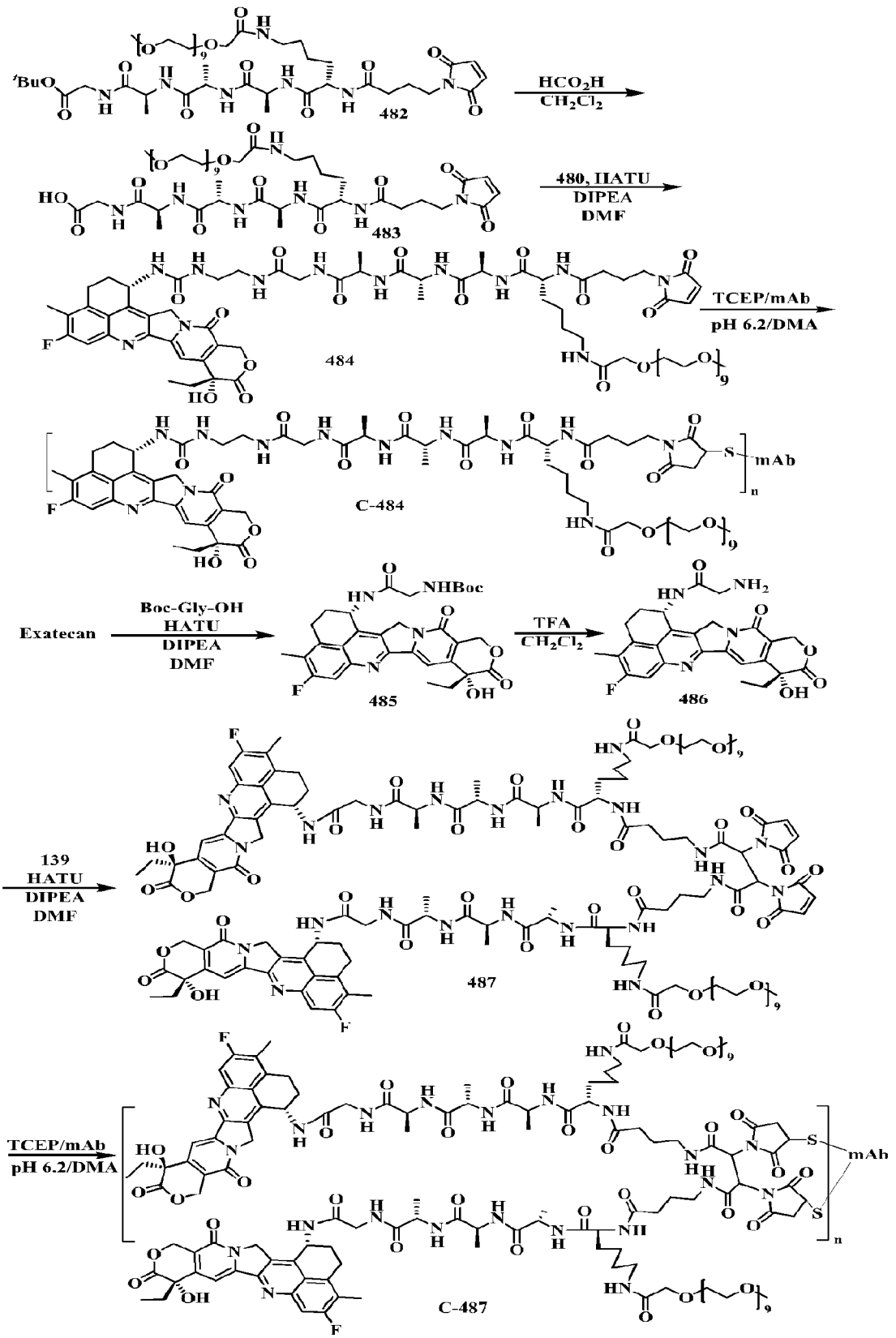

Fig. 39

CA 03236754 2024-4-30

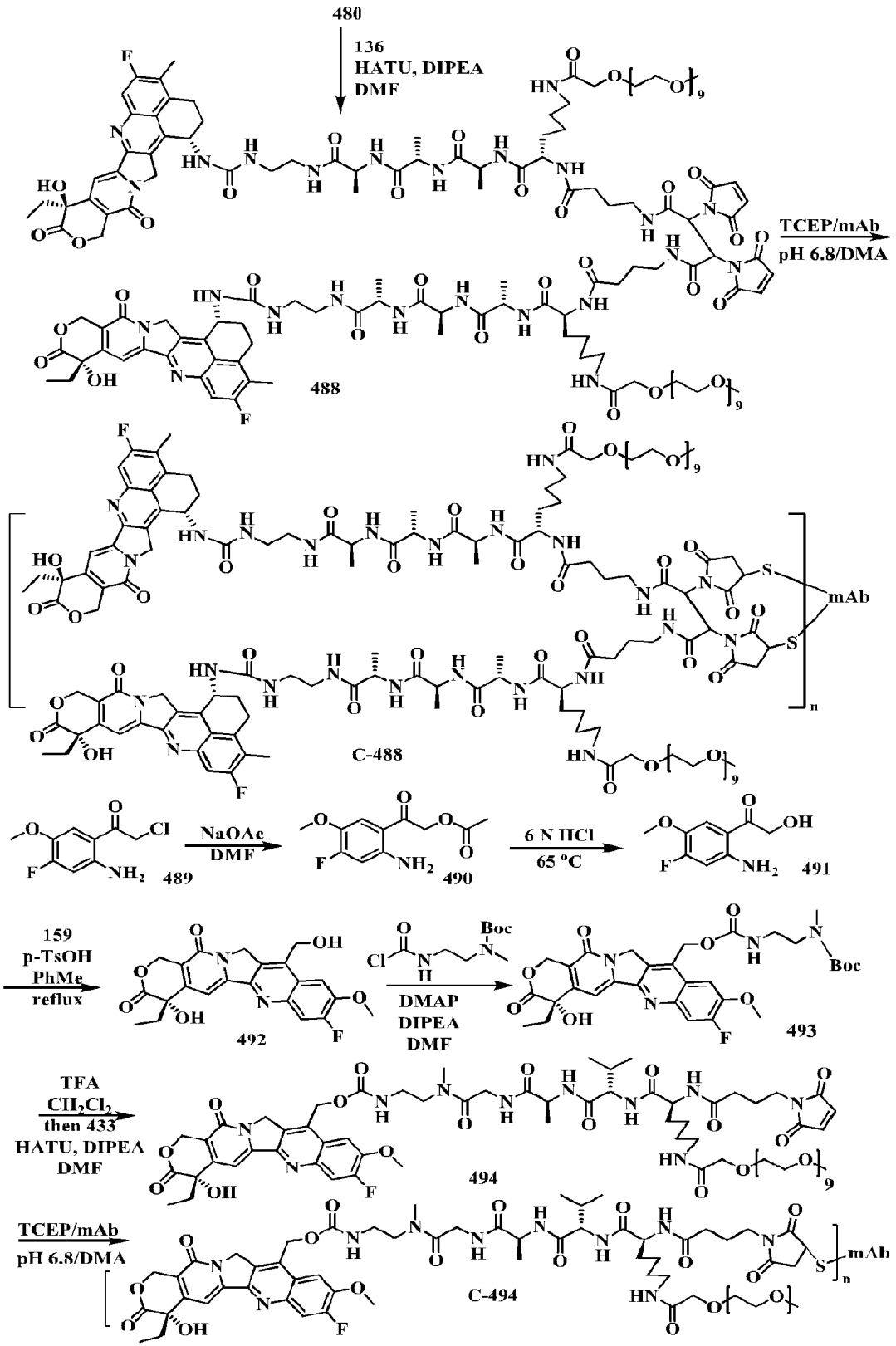

Fig. 40

CA 03236754 2024-4-30

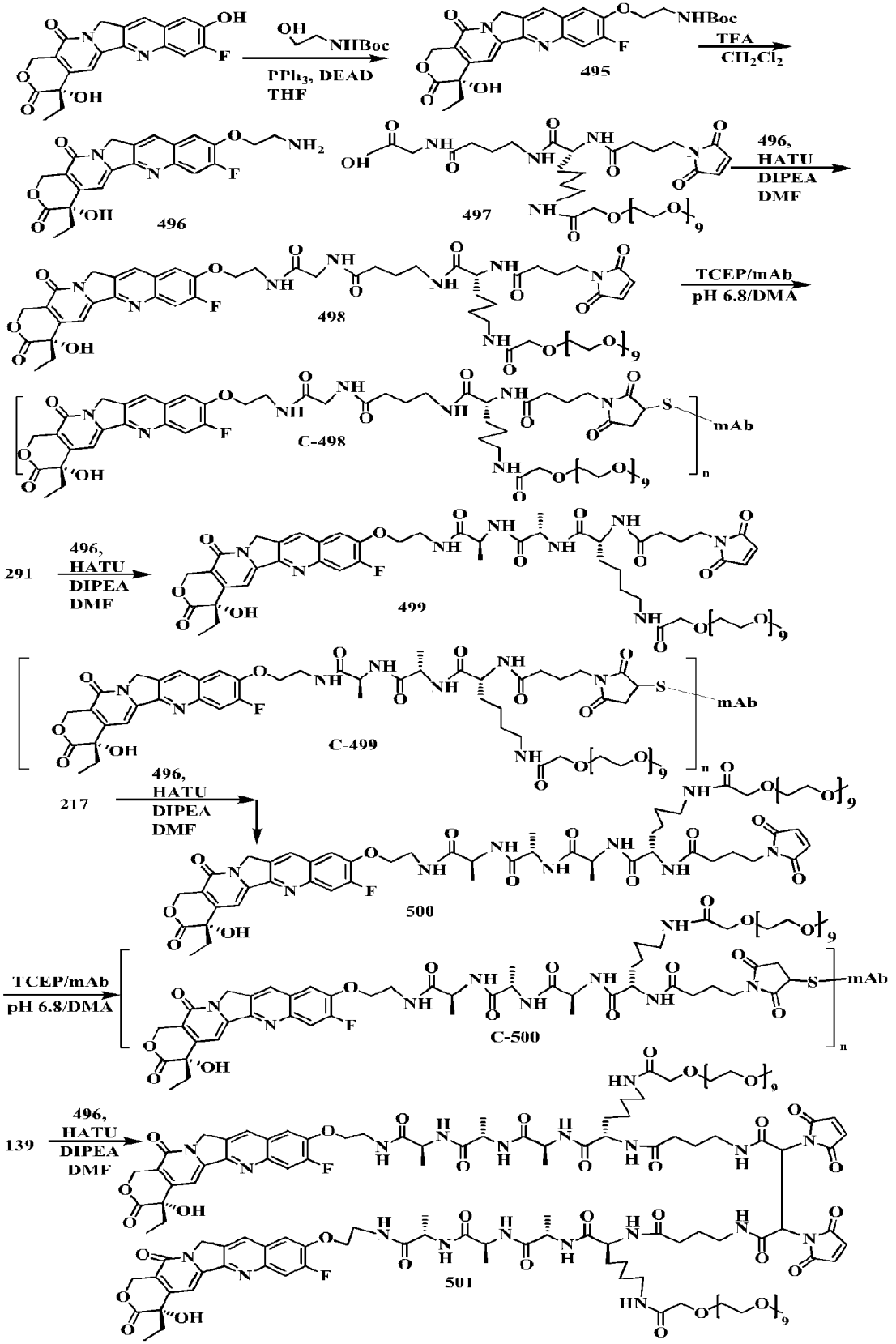

Fig. 41

CA 03236754 2024-4-30

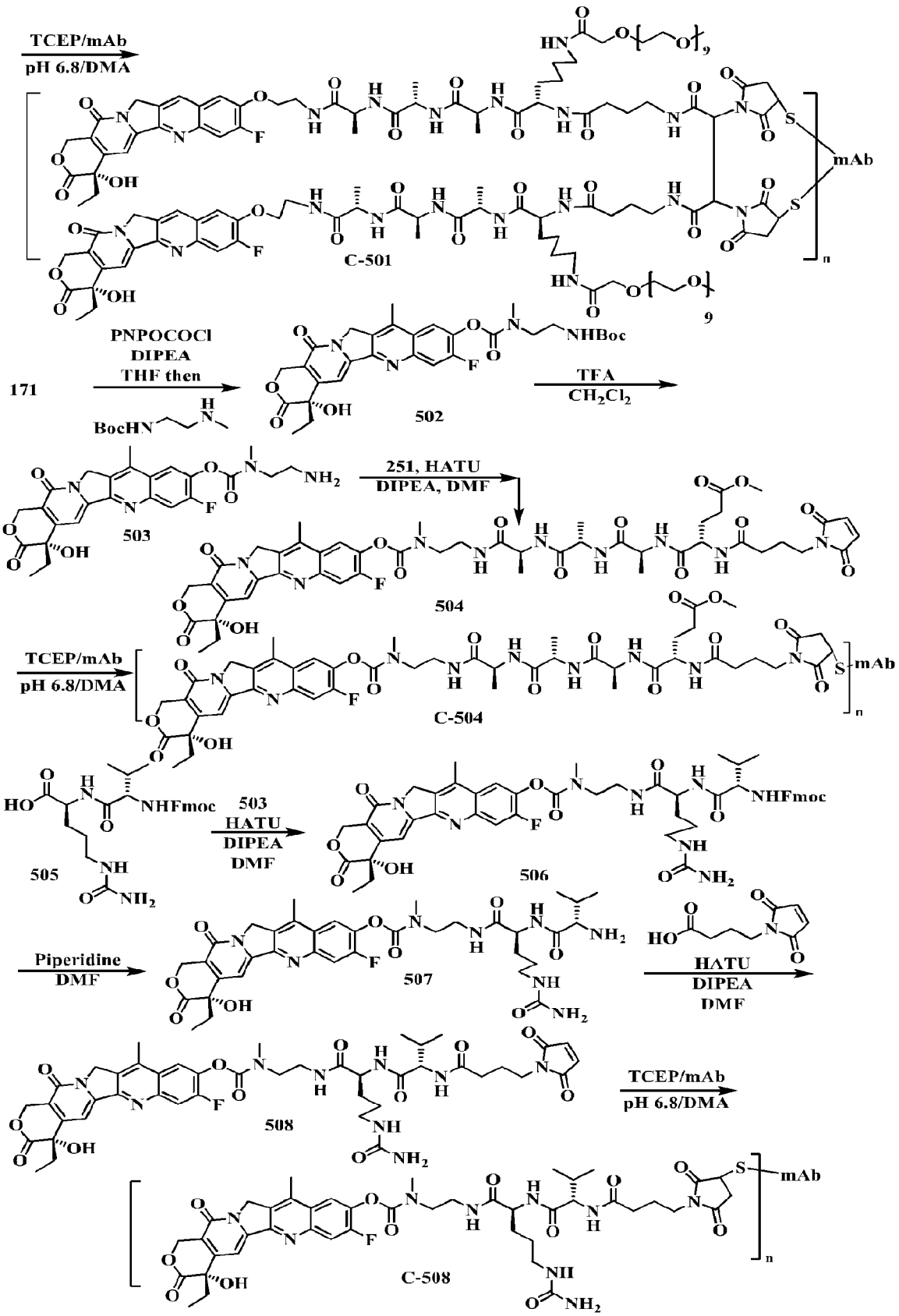

Fig. 42

CA 03236754 2024-4-30

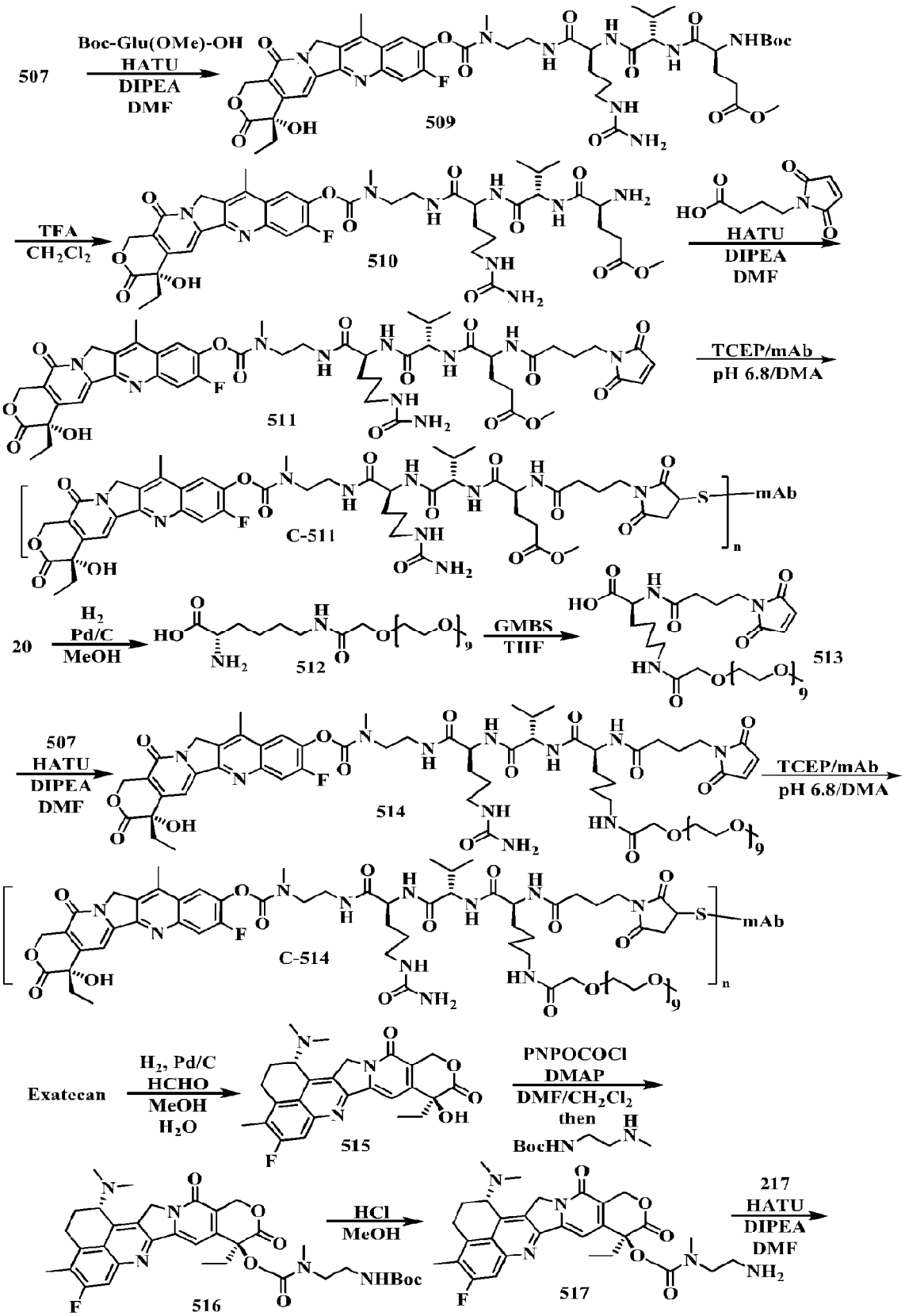

Fig. 43

CA 03236754 2024-4-30

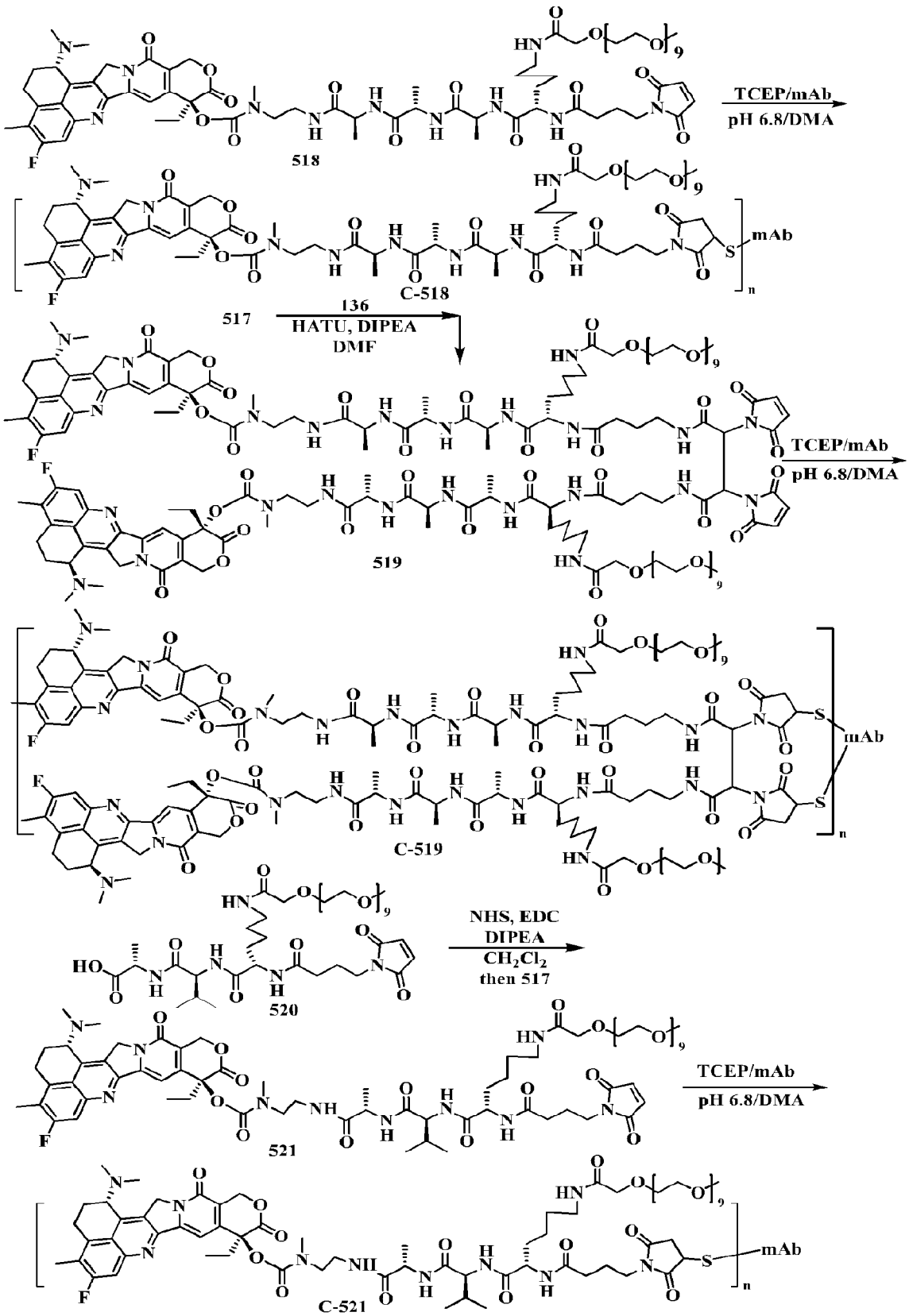

Fig. 44

CA 03236754 2024-4-30

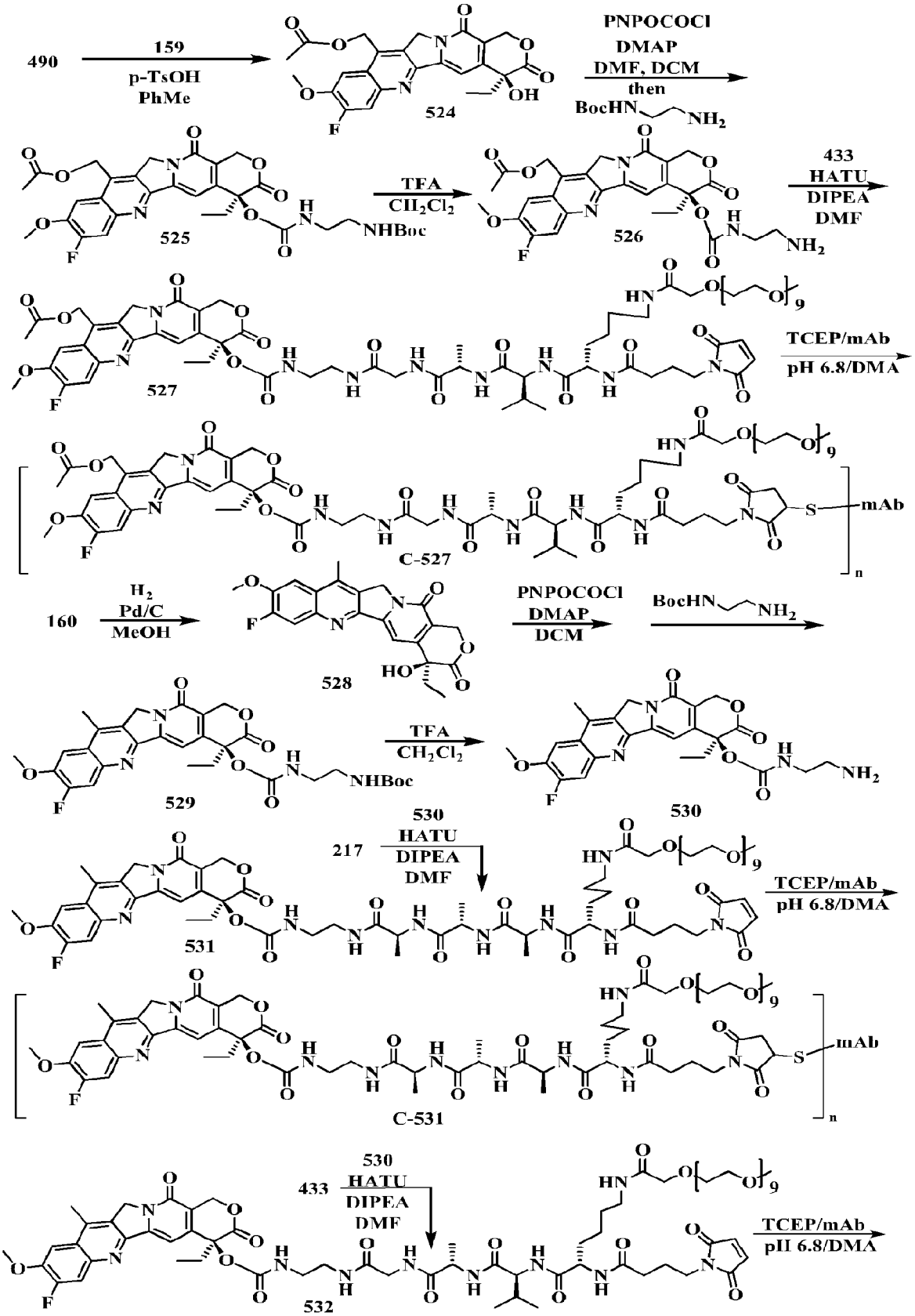

Fig. 45

CA 03236754 2024-4-30

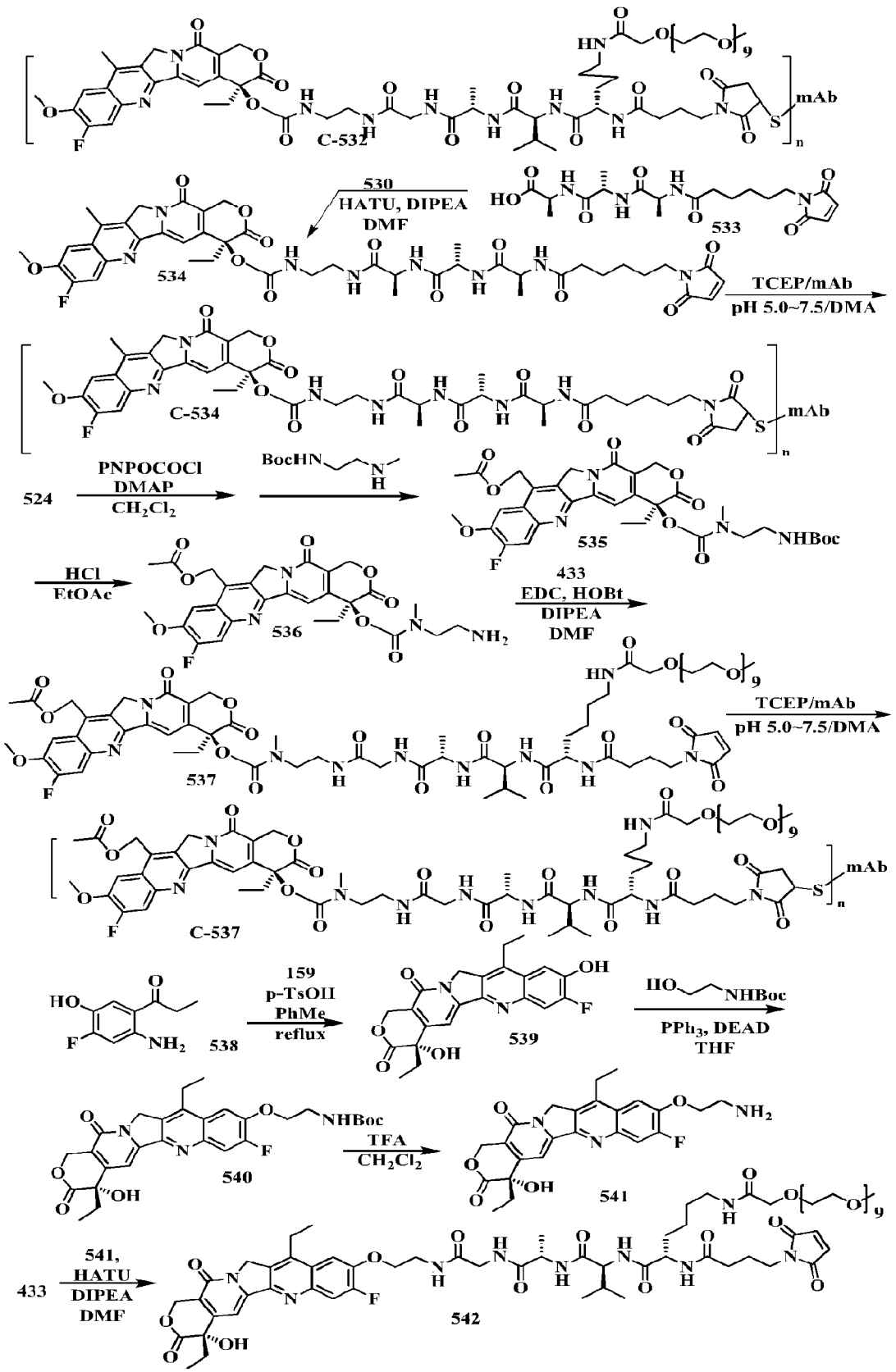

Fig. 46

CA 03236754 2024-4-30

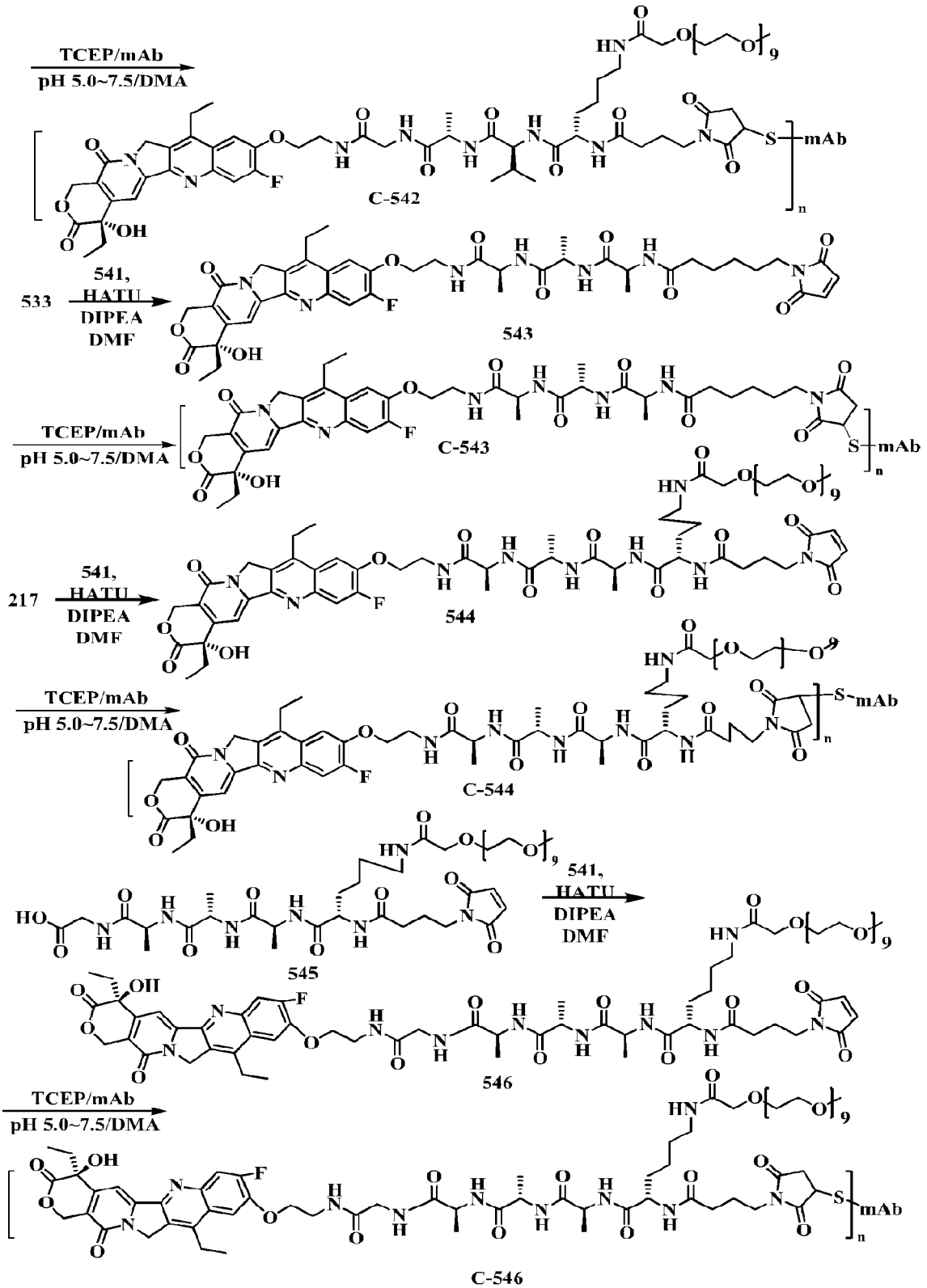

Fig. 47

CA 03236754 2024-4-30

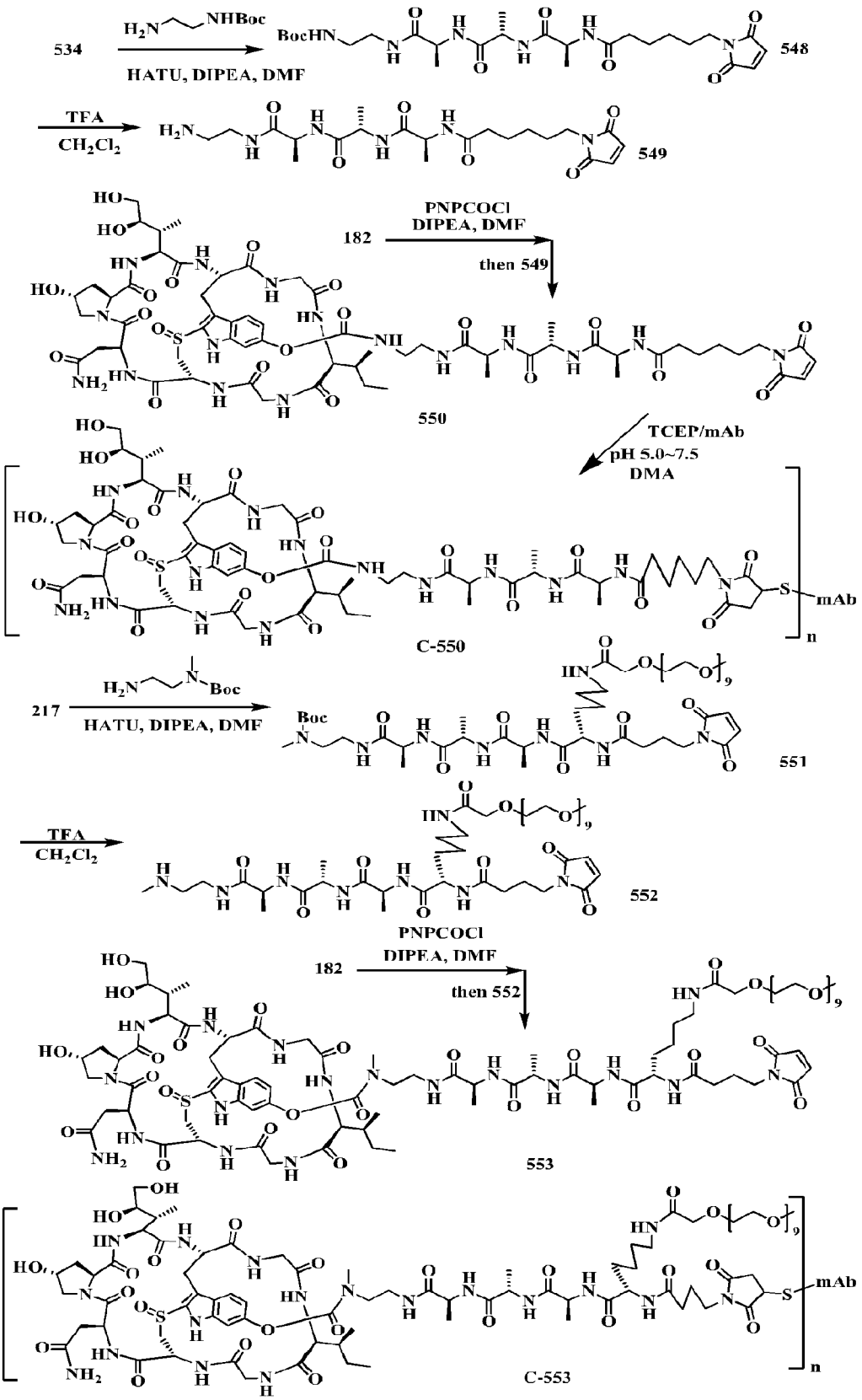

Fig. 48

CA 03236754 2024-4-30

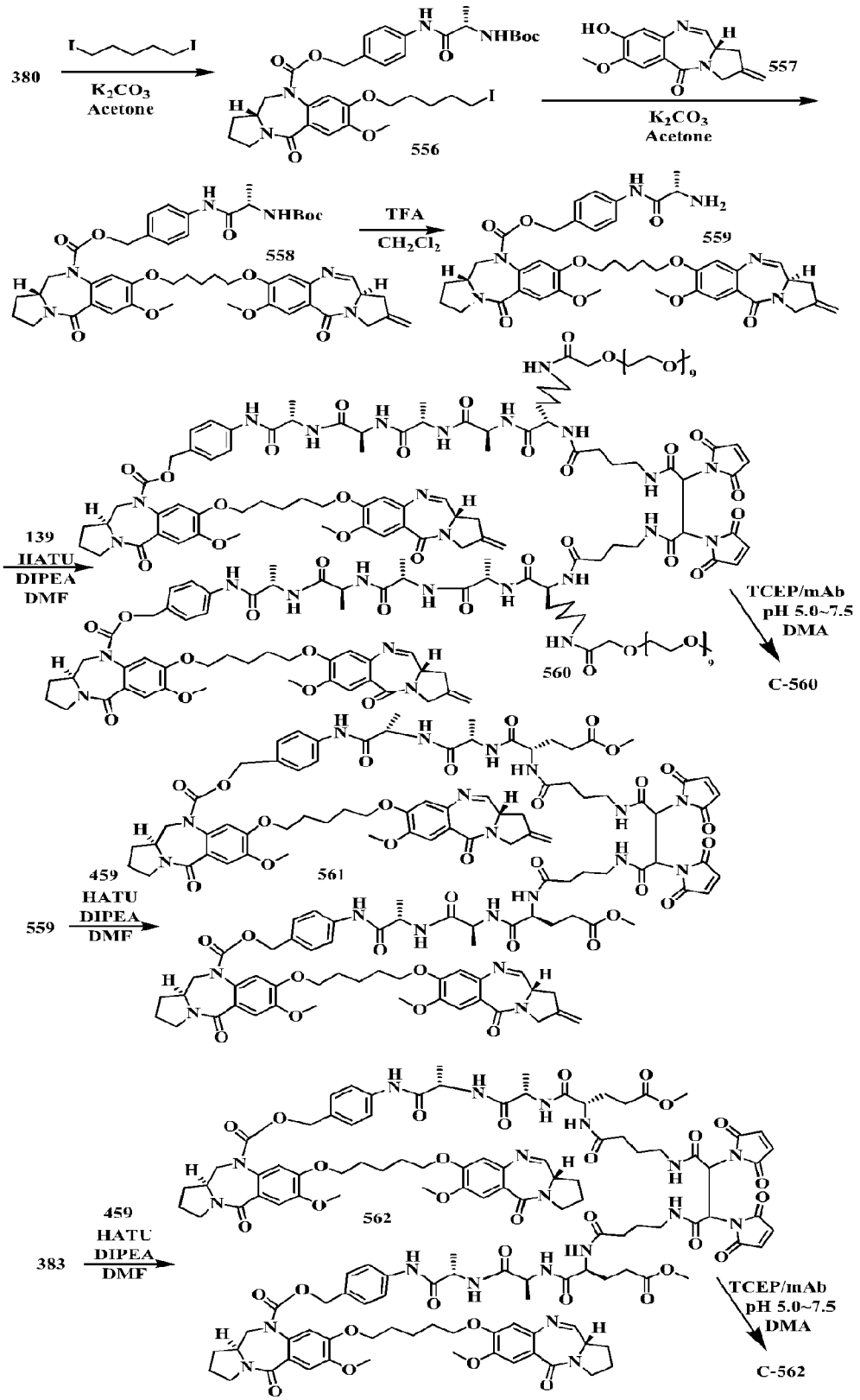

Fig. 49

CA 03236754 2024-4-30

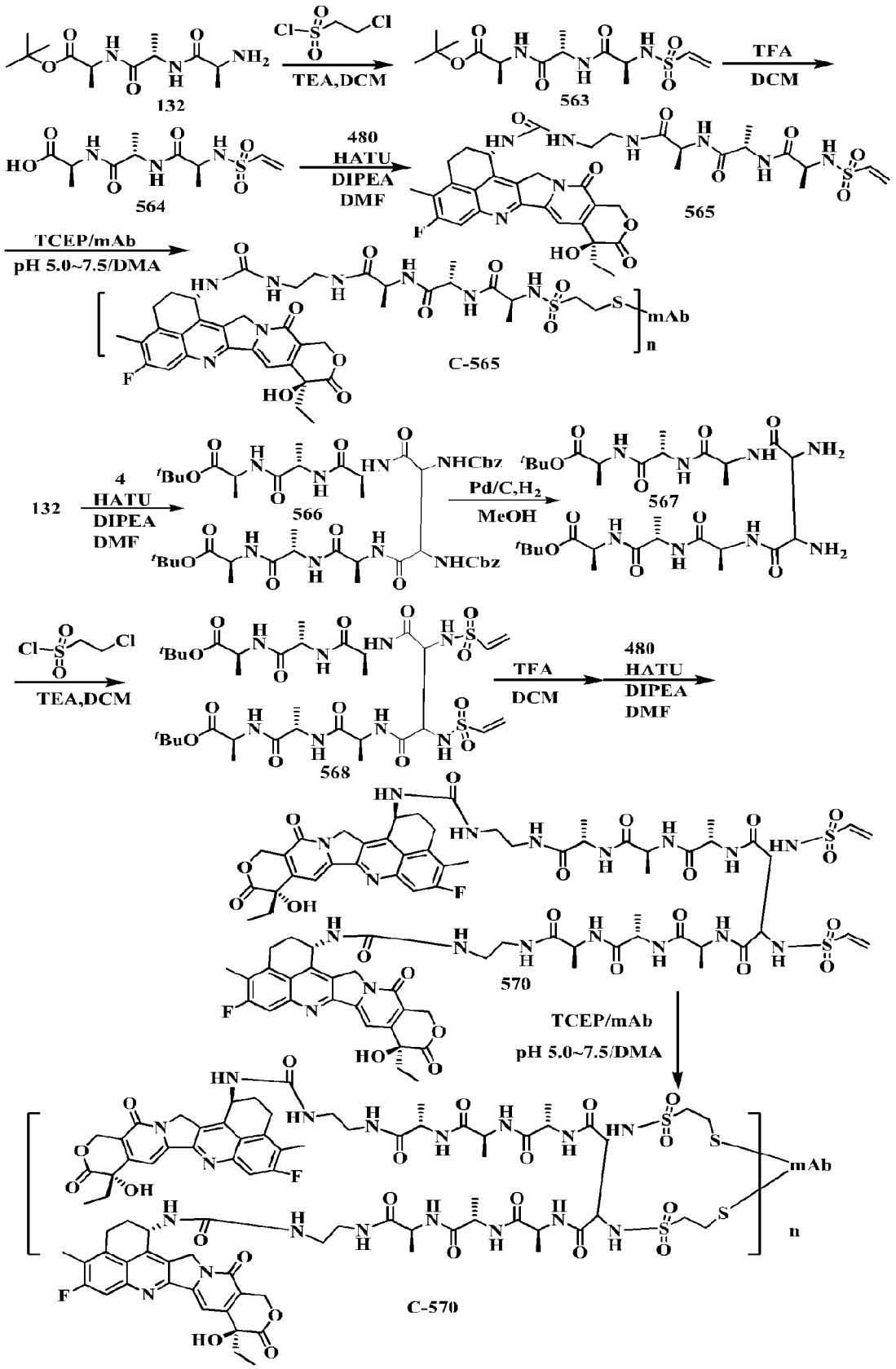

Fig. 50

CA 03236754 2024-4-30

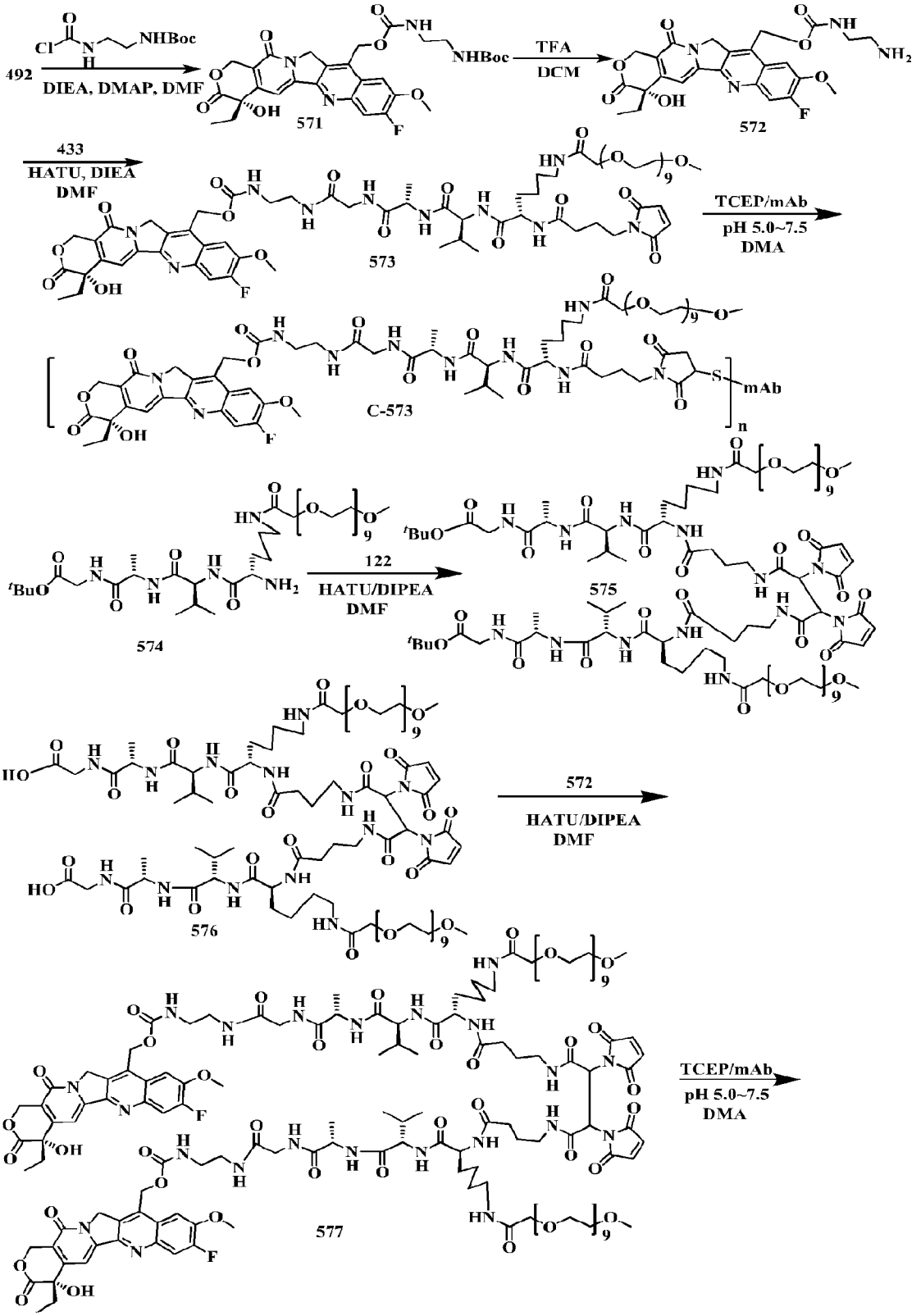

Fig. 51

CA 03236754 2024-4-30

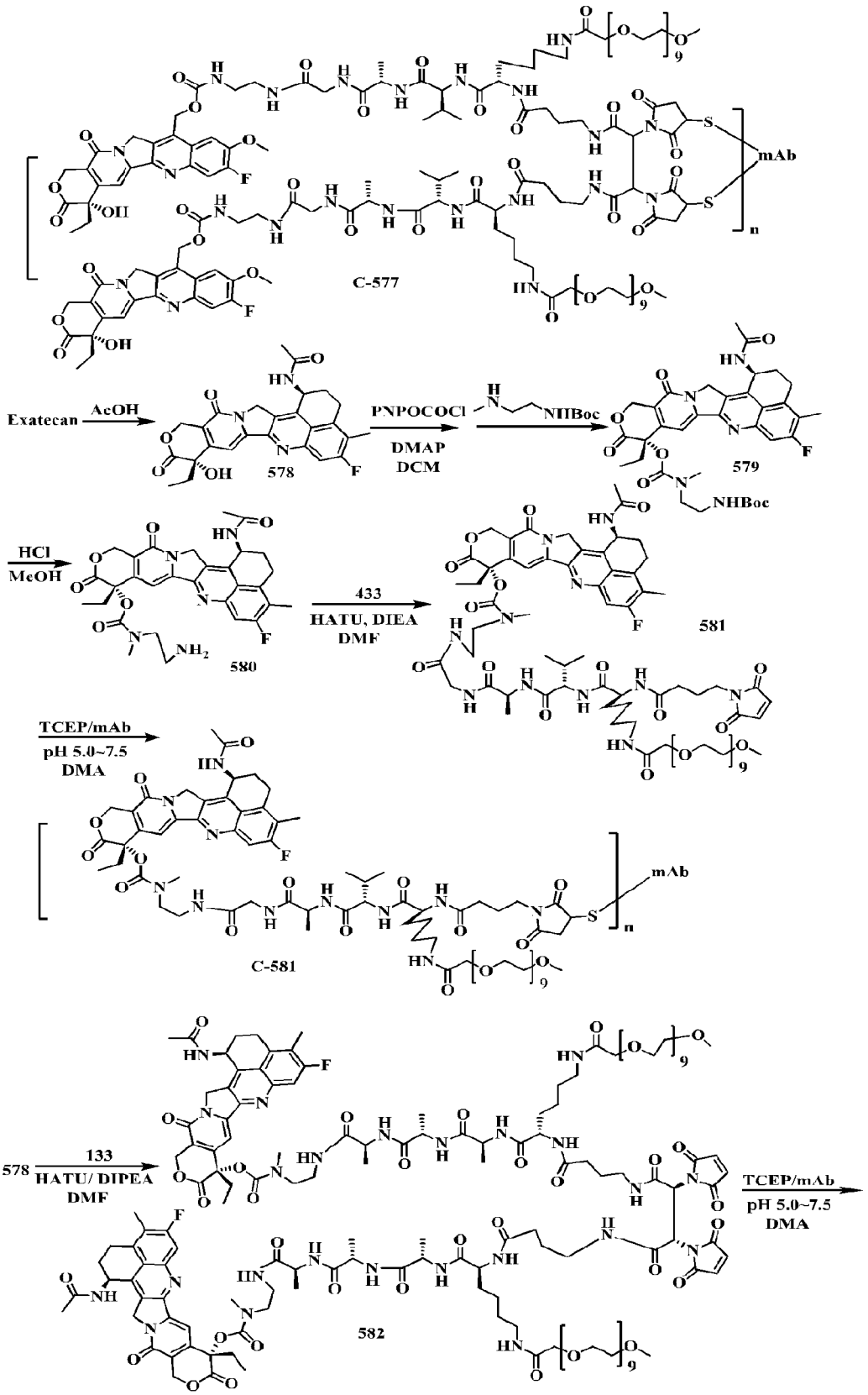

Fig. 52

CA 03236754 2024-4-30

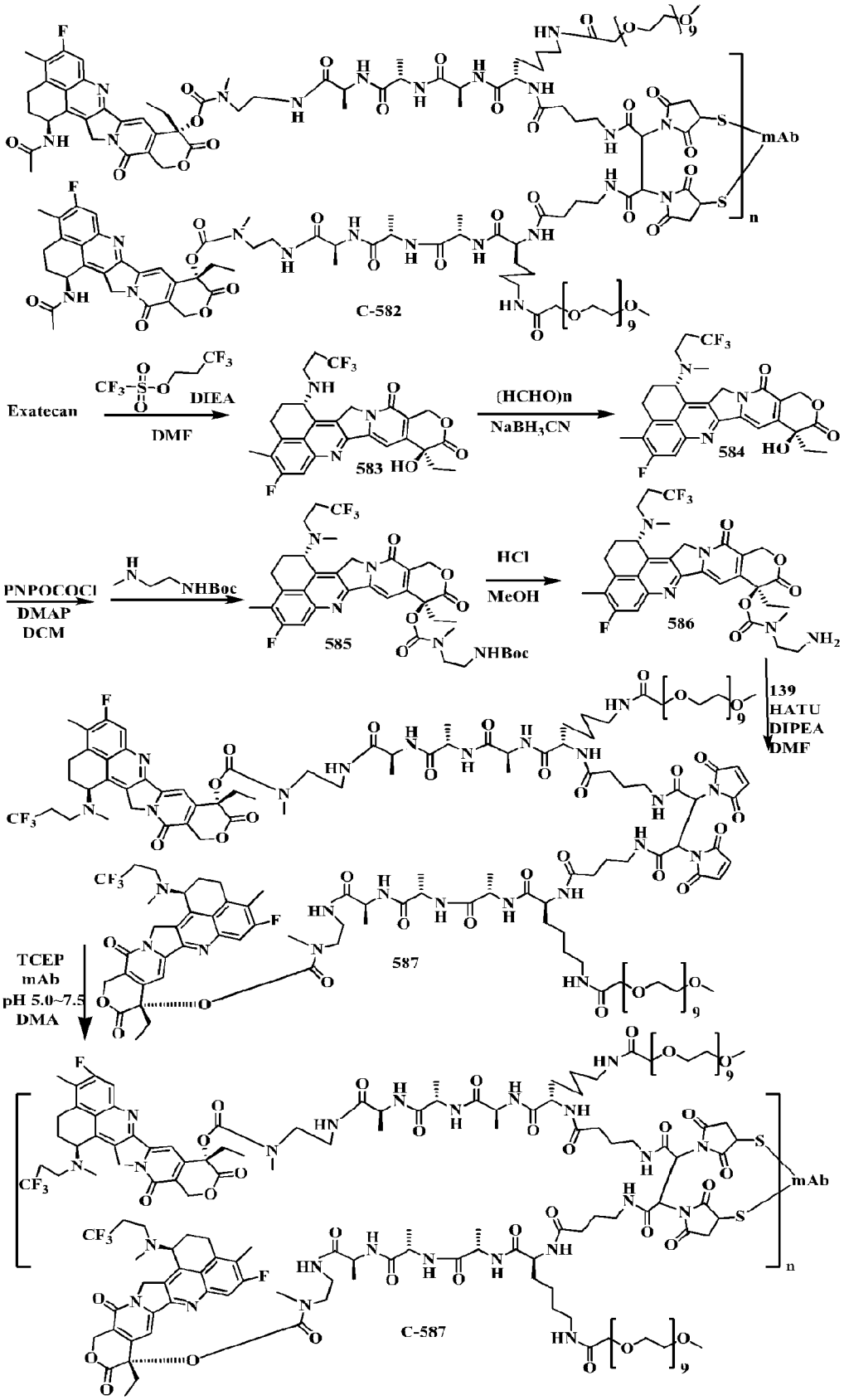

Fig. 53

CA 03236754 2024-4-30

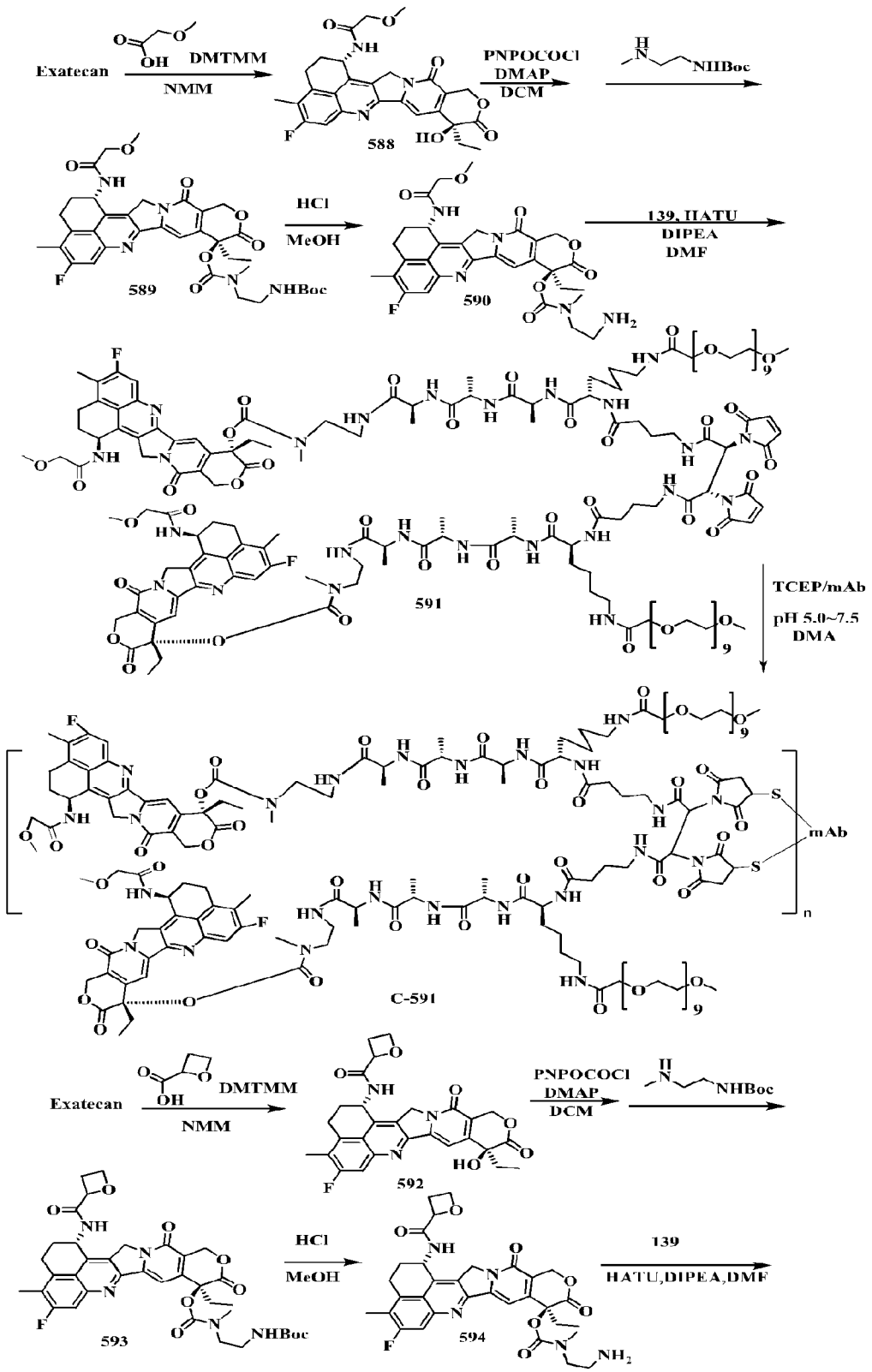

Fig. 54

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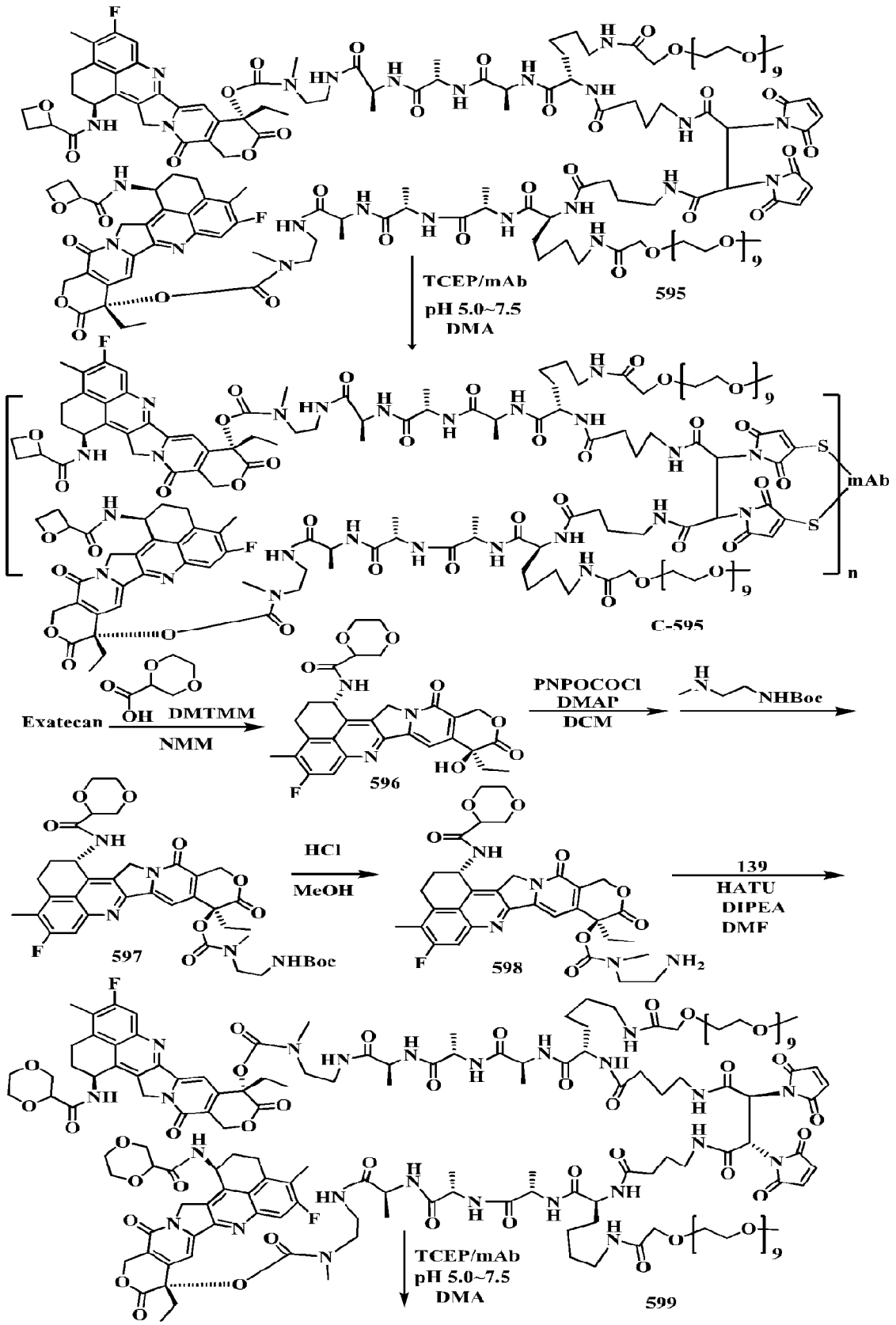

Fig. 55

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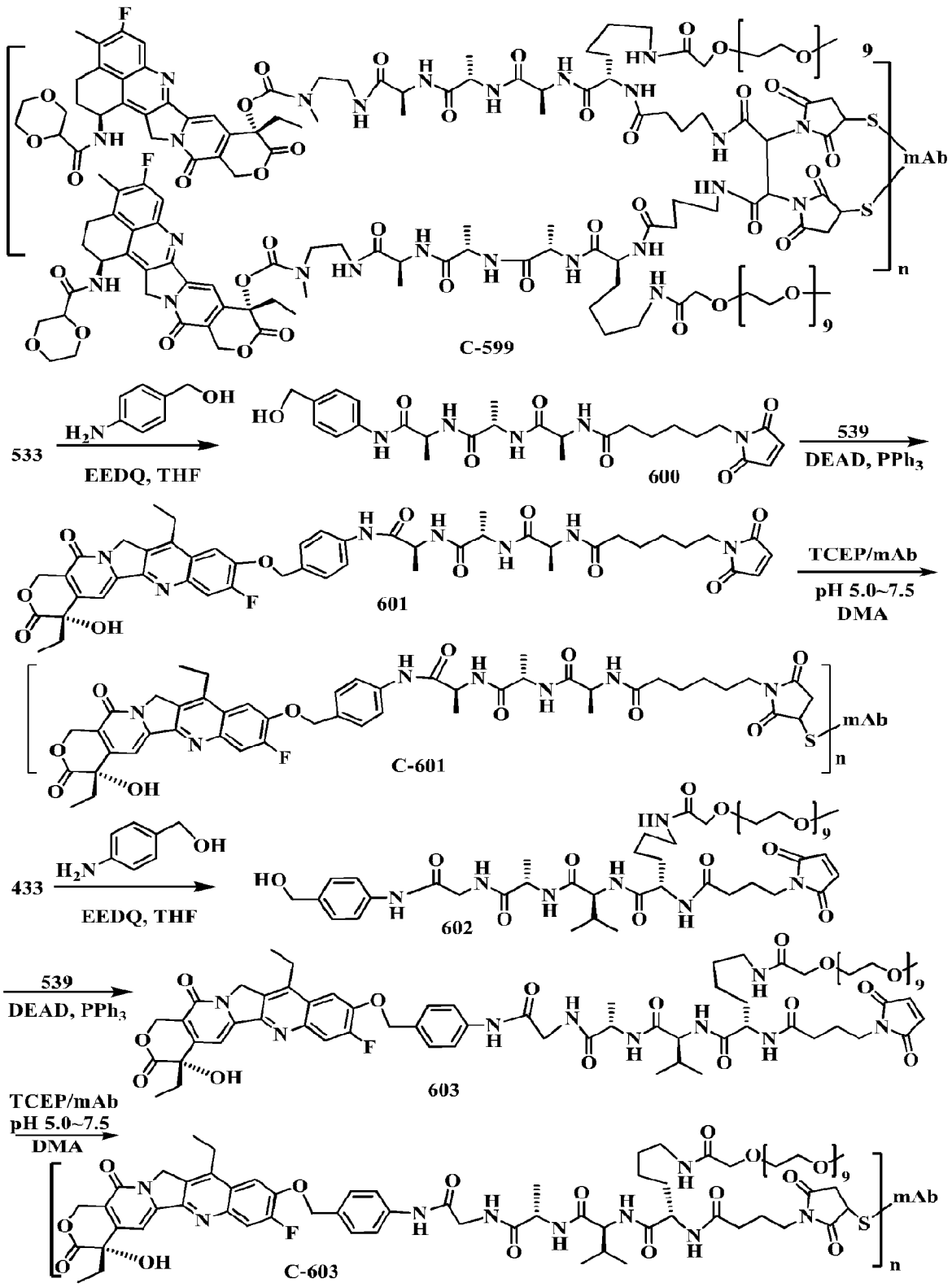

Fig. 56

CA 03236754 2024-4-30

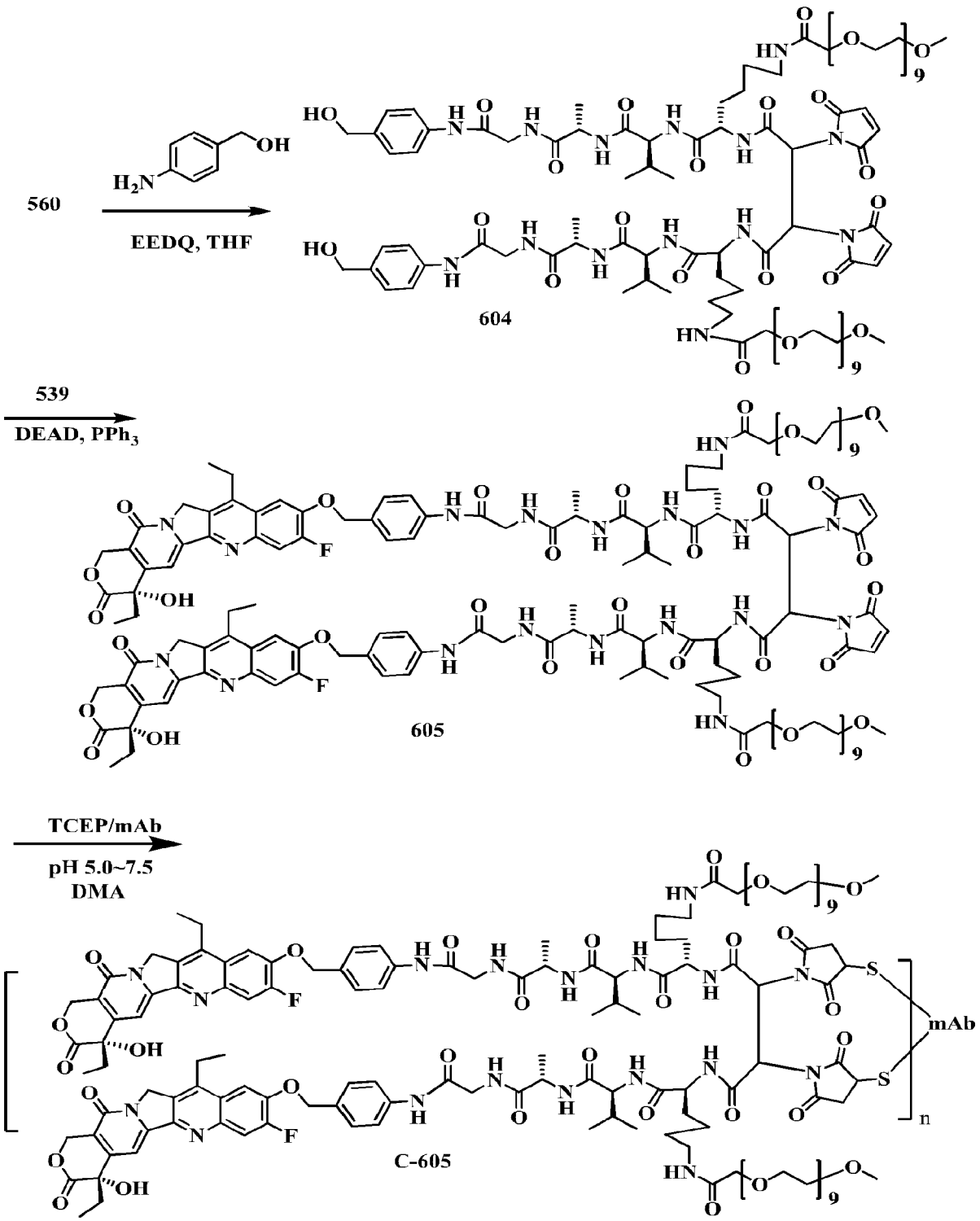

Fig. 57

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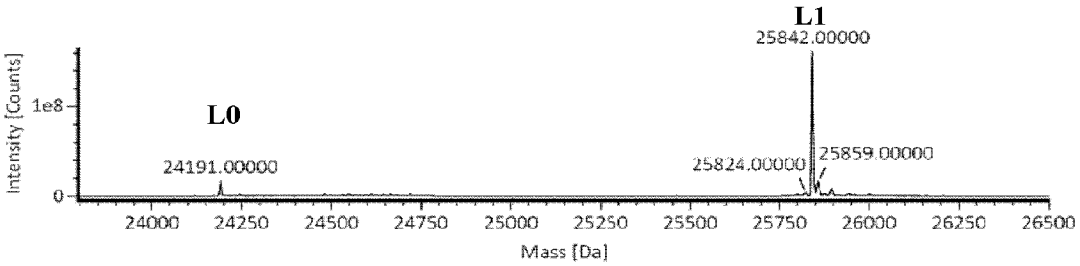
(a). A light chain of a BCMA-Tub ADC:



(b). A heavy chain of a BCMA-Tub ADC:

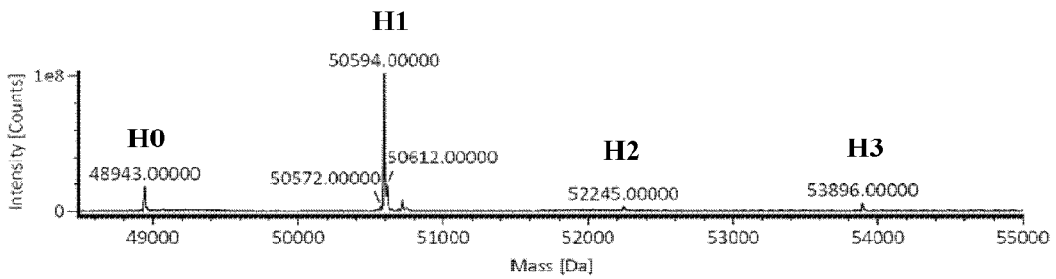


Fig. 58 (a), (b)

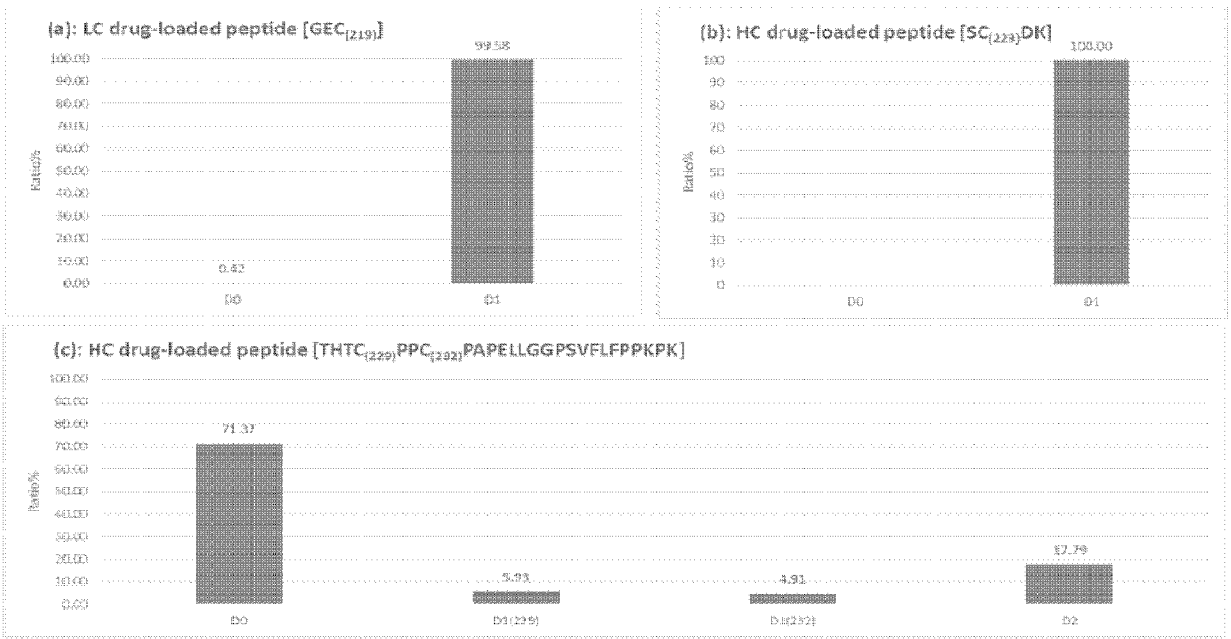


Fig. 59

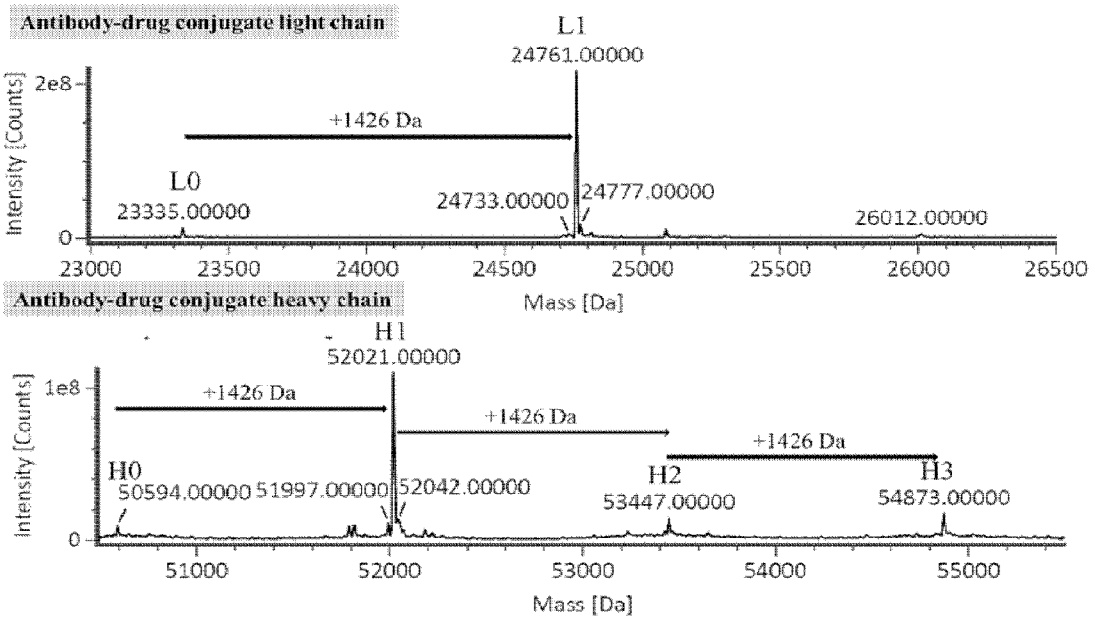

Antibody-drug conjugate light chain
L1
24761.00000
2e8
Intensity [Counts]
+1426 Da
L0
23335.00000
24733.00000
24777.00000
26012.00000
0
23000
23500
24000
24500
25000
25500
26000
26500
Mass [Da]
Antibody-drug conjugate heavy chain
H1
52021.00000
1e8
+1426 Da
+1426 Da
+1426 Da
H0
50594.00000
51997.00000
52042.00000
H2
53447.00000
H3
54873.00000
0
51000
52000
53000
54000
55000
Mass [Da]

Fig . 60

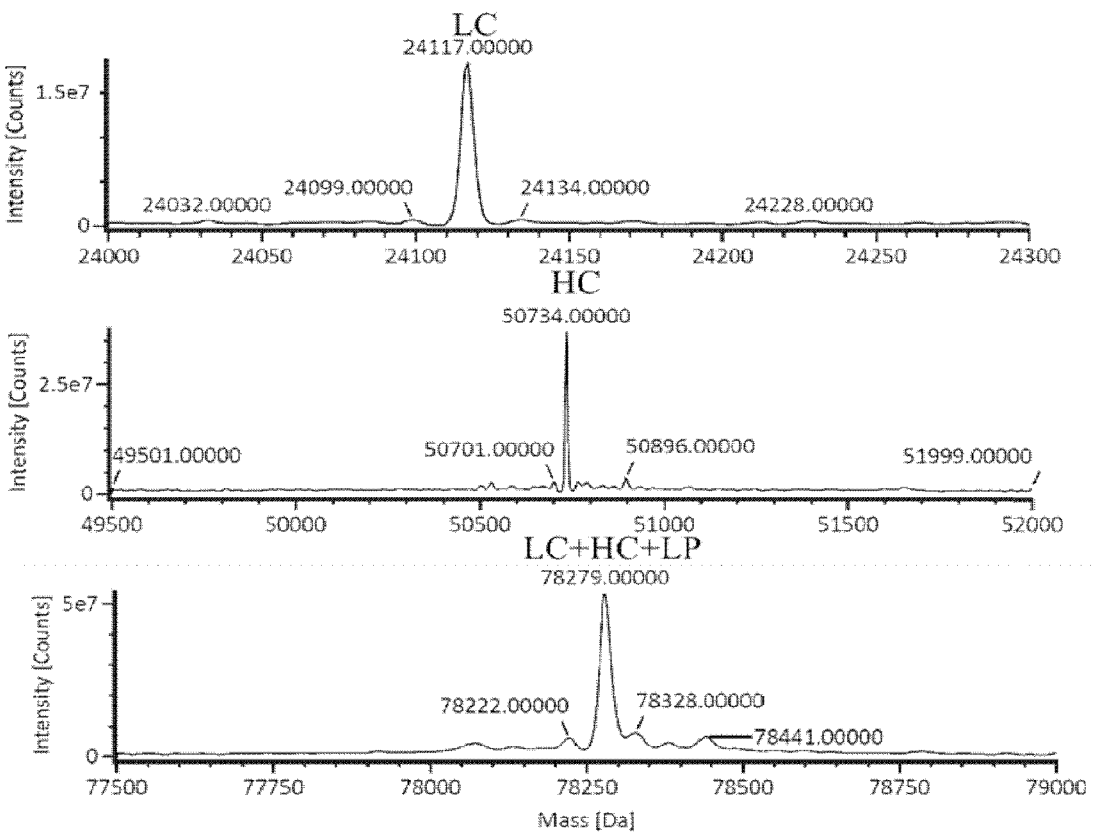

LC
24117.00000
1.5e7
Intensity [Counts]
24032.00000
24099.00000
24134.00000
24228.00000
0
24000
24050
24100
24150
24200
24250
24300
HC
50734.00000
2.5e7
Intensity [Counts]
49501.00000
50701.00000
50896.00000
51999.00000
0
49500
50000
50500
51000
51500
52000
LC+HC+LP
78279.00000
5e7
Intensity [Counts]
78222.00000
78328.00000
78441.00000
0
77500
77750
78000
78250
78500
78750
79000
Mass [Da]

Fig. 61

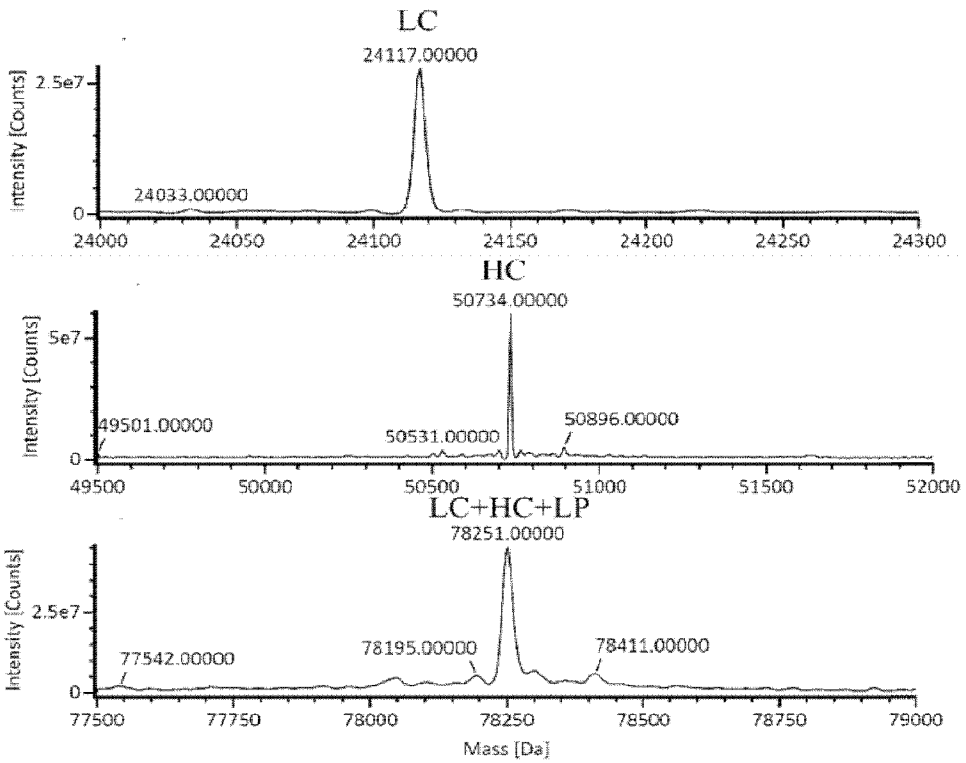


Fig. 62

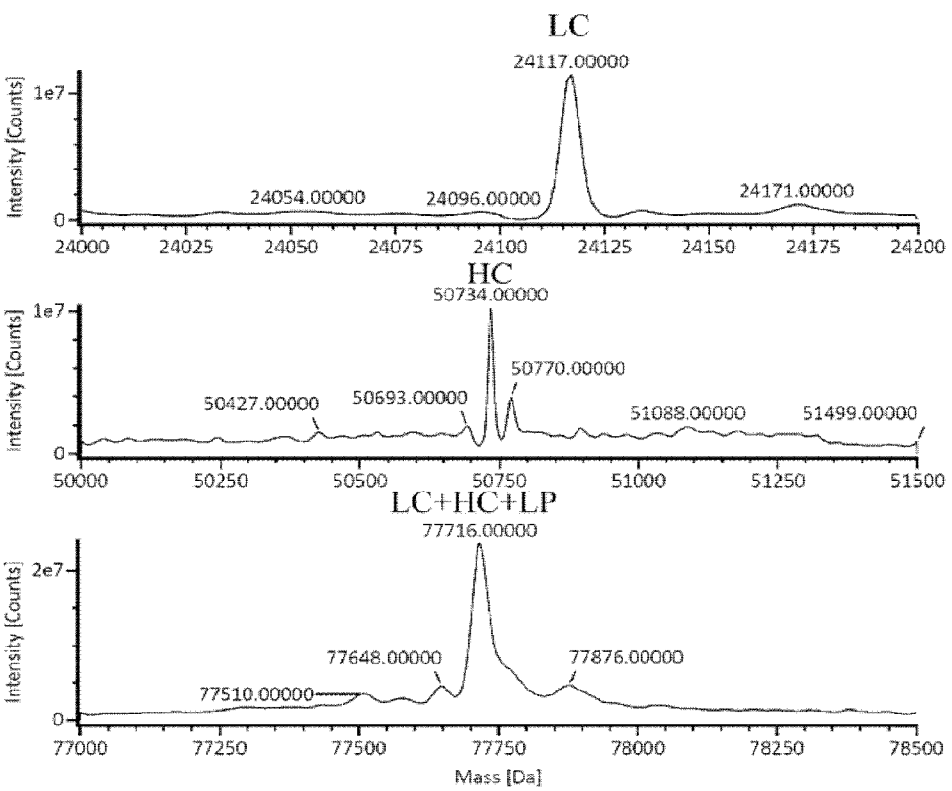


Fig. 63

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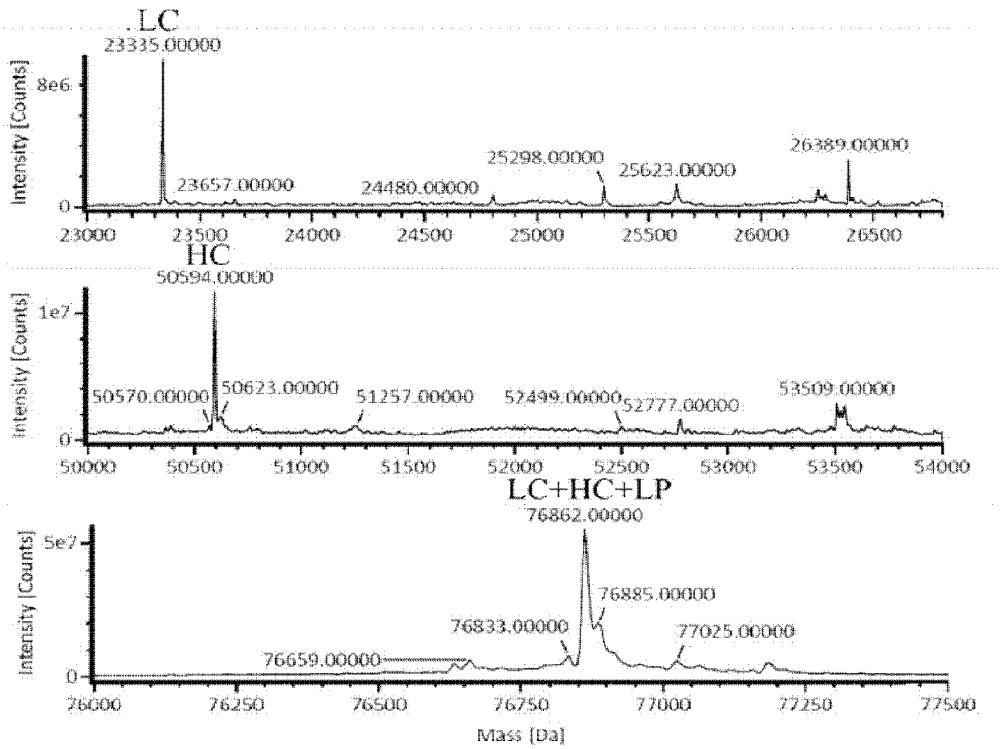

Fig. 64

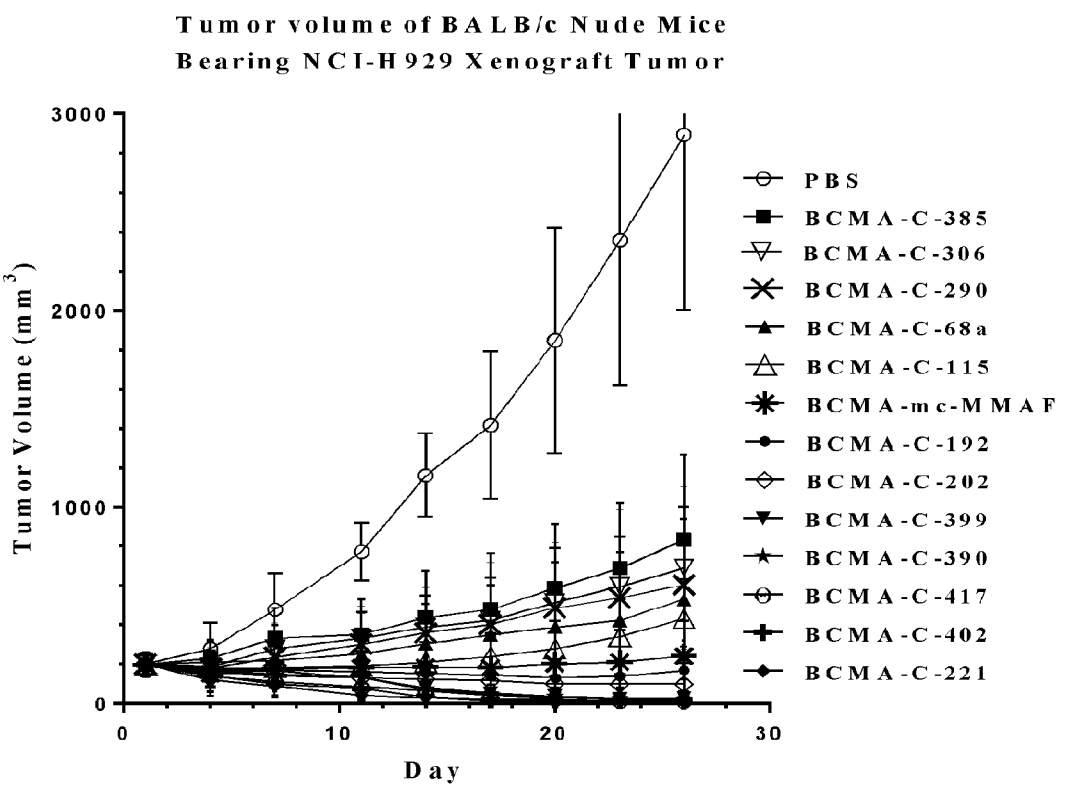

Fig. 65

CA 03236754 2024-4-30

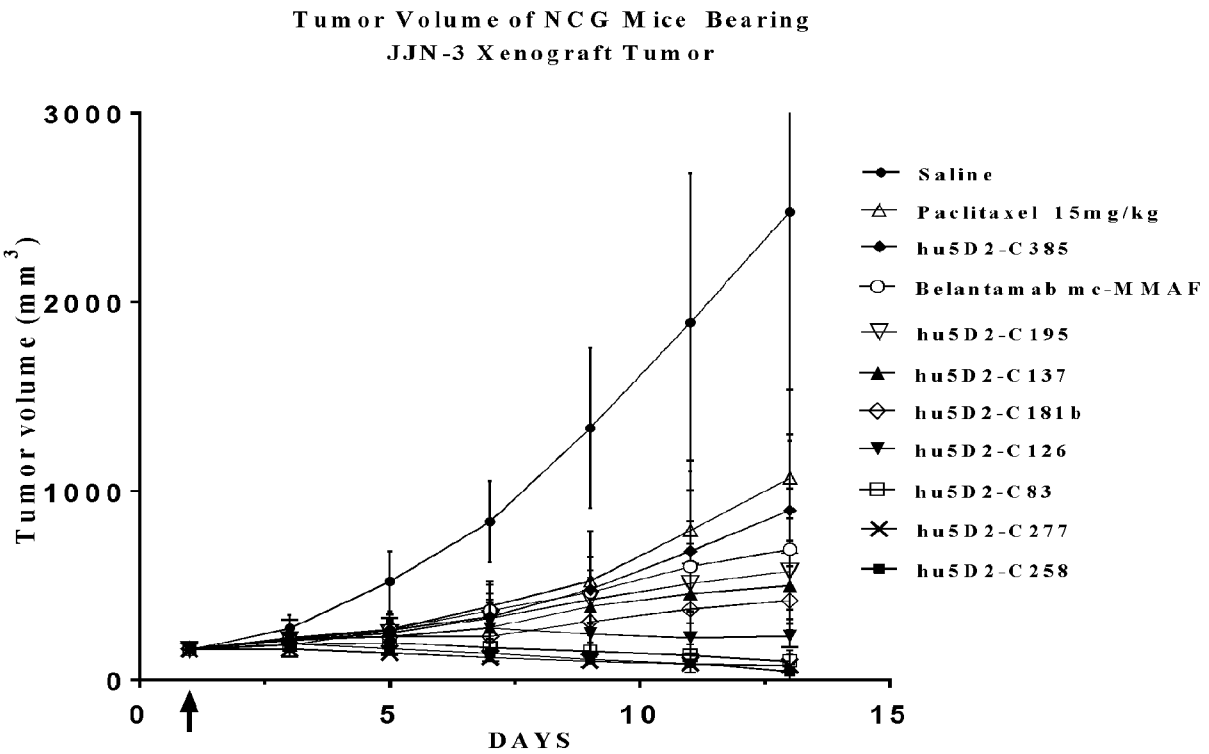
Tumor Volume of NCG Mice Bearing
JJN-3 Xenograft Tumor
Tumor volume (mm3)
3000
2000
1000
0
0
5
10
15
DAYS
Saline
Paclitaxel 15mg/kg
hu5D2-C385
Belantamab mc-MMAF
hu5D2-C195
hu5D2-C137
hu5D2-C181b
hu5D2-C126
hu5D2-C83
hu5D2-C277
hu5D2-C258

Fig.66

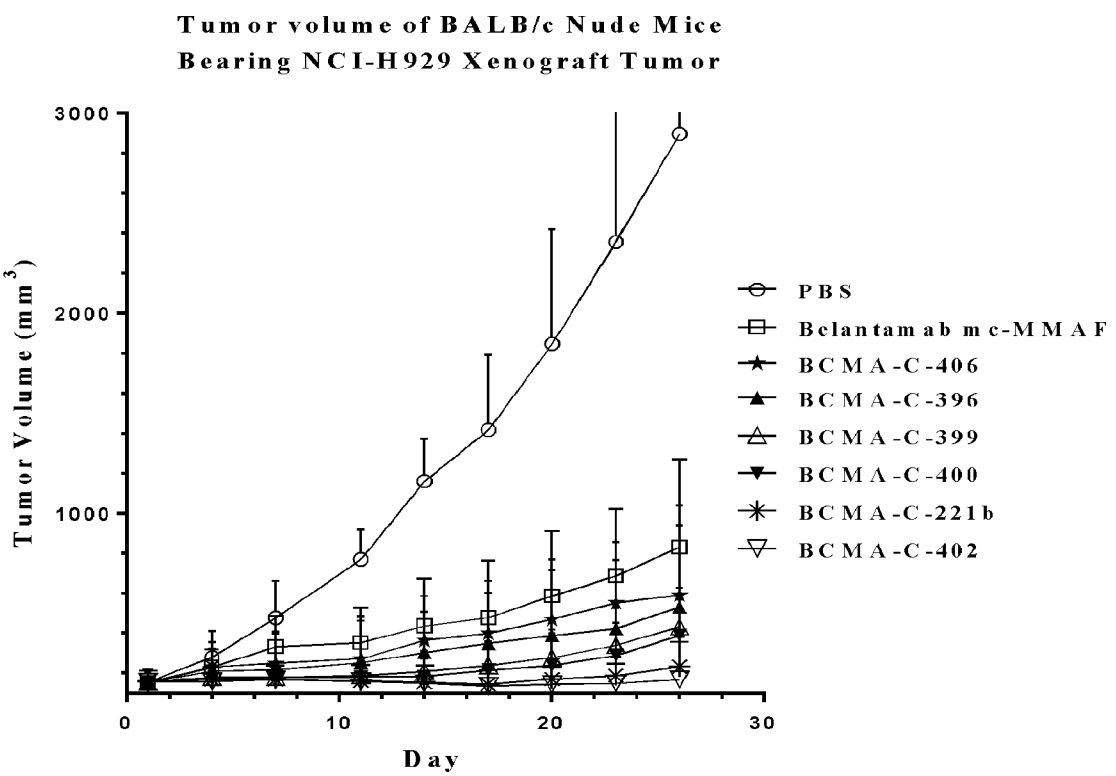
Tumor volume of BALB/c Nude Mice
Bearing NCI-H929 Xenograft Tumor
Tumor Volume (mm3)
3000
2000
1000
0
10
20
30
Day
PBS
Belantamab mc-MMAF
BCMA-C-406
BCMA-C-396
BCMA-C-399
BCMA-C-400
BCMA-C-221b
BCMA-C-402

Fig. 67

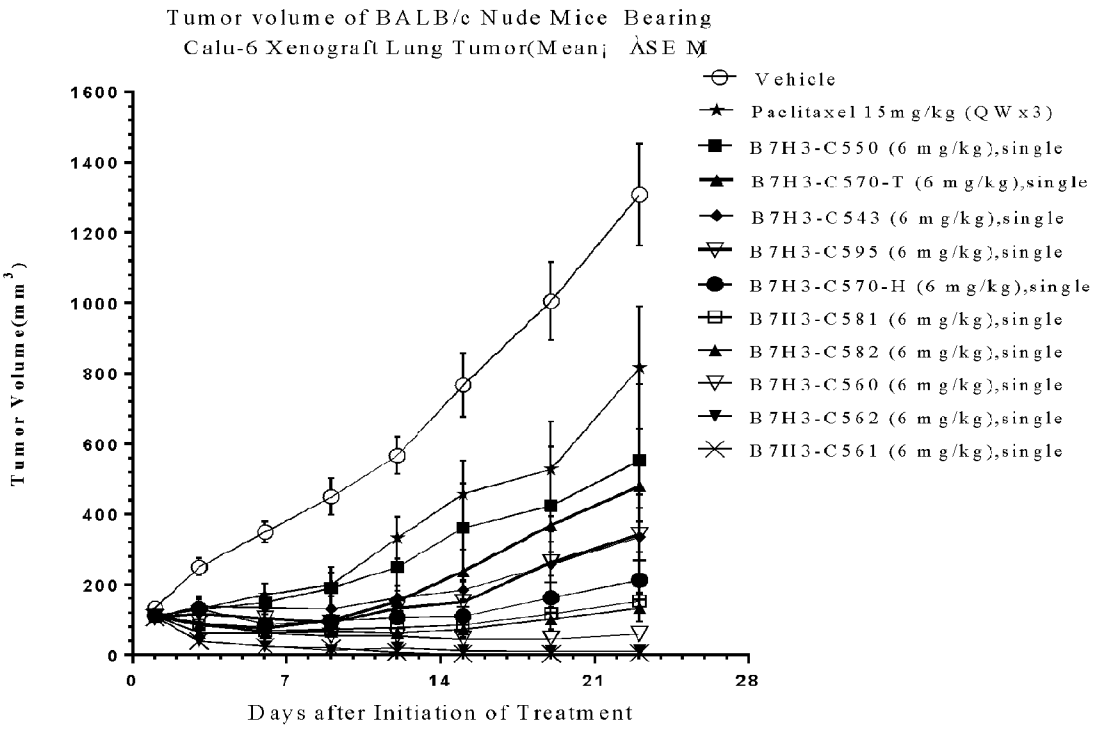

Fig. 68

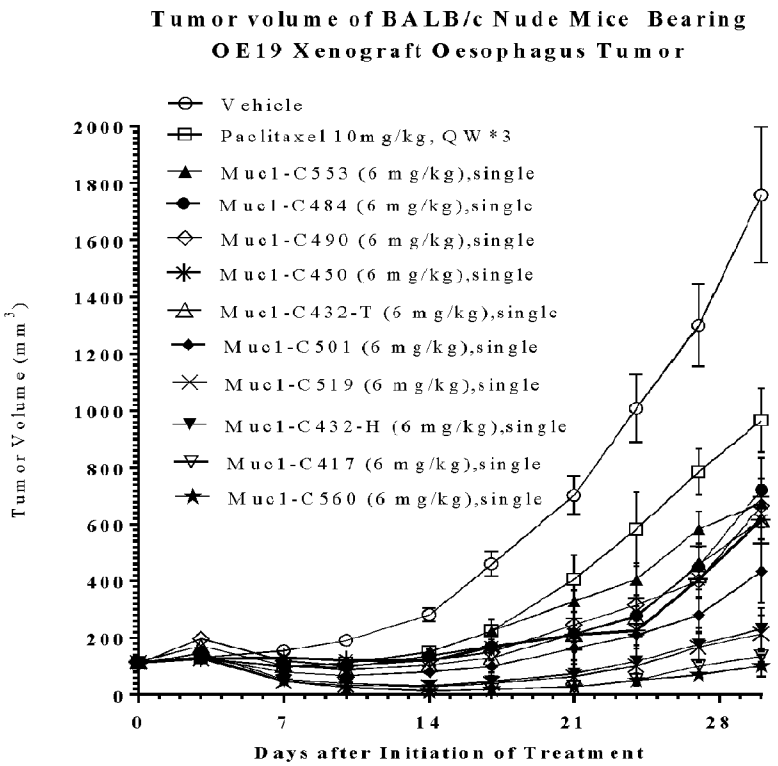

Fig. 69

CA 03236754 2024-4-30