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(54) **HYDROPHILIC LINKERS AND THEIR USES FOR CONJUGATION OF DRUGS TO CELL BINDING MOLECULES**

HYDROPHILE BINDER UND DEREN VERWENDUNG ZUR KONJUGATION VON WIRKSTOFFEN AN ZELLBINDENDE MOLEKÜLE

LIEURS HYDROPHILES ET LEURS UTILISATIONS POUR LA CONJUGAISON DE MÉDICAMENTS À DES MOLÉCULES SE LIANT AUX CELLULES

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- **BLOCK E ET AL: "Prepackaged Ramberg-Backlund reagents: useful tools for organic synthesis", TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 60, no. 35, 23 August 2004 (2004-08-23), pages 7525-7541, XP004771414, ISSN: 0040-4020, DOI: 10.1016/J.TET.2004.06.032**

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EX1078

EP 2 922 818 B1

Description**FIELD OF THE INVENTION**

[0001] The present invention relates to the preparation of novel hydrophilic linkers used for the conjugation of a drug, in particular, a cytotoxic agent to a biological molecule. The present invention also relates to methods of making cell-binding agent-drug (cytotoxic agent) conjugates comprising either modification of drugs with these hydrophilic linkers first, followed by reaction with cell-binding agents; or modification of cell-binding agents with these hydrophilic linkers first, followed by reaction with drugs.

BACKGROUND OF THE INVENTION

[0002] Nowadays the development on targeted cancer therapy requires not only to supplement the conventional chemotherapy and radiotherapy while sparing healthy cells, greatly reducing or eliminating the often unpalatable side effects, but also aim to overcome drug resistance (Turk, D. and Szakács, G., Curr Opin Drug Discov Devel. 2009, 12, 246; Zhao, R. et al, J. Med. Chem. 2011, 56, 5404; Yauch, R. L, Settleman, J. Curr Opin Genet Dev. 2012, 22, 45). There are several systemic deliveries for targeted treatment of tumor that have been studied during the past three decades: Heat-activated targeted drug delivery; Tissue-selective drug delivery for cancer using carrier-mediated transport systems; Tumor-activated prodrug therapy for targeted delivery of chemotherapy; Pressure-induced filtration of drug across vessels to tumor; Promoting selective permeation of the anticancer agent into the tumor; Two-step targeting using a bispecific antibody; Site-specific delivery and light-activation of anticancer proteins. Many special formulations and carriers have been studied for target delivery of anticancer drugs, such as Albumin-based drug carriers; Carbohydrate-enhanced chemotherapy; Proteins and peptides based drug carriers; Fatty acids as targeting vectors linked to active drugs; Microsphere carriers; Monoclonal antibodies as carriers; Vitamins, e.g. folates as carriers; Nanoparticle carriers; Liposome carriers, e. g. pegylated liposomes (enclosed in a polyethylene glycol bilayer); Polyethylene glycol (PEG) carriers; Single-chain antigen-binding molecule carriers; Polymeric micelle carriers; Lipoprotein-based drug carriers; Dendrimers; etc. An ideal drug delivery vehicle must be non-toxic, biocompatible, non-immunogenic, and biodegradable (Scott, R; Crabbe, D; et al (2008) Expert Opin. Drug Deli. 5, 459) and avoid recognition by the host's defense mechanisms (Saltzman, W.; Torchilin, V. (2008). "Drug delivery systems" Access Science. McGraw-Hill Co.). The link between the delivery vehicles, in particular, antibodies and the cell-killing agent plays a critical role in the development of targeted drug delivery systems, as the nature of the linker significantly affects the potency, selectivity and the pharmacokinetics of the resulting conjugates (Zhao, R.; Wilhelm, S. et al, (2011) J. Med. Chem. 36, 5404; Doronina, S.; Mendelsohn, B.; et al, (2006) Bioconjug Chem, 17, 114; Hamann, P.; Hinman, L; et al. (2005) Bioconjug Chem. 16, 346). Four types of linkers had been used for preparation of cell binding agent-drug conjugates that have entered the clinic: (a) acid-labile linkers, exploiting the acidic endosomal and lysosomal intracellular microenvironment; (b) linkers cleavable by lysosomal proteases; (c) chemically stable thioether linkers that release a lysyl adduct after proteolytic degradation of the antibody inside the cell; and (d) disulfide-containing linkers, which are cleaved upon exposure to an intracellular thiol (Zhao, R.; Wilhelm, S. et al, 2011 J. Med. Chem. 36, 5404).

[0003] Conjugates of cell-binding agents with drugs or modified chemical compounds via different types of linkers have been described (U.S. Patent Nos. 4,680,338, 5,122,368, 5,141,648, 5,208,020, 5,416,064; 5,475,092, 5,543,390, 5,563,250 5,585,499, 5,880,270, 6,214,345, 6,436,931, 6,372,738, 6,340,701, 6,989,452, 7,129,261, 7,375,078, 7,498,302, 7,507,420, 7,691,962, 7,910,594, 7,968,586, 7,989,434, 7,994,135, 7,999,083, 8,153,768, 8,236,319, Zhao, R.; et al, (2011) J. Med. Chem. 36, 5404; Doronina, S.; et al, (2006) Bioconjug Chem, 17, 114; Hamann, P.; et al. (2005) Bioconjug Chem. 16, 346). Typically, in these conjugates, the cell-binding agents are first modified with a bifunctional agent such as SPDP (*N*-succinimidyl 3-(2-pyridyldithio) propionate), or SMCC (succinimidyl-4-(*N*-maleimidomethyl)cyclohexane-1-carboxylate), or SPDB (*N*-succinimidyl 4-(2-pyridyldithio)butanoate), to introduce an active disulfide or a maleimido moiety. Reaction with a thiol-containing cytotoxic drug provides a conjugate in which the cell-binding agent, such as a monoclonal antibody, and drug are linked via disulfide bonds or thioether bonds.

[0004] However, the use of the cell binding molecule-drug conjugates, such as antibody-drug conjugates (ADCs), in developing therapies for a wide variety of cancers has been limited both by the availability of specific targeting agents (carriers) as well as the conjugation methodologies which result in the formation of protein aggregates when the amount of the drugs that are conjugated to the carrier (i.e., the drug loading) is increased. Normally the tendency for cytotoxic drug conjugates to aggregate is especially problematic when the conjugation reactions are performed with the hydrophobic linkers. Since higher drug loading increases the inherent potency of the conjugate, it is desirable to have as much drug loaded on the carrier as is consistent with retaining the affinity of the carrier protein. The presence of aggregated protein, which may be nonspecifically toxic and immunogenic, and therefore must be removed for therapeutic applications, makes the scale-up process for the production of these conjugates more difficult and decreases the yield of the products.

[0005] WO 2012/145112 describes sulfoxide or selenium containing linkers for conjugating cytotoxic drug to a cell-

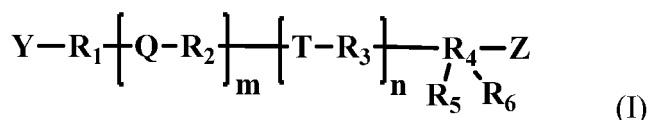
binding agent. US, 4,227,918 describes halogenoethyl sulphones to be applied to a plant or habitat for regulating growth of plants. Brouwer, et al., Bioorg. Med. Chem. 15 (2007) 6985-6993 describe chloromethyl sulfoxides as a new class of selective irreversible cysteine protease inhibitors. Block, et al., Tetrahedron 60 (2004) 7525-7541 describes synthesis and reactions of several α,β -unsaturated chloromethyl sulfones, which are described as being 'prepackaged' Ramberg-Bäckland reagents.

[0006] Consequently, there is a critical need to improve methods for conjugating drugs/cytotoxic drugs to carriers (cell binding molecules) that minimize the amount of aggregation and thereby allow for as high a drug loading as possible through application of a hydrophilic cross-linker.

SUMMARY OF THE INVENTION

[0007] The present invention provides hydrophilic linkers containing phosphinate, sulfonyl, and/or sulfoxide groups to link drugs to a cell-binding agent (e.g., an antibody). The preferred formula of the cell binding molecule - hydrophilic linker- drug conjugates can be represented as: Cb-(L-Drug)_n, wherein Cb is a cell-binding agent, L is a hydrophilic linker, Drug is a drug molecule, and n is an integer from 1 to 20. The advantages in applying the hydrophilic linker in the cell molecule-drug conjugate are: a). reducing the aggregation of the conjugates in water based media; b). enabling higher drug-per-cell binding molecule-ratio conjugate, resulting in higher potency; c). being retained inside the target cell after the drug-linker released from the conjugates, which can combat permeability-glycoprotein (Pgp)-expressing multidrug resistant (MDR) cells.

[0008] In one aspect of the present invention, the hydrophilic linker is represented by formula (I) wherein Y can react with a cell-binding agent and Z can react with a cytotoxic drug:



Wherein:

Y represents a functional group that enables reaction with a cell-binding agent;

Q and T are either -P(=O)(OM)-, or -S(O₂)-, or -S(O)-;

m and n are integer from 0 to 5, but not 0 at the same time; In addition, when m = 1, n = 0, Q is not -P(=O)(OM)-; or when n = 1, m = 0, T is not -P(=O)(OM)-;

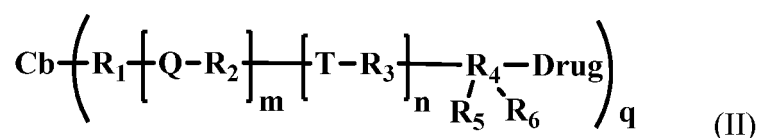
Z represents a functional group that enables linkage of a cytotoxic drug via a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, amine (secondary, tertiary, or quaternary), imine, cycloheteroalkyl, heteroaromatic, alkoxime or amide bond, the said functional group Z being selected from thiol, disulfide, amino, carboxy, aldehydes, maleimido, haloacetyl, hydrazines and hydroxy;

R₁, R₂, R₃, R₄, R₅ and R₆, are the same or different and are H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or 1-6 carbon atoms of esters, ether, amide, or polyethyleneoxy unit of formula (OCH₂CH₂)_p, wherein p is an integer from 0 to 1000, or combination thereof;

or R₁, R₂, R₃ and R₄ are respectively a chain of atoms selected from C, N, O, S, Si, and P that covalently connects the cell-surface binding ligand, the phosphinate or sulfonyl group, the conjugated drug and among themselves (R₁, R₂, R₃ and R₄), wherein the said atoms are combined in any chemically relevant ways, such as forming alkylene, alkenylene, and alkynylene, ethers, polyoxyalkylene, esters, amines, imines, polyamines, hydrazines, hydrazones, amides, ureas, semicarbazides, carbazides, alkoxyamines, alkoxyamines, urethanes, amino acids, peptides, acyloxylamines, hydroxamic acids, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt, wherein R₁, R₂ and R₃ are described above.

[0009] In another aspect, this invention provides a cell-binding agent-drug conjugate of formula (II), in which the cell-binding agent, Cb, and the drug, Drug, have reacted at the two ends of the hydrophilic linker:



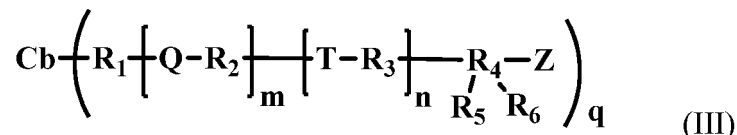
wherein:

Cb represents a cell-binding agent;

Drug represents the drug linked to the cell-binding agent via the hydrophilic linker by a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

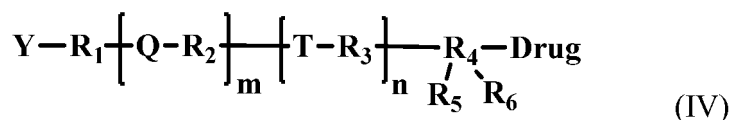
q is 1 ~ 20; Q, T, m, n, R₁, R₂, R₃, R₄, R₅, R₆ and M are described the same previously in formula (I).

[0010] In a further aspect, the present invention provides a modified cell-binding agent of formula (III), in which the cell-binding agent, Cb, has reacted with the hydrophilic linker, which still has Z, a group capable of reacting with a drug:



[0011] Wherein the substituents are as defined above.

[0012] In an even further aspect, the present invention provides a modified drug of formula (IV), in which the drug, Drug, has reacted with the hydrophilic linker, which still has Y, a group capable of reacting with the cell-binding agent:



[0013] Wherein the substituents are as defined above.

[0014] The present invention further relates to a method of making a cell-binding molecule-drug conjugate of formula (II), wherein the drug is linked to a cell-binding agent via the hydrophilic linker.

[0015] The present disclosure also relates to a method of making a modified cell-binding molecule of formula (III), wherein the cell-binding molecule is reacted with the hydrophilic linker.

[0016] The present disclosure also relates to a method of making a modified drug of formula (IV), wherein the drug is reacted with the hydrophilic linker.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017]

Figure 1 shows the synthesis of diphosphinate-containing cross-linking reagents that contain a pyridyldisulfide group and a reactive carboxylic acid ester, and the linker used for the conjugation of an antibody. Ammonium phosphinate are first converted into bis(trimethylsilyl) phosphonite, followed by Michael addition with an acrylate and then substitution reaction with excess amount of 1,2-dibromo ethane to form (2-bromoethyl)(3-ethoxy-3-oxopropyl)phosphinic acid (**4**). The bromoethyl phosphinic acid moiety (**5**) was then substituted with bis(trimethylsilyl) phosphonite (**2**) and 1,2-dibromo ethane to generate (2-bromoethyl)(2-(ethoxy(3-ethoxy-3-oxopropyl)phosphoryl)ethyl)phosphinic acid (**8**), whose bromide group was then replaced by potassium ethyl xanthogenate, followed by basic hydrolysis and a substitution reaction with an excess of 2,2'-dithiobispyridine, as well as condensation reaction of the acid **10** with *N*-hydroxysuccinimide (NHS) in an acid medium using the carbodiimide coupling agent EDC to give the diphosphinate linker (**11**). The linker **11** can be used for the conjugation of drugs to a cell binding molecule (such as antibody). Figure 2 shows the synthesis of a triphosphinate-containing linker **18** that contains a pyridyldisulfide group and a reactive carboxylic acid ester. The linker can be used for the conjugation of a drug to cell binding molecule via a disulfide bond.

Figures 3 shows the synthesis of tetraphosphinate-containing cross linkers **23** that contain a reactive carboxylic acid ester and a pyridyldisulfide group, enabling linkage of a drug to a cell binding molecule via a disulfide bond.

Figure 4 shows the synthesis of diphosphinate-containing cross-linker **26** that contain a maleimido group and a reactive carboxylic acid ester enabling linkage of a drug to a cell binding molecule via a thioether bond

Figures 5 shows the synthesis of monophosphinate, diphosphinate, triphosphinate and tetraphosphinate-containing

linkers that contain a pyridyldisulfide group and a reactive carboxylic acid ester via substitution of ethyl 2-bromoacetate with bis(trimethylsilyl) phosphonite (2).

Figure 6 shows the synthesis of linking reagents that contain a vinylsulfonyl (55), a monosulfonyl (61) and disulfonyl (69) groups.

Figure 7 shows the synthesis of mono-, and di-sulfonyl linkers

Figure 8 shows the synthesis of mono-sulfonyl linkers containing polyethylene glycols.

Figure 9 shows the synthesis of di-sulfonyl linkers containing polyethylene glycols. The linker can be used for the conjugation of an antibody or a protein via a disulfide bond.

Figure 10 shows the synthesis of a hydrophilic linker containing a phosphinic acid and a sulfonyl group.

Figure 11 shows the synthesis of a hydrophilic linker containing a phosphinate, a sulfonyl and a ketone groups that can be used for the conjugation of a drug to an antibody or a protein via a hydrazone bond.

Figure 12 shows the synthesis of hydrophilic linkers that contain a disulfonyl, polyethylene glycols, a much hindered pyridyldisulfide and a reactive carboxylic acid ester groups via substitution of 1,3-dibromo-3-methylbutane. The linker is used for the conjugation of drugs to an antibody or a protein via a hindered disulfide bond.

Figure 13 shows the synthesis of hydrophilic linkers containing a phosphinate and a sulfonyl groups that are used for the conjugation of drugs to a cell binding molecule either via a triazole or via a thioether bond.

Figures 14, shows synthesis of hydrophilic linkers that contain a disulfonyl, phosphinate, a pyridyldisulfide group, a polyethylene glycol (PEG) chain and a reactive carboxylic acid ester. The linkers are used for the conjugation of a cell binding molecule via cell thioether bond

Figures 15 shows synthesis of hydrophilic linkers that contain a disulfonyl, phosphinate, an alkoxyamino and a maleimido substituents, enabling ketone or aldehyde-containing drug to link to an antibody via a thioether and an alkoxime bond..

Figure 16 shows the synthesis of disulfonyl-containing linkers that contains an alkoxyamino and a maleimido substituent, enabling ketone or aldehyde-containing drug to link to an antibody via a thioether and an alkoxime bond.

Figure 17 shows the synthesis of sulfoxide-containing and disulfoxide-containing linkers that are used for the conjugation of drugs to a cell binding molecule via a disulfide bond.

Figures 18 show the synthesis of a disulfonyl-containing linker (221) that used for conjugation of amine-containing cytotoxic drugs to an antibody via the Val-Cit-PABC linkage.

Figure 19 (19-a~19-z) shows the antibody-drug conjugate (ADC) structures of the typical cytotoxic agents (the analogs of tubulysins, calicheamicins, maytansinoids, auristatins, doxorubicin, daunorubicin, CC-1065, pyrrolobenzodiazepine dimmers) via the hydrophilic linkers of this patent.

Figure 20 shows the use of a hydrophilic linker (86) in modifying a cell-binding agent (antiHer2 antibody) and following by production of a cell-binding agent-drug (TZ03) conjugate containing the hydrophilic linker.

Figure 21 shows 5 days in vivo assays of the cytotoxicity of the antiCD22-TZ041 (tubulysin analog) conjugate with different drug load ratios via a hydrophilic linker (86).

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

[0018] "Alkyl" means an aliphatic hydrocarbon group which may be straight or branched having 1 to 8 carbon atoms in the chain or cyclic. "Branched" means that one or more lower 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-methylhexyl, 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 C₁-C₈ alkyl group can be unsubstituted or substituted with one or more groups including, but not limited to, -C₁-C₈ alkyl, -O-(C₁-C₈ alkyl), -aryl, -C(O)R', -OC(O)R', -C(O)OR', -C(O)NH₂, -C(O)NHR', -C(O)N(R')₂-NHC(O)R', -S(O)₂R', -S(O)R', -OH, -halogen (F, Cl, Br or I), -N₃, -NH₂, -NH(R'), -N(R')₂ and -CN; where each R' is independently selected from -C₁-C₈ alkyl and aryl.

[0019] A "C₃-C₈ carbocycle" means a 3-, 4-, 5-, 6-, 7- or 8-membered saturated or unsaturated non-aromatic carbocyclic ring. Representative C₃-C₈ 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 C₃-C₈ carbocycle group can be unsubstituted or substituted with one or more groups including, but not limited to, -C₁-C₈ alkyl, -O-(C₁-C₈ alkyl), -aryl, -C(O)R', -OC(O)R', -C(O)OR', -C(O)NH₂, -C(O)NHR', -C(O)N(R')₂-NHC(O)R', -S(O)₂R', -S(O)R', -OH, -halogen, -N₃, -NH₂, -NH(R'), -N(R')₂ and -CN; where each R' is independently selected from -C₁-C₈ alkyl and aryl.

[0020] A "C₃-C₈carbocyclo" refers to a C₃-C₈ carbocycle group defined above wherein one of hydrogen atoms on

the carbocycle is replaced with a bond.

[0021] "Heterocycle" refers to an aromatic or non-aromatic C₃~C₄ carbocycle in which one to four of the ring carbon atoms are independently replaced with a heteroatom from the group of O, N, S, Se, and P. Preferable heteroatoms are oxygen, nitrogen and sulphur. Suitable heterocyclics are also disclosed in The Handbook of Chemistry and Physics, 76th Edition, CRC Press, Inc., 1995-1996, p. 2-25 to 2-26, the disclosure of which is hereby incorporated by reference.

[0022] Preferred non aromatic heterocyclic include, but are not limited to pyrrolidinyl, pyrazolidinyl, imidazolidinyl, oxiranyl, tetrahydrofuranyl, dioxolanyl, tetrahydro-pyranyl, dioxanyl, dioxolanyl, piperidyl, piperazinyl, morpholinyl, pyranyl, imidazolyl, pyrrolinyl, pyrazolyl, thiazolidinyl, tetrahydrothiopyranyl, dithianyl, thiomorpholinyl, dihydropyranyl, tetrahydropyranyl, dihydropyranyl, tetrahydro-pyridyl, dihydropyridyl, tetrahydropyridinyl, dihydrothiopyranyl, azepanyl, as well as the fused systems resulting from the condensation with a phenyl group.

[0023] "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.

[0024] "Halogen atom" refers to fluorine, chlorine, bromine or iodine atom; preferably bromine and chlorine atom.

[0025] "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.

[0026] "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.

[0027] 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.

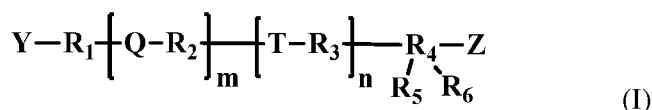
[0028] The pharmaceutical salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared via reaction the free acidic or basic forms of these compounds with a stoichiometric amount 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.

[0029] The novel conjugates disclosed herein use hydrophilic cross-linkers. Examples of some suitable cross-linkers and their synthesis are shown in Figures 1 to 18.

THE HYDROPHILIC LINKERS

[0030] The synthetic routes to produce hydrophilic cross linkers as well as the preparation of the conjugates of drugs to a cell binding molecules of the present invention are shown in Figures 1-19. The hydrophilic cross linkers possess three elements: a) substituents that are either phosphinate, or sulfonyl or sulfoxide groups, or mixed of these groups, b) a group, such as a *N*-hydroxysuccinimide ester, maleimido group, haloacetyl group, and hydrazide, capable of reaction with a cell-binding agent, and c) a group, such as but not limited to, a disulfide, maleimide, haloacetyl, aldehyde, ketone, azide, amine, alkoxyamino and hydrazide, capable of reaction with a drug. The hydrophilic substituents can be introduced by methods described herein. For example of the phosphinate substituents, they can be introduced by first treating a commercially available ammonium phosphinate with an acrylate via Michael addition and followed by substitution of excess amount of dibromo alkane to a phosphinate group. For example of the sulfonyl and sulfoxide substituents, they can be introduced by first generation of thioether components, followed by oxidation of these components. More detail synthesis of the hydrophilic linkers and their uses for the preparation of cell binding ligand-drug conjugates of this invention are disclosed in the figures 1-19.

[0031] Preferably, the hydrophilic linkers are compounds of the formula (I) below:



wherein:

Y represents a functional group that enables reaction with a cell-binding agent;

Q and T are either -P(=O)(OM)-, or -S(O₂)-, or -S(O)-;

m and n are integer from 0 to 5, but not 0 at the same time; In addition, when m = 1, n = 0, Q is not -P(=O)(OM)-; or when n = 1, m = 0, T is not -P(=O)(OM)-;

Z represents a functional group that enables linkage of a cytotoxic drug via a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, amine (secondary, tertiary, or quaternary), imine, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

R₁, R₂, R₃, R₄, R₅ and R₆, are the same or different and are H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or 1-6 carbon atoms of esters, ether, amide, or polyethyleneoxy unit of formula (OCH₂CH₂)_p, wherein p is an integer from 0 to about 1000, or combination thereof.

[0032] In another embodiment, R₁, R₂, R₃, and R₄ can be respectively a chain of atoms selected from C, N, O, S, Si, and P that covalently connects the cell-surface binding ligand, the phosphinate or sulfonyl or sulfoxide group, the conjugated drug and themselves (R₁, R₂, R₃ and R₄). The atoms used in forming the hydrophilic linker may be combined in all chemically relevant ways, such as forming alkylene, alkenylene, and alkynylene, ethers, polyoxyalkylene, esters, amines, imines, polyamines, hydrazines, hydrazones, amides, ureas, semicarbazides, carbazides, alkoxyamines, alkoxyamines, urethanes, amino acids, acyloxyamines, hydroxamic acids, and many others. In addition, it is to be understood that the atoms forming the linker (L) may be either saturated or unsaturated, or may be radicals, or may be cyclized upon each other to form divalent cyclic structures, including cyclo alkanes, cyclic ethers, cyclic amines, arylenes, heteroarylenes, and the like in the linker.

[0033] M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt. R₁, R₂ and R₃ are described above.

[0034] Examples of the functional group, Y, that enables reaction with a cell-binding agent include amine reacting agents such as but not limited to N-hydroxysuccinimide esters, p-nitrophenyl esters, dinitrophenyl esters, pentafluorophenyl esters; thiol reactive agents such as but not limited to pyridyldisulfides, nitropyridyldisulfides, maleimides, haloacetates and carboxylic acid chlorides.

[0035] Examples of the functional group, Z, which enables linkage of a cytotoxic drug, include groups that enable linkage via an either disulfide, or thioether, thioester, peptide, hydrazone, ester, carbamate, carbanate, alkoxime or amide bond. Such functional groups include, but are not limited to, thiol, disulfide, amino, carboxy, aldehydes, maleimido, haloacetyl, hydrazines, and hydroxy.

[0036] In preferred embodiments, R₁, R₂, R₃, and R₄, are linear alkyl having from 1-6 carbon atoms, or polyethyleneoxy unit of formula (OCH₂CH₂)_p, p = 1-100,

[0037] The synthesis of 2-dithio-pyridyl containing cross-linkers of formulae (I) is shown, for example, in Figures 1, 2, 3, 5, 6, 7, 8, 9, 10, 12, 13, 14, and 17. The synthesis of maleimido-containing cross linkers of the formula (I) is shown, for example, in Figures 4, 8, 9, 10, 12, 14, and 18. The synthesis of thioether-containing cross linkers of the formula (I) is shown, for example, in Figures 6, 8, 10, and 13. The synthesis of polyethylene glycol-containing hydrophilic cross linkers of formula (I) is shown, for example, in Figures 8, 9, and 14. The synthesis of azide-containing hydrophilic cross linkers of formula (I) for Huisgen 1,3-dipolar cycloaddition of azides to alkynes is shown, for example, in Figures 13. The synthesis of hydrophilic cross linkers of formula (I) bearing a hydrazide or ketone moieties enabling linkage via acid-labile bonds is shown, for example, in Figures 11, 16 and 18. The synthesis of hydrophilic cross linkers of formula (I) bearing an alkoxyamino moiety enabling linkage via alkoxime bonds is shown, for example, in Figure 15 and 16. The synthesis of dipeptide-containing cross linkers of the formula (I) is shown, for example, in Figure 18.

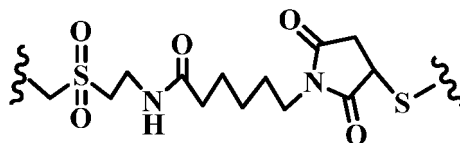
CELL-BINDING AGENT-DRUG CONJUGATES

[0038] The conjugates of the present invention can be represented by the following formula, Cb-(L-Drug)_n, wherein Cb is a cell-binding agent, L is a hydrophilic linker, Drug is a drug molecule, and n is an integer from 1 to 20.

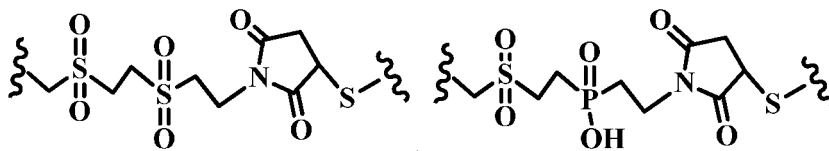
[0039] The hydrophilic linker L may be composed of one or more linker components. Exemplary linker components include 6-maleimidocaproyl ("MC"), maleimidopropanoyl ("MP"), valine-citrulline ("val-cit" or "vc"), alanine-phenylalanine ("ala-phe" or "af"), p-aminobenzyloxycarbonyl ("PAB"), 4-thiopentanoate ("SPP"), 4-(N-maleimidomethyl)cyclohexane-1 carboxylate ("MCC"), (4-acetyl)aminobenzoate ("SIAB"), 4-thio-butyrate (SPDB), 4-thio-2-hydroxysulfonyl-butyrate (2-

Sulfo-SPDB), ethyleneoxy $-\text{CH}_2\text{CH}_2\text{O}-$ as one or more repeating units ("EO" or "PEO"). Additional linker components are known in the art and some are described herein.

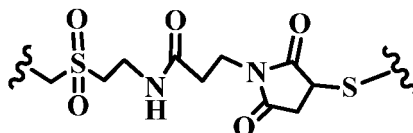
[0040] Example structures of these components containing linkers are:



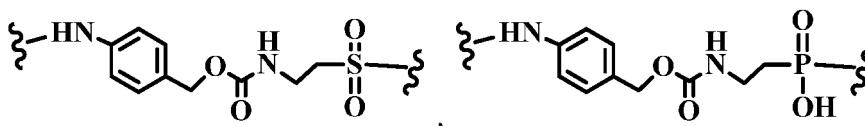
(MC, 6-maleimidocaproyl containing)



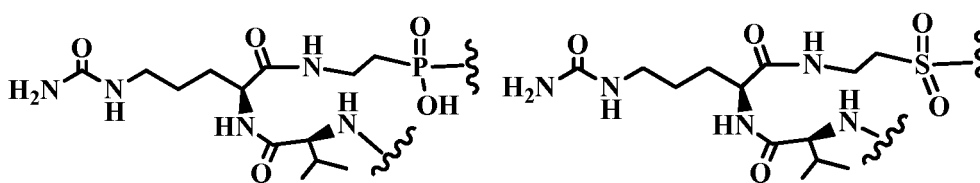
(ME, maleimidoethyl containing).



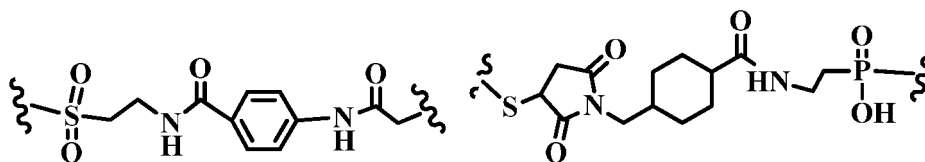
(MP, maleimidopropanoyl containing)



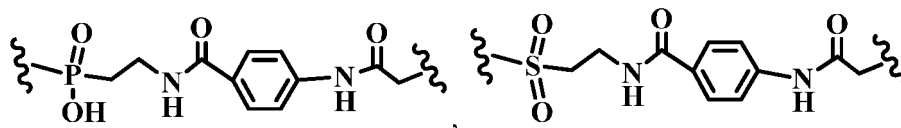
(PAB, p-aminobenzyloxycarbonyl containing)



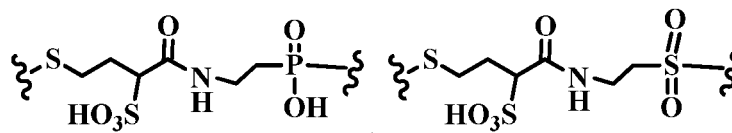
(valine-citrulline containing)



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

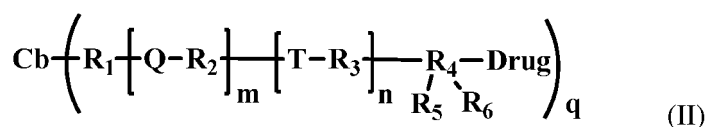


((4-acetyl)aminobenzoate containing)



(4-thio-2-hydroxysulfonyl-butylate, 2-sulfo-SPDB)

[0041] Preferably, the conjugates have the following formula (II):



wherein:

Cb represents a cell-binding agent;

Drug represents the drug linked to the cell-binding agent via the hydrophilic linkers of this invention by a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, heterocyclic ring, amine, imine, alkoxime or amide bond;

q is 1 ~ 20; Q, T, m, n, R₁, R₂, R₃, R₄, R₅, R₆ and M are described the same previously in formula (I).

[0042] As described in more detail below, the drug can be any of many small molecule drugs, including, but not limited to, tubulysins, calicheamicins, auristatins, maytansinoids, CC-1065 analogs, morpholinos doxorubicins, taxanes, cryptophycins, epothilones, and benzodiazepine dimers (e.g., dimmers of pyrrolobenzodiazepine (PBD) or tomaymycin), indolinobenzodiazepines, imidazobenzothiadiazepines, or oxazolidinobenzodiazepines).

[0043] To synthesize the conjugate, the cell-binding agent can be first modified with the hydrophilic linkers of the present invention to introduce reactive disulfide groups, maleimido, haloacetyl, azide, 1-yne, ketone, or hydrazide groups. Synthesis of the cell-binding agent-drug conjugates linked via disulfide bonds is achieved by a disulfide exchange between the disulfide bond in the modified cell-binding agent and a drug containing a free thiol group. Synthesis of the cell-binding agent-drug conjugates linked via thioether is achieved by reaction of the maleimido or haloacetyl or ethylsulfonyl modified cell-binding agent and a drug containing a free thiol group. Synthesis of conjugates bearing an acid labile hydrazone link 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., Hinman, L. M., et al, Cancer Res. 53, 3336-334, 1993; B. Laguzza et al., J. Med. Chem., 32; 548-555, 1959; P. Trail et al., Cancer Res., 57; 100-105, 1997).

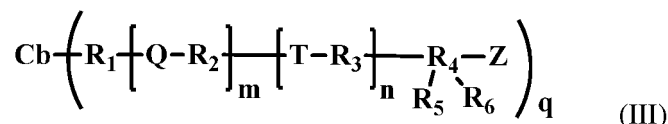
[0044] Alternatively, the drug can be modified with the hydrophilic linkers of the present invention to give a modified drug of formula (IV) bearing functionality capable of reacting with a cell binding agent. For example a thiol-containing drug can be reacted with the hydrophilic linker of formula (I) bearing a maleimido or a haloacetyl or an ethylsulfonyl substituent at neutral pH in aqueous buffer to give a drug connected to the hydrophilic linker via a thioether link. A thiol-containing drug can undergo disulfide exchange with a hydrophilic linker bearing a pyridyldithio moiety to give a modified drug attached via a disulfide bond to the hydrophilic cross linker. A drug bearing a hydroxyl group or a thiol group can be reacted with a hydrophilic linker bearing a halogen of this invention, in the presence of a mild base, to give a modified drug bearing an ether or thiol ether link. A hydroxyl group containing drug can be condensed with a hydrophilic cross linker of formula (I) bearing a carboxyl group, in the presence of a dehydrating agent, such as EDC or dicyclohexylcarbodiimide, to give an ester link. An amino group containing drug can similarly undergo condensation with a carboxyl group on the hydrophilic linker of formula (I) to give an amide bond.

[0045] The conjugate may be purified by standard biochemical means, such as gel filtration on a Sephadex G25 or

Sephacryl S300 column, adsorption chromatography, and ion exchange or by dialysis. In some cases (e.g. folic acid, melanocyte stimulating hormone, EGF etc) the cell-binding agent-drug conjugates can be purified by chromatography such as by HPLC, medium pressure column chromatography or ion exchange chromatography.

MODIFIED CELL-BINDING AGENTS

[0046] The cell-binding agent modified by reaction with linkers of the present invention are preferably represented by the formula (III)



wherein the substituents are as described above for the hydrophilic linkers and the cell-binding agent drug conjugates.

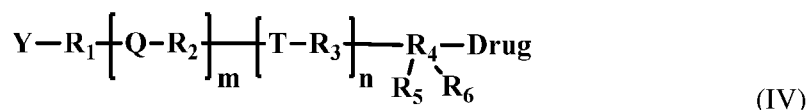
[0047] In preferred embodiments, Z is a disulfide substituent, a maleimido, haloacetyl group, or an *N*-hydroxysuccinimide ester, and Cb linked with R₁ is through thioether, amide, or disulfide bond. The modified cell-binding agent can be prepared via a reaction of the cell-binding agent with the hydrophilic linkers by methods known in the art for other cross-linkers (U.S. Patent Nos. 5,846,545, 5,585,499, 5,475,092, 5,414,064, 5,208,020, and 4,563,304; Carlsson, J. et al. *Biochem. J.* (1978) 173, 723-737(1978); Goff, D. A., *BioConjugate Chem.* (1990), 1, 381-386; L. Delprino et al. *J. Pharm. Sci.* (1993), 82, 506-512; S. Arpicco et al., *Bioconjugate Chem*(1997), 8, 327-337).

[0048] Advantageously, because the phosphinate groups and sulfonyl groups on the hydrophilic linkers are soluble in water or require only a small percentage of organic solvent to maintain solubility in aqueous solution, the reaction between the cell-binding agent and the cross-linker can be conducted in aqueous solution. The cross-linking reagent is dissolved in aqueous buffer, optionally containing a small amount (typically <10% by volume) of a polar organic solvent that is miscible with water, for example different alcohols, such as methanol, ethanol, and propanol, acetone, acetonitrile, tetrahydrofuran (THF), 1,4-dioxane, dimethyl formamide (DMF), dimethyl acetamide (DMA), or dimethylsulfoxide (DMSO) at a high concentration, for example 1-100 mM, and then an appropriate aliquot is added to the buffered aqueous solution of the cell-binding agent. An appropriate aliquot is an amount of solution that introduces 1-10 cross-linking groups per cell-binding agent, preferably 1-5 groups, and the volume to be added should not exceed 10 %, preferably 5 %, and most preferably 0-3 % of the volume of the cell-binding agent solution. The aqueous solutions for the cell-binding agents are buffered between pH 6 and 9, preferably between 6.5 and 7.5 and can contain any non-nucleophilic buffer salts useful for these pH ranges. Typical buffers include phosphate, triethanolamine HCl, HEPES, and MOPS buffers, which can contain additional components, such as cyclodextrins, sucrose and salts, for examples, NaCl and KCl. After the addition the reaction is incubated at a temperature of from 4 °C to 40 °C, preferably at ambient temperature. The progress of the reaction can be monitored by measuring the increase in the absorption at 320 nm or another appropriate wavelength. After the reaction is complete, isolation of the modified cell-binding agent can be performed in a routine way, using for example gel filtration chromatography, or adsorptive chromatography.

[0049] The extent of modification can be assessed by measuring the absorbance of the nitropyridine thione, dinitropyridine dithione, pyridine thione, carboxamidopyridine dithione and dicarboxamidopyridine dithione group released. Figure 20 shows the results from the modification of the cell-binding agent, the her2 antibody, with a hydrophilic cross-linker of the present invention. The time course of linker/antibody (L/A) incorporation is shown, for example, along with the drugs/antibody (D/A) linked. The hydrophilic cross-linkers described herein have diverse functional groups that can react with any cell-binding agent that possesses a suitable substituent. For example cell-binding agents bearing an amino or hydroxyl substituent can react with cross linkers bearing an *N*-hydroxysuccinimide (NHS) ester, cell-binding agents bearing a thiol substituent can react with cross linkers bearing a maleimido or haloacetyl group. Additionally, cell-binding agents bearing a carbonyl substituent can react with cross linkers bearing a hydrazide or a hydroxylamine. One skilled in the art can readily determine which linker to use based on the known reactivity of the available functional group on the cell-binding agent.

MODIFIED CYTOTOXIC DRUGS

[0050] The cytotoxic drugs modified by reaction with cross-linkers of the present invention are preferably represented by the formula (IV):



wherein the substituents are as defined above.

[0051] In preferred embodiments, Y is a disulfide substituent, a maleimido, haloacetyl group, or an *N*-hydroxysuccinimide ester.

[0052] The modified drugs can be prepared by reacting the drug with the cross linkers of the present invention to give a modified drug of formula (IV) bearing a functionality capable of reacting with a cell binding agent. For example a thiol-containing drug can be reacted with the cross linker of formula (I) bearing a maleimido substituent at neutral pH in aqueous buffer to give a drug connected to the hydrophilic linker via thioether linkage. A thiol-containing drug can undergo disulfide exchange with a hydrophilic linker bearing a pyridyldithio moiety to give a modified drug attached via a disulfide bond to the hydrophilic cross linker. A drug bearing a hydroxyl group can be reacted with a cross linker bearing a halogen, in the presence of a mild base, to give a modified drug bearing an ether link. A hydroxyl group containing drug can be condensed with a cross linker of formula (I) bearing a carboxyl group, in the presence of a dehydrating agent, such as EDC or dicyclohexylcarbodiimide (DCC), to give an ester link. A drug bearing a thiol group can be reacted with a cross linker bearing a maleimido or a vinylsulfonyl, or a haloacetyl group, to give a modified drug bearing thioether link. An amino group containing drug can similarly undergo condensation with a carboxyl group on the hydrophilic cross linker of formula (I) to give an amide bond. The modified drug can be purified by standard methods such as column chromatography over silica gel or alumina, crystallization, preparatory thin layer chromatography, ion exchange chromatography or HPLC.

CELL-BINDING AGENTS

[0053] The cell-binding molecule that comprises the conjugates and the modified cell-binding agents of the present invention may be of any kind presently known, or that become known, molecule that binds to, complexes with or reacts with a moiety of a cell population sought to be therapeutically or otherwise biologically modified.

[0054] The cell binding agents include, but are not limited to, large molecular weight proteins such as, for example, full-length antibodies (polyclonal antibodies, monoclonal antibodies, dimers, multimers, multispecific antibodies (e.g., bispecific antibodies); single chain antibodies; fragments of antibodies such as Fab, Fab', F(ab')₂, F_v, [Parham, J. Immunol. 131, 2895-2902 (1983)], fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies, CDR's, and epitope-binding fragments of any of the above which immuno-specifically bind to cancer cell antigens, viral antigens, microbial antigens or a 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 170:4854-4861); interferons (such as type I, II, III); peptides; lymphokines such as IL-2, IL-3, IL-4, IL-6, 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, 155-158 (1984)]; vaccinia growth factors (VGF); fibroblast growth factors (FGFs); smaller molecular weight 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. 932-937 (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); 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, 19, 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 capsids (Flenniken, et al, Viruses Nanotechnol. 2009, 327, 71-93). In general monoclonal antibodies are preferred as a cell-surface binding agent if an appropriate one is available. And antibodies may be murine, human, humanized, chimeric, or derived from other species.

[0055] 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:

495-497). 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.

[0056] 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.

[0057] 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, 20 mm glutamine, 20% fetal calf serum and with an anti-foaming agent, such as polyoxyethylene-polyoxypropylene block copolymer.

[0058] 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: 4949-4953 (1983); Geysen et al., *Proc. Natl. Acad. Sci. USA*, 82: 178-182 (1985); Lei et al. *Biochemistry* 34(20): 6675-6688, (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.

[0059] 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* 352:264-628 (1991); Huse et al., *Science* 246:1275-1281 (1989).

[0060] 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. USA*. 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, Inc.), the HuMAb-Mouse (Medarex/BMS), the VelociMouse (Regeneron), see also U.S. Pat. No. 6,596,541, 6,207,418, No. 6,150,584, No. 6,111,166, No. 6,075,181, No. 5,922,545, Nos. 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.

[0061] 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 immunospecific 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.

[0062] Apart from an antibody, a 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 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 immunoglobulin 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 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, as long as such attachment permits the peptide or protein to retain its antigen binding specificity.

[0063] Examples of antibodies used for conjugation of drugs via the hydrophilic linkers of this prevention for treating cancer, autoimmune disease, and infectious disease include, but are not limited to, 3F8 (anti-GD2), Abagovomab (anti CA-125), Abciximab (anti CD41 (integrin α -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), Anrukizumab (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, anti-CD25 (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 (Erbix, IMC-C225, anti-EGFR), Citatuzumab bogatox (anti-EpCAM), Cixutumumab (anti-IGF-1), Clenoliximab (anti-CD4), Clivatuzumab (anti-MUCI), 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, Ecomeximab (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), Gavilimumab (anti-CD147 (basigin)), Gemtuzumab (anti-CD33), Girentuximab (anti-carbonic anhydrase 9), Glembatumumab (CR011, anti-GPNMB), Golimumab (Simponi, anti-TNF- α), Gomaliximab (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), Lemaesomab (anti-NCA-90 (granulocyte antigen)), Lerdelimomab (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), Metelimomab (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), Odulimumab (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), Pentumomab (Theragyn, anti-MUCI), 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-CD 154 (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 $\alpha v\beta_3$), 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)), Zolimumab (anti-CD5), Etanercept (Enbrel®), Alefacept (Amevive®), Abatacept (Orencia®), Rilonecept (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 (Oncolad®, for prostate cancers), HNK20 (OraVax Inc. for respiratory syncytial virus), ImmurAIT (from Immunomedics for NHL), Lym-1 (anti-HLA-DRIO, 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, TP $\alpha\beta$ (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 Systems, NJ) and Cetuximab (ImClone, NJ) .

[0064] Other antibodies as binding 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), DLL4 (Δ -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 glycolipid, melanoma), GD3 idotype (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 ($\alpha v\beta_3$, $\alpha_5\beta_1$, $\alpha_6\beta_4$, $\alpha_{II}\beta_3$, $\alpha_5\beta_5$, $\alpha v\beta_5$, 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 apoptosis 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, 247-253 (2009); Novellino et al, Cancer Immunol Immunother. 54(3), 187-207 (2005). Franke, et al, Cancer Biother Radiopharm. 2000, 15, 459-76). Examples of these antigens that antibodies against are: Many other Cluster of Differentiations (CD4, CD5, CD6, CD7, CD8, CD9, CD10, CD11a, CD11b, CD11c, CD12w, CD14, CD15, CD16, CDw17, CD18, CD21, CD23, CD24, CD25, CD26, CD27, CD28, CD29, CD31, CD32, CD34, CD35, CD36, CD37, CD41, CD42, CD43, CD44, CD45, CD46, CD47, CD48, CD49b, CD49c, CD53, CD54, CD55, CD58, CD59, CD61, CD62E, CD62L, CD62P, CD63, CD68, CD69, CD71, CD72, CD79, CD81, CD82, CD83, CD86, CD87, CD88, CD89, CD90, CD91, CD95, CD96, CD100, CD103, CD105, CD106, CD109, CD117, CD120, CD127, CD133, CD134, CD135, CD138, CD141, CD142, CD143, CD144, CD147, CD151, CD152, CD154, CD156, CD158, CD163, CD166, CD168, CD184, CDw186, CD195, CD202 (a, b), CD209, CD235a, CD271, CD303, CD304), Annexin A1, Nucleolin, Endoglin (CD105), ROBO4, Amino-peptidase N, -like-4 (DLL4), VEGFR-2 (CD309), CXCR4 (CD184), Tie2, B7-H3, WT1, MUC1, LMP2, HPV E6 E7, EGFRvIII, HER-2/neu, Idiotype, MAGE A3, p53 nonmutant, NY-ESO-1, GD2, CEA, MelanA/MART1, Ras mutant, gp100, p53 mutant, Proteinase3 (PR1), bcr-abl, Tyrosinase, Survivin, hTERT, Sarcoma translocation break-points, EphA2, PAP, ML-IAP, AFP, EpCAM, ERG (TMPRSS2 ETS fusion gene), NA17, PAX3, ALK, Androgen receptor, Cyclin B1, Polysialic acid, MYCN, RhoC, TRP-2, GD3, Fucosyl GM1, Mesothelin, PSCA, MAGE A1, sLe(a), CYP1B1, PLAC1, GM3, BORIS, Tn, GloboH, ETV6-AML, NY-BR-1, RGS5, SART3, STn, Carbonic anhydrase IX, PAX5, OY-TES1, Sperm protein 17, LCK, HMWMAA, AKAP-4, SSX2, XAGE 1, B7H3, Legumain, Tie 2, Page4, VEGFR2, MAD-CT-1, FAP, PDGFR- β , MAD-CT-2, Fos-related antigen 1.

[0065] In another specific embodiment, the cell-binding -drug conjugates via the hydrophilic linkers of this invention are used for the treatment of cancers. The cancers include, but are not limited, Adrenocortical Carcinoma, Anal Cancer, Bladder Cancer, Brain Tumor (Adult, Brain Stem Glioma, Childhood, Cerebellar Astrocytoma, Cerebral Astrocytoma, Ependymoma, Medulloblastoma, Supratentorial Primitive Neuroectodermal and Pineal Tumors, Visual Pathway and Hypothalamic Glioma), Breast Cancer, Carcinoid Tumor, Gastrointestinal, Carcinoma of Unknown Primary, Cervical Cancer, Colon Cancer, Endometrial Cancer, Esophageal Cancer, Extrahepatic Bile Duct Cancer, Ewings Family of Tumors (PNET), Extracranial Germ Cell Tumor, Eye Cancer, Intraocular Melanoma, Gallbladder Cancer, Gastric Cancer (Stomach), Germ Cell Tumor, Extragonadal, Gestational Trophoblastic Tumor, Head and Neck Cancer, Hypopharyngeal Cancer, Islet Cell Carcinoma, Kidney Cancer (renal cell cancer), Laryngeal Cancer, Leukemia (Acute Lymphoblastic, Acute Myeloid, Chronic Lymphocytic, Chronic Myelogenous, Hairy Cell), Lip and Oral Cavity Cancer, Liver Cancer, Lung Cancer (Non-Small Cell, Small Cell, Lymphoma (AIDS-Related, Central Nervous System, Cutaneous T-Cell, Hodgkin's Disease, Non-Hodgkin's Disease, Malignant Mesothelioma, Melanoma, Merkel Cell Carcinoma, Metastatic Squamous Neck Cancer with Occult Primary, Multiple Myeloma, and Other Plasma Cell Neoplasms, Mycosis Fungoides, Myelodysplastic Syndrome, Myeloproliferative Disorders, Nasopharyngeal Cancer, Neuroblastoma, Oral Cancer, Oropharyngeal Cancer, Osteosarcoma, Ovarian Cancer (Epithelial, Germ Cell Tumor, Low Malignant Potential Tumor), Pancreatic Cancer (Exocrine, Islet Cell Carcinoma), Paranasal Sinus and Nasal Cavity Cancer, Parathyroid Cancer, Penile Cancer, Pheochromocytoma Cancer, Pituitary Cancer, Plasma Cell Neoplasm, Prostate Cancer Rhabdomyosarcoma, Rectal Cancer, Renal Cell Cancer (kidney cancer), Renal Pelvis and Ureter (Transitional Cell), Salivary Gland Cancer, Sezary Syndrome, Skin Cancer, Skin Cancer (Cutaneous T-Cell Lymphoma, Kaposi's Sarcoma, Melanoma), Small Intestine Cancer, Soft Tissue Sarcoma, Stomach Cancer, Testicular Cancer, Thymoma (Malignant), Thyroid Cancer, Urethral Cancer, Uterine Cancer (Sarcoma), Unusual Cancer of Childhood, Vaginal Cancer, Vulvar Cancer, Wilms' Tumor.

[0066] In another specific embodiment, the cell-binding-drug conjugates via the hydrophilic linkers of this invention are used in accordance with the compositions and methods for the treatment or prevention of an autoimmune disease. The autoimmune diseases include, but are not limited, Achlorhydra Autoimmune Active Chronic Hepatitis, Acute Disseminated Encephalomyelitis, Acute hemorrhagic leukoencephalitis, Addison's Disease, Agammaglobulinemia, Alopecia areata, Amyotrophic Lateral Sclerosis, Ankylosing Spondylitis, Anti-GBM/TBM Nephritis, Antiphospholipid syndrome, Antisynthetase syndrome, Arthritis, Atopic allergy, Atopic Dermatitis, Autoimmune Aplastic Anemia, Autoimmune cardiomyopathy, Autoimmune hemolytic anemia, Autoimmune hepatitis, Autoimmune inner ear disease, Autoimmune lymphoproliferative syndrome, Autoimmune peripheral neuropathy, Autoimmune pancreatitis, Autoimmune polyendocrine syndrome Types I, II, & III, Autoimmune progesterone dermatitis, Autoimmune thrombocytopenic purpura, Autoimmune uveitis, Balo disease/Balo concentric sclerosis, Behcet's Syndrome, Berger's disease, Bickerstaff's encephalitis, Blau syndrome, Bullous Pemphigoid, Castleman's disease, Chagas disease, Chronic Fatigue Immune Dysfunction Syndrome, Chronic inflammatory demyelinating polyneuropathy, Chronic recurrent multifocal osteomyelitis, Chronic Lyme disease, Chronic obstructive pulmonary disease, Churg-Strauss syndrome, Cicatricial Pemphigoid, Coeliac Disease, Cogan syndrome, Cold agglutinin disease, Complement component 2 deficiency, Cranial arteritis, CREST syndrome, Crohn's Disease (a type of idiopathic inflammatory bowel diseases), Cushing's Syndrome, Cutaneous leukocytoclastic angiitis, Dego's disease, Dercum's disease, Dermatitis herpetiformis, Dermatomyositis, Diabetes mellitus type 1, Diffuse cutaneous systemic sclerosis, Dressler's syndrome, Discoid lupus erythematosus, Eczema, Endometriosis, Entesitis-related

arthritis, Eosinophilic fasciitis, Epidermolysis bullosa acquisita, Erythema nodosum, Essential mixed cryoglobulinemia, Evan's syndrome, Fibrodysplasia ossificans progressiva, Fibromyalgia, Fibromyositis, Fibrosing aveolitis, Gastritis, Gastrointestinal pemphigoid, Giant cell arteritis, Glomerulonephritis, Goodpasture's syndrome, Graves' disease, Guillain-Barré syndrome, Hashimoto's encephalitis, Hashimoto's thyroiditis, Haemolytic anaemia, Henoch-Schonlein purpura, Herpes gestationis, Hidradenitis suppurativa, Hughes syndrome (See Antiphospholipid syndrome), Hypogammaglobulinemia, Idiopathic Inflammatory Demyelinating Diseases, Idiopathic pulmonary fibrosis, Idiopathic thrombocytopenic purpura (See Autoimmune thrombocytopenic purpura), IgA nephropathy (Also Berger's disease), Inclusion body myositis, Inflammatory demyelinating polyneuropathy, Interstitial cystitis, Irritable Bowel Syndrome, Juvenile idiopathic arthritis, Juvenile rheumatoid arthritis, Kawasaki's Disease, Lambert-Eaton myasthenic syndrome, Leukocytoclastic vasculitis, Lichen planus, Lichen sclerosus, Linear IgA disease (LAD), Lou Gehrig's Disease (Also Amyotrophic lateral sclerosis), Lupoid hepatitis, Lupus erythematosus, Majeed syndrome, Ménière's disease, Microscopic polyangiitis, Miller-Fisher syndrome, Mixed Connective Tissue Disease, Morphea, Mucha-Habermann disease, Muckle-Wells syndrome, Multiple Myeloma, Multiple Sclerosis, Myasthenia gravis, Myositis, Narcolepsy, Neuromyelitis optica (Devic's Disease), Neuro-myotonia, Occular cicatricial pemphigoid, Opsoclonus myoclonus syndrome, Ord thyroiditis, Palindromic rheumatism, PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus), Paraneoplastic cerebellar degeneration, Paroxysmal nocturnal hemoglobinuria, Parry Romberg syndrome, Parsonnage-Turner syndrome, Pars planitis, Pemphigus, Pemphigus vulgaris, Pernicious anaemia, Perivenous encephalomyelitis, POEMS syndrome, Polyarteritis nodosa, Polymyalgia rheumatica, Polymyositis, Primary biliary cirrhosis, Primary sclerosing cholangitis, Progressive inflammatory neuropathy, Psoriasis, Psoriatic Arthritis, Pyoderma gangrenosum, Pure red cell aplasia, Rasmussen's encephalitis, Raynaud phenomenon, Relapsing polychondritis, Reiter's syndrome, Restless leg syndrome, Retroperitoneal fibrosis, Rheumatoid arthritis, Rheumatoid fever, Sarcoidosis, Schizophrenia, Schmidt syndrome, Schnitzler syndrome, Scleritis, Scleroderma, Sjögren's syndrome, Spondyloarthropathy, Sticky blood syndrome, Still's Disease, Stiff person syndrome, Subacute bacterial endocarditis, Susac's syndrome, Sweet syndrome, Sydenham Chorea, Sympathetic ophthalmia, Takayasu's arteritis, Temporal arteritis (giant cell arteritis), Tolosa-Hunt syndrome, Transverse Myelitis, Ulcerative Colitis (a type of idiopathic inflammatory bowel diseases), Undifferentiated connective tissue disease, Undifferentiated spondyloarthropathy, Vasculitis, Vitiligo, Wegener's granulomatosis, Wilson's syndrome, Wiskott-Aldrich syndrome

[0067] In another specific embodiment, a binding molecule used for the conjugate via the hydrophilic linkers of this invention for the treatment or prevention of an autoimmune disease includes, but are not limited to, anti-elastin antibody; Abys against epithelial cells antibody; Anti-Basement Membrane Collagen Type IV Protein antibody; Anti-Nuclear Antibody; Anti ds DNA; Anti ss DNA; Anti Cardiolipin Antibody IgM, IgG; anti-celiac antibody; Anti Phospholipid Antibody IgK, IgG; Anti SM Antibody; Anti Mitochondrial Antibody; Thyroid Antibody; Microsomal Antibody, T-cells antibody; Thyroglobulin Antibody, Anti SCL-70; Anti-Jo; Anti-U.sub.IRNP; Anti-La/SSB; Anti SSA; Anti SSB; Anti Perital Cells Antibody; Anti Histones; Anti RNP; C-ANCA; P-ANCA; Anti centromere; Anti-Fibrillarin, and Anti GBM Antibody, Anti-ganglioside antibody; Anti-Desmoglein 3 antibody; Anti-p62 antibody; Anti-splOO antibody; Anti-Mitochondrial(M2) antibody; Rheumatoid factor antibody; Anti-MCV antibody; Anti-topoisomerase antibody; Anti-neutrophil cytoplasmic(cANCA) antibody;

[0068] In certain preferred embodiments, the binding molecule for the conjugate in the present invention, can bind to both a receptor or a receptor complex expressed on an activated lymphocyte which is associated with an autoimmune disease. The receptor or receptor complex can comprise an immunoglobulin gene superfamily member (e.g. CD2, CD3, CD4, CD8, CD19, CD20, CD22, CD28, CD30, CD37, CD38, CD56, CD70, CD79, CD90, CD125, CD152/CTLA-4, PD-1, or ICOS), a TNF receptor superfamily member (e.g. CD27, CD40, CD95/Fas, CD134/OX40, CD137/4-1BB, INF-R1, TNFR-2, RANK, TACI, BCMA, osteoprotegerin, Apo2/TRAIL-R1, TRAIL-R2, TRAIL-R3, TRAIL-R4, and APO-3), an integrin, a cytokine receptor, a chemokine receptor, a major histocompatibility protein, a lectin (C-type, S-type, or I-type), or a complement control protein.

[0069] In another specific embodiment, useful binding ligands that are immunospecific for a viral or a microbial antigen are humanized or human monoclonal antibodies. As used herein, the term "viral antigen" includes, but is not limited to, any viral peptide, polypeptide protein (e.g. HIV gp120, HIV nef, RSV F glycoprotein, influenza virus neuraminidase, influenza virus hemagglutinin, HTLV tax, herpes simplex virus glycoprotein (e.g. gB, gC, gD, and gE) and hepatitis B surface antigen) that is capable of eliciting an immune response. As used herein, the term "microbial antigen" includes, but is not limited to, any microbial peptide, polypeptide, protein, saccharide, polysaccharide, or lipid molecule (e.g., a bacterial, fungi, pathogenic protozoa, or yeast polypeptide including, e.g., LPS and capsular polysaccharide 5/8) that is capable of eliciting an immune response. Examples of antibodies available for the viral or microbial infection include, but are not limited to, Palivizumab which is a humanized anti-respiratory syncytial virus monoclonal antibody for the treatment of RSV infection; PRO542 which is a CD4 fusion antibody for the treatment of HIV infection; Ostavir which is a human antibody for the treatment of hepatitis B virus; PROTVIR which is a humanized IgG.sub.1 antibody for the treatment of cytomegalovirus; and anti-LPS antibodies.

[0070] The cell binding molecules-drug conjugates via the hydrophilic linkers of this invention can be used in the

treatment of infectious diseases. These infectious diseases include, but are not limited to, *Acinetobacter* infections, Actinomycosis, African sleeping sickness (African trypanosomiasis), AIDS (Acquired immune deficiency syndrome), Amebiasis, Anaplasmosis, Anthrax, *Arcanobacterium haemolyticum* infection, Argentine hemorrhagic fever, Ascariasis, Aspergillosis, Astrovirus infection, Babesiosis, *Bacillus cereus* infection, Bacterial pneumonia, Bacterial vaginosis, Bacteroides infection, Balantidiasis, Baylisascaris infection, BK virus infection, Black piedra, *Blastocystis hominis* infection, Blastomycosis, Bolivian hemorrhagic fever, *Borrelia* infection, Botulism (and Infant botulism), Brazilian hemorrhagic fever, Brucellosis, *Burkholderia* infection, Buruli ulcer, Calicivirus infection (Norovirus and Sapovirus), *Campylobacteriosis*, Candidiasis (Moniliasis; Thrush), Cat-scratch disease, Cellulitis, Chagas Disease (American trypanosomiasis), Chancroid, Chickenpox, Chlamydia, *Chlamydomydia pneumoniae* infection, Cholera, Chromoblastomycosis, Clonorchiasis, *Clostridium difficile* infection, Coccidioidomycosis, Colorado tick fever, Common cold (Acute viral rhinopharyngitis; Acute coryza), Creutzfeldt-Jakob disease, Crimean-Congo hemorrhagic fever, Cryptococcosis, Cryptosporidiosis, Cutaneous larva migrans, Cyclosporiasis, Cysticercosis, Cytomegalovirus infection, Dengue fever, Dientamoebiasis, Diphtheria, *Diphyllobothriasis*, *Dracunculiasis*, Ebola hemorrhagic fever, Echinococcosis, Ehrlichiosis, Enterobiasis (Pinworm infection), *Enterococcus* infection, Enterovirus infection, Epidemic typhus, Erythema infectiosum (Fifth disease), Exanthem subitum, Fasciolopsiasis, Fasciolosis, Fatal familial insomnia, Filariasis, Food poisoning by *Clostridium perfringens*, Free-living amebic infection, *Fusobacterium* infection, Gas gangrene (*Clostridial myonecrosis*), Geotrichosis, Gerstmann-Sträussler-Scheinker syndrome, Giardiasis, Glanders, *Gnathostomiasis*, Gonorrhea, Granuloma inguinale (Donovanosis), Group A streptococcal infection, Group B streptococcal infection, *Haemophilus influenzae* infection, Hand, foot and mouth disease (HFMD), Hantavirus Pulmonary Syndrome, *Helicobacter pylori* infection, Hemolytic-uremic syndrome, Hemorrhagic fever with renal syndrome, Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, Hepatitis E, Herpes simplex, Histoplasmosis, Hookworm infection, Human bocavirus infection, Human ewingii ehrlichiosis, Human granulocytic anaplasmosis, Human metapneumovirus infection, Human monocytic ehrlichiosis, Human papillomavirus infection, Human parainfluenza virus infection, Hymenolepiasis, Epstein-Barr Virus Infectious Mononucleosis (Mono), Influenza, Isosporiasis, Kawasaki disease, Keratitis, *Kingella kingae* infection, Kuru, Lassa fever, Legionellosis (Legionnaires' disease), Legionellosis (Pontiac fever), Leishmaniasis, Leprosy, Leptospirosis, Listeriosis, Lyme disease (Lyme borreliosis), Lymphatic filariasis (Elephantiasis), Lymphocytic choriomeningitis, Malaria, Marburg hemorrhagic fever, Measles, Melioidosis (Whitmore's disease), Meningitis, Meningococcal disease, Metagonimiasis, Microsporidiosis, *Molluscum contagiosum*, Mumps, Murine typhus (Endemic typhus), *Mycoplasma pneumoniae*, Mycetoma, Myiasis, Neonatal conjunctivitis (*Ophthalmia neonatorum*), (New) Variant Creutzfeldt-Jakob disease (vCJD, nvCJD), Nocardiosis, Onchocerciasis (River blindness), Paracoccidioidomycosis (South American blastomycosis), Paragonimiasis, Pasteurellosis, *Pediculus capitis* (Head lice), *Pediculus corporis* (Body lice), *Pediculus pubis* (Pubic lice, Crab lice), Pelvic inflammatory disease, Pertussis (Whooping cough), Plague, Pneumococcal infection, *Pneumocystis pneumoniae*, Pneumonia, Poliomyelitis, *Prevotella* infection, Primary amoebic meningoencephalitis, Progressive multifocal leukoencephalopathy, Psittacosis, Q fever, Rabies, Rat-bite fever, Respiratory syncytial virus infection, Rhinosporidiosis, Rhinovirus infection, Rickettsial infection, Rickettsialpox, Rift Valley fever, Rocky mountain spotted fever, Rotavirus infection, Rubella, Salmonellosis, SARS (Severe Acute Respiratory Syndrome), Scabies, Schistosomiasis, Sepsis, Shigellosis (Bacillary dysentery), Shingles (Herpes zoster), Smallpox (Variola), Sporotrichosis, Staphylococcal food poisoning, Staphylococcal infection, Strongyloidiasis, Syphilis, Taeniasis, Tetanus (Lockjaw), *Tinea barbae* (Barber's itch), *Tinea capitis* (Ringworm of the Scalp), *Tinea corporis* (Ringworm of the Body), *Tinea cruris* (Jock itch), *Tinea manuum* (Ringworm of the Hand), *Tinea nigra*, *Tinea pedis* (Athlete's foot), *Tinea unguium* (Onychomycosis), *Tinea versicolor* (Pityriasis versicolor), Toxocariasis (Ocular Larva Migrans), Toxocariasis (Visceral Larva Migrans), Toxoplasmosis, Trichinellosis, Trichomoniasis, Trichuriasis (Whipworm infection), Tuberculosis, Tularemia, *Ureaplasma urealyticum* infection, Venezuelan equine encephalitis, Venezuelan hemorrhagic fever, Viral pneumonia, West Nile Fever, White piedra (*Tinea blanca*), *Yersinia pseudotuberculosis* infection, Yersiniosis, Yellow fever, Zygomycosis.

[0071] The cell binding molecules, which are more proffered to be antibodies described in this patent that are against pathogenic strains include, but are not limit, *Acinetobacter baumannii*, *Actinomyces israelii*, *Actinomyces gerencseriae* and *Propionibacterium propionicus*, *Trypanosoma brucei*, HIV (Human immunodeficiency virus), *Entamoeba histolytica*, *Anaplasma* genus, *Bacillus anthracis*, *Arcanobacterium haemolyticum*, Junin virus, *Ascaris lumbricoides*, *Aspergillus* genus, Astroviridae family, *Babesia* genus, *Bacillus cereus*, multiple bacteria, *Bacteroides* genus, *Balantidium coli*, *Baylisascaris* genus, BK virus, *Piedraia hortae*, *Blastocystis hominis*, *Blastomyces dermatitidis*, Machupo virus, *Borrelia* genus, *Clostridium botulinum*, *Sabia*, *Brucella* genus, usually *Burkholderia cepacia* and other *Burkholderia* species, *Mycobacterium ulcerans*, Caliciviridae family, *Campylobacter* genus, usually *Candida albicans* and other *Candida* species, *Bartonella henselae*, Group A *Streptococcus* and *Staphylococcus*, *Trypanosoma cruzi*, *Haemophilus ducreyi*, Varicella zoster virus (VZV), *Chlamydia trachomatis*, *Chlamydomydia pneumoniae*, *Vibrio cholerae*, *Fonsecaea pedrosoi*, *Clonorchis sinensis*, *Clostridium difficile*, *Coccidioides immitis* and *Coccidioides posadasii*, Colorado tick fever virus, rhinoviruses, coronaviruses, CJD prion, Crimean-Congo hemorrhagic fever virus, *Cryptococcus neoformans*, *Cryptosporidium* genus, *Ancylostoma braziliense*; multiple parasites, *Cyclospora cayetanensis*, *Taenia solium*, Cytomegalovirus, Dengue viruses (DEN-1, DEN-2, DEN-3 and DEN-4) - Flaviviruses, *Dientamoeba fragilis*, *Corynebacterium diph-*

theriae, *Diphyllobothrium*, *Dracunculus medinensis*, *Ebolavirus*, *Echinococcus* genus, *Ehrlichia* genus, *Enterobius vermicularis*, *Enterococcus* genus, *Enterovirus* genus, *Rickettsia prowazekii*, *Parvovirus B19*, *Human herpesvirus 6* and *Human herpesvirus 7*, *Fasciolopsis buski*, *Fasciola hepatica* and *Fasciola gigantica*, FFI prion, *Filarioidea* superfamily, *Clostridium perfringens*, *Fusobacterium* genus, *Clostridium perfringens*; other *Clostridium* species, *Geotrichum candidum*, GSS prion, *Giardia intestinalis*, *Burkholderia mallei*, *Gnathostoma spinigerum* and *Gnathostoma hispidum*, *Neisseria gonorrhoeae*, *Klebsiella granulomatis*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Haemophilus influenzae*, *Enteroviruses*, mainly *Coxsackie A virus* and *Enterovirus 71*, *Sin Nombre virus*, *Helicobacter pylori*, *Escherichia coli* O157:H7, *Bunyaviridae* family, *Hepatitis A Virus*, *Hepatitis B Virus*, *Hepatitis C Virus*, *Hepatitis D Virus*, *Hepatitis E Virus*, *Herpes simplex virus 1*, *Herpes simplex virus 2*, *Histoplasma capsulatum*, *Ancylostoma duodenale* and *Necator americanus*, *Hemophilus influenzae*, *Human bocavirus*, *Ehrlichia ewingii*, *Anaplasma phagocytophilum*, *Human metapneumovirus*, *Ehrlichia chaffeensis*, *Human papillomavirus*, *Human parainfluenza viruses*, *Hymenolepis nana* and *Hymenolepis diminuta*, *Epstein-Barr Virus*, *Orthomyxoviridae* family, *Isospora belli*, *Kingella kingae*, *Klebsiella pneumoniae*, *Klebsiella ozaenas*, *Klebsiella rhinoscleromatis*, *Kuru prion*, *Lassa virus*, *Legionella pneumophila*, *Legionella pneumophila*, *Leishmania* genus, *Mycobacterium leprae* and *Mycobacterium lepromatosis*, *Leptospira* genus, *Listeria monocytogenes*, *Borrelia burgdorferi* and other *Borrelia* species, *Wuchereria bancrofti* and *Brugia malayi*, *Lymphocytic choriomeningitis virus (LCMV)*, *Plasmodium* genus, *Marburg virus*, *Measles virus*, *Burkholderia pseudomallei*, *Neisseria meningitidis*, *Metagonimus yokagawai*, *Microsporidia* phylum, *Molluscum contagiosum virus (MCV)*, *Mumps virus*, *Rickettsia typhi*, *Mycoplasma pneumoniae*, numerous species of bacteria (*Actinomyces* and *Actinomyces*) and fungi (*Eumycetozoa*), parasitic dipterous fly larvae, *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, vCJD prion, *Nocardia asteroides* and other *Nocardia* species, *Onchocerca volvulus*, *Paracoccidioides brasiliensis*, *Paragonimus westermani* and other *Paragonimus* species, *Pasteurella* genus, *Pediculus humanus capitis*, *Pediculus humanus corporis*, *Phthirus pubis*, *Bordetella pertussis*, *Yersinia pestis*, *Streptococcus pneumoniae*, *Pneumocystis jirovecii*, *Poliovirus*, *Prevotella* genus, *Naegleria fowleri*, *JC virus*, *Chlamydia psittaci*, *Coxiella burnetii*, *Rabies virus*, *Streptobacillus moniliformis* and *Spirillum minus*, *Respiratory syncytial virus*, *Rhinosporidium seeberi*, *Rhinovirus*, *Rickettsia* genus, *Rickettsia akari*, *Rift Valley fever virus*, *Rickettsia rickettsii*, *Rotavirus*, *Rubella virus*, *Salmonella* genus, *SARS coronavirus*, *Sarcoptes scabiei*, *Schistosoma* genus, *Shigella* genus, *Varicella zoster virus*, *Variola major* or *Variola minor*, *Sporothrix schenckii*, *Staphylococcus* genus, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Strongyloides stercoralis*, *Treponema pallidum*, *Taenia* genus, *Clostridium tetani*, *Trichophyton* genus, *Trichophyton tonsurans*, *Trichophyton* genus, *Epidermophyton floccosum*, *Trichophyton rubrum*, and *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Hortaea werneckii*, *Trichophyton* genus, *Malassezia* genus, *Toxocara canis* or *Toxocara cati*, *Toxoplasma gondii*, *Trichinella spiralis*, *Trichomonas vaginalis*, *Trichuris trichiura*, *Mycobacterium tuberculosis*, *Francisella tularensis*, *Ureaplasma urealyticum*, *Venezuelan equine encephalitis virus*, *Vibrio cholerae*, *Guanarito virus*, *West Nile virus*, *Trichosporon beigeli*, *Yersinia pseudotuberculosis*, *Yersinia enterocolitica*, *Yellow fever virus*, *Mucorales* order (*Mucormycosis*) and *Entomophthorales* order (*Entomophthoramycosis*), *Pseudomonas aeruginosa*, *Campylobacter (Vibrio) fetus*, *Aeromonas hydrophila*, *Edwardsiella tarda*, *Yersinia pestis*, *Shigella dysenteriae*, *Shigella flexneri*, *Shigella sonnei*, *Salmonella typhimurium*, *Treponema pertense*, *Treponema caratense*, *Borrelia vincentii*, *Borrelia burgdorferi*, *Leptospira icterohemorrhagiae*, *Pneumocystis carinii*, *Brucella abortus*, *Brucella suis*, *Brucella melitensis*, *Mycoplasma* spp., *Rickettsia prowazekii*, *Rickettsia tsutsugumushi*, *Chlamydia* spp.; pathogenic fungi (*Aspergillus fumigatus*, *Candida albicans*, *Histoplasma capsulatum*); protozoa (*Entamoeba histolytica*, *Trichomonas tenax*, *Trichomonas hominis*, *Trypanosoma gambiense*, *Trypanosoma rhodesiense*, *Leishmania donovani*, *Leishmania tropica*, *Leishmania braziliensis*, *Pneumocystis pneumonia*, *Plasmodium vivax*, *Plasmodium falciparum*, *Plasmodium malariae*); or Helminths (*Schistosoma japonicum*, *Schistosoma mansoni*, *Schistosoma haematobium*, and hookworms).

[0072] Other antibodies as cell binding ligands used in this invention for treatment of viral disease include, but are not limited to, antibodies against antigens of pathogenic viruses, including as examples and not by limitation: *Poxviridae*, *Herpesviridae*, *Adenoviridae*, *Papovaviridae*, *Enteroviridae*, *Picornaviridae*, *Parvoviridae*, *Reoviridae*, *Retroviridae*, influenza viruses, parainfluenza viruses, mumps, measles, respiratory syncytial virus, rubella, *Arboviridae*, *Rhabdoviridae*, *Arenaviridae*, *Non-A/Non-B Hepatitis virus*, *Rhinoviridae*, *Coronaviridae*, *Rotoviridae*, *Oncovirus* [such as, *HBV* (*Hepatocellular carcinoma*), *HPV* (*Cervical cancer*, *Anal cancer*), *Kaposi's sarcoma-associated herpesvirus* (*Kaposi's sarcoma*), *Epstein-Barr virus* (*Nasopharyngeal carcinoma*, *Burkitt's lymphoma*, *Primary central nervous system lymphoma*), *MCPyV* (*Merkel cell cancer*), *SV40* (*Simian virus 40*), *HCV* (*Hepatocellular carcinoma*), *HTLV-I* (*Adult T-cell leukemia/lymphoma*)], Immune disorders caused virus: [such as *Human Immunodeficiency Virus (AIDS)*]; Central nervous system virus: [such as, *JCV* (*Progressive multifocal leukoencephalopathy*), *MeV* (*Subacute sclerosing panencephalitis*), *LCV* (*Lymphocytic choriomeningitis*), *Arbovirus encephalitis*, *Orthomyxoviridae* (probable) (*Encephalitis lethargica*), *RV* (*Rabies*), *Chandipura virus*, *Herpesviral meningitis*, *Ramsay Hunt syndrome type II*; *Poliovirus* (*Poliomyelitis*, *Post-polio syndrome*), *HTLV-I* (*Tropical spastic paraparesis*)]; *Cytomegalovirus* (*Cytomegalovirus retinitis*, *HSV* (*Herpetic keratitis*)); *Cardiovascular virus* [such as *CBV* (*Pericarditis*, *Myocarditis*)]; *Respiratory system/acute viral nasopharyngitis/viral pneumonia*: [*Epstein-Barr virus* (*EBV infection/Infectious mononucleosis*), *Cytomegalovirus*; *SARS coronavirus* (*Severe acute respiratory syndrome*) *Orthomyxoviridae*: *Influenzavirus A/B/C* (*Influenza/Avian influenza*), *Paramyxovirus*: *Human*

parainfluenza viruses (Parainfluenza), RSV (Human respiratory syncytial virus), hMPV]; Digestive system virus [MuV (Mumps), Cytomegalovirus (Cytomegalovirus esophagitis); Adenovirus (Adenovirus infection); Rotavirus, Norovirus, Astrovirus, Coronavirus; HBV (Hepatitis B virus), CBV, HAV (Hepatitis A virus), HCV (Hepatitis C virus), HDV (Hepatitis D virus), HEV (Hepatitis E virus), HGV (Hepatitis G virus)]; Urogenital virus [such as, BK virus, MuV (Mumps)].

[0073] According to a further object, the present invention also concerns pharmaceutical compositions comprising the conjugate via the hydrophilic linkers of the invention together with a pharmaceutically acceptable carrier for treatment of cancer and autoimmune disorders. The method for treatment of cancer and autoimmune disorders can be practiced *in vitro*, *in vivo*, or *ex vivo*. Examples of *in vitro* uses include treatments of cell cultures in order to kill all cells except for desired variants that do not express the target antigen; or to kill variants that express undesired antigen. Examples of *ex vivo* uses include treatments of hematopoietic stem cells (HSC) prior to the performance of the transplantation (HSCT) into the same patient in order to kill diseased or malignant cells. For instance, clinical *ex vivo* treatment to remove tumour cells or lymphoid cells from bone marrow prior to autologous transplantation in cancer treatment or in treatment of autoimmune disease, or to remove T cells and other lymphoid cells from allogeneic bone marrow or tissue prior to transplant in order to prevent graft-versus-host disease, can be carried out as follows. Bone marrow is harvested from the patient or other individual and then incubated in medium containing serum to which is added the conjugate of the invention, concentrations range from about 1 pM to 0.1 mM, for about 30 minutes to about 48 hours at about 37 °C. The exact conditions of concentration and time of incubation (=dose) are readily determined by the skilled clinicians. After incubation the bone marrow cells are washed with medium containing serum and returned to the patient by i.v. infusion according to known methods. In circumstances where the patient receives other treatment such as a course of ablative chemotherapy or total-body irradiation between the time of harvest of the marrow and reinfusion of the treated cells, the treated marrow cells are stored frozen in liquid nitrogen using standard medical equipment.

[0074] For clinical *in vivo* use, the conjugate via the linkers of the invention will be supplied as solutions or as a lyophilized solid that can be redissolved in sterile water for injection. Examples of suitable protocols of conjugate administration are as follows. Conjugates are given weekly for 8 weeks as an i.v. bolus. Bolus doses are given in 50 to 500 ml of normal saline to which human serum albumin (e.g. 0.5 to 1 mL of a concentrated solution of human serum albumin, 100 mg/mL) can be added. Dosages will be about 50 µg to 20 mg/kg of body weight per week, i.v. (range of 10 µg to 200 mg/kg per injection). 8 weeks after treatment, the patient may receive a second course of treatment. Specific clinical protocols with regard to route of administration, excipients, diluents, dosages, times, etc., can be determined by the skilled clinicians.

[0075] Examples of medical conditions that can be treated according to the *in vivo* or *ex vivo* methods of killing selected cell populations include malignancy of any types of cancer, autoimmune diseases, graft rejections, and infections (viral, bacterial or parasite).

[0076] The amount of a conjugate which is required to achieve the desired biological effect, will vary depending upon a number of factors, including the chemical characteristics, the potency, and the bioavailability of the conjugates, the type of disease, the species to which the patient belongs, the diseased state of the patient, the route of administration, all factors which dictate the required dose amounts, delivery and regimen to be administered.

[0077] In general terms, the conjugates via the linkers of this invention may be provided in an aqueous physiological buffer solution containing 0.1 to 10% w/v conjugates for parenteral administration. Typical dose ranges are from 1 µg/kg to 0.1 g/kg of body weight per day; a preferred dose range is from 0.01 mg/kg to 20 mg/kg of body weight per day or an equivalent dose in a human child. The preferred dosage of drug to be administered is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, the formulation of the compound, the route of administration (intravenous, intramuscular, or other), the pharmacokinetic properties of the compound by the chosen delivery route, and the speed (bolus or continuous infusion) and schedule of administrations (number of repetitions in a given period of time).

[0078] The conjugates via the linkers of the present invention are also capable of being administered in unit dose forms, wherein the term "unit dose" means a single dose which is capable of being administered to a patient, and which can be readily handled and packaged, remaining as a physically and chemically stable unit dose comprising either the active conjugate itself, or as a pharmaceutically acceptable composition, as described hereinafter. As such, typical total daily dose ranges are from 0.01 to 100 mg/kg of body weight. By way of general guidance, unit doses for humans range from 1 mg to 3000 mg per day. Preferably the unit dose range is from 1 to 500 mg administered one to four times a day, and even more preferably from 10 mg to 500 mg, once a day. Conjugates provided herein can be formulated into pharmaceutical compositions by admixture with one or more pharmaceutically acceptable excipients. Such unit dose compositions may be prepared for use by oral administration, particularly in the form of tablets, simple capsules or soft gel capsules; or intranasally, particularly in the form of powders, nasal drops, or aerosols; or dermally, for example, topically in ointments, creams, lotions, gels or sprays, or via transdermal patches.

DRUGS/CYTOTOXIC AGENTS

[0079] Drugs that can be conjugated to a cell-binding molecule in the present invention are small molecule drugs including cytotoxic agents, which can be linked to or after they are modified for linkage to the cell-binding agent. A "small molecule drug" is broadly used herein to refer to an organic, inorganic, or organometallic compound that may have a molecular weight of for example 100 to 1800, more suitably from 120 to 1400. Small molecule drugs are well characterized in the art, such as in WO05058367A2, and in U.S. Patent No. 4,956,303, among others and are incorporated in their entirety by reference. The drugs include known drugs and those that may become known drugs.

[0080] Drugs that are known include, 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., dimers of pyrrolbenzodiazepine (PBD) or tomaymycin, indolinobenzodiazepines, imidazobenzothiadiazepines, or oxazolidinobenzodiazepines); Nitrosoureas: (carmustine, lomustine, chlorozotocin, fotemustine, nimustine, ranimustine); Alkylsulphonates: (busulfan, treosulfan, improsulfan and piposulfan); Triazines: (dacarbazine); Platinum containing compounds: (carboplatin, cisplatin, oxaliplatin); aziridines, such as benzodopa, carbouquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphoramide and trimethylolomelamine]; b). Plant Alkaloids: such as Vinca alkaloids: (vincristine, vinblastine, vindesine, vinorelbine, navelbin); Taxoids: (paclitaxel, docetaxol) and their analogs, Maytansinoids (DM1, DM2, DM3, DM4, maytansine and ansamitocins) and their analogs, cryptophycins (particularly cryptophycin 1 and cryptophycin 8); epothilones, eleutherobin, discodermolide, bryostatins, dolostatins, auristatins, tubulysins, cephalostatins; pancratistatin; a sarcodictyin; spongistatin; c). DNA Topoisomerase Inhibitors: such as [Epidophyllins: (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, deferroxamine)]; [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: (goserelin, leuprolide acetate); Antiandrogens: (bicalutamide, flutamide, calusterone, dromostanolone propionate, epitostanol, 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, demethoxyhypocrellin 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 γ 1, δ 1, α 1 and β 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 antibiotic chromomorphores), aclacinomysins, actinomycin, anthramycin, azaserine, bleomycins, cactinomycin, carabacin, 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, alloectin-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, mitoxantrone, 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) ; Thapsi-

gargin, 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; PSK®; razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2, 2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verrucarín 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, astramicin, gentamicin (netilmicin, sisomicin, isepamicin), hygromycin B, kanamycin (amikacin, arbekacin, bekanamycin, dibekacin, tobramycin), neomycin (framycetin, paromomycin, ribostamycin), netilmicin, spectinomycin, streptomycin, tobramycin, verdamycin; b). Amphenicols: azidamfenicol, chloramphenicol, florfenicol, thiamphenicol; c). Ansamycins: geldanamycin, herbimycin; d). Carbapenems: biapenem, doripenem, ertapenem, imipenem/cilastatin, meropenem, panipenem; e). Cepheims: 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, ceftazolidime, cefuroxime, cefixime, cefdinir, cefditoren, cefepime, cefetamet, cefmenoxime, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotiam, cefozopran, cephalixin, cefpimizole, cefpiramide, cefpirome, cefpodoxime, cefprozil, cefquinome, cefsulodin, ceftazidime, cefteteram, ceftibuten, ceftioleone, ceftizoxime, ceftobiprole, ceftriaxone, cefuroxime, cefuzonam, *cephamycin* (cefroxitin, 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 phenoxymethylpenicillin, 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: pristnamycin, quinupristin/dalfopristin; r). Sulfonamides: mafenide, prontosis, 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: annomycin, arspenamine, bactoprenol inhibitors (Bacitracin), DADAL/AR inhibitors (cycloserine), dictyostatin, discodermolide, eleutherothin, epothilone, ethambutol, etoposide, faropenem, fusidic acid, furazolidone, isoniazid, laulimalide, metronidazole, mupirocin, mycolactone, NAM synthesis inhibitors (e. g. fosfomicin), nitrofurantoin, paclitaxel, platen-simycin, pyrazinamide, quinupristin/dalfopristin, rifampicin (rifampin), tazobactam tinidazole, uvaricin;

4). Anti-viral drugs: a). Entry/fusion inhibitors: aplatviroc, 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, dextelvucitabine, 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, racicivir, ribavirin, stampidine, stavudine (d4T), taribavirin (viramidine), telbivudine, tenofovir, trifluridine valaciclovir.

valganciclovir, zalcitabine (ddC), zidovudine (AZT); f). Non-nucleosides: amantadine, atevirdine, 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 hydrophilic linker of the present invention also include radioisotopes. Examples of radioisotopes (radionuclides) are ^3H , ^{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): 1137-1146). The cell binding molecules, e.g. an antibody can be labeled with ligand reagents through the hydrophilic 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, N.Y., Pubs. (1991). Chelating ligands which may complex a metal ion include DOTA, DOTP, DOTMA, DTPA and TETA (Macrocyclics, Dallas, Tex.).

6) The present disclosure also relates to pharmaceutically acceptable salts, acids or derivatives of any of the above drugs.

[0081] Cytotoxic agents include tubulysins, maytansinoids, taxanoids (taxanes), CC-1065 analogs, daunorubicin and doxorubicin compounds, benzodiazepine dimers (e.g., dimers of pyrrolobenzodiazepine (PBD), tomaymycin, anthramycin, indolinobenzodiazepines, imidazobenzothiadiazepines, or oxazolidinobenzodiazepines), calicheamicins and the enediyne antibiotics, actinomycin, azaserines, bleomycins, epirubicin, tamoxifen, idarubicin, dolastatins/auristatins (e.g. monomethyl auristatin E, MMAE, MMAF, auristatin PYE, auristatin TP, Auristatins 2-AQ, 6-AQ, EB (AEB), and EFP (AEFP)), duocarmycins, thiotepa, vincristine, hemisterilins, and esperamicins, and their analogues and derivatives thereof.

[0082] Tubulysins that are preferred for conjugation in the present invention 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, 238-240. Wipf, P.; et al. Org. Lett., 2004, 6, 4057-4060. Pando, O.; et al. J. Am. Chem. Soc., 2011, 133, 7692-7695. Reddy, J. A.; et al. Mol. Pharmaceutics, 2009, 6, 1518-1525. Raghavan, B.; et al. J. Med. Chem., 2008, 51, 1530-1533. Patterson, A. W.; et al. J. Org. Chem., 2008, 73, 4362-4369. Pando, O.; et al. Org. Lett., 2009, 11 (24), pp 5567-5569. Wipf, P.; et al. Org. Lett., 2007, 9 (8), 1605-1607. Friestad, G. K.; Org. Lett., 2004, 6, pp 3249-3252. Hillary M. Peltier, H. M.; et al. J. Am. Chem. Soc., 2006, 128, 16018-16019. Chandrasekhar, S.; et al. J. Org. Chem., 2009, 74, 9531-9534. Liu, Y.; et al. Mol. Pharmaceutics, 2012, 9, 168-175. Friestad, G. K.; et al. Org. Lett., 2009, 11, 1095-1098. Kubicek, K.; et al., Angew Chem Int Ed Engl, 2010, 49: p. 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), PCT WO 2010034724. Leamon, C.; et al, PCT WO 2010033733, WO 2009002993. Ellman, J.; et al, PCT WO 2009134279; PCT WO 2009012958, US appl. 20110263650, 20110021568, Matschiner, G.; et al, PCT WO 2009095447. Vlahov, I.; et al, PCT WO 2009055562, WO 2008112873. Low, P.; et al, PCT WO 2009026177. Richter, W., PCT WO 2008138561. Kjems, J.; et al, PCT WO 2008125116. Davis, M.; et al, PCT WO 2008076333. Diener, J.; et al, U.S. Pat. Appl. 20070041901, WO 2006096754. Matschiner, G.; et al, PCT WO 2006056464. Vaghefi, F.; et al, 5 PCT WO 2006033913. Doemling, A., Ger. Offen. DE 102004030227; PCT WO 2004005327; WO 2004005326; WO 2004005269. Stanton, M.; et al, U.S. Pat. Appl. Publ. 20040249130. Hoefle, G.; et al, Ger. Offen. DE 10254439; DE 10241152; DE 10008089. Leung, D.; et al, PCT WO 2002077036. Reichenbach, H.; et al, Ger. Offen. DE 19638870; Wolfgang, R.; US 20120129779, Chen, H., US appl. 20110027274. The preferred structure of tubulysins for conjugation of cell binding molecules are described in the patent application of PCT/IB2012/053554

[0083] Calicheamicins and their related enediyne antibiotics are described in: Nicolaou, K. C. et al, Science 1992, 256, 1172-1178; Proc. Natl. Acad. Sci USA. 1993, 90, 5881-5888), 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.

[0084] Maytansinoids and maytansinol analogues are described in U.S. Patent Nos. 4,256,746, 4,361,650 and 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, 8,163,888.

[0085] Taxanes, which includes Paclitaxel (Taxol), a cytotoxic natural product, and docetaxel (Taxotere), a semi-

synthetic derivative, and their analogs are exemplified in: K C. Nicolaou et al., J. Am. Chem. Soc. 117, 2409-2420, (1995); Ojima et al., J. Med. Chem. 39:3889-3896 (1996); 40:267-278 (1997); 45, 5620-5623 (2002); Ojima et al., Proc. Natl. Acad. Sci., 96:4256-4261 (1999); Kim et al., Bull. Korean Chem. Soc., 20, 1389-1390 (1999); Miller, et al. J. Med. Chem., 47, 4802-4805 (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; 7,667,054.

[0086] 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; 6654-6661, 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, 8,012,978.

[0087] Daunorubicin/Doxorubicin and their synthesis are exemplified in: Hurwitz, E., et al., Cancer Res. 35, 1175-1181 (1975). Yang, H. M., and Reisfeld, R. A., Proc. Natl. Acad. Sci. 85, 1189-1193 (1988); Pietersz, C. A., E., et al., E., et al., "Cancer Res. 48, 926-9311 (1988); Trouet, et al., 79, 626-629 (1982); Z. Brich et al., J. Controlled Release, 19, 245-258 (1992); Chen et al., Syn. Comm., 33, 2377-2390, 2003; King et al., Bioconj. Chem., 10, 279-288, 1999; King et al., J. Med. Chem., 45, 4336-4343, 2002; Kratz et al., J Med Chem. 45, 5523-33. 2002; Kratz et al., Biol Pharm Bull. Jan. 21, 56-61, 1998; Lau et al., Bioorg. Med. Chem. 3, 1305-1312, 1995; Scott et al., Bioorg. Med. Chem. Lett. 6, 1491-1496; 1996; Watanabe et al., Tokai J. Experimental Clin. Med. 15, 327-334, 1990; Zhou et al., J. Am. Chem. Soc. 126, 15656-7, 2004; WO 01/38318; U.S. Patent No.). 5,106,951; 5,122,368; 5,146,064; 5,177,016; 5,208,323; 5,824,805; 6,146,658; 6,214,345; 7569358; 7,803,903; 8,084,586; 8,053,205.

[0088] The auristatins (e. g. auristatin E (AE) auristatin EB (AEB), auristatin EFP (AEFP), monomethyl auristatin E (MMAE), Monomethylauristatin (MMAF), Auristatin F phenylene diamine (AFP) and a phenylalanine variant of MMAE) which are synthetic analogs of dolastatins, are described in Int. J. Oncol. 15:367-72 (1999); Molecular Cancer Therapeutics, vol. 3, No. 8, pp. 921-932 (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.

[0089] The benzodiazepine dimers (e. g. dimers of pyrrolbenzodiazepine (PBD) or (tomaymycin), indolinobenzodiazepines, imidazobenzothiadiazepines, or oxazolidinobenzodiazepines) which are preferred cytotoxic agents according to the present invention are exemplified in the art: 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.

[0090] Analogues and derivatives of the cytotoxic drugs/agents described in the present patent can be conjugated via a hydrophilic linker of the present patent. One skilled in the art of drugs/cytotoxic agents will readily understand that each of the drugs/cytotoxic agents described herein can be modified in such a manner that the resulting compound still retains the specificity and/or activity of the starting compound. The skilled artisan will also understand that many of these compounds can be used in place of the drugs/cytotoxic agents described herein.

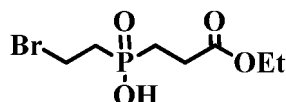
EXAMPLES

[0091] The invention is further described in the following examples, which are not intended to limit the scope of the invention. Cell lines described in the following examples were maintained in culture according to the conditions specified by the American Type Culture Collection (ATCC) or Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH,

Braunschweig, Germany (DMSZ), unless otherwise specified. Cell culture reagents were obtained from Invitrogen Corp., unless otherwise specified. All anhydrous solvents were commercially obtained and stored in Sure-seal bottles under nitrogen. All other reagents and solvents were purchased as the highest grade available and used without further purification. NMR spectra were recorded on Varian Mercury 300 MHz Instrument. Chemical shifts (δ) are reported in parts per million (ppm) referenced to tetramethylsilane at 0.00 and coupling constants (J) are reported in Hz. Low resolution mass spectral data were acquired on a Waters Micromass ZMD mass spec with Waters 2795 HPLC separations module and the 2996 photodiode array detector.

Example 1: (2-Bromoethyl)(3-ethoxy-3-oxopropyl)phosphinic acid (or ethyl 3-[2-Bromoethyl(hydroxy)phosphinyl]propanoate) (**4**)

[0092]



[0093] A mixture of ammonium hypophosphite (8.00 g, 96 mmol) and hexamethyldisilazane (20.0 mL, 96 mmol) was heated at 120 °C for 1 h under argon. After the mixture was cooled to 0 °C, ethyl acrylate (10.4 mL, 96 mmol) was carefully added dropwise, and the resulting mixture was stirred at 50 °C for 2 h. Then the mixture was cooled to room temperature, dibromoethane (40.0 mL) was added, and the mixture was stirred for 5 h at 120 °C. The formed trimethylbromosilane and excess dibromoethane were removed under vacuum. Then 100 mL of aqueous ethanol (1:1) were added dropwise to the residue and refluxed for 0.5 h. Then the solvent was removed under vacuum and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and the solvent was removed under vacuum to give the title compound **4** (10.85 g, 41% yield). ^1H NMR (300 MHz, CD_3OD): δ 1.26 (t, J = 7.1 Hz, 3H), 2.07 (m, 2H), 2.42 (m, 2H), 2.62 (m, 2H), 3.59 (m, 2H), 4.15 (q, J = 7.1 Hz, 2H). ^{31}P NMR (100 MHz, CD_3OD): δ 49.5; ESI MS m/z - $\text{C}_7\text{H}_{13}\text{BrO}_4\text{P}$ (M-H), calcd. 271.98, found 271.97.

Example 2. Ethyl 3-[2-Bromoethyl(ethoxy)phosphinyl]propanoate (**5**) and Ethyl 3-[Ethoxy(vinyl)phosphinyl]propanoate (**6**).

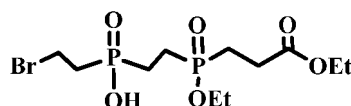
[0094]



[0095] An amount of 10.84 g of **4** (20 mmol) was treated with 100.0 mL of triethyl orthoformate, and the mixture was refluxed with a Dean-Stark trap to remove ethanol and ethyl formate. Excess triethyl orthoformate was removed under vacuum to give **5** and **6** ([39.2:60.8 ^{31}P NMR ratio], 11.83 g). **6**: ^1H NMR (300 MHz, CD_3OD) δ 1.27 (m, 6H), 2.19 (m, 2H), 2.57 (m, 2H), 4.11 (m, 4H), 6.36 (m, 3H). ^{31}P NMR (100 MHz, CD_3OD): δ 44.9; **5**: ^{31}P NMR (100 MHz, CD_3OD) δ 53.3; ESI MS m/z^+ , **5**: 323.01 (M + Na), **6**: 243.09 (M + Na).

Example 3. (2-bromoethyl)(2-(ethoxy(3-ethoxy-3-oxopropyl)phosphoryl)ethyl)phosphinic acid (**8**).

[0096]

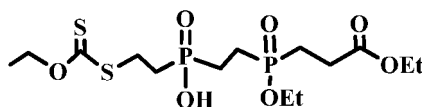


[0097] A mixture of ammonium hypophosphite (8.00 g, 96 mmol) and hexamethyldisilazane (20.0 mL, 96 mmol) was heated at 120 °C for 1 h under argon. After the mixture was cooled to 0 °C, ethyl acrylate (10.4 mL, 96 mmol) was carefully added dropwise, and the resulting mixture was stirred at 50 °C for 2 h. Then the mixture of compound **5** and **6** (10.0 g, 38.4 mmol estimated from above ratio) was added and heated at 120 °C for 2 h under argon, followed by addition

of 1,2-dibromoethane (40 ml) and the mixture was stirred for 5 h at 120 °C. After the solvent was removed under vacuum, 100 mL of aqueous ethanol (1:1) were added dropwise to the residue and refluxed for 0.5 h. The mixture was concentrated and purified by SiO₂ chromatographic column (1:20 to 1:10 MeOH/CH₂Cl₂) to afford the title compound **8** (6.48 g, 43% yield). ESI MS m/z- 391.2 (M - H).

Example 4. (2-(ethoxy(3-ethoxy-3-oxopropyl)phosphoryl)ethyl)(2-((ethoxycarbonothioyl)thio)ethyl)phosphinic acid (**9**).

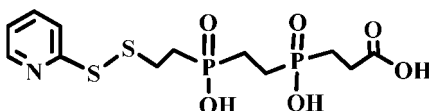
[0098]



[0099] Compound **8** (6.01 g, 15.30 mmol) in 150 ml of ethanol was added Potassium ethyl xanthogenate (3.00 g, 18.75 mmol). After being stirred under Ar for 3 h, the mixture was acidified with 3 M H₃PO₄ to pH 3.0. The mixture was concentrated, and purified on a SiO₂ column eluted with water/MeCN/HOAc (1:10:0.01), pooled the fraction, added DMF (~5 ml), evaporated to dryness to afford the title compound **9** (5.38 g, 83% yield). ESI MS, m/z- 433.10 (M-H).

Example 5. 3-(Hydroxy(2-(hydroxy(2-(pyridin-2-yl)disulfanyl)ethyl)phosphoryl)ethyl)phosphoryl)propanoic acid (**10**)

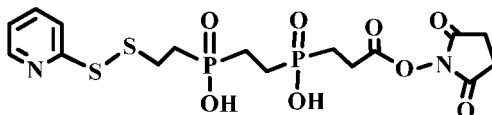
[0100]



[0101] Compound **9** (5.00 g, 11.51 mmol) in 100 ml of methanol was added 50 ml of 3 M NaOH. After being stirred under Ar for 3 h, the mixture was neutralized with 3 M H₃PO₄ to pH 7.2 under Ar. The mixture was added dropwise to the solution of 1,2-bis(pyridin-2-yl)disulfane (10.0 g, 45.45 mmol) in 200 ml of methanol. After being stirred for 4 h under Ar, the mixture was concentrated, diluted with EtOAc/Hexane (1:1), separated, and the organic layer was washed with pure water (3 x 25 ml) while the generated each of aqueous layer was washed with EtOAc/Hexane (1:1, 35 ml). The aqueous layers were combined, acidified with HCl/HOAc to pH ~2, concentrated to ~10 ml, diluted with MeCN (60 ml), sonicated (or quickly stirred) for 1 h, filtered, washed the pellet with water/MeCN (1:10). The solution was then concentrated and purified on a SiO₂ column eluted with water/MeCN/HOAc (1:8:0.01), pooled the fraction, added DMF (~5 ml), evaporated to dryness to afford the title compound **10** (3.62 g, 79% yield). ESI MS, m/z- 398.02 (M-H).

Example 6. (3-((2,5-dioxopyrrolidin-1-yl)oxy)-3-oxopropyl)(2-(hydroxy(2-(pyridin-2-yl)disulfanyl)ethyl)phosphoryl)ethyl)phosphinic acid (**11**).

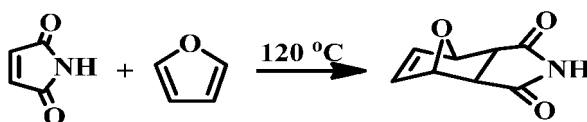
[0102]



[0103] Compound **10** (200 g, 5.01 mmol) in DMA (50 ml) was added 0.2 ml of HCl (conc) and the mixture was evaporated to dryness. Then the compound redissolved in dry DMA (60 ml) was added, NHS (0.80 g, 6.95 mmol) and EDC (3.00 g, 15.62 mmol). The mixture was stirred under Ar overnight, evaporated and purified on short C-18 chromatography eluted with water/dioxane at 4°C. The fractions containing the product were pooled, freeze-dried at -78°C, lyophilized to afford the title compound (1.26 g, 51% yield). MS m/z-495.2 (M-H).

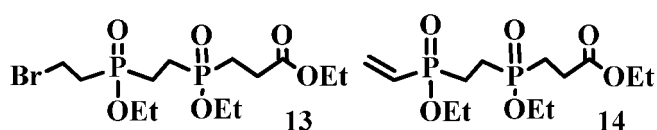
Example 7. 3, 6-endoxo- -tetrahydrophthalhide

[0104]



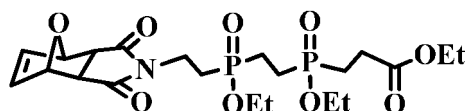
[0105] Maleimide (10.0 g, 103.0 mmol) in ethylether (350 ml) was added furan (11.0 ml, 151.2 mmol). The mixture was heated inside a 1 L of autoclave bomb at 100°C for 8 h. The bomb was cooled down to room temperature, and the inside solid was rinsed with methanol, concentrated and crystallized in ethyl acetate/hexane to afford 16.9 g (99%) of the title compound. ¹H NMR (DMF-d₇, 300 MHz): 11.06 (s, 1H) (NH), 6.61 (m, 2H), 5.15 (m, 2H), 2.97 (m, 2H). ¹³C NMR 178.86, 137.72, 82.05, 49.93. MS m/z+ 188.4 (M + Na).

Example 8. Ethyl 3-((2-((2-bromoethyl)(ethoxy)phosphoryl)ethyl)(ethoxy)phosphoryl) propanoate (**13**), Ethyl 3-(ethoxy(2-(ethoxy(vinyl)phosphoryl)ethyl)phosphoryl) propanoate (**14**).



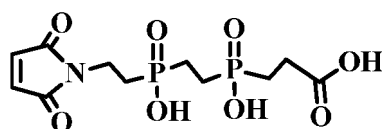
[0107] Compound **8** (4.51 g, 11.47 mmol) was treated with 100.0 mL of triethyl orthoformate, and the mixture was refluxed with a Dean-Stark trap to remove ethanol and ethyl formate. Excess triethyl orthoformate was removed under vacuum to give the mixture of **13** and **14**. ESI MS m/z+, **13**: 443.10 (M + Na), **14**: 363.20 (M + Na).

Example 9. Ethyl 3-((2-((2-(3,6-endoxo-Δ-tetrahydrophthalido)ethyl)(ethoxy)phosphoryl)ethyl)(ethoxy)phosphoryl)propanoate, or ethyl 3-((2-((2-((3aR,4R,7S)-1,3-dioxo-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisindol-2(3H)-yl)ethyl)(ethoxy)phosphoryl)ethyl)(ethoxy)phosphoryl)propanoate (**24**)



[0109] 3, 6-Endoxo- Δ-tetrahydrophthalide (2.40 g, 14.55 mmol) in DMA (60 ml) was added K₂CO₃ (4.2 g, 30.39 mmol) and KI (0.40 g, 3.45 mmol). After stirring under Ar for 1 hr, the mixture of compound **13** and **14** (2.6 g, ~6.80 mmol estimated) in DMA (10 ml) was added. The mixture was stirred under Ar overnight, evaporated, re-dissolved in EtOAc (100 ml), washed with water (2 x 50 ml) and 1.0 M NaH₂PO₄ (2 x 50 ml), dried over Na₂SO₄, filtered, evaporated and purified by SiO₂ chromatography eluted with EtOAc/hexane (1:10 ~ 1:5) to afford the title compound (2.64 g, 77% yield). ESI MS m/z+ 528.60 (M + Na).

Example 10. 3-((2-((2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl)(hydroxy)phosphoryl)ethyl)(hydroxy)phosphoryl)propanoic acid (**25**)

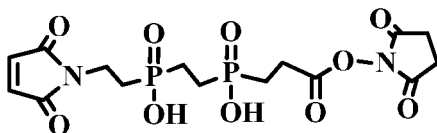


[0111] Compound **24** (2.60 g, 5.14 mmol), in the mixture of DMA (20 ml), toluene (20 ml) and HCl (8N, 10 ml) was heated at 120 ~ 140°C for 8 h. During the reaction time, 5 x 10 ml of water was gradually added to keep the reaction volume around 40 ml. The mixture was concentrated and purified by C-18 chromatography eluted with (1:10:0.01 to

1:3:0.01) water/CH₃CN/HOAc to afford the title compound (1.12 g, 62% yield). ESI MS m/z- 352.10 (M - H).

Example 11. (2-((2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)ethyl)(hydroxy)phosphoryl)ethyl)(3-((2,5-dioxopyrrolidin-1-yl)oxy)-3-oxopropyl)phosphinic acid (**26**)

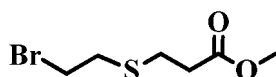
[0112]



[0113] Compound **25** (1.10 g, 3.11 mmol) in DMA (50 ml) was added 0.1 ml of HCl (conc) and the mixture was evaporated to dryness. Then the compound redissolved in dry DMA (40 ml) was added NHS (0.41 g, 3.56 mmol) and EDC (2.00 g, 10.42 mmol). The mixture was stirred under Ar overnight, evaporated and purified on SiO₂ chromatography eluted with 1:1:1% Acetone/DCM/HOAc, pooled the fractions, evaporated and solidified with EtOH/Tol/Hexane to afford the title compound (712 mg, 51% yield). ESI MS m/z- 449.10 (M-H).

Example 12. methyl 3-((2-bromoethyl)thio)propanoate (**52**)

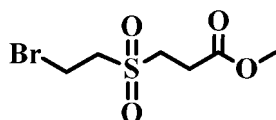
[0114]



[0115] A mixture of methyl 3-mercaptopropanoate (5.20 g, 51.6 mmol) and 1,2-dibromoethane (30 ml, 348.1 mmol) in DIPEA (100 ml) was stirred at 45°C for 8 h. The mixture was concentrated under vacuum and purified on SiO₂ eluted with EtOAc/Hexane (1:12 to 1:5) to give the title compound **52** (9.09 g, 78% yield). ESI MS m/z- 249.20 (M + Na).

Example 13. methyl 3-((2-bromoethyl)sulfonyl)propanoate (**53**)

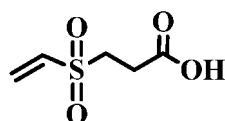
[0116]



[0117] Methyl 3-((2-bromoethyl)thio)propanoate **52** (4.50 g, 19.91 mmol) in acetic acid (40 ml), H₂O₂ (30%, 20 ml) and KMnO₄ (1.00g, 6.33 mmol) was stirred overnight. The mixture was concentrated, diluted with EtOAc (100 ml) and 1 M NaH₂PO₄ (150 ml), separated, the aqueous layer was extracted with EtOAc (2 x 100 ml). The organic layers were combined, dried over Na₂SO₄, filtered, concentrated and purified on SiO₂ column eluted with EtOAc/Hexane (1:10 ~ 1:5) to afford the title compound (4.05g, 79% yield). ESI MS m/z+281.02 (M + Na).

Example 14. 3-(Vinylsulfonyl)propanoic acid (**54**)

[0118]

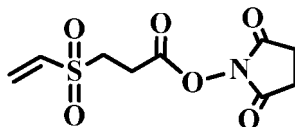


[0119] The compound **53** (4.0 g, 15.50 mmol) in 50 ml of THF was added 1 M NaOH (50 ml). After stirred under Ar for 24 h, the mixture was adjusted pH = ~ 7 with 1 M HCl at 4°C, concentrated, diluted with EtOAc (100 ml), separated. The aqueous layer was extracted with EtOAc (4 x 80 ml). The organic layers were combined, dried over Na₂SO₄,

filtered, evaporated, and SiO₂ chromatographic purification (1:15 to 1:10 MeOH/CH₂Cl₂) to afford the title compound **54** (1.80 g, 71% yield). ESI MS m/z- 163.10 (M-H).

Example 15. 2,5-dioxopyrrolidin-1-yl 3-(vinylsulfonyl)propanoate (55)

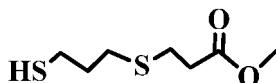
[0120]



[0121] Compound **54** (1.70 g, 10.36 mmol) in DMA (50 ml) was added NHS (1.75 g, 15.21 mmol) and EDC (5.00 g, 26.04 mmol). The mixture was stirred under Ar overnight, evaporated and purified on SiO₂ chromatography eluted with EtOAc/Hexane (1:10 ~ 1:4), pooled the fractions and evaporated to afford the title compound (2.24g, 83% yield). ESI MS m/z+ 284.10 (M+Na).

Example 16. methyl 3-((3-mercaptopropyl)thio)propanoate (64).

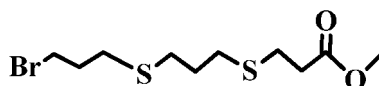
[0122]



[0123] Compound **63** (10.010 g, 60.25 mmol) in DMA (40 ml) was added propane-1,3-dithiol (40.0 g, 370.3 mmol) and DIPEA (100 ml). The mixture was stirred at 45 °C under Ar for 8 h, evaporated and purified on SiO₂ chromatography eluted with 1:10:0.01% EtOAc/DCM/HOAc, pooled the fractions, and evaporated to afford the title compound (9.58 g, 82% yield). ESIMS m/z+ 217.2 (M+Na).

Example 17. Methyl 3-((3-((3-bromopropyl)thio)propyl)thio)propanoate (65)

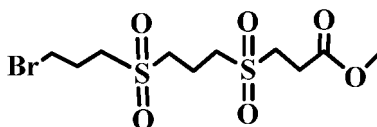
[0124]



[0125] Compound **64** (5.01 g, 25.76 mmol) in DMA (40 ml) was added 1,3-dibromopropane (30.0 g, 150.0 mmol) and DIPEA (100 ml). The mixture was stirred at 45 °C under Ar for 8 h, evaporated and purified on SiO₂ chromatography eluted with EtOAc/hexane (1:10 to 1:5), pooled the fractions, evaporated to afford the title compound **65** (6.87 g, 85% yield). ESIMS m/z+ 337.2 (M+Na).

Example 18. methyl 3-((3-((3-bromopropyl)sulfonyl)propyl)sulfonyl)propanoate (66)

[0126]

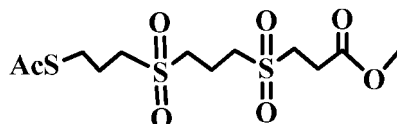


[0127] Compound **65** (6.70 g, 21.33 mmol) was in acetic acid (40 ml) was added H₂O₂ (33%, 20 ml) and KMnO₄ (1.01 g, 6.33 mmol). The mixture was stirred at 40 °C overnight. The mixture was concentrated, diluted with EtOAc (100 ml) and 1 M NaH₂PO₄ (100 ml), separated. The aqueous layer was extracted with EtOAc (2 x 80 ml). The organic layers were combined, dried over Na₂SO₄, filtered, evaporated, purified by SiO₂ chromatography eluted with EtOAc/hexane

(1:10 ~ 1:4) to afford the title compound (6.69 g, 83% yield). ESI MS m/z + 401.10 (M + Na).

Example 19. methyl 3-((3-((3-(acetylthio)propyl)sulfonyl)propyl)sulfonyl)propanoate (**67**)

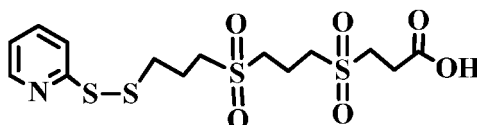
[0128]



[0129] Compound **66** (6.60 g, 17.46 mmol) in 100 ml of THF was added thioacetic acid (3.0 ml, 41.97 mmol) and DIPEA (20 ml, 115.0 mmol). The mixture was stirred at 40°C overnight, evaporated, co-evaporated with acetic acid (5 ml)/toluene (200 ml), and purified with SiO₂ chromatography eluted with EtOAc/Hexane (1:10 to 1:4) to afford the title compound (5.22 g, 80% yield). ESI MS m/z + 397.10 (M+Na).

Example 20. 3-((3-((3-(pyridin-2-yl)disulfanyl)propyl)sulfonyl)propyl)sulfonyl)propanoic acid (**68**)

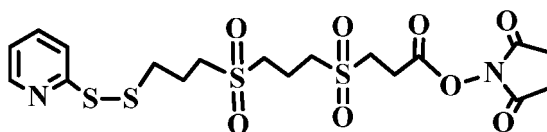
[0130]



[0131] Compound **67** (5.20 g, 13.90 mmol) in 100 ml of methanol was added 50 ml of 3 M NaOH. After being stirred under Ar for 3 h, the mixture was neutralized with 3 M H₃PO₄ to pH 7.2 under Ar. The mixture was added dropwise to the solution of 1,2-bis(5-pyridin-2-yl)disulfane (15.0 g, 68.18 mmol) in 200 ml of methanol. After being stirred for 24 h under Ar, the mixture was concentrated, diluted with EtOAc/Hexane (1:1), separated, and the organic layer was washed with pure water (3 x 25 ml) while the generated each of aqueous layer was washed with EtOAc/Hexane (1:1, 35 ml). The aqueous layers were combined, acidified with HCl/HOAc to pH 3 ~ 4, concentrated to ~ 10 ml, diluted with MeCN (60 ml), sonicated (or quickly stirred) for 1 h, filtered, washed the pellet with water/MeCN (1:10). The solution was then concentrated and purified on a SiO₂ column eluted with CH₃OH/CH₂Cl₂/HOAc (1:10:0.01), pooled the fraction, evaporated to dryness to afford the title compound **68** (5.93 g, 82% yield). ESI MS, m/z - 426.10 (M-H).

Example 21. 2,5-dioxopyrrolidin-1-yl 3-((3-((3-(pyridin-2-yl)disulfanyl)propyl)sulfonyl)propyl)sulfonyl)propanoate (**69**).

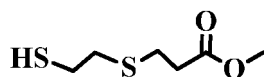
[0132]



[0133] Compound **68** (2.50 g, 6.08 mmol) in DMA (50 ml) was added NHS (0.80 g, 6.96 mmol) and EDC (3.00 g, 15.62 mmol). The mixture was stirred under Ar overnight, evaporated and purified on SiO₂ chromatography eluted with EtOAc/DCM (1:10 to 1:5), pooled the fractions and evaporated to afford the title compound (2.74 g, 86% yield). ESI MS m/z + 547.10 (M+Na).

Example 22. methyl 3-((3-mercaptopropyl)thio)propanoate (**71**).

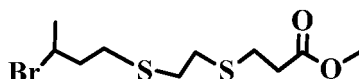
[0134]



[0135] Methyl 3-bromopropanoate **51** (10.010 g, 60.24 mmol) in DMA (80 ml) was added ethane-1,2-dithiol (40.0 g, 425.4 mmol) and DIPEA (150 ml). The mixture was stirred at 45 °C under Ar for 8 h, evaporated and purified on SiO₂ chromatography eluted with 1:10:0.01% EtOAc/DCM/HOAc, pooled the fractions, and evaporated to afford the title compound **71** (8.56 g, 79% yield). ESIMS m/z+ 203.10 (M+Na).

Example 23. methyl 3-((2-((3-bromobutyl)thio)ethyl)thio)propanoate (**82**).

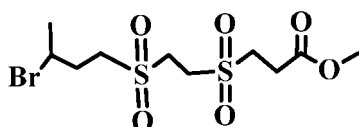
[0136]



[0137] Compound **71** (8.51 g, 47.26 mmol) in DMA (40 ml) was added 1,3-dibromobutane (30.0 g, 140.25 mmol) and DIPEA (100 ml). The mixture was stirred at 45 °C under Ar for 8 h, evaporated and purified on SiO₂ chromatography eluted with EtOAc/hexane (1:10 to 1:5), pooled the fractions, evaporated to afford the title compound **82** (12.16 g, 82% yield). ESI MS m/z+ 337.2 (M+Na).

Example 24. methyl 3-((2-((3-bromobutyl)sulfonyl)ethyl)sulfonyl)propanoate (**83**).

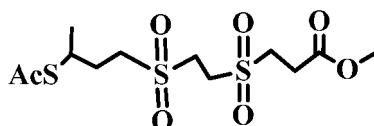
[0138]



[0139] Compound **82** (6.00 g, 19.10 mmol) was in acetic acid (40 ml) was added H₂O₂ (33%, 20 ml) and KMnO₄ (1.01 g, 6.33 mmol). The mixture was stirred at 40 °C overnight. The mixture was concentrated, diluted with EtOAc (100 ml) and 1 M NaH₂PO₄ (100 ml), separated. The aqueous layer was extracted with EtOAc (2 x 80 ml). The organic layers were combined, dried over Na₂SO₄, filtered, evaporated, purified by SiO₂ chromatography eluted with EtOAc/hexane (1:10 ~ 1:4) to afford the title compound **83** (6.01 g, 83% yield). ESI MS m/z+ 401.02 (M + Na).

Example 25. methyl 3-((2-((3-(acetylthio)butyl)sulfonyl)ethyl)sulfonyl)propanoate (**84**).

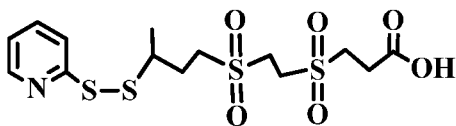
[0140]



[0141] Compound **83** (6.0 g, 15.87 mmol) in 100 ml of THF was added thioacetic acid (3.0 ml, 41.97 mmol) and DIPEA (20 ml, 115.0 mmol). The mixture was stirred at 50 °C overnight, evaporated, co-evaporated with acetic acid (5 ml)/toluene (200 ml), and purified with SiO₂ chromatography eluted with EtOAc/Hexane (1:10 to 1:4) to afford the title compound **84** (4.27 g, 72% yield). ESI MS m/z+ 397.20 (M+Na).

Example 26. 3-((2-((3-(pyridin-2-yl)disulfanyl)butyl)sulfonyl)ethyl)sulfonyl)propanoic acid (**85**).

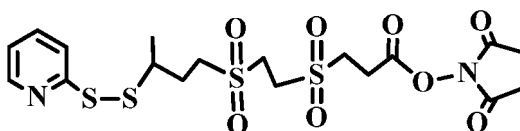
[0142]



[0143] Compound **84** (2.10 g, 5.61 mmol) in 100 ml of methanol was added 50 ml of 2 M NaOH. After being stirred under Ar for 1 h, the mixture was neutralized with 3 M H₃PO₄ to pH 7.2 under Ar. The mixture was added dropwise to the solution of 1,2-bis(5-pyridin-2-yl)disulfane (6.0 g, 27.27 mmol) in 100 ml of methanol. After being stirred for 15 h under Ar, the mixture was concentrated, diluted with EtOAc/Hexane (1:1), separated, and the organic layer was washed with pure water (3 x 25 ml) while the generated each of aqueous layer was washed with EtOAc/Hexane (1:1, 35 ml). The aqueous layers were combined, acidified with HCl/HOAc to pH 3 ~ 4, concentrated to ~ 10 ml, diluted with MeCN (60 ml), sonicated for 1 h, filtered, washed the pellet with water/MeCN (1:10). The solution was then concentrated and purified on a SiO₂ column eluted with CH₃OH/CH₂Cl₂/HOAc (1:10:0.01), pooled the fraction, evaporated to dryness to afford the title compound **85** (1.98 g, 82% yield). ESI MS, m/z- 426.10 (M-H).

Example 27. 2,5-dioxopyrrolidin-1-yl 3-((2-((3-(pyridin-2-yl)disulfanyl)butyl)sulfonyl)-ethyl)sulfonyl)propanoate (**86**).

[0144]



[0145] Compound **85** (1.00 g, 2.34 mmol) in DMA (50 ml) was added NHS (0.41 g, 3.56 mmol) and EDC (2.00 g, 10.42 mmol). The mixture was stirred under Ar overnight, evaporated and purified on SiO₂ chromatography eluted with EtOAc/DCM (1:10 to 1:5), pooled the fractions and evaporated to afford the title compound **86** (993 mg, 81% yield). ESIMS m/z+ 547.10 (M+Na).

Example 28. Modification of antibody with phosphinate linker

[0146] The antiHer2 antibody is modified with phosphinate linker at 8 mg/mL antibody, a 10 fold molar excess of phosphinate linker (~30mM stock solution in DMA). The reaction is carried out in 100 mM NaH₂PO₄, pH7.4 buffer with DMA (5% v/v) for 15, 30, 60, 120, and 240 minutes at 25 °C. The modified antiHer2 was purified by G25 column with 50 mM NaH₂PO₄, 50 mM NaCl, and 2 mM EDTA, pH6.5 to remove the excess phosphinate linker.

Example 29: Conjugate synthesis.

[0147] A hydrophilic linker containing thiopyridine (SPP) linker was dissolved in DMA at a concentration of approximately 10 mM. An antibody was dialyzed into buffer A (50 mM NaH₂PO₄, 50 mM NaCl, 2 mM EDTA, pH 6.5). For the linker reaction, the antibody was at 8 mg/ml, and 4-6 equivalents of linker were added while stirring in the presence of 5% (v/v) DMA. The reaction was allowed to proceed at ambient temperature for 90 minutes. Unreacted linker was removed from the antibody by Sephadex G25 gel filtration using a Sephadex G25 column equilibrated with Buffer A at pH 6.5 or 150 mM potassium phosphate buffer containing 100 mM NaCl, pH 7.4 as indicated. For the SPP containing linker, the extent of modification was assessed by release of pyridine-2-thione using 50 mM DTT and measuring the absorbance at 343 nm as described below ($\epsilon_{343} = 8080 \text{ M}^{-1} \text{ cm}^{-1}$ for free pyridine-2-thione). For the conjugation reaction, thiol-containing drug (such tubulysin TZ041) was dissolved in DMA (*N,N*-dimethylacetamide) at a concentration of approximately 10 mM. The drug (1 - 1.5-fold molar excess relative to the number of linker molecules per antibody as indicated) was slowly added with stirring to the antibody which was at a concentration of 2.5 mg/ml in buffer A (pH 6.5 or pH 7.4) in a final concentration of 3% (v/v) DMA. The reaction was allowed to proceed at ambient temperature for the indicated times. Drug-conjugated antibody was purified using a Sephadex G25 column equilibrated with buffer B (PBS (NaH₂PO₄), pH 6.5). The extent of drug conjugation to antibody was assessed by measuring A₂₅₄ and A₂₈₀ of the conjugate..

Example 30. *In vitro* cytotoxicity evaluation of a tubulysin (ZT041) conjugates of antibodies with a disulfide linkers containing sulfonyl groups:

[0148] The targeted cells (e.g. Ramos cells, 20,000 cells) were cultured in the presence of various concentrations of unconjugated antibody or the antibody conjugate for 96 hours after which cell viability was measured by propidium iodide exclusion and analyzed by flow cytometry using a Becton Dickinson FACSort (Becton Dickinson, Franklin Lakes, NJ). Red fluorescent intensity (emission at 617 nm in the FL2 channel) of the cells excited at 488 nm was measured. The regions for viable cells were also set using both the forward light scatter and right-angle light scatter properties of the cells. The loss of viability was determined by the loss of cells from within the gated region defining viable cells. The average number of viable cells per 6 replicate cultures was calculated. The survival fraction was plotted versus conjugate concentration to determine the IC_{50} value (50% cell killing concentration) of the conjugate.

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[0149]

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US Patent Application Nos. 20120201809, 20120082617, 20120034295, 20110293513, 20110076722, 20110064753, 20110064752, 20110064666, 20100189727, 20100136652, 20100104589, 20100074840, 20100062008, 20090176253, 20090088390

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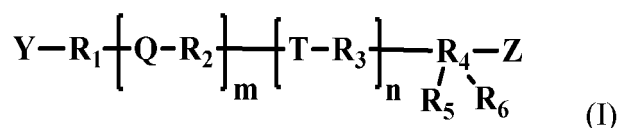
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Claims

1. A hydrophilic linker of the formula (I)



wherein:

Y represents a functional group that enables reaction with a cell-binding agent;

Q and T are either -P(=O)(OM)-, or -S(O₂)-, or -S(O)-;

m and n are integer from 0 to 5, but not 0 at the same time; in addition, when m = 1, n = 0, Q is not -P(=O)(OM)-; or when n = 1, m = 0, T is not -P(=O)(OM)-;

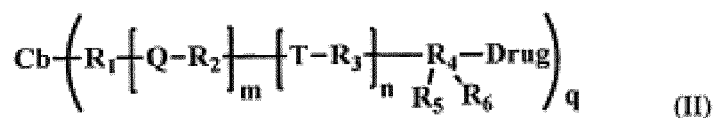
Z represents a functional group that enables linkage of a cytotoxic drug via a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, amine (secondary, tertiary, or quaternary), imine, cycloheteroalkyl, heteroaromatic, alkoxime or amide bond, the said functional group Z being selected from thiol, disulfide, amino, carboxy, aldehydes, maleimido, haloacetyl, hydrazines and hydroxy;

R₁, R₂, R₃, R₄, R₅ and R₆, are the same or different and are H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or 1-6 carbon atoms of esters, ether, amide, or polyethyleneoxy unit of formula (OCH₂CH₂)_p, wherein p is an integer from 0 to 1000, or combination thereof;

or R₁, R₂, R₃ and R₄ are respectively a chain of atoms selected from C, N, O, S, Si, and P that covalently connects the cell-surface binding ligand, the phosphinate or sulfonyl group, the conjugated drug and among themselves (R₁, R₂, R₃ and R₄), wherein the said atoms are combined in any chemically relevant ways ;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt, wherein R₁, R₂ and R₃ are as described hereinabove.

2. A cell-binding agent-drug conjugate of formula (II)



wherein:

Cb represents a cell-binding agent/molecule;

"Drug" represents a drug linked to the cell-binding agent via the hydrophilic linker by a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, cycloheteroalkylene, heteroaromatic, alkoxime or amide bond;

Q and T are either -P(=O)(OM)-, or -S(O₂)-, or -S(O)-;

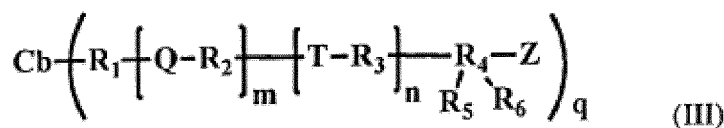
m and n are integers from 0 to 5, but not 0 at the same time; in addition, when m = 1, n = 0, Q is not -P(=O)(OM)-; or when n = 1, m = 0, T is not -S(O)-; -P(=O)(OM)-; q is an integer from 1 to 20;

R₁, R₂, R₃, R₄, R₅ and R₆, are the same or different and are H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or 1-6 carbon atoms of esters, ether, amide, or polyethyleneoxy unit of formula (OCH₂CH₂)_p, wherein p is an integer from 0 to 1000, or combination thereof;

or R₁, R₂, R₃ and R₄ are respectively a chain of atoms selected from C, N, O, S, Si, and P that covalently connects the cell-surface binding ligand, the phosphinate or sulfonyl group, the conjugated drug and among themselves (R₁, R₂, R₃ and R₄), wherein the said atoms are combined in any chemically relevant ways;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt, wherein R₁, R₂ and R₃ are as described hereinabove.

3. A compound of formula (III):



wherein:

Cb represents a cell-binding agent/molecule;

Z represents a functional group that enables reaction with a cytotoxic drug;

Q and T are either -P(=O)(OM)-, or -S(O₂)-, or -S(O)-;

m and n are integers from 0 to 5, but not 0 at the same time; in addition, when m = 1, n = 0, Q is not -P(=O)(OM)-; or when n = 1, m = 0, T is not -P(=O)(OM)-; q is an integer from 1 to 20;

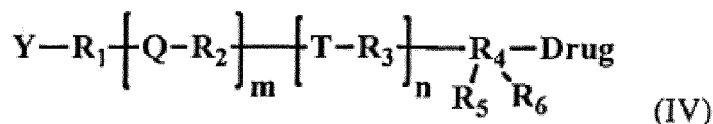
Z represents a functional group that enables linkage of a cytotoxic drug via a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, amine (secondary, tertiary, or quaternary), imine, cycloheteroalkyl, heteroaromatic, alkoxime or amide bond;

R₁, R₂, R₃, R₄, R₅ and R₆, are the same or different and are H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or 1-6 carbon atoms of esters, ether, amide, or polyethyleneoxy unit of formula (OCH₂CH₂)_p, wherein p is an integer from 0 to 1000, or combination thereof;

or R₁, R₂, R₃ and R₄ are respectively a chain of atoms selected from C, N, O, S, Si, and P that covalently connects the cell-surface binding ligand, the phosphinate or sulfonyl group, the conjugated drug and among themselves (R₁, R₂, R₃ and R₄), wherein the said atoms are combined in any chemically relevant ways;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt, wherein R₁, R₂ and R₃ are as described hereinabove.

4. A compound of formula (IV):



wherein:

Y represents a functional group that enables reaction with a cell-binding agent;

Q and T are either -P(=O)(OM)-, or -S(O₂)-, or -S(O)-;

m and n are integers from 0 to 5, but not 0 at the same time; in addition, when m = 1, n = 0, Q is not -P(=O)(OM)-; or when n = 1, m = 0, T is not -P(=O)(OM)-;

"Drug" represents a drug linked to the cell-binding agent via the hydrophilic linker by a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

R₁, R₂, R₃, R₄, R₅ and R₆, are the same or different and are H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or 1-6 carbon atoms of esters, ether, amide, or polyethyleneoxy unit of formula (OCH₂CH₂)_p, wherein p is an integer from 0 to 1000, or combination thereof;

or R₁, R₂, R₃ and R₄ are respectively a chain of atoms selected from C, N, O, S, Si, and P that covalently connects the cell-surface binding ligand, the phosphinate or sulfonyl group, the conjugated drug and among themselves (R₁, R₂, R₃ and R₄), wherein the said atoms are combined in any chemically relevant ways;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt, wherein R₁, R₂ and R₃ are as described hereinabove.

5. The conjugate of claim 2 or the compound of claim 4, wherein the "Drug" is selected from:

1). Chemotherapeutic agents: a). Alkylating agents: selected from Nitrogen mustards (chlorambucil, chlornaphazine, cyclophosphamide, dacarbazine, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, mannometrine, mitobronitol, melphalan, mitolactol, pipobroman, novembichin, phenesterine, prednimustine, thiotepa, trofosfamide, uracil mustard); CC-1065 (including its synthetic analogues of adozelesin, carzelesin and bizelesin); duocarmycin (including its synthetic analogues, KW-2189 and CBI-TMI); benzodiazepine dimers (selected from dimmers of pyrrolbenzodiazepine (PBD) or tomaymycin, indolinobenzodiazepines, imidazobenzothiadiazepines, or oxazolidinobenzodiazepines); Nitrosoureas (carmustine, lomustine, chlorozotocin, fotemustine, nimustine, ranimustine); Alkylsulphonates (busulfan, treosulfan, improsulfan and piposulfan); Triazines (dacarbazine); Platinum containing compounds: (carboplatin, cisplatin, oxaliplatin); aziridines (benzodopa, carboquone, meturedopa, and uredopa); ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate and trimethylolomelamine; b). Plant Alkaloids selected from: Vinca alkaloids (vincristine, vinblastine, vindesine, vinorelbine, navelbin); Taxoids (paclitaxel, docetaxol) and their synthetic analogs, Maytansinoids (DM1, DM2, DM3, DM4, DM5, DM6, DM7, maytansine and ansamitocins) and their synthetic analogs, cryptophycins (cryptophycin 1 and cryptophycin 8); epothilones, eleutherobin, discodermolide, bryostatins, dolostatins, auristatins, tubulysins, cephalostatins; pancratistatin; a sarcodictyin; spongistatin; c). DNA Topoisomerase Inhibitors selected from 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 selected from: [Anti-folate which is selected from: DHFR inhibitors methotrexate, trimetrexate, denopterin, pteropterin, aminopterin (4-aminopteroic acid); IMP dehydrogenase Inhibitors (mycophenolic acid, tiazofurin, ribavirin, EICAR); Ribonucleotide reductase Inhibitors (hydroxyurea, deferroxamine); Pyrimidine analogs selected from 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 selected from Receptor antagonists which is selected from: Anti-estrogen: (megestrol, raloxifene, tamoxifen); LHRH agonists(goserelin, leuprolide acetate); Anti-androgens (bicalutamide, flutamide, calusterone, dromostanolone propionate, epitioestanol, goserelin, leuprolide, mepitioestane, nilutamide, testolactone, trilostane and other androgens inhibitors); Retinoids/Deltoids which is selected from: 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 selected from 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 selected from the enediyne antibiotics (including calicheamicins, calicheamicin γ 1, δ 1, α 1 and β 1; dynemicin, including dynemicin A and deoxydynemicin; esperamicin, kedarcidin, C-1027, maduropeptin, neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, anthramycin, azaserine, bleomycins, cactinomycin, carabacin, 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: selected from Polyketides (acetogenins), bullatacin and bullatacinone; gemcitabine, epoxomicins (carfilzomib), bortezomib, thalidomide, lenalidomide, pomalidomide, tosedostat, zybrestat, PLX4032, STA-9090, Stimuvax, alloectin-7, Xegeva, Provenge, Yervoy, Isoprenylation inhibitors (including Lovastatin), Dopaminergic neurotoxins (including 1-methyl-4-phenylpyridinium ion), Cell cycle inhibitors (including staurosporine), Actinomycins (including Actinomycin D, dactinomycin), Bleomycins (bleomycin A2, bleomycin B2, peplomycin), Anthracyclines (daunorubicin, doxorubicin (adriamycin), idarubicin, epirubicin, pirarubicin, zorubicin, mttoxantrone, MDR inhibitors (verapamil), Ca^{2+} ATPase inhibitors (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, selected from aminoglutethimide, mitotane, trilostane; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; arabinoside, bestabucil; bisantrene; edat-raxate; 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; PSK®; razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2, 2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verrucaric acid, roridin A and anguidine); urethane, siRNA, antisense drugs; 2). Anti-autoimmune disease agents: cyclosporine, cyclosporine A, aminocaproic acid, azathioprine, bromocriptine, chlorambucil, chloroquine, cyclophosphamide, corticosteroids (amcinonide, betamethasone, budesonide, hydrocortisone, flunisolide, fluticasone propionate, fluocortolone danazol, dexamethasone, Triamcinolone acetonide, beclomethasone dipropionate), DHEA, enanercept, hydroxychloroquine, infliximab, meloxicam, methotrexate, mofetil, mycophenolate, prednisone, sirolimus, tacrolimus.

3). Anti-infectious disease agents, a). Aminoglycosides: amikacin, astromycin, 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). Cepheids: carbacephem (loracarbef), cefacetrile, cefaclor, cefradine, cefadroxil, cefalonium, cefaloridine, cefalotin or cefalothin, cefalexin, cefaloglycin, cefamandole, cefapirin, cefatrizine, cefazafur, cefazedone, cefazolin, cefbuperazone, cefcapene, cefdaloxime, cefepime, cefminox, cefoxitin, cefprozil, cefroxadine, ceftazidime, cefuroxime, cefixime, cefdinir, cefditoren, cefepime, cefetamet, cefmenoxime, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotiam, cefozopran, cephalixin, cefpimizole, cefpiramide, cefpirome, cefpodoxime, cefprozil, cefquinome, cefsulodin, ceftazidime, cefteteram, ceftibuten, ceftioleone, ceftizoxime, ceftobiprole, ceftriaxone, cefuroxime, cefuzonam, cephamycin (cefoxitin, cefotetan, cefmetazole), oxacephem (flomoxef, latamoxef); f). Glycopeptides: bleomycin, vancomycin (oritavancin, telavancin), teicoplanin (dalbavancin), ramoplanin; g). Glycylcyclines (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; 1). Monobactams: aztreonam, tigemonam; m). Oxazolidinones: linezolid; n). Penicillins: amoxicillin, ampicillin (pivampicillin, hetacillin, bacampicillin, metampicillin, talampicillin), azidocillin, azlocillin, benzylpenicillin, benzathine benzylpenicillin, benzathine phenoxymethylpenicillin, 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, dano-

floxacin, difloxacin, enoxacin, enrofloxacin, floxin, garenoxacin, gatifloxacin, gemifloxacin, grepafloxacin, kano trovafloxacin, levofloxacin, lomefloxacin, marbofloxacin, moxifloxacin, nadifloxacin, norfloxacin, orbifloxacin, ofloxacin, pefloxacin, trovafloxacin, grepafloxacin, sitafloxacin, sparfloxacin, temafloxacin, tosusfloxacin, trovafloxacin; q). Streptogramins: pristinamycin, quinupristin/dalfopristin); r). Sulfonamides: mafenide, prontosil, sulfacetamide, sulfamethizole, sulfanilimide, sulfasalazine, sulfisoxazole, trimethoprim, trimethoprim-sulfamethoxazole (co-trimoxazole); s). Steroid antibacterials (fusidic acid); t). Tetracyclines: doxycycline, chlortetracycline, clomocycline, demeclocycline, lymecycline, meclocycline, metacycline, minocycline, oxytetracycline, penimepicycline, rolitetracycline, tetracycline, glycylicyclines (tigecycline); u). Other types of antibiotics:annonacin, arspenamine, 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 (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, clevidine, 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), 1-nucleosides (β -1-thymidine and β -1-2'-deoxycytidine), penciclovir, racivir, ribavirin, stampidine, stavudine (d4T), taribavirin (viramidine), telbivudine, tenofovir, trifluridine valaciclovir, valganciclovir, zalcitabine (ddC), zidovudine (AZT); f). Non-nucleosides: amantadine, atevirdine, 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 antiviral drugs: abzime, 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 radioisotopes selected from (radionuclides) ^3H , ^{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 .

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

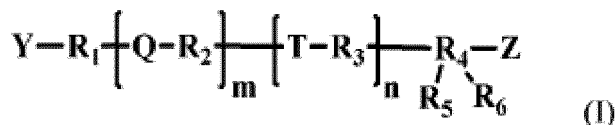
6. The conjugate of claim 2 or the compound of claim 4, wherein "Drug" is selected from tubulysins, calicheamicins, auristatins, maytansinoids, CC-1065 analogs, morpholinos doxorubicins, taxanes, cryptophycins, epothilones, and benzodiazepine dimers (selected from dimers of pyrrolobenzodiazepine (PBD) or tomaymycin, indolinobenzodiazepines, imidazobenzothiadiazepines, or oxazolidinobenzodiazepines), siRNA or a combination thereof, and pharmaceutically acceptable salts, or acids of any of the above.
7. The conjugate of claim 2 or the compound of claim 3 wherein the cell binding agent/molecule is selected from antibodies, proteins, vitamins (folates), peptides, polymeric micelles, liposomes, lipoprotein-based drug carriers, nano-particle drug carriers, dendrimers, and combination thereof.
8. The conjugate of claim 2 or the compound of claim 3, wherein the cell-binding agent binds to target cells which are selected from tumor cells, virus infected cells, microorganism infected cells, parasite infected cells, autoimmune cells, activated cells, myeloid cells, activated T-cells, B cells, or melanocytes; cells expressing the CD19, CD20, CD22, CD30, CD33, CD37, CD38, CD40, CD 51, CD52, CD56, CD66, CD70, CD74, CD79, CD80, CD98, CD125, CD221, CD227, CD262, CD309, CD326, CEACAM3, CEACAM5 (carcinoembryonic antigen), DLL4 (Δ -like-4), EGFR, CTLA4, CXCR4 (CD184), Endoglin (CD105), EPCAM (epithelial cell adhesion molecule), ERBB2 (Epidermal Growth Factor Receptor 2), FCGR1, FOLR (folate receptor), GD2 ganglioside, G-28 (a cell surface antigen glyvolipid), GD3 idiotyp, Heat shock proteins, HER1, HER2, HLA-DR10, HLA-DRB, human chorionic gonadotropin, IGF1R (insulin-like growth factor 1 receptor), IL-2 receptor (interleukin 2 receptor), IL-6R (interleukin 6 receptor), Integrins ($\alpha\text{v}\beta 3$, $\alpha 5\beta 1$, $\alpha 6\beta 4$, $\alpha \text{II}\beta 3$, $\alpha 5\beta 5$, $\alpha \text{v}\beta 5$), MAGE-1, MAGE-2, MAGE-3, MAGE 4, anti-transferrin receptor, p97, MS4A1 (membrane-spanning 4-domains subfamily A member 1), MUC1 or MUC1-KLH, MUC16 (CA125), CEA, gp100, MART1, MPG, MS4A1 (membrane-spanning 4-domains subfamily A), Nucleolin, Neu oncogene product, P21, Paratope of anti-(N-glycolylneuraminic acid), PLAP-like testicular alkaline phosphatase, PSMA, PSA, ROBO4, TAG 72 (tumor associated glycoprotein 72), T cell transmembrane protein, Tie (CD202b), TNFRSF10B (tumor necrosis factor receptor superfamily member 10B), TNFRSF13B (tumor necrosis factor receptor superfamily

member 13B), TPBG (trophoblast glycoprotein), TRAIL-R1 (Tumor necrosis apoptosis Inducing ligand Receptor 1), VCAM-1 (CD106), VEGF, VEGF-A, VEGF-2 (CD309), CanAg, CALLA, and cells expressing insulin growth factor receptor, or epidermal growth factor receptor.

- 5 **9.** The conjugate of claim **2** or the compound of claim **3**, wherein the cell-binding agent is an antibody, a single chain antibody, an antibody fragment that binds to the target cell, a monoclonal antibody, a single chain monoclonal antibody, or 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, a lymphokine, a hormone, a vitamin, a growth factor, a colony stimulating factor, or a nutrient-transport molecule.
- 10
- 15 **10.** The conjugate or the compound according to claim **8**, wherein the tumor cells are selected from 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, testicular cancer cells, or any cells that grow and divide at an unregulated, quickened pace to cause cancers.
- 20 **11.** A pharmaceutical composition comprising a therapeutically effective amount of the immunoconjugate of claims **2**, and a pharmaceutically acceptable salt, carrier, diluent, or excipient therefore, or a combination therefore, for the treatment or prevention of a cancer, or an autoimmune disease, or an infectious disease.
- 25 **12.** The conjugate of claims **2** or the compound of claim **4**, wherein the drug/cytotoxic agent are selected from a toxin, a chemotherapeutic agent, a drug moiety, an antibiotic, a radioactive isotope, and a nucleolytic enzyme.
- 30 **13.** The conjugate of claim **2**, which is an immunoconjugate having the formula $Cb-(L-Drug)_n$, wherein Cb is a cell-binding agent, L is the hydrophilic linker, Drug is a drug molecule, and n is an integer from 1 to 20.
- 35 **14.** The conjugate of claim **13**, which is an immunoconjugate wherein the hydrophilic linker L is composed of one or more linker components of 6-maleimidocaproyl (MC), maleimidopropanoyl (MP), valine-citrulline (val-cit), alanine-phenylalanine (ala-phe), p-aminobenzyloxycarbonyl (PAB), 4-thio-pentanoate (SPP), 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (MCC), 4-thio-butyrate (SPDB), maleimidoethyl containing (ME), 4-thio-2-hydroxysulfonyl-butyrate (2-Sulfo-SPDB) and (4-acetyl)aminobenzoate (SIAB).
- 40 **15.** The conjugate of claim **2** or **13**, which is an immunoconjugate wherein Drug is selected from tubulysins, maytansinoids, taxanoids (taxanes), CC-1065 analogs, daunorubicin and doxorubicin compounds, benzodiazepine dimers (including dimers of pyrrolbenzodiazepine (PBD), tomaymycin, anthramycin, indolinbenzodiazepines, imidazobenzothiadiazepines, or oxazolidinobenzodiazepines), calicheamicins and the enediyne antibiotics, actinomycin, azaserines, bleomycins, epirubicin, tamoxifen, idarubicin, dolastatins/auristatins (selected from. monomethyl auristatin E, MMAE, MMAF, auristatin PYE, auristatin TP, Auristatins 2-AQ, 6-AQ, EB (AEB), and EFP (AEFP)), duocarmycins, thiotepa, vincristine, hemiasterlins, and esperamicins.
- 45 **16.** The conjugate of claims **2** or **13**, which is an immunoconjugate having in vitro, in vivo or ex vivo cell killing activity.
- 50 **17.** The immunoconjugate of claim **13**, wherein the linker comprises either a peptide of 1-20 units of natural or non-natural amino acids, or a p-aminobenzyl unit, or a 6-maleimidocaproyl unit, or a disulfide unit, or a thioether unit, or a hydrozone unit, or an alkoxime unit.
- 55 **18.** The immunoconjugate of claim **13**, wherein the linker is cleavable by a protease.
- 19.** A pharmaceutical composition comprising the conjugate of claim **2** or **13**, and a pharmaceutically acceptable carrier.
- 20.** A pharmaceutical composition comprising a therapeutically effective amount of the conjugate of claim **2** or **13**, wherein the composition is administerable concurrently with other therapeutic agents selected from chemotherapeutic agent, radiation therapy, immunotherapy agents, autoimmune disorder agents, anti-infectious agents or other immunoconjugates for synergistically effective treatment or prevention of a cancer, or an autoimmune disease, or an infectious disease.

Patentansprüche

1. Hydrophiler Linker der Formel (1)



wobei:

Y eine Funktionsgruppe darstellt, die die Reaktion mit einem Zellbindemittel ermöglicht;

Q und T entweder -P(=O)(OM)-, oder -S(O₂)-, oder -S(O)- sind;

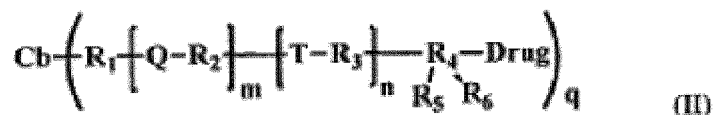
m und n Integer von 0 bis 5 sind, aber nicht gleichzeitig 0 sind; außerdem, wenn m = 1 und n = 0 sind, ist Q nicht -P(=O)(OM)-; oder wenn n = 1 und m = 0 sind, ist T nicht -P(=O)(OM)-;

Z eine Funktionsgruppe darstellt, die ein zytotoxisches Arzneimittel über ein Disulfid, Thioäther, Thioester, Peptid, Hydrazone, Äther, Ester, Carbamat, Carbonat, (sekundäres, tertiäres oder quaternäres) Amin, Imin, Cycloheteroalkyl, Heteroaromaten, Alkoxim oder Amidbindungen binden kann, wobei die Funktionsgruppe Z zusammengesetzt ist aus Thiol, Disulfid, Amino, Carboxy, Aldehyden, Maleimid, Halogenacetyl, Hydrazin und Hydroxyl;

R₁, R₂, R₃, R₄, R₅ and R₆ gleich oder verschieden und H sind, wobei das lineare Alkyl 1 bis 6 Kohlenstoffatome aufweist, verzweigtes oder zyklisches Alkyl 3 bis 6 Kohlenstoffatome aufweist, lineares, verzweigtes oder zyklisches Alkenyl oder Alkynyl 1 bis 6 Kohlenstoffatome von Ester, Äther, Amid oder Polyethylenoxyeinheiten der Formel (OCH₂CH₂)_p aufweist, wobei p eine ganze Zahl von 0 bis 1000 oder eine Kombination davon ist; oder R₁, R₂, R₃ und R₄ jeweils eine Atomkette bestehend aus C, N, O, S, Si und P sind, die den Zelloberflächenbindungs-liganden, die Phosphinat- oder Sulfonylgruppe, das konjugierte Doppelbindungen enthaltende Arzneimittel und die Elemente untereinander kovalent verbindet (R₁, R₂, R₃ and R₄), wobei die Atome auf irgendeine chemisch relevante Weise kombiniert sind;

M gleich H oder Na oder K oder N⁺R₁R₂R₃ oder ein medizinisches Salz sind, wobei R₁, R₂ und R₃ wie oben beschrieben sind.

2. Zellbindemittel-Wirkstoffkonjugat der Formel (II)



wobei:

Cb ein Zellbindemittel/-molekül repräsentiert;

"Drug" ein Arzneimittel darstellt, das über einen hydrophilen Linker durch eine Disulfid-, Thioäther-, Thioester-, Peptid-, Hydrazone-, Äther-, Ester-, Carbamat-, Carbonat-, Cycloheteroalkyl-, Heteroaromaten-, Alkoxim- oder Amidbindung mit dem Zellbindemittel verbunden ist;

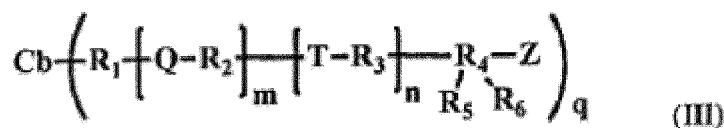
Q und T entweder -P(=O)(OM)-, oder -S(O₂)-, oder -S(O)- sind;

m und n Integer von 0 bis 5 sind, aber nicht gleichzeitig 0 sind; außerdem, wenn m = 1 und n = 0 sind, ist Q nicht -P(=O)(OM)-; oder wenn n = 1 und m = 0 sind, ist T nicht -S(O)-; -P(=O)(OM)-; q ein Integer von 1 bis 20 ist;

R₁, R₂, R₃, R₄, R₅ and R₆ gleich oder verschieden und H sind, wobei das lineare Alkyl 1 bis 6 Kohlenstoffatome aufweist, verzweigtes oder zyklisches Alkyl 3 bis 6 Kohlenstoffatome aufweist, lineares, verzweigtes oder zyklisches Alkenyl oder Alkynyl 1 bis 6 Kohlenstoffatome von Ester, Äther, Amid oder Polyethylenoxyeinheiten der Formel (OCH₂CH₂)_p aufweist, wobei p eine ganze Zahl von 0 bis 1000 oder eine Kombination davon ist; oder R₁, R₂, R₃ und R₄ jeweils eine Atomkette bestehend aus C, N, O, S und Si sind, die den Zelloberflächenbindungs-liganden, die Phosphinat- oder Sulfonylgruppe, das konjugierte Doppelbindungen enthaltende Arzneimittel und die Elemente untereinander kovalent verbindet (R₁, R₂, R₃ and R₄), wobei die Atome auf irgendeine chemisch relevante Weise kombiniert sind;

M gleich H oder Na oder K oder N⁺R₁R₂R₃ oder ein medizinisches Salz sind, wobei R₁, R₂ und R₃ wie oben beschrieben sind.

3. Verbindungen der Formel (III):



wobei:

Cb ein Zellbindemittel/-molekül repräsentiert;

Y eine Funktionsgruppe darstellt, die die Reaktion mit einem zytotoxischen Arzneimittel ermöglicht;

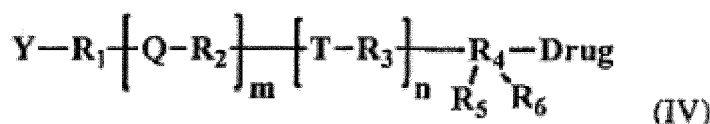
Q und T entweder -P(=O)(OM)-, oder -S(O₂)-, oder -S(O)- sind;

m und n Integer von 0 bis 5 sind, aber nicht gleichzeitig 0 sind; außerdem, wenn m = 1 und n = 0 sind ist Q nicht -P(=O)(OM)-; oder wenn n = 1 und m = 0 sind ist T nicht -P(=O)(OM)-; q ein Integer von 1 bis 20 ist;

Z eine Funktionsgruppe darstellt, die ein zytotoxisches Arzneimittel über ein Disulfid, Thioäther, Thioester, Peptid, Hydrazon, Äther, Ester, Carbamat, Carbonat, (sekundäres, tertiäres oder quaternäres) Amin, Imin, Cycloheteroalkyl, Heteroaromaten, Alkoxim oder Amidbindungen binden kann;

R₁, R₂, R₃, R₄, R₅ and R₆ gleich oder verschieden und H sind, wobei das lineare Alkyl 1 bis 6 Kohlenstoffatome aufweist, verzweigtes oder zyklisches Alkyl 3 bis 6 Kohlenstoffatome aufweist, lineares, verzweigtes oder zyklisches Alkenyl oder Alkinyl 1 bis 6 Kohlenstoffatome von Ester, Äther, Amid oder Polyethylenoxyeinheiten der Formel (OCH₂CH₂)_p aufweist, wobei p eine ganze Zahl von 0 bis 1000 oder eine Kombination davon ist; oder R₁, R₂, R₃ und R₄ jeweils eine Atomkette bestehend aus C, N, O, S, Si und P sind, die den Zelloberflächenbindungsliganden, die Phosphinat- oder Sulfonylgruppe, das konjugierte Doppelbindungen enthaltende Arzneimittel und die Elemente untereinander kovalent verbindet (R₁, R₂, R₃ and R₄), wobei die Atome auf irgendeine chemisch relevante Weise kombiniert sind;M gleich H oder Na oder K oder N⁺R₁R₂R₃ oder ein medizinisches Salz sind, wobei R₁, R₂ und R₃ wie oben beschrieben sind.

4. Verbindungen der Formel (IV):



wobei:

Y eine Funktionsgruppe darstellt, die die Reaktion mit einem Zellbindemittel ermöglicht;

Q und T entweder -P(=O)(OM)-, oder -S(O₂)-, oder -S(O)- sind;

m und n Integer von 0 bis 5 sind, aber nicht gleichzeitig 0 sind; außerdem, wenn m = 1 und n = 0 sind, ist Q nicht -P(=O)(OM)-; oder wenn n = 1 und m = 0 sind, ist T nicht -P(=O)(OM)-;

"Drug" ein Arzneimittel darstellt, das über einen hydrophilen Linker durch eine Disulfid-, Thioäther-, Thioester-, Peptid-, Hydrazon-, Äther-, Ester-, Carbamat-, Carbonat-, Cycloheteroalkyl-, Heteroaromaten-, Alkoxim- oder Amidbindung mit dem Zellbindemittel verbunden ist;

R₁, R₂, R₃, R₄, R₅ and R₆ gleich oder verschieden und H sind, wobei das lineare Alkyl 1 bis 6 Kohlenstoffatome aufweist, verzweigtes oder zyklisches Alkyl 3 bis 6 Kohlenstoffatome aufweist, lineares, verzweigtes oder zyklisches Alkenyl oder Alkinyl 1 bis 6 Kohlenstoffatome von Ester, Äther, Amid oder Polyethylenoxyeinheiten der Formel (OCH₂CH₂)_p aufweist, wobei p eine ganze Zahl von 0 bis 1000 oder eine Kombination davon ist; oder R₁, R₂, R₃ und R₄ jeweils eine Atomkette bestehend aus C, N, O, S, Si und P sind, die den Zelloberflächenbindungsliganden, die Phosphinat- oder Sulfonylgruppe, das konjugierte Doppelbindungen enthaltende Arzneimittel und die Elemente untereinander kovalent verbindet (R₁, R₂, R₃ and R₄), wobei die Atome auf irgendeine chemisch relevante Weise kombiniert sind;M gleich H oder Na oder K oder N⁺R₁R₂R₃ oder ein medizinisches Salz sind, wobei R₁, R₂ und R₃ wie oben beschrieben sind.

5. Konjugat gemäß Anspruch 2 oder die Verbindung gemäß Anspruch 4, wobei das "Drug" zusammengesetzt ist aus:

1). Chemotherapeutika: a). Alkylierungsmittel: zusammengesetzt aus Stickstoffsengas (Chlorambuzil, Chloma-
 phazin, Cyclophosphamid, Dacarbazin, Estramustin, Ifosfamid, Mechlorethamin, Mechlorethaminoxidhydro-
 chlorid, Mannomustin, Mitobronitol, Melphalan, Mitolactol, Pipobroman, Novembichin, Phenesterin, Pred-
 nimustin, Thiotepa, Trofosfamid, Uracilsenf); CC-1065 (einschließlich seiner synthetischen Analoga Adozelesin,
 Carzelesin und Bizelesin); Duocarmycin (einschließlich seiner synthetischen Analoga KW-2189 und CBI TMI);
 Benzodiazepindimere (zusammengesetzt aus den Dimeren von Pyrrolbenzodiazepin (PBD) oder Tomaymy-
 cin, Indolinobenzodiazepinen, Imidazobenzothiadiazepinen oder Oxazolidinobenzodiazepinen); Nitrosäuren
 (Carmustin, Lomustin, Chlorozotocin, Fotemustin, Nimustin, Ranimustin); Alkylsulfonate (Busulfan, Treosulfan,
 Improsulfan und Puposulfan); Triazene (Dacarbazin); platinhaltige chemische Verbindungen: (Carboplatin, Ci-
 splatin, Oxaliplatin); Aziridine (Benzodopa, Carboquon, Meturedopa und Uredopa); Ethylenimine und Methyl-
 amelamine einschließlich Altretamin, Triethylenmelamin, Triethylenphosphoramid, Triethylenlithiophosphorsäu-
 reamid und Trimethylololmelamin; b). Pflanzenalkaloide zusammengesetzt aus: Vincaalkaloide (Vincristin, Vin-
 blastin, Vindesin, Vinorelbin, Navelbin); Taxoide (Paclitaxel, Docetaxol) und ihre synthetischen Analoga May-
 tansinoide (DMI, DM2, DM3, DM4, DM5, DM6, DM7, Maytansine und Ansamitocine) und ihre synthetischen
 Analoga Cryptophycine (Cryptophycin 1 und Cryptophycin 8); Epothilone, Eleutherobin, Discodermolid, Bryo-
 statine, Dolostatine, Auristatine, Tubulysine, Cephalostatine; Pancratistatin; ein Sarcodictyin; Spongistatin; e).
 DNA-Topoisomerase-Inhibitoren zusammengesetzt aus Epipodophyllinen (9-Aminocamptothecin, Camptothe-
 cin, Crinnotol, Daunomycin, Etoposid, Etoposidphosphat, Irinotecan, Mitoxantron, Novantron, Retinoidsäuren
 (Retinole), Teniposid, Topotecan, 9-Nitrocamptothecin (RFS 2000)); Mitomycin (Mitomycin C); d). Anti-Meta-
 boliten zusammengesetzt aus: [Antifolat zusammengesetzt aus: DHFR-Inhibitoren Methotrexat, Trimetrexat,
 Denopterin, Pteropterin, Aminopterin (4-Aminoptersäure); IMP-Dehydrogenase-Inhibitoren (Mycophenolsäure,
 Tiazofurin, Ribavirin, EICAR); Ribonukleotid-Reduktase-Inhibitoren (Hydroxyharnstoff, Deferoxamin); Pyrimi-
 din-Analoga zusammengesetzt aus Uracil-Analoga (Ancitabin, Azacitidin, 6-Azaauridin, Capecitabin (Xeloda),
 Carmofur, Cytarabin, Didesoxyuridin, Doxifluridin, Enocitabin, 5-Fluorouracil, Floxuridin, Ratitrexed (Tomudex));
 Cytosin-Analoga (Cytarabin, Cytosinarabinosid, Fludarabin); Purin-Analoga (Azathioprin, Fludarabin, Mercap-
 topurin, Thiamiprin, Thioguanin); Folsäureregulator, (Frolinsäure); e). Hormontherapien zusammengesetzt
 aus Rezeptor-Antagonisten, diese zusammengesetzt aus: Antiestrogen: (Megestrol, Raloxifen, Tamoxifen);
 LHRH-Agonisten (Goserelin, Leuprolidacetat); Antiandrogene (Bicalutamid, Flutamid, Calusteron, Dromosta-
 nolonpropionat, Epiostanol, Goserelin, Leuprolid, Meptiostan, Nilutamid, Testolacton, Trilostan und andere
 Androgen-Inhibitoren); Retinoide / Deltoide, diese zusammengesetzt sind aus: Vitamin D3-Analoga (CB 1093,
 EB 1089 KH 1060, Cholecalciferol, Ergocalciferol); photodynamische Therapien (Verteporfin, Phthalocyanin,
 Photosensibilisator Pc4, Demethoxy-Hypocrellin A); Cytokine (Alpha-Interferon, Interferon-D-gamma, Tumor-
 Nekrose-Faktor (TNFs), menschliche Proteine, die eine TNF-Domäne enthalten); f). Kinase-Inhibitoren zusam-
 mengesetzt aus BIBW 2992 (Anti-EGFR / Erb2), Imatinib, Gefitinib, Pegaptanib, Sorafenib, Dasatinib, Sunitinib,
 Erlotinib, Nilotinib, Lapatinib, Axitinib, Pazopanib, Vandetanib, E7080 (Anti-VEGFR2), Mubritinib, Ponatinib
 (AP24534), Bufenitib (INNO-406), Bosutinib (SKI-606), Cabozantinib, Vismodegib, Iniparib, Ruxolitinib,
 CYT387, Axitinib, Tivozanib, Sorafenib, Bevacizumab, Cetuximab, Trastuzumab, Ranibizumab, Panitumumab,
 Ispinesib; g). Antibiotika zusammengesetzt aus den Endiin-Antibiotika (einschließlich Calicheamicine, Caliche-
 amicin, γ 1, δ 1, α I und β I); Dynemicin, einschließlich Dynemicin A und Deoxydynemicin; Esperamicin, Kedarcidin,
 C-1027, Maduropeptin, Neocarzinostatin-Chromophor und verwandte chromoproteinendiin-antibiotische Chro-
 mophore), Aclacinomysine, Actinomycin, Authramycin, Azaserin, Bleomycine, Kactinomycin, Carabycin, Car-
 minomycin, Carzinophilin; Chromomycine, Dactinomycin, Daunorubicin, Detorubicin, 6-Diazo-5-oxo-L-norleu-
 cin, Doxorubicin, Morpholino-Doxorubicin, Cyanomorpholino-Doxorubicin, 2-Pyrrolino-Doxorubicin und Deoxy-
 doxorubicin, Epirubicin, Esorubicin, Idarubicin, Marcellomycin, Nitomycine, Mycophenolsäure Nogalamycin,
 Olivomycine, Peplomycin, Potfiromycin, Puromycin, Quelamycin, Rodorubicin, Streptonigrin, Streptozocin, Tu-
 bercidin, Ubenimex, Zinostatin, Zorubicin; f). Andere: zusammengesetzt aus Polyketiden (Acetogeninen), Bul-
 latacin und Bullatacinon; Gemcitabin, Epoxomicine (Carfilzomib), Bortezomib, Thalidomid, Lenalidomid, Poma-
 lidomid, Tosedostat, Zybrestat, PLX4032, STA-9090, Stimuvax, Allovecin-7, Xegeva, Provenge, Yervoy, Iso-
 prennylierungsinhibitoren (einschließlich Lovastatin), dopaminergene Neurotoxinen (einschließlich 1- Methyl-4-
 phenylpyridiniumion), Zellzyklusinhibitoren (einschließlich Staurosporin), Actinomycine (einschließlich Actino-
 mycin D, Dactinomycin), Bleomycine (Bleomycin A2, Bleomycin B2, Peplomycin), Anthracycline (Daunorubicin,
 Doxorubicin (Adriamycin), Idarubicin, Epirubicin, Pirarubicin, Zorubicin, Mtoxaantron, MDR-Inhibitoren (Verapa-
 mil), Ca^{2+} -ATPase-Inhibitoren (Thapsigargin), Histon-Deacetylase-Inhibitoren (Vorinostat, Romidepsin, Pano-
 binostat, Valproinsäure, Mocetinostat (MGCD0103), Belinostat, PCI-24781, Entinostat, SB939, Resminostat,
 Givinostat, AR-42, CUDC-101, Sulforaphan, Trichostatin A); Thapsigargin, Celecoxib, Glitazone, Epigallocate-
 chingallat, Disulfiram, Salinosporamid A; Anti-Adrenale zusammengesetzt aus Aminoglutethimid, Mitotan, Tri-
 lostan; Aceglaton; Aldophosphamidglycosid; Aminolävulinsäure; Amsacrin; Arabinosid, Bestrabucil; Bisantren;
 Edatraxat; Entschäumung; Demecolcin; Diaziquon; Eflomithin (DFMO), Elfomithin; Elliptiniumacetat, Etoglucid;

Galliumnitrat; Gacytosin, Hydroxyharnstoff; Ibandronat, Lentinan; Ionidamin; Mitoguazon; Mitoxantron; Mopidamol; Nitracrin; Pentostatin; Phenamet; Pirarubicin; Podophyllinsäure; 2-Ethylhydrazid; Procarbazin; PSK®; Razoxan; Rhizoxin; Sizofiran; Spirogermanium; Tenuazonsäure; Triazinon; 2, 2', 2''-Trichlortriethylamin; Trichothecene (insbesondere T-2-Toxin, Verrucaridin A, Roridin A und Anguidin); Urethan, siRNA, Antisense-Arzneimittel;

2). Mittel gegen Autoimmunerkrankungen: Cyclosporin, Cyclosporin A, Aminocapronsäure, Azathioprin, Bromocriptin, Chlorambucil, Chloroquin, Cyclophosphamid, Corticosteroide (Aminonid, Betamethason, Budesonid, Hydrocortison, Flunisolid, Fluticasonpropionat, Fluocortolondanazol, Dexamethason, Triamcinolonacetonid, Beclometasondipropionat), DHEA, Enanercept, Hydroxychloroquin, Infliximab, Meloxicam, Methotrexat, Mofetil, Mycophenolat, Prednison, Sirolimus, Tacrolimus.

3). Mittel gegen Infektionskrankheiten, a). Aminoglykoside: Amikacin, Astromycin, Gentamicin (Netilmicin, Sisomicin, Isepamicin), Hygromycin B, Kanamycin (Amikacin, Arbekacin, Bekanamycin, Dibekacin, Tobramycin), Neomycin (Framycetin, Paromomycin, Ribostamycin), Netilmicin, Spectinomycin, Streptomycin, Tobramycin, Verdamycin; b). Amphenicole: Azidamfenicol, Chloramphenicol, Florfenicol, Thiamphenicol; e). Ansamycine: Geldanamycin, Herbinomycin; d). Carbapeneme: Biapenem, Doripenem, Ertapenem, Imipenem / Cilastatin, Meropenem, Panipenem; e). Cepheme: Carbacephem (Loracarbef), Cefacetril, Cefaclor, Cefradin, Cefadroxil, Cefalonium, Cefaloridin, Cefalotin oder Cefalothin, Cefalexin, Cefalogycin, Cefamandol, Cefapirin, Cefatrizin, Cefazafur, Cefazedon, Cefazolin, Cefbuperazon, Cefcapen, Cefdaloxim, Cefepim, Cefminox, Cefoxitin, Cefprozil, Cefroxadin, Ceftezole, Cefuroxim, Cefixim, Cefdinir, Cefditoren, Cefepim, Cefetamet, Cefmenoxim, Cefodizim, Cefonicid, Cefoperazon, Ceforanid, Cefotaxim, Cefotiam, Cefozopran, Cephalixin, Cefpimizol, Cefpiramid, Cefpirom, Cefpodoxim, Cefprozil, Cefquinom, Cefsulodin Cefotaxim, Cefteram, Cefibuten, Ceftiofen, Ceftizoxim, Ceftobiprol, Ceftriaxon, Cefuroxim, Cefuzonam, Cephamycin (Cefoxitin, Cefotetan, Cefmetazol), Oxacephem (Flomoxef, Latamoxef); f). Glycopeptide: Bleomycin, Vancomycin (Oritavancin, Telavancin), Teicoplanin (Dalbavancin), Ramoplanin; g). Glycylcycline (Tigecyclin); g). β -Lactamase-Inhibitoren: Penam (Sulbactam, Tazobactam), Clavam (Clavulansäure); i). Lincosamide: Clindamycin, Lincomycin; j). Lipopeptide: Daptomycin, A54 | 45, Calcium-abhängige Antibiotika (CDA); k). Makrolide: Azithromycin, Kethromycin, Clarithromycin, Dirithromycin, Erythromycin, Flurithromycin, Josamycin, Ketolid (Telithromycin, Cethromycin), Midecamycin, Miocamycin, Oleandomycin, Rifamycine (Rifampicin, Rifampicin, Rifabutin, Rifapentin), Rokitamycin, Roxithromycin, Spectinomycin, Spiramycin, Tacrolimus (FK506), Troleandomycin, Telithromycin; l). Monobactame: Aztreonam, Tigemonam; m). Oxazolidinone: Linezolid; n). Penicilline: Amoxicillin, Ampicillin (Pivampicillin, Hetacillin, Bacampicillin, Metampicillin, Talampicillin), Azidocillin, Azlocillin, Benzylpenicillin, Benzathin Benzylpenicillin, Benzathin Phenoxymethylpenicillin, Clometocillin, Procain Benzylpenicillin, Carbenicillin (Carindacillin), Cloxacillin, Dicloxacillin, Epicillin, Flucloxacillin, Mecillinam (Pivmecillinam), Mezlocillin, Meticillin, Nafcillin, Oxacillin, Penamocillin, Penicillin, Phenethicillin, Phenoxymethylpenicillin, Piperacillin, Propicillin, Sulbenicillin, Temocillin, Ticarcillin; o). Polypeptide: Bacitracin, Colistin, Polymyxin B; p). Chinolone: 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, Sitafoxacin, Sparfloxacin, Temafloxacin, Tosufloxacin, Trovafloxacin; q). Streptogramine: Pristinamycin, Quinupristin (Dalfopristin); r). Sulfonamide: Mafenid, Prontosil, Sulfacetamid, Sulfamethizol, Sulfanilimid, Sulfasalazin, Sulfisoxazol, Trimethoprim, Trimethoprim-Sulfamethoxazol (Cotrimoxazol); s). Steroid-Antibiotika (Fusidinsäure); t). Tetracycline: Doxycyclin, Chlortetracyclin, Clomocyclin, Demeclocyclin, Lymecyclin, Meclocyclin, Metacyclin, Minocyclin, Oxytetracyclin, Penimepicyclin, Rolitetracyclin, Tetracyclin, Glycylcycline (Tigecyclin); u). Andere Arten von Antibiotika: Annonacin, Arsphenamin, Bactoprenol-Inhibitoren (Bacitracin), DADAL/AR-Inhibitoren (Cycloserin), Dictyostatin, Discodermolide, Eleutherobin, Epothilon, Ethambutol, Etoposid, Faropenem, Fusidinsäure, Furazolidon, Isoniazid, Laulimalid, Metronidazol, Mupirocin, Mycolacton, synthetische NAM-Inhibitoren (Fosfomycin), Nitrofurantoin, Paclitaxel, Platensimycin, Pyrazinamid, Quinupristin / Dalfopristin, Rifampicin (Rifampicin), Tazobactam, Tinidazol, Uvaricin;

4). Virenschutz-Medikamente: a). Eintrags- / Fusionsinhibitoren: Aplaviroc, Maraviroc, Vicriviroc, *gp41* (Enfuvirtid), PRO 140, CD4 (Ibalizumab); b). Integrase-Hemmer: Raltegravir, Elvitegravir, Globoidnan A; c). Reifungshemmer: Bevirimat, Vitravir; d). Neuraminidasehemmer: Oseltamivir, Zanamivir, Peramivir; e). Nukleoside und Nukleotide: Abacavir, Aciclovir, Adefovir, Amdoxovir, Apricitabin, Brivudin, Cidofovir, Clevudin, Dextro-citabine, Didanosin (ddI), Elvucitabin, Emtricitabin (FTC), Entecavir, Famciclovir, Fluoruracil (5-FU), 3'-FluoroD-substituiert 2',3'-Dideoxynucleosidanaloge (3'-Fluor-2',3'-didesoxythymidin (FLT) und 3'-Fluor-2',3'-dideoxyguanosin (FLG), Fomivirsen, Ganciclovir, Idoxuridin, Lamivudin (3TC), I-Nukleoside (β -1-Thymidin und β -1-2'-Desoxycytidin), Penciclovir, Racivir, Ribavirin, Stampidin, Stavudin (d4T), Taribavirin (Viramidin), Telbivudin, Tenofovir, Trifluridin Valaciclovir, Valganciclovir, Zalcitabin (ddC), Zidovudin (AZT); f). Nicht-Nukleoside: Amantadin, Ateviridin, Capravirin, Diarylpyrimidine (Etravirin, Rilpivirin), Delavirdin, Docosanol, Emivirin, Efavirenz,

Foscamet (Phosphonoameisensäure), Imiquimod, Interferon alfa, Lovirid, Lodenosin, Methisazon, Nevirapin, NOV-205, Peginterferon alfa Podophyllotoxin, Rifampicin, Rimantadin, Resiquimod (R-848), Tromantadin; g). Proteasehemmer: Amprenavir, Atazanavir, Boceprevir, Darunavir, Fosamprenavir, Indinavir, Lopinavir, Nelfinavir, Pleconaril, Ritonavir, Saquinavir, Telaprevir (VX-950), Tipranavir; h). Andere Arten von Anti-Viren-Medikamente: Abzyme, Arbidol, Calanolid A, Ceragenin, Cyanovirin-n, Diarylpyrimidine, Epigallocatechingallat (EGCG), Foscamet, Griffithsin, Taribavirin (Viramidin), Hydroxyharnstoff, KP-1461, Miltefosin, Pleconaril, Portmantau-Hemmer, Ribavirin Seliciclib.

5) Radioisotope zusammengesetzt aus (den Radionukliden) ^3H , ^{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 oder ^{213}Bi .

6) Pharmazeutisch verträgliche Salze oder Säuren der obigen Arzneimittel.

6. Konjugat gemäß Anspruch 2 oder chemische Verbindung gemäß Anspruch 4, wobei das "Drug" zusammengesetzt ist aus Tubulysinen, Calicheamicinen, Auristatinen, Maytansinoiden, CC-1065-Analoga, Morpholinos Doxorubicinen, Taxanen, Cryptophycinen, Epothilonen und Benzodiazepindimeren (zusammengesetzt aus Dimeren von Pyrrolbenzodiazepin) (PBD) oder Tomaymycin, Indolinbenzodiazepine, Imidazobenzothiadiazepine oder Oxazolidinobenzodiazepine, siRNA oder eine Kombination davon und pharmazeutisch verträgliche Salze oder Säuren der obigen Substanzen.

7. Konjugat gemäß Anspruch 2 oder chemische Verbindung gemäß Anspruch 3, wobei das/die Zellbindemittel/-moleküle zusammengesetzt sind aus Antikörpern, Proteinen, Vitaminen (Folsäuren), Peptiden, polymeren Mizellen, Liposomen, auf Lipoprotein basierenden Wirkstoffträgern, Nanopartikel-Wirkstoffträgern, Dendrimeren und Kombinationen davon.

8. Konjugat gemäß Anspruch 2 oder chemische Verbindung gemäß Anspruch 3, wobei sich das Zellbindemittel an Zielzellen bindet, die zusammengesetzt sind aus Tumorzellen, virusinfizierten Zellen, Mikroorganismus-infizierten Zellen, Parasiten-infizierten Zellen, Autoimmunzellen, aktivierten Zellen, Knochenmarkzellen, aktivierten T-Zellen, B-Zellen oder Melanozyten; Zellen, die CD19, CD20, CD22, CD30, CD33, CD37, CD38, CD40, CD51, CD52, CD56, CD66, CD70, CD74, CD79, CD80, CD98, CD125, CD221, CD227, CD262, CD309, CD326 exprimieren, CEACAM3, CEACAM5 (karzinoembryonales Antigen), DLL4 (Δ -like-4), EGFR, CTLA4, CXCR4 (CD184), Endoglin (CD105), EPCAM (epitheliales Zelladhäsionsmolekül), ERBB2 (epidermaler Wachstumsfaktorrezeptor 2), FCGRI, FOLR (Folat-rezeptor), GD2-Gangliosid, G-28 (das Zelloberflächenantigen Glycolipid), GD3-Idiotyp, Hitzeschockproteine, HER1, HER2, HLA-DR10, HLA-DRB, menschliches Choriongonadotropin, IGF1R (insulinähnlicher Wachstumsfaktor-1-Rezeptor), IL-2-Rezeptor (Interleukin-2-Rezeptor), IL-6R (Interleukin-6-Rezeptor), Integrine ($\alpha\text{v}\beta 3$, $\alpha 5\beta 1$, $\alpha 6\beta 4$, $\alpha 11\beta 3$, $\alpha 5\beta 5$, $\alpha \text{v}\beta 5$), MAGE-1, MAGE-2, MAGE-3, MAGE-4, Anti-Transferrin-Rezeptor, p97, MS4AI (membranüberspannende 4-Domänen-Unterfamilie A Mitglied 1), MUC1 oder MUC1-KLH, MUC16 (CA125), CEA, gp100, MART1, MPG, MS4AI (membranüberspannende 4-Domänen-Unterfamilie A), Nucleolin, Neu-Onkogen-Produkt, P21, Paratop der Anti-(N-Glycolylneuraminsäure), PLAP-artige testikulär-alkalische Phosphatase, PSMA, PSA, ROB04, TAG 72 (Tumorassoziiertes Glycoprotein 72), T-Zellen-Transmembranprotein, Tie (CD202b), TNFRSF10B (Tumornekrosefaktor-Rezeptor-Überfamilie-Mitglied 10B), TNFRSF13B (Tumornekrosefaktor-Rezeptor-Überfamilie-Mitglied 13B), TPBG (Trophoblasten-Glykoprotein), TRAIL-R1 (Tumor-Nekrose-Apoptosis-induzierender Ligand-Rezeptor 1), VCAM-1 (CD106), VEGF, VEGF-A, VEGF-2 (CD309), CanAg, CALLA und Zellen, die den Insulin-Wachstumsfaktor-Rezeptor oder den epidermalen Wachstumsfaktor-Rezeptor exprimieren.

9. Konjugat gemäß Anspruch 2 oder chemische Verbindung gemäß Anspruch 3, wobei das Zellbindemittel ist: ein Antikörper, ein einkettiger Antikörper, ein sich an die Zielzelle bindendes Antikörperfragment, ein monoklonaler Antikörper, ein einkettiger monoklonaler Antikörper oder ein sich an die Zielzelle bindendes monoklonales Antikörperfragment, ein chimärer Antikörper, ein sich an die Zielzelle bindendes chimäres Antikörperfragment, ein Domänen-Antikörper, ein sich an die Zielzelle bindendes Domänen-Antikörperfragment, ein wieder zum Vorschein gekommener Antikörper, ein wieder zum Vorschein gekommener einkettiger Antikörper oder ein wieder zum Vorschein gekommenes sich an die Zielzelle bindendes Antikörperfragment, ein humanisierter Antikörper oder ein wieder zum Vorschein gekommener Antikörper, ein humanisierter einkettiger Antikörper oder ein sich an die Zielzelle bindendes humanisiertes Antikörperfragment, ein Lymphokin, ein Hormon, ein Vitamin, ein Wachstumsfaktor, ein das Koloniewachstum stimulierender Faktor oder ein Nährstofftransportmolekül.

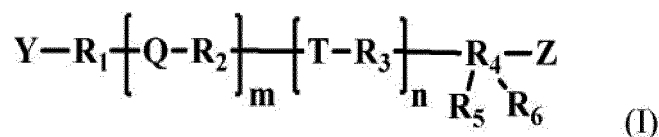
10. Konjugat oder chemische Verbindung gemäß Anspruch 8, wobei die Tumorzellen zusammengesetzt sind aus Lymphomzellen, Myelomzellen, Nierenzellen, Brustkrebszellen, Prostatakrebszellen, Eierstockkrebszellen, Darmkrebszellen, Magenkrebszellen, Schuppenkrebszellen, kleinzellige Lungenkrebszellen, Hodenkrebszellen oder andere Zellen, die (sich) in einem ungeregelten und sich beschleunigendem Tempo wachsen und teilen und dabei Krebs

verursachen.

11. Arzneimittelzusammensetzung, umfassend eine therapeutisch wirksame Menge des Immunkonjugats gemäß Anspruch 2 und ein dafür geeignete/s/r pharmazeutisch verträgliches Salz, Träger, Verdünnungsmittel, Exzipient oder Kombination zur Behandlung oder Vorbeugung von oder gegen Krebs, einer Autoimmunkrankheit oder Infektionskrankheit.
12. Konjugat gemäß Anspruch 2 oder die chemische Verbindung gemäß Anspruch 4, wobei das Arzneimittel / zytotoxische Mittel zusammengesetzt ist aus einem Toxin, einem Chemotherapeutikum, einer Arzneimittelrest, einem Antibiotikum, einem radioaktiven Isotop und einem nukleolytischen Enzym.
13. Konjugat gemäß Anspruch 2, welches ein Immunkonjugat mit der Formel $Cb-(LD\ Drug)_n$ ist, wobei Cb ein Zellbindemittel, Lis der hydrophile Linker, Arzneimittel ein Wirkstoffmolekül und n eine ganze Zahl von 1 bis 20 ist.
14. Konjugat gemäß Anspruch 13, das ein Immunkonjugat ist, wobei der hydrophile Linker Lis zusammengesetzt ist aus einer oder mehreren Linkerkomponenten von 6-Maleimidocaproyl (MC), Maleimidopropanoyl (MP), Valin-Citrullin (Val-Cit), Alanin-Phenylalanin (Ala- phe), p-Aminobenzoyloxycarbonyl (PAB), 4-Thiopentanoat (SPP), 4-(N-Maleimidomethyl) cyclohexan-1-carboxylat (MCC), 4-Thio-Butyrat (SPDB), Maleimidoethyl-haltige (ME), 4-Thio-2-Hydroxysulfonylbutyrat (2-Sulfo-SPDB) und (4-Acetyl) Aminobenzoessäureester (SIAB).
15. Konjugat gemäß Anspruch 2 oder 13, das ein Immunkonjugat ist, wobei das Arzneimittel zusammengesetzt ist aus Tubulysinen, Maytansinoiden, Taxanoiden (Taxanen), CC-1065-Analoga, Daunorubicin- und Doxorubicinverbindungen, Benzodiazepindimeren (einschließlich Dimeren von Pyrrolbenzodiazepin (PBD), Tomaymycin, Anthramycin, Indolinobenzodiazepine, Imidazobenzothiadiazepine oder Oxazolidinobenzodiazepine), Calicheamicine und Endiinantibiotika, Actinomycin, Azaserine, Bleomycine, Epirubicin, Tamoxifen, Idarubicin, Dolastatine / Auristatine (zusammengesetzt aus Monomethylauristatin E, MMAE, MMAF, Auristatin PYE, Auristatin TP, Auristatins 2-AQ, 6-AQ, EB (AEB) und EFP (AEFP), Duocarmycin, Thiotepa, Vincristin, Hemiasterlin und Esperarrucin.
16. Konjugat gemäß Anspruch 2 oder 13, das ein Immunkonjugat mit zelltötender in vitro, in vivo oder ex vivo Aktivität ist.
17. Immunkonjugat gemäß Anspruch 13, wobei der Linker entweder ein Peptid mit 1 bis 20 Einheiten natürlicher oder nicht-natürlicher Aminosäuren oder eine p-Aminobenzyl-Einheit oder eine 6-Maleimidocaproyl-Einheit oder eine Disulfid-Einheit oder eine Thioether-Einheit oder eine Hydrozoneinheit oder eine Alkoximeinheit umfasst.
18. Immunkonjugat gemäß Anspruch 13, wobei der Linker durch eine Protease spaltbar ist.
19. Pharmazeutische Zusammensetzung, umfassend das Konjugat gemäß Anspruch 2 oder 13 und einen pharmazeutisch verträglichen Träger.
20. Pharmazeutische Zusammensetzung, umfassend eine therapeutisch wirksame Menge des Konjugats gemäß Anspruch 2 oder 13, wobei die Zusammensetzung zur synergistisch wirksamen Behandlung oder Prävention von Krebs, einer Autoimmunkrankheit oder einer Infektionskrankheit gleichzeitig mit anderen therapeutischen Mitteln verabreicht werden kann, bei denen es sich handelt um Chemotherapeutika, Strahlentherapien, Immuntherapiemittel, Autoimmunkrankheitsmittel, antiinfektiöse Mittel oder andere Immunkonjugate.

Revendications

1. Un lieu hydrophile de formule (I)



dans lequel :

Y représente un groupe fonctionnel qui permet la réaction avec un agent de liaison cellulaire ;

Q et T sont -P(=O)(OM)-, ou -S(O₂)-, ou -S(O)-;

m et n sont des nombres entiers de 0 à 5, mais ne valant pas de 0 en même temps ; de plus, lorsque m = 1, n = 0, Q n'est pas -P(=O)(OM)-; ou lorsque n = 1, m = 0, T n'est pas -P(=O)(OM)-;

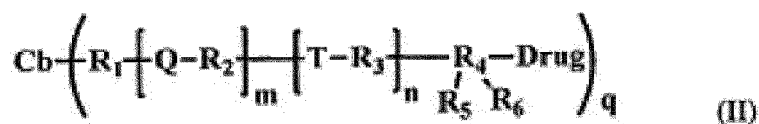
Z représente un groupe fonctionnel qui permet la liaison d'un médicament cytotoxique via une liaison disulfure, thioéther, thioester, peptide, hydrazone, éther, ester, carbamate, carbonate, amine (secondaire, tertiaire ou quaternaire), imine, cyclohétéroalkyle, hétéroaromatique, alcoxime ou liaison amide, ledit groupe fonctionnel Z étant choisi parmi un thiol, un disulfure, un amino, un carboxy, des aldéhydes, un maléimido, un haloacétyle, des hydrazines et un hydroxy ;

R₁, R₂, R₃, R₄, R₅ et R₆ sont identiques ou différents et sont H, un alkyle linéaire ayant de 1 à 6 atomes de carbone, un alkyle ramifié ou cyclique ayant de 3 à 6 atomes de carbone, un alcényle linéaire ou ramifié ou cyclique ou alcynyle, ou 1-6 atomes de carbone d'un ester, d'un éther, d'un amide ou d'un motif polyéthylène-oxy de formule (OCH₂CH₂)_p, où p est un nombre entier de 0 à 1000, ou une combinaison de ceux-ci ;

ou R₁, R₂, R₃ et R₄ sont respectivement une chaîne d'atomes choisis parmi C, N, O, S, Si et P qui relie de manière covalente le ligand de liaison à la surface cellulaire, le groupe phosphinate ou sulfonyle, le médicament conjugué et entre eux (R₁, R₂, R₃ et R₄), dans laquelle lesdits atomes sont combinés de n'importe quelles manières chimiquement pertinentes ;

M est H, ou Na, ou K, ou N⁺R₁R₂R₃ ou un sel pharmaceutique, dans lequel R₁, R₂ et R₃ sont tels que décrits ci-dessus.

2. Un conjugué agent de liaison cellulaire-médicament de formule (II)



dans lequel :

Cb représente un agent / une molécule liant les cellules ;

« Drug » représente un médicament lié à l'agent de liaison cellulaire via le lieu hydrophile par un pont disulfure, thioéther, thioester, peptide, hydrazone, éther, ester, carbamate, carbonate, cyclohétéroalcane, hétéroaromatique, alcoxime ou amide ;

Q et T sont -P(=O)(OM)-, ou -S(O₂)-, ou -S(O)-;

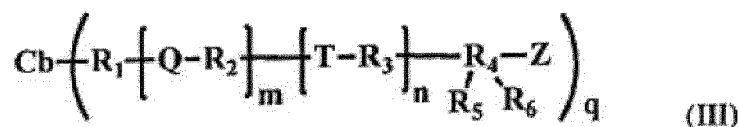
m et n sont des nombres entiers de 0 à 5, mais ne valant pas 0 en même temps; de plus, lorsque m = 1, n = 0, Q n'est pas -P(=O)(OM)-; ou lorsque n = 1, m = 0, T n'est pas ou -S(O)-; -P(=O)(OM)-; q est un nombre entier de 1 à 20 ;

R₁, R₂, R₃, R₄, R₅ et R₆ sont identiques ou différents et sont H, alkyle linéaire ayant de 1 à 6 atomes de carbone, alkyle ramifié ou cyclique ayant de 3 à 6 atomes de carbone, alcényle linéaire ou ramifié ou cyclique ou alcynyle, ou 1-6 atomes de carbone d'un ester, d'un éther, d'un amide ou d'un motif polyéthylène-oxy de formule (OCH₂CH₂)_p, où p est un nombre entier de 0 à 1000, ou une combinaison de ceux-ci ;

ou R₁, R₂, R₃ et R₄ sont respectivement une chaîne d'atomes choisis parmi C, N, O, S, Si, et P qui relie de manière covalente le ligand de liaison de surface cellulaire, le groupe phosphinate ou sulfonyle, le médicament conjugué et entre eux (R₁, R₂, R₃ et R₄), dans laquelle lesdits atomes sont combinés de toute manière chimiquement pertinente ;

M est H, ou Na, ou K, ou N⁺R₁R₂R₃ ou un sel pharmaceutique, dans lequel R₁, R₂ et R₃ sont tels que décrits ci-dessus.

3. Un composé de formule (III) :



dans lequel :

Cb représente un agent / une molécule liant les cellules ;

Z représente un groupe fonctionnel qui permet la réaction avec un médicament cytotoxique ;

Q et T sont -P(=O)(OM)-, ou -S(O₂)-, ou -S(O)-;

m et n sont des entiers de 0 à 5, mais ne valent pas 0 en même temps ; de plus, lorsque m = 1, n = 0, Q n'est pas -P(=O)(OM)- ; ou lorsque n = 1, m = 0, T n'est pas -P(=O)(OM)- ; q est un nombre entier de 1 à 20 ;

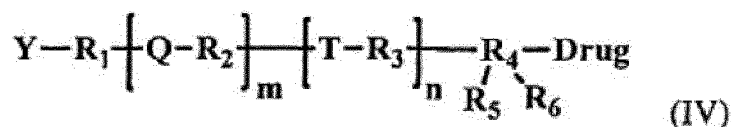
Z représente un groupe fonctionnel qui permet la liaison d'un médicament cytotoxique via un pont disulfure, thioéther, thioester, peptide, hydrazone, éther, ester, carbamate, carbonate, amine (secondaire, tertiaire ou quaternaire), imine, cyclohétéroalkyle, hétéroaromatique, alcoxime ou amide ;

R₁, R₂, R₃, R₄, R₅ et R₆ sont identiques ou différents et sont H, alkyle linéaire ayant de 1 à 6 atomes de carbone, alkyle ramifié ou cyclique ayant de 3 à 6 atomes de carbone, alcényle linéaire ou ramifié ou cyclique ou alcynyle, ou 1-6 atomes de carbone d'un ester, d'un éther, d'un amide ou d'un motif polyéthylène-oxy de formule (OCH₂CH₂)_p, où p est un nombre entier de 0 à 1000, ou une combinaison de ceux-ci ;

ou R₁, R₂, R₃ et R₄ sont respectivement une chaîne d'atomes choisis parmi C, N, O, S, Si et P qui relie de manière covalente le ligand de liaison à la surface cellulaire, le groupe phosphinate ou sulfonyle, le médicament conjugué et entre eux (R₁, R₂, R₃ et R₄), dans laquelle lesdits atomes sont combinés de n'importe quelles manières chimiquement pertinentes ;

M est H, ou Na, ou K, ou N⁺R₁R₂R₃ ou un sel pharmaceutique, dans lequel R₁, R₂ et R₃ sont tels que décrits ci-dessus.

4. Un composé de formule (IV) :



dans lequel :

Y représente un groupe fonctionnel qui permet la réaction avec un agent de liaison cellulaire ;

Q et T sont -P(=O)(OM)-, ou -S(O₂)-, ou -S(O)-;

m et n sont des nombres entiers de 0 à 5, mais ne valent pas 0 en même temps ; de plus, lorsque m = 1, n = 0, Q n'est pas -P(=O)(OM)- ; ou lorsque n = 1, m = 0, T n'est pas -P(=O)(OM)- ;

« Drug » représente un médicament lié à l'agent de liaison cellulaire via le lieu hydrophile par un pont disulfure, thioéther, thioester, peptide, hydrazone, éther, ester, carbamate, carbonate, cyclohétéroalcane, hétéroaromatique, alcoxime ou amide ;

R₁, R₂, R₃, R₄, R₅ et R₆ sont identiques ou différents et sont H, alkyle linéaire ayant de 1 à 6 atomes de carbone, alkyle ramifié ou cyclique ayant de 3 à 6 atomes de carbone, alcényle linéaire ou ramifié ou cyclique ou alcynyle, ou 1-6 atomes de carbone d'un ester, d'un éther, d'un amide ou d'un motif polyéthylène-oxy de formule (OCH₂CH₂)_p, où p est un nombre entier de 0 à 1000, ou une combinaison de ceux-ci ;

ou R₁, R₂, R₃ et R₄ sont respectivement une chaîne d'atomes choisis parmi C, N, O, S, Si et P qui relie de manière covalente le ligand de liaison à la surface cellulaire, le groupe phosphinate ou sulfonyle, le médicament conjugué et entre eux (R₁, R₂, R₃ et R₄), dans laquelle lesdits atomes sont combinés de n'importe quelles manières chimiquement pertinentes ;

M est H, ou Na, ou K, ou N⁺R₁R₂R₃ ou un sel pharmaceutique, dans lequel R₁, R₂ et R₃ sont tels que décrits ci-dessus.

5. Le conjugué selon la revendication 2 ou le composé de la revendication 4, dans lequel le « Drug » est choisi parmi :

1). Les agents chimiothérapeutiques : a). Les agents alkylants : choisis parmi les moutardes azotées (chlorambucil, chlormaphazine, cyclophosphamide, dacarbazine, estramustine, ifosfamide, méchloréthamine, chlorhydrate d'oxyde de méchloréthamine, mannometrine, mitobronitol, melphalan, mitolactol, pipobroman, novembichine, phénestérine, prednimustine, thiotépa, trofosfamide, moutarde à l'uracile). CC-1065 (y compris ses analogues synthétiques de l'adozélésine, de la carzélésine et de la bizélésine) ; la duocarmycine (y compris ses analogues synthétiques, KW-2189 et CBI-TMI) ; les dimères de benzodiazépine (choisis parmi les dimères de pyrrolbenzodiazépine (PBD) ou de tomaymycine, les indolinbenzodiazépines, les imidazobenzothiadiazépines ou les oxazolidinobenzodiazépines) ; les nitrosourées (carmustine, lomustine, chlorozotocine, fotémustine, nimustine, ranimustine) ; les alkylsulfonates (busulfan, treosulfan, improsulfan et piposulfan) ; Les triazènes

(dacarbazine) ; les composés contenant du platine : (carboplatine, cisplatine, oxaliplatine) ; les aziridines (benzodopa, carboquone, meturedopa et uredopa) ; les éthylénimines et les méthylamélamines comprenant l'altré-
 5 tamine, la triéthylènemélamine, le triéthylèneposphoramide, le triéthylènethiophospha-amide et la triméthylolomélamine ; b). Les plantes alcaloïdes choisies parmi : les alcaloïdes Vinca (vincristine, vinblastine, vindésine, vinorelbine, navelbin) ; les taxoïdes (paclitaxel, docétaxol) et leurs analogues synthétiques, Maytan-
 10 sinoïdes (DMI, DM2, DM3, DM4, DM5, DM6, DM7, maytansine et ansamitocines) et leurs analogues synthéti-
 ques, cryptophycines (cryptophycine 1 et cryptophycine 8) ; les épothilones, l'éleuthérobine, le discodermolide, les bryostatines, les dolostatines, les auristatines, les tubulysines, les céphalostatines ; la pancratistatine ; une
 15 sarcodictyine ; la spongistatine ; c). Les inhibiteurs de l'ADN topoisomérase choisis parmi les épipodophyllines (9-aminocamptothécine, camptothécine, crisnatol, daunomycine, étoposide, étoposide phosphate, irinotécan, mitoxantrone, novantrone, acides rétinoïques (rétinols), téniposide, topotécan, 9-nitrocamptothécine (RFS
 20 2000)) ; les mitomycines (mitomycine C) ; d). Anti-métabolites choisis parmi : [Anti-folate qui est choisi parmi : les inhibiteurs de la DHFR, le méthotrexate, le trimétrexate, la denoptérine, la pteroptérine, l'aminoptérine (acide 4-aminoptéroïque) ; les inhibiteurs de l'IMP déshydrogénase (acide mycophénolique, tiazofurine, ribavirine, EICAR) ; les inhibiteurs de la ribonucléotide réductase (hydroxyurée, déféroxamine) ; les analogues de pyrimi-
 25 dine choisis parmi les analogues de l'uracile (ancitabine, azacitidine, 6-azauridine, capécitabine (Xeloda), car-
 mofur, cytarabine, didésoxyuridine, doxifluridine, énocitabine, 5-fluorouracile, floxuridine, ratitrexed (Tomudex)) ; les analogues de la cytosine (cytarabine, cytosine arabinoside, fludarabine) ; les analogues de la
 30 purine (azathioprine, fludarabine, mercaptopurine, thiamiprine, thioguanine) ; l'acide folique régénérateur, (aci-
 de frolinique) ; e). Les thérapies hormonales choisies parmi les antagonistes des récepteurs, qui sont choisies
 35 parmi : Anti-oestrogène : (mégesterol, raloxifène, tamoxifène) ; les agonistes de la LHRH (goserline, acétate
 de leuprolide) ; Anti-androgènes (bicalutamide, flutamide, calusterone, propionate de dromostanolone, épi-
 tiostanol, goséréline, leuprolide, mépitostane, nilutamide, testolactone, trilostane et autres inhibiteurs des
 40 androgènes) ; les rétinoïdes / deltoïdes qui sont choisis parmi : des analogues de la vitamine D3 (CB 1093, EB
 1089 KH 1060, cholécalficérol, ergocalcicérol) ; les thérapies photodynamiques (vertéporfine, phtalocyanine,
 photosensibilisateur Pc4, déméthoxy-hypocrelline A) ; Les cytokines (interféron alpha, interféron gamma, fac-
 45 teur de nécrose tumorale (TNF), protéines humaines contenant un domaine TNF) ; f). Les inhibiteurs de kinases
 choisis parmi BIBW 2992 (anti-EGFR / Erb2), l'imatinib, le géfitinib, le pegaptanib, le sorafénib, le dasatinib, le
 50 sunitinib, l'erlotinib, le nilotinib, le lapatinib, l'axitinib, le pazopanib, le vandétanib, l'E7080 (anti-VEGFR2), le
 mubritinib, le ponatinib (AP24534), le bafétinib (INNO-406), le bosutinib (SKI-606), le cabozantinib, le vismo-
 degib, l'iniparib, le ruxolitinib, le CYT387, l'axitinib, le tivozanib, le sorafenib, le bevacizumab, le cetuximab, le
 55 Trastuzumab, le Ranibizumab, le Panitumumab, l'ispinesib ; g). Les antibiotiques choisis parmi les antibiotiques
 enediyne (y compris la calichéamicine, la calichéamicine, $\gamma 1$, $\delta 1$, $\alpha 1$ et $\beta 1$, la dynemicine, y compris la dynemicine
 A et la deoxydynemicine, l'esperamicine, la kedarcidine, le C-1027, la maduropeptine, le chromophore de
 60 néocarzinostatine et les chromophores antibiotiques de chromoprotéine enediyne), l'aclacinomysines,
 l'actinomycine, l'authramycine, l'azasérine, les bléomycines, la cactinomycine, la carabicine, la carminomycine,
 la carzinophiline ; les chromomycines, la dactinomycine, la daunorubicine, la détórubicine, la 6-diazo-5-oxo-L-
 65 norleucine, la doxorubicine, la morpholino-doxorubicine, la cyanomorpholino-doxorubicine, la 2-pyrrolino-doxo-
 rubicine et la désoxydoxorubicine, l'épirubicine, l'esorubicine, l'idarubicine, la marcellomycine, nitomycines,
 70 acide mycophénolique la nogalamycine, les olivomycines, la péplomycine, la potfiromycine, la puromycine, la
 quelamycine, la rodorubicine, la streptonigrine, la streptozocine, la tubercidine, l'ubenimex, la zinostatine, la
 zorubicine ; f). Autres : choisis parmi les polycétides (acétogénines), la bullatacine et la bullatacinone ; la gem-
 75 citabine, les époxomicines (carfilzomib), le bortézomib, le thalidomide, le lénalidomide, le pomalidomide, le
 tosédostat, le zybrestat, le PLX4032, le STA-9090, le Stimuvax, l'allovectine-7, le Xegeva, le Provenge, le
 80 Yervoy, les inhibiteurs d'isoprénnylation (y compris la lovastatine), les neurotoxines dopaminergiques (y compris
 1-méthyl-4-phénylpyridinium), les inhibiteurs du cycle cellulaire (y compris la staurosporine), les actinomycines
 (y compris actinomycine D, dactinomycine), les bléomycines (bléomycine A2, bléomycine B2, péplomycine),
 85 les anthracyclines (daunorubicine, doxorubicine (adriamycine), l'idarubicine, l'épirubicine, al pirarubicine, la
 zorubicine, le mttoxantrone, les inhibiteurs de la MDR (vérapamil), les inhibiteurs de la Ca^{2+} ATPase (thapsigar-
 90 gine), les inhibiteurs de l'histone désacétylase (Vorinostat, Romidepsin, Panobinostat, acide valproïque, mo-
 cétinostat (MGCD0103), Belinostat, PCI-24781, Entinostat, SB939, Resminostat, Givinostat, l'AR-42, le CUDC-
 101, sulforaphane, Trichostatine A) ; le Thapsigargin le Celécoxib, les glitazones, le gallate d'épigallocatechine,
 le Disulfirame, le Salinosporamide A. ; Anti-surrénales, choisies parmi l'aminogl utéthimide, le mitotane, le
 95 trilostane ; l'aceglatone ; l'aldophosphamide glycoside ; l'acide aminolévulinique ; l'amsacrine ; l'arabinoside,
 le bestrabucil ; le bisantrène ; l'edatraxate ; le défofamine ; la démécoldine ; le diaziquone ; l'éflomithine (DFMO),
 l'elfomithine ; l'acétate d'elliptinium, l'étoyclucide ; le nitrate de gallium ; la gacytosine, l'hydroxyurée ; l'ibandro-
 100 nate, la lentinane ; la lonidamine ; la mitoguazone ; la mitoxantrone ; le mopidamol ; la nitracrine ; la
 pentostatine ; le phenamet ; la pirarubicine ; l'acide podophyllinique ; Le 2-éthylhydrazide ; la procabazine ; le

PSK® ; le razoxane ; la rhizoxine ; le sizofiran ; spirogermanium ; l'acide ténazoïque ; le triaziquone ; le 2,2',2"-trichlorotriéthylamine ; les trichothécènes (en particulier la toxine T-2, la verrucarine A, la roridine A et l'anguidine) ; l'uréthane, la siRNA, les médicaments antisens ;

2). Les agents pathogènes anti-auto-immunes : la cyclosporine, la cyclosporine A, l'acide aminocaproïque, l'azathioprine, la bromocriptine, le chlorambucil, la chloroquine, le cyclophosphamide, les corticostéroïdes (aminonide, bétaméthasone, budésone, hydrocortisone, flunisolide, propionate de fluticasone, fluocortolone, d-nazol, dexaméthasone, triamcinolone acétonide, dipropionate de béclo-métasone), la DHEA, l'énanercept, l'hydroxychloroquine, l'infliximab, le méloxicam, le méthotrexate, le mofétil, la mycophénylate, la prednisone, le sirolimus, le tacrolimus.

3). Les agents pathogènes anti-infectieux, a). Les aminoglycosides : amikacine, astromicine, gentamicine (nétilmicine, sisomicine, isépa-micine), hygromycine B, kanamycine (amikacine, arbekacine, békanamycine, dibé-kacine, tobramycine), néomycine (framycétine, paromomycine, ribostamycine), nétilmicine, spectinomycine, streptomycine, tobramycine, verdamicine ; b). Les amphenicols : azidamfenicol, chloramphenicol, florfenicol, thiamphenicol ; c). Les ansamycines : geldanamycine, herbimycine ; d). Les carbapénèmes : biapénème, doripénème, ertapénème, imipénème / cilastatine, méropénème, panipénème ; e). Les céphèmes : carbacephème (loracarbef), céfacétrile, céfacylor, céfradine, céfadroxil, céfalonium, céfaloridine, céfalotine ou céfalo-thine, cé-falexine, cefaloglycine, céfamandole, céfapirine, céfatrizine, cefazaflur, cefazedone, céfazoline, cefbupérazone, cefcapene, cefdaloxime, céfépime, cefminox, céfoxitine, cefprozil, cefroxadine, ceftézole, céfuroxime, cefixime, cefdinir, cefditoren, céfépime, cefetamet, cefménoxime, céfodizime, cefonicid, céfopérazone, ceforanide, ce-fotaxime, cefotiam, cefozopran, cephalixin, cefpimizole, cefpiramide, cefpirome, cefpodoxime, cefprozil, ce-fquinome, cefsulodin, ceftazidime, ceftaram, ceftibuten, ceftiole, ceftizoxime, ceftobiprole, ceftriaxone, ce-furoxime, cefuzonam, cephamycin (céfoxitine, céfotétan, céfmétazole), oxacéphème (flomoxef, latamoxef) ; f). Glycopeptides : bléomycine, vancomycine (oritavancine, télavancine), téicoplanine (dalbavancine), ramoplanine ; g). Les glycylicyclines (tigécycline) ; g). Les inhibiteurs de la β -lactamase : le penam (sulbactam, tazobactam), le clavam (acide clavulanique) ; i). Les lincosamides : clindamycine, lincomycine ; j). Les lipopeptides : daptomycine, A54145, antibiotiques calcium-dépendants (CDA) ; k). Les macrolides : azithromy-cine, céthromycine, clarithromycine, dirithromycine, érythromycine, flurithromycine, josamycine, cétolide (té-lithromycine, céthromycine), midécamycine, miocamycine, oléandomycine, rifamycines (rifampicine, rifampici-ne, rifabutine, rifapentine), rokitamycine, roxithromycine, spectinomycine, spiramycine, tacrolimus (FK506), la troléandomycine, la télithromycine ; l). Les monobactams : aztréonam, tigemonam ; m). Les oxazolidinones : linézolide ; n). Les pénicillines : amoxicilline, ampicilline (pivampicilline, hétacilline, bacampicilline, métampicil-line, talampicilline), azidocilline, azlocilline, benzylpénicilline, benzathine benzylpénicilline, benzathine Phénoxy-méthylpénicilline, clometocilline, lbenzylpénicilline procaïne, lcarbénicilline (carindacilline), la cloxacilline, la dicloxacilline, la épécilline, la flucloxacilline, le mécillinam (pivmecillinam), la mézlocilline, la méticilline, la naf-cilline, l'oxacilline, la pénamécilline, la pénicilline, la phénéticilline, la phénoxy-méthylpénicilline, la pipéracilline, la propicilline, la sulbénicilline, la temocilline, la ticarcilline ; o). Les polypeptides : bacitracine, colistine, poly-myxine B ; p). Les quinolones : alatrofloxacin, balofloxacin, ciprofloxacin, clinafloxacin, danofloxacin, di-floxacin, énoxacin, enrofloxacin, floxine, garenoxacin, gatifloxacin, gémifloxacin, grepafloxacin, kano trovafloxacin, lévofloxacin, lomefloxacin, marbofloxacin, moxifloxacin, nadifloxacin, norfloxacin, orbi-floxacin, ofloxacin, péfloxacin, trovafloxacin, grepafloxacin, sitafloxacin, sparfloxacin, temafloxacin, tosufloxacin, trovafloxacin ; q). Les streptogramines : pristnamycine, quinupristine / dalfopristine ; r). Les sulfonamides : mafénide, prontosil, sulfacétamide, sulfaméthizole, sulfanilimide, sulfasalazine, sulfisoxazole, triméthoprim, triméthoprim-sulfaméthoxazole (co-trimoxazole) ; s). Les antibactériens stéroïdiens (acide fusidique) ; t). Les tétracyclines : doxycycline, chlortétracycline, clomocycline, déméclocycline, lymécycline, méclocycline, métacycline, minocycline, oxytétracycline, pénimepicycline, rolitétracycline, tétracycline, glycyli-cyclines (tigécycline) ; u). Autres types d'antibiotiques : l'annonacine, l'arsphenamine, les inhibiteurs de la bac-toprénole (bactéridine), les inhibiteurs DADAL /AR (cyclosérine), la dictyostatine, le discodermolide, l'éleuthé-roline, l'épothilone, l'éthambutol, l'étoposide, le faropénème, l'acide fusidique, la furazolidone, l'isoniazide, le latralimide, le métronidazole, la mupirocine, la mycolactone, les inhibiteurs de la synthèse du NAM (fosfomycine), la nitrofurantoïne, le paclitaxel, la platensimycine, la pyrazinamide, la quinupristine / dalfopristine, la rifampicine (rifampicine), le tazobactam tinidazole, l'uvaricine ;

4). Les médicaments anti-viraux : a). Les inhibiteurs d'entrée/ fusion : aplaviroc, maraviroc, vicriviroc, gp41 (enfuvirtide), PRO 140, CD4 (ibalizumab) ; b). Les inhibiteurs de l'intégrase : raltégravir, elvitégravir, globoïdane A ; c). Les inhibiteurs de la maturation : bevirimat, vivecon ; d). Les inhibiteurs de la neuraminidase : oseltamivir, zanamivir, péravimivir ; e). Les nucléosides et nucléotides : abacavir, aciclovir, adéfovir, amdoxovir, apricitabine, brivudine, cidofovir, clevudine, dexelvucitabine, didanosine (ddI), elvucitabine, emtricitabine (FTC), entécavir, famciclovir, fluorouracile (5-FU), substitué 3'-fluoro- Analogues de 2', 3'-didésoxynucléoside (3'-fluoro-2', 3'-didésoxythymidine (FLT) et 3'-fluoro-2', 3'-didésoxyguanosine (FLG), fomivirsén, ganciclovir, idoxuridine, lami-

vudine (3TC), 1-nucléosides (β -1-thymidine et β -1-2'-désoxycytidine), penciclovir, racivir, ribavirine, stampidine, stavudine (d4T), taribavirine (viramidine), telbivudine, ténofovir, trifluridine valaciclovir, valganciclovir, zalcitabine (ddC), zidovudine (AZT), f). Les non-nucléosides : amantadine, ateviridine, capravirine, diarylpyrimidines (étravirine, rilpivirine), delavirdine, docosanol, éfavirine, éfavirenz, foscarnet (acide phosphonoformique), imiquimod, interféron alfa, loviride, lodénosine, méthisazone, névirapine, NOV-205, peginterféron alfa, la podophylotoxine, rifampicine, rimantadine, resiquimod (R-848), tromantadine ; g). Les inhibiteurs de la protéase : amprénavir, atazanavir, bocéprévir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, pleconaril, ritonavir, saquinavir, télaprévir (VX-950), tipranavir ; h). Les autres types de médicaments antiviraux : abzyme, arbidol, calanolide a, céragénine, cyanovirine-n, diarylpyrimidines, gallate d'épigallocatechine (EGCG), foscarnet, grifithsine, taribavirine (viramidine), hydroxyurée, KP-1461, miltéfosine, pleconaril, inhibiteurs de portmanteau, ribavirine, le séléciclib.

5) Les radio-isotopes choisis parmi (radionucléides) ^3H , ^{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 ou ^{213}Bi .

6). Les sels ou les acides pharmaceutiquement acceptables de l'un quelconque des médicaments ci-dessus.

6. Le conjugué selon la revendication 2 ou composé selon la revendication 4, dans lequel le « Drug » est choisi parmi les tubulysines, les calichéamicines, les auristatines, les maytansinoïdes, les analogues CC-1065, les morpholinos doxorubicines, les taxanes, les cryptophycines, les épithilones et les dimères benzodiazépines (choisis parmi les dimères de pyrrolbenzodiazépine (PBD) ou de tomaymycine, d'indolinobenzodiazépines, d'imidazobenzothiadiazépines ou d'oxazolidinobenzodiazépines), de siRNA ou d'une combinaison de ceux-ci, et de sels pharmaceutiquement acceptables, ou d'acides de l'un quelconque de ceux ci-dessus.

7. Le conjugué selon la revendication 2 ou composé selon la revendication 3, dans lequel l'agent / molécule de liaison cellulaire est choisi parmi les anticorps, les protéines, les vitamines (folates), les peptides, les micelles polymériques, les liposomes, les transporteurs de médicaments à base de lipoprotéines, les nano-particules transporteuses de médicaments, les dendrimères et une combinaison de ceux-ci.

8. Le conjugué selon la revendication 2 ou le composé selon la revendication 3, dans lequel l'agent de liaison cellulaire se lie à des cellules cibles qui sont choisies parmi des cellules tumorales, des cellules infectées par des virus, des cellules infectées par des microorganismes, des cellules auto-immunes, des cellules activées des cellules, des cellules T activées, des cellules B ou des mélanocytes ; des cellules exprimant le CD19, CD20, CD22, CD30, CD33, CD37, CD38, CD40, CD 51, CD52, CD56, CD66, CD70, CD74, CD79, CD80, CD98, CD125, CD221, CD227, CD262, CD309, CD326, CEACAM3, CEACAM5 (antigène carcino-embryonnaire), DLL4 (4 protéines de type delta), l'EGFR, CTLA4, CXCR4 (CD184), l'Endoglin (CD105), l'EPCAM (molécule d'adhésion cellulaire épithéliale), l'ERBB2 (récepteur de facteur de croissance épithérmique 2), le FCGR1, le FOLR (récepteur du folate), le ganglioside GD2, le G-28 (antigène de surface cellulaire glycolipide), l'idiotype GD3, des protéines de choc thermique, l'HER1, HER2, HLA-DR10, HLA-DRB, la gonadotrophine chorionique humaine, l'IGF1R (croissance analogue à l'insuline récepteur du facteur 1), le récepteur de l'IL-2 (récepteur de l'interleukine 2), l'IL-6R (récepteur de l'interleukine 6), les intégrines ($\alpha\text{v}\beta 3$, $\alpha 5\beta 1$, $\alpha 6\beta 4$, $\alpha 11\beta 3$, $\alpha 5\beta 5$, $\alpha\text{v}\beta 5$), le MAGE-1, MAGE-2, MAGE- 3, MAGE 4, le récepteur anti-transferrine, le p97, le MS4A1 (l'élément 1, transmembranaire humain, de sous-famille A, à 4 domaines), le MUC1 ou MUC1-KLH, MUC16 (CA125), CEA, gp100, MART1, MPG, MS4A1 (transmembranaire humain, de sous-famille A, à 4 domaines), la nucleonine, le produit Neu oncogene, le P21, le paratope d'acide anti- (N-glycolylneuraminique), le phosphatase alcaline testiculaire de type PLAP, PSMA, PSA, ROB04, TAG 72 (glycoprotéine 72 associée aux tumeurs), la protéine transmembranaire des lymphocytes T, le Tie (CD202b), le TNFRSF10B (membre de la superfamille du récepteur du facteur de nécrose tumorale 10B), le TNFRSF13B (membre de la superfamille du récepteur du facteur de nécrose tumorale 13B), le TPBG (glycoprotéine du trophoblaste), le TRAIL-R1 (récepteur du ligand inducteur de la nécrose tumorale 1), le VCAM-1 (CD106), VEGF, VEGF-A, VEGF-2 (CD309), le CanAg, le CALLA et des cellules exprimant le récepteur du facteur de croissance de l'insuline, ou le récepteur du facteur de croissance épidermique.

9. Le conjugué selon la revendication 2 ou composé selon la revendication 3, dans lequel l'agent de liaison aux cellules est un anticorps, un anticorps monocaténaire, un fragment d'anticorps qui se lie à la cellule cible, un anticorps monoclonal, un anticorps monoclonal monocaténaire ou un fragment d'anticorps monoclonal qui lie la cellule cible, un anticorps chimérique, un fragment d'anticorps chimérique qui se lie à la cellule cible, un anticorps de domaine, un fragment d'anticorps de domaine qui se lie à la cellule cible, un anticorps resurfacé, un fragment d'anticorps resurfacé qui se lie à la cellule cible, un anticorps humanisé ou un anticorps resurfacé, un anticorps monocaténaire humanisé, ou un fragment d'anticorps humanisé qui se lie à la cellule cible, une lymphokine, une hormone, une vitamine, un facteur de croissance, un facteur de stimulation des colonies, ou une molécule de transport des nutri-

ments.

10. Le conjugué ou composé selon la revendication 8, dans lequel les cellules tumorales sont choisies parmi les cellules
 5 lymphomateuses, les cellules myélomateuses, les cellules rénales, les cellules cancéreuses du sein, les cellules
 cancéreuses de la prostate, les cellules cancéreuses ovariennes, les cellules cancéreuses gastriques, les cancers
 squameux, les cellules cancéreuses pulmonaires à petites cellules, les cellules cancéreuses testiculaires, ou toute
 cellule qui croît et se divise à un rythme non régulé et accéléré pour provoquer des cancers.
11. Une composition pharmaceutique comprenant une quantité thérapeutiquement efficace de l'immunoconjugué selon
 10 la revendication 2, et un sel, support, diluant ou excipient pharmaceutiquement acceptable par conséquent, ou une
 combinaison de ceux-ci, pour le traitement ou la prévention d'un cancer ou d'une maladie auto-immune, ou une
 maladie infectieuse.
12. Le conjugué selon la revendication 2 ou le composé selon la revendication 4, dans lequel l'agent médicamenteux
 15 / cytotoxique est choisi parmi une toxine, un agent chimiothérapeutique, un fragment de médicament, un antibiotique,
 un isotope radioactif et une enzyme nucléolytique.
13. Le conjugué selon la revendication 2, qui est un immunoconjugué de formule $Cb-(LD-Drug)_n$, dans lequel Cb est
 20 un agent de liaison cellulaire, L est le lieu hydrophile, Drug est une molécule de médicament, et n est un nombre
 entier de 1 à 20.
14. Le conjugué selon la revendication 13, qui est un immunoconjugué dans lequel le lieu hydrophile L est composé
 d'un ou plusieurs composants lieurs de 6-maléimidocaproyle (MC), maléimidopropanoyl (MP), valine-citrulline (val-
 25 cit), alanine-phénylalanine (ala-phe), p-aminobenzoyloxycarbonyl (PAB), 4-thiopentanoate (SPP), 4-(N-maléimido-
 méthyl) cyclohexane-1-carboxylate (MCC), 4-thio-butyrat (SPDB), maléimidoéthyle (ME), 4-thio-2-hydroxysulfonyl-
 butyrat (2-Sulfo-SPDB) et de (4-acétyl) aminobenzoate (SIAB).
15. Le conjugué selon la revendication 2 ou 13, qui est un immunoconjugué dans lequel le Médicament est choisi parmi
 30 les tubulysines, les maytansinoïdes, les taxanoïdes (taxanes), les analogues CC-1065, les daunorubicines et les
 doxorubicines, les benzodiazépines dimères (y compris les dimères de pyrrolobenzodiazépine (PBD), la tomaymy-
 cine, les anthichycines, les indolinobenzodiazépines, les imidazobenzothiadiazépines, ou les oxazolidinobenzodia-
 zépines), les calichéamicines et les antibiotiques enediyne, l'actinomycine, les azasérines, les bléomycines, l'épi-
 35 rubicine, le tamoxifène, l'idarubicine, les dolastatines / auristatines (choisis parmi les monométhyl auristatines E,
 MMAE, MMAF, l'auristatine PYE, l'auristatine TP, les auristatines 2-AQ, 6-AQ, EB (AEB) et EFP (AEFP)), les
 duocarmycines, le thiotépa, le vincristine, les hémiasterlines et esperrucines.
16. Le conjugué des revendications 2 ou 13, qui est un immunoconjugué ayant une activité de destruction cellulaire in
 vitro, in vivo ou ex vivo.
17. L'immunoconjugué selon la revendication 13, dans lequel le lieu comprend soit un peptide de 1 à 20 unités d'acides
 40 aminés naturels ou non naturels, soit une unité p-aminobenzyle, soit une unité 6-maléimidocaproyle, soit une unité
 disulfure, soit une unité thioéther, ou une unité hydrozone, ou une unité alcoxime.
18. L'immunoconjugué selon la revendication 13, dans lequel le lieu est clivable par une protéase.
19. Une composition pharmaceutique comprenant le conjugué de la revendication 2 ou 13, et un véhicule pharmaceu-
 45 tiquement acceptable.
20. Une composition pharmaceutique comprenant une quantité thérapeutiquement efficace du conjugué selon la re-
 50 vendication 2 ou 13, dans laquelle la composition peut être administrée concurremment avec d'autres agents thé-
 rapeutiques choisis parmi l'agent chimiothérapeutique, la radiothérapie, les agents d'immunothérapie, les agents
 auto-immunes, les agents anti-infectieux ou autres immunoconjugués pour un traitement synergique efficace ou la
 prévention d'un cancer, ou d'une maladie auto-immune, ou d'une maladie infectieuse.

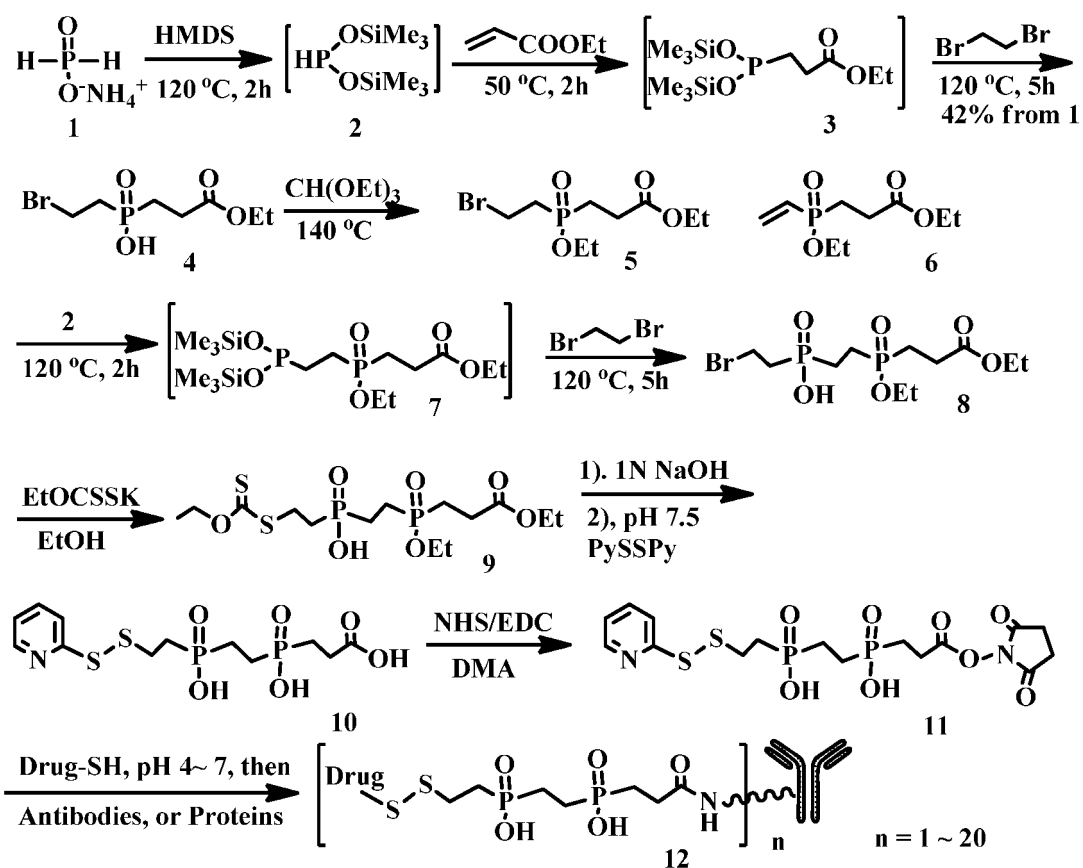


Fig. 1. The synthesis of a di-phosphinic acid linker.

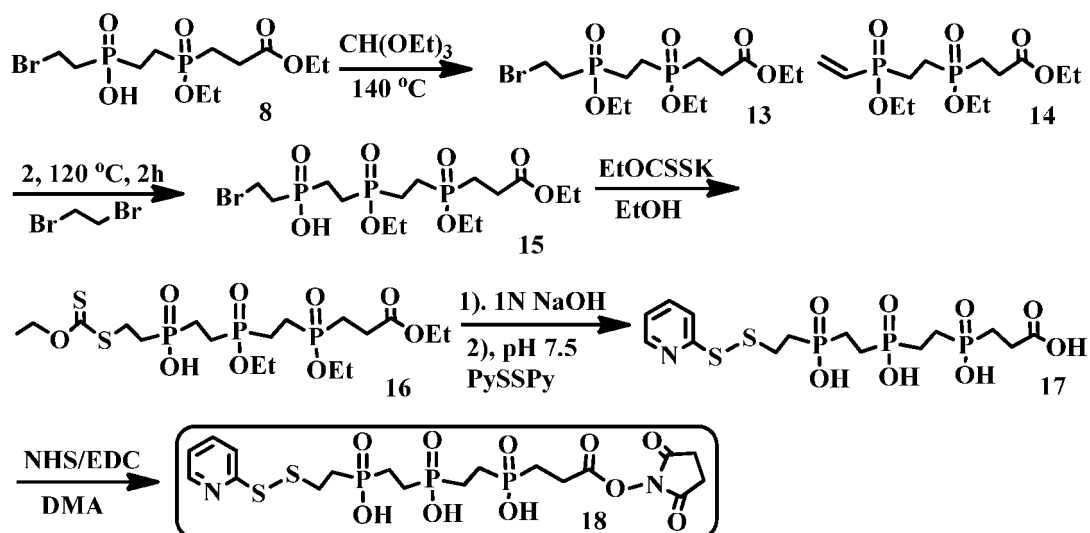


Fig. 2. The synthesis of a tri-phosphinic acid linker

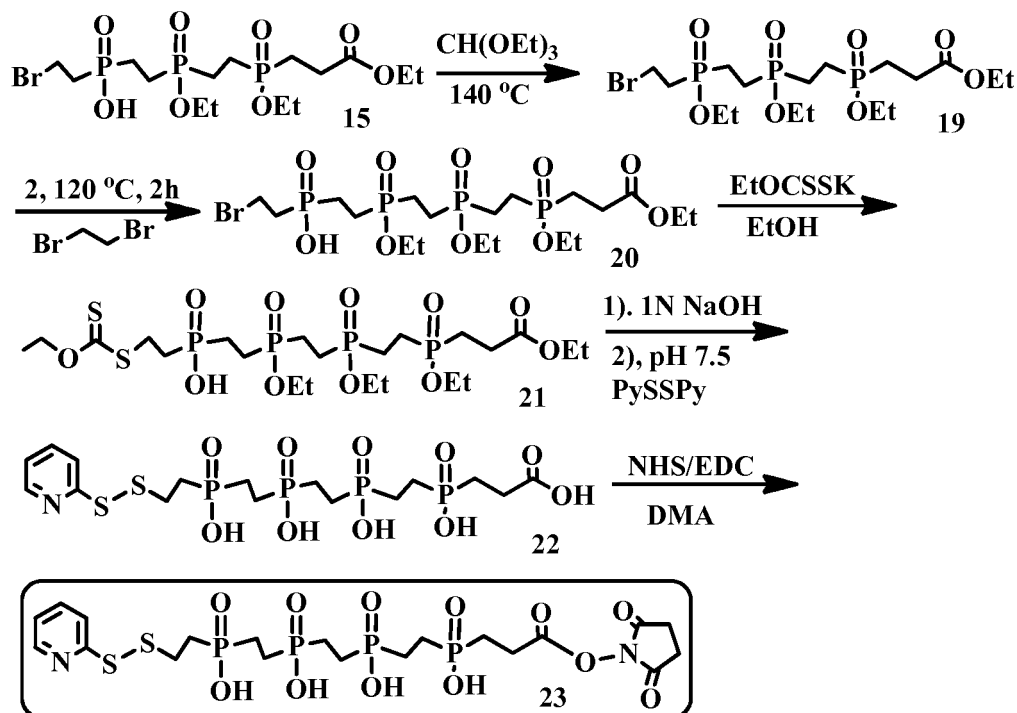


Fig. 3. The synthesis of a tetra-phosphinic acid linker

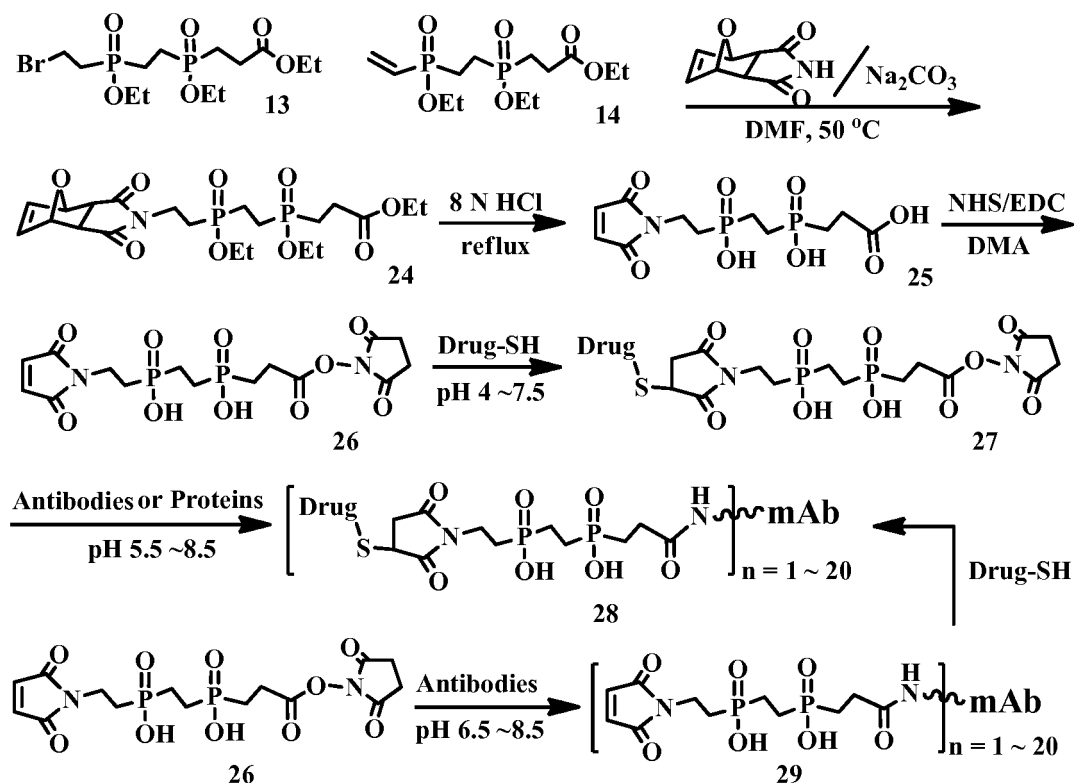


Fig. 4. The synthesis of a di-phosphinic acid linker.

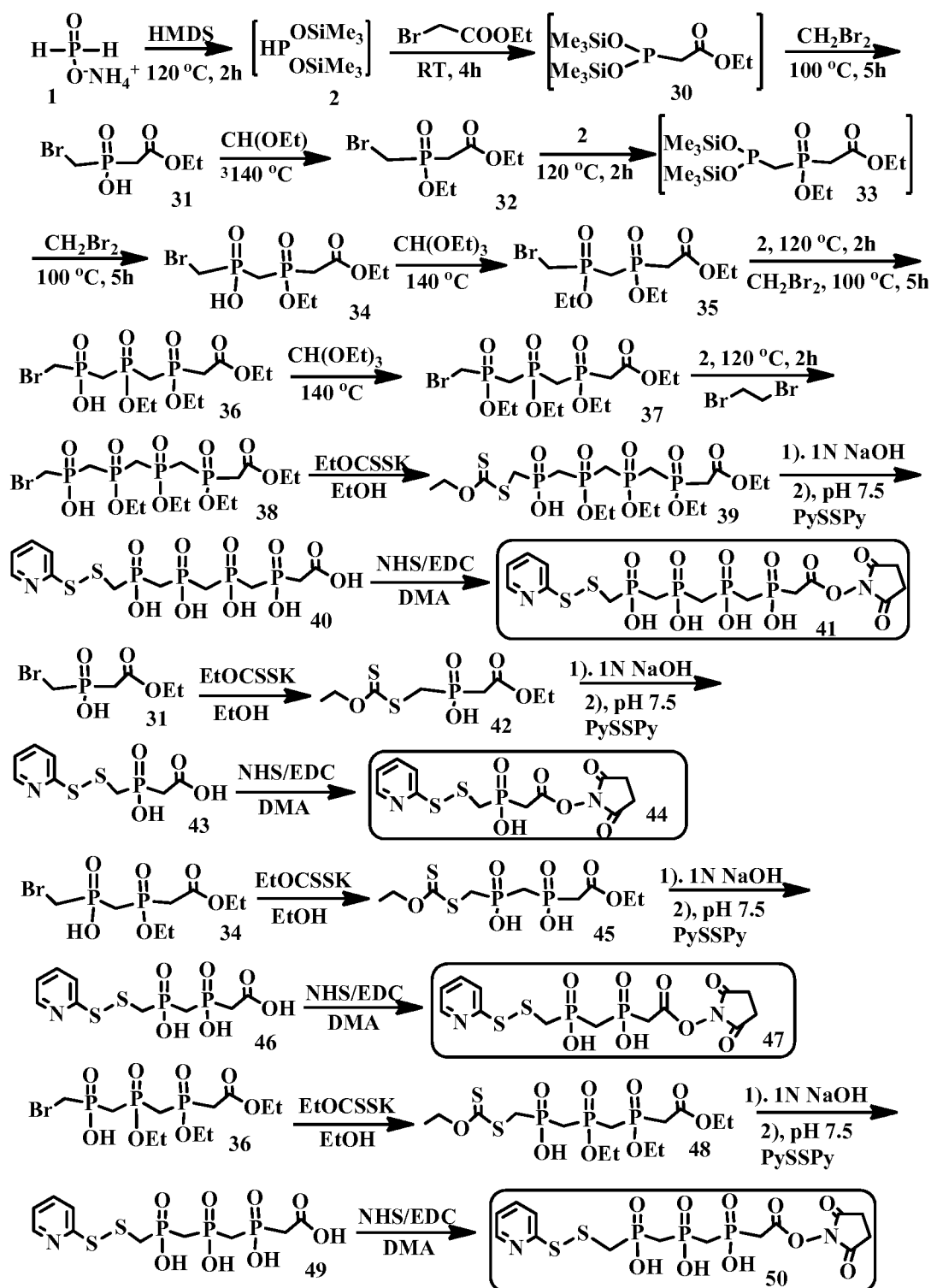


Fig. 5. The synthesis of mono-, bi- tri- and tetra-phosphinate linkers

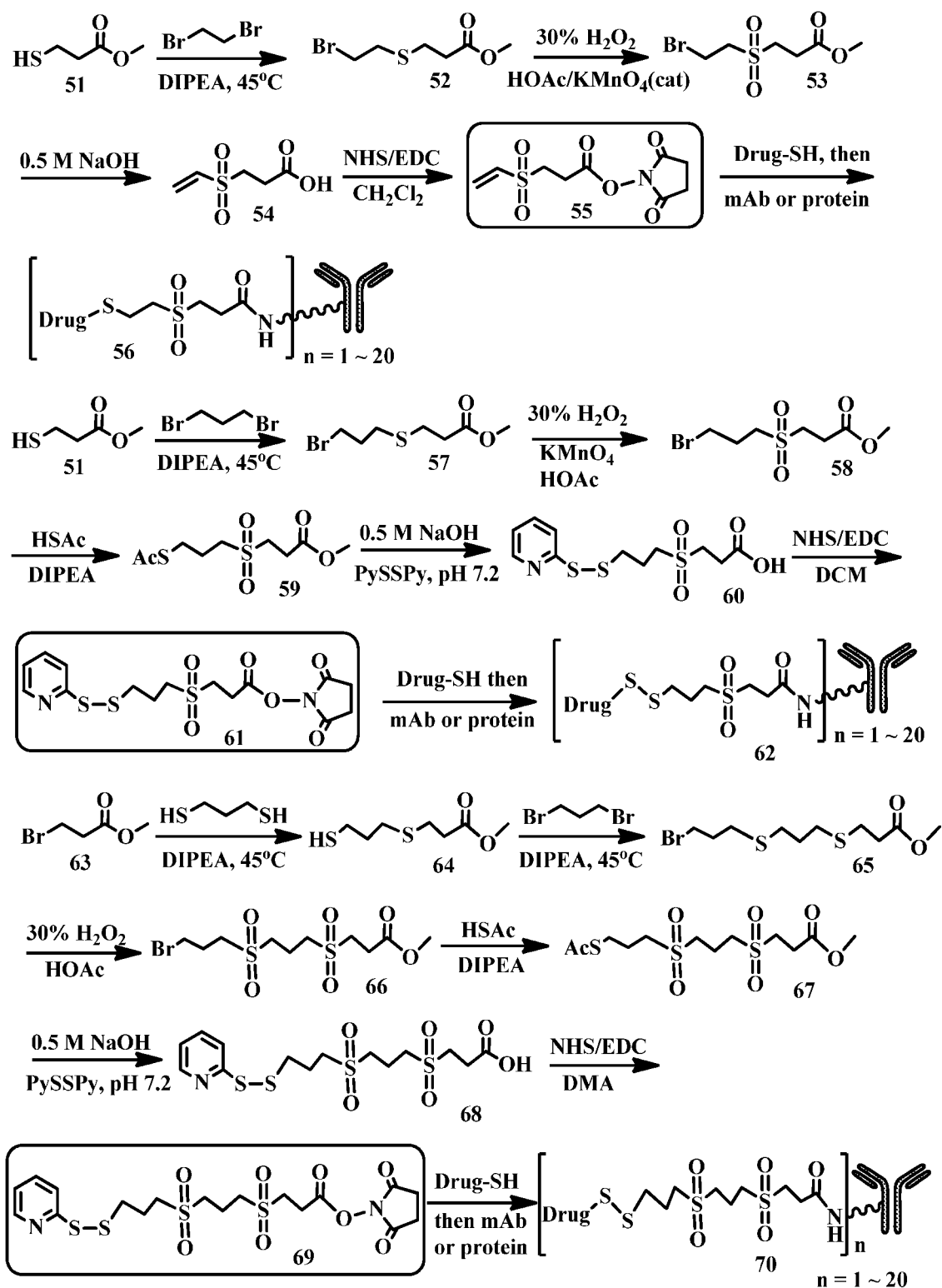


Fig 6. The synthesis of mono-, and di-sulfonyl linkers

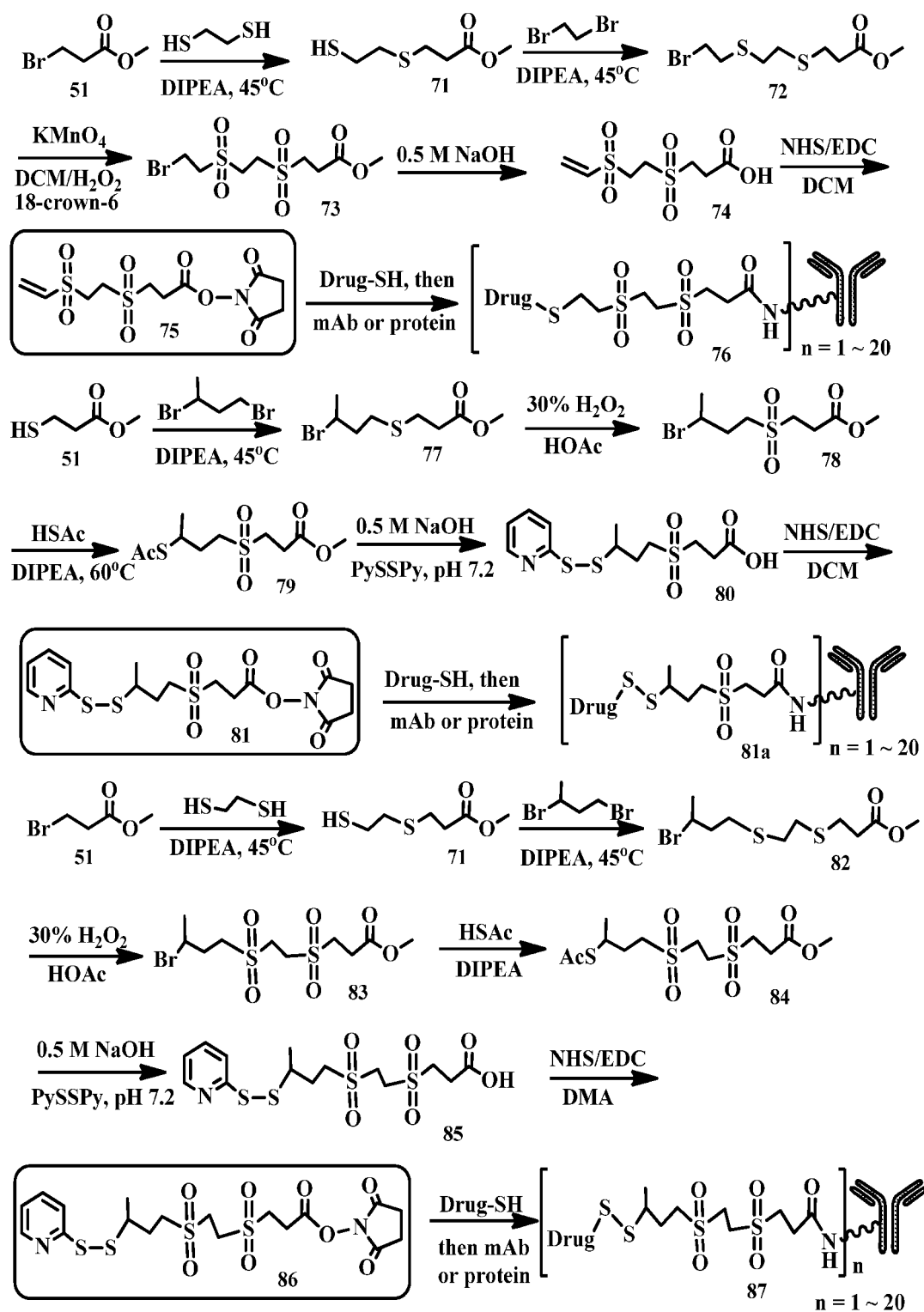


Fig. 7. The synthesis of mono-, and di-sulfonyl linkers

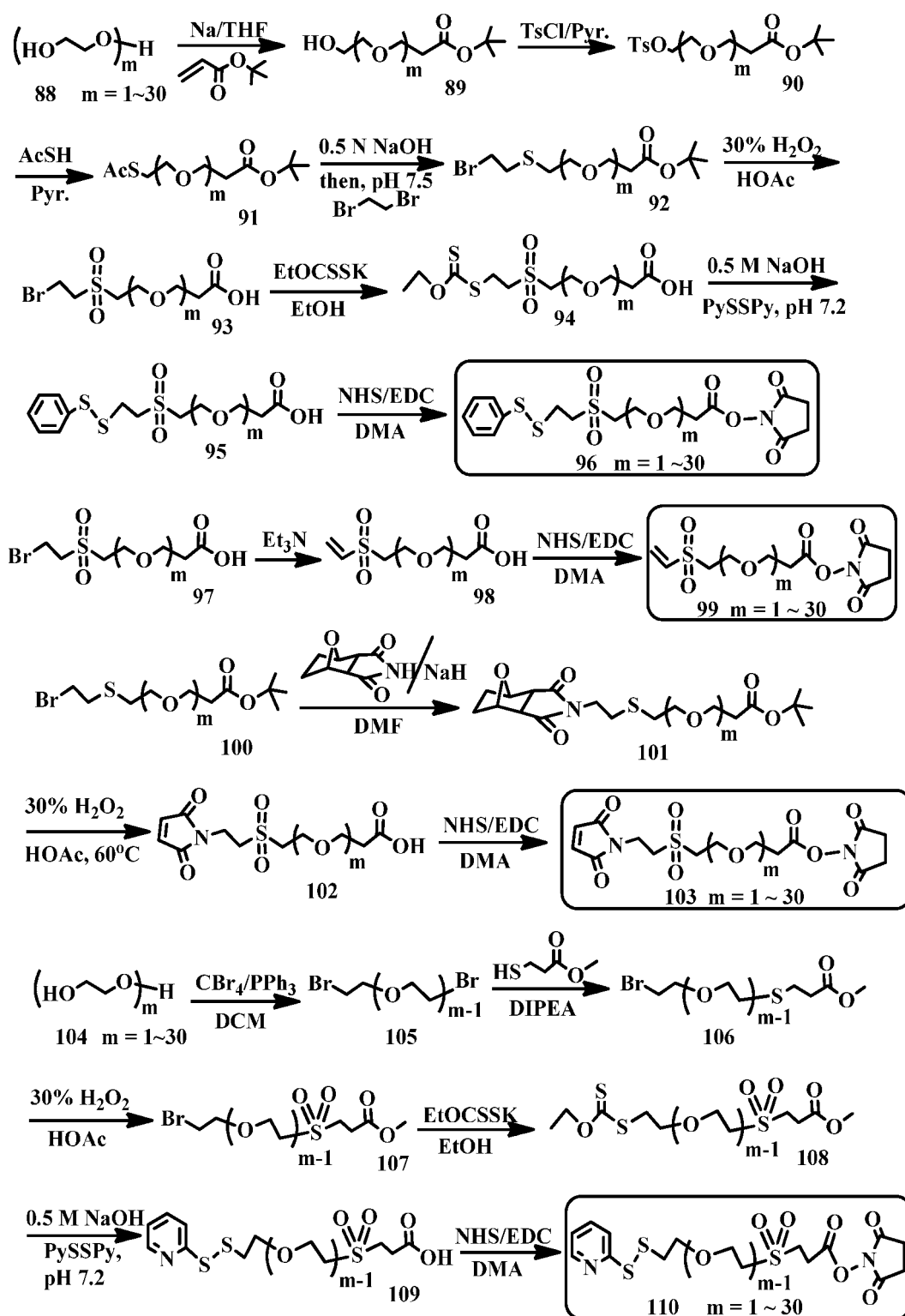


Fig. 8. The synthesis of mono-sulfonyl linkers containing polyethylene glycols.

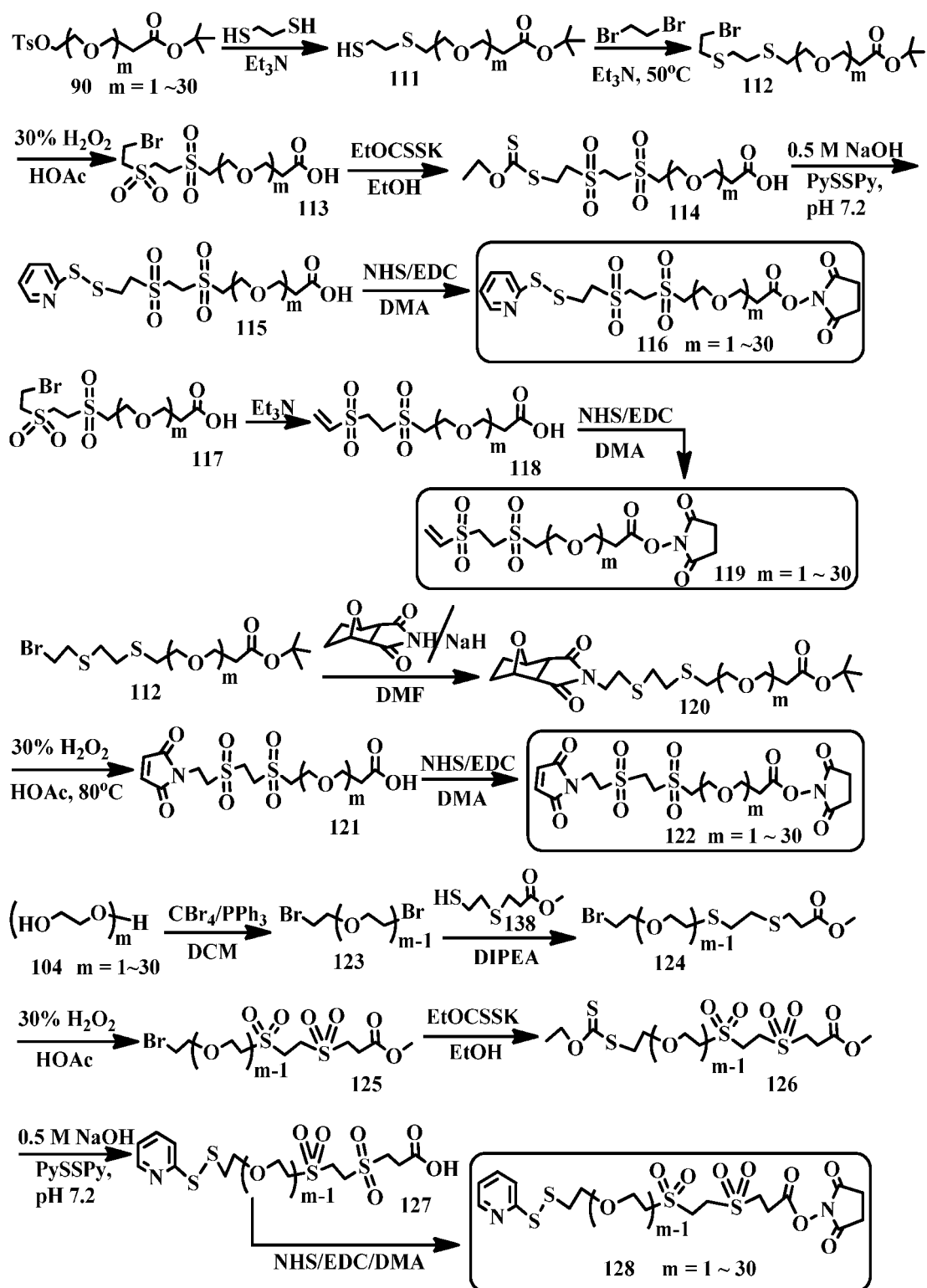


Fig. 9. The synthesis of di-sulfonyl linkers containing polyethylene glycols.

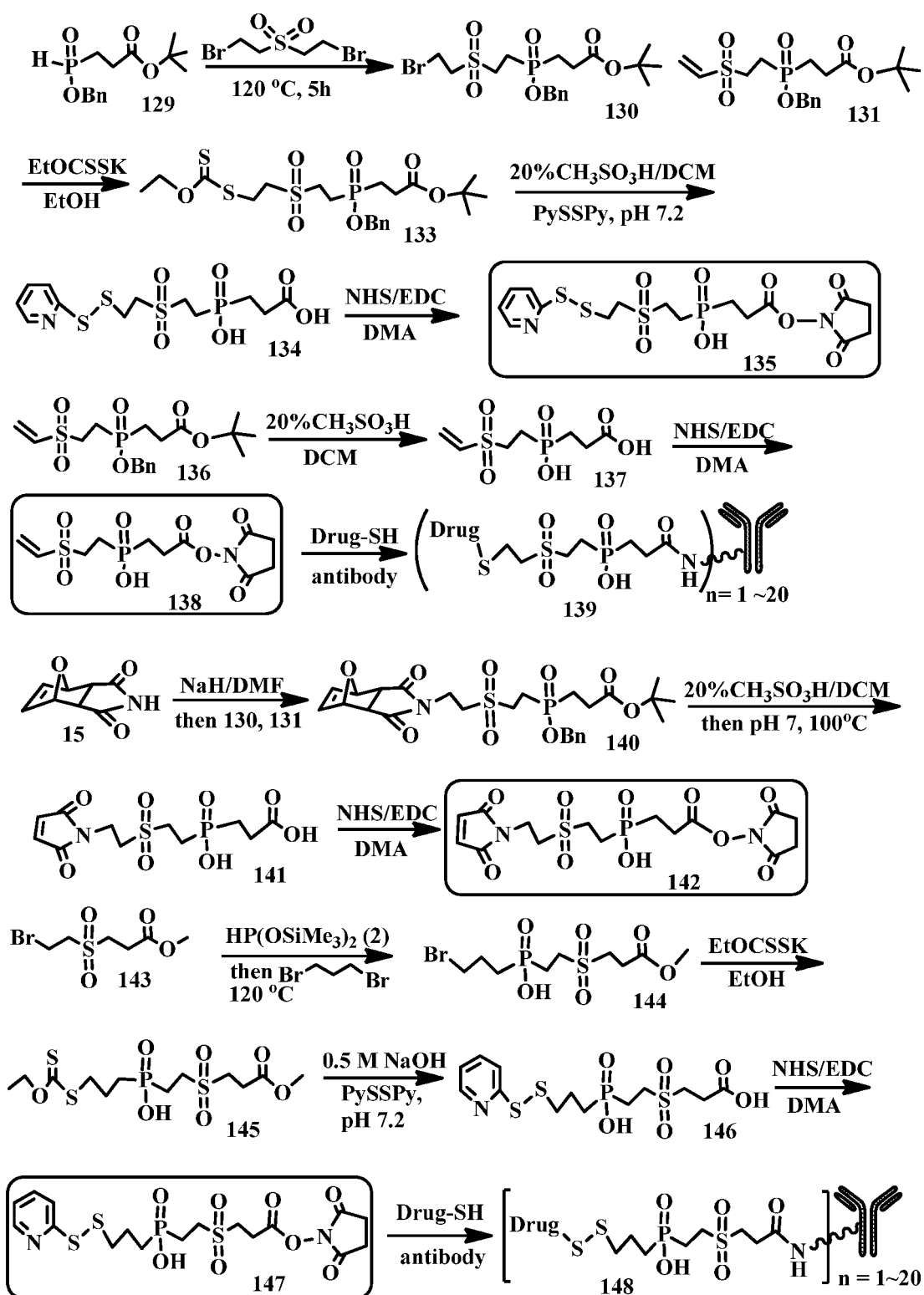


Fig. 10. The synthesis of sulfonyl linkers containing a phosphinic acid.

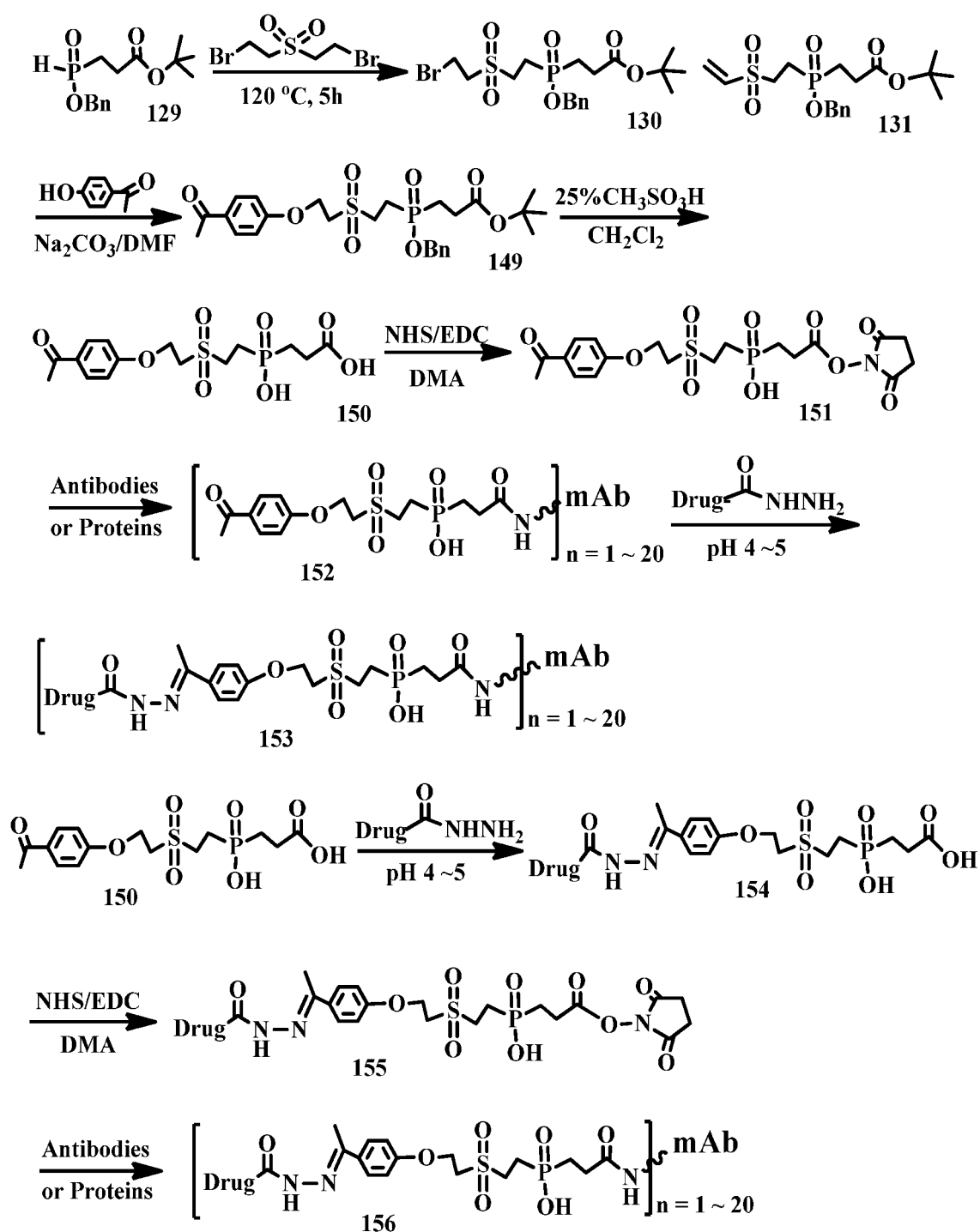


Fig. 11. The synthesis a hydrophilic linker contain contain a phosphinate, a sulfonyl and a ketone groups that can be used for the conjugation of a drug to an antibody or a protein via a hydrazone bond.

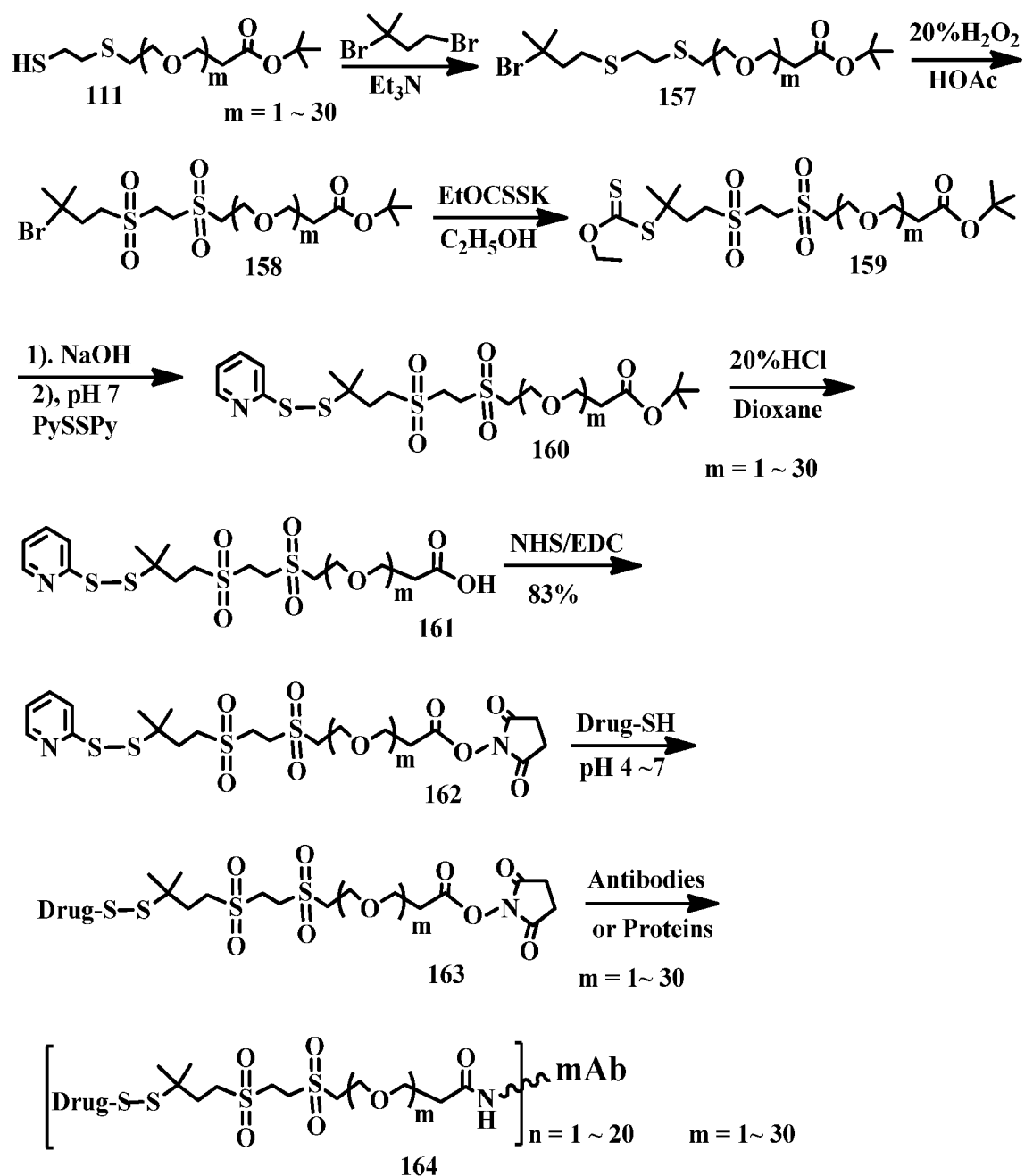


Fig. 12. The synthesis of hydrophilic linkers that contain a disulfonyl, polyethylene glycols, a very hindered pyridyldisulfide group and a reactive carboxylic acid ester via substitution of 1,3-dibromo-3-methylbutane. The linker is used for the conjugation of an antibody or a protein via a hinder disulfide bond.

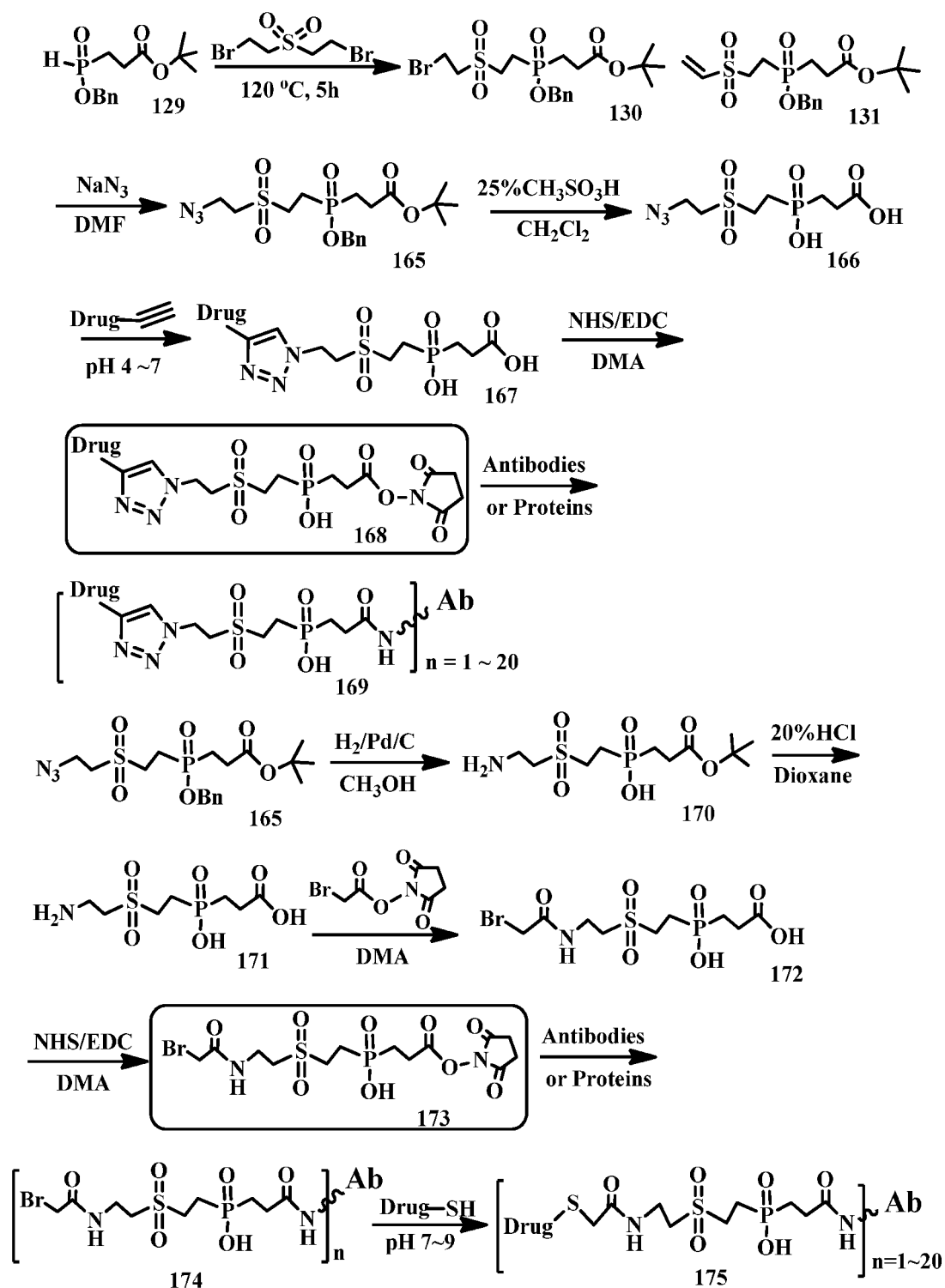


Fig. 13. . The synthesis of hydrophilic linkers containing a phosphinate and a sulfonyl groups that are used for the conjugation of drugs to a cell binding molecule either via a triazole or via a thioether bond.

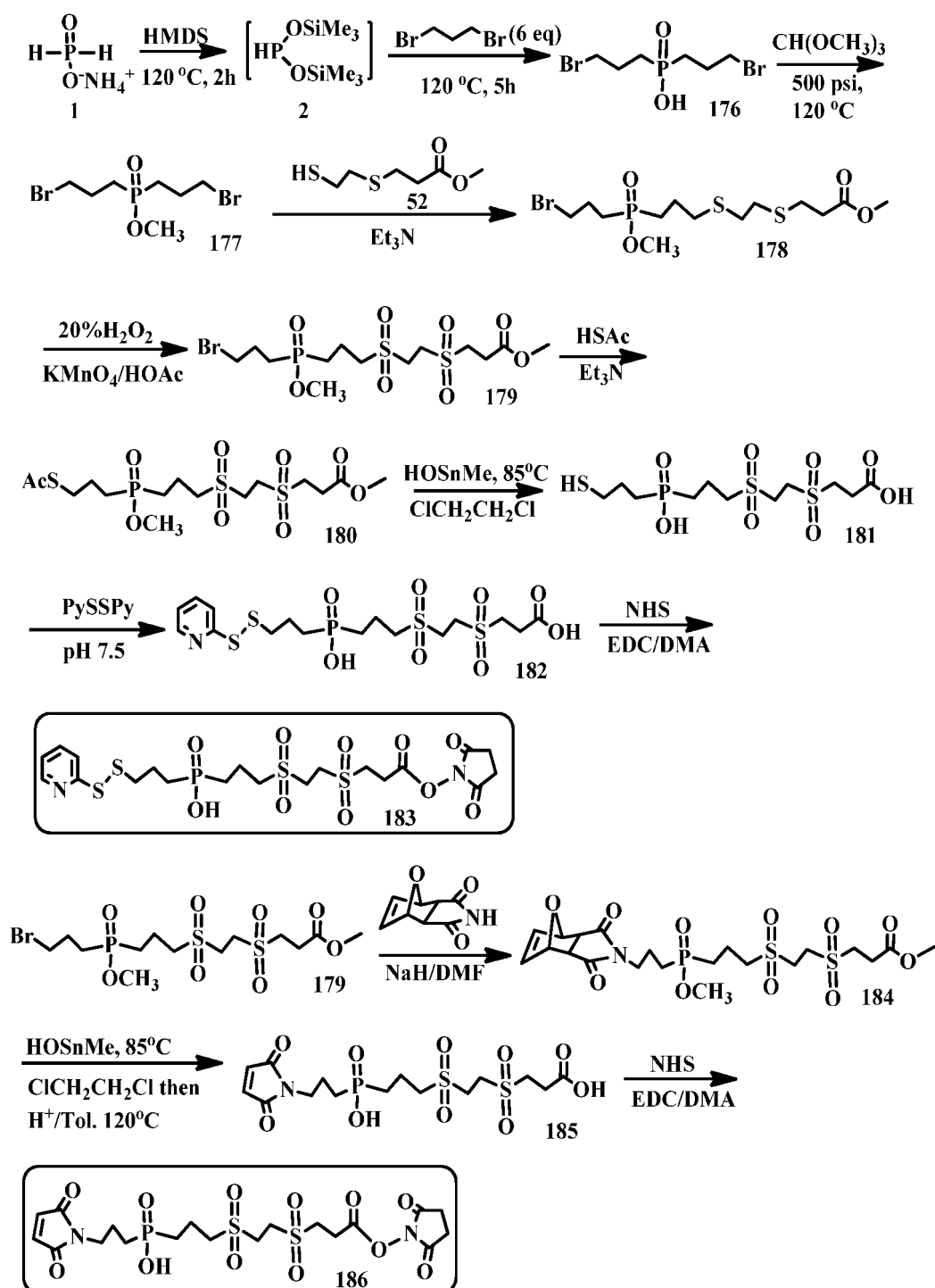


Fig. 14. The synthesis of hydrophilic linkers that contain a disulfonate, phosphinate, a pyridyldisulfide group, a polyethyleneglycol (PEG) chain and a reactive carboxylic acid ester. The linkers are used for the conjugation of a cell binding molecule via cell thioether bond

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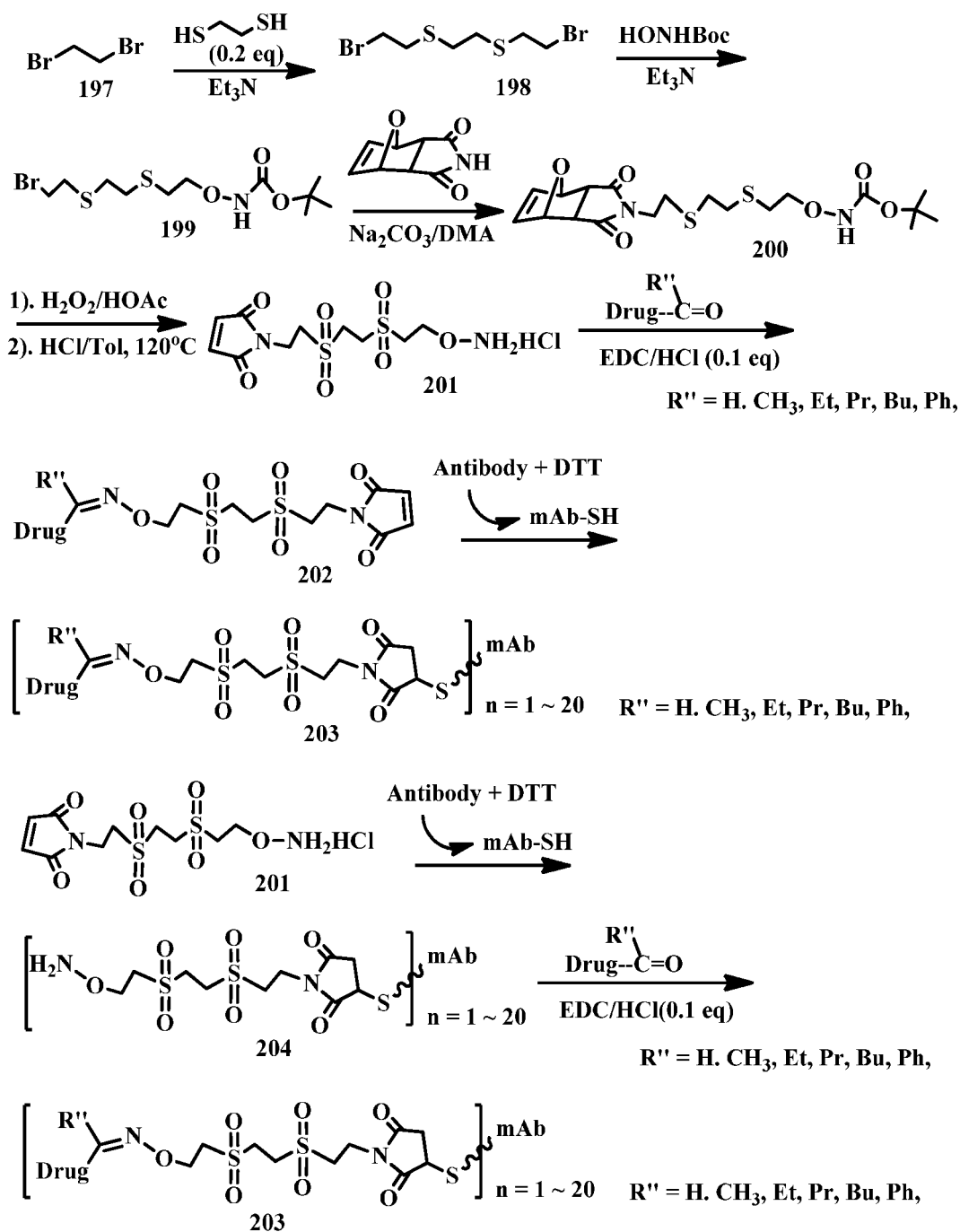


Fig. 16. The synthesis of disulfonyl-containing linkers that contains an alkoxyamino and a maleimido substituent, enabling ketone or aldehyde- containing drug to link to an antibody via a thioether and an alkoxime bond.

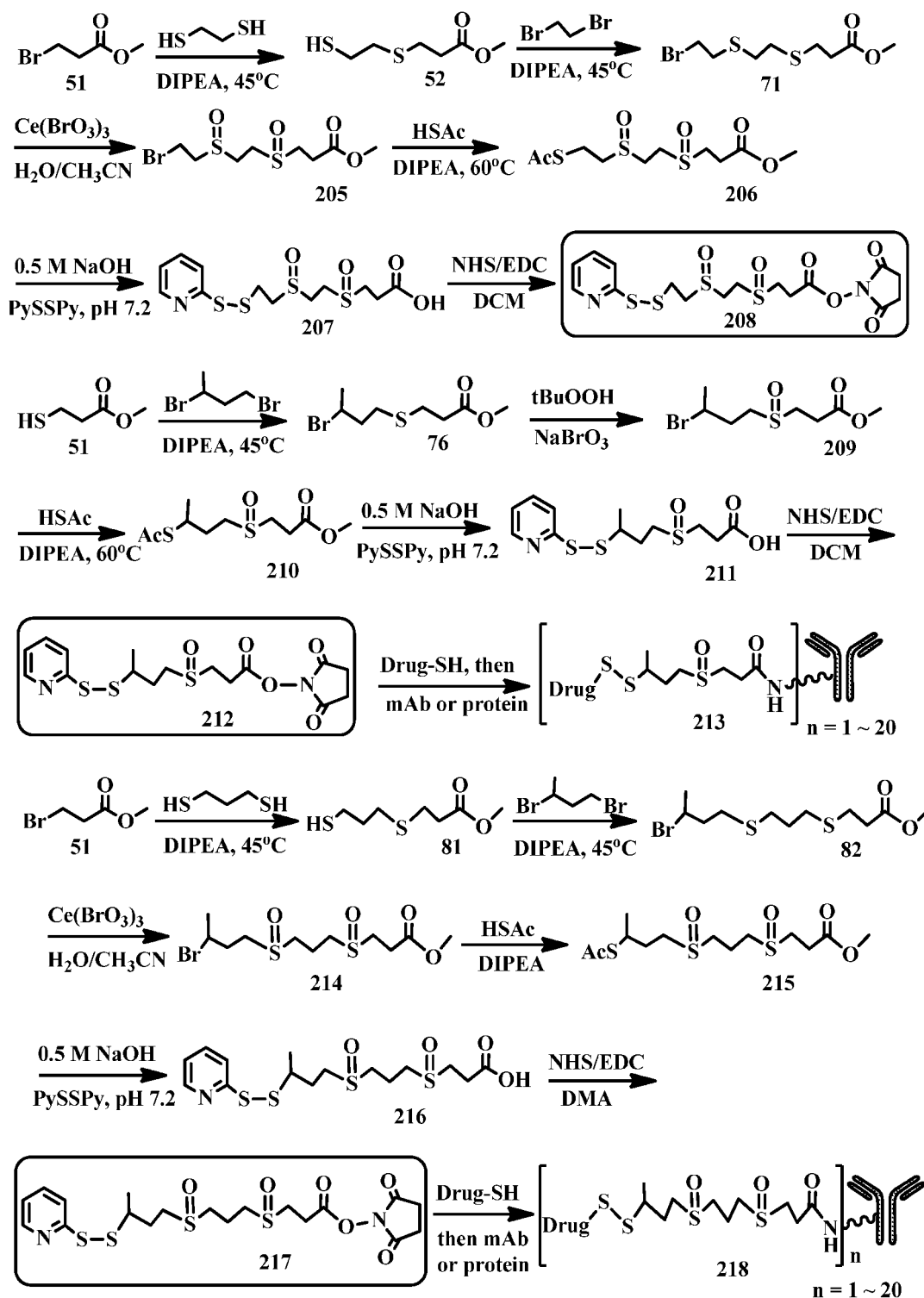


Fig. 17. The synthesis of sulfoxide-containing and disulfoxide-containing linkers that are used for the conjugation of drugs to a cell binding molecule via a disulfide bond.

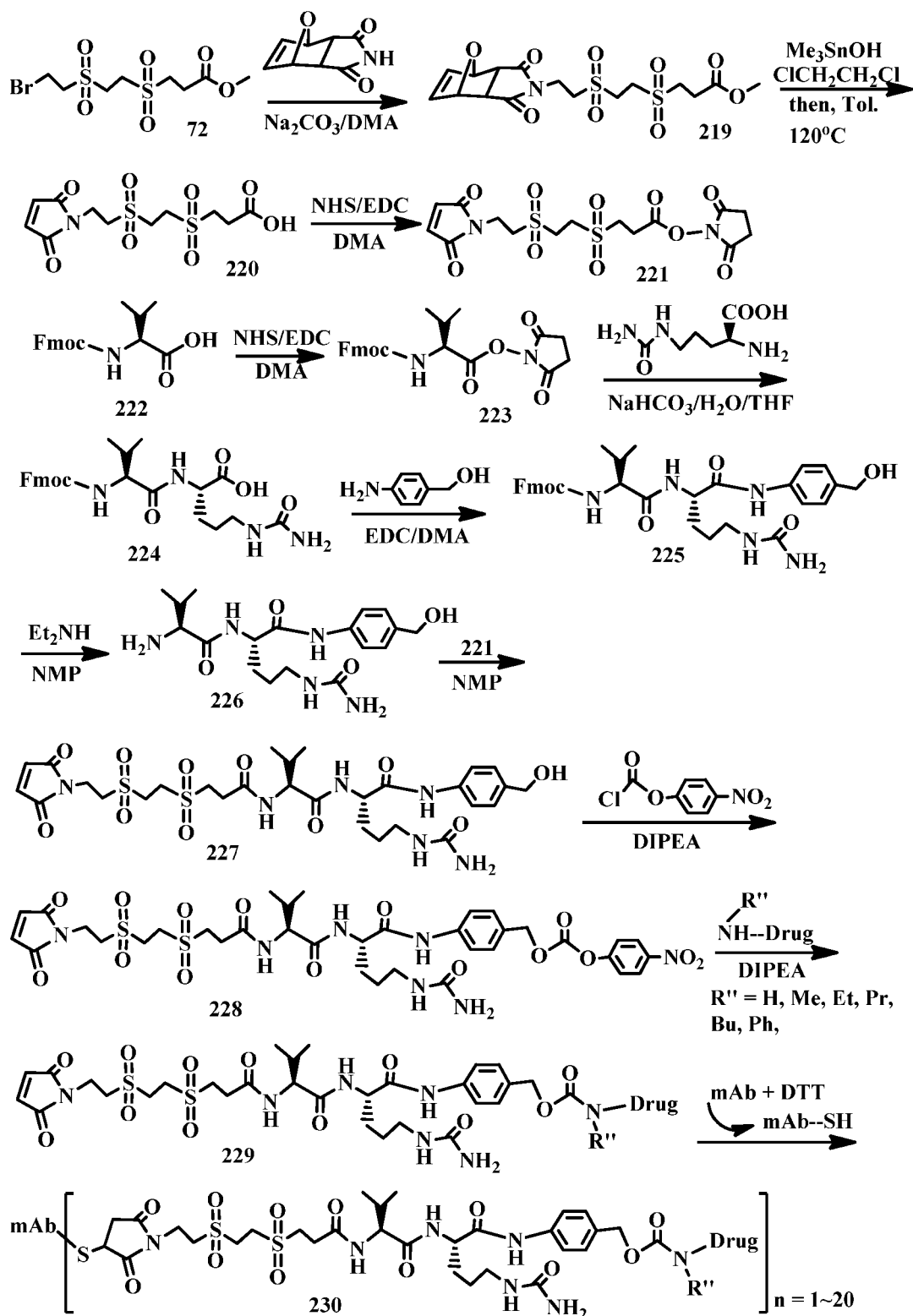
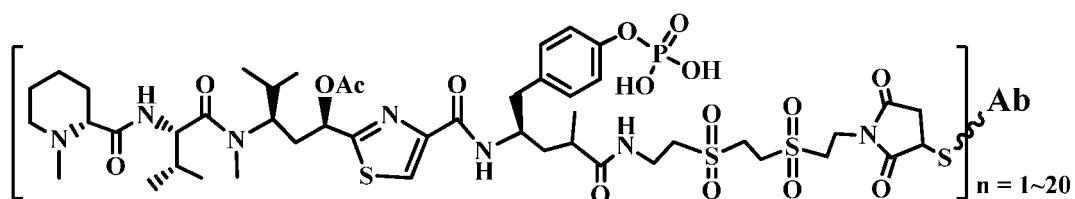
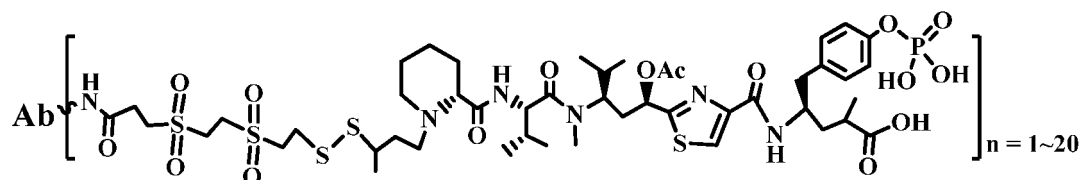


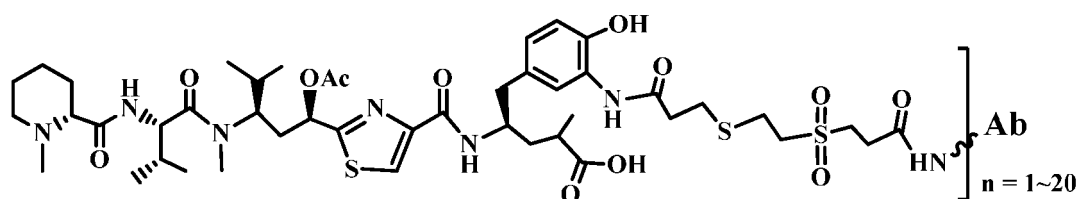
Fig. 18. The synthesis of a disulfonyl-containing linker (221) that used for conjugation of amine-containing cytotoxic drugs to an antibody via the Val-Cit-PABC linkage.



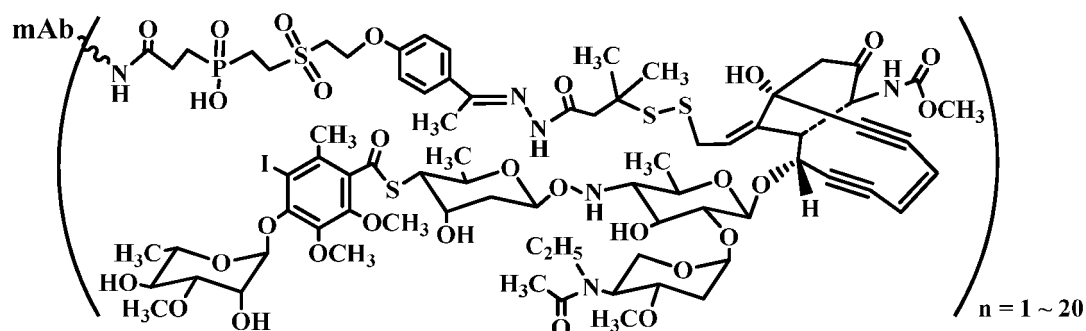
19-a). ADC structure of a tubulysin analog through a disulfonyl linker.



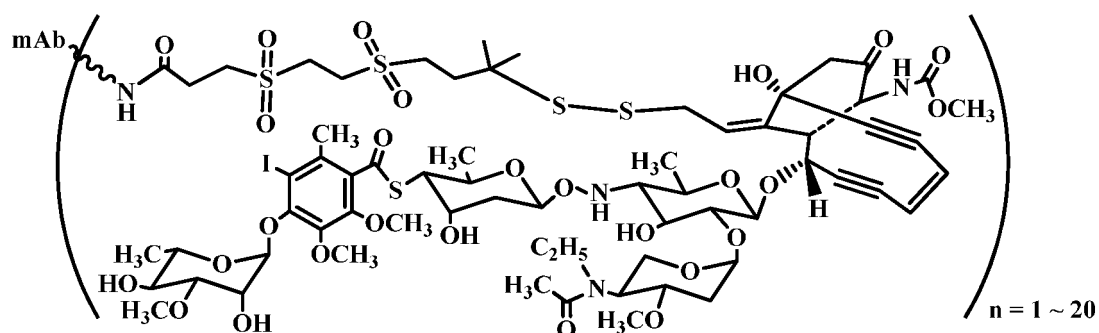
19-b). ADC structure of a tubulysin analog through a disulfonyl linker.



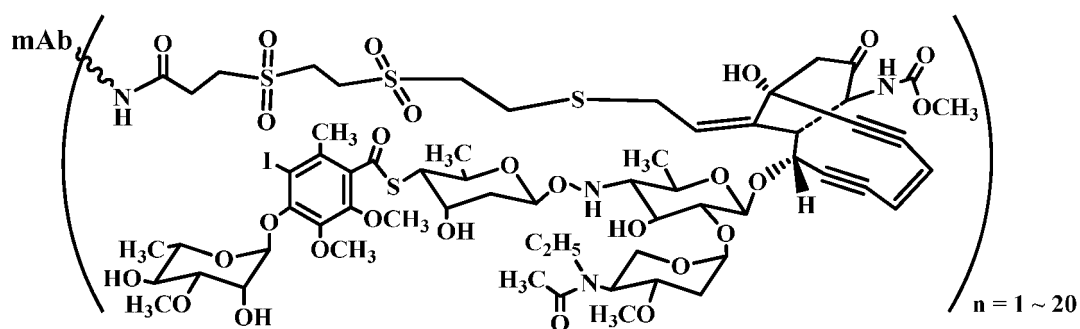
19-c). ADC structure of a tubulysin analog through a sulfonyl linker.



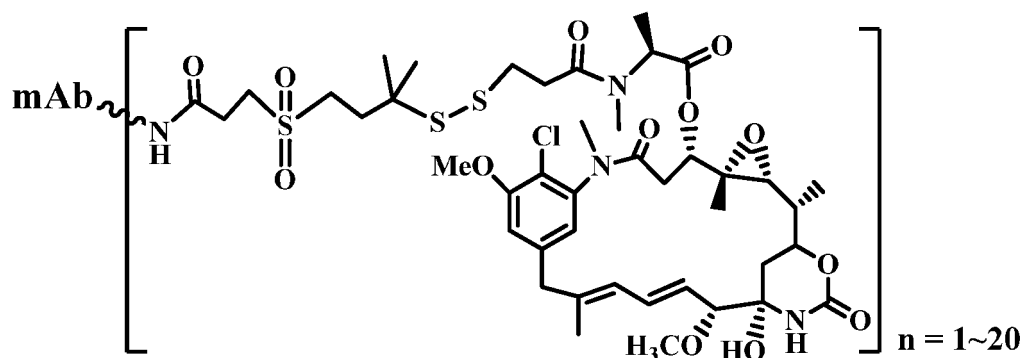
19-d). ADC structure of a calicheamicin analog through a hydrophilic linker (via hydrazone and disulfide linkage).



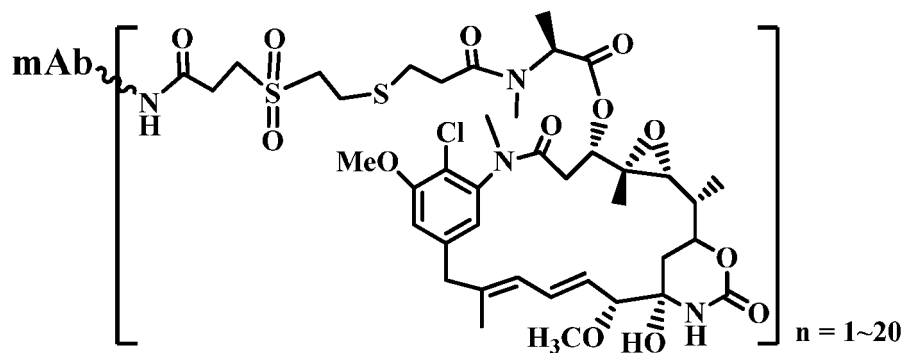
19-e). ADC structure of a calicheamicin analog via a hydrophilic linker (disulfide linkage).



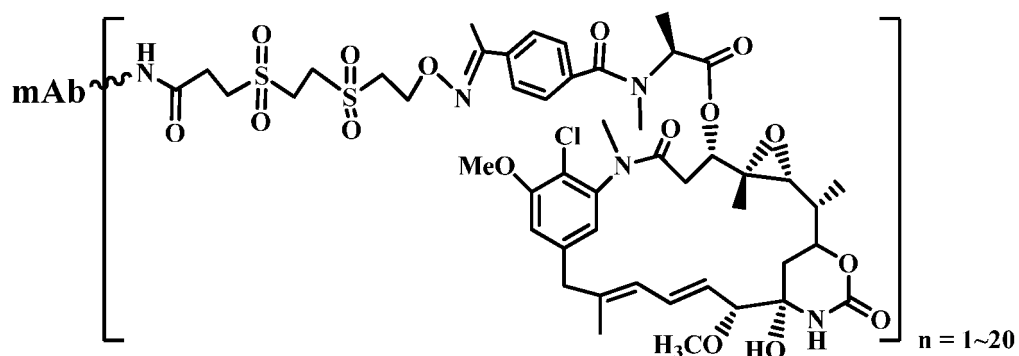
19-f). ADC structure of a calicheamicin analog via a hydrophilic linker (thioether linkage).



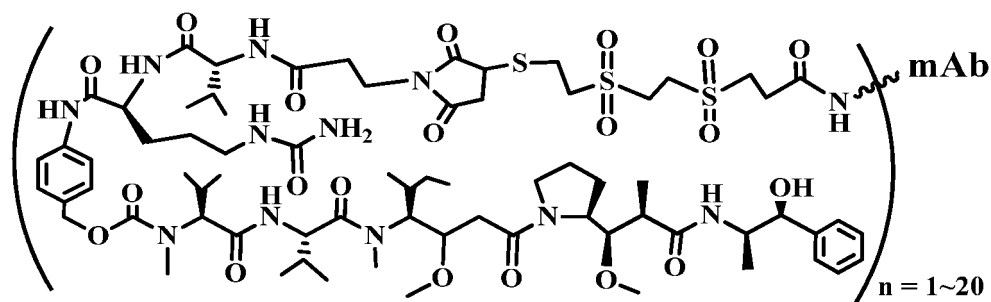
19-g). ADC structure of a Maytansinoid (DM1) via a hydrophilic linker (disulfide linkage).



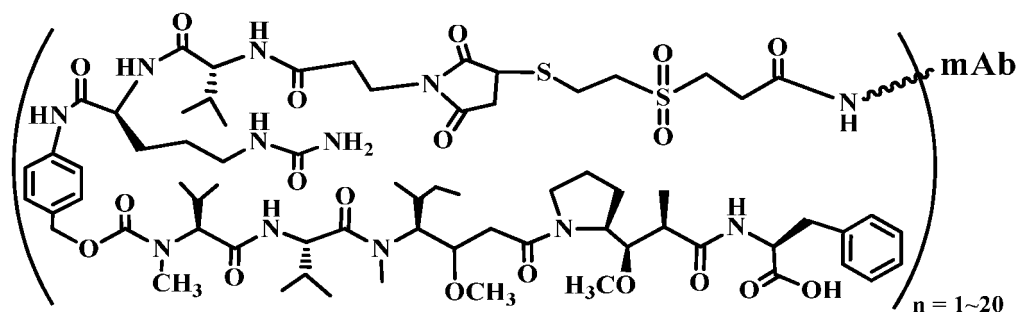
19-h). ADC structure of a Maytansinoid (DM1) via a hydrophilic linker (thioether linkage).



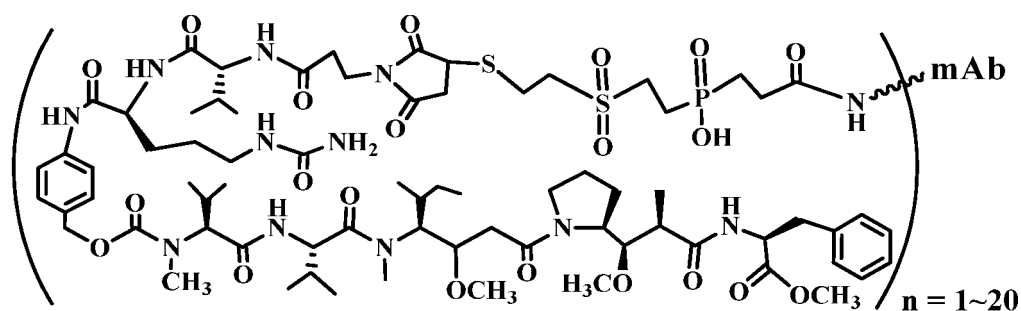
19-i). ADC structure of a Maytansinoid via a hydrophilic linker (via alkoxime linkage).



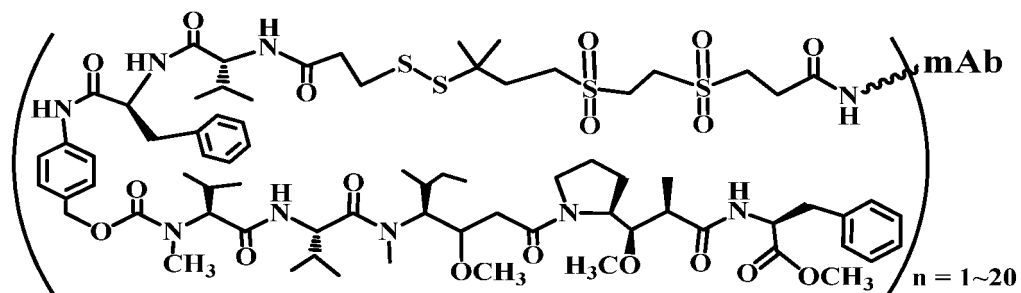
19-j). ADC structure of an auristatin analog (monomethyl auristatin E (MMAE)) through a hydrophilic linker (thioether and citrulline-valine peptide linkages).



19-k). ADC structure of an auristatin analog (monomethyl auristatin F (MMAF)) through a hydrophilic linker (thioether and citrulline-valine peptide linkages).



19-l). ADC structure of monomethyl auristatin F-OMe (MMAF-OMe) through a hydrophilic linker (thioether and citrulline-valine peptide linkages).

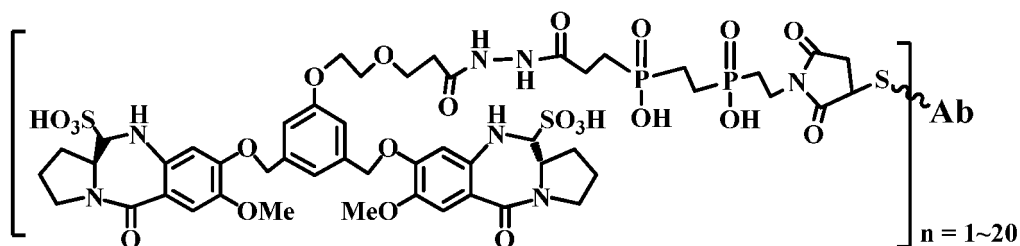


19-m). ADC structure of monomethyl auristatin F-OMe (MMAF-OMe) through a hydrophilic linker (disulfide and citrulline-valine peptide linkage) of this patent.

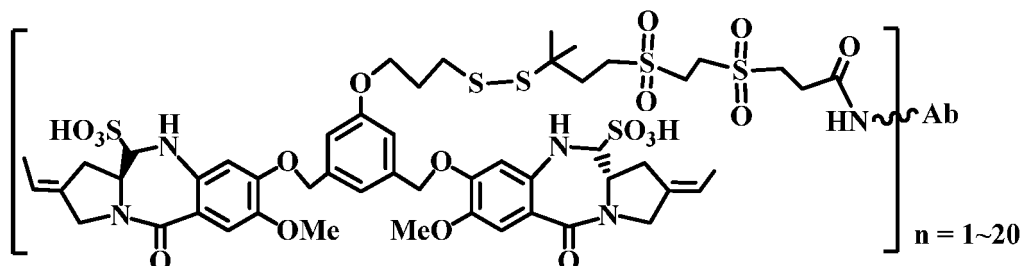
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$n = 1 \sim 20$

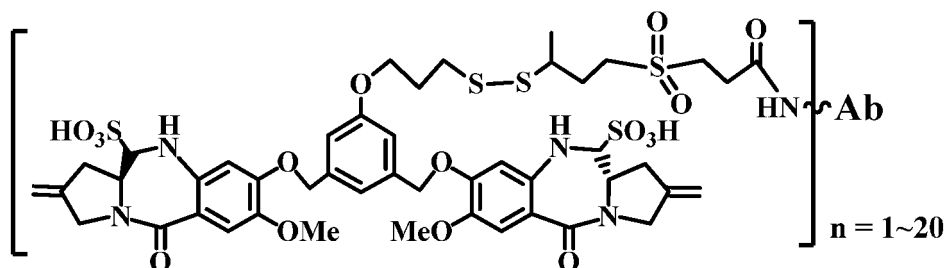
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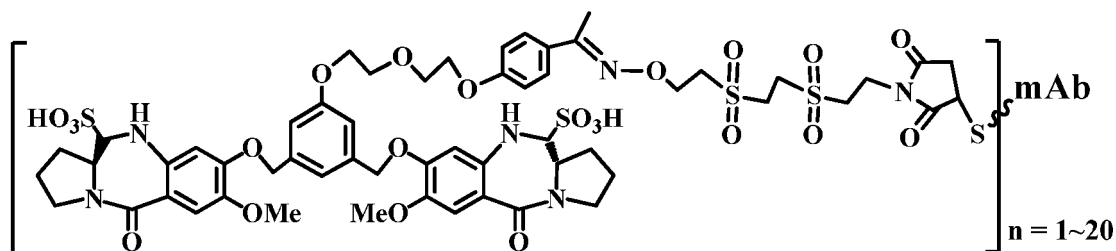
19-r). ADC structure of a pyrrolobenzodiazepine dimer prodrug through a hydrophilic linker (hydrazide linkage) of this patent.



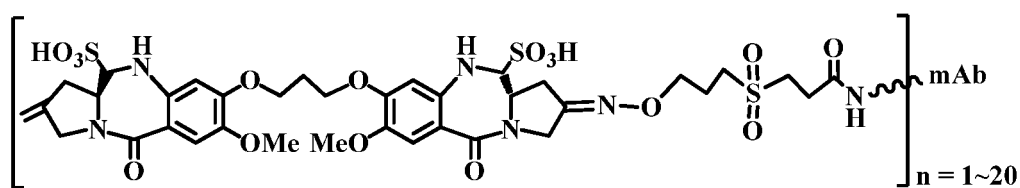
19-s). ADC structure of a pyrrolobenzodiazepine (tomaymycin) dimer prodrug through a hydrophilic linker (disulfide bond linkage) of this patent.



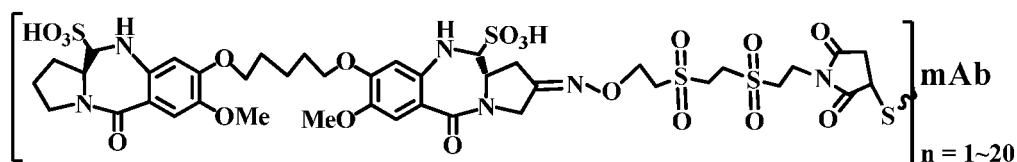
19-t). ADC structure of a pyrrolobenzodiazepine dimer prodrug through a hydrophilic linker (disulfide bond linkage) of this patent.



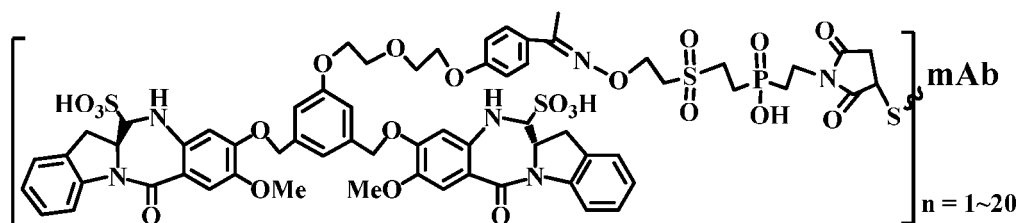
19-u). ADC structure of a pyrrolobenzodiazepine dimer prodrug through a hydrophilic linker (alkoxime bond linkage) of this patent.



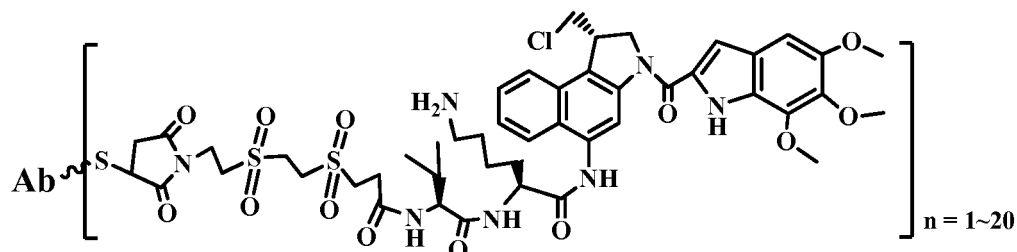
19-v). ADC structure of a pyrrolobenzodiazepine dimer prodrug through a hydrophilic linker (alkoxime bond linkage) of this patent.



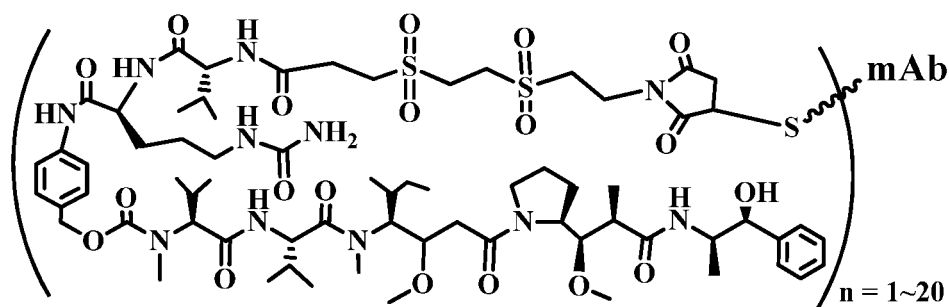
19-w). ADC structure of a pyrrolobenzodiazepine dimer prodrug through a hydrophilic linker (alkoxime bond linkage) of this patent.



19-x). ADC structure of an indolinobenzodiazepine dimer prodrug through a hydrophilic linker (alkoxime bond linkage) of this patent.



19-y). ADC structure of a duocarmycin analog via a hydrophilic linker (peptide linkage).



19-z). ADC structure of an auristatin analog through a hydrophilic linker (thioether and citrulline-valine peptide linkages).

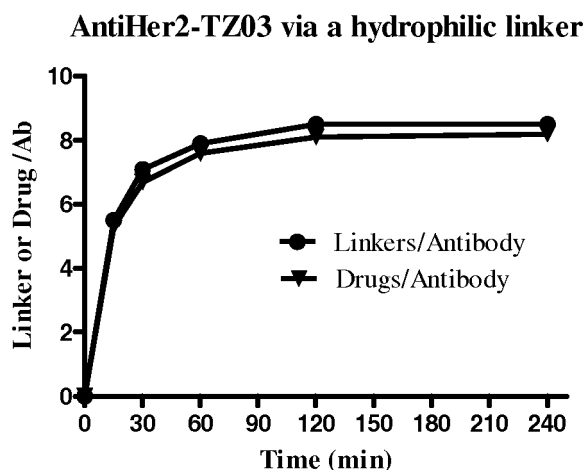


Fig. 20. The use of a hydrophilic linker (86) in modifying a cell-binding agent (antiHer2 antibody) and following by production of a cell-binding agent-drug (TZ03) conjugate containing the hydrophilic linker.

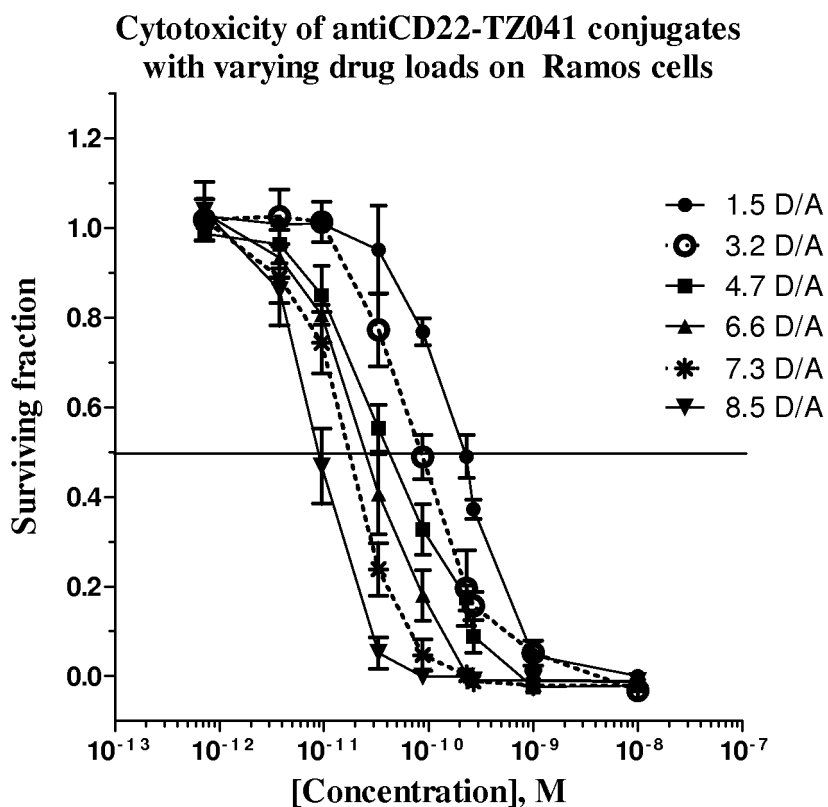


Fig. 21. 5 days in vitro assays of the cytotoxicity of the antiCD22-TZ041 (tubulysin analog) conjugate with different drug load ratios via a hydrophilic linker (86).

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