

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	MAIL STOP AMENDMENT
Zhao, R. Yongxin	)	
	)	Group Art Unit: 1643
Application No.: 14/432,073	)	
	)	Examiner: Canella, Karen A
Filed: March 27, 2015	)	
	)	Confirmation No.: 6938
For: HYDROPHILIC LINKERS AND	)	
THEIR USES FOR CONJUGATION	)	
OF DRUGS TO A CELL BINDING	)	
MOLECULES	)	

AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

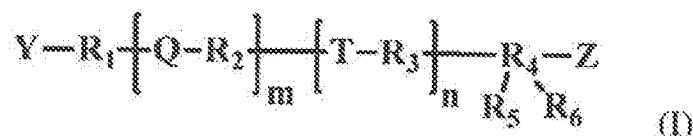
In response to the Official Action dated August 15, 2017, please amend the above identified application as follows.

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

1. (Currently Amended) A hydrophilic linker of formula (I)



wherein:

Y represents a functional group that enables reaction of the hydrophilic linker 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; provided that when m=1, n=0, Q is not -P(=O)(OM)-; and when n=1, m=0, T is not -P(=O)(OM)-;

Z represents a functional group that enables linkage of the hydrophilic linker to a cytotoxic drug via a disulfide, thioether, thioester, ~~peptide~~, hydrazone, ether, ester, carbamate, carbonate, secondary, tertiary, or ~~quaternary~~ quaternary amine, imine, cycloheteroalkyane, heteroaromatic, alkoxime or amide bond;

~~R₁, R₂, R₃, and 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 esters, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof,

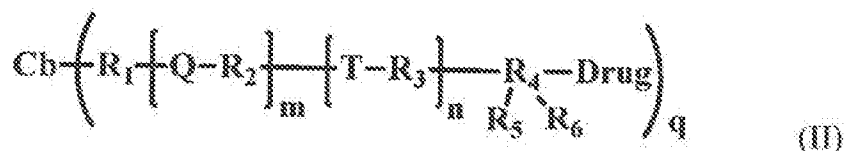
or R₁, R₂, R₃ and R₄ are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R₁, R₂, R₃ and R₄);

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 ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or $\text{N}^+\text{R}_1\text{R}_2\text{R}_3$ or a pharmaceutical salt.

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



wherein:

Cb represents a cell-binding agent;

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 $\text{-S(O}_2\text{)-}$, or -S(O)- ;

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

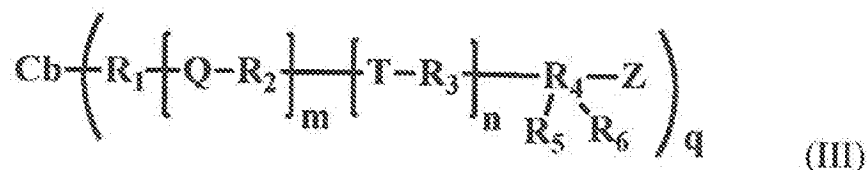
R_1 , R_2 , R_3 , and R_4 , ~~R_5 and R_6~~ , are the same or different and are H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or esters, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof,

or R_1 , R_2 , R_3 and R_4 are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4);

R_5 and R_6 , 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 ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or $N^+R_1R_2R_3$ or a pharmaceutical salt.

3. (Currently Amended) A compound of formula (III):



wherein:

Cb represents a cell-binding agent;

Q and T are either -P(=O)(OM)- , or $\text{-S(O}_2\text{)-}$, or -S(O)- ;

m and n are integer from 0 to 5, but not 0 at the same time; provided that when $m=1$, $n=0$,

Q is not -P(=O)(OM)- ; and 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 the compound to a cytotoxic drug via a disulfide, thioether, thioester, ~~peptide~~, hydrazone, ether, ester, carbamate, carbonate, secondary, tertiary, or ~~quaternary~~ quaternary amine, imine, cycloheteroalkylene, heteroaromatic, alkoxime or amide bond;

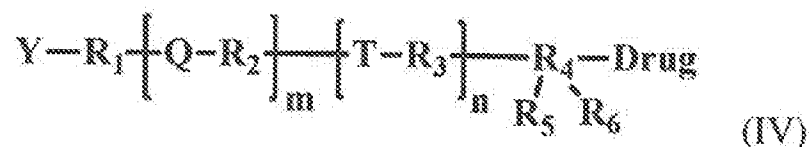
R_1 , R_2 , R_3 , and R_4 , R_5 and R_6 , are the same or different and are ~~H~~, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or esters, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof,

or R_1 , R_2 , R_3 and R_4 are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4);

R_5 and R_6 , 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 ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or $N^+R_1R_2R_3$ or a pharmaceutical salt.

4. (Currently Amended) A compound of formula (IV):



wherein:

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

Q and T are either $-P(=O)(OM)-$, or $-S(O_2)-$, or $-S(O)-$;

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

R_1 , R_2 , R_3 , and R_4 , ~~R_5 and R_6~~ , 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 esters, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof,

or R_1 , R_2 , R_3 and R_4 are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4);

R_5 and R_6 , 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 ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or $N^+R_1R_2R_3$ or a pharmaceutical salt.

5. (Currently Amended) The conjugate of claim 2, wherein the Drug is selected from the group consisting of:

1). ~~chemotherapeutic agents selected from the group consisting of comprising~~ a). Alkylating agents ~~selected from the group consisting of comprising~~ Nitrogen mustards ~~selected from the group consisting of comprising~~ chlorambucil, chlornaphazine, cyclophosphamide, dacarbazine, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, mannomustine, mitobronitol, melphalan, mitolactol, pipobroman, novembichin, phenesterine, prednimustine, thiotepa, trofosfamide, uracil mustard; CC-1065 and adozelesin, carzelesin and bizelesin ~~synthetic analogues thereof~~; duocarmycin, ~~and synthetic analogues of~~ KW-2189 and CBI-TMI; benzodiazepine dimers ~~selected from the group consisting of comprising~~ dimers of pyrrolbenzodiazepine (PBD) or tomaymycin, indolinbenzodiazepines, imidazobenzothiadiazepines, or oxazolidinobenzodiazepines; Nitrosourea ~~selected from the group consisting of comprising~~ carmustine, lomustine, chlorozotocin, fotemustine, nimustine, ranimustine; Alkylsulphonates ~~selected from the group consisting of comprising~~ busulfan, treosulfan, improsulfan and piposulfan; Triazenes[~~·~~]; (dacarbazine); Platinum containing compounds ~~selected from the group consisting of comprising~~ carboplatin, cisplatin, oxaliplatin; aziridines ~~selected from the group consisting of comprising~~ benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide triethylenephosphoramide, triethylenethiophosphoramide and trimethylolomelamine; b). Plant Alkaloids ~~selected from the group consisting of comprising~~ Vinca alkaloids ~~selected from the group consisting of comprising~~ vincristine, vinblastine, vindesine, vinorelbine, navelbin; Taxoids ~~selected from the group consisting of comprising~~ paclitaxel, and docetaxol and analogs thereof, Maytansinoids ~~selected from the group consisting of comprising~~ DM1, DM2, DM3, DM4, DMS, DM6, DM7, maytansine and ansamitocins ~~and analogs thereof~~, cryptophycins ~~selected from the group consisting of comprising~~ cryptophycin 1 and cryptophycin 8; epothilones, eleutherobin, discodermolide, bryostatins, dolostatins, auristatins, tubulysins, cephalostatins; pancratistatin; a sarcodictyin; spongistatin; c). DNA Topoisomerase Inhibitors ~~selected from the group consisting of comprising~~ Epipodophyllins ~~selected from the group consisting of comprising~~ 9-aminocamptothecin, camptothecin, crisnatol, daunomycin, etoposide, etoposide phosphate, irinotecan, mitoxantrone, novantrone, retinoic

acids, (retinols), teniposide, topotecan, 9-nitrocamptothecin (RFS 2000); mitomycins[[]]; d). Anti-metabolites ~~selected from the group consisting of comprising~~ Anti-folate ~~selected from the group consisting of comprising~~ DHFR inhibitors ~~selected from the group consisting of comprising~~ methotrexate, trimetrexate, denopterin, pteropterin, and aminopterin (4-aminopteroic acid) ~~or the other folic acid analogues thereof~~; IMP dehydrogenase Inhibitors ~~selected from the group consisting of comprising~~ mycophenolic acid, tiazofurin, and ribavirin, EICAR; Ribonucleotide reductase Inhibitors ~~selected from the group consisting of comprising~~ hydroxyurea and deferoxamine; Pyrimidine analogs compounds ~~U~~ ~~selected from the group consisting of compounds comprising uracil-analogs compounds~~ ~~selected from the group consisting of comprising~~ ancitabine, azacitidine, 6-azauridine, capecitabine (Xeloda), carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, 5-Fluorouracil, floxuridine, and ratitrexed (Tomudex); Cytosine-analogs compounds ~~selected from the group consisting of comprising~~ cytarabine, cytosine arabinoside, and fludarabine; Purine-analogs compounds ~~selected from the group consisting of comprising~~ azathioprine, fludarabine, mercaptopurine, thiamiprine, and thioguanine; folic acid replenisher; e). Hormonal therapies ~~selected from the group consisting of comprising~~ Receptor antagonists ~~selected from the group consisting of comprising~~ anti-estrogen ~~selected from the group consisting of comprising~~ megestrol, raloxifene, and tamoxifen; LHRH agonists ~~selected from the group consisting of comprising~~ goserelin, and leuprolide acetate; anti-androgens ~~selected from the group consisting of comprising~~ bicalutamide, flutamide, calusterone, dromostanolone propionate, epitiostanol, goserelin, leuprolide, mepitiothane, nilutamide, testolactone, and trilostane; Retinoids/Deltoids ~~selected from the group consisting of comprising~~ Vitamin D3 analogs compounds ~~selected from the group consisting of comprising~~ CB 1093, EB 1089, KH 1060, cholecalciferol, and ergocalciferol; photodynamic therapies ~~selected from the group consisting of comprising~~ verteporfin, phthalocyanine, photo sensitizer Pc4, and demethoxy-hypocrellin A; cytokines ~~selected from the group consisting of comprising~~ Interferon-alpha, Interferon-gamma, tumor necrosis factor (TNFs), and human proteins containing a TNF domain; f). Kinase inhibitors ~~selected from the group consisting of comprising~~ 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, and ispinesib; g). antibiotics ~~selected from the group consisting of comprising~~ enediyne antibiotics ~~selected from the group consisting of comprising~~ calicheamicins ~~selected from the group consisting of comprising~~ calicheamicin γ 1, δ 1, α 1 ~~and~~ β 1; dynemicin selected from the group consisting of dynemicin A and deoxydynemicin; esperamicin, kedarcidin, C-1027, maduropeptin, neocarzinostatin chromophore and chromoprotein enediyne antiobiotic chromomophores, aclacinomysins, actinomycins, authramycin, azaserine, bleomycins, cactinomycin, carabycin, 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; h). polyketides (~~acetogenins~~) ~~selected from the group consisting of comprising~~ bullatacin and bullatacinone; gemcitabine, epoxomicins, bortezomib, thalidomide, lenalidomide, pomalidomide, tosedostat, zybrestat, PLX4032, STA-9090, Stimuvax, allovectin-7, Xegeva, Provenge, Yervoy, Isoprenylation inhibitors, Dopaminergic neurotoxins, Cell cycle inhibitors, ~~Actinomycins selected from the group consisting of Actinomycin D, and dactinomycin, Bleomycins selected from the group consisting of bleomycin A2, bleomycin B2, and peplomycin, Anthracyclines selected from the group consisting of comprising~~ daunorubicin, doxorubicin (adriamycin), idarubicin, epirubicin, pirarubicin, zorubicin, and mitoxantrone, MDR inhibitors, Ca^{2+} ATPase inhibitors, Histone deacetylase inhibitors ~~selected from the group consisting of comprising~~ Vorinostat, Romidepsin, Panobinostat, Valproic acid, Mocetinostat (MGCD0103), Belinostat, PCI-24781, Entinostat, SB939, Resminostat, Givinostat, AR-42, CUDC-101, sulforaphane, and Trichostatin A; ~~Thapsigargin~~, Celecoxib, glitazones, epigallocatechin gallate, Disulfiram, Salinosporamide A.; Anti-adrenals ~~selected from the group consisting of comprising~~ aminogluthethimide, mitotane, and trilostane; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; arabinoside, bestabucil; 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 ~~selected from the group consisting of~~ comprising T-2 toxin, verrucarins A, roridin A and anguidine; urethane, siRNA, antisense drugs;

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

3). anti-infectious disease agents ~~selected from the group consisting of~~ comprising a). Aminoglycosides ~~selected from the group consisting of~~ comprising amikacin, astromicin, gentamicin (netilmicin, sisomicin, isepamicin), hygromycin B, kanamycin (amikacin, arbekacin, bekanamycin, dibekacin, tobramycin), neomycin (framycetin, paromomycin, ribostamycin), netilmicin, spectinomycin, streptomycin, ~~tobramycin~~, and verdamycin; b). Amphenicols ~~selected from the group consisting of~~ comprising azidamfenicol, chloramphenicol, florfenicol, and thiamphenicol; c). Ansamycins ~~selected from the group consisting of~~ comprising geldanamycin, and herbimycin; d). Carbapenems ~~selected from the group consisting of~~ comprising biapenem, doripenem, ertapenem, imipenem/cilastatin, meropenem, and panipenem; e). Cepheims ~~selected from the group consisting of~~ comprising 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, ceftezole, cefuroxime, cefixime, cefdinir, cefditoren, cefepime, cefetamet, cefmenoxime, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotiam, ceftazidime, cefepime, cefpimizole, cefpiramide, cefpirome, cefpodoxime, cefprozil, cefquinome, cefsulodin, ceftazidime, cefteteram, ceftibuten, ceftiolene, ceftizoxime, ceftobiprole, ceftriaxone, cefuroxime, cefuzonam, cephamycin (cefotetan, cefmetazole), and oxacephem (flomoxef, latamoxef); f).

Glycopeptides ~~selected from the group consisting of~~ comprising bleomycin, vancomycin (oritavancin, telavancin), teicoplanin (dalbavancin), and ramoplanin; g). Glycylcyclines; h). β -Lactamase inhibitors ~~selected from the group consisting of~~ comprising penam (sulbactam, tazobactam), and clavam (clavulanic acid); i). Lincosamides ~~selected from the group consisting of~~ comprising clindamycin, and lincomycin; j). Lipopeptides ~~selected from the group consisting of~~ comprising daptomycin, A54145, and calcium-dependent antibiotics (CDA); k). Macrolides ~~selected from the group consisting of~~ comprising azithromycin, cethromycin, clarithromycin, dirithromycin, erythromycin, flurithromycin, josamycin, ketolide (telithromycin, cethromycin), midecamycin, miocamycin, oleandomycin, rifamycins (rifampicin, rifampin, rifabutin, rifapentine), rokitamycin, roxithromycin, spectinomycin, spiramycin, taerolimus (FK506), troleandomycin, and telithromycin; l). Monobactams ~~selected from the group consisting of~~ comprising aztreonam, and tigemonam; m). Oxazolidinones; n). Penicillins ~~selected from the group consisting of~~ comprising 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, and ticarcillin; o). Polypeptides ~~selected from the group consisting of~~ comprising bacitracin, colistin, and polymyxin B; p). Quinolones ~~selected from the group consisting of~~ comprising 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, and trovafloxacin; q). Streptogramins ~~selected from the group consisting of~~ comprising pristinamycin, and quinupristin/dalfopristin; r). Sulfonamides ~~selected from the group consisting of~~ comprising mafenide, prontosil, sulfacetamide, sulfamethizole, sulfanilimide, sulfasalazine, sulfisoxazole, trimethoprim, and trimethoprim-sulfamethoxazole (co-trimoxazole); s). Steroid antibacterials; t). Tetracyclines ~~selected from the group consisting of~~ comprising doxycycline, chlortetracycline, clomocycline, demeclocycline, lymecycline,

meclocycline, metacycline, minocycline, oxytetracycline, penimepicycline, rolitetracycline, and tetracycline, and glycylcyclines; u). antibiotics selected from the group consisting of comprising amonacrin, arspenamine, bactoprenol inhibitors (Bactracin), DADAL/AR inhibitors (eyeleserine), dictyostatin, discodermolide, eleutherobin, epothilone, ethambutol, etoposide, faropenem, fusidic acid, furazolidone, isoniazid, laulimalide, metronidazole, mupirocin, mycolactone, NAM synthesis inhibitors, nitrofurantoin, paclitaxel, platensimycin, pyrazinamide, quinupristin/dalfopristin, rifampicin (rifampin), tazobactam, tinidazole, and uvaricin;

4). anti-viral drugs selected from the group consisting of comprising a). Entry/fusion inhibitors selected from the group consisting of comprising aplaviroc, maraviroc, vicriviroc, gp41 (enfuvirtide), PRO 140, and CD4 (ibalizumab); b). Integrase inhibitors selected from the group consisting of comprising raltegravir, elvitegravir, and globoidnan A; c). Maturation inhibitors selected from the group consisting of comprising bevirimat, and vivecon; d). Neuraminidase inhibitors selected from the group consisting of comprising oseltamivir, zanamivir, and peramivir; e). Nucleosides & nucleotides selected from the group consisting of comprising 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 compounds comprising (e.g. 3'-fluoro-2',3'-dideoxythymidine (FLT) and 3'-fluoro-2',3'-dideoxyguanosine (FLG), fomivirsen, ganciclovir, idoxuridine, lamivudine (3TC), 1-nucleosides selected from the group consisting of comprising β -1-thymidine and β -1-2'-deoxycytidine), penciclovir, racivir, ribavirin, stampidine, stavudine (d4T), taribavirin (viramidine), telbivudine, tenofovir, trifluridine valaciclovir, valganciclovir, zalcitabine (ddC), and zidovudine (AZT); f). non-nucleosides selected from the group consisting of comprising amantadine, ateviridine, capravirine, diarylpyrimidines (etravirine, rilpivirine), delavirdine, docosanol, emivirine, efavirenz, foscarnet (phosphonoformic acid), imiquimod, interferon alfa, loviride, lodenosine, methisazone, nevirapine, NOV-205, peginterferon alfa, podophyllotoxin, rifampicin, rimantadine, resiquimod (R-848), and tromantadine; g). protease inhibitors selected from the group consisting of comprising amprenavir, atazanavir, boceprevir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, pleconaril, ritonavir, saquinavir, telaprevir (VX-950), and tipranavir; h). anti-virus drugs selected from the group consisting of comprising abzyme, arbidol,

calanolide A, ceragenin, cyanovirin-n, diarylpyrimidines, epigallocatechin gallate (EGCG), foscarnet, griffithsin, taribavirin (viramidine), hydroxyurea, KP-1461, miltefosine, pleconaril, portmanteau inhibitors, ribavirin, and seliciclib;

5). any of 1) to 4) having a radioisotopes selected from of (radionuclides) ^3H , ^{11}C , ^{14}C , ^{18}F , ^{32}P , ^{35}S , ^{64}Cu , ^{68}Ga , ^{86}Y , $^{99\text{m}}\text{Tc}$, ^{111}In , ^{123}I , ^{124}I , ^{125}I , ^{131}I , ^{133}Xe , ^{177}Lu , ^{211}At , or ^{213}Bi ; and

6). pharmaceutically acceptable salts[[,]] or acids ~~or derivatives~~ of any of the above ~~drugs~~ 1) to 5).

6. (Currently Amended) The conjugate of claim 2, wherein "Drug" is selected from the group consisting of tubulysins, calicheamicins, auristatins, maytansinoids, CC-1065 ~~analogues~~ compounds, morpholinos doxorubicins, taxanes, cryptophycins, epothilones, and benzodiazepine dimers, siRNA or a combination thereof, and pharmaceutically acceptable salts[[,]] or acids ~~or derivatives~~ of any of the above.

7. (Previously Presented) The conjugate of claim 2, wherein the cell binding agent is selected from the group consisting of antibodies, proteins, vitamins, peptides, polymeric micelles, liposomes, lipoprotein-based drug carriers, nano-particle drug carriers, dendrimers, and combination thereof.

8. (Previously Presented) The conjugate of claim 2, wherein the cell-binding agent is configured to bind to target cells which are selected from the group consisting of 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, CD51, 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 glycolipid), GD3 idio type, 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 ($\alpha\text{v}\beta 3$, $\alpha 5\beta 1$, $\alpha 6\beta 4$, $\alpha 11\beta 3$, $\alpha 5\beta 5$, $\alpha\text{v}\beta 5$), 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.

9. (Previously Presented) The conjugate of claim 2, wherein the cell-binding agent is an antibody, a single chain antibody, an antibody fragment that binds to a 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. (Previously Presented) The conjugate of claim 8, wherein the tumor cells are selected from the group consisting of lymphoma cells, myeloma cells, renal cells, breast cancer cells, prostate cancer cells, ovarian cancer cells, colorectal cancer cells, gastric cancer cells, squamous cancer cells, small-cell lung cancer cells, testicular cancer cells, and cells that grow and divide at an unregulated, quickened pace to cause cancers.

11. (Previously Presented) A pharmaceutical composition comprising a therapeutically effective amount of the conjugate of claim 2, and a pharmaceutically acceptable salt, carrier, diluent, or excipient therefor.

12. (Previously Presented) The conjugate of claim 2, wherein the drug is selected from the group consisting of a toxin, a chemotherapeutic agent, a drug moiety, an antibiotic, a radioactive isotope, and a nucleolytic enzyme.

13. (Canceled)

14. (Previously Presented) The conjugate of claim 2, wherein the conjugate comprises 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).

15. (Currently Amended) The conjugate of claim 2, wherein Drug is selected from the group consisting of tubulysins, maytansinoids, taxanoids (taxanes), CC-1065-analogs compounds, daunorubicin and doxorubicin compounds, benzodiazepine dimers (e.g., dimers of pyrrolbenzodiazepine (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, hemiasterlins, and esperamicins, ~~and analogues and derivatives thereof.~~

16. (Previously Presented) The conjugate of claim 2, having in vitro, in vivo or ex vivo cell killing activity.

17. (Previously Presented) The conjugate of claim 2, wherein the conjugate comprises either a peptide of 1-20 units of natural or unnatural 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.

18. (Previously Presented) The conjugate of claim 2, wherein the conjugate is cleavable by a protease.

19. (Previously Presented) A pharmaceutical composition comprising the conjugate of claim 2, and a pharmaceutically acceptable carrier.

20. (Previously Presented) A pharmaceutical composition comprising a therapeutically effective amount of the conjugate of claim 2, and a chemotherapeutic agent, radiation therapy agent, immunotherapy agent, autoimmune disorder agent, or anti-infectious agent.

21. (New) The hydrophilic linker of claim 1, wherein Z comprises a thiol, disulfide, amino, carboxy, aldehydes, maleimido, haloacetyl, hydrazine or hydroxyl group.

REMARKS

Entry of the foregoing, reconsideration of the subject matter identified in caption, as amended, pursuant to and consistent with 37 C.F.R. §1.111, and in light of the remarks which follow, are respectfully requested.

In the Amendment, claims 1-6 and 15 have been amended to further improve their form and/or clarity. New claim 21 has been added. Support for claim 21 can be found in the specification, for example, page 12, lines 17-21. Claim 13 was previously cancelled. No new matter has been added. Upon entry of the Amendment, claims 1-12 and 14-21 will be all the claims pending in the application.

I. Response to Claim Objection

Claim 5 was objected to for informalities. Applicant respectfully submits that claim 5 as amended does not contain informalities.

In the Amendment, claim 5 has been amended to address the issues raised in the Office Action. Accordingly, withdrawal of the objection is respectfully requested.

II. Response to Rejections under 35 U.S.C. § 112

a. Claims 1-12 and 14-20 were rejected under 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite. Applicant respectfully submits that the claims as amended are in compliance with the § 112 requirements.

In the Amendment, the claims have been amended to address various issues raised in the Office Action. Particularly, R₁, R₂, R₃, and R₄, as defined are not H.

(B) The Office Action asserts that:

Claim 1 recites "Z represents a functional group that enables linkage of the hydrophilic linker to a cytotoxic drug via a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, secondary or tertiary or quaternary amine, imine, cycloheteroalkylene, heteroaromatic, alkoximine or amide bond". It is unclear if the recited species of disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, secondary or tertiary or quaternary amine, imine, cycloheteroalkylene, heteroaromatic, alkoximine or amide bond are required as part of the "Z" moiety, or if the recited species are intended to be part of the cytotoxic drug. (Office Action at pages 3-4)

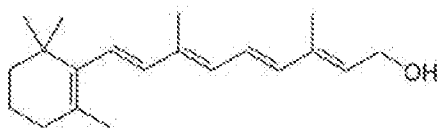
Applicant respectfully submits that the definition of Z is clear and understood by one of ordinary skill in the art. As correctly understood by the Examiner, Z is only required to enable linkage of the hydrophilic linker to a cytotoxic drug via a specified bond. That is, there is no requirement that the specified bond be, either entirely or partially, contained in Z or in the cytotoxic drug.

Further, it is well established that breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971); *In re Gardner*, 427 F.2d 786, 788, 166 USPQ 138, 140 (CCPA 1970).

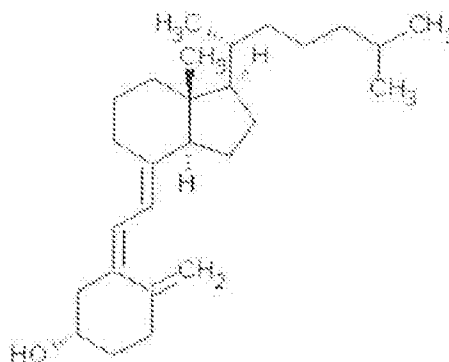
(C) The Office Action asserts that:

claim 5 recites the broad recitation "retinols", and the claim also recites CB1093, RB1089, KH1060, cholecalciferol and ergocalciferol (page 7, 1e) which is the narrower statement of the range/limitation. (Office Action at page 4)

Applicant respectfully disagrees. Specifically, as shown in the formulae below (see <https://www.thoughtco.com/vitamin-chemical-structures-4064208>), Vitamin A (Retinol) is different from Vitamin D3 which analog CB1093, RB1089, KH1060, cholecalciferol and ergocalciferol belong to.



Vitamin A (Retinol)



Vitamin D3

As such, CB1093, RB1089, KH1060, cholecalciferol and ergocalciferol are not "the narrower statement of the range/limitation" of "the broad recitation 'retinols,'" contrary to the Examiner's assertion.

Moreover, it is well established that "the double inclusion of an element by members of a Markush group is not, in itself, sufficient basis for objection to or rejection of claims." Therefore, the mere fact that a compound may be embraced by more than one member of a

Markush group recited in the claim does not necessarily render the scope of the claim unclear. For example, the Markush group, "selected from the group consisting of amino, halogen, nitro, chloro and alkyl" should be acceptable even though "halogen" is generic to "chloro." See MPEP 2173.05(h).

In view of the above, reconsideration and withdrawal of the rejection are respectfully requested.

b. Claims 5, 6 and 15 were rejected under 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement.

The Office Action asserts that:

The instant specification has failed to describe any analog or derivative originating from the large genus of chemotherapeutic, anti-autoimmune, anti-infectious, or anti-viral compounds or radioisotopes recited in the specification to be analogs or derivatives. (Office Action at page 7)

While not conceding the propriety of this rejection, and to expedite prosecution, the claims have been amended to delete the phrases "analogs" and "derivatives." Accordingly, withdrawal of the rejection is respectfully requested.

c. Claims "13 and 30-32" [sic] were rejected under 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the enablement requirement.

The Office Action asserts that:

It is clear that the biological activity of the Drug [recited in claim 5] incorporated into the compound must be preserved in order for the claimed compounds to be used by one of skill in the art.... The specification provides no teaching or guidance on the modification of the multitude of drugs, including multi-component products and cells, to provide a free thiol group for conjugation to the linker such that the modification and/or the conjugation of the drug, products or cells preserves the required function of the drug, multicomponent products or cells.... one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to make and use the broadly claimed compounds of claim 5. (Office Action at pages 7-8)

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *United States v. Teletronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

In the present case, the drugs recited in claim 5 each have a functional group or can be introduced with a functional group through a chemical reaction. One skilled in the art would be able to synthesize conjugates of the drugs via a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, secondary, tertiary, or quaternary amine, imine, cycloheteroalkane, heteroaromatic, alkoxime or amide bond by using the linkers described in the present application.

In view of the above, reconsideration and withdrawal of the rejection are respectfully requested.

III. Response to Rejection under 35 U.S.C. § 102

Claims 1-7 were rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,094,848 to Brixner. Applicant respectfully traverses the rejection for the following reasons.

Brixner discloses a pharmaceutical agent covalently bonded via a diphosphate or amidated diphosphate bond, i.e., $-L^1-DP-L^2$ or $-L^1-DP(A)-L^2-$, to a targeting moiety

(abstract). Particularly, Brixner discloses

$$\begin{array}{ccc} \text{O} & & \text{O} \\ \parallel & & \parallel \\ -\text{O}-\text{P}-\text{O}-\text{P}-\text{O}- & & -\text{X}^1-\text{P}-\text{O}-\text{P}-\text{X}^1- \\ | & & | \\ \text{O}^- & & \text{O}^- \end{array}$$

and

$$\begin{array}{ccc} \text{O} & & \text{O} \\ \parallel & & \parallel \\ -\text{X}^1-\text{P}-\text{O}-\text{P}-\text{X}^1- & & \\ | & & | \\ \text{O}^- & & \text{O}^- \end{array}$$

wherein one X^1 is O and the other is NH.

The Office Action asserts that:

The compound of Brixner comprising the diphosphate meet [sic] the limitation of the instant claims 1-4 wherein Q and T are both $-P=O(OM)-$, $m=1$, $n=1$, wherein R_2 is "O" that covalently connects the phosphinate group to the second phosphinate group. (Office Action at page 10)

Applicant respectfully disagrees. Specifically, the present claims define, among others, R_2 , to be "a chain of atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects...." It is clear that the "chain of atoms" contains more than one atom. As such, the diphosphate bond disclosed in Brixner does not meet the requirements of the present claims.

Nonetheless, to expedite prosecution, claims 1-4 have been amended to specify "a chain of two or more atoms."

In view of the above, reconsideration and withdrawal of the rejection are respectfully requested.

IV. New Claim

Newly added claim 21 depends from claim 1 and thus is patentable at least by virtue of its dependency.

V. Conclusion

From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order and such action is earnestly solicited. If there are any questions concerning this paper or the application in general, the Examiner is invited to telephone the undersigned at his earliest convenience.

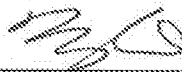
The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17 and 1.20(d) and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: November 15, 2017

By: _____



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