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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/014,390	10/16/2019	10131682	1518-005USRE	4956
21839 7590 06/12/2020 BUCHANAN, INGERSOLL & ROONEY PC POST OFFICE BOX 1404 ALEXANDRIA, VA 22313-1404			EXAMINER JONES, DWAYNE C	
			ART UNIT 3991	PAPER NUMBER
			MAIL DATE 06/12/2020	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.



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***EX PARTE* REEXAMINATION COMMUNICATION TRANSMITTAL FORM**

REEXAMINATION CONTROL NO. 90/014,390.

PATENT UNDER REEXAMINATION 10131682.

ART UNIT 3991.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the *ex parte* reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Office Action in Ex Parte Reexamination	Control No. 90/014,390	Patent Under Reexamination 10131682	
	Examiner Dwayne C Jones	Art Unit 3991	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

- a. ☐ Responsive to the communication(s) filed on _____.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
- b. ☐ This action is made FINAL.
- c. ☒ A statement under 37 CFR 1.530 has not been received from the patent owner.

A shortened statutory period for response to this action is set to expire 2 month(s) from the mailing date of this letter. Failure to respond within the period for response will result in termination of the proceeding and issuance of an *ex parte* reexamination certificate in accordance with this action. 37 CFR 1.550(d). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).** If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|---|
| 1. ☒ Notice of References Cited by Examiner, PTO-892. | 3. ☐ Interview Summary, PTO-474. |
| 2. ☐ Information Disclosure Statement, PTO/SB/08. | 4. ☐ _____. |

Part II SUMMARY OF ACTION

- 1a. ☒ Claims 1-21 are subject to reexamination.
- 1b. ☐ Claims _____ are not subject to reexamination.
2. ☐ Claims _____ have been canceled in the present reexamination proceeding.
3. ☐ Claims _____ are patentable and/or confirmed.
4. ☒ Claims 1-21 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ The drawings, filed on _____ are acceptable.
7. ☐ The proposed drawing correction, filed on _____ has been (7a) ☐ approved (7b) ☐ disapproved.
8. ☐ Acknowledgment is made of the priority claim under 35 U.S.C. 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of the certified copies have
1 ☐ been received.
2 ☐ not been received.
3 ☐ been filed in Application No. _____.
4 ☐ been filed in reexamination Control No. _____.
5 ☐ been received by the International Bureau in PCT application No. _____.
* See the attached detailed Office action for a list of the certified copies not received.
9. ☐ Since the proceeding appears to be in condition for issuance of an *ex parte* reexamination certificate except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte* Quayle, 1935 C.D. 11, 453 O.G. 213.
10. ☐ Other: _____

cc: Requester (if third party requester)

U.S. Patent and Trademark Office
PTOL-466 (Rev. 08-13)

Office Action in Ex Parte Reexamination

Part of Paper No. 20200108

DETAILED ACTION

Ex Parte Reexamination: First Office Action on the Merits

Procedural Posture

- On 11/20/2018: US Patent No. 10,131,682 B2 (referred to as '682 Patent) issued with claims 1-21.
- On 10/16/2010: Third Party Requester (*i.e.*, Requester) filed a Request for *ex parte* reexamination request for claims 1-21. This reexamination proceeding is assigned Control No. 90/014,390.
- On 11/27/2019: A Determination of an Order GRANTING *ex parte* reexamination was mailed.

No Patent Owner Statement under 37 CFR 1.530 was filed.

Notice of Pre-AIA or AIA Status

1. The present proceeding is being examined under the pre-AIA first to invent provisions.

Priority

2. Control No. 90/014,390 filed on 10/16/2019 is a reexamination proceeding of US Patent No. 10,131,682 B2, which issued to Zhao on 11/20/2018 with claims 1-21 from US Patent Application No. 14/432,073, which is the US National phase application pursuant to 35 U.S.C. 371 of the parent International Application of PCT/IB2012/056700 that was filed on 11/24/2012.

Claim Interpretation

3. During reexamination, claims are given the broadest reasonable interpretation consistent with the specification and limitations in the specification are not read into the claims. *In re*

Yamamoto, 740 F.2d 1569, 222 USPQ 934 (Fed. Cir. 1984). See MPEP §2258,I,G and MPEP 2111.01.

4. Regarding the definitions of R₁, R₂, R₃, and R₄ in claims 1, 3, 18 and 20, two separate definition groups (*i.e.*, **Group I** or **Group II**) define these four variables. This is because the word “or” is located between these two groups, as illustrated from the following claim recitation:

R₁, R₂, R₃, and R₄, are the same or different and are absent, 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 (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);

5. The **Group I** claim definition of variables R₁, R₂, R₃, and R₄ is recited in column 48, lines 54-61 (claim 1), column 49, lines 35-42 (claim 3); column 54, lines 23-30 (claim 18); and column 55, lines 4-11 (claim 20).

6. Alternatively, the **Group II** claim definition of variables R₁, R₂, R₃, and R₄ is recited in column 48, lines 62-67 (claim 1), column 49, lines 43-48 (claim 3); column 54, lines 31-36 (claim 18); and column 55, lines 12-17 (claim 20).

7. For these reasons, whatever group (*i.e.*, **Group I** or **Group II**) defines a particular variable selected from R₁, R₂, R₃, and R₄, the remaining variables are interpreted to be described in the same definition group.

8. Moreover, the '682 Patent defines the term “alkyl” as an aliphatic hydrocarbon group, which may be straight or branched having 1 to 8 carbon atoms in the chain or cyclic (column 6, lines 9-11). The '682 Patent further defines that a C₁-C₈ alkyl group can be unsubstituted or substituted with one or more groups, but not limited to, -O-(C₁-C₈ alkyl) (column 6, lines 21-

28). As such, an alkyl moiety is interpreted to be optionally substituted by a litany of groups such as a thioether (–S–(C₁–C₈ alkyl) moiety.

9. Claim 14 is directed to a conjugate of claim 3, wherein the drug is derived from a drug containing a –SH, –CONHNH₂, –CCH (*i.e.*, terminal alkyne), –COR” or –NHR”, wherein R” is H, CH₃, Et, Pr, Bu, or Ph; **and/or** the cell-binding agent is antibody or protein (emphasis added).

10. The presence of the “**and/or**” phrase allows claim 14 to have two (2) different interpretations.

11. **Regarding the 1st Interpretation:** the conjugate of claim 14 requires both:

- a. the drug to be derived from a drug containing –SH, –CONHNH₂, –CCH (*i.e.*, terminal alkyne), –COR” or –NHR”, wherein R” is H, CH₃, Et, Pr, Bu, or Ph (Limitation No.1); **and**
- b. the cell-binding agent to be an antibody or a protein (Limitation No. 2).

12. **Regarding the 2nd Interpretation:** the conjugate of claim 14 requires:

- a. **either** the drug to be derived from a drug containing –SH, –CONHNH₂, –CCH (*i.e.*, terminal alkyne), –COR” or –NHR”, wherein R” is H, CH₃, Et, Pr, Bu, or Ph (Limitation No. 1);
- b. **or** the cell-binding agent to be an antibody or a protein (Limitation No. 2).

13. Similarly, claims 19 and 21 are construed in this fashion due to the presence of the phrase “**and/or**”, except for referring to the conjugate of claim 18 with a cytotoxic drug or to the conjugate of claim 20 with a drug, respectively (emphasis added).

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. **Claims 3-8, 10-12, 14-16, 20, and 21 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by WO'497.**

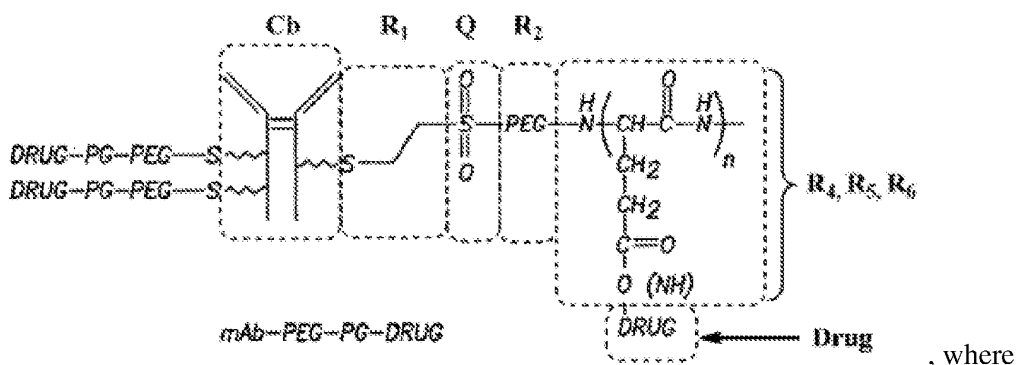
16. The **WO'497** reference discloses hydrophilic conjugate molecules for selective delivery of therapeutic agents (*e.g.*, chemotherapeutic drugs, hormonal agents and diagnostic agents) to tumors or other tissues (Abstract; page 5, lines 2-4). These compositions include conjugates of a ligand, a polymer spacer, a polymer carrier, and a therapeutic agent(s) (page 2, lines 16-29). The ligand (*i.e.*, targeting moiety) preferably is mAb, a peptide or a protein (page 8, lines 1-21). Therapeutic agents embrace drugs, chemotherapeutic drugs, particularly Adriamycin (*i.e.*, doxorubicin), diagnostic agents, hormonal drugs, and other compounds (page 2, lines 24-25; page 8, lines 22-31 and claim 21).

17. The polymer carrier and therapeutic agent are bonded to each other by an amide, thioether, disulfide, thiourethane, hydrazine or ester bond, and preferentially by an amide or an ester bond (page 6, lines 24-26). Preferably, poly(l-glutamic acid) (*i.e.*, PG) is attached as the polymer carrier to the therapeutic agent, while the polymer spacer (*i.e.*, polyethylene glycol, PEG) is between the ligand and the polymer carrier (page 7, lines 4-5 and 20).

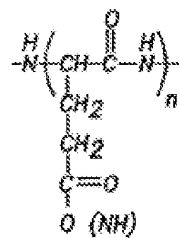
18. Due to the affinity of the ligand for the diseased tissue, the therapeutic agent is selectively delivered to the tissue (*e.g.*, tumor), where it exerts its medicinal effect (*e.g.*, inhibition or killing of the tumor cells) (page 11, lines 28-32). WO'497 highlights a method of synthesizing conjugate molecules with therapeutics (page 3, lines 18-29). In fact, Figure 2 exemplifies the synthetic scheme with mAb-PEG-PG-DRUG conjugates and hydrophilic linkers having a PEG group and a SO₂ moiety for linking the antibody and drug together.

19. **With respect to claim 3 in view of the Group I claim interpretation of variables R₁, R₂, R₃, and R₄**, the mAb-PEG-PG-DRUG of WO'497 (*i.e.*, Figure 2) is correlated to the instant

variables of **claim 3** (indicated below with the encircled dashed lines). The resulting representation depicted as:



- *instant Cb* corresponds to the cell-binding agent of **-mAb** of WO'497;
- *instant R₁* corresponds to **-S-CH₂-CH₂-** (*i.e.*, substituted alkyl with 2 C atoms) of WO'497;
- *instant Q* corresponds to **-SO₂-** of WO'497;
- *instant R₂* corresponds to polymer spacer of **-PEG-** of WO'497;
- *instant m* (not depicted in the above representation) corresponds to 1 of WO'497;
- *instant T* is not depicted in the above representation since *instant n* = 0;
- *instant R₃* is **absent**, and not depicted in the above representation since *instant n* = 0;
- *instant n* (not depicted in the above representation) corresponds to 0 of WO'497;



- *instant R₄* corresponds to the polymer carrier (PG), *i.e.*, with 5 C atoms) of WO'497;
- *instant R₅* is **absent**;
- *instant R₆* is **absent**;
- *instant Drug* corresponds to **-DRUG** of WO'497 (*e.g.*, doxorubicin) that is connected to the linker by an ester or amide bond; and
- *instant q* is depicted in formula II, but not defined in **claim 3**. In this case, *instant q* = 1.

20. With respect to **claim 3** in view of the Group II claim interpretation of variables **R₁**, **R₂**, **R₃**, and **R₄**, the mAb-PEG-PG-DRUG of WO'497 (*i.e.*, Figure 2) is correlated to the instant variables of **claim 3** (indicated below with the encircled dashed lines). The resulting

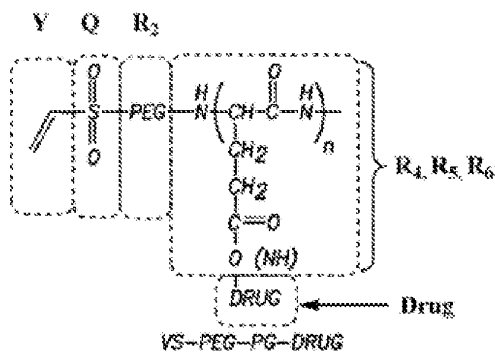
[illegible]

- $$\begin{array}{c} \text{H} \quad \quad \quad \text{O} \\ | \quad \quad \quad || \\ -\text{N}-(\text{CH}-\text{C}-\text{N})- \\ | \quad \quad \quad | \\ \text{CH}_2 \quad \quad \quad \text{H} \\ | \quad \quad \quad | \\ \text{CH}_2 \quad \quad \quad \text{O} \\ | \quad \quad \quad | \\ \text{C}=\text{O} \\ | \\ \text{O} \text{ (NH)} \end{array} \quad n$$

- **instant R_4** corresponds to the polymer carrier (PG), i.e.,  (i.e., a chain of two or more atoms of C, N, and O) of WO'497;
- **instant R_5** is absent;
- **instant R_6** is absent;
- **instant Drug** corresponds to **–DRUG** of WO'497 (e.g., doxorubicin) that is connected to the linker by an ester or amide bond; and
- **instant q** is depicted in formula II, but not defined in **claim 3**. In this case, **instant $q = 1$** .

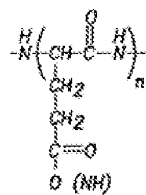
¹ VS represents a vinylsulfone moiety.

variables of **claim 20** (indicated below with the encircled dashed lines). The resulting representation depicted as:



, where

- *instant Y* corresponds to $\text{H}_2\text{C}=\text{CH}-$ of WO'497;
- *instant R₁* (not depicted in the above representation) is **absent**;
- *instant Q* corresponds to $-\text{SO}_2-$ of WO'497;
- *instant R₂* corresponds to $-\text{PEG}-$ of WO'497;
- *instant m* (not depicted in the above representation) corresponds to 1 of WO'497;
- *instant T* is not depicted in the above representation since *instant n* = 0;
- *instant R₃* is **absent**, and not depicted in the above representation since *instant n* = 0;
- *instant n* (not depicted in the above representation) corresponds to 0 of WO'497;



- *instant R₄* corresponds to polymer carrier (PG), i.e., (i.e., ester/amide with 5 C atoms) of WO'497;
- *instant R₅* is **absent**;
- *instant R₆* is **absent**;
- *instant Drug* corresponds to $-\text{DRUG}$ of WO'497 (e.g., doxorubicin) that is connected to the linker by an ester or amide bond.

22. With respect to claims 4, 5, 8, and 10, the therapeutic agents of WO'497 embrace drugs, chemotherapeutic drugs, e.g., doxorubicin, taxol, cisplatin, methotrexate, etoposide, and 5-FU, diagnostic agents, hormonal drugs, and other compounds (page 2, lines 24-25; page 8, line 22 to page 9, line 3; and claim 21).

23. **With respect to claims 6 and 7**, WO'497 exemplifies mAb as the ligand (*i.e.*, cell-binding agent) (page 8, lines 1-18 and Figure 2).

24. **With respect to claim 11**, the therapeutic agent is selectively delivered to the diseased tissue (*i.e.*, tumor) where it exerts its medicinal effect (*e.g.*, inhibition or killing of tumor cells) due to the affinity of the ligand for the diseased tissue (page 11, lines 28-32 and from page 23, line 25 to page 25, line 11).

25. **With respect to claim 12**, the therapeutic conjugates of WO'497 also include linkers joining the polymer carrier to the therapeutic agent. Examples of linkers are aliphatic chains, lipids, amino acids or peptides, and preferably poly(l-glutamic acid) (page 6, lines 28-29 and page 7, lines 4-5).

26. **With respect to claims 14 and 21**, the polymer carrier and therapeutic agent of WO'497 are bonded to each other, *e.g.*, by a thioether, disulfide, thiourethane, or hydrazine bond, and more preferably by an amide or ester bond (page 6, lines 24-26). WO'497 further discloses conjugating Adriamycin (*i.e.*, doxorubicin) to the side-chain carboxyl groups in the PG block of VS-PEG-PG via *p*-nitrophenol activated esters, IIDQ, or a carbodiimide-mediated reaction (page 17, lines 11-16). The ligand of WO'497 is a protein or preferably a mAb (page 8, lines 1-21). Since Adriamycin has a $-NH_2$ moiety and mAb is a ligand in WO'497, both the **1st & 2nd**

Interpretations of the *Claim Interpretation* section of this Office Action are met by WO'497.

27. **With respect to claims 15 and 16**, the WO'497 composition comprises a conjugate molecule and a pharmaceutically acceptable carrier (page 3, lines 1-3 and claim 23).

Claim Rejections - 35 USC § 102 and 35 USC § 103

28. The text of those sections of Title 35, U.S. Code not included in this action are stated previously in this Office action.

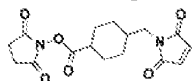
29. The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

30. **Claims 3-8, 10, 11, 13, 14, 15, and 16 are rejected under pre-AIA 35 U.S.C. 102 (b) as anticipated by or, in the alternative, under pre-AIA 35 U.S.C. 103(a) as obvious over PGPUB'053 as evidenced by Handbook of Preservatives.**

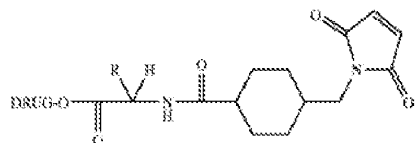
31. **PGPUB'053** discloses therapeutic immunoconjugates with the improved ability to target cancer cells, infectious disease organisms, and to treat autoimmune diseases (Title; Abstract and [0001]). The immunoconjugates comprise (a) a targeting moiety (*e.g.*, mAb); (b) a chemotherapeutic moiety (*e.g.*, doxorubicin, camptothecin, taxanes, and geldanamycin); and (c) a linker binding to: (c1) the targeting moiety via a thiol group; and (c2) the chemotherapeutic moiety via an intracellularly-cleavable moiety other than a hydrazone. The linker particularly comprises an amino acid moiety & a thiol-reactive group that bonds to a thiol group on the targeting moiety ([0009]-[0015], [0033], [0034], [0035], [0043], [0045] and claims 1 and 16). In fact, the thiol-reactive group preferably is a maleimide (*e.g.*, SMCC²), chloroacetamide,

² SMCC represents Succinimidyl 4-(*N*-maleimidomethyl)cyclohexane-1-carboxylate, depicted as:



bromoacetamide, iodoacetamide, and vinylsulfone that is reacted with the α -amino moiety of an amino acid in the linking moiety.

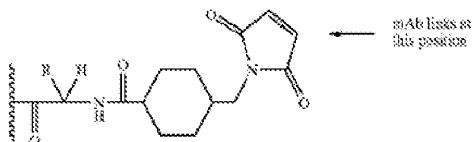
32. The products resulting from the reaction of SMCC and the chemotherapeutic moiety (*i.e.*, DRUG) with an amino acid radical have the general structures:



, where the R moiety is the side chain of an amino acid and



the moiety. Next, the linker binds to the targeting moiety (*e.g.*, mAb) via the thiol group at the thiol-reactive group *e.g.*, a maleimide, which is depicted as:



([0033], [0045], [0046], [0048], claims 9-10).

33. As mentioned previously, PGPUB'053 preferably lists a small genus of five (5) thiol-reactive groups (*i.e.*, maleimide, chloroacetamide, bromoacetamide, iodoacetamide, and vinylsulfone) that bond to a thiol group on the targeting moiety. PGPUB'053 portrays the maleimide thiol-reactive group of SMCC. In view of the disclosure of PGPUB'053, one skilled in the art would at once envisage the instantly claimed vinylsulfone species from a small genus of five well-delineated, thiol-reactive groups. See MPEP §2131.02, III.

34. Substituting the maleimide (*i.e.*, thiol-reactive group) in the above depicted structure for a vinylsulfone (*i.e.*, another thiol-reactive group), results in the following linker-drug compound:
DRUG–O–C(=O)CRH–NH–SO₂–CH=CH₂. Next, the reaction of the vinylsulfone moiety in the above linking structure with a thiol (–SH) of mAb results in the following immunoconjugate:

DRUG-O-C(=O)CRHNH-SO₂-CH₂CH₂-S-mAb (compare to **instant claim 3**). Since one skilled in the art can readily envisage one thiol-reactive group (*i.e.*, vinylsulfone) from a list of sufficiently limited and suitable alternatives on the linker, PGPUB'053 anticipates the instant claims.

35. Alternatively, claims 3-8, 10, 11, 13, 14, 15, and 16 are rendered obvious over PGPUB'053 due to the following three rationales. First, the structurally similar subgeneric linking compounds of PGPUB'053 and those claimed share a useful property as immunoconjugates to deliver targeted drugs with mAb. As such, the artisan has motivation to choose the claimed subgenus from the genus based on reasonable expectation that structurally similar species usually have similar properties. See also *In re Dillion*, 919 F.2d 688, 692-693, 697, 698, 16 USPQ2d 1897, 1901, 1904-05 (Fed. Cir. 1990) (*en banc*) and MPEP §2144.08. Second, the substitution of one thiol-reactive group *i.e.*, maleimide, from a list of recognized equivalents *i.e.*, maleimide, chloroacetamide, bromoacetamide, iodoacetamide, and vinylsulfone as taught by PGPUB'053 on the linker would have been obvious to bond mAb (via a thiol) to a thiol-reactive group with a reasonable expectation of success. See also *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958) and MPEP §2144.06,II. Third, the selection of a known thiol-reactive group based on its suitability for the intended use to bond the mAb to the linker of the immunoconjugate as taught by PGPUB'053 supports a *prima facie* obviousness determination.

See also *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945) and MPEP §2144.07.

36. **Regarding claim 3 in view of the Group II claim interpretation of variables R₁, R₂, R₃, and R₄**, the above-depicted, sulfone-containing immunoconjugate of PG PUB'053 is correlated to the instant variables of **claim 3**. The resulting representation depicted as:

37. **DRUG–O–C(=O)–C(R)H–NH–SO₂–CH₂CH₂–S–mAb**, where

- *instant Cb* corresponds to **–mAb** of PG PUB'053;
- *instant R₁* corresponds to **–CH₂–CH₂–S–** (*i.e.*, a chain of two or more atoms of C and S) of PG PUB'053;
- *instant Q* corresponds to **–SO₂–** of PG PUB'053;
- *instant R₂* corresponds to **–C(R)H–NH–** (*i.e.*, a chain of two or more atoms of C, N, O, and S atoms), where R is the side chain of an amino acid of PG PUB'053;
- *instant m* (not depicted in the above representation) corresponds to 1 of PG PUB'053;
- *instant T* is not depicted in the above representation since *instant n* = 0;
- *instant R₃* is not depicted in the above representation since *instant n* = 0;
- *instant n* (not depicted in the above representation) corresponds to 0 of PG PUB'053;
- *instant R₄* corresponds to **–O–C(=O)–** (*i.e.*, a chain of two or more atoms of C and O) of PG PUB'053;
- *instant R₅* is **absent**;
- *instant R₆* is **absent**;
- *instant Drug* corresponds to **DRUG–** (*e.g.*, doxorubicin or taxanes ([0034]) of PG PUB'053 connected to the linker by an ester bond; and
- *instant q* is depicted in formula (II), but not defined in **claim 3**. *Instant q* = 1 in this case.

38. **Regarding claims 4, 5, 8, and 10**, PG PUB'053 preferably discloses doxorubicin, epirubicin, camptothecin, irinotecan, topotecan, taxanes, geldanamycin, ansamycins, and epothilones as chemotherapeutic moieties ([0034] and claim 15).

39. **Regarding claims 6 and 7**, PG PUB'053 exemplifies mAb as the targeting moiety (*i.e.*, cell-binding agent, CBA) ([0035]; claims 16-20).

40. **Regarding claim 11**, diseases that are treated preferably with anti-CD74 antibodies include non-Hodgkin's lymphoma, melanoma, and multiple myeloma. The expression of the CD74 antigen on the surface of the target cells enables the targeting LL1 antibody (*i.e.*, anti-

CD74) to be internalized along with any chemotherapeutic agent it carries as a “payload.” This allows a high and therapeutic concentration of the LL1-chemotherapeutic drug immunoconjugate of PGBUP’053 to accumulate inside such target cells [0001], [0016], [0041], [0053]-[0056], and [0062]). As such, the limitations of **claim 11** are met.

41. **Regarding claim 12**, PGPUB’053 preferably discloses that the intracellularly-cleavable moiety of the linker has a peptide bond cleavable by intracellular enzymes ([0033] and claim 5). Additionally, the linker contains *inter alia* one or more internal basic amino acids ([0038]).

42. **Regarding claim 13**, the linker is bound to the targeting moiety and to the chemotherapeutic agent by an intracellularly-cleavable moiety. Once internalized into the cell that mAb recognizes and binds to a receptor, the cleavable moiety preferably is a peptide bond severable by intracellular enzymes, namely esterases and amidases (*i.e.*, protease enzymes) ([0015], [0033], and [0044] and claim 5).

43. **Regarding claim 14**, PGPUB’053 specifically discloses mAb as the cell-binding agent (CBA) and the drug as doxorubicin ([0034] and [0035] and claims 15-20). Because doxorubicin has a –NH₂ moiety and mAb represents CBA in PGPUB’053, both the **1st & 2nd Interpretations** of the ***Claim Interpretation*** section of this Office Action are met by PGPUB’053.

44. **Regarding claims 15 and 16**, the immunoconjugates of PGPUB’053 contain a targeting moiety and a therapeutic moiety connected by an intracellularly-cleavable linkage that increases therapeutic efficacy, thus having the improved ability to target *inter alia* cancer cells ([0001]). Administering the targeting LL1 antibody (*i.e.*, anti-CD74) with a chemotherapeutic agent, affords a high and therapeutic concentration of the LL1-chemotherapeutic drug immunoconjugate to accumulate inside such target cells ([0055]). As such, the therapeutically effective amount limitation in **claim 15** is met.

45. In addition, PGPUB'053 teaches the linker comprises *inter alia* a water-solubilizing moiety *e.g.*, EDTA or DOTA, at the C-terminus ([0033] and [0038] and claims 14 and 31).

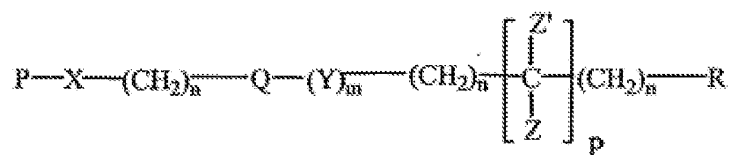
Handbook of Preservatives evidences that EDTA (*i.e.*, ethylenediaminetetraacetic acid) is a pharmaceutical excipient (page 385, left column). As such, the immunoconjugate of PGPUB'053 combined with EDTA meets the pharmaceutical excipient and carrier limitations of **claims 15 and 16**.

Claim Rejections - 35 USC § 103

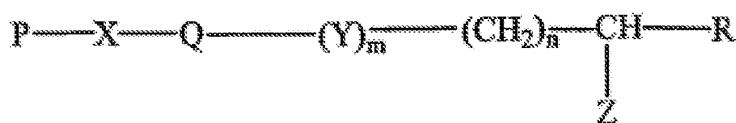
46. **Claims 1-4, 6-9, and 11-21 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over WO'577.**

47. **WO'577** is directed to hydrophilic polymers (*i.e.*, linkers) and conjugates to biologically-active agents (*i.e.*, antibodies and drugs) (Abstract and page 1, lines 2-11). The hydrophilic linkers of WO'577 have improved therapeutic benefits *e.g.*, enhancing solubility & stability as well as prolonging blood circulation half-life of molecules while minimizing undesirable side-effects (page 1, lines 9-11 and page 4, lines 19-22). First, WO'577 discloses an activated polyalkylene glycol compound (PGC) represented by Formulas I and Ia:

Formula I



Formula Ia



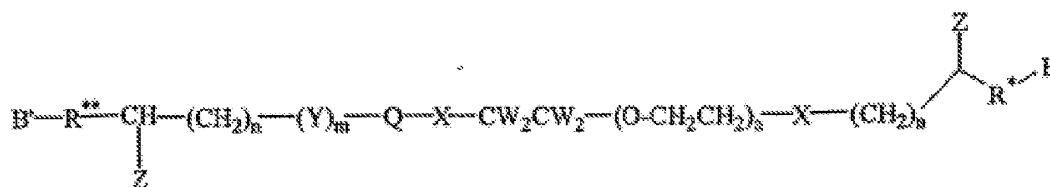
where P is a polyethylene glycol

Formula II:

moiety having a PEGylated structure of Formula II: $E-(O-CH_2CH_2)_n-$ (pages 4-7 of WO'577).

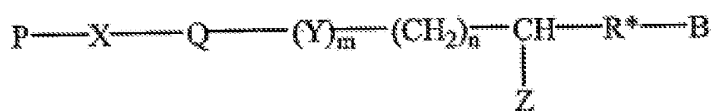
Second, WO'577 discloses a polyalkylene glycol linker conjugated to different biologically-active compounds where R* is bonded to a biologically-active compound (B) and R** is bonded to another biologically-active compound (B') represented by a composition of Formula XXIV:

Formula XXIV:



(from page 37, line 4 to page 38, line 2). Third, WO'577 discloses (1) a compound with a hydrophilic linker conjugated with an antibody depicted by Formula XIVa and (2) a compound with a hydrophilic linker conjugated to a drug also represented by Formula XIVa:

Formula XIVa:

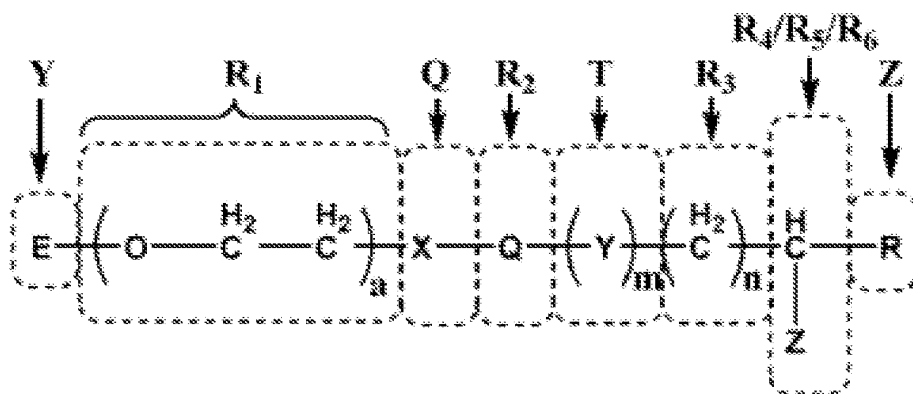


(from page 19, line 21 to page 21,

line 7). The variables in the structures of Formula I, Formula Ia, II, XXIV, and XIVa are discussed in detail below.

48. **Regarding claim 1 in view of the Group I and II claim interpretations of variables R₁, R₂, R₃, and R₄,** the combination of the hydrophilic linkers of Formulas I, Ia, and II of

WO'577 is correlated to the instant formula (I) variables of **claim 1** (indicated below with the encircled dashed lines), thereby resulting in the following representation:



where

- **instant Y** corresponds to **E**– of WO'577, where **E** is a moiety (*i.e.*, functional group) suitable for forming a bond between a compound of Formulas I and Ia along with a biologically-active compound **B** and **B'** (which will be discussed later under claim 3).
 - examples of **E** moieties are carboxylic acid, ester, hydroxyl, carbonate, thiol, amine, hydrazide, isocyanate, and maleimide groups (from page 6, line 29 to page 7, line 11 and from page 34, line 23 to page 35, line 12).
 - examples of biologically-active molecules are peptides, proteins, antibodies, anti-tumor agents, hormones, antibiotics, anti-viral agents, antimicrobial agents, germicidal agents, cholesterol lowering agents, oncolytic agents, antiandrogens, antiandrogens, and various other types of drugs (from page 60, line 6 to page 63, line 2);
- **instant R₁** corresponds to $-(OCH_2CH_2)_a-$ of WO'577, where **a** is an integer from 4 to 10,000 (page 6, lines 29-33 and page 35, line 2);
- **instant Q** corresponds to **–X–** of WO'577, where **X** is O, S, CO, CO₂, COS, SO, SO₂, CONR', SO₂NR', or NR', and where **R'** is H, a straight- or branched-chain, saturated or unsaturated C₁ to C₂₀ alkyl or heteroalkyl group, C₃ to C₈ saturated or unsaturated cyclic alkyl or cyclic heteroalkyl, an optionally substituted aryl or heteroaryl or an optionally substituted alkaryl where the alkyl is a C₁ to C₂₀ saturated or unsaturated alkyl or heteroalkyl group (page 5, line 31 and page 6, lines 10-18);
- **instant R₂** corresponds to **–Q–** of WO'577, where **Q** is C₃ to C₈ saturated or unsaturated cyclic alkyl or cyclic heteroalkyl, optionally substituted aryl or heteroaryl group, or optionally substituted alkaryl where the alkyl is a C₁ to C₂₀ saturated or unsaturated alkyl or heteroalkyl group (page 6, lines 1-9);

- *instant m* (not depicted in the above representation) corresponds to 1 of WO'577;
- *instant T* corresponds to $-(Y)_m-$ of WO'577, where **Y** is O, S, CO, CO₂, COS, SO, SO₂, CONR', SO₂NR', or NR', where **R'** was defined previously, and **m** is 0-1 (page 5, line 31 and page 6, lines 10-18);
- *instant R₃* corresponds to $-(CH_2)_n-$ of WO'577, where **n** is 0-5 (page 5, lines 30-31);
- *instant n* (not depicted in the above representation) corresponds to 1 of WO'577;
- *instant R₄/R₅/R₆* correspond to $-CZH-$ of WO'577, where **Z** is H, a straight- or branched-chain, saturated or unsaturated C₁ to C₂₀ alkyl or heteroalkyl group, C₃ to C₈ saturated or unsaturated cyclic alkyl or cyclic heteroalkyl, an optionally substituted aryl or heteroaryl or an optionally substituted alkaryl where the alkyl is a C₁ to C₂₀ saturated or unsaturated alkyl or heteroalkyl group (page 5, line 31 and page 6, lines 10-18);
- *instant Z* corresponds to $-R$ of WO'577, where **R** is a moiety (*i.e.*, functional group) suitable for forming a bond between a compound of Formulas I and Ia and a biologically-active compound. The **R** moiety is *inter alia* carboxylic acid, ester, hydroxyl, carbonate, thiol, amine, hydrazide, isocyanate, epoxide, acrylamide or maleimide (page 5, lines 21-22 and page 6, lines 21-28).

49. **Regarding claim 3 in view of the Group I and II claim interpretations of variables**

R₁, R₂, R₃, and R₄, the cell-binding agent and drug conjugate of Formula XXIV of WO'577 is

correlated to the instant variables of formula (II) of **claim 3**, thereby resulting in the following representation:



where

- *instant Cb* corresponds to $\mathbf{B}'\text{--}$ of WO'577, where $\mathbf{B}'$ is another biologically-active compound (*e.g.*, antibody) after conjugation with $\mathbf{R}^{**}$ (which is discussed below);
- *instant R₁* corresponds to $\text{--}\mathbf{R}^{**}\text{--}\mathbf{CHZ}\text{--}(\mathbf{CH}_2)_n\text{--}$ of WO'577,
 - where $\mathbf{R}^{**}$ is a linking moiety formed from the reaction of $\mathbf{R}''$ and $\mathbf{B}'$ (*inter alia* page 37, lines 22-27; page 38, lines 1-2; and from page 60, line 6 to page 63, line 2);
 - where $\mathbf{R}''$ is a moiety (*i.e.*, functional group) suitable for forming a bond between the hydrophilic linker and a biologically active compound $\mathbf{B}'$
 - where $\mathbf{Z}$ is H, a straight- or branched-chain, saturated or unsaturated C₁ to C₂₀ alkyl or heteroalkyl group, and n is 0-5 (*inter alia* page 37, lines 8-11);
- *instant Q* corresponds to $\text{--}(\mathbf{Y})_m\text{--}$ of WO'577, where $\mathbf{Y}$ is O, S, CO, CO₂, COS, SO, SO₂, CONR', SO₂NR', or NR', where $\mathbf{R}'$ is H, a straight- or branched-chain, saturated or unsaturated C₁ to C₂₀ alkyl or heteroalkyl group, where m is 0-1 (page 37, lines 9-11);
- *instant R₂* corresponds to $\text{--}\mathbf{Q}\text{--}$ of WO'577, where $\mathbf{Q}$ is C₃ to C₈ saturated or unsaturated cyclic alkyl or cyclic heteroalkyl, optionally substituted aryl or heteroaryl group, or optionally substituted alkaryl where the alkyl is a C₁ to C₂₀ saturated or unsaturated alkyl or heteroalkyl group (page 37, lines 13-21);
- *instant m* (not depicted in the above representation) corresponds to 1 of WO'577;
- *instant T* corresponds to $\text{--}\mathbf{X}\text{--}$ of WO'577, where $\mathbf{X}$ is O, S, CO, CO₂, COS, SO, SO₂, CONR', SO₂NR', or NR', where $\mathbf{R}'$ was defined previously (page 37, lines 9-12);
- *instant R₃* corresponds to $\text{--}\mathbf{CW}_2\mathbf{CW}_2\text{--}(\mathbf{O}\text{--}\mathbf{CH}_2\mathbf{CH}_2)_a\text{--}\mathbf{X}\text{--}$ of WO'577,
 - where $\mathbf{W}$ is H or C₁ to C₇ alkyl,
 - where a is 4-10,000, and
 - where $\mathbf{X}$ is O, S, CO, CO₂, COS, SO, SO₂, CONR', SO₂NR', or NR', where $\mathbf{R}'$ was defined previously (page 37, lines 9-11);
- *instant n* (not depicted in the above representation) corresponds to 1 of WO'577;

- *instant R₄/R₅/R₆* correspond to $-(CH_2)_n-CHZ-$ of WO'577 and,
 - where **n** is 0-5,
 - where **Z** is **H**, a straight- or branched-chain, saturated or unsaturated C₁ to C₂₀ alkyl or heteroalkyl group, C₃ to C₈ saturated or unsaturated cyclic alkyl or cyclic heteroalkyl, an optionally substituted aryl or heteroaryl or an optionally substituted alkaryl where the alkyl is a C₁ to C₂₀ saturated or unsaturated alkyl or heteroalkyl group (page 5, line 31 and page 6, lines 10-18);
- *instant Drug* corresponds to $-R^*-B$ of WO'577,
 - and where **R*** is a linking moiety formed from the reaction of **R** with **B** (*i.e.*, a biologically active compound), and where **R** is a moiety (*i.e.*, functional group) suitable for forming a bond between the compound of Formula XXIV and **B** (page 5, lines 21-22 and page 6, lines 21-28; page 37, lines 8-11 and 22-27 and page 38, lines 1-2);
 - where **B** is a biologically-active compound (*e.g.*, anti-tumor agent) after conjugation with **R*** (page 37, lines 22-27; page 38, lines 1-2; and from page 60, line 6 to page 63, line 2);
- *instant q* is depicted in formula (II), but not defined in **claim 3**. *Instant q* = 1 in this case.

50. Regarding claim 18 in view of the Group I claim interpretations of variables **R₁**, **R₂**, **R₃**, and **R₄**, the combination of the polyalkylene glycol polymer of Formula II of WO'577 with the hydrophilic composition of Formula XIVa of WO'577 having a cell-binding agent is

correlated to the instant variables of formula (III) of **claim 18**, thereby resulting in the following representation:

$(E-(OCH_2CH_2)_a-X-Q-(Y)_m-(CH_2)_n-CHZ-R^*)_q-B$ formula (III),

where

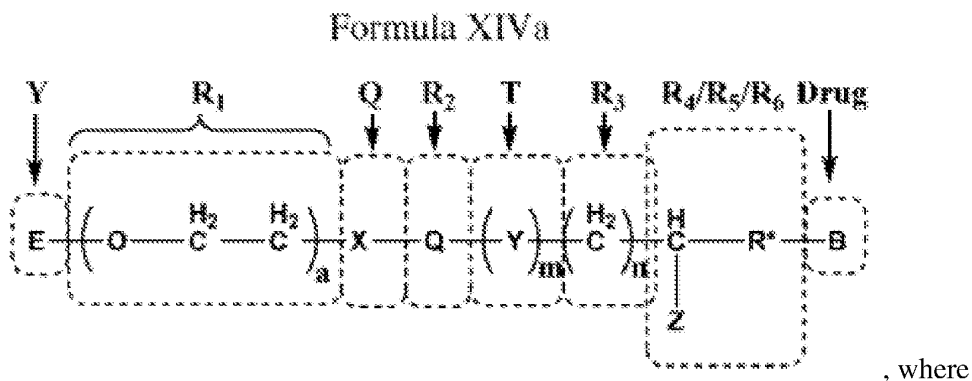
- *instant Z* corresponds to **E**– of WO'577, where **E** is a moiety (*i.e.*, functional group) suitable for forming a bond between the compound of Formula XIVa and a biologically-active compound (from page 20, line 28 to page 21, line 14);
- *instant R₄/R₅/R₆* (not depicted in the above representation) are **absent**;
- *instant R₃* corresponds to $-(OCH_2CH_2)_a-$ of WO'577, where **a** is an integer from 4 to 10,000 (page 20, lines 29-32);
- *instant T* corresponds to $-X-$ of WO'577, where **X** is O, S, CO, CO₂, COS, SO, SO₂, CONR', SO₂NR', or NR', where **R'** is H, a straight- or branched-chain, saturated or unsaturated C₁ to C₂₀ alkyl or heteroalkyl group, C₃ to C₈ saturated or unsaturated cyclic alkyl or cyclic heteroalkyl, an optionally substituted aryl or heteroaryl or an optionally substituted alkaryl where the alkyl is a C₁ to C₂₀ saturated or unsaturated alkyl or heteroalkyl group (page 20, lines 5-14);
- *instant n* (not depicted in the above representation) corresponds to 1 of WO'577;
- *instant R₂* corresponds to $-Q-$ of WO'577, where **Q** is C₃ to C₈ saturated or unsaturated cyclic alkyl or cyclic heteroalkyl, optionally substituted aryl or heteroaryl group, or optionally substituted alkaryl where the alkyl is a C₁ to C₂₀ saturated or unsaturated alkyl or heteroalkyl group (from page 19, line 27 to page 20, line 4);
- *instant Q* corresponds to $-(Y)_m-$ of WO'577, where **Y** is O, S, CO, CO₂, COS, SO, SO₂, CONR', SO₂NR', or NR', where **R'** was defined previously and **m** is 0-1 (page 19, line 26 and page 20, lines 5-14 and 18);
- *instant m* (not depicted in the above representation) corresponds to 1 of WO'577;
- *instant R₁* corresponds to $-(CH_2)_n-CHZ-R^*-$ of WO'577,
 - where **n** is 0-5,
 - where **Z** is H, a straight- or branched-chain, saturated or unsaturated C₁ to C₂₀ alkyl or heteroalkyl group, C₃ to C₈ saturated or unsaturated cyclic alkyl or cyclic heteroalkyl, an optionally substituted aryl or heteroaryl or an optionally

substituted alkaryl where the alkyl is a C₁ to C₂₀ saturated or unsaturated alkyl or heteroalkyl group (page 20, lines 5-14), and

- where **R*** is a linking moiety formed from the reaction of **R** with **B** (*i.e.*, a biologically active compound or precursor thereof), and where **R** is a moiety suitable for forming a bond between the compound of Formula XIVa and **B** (*inter alia* page 6, lines 21-28 and page 20, lines 5-27);
- **instant Cb** corresponds to **-B** of WO'577, where **B** is a biologically-active compound (*i.e.*, an antibody) after conjugation with **R**. The **R** moiety was defined previously (*inter alia* page 5, lines 21-22; page 6, lines 21-28; page 20, lines 17-27; and from page 60, line 6 to page 63, line 2).
- **instant q** corresponds to 1 of WO'577.

51. **Regarding claim 20 in view of the Group I and II claim interpretations of variables**

R₁, R₂, R₃, and R₄, the combination of the polyalkylene glycol polymer of Formula II of WO'577 with the hydrophilic composition of Formula XIVa having a drug of WO'577 is correlated to the instant variables of formula (IV) of **claim 20** (indicated below with the encircled dashed lines), thereby resulting in the following representation:



- **instant Y** corresponds to **E-** of WO'577, where **E** is a moiety (*i.e.*, functional group) suitable for forming a bond between the compound of Formula XIVa and a biologically-active compound (from page 20, line 28 to page 21, line 14);
- **instant R₁** corresponds to **-(OCH₂CH₂)_a-** of WO'577, where **a** is an integer from 4 to 10,000 (page 20, lines 29-32);
- **instant Q** corresponds to **-X-** of WO'577, where **X** is O, S, CO, CO₂, COS, SO, SO₂, CONR', SO₂NR', or NR', where **R'** is H, a straight- or branched-chain, saturated or

unsaturated C₁ to C₂₀ alkyl or heteroalkyl group, C₃ to C₈ saturated or unsaturated cyclic alkyl or cyclic heteroalkyl, an optionally substituted aryl or heteroaryl or an optionally substituted alkaryl where the alkyl is a C₁ to C₂₀ saturated or unsaturated alkyl or heteroalkyl group (page 19, line 26 and page 20, lines 5-14);

- *instant R₂* corresponds to –**Q**– of WO'577, where **Q** is C₃ to C₈ saturated or unsaturated cyclic alkyl or cyclic heteroalkyl, optionally substituted aryl or heteroaryl group, or optionally substituted alkaryl where the alkyl is a C₁ to C₂₀ saturated or unsaturated alkyl or heteroalkyl group (from page 19, line 27 to page 20, line 4);
- *instant m* (not depicted in the above representation) corresponds to 1 of WO'577;
- *instant T* corresponds to –(**Y**)_{**m**}– of WO'577, where **Y** is O, S, CO, CO₂, COS, SO, SO₂, CONR', SO₂NR', or NR', where **R'** was defined previously, and **m** is 0-1 (page 19, line 26 and page 20, lines 5-14 and 18);
- *instant R₃* corresponds to –(**CH₂**)_{**n**}– of WO'577, where **n** is 0-5 (page 20, line 19);
- *instant n* (not depicted in the above representation) corresponds to 1 of WO'577;
- *instant R₄/R₅/R₆* correspond to –**CHZ**– of WO'577,
 - where **Z** is H, a straight- or branched-chain, saturated or unsaturated C₁ to C₂₀ alkyl or heteroalkyl group, C₃ to C₈ saturated or unsaturated cyclic alkyl or cyclic heteroalkyl, an optionally substituted aryl or heteroaryl or an optionally substituted alkaryl where the alkyl is a C₁ to C₂₀ saturated or unsaturated alkyl or heteroalkyl group (page 20, lines 5-14), and
- *instant Drug* corresponds to –**R***–**B** of WO'577,
 - where **R*** is a linking moiety formed from the reaction of **R** with **B** (*i.e.*, a biologically active compound), and where **R** is a moiety suitable for forming a

bond between the compound of Formula XIVa and **B** (*inter alia* page 6, lines 21-28 and page 20, lines 5-27);

- where **B** is a biologically-active compound (*i.e.*, anti-tumor agent) after conjugation with **R** (page 20, line 17; and from page 60, line 6 to page 63, line 2); and
- the **R** moiety was defined previously (*inter alia* page 5, lines 21-22; page 6, lines 21-28; and page 20, lines 17-27; and from page 60, line 6 to page 63, line 2).

52. WO'577 does not exemplify a hydrophilic linking moiety with SO, SO₂ or

SO₂NR' groups as claimed.

53. However, the artisan would have found it obvious to select the SO, SO₂ or

SO₂NR' groups as suitable moieties from the finite list of possible groups specifically identified in WO'577. This is because WO'577 provides a list of appropriate groups *i.e.*, O, S, CO, CO₂, COS, SO, SO₂, CONR', SO₂NR', or NR' to represent the X and Y variables in the hydrophilic linking moiety. See also *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 538, 421, 82 USPQ2d 1385, 1397 (2007).

54. Additionally, the artisan would have been motivated to substitute equivalents known for the same purpose since WO'577 recognizes the equivalency between these SO, SO₂ or SO₂NR' groups to improve therapeutic benefits (*e.g.*, enhancing solubility & stability while minimizing undesirable side effects) of the delivered drug via the hydrophilic (*i.e.*, PEGylated) linker. This is because substituting equivalents known for the same purpose has been held to be *prima facie* obvious. See also *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958) and MPEP §2144.06. At the time of the invention, one having ordinary skill in the art would have been motivated to select SO, SO₂ or SO₂NR' from a finite group of suitable and equivalent moieties. This selection of SO, SO₂ or SO₂NR' moieties enhances therapeutic benefits of the hydrophilic drug conjugate, while reducing adverse reactions with a predictable and reasonable expectation of success to

arrive at the invention in **claims 1, 3, 18, and 20**. Furthermore, the claimed compounds and those of WO'577 are expected to have similar properties *e.g.*, enhancing solubility & stability as well as prolonging blood circulation half-life of molecules while minimizing undesirable side-effects since they are closely similar in structure. See *In re Payne*, 606 F.2d 33, 313, 203 USPQ 245, 254 (CCPA 1979).

55. **Regarding claim 2**, R of WO'577 is a moiety (*i.e.*, functional group) suitable for forming a bond between a compound of Formulas I or Ia and a biologically-active compound. The R variable is *inter alia* a carboxylic acid, ester, hydroxyl, carbonate, thiol, amine, hydrazide, or maleimide moiety (page 6, lines 21-28).

56. **Regarding claims 4 and 8**, WO'577 discloses a litany of biologically-active molecules namely small molecules, lymphokines, anti-tumor agents, antibiotics, anti-viral agents, steroidal agents, germicidal agents, cholesterol lowering agents, oncolytic agents, antiandrogens, and antimalarial agents (from page 60, line 31 to page 62, line 2).

57. **Regarding claims 6 and 7**, WO'577 discloses biologically-active molecules *inter alia* antibodies (page 61, lines 7-12).

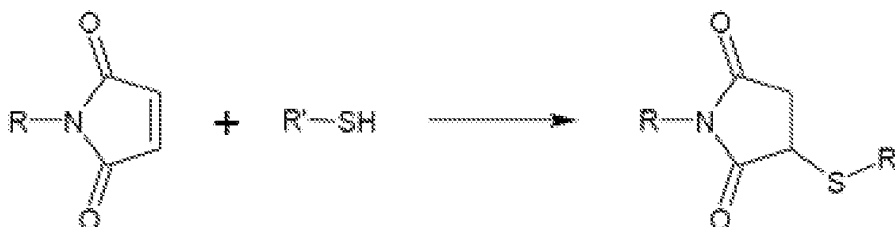
58. **Regarding claim 9**, WO'577 fails to disclose the specific maleimido groups of 6-maleimidocaproyl, 4-(*N*-maleimidomethyl)cyclohexane-1-carboxylate, maleimidopropanyl, and maleimidoethyl as claimed. However, the artisan recognizes numerous reaction mechanisms available to facilitate conjugation of the activated polyalkylene glycol compound (PGC) to B (*e.g.*, mAb). WO'577 particularly teaches a stable thioether linkage occurs when R (*i.e.*, a functional group suitable for forming a bond between the PGC and B) has a maleimide group reacted³ with a sulfhydryl (–SH) group of variable B (page 62, lines 12-29). In the absence of

³ General Reaction of a Maleimide with a Thiol to produce a Thioether:

unexpected evidence, the linking moiety of WO'577 is capable of forming bonds between the hydrophilic linker and biologically-active agents (page 60, lines 25-30).

59. At the time of the invention, one having ordinary skill in the art would have found it obvious that a linker having a maleimide functional group *e.g.*, maleimidopropanyl, maleimidoethyl, 6-maleimidocaproyl, and 4-(*N*-maleimidomethyl)cyclohexane-1-carboxylate would readily react with a -SH group of mAb as taught by WO'577. As such, the artisan would have been motivated to apply this conventional reaction between a compound having a maleimide group and a thiol moiety to the specific maleimide-containing conjugates as claimed to produce a stable thioether bond having improved therapeutic benefits of the immunoconjugate while minimizing adverse effects with a reasonable expectation of success.

60. **Regarding claim 11**, the specific antiviral activity of PEGylated IFN- β -1a samples were tested on human lung carcinoma cells (A549 cells) exposed to the encephalomyocarditis (EMC) virus. In fact, Table 4 specifically shows EC₅₀ values (*i.e.*, the concentration at which 50% of the



cells were killed) of PEGylated IFN- β -1a samples, thereby meeting the cell killing activity limitation (Example 3, from page 125, line 5 to page 126, line 14).

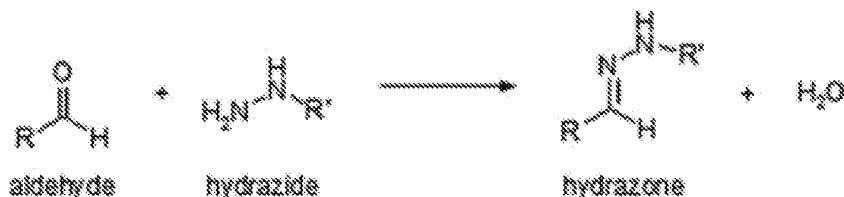
61. **Regarding claim 12**, the hydrazide⁴ group (variable R) of WO'577 reacts⁵ (covalently couples) to an aldehyde group on a sugar moiety, thereby forming a hydrazone⁶ linkage (R*-B). WO'577 also discloses forming a stable thioether linkage by reacting a maleimidyl group of variable R with a sulfhydryl (-SH) group of variable B (page 62, lines 12-29).

62. **Regarding claim 13**, WO'577 teaches unmodified and 20 kDa mPEG-O-2-methylpropionaldehyde-modified IFN- β -1a were digested with endoproteinase Lys-C (page 117, lines 32-33; from page 120, line 32 to page 121, line 1; and page 124, lines 15-18).

63. **Regarding claims 14, 19, and 21**, WO'577 covalently couples the hydrazide (*e.g.*, -C(O)NHNH₂) group of R to an aldehyde group on a sugar moiety to produce a hydrazone (*e.g.*, -CH=NNH₂) linkage (*i.e.*, R*-B). WO'577 also discloses forming a stable thioether linkage by reacting the maleimidyl group R with a sulfhydryl (-SH) group of variable B. The biologically-active compounds (*i.e.*, drugs) of WO'577 contain the functional groups of sulfhydryls, hydrazides, aldehydes, and carbonyls for covalent attachment to the polyalkylene glycol compound (PGC) to facilitate conjugation activation to a biologically-active compound (page 62,

⁴ General structure of a Hydrazide is represented as E(=O)NHNH₂, and more specifically a carbohydrazide is represented as RC(=O)NHNH₂.

⁵ General Reaction of a Hydrazide with an Aldehyde to produce a Hydrazone:



⁶ Issued claim 12 of the '682 Patent lists a "hydrozone [*sic*] unit" vs hydrazone unit. As such, this is viewed as a typographical error.

lines 3-19). WO'577 further discloses proteins and antibodies as biologically-active compounds (page 61, lines 7-12). Because the drugs have –SH, –CONHNH₂, and –COR", where R" is H, CH₃, Et, Pr, Bu, or Ph as claimed and proteins & antibodies are examples of cell-binding agents, both the **1st & 2nd Interpretations** of the *Claim Interpretation* section of this Office Action are met by WO'577.

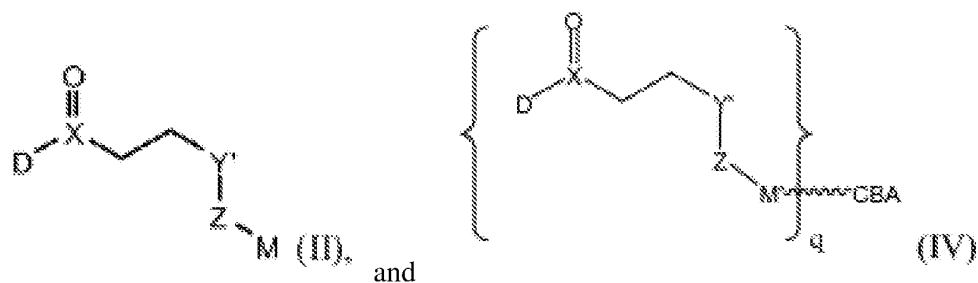
64. **Regarding claims 15-17**, WO'577 discloses pharmaceutical compositions containing hydrophilic polymers conjugated to biologically-active compounds (*i.e.*, mAb and Drugs) with pharmaceutically acceptable carriers (page 38, lines 20-22; claim 219), thus meeting the pharmaceutically acceptable carrier limitations of **claims 15 and 16**.

WO'577 also discloses methods of treating viral infections with an effective amount of a composition having the conjugate of Formula XXIV (from page 52, line 18 to page 53, line 11; claim 298), thus meeting the therapeutically effective amount limitation in **claims 15 and 17**. Moreover, WO'577 teaches the pharmaceutical composition may also contain an additional biologically-active agent *inter alia* a protein, small molecule, nucleoside, anti-tumor agents,

antibiotics, anti-viral agents, thereby meeting the drug limitation of **claim 17** (page 38, lines 21-26; page 61, lines 1-23).

65. **Claims 3-11, 13-17, 20, and 21 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over WO'112.**

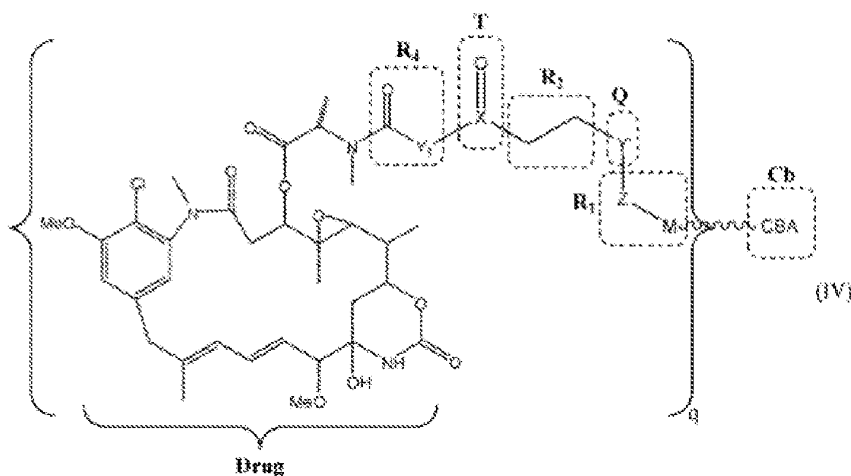
66. The **WO'112** reference discloses cytotoxic linking compounds (*i.e.*, formula (II)) and cytotoxic linking conjugates (*i.e.*, formula (IV)) to cell-binding agents (*i.e.*, CBA) depicted respectively as:



(Abstract and [02], [47] -[49], [67], and [97]-[108]). These linking compounds and conjugates of WO'112 inhibit abnormal cell growth and treat proliferative disorders ([162] and claim 79). The cytotoxic linking compounds (formula II) and the cytotoxic conjugates with CBAs (formula IV) both contain a sulfoxide ($-S(=O)-$) representing variable X and a sulfone ($-S(=O)_2-$) representing variable Y' ([06], [09], and [20]). Preferably, a maytansinoid compound represents the cytotoxic agent of D in these two linkers ([67], [78], and [79]). The linking component in these conjugates are an important element in targeted anti-cancer agents, which possess an optimal therapeutic window: high activity (potency) at a low, non-toxic dose ([02], Figures 1

and 2). As such, WO'112 discloses the need for new linking components to improve the efficacy of anti-cancer agents.

67. Regarding claim 3 in view of the Group I claim interpretation of variables **R₁**, **R₂**, **R₃**, and **R₄**, the cell-binding agent and cytotoxic linking conjugates of formula (IV) of WO'112 are correlated to the instant **claim 3** variables of formula (II) (indicated below with the encircled dashed lines), thereby resulting in the following representation:



, where

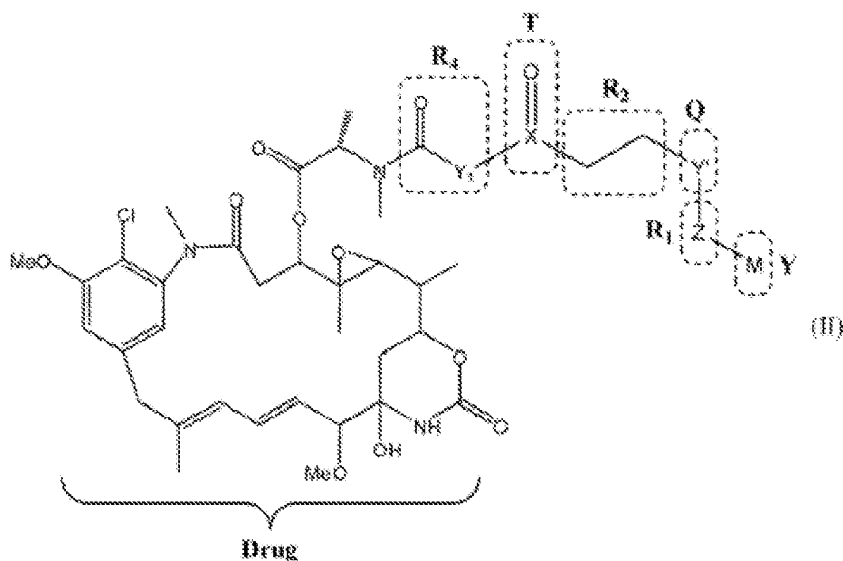
- *instant Cb* corresponds to **–CBA** of WO'112, where **CBA** is an antibody, antibody fragment, chimeric antibody, or mAb ([97]-[100], claims 74-77, *exemplified* in FIG 1-5);
- *instant R₁* corresponds to **–Z–M'⁷–** of WO'112, where
 - where **Z** is *inter alia* alkyl and cycloalkyl ([75]);
 - where **M'** is a linking moiety, which is the resulting chemical moiety of the linking group after covalently linking to the CBA ([9], [60], [61], [63], and [74]);
- *instant Q* corresponds to **–Y'–** of WO'112, where **Y'** is *preferred* to be **–S(=O)₂–** ([75]);
- *instant R₂* corresponds to **–CH₂CH₂–** of WO'112;

⁷ It is noted that M' should be listed in the above representation of formula (IV), rather than M.

- *instant m* (not depicted in the above representation) corresponds to 1 of WO'112;
- *instant T* corresponds to $-X(=O)-$ of WO'112, where **X** is *embodied* as S, thus resulting in $-S(=O)-$ [122]);
- *instant R₃* (not depicted in the above representation) is **absent**;
- *instant n* (not depicted in the above representation) corresponds to 1 of WO'112;
- *instant R₄* corresponds to $-C(=O)Y_1-$ of WO'112, where **Y₁** is $(CR_7R_8)_l(CR_5R_6)_m(CR_3R_4)_nCR_1R_2-$, where in a *preferred* embodiment **R₁-R₈** are H and I and **m** are 0 and **n** is 1, thus resulting in $-C(=O)CH_2CH_2-$ ([67]);
- *instant R₅ and R₆* (not depicted in the above representation) are **absent**;
- *instant Drug* corresponds to a **cytotoxic agent**— in a *more preferred* embodiment the cytotoxic agent is a **maytansinoid** of structural formula A1 that is connected to the linker with an amide (*i.e.*, peptide) bond ([67]);
- *instant q* (depicted in formula (II), but not defined in **claim 3**) corresponds to **q** (*i.e.*, 1-20) of WO'112.

68. Regarding claim 20 in view of the Group I claim interpretation of variables **R₁, R₂, R₃, and R₄**, the cytotoxic linking compounds of formula (II) of WO'112 are correlated to instant

claim 20 variables of formula (IV) (indicated below with the encircled dashed lines), thereby resulting in the following representation:



where

- **instant Y** corresponds to $-\mathbf{M}$ of WO' 112, where $\mathbf{M}$ is a linking group (*i.e.*, functional group) that can react with a CBA to form a covalent bond ([06], [60], [61], [100], and claims 36-38);
- **instant R₁** corresponds to $-\mathbf{Z}-$ of WO' 112, where $\mathbf{Z}$ is *inter alia* alkyl and cycloalkyl ([75] and [85]);
- **instant Q** corresponds to $-\mathbf{Y}'-$ of WO' 112, where $\mathbf{Y}'$ is *preferred* to be $-\text{S}(=\text{O})_2-$ ([75] and [86]);
- **instant R₂** corresponds to $-\text{CH}_2\text{CH}_2-$ of WO' 112;
- **instant m** (not depicted in the above representation) corresponds to 1 of WO' 112;
- **instant T** corresponds to $-\mathbf{X}(=\text{O})-$ of WO' 112, where $\mathbf{X}$ is *embodied* as S, thus resulting in $-\text{S}(=\text{O})-$ [68] and [85]);
- **instant R₃** (not depicted in the above representation) is **absent**;

- *instant n* (not depicted in the above representation) corresponds to 1 of WO'112;
- *instant R₄* corresponds to $-\text{C}(=\text{O})\text{Y}_1-$ of WO'112, where Y_1 is $(\text{CR}_7\text{R}_8)_l(\text{CR}_5\text{R}_6)_m(\text{CR}_3\text{R}_4)_n\text{CR}_1\text{R}_2-$, where in a *preferred* embodiment R_1-R_8 are H and I and m are 0 and n is 1, thus resulting in $-\text{C}(=\text{O})\text{CH}_2\text{CH}_2-$ ([67]);
- *instant R₅ and R₆* (not depicted in the above representation) are **absent**; and
- *instant Drug* corresponds to a **cytotoxic agent**— in a *more preferred* embodiment the cytotoxic agent is a **maytansinoid** of structural formula A1 that is connected to the liner with an amide (*i.e.*, peptide) bond ([67]).

69. Although WO'112 teaches linkers and conjugates with preferred and overlapping embodiments that correlate with those instantly claimed, the WO'112 variables of X, Y', Y₁, and Z need to be selected to arrive at the claimed compounds and conjugates. The artisan would have found it obvious to select S for the X variable (*i.e.*, $-\text{X}(=\text{O})-$) as a suitable moiety from a finite list of two possible groups of WO'112, thus teaching the equivalence between $-\text{S}(=\text{O})-$ and $-\text{Se}(=\text{O})-$ moieties as the X variable. As such, the artisan would have been motivated to substitute equivalents known for the same purpose. See also *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958).

70. Additionally, the artisan would have found it obvious to select the variables of Y', Z, and Y₁, respectively as $-\text{S}(=\text{O})_2-$, (alkyl & cycloalkyl), and $-\text{CH}_2\text{CH}_2-$, because these moieties are in fact preferred embodiments of WO'112. The motivation for these selections and preferred embodiments is to develop linking compounds or conjugates that attach covalently to drugs and cell-binding agents having an optimal therapeutic dose with high activity and reduced toxicity with a reasonable expectation of success, thereby arriving at the invention in **claims 3 and 20**. Since the compounds of WO'112 and those instantly claimed are closely similar in structure,

they are further expected to have similar properties. See *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979).

71. **Regarding claims 4, 5, 8, and 10**, WO'112 provides maytansinoids, taxoids, CC-1065, and dolastatin as examples of cytotoxic agents ([47]-[49] and [67]).

72. **Regarding claims 6 and 7**, WO'112 teaches peptides, antibodies, and proteins as cell-binding agents ([97] and [98]).

73. **Regarding claim 9**, WO'112 fails to disclose the specific maleimido groups of 6-maleimidocaproyl, 4-(*N*-maleimidomethyl)cyclohexane-1-carboxylate, maleimidopropanyl, and maleimidoethyl as claimed.

74. However, the artisan recognizes numerous reaction mechanisms available to facilitate suitable conjugation of the linker to the Drug and CBA ([60] and [61]). In particular, WO'112 discloses that maleimide (linking group) is chemically linked to a thiol of a CBA (*e.g.*, mAb) ([61]) via a preferred thioether bond ([60]).

75. At the time of the invention, the artisan would have found it obvious that a linking group having a maleimide functional group *e.g.*, maleimidopropanyl, maleimidoethyl, 6-maleimidocaproyl, and 4-(*N*-maleimidomethyl)cyclohexane-1-carboxylate would readily react with a –SH group of a CBA to form a thioether bond as taught by WO'112. In the absence of unexpected results, the artisan would have been motivated to apply this conventional reaction between a general compound having a maleimide group and a thiol moiety to the specific maleimide-containing conjugates as claimed to produce the preferred thioester bond having an

optimal therapeutic dose while minimizing adverse effects with a reasonable expectation of success.

76. **Regarding claim 11**, the term “cytotoxic agent” of WO’112 refers to any compound resulting in the death of a cell, induces cell death or decreases cell viability ([47] and [161]).

77. **Regarding claim 13**, suitable chemical bonds on the conjugate include peptidase-labile bonds and esterase-labile linkers ([60] and [109]).

78. **Regarding claims 14 and 21**, WO’112 discloses maytansinoids as cytotoxic agents and further exemplifies reacting a thiol-containing cytotoxic agent (*e.g.*, D-SH) with a maleimide-containing heterobifunctional linker to ultimately generate a succinimidyl thioether ([09], [180], claims 55 and 56). WO’112 additionally discloses peptides, proteins, antibodies, especially mAb as cell-binding agents ([97] and [98]). Since there is cytotoxic agent having a –SH and mAb is a CBA both the **1st & 2nd Interpretations** of the *Claim Interpretation* section of this Office action are met by WO’112.

79. **Regarding claims 15-17**, WO’112 discloses pharmaceutical compositions containing linking compounds and conjugates to drugs and antibodies with a pharmaceutically acceptable carrier, thus meeting the pharmaceutically acceptable carrier limitations of **claims 15 and 16** ([10]).

80. WO’112 discloses methods of treating *inter alia* a proliferative disorder, an autoimmune disorder, and a viral disease by administering to a mammal a therapeutically effective amount of the conjugate, thus meeting the therapeutically effective amount limitation in **claims 15 and 17** ([11] and claim 79). WO’112 further teaches the pharmaceutical composition contains an

additional chemotherapeutic agent, thereby meeting the drug limitation of **claim 17** ([11 and [53]-[55] and claims 78 and 80).

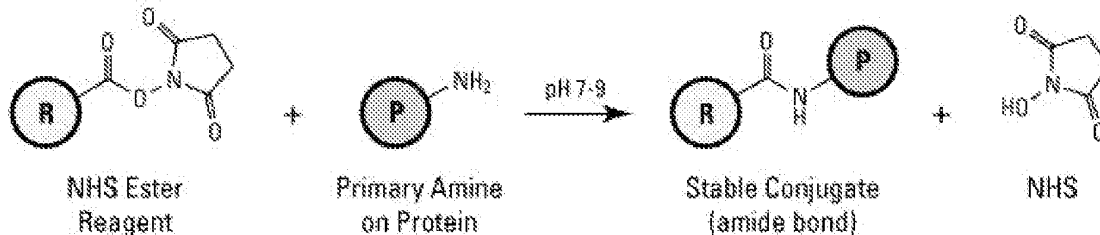
81. **Claims 9, 12, and 13 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over WO'577 as applied to claims 1-4, 6-9, 11-21 above, and further in view of US'345.**

82. **WO'577** was discussed previously.

83. Although WO'577 does not disclose that the linking moiety contains either (1) the amino acid residues of valine-citrulline or alanine-phenylalanine or (2) a *p*-aminobenzyloxycarbonyl (*i.e.*, PABC) component, the hydrophilic linking moiety of WO'577 is suited for forming bonds between the hydrophilic linker and biologically-active compounds (page 60, lines 25-30). The artisan recognizes numerous reaction mechanisms available to facilitate conjugation of the activated PGC to a biologically-active compound. For example, WO'577 discloses reacting⁸ *N*-hydroxysuccimide (NHS) ester with an amine, especially amines present on the N-termini of peptides and proteins, to form an amide bond (page 62, lines 3-29).

84. **Regarding claim 9, US'345** does, however, disclose conjugates that join the drug to the ligand via a peptide linker, namely Val-Cit or Phe-Ala groups. In the linker of US'345, the amino acid residue sequence is specifically tailored to selectively cleave from the drug conjugate

⁸ General Reaction Chemistry for NHS Ester and a Primary Amine:



by a tumor-associated protease. This delivers the drugs at the tumor site in a pharmacologically active form. In comparison with ligand-drug linkers that rely on simple acid hydrolysis for drug release, the enzymatic cleavage *e.g.*, by lysosomal proteases of US'345 provides significantly less systemic toxicity due to premature linker hydrolysis in the blood. Not only do the drug conjugates of US'345 deliver higher drug amounts to the tumor cells, but these methods result in longer storage life and simplified handling conditions for the conjugates (Abstract; from column 1, line 24 to column 2, line 45; column 3, lines 19-36; claim 1; column 4, lines 1-28 and 34-39).

85. It would have been obvious to the artisan to incorporate the tailored amino acid residues of Val-Cit or Phe-Ala as taught by US'345 in the linker moiety of WO'577 to cleave these amino acid residues selectively by a tumor-associated protease. As such, the artisan would have been motivated to include these amino acid modifications of US'345 in the hydrophobic linker of WO'577 to release the drug in a pharmacologically active form at the targeted tumor cells while simultaneously decreasing systemic toxicity and increasing the storage life of the conjugate with a reasonable expectation of success.

86. **Regarding claim 12**, US'345, however, additionally discloses including a self-immolative spacer moiety, preferably PABC (*i.e.*, *p*-aminobenzyloxycarbonyl), in the drug conjugate linker (column 6, lines 20-32). The presence of the self-immolative spacer in the linker expands the distance between the peptide moiety and the drug, thus improving the stability of the drug conjugate by making the drug pharmacologically inactive in the absence of the target enzyme (from column 4, line 54 to column 5, line 15).

87. At the time of the invention, the artisan would have been motivated to incorporate the self-immolative spacer moiety of PABC as taught by US'345 in the linker moiety of WO'577

with a reasonable expectation of successfully improving the stability and release of the drug in a pharmacologically active form after the targeted enzymatic cleavage.

88. **Regarding claim 13**, the amino acid sequence of the drug-conjugate of US'345 is specifically tailored to be enzymatically cleaved by a tumor-associated protease (column 4, lines 25-28 and from column 4, line 54 to column 5, line 15).

89. **Claims 9, 12, and 13 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over WO'497 as applied to claims 3-11, 13-17, 20, and 21 above, and further in view of US'345.**

90. **WO'497** was discussed previously.

91. Although WO'497 does not disclose that the linking moiety contains either (1) the amino acid residues of valine-citrulline or alanine-phenylalanine or (2) a *p*-aminobenzyloxycarbonyl (*i.e.*, PABC) component, WO'497 teaches useful linkers *e.g.*, aliphatic chains, lipids, amino acids or peptides between the polymer carrier and the drug. WO'497 also teaches the polymer spacer and polymer carrier may be joined *inter alia* by an amide bond (page 6, lines 21-24 and 28-31).

92. **Regarding claim 9**, US'345 does, however, disclose conjugates that join the drug to the ligand via a peptide linker, namely Val-Cit or Phe-Ala groups. In the linker of US'345, the amino acid residue sequence is specifically tailored to selectively cleave from the drug conjugate by a tumor-associated protease. This delivers the drugs at the tumor site in a pharmacologically active form. In comparison with ligand-drug linkers that rely on simple acid hydrolysis for drug release, the enzymatic cleavage *e.g.*, by lysosomal proteases of US'345 provides significantly less systemic toxicity due to premature linker hydrolysis in the blood. Not only do the drug

conjugates of US'345 deliver higher drug amounts to the tumor cells, but these methods result in longer storage life and simplified handling conditions for the conjugates (Abstract; from column 1, line 24 to column 2, line 45; column 3, lines 19-36; claim 1; column 4, lines 1-28 and 34-39).

93. It would have been obvious to the artisan to incorporate the tailored amino acid residues of Val-Cit or Phe-Ala as taught by US'345 in the linker moiety of WO'497 to cleave these amino acid residues selectively by a tumor-associated protease. As such, the artisan would have been motivated to include these amino acid modifications of US'345 in the linker of WO'497 to release the drug in a pharmacologically active form at the targeted tumor cells while simultaneously decreasing systemic toxicity and increasing the storage life of the conjugate with a reasonable expectation of success.

94. **Regarding claim 12**, US'345, however, additionally discloses including a self-immolative spacer moiety, preferably PABC (*i.e.*, *p*-aminobenzyloxycarbonyl) in the drug conjugate linker (column 6, lines 20-32). The presence of the self-immolative spacer to the linker expands the distance between the peptide moiety and the drug, thus improving the stability of the drug conjugate by making the drug pharmacologically inactive in the absence of the target enzyme (from column 4, line 54 to column 5, line 15).

95. At the time of the invention, the artisan would have been motivated to include the self-immolative spacer moiety of PABC as taught by US'345 in the linker moiety of WO'497 with a reasonable expectation of successfully improving the stability and release of the drug in a pharmacologically active form after enzymatic cleavage.

96. **Regarding claim 13**, the amino acid sequence of the drug-conjugate of US'345 is specifically tailored to be enzymatically cleaved by a tumor-associated protease (column 4, lines 25-28 and from column 4, line 54 to column 5, line 15).

97. Regarding the proposed rejection of claims 1 and 2 under pre-AIA 35 U.S.C. 103(a) as being unpatentable over the combination of WO'112 and Morales-Sanfrutos, the combination of WO'112 and Morales-Sanfrutos does not disclose or reasonably suggest the subject matter in claims 1 and 2 in view of the following reasons.

98. First, WO'112 does not teach a linking moiety without conjugation to a drug (D) as required by instant claim 1. This is because the WO'112 compound of formula (II) specifies the conjugation to a drug. Second, the WO'112 formula (II) drug attached to $>S=O$ via the Y_1 moiety (*e.g.*, $-C(=O)CH_2CH_2-$) does not teach or reasonably suggest that the cytotoxic drug has a functional group that bonds to the linker via the specifically claimed disulfide, thioether, thioester, hydrazine, ether, ester, carbamate, carbonate, 2°, 3° or 4° amine, imine, cycloheteroalkane, heteroaromatic, alkoxime or amide bonds. Third, since Morales-Sanfrutos is directed to the bioconjugation of proteins to biological macromolecules, detection levels, and solid supports via the Michael-type addition of vinyl sulfones, the combination of WO'112 with Morales-Sanfrutos is counterproductive to arrive at the unconjugated hydrophilic linking moiety of instant claim 1. Fourth, there is no motivation to replace the sulfone ($>S=O$) moiety of WO'112 with the vinylsulfone ($-S(=O)_2-CH=CH_2$) moiety of Morales-Sanfrutos in the linker to arrive at instant claim 1. Consequently, the Morales-Sanfrutos reference fails to correct the inadequate teachings of WO'112 and equally fails to provide the artisan with motivation to arrive at the unconjugated linking moiety of instant claims 1 and 2.

Conclusion

99. Claims 1-21 are pending and undergoing reexamination.

100. Claims 1-21 are rejected.

Extensions of Time

Extensions of time under 37 CFR 1.136(a) will not be permitted in these proceedings because the provisions of 37 CFR 1.136 apply only to “an applicant” and not to parties in a reexamination proceeding. Additionally, 35 U.S.C. 305 requires that *ex parte* reexamination proceedings “will be conducted with special dispatch” (37 CFR 1.550(a)). Extensions of time in *ex parte* reexamination proceedings are provided for in 37 CFR 1.550(c).

Future Amendment

Patent Owner is notified that any proposed amendment to the specification and/or claims in this reexamination proceeding must comply with 37 CFR 1.530(d)-(j), must be formally presented pursuant to 37 CFR 1.52(a) and (b), and must contain any fees required by 37 CFR 1.20(c).

In particular, 37 CFR 1.530(i) states: “All amendments must be made relative to the patent specification, including claims, and drawings, which are in effect as of the date of filing the request for reexamination.” As a result, each amendment to the claims should be made relative to the originally patented claims and not to the previous amendment. Any changes must include brackets (not strikethroughs) for the matter to be omitted and underlining for added matter (See 37 CFR 1.530(f)(1)(2)). The Patent Owner is directed to MPEP 2250 (IV) containing examples of claim amendments in reexamination proceedings.

In addition, Patent Owner is notified to provide a complete listing of all pending claims and their respective status (*i.e.*, original, cancelled, amended, and new) undergoing reexamination that complies with 37 CFR 1.530(d)-(j).

Ongoing Duty to Disclose

The Patent Owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 10,131,682 B2 throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286.

Future Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D.C. Jones whose telephone number is (571) 272-0578. The examiner can normally be reached on Mondays-Fridays from 10:00 am to 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Jean Witz, may be reached at (571) 272-0927. The official fax no. for the organization where this application is assigned is (571) 273-9900.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about Private PAIR Portal homepage: <https://ppair.uspto.gov/epatent/portal/home> and Private PAIR: <https://ppair.uspto.gov/epatent/myportal/privatepair>. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 1-866-217-9197 (toll free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 1-800-786-9199 (In USA or CANADA) or 571-272-1000.

All correspondence relating to this *ex parte* reexamination proceeding should be directed:

By Mail to: Mail Stop *Ex Parte* Reexam
 Central Reexamination Unit
 Commissioner for Patents
 United States Patent & Trademark Office
 P.O. Box 1450
 Alexandria, VA 22313-1450

By FAX to: (571) 273-9900
 Central Reexamination Unit

By hand: Customer Service Window
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Patent Reexamination Specialist
CRU, Art Unit 3991

/Bruce Campell/
Patent Reexamination Specialist
Central Reexamination Unit 3991

/TIMOTHY M SPEER/
Supervisory Patent Examiner, Art Unit 3991

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re <i>Ex Parte</i> Reexamination of	)	MAIL STOP <i>EX PARTE</i>
U.S. Patent No. 10,131,682	)	REEXAMINATION - AMENDMENT
R. Zhao	)	Attn: Central Reexamination Unit
Reexamination Control No.: 90/014,390	)	Group Art Unit: 3991
Filed: October 16, 2019	)	Examiner: JONES, DWAYNE C
For: HYDROPHILIC LINKERS AND	)	Confirmation No.: 4956
THEIR USES FOR CONJUGATION	)	
OF DRUGS TO A CELL BINDING	)	
MOLECULES	)	

**AMENDMENT IN RESPONSE TO OFFICE ACTION IN *EX PARTE*
REEXAMINATION**

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

Commissioner:

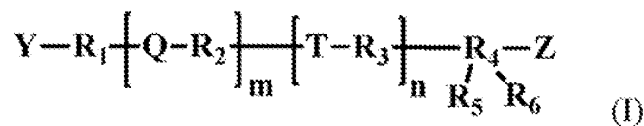
In response to the non-final Office Action issued on June 12, 2020, Patent Owner submits the following amendments and remarks.

AMENDMENTS TO THE CLAIMS:

Please amend claims 1, 3, 18 and 20, and add new claims 22-34. The remaining claims are not changed by this paper and have not been represented below in accordance with 37 C.F.R. § 1.530(d) through (j) and M.P.E.P. § 2250. All changes are shown relative to the set of claims that appear in U.S. Patent No. 10,131,682 issued on November 20, 2018.

LISTING OF CLAIMS:

1. (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)-; when n=1, m=0, T is not -P(=O)(OM)-; and when Q or T is -S(O₂)-, m and n are not 0[.];

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

R₁, R₂, R₃, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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,

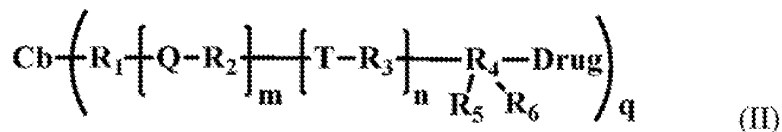
or R₁, R₂, R₃ and R₄ are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R₁, R₂, R₃ and R₄),
provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or branched 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, R₁, R₃ or R₄;

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt.

2. (Original)

3. (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, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

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)-;

R₁, R₂, R₃, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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), provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or branched 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, R₁, R₃ or R₄;

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt,

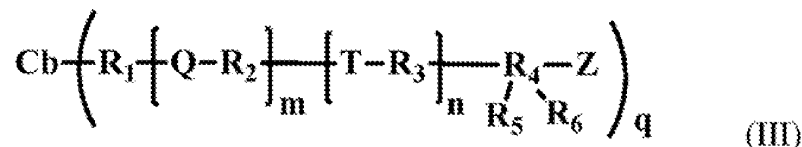
provided that:

when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p, and

when (i) Q is -S(O₂)-, m is 1, and n is 0, or (ii) T is -S(O₂)-, n is 1 and m is 0, R₁ is not a chain of three atoms selected from the group consisting of C and S.

4-17. (Original)

18. (Amended) A compound of formula (III):



wherein:

Cb represents 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)-;

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, hydrazone, ether, ester, carbamate, carbonate, secondary, tertiary, or quaternary amine, imine, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

R₁, R₂, R₃, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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)₂, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or branched chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that

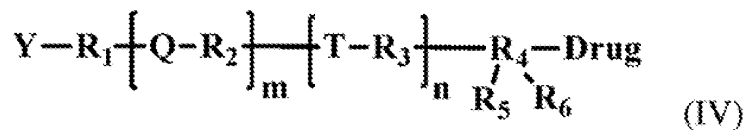
covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug, R₁, R₃ or R₄;

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt.

19. (Original)

20. (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(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)-;

"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, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or

branched alkenyl or alkynyl, or ester, 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), provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or branched 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, R₁, R₃ or R₄;

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt,

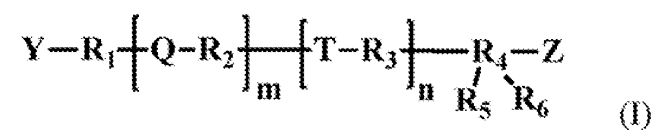
provided that:

when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p, and

when (i) Q is -S(O₂)-, m is 1, and n is 0, or (ii) T is -S(O₂)-, n is 1 and m is 0, Y is an N-hydroxysuccinimide (NHS) ester, p-nitrophenyl ester, dinitrophenyl ester, pentafluorophenyl ester, pyridyldisulfide, nitropyridyldisulfide, maleimide, haloacetate, carboxylic acid chloride, hydrazide or hydroxylamine.

21. (Original)

22. (New) 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)-; when n=1, m=0, T is not -P(=O)(OM)-; and when Q or T is -S(O₂)-, m and n are not 0;

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

R₁, R₂, R₃, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

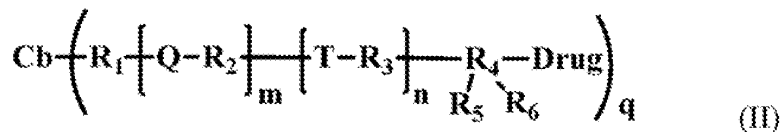
or R₁, R₂, R₃ and R₄ are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R₁, R₂, R₃ and R₄);

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt; and

wherein the hydrophilic linker comprises at least one -P(=O)(OM)-.

23. (New) 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, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

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)-;

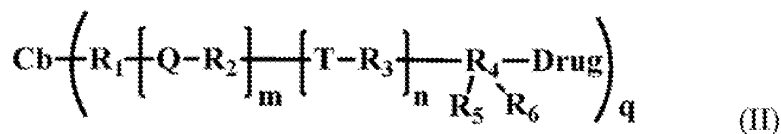
R₁, R₂, R₃, and R₄, are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula (OCH₂CH₂)_p, 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 absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt, and wherein the conjugate comprises at least one -P(=O)(OM)-.

24. (New) 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, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

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

m and n are integer from 1 to 5;

R₁, R₂, R₃, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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), provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or branched 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, R₁, R₃ or R₄,

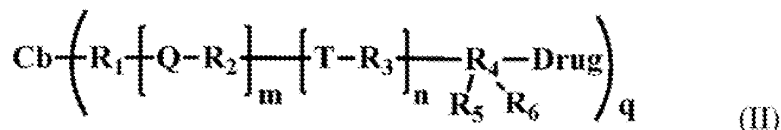
provided that when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p;

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt.

25. (New) The cell-binding agent-drug conjugate of claim 24, wherein when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p; and each of remaining R₁, R₂, R₃ and R₄ comprises an alkyl or (OCH₂CH₂)_p.

26. (New) 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, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

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

m and n are integer from 1 to 5;

R₁, R₂, R₃, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or

branched alkenyl or alkynyl, or ester, 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,

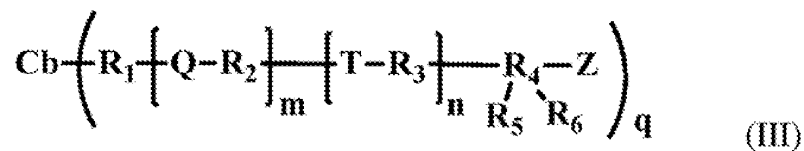
or R₁, R₂, R₃ and R₄ are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R₁, R₂, R₃ and R₄), provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or branched 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, R₁, R₃ or R₄;

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt,

provided that when Q and T are each independently -S(O₂)- or -S(O)-, m is 1 and n is 1, R₂ is absent, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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 R₂ is a branched 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, R₃ or R₄.

27. (New) A compound of formula (III):



wherein:

Cb represents 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)-;

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, hydrazone, ether, ester, carbamate, carbonate, secondary, tertiary, or quaternary amine, imine, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

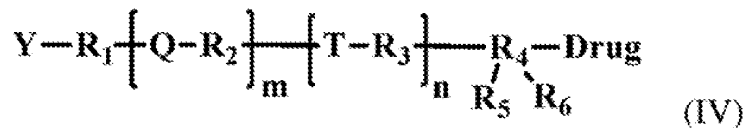
R₁, R₂, R₃, and R₄, are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula (OCH₂CH₂)_p, 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 absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt, and wherein the conjugate comprises at least one -P(=O)(OM)-.

28. (New) 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(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)-;

"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;

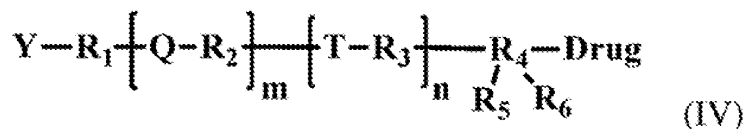
R₁, R₂, R₃, and R₄, are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula (OCH₂CH₂)_p, 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 absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt, and wherein the conjugate comprises at least one -P(=O)(OM)-.

29. (New) 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(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)-;

"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, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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), provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or branched 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, R₁, R₃ or R₄;

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

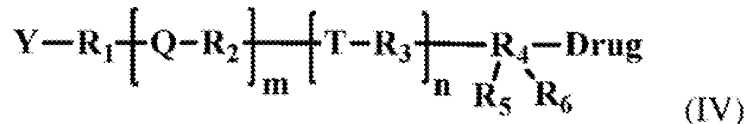
M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt,

provided that:

when Q and T are each independently -S(O₂)- or -S(O)-, m is 1 and n is 1, R₂ is absent, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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 R₂ is a branched 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, R₃ or R₄; and

when (i) Q is -S(O₂)-, m is 1, and n is 0, or (ii) T is -S(O₂)-, n is 1 and m is 0, Y is an N-hydroxysuccinimide (NHS) ester, p-nitrophenyl ester, dinitrophenyl ester, pentafluorophenyl ester, pyridyldisulfide, nitropyridyldisulfide, maleimide, haloacetate, carboxylic acid chloride, hydrazide or hydroxylamine.

30. (New) 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(O₂)-, or -S(O)-;

m and n are integer from 1 to 5;

"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, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear

alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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), provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or branched 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, R₁, R₃ or R₄;

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt,

provided that when Q and T are each independently -S(O₂)- or -S(O)-, m is 1 and n is 1, R₂ is absent, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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 R₂ is a branched 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, R₃ or R₄.

31. (New) The compound of claim 30, wherein when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p.

32. (New) The compound of claim 31, wherein when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p; and each of remaining R₁, R₂, R₃ and R₄ comprises an alkyl or (OCH₂CH₂)_p.

33. (New) The conjugate of claim 3, wherein when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p; and each of remaining R₁, R₂, R₃ and R₄ comprises an alkyl or (OCH₂CH₂)_p.

34. (New) The compound of claim 20, wherein when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p; and each of remaining R₁, R₂, R₃ and R₄ comprises an alkyl or (OCH₂CH₂)_p.

REMARKS

In view of the above amendments and the following remarks, Patent Owner respectfully requests reconsideration of the rejections set forth in the Office Action of June 12, 2020 ("Office Action").

I. Statement of the Substance of the Interview

Patent Owner wishes to thank Examiners Dwanye Jones, Bruce Campell and Jean Witz (hereinafter collectively "Examiner") for their participation in a telephonic interview conducted on August 11, 2020. During the interview, the proposed claim amendments and the cited references were discussed.

First, the Examiner pointed out potential non-compliance and 112 issues with the proposed claim 1 and reproduced issued claim 4. It was agreed that the non-amended original claims will not be presented in the Amendment. Patent Owner's representative agreed to make the corrections in claim 1.

Patent Owner's representative then explained the claim amendments proposed for independent claims 1, 3, 18 and 20, and how the claims as amended differ from the compounds disclosed in the cited references.

Specifically, WO '577 discloses compounds wherein Q, which allegedly corresponds to R₂ in formulae (I)-(IV) recited in claims 1, 3, 18 and 20 of the present patent, respectively, is required to have a cyclic structure. On the other hand, R₂ as defined in claims 1, 3, 18 and 20 as amended does not contain a cyclic structure. The Examiner agreed that such amendment is sufficient to overcome the rejections based on WO '577.

Turning to WO '497, WO '497 allegedly discloses compounds corresponding to formula (II) recited in claim 3 of the present patent wherein R₁ is S-CH₂-CH₂, and corresponding to formula (IV) recited in claim 20 of the present patent wherein Y is vinyl. On the other hand, claim 3 as amended recites that when (i) Q is -S(O₂)-, m is 1, and n is 0, or (ii) T is -S(O₂)-, n is 1 and m is 0, R₁ is not a chain of three atoms selected from the group consisting of C and S. Further, claim 20 as amended recites that when (i) Q is -S(O₂)-, m is 1, and n is 0, or (ii) T is -S(O₂)-, n is 1 and m is 0, Y is an N-hydroxysuccinimide (NHS) ester, p-nitrophenyl ester, dinitrophenyl ester, pentafluorophenyl ester, pyridyldisulfide, nitropyridyldisulfide, maleimide,

haloacetate, carboxylic acid chloride, hydrazide or hydroxylamine. The Examiner agreed that claims 3 and 20 as amended do not encompass the compounds of WO '497.

Further, the Examiner agreed that WO '497 does not disclose compounds of formulae (II) and (IV) wherein m is 1-5 and n is 1-5.

Turning to WO '112, claims 3 and 20 as amended recite that when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p. The Examiner agreed that such amendments would exclude the compounds of WO '112 and requested that Patent Owner pointed out the relevant definitions/descriptions in WO '112. In this regard, in annotated formula (IV) of WO '112, the portions allegedly corresponding to R₁, R₂, and R₄ in formula (II) recited in claim 3 of the present patent are respectively Z-M', CH₂CH₂, and C(=O)Y₁, wherein Y₁ represents (CR₇R₈)₁(CR₅R₆)_m(CR₃R₄)_nCR₁R₂, Z is alkyl, a cycloalkyl, a heterocyclyl, an aryl, a heteroaryl, or -N(R^b)-R^d-, and M' is a linking moiety, for example, -C(=O)-, -NH-C(=O)-CH₂-, -S-, -CH₂S-, -CH(Me)-S-, -C(Me₂)-S-, -NR⁸-, -CH₂NR⁸-, or -NR⁸N=, wherein R⁸ is -H or a C₁₋₄ alkyl (WO '112, paragraphs [0067], [0074] and [0075]). That is, none of these portions contains a polyethyleneoxy unit of formula (OCH₂CH₂)_p.

The Examiner also agreed that WO '112 does not disclose the compounds of formulae (II) and (IV) recited in claims 3 and 20 of the present patent wherein when m is 1 and n is 1, R₂ is not a linear alkyl or straight chain of atoms.

Turning to US '053, the Examiner explained the reasons for the modification of the compound of US '053 and indicated that US '053 does not disclose the compounds of formula (II) recited in claim 3 of the present patent wherein when (i) Q is -S(O₂)-, m is 1, and n is 0, or (ii) T is -S(O₂)-, n is 1 and m is 0, R₁ is not a chain of three atoms selected from the group consisting of C and S.

Finally, the Examiner kindly reminded the manner for presenting claim amendments and that a response should include a section of Statement of the Substance of the Interview.

II. Status of Claims

Claims 1-21 of U.S. Patent No. 10,131,682 (herein "the present patent") are subject to reexamination. Claims 1, 3, 18 and 20 are independent claims. Claim 2 depends from claim 1.

Claims 4-17 depend from claim 3. Claim 19 depends from claim 18. Claim 21 depends from claim 20.

In the Amendment, claims 1, 3, 18 and 20 have been amended, and new claims 22-34 have been added.

Specifically, claims 1, 3, 18 and 20 have been amended to recite provisos that “when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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 ... when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or branched 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, R₁, R₃ or R₄.” Support for these amendments can be found in the patent, for example, issued claims 1, 3, 18 and 20 of the present patent.

Claims 3 and 20 have been amended to recite a proviso that “when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p.” Support for these amendments can be found in the patent, for example, issued claims 3 and 20 of the present patent; col. 9, lines 8-10; and Figs. 8, 9 and 12.

Claim 3 has also been amended to recite a proviso that “when (i) Q is -S(O₂)-, m is 1, and n is 0, or (ii) T is -S(O₂)-, n is 1 and m is 0, R₁ is not a chain of three atoms selected from the group consisting of C and S.” Support for this amendment can be found in the patent, for example, issued claim 3 of the present patent.

Claim 20 has also been amended to recite proviso that “when (i) Q is -S(O₂)-, m is 1, and n is 0, or (ii) T is -S(O₂)-, n is 1 and m is 0, Y is an N-hydroxysuccinimide (NHS) ester, p-nitrophenyl ester, dinitrophenyl ester, pentafluorophenyl ester, pyridyldisulfide, nitropyridyldisulfide, maleimide, haloacetate, carboxylic acid chloride, hydrazide or hydroxylamine. Support for this amendment can be found in the patent, for example, col. 8, lines 61-67; and col. 13, lines 51-60.

New claims 22, 23, 27 and 28 correspond to issued claims 1, 3, 18 and 20 of the present patent, respectively, and further recite that the hydrophilic linker/conjugate/compound comprises

at least one -P(=O)(OM)-. Support for claims 22, 23, 27 and 28 can be found in the disclosure, for example, issued claims 1, 3, 18 and 20 of the present patent.

New claim 24 corresponds to issued claim 3 of the present patent, and further defines m, n and R₁-R₄. Support for claim 24 can be found in the disclosure, for example, issued claim 3 of the present patent; col. 9, lines 8-10; and Figs. 8, 9 and 12.

New claim 25 depends from claim 24, and further defines R₁-R₄. Support for claim 25 can be found in the disclosure, for example, col. 9, lines 8-10.

New claim 26 corresponds to issued claim 3 of the present patent, and further defines m, n and R₂. Support for claim 26 can be found in the disclosure, for example, issued claim 3 of the present patent.

New claim 29 corresponds to issued claim 20 of the present patent, and further defines R₂. Support for claim 24 can be found in the disclosure, for example, issued claim 20 of the present patent; col. 8, lines 61-67; and col. 13, lines 51-60.

New claim 30 corresponds to issued claim 20 of the present patent, and further defines m, n and R₂. Support for claim 30 can be found in the disclosure, for example, issued claim 20 of the present patent; col. 9, lines 8-10; and Figs. 8, 9 and 12.

New claim 31 depends from claim 30, and further defines R₁-R₄. Support for claim 31 can be found in the disclosure, for example, col. 9, lines 8-10.

New claim 32 depends from claim 30, and further defines R₁-R₄. Support for claim 32 can be found in the disclosure, for example, col. 9, lines 8-10.

New claim 33 depends from claim 3, and further defines R₁-R₄. Support for claim 33 can be found in the disclosure, for example, col. 9, lines 8-10.

New claim 34 depends from claim 20, and further defines R₁-R₄. Support for claim 34 can be found in the disclosure, for example, col. 9, lines 8-10.

Upon entry of the present amendments, claims 1-34 will be pending. No new matter is being added by the above amendments, and the amendments do not enlarge the scope of the claims being presented.

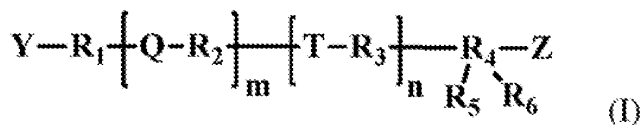
III. Response to Rejections under 35 U.S.C. §§ 102 and 103

- a. Claims 3-8, 10-12, 14-16, 20, and 21 were rejected under pre-AIA 35 U.S.C. § 102(b) as allegedly being anticipated by WO02/087497 (herein “WO ‘497”).
- b. Claims 3-8, 10, 11, 13, 14, 15, and 16 were rejected under pre-AIA 35 U.S.C. § 102(b) as allegedly being anticipated by, or in the alternative, pre-AIA 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent Application Publication No. 2004/0185053 to Govindan (herein “US ‘053”) as evidenced by Handbook of Preservatives.
- c. Claims 1-4, 6-9, and 11-21 were rejected under pre-AIA 35 U.S.C. § 103(a) as allegedly being unpatentable over WO03/061577 (herein “WO ‘577”).
- d. Claims 3-11, 13-17, 20, and 21 were rejected under pre-AIA 35 U.S.C. § 103(a) as allegedly being unpatentable over WO2012/145112 (herein “WO ‘112”).
- e. Claims 9, 12, and 13 were rejected under pre-AIA 35 U.S.C. § 103(a) as allegedly being unpatentable over WO ‘577 and further in view of U.S. Patent No. 6,214,345 to Firestone et al. (herein “Firestone et al.”).
- f. Claims 9, 12, and 13 were rejected under pre-AIA 35 U.S.C. § 103(a) as allegedly being unpatentable over WO ‘497 and further in view of Firestone et al.

Patent Owner respectfully submits that the claims as amended are novel and patentable over the cited references for at least the following reasons.

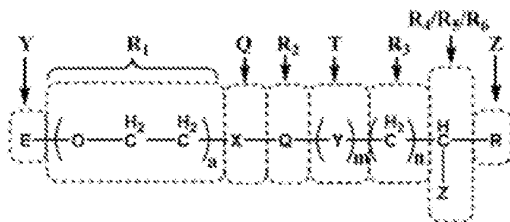
I. Independent Claim 1

Claim 1 recites a hydrophilic linker of formula (I):



WO ‘577

The Office Action cited WO ‘577 as allegedly disclosing following formula Ia:



WO '577 discloses that Q is a C3 to C8 saturated or unsaturated *cyclic alkyl or cyclic heteroalkyl* (including fused bicyclic and bridged bi cyclic ring structures), a substituted or unsubstituted *aryl or heteroaryl* group, or a substituted or unsubstituted *alkaryl* wherein the alkyl is a C1 to C20 saturated or unsaturated alkyl or heteroalkaryl group, wherein the substituents are selected from the group consisting of halogen, hydroxyl, carbonyl, carboxylate, ester, formyl, acyl, thiocarbonyl, thioester, thioacetate, thiofonnate, alkoxy, phosphoryl, phosphonate, phosphinate, amino, amido, amidine, imine, cyano, nitro, azido, sulfhydryl, sulfate, sulfonamido, sulfonyl, heterocyclyl, aralkyl, aromatic moiety, heteroaromatic moiety, imino, sulfamoyl, sulfonate, silyl, ether, and alkylthio (pages 5-6).

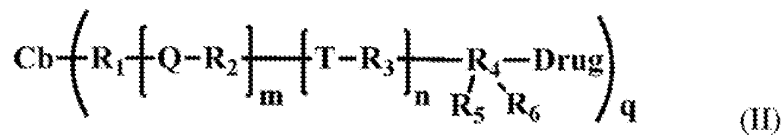
That is, Q, which allegedly corresponds to R₂ in formula (I) recited in claim 1 of the present patent, is required to have a cyclic structure.

On the other hand, R₂ in formula (I) recited in claim 1 of the present patent, as amended, is, when Q and T is SO or SO₂, not a cyclic group by itself.

For at least this reason, the above compound of formula Ia described in WO '577 does not meet all the requirements for formula (I) recited in claim 1 of the present patent, which the Examiner agreed during the Interview.

II. Independent Claim 3

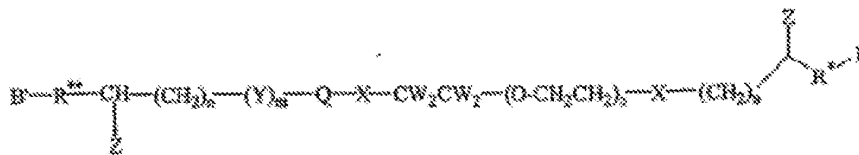
Claim 3 recites a cell-binding agent-drug conjugate of formula (II):



II-1. WO '577

The Office Action cited WO '577 as allegedly disclosing the following:

Formula XXIV:



Note that in formula XXIV of WO '577, Q is defined (pages 85-86) as the same as in formula I discussed in above Section I. That is, Q, which allegedly corresponds to R₂ in formula (II) recited in claim 3 of the present patent, is required to have a cyclic structure.

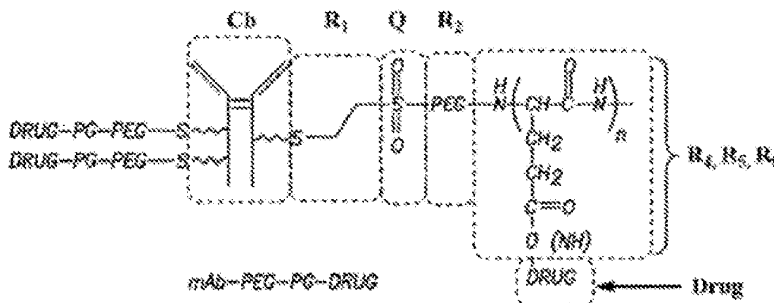
On the other hand, R₂ in formula (II) recited in claim 3 of the present patent, as amended, is, when Q and T is SO or SO₂, not a cyclic group by itself. For at least this reason, WO '577 does not disclose all the features of claim 3 of the present patent, which the Examiner agreed during the Interview.

Firestone et al. was cited merely against dependent claims 9, 12 and 13, and does not rectify the above noted deficiency of WO '577. As such, the proposed combination of WO '577 and Firestone et al. still would not lead to the claimed invention defined in claim 3 of the present patent.

II-2. WO '497

WO '497 relates to conjugate molecules comprising a ligand or targeting moiety bonded to a polymer spacer, a polymer carrier bonded to the polymer spacer, and a therapeutic agent bound to the polymer carrier (with or without a linker) (abstract).

The Office Action cited WO '497 as allegedly disclosing the following compound which corresponding to formula (II) recited in claim 3 of the present patent wherein R₅ and R₆ are absent, and R₄ is an ester/amide with 5C atoms:



Patent Owner respectfully disagrees.

(a) In the case that the blocked portion when n is 1 (hereinafter “Portion I”) is considered by the Examiner to correspond to R₄ in formula (II) of claim 3 of the present patent:

Portion I is covalently connected to “R₂”, Drug and the unspecified polymer carrier (i.e., three covalent bonding).

On the other hand, in formula (II) recited in claim 3 of the present patent, R₄ is covalently connected to R₂ (or R₃) and Drug (i.e., two covalent bonding), which is different from Portion I of WO ‘497. That is, Portion I does not meet the requirements for R₄ in formula (II) of claim 3 of the present patent, wherein R₅ and R₆ are absent.

(b) In the case that the blocked portion taking into consideration of the entire polymer spacer (“n” repeating units) and carrier (hereinafter “Portion II”), is considered to correspond to R₄ in formula (II) of claim 3 of the present patent:

WO ‘497 discloses that the polymer carrier preferably has a number average molecular weight of at least about 1,000 daltons and the poly(l-glutamic acid) preferably has a number average molecular weight of about 1,000 daltons to about 100,000 daltons (page 7, lines 14-17). In Example 2 of WO ‘497, which is depicted in Fig. 2, poly(l-glutamic acid) (PG, MW 31K) was used (page 15, lines 6-7). It is clear to one of ordinary skill in the art that Portion II would include far more than 6 carbon atoms. As such, Portion II cannot be “an ester/amide with 5 C atoms” and does not meet the requirements for R₄ in formula (II) of claim 3 of the present patent.

In view of the foregoing, Patent Owner respectfully submits that the rejections of claim 3 based on WO ‘497 (Group 1) are improper.

Moreover, claim 3 of the present patent as amended recites that when (i) Q is -S(O₂)-, m is 1, and n is 0, or (ii) T is -S(O₂)-, n is 1 and m is 0, R₁ is not a chain of three atoms selected from the group consisting of C and S.

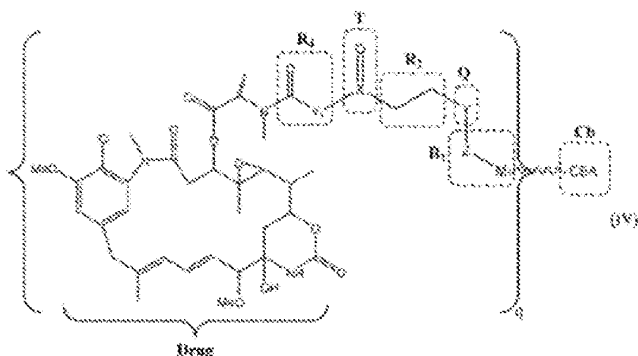
On the other hand, the portion in the above compound of WO ‘497, which allegedly corresponds to R₁ in formula (II) of claim 3 of the present patent, is -CH₂-CH₂-S- which is a chain containing three atoms.

For at least this reason, the above compound of WO ‘497 does not meet all the requirements for formula (II) of claim 3 of the present patent, which the Examiner agreed during the Interview.

Firestone et al. was cited merely against dependent claims 9, 12 and 13, and does not rectify the above noted deficiency of WO '497. As such, the proposed combination of WO '497 and Firestone et al. still would not lead to the claimed invention defined in claim 3 of the present patent.

II-3. WO '112

The Office Action cited WO '112 as allegedly disclosing the following formula (IV):



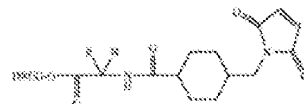
In the above formula, none of the portions allegedly corresponding to R_1 , R_2 and R_4 in formula (II) of claim 3 of the present patent contains a polyethyleneoxy unit of formula $(OCH_2CH_2)_p$. Specifically, in above annotated formula (IV) of WO '112, the portions allegedly corresponding to R_1 , R_2 , and R_4 in formula (II) recited in claim 3 of the present patent are respectively $Z-M'$, CH_2CH_2 , and $C(=O)Y_1$, wherein Y_1 represents $(CR_7R_8)_l(CR_5R_6)_m(CR_3R_4)_nCR_1R_2$, Z is alkyl, a cycloalkyl, a heterocyclyl, an aryl, a heteroaryl, or $-N(R^b)-R^d$, and M' is a linking moiety, for example, $-C(=O)-$, $-NH-C(=O)-CH_2$, $-S-$, $-CH_2S-$, $-CH(Me)-S-$, $-C(Me_2)-S-$, $-NR^8-$, $-CH_2NR^8-$, or $-NR^8N=$, wherein R^8 is $-H$ or a C_{1-4} alkyl (paragraphs [0067], [0074] and [0075]). It is clear that none of the above mentioned portions contains a polyethyleneoxy unit of formula $(OCH_2CH_2)_p$.

On the other hand, claim 3 of the present patent as amended recites that when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, at least one of R_1 , R_2 , R_3 and R_4 comprises the polyethyleneoxy unit of formula $(OCH_2CH_2)_p$.

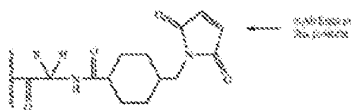
For at least this reason, the above compound of formula (IV) described in WO '112 does not meet all the requirements for formula (II) defined in claim 3 of the present patent, which the Examiner agreed during the Interview.

II-4. US '053

The Office Action cited US '053 as allegedly teaching reacting



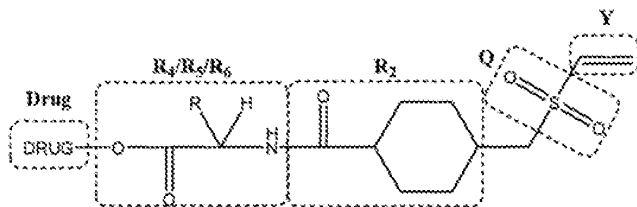
, where the R moiety is the side chain of an amino acid and  moiety, with the targeting moiety (*e.g.*, mAb) via the thiol group at the thiol-reactive group *e.g.*, a maleimide,



US '053 also discloses thiol reactive groups including maleimide, chloroacetamide, bromoacetamide, iodoacetamide, and vinylsulfone that bond to a thiol group on the targeting moiety.

The Office Action further alleged that “one skilled in the art would at once envisage the instantly claimed vinyl sulfone species from a small genus of five well-delineated, thiol-reactive groups,” or it would have been obvious to “[substitute] one thiol-reactive group, *i.e.*, maleimide, from a list of recognized equivalents,” resulting in the following linker-drug compound: DRUG-O-C(=O)CRH₂NH-SO₂-CH=CH₂, which then reacts with a thiol (-SH) of mAb and provides DRUG-O-C(=O)CRH₂NH-SO₂-CH₂CH₂-S-mAb (Office Action at pages 11-12).

The Examiner appeared to miss a portion in the proposed structure. It is presumed that the following structure was intended:



It is clear that in the above formula, the portion allegedly corresponding to R₂ in formula (II) of claim 3 of the present patent contains a cyclic structure.

On the other hand, R₂ as defined in claim 3 of the present patent as amended does not encompass a cyclic structure.

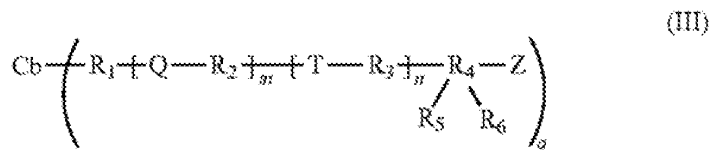
For at least this reason, the above compound of US '053 does not meet all the requirements for formula (II) of claim 3 of the present patent.

Moreover, US '053 states that "the cyclohexyl group in the linker is thought to stabilize the amide functionality formed from the reaction of SMCC [succinimidyl [4-maleimidomethyl]cyclohexane-1-carboxylate] and the amino acid α -amino group" (paragraph [0047]). As such, one of ordinary skill in the art understands the criticality of the cyclohexyl group and would not have been motivated to replace the cyclohexyl group.

Additionally, claim 3 of the present patent as amended recites that when (i) Q is $-\text{S}(\text{O}_2)-$, m is 1, and n is 0, or (ii) T is $-\text{S}(\text{O}_2)-$, n is 1 and m is 0, R_1 is not a chain of three atoms selected from the group consisting of C and S. The Examiner agreed that US '053 fails to teach this feature.

III. Independent Claim 18

Claim 18 recites a compound of formula (III):



WO '577

The Office Action cited WO '577 as allegedly disclosing the following:



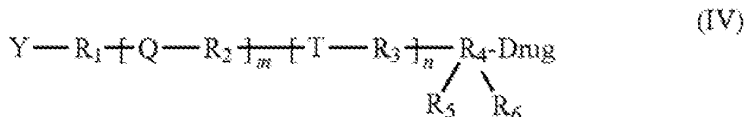
In the above formula of WO '577, Q is defined (page 22) as the same as in formula I discussed in above Section I. That is, Q, which allegedly corresponds to R_2 in formula (III) recited in claim 18 of the present patent, is required to have a cyclic structure.

On the other hand, R_2 in formula (III) recited in claim 18 of the present patent, as amended, is, when Q and T are each independently $-\text{S}(\text{O}_2)-$ or $-\text{S}(\text{O})-$, not a cyclic group by itself.

For at least this reason, the above compound of WO '577 does not meet all the requirements of formula (III) recited in claim 18 of the present patent, which the Examiner agreed during the Interview.

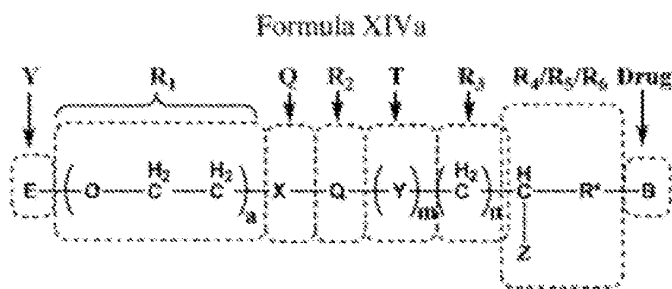
IV. Independent Claim 20

Claim 20 recites a conjugate of formula (IV):



IV-1. WO '577

The Office Action cited WO '577 as allegedly disclosing the following formula XIVa:



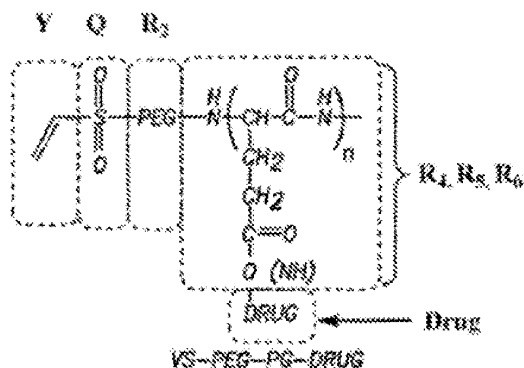
In the above formula of WO '577, Q is defined (page 22) as the same as in formula I discussed in above Section I. That is, Q, which allegedly corresponds to R₂ in formula (IV) recited in claim 20 of the present patent, is required to have a cyclic structure.

On the other hand, R₂ in formula (IV) recited in claim 20 of the present patent, as amended, is, when Q and T are each independently -S(O₂)- or -S(O)-, not a cyclic group by itself.

For at least this reason, the above compound of WO '577 does not meet all the requirements of formula (IV) recited in claim 20 of the present patent, which the Examiner agreed during the Interview.

IV-2. WO '497

The Office Action cited WO '497 as allegedly disclosing the following formula:



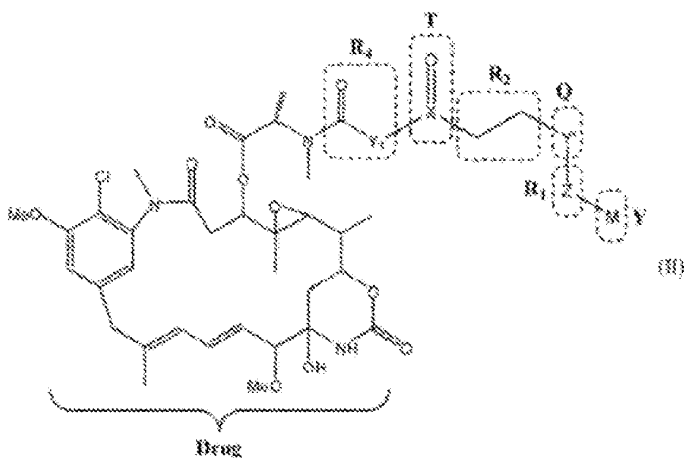
In the above formula of WO '497, the portion allegedly corresponding to Y in formula (IV) recited in claim 20 of the present patent, is a vinyl group (-=).

On the other hand, claim 20 of the present patent, as amended, recites that "when (i) Q is -S(O₂)-, m is 1, and n is 0, or (ii) T is -S(O₂)-, n is 1 and m is 0, Y is an N-hydroxysuccinimide (NHS) ester, p-nitrophenyl ester, dinitrophenyl ester, pentafluorophenyl ester, pyridyldisulfide, nitropyridyldisulfide, maleimide, haloacetate, carboxylic acid chloride, hydrazide or hydroxylamine," which does not encompass a vinyl group.

For at least this reason, the above compound of WO '497 does not meet all the requirements of formula (IV) recited in claim 20 of the present patent, which the Examiner agreed during the Interview.

IV-3. WO '112

The Office Action cited WO '112 as allegedly disclosing the following formula (II):



In the above formula, none of the portions allegedly corresponding to R₁, R₂ and R₄ in formula (IV) of claim 20 of the present patent contains a polyethyleneoxy unit of formula (OCH₂CH₂)_p. Specifically, in above annotated formula (II) of WO '112, the portions allegedly corresponding to R₁, R₂, and R₄ in formula (II) recited in claim 3 of the present patent are respectively Z, CH₂CH₂, and C(=O)Y₁, wherein Y₁ represents (CR₇R₈)_l(CR₅R₆)_m(CR₃R₄)_nCR₁R₂, and Z is alkyl, a cycloalkyl, a heterocyclyl, an aryl, a heteroaryl, or -N(R^b)-R^d- (paragraphs [0067] and [0075]). It is clear that none of the above mentioned portions contains a polyethyleneoxy unit of formula (OCH₂CH₂)_p.

On the other hand, claim 20 of the present patent as amended recites that when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p.

For at least this reason, the above compound of formula (II) described in WO '112 does not meet all the requirements for formula (IV) defined in claim 20 of the present patent.

In view of the foregoing, Patent Owner respectfully submits that claims 1, 3, 18 and 20 are novel and patentable over the cited references. Claims 2, 4-17, 19 and 21 depend from claim 1, 3, 18 or 20, and thus are patentable at least by virtue of their dependency. Accordingly, the rejections should be withdrawn.

IV. New Claims

a. New claims 22, 23, 27 and 28 correspond to issued claims 1, 3, 18 and 20 of the present patent, respectively, and further recite that the hydrophilic linker/conjugate/compound comprises at least one -P(=O)(OM)-. None of the compounds in the cited references relied upon by the Examiner contains -P(=O)(OM)-.

b. New claim 24 corresponds to issued claim 3 of the present patent, and further recites that: (i) m and n are integer from 1 to 5; (ii) when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p; and (iii) when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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 R₂ is a straight or branched 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, R₁, R₃ or R₄.

On the other hand, as noted above, in the compounds of WO '577, which were relied upon by the Examiner, Q, which allegedly corresponds to R₂ in formulae (II) recited in claim 24, is required to have a cyclic structure.

Further, the compounds of WO '497, which were relied upon by the Examiner, contain only one SO₂, and do not correspond to formulae (II) recited in claim 24 wherein m and n are integer from 1 to 5.

Still further, as noted above, in the compounds of WO '112, none of the portions allegedly corresponding to R₁, R₂, and R₄ in formula (II) recited in claim 24 are respectively contains a polyethyleneoxy unit of formula (OCH₂CH₂)_p. Therefore, those compounds do not correspond to formulae (II) recited in claim 24 wherein when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p.

Moreover, the compounds of US '053, which were relied upon by the Examiner, contain only one SO₂, and do not correspond to formulae (II) recited in claim 24 wherein m and n are integer from 1 to 5.

c. New claim 26 corresponds to issued claim 3 of the present patent, and further recites that: (i) m and n are integer from 1 to 5; (ii) when Q and T are each independently -S(O₂)- or -S(O)-, m is 1 and n is 1, R₂ is absent, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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 R₂ is a branched 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, R₃ or R₄; and (iii) when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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 R₂ is a straight or branched 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, R₁, R₃ or R₄.

On the other hand, as noted above, in the compounds of WO '577, which were relied upon by the Examiner, Q, which allegedly corresponds to R₂ in formulae (II) recited in claim 26, is required to have a cyclic structure.

Further, the compounds of WO '497, which were relied upon by the Examiner, contain only one SO₂, and do not correspond to formulae (II) recited in claim 26 wherein m and n are integer from 1 to 5.

Still further, as noted above, in the compounds of WO '112, the portion allegedly corresponding to R₂ in formula (II) recited in claim 26 is CH₂CH₂. Therefore, those compounds do not correspond to formulae (II) recited in claim 26 wherein when Q and T are each independently -S(O₂)- or -S(O)-, m is 1 and n is 1, R₂ is absent, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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 R₂ is a branched 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, R₃ or R₄.

Moreover, the compounds of US '053, which were relied upon by the Examiner, contain only one SO₂, and do not correspond to formulae (II) recited in claim 26 wherein m and n are integer from 1 to 5.

d. New claim 29 corresponds to issued claim 20 of the present patent, and further recites that: (i) when Q and T are each independently -S(O₂)- or -S(O)-, m is 1 and n is 1, R₂ is absent, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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 R₂ is a branched 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, R₃ or R₄; (ii) when (i') Q is -S(O₂)-, m is 1, and n is 0, or (ii') T is -S(O₂)-, n is 1 and m is 0, Y is an N-hydroxysuccinimide (NHS) ester, p-nitrophenyl ester, dinitrophenyl ester, pentafluorophenyl

ester, pyridyldisulfide, nitropyridyldisulfide, maleimide, haloacetate, carboxylic acid chloride, hydrazide or hydroxylamine; and (iii) when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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 R₂ is a straight or branched 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, R₁, R₃ or R₄.

On the other hand, as noted above, in the compounds of WO '577, which were relied upon by the Examiner, Q, which allegedly corresponds to R₂ in formulae (IV) recited in claim 29, is required to have a cyclic structure.

Further, as noted above, in the compounds of WO '497, which were relied upon by the Examiner, the portion allegedly corresponding to Y in formula (IV) recited in claim 29, is a vinyl group (=). Accordingly, those compounds do not correspond to formula (IV) recited in claim 29 wherein when (i) Q is -S(O₂)-, m is 1, and n is 0, or (ii) T is -S(O₂)-, n is 1 and m is 0, Y is an N-hydroxysuccinimide (NHS) ester, p-nitrophenyl ester, dinitrophenyl ester, pentafluorophenyl ester, pyridyldisulfide, nitropyridyldisulfide, maleimide, haloacetate, carboxylic acid chloride, hydrazide or hydroxylamine.

Moreover, as noted above, in the compounds of WO '112, which were relied upon by the Examiner, the portion allegedly corresponding to R₂ in formula (IV) recited in claim 29, is CH₂CH₂. Accordingly, those compounds do not correspond to formula (IV) recited in claim 29 wherein when Q and T are each independently -S(O₂)- or -S(O)-, m is 1 and n is 1, R₂ is absent, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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 R₂ is a branched 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, R₃ or R₄.

e. New claim 30 corresponds to issued claim 20 of the present patent, and further recites that: (i) m and n are integer from 1 to 5; (ii) when Q and T are each independently -S(O₂)- or -

S(O)-, m is 1 and n is 1, R₂ is absent, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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 R₂ is a branched 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, R₃ or R₄; and (iii) when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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 R₂ is a straight or branched 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, R₁, R₃ or R₄.

On the other hand, as noted above, in the compounds of WO '577, which were relied upon by the Examiner, Q, which allegedly corresponds to R₂ in formulae (II) recited in claim 30, is required to have a cyclic structure.

Further, the compounds of WO '497, which were relied upon by the Examiner, contain only one SO₂, and do not correspond to formulae (IV) recited in claim 30 wherein m and n are integer from 1 to 5.

Moreover, as noted above, in the compounds of WO '112, the portion allegedly corresponding to R₂ in formula (IV) recited in claim 30 is CH₂CH₂. Therefore, those compounds do not correspond to formulae (IV) recited in claim 30 wherein when Q and T are each independently -S(O₂)- or -S(O)-, m is 1 and n is 1, R₂ is absent, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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 R₂ is a branched 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, R₃ or R₄.

In view of the foregoing, Patent Owner respectfully submits that claims 22-24 and 26-30 are patentable over the cited references. Further, claims 25 and 31-34 depend from claims 24, 30, 3 and 20, respectively, and thus are patentable at least by virtue of their dependency.

V. Conclusion

From the foregoing, allowance of all the pending claims under reexamination is believed to be next in order and such action is earnestly solicited. If there are any questions concerning this paper or the patent 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: August 12, 2020

By: /Fang Liu/
Fang Liu
Registration No. 51283

Customer No. 21839
703 836 6620

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re <i>Ex Parte</i> Reexamination of	)	MAIL STOP <i>EX PARTE</i>
	)	REEXAMINATION
U.S. Patent No. 10,131,682	)	
	)	Group Art Unit: 3991
Reexamination Control No.: 90/014,390	)	
	)	Examiner: JONES, DWAYNE C
Filed: October 16, 2019	)	
	)	Confirmation No.: 4956
For: HYDROPHILIC LINKERS AND	)	
THEIR USES FOR CONJUGATION	)	
OF DRUGS TO A CELL BINDING	)	
MOLECULES	)	
	)	
	)	

CERTIFICATE OF SERVICE

Commissioner for Patents
Attn: Central Reexamination Unit
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

In compliance with 37 C.F.R. § 1.550 and in accordance with 37 C.F.R. § 1.248, the undersigned hereby certifies that a copy of Patent Owner's Amendment in Response to the Office Action of June 12, 2020, along with a Certificate of Service, were served in their entireties on the Third Party Requester by first class mail on August 12, 2020, to the following correspondence address of the Third Party Requester:

The Marbury Law Group, PLLC
11800 Sunrise Valley Drive, 15th Floor
Reston, VA 20191

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: August 12, 2020

By: /Fang Liu/
Fang Liu
Registration No. 51283

Customer No. 21839
703 836 6620

Electronic Patent Application Fee Transmittal				
Application Number:		90014390		
Filing Date:		16-Oct-2019		
Title of Invention:		HYDROPHILIC LINKERS AND THEIR USES FOR CONJUGATION OF DRUGS TO A CELL BINDING MOLECULES		
First Named Inventor/Applicant Name:		10131682		
Filer:		Fang Liu/Sarah Noel		
Attorney Docket Number:		1518-005USRE		
Filed as Small Entity				
Filing Fees for ex parte reexam				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
REEXAMINATION INDEPENDENT CLAIMS	2821	8	230	1840
REEXAMINATION CLAIMS IN EXCESS OF 20	2822	13	50	650
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				2490



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/014,390	10/16/2019	10131682	1518-005USRE	4956

21839 7590 08/24/2020
BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER

JONES, DWAYNE C

ART UNIT	PAPER NUMBER
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3991

MAIL DATE	DELIVERY MODE
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08/24/2020

PAPER

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The time period for reply, if any, is set in the attached communication.



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11800 SUNRISE VALLEY DRIVE
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RESTON, VA 20191

***EX PARTE* REEXAMINATION COMMUNICATION TRANSMITTAL FORM**

REEXAMINATION CONTROL NO. 90/014,390.

PATENT UNDER REEXAMINATION 10,131,682.

ART UNIT 3991.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the *ex parte* reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

<i>Ex Parte Reexamination Interview Summary</i>	Control No. 90/014,390	Patent Under Reexamination 90/014390	
	Examiner Dwayne C Jones	Art Unit 3991	AIA (FITF) Status No
All participants (USPTO personnel, patent owner, patent owner's representative):			
(1) <u>Dwayne Jones</u>	(3) <u>Bruce Campell</u>		
(2) <u>Jean Witz</u>	(4) <u>Fang Liu</u>		
Date of Interview: <u>11 August 2020</u> Type: a) ☒ Telephonic b) ☐ Video Conference c) ☐ Personal (copy given to: 1) ☐ patent owner 2) ☐ patent owners representative) Exhibit shown or demonstration conducted: d) ☒ Yes e) ☐ No. If Yes, brief description: <u>Proposed Amended Claims</u> Agreement with respect to the claims f) ☒ was reached. g) ☐ was not reached. h) ☐ N/A. Any other agreement(s) are set forth below under "Description of the general nature of what was agreed to..." Claim(s) discussed: <u>1,3-4,18 and 20</u> . Identification of prior art discussed: <u>WO'577; WO'497; WO'112; and PGPUB'053</u> . Description of the general nature of what was agreed to if an agreement was reached, or any other comments: <u>See Continuation Sheet</u> . (A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims patentable, if available, must be attached. Also, where no copy of the amendments that would render the claims patentable is available, a summary thereof must be attached.) A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION MUST INCLUDE PATENT OWNER'S STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. (See MPEP § 2281). IF A RESPONSE TO THE LAST OFFICE ACTION HAS ALREADY BEEN FILED, THEN PATENT OWNER IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO PROVIDE THE MANDATORY STATEMENT OF THE SUBSTANCE OF THE INTERVIEW (37 CFR 1.560(b)). THE REQUIREMENT FOR PATENT OWNERS STATEMENT CAN NOT BE WAIVED. EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).			
/Dwayne C. Jones/ Patent Reexam. Specialist, CRU 3991	/Bruce Campell/ Patent Reexam. Specialist, CRU 3991		
cc: Requester (if third party requester)			

Continuation of Description of the general nature of what was agreed to if an agreement was reached, or any other comments:

Regarding noncompliant claims, various claims presented in the proposed amendment were not in compliance pursuant to 37CFR 1.530. The following two examples are illustrative of the sundry examples listed in the proposed amendment. Issued claim 1 for variables m & n has a superscripted period between these two variables (column 48, line 45) vs. the newly introduced comma in the proposed amendment without bracketing & underlining. Next, issued claim 4 under the section entitled "e) Hormonal therapies" lists "goserelin" (column 50, line 40) vs. its submission in the proposed amendment as "goscrclin" without bracketing & underlining pursuant to 37CFR1.530. It was suggested to Patent Owner (PO)'s attorney to list the status of original claims rather than reproducing the entire claim.

Regarding the proposed amendments to independent claims 1, 3, 18, and 20, there is now no longer antecedent basis under 35USC112, 2nd paragraph for the group "(R1, R2, R3, and R4)" due to the deletion of R2 from its original positions in the issued claims of the patent.

Regarding the outstanding WO'577 rejection, the deletion of cyclic structures (i.e., cyclic alkyl, cyclic heteroalkyl, aryl, heteroaryl, and alkaryl) from the R2 variable makes WO'577 no longer germane to the proposed claims.

Regarding the outstanding WO'497 rejection, the newly proposed proviso in claim 3 that requires when Q is -S(O)₂-, m=1, n=0, or T is -S(O)₂-, n=1, m=0, the R1 variable is "not a chain of three atoms selected from the group consisting of C and S". As such, the -SCH₂CH₂- moiety of WO'497 (which correlates to the instant R1 variable) is now excluded. Accordingly, WO'497 does not meet the instantly claimed limitations. Also, because the Materials and Methods section of WO'497 specifically lists the poly-L-glutamic acid (PG) with a MW of 31K (page 15, lines 6-7 and page 17, lines 10-24 for Example 2 and manifested by Figure 2), the PG compound (which corresponds to the instant R4 variable) portrayed in Figure 2 would necessarily include more than 6 carbon atoms as required by the Group I claim interpretation of instant variables R1, R2, R3, and R4.

Finally, the proposed amendment to claim 20 now includes a proviso that excludes the instant Y variable from being represented by a vinyl moiety i.e., -CH=CH₂. For these additional reasons, WO'497 is not relevant to the proposed claims.

Regarding the outstanding WO'112 rejection, the newly added proviso requires at least one of the R1, R2, R3, and R4 variables is represented by a polyethyleneoxy unit of formula (OCH₂CH₂)_p and p = 1-1000. As such, WO'112 is no longer relevant to the instant claims.

Regarding the outstanding PGPUB'053 rejection, PO's attorney argued that the proposed amendment to R2 that removed cyclic moieties would overcome PGPUB'053 because the linking compound purportedly has a cyclohexyl moiety. However, the rejection of record states that the linking moiety of PGPUB'053 was being replaced by the portrayed thiol-reactive group of SMCC ([0045] and [0048]) for another thiol-reactive group i.e., vinylsulfone. As such, the modified linking moiety with a vinylsulfone results in a structure having the formula of DRUG-O-C(=O)CRHNH-SO₂-CH=CH₂ as stated paragraphs 32-34, 36, and 37 in the rejection of record. Accordingly, PO's assertion of the proposed amendment to R2 would not overcome the PGPUB'053 rejection. However, PO's proposed amendment to R1 that excludes a chain of three atoms selected from the group consisting of C and S (i.e., -SCH₂CH₂-) when Q is -S(O)₂-, m=1, n=0, or T is -S(O)₂-, n=1, m=0 now renders PGPUP'053 irrelevant to the amended claims.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/014,390	10/16/2019	10131682	1518-005USRE	4956

21839 7590 09/28/2020
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EXAMINER

JONES, DWAYNE C

ART UNIT	PAPER NUMBER
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3991

MAIL DATE	DELIVERY MODE
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09/28/2020

PAPER

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RESTON, VA 20191

***EX PARTE* REEXAMINATION COMMUNICATION TRANSMITTAL FORM**

REEXAMINATION CONTROL NO. 90/014,390.

PATENT UNDER REEXAMINATION 10131682.

ART UNIT 3991.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the *ex parte* reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

DETAILED ACTION
Ex Parte Reexamination:

Final Rejection

Procedural Posture

- On 11/20/2018: US Patent No. 10,131,682 (referred to as '682 Patent) issued with claims 1-21.
- On 10/16/2010: Third Party Requester (*i.e.*, Requester) filed a Request for ex parte reexamination request for claims 1-21. This reexamination proceeding is assigned Control No. 90/014,390.
- On 11/27/2019: A Determination of an Order GRANTING ex parte reexamination was mailed.
- No Patent Owner Statement under 37 CFR 1.530 was filed after the Order.
- On 06/12/2020: A First Office Action on the Merits was mailed.
- On 08/11/2010: Interview was convened (the Interview Summary was mailed on 08/24/2020).
- On 08/12/2020: Patent Owner filed amendments and arguments.

Notice of Pre-AIA or AIA Status

1. The present proceeding is being examined under the pre-AIA first to invent provisions.

Information Disclosure Statement

2. The information disclosure statement filed 08/13/2020 (7 sheets) fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.
3. In particular, no copies of *Non-Patent Literature Documents with Citation Nos. 10 and 11* were submitted. See enclosed copies of PTO/SB/08a.

Amendment of 08/12/2020

4. Claims 1, 3, 18, and 20 are amended.
5. Claims 2, 4-17, 19, and 21 are amended.
6. Claims 22-34 are newly added.

Withdrawn Rejections

7. The rejection of claims 3-8, 10-12, 14-16, 20, and 21 under pre-AIA 35 U.S.C. 102(b) as being anticipated by WO'497 is withdrawn in view of Patent Owner's arguments and amendments filed on 08/12/2020.
8. The rejection of claims 3-8, 10, 11, 13, 14, 15, and 16 under pre-AIA 35 U.S.C. 102(b) as anticipated by or, in the alternative, under pre-AIA 35 U.S.C. 103(a) as obvious over PGPUB'053 as evidenced by Handbook of Preservatives is withdrawn in view of Patent Owner's amendment filed on 08/12/2020. See ***Response to Amendment & Arguments*** section of this Action for the rationale rendering the PGPUB'053 reference irrelevant to the amended claims.
9. The rejection of claims 1-4, 6-9, and 11-21 under pre-AIA 35 U.S.C. 103(a) as being unpatentable over WO'577 is withdrawn in view of Patent Owner's arguments and amendments filed on 08/12/2020.
10. The rejection of claims 3-11, 13-17, 20, and 21 under pre-AIA 35 U.S.C. 103(a) as being unpatentable over WO'112 is withdrawn in view of Patent Owner's arguments and amendments filed on 08/12/2020.
11. The rejection of claims 9, 12, and 13 under pre-AIA 35 U.S.C. 103(a) as being unpatentable over WO'577 as applied to claims 1-4, 6-9, 11-21 above, and further in view of US'345 is withdrawn in view of Patent Owner's arguments and amendments filed on 08/12/2020.

12. The rejection of claims 9, 12, and 13 under pre-AIA 35 U.S.C. 103(a) as being unpatentable over WO'497 as applied to claims 3-11, 13-17, 20, and 21 above, and further in view of US'345 is withdrawn in view of Patent Owner's arguments and amendments filed on 08/12/2020.

New Claim Objections

13. **Claims 1, 3-17, 20, 22-30, and 33 are objected to because of the following informalities:**

14. **Regarding claim 1**, the amendment of 08/12/2020 adds a comma “ , ” but fails to delete a superscripted period “ . ” with brackets between the variables of m and n as listed in column 48, line 45 of the issued patent. As such, **claim 1** is non-compliant pursuant to 37 CFR 1.530(f)(1) and 37 CFR 1.530(i).

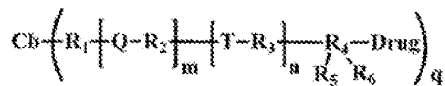
15. **Regarding claim 3**, the amendment of 08/12/2020 adds the word “and” *immediately after* the phrase “Q is not $-P(=O)(OM)-$,” without underlining (as listed in column 49, line 33 of the issued patent). Moreover, **claim 3** as amended fails to use brackets in order to delete the phrase “and when Q or T is $-S(O)-$, m and n are not 0:” (as listed in column 49, lines 33-34 of the issued patent). As such, **claim 3** is non-compliant pursuant to 37 CFR 1.530(f)(1), 37 CFR 1.530(f)(2), and 37 CFR 1.530(i).

16. **Regarding claim 20**, the amendment of 08/12/2020 adds a comma “ , ” without underling *immediately after* the phrase “M is H” as compared to the issued patent in column 55, line 25. As such, **claim 20** is non-compliant pursuant to 37 CFR 1.530(f)(2) and 37 CFR 1.530(i).

17. **Regarding claims 22-24 and 26-30**, the newly added phrase “m and n are integer” is incorrect in subject number agreement. As such, the word “integer” should be replaced with its plural form *i.e.*, “integers” in order to agree in number with the two subjects of m and n.
18. **Regarding claim 33**, the bond “ – ” is not directly attached to the sulfoxide moiety *i.e.*, “– S(O)–” in lines 1 and 2 of *new claim 33*. As such, the sulfoxide moiety should be listed as “–S(O)–”.
19. **Further regarding claims 4-17, 25, and 33**, these claims are objected to as being dependent upon rejected base claim 3 as *amended* (*i.e.*, claims 4-17 and 33) and *new* base claim 24 (*i.e.*, claim 25), thus **dependent claims 4-17, 25, and 33** are patentable and should be rewritten independent form. See MPEP § 2260.01.
20. Appropriate correction is required.

New Claim Rejections - 35 USC § 112

21. The following is a quotation of 35 U.S.C. 112(b):
- (b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.
22. The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
- The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
23. **Claims 23, 24, and 26 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.**
24. Independent **claims 23, 24, and 26** depict a cell-binding agent-drug conjugate of formula (II) as:



. However, variable q is not defined in these

claims, thus causing confusion and ambiguity to one skilled in the art.

New Claim Rejections - 35 USC § 305

25. **Claims 3 and 23 are rejected under 35 U.S.C. 305 as enlarging the scope of the claim(s) of the patent being reexamined.**

In 35 U.S.C. 305, it is stated that “[n]o proposed amended or new claim enlarging the scope of a claim of the patent will be permitted in a reexamination proceeding...” A claim presented in a reexamination “enlarges the scope” of the patent claim(s) where the claim is broader than each and every claim of the patent. A claim is broader in scope than the original claims if it contains within its scope any conceivable product or process which would not have infringed the original patent. A claim is broadened if it is broader in any one respect, even though it may be narrower in other respects.

26. As issued in column 49, lines 31-34, **claim 3** published with the following proviso as highlighted below regarding the m and n variables:

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 $\text{---P(---O)} \text{---}$
 (OM)-; when n=1, m=0, T is not $\text{---P(---O)} \text{---}$ (OM)-; and
 when Q or T is ---S(O)--- , m and n are not 0.

. **Claim 3** as amended, however, fails

to include the above-stated and highlighted phrase “and when Q or T is ---S(O)--- , m and n are not 0.” Similarly, *new claim 23* also fails to include the phrase “and when Q or T is ---S(O)--- , m and n are not 0.” as in issued claim 3. As such, *amended claim 3* and *new claim 23* have enlarged the scope of issued patent claims in this reexamination proceeding even though these two claims are narrower in other respects *e.g.*, the R₂ variable for *amended claim 3* and the newly added provisos regarding Q or T. For these reasons, **claims 3 and 23** are rejected under 35 USC §305 for enlarging the scope of the issued claims in the patent.

Response to Amendment & Arguments

27. Patent Owner’s asserted argument where the amendment to R₂ is not a cyclic moiety is not found persuasive to overcome PGPGUB’053 (pages 28-29 of the Patent Owner’s Arguments

of 08/12/2020). This is because the cyclohexyl moiety of PGPUB'053 as well as the carbonyl directly attached to it are each derived from SMCC not a vinyl sulfone.

28. However, Patent Owner's amendment to R₁ that excludes a chain of three atoms selected from C and S (*e.g.*, -CH₂CH₂-S-) when Q = -S(O)₂-, m=1, n=0 or T = -S(O)₂-, m=1, n=0, renders PGPUB'053 irrelevant to the instantly amended claims. This is due to the fact that the vinyl sulfone *i.e.*, a chain of three atoms selected from C and S is now excluded from the PGPUB'053 immunoconjugate.

29. In summary, all previous rejections are withdrawn in view of: (1) the arguments and amendments of 08/12/2020 furnished by the Patent Owner; (2) the reasons set forth in the Interview Summary of 08/11/2020 (mailed on 08/24/2020); and (3) finally the above-stated reasons that overcome PGPUB'053. However, the amendment of 08/12/2020 has resulted in new claim objections and rejections as detailed *supra* in this Final Office Action.

Conclusion

- 30. Claims 1-34 are pending and undergoing reexamination.
- 31. Claims 2, 18, 19, 21, 31, 32, and 34 are patentable.
- 32. Claims 1, 3-17, 20, 22-30, and 33 are objected.
- 33. Claims 3, 23, 24, and 26 are rejected.
- 34. Claims 1-34 are free of the prior art of record.

35. Patent owner's amendment filed 08/12/2020 necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

36. A shortened statutory period for response to this action is set to **expire 2 MONTHS** from the mailing date of this action.

37. **Extensions of time under 37 CFR 1.136(a) do not apply in reexamination proceedings.** The provisions of 37 CFR 1.136 apply only to "an applicant" and not to parties in a reexamination proceeding. Further, in 35 U.S.C. 305 and in 37 CFR 1.550(a), it is required that reexamination proceedings "will be conducted with special dispatch within the Office."

38. **Extensions of time in reexamination proceedings are provided for in 37 CFR 1.550(c).** A request for extension of time must specify the requested period of extension and it must be accompanied by the petition fee set forth in 37 CFR 1.17(g). Any request for an extension in a third party requested ex parte reexamination must be filed on or before the day on which action by the patent owner is due, and the mere filing of a request will not effect any extension of time. A request for an extension of time in a third party requested ex parte

reexamination will be granted only for sufficient cause, and for a reasonable time specified. Any request for extension in a patent owner requested ex parte reexamination (including reexamination ordered under 35 U.S.C. 257) for up to two months from the time period set in the Office action must be filed no later than two months from the expiration of the time period set in the Office action. A request for an extension in a patent owner requested ex parte reexamination for more than two months from the time period set in the Office action must be filed on or before the day on which action by the patent owner is due, and the mere filing of a request for an extension for more than two months will not effect the extension. The time for taking action in a patent owner requested ex parte reexamination will not be extended for more than two months from the time period set in the Office action in the absence of sufficient cause or for more than a reasonable time.

The filing of a timely first response to this final rejection will be construed as including a request to extend the shortened statutory period for an additional two months. In no event, however, will the statutory period for response expire later than SIX MONTHS from the mailing date of the final action. See MPEP § 2265.

Future Amendment

Patent Owner is notified that any proposed amendment to the specification and/or claims in this reexamination proceeding must comply with 37 CFR 1.530(d)-(j), must be formally presented pursuant to 37 CFR 1.52(a) and (b), and must contain any fees required by 37 CFR 1.20(c).

In particular, 37 CFR 1.530(i) states: "All amendments must be made relative to the patent specification, including claims, and drawings, which are in effect as of the date of filing the request for reexamination." As a result, each amendment to the claims should be made relative to the originally patented claims and not to the previous amendment. Any changes must include brackets (not strikethroughs) for the matter to be omitted and underlining for added matter (See 37 CFR 1.530(f)(1)(2)). The Patent Owner is directed to MPEP 2250 (IV) containing examples of claim amendments in reexamination proceedings.

In addition, Patent Owner is notified to provide a complete listing of all pending claims and their respective status (*i.e.*, original, cancelled, amended, and new) undergoing reexamination that complies with 37 CFR 1.530(d)-(j).

Ongoing Duty to Disclose

The Patent Owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 10,131,682 B2 throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286.

Future Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D.C. Jones whose telephone number is (571) 272-0578. The examiner can normally be reached on Mondays-Fridays from 10:00 am to 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jean Witz, may be reached at (571) 272-0927. The official fax no. for the organization where this application is assigned is (571) 273-9900.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about Private PAIR Portal homepage: <https://ppair.uspto.gov/epatent/portal/home> and Private PAIR: <https://ppair.uspto.gov/epatent/myportal/privatepair>. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 1-866-217-9197 (toll free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 1-800-786-9199 (In USA or CANADA) or 571-272-1000.

All correspondence relating to this *ex parte* reexamination proceeding should be directed:

By EFS: Registered users may submit via the electronic filing system EFS-Web at:
<https://efs.uspto.gov/efile/myportal/efs-registered>

By Mail to: Mail Stop *Ex Parte* Reexam
Central Reexamination Unit
Commissioner for Patents
United States Patent & Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

By FAX to: (571) 273-9900
Central Reexamination Unit

By hand: Customer Service Window
Randolph Building
401 Dulany Street
Alexandria, VA 22314

/Dwayne C. Jones/
Patent Reexamination Specialist
CRU, Art Unit 3991

/Bruce Campell/
Patent Reexamination Specialist
Central Reexamination Unit 3991

/TIMOTHY M SPEER/
Supervisory Patent Examiner, Art Unit 3991

Office Action in Ex Parte Reexamination	Control No. 90/014,390	Patent Under Reexamination 10131682	
	Examiner Dwayne C Jones	Art Unit 3991	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

- a. ☒ Responsive to the communication(s) filed on 12 August 2020.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.
- b. ☒ This action is made FINAL.
- c. ☐ A statement under 37 CFR 1.530 has not been received from the patent owner.

A shortened statutory period for response to this action is set to expire 2 month(s) from the mailing date of this letter. Failure to respond within the period for response will result in termination of the proceeding and issuance of an *ex parte* reexamination certificate in accordance with this action. 37 CFR 1.550(d). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c)**. If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|---|
| 1. ☐ Notice of References Cited by Examiner, PTO-892. | 3. ☐ Interview Summary, PTO-474. |
| 2. ☒ Information Disclosure Statement, PTO/SB/08. | 4. ☐ ____. |

Part II SUMMARY OF ACTION

- 1a. ☒ Claims 1-34 are subject to reexamination.
- 1b. ☐ Claims ____ are not subject to reexamination.
2. ☐ Claims ____ have been canceled in the present reexamination proceeding.
3. ☒ Claims 2,18-19,21,31-32 and 34 are patentable and/or confirmed.
4. ☒ Claims 3,23-24 and 26 are rejected.
5. ☒ Claims 1,3-17,20,22-30 and 33 are objected to.
6. ☐ The drawings, filed on ____ are acceptable.
7. ☐ The proposed drawing correction, filed on ____ has been (7a) ☐ approved (7b) ☐ disapproved.
8. ☐ Acknowledgment is made of the priority claim under 35 U.S.C. 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of the certified copies have
1 ☐ been received.
2 ☐ not been received.
3 ☐ been filed in Application No. ____.
4 ☐ been filed in reexamination Control No. ____.
5 ☐ been received by the International Bureau in PCT application No. ____.
- * See the attached detailed Office action for a list of the certified copies not received.
9. ☐ Since the proceeding appears to be in condition for issuance of an *ex parte* reexamination certificate except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte* Quayle, 1935 C.D. 11, 453 O.G. 213.
10. ☐ Other: ____

cc: Requester (if third party requester)

U.S. Patent and Trademark Office
PTOL-466 (Rev. 08-13)

Office Action in Ex Parte Reexamination

Part of Paper No. 20200922

DO NOT ENTER: /DJ/
10/22/2020

90/014,390 - GAU: 3991

Attorney Docket No. 0088597-000018

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re <i>Ex Parte</i> Reexamination of	)	MAIL STOP <i>EX PARTE</i>
U.S. Patent No. 10,131,682	)	REEXAMINATION - AF
R. Yongxin Zhao	)	Attn: Central Reexamination Unit
Reexamination Control No.: 90/014,390	)	Group Art Unit: 3991
Filed: October 16, 2019	)	Examiner: JONES, DWAYNE C
For: HYDROPHILIC LINKERS AND	)	Confirmation No.: 4956
THEIR USES FOR CONJUGATION	)	
OF DRUGS TO A CELL BINDING	)	
MOLECULES	)	

**AMENDMENT IN RESPONSE TO OFFICE ACTION IN *EX PARTE*
REEXAMINATION**

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

Commissioner:

In response to the final Office Action issued on September 28, 2020, Patent Owner submits the following amendments and remarks.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re <i>Ex Parte</i> Reexamination of	)	MAIL STOP <i>EX PARTE</i>
U.S. Patent No. 10,131,682	)	REEXAMINATION - AF
R. Yongxin Zhao	)	Attn: Central Reexamination Unit
Reexamination Control No.: 90/014,390	)	Group Art Unit: 3991
Filed: October 16, 2019	)	Examiner: JONES, DWAYNE C
For: HYDROPHILIC LINKERS AND	)	Confirmation No.: 4956
THEIR USES FOR CONJUGATION	)	
OF DRUGS TO A CELL BINDING	)	
MOLECULES	)	

**AMENDMENT IN RESPONSE TO OFFICE ACTION IN *EX PARTE*
REEXAMINATION**

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

Commissioner:

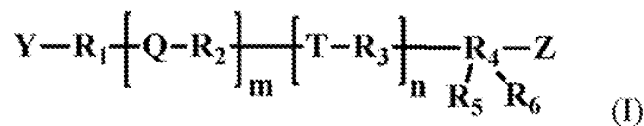
In response to the final Office Action issued on September 28, 2020, Patent Owner submits the following amendments and remarks.

AMENDMENTS TO THE CLAIMS:

Please amend claims 1, 3, 18 and 20, and add new claims 22-34. The remaining claims are not changed by this paper and have not been represented below in accordance with 37 C.F.R. § 1.530(d) through (j) and M.P.E.P. § 2250. All changes are shown relative to the set of claims that appear in U.S. Patent No. 10,131,682 issued on November 20, 2018.

LISTING OF CLAIMS:

1. (Twice 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)-; when n=1, m=0, T is not -P(=O)(OM)-; and when Q or T is -S(O₂)-, m and n are not 0;

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

R₁, R₂, R₃, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched 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,

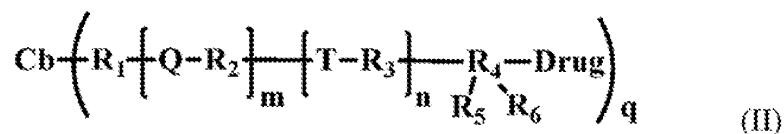
or R_1 , R_2 , R_3 and R_4 are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4), provided that when Q and T are each independently $-\text{S}(\text{O}_2)-$ or $-\text{S}(\text{O})-$, R_2 is a straight or branched 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, R_1 , R_3 or R_4 ;

R_5 and R_6 , are the same or different and are absent, 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. (Original)

3. (Twice 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, cycloheteroalkane, heteroaromatic, alkoime or amide bond;

q is an integer from 1 to 20; Q and T are either $-\text{P}(=\text{O})(\text{OM})-$, or $-\text{S}(\text{O}_2)-$, or $-\text{S}(\text{O})-$;

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)-; when n=1, m=0, T is not -P(=O)(OM)-; and when Q or T is -S(O)-, m and n are not 0[[:]];

R₁, R₂, R₃, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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)₂, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or branched 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, R₁, R₃ or R₄;

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

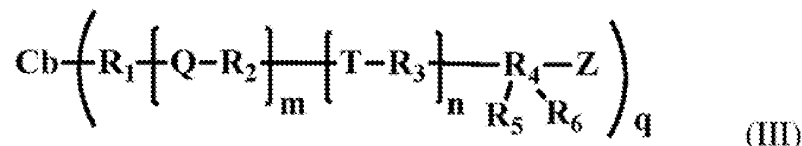
M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt,
provided that:

when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p, and

when (i) Q is -S(O₂)-, m is 1, and n is 0, or (ii) T is -S(O₂)-, n is 1 and m is 0, R₁ is not a chain of three atoms selected from the group consisting of C and S.

4-17. (Original)

18. (Amended) A compound of formula (III):



wherein:

Cb represents 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)-;

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, hydrazone, ether, ester, carbamate, carbonate, secondary, tertiary, or quaternary amine, imine, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

R₁, R₂, R₃, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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,

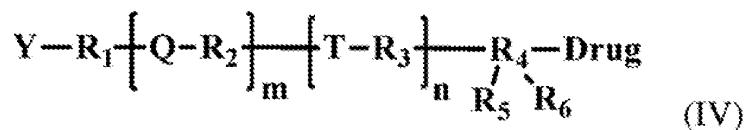
or R₁, R₂, R₃ and R₄ are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R₁, R₂, R₃ and R₄), provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or branched 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, R₁, R₃ or R₄;

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt.

19. (Original)

20. (Twice 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(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)-;

"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, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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)_x, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or branched 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, R₁, R₃ or R₄;

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H_x or Na, or K_x or N⁺R₁R₂R₃ or a pharmaceutical salt_x

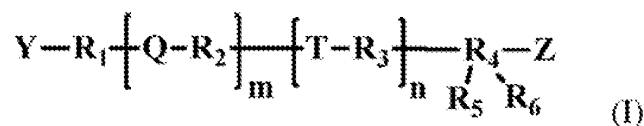
provided that:

when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p, and

when (i) Q is -S(O₂)-, m is 1, and n is 0, or (ii) T is -S(O₂)-, n is 1 and m is 0, Y is an N-hydroxysuccinimide (NHS) ester, p-nitrophenyl ester, dinitrophenyl ester, pentafluorophenyl ester, pyridyldisulfide, nitropyridyldisulfide, maleimide, haloacetate, carboxylic acid chloride, hydrazide or hydroxylamine.

21. (Original)

22. (New) 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 integers from 0 to 5, but not 0 at the same time; provided that when m=1, n=0, Q is not -P(=O)(OM)-; when n=1, m=0, T is not -P(=O)(OM)-; and when Q or T is -S(O₂)-, m and n are not 0;

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

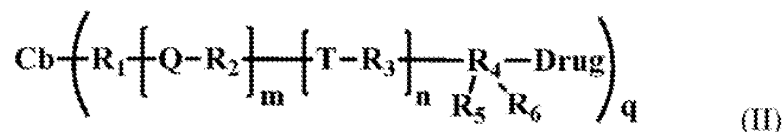
R₁, R₂, R₃, and R₄, are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula (OCH₂CH₂)_p, 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 absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt; and
wherein the hydrophilic linker comprises at least one -P(=O)(OM)-.

23. (New) 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,
cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

q is an integer from 1 to 20; 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; provided that when m=1,
n=0, Q is not -P(=O)(OM)-; when n=1, m=0, T is not -P(=O)(OM)-; and when Q or T is -S(O)-,
m and n are not 0;

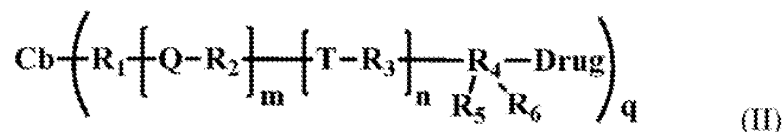
R₁, R₂, R₃, and R₄, are the same or different and are absent, linear alkyl having from 1-6
carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or
cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy
unit of formula (OCH₂CH₂)_p, 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 absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination
thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt, and
 wherein the conjugate comprises at least one -P(=O)(OM)-.

24. (New) 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,
 cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

q is an integer from 1 to 20; Q and T are either -P(=O)(OM)-, or -S(O₂)-, or -S(O)-;

m and n are integers from 1 to 5;

R₁, R₂, R₃, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination
 thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear
 alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or
 branched alkenyl or alkynyl, or ester, 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),
 provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or
 branched 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, R_1 , R_3 or R_4 ,

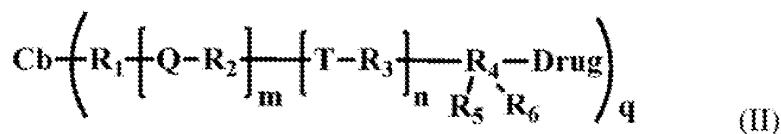
provided that when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, at least one of R_1 , R_2 , R_3 and R_4 comprises the polyethyleneoxy unit of formula $(OCH_2CH_2)_p$;

R_5 and R_6 , are the same or different and are absent, 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.

25. (New) The cell-binding agent-drug conjugate of claim 24, wherein when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, at least one of R_1 , R_2 , R_3 and R_4 comprises the polyethyleneoxy unit of formula $(OCH_2CH_2)_p$; and each of remaining R_1 , R_2 , R_3 and R_4 comprises an alkyl or $(OCH_2CH_2)_p$.

26. (New) 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, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

q is an integer from 1 to 20; Q and T are either $-P(=O)(OM)-$, or $-S(O_2)-$, or $-S(O)-$;

m and n are integers from 1 to 5;

R_1 , R_2 , R_3 , and R_4 , are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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.

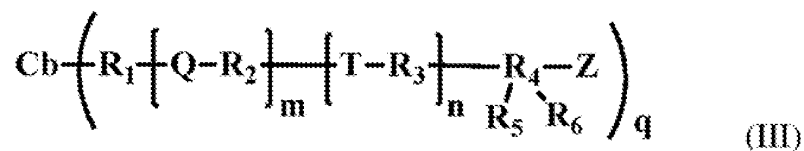
or R₁, R₂, R₃ and R₄ are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R₁, R₂, R₃ and R₄), provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or branched 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, R₁, R₃ or R₄;

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt,

provided that when Q and T are each independently -S(O₂)- or -S(O)-, m is 1 and n is 1, R₂ is absent, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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 R₂ is a branched 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, R₃ or R₄.

27. (New) A compound of formula (III):



wherein:

Cb represents 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; 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, hydrazone, ether, ester, carbamate, carbonate, secondary, tertiary, or quaternary amine, imine, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

R₁, R₂, R₃, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

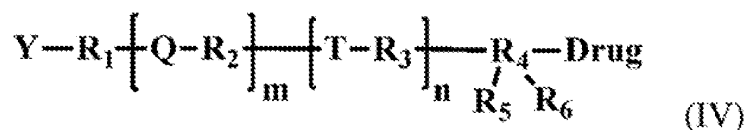
or R₁, R₂, R₃ and R₄ are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R₁, R₂, R₃ and R₄);

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt, and

wherein the conjugate comprises at least one -P(=O)(OM)-.

28. (New) 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(O₂)-, or -S(O)-;

m and n are integers 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;

R₁, R₂, R₃, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

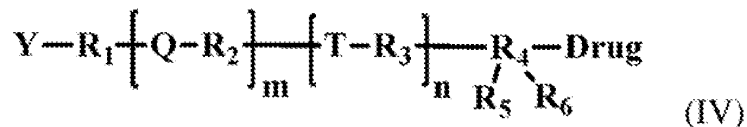
or R₁, R₂, R₃ and R₄ are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R₁, R₂, R₃ and R₄);

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt, and

wherein the conjugate comprises at least one -P(=O)(OM)-.

29. (New) 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(O₂)-, or -S(O)-;

m and n are integers 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;

R₁, R₂, R₃, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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), provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or branched 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, R₁, R₃ or R₄;

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

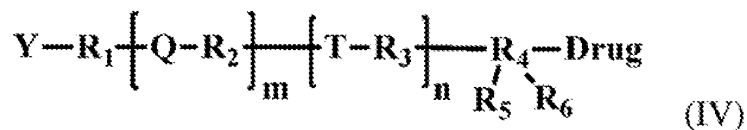
M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt,

provided that:

when Q and T are each independently -S(O₂)- or -S(O)-, m is 1 and n is 1, R₂ is absent, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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 R₂ is a branched 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, R₃ or R₄; and

when (i) Q is -S(O₂)-, m is 1, and n is 0, or (ii) T is -S(O₂)-, n is 1 and m is 0, Y is an N-hydroxysuccinimide (NHS) ester, p-nitrophenyl ester, dinitrophenyl ester, pentafluorophenyl ester, pyridyldisulfide, nitropyridyldisulfide, maleimide, haloacetate, carboxylic acid chloride, hydrazide or hydroxylamine.

30. (New) 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(O₂)-, or -S(O)-;

m and n are integers from 1 to 5;

"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, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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), provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or branched 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, R₁, R₃ or R₄;

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt,

provided that when Q and T are each independently -S(O₂)- or -S(O)-, m is 1 and n is 1, R₂ is absent, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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 R₂ is a branched 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, R₃ or R₄.

31. (New) The compound of claim 30, wherein when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p.

32. (New) The compound of claim 31, wherein when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p; and each of remaining R₁, R₂, R₃ and R₄ comprises an alkyl or (OCH₂CH₂)_p.

33. (New) The conjugate of claim 3, wherein when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p; and each of remaining R₁, R₂, R₃ and R₄ comprises an alkyl or (OCH₂CH₂)_p.

34. (New) The compound of claim 20, wherein when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p; and each of remaining R₁, R₂, R₃ and R₄ comprises an alkyl or (OCH₂CH₂)_p.

REMARKS

In view of the above amendments and the following remarks, Patent Owner respectfully requests reconsideration of the objection and rejections set forth in the Office Action of September 28, 2020 ("Office Action").

I. Status of Claims

Claims 1-21 of U.S. Patent No. 10,131,682 (herein "the present patent") are subject to reexamination. Claims 1, 3, 18 and 20 are independent claims. Claim 2 depends from claim 1. Claims 4-17 depend from claim 3. Claim 19 depends from claim 18. Claim 21 depends from claim 20.

In the Amendment filed on August 12, 2020, claims 1, 3, 18 and 20 were amended, and claims 22-34 were added. In the present Amendment, claims 1, 3, 20, 22-24, 26-30 and 33 have been further amended as detailed below.

Claim 1 has been amended to further improve its form, by replacing a superscripted period "." with a comma ",".

Claims 3, 23, 24 and 26 have been amended to recite that "q is an integer from 1 to 20." Support for this amendment can be found in the disclosure, for example, col. 11, line 56; col. 12, lines 59-61; issued claim 18; Figs. 1, 6, 7, 10-13 and 15-19-z) of the present patent.

Claim 20 has been amended to further improve its form, by adding two commas ",".

Claims 22-24 and 26-30 have been amended to further improve their form, by replacing "m and n are integer from 0 to 5" with "m and n are integers from 0 to 5."

Claim 33 has been amended to further improve its form, by keeping "-S(O)-" together in the same line.

No new matter is being added by the above amendments, and the amendments do not enlarge the scope of the claims being presented.

Applicant respectfully submits that entry of the amendments, after final, is proper, at least because they substantially adopt the Examiner's suggestion and place the application either in condition for allowance or in better form for appeal. See M.P.E.P. § 714.12. Upon entry of the present amendments, claims 1-34 will be all the claims pending.

Patent Owner notes with appreciation that claims 2, 18-19, 21, 31-32 and 34 have been indicated to be patentable.

II. Information Disclosure Statement

The Office Action asserted that copies of Non-Patent Literature Documents with Citation Nos. 10 and 11 in the Information Disclosure Statement filed on August 13, 2020, were not submitted.

With regard to the above noted Citation No. 11, the page number indicated on the Form PTO/SB/08 previously filed with the Information Disclosure Statement on August 13, 2020, was incorrect, i.e., “253 pages” should read “16 pages,” and a copy of this document was indeed submitted and reflected in the USPTO PAIR database. Nonetheless, this document was again included in a subsequent Information Disclosure Statement filed on October 1, 2020.

With regard to the above noted Citation No. 10, a copy is attached hereto for the Examiner’s consideration.

III. Response to Objection to Claims

Claims 1, 3-17, 20, 22-30, and 33 were objected to for alleged informalities. Patent Owner respectfully submits that the claims as amended do not contain informalities.

(a) Regarding claim 1, the Office Action asserted that “the amendment of 08/12/2020 adds a comma ‘,’ but fails to delete a superscripted period ‘.’ with brackets.” In the Amendment, claim 1 has been further amended as the Examiner suggested.

(b) Regarding claim 3, the Office Action asserted that “the amendment of 08/12/2020 adds the word ‘and’ *immediately* after the phrase ‘Q is not -P(=O)(OM)-;’ without underlining... fails to use brackets in order to delete the phrase ‘and when Q or T is -S(O)-, m and n are not O.’” In the Amendment, the corresponding proviso recited in issued claim 3 has been reinstated.

(c) Regarding claim 20, the Office Action asserted that “the amendment of 08/12/2020 adds a comma ‘,’ without underling *immediately after* the phrase ‘M is H.’” In the Amendment, claim 20 has been further amended as the Examiner suggested.

(d) Regarding claims 22-24 and 26-30, the Office Action asserted that “the newly added phrase ‘m and n are integer’ is incorrect in subject number agreement.” In the Amendment, claims 22-24 and 26-30 have been further amended as the Examiner suggested.

(e) Regarding claim 33, the Office Action asserted that “the bond ‘-’ is not directly attached to the sulfoxide moiety i.e., ‘-S(O)-.’” In the Amendment, claim 33 has been further amended as the Examiner suggested.

In view of the foregoing, withdrawal of the objection is respectfully requested.

IV. Response to Rejection under 35 U.S.C. § 112

Claims 23, 24, and 26 were rejected under 35 U.S.C. § 112(b) as allegedly being indefinite. Patent Owner respectfully submits that the claims as amended are not indefinite.

The Office Action asserted that variable q in formula II is not defined in the claims. In response, the claims have been amended to add the definition for q. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

V. Response to Rejection under 35 U.S.C. § 305

Claims 3 and 23 were rejected under 35 U.S.C. § 305 as allegedly enlarging the scope of the claims of the patent. Patent Owner respectfully submits that the claims as amended do not enlarge the scope of the issued claims.

In the Amendment, claim 3 as amended as well as new claim 23 retain the same language at issue as issued claim 3. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

VI. Conclusion

From the foregoing, allowance of all the pending claims under reexamination is believed to be next in order and such action is earnestly solicited. If there are any questions concerning this paper or the patent 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: October 20, 2020

By: /Fang Liu/
Fang Liu
Registration No. 51283

Customer No. 21839
703 836 6620



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/014,390	10/16/2019	10131682	0088597-000018	4956

21839 7590 10/29/2020
BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER

JONES, DWAYNE C

ART UNIT	PAPER NUMBER
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3991

MAIL DATE	DELIVERY MODE
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10/29/2020

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.



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RESTON, VA 20191

***EX PARTE* REEXAMINATION COMMUNICATION TRANSMITTAL FORM**

REEXAMINATION CONTROL NO. 90/014,390.

PATENT UNDER REEXAMINATION 10131682.

ART UNIT 3991.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the *ex parte* reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

<i>Ex Parte Reexamination Advisory Action</i>	Control Number 90/014,390	Patent Under Reexamination 10,131,682	
	Examiner Dwayne C Jones	Art Unit 3991	AIA (FITF) Status No

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

THE PROPOSED RESPONSE FILED 20 October 2020 FAILS TO OVERCOME ALL OF THE REJECTIONS IN THE FINAL REJECTION MAILED 28 September 2020. Therefore, unless a timely appeal is filed, or other appropriate action by the patent owner is taken to overcome all of the outstanding rejection(s), this *ex parte* reexamination proceeding WILL BE TERMINATED and a Notice of Intent to Issue *Ex Parte* Reexamination Certificate will be mailed in due course. Any finally rejected claims, or claims objected to, will be CANCELLED.

THE PERIOD FOR RESPONSE IS EXTENDED TO RUN 4 MONTHS FROM THE MAILING DATE OF THE FINAL REJECTION.

(Extensions of time are governed by 37 CFR 1.550(c))

1. ☐ Appellant's Brief is due two months from the date of the Notice of Appeal filed on _____ (or within the extended period for response set forth above, whichever is later). See 37 CFR 1.191(d) and 37 CFR 1.192(a).
2. ☒ The proposed amendment(s) will not be entered because:
 - (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);
 - (b) ☐ they raise the issue of new matter (see NOTE below);
 - (c) ☒ they are not deemed to place the proceeding in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
 - (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: See Continuation Sheet
3. ☒ Patent owner's proposed response filed 20 October 2020 has overcome the following rejection(s): See Continuation Sheet
4. ☐ The proposed new or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☐ An affidavit(s)/declaration(s) under **37 CFR 1.130(b)** was/were filed on _____.
6. ☐ The a) ☐ affidavit/declaration, b) ☐ exhibit, or c) ☐ request for reconsideration has been considered but does NOT overcome the rejection(s) because: _____.
7. ☐ The affidavit/declaration or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
8. ☒ For purposes of Appeal, the proposed amendment(s) a) ☒ will not be entered or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:
 Claim(s) patentable and/or confirmed: 2,18-19,21,31-32 and 34
 Claim(s) objected to: 1,3-17,20,22-30 and 33
 Claim(s) rejected: 3,23-24 and 26
 Claim(s) not subject to reexamination: _____
9. ☐ The drawing correction filed on _____ a) ☐ has b) ☐ has not been approved by the Examiner.
10. ☒ Note the attached Information Disclosure Statement(s), PTO-1449, Paper No(s) 10/01/2020.
11. ☒ Other: See Continuation Sheet

/TIMOTHY M SPEER/
 Supervisory Patent Examiner, Art Unit
 3991

cc: Requester (if third party requester)

Continuation of 2. (a)(c) NOTE:

The proposed after final amendment will not be entered because the amendment fails to comply with 37 CFR 1.116(b)(2):

The proposed amendment of 10/20/2020 does not comply with 37 CFR 1.530(f)(1). In particular, the proposed amendment to claims 1 and 3 specifically uses double brackets i.e., "[[]]" in stead of single brackets "[]". As such, the proposed deletion of subject matter does not comply with 37 CFR 1.530(f)(1).

Continuation of 3. Patent Owner's response filed has overcome the following rejection(s):

The proposed amendment of 10/20/2020, if entered, would overcome the 35 USC 112(b) rejection of claims 23, 24, and 26 as well as the 35 USC 305 rejection of claims 3 and 23 as set forth in the Final Office Action of 09/28/2020.

Continuation of 11. Other:

It is further noted that the proposed amendment of 10/20/2020, if entered, would also overcome the claim objections as set forth in the Final Office Action of 09/28/2020 under the condition that Patent Owner uses single brackets in lieu of double brackets to delete subject matter pursuant to 37 CFR 1.530 (f)(1) particularly in claims 1 and 3 as stated above in 2(a)(c) of this Advisory Action.

/Dwayne C. Jones/ & /Bruce Campell/
Patent Reexamination Specialists, CRU 3991

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re <i>Ex Parte</i> Reexamination of	)	MAIL STOP <i>EX PARTE</i>
U.S. Patent No. 10,131,682	)	REEXAMINATION - AF
R. Yongxin Zhao	)	Attn: Central Reexamination Unit
Reexamination Control No.: 90/014,390	)	Group Art Unit: 3991
Filed: October 16, 2019	)	Examiner: JONES, DWAYNE C
For: HYDROPHILIC LINKERS AND	)	Confirmation No.: 4956
THEIR USES FOR CONJUGATION	)	
OF DRUGS TO A CELL BINDING	)	
MOLECULES	)	

**AMENDMENT IN RESPONSE TO OFFICE ACTION IN *EX PARTE*
REEXAMINATION**

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

Commissioner:

This is in response to the final Office Action issued on September 28, 2020, and further to the Advisory Action issued on October 29, 2020. The Amendment filed on October 20, 2020, is not entered.

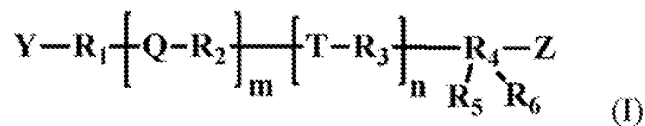
Patent Owner submits the following amendments and remarks.

AMENDMENTS TO THE CLAIMS:

Please amend claims 1, 3, 18 and 20, and add new claims 22-34. The remaining claims are not changed by this paper and have not been represented below in accordance with 37 C.F.R. § 1.530(d) through (j) and M.P.E.P. § 2250. All changes are shown relative to the set of claims that appear in U.S. Patent No. 10,131,682 issued on November 20, 2018.

LISTING OF CLAIMS:

1. (Twice 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]integers from 0 to 5, but not 0 at the same time; provided that when m=1, n=0, Q is not -P(=O)(OM)-; when n=1, m=0, T is not -P(=O)(OM)-; and when Q or T is -S(O₂)-, m and n are not 0[.];

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

R₁, R₂, R₃, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched 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,

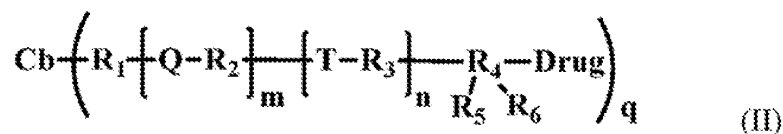
or R_1 , R_2 , R_3 and R_4 are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4), provided that when Q and T are each independently $-\text{S}(\text{O}_2)-$ or $-\text{S}(\text{O})-$, R_2 is a straight or branched 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, R_1 , R_3 or R_4 ;

R_5 and R_6 , are the same or different and are absent, 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. (Original)

3. (Twice 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, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

q is an integer from 1 to 20; Q and T are either $-\text{P}(=\text{O})(\text{OM})-$, or $-\text{S}(\text{O}_2)-$, or $-\text{S}(\text{O})-$;

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

R₁, R₂, R₃, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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)₂, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or branched 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, R₁, R₃ or R₄;

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

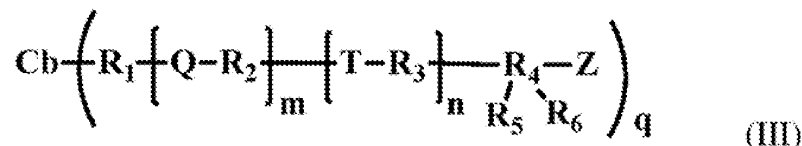
M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt,
provided that:

when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p, and

when (i) Q is -S(O₂)-, m is 1, and n is 0, or (ii) T is -S(O₂)-, n is 1 and m is 0, R₁ is not a chain of three atoms selected from the group consisting of C and S.

4-17. (Original)

18. (Amended) A compound of formula (III):



wherein:

Cb represents a cell-binding agent;

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

m and n are [integer]integers 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, hydrazone, ether, ester, carbamate, carbonate, secondary, tertiary, or quaternary amine, imine, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

R₁, R₂, R₃, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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,

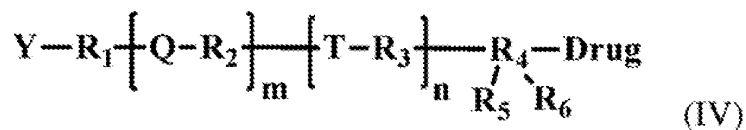
or R₁, R₂, R₃ and R₄ are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R₁, R₂, R₃ and R₄), provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or branched 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, R₁, R₃ or R₄;

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt.

19. (Original)

20. (Twice 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(O₂)-, or -S(O)-;

m and n are [integer]integers 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;

R₁, R₂, R₃, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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)_x, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or branched 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, R₁, R₃ or R₄;

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H_x or Na, or K_x or N⁺R₁R₂R₃ or a pharmaceutical salt_x

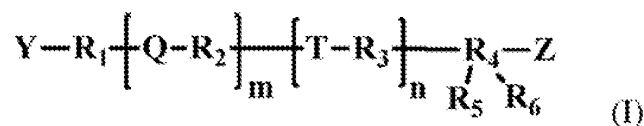
provided that:

when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p, and

when (i) Q is -S(O₂)-, m is 1, and n is 0, or (ii) T is -S(O₂)-, n is 1 and m is 0, Y is an N-hydroxysuccinimide (NHS) ester, p-nitrophenyl ester, dinitrophenyl ester, pentafluorophenyl ester, pyridyldisulfide, nitropyridyldisulfide, maleimide, haloacetate, carboxylic acid chloride, hydrazide or hydroxylamine.

21. (Original)

22. (New) 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 integers from 0 to 5, but not 0 at the same time; provided that when m=1, n=0, Q is not -P(=O)(OM)-; when n=1, m=0, T is not -P(=O)(OM)-; and when Q or T is -S(O₂)-, m and n are not 0;

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

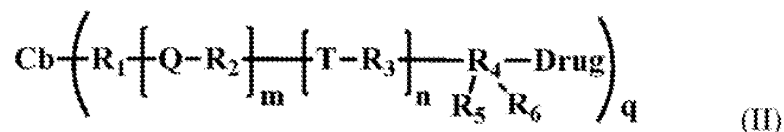
R₁, R₂, R₃, and R₄, are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula (OCH₂CH₂)_p, 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 absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt; and
wherein the hydrophilic linker comprises at least one -P(=O)(OM)-.

23. (New) 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,
cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

q is an integer from 1 to 20; 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; provided that when m=1,
n=0, Q is not -P(=O)(OM)-; when n=1, m=0, T is not -P(=O)(OM)-; and when Q or T is -S(O)-,
m and n are not 0;

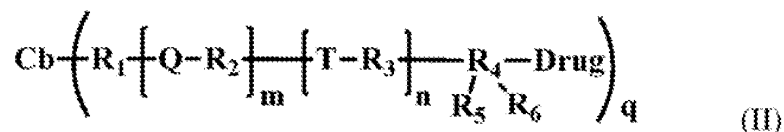
R₁, R₂, R₃, and R₄, are the same or different and are absent, linear alkyl having from 1-6
carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or
cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy
unit of formula (OCH₂CH₂)_p, 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 absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination
thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt, and
 wherein the conjugate comprises at least one -P(=O)(OM)-.

24. (New) 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,
 cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

q is an integer from 1 to 20; Q and T are either -P(=O)(OM)-, or -S(O₂)-, or -S(O)-;

m and n are integers from 1 to 5;

R₁, R₂, R₃, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination
 thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear
 alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or
 branched alkenyl or alkynyl, or ester, 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),
 provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or
 branched 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, R_1 , R_3 or R_4 ,

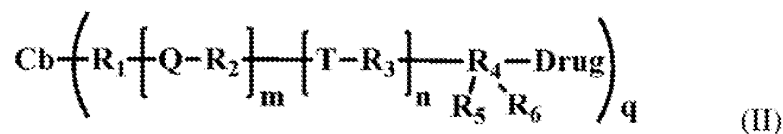
provided that when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, at least one of R_1 , R_2 , R_3 and R_4 comprises the polyethyleneoxy unit of formula $(OCH_2CH_2)_p$;

R_5 and R_6 , are the same or different and are absent, 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.

25. (New) The cell-binding agent-drug conjugate of claim 24, wherein when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, at least one of R_1 , R_2 , R_3 and R_4 comprises the polyethyleneoxy unit of formula $(OCH_2CH_2)_p$; and each of remaining R_1 , R_2 , R_3 and R_4 comprises an alkyl or $(OCH_2CH_2)_p$.

26. (New) 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, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

q is an integer from 1 to 20; Q and T are either $-P(=O)(OM)-$, or $-S(O_2)-$, or $-S(O)-$;

m and n are integers from 1 to 5;

R_1 , R_2 , R_3 , and R_4 , are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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.

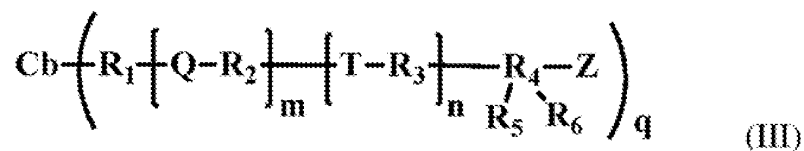
or R₁, R₂, R₃ and R₄ are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R₁, R₂, R₃ and R₄), provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or branched 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, R₁, R₃ or R₄;

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt,

provided that when Q and T are each independently -S(O₂)- or -S(O)-, m is 1 and n is 1, R₂ is absent, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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 R₂ is a branched 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, R₃ or R₄.

27. (New) A compound of formula (III):



wherein:

Cb represents 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; 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, hydrazone, ether, ester, carbamate, carbonate, secondary, tertiary, or quaternary amine, imine, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

R₁, R₂, R₃, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

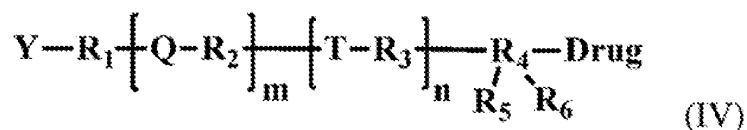
or R₁, R₂, R₃ and R₄ are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R₁, R₂, R₃ and R₄);

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt, and

wherein the conjugate comprises at least one -P(=O)(OM)-.

28. (New) 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(O₂)-, or -S(O)-;

m and n are integers 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;

R₁, R₂, R₃, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

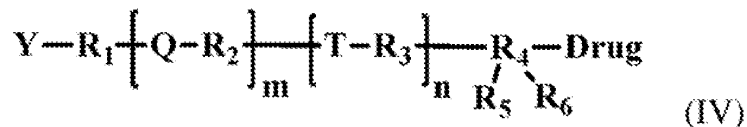
or R₁, R₂, R₃ and R₄ are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R₁, R₂, R₃ and R₄);

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt, and

wherein the conjugate comprises at least one -P(=O)(OM)-.

29. (New) 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(O₂)-, or -S(O)-;

m and n are integers 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;

R₁, R₂, R₃, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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), provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or branched 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, R₁, R₃ or R₄;

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

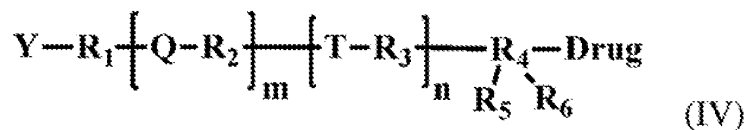
M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt,

provided that:

when Q and T are each independently -S(O₂)- or -S(O)-, m is 1 and n is 1, R₂ is absent, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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 R₂ is a branched 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, R₃ or R₄; and

when (i) Q is -S(O₂)-, m is 1, and n is 0, or (ii) T is -S(O₂)-, n is 1 and m is 0, Y is an N-hydroxysuccinimide (NHS) ester, p-nitrophenyl ester, dinitrophenyl ester, pentafluorophenyl ester, pyridyldisulfide, nitropyridyldisulfide, maleimide, haloacetate, carboxylic acid chloride, hydrazide or hydroxylamine.

30. (New) 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(O₂)-, or -S(O)-;

m and n are integers from 1 to 5;

"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, and R₄, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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), provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or branched 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, R₁, R₃ or R₄;

R₅ and R₆, are the same or different and are absent, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt,

provided that when Q and T are each independently -S(O₂)- or -S(O)-, m is 1 and n is 1, R₂ is absent, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, 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 R₂ is a branched 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, R₃ or R₄.

31. (New) The compound of claim 30, wherein when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p.

32. (New) The compound of claim 31, wherein when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p; and each of remaining R₁, R₂, R₃ and R₄ comprises an alkyl or (OCH₂CH₂)_p.

33. (New) The conjugate of claim 3, wherein when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p; and each of remaining R₁, R₂, R₃ and R₄ comprises an alkyl or (OCH₂CH₂)_p.

34. (New) The compound of claim 20, wherein when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p; and each of remaining R₁, R₂, R₃ and R₄ comprises an alkyl or (OCH₂CH₂)_p.

REMARKS

In view of the above amendments and the following remarks, Patent Owner respectfully requests reconsideration and withdrawal of the objection and rejections set forth in the Office Action of September 28, 2020 (“Office Action”) and the Advisory Action of October 29, 2020 (“Advisory Action”).

I. Status of Claims

Claims 1-21 of U.S. Patent No. 10,131,682 (herein “the present patent”) are subject to reexamination. Claims 1, 3, 18 and 20 are independent claims. Claim 2 depends from claim 1. Claims 4-17 depend from claim 3. Claim 19 depends from claim 18. Claim 21 depends from claim 20.

In the Amendment filed on August 12, 2020, claims 1, 3, 18 and 20 were amended, and claims 22-34 were added.

In the Amendment filed on October 20, 2020, amendments to claims 1, 3, 20, 22-24, 26-30 and 33 were proposed; however, they are not entered.

In the present Amendment, claims 1, 3, 20, 22-24, 26-30 and 33 have been further amended as detailed below.

Claim 1 has been amended to further improve its form, by replacing a superscripted period “.” with “,”.

Claims 3, 23, 24 and 26 have been amended to recite that “q is an integer from 1 to 20.” Support for this amendment can be found in the disclosure, for example, col. 11, line 56; col. 12, lines 59-61; issued claim 18; Figs. 1, 6, 7, 10-13 and 15-19-z) of the present patent.

Claim 3 has also been amended to further improve its form, by replacing “.” with “,”.

Claim 20 has been amended to further improve its form, by adding two commas “,”.

Claims 1, 3, 18, 20, 22-24 and 26-30 have been amended to further improve their form, by replacing “m and n are integer from 0 (or 1) to 5” with “m and n are integers from 0 (or 1) to 5.”

Claim 33 has been amended to further improve its form, by keeping “-S(O)-” together in the same line.

No new matter is being added by the above amendments, and the amendments do not enlarge the scope of the claims being presented.

Applicant respectfully submits that entry of the amendments, after final, is proper, at least because they substantially adopt the Examiner's suggestion and place the application either in condition for allowance or in better form for appeal. See M.P.E.P. § 714.12. Upon entry of the present amendments, claims 1-34 will be all the claims pending.

Patent Owner notes with appreciation that claims 2, 18-19, 21, 31-32 and 34 have been indicated to be patentable.

II. Response to Objection to Claims

Claims 1, 3-17, 20, 22-30, and 33 were objected to for alleged informalities. Patent Owner respectfully submits that the claims as amended do not contain informalities.

(a) Regarding claim 1, the Office Action asserted that "the amendment of 08/12/2020 adds a comma ',' but fails to delete a superscripted period '·' with brackets." In the Amendment, claim 1 has been further amended as the Examiner suggested.

(b) Regarding claim 3, the Office Action asserted that "the amendment of 08/12/2020 adds the word 'and' *immediately* after the phrase 'Q is not -P(=O)(OM)-;' without underlining... fails to use brackets in order to delete the phrase 'and when Q or T is -S(O)-, m and n are not 0:'." In the Amendment, the corresponding proviso recited in issued claim 3 has been reinstated.

(c) Regarding claim 20, the Office Action asserted that "the amendment of 08/12/2020 adds a comma ',' without underling *immediately after* the phrase 'M is H.'" In the Amendment, claim 20 has been further amended as the Examiner suggested.

(d) Regarding claims 22-24 and 26-30, the Office Action asserted that "the newly added phrase 'm and n are integer' is incorrect in subject number agreement." In the Amendment, claims 22-24 and 26-30 (as well as claims 1, 3, 18 and 20) have been further amended as the Examiner suggested.

(e) Regarding claim 33, the Office Action asserted that "the bond '-' is not directly attached to the sulfoxide moiety i.e., '-S(O)-.'" In the Amendment, claim 33 has been further amended as the Examiner suggested.

The Advisory Action stated that “the proposed amendment, if entered, would overcome the claim objections.” In view of the foregoing, withdrawal of the objection is respectfully requested.

III. Response to Rejection under 35 U.S.C. § 112

Claims 23, 24, and 26 were rejected under 35 U.S.C. § 112(b) as allegedly being indefinite. Patent Owner respectfully submits that the claims as amended are not indefinite.

The Office Action asserted that variable q in formula II is not defined in the claims. In response, the claims have been amended to add the definition for q.

The Advisory Action stated that “the proposed amendment, if entered, would overcome [this] rejection.” Accordingly, withdrawal of the rejection is respectfully requested.

IV. Response to Rejection under 35 U.S.C. § 305

Claims 3 and 23 were rejected under 35 U.S.C. § 305 as allegedly enlarging the scope of the claims of the patent. Patent Owner respectfully submits that the claims as amended do not enlarge the scope of the issued claims.

In the Amendment, claim 3 as amended as well as new claim 23 retain the same language at issue as issued claim 3.

The Advisory Action stated that “the proposed amendment, if entered, would overcome [this] rejection.” Accordingly, withdrawal of the rejection is respectfully requested.

V. Response to the Advisory Action

The Advisory Action indicated that the proposed amendment filed on October 20, 2020 does not comply with 37 C.F.R. § 1.530(f)(1) due to use of double brackets instead of single brackets in claims 1 and 3.

In the present Amendment, single brackets are being used. Patent Owner respectfully submits that the present Amendment is in full compliance with the 37 C.F.R. § 1.530 requirements and thus should be entered.

VI. Conclusion

From the foregoing, allowance of all the pending claims under reexamination is believed to be next in order and such action is earnestly solicited. If there are any questions concerning this paper or the patent 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 3, 2020

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Electronic Acknowledgement Receipt	
EFS ID:	41019564
Application Number:	90014390
International Application Number:	
Confirmation Number:	4956
Title of Invention:	HYDROPHILIC LINKERS AND THEIR USES FOR CONJUGATION OF DRUGS TO A CELL BINDING MOLECULES
First Named Inventor/Applicant Name:	10131682
Customer Number:	21839
Filer:	Fang Liu/Sarah Noel
Filer Authorized By:	Fang Liu
Attorney Docket Number:	0088597-000018
Receipt Date:	03-NOV-2020
Filing Date:	16-OCT-2019
Time Stamp:	11:22:03
Application Type:	Reexam (Patent Owner)

Payment information:

Submitted with Payment	no				
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Reexam Certificate of Service	Certificate.pdf	136071 0525b1f6ea2befbe2ef9411f6c9d5dec0a668da441	no	1
Warnings:					

Information:					
2		Amendment.pdf	331755	yes	22
			37ab3f7c21c9e7bc07fd355d54493122d46e2e7a		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Applicant Arguments/Remarks Made in an Amendment		19	22	
	Claims		2	18	
	Response After Final Action		1	1	
Warnings:					
Information:					
Total Files Size (in bytes):			467826		
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