



杭州多禧生物科技有限公司
HANGZHOU DAC BIOTECHNOLOGY CO., LTD

***SYNAFFIX B.V. v.
HANGZHOU DAC BIOTECH CO., LTD.***

IPR2022-01531

U.S. Patent No. 10,131,682 C1

Patent Owner DAC's Hearing Demonstratives

June 12, 2025

Grounds and Challenged Claims

- SynAffix challenges claims 1-17, 20-21, 24-26, and 29-34 on five grounds.

Ground	Challenged Claims
1. Morales-Sanfrutos as evidence by Straus (§ 102)	1-3, 6, 24-25, 33
2. Harris (§§ 102, 103)	1, 20-21, 29-31
3. Singh in view of Harris (§ 103)	1-8, 10-12, 14-17, 20-21, 24, 26, 29-31
4. Singh in view of Harris and Bhakta (§ 103)	9, 13
5. Singh in view of Harris and Snow (§ 103)	2, 25, 32-34

Petition at 3.

Summary of Disputed Issues

Claim Construction

- **“Y represents a functional group that enables reaction ... with a cell-binding agent”**
 - > *DAC's construction:* “Y” must “by itself be a functional group that independently enables reaction with a cell-binding agent”
- **“Cell-binding agent”**
 - > *DAC's construction:* A “molecule that binds to, complexes with or reacts with a moiety of a cell population sought to be therapeutically or otherwise biologically modified”

Patent Owner's Response (POR) at 19, 28.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Vinyl Sulfone, Not Just Vinyl, Is the “Y” in the Asserted References

- For **all five grounds**, Petitioner relies on reference compounds containing a vinyl sulfone functional group
- **Vinyl sulfone**, not just vinyl, is the functional group that **enables the reaction** in each of these references
- **Both parties’ experts**—Dr. Tumey and Dr. Chari—**agree**
- **Vinyl sulfone**, as a whole, should be **mapped to “Y”**
- Petitioner incorrectly maps only vinyl to Y, so that it can map the sulfone to Q, which would otherwise be absent in the references

POR at 30-71.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Ground 1: No Anticipation over Morales-Sanfrutos and Straus

- Because Petitioner maps only the vinyl to Y and the sulfone to Q, Petitioner fails to show anticipation under DAC's construction
 - > Both parties' experts agree that vinyl sulfone, not vinyl alone, enables the Michael addition reaction in Morales-Sanfrutos
 - > Dondoni does **not** demonstrate that vinyl alone enables the Michael addition reaction of Morales-Sanfrutos
 - Dondoni describes a photoinduced reaction, a completely different reaction from the Michael addition reaction

POR at 37-42; Sur-Reply at 12-17.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Ground 1: No Anticipation over Morales-Sanfrutos and Straus

- Petitioner's alternative theory, mapping a terminal alkyne to Y, fails for two independent reasons:
 - > Morales-Sanfrutos does not disclose **any** terminal alkyne reacting with the horseradish peroxidase (HRP)—no evidence of its terminal alkyne enabling a reaction with the HRP
 - > A terminal alkyne is not independently reactive—no dispute the alkyne requires a copper catalyst to react with an azide
- Morales-Sanfrutos does not disclose any cell-binding agent—the HRP in Morales-Sanfrutos is a reporter used in cell-free assays

POR at 42-49; Sur-Reply at 16-18.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Ground 2: No Anticipation or Obviousness over Harris

- Because Petitioner maps only the vinyl to Y and the sulfone to Q, Petitioner fails to show either anticipation or obviousness under DAC's construction
- A POSA would not at once envisage any claimed compounds from Harris's broad genus disclosure
- Harris does not disclose a cell-binding agent
- Harris is not analogous art
- Petitioner's cursory obviousness analysis fails its burden of proof

POR at 53-60; Sur-Reply at 19-21.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Ground 3: No Obviousness over Singh in View of Harris

- Because Petitioner maps only the vinyl to Y and the sulfone to Q, Petitioner fails to show obviousness under DAC's construction
- Singh does not disclose any exemplary compound containing a sulfone or a vinyl sulfone—Petitioner and Dr. Chari admit as such
- Singh refers to vinyl sulfone only once as a “Z” “reactive functionality,” among many others
- A POSA would not have been motivated to modify Singh's linkers to add vinyl sulfone to arrive at any of the claimed compounds
- Petitioner's obviousness arguments are driven by hindsight

POR at 61-67; Sur-Reply at 21-26.

Ground 4: No Obviousness over Singh in View of Harris and Bhakta

- Same reasons for Ground 3 apply to Ground 4
- In addition:
 - > Petitioner does not explain sufficiently in the Petition how to modify any compound from Singh to arrive at any claimed compound
 - > Petitioner's belated analysis in its Reply still fails to properly map any alleged modification of Singh to any claimed compound to show all the claimed elements are met

POR at 68; Sur-Reply at 26-27.

Ground 5: No Obviousness over Singh in View of Harris and Snow

- Same reasons for Ground 3 apply to Ground 5
- In addition:
 - > Petitioner applies hindsight to select a specific structural formula and specific structural elements over numerous other possibilities disclosed in Snow
 - > Nothing suggests that Snow's linkers "impart higher water solubility" as Petitioner argues; the alleged modifications of Singh would make the linkers more hydrophobic and less soluble

POR at 69-71; Sur-Reply at 27-28.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Overview of the '682 Patent

U.S. Patent 10,131,682 C1

(12) United States Patent Zhao	(10) Patent No.: US 10,131,682 B2 (45) Date of Patent: Nov. 20, 2018
(54) HYDROPHILIC LINKERS AND THEIR USES FOR CONJUGATION OF DRUGS TO A CELL BINDING MOLECULES	(56) References Cited U.S. PATENT DOCUMENTS
(71) Applicant: Hangzhou DAC Biotech Co., Hangzhou (CN)	
(72) Inventor: R. Yongxin Zhao, Lexington, MA (US)	
(73) Assignee: HANGZHOU DAC BIOTECH CO., LTD., Hangzhou (CN)	
(*) Notice: Subject to any disclaimer, the patent is extended or adjusted U.S.C. 154(b) by 250 days.	
(21) Appl. No.: 14/432,073	
(22) PCT Filed: Nov. 24, 2012	

(12) EX PARTE REEXAMINATION CERTIFICATE (11787th) United States Patent Zhao		(10) Number: US 10,131,682 C1 (45) Certificate Issued: Jan. 4, 2021
(54) HYDROPHILIC LINKERS AND THEIR USES FOR CONJUGATION OF DRUGS TO A CELL BINDING MOLECULES	<i>C07D 207/46</i> (2006.01) <i>C07D 401/12</i> (2006.01) <i>A61K 31/10</i> (2006.01) <i>A61K 31/454</i> (2006.01) <i>C07F 9/58</i> (2006.01)	
(71) Applicant: Hangzhou DAC Biotech Co., Ltd., Hangzhou (CN)	(52) U.S. Cl. CPC <i>C07F 9/572</i> (2013.01); <i>A61K 31/10</i> (2013.01); <i>A61K 31/454</i> (2013.01); <i>A61K 31/662</i> (2013.01); <i>A61K 47/6889</i> (2017.08); <i>C07D 207/46</i> (2013.01); <i>C07D 401/12</i> (2013.01); <i>C07F 9/58</i> (2013.01)	
(72) Inventor: R. Yongxin Zhao, Lexington, MA (US)	(58) Field of Classification Search None See application file for complete search history.	
(73) Assignee: HANGZHOU DAC BIOTECH CO., LTD., Hangzhou (CN)	(56) References Cited To view the complete listing of prior art documents cited during the proceeding for Reexamination Control Number 90/014,390, please refer to the USPTO's public Patent Application Information Retrieval (PAIR) system under the Display References tab. <i>Primary Examiner</i> — Dwayne C. Jones	
Reexamination Request: No. 90/014,390, Oct. 16, 2019	(57) ABSTRACT Cell binding agent-drug conjugates comprising hydrophilic linkers, and methods of using such linkers and conjugates are provided.	
Reexamination Certificate for: Patent No.: 10,131,682 Issued: Nov. 20, 2018 Appl. No.: 14/432,073 PCT Filed: Nov. 24, 2012 PCT No.: PCT/IB2012/056700 § 371 (c)(1), Mar. 27, 2015 (2) Date: Mar. 27, 2015 PCT Pub. No.: WO2014/080251 PCT Pub. Date: May 30, 2014		
(51) Int. Cl. <i>C07F 9/572</i> (2006.01) <i>A61K 47/68</i> (2017.01) <i>A61K 31/662</i> (2006.01)		

- Priority filing date: **November 24, 2012**
- Originally issued with **21 claims**
- After *ex parte* reexamination, **claims 1, 3, 18, and 20 amended; claims 22-34 added**

POR at 7; EX1001; EX1002.

Challenged Claims Recite Three Different Formulas

- Challenged independent claims recite different formulas relating to linkers (I), conjugates (II), and linker-drug compounds (IV)

Claim	Structure	Formula
1	$Y-R_1-Q-R_2-T-R_3-R_4-Z$ $\begin{array}{c} \diagup \quad \diagdown \\ R_5 \quad R_6 \end{array}$	I
3, 24, 26	$Cb \left(R_1-Q-R_2-T-R_3-R_4-Drug \right)_q$ $\begin{array}{c} \diagup \quad \diagdown \\ R_5 \quad R_6 \end{array}$	II
20, 29, 30	$Y-R_1-Q-R_2-T-R_3-R_4-Drug$ $\begin{array}{c} \diagup \quad \diagdown \\ R_5 \quad R_6 \end{array}$	IV

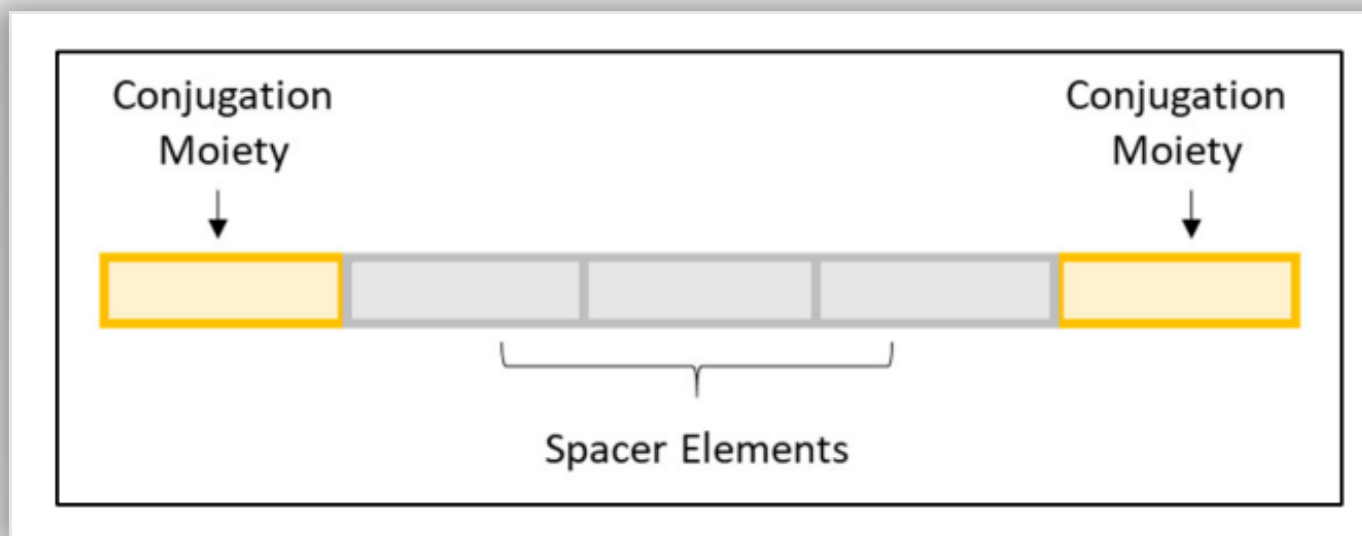
POR at 1, 8; EX1001; EX1002.

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

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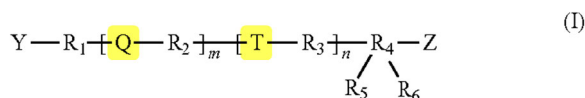
Linkers Contain Conjugation Moieties and Spacer Elements

- **Conjugation moieties** at the end for reacting or linking to antibody or drug
- **Spacer elements** in the middle to provide the linker structure and space between the antibody and the drug



Q and T Are Spacer Elements in the Linker, Defined by Structures

1. 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 $-S(O_2)-$, 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 $-S(O_2)-$, 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;

EX1002 at 2.

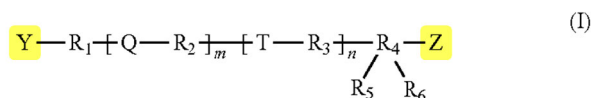
Phosphinate	Sulfone / Sulfonyl	Sulfoxide
$\begin{array}{c} O \\ // \\ P \\ \backslash \\ OM \end{array}$	$\begin{array}{c} O \\ \\ S \\ \\ O \end{array}$	$\begin{array}{c} S \\ \\ O \end{array}$

- The hydrophilic linkers with the phosphinate, sulfone, and/or sulfoxide spacer elements:
 - > Reduce the aggregation of the conjugates
 - > Result in higher potency of the conjugates
 - > Allow the drug to be retained inside the target cell after the drug-linker is released from the conjugate

POR at 11-12; EX1001; EX1002.

Y and Z Are Conjugation Moieties in the Linker, Defined by Functions

1. 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 $-\text{P}(=\text{O})(\text{OM})-$, 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 $-\text{P}(=\text{O})(\text{OM})-$; when $n=1$, $m=0$, T is not $-\text{P}(=\text{O})(\text{OM})-$; and when Q or T is $-\text{S}(\text{O}_2)-$, 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;

- “Y” is “a functional group that enables reaction of the hydrophilic linker with a cell-binding agent”
- “Z” is “a functional group that enables linkage of the hydrophilic linker to a cytotoxic drug” via certain types of bond

EX1002 at 2.

POR at 2, 9; EX1002.

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

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Claim Construction: The “Y” Term

Pre-Institution DRP Decision Is Not Law of the Case, as SynAffix Argues

“[T]he Board is not bound by any findings made in its Institution Decision. At that point, the Board is considering the matter preliminarily without the benefit of a full record. The Board is free to change its view of the merits after further development of the record, and ***should do so*** if convinced its initial inclinations were wrong. To conclude otherwise would collapse these two very different analyses into one, which we decline to do.”

Trivascular, Inc. v. Samuels, 812 F.3d 1056, 1068
(Fed. Cir. 2016) (emphasis in original).

Sur-Reply at 1-3.

Plain Meaning Controls, Absent Clear Lexicography or Disclaimer

“There are **only two** exceptions to [the] general rule” that claim terms “are generally given their ordinary and customary meaning as understood by a [POSA] when read in the context of the specification and prosecution history”: “**1)** when a patentee sets out a definition and acts as his own lexicographer, or **2)** when the patentee disavows the full scope of a claim term either in the specification or during prosecution.”

Thorner v. Sony Comput. Entm’t Am. LLC,
669 F.3d 1362, 1365 (Fed. Cir. 2012).

POR at 18-19.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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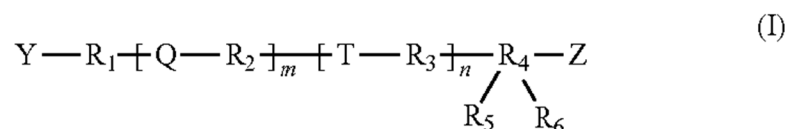
The “Y” Term Should Be Construed as Its Plain Meaning

- “Y represents a functional group that enables reaction ... with a cell-binding agent”
 - > *DAC’s construction*: “Y” must “by itself be a functional group that independently enables reaction with a cell-binding agent”
 - > *SynAffix’s construction*: “Q-Y can be met by vinyl sulfone”
- DAC’s construction is consistent with the plain and ordinary meaning of the claim language and the intrinsic record
- No clear and unmistakable lexicography or disclaimer of “Y”

POR at 19; Reply at 2.

The Claim Language Supports DAC's Construction

1. 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 $-\text{P}(=\text{O})(\text{OM})-$, or $-\text{S}(\text{O}_2)-$, or $-\text{S}(\text{O})-$;

- The claim language plainly requires that Y itself be a functional group that independently enables the reaction
- The claims do not refer to any other element, such as “Y and Q”, to enable the reaction

POR at 19-21; EX1002 at 2.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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The Claim Language Supports DAC's Construction

- The claims define Y and Q as separate and distinct elements

Formula I	Formula IV
$Y-R_1-Q-R_2-T-R_3-R_4-Z$ $\begin{array}{c} \diagup \quad \diagdown \\ R_5 \quad R_6 \end{array}$	$Y-R_1-Q-R_2-T-R_3-R_4-\text{Drug}$ $\begin{array}{c} \diagup \quad \diagdown \\ R_5 \quad R_6 \end{array}$

- SynAffix's expert, Dr. Chari, agrees

25. The Q and T variables of formulas (I), (II), and (IV) are identically defined and are selected from -P(=O)(OM)-, or -S(O₂)-, or -S(O)-. Depending on

26. The Y variable is present in both formulas (I) and (IV) and is defined as a functional group that enables reaction of the hydrophilic linker with a cell-binding agent.

POR at 19-21; EX1003 at ¶¶ 25-26.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Becton Applies, as Confirmed by the Context of the '682 Patent

“Where a claim lists elements separately, the clear implication of the claim language is that those elements are distinct components of the patented invention.”

Becton, Dickinson & Co. v. Tyco Healthcare Grp., LP, 616 F.3d 1249 1254 (Fed. Cir. 2010) (cleaned up).

See also Regeneron Pharms., Inc. v. Mylan Pharms. Inc., 130 F.4th, 1372, 1379 (Fed. Cir. 2025) (collecting cases).

POR at 21-22; Sur-Reply at 3-6.

Becton Applies, as Confirmed by the Context of the '682 Patent

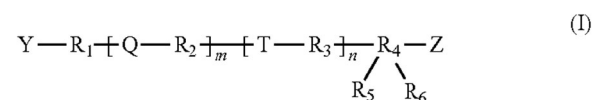
- The intrinsic record of the '682 patent supports a construction that the Y and Q elements are separate and distinct
 - > The **claimed formula** depicts Y and Q as separate and distinct elements
 - > The **specification** consistently describes the Y conjugation moiety separately from the Q spacer element
 - > During **prosecution**, Y and Q are treated as separate elements, mapped to distinctly different structural elements in the reference compounds

POR at 21-22; Sur-Reply at 3-6.

The Claim Language Supports DAC's Construction

- The claims define “Y” and “Z” differently
- A **reaction** is the chemical process by which chemicals react
- A **linkage** is a covalent connection between atoms
- “Y” is not “broader” than “Z” as SynAffix asserts

1. 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 $-\text{P}(=\text{O})(\text{OM})-$, 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 $-\text{P}(=\text{O})(\text{OM})-$; when $n=1$, $m=0$, T is not $-\text{P}(=\text{O})(\text{OM})-$; and when Q or T is $-\text{S}(\text{O}_2)-$, 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;

POR at 6-7, 22-24; Sur-Reply at 6-7; EX1002 at 2.

The Claim Language Supports DAC's Construction

- Dr. Chari explained that “**linkage**” means just “to connect” or “a covalent bond”

Q. And what would a POSA understand linkage to mean in that context?

A. Just to connect the link together. It means it's connected. You can say it's a covalent bond.

POR at 24; EX2037 at 15:18-16:3.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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The Claim Language Supports DAC's Construction

- Dr. Chari explained that “**reaction**” means “the process to get” “two things together”, and “enabling reaction” means “it can react”

Q. And what would a POSA in 2012 understand "reaction" to mean?

A. A reaction is something -- you put two things together to get something else. It's reacted. They don't react separately by each other.

Q. Is reaction the process to get that connection together?

A. Yes, that's correct.

Q. And a POSA would have understood that in 2012?

A. Yes.

EX2037 at 33:6-17.

Q. And when I say, "enabling the reaction," what do you understand that to mean?

A. It means it can react. Say you have nucleophile or whatever, it would react. It can react from nucleophile. Nucleophile, N-U-C-L-E-O-P-H-I-L-E.

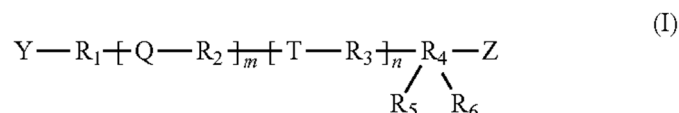
EX2037 at 22:4-9.

POR at 24.

The Specification Supports DAC's Construction

- The specification describes “Y” as an independently reactive functional group that enables reaction with a cell-binding agent
- The specification does not alter the plain meaning of “Y”

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



wherein:

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

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

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

EX1001 at 8:61-67.

EX1001 at 8:11-25.

POR at 22-23.

The Specification Supports DAC's Construction

- All examples of “Y” in specification are independently reactive

drugs/antibody (D/A) linked. The hydrophilic cross-linkers described herein have diverse functional groups that can react with any cell-binding agent that possesses a suitable substituent. For example cell-binding agents bearing an amino or hydroxyl substituent can react with cross linkers bearing an N-hydroxysuccinimide (NHS) ester, cell-binding agents bearing a thiol substituent can react with cross linkers bearing a maleimido or haloacetyl group. Additionally, cell-binding agents bearing a carbonyl substituent can react with cross linkers bearing a hydrazide or a hydroxylamine. One skilled in the art can readily determine which linker to use based on the known reactivity of the available functional group on the cell-binding agent.

EX1001 at 13:51-63.

143. For Formulas I and IV, the specification provides examples of the reactivity of Y with certain functional groups (substituents) on a cell-binding agent. In particular, Y can be reactive with (1) an amine substituent, (2) a thiol substituent, (3) a hydroxyl substituent, or (4) a carbonyl substituent. *See id.* at 13:54-60. The specification provides examples of functional groups that possess this reactivity and discloses amine reactive agents (*e.g.*, N-hydroxysuccinimide esters, p-nitrophenylesters, dinitrophenyl esters, pentafluorophenyl esters), thiol reactive agents (*e.g.*, pyridyldisulfides, nitropyridyldisulfides, maleimides, haloacetates and carboxylic acid chlorides), carbonyl reactive agents (*e.g.*, hydrazide or hydroxylamine), or hydroxyl reactive agents (*e.g.*, N-hydroxysuccinimide esters) (*See id.* at 8:61-67, 13:54-60.) In each of these cases, the Y group is independently sufficient for reactivity with the cell-binding agent, and does not in any way depend on the presence or absence of a Q or T.

EX2038 at ¶ 143.

POR at 22.

The Specification Supports DAC's Construction

- Not all examples of “Z” in the specification are independently reactive

physiological conditions. EX2038 at ¶ 64; EX1063 at 15:11-16:18, 18:7-21. In contrast, the '682 patent when discussing the “Z” functional group includes examples of both functional groups that independently enable reaction with and linkage to a cytotoxic drug under physiological conditions (such as maleimido and haloacetyl), and functional groups that require additional activation (*e.g.*, a catalyst or chemical reagent) for a reaction to take place (such as amino, carboxy, aldehydes, and hydroxy). EX1001 at 9:1-7.

Sur-Reply at 6-7, 13; EX2047 at ¶ 21.

The Specification Supports DAC's Construction

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

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

- The specification provides different examples of “Y” and “Z”
- All examples of “Y” are independently reactive
- Only some examples of “Z” are independently reactive, others are not
- The examples show “Y” is not broader than “Z”, as SynAffix argues

POR at 6-7, 22-24; Sur-Reply at 6-7; EX1001 at 8:61-67, 9:1-7.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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The Prosecution History Supports DAC's Construction

A party “seeking to invoke prosecution history disclaimer bears the burden of proving the existence of a **clear and unmistakable** disclaimer.”

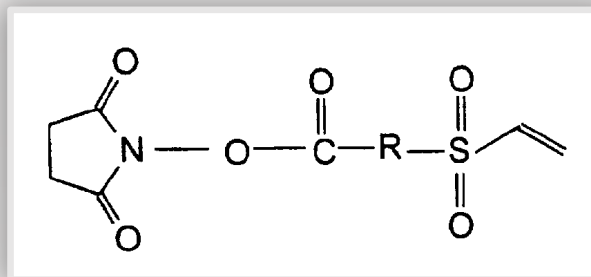
Trivascular, Inc. v. Samuels, 812 F.3d 1056, 1063-64
(Fed. Cir. 2016) (cleaned up).

- No clear and unmistakable disclaimer in the prosecution history to alter the plain meaning of the “Y” term

POR at 23-24; Sur-Reply at 9-11.

The Prosecution History Supports DAC's Construction: Rejection Based on Lees

- The Examiner's statements regarding a rejection based on **Lees**:



EX2026 (Lees) at 24.

and a protein to the other (page 23, lines 17-19). The NHS vinylsulfone or Lees anticipates instant formula 55 shown in Figure 6 of the instant specification. Therefore the NHS portion represents a functional group that enables reaction of the linker with a cell binding agent, and the vinyl group enables linkage of the linker to a cytotoxic drug as indicated by structure 56 of Figure 6.

POR at 23-24; EX1018 at 42-43.

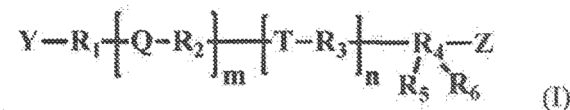
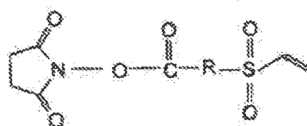
The Prosecution History Supports DAC's Construction: Rejection Based on Lees

- The Applicant's statements regarding the rejection based on **Lees**:

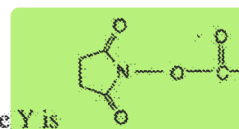
III. Response to Rejection under 35 U.S.C. § 102

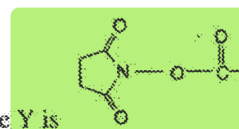
Claim 1 was rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by WO 97/41897 to Lees. Applicant respectfully submits that claim 1 as amended is novel and patentable over Lees for at least the following reasons.

Lees discloses protein/polysaccharide conjugates prepared via a heterobifunctional vinylsulfone, such as an N-hydroxysuccinimide vinylsulfone having the following structure:



This compound corresponds to



recited in claim 1 of the present application, where Y is , Q (or T) is $-S(O_2)-$, m (or n) is 1, n (or m) is 0, $R_2(R_3)$ and R_4-R_6 are absent, and Z is .

On the other hand, claim 1 of the present application recites that when Q or T is $-S(O_2)-$, m and n are not 0, thereby excluding the above noted compound described in Lees.

POR at 23-24;
EX1018 at 62.

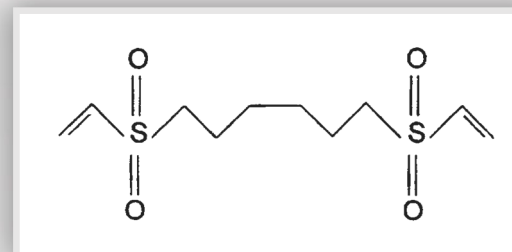
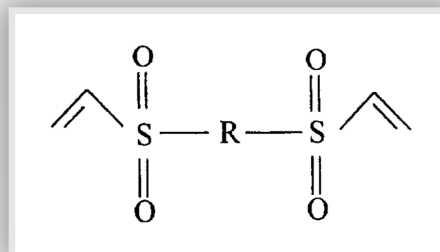
The Prosecution History Supports DAC's Construction: Rejection Based on Lees

- Neither the Examiner nor the Applicant mapped the vinyl in **Lees** to “Y”
- When discussing the rejection over Lees, the Applicant mapped “Z” to vinyl, and “Y” to the entire reactive NHS ester group
- The reactive **NHS ester** independently enables reaction, and the mapping supports DAC's construction
- Mapping “Z” to vinyl is *not* a clear and unmistakable redefinition or disclaimer of the plain meaning of “Y”—the claims and the specification use different words to define Y and Z

POR at 23-24.

The Prosecution History Supports DAC's Construction: Rejection Based on Lees

- **Lees** expressly discloses the following compounds:

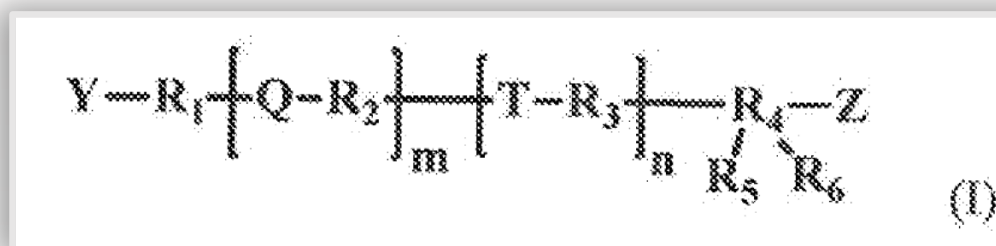


EX2026 at 22-23.

- Mapping Y to vinyl would render claim 1 anticipated by **Lees**



*If mapping vinyl to Y and Z,
sulfone to Q and T, with m and n being
1, R₁, R₃, R₄, R₅, and R₆ being absent*

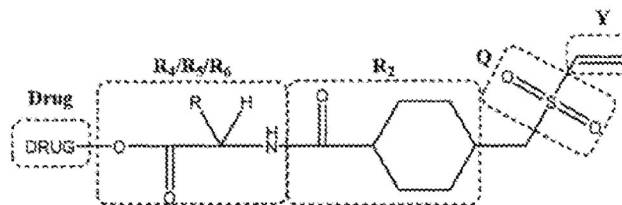


POR at 24.

The Prosecution History Supports DAC's Construction: Rejection of Claim 3

- Statements regarding a rejection of **claim 3** does not alter the meaning of "Y"
- Applicant's statements are too vague and ambiguous to constitute a clear disclaimer

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 R_2 in formula (II) of **claim 3** of the present patent contains a cyclic structure.

On the other hand, R_2 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.

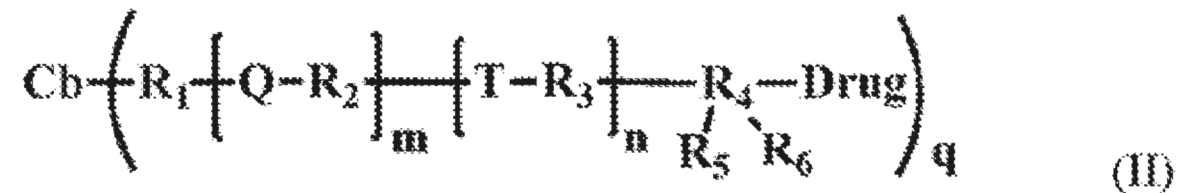
POR at 24-25;
EX1019 at 72-73.

The Prosecution History Supports DAC's Construction: Rejection of Claim 3

- **Claim 3** does not even recite any “Y” functional group

II. Independent Claim 3

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



POR at 24-25; EX1019 at 68.

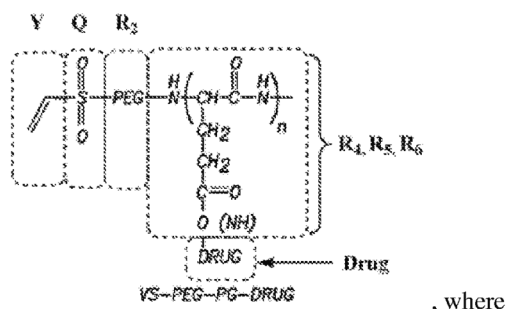
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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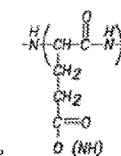
The Prosecution History Supports DAC's Construction: Rejection of Claim 20

- Statements regarding a rejection of **claim 20** does not alter the meaning of “Y”
- The **Examiner** mapped Y to vinyl in WO'497:

21. With respect to **claim 20** in view of the Group I claim interpretation of variables **R₁**, **R₂**, **R₃**, and **R₄** the VS¹-PEG-PG-DRUG of WO'497 (*i.e.*, Figure 2) is correlated to the instant variables of **claim 20** (indicated below with the encircled dashed lines). The resulting representation depicted as:



- instant Y** corresponds to **H₂C=CH-** of WO'497;
- instant R₁** (not depicted in the above representation) is **absent**;
- instant Q** corresponds to **-SO₂-** of WO'497;
- instant R₂** corresponds to **-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 **-DRUG** of WO'497 (*e.g.*, doxorubicin) that is connected to the linker by an ester or amide bond.

Sur-Reply at 9-10; EX1019 at 9-10.

The Prosecution History Supports DAC's Construction: Rejection of Claim 20

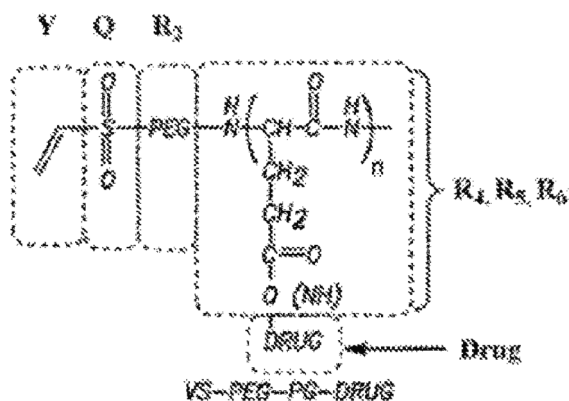
- The **Applicant's** response statements regarding the rejection of **claim 20** are too vague and ambiguous to constitute a clear disclaimer

Turning to WO '497, WO '497 allegedly discloses compounds corresponding to formula (II) recited in claim 3 of the present patent wherein R_1 is $S-CH_2-CH_2$, 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 $-S(O_2)-$, m is 1, and n is 0, or (ii) T is $-S(O_2)-$, 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. Further, claim 20 as amended recites that when (i) Q is $-S(O_2)-$, m is 1, and n is 0, or (ii) T is $-S(O_2)-$, 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.

Sur-Reply at 9-10; EX1019 at 63-64.

The Prosecution History Supports DAC's Construction: Rejection of Claim 20

- The **Applicant's** response statements regarding the rejection of **claim 20** are too vague and ambiguous to constitute a clear disclaimer



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.

Sur-Reply at 8-9; EX1019 at 75.

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

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No Clear and Unmistakable Disclaimer Based on Ambiguous Statements

“An applicant’s silence in response to an examiner’s characterization of a claim does not reflect the applicant’s clear and unmistakable acquiescence to that characterization if the claim is eventually allowed on grounds unrelated to the examiner’s unrebutted characterization.”

3M Innovative Props. Co. v. Avery Dennison Corp.,
350 F.3d 1365, 1374-74 (Fed. Cir. 2003).

“[T]he examiner’s unilateral remarks alone do not affect the scope of the claim.”

H. Lundbeck A/S v. Lupin Ltd., 87 F.4th 1361, 1374 (Fed. Cir. 2023).

Sur-Reply at 8-9.

No Clear and Unmistakable Disclaimer Based on Ambiguous Statements

“[W]e have thus consistently rejected prosecution statements too vague or ambiguous to qualify as a disavowal of claim scope.”

Omega Eng'g Inc. v. Raytek Corp., 334 F.3d 1314, 1324-25 (Fed. Cir. 2003).

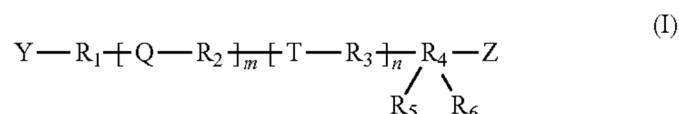
“To act as its own lexicographer, a patentee must clearly set forth a definition of the disputed claim term other than its plain and ordinary meaning. . . . To constitute disclaimer, there must be a clear and unmistakable disclaimer.”

Thorner v. Sony Computer Ent. Am. LLC, 669 F.3d 1362, 1365-67 (Fed. Cir. 2012)
(internal quotation marks and citation omitted).

POR at 19-23; Sur-Reply at 8-9.

Dictionary Definitions of “Functional Group” Supports DAC’s Construction

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



wherein:

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

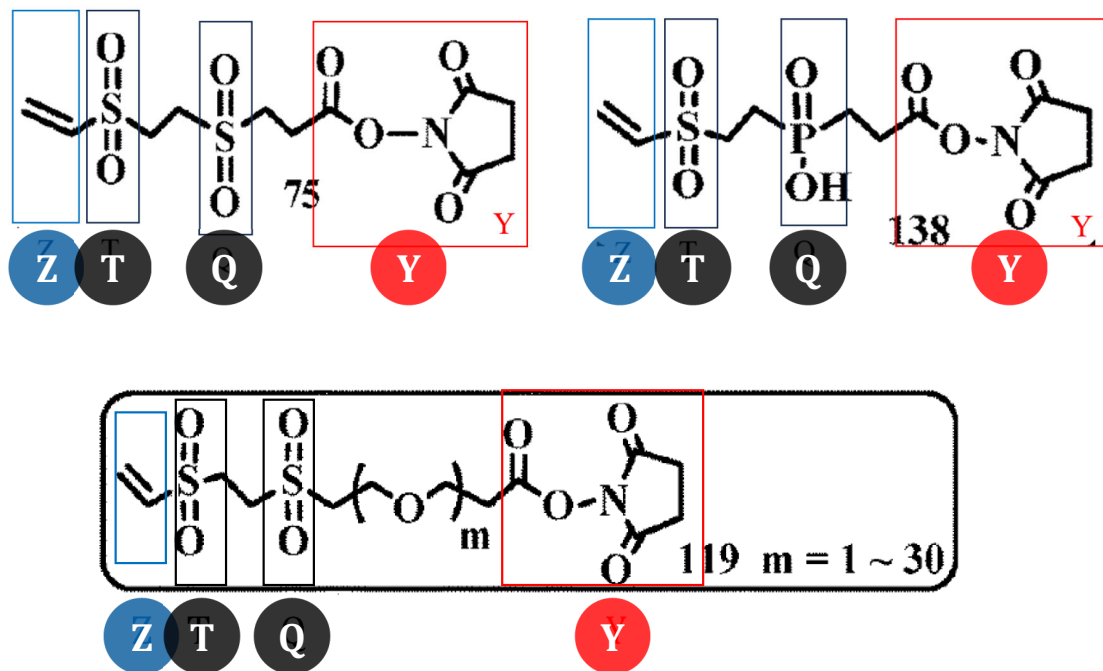
Q and T are either $-\text{P}(=\text{O})(\text{OM})-$, or $-\text{S}(\text{O}_2)-$, or $-\text{S}(\text{O})-$;

EX1001 at 8:11-25.

- Dr. Chari agreed that “**functional group**” means “a **specific identifiable group of atoms** within a molecule that directly contributes to its characteristic chemical properties and reactivity”
- Other dictionaries provide similar definitions, e.g., “a group of atoms that reacts **as a single unit** and determines the properties and structure of a class of chemicals”
- The “Y” group, **as a single unit**, must be capable of and responsible for the reaction with a cell-binding agent

POR at 24-25; EX1002; EX2037 at 10:5-11; EX2042.

DAC's Construction Does Not Exclude the Disclosed Embodiments



- Examples **75**, **119**, and **138** of the patent are within the scope of claim 1 under DAC's proposed construction

POR at 24-25.

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

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DAC's Construction of "Y" Is Consistent with the DRP's Analysis

- DRP concluded that compounds **75** and **138** fall within claim 1
 - > DAC's construction does not exclude these compounds
- DRP found that "Z" was mapped to vinyl during prosecution but never found "Y" mapped to vinyl during prosecution
 - > DAC's construction is consistent with mapping "Z" to vinyl and "Y" to an entire reactive NHS ester group

Sur-Reply at 1-3.

SynAffix's Proposed Construction Is Unsupported and Incorrect

that vinyl sulfone cannot satisfy Q-Y should again be rejected. The claim language, intrinsic evidence, and precedent all support Petitioner's position that Q-Y can be met by vinyl sulfone.

Reply at 2.

- SynAffix ignores that the plain claim language requires “Y”, not “Q-Y”, to be a functional group that enables reaction with a cell-binding agent
- SynAffix's own expert, Dr. Chari, agrees with DAC, not SynAffix, that vinyl **cannot** be “Y”, and vinyl sulfone can be “Y” because the sulfone enables the reaction

POR at 19-28; Sur-Reply at 3-11.

SynAffix's Expert, Dr. Chari, Agrees with DAC's Construction

- Dr. Chari admitted (1) vinyl and vinyl sulfone are different functional groups, and (2) vinyl “won’t react by itself” and it needs “something else” to activate it

Q. And a POSA in 2012 would have understood that vinyl is a functional group, right?

A. Yes.

Q. Would a POSA have understood that a vinyl enables linkage via a thioether bond?

A. No. Vinyl won't react unless there is some reactivating thing. It doesn't react by itself. You would have something else other than vinyl. I don't think it would react, no. It won't react by itself.

POR at 27; EX2037 at 19:15-24.

SynAffix's Expert, Dr. Chari, Agrees with DAC's Construction

- Dr. Chari admitted vinyl alone would not enable reaction with a cell-binding agent in the context of the '682 patent (e.g., reactions in water)

Q. So a vinyl alone would not be able to enable the reaction?

A. Not unless you do some kind of real reaction; not a normal reaction. Like, you do it in water.

Q. And the '682 patent is talking about normal reactions?

A. Exactly. I mean, not normal. I mean, you can have some heated reaction disorder; something that is not normally used in the context of this patent.

POR at 27; EX2037 at 20:17-21:3.

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

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SynAffix's Expert, Dr. Chari, Agrees with DAC's Construction

- Dr. Chari admitted (1) vinyl “doesn’t react by itself” because it is “not reactive”, and (2) vinyl “needs to be activated so it can react”, “something to activate the carbon”

Q. Why wouldn't vinyl react by itself?

A. It's not reactive. You need to have something next to it to make it react, like sulphur or carbonate or something like that. It doesn't react by itself. It needs to be activated so it can react. A POSA would understand vinyl does not react by itself.

Q. And why would a POSA understand that vinyl is unreactive by itself?

A. A POSA would know what makes a reaction happen. The carbon does not charge enough for it to -- the way reactions work is you need to have an attack on the carbon. The carbon is not positively charged enough for the reaction to occur. It needs something to activate the carbon to make sure it can react.

POR at 27; EX2037 at 20:1-16.

SynAffix's Expert, Dr. Chari, Agrees with DAC's Construction

- Dr. Chari admitted (1) vinyl and vinyl sulfone are different functional groups, and (2) vinyl sulfone is “much more reactive” than vinyl

Q. Is a vinyl sulfone functional group different than a vinyl functional group?

A. Yes. It's much more reactive.

Q. And a POSA would have known that those were different functional groups in 2012, right?

A. Yes.

POR at 27; EX2037 at 21:11-16.

SynAffix's Expert, Dr. Chari, Agrees with DAC's Construction

- Dr. Chari admitted it is the **sulfone** in vinyl sulfone that enables the reaction, because “[s]ulfone would be the reason why it would react”

Q. In the vinyl sulfone, what is the atom that's enabling the reaction?

A. All you need is -- you need some group that will activate the vinyl sulfone. You need one that helps draw electrons from the vinyl to make it react. Sulfone would be the reason why it would react.

Q. So sulfone would be what would be enabling the reaction?

A. Exactly.

Q. And when I say, "enabling the reaction," what do you understand that to mean?

A. It means it can react. Say you have nucleophile or whatever, it would react. It can react from nucleophile. Nucleophile, N-U-C-L-E-O-P-H-I-L-E.

POR at 27; EX2037 at 21:17-22:9.

SynAffix's Expert, Dr. Chari, Agrees with DAC's Construction

- Dr. Chari admitted **vinyl sulfone, not vinyl, is the “Y”** because “you need a vinyl sulfone to enable the reaction” and “vinyl alone would not be sufficient”

In your opinion, compound 75 is showing the vinyl as Y?

A. (Witness reviews document) Vinyl sulfone, I would say. Vinyl sulfone is Y.

Q. The vinyl sulfone, in your opinion, together is Y?

A. Exactly.

Q. And how about for compound 99 on the next page, Sheet 6 of 23?

A. The same. The vinyl sulfone is Y.

Q. And how about compound 119 on Sheet 7 of 23?

A. It looks like the vinyl sulfone is Y.

Q. And one more page. Turn to Sheet 8 of 23, compound 138. What's Y there?

A. Also vinyl sulfone.

Q. Why do you say that for each of compounds 75, 99, 119 and 138?

A. It says it enables a reaction. To me, you need a vinyl sulfone to enable the reaction. That's why I say that.

Q. The vinyl alone would not be sufficient?

A. No; not to -- no.

POR at 27; EX2037 at 48:14-49:12.

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

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SynAffix's Expert, Dr. Chari, Agrees with DAC's Construction

- Dr. Chari confirmed in his second deposition that his opinions regarding vinyl, sulfone, and vinyl sulfone have not changed

Q. And in the Michael addition reaction a vinyl group needs something else to activate the carbon to make it reactive; right?

A. That's correct.

Q. And you had previously stated that the vinyl group cannot react by itself and the adjacent sulfone is necessary to activate the vinyl to enable the Michael addition reaction; right?

A. That's correct. Yes.

Q. And you would agree that your opinions with respect to whether vinyl in the context of a Michael addition reaction can react by itself have not changed; correct?

A. Not changed, no.

Q. So the adjacent sulfone in the vinyl sulfone group activates the vinyl to make the reaction going; right?

A. That is correct.

Q. And without the adjacent sulfone, the Michael addition reaction would not proceed with just the vinyl group; right?

A. I don't think it does.

Q. There's no reason for you to think it does; right?

A. Right. Correct.

EX2046 at 13:8-11, 19:14-20:18.

Claim Construction: “Cell-Binding Agent”

“Cell-binding agent”

- ***DAC’s construction:*** A “cell-binding agent” is a “molecule that binds to, complexes with or reacts with a moiety of a cell population sought to be therapeutically or otherwise biologically modified”
- ***SynAffix’s construction:*** Any agent that binds to cells
- The Board adopted DAC’s proposed construction in the institution decision.

POR at 28-29; Reply at 12-13; ID at 20-21.

The Specification Defines the Meaning of “Cell-Binding”

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

POR at 28-29; Sur-Reply at 11; EX1001 at 14:39-44.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Dr. Chari Agrees that Specification Defines “Cell-Binding” Molecule

Q. And my question for you is, Column 14, Lines 39 through 44 provide a definition that the '682 patent used for a cell-binding agent?

MR. HOUSTON: Objection, form.

A. A cell-binding molecule, yeah.

POR at 28-29; EX2037 at 51:24-52:4.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Ground 1: Morales-Sanfrutos and Straus (§ 102)

Asserted References: Morales-Sanfrutos (EX1005)

Vinyl Sulfone Bifunctional Tag Reagents for Single-Point Modification of Proteins

Julia Morales-Sanfrutos, Francisco Javier Lopez-Jaramillo, Fernando Hernandez-Mateo, and Francisco Santoyo-Gonzalez*

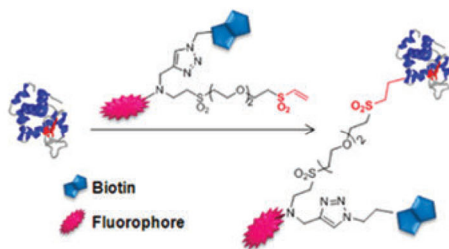
Departamento de Química Orgánica, Facultad de Ciencias, Instituto de Biotecnología, Universidad de Granada, 18071 Granada, Spain

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Published on Web 05/24/2010

J. Org. Chem. **2010**, 75, 4039–4047



The introduction of multiple labels onto biomolecules is a challenge. We report herein the synthesis of vinyl sulfone derivatized bifunctional tag single attachment point reagents (BTSAP) bearing biotin and a fluorescent tag and their applications in proteins for the introduction of multiple labels by means of the Michael type addition of the electrophilic vinyl sulfone group. These BTSAP reagents

POR at 31-36; EX1005.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Asserted References: Straus (EX1006)

Histochemistry (1986) 85:277-285

Histochemistry
© Springer-Verlag 1986

Unusual binding sites for horseradish peroxidase on the surface of cultured and isolated mammalian cells

Suppression of binding by certain nucleotides and glycoproteins, and a role for calcium

W. Straus* and J.M. Keller

Department of Biological Chemistry and Structure, University of Health Sciences/The Chicago Medical School,
3333 Green Bay Road, North Chicago, Illinois 60064, USA

Accepted March 8, 1986

Summary. Binding sites for horseradish peroxidase (HRP), with unusual properties, were detected on the surface of cultured and isolated cells after the cells (on cover slips) had been quickly dried, fixed in cold methanol, and post-fixed in a paraformaldehyde solution. The reaction for sur-

POR at 36-37; EX1006.

Morales-Sanfrutos Does Not Anticipate the Claims

To prove anticipation, Petitioner must demonstrate that “the ***four corners of a single, prior art document*** describe every element of the claimed invention” as “***arranged or combined in the same way as in the claim.***”

Net MoneyIN, Inc. v. VeriSign, Inc.,
545 F.3d 1359, 1369-70 (Fed. Cir. 2008).

POR at 30, 38.

Morales-Sanfrutos Discloses Vinyl Sulfone as the Reactive Functional Group for the Michael Addition Reaction

enzymatic activity or fluorescence). Herein, we report on the synthesis of bifunctional tag single-attachment-point reagents (BTSAP) bearing both biotin (affinity tag) and a fluorophore (fluorescent tag) and a vinyl sulfone function as a reactive linking group. As we have recently reported¹⁸ vinyl sulfone is an appealing function for protein conjugation through the Michael-type addition with the amine and thiol groups present in the proteogenic residues under mild conditions that are compatible with their biological function. These new vinyl sulfone BTSAP rea-

EX1005 at 2.

tion chemistries used on those strategies.³¹ Moreover, the vinyl sulfone group possess a broader reactivity as they react with the amine, thiol, and imidazole groups naturally present in proteins.

Conclusions

The combination of biotin as an anchor point and a fluorophore as a reporter group in a single compound leads to versatile bifunctional labeling reagents, especially appealing when functionalized with the vinyl sulfone group, whose reactivity toward proteins in “green” conditions has been previously reported.¹⁸ The synthesis of the vinyl sulfone

EX1005 at 6.

POR at 31.

Dr. Chari: Vinyl Sulfone, not Vinyl, is the “Y” in Morales-Sanfrutos

Q. In compound 11, what is the part of that molecule that would correspond to the Y that enables reaction with the horseradish peroxidase?

A. The vinyl sulfone in compound 11.

Q. And why do you say that?

A. Because it's the only reactive group left of the whole molecule that I can see. So it would have to react. It's the only reactive group.

Q. Not the vinyl alone?

A. No. I think vinyl alone will not react.

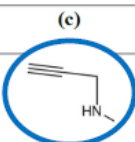
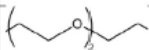
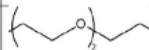
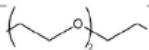
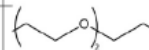
POR at 39-40; EX2037 at 52:16-53:1.

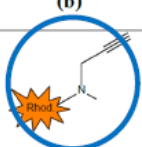
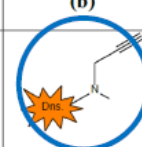
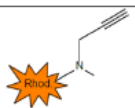
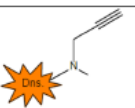
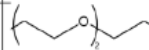
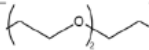
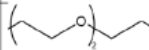
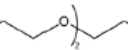
DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

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Petitioner Maps Only Vinyl to Y, Allowing It to Map Sulfone to Q

- In 1, 2(a), 2(b), 4(a), and 5(a), Petitioner maps **vinyl** to Y

Morales-Sanfrutos' Compounds 1-2 (Table B1)				
'682 (I)	Compound 1	Compound 2		
		(a)	(b)	(c)
Y				
Z				
R ₁	absent ⁵	absent	absent	
m	1	1	1	1
Q	-SO ₂ -	-SO ₂ -	-SO ₂ -	-SO ₂ -
R ₂				
p	2	2	2	2
n	1	1	1	1
T	-SO ₂ -	-SO ₂ -	-SO ₂ -	-SO ₂ -

'682 (I)	Compound 4		Compound 5	
	(a)	(b)	(a)	(b)
Y				
Z				
R ₁	absent		absent	
m	1	1	1	1
Q	-SO ₂ -	-SO ₂ -	-SO ₂ -	-SO ₂ -
R ₂				
p	2	2	2	2
n	1	1	1	1
T	-SO ₂ -	-SO ₂ -	-SO ₂ -	-SO ₂ -

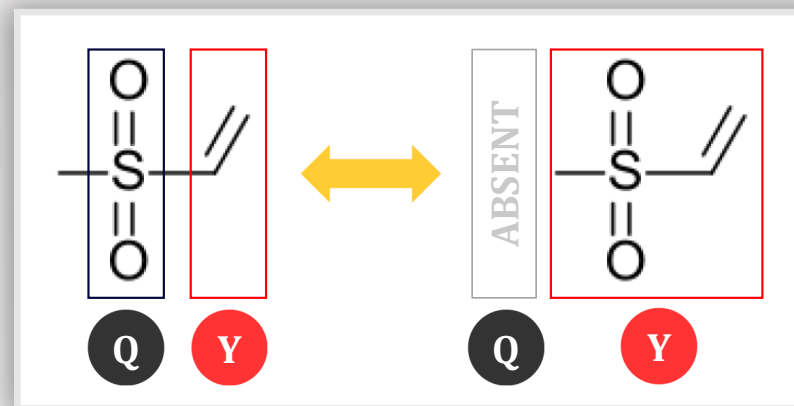
POR at 41-42.

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

66

No Anticipation over Morales-Sanfrutos and Straus

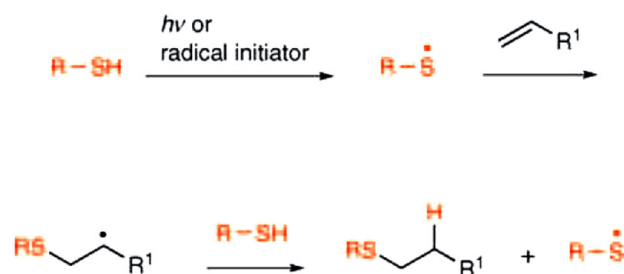
- Because Petitioner maps only the **vinyl to Y** and the sulfone to Q, Petitioner fails to show anticipation under DAC's construction
 - > Morales-Sanfrutos expressly identifies **vinyl sulfone**, not vinyl, as the reactive functional group to enable the Michael addition reaction
 - > Dr. Chari admitted **vinyl sulfone**, not vinyl alone, enables the Michael addition reaction in Morales-Sanfrutos



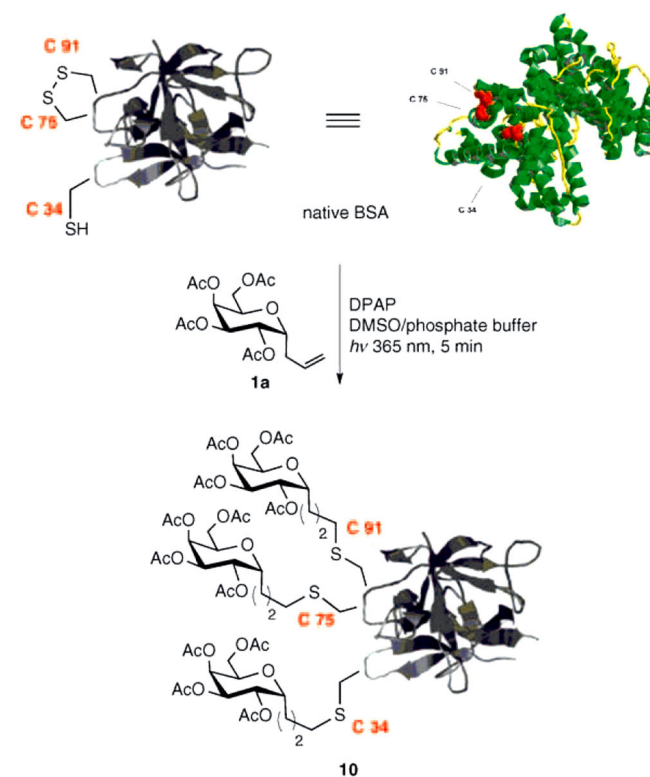
POR at 37-42; Sur-Reply at 12-17.

Dondoni Does Not Cure the Fatal Defect in SynAffix's Anticipation Theory

- Dondoni, describing a photoinduced reaction, does **not** show vinyl alone enables any Michael addition reaction (a **different reaction**)
- No evidence Morales-Sanfrutos's compounds would undergo a photoinduced reaction of Dondoni with the HRP (a heme protein)



Scheme 1. Mechanism of thiol-ene coupling (TEC).



Scheme 3. Preparation of BSA glycoconjugate 10.

Sur-Reply at 12-16; EX1064.

Dr. Chari Admits Dondoni Discloses a Different Reaction Than the Michael Addition Reaction Disclosed in Morales-Sanfrutos

Q. And the photoinduced reaction described in Dondoni is not a Michael addition reaction; right?

A. No. No. Right.

Q. No, it's not; right?

A. No, it's not.

Q. The only example you provide in your declaration is Scheme 3 from Dondoni; right?

A. That's correct.

Q. Scheme 3 of Dondoni does not disclose any compound containing a vinyl sulfone group; correct?

A. That's correct.

Q. Dondoni does not describe any photoinduced reaction that reacts any compound containing a vinyl sulfone with a cell-binding agent; right?

A. That's correct.

Q. So you would agree that each of compounds 1, 2, 4, and 5 of Morales contains additional functional groups that are not present in compound 1a of Dondoni; right?

A. That's correct; yes.

Q. And you do not cite any reference reporting of photoinduced reaction using the condition described in Scheme 3 of Dondoni and involving the reaction of a compound with a vinyl sulfone group; right?

A. That's correct.

Sur-Reply at 12-16; EX2046 at 27:12-16, 28:2-13, 31:10-12, 39:16-19, 56:16-57:8.

Dr. Chari Has No Opinion Whether Dondoni's Photoinduced Reaction Would Cause Denaturation of the HRP in Morales-Sanfrutos

And you don't know one way or another whether the photoinduced thiol reaction relied on in Dondoni would cause denaturation of HRP or not; right?

A. That's correct.

Q. And Morales does not describe any photoinduced reaction that reacts a vinyl group with HRP; right?

A. He does a vinyl sulfone, doesn't he, Morales?

Q. Right.

Morales describes a Michael addition reaction involving vinyl sulfone; right.

A. That's correct, yes.

Sur-Reply at 12-16; EX2046 at 54:10-23.

Dondoni's Photoinduced Reaction Is Not Applicable to Morales-Sanfrutos

■ Dr. Tumey:

25. First, the two papers set forth fundamentally different reaction mechanisms and conditions that don't allow for simple substitutability in any way. The vinyl sulfone in Morales-Sanfrutos' approach undergoes a nucleophilic Michael-type addition, where the electron-withdrawing sulfone group activates the double bond toward nucleophilic attack by thiols or amines through an ionic pathway under mild conditions without additional chemical reagents or catalysts. As Dr. Chari agrees, this reaction does not require UV light. EX2046 at 26:17-19. In

26. Second, compounds 1, 2(a), 2(b), 4(a), and 5(a) of Morales-Sanfrutos, on which Dr. Chari relied for analyzing claim 1 under Ground 1 (EX2046 at 55:6-9), are structurally different from compound 1a in Scheme 3 of Dondoni. Morales Sanfrutos uses complex bifunctional tags that contain additional functional groups that are not found in compound 1a of Dondoni, which is a simple allyl glycoside.

27. Third, as explained above, Dondoni shows that photoinduced TEC with BSA led to unexpected side reactions such as cleavage of disulfide bonds in proteins; formation of multiple glycosylation sites beyond the target cysteine; and potential damage to protein structure due to UV irradiation and/or disulfide bond cleavage.

* * *

bonds. In addition, HRP is a heme-containing protein and its aromatic heme moiety absorbs 365 nm wavelength UV light, which will interfere with the photoinduced TEC reaction of Dondoni. Moreover, the photoactivated heme in the HRP could potentially damage or denature the HRP protein. Dr. Chari admits that he does not know whether or not the photoinduced TEC of Dondoni would cause disulfide bond cleavage in HRP or denature the HRP protein. EX2046 at 54:2-14. A POSA would not have found Dondoni to be relevant or applicable to Morales-Sanfrutos.

Sur-Reply at 12-16; EX2047 at ¶¶ 25-28.

Dr. Chari Admits Dondoni's Reaction Requires UV Light to Activate the Vinyl: Vinyl Is Not Independently Reactive

Q. In Scheme 3 bovine serum albumin was reacted with compound 1a; correct?

A. That's correct.

So the reaction between compound 1a and BSA required UV light with a wavelength of 365 nanometer; right?

A. That's correct.

Q. What does the UV light do here in this reaction of compound 1a?

A. The free radical formation.

A. Helps free radical formation.

Q. So the UV light is necessary to generate free radical for the reaction to proceed.

A. That's correct. That's my understanding.

Q. Because Dondoni describes a photoinduced reaction, the UV light is necessary for the reaction to proceed; correct?

A. That's my understanding; that's correct.

Q. So without the UV light the vinyl group in compound 1a will not react with BSA; right?

A. That's what I think. You need some radical catalyst. Radical catalyst.

Q. So you need something --

A. To form a radical. To initiate the reaction.

Q. Okay. You need something to generate a radical species to initiate --

A. Exactly. That's correct.

Q. -- the reaction?

A. Yes.

Q. And UV light does that in the system.

A. Yeah.

Sur-Reply at 12-16; EX2046 at 31:13-15; 32:8-19, 38:10-13, 39:2-15.

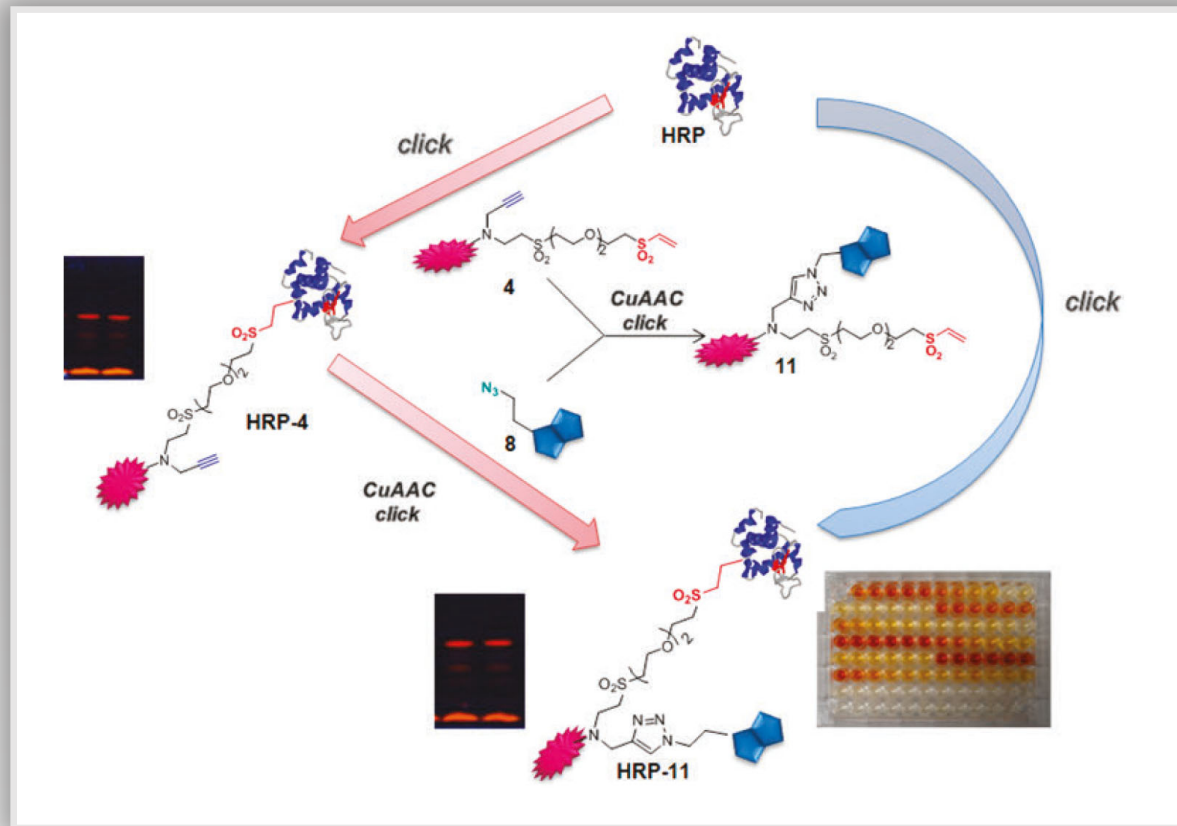
Alternative Mapping of Morales-Sanfrutos Does Not Anticipate

- Petitioner's alternative theory, **mapping a terminal alkyne to Y**, in 2(c), 4(b), and 5(b), fails for two independent reasons:
 - > Morales-Sanfrutos does not disclose **any** terminal alkyne reacting with the horseradish peroxidase (HRP)—no evidence of its terminal alkyne enabling a reaction with the HRP
 - Dr. Chari agrees (EX2037 at 30:5-32:2)
 - > A terminal alkyne, **requiring a copper catalyst** to react, is not independently reactive—no dispute a terminal alkyne requires a copper catalyst to react with an azide
 - Dr. Chari agrees (EX2046 at 61:8-10)

POR at 42-44; Sur-Reply at 16-17.

The Alkyne in Morales-Sanfrutos is “Z” that Enables Linkage to a Drug

- Nowhere does Morales-Sanfrutos disclose the alkyne enables any reaction with the HRP, the alleged cell-binding agent



POR at 42-44; Sur-Reply at 16-17; EX1005 at 6; see also EX2037 at 30:5-32:2.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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The Alkyne in Morales-Sanfrutos Was Not Reacted with Any Protein

- Morales-Sanfrutos emphasizes that “copper catalyst is toxic for living organisms and induces degradation of the structures of the biomolecule in intro”
- Mapping alkyne to Y for reaction with a cell-binding agent is contrary to Morales-Sanfrutos’s express teaching against doing so
- No showing that the four corners of Morales-Sanfrutos disclose a compound with elements “*arranged or combined in the same way as in the claim*”

POR at 42-44; Sur-Reply at 16-17.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

75

Morales-Sanfrutos Does Not Disclose Any Cell-Binding Agent

- The HRP in Morales-Sanfrutos is a **reporter** for biological assays

groups is limited. The glycoprotein horseradish peroxidase (HRP) was the protein of choice because besides its biotechnological relevance (HRP has been coupled to other molecules to use the peroxidase activity as a reporter), its structure is known (PDB access code 6atj²⁶) and the carbohydrate residues that may hinder the reactive sites are characterized.²⁷ The

EX1005 at 3.

link a recognition system. The labeling of HRP with biotin-containing reagents is an attractive and general strategy to generate a dual reporter group (i.e., fluorescence and peroxidase activity) that may be also coupled to any recognition system such as antibody antigen or lectin carbohydrate via biotin avidin affinity. Although the previous experi-

EX1005 at 4.

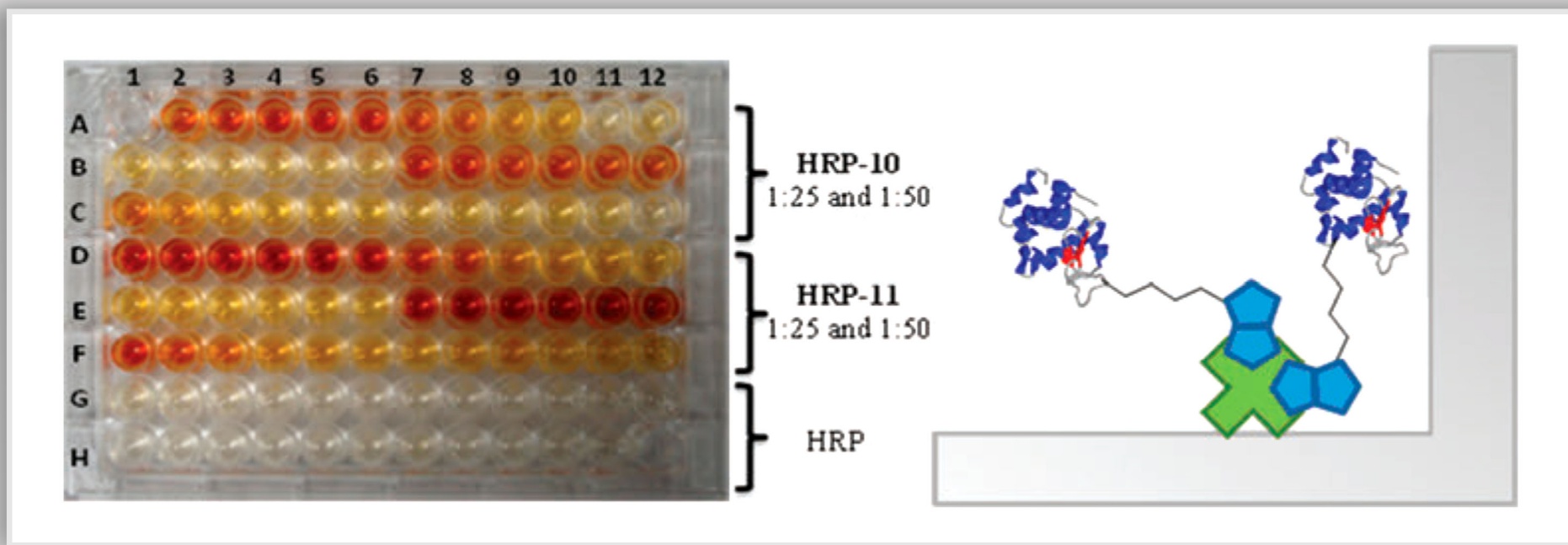
compatible with the biological nature of proteins. For the particular case of HRP, the conjugation yields a dual reporter group (fluorescence and peroxidase activity) that can be coupled to any recognition system via biotin avidin affinity.

EX1005 at 6.

POR at 44-45; Sur-Reply at 18.

Morales-Sanfrutos Does Not Disclose Any Cell-Binding Agent

- The HRP in Morales-Sanfrutos is a **reporter** for biological assays



POR at 45; EX2038 at ¶¶ 166-168; EX1005 at 5.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

77

Petitioner Improperly Relies on a Second Reference—Straus

“Although we have permitted the use of additional references to confirm the contents of the allegedly anticipating reference, we have made clear that anticipation does not permit an additional reference to supply a missing claim limitation.”

Teleflex, Inc. v. Ficosa N. Am. Corp.,
299 F.3d 1313, 1335 (Fed. Cir. 2002).

POR at 45-46.

Straus Does Not Fill the Gap in Morales-Sanfrutos's Disclosure

Before these results are discussed, the special type of fixation used in these experiments has to be pointed out. Isolated cells, or cells grown on cover slips, were quickly dried, treated with cold methanol, and were then post-fixed in a formaldehyde solution. The initial treatment of dried cells with cold methanol was essential to obtain a strong binding of HRP to the plasma membrane and to prevent a significant “background” adsorption of HRP. These observations suggest that the HRP-binding protein may be washed out of the cell surface during conventional types of fixation. Although the fine structure of the cells was not well preserved after the fixation of dried cells with methanol, the preservation was sufficient to study the binding of HRP to the cell surface.

- Straus, a decades-old reference, studied HRP under highly artificial conditions not used or contemplated by Morales-Sanfrutos

POR at 46-48; Sur-Reply at 17-18; EX1006 at 6.

Claim 2

- Dependent claim 2 requires “Z comprises a thiol, disulfide, **amino**, carboxy, aldehydes, maleimido, haloacetyl, hydrazine or hydroxyl group”
- SynAffix’s mapping of **vinyl to Y** and propargyl amine to Z fails under DAC’s proposed construction (as discussed for claim 1)
- SynAffix belatedly presents new theory, based on Singh (EX1008), in its Reply (at 22) to map **vinyl to Z**, which should be disregarded

and 5(b) disclosed in Table B2 also satisfy all limitations of claim 2, with claim 2 met because the vinyl (as Z) reacts with thiol-containing cytotoxic drugs to form a thioether bond (*see, e.g.*, Ex. 1008, ¶¶[0007], [0101]-[0102], [0132]-[0134]).

POR at 48-49; Sur-Reply at 18.

Ground 2: Harris (§§ 102, 103)

Asserted Reference: Harris (EX1007)

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau		
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)		
(51) International Patent Classification ⁶ : C08G 65/32, A61K 47/48	A1	(11) International Publication Number: WO 95/13312 (43) International Publication Date: 18 May 1995 (18.05.95)
(21) International Application Number: PCT/US94/13013 (22) International Filing Date: 14 November 1994 (14.11.94) (30) Priority Data: 151,481 12 November 1993 (12.11.93) US (60) Parent Application or Grant (63) Related by Continuation 151,481 (CON) US Filed on 12 November 1993 (12.11.93)		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ). Published <i>With international search report.</i> <i>With amended claims.</i>
(71) Applicant (for all designated States except US): SHEARWATER POLYMERS, INC. [US/US]; 2130 Memorial Parkway, S.W., Huntsville, AL 35801 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): HARRIS, J., Milton [US/US]; 3119 Highland Plaza, Huntsville, AL 35801 (US).		

(54) Title: WATER SOLUBLE ACTIVE SULFONES OF POLY(ETHYLENE GLYCOL)

POR at 50-53; EX1007.

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

82

Harris Discloses Sulfone and “Active Sulfone Moieties” as the Reactive Functional Group for the Michael Addition Reaction

A poly(ethylene glycol) derivative is disclosed that is activated with a sulfone moiety for selective attachment to thiol moieties on molecules and surfaces. The activated PEG is water soluble, hydrolytically stable for extended periods, and forms hydrolytically stable linkages with thiol moieties. The linkages generally are not reversible in reducing environments. The PEG derivative is useful for modifying the characteristics of substances including modifying biologically active molecules and surfaces for biocompatibility. Methods for synthesizing the active PEG and for preparing conjugates of the active PEG and other substances, including biologically active substances, are also disclosed.

EX1007 at 1.

The invention provides water soluble and hydrolytically stable derivatives of poly(ethylene glycol) ("PEG") polymers and related hydrophilic polymers having one or more active sulfone moieties. These polymer derivatives with active sulfone moieties are highly selective for coupling with thiol moieties instead of amino moieties on molecules and on surfaces, especially at pHs of about 9 or less. The sulfone

EX1007 at 8.

Specific sulfone moieties for the activated polymers of the invention are those having at least two carbon atoms joined to the sulfone group $-SO_2-$ with a reactive site for thiol specific coupling reactions on the second carbon from the sulfone group.

EX1007 at 9.

POR at 50-54.

SynAffix Maps Only Vinyl or Halo-Ethyl to Y, Allowing It to Map Sulfone to Q

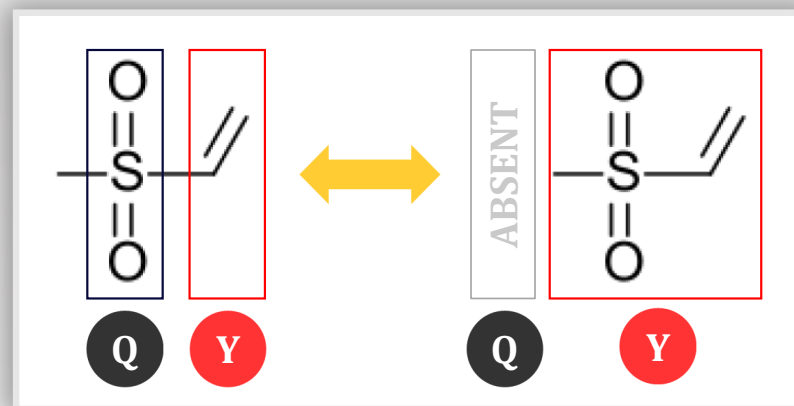
1962)). Specifically, when R and Y in Harris are vinyl sulfone and/or halo-ethyl sulfone (*see, e.g.*, EX1007, 19:10-15 and 24-30), this aligns with Y of formula (I) in the '682 patent being vinyl ($-\text{CH}=\text{CH}_2$) or halo-ethyl ($-\text{CH}_2-\text{CH}_2-\text{X}$), R_1 being absent, Q being sulfonyl, R_2 being $(\text{OCH}_2\text{CH}_2)_n$ (where n is disclosed to have typical values of 5, 34, 45 and 110), m and n each being 1, T being sulfonyl, R_3 and $-\text{R}_4(\text{R}_5)(\text{R}_6)-$ being absent, and Z being vinyl ($-\text{CH}=\text{CH}_2$) or halo-ethyl ($-\text{CH}_2-\text{CH}_2-\text{X}$). EX1003, ¶103. Vinyl and halo-ethyl groups located adjacent to a sulfone

Petition at 38-39.

POR at 53-54; see also POR at 58-60.

No Anticipation or Obviousness over Harris

- Because Petitioner maps only the **vinyl or halo-ethyl to Y** and the sulfone to Q, Petitioner fails to show anticipation or obviousness under DAC's construction
- In addition:
 - > A POSA would not at once envisage any claimed compounds from Harris's broad genus disclosure
 - > Harris does not disclose a cell-binding agent



POR at 53-60.

A POSA Would Not At Once Envisage Any Claimed Compounds From Harris's Broad Genus Disclosure

One straight chain PEG derivative of the invention for biological and biotechnical applications has the basic structure $R-(OCH_2CH_2)_n-Y$. The PEG monomer OCH_2CH_2 preferably is substantially unsubstituted and unbranched along the polymer backbone. The subscript " n " can equal from about 5 to 3,000. A more typical

* * *

In the above structure, Y represents $-SO_2-CH=CH_2$ or $-SO_2-CH_2-CH_2-X$ where X is a halogen. R represents a group that may be the same or different from Y. R can be H-, H_3C- , $CH_2=CH-SO_2-$, $Cl-CH_2-CH_2-SO_2-$, or a polymer activating group other than $CH_2=CH-SO_2-$, $Cl-CH_2-CH_2-SO_2-$, such as is referred to with respect to the above patents and published patent applications.

POR at 54-55, 58-59;
EX2038 at ¶¶ 209-211, 219-220;
EX1007 at 21.

Harris's Broad Genus Does Not Anticipate any Claimed Compound

PEG vinyl sulfone and its precursors and derivatives can be used for attachment directly to surfaces and molecules having a thiol moiety. However, more typically a heterobifunctional PEG derivative having a sulfone moiety on one terminus and a different functional moiety on the opposite terminus group will be attached by the different moiety to a surface or molecule. When substituted with one of the other

Other active groups for heterobifunctional sulfone-activated PEGs can be selected from among a wide variety of compounds. For biological and biotechnical applications, the substituents would typically be selected from reactive moieties typically used in PEG chemistry to activate PEG such as the aldehydes, trifluoroethylsulfonate, which is also sometimes called tresylate, n-hydroxylsuccinimide ester, cyanuric chloride, cyanuric fluoride, acyl azide, succinate, the p-diazo benzyl group, the 3-(p-diazophenylloxy)-2-hydroxy propyloxy group, and others.

Examples of active moieties other than sulfone are shown in Davis et al. U.S. Patent No. 4,179,337; Lee et al. U.S. Patent Nos. 4,296,097 and 4,430,260; Iwasaki et al. 4,670,417; Katre et al. U.S. Patent Nos. 4,766,106; 4,917,888; and 4,931,544; Nakagawa et al. U.S. Patent No. 4,791,192; Nitecki et al. U.S. Patent No. 4,902,502 and 5,089,261; Saifer U.S. Patent No. 5,080,891; Zalipsky U.S. Patent No. 5,122,614; Shadle et al. U.S. Patent No. 5,153,265; Rhee et al. U.S. Patent No. 5,162,430; European Patent Application Publication No. 0 247 860; and PCT International Application Nos. US86/01252; GB89/01261; GB89/01262; GB89/01263; US90/03252; US90/06843; US91/06103; US92/00432; and US92/02047, the contents of which are incorporated herein by reference.

POR at 54-55, 58-59; EX2038 at ¶¶ 209-211, 219-220; EX1007 at 19-20.

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

87

Dr. Chari Did Not Analyze the Number of Possible Linkers Disclosed by Harris

Q. Sure. Would all of the different groups that could be added on to the linkers or spacers that could be used, using the disclosures of Harris, did you do any calculations to see the total number?

A. No.

Q. Do you know what the total number of possible combinations in Harris is?

A. No.

POR at 55; EX2037 at 40:15-22.

Additional Reasons for No Obviousness over Harris

- The decades-old Harris is not analogous art
 - > Harris is not from the same field of endeavor as the '682 patent
 - > Harris is not reasonably pertinent to the problem facing the '682 patent

Field of the Invention

This invention relates to active derivatives of poly(ethylene glycol) and related hydrophilic polymers and to methods for their synthesis for use in modifying the characteristics of surfaces and molecules.

- Petitioner's single-paragraph cursory obviousness analysis fails its burden of proof

POR at 52, 56-57; Sur-Reply at 21; EX2038 at ¶¶ 202-203; EX1007 at 3.

Ground 3: Singh in View of Harris (§ 103)

Asserted References: Singh (EX1008) and Harris (EX1007)

(19) **United States**

(12) **Patent Application Publication**
Singh et al.

(10) **Pub. No.: US 2010/0129314 A1**

(43) **Pub. Date: May 27, 2010**

(54) **POTENT CONJUGATES AND HYDROPHILIC LINKERS**

Publication Classification

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(21) Appl. No.: **12/574,466**

(22) Filed: **Oct. 6, 2009**

Related U.S. Application Data

(63) Continuation-in-part of application No. 12/433,668, filed on Apr. 30, 2009, now abandoned.

(60) Provisional application No. 61/049,289, filed on Apr. 30, 2008.

(51) **Int. Cl.**
A61K 39/395 (2006.01)
A61K 38/19 (2006.01)
A61K 38/43 (2006.01)
A61K 38/22 (2006.01)
C07K 14/52 (2006.01)
C07K 16/28 (2006.01)
C07K 14/575 (2006.01)
C07K 14/00 (2006.01)
C07D 498/18 (2006.01)
A61P 31/12 (2006.01)
A61P 35/00 (2006.01)
A61P 37/00 (2006.01)
A61P 37/06 (2006.01)
A61P 33/00 (2006.01)
C12N 9/96 (2006.01)
(52) **U.S. Cl.** **424/85.1**; 424/181.1; 424/94.3;
514/2; 530/351; 530/391.9; 530/399; 530/408;
540/462; 435/188

(57) ABSTRACT

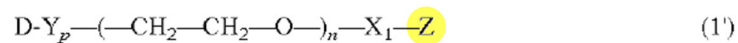
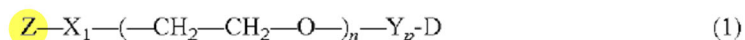
Linkers for binding drugs to cell binding agents are modified to hydrophilic linkers by incorporating a polyethylene glycol spacer. The potency or the efficacy of the cell-binding agent-drug conjugates is surprisingly enhanced several folds in a variety of cancer cell types, including those expressing a low number of antigens on the cell surface or cancer cells that are resistant to treatment. A method for preparing maytansinoids bearing a thioether moiety and a reactive group which allows the maytansinoid to be linked to a cell-binding agent in essentially a single step is also provided.

POR at 61; EX1008.

Singh Discloses Genus Structures with “Z” as a “Reactive Functionality”

- Singh describes vinyl sulfone, not vinyl, as a “reactive functionality,” among many other possibilities

[0014] Accordingly, the present invention provides a compound of formula (1) or a specific compound of formula (1'):



wherein:

Z represents a reactive functionality that can form an amide or a thioether bond with a cell-binding agent;

D represents a drug;

X represents an aliphatic, an aromatic or a heterocyclic group attached to the cell-binding agent via a thioether bond, an amide bond, a carbamate bond, or an ether bond;

Y represents an aliphatic, an aromatic or a heterocyclic group attached to the drug via a covalent bond selected from the group consisting of a thioether bond, an amide bond, a carbamate bond, an ether bond, an amine bond, a carbon-carbon bond and a hydrazone bond;

[0134] As used herein, the term “reactive functionality” refers to an amine-, a thiol- or a hydroxyl-reactive functionality. In other words, the reactive functionality can react with amine, sulfhydryl(thiol), or hydroxyl group present on cell-binding agent. For example, for amine-reactive functionality, the functionality could be a reactive carboxylic ester (including N-succinimidyl, N-sulfosuccinimidyl, N-phthalimidyl, N-sulfophthalimidyl, 2-nitrophenyl, 4-nitrophenyl, 2,4-dinitrophenyl, 3-sulfo-4-nitrophenyl, 3-carboxy-4-nitrophenyl, tetrafluorophenyl esters), a reactive sulfonic acid derivative, or a reactive thioester to give an amide bond; for thiol-reactive functionality, the functionality could be a maleimide, a haloacetamide, or a vinyl sulfone to give a thioether bond; and, for hydroxyl-reactive functionality, the functionality could be a reactive carboxylic ester to give an ester bond.

POR at 61; Sur-Reply at 21-23; EX1008.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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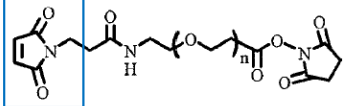
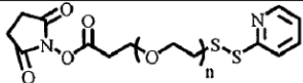
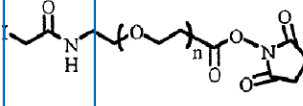
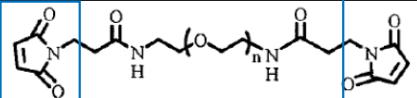
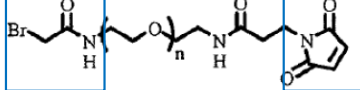
Singh Does Not Teach any Linker with the Claimed Q or T Element

- Singh mentions vinyl sulfone only **once** in [0134], not elsewhere
- Singh does not disclose **any** exemplified compound that contains a sulfone or vinyl sulfone group
- Petitioner admits that Singh does **not** teach either Q or T:
 - > “Singh discloses bifunctional PEG cross-linkers containing each element of claim 1, **save Q and T ...**” (Petition at 44)
- Dr. Chari, a co-inventor of Singh, confirmed that Singh “doesn’t include sulfones” (EX2037 at 38:15-39:1; EX2046 at 98:15-23)

POR at 61; Sur-Reply at 23; EX1008.

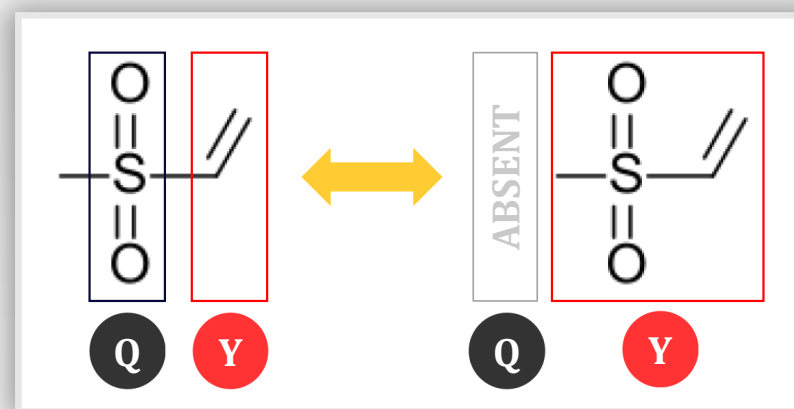
Petitioner's Modification of Singh Would Not Result in Any Compound that Falls within the Scope of the Claims

Table A1

Entry	Bifunctional PEG Cross-linkers	Figs.
1		4, 8
2		6B, 12
3		10
4		13, 15
5		16B, 18

Petition at 13, 47-49.

- Petitioner cherry-picks linkers from Singh and argues a POSA would substitute **vinyl sulfone** for the “**reactive functionalities**” in the linkers
- Even so, the modified structures would not fall within the claims because Petitioner maps **vinyl** to Y and sulfone to Q; Q would be absent if mapping vinyl sulfone to Y



POR at 61-67; Sur-Reply at 22-23.

No Obviousness over Singh in View of Harris

- Because Petitioner maps only the **vinyl to Y** and the sulfone to Q, Petitioner fails to show obviousness under DAC's construction
- In addition:
 - > A POSA would not have modifies Singh to substitute vinyl sulfone for maleimide or halo-acetamide as Petitioner argues—Harris does not provide any such motivation
 - > Singh's single reference to “vinyl sulfone” as one of many possible “**reactive functionalities**” would not have motivated a POSA to add sulfone as a **spacer element** to the linkers

POR at 61-67; Sur-Reply at 22-26.

No Motivation to Modify Singh's Structures with Vinyl Sulfone as the "Reactive Functionality"

[0134] As used herein, the term "reactive functionality" refers to an amine-, a thiol- or a hydroxyl-reactive functionality. In other words, the reactive functionality can react with amine, sulfhydryl(thiol), or hydroxyl group present on cell-binding agent. For example, for amine-reactive functionality, the functionality could be a reactive carboxylic ester (including N-succinimidyl, N-sulfosuccinimidyl, N-phthalimidyl, N-sulfophthalimidyl, 2-nitrophenyl, 4-nitrophenyl, 2,4-dinitrophenyl, 3-sulfo-4-nitrophenyl, 3-carboxy-4-nitrophenyl, tetrafluorophenyl esters), a reactive sulfonic acid derivative, or a reactive thioester to give an amide bond; for thiol-reactive functionality, the functionality could be a maleimide, a haloacetamide, or a vinyl sulfone to give a thioether bond; and, for hydroxyl-reactive functionality, the functionality could be a reactive carboxylic ester to give an ester bond.

- None of Singh's exemplary structures include linkers with vinyl sulfone as the "reactive functionality"
- Vinyl sulfone is listed as one of many possible "reactive functionalities"

POR at 63-65; Sur-Reply at 23-25; EX1008 at [0134].

Dr. Chari's Testimony Supports No Motivation to Modify Singh

Q. You agree with me that the work you did and that's discussed in here published in 2010 does not include the Q and T elements of the '682 patent's claims, right?

A. Q and T; are those the sulfones?

Q. Yes.

A. It doesn't include sulfones, that's right.

POR at 61; EX2037 at 38:15-21.

Dr. Chari's Testimony Supports No Motivation to Modify Singh

Q. So with your publication in 2010, you thought it was sufficient to use polyethylene glycol alone to achieve the hydrophilicity?

A. Right. For what we needed, yes.

Q. Did you have any regret about that?

A. No.

* * *

Q. In your view, there was no reason to add anything else?

A. Not at that time, right.

POR at 61; EX2037 at 39:14-19, 40:3-5.

No Motivation to Modify Singh's Structures with Vinyl Sulfone to Improve Solubility or Drug Uptake

- No evidence that a POSA would have been motivated to modify the Singh structures “when dealing with more hydrophobic drugs” or “when the PEG chain must be kept short” as SynAffix argues
- No evidence that substituting vinyl sulfone for either maleimide or halo-acetamide in Singh's linkers would:
 - > Increase water solubility or hydrophilicity
 - > Improve drug uptake of the conjugate

Sur-Reply at 24-25.

Dr. Chari Presented No Evidence that Substituting Vinyl Sulfone Would Increase Water Solubility or Hydrophilicity

Q. And so, Doctor Chari, do you know what LogP is?

A. What is what?

Q. LogP.

A. Log -- LogP?

Q. LogP.

A. Yeah, solubility. That's correct. Yeah.

A. Measure of solubility. Water solubility.

Q. Right. And LogP is an indicator for hydrophobicity --

A. That's correct.

Q. -- or hydrophilicity of a molecule; right?

A. Oh, sorry.

Q. That's right, right?

A. That's correct.

Q. Yeah. So you did not provide any LogP calculation for any of the compounds containing maleimide or vinyl sulfone in your declaration; correct?

A. That's correct.

Q. Okay. And you did not provide any data to show vinyl sulfone will have better solubility than maleimide in your declaration; correct?

A. That's correct.

Sur-Reply at 24; EX2046 at 114:9-116:2.

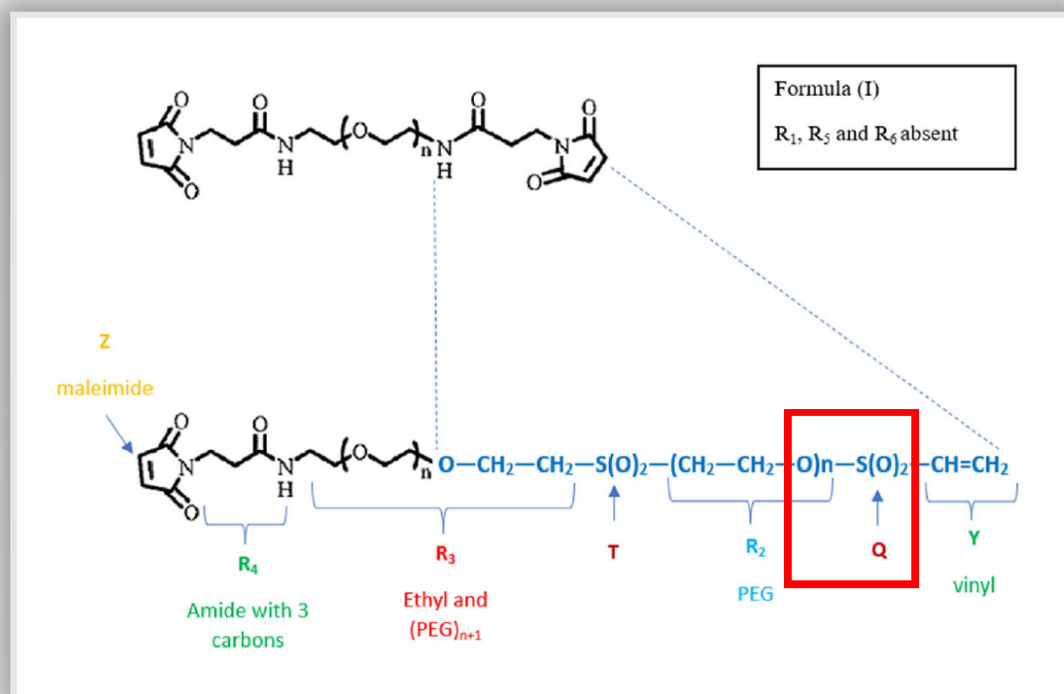
SynAffix Presented No Evidence that “Figure 36” Would Have Motivated a POSA to Add Sulfone to the Linker

"_n" can equal from about 5 to 3,000. A more typical range is from about 5 to 2,200, which corresponds to a molecular weight of from about 220 to 100,000. Still more typical is a range of from about 34 to 1,100, which corresponds to a molecular weight range of from about 1,500 to 50,000. Most applications will be accomplished with molecular weights in the neighborhood of 2,000 to 5,000, which corresponds to a value of _n of from about 45 to 110.

- No evidence that a POSA would have been motivated to modify the Singh structures “when the PEG chain must be kept short”
 - > Figure 36 of Singh only reports *in vitro* data of six conjugates
- Harris teaches long PEG linkers are preferred; a POSA would not look to Harris to modify Singh to achieve a shorter PEG linker
- A POSA would not have selected just the sulfone from Harris

Sur-Reply at 24-25; EX1007 at 21.

No Motivation to Substitute a Harris Linker for Maleimide (Claim 2)



- New theory not raised in Petition
- No articulated reason as to why a POSA would have made the purported modification
- Contradicts argument that “PEG chain must be kept short”
- Introduces an unstable sulfonate ester
- Improperly maps vinyl sulfone to Y and Q

Sur-Reply at 25-26.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

102

Ground 4: Singh in View of Harris and Bhakta (§ 103)

Asserted References: Singh (EX1008), Harris (EX1007), and Bhakta (EX1011)

(19) **United States**

(12) **Patent Application Publication**
Bhakta et al.

(10) **Pub. No.: US 2011/0301334 A1**

(43) **Pub. Date: Dec. 8, 2011**

(54) **CYSTEINE ENGINEERED ANTIBODIES AND
CONJUGATES**

C07K 17/00 (2006.01)

C07K 16/46 (2006.01)

C07K 16/22 (2006.01)

(76) Inventors: **Sunil Bhakta**, San Ramon, CA
(US); **Jagath R. Junutula**,
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(52) **U.S. Cl. 530/387.3; 530/387.1; 530/391.3;
530/389.2; 530/389.1; 530/391.7; 530/391.1;
530/391.5; 530/391.9**

(21) Appl. No.: **13/154,672**

(22) Filed: **Jun. 7, 2011**

Related U.S. Application Data

(60) Provisional application No. 61/352,728, filed on Jun.
8, 2010.

Publication Classification

(51) **Int. Cl.**

C07K 16/00 (2006.01)

C07K 19/00 (2006.01)

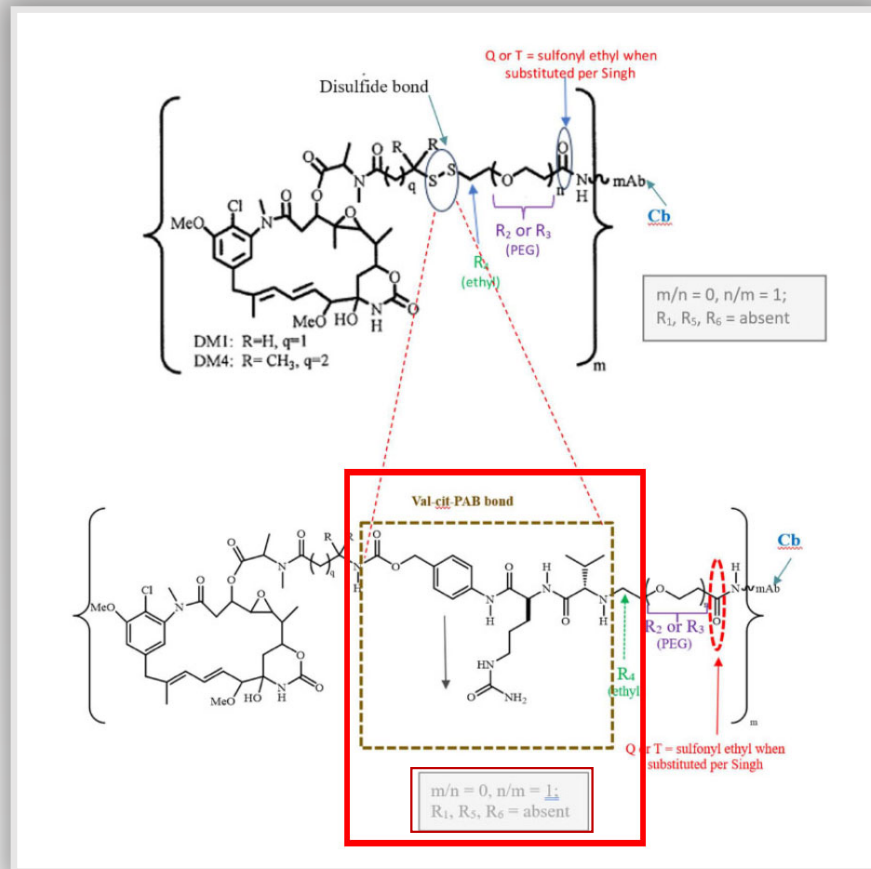
C07K 16/28 (2006.01)

(57) **ABSTRACT**

Cysteine engineered antibodies comprising a free cysteine amino acid in the heavy chain or light chain are prepared by mutagenizing a nucleic acid sequence of a parent antibody and replacing one or more amino acid residues by cysteine to encode the cysteine engineered antibody; expressing the cysteine engineered antibody; and isolating the cysteine engineered antibody. Certain highly reactive cysteine engineered antibodies were identified by the PHESELECTOR assay. Isolated cysteine engineered antibodies may be covalently attached to a capture label, a detection label, a drug moiety, or a solid support.

POR at 67; EX1011.

The Alleged Modification of Singh in View of Harris and Bhakta Does Not Render Claims 9 and 13 Obvious



- SynAffix failed to explain specifically how a POSA would have modified Singh in view of Bhakta, let alone with a reasonable expectation of success
- In its Reply, SynAffix again fails to show how the modified structure meets all the claims' requirement for R₁, R₄, R₅, and R₆
- SynAffix incorrectly states that R₄ is ethyl and "R₁, R₅, R₆ = absent" when the R₁/R₄/R₅/R₆ part of the modified structure is more than just ethylene

POR at 68-69; Sur-Reply at 26-27.

DEMONSTRATIVE EXHIBIT - NOT EVIDENCE

105

Ground 5: Singh in View of Harris and Snow (§ 103)

Asserted References: Singh (EX1008), Harris (EX1007), and Snow (EX1010)

United States Patent [19]

Snow et al.

US005414135A

[11] Patent Number: **5,414,135**

[45] Date of Patent: **May 9, 1995**

[54] **VINYL SULFONE COUPLING OF
POLYOXYALKYLENES TO PROTEINS**

[75] Inventors: **Robert A. Snow**, West Chester; **David
L. Ladd**, Wayne, both of Pa.

[73] Assignee: **Sterling Winthrop Inc.**, Malvern, Pa.

[21] Appl. No.: **153,553**

[22] Filed: **Nov. 16, 1993**

Related U.S. Application Data

[63] Continuation of Ser. No. 815,722, Dec. 30, 1991, abandoned.

[51] Int. Cl.⁶ **C07C 315/04; C07C 317/04**

[52] U.S. Cl. **568/29; 568/30;
568/31; 568/32; 568/33**

[58] Field of Search **568/30, 32, 33, 29,
568/31**

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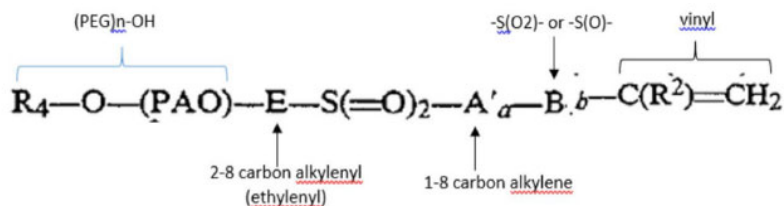
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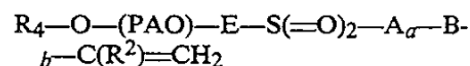
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POR at 69; EX1010.

The Alleged Modification of Singh in View of Harris and Bhakta Does Not Render Claims 2, 25, and 32-34 Obvious



The thus formed polyalkylene oxide vinyl sulfone reagents of the present invention are represented by the structural formula:



wherein:

R_4 is H or an alkyl or an aralkyl group of 1 to 8 carbon atoms which may be substituted with an alkoxy group of 1 to 3 carbon atoms;

PAO is a polyalkylene oxide having an average molecular weight in the range of 250 to 200,000 daltons; and

E, A, a, B, b, and R^2 are defined above.

- Hindsight-based selection of purported structure from Snow
 - > Snow discloses a broad genus for the various variables – E, A, B, R^2 and R^4
 - > Snow discloses a series of “preferred”, “more preferred”, and “even more preferred” embodiments
- No motivation to modify Singh
 - > Snow is silent regarding whether its linkers impart “higher water solubility”
 - > The addition of alkyl groups decreases, not increases, hydrophilicity

POR at 69-71; Sur-Reply at 27-28; EX2038 at ¶¶ 249-253; EX1010 at 7:51-56.