

# Petitioner's Demonstrative Slides

*SynAffix B.V. v. Hangzhou DAC Biotech Co., Ltd.*

IPR2022-01531 – U.S. Patent No. 10,131,682

**June 12, 2025**

# Grounds at Issue

| Grounds of Unpatentability                                                                   | Basis                 | Challenged Claims                               |
|----------------------------------------------------------------------------------------------|-----------------------|-------------------------------------------------|
| <b>Ground I: Anticipation Morales-Sanfrutos (Ex. 1005) as evidenced by Straus (Ex. 1006)</b> | <b>§102</b>           | <b>1-3, 6, 24, 25, 33</b>                       |
| <b>Ground II: Anticipation by or Obviousness over Harris (Ex. 1007)</b>                      | <b>§102/<br/>§103</b> | <b>1, 20, 21, 29-31</b>                         |
| <b>Ground III: Obviousness over Singh (Ex. 1008) in view of Harris</b>                       | <b>§103</b>           | <b>1-8, 10-12, 14-17, 20, 21, 24, 26, 29-31</b> |
| <b>Ground IV: Obviousness over Singh in view of Harris and Bhakta (Ex. 1011)</b>             | <b>§103</b>           | <b>9, 13</b>                                    |
| <b>Ground V: Obviousness over Singh in view of Harris and Snow (Ex. 1010)</b>                | <b>§103</b>           | <b>2, 25, 32-34</b>                             |

# Primary Issues in Dispute

1. Claim Construction Issues
  - a. Q-Y-T-Z Terms
  - b. "Cell-binding agent"
2. Anticipation by Morales-Sanfrutos
  - a. "Vinyl sulfone" under either party's construction
  - b. HRP is a cell-binding agent
  - c. Mapping of propargyl amine to claims 1-2
3. Anticipation by/Obviousness over Harris
4. Singh + Harris Obviousness
5. Singh + Harris + Bhakta Obviousness
6. Singh + Harris + Snow Obviousness



US010131682B2

|                                                                                                    |      |                                               |
|----------------------------------------------------------------------------------------------------|------|-----------------------------------------------|
| (54) HYDROPHILIC LINKERS AND THEIR USES<br>FOR CONJUGATION OF DRUGS TO A CELL<br>BINDING MOLECULES | (56) | References Cited<br><br>U.S. PATENT DOCUMENTS |
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(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 250 days.

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| (27) DCT Data No.: | W3370143080551 | 4,491,632 A | 1/1985 | Wands et al.       |

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| PCT Pub. Date: May 30, 2014 | 4,493,890 A | 1/1985 | Morris             |
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| (65) Prior Publication Data | 4,663,453 A | 5/1987 | Glanckowski et al. |

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| <i>C07F 9/32</i>   | (2006.01) | DE | 196 38 870 A1 | 3/1998                   |
| <i>A61K 47/68</i>  | (2017.01) |    |               | (Continued)              |
| <i>C07F 9/58</i>   | (2006.01) |    |               |                          |

Sangha and Butts, *Clinical Cancer Research*, 2007, vol. 13, suppl. 15, pp. 4652s-4654s.\*

**C07D 207:46** (2013.01); **C07D 401/12** (2013.01); **C07F 9/001** (2013.01); **C07F 9/002** (2013.01); **C07F 9/3235** (2013.01); **C07F 9/58** (2013.01); **C07F 9/6561** (2013.01); **C74 9/65583** (2013.01); **Y02A 50/402** (2018.01); **Y02A 50/409** (2018.01); **Y02A 50/415** (2018.01); **Y02A 50/463** (2018.01); **Y02A 50/469** (2018.01); **Y02A 50/485** (2018.01)

(58) **Field of Classification Search** are provided.  
None  
See application file for complete search history. **21 Claims, 23 Drawing Sheets**

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Sangha and Butts, *Clinical Cancer Research*, 2007, vol. 13, suppl. 15, pp. 4652s-4654s.\*

**ABSTRACT**

**21 Claims, 23 Drawing Sheets**

21 Claims, 23 Drawing Sheets

$$\text{Y}-\text{R}_1-\text{Q}-\text{R}_2-\text{T}-\text{R}_3-\text{R}_4-\text{Z} \quad (1)$$

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

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  $\neg P(=O)(OM)-$ ; when  $n=1$ ,  $m=0$ , T is not  $\neg P(=O)(OM)-$ ; and when Q or T is  $\neg S(O_2)-$ , m and n are not 0f:]

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;

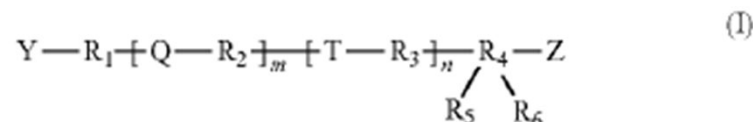
or R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub>), *provided that when Q and T are each independently —S(O)<sub>2</sub>— or —S(O)—, R<sub>2</sub> 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<sub>1</sub>, R<sub>3</sub> or R<sub>4</sub>; R<sub>5</sub> and R<sub>6</sub>, 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<sub>2</sub>CH<sub>2</sub>)<sub>p</sub>, wherein p is an integer from 1 to about 1000, or combination thereof; M is H, or Na, or K, or N<sup>+</sup>R<sub>1</sub>R<sub>2</sub>R<sub>3</sub> or a pharmaceutical salt.*

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

# Claim Construction

## "Y" and "Z" Limitations – Claim 1

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..."
  
- "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" and "Z" Limitations – Determination by the DRP

DRP\_PTAABDecision@uspto.gov  
571-272-7822

Paper 23  
Date: March 4, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE  
BEFORE THE PATENT TRIAL AND APPEAL BOARD

SYNAFFIX B.V.,  
Petitioner,

v.

HANGZHOU DAC BIOTECH CO., LTD.,  
Patent Owner.

IPR2022-01531  
Patent 10,131,682 C1

Before MICHAEL W. KIM, Acting Deputy Chief Administrative Patent Judge, JANET A. GONGOLA, Vice Chief Administrative Patent Judge, and JAMES A. WORTH, Acting Senior Lead Administrative Patent Judge.  
WORTH, Acting Senior Lead Administrative Patent Judge.

DECISION  
Granting Rehearing; Decision on Rehearing  
37 C.F.R. §§ 42.5, 42.71

## I. INTRODUCTION

### A. Background and Summary

On February 9, 2023, SynAffix B.V. ("Petitioner") filed a Petition (Paper 2) requesting an *inter partes* review of claims 1–17, 20, 21, 24–26, and 29–34 of U.S. Patent No. 10,131,682 C1 (Exs. 1001, 1002

- "[W]hen the hydrophilic linker contains a vinylsulfone group, we determine that **the vinyl group should be mapped to Y or Z, and the sulfone group should be mapped to Q or T.**
- We determine that such mapping satisfies the **"enables reaction"** and **"enables linkage"** requirements of claim 1."
- "... ORDERED that the case is remanded to the panel for further proceedings **consistent with this opinion.**"

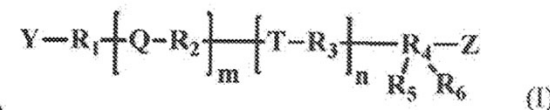
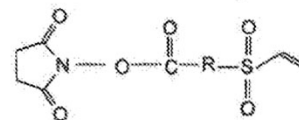
## "Y" and "Z" Limitations – Prior Determination by the DRP

- During prosecution of the original claims (prior to reexamination) in response to a rejection of then-pending Claim 1, Applicant acknowledged that WO97/41897 (Lees) disclosed conjugates having a heterobifunctional vinyl sulfone.
- Rather than assert that sulfone alone could not meet the requirements of Y or Z, Applicant instead distinguished Lees by amending Claim 1 to require that, "when Q or T is  $-S(O_2)-$ , m and n are not 0, thereby excluding the above noted compound described in Lees."

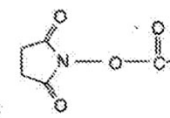
### III. Response to Rejection under 35 U.S.C. § 102

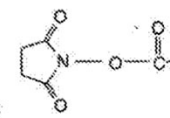
Claim 1 was rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by WO 97/41897 to Lees. Applicant respectfully submits that claim 1 as amended is novel and patentable over Lees for at least the following reasons.

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.

# "Y" and "Z" Limitations – Prior Determination by the DRP

DRP\_PTABDecision@uspto.gov  
571-272-7822

Paper 23  
Date: March 4, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE  
BEFORE THE PATENT TRIAL AND APPEAL BOARD

SYNAFFIX B.V.,  
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HANGZHOU DAC BIOTECH CO., LTD.,  
Patent Owner.

IPR2022-01531  
Patent 10,131,682 C1

Before MICHAEL W. KIM, *Acting Deputy Chief Administrative Patent Judge*, JANET A. GONGOLA, *Vice Chief Administrative Patent Judge*, and JAMES A. WORTH, *Acting Senior Lead Administrative Patent Judge*,  
WORTH, *Acting Senior Lead Administrative Patent Judge*.

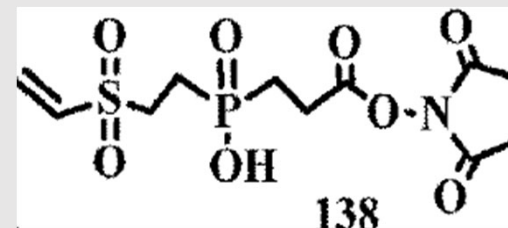
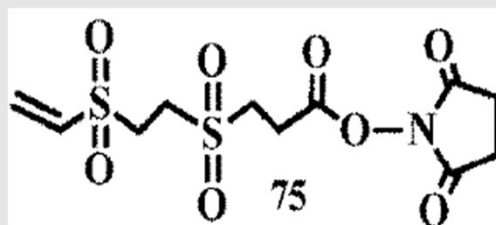
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Granting Rehearing: Decision on Rehearing  
37 C.F.R. §§ 42.5, 42.71

## I. INTRODUCTION

### A. Background and Summary

On February 9, 2023, SynAffix B.V. ("Petitioner") filed a Petition (Paper 2) requesting an *inter partes* review of claims 1–17, 20, 21, 24–26, and 29–34 of U.S. Patent No. 10,131,682 C1 (Exs. 1001, 1002

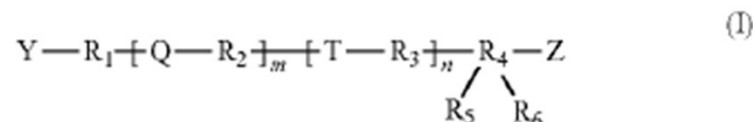
- Similarly, the DRP noted Applicant's express reliance on Compounds 75 (having two sulfone groups) and Compound 138 (having one sulfone group and one phosphinate group) to support its claim amendment during reexamination, indicating that those compounds were not disclaimed and were within the scope of Claim 1 as asserted in the Petition.
- In each compound, vinyl sulfone **cannot** be Y or Z alone. It must be Q-Y or T-Z.



Ex. 1001, Figs. 7, 10

## "Y" and "Z" Limitations – Claim 1

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..."
  
- "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" and "Z" Limitations – Expert Testimony

- As Patent Owner's expert admits, for Z to form a "linkage" via one of the listed bond types, **a chemical reaction is necessarily required.**

**Dr. Tumey**  
**(Patent Owner's expert)**

Ex. 1063, 12:11-15:10

Q . . . So when Z forms a linkage to a drug via one of those chemical bonds that are listed, that requires one or more chemical reactions to occur to form the bond; is that fair?

A Yes.

. . .

Q And Z is a conjugation moiety that enables linkage of the linker to a drug, correct?

ATTORNEY MATTES: Objection. Form.

A Yes, that is what I say.

Q So to carry out their functions, both Y and Z have to undergo a chemical reaction of some sort, one or more chemical reactions of some sort, correct?

ATTORNEY MATTES: Objection. Form.

A Yes.

## 12

## No Separateness Requirement

- There is no requirement for separate structures where, as here, such separate structures are not necessary to avoid “nonsensical” results.

In *Becton*, we stated “[w]here a claim lists elements separately, the clear implication of the claim language is that those elements are distinct components of the patented invention.” 616 F.3d at 1254 (cleaned up) (citations omitted). But **part of our rationale in *Becton* was that it would render the asserted claims “nonsensical” for the claimed “spring means” to be connected to the “hinged arm” if they were the same structure.** *Id.* at 1255. **No similar “nonsensical” result arises here . . . .**

*Bot M8 LLC v. Sony Interactive Ent. LLC*, No. 2022-1569, 2023 WL 5606978, at \*4 (Fed. Cir. Aug. 30, 2023) (emphasis added)

See also *Google LLC v. EcoFactor, Inc.*, 92 F.4th 1049, 1058 (Fed. Cir. 2024) ; *Powell v. Home Depot U.S.A., Inc.*, 663 F.3d 1221, 1231 (Fed. Cir. 2011).

# Patent Specification's Formula's I-IV

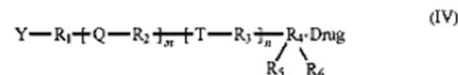
- Based on the specification, a POSA would readily conclude that:
  - (1) Formula I's linkers are used to create Formulas III-IV's modified/conjugated molecules, and
  - (2) those linkers are then linked again to create the conjugates of Formula II.

| Structure                                                                                                    | Formula |
|--------------------------------------------------------------------------------------------------------------|---------|
| $Y-R_1-Q-R_2-T-R_3-R_4-Z$ <p style="text-align: center;"><math>R_5 \quad R_6</math></p>                      | I       |
| $Cb \left( R_1-Q-R_2-T-R_3-R_4-Drug \right)_q$ <p style="text-align: center;"><math>R_5 \quad R_6</math></p> | II      |
| $Cb \left( R_1-Q-R_2-T-R_3-R_4-Z \right)_q$ <p style="text-align: center;"><math>R_5 \quad R_6</math></p>    | III     |
| $Y-R_1-Q-R_2-T-R_3-R_4-Drug$ <p style="text-align: center;"><math>R_5 \quad R_6</math></p>                   | IV      |

- If vinyl sulfone cannot serve as the Q-Y groups, this would lead to an absurd result, i.e.:
  - (1) a linker with a terminal vinyl sulfone could meet the requirements of Claim 3/Formula II once reacted with a CBA via the vinyl group, but...
  - (2) the same linker would be **incapable** of meeting the requirements of Claim 1/Formula I.

# '682 Patent – Claim 20

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

"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;

$\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ , and  $\text{R}_4$ , 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  $(\text{OCH}_2\text{CH}_2)_p$ , wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently  $-\text{S}(\text{O}_2)-$  or  $-\text{S}(\text{O})-$ ,  $\text{R}_2$  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  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ , or  $\text{R}_4$ , comprises more atoms than O, S, Si, or a binding ligand;

conjugated drug and among themselves ( $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$  and  $\text{R}_4$ ), provided that

when Q and T are both  $-\text{S}(\text{O}_2)-$ ,  $\text{R}_5$  and  $\text{R}_6$ , are not both linear alkyl, cyclic alkyl, branched alkyl, or amide having from 1 to 6 carbon atoms;

when Q and T are both  $-\text{S}(\text{O}_2)-$ ,  $\text{R}_5$  and  $\text{R}_6$ , are not both linear alkyl, cyclic alkyl, branched alkyl, or amide having from 1 to 6 carbon atoms;

when Q and T are both  $-\text{S}(\text{O}_2)-$ ,  $\text{R}_5$  and  $\text{R}_6$ , are not both linear alkyl, cyclic alkyl, branched alkyl, or amide having from 1 to 6 carbon atoms;

when Q and T are both  $-\text{S}(\text{O}_2)-$ ,  $\text{R}_5$  and  $\text{R}_6$ , are not both linear alkyl, cyclic alkyl, branched alkyl, or amide having from 1 to 6 carbon atoms;

when Q and T are both  $-\text{S}(\text{O}_2)-$ ,  $\text{R}_5$  and  $\text{R}_6$ , are not both linear alkyl, cyclic alkyl, branched alkyl, or amide having from 1 to 6 carbon atoms;

when Q and T are both  $-\text{S}(\text{O}_2)-$ ,  $\text{R}_5$  and  $\text{R}_6$ , are not both linear alkyl, cyclic alkyl, branched alkyl, or amide having from 1 to 6 carbon atoms;

when Q and T are both  $-\text{S}(\text{O}_2)-$ ,  $\text{R}_5$  and  $\text{R}_6$ , are not both linear alkyl, cyclic alkyl, branched alkyl, or amide having from 1 to 6 carbon atoms;

when Q and T are both  $-\text{S}(\text{O}_2)-$ ,  $\text{R}_5$  and  $\text{R}_6$ , are not both linear alkyl, cyclic alkyl, branched alkyl, or amide having from 1 to 6 carbon atoms;

when Q and T are both  $-\text{S}(\text{O}_2)-$ ,  $\text{R}_5$  and  $\text{R}_6$ , are not both linear alkyl, cyclic alkyl, branched alkyl, or amide having from 1 to 6 carbon atoms;

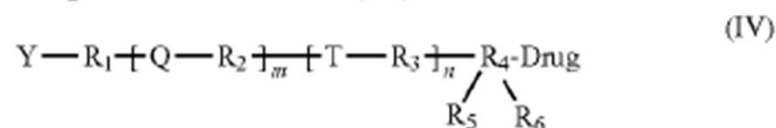
when Q and T are both  $-\text{S}(\text{O}_2)-$ ,  $\text{R}_5$  and  $\text{R}_6$ , are not both linear alkyl, cyclic alkyl, branched alkyl, or amide having from 1 to 6 carbon atoms;

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

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, Y is an N-hydroxysuccinimide (NHS) ester, p-nitrophenyl ester, dinitrophenyl ester, pentafluorophenyl ester, pyridyldisulfide, nitropyridyldisulfide, maleimide, haloacetate, carboxylic acid chloride, hydrazide or hydroxylamine.

## "Y" Limitation – Claim 20

20. A compound of formula (IV):



wherein:

- "Y represents a functional group the enables reaction of the compound with a cell-binding agent..."
- "when (i) Q is -S(O)-, m is 1, and n is 0, or (ii) T is -S(O<sub>2</sub>)-, 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"

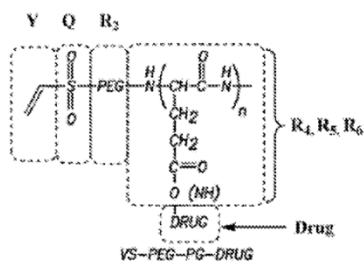
# Intrinsic Evidence Shows "Y" Mapped to a Vinyl Group

- During reexamination, the Examiner mapped the vinyl sulfone of WO'497 to the claimed Q-Y group.
- In response, Applicant reiterated the same mapping and acknowledged the vinyl group as Y.

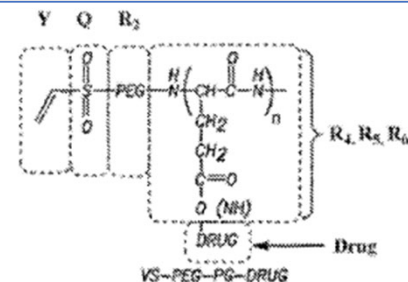
21. With respect to claim 20 in view of the Group I claim interpretation of variables R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> the VS<sup>1</sup>-PEG-PG-DRUG of WO'497 (*i.e.*, Figure 2) is correlated to the instant

<sup>1</sup> 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 H<sub>2</sub>C=CH- of WO'497;
  - instant R<sub>1</sub> (not depicted in the above representation) is absent;
  - instant Q corresponds to -SO<sub>2</sub>- of WO'497;



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 (=).

**Applicant Remarks**  
Ex. 1019 at 75

**Examiner Claim Interpretation**  
Ex. 1019 at 9-10

# Patent Owner Mischaracterizes the Amendments on Reexam

**Patent Owner Sur-Reply at 9:** “The patentee then stated that ‘Y ... does not encompass a vinyl group.’ EX1019, 75. If any [sic, anything], this statement makes clear that Y does not include a vinyl group.”

when (i) Q is -S(O<sub>2</sub>)-, m is 1, and n is 0, or (ii) T is -S(O<sub>2</sub>)-, 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.

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(O<sub>2</sub>)-, m is 1, and n is 0, or (ii) T is -S(O<sub>2</sub>)-, 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.

**Amendment and  
Applicant Remarks**  
Ex. 1019, 51, 75

## Rexxam Prosecution History

### ■ Claim 1:

- "Y represents a functional group the enables reaction of the hydrophilic linker with a cell-binding agent"

### ■ Claim 20:

- "Y represents a functional group that enables reaction of the compound with a cell-binding agent..."
- "... when (i) Q is  $-S(O)-$ , 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.

# Anticipation by Morales-Sanfrutos

# Morales-Sanfrutos Anticipates Claims 1 and 2

- Petitioner identified four compounds from Morales-Sanfrutos that meet claim 1
- Three of these (compounds 2-4) also meet claim 2 via the propargyl amine group

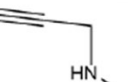
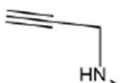
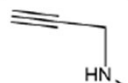
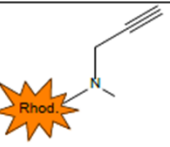
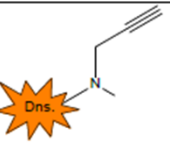
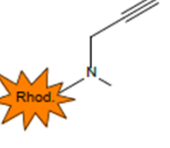
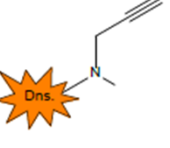
Table B1

| Cmpd           | Bifunctional PEG Cross-linkers |
|----------------|--------------------------------|
| 1              |                                |
| 2              |                                |
| 4 <sup>4</sup> |                                |
| 5 <sup>3</sup> |                                |

# Morales-Sanfrutos Anticipates Claims 1 and 2

- Petitioner identified Morales-Sanfrutos' Y and Z groups in Table B2 of the Petition

**Table B2**

| Morales-Sanfrutos' Compounds 1-2 (Table B1) |                                                                                       |                                                                                       |                                                                                       |                                                                                       |
|---------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| '682<br>(I)                                 | Compound 1                                                                            | Compound 2                                                                            |                                                                                       |                                                                                       |
|                                             |                                                                                       | (a)                                                                                   | (b)                                                                                   | (c)                                                                                   |
| <b>Y</b>                                    |    |    |    |    |
| <b>Z</b>                                    |    |    |    |    |
| '682<br>(I)                                 | Compound 4                                                                            |                                                                                       | Compound 5                                                                            |                                                                                       |
|                                             | (a)                                                                                   | (b)                                                                                   | (a)                                                                                   | (b)                                                                                   |
| <b>Y</b>                                    |  |  |  |  |
| <b>Z</b>                                    |  |  |  |  |

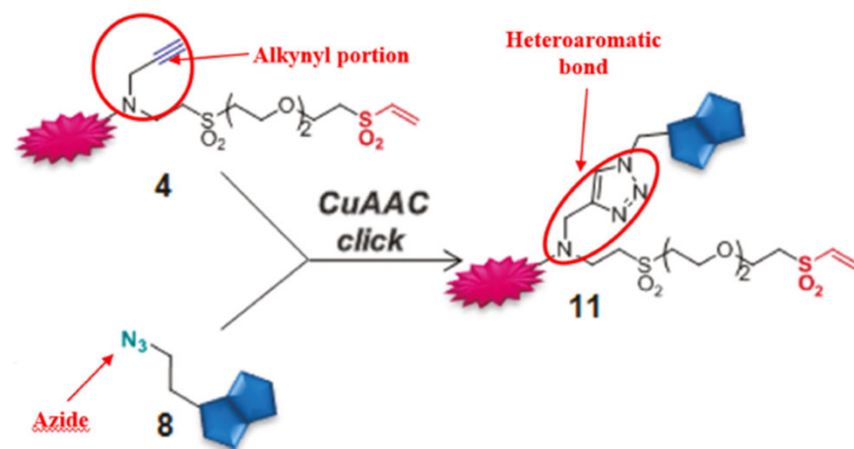
## Morales-Sanfrutos Anticipates Claims 1 and 2

- Claim 2: The hydrophilic linker of claim 1, wherein Z comprises a thiol, disulfide, amino, carboxy, aldehydes, maleimido, haloacetyl, hydrazine or hydroxyl group.

**Dr. Chari**  
**(Petitioner's expert)**

Ex. 1076, ¶22

I would like to point out and clarify that propargylamine groups such as disclosed and utilized in Morales-Sanfrutos have two potential points of reactivity/attachment. First, as I noted in my first declaration with respect to claim 1 (Ex. 1003, ¶87), the alkynyl portion (i.e., the triple-bonded carbons) of the propargylamine can react with azide-functionalized drugs, as expressly disclosed in Morales-Sanfrutos. Morales-Sanfrutos' Scheme 4 is reproduced below with added annotations to further illustrate my point:



Vinyl  
Alone as "Y"

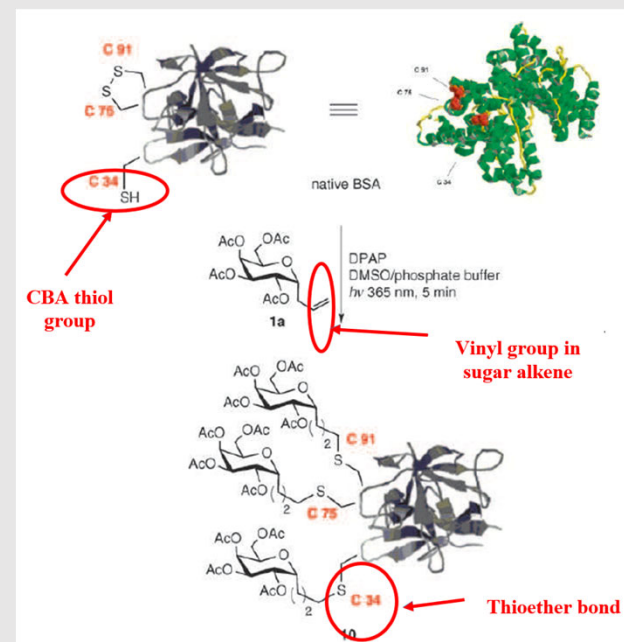
# Vinyl Alone Can React With CBAs

- Dr. Chari testified at length regarding reaction schemes where vinyl alone can react and link to cell-binding agents, which were known before the priority date.
- One such reaction scheme is disclosed in Dondoni.

“[T]here are in fact other reaction schemes where vinyl alone can serve as a functional group that can link to cell-binding agents (CBAs). One that is directly applicable to the attachment to HRP in Morales-Sanfrutos is a thiol–ene reaction, which was known in the art before the priority date.

...

Dondoni et al., describes photoinduced thiol–ene coupling as a strategy for linking substrates, such as sugar alkenes (i.e., vinyl groups) to thiol-bearing cysteine residues on proteins and peptides, such as bovine serum albumin (BSA). . . .”

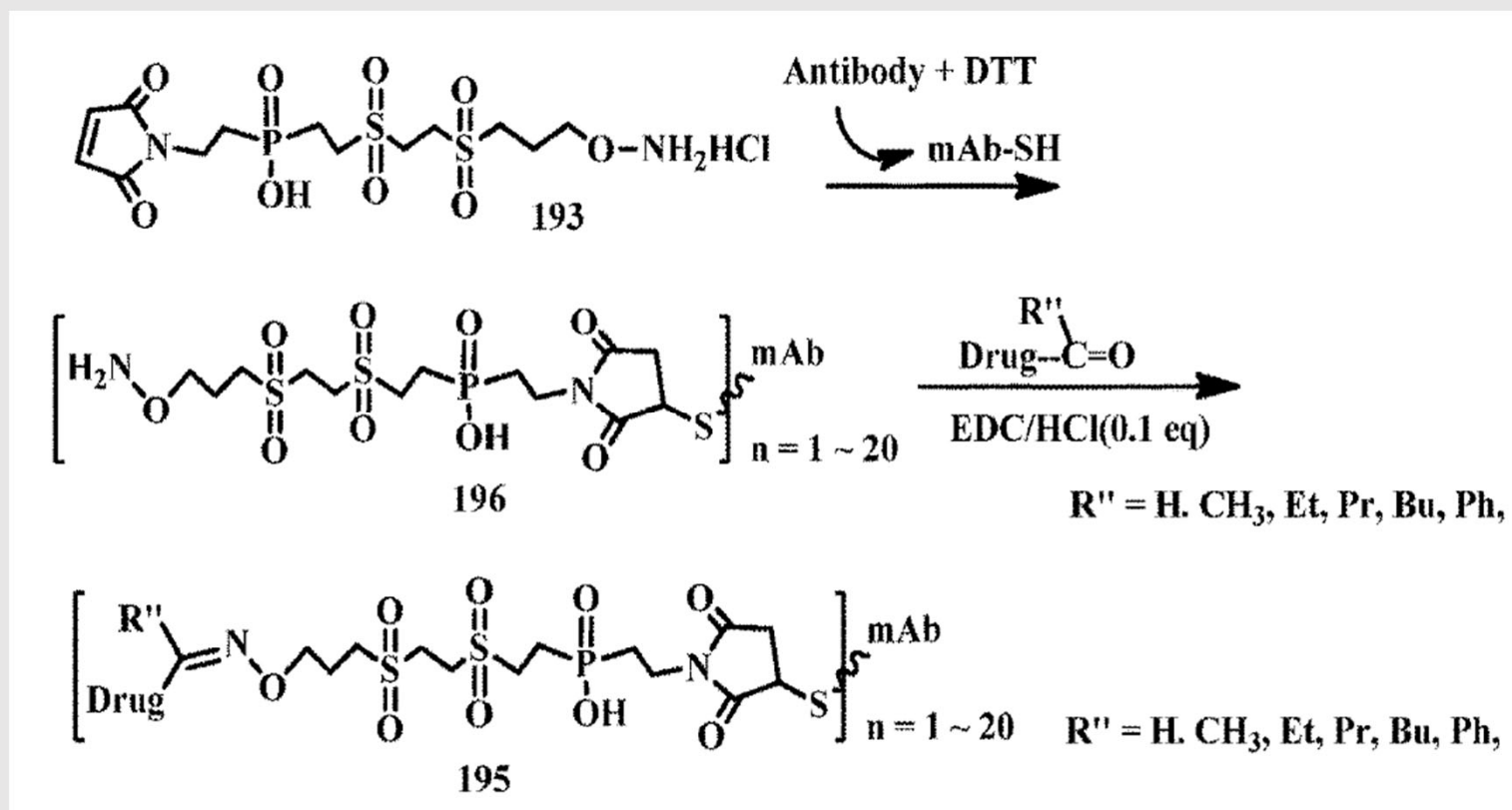


**Dr. Chari**  
**(Petitioner's expert)**

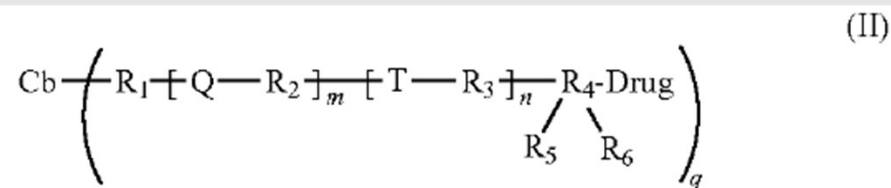
Ex. 1076, ¶¶6-8

## Vinyl Alone Can React With CBAs

- Figure 15 of the '682 patent is informative:



## Morales-Sanfrutos Discloses a "Cell-Binding Agent" (Claim 3)



- A "cell-binding agent" is not the same as a "cell-binding molecule."

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

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.

Ex. 1001, 14:39-44

### Dr. Tumey (Patent Owner's expert)

A . . . Because in claim 3, for example, there is a linkage to a cell-binding agent. And you can't have a linkage to a molecule without creating yet another molecule. You can't have a molecule that encompasses two molecules, right. . . .

Ex. 1063, 56:8-12

# HRP is a Known Cell-Binding Agent

- A POSA would have understood HRP to be a cell-binding agent, as evidenced by Straus.

**Dr. Baker**  
**(Petitioner's expert)**  
Ex. 1087, 37:20-38:7

Q . . . [A]bout how many cell-binding experiments have you or your lab conducted?

. . .

**A . . . I believe the estimate would be in the tens of thousands.. . .**

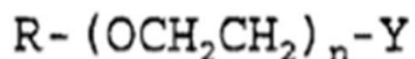
14. Taking all of Straus' reported results together, or even considering them individually, a POSA would have understood that Straus reports that HRP binds to the surfaces of the cell types described, with HRP binding to some of the listed cell types more strongly than others. This is typical of cell binding agents, where the agent binds more strongly to some types of cells and less strongly to other types of cells.

23. Consequently, the fact that Straus used well-known cell fixation techniques (even if this did kill the cells as part of the process) and addressed (and discounted) potential artifacts would not have led a POSA to question whether HRP binds to the surfaces of living cells of the identified types, but rather just the opposite. A POSA would take away from Straus an understanding that HRP does in fact bind to the surfaces of living cells of the identified types and would have been reasonable in believing that to be the case.<sup>3</sup> This is my opinion based on my knowledge of and expertise with cell fixation techniques and cell binding experiments.

# Harris Anticipation/ Obviousness

## A POSA Readily Understand Harris' Teachings

- Harris' teachings disclose a limited and manageable number of combinations that would have been readily understood by a POSA.
- Harris discloses the following formula, and further expressly identifies:
  - (1) vinyl sulfone and haloethyl sulfone as potential Y groups;
  - (2) vinyl sulfone, haloethyl sulfone, methyl, and hydrogen as potential R groups; and thus
  - (3) bis vinyl sulfone.



In the above structure, Y represents -SO<sub>2</sub>-  
25 CH=CH<sub>2</sub> or -SO<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-X where X is a halogen. R  
represents a group that may be the same or different  
from Y. R can be H-, H<sub>3</sub>C-, CH<sub>2</sub>=CH-SO<sub>2</sub>-, Cl-CH<sub>2</sub>-CH<sub>2</sub>-SO<sub>2</sub>-,  
or a polymer activating group other than CH<sub>2</sub>=CH-SO<sub>2</sub>-,  
Cl-CH<sub>2</sub>-CH<sub>2</sub>-SO<sub>2</sub>-, such as is referred to with respect to  
30 the above patents and published patent applications.

A linear PEG with active hydroxyls at each  
35 end can be activated at each end with vinyl sulfone or  
its precursor or derivatives of similar reactivity to  
become bifunctional. The bifunctional structure, PEG  
bis vinyl sulfone, for example, is sometimes referred  
to as a dumbbell structure and can be used, for  
example, as a linker or spacer to attach a biologically  
5 such biologically active molecule to the PEG molecule.  
The stability of the sulfone moiety against hydrolysis  
makes it particularly useful for bifunctional or  
heterobifunctional applications.

## Harris' Anticipation of Claims 1, 20-21, 29-31

- Harris' vinyl sulfone-containing linkers anticipate (or render obvious) each of the challenged claims:

| Claim | Q/T Requirement | Harris' relevant disclosure                       |
|-------|-----------------|---------------------------------------------------|
| 1     | Q and T         | Bis vinyl sulfones                                |
| 20    | Q or T          | Bis vinyl sulfones and hetero-functional sulfones |
| 21    | Q or T          | Bis vinyl sulfones and hetero-functional sulfones |
| 29    | Q or T          | Bis vinyl sulfones and hetero-functional sulfones |
| 30    | Q and T         | Bis vinyl sulfones                                |
| 31    | Q and T         | Bis vinyl sulfones                                |

Singh & Harris render Claims 1-8,  
10-12, 14-17, 20-21, 24, 26, and 29-  
31 Obvious

## Claims 1-8, 10-12, 14-17, 20-21, 24, 26, 29-31 are obvious in view of Singh and Harris

- Singh discloses ADC linkers comprising:
  - pyridyldisulfide, maleimide, iodo- or bromoacetamide, or NHS ester groups as reactive functionalities that enable linkage to cytotoxic drugs (Z)
  - maleimide, iodo- or bromo-acetamide, and NHS ester groups as reactive functionalities that enable linkage to CBAs (Y)
- While Singh's depicted PEG linkers lack sulfonyl groups, Singh expressly suggests the use of vinyl sulfones as a thiol-reactive functionality and teaches their equivalence to maleimide and haloacetamides for this purpose.

[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

- A POSA would have been motivated to replace one or both of the reactive functionalities in Singh's bifunctional PEG cross-linkers with a vinyl sulfone group, satisfying the limitations of claim 1

## **Claims 1-8, 10-12, 14-17, 20-21, 24, 26, 29-31 are obvious in view of Singh and Harris**

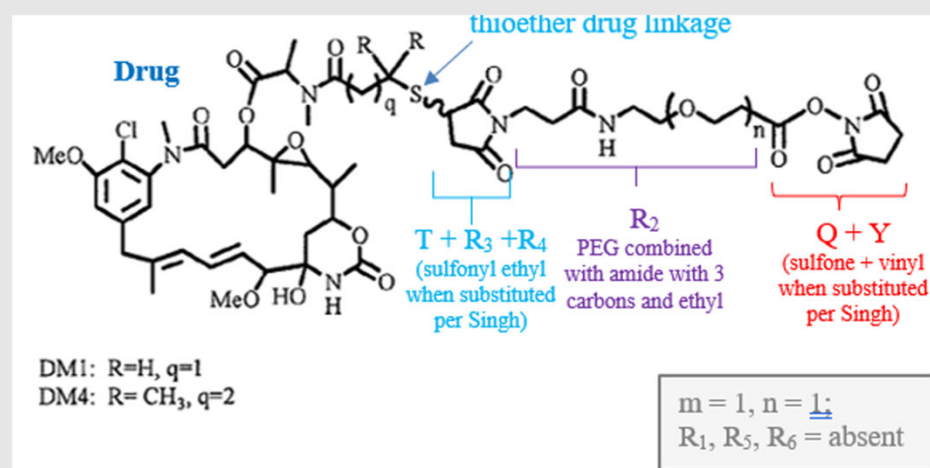
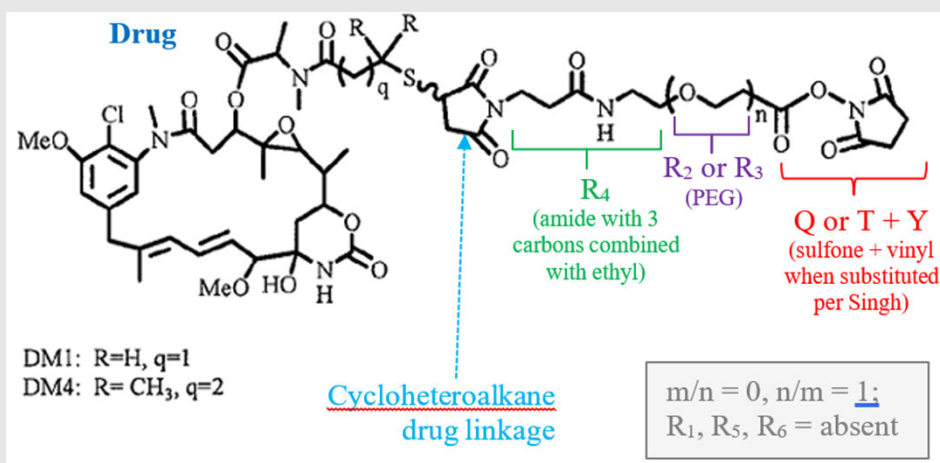
- Singh teaches that more hydrophilic linkers permit conjugation of high drug loads to an antibody without aggregation or precipitation, and enhance ADC potency
- A POSA would be motivated to further improve the solubility of ADC linkers that are conjugated to hydrophobic drugs, at high drug loads because improving water solubility of ADCs is correlated with enhanced potency and reduced aggregation
- Exemplary situations where PEG alone may not be sufficient include:
  - conjugation to exceptionally hydrophobic drugs
  - when the PEG chain must be kept short

**Claims 1-8, 10-12, 14-17, 20-21, 24, 26, 29-31  
are obvious in view of Singh and Harris**

- A POSA would have been further motivated to substitute the reactive functionalities in Singh's linkers with vinyl sulfones in view of Harris with reasonable expectation of success
  - Harris' vinyl sulfone-containing PEG linkers and Singh's PEG linkers serve the same purpose: link two biologically-active molecules (e.g., proteins, pharmaceuticals) via thiol linkages
  - Harris' vinyl sulfonyl-containing PEG linkers are "infinitely soluble in water" and enable otherwise insoluble molecules (e.g., hydrophobic drugs) to be soluble in water
  - Harris' vinyl sulfonyl-containing PEG linkers permit thiol-based reactions resulting in hydrolytically stable bonds

## Claims 1-8, 10-12, 14-17, 20-21, 24, 26, 29-31 are obvious in view of Singh and Harris

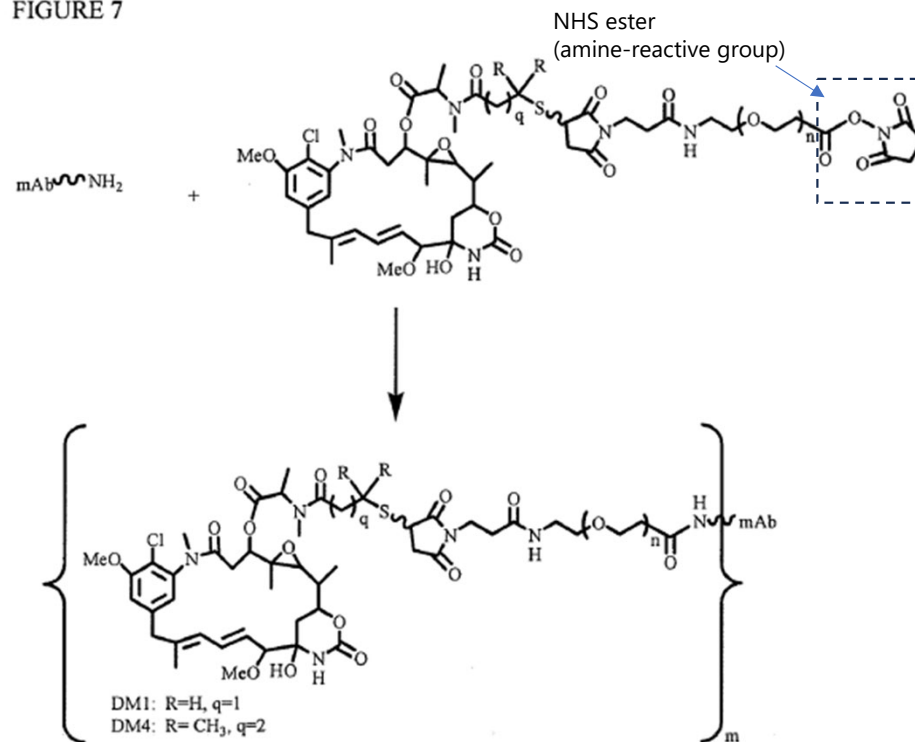
- It would have been obvious for a POSA to substitute an amide bond forming group (e.g., NHS ester) of Singh's PEG linker with vinyl sulfone, as shown in Table C2 of the Petition



## Claims 1-8, 10-12, 14-17, 20-21, 24, 26, 29-31 are obvious in view of Singh and Harris

- Like NHS-esters, Harris and Snow both expressly disclose that vinyl sulfones can react with **amines** on proteins (e.g., antibody), and would thus bond with the same cell-binding agent or drug as an NHS-ester

FIGURE 7



30 foregoing examples are merely illustrative of the adducts of polyethylene glycol to divinyl sulfone. The reactivities of the residual vinyl sulfone group toward amines on proteins could be increased, for example, by employing bis(vinyl sulfonyl) methane or bis(vinyl sulfonylmethyl) ether.

Snow, col 22: 31-35

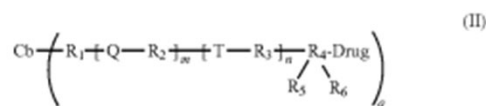
The above kinetic studies demonstrate the following points. PEG vinyl sulfone is much more reactive with thiol groups than with amino groups, indicating that attachment of PEG vinyl sulfone to a protein containing both cysteine and lysine groups proceeds primarily by reaction with cysteine. Since

Harris, page 28, lines 17-21

A POSA Would Have Combined Singh with  
Harris and Bhakta

# Claims 9 and 13 are obvious in view of Singh, Harris, and Bhakta

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



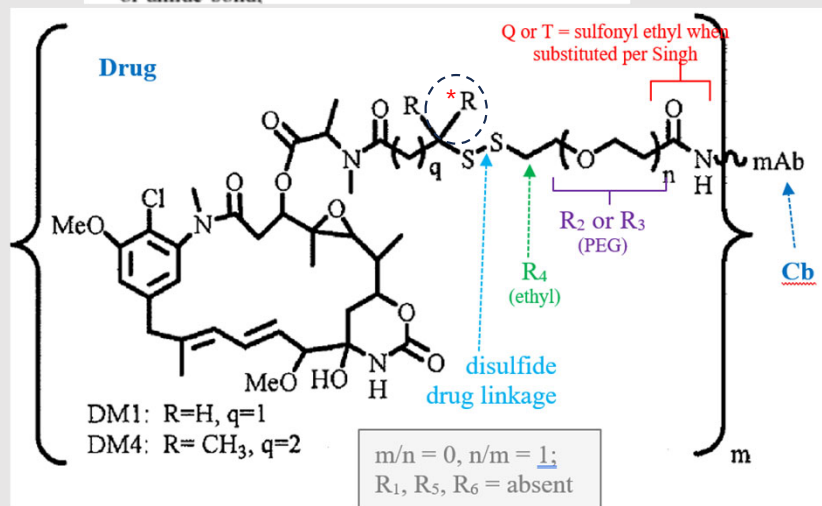
wherein:

Cb represents a cell-binding agent;

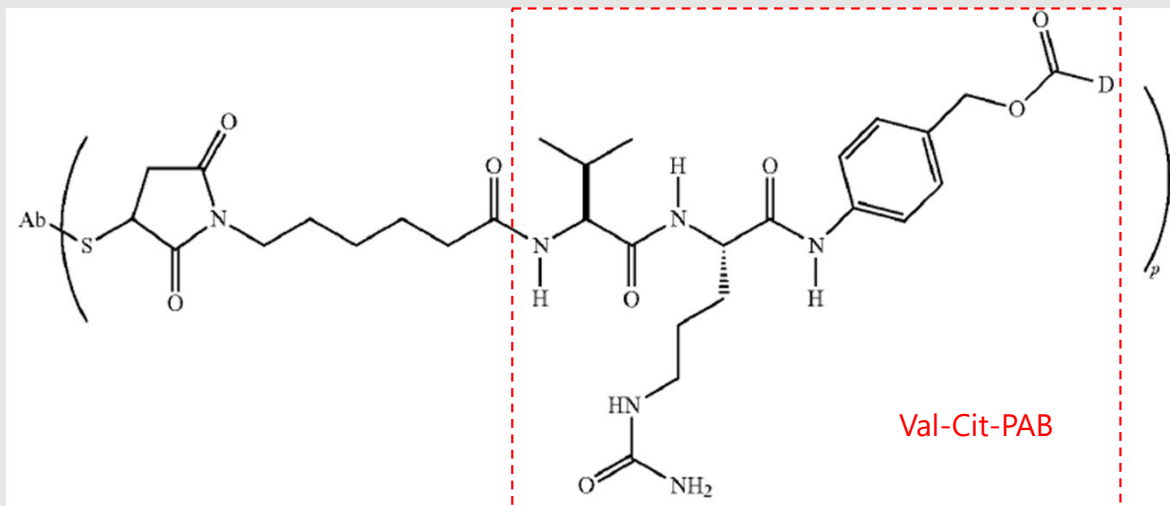
Drug represents a drug linked to the cell-binding agent via the hydrophilic linker by a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

9. The conjugate of claim 3, wherein the conjugate comprises one or more linker components of 6-maleimido-caproyl, maleimidopropanoyl, valine-citrulline, alanine-phenylalanine, p-aminobenzyloxycarbonyl, 4-thio-pentanoate, 4-(N-maleimidomethyl)cyclohexane-1-carboxylate, 4-thio-butyrate, maleimidoethyl, 4-thio-2-hydroxysulfonyl-butyrate and (4-acetyl)aminobenzoate.

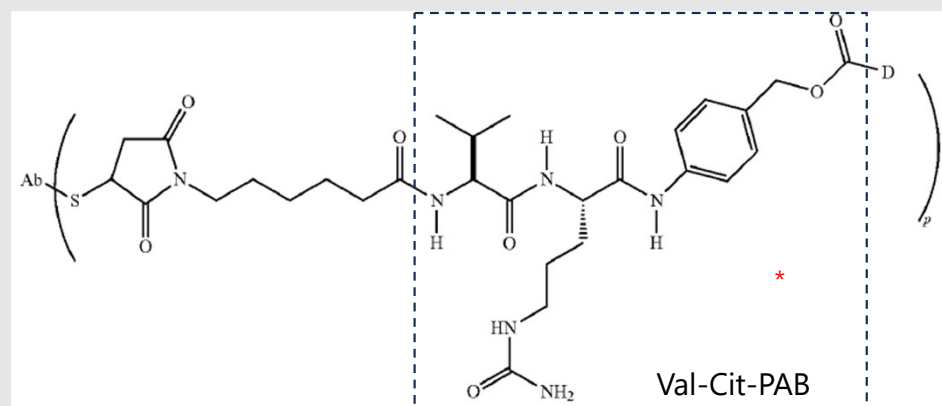
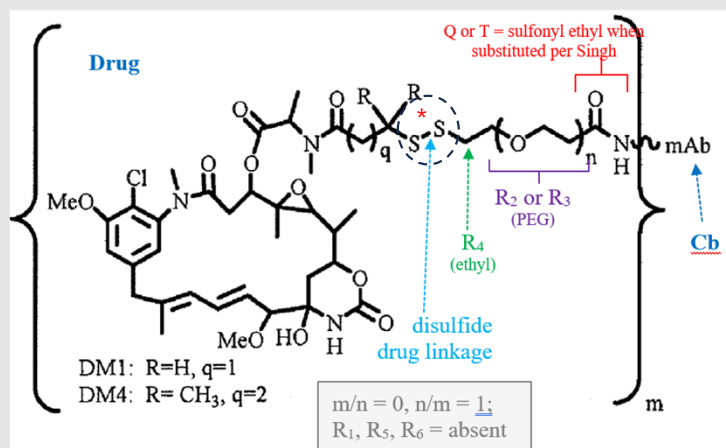
13. The conjugate of claim 3, wherein the conjugate is cleavable by a protease



\* Protease cleavage site



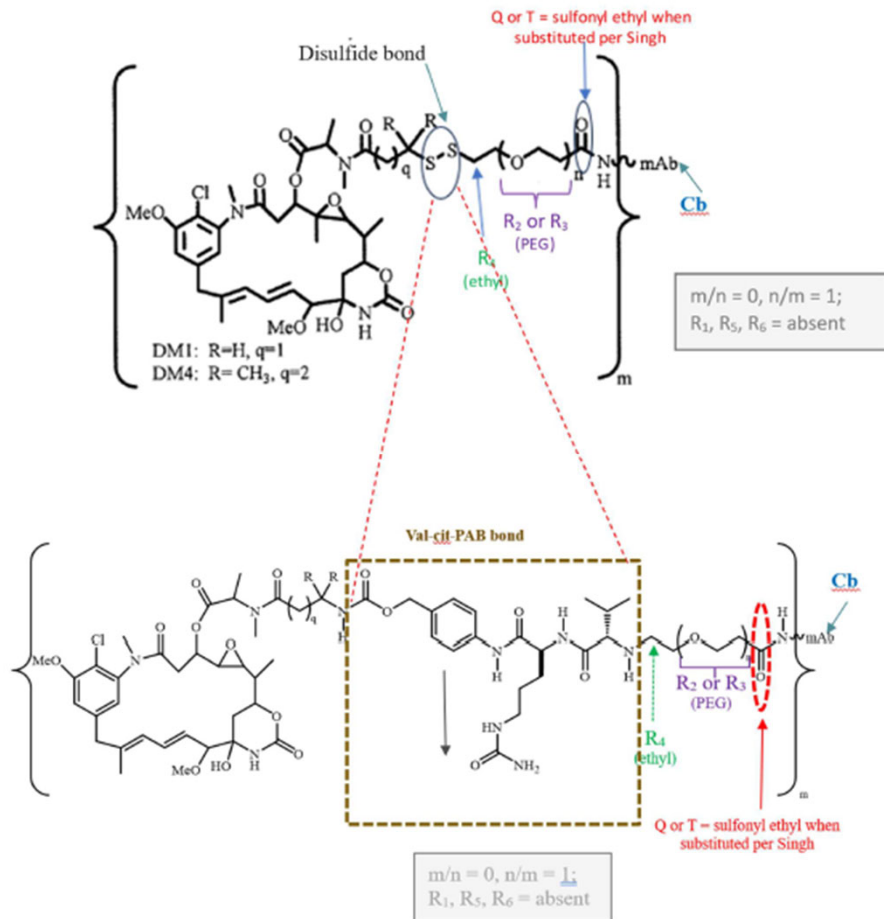
# Claims 9 and 13 are obvious in view of Singh, Harris, and Bhakta



\* Protease cleavage site

- Both disulfide linkages and Val-Cit-PAB peptide linkages are functionally equivalent: cleavable by proteases in vivo
- Val-Cit-PAB linkages are advantageous over disulfide linkages due to selective drug release at target cancer cells via tumor-specific proteases
- One of ordinary skill in the art would be motivated to replace disulfide linkages in Singh's conjugate compounds

## Claims 9 and 13 are obvious in view of Singh, Harris, and Bhakta

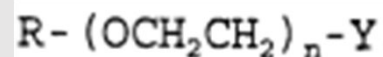
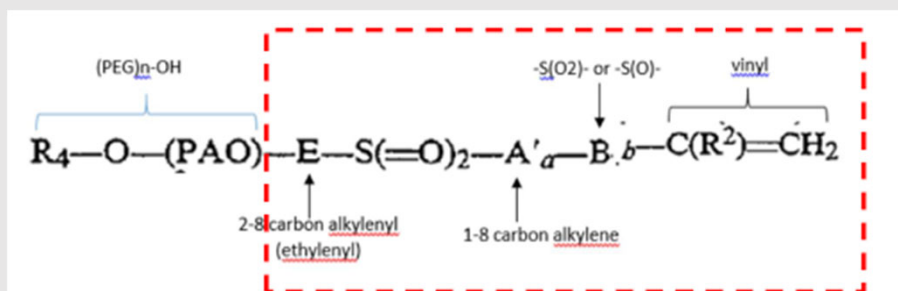


- The substitutions discussed in the Petition satisfy all limitations of claims 9 and 13
  - Replace the amide bond forming group (such as N-hydroxysuccinimide) with ***sulfonyl ethyl***
  - Substitute the disulfide-drug bond with Bhakta's ***val-cit-PAB-drug bond***

# A POSA Would Have Selected Snow's Identified Structures

## A POSA Would Select Snow's Structures to Couple PEG to Proteins

- Snow discloses various PEG-vinyl sulfone conjugates, where the bis sulfone portion are *directly* coupled to PEG (i.e., PAO) via the "E" group between PAO and a sulfone group
- Harris's and Snow's PEG-vinyl sulfone conjugates show preferential reactivity with thiol (sulfhydryl) groups on proteins (same purpose)



free sulfhydryl groups. The rate of addition of the reagent of this invention to free sulfhydryl groups can be shown to be faster than the rate of addition to amino groups, and this can be shown unequivocally using amino acids containing these functional groups as models for the proteins. 60

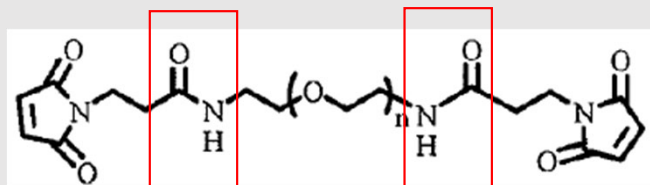
(containing -NH-). The selectivity of PEG vinyl sulfone for thiols means that PEG can be selectively attached to cysteine units, thus preserving protein activity for specific proteins and controlling the number of PEG molecules attached to the protein. 15

## A POSA Would Combine Singh, Harris and Snow

- Harris discloses that PEG spacers including sulfonyl moieties are highly water-soluble
- A POSA would be motivated to further improve the solubility of Singh's PEG linkers conjugated to exceptionally hydrophobic drugs at high drug loads that are prone to aggregation/precipitation

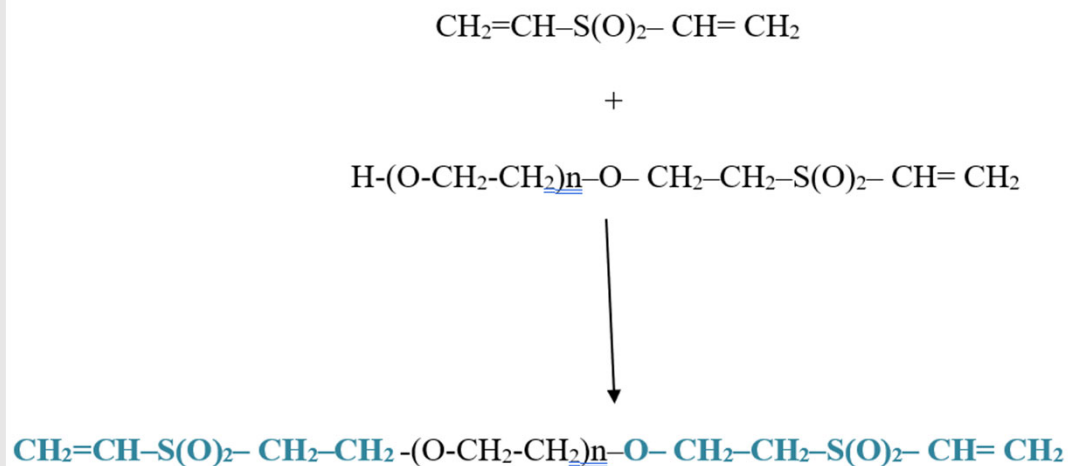
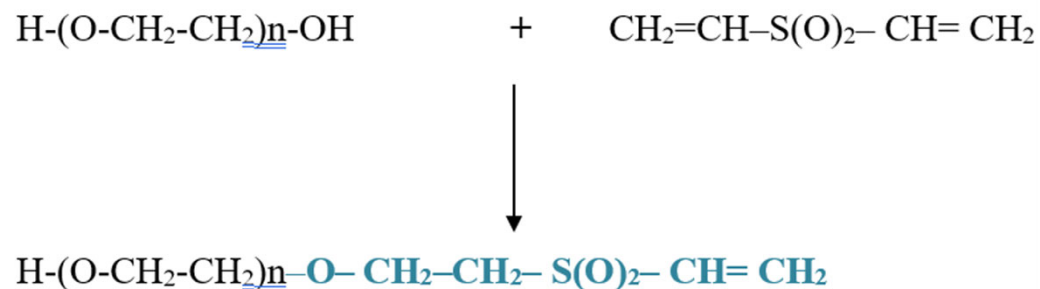
## Practical Considerations of Using Bisvinyl Sulfone in ADC Linkers

- The skilled artisan would have been motivated to replace **at least one of the maleimide-containing arms** in Singh's bifunctional bismaleimide PEG crosslinking agent with the bis-vinyl sulfone group of Snow to enhance hydrophilicity of the PEG linkers conjugated to exceptionally hydrophobic drugs
- The amide linkages present on both ends of PEG in Singh's linkers (i.e., remnants of the NHS-ester reaction) are merely needed to facilitate attachment of the PEG moiety to the terminal maleimide groups.



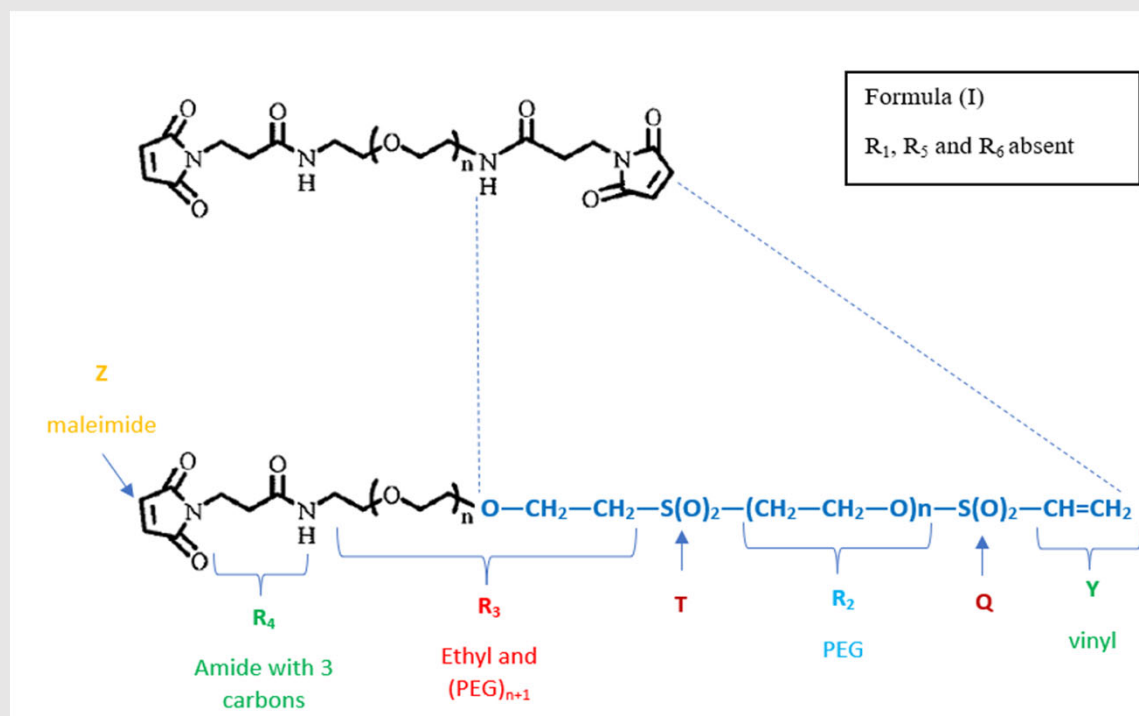
- Unlike the above bis-maleimide PEG linkers of Singh, the thiol-reactive vinyl sulfones can be directly coupled to the PEG moiety **without the need for intervening amide linkages**

## Exemplary Reaction Schematic for Vinyl-sulfone coupling to PEG

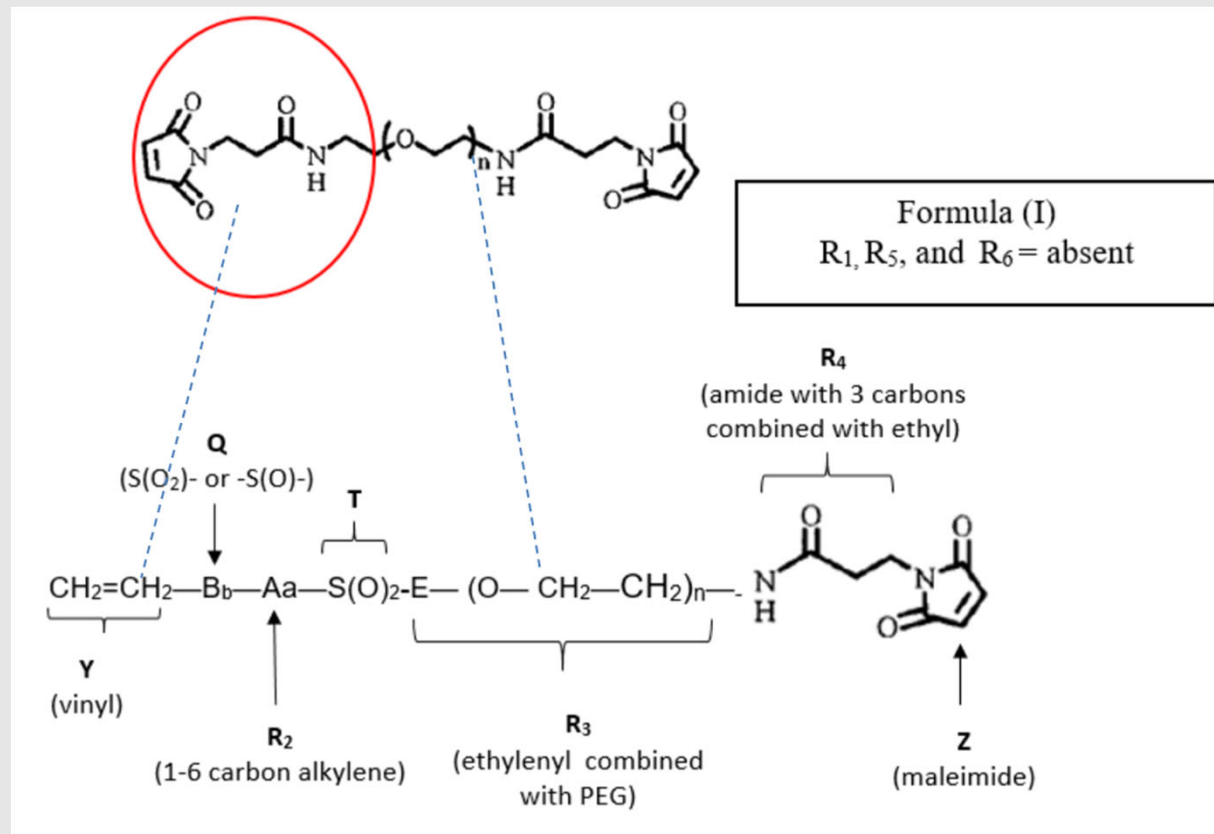


## Claim 2 is obvious in view of Singh and Harris

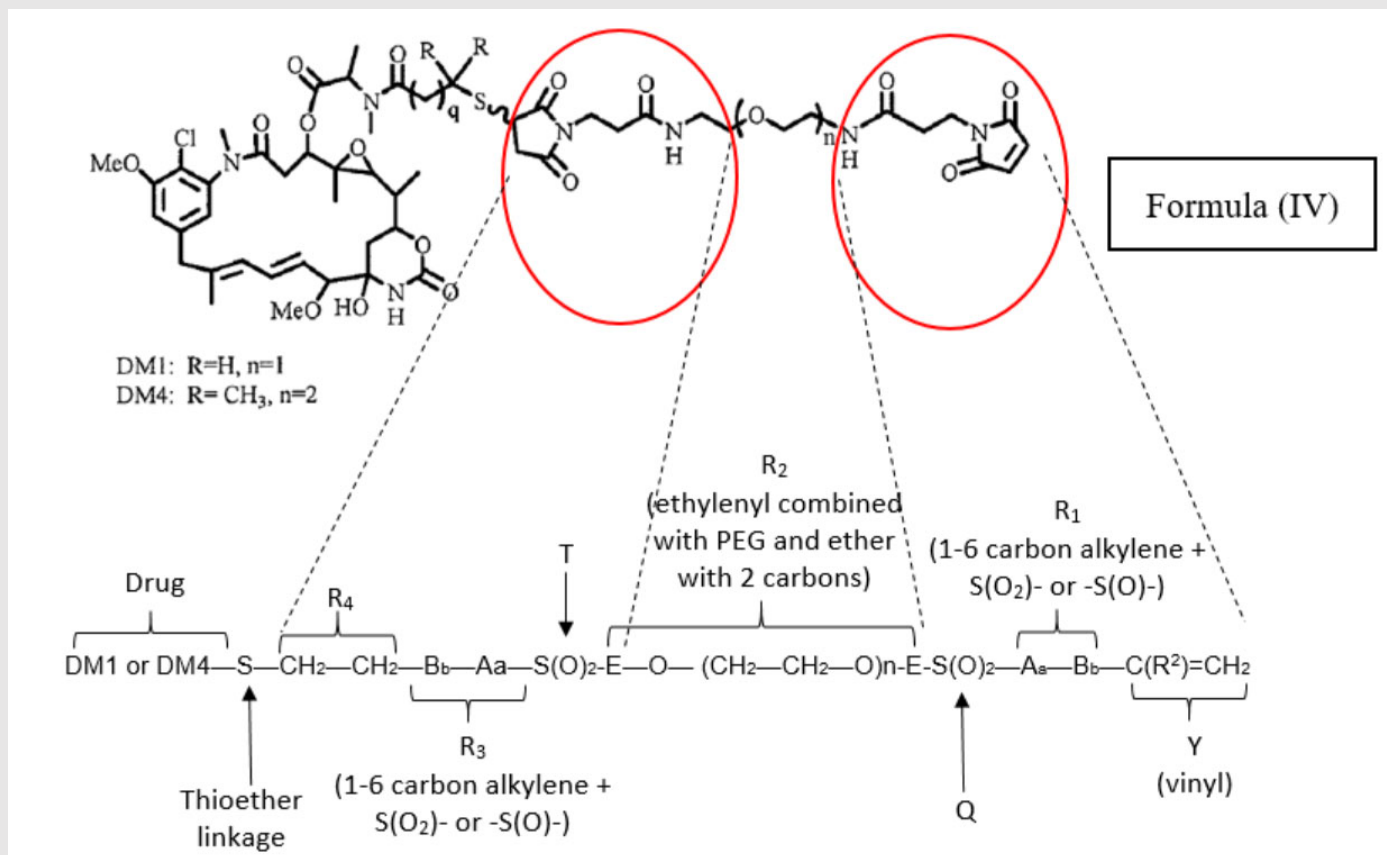
- A POSA would envision substituting Harris' related sulfonyl functionalities (e.g., PEG bis-vinyl sulfone) as thiol-reactive groups for maleimide (depicted as Y group) in Singh's linker with to obtain the beneficial qualities of vinyl sulfones (improved water solubility, hydrolytically stable bonds)



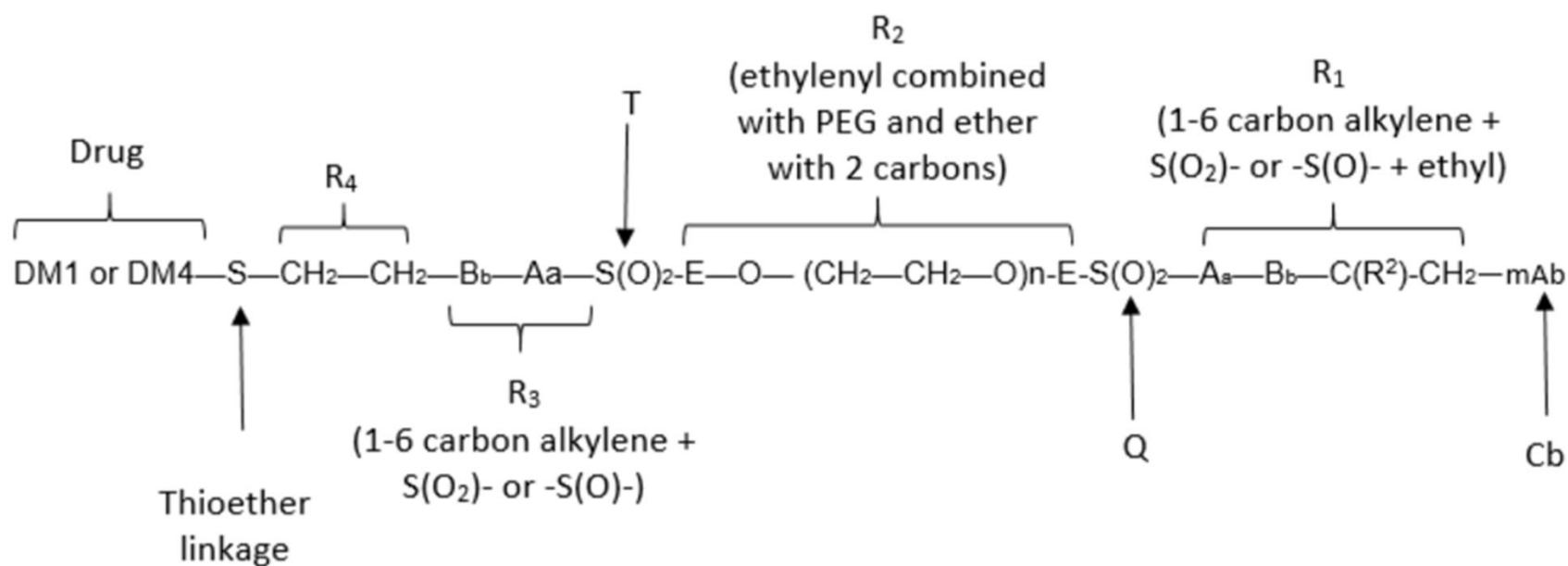
## Alternatively, Claim 2 is obvious in view of Singh, Harris, and Snow



## Claims 32 and 34 are obvious in view of Singh, Harris, and Snow

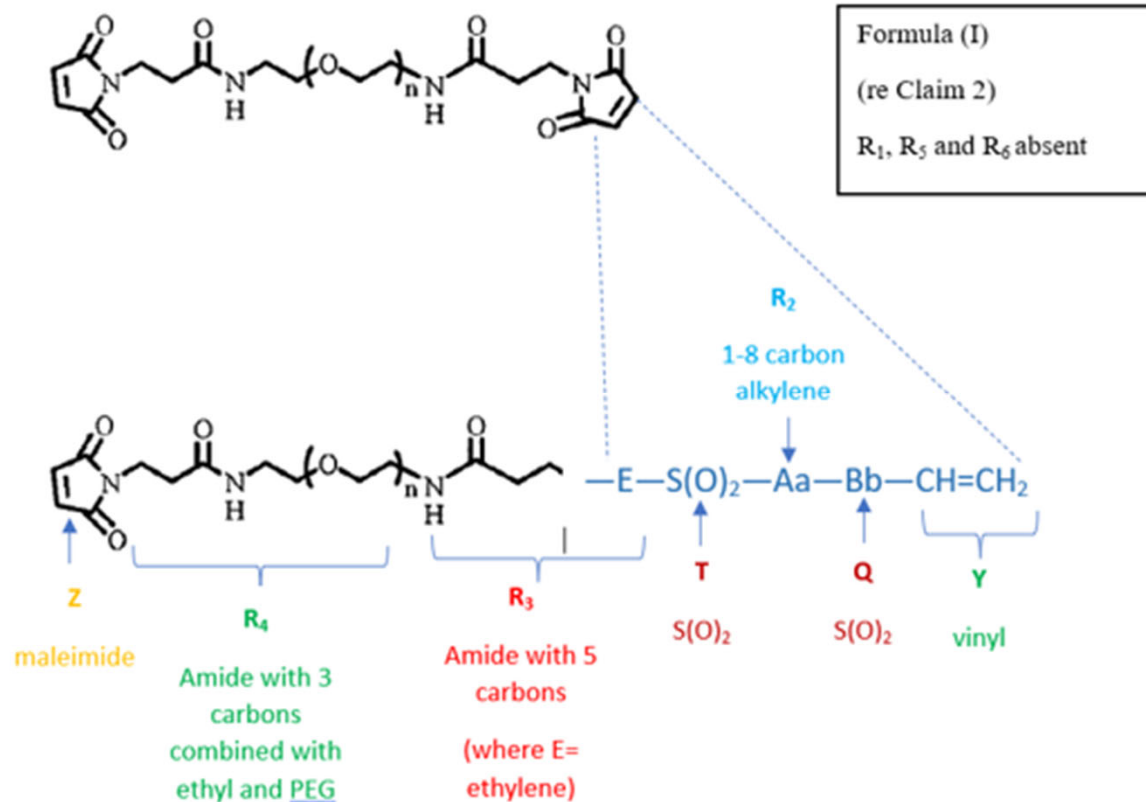


## Claims 25 and 33 are obvious in view of Singh, Harris, and Snow

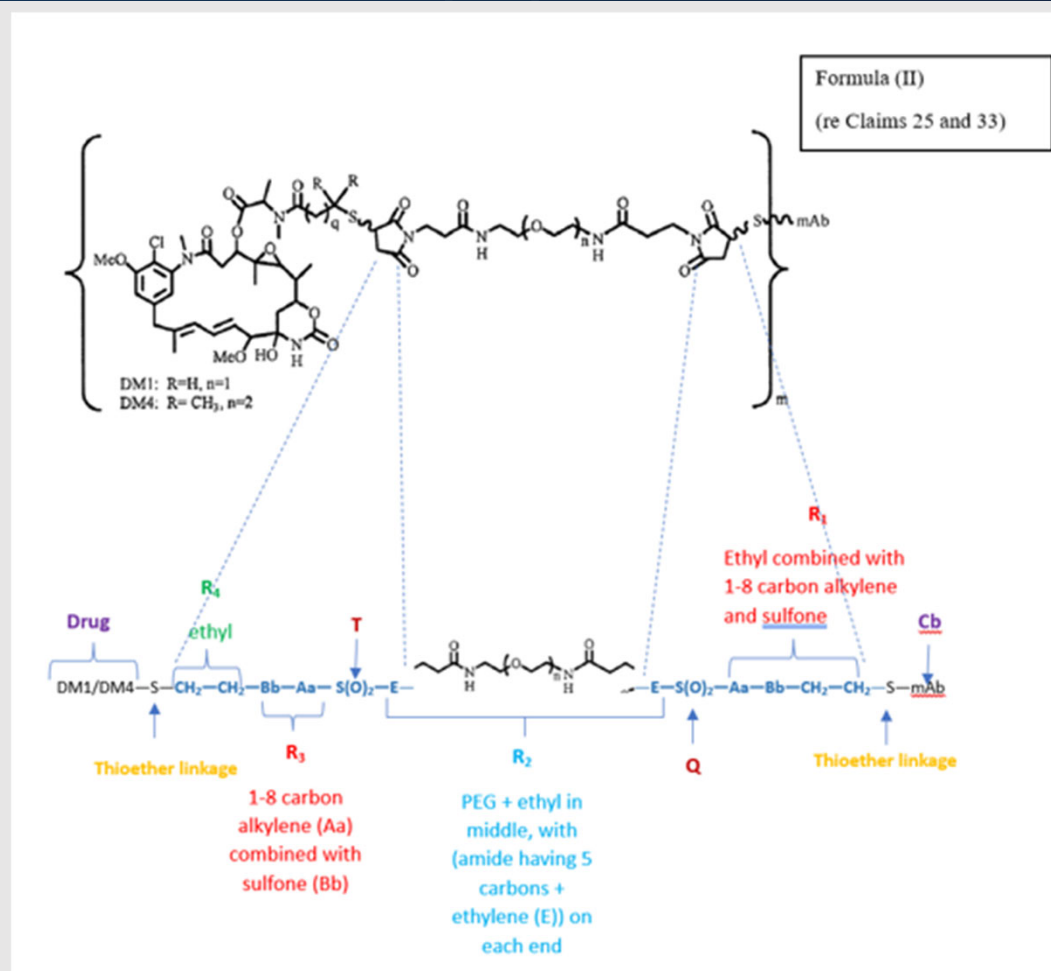


# Appendix Figures

## Claims 2, 25 and 32-34 are obvious in view of Singh, Harris, and Snow even under Board's proposed substitution



## Claims 2, 25 and 32-34 are obvious in view of Singh, Harris, and Snow even under Board's proposed substitution



## Claims 2, 25 and 32-34 are obvious in view of Singh, Harris, and Snow even under Board's preferred substitutions

