

Inter Partes Review No.: IPR2022-01531

Chari Declaration

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

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

Patent No. 10,131,682

Ex Parte Reexamination Certificate Issued: January 4, 2021

Title: HYDROPHILIC LINKERS AND THEIR USES FOR CONJUGATION OF
DRUGS TO A CELL BINDING MOLECULES

Inter Partes Review No. IPR2022-01531

DECLARATION OF DR. RAVI CHARI

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I, Dr. Ravi Chari, declare and state as follows:

I. INTRODUCTION

1. I am over the age of eighteen (18) and otherwise competent to make this declaration.

2. I have been retained by Foley & Lardner, LLP, counsel for Petitioner, as an expert declarant in the above captioned *inter partes* review (“IPR”). I have reviewed U.S. Patent No. 10,131,682 (the ’682 patent, EX1001) to assess its patentability and provide my opinions about such patentability.

3. I am being compensated for my time on an hourly basis in connection with this IPR. My compensation is not contingent on the conclusions I reach herein or on the specifics of my testimony. I have no financial stake in the outcome of this proceeding.

II. BACKGROUND AND QUALIFICATIONS

4. I have extensive research experience in drug design, multi-step organic synthesis, enzymology and inhibitor design, medicinal chemistry, drug delivery, antibody purification, antibody conjugation, and protein biochemistry.

5. I am also currently a Biotechnology Consultant at RChari Consulting (July 2019-present), where I advise clients on all aspects of antibody-drug conjugates (ADCs) including their chemistry, biochemistry, and pharmacology.

6. Prior to July 2019, I was the Vice President of Chemistry & Biochemistry at ImmunoGen Inc. in Waltham, MA, a company engaged in the development of novel pharmaceuticals for oncotherapeutics. During my tenure at ImmunoGen Inc. (1988-2019), I was a Member of the Senior Management Team. I am a Fellow of the American Institute for Medical and Biological Engineering (AIMBE).

7. In 1986-1987, I was a Research Scientist at Harvard Medical School & Dana Farber Cancer Institute in Boston. I was also a Research Scientist at University of Maryland in 1985 and at Yale Medical School between 1980-1984, where I was awarded the Yale-Celanese Research Fellowship.

8. My research interests include medicinal chemistry, antibody purification and conjugation, as well as targeted drug delivery as it relates to cancer therapy. I have authored or co-authored over 60 peer-reviewed articles and am an inventor on 102 issued U.S. Patents in these areas, including the composition of matter patent on the FDA-approved product Kadcyła® for breast cancer therapy. I

have formulated a research program for the targeted delivery of chemotherapeutic agents and received over \$1.5 million in competitive research funding to advance the same. I have regularly given invited lectures on the design and synthesis of chemotherapeutics and linkers, the modification of monoclonal antibodies, and their use in antibody drug conjugates at several national and international conferences.

9. Included among my publications are studies on the targeted delivery of cytotoxic drugs to tumors. Specific studies include the synthesis and evaluation of hydrophilic linkers for antibody-maytansinoid conjugates, and the antitumor efficacy of targeted delivery of several cytotoxic drugs including maytansinoids, CC-1065 analogs, taxane drugs etc.

10. Because of my expertise in the design and synthesis of chemotherapeutic drugs and antibody drug conjugates for targeted cancer therapy, I have served as Member of the Editorial board of the journals MABs and ChemMedChem. I am also a recipient of the Boston Business Journal “Champions in Health Care” award (2013) and the World ADC award for “Longstanding Contribution” to the ADC field (2018).

11. I received a Bachelor of Science degree in Chemistry, with Honors, and a Master of Science degree in Chemistry from the University of Delhi, India in 1971

and 1973, respectively. In 1975, I received a Master of Philosophy in Life Science from Jawaharlal Nehru University, New Delhi, India. In 1979, I received a Doctorate degree in Chemistry at the University of Detroit in Michigan.

12. Based on my education, research and experience, I consider myself to be at least a person of ordinary skill in the art.

III. DOCUMENTS AND INFORMATION CONSIDERED

13. In providing the information and opinions in this declaration, I have reviewed the documents listed below:

Ex. No.	Prior Art Citation
EX1001	U.S. Patent No. 10,131,682 (“the ’682 Patent”)
EX1005	Morales-Sanfrutos-Sanfrutos <i>et al.</i> , “Vinyl Sulfone Bifunctional Tag Reagents for Single-Point Modification of Proteins,” <i>J. Org. Chem.</i> 75, no. 12 (2010): 4039-4047 (“Morales-Sanfrutos-Sanfrutos”)
EX1006	Straus & Keller, “Unusual Binding Sites for Horseradish Peroxidase on the Surface of Cultured and Isolated Mammalian Cells,” <i>Histochemistry</i> 85, July 1986, pages 277-285 (“Straus”)
EX1007	International Publication No. WO 1995/013312 (“Harris”)
EX1008	U.S. Patent Publication No. 2010/0129314 (“Singh”)
EX1009	U.S. Patent No. 5,208,020 (“Chari”)
EX1010	U.S. Patent No. US 5,414,135 (“Snow”)
EX1011	US Patent Publication No. 2011/0301334 (“Bhakta”)
EX1014	Thomas <i>et al.</i> , “Application of Strain-Promoted Azide-Alkyne Cycloaddition and Tetrazine Ligation to Targeted Fc-Drug Conjugates,” <i>Bioconjug Chem.</i> , 23(10), October 2012, pages 2007–2013 (“Thomas”)

EX1015	Kathrin-Maria Roy <i>et al</i> , <i>Sulfones and Sulfoxides</i> , Ullmann's Encyclopaedia of Industrial Chemistry, Vol. 34, page 571 (2003) (“Roy”)
EX1016	Zhao <i>et al.</i> , Synthesis and Evaluation of Hydrophilic Linkers for Antibody-Maytansinoid Conjugates, <i>J. Med. Chem.</i> 2011, 54, 3606–3623 (“Zhao”)
EX1017	U.S. Patent No. 6,214,345 (“Firestone”)
EX1045	French Application No. FR 10/52589 priority document, filed 6 April 2010 and Certified English translation thereof
EX1046	International Publication No. WO2011124571
EX1047	U.S. Patent No. 5,122,614 (“Zalipsky”)
EX1048	Boja & Fales, <i>Anal. Chem.</i> 2001, 73, pages 3576-3582 (“Boja”)
EX1049	Lewis Phillips <i>et al.</i> , <i>Cancer Res</i> (2008) 68 (22): 9280–9290
EX1050	US Patent No. 8,236,319 (“Chari”)
EX1051	Pietersz <i>et al.</i> , <i>Advances in Immunology</i> Vol. 56: 301-387 (1994).
EX1052	Trail & Bianchi, <i>Current Opinion in Immunology</i> 11:584–588 (1999).
EX1053	Ghose <i>et al.</i> , <i>Journal of the National Cancer Institute</i> , Vol. 61(3): 657–676 (1978) (“Ghose”)
EX1054	Panousis & Pietersz, <i>Drugs & Aging</i> 15 (1): 1-13 (1999)
EX1055	Alley <i>et al.</i> , <i>Bioconjug Chem.</i> 2008 Mar;19(3):759-65 (“Alley”).
EX1056	Doronina <i>et al.</i> , <i>Nature Biotech</i> 21(7):778-784 (2003) (“Doronina”).

IV. APPLICABLE LEGAL STANDARDS

14. In expressing my opinions and considering the subject matter of the claims of the '682 patent, I am relying on legal standards explained to me by Petitioner's attorneys. I have applied my understanding of these standards in my analysis as detailed below.

A. Prior Art

15. I have been informed that the law provides certain categories of information, known as prior art, that may be used to render patent claims anticipated or obvious. I have also been informed that the Morales-Sanfrutos, Straus, Harris, Singh, Snow and Bhakta references I discuss in this declaration were available to members of the public as of November 24, 2012, and are therefore prior art to the '682 patent. In fact, the Morales-Sanfrutos, Straus, Harris, Singh, and Snow references were published more than one year before November 24, 2012, and were thus available to persons of ordinary skill in the art as of November 24, 2011, which I understand is referred to as the "critical date" for the '682 patent. While Bhakta was first published on December 8, 2011, I am informed it names another inventor (*i.e.*, the inventors differ from those of the '682 patent) and was effectively filed June 8, 2010, the date of the provisional application to which it claims priority. Bhakta was thus available to persons of ordinary skill in the art as of November 24, 2012.

B. Person of Ordinary Skill in the Art (POSA)

16. I understand that the assessment of the patentability of the claims of the '682 patent must be undertaken from the perspective of the POSA as of the earliest priority date of the '682 patent, which I have been informed is November 24, 2012.

17. With respect to the level of ordinary skill in the art at the relevant time, I understand that factors such as the education level of those working in the field, the level of sophistication of the technology in question, the types of problems encountered in the art, the prior art solutions to those problems, and the speed at which innovations are made may help establish the level of skill in the art. I understand that a POSA is assumed to be aware of all pertinent prior art, and that a POSA has the ability to understand the technology, draw inferences, and make modest adaptations or advances. A POSA is thus a person of ordinary creativity, not an automaton.

C. Claim Construction

18. I understand that the first step in comparing prior art to patent claims is to properly construe the claims to determine claim scope and meaning. I understand that in IPR proceedings, claim terms are presumed to take on the ordinary and customary meaning that they would have to a POSA in the context of the entire disclosure of the specification. I also understand that if an inventor acts as his or her own lexicographer, the definition must be set forth in the specification with reasonable clarity, deliberateness, and precision.

D. Anticipation

19. I understand that, once the claims of a patent have been properly construed, determining anticipation of a patent claim requires a comparison of the properly construed claim language to the prior art on a limitation-by-limitation basis. I understand that a prior art reference “anticipates” a claim, and thus renders the claim unpatentable, if all elements of the claim are disclosed in that prior art reference, either explicitly or inherently (*i.e.*, necessarily present or implied).

E. Obviousness

20. I have been instructed by counsel on the law regarding obviousness, and understand that even if a patent is not anticipated, it will be unpatentable if the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the pertinent art. For the purposes of obviousness, I understand that a POSA may rely on a single prior art reference or multiple references in combination.

21. I have been informed that the following factors are considered when determining whether a patent claim would have been obvious to a POSA: (1) the scope and content of the prior art, (2) the differences between the prior art and the claims, (3) the level of ordinary skill in the pertinent art, and (4) the existence of

secondary considerations of nonobviousness. These secondary considerations, which I understand are also called “objective indicia” may include factors such as: (1) the invention’s satisfaction of a long-felt unmet need in the art; (2) unexpected results of the invention; (3) skepticism of the invention by experts; (4) commercial success of an embodiment of the invention; and (5) praise by others for the invention. I have also been informed that there must be an adequate nexus or connection between the evidence that is the basis for an asserted secondary consideration and the scope of the claimed invention.

22. I have been informed that a claimed invention can be rendered obvious when, for example, there is some teaching, suggestion, or motivation in the prior art that would have led a POSA to modify the prior art reference or to combine prior art reference disclosure to arrive at the claimed invention. In other words, even if one reference does not show the whole of the invention, if it would have been obvious to a person of ordinary skill in the art at the relevant time to add the missing pieces to the invention (for example as a matter of standard practice or application of a well-known principle in the field), then a single reference can render a claim invalid even if it does not show the whole invention. Moreover, a combination of two or more prior art references can render a claim invalid as obvious whether or not there is an explicit suggestion in one of the references to combine the two references, if as

a matter of skill or practice in the field it would routine to do so. Further, I understand that obviousness does not require absolute predictability. Only a reasonable expectation that the beneficial result will be achieved by the modifications or combination is necessary to show obviousness.

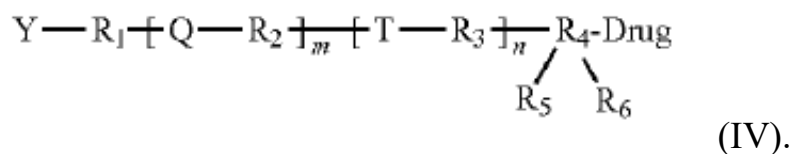
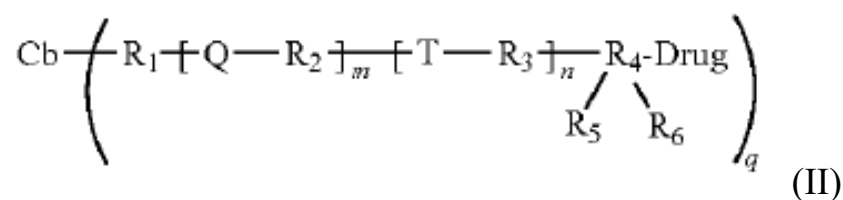
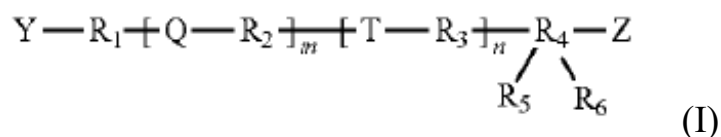
V. QUALIFICATIONS AND KNOWLEDGE OF A PERSON OF ORDINARY SKILL IN THE ART

23. Based on my knowledge and expertise, in my opinion a POSA at the time of the alleged invention of the '682 patent would have had a PhD degree in organic chemistry, biochemistry, medicinal chemistry and/or pharmacology, along with 1-2 years of relevant applied research and/or industry experience in the field of linkers and conjugates for biologically active molecules. Alternatively, a POSA would have had a Master's or Bachelor's degree in one of these same fields with, respectively, at least 3-5 or 5-7 years work experience. Such a person would have been familiar with protein/drug conjugates, including antibody-drug conjugates, the use of antibodies to selectively target cells and tissues associated with various diseases and conditions, linker design and selective attachment of the linker to proteins/antibodies and drugs, including targeted release of the drugs, as well as the need for water soluble conjugates for use with hydrophobic drugs, and methods for enhancing the potency of the protein/antibody-drug conjugates.

VI. THE '682 PATENT

A. Overview of the '682 Patent

24. The '682 patent relates to numerous hydrophilic linkers containing phosphinate, sulfonyl, and/or sulfoxide groups, and cell-binding agent-drug conjugates including such linkers. EX1001, 2:53-55. The challenged claims are directed to a bifunctional hydrophilic linker of formula (I) (claims 1-2), a cell-binding agent-drug conjugate of formula (II) (claims 3-17, 24-26, and 33), and a drug conjugated monofunctional linker compound of formula (IV) (claims 20-21, 29-32, and 34), reproduced below:



A complete listing of the challenged claims is attached as an appendix to this declaration.

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 the values of m and n, one or both of Q and T are present in the claimed linkers. In claims 1, 3, 20, 22, and 29, m and n are integers from 0 to 5, but not 0 at the same time, and provided that (i) when m=1 and n=0, Q is not -P(=O)(OM)-, and (ii) when m=0 and n=1, T is not -P(=O)(OM)-. Certain claims further require that m and n are not 0 when Q or T are -S(O₂)- (claims 1, 22) or -S(O)- (claims 3). Claims 24, 26, and 30 define m and n as integers from 1 to 5.

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.

27. The “Drug” variable is present in both formulas (II) and (IV), defined as 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.

28. The Z variable of formula (I) represents a functional group that enables linkage 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.

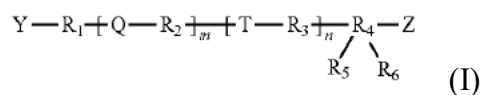
29. The “Cb” variable of formula (II) represents a cell-binding agent.

30. Each independent claim provides two broad, overlapping definitions of R₁, R₂, R₃ and R₄ for one of formulas (I), (II) and (IV). In the first definition, R₁-R₄ are the same or different and are absent or selected from specific short hydrocarbon or other chains (i.e., ester, ether or amide) or a polyoxyethylene unit of formula (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combinations of any of the foregoing. *See, e.g.*, EX1002, 1:46-2:4, 2:37-62, 4:25-50. Alternatively, in the second definition, R₁, R₂, R₃ and R₄ are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or branched chain. The second definition also specifies connections among the groups and the rest of the linker. *Id.*

31. R_5 and R_6 are defined identically in formulas (I), (II) and (IV) as being the same or different, and are absent, H, or selected from many of the same groups appearing in the first definition of R_1 - R_4 . *Id.*

32. Independent claim 1, from which claim 2 depends, recites:

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(O₂)-, or -S(O)-;

m and n are integers from 0 to 5, but not 0 at the same time; provided that

when m=1, n=0, Q is not -P(=O)(OM)-; when n=1, m=0, T is not -

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

Z represents a functional group that *enables* linkage of the hydrophilic linker to a cytotoxic drug via a disulfide, thioether, thioester, hydrazone, ether, ester, carbamate, carbonate, secondary, tertiary, or quaternary

amine, imine, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

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

or

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

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

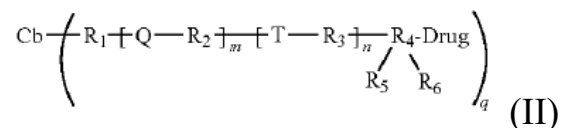
R₅ and R₆ are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

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

33. Claim 2 of the '682 patent depends from claim 1 and specifies that Z comprises a thiol, disulfide, amino, carboxy, aldehydes, maleimido, haloacetyl, hydrazine or hydroxyl group.

34. Independent claim 3, from which claims 4-17 and 33 depend, recites:

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;

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

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

R₁, R₂, R₃, and R₄ are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of

formula $(\text{OCH}_2\text{CH}_2)_p$, 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 $-\text{S}(\text{O})-$, 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

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

R_5 and R_6 are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or $N^+R_1R_2R_3$ or a pharmaceutical salt, provided that:

when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, at least one of

R_1 , R_2 , R_3 and R_4 comprises the polyethyleneoxy unit of formula

$(OCH_2CH_2)_p$, and

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.

35. The dependent claims of independent claim 3 further specify: the identity of the Drug (claims 4-5, 8, 10), the identity of the cell-binding agent (claims 6-7), the identity of additional linker components (claims 9, 12), that the conjugate has in vitro, in vivo or ex vivo cell killing activity (claim 11), that the conjugate is cleavable by a protease (claim 13), that the Drug is derived from a drug containing

a —SH, —CONHNH₂, —≡, —COR" or —NHR", wherein R" is H, CH₃, Et, Pr, Bu, or Ph; and/or the cell-binding agent is an antibody or protein (claim 14), the identity of R₁, R₂, R₃ and R₄ (claim 33), pharmaceutical compositions comprising the conjugate of claim 3 and a pharmaceutically acceptable salt, carrier, diluent, or excipient therefor (claims 15-16), and pharmaceutical compositions comprising the conjugate of claim 3 and a chemotherapeutic agent, radiation therapy agent, immunotherapy agent, autoimmune disorder agent, or anti-infectious agent (claim 17).

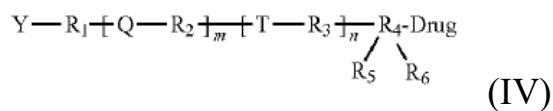
36. Independent claim 24 recites a narrower scope of the cell-binding agent-drug conjugate recited in claim 3 by specifying that m and n are integers from 1 to 5, and dependent claim 25 further limits the identity of R₁, R₂, R₃ and R₄.

37. Independent claim 26 recites narrower embodiments of the cell-binding agent-drug conjugate recited in claim 3 by specifying that m and n are integers from 1 to 5 and further limiting the identity of R₂.

38. Independent claim 20, from which claims 21 and 34 depend on, recites:

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 -P(=O)(OM)-, or -S(O₂)-, or -S(O)-;

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

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

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

combination thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof,

or

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

R₅ and R₆ are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6

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

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

when Q and T are each independently $-\text{S}(\text{O}_2)-$ or $-\text{S}(\text{O})-$, at least one of R_1 , R_2 , R_3 and R_4 comprises the polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, and

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.

39. The dependent claims of independent claim 20 further specify: that the Drug is derived from a drug containing a $-\text{SH}$, $-\text{CONH}\text{NH}_2$, $-\equiv$, $-\text{COR}''$ or $-\text{NHR}''$, wherein R'' is H, CH_3 , Et, Pr, Bu, or Ph; and/or the cell-binding agent is an antibody or protein (claim 21), and further limits the identity of R_1 , R_2 , R_3 and R_4 (claim 34).

40. Independent claim 29 recites narrower embodiments of the compound recited in claim 20 by limiting the identity of R_2 when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, m and n is 1.

41. Independent claim 30 recites narrower embodiments of the compound recited in claim 20 by specifying that m and n are integers from 1 to 5 and limiting the identity of R_2 when Q and T are each independently $-S(O_2)-$ or $-S(O)-$ and dependent claims 31-32, further limit the identity of R_1 , R_2 , R_3 and R_4 .

42. Although thirty Examples are provided in the '682 specification (EX1001, 36:55-47:14), the specification discloses conjugation synthesis and in vitro cytotoxicity evaluation for only a single linker containing 2 sulfonyl groups: 2,5-dioxopyrrolidin-1-yl3-((2-((3-(pyridin-2-yl)disulfanyl)butyl)sulfonyl)-ethyl)sulfonyl)propanoate (a.k.a. compound 86) (Examples 29-30 and FIG. 21).

43. Moreover, none of the Examples demonstrate that the claimed compositions exhibit any surprising or unexpected effects whatsoever. Rather, the '682 patent merely asserts that "Advantageously, because the . . . sulfonyl groups on the hydrophilic linkers are soluble in water or require only a small percentage of organic solvent to maintain solubility in aqueous solution, the reaction between the cell-binding agent and the cross-linker can be conducted in aqueous solution." As

discussed in detail below, the use of linkers containing sulfone groups and PEG to impart water solubility to conjugates was already known in the art for at least 22 years before the priority date of the '682 patent.

VII. STATE OF THE ART & SCOPE AND CONTENT OF THE PRIOR ART REFERENCES

A. Technical Background Introduction

44. For over six decades, antibody-drug conjugates (ADCs) have been developed and used as means for selectively targeting cells or tissues expressing target tumor-associated antigens to deliver various cytotoxic anti-cancer agents. EX1009, 1:20-45; EX1053, abstract; EX1054, 1-2; EX1051, 301, EX1052, 584. Because ADCs “function as ‘smart bombs’ that allow the toxin to bypass healthy tissue and hit only the targets of interest,” they produce fewer side-effects than administration of the free cytotoxic agents. EX1014¹, 2007; *see also, e.g.*, EX1009, 4:63-68.

¹ This article can be readily retrieved by virtue of the search tool hosted by the journal site ACS publications. Multiple search queries, for example title and keyword searches, all successfully retrieved the Thomas reference. I performed these searches on January 25, 2023.

45. However, clinical use of ADCs initially faced several practical limitations that were later overcome, including diminished potency, “especially when antigen expression on the target cancer cell is low, or when the target cancer cells are resistant to treatment.” EX1008, ¶[0006]. Additionally, “[a]ttempts to attain higher drug/antibody ratios (DAR) often failed, particularly if both the cytotoxic agent and the linker were hydrophobic, ADC aggregation, loss of affinity for the target antigen, and rapid clearance from circulation.” EX1016, 3607 (citations omitted). At the same time, it was recognized that “[t]he link between the antibody and the cell-killing agent plays a critical role in the development of ADCs, as the nature of the linker significantly affects the potency, selectivity and pharmacokinetics of the resulting conjugate.” EX1016, 3606. Water solubility in particular, was recognized as very useful for overcoming many of the above-identified concerns initially encountered with ADC linkers. EX1008, Abstract, ¶¶[0002], [0009], [0011], [0078]; EX1016, 3607. As such, well prior to 2012, suitable hydrophilic linkers were developed to create drug conjugates that overcame the foregoing challenges, producing ADCs with better potency and target affinity combined with reduced aggregation and systemic clearance, as evidenced by the prior art discussed below

B. Harris (EX1007)

46. Harris, entitled “Water soluble active sulfones of poly(ethylene glycol),” is International Publication No. WO 1995/013312, published May 18, 1995. I have been informed that Harris is prior art to the ’682 patent under at least 35 U.S.C. §102(a)(1) because it was publicly available more than one year prior to the earliest priority date for the ’682 patent, November 24, 2012.

47. Harris discloses “water soluble and hydrolytically stable derivatives of poly(ethylene glycol) (‘PEG’) polymers and related hydrophilic polymers having one or more active sulfone moieties.” EX1007, 6:8-11; *id.*, 16:14-17 and 24-25, claims 29-30. The sulfone-containing PEG derivatives of Harris are useful for generating conjugates that link two different biologically active moieties such as proteins, pharmaceuticals, and vitamins, wherein at least one of the biologically active moieties has a reactive thiol moiety. EX1007, claims 33-34, 16:34-17:5, Abstract.

48. Harris’ PEG/sulfone “derivatives are considered infinitely soluble in water or as approaching infinite solubility and can enable otherwise insoluble molecules to pass into solution when conjugated with the derivatives.” EX1007, 19:34-37. Harris further discloses that the “sulfone moiety, the linkage between the [PEG] polymer and the sulfone moiety, and the linkage between the thiol moiety and

the sulfone moiety . . . are stable against hydrolysis for extended periods in aqueous environments at pHs of about 11 or less.” *Id.*, 6:15-21; 14:1-5. A POSA would have understood that the PEG/sulfone derivatives disclosed in Harris are thus hydrophilic and stable in water.

49. Harris discloses a PEG derivative that has the basic structure: R-(OCH₂CH₂)_n-Y, wherein Y of Harris represents -SO₂-CH=CH₂ (i.e., vinyl sulfone) or -SO₂-CH₂-CH₂-X where X is a halogen (i.e., a haloethyl sulfone); n can be about 5 to 3,000 (including 5 to 2,200, 34 to 1,100, and 45 to 110); R in Harris’ basic structure represents a group that is the same or different from Y and thus can be CH₂=CH-SO₂-, or Cl-CH₂-CH₂-SO₂-.” EX1007, 19:10-30. Harris therefore discloses PEG derivatives with one or two sulfonyl groups, including PEG bis-vinyl sulfone. *Id.*, 18:34-19:2.

50. Harris also describes heterobifunctional PEG derivatives having a sulfone moiety on one terminus and a different functional moiety on the opposite terminus that can be used “to carry a protein or other biologically active molecule by sulfone linkages on one end and by another linkage on the other end, such as an amine linkage, to produce a molecule having two different activities.” EX1007, 17:24-34. Harris discloses that other active groups for heterobifunctional sulfone-activated PEGs can be selected from among a wide variety of compounds including

among others, *N*-hydroxysuccinimide ester, acyl azide, and succinate. EX1007, 18:5-30, claim 35. The latter are known activating groups that form amide bonds with amines. Similarly, Harris also cites a U.S. patent to Zalipsky (EX1047) as disclosing use of, *e.g.*, PEG-*N*-succinimide carbonate for formation of a urethane linkage from, *e.g.*, a lysine epsilon –NH₂ group. EX1007, 3:28-35. Harris acknowledges that Zalipsky's method, which uses excess PEG derivative "is adequate for attachment of the lysine fraction of a protein to a PEG derivative at one active site on the PEG derivative." EX1007, 4:2-12. Harris thus, expressly recommends use of vinyl sulfones and other active sulfones in combination with non-sulfone activating groups known in the art on either end of its PEG-based linkers.

51. A POSA would therefore have understood that Harris' PEG derivatives may comprise an active sulfone moiety (*e.g.*, vinyl sulfone or haloethyl sulfone) at one or both termini of the PEG linker and that are useful for linking two different moieties, including, *e.g.*, proteins and drugs.

52. Harris further discloses that "polymer derivatives with active sulfone moieties are highly selective for coupling with thiol moieties instead of amino moieties on molecules," and 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

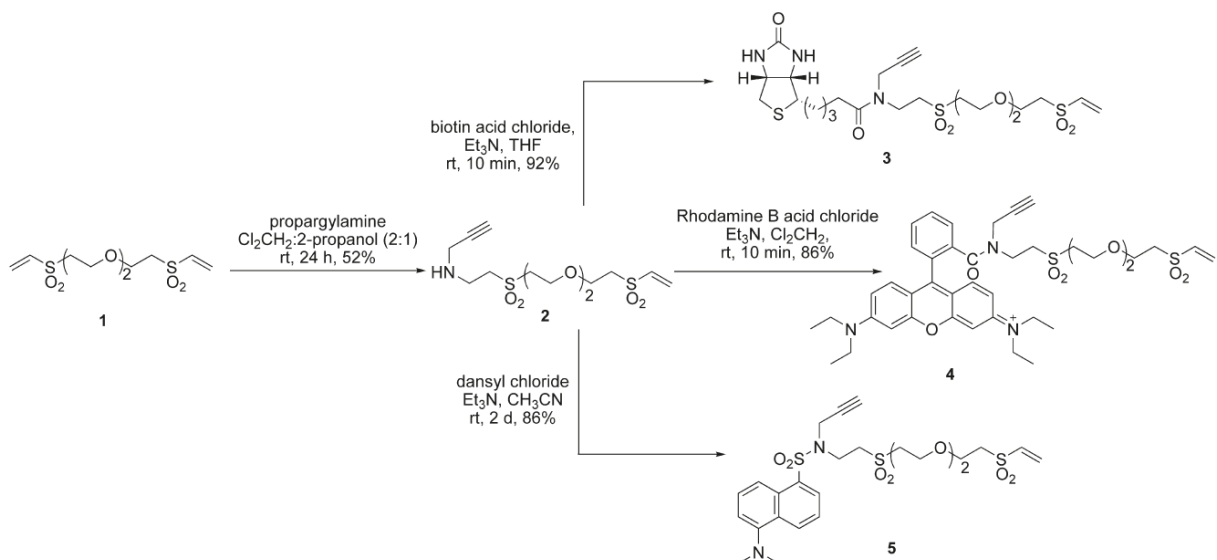
to the protein.” EX1007, 6:12-15 and 26:11-15. A POSA would have understood that Harris’ PEG/sulfone derivatives may be selectively attached to one or more cysteine residues on proteins.

C. Morales-Sanfrutos (EX1005)

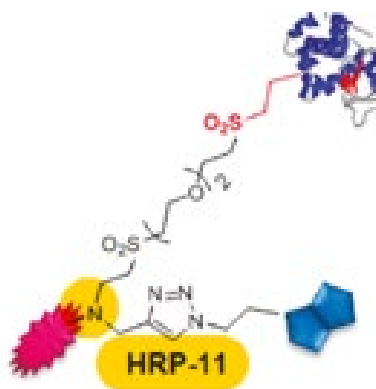
53. Morales-Sanfrutos is entitled “Vinyl Sulfone Bifunctional Tag Reagents for Single-Point Modification of Proteins.” I understand that Morales-Sanfrutos was first published in the journal *J. Org. Chem.* 75: 4039–4047, in May 2010. I have been informed that Morales-Sanfrutos is prior art to the ’682 patent under at least 35 U.S.C. §102(a)(1) because it was publicly available more than one year prior to the earliest priority date for the ’682 patent, November 24, 2012.

54. Morales-Sanfrutos describes several examples of alkyne vinyl sulfone derivatized tags (AVST) as shown in Scheme 1, reproduced below. EX1005, 4041

SCHEME 1. Synthesis of Alkyne Vinyl Sulfone Derivatized Tags (AVST) 3–5



55. These bifunctional PEG linker compounds were linked to both the horse radish peroxidase (HRP) enzyme and biotin, among other moieties. EX1005, 4041, 4044. Morales-Sanfrutos also discloses the HRP-11 conjugate having the following structure, where the jagged oval represents the fluorescent dye rhodamine B and the bicyclic structure represents biotin:



56. Morales-Sanfrutos further discloses that “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***” and that “Michael-type addition between vinyl sulfone and thiols is accepted as a click reaction.” *Id.*, 4040, 4044. Morales-Sanfrutos expressly states that “the AVST compounds clearly establish that the vinyl sulfone chemistry is a valuable methodology for the introduction of clickable groups with similar characteristics to other traditional bioconjugation strategies (*i.e.*, activated esters-lysine or maleimide-Cys) used for this same purpose with **the major advantage of the vinyl sulfone stability in water over the activation chemistries used on those strategies.**” EX1005, 4043-44 (emphasis added).

57. Consequently, a POSA would have understood that the vinyl sulfone PEG linker compounds of Morales-Sanfrutos are water soluble, and may be conjugated to amine or thiol groups present in proteins.

D. Straus (EX1006)

58. Straus is entitled “Unusual Binding Sites for Horseradish Peroxidase on the Surface of Cultured and Isolated Mammalian Cells.” I understand that Straus was first published in the journal, *Histochemistry*, 85: 277-285 in July 1986. I have been informed that Straus is prior art to the '682 patent under at least 35 U.S.C.

§102(a)(1) because it was publicly available more than one year prior to the earliest priority date for the '682 patent, November 24, 2012.

59. Straus discloses that the horseradish peroxidase (HRP) enzyme may bind to the surface of a variety of cells, including macrophages, fibroblasts, mast cells and endothelial cells. EX1006, 277. Accordingly, a POSA would have understood that horseradish peroxidase is a cell-binding agent based on the disclosure of Straus.

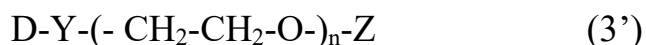
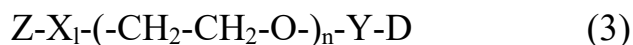
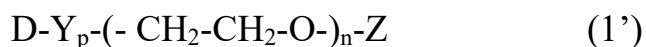
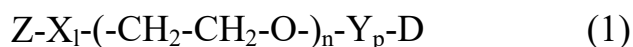
E. Singh (EX1008)

60. Singh, entitled “Potent conjugates and hydrophilic linkers,” is US Patent Application Publication No. 2010/0129314, published May 27, 2010. I have been informed that Singh is prior art to the '682 patent under at least 35 U.S.C. §102(a)(1) because it was publicly available more than one year prior to the earliest priority date for the '682 patent, November 24, 2012.

61. Singh discloses linkers that are useful for generating cell-binding agent-drug conjugates that “are active across a broad spectrum of tumors, particularly in low antigen expressing or drug resistant tumors.” EX1008, ¶[0008]. Singh demonstrates that “when traditional linkers . . . are modified to hydrophilic linkers by incorporating a polyethylene glycol [PEG_n (-CH₂CH₂O)_n] spacer, the potency or

the efficacy of the cell-binding agent-drug conjugates is surprisingly enhanced several fold in a variety of cancer cell types.” EX1008, ¶[0009].

62. Singh expressly discloses PEG cross-linkers as compounds of formulas (1), (1'), (3), and (3'):



63. In each formula, a drug (D) is attached at one end of a PEG chain and a reactive functionality (Z) is attached at the other end. EX1008, ¶¶[0014], [0016], [0080], [0090]. Z “can form an amide or *a thioether bond* with a cell-binding agent.” *Id.* Singh describes exemplary reactive functionalities including “amine-reactive functionality, where the functionality could be a reactive carboxylic ester” such as an N-succinimidyl ester “to give an amide bond,” and “thiol-reactive functionality...that could be a maleimide, haloacetamide, or a *vinyl sulfone* to form a thioether bond.” EX1008, ¶[0134] (emphasis added), see also ¶[0136], FIGS. 4, 13. Singh also discloses PEG cross-linkers where a cell-binding agent such as an antibody (*e.g.*, mAb) is attached at one end of a PEG chain and a reactive

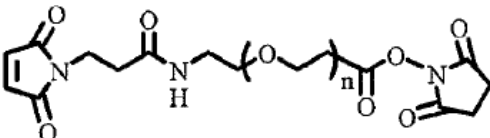
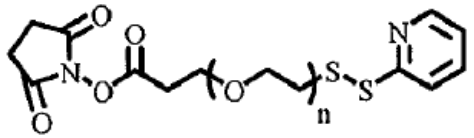
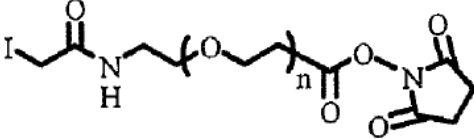
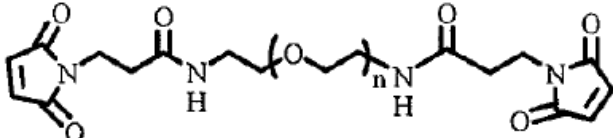
functionality is attached at the other end (*i.e.*, compounds of formulas (2) $\text{CB}—[\text{X}_l—(\text{—CH}_2\text{—CH}_2\text{—O—})_n\text{—Y}_p\text{—D}]_m$, and (2') $\text{D—Y}_p\text{—}(\text{—CH}_2\text{—CH}_2\text{—O—})_n\text{—CB}$. EX1008, ¶¶ [0137]-[0138], [0219], [0221], and FIGS. 8, 10, 12, 15, 18, 21. The main difference between each pair of linkers is the direction of the PEG within the linker. For example, the PEG oxygen is adjacent to Y in formulas (1), (2) and (3), and is adjacent to Z in formulas (1'), and (3').

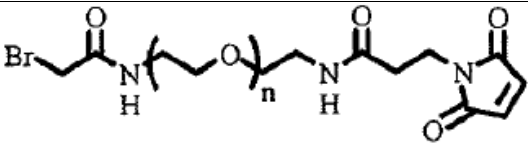
64. In Singh's formulas (1), (1'), (3), and (3'), l may be 0 or 1. EX1008, ¶¶ [0014], [0016]. When present (l=1), X represents an aliphatic, an aromatic or a heterocyclic unit attached to the cell-binding agent via a thioether bond, an amide bond, a carbamate bond, or an ether bond. *Id.* In formulas (1) and (1'), p may be 0 or 1. EX1008, ¶ [0014]. When present (p=1), Y represents an aliphatic, an aromatic or a heterocyclic unit 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. *Id.* In formulas (3) and (3'), Y is always present, and represents an aliphatic, an aromatic or a heterocyclic unit attached to the drug via a disulfide bond. *Id.*, ¶ [0016]. Variable n, which pertains to the number of ethyleneoxy subunits present in the PEG group, is an integer from 1 to 2000 in formulas (1) and (1'), but is 1-14 in formulas (3) and (3'). EX1008, ¶¶ [0014], [0080]. Preferred values of n in formulas (1) and (1') are

1-100, 1-14, and most preferred is 1-4. EX1008, ¶[0082]. Numerous examples of these PEG cross-linkers are given in FIGS. 4, 5, 6A, 7, 9, 11, 13, 14, 16A, 17, 19A, 20, and Examples II and III of Singh.

65. Singh's PEG cross-linkers may be prepared by coupling a "bifunctional PEG-containing cross linker" to a drug or an antibody. EX1008, ¶¶[0136]-[00138], [0217]-[0219], [0221]-[0222]. Examples of the disclosed bifunctional PEG cross-linkers in EX1008 are shown in Table A1, along with a reference to the figures in which they appear.

Table A1

Entry	Bifunctional PEG Cross-linkers	FIGS.
1		4, 8
2		6B, 12
3		10
4		13, 15

5		16B, 18
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66. These bifunctional crosslinkers include a PEG having n subunits just as in the PEG crosslinker formulas, where n is defined throughout Singh to be an integer of 1-2000, 1-100, 1-14 or 2-8, and most preferably, 1-4. EX1008, ¶¶[0014]-[0017], [0080], [0082], [0084], [0087], [0090]-[0093], [0095].

67. After coupling the bifunctional PEG cross-linker to a drug at one end of the cross-linker (to give compounds of formulas (1), (1'), (3), (3')), *e.g.*, through a maleimide, iodo- or bromoacetamide, the remaining reactive functionality may be used to couple the antibody to the linker to form an ADC of formulas (2), (2'), (4) or (4'). The ADCs were prepared, *e.g.*, by modifying the antibody with the PEG crosslinker at a lysine side chain amino group via an amide bond (see, *e.g.*, FIGS. 7, 9, 11) or to a cysteine thiol via a thioether bond (see, *e.g.*, FIGS. 14, 17, 20). EX1008, ¶¶[0137], [0209], [0214], [0220], [0221].

68. Alternatively, after coupling the bifunctional PEG cross-linker to an antibody at one end of the cross-linker, *e.g.*, through a maleimide, iodo- or bromoacetamide, or NHS ester, the remaining reactive functionality may again be used to couple the drug to the linker to form an ADC. EX1008, ¶¶[0136]-[0137],

FIGS. 8, 10, 12, 15, 18, 21. The drugs may be part of the crosslinker or subsequently added. EX1008, ¶¶[0007], [0014], [0080].

69. Compared to ADCs with traditional hydrophobic linkers, the potency/efficacy of Singh's hydrophilic PEG ADCs was "enhanced several fold in a variety of cancer cell types, including those expressing a low number of antigens on the cell surface" and "toward cell lines that are resistant to treatment." EX1008, ¶[0009]. Singh further discloses that incorporation of its hydrophilic PEG linkers "allowed the conjugation of up to 15 molecules of a drug per antibody molecule with high yield and no aggregation or precipitation" and these conjugates "bound with high affinity to target antigen (similar to that of unmodified antibody)." EX1008, ¶[0011].

70. A POSA would have understood that the PEG-containing ADCs of Singh are correlated with the enhanced cytotoxicity/potency in target cancer cells and reduced aggregation.

F. Bhakta (EX1011)

71. Bhakta, entitled "Cysteine engineered antibodies and conjugates" is U.S. Patent Publication No. 2011/0301334, published December 8, 2011. I have been informed that Bhakta is prior art to the '682 patent under at least 35 U.S.C.

§102(a)(2) because Bhakta names another inventor and was effectively filed June 8, 2010.

72. Bhakta expressly discloses an antibody-drug conjugate (ADC) including “a cysteine engineered antibody (Ab), and a drug moiety (D) wherein the antibody has one or more free cysteine amino acids, and the antibody is attached through the one or more free cysteine amino acids by a linker moiety (L) to D; the composition having Formula I: $Ab-(L-D)_p$, where p is 1, 2, 3, or 4.” EX1011, ¶¶[0211]-[0212].

73. Bhakta also discloses the advantages of including cleavable peptide linker components within ADCs to permit protease-mediated release of active drugs. Specifically, Bhakta notes the “linker may comprise amino acid residues which links the antibody (Ab) to the drug moiety (D) of the cysteine engineered antibody-drug conjugate (ADC) of the invention,” and that the “*amino acid residues may form a dipeptide*” as well as longer peptides. Both natural amino acids and “*and non-naturally occurring amino acid analogs, such as citrulline*” may be used. EX1011, ¶[0244]. In fact, Bhakta expressly discloses

[u]seful amino acid residue units can be designed and optimized in their selectivity for enzymatic cleavage by a particular enzymes, for example, a tumor-associated protease to liberate an active drug moiety. In one

EX1011, ¶[0245] (emphasis added)

CC(C)[C@@H](NC(=O)NCCCNC(=O)Nc1ccc(cc1)COC(=O)D)C(=O)NCCCCCNC2C(=O)CC(S*)C2=O

MC-val-cit-PAB

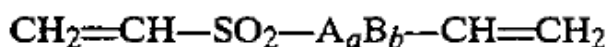
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comprising the dipeptides disclosed in Bhakta (*e.g.*, valine-citrulline) are cleavable by proteases.

G. Snow (EX1010)

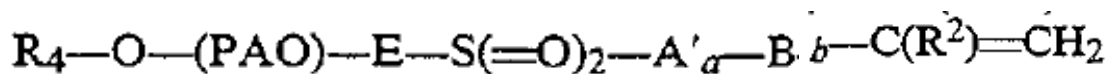
76. Snow, entitled “Vinyl sulfone coupling of polyoxyalkylenes to proteins,” is US Patent No. 5,414,135, first published May 9, 1995. I have been informed that Snow is prior art to the '682 patent under at least 35 U.S.C. §102(a)(1) because it was publicly available more than one year prior to the earliest priority date for the '682 patent, November 24, 2012.

77. Snow discloses the bis(vinyl sulfone) reagent



where A is an alkylene radical of 1-8 carbon atoms, a is 1; B is a sulfoxide or a sulfone group; and b is 1. EX1010, 7:14-27.

78. Snow further discloses a class of polyalkylene oxide vinyl sulfone reagents that are useful for generating protein conjugates, are hydrolytically stable, and react with proteins in aqueous media. *Id.*, abstract, 4:36-42. Snow expressly discloses polyalkylene oxide bis(vinyl sulfone) reagents represented by the formula:



where R_4 is H, PAO is a polyalkylene oxide having an average molecular weight in the range of 250-200,000 daltons, E is alkylene group of 1-8 carbons or an alkylenyl group of 2-8 carbons, A is an alkylene radical of 1-8 carbon atoms which may be saturated, a is 1, B is a sulfoxide group, b is 1, and R^2 is H. *Id.*, claim 1, 7:51-65, 5:61-63. Snow discloses that its polyalkylene oxide-vinyl sulfone reagents can react with accessible sulfhydryl groups on proteins at a faster rate than the rate of addition to amino groups. *Id.*, 9:58-63.

79. A POSA would have understood that Snow's PEG/sulfone derivatives may be selectively attached to sulfhydryl groups instead of amine groups on proteins.

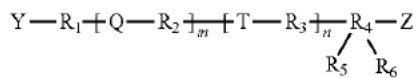
VIII. OPINIONS RELATING TO VALIDITY OF THE CLAIMS

A. The Challenged Claims 1-3, 6, 24-25, and 33 Are Unpatentable Over Morales-Sanfrutos, as evidenced by Straus

1. Claims 1-2 are Unpatentable Over Morales-Sanfrutos

80. Although I have been informed that the preamble does not necessarily limit the scope of a claim, I have not considered and take no position on whether the preamble of claim 1 is limiting.

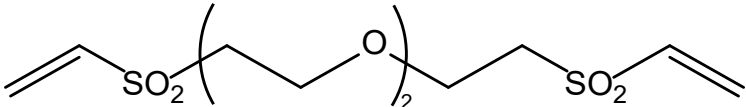
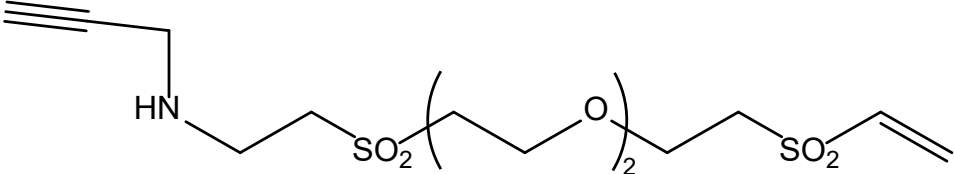
81. Claim 1 is directed to the hydrophilic linker of formula (I):

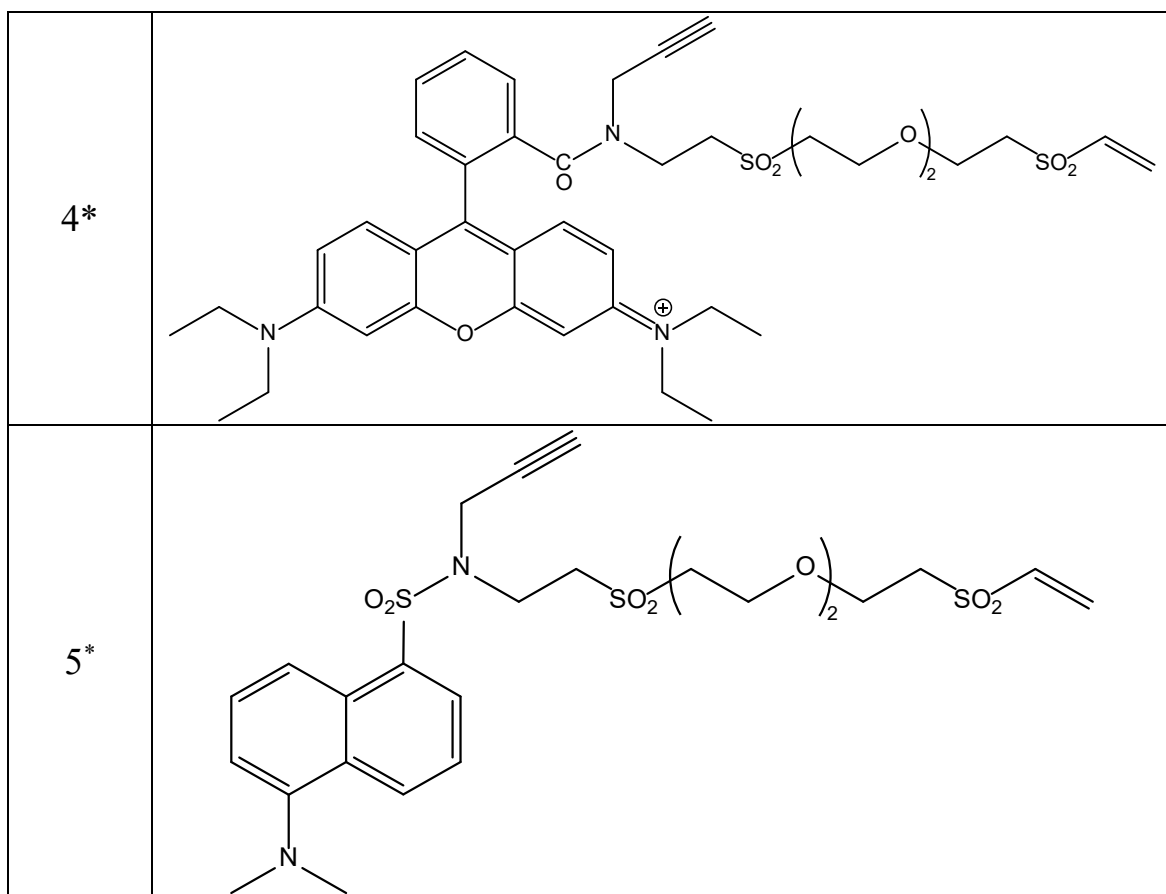


, wherein each variable is defined from among a vast array of possible choices. Formula (I) defines an organic compound with sulfones, sulfoxides and other functional groups, whereas “hydrophilic linker” refers to, respectively, a property of the compound (hydrophilic) and the intended use for the compound (linking). Additionally, the term “hydrophilic linker” places no further restriction on the inherent hydrophilicity of the compounds represented by formula (I) such as specific water solubility levels.

82. Morales-Sanfrutos describes every element of claim 1 because it discloses at least four bifunctional vinyl sulfone PEG derivatives. EX1005, 4041 (Scheme I), 4044 (Scheme 4). These compounds are shown in Table B1.

Table B1

Cmpd	Bifunctional PEG Cross-linkers
1	
2	



*The rhodamine group in compound 4 and the dansyl group in compound 5 will be abbreviated, respectively, “Rhod.” and “Dns.” to simplify structural representations where they appear.

83. Each of the four bifunctional vinyl sulfone PEG compounds tracks with the variables defining the compound of formula (I) in claim 1. Formula (I) of the '682 patent is so broad that the compounds of Morales-Sanfrutos satisfy its variables in more than one way, only a few of which are shown in Table B2 in the columns labeled 2(a), 2(b), 2(c) and so forth.

Table B2

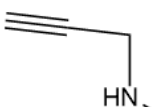
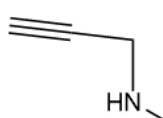
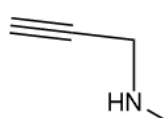
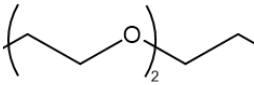
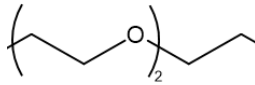
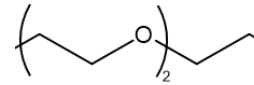
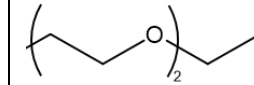
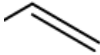
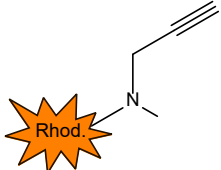
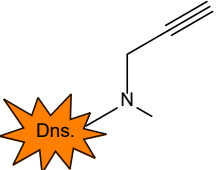
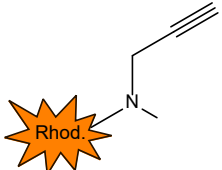
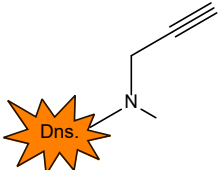
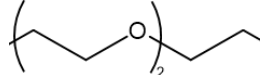
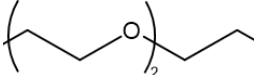
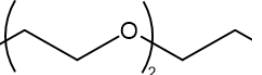
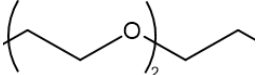
	Morales-Sanfrutos' Compounds 1-2 (Table B1)			
'682 (I)	Compound 1	Compound 2		
		(a)	(b)	(c)
Y				
Z				
R₁	absent	absent	absent	
m	1	1	1	1
Q	-SO ₂ -	-SO ₂ -	-SO ₂ -	-SO ₂ -
R₂				
p	2	2	2	2
n	1	1	1	1
T	-SO ₂ -	-SO ₂ -	-SO ₂ -	-SO ₂ -
R₃	absent		CH ₂	absent
R₄	absent	absent	CH ₂	absent

Table B2 (continued)

'682 (I)	Compound 4		Compound 5	
	(a)	(b)	(a)	(b)
Y				
Z				
R₁	absent		absent	
m	1	1	1	1
Q	-SO ₂ -	-SO ₂ -	-SO ₂ -	-SO ₂ -
R₂				
p	2	2	2	2
n	1	1	1	1
T	-SO ₂ -	-SO ₂ -	-SO ₂ -	-SO ₂ -
R₃		absent	absent	absent
R₄	absent	absent		absent

84. For example, comparing Claim 1's formula (I) and one embodiment of Morales-Sanfrutos' compound 2 shown in column 2(a) of Table B2 above, Y may

be vinyl ($-\text{CH}=\text{CH}_2$), R_1 is absent, $m=1$, Q is sulfonyl ($-\text{S}(\text{O}_2)-$), R_2 is ethylene in combination with two PEG units $(\text{OCH}_2\text{CH}_2)_2$ (referred to hereinafter as “the ethylene-bis-ethyleneoxy group”), where $p=2$. Further, $n=1$, T is sulfonyl ($-\text{S}(\text{O}_2)-$), R_3 is ethylene, $-\text{R}_4(\text{R}_5)(\text{R}_6)-$ is absent, and Z may be the alkynyl group indicated in Table B2. The ethylene-bis-ethyleneoxy group in compound 2 falls within the part of R_2 ’s definition that allows for a combination of a linear C_{1-6} alkyl and a PEG having 1-1000 ethylene oxy subunits. The remaining ethylene groups fall within the definitions of R_3 or R_4 , or as shown in column 2(b), one methylene group is assigned to each of R_3 and R_4 , since both variables may be C_{1-6} alkyl. Alternatively, as shown in column 2(c), Morales-Sanfrutos’ compound 2 maps to claim 1 starting from the other end of the linker, wherein Y is the alkynyl group, Z is the vinyl group, R_1 is ethylene and R_3 and R_4 are absent; the remaining variables (m , Q , R_2 , p , T and n) are the same as before. Table B2 shows that Morales-Sanfrutos’ disclosed compounds 1, 4, and 5 likewise fall within claim 1’s broad scope—sometimes in multiple different ways (e.g., columns 4(a)-(b) and 5(a)-(b))—with each being equally anticipatory. .

85. Thus, a POSA would have understood that because compounds 1-2 and 4-5 of Morales-Sanfrutos satisfies all elements recited in claim 1 of the ’682 patent, Morales-Sanfrutos anticipates claim 1 of the ’682 patent.

86. Claim 1 of the '682 patent ***does not require*** actual conjugation of the compound of formula (I) to a cell-binding agent. Rather it merely requires that Y is a functional group that ***enables*** reaction of the compound of formula (I) with a cell-binding agent. Vinyl groups located adjacent to a sulfone moiety are known in the art as functional groups that can react with functional groups present in cell-binding agents (*e.g.*, at thiol groups). *See e.g.*, EX1005, 4043-4044. Indeed, the '682 patent discloses exemplary compounds of formula (I) that contain a vinyl functional group located adjacent to a sulfone moiety which is capable of reacting with a thiol (–SH) functional group. *See* EX1001, FIGs. 7-10 (showing compound 75, compound 99, compound 119 and compound 138, respectively).

87. Likewise, claim 1 of the '682 patent ***does not require*** conjugation of the compound of formula (I) to a cytotoxic drug. Rather claim 1 simply requires that Z is a functional group that ***enables*** reaction of the compound of formula (I) with 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. Claim 1 places no other limits on the size or nature of the Z group, and the '682 specification does not define the Z group further. The alkynyl functionality is known in the art as a group that can react with an N₃ group (*e.g.*, on a cytotoxic drug) to form a heteroaromatic

bond and Morales-Sanfrutos discloses an alkynyl used to link biotin (an example of a drug) to a sulfone-containing linker. EX1005, 4041 (Scheme 1), 4043-4044 (Scheme 4). Notably, the '682 patent discloses a compound of formula (I) that contains an N₃ functional moiety that is capable of reacting with an alkynyl group on a drug, to form the exact same heteroaromatic bond disclosed years before in Morales-Sanfrutos . EX1001, FIG. 13 (compound 166). Claim 2 further specifies that Z comprise a thiol, disulfide, **amino**, carboxy, aldehydes, maleimido, haloacetyl, hydrazine or hydroxyl group. As shown in Table B1, Morales-Sanfrutos' compound 2 has an amino group. Morales-Sanfrutos shows that the drug biotin may be attached to this amino group via an amide bond, meeting claim 2's definition of Z. EX1005, 18:5-15.

88. Accordingly, Morales-Sanfrutos discloses all elements of claims 1-2 of the '682 patent, it is my opinion that the claims were anticipated as of November 24, 2012.

2. Claims 3, 6, 24-25 and 33 Are Unpatentable Over Morales-Sanfrutos, as evidenced by Straus

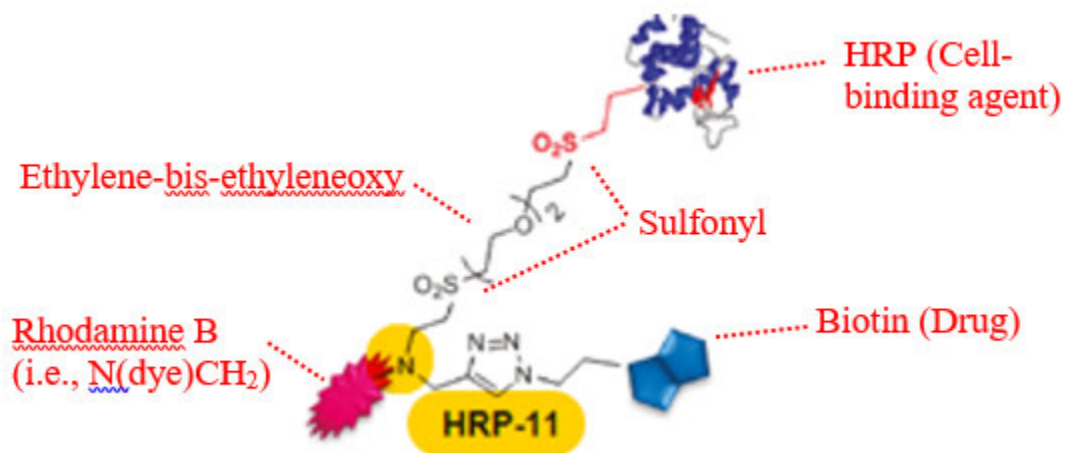
89. Independent claims 3 and 24 are directed to the cell-binding agent-

drug conjugate of formula (II):
$$\text{Cb} \left(\text{R}_1 - \text{T} - \text{Q} - \text{R}_2 - \text{T}_m - \text{T} - \text{R}_3 - \text{T}_n - \text{R}_4 - \text{Drug} \right)_q$$
, wherein each

variable is defined from among many possible choices. Formula (II) defines an organic compound with sulfones, sulfoxides and other functional groups, whereas “cell-binding agent-drug conjugate” refers both to a property of the compound (cell-binding) and an intended use (drug) for the compound.

90. HRP is a known cell-binding agent, as evidenced by Straus. EX1006, 277. The '682 patent defines a small molecule drug as “an organic, inorganic, or organometallic compound that may have a molecular weight of for example 100 to 1800” Dalton (Da) or g/mol. EX1001, 29:43-54.

91. Morales-Sanfrutos discloses the cell-binding agent-drug conjugate HRP-11 conjugate (EX1005, 4044), a species encompassed by the claimed genus of formula (II). Morales-Sanfrutos shows the HRP-11 conjugate having the following structure, where the jagged oval represents the fluorescent dye rhodamine B and the bicyclic structure represents biotin:

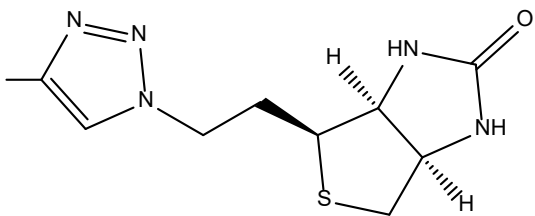
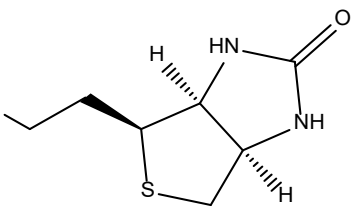
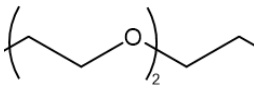
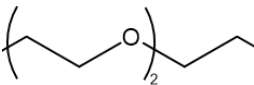
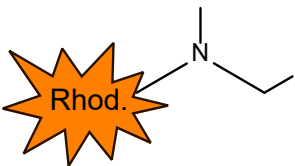
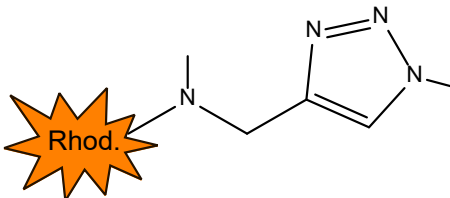


92. According to the '682 patent, biotin falls within the scope of the recited term “Drug” because biotin is an organic compound having a molecular weight of 244.3 Da.

93. As shown in Table B3 below, each part of the HRP-11 conjugate tracks with the variables defining the compound of formula (II).

Table B3

	HRP-11 Conjugate	
'682 (II)	A	B
Cb	HRP	HRP
q	1	1

Drug		
R₁		
m	1	1
Q	-SO ₂ -	-SO ₂ -
R₂		
p	2	2
n	1	1
T	-SO ₂ -	-SO ₂ -
R₃		
R₄		

94. Specifically, with respect to the HRP-11 conjugate, Cb is horseradish peroxidase (HRP), q is 1, R₁ is ethylene, Q is sulfonyl (–S(O₂)–), R₂ is ethylene in combination with two PEG units (OCH₂CH₂)₂ (*a.k.a.*, ethylene-bis-ethyleneoxy), m is 1, T is sulfonyl (–S(O₂)–), R₃ is ethylene, and n is 1. Further, R₄ is -N(dye)CH₂–, R₅ and R₆ are absent, and Drug is biotin (see, *e.g.*, EX1045,4:11-26

(disclosing that biotin may be used as a pharmaceutical to treat diseases); *see also* EX1046, 4:11-26²) linked to the cell-binding agent via a heteroaromatic bond.

Alternatively, because the scope of R₄ and Drug in formula(II) is so vast, R₄ may be -N(dye)-CH₂-(triazole)-, with R₅ and R₆ absent as before, and Drug is biotin linked to the cell-binding agent via a heteroaromatic bond that is formed via the heterocyclic triazole function of R₄. These two applications of Morales-Sanfrutos' HRP-11 conjugate to formula (II) of claims 3 and 24 are delineated in Table B3.

95. The '682 patent neither defines a "chain of two or more atoms" nor limits it to any particular type of chain (*e.g.*, it is not limited to acyclic chains). Hence, a POSA would appreciate the broad coverage of this limitation, and would understand it to encompass each of the ethylene groups (R₁ and R₃), ethylene-bis-ethyleneoxy group (R₂), and the N(dye)CH₂ group with or without the triazole in the HRP-11 conjugate, since each of R₁-R₄ may be a a chain of *two or more atoms selected from the group consisting of C, N, O, S, Si, and P* that are covalently

² EX1046 is a copy of International Publication No. WO2011124571, which claims priority to French Application No. FR 10/52589, filed 6 April 2010. The FR 10/52589 priority document and a certified translation thereof is submitted herewith (EX1045).

connected to a cell-surface binding ligand, a sulfonyl group, a drug and among themselves (R_1 , R_2 , R_3 and R_4).

96. Therefore, because Morales-Sanfrutos discloses all of the limitations of claims 3 and 24 of the '682 patent, as evidenced by Straus, it is my opinion that the claims were anticipated as of November 24, 2012.

97. Dependent claims 25 and 33 further specify that when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, at least one of R_1 , R_2 , R_3 and R_4 comprises the polyethyleneoxy unit of formula $(OCH_2CH_2)_p$; and each of remaining R_1 , R_2 , R_3 and R_4 comprises an alkyl or $(OCH_2CH_2)_p$. As discussed above, in the HRP-11 conjugate, R_1 and R_3 are ethylene (i.e., an alkyl group), Q and T are sulfonyl, R_2 is ethylene in combination with two ethyleneoxy (PEG) units $(OCH_2CH_2)_2$, m and n are 1, and R_4 is $-N(\text{dye})CH_2-$ or $-N(\text{dye})CH_2(1,4 \text{ triazole})-$, which comprises a methyl (i.e., alkyl) group. The limitations of claims 25 and 33 are thus expressly taught by Morales-Sanfrutos.

98. Dependent claim 6 further specifies that the cell-binding agent is selected from the group consisting of antibodies, proteins, vitamins, peptides, polymeric micelles, liposomes, lipoprotein-based drug carriers, nano-particle drug carriers, dendrimers, and combinations thereof. As discussed above, the HRP-11

conjugate disclosed in Morales-Sanfrutos comprises HRP, a protein known for its cell-binding properties. EX1006, 277. Morales-Sanfrutos thus anticipates claim 6.

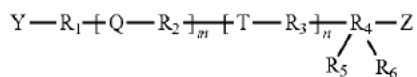
99. Therefore, because Morales-Sanfrutos discloses every element of claims 3, 6, 24-25 and 33 of the '682 patent, it is my opinion that the claims were anticipated as of November 24, 2012.

B. The Challenged Claims 1, 20-21, and 29-31 Are Unpatentable Over Harris

100. Although I have been informed that the preamble does not necessarily limit the scope of a claim, I have not considered and take no position on whether the preamble is limiting. Instead, I have been asked to assume that the preamble is limiting for my analysis.

1. Claim 1 is Unpatentable

101. Independent claim 1 is directed to the hydrophilic linker of formula (I):



, wherein each variable is defined from among a vast array of possible choices.

102. It is my opinion that Harris discloses the preamble because Harris expressly discloses a hydrophilic linker as well as formula (I) for the reasons discussed below.

103. Harris discloses “water soluble and hydrolytically stable derivatives of poly(ethylene glycol) (‘PEG’) polymers and related hydrophilic polymers having one or more active sulfone moieties.” EX1007, 6:8-11. Harris’ basic structure, R-(OCH₂CH₂)_n-Y, encompasses PEG derivatives comprising two sulfone moieties that track with the variables defining the compound of formula (I) claimed in the ’682 patent. 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 (-CH=CH₂) or halo-ethyl (-CH₂-CH₂-X), R₁ being absent, Q being sulfonyl, R₂ being (OCH₂CH₂)_n (where n is disclosed to have typical values of 5, 34, 45 and 110 (EX1007, 19:10-23)), m and n each being 1, T being sulfonyl, R₃ and -R₄(R₅)(R₆)- being absent, and Z being vinyl (-CH=CH₂) or halo-ethyl (-CH₂-CH₂-X).

104. Thus, the vinyl and halo-ethyl groups located adjacent to sulfone moieties in Harris can serve either as Y or Z of formula (I) in the ’682 patent because they are known in the art as functional groups that react with thiol moieties whether present in cell-binding agents (*e.g.*, antibodies) or in cytotoxic drugs to form thioether or thioester linkages. *See e.g.*, EX1005, 4043-4044; EX1007, 26:7-15 and 28:17-27. Accordingly, Harris discloses all elements of independent claim 1.

105. Claim 1 is also obvious over Harris, because Harris' basic structure suggests each element of formula (I) of claim 1 as described above. A POSA would have been motivated to prepare PEG bis-vinyl sulfones having, e.g., 5, 34, 45 or 110 ethyleneoxy subunits because Harris teaches that such bifunctional PEGS are water soluble, hydrolytically stable, selective for coupling with thiol moieties, and form stable thioether linkages with proteins and pharmaceuticals. EX1007, 6:8-21, 6:28-33, claim 34. Furthermore, the PEG groups may be linear or branched. EX1007, 19:10-23; 17:9-20. A POSA would have had a reasonable expectation of success in making a PEG bis-vinyl sulfone as Example 1 of Harris expressly show how to prepare terminal PEG vinyl sulfone derivatives. Harris also demonstrates their aqueous stability (Example 3) and use by coupling to thiol-containing compounds, including proteins (Examples 2, 4). Accordingly, Harris renders claim 1 obvious. Therefore, because Harris discloses all of the elements of claim 1 of the '682 patent, it is my opinion that claim 1 was anticipated or obvious as of November 24, 2012.

2. Claims 20-21 and 29-31 Are Unpatentable

106. Independent claims 20 and 29-30 are directed to a compound of formula

(IV):
$$Y-R_1-Q-R_2-\text{---}_n-T-R_3-\text{---}_n-R_4-\text{Drug}$$

$$\begin{array}{c} R_5 \\ R_6 \end{array}$$
, wherein each variable is defined from among a vast array of possible choices. Each of claims 20 and 29-30 include

overlapping definitions of the variables in Formula (IV) as noted above in Section VI.A.

107. Also described in Section VII.B, the PEG derivatives disclosed in Harris are useful for generating conjugates linking two different biologically active moieties such as proteins, pharmaceuticals, and vitamins, wherein at least one of the biologically active moieties has a reactive thiol moiety. EX1007, claims 33-34, 16:34-17:5, and abstract. Harris further discloses that “**Pharmaceuticals** from aspirin to penicillin can be usefully modified by attachment of active sulfone polymer derivatives if these **pharmaceuticals are modified to contain thiol moieties.**” EX1007, 6:28-31 (emphasis added). Hence, Harris discloses conjugates where pharmaceuticals containing thiols are attached to its PEG derivatives via reaction with a vinyl sulfone to provide a drug-PEG linker (*i.e.*, Drug-S-CH₂CH₂-SO₂-PEG-R) containing one or two sulfones.

108. Harris’ basic structure, R-(OCH₂CH₂)_n-Y, also discloses PEG derivatives comprising two sulfone moieties that track with the variables defining the compound of formula (IV) claimed in the ’682 patent. Specifically, with respect to the basic structure disclosed in Harris, for each of claims 20, 29 and 30, Y of formula (IV) described in the ’682 patent is -CH=CH₂ or -CH₂-CH₂-X where X is a halogen; R₁ is absent; m=1, Q is -SO₂-, R₂ is (OCH₂CH₂)_n (a PEG having about 5 to

about 2,200 subunits or any of 5, 34, 45, or 110 ethyleneoxy subunits); $n=1$, T is SO_2^- and R_3 is methylene; $R_4(R_5)(R_6)$ is methylene; and Drug is a pharmaceutical linked via a thioether linkage to an ethylene group resulting from reaction of the thiol-containing drug with the vinyl sulfone. Alternatively, one of R_3 and $R_4(R_5)(R_6)$ is absent and the other is ethylene. The ethylene group in the basic structure of Harris respectively meet the definitions of R_3 and $R_4(R_5)(R_6)$ in formula (IV) because each of these groups may be C_{1-6} alkylene or absent.

109. Additionally, Harris discloses heterobifunctional PEG derivatives comprising a single sulfone moiety (*supra* ¶50) that track with the variables defining the compound of formula (IV) of the '682 patent. Specifically, with respect to formula (IV), Harris' basic structure discloses a linker where Y of formula (IV) is N-hydroxysuccinimide (NHS) ester (EX1007, 18:5-15); R_1 is $(\text{OCH}_2\text{CH}_2)_n$ (PEG having about 5 to 2,200 subunits or about 5, 34, 45 or 110 ethyleneoxy subunits); Q and R_2 are absent and m is 0; T is SO_2^- , R_3 is methylene, and n is 1; $R_4(R_5)(R_6)$ is methylene; and Drug is a pharmaceutical linked via a thioester or thioether linkage. The PEG and methylene groups in the basic structure of Harris respectively meet the definitions of PEG in R_1 and C_{1-6} alkylene in R_3 and R_4 , respectively.

110. N-hydroxysuccinimide (NHS) ester is known in the art for its ability to react with cell-binding agents comprising a reactive amine group (*e.g.*, a lysine

epsilon amino in antibodies). *See, e.g.*, EX1008, FIGs. 7-12. As discussed above in Section VIII.B.1, vinyl and halo-ethyl groups located adjacent to a sulfone moiety are known in the art as functional groups that react with thiol moieties present in cell-binding agents (*e.g.*, antibodies) or cytotoxic drugs to form thioether or thioester linkages. EX1007, 26:7-15 and 28:17-27. Accordingly, Harris discloses all elements of independent claims 20, and 29-30.

111. In the alternative, independent claims 20, 29 and 30 would also have been obvious over Harris. Harris' teachings concerning bifunctional and heterobifunctional sulfone-containing PEG derivatives as disclosed above are relied on to teach each element of formula (IV). To the extent that a POSA would need to select and/or combine teachings within Harris to arrive at the claimed drug-linkers of formula (IV), the POSA would have been motivated to do so and would have had a reasonable expectation of success for the same reasons given in §VIII.B.1. Additionally, with respect to heterobifunctional linkers, a POSA would have been motivated to select NHS and reasonably expect to succeed in preparing such derivatives as NHS is an example of the "reactive moieties typically used in PEG chemistry to activate PEG" and is known to form a "stable amine linkage," *i.e.*, an amide, that could be attached, *e.g.*, to a lysine group in proteins. EX1007, 17:34-18:15.

112. Dependent claim 31 further specify that when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, **at least one** of R_1 , R_2 , R_3 and R_4 comprises the polyethyleneoxy unit of formula $(OCH_2CH_2)_p$. As discussed above, Harris discloses PEG derivatives comprising two sulfone moieties, wherein Y of formula (IV) described in the '682 patent is $-CH=CH_2$ or $-CH_2-CH_2-X$ where X is a halogen; R_1 is absent; Q is $-SO_2-$, **R_2 is $(OCH_2CH_2)_n$** , m is 1; T is $-SO_2-$, R_3 is methylene, n is 1; $R_4(R_5)(R_6)$ is methylene; and Drug is a pharmaceutical that linked via a thioester or thioether linkage.

113. Dependent claim 21 specifies that the drug is derived from a drug containing a **$-SH$** , $-CONHNH_2$, $-C\equiv$, $-COR''$ or $-NHR''$, wherein R'' is H, CH_3 , Et, Pr, Bu, or Ph. Harris discloses that drugs “from aspirin to penicillin” can be modified to contain thiol moieties. EX1007, 6:28-31. Modifying drugs to include a thiol moiety was performed on a regular basis in the industry prior to November 24, 2012. See, e.g., EX1009, Fig. 3; EX1008, ¶[0144], FIGs. 46-52 (describing ADCs including the maytansinoid DM1, a maytansine modified to have a free thiol group).

114. Therefore, because Harris discloses all of the elements of claims 20-21 and 29-31 of the '682 patent, it is my opinion that the claims were anticipated or obvious as of November 24, 2012.

C. The Challenged Claims 1-8, 10-12, 14-17, 20-21, 24, 26, and 29-31 Are Unpatentable Over Singh in view of Harris

115. Although it is my opinion that Harris anticipates or renders obvious claims 1, 20-21, and 29-31 of the '682 patent, to the extent that it may be argued that Harris does not directly disclose a cell-binding agent, it would have been obvious to a POSA to do so based on the disclosure of Singh in view of the disclosure of Harris. As outlined above, Harris discloses the elements of claims 1, 20-21, and 29-31. *See* Section VIII.B.

1. Claims 1-2 Are Unpatentable

116. As discussed above, claims 1 and 2 are directed to hydrophilic linkers

of formula (I),

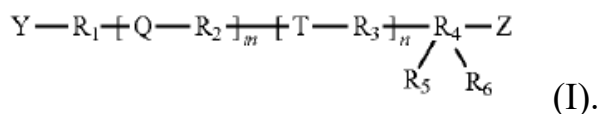
$$Y-R_1-Q-R_2-\text{---}_m-T-R_3-\text{---}_n-R_4-Z$$

$\swarrow \searrow$
 $R_5 \quad R_6$

(I), wherein each variable is defined from among a vast array of possible choices.

117. Singh discloses bifunctional PEG cross-linkers containing each element of claim 1, save Q and T. For the reasons given below, it would have been obvious to a POSA to modify Singh's cross-linkers to incorporate the water soluble, sulfonyl moieties present in the PEG derivatives disclosed in Harris.

118. The bifunctional PEG cross-linkers disclosed in Singh track closely with the variables defining the compound of formula (I) of the '682 patent:



119. The Singh cross-linkers include a reactive functionality on each end of the linker. As illustrated in Table A1 above in Section VII.E, the reactive functionalities of the Singh cross-linkers, namely the maleimide, iodo- or bromoacetamide, and NHS ester groups, are functional groups that enable reaction of the hydrophilic linker with a cell-binding agent and therefore meet the definition of Y in formula (I) of the '682 patent. EX1008, ¶[0136] (indicating that bifunctional PEG-containing cross-linkers contain a reactive functionality for reaction with a cell-binding agent).

120. The second reactive functionality of each cross-linker, *e.g.*, the pyridyldisulfide, maleimide, iodo- or bromoacetamide, or NHS ester groups, are functional groups that enable linkage of the hydrophilic linker to a cytotoxic drug via, among others, a disulfide, thioether, ether, amine, or amide bond and therefore meet the definition of Z in formula (I) of the '682 patent. See, *e.g.*, EX1008, FIGs. 7-17.

121. Singh's bifunctional PEG cross-linkers meet the definitions of R_1 - R_4 as well. As permitted by claim 1, R_1 and R_3 are absent but PEG and atoms linked to the PEG meet the definitions of R_2 and R_4 . Specifically, claim 1, provides that R_2 may be a "polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000," or one of various short carbon chains, "or combination thereof." EX1001, claim 1. Singh's bifunctional cross-linkers each include $(OCH_2C_2)_n$, where Singh's variable " n " meets the definition of " p " since n can be any integer within the disclosed ranges of 1-2000, 1-100, 1-14, and 1-4. EX1008, ¶¶[0082], [0087].

122. The atoms between the PEG group and the second reactive functionality (serving as Z) in Singh's linkers meet the definition of R_4 , which is defined similarly to R_2 . For linkers where PEG is directly linked to the second reactive functionality, R_4 is then absent as claim 1 permits. See Table C1.

123. Table C1 below shows how the bifunctional PEG cross-linkers of Singh meet each element of formula (I) in claim 1 of the '682 patent other than Q or T . Formula (I) of the '682 patent is so broad that the cross-linkers of Singh satisfy its definitions in more than one way, only a few of which are shown.

Table C1

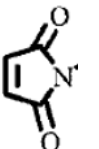
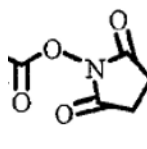
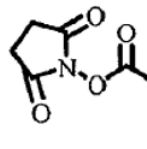
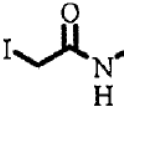
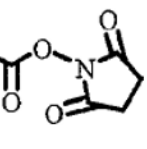
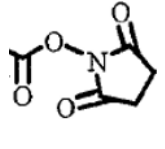
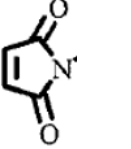
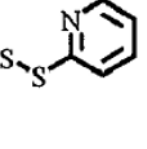
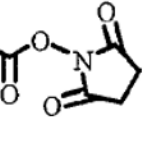
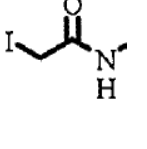
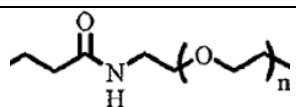
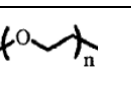
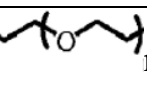
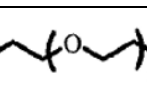
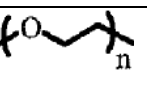
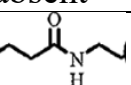
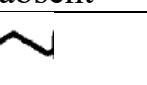
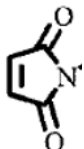
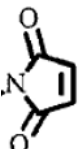
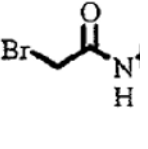
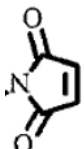
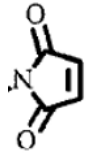
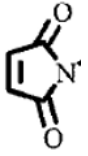
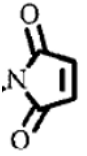
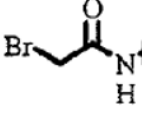
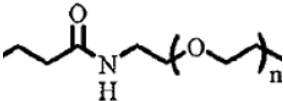
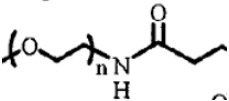
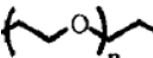
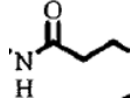
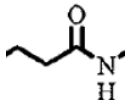
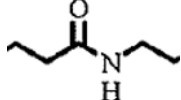
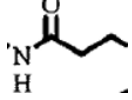
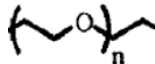
	Singh's Compounds (Table A1)				
'682 (I)	1		2	3	
	(a)	(b)		(a)	(b)
Y					
Z					
R ₁	absent	absent	absent	absent	absent
R ₂					
p	n=1-2000, 1-100, 1-14, 1-4	n=1-2000, 1-100, 1-14, 1-4	n=1-14	n=1-2000, 1-100, 1-14, 1-4	n=1-2000, 1-100, 1-14, 1-4
R ₃	absent	absent	absent	absent	absent
R ₄	absent		absent	absent	

Table C1 (continued)

	Singh's Compounds (Table A1)			
'682 (I)	4		5	
	(a)	(b)	(a)	(b)
Y				

Z				
R₁	absent	absent	absent	absent
R₂				
p	n=1-2000, 1-100, 1-14, 1-4	n=1-2000, 1-100, 1-14, 1-4	n=1-2000, 1-100, 1-14, 1-4	n=1-2000, 1-100, 1-14, 1-4
R₃	absent	absent	absent	absent
R₄				

124. Although Singh's PEG cross-linkers lack sulfonyl groups, Singh itself suggests the use of vinyl sulfones as a thiol-reactive functionality and its functional equivalence to maleimide and haloacetamide functional moieties. EX1008, ¶[0134].

125. As such, a POSA would have understood that the maleimide and haloacetamide reactive functionalities in the bifunctional PEG cross-linkers of Singh can be replaced with a vinyl sulfone group for the purpose of forming thioether or thioester linkages, resulting in Q or Q and T each being a sulfone group, and Y or Y and Z, each being a vinyl group. Such substitutions, as expressly taught by Singh, would thereby fully satisfy claim 1's formula I.

126. Moreover, a POSA would have been further motivated to incorporate vinyl sulfones in Singh's bifunctional PEG cross-linkers (providing Q and/or T) and reasonably expect success in doing so in view of Harris. As discussed above in in Section VIII.B.1, the basic structure: $R-(OCH_2CH_2)_n-Y$ disclosed in Harris encompasses hydrophilic PEG derivatives comprising one or two sulfone moieties that are useful for conjugating two biologically active molecules (*e.g.*, proteins, pharmaceuticals), where at least one of the biologically active molecules *has a reactive thiol moiety*. EX1007, claims 33-34, 3:28-35, 16:34-17:5, 18:5-30, 19:10-15 and 24-30 and Abstract.

127. A POSA would have understood that Harris' vinyl sulfone PEG derivatives are nearly identical to the bifunctional PEG cross-linkers of Singh and serve the same purpose: to link two biologically active molecules with a hydrophilic linker that imparts good water solubility to the resulting conjugate.

128. A POSA would have further appreciated that Harris' sulfonyl-containing PEG derivatives offer several advantages such as water solubility, hydrolytic stability, and selective attachment to cysteine residues in proteins (*e.g.*, antibodies). First, Harris' PEG "polymer derivatives with active sulfone moieties are highly selective for coupling with thiol moieties instead of amino moieties on molecules," and 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.”

EX1007, 6:12-15 and 26:11-15. Second, Harris’ sulfonyl-containing PEG derivatives “are considered *infinitely soluble* in water or as approaching infinite solubility and can enable *otherwise insoluble molecules* to pass into solution when conjugated with the derivative.” EX1007, 19:34-37 (emphasis added). Third, while the “utility of many PEG derivatives is limited because they react rapidly with water, thus interfering with attempts to attach the [PEG] derivative to molecules and surfaces under aqueous conditions,” PEG vinyl sulfone and PEG chloroethyl sulfone are stable in water. EX1007, 28:29-34.

129. A POSA would therefore have been motivated to incorporate Harris’ vinyl sulfones and related sulfonyl functionality, which are reactive functionalities that can form a thioether bond, into the ADC linkers of Singh to obtain the benefits of doing so. The resulting PEG linkers provide active sulfone moieties that are hydrolytically stable, enable water-insoluble molecules (*e.g.*, hydrophobic drugs) to be dissolved in water, promote selective attachment to cysteine units on proteins, and preserve activity for specific proteins EX1007, 6:8-15, 19:31-37, and 26:11-15. In contrast, haloacetamides can non-selectively react with both thiol and amino groups on proteins (*e.g.*, EX1048, 3577, FIGs. 3A-3B),

and require prolonged reaction times at high pH (~8.0), which are less desirable if not unsuitable for conjugation reactions. For example, Alley discloses that for “the bromoacetamides, the reduced antibodies were adjusted to pH 8 with sodium borate and incubated with 2 equiv of bac-vc-MMAF or bac-MMAF per antibody cysteine **for 4 h** at 25 °C.” EX1055, 760 (citations omitted). In contrast, thiol-maleimide reactions proceed much more efficiently at pH 8, using only a 1.1-fold excess of the toxic drug-linker at 4 °C for *1 hour*. See EX1056, 783.

130. A POSA would have also expected that combining the disclosures of Singh and Harris would successfully yield hydrophilic ADC linkers having desirable functional properties. For example, Singh discloses attaching PEG linkers to -SH groups on drugs via a bis-maleimide containing PEG linker, and that maleimide and haloacetamide moieties are functionally equivalent to vinyl sulfone for the purpose of forming thioether bonds. EX1008, ¶[0134], FIGs. 50-51. Examples 1 and 2 of Harris describe how to synthesize a PEG linker comprising a terminal vinyl sulfone or chloro-ethyl sulfone group and how to couple these sulfone containing PEG linkers to molecules comprising free -SH groups, respectively. EX1007, 21:26-28:28. Thus, a POSA would understand how to achieve these substitutions. Harris discloses that the vinyl sulfone PEG linkers are highly water soluble, hydrolytically stable and show selective reactivity with -SH groups relative to amino groups,

especially at pHs of about 9 or less. EX1007, 14:1-7, 19:31-36, 27:21-28:28, and 29:1-22. Indeed, Example 4 of Harris validates the preferential attachment of the vinyl sulfone PEG linker to –SH groups in cysteine residues (instead of the –NH₂ group on lysine) in protein conjugation experiments. EX1007, 30:3-29. Achieving high drug/antibody ratios (DAR) often fails when both the cytotoxic agent and the linker are hydrophobic due to ADC aggregation, loss of affinity for the target antigen, and rapid clearance from circulation. EX1016, 3607. Singh actually discloses that hydrophilic PEG linkers enhanced the potency or the efficacy of cell-binding agent-drug conjugates several fold compared with traditional linkers (e.g. SMCC, SIAB). EX1008, ¶[0009], ¶[0221]. Additionally, “incorporation of hydrophilic linkers allowed the conjugation of up to 15 molecules of a drug per antibody molecule with high yield and no aggregation or precipitation” and these conjugates “bound with high affinity to target antigen (similar to that of unmodified antibody).” EX1008, ¶[0011]; see also EX1016, abstract, 3607.

131. The sulfonyl-containing PEG derivatives of Harris are “*infinitely soluble* in water or as approaching infinite solubility and can enable *otherwise insoluble molecules* to pass into solution when conjugated with the derivative.” EX1007, 19:34-37 (emphasis added). Thus, modifying the PEG-containing ADC linkers of Singh to *include* vinyl sulfones or related sulfonyl derivatives as a reactive

functionality that can form a thioether bond with a cell-binding agent or drug would be expected to have comparable, *if not higher*, hydrophilicity, and conjugates including the same would be expected to exhibit the same advantageous properties (enhanced potency, lower level of aggregation, less precipitation) as the PEG-containing ADC linkers of Singh.

132. Because a POSA would have understood that Singh and Harris relate to substantially similar subject matter and that the PEG containing linkers of each are hydrophilic and are being used for their known purposes, a POSA would have reasonably expected success in combining the disclosure of Singh and Harris in the manner claimed.

133. Dependent claim 2 of the '682 patent specifies that Z comprises a thiol, disulfide, amino, carboxy, aldehydes, maleimido, haloacetyl, hydrazine or hydroxyl group. Singh and/or Harris is relied upon to disclose the limitations of claim 2 as set forth in Table C1 and Section VIII.B, respectively.

134. Therefore, because the combination of Singh and Harris discloses all of the elements of claims 1-2 of the '682 patent, it is my opinion that the claims would have been obvious to a POSA as of November 24, 2012, in view of this prior art.

2. Claims 20-21 and 29-31 Are Unpatentable

135. Claims 20-21 and 29-31 are directed to the compound of

formula (IV)

$$Y-R_1-Q-R_2-T-R_3-R_4-Drug$$

(IV), wherein each variable is

defined from among a vast array of possible choices. In addition to Harris disclosing each of the elements of claims 20-21 and 29-31 as set forth in Section VIII.B.2, claims 20-21 and 29-31 also would have been obvious over Singh in view of Harris.

136. Singh discloses PEG drug crosslinkers containing each element of claims 20 and 29-30, except for Q and T. For the reasons given below, it would also have been obvious to modify the PEG drug crosslinkers disclosed in Singh to incorporate the water soluble, thiol-reactive sulfonyl moieties present in the PEG derivatives disclosed in Harris.

137. The PEG drug crosslinker disclosed as a compound of formula (1) in Singh, $Z-X_1-(CH_2-CH_2-O)_n-Y_p-D$, tracks with nearly every variable defining the compound of formula (IV) of the '682 patent. Similarly, the compounds of formulas (1'), (3) and (3') also track with nearly every variable of the compound of formula (I) of the '682 patent for essentially the same reasons.

138. For example, in Singh's compound of formula (1), Z is "a reactive functionality that can form an *amide or a thioether* bond with *a cell-binding agent*" and therefore meets the definition of Y of formula (IV) in the '682 patent, which "represents a functional group that enables reaction of the compound with a cell-binding agent." Singh's Z group also meets at least the Q variable of '682's formula (IV) because Singh discloses vinyl sulfone—a reactive functionality that forms thioether bonds—as one of only three such groups (along with haloacetamide and maleimide). EX1008, ¶[0134]. In this case, Y of formula (IV) is vinyl, Q is sulfonyl, m=1 and, as permitted by the claims, R₁ is absent from Singh's compound of formula (1).

139. The PEG group of formula (1) (i.e., (OCH₂CH₂)_n where n is any of 1-2000, 1-100, 1-14, 1-4) meets the '682's definition of R₂, which can include a "polyethylene oxy unit of formula (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000." EX1008, ¶[0082]. Claim 20 further requires one of R₁-R₄ to comprise PEG when Q and T are each SO₂, and Singh's PEG group meets this requirement too. Singh's formula (1) compound optionally contains an X group linking the PEG to the Z group. When present (i.e., Singh's X_l where l=1) the X group is also part of R₂ as an "aliphatic ... unit attached to the cell-binding agent via a thioether bond, an amide bond, a carbamate bond, or an ether bond," (EX1008, ¶¶[0014], [0080])

because R_2 's definition permits combinations of PEG with “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.”

140. Although claims 29 and 30, impose additional restrictions on R_2 (e.g., if present, alkyl is branched having 3-6 carbons) when Q and T are both SO_2 , the rest of R_2 definition remains unchanged and is still met by Singh's PEG and X groups in formula (1). In embodiments of Singh's formula (1) having only one sulfone (e.g., those that meet the definitions of Q and R_2), R_3 is absent ($n=0$) as permitted by the claims. Alternatively, in such embodiments, Q and R_2 are absent ($m=0$), T is present and $(OCH_2CH_2)_n$ and X meet the definition of R_3 ($n=1$), which is defined even more broadly than R_2 .

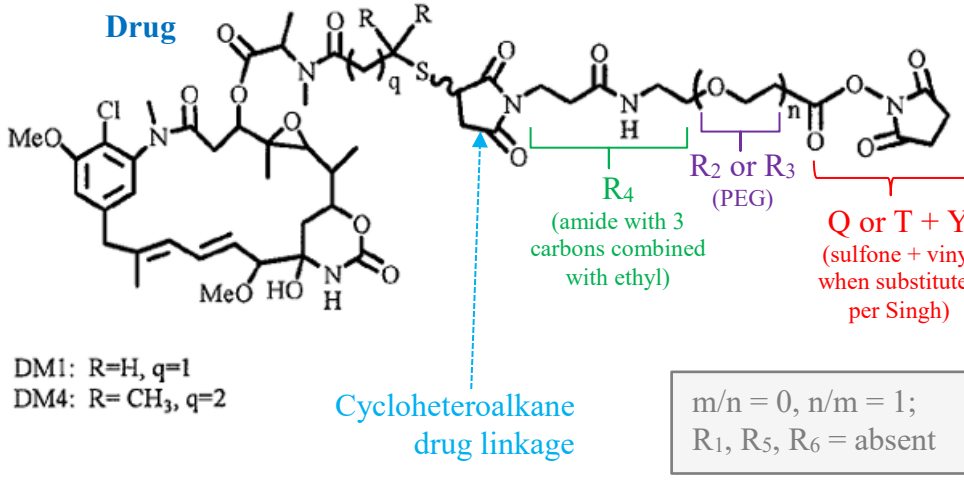
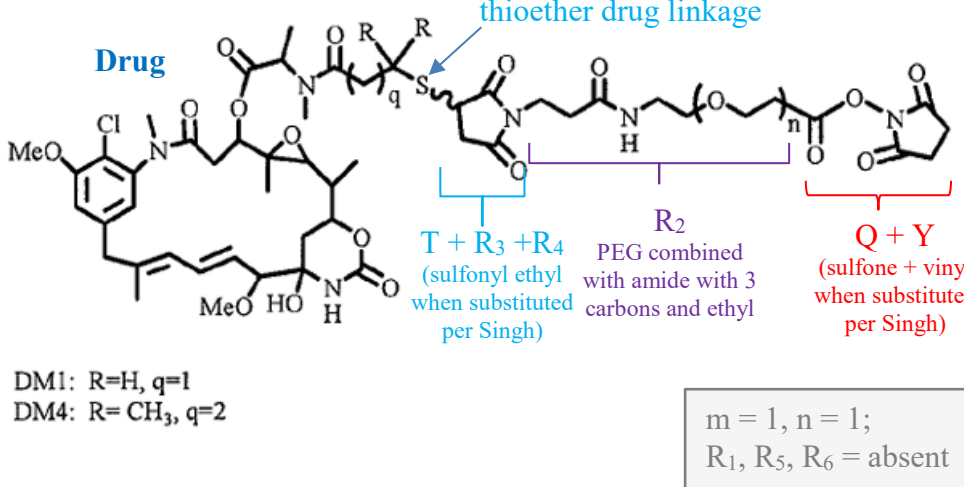
141. The Y group of the compound of formula (1) of Singh, when present ($p=1$) as an aliphatic unit ***attached to the drug*** via a thioether bond, an amide bond, a carbamate bond, an ether bond, or an amine bond, meets the definition of R_4 , (whose definition is identical to R_1 and R_3), with R_5 and R_6 as H or absent. D of formula (1) is a drug and meets formula (IV)'s definition of Drug .

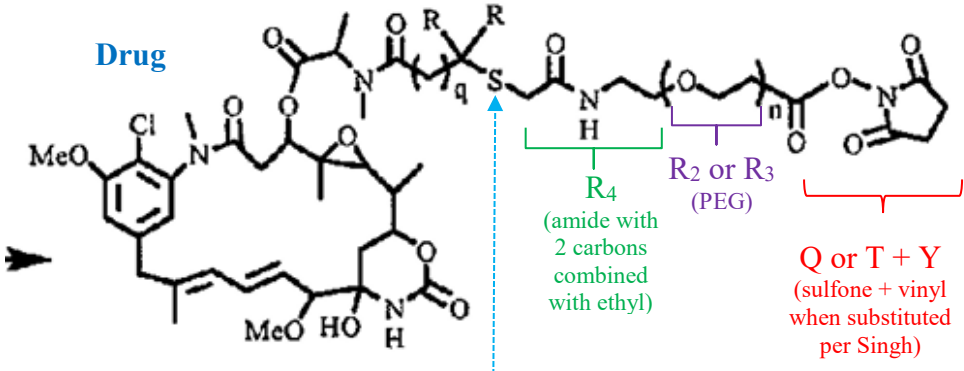
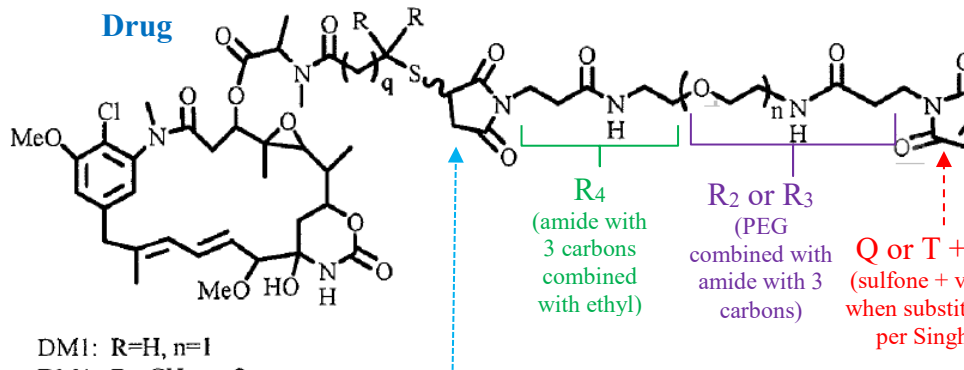
142. Singh's Y group in formula (I) can also provide a first or second sulfonyl group because in order to provide a thioether bond to the drug, the precursor

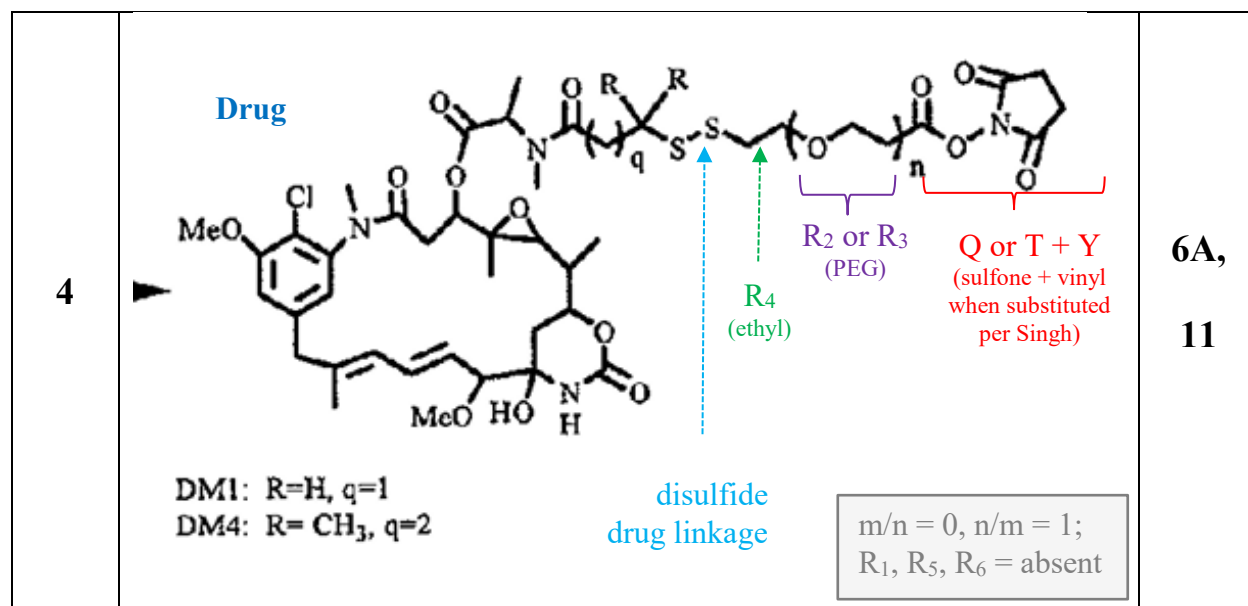
(i.e., the bifunctional PEG crosslinker discussed in the previous section) must include thiol reactive moieties which Singh discloses as including vinyl sulfones. For at least the same reasons discussed above (*supra* §VIII.C.1), a POSA would have been motivated to incorporate vinyl sulfones as the Z group in formula (I) of Singh and/or attach the drug using a vinyl sulfone in view of Harris and would have had a reasonable expectation of success in doing so.

143. Claims 20 and 29 encompass drug-linkers with only a single sulfonyl group and require that the Y group of formula (IV) be selected from common activating groups such as NHS ester. Singh's formula (1) suggests such embodiments as well. As noted above, when Y of Singh's formula (1) is sulfonyl ethyl with a thioether link to the drug, Singh's Z may be reactive functionalities that form a thioether or **amide** bond. EX1008, [0080]. Singh discloses that NHS is not only an amide bond forming reactive functionality, but employs it in a number of Drug linker conjugates reproduced in Table C2, below. EX1008, ¶[0134]. In addition to compounds of formula (1), (1'), (3) and (3'), Singh discloses examples of such PEG drug crosslinkers in Figs. 4, 5, 6A, 13 and 16A and the accompanying text. As shown in Table C2 below, these compounds also map to and suggest compounds of '682's formula (IV).

Table C2

Entry	Singh's PEG Drug Crosslinkers	FIGs.
1	 DM1: R=H, q=1 DM4: R=CH₃, q=2 Cycloheteroalkane drug linkage m/n = 0, n/m = 1; R₁, R₅, R₆ = absent	4, 7
1	 DM1: R=H, q=1 DM4: R=CH₃, q=2 thioether drug linkage m = 1, n = 1; R₁, R₅, R₆ = absent	4, 7

2	 DM1: R=H, q=1 DM4: R=CH₃, q=2 thioether drug linkage m/n = 0, n/m = 1; R₁, R₅, R₆ = absent	5, 9
3	 DM1: R=H, n=1 DM4: R=CH₃, n=2 Cycloheteroalkane drug linkage m/n = 0, n/m = 1; R₁, R₅, R₆ = absent	13, 14



144. As shown in Table C2, each PEG drug crosslinker compound includes one of two maytansinoids (labelled DM1 or DM4), a cytotoxic anticancer drug at one end of the crosslinker. Each maytansinoid is attached to the rest of the crosslinker via a thioether bond or a disulfide bond. Each PEG drug crosslinker includes at its other end, an NHS ester or maleimide derivative that can form, respectively, an amide or a thioether bond with a cell-binding agent, *i.e.*, antibody, to form an ADC. EX1008, FIGs. 4-6A, 14, 16A, 19A. As shown in Table C2, replacing these NHS ester or maleimide functionalities with a vinyl sulfone-drug linkage suggests compounds of '682's formula (IV).

145. Similarly, further substituting the maleimide-drug linkage in Table C2 with a vinyl sulfone-drug linkage also suggests compounds of '682's formula (IV).

146. Table C2.1 below shows in more detail how the PEG drug crosslinker compounds of Singh meet each element of formula (IV) in claim 20-21 and 29-31 of the '682 patent other than Q or T. Formula (IV) of the '682 patent is so broad that Singh's compounds satisfy its definitions in more than one way, only a few of which are shown.

Table C2.1

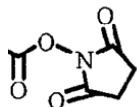
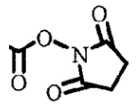
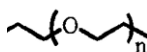
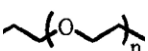
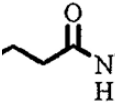
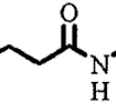
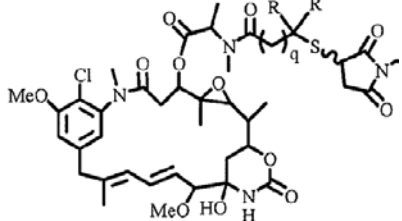
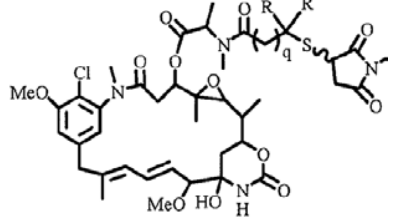
	Singh's Compounds (Table C2)	
'682 (IV)	1	
Y	(a)	(b)
		
R ₁	absent	absent
R ₂		absent
p	n=1-2000, 1-100, 1-14, 1-4	n=1-2000, 1-100, 1-14, 1-4
R ₃	absent	
R ₄		
Drug	 DM1: R=H, q=1 DM4: R=CH₃, q=2	 DM1: R=H, q=1 DM4: R=CH₃, q=2

Table C2.1 (continued)

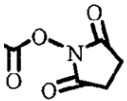
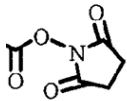
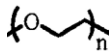
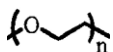
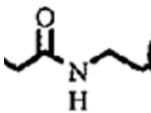
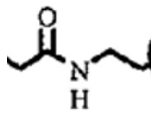
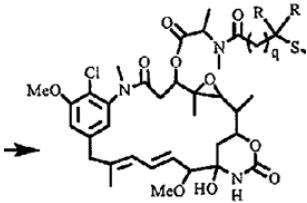
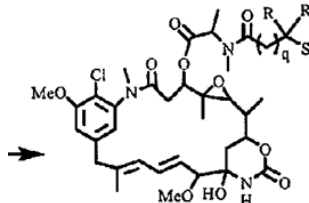
	Singh's Compounds (Table C2)	
'682 (IV)	2	
Y	(a)	(b)
		
R₁	absent	absent
R₂	absent	
p	n=1-2000, 1-100, 1-14, 1-4	n=1-2000, 1-100, 1-14, 1-4
R₃		absent
R₄		
Drug	 DM1: R=H, q=1 DM4: R=CH₃, q=2	 DM1: R=H, q=1 DM4: R=CH₃, q=2

Table C2.1 (continued)

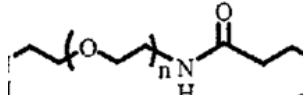
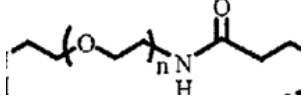
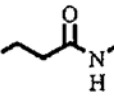
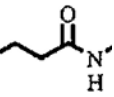
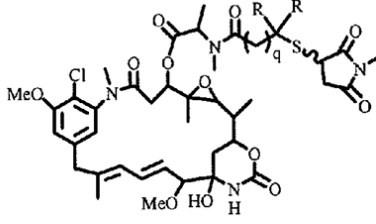
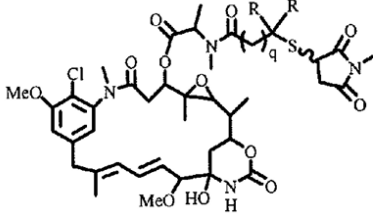
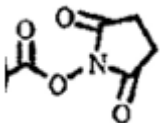
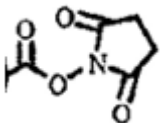
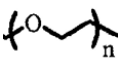
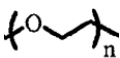
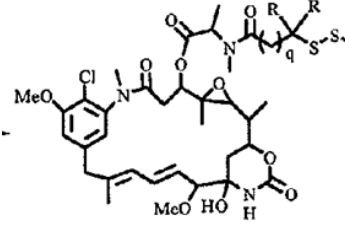
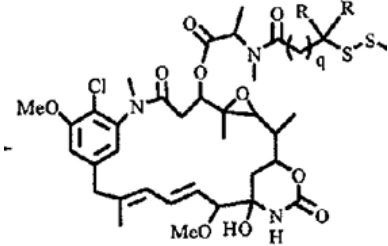
	Singh's Compounds (Table C2)	
'682 (IV)	3	
	(a)	(b)
Y		
R₁	absent	absent
R₂		absent
p	n=1-2000, 1-100, 1-14, 1-4	n=1-2000, 1-100, 1-14, 1-4
R₃	absent	
R₄		
Drug		

Table C2.1 (continued)

	Singh's Compounds (Table C2)	
'682 (IV)	4	
	(a)	(b)
Y		
R₁	absent	absent
R₂		absent
p	n=1-2000, 1-100, 1-14, 1-4	n=1-2000, 1-100, 1-14, 1-4
R₃	absent	
R₄		
Drug		

147. The exemplary PEG drug linker compounds of Singh differ from formula (IV) of the '682 patent as both Q and T are absent, whereas independent

claims 20 and 29 require at least one of Q and T to be present, and independent claim 30 of the '682 patent requires the presence of both Q and T.

148. A POSA would have been motivated to substitute thiol reactive groups that can react with a cysteine in a cell-binding agent (e.g., the maleimide in compound 3) and/or the reactive functionality forming the thioether bond (e.g., maleimide, iodo- or bromo-acetamide) to the drug (Y in Singh's formulas (1), (1'), (3) and (3')) with vinyl sulfone or other sulfones as taught by Harris.

149. Moreover, a POSA would also have been motivated to replace the amide bond forming groups (such as N-hydroxysuccinimide in compounds 1, 2, and 4) with vinyl sulfones because i) Singh itself suggests thiol-reactive groups such as vinyl sulfones may be used as Z groups in compounds of formulas (1)/(1') and (3)/(3') and ii) Harris discloses several advantages for doing so as previously explained. *Supra*, §VIII.C.1

150. For the same reasons described above in Section VIII.C.1, a POSA also would have had a reasonable expectation of success that combining the disclosure of Singh and Harris would successfully yield hydrophilic PEG drug crosslinkers having desirable functional properties and that could be used to prepare ADCs by reacting the crosslinkers with suitable antibodies.

151. Dependent claim 21 requires that the drug is derived from a drug containing a **–SH**, –CONHNH₂, –≡, –COR" or –NHR", wherein R" is H, CH₃, Et, Pr, Bu, or Ph. Harris discloses that drugs like aspirin and penicillin can be modified to contain thiol moieties, which can then be reacted with vinyl sulfones. EX1007, 6:28-31. Singh also discloses that its PEG spacers may be reacted with “a thiol-containing maytansinoid drug” or “an amine-containing maytansinoid.” EX1008, ¶¶[0136], [0139]. Indeed, a POSA will understand that the drug in each of compounds 1-4 in Table C2.1 was derived from a drug containing a –SH.

152. Dependent claim 31 further specifies that when Q and T are each independently –S(O₂)– or –S(O)–, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p. As shown in Table C2.1 and discussed with respect to claims 20 and 29, each of Singh’s PEG-drug linkers comprise PEG matching R₂ and/or R₃.

153. Therefore, because the combination of Singh and Harris discloses all of the elements of claims 20-21 and 29-31 of the ’682 patent, it is my opinion that the claims would have been obvious to a POSA as of November 24, 2012, in view of this prior art.

3. Claims 3-8, 10-12, 14-17, 24, and 26 are Unpatentable

154. Independent claims 3 and 24 are directed to a “cell-binding agent-drug

conjugate of formula (II),
$$\text{Cb} - \left(\text{R}_1 - \text{Q} - \text{R}_2 - \text{T} - \text{R}_3 - \text{R}_4 - \text{Drug} \right)_q \quad \text{(II)}$$
 wherein each variable is defined from among a vast array of possible choices.

155. The primary difference between Formula (II) and Formula (IV) of the '682 patent is that a cell-binding agent (Cb) is present in Formula (II) instead of Y. For the reasons set forth below, claims 3, 24 and 26 would have been obvious to a POSA over Singh in view of Harris. Specifically, it would have been obvious to modify the cell-binding agent-drug conjugates taught in Singh to include the water soluble, active sulfone moieties present in the PEG derivatives disclosed in Harris.

156. Although I have been informed that the preamble does not necessarily limit the scope of a claim, I have not considered and take no position on whether the preamble is limiting. Instead, I have been asked to assume that the preamble is limiting for my analysis. Nevertheless, the combination of Singh and Harris teaches this limitation because it merely refers to compounds of formula (II) and fails to further limit the scope of the claims.

157. Singh expressly discloses a “cell-binding agent-drug conjugate.” Singh discloses cell-binding drug conjugates in its formulas (2)/(2') and (4)/(4') (EX1008, ¶¶[0015], [0017], [0084], [0093]) and provides examples of each in Figs. 1-3, 7-12, 14-15, 17-18, and 20-21 and accompanying text. EX1008, ¶¶[0136]-[0138], [0214], [0218]-[0221]. As with the '682 formulas (II) and (IV), the primary differences between Singh's formulas (2)/(2') and formulas (1)/(1') are that a cell-binding agent CB is present in formulas (2)/(2') in place of Z and that it is bound to m (=2-15) drug-linkers.³ Singh's disclosure of D, Y, p, n, X, and l for formulas (2)/(2') is identical to its disclosure of those variables for formulas (1)/(1'). Compare EX1008, ¶¶[0014], [0080] with ¶¶[0015], [0084]). As discussed in Section VIII.C.1-VIII.C.2, Singh in combination with Harris teaches or suggests all variables in common between formulas (II) and (IV) of the '682 patent, including sulfonyl groups meeting the definition of Q and T.

158. Additionally, a POSA would understand that the cell-binding agent and variable m of Singh's compounds (EX1008, ¶¶[0146]-[0156]) are identical to the

³ Similarly, formulas (4)/(4') are identical to formulas (3)/(3') except a cell-binding agent CB is present in formula (4)/(4') instead of Z, and CB is attached to m (2-15) drug-linkers. EX1008, [0016]-[0017], [0090]-[0095].

cell binding agent and q as defined in claims 3, 24 and 26 of the '682 patent (EX1001, 14:38-15:31). Thus, claims 3, 24, and 26 would have been obvious over the compounds of formulas (2)/(2') and (4)/(4') of Singh in view of its and Harris' teachings concerning vinyl sulfones based on the same motivation to combine and reasonable expectation of success detailed above in Section VIII.C.1-VIII.C.2.

159. Specifically, the cell-binding agent-drug conjugate of formula (2) in Singh, $CB-[X_1-(CH_2-CH_2-O)_n-Y_p-D]_m$, tracks with nearly every variable defining the conjugate of formula (II) of the '682 patent. Similarly, the compounds of formulas (2'), (4) and (4') also track with nearly every variable of the compound of formula (II) of the '682 patent for essentially the same reasons.

160. For example, in Singh's compound of formula (2), CB is "***a cell-binding agent***" and therefore meets the definition of Cb of formula (II) in the '682 patent, and "m is an integer from 2 to 15," which satisfies the definition of q of formula (II) in the '682 patent, which "is an integer from 1 to 20.

161. The X group of Singh's compound of formula (2), when present (*i.e.*, $l=1$, not 0) as an "aliphatic ... unit attached to the cell-binding agent via a thioether bond, an amide bond, a carbamate bond, or an ether bond," may be R_1 , which permits combinations of "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,” and $(\text{OCH}_2\text{CH}_2)_n$, where n can be any of 1-2000, 1-100, 1-14, 1-4, etc., meets the definition of R_2 (R_2 may be a “polyethylene oxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000”), m and p ($m=1$, $p=1$ -1000). R_3 is then absent ($n=0$) from Singh’s compound.

162. Alternatively, R_1 is absent from Singh’s compound of formula (2), but $(\text{OCH}_2\text{CH}_2)_n$, where n can be any of 1-2000, 1-100, 1-14, 1-4, etc., meets the definitions of R_2 , m and p ($m=1$, $p=1$ -1000). The X group of Singh’s compound of formula (2), when present (*i.e.*, $l=1$, not 0) as an “aliphatic ... unit attached to the cell-binding agent via a thioether bond, an amide bond, a carbamate bond, or an ether bond,” may also be part of R_2 , which permits combinations of “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” and PEG. R_3 is absent ($n=0$) from Singh’s compound.

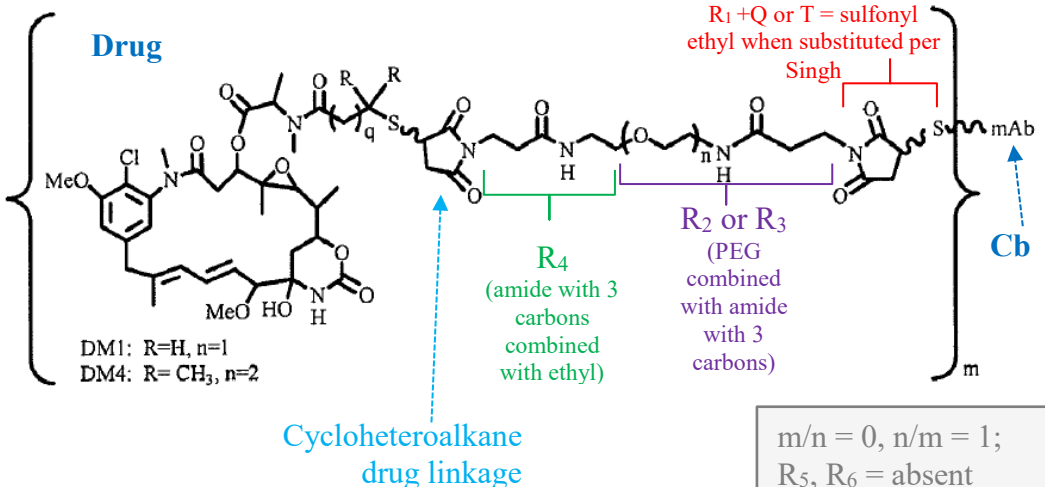
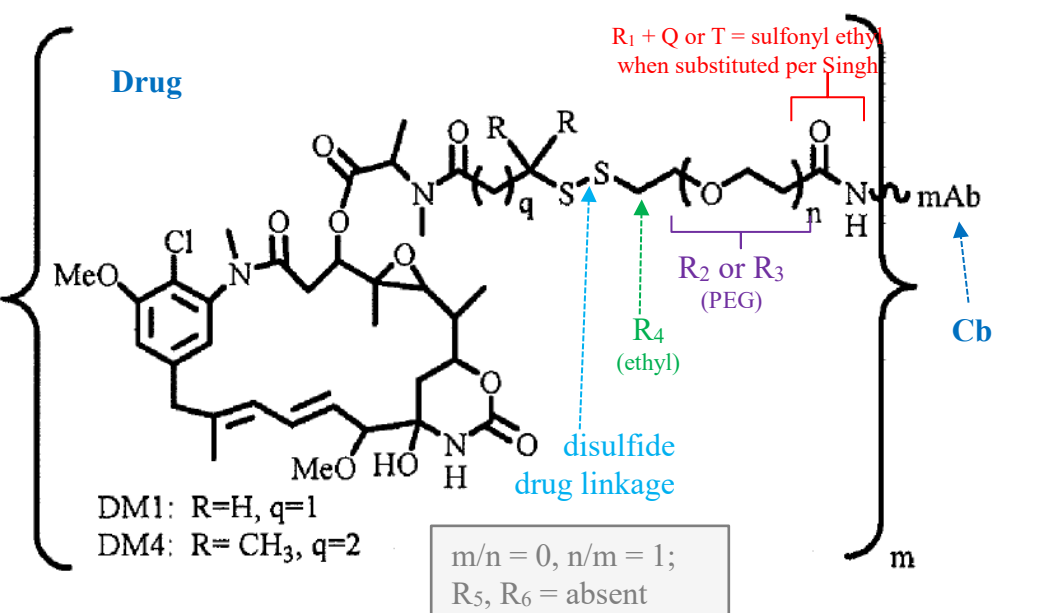
163. Alternatively, R_1 and R_2 may be absent ($m=0$), and $(\text{OCH}_2\text{CH}_2)_n$ of the compound of formula (2) meets the definition of R_3 ($n=1$), as it is defined similarly, but even more broadly than R_2 .

164. The Y group of the compound of formula (2) of Singh, when present ($p=1$), is an aliphatic, an aromatic or a heterocyclic unit ***attached to the drug*** via a thioether bond, an amide bond, a carbamate bond, an ether bond, or an amine bond, and meets the definition of R_4 , in which $(R_5)(R_6)-$ can be absent, and Drug is a drug that is linked via a thioether, amide, carbamate, ether, or hydrazone linkage.

165. In addition to compounds of formulas (2), (2'), (4) and (4'), Singh discloses a number of specific examples of ADCs as shown in Table C3 along with a reference to the figures in which they appear. Singh's compounds are ADCs in which a PEG-containing linker is conjugated to an antibody via an amide or thioether bond and to a drug via a thioether or disulfide bond. EX1008, Figs.1-3, 14, 17, 20. As shown in Table C3 below, the exemplary drug linker compounds of Singh differ from formula (II) of claims 3, 24, and 26 only in that Q and T are absent.

Table C3

No.	Antibody Drug Conjugates of Singh	FIGs.
1	DM1: R=H, q=1 DM4: R=CH₃, q=2 $R_1 + T \text{ or } Q = \text{sulfonyl ethyl when substituted per Singh}$ R_4 (amide with 3 carbons combined with ethyl) $R_2 \text{ or } R_3$ (PEG) $m/n = 0, n/m = 1;$ $R_5, R_6 = \text{absent}$	1, 7-8
1	DM1: R=H, q=1 DM4: R=CH₃, q=2 $Q + R_1 = \text{sulfonyl ethyl when substituted per Singh}$ R_2 (PEG combined with amide with 3 carbons and ethyl) $T + R_3 + R_4$ (sulfonyl ethyl when substituted per Singh) $m = 1, n = 1;$ $R_5, R_6 = \text{absent}$	1, 7-8

3	 Drug DM1: R=H, n=1 DM4: R=CH₃, n=2 R₁+Q or T = sulfonyl ethyl when substituted per Singh R₂ or R₃ (PEG combined with amide with 3 carbons) R₄ (amide with 3 carbons combined with ethyl) Cycloheteroalkane drug linkage m/n = 0, n/m = 1; R₅, R₆ = absent	14, 15
4	 Drug DM1: R=H, q=1 DM4: R=CH₃, q=2 R₁+Q or T = sulfonyl ethyl when substituted per Singh R₂ or R₃ (PEG) R₄ (ethyl) disulfide drug linkage m/n = 0, n/m = 1; R₅, R₆ = absent	3, 11, 12

166. As shown in Table C3, the ADC is conjugated to an antibody via an amide or thioether bond, and to a drug via a thioether or disulfide bond to yield conjugates of formulas (2), (2'), (4), and (4'). EX1008, FIGs.1-3, 14, 17, 20.

167. Table C3.1 below shows in more detail how the cell-binding agent drug conjugates of Singh meet each element of formula (II) in claims 3, 24 and 26 of the

'682 patent other than Q or T. Formula (II) of the '682 patent is so broad that the cross-linkers of Singh satisfy its definitions in more than one way, only a few of which are shown.

Table C3.1

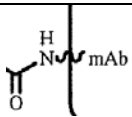
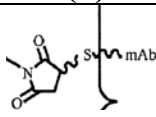
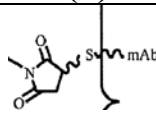
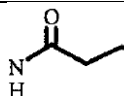
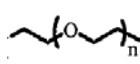
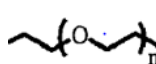
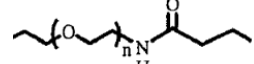
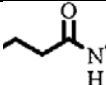
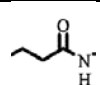
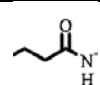
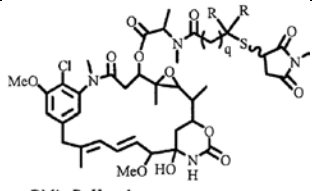
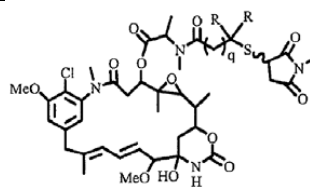
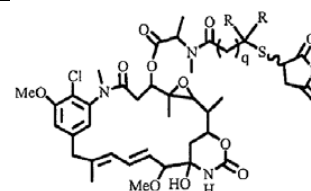
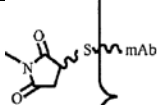
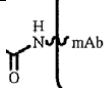
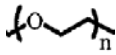
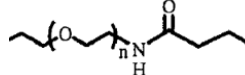
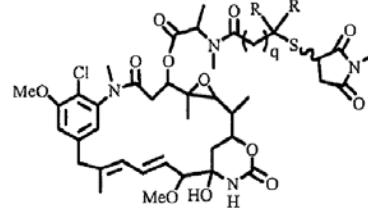
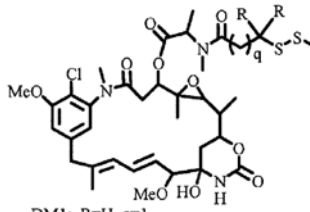
Singh Antibody-Drug Conjugates (from Table C3)			
'682 (IV)	1	3	
		(a)	(b)
Cb			
R₁	absent		absent
R₂			
p	n=1-2000, 1-100, 1-14, 1-4	n=1-2000, 1-100, 1-14, 1-4	n=1-2000, 1-100, 1-14, 1-4
R₃	absent	absent	absent
R₄			
Dru g	 DM1: R=H, q=1 DM4: R=CH ₃ , q=2	 DM1: R=H, n=1 DM4: R=CH ₃ , n=2	 DM1: R=H, n=1 DM4: R=CH ₃ , n=2
q	2-15	2-15	2-15

Table C3.1 (Continued)

Singh Antibody-Drug Conjugates (from Table C3)		
'682	3	4
(IV)		
Cb		
R₁	absent	absent
R₂	absent	
p	n=1-2000, 1-100, 1-14, 1-4	n=1-14
R₃		absent
R₄		
Drug	 DM1: R=H, n=1 DM4: R=CH ₃ , n=2	 DM1: R=H, q=1 DM4: R=CH ₃ , q=2
q	2-15	3 to 8

168. The exemplary drug linker compounds of Singh differ from formula (II) of the '682 patent as both Q and T are absent. Claims 24 and 26 of the '682 patent differs from claim 3 because the conjugates require the presence of both Q and T.

169. For the same reasons given in Section VIII.C.1-2 above, a POSA would have been motivated to substitute the sulfonyl ethyl group in for either the linking moiety to the antibody and/or the linking moiety to the drug. For example, a POSA would have been motivated to substitute Singh's Y group attached to the drug via a thioether bond (*e.g.*, arising from a maleimide, or iodo- or bromo-acetamide functionality) and /or Singh's X group attached to the cell-binding agent via a thioether bond (*e.g.*, arising from a maleimide, iodo- or bromo-acetamide functionality) of Singh's formula (2) or (2'), with the vinyl sulfone or other sulfones of Harris because (a) the vinyl sulfone or related sulfone moieties of Harris are functionally equivalent to maleimide, or iodo- or bromo-acetamide moieties, (b) the sulfonyl-containing PEG linkers are hydrolytically stable, almost infinitely soluble in water, and permit selective attachment of drug-PEG linkers to one or more cysteine residues on proteins. EX1007, 6:8-15, 19:31-37, and 26:11-15.

170. Further, a POSA would have expected that combining the disclosure of Singh and Harris would lead to the successful generation of ADCs with enhanced

potency/cytotoxicity. Singh discloses that its hydrophilic PEG-containing linkers improves the “potency or efficacy of the cell-binding agent-drug conjugates” in various “cancer cell types, including those expressing a low number of antigens on the cell” and that its hydrophilic linkers allowed the conjugation of up to 15 molecules of a drug per antibody molecule with high yield and no aggregation or precipitation. EX1008, ¶¶[0009], [0011]. A POSA would have expected that ADCs that include the hydrophilic vinyl sulfone or related sulfone moieties of Harris would exhibit *comparable to elevated solubility*, and thus similar therapeutic properties (enhanced cytotoxicity/potency and high number of drug molecules (1-15) per antibody molecule *etc.*) as the PEG-containing ADCs of Singh.

171. Because the hydrophilic properties of the PEG-containing ADCs of Singh are correlated with the enhanced cytotoxicity/potency in target cancer cells (EX1008, ¶¶[0009], [0011]), and PEG spacers including sulfonyl moieties are “infinitely soluble in water” (EX1007, 19:34-37), a POSA would have had a reasonable expectation of success in combining the disclosure of Singh and Harris in the manner claimed.

172. Dependent claims 4-5, 8 and 10 further define the “Drug” of formula (II) as being selected from a large Markush group of therapeutic agents. Singh discloses multiple exemplary cytotoxic drugs capable of being linked to a cell-

binding agent including *maytansinoids*, DNA-binding drugs such as *CC-1065*, *calicheamicins*, *doxorubicin*, vinca alkaloids, *cryptophycins*, *dolastatin*, *auristatin*, *tubulysin*, *epothilones*, taxoids and siRNA. EX1008, ¶¶[0165]-[0167]. Maytansinoids, CC-1065, calicheamicins, doxorubicin, cryptophycins, dolastatin, auristatin, tubulysin, and epothilones are known chemotherapeutic agents.

173. Dependent claims 6-7 and 14 further specify the identity of the cell-binding agent, such as an antibody, a protein, a lymphokine, a hormone, a growth factor, and a colony stimulating factor. Singh defines cell-binding agents as “proteins (*e.g.*, immunoglobulin and non-immunoglobulin proteins) that bind specifically to target antigens on cancer cells” and that examples of cell-binding agents include antibodies, epitope binding fragments of antibodies such as sFv, Fab, Fab’, and F(ab’)₂, Ankyrin repeat proteins, interferons, lymphokines, hormones, growth factors and colony-stimulating factors. EX1008, ¶¶[0146]-[0156]. Harris likewise discloses that its PEG sulfonyl conjugates may include proteins. EX1007, 6:31-7:2.

174. Claims 11, 12, 14, each depend from claim 3. Claim 11 specifies that the conjugate of claim 3 has in vitro, in vivo or ex vivo cell killing activity; claim 12 specifies that the conjugate “comprises . . . *a thioether unit*,” and claim 14 alternatively recites that in the conjugate, the “Drug is derived from *a drug*

containing a —SH, -CONHNH₂, —≡, —COR" or —NHR", wherein R" is H, CH₃, Et, Pr, Bu, or Ph.” Singh discloses that cell-binding agent-drug conjugates bearing PEG spacers exhibited a “superstoichiometric increase in cytotoxicity toward target cancer cells by as much as a 260-650 fold enhancement in potency . . . as compared to traditionally prepared conjugates with similar drug loads.” EX1008, ¶[0078]. A POSA would have expected at least as good if not better performance when incorporating one or two vinyl sulfones given their impartation of even better water solubility.

175. Moreover, Singh discloses ADCs in which the drug (containing a **thiol**) may be attached to a Y group by a **thioether bond** and/or the cell binding agent (bearing a cysteine thiol or lysine amine) may be attached to, an X group by a **thioether bond or an amide bond**. EX1008, ¶¶[0015], [0017], [0084]-[0085], [0093], see also FIGS. 1-2, 7-9, 14, 17-18, 21. Likewise, Harris discloses that drugs “from aspirin to penicillin” can be modified to contain thiol moieties. EX1007, 6:28-31.

176. Dependent claims 15-16 recite pharmaceutical compositions comprising the conjugate of claim 3 and a pharmaceutically acceptable salt, carrier, diluent, or excipient therefor, whereas dependent claim 17 recites a “pharmaceutical composition comprising a therapeutically effective amount of the conjugate of claim

3, and a chemotherapeutic agent, radiation therapy agent, immunotherapy agent, autoimmune disorder agent, or anti-infectious agent.” Singh discloses that “*cell-binding agent drug conjugates (e.g., immunoconjugates)* can be used with suitable *pharmaceutically acceptable carriers, diluents, and/or excipients*, which are well known, and can be determined, by one of skill in the art as the clinical situation warrants.” EX1008, ¶[0174]. Moreover, Singh discloses that “cell-binding agent drug conjugates (*e.g., immunoconjugates*) of this invention can also be used in combination with *chemotherapeutic agents*.” EX1008, ¶[0171]

177. Therefore, because the combination of Singh and Harris discloses all of the elements of claims 3-8, 10-12, 14-17, 24, and 26 of the '682 patent, it is my opinion that the claims would have been obvious to a POSA as of November 24, 2012, in view of this prior art.

D. The Challenged Claims 9 and 13 Are Obvious Over Singh in View of Harris and Bhakta

178. Dependent claim 9, which depends from claim 3, recites the limitation “wherein the conjugate comprises one or more linker components of . . . *valine-citrulline, alanine-phenylalanine, . . . and (4-acetyl)aminobenzoate*.” Claim 13, which depends from claim 3, recites the limitation “wherein the conjugate is cleavable by a protease.”

179. Bhakta expressly discloses an ADC comprising a cysteine engineered antibody, and a drug moiety wherein the antibody has one or more free cysteine amino acids, and the antibody is attached through the one or more free cysteine amino acids by a linker to the drug moiety. EX1011, ¶¶[0211]-[0212]. Bhakta further discloses that the linker may comprise amino acid residues which link the antibody to the drug moiety of the cysteine engineered ADC, including dipeptides such as valine-citrulline (vc or val-cit) that can be cleaved by cathepsin B, C and D, or a plasmin protease. EX1011, ¶¶[0244]-[0245].

180. It was also known to use combinations of the dipeptide val-cit with the PAB as described in Bhakta. EX1011, ¶[0250]. When the val-cit dipeptide is cleaved from the PAB by cathepsins associated with the target cancer cell, the ester linkage to the drug subsequently hydrolyzes as well, releasing the drug within the cancer cell.

181. ADCs utilizing the disulfide linkages of Singh were previously found to exhibit reduced efficacy, greater off target toxicity and poor serum stability. EX1049, abstract. A POSA would have been motivated to use the well known val-cit-PAB linker of Bhakta to replace, *e.g.*, the disulfide linkage of Singh in order to obtain the selective and efficient release of the Drug, at target cancer cells. A POSA would have expected success, because by the time the '682 patent was filed, the

chemistry of this linker was well established and proven in human patients. EX1017, 101:1-104:43.

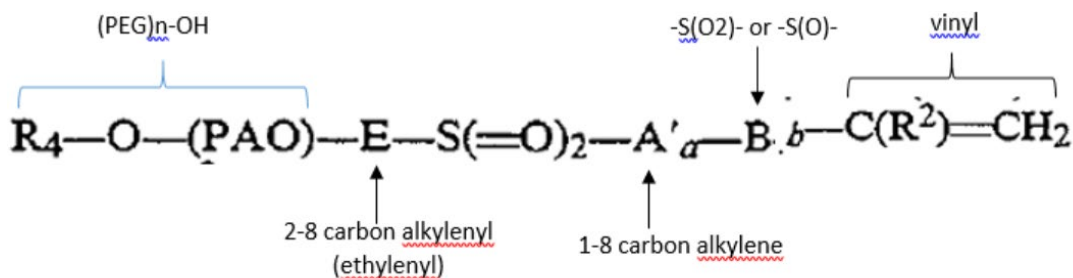
182. Therefore, because the combination of Singh, Harris and Bhakta discloses all of the elements of claims 9 and 13 of the '682 patent, it is my opinion that the claims would have been obvious to a POSA as of November 24, 2012, in view of this prior art.

E. The Challenged Claims 2, 25 and 32-34 are obvious over Singh in view of Harris and Snow

183. Claim 2 (which depends from claim 1) specifies that Z comprises a thiol, disulfide, amino, carboxy, aldehydes, maleimido, haloacetyl, hydrazine or hydroxyl group. Claim 25 (which depends from claim 24), claim 32 (which depends from claim 30), claim 33 (which depends from claim 3) and claim 34 (which depends from claim 20) each recite “wherein when Q and T are each independently -S(O₂)- or -S(O)-, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p; and each of remaining R₁, R₂, R₃ and R₄ comprises an alkyl or (OCH₂CH₂)_p.”

184. Snow discloses vinyl sulfone linkers containing PEG polymers ranging from 250-100,000 daltons (EX1010, 7:51-65), which overlap with the class of water soluble sulfone containing PEG polymers disclosed in Harris. EX1007,

19:10-17 and 24-30. In particular, Snow contemplates polyalkylene oxide bis-vinyl sulfone linkers represented by the formula:

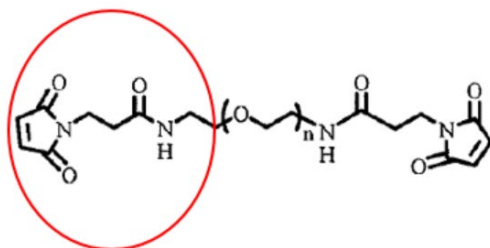


185. Like Harris, Snow discloses that its polyalkylene oxide vinyl sulfone reagents show preferential reactivity with accessible sulfhydryl groups on proteins. EX1010, 9:58-63; EX1007, 6:12-15, 26:11-15.

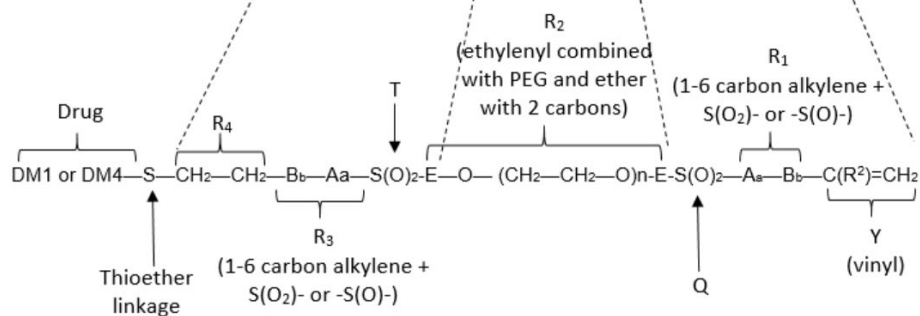
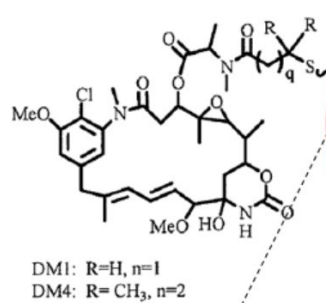
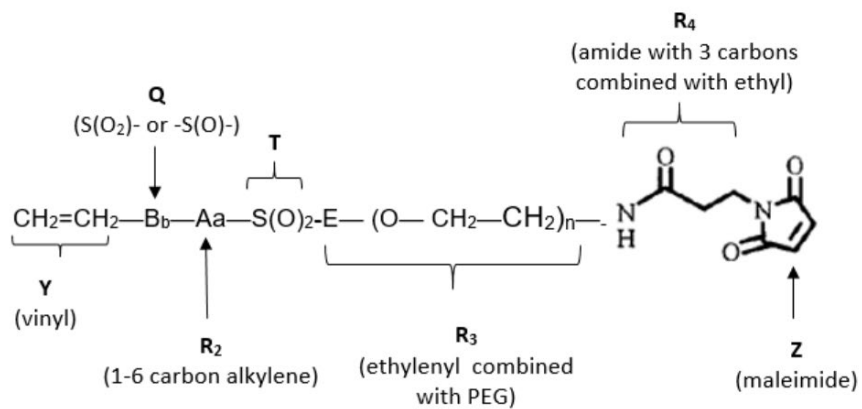
186. As shown in Tables A1 and C2, Singh discloses a bifunctional bis-maleimide PEG crosslinker that can be conjugated to a thiol-bearing maytansinoid drug (DM1 or DM4). A POSA would be motivated to further improve the solubility of ADC linkers that are conjugated to exceptionally hydrophobic drugs like maytansinoids, at high drug loads, where they are prone to aggregation/precipitation. *Supra*, ¶¶63-63, 125-6, 164; see also, EX1050, 2:19-25, 10:20-25, 64:59-67 (disclosing the need to increase hydrophilicity of maleimide ADC linkers and demonstrating the improved efficacy of charged sulfo-maleimide linkers relative to uncharged maleimide linkers). Moreover, sulfones and sulfoxides

were known for their water-soluble properties, as early as 2000. EX1015, 573, 577, 582.

187. As such, a POSA 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 because such substitutions would further enhance the hydrophilicity of the PEG linkers conjugated to exceptionally hydrophobic drugs. A POSA would have had a reasonable expectation of success because bis-vinyl sulfone linkers of Snow would be highly water soluble, and thus show enhanced cytotoxicity when conjugated to a high load of exceptionally hydrophobic drugs. The diagrams below show how the modified linkers match up with claimed linkers. *Id.*

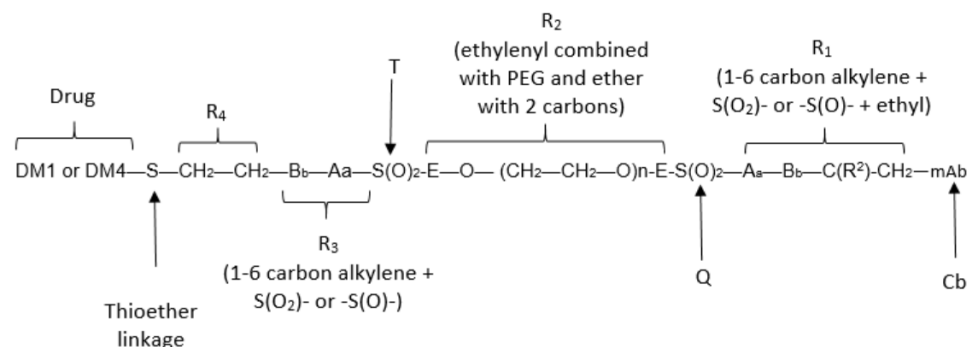


Formula (I)
R₁, R₅, and R₆ = absent



Formula (IV)

Formula (III)



188. Because improving water solubility of ADCs is correlated with enhanced potency and reduced aggregation (see EX1008, ¶¶[0009], [0011], [0221]), a POSA would have had a reasonable expectation of success in combining the disclosure of Singh, Harris and Snow in the manner claimed.

189. Therefore, because the combination of Singh, Harris and Snow discloses all of the elements of claims 2, 25 and 32-34 of the '682 patent, it is my opinion that the claims would have been obvious to a POSA as of November 24, 2012, in view of this prior art.

* * * * *

I hereby declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct, and that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true. I understand that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. § 1001).

Executed on

February 9, 2023

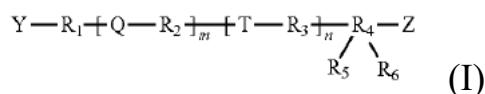


Ravi Chari

APPENDIX

LISTING OF CHALLENGED '682 CLAIMS

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(O₂)-, or -S(O)-;

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

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

R₁, R₂, R₃, and R₄, are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon

atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, 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 $-\text{S}(\text{O})-$, 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

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

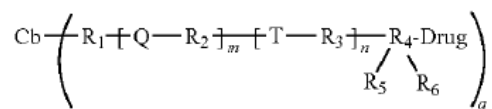
R_5 and R_6 , are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms,

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

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

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

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;

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

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

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

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

among themselves (R_1 , R_2 , R_3 and R_4), provided that when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, R_2 is a straight or branched chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug, R_1 , R_3 or R_4 ;

R_5 and R_6 , are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or $N^+R_1R_2R_3$ or a pharmaceutical salt, provided that: when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, at least one of R_1 , R_2 , R_3 and R_4 comprises the polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, and 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.

4. The conjugate of claim 3, wherein the Drug is selected from the group consisting of 1) therapeutic agents comprising a). Alkylating agents comprising

chlorambucil, chlornaphazine, cyclophosphamide, dacarbazine, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, mannomustine, mitobronitol, melphalan, mitolactol, pipobroman, novembichin, phenesterine, prednimustine, thiotepa, trofosfamide, uracil mustard, CC-1065, adozelesin, carzelesin, bizelesin, duocarmycin, KW-2189, CBI-TMI, pyrrolobenzodiazepine dimers, tomaymycin dimers, indolinobenzodiazepine dimers, imidazobenzothiadiazepine dimers, oxazolidinobenzodiazepine dimers, carmustine, lomustine, chlorozotocin, fotemustine, nimustine, ranimustine, busulfan, treosulfan, improsulfan piposulfan, Triazenes, dacarbazine, carboplatin, cisplatin, oxaliplatin, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate or trimethylolomelamine; b). Plant Alkaloids comprising vincristine, vinblastine, vindesine, vinorelbine, navelbin, paclitaxel, docetaxol, Maytansinoids comprising DM1, DM2, DM3, DM4, DM5, DM6, or DM7, maytansine, ansamitocins, cryptophycin 1, cryptophycin 8, epothilones, eleutherobin, discodermolide, bryostatins, dolostatins, auristatins, tubulysins, cephalostatins, pancratistatin, sarcodictyin A or spongistatin; c). DNA Topoisomerase Inhibitors comprising 9-aminocamptothecin, camptothecin, crisnatol, daunomycin, etoposide, etoposide phosphate, irinotecan, mitoxantrone, novantrone, retinoic acids, retinols, teniposide, topotecan, 9-nitrocamptothecin, or mitomycins; d). Anti-metabolites

comprising methotrexate, trimetrexate, denopterin, pteropterin, aminopterin, mycophenolic acid, tiazofurin, ribavirin, EICAR, hydroxyurea, deferoxamine, ancitabine, azacitidine, 6-azauridine, capecitabine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, 5-Fluorouracil, floxuridine, ratitrexed, cytarabine, cytosine arabinoside, fludarabine, azathioprine, fludarabine, mercaptopurine, thiamiprine, thioguanine, and a folic acid replenisher; e).

Hormonal therapies comprising Receptor antagonists comprising Anti-estrogen selected from the group consisting of megestrol, raloxifene, and tamoxifen; LHRH agonists comprising goserelin, and leuprolide acetate; Anti-androgens comprising bicalutamide, flutamide, calusterone, dromostanolone propionate, epitiostanol, goserelin, leuprolide, mepitiothane, nilutamide, testolactone, and trilostane; f).

Vitamin D3 compounds comprising CB 1093, EB 1089 KH 1060, cholecalciferol, or ergocalciferol; g). Photodynamic therapies comprising verteporfin, phthalocyanine, photo sensitizer Pc4, or demethoxy-hypocrellin A; h). Cytokines comprising Interferon-alpha, Interferon-gamma, tumor necrosis factor (TNFs), or human proteins containing a TNF domain; i). Kinase inhibitors comprising, imatinib, gefitinib, pegaptanib, sorafenib, dasatinib, sunitinib, erlotinib, nilotinib, lapatinib, axitinib, pazopanib, vandetanib, mubritinib, ponatinib, bafetinib, bosutinib, cabozantinib, vismodegib, iniparib, ruxolitinib, CYT387, axitinib, tivozanib, sorafenib, or ispinesib; j). antibiotics comprising calicheamicin

.gamma.1, .delta.1, .alpha.1 or .beta.1, dynemicin A, deoxydynemicin, esperamicin, kedarcidin, C-1027, maduropeptin, neocarzinostatin chromophore, chromoprotein enediyne antibiotic chromomophores, aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabycin, carminomycin, carzinophilin; chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin, deoxydoxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, nitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, or zorubicin; k). Polyketides comprising bullatacin or bullatacinone; gemcitabine, epoxomicins, bortezomib, thalidomide, lenalidomide, pomalidomide, tosedostat, fosbretabulin, vemurafib, gentespib, tecemotide, Isoprenylation inhibitors, Dopaminergic neurotoxins, Cell cycle inhibitors, Actinomycin D, bleomycin A2, bleomycin B2, peplomycin, daunorubicin, adriamycin, idarubicin, epirubicin, pirarubicin, zorubicin, mttoxantrone, MDR inhibitors, Ca^{+2} ATPase inhibitors, Vorinostat, Romidepsin, Panobinostat, Valproic acid, Mocetinostat, Belinostat, PCI-24781, Entinostat, SB939, Resminostat, Givinostat, AR-42, CUDC-101, sulforaphane, Trichostatin A, Celecoxib, glitazones, epigallocatechin gallate, Disulfiram, Salinosporamide A, aminoglutethimide, mitotane, trilostane;

aceglatone, aldophosphamide glycoside; aminolevulinic acid, amsacrine, arabinoside, bestrabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone, eflornithine, elformithine, elliptinium acetate, etoglucid, gallium nitrate, gacytosine, hydroxyurea, ibandronate, lentinan, lonidamine, mitoguazone, mitoxantrone, mopidamol, nitracrine, pentostatin, phenamet, pirarubicin, podophyllinic acid, 2-ethylhydrazide, procarbazine, razoxane, rhizoxin, sizofiran, spirogermanium, tenuazonic acid, triaziquone; 2,2',2''-trichlorotriethylamine, T-2 toxin, verrucarins A, roridin A, anguidine, urethane, siRNA, or antisense drugs; 2). Anti-autoimmune disease agents comprising cyclosporine, cyclosporine A, aminocaproic acid, azathioprine, bromocriptine, chlorambucil, chloroquine, cyclophosphamide, amcinonide, betamethasone, budesonide, hydrocortisone, flunisolide, fluticasone propionate, fluocortolone, danazol, dexamethasone, Triamcinolone acetonide, beclometasone dipropionate, DHEA, enanercept, hydroxychloroquine, meloxicam, methotrexate, mofetil, mycophenylate, prednisone, sirolimus, or tacrolimus; 3). Anti-infectious disease agents comprising amikacin, astromicin, netilmicin, sisomicin, isepamicin, hygromycin B, arbekacin, bekanamycin, dibekacin, tobramycin, framycetin, paromomycin, ribostamycin, spectinomycin, streptomycin, verdamicin, azidamfenicol, chloramphenicol, florfenicol, thiamphenicol, geldanamycin, herbimycin, biapenem, doripenem, ertapenem, imipenem, meropenem, panipenem, carbacephem, cefacetrile, cefaclor,

cefradine, cefadroxil, cefalonium, cefaloridine, cefalotin, cefalothin, cefalexin, cefaloglycin, cefamandole, cefapirin, cefatrizine, cefazaflur, cefazedone, cefazolin, cefbuperazone, cefcapene, cefdaloxime, cefepime, cefminox, cefoxitin, cefprozil, cefroxadine, ceftezole, cefuroxime, cefixime, cefdinir, cefditoren, cefepime, cefetamet, cefmenoxime, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotiam, ceftazidime, cefpodoxime, cefepime, cefpodoxime, cefprozil, cefquinome, cefsulodin, ceftazidime, ceftazidime, ceftibuten, ceftiolene, ceftizoxime, ceftobiprole, ceftriaxone, cefuroxime, cefuzonam, cefotetan, cefmetazole, flomoxef, and latamoxef, bleomycin, vancomycin, teicoplanin, ramoplanin, Glycylcyclines, penam clavam, clindamycin, and lincomycin, daptomycin, A54145, calcium-dependent antibiotics, azithromycin, cethromycin, clarithromycin, dirithromycin, erythromycin, flurithromycin, josamycin, ketolide, midecamycin, miocamycin, oleandomycin, rifamycins, rokitamycin, roxithromycin, spectinomycin, spiramycin, troleandomycin, telithromycin, aztreonam, tigemonam, Oxazolidinones, amoxicillin, ampicillin, azidocillin, azlocillin, benzylpenicillin, benzathine benzylpenicillin, benzathine phenoxymethylpenicillin, clometocillin, procaine benzylpenicillin, carbenicillin, cloxacillin, dicloxacillin, epicillin, flucloxacillin, mecillinam, mezlocillin, meticillin, nafcillin, oxacillin, penamecillin, penicillin, pheneticillin, phenoxymethylpenicillin, piperacillin, propicillin, sulbenicillin,

temocillin, ticarcillin, bacitracin, colistin, polymyxin B, alatrofloxacin, balofloxacin, ciprofloxacin, clinafloxacin, danofloxacin, difloxacin, enoxacin, enrofloxacin, floxin, garenoxacin, gatifloxacin, gemifloxacin, grepafloxacin, kano trovafloxacin, levofloxacin, lomefloxacin, marbofloxacin, moxifloxacin, nadifloxacin, norfloxacin, orbifloxacin, ofloxacin, pefloxacin, trovafloxacin, grepafloxacin, sitafloxacin, sparfloxacin, temafloxacin, tosufloxacin, trovafloxacin, pristnamycin, quinupristin/dalfopristin, mafenide, prontosil, sulfacetamide, sulfamethizole, sulfanilimide, sulfasalazine, sulfisoxazole, trimethoprim, trimethoprim-sulfamethoxazole, Steroid antibacterials, doxycycline, chlortetracycline, clomocycline, demeclocycline, lymecycline, meclocycline, metacycline, minocycline, oxytetracycline, penimepicycline, rolitetracycline, tetracycline, annonacin, arsphenamine, bactoprenol inhibitors, DADAL/AR inhibitors, dictyostatin, discodermolide, eleutherobin, epothilone, ethambutol, etoposide, faropenem, fusidic acid, furazolidone, isoniazid, laulimalide, metronidazole, mupirocin, mycolactone, NAM synthesis inhibitors, nitrofurantoin, paclitaxel, platensimycin, pyrazinamide, rifampin, tazobactam tinidazole, or uvaricin; 4). Anti-viral drugs comprising aplaviroc, maraviroc, vicriviroc, enfuvirtide, PRO 140, raltegravir, elvitegravir, globoidnan A, bevirimat, vivecon, oseltamivir, zanamivir, peramivir, abacavir, aciclovir, adefovir, amdoxovir, apricitabine, brivudine, cidofovir, clevudine, dexelvucitabine, didanosine,

elvucitabine, emtricitabine, entecavir, famciclovir, fluorouracil, 3'-fluoro-2',3'-dideoxythymidine and 3'-fluoro-2',3'-dideoxyguanosine, fomivirsen, ganciclovir, idoxuridine, lamivudine, .beta.-1-thymidine, .beta.-1-2'-deoxycytidine, penciclovir, racivir, stampidine, stavudine, taribavirin, telbivudine, tenofovir, trifluridine valaciclovir, valganciclovir, zalcitabine, zidovudine amantadine, ateviridine, capravirine, diarylpyrimidines, delavirdine, docosanol, emivirine, efavirenz, foscarnet, imiquimod, interferon alfa, loviride, lodenosine, methisazone, nevirapine, NOV-205, peginterferon alfa, podophyllotoxin, rifampicin, rimantadine, resiquimod, tromantadine; amprenavir, atazanavir, boceprevir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, pleconaril, ritonavir, saquinavir, telaprevir, tipranavir, umifenovir, calanolide-a, ceragenin, cyanovirin-n, epigallocatechin gallate, foscarnet, griffithsin, hydroxyurea, KP-1461, miltefosine, pleconaril, ribavirin, or seliciclib; 5). a radioisotopes of ^3H , ^{11}C , ^{14}C , ^{18}F , ^{32}P , ^{35}S , ^{64}Cu , ^{68}Ga , ^{86}Y , ^{99}Tc , ^{111}In , ^{123}I , ^{124}I , ^{125}I , ^{131}I , ^{133}Xe , ^{177}Lu , ^{211}At , or ^{213}Bi ; and 6) the pharmaceutically acceptable salts or acids of any of the above drugs.

5. The conjugate of claim 3, wherein Drug is selected from the group consisting of tubulysins, calicheamicins, auristatins, maytansinoids, CC-1065

compounds, morpholinos doxorubicins, taxanes, cryptophycins, epothilones, and benzodiazepine dimers, siRNA or a combination thereof, and pharmaceutically acceptable salts or acids of any of the above.

6. The conjugate of claim 3, wherein the cell binding agent is selected from the group consisting of antibodies, proteins, vitamins, peptides, polymeric micelles, liposomes, lipoprotein-based drug carriers, nano-particle drug carriers, dendrimers, and combination thereof.

7. The conjugate of claim 3, wherein the cell-binding agent is an antibody, a single chain antibody, an antibody fragment that binds to a target cell, a monoclonal antibody, a single chain monoclonal antibody, or a monoclonal antibody fragment that binds the target cell, a chimeric antibody, a chimeric antibody fragment that binds to the target cell, a domain antibody, a domain antibody fragment that binds to the target cell, a resurfaced antibody, a resurfaced single chain antibody, or a resurfaced antibody fragment that binds to the target cell, a humanized antibody or a resurfaced antibody, a humanized single chain antibody, or a humanized antibody fragment that binds to the target cell, a

lymphokine, a hormone, a vitamin, a growth factor, a colony stimulating factor, or a nutrient-transport molecule.

8. The conjugate of claim 3, wherein the drug is selected from the group consisting of a toxin, a chemotherapeutic agent, a drug moiety, an antibiotic, a radioactive isotope, and a nucleolytic enzyme.

9. The conjugate of claim 3, wherein the conjugate comprises one or more linker components of 6-maleimidocaproyl, 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.

10. The conjugate of claim 3, wherein Drug is selected from the group consisting of tubulysins, maytansinoids, taxanoids, CC-1065 compounds, daunorubicin and doxorubicin compounds, benzodiazepine dimers, calicheamicins and the enediyne antibiotics, actinomycin, azaserines, bleomycins, epirubicin,

tamoxifen, idarubicin, dolastatins/auristatins, duocarmycins, thiotepa, vincristine, hemiasterlins, and esperamicins.

11. The conjugate of claim 3, having in vitro, in vivo or ex vivo cell killing activity.

12. The conjugate of claim 3, wherein the conjugate comprises either a peptide of 1-20 units of natural or unnatural amino acids, or a p-aminobenzyl unit, or a 6-maleimidocaproyl unit, or a disulfide unit, or a thioether unit, or a hydrozone unit, or an alkoxime unit

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

14. The conjugate of claim 3, wherein the drug is derived from a drug containing a --SH, --CONHNH₂, --≡, --COR" or --NHR", wherein R" is H, CH₃, Et, Pr, Bu, or Ph; and/or the cell-binding agent is an antibody or protein.

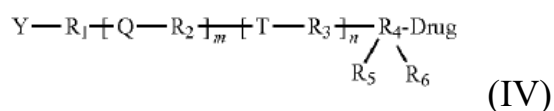
15. A pharmaceutical composition comprising a therapeutically effective amount of the conjugate of claim 3, and a pharmaceutically acceptable salt, carrier, diluent, or excipient therefor.

16. A pharmaceutical composition comprising the conjugate of claim 3, and a pharmaceutically acceptable carrier.

17. A pharmaceutical composition comprising a therapeutically effective amount of the conjugate of claim 3, and a chemotherapeutic agent, radiation therapy agent, immunotherapy agent, autoimmune disorder agent, or anti-infectious agent.

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 $-P(=O)(OM)-$, or $-S(O_2)-$, or $-S(O)-$;

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

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

R_1 , R_2 , R_3 , and R_4 , are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, 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 $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof,

or

R_1 , R_2 , R_3 and R_4 are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4), provided that when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, R_2 is a straight or branched chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug, R_1 , R_3 or R_4 ;

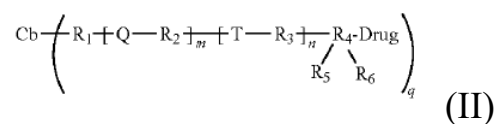
R_5 and R_6 , are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or $N^+R_1R_2R_3$ or a pharmaceutical salt, provided that: when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, at least one of R_1 , R_2 , R_3 and R_4 comprises the polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, and 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.

21. The conjugate of claim 20, wherein the drug is derived from a drug containing a --SH, --CONHNH₂, --≡, --COR" or --NHR", wherein R" is H, CH₃, Et, Pr, Bu, or Ph; and/or the cell-binding agent is an antibody or protein.

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



wherein:

Cb represents a cell-binding agent;

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

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

m and n are integers from 1 to 5;

R_1 , R_2 , R_3 , and R_4 , are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, 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 $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof,

or

R_1 , R_2 , R_3 and R_4 are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4), provided that when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, R_2 is a straight or branched chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently

connects a cell-surface binding ligand, a phosphinate, or sulfonyl group, a conjugated drug, R_1 , R_3 or R_4 ,

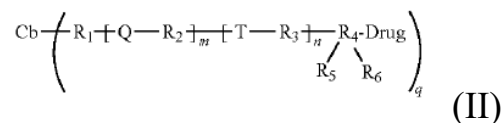
provided that when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, at least one of R_1 , R_2 , R_3 and R_4 comprises the polyethyleneoxy unit of formula $(OCH_2CH_2)_p$,

R_5 and R_6 are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

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

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

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



wherein:

Cb represents a cell-binding agent;

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

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

m and n are integers from 1 to 5;

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

polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof

or

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

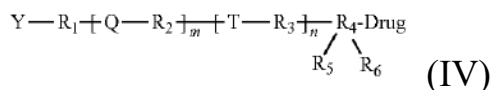
R_5 and R_6 , are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$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

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

provided that when Q and T are each independently -S(O₂)- or -S(O)-, m is 1 and n is 1, R₂ is absent, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof or

R₂ is a branched chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug, R₃ or R₄.

29. A compound of formula (IV):



wherein:

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

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

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

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

R_1 , R_2 , R_3 , and R_4 , are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof provided that when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, 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 $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof

or

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

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

R₅ and R₆, are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula (OCH₂CH₂)_p wherein p is an integer from 1 to about 1000, or combination thereof

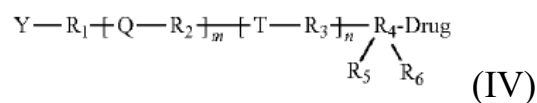
M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt,
provided that:

when Q and T are each independently -S(O₂)- or -S(O)-, m is 1 and n is 1, R₂ is absent, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof or

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

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

30. A compound of formula (IV):



wherein:

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

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

m and n are integers from 1 to 5;

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

R₁, R₂, R₃, and R₄, are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon

atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, 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 $-\text{S}(\text{O})-$, 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

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

R_5 and R_6 , are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms,

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

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

provided that when Q and T are each independently $-\text{S}(\text{O}_2)-$ or $-\text{S}(\text{O})-$, m is 1 and n is 1, R_2 is absent, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof or

R_2 is a branched chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug, R_3 or R_4 .

31. The compound of claim 30, wherein when Q and T are each independently $-\text{S}(\text{O}_2)-$ or $-\text{S}(\text{O})-$, at least one of R_1 , R_2 , R_3 and R_4 comprises the polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$.

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

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

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