

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SYNAFFIX B.V.,
Petitioner,

v.

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

IPR2022-01531
Patent No 10,131,682

**DECLARATION OF DR. LAWRENCE NATHAN TUMEY
IN SUPPORT OF PATENT OWNER'S SUR-REPLY**

I, Lawrence Nathan Tumey, Ph.D., declare as follows:

I. INTRODUCTION

1. I have been asked to provide my expert opinion regarding Petitioner's arguments in their Reply Brief and Dr. Chari's second expert declaration (EX1076) concerning whether vinyl alone can serve as a functional group that enables reaction with cell-binding agents (CBAs) in the context of the '682 patent to support Petitioner's Ground 1. In my opinion, Petitioner's new reference, Dondoni (EX1064), does not demonstrate that vinyl alone can independently enable reaction with a CBA under physiologically acceptable conditions as required by the '682 patent. Rather, the reaction described in Dondoni requires additional activation via UV light and a photoinitiator (DPAP), confirming that vinyl alone is not independently reactive.

2. Furthermore, a person of ordinary skill in the art (POSA) would not have considered applying Dondoni's photoinduced thiol-ene coupling (TEC) reaction to Morales-Sanfrutos' vinyl sulfone chemistry due to fundamental differences in reaction mechanisms, reaction conditions, structural differences in the compounds, and potential for undesired side reactions. As Dr. Chari stated in his first and second depositions, in a Michael addition reaction between a vinyl sulfone and a thiol or amino group from a CBA, the functional group that enables the reaction is the vinyl sulfone, not vinyl alone. EX2037 at 20:17-21, 21:17-22:9, 52:5-

53:1; EX2046 at 18:16-20:18. Dondoni's photoinduced TEC reaction does not change the fundamental fact that the functional group that enables the Michael addition reaction described in Morales-Sanfrutos is vinyl sulfone, not vinyl alone.

3. My qualifications and professional experience are described in my curriculum vitae, copies of which were provided previously as EX2002 and EX2038 (Appendix B). I also included a summary of my qualifications and professional experience in my May 26, 2023 declaration (EX2001 at ¶¶ 6-13) and December 6, 2024 declaration (EX2038 at ¶¶ 6-13).

II. MATERIALS CONSIDERED

4. The opinions contained in this Declaration are based on the documents I reviewed, as well as my education, years of professional experience, and knowledge. In forming my opinions expressed in this Declaration, I have reviewed and considered the materials set forth in my first two declarations (*e.g.*, EX2001 at ¶¶ 14-16 and EX2038 at ¶¶ 14-16) as well as the following additional documents:

- Petitioner's Reply Brief (Paper 36);
- Second Declaration of Dr. Ravi Chari (EX1076);
- Transcript of the April 16, 2025 deposition of Dr. Ravi Chari (EX2046); and
- Dondoni *et al.*, *Chem. Eur. J.* 15, 11444–11449 (2009) ("Dondoni") (EX1064).

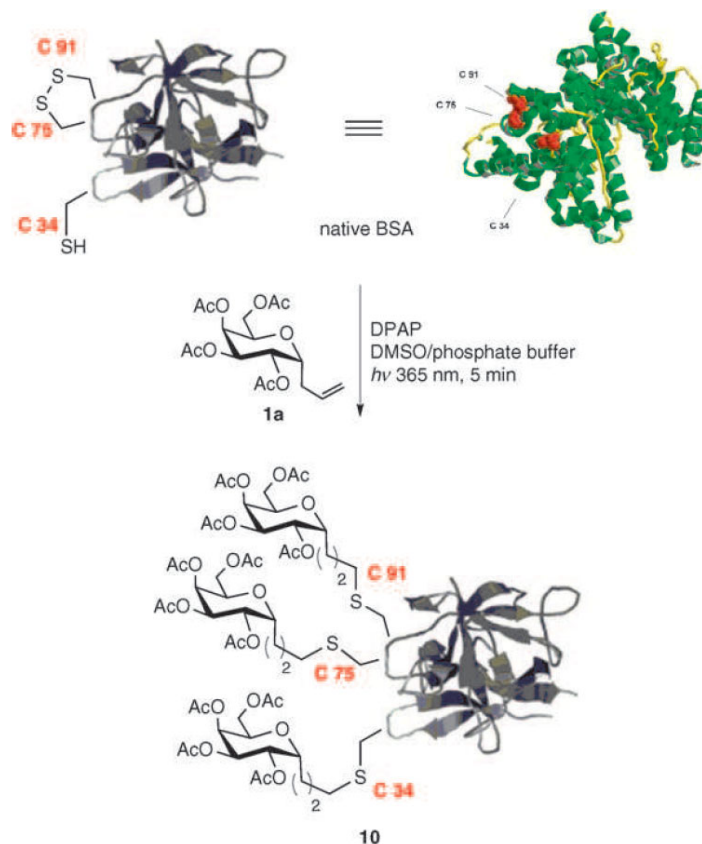
III. RESPONSE TO SYNAFFIX'S NEW REFERENCE

5. Dondoni (EX1064) is an article authored by Dondoni *et al.*, published in *Chemistry – A European Journal* (2009), and titled “A New Ligation Strategy for Peptide and Protein Glycosylation: Photoinduced Thiol-Ene Coupling.”

6. Dondoni states that it developed a new “ligation strategy that allows performing [a] glycopeptide and glycoprotein assembly in a site specific manner” through “[a] photoinduced coupling of an alkenyl C-glycoside with a peptide or protein containing a free sulfhydryl group.” EX1064 at 1. Dondoni reports that the “goal of this study comprised the glycosylation of a cysteine residue embedded in a protein.” EX1064 at 4. Glycosylation of a protein means the attachment of one or more sugar molecules to specific amino acid residues on a protein.

7. Dondoni reacts bovine serum albumin (“BSA”) with a “sugar alkene” compound (compound **1a**), via photoinduced coupling. EX1064 at 4 (Scheme 3). BSA was “known to contain one free cysteine residue at position 34.” *Id.* The terminal alkene (or vinyl) group of compound **1a** is connected to a simple acetyl-substituted sugar via a methylene (–CH₂–) bridge. Dondoni states that the reaction took place in the presence of DPAP, DMSO/pH 7.4 phosphate buffer, and irradiation by UV light having a wavelength of 365 nm for 5 min to 1 hour. *Id.* at 4-5. DPAP is “2,2-dimethoxy-2-phenyl-acetophenone” and serves as a “sensitizer” or “photoinitiator” for the photoinduced thiol-ene coupling reaction between BSA and

compound **1a**. EX1064 at 2. Dondoni reports that under these conditions, irradiation of BSA and compound **1a** resulted in the BSA glycoconjugate **10** after 1 hour where three galactoside residues were introduced at cysteine residues at positions 34, 75, and 91, as shown in Scheme 3. EX1064 at 4. Dondoni verified this result using MALDI-TOF analysis, which revealed peaks corresponding to masses for native BSA and glycosylated BSA **10**, with “a shift corresponding to the addition of three molecules of galactoside **1a** per protein (Figure 2).” *Id.*



Scheme 3. Preparation of BSA glycoconjugate **10**.

8. Dondoni reports that BSA glycosylation via photoinduced TEC involved more than just the expected Cys-34 residue. Tryptic digestion of the

glycosylated BSA (compound **10**) followed by ESI-QTOF MS/MS analysis revealed glycosylation occurred at both Cys-34 and Cys-75, with a third glycosylation site remaining undetermined by the ESI-QTOF MS/MS analysis. EX1064 at 4. Dondoni determined that UV irradiation caused an unexpected photocleavage of the 75↔91 disulfide bridge in BSA, likely through an electron transfer process from photoexcited tryptophan residues to nearby cysteine S-S bonds. *Id.*; *see also id.* at 5 (“Very likely, disulfide bond cleavage was due to an electron transfer process from photoexcited tryptophan residues.”). This electron transfer created additional reactive thiol groups at previously disulfide-linked cysteines, allowing for attachment of more galactoside units than initially expected.

9. Dondoni reports that extended irradiation by UV light (2 hours) resulted in seven glycoside residues being incorporated into the BSA protein, further supporting the observed hyperglycosylation mechanism through reactions with additional reactive thiol groups after extended UV irradiation. EX1064 at 4. Dondoni describes its efforts to “identif[y] a reaction window for selective Cys-34 glycosylation ... by considering shorter irradiation times (45, 30, 15, 5, 3, 2, 1, 0.5 min) and/or aerobic conditions.” *Id.* Dondoni reports that “[u]nfortunately, this goal could not be achieved by these experiments.” *Id.* at 4-5. Dondoni reports that BSA glycoconjugate **10** (with three galactoside residues added to BSA) could be synthesized “under aerobic conditions in five minutes.” *Id.* at 5. Dondoni reports,

however, that with irradiation times shorter than five minutes, “no glycosylation took place” as “intact BSA was detected by MALDA-TOF analysis.” *Id.* at 5. Thus, Dondoni was unable to selectively glycosylate Cys-34 as the experiments provided either BSA glycoconjugate **10** with three galactoside residues, or no glycosylation.

10. Dondoni does not report whether BSA retained its protein structure or folding after the photoinduced TEC reaction described in Scheme 3. Dondoni also does not report on whether the modified BSA retained its biological activity after the photoinduced reaction. While Dondoni states that they were seeking “non-denaturing reaction media” for the protein glycosylation, that referred to the use of “an aqueous solution at physiological pH eventually diluted with salts”; in other words, the use of the DMSO/pH 7.4 phosphate buffer. EX1064 at 3. As noted, Dondoni observes that UV light irradiation caused cleavage of disulfide-linked cysteines to provide additional reactive thiol groups in BSA. EX1064 at 4. Further, exposure of BSA to UV irradiation for up to 2 hours caused seven reactive sites to become glycosylated. *Id.*

11. The cleavage of disulfide bridges typically causes significant structural changes in proteins. Disulfide bonds are covalent linkages formed between the thiol groups of cysteine residues, and they play crucial roles in stabilizing protein tertiary structure. When disulfide bridges are cleaved local rigidity is lost, the protein often becomes more flexible and can undergo partial unfolding, hydrophobic regions that

were previously buried in the protein core may become exposed, secondary structure elements can be destabilized, and enzymatic activity may be altered.

12. BSA contains 17 interchain disulfide bridges and 1 free sulfhydryl group (at Cys-34) that remains unbound at pH 5-7. These disulfide bonds form the structural framework that maintains the protein's three-dimensional conformation. The formation of these disulfide bonds between correct pairs of cysteine residues is essential for BSA's proper folding, activity, and stability. They play crucial roles in determining protein functionality, including foaming, gelling, and emulsifying properties in various systems.

IV. VINYL ALONE IS NOT A FUNCTIONAL GROUP THAT ENABLES REACTION WITH A CBA IN MORALES-SANFRUTOS

13. As I explained in my prior declaration, Morales-Sanfrutos states that the vinyl sulfone group (not vinyl alone) is the reactive functional group that enables reaction of the compounds disclosed therein with horseradish peroxidase (HRP). *See, e.g.*, EX2038 at ¶¶ 161-162, 164; *see also id.* at ¶ 80. Morales Sanfrutos does this via what is often referred to in the art (and as Morales-Sanfrutos also states) as a Michael-type addition reaction or Michael addition reaction. EX1005 at 1, 2, 6.

14. As I explained, in the context of a Michael addition reaction, as an electron withdrawing group, the sulfonyl pulls electrons away from the vinyl group towards its oxygen atoms, leaving the vinyl (i.e., a terminal alkene) destabilized and attracted to a nucleophilic substituent (electron donor) that can contribute electrons

to fill this void, such as an endogenous amino acid residue bearing an amino or thiol group. EX2038 at ¶ 80. Thus, when a protein undergoes a reaction with a linker bearing vinyl sulfone as a conjugation moiety, the electrons from nucleophilic group on the protein (an amino or thiol group) will be attracted to the destabilized vinyl and facilitate the conversion of the vinyl (C=C) into an ethylene (C-C), thereby creating a new covalent bond between the terminal carbon on the linker and the nucleophilic group on the protein. *Id.* It is important to reiterate that it is the vinyl sulfone as a whole that enables the conjugation reaction because it is specifically reactive with endogenous amino acids on a protein or protein fragment. *Id.* If the vinyl is not directly bonded to a strong electron withdrawing group, such as sulfonyl, then it is not reactive as a conjugation moiety to enable the reaction.

15. Dr. Chari agrees. *See* EX2037 at 19:15-22:9, 48:6-49:12, 52:5-53:1. Dr. Chari previously stated that vinyl alone cannot enable reaction of a linker with a cell-binding agent. EX2038 at ¶ 65 (citing EX2037 at 20:17-21, 52:5-53:1). He explained that the sulfone part of the vinyl sulfone enables the reaction. *Id.* (EX2037 at 21:17-22:9; 52:16-53:1). Dr. Chari appears to still agree with me that vinyl alone cannot enable reaction of a linker to a cell binding agent. He now seems to limit this opinion to the context of a Michael-addition reaction. EX1076 at ¶ 6 (stating “While I testified in my first deposition that vinyl alone will not react without assistance

from an adjacent sulfone group, I was focused at that time specifically on the Michael-type addition reaction.”); *see also* EX2046 at 18:2-20:18.

16. Morales-Sanfrutos does not disclose any chemical group other than vinyl sulfone as a functional group that enables reaction with HRP, and Dr. Chari has not identified any chemical group other than vinyl sulfone that enables reaction with HRP in Morales-Sanfrutos. EX2037 at 19:15-22:9, 48:6-49:12, 52:5-53:1; EX2046 at 18:2-20:18. Morales-Sanfrutos also does not disclose any other reaction scheme for a vinyl group other than a Michael-addition reaction. Therefore, as I have previously stated, a POSA would understand Morales-Sanfrutos to teach vinyl sulfone (not vinyl alone) as a functional group that enables reaction with HRP and would not have understood that vinyl alone in Morales-Sanfrutos would be able to do so. Dr. Chari does not appear to dispute this. EX2046 at 18:2-20:18. As I have previously stated, the vinyl sulfone functional group is intrinsically reactive to enable reaction with HRP. Dr. Chari agrees that the Michael addition reaction of Morales-Sanfrutos only involved mixing the vinyl sulfone containing compound with HRP in an aqueous buffer for the reaction to proceed. EX2046 at 20:19-23.

17. Dr. Chari appears to also suggest that the reaction conditions used for the Michael addition reaction in Morales-Sanfrutos of pH 8.5 and 37 °C were higher than normal pH and temperature, and that the reaction was “base” catalyzed. EX2046 at 20:19-23:18. I disagree. The Michael addition reaction of Morales-

Sanfrutos in an aqueous buffer of pH 8.5 at 37 °C is a common condition for preparing cell-binding conjugates in aqueous environments. The Michael addition reaction of Morales-Sanfrutos between vinyl sulfone and HRP does not require any chemical catalyst, such as a copper catalyst required for coupling an azide group to a terminal alkyne group, which is being regenerated or recycled during the reaction. In the basic aqueous buffer of Morales-Sanfrutos, the thiol group is deprotonated to make it nucleophilic for reacting with the electrophilic vinyl in the vinyl sulfone functional group.

18. Dr. Chari states that outside the context of a Michael-addition reaction (and thus, outside the context of Morales-Sanfrutos), that “vinyl alone can serve as a functional group that can link to cell-binding agents (CBAs).”¹ See EX1076 at ¶¶ 6, 8-9. Dr. Chari specifically points to Scheme 3 of Dondoni to support his statement. See EX2046 at 27:17-28:13.

19. I disagree with Dr. Chari that Dondoni and, in particular, Scheme 3 demonstrate that vinyl alone can serve as a functional group that enables reaction

¹ While Dr. Chari states that “there are in fact other reaction schemes where vinyl alone can serve as a functional group . . . ,” EX1076 at ¶ 6, I note that he only provided one example from Dondoni (i.e., Scheme 3) in support of his statement. See EX2046 at 27:17-28:13.

with cell-binding agents in the context of the '682 patent. Scheme 3 of Dondoni does not demonstrate that vinyl alone can independently enable reaction with a CBA in the context of the '682 patent. As I explained above, Scheme 3 illustrates how the photoinduced TEC reaction works to glycosylate BSA. The reaction specifically requires both UV light ($h\nu$ 365 nm) and the photoinitiator DPAP² to proceed, creating a radical-mediated coupling between the free thiol group from cysteine residues in BSA and the vinyl group of compound **1a**. In Dondoni, both the light activation and the photoinitiator are essential components for the reaction to proceed, as they generate the thiyl radical that adds to the vinyl group. EX1064 at 2 (Scheme 1); EX2046 at 32:8-19, 39:2-15.

² The role of DPAP in the photoinduced thiol-ene reaction is to absorb light energy at 365 nm wavelength; generate reactive radical species when exposed to this light; and initiated the radical-mediated thiol-ene coupling process. When DPAP absorbs UV light, it undergoes homolytic cleavage to form phosphinoyl and benzoyl radicals. These radicals then remove hydrogen from the thiol groups in BSA (like the free cysteine at position 34), creating thiyl radicals. These thiyl radicals subsequently attack the carbon-carbon double bond of the vinyl group of compound **1a**, forming a carbon-centered radical that then removes hydrogen from another thiol group, propagating the reaction chain. *See, e.g.*, EX1064 at 2 (Scheme 1).

20. Without DPAP or an alternative photoinitiator, the reaction with BSA would not proceed under the conditions of Scheme 3. Without DPAP (or an alternative photoinitiator), there is no functional group that can absorb the energy from the 365 nm wavelength UV light—thus preventing the formation of free radicals and the subsequent reaction. Without a photoinitiator, the reaction rates would be extremely slow (if they occur at all) and the yields would be negligible for practical purposes.³ Dr. Chari admits that without the UV light the vinyl group in

³ Although Dr. Chari admits that he has not used DPAP himself, EX2046 at 38:18-39:1, he appears to question whether the photoinitiator DPAP is necessary for the reaction described in Scheme 3 of Dondoni. *See id.* at 32:20-34:1. Dondoni reports a reaction of compound **1a** with compound **2** (*N*-Fmoc cysteine, an amino acid) under various conditions (Table 1 of Dondoni) including in the presence of 5 mol% of DPAP and 365 nm UV light that “resulted in a low conversion of **1a** (75%, entry 9 [of Table 1]).” EX1064 at 2. Regarding this reaction, which involves a different starting material (compound **2**, not BSA), Dr. Chari states that 75% “is pretty high yield for a reaction chemistry.” EX2046 at 34:22-35:21. But as shown in Table 1 of Dondoni, the “75%” is the “conversion” rate estimated from the crude reaction mixtures, and the actual yield is “56%” for entry 9. EX1064 at 2 (Table 2). Entry 4 of the same table shows that a reaction with 10 mol% of DPAP and 365 nm

compound **1a** would not react with BSA. EX2046 at 39:2-15. The photoinitiator is specifically designed to efficiently absorb the UV radiation and generate the necessary radical species to start and propagate the radical-mediated reaction chain. Thus, Scheme 3 of Dondoni does not demonstrate that vinyl alone can independently enable reaction with a CBA given that the reaction requires both UV light and DPAP to generate the free radicals required to enable the reaction—vinyl alone cannot do that.

21. As I explained previously, in order for a functional group to be mapped to the “Y” group in the context of the ’682 patent, the functional group must independently enable reaction with a CBA. The ’682 patent provides examples of “Y” groups that are independently sufficient for reactivity with a CBA under physiological conditions (*e.g.*, pH 6.5-8.5, aqueous buffers, about 20-25 °C to about 37 °C). Like the vinyl sulfone functional group in the compounds of Morales-Sanfrutos, none examples of “Y” in the ’682 patent require a catalyst (*e.g.*, a copper catalyst required for reacting an azide with a terminal alkyne) or additional reagents

UV light provided a “>95%” conversion rate and a “78%” yield (*id.*), which are significantly higher than those reported for entry 9. This shows DPAP has a critical role in the photoinduced reaction of Dondoni. As the authors of Dondoni stated, “the amount of sensitizer was key to reaction efficiency.” EX1064 at 2.

(*e.g.*, the UV and DPAP required for the photoinduced reaction of Dondoni) to react with a CBA. The specification provides examples of “Y” functional groups that possess this intrinsic reactivity, such as N-hydroxysuccinimide esters, p-nitrophenyl esters, dinitrophenyl esters, pentafluorophenyl esters, pyridyldisulfides, nitropyridyldisulfides, maleimides, haloacetates, carboxylic acid chloride, hydrazide and hydroxylamine. *See* EX1001 at 8:61-67, 13:54-60. In each of these cases, as I stated, the Y group is independently sufficient for reactivity with the CBA under physiological conditions. EX2038 at ¶ 64; EX1063 at 15:11-16:18, 18:7-21. In contrast, the ’682 patent when discussing the “Z” functional group includes examples of both functional groups that independently enable reaction with and linkage to a cytotoxic drug under physiological conditions (such as maleimido and haloacetyl), and functional groups that require additional activation (*e.g.*, a catalyst or chemical reagent) for a reaction to take place (such as amino, carboxy, aldehydes, and hydroxy). EX1001 at 9:1-7.

22. Contrary to Dr. Chari’s statements with respect to Dondoni, Scheme 3 of Dondoni instead demonstrates that the vinyl group (like the vinyl in Morales-Sanfrutos) needs to be activated for the reaction to occur and, therefore, does not serve as a functional group that independently enables reaction with a CBA. In Morales-Sanfrutos’ Scheme 4, the vinyl sulfone group serves as an electrophilic reactive functional group that enables conjugation under physiological conditions

without additional reagents or catalysts. In the vinyl sulfone functional group, the sulfone withdraws electrons from the adjacent vinyl, making it highly susceptible to nucleophilic attack by thiols or amines in a Michael-type addition reaction. As such, the entire vinyl sulfone group is the functional group that enables the reaction in Morales-Sanfrutos. In Dondoni's Scheme 3, the DPAP photoinitiator and UV light serve as the activation system that triggers the TEC reaction. When exposed to UV light at 365 nm, DPAP generates radicals that interact with thiol groups, creating thiyl radicals that then attack the terminal alkene bond (vinyl) in a radical chain mechanism. In both cases, these components play crucial roles as reaction activators, though they operate through fundamentally different mechanisms—the sulfone moiety that is part of the vinyl sulfone functional group provides continuous electronic activation through an ionic pathway, while the DPAP/UV system provides temporal control of activation through a radical pathway.

23. Dr. Chari then states that a POSA would understand that using Dondoni's reaction conditions with Morales-Sanfrutos' vinyl-containing compounds (1, 2(a), 2(b), 4(a), and 5(a)) would enable reaction with thiol groups in HRP or other CBAs under physiologically acceptable conditions. EX1076 at ¶¶ 9-10. He then concludes that this would satisfy the claim limitation for element "Y" even under the construction of "Y" I set forth previously. *Id.* I disagree.

24. As an initial matter, other than stating so, Dr. Chari does not explain why a POSA would have an understanding that “using Dondoni’s reaction conditions with Morales-Sanfrutos’ vinyl-containing compounds (1, 2(a), 2(b), 4(a), and 5(a)) would enable reaction with thiol groups in HRP or other CBAs under physiologically acceptable conditions.” EX1076 at ¶ 10. Nonetheless, it is my opinion that a POSA would not have understood or considered applying the photoinduced TEC reaction scheme from Dondoni to the vinyl sulfone reaction scheme in Morales-Sanfrutos for several reasons.

25. First, the two papers set forth fundamentally different reaction mechanisms and conditions that don’t allow for simple substitutability in any way. The vinyl sulfone in Morales-Sanfrutos’ approach undergoes a nucleophilic Michael-type addition, where the electron-withdrawing sulfone group activates the double bond toward nucleophilic attack by thiols or amines through an ionic pathway under mild conditions without additional chemical reagents or catalysts. As Dr. Chari agrees, this reaction does not require UV light. EX2046 at 26:17-19. In contrast, Dondoni’s TEC reaction proceeds through a radical mechanism initiated by UV irradiation (365 nm) of a photoinitiator (DPAP), which generates thiyl radicals that add to unactivated terminal carbon-carbon double bonds. This photoinduced reaction requires specific conditions (UV light, photoinitiator). While both reactions form stable thioether linkages, they differ significantly in at least their

initiation requirements, reagents, and reaction conditions. EX2046 at 27:8-16, 54:15-23.

26. Second, compounds 1, 2(a), 2(b), 4(a), and 5(a) of Morales-Sanfrutos, on which Dr. Chari relied for analyzing claim 1 under Ground 1 (EX2046 at 55:6-9), are structurally different from compound **1a** in Scheme 3 of Dondoni. Morales Sanfrutos uses complex bifunctional tags that contain additional functional groups that are not found in compound **1a** of Dondoni, which is a simple allyl glycoside. EX2046 at 39:16-19. Indeed, Dr. Chari agreed that these compounds contained additional functional groups besides vinyl sulfone including, for example, an additional vinyl sulfone (compound 1), an alkyne group (compound 2), an alkyne and a fluorophore (compounds 4 and 5). EX2046 at 30:11-31:12; 55:10-57:8. Dr. Chari did not cite to any reference nor provide any explanation as to how the application of photoinduced TEC reaction would impact the compounds of Morales-Sanfrutos that contain these additional functional groups. *Id.*

27. Third, as explained above, Dondoni shows that photoinduced TEC with BSA led to unexpected side reactions such as cleavage of disulfide bonds in proteins; formation of multiple glycosylation sites beyond the target cysteine; and potential damage to protein structure due to UV irradiation and/or disulfide bond cleavage. Dr. Chari agrees that the photoinduced reaction of Dondoni caused disulfide bond cleavage in BSA and the introduction of three (not just one) galactoside residues.

EX2046 at 40:6-15, 41:8-10, 50:4-14. Dr. Chari further agrees that, despite trying different conditions, Dondoni failed to selectively add only one galactoside residue to the BSA without causing disulfide cleavage. EX2046 at 51:15-54:1. A POSA would recognize these issues as significant drawbacks for applying this method to the labeling studies of Morales-Sanfrutos given that HRP has at least four disulfide bonds. In addition, HRP is a heme-containing protein and its aromatic heme moiety absorbs 365 nm wavelength UV light, which will interfere with the photoinduced TEC reaction of Dondoni. Moreover, the photoactivated heme in the HRP could potentially damage or denature the HRP protein. Dr. Chari admits that he does not know whether or not the photoinduced TEC of Dondoni would cause disulfide bond cleavage in HRP or denature the HRP protein. EX2046 at 54:2-14. A POSA would not have found Dondoni to be relevant or applicable to Morales-Sanfrutos.

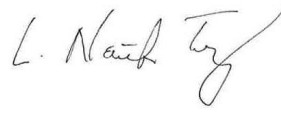
28. Fourth, and finally, Dr. Chari has not identified any reason why a POSA would have used the photoinduced TEC reaction of Dondoni for the compounds disclosed in Morales-Sanfrutos given that Morales-Sanfrutos specifically presents vinyl sulfone chemistry as advantageous. Substituting photoinduced TEC would undermine the stated advantages in Morales-Sanfrutos without providing any clear benefit.

V. CONCLUSION

29. In signing this Declaration, I recognize that the Declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross-examination in the case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States either in person or virtually during the time allotted for cross-examination.

I declare under penalty of perjury under the laws of the State of New York that the foregoing is true and correct to the best of my knowledge.

Executed on this 25th day of April, 2025, at Binghamton, New York.

A handwritten signature in black ink, appearing to read "L. Nathan Tumey", with a stylized flourish at the end.

Dr. L. Nathan Tumey