

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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HANGSEN INTERNATIONAL GROUP LTD.,

Petitioner

v.

ZANOPRIMA LIFESCIENCES, LTD.,

Patent Owner.

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IPR2023-\_\_\_\_\_

U.S. Patent No. 10,913,962

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**DECLARATION OF JEFFREY D. WINKLER, PH.D.**

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I, Jeffrey D. Winkler, declare as follows:

**I. INTRODUCTION**

1. I have been retained by Hangsen International Group Ltd. (“Hangsen”) to opine as an expert in connection with their Petition for *Inter Partes* Review challenging the validity of claims 1-14 of U.S. Patent No. 10,913,962 (Ex. 1001, the “’962 Patent”).

2. I am being compensated at my usual consulting rate of \$850 per hour for my analysis in this matter. I will also be reimbursed for reasonable and customary expenses. Should I sit for deposition or otherwise offer live testimony, I will be compensated at a rate of \$10,000 per day. My compensation does not depend on the outcome of this proceeding or any co-pending proceeding. I have no financial interest in the outcome of this proceeding.

3. I have been asked to provide opinions regarding whether the claims of the ’962 Patent are patentable over the prior art. I have also been asked to provide opinions regarding the meaning of the claim terms “enzyme capable of reducing an imine group to form more (S)-nornicotine than (R)-nornicotine” and “wherein the (S)-nicotine is obtained with an enantiomeric excess of at least 90%, either with or without a step of separating (S)-nicotine from (R)-nicotine.” I understand that this declaration, which reflects my opinions and experience, will be used in support of Hangsen’s Petition for *inter partes* review of the ’962 Patent.

4. This declaration is based on the information currently available to me. The opinions set forth in this declaration are based on my personal knowledge and experience, my professional judgment, and my analysis of the materials and information referenced in this declaration and its exhibits. Certain of my opinions are rendered from the perspective of a person of ordinary skill in the art (“POSITA”), which I discuss in more detail below.

## **II. REVIEW AND USE OF DOCUMENTS AND OTHER MATERIALS**

5. To familiarize myself with the facts of this case and to formulate my opinions, I reviewed the ’962 Patent and its file history. I also considered U.S. Patent No. 8,367,837 (Ex. 1003, “Divi”); Tom Moody, “Biocatalysis: Genes to GMP,” *Speciality Chemicals Magazine*, pp. 12-14 (January 2016) (Ex. 1004, “Moody”); *Enzymicals*, 2017 Portfolio (Ex. 1006, “Enzymicals”); U.S. Patent No. 9,556,142 (Ex. 1008, “Arnold”); Dennis Wetzl et al., “Expanding the Imine Reductase Toolbox by Exploring the Bacterial Protein-Sequence Space,” *ChemBioChem* 2015, 16, 1749-1756 (Ex. 1009, “Wetzl”); Stefan Velikogne et al., “Sequence-Based *In-silico* Discovery, Characterization, and Biocatalytic Application of a Set of Imine Reductases,” *ChemCatChem* 2018, 10, 3236-3246 (Ex. 1011, “Velikogne”); International Patent Application Publication WO 2014/174505 (Ex. 1013, “Sheldon”); “Chemical and physical basics of routine formaldehyde fixation,” *J. of Oral and Maxillofacial Pathology*, Vol. 16, Issue 3, pp. 400-405 (Sep. – Dec. 2012) (Ex. 1016); the dictionary definition of

“polyoxymethylene” from the *McGraw-Hill Dictionary of Scientific and Technical Terms* (Ex. 1017); and the dictionary definition of “excipient” from *McGraw-Hill Dictionary of Scientific and Technical Terms* (Ex. 1018).

6. I have also relied on my education, experience, and knowledge of practices and principles in the field of organic synthesis and in the use of enzymes in chemical reactions, as well as my understanding of the applicable legal principles described below.

7. At deposition, or if called to testify at any hearing in this proceeding, I may rely on any documents and things produced by the parties in this action, papers submitted by the parties in this action, any expert testimony offered to support any position, and publicly available materials.

8. I may also rely on visual aids or demonstrative exhibits to demonstrate the basis of my opinions, including patent drawings, diagrams, and other graphical presentations describing the disclosures in the '962 Patent, as well as prior-art designs, operations, reactions, and functions.

9. To the extent not listed above, I have also considered all items referenced in this declaration. I reserve the right to supplement this declaration to address any further information produced by the patent owner or that becomes publicly available. While I may cite to documents in the body of this declaration, any such citation is not necessarily an admission that any such document constitutes the primary basis of my opinion. For example, with respect to the prior

art, while I have read and cited to the prior art, my knowledge, experience, and inspection of the prior art has informed me of the prior art's characteristics. Any citation to the prior art is not necessarily the only source of my understanding and opinions.

### **III. BACKGROUND AND QUALIFICATIONS**

10. I am over eighteen years of age, and I am competent to testify as to the matters in this Declaration if I am called upon to do so. A copy of my current curriculum vitae is Exhibit 1021 and provides an accurate identification of my background and experience. For the Board's convenience, I provide an abbreviated overview of my qualifications here.

11. I am a technical expert in the subject matter relevant to this matter, including organic synthesis, chiral synthesis, and the use of enzymes in chemical reactions.

12. I am a professor of chemistry with more than 35 years of experience in academia, as well as experience in drug design. For over three decades, my laboratory has focused and continues to focus on the development of new methodology in organic synthesis and the application of this methodology to the synthesis of naturally occurring compounds and molecules of design (i.e., unnatural products) with important biological activity.

13. In 1977, I received my Bachelor of Arts, cum laude, in Chemistry from Harvard College. In 1978, I received my Master of Arts in Chemistry from

Columbia University. In 1981, I received my Ph.D. in Chemistry from Columbia University. From 1981 to 1983, I was an American Cancer Society post-doctoral fellow in the laboratory of Professor Ronald Breslow in the Chemistry Department at Columbia University.

14. From July 1990 until June 1996, I was an Associate Professor in the Department of Chemistry at the University of Pennsylvania (the “University”). From July 1996 until present, I have been a Professor in the University’s Department of Chemistry. In January 2001, I became the University’s Merriam Professor of Chemistry, a position I still hold today. In July 2018, I became the Undergraduate Chair in the University’s Department of Chemistry.

15. In the first part of my research career, from 1983 to 2002, I focused my efforts on the development of new chemical reactions, such as the intramolecular dioxenone photocycloaddition and the intramolecular vinylogous amide cycloaddition reaction cascades, and the application of those reactions to the synthesis of naturally occurring compounds with important biological activity, like taxol, an important anticancer drug. During those years, my laboratory completed the first syntheses of the natural products manzamine (an alkaloid with antimalarial properties), saudin (a hypoglycemic agent), and ingenol (an anticancer substance). These activities have all involved the stereoselective synthesis of molecules with important biological activity.

16. Since 2002, my laboratory has been actively engaged in collaborative research with biological laboratories at the School of Medicine (SOM) at the University of Pennsylvania, the Wistar Institute (the nation's first independent biomedical research facility, which is located on the campus of the University of Pennsylvania), and the Children's Hospital of Philadelphia (CHOP).

17. The collaborations with the SOM have been directed toward the synthesis of new drugs for the treatment of tuberculosis, and a series of new anticancer agents. The collaborations with scientists at the Wistar Institute have been directed toward the development of new therapies for the treatment of melanoma. The work at CHOP has been directed toward the development of new drugs for the treatment of acute lymphoblastic leukemia.

18. In each of these projects, I have been responsible for both the design and synthesis of new chemical compounds that could be used for the development of new drug candidates. These projects each highlight the important synergy between chemists, including those with expertise in the design and synthesis of molecules, and biologists, who typically identify the pathways or receptors that the drugs that the chemists develop will target. My participation in these projects has given me the opportunity to evaluate biological activity data on the new compounds that we have prepared, and to develop ideas on the structure-activity relationships of the compounds that we have prepared.

19. In 2013, I became, and remain, a member of the Atrin Pharmaceuticals LLC Scientific Advisory Board. Atrin is a private biopharmaceutical company working on targeting DNA damage and response pathways to treat a broad range of cancers.

20. In 2018, I co-founded, with Dr. Ravi Amaravadi at the SOM, Pinpoint Therapeutics LLC, a start-up company at the Penn Center for Innovation, working on the development of anticancer drugs that target autophagy and other lysosomal processes.

21. I have received numerous professional awards and honors. I was named a Fellow of the Japan Society for the Promotion of Science in 2010. I was awarded the American Chemical Society Cope Scholar Award in 2000 for excellence in organic chemistry, and a two-year Alfred P. Sloan Research Fellowship in 1987, which recognizes “scholars of outstanding promise [with] unique potential to make substantial contributions to their field.” In addition, my research has been supported by an American Cyanamid Company Young Faculty Award (1989-1992), a NIH-NCI Research Career Development Award (1988-1993), and a Merck Foundation Award for Faculty Development (1985). I received the Philadelphia Organic Chemists’ Club Award in 2006, the Lindback Award for Distinguished Teaching at the University of Pennsylvania in 2007, and the Ira H. Abrams Memorial Award for Distinguished Teaching, the highest honor

bestowed for teaching by the School of Arts and Sciences at the University of Pennsylvania, in 2016.

22. I was recognized as the 2018 Founder of the Year by the Penn Center for Innovation Ventures (PCIV) for my participation in interdisciplinary work in drug development, culminating in the company that I co-founded with Dr. Ravi Amaravadi.

23. During my time at the University, I have taught both undergraduate organic chemistry as well as several graduate-level courses in the Department of Chemistry, including Organic Reaction Mechanisms, Bioorganic Chemistry, and Special Topics in Organic Chemistry. I also have extensive experience with the stereoselective synthesis of biologically active compounds, including the use of enzymes as reagents to prepare chiral molecules in my own laboratory.

24. Since 2002, I have given over 80 invited lectures at universities, conferences and various companies, typically pharmaceutical companies, around the world in the areas of the design and synthesis of organic molecules. I have authored or co-authored over 140 peer-reviewed articles published in scholarly journals, including 42 articles since 2012.

25. I am a named inventor on 17 patents, patent applications, and provisional patents relating to the areas of my expertise.

26. From its inception in 1999 until the end of 2018, I served as an Associate Editor of *Organic Letters*, a premier journal for communications in

organic chemistry, by the American Chemical Society. This is a journal in the field of organic chemistry for the publication of preliminary reports on cutting-edge research, creative approaches, and innovative ideas in a broad range of organic chemistry research, including the use of enzymes in organic synthesis.

27. Over the course of my career, I have also participated in consulting in the pharmaceutical industry, both in one-day visits to a variety of well-known pharmaceutical research organizations, like Merck and Pfizer, as well as more extended on-site relationships, such as one I had with Wyeth (that ultimately became Pfizer) during the 1990-2000 time period.

28. During the 2001-2002 academic year, I spent a sabbatical at Bristol-Myers Squibb, a pharmaceutical company at which I had the opportunity to teach a course on organic chemistry (both organic reaction mechanisms and the basics of synthetic methodology), as well as participate in ongoing drug development programs. During this period of time, and more recently in my work with various biological collaborators at the University of Pennsylvania, I have had the opportunity to develop a clear understanding of the working role of biologists in the drug development process.

#### **IV. THE APPLICABLE LAW**

29. I am not an attorney, and I am not providing any expert opinions on the law. I have been advised, however, of certain basic legal principles applicable

to my analysis in this report, and I have applied those principles in forming my opinions.

**A. General Patent Law**

30. I understand that determining the validity of a patent requires a two-step approach. First, the meaning and scope of the patent claims must be determined, then the construed claims are compared to the prior art. If a claim was known in or would have been obvious over the prior art, the claim is invalid.

31. I understand that, in the context of an *inter partes* review, the prior art may include patents and other printed publications.

**B. Level of Ordinary Skill in the Art**

32. I understand that there is a concept in patent law known as the “person of ordinary skill in the art.” I understand that this concept refers to a hypothetical person trained in the relevant technical field of a patent without possessing extraordinary or otherwise exceptional skill. I further understand that factors such as the educational level of those working in the field, the sophistication of the technology, the types of problems encountered in the art, prior-art solutions to those problems, and the speed at which innovations are made may help to establish the level of skill in the art. I understand that the level of skill of the person of ordinary skill in the art is to be assessed at the effective filing date of the claimed invention.

33. I am assessing the level of ordinary skill in the art as of November 16, 2018, which I understand to be the earliest effective filing date on which the patent owner could rely.

**C. Claim Construction**

34. I understand that claims are generally given their ordinary and customary meaning in light of the entire disclosure as read by a person of ordinary skill in the relevant art at the effective filing date.

35. I understand that the application giving rise to the '962 Patent was filed as a national stage application on March 22, 2019, from a PCT application filed March 12, 2019, and claims priority to European patent application 18206826, which the face of the '962 Patent states was filed on November 16, 2018. Any reference to the considerations, knowledge, or applications of a person of ordinary skill in the art is made with respect to the November 16, 2018, timeframe.

36. I understand that a claim term will not receive its ordinary meaning, however, if the patentee acted as his own lexicographer and set forth a definition of a disputed claim term either in the specification or during prosecution. Moreover, I understand that a patentee may disavow or disclaim a portion of the scope of a term whose ordinary meaning would otherwise be broader.

37. I further understand that in determining the ordinary and customary meaning of a claim term, one first looks to the claim language itself and its usage

in context with other claim terms. One should also consider the intrinsic evidence—the written description, drawings, and prosecution history—including any related patents. I understand that a claim cannot be construed divorced from the context of the intrinsic evidence. I further understand that the specification is the single best guide to the meaning of a disputed claim term. For example, I understand that the problem the inventor was attempting to solve, as described in the specification, is a relevant consideration for claim construction.

38. I understand that if the meaning of a term is clear from the claim language and the intrinsic evidence, the claim construction stops there. If the meaning of the claims cannot be determined after assessing the intrinsic evidence, then extrinsic evidence, such as expert testimony, dictionaries, and treatises, may be considered. Regardless of whether extrinsic evidence is considered, I understand that a claim construction cannot be inconsistent with the intrinsic evidence.

#### **D. Anticipation**

39. I understand that to prove anticipation of a claim under 35 U.S.C. § 102 in *inter partes* review, the challenger of the patent claim's validity must show that all the limitations of that claim were described in a single previously printed publication or patent.

40. To anticipate a claim, the prior art need not use the same words as the claim, but all the limitations of the claim must have been disclosed, either

expressly in words, or inherently to a person of ordinary skill in the art at the effective filing date such that, by looking at that one reference, that person could make and use the claimed invention.

41. I understand that a prior-art document anticipates a claim when it expressly discloses every limitation of the claim within the four corners of the document, arranged and combined in the same way as recited in the claim.

42. I further understand that even when a prior-art document does not expressly disclose every limitation of the claim, it may inherently anticipate the claim when the reference's disclosure makes clear to a person of ordinary skill in the art that any missing descriptive matter is necessarily present in the disclosure. I understand that the question of whether missing descriptive matter is inherent in a prior-art reference may be answered by looking to extrinsic evidence. I further understand that inherency may not be established by probabilities or possibilities, and the mere fact that a certain thing might result from a given set of circumstances is insufficient.

43. I understand that when considering the disclosure of a prior-art document, one reviews it from the perspective of a person of ordinary skill in the art at the effective filing date.

44. I understand that in an *inter partes* review, anticipation must be shown by the preponderance of the evidence—in other words, that the claims are more likely than not unpatentable.

**E. Obviousness**

45. I understand that to prove obviousness of a claim under 35 U.S.C. § 103 in *inter partes* review, the challenger of the patent claim's validity must show that the differences between what is claimed and the prior art are such that what is claimed, as a whole, would have been obvious before the effective filing date to a person of ordinary skill in the art.

46. I understand that in assessing the obviousness of a claim, several factual assessments are made, including the scope and content of the prior art, the differences between the prior art and the claims at issue, the level of ordinary skill in the pertinent art at the effective filing date, and any so-called secondary considerations.

47. I understand that secondary considerations include copying, a long-felt but unsolved need in the art, the failure of others, commercial success, unexpected results, unexpected properties, licenses or other evidence of industry respect, and skepticism of skilled artisans before the invention was made.

48. I understand that a claim is obvious if it is shown that each element of the claim is shown to have been known in the art and that a person of ordinary skill in the art before the effective filing date would have been motivated to combine the elements as claimed and would have had a reasonable expectation of success in making the combination.

49. I further understand that it is not permissible to use hindsight in assessing whether a claim is obvious. Rather, I understand that to assess obviousness, one must stand in the shoes of a person of ordinary skill in the art before the effective filing date who is trying to address the issues or solve the problems faced by the inventor, considering what was known before the effective filing date.

## **V. LEVEL OF ORDINARY SKILL IN THE ART**

50. Having reviewed the '962 Patent, in my opinion, the relevant "art" pertains to organic synthesis, specifically chiral synthesis and the use of enzymes in chemical reactions.

51. Considering the relevant factors, in my opinion, a person of ordinary skill in the art as of November 16, 2018, would have a Ph.D. in a relevant field of organic chemistry or biochemistry, with at least several years of research experience gained during those Ph.D. studies or afterwards in the area of organic synthesis, including chiral synthesis, and the use of enzymes in reactions. In my opinion, a person of ordinary skill in the art could also include a person with a lesser academic degree but with several additional years of experience sufficient to develop equivalent experience in synthetic organic chemistry, such as in pharmaceutical applications or in the chiral synthesis of compounds with biological activity.

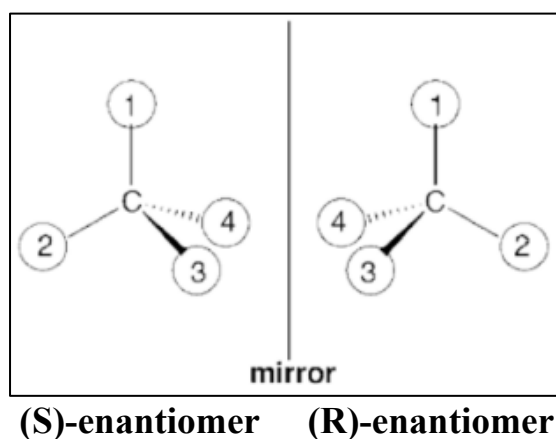
52. Under this standard, I would qualify as a person of ordinary skill in the art. As of November 16, 2018, I held multiple collegiate degrees, including a Bachelor's degree, a Master's degree, and a Ph.D., all in chemistry. As of November 16, 2018, I had decades of research experience in the stereoselective synthesis of both designed and naturally occurring molecules having important biological activities. I also had more than three decades' experience in researching the synthesis of new drugs and anticancer agents, which has also involved significant experience in stereoselective synthesis. As part of my research activities, by November 16, 2018, I had extensive experience with using enzymes as reagents to prepare chiral molecules in my laboratory. I have also spent my career training and working with others who qualify as a person of ordinary skill in the art.

53. I am familiar with the level of ordinary skill in the art as of November 16, 2018. To the extent that the patent owner's assessment of the relevant art or the level of skill in the art differs, I reserve the right to address that assessment.

## **VI. OVERVIEW OF STEREOCHEMISTRY**

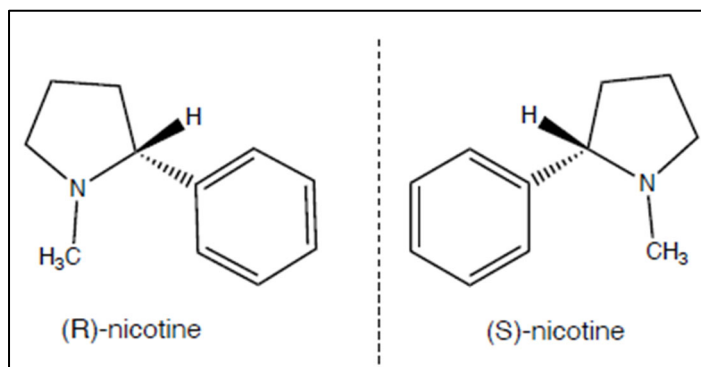
54. Molecules have three-dimensional structures. Some molecules, which have four different substituents about a tetrahedral carbon, may have the same chemical formula yet have different three-dimensional orientations in space; they may be present as non-superimposable mirror-images of each other. These are called "chiral" molecules. The mirror-image molecules are called "enantiomers."

55. To distinguish the two enantiomers, chemists call one the (R)-enantiomer and the other the (S)-enantiomer. That designation is made by ordering the four substituents on a tetrahedral carbon from largest (1) to smallest (4) and then orienting the smallest substituent (4) away from the observer. The remaining three substituents, in descending order, from (1) to (3), have a counterclockwise orientation for the (S)-configuration, as shown on the left-hand diagram, or a clockwise orientation for the (R)-configuration, as shown on the right-hand diagram. When a 50/50 mixture of (R)- and (S)-enantiomers exists, the mixture is called “racemic.” I provide an example of a generic chiral molecule showing its two enantiomers below:



56. The above example shows conventions used by chemists to illustrate three-dimensional structure. Normal lines are considered to be in the plane of the paper, while solid wedges reach toward the reader, and dashes extend away from the reader.

57. Nicotine is an example of a molecule with (R)- and (S)-enantiomeric forms. I provide the structures of (R)-nicotine and (S)-nicotine below:

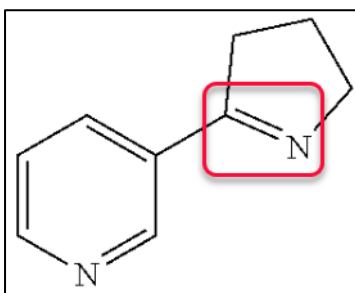


58. Properties of enantiomers may differ significantly when those properties depend on the specific arrangement of atoms in space. A well-known undergraduate organic chemistry text, *Organic Chemistry* by Francis A. Carey (6th ed.), states that “[e]nantiomers can have striking differences, in properties that depend on the arrangement of atoms in space.” Ex. 1022 at 310. Often, biological systems depend on receptors and enzymes to carry out biological processes, and these receptors and enzymes may interact selectively with one enantiomer of a molecule in preference to the other enantiomer, a concept known as chiral recognition. *Id.* at 311. For example, “it is acknowledged that (S)-nicotine ... is significantly more active than (R)-nicotine.” Ex. 1001 at 1:36-41.

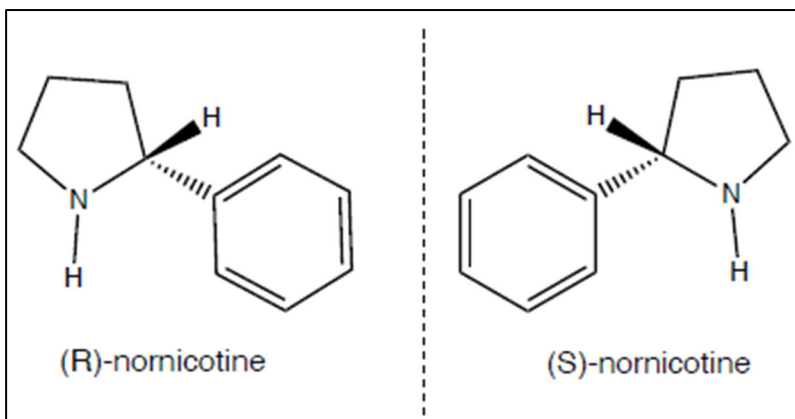
59. The prior art taught that a racemic mixture of (R,S)-nicotine could be synthesized by reducing a molecule known as myosmine to its racemic reduction product, (R,S)-nornicotine, and then methylating the racemic (R,S)-nornicotine to obtain (R,S)-nicotine as a racemic mixture. *See generally* Ex. 1003 and Ex. 1008.

The prior art also taught that (S)-nicotine could be separated (or “resolved”) from the racemic (R,S)-nicotine mixture. *Id.* Thus, the reaction pathway from myosmine to (S)-nicotine was well-known to a person of ordinary skill in the art.

60. Myosmine is an imine, which would have been evident to a person of ordinary skill in the art. An imine is characterized by a carbon-nitrogen double bond (C=N). I have indicated the imine bond in myosmine in red below:



61. Imines such as myosmine are “prochiral,” which also would have been evident to a person of ordinary skill in the art. When a prochiral imine is reduced to its corresponding amine product, the derived amine can have one of its two possible enantiomeric forms, the (R)-amine or the (S)-amine. The resulting amine is a chiral molecule. When the imine bond of myosmine is reduced, it becomes either (R)-nornicotine, (S)-nornicotine, or a mixture thereof. I have provided depictions of (R)-nornicotine and (S)-nornicotine below:



## VII. OVERVIEW OF IMINE REDUCTASES IN BIOCATALYSIS

62. A class of enzymes known as “imine reductases” was extensively researched and characterized before the effective filing date of the ’962 Patent. The ’962 Patent states that a person of ordinary skill in the art “is familiar” with imine reductases. Ex. 1001 at 3:31-39.

63. As the name indicates, imine reductases reduce imines to form their corresponding amines. Unlike reductions using hydrogen gas and an achiral (non-chiral) metal catalyst (which form racemic mixtures), reductions using imine reductases are characteristically stereoselective: a prochiral imine is typically reduced to give a preponderance of either the (R)-amine or the (S)-amine, depending on the stereochemical selectivity of the imine reductase.

64. The prior art shows that imine reductases commonly reduced a given prochiral imine to selectively generate either its (R)-amine or (S)-amine. A person of ordinary skill in the art (POSITA) would have understood that the extent of the selectivity is typically measured by the parameter of enantiomeric excess, which is the excess of the predominant enantiomer as a percentage of the entire mixture,

and that the enantiomeric excesses produced by imine reductases can be 99% or more. The prior art also shows that imine reductases have a characteristically broad substrate scope, meaning that any given imine reductase tends to selectively reduce a wide range of prochiral imines to their corresponding chiral amines, providing a preponderance of either the (R)- or (S)-amine product.

65. Before November 16, 2018, it was a well-known technique to “screen” a series of enzymes against a particular target substrate. A person of ordinary skill in the art would have understood that it was a standard technique to screen imine reductases that would react with a given prochiral imine to stereoselectively yield a target chiral amine (selective formation of either the (R)- or (S)-amine product). Before November 16, 2018, enzyme screening services were available commercially. Enzyme screening service providers offered in-house screening services against large enzyme libraries and even sold standard imine reductase screening kits.

## **VIII. OVERVIEW OF THE '962 PATENT**

66. The '962 Patent describes demand for “tobacco replacement products” driven by the addictive nature of the (S)-enantiomer of nicotine, a chemical occurring naturally in tobacco, and a “growing concern around the detrimental impact of traditional cigarette products on consumer health,” including due to cancer-causing compounds present in tobacco. Ex. 1001 at 1:11-27. Nicotine is used therapeutically, including “to treat nicotine dependence.” *Id.* at 1:27-30.

67. The '962 Patent describes two problems with obtaining nicotine for tobacco replacement or therapeutic uses: enantiomeric purity and chemical purity. First, the '962 Patent states that “(S)-nicotine ... is significantly more active than (R)-nicotine,” so “the demand in the tobacco industry and in the pharmaceutical field is for nicotine with a high level of enantiomeric purity with respect to the (S) enantiomer.” *Id.* at 1:31-41. Second, “obtaining a high level of chemical purity is also of importance in both the pharmaceutical and tobacco industries—chemical purity referring to the amount of nicotine (i.e. both (R) and (S) enantiomeric forms) in comparison to non-nicotine impurities.” *Id.* at 1:45-51. Chemical purity is required by pharmaceutical standards, and impurities in tobacco-derived nicotine might be carcinogenic. *Id.* at 1:51-60. Nicotine extracted from tobacco “typically has a chemical purity of less than 95% due [to] the presence of related alkaloid impurities,” which are chemically similar to nicotine and “difficult to remove.” *Id.* at 1:61-2:4.

68. Chemical syntheses were known and produced a racemic mixture of (R,S)-nicotine, which required a separation step to obtain (S)-nicotine. *Id.* at 2:7-13. The '962 Patent aimed to “synthesiz[e] (S)-nicotine in preference to the (R)-enantiomer with high enantiomeric selectivity whilst also achieving high chemical purity.” *Id.* at 2:23-26.

69. The '962 Patent began with a well-known, short reaction pathway of reducing myosmine to form nornicotine and methylating the nornicotine to form

nicotine, using a stereoselective enzyme catalyst instead of the previously described non-stereoselective metal catalyst to reduce myosmine. *See id.* at 2:30-51. The '962 Patent admits familiarity with the imine myosmine, stating that “[t]he skilled person will be familiar with appropriate reaction schemes to make myosmine.” *Id.* at 3:29-30.

70. In addition to having familiarity with myosmine, a person of ordinary skill in the art would have also been familiar with enzymes having imine reductase activity (also known as “imine reductases” or “IREDs”). The '962 Patent states that “the enzyme with imine reductase activity used in the process disclosed herein is an enzyme capable of catalysing the conversion of myosmine to (S)-nornicotine” and states that “[t]he skilled person is familiar with such enzymes.” *Id.* at 3:35-39.

71. In fact, imine reductases were well-characterized before the '962 Patent was filed. As the name suggests, imine reductases reduce imines to form amines. Unlike reductions using hydrogen gas and an achiral metal catalyst (which form racemic mixtures), reductions using imine reductases are characteristically stereoselective: a prochiral imine is reduced to either the (R)-amine or the (S)-amine in with high selectivity. Imine reductases were also known to have a broad substrate scope, meaning that any given imine reductase tended to reduce a wide range of prochiral imines to their corresponding chiral amines.

72. In my opinion, obtaining imine reductases was trivial by November 16, 2018. Techniques for identifying proteins of interest using protein databases,

expressing the proteins in bacteria, and testing the expressed proteins for activity were routine by that time. In fact, the '962 Patent indicates that working imine reductases were available commercially from Enzymicals and Almac Group. *Id.* at 4:7-14.

73. In my opinion, by November 16, 2018, it was a well-known technique to “screen” for imine reductases that would react with a given prochiral imine to yield a target chiral amine, either the (R)- or (S)-amine, selectively. Enzyme screening services were available commercially, including through Enzymicals and Almac Group.

74. The '962 Patent has 14 claims. Claim 1 is an independent claim. Claims 2-14 depend from claim 1. Claim 1 is reproduced below:

1. A process of making (S)-nicotine comprising the steps of:
  - (i) reducing myosmine with an enzyme with imine reductase activity to form (S)-nornicotine; and
  - (ii) methylating the (S)-nornicotine formed from step (i) to form (S)-nicotine;wherein step (ii) is carried out by way of reductive methylation; and  
wherein in step (ii) the (S)-nornicotine is reductively methylated, using formaldehyde or a formaldehyde-based compound in the presence of a reductant.

75. Claim 1 thus recites the well-known synthesis of nicotine by reducing the imine myosmine to form nornicotine, then methylating the nornicotine to form nicotine. The reduction of myosmine to (S)-nornicotine is catalyzed using any

“enzyme with imine reductase activity” accepting the imine myosmine as a substrate and forming the (S)-enantiomer of its amine, nornicotine. The methylation of nornicotine proceeds according to a standard and very well recognized technique for N-methylation.

76. In my opinion, for the reasons detailed below, the '962 Patent claims a well-known reaction pathway catalyzed by known enzymes that were (a) available commercially, (b) known to reduce imines stereoselectively and (c) had broad substrate scope. The claims of the '962 Patent are the product of a routine application of enzymatic chemistry to a known reaction.

## IX. CLAIM CONSTRUCTION

**A. The plain and ordinary meaning of the term “enzyme with imine reductase activity to form (S)-nornicotine” is “enzyme capable of reducing an imine group to form more (S)-nornicotine than (R)-nornicotine.”**

77. Independent claim 1 of the '962 Patent recites, in part, “an enzyme with imine reductase activity to form (S)-nornicotine.”

78. In my opinion, based on the claim language, the definition in the '962 Patent, and the meaning of that definition to a person of ordinary skill in the art, the term “enzyme with imine reductase activity to form (S)-nornicotine” would be understood according to its plain and ordinary meaning, which is “enzyme capable of reducing an imine group to form more (S)-nornicotine than (R)-nornicotine.”

79. First, the '962 Patent expressly defines “enzyme with imine reductase activity” as follows:

As used herein, an “enzyme with imine reductase activity” refers to an enzyme capable of asymmetrically reducing an imine group, in particular a secondary imine group, to the corresponding amine group, in particular a secondary amine group. In particular, the enzyme with imine reductase activity used in the process disclosed herein is an enzyme capable of catalysing the conversion of myosmine to (S)-nornicotine.

*Id.* at 3:31-36.

80. The express definition of the term “enzyme with imine reductase activity” in the '962 Patent includes the phrase “capable of asymmetrically reducing an imine group.” In the field and in the context of yields of chiral chemical reactions, the term “asymmetrically” means yielding unequal amounts of (S) and (R) products. In other words, if the reaction in question yields 51% (S) and 49% (R), then that reaction happened asymmetrically toward the (S)-enantiomer. In the field, there is no minimum threshold for a reaction to be asymmetric, other than the reaction yielding more of one enantiomer than the other. Thus, in my opinion and in the specific context of claim 1, “capable of asymmetrically reducing an imine group” simply means “capable of reducing an imine group to form more (S)-nornicotine than (R)-nornicotine.”

81. This plain and ordinary meaning also accounts for the enantioselective goals of the '962 Patent. Accordingly, in my opinion, the term “enzyme with imine reductase activity to form (S)-nornicotine” would be understood according to its

plain and ordinary meaning, which is “enzyme capable of reducing an imine group to form more (S)-nornicotine than (R)-nornicotine.”

**B. The plain and ordinary meaning of “wherein the (S)-nicotine is obtained with an enantiomeric excess of at least 90%, preferably at least 95%, more preferably at least 98%, most preferably at least 99%,” if the term is not indefinite, is “wherein the (S)-nicotine is obtained with an enantiomeric excess of at least 90%, either with or without a step of separating (S)-nicotine from (R)-nicotine.”**

82. Dependent claim 9 of the '962 Patent recites, “The process of claim 1, wherein the (S)-nicotine is obtained with an enantiomeric excess of at least 90%, preferably at least 95%, more preferably at least 98%, most preferably at least 99%.”

83. In my opinion, it is unclear whether claim 9 requires obtaining (S)-nicotine only with an enantiomeric excess of at least 90%, rendering the remainder of the claim meaningless, or whether some higher level of enantiomeric excess is required, as multiple higher percentages are recited. I understand that one generally does not ignore phrases in the body of a claim, but I do not know where to draw the line between what falls within the scope of the claim and what falls outside of the claim.

84. However, assuming that the various “preferably” phrases can simply be ignored, in my opinion, based on the claim language, the definition in the '962 Patent, and the meaning of that definition to a person of ordinary skill in the art, the term “wherein the (S)-nicotine is obtained with an enantiomeric excess of at

least 90%, preferably at least 95%, more preferably at least 98%, most preferably at least 99%” would best be understood as “wherein the (S)-nicotine is obtained with an enantiomeric excess of at least 90%, either with or without a step of separating (S)-nicotine from (R)-nicotine.”

85. Nothing in Claim 9 states that a step of separation (or “resolution” as it is often called in the field) is forbidden. Claim 9 recites that “the (S)-nicotine is obtained” with a certain enantiomeric excess—it is not explicit about *how* that excess is achieved. By reciting that “the (S)-nicotine *is obtained* with an enantiomeric excess of at least 90%,” claim 9 recites a result. Claim 1, in contrast, recites a “process of making (S)-nicotine *comprising* the steps of ... “methylating the (S)-nornicotine formed from step (i) *to form* (S)-nicotine.” In my opinion, the plain and ordinary meaning of the relevant portions of claim 1 is that an unspecified amount of (S)-nicotine is “formed” without excluding any additional steps, such as a resolution. Claim 9 is consistent with this reading and recites an end result, either after the steps of claim 1 or after the steps of claim 1 plus one or more unspecified additional steps (such as a resolution).

86. In my opinion, a person of ordinary skill in the art would have understood that enantiomeric excess can be achieved by a stereospecific reaction (one in which one of two possible enantiomeric products is obtained selectively), resolution (by separation of the mixture of enantiomers in a mixture after the reaction, which is not stereospecific), or both (forming one enantiomer in some

amount of enantiomeric excess, then separating the two enantiomers to increase the excess).

87. Thus, when a person of ordinary skill in the art reads the language “the (S)-nicotine is obtained” with a certain enantiomeric excess, the person of ordinary skill in the art would have understood that the final result must have that level of enantiomeric excess. In my opinion, this could be achieved by an enzymatic reaction that yields less than the required level of enantiomeric excess followed by a subsequent separation step to meet the required level of enantiomeric excess. This is the plain reading of claims 1 and 9, and nothing in the claims or the specification excludes it.

## **X. OVERVIEW OF MY OPINIONS**

88. I was asked to provide my opinions as to whether the claims of the '962 Patent are patentable in view of the prior art.

89. In my opinion, all claims of the '962 Patent are invalid because they would have been obvious to a person of ordinary skill in the art before November 16, 2018.

90. Summarily, in my opinion:

- Claims 1-14 are obvious by Divi, Moody, and Enzymicals;
- Claims 6 and 12 are obvious by Divi, Moody, Enzymicals, and Arnold;
- Claims 7-8 are obvious by Divi, Moody, Enzymicals, and Sheldon;

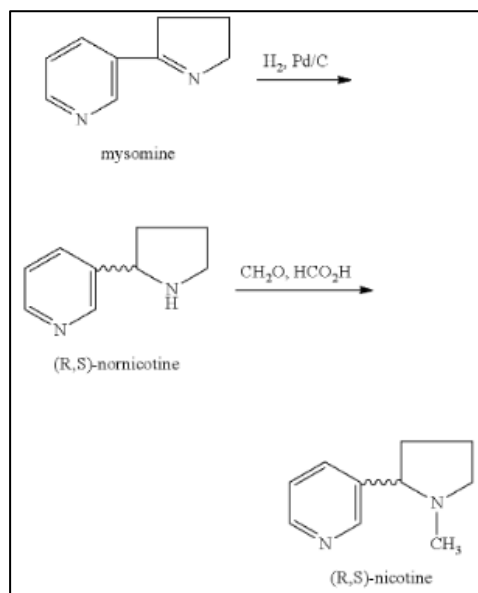
- Claims 1-14 are obvious by Divi, Moody, Velikogne, and Wetzl;
- Claims 6 and 12 are obvious by Divi, Moody, Velikogne, Wetzl, and Arnold;
- Claims 7-8 are obvious by Divi, Moody, Velikogne, Wetzl, and Sheldon.

91. I will first discuss each item of prior art. I will then analyze each claim to show how the claims are obvious by the prior art.

## XI. OVERVIEW OF THE PRIOR ART

### A. Divi

92. Divi discloses a synthesis of (R,S)-nicotine by reducing myosmine to (R,S)-nornicotine and methylating the (R,S)-nornicotine to (R,S)-nicotine, as depicted:



Ex. 1003 at 2:35-3:15 (synthesis of myosmine omitted). Divi explains that

“[m]yosmine is hydrogenated to (R,S)-nornicotine, which on N-methylation gives

(R,S)-nicotine.” *Id.* at 3:16-19. Specifically, [c]atalytic hydrogenation of myosmine resulted in (R,S)-nornicotine.” *Id.* at 3:60-61. Then, “[c]onversion of (R,S)-nornicotine to (R,S)-nicotine was carried out by N-methylation using formaldehyde and formic acid as reported in the literature.” *Id.* at 4:8-11. Divi discloses that “[t]he most convenient way to prepare (R,S)-nicotine is through myosmine” and that “this process provides an attractive and economical method for the production of synthetic (S)-nicotine.” *Id.* at 2:21-25 and 3:16-19.

93. In my opinion, a person of ordinary skill in the art looking to synthesize (S)-nicotine would have looked toward Divi, which explains that beginning the synthesis with myosmine is the “most convenient way” to prepare nicotine. *Id.* at 3:16-19. My understanding is confirmed by the ’962 Patent, which admits that a person of ordinary skill in the art is “familiar with appropriate reaction schemes to make myosmine.” Ex. 1001 at 3:29-30.

94. Divi also discloses that the “unwanted” (R)-nicotine is separated from the racemic (R,S)-nicotine mixture. In my opinion, a person of ordinary skill in the art would have recognized that avoiding a resolution step, by the selective preparation of the desired (S)-enantiomer of nicotine, would further improve the reaction.

95. I understand that Divi is not listed as one of the “References Cited” on the face of the ’962 Patent, and there is no evidence that the Examiner considered Divi. A patent issuing from a divisional application of Divi is, however, briefly

mentioned in the specification, which states only that Divi teaches that a racemic mix of nicotine is made, not that Divi teaches the reaction pathway of myosmine to nornicotine to nicotine.

96. I understand that Divi qualifies as prior art under 35 U.S.C. § 102(a)(1)-(2).

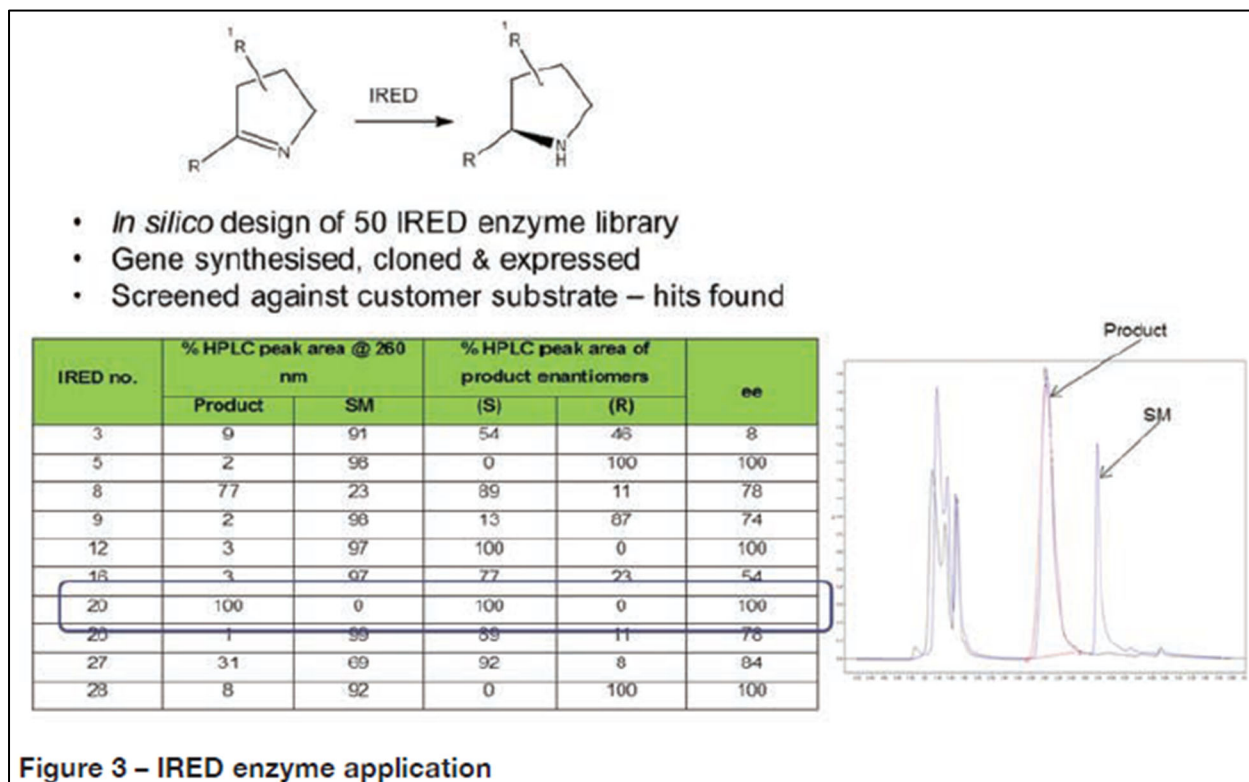
**B. Moody**

97. Moody discloses that the use of biocatalysts in modern chemical and pharmaceutical production is well-accepted. “The paradigm shift for the acceptance of biocatalysts is persistent and at the forefront of research within the fine chemicals and pharmaceuticals industries.” Ex. 1004 at 12. Moody discloses that “[b]ioprocessing is now the norm rather than the exception at Almac and has resulted in significant cost reductions for the production of GMP and non-GMP APIs, intermediates, and fine chemicals.” *Id.* According to Moody, “[b]iocatalysis has become the workhorse of the chemists’ toolbox for chiral chemistry.” *Id.* Moody states that “[e]nzyme processes are now at the epicentre of key drivers in process design, scale-up and economics” and that “[t]he synthetic power of enzymes is their unequalled selectivity for the chemical reactions they catalyse.” *Id.*

98. Moody discloses a successful “imine reductase (IRED) project where Almac specifically designed 50 IREDs for the enantioselective reduction of the imine.” *Id.* Almac “computational scientists designed the enzymes, molecular

biologists cloned and prepared the enzymes and finally the chemists screened the enzymes, resulting in the identification of an active and selective IRED catalyst.”

*Id.* at 12-13. Moody summarized the successful imine reductase screen in the following figure:



99. I understand that Moody is not listed as one of the “References Cited” on the face of the ’962 Patent, and there is no evidence that the Examiner considered Moody.

100. I understand that Moody qualifies as prior art under 35 U.S.C. § 102(a)(1).

### C. Enzymicals

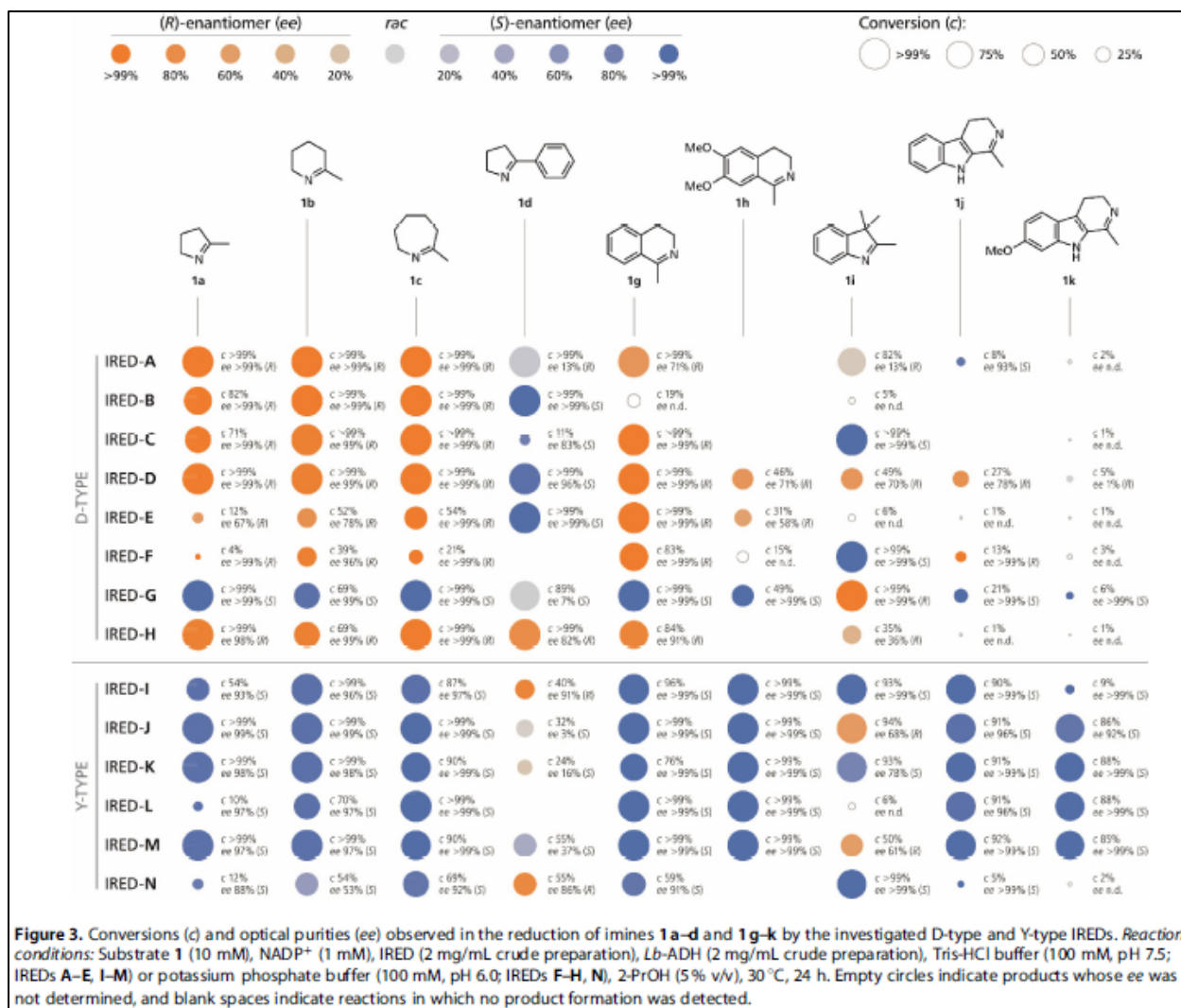
101. Enzymicals discloses a “continually expanding toolbox with innovative biocatalysts and a range of proteins,” including “Imine Reductases” in the “biocatalytic toolbox.” Ex. 1006 at 9. Enzymicals specifically discloses four separate imine reductases available to order, two of which were (R)-selective and two of which were (S)-selective, as well as an imine reductase “screening kit” containing all four imine reductases available to order. *Id.* at 38, 40. Enzymicals discloses “a tailor-made protein expression and optimization service.” *Id.* at 3. Enzymicals further advertises an in-house enzyme screening service that screens a given substrate “to find out the most suitable enzyme for your desired reaction,” that “[m]utants with enhanced substrate specificity and/or increased stereoselectivity towards appropriate substrates are available on request,” and that “an in-house screening with suitable enzyme classes about all available enzymes from public or private panel” was available. *Id.* at 48, 52.

102. I understand that Enzymicals is not listed as one of the “References Cited” on the face of the ’962 Patent, and there is no evidence that the Examiner considered Enzymicals.

103. I understand that Enzymicals qualifies as prior art under 35 U.S.C. § 102(a)(1).

#### **D. Velikogne**

104. Velikogne discloses that “a large number of imine reductases have been identified and heterologously expressed, and their substrate scope, their kinetic properties, their three-dimensional structure and their applicability in preparative-scale reactions have been investigated.” Ex. 1011 at 3236. Velikogne disclosed that a database of over 1,400 putative imine reductases existed and experimentally demonstrated that a screen of 14 imine reductases reduced a broad range of prochiral imines to their corresponding chiral amines. *Id.* at 3237, 3240. Figure 3 illustrates the activities and stereoselectivities of the screened imine reductases across the range of imine substrates:



105. I understand that Velikogne is not listed as one of the “References Cited” on the face of the ’962 Patent, and there is no evidence that the Examiner considered Velikogne.

106. I understand that Velikogne qualifies as prior art under 35 U.S.C. § 102(a)(1).

## E. Wetzl

107. Wetzl discloses that imine reductases reduced imines to chiral amines across “a broad range of substrates.” Ex. 1009 at 1749. Wetzl discloses that imine

reductases had “utility ... for the asymmetric reduction of a broad panel of cyclic imines producing chiral secondary and tertiary amines.” *Id.* Wetzl discloses an experimental enzyme screen to characterize about 20 imine reductases and finds that the “vast majority of the tested IRED candidates displayed good conversions (>90%) against nearly all of the tested substrates as well as good to excellent enantioselectivities, often yielding the corresponding product with an enantiomeric excess > 90%.” *Id.* at 1750.

108. I understand that Wetzl is not listed as one of the “References Cited” on the face of the '962 Patent, and there is no evidence that the Examiner considered Wetzl.

109. I understand that Wetzl qualifies as prior art under 35 U.S.C. § 102(a)(1).

#### **F. Arnold**

110. Arnold discloses a synthesis of nicotine by forming myosmine, reducing myosmine to (R,S)-nornicotine, and methylating (R,S)-nornicotine using formaldehyde and formic acid to form (R,S)-nicotine. Ex. 1008 at 2:28-3:10. Examples 4 and 5 of Arnold disclose a synthesis of nicotine from myosmine that proceeds without isolating the nornicotine from the reaction mixture before methylating the nornicotine to form nicotine. *Id.* at 7:33-52.

111. I understand that Arnold was considered during the prosecution of the '962 Patent and is the only reference cited in this Declaration that can be shown to have been considered by the Examiner.

112. I understand that Arnold qualifies as prior art under 35 U.S.C. § 102(a)(1)-(2).

**G. Sheldon**

113. Sheldon discloses a synthesis of (S)-nicotine from pseudooxynicotine using an imine reductase biocatalyst. Ex. 1013 at 18-21. Sheldon also discloses that “imine reductase enzymes are commercially available, for example, from Enzymicals AG.” *Id.* at 18. Sheldon also discloses that the synthesis of nicotine using an imine reductase preferably occurs in water or an aqueous salt solution or a buffer “to avoid denaturation of the reductase enzymes.” *Id.* at 21.

114. I understand that Sheldon is not listed as one of the “References Cited” on the face of the '962 Patent, and there is no evidence that the Examiner considered Sheldon. Sheldon is briefly mentioned in the specification. While the specification mentions that Sheldon teaches “a synthetic process for producing (S)-nicotine using an enzyme as a biocatalyst,” Ex. 1001 at 2:14-16, it fails to disclose that Sheldon teaches a synthesis of (S)-nicotine from pseudooxynicotine using an imine reductase. Ex. 1013 at 18-21.

115. I understand that Sheldon qualifies as prior art under 35 U.S.C. § 102(a)(1)-(2).

## **XII. SPECIFIC GROUNDS OF INVALIDITY**

### **A. Divi, Moody, and Enzymicals Render Claims 1-14 of the '962 Patent Obvious**

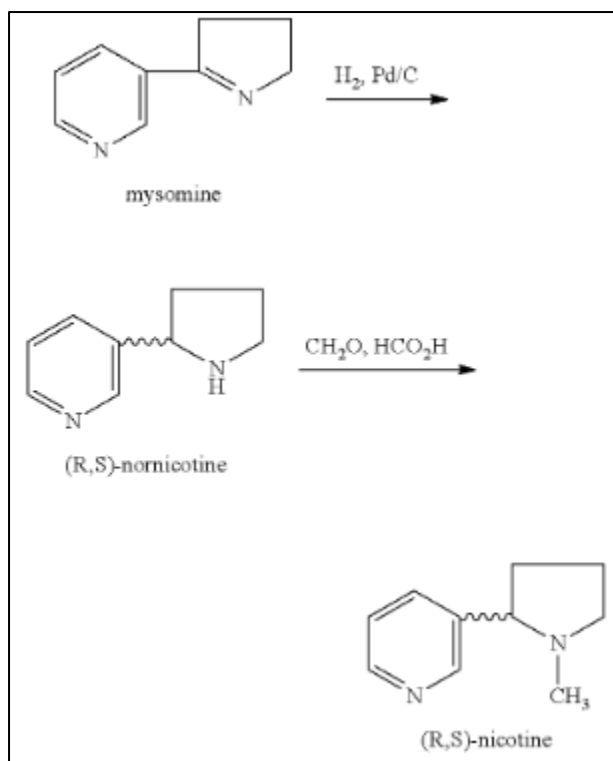
116. In my opinion, claims 1-14 are obvious by the disclosures of Divi, Moody, and Enzymicals. As I explain below, a person of ordinary skill in the art would have been motivated to combine the teachings of Divi, Moody, and Enzymicals and would have had a reasonable expectation of success in doing so.

#### **1. Divi, Moody, and Enzymicals Render Claim 1 of the '962 Patent Obvious**

117. In my opinion, claim 1 is obvious by Divi, Moody, and Enzymicals, as explained below.

##### **a. “A process for making (S)-nicotine comprising the steps of:”**

118. I understand that the preamble is not limiting. Divi discloses that syntheses of (S)-nicotine were known in the art, and that using chiral reagents and chiral catalysts were also known but were expensive. Ex. 1003 at 1:64-2:3. Divi's synthesis of (R,S)-nicotine is depicted as follows:



119. *Id.* at 2:35-3:15 (synthesis of mysomine omitted). Divi also discloses that the synthesized (R,S)-nicotine is followed by a resolution step to separate (S)-nicotine from the “unwanted” (R)-nicotine. *Id.* at 2:8-11. Divi summarizes that “this process provides an attractive and economical method for the production of synthetic (S)-nicotine.” *Id.* at 2:21-25.

120. In my opinion, a person of ordinary skill in the art would have naturally looked at the reaction disclosed in Divi as a logical starting point, while recognizing that the selective formation of (S)-nicotine, thereby avoiding a resolution step, would further improve the reaction.

**b. “(i) reducing mysomine with an enzyme with imine reductase activity to form (S)-nornicotine; and”**

- i. Divi disclosed that the reduction of mysomine by reducing the imine bond yields nornicotine.*

121. Divi teaches that “[t]he most convenient way to prepare (R,S)-nicotine is through myosmine (Scheme 3). Myosmine is hydrogenated to (R,S)-nornicotine, which on N-methylation gives (R,S)-nicotine.” Ex. 1003 at 3:16-19; *see also id.* at 2:8-11, 2:21-25, 2:35-3:16, 4:8-11. Specifically, “[c]atalytic hydrogenation of myosmine resulted in (R,S)-nornicotine.” *Id.* at 3:60-61.

122. A person of ordinary skill in the art would understand that myosmine is reduced when it is “hydrogenated” to nornicotine. A person of ordinary skill in the art would have recognized that the Divi reaction is an achiral reaction and that absent a chiral reagent (such as an enzyme), the reaction results in a racemic product unless resolved.

123. A person of ordinary skill in the art would have also recognized that the reduction of myosmine to nornicotine in Divi proceeded by reducing the C=N imine bond of myosmine, converting it to the corresponding amine, nornicotine.

ii. *Moody disclosed that enzyme-catalyzed reactions proceed to give selective formation of chiral products, and were well-established in industrial applications.*

124. Moody discloses that the use of biocatalysts in modern chemical and pharmaceutical production is well-accepted. “The paradigm shift for the acceptance of biocatalysts is persistent and at the forefront of research within the fine chemicals and pharmaceuticals industries.” Ex. 1004 at 12. Moody discloses that “[b]ioprocessing is now the norm rather than the exception at Almac and has

resulted in significant cost reductions for the production of GMP and non-GMP APIs, intermediates, and fine chemicals.” *Id.*

125. Moody disclosed that “[o]ff-the-shelf and specifically designed enzymes can be accessed within days and weeks respectively. These timelines allow synthetic chemists to include enzyme processing in their synthetic toolbox.” *Id.* According to Moody, not only was biocatalysis accepted in synthetic chemistry, but “[b]iocatalysis has become the workhorse of the chemists’ toolbox for chiral chemistry.” *Id.* Moody praised incorporating enzyme-catalysts into synthetic reaction pathways, stating that “[e]nzyme processes are now at the epicentre of key drivers in process design, scale-up and economics.” *Id.*

126. Further, Moody recognized that “[t]he synthetic power of enzymes is their ***unequalled selectivity*** for the chemical reactions they catalyse” and described “an imine reductase (IRED) project where Almac specifically designed 50 IREDS for the enantioselective reduction of the imine.” *Id.* at 12 and Fig. 3 (highlighting an enantiomeric excess of 100 of the (S)-enantiomer from an IRED-catalyzed reaction).

127. Thus, in my opinion, a person of ordinary skill in the art would have known that enzymes were effective in the industrial production of chiral compounds, available commercially, and were the “workhorse” in the “toolbox for chiral chemistry.”

iii. *Moody and Enzymicals disclosed that imine reductases reduce imines to chiral amines asymmetrically.*

128. Enzymicals discloses that “[i]mine reductases (IREDs) catalyze the reduction of imines to amines by using NAD(P)H as a hydride source.” Ex. 1006 at 39. Enzymicals disclosed that the “transformation of prochiral imines to chiral amines using IREDs offer quantitative asymmetric route to amine products of high optical purity. So these enzymes can have a valuable complementary role to play in chiral amine synthesis.” *Id.* Enzymicals disclosed four imine reductases and an imine reductase “screening kit” containing the four imine reductases, all available for purchase. *Id.* at 38. Of the four imine reductases, two were (R)-selective and two were (S)-selective. *Id.* at 40. Similarly, Moody disclosed that enzymes were the “workhorse of the chemists’ toolbox for chiral chemistry” and that imine reductases enabled “the enantioselective reduction of the imine.” Ex. 1004 at 12 and Fig. 3.

129. Thus, in my opinion, a person of ordinary skill in the art would have known that imine reductases reduced imines to amines asymmetrically. In my opinion, a person of ordinary skill in the art also would have been exposed to papers from companies like Enzymicals and Almac that offered imine reductases and described the utility of using imine reductases to asymmetrically reduce imines to chiral amines.

- iv. *Enzymicals disclosed imine reductase screening kits available for purchase and in-house screening services with a large set of enzymes, and Moody disclosed the commercial availability of enzymes for a customer's target substrate.*

130. Enzymicals disclosed a “continually expanding toolbox with innovative biocatalysts,” including “Imine Reductases” in the “biocatalytic toolbox.” Ex. 1006 at 9. Enzymicals disclosed four separate imine reductases, two of which were (R)-selective and two of which were (S)-selective, as well as an imine reductase “screening kit” containing all four imine reductases available commercially. *Id.* at 38, 40. Enzymicals further disclosed an in-house enzyme screening service that would screen a given substrate “to find out the most suitable enzyme for your desired reaction.” *Id.* at 48. Enzymicals further disclosed that it offered mutant enzymes with “enhanced substrate specificity and/or increased stereoselectivity towards appropriate substrates” that were “available on request” and that “an in-house screening with suitable enzyme classes about all available enzymes from public or private panel” was available. *Id.* at 48, 52.

131. Moody similarly described that “[o]ff-the-shelf and specifically designed enzymes can be accessed within days and weeks respectively” and that “enzyme processing” was a part of chemists’ “synthetic toolbox.” Ex. 1004 at 12. Moody also disclosed that “Almac can rapidly access specifically built enzyme libraries for specific customer substrates.” *Id.* Moody further stated that “[u]sing this technology, [Almac] can take customer substrates and by performing complex

dockings studies can build tailored catalysts for the customer substrate.” *Id.* And Moody disclosed that Almac could build tailored imine reductases designed to reduce a specific customer imine substrate. *Id.*

132. In my opinion, a person of ordinary skill in the art would have recognized that Enzymicals offered enzyme screens and screening services for identifying imine reductases to catalyze the reduction of imines on production scale. A person of ordinary skill in the art would have considered an enzyme screen to be a standard technique. In my opinion, a person of ordinary skill in the art would have known that Enzymicals and Almac offered commercial screening services to screen a given imine substrate and identify an optimal imine reductase for the substrate. Further, in my opinion, a person of ordinary skill in the art would have understood that these services could specifically design imine reductases for activity against a given imine substrate and had done so successfully.

- v. *A person of ordinary skill in the art would have been motivated to screen imine reductases using Enzymicals or Almac to find an imine reductase catalyzing the asymmetric reduction of myosmine to (S)-nornicotine.*

133. In my opinion, a person of ordinary skill in the art would have recognized that the Divi reaction provided an opportunity for a stereoselective reaction at the step where myosmine is reduced to nornicotine. In my opinion, a person of ordinary skill in the art would have understood from the nicotine reaction pathway disclosed in Divi that the conversion of myosmine, an imine, to

nornicotine, the corresponding amine, requires reducing the imine bond of myosmine.

134. The '962 Patent admits that “[t]he skilled person is familiar with” imine reductases. Ex. 1001 at 3:32-41. In my opinion, a person of ordinary skill in the art, being familiar with enzymes with imine reductase activity, would have known that imine reductases reduced prochiral imines to their corresponding amines asymmetrically. As such, in my opinion, a person of ordinary skill in the art would have been motivated to use an imine reductase to catalyze the reduction of myosmine, which is a prochiral imine, to (S)-nornicotine, a chiral secondary amine, asymmetrically.

135. For example, Moody disclosed that “[b]iocatalysis has become the workhorse of the chemists’ toolbox for chiral chemistry” and that “[t]he synthetic power of enzymes is their *unequalled selectivity* for the chemical reactions they catalyse.” Ex. 1004 at 12. And Enzymicals disclosed that the “transformation of prochiral imines to chiral amines using IREDs offer quantitative asymmetric route to amine products of high optical purity. So these enzymes can have a valuable complementary role to play in chiral amine synthesis.” Ex. 1006 at 39.

136. In fact, the '962 Patent admits that commercially available sources of imine reductases, including Enzymicals and Almac Group, were known. Ex. 1001 at 4:7-14 (disclosing that nine imine reductases disclosed to reduce myosmine to (S)-nornicotine asymmetrically were “available from Enzymicals” and that another

imine reductase was “available from Almac Group”). In my opinion, a person of ordinary skill in the art would have also known from Enzymicals and Moody that imine reductases were widely available commercially. In my opinion, a person of ordinary skill in the art would have also been motivated by the disclosures of Enzymicals and Moody to use an imine reductase to asymmetrically reduce myosmine to (S)-nornicotine. Further still, in my opinion, a person of ordinary skill in the art would have understood from Moody and Enzymicals that commercial services could analyze a “customer substrate” imine (such as myosmine), build a custom enzyme screen of imine reductases specifically targeting the reduction of myosmine, and discover an imine reductase “for the enantioselective reduction of the imine.” Ex. 1004 at 12.

137. Thus, in my opinion, a person of ordinary skill in the art, knowing that the Divi reaction could be made stereoselective at the step of reducing myosmine to nornicotine, would have been motivated to use an imine reductase to reduce myosmine to (S)-nornicotine asymmetrically. In my opinion, a person of ordinary skill in the art would have been motivated to apply the teachings of Enzymicals or Moody (or both) to use Enzymicals or Almac to identify an imine reductase capable of reducing myosmine to (S)-nornicotine asymmetrically and use that imine reductase to catalyze the asymmetric reduction of myosmine to (S)-nornicotine.

- vi. *A person of ordinary skill in the art would have had a reasonable expectation of success that Enzymicals or Almac would identify an imine reductase that would asymmetrically reduce myosmine to (S)-nornicotine.*

138. In my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success that Enzymicals or Almac (or both) would identify an imine reductase to reduce myosmine to (S)-nornicotine asymmetrically. Enzymicals sold a screening kit of four imine reductases and disclosed that it would screen a given substrate such as myosmine “to find out the most suitable enzyme for your desired reaction.” Ex. 1006 at 38, 40, 48. Enzymicals further disclosed that it offered mutant enzymes with “enhanced substrate specificity and/or increased stereoselectivity towards appropriate substrates” that were “available on request” and that “an in-house screening with suitable enzyme classes about all available enzymes from public or private panel” was available. *Id.* at 52.

139. In my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success that an imine reductase from Enzymicals would reduce myosmine to (S)-nornicotine asymmetrically, as Enzymicals advertised screening kits to find the correct enzyme and offered to perform a screen in-house against a wider selection of imine reductases.

140. In my opinion, a person of ordinary skill in the art would have further known from Moody that Almac could analyze a “customer substrate” imine, build

a custom enzyme screen of imine reductases specifically targeting the reduction of the imine, and discover an imine reductase “for the enantioselective reduction of the imine.” Ex. 1004 at 12. In my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success that Almac’s enzyme screen would yield an imine reductase that reduced myosmine to (S)-nornicotine asymmetrically, as Moody disclosed that Almac had successfully identified an imine reductase to reduce a target imine to the (S)-amine with 100% enantiomeric excess (“ee”). Ex. 1004 at 12, Fig. 3. Moody disclosed a successful “imine reductase (IRED) project where Almac specifically designed 50 IREDs for the enantioselective reduction of the imine.” *Ex. 1004* at 12. Almac “computational scientists designed the enzymes, molecular biologists cloned and prepared the enzymes and finally the chemists screened the enzymes, resulting in the identification of an active and selective IRED catalyst. *Id.* at 12-13. The IRED enzyme screen yielded a high-activity, high-selectivity imine reductase that asymmetrically reduced a customer-identified imine. *Id.* at 12-13, Fig. 3. Moody summarized the successful imine reductase screen as follows:

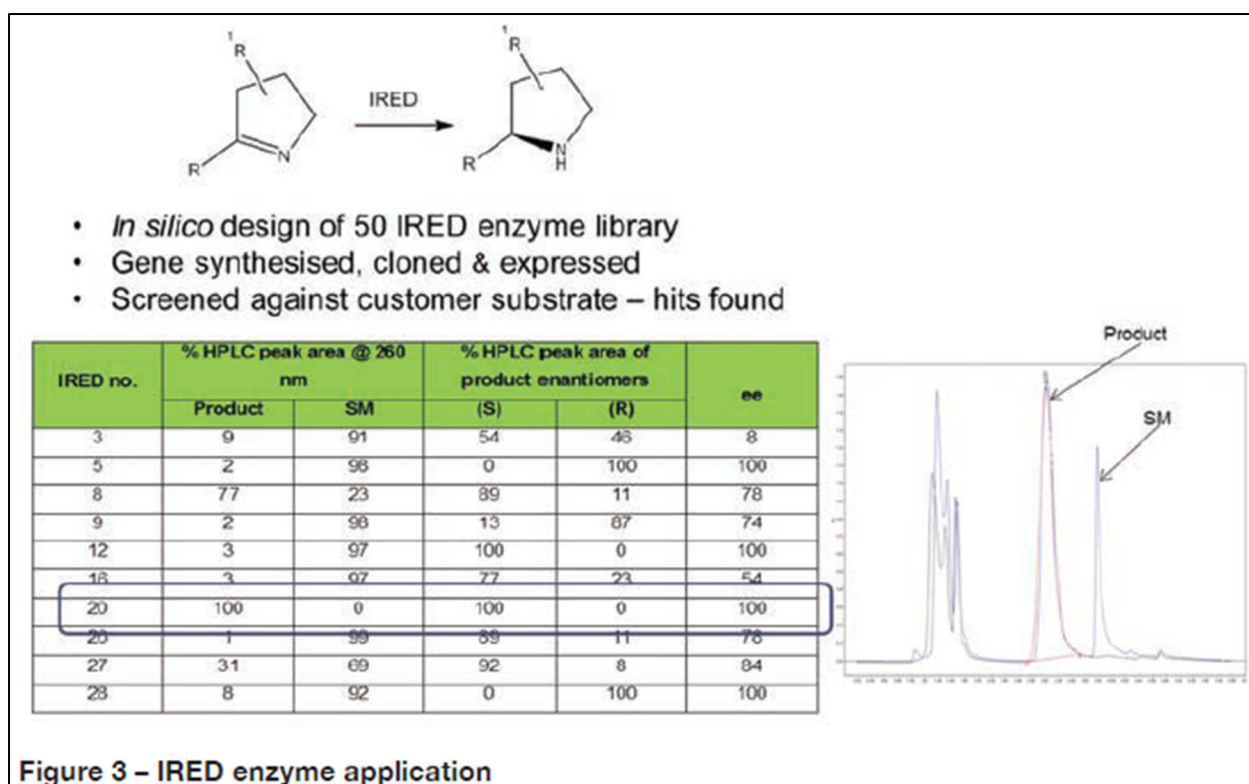


**Figure 3 – IRED enzyme application**

141. Thus, in my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success that a screen by Enzymicals or Almac would identify an appropriate imine reductase to reduce myosmine to (S)-nornicotine asymmetrically. Moody described how Almac designed and executed an imine reductase screen to find an imine reductase that reduced a customer-provided target imine with high activity and high selectivity. As Moody disclosed a specific experience in identifying an imine reductase that reduced a target imine provided by a customer to the (S)-amine with 100% ee, in my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success that Enzymicals or Almac would successfully identify an imine reductase capable of reducing myosmine to (S)-nornicotine asymmetrically.

**c. “(ii) methylating the (S)-nornicotine formed from step (i) to form (S)-nicotine;”**

142. Divi discloses a step of methylating (R,S)-nornicotine to form (R,S)-nicotine. Ex. 1003 at 3:16-19; 4:8-11 (“Conversion of (R,S)-nornicotine to (R,S)-nicotine was carried out by N-methylation using formaldehyde and formic acid as reported in the literature.”); 6:42-45 (“converting the (R,S)-nornicotine to (R,S)-nicotine by N-methylation”).

143. In my opinion, a person of ordinary skill in the art would have understood that the N-methylation step in Divi does not impart or change the chirality of the molecule. The application of Divi’s N-methylation step to (S)-nornicotine would generate (S)-nicotine, in analogy to Divi’s conversion of (R,S)-nornicotine to (R,S)-nicotine. In my opinion, a person of ordinary skill in the art would have known that the chirality of nicotine methylation product is determined by the chirality of the nornicotine entering the N-methylation step.

**d. “wherein step (ii) is carried out by way of reductive methylation; and”**

144. Divi discloses methylating nornicotine to form nicotine by reductive methylation, as discussed above. In my opinion, the methylation disclosed in Divi is a reductive methylation. Divi disclosed methylating nornicotine to form nicotine using formaldehyde and formic acid, which a POSITA would have known are the reaction conditions that are typically used in a reductive methylation. Ex. 1003 at

4:8-11 (disclosing the methylation of nornicotine to form nicotine using formaldehyde and formic acid).

- e. **“wherein in step (ii) the (S)-nornicotine is reductively methylated, using formaldehyde or a formaldehyde-based compound in the presence of a reductant.”**

145. Divi discloses reductively methylating nornicotine using formaldehyde in the presence of a reductant. Divi disclosed methylating nornicotine using formaldehyde and formic acid. Ex. 1003 at 4:8-11. In this reaction, formic acid is the reductant.

## **2. Divi, Moody, and Enzymicals Render Claim 2 of the '962 Patent Obvious**

146. In my opinion, claim 2 is obvious by Divi, Moody, and Enzymicals, as discussed below.

- a. **“The process of claim 1”**

147. Claim 1 is obvious by Divi, Moody, and Enzymicals. *See* Section XII.A.1.

- b. **“wherein formaldehyde is introduced as part of an aqueous solution.”**

148. Divi discloses introducing formaldehyde as part of an aqueous solution. Divi discloses methylating nornicotine using formaldehyde and formic acid. Ex. 1003 at 4:8-11. Divi discloses: “To a solution of nornicotine (50 g 0.338 mol) in 100 ml water a mixture of 37% formaldehyde (49.7g, 1.656 mol) and 85% formic acid (37.26g 0.81 moles) was added and stirred at 85°C for 20 hrs.” *Id.* at

5:26-29. In my opinion, a person of ordinary skill in the art would have understood that when Divi added the formaldehyde/formic acid, it was introduced as part of an aqueous solution.

**3. Divi, Moody, and Enzymicals Render Claim 3 of the '962 Patent Obvious**

149. In my opinion, claim 3 of the '962 Patent is obvious by Divi, Moody, and Enzymicals, as discussed below.

**a. “The process of claim 1”**

150. Claim 1 is obvious by Divi, Moody, and Enzymicals. *See* Section XII.A.1.

**b. “wherein the formaldehyde-based compound is a dimer of formaldehyde, a polymer of formaldehyde, or an acetal of formaldehyde.”**

151. Divi discloses that “the formaldehyde-based compound is a dimer of formaldehyde, a polymer of formaldehyde, or an acetal of formaldehyde.” The '962 Patent defines a “formaldehyde-based compound” as any compound capable of generating formaldehyde *in situ* and states that a formaldehyde-based compound is “preferably” a polymer of formaldehyde. Ex. 1001 at 5:58-6:14. In my opinion, a person of ordinary skill in the art would have known that formaldehyde naturally forms polymers in aqueous solution. *See, e.g.*, Ex. 1016 at 401; *see also* Ex. 1017. Thus, in my opinion, Divi’s disclosure of formaldehyde solution inherently discloses a polymer of formaldehyde.

**4. Divi, Moody, and Enzymicals Render Claim 4 of the '962 Patent Obvious**

152. In my opinion, claim 4 of the '962 Patent is obvious by Divi, Moody, and Enzymicals, as discussed below.

**a. “The process of claim 1,”**

153. Claim 1 is obvious by Divi, Moody, and Enzymicals. *See* Section XII.A.1.

**b. “wherein the reductant is formic acid, sodium cyanoborohydride, or palladium/hydrogen.”**

154. Divi discloses the N-methylation of nornicotine using formaldehyde and formic acid. Ex. 1003 at 4:8-11. In this reaction, formic acid is the reductant.

**5. Divi, Moody, and Enzymicals Render Claim 5 of the '962 Patent Obvious**

155. In my opinion, claim 5 of the '962 Patent is obvious by Divi, Moody, and Enzymicals, as discussed below.

**a. “The process of claim 1,”**

156. Claim 1 is obvious by Divi, Moody, and Enzymicals. *See* Section XII.A.1.

**b. “wherein the reductant is formic acid.”**

157. Divi discloses the N-methylation of nornicotine using formaldehyde and formic acid. Ex. 1003 at 4:8-11. In this reaction, formic acid is the reductant.

**6. Divi, Moody, and Enzymicals Render Claim 6 of the '962 Patent Obvious.**

158. In my opinion, claim 6 of the '962 Patent is obvious by Divi, Moody, and Enzymicals, as discussed below.

**a. “The process of claim 1,”**

159. Claim 1 is obvious by Divi, Moody, and Enzymicals. *See* Section XII.A.1.

**b. “wherein the process is carried out without isolation of the (S)-nornicotine formed from step (i).”**

160. In my opinion, a person of ordinary skill in the art would have been motivated to reduce or remove unnecessary isolation steps in a multi-step reaction sequence, where a multi-step reaction sequence is any sequence involving more than one chemical step. In the synthesis of nicotine, a POSITA would recognize that there are two distinct chemical steps: (1) the reduction of myosmine to nornicotine, and (2) the reductive methylation of nornicotine to give nicotine. A POSITA would have been motivated to avoid the isolation of the intermediate nornicotine and to isolate only the nicotine at the end of the sequence, if such a process could lead to comparable purity of the final product and/or lead to an enhanced overall yield. A POSITA would have been motivated to avoid that isolation step because it could have reduced costs and there would be a reasonable expectation that the overall yield would be higher. It would have been obvious to a POSITA to try to prepare nicotine using the enzyme-catalyzed reaction without

isolation of the nornicotine intermediate but simply to proceed to the reductive methylation step to reduce costs and solvent waste, and potentially improve the yield and efficiency of the process.

161. Additionally, there are only two ways to run the reaction sequence from myosmine to nicotine: with isolation of the nornicotine, and without isolation of the nornicotine. In my opinion, it would have been obvious to try the reaction without isolation of the (S)-nornicotine from step (i)—particularly when using an enzyme catalyst instead of a metal catalyst—as there were only two options and successfully completing the reaction without isolating the (S)-nornicotine would reduce costs, reduce solvent waste, and potentially improve the yield and efficiency of the process.

**7. Divi, Moody, and Enzymicals Render Claim 7 of the '962 Patent Obvious**

162. In my opinion, claim 7 of the '962 Patent is obvious by Divi, Moody, and Enzymicals, as discussed below.

**a. “The process of claim 1,”**

163. Claim 1 is obvious by Divi, Moody, and Enzymicals. *See* Section XII.A.1.

**b. “wherein in step (i) the (S)-nornicotine is formed as part of an aqueous solution, and wherein step (ii)**

**comprises methylating the (S)-nornicotine contained within the aqueous solution.”**

164. In my opinion, it would have been obvious to a person of ordinary skill in the art that when using a biocatalyst to reduce myosmine to nornicotine, the reduction of myosmine would take place in aqueous solution because enzymes naturally function in aqueous solutions. Consistently, Enzymicals disclosed that it provided enzymes as a “[c]oncentrated liquid aqueous culture supernatant.” Ex. 1006 at 51. Accordingly, in my opinion, a person of ordinary skill in the art would have run the biocatalyzed reaction of myosmine to (S)-nornicotine in an aqueous solution to ensure that the imine reductase enzyme functions optimally.

165. Further, Divi disclosed that the methylation of nornicotine to form nicotine was conducted while the nornicotine was present in an aqueous solution. Ex. 1003 at 5:26-29.

**8. Divi, Moody, and Enzymicals Render Claim 8 of the '962 Patent Obvious**

166. In my opinion, claim 8 of the '962 Patent is obvious by Divi, Moody, and Enzymicals, as discussed below.

**a. “The process according to claim 7,”**

167. Claim 7 is obvious by Divi, Moody, and Enzymicals. *See* Section XII.A.7.

- b. “wherein in step (ii) the (S)-nornicotine is reductively methylated using formaldehyde introduced as part of an aqueous solution.”**

168. Divi discloses that the methylation of nornicotine to form nicotine was conducted by introducing formaldehyde as part of an aqueous solution. Ex. 1003 at 5:26-29.

**9. Divi, Moody, and Enzymicals Render Claim 9 of the '962 Patent Obvious**

169. In my opinion, claim 9 of the '962 Patent is obvious by Divi, Moody, and Enzymicals, as discussed below.

- a. “The process of claim 1,”**

170. Claim 1 is obvious by Divi, Moody, and Enzymicals. *See* Section XII.A.1.

- b. “wherein the (S)-nicotine is obtained with an enantiomeric excess of at least 90%, preferably at least 95%, more preferably at least 98%, most preferably at least 99%.”**

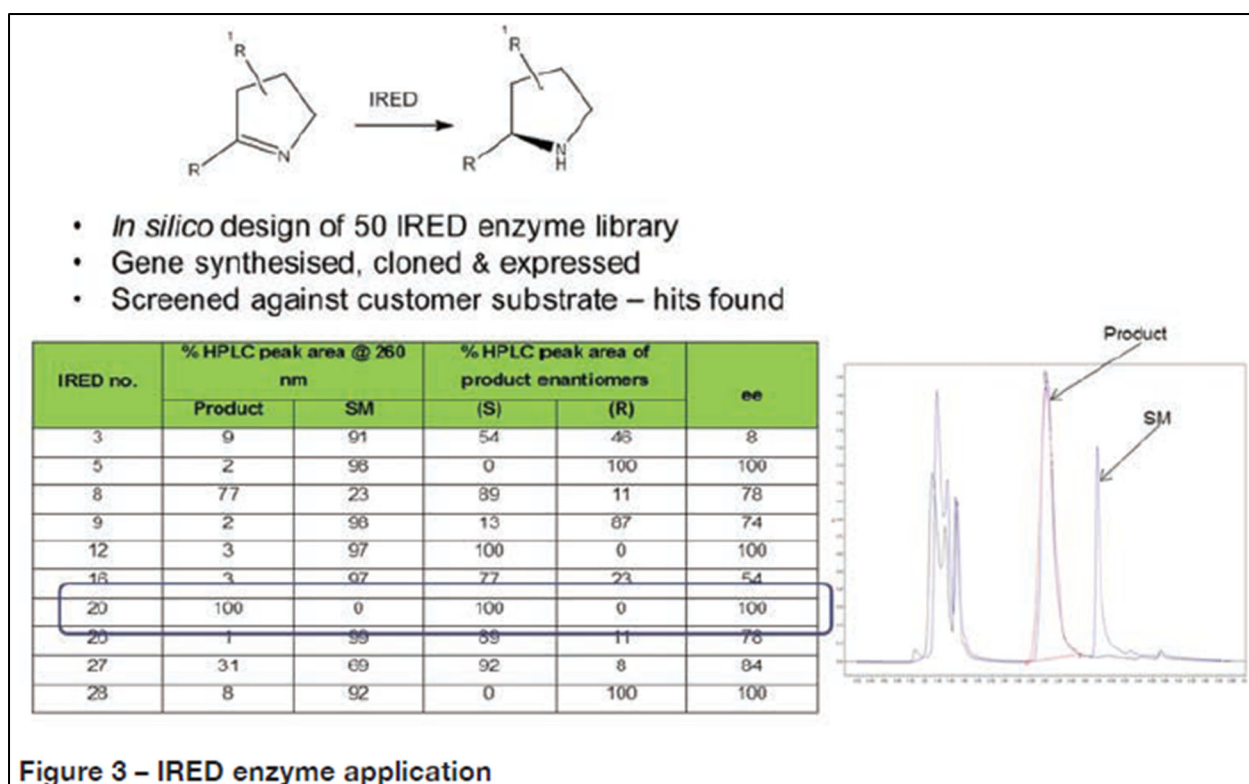
171. As I discussed in Section XII.A.1., a person of ordinary skill in the art would have been motivated to improve the myosmine-nornicotine-nicotine reaction of Divi by using an imine reductase biocatalyst as taught by Moody and Enzymicals and would have had a reasonable expectation of success in doing so.

172. Enzymicals disclosed that the “transformation of prochiral imines to chiral amines using IREDs offer quantitative asymmetric route to amine products of high optical purity. So these enzymes can have a valuable complementary role

to play in chiral amine synthesis.” Ex. 1006 at 39. Enzymicals also disclosed that imine reductases offered by Enzymicals reduced three different imine substrates into chiral amines with 99% enantiomeric excess. *Id.* at 40. In my opinion, a person of ordinary skill in the art would have understood from Enzymicals that imine reductases accept a broad range of imine substrates and convert those imines to their corresponding amines in an asymmetric manner—often with 99% or greater enantiomeric excess.

173. In my opinion, a person of ordinary skill in the art would have also had a reasonable expectation of success that, even if the standard imine reductases screening kit sold by Enzymicals did not reduce myosmine to (S)-nornicotine asymmetrically, Enzymicals could screen myosmine against a larger panel of imine reductases to identify the imine reductases having very high “substrate specificity” for myosmine and “increased stereoselectivity” toward the formation of (S)-nornicotine.

174. In fact, Moody disclosed an enzyme screen of imine reductases for a customer-provided imine substrate, which “result[ed] in the identification of an active and selective IRED catalyst.” Ex. 1004 at 12-13. The imine reductase identified from the enzyme screen converted the customer-provided imine substrate to the (S)-amine product with an enantiomeric excess of 100%—all of the amine obtained was the (S)-enantiomer:



*Id.* at Fig. 3.

175. Thus, in my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success that a screen of imine reductases would identify an imine reductase that would reduce myosmine to (S)-nornicotine with an enantiomeric excess of at least 90%, as predicted and advertised by Enzymicals and as demonstrated in Moody.

176. In my opinion, a person of ordinary skill in the art would have understood that the enantiomeric excess of (S)-nicotine would depend on the enantiomeric excess resulting from the reduction of myosmine to (S)-nornicotine. A person of ordinary skill in the art would have known that the N-methylation of nornicotine would not change the chirality of the molecule. Thus, the enantiomeric

excess of (S)-nicotine relative to (R)-nicotine following methylation would be the same as the enantiomeric excess of (S)-nornicotine relative to (R)-nornicotine. Because, in my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success that the reduction of myosmine to (S)-nornicotine using an imine reductase would result in an enantiomeric excess of (S)-nornicotine of at least 90% (and in some cases as high as 100%), the person of ordinary skill in the art would have also expected to achieve (S)-nicotine in the same enantiomeric excess of at least 90%.

**10. Divi, Moody, and Enzymicals Render Claim 10 of the '962 Patent Obvious**

177. In my opinion, claim 10 of the '962 Patent is obvious by Divi, Moody, and Enzymicals, as discussed below.

- a. **“A process for producing a pharmaceutical composition, comprising forming (S)-nicotine according to the process of claim 1, and including the (S)-nicotine in the pharmaceutical composition together with one or more pharmaceutical excipients.”**

178. I understand that preambles are generally not limiting and that the preamble here (“A process for producing a pharmaceutical composition”) is not limiting. Claim 1 is obvious by Divi, Moody, and Enzymicals. *See* Section XII.A.1. Thus, in my opinion, the step of “forming (S)-nicotine according to the process of claim 1” is also obvious.

179. Divi discloses including (S)-nicotine in a pharmaceutical composition together with one or more pharmaceutical excipients. Divi discloses that “[t]reating nicotine dependence requires therapeutic use of nicotine. Nicotine is given to patients through dermal patches, gums, creams, lozenges, nasal sprays or electronic cigarettes to wean them away from smoking.” Ex. 1003 at 1:32-36. This discussion of nicotine in Divi expressly refers to (S)-nicotine, as the “Background of the Invention” section introduces nicotine as the (S)-enantiomer. *Id.* at 1:21-22. In my opinion, a person of ordinary skill in the art would have understood that the pharmaceutical compositions in Divi, such as gum, cream, and lozenges inherently include pharmaceutical excipients. Ex. 1018.

180. An excipient is “[a]ny inert substance combined with an active drug for preparing an agreeable or convenient dosage form.” *Id.* Here, (S)-nicotine is the active drug, and things like gum base, flavors, emollients, emulsifiers, preservatives, solvents, and the like are examples of inert substances to prepare an agreeable or convenient dosage form.

#### **11. Divi, Moody, and Enzymicals Render Claim 11 of the ’962 Patent Obvious**

181. In my opinion, claim 11 of the ’962 Patent is obvious by Divi, Moody, and Enzymicals, as discussed below.

**a. “The process of claim 10,”**

182. Claim 10 is obvious by Divi, Moody, and Enzymicals. *See* Section XII.A.10.

**b. “wherein the pharmaceutical composition is a transdermal patch, a lozenge, or an inhalation formulation.”**

183. Divi discloses (S)-nicotine in a pharmaceutical composition in each of a transdermal patch, a lozenge, and an inhalation formulation. Ex. 1003 at 1:32-36 (disclosing pharmaceutical preparations of (S)-nicotine including “dermal patches,” “lozenges,” “nasal sprays,” and “electronic cigarettes”).

**12. Divi, Moody, and Enzymicals Render Claim 12 of the ’962 Patent Obvious**

184. In my opinion, claim 12 of the ’962 Patent is obvious by Divi, Moody, and Enzymicals, as discussed below.

**a. “A process for producing a formulation for an electronic cigarette device, comprising forming (S)-nicotine according to the process of claim 1, and including the (S)-nicotine in a solvent with one or more additives.”**

185. I understand that preambles are generally not limiting and that the preamble here (“A process for producing a formulation for an electronic cigarette device”) is not limiting. Claim 1 is obvious by Divi, Moody, and Enzymicals. *See* Section XII.A.1. Thus, in my opinion, the step of “forming (S)-nicotine according to the process of claim 1” is also obvious.

186. Divi discloses including (S)-nicotine in a solvent with one or more additives. For example, Divi discloses that “[t]reating nicotine dependence requires therapeutic use of nicotine. Nicotine is given to patients through dermal patches, gums, creams, lozenges, nasal sprays or electronic cigarettes to wean them away from smoking.” Ex. 1003 at 1:32-36. This discussion of nicotine in Divi expressly refers to (S)-nicotine, as the “Background of the Invention” section introduces nicotine as the (S)-enantiomer. *Id.* at 1:21-22. It would have been obvious to a person of ordinary skill in the art that (S)-nicotine formulations such as gums, creams, and lozenges would have included (S)-nicotine in a solvent with one or more additives.

187. Additionally, Arnold discloses that “[n]icotine is currently included as a dilute solution, typically in combination [with] flavor, in liquid vaporization devises (commonly known as vaporizers), as well as cessation devises such as patches and gums.” Ex. 1008 at 1:23-26. In my opinion, a person of ordinary skill in the art would have known that at least the electronic cigarette formulations of (S)-nicotine involve “including the (S)-nicotine in a solvent with one or more additives” as claimed. Thus, a person of ordinary skill in the art would have understood this to be disclosed in Divi’s teaching of adding (S)-nicotine to an electronic cigarette formulation.

**13. Divi, Moody, and Enzymicals Render Claim 13 of the '962 Patent Obvious**

188. In my opinion, claim 13 of the '962 Patent is obvious by Divi, Moody, and Enzymicals, as discussed below.

**a. “The process of claim 2,”**

189. Claim 2 is obvious by Divi, Moody, and Enzymicals. *See* Section XII.A.2.

**b. “wherein the reductant is formic acid, sodium cyanoborohydride, or palladium/hydrogen.”**

190. Divi discloses the N-methylation of nornicotine using formaldehyde and formic acid. Ex. 1003 at 4:8-11. In this reaction, formic acid is the reductant.

**14. Divi, Moody, and Enzymicals Render Claim 14 of the '962 Patent Obvious**

191. In my opinion, claim 14 of the '962 Patent is obvious by Divi, Moody, and Enzymicals, as discussed below.

**a. “The process of claim 2,”**

192. Claim 2 is obvious by Divi, Moody, and Enzymicals. *See* Section XII.A.2.

**b. “wherein the reductant is formic acid.”**

193. Divi discloses the N-methylation of nornicotine using formaldehyde and formic acid. Ex. 1003 at 4:8-11. In this reaction, formic acid is the reductant.

**B. Divi, Moody, Enzymicals, and Arnold Renders Claims 6 and 12 of the '962 Patent Obvious**

194. In my opinion, claims 6 and 12 are obvious by the disclosures of Divi, Moody, Enzymicals, and Arnold. As I explain below, a person of ordinary skill in the art would have been motivated to combine the teachings of Divi, Moody, Enzymicals, and Arnold and would have had a reasonable expectation of success in doing so.

**1. Divi, Moody, Enzymicals, and Arnold Render Claim 6 of the '962 Patent Obvious**

195. In my opinion, claim 6 is obvious by Divi, Moody, Enzymicals, and Arnold, as explained below.

**a. “The process of claim 1,”**

196. Claim 1 is obvious by Divi, Moody, and Enzymicals. *See* Section XII.A.1.

**b. “wherein the process is carried out without isolation of the (S)-nornicotine formed from step (i).”**

197. In my opinion, a person of ordinary skill in the art would have been motivated to reduce or remove unnecessary isolation steps in a multi-step reaction sequence, where a multi-step reaction sequence is any sequence involving more than one chemical step. In the synthesis of nicotine, a POSITA would recognize that there are two distinct chemical steps: (1) the reduction of myosmine to nornicotine, and (2) the reductive methylation of nornicotine to give nicotine. A POSITA would have been motivated to avoid the isolation of the intermediate

nornicotine and to isolate only the nicotine at the end of the sequence, if such a process could lead to comparable purity of the final product, decrease costs, and/or lead to an enhanced overall yield. A POSITA would have been motivated to avoid that isolation step because it could have reduced costs and there would be a reasonable expectation that the overall yield would be higher. It would have been obvious to a POSITA to try to prepare nicotine using the enzyme-catalyzed reaction without isolation of the nornicotine intermediate but simply to proceed to the reductive methylation step to reduce costs and solvent waste, and potentially improve the yield and efficiency of the process.

198. The synthesis of nicotine from the reduction of myosmine to form nornicotine and the methylation of nornicotine to form nicotine without isolating the nornicotine from the reaction mixture was known in the art. For example, Arnold discloses the synthesis of nicotine via the formation of myosmine, the reduction of myosmine to form (R,S)-nornicotine, and the methylation of the (R,S)-nornicotine using formaldehyde and formic acid to form (R,S)-nicotine. Ex. 1008 at 2:28-3:10.

199. Examples 4 and 5 of Arnold disclose forming (R,S)-nicotine without isolation of the (R,S)-nornicotine formed from the reduction of myosmine. In my opinion, a person of ordinary skill in the art would have known that Examples 4 and 5 teach the formation of myosmine (*id.* at 7:33-40 and 7:56-65), the reduction of myosmine to (R,S)-nornicotine (*id.* at 7:40-43 and 7:65-8:3), and the N-

methylation of the (R,S)-nornicotine to form (R,S)-nicotine (*id.* at 7:43-52 and 8:4-9). In my opinion, a person of ordinary skill in the art would have understood that Examples 4-5 of Arnold are conducted without isolating the (R,S)-nornicotine from the reaction mixture because other examples specify when and where an isolation step occurs. *Compare* Ex. 1008 at 6:51-7:8 (Example 2) *with id.* at 7:33-52 (Example 4) and 7:56-8:9 (Example 5).

200. In my opinion, a person of ordinary skill in the art would have been motivated to look to Arnold and apply the teachings of Arnold because Arnold is in the field of nicotine synthesis, teaches a reaction sequence that reduces myosmine to form nornicotine, and then methylates nornicotine to form nicotine, and discusses appropriate reaction conditions for such a synthesis of nicotine. And the '962 Patent admits that the "field of the invention" is "a process for synthetically producing (S)-nicotine." Ex. 1001 at 1:5-7. As such, in my opinion, a person of ordinary skill in the art would have been motivated to look to Arnold's teachings about acceptable reaction conditions when reducing myosmine to form nornicotine and methylating nornicotine to form nicotine and would have had a reasonable expectation of success applying Arnold to form (S)-nicotine without first isolating the (S)-nornicotine from the reaction.

**2. Divi, Moody, Enzymicals, and Arnold Render Claim 12 of the '962 Patent Obvious**

201. In my opinion, claim 12 is obvious by Divi, Moody, Enzymicals, and Arnold, as explained below.

- a. “A process for producing a formulation for an electronic cigarette device, comprising forming (S)-nicotine according to the process of claim 1, and including the (S)-nicotine in a solvent with one or more additives.”**

202. Claim 1 is obvious by Divi, Moody, and Enzymicals. *See* Section XII.A.1. Thus, in my opinion, the step of “forming (S)-nicotine according to the process of claim 1” is also obvious.

203. I understand that preambles are generally not limiting, but even if the preamble is held to be limiting, claim 12 is still obvious. Divi discloses including (S)-nicotine in a solvent with one or more additives. For example, Divi discloses that “[t]reating nicotine dependence requires therapeutic use of nicotine. Nicotine is given to patients through dermal patches, gums, creams, lozenges, nasal sprays or electronic cigarettes to wean them away from smoking.” Ex. 1003 at 1:32-36. This discussion of nicotine in Divi expressly refers to (S)-nicotine, as the “Background of the Invention” section introduces nicotine as the (S)-enantiomer. *Id.* at 1:21-22.

204. Arnold discloses that “[n]icotine is currently included as a dilute solution, typically in combination [with] flavor, in liquid vaporization devices

(commonly known as vaporizers), as well as cessation devises such as patches and gums.” Ex. 1008 at 1:23-26. In my opinion, a person of ordinary skill in the art would have known that at least the electronic cigarette formulations of (S)-nicotine involve “including the (S)-nicotine in a solvent with one or more additives” as claimed.

**C. Divi, Moody, Enzymicals, and Sheldon Render Claims 7-8 of the '962 Patent Obvious**

205. In my opinion, claims 7-8 are obvious by the disclosures of Divi, Moody, Enzymicals, and Sheldon. As I explain below, a person of ordinary skill in the art would have been motivated to combine the teachings of Divi, Moody, Enzymicals, and Sheldon and would have had a reasonable expectation of success in doing so.

**1. Divi, Moody, Enzymicals, and Sheldon Render Claim 7 of the '962 Patent Obvious**

206. In my opinion, claim 7 is obvious by Divi, Moody, Enzymicals, and Sheldon, as explained below.

**a. “The process of claim 1,”**

207. Claim 1 is obvious by Divi, Moody, and Enzymicals. *See* Section XII.A.1.

**b. “wherein in step (i) the (S)-nornicotine is formed as part of an aqueous solution, and wherein step (ii)**

**comprises methylating the (S)-nornicotine contained within the aqueous solution.”**

208. Sheldon discloses the preparation of nicotine “by the enzymatic reduction of pseudooxynicotine using imine reductase enzymes.” Ex. 1013 at 18. Sheldon discloses that an imine reductase “refers to an enzyme that catalyzes the reduction of an imine, or of an iminium cation, optionally in a stereoselective manner.” *Id.* Sheldon teaches the imine-reductase-catalyzed reduction of pseudooxynicotine to nicotine in an aqueous solution that “is preferably water (as is known in the art, an aqueous salt solution or a buffer may be used as needed in order to avoid denaturation of the reductase enzymes).” *Id.* at 21.

209. In my opinion, a person of ordinary skill in the art would have understood from Sheldon that imine reductases should be used in an aqueous solution, such as water or a buffered solution, to avoid denaturing the enzyme. In my opinion, a person of ordinary skill in the art looking to catalyze the reduction of myosmine to (S)-nornicotine using an imine reductase would have recognized that the reaction should take place in aqueous solution to avoid denaturing the imine reductase.

210. In my opinion, a person of ordinary skill in the art would have been motivated to look to Sheldon and apply the teachings of Sheldon because Sheldon is in the field of nicotine synthesis as well as the field of biocatalytic synthesis and provides disclosure about employing imine reductases in the synthesis of nicotine.

The '962 Patent admits both that the “field of the invention” is “a process for synthetically producing (S)-nicotine” and that a person of ordinary skill in the art would have been “familiar” with imine reductases. Ex. 1001 at 1:5-7 and 3:31-41. As such, in my opinion, a person of ordinary skill in the art would have been motivated to look to Sheldon’s teachings about using an imine reductase as a biocatalyst in a synthesis of nicotine and would have had a reasonable expectation of success in using an aqueous solution to form (S)-nornicotine from the imine reductase-catalyzed reduction of myosmine, as Sheldon taught that an imine-reductase-catalyzed synthesis of nicotine should proceed in aqueous solution to avoid denaturing the enzyme.

211. Further, Divi disclosed that the methylation of nornicotine to form nicotine was conducted while the nornicotine was present in an aqueous solution. Ex. 1003 at 5:26-29.

**2. Divi, Moody, Enzymicals, and Sheldon Render Claim 8 of the '962 Patent Obvious**

212. In my opinion, claim 8 is obvious by Divi, Moody, Enzymicals, and Sheldon, as explained below.

**a. “The process according to claim 7,”**

213. Claim 7 is obvious by Divi, Moody, Enzymicals, and Sheldon. *See* Section XII.C.1.

- b. “wherein in step (ii) the (S)-nornicotine is reductively methylated using formaldehyde introduced as part of an aqueous solution.”**

214. Divi discloses that the methylation of nornicotine to form nicotine was conducted by introducing formaldehyde as part of an aqueous solution. Ex. 1003 at 5:26-29.

**D. Divi, Moody, Velikogne, and Wetzl Render Claims 1-14 of the '962 Patent Obvious**

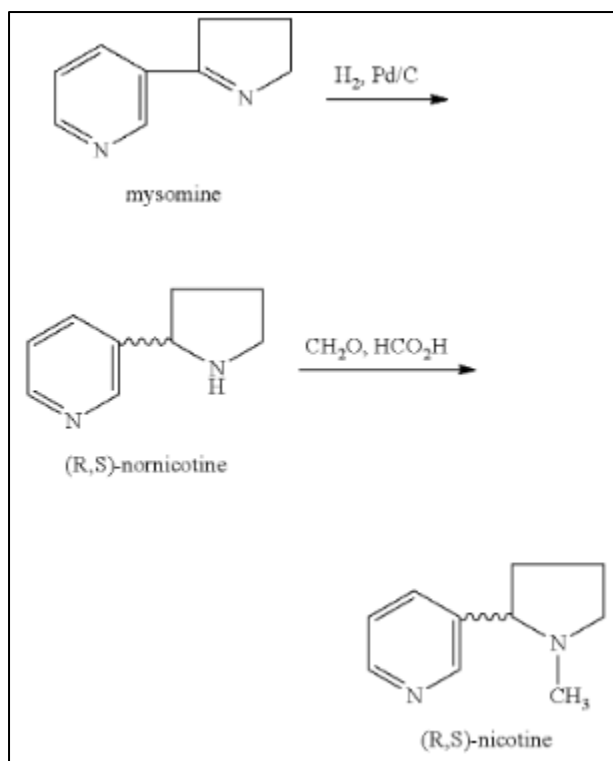
215. In my opinion, claims 1-14 are obvious by the disclosures of Divi, Moody, Velikogne, and Wetzl. As I explain below, a person of ordinary skill in the art would have been motivated to combine the teachings of Divi, Moody, Velikogne, and Wetzl and would have had a reasonable expectation of success in doing so.

**1. Divi, Moody, Velikogne, and Wetzl Render Claim 1 of the '962 Patent Obvious**

216. In my opinion, claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl, as explained below.

- a. “A process for making (S)-nicotine comprising the steps of:”**

217. Divi discloses that syntheses of (S)-nicotine were known in the art, and that using chiral reagents and chiral catalysts were also known but were expensive. Ex. 1003 at 1:64-2:3. Divi’s synthesis of (R,S)-nicotine is depicted as follows:



218. *Id.* at 2:35-3:15 (synthesis of mysomine omitted). Divi also discloses that the synthesized (R,S)-nicotine is followed by a resolution step to separate (S)-nicotine from the “unwanted” (R)-nicotine. *Id.* at 2:8-11. Divi summarizes that “this process provides an attractive and economical method for the production of synthetic (S)-nicotine.” *Id.* at 2:21-25.

219. In my opinion, a person of ordinary skill in the art would have naturally looked at the reaction disclosed in Divi as a logical starting point, while recognizing that avoiding a resolution step would further improve the reaction.

**b. “(i) reducing mysomine with an enzyme with imine reductase activity to form (S)-nornicotine; and”**

- i. Divi disclosed that the reduction of mysomine by reducing the imine bond yields nornicotine.*

220. Divi teaches that “[t]he most convenient way to prepare (R,S)-nicotine is through myosmine (Scheme 3). Myosmine is hydrogenated to (R,S)-nornicotine, which on N-methylation gives (R,S)-nicotine.” Ex. 1003 at 3:16-19; *see also id.* at 2:8-11, 2:21-25, 2:35-3:16, 4:8-11. Specifically, “[c]atalytic hydrogenation of myosmine resulted in (R,S)-nornicotine.” *Id.* at 3:60-61.

221. A person of ordinary skill in the art would have understood that myosmine is reduced when it is “hydrogenated” to nornicotine. A person of ordinary skill in the art would have recognized that the Divi reaction is an achiral reaction and that absent a chiral reagent (such as an enzyme), the reaction results in a racemic product unless resolved.

222. A person of ordinary skill in the art would have also recognized that the reduction of myosmine to nornicotine in Divi proceeded by reducing the C=N imine bond of myosmine, converting it to the corresponding amine, nornicotine.

ii. *Moody disclosed that enzyme-catalyzed reactions proceed to give selective formation of chiral products, and were well-established in industrial applications; Wetzl and Velikogne disclosed that enzyme-catalyzed reactions yielded asymmetric, chiral products.*

223. Moody discloses that the use of biocatalysts in modern chemical and pharmaceutical production is well-accepted. “The paradigm shift for the acceptance of biocatalysts is persistent and at the forefront of research within the fine chemicals and pharmaceuticals industries.” Ex. 1004 at 12. Moody disclosed

that “[b]ioprocessing is now the norm rather than the exception at Almac and has resulted in significant cost reductions for the production of GMP and non-GMP APIs, intermediates, and fine chemicals.” *Id.*

224. Moody disclosed that “[o]ff-the-shelf and specifically designed enzymes can be accessed within days and weeks respectively. These timelines allow synthetic chemists to include enzyme processing in their synthetic toolbox.” *Id.* According to Moody, not only was biocatalysis accepted in synthetic chemistry, but “[b]iocatalysis has become the workhorse of the chemists’ toolbox for chiral chemistry.” *Id.* Moody praised incorporating enzyme-catalysts into synthetic reaction pathways, stating that “[e]nzyme processes are now at the epicentre of key drivers in process design, scale-up and economics.” *Id.*

225. Further, Moody recognized that “[t]he synthetic power of enzymes is their *unequalled selectivity* for the chemical reactions they catalyse” and described “an imine reductase (IRED) project where Almac specifically designed 50 IREDS for the enantioselective reduction of the imine.” *Id.* at 12 and Fig. 3 (highlighting an enantiomeric excess of 100 of the (S)-enantiomer from an IRED-catalyzed reaction).

226. Similarly, Wetzl and Velikogne each disclosed that biocatalytic reactions yielded asymmetric, chiral products. Ex. 1009 at 1749; Ex. 1011 at 3236.

227. Thus, in my opinion, a person of ordinary skill in the art would have known that enzymes were effective in the industrial production of chiral

compounds, available commercially, and were the “workhorse” in the “toolbox for chiral chemistry.”

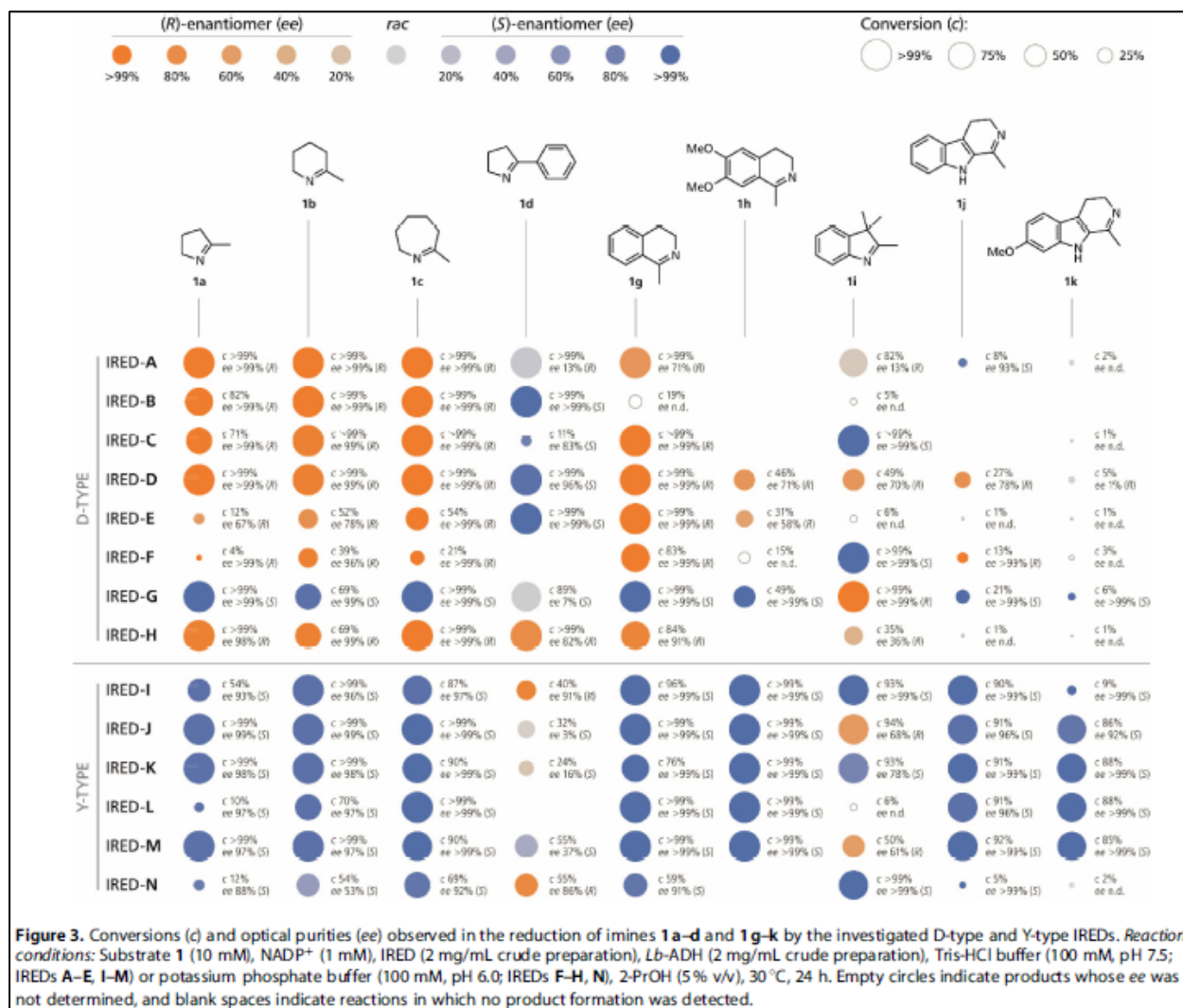
iii. *Moody disclosed that imine reductases reduce imines to chiral amines asymmetrically. Velikogne and Wetzl disclosed that imine reductases reduce a broad spectrum of imines to chiral amines asymmetrically.*

228. Moody disclosed that enzymes were the “workhorse of the chemists’ toolbox for chiral chemistry” and that imine reductases enabled “the enantioselective reduction of the imine.” Ex. 1004 at 12 and Fig. 3.

229. Wetzl disclosed that imine reductases reduced imines to chiral amines across “a broad range of substrates.” Ex. 1009 at 1749. Wetzl disclosed that imine reductases had “utility ... for the asymmetric reduction of a broad panel of cyclic imines producing chiral secondary and tertiary amines.” *Id.* A POSITA would know that myosmine is a cyclic imine and that (S)-nornicotine is a chiral secondary amine. Wetzl ran an enzyme screen to characterize about 20 imine reductases and found that the “vast majority of the tested IRED candidates displayed good conversions (>90%) against nearly all of the tested substrates as well as good to excellent enantioselectivities, often yielding the corresponding product with an enantiomeric excess > 90%.” *Id.* at 1750.

230. Velikogne disclosed that “a large number of imine reductases have been identified and heterologously expressed, and their substrate scope, their kinetic properties, their three-dimensional structure and their applicability in

preparative-scale reactions have been investigated.” Ex. 1011 at 3236. Velikogne demonstrated that a screen of 14 imine reductases reduced a broad panel of imines to their corresponding amines. *Id.* at 3240. Velikogne’s Figure 3 illustrates the activities and stereoselectivities of the 14 imine reductases across the range of imine substrates:



231. In my opinion, a person of ordinary skill in the art would have understood from Velikogne’s imine reductase screen that most imine reductases reduce a wide range of different imines. In fact, every single screened imine was

reduced by at least two imine reductases to the corresponding (S)-amine with at least 99% excess.

232. Thus, in my opinion, a person of ordinary skill in the art would have known that imine reductases reduced a broad spectrum of imines to chiral amines asymmetrically.

iv. *Moody disclosed the commercial availability of custom enzyme screens for a customer's substrates.*

233. Moody described that “[o]ff-the-shelf and specifically designed enzymes can be accessed within days and weeks respectively” and that “enzyme processing” was a part of chemists’ “synthetic toolbox.” Ex. 1004 at 12. Moody also disclosed that “Almac can rapidly access specifically built enzyme libraries for specific customer substrates.” *Id.* Moody further stated that “[u]sing this technology, [Almac] can take customer substrates and by performing complex dockings studies can build tailored catalysts for the customer substrate.” *Id.* And Moody disclosed that Almac could build tailored imine reductases designed to reduce a specific customer imine substrate. *Id.*

234. In my opinion, a person of ordinary skill in the art would have recognized that Almac offered commercial screening services to screen a given imine substrate and identify an optimal imine reductase for the substrate. A person of ordinary skill in the art would have considered an enzyme screen to be a standard technique. Further, in my opinion, a person of ordinary skill in the art

would have understood that these services could specifically design imine reductases for activity against a given imine substrate and that this had been done successfully with other structurally related imines.

- v. *A person of ordinary skill in the art would have been motivated to screen imine reductases using Almac to find an imine reductase catalyzing the asymmetric reduction of myosmine to (S)-nornicotine.*

235. In my opinion, a person of ordinary skill in the art would have recognized that the Divi reaction provided an opportunity for a stereoselective reaction at the step where myosmine is reduced to nornicotine. In my opinion, a person of ordinary skill in the art would have understood from the nicotine reaction pathway disclosed in Divi that the conversion of myosmine, an imine, to nornicotine, the corresponding amine, requires reducing the imine bond of myosmine.

236. The '962 Patent admits that "[t]he skilled person is familiar with" imine reductases. Ex. 1001 at 3:32-41. In my opinion, a person of ordinary skill in the art, being familiar with enzymes with imine reductase activity, would have known that imine reductases reduced imines to their corresponding amines asymmetrically. As such, in my opinion, a person of ordinary skill in the art would have been motivated to use an imine reductase to catalyze the reduction of myosmine to (S)-nornicotine asymmetrically.

237. For example, Moody disclosed that “[b]iocatalysis has become the workhorse of the chemists’ toolbox for chiral chemistry” and that “[t]he synthetic power of enzymes is their *unequalled selectivity* for the chemical reactions they catalyse.” Ex. 1004 at 12.

238. In fact, the ’962 Patent admits that commercially available sources of imine reductase biocatalysts, including Almac Group, were known. Ex. 1001 at 4:7-14 (disclosing that an imine reductase disclosed to reduce myosmine to (S)-nornicotine asymmetrically was “available from Almac Group”). In my opinion, a person of ordinary skill in the art would have also known from Moody that imine reductases were widely available commercially. In my opinion, a person of ordinary skill in the art would have also been motivated by the disclosures of Moody to use an imine reductase to asymmetrically reduce myosmine to (S)-nornicotine. Further still, in my opinion, a person of ordinary skill in the art would have understood from Moody that Almac could analyze a “customer substrate” imine (such as myosmine), build a custom enzyme screen of imine reductases specifically targeting the reduction of myosmine, and discover an imine reductase “for the enantioselective reduction of the imine.” Ex. 1004 at 12.

239. In my opinion, disclosures from Velikogne and Wetzl would have also motivated a person of ordinary skill in the art to catalyze the reduction of myosmine to (S)-nornicotine asymmetrically using an imine reductase. Wetzl recognized the motivation to use a biocatalyst to synthesize chiral amines

asymmetrically to improve yield and reduce the need for an enantiomeric resolution step—one of the issues the '962 Patent attempted to address. Ex. 1009 at 1749-50. Further, Wetzl described imine reductases as having utility “for the asymmetric reduction of a broad panel of cyclic imines producing chiral secondary and tertiary amines,” and characterized imine reductases as “synthetically useful enzymatic tools” in the “IRED toolbox” “for the asymmetric synthesis of amines.” A POSITA would have recognized that myosmine is a cyclic imine and that (S)-nornicotine is a chiral secondary amine. Id. at 1749-50, 1753. Thus, in my opinion, the consistent descriptions of imine reductases as “synthetically useful enzymatic tools for the asymmetric synthesis of amines” by Wetzl and Velikogne would have motivated a person of ordinary skill in the art to use an imine reductase in the Divi reaction to reduce myosmine to (S)-nornicotine asymmetrically.

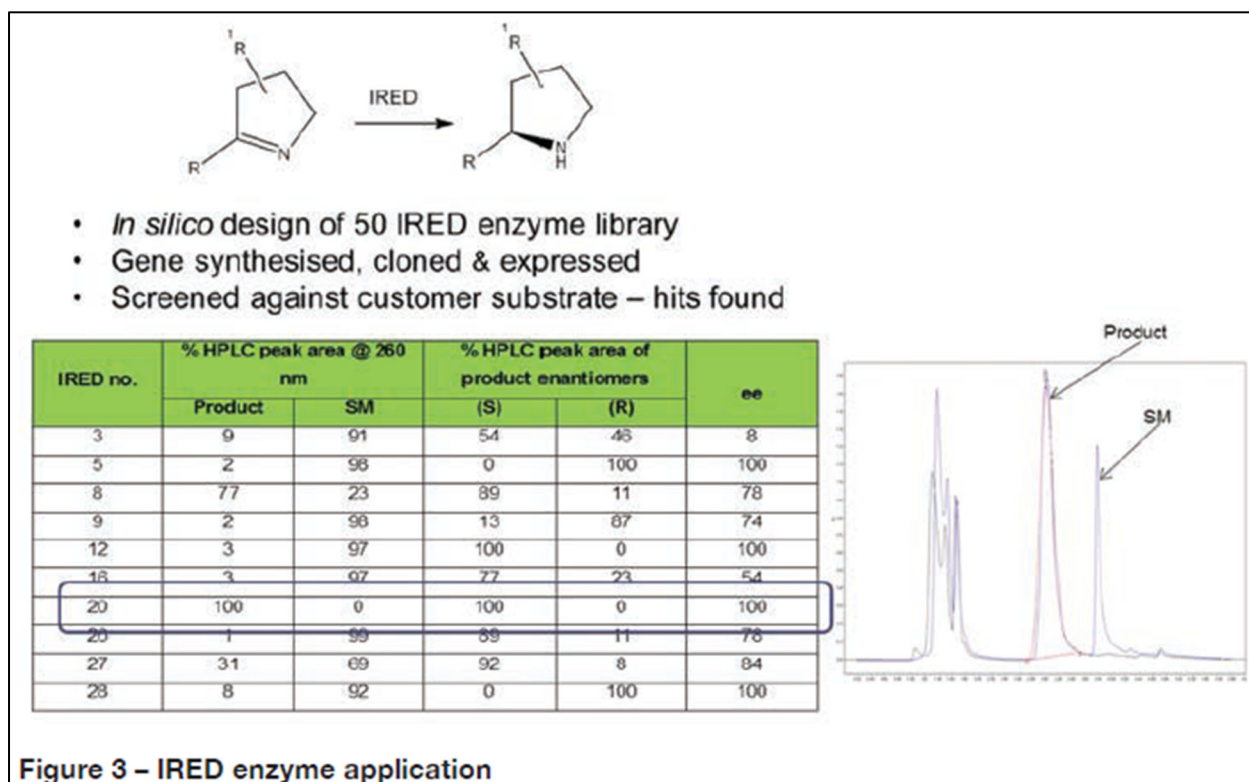
240. Thus, in my opinion, a person of ordinary skill in the art, knowing that the Divi reaction could be made stereoselective at the step of reducing myosmine to nornicotine, would have been motivated to use an imine reductase to reduce myosmine to (S)-nornicotine asymmetrically to improve yield and simplify, if not eliminate, the need to resolve (S)-nicotine from a racemic mixture. In my opinion, a person of ordinary skill in the art would have been motivated to apply the teachings of Moody to use Almac to identify an imine reductase capable of reducing myosmine to (S)-nornicotine asymmetrically and use that imine reductase to catalyze the asymmetric reduction of myosmine to (S)-nornicotine.

- vi. *A person of ordinary skill in the art would have had a reasonable expectation of success that Almac would identify an imine reductase that would asymmetrically reduce myosmine to (S)-nornicotine.*

241. In my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success that Almac would identify an imine reductase to reduce myosmine to (S)-nornicotine asymmetrically. An enzyme screen was a standard technique to determine whether an enzyme had activity on a given substrate before the '962 Patent.

242. In my opinion, a person of ordinary skill in the art would have known from Moody that Almac could analyze a “customer substrate” imine, build a custom enzyme screen of imine reductases specifically targeting the reduction of the imine, and discover an imine reductase “for the enantioselective reduction of the imine.” Ex. 1004 at 12. In my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success that Almac’s enzyme screen would yield an imine reductase that reduced myosmine to (S)-nornicotine asymmetrically, as Moody disclosed that Almac had successfully identified an imine reductase to reduce a target imine to the (S)-amine with 100% ee. Ex. 1004 at 12, Fig. 3. Moody disclosed a successful “imine reductase (IRED) project where Almac specifically designed 50 IREDs for the enantioselective reduction of the imine.” Ex. 1004 at 12. Almac “computational scientists designed the enzymes, molecular biologists cloned and prepared the enzymes and finally the chemists

screened the enzymes, resulting in the identification of an active and selective IRED catalyst. Id. at 12-13. The IRED enzyme screen yielded a high-activity, high-selectivity imine reductase that asymmetrically reduced a customer-identified imine. Id. at 12-13, Fig. 3. Moody summarized the successful imine reductase screen as follows:



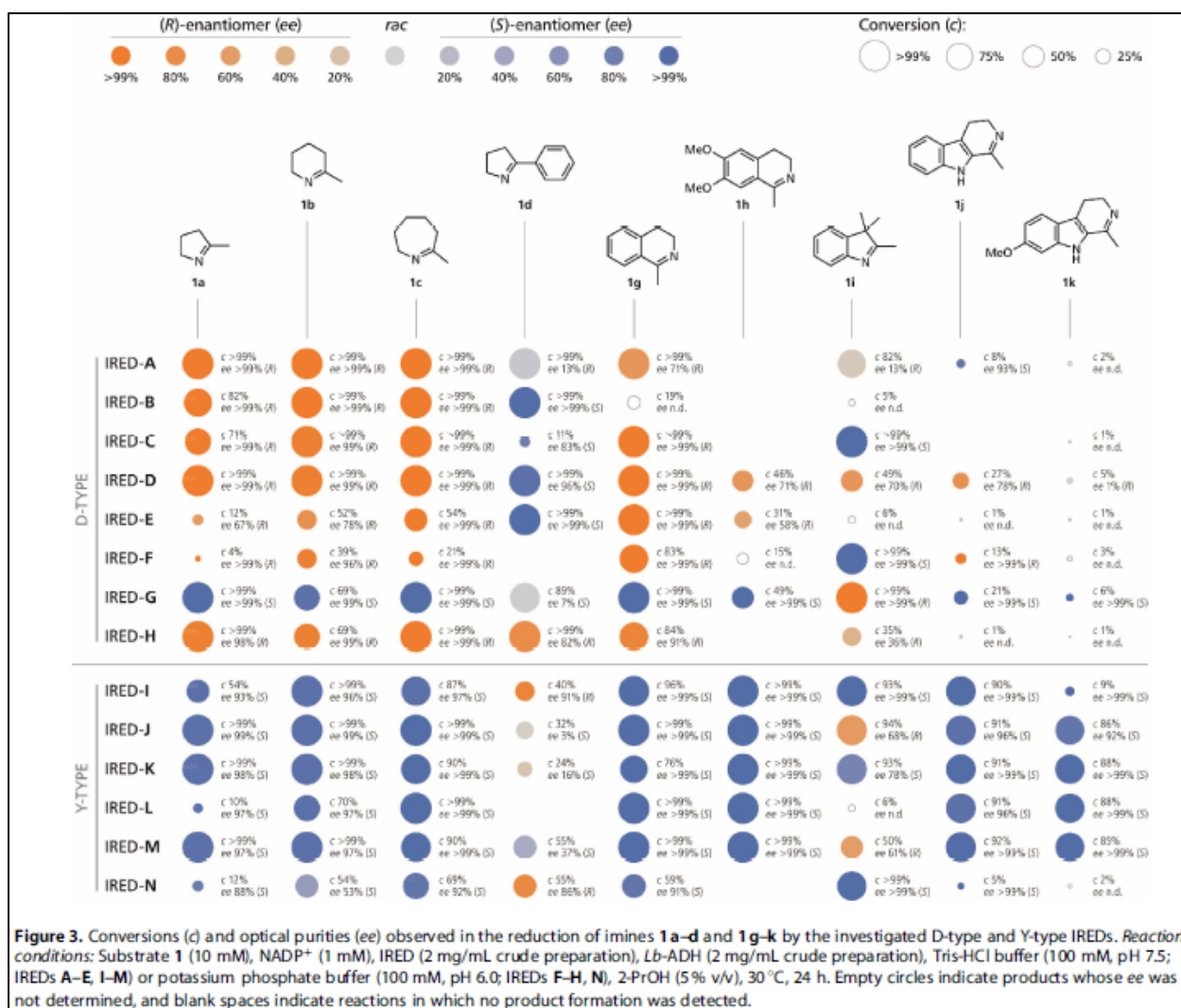
243. Thus, in my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success that an enzyme screen would reveal an imine reductase that reduced myosmine selectively to (S)-nornicotine because Moody described how Almac designed and executed an imine reductase screen to find an imine reductase that reduced a customer-provided target imine with high activity and high selectivity. As Moody disclosed a specific experience in

identifying an imine reductase that reduced a target imine provided by a customer to the (S)-amine with 100% ee, in my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success that Almac would successfully identify an imine reductase capable of reducing myosmine to (S)-nornicotine asymmetrically.

244. Velikogne demonstrated that by screening a limited, diverse set of imine reductases, a person of ordinary skill in the art would likely find an imine reductase that would selectively reduce an imine to the (S)-amine. Velikogne described how a person of ordinary skill in the art could create and run a custom enzyme screen to test the activity of numerous imine reductases against an imine substrate.

245. Wetzl disclosed that “[t]he vast majority of the tested IRED candidates displayed good conversions (>90%) against nearly all of the tested substrates as well as good to excellent enantioselectivities, often yielding the corresponding product with an enantiomeric excess >90%.”

246. In my opinion, a person of ordinary skill in the art would have known that imine reductases reduced prochiral imines to chiral amines across a broad range of substrates. Ex. 1009 at 1749; Ex. 1011 at 3240. Velikogne’s Figure 3 illustrates the activities and stereoselectivities of the 14 imine reductases across the range of imine substrates:



247. Velikogne's limited screen resulted in every single screened imine substrate being selectively reduced to the corresponding (S)-amine by at least two imine reductases with at least 99% enantiomeric excess. In my opinion, a person of ordinary skill in the art following Velikogne's teachings would have had a reasonable expectation of success of finding at least one enzyme reducing myosmine to (S)-nornicotine selectively.

248. Thus, in my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success that an enzyme screen would identify an

appropriate imine reductase to reduce myosmine to (S)-nornicotine asymmetrically.

**c. “(ii) methylating the (S)-nornicotine formed from step (i) to form (S)-nicotine;”**

249. Divi discloses a step of methylating (R,S)-nornicotine to form (R,S)-nicotine. Ex. 1003 at 3:16-19; 4:8-11 (“Conversion of (R,S)-nornicotine to (R,S)-nicotine was carried out by N-methylation using formaldehyde and formic acid as reported in the literature.”); 6:42-45 (“converting the (R,S)-nornicotine to (R,S)-nicotine by N-methylation”).

250. In my opinion, a person of ordinary skill in the art would have understood that the N-methylation step in Divi does not impart or change the chirality of the molecule. The application of Divi’s N-methylation step to (S)-nornicotine would generate (S)-nicotine, in analogy to Divi’s conversion of (R,S)-nornicotine to (R,S)-nicotine. In my opinion, a person of ordinary skill in the art would have known that the chirality of the product nicotine is determined by the chirality of the nornicotine substrate entering the N-methylation step.

**d. “wherein step (ii) is carried out by way of reductive methylation; and”**

251. Divi discloses methylating nornicotine to form nicotine by reductive methylation, as discussed above. In my opinion, the methylation disclosed in Divi is a reductive methylation. Divi disclosed methylating nornicotine to form nicotine using formaldehyde and formic acid, which a POSITA would have known are the

reaction conditions that are typically used in a reductive methylation. Ex. 1003 at 4:8-11 (disclosing the methylation of nornicotine to form nicotine using formaldehyde and formic acid).

- e. **“wherein in step (ii) the (S)-nornicotine is reductively methylated, using formaldehyde or a formaldehyde-based compound in the presence of a reductant.”**

252. Divi discloses reductively methylating nornicotine using formaldehyde in the presence of a reductant. Divi disclosed methylating nornicotine using formaldehyde and formic acid. Ex. 1003 at 4:8-11. In this reaction, formic acid is the reductant.

## **2. Divi, Moody, Velikogne, and Wetzl Render Claim 2 of the '962 Patent Obvious**

253. In my opinion, claim 2 is obvious by Divi, Moody, Velikogne, and Wetzl as discussed below.

- a. **“The process of claim 1”**

254. Claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section XII.D.1.

- b. **“wherein formaldehyde is introduced as part of an aqueous solution.”**

255. Divi discloses introducing formaldehyde as part of an aqueous solution. Divi discloses methylating nornicotine using formaldehyde and formic acid. Ex. 1003 at 4:8-11. Divi discloses: “To a solution of nornicotine (50 g 0.338 mol) in 100 ml water a mixture of 37% formaldehyde (49.7g, 1.656 mol) and 85%

formic acid (37.26g 0.81 moles) was added and stirred at 85°C for 20 hrs.” *Id.* at 5:26-29. In my opinion, a person of ordinary skill in the art would have understood that when Divi added the formaldehyde/formic acid, it was introduced as part of an aqueous solution.

**3. Divi, Moody, Velikogne, and Wetzl Render Claim 3 of the '962 Patent Obvious**

256. In my opinion, claim 3 of the '962 Patent is obvious by Divi, Moody, Velikogne, and Wetzl, as discussed below.

**a. “The process of claim 1”**

257. Claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section XII.D.1.

**b. “wherein the formaldehyde-based compound is a dimer of formaldehyde, a polymer of formaldehyde, or an acetal of formaldehyde.”**

258. Divi discloses that “the formaldehyde-based compound is a dimer of formaldehyde, a polymer of formaldehyde, or an acetal of formaldehyde.” The '962 Patent defines a “formaldehyde-based compound” as any compound capable of generating formaldehyde *in situ* and states that a formaldehyde-based compound is “preferably” a polymer of formaldehyde. Ex. 1001 at 5:58-6:14. In my opinion, a person of ordinary skill in the art would have known that formaldehyde naturally forms polymers. *See, e.g.*, Ex. 1016 at 401; *see also* Ex. 1017. Thus, in my opinion,

Divi's disclosure of formaldehyde solution inherently discloses a polymer of formaldehyde.

**4. Divi, Moody, Velikogne, and Wetzl Render Claim 4 of the '962 Patent Obvious**

259. In my opinion, claim 4 of the '962 Patent is obvious by Divi, Moody, Velikogne, and Wetzl, as discussed below.

**a. "The process of claim 1,"**

260. Claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section XII.D.1.

**b. "wherein the reductant is formic acid, sodium cyanoborohydride, or palladium/hydrogen."**

261. Divi discloses the N-methylation of nornicotine using formaldehyde and formic acid. Ex. 1003 at 4:8-11. In this reaction, formic acid is the reductant.

**5. Divi, Moody, Velikogne, and Wetzl Render Claim 5 of the '962 Patent Obvious**

262. In my opinion, claim 5 of the '962 Patent is obvious by Divi, Moody, Velikogne, and Wetzl, as discussed below.

**a. "The process of claim 1,"**

263. Claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section XII.D.1.

**b. "wherein the reductant is formic acid."**

264. Divi discloses the N-methylation of nornicotine using formaldehyde and formic acid. Ex. 1003 at 4:8-11. In this reaction, formic acid is the reductant.

**6. Divi, Moody, Velikogne, and Wetzl Render Claim 6 of the '962 Patent Obvious.**

265. In my opinion, claim 6 of the '962 Patent is obvious by Divi, Moody, Velikogne, and Wetzl, as discussed below.

**a. “The process of claim 1,”**

266. Claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section XII.D.1.

**b. “wherein the process is carried out without isolation of the (S)-nornicotine formed from step (i).”**

267. In my opinion, a person of ordinary skill in the art would have been motivated to reduce or remove unnecessary isolation steps in a multi-step reaction sequence, where a multi-step reaction sequence is any sequence involving more than one chemical step. In the synthesis of nicotine, a POSITA would recognize that there are two distinct chemical steps: (1) the reduction of myosmine to nornicotine, and (2) the reductive methylation of nornicotine to give nicotine. A POSITA would have been motivated to avoid the isolation of the intermediate nornicotine and to isolate only the nicotine at the end of the sequence, if such a process could lead to comparable purity of the final product and/or an enhanced overall yield. A POSITA would have been motivated to avoid that isolation step because it could have reduced costs and there would be a reasonable expectation that the overall yield would be higher. It would have been obvious to a POSITA to try to prepare nicotine using the enzyme-catalyzed reaction without isolation of the

nornicotine intermediate but simply to proceed to the reductive methylation step to reduce costs and solvent waste, and potentially improve the yield and efficiency of the process.

268. Additionally, there are only two ways to run the reaction sequence from myosmine to nicotine: with isolation of the nornicotine, and without isolation of nornicotine. In my opinion, it would have been obvious to try the reaction without isolation of the (S)-nornicotine from step (i), as there were only two options and successfully completing the reaction without isolating the (S)-nornicotine would reduce costs and solvent waste, and potentially improve the yield and efficiency of the process.

**7. Divi, Moody, Velikogne, and Wetzl Render Claim 7 of the '962 Patent Obvious**

269. In my opinion, claim 7 of the '962 Patent is obvious by Divi, Moody, Velikogne, and Wetzl, as discussed below.

**a. “The process of claim 1,”**

270. Claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section XII.D.1.

**b. “wherein in step (i) the (S)-nornicotine is formed as part of an aqueous solution, and wherein step (ii) comprises methylating the (S)-nornicotine contained within the aqueous solution.”**

271. In my opinion, it would have been obvious to a person of ordinary skill in the art that when using a biocatalyst to reduce myosmine to nornicotine, the

reduction of myosmine would preferably take place in aqueous solution because enzymes naturally function in aqueous solutions. For example, Velikogne described the conditions of the enzymatic reductions when screening for imine reductase activity toward the end of the paper. Ex. 1011 at 3243-3244. Velikogne prepared both a “substrate stock” of the imine substrates in 2-propanol (which is also known as isopropanol or isopropyl alcohol) and a second stock solution of alcohol dehydrogenase, enzyme cofactor NADP<sup>+</sup>, and buffer. *Id.* The buffer was either a Tris-hydrochloric acid or a potassium phosphate buffer. *Id.* at 3244. Both buffers are aqueous solutions that maintain a steady pH. The imine reductase screens took place by adding 25 microliters of substrate stock and 475 microliters of the second aqueous stock to a tube containing the imine reductase. *Id.* at 3244. Velikogne further discloses that an alcohol dehydrogenase is used as an auxiliary enzyme and isopropanol is used “as co-substrate for cofactor regeneration.” *Id.* at 3237; *see also id.* at 3239 (“employing isopropanol (5% v/v) as cheap and innocuous sacrificial co-substrate”). Velikogne’s imine reductase reductions thus took place in an aqueous solution. Accordingly, in my opinion, a person of ordinary skill in the art would have run the biocatalyzed reaction of myosmine to (S)-nornicotine in an aqueous solution to ensure that the imine reductase enzyme functions optimally.

272. Further, Divi disclosed that the methylation of nornicotine to form nicotine was conducted while the nornicotine was present in an aqueous solution. Ex. 1003 at 5:26-29.

**8. Divi, Moody, Velikogne, and Wetzl Render Claim 8 of the '962 Patent Obvious**

273. In my opinion, claim 8 of the '962 Patent is obvious by Divi, Moody, Velikogne, and Wetzl, as discussed below.

**a. “The process according to claim 7,”**

274. Claim 7 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section XII.D.7.

**b. “wherein in step (ii) the (S)-nornicotine is reductively methylated using formaldehyde introduced as part of an aqueous solution.”**

275. Divi discloses that the methylation of nornicotine to form nicotine was conducted by introducing formaldehyde as part of an aqueous solution. Ex. 1003 at 5:26-29.

**9. Divi, Moody, Velikogne, and Wetzl Render Claim 9 of the '962 Patent Obvious**

276. In my opinion, claim 9 of the '962 Patent is obvious by Divi, Moody, Velikogne, and Wetzl, as discussed below.

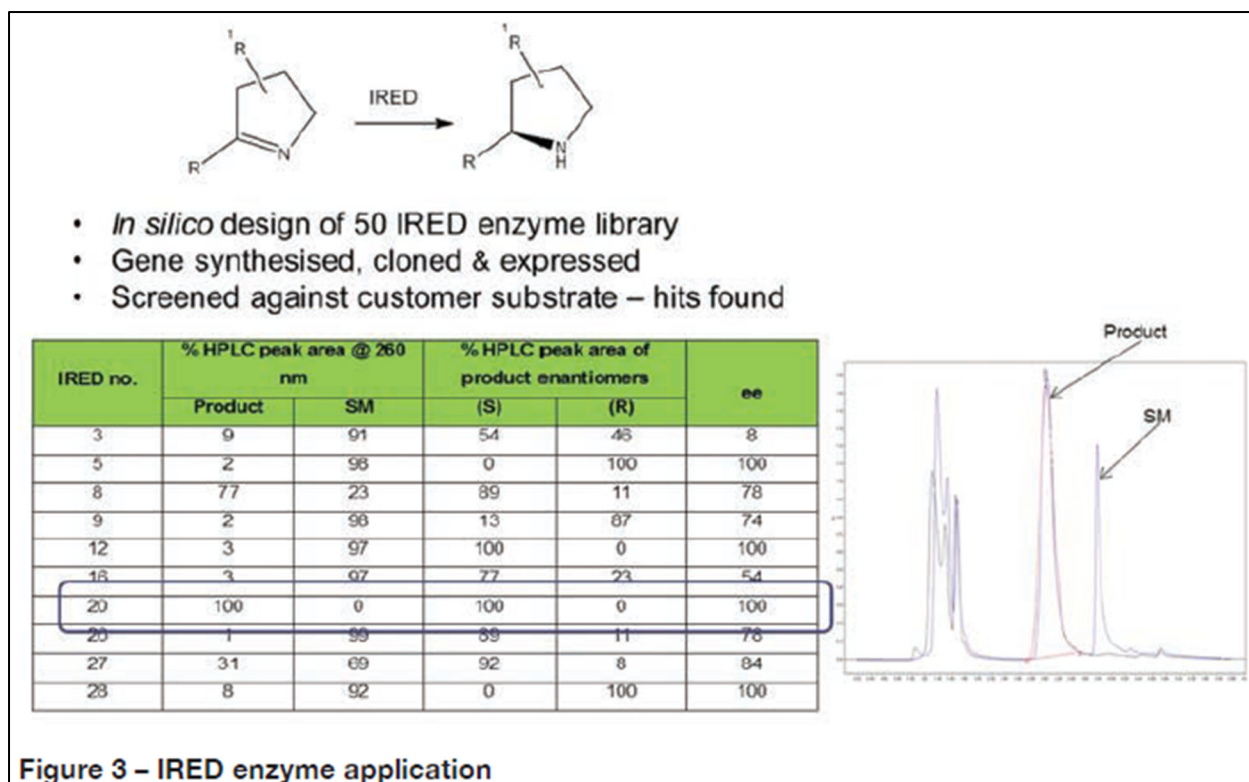
**a. “The process of claim 1,”**

277. Claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section XII.D.1.

- b. “wherein the (S)-nicotine is obtained with an enantiomeric excess of at least 90%, preferably at least 95%, more preferably at least 98%, most preferably at least 99%.”**

278. As I discussed in Section XII.D.1., a person of ordinary skill in the art would have been motivated to improve the myosmine-nornicotine-nicotine reaction of Divi by using an imine reductase biocatalyst as taught by Moody, Velikogne, and Wetzl and would have had a reasonable expectation of success in doing so.

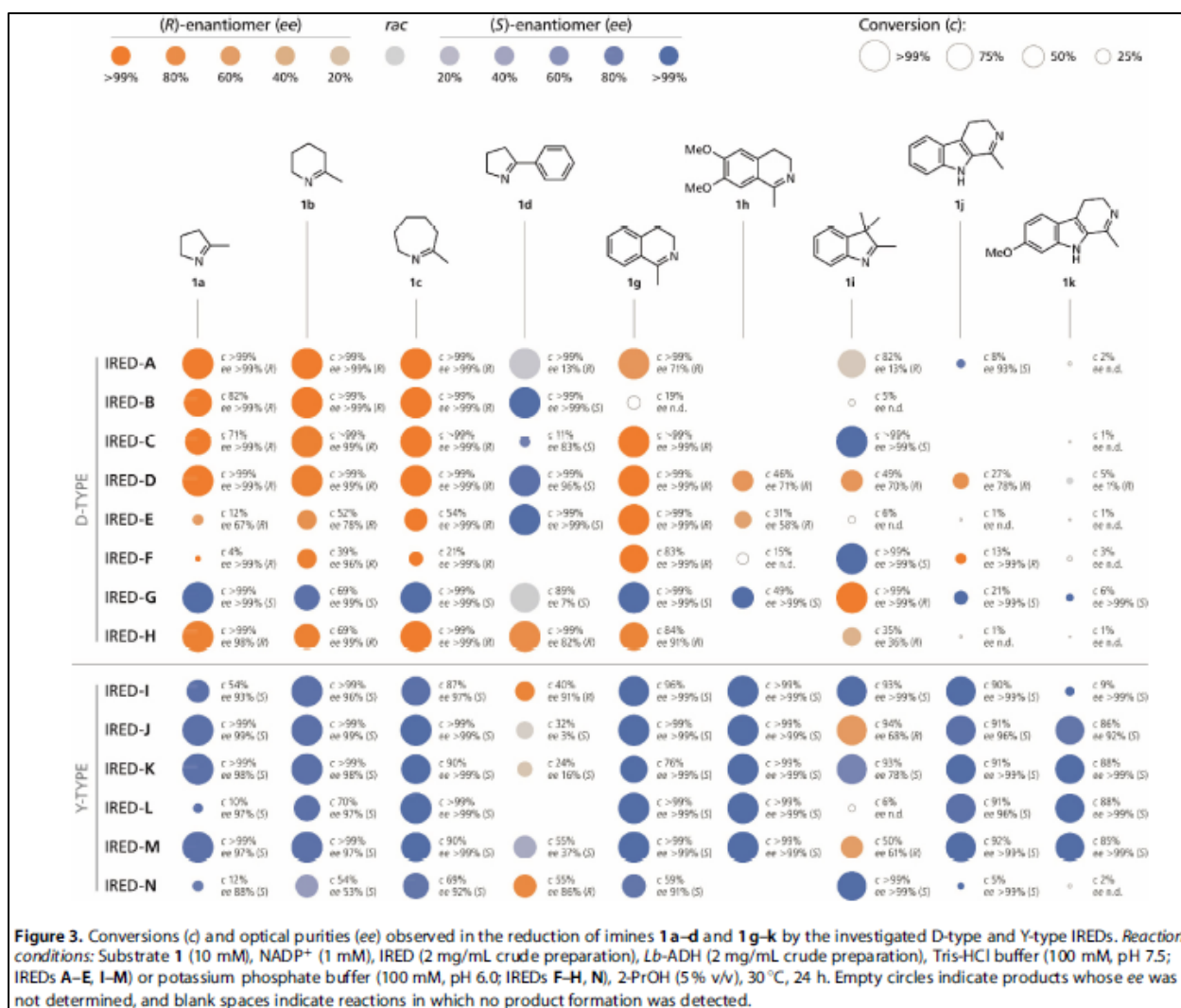
279. Moody disclosed an enzyme screen of imine reductases for a customer-provided imine substrate, which “result[ed] in the identification of an active and selective IRED catalyst.” Ex. 1004 at 12-13. The imine reductase identified from the enzyme screen converted the customer-provided imine substrate to the (S)-amine product with an enantiomeric excess of 100%—all of the amine obtained was the (S)-enantiomer:



*Id.* at Fig. 3.

280. Moreover, Wetzl screened imine reductases and found that the “vast majority of the tested IRED candidates displayed good conversions (>90%) against nearly all of the tested substrates as well as good to excellent enantioselectivities, often yielding the corresponding product with an enantiomeric excess > 90%.” Ex. 1009 at 1750. Thus, in my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success that an imine reductase would reduce myosmine to (S)-nornicotine with an enantiomeric excess of at least 90%.

281. Velikogne screened numerous imine reductases against numerous substrates. Ex. 1011 at 3240. Velikogne’s Figure 3 illustrates the activities and stereoselectivities of the 14 imine reductases across the range of imine substrates:



282. Velikogne's limited screen resulted in every single screened imine substrate being selectively reduced to the corresponding (S)-amine by at least two imine reductases with at least 99% enantiomeric excess. In my opinion, a person of ordinary skill in the art following Velikogne's teachings would have had a reasonable expectation of success of finding at least one enzyme reducing myosmine to (S)-nornicotine selectively.

283. In my opinion, a person of ordinary skill in the art would have understood that the enantiomeric excess of (S)-nicotine would depend on the

enantiomeric excess resulting from the reduction of myosmine to (S)-nornicotine.

A person of ordinary skill in the art would have known that the N-methylation of nornicotine would not change the chirality of the molecule. Thus, the enantiomeric excess of (S)-nicotine relative to (R)-nicotine following methylation would be the same as the enantiomeric excess of (S)-nornicotine relative to (R)-nornicotine.

Because, in my opinion, a person of ordinary skill in the art would have had a reasonable expectation of success that the reduction of myosmine to (S)-nornicotine using an imine reductase would result in an enantiomeric excess of (S)-nornicotine of at least 90% (and in some cases as high as 100%), the person of ordinary skill in the art would also expect to achieve (S)-nicotine in the same enantiomeric excess of at least 90%.

**10. Divi, Moody, Velikogne, and Wetzl Render Claim 10 of the '962 Patent Obvious**

284. In my opinion, claim 10 of the '962 Patent is obvious by Divi, Moody, Velikogne, and Wetzl, as discussed below.

- a. **“A process for producing a pharmaceutical composition, comprising forming (S)-nicotine according to the process of claim 1, and including the (S)-nicotine in the pharmaceutical composition together with one or more pharmaceutical excipients.”**

285. I understand that preambles are generally not limiting and that the preamble here (“A process for producing a pharmaceutical composition”) is not limiting. Claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section

XII.D.1. Thus, in my opinion, the step of “forming (S)-nicotine according to the process of claim 1” is also obvious.

286. Divi discloses including (S)-nicotine in a pharmaceutical composition together with one or more pharmaceutical excipients. Divi discloses that “[t]reating nicotine dependence requires therapeutic use of nicotine. Nicotine is given to patients through dermal patches, gums, creams, lozenges, nasal sprays or electronic cigarettes to wean them away from smoking.” Ex. 1003 at 1:32-36. This discussion of nicotine in Divi expressly refers to (S)-nicotine, as the “Background of the Invention” section introduces nicotine as the (S)-enantiomer. *Id.* at 1:21-22. In my opinion, a person of ordinary skill in the art would have understood that the pharmaceutical compositions in Divi, such as gum, cream, and lozenges, inherently include pharmaceutical excipients. Ex. 1018.

287. An excipient is “[a]ny inert substance combined with an active drug for preparing an agreeable or convenient dosage form.” *Id.* Here, (S)-nicotine is the active drug, and things like gum base, flavors, emollients, emulsifiers, preservatives, solvents, and the like are examples of inert substances to prepare an agreeable or convenient dosage form.

**11. Divi, Moody, Velikogne, and Wetzl Render Claim 11 of the '962 Patent Obvious**

288. In my opinion, claim 11 of the '962 Patent is obvious by Divi, Moody, Velikogne, and Wetzl, as discussed below.

**a. “The process of claim 10,”**

289. Claim 10 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section XII.D.10.

**b. “wherein the pharmaceutical composition is a transdermal patch, a lozenge, or an inhalation formulation.”**

290. Divi discloses (S)-nicotine in a pharmaceutical composition in each of a transdermal patch, a lozenge, and an inhalation formulation. Ex. 1003 at 1:32-36 (disclosing pharmaceutical preparations of (S)-nicotine including “dermal patches,” “lozenges,” “nasal sprays,” and “electronic cigarettes”).

**12. Divi, Moody, Velikogne, and Wetzl Render Claim 12 of the ’962 Patent Obvious**

291. In my opinion, claim 12 of the ’962 Patent is obvious by Divi, Moody, Velikogne, and Wetzl, as discussed below.

**a. “A process for producing a formulation for an electronic cigarette device, comprising forming (S)-nicotine according to the process of claim 1, and including the (S)-nicotine in a solvent with one or more additives.”**

292. I understand that preambles are generally not limiting and that the preamble here (“A process for producing a formulation for an electronic cigarette device”) is not limiting. Claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section XII.D.1. Thus, in my opinion, the step of “forming (S)-nicotine according to the process of claim 1” is also obvious.

293. Divi discloses including (S)-nicotine in a solvent with one or more additives. For example, Divi discloses that “[t]reating nicotine dependence requires therapeutic use of nicotine. Nicotine is given to patients through dermal patches, gums, creams, lozenges, nasal sprays or electronic cigarettes to wean them away from smoking.” Ex. 1003 at 1:32-36. This discussion of nicotine in Divi expressly refers to (S)-nicotine, as the “Background of the Invention” section introduces nicotine as the (S)-enantiomer. *Id.* at 1:21-22. It would have been obvious to a person of ordinary skill in the art that (S)-nicotine formulations such as gums, creams, and lozenges would have included (S)-nicotine in a solvent with one or more additives.

294. Additionally, Arnold discloses that “[n]icotine is currently included as a dilute solution, typically in combination [with] flavor, in liquid vaporization devises (commonly known as vaporizers), as well as cessation devises such as patches and gums.” Ex. 1008 at 1:23-26. In my opinion, a person of ordinary skill in the art would have known that at least the electronic cigarette formulations of (S)-nicotine necessarily involve “including the (S)-nicotine in a solvent with one or more additives,” as claimed. Thus, a person of ordinary skill in the art would have understood this to be disclosed in Divi’s teaching of adding (S)-nicotine to an electronic cigarette formulation.

**13. Divi, Moody, Velikogne, and Wetzl Render Claim 13 of the '962 Patent Obvious**

295. In my opinion, claim 13 of the '962 Patent is obvious by Divi, Moody, Velikogne, and Wetzl, as discussed below.

**a. “The process of claim 2,”**

296. Claim 2 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section XII.D.2.

**b. “wherein the reductant is formic acid, sodium cyanoborohydride, or palladium/hydrogen.”**

297. Divi discloses the N-methylation of nornicotine using formaldehyde and formic acid. Ex. 1003 at 4:8-11. Formic acid is the reductant.

**14. Divi, Moody, Velikogne, and Wetzl Render Claim 14 of the '962 Patent Obvious**

298. In my opinion, claim 14 of the '962 Patent is obvious by Divi, Moody, Velikogne, and Wetzl, as explained below.

**c. “The process of claim 2,”**

299. Claim 2 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section XII.D.2.

**d. “wherein the reductant is formic acid.”**

300. Divi discloses the N-methylation of nornicotine using formaldehyde and formic acid. Ex. 1003 at 4:8-11. Formic acid is the reductant.

**E. Divi, Moody, Velikogne, Wetzl, and Arnold Render Claims 6 and 12 of the '962 Patent Obvious**

301. In my opinion, claims 6 and 12 are obvious by the disclosures of Divi, Moody, Velikogne, Wetzl, and Arnold. As I explain below, a person of ordinary skill in the art would have been motivated to combine the teachings of Divi, Moody, Velikogne, Wetzl, and Arnold and would have had a reasonable expectation of success in doing so.

**1. Divi, Moody, Velikogne, Wetzl, and Arnold Render Claim 6 of the '962 Patent Obvious**

302. In my opinion, claim 6 is obvious by Divi, Moody, Velikogne, Wetzl, and Arnold, as explained below.

**a. “The process of claim 1,”**

303. Claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section XII.D.1.

**b. “wherein the process is carried out without isolation of the (S)-nornicotine formed from step (i).”**

304. In my opinion, a person of ordinary skill in the art would have been motivated to reduce or remove unnecessary isolation steps in a multi-step reaction sequence, where a multi-step reaction sequence is any sequence involving more than one chemical step. In the synthesis of nicotine, a POSITA would recognize that there are two distinct chemical steps: (1) the reduction of myosmine to nornicotine, and (2) the reductive methylation of nornicotine to give nicotine. A POSITA would have been motivated to avoid the isolation of the intermediate

nornicotine and to isolate only the nicotine at the end of the sequence, if such a process could lead to comparable purity of the final product and/or an enhanced overall yield. A POSITA would have been motivated to avoid that isolation step because it could have reduced costs and there would be a reasonable expectation that the overall yield would be higher. It would have been obvious to a POSITA to try to prepare nicotine using the enzyme-catalyzed reaction without isolation of the nornicotine intermediate but simply to proceed to the reductive methylation step to reduce costs and solvent waste, and potentially improve the yield and efficiency of the process.

305. The synthesis of nicotine from the reduction of myosmine to form nornicotine and the methylation of nornicotine to form nicotine without isolating the nornicotine from the reaction mixture was known in the art. For example, Arnold discloses the synthesis of nicotine via the formation of myosmine, the reduction of myosmine to form (R,S)-nornicotine, and the methylation of the (R,S)-nornicotine using formaldehyde and formic acid to form (R,S)-nicotine. Ex. 1008 at 2:28-3:10.

306. Examples 4 and 5 of Arnold disclose forming (R,S)-nicotine without isolation of the (R,S)-nornicotine formed from the reduction of myosmine. In my opinion, a person of ordinary skill in the art would have known that Examples 4 and 5 teach the formation of myosmine (*id.* at 7:33-40 and 7:56-65), the reduction of myosmine to (R,S)-nornicotine (*id.* at 7:40-43 and 7:65-8:3), and the N-

methylation of the (R,S)-nornicotine to form (R,S)-nicotine (*id.* at 7:43-52 and 8:4-9). In my opinion, a person of ordinary skill in the art would have understood that Examples 4-5 of Arnold are conducted without isolating the (R,S)-nornicotine from the reaction mixture because other examples specify when and where an isolation step occurs. *Compare* Ex. 1008 at 6:51-7:8 (Example 2) *with id.* at 7:33-52 (Example 4) and 7:56-8:9 (Example 5).

307. In my opinion, a person of ordinary skill in the art would have been motivated to look to Arnold and apply the teachings of Arnold because Arnold is in the field of nicotine synthesis, teaches a reaction sequence that reduces myosmine to form nornicotine and then methylates nornicotine to form nicotine, and discusses appropriate reaction conditions for such a synthesis of nicotine. And the '962 Patent admits that the "field of the invention" is "a process for synthetically producing (S)-nicotine." Ex. 1001 at 1:5-7. As such, in my opinion, a person of ordinary skill in the art would have been motivated to look to Arnold's teachings about acceptable reaction conditions when reducing myosmine to form nornicotine and methylating nornicotine to form nicotine and would have had a reasonable expectation of success applying Arnold to form (S)-nicotine without first isolating the (S)-nornicotine from the reaction.

**2. Divi, Moody, Velikogne, Wetzl, and Arnold Render Claim 12 of the '962 Patent Obvious**

308. In my opinion, claim 12 is obvious by Divi, Moody, Velikogne, Wetzl, and Arnold, as explained below.

- a. “A process for producing a formulation for an electronic cigarette device, comprising forming (S)-nicotine according to the process of claim 1, and including the (S)-nicotine in a solvent with one or more additives.”**

309. Claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section XII.D.1. Thus, in my opinion, the step of “forming (S)-nicotine according to the process of claim 1” is also obvious.

310. I understand that preambles are generally not limiting, but even if the preamble is held to be limiting, claim 12 is still obvious. Divi discloses including (S)-nicotine in a solvent with one or more additives. For example, Divi discloses that “[t]reating nicotine dependence requires therapeutic use of nicotine. Nicotine is given to patients through dermal patches, gums, creams, lozenges, nasal sprays or electronic cigarettes to wean them away from smoking.” Ex. 1003 at 1:32-36. This discussion of nicotine in Divi expressly refers to (S)-nicotine, as the “Background of the Invention” section introduces nicotine as the (S)-enantiomer. *Id.* at 1:21-22.

311. Arnold discloses that “[n]icotine is currently included as a dilute solution, typically in combination [with] flavor, in liquid vaporization devices

(commonly known as vaporizers), as well as cessation devises such as patches and gums.” Ex. 1008 at 1:23-26. In my opinion, a person of ordinary skill in the art would have known that at least the electronic cigarette formulations of (S)-nicotine involve “including the (S)-nicotine in a solvent with one or more additives” as claimed.

**F. Divi, Moody, Velikogne, Wetzl, and Sheldon Render Claims 7-8 of the '962 Patent Obvious**

312. In my opinion, claims 7-8 are obvious by the disclosures of Divi, Moody, Velikogne, Wetzl, and Sheldon. As I explain below, a person of ordinary skill in the art would have been motivated to combine the teachings of Divi, Moody, Velikogne, Wetzl, and Sheldon and would have had a reasonable expectation of success in doing so.

**1. Divi, Moody, Velikogne, Wetzl, and Sheldon Render Claim 7 of the '962 Patent Obvious**

313. In my opinion, claim 7 is obvious by Divi, Moody, Velikogne, Wetzl, and Sheldon, as explained below.

**a. “The process of claim 1,”**

314. Claim 1 is obvious by Divi, Moody, Velikogne, and Wetzl. *See* Section XII.D.1.

**b. “wherein in step (i) the (S)-nornicotine is formed as part of an aqueous solution, and wherein step (ii)**

**comprises methylating the (S)-nornicotine contained within the aqueous solution.”**

315. Sheldon discloses the preparation of nicotine “by the enzymatic reduction of pseudooxynicotine using imine reductase enzymes.” Ex. 1013 at 18. Sheldon discloses that an imine reductase “refers to an enzyme that catalyzes the reduction of an imine, or of an iminium cation, optionally in a stereoselective manner.” *Id.* Sheldon teaches the imine-reductase-catalyzed reduction of pseudooxynicotine to nicotine in an aqueous solution that “is preferably water (as is known in the art, an aqueous salt solution or a buffer may be used as needed in order to avoid denaturation of the reductase enzymes).” *Id.* at 21.

316. In my opinion, a person of ordinary skill in the art would have understood from Sheldon that imine reductases should be used in an aqueous solution, such as water or a buffered solution, to avoid denaturing the enzyme. In my opinion, a person of ordinary skill in the art looking to catalyze the reduction of myosmine to (S)-nornicotine using an imine reductase would have recognized that the reaction should take place in an aqueous solution to avoid denaturing the imine reductase.

317. In my opinion, a person of ordinary skill in the art would have been motivated to look to Sheldon and apply the teachings of Sheldon because Sheldon is in the field of nicotine synthesis as well as the field of biocatalytic synthesis and provides disclosure about employing imine reductases in the synthesis of nicotine.

The '962 Patent admits both that the “field of the invention” is “a process for synthetically producing (S)-nicotine” and that a person of ordinary skill in the art would have been “familiar” with imine reductases. Ex. 1001 at 1:5-7 and 3:31-41. As such, in my opinion, a person of ordinary skill in the art would have been motivated to look to Sheldon’s teachings about using an imine reductase as a biocatalyst in a synthesis of nicotine and would have had a reasonable expectation of success in using an aqueous solution to form (S)-nornicotine from the imine reductase-catalyzed reduction of myosmine, as Sheldon taught that an imine-reductase-catalyzed synthesis of nicotine should proceed in aqueous solution to avoid denaturing the enzyme.

318. Further, Divi disclosed that the methylation of nornicotine to form nicotine was conducted while the nornicotine was present in an aqueous solution. Ex. 1003 at 5:26-29.

**2. Divi, Moody, Velikogne, Wetzl, and Sheldon Render Claim 8 of the '962 Patent Obvious**

319. In my opinion, claim 8 is obvious by Divi, Moody, Velikogne, Wetzl, and Sheldon, as explained below.

**a. “The process according to claim 7,”**

320. Claim 7 is obvious by Divi, Moody, Velikogne, Wetzl, and Sheldon. *See* Section XII.F.1.

- b. “wherein in step (ii) the (S)-nornicotine is reductively methylated using formaldehyde introduced as part of an aqueous solution.”**

321. Divi discloses that the methylation of nornicotine to form nicotine was conducted by introducing formaldehyde as part of an aqueous solution. Ex. 1003 at 5:26-29.

### **XIII. CONCLUSION**

322. For the foregoing reasons, it is my opinion that claims 1-14 of the '962 Patent are not patentable.

323. I declare under penalty of perjury that the foregoing is true and correct. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true. I understand that perjury and/or a willful false statement and the like are punishable by fine or imprisonment, or both (18 U.S.C. § 1001) and may jeopardize the paper with which this declaration is being submitted.

Executed on: January 12, 2023

/Jeffrey D. Winkler/

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