UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

THORNE RESEARCH, INC. and THORNE HEALTHTECH, INC.,
Petitioners,

v.

THE QUEEN'S UNIVERSITY OF BELFAST, and CHROMADEX, INC.,
Patent Owners.

Patent No. 12,252,506

DECLARATION OF GLENN PRESTWICH, PH.D.

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I, Dr. Glenn D. Prestwich, declare as follows:

I. QUALIFICATIONS

1. I have been retained on behalf of Thorne HealthTech, Inc. ("Thorne") to provide opinions based on my skills, knowledge, training, education, and experience and my examination of the materials cited herein. I have significant scientific and technological experience in synthetic organic and medicinal chemistry, as well as in biology, biochemistry, and bioengineering.

2. I obtained my B.S. with Honors in Chemistry in 1970 from the California Institute of Technology in Pasadena, CA, and my Ph.D. in Organic Chemistry in 1974 from Stanford University in Palo Alto, CA.

3. In 1974, and again in 1977, I worked in the Department of Chemistry at Cornell University in Ithaca, NY, pursuant to an NIH postdoctoral fellowship. Between 1974 and 1977, I was a Research Scientist in the Chemistry Unit of the International Centre of Insect Physiology and Ecology ("ICIPE") in Nairobi, Kenya.

4. I started my academic career in 1977 as an Assistant Professor of Chemistry at the State University of New York at Stony Brook ("SUNY, Stony Brook"). I continued working there until 1996, and during my tenure I became an Associate Professor and then a Full Professor of Chemistry. Beginning in 1992 and through 1996, I was also a Professor of Biochemistry and Cellular Biology, and I

was the Director of the New York State Center for Advanced Technology in Biotechnology at SUNY, Stony Brook.

5. In 1996, I was recruited to the University of Utah in Salt Lake City, UT as Presidential Professor and Chair of Medicinal Chemistry, where I also held several adjunct or research positions, including: Research Professor of Biochemistry; Adjunct Professor of Chemistry, Adjunct Professor of Bioengineering, and Adjunct Professor of Surgery. From 2008–2018, I was also the Presidential Special Assistant for Faculty Entrepreneurship, and I founded and led the Entrepreneurial Faculty Scholar program at the University of Utah. I currently hold the rank of Emeritus Professor of Medicinal Chemistry and retain several of my adjunct and research positions at the University of Utah.

6. From 2015–2018, I was the Chancellor's Distinguished Visiting Professor at Washington State University ("WSU"), and I co-founded the Entrepreneurial Faculty Ambassadors program. Beginning in 2018, and finishing at the end of 2021, I held the position of President's Distinguished Professor and worked primarily at Health Sciences Spokane in Spokane, WA. In this position, I was tasked with developing and growing an ecosystem of innovation and entrepreneurship in Spokane, including creation of Spinout Space in Spokane, a.k.a, "sp3nw," a life sciences innovation hub. I am the Founding Director of sp3nw, and I have facilitated the founding of over 18 new life science companies since January

2020. In addition, I was Principal Investigator on a grant from the United States Economic Development Administration to build a Flexible Infrastructure for Resilient Entrepreneurship ("FIRE"). I then assisted with securing an award for the Evergreen Bioscience Innovation Cluster ("EBIC") from Washington State's Department of Commerce. EBIC's goal is to build a membership organization to create, grow, and nurture a robust pharmaceutical and medical device and pharmaceutical supply chain in the Mountain Northwest. I am a member of EBIC and hold the entrepreneur seat on the Board of Directors for EBIC. I am currently the President's Distinguished Professor Emeritus at WSU.

7. I became engaged as an academic-based entrepreneur in co-founding companies and working with start-up companies based on faculty technologies in 1992, and I have held various titles at several of these companies, including: co-founder of Clear Solutions Biotech; co-founder and Chief Scientific Officer of Echelon Biosciences, Incorporated; Science Advisor of Echelon Biosciences, Incorporated; co-founder and Chief Scientific Officer of Sentrx Surgical, Inc.; Senior Scientific Advisor of Carbylan BioSurgery, Inc.; co-founder and Chief Scientific Officer of Glycosan Biosystems, Inc.; Senior Scientific Advisor of Sentrx Animal Care, Inc.; founder and manager, Clear Solutions Biomedical LLC; co-founder and Chief Scientific Officer of GlycoMira, LLC and GlycoMira Therapeutics, Inc.; Scientific Advisor of BioTime, Inc.; co-founder and Manager of

Deuteria Agrochemicals; co-founder and Manager of Deuteria Biomaterials LLC; co-founder and Chief Executive Officer of Metallosensors, Inc.; co-founder and President of Matrix Diagnostics Biosystems, Inc.; co-founder and Vice President, Maana Discoveries, Inc.; Director of Brickell Biotech, Inc.; Scientific Advisor of BioTime (now Lineage Cell Therapeutics); Scientific Advisory Board Member for Organovo; Scientific Advisory Board Member for Modern Meadow; and former Scientific Advisory Board Member, Executive Vice President and Chief Scientific Officer of Chemistry at Symic Bio, Inc.; Scientific Advisor to Valitor, Inc.; Scientific Advisor to Rebel Medicine, Inc.; Scientific Advisor to Shasqi, Inc.; Scientific Advisor to Tambo, Inc., Scientific Advisor to Amasa Therapeutics, Inc; Scientific Advisor to IHP Therapeutics; Scientific Advisor to Glycologix; Scientific Consultant to Endo Pharmaceuticals; Scientific Consultant to Teleflex, Inc.; and Science and Innovation Advisor to HTL Biotechnology.

8. I have also held several visiting and adjunct professorships, including being: Visiting Professor at the Department of Chemistry at Harvard University in 1992; Adjunct Professor of Biology at Utah State University; and Chancellor's Distinguished Visiting Professor at Washington State University.

9. Over the course of my career, my research has focused in the areas of synthetic and structural organic chemistry, medicinal chemistry, chemical ecology, bioengineering, and targeted drug delivery. My research activities encompassed a

number of diverse areas, including: (i) chemistry and biochemistry of natural compounds, pheromones, and hormones, including structure determinations using x-ray crystallography; (ii) purification, cloning, expression and mechanistic studies of proteins important in insect olfaction, insect development, vertebrate steroid metabolism, and vertebrate lipid signaling, (iii) discovery of cholesterol-lowering drugs by inhibition of key biosynthetic enzymes; (iv) development of chemical and photochemical cross-linking reagents and protocols for modification and purification of macromolecules, including proteins and glycosaminoglycans; (v) chemical synthesis and uses of affinity reagents for biological studies of phosphoinositides and lysophospholipids; (vi) development of new reagents for lipid signaling in cell biology and cancer treatment; (vii) chemical synthesis of chemically-modified and/or crosslinked hyaluronan and other glycosaminoglycan and protein-based biomaterials for wound repair, cartilage repair, tissue engineering, bioprinting, cell therapy, scar-free healing, and toxicology and tumor xenograft models; and (viii) invention and synthesis of sulfated glycosaminoglycan analogues as inflammation modulators for clinical utility in treatment of inflammation of skin, bladder, periodontal, and sinus tissues, and for treating oral mucositis due to radiation therapy in head and neck cancer.

10. I have published over 606 original peer-reviewed research publications as of February 2026, as well as four books and edited symposia, and

60 book chapters and symposium papers. I have given more than 690 invited lectures since 1975. I am also a named inventor on more than 100 patents and patent applications, of which at least 50 U.S. and foreign patents have issued. These inventions cover many areas, including the control of insect pests, cholesterol lowering agents, labeled phospholipids and phosphoinositides in drug discovery assays, anti-cancer and anti-angiogenic agents, signal transduction modifiers, mercury sensing chemicals, radiodense hydrogel spacers for use in radiation therapy, wound-healing and regenerative medicine compositions, anti-inflammatory drugs, as well as the compositions and uses for a wide variety of chemically-modified hyaluronan (also known as hyaluronic acid, or HA) derivatives.

11. Many of my numerous awards and honors are summarized in my curriculum vitae (CV), which is attached as EX1014. I received peer and community recognition and numerous awards for my work, including the Alfred P. Sloan Research Award (1981-85) and Camille and Henry Dreyfus Teacher-Scholar Award (1981-86). In 2001, I was awarded the prestigious Silverstein-Simeone Award of the International Society of Chemical Ecology, for lifetime research achievements in the chemistry, biology and biochemistry of insect chemical communication.

12. I received both the 1998 Paul Dawson Biotechnology Award and the 2008 Volwiler Research Award of the American Association of Colleges of Pharmacy. I was elected as a Fellow of the American Institute for Medical and Biological Engineering in 2005, named one of vSpring's Top 100 Entrepreneurs in 2005 and 2006, and selected as a recipient of a TIAA-CREF "Greater Good" award (2006), as a Utah Business Magazine "Health Care Hero" for 2006. I was awarded the Utah Governor's Medal for Science and Technology for 2006. In 2010, I received the University of Utah's Distinguished Scholarly and Creative Research Award, and in 2014 I was awarded the University of Utah's Distinguished Innovation and Impact Award. In 2010, I received the "Rooster Prize" of the International Society for Hyaluronan Science ("ISHAS") for outstanding contributions to HA-derived products; I am currently the Vice President of the Applied Division of ISHAS. In 2013, I was inducted as a Fellow of the National Academy of Inventors, and in 2018, I was elected as a Fellow of the American Association for the Advancement of Science.

13. I have been a member of the American Chemical Society since 1970, a member of the American Association for the Advancement of Science since 1975, a member of Sigma Xi since 1977, an American Associate of the Colleges of Pharmacy since 1998, the Alternate Councilor for the Division of Medicinal Chemistry for the American Chemical Society between 2002 to 2004, a member of

the American Association for Cancer Research from 2003–2017, a member of the Society for Biomaterials since 2003, and a member of the International Society for Hyaluronan Sciences since 2004.

14. I have been a reviewer of manuscripts and grants for more than 50 journals, including Nature, Science, Journal of Biological Chemistry, Journal of Organic Chemistry, Proceedings of the National Academy of Sciences of the United States of America, and Journal of the American Chemical Society. I have also served on the editorial and advisory board for many journals, including: Bioconjugate Chemistry, Macromolecular Biosciences, Current Opinion in Chemical Biology, Perspectives in Medicinal Chemistry, Advanced Therapeutics, and currently for Science Translational Medicine.

II. SCOPE OF WORK

15. I understand from Thorne's counsel that a petition is being filed with the United States Patent and Trademark Office for Inter Partes Review of U.S. Patent No. 12,252,506 ("the '506 patent", EX1001), to Marie Migaud et al., and is entitled "Methods of Preparing Nicotinamide Riboside and Derivatives Thereof." I understand that the '506 patent is assigned to The Queen's University of Belfast ("Queen's University"). I have been informed by Thorne's counsel that ChromaDex, Inc. ("ChromaDex") and/or Niagen Bioscience ("Niagen") may also have certain rights to the '506 patent.

16. I have been retained by Thorne HealthTech, Inc. ("Thorne") to offer an expert opinion on the validity of claims 1-12 and 21-35 of the '506 patent. I receive $800 per hour for my services. No part of my compensation is dependent on my opinions, and I have no financial interest in the outcome of this proceeding.

17. I have been specifically asked to provide my opinion whether there is written description and enablement support in the priority chain before the April 26, 2023, filing date of the application that resulted in the '506 patent, and whether claims 1-12 and 21-35 of the '506 patent are unpatentable if they are not entitled to a pre-April 26, 2023 priority date. In connection with this analysis, I have reviewed the '506 patent (EX1001), its file history (EX1002), as well as the patent applications and patents to which the '506 patent claims priority (EX1003-EX1008). I have also reviewed and considered other documents in arriving at my opinions and cite them in this declaration.

III. LEGAL STANDARDS

18. I understand from Thorne's counsel that the United States Patent and Trademark Office may cancel issued claims of the '506 patent if the Petitioner (here, Thorne) demonstrates that the claims fail to satisfy the requirements of patentability that the claims must be novel and non-obvious.

19. I also understand that a claimed invention is not entitled to claim the benefit of an earlier-filed patent application if that earlier-filed patent application

did not provide, among other aspects, adequate written description and enablement to support the full scope of the claimed invention.

A. Claim Construction

20. I have been advised that the claims should be understood according to their ordinary and customary meaning as understood by a person having ordinary skill in the art at the time of the invention in light of the language of the claims, the specification, and the prosecution history of record. I have been provided a copy of the prosecution history of U.S. Patent Application No. 18/307,733 (EX1002), which issued as the '506 patent. I have applied the plain and ordinary meaning of the claims in my analysis below. Additionally, the specification and prosecution history discuss the meaning ascribed to some claim terms, and I address these terms when discussing the corresponding claims.

21. I understand that the term "comprising" in a claim indicates that the claim includes at least the listed elements, but that the claim can also encompass additional, unstated elements.

B. Written Description

22. I understand that, in deciding whether a patent application satisfies the written description requirement, one must consider the description from the viewpoint of a person skilled in the field of technology at the time of the invention. The written description requirement is satisfied if the patent application clearly

reasonably conveys to a person of ordinary skill in the art to which it pertains or with which it is most nearly connected that the inventor possessed (i.e., invented) the full scope of the claimed invention at the time of the invention.

23. I have additionally been instructed that the written description requirement may be satisfied in appropriate circumstances by a combination of the words, structures, figures, diagrams, formulas, etc., contained in the patent application. But a specification that merely renders the invention obvious does not satisfy the written description requirement if it does not reasonably convey that the applicants invented what is claimed. Indeed, if the specification merely provides a "wish" or a "plan" for obtaining the claimed invention rather than a description of the invention itself, the specification fails to provide adequate written description support. A research hypothesis does not constitute written description support for a claimed invention.

24. I understand that the full scope of a claim or any particular requirement in a claim need not be expressed in the specification in the exact same words as in the claim, nor is doing so necessarily sufficient to find written description support for the claims. The test is whether the specification clearly conveys to a person ordinarily skilled in the field of technology of the patent at the time of filing that the applicant possessed (i.e., invented) the full scope of the claim (including each individual requirement) at the critical date.

25. I understand that some factors that may be useful for evaluating written description support include: (1) the maturity of the science or technology; (2) the existing knowledge in the particular field; (3) the predictability of the aspect at issue; and (4) the extent and content of the prior art.

C. Enablement

26. I understand that a claim lacks enablement if the specification does not contain a sufficiently full, clear, concise, and exact description of the manner and process of making and using the full scope of the claimed invention to enable a person ordinarily skilled in the field to make and use the invention without undue experimentation at the critical date. However, some experimentation to make and use the invention is allowable if it is not undue.

27. I understand that in deciding whether a person having ordinary skill in the art would have to engage in undue experimentation to make and use the invention, several factors may be considered:

- the nature of the invention
- the state of the art
- the breadth of the claimed invention
- the amount of guidance presented in the patent
- whether the patent discloses specific working examples of the claimed invention

- the time and cost of any necessary experimentation and how routine any necessary experimentation is in the relevant field of technology
- the predictability of the relevant field of technology; and
- the level of ordinary skill in the relevant field of technology.

28. I understand that no one factor alone necessarily controls. Rather, whether the degree of experimentation required is undue may involve weighing these factors in the context of the claimed invention and the state of the art at the time of the original application, to determine whether a person skilled in the art would need to engage in undue experimentation to make and use the full scope of the claimed invention. I also understand that if claims require a logical impossibility, then those claims lack enablement.

D. Anticipation

29. I understand that anticipation requires disclosure in a single reference of every element of a claim as arranged in the claim. I understand that the disclosure may be express but that it also may be satisfied by inherency when the element is necessarily present in the reference despite an absence of express disclosure. I understand that prior art disclosure of a species anticipates a genus that encompasses the species, that prior art disclosure of a point in a claimed range anticipates the claimed range, and that prior art disclosure of a range overlapping with a claimed range anticipates the claimed range (where nothing critical has been

demonstrated about the claimed range). In other words, if the prior art discloses a range that overlaps with the claimed range, the claimed range is anticipated unless the patent describes something particularly unique or critical about the specific claimed range.

E. Obviousness

30. I understand that a claimed invention is unpatentable for obviousness if the differences between the invention and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art by the critical date.

31. It is further my understanding that a determination of obviousness requires inquiries into: (1) the scope and content of the prior art when the invention was made; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art when the invention was made; and, to the extent it exists, (4) objective evidence (secondary considerations) the patent owner asserts to prove the claims are not obvious despite what the prior art might suggest.

32. I understand that a claim is obvious when all of the claimed elements were known in the prior art and one skilled in the art would have had reason to combine (or modify) the elements as claimed with a reasonable expectation of success. I understand that obviousness may also be shown by demonstrating that it would have been obvious to modify what is taught in a single prior-art reference to

create the patented invention or by combining teachings of two or more prior art references. I understand that, in order for a claimed invention to be considered obvious based on a combination of prior art references, there must be some rational underpinning for the proposed combination. I understand that improper hindsight, using the challenged patent as a guide, must not be used when determining whether a person having ordinary skill in the art would make the proposed combination. Thus, a conclusion of obviousness must be firmly based on prior-art knowledge and the skill of a person having ordinary skill in the art at the time the invention was made, without the improper use of post-filing knowledge.

33. In determining whether a particular combination of prior art teachings would have been obvious, I understand that the following are examples of approaches and rationales that may be considered:

(a) Combining prior art elements according to known methods to yield predictable results;

(b) Simply substituting one known element for another to obtain predictable results;

(c) Using a known technique to improve similar devices (methods, or products) in the same way;

(d) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

(e) Applying a technique or approach that would have been "obvious to try" (choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success);

(f) Appreciating known work in one field of endeavor that may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been predictable to one of ordinary skill in the art; or

(g) Following some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art teachings to arrive at the claimed invention.

34. I understand that obviousness may be established by showing that all of the claimed elements were known in the prior art and that a person skilled in the art would have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art.

F. Secondary Considerations of Nonobviousness

35. With regard to secondary considerations of nonobviousness, I understand that objective evidence may be considered as an indication that the claimed invention would not have been obvious at the time the claimed invention

was made. I understand that the purpose of secondary considerations is to prevent an improper hindsight analysis of the obviousness of the claims.

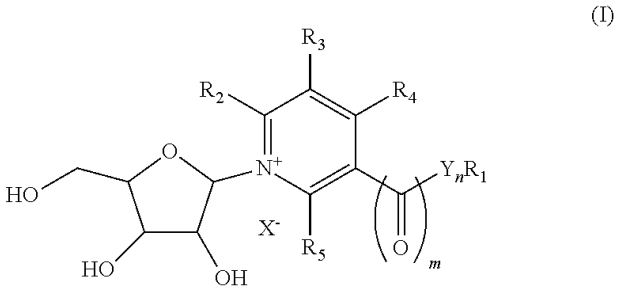
36. I also understand that there are several factors that may be considered as secondary considerations. These factors include commercial success of the invention, industry praise for the invention, skepticism of the invention, licensing of the invention, copying of the invention, long-felt need that the invention solved, failure of others, and unexpected results of the invention.

37. I understand that, in order for evidence of secondary considerations to be significant, there must be a sufficient nexus between the claimed invention and the evidence of secondary considerations. I understand that this nexus must provide a link between the merits of the claimed invention and the evidence of secondary considerations provided.

IV. OVERVIEW OF THE PATENT

38. I have reviewed the ’506 patent in its entirety including the specification, the figures, and the claims. The title of this patent is “Methods of preparing nicotinamide riboside and derivatives thereof.” The Abstract of the ’506 patent states:

> Methods of preparing nicotinamide riboside and derivatives thereof. In an aspect, the invention relates to a method of preparing a compound of formula (I).



EX1001 ('506 patent), Abstract.

39. The specification describes the synthesis of compounds of formula (I), and in particular of nicotinamide riboside derivatives of formula (I). *E.g.*, EX1001, 2:18-28, Figure 2, Figure 3. The specification also describes counter ions paired with the compounds of formula (I). *Id.*, 2:29-34, Figure 5.

40. The specification admits that nicotinamide riboside and its derivatives had known protocols for their preparation, and that there was desire to use them as nutritional supplements. *Id.*, 1:28-64. For example, it was known in the field to make nicotinamide riboside with the triflate ($^{-}$OTf) counterion, but to exchange the triflate for a different ion to avoid toxicity during the production of nutritional supplements. *Id.* ("[T]rimethylsilyl trifluoromethanesulfonate (TMSOTf) is used as the catalyst in the disclosed method, and results in the prepared compounds inevitably being in the form of their triflate ($^{-}$OTf) salts. The triflate salt form of nicotinamide riboside, or derivatives thereof, is not suitable for use as a nutritional supplement, because of its associated toxicity."). The specification explains that

ion exchange could be used with, for example, reverse phase liquid chromatography, to replace the triflate counterion. *Id.*

41. In addition to formula (I), the specification of the '506 patent discusses certain precursor molecules that can be used to make formula (I). EX1001, 2:37-3:24 (method of preparing a compound of formula (I) from a compound of formula (II)), 6:66-7:18 (formula (II) prepared from a compound of formula (III)), 8:15-34 (formula (III) prepared from a compound of formula (IV)). These precursor molecules begin with a compound having formula (IV), and proceed serially through a compound having each of formulas (III) and (II) before ultimately achieving a compound of formula (I). EX1001, 2:37-3:24, 6:66-7:18, 8:15-34; Figure 2.

42. Throughout the figures and description of the '506 patent, formula (IV) is universally described as having protecting groups at what formula (IV) calls R_6-R_8. EX1001, 8:17-28 ("n, m, Y, ***R_1-R_8*** and X^- are ***as defined above***."); *id.*, 7:1-16 ("***R_6, R_7 and R_8***, which may be the same or different, ***are each independently a hydroxyl-protecting group***."). The specification explains that the purpose of providing protecting groups at what formula (IV) describes as R_6-R_8 is to protect the adjacent oxygens from unwanted reactions. The specification also explains that the choice of protecting groups can also increase the lipophilicity and thereby

facilitate migration of formula (III) product into the organic phase of the solution or mixture of organic and aqueous solvents. EX1001, 7:22-41; *id.*, 8:66-4.

43. The claims of the ’506 patent recite the impossibility of R_6-R_8 being hydrogen, contrary to the specification’s clear definition that formula (IV) R_6-R_8 must be hydroxyl-protecting groups. This recited impossibility is beyond what was described in the priority documents leading to the application that issued as the ’506 patent. As I will discuss in further detail below, ***this impossibility of R_6-R_8 being hydrogen atoms in formula (IV) occurred for the very first time on April 26, 2023***, upon filing of the application that resulted in issuance of the ’506 patent.

V. PROSECUTION HISTORY OF THE PATENT

44. During prosecution of the ’506 patent, the applicant did not inform the Examiner that it was claiming subject matter not described in the earlier priority documents the applicant relied upon. I understand from the face of the ’506 patent that the application that resulted in its issuance was filed on April 26, 2023, but claims the benefit of earlier priority dates. For example, it claims priority to United Kingdom Patent Application No. 1313465.5 (filed Jul. 29, 2013) (EX1003), International Patent Application No. PCT/EP2014/065971 (filed Jul. 24, 2014) (EX1004), U.S. Patent No. 10,000,519 (filed Jan. 29, 2016) (EX1005), U.S. Patent No. 10,815,262 (filed Feb. 27, 2018) (EX1006), U.S. Patent No. 11,584,770 (filed May 29, 2020) (EX1007), and U.S. Patent Application No. 17/736,834 (now U.S.

Patent No. 11,981,698, filed May 4, 2022) (EX1008). EX1001, (63), (30), 1:4-19. As I explain further below, it is my opinion that the ’506 patent claims are entitled to a priority date no earlier than April 26, 2023.

45. During prosecution of U.S. App. No. 18/307,733 (“the ’733 application”), which issued as the ’506 patent, I read that the examiner made rejections only under nonstatutory double patenting and indefiniteness. EX1002, 96-101. In reviewing the file history of the ’733 application, I do not see any indication that the examiner evaluated whether the claimed subject matter was entitled to a priority date earlier than April 26, 2023. I do not see any indication that the applicant informed the patent examiner that the ’733 application was the first application in the priority chain to recite the logical impossibility of R_6-R_8 of formula (IV) as being hydrogen atoms, whereas the definition clearly requires R_6-R_8 to be hydroxyl-protecting groups. I understand the patent examiner allowed the application with no additional rejection and without providing any reasons for allowing the claims. *Id.*, 184. As I detail further below, it is my opinion that the ’506 patent claims are not entitled to a priority date earlier than April 26, 2023, that there is anticipatory prior art to many claims of the ’506 patent when its correct priority date is considered, and that combined prior art to claims of the ’506 patent render the claims obvious when the correct priority date is considered. Taken together, it is my opinion that the allowance of the claims was granted in error.

VI. LEVEL OF SKILL IN THE ART

46. I have been advised by Thorne's counsel that "a person having ordinary skill in the art" (POSA) is a hypothetical person to whom one could assign a routine task with reasonable confidence that the task would be successfully carried out. I have been advised further that, in determining the level of ordinary skill in the art that someone would have had at the time the claimed invention was made, I should consider: (1) the levels of education and experience of persons working in the field; (2) the types of problems encountered in the field; and (3) the sophistication of the technology.

47. The '506 patent states that "[t]he invention relates to methods of preparing nicotinamide riboside and derivatives thereof." EX1001 ('506 patent), 1:23-24. The patent claims are directed to compounds of Formula (IV), nutritional supplements comprising such compounds, and methods of making isomerically pure compounds of Formula (IV). The field of the invention of the '506 patent is thus related to the organic chemistry synthesis of nicotinamide riboside derivatives.

48. Based on my specialized education, knowledge, training, and experience, I am familiar with the level of skill of a person having ordinary skill in the art as of the critical date. It is my opinion that a person having ordinary skill in the art of the '506 patent in April 2023 and as far back as the earliest claimed priority date in 2013 would have had an advanced degree (e.g., Ph.D., M.S., or

equivalent), in organic chemistry, medicinal chemistry, nutritional science, pharmaceutical science, or a related field. I was a person having at least ordinary skill in the art by this definition before April 26, 2023, as well as before the earliest claimed priority date of July 29, 2013, and I still am a person having at least ordinary skill in the art by said definition.

VII. SUMMARY OF OPINIONS

49. In my opinion, none of the claims of the ’506 patent were entitled to a priority date before April 26, 2023. It is also my opinion that each of claims 1-12, 21-28, 31, and 34-35 is anticipated, and that claims 29-30 and 32-33 would have been obvious, in view of prior art references.

50. I have evaluated whether the patents and patent applications to which the ’506 patent claims priority provide written description support for the subject matter claimed in the ’506 patent. As I explain further below, it is my opinion that the prior-filed applications do not provide adequate written description support for the claims of the ’506 patent, and thus the claims of the ’506 patent are entitled to a priority date of no earlier than April 26, 2023—the filing date of the ’733 application. I explain my opinion further below in Section X.B.

51. I have also evaluated whether the patent applications to which the ’506 patent claims priority enable the subject matter claimed in the ’506 patent. As I explain further below, it is my opinion that the prior-filed applications do not

enable the claims of the ’506 patent, and thus the claims of the ’506 patent are entitled to a priority date of no earlier than April 26, 2023—the filing date of the ’733 application. I explain my opinion further below in Section X.C.

52. I have evaluated whether the prior art ’184 publication (EX1022) discloses the claimed features of the ’506 patent. As I explain further below, it is my opinion that the ’184 publication discloses each and every element of claims 1-12, 21-28, 31, and 34-35 of the ’506 patent. Based on my conclusion that the claims of the ’506 patent lack written description or enablement support before 2023, it is my understanding that the ’184 publication is prior art, and the ’184 publication anticipates claims 1-12, 21-28, 31, and 34-35 of the ’506 patent. I explain my opinion further below in Section XI.

53. I have evaluated whether the combined prior art references of the ’184 publication (EX1022) and the GRAS Notice (“GRAS,” EX1017) discloses the claimed features of the ’506 patent. As I explain further below, it is my opinion that the combination of the ’184 publication and GRAS render obvious each of claims 29-30 and 32-33 of the ’506 patent. Based on my conclusion that the claims of the ’506 patent lack written description or enablement support before 2023, it is my understanding that the ’184 publication and GRAS are prior art, and the combination of the ’184 publication and GRAS renders obvious claims 29-30 and 32-33 of the ’506 patent. I explain my opinion further below in Section XII.

VIII. TECHNICAL BACKGROUND

54. Nicotinamide riboside is known in the scientific community to provide beneficial effects when administered as an oral supplement. Nicotinamide adenine dinucleotide (NAD^+) plays a crucial role in the biological systems of cell metabolism and responses to oxidative stress. EX1009 (Schabert), 1. Decreased NAD^+ levels are associated with, among other things, aging, age-related disease, obesity, and type 2 diabetes. EX1009, 1; *see also* EX1022 ('184 publication), [0002] ("nicotinamide riboside has been shown in mice to enhance oxidative metabolism and protect against high-fat diet induced obesity, which has resulted in significant interest in nicotinamide riboside and its derivatives"). Supplements to provide increased levels of NAD^+—namely through supplementation of NAD^+ precursors such as nicotinamide riboside (NR^+)—are therefore of interest to the scientific community. EX1009, 1; EX1022, [0003]-[0005]. The supplemental NR^+ is converted *in vivo* to NAD^+ by NR^+ kinase or by nucleoside phosphorylase and nicotinamide salvage pathway. EX1009, 1-2.

55. Nicotinamide riboside supplements are favored over other NAD^+ precursors and have shown beneficial effects for numerous diseases. As explained by Schabert et al.:

> When orally supplemented, a preventative and therapeutic effect in numerous diseases has been observed in association with increased NAD^+ levels. NR^+ is preferred over other NAD^+ precursors because its

> use is not related to serious side effects or flushing, as has been observed with other NAD^+ precursors.[1]

EX1009 (Schabert), 2; *see also* EX1022 ('184 publication), [0002] ("Since nicotinamide riboside is a naturally occurring compound, nicotinamide riboside and its derivatives have great potential as natural, nutritional supplements, which may provide health benefits without causing side effects.").

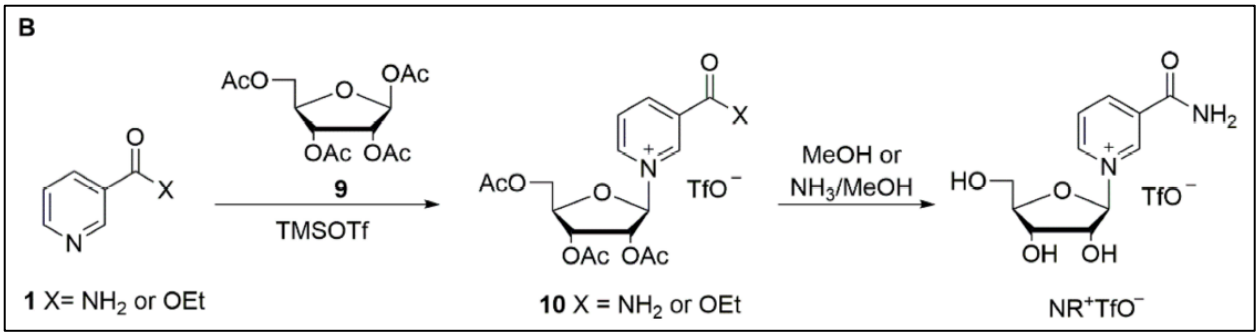
56. Previously, salts of nicotinamide riboside were produced using halides, such as bromide, or triflate, but some of those compositions were toxic and thus were not viable as dietary supplements. EX1009 (Schabert), 2 ("Until now, only the bromide and the chloride of NR^+ were known as crystalline salts…. Due to its toxicity, the bromide salt is unsuitable as a food supplement."); EX1022 ('184 publication), [0003] ("The triflate salt form of nicotinamide riboside, or derivatives thereof, is not suitable for use as a nutritional supplement, because of its associated toxicity. Thus, the compounds…require an additional step to exchange the triflate anion for an anion that would be pharmaceutically acceptable…utilizing for example, reverse phase liquid chromatography as disclosed."). Instead, those in the field focused on the chloride salt of nicotinamide riboside. EX1009, 2 ("the chloride salt of NR^+ is currently commercially available

[1] Citations omitted from quote.

as a dietary supplement."); EX1017 (GRAS), 3 (nicotinamide riboside chloride safe "as an ingredient in vitamin waters, protein shakes, nutrition bars, gum and chews, based upon scientific procedures").

57. It was also known in the field that only the beta (β) anomer form of nicotinamide riboside was biologically active. *See* EX1009 (Schabert), 2 ("Since only the β form is biologically active, high stereoselectivity toward the β NR^+ anomer is highly desirable."). Thus, while some synthetic pathways to forming nicotinamide riboside could provide other salts, such pathways were not viable for the manufacture of supplements because "synthesis of NR^+ often achieves poor stereoselectivity, with formation of a mixture of α and β NR^+ anomers." EX1009 (Schabert), 2; *see also* EX1022 ('184 publication), [0129] (preferring methods "producing the desired β-anomer. This is in contrast, for example, to Tanimori et al [EX1015], which is not stereoselective and produces significant amounts of the α-anomer, which is undesirable.").

58. One well-known alternative synthesis for forming nicotinamide riboside derivatives was to combine acetylated (i.e., hydroxyl-group protected) ribose with the corresponding substituted pyridine in the presence of Friedel-Crafts catalyst (e.g., TMSOTf— trimethylsilyl trifluoromethanesulfonate), forming the triacetylated (***protected***) nicotinamide riboside as a triflate salt. EX1009 (Schabert), 4 (citing Tanimori (EX1015)); *see also id.*, Scheme 2B (reproduced below).



As explained in the prior art, the protected triflate salt was then deprotected (i.e., the acetyl protecting groups were removed) via methanolysis, resulting in the deprotected nicotinamide riboside triflate salt. EX1009, 4 & Scheme 2B; *see also* EX1015 (Tanimori), EX1016 (Franchetti). Because "the triflate is not a pharmaceutically acceptable counter ion," it was known in the field that "ion exchange is required." EX1009 (Schabert), 4; *see also* EX1022 ('184 publication), [0003] ("the compounds…require an additional step to exchange the triflate anion for an anion that would be pharmaceutically acceptable…utilizing for example, reverse phase liquid chromatography as disclosed.").

59. Thus, the prior art disclosed the benefits of nicotinamide riboside (NR^+) salts as supplements as well as methods of their manufacture. It was well-known in the field that such compounds could be made as triflate salts, and thereafter be subjected to a form of ion exchange in order to generate salts suitable for administration as a supplement.

IX. ANALYSIS OF ASSERTED REFERENCES

A. The ’184 Publication

60. United States Patent Application Publication Number US 2016/0168184 (“the ’184 publication”, EX1022) published June 16, 2016. I understand it is prior art that published before the earliest priority date to which the ’506 patent subject matter was entitled of April 26, 2023.

61. The ’184 publication discloses the synthesis of nicotinamide riboside (NR^+) salts in a way to “avoid or mitigate the disadvantages of the prior art” which “present obstacles to the scaling up…for commercial or industrial use, and which, therefore, greatly limit the commercial opportunities.” EX1022, [0005]-[0006]. The ’184 publication explains a process of forming desirable nicotinamide riboside salts from an undesirable salt via reduction of a hydroxyl-protected version of nicotinamide riboside, deprotection of the hydroxyl-protecting groups, and introduction of a different counterion, such as a chloride salt. EX1022, Scheme B & Figure 3; *id.*, [0137] (“triacetyl nicotinamide riboside, triflate salt may be used to prepare triacetyl-1,4-dihydronicotinamide riboside, as described in Example 1(A), and that triacetyl-1,4-dihydronicotinamide riboside may be used to prepare 1-(beta-D-ribofuranosyl)-1,4-dihydronicotinamide, as described in Example 2, and that 1-(beta-D-ribofuranosyl)-1,4-dihydronicotinamide may be used to prepare nicotinamide riboside, chloride salt”). The ’184 publication explains that its

methods "provide for the minimization of solvent use, purification and reaction time." EX1022, [0129].

B. GRAS

62. The Generally Recognized as Safe (GRAS) Determination for nicotinamide riboside chloride ("GRAS") (EX1017) is a notification to the FDA that was filed March 9, 2016. I understand it is prior art that published before the earliest priority date to which the '506 patent subject matter was entitled of April 26, 2023.[2]

63. GRAS is a summary from an expert panel that evaluated the safety of nicotinamide riboside chloride "as an ingredient in vitamin waters, protein shakes,

[2] EX1017 can be accessed directly from the FDA at the GRAS Notices website: https://www.hfpappexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices. A user can scroll down and find the listing for nicotinamide riboside and click the link to access the page hosting EX1017. *See* EX1019, 36. Alternatively, searching for "nicotinamide riboside" takes the user directly to the nicotinamide riboside chloride GRAS (https://www.hfpappexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=635) (*see* EX1018), which provides EX1017 as a .pdf download. The FDA website has been providing this information since at least January 2021, as shown by the following Internet Archive websites: https://web.archive.org/web/20201222145917/https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&sort=GRN_No&order=DESC&showAll=true&type=basic&search= (GRAS Notices website, saved December 2020) (*see* EX1020); https://web.archive.org/web/20210124164020/https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=635 (nicotinamide riboside chloride GRAS, saved January 2021) (*see* EX1021).

nutrition bars, gum and chews." EX1017, 000003. GRAS envisions large-scale production of its nicotinamide riboside salt, with over 10% of the total U.S. population estimated as consumers of its proposed food uses. *Id.*, 000039. As part of its safety evaluation, GRAS provides batch analysis and requirements concerning impurities, residual solvents, and water. *Id.*, 000028-000030 & Table 2.

X. '506 PATENT EARLIEST PRIORITY IS APRIL 26, 2023

64. I have been informed that, in order for a claim to benefit from the right to priority to an earlier-filed patent application, that earlier-filed application must both: (1) disclose the claimed subject matter with sufficient detail to satisfy the written description requirement of 35 U.S.C. § 112; and (2) provide sufficient detail so as to meet the enablement requirement of 35 U.S.C. § 112. If either requirement is not satisfied, the claim at issue is unable to claim priority to the earlier-filed parent application.

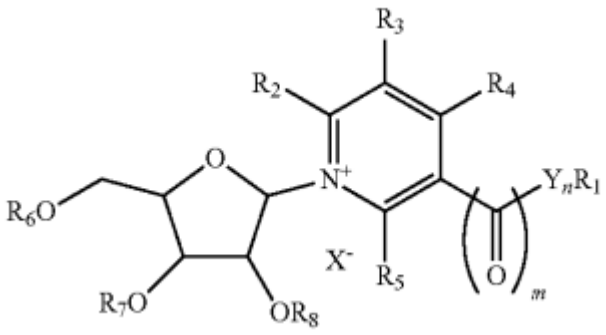
65. It is my opinion that the patents and patent applications upon which the '506 patent relies for priority do not convey to the POSA that the inventors of the '506 patent possessed (i.e., invented) the claimed subject matter. It is also my opinion that the applications and patents upon which the '506 patent relies for priority do not enable a POSA to practice the claimed invention—that is, to make and use the full scope of the claimed invention—without undue experimentation.

66. The earliest-filed patent application for which priority is claimed by the ’506 patent is GB 1313465.5 (EX1003). The next application cited by the ’506 patent for priority is PCT/EP2014/065971 (EX1004). The next patent cited by the ’506 patent for priority is U.S. Patent No. 10,000,519 (EX1005). The next patent cited by the ’506 patent for priority is U.S. Patent No. 10,815,262 (EX1006). The next patent cited by the ’506 patent for priority is U.S. Patent No. 11,584,770 (EX1007). The next application cited by the ’506 patent for priority is U.S. Patent Application No. 17/736,834 (now U.S. Patent No. 11,981,698) (EX1008). For efficiency purposes, I will refer to these documents collectively as the priority documents.

A. All Priority Documents Define R_6, R_7, and R_8 of Formula (IV) as Hydroxyl-Protecting Groups.

67. The specifications of the priority documents all define Formula (IV) R_6-R_8 as hydroxyl-protecting groups. For example, the specifications of the priority documents each provide the following structure for formula (IV) only once (reproduced below).

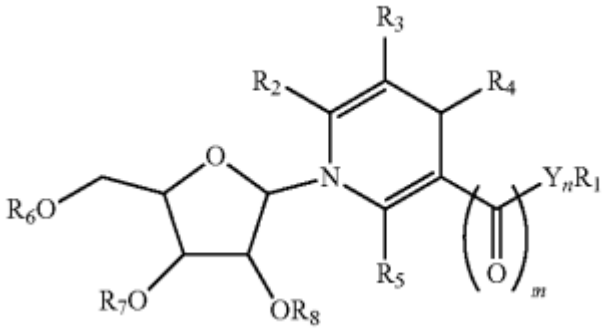
(IV)



EX1003, 10:28-31; EX1004, 10:28-31; EX1005, 8:17-28; EX1006, 8:17-28; EX1007, 8:20-31; EX1008, 8:17-28. They each explain that "n, m, Y, ***R_1-R_8*** and X^- are ***as defined above***." EX1003, 11:1; EX1004, 11:1; EX1005, 8:30; EX1006, 8:31; EX1007, 8:34; EX1008, 8:30.[3] R_6, R_7, and R_8 are defined above in each document for formula (III), and the specifications of the priority documents uniformly define R_6, R_7, and R_8 as being limited to "hydroxyl-protecting groups."

68. The reference to R_1-R_8 of formula (IV) being "defined above" in each of the specifications of the priority documents directs the POSA to the definition for R_1-R_8 immediately above formula (IV). This definition arrives in the priority documents' disclosure of formula (III), which immediately preceded formula (IV) in the specifications, and is the compound that immediately follows formula (IV) in the synthesis scheme. The specifications of the priority documents uniformly describe formula (III):

(III)



[3] Unless indicated otherwise, all bold-italic emphases are added.

"wherein n, m, Y and R_1-R_5 are as defined above; and ***R_6, R_7 and R_8***, which may be the same or different, ***are each independently a hydroxyl-protecting group***." EX1003, 8:30-9:6; EX1004, 8:30-9:6; EX1005, 7:1-16; EX1006, 7:1-16; EX1007, 7:3-19; EX1008, 7:1-16. The definition of formula (IV) limiting R_6-R_8 to hydroxyl-protection groups is the only definition of R_6-R_8 provided in the specifications of the priority documents. The specifications of the priority documents thus uniformly define R_6, R_7 and R_8 as ***hydroxyl-protecting groups***. A POSA would know that the hydroxyl-protecting groups temporarily "mask" the hydroxyl functional group, and thus block unwanted chemical transformations of the hydroxyl group. Thus, the specifications of the priority documents uniformly define each of R_6-R_8 as a hydroxyl-protecting group (EX1003, 8:30-9:6; EX1004, 8:30-9:6; EX1005, 7:1-16; EX1006, 7:1-16; EX1007, 7:3-19; EX1008, 7:1-16). A POSA would have understood this excludes, e.g., hydrogen.

69. Despite this clear definition, the '506 patent claims recite a logical impossibility, requiring hydroxyl-protecting groups by reciting defined formula (IV) R_6-R_8, yet reciting a conflicting identification of R_6-R_8 as hydrogen (or in some cases phosphate). For example, independent claim 1 recites "R_6, R_7, and R_8, which may be the same or different, are ***each independently H*** or a hydroxyl-protecting group; or wherein ***R_6 is a phosphate***." Independent claim 6 similarly recites "R_6, R_7, and R_8, which may be the same or different, are ***each***

independently H or a hydroxyl-protecting group; or where ***R_6 is a phosphate***." Independent claim 13, reciting a method of making an isomerically pure compound of formula (IV), similarly recites "R_6-R_8, which may be the same or different, are ***each independently H*** or a hydroxyl-protecting group; or wherein ***R_6 is a phosphate***." Independent claim 18 likewise recites "R_6, R_7, and R_8, which may be the same or different, are ***each independently H*** or a hydroxyl-protecting group; or where ***R_6 is a phosphate***." Finally, independent claim 37 recites "R_6-R_8, which may be the same or different, are ***each independently H*** or a hydroxyl-protecting group." Thus, each independent claim recites a logical impossibility that is not supported by the disclosures of the priority documents.

B. Lack of Written Description.

70. I have reviewed each of the priority documents to evaluate whether there is written description support for formula (IV) having R_6-R_8 as anything other than hydroxyl-protecting groups. There is not. Based on my review, I have concluded that the claims lack written description support before April 26, 2023.

71. With respect to disclosure of R_6-R_8 in formula (IV), each of the priority documents is essentially identical. I therefore discuss the documents together in the aggregate and provide parallel citations for each individual document for each point below. As I explain further below, for each of the priority documents, the specifications uniformly disclose R_6, R_7, and R_8 in formula (IV) as

being limited to hydroxyl-protecting groups. EX1003, 10:27-11:10, 8:29-9:6; EX1004, 10:27-11:10, 8:29-9:6; EX1005, 8:14-34, 6:66-7:18; EX1006, 8:14-35, 6:66-7:18; EX1007, 8:18-38, 7:1-21; EX1008, 8:15-34, 6:66-7:18.

72. As I explained above in Section X.A, the specifications of all the priority documents uniformly define Formula (IV) R_6-R_8 as limited to hydroxyl-protecting groups. A POSA would have understood that though this definition *requires* each of R_6, R_7 and R_8 to be a hydroxyl-protecting group, they need not all be the same hydroxyl-protecting group. More specifically, "[s]uitable ***R_6, R_7 and R_8*** moieties include, but are not limited to, ester-type protecting groups, ether-type protecting groups, and silyl-type protecting groups." EX1003, 9:12-13; EX1004, 9:12-13; EX1005, 7:19-22; EX1006, 7:19-22; EX1007, 7:22-24; EX1008, 7:19-21. The priority documents describe the applicability of typical protecting groups:

> As used herein, the term "ester-type protecting group" is intended to mean a protecting group that forms an ester bond for the purpose of hydroxyl protection and which may be substituted or unsubstituted. Suitable ester-type protecting groups include, but are not limited to, acetyl, propionyl, isopropionyl, benzoyl, and trihaloacetyl, optionally trifluoroacetyl or trichloroacetyl.
>
> As used herein, the term "ether-type protecting group" is intended to mean a protecting group that forms an ether bond for the purpose of hydroxyl protection and which may be substituted or unsubstituted. Suitable ether-type protecting groups include, but are not limited to, benzyl, p-methoxybenzyl, methoxymethyl and allyl ethers.
>
> As used herein, the term "silyl-type protecting group" refers to a protecting group that forms a silyloxy bond for the purpose of hydroxyl protection. Examples thereof from trimethylsilyl,

> triethylsilyl, triisopropylsilyl, 2-(trimethylsilyl)ethoxymethyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl and tetraisopropyldisilyl.

EX1003, 9:15-28; EX1004, 9:15-38; EX1005, 7:22-41; EX1006, 7:22-41; EX1007, 7:25-44; EX1008, 7:22-41. In each case, the "purpose of hydroxyl protection" means masking the intrinsic reactivity of the hydroxyl groups (e.g., deprotonation, oxidation, reaction with electrophiles). This masks the reactivity of the hydroxyl groups and thereby temporarily protects the hydroxyl functional group from undergoing a variety of undesired reactions during subsequent reactions.

73. Deliberate distinctions made in the specifications of the priority documents between hydroxyl-protecting groups and hydrogen atoms is consistent with the plain meaning of those terms as a POSA would have understood them when each of the priority applications was filed. The hydrogen atom of a hydroxyl functional group—that is, the hydrogen atom covalently bonded to an oxygen atom (—OH)—is not itself a hydroxyl-protecting group, because it does not mask the intrinsic reactivity of the hydroxyl group. This understanding is confirmed by the '506 patent claims themselves, which distinguish hydrogen from hydroxyl-protecting groups. *See, e.g.*, claim 1 ("independently H ***or*** a hydroxyl-protecting group"). Likewise, the claims also distinguish phosphate from hydroxyl-protecting groups. *Id.* ("…***or*** wherein R_6 is a phosphate"). The impossibility of anything other than hydroxyl-protecting groups at R_6-R_8 for Formula (IV) was first introduced no

earlier than 2023, specifically in the claims that ultimately issued in the '506 patent. EX1002, 2-9.

74. Protecting groups are commonly utilized in chemistry to prevent a reaction that would modify an important functional group in an undesired fashion at an inappropriate time during synthesis. EX1012 (Clayden), 632-37. In the case of hydroxyl-protecting groups, they are covalently bonded to the oxygen (rendering it "protected") and are later removed in a process referred to as "deprotection." *Id.* A POSA would not have understood, for example, a hydrogen atom to be a hydroxyl-protecting group because the hydrogen atom is—by definition of a hydroxyl group—a part of the hydroxyl functional group rather than a protecting group for the hydroxyl functional group. The limitation by the priority documents of R_6-R_8 in formula (IV) to hydroxyl-protecting groups is consistent with the description in the priority documents that they will use "a deprotecting agent" to remove the protecting groups from R_6-R_8 and thereby form the compound of formula (II) from formula (III). EX1003, 9:8, 9:36-10:2; EX1004, 9:8, 9:36-10:2; EX1005, 7:17, 7:47-56; EX1006, 7:17, 7:47-56; EX1007, 7:20, 7:50-59; EX1008, 7:17, 7:47-56.

75. Every description of R_6-R_8 in the written descriptions of the priority documents uniformly applies this definition, consistent with its plain meaning as a POSA would have understood it at the time of filing. For example, the

specifications of the priority documents state "Optionally, ***the R_6, R_7 and R_8 moieties*** are selected from ***substituted and unsubstituted acetyl, and substituted and unsubstituted benzoyl***. Optionally, at least two of ***R_6, R_7 and R_8*** are selected from ***unsubstituted acetyl or unsubstituted benzoyl***." EX1003, 9:30-34; EX1004, 9:30-34 (same); EX1005, 7:42-46 (same); EX1006, 7:42-46 (same); EX1007, 7:45-49 (same); EX1008, 7:42-46 (same); *see also* EX1003, 9:36-10:2 ("Optionally, when ***R_6, R_7 and R_8 each comprise unsubstituted acetyl or unsubstituted benzoyl***…"); EX1004, 9:36-10:2 (same); EX1005, 7:47-56 (same); EX1006, 7:42-46 (same); EX1007, 7:50-59 (same); EX1008, 7:47-56 (same); EX1003, 10:19-26 ("Optionally, in an embodiment of formula (III), n is 0, m is 1, R_1 is NH_2, R_2-R_5 are each H, and ***R_6-R_8 are each acetyl***. Further optionally, in another embodiment of formula (III), n is 1, Y is O, m is 1, R_1 is ethyl, R_2-R_5 are each H, and ***R_6-R_8 are each acetyl***. Still further optionally, in another embodiment of formula (III), n is 0, m is 1, R_1 is NH_2, R_2-R_5 are each H, and ***R_6-R_8 are each benzoyl***."); EX1004, 10:19-26 (same); EX1005, 8:6-13 (same); EX1006, 8:6-13 (same); EX1007, 8:9-17 (same); EX1008, 8:6-13 (same). A POSA would have understood that acetyl and benzoyl were common hydroxyl-protecting groups. *See, e.g.*, EX1015, EX1016. None of these examples are consistent with reciting R_6-R_8 as anything other than a hydroxyl-protecting group.

76. In addition to protecting the hydroxyl groups of formula (IV) from undesired reactions while forming a compound of formula (III), the specifications of the priority documents uniformly provide another reason for the way they defined R_6-R_8 of formula (IV). Specifically, the specifications of the priority documents explain that having hydroxyl-protecting groups at R_6-R_8 decreases polarity as compared to the hydroxyl functional group to facilitate solubility in an organic solvent for purposes of the reaction and the reaction work-up that allows both synthesis and isolation of a compound of formula (III) from a compound of formula (IV). *See, e.g.,* EX1003, 11:40-12:2 ("It will be appreciated by a skilled person that ***the hydroxyl protecting groups R_6, R_7 and R_8, are required to be lipophilic*** to the extent that the reduced compound of formula (III), once prepared, ***migrates into the organic phase*** of the bi-phasic reaction medium formed by the aqueous solution (aqueous phase) and organic solvent (organic phase)."); EX1004, 11:40-12:2 (same); EX1005, 8:66-9:4 (same); EX1006, 9:1-8 (same); EX1007, 9:2-9 (same); EX1008, 8:66-9:4 (same). As specific examples, the specifications of the priority documents each explains that acetyl is a favorable protecting group for each of R_6-R_8. EX1003, 12:7-8 ("Optionally, in an embodiment of formula (IV), n is 0, m is 1, R_1 is NH_2, R_2-R_5 are each H, ***R_6-R_8 are each acetyl***, and X^- is $^-$OTf."); EX1004, 12:7-8 (same); EX1005, 9:10-12 (same); EX1006, 9:12-15 (same); EX1007, 9:13-16 (same); EX1008, 9:8-10 (same); EX1003, 11:17-19 ("Optionally,

when at least two of ***R_6, R_7 and R_8 comprise unsubstituted acetyl***, the organic solvent is selected from dichloromethane, 1,2-chloroethane, n-butyl acetate, chloroform and ethyl acetate, or a combination thereof, further optionally ethyl acetate."); EX1004, 11:17-19 (same); EX1005, 8:40-44 (same); EX1006, 8:41-46 (same); EX1007, 8:44-48 (same); EX1008, 8:40-44 (same). Claiming R_6-R_8 as anything other than a hydroxyl-protecting group would not be consistent with this disclosure of the priority documents. In other words, the unprotected hydroxyl group, in the case of R_6, R_7 and R_8 = H, in addition to becoming undesirably modified, would no longer permit liquid-liquid partitioning of the more polar unprotected hydroxyl group from the lipophilic protected ester derivatives into the water-immiscible non-aqueous organic solvent listed at e.g. EX1003, 11:17-19. *See also* EX1004, 11:17-19 (same); EX1005, 8:40-44 (same); EX1006, 8:41-46 (same); EX1007, 8:44-48 (same); EX1008, 8:40-44 (same).

77. As explained above in Section X.A, the later-filed claims of the '506 patent recite a logical impossibility, requiring R_6-R_8 to be hydroxyl-protecting groups by reciting defined formula (IV), yet reciting a conflicting identification of R_6-R_8 as hydrogen (or in some cases phosphate). For example, independent claim 1 recites "R_6, R_7, and R_8, which may be the same or different, are ***each independently H*** or a hydroxyl-protecting group; or wherein ***R_6 is a phosphate***." Independent claim 6 similarly recites "R_6, R_7, and R_8, which may be the same or

different, are ***each independently H*** or a hydroxyl-protecting group; or where ***R_6 is a phosphate***." Each independent claim similarly recites a logical impossibility that is not supported by the disclosures of the priority documents.

78. For at least the reasons I described above, it is my opinion that the specifications of the priority documents each fail to provide written description support for the claims of the '506 patent. As explained above, the priority documents define R_6, R_7, and R_8 in formula (IV) as limited to hydroxyl-protecting groups. *See also supra*, Section X.A. None of the specifications of the priority documents convey to a POSA that the applicants invented formula (IV) as including anything other than hydroxyl-protecting groups as R_6, R_7, and R_8. Put differently, if I were asked whether the specifications of the priority documents conveyed prior to April 2023 to a POSA that the applicant possessed (i.e., invented) the full scope of the claim (including each individual requirement) at the critical date, my answer would be an unequivocal "No."

79. As I explained above, I understand that the following factors can be relevant to a determination of written description: (i) the maturity of the science or technology; (ii) the existing knowledge in the particular field; (iii) the predictability of the aspect at issue; and (iv) the extent and content of the prior art. I have addressed each of these factors in my discussion above. For the sake of

brevity, I will not repeat everything under the heading of a particular factor. Nonetheless, I provide a brief summary below of the facts relating to each factor.

1. Maturity of Science or Technology

80. This factor – the maturity of the science or technology – supports finding no written description support in the priority documents for the claims of the ’506 patent. As discussed in detail above, the science and technology were sufficiently mature to understand the difference between a hydroxyl-protecting group and other components, including hydrogen and phosphate, and to understand that, e.g., a hydrogen is not a hydroxyl-protecting group. The field was mature enough that it was predictable that hydrogen is not a hydroxyl-protecting group. It was, at the same time, not predictable how one would perform the synthesis, based on the priority documents, of formula (IV) having R_6-R_8 hydrogens, which is a logical impossibility because the definition requires that R_6-R_8 are hydroxyl-protecting groups and hydrogen atoms are not protecting groups. Because the claims of the ’506 patent all encompass R_6-R_8 to include components other than hydroxyl-protecting groups, while the priority documents define R_6-R_8 as strictly requiring hydroxyl-protecting groups, this factor supports a finding of “no written description.”

2. Existing Knowledge in the Particular Field.

81. This factor – existing knowledge in the field – also supports finding of no support for adequate written description in the priority documents for the claims of the ’506 patent. As discussed in detail above, the existing knowledge in the field clearly differentiated between a hydroxyl-protecting group and other components of a molecule undergoing chemical reactions. Moreover, POSAs in the field understood that a hydrogen is not, and cannot be, a hydroxyl-protecting group. Because the claims of the ’506 patent all encompass R_6-R_8 to include components other than hydroxyl-protecting groups, while the priority documents define R_6-R_8 as strictly requiring hydroxyl-protecting groups, this factor supports a finding of “no written description.”

3. Predictability of the Aspect at Issue.

82. This factor – predictability – also supports a finding of no support for adequate written description in the priority documents for the claims of the ’506 patent. As discussed in detail above, it was predictable to a POSA at the time that components that are not hydroxyl-protecting groups are, thus, not a hydroxyl-protecting group. Because the claims of the ’506 patent all encompass R_6-R_8 to include components other than hydroxyl-protecting groups, while the priority documents define R_6-R_8 as strictly requiring hydroxyl-protecting groups, this factor supports a finding of “no written description.”

4. Extent and Content of the Prior Art.

83. This factor – extent and content of the art – also supports a finding of no support for adequate written description in the priority documents for the claims of the ’506 patent. As discussed in detail above, the prior art unambiguously differentiated between a hydroxyl-protecting group and other components, such as a hydrogen, and understood that such other components (e.g., a hydrogen) are not hydroxyl-protecting groups. Because the claims of the ’506 patent all encompass R_6-R_8 to components other than hydroxyl-protecting groups, while the priority documents define R_6-R_8 as strictly requiring that they are hydroxyl-protecting groups, this factor supports a finding of “no written description.”

84. For the foregoing reasons, it is my opinion that the claims of the ’506 patent lack written description support in the priority documents and are entitled to a priority date no earlier than April 26, 2023.

C. Lack of Enablement

85. It is my opinion that the specifications of the priority documents do not describe the claimed invention in the ’506 patent in sufficient detail so as to allow a POSA to make and use the full scope of the claimed invention without undue experimentation; in other words, the specifications of the priority documents fail to enable the claimed invention. As I describe below, because the specifications of the priority documents do not enable the claimed invention, it is

my opinion that the claims of the ’506 patent are entitled to a priority date no earlier than April 26, 2023.

86. As I explained above, I understand that in order to decide whether the claimed subject matter is enabled or whether a POSA would have to engage in undue experimentation to make and use the invention, several factors may be considered:

- the nature of the invention;
- the state of the art;
- the breadth of the claimed invention;
- the amount of guidance presented in the patent;
- whether the patent discloses specific working examples of the claimed invention;
- the time and cost of any necessary experimentation and how routine any necessary experimentation is in the relevant field of technology;
- the predictability of the relevant field of technology; and
- the level of ordinary skill in the relevant field of technology.

I address each of these factors below.

1. The Nature of the Invention

87. The nature of the invention is a precursor molecule (formula IV), in which the specifications of the priority documents define R_6, R_7 and R_8 as limited

to hydroxyl-protecting groups. EX1003, 8:30-9:6 ("R_6, R_7 and R_8 which may be the same or different, are each independently a hydroxyl-protecting group"); EX1004, 8:30-9:6 (same); EX1005, 7:1-16 (same); EX1006, 7:1-16 (same); EX1007, 7:3-19 (same); EX1008, 7:1-16 (same). The later claims of the '506 patent, however, recite the logical impossibility of R_6-R_8 being hydrogen where the definition requires that R_6-R_8 are hydroxyl-protecting groups. Accordingly, the nature of the invention is a logical impossibility. I understand that claims that require a logical impossibility necessarily lack enablement.

2. The Amount of Guidance Presented in the Priority Documents

88. The guidance in the specifications of the priority documents weighs against enablement. From the guidance of the specifications, it is clear that formula (IV) R_6, R_7 and R_8 are limited to hydroxyl-protecting groups. For example, the specifications of the priority documents clearly and expressly define each of R_6, R_7 and R_8 as limited to hydroxyl-protecting groups, and thus R_6, R_7 and R_8 ***cannot be*** hydrogen. EX1003, 8:30-9:6 ("R_6, R_7 and R_8, which may be the same or different, ***are each independently a hydroxyl-protecting group***"); EX1004, 8:30-9:6 (same); EX1005, 7:1-16 (same); EX1006, 7:1-16 (same); EX1007, 7:3-19 (same); EX1008, 7:1-16 (same). The specifications of the priority documents explain one benefit of limiting R_6, R_7 and R_8 to hydroxyl-protecting groups is to promote the association of the subsequent formula (III) compound with the organic

phase in the biphasic mixture of organic and aqueous solutions. EX1003, 11:33-38; EX1004, 11:33-38; EX1005, 8:59-65; EX1006, 8:61-67; EX1007, 8:63-9:2; EX1008, 8:59-65; *see also* EX1003, 11:40-12:2 (explaining the benefits of a lipophilic group at R_6, R_7 and R_8 so that, once prepared, the compound of formula (III) "migrates into the organic phase of the biphasic reaction medium."); EX1004, 11:40-12:2 (same); EX1005, 8:66-9:4 (same); EX1006, 9:1-8 (same); EX1007, 9:2-9 (same); EX1008, 8:66-9:4 (same). A POSA would have recognized that having R_6, R_7 or R_8 as anything other than a hydroxyl-protecting group would be ***operationally impractical***: doing so would be detrimental to the methods disclosed in the priority documents. Indeed, the priority documents explain:

> The protecting groups used in the preparation of compounds of formula (III) from compounds of formula (IV) ***may advantageously be chosen to be sufficiently lipophilic so that they facilitate the migration of the compounds of formula (III) into the organic phase of the reaction medium, for ease of extraction***.

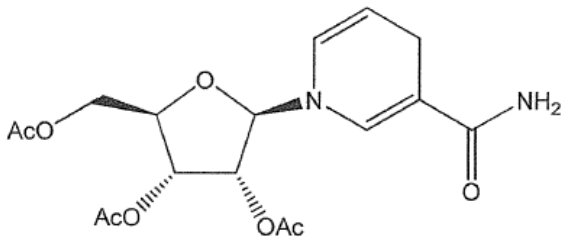
EX1003, 15:22-25; EX1004, 15:22-25; EX1005, 11:27-32; EX1006, 11:27-32; EX1007, 11:26-31; EX1008, 11:9-14. A POSA would have understood that formula (IV) having anything other than lipophilic hydroxyl protecting groups at R_6, R_7 or R_8 would be impractical for use with the methods described in the priority documents. As explained above, all discussion of R_6, R_7 and R_8 in formula (IV) in the specifications of the priority documents is limited to hydroxyl-protecting groups. The guidance in the specifications of the priority documents thus

uniformly limits R_6, R_7 and R_8 in formula (IV) to hydroxyl-protecting groups. The priority document specifications' guidance thus weighs against enablement.

3. Specific Working Examples

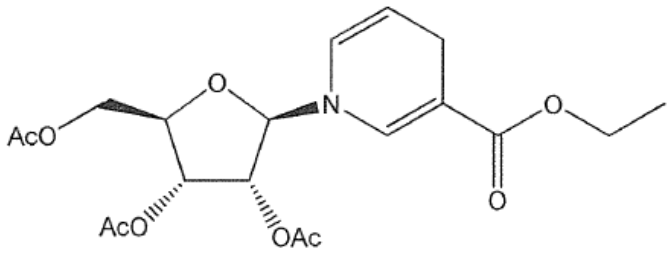
89. All working examples of formula (IV) in the priority documents provide that each of R_6, R_7 and R_8 in formula (IV) are hydroxyl-protecting groups, and more specifically are ***the same*** hydroxyl-protecting groups.

90. More specifically, the only working examples in the specification of the priority documents use all acetyl or all benzoyl as R_6-R_8 protecting groups. Indeed, Example 1(A) describes formula (IV) as ***triacetyl*** nicotinamide riboside triflate salt (i.e., each of R_6, R_7 and R_8 are acetyl). EX1003, 17:13-18:17; EX1004, 17:13-18:17; EX1005, 13:1-14:9; EX1006, 13:1-14:9; EX1007, 12:60-11:66; EX1008, 12:44-13:51; *see also* EX1003, Fig. 4 (the corresponding product formula (III) of the dithionite-reduced 1,4-dihydronicotinamide form is shown below); EX1004, Fig. 4 (same); EX1005, Fig. 4 (same); EX1006, Fig. 4 (same); EX1007, Fig. 4 (same); EX1008, Fig. 4 (same).



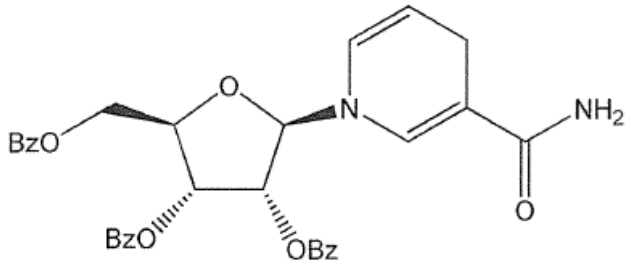
triacetyl-1,4-dihydronicotinamide riboside

Example 1(B) describes formula (IV) as ***triacetyl*** O-ethyl nicotinate riboside triflate salt (i.e., each of R_6, R_7 and R_8 are again acetyl). EX1003, 18:20-19:15; EX1004, 18:20-19:15; EX1005, 14:11-15:4; EX1006, 14:11-15:3; EX1007, 14:1-58; EX1008, 13:52-14:44; *see also* EX1003, Fig. 4 (the reduced 1,4-dihydronicotinamide form in formula (III) is shown below); EX1004, Fig. 4 (same); EX1005, Fig. 4 (same); EX1006, Fig. 4 (same); EX1007, Fig. 4 (same); EX1008, Fig. 4 (same).



triacetyl O-ethyl-1,4-dihydronicotinate riboside

Example 1(C) describes formula (IV) as ***tribenzoyl*** nicotinamide riboside triflate salt (i.e., each of R_6, R_7 and R_8 are benzoyl). EX1003, 19:17-20:14; EX1004, 19:17-20:14; EX1005, 15:6-16:2; EX1006, 15:5-16:2; EX1007, 14:60-15:54; EX1008, 14:45-15:38; *see also* EX1003, Fig. 4 (the reduced 1,4-dihydronicotinamide form in formula (III) is shown below); EX1004, Fig. 4 (same); EX1005, Fig. 4 (same); EX1006, Fig. 4 (same); EX1007, Fig. 4 (same); EX1008, Fig. 4 (same).



tribenzoyl-1,4-dihydronicotinamide riboside

Thus, the specification of each priority document ***only*** provides working examples where R_6, R_7 and R_8 in formula (IV) are all the same, and only one of two specific hydroxyl-protecting groups, i.e., benzoyl or acetyl.

91. The specification of the priority documents also fails to provide ***any*** working examples where R_6, R_7 and R_8 are different from one another. The specification of the priority documents also fails to provide ***any*** working examples where R_6 is a phosphate. The specification of the priority documents also fails to provide ***any*** working examples where R_6, R_7 and R_8 include an ether-type protecting group. The specification of the priority documents also fails to provide ***any*** working examples where R_6, R_7 and R_8 include a silyl-type protecting group. The specification of the priority documents also fails to provide ***any*** working examples where R_6, R_7 and R_8 are an ester-type protecting group other than acetyl or benzoyl.

92. Additionally, each of the formula (IV) working examples use ***triflate salt***. *See* EX1003, 17:13-20:14 (Example 1(A) ("A compound of formula (IV),

namely triacetyl nicotinamide riboside, ***triflate*** ($CF_3SO_3^-$, also known as —OTf) ***salt***"), Example 1(B) ("A compound of formula (IV), namely triacetyl O-ethyl nicotinate riboside, ***triflate*** (—OTf) ***salt***"), Example 1(C) ("A compound of formula (IV), namely tribenzoyl nicotinamide riboside, ***triflate*** (—OTf) ***salt***")); EX1004, 17:13-20:14 (same); EX1005, 13:1-16:2 (same); EX1006, 13:1-16:2 (same); EX1007, 12:60-54 (same); EX1008, 12:44-15:38 (same). The specification of the priority documents fail to provide any working examples of an alternative anion.

93. Moreover, the '506 patent claim 10 recites "a nutritional supplement composition comprising a compound of claim 1 [reciting formula (IV)]." But as explained above, the only working examples of formula (IV) in the priority documents were triflate salts. There are no working examples of a supplement including a triflate salt, and for good reason: the specifications of the priority documents explicitly instruct POSAs to ***avoid*** using a triflate salt in any nutritional supplement. EX1003, 1:27-29 ("The triflate salt form of nicotinamide riboside, or derivatives thereof, is ***not suitable for use as a nutritional supplement***, because of its associated toxicity."); EX1004, 1:27-29 (same); EX1005, 1:49-52 (same); EX1006, 1:47-50 (same); EX1007, 1:50-53 (same); EX1008, 1:53-56 (same). Thus, the only working examples of formula (IV) are chemical intermediates, or chemical precursor molecules to the actual molecules in the nutritional supplement.

In addition, the specifications of the priority documents describe these triflate salt intermediates as ***unsuitable and dangerous for use as a nutritional supplement***.

94. The working examples thus weigh against enablement.

4. The Breadth of the Claimed Invention

95. In contrast to the narrow disclosure of the priority documents that R_6-R_8 of formula (IV) are limited to hydroxyl-protecting groups, the claims of the '506 patent recite a logical impossibility. As discussed above regarding the nature of the invention, the guidance provided, and the working examples, there is no support in the priority documents for this logical impossibility. Accordingly, this factor weighs against finding enablement.

5. Necessary Experimentation

96. As discussed above, the specifications of the priority documents limit R_6, R_7 and R_8 of formula (IV) to hydroxyl-protecting groups, and all the working examples provided (wherein all of R_6, R_7 and R_8 are either the lipophilic acetyl or benzoyl esters) are limited to formula (IV) R_6, R_7 or R_8 hydroxyl-protecting groups. As R_6, R_7 or R_8 in formula (IV) being hydrogen is a logical impossibility, and indeed would introduce an operational impossibility, the experimentation required would be undue.

6. Predictability of the Field

97. This factor also supports finding no enablement in the priority documents for the claims of the '506 patent. As discussed in detail above, it was

predictable to a POSA at the time that the illogical use of hydrogen as a hydroxyl-protecting group—which it logically, operationally, and chemically cannot be—would ***predictably alter*** the course of the reaction and jeopardize successful completion of the synthesis as described. At the same time, it was ***not predictable*** how one could even perform the synthesis taught by the priority documents based on the logical impossibility of R_6-R_8 in formula (IV) being hydrogens. This factor thus supports lack of enablement.

7. Level of Ordinary Skill in the Art

98. It is my opinion that a POSA would have a high level of education and experience, including an advanced degree, such as an M.Sc. or a Ph.D. in chemistry or a related subject. *See* Section VI, above. Such a qualified POSA would have recognized that the claims of the '506 patent encompass a logical impossibility not disclosed in the priority documents. It is also my opinion that the POSA's knowledge, training, and experience would not provide the expertise necessary to resolve the logical impossibility posed by the claims at issue. Accordingly, this factor also supports lack of enablement.

8. The State of the Art

99. The state of the art does not make up for the lack of enablement in the priority documents for what is claimed. As discussed in detail above, the state of the art differentiated between a hydroxyl-protecting group and a hydrogen, and it

also understood that a hydrogen is not a hydroxyl-protecting group. The state of the art thus does not resolve the logical impossibility posed by the claims at issue. Accordingly, this factor also weighs against finding enablement.

100. In sum, and considering all the aforementioned factors, it is my opinion that the priority documents do not enable a POSA to make and use the full scope of the claimed invention without undue experimentation. Therefore, it is also my opinion that the claims of the '506 patent are not entitled to any chronological priority that would arise from any previously-filed applications.

XI. '506 PATENT CLAIMS 1-12, 21-28, 31, AND 34-35 WERE ANTICIPATED BY THE '184 PUBLICATION.

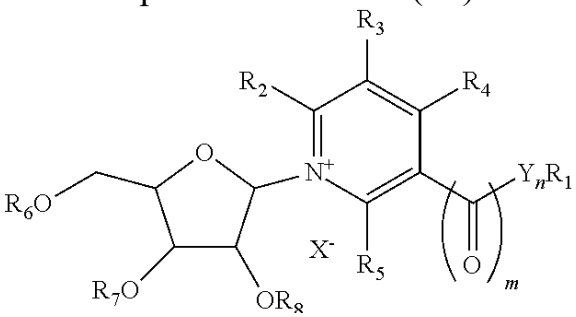
101. For the reasons discussed in detail below, it is my opinion that each of claims 1-12, 21-28, 31, and 34-35 of the '506 patent was anticipated, as exemplified by disclosures in the '184 publication (EX1022). I have evaluated below whether the '184 publication discloses each and every element of each of claims 1-12, 21-28, 31, and 34-35 of the '506 patent. As I explain in detail below, my answer to this question would be an unequivocal "Yes."

102. As a high-level summary, the '184 publication discloses hydroxyl-protected nicotinamide riboside salts, as well as methods of synthesizing the same. The '184 publication describes how nicotinamide riboside salts could be useful as nutritional supplements.

103. The sections below explain in more detail how the '184 publication discloses each and every element of claims 1-12, 21-28, 31, and 34-35. I first analyze independent claim 1 of the challenged '506 patent. Thereafter, I analyze, in turn, independent and dependent claims 2-12, 21-28, 31, and 34-35.

A. Claim 1

1. A compound of formula (IV):



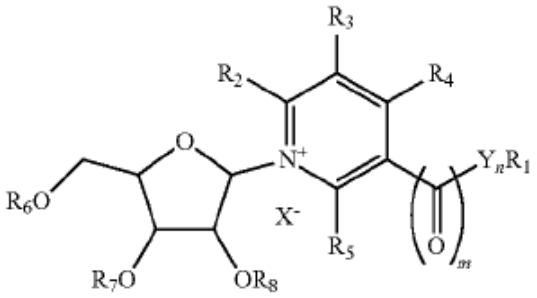
or the beta-anomer thereof,
where:
n is 0 and Y is absent;
m is 1;
R_1 is a substituted or unsubstituted primary amino;
R_2-R_5 are each H;
R_6, R_7 and R_8, which may be the same or different, are each independently H or a hydroxyl-protecting group; or wherein R_6 is a phosphate; and
X^- is an anion selected from an anion of a substituted carboxylic acid, an anion of an unsubstituted carboxylic acid other than an anion of formic acid, an anion of a substituted or unsubstituted phosphate, an anion of a substituted or unsubstituted sulfate, an anion of a substituted or unsubstituted carbonate, and an anion of a substituted or unsubstituted carbamate.

104. I have reproduced above claim 1 of the '506 patent. The '184 publication discloses a compound of formula (IV), used as a starting material for

forming formula (III) (e.g., hydroxyl-group-protected 1,4-dihydronicotinamide riboside). EX1022, [0087]-[0089]:

[0087] Optionally, the compound of formula (III) is prepared by reacting a compound of formula (IV)

(IV)



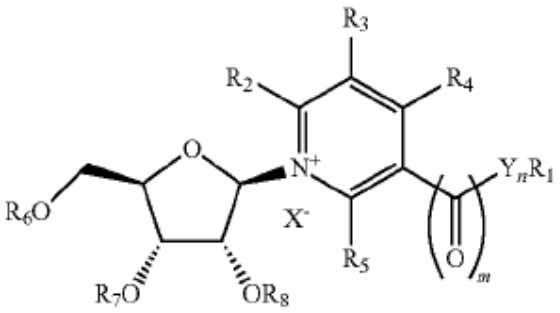
[0088] wherein

[0089] n, m, Y, R_1-R_8 and X^- are as defined above;

105. The '184 publication discloses compounds having each and every feature of the '506 patent claim 1. The structure depicted in the '184 publication as formula (IVA) is "the β-anomer" of claim 1's formula (IV). EX1022, [0124]-[0126]:

[0124] Optionally, the compound of formula (IV) has the formula (IVA), i.e. is the β-anomer,

(IVA)



[0125] wherein

[0126] n, m, Y, R_1-$R_8$and X^- are as defined above.

The '184 publication also teaches that each of the variables "n, m, Y, R_1-R_8 and X^- are as defined above" (EX1022, [0089], [0126]) and defines that "R_6, R_7 and R_8, which may be the same or different, are each independently a hydroxyl-protecting group" (EX1022, [0070]). The '184 publication also describes where: n is 0 and Y is therefore absent; m is 1; R_1 is an unsubstituted primary amino (i.e., —NH_2); and R_2-R_5 are each H. EX1022, [0011]-[0015] (reproduced below, annotations added):

[0011] n is 0 or 1;

[0012] m is 0 or 1;

[0013] Y is O or S;

[0014] R_1 is selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted primary or secondary amino, and substituted or unsubstituted azido;

[0015] R_2-R_5 which may be the same or different, are each independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, and substituted or unsubstituted aryl; and

Additionally, the '184 publication's anion (X^-) overlaps directly with the '506 patent claimed anion (X^-) where the anion is "selected from ***an anion of a substituted or unsubstituted carboxylic acid***, a halide, a substituted or unsubstituted sulfonate, ***a substituted or unsubstituted phosphate, a substituted or unsubstituted sulfate, a substituted or unsubstituted carbonate, and a substituted or unsubstituted carbamate***." EX1022, [0016].

106. Accordingly, the '184 publication discloses each and every claim limitation of independent claim 1. Because the '184 publication published before the earliest priority date to which the '506 patent is entitled (*see* Section X, above), the '184 publication anticipates independent claim 1.

B. Claim 2

2. The compound of claim 1, wherein R_1 is —NH_2.

107. Claim 2 additionally recites R_1 is —NH_2. As I have previously addressed above, claim 1 is anticipated by the '184 publication. Additionally, as I explained above, the '184 publication discloses where R_1 is an unsubstituted primary amino (i.e., —NH_2). *See* EX1022 (the '184 publication), [0014].

108. Accordingly, the '184 publication anticipates claim 2.

C. Claim 3

> **3.** The compound of claim 1, wherein R_6, R_7 and R_8, which may be the same or different, are each independently H or a hydroxyl-protecting group.

109. Claim 3 additionally recites R_6, R_7 and R_8 may be the same or different, and are each independently H or a hydroxyl-protecting group. As I have previously addressed above, claim 1 is anticipated by the '184 publication. Additionally, as I explained above, the '184 publication discloses where R_6, R_7 and R_8 are the same, and are each a hydroxyl-protecting group. *See* EX1022 (the '184 publication), [0070] ("R_6, R_7 and R_8, which may be the same or different, are each independently a hydroxyl-protecting group").

110. Accordingly, the '184 publication anticipates claim 3.

D. Claim 4

> **4.** The compound of claim 3, wherein X^- is an anion, selected from an anion of an unsubstituted carboxylic acid other than an anion of formic acid, an anion of an unsubstituted phosphate, an anion of an unsubstituted sulfate, an anion of an unsubstituted carbonate, and an anion of an unsubstituted carbamate.

111. Claim 4 additionally recites X^- is an anion, selected from an anion of an unsubstituted carboxylic acid other than an anion of formic acid, an anion of an unsubstituted phosphate, an anion of an unsubstituted sulfate, an anion of an unsubstituted carbonate, and an anion of an unsubstituted carbamate. As I have previously addressed above, claim 1 is anticipated by the '184 publication. Additionally, as I explained above, the '184 publication discloses where X^- is an anion, selected from an anion of an unsubstituted carboxylic acid, an anion of an unsubstituted phosphate, an anion of an unsubstituted sulfate, an anion of an unsubstituted carbonate, and an anion of an unsubstituted carbamate. *See* EX1022 (the '184 publication), [0016] ("selected from ***an anion of a*** substituted or ***unsubstituted carboxylic acid***, a halide, a substituted or unsubstituted sulfonate, a substituted or ***unsubstituted phosphate***, a substituted or ***unsubstituted sulfate,*** a substituted or ***unsubstituted carbonate,*** and a substituted or ***unsubstituted carbamate***.").

112. Accordingly, the '184 publication anticipates claim 4.

E. Claim 5

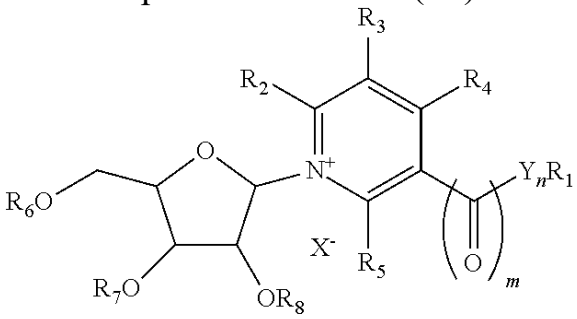
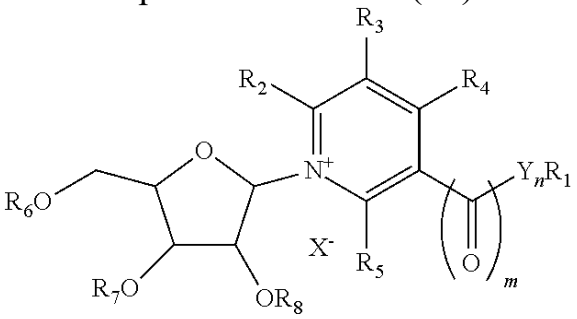
> **5.** The compound of claim 3, wherein X^- is an anion of a substituted monocarboxylic acid or an anion of an unsubstituted monocarboxylic acid other than an anion of formic acid.

113. Claim 5 additionally recites X^- is an anion of a substituted monocarboxylic acid or an anion of an unsubstituted monocarboxylic acid other

than an anion of formic acid. As I have previously addressed above, claim 3 is anticipated by the ’184 publication. Additionally, the ’184 publication discloses where X^- is an anion of a substituted monocarboxylic acid or an anion of an unsubstituted monocarboxylic acid. *See* EX1022 (the ’184 publication), [0027] (“X^- is an anion of a substituted or unsubstituted carboxylic acid selected from an anion of ***a substituted or unsubstituted monocarboxylic acid*** and an anion of a substituted or unsubstituted dicarboxylic acid.”).

114. Accordingly, the ’184 publication anticipates claim 5.

F. Claim 6

Claim 1	Claim 6
1. A compound of formula (IV):  or the beta-anomer thereof, where: n is 0 and Y is absent; m is 1; R_1 is a substituted or unsubstituted primary amino; R_2-R_5 are each H; R_6, R_7 and R_8, which may be the same or different, are each independently H or a hydroxyl-protecting group; or wherein R_6 is a phosphate; and	**6.** A compound of formula (IV):  or the beta-anomer thereof, where: n is 0 and Y is absent; m is 1; R_1 is a substituted or unsubstituted primary amino; R_2-R_5 are each H; R_6, R_7 and R_8, which may be the same or different, are each independently H or a hydroxyl-protecting group; or ***where*** R_6 is a phosphate; and

X^- is an anion selected from an anion of a substituted carboxylic acid, an anion of an unsubstituted carboxylic acid other than an anion of formic acid, an anion of a substituted or unsubstituted phosphate, an anion of a substituted or unsubstituted sulfate, an anion of a substituted or unsubstituted carbonate, and an anion of a substituted or unsubstituted carbamate.	X^- is an anion ***of a substituted or unsubstituted aminodicarboxylic acid***.

115. I have reproduced above independent claim 6 of the ’506 patent alongside independent claim 1 of the ’506 patent. Claim 6 is substantially identical to claim 1 except it recites X^- is an anion of a substituted or unsubstituted aminodicarboxylic acid. EX1001, Claim 6. As I have previously addressed above, claim 1 is anticipated by the ’184 publication, and for the same reasons the ’184 publication anticipates the overlapping claimed subject matter of claim 6. *See* Section XI.A. Additionally, the ’184 publication discloses where X^- is an anion of a substituted or unsubstituted aminodicarboxylic acid (e.g., substituted or unsubstituted versions of glutamic acid, an aminodicarboxylic acid) (*see* EX1022, [0030]). EX1022 (the ’184 publication), [0030] (“X^- is an anion of a substituted or unsubstituted amino-monocarboxylic acid or an anion of ***a substituted or unsubstituted amino-dicarboxylic acid***.”).

116. Accordingly, the ’184 publication anticipates independent claim 6.

G. Claim 7

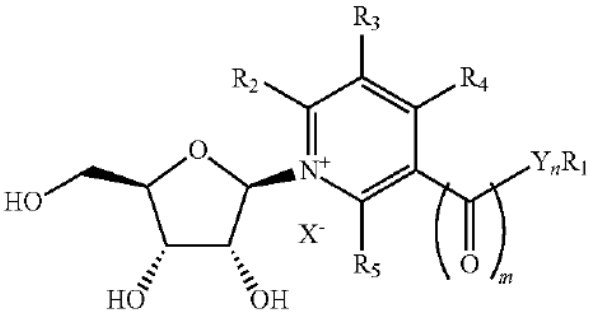
7. The compound of claim 1, wherein X^- is selected from the group consisting of acetate, trifluoroacetate, ascorbate, lactate, propionate and butyrate.

117. Claim 7 additionally recites X^- is selected from the group consisting of acetate, trifluoroacetate, ascorbate, lactate, propionate and butyrate. As I have previously addressed above, claim 1 is anticipated by the '184 publication. Additionally, the '184 publication discloses where X^- is selected from the group including acetate, trifluoroacetate, ascorbate, lactate, propionate and butyrate. *See* EX1022 (the '184 publication), [0035] ("X^- is selected from chloride, ***acetate***, formate, ***trifluoroacetate***, ***ascorbate***, aspartate, glutamate and ***lactate***. Further optionally, X^- is selected from chloride, ***acetate***, formate and ***trifluoroacetate***."), [0029] ("X^- is an anion of an unsubstituted monocarboxylic acid selected from formic acid, acetic acid, propionic acid and butyric acid, being formate, ***acetate***, ***propionate*** and ***butyrate***, respectively").

118. Accordingly, the '184 publication anticipates claim 7.

H. Claim 8

8. The compound of claim 1 of formula:



where:
n is 0 and Y is absent;
m is 1;
R_1 is —NH_2;
R_2-R_5 are each H; and
X^- is an anion of a substituted monocarboxylic acid or an anion of an unsubstituted monocarboxylic acid other than formic acid.

119. As I explained above, the priority documents consistently defined that R_6-R_8 in formula (IV) each must be a hydroxyl-protecting group. *See* Section X.A. The '506 patent claim 8 recites a logical impossibility. Claim 8 depends from claim 1, which recites defined formula (IV). *See* Section XI.A. As explained above, claim 1 and claims that depend therefrom thus require R_6-R_8 to be hydroxyl-protecting groups. Yet claim 8 also recites a conflicting identification of R_6-R_8 as hydrogen. EX1001, claim 8 (replacing R_6-R_8 with H in the chemical structure). A POSA would have understood that the claims require R_6-R_8 as hydroxyl-protecting groups, consistent with the specifications of the priority documents. *See* Section X.

120. For the limited purposes of my evaluation below, I accept for the sake of argument the logical impossibility that R_6-R_8 may be replaced with hydrogens as depicted in claim 8—though this cannot be within the scope of independent claim

1. Nonetheless, the '184 publication discloses the chemical formula depicted in claim 8. As explained with regard to claim 1, the '184 publication describes its formulae in beta-anomer form (i.e., the same anomer form as depicted in claim 8) where: n is 0 and Y is therefore absent; m is 1; R_1 is an unsubstituted primary amino (i.e., —NH_2); and R_2-R_5 are each H. EX1022, [0011]-[0015] (reproduced below, annotations added):

[0011] n is 0 or 1;

[0012] m is 0 or 1;

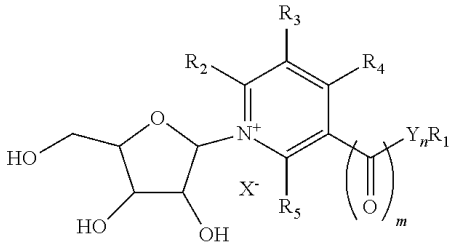
[0013] Y is O or S;

[0014] R_1 is selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted primary or secondary amino, and substituted or unsubstituted azido;

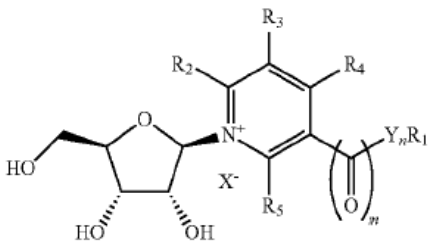
[0015] R_2-R_5 which may be the same or different, are each independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, and substituted or unsubstituted aryl; and

The '184 publication describes these variables as also applying to its formula (I). EX1022, [0009]; *see also id*, [0115] (formula (IA)).

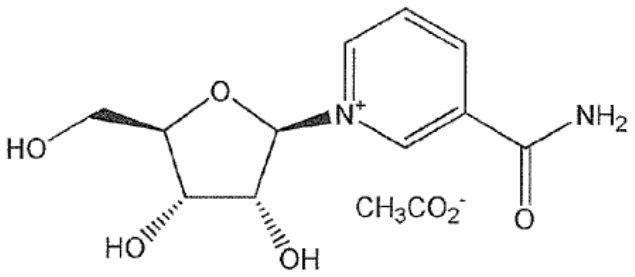
(I)



(IA)



The ’184 publication also discloses X^- is an anion of a substituted monocarboxylic acid or an anion of an unsubstituted monocarboxylic acid, such as acetate. EX1022, [0027] (“an anion of a substituted or unsubstituted monocarboxylic acid”), [0029] (“an unsubstituted monocarboxylic acid selected from formic acid, acetic acid…”). The ’184 publication provides an illustration of such a formula having X^- as acetate, an unsubstituted monocarboxylic acid. *Id.*, Figure 5 (relevant portion reproduced below).

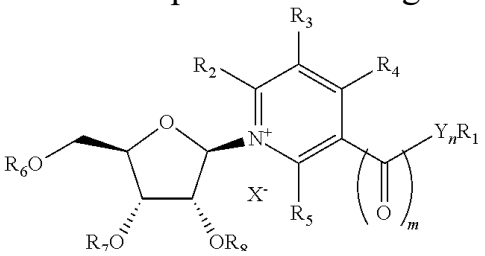


nicotinamide riboside, acetate salt

121. Accordingly, the ’184 publication anticipates claim 8.

I. Claim 9

9. The compound according to claim 1 of formula:



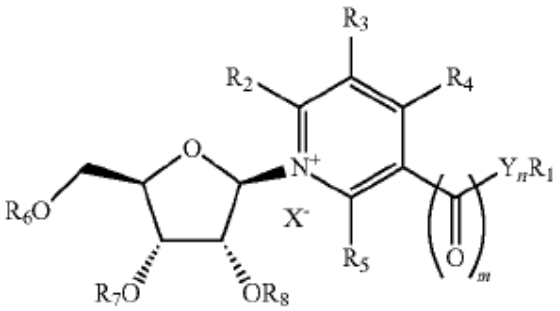
where:
n is 0 and Y is absent;
m is 1;
R_1 is —NH_2
R_2-R_5 are each H;

R_6, R_7 and R_8, which may be the same or different, are each independently a hydroxyl-protecting group selected from unsubstituted acetyl, and unsubstituted benzoyl; and
X^- is an anion of a substituted monocarboxylic acid, or an anion of an unsubstituted monocarboxylic acid other than formic acid.

122. Claim 9 depicts the beta-anomer form of formula (IV) provided in claim 1 and additionally recites n is 0 and Y is absent; m is 1; R_1 is —NH_2; R_2-R_5 are each H; R_6, R_7 and R_8, which may be the same or different, are each independently a hydroxyl-protecting group selected from unsubstituted acetyl, and unsubstituted benzoyl; and X^- is an anion of a substituted monocarboxylic acid, or an anion of an unsubstituted monocarboxylic acid other than formic acid. As I have previously addressed above, claim 1 is anticipated by the '184 publication. Additionally, as I explained above, the '184 publication discloses the beta-anomer of formula (IV) as depicted in claim 9. EX1022, [0124]-[0126]:

[0124] Optionally, the compound of formula (IV) has the formula (IVA), i.e. is the β-anomer,

(IVA)



[0125] wherein

[0126] n, m, Y, R_1-$R_8$and X^- are as defined above.

The ’184 publication also describes formula (IV) where: n is 0 and Y is therefore absent; m is 1; R_1 is an unsubstituted primary amino (i.e., —NH_2); and R_2-R_5 are each H. EX1022, [0011]-[0015] (reproduced below, annotations added), [0126]:

> **[0011]** n is 0 or 1;
>
> **[0012]** m is 0 or 1;
>
> **[0013]** Y is O or S;
>
> **[0014]** R_1 is selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted primary or secondary amino, and substituted or unsubstituted azido;
>
> **[0015]** R_2-R_5 which may be the same or different, are each independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, and substituted or unsubstituted aryl; and

Further, the ’184 publication discloses that R_6, R_7 and R_8, which may be the same or different, are each independently a hydroxyl-protecting group selected from unsubstituted acetyl, and unsubstituted benzoyl. EX1022, [0077]-[0078] (“Optionally, the R_6, R_7 and R_8 moieties are selected from substituted and ***unsubstituted acetyl***, and substituted and ***unsubstituted benzoyl***. Optionally, at least two of R_6, R_7 and R_8 are selected from ***unsubstituted acetyl or unsubstituted benzoyl***.”). The ’184 publication also discloses X^- is an anion of a substituted monocarboxylic acid or an anion of an unsubstituted monocarboxylic acid, such as acetate. EX1022, [0027] (“an anion of a substituted or unsubstituted

monocarboxylic acid"), [0029] ("an unsubstituted monocarboxylic acid selected from formic acid, acetic acid…").

123. Accordingly, the '184 publication anticipates claim 9.

J. Claim 10

10. A nutritional supplement composition comprising a compound of claim 1.

124. Claim 10 additionally recites a nutritional supplement composition comprising a compound of claim 1. As I have previously addressed above, claim 1 is anticipated by the '184 publication. Additionally, the '184 publication describes its method "may be used to introduce a counter ion of choice to the prepared compounds, thereby producing compounds ***suitable for use as nutritional supplements*** or otherwise." EX1022 (the '184 publication), [0008]. The '184 publication also explains its "methods conveniently enable the preparation of compounds having potential use as nutritional supplements or otherwise." *Id.*, [0128].

125. Accordingly, the '184 publication describes the use of its compositions for nutritional supplements, and anticipates claim 10.

K. Claim 11

11. The nutritional supplement composition of claim 10, wherein R_1 is —NH_2 and X^- is an anion of a substituted or unsubstituted dicarboxylic acid.

126. Claim 11 additionally recites R_1 is —NH_2 and X^- is an anion of a substituted or unsubstituted dicarboxylic acid. As I have previously addressed above, claim 10 is anticipated by the '184 publication. Additionally, I have explained that the '184 publication discloses R_1 is —NH_2 (*see* Sections XI.A-XI.B (Claim 1, Claim 2)) and that the '184 publication discloses X^- is an anion of a substituted or unsubstituted dicarboxylic acid (*see* Section XI.A (Claim 1)).

127. Accordingly, the '184 publication anticipates claim 11.

L. Claim 12

> **12.** The nutritional supplement composition of claim 10, wherein R_1 is —NH_2 and R_6, R_7 and R_8, which may be the same or different, are each independently H or a hydroxyl-protecting group selected from unsubstituted acetyl, and unsubstituted benzoyl.

128. Claim 12 additionally recites R_1 is —NH_2 and R_6, R_7 and R_8, which may be the same or different, are each independently H or a hydroxyl-protecting group selected from unsubstituted acetyl, and unsubstituted benzoyl. As I have previously addressed above, claim 10 is anticipated by the '184 publication. Additionally, I have explained that the '184 publication discloses R_1 is —NH_2 (*see* Sections XI.A-XI.B (Claim 1, Claim 2)) and also discloses R_6, R_7 and R_8 are each a hydroxyl-protecting group selected from unsubstituted acetyl, and unsubstituted benzoyl (*see* Section XI.I (Claim 9)).

129. Accordingly, the '184 publication anticipates claim 12.

M. Claim 21

> **21.** The compound of claim 1, wherein R_6, R_7 and R_8, which may be the same or different, are each independently H or a hydroxyl-protecting group selected from unsubstituted acetyl, and unsubstituted benzoyl.

130. Claim 21 additionally recites R_6, R_7 and R_8, which may be the same or different, are each independently H or a hydroxyl-protecting group selected from unsubstituted acetyl, and unsubstituted benzoyl. As I have previously addressed above, claim 1 is anticipated by the '184 publication. Additionally, the '184 publication discloses R_6, R_7 and R_8, which may be the same or different, are each independently a hydroxyl-protecting group selected from unsubstituted acetyl, and unsubstituted benzoyl. EX1022, [0077]-[0078] ("Optionally, the R_6, R_7 and R_8 moieties are selected from substituted and ***unsubstituted acetyl***, and substituted and ***unsubstituted benzoyl***. Optionally, at least two of R_6, R_7 and R_8 are selected from ***unsubstituted acetyl or unsubstituted benzoyl***.").

131. Accordingly, the '184 publication anticipates claim 21.

N. Claim 22

> **22.** The compound of claim 2, wherein X^- is an anion of a substituted or unsubstituted dicarboxylic acid.

132. Claim 22 additionally recites X^- is an anion of a substituted or unsubstituted dicarboxylic acid. As I have previously addressed above, claim 2 is anticipated by the '184 publication. The '184 publication also discloses where X^- is an anion of a substituted or unsubstituted dicarboxylic acid. *See* EX1022

(the ’184 publication), [0027] (“X^- is an anion of a substituted or unsubstituted carboxylic acid selected from an anion of a substituted or unsubstituted monocarboxylic acid and ***an anion of a substituted or unsubstituted dicarboxylic acid.***”).

133. Accordingly, the ’184 publication anticipates claim 22.

O. Claim 23

23. The compound of claim 6, wherein X^- is selected from aspartate and glutamate.

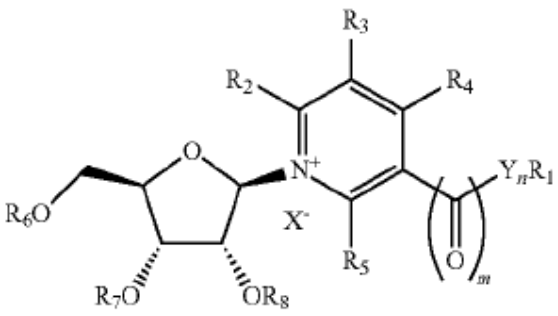
134. Claim 23 additionally recites X^- is selected from aspartate and glutamate. As I have previously addressed above, claim 6 is anticipated by the ’184 publication. The ’184 publication also discloses where X^- is selected from aspartate and glutamate. *See* EX1022 (the ’184 publication), [0035] (“X^- is selected from chloride, acetate, formate, trifluoroacetate, ascorbate, ***aspartate, glutamate*** and lactate***.***”); *see also id.*, [0030], [0094] (“$X^-$is selected from ascorbate, ***glutamate, aspartate***, lactate and acetate”).

135. Accordingly, the ’184 publication anticipates claim 23.

P. Claim 24

24. The compound of claim 6, wherein the compound is the beta-anomer;
n is 0 and Y is absent;
m is 1;
R_1 is —NH_2
R_2-R_5 are each H;
R_6, R_7 and R_8 are each H; and
X^- is an anion of a substituted or unsubstituted aminodicarboxylic acid.

136. Claim 24 additionally recites the compound is the beta-anomer; n is 0 and Y is absent; m is 1; R_1 is —NH_2; R_2-R_5 are each H; R_6, R_7 and R_8 are each H; and X^- is an anion of a substituted or unsubstituted aminodicarboxylic acid. As I have previously addressed above, claim 6 is anticipated by the '184 publication. Additionally, as I explained above, the '184 publication discloses the beta-anomer of formula (IV). EX1022, [0124]-[0126]:

> **[0124]** Optionally, the compound of formula (IV) has the formula (IVA), i.e. is the β-anomer,
>
> (IVA)
>
> 
>
>
> **[0125]** wherein
>
> **[0126]** n, m, Y, R_1-$R_8$and X^- are as defined above.

The '184 publication also describes where: n is 0 and Y is therefore absent; m is 1; R_1 is an unsubstituted primary amino (i.e., —NH_2); and R_2-R_5 are each H. EX1022, [0011]-[0015] (reproduced below, annotations added):

[0011] n is 0 or 1;

[0012] m is 0 or 1;

[0013] Y is O or S;

[0014] R_1 is selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted primary or secondary amino, and substituted or unsubstituted azido;

[0015] R_2-R_5 which may be the same or different, are each independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, and substituted or unsubstituted aryl; and

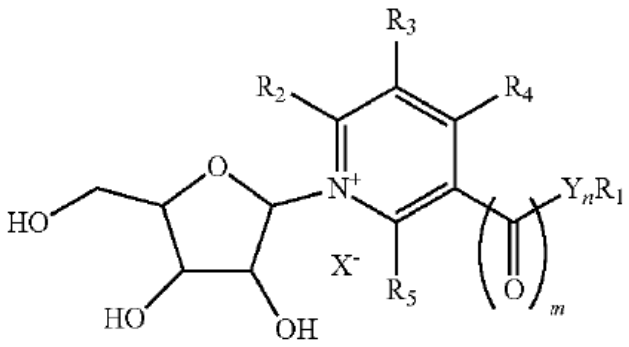
The '184 publication also discloses where X^- is an anion of a substituted or unsubstituted aminodicarboxylic acid (e.g., substituted or unsubstituted versions of glutamic acid, an aminodicarboxylic acid) (*see* EX1022, [0030]). EX1022 (the '184 publication), [0030] ("X^- is an anion of a substituted or unsubstituted amino-monocarboxylic acid or an anion of ***a substituted or unsubstituted amino-dicarboxylic acid***.").

137. Claim 24 purports to depend from claim 6, and as I explained above, independent claim 6 requires Formula (IV), which, by definition requires that "R_6, R_7 and R_8, which may be the same or different, are each independently ***a hydroxyl-protecting group***." EX1022, [0070]; *see also* Sections XI.A, XI.F. The limitation of claim 24 that "R_6, R_7 and R_8 are each H" does not add anything possible, and thus does not further limit the claim. *See* Sections X.A-X.C, above (no written description or enablement for this limitation). Thus, R_6, R_7 and R_8 must each be a

hydroxyl-protecting group, and this limitation is anticipated for the same reasons as explained with claim 6. *See* Section XI.F.

138. For the limited purposes of my evaluation below, I accept for the sake of argument the logical impossibility that R_6-R_8 may be replaced with hydrogens as depicted in claim 24—though this cannot be within the scope of independent claim 6. Nonetheless, the '184 publication discloses the chemical formula depicted in claim 24. *See* Section XI.H (claim 8), above. The '184 publication discloses formula (I), which requires the positions corresponding with R_6, R_7 and R_8 to each be H. EX1022, [0009] (reproduced below):

(I)



Each of the additional features of claim 24 (the compound is the beta-anomer; n is 0 and Y is absent; m is 1; R_1 is —NH_2; R_2-R_5 are each H; and X^- is an anion of a substituted or unsubstituted aminodicarboxylic acid) are also recited with regard to Formula (I). EX1022, [0009]-[0016], [0030]. Thus, though not within the scope of independent claim 6 (R_6, R_7 and R_8 must each be a hydroxyl-protecting group), the structure of claim 24 is in the prior art.

139. Accordingly, the ’184 publication anticipates claim 24.

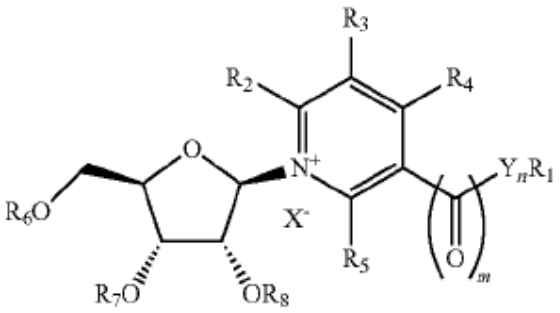
Q. Claim 25

25. The compound of claim 6, wherein the compound is the beta-anomer;
n is 0 and Y is absent;
m is 1;
R_1 is —NH_2
R_2-R_5 are each H;
R_6, R_7 and R_8, which may be the same or different, are each independently a hydroxyl-protecting group selected from unsubstituted acetyl, and unsubstituted benzoyl; and
X^- is an anion of a substituted or unsubstituted aminodicarboxylic acid.

140. Claim 25 additionally recites the compound is the beta-anomer; n is 0 and Y is absent; m is 1; R_1 is —NH_2; R_2-R_5 are each H; R_6, R_7 and R_8, which may be the same or different, are each independently a hydroxyl-protecting group selected from unsubstituted acetyl, and unsubstituted benzoyl; and X^- is an anion of a substituted or unsubstituted aminodicarboxylic acid. As I have previously addressed above, claim 6 is anticipated by the ’184 publication. Additionally, as I explained above, the ’184 publication discloses the beta-anomer of formula (IV). EX1022, [0124]-[0126]:

[0124] Optionally, the compound of formula (IV) has the formula (IVA), i.e. is the β-anomer,

(IVA)



[0125] wherein

[0126] n, m, Y, R_1-$R_8$and X^- are as defined above.

The '184 publication also describes where: n is 0 and Y is therefore absent; m is 1; R_1 is an unsubstituted primary amino (i.e., —NH_2); and R_2-R_5 are each H. EX1022, [0011]-[0015] (reproduced below, annotations added):

[0011] n is 0 or 1;

[0012] m is 0 or 1;

[0013] Y is O or S;

[0014] R_1 is selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted primary or secondary amino, and substituted or unsubstituted azido;

[0015] R_2-R_5 which may be the same or different, are each independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, and substituted or unsubstituted aryl; and

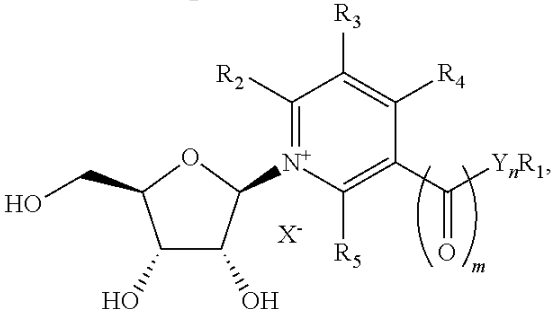
Further, the '184 publication discloses R_6, R_7 and R_8, which may be the same or different, are each independently a hydroxyl-protecting group selected from

unsubstituted acetyl, and unsubstituted benzoyl. EX1022, [0077]-[0078] ("Optionally, the R_6, R_7 and R_8 moieties are selected from substituted and ***unsubstituted acetyl***, and substituted and ***unsubstituted benzoyl***. Optionally, at least two of R_6, R_7 and R_8 are selected from ***unsubstituted acetyl or unsubstituted benzoyl***."). The '184 publication also discloses where X^- is an anion of a substituted or unsubstituted aminodicarboxylic acid (e.g., substituted or unsubstituted versions of glutamic acid, an aminodicarboxylic acid) (*see* EX1022, [0030]). EX1022 (the '184 publication), [0030] ("X^- is an anion of a substituted or unsubstituted amino-monocarboxylic acid or an anion of ***a substituted or unsubstituted amino-dicarboxylic acid***.").

141. Accordingly, the '184 publication anticipates claim 25.

R. Claim 26

26. The compound of claim 1 of formula:



where:
n is 0 and Y is absent;
m is 1;
R_1 is —NH_2;
R_2-R_5 are each H; and
X^- is an anion of a substituted or unsubstituted dicarboxylic acid.

142. Claim 26 additionally recites the compound of claim 1 where n is 0 and Y is absent; m is 1; R_1 is —NH_2; R_2-R_5 are each H; and X^- is an anion of a substituted or unsubstituted dicarboxylic acid. Claim 26 changes the Markush figure of claim 1 so that each of the R_6, R_7 and R_8 groups are instead H. As I have previously addressed above, claim 1 is anticipated by the '184 publication.

143. As I explained above, the priority documents consistently defined that R_6-R_8 in formula (IV) each must be a hydroxyl-protecting group. *See* Section X.A. The '506 patent claim 26 recites a logical impossibility. Claim 26 depends from claim 1, which recites defined formula (IV). *See* Section XI.A. As explained above, claim 1 and claims that depend therefrom thus require R_6-R_8 to be hydroxyl-protecting groups. Yet claim 26 also recites a conflicting identification of R_6-R_8 as hydrogen. EX1001, claim 26 (replacing R_6-R_8 with H in the chemical structure). A POSA would have understood that the claims require R_6-R_8 as hydroxyl-protecting groups, consistent with the specifications of the priority documents. *See* Section X.

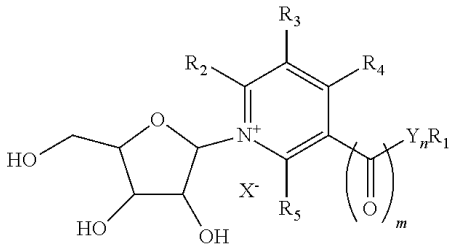
144. For the limited purposes of my evaluation below, I accept for the sake of argument the logical impossibility that R_6-R_8 may be replaced with hydrogens as depicted in claim 26—though this cannot be within the scope of independent claim 1. Nonetheless, the '184 publication discloses the chemical formula depicted in claim 26. As explained with regard to claim 1, the '184 publication describes its formulae in beta-anomer form (i.e., the same anomer form as depicted in claim 26)

where: n is 0 and Y is therefore absent; m is 1; R_1 is an unsubstituted primary amino (i.e., —NH_2); and R_2-R_5 are each H. EX1022, [0124]-[0126], [0011]-[0015] (reproduced below, annotations added):

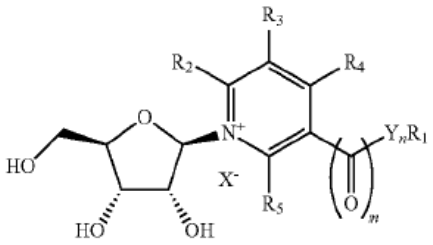
> **[0011]** n is 0 or 1;
>
> **[0012]** m is 0 or 1;
>
> **[0013]** Y is O or S;
>
> **[0014]** R_1 is selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted primary or secondary amino, and substituted or unsubstituted azido;
>
> **[0015]** R_2-R_5 which may be the same or different, are each independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, and substituted or unsubstituted aryl; and

The ’184 publication describes these variables as also applying to its formula (I). EX1022, [0009]; *see also id*, [0115] (formula (IA)).

(I)



(IA)



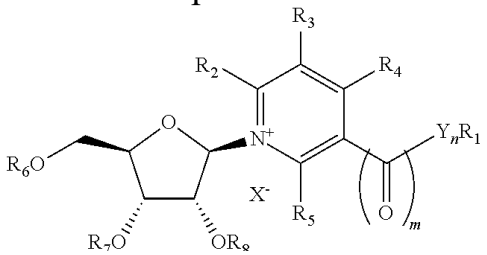
The ’184 publication also discloses where X^- is an anion of a substituted or unsubstituted dicarboxylic acid. *See* EX1022 (the ’184 publication), [0027] (“X^- is an anion of a substituted or unsubstituted carboxylic acid selected from an anion of

a substituted or unsubstituted monocarboxylic acid and ***an anion of a substituted or unsubstituted dicarboxylic acid.***").

145. Accordingly, the '184 publication anticipates claim 26.

S. Claim 27

27. The compound of claim 1 of formula:



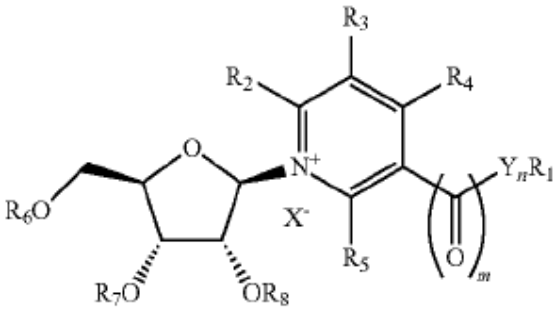
where:
n is 0 and Y is absent;
m is 1;
R_1 is —NH_2
R_2-R_5 are each H;
R_6, R_7 and R_8, which may be the same or different, are each independently a hydroxyl-protecting group selected from unsubstituted acetyl, and unsubstituted benzoyl; and
X^- is an anion of a substituted or unsubstituted dicarboxylic acid.

146. Claim 27 depicts the beta-anomer form of formula (IV) provided in claim 1 and additionally recites n is 0 and Y is absent; m is 1; R_1 is —NH_2; R_2-R_5 are each H; R_6, R_7 and R_8, which may be the same or different, are each independently a hydroxyl-protecting group selected from unsubstituted acetyl, and unsubstituted benzoyl; and X^- is an anion of a substituted or unsubstituted dicarboxylic acid. As I have previously addressed above, claim 1 is anticipated by the '184 publication. Additionally, as I explained above, the '184 publication

discloses the beta-anomer of formula (IV) as depicted in claim 27. EX1022, [0124]-[0126]:

[0124] Optionally, the compound of formula (IV) has the formula (IVA), i.e. is the β-anomer,

(IVA)



[0125] wherein

[0126] n, m, Y, R_1-$R_8$and X^- are as defined above.

The '184 publication also describes where: n is 0 and Y is therefore absent; m is 1; R_1 is an unsubstituted primary amino (i.e., —NH_2); and R_2-R_5 are each H. EX1022, [0011]-[0015] (reproduced below, annotations added):

[0011] n is 0 or 1;

[0012] m is 0 or 1;

[0013] Y is O or S;

[0014] R_1 is selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted primary or secondary amino, and substituted or unsubstituted azido;

[0015] R_2-R_5 which may be the same or different, are each independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, and substituted or unsubstituted aryl; and

Further, the ’184 publication discloses R_6, R_7 and R_8, which may be the same or different, are each independently a hydroxyl-protecting group selected from unsubstituted acetyl, and unsubstituted benzoyl. EX1022, [0077]-[0078] (“Optionally, the R_6, R_7 and R_8 moieties are selected from substituted and ***unsubstituted acetyl***, and substituted and ***unsubstituted benzoyl***. Optionally, at least two of R_6, R_7 and R_8 are selected from ***unsubstituted acetyl or unsubstituted benzoyl***.”). The ’184 publication also discloses where X^- is an anion of a substituted or unsubstituted dicarboxylic acid. *See* EX1022 (the ’184 publication), [0027] (“X^- is an anion of a substituted or unsubstituted carboxylic acid selected from an anion of a substituted or unsubstituted monocarboxylic acid and ***an anion of a substituted or unsubstituted dicarboxylic acid.***”).

147. Accordingly, the ’184 publication anticipates claim 27.

T. Claims 28 and 31

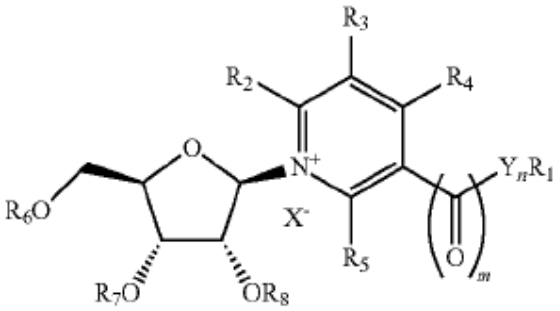
28. The compound of claim 1 that is a beta-anomer.

31. The compound of claim 6 that is a beta-anomer.

148. Claims 28 and 31 each additionally recite that the compound of claims 1 and 6 (respectively) is a beta-anomer. As I have previously addressed above, claims 1 and 6 are each anticipated by the ’184 publication.

149. I explained above that the ’184 publication describes the beta-anomer of the claimed compounds. *See* Section XI.A (claim 1); Section XI.F (claim 6).

The ’184 publication discloses the beta-anomer of formula (IV) as required in claims 28 and 31. EX1022, [0124]-[0126]:

> **[0124]** Optionally, the compound of formula (IV) has the formula (IVA), i.e. is the β-anomer,
>
> (IVA)
>
> 
>
>
> **[0125]** wherein
>
> **[0126]** n, m, Y, R_1-$R_8$and X^- are as defined above.

150. Accordingly, the ’184 publication anticipates claims 28 and 31.

U. Claim 34

> **34.** A nutritional supplement composition comprising a compound of claim 6.

151. Claim 34 additionally recites a nutritional supplement composition comprising a compound of claim 6. As I have previously addressed above, claim 6 is anticipated by the ’184 publication. Additionally, the ’184 publication describes its method “may be used to introduce a counter ion of choice to the prepared compounds, thereby producing compounds ***suitable for use as nutritional supplements*** or otherwise.” EX1022 (the ’184 publication), [0008]. The ’184 publication also explains its “methods conveniently enable the preparation of

compounds having potential use as nutritional supplements or otherwise." *Id.*, [0128].

152. Accordingly, the '184 publication describes the use of its compositions for nutritional supplements, and anticipates claim 34.

V. Claim 35

35. The nutritional supplement composition of claim 34, wherein R_1 is —NH_2.

153. Claim 35 additionally recites R_1 is —NH_2. As I have previously addressed above, claim 34 is anticipated by the '184 publication. Additionally, I have explained that the '184 publication discloses R_1 is —NH_2 (*see* Sections XI.P, XI.Q (Claim 24, Claim 25)). EX1022, [0011]-[0015].

154. Accordingly, the '184 publication anticipates claim 35.

155. Thus, for the reasons described above, it is my opinion that the '184 publication (EX1022) anticipates each of claims 1-12, 21-28, 31, and 34-35.

XII. '506 PATENT CLAIMS 29-30 AND 32-33 WERE OBVIOUS OVER THE '184 PUBLICATION AND GRAS

156. For the reasons discussed in detail below, it is my opinion that each of claims 29-30 and 32-33 of the '506 patent was obvious as a whole. The obviousness of claims 29-30 and 32-33 is exemplified by the disclosures in the '184 publication and GRAS reference.

157. I have evaluated below whether the combination of the '184 publication and GRAS disclose each and every element of each of claims 29-30

and 32-33 of the ’506 patent. I have also analyzed whether a person having ordinary skill in the art before the April 2023 critical date would have had good reason to combine these references in a manner that satisfies each claim as a whole with a reasonable expectation of success. As I explain in detail below, the answer to each of these questions is an unequivocal “Yes.”

158. Each of claims 29-30 and 32-33 require, among other limitations, an amount of “chemical purity” and “diastereomeric purity.” EX1001, Claims 29-30, 32-33. In my review of the priority documents (Section X), as well as in my review of the ’506 patent itself, I do not see descriptive support for “chemical purity.” I observe that the ’506 patent does not use the words “chemical purity” other than in the claims, it does not include a definition of “chemical purity,” and it does not have any examples of “chemical purity.” For compounds having the claimed formula (IV), the ’506 patent only describes compounds of formula (IV) as obtained as a crude intermediate with less than 10% remaining starting material (EX1001, 14:22-41, 15:17-38), but there is never a disclosure of the overall purity of the formula (IV) crude mixture being evaluated. For example, beyond remaining starting material, a POSA may expect byproducts or other contaminants in the crude mixture of formula (IV) as described in the ’506 patent. It is therefore my opinion that the ’506 patent fails to provide sufficient written description for the claim term “chemical purity.”

159. Similarly, in my review of the priority documents (Section X), as well as in my review of the ’506 patent itself, I do not see descriptive support for “diastereomeric purity.” I observe that the ’506 patent does not use the words “diastereomeric purity” other than in the claims, it does not include a definition of “diastereomeric purity,” and it does not include any examples of “diastereomeric purity.” Thus, it is my opinion that the ’506 patent also fails to provide sufficient written description support for the claim term “diastereomeric purity.” The lack of disclosure of chemical purity and diastereomeric purity are additional reasons why the priority documents do not demonstrate to the POSA that the inventors possessed (or otherwise sufficiently described) claimed compounds of formula (IV) having the now-claimed chemical and diastereomeric purities.

160. As a high-level summary, the ’184 publication discloses derivatives of nicotinamide riboside. EX1022, [0150]-[0151]. The ’184 publication also describes its nicotinamide riboside derivatives are used for “producing compounds suitable for use as nutritional supplements.” EX1022, [0008].

161. GRAS provides a description that outlines how a nicotinamide riboside salt (there, the chloride salt) could be safely administered as a supplement for human consumption. EX1017, 00003. GRAS evaluates the production process of nicotinamide riboside salts and outlines specific limits “for the final product to

comply with appropriate controls on residual solvents and other processing aids for food." *Id.*, 000026.

162. The '184 publication describes additional salts that may be used in place of the nicotinamide riboside chloride listed in GRAS, and explains other salts are suitable for use as nutritional supplements. *See, e.g.*, EX1022, [0008], [0035]:

> Optionally, X^- is selected from chloride, acetate, formate, trifluoroacetate, ascorbate, aspartate, glutamate and lactate. Further optionally, X^- is selected from chloride, acetate, formate and trifluoroacetate.

163. It is my opinion that it would have been obvious to a POSA to employ the nutritional supplement standards described by the nicotinamide riboside chloride salt in GRAS for the '184 publication's salts of nicotinamide riboside derivatives, and the POSA would have had a reasonable expectation of success in employing said standards.

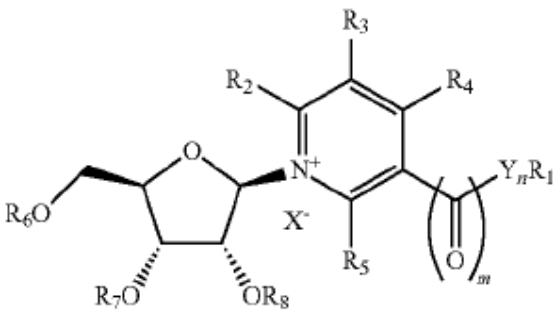
A. Claims 29 and 32

> **29.** The compound of claim 1 that is a beta-anomer; wherein the compound has greater than 90% chemical purity, and comprises at least 98% diastereomeric purity of the beta-D-ribofuranosyl configuration.
>
> **32.** The compound of claim 6 that is a beta-anomer; wherein the compound has greater than 90% chemical purity, and comprises at least 98% diastereomeric purity of the beta-D-ribofuranosyl configuration.

164. I have described above that the '184 publication discloses each and every element of claims 1 and 6, upon which claims 29 and 32, respectively, rely. Sections XI.A, XI.F, above. Each of claims 29 and 32 additionally recite the

compound is a beta-anomer, has greater than 90% chemical purity, and comprises at least 98% diastereomeric purity of the beta-D-ribofuranosyl configuration.

165. I explained above that the '184 publication describes the beta-anomer. *See* Section XI.A (claim 1); Section XI.F (claim 6). The '184 publication therefore discloses the beta-anomer of formula (IV) as required in claims 29 and 32. EX1022, [0124]-[0126]:

> **[0124]** Optionally, the compound of formula (IV) has the formula (IVA), i.e. is the β-anomer,
>
> (IVA)
>
> 
>
> **[0125]** wherein
>
> **[0126]** n, m, Y, R_1-$R_8$and X^- are as defined above.

166. In my review of the '506 patent specification, I noted that there was no descriptive support for "chemical purity" or "diastereomeric purity." With regard to "chemical purity" of formula (IV), I observe that the '506 patent discloses using the claimed formula (IV) intermediate in a "crude reaction mixture (containing some unreacted ethyl nicotinate and starting sugar, <10%)" and was thereafter reduced to form formula (III) without further purification. EX1001,

14:22-41; *id.*, 15:17-38 (similar, with "starting benzoate sugar, <10%"). The '506 patent does not disclose evaluating the purity of the crude reaction mixture beyond the mention of the presence of less than 10% of the unreacted starting materials.

167. GRAS describes its nicotinamide riboside salt is isolated with greater than 90% chemical purity. GRAS explains that there are specifications set for the nicotinamide riboside salt to control "impurities to assure acceptable final product." EX1017, 000029. More specifically, GRAS sets a parameter requiring at least 95% purity, and batch testing demonstrated even higher levels of purity (99.2%, 99.9%, 97.8%). *Id.*, 000030 & Table 2 (reproduced below, annotated by me).

Table 2. Specifications and Batch Analyses for Commercial Batches of Niagen

Parameter	Specifications	Method***	Batch 14207	Batch 14209	Batch 15201
Color	White to light brown	Visual	White to Off-white	White to Off-white	White to light brown
Form	Powder	Visual	Powder	Powder	Powder
Purity	95 – 102 (wt%) by HPLC	99.1-CD-3.0-000591	99.2	99.9	97.8
Identification	Conforms to structure by NMR	99.1-CD-1.0-000122	Conforms	Conforms	Conforms
Water Content	≤0 1%	99.1-CD-6.0-000094	0.1%	0.1%	0.1%

Thus, GRAS demonstrates its nicotinamide riboside has greater than 90% chemical purity.

168. Additionally, in my review of the '506 patent specification I noted that with regard to "diastereomeric purity" of formula (IV), the '506 patent discloses using the claimed formula (IV) as an intermediate in a crude mixture without purification. To the extent a POSA would rely on this crude mixture as

providing a compound having the claimed diastereomeric purity, this is the same as what was disclosed in the '184 publication. EX1022, [0150]-[0151] ("6.51 (d, 1H, J=4.1 Hz, H-1 (anomeric))").

169. Accordingly, the combination of the '184 publication and GRAS teaches all of the elements of each of claims 29 and 32, and thus renders the claims obvious.

B. Claims 30 and 33

> **30.** The compound of claim 1 that is a beta-anomer; wherein the compound has greater than 90% chemical purity, comprises at least 98% diastereomeric purity of the beta-D-ribofuranosyl configuration; and contains <3000 ppm methanol, under 0.1% (w/w) other solvents and under 0.2% (w/w) water.
>
> **33.** The compound of claim 6 that is a beta-anomer; wherein the compound has greater than 90% chemical purity, comprises at least 98% diastereomeric purity of the beta-D-ribofuranosyl configuration; and contains <3000 ppm methanol, under 0.1% (w/w) other solvents and under 0.2% (w/w) water.

170. I have described above that the '184 publication discloses each and every element of claims 1 and 6, upon which claims 30 and 33, respectively, rely. Sections XI.A, XI.F, above. Each of claims 30 and 33 additionally recite the compound is a beta-anomer; the compound has greater than 90% chemical purity, comprises at least 98% diastereomeric purity of the beta-D-ribofuranosyl configuration; and contains <3000 ppm methanol, under 0.1% (w/w) other solvents and under 0.2% (w/w) water. As I described for each of claims 29 and 32 above,

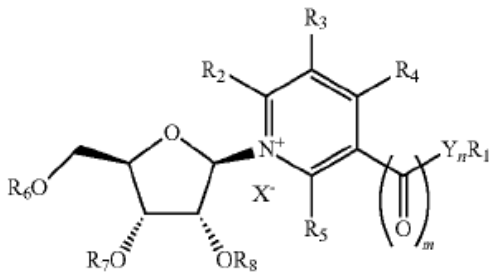
the ’184 publication and GRAS describes nicotinamide riboside derivatives that are the beta-anomer, wherein the compound has greater than 90% chemical purity, and wherein it comprises at least 98% diastereomeric purity of the beta-D-ribofuranosyl configuration. Section XII.A.

a. Beta-anomer

171. I explained above that the ’184 publication describes the beta-anomer of the claimed compounds. *See* Section XI.A (claim 1); Section XI.F (claim 6); *see also* Section XII.A. The ’184 publication discloses the beta-anomer of formula (IV) as required in claims 30 and 33. EX1022, [0124]-[0126]:

[0124] Optionally, the compound of formula (IV) has the formula (IVA), i.e. is the β-anomer,

(IVA)



[0125] wherein

[0126] n, m, Y, R_1-$R_8$and X^- are as defined above.

b. Purity

172. As I explained above, (Section XII.A), in my review of the ’506 patent specification, I noted that there was no descriptive support for “chemical purity” or “diastereomeric purity.” With regard to “chemical purity” of compounds

having the claimed formula (IV), the '506 patent only describes the compounds of formula (IV) as being obtained as a "crude reaction mixture (containing some unreacted ethyl nicotinate and starting sugar, <10%)" and was thereafter reduced to form formula (III). EX1001, 14:22-41; *id.*, 15:17-38 (similar, with "starting benzoate sugar, <10%"). The '506 patent does not describe evaluating the formula (IV) crude mixture for overall purity to address anything other than relative amounts of remaining starting material.

173. GRAS describes its nicotinamide riboside salt is isolated with greater than 90% chemical purity. GRAS explains that there are specifications set for the nicotinamide riboside salt to control "impurities to assure acceptable final product." EX1017, 000029. More specifically, GRAS sets a parameter requiring at least 95% purity, and batch testing demonstrated even higher levels of purity (99.2%, 99.9%, 97.8%). *Id.*, 000030 & Table 2 (reproduced below, annotated by me).

Table 2. Specifications and Batch Analyses for Commercial Batches of Niagen

Parameter	Specifications	Method***	Batch 14207	Batch 14209	Batch 15201
Color	White to light brown	Visual	White to Off-white	White to Off-white	White to light brown
Form	Powder	Visual	Powder	Powder	Powder
Purity	95 – 102 (wt%) by HPLC	99.1-CD-3.0-000591	99.2	99.9	97.8
Identification	Conforms to structure by NMR	99.1-CD-1.0-000122	Conforms	Conforms	Conforms
Water Content	≤ 0 1%	99.1-CD-6.0-000094	0.1%	0.1%	0.1%

Thus, GRAS demonstrates its nicotinamide riboside has greater than 90% chemical purity.

174. Additionally, in my review of the ’506 patent specification I noted that with regard to “diastereomeric purity” of formula (IV), the ’506 patent discloses using the claimed formula (IV) as an intermediate in a crude mixture without purification. *See e.g.* EX1001, Example 1(A)-(C); *see also* Section XII.A. To the extent that a POSA would rely on this crude mixture as providing a compound having the claimed diastereomeric purity, this is the same as what was disclosed in the ’184 publication. EX1022, [0150]-[0151] (“6.51 (d, 1H, J=4.1 Hz, H-1 (anomeric))”).

c. Methanol, Solvents, and Water

175. GRAS requires that for nicotinamide riboside salt supplement, the amount of residual methanol present must be less than 740 ppm. EX1017, 000026-27 (“A residual amount of methanol in finished product of ≤ 740 ppm is determined to be GRAS [Generally Recognized As Safe]…”). In practice, the amount of methanol identified in commercial batches of the nicotinamide riboside salt supplement is significantly less than the claimed <3000 ppm methanol. Batches of the nicotinamide riboside salt were determined to have 172 ppm, 263 ppm, and 631 ppm. *See id.*, 000030, Table 2 (reproduced below, with red annotation added by me).

Table 2. Specifications and Batch Analyses for Commercial Batches of Niagen					
Parameter	**Specifications**	**Method*** **	**Batch 14207**	**Batch 14209**	**Batch 15201**
Color	White to light brown	Visual	White to Off-white	White to Off-white	White to light brown
Form	Powder	Visual	Powder	Powder	Powder
Purity	95 – 102 (wt%) by HPLC	99.1-CD-3.0-000591	99.2	99.9	97.8
Identification	Conforms to structure by NMR	99.1-CD-1.0-000122	Conforms	Conforms	Conforms
Water Content	≤ 0 1%	99.1-CD-6.0-000094	0.1%	0.1%	0.1%
Residual Solvents					
Acetone	≤ 3000 ppm	99.1-CD-7.0-000115	1140	1576	1776
Methanol	≤ 740 ppm	99.1-CD-7.0-000115	172	263	631
Acetonitrile	ND*	99.1-CD-7.0-000115	ND	ND	ND
Methyl *t*-Butyl Ether	ND*	99.1-CD-7.0-000115	ND	ND	ND

176. The batches of nicotinamide riboside salt listed in GRAS had low levels of other solvent impurities (e.g., Batch 14207, 0.1140% (w/w)). It is my opinion that a POSA would have sought to decrease this level of solvent even further. For example, GRAS identified potential issues of acetone impurity, and attempts were made to minimize such solvent impurities (EX1017, 000055). Further reduction of solvent impurities would be achieved through routine optimization. It is my opinion that disclosure in GRAS of other solvent amount so close to the claimed less than 0.1% (w/w) value renders that claim element obvious, especially in view of the desire to continue decreasing solvent impurity for the nutritional supplement.

177. GRAS requires that for nicotinamide riboside salt supplement, the amount of water present must be less than the claimed "under 0.2% (w/w)." For example, commercial batches of the nicotinamide riboside in GRAS were required

by specification to have ≤ 0.1% water content. EX1017, 000030 & Table 2. Batches of the nicotinamide riboside salt were each determined to have 0.1% water content. *Id.*, 000030, Table 2 (reproduced below, with red annotation added by me).

Table 2. Specifications and Batch Analyses for Commercial Batches of Niagen

Parameter	Specifications	Method***	Batch 14207	Batch 14209	Batch 15201
Color	White to light brown	Visual	White to Off-white	White to Off-white	White to light brown
Form	Powder	Visual	Powder	Powder	Powder
Purity	95 – 102 (wt%) by HPLC	99.1-CD-3.0-000591	99.2	99.9	97.8
Identification	Conforms to structure by NMR	99.1-CD-1.0-000122	Conforms	Conforms	Conforms
Water Content	≤ 0 1%	99.1-CD-6.0-000094	0.1%	0.1%	0.1%

178. Accordingly, the combination of the '184 publication and GRAS teaches all of the elements of each of claims 30 and 33, and renders the claims obvious as a whole.

C. Motivation to Combine

179. GRAS describes the summary of a regulatory advisory panel on how nicotinamide riboside salt (chloride) may be safely administered as a supplement for human consumption. EX1017, 00003. It also envisions mass-scale production of its nicotinamide riboside salt, with "over 10% of the total U.S. population of 2+ years [being] identified as consumers of" the product from proposed supplemented food uses. *Id.*, 000039. GRAS evaluates the production process of nicotinamide riboside salts and outlines specific limits "for the final product to comply with

appropriate controls on residual solvents and other processing aids for food." *Id.*, 000026.

180. The '184 publication recognizes that the nicotinamide riboside chloride salt in GRAS is just one of many suitable salts, and seeks to provide additional suitable salts that avoid the use of triflate salts. EX1022, [0003]. The '184 publication describes a synthetic pathway involving derivatives of nicotinamide riboside and their application for use as nutritional supplements. *Id.*, [0008] (the method "may be used to introduce a counter ion of choice to the prepared compounds, thereby producing compounds ***suitable for use as nutritional supplements*** or otherwise.").

181. It is my opinion that it would have been obvious to a POSA to employ the nutritional supplement safety standards described for the nicotinamide riboside chloride salt of GRAS for the salts of nicotinamide riboside in the '184 publication, in order to provide suitable substitutes to the chloride salt while maintaining quality and safety for a food supplement.

D. Reasonable Expectation of Success

182. Persons having ordinary skill in the art (POSAs) would have had a reasonable expectation of success employing the GRAS-disclosed parameters (e.g., purity, methanol content, solvent content, and water content) for its nicotinamide riboside chloride with the nicotinamide riboside salts of the '184 publication.

Indeed, the ’184 publication envisioned its nicotinamide riboside salts as suitable substitutes for the chloride salt, and a POSA would have had a reasonable expectation of success in so substituting it. *See, e.g.*, EX1022, [0035] (“X^- is selected from chloride, acetate, formate, trifluoroacetate, ascorbate, aspartate, glutamate and lactate. Further optionally, X^- is selected from chloride, acetate, formate and trifluoroacetate.”).

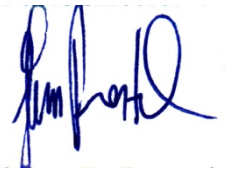
183. Accordingly, the POSA had good reason to combine the ’184 publication and GRAS to arrive at the claimed invention, and the POSA would have had a reasonable expectation of success in arriving at the claimed invention.

XIII. CONCLUDING STATEMENTS

184. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

185. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements

and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.



Dated: 19 June, 2026 By: _____
Glenn D. Prestwich, Ph.D.

XIV. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 12,252,506
1002	Prosecution history for U.S. Patent App. No. 18/307,733
1003	United Kingdom Patent Application No. 1313465.5
1004	International Patent Application No. PCT/EP2014/065971
1005	U.S. Patent No. 10,000,519
1006	U.S. Patent No. 10,815,262
1007	U.S. Patent No. 11,584,770
1008	U.S. Patent No. 11,981,698
1009	G. Schabert et al., *New Crystalline Salts of Nicotinamide Riboside as Food Additives*, MOLECULES 26, 2729 (2021).
1010	*Intentionally left blank*
1011	*Intentionally left blank*
1012	JONATHAN CLAYDEN ET AL., ORGANIC CHEMISTRY (2009).
1013	*Intentionally left blank*
1014	Dr. Glenn Prestwich CV
1015	S. Tanimori et al., *An Efficient Chemical Synthesis of Nicotinamide Riboside (NAR) and Analogs*, BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 12, 1135 (2002).
1016	P. Franchetti et al., *Stereoselective synthesis of nicotinamide β-riboside and nucleoside analogs*, BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 14, 4655 (2004).

1017	SPHERIX CHROMADEX CONSULTING, Generally Recognized as Safe (GRAS) Determination for Niagen™ (Nicotinamide Riboside Chloride), No. 635 (Mar. 3, 2016), *available at* https://www.hfpappexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=635
1018	*GRN No. 635: Nicotinamide riboside chloride*, FDA, https://www.hfpappexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=635 (last visited Apr. 24, 2026)
1019	*GRAS Notices*, FDA https://www.hfpappexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices (last visited Apr. 24, 2026)
1020	Archived *GRAS Notices*, FDA https://web.archive.org/web/20201222145917/https:/www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&sort=GRN_No&order=DESC&showAll=true&type=basic&search= (archived Dec. 22, 2020)
1021	Archived *GRN No. 635: Nicotinamide riboside chloride*, FDA, https://web.archive.org/web/20210124164020/https:/www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=635 (archived Jan. 24, 2021)
1022	U.S. Patent Application Publication No. US 2016/0168184