

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

Petitioners,

v.

CHROMADEX, INC.

Patent Owner.

IPR2026-00400

U.S. Patent No. 12,252,506

**DECLARATION OF RON BIHOVSKY, PH.D.
IN SUPPORT OF PATENT OWNER'S PRELIMINARY RESPONSE**

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EXHIBIT LIST

Exhibit	Description
2001	Conference and Scheduling Order, Case No. 2:26-cv-01758-RMG (D.S.C.)
2002	Complaint for Declaratory Judgment, Case No. 2:26-cv-01758-RMG (D.S.C.)
2003	Notice of Filing Proof of Service, Case No. 2:26-cv-01758-RMG (D.S.C.)
2004	U.S. Patent No. 11,981,698 to Migaud et al.
2005	U.S. Patent No. 11,584,770 to Migaud et al.
2006	U.S. Patent No. 10,815,262 to Migaud et al.
2007	U.S. Patent No. 10,000,519 to Migaud et al.
2008	U.S. Patent No. 10,815,262 File History
2009	U.S. Patent Publication No. 2018/0186824 to Migaud et al.
2010	Answer and Counterclaim, Case No. 2:26-cv-01758-RMG (D.S.C.)
2011	Declaration of Ron Bihovsky, Ph.D. in support of Patent Owner's Preliminary Response
2012	Curriculum Vitae of Dr. Ron Bihovsky
2013	Clayden et al., Organic Chemistry (2nd ed. 2012)
2014	U.S. Patent Application Publication No. 2005/0010603 A1

I, Ron Bihovsky, declare as follows:

1. I have been engaged by King & Spalding LLP on behalf of ChromaDex, Inc. (“Patent Owner”), to provide this Declaration concerning the technical subject matter relevant to the petition for *Inter Partes* Review (“Petition”) of U.S. Patent 12,252,506 (“the ’506 patent”) (IPR2026-00400).

2. I am over 18 years of age. I have personal knowledge of the facts stated in this Declaration and could testify competently to them if asked to do so.

3. I have reviewed and am familiar with the specification and the claims of the ’506 patent. In general, I will cite to the specification of a United States patent using the following formats: (Exhibit No. Col:Line Number(s)) or (Exhibit No. Paragraph Number(s)). For example, the citation (EX1001, 1:1–10) points to the ’506 patent specification at column 1, lines 1–10. Also, for convenience, I use italics to denote limitations from the challenged claims.

4. All the opinions in this Declaration are based on the documents I reviewed and my knowledge, experience, training and professional judgment. In forming the opinions expressed in this Declaration, I reviewed the Petition for *Inter Partes* Review of U.S. Patent No. 12,252,506 and supporting exhibits.

5. I have been asked to provide my technical opinions regarding how a person of ordinary skill in the art (POSA) would have understood the claims of the ’506 patent at the time of the alleged invention. I have also been asked to provide

my technical opinions on how concepts in the '506 patent specification relate to claim limitations of the '506 patent. In reaching the opinions provided herein, I have considered the '506 patent, its prosecution history, and the references cited herein and have drawn as appropriate on my own education, training, research, knowledge, and personal and professional experience.

I. QUALIFICATIONS

6. In formulating my opinions, I have relied on my knowledge, training, and experience in the relevant field, which I will summarize briefly. A more detailed summary of my background, experience, and publications is set forth in my curriculum vitae (CV), which is submitted as Exhibit 2012.

7. I am a practicing organic and medicinal chemist with more than 40 years of experience. My education and experience in the fields of organic and medicinal chemistry have led to my expertise in organic synthesis, drug design, lead optimization, structure-activity relationships and molecular modeling.

8. I currently serve as the president and founder of Key Synthesis LLC in Wynnewood, PA. I have been employed at Key Synthesis LLC since 2001 and have conducted numerous organic syntheses and medicinal chemistry projects. During my time at Key Synthesis LLC, I have designed and successfully synthesized various enzyme inhibitors, receptor antagonists, enzyme substrates, and synthetic intermediates for the pharmaceutical and biotechnology industries. I also serve as an

intellectual property consultant at Key Synthesis LLC for various companies and intellectual property firms. As a consultant, I have performed various chemical experiments to determine the validity of patent claims, have been an organic chemistry and medicinal chemistry expert in over 100 Hatch-Waxman pharmaceutical patent litigation cases, and have been deposed and testified in high-profile cases.

9. From 2001 to 2003, I also served as an Adjunct Professor of Chemistry at Villanova University in Villanova, PA, where I created and taught a graduate-level medicinal chemistry course, as well as undergraduate organic chemistry courses.

10. I also serve on the Steering Committee of the Chemical Consultants Network and was its Treasurer from 2007 to 2008 and Chair from 2009 to 2012. Chemical Consultants Network is a topical group of the American Chemical Society that works to support chemical consultants.

11. I served as a Principal Project Chemist and a Medicinal Chemistry Senior Scientist at Cephalon, Inc., in West Chester, PA from 1992 to 2001. During my time at Cephalon, Inc., my research group investigated compounds that could be used in the treatment of cerebral ischemia and cancer. Some of the compounds I investigated were novel, potent, selective heterocyclic inhibitors of poly(ADP-ribose) polymerase (PARP), and novel peptide-mimetic and non-peptide cell-

permeable calpain inhibitors. The discovery of these inhibitors involved screening libraries of compounds and optimization of hit compounds. I also coordinated with a multidisciplinary team of 20 biochemists, pharmacologists, cell biologists and medicinal chemists to evaluate results and plan future directions and supervised a team of 7-10 medicinal chemists during the development of calpain inhibitors.

12. I was employed as a Medicinal Chemistry Scientist at Berlex Laboratories in Cedar Knolls, NJ from 1987 to 1992. While at Berlex Laboratories, I was a project leader in cardiovascular research and directed a group of medicinal chemists in the synthesis of enzyme inhibitors and peptide mimetics. My team designed and synthesized highly potent endothelin-converting enzyme inhibitors, investigated the mechanisms of the epoxysuccinate class of cysteine protease inhibitors, identified novel peptide-mimetic constructs capable of incorporation into angiotensin II, and performed molecular modeling simulations of peptides, peptide mimetics, and enzyme inhibitors.

13. I worked as an Assistant Professor of Chemistry at the State University of New York at Stony Brook, NY from 1980 to 1987. My research group and I synthesized biologically significant natural products such as biotin, oudenone, civet acid, C-glycoside antibiotics, lignans, and tetrahydroisoquinolines. My group also generated α -halo ethers and oxonium ions and utilized these compounds in organic synthesis reactions. My group also determined the structures of crown gall tumor

metabolites and the regioselectivity of the Pictet-Spengler reaction. In addition to performing organic chemistry reactions, I also wrote computer software programs for literature reference retrieval and elemental analysis, and supervised the research projects of postdoctoral fellows, graduate students, and undergraduates. I also taught graduate-level synthetic organic chemistry courses and undergraduate-level organic chemistry courses.

14. From 1978 to 1980, I worked as an NIH Postdoctoral Fellow at the University of Wisconsin in Madison, WI. My NIH Postdoctoral Fellowship research focused on the organic synthesis and structure elucidation of natural products with smooth-muscle contracting properties. I synthesized natural products, introduced chirality into natural products via microbial transformations, and elucidated the structures of compounds with smooth muscle-contracting activity (*e.g.*, leukotriene and G-acid) from animal tissue. I also performed smooth-muscle contraction bioassays.

15. From 1972 to 1978, I was a Graduate Student at the University of California in Berkeley, CA. My doctoral research involved the organic synthesis of anatoxin-a via intramolecular cyclization of iminium ions and determination of the structure of saxitoxin, a potent marine neurotoxin. I also developed a sensitive oxidative fluorescence assay for saxitoxin, cultured microscopic marine algae, isolated their toxins, and performed bioassays to aid in their isolation.

16. I received a Bachelor of Science (BSc; Magna cum laude) degree in Chemistry from the State University of New York at Stony Brook in 1970. I received a Doctor of Philosophy (PhD) degree in Organic Chemistry from the University of California in Berkeley in 1977.

17. I have published 51 peer-reviewed original contributions in high-caliber chemistry and medical journals including *Journal of the American Chemical Society*, *Journal of Organic Chemistry*, *Journal of Medicinal Chemistry*, *Biochemical Journal*, *Molecular Cancer Therapeutics* and *Journal of Natural Products*.

18. I have been granted 19 US patents and numerous foreign patents based on my research.

19. Based on my education, experience, and qualifications, I consider myself to be an expert in the fields of organic chemistry and medicinal chemistry. In addition, based on my training and experience as an organic chemist, I am familiar with the use of protecting groups, including those mentioned in the '506 patent, during the synthesis of compounds that contain hydroxyl groups.

20. I am being compensated in this case at my standard rates for consulting and for providing deposition and trial testimony. My compensation is not dependent on the opinions that I express or the outcome of this lawsuit. I do not have any financial interest in any party to these litigations, or in the outcome of this litigation.

II. UNDERSTANDING OF RELEVANT LEGAL PRINCIPLES

21. I am not a lawyer, and I will not provide any legal opinions. Although I am not a lawyer, I have been advised that certain legal standards are to be applied by technical experts in forming opinions regarding the meaning and validity of patent claims.

A. Claim Construction

22. I understand that claims should be given their ordinary and customary meaning as understood by a person having ordinary skill in the art (POSA) at the time of the invention, in light of the language of the claims, the specification, and the prosecution history of record.

23. I understand that it is improper to limit a claim based on limitations in the specification that are not part of the claim and that claims should not be limited to a preferred embodiment or to examples listed within the patent specification when the claim language is broader than the embodiment.

24. I understand that patent inventors may act as their own lexicographers by clearly setting forth a definition of a claim term and clearly expressing their intent to redefine the term.

B. Anticipation

25. I understand that a patent claim is invalid if it is anticipated by the prior art from the perspective of a POSA at the time the invention was made.

26. I have been informed that a patent claim is invalid as anticipated if a single prior art disclosure describes every element of the claimed invention, such that a POSA could practice the invention without undue experimentation. The elements must be arranged as required by the claim, but the prior art disclosure need not use identical terminology as the claim.

C. Obviousness

27. I understand that a patent claim is invalid if it is obvious in view of the prior art, and that a claim can be unpatentable even if all of the requirements of the claim cannot be found in a single prior art reference.

28. I have been informed that a patent claim is invalid if it would have been obvious to a person of ordinary skill in the art. In analyzing the obviousness of a claim, I understand the following factors may be taken into account: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims; (3) the level of ordinary skill in the art; and (4) any so called “secondary considerations” of nonobviousness if they are present.

29. I have been informed that a claim can be obvious in light of a single prior art reference or multiple prior art references. I understand that to prove that prior art or a combination of prior art renders a patent obvious, it is necessary to:

- 1) Identify the particular references that, singly or in combination, make the patent obvious;

- 2) Specifically identify which elements of the patent claim appear in each of the asserted references; and
- 3) Explain why a person of ordinary skill in the art would have combined the references, and how they would have done so, to create the inventions claimed in the patent. I further understand that exemplary rationales that may support a conclusion of obviousness include:
 - Combining prior art elements according to known methods to yield predictable results;
 - Simple substitution of a known element for another to obtain predictable results;
 - Use of known technique(s) to improve similar devices (methods or products) in the same way;
 - Applying a known technique to a known device (method or product) ready for improvement to yield predictable results;
 - “Obvious to try” – choosing from a finite number of identified, predictable solutions with a reasonable expectation of success;
 - Known work in one field of endeavor may prompt variations of the work for use in either the same field or a different field based on design incentives or other market forces if the variations are predicable to a person of ordinary skill in the art; and
 - Some teaching, suggestion, or motivation in the prior art that would have led a person of ordinary skill in the art to modify the prior art reference or to combine the prior art reference teachings to arrive at the claimed invention.

30. I understand that secondary considerations that may be relevant to nonobviousness include commercial success of a practicing product, where that success is attributable to the patented features (i.e., where a nexus is shown); long-felt but unsolved need; failure of others to achieve what the patentee achieved; and the presence of copying or licensing.

31. I have been informed that, in considering obviousness, hindsight reasoning derived from the patent-at-issue may not be used. In other words, it is impermissible to use the claimed invention, or disclosure of the subject patent, as a template to piece together existing elements in the prior art to arrive at the claimed invention.

D. Priority Claims

32. I understand that a later-filed application may claim the benefit of an earlier filing date only if the earlier application complies with written description and enablement requirements, which are described below.

33. I understand this inquiry looks at the priority document as a whole and that its specification text, figures, drawings, and originally-filed claims all may serve as a basis for support. I further understand that in the context of chemical patents, structural formulas and drawings depicting the claimed compound can satisfy the requirement even absent a textual description.

E. Written Description Support

34. I understand that for claims to have written description support, the patent specification must reasonably convey to a POSA that the inventor had possession of the claimed subject matter as of the filing date. The specification must describe the invention in sufficient detail such that a POSA can reasonably conclude the inventor had possession of the claimed invention.

35. I understand that written description support may be found in the patent's specification as a whole, including the originally-filed claims or any other portion of the originally-filed specification. I understand that in the chemical arts, this support may be shown through words, structures, figures, diagrams, formulas, etc.

36. I am informed that an adequate written description of a claimed genus requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus.

F. Enablement

37. I understand that claims must be enabled by the patent specification, such that the specification enables any person skilled in the art to make and use the claimed invention without undue experimentation.

38. Factors relevant to assessing whether experimentation is undue include (1) the quantity of experimentation necessary; (2) the amount of direction or

guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. I understand this analysis to be holistic and that some experimentation is permitted.

III. THE '506 PATENT

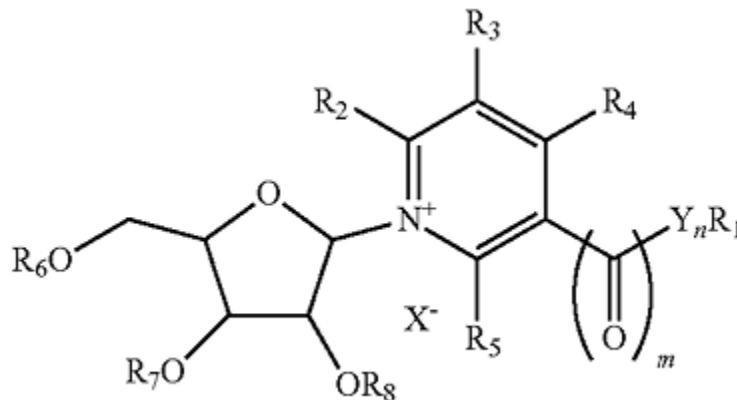
A. Summary Of The '506 Patent

39. The '506 patent concerns methods of preparing nicotinamide riboside (NR), nicotinate riboside, and derivatives thereof in novel, chemically stable, pharmaceutically acceptable salt forms, together with the resulting isomerically pure compounds and nutritional supplement compositions. Ex. 1001, 1:23-24. The '506 patent discloses a chemical process for incorporating pharmaceutically safe counter-ions into nicotinamide riboside, nicotinate riboside, and related compounds, as well as the beta-anomer compounds that this process reliably produces. Ex. 1001, 2:26-34.

40. The '506 patent explains that researchers had long recognized NR as a valuable NAD⁺ precursor with potential nutritional and pharmaceutical applications, but that known synthetic routes were poorly suited to commercial production. Ex. 1001, 1:42-2:23. Against this backdrop, the inventors of the '506 patent sought to provide “a novel, useful and efficient method for the preparation of

NR and derivatives” that avoids the disadvantages of the prior art. Ex. 1001, 2:26-29.

41. The '506 patent issued with 43 claims, including five independent claims. Generally, the claims are directed to a genus of novel, pharmaceutically acceptable salt forms of nicotinamide riboside and related compounds, as well as methods of synthesizing such salt forms. For purposes of this declaration, the most relevant portion of the claims is the recitation of “[a] compound of formula (IV)...where...*R₆, R₇, and R₈*, which may be the same or different, *are each independently H or a hydroxyl-protecting group....*”



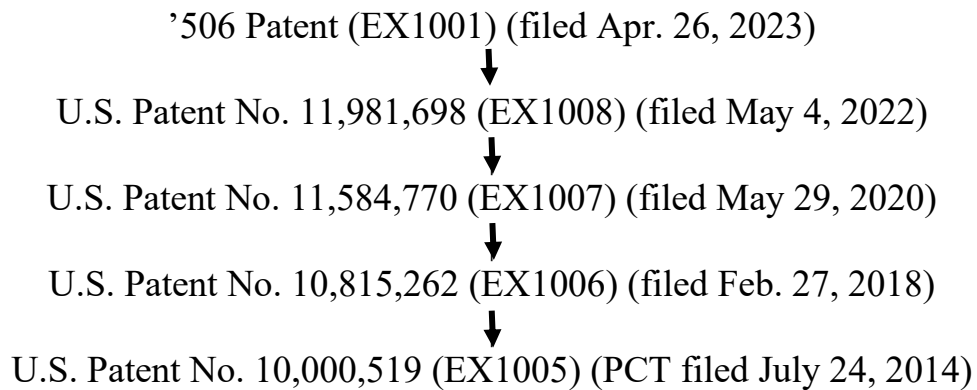
Ex. 1001, cl. 1. This limitation appears in all five independent claims. Ex. 1001, cls. 1, 6, 13, 18, 37.

B. The '506 Patent's Priority Claims

42. I understand the '506 patent claims priority to a British application no. 1313465.5, filed July 29, 2013 (EX1003, “the British Application”). EX1001,

Cover. I understand the '506 patent claims this date—July 29, 2013—as the earliest possible priority date. *Id.*

43. I further understand that the '506 patent is the youngest (or most recently filed) member of a continuation chain:



EX1001, Cover. That is, the '506 patent is a continuation of the '698 patent, which is a continuation of the '770 patent, which is a continuation of the '262 patent, which is a continuation of the '519 patent, all of which claim priority to the British application.

44. Claims 1-5 and 7-12 of the '506 patent were provisionally rejected on the ground of non-statutory double patenting as allegedly being unpatentable over claims 1-29 of '519 and claims 1-3 of the '770 patent. I have been informed that these objections were resolved with a Terminal Disclaimer, disclaiming any term of the '506 patent that would extend beyond the expiration dates of the grandparent '770 patent, as well as the great, great grandparent '519 patent. EX 1002, '506

Prosecution History pp. 146, 152, 178. I have also been informed that no terminal disclaimer was filed for the parent '698 patent or the grandparent '262 patent.

45. Upon review, the specifications of the '506 patent, '698 patent, '770 patent, '262 patent, and '519 patent are substantively identical. *See* EX1001, EX1008, EX1007, EX1006, EX1005.

C. Claim Construction

46. Petitioner has not proposed any terms for construction.

47. I apply the plain and ordinary meaning of all claim terms based on my reading of the '506 patent.

D. Level Of Ordinary Skill In The Art

48. I understand that certain issues relating to the validity of the '506 patent must be judged from the perspective of a person of ordinary skill in the relevant art, as I discuss below. I have been asked to define the level of a “person having ordinary skill in the art” or “POSA” that someone would have had at the time the alleged invention as claimed was made. In deciding the level of ordinary skill, I have considered the following factors, which I have been informed are relevant in determining the level of ordinary skill in the art:

- The levels of education and experience of persons working in the field;
- The types of problems encountered in the art;
- The prior art solutions to these problems;

- The rapidity with which innovations are made; and
- The sophistication of the technology.

49. A POSA at the time of the invention of the '506 patent (July 2013) would have had a graduate degree in organic chemistry, material science, medicinal chemistry, pharmaceutical chemistry, or a related field, and four to six years of experience in the synthesis, purification, analysis, design, and/or formulation of pharmaceutical compounds and derivatives.

50. I understand that Petitioner has defined the level of ordinary skill in the art as:

A person of ordinary skill in the art (POSA) as of April 26, 2023 would typically have a M.S. or Ph.D. in organic chemistry, medicinal chemistry, nutritional science, pharmaceutical science, or allied fields. This definition of a POSA would also apply as of July 29, 2013.

(Petition, 9.)

51. Despite variations in these two positions, these variations would not alter my specific opinions expressed in this Declaration.

52. Based on either standard, I was at least a person of ordinary skill in the art at the time of the invention of the '506 patent.

IV. THE CITED PRIOR ART REFERENCES

53. I understand that Petitioner and its expert, Dr. Prestwich, allege that the following grounds invalidate the '506 Patent.

Ground 1	Section 102	Anticipated by the '184 Publication	'506 patent, claims 1-12, 21-28, 31, and 34-35
Ground 2	Section 103(a)	Obvious over the '184 Publication and GRAS	'506 patent, claims 29-30 and 32-33

Petition, p. 11.

54. The petition cites two references as “prior art.” However, both references post-date the '506 patent's claimed priority date of July 29, 2013 by nearly three years.

55. I understand, therefore, that Petitioner's prior art only qualifies as prior art (and its grounds only succeed) if the '506 patent is not entitled to claim priority to either of the British Application or the '519 patent. *See supra* Section III(B).

A. The '184 Publication (EX1022)

56. U.S. Pre-Grant Publication No. 2016/0168184 A1 (the “'184 Publication”) was published on June 16, 2016, nearly three years after the priority date of the '506 patent. EX1022.

57. I understand that the '184 Publication is a publication of application number 14/908,831, which eventually issued as the '519 patent (EX1005)—the great, great grandparent of the '506 patent. *See supra* Section III(B).

B. GRAS Notice No. 635 (EX1017)

58. GRAS Notice No. 635 was filed with the FDA on March 29, 2016, almost three years after the priority date of the '506 patent. EX1017; EX1018. I

understand that Petitioner relies on this reference only to support its analysis of dependent claims 29-30 and 32-33 under Ground 2.

V. ANALYSIS

59. For purposes of this declaration, I have been asked specifically to evaluate Petitioner's and Dr. Prestwich's assertion that the '506 patent is unable to claim priority to any filing date besides its own, because the prior applications in its priority chain allegedly lack written description support and enablement for R₆, R₇, and R₈ in formula (IV) being independently hydrogen (H), as recited, for example, in claim 1 of the '506 patent. Petition at pp. 12-29. Specifically, Petitioner and Dr. Prestwich argue that the priority documents allegedly "do not reasonably convey to a POSA that the inventors had possession of the subject matter claimed" and that "it is [allegedly] impossible for any of the priority documents to provide enablement support." Petition at pp. 15, 20-21.

60. First, the British Application (and the other applications) to which the '506 cites priority clearly provides support for every claim element—including those where R₆, R₇, and R₈ are hydrogen—in the claims challenged by the Petition. Thus, the '184 Publication—a publication of the '506 patent's great, great grandparent application and Petitioner's sole primary prior art reference—is not prior art. Second, Petitioner's and Dr. Prestwich's arguments all fail, because they depend upon a faulty premise—i.e., Petitioner's claim that "[t]he '506 patent claims recite a

logical impossibility.” Petition at p. 12. As I explain below, there is no logical impossibility.

A. The British Application Supports and Enables the '506 Patent's Claims

61. The British Application to which the '506 patent claims priority provides written description support and enablement for the claims of the '506 patent and, specifically, for compounds of formula (IV) in which R₆, R₇, and R₈ are independently hydrogen.

62. To understand how the British Application provides support for compounds of formula (IV) in which R₆, R₇, and R₈ are hydrogen, it is necessary to understand the structural relationship between formula (I) and formula (IV) as disclosed in the specification.

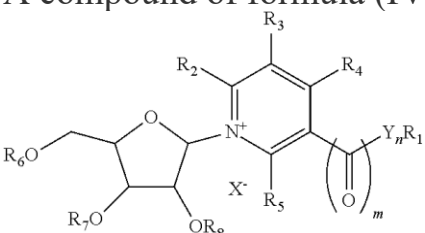
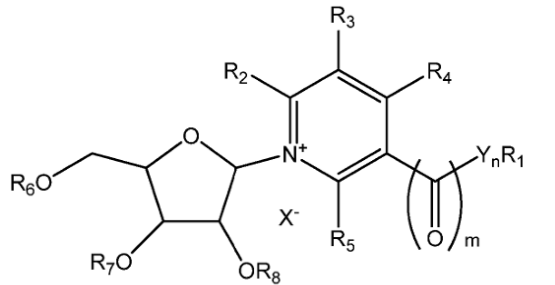
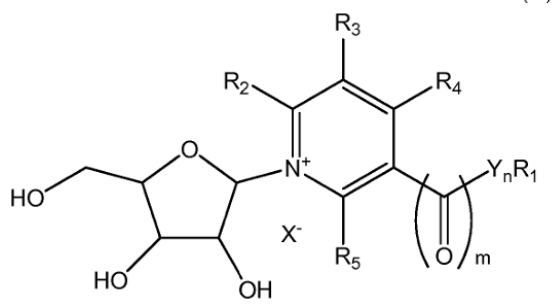
63. Formula (I), disclosed at page 2 of the British Application, illustrates a cationic pyridinium heterocycle with an optional carbonyl-containing group at the 3-position bonded to C1' of ribofuranose, the fundamental scaffold underlying nicotinamide riboside and related metabolites. EX1003, p. 2.¹ Critically, in formula (I), each of the three oxygen atoms at carbons C2', C3', and C5' of the ribose ring carries only a hydrogen atom—i.e., the hydroxyl groups are unprotected and exist as free -OH groups. EX1003, p. 2; EX1001, 3:5-24.

¹ Pages cited in EX1003 refer to the native pagination contained in the document.

64. Formula (IV), disclosed at page 10 of the British Application, retains the same pyridinium-ribose core but generalizes the three ribose hydroxyl positions. EX1003, p. 10. Rather than fixing unprotected -OH groups at C2', C3', and C5', formula (IV) introduces variable groups—designated R₆, R₇, and R₈—on the oxygen atoms bonded to those carbons. EX1003, p. 10; EX1001, 8:55-67. Formula (IV) is therefore broader than formula (I)—for example, among other compounds, it encompasses compounds bearing hydroxyl-protecting groups at the R₆, R₇, and R₈ positions as well as compounds in which those positions are bonded only to hydrogen (thus, the hydroxyl groups are unprotected).

65. A POSA reading the British Application would immediately recognize that formula (I) is a subset of formula (IV). Any compound satisfying formula (I), where the hydroxyl groups are unprotected, necessarily also satisfies formula (IV) when R₆, R₇, and R₈ are each H. EX1003, pp. 2, 10; *Compare* EX1001, formula (I) *with id.*, formula (IV). The two formulas share an identical pyridinium-ribose core; the sole distinction is that formula (IV) employs the variables R₆, R₇, and R₈ at positions that formula (I) has specified as hydrogen. A POSA would recognize this as a conventional genus/species relationship: formula (IV) represents the genus, and formula (I) constitutes a species within that genus corresponding to the case where R₆, R₇, and R₈ are each H.

66. I have reviewed each element of Claim 1 of the '506 patent against the disclosures of the British Application and confirm that every element finds express support:

Claim 1 of '506	British Application (EX1003)
A compound of formula (IV):  or the beta-anomer thereof, where:	 (IV)  (I) EX1003 at pp. 2, 10.
n is 0 and Y is absent;	"n is 0 or 1" – EX1003, p. 2; Claim 1
m is 1;	"m is 0 or 1" – EX1003, p. 2; Claim 1
R ₁ is a substituted or unsubstituted primary amino;	"R ₁ is selected from . . . substituted or unsubstituted primary or secondary amino . . ." – EX1003, p. 2; Claim 1
R ₂ -R ₅ are each H;	"R ₂ -R ₅ , which may be the same or different, are each independently selected from H . . ." – EX1003, p. 2; Claim 1
R ₆ , R ₇ and R ₈ , which may be the same or different, are each independently	(see below)
H	formula (I) structure – EX1003, p. 2 (showing unprotected hydroxyls at C2', C3' and C5', R ₆ , R ₇ , and R ₈ are each H); EX1003, Fig. 1: nicotinamide riboside

	with free -OH groups at all three positions. In addition, R₆, R₇, and R₈ may be <i>independently</i> hydrogen because the specification discloses that optionally, at least two of them are hydroxyl protecting groups. <i>See</i> formula (IV) – EX1003, p. 9
or a hydroxyl-protecting group;	formula (IV) – EX1003, p. 9 (“<u>Optionally</u>, the R₆, R₇ and R₈ moieties are selected from substituted and unsubstituted acetyl, and substituted and unsubstituted benzoyl. Optionally, at least two of R₆, R₇ and R₈ are selected from unsubstituted acetyl or unsubstituted benzoyl.”).
or wherein R ₆ is a phosphate; and	EX1003, Fig. 1 (showing nicotinamide mononucleotide and nicotinate mononucleotide with phosphate), p. 16 (“Figure 1 shows the β-anomer forms of nicotinamide riboside, nicotinate riboside, nicotinamide mononucleotide and nicotinate mononucleotide, without counter ions”).
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.	EX1003, p. 3 (“X⁻ is an anion, 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”).

67. Figure 1 of the British Application explicitly discloses compounds of formula (IV) where R₆, R₇, and R₈ are each H.

68. Figure 1 illustrates the β -anomer forms of four specific compounds—nicotinamide riboside, nicotinate riboside, nicotinamide mononucleotide, and nicotinate mononucleotide—illustrated “without counter ions.” EX1003, Fig. 1, p. 1. The ’506 patent reproduces this same Figure 1. EX1001, Fig. 1. Each of these four structures is drawn with unambiguous unprotected hydroxyl groups (-OH) on carbons C2’ and C3’ of the ribose ring (i.e., R_7 and R_8 are each H). EX1003, Fig. 1; EX1001, Fig. 1. For nicotinamide riboside and nicotinate riboside, the C5’ oxygen likewise is bonded only to hydrogen (i.e., $R_6 = H$). EX1003, Fig. 1. For the mononucleotides, $R_6 = PO_3H_2$).

69. Figure 1 constitutes an unambiguous, express disclosure of compounds within formula (IV) where R_6 , R_7 , and R_8 are each hydrogen. A POSA does not need to infer or deduce this—as Petitioner concedes, the structures are drawn out in full, with unprotected hydroxyl groups visible at each relevant position on the ribose ring. Petitioner at p. 37 (“The ’184 publication depicts its formula (I) having H at positions corresponding to R_6 - R_8 of formula (IV) having the anomeric form represented in claim 8.”). As I explain further below, all four molecules illustrated in Figure 1 fall within the genus of formula (IV):

- Nicotinamide riboside is a compound of formula (IV) wherein $n = 0$, Y is absent, $m = 1$, $R_1 = NH_2$, R_2 - R_5 are each H, R_6 - R_8 are each H, and X^- is an anion. EX1003, p. 2, Fig. 1.

- Nicotinate riboside is a compound of formula (IV) wherein $n = 1$, $Y = O$, $m = 1$, R_1 - R_5 are each H, R_6 - R_8 are each H, and X^- is an anion. EX1003, p. 2, Fig. 1.
- Nicotinamide mononucleotide is a compound of formula (IV) wherein $n = 0$, Y is absent, $m = 1$, $R_1 = NH_2$, R_2 - R_5 are each H, $R_6 = PO_3H_2$, R_7 - R_8 are each H, and X^- is an anion. EX1003, Fig. 1.
- Nicotinate mononucleotide is a compound of formula (IV) wherein $n = 1$, $Y = O$, $m = 1$, R_1 - R_5 are each H, $R_6 = PO_3H_2$, R_7 - R_8 are each H, and X^- is an anion. EX1003, Fig. 1.

70. Thus, the British Application does not merely allude to or suggest the existence of formula (IV) compounds where R_6 , R_7 , and R_8 are each H. It draws them explicitly, in the Figures, as specific, identified molecules of central importance to the disclosed invention.

71. The specification of the British Application reinforces what Figure 1 illustrates structurally. The specification states that Figure 1 “shows the β -anomer forms of nicotinamide riboside, nicotinate riboside, nicotinamide mononucleotide, and nicotinate mononucleotide, without counter ions.” EX1003, p. 16.

72. Because the specification of the British Application discloses multiple species within the genus of formula (IV) compounds, the Application conveys to a POSA that the inventors had possession of the genus of formula (IV) compounds in

which R_6 - R_8 may be independently selected from hydrogen, hydroxyl-protecting groups, or PO_3H_2 .

73. A POSA would understand that formula (IV)—in effect—defines a genus of compounds: a ribose-pyridinium salt with variable groups R_6 - R_8 at the ribose hydroxyl positions. Each specific selection of substituents at the variable positions produces a distinct species within that genus. And the specification discloses multiple species:

- Species where R_6 , R_7 , and R_8 are each acetyl (hydroxyl-protecting groups): disclosed in the working examples as triacetyl nicotinamide riboside triflate salt. EX1003, pp. 17-18; EX1001, 12:52-13:58 (Example 1A).
- Species where R_6 , R_7 , and R_8 are each benzoyl (hydroxyl-protecting groups): disclosed in the working examples as tribenzoyl nicotinamide riboside triflate salt. EX1003, pp. 19-20; EX1001, 14:52-15:48 (Example 1C).
- Species where R_6 , R_7 , and R_8 are each H (unprotected hydroxyls): disclosed expressly in Figure 1 (nicotinamide riboside and nicotinate riboside). EX1003, p. 12, Fig. 1; EX1001, Fig. 1.
- Species where $R_6 = \text{PO}_3\text{H}_2$, and R_7 and R_8 are each H: disclosed in Figure 1 (nicotinamide mononucleotide and nicotinate mononucleotide). EX1003, Fig. 1.
- Species where at least two of R_6 , R_7 , and R_8 are hydroxyl protecting groups, such as unsubstituted acetyl or unsubstituted benzoyl. EX1003, p. 9

74. The disclosure of these species spans a range of substituents at R₆-R₈ (hydrogen, protecting groups, and PO₃H₂) and conveys to a POSA that the inventors had possession of the genus of formula (IV) compounds in which R₆-R₈ may be independently selected from hydrogen, hydroxyl-protecting groups, or PO₃H₂. To further illustrate this point, I note that nicotinamide riboside may accurately be described in either of the following ways:

- A compound of formula (I) wherein n is 0, m is 1, R₁ is NH₂, and R₂-R₅ are H.
- A compound of formula (IV) wherein n is 0, m is 1, R₁ is NH₂, and R₂-R₅ are H, and R₆-R₈ are H.

Thus, these are two different ways of describing the same compound. Similarly, nicotinate riboside may accurately be described in either of the following ways:

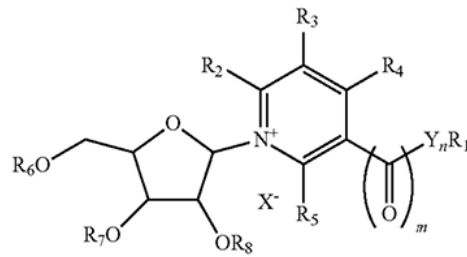
- A compound of formula (I) wherein n is 1, m is 1, Y is O, and R₁-R₅ are H.
- A compound of formula (IV) wherein n is 1, m is 1, Y is O, and R₁-R₈ are H.

Thus, formula (IV) encompasses all four structures of Figure 1. EX1003, pp. 2, 10, Fig. 1. A POSA would understand that formula (IV) was intentionally designed as the broader structural framework and its R₆-R₈ variable positions were meant to accommodate substituents including hydrogen.

B. The '506 Patent Does Not Recite a Logical Impossibility

75. Independent claim 1 of the '506 patent recites:

1. A compound *of formula (IV)*:



or the beta-anomer thereof,

where: n is 0 and Y is absent;

m is 1;

R₁ is a substituted or unsubstituted primary amino;

R₂-R₅ are each H;

R₆, R₇ and R₈, which may be the same or different, are each independently H or a hydroxyl-protecting group; or wherein R₆ is a phosphate; and

X⁻ is an anion selected from an anion of a substituted carboxylic acid .

. . and an anion of a substituted or unsubstituted carbamate.

EX1001, cl. 1 (emphasis added). The other independent claims similarly claim a “compound of formula (IV)” in which R₆-R₈ may be “independently H or a hydroxyl-protecting group.” EX1001, cls. 6, 13, 18, 37.

76. Despite the independent claims explicitly defining R₆-R₈ as “each independently H or a hydroxyl-protecting group,” both Petitioner and Dr. Prestwich argue that the claims’ recitation of “formula (IV)” requires that R₆-R₈ be hydroxyl-protecting groups only. Petition at 12; EX1013 at pp. 32-35. Petitioner and Dr. Prestwich then rely on this alleged contradiction within the claims to assert that there

is a logical impossibility, which makes written description support and enablement impossible. Petition at pp. 15, 20-21; EX1013 at ¶¶ 77-78.

77. Neither the claims nor the specification of the '506 patent support Petitioner's and Dr. Prestwich's restricted reading of "formula (IV)," recited in all independent claims. When the claims of the '506 patent are read properly, within the context of the surrounding claims and specification—and more significantly from the perspective of a POSA—there is no logical impossibility. First, the specification does not support redefining formula (IV) based on one embodiment of formula (III), as Petitioner and Dr. Prestwich have done. Second, the language of the claims themselves confirm that Petitioner's narrow interpretation of formula (IV) cannot be correct. Finally, the prosecution history of the '506 patent offers further evidence—validated by the USPTO—that formula (IV) is defined by the entirety of the specification and not just one example formula (III).

1. The specification does not support restricting formula (IV) based on one embodiment of formula (III).

78. Petitioner's and Dr. Prestwich's arguments are all essentially founded on the same mistaken reading of the specification—specifically, their understanding that the R groups (e.g., R₆-R₈) of the claimed compound of formula (IV) must be limited by one specific embodiment of formula (III). Petition at 12, 15, 20-21; EX1013 at ¶¶ 67-69.

79. As I will explain in detail, the specification does not support such a narrow reading of the claims. First, a POSA would not understand the specification's disclosures of an "optional" synthetic pathway to mean that all formula (IV) compounds must necessarily be a precursor to the "optional" example of a formula (III) intermediary. Second, a POSA would not understand formula (IV)'s general cross-reference "as defined above" to be limited only to the singular example that immediately precedes it, to the exclusion of all other disclosure "above" formula (IV). Third, nothing in the '506 patent's claims or specification expressly limits the claim terms in a way that supports Petitioner's position. I will address each of these points in turn.

80. The language of the '506 patent specification makes clear that the conversion of a formula (IV) compound to a formula (III) compound is presented as one available synthetic option—not as a mandatory or exclusive pathway. As I explain below, the scope of formula (IV) cannot be understood to be limited to only a subset of formula (IV) compounds suitable for preparing Petitioner's hand-picked example of a formula (III) compound.

81. The specification introduces an exemplary pathway with the word "[o]ptionally," stating, "[o]ptionally, the compound of formula (III) is prepared by reacting a compound of formula (IV)." EX1001, 8:15-34. To a POSA in the chemical arts, the word "optionally" conveys that what follows is a permitted but non-

compulsory step. Therefore, the inclusion of formula (III) as a synthetic intermediate is optional. Reading the word to mean “necessarily” or “exclusively”—as Petitioner’s position requires—would contradict its plain and ordinary meaning. The inventors’ deliberate selection of this qualifier signals that the formula (IV)-to-formula-(III) reaction is one disclosed approach among potentially others, rather than the sole route by which every formula (III) compound must be obtained or a restriction that confines the structural features of every formula (IV) compound.

82. The specification’s treatment of Figure 2 reinforces this understanding. The patent states that Figure 2 “depicts Scheme A, which is a scheme illustrating, *in general terms*, that compounds of formula (IV) *may be used* to prepare compounds of formula (III), as described in Example 1.” EX1001, 12:12-17 (emphasis added). The phrase “in general terms” indicates that Scheme A is a high level illustration of the chemistry, not an exhaustive or definitional statement about the formula (IV) genus. The specification employs the same permissive verb phrase—“may be used” at every step in the depicted sequence: compounds of formula (IV) “may be used to prepare” compounds of formula (III); compounds of formula (III) “may be used to prepare” compounds of formula (II); and compounds of formula (II) “may be used to prepare” compounds of formula (I). EX1001, 12:13-20. In chemistry, describing a transformation as one that “may be” performed communicates that the transformation is feasible—not that it is required. None of this language imposes a

mandate that formula (IV) compounds must function as precursors to formula (III) compounds, and it certainly does not dictate that every compound falling within the formula (IV) genus must carry the precise structural features needed for such a conversion.

83. It is also significant that the patent introduces the entirety of the examples and figures section with express non-limiting language. Immediately before describing Figures 1 through 5, the specification states that “[e]mbodiments of the present invention will now be described, with reference to the accompanying, non-limiting examples and drawings.” EX1001, 12:7-9. A POSA would understand that the embodiments do not circumscribe the full reach of the claimed invention. Petitioner’s theory effectively asks the Board to disregard this qualifier and treat the synthesis depicted in Scheme A as though it were compulsory, thereby restricting the scope of formula (IV). Doing so would convert a voluntary example into a universal definitional requirement—a reading that conflicts with the inventors’ own characterization of the drawings.

84. Furthermore, the specification discusses the advantages of using formula (IV) compounds as starting materials in terms that assume optionality rather than necessity. For instance, Petitioner is incorrect in its assertion that R_6 , R_7 , and R_8 are “uniformly limited” to lipophilic groups. Petition at p. 24. In fact, when describing the lipophilicity of protecting groups, the patent notes that:

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.

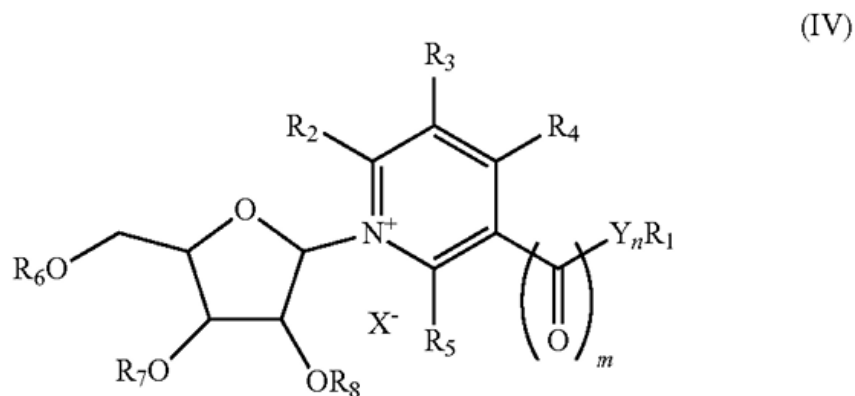
EX1001, 11:14-19 (emphasis added). That is, the specification describes a single, specific laboratory scenario—i.e., where a chemist uses a mixture of water and an organic solvent (a “biphasic” system, because it has two distinct liquid layers) to separate and isolate the desired product. *See id.* In this particular method, having lipophilic protecting groups at R₆, R₇, and R₈ is useful because it causes the formula (III) product to migrate out of the water layer and into the organic layer, making it easier to collect.

85. Critically, a POSA would readily understand that this two-layer extraction method is just one of many well-known techniques that chemists routinely use to separate and purify chemical products. And many of these well-known methods of separation would not require lipophilic protecting groups—for example, column chromatography, precipitation and crystallization, filtration, and/or solid-phase or resin-based methods. The specification’s disclosure of what may be “advantageous” is relevant to only a single, exemplary method of separation and isolation that is ultimately, optional. The permissive language reinforces that this is

a practical benefit of one approach—without suggesting that formula (IV) compounds can only exist as precursors to formula (III) intermediates.

86. To overcome this permissive language, Petitioner and Dr. Prestwich rely heavily on the phrase “as defined above” to narrow the claimed formula (IV) compound. But their position demonstrates a fundamental misunderstanding of both the specification and chemical formulas.

87. Formula (IV) is one of four generic formulas included in the '506 patent specification:

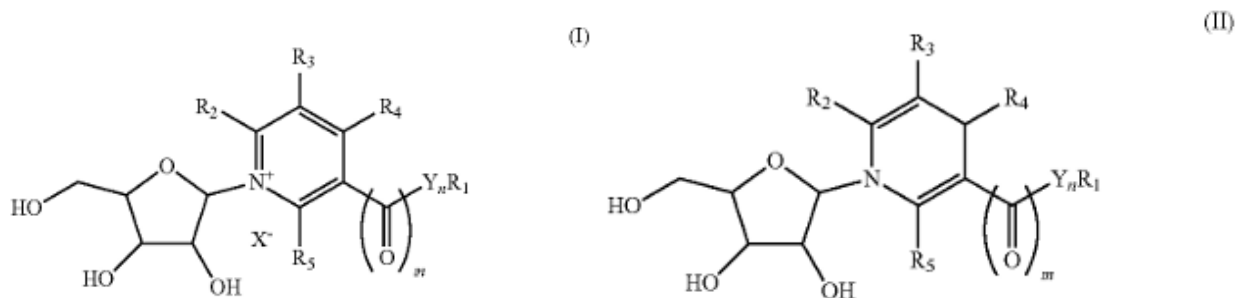


EX1001, col. 8.

88. Column 8 of the '506 patent specification explains that “optionally, the compound of formula III is prepared by reacting a compound of formula (IV),” wherein R₁-R₈ “are as defined above.” EX1001, 8:14-30 (emphasis added). Above formula (IV), the specification describes each of formulas (I)-(III). *See generally* EX1001, 2:38-8:49 (describing many “**optional**” and exemplary embodiments or compounds of each formula). Contrary to the Petitioner and Dr. Prestwich’s

characterizations, nothing in the discussion of formula (IV) specifically limits these variables to any particular embodiment of formula (III). *See* EX1001, 8:15-30.

89. Indeed, formula (III)—just like formula (IV)—describes some of its variables more broadly “as defined above,” referencing the above discussion of formulas (I)-(II). EX1001, 8:30. While R_6 - R_8 are described as “each independently a hydroxyl-protecting group” in formula (III), incorporation of these protecting groups is *optional*. EX1001, 8:42-51. In formulas (I) and (II), R_6 - R_8 are not explicitly present, but are defined in their structural formulas as H:



EX1001, col. 2 (formula (I)), col. 3 (formula (II), 2:40-3:17.

90. Petitioner’s position that formula (I) and (II) should be excluded from the “defined above” reference because “R-groups do not appear on any of formulae (I) or (II)” betrays a basic misreading of what the chemical formulas actually represent.

91. Because many different compounds of a particular formula may exist (something acknowledged by the ’506 patent, which describes optional variations and optional steps), it would be impractical for a POSA to draw each and every entire

molecule when discussing a family of related compounds. Rather, a POSA would more commonly use a general, open-ended formula to illustrate a common core structure, while allowing for variables at certain positions in the formula. It is generally understood that:

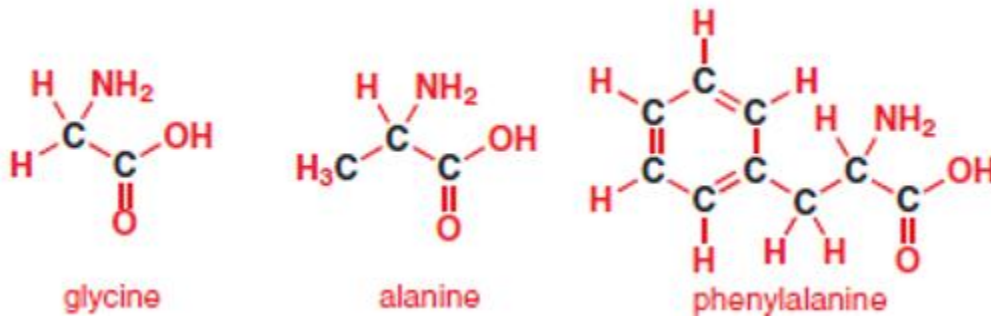
[T]he chemistry of organic molecules depends much less on the number or the arrangement of carbon or hydrogen atoms than on the other types of atoms (O, N, S, P, Si...) in the molecule. We call parts of molecules containing small collections of these other atoms functional groups, simply because they are groups of atoms that determine the way the molecule works.

EX2013 at p. 16. “We can consider the chains and rings of carbon atoms we find in molecules as their skeletons, which support the functional groups.” *Id.* at p. 17.

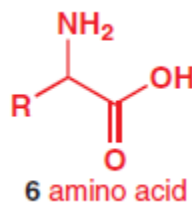
92. Variable positions in a molecule are typically denoted by the capital letter “R,” with R₁, R₂, etc. used to distinguish multiple variable positions. Although the letter “R” was originally used as an abbreviation for “radical,” it is now commonly interpreted as representing “the rest of the molecule,” as I will demonstrate below. In practice, it serves as a placeholder indicating whichever group of atoms occupies that particular position in the molecular structure.

93. As explained by the same author Petitioner and Dr. Prestwich cite (*see* EX1012), “R in a structure can mean *anything*—it’s a sort of wild card.” EX2013 at

p. 24. The author provides an example, illustrating three amino acid molecules that include great variety, despite being in the same small class of molecules:



EX2013 at p. 16. The author also illustrates the following generic formula (“structure 6”):



EX2013 at p. 24. As the author explains:

“[S]tructure 6 would indicate any amino acid, if R = H it is glycine, if R = Me it is alanine...As we’ve mentioned before, and you will see later, the reactivity of organic molecules is so dependent on their functional groups that the rest of the molecule can be irrelevant. In these cases, we can choose just to call it R.”

EX2013 at p. 24. That is, a POSA would not understand an R-group to be the literal text or letters “R₆,” “R₇” or “R₈” that are printed in the molecular structure. Rather, the R-group identifies a position on the molecular structure that may be occupied by variable substituents. (Compare “glycine,” “alanine,” and “phenylalanine” with

structure 6 in EX2013 at pp. 16, 24.) Accordingly, a POSA would understand formula (I)'s inclusion of H at the "R₆," "R₇" and "R₈" positions of formula (IV) to mean that "R₆," "R₇" and "R₈" may be hydrogen, even though they are no longer labeled with variable placeholders.

94. The practice of using R groups and other letters to represent a genus of structures is very common in chemical patents. These generic structures (or formulas) are referred to as Markush structures, which "are frequently incorporated into the claims of chemical patent applications, patents, [and] publications." EX2014 at [0002]-[0003], Title.

"Generally, Markush chemical groupings are in the form of generic chemical structures, wherein one or more nodes of the representation of a chemical structure can be enumerated as two or more real possibilities. For example, a node in a Markush chemical structure may be described as 'R¹', and R¹ may be described as being equivalent to a halogen or lower alkyl group, i.e., fluorine, chlorine, bromine, iodine, methyl, ethyl, propyl, butyl, pentyl, or hexyl (unless lower alkyl is defined differently).

EX2014 at [0003]. It is well understood that Markush structures may encompass many possible real structures, while a patent claim might specifically recite only a subset of actual compounds. *Id.* at [0004]. Identifying a specific substituent for an R-group in a given embodiment does not strip that position of its variability under the broader formula. *See, e.g.*, EX2013 at p. 24.

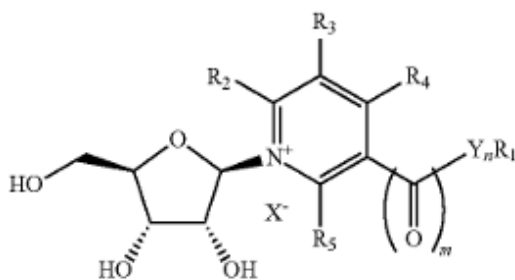
95. Consistent with this common practice, the '506 patent discloses four generic formulas (I)-(IV), each of which describes a family of ribose-based compounds related to nicotinamide riboside. When evaluated by a POSA at the time of the invention—in light of the claim language, specification, and prosecution history—the independent claims' recitation of “a compound of formula (IV)” is not reciting only one, specific compound of formula (IV); rather, it provides a template for a genus of molecules that each, independently, qualify as a species within that genus. That is, the preamble of the '506 patent's claims orients a POSA to the class of compounds claimed, as limited by the rest of the claim. *See* EX1001, cl. 1.

2. The language of dependent claims shows Petitioner's interpretation to be wrong.

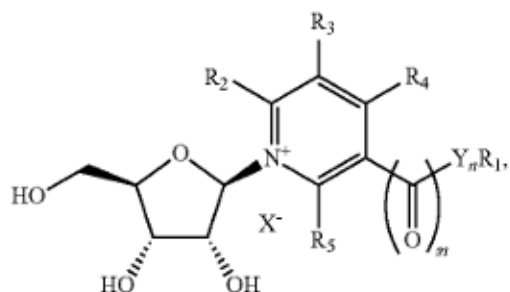
96. Dependent claims 8 and 26 are clear examples that contradict Petitioner's assertion that examples in the '506 patent's specification narrow the scope of formula (IV) and create a logical impossibility.

97. Claims 8 and 26 each depend from claim 1—which is directed to “[a] compound of formula (IV).” EX1001, cls. 1, 8, 26. Both dependent claims recite a compound “of claim 1” of a formula:

8. The compound of claim 1 of formula:



26. The compound of claim 1 of formula:



EX1001, cls. 8, 26. These structures correspond to the beta-D-ribofuranosyl configurations of formula (I) compounds. Because claims 8 and 26 depend from claim 1, every compound they encompass must, by definition, satisfy the requirements of claim 1 and therefore fall within the genus of formula (IV).

3. The prosecution history shows Petitioner's interpretation to be wrong.

98. The '262 Patent (EX1006) is the great grandparent of the '506 Patent, contains a materially identical specification, and was evaluated by the same examiner that evaluated the '506 patent and the other patents in the same continuation chain. *Compare* EX1006 with EX1001; EX1008; EX1007; EX1005. The '262 patent independently confirms that R₆-R₈ may each be hydrogen, even within the framework of a formula outside of formula (I).

99. Claim 1 of the '262 Patent recites compounds of formula (III), requiring "R₆, R₇, and R₈, which may be the same or different, are each independently a hydroxyl protecting group or are each H." EX1006, cl. 1. The disjunctive "or" in this claim language unambiguously establishes that the shared specification supports that

R₆, R₇, and R₈ may each be H as a permissible alternative to hydroxyl-protecting groups—*within the very formula* (i.e., formula (III)) that Petitioner asserts is restricted to protecting groups alone.

100. The application as originally filed and as issued contains similar language as the '506 patent:

Claim	Relevant Claim Language
'506 patent, cls. 1, 6, 13, 18, 37	"A compound of formula (IV)...where... <i>R₆, R₇, and R₈, which may be the same or different, are each independently H or a hydroxyl-protecting group</i> "
'262 patent (Ex. 1006), cl. 1	"A compound of formula (III)...wherein... <i>R₆, R₇, and R₈, which may be the same or different, are each independently a hydroxyl protecting group or are each H</i> "
'262 patent (Ex. 1006), cl. 2	" <i>wherein R₆, R₇, and R₈ are each H.</i> "

101. This limitation did not go overlooked during prosecution. The examiner initially rejected the claims based on anticipation by two different prior art references. EX2008 ('262 Prosecution History), pp. 221-23. In response, the applicant amended claim 1 (a compound of formula (III)) to further specify circumstances in which R₆, R₇, and R₈ were not all simultaneously H:

R₆, R₇, and R₈, which may be the same or different, are each independently a hydroxyl protecting group or are each H ... provided that when n is 1, m is 1, Y is O, R₁ is unsubstituted alkyl wherein alkyl is methyl, and R₂ – R₅ are each H, then R₆, R₇, and R₈ are not all simultaneously H or unsubstituted acetyl;

further provided that when n is 0, m is 1, R₁ is NH₂, and R₂ – R₅ are each H, then R₆, R₇, and R₈ are not all simultaneously H or unsubstituted benzoyl...

EX2008 ('262 Prosecution History), p. 197 (underlining in original to show amendment). This amendment highlighted the precise language which Petitioner now calls into question—i.e., whether or not there is support for R₆-R₈ being hydrogen. And the very first dependent claim—dependent claim 2 of the '262 patent—specifically requires that R₆, R₇, and R₈ be hydrogen. EX1006, cl. 2.

102. The applicant cited paragraphs [0010-0014, 0016, 0055, and 0077-0078] of the published '262 application as providing support—including the very same formula (I) embodiment that I discuss above. EX2008 ('262 Prosecution History), p. 203; EX2009 ('262 Application Publication), [0010]-[0014], [0016], [0055], [0077]-[0078]. The cited paragraphs [0010]-[0014] describe “a compound of formula (I),” in which R₆-R₈ are hydrogen. EX2009, [0010]-[0014]; *see also id.*, [0016] (explaining that R₂-R₅ may similarly be H), [0055] (defining an “alkyl” within the disclosure following formula (II)). And paragraphs [0077]-[0078] disclose multiple “optional” variations of “the R₆, R₇, and R₈ moieties” contained in formula (III). EX2009, [0077]-[0078]. That is, the applicant relied on the combined disclosures associated with formulas (I), (II), and (III) as supporting a claimed compound of formula (III)—confirming that these disclosures were intended to function as a whole and that Petitioner’s singling out of formula (IV) is wrong.

103. When considering this amendment, the examiner considered the variables R_6 , R_7 , and R_8 particularly. He issued a final rejection—in part—under Section 112(b), finding the new language rendered the claims indefinite, as “the metes and bounds of variables R_6 , R_7 , and R_8 ” were unclear. EX2008 (‘262 Prosecution History), pp. 183-84. The applicant subsequently amended the claimed compound of formula (III):

R_6 , R_7 , and R_8 , which may be the same or different, are each independently a hydroxyl protecting group or are each H, ~~optionally wherein the hydroxyl protecting group is substituted or unsubstituted acetyl, or substituted or unsubstituted benzoyl;~~ provided that when n is 1, m is 1, Y is O, R_1 is ~~unsubstituted alkyl wherein alkyl is methyl,~~ and $R_2 - R_5$ are each H, then R_6 , R_7 , and R_8 are not all simultaneously H or unsubstituted acetyl;

further provided that when n is 1, m is 1, Y is O, R_1 is methyl, R_3 and R_4 are methyl, and R_2 and R_5 are each H, then R_6 , R_7 , and R_8 are not all simultaneously H or unsubstituted acetyl; and

yet further provided that when n is 0, m is 1, R_1 is NH_2 , and $R_2 - R_5$ are each H, then R_6 , R_7 , and R_8 are not all simultaneously H or unsubstituted benzoyl.

EX2008 (‘262 Prosecution History), pp. 143-44 (underlining in original to show amendment). And dependent claim 2 remained the same—requiring that R_6 , R_7 , and R_8 , each be hydrogen. EX1006, cl. 2. The applicant again cited the same

paragraphs—the formula (I) embodiment—for written support. Ex. 2008 (‘262 Prosecution History), p. 138 (citing Ex. 2009 (‘262 Application Publication), [0010]-[0014], [0016], [0055], [0077]-[0078]).

104. The Examiner accepted the amendment, finding no lack of written description or enablement and allowing the claims to issue. Ex. 1006 (‘262 Patent), cls. 1-2. That is, *the examiner found no issue (because there is no issue) in the applicant’s reliance on a formula (I) compound as support for the claimed formula (III) compound. See id.* This confirms my opinion that the substantively identical specification adequately supports R₆, R₇, and R₈ are each H, even within the framework of formula (III) or formula (IV).

105. It follows therefore that, even if one were to accept Petitioner’s premise that formula (IV) is limited by a specific embodiment of formula (III) (which it is not), R₆, R₇, and R₈ cannot be restricted to hydroxyl-protecting groups. The issued claims and prosecution record of the ‘262 patent demonstrate that the shared specification provides adequate support for R₆, R₇, and R₈ each independently being hydrogen within formula (III) itself (and therefore, by Petitioner’s logic, formula (IV)).

* * *

106. Thus, when the claims are read within the context of the specification and from the perspective of a POSA, there is no logical impossibility. Rather, it is

a straightforward claiming of a compound of formula (IV), as defined by the subsequent limitations, including that R₆, R₇, and R₈ are each “independently H or a hydroxyl-protecting group.” *E.g.*, EX1001, cl. 1 (emphasis added).

107. Accordingly, Petitioner’s and Dr. Prestwich’s argument that it would be impossible to support or enable a logical impossibility is inapplicable.

VI. CONCLUSION

108. Based on my review of the British Application, the ’506 patent, and the prosecution history of the ’262 patent, it is my opinion that the British Application provides adequate written-description support and enablement for compounds of formula (IV) in which R₆, R₇, and R₈ are each independently H or a hydroxyl-protecting group, as recited in the independent claims of the ’506 patent. This conclusion follows from multiple independent lines of evidence:

- (a) The structural relationship between formula (I) (where R₆, R₇, and R₈ are each H by definition) and formula (IV) (the broader genus encompassing formula (I));
- (b) Express illustration in Figure 1 of specific named compounds with unprotected hydroxyl groups at all R₆, R₇, and R₈ positions;
- (c) The specification’s disclosure of the synthetic pathway, which produces formula (I) compounds (R₆, R₇, and R₈ are each H) as end products;
- (d) The element-by-element correspondence between claim 1 of the ’506 patent and the British Application’s disclosures; and

- (e) The '262 patent's express claim language and prosecution history confirming that the substantively identical specification supports R_6 , R_7 , and R_8 are each H.

109. Each of these independently demonstrates that the inventors possessed the claimed subject matter as of the July 29, 2013 priority date and could have made the full scope of the claimed invention without undue experimentation. Taken together, they leave no doubt that a POSA reviewing the British Application would understand it to disclose compounds of formula (IV) with R_6 , R_7 , and R_8 are each H.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further 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.

Executed this 22nd day of September 2026 in Wynnewood, Pennsylvania.

Respectfully submitted,

A handwritten signature in cursive script, appearing to read "Ron Bihovsky", is written over a horizontal line.

Ron Bihovsky, Ph.D.