

Filed on behalf of: Thorne Research, Inc. and Thorne HealthTech, Inc.

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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.

Case IPR2026-00400
Patent US 12,252,506 B2

PETITION FOR INTER PARTES REVIEW

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	BACKGROUND	4
III.	THE '506 PATENT	5
	A. Specification	6
	B. Challenged Claims	7
	C. Prosecution History	8
	D. Level of Ordinary Skill	9
IV.	CITED ART.....	9
	A. The '184 Publication	9
	B. GRAS	10
V.	STATEMENT OF THE PRECISE RELIEF REQUESTED FOR EACH CLAIM CHALLENGED.....	10
VI.	CLAIM CONSTRUCTION	11
VII.	DETAILED EXPLANATION FOR GROUNDS OF UNPATENTABILITY	12
	A. No Right to Priority Before April 2023	12
	B. [Ground 1] Claims 1-12, 21-28, 31, and 34-35 Are Anticipated by the '184 Publication.....	29
	C. [Ground 2] Claims 29-30 and 32-33 Are Obvious over the '184 Publication and GRAS	54
VIII.	CONCLUSION.....	61
IX.	GROUNDS FOR STANDING.....	62
X.	MANDATORY NOTICES UNDER 37 C.F.R. § 42.8.....	62
XI.	CERTIFICATE OF COMPLIANCE	63
XII.	PAYMENT OF FEES UNDER 37 C.F.R. §§42.15(A) AND 42.103.....	64
XIII.	APPENDIX – LIST OF EXHIBITS.....	65

I. INTRODUCTION

Thorne Research, Inc. and Thorne HealthTech, Inc. (collectively, “Petitioners,” or “Thorne”) request IPR to cancel claims 1-12 and 21-35 of U.S. Patent 12,252,506 (the “’506 Patent”, EX1001). As this petition shows, these claims are unpatentable.

Thorne Research, Inc. is an American company based in Summerville, South Carolina. Its mission is to empower individuals to live healthier for longer through personalized, science-backed solutions. Thorne believes personalized, scientific wellness can extend the duration of one's health span, create happier and healthier lives, and help people feel their best at every age and life stage. As an important supplier of supplements including nicotinamide riboside hydrogen malate, Thorne is redefining what it means to live healthier for longer.

Thorne’s customers have benefited from Thorne selling nicotinamide riboside products since at least 2021. That same year, researchers coordinating with one of Thorne’s suppliers, Biosynth Carbosynth, reported an improvement over supplements previously-marketed by a company called ChromaDex Corp. (now also known as Niagen Bioscience).¹ EX1009 (Schabert 2021). Schabert 2021

¹ The Queen’s University of Belfast, Niagen Bioscience, and ChromaDex Corp.

reported that synthesis of ChromaDex’s nicotinamide riboside chloride proved to be “challenging, expensive, and low yielding, making it cumbersome for large-scale industrial production.” EX1009, Abstract. Schabert 2021 described a single-pot, high-yield manufacturing process for making nicotinamide riboside hydrogen malate that was “suitable for multi-ton scale production.” *Id.* Finding over the ensuing years that many consumers preferred Biosynth’s improved nicotinamide riboside ***hydrogen malate*** over its own nicotinamide riboside ***chloride*** product,

have each held themselves out to be the owner of the ’506 Patent. On its face, the ’506 Patent is assigned to The Queen’s University of Belfast. EX1001, (71), (73). The USPTO Assignment Database also indicates the ’506 Patent is assigned to The Queen’s University of Belfast. EX1023. Papers have been filed with the USPTO purporting to show some conveyance of rights to ChromaDex, Inc. EX1002 at 233-264. Niagen Biosciences has publicly stated that it is the assignee and owner of the ’506 Patent. EX1024 (press release alleging that Niagen had “acquired a comprehensive portfolio of existing patents covering nicotinamide riboside (NR) and its salt forms from Queen’s University Belfast[.]”); *id.* at 1-2 (“This acquisition establishes Niagen Biosciences as the sole owner of the most comprehensive and defensible intellectual property portfolio in the NAD+ industry[.]” and “[t]he acquired patents include...U.S. Patent No. 12,252,506[.]”). Niagen BioSciences’ Form 10-K, filed with the United States Securities and Exchange Commission for the 2025 fiscal year lists the ’506 Patent among the intellectual property rights either owned or licensed by Niagen and specifies that the ’506 Patent is “[o]wned by Niagen Bioscience[.]” EX1025 at 9-10.

ChromaDex shifted scope. ChromaDex introduced a new patent claim into an existing portfolio acquired from a foreign entity to preempt something it never invented. In 2025, ChromaDex's recently-evolved patent claim issued in the '506 Patent. EX1026

But patent owners are not permitted to claim what they did not invent. Nor are they permitted to claim something they did not enable. As explained by Dr. Glenn Prestwich, the claims of the '506 patent are a new Frankenstein creation reciting a "formula (IV)" that conflicts with how subject matter is defined in the specification and priority documents. Those newly concocted claims are not entitled to a priority date before 2023 because the priority documents defined formula (IV) R_6 - R_8 as hydroxyl-protecting groups, but the claims add formula (IV) R_6 - R_8 hydrogen. As hydrogen is definitionally not a recited hydroxyl-protecting group, ChromaDex's alteration of the claimed subject matter to recite an impossibility makes ChromaDex's earlier patent publication anticipatory prior art to most of the claims of the '506 Patent. The remaining challenged claims merely recite obvious variations that were conventional in light of the prior art available at the time. The challenged claims thus should be found unpatentable and cancelled, leaving ChromaDex to sell its chloride product and Thorne to sell its hydrogen malate product, just as was the status quo before 2023.

II. BACKGROUND

Nicotinamide riboside is an oral supplement that is a precursor for nicotinamide adenine dinucleotide (NAD⁺), a vitamin B₃ derivative produced naturally by the body. It is involved in cell metabolism and responses to oxidative stress, while decreased NAD⁺ levels are associated with, e.g., aging, age-related disease, type 2 diabetes, and obesity. EX1009, 1. Nicotinamide riboside supplements, by virtue of providing a direct precursor, can provide increased levels of NAD⁺. *Id.*, 1-2; EX1013, ¶54.

Artisans were aware that nicotinamide riboside supplements were, in particular, favored as an NAD⁺ precursor.

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.

EX1009, 2. But previous salts of nicotinamide riboside had complications.

Common salts formed during the synthesis of nicotinamide riboside were bromide and triflate, but these salts were toxic and unsuitable as dietary supplements.

EX1009, 2; EX1013, ¶¶55-56. Nicotinamide riboside chloride salt was a known alternative that presented qualities acceptable for nutritional supplement (*see, e.g.*, EX1017), but synthesis of the chloride salt was “challenging, expensive, and low

yielding, making it cumbersome for large-scale industrial production.” EX1009, Abstract.

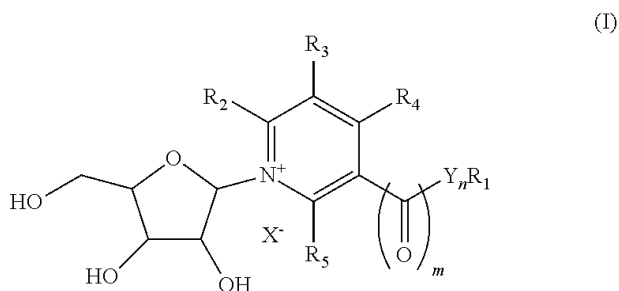
Artisans understood that only the beta-form of nicotinamide riboside was biologically active, and thus synthetic pathways for forming nicotinamide riboside salts were directed toward achieving high stereoselectivity. EX1009, 2; EX1013, ¶¶57. One synthetic pathway to forming nicotinamide riboside salts was to form triacetylated nicotinamide riboside as a triflate salt, and then deprotect (remove) the hydroxyl-protecting acetyl functional groups. EX1009, 4; EX1015, Scheme 2B; EX1016. But the resulting triflate salt still required ion exchange because the triflate was known not to be pharmaceutically acceptable as a counter ion. EX1013, ¶¶58-59. Such ion exchange could be conducted with, for example, reverse phase liquid chromatography. *Id.*

III. THE '506 PATENT

The '506 Patent claims—but is not entitled to—priority to United Kingdom Patent Application No. 1313465.5 (EX1003), filed on July 29, 2013, International Patent Application PCT/EP2014/065971 (EX1004), filed Jul. 24, 2014, a U.S. application that issued as US 10,000,519 (EX1005), filed Jan. 29, 2016, a U.S. application that issued as US 10,815,262 (EX1006), filed Feb. 27, 2018, a U.S. application that issued as US 11,584,770 (EX1007), filed May 29, 2020, and a U.S. application that issued as US 11,981,698 (EX1008), filed May 4, 2022.

A. Specification

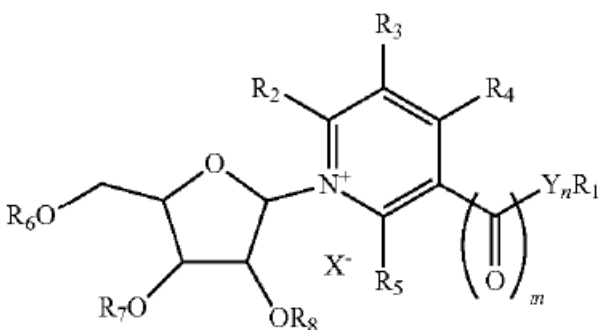
The '506 patent concerns "Methods of preparing nicotinamide riboside and derivatives thereof." EX1001, Title. The specification describes methods of preparing nicotinamide riboside ("NR⁺") salts of formula (I):



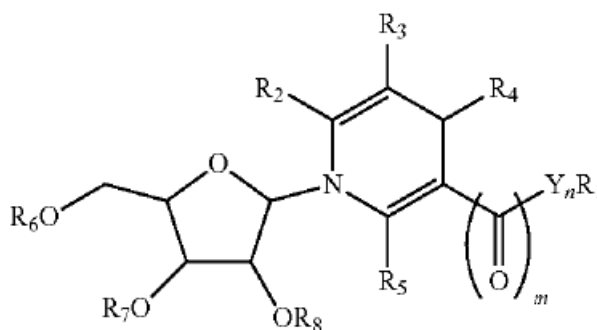
EX1001, Abstract; EX1013, ¶¶38-39. It explains that nicotinamide riboside was already known in the art as a desirable nutritional supplement, and that there were well-known means of preparing the compound and assorted salts. EX1013, ¶40. For example, common methods of forming nicotinamide riboside resulted in the formation of triflate salts, which was "not suitable for use as a nutritional supplement, because of its associated toxicity," so ion exchange could be applied to provide a different counterion. EX1001, 1:28-64; EX1013, ¶40.

The specification provides certain precursor molecules and methods for forming NR⁺ salts of formula (I). It explains, stepwise, that formula (I) is prepared from a compound of formula (II), which in turn is prepared from a compound of formula (III), which in turn is prepared from a compound of formula (IV). EX1001, 2:37-3:24, 6:66-7:18, 8:15-34 & Figure 2; EX1013, ¶41.

Formulae (IV) and (III) (reproduced below) are the only two formulae in the '506 patent with R-groups R₆-R₈. EX1001, 7:1-12, 8:18-28, Figure 2; EX1013, ¶¶41, 67.



Formula (IV)



Formula (III)

The '506 patent defines that R₆-R₈ are hydroxyl-protecting groups. EX1001, 8:17-28 (formula (IV) “n, m, Y, **R₁-R₈** and X⁻ are *as defined above*.”); *id.*, 7:1-16 (formula (III) “**R₆, R₇ and R₈**, which may be the same or different, *are each independently a hydroxyl-protecting group*.”). These R-groups do not appear on any of formulae (I) or (II), and thus there is no other definition “above” in the specification. The purpose of the hydroxyl-protecting group is to prevent unwanted reactions, as well as ensuring lipophilicity to facilitate migration of product in formula (III) into organic phase of its reaction. *Id.*, 7:22-41, 8:66-4; EX1013, ¶42.

B. Challenged Claims

Each challenged claim concerns compounds of formula (IV) and methods of making the same. However, the claims recite a logical impossibility: the claims require formula (IV), which by definition has R₆-R₈ hydroxyl-protecting groups,

yet also recite R₆-R₈ as hydrogen. EX1001, claims; EX1013, ¶43. Because hydrogen is not a hydroxyl-protecting group, the claims thus recite an impossibility. This impossibility did not appear in any of the pre-2023 patent applications to which the '506 patent claims priority. Thus, the claimed impossibility—formula (IV) R₆-R₈ as hydrogen—appeared for the first time, at the earliest, with the April 26, 2023 filing date of the application that issued as the '506 patent. EX1013, ¶¶43, 64-78.

C. Prosecution History

Applicant Queens University of Belfast (“Queen’s University”) did not inform the USPTO that it was shifting scope of its claims as compared to the priority documents. *See generally* EX1002; EX1013, ¶44. During examination of the '733 application that issued as the '506 patent, the examiner only made rejections for nonstatutory double patenting and for indefiniteness. EX1002, 96-101. There is no indication in the prosecution history that the examiner evaluated whether the claimed subject matter was entitled to priority earlier than April 26, 2023. EX1013, ¶45. Nor is there any indication that the applicant informed the examiner that the '733 application was the first place in the priority chain to recite the impossibility of R₆-R₈ of formula (IV) as being hydrogen, while the definition requires R₆-R₈ to be hydroxyl-protecting groups. EX1013, ¶45; *see generally* EX1002. The examiner allowed the application with no additional rejection and

without providing reasons for allowance. EX1002, 184.

D. Level of Ordinary Skill

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. EX1013, ¶¶46-48. This definition of a POSA would also apply as of July 29, 2013. *Id.*

This petition is supported by the declaration of Dr. Glenn Prestwich, who is, *inter alia*, Emeritus Professor of Medicinal Chemistry at the University of Utah. Dr. Prestwich is well qualified to opine from the perspective of a POSA in this case. EX1013, ¶¶1-14, 46-48. As Dr. Prestwich explains, and as addressed further below, the challenged claims would not have been considered new or non-obvious to a POSA at the relevant time. *Id.*, ¶¶49-53.

IV. CITED ART

As explained in detail herein, the '184 publication alone anticipates most claims and renders obvious the remaining challenged claims when combined with GRAS. The '184 publication (the sole reference asserted in Ground 1) was not considered during prosecution. GRAS was previously considered by the Office in connection with the claims of the '506 patent but not in combination with the '184 publication.

A. The '184 Publication

United States Patent Application Publication Number US 2016/0168184

(“the ’184 publication,” EX1022) published June 16, 2016. The ’184 publication is prior art to the challenged claims at least under 35 U.S.C. 102(a)(1). EX1013, ¶60.

The ’184 publication discloses synthesis of nicotinamide riboside salts for use in nutritional supplements. EX1022, [0005]-[0006]; EX1013, ¶61. The nicotinamide riboside salts were prepared from triflate salts with a process involving hydroxyl-protected derivatives of nicotinamide riboside. EX1013, ¶61.

B. GRAS

Generally Recognized as Safe (GRAS) Notice No. 635 (“GRAS,” EX1017) is a notification provided to the Food and Drug Administration (FDA). EX1013, ¶62. The FDA makes public GRAS Notices, including EX1017, on a searchable database. EX1018-EX1021; EX1013, ¶62&n.2. GRAS Notice No. 635 was filed March 29, 2016 and closed August 3, 2016. EX1018. GRAS was available to the public and is prior art to the challenged claims at least under 35 U.S.C. 102(a)(1). EX1013, ¶62 & n.2.

GRAS describes nicotinamide riboside chloride as a nutritional supplement and provides safety guidelines for its large-scale manufacture. EX1017, 000003, 000039; EX1013, ¶63. These guidelines include requirements for impurities, residual solvents, and water. EX1017, 000028-000030 & Table 2; EX1013, ¶63.

V. STATEMENT OF THE PRECISE RELIEF REQUESTED FOR EACH CLAIM CHALLENGED

Petitioners request review of claims 1-12 and 21-35 of the ’506 patent under

35 U.S.C. §311 and AIA §6. The grounds for relief are as follows:

Ground	Claims	Summary
1	1-12, 21-28, 31, and 34-35	Anticipated under 35 U.S.C. § 102 by the '184 publication
2	29-30 and 32-33	Obvious under 35 U.S.C. § 103 over the '184 publication and GRAS

VI. CLAIM CONSTRUCTION

Claims should be understood according to their ordinary and customary meaning as understood by POSA at the time of the invention in light of the language of the claims, the specification, and the prosecution history of record. 37 C.F.R. §42.200; *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-14 (Fed. Cir. 2005) (en banc). The Board need construe claims only to the extent necessary to resolve a controversy. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Matal*, 868 F.3d 1013, 1017 (Fed. Cir. 2017). EX1013, ¶¶20-21.

Claims will be understood according to an express definition provided in the specification of the patent. *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1578 (Fed. Cir. 1995) (“[T]he definition in the patent documents controls the claim interpretation.”); *Phillips*, 415 F.3d at 1321 (“the specification ‘acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication.’”); *Volkswagen Group of Am., Inc. v. Mich. Motor Techs.*,

LLC, IPR2020-00229 Paper 13, 9-12 (Jul. 6, 2020).

VII. DETAILED EXPLANATION FOR GROUNDS OF UNPATENTABILITY

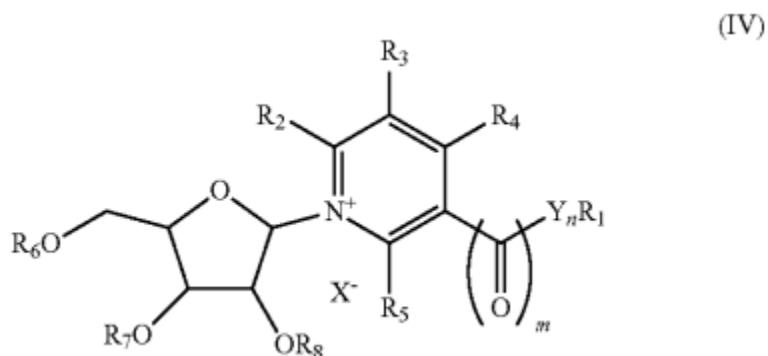
A. No Right to Priority Before April 2023

For a patent to receive benefit of an earlier filed patent application, the previously-filed application must provide § 112 support for the patent claims. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (The specification of the earlier application “must ‘contain a written description of the invention and the manner and process of making and using it, in such full, clear, concise, and exact terms,’ 35 U.S.C. § 112 ¶ 1, to enable an ordinarily skilled artisan to practice the invention *claimed* in the” instant patent.) (quoting *New Railhead Mfg., L.L.C. v. Vermeer Mfg. Co.*, 298 F.3d 1290, 1294 (Fed. Cir. 2002)); *see also Transco Prods. v. Performance Contracting, Inc.*, 38 F.3d 551, 557 n.6 (Fed. Cir. 1994) (“a continuing application is entitled to rely on the filing date of an earlier application only with respect to subject matter common to both applications.”).

The ’506 patent claims recite a logical impossibility that does not have written description or enablement support from any of the previously-filed applications in the patent family. The priority documents upon which the ’506 patent relies for priority neither show that the inventors possessed the claimed subject matter, nor do they enable a POSA to practice the claimed invention.

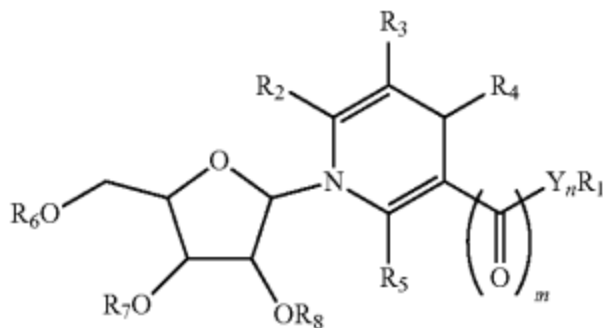
EX1003-EX1008; EX1013, ¶¶64-66. The '506 patent is therefore entitled to priority no earlier than April 26, 2023—the filing date of the '733 application, from which the '506 patent issued.

All claims of the '506 patent concern formula (IV), and all priority documents define formula (IV) R₆-R₈ as hydroxyl-protecting groups. *Compare* EX1001, claims *with* EX1003-EX1008; *see also* EX1013, ¶67. Each priority document illustrates formula (IV) as reproduced below:



EX1003, 10:28-31; EX1004, 10:28-31; EX1005, 8:17-28; EX1006, 8:17-28; EX1007, 8:20-31; EX1008, 8:17-28. The priority documents each explain that for formula (IV), “n, m, Y, **R₁-R₈** and X⁻ are *as defined above*.” EX1003, 11:1; EX1004, 11:1; EX1005, 8:30; EX1006, 8:31; EX1007, 8:34; EX1008, 8:30. This, in turn, directs the POSA to the definition for R₁-R₈ immediately above formula (IV), which is the disclosure of formula (III). The priority documents uniformly describe formula (III):

(III)



“wherein n, m, Y and R₁-R₅ are as defined above; and **R₆, R₇ and R₈**, 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; *see also* EX1013, ¶68.

Thus, formula (IV) is consistently defined throughout the priority documents with R₆-R₈ limited to hydroxyl-protection groups. Yet contrary to this clear definition, the '506 patent claims recite a logical impossibility: the claims require hydroxyl-protecting groups by virtue of reciting defined formula (IV) R₆-R₈, but also recite a conflicting identification of R₆-R₈ as hydrogen (or in some cases phosphate). EX1001, claims; EX1013, ¶69. This logical impossibility is not supported by the disclosure of the priority documents, and thus the '506 patent claims are entitled to priority no earlier than April 26, 2023.

1. The Priority Documents Fail to Provide Written Description Support for '506 Patent Claims

Patent claims are only entitled to the priority date of an earlier-filed application if the earlier-filed application contains sufficient written description

under 35 U.S.C. § 112 to support the subsequent claims. *Hologic, Inc. v. Smith & Nephew, Inc.*, 884 F.3d 1357, 1361 (Fed. Cir. 2018). “[T]he test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

The priority documents do not reasonably convey to a POSA that the inventors had possession of the subject matter claimed in the ’506 patent. EX1013, ¶70. Accordingly, the priority documents do not contain sufficient written description support for the ’506 patent claims. The ’506 patent claims thus are not entitled to a priority date of any of the earlier-filed applications.

Each of the priority documents consistently defined formula (IV) R_6 - R_8 as limited to hydroxyl-protecting groups. EX1013, ¶¶71-72; 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. These documents required formula (IV) have R_6 - R_8 , and defined “***R₆, R₇ and R₈***, 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; *see also* EX1013, ¶¶67-68.

Hydrogen is not a “hydroxyl-protecting group” as required by formula (IV)

R₆-R₈. EX1013, ¶73. A POSA would have understood that a hydrogen atom cannot mask reactivity of the hydroxyl group, and is not a hydroxyl-protecting group. *Id.*, ¶¶73-74. The plain language of the claims also deliberately distinguish hydrogen from hydroxyl-protecting groups. *E.g.*, EX1001 claim 1 (“independently H **or** a hydroxyl-protecting group”); EX1013, ¶73. A POSA would have understood that hydrogen is itself **part of** the hydroxyl functional group, so it is not a hydroxyl-protecting group. EX1013, ¶74; *see also* EX1012, 632-37.

The priority documents never disclose hydrogen as a hydroxyl-protecting group. Instead, they recite as hydroxyl-protecting groups the type of functional groups that a POSA would recognize as hydroxyl-protecting groups. EX1003, 9:15-28; EX1004, 9:15-38; EX1005, 7:22-41; EX1006, 7:22-41; EX1007, 7:25-44; EX1008, 7:22-41; EX1013, ¶72. Indeed, the priority document specifications place particular emphasis on the use of the traditional acetyl and benzoyl hydroxyl protecting groups. EX1003, 9:30-34 (R₆, R₇ and R₈ selected from substituted and unsubstituted acetyl, and substituted and unsubstituted benzoyl); 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 **R₆, R₇ and R₈ 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, R₁ is NH₂, R₂-R₅ are each H, and ***R₆-R₈ are each acetyl***. Further optionally, in another embodiment of formula (III), n is 1, Y is O, m is 1, R₁ is ethyl, R₂-R₅ are each H, and ***R₆-R₈ are each acetyl***. Still further optionally, in another embodiment of formula (III), n is 0, m is 1, R₁ is NH₂, R₂-R₅ are each H, and ***R₆-R₈ 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); *see also*, e.g., EX1016, Scheme 1 (acetyl and benzoyl as protecting groups), Figure 1 (same), Scheme 2 (same); EX1015, 1136 (same). Each of the priority document examples is consistent with R₆-R₈ limited to hydroxyl-protecting groups. EX1013, ¶75.

The priority documents’ emphasis of acetyl and benzoyl as hydroxyl-protecting groups also comports with the direction of the priority documents to use R₆-R₈ to facilitate migration of intermediate formula (III) into the organic phase during reaction. EX1003, 11:40-12:2; EX1004, 11:40-12:2; EX1005, 8:66-9:4; EX1006, 9:1-8; EX1007, 9:2-9; EX1008, 8:66-9:4. The priority documents describe, e.g., the combination of the acetyl protecting group with specific organic solvents. EX1003, 11:17-19; EX1004, 11:17-19; EX1005, 8:40-44; EX1006, 8:41-46; EX1007, 8:44-48; EX1008, 8:40-44. A POSA would have understood that such facilitation of migration into organic phase would not have been accomplished by R₆-R₈ hydrogen. EX1013, ¶76.

The priority documents do not reasonably convey to a POSA that the inventors had possession of the logical impossibility recited by the '506 patent claims—requiring hydroxyl-protecting groups by reciting defined formula (IV) R₆-R₈, yet reciting a conflicting identification of R₆-R₈ as hydrogen (or in some cases phosphate). EX1013, ¶77; *see also, e.g.*, EX1001, claim 1 (“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*.”). EX1013, ¶¶77-78. Moreover, a POSA would have understood that the claimed impossibility (reciting hydrogen as R₆-R₈ in Formula (IV)) was first introduced no earlier than April 26, 2023 via the claims that ultimately issued in the '506 patent. EX1002, 2-9; EX1013, ¶¶73, 78. Accordingly, the priority documents do not provide written description support for the '506 patent claims. The '506 patent claims are thus not entitled to a priority date of any of the earlier-filed applications. EX1013, ¶¶78, 84.

The priority documents also fail to provide descriptive support for, *inter alia*, the “chemical purity” and “diastereomeric purity” limitations of claims 29-30 and 32-33. *See* Section VII.C. Other than in the claims, the '506 patent does not use the words “chemical purity,” include a definition of “chemical purity” or have any examples of any “chemical purity.” EX1013, ¶158. With regard to compounds having the claimed formula (IV), the '506 patent only describes the compound of formula (IV) as being obtained as a *crude intermediate* having <10% starting

material. EX1001, 14:22-41; *id.*, 15:17-38; EX1013, ¶158. But the '506 patent never describes evaluating the formula (IV) crude mixture for overall purity (i.e., addressing anything beyond starting material). Thus, the '506 patent fails to provide written description for the claimed “chemical purity.” EX1013, ¶158. Likewise, with regard to “diastereomeric purity,” the '506 patent does not use the words “diastereomeric purity,” include a definition of “diastereomeric purity” or have any examples of “diastereomeric purity.” EX1013, ¶159. Thus, the priority documents also fail to demonstrate to a POSA that the inventors were in possession of—or otherwise provided adequate written description support for—the claimed compounds of formula (IV) having the recited “chemical purity” and “diastereomeric purity” as required by claims 29-30 and 32-33. EX1013, ¶¶158-159.

The *Capon* factors (as applied to the facts above), likewise support that the '506 patent claims do not have written description support in the priority documents and are thus not entitled to the priority date of any of the earlier-filed applications. EX1013, ¶¶79-83. *Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005) (“the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter”). In particular, the knowledge in the field, including as expressed in the prior art, distinguishes

rather than conflates hydroxyl-protecting groups from hydrogen. EX1013, ¶81. The field was sufficiently mature that it was predictable that hydrogen is not a hydroxyl-protecting group but unpredictable how to perform the synthesis taught by each of the priority documents based on the logical impossibility of formula (IV) having R₆-R₈ hydrogens. EX1013, ¶80. Accordingly, these factors likewise support finding the claims lack written description support before 2023.

2. The Priority Documents Fail to Provide Enablement Support for the '506 Claims

None of the priority documents provide enablement support for the challenged '506 patent claims, and thus the challenged claims cannot benefit from the filing dates of those priority documents. EX1013, ¶¶85-86. With regard to the first application, which was filed in the United Kingdom (EX1003), and the PCT application (EX1004), a “foreign patent application must meet the requirements of 35 U.S.C. § 112, first paragraph, in order for a later filed United States application to be entitled to the benefit of the foreign filing date under 35 U.S.C. § 119.” *In re Ziegler*, 992 F.2d 1197, 1200 (Fed. Cir. 1993). Likewise, with regard to each of the other priority documents (EX1005-EX1008), 35 U.S.C.S. § 120 requires that, for later-filed claims to benefit from an earlier U.S. patent application, the subject matter must be “disclosed in the manner provided by section 112(a).”

Moreover, it is *impossible* for any of the priority documents to provide enablement support for the subject matter recited in the challenged claims because

the '506 patent claims encompass an impossibility. *See* Section VII.A.1; EX1013, ¶87 ('506 patent claims “recite the logical impossibility of R₆-R₈ being hydrogen where the definition requires that R₆-R₈ are hydroxyl-protecting groups”). Where claims recite a logical impossibility, there can be no enablement support, and thus there can be no right to priority to any of the priority documents. *See Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1359 (Fed. Cir. 1999) (“clause [d] requires determining a quantity from the sum of that exact same quantity and something else, or symbolically, $A = A + B$, which is impossible, where, as here, B is not equal to zero. Accordingly, we hold that the correctly construed claims are invalid because they are inoperative, and thus the claims fail to comply with the utility and enablement requirements of 35 U.S.C. §§ 101 and 112, P 1, respectively.”). With regard to the '506 patent, the definition of formula (IV) limits R₆-R₈ to hydroxyl-protecting groups, but claim recites the impossibility of R₆-R₈ being hydrogen (symbolically, the claims recite $A [R_6-R_8] = A [\text{hydroxyl-protecting groups}]$ or $B [\text{hydrogen}]$, where B is not A). Such claims are impossible and thus cannot be enabled.

Accordingly, the '506 patent cannot receive the benefit from the filing dates of any of the priority documents because those priority documents cannot provide enablement support for the claimed impossible subject matter. *See Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 956 (Fed. Cir. 1983) (“Because it is for the invention

as claimed that enablement must exist, and because the impossible cannot be enabled, a claim containing a limitation impossible to meet may be held invalid under § 112.”); *Trs. of Bos. Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1364 (Fed. Cir. 2018) (“Defendants showed that epitaxially growing a monocrystalline layer directly on an amorphous layer would have required undue experimentation—indeed, that it is impossible.... We conclude that claim 19 is not enabled as a matter of law.”); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992) (“If the claimed subject matter is inoperable, the patent may indeed be invalid for failure to meet the utility requirement of § 101 and the enablement requirement of § 112.”).

The discussion that follows analyzes enablement support from the priority documents by reviewing individual factors the Federal Circuit has said may be relevant to determining enablement of a claim. *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371 (Fed. Cir. 1999) (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)). The priority documents fail to provide enablement support for the claimed subject matter; thus, the ’506 patent claims are not entitled to priority before April 26, 2023. EX1013, ¶¶85-86.

**i. The Impossible Nature of the Invention
Favors a Finding of No Enablement**

The nature of the invention (*Wands* factor 4) involves compounds of formula

(IV), which is a precursor molecule that the priority documents defined to require R₆, R₇ and R₈ as hydroxyl-protecting groups. EX1013, ¶87; EX1003, 8:30-9:6 (“R₆, R₇ and R₈ 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). But the ’506 patent claims recite a logical impossibility, where R₆-R₈ are hydrogen, while the definition requires a hydroxyl-protecting group. Thus, the nature of the invention is itself a logical impossibility, and cannot find enablement support in any of the priority documents. EX1013, ¶87.

ii. The Contrary Guidance in the Priority Documents and Limited Working Examples Favors a Finding of No Enablement

The contrary guidance and limited working examples (*Wands* factors 2 and 3) in the priority documents weigh against finding enablement for the ’506 patent claimed subject matter.

The priority documents’ guidance is clear that formula (IV) R₆, R₇ and R₈ must be hydroxyl-protecting groups. The priority documents explicitly define each of formula (IV)’s R₆, R₇ and R₈ as hydroxyl-protecting groups, and thus R₆, R₇ and R₈ ***cannot be*** hydrogen. EX1003, 8:30-9:6 (“R₆, R₇ and R₈, 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); EX1013, ¶88. The priority documents direct the POSA to utilize R₆, R₇ and R₈ hydroxyl-protecting groups that will, *inter alia*, promote the association of the subsequent formula (III) compound with the organic phase. 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 (guiding the POSA to use a lipophilic group at R₆, R₇ and R₈ 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). The priority documents’ guidance thus uniformly limits formula (IV) R₆, R₇ and R₈ to hydroxyl-protecting groups—contrary to the impossibility claimed by the ’506 patent. EX1013, ¶88.

Consistent with the guidance, all working examples of the ’506 patent priority documents are limited to formula (IV) R₆, R₇ and R₈ as hydroxyl-protecting groups—and more specifically, to where each of R₆, R₇ and R₈ are the same hydroxyl-protecting groups. EX1013, ¶89. Each of the working examples of the priority documents use either all acetyl or all benzoyl R₆-R₈ protecting groups. Uniformly through the priority documents, Example 1(A) describes formula (IV) as *triacetyl* nicotinamide riboside triflate salt, where R₆, R₇ and R₈ are each 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. Likewise, the priority documents consistently describe Example 1(B) where formula (IV) is *triacetyl* O-ethyl nicotinate riboside triflate salt—i.e., R₆, R₇ and R₈ are again each 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. Finally, the priority documents, with regard to Example 1(C), describe formula (IV) as *tribenzoyl* nicotinamide riboside triflate salt, where R₆, R₇ and R₈ are each benzoyl). Thus, the specification of each priority document *only* provides working examples where formula (IV) R₆, R₇ and R₈ are all the same, and only one of two specific hydroxyl-protecting groups—acetyl or benzoyl. The priority documents do not provide any working examples of the impossibility where formula (IV) R₆, R₇ or R₈ are hydrogen. EX1013, ¶¶89-90.

The priority documents do not provide *any* working examples with other variations to formula (IV) (EX1013, ¶91), much less any working examples that would enable the impossible subject matter of the '506 patent claims. These working examples are also limited and contrary to the claimed subject matter because each formula (IV) working example recites the use of a *triflate salt* while the claims exclude said salts. EX1003, 17:13-20:14 (Example 1(A) (“A compound of formula (IV), namely triacetyl nicotinamide riboside, *triflate* (CF₃SO₃[−], 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 working examples are thus limited in scope and fail to provide enablement for the challenged claims for this reason as well. Moreover, the ’506 patent claim 10 recites “a nutritional supplement composition comprising a compound of claim 1 [including formula (IV)].” But the only working examples of formula (IV) in the priority documents are triflate salts, and the priority documents explicitly instruct POSAs to *avoid* triflate salt from 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). EX1013, ¶¶92-93.

Thus, the only priority document working examples of formula (IV) are precursor molecules that were described as unsuitable and dangerous for use as a nutritional supplement. These working examples also do not encompass the impossibility where R₆, R₇ or R₈ are hydrogen. The limited working examples thus favor finding that the priority documents fail to provide enablement for the subject matter of the ’506 patent claims. EX1013, ¶94.

**iii. The Unsupported Breadth of the Claims
Favors a Finding of No Enablement**

While the priority documents provide narrow disclosure, requiring that formula (IV) R₆-R₈ is limited to hydroxyl-protecting groups, the claims encompass a logical impossibility that is not consistent with the priority documents' disclosure. Because there is no support in the priority documents for the claimed impossibility, the breadth of the claims (*Wands* factor 8) weighs against finding enablement. EX1013, ¶95.

**iv. The Amount of Experimentation is Undue
and Favors a Finding of No Enablement**

The priority documents' guidance expressly limits R₆, R₇ and R₈ of formula (IV) to hydroxyl-protecting groups, and the specific working examples of formula (IV) each recite all R₆, R₇ and R₈ are either acetyl or benzoyl hydroxyl-protecting groups. Thus, there is no direction given in the priority documents to practice the impossibility where any of formula (IV) R₆, R₇ or R₈ is hydrogen. Because formula (IV) having any of R₆, R₇ or R₈ as hydrogen is a logical impossibility, the experimentation required to practice that impossibility would be undue. Thus, the amount of experimentation necessary (*Wands* factor 1) weighs against finding enablement. EX1013, ¶96.

v. The Unpredictability of the Field Favors a Finding of No Enablement

The unpredictability of the art (*Wands* factor 7) also weighs against finding enablement in the priority documents for the claims of the '506 patent. It was predictable to a POSA in the field that hydrogen is not a hydroxyl-protecting group. EX1013, ¶¶73, 97. A POSA would have known that the hydroxyl functional group is not itself a hydroxyl-protecting group, nor is hydrogen a hydroxyl-protecting group. Hydroxyl-protecting groups are utilized to mask the intrinsic reactivity of the hydroxyl group, and the hydrogen atom is distinguishable from hydroxyl protecting groups. EX1013, ¶73. In contrast, a POSA could not have predicted how to even perform the synthesis taught by each of the priority documents based on the logical impossibility of formula (IV) having R₆-R₈ hydrogens. EX1013, ¶97. Thus, the unpredictability of the field weighs against finding enablement in the priority documents.

vi. The Relative Skill of Those in the Art Favors a Finding of No Enablement

A person of ordinary skill in the art 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 III.D. Such a trained person would recognize that the claims of the '506 patent encompass a logical impossibility that is not enabled by the priority documents. EX1013, ¶98. Additionally, the POSA's

knowledge, training, and experience would not provide the expertise necessary to resolve the logical impossibility of the '506 patent claims. *Id.* Thus, the relative skill of those in the art (*Wands* factor 6) weighs against finding enablement in the priority documents.

vii. The State of the Art Favors a Finding of No Enablement

The state of the art differentiated between hydroxyl-protecting groups and hydrogen. EX1013, ¶73. Moreover, the art did not resolve the '506 patent claims' logical impossibility. EX1013, ¶99. The state of the art (*Wands* factor 5) thus also weighs against finding enablement in the priority documents for the '506 patent claimed subject matter.

As the factor-by-factor analysis confirms above, the claims of the '506 patent are not enabled by the priority documents, and are therefore not entitled to a priority date before April 26, 2023. EX1013, ¶100. The '184 publication qualifies as prior art to the asserted claims.

B. [Ground 1] Claims 1-12, 21-28, 31, and 34-35 Are Anticipated by the '184 Publication

The '506 patent claims all encompass the logical impossibility of formula (IV), which requires R₆-R₈—explicitly and consistently defined as hydroxyl-protecting groups throughout the priority documents (EX1003-EX1008)—where R₆, R₇ or R₈ is hydrogen. Section VII.A, above. As discussed above, the claims

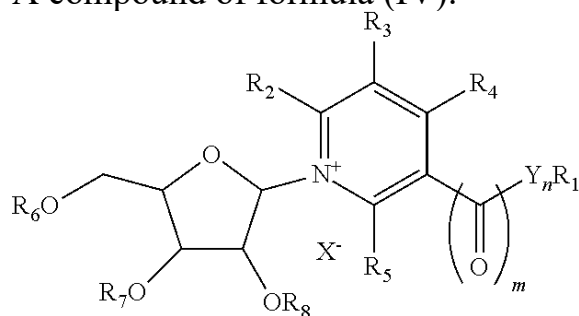
thus are not entitled to a filing date prior to April 26, 2023. Section VII.A, above. Accordingly, the '184 publication constitutes prior art to the challenged claims.

A POSA would have recognized claims 1-12, 21-28, 31, and 34-35 of the '506 patent are anticipated by the '184 publication. EX1013, ¶¶101-103. For example, the '184 publication discloses the synthesis of nicotinamide riboside (NR^+) salts with use of formula IV R_6 - R_8 hydroxyl-protected groups. EX1022, Scheme B & Figure 3, [0137]; EX1013, ¶¶60-61. The discussion below cites exemplary prior art disclosure on an element-by-element basis.

1. Claim 1

i. [1.A] Formula (IV)

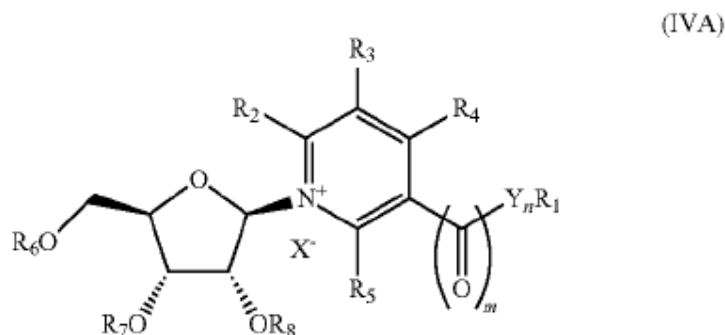
A compound of formula (IV):



or the beta-anomer thereof,
where:

The '184 publication discloses claim element [1.A]. EX1013, ¶¶104-105. For example, the '184 publication discloses a compound having a structure encompassed by Formula (IV)'s Markush structure. *See* EX1022, [0124]-[0126].

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



[0125] wherein

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

The '184 publication's nicotinamide riboside is the *beta-anomer* of the structure.

EX1022, [0124] ("Optionally, the compound of formula (IV) has the formula (IVA), i.e. is the β -anomer."); EX1013, ¶¶104-105.

ii. [1.B] n , m , and R-substitutions

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

The '184 publication discloses claim element [1.B]. EX1022, [0011]-[0015], [0070], [0089], [0126]; EX1013, ¶¶105-106. For example, the '184 publication discloses a nicotinamide riboside salt with the structure of formula (IV) where n is 0 and Y is absent; m is 1; R_1 is an unsubstituted primary amino (i.e., $-\text{NH}_2$); and

R₂-R₅ are each H. EX1013, ¶105. Additionally, the '184 publication discloses that “R₆, R₇ and R₈, which may be the same or different, are each independently a hydroxyl-protecting group” (EX1022, [0070]). EX1013, ¶105.

iii. [1.C] Anions

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.

The '184 publication discloses claim element [1.C]. EX1022, [0016]; EX1013, ¶105. The '184 publication provides multiple anions (A⁻) that overlap the claimed anion (X⁻). For example, The '184 publication anions include “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]; EX1013, ¶105.

In view of the foregoing, the '184 publication anticipates claim 1. EX1013, ¶106.

2. Claim 2

The compound of claim 1, wherein R₁ is —NH₂.

Claim 2 depends from claim 1, which is anticipated by the '184 publication

as discussed above. The '184 publication also discloses R_1 is $—NH_2$. For example, the '184 publication describes its R_1 is an unsubstituted primary amino (i.e., $—NH_2$). *See, e.g.*, EX1022, [0014]. The '184 publication thus anticipates claim 2. EX1013, ¶¶107-108.

3. Claim 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.

Claim 3 depends from claim 1, which is anticipated by the '184 publication as discussed above. The '184 publication also discloses R_6 , R_7 and R_8 are the same, and are each a hydroxyl-protecting group. *See, e.g.*, EX1022, [0070] (“ R_6 , R_7 and R_8 , which may be the same or different, are each independently a hydroxyl-protecting group”). The '184 publication thus anticipates claim 3. EX1013, ¶¶109-110.

4. Claim 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.

Claim 4 depends from claim 3, which is anticipated by the '184 publication as discussed above. The '184 publication also discloses 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, e.g.*, EX1022, [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.”). The ’184 publication thus anticipates claim 4. EX1013, ¶¶111-112.

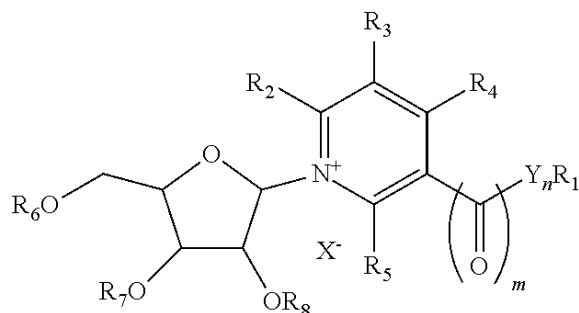
5. Claim 5

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.

Claim 5 depends from claim 3, which is anticipated by the ’184 publication as discussed above. The ’184 publication also discloses where X^- is an anion of a substituted monocarboxylic acid or an anion of an unsubstituted monocarboxylic acid. *See, e.g.*, EX1022, [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.”). The ’184 publication thus anticipates claim 5. EX1013, ¶¶113-114.

6. Claim 6

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 where R₆ is a phosphate; and

X⁻ is an anion of a substituted or unsubstituted aminodicarboxylic acid.

Independent claim 6 is substantively the same as independent claim 1, except it more narrowly requires “X⁻ is an anion of a substituted or unsubstituted aminodicarboxylic acid.” See EX1013, ¶115. Claim 1 is anticipated by the ’184 publication as discussed above, and the same features of claim 6 are anticipated for at least the same reasons. EX1013, ¶115. The ’184 publication also discloses X⁻ is an anion of a substituted or unsubstituted aminodicarboxylic acid. See, e.g., EX1022, [0030] (“X⁻ is an anion of a substituted or unsubstituted aminomonocarboxylic acid or an anion of *a substituted or unsubstituted aminodicarboxylic acid.*”). The ’184 publication thus anticipates claim 6. EX1013, ¶¶115-116.

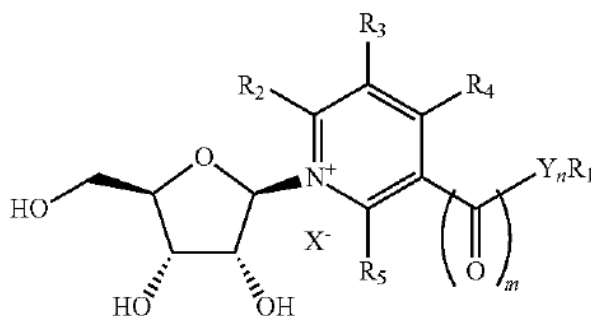
7. Claim 7

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

Claim 7 depends from claim 1, which is anticipated by the '184 publication as discussed above. The '184 publication also discloses X⁻ is selected from the group including acetate, trifluoroacetate, ascorbate, lactate, propionate and butyrate. *See, e.g.*, EX1022, [0035] ("X⁻ is selected from chloride, **acetate**, formate, **trifluoroacetate**, **ascorbate**, aspartate, glutamate and **lactate**."), [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"). The '184 publication thus anticipates claim 7. EX1013, ¶¶117-118.

8. Claim 8

The compound of claim 1 of formula:



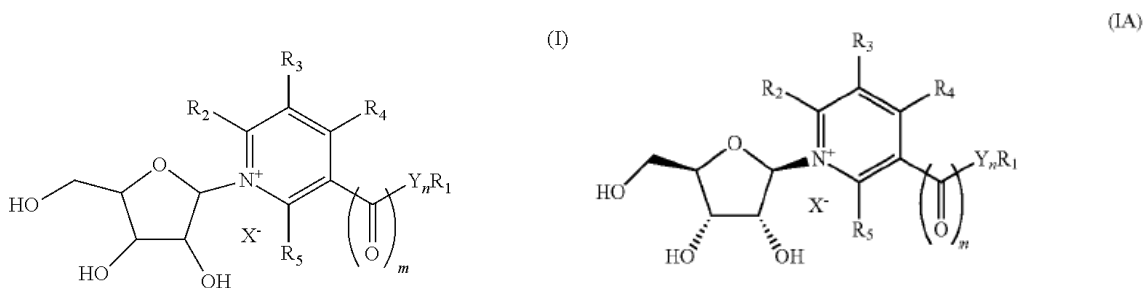
where:

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.

Claim 8 depends from claim 1, which is anticipated by the '184 publication as discussed above. Independent claim 1 recites formula (IV), and as discussed above, thus requires that each of R_6-R_8 are hydroxyl-protecting groups. Claim 8 requires the logical impossibility that each of these R_6-R_8 are instead H. EX1013, ¶119. This limitation does not further limit the claim because it instead presents a logical impossibility (as discussed above). But even if, *arguendo*, one were to embrace the logical impossibility of R_6-R_8 as H, this compound would be anticipated by the '184 publication. 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. EX1022, [0009]; *see also id*, [0115] (formula (IA)).



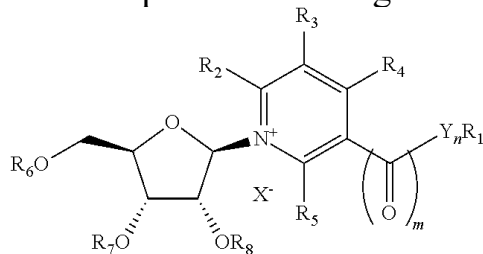
The '184 publication also discloses for formula (I): n is 0 and Y is therefore absent; m is 1; R_1 is an unsubstituted primary amino (i.e., $—NH_2$); and R_2-R_5 are each H. EX1022, [0011]-[0015]; EX1013, ¶120 (reproduced below, annotations added):

[0011] n is 0 or 1;
 [0012] m is 0 or 1;
 [0013] Y is O or S;
 [0014] R₁ 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] R₂-R₅ 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 X⁻ is an anion of a substituted monocarboxylic acid or an anion of an unsubstituted monocarboxylic acid other than formic acid (e.g., acetic acid). EX1022, [0027] ("an anion of a substituted or unsubstituted monocarboxylic acid"), [0029] ("an unsubstituted monocarboxylic acid selected from formic acid, acetic acid..."), Figure 5. The '184 publication thus anticipates claim 8. EX1013, ¶¶119-121.

9. Claim 9

The compound according to claim 1 of formula:



where:

n is 0 and Y is absent;
 m is 1;

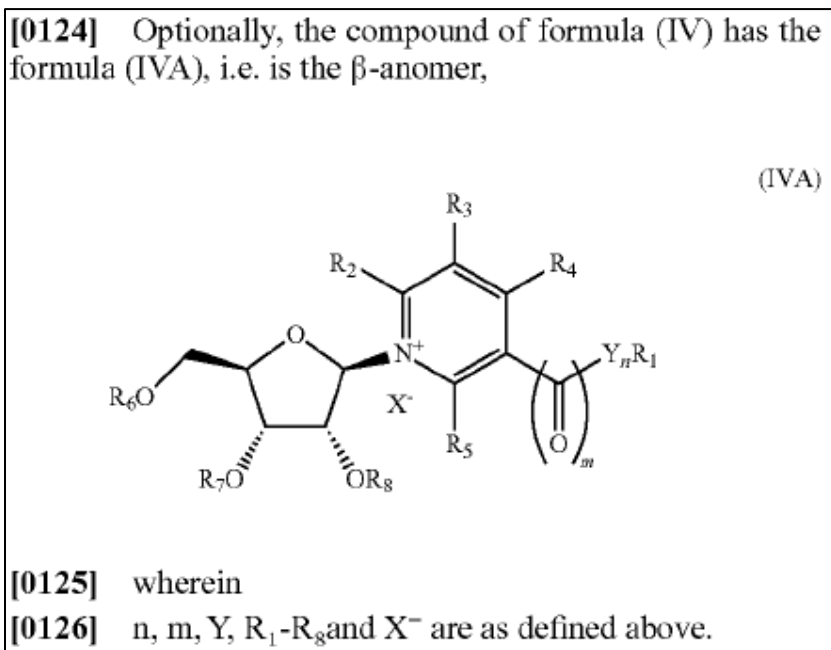
R_1 is $-\text{NH}_2$

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.

Claim 9 depends from claim 1, which is anticipated by the '184 publication as discussed above. The '184 publication also discloses the beta-anomer of formula (IV). EX1022, [0124]-[0126]:



The '184 publication discloses: n is 0 and Y is thus absent; m is 1; R_1 is an unsubstituted primary amino (i.e., $-\text{NH}_2$); and R_2 - R_5 are each H. EX1022, [0011]-[0015]; EX1013, ¶¶122. The '184 publication also 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 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*.”). The ’184 publication teaches 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 thus anticipates claim 9. EX1013, ¶¶122-123.

10. Claims 10 & 34

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

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

Claim 10 depends from claim 1, which is anticipated by the ’184 publication as discussed above. Claim 34 depends from claim 6, which is anticipated by the ’184 publication as discussed above. The ’184 publication also 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, [0008]; *see also id.*, [0128] (explaining its “methods conveniently enable the preparation of compounds having potential *use*

as nutritional supplements or otherwise.”). The ’184 publication thus anticipates claims 10 and 34. EX1013, ¶¶124-125 (claim 10), ¶¶151-152 (claim 34).

11. Claim 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.

Claim 11 depends from claim 10, which is anticipated by the ’184 publication as discussed above. The ’184 publication also discloses R_1 is $—NH_2$ (see Sections VII.B.1-VII.B.2 (Claim 1, Claim 2); EX1022, [0014]) and that X^- is an anion of a substituted or unsubstituted dicarboxylic acid (EX1022, [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*.”). The ’184 publication thus anticipates claim 11. EX1013, ¶¶126-127.

12. Claim 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.

Claim 12 depends from claim 10, which is anticipated by the ’184 publication as discussed above. The ’184 publication also discloses R_1 is $—NH_2$ (see Sections VII.B.1-VII.B.2 (Claim 1, Claim 2); EX1022, [0014]) and also

discloses R₆, R₇ and R₈ are each a hydroxyl-protecting group selected from unsubstituted acetyl, and unsubstituted benzoyl (*see* Section VII.B.9 (Claim 9); EX1022, [0077]-[0078]). The '184 publication thus anticipates claim 12. EX1013, ¶¶128-129.

13. Claim 21

The compound of claim 1, wherein R₆, R₇ and R₈, which may be the same or different, are each independently H or a hydroxyl-protecting group selected from unsubstituted acetyl, and unsubstituted benzoyl.

Claim 21 depends from claim 1, which is anticipated by the '184 publication as discussed above. The '184 publication also discloses R₆, R₇ and R₈ may be the same or different, and are each independently a hydroxyl-protecting group selected from unsubstituted acetyl, and unsubstituted benzoyl. EX1022, [0077]-[0078] (“Optionally, 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*.”). The '184 publication thus anticipates claim 21. EX1013, ¶¶130-131.

14. Claim 22

The compound of claim 2, wherein X⁻ is an anion of a substituted or unsubstituted dicarboxylic acid.

Claim 22 depends from claim 2, which is anticipated by the '184 publication as discussed above. The '184 publication also discloses X⁻ is an anion of a

substituted or unsubstituted dicarboxylic acid. EX1022, [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.***”). The ’184 publication thus anticipates claim 22. EX1013, ¶¶132-133.

15. Claim 23

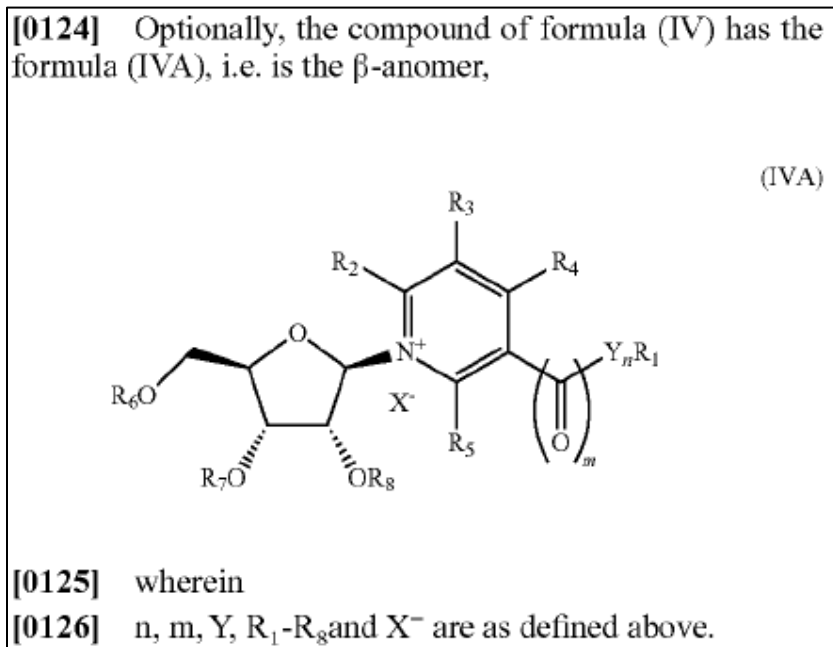
The compound of claim 6, wherein X⁻ is selected from aspartate and glutamate.

Claim 23 depends from claim 6, which is anticipated by the ’184 publication as discussed above. The ’184 publication also discloses X⁻ is selected from aspartate and glutamate. EX1022, [0035] (“X⁻ is selected from chloride, acetate, formate, trifluoroacetate, ascorbate, ***aspartate, glutamate*** and lactate.”); *id.*, [0030], [0094] (“X⁻ is selected from ascorbate, ***glutamate, aspartate***, lactate and acetate”). The ’184 publication thus anticipates claim 23. EX1013, ¶¶134-135.

16. Claim 24

The compound of claim 6, wherein the compound is the beta-anomer;
n is 0 and Y is absent;
m is 1;
R₁ is —NH₂
R₂-R₅ are each H;
R₆, R₇ and R₈ are each H; and
X⁻ is an anion of a substituted or unsubstituted aminodicarboxylic acid.

Claim 24 depends from claim 6, which is anticipated by the '184 publication as discussed above. The '184 publication also discloses the beta-anomer of formula (IV). EX1022, [0124]-[0126]:



The '184 publication discloses where: n is 0 and Y is therefore absent; m is 1; R₁ is an unsubstituted primary amino (i.e., —NH₂); and R₂-R₅ 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] R₁ 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] R₂-R₅ 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

EX1013, ¶136. The '184 publication also discloses X⁻ is an anion of a substituted or unsubstituted aminodicarboxylic acid. EX1022, [0030] ("X⁻ is an anion of a substituted or unsubstituted amino-monocarboxylic acid or an anion of *a substituted or unsubstituted amino-dicarboxylic acid*.").

Claim 24 requires the logical impossibility that R₆, R₇ and R₈ are each H. EX1013, ¶137. This limitation does not add anything, and thus does not further limit the claim because it instead presents a logical impossibility (as discussed above). But even if, *arguendo*, one were to embrace the logical impossibility of R₆-R₈ as H, this compound is also anticipated by the '184 publication. The '184 publication depicts its formula (I) having H at positions corresponding to R₆-R₈ of formula (IV). EX1022, [0009], [0115] (formula (IA)). The '184 publication thus anticipates claim 24. EX1013, ¶¶136-139.

17. Claim 25

The compound of claim 6, wherein the compound is the beta-anomer;
n is 0 and Y is absent;
m is 1;
R₁ is —NH₂
R₂-R₅ are each H;
R₆, R₇ and R₈, 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.

Claim 25 depends from claim 6, which is anticipated by the '184 publication as discussed above. The '184 publication also discloses the beta-anomer of formula (IV). EX1022, [0124]; EX1013, ¶140. The '184 publication discloses: n is 0 and Y is therefore absent; m is 1; R₁ is an unsubstituted primary amino (i.e., —NH₂); and R₂-R₅ 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] R₁ 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;

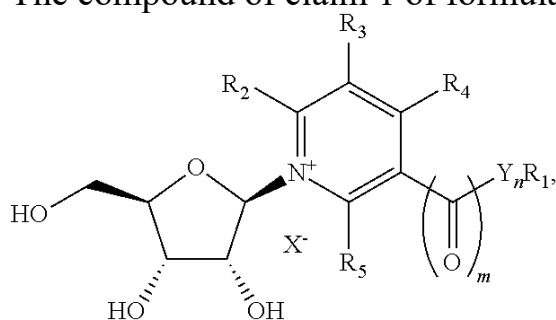
[0015] R₂-R₅ which may be the same or different, are each independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, and substituted or unsubstituted aryl; and

EX1013, ¶140. The '184 publication also discloses R₆, R₇ and R₈, 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 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*.”). The ’184 publication also discloses X⁻ is an anion of a substituted or unsubstituted aminodicarboxylic acid. EX1022, [0030] (“X⁻ is an anion of a substituted or unsubstituted amino-monocarboxylic acid or an anion of a *substituted or unsubstituted amino-dicarboxylic acid*.”). The ’184 publication thus anticipates claim 25. EX1013, ¶¶140-141.

18. Claim 26

The compound of claim 1 of formula:



where:

n is 0 and Y is absent;

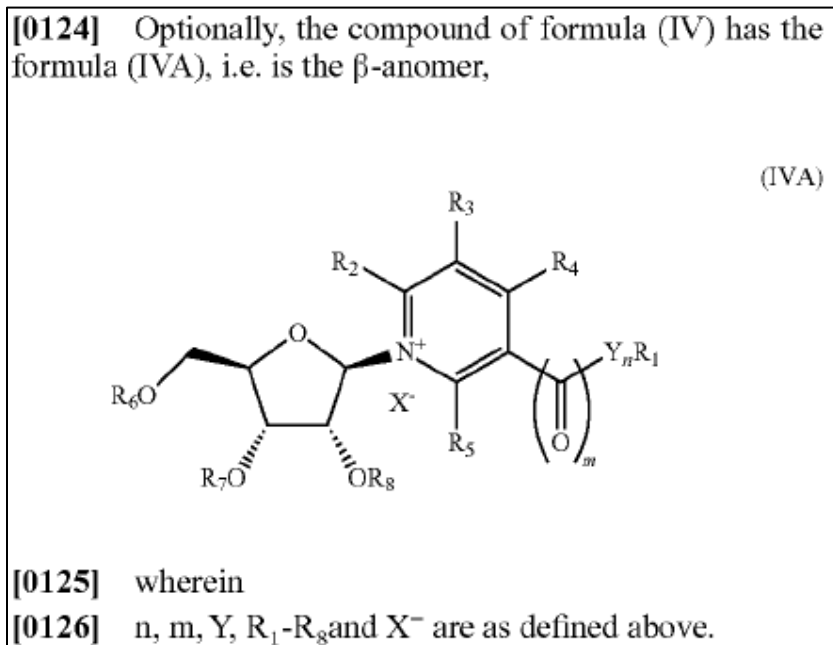
m is 1;

R₁ is —NH₂;

R₂-R₅ are each H; and

X⁻ is an anion of a substituted or unsubstituted dicarboxylic acid.

Claim 26 depends from claim 1, which is anticipated by the '184 publication as discussed above. The '184 publication also discloses the beta-anomer of formula (IV). EX1022, [0124]-[0126]:



EX1013, ¶144. The '184 publication discloses where: n is 0 and Y is therefore absent; m is 1; R₁ is an unsubstituted primary amino (i.e., —NH₂); and R₂-R₅ 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] R₁ 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] R₂-R₅ 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

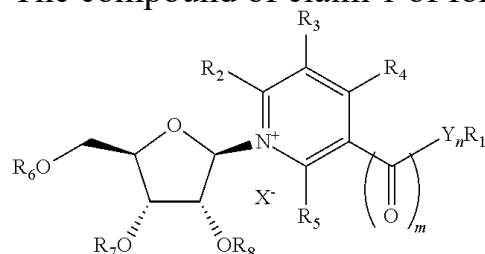
EX1013, ¶144. The '184 publication also discloses X⁻ is an anion of a substituted or unsubstituted dicarboxylic acid. EX1022, [0027] ("X⁻ is an anion of a substituted or unsubstituted carboxylic acid selected from an anion of a substituted or unsubstituted monocarboxylic acid and *an anion of a substituted or unsubstituted dicarboxylic acid.*").

Claim 26 requires the logical impossibility that R₆, R₇ and R₈ are each H. EX1013, ¶¶142-143. This limitation does not add anything, and thus does not further limit the claim because it instead presents a logical impossibility (as discussed above). But even if, *arguendo*, one were to embrace the logical impossibility of R₆-R₈ as H, this compound is also anticipated by the '184 publication. The '184 publication depicts its formula (I) having H at positions corresponding to R₆-R₈ of formula (IV). EX1022, [0009], [0115] (formula (IA)); EX1013, ¶144. The '184 publication thus anticipates claim 26. EX1013, ¶¶142-

145.

19. Claim 27

The compound of claim 1 of formula:



where:

n is 0 and Y is absent;

m is 1;

R₁ is —NH₂

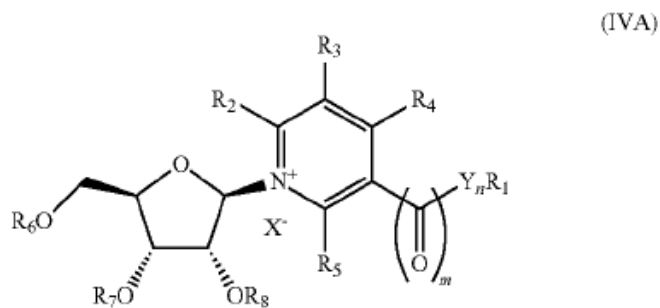
R₂-R₅ are each H;

R₆, R₇ and R₈, 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.

Claim 27 depends from claim 1, which is anticipated by the '184 publication as discussed above. The '184 publication also 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,



[0125] wherein

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

EX1013, ¶146. The '184 publication discloses: n is 0 and Y is therefore absent; m is 1; R_1 is an unsubstituted primary amino (i.e., $-\text{NH}_2$); 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

EX1013, ¶146. The '184 publication also discloses R_6 , R_7 and R_8 may be the same or different, and are each independently a hydroxyl-protecting group selected from

unsubstituted acetyl, and unsubstituted benzoyl. EX1022, [0077]-[0078] (“Optionally, 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*.”). The ’184 publication also discloses X⁻ is an anion of a substituted or unsubstituted dicarboxylic acid. EX1022, [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*.”). The ’184 publication thus anticipates claim 27. EX1013, ¶¶146-147.

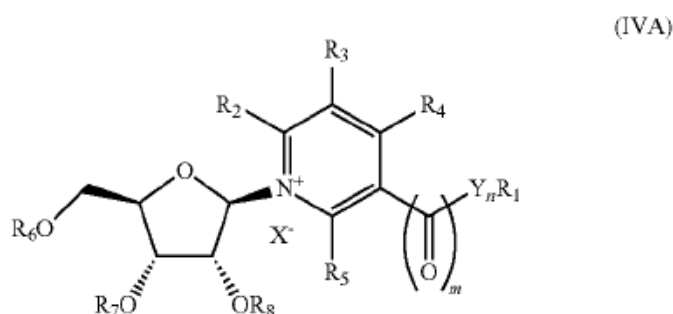
20. Claims 28 & 31

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

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

Claim 28 depends from claim 1, which is anticipated by the ’184 publication as discussed above. Claim 31 depends from claim 6, which is anticipated by the ’184 publication as discussed above. The ’184 publication also 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,



[0125] wherein

[0126] n, m, Y, R₁-R₈ and X⁻ are as defined above.

EX1013, ¶149. The '184 publication thus anticipates claims 28 and 31. EX1013, ¶¶148-150.

21. Claim 35

The nutritional supplement composition of claim 34, wherein R₁ is —NH₂.

Claim 35 depends from claim 34, which is anticipated by the '184 publication as discussed above. The '184 publication also discloses R₁ is —NH₂ (see Sections VII.B.1-VII.B.2 (Claim 1, Claim 2); EX1022, [0014]). The '184 publication thus anticipates claim 35. EX1013, ¶¶153-154.

Accordingly, the '184 publication anticipates each of claims 1-12, 21-28, 31, and 34-35. EX1013, ¶155.

C. [Ground 2] Claims 29-30 and 32-33 Are Obvious over the '184 Publication and GRAS

A POSA would have recognized claims 29-30 and 32-33 of the '506 patent were obvious as exemplified by the '184 publication and GRAS. EX1013, ¶¶156-163.

The '184 publication discloses derivatives of nicotinamide riboside identified in its examples. EX1022, [0150]-[0151]; EX1013, ¶160. The '184 publication also describes its nicotinamide riboside derivatives are used for “producing compounds suitable for use as nutritional supplements.” EX1022, [0008]; EX1013, ¶160.

GRAS describes how nicotinamide riboside chloride salt may be safely administered as a nutritional supplement for human consumption by, *inter alia*, providing specific limits of impurities and solvent amounts “for the final product to comply with appropriate controls on residual solvents and other processing aids for food.” EX1017, 000026; EX1013, ¶161.

The '184 publication describes salts that may be used in place of GRAS's nicotinamide riboside chloride salt and a POSA would have understood the '184 publication is teaching the disclosed salts are suitable for use with nicotinamide riboside. EX1022, [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.”);

EX1013, ¶162.

As Dr. Prestwich explains, a POSA would have had good reason to apply the previously-approved nutritional supplement standards described by GRAS' nicotinamide riboside chloride salt for the '184 publication's nicotinamide riboside salts. EX1013, ¶¶163, 179-181. Employing the nutritional supplement safety standards outlined by GRAS for the '184 publication's salts of nicotinamide riboside would enable the POSA to prepare additional salts (i.e., not limited to the GRAS-approved chloride salt) of nicotinamide riboside for use in nutritional supplements. EX1013, ¶¶179-181.

Additionally, as Dr. Prestwich explains, a POSA would have reasonably expected success in combining the GRAS parameters for the '184 publication's nicotinamide riboside salts. EX1013, ¶¶182-183. This is consistent with the teaching of the '184 publication, which envisioned its nicotinamide riboside salts as suitable substitutes for the chloride salt approved under GRAS. *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."); EX1013, ¶¶182-183.

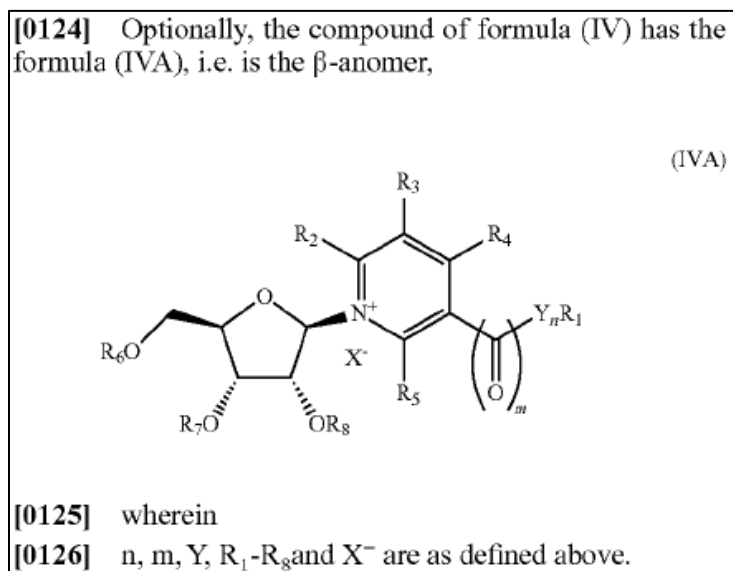
1. Claims 29 & 32

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.

Claim 29 depends from claim 1, which is anticipated by the '184 publication as discussed above. Section VII.B.1. Claim 32 depends from claim 6, which is anticipated by the '184 publication as discussed above. Section VII.B.6. The '184 publication also describes its nicotinamide riboside derivative is the *beta*-anomer. EX1022, [0124]-[0126]:



EX1013, ¶165.

As an initial matter, the '506 patent does not provide descriptive support for the claim including “chemical purity.” EX1013, ¶166; Section VII.A.1.

Concerning the claimed formula (IV), the '506 patent only explains the compound

of formula (IV) was obtained as a crude intermediate having <10% starting material. EX1001, 14:22-41; *id.*, 15:17-38; EX1013, ¶166. But the '506 patent and priority documents all fail to otherwise disclose what is meant by “chemical purity” and did not appear to take into account byproducts or other undesired materials in the reaction.

Nonetheless, 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; EX1013, ¶167. GRAS requires 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); EX1013, ¶167.

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%

The '506 patent also does not provide descriptive support for the claim including “diastereomeric purity.” EX1013, ¶168; section VII.A.1. As explained above, the '506 patent discloses using the claimed formula (IV) as an intermediate in a crude mixture without purification. To the extent Patent Owners rely on this, this is the same as what is disclosed in the '184 publication. EX1022, [0150]-

[0151]. Patent Owners cannot point to anything in the '506 patent in this regard that is not also found in the prior art '184 publication.

Thus, the combination of the '184 publication and GRAS teaches all of the elements of each of claims 29 and 32, and renders the claims obvious as a whole.

EX1013, ¶¶164-169.

2. Claims 30 & 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.

Claims 30 and 33 depend from claims 1 and 6, respectively, which are anticipated by the '184 publication as discussed above. Additionally, as described with claims 29 and 32 above, the '184 publication and GRAS describe 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 (to the extent Patent Owners rely on the '506 patent specification as disclosing said diastereomeric purity). EX1013, ¶¶170-174; section VII.C.1. For at least the

reasons described above, each of these claim limitations is rendered obvious by the combination of the '184 publication and GRAS. Section VII.C.1; EX1013, ¶¶170-174.

Moreover, GRAS describes 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]...”). The amount of methanol identified in GRAS’s commercial batches was significantly less than 3000 ppm methanol: the batches of nicotinamide riboside salt tested in GRAS had 172 ppm, 263 ppm, and 631 ppm methanol. *See id.*, 000030, Table 2 (reproduced below, annotated); EX1013, ¶175.

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	$\leq 0.1\%$	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 <i>t</i> -Butyl Ether	ND*	99.1-CD-7.0-000115	ND	ND	ND

GRAS’s nicotinamide riboside salts also had low levels of other solvent impurities (e.g., Batch 14207, 0.1140% (w/w)). EX1017, Table 2. Even if lacking a

presumption of obviousness, GRAS's other solvent impurity disclosure indicates that the claimed language differs insignificantly from the prior art. *See* MPEP 2144.05 (“[A] *prima facie* case of obviousness exists where the claimed ranges or amounts do not overlap with the prior art but are merely close.”) (citing *In re Becket*, 88 F.2d 684 (CCPA 1937) (“Where the component elements of alloys are the same, and where they approach so closely the same range of quantities as is here the case, it seems that there ought to be some noticeable difference in the qualities of the respective alloys.”)); *see also In re Aller*, 220 F.2d 454 (CCPA 1955) (affirming an obviousness rejection of a claim to a chemical process reciting use of 25-70% sulfuric acid at 40-80 degrees when the prior art disclosed the same reaction with 10% sulfuric acid at 100 degrees); *In re Hill*, 284 F.2d 955 (CCPA 1960) (affirming an obviousness rejection of a claim to a chemical process conducted at 150-250 degrees when the prior art disclosed the same reaction at 300 degrees). Furthermore, as Dr. Prestwich explains, a POSA would have recognized that it was desirable to minimize solvent impurities, and doing so was a matter of routine optimization. EX1013, ¶176.

With regard to the claim requirement that the nicotinamide riboside salts have less than 0.2% water content, GRAS describes this expressly. EX1017, 000030 & Table 2; EX1013, ¶177. For example, batches of nicotinamide riboside salts were each determined by GRAS to have 0.1% water content. EX1017,

000030, Table 2 (reproduced below, annotated); EX1013, ¶177.

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, the combination of the '184 publication and GRAS teaches all of the elements of each of claims 30 and 33, and renders each of the claims obvious as a whole. EX1013, ¶¶170-178.

Accordingly, the combination of the '184 publication and GRAS renders obvious each of claims 29-30 and 32-33.

VIII. CONCLUSION

Claims 1-12 and 21-35 are unpatentable. Thorne respectfully requests an IPR so these claims may be canceled.

Respectfully submitted,

Dated: 22 June 2026

/ Michael T. Rosato /
Michael T. Rosato, Lead Counsel
Reg. No. 52,182

IX. GROUNDS FOR STANDING

Petitioners certify that, under 37 C.F.R. §42.104(a), the '506 patent is available for inter partes review, and Petitioners are not barred or estopped from requesting *inter partes* review of the '506 patent on the grounds identified.

X. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

Real Party-in-Interest (37 C.F.R. § 42.8(b)(1)): Thorne Research, Inc. and Thorne HealthTech, Inc. are the petitioners and real parties-in-interest. Thorne Research, Inc. is a wholly-owned subsidiary of Thorne HealthTech, Inc., which is a subsidiary of LC10 Healthspan Aggregator LP via Healthspan Holdings, LP; Healthspan Topco, LLC; Healthspan Intermediate, LLC; and Healthspan Buyer, LLC. Thorne owns subsidiaries Thorne Lab Inc. and Thorne YouCare Ltd. (Hong Kong), each of which has no operations or activities and is either planned for or in the process of dissolution.

Thorne purchases nicotinamide riboside products from Biosynth Carbosynth via NR Therapeutics, and Thorne maintains a contractual relationship with Pattern Inc. relating to the sale of certain nicotinamide products.

Related Matters (37 C.F.R. § 42.8(b)(2)): Thorne Rsch., Inc. v. Niagen Biosciences, Inc., No. 2:26-cv-01758-RMG (D.S.C.) (Declaratory judgment of non-infringement of U.S. Patent No. 12,252,506).

Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3)):

Lead Counsel: Michael T. Rosato (Reg. No. 52,182)

Back-Up Counsel: Jad A. Mills (Reg. No. 63,344); Wendy Devine (Reg. No. 61,309); Garrett T. Potter (Reg. No. 76,602)

Service Information – 37 C.F.R. § 42.8(b)(4). Petitioners hereby consent to electronic service.

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XI. CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 11,068 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Dated: June 22, 2026

/ Michael T. Rosato /
Michael T. Rosato, Lead Counsel
Reg. No. 52,182

XII. PAYMENT OF FEES UNDER 37 C.F.R. §§42.15(A) AND 42.103

The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 23-2415.

XIII. 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., <i>New Crystalline Salts of Nicotinamide Riboside as Food Additives</i> , MOLECULES 26, 2729 (2021).
1010	<i>Intentionally left blank</i>
1011	<i>Intentionally left blank</i>
1012	JONATHAN CLAYDEN ET AL., ORGANIC CHEMISTRY (2009).
1013	Declaration of Dr. Glenn Prestwich
1014	Dr. Glenn Prestwich CV
1015	S. Tanimori et al., <i>An Efficient Chemical Synthesis of Nicotinamide Riboside (NAR) and Analogs</i> , BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 12, 1135 (2002).
1016	P. Franchetti et al., <i>Stereoselective synthesis of nicotinamide β-ribose and nucleoside analogs</i> , BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 14, 4655 (2004).
1017	SPHERIX CHROMADDEX CONSULTING, Generally Recognized as Safe

	(GRAS) Determination for Niagen™ (Nicotinamide Riboside Chloride), No. 635 (Mar. 3, 2016), <i>available at</i> https://www.hfpappexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=635
1018	<i>GRN No. 635: Nicotinamide riboside chloride</i> , FDA, https://www.hfpappexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=635 (last visited Apr. 24, 2026)
1019	<i>GRAS Notices</i> , FDA https://www.hfpappexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices (last visited Apr. 24, 2026)
1020	Archived <i>GRAS Notices</i> , FDA https://web.archive.org/web/20201222145917/https://www.cfsanappsext.ernal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&sort=GRN_No&order=DESC&showAll=true&type=basic&search= (archived Dec. 22, 2020)
1021	Archived <i>GRN No. 635: Nicotinamide riboside chloride</i> , FDA, https://web.archive.org/web/20210124164020/https://www.cfsanappsext.ernal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=635 (archived Jan. 24, 2021)
1022	U.S. Patent Application Publication No. US 2016/0168184
1023	USPTO Assignment Center, <i>Patent Assignment Abstract of Title for Patent No. 12,252,506</i> , https://assignmentcenter.uspto.gov/search/patent/abstract%3FpatentNumber%3D12252506 (last visited June 22, 2026).
1024	<i>Niagen Bioscience Acquires Existing Core Nicotinamide Riboside (NR) Patent Portfolio from Queen's University Belfast</i> , NIAGEN BIOSCIENCE, INC. (Dec. 22, 2025), https://investors.niagenbioscience.com/news/news-details/2025/Niagen-Bioscience-Acquires-Existing-Core-Nicotinamide-Riboside-NR-Patent-Portfolio-from-Queens-University-Belfast/default.aspx (last visited June 17, 2026).
1025	Niagen Bioscience, Inc., Annual Report (Form 10-K) (Mar. 4, 2026), https://www.sec.gov/Archives/edgar/data/1386570/0001386570260000

	24/nageform10-k.pdf .
1026	<i>Niagen Bioscience Secures U.S. Patent for the Composition of Matter for Nicotinamide Riboside (NR) Salt Forms</i> , NIAGEN BIOSCIENCE, INC. (Mar. 20, 2025), https://investors.niagenbioscience.com/news/news-details/2025/Niagen-Bioscience-Secures-U-S--Patent-for-the-Composition-of-Matter-for-Nicotinamide-Riboside-NR-Salt-Forms/ (last visited June 17, 2026).

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§42.6(e) and 42.105(a), this is to certify that I caused to be served a true and correct copy of the foregoing Petition for Inter-Parties Review of U.S. Patent No. 12,252,506 (and accompanying Exhibits 1001-1009 and 1012-1026) by overnight courier (Federal Express or UPS), on this 22nd day of June, on the Patent Owner at the correspondence address of record for the subject patent and other address known to the Petitioner as likely to effect service as follows:

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Respectfully submitted,

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