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Plaintiffs Thorne Research, Inc. (“Thorne Research”) and Thorne HealthTech, Inc. (“Thorne HealthTech”) (collectively, “Thorne” or “Plaintiffs”), by and through their counsel, hereby submit this memorandum in opposition to Niagen Bioscience, Inc. (“Niagen”) and The Queen’s University of Belfast’s (“QUB”) (collectively, “Defendants”) Motion to Strike or, in the Alternative, Dismiss Plaintiffs’ Counter-Counterclaims. In the alternative, Plaintiffs submit this Motion to Amend (and incorporated memorandum of law) moving the Court for leave to file an Amended Complaint in this matter pursuant to Rule 15. A copy of the proposed Amended Complaint is attached hereto as Exhibit A and a redline of the Amended Complaint is attached hereto as Exhibit B.

I. INTRODUCTION

This case revolves around a single patent, U.S. Patent No. 12,252,506 (the “’506 Patent”), that three different entities have used to harass a competitor, Thorne. Each of these three entities—Niagen, QUB, and ChromaDex, Inc. (“ChromaDex”)—has held itself out as the owner of the ’506 Patent and leveraged the ’506 Patent in efforts to restrain Thorne’s ability to sell its products. Thorne sought to end this harassment, naming all three entities as defendants in a declaratory judgement of non-infringement claim, so that this Court could enter a judgement that binds all parties thereby providing finality for Thorne and the Court. When ChromaDex counterclaimed for infringement, Thorne responded by seeking a declaratory judgement of invalidity, and once again, named all three defendants having ownership interests in the ’506 Patent.

Niagen and QUB now argue that procedural technicalities should allow them to avoid being subject to a final resolution regarding invalidity of the ’506 Patent. Simultaneously, Defendants refuse consent to allow Thorne to amend its Complaint to add its declaratory judgement for invalidity claim against all three. Defendants’ manipulation of the pleadings

creates duplicative briefing, invites piecemeal litigation, and runs contrary to the Federal Rules that favor resolving cases on the merits rather than technicalities or clever pleadings. Thorne, therefore, opposes Defendants' motion and, in the alternative, moves for leave to file an Amended Complaint. By granting leave to amend the Complaint, the Court will resolve Niagen and QUB's procedural objections, and moot QUB's duplicative jurisdictional arguments, so that this case can be decided on the merits.

II. BACKGROUND

Procedural Background. Thorne filed suit on April 28, 2026 against Niagen, QUB, and ChromaDex, seeking declaratory judgement of non-infringement of the '506 Patent along with three business-tort claims. D.I. 1, ¶¶ 6-8, 49-73. Thorne alleged all three defendants, each having held themselves out as owners of the '506 Patent, acted in concert to harass Thorne and prevent it from selling its nicotinamide riboside (NR) products ("Thorne NR Products"). *Id.*, ¶¶ 9-41. While both Niagen and ChromaDex answered Thorne's claim for non-infringement, only ChromaDex counterclaimed for infringement. D.I. 18 at 15, 26-30 (¶¶ 45-61). Meanwhile, QUB filed a motion to dismiss for lack of subject matter jurisdiction and failure to state a claim (*see* D.I. 27), which Thorne opposed, citing the need for further discovery on QUB's ownership interests (*see* D.I. 33 at 1-2). Thorne answered ChromaDex's counterclaim and sought declaratory judgement of invalidity of the '506 Patent, and again, named all three defendants having an ownership interest in the '506 Patent. D.I. 30. Niagen and QUB now move to strike Thorne's claim of invalidity of the '506 Patent against them on the grounds that neither filed a counterclaim of infringement against Thorne.¹

¹ Niagen and QUB did not even attempt to meet and confer with Thorne prior to filing their motion to strike, in violation of Local Rule 7.02.

Defendants' Relationship and Leverage of the '506 Patent. Defendants are no strangers to each other or to Thorne. Niagen is the parent company of ChromaDex that has publicly stated its ownership interest in the '506 Patent. D.I. 1, ¶¶ 7, 20-22. Niagen harassed Thorne via an APEX submission regarding the '506 Patent that was signed from a Niagen email address. *Id.*, ¶ 18. Less than 2 weeks ago, and *after* defendants filed the present motion, Niagen offered Thorne settlement terms concerning rights in the '506 Patent. *Infra* § VI.A. QUB and ChromaDex share a “broad[] research relationship” that has persisted since at least 2015. D.I. 18 at 21 (¶ 23). This relationship was ongoing when QUB filed the application that became the '506 Patent—U.S. Application No. 18/307,733 (“’733 Application”)—on April 26, 2023. D.I. 33 at 3-5. QUB does not dispute that it was the owner of the '506 Patent when Chromadex sent Thorne threatening letters, dated May 13, 2025 and July 22, 2025, about the '506 Patent.

While QUB contends that it assigned its rights to the '506 Patent to ChromaDex in a December 2025 agreement, the scope of the ownership rights QUB retains is unclear for the reasons discussed in Thorne's Opposition to QUB's Motion to Dismiss. *Id.* at 9-14. Moreover, the timing of the alleged assignment and Niagen's initiation of an APEX complaint a mere three months later raises questions of whether the assignment is an attempt to shield highly relevant discovery behind burdensome foreign discovery processes.

Conferral. The day after Defendants filed the present motion to strike, on September 24, 2026, Thorne contacted Defendants and explained that the motion was procedural and not substantive and thus imposed an unnecessary burden on the Court and the parties. In view of that, Thorne suggested that Defendants withdraw the motion to strike and the parties stipulate that the already-filed briefing regarding QUB's first motion to dismiss apply equally to QUB's duplicative, second motion to dismiss. Thorne further noted that the alleged procedural issue in

Defendants' motion would be mooted if Thorne amended the Complaint, and thus if Defendants did not opt to withdraw their motion, Thorne requested consent to amend the Complaint to cure any procedural issue (thereby avoiding unnecessary motion practice). Exhibit C at 2-3.

Defendants responded five days later and refused to withdraw their motion or consent to amendment of the Complaint. *Id.* at 1. Thorne, therefore, has no choice other than to file the present opposition and alternative motion for leave to amend its Complaint.

III. LEGAL STANDARD

A. Rule 12(f)

Under Federal Rule of Civil Procedure 12(f), a court has discretion to “strike from a pleading an insufficient defense or any redundant, immaterial, impertinent, or scandalous matter.” The Fourth Circuit views Rule 12(f) motions with disfavor “because striking a portion of a pleading is a drastic remedy and because it is often sought by the movant simply as a dilatory tactic.” *Melvin v. Soc. Sec. Admin.*, 126 F. Supp. 3d 584, 596 (E.D.N.C. 2015) (citation omitted). Accordingly, Rule 12(f) “imposes a sizable burden on the movant.” *United States v. Valentine*, 751 F. Supp. 3d 617, 625 (E.D.N.C. 2024) (citation omitted).

A district court should deny a request to strike unless the challenged allegations “have no possible relation to the controversy and may cause prejudice to one of the parties.” *Graff v. Prime Retail, Inc.*, 172 F. Supp. 2d 721, 731 (D. Md. 2001) (citation omitted). This Court has recognized that motions to strike are denied unless the challenged matter has “no possible relation or logical connection to the subject matter of the controversy[.]” *Gyro-Trac Corp. v. King Kong Tools, LLC*, No. 21-2137-RMG, 2022 WL 669609, at *2 (D.S.C. Mar. 4, 2022) (citation omitted). Courts “view the [portion of the] pleading under attack in a light most favorable to the pleader[.]” *Valentine*, 751 F. Supp. 3d at 625 (citation omitted; alteration in original). Generally, courts will “deny motions to strike absent some showing ‘of significant

prejudice to one or more of the parties to the action[.]” *Id.* (quoting *Bailey v. Fairfax Cnty. Va.*, No. 10-1031, 2010 WL 5300874, at *4 (E.D. Va. Dec. 21, 2010) and citing *Staley v. McDonough*, No. 22-317-LCB, 2023 WL 5021196, at *5 (M.D.N.C. Aug. 7, 2023) (“District courts do not grant Rule 12(f) motions unless the moving party shows prejudice”)).

B. Rule 15

Under Rule 15(a)(2), a party may amend its complaint with leave of the court or with the consent of the defendant, and the “court should freely give leave when justice so requires.” Fed. R. Civ. P. 15(a)(2). The Fourth Circuit has stated that “[i]t is this Circuit’s policy to liberally allow amendment[.]” *Galustian v. Peter*, 591 F.3d 724, 729 (4th Cir. 2010). “This liberal rule gives effect to the federal policy in favor of resolving cases on their merits instead of disposing of them on technicalities.” *Laber v. Harvey*, 438 F.3d 404, 426 (4th Cir. 2006). “A motion to amend should be denied ‘*only when* the amendment would be prejudicial to the opposing party, there has been bad faith on the part of the moving party, or the amendment would be futile.’” *HCMF Corp. v. Allen*, 238 F.3d 273, 276 (4th Cir. 2001) (quoting *Edwards v. City of Goldsboro*, 178 F.3d 231, 242 (4th Cir. 1999)).

IV. ARGUMENT

A. The Court Should Deny Niagen and QUB’s Motion to Strike

Thorne’s Claim Is Related to This Controversy, and Niagen and QUB Are Interested Parties to It. Niagen and QUB bring this motion under Rule 12(f) entirely on procedural technicalities in direct contradiction to “this Court’s preference for matters to be resolved on their merits rather than by technicalities or clever pleading.” *Bucklew v. Derst Baking Co., LLC*, No. 24-148-RMG, 2024 WL 4773208, at 2 (D.S.C. Sept. 9, 2024). Tellingly, Niagen and QUB never argue that Thorne’s counter-counterclaim bears no possible relation to the subject matter of this controversy or prejudices them in any way, which is required for relief under Rule 12(f).

See Graff, 172 F. Supp. 2d at 731 (Rule 12(f) motions “usually should be denied unless the allegations ‘have no possible relation to the controversy and may cause prejudice to one of the parties.’”) (citation omitted). This is because they cannot. Thorne’s claim for declaratory judgement of invalidity of the ’506 Patent turns on the very same patent and the same disputed ownership rights already before this Court. *E.g.*, D.I. 1, ¶¶ 12-23, 26 n.2; D.I. 18 at 21 (¶¶ 23-26), 27 (¶ 46); D.I. 27-1 at 3-4. Defendants’ sole objection is one of self-manufactured labeling because only ChromaDex chose to bring its counterclaim, rather than Niagen or QUB. That is not a basis to strike a claim that is indisputably related to this litigation.²

Defendants’ motion—especially in light of their refusal to cooperate with Thorne to resolve their procedural objections—reads as a dilatory tactic to avoid adjudication on the merits so that Defendants can continue to harass Thorne. Niagen and QUB have each held themselves out as an owner of the ’506 Patent and leveraged the ’506 Patent to harass Thorne. For example, Niagen identified itself as the ’506 Patent’s owner in its own Securities and Exchange Commission filings and used the patent directly against Thorne when it submitted an APEX request against Thorne regarding the ’506 Patent. D.I. 1, ¶¶ 18, 22. Niagen also continues to act in concert with ChromaDex as evidenced by Niagen offering settlement terms to Thorne less than two weeks ago that concern rights in the ’506 Patent.³ Decl. of Wendy L. Devine, ¶ 6.

² To the extent Defendants argue that Fed. R. Civ. P. 7(a) does not authorize Thorne’s counterclaim, it answers only which *type* of pleading is authorized—an answer to a counterclaim, as opposed to some other filing—not which existing parties that pleading may address. Defendants conflate the two, treating a rule about pleading format as if it also limits pleading content; that question is governed by Rules 13, 18, and 20.

³ Thorne references this fact only to show that Niagen continues to act in concert with ChromaDex as a party having interest in the ’506 Patent. *See Coakley & Williams Constr., Inc. v. Structural Concrete Equip., Inc.*, 973 F.2d 349, 353 (4th Cir. 1992) (explaining “settlement offers are only inadmissible when offered to prove liability or damages[,]” (citing Fed. R. Evid. 408(a))); *see also A123 Sys., Inc. v. Hydro-Quebec*, 626 F.3d 1213, 1217-19 (Fed. Cir. 2010). (continued...)

While only ChromaDex chose to counterclaim for infringement, Niagen, with ChromaDex, offered settlement terms to resolve this litigation that involve rights in the '506 Patent. *Id.* As Thorne explained in its Opposition to QUB's Motion to Dismiss (D.I. 33), incorporated by reference here, QUB filed and prosecuted the application that became the '506 Patent. QUB did so in 2023—well into its decade-long relationship with ChromaDex and more than two years after Thorne began selling the products that Defendants' now claim infringe their recently issued patent. QUB does not dispute that it was the owner of the '506 Patent when Chromadex sent Thorne threatening letters, dated May 13, 2025 and July 22, 2025, about the '506 Patent. QUB then retained ownership of the patent through at least December 2025.⁴ D.I. 33 at 4-5; D.I. 18 at 16-17 (¶¶ 5-6).

Resolving validity without the patent owner invites the inconsistent, multiplicitous litigation courts guard against. *A123 Sys*, 626 F.3d at 1222. Thorne cannot obtain an adequate judgment with certainty unless Niagen and QUB are bound. *See id.* at 1218-19.

Defendants' Authority is Inapposite. The case law that Niagen and QUB rely on in support of their Rule 12(f) motion is inapposite. In *Hess v. Lander University*, the plaintiff asserted no new claim, sought no leave to amend, and simply mislabeled her reply a "counterclaim." No. 04-1474, 2005 WL 8162858, at *1-2 & nn.1-2 (D.S.C. Jan. 12, 2005). Thorne, by contrast, asserted a substantive claim and has moved, in the alternative, for leave to amend. *Infra* § III.

(finding participation of the patentee was necessary to a suit of non-infringement because it had interests in the patent).

⁴ The interests QUB retains today are disputed for reasons discussed in Thorne's Opposition to QUB's Motion to Dismiss. D.I. 33 at 9-14.

Bonumose Biochem LLC v. Zhang and A.L. Williams & Assocs., Inc. v. D.R. Richardson & Assocs., Inc. are equally inapposite—both involved counterclaims against nonparty strangers who were never joined. No. 17-033, 2018 WL 6517456, at *3-4 (W.D. Va. Dec. 11, 2018); 98 F.R.D. 748, 753-54 (N.D. Ga. 1983). Niagen and QUB are not strangers; Niagen has appeared and answered, and QUB has appeared through its motion to dismiss.⁵ Thus, both have litigated this case from the start. Neither case cited by Defendants suggests that a claim against an existing party must be stricken for want of a formal Rule 19 or Rule 20 motion.

The Compulsory-Counterclaim Framework Confirms Thorne’s Claim Belongs Here.

Thorne’s claim squarely belongs in this suit in the interests of finality and *res judicata*. The Fourth Circuit’s compulsory-counterclaim framework asks whether the claim and counterclaim share the same facts and law, whether the same evidence proves both, and whether they are logically related. *Painter v. Harvey*, 863 F.2d 329, 331 (4th Cir. 1988). Critically, it also asks whether “res judicata bar[s] a subsequent suit” (*id.*), which includes having the same “identity of parties or their privies[.]” *Nash Cnty. Bd. of Ed. v. Biltmore Co.*, 640 F.2d 484, 486-87 (4th Cir. 1981)); *see also Brunenkant v. Pub. Storage Operating Co.*, No. 24-2375, 2025 WL 2959610, at *3-5 (D. Md. Oct. 20, 2025) (denying defendants’ motion to strike plaintiff’s counterclaim-in-reply under the four-factor test). Thorne’s claim of invalidity and ChromaDex’s counterclaim of infringement both turn on the scope of the claims, prosecution, and ownership of the ’506 Patent and will be proved through substantially the same evidence. But, at least presently, Thorne cannot be sure that Niagen and QUB’s interests are “so identified in interest with [ChromaDex]” such that ChromaDex “represents precisely the same legal right[s]” as Niagen and QUB for the

⁵ QUB cannot simultaneously litigate a jurisdictional motion before this Court and claim to be a procedural non-entity for joinder purposes.

purposes of *res judicata*.⁶ *Nash Cnty. Bd. of Ed.*, 640 F.2d at 493. Therefore, Thorne cannot have certainty that it will not “fac[e] multiple lawsuits on the same patent[]” without Niagen and QUB as parties to its invalidity claim. *TexasLDPC Inc. v. Broadcom Inc.*, No. 25-1074, 2026 WL 2683031, at *7 (Fed. Cir. Sept. 14, 2026) (citation omitted).

Defendants’ Joinder Arguments Are Improper. Defendants invoke joinder of parties through Rule 13(h). D.I. 41 at 4. However, Rule 13(h) does not apply in this case because it governs the addition of persons who are ***strangers*** to the action. *See* 6 Fed. Prac. & Proc. Civ. § 1435 (3d ed.) (“[A] person who already is a party to the action cannot be made an additional party under Rule 13(h).”). Thus, Defendants invoke the wrong rule entirely: a joinder-of-new-parties rule cannot be violated by pleading a claim against an entity that is already a party to the case. To the extent Defendants continue to advance misjoinder theories, the Fourth Circuit has resolved joinder disputes through Rule 15. *See Galustian*, 591 F.3d at 730 (explaining Rule 15(a) applies to amendments that add parties); *see, e.g., TELECO, Inc. v. Mutolo*, No. 23-3563-DCC, 2025 WL 3280842, at *7-8 (D.S.C. Nov. 25, 2025) (analyzing joinder disputes under the Rule 15 standard).

Even if the Court were to credit Niagen and QUB’s premise that they should have been brought into the counterclaim through a Rule 13(h) motion rather than named directly, the remedy they seek—striking or dismissing Thorne’s claim outright—is not available. Rule 21

⁶ It is well established as a matter of Federal Circuit law that a counterclaim of patent infringement is compulsory to a declaratory judgment seeking noninfringement of the same patent and product at issue. *Capo, Inc. v. Dioptics Med. Prods., Inc.*, 387 F.3d 1352, 1356 (Fed. Cir. 2004); *see also Polymer Indus. Prods. Co. v. Bridgestone/Firestone, Inc.*, 347 F.3d 935, 939-40 (Fed. Cir. 2003) (explaining a party who fails to bring such compulsory counterclaim cannot avoid its waiver by relying on the “further relief” provision of 28 U.S.C.A. § 2202). To the extent the Court finds Niagen is not an opposing party because it did not counterclaim for infringement, Thorne respectfully requests that Niagen be held to that position as a party who has waived all present and future claims of infringement against Thorne relating to the ’506 Patent.

provides that “[m]isjoinder of parties is not a ground for dismissing an action”; instead, the Court may, “on just terms,” correct any joinder defect directly. Fed. R. Civ. P. 21. Because Niagen and QUB must be bound by any judgment on the ’506 Patent’s validity, the sensible exercise of the Court’s Rule 21 authority on these facts is to add Niagen and QUB as parties, not drop them—precisely the outcome Thorne’s claim already achieves.

Striking the claims, in any event, would serve no purpose but delay: Niagen and QUB must ultimately be bound by any validity judgment, and the Court can resolve all related claims in one pleading by letting the claim proceed, or, in the alternative, granting leave to amend. *See infra* § III; Fed. R. Civ. P. 1 (directing that the Rules secure the “just, speedy, and inexpensive determination of every action[.]”).

B. The Court Should Deny QUB’s Second Motion to Dismiss for the Same Reasons Briefed in Thorne’s Opposition to QUB’s First Motion to Dismiss

QUB asks this Court to dismiss Thorne’s claim for declaratory judgement of invalidity of the ’506 Patent for the “same reasons” it already sets forth in its first motion. D.I. 41 at 5-6. Asking this Court to resolve the same jurisdictional question twice, on two briefs directed at two pleadings, is duplicative, burdens this Court, and is contrary to the “just, speedy, and inexpensive determination of every action[.]” Fed. R. Civ. P. 1. Nonetheless, since QUB refused to stipulate that the briefing on the first motion is applicable to the duplicative, second motion, Thorne addresses it here. Thorne opposes QUB’s second motion for the same reasons set forth in its Opposition to QUB’s first motion (D.I. 33), which Thorne incorporates by reference.

In short, QUB once again asks this Court to rely on its unilateral representation of a redacted agreement that does not show QUB has assigned away all of its interest in the ’506 Patent. D.I. 41 at 5-6. However, the Court must examine the substance of the agreement itself to determine whether QUB retains interests in the ’506 Patent sufficient to make out a controversy

between QUB and Thorne. D.I. 33 at 9, 12-13. The Court must also afford additional discovery since the jurisdictional challenge is intertwined with the question of who owned which rights to the '506 Patent, and when, bearing directly on the merits of this case. *Id.* at 12-14; *see Kerns v. United States*, 585 F.3d 187, 193 (4th Cir. 2009). At a minimum, QUB's second motion should also be denied as premature since QUB has not provided any additional basis to support its "absolute" assignment of all interests in the '506 Patent.

C. (In the Alternative) The Court Should Grant Thorne Leave to Amend its Complaint

To the extent the Court is not inclined to wade through the procedural morass of the counterclaim dispute, the Court can still reach the merits of the claims because the only potential barrier is a curable pleading deficiency resolved by granting leave to amend the Complaint. Thorne timely moves to amend its Complaint as the deadline to amend the pleadings even under the fastest proposed schedule is November 12, 2026, under the Scheduling Order. *See* D.I. 19 at 2; *see also Davis v. Piper Aircraft Corp.*, 615 F.2d 606, 613 (4th Cir. 1980) (explaining delay alone is an insufficient basis for denial); *c.f. State Farm Mut. Auto. Ins. Co. v. Wierenga*, No. 23-4633-RMG, 2025 WL 4230467 (D.S.C. May 12, 2025) (granting leave to amend counterclaim for good cause even after deadline). This Court has granted leave to amend under similar circumstances. *See 25 Calhoun CMB, LLC v. Concord Park/Charleston, LLC*, No. 19-2537-RMG, 2020 WL 2489081, at *1 n.1 (D.S.C. May 14, 2020) (granting leave to amend where plaintiff moved to amend before the scheduling order deadline). Further, Thorne sought to avoid all prejudice, conserve judicial resources, and minimize cost to all litigants by immediately reaching out to Defendants after the motion to strike was filed, seeking consent to amend the Complaint. When Defendants refused, Thorne promptly filed this Motion. *Supra* § II.

The Court should grant leave to amend because the amendment (1) is not prejudicial to defendants, (2) is sought in good faith, and (3) amendment would not be futile. *Sisk v. Abbott Lab's*, No. 11-cv-159, 2011 WL 13214075, at *1 (W.D.N.C. Aug. 19, 2011) (citation omitted).

No Prejudice. Amendment will not prejudice Defendants because Niagen and QUB are existing parties, discovery is in its very early stages, and the proposed amended complaint does not add new facts to this case. Regardless of the procedural technicalities, all three defendants have an interest in the '506 Patent, and all three defendants have engaged in a harassment campaign against Thorne, which forms the basis of Thorne's initial claim for non-infringement and its proposed amended claim of invalidity. In determining whether an amendment is prejudicial to the opposing party, courts evaluate the nature and the timing of the amendment. *Laber*, 438 F.3d at 427. While delay alone is insufficient to deny a motion to amend, courts are more likely to find proposed amendments prejudicial to opposing parties in cases that have progressed closer towards judgment. *Id.*

Thorne's proposed amendment adds only a cause of action seeking declaratory judgment for invalidity arising out of the same occurrence as its initial declaratory judgment claim for non-infringement. Thorne's causes of action are all based on the same allegations that Niagen and QUB acted in concert with ChromaDex to harass Thorne related to their asserted ownership of the '506 Patent and their targeting of Thorne's NR Products. Niagen and QUB cannot claim prejudice due to lack of notice when they were made "fully aware of the events giving rise to the action" at the outset of this case. *See Davis*, 615 F.2d at 613. Thorne's amendment will not implicate any additional facts because it mirrors the counter-counterclaim that Thorne filed, and, as such, in no way prejudices the preparation of their case. *Id.* Further, this does not amount to prejudice because Thorne has sought leave to amend with ample time and there is no specter of

eve-of-trial unfairness. *Bucklew*, 2024 WL 4773208 at *2 (granting leave to amend due to early stage of litigation and lack of real prejudice to defendants).

No Bad faith. Niagen and QUB cannot claim bad faith because there is no “obvious design by dilatoriness to harass[.]” *Davis*, 615 F.2d at 613. Typically, courts deny amendments as bad faith if they have no legitimate purpose other than delay or are brought with the intent was to gain an “ulterior tactical advantage.” *Earp v. Fed. Express Corp.*, No. 25-52, 2026 WL 945735, at *2 (N.D.W.Va. Apr. 7, 2026) (citation omitted). As explained above, when ChromaDex initiated its infringement counterclaim, Thorne was required to bring its claim that the patent is invalid. *Supra* § IV(A). Thorne promptly filed its counter-counterclaim that put all defendants on notice that Thorne sought a declaratory judgment of invalidity. Both Niagen and QUB have held themselves out, at the very least, as owners of the ’506 Patent, at various times. When Defendants raised procedural concerns regarding the scope of Thorne’s counter-counterclaim, Thorne offered to amend the Complaint to address those concerns. Because Defendants have flatly refused to cooperate, Thorne now seeks leave of court under Rule 15.

No Futility. Thorne’s declaratory judgment claim for invalidity of the ’506 Patent is meritorious, so Defendants cannot impede amendment based on futility. *Davis*, 615 F.2d at 613. A court should only deny an amendment due to futility “when the proposed amendment is clearly insufficient or frivolous on its face.” *Johnson v. Oroweat Foods Co.*, 785 F.2d 503, 510 (4th Cir. 1986). To state a claim for patent invalidity, a party must show the patent fails to meet one or more conditions or requirements of patentability set forth in Title 35 of the U.S. Code. *See Automated Merch. Sys., Inc. v. Crane Co.*, No. 03-88, 2012 WL 12892415, at *2 (N.D.W. Va. Mar. 1, 2012).

Thorne's pleading is sufficient to allege invalidity because it details the statutory deficiencies of the '506 Patent. D.I. 30 at 23-29 (¶¶ 17-59). *Hand Held Prods., Inc. v. Code Corp.*, No. 17-167-RMG, 2017 WL 2537235, at *2-4 (D.S.C. June 9, 2017) (denying dismissal of invalidity counterclaim because the answer "provides ample factual support"). Thorne's invalidity claim arises from the same harassment campaign by Defendants against Thorne that is described in the original Complaint, and Thorne seeks leave to amend its Complaint only to plead minor additional supporting facts related to its invalidity contentions—facts that mirror its current counter-counterclaim. *See 25 Calhoun CMB*, 2020 WL 2489081 at *3 (finding no prejudice where there was proper basis for the additional claims that related to the same transaction as the original claims).

Accordingly, Defendants have no basis to argue amendment is improper and the Court has no barrier to furthering the "goal of providing a just, speedy, and inexpensive determination of every action and this Court's preference for matters to be resolved on their merits rather than by technicalities or clever pleading." *Bucklew*, 2024 WL 4773208 at *2 (internal quotations omitted).

V. CONCLUSION

For the foregoing reasons, Thorne respectfully requests that the Court deny Defendants' Motion to Strike or, in the Alternative, grant Thorne's Motion to Amend and grant leave to file their proposed Amended Complaint.

Dated: October 7, 2026

Respectfully submitted,

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*Attorneys for Plaintiffs Thorne Research, Inc.
and Thorne HealthTech, Inc.*

CERTIFICATE OF SERVICE

I hereby certify that on October 7, 2026, a true and correct copy of the foregoing was electronically filed and served upon all attorneys of record in this case via the Court's CM/ECF system.

/s/Addie K. S. Ries

Addie K. S. Ries

EXHIBIT A

from the marketplace, made allegations of patent infringement, and filed a complaint through Amazon's Patent Evaluation Express ("APEX") procedure seeking removal of Thorne's product listings. Defendants' allegations are without merit. Thorne brings this action to obtain a judicial declaration that its products do not infringe any valid and enforceable claim of the '506 Patent.

THE PARTIES

3. Thorne Research is a South Carolina corporation with its principal place of business at 620 Omni Industrial Blvd., Summerville, South Carolina 29486.

4. Thorne HealthTech is a Delaware corporation with its principal place of business at 620 Omni Industrial Blvd., Summerville, South Carolina 29486. Thorne Research is a wholly owned subsidiary of Thorne HealthTech.

5. Founded in 1984, Thorne is a science-driven wellness company developing innovative solutions for a personalized approach to health and wellness. Thorne seeks to bring the scientific rigor of biopharmaceuticals to the prevention space to help people live longer, healthier lives. Thorne offers unique, vertically-integrated brands to provide personalized data, products and services that empower individuals to take a proactive approach to improve and maintain their health over their lifetime. By combining its proprietary multi-omics database, artificial intelligence and digital health content with its science-backed nutritional supplements, Thorne delivers a total system for wellness. Thorne has spent millions of dollars researching and developing novel products to improve the health and wellness of people.

6. On information and belief, Niagen is a Delaware corporation with its principal place of business at 10900 Wilshire Boulevard, Suite 600, Los Angeles, California 90024.

7. On information and belief, ChromaDex is a California corporation with its principal place of business at 10900 Wilshire Boulevard, Suite 600, Los Angeles, California 90024. On information and belief, ChromaDex is a wholly owned subsidiary of Niagen.

8. On information and belief, the University of Belfast is a public research university in Belfast, Northern Ireland, United Kingdom, whose address is University Road, Belfast BT7 1NN, United Kingdom.

BACKGROUND

9. On information and belief, Defendants' baseless allegations that the Thorne NR Products infringe the '506 Patent are a continuation of Defendants' harassment of Thorne that spans several years.

A. Defendants' Unsuccessful Prior Attacks on Thorne

10. In prior litigation, ChromaDex accused Thorne of infringing U.S. Pat. Nos. 8,197,807 (the "'807 Patent") and 8,383,086 (the "'086 Patent")—patents it licensed from Dartmouth College. Like the '506 Patent, the '807 and '086 Patents are directed to compositions of nicotinamide riboside ("NR"). *ChromaDex, Inc. v. Thorne Rsch., Inc.*, No. 1:21-cv-04241-ER (S.D.N.Y.) (hereinafter, "Failed ChromaDex Litigation"). Now, ChromaDex—in concert with the other Defendants—is attacking one of the same Thorne products (NiaCel[®] 400) that it attacked in the Failed ChromaDex Litigation. *ChromaDex, Inc., et al. v. Thorne Rsch., Inc.*, No. 1:21-cv-04241-ER, D.I. 1, ¶ 13 (S.D.N.Y. May 12, 2021).

11. The Failed ChromaDex Litigation ended because both of ChromaDex's patents were invalidated. The relevant claims of the '086 Patent were found unpatentable by the Patent Trial and Appeal Board, and a District Court (affirmed by the Federal Circuit Court of Appeals) found the relevant claims of the '807 Patent invalid.¹ *Thorne Rsch., Inc. v. Trustees of Dartmouth College*, IPR2021-00268, Paper No. 63 at 41 (PTAB May 31, 2022); *ChromaDex, Inc. v. Elysium*

¹ ChromaDex asserted the '807 Patent against another competitor in a separate action. *ChromaDex, Inc. v. Elysium Health, Inc.*, C.A. No. 18-1434-CFC-JLH (D. Del.).

Health, Inc., 59 F.4th 1280, 1286 (Fed. Cir. 2023). In view of that invalidation, the litigation against Thorne was dismissed. *ChromaDex, Inc., et al. v. Thorne Rsch., Inc.*, No. 1:21-cv-04241-ER, D.I. 31 (S.D.N.Y. Jan. 4, 2024).

B. The '506 Patent

12. The '506 Patent is entitled “Methods of Preparing Nicotinamide Riboside and Derivates Thereof,” and was issued by the United States Patent and Trademark Office (“USPTO”) on March 18, 2025. A true and correct copy of the '506 Patent is attached hereto as Exhibit 1.

13. The University of Belfast, Niagen, and ChromaDex have each held themselves out to be the owner of the '506 Patent.

14. On its face, the '506 Patent is assigned to the University of Belfast.

15. The USPTO Assignment Database indicates that the '506 Patent is assigned to the University of Belfast. Ex. 2.

16. In a signed exhibit to Amazon’s APEX Agreement, Defendants asserted “ChromaDex, Inc. is the owner of the ['506] patent pursuant to an assignment from The Queens Belfast (Great Britain) dated December 16, 2025.” Ex. 3 (the “APEX Agreement”) at 2.

17. That APEX Agreement is signed by “Carlos Lopez, SVP, General Counsel, ChromaDex, Inc.” *Id.*

18. That APEX Agreement states that Carlos Lopez’s email address is carlos.lopez@niagenbio.com. *Id.*

19. On its face, the website niagenbio.com concerns Defendant Niagen, not Defendant ChromaDex.

20. Niagen has publicly stated that it is the assignee and owner of the '506 Patent.

21. For example, on December 22, 2025, Niagen stated in a press release that Niagen

had “acquired a comprehensive portfolio of existing patents covering nicotinamide riboside (NR) and its salt forms from Queen’s University Belfast[.]” Ex. 4 at 1. The press release also stated “[t]his 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[.]” *Id.* at 1-2.

22. Niagen’s 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[.]” Ex. 5 at 9-10.

23. On information and belief, the University of Belfast, Niagen, and ChromaDex are operating in concert to threaten Thorne with enforcement of the ’506 Patent.

C. ChromaDex’s Cease and Desist Letters to Thorne

24. On September 20, 2024, ChromaDex sent a letter to Thorne asserting that “Thorne’s use of NR Malate in its nutritional supplement products infringes upon the rights of ChromaDex[.]” including certain claims of U.S. Pat. No. 11,242,364 (the “’364 Patent”).

25. Thorne responded on October 25, 2024, stating that “Thorne’s use of NR Malate in its products does not fall within the scope of any of the claims of the ’364 patent.”

26. On May 13, 2025, ChromaDex sent Thorne another letter seeking details of the confidential manufacturing process for the NR Malate in Thorne’s products. In this letter, ChromaDex further stated that it was “provid[ing] Thorne notice of the recent issuance of [the ’506 Patent][,]” that “ChromaDex holds exclusive rights to the ’506 [sic] Patent[.]”² and “request[ed] that Thorne reconsider discussing . . . cooperation between the two companies.”

² Niagen announced it had acquired the ’506 Patent seven months later. *Supra*, ¶ 21.

27. Thorne responded on July 17, 2025, stating that ChromaDex's "notice" of the '506 Patent was without context, and requesting further explanation if ChromaDex sought a response.

28. On July 22, 2025, ChromaDex sent Thorne another letter alleging that its prior "notice" of the '506 Patent was instead a cease and desist demand. Specifically, ChromaDex stated:

We informed you that claims 1 and 26 of the '506 [sic] patent claim the NR malate compound. You had previously acknowledged that Thorne sells products containing NR malate (for example, its Niacel product), and understand that 35 U.S.C. §271(a) prohibits, inter alia, the sale of any patented invention during the term of the patent. That the sale of Niacel and any other Thorne product containing NR malate infringes the '506 patent is a tautology.

[...]

It remains ChromaDex's preference that the parties directly discuss an amicable resolution to this matter. If Thorne declines this invitation, we ask that it . . . confirm that it will cease all sales of Niacel and any other product containing NR malate (including sales by partners such as the Mayo Clinic, which we observe is selling the Niacel product on its website) and destroy all existing NR malate product and inventory in its possession or control.

29. ChromaDex did not further communicate with Thorne regarding the '506 Patent after the July 22, 2025 letter.

D. Defendants Initiate an APEX Evaluation Against Thorne

30. Amazon.com, Inc. ("Amazon") offers the APEX procedure "[t]o efficiently resolve claims that third-party product listings [on Amazon] infringe utility patents[.]" Ex. 6 at 1.

31. An APEX evaluation is initiated when a U.S. utility patent owner submits an APEX agreement to Amazon identifying a patent and Amazon Standard Identification Number ("ASIN") of the products sold by third parties on Amazon that the patent owner alleges infringe the patent. Ex. 3 at 1, 2. Amazon then sends the patent owner-completed APEX agreement to the product seller and provides three options to continue selling the accused products on Amazon: (1) resolve the claim with the patent owner directly; (2) show that the product seller and patent owner are

already in patent litigation, or that the product seller filed a declaratory judgment claim for noninfringement of the patent; or (3) opt in to the APEX evaluation by executing and returning the APEX agreement. Ex. 7 at 1. If the product seller does not respond consistent with one of these three options within three weeks, the listings for the products identified by the patent owner are removed from Amazon. *Id.*

32. On information and belief, when an APEX agreement is submitted to Amazon, Amazon does not take any steps to confirm the submitter is the patent owner.

33. On information and belief, an infringement complaint on Amazon—such as initiation of an APEX evaluation—negatively impacts the “health score” of seller accounts. *E.g.*, Ex. 8 at 2-4, 6. On information and belief, there is a direct correlation between said “health score” and seller revenue, for example, by impacting search visibility (a lower health score leads to lower search visibility, meaning fewer sales). *E.g.*, Ex. 9 at 3-5.

34. Thorne has a contractual relationship with Pattern Inc. (“Pattern”) relating to the sale of its products on Amazon.

35. On April 10, 2026—after almost nine months of silence from ChromaDex—Pattern received notice that ChromaDex initiated an APEX evaluation regarding Thorne’s products. Ex. 7. Pattern sent that notice to Thorne. The notice stated that ChromaDex claimed that ten ASINs sold on Amazon infringed the ’506 Patent. Ex. 3 at 2. Three of the ASINs were associated with Thorne products. Ex. 7 at 1.

E. Thorne’s NR Products

36. The April 10, 2026 APEX Notice Email identified three Thorne products which include nicotinamide riboside: (1) ResveraCel® (ASIN B097Z5387H); (2) SynaQuell® (ASIN B0B14F9PSR); and (3) NiaCel® 400 (ASIN B08WPXPTD8). *Id.* at 1. Each of these Thorne

products is manufactured and sold from Thorne's facilities in South Carolina.

37. ResveraCel® is a dietary supplement designed to promote healthy aging, support cellular metabolism, and enhance NAD⁺ production to boost cellular energy and metabolism.

38. SynaQuell® is a brain health supplement designed to enhance cellular energy production and promote a healthy balance of inflammatory cytokines, particularly for individuals involved in contact sports.

39. NiaCel® 400 is a dietary supplement containing nicotinamide riboside and betaine anhydrous to support healthy aging and optimize vitality.

40. Thorne sells ResveraCel®, SynaQuell®, and NiaCel® 400 direct to consumers on its website, www.thorne.com. Thorne has a contractual relationship with Pattern relating to the sale of these products on Amazon.

41. Thorne sells additional products containing nicotinamide riboside that are not the subject of Defendants' APEX notice. Together with ResveraCel®, SynaQuell®, and NiaCel® 400, all Thorne products that contain nicotinamide riboside malate are the "Thorne NR Products."

JURISDICTION, VENUE, AND JOINDER

42. Thorne incorporates by reference the preceding paragraphs as if fully set forth herein.

43. This Court has subject matter jurisdiction over Thorne's claims pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202, as well as the patent laws of the United States, 35 U.S.C. § 1, *et seq.*

44. This Court has supplemental jurisdiction over Thorne's claims arising under the laws of South Carolina pursuant to 28 U.S.C. § 1367 because Thorne's state law claims are so related to Thorne's federal law claims such that they form part of the same case or controversy and derive from a common nucleus of operative facts.

45. This Court has personal jurisdiction over Niagen because it purposefully directed enforcement activities relating to the '506 Patent to Thorne Research in South Carolina in an improper attempt to block sales of Thorne's products from South Carolina. Thorne Research is a South Carolina entity with headquarters and manufacturing facilities in Summerville, South Carolina, who markets and sells the Thorne NR Products in and from South Carolina. Niagen purposefully acted in concert with ChromaDex and the University of Belfast to direct communications at Thorne levying threats to enforce the '506 Patent—a patent Niagen asserts that it owns—against Thorne and acted in concert with ChromaDex to initiate the APEX evaluation attacking Thorne's ResveraCel[®], SynaQuell[®], and NiaCel[®] 400 products alleging infringement of the '506 Patent. Venue is proper for Niagen in this District pursuant to 28 U.S.C. § 1391 for the same reason.

46. This Court has personal jurisdiction over ChromaDex because it purposefully directed enforcement activities relating to the '506 Patent to Thorne Research in South Carolina in an improper attempt to block sales of Thorne's products from South Carolina. Thorne Research is a South Carolina entity with headquarters and manufacturing facilities in Summerville, South Carolina, who markets and sells the Thorne NR Products in and from South Carolina. ChromaDex purposefully acted in concert with Niagen and the University of Belfast to direct communications at Thorne levying threats to enforce the '506 Patent—a patent ChromaDex also asserts that it owns—against Thorne and initiate the APEX evaluation attacking Thorne's ResveraCel[®], SynaQuell[®], and NiaCel[®] 400 products based on the patent. Venue is proper for ChromaDex in this District pursuant to 28 U.S.C. § 1391 for the same reason.

47. This Court has personal jurisdiction over the University of Belfast under Fed. R. Civ. P. 4(k)(2). This is because: (a) the claims in this action arise under federal law; (b) the

University of Belfast is not subject to the jurisdiction to any state's courts of general jurisdiction; and (c) exercising jurisdiction over the University of Belfast is consistent with the U.S. Constitution. This Court also has personal jurisdiction over the University of Belfast because it purposefully directed enforcement activities relating to the '506 Patent to Thorne Research in South Carolina in an improper attempt to block sales of Thorne's products from South Carolina. Thorne Research is a South Carolina entity with headquarters and manufacturing facilities in Summerville, South Carolina, who markets and sells the Thorne NR Products in and from South Carolina. On information and belief, the University of Belfast purposefully acted in concert with Niagen and ChromaDex to direct communications at Thorne levying threats to enforce the '506 Patent—a patent assigned on its face and in the USPTO Assignment Database to the University of Belfast—against Thorne and acted in concert with ChromaDex to initiate the APEX evaluation attacking Thorne's ResveraCel[®], SynaQuell[®], and NiaCel[®] 400 products based on the '506 Patent. Venue is proper for the University of Belfast in this District pursuant to 28 U.S.C. § 1391 for the same reason. Venue is also proper for the University of Belfast in this District pursuant to 28 U.S.C. § 1391(c)(3) because the University of Belfast is a foreign entity and may be sued in any judicial district.

48. Joinder of the Defendants is proper pursuant to Rules 19 and/or 20 of the Federal Rules of Civil Procedure and 35 U.S.C. § 299 because the conduct alleged herein raises an immediate, real, substantial, and justiciable controversy between Thorne and Defendants as to whether Thorne is infringing or has infringed the '506 Patent and whether the '506 Patent is invalid, arises out of the same transaction, occurrence, or series of transactions or occurrences relating to enforcement of the '506 Patent against Thorne, and poses questions of fact common to all Defendants.

CLAIMS FOR RELIEF

COUNT I: Declaratory Judgment of Noninfringement

49. Thorne incorporates by reference the preceding paragraphs as if fully set forth herein.

50. On information and belief, the '506 Patent is owned by one or more of the Defendants.

51. Defendants have asserted that the Thorne NR Products infringe the '506 Patent, both in cease and desist letters and in initiating an APEX evaluation.

52. The Thorne NR Products do not infringe, directly or indirectly, any valid and enforceable claim of the '506 Patent.

53. Each and every claim of the '506 Patent requires “[a] compound of formula (IV)” or “[a] method of making an isomerically pure compound of formula (IV).” Ex. 1 at Claims. The specification definition of formula (IV) requires that R₆, R₇, and R₈ must be “each independently a hydroxyl-protecting group.” *Id.* at 7:14-15, 8:16-30 (compound of formula (IV) defining R₁–R₈ “as defined above”, and wherein R₆, R₇, and R₈ “are each independently a hydroxyl-protecting group”). The Thorne NR Products do not contain a compound of formula IV where each of R₆, R₇, and R₈ are a hydroxyl-protecting group. Therefore, the Thorne NR Products, and the method of making them, do not infringe any claim of the '506 Patent.

54. An actual, substantial, and continuing controversy exists between Thorne and the Defendants with respect to whether Thorne infringes any valid and enforceable claim of the '506 Patent, warranting the issuance of a declaratory judgment of noninfringement.

55. Thorne seeks a declaration that it does not infringe any valid and enforceable claim of the '506 Patent. Without a declaratory judgment of noninfringement, Thorne has and will continue to suffer uncertainty and unquantifiable financial and business risks because of

Defendants' allegations that the Thorne NR Products infringe the '506 Patent.

COUNT II: Tortious Interference with a Contract

56. Thorne incorporates by reference the preceding paragraphs as if fully set forth herein.

57. Defendants have engaged in tortious interference with a contract in violation of the common law.

58. Specifically, Thorne has contractual relationships with Pattern to distribute the Thorne NR Products sold on Amazon. On information and belief, Defendants each knew, or should have known, about Thorne's contractual relationship with Pattern. On information and belief, Defendants acted in concert to improperly allege infringement of the '506 patent and initiate the APEX evaluation, which was designed to cause a breach of the contract between Pattern and Thorne, without justification.

59. Defendants have caused, and will continue to cause, immediate and irreparable injury to Thorne, including injury to its business, reputation, and goodwill, for which there is no adequate remedy at law. Therefore, Thorne is entitled to an injunction restraining Defendants from engaging in any further acts and requiring Defendants to withdraw the meritless APEX evaluation.

60. Thorne is entitled to the damages it incurred as a result of Defendants' tortious interference with Thorne's contract with Pattern including, but not limited to, the attorney and filing fees incurred in filing this suit to respond to Defendants' meritless APEX evaluation. Thorne also seeks punitive damages for Defendants' tortious interference with Thorne's contract with Pattern.

COUNT III: Intentional Interference with Prospective Contractual Relations

61. Thorne incorporates by reference the preceding paragraphs as if fully set forth herein.

62. Defendants have engaged in tortious interference with prospective contractual relations in violation of the common law.

63. Specifically, Thorne has economic relationships with Amazon, Pattern, and end-user consumers with respect to the sale of the Thorne NR Products, as described herein. These relationships provided Thorne with the probability of future economic benefit and reasonable expectation of prospective contracts for sales of the Thorne NR Products. Defendants, working in concert through ChromaDex, improperly initiated an APEX evaluation, alleging ResveraCel®, SynaQuell®, and NiaCel® 400 infringe the '506 Patent. Defendants did so for the improper purpose of harming Thorne's sales.

64. By initiating an improper, meritless APEX evaluation against the ResveraCel®, SynaQuell®, and NiaCel® 400 products, Defendants intentionally interfered with Thorne's potential future contracts regarding the Thorne NR Products with Amazon, Pattern, and end-user consumers, causing injury to Thorne. On information and belief, Defendants also negatively impacted Thorne's Amazon account health rating, lowering, among other things, the search visibility of Thorne's products on Amazon, thereby interfering with said future economic benefits, causing injury to Thorne in the form of lost sales.

65. Thorne also has economic relationships with authorized resellers and end-user consumers (who purchase directly from thorne.com) with respect to the sale of the Thorne NR Products. These relationships provided Thorne with the probability of future economic benefit in the form of prospective contracts for sales of the Thorne NR Products. Defendants improperly initiated an APEX evaluation, alleging ResveraCel®, SynaQuell®, and NiaCel® 400 infringe the '506 Patent. Defendants did so for the improper purpose of harming Thorne's sales.

66. By initiating an improper, meritless APEX evaluation against the ResveraCel®,

SynaQuell®, and NiaCel® 400 products, Defendants intentionally interfered with Thorne's potential future contracts regarding the Thorne NR Products with authorized resellers and end-user consumers (who purchase directly from thorne.com), causing injury to Thorne.

67. Defendants have caused, and will continue to cause, immediate and irreparable injury to Thorne, including injury to its business, reputation, and goodwill, for which there is no adequate remedy at law. Therefore, Thorne is entitled to an injunction restraining Defendants from engaging in any further acts and requiring Defendants to withdraw the meritless APEX evaluation.

68. Thorne is entitled to the damages it incurred as a result of Defendants' intentional interference with Thorne's prospective contractual relations with Amazon, Pattern, authorized resellers, and end-user consumers including, but not limited to, the attorney and filing fees incurred in filing this suit to respond to Defendants' meritless APEX evaluation. Thorne also seeks punitive damages for Defendants' intentional interference with Thorne's prospective contractual relations with Amazon, Pattern, authorized resellers, and end-user consumers.

COUNT IV: Unfair Competition (S.C. Code § 39-5-10)

69. Thorne incorporates by reference the preceding paragraphs as if fully set forth herein.

70. Defendants have engaged in unfair competition in violation of the South Carolina Unfair Trade Practices Act (S.C. Code § 39-5-10, *et seq.*) ("SCUTPA").

71. Defendants, working in concert, engaged in an unfair act in the conduct of trade or commerce to initiate an unfounded APEX evaluation targeting Thorne's ResveraCel®, SynaQuell®, and NiaCel® 400 products for the improper reason of harming Thorne's existing and potential business relations, and sales. Initiating a meritless APEX evaluation impacts the public interest, for example, as it improperly restrains and impedes legitimate marketplace competition. Thorne suffered monetary loss in the form of attorney and filing fees related to the institution of

this action, as well as potential lost sales as a result of Defendants' baseless APEX evaluation, as discussed herein.

72. Defendants knew, or in the exercise of reasonable care should have known, that their actions were in violation of SCUTPA, but willfully proceeded with the meritless APEX evaluation. Thorne is therefore entitled to recover treble damages.

73. Defendants have caused, and will continue to cause, immediate and irreparable injury to Thorne, including injury to its business, reputation, and goodwill, for which there is no adequate remedy at law. Therefore, Thorne is entitled to an injunction restraining Defendants from engaging in any further acts and requiring Defendants to withdraw the meritless APEX evaluation. Such an injunction would be in the public interest.

COUNT V: Declaratory Judgment of Invalidity

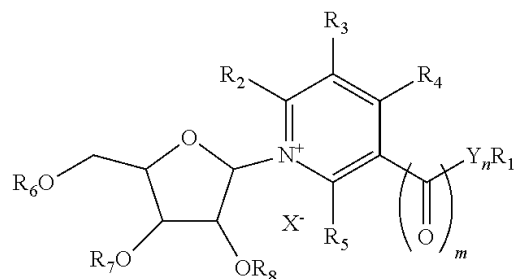
74. Thorne incorporates by reference the preceding paragraphs as if fully set forth herein.

75. The claims of the '506 Patent are invalid because they fail to meet one or more conditions of patentability set forth in Title 35 of the U.S. Code, including, but not limited to, 35 U.S.C. §§ 101, 102, 103, and/or 112.

76. Nicotinamide riboside is an oral supplement that is a precursor for nicotinamide adenine dinucleotide (NAD⁺), a vitamin B3 derivative produced naturally by the body.

77. The title of the '506 Patent is "Methods of Preparing Nicotinamide Riboside and Derivatives Thereof[.]"

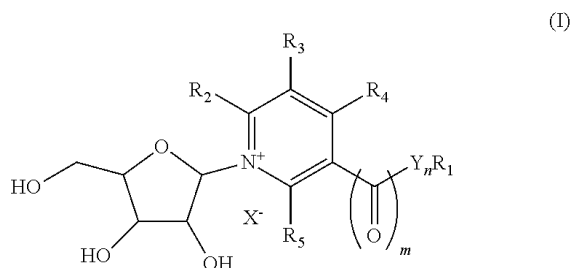
78. Independent claim 1 of the '506 Patent recites "[a] compound of formula (IV)" having the following structure:



79. Independent claim 1 of the '506 Patent recites 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[.]”

80. Asserted claims 2, 3, 10-12, and 26 depend from claim 1 and thus, recite each and every element of claim 1.

81. The specification of the '506 Patent describes a method of preparing nicotinamide riboside (“NR⁺”) salts of formula (I):

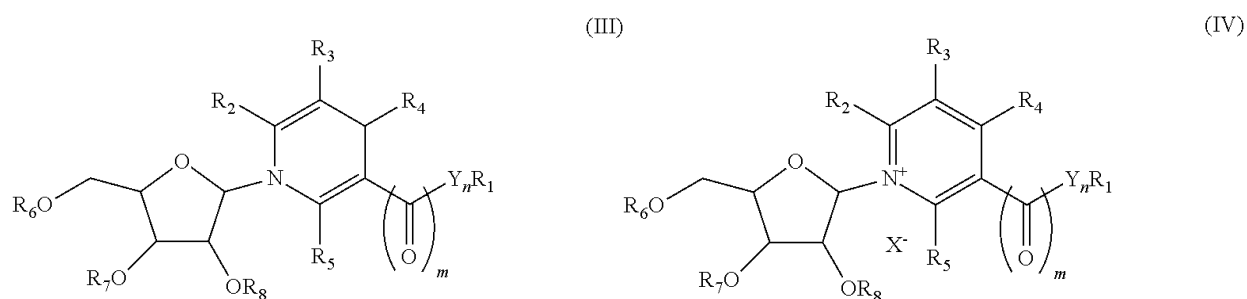


82. The specification of the '506 Patent states that the compound of formula (IV) is used as a precursor molecule to prepare the compound of formula (III) to produce the compound of formula (I):

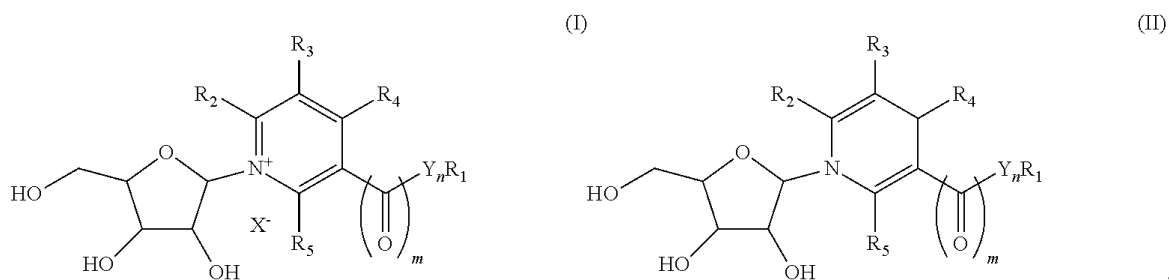
- a) “FIG. 2 depicts Scheme A, which is a scheme illustrating . . . that compounds of formula (IV) may be used to prepare compounds of formula (III), . . . ; that compounds of formula (III) may be used to prepare compounds of formula (II), . . . ; and that compounds of formula (II) may be used to prepare compounds of formula (I) . . . ” (*id.* at 12:13-20);

- b) “[T]he compound of formula (III) is prepared by reacting a compound of formula (IV)” (*id.* at 8:14-15); and
- c) “The methods for the preparation of compounds of formula (I) starting from compounds of formula (IV) are also very efficient and produce very good yields[.]” (*id.* at 10:63-65).

83. The specification of the '506 Patent states that the compounds of formula (III) and formula (IV) have R-groups R₆, R₇ and R₈:



84. The specification of the '506 Patent states that the compounds of formula (I) and formula (II) have the following structures:



85. The specification of the '506 Patent states that the compounds of formula (I) and formula (II) do not contain R-groups R₆, R₇ or R₈.

86. The specification of the '506 Patent does not state that the compound of formula (I) is an example of the compound of formula (IV).

87. The specification of the '506 Patent does not state that the compound of formula (II) is an example of the compound of formula (IV).

88. The specification of the '506 Patent describes the compound of formula (IV) as having “hydroxyl protecting groups R₆, R₇ and R₈[.]” *Id.* at 8:66-67.

89. Hydrogen is not a hydroxyl protecting group.

90. The '506 Patent does not teach or disclose that hydrogen is a hydroxyl protecting group.

91. If R₆ is a hydrogen in the compound of formula (IV), then R₆ is not a hydroxyl protecting group.

92. If R₇ is a hydrogen in the compound of formula (IV), then R₇ is not a hydroxyl protecting group.

93. If R₈ is a hydrogen in the compound of formula (IV), then R₈ is not a hydroxyl protecting group.

94. The specification of the '506 Patent states that the “hydroxyl protecting groups R₆, R₇ and R₈, are required to be lipophilic” in the compound of formula (IV). *Id.* at 8:66-67.

95. The specification of the '506 Patent states “[t]he 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.” *Id.* at 11:14-19.

96. The specification of the '506 Patent describes the compound of formula (IV) where “at least two of R₆, R₇ and R₈ comprise unsubstituted acetyl[.]” *Id.* at 8:40-44.

97. The specification of the '506 Patent exemplifies the compound of formula (IV) where “n is 0, m is 1, R₁ is NH₂, R₂-R₅ are each H, R₆-R₈ are each acetyl, and X⁻ is ⁻OTf.” *Id.* at 9:8-10.

98. The specification of the '506 Patent describes the compound of formula (IV) "in the form of the triflate salt[]" (*id.* at 10:42-44) and exemplifies: (A) "triacyetyl nicotinamide riboside, triflate (CF_3SO_3^- , also known as —OTf) salt" (*id.* at 12:64-66); (B) "triacyetyl O-ethyl nicotinate riboside, triflate (—OTf) salt" (*id.* at 13:66-67); and (C) "tribenzoyl nicotinamide riboside, triflate (—OTf) salt" (*id.* at 14:58-60).

99. The specification of the '506 Patent does not contain any working examples of the compound of formula (IV) where R_6 , R_7 or R_8 is a hydrogen.

100. The specification of the '506 Patent does not describe the compound of formula (IV) where R_6 is not a hydroxyl protecting group.

101. The specification of the '506 Patent does not describe the compound of formula (IV) where R_7 is not a hydroxyl protecting group.

102. The specification of the '506 Patent does not describe the compound of formula (IV) where R_8 is not a hydroxyl protecting group.

103. The specification of the '506 Patent does not describe the compound of formula (IV) where R_6 is a hydrogen.

104. The specification of the '506 Patent does not describe the compound of formula (IV) where R_7 is a hydrogen.

105. The specification of the '506 Patent does not describe the compound of formula (IV) where R_8 is a hydrogen.

106. Claim 1's recitation that " R_6 , R_7 and R_8 , which may be the same or different, are each independently H" in the compound of formula (IV) is not described in the specification of the '506 Patent.

107. Claim 1 of the '506 Patent lacks written description and is invalid under 35 U.S.C.

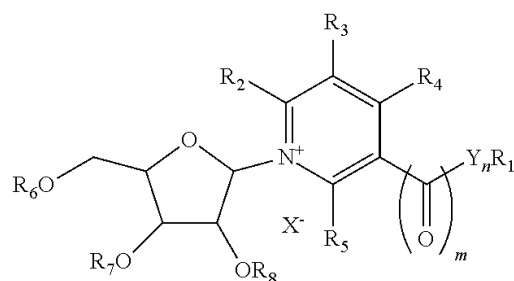
§ 112.

108. Claim 1 of the '506 Patent lacks enablement and is invalid under 35 U.S.C. § 112.

109. Claims 2-3, 10-12, and 26 depend from claim 1 and thus, recite each and every element of claim 1. Therefore, claims 2-3, 10-12, and 26 of the '506 Patent also lack written description and enablement, and are invalid under 35 U.S.C. § 112.

110. The '506 Patent was filed on April 26, 2023 as U.S. Application No. 18/307,733 (“’733 Application”).

111. Claim 1 filed on April 26, 2023 in the '733 Application recites “[a] compound of formula (IV):



... where: ... R₆, R₇ and R₈, which may be the same or different, are each independently H.”

112. The compound of formula (IV) having R₆, R₇ and R₈ as hydrogen appeared for the first time, at the earliest, with the April 26, 2023 filing date of the '733 Application that issued as the '506 Patent.

113. The '506 Patent claims are entitled to priority no earlier than April 26, 2023.

114. U.S. Patent Application Publication No. 2016/0168184 (“’184 Publication”) published on June 16, 2016. Ex. 10.

115. The '184 Publication is prior art to the asserted claims in the '506 Patent.

116. The '184 Publication anticipates the asserted claims in the '506 Patent for the reasons described in IPR2026-00400; thus, the asserted claims in the '506 Patent are invalid under

35 U.S.C. § 102.

117. The asserted claims in the '506 Patent are obvious variations that are conventional in light of the prior art available for the reasons described in IPR2026-00400; thus, the asserted claims in the '506 Patent are invalid under 35 U.S.C. § 103.

118. Thorne is entitled to a judicial declaration that the claims of the '506 Patent are invalid.

PRAYER FOR RELIEF

WHEREFORE, Thorne respectfully requests that the Court enter judgment in its favor and against the Defendants as follows:

- (a) Declaring that Thorne has not infringed, induced others to infringe, or contributed to the infringement of any claim of the '506 Patent, directly or indirectly, literally or under the doctrine of equivalents;
- (b) A permanent injunction enjoining Defendants and their officers, directors, owners, members, partners, employees, agents, attorneys, successors, assigns, and all persons acting in concert or in participation with them, from:
 - (1) Asserting, threatening to assert, or causing to be asserted any claim of the '506 Patent against Thorne or any of Thorne's customers, suppliers, distributors, or partners;
 - (2) Representing, stating, or implying in any manner—whether orally, in writing, or through any other medium—that the Thorne NR Products infringe any valid and enforceable claim of the '506 Patent;
 - (3) Initiating, maintaining, or threatening any action, suit, or proceeding alleging infringement of the '506 Patent by Thorne or any party in privity with Thorne; and

- (4) Otherwise interfering with Thorne's right to make, use, sell, offer for sale, or import its products and services free from claims of infringement of the '506 Patent;
- (c) Declaring that pursuant to 28 U.S.C. §§ 2201 and 2202, one or more claims of U.S. Patent No. 12,252,506 (the "'506 Patent"), including but not limited to claims 1–3, 10–12, and 26, are invalid for failure to comply with one or more requirements of Title 35 of the United States Code, including without limitation 35 U.S.C. §§ 101, 102, 103, and 112;
- (d) Declaring that the asserted claims of the '506 Patent are invalid for lack of written description and/or lack of enablement under 35 U.S.C. § 112(a);
- (e) Declaring that the asserted claims of the '506 Patent are invalid as indefinite under 35 U.S.C. § 112(b);
- (f) Declaring that the asserted claims of the '506 Patent are invalid as anticipated and/or obvious under 35 U.S.C. §§ 102 and/or 103 in view of the prior art;
- (g) Adjudging this to be an exceptional case under 35 U.S.C. § 285, and awarding to Thorne its reasonable attorneys' fees, costs, and expenses;
- (h) An award of compensatory damages in an amount to be proven at trial, including damages for lost contractual benefits, lost revenues, and harm to Thorne's existing contractual relationships with its commercial partners;
- (i) A finding that Defendants' interference was intentional and unjustified, and an award of punitive damages in an amount sufficient to punish Defendants for their conduct and to deter similar conduct in the future;
- (j) A permanent injunction enjoining Defendants and their officers, directors, owners,

- members, partners, employees, agents, attorneys, successors, assigns, and all persons acting in concert or participation with them, from taking any action intended or reasonably likely to interfere with, disrupt, or cause the breach of any existing contractual relationship between Thorne and any commercial partner;
- (k) An award of compensatory damages in an amount to be proven at trial, including damages for lost prospective business relationships, lost sales, and harm to Thorne's business reputation and goodwill;
 - (l) A finding that Defendants acted with actual malice or with a willful and wanton disregard for Thorne's rights, and an award of punitive damages in an amount sufficient to punish Defendants for their conduct and to deter similar conduct in the future;
 - (m) A permanent injunction enjoining Defendants and their officers, directors, owners, members, partners, employees, agents, attorneys, successors, assigns, and all persons acting in concert or participation with them, from making any further false, misleading, or disparaging statements or representations regarding Thorne or the Thorne NR Products to any existing or prospective end-user consumers, resellers, or commercial partners;
 - (n) A finding that Defendants engaged in unfair and deceptive acts and practices in violation of S.C. Code § 39-5-20;
 - (o) An award of actual damages in an amount to be proven at trial;
 - (p) A finding that Defendants' violations were willful and knowing, and an award of three times Thorne's actual damages pursuant to S.C. Code § 39-5-140(a);
 - (q) A permanent injunction enjoining Defendants and their officers, directors, owners,

members, partners, employees, agents, attorneys, successors, assigns, and all persons acting in concert or participation with them, from engaging in any further unfair or deceptive acts or practices directed at Thorne, Thorne's products, or Thorne's end-user consumers, resellers, and commercial partners;

- (r) An award of reasonable attorneys' fees and costs pursuant to S.C. Code § 39-5-140(a);
- (s) An award to Thorne of its costs of suit incurred herein, pursuant to 28 U.S.C. § 1920 and Fed. R. Civ. P. 54(d);
- (t) Pre- and post-judgment interest at the maximum rate allowed by law; and
- (u) Granting to Thorne any further relief this Court may deem just, proper, or equitable.

Respectfully submitted,

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EXHIBIT 1



US012252506B2

(12) **United States Patent**
Migaud et al.

(10) **Patent No.:** **US 12,252,506 B2**

(45) **Date of Patent:** ***Mar. 18, 2025**

(54) **METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF**

FOREIGN PATENT DOCUMENTS

(71) Applicant: **The Queen's University of Belfast,**
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WO	WO 1993/08288	4/1993
WO	WO 2002/04478	1/2002
WO	WO 2007/061798	5/2007
WO	WO 2011/081942	7/2011

(72) Inventors: **Marie Migaud,** Lurgan (GB); **Philip Redpath,** Portadown (GB); **Kerri Crossey,** Magherafelt (GB); **Mark Doherty,** Newtownabbey (GB)

OTHER PUBLICATIONS

(73) Assignee: **The Queen's University of Belfast,**
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U.S. Appl. No. 14/908,831, filed Jan. 29, 2016, Patented.
U.S. Appl. No. 15/905,922, filed Feb. 17, 2018, Patented.
U.S. Appl. No. 16/886,985, filed May 29, 2020, Patented.
U.S. Appl. No. 17/736,834, filed May 5, 2022, Pending.

(Continued)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 6 days.

This patent is subject to a terminal disclaimer.

Primary Examiner — Patrick T Lewis

(74) Attorney, Agent, or Firm — Leydig, Voit & Mayer, Ltd.

(21) Appl. No.: **18/307,733**

(57)

ABSTRACT

(22) Filed: **Apr. 26, 2023**

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

(65) **Prior Publication Data**

US 2024/0101588 A1 Mar. 28, 2024

Related U.S. Application Data

(63) Continuation of application No. 17/736,834, filed on May 4, 2022, now Pat. No. 11,981,698, which is a continuation of application No. 16/886,985, filed on May 29, 2020, now Pat. No. 11,584,770, which is a continuation of application No. 15/905,922, filed on Feb. 27, 2018, now Pat. No. 10,815,262, which is a continuation of application No. 14/908,831, filed as application No. PCT/EP2014/065971 on Jul. 24, 2014, now Pat. No. 10,000,519.

(30) **Foreign Application Priority Data**

Jul. 29, 2013 (GB) 1313465

(51) **Int. Cl.**

C07H 19/048 (2006.01)
C07H 1/00 (2006.01)
C07H 1/06 (2006.01)
C07H 19/04 (2006.01)

(52) **U.S. Cl.**

CPC **C07H 19/048** (2013.01); **C07H 1/00** (2013.01); **C07H 1/06** (2013.01); **C07H 19/04** (2013.01); **Y02P 20/582** (2015.11)

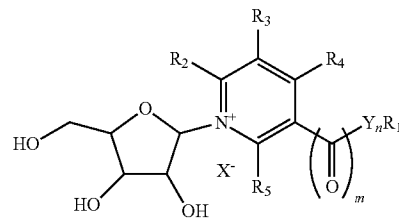
(58) **Field of Classification Search**

None
See application file for complete search history.

(56) **References Cited**

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10,000,519 B2	6/2018	Migaud et al.
11,584,770 B2	2/2023	Migaud et al.
2018/0186824 A1	7/2018	Migaud et al.



(I)

wherein

n is 0 or 1;

m is 0 or 1;

Y is O or S;

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;

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

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.

43 Claims, 5 Drawing Sheets

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(56)

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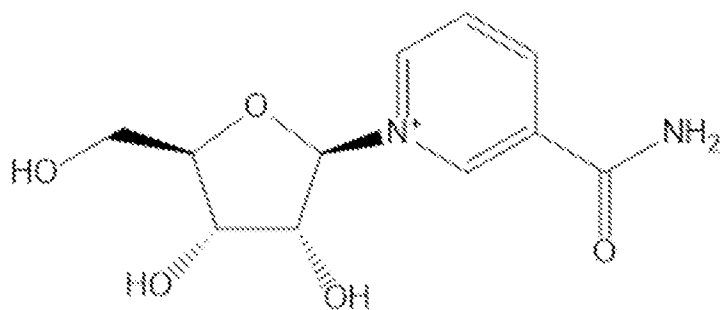
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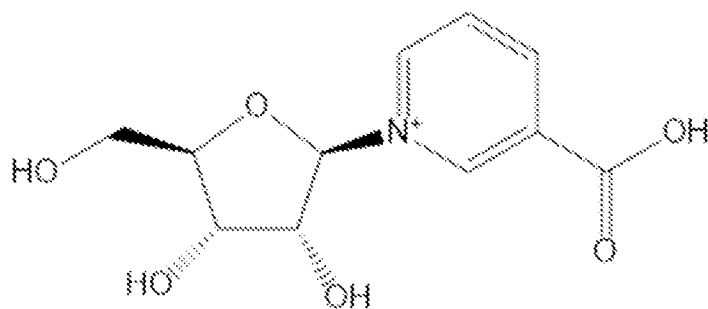
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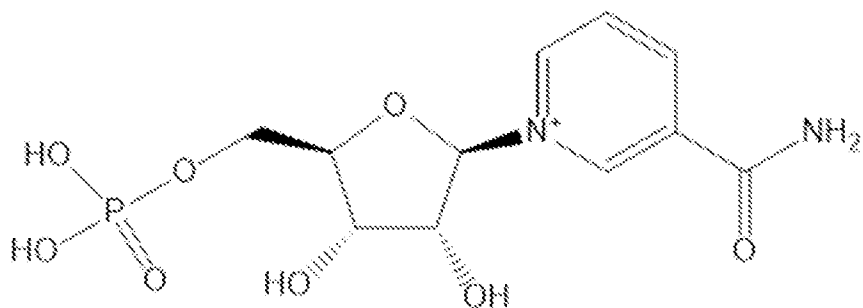
International Search Report and Written Opinion corresponding to International Application No. PCT/EP2014/065971, mailed Sep. 4, 2014, 10 pages.

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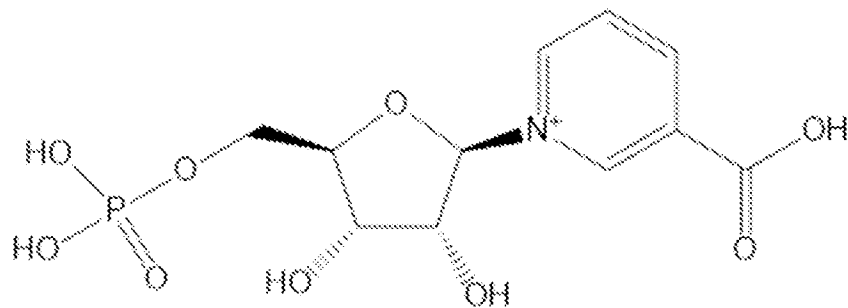
Nicotinamide riboside



Nicotinate riboside



Nicotinamide mononucleotide



Nicotinate mononucleotide

Figure 1

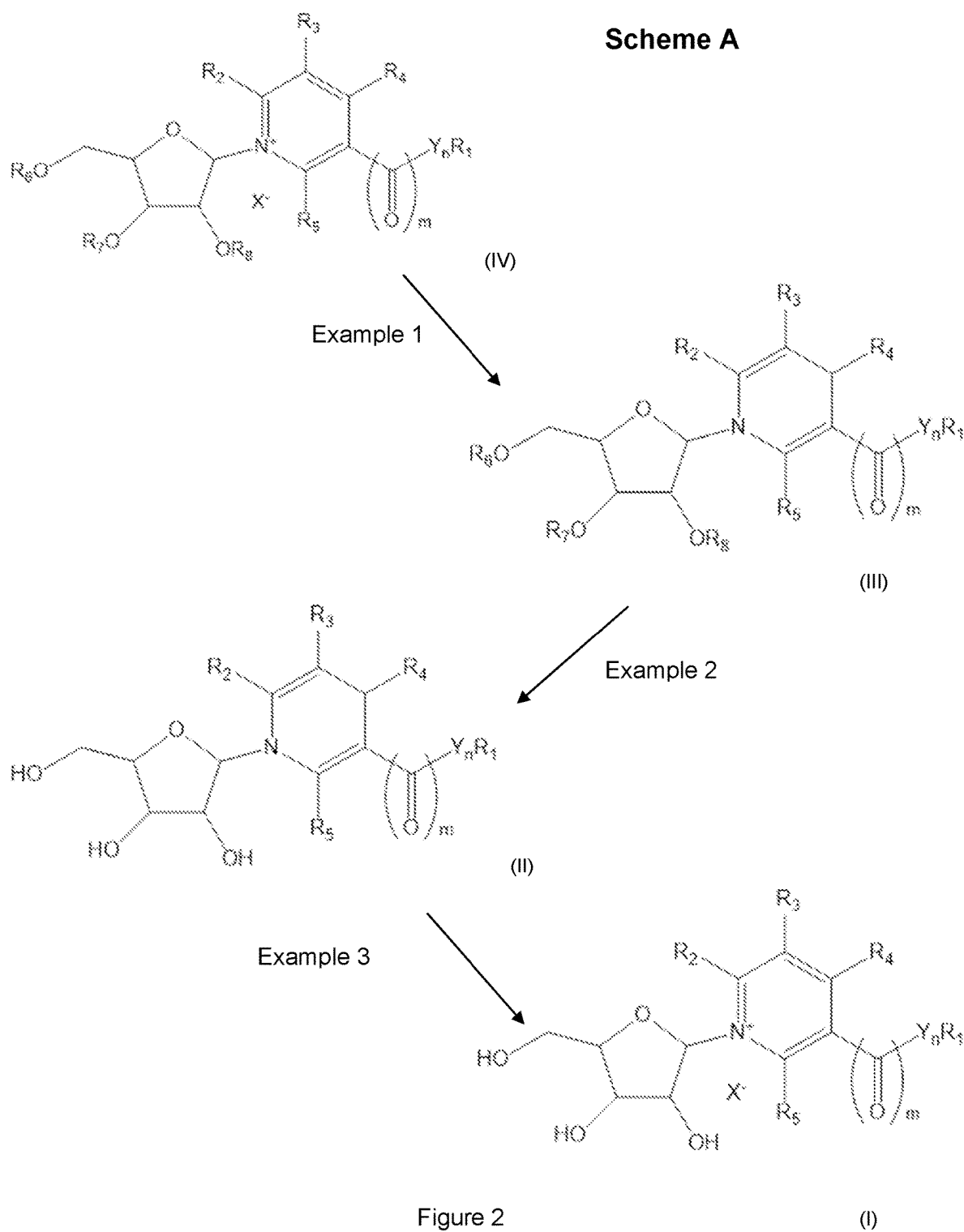
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Scheme A



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Scheme B

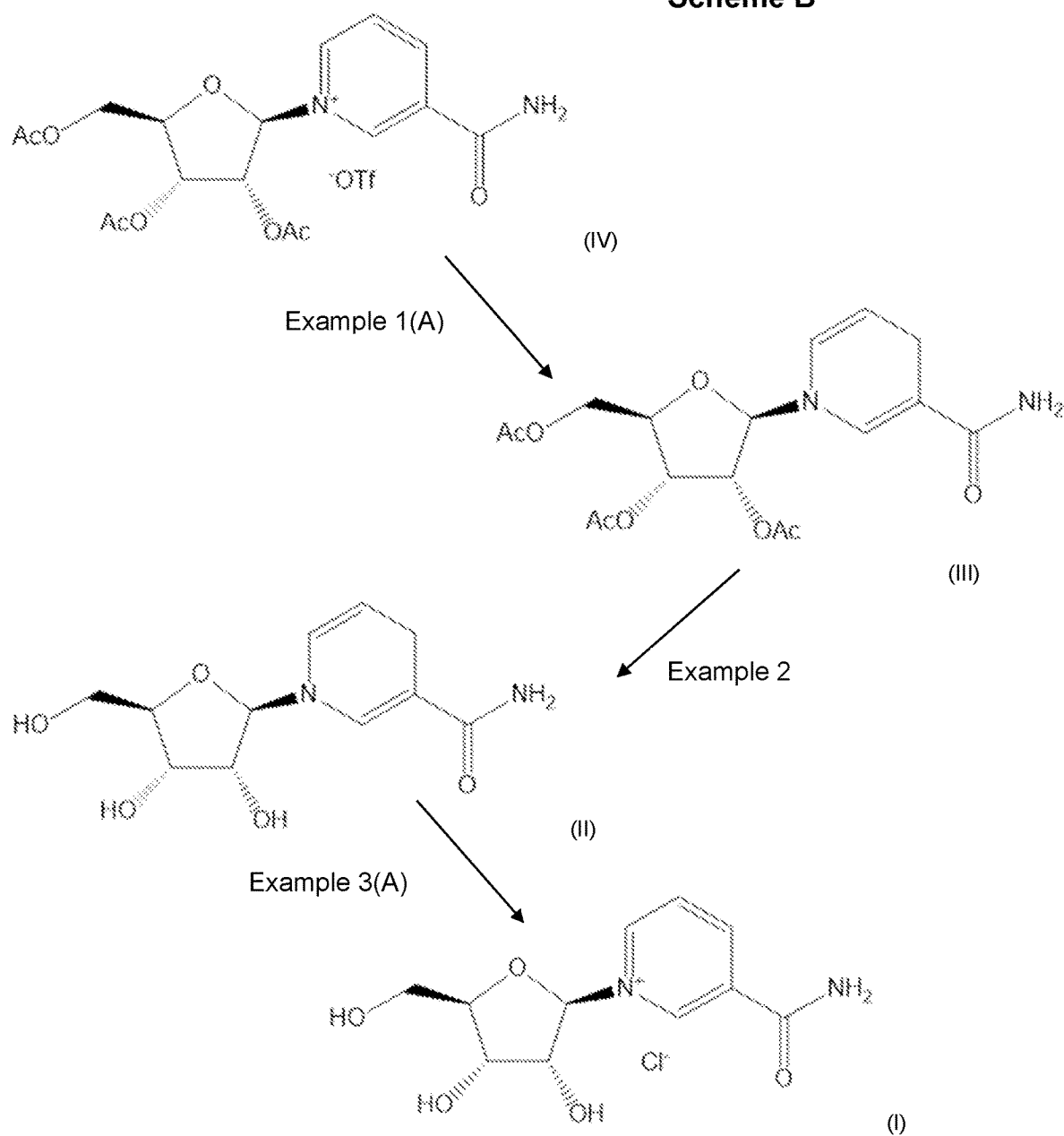
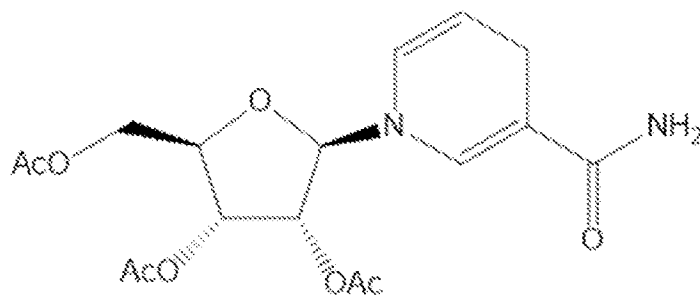
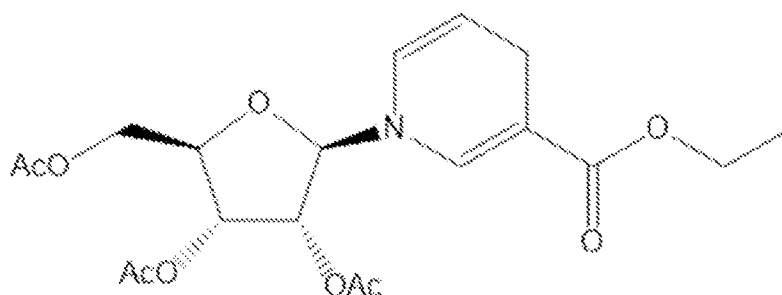


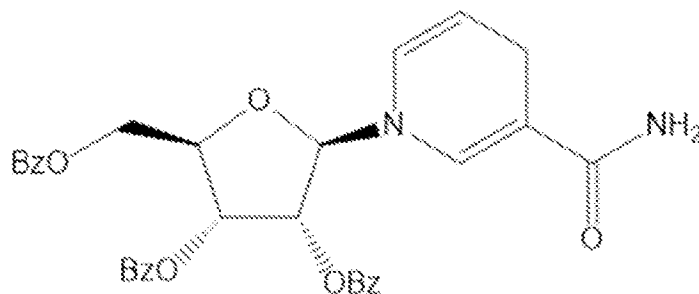
Figure 3

U.S. Patent**Mar. 18, 2025****Sheet 4 of 5****US 12,252,506 B2**

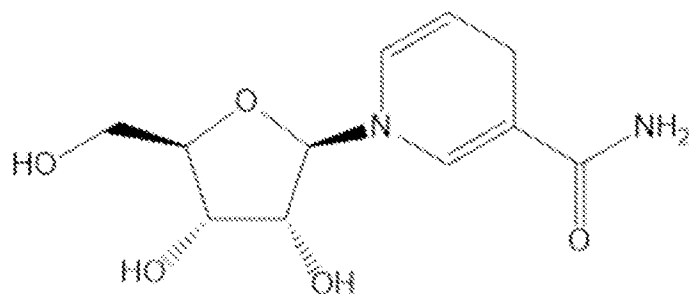
triacetyl-1,4-dihydronicotinamide riboside



triacetyl O-ethyl-1,4-dihydronicotinate riboside



tribenzoyl-1,4-dihydronicotinamide riboside



reduced nicotinamide riboside

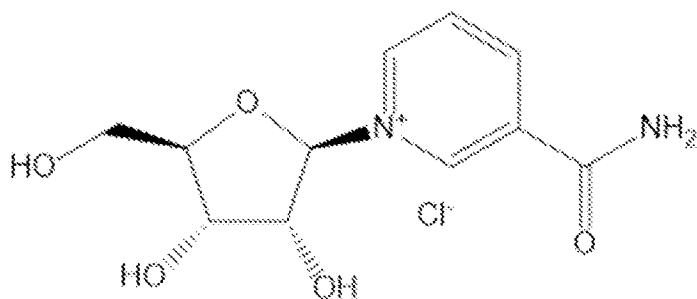
(1-(beta-D-ribofuranosyl)-1,4-dihydronicotinamide)

Figure 4

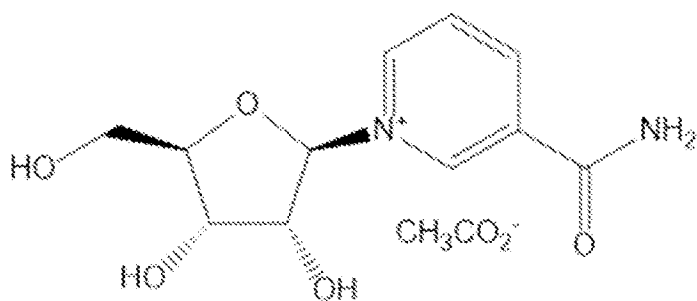
U.S. Patent

Mar. 18, 2025

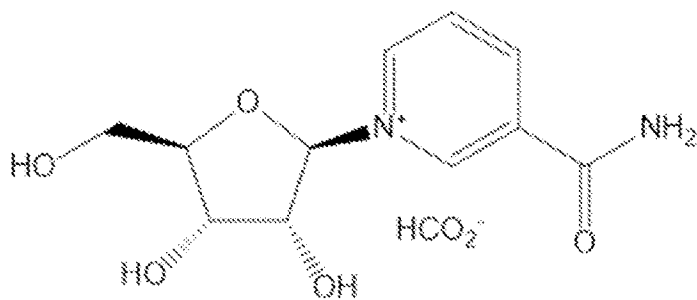
Sheet 5 of 5

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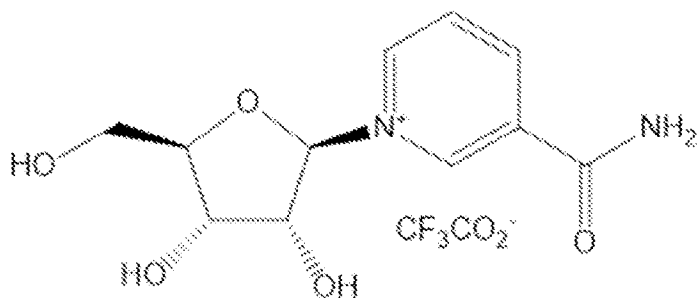
nicotinamide riboside, chloride salt



nicotinamide riboside, acetate salt



nicotinamide riboside, formate salt



nicotinamide riboside, trifluoroacetate salt

Figure 5

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1

METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF**CROSS-REFERENCE TO RELATED APPLICATIONS**

This application is a continuation of U.S. application Ser. No. 17/736,834, filed May 5, 2022, which is a continuation of U.S. application Ser. No. 16/886,985, filed May 29, 2020, now U.S. Pat. No. 11,584,770, which is a continuation of U.S. application Ser. No. 15/905,922, filed Feb. 27, 2018, now U.S. Pat. No. 10,815,262, which is a continuation of U.S. application Ser. No. 14/908,831, filed Jan. 29, 2016, now U.S. Pat. No. 10,000,519, which is a U.S. National Stage under 35 U.S.C. 371 of PCT/EP2014/065971, filed Jul. 24, 2014, and which claims priority from United Kingdom Patent Application No. 1313465.5, filed on Jul. 29, 2013. Each of these applications is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

The invention relates to methods of preparing nicotinamide riboside and derivatives thereof.

BACKGROUND TO THE INVENTION

Nicotinamide riboside and derivatives thereof, including nicotinate riboside, nicotinamide mononucleotide and nicotinate mononucleotide, are metabolites of nicotinamide adenine dinucleotide (NAD⁺). The β -anomer forms of nicotinamide riboside, nicotinate riboside, nicotinamide mononucleotide and nicotinate mononucleotide are shown, without counter ions, in FIG. 1. As a NAD⁺ precursor, nicotinamide riboside has been shown in mice to enhance oxidative metabolism and protect against high-fat diet induced obesity, which has resulted in significant interest in nicotinamide riboside and its derivatives. Since nicotinamide riboside is a naturally occurring compound, nicotinamide riboside and its derivatives have great potential as natural, nutritional supplements, which may provide health benefits without causing side effects. One limitation in the commercial exploitation of nicotinamide riboside and derivatives thereof, as nutritional supplements, or otherwise, is that known synthetic protocols for preparing nicotinamide riboside and derivatives thereof have disadvantages, rendering them unsuitable for scaling up for commercial or industrial use.

WO 2007/061798 describes a method for the preparation of nicotinamide riboside and derivatives thereof. However, the disclosed method has a number of disadvantages. For example, trimethylsilyl trifluoromethanesulfonate (TMSOTf) is used as the catalyst in the disclosed method, and results in the prepared compounds inevitably being in the form of their triflate (⁻OTf) salts. The triflate salt form of nicotinamide riboside, or derivatives thereof, is not suitable for use as a nutritional supplement, because of its associated toxicity. Thus, the compounds produced by the disclosed method are not suitable for use as they are prepared, and require an additional step to exchange the triflate anion for an anion that would be pharmaceutically acceptable and therefore suitable for commercialisation, utilizing for example, reverse phase liquid chromatography as disclosed. Additionally, nicotinamide riboside is chemically labile, in particular under the chromatographic conditions used in the disclosed method. It is therefore proposed that the chromatographic conditions used could result in batches

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of less than optimum purity and, within the batches, great variability in terms of the side products produced. Another disadvantage is that careful control of the temperature of the reaction is necessary to minimise decomposition in the final stages of the synthesis of nicotinamide riboside, yet the disclosed method is exothermic and is therefore prone to microenvironment thermal fluctuation, especially in the event of large scale production set up.

Tanimori et al (S. Tanimori, T. Ohta and M. Kiriha, *Bioorganic & Medicinal Chemistry Letters*, 2002, 12, 1135-1137) and Franchetti et al (P. Franchetti, M. Pasqualini, R. Petrelli, M. Ricciutelli, P. Vita and L. Cappellacci, *Bioorganic & Medicinal Chemistry Letters*, 2004, 14, 4655-4658) also describe methods for the preparation of nicotinamide riboside. However, these methods also have the disadvantage of inevitably resulting in the preparation of the triflate salt by virtue of using TMSOTf as catalyst.

In summary, the disclosed methods have disadvantages which present obstacles to the scaling up of the method for commercial or industrial use, and which, therefore, greatly limit the commercial opportunities for the methods and the resultant compounds.

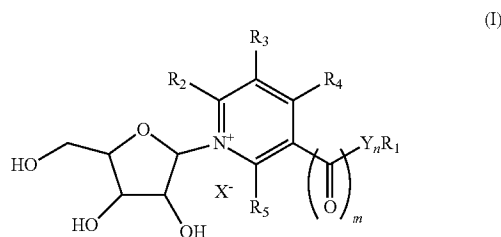
It is therefore an object of the invention to avoid or mitigate the disadvantages of the prior art.

It is also an object of the invention to provide a novel, useful and efficient method for the preparation of nicotinamide riboside and derivatives thereof.

It is also an object of the invention to provide a method for the preparation of nicotinamide riboside and derivatives thereof, whereby the method may be used to introduce a counter ion of choice to the prepared compounds, thereby producing compounds suitable for use as nutritional supplements or otherwise.

SUMMARY OF THE INVENTION

According to the present invention, there is provided a method of preparing a compound of formula (I)



wherein

n is 0 or 1;

m is 0 or 1;

Y is O or S;

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;

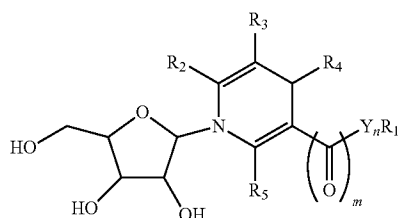
R₂-R₅, which may be the same or different, are each independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, and substituted or unsubstituted aryl; and

X⁻ is an anion, selected from an anion of a substituted or unsubstituted carboxylic acid, a halide, a substituted or

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unsubstituted sulfonate, a substituted or unsubstituted phosphate, a substituted or unsubstituted sulfate, a substituted or unsubstituted carbonate, and a substituted or unsubstituted carbamate; comprising reacting a compound of formula (II)



wherein n, m, Y and R₁-R₅ are as defined above; with a compound of the formula Z⁺X⁻, wherein X⁻ is as defined above, and wherein Z⁺ is a N-containing cation; in the presence of an aqueous solution and a carbon-containing catalyst; to form the compound of formula (I).

Optionally, Z⁺ is selected from a substituted or unsubstituted ammonium, a substituted or unsubstituted pyridinium, a substituted or unsubstituted pyrrolidinium, a substituted or unsubstituted imidazolium and a substituted or unsubstituted triazolium.

Optionally, Z⁺ is a substituted or unsubstituted ammonium of the formula N⁺HR^IR^{II}R^{III}, wherein R^I, R^{II} and R^{III}, 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.

Optionally, Z⁺ is an unsubstituted ammonium of the formula NH₄⁺.

Optionally, 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.

Optionally, X⁻ is an anion of a substituted monocarboxylic acid, further optionally an anion of a substituted propanoic acid or an anion of a substituted acetic acid. Optionally, X⁻ is an anion of a substituted propanoic acid, further optionally an anion of a hydroxy propanoic acid, still further optionally an anion of 2-hydroxypropanoic acid, being lactic acid, the anion of lactic acid being lactate. Optionally, X⁻ is an anion of a substituted acetic acid, being a substituted acetate, further optionally a trihaloacetate selected from trichloroacetate, tribromoacetate and trifluoroacetate. Still further optionally, the trihaloacetate is trifluoroacetate.

Optionally, 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.

Optionally, X⁻ is an anion of a substituted or unsubstituted amino-monocarboxylic acid or an anion of a substituted or unsubstituted amino-dicarboxylic acid. Further optionally, X⁻ is an anion of an amino-dicarboxylic acid, optionally selected from glutamic acid and aspartic acid, being glutamate and aspartate, respectively.

Optionally, X⁻ is an anion of ascorbic acid, being ascorbate.

Optionally, X⁻ is a halide selected from chloride, bromide, fluoride and iodide, further optionally chloride or bromide.

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Optionally, X⁻ is a substituted or unsubstituted sulfonate. Further optionally, X⁻ is a trihalomethanesulfonate selected from trifluoromethanesulfonate, tribromomethanesulfonate and trichloromethanesulfonate. Still further optionally, the trihalomethanesulfonate is trifluoromethanesulfonate.

Optionally, X⁻ is a substituted or unsubstituted carbonate, further optionally hydrogen carbonate.

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.

Optionally, the compound of the formula Z⁺X⁻ is selected from ammonium chloride, ammonium acetate, ammonium formate, ammonium trifluoroacetate, ammonium ascorbate, ammonium aspartate, ammonium glutamate and ammonium lactate. Further optionally, the compound of the formula Z⁺X⁻ is selected from ammonium chloride, ammonium acetate, ammonium formate and ammonium trifluoroacetate.

Optionally, the compound of formula (II) and the carbon-containing catalyst are present in a respective molar ratio of from about 10:1 to about 1:10, optionally from about 5:1 to about 1:5, further optionally from about 4:1 to about 1:4, still further optionally about 1:1 or 1:2 or 1:3 or 1:4.

Suitable carbon-containing catalysts include, but are not limited to, activated charcoal or graphite.

As used herein, the term "activated charcoal" is intended to mean a carbon containing material processed to be highly porous thereby increasing the surface area of the material. The term "activated charcoal" is intended to be synonymous with the term "activated carbon". The activated charcoal may be in the form of powders and/or fibres and/or granules and/or pellets. Optionally, the activated charcoal may act as a support for a metal. Suitable metals include, but are not limited to, transition metals. Suitable transition metals include, but are not limited to the platinum group metals, optionally selected from ruthenium, rhodium, palladium, osmium, iridium, and platinum, or a combination thereof.

Optionally, the aqueous solution consists essentially of water.

Optionally, the aqueous solution comprises, in addition to water, an organic solvent.

Suitable organic solvents include, but are not limited to, substituted or unsubstituted ethers, substituted or unsubstituted esters, substituted or unsubstituted ketones, substituted or unsubstituted aliphatic or aromatic hydrocarbons, and combinations thereof.

Optionally, the organic solvent, when present, comprises an ether selected from diethyl ether, methyl tert-butyl ether, ethyl tert-butyl ether, di-tert-butyl ether, diisopropyl ether, dimethoxymethane, tetrahydrofuran, 2-methyltetrahydrofuran, and tetrahydropyran, or a combination thereof.

Optionally, the organic solvent, when present, comprises an ester selected from methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, isobutyl acetate and n-butyl acetate, or a combination thereof.

Optionally, the organic solvent, when present, comprises a ketone selected from methyl isobutyl ketone and methyl isopropyl ketone, or a combination thereof.

Optionally, the organic solvent, when present, comprises an unsubstituted aliphatic hydrocarbon solvent selected from pentane, hexane, cyclohexane and heptane, or a combination thereof.

Optionally, the organic solvent, when present, comprises a substituted aliphatic hydrocarbon solvent, optionally a halogenated aliphatic hydrocarbon solvent, further optionally a chlorinated aliphatic hydrocarbon solvent selected from dichloromethane, trichloromethane, tetrachloromethane,

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ane, 1,2-chloroethane, 1, 1, 1-trichloroethane and trichloroethylene, or a combination thereof.

Optionally the organic solvent, when present, comprises an aromatic hydrocarbon solvent selected from benzene, toluene, ethylbenzene and xylene, or a combination thereof.

Optionally, the aqueous solution comprises water and organic solvent in a respective ratio by volume of from about 1:5 to about 5:1, optionally from about 1:3 to about 3:1, further optionally from about 1:2 to about 2:1, still further optionally about 1:1.

Optionally, the reaction is carried out in a pH range of from about 6 to about 8, optionally from about 6.5 to about 7.5.

Optionally, the reaction is carried out at a temperature of from about 10° C. to about 40° C., optionally from about 15° C. to about 35° C., further optionally from about 15° C. to about 30° C., still further optionally from about 15° C. to about 20° C., even further optionally from about 20° C. to about 25° C., even further optionally at a temperature of about 20° C. or 21° C. or 22° C. or 23° C. or 24° C. or 25° C.

Optionally, the reaction is carried out for a period of time of from about 1 minute to about 180 minutes, optionally, from about 2 minutes to about 120 minutes, further optionally from about 5 minutes to about 120 minutes, still further optionally from about 10 minutes to about 120 minutes, even further optionally from about 20 minutes to about 120 minutes, even further optionally from about 30 minutes to about 120 minutes, still further optionally from about 60 minutes to about 120 minutes, even further optionally from about 60 minutes to about 90 minutes, still further optionally about 60 minutes or 70 minutes or 80 minutes.

Optionally, the method further comprises a filtration step to remove the carbon-containing catalyst from the prepared compound of formula (I). Suitable filtration means for use in the filtration step include, but are not limited to, syringe filters and/or paper filters, and/or any inert, insoluble substance capable of acting as a filter, e.g. alumina and/or silica and/or diatomaceous earth. It will be appreciated any other suitable filtration means may be used.

As used herein, the term “substituted” is intended to mean that any one or more hydrogen atoms is replaced with any suitable substituent, provided that the normal valency is not exceeded and the replacement results in a stable compound. Suitable substituents include, but are not limited to, alkyl, alkylaryl, aryl, heteroaryl, halide, hydroxyl, carboxylate, carbonyl (including alkylcarbonyl and arylcarbonyl), phosphate, amino (including alkylamino, dialkylamino, hydroxylamino, dihydroxylamino, alkyl hydroxylamino, arylamino, diarylamino and alkylaryl amino), thiol (including alkylthiol, arylthiol and thiocarboxylate), sulfate, nitro, cyano and azido.

As used herein, the term “alkyl” is intended to mean a substituted or unsubstituted, saturated or unsaturated, optionally saturated, linear, branched or cyclic, aliphatic hydrocarbon, having from 1 to 12 carbon atoms, optionally from 1 to 10 carbon atoms, further optionally from 1 to 8 carbon atoms, still further optionally from 1 to 6 carbon atoms, even still further optionally 1 or 2 or 3 or 4 or 5 carbon atoms. Suitable alkyls include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, iso-pentyl, n-hexyl, iso-hexyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Optionally, when Y is O, n is 1, and m is 1, ethyl is preferred.

As used herein, the term “alkenyl” is intended to mean a substituted or unsubstituted, linear, branched or cyclic, aliphatic hydrocarbon, having at least one carbon-carbon

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double bond, and having from 2 to 12 carbon atoms, optionally from 2 to 10 carbon atoms, further optionally from 2 to 8 carbon atoms, still further optionally from 2 to 6 carbon atoms, even still further optionally 2 or 3 or 4 or 5 carbon atoms. Suitable alkenyl groups include, but are not limited to, ethenyl, propenyl and butenyl.

As used herein, the term “alkynyl” is intended to mean a substituted or unsubstituted, linear, branched or cyclic, aliphatic hydrocarbon, having at least one carbon-carbon triple bond, and having from 2 to 12 carbon atoms, optionally from 2 to 10 carbon atoms, further optionally from 2 to 8 carbon atoms, still further optionally from 2 to 6 carbon atoms, even still further optionally 2 or 3 or 4 or 5 carbon atoms. Suitable alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, and the like.

As used herein, the term “aryl” is intended to mean a substituted, unsubstituted, monocyclic or polycyclic, aromatic hydrocarbon. Suitable aryls include, but are not limited to, substituted or unsubstituted phenyl, and substituted or unsubstituted heteroaryl.

Optionally, the substituted or unsubstituted primary or secondary amino is selected from substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted hydroxylamino, substituted or unsubstituted dihydroxylamino, and substituted or unsubstituted alkyl hydroxylamino.

Optionally, the substituted or unsubstituted azido is selected from substituted or unsubstituted alkyl azido and substituted or unsubstituted aryl azido.

It will be appreciated that, when n is 0 and m is 0, R₁ is directly attached to the pyridine ring or to the pyridinium ring, as appropriate.

Optionally, in an embodiment of formula (I), n is 0, m is 1, R₁ is NH₂, R₂-R₅ are each H, and X⁻ is selected from chloride, acetate, formate and trifluoroacetate.

Optionally, in an embodiment of formula (II), n is 0, m is 1, R₁ is NH₂, and R₂-R₅ are each H.

Optionally, the compound of formula (II) and the compound of the formula Z⁺X⁻ are present in a respective molar ratio of from about 1:5 to about 5:1, optionally from about 1:3 to about 3:1, further optionally from about 1:2 to about 2:1, still further optionally about 1:1.

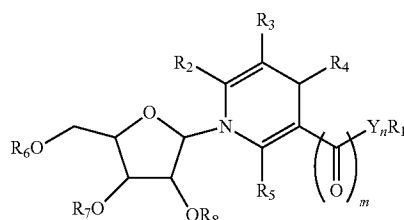
Optionally, the method comprises stirring the reactants, optionally using a magnetic or mechanical stirrer, further optionally an overhead mechanical stirrer.

In an embodiment, the carbon-containing catalyst used in the preparation of a compound of formula (I) may be provided in the form of an activated charcoal column, for example an activated charcoal material such as those supplied by Sigma Aldrich under the trade names NORIT (Trade Mark) or DARCO (Trade Mark), or from Carbo-Chem, W Lancaster Ave, Ardmore, PA 19003, USA, or a carbon supported catalyst in a CatCart Packer (Trade Mark) column from ThalesNano, Graphisoft Park, Záhony u. 7. H-1031 Budapest, Hungary. In this embodiment, the activated charcoal column may be used as part of any suitable liquid chromatography system, including, but not limited to, a fast protein liquid chromatography (FPLC) or a high performance liquid chromatography (HPLC) system, or a flow chemistry system, such as the ThalesNano (Trade Mark) H-cube systems and related flow reactors, available from ThalesNano, details provided above. In this case, the reactants would be recirculated onto the column in a continuous manner until the compound of formula (II) is no longer detected by UV at 340 nm.

Optionally, the compound of formula (II) is prepared by reacting a compound of formula (III)

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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;
with a deprotecting agent;
to form the compound of formula (II).

Suitable R₆, R₇ and R₈ moieties include, but are not
limited to, ester-type protecting groups, ether-type protect-
ing groups, and silyl-type protecting groups.

As used herein, the term "ester-type protecting group" is
intended to mean a protecting group that forms an ester bond
for the purpose of hydroxyl protection and which may be
substituted or unsubstituted. Suitable ester-type protecting
groups include, but are not limited to, acetyl, propionyl,
isopropionyl, benzoyl, and trihaloacetyl, optionally trifluoro-
acetyl or trichloroacetyl.

As used herein, the term "ether-type protecting group" is
intended to mean a protecting group that forms an ether bond
for the purpose of hydroxyl protection and which may be
substituted or unsubstituted. Suitable ether-type protecting
groups include, but are not limited to, benzyl, p-methoxy-
benzyl, methoxymethyl and allyl ethers.

As used herein, the term "silyl-type protecting group"
refers to a protecting group that forms a silyloxy bond for the
purpose of hydroxyl protection. Examples thereof from
trimethylsilyl, triethylsilyl, triisopropylsilyl, 2-(trimethylsi-
lyl)ethoxymethyl, tert-butyldimethylsilyl, tert-butyldi-
phenylsilyl and tetraisopropylsilyl.

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.

Optionally the deprotecting agent is an acid or a base.
Deprotection can also be achieved by catalytic hydrogenation
(Pd/C; H₂) for the aromatic ether protecting groups and
by fluoride-catalysed chemistry (e.f. TBAF in THF) for all
the silyl ethers. Optionally, when R₆, R₇ and R₈ each
comprise unsubstituted acetyl or unsubstituted benzoyl, the
deprotecting agent is a base, optionally selected from NH₃,
Na₂CO₃ and NaOH. It will be appreciated by a skilled
person that any other conventional deprotecting agent may
be used.

Optionally, the reaction is carried out in the presence of a
protic or aprotic solvent or a combination thereof.

Suitable protic solvents include, but are not limited to,
water, substituted or unsubstituted alcohol, or a combination
thereof. Suitable substituted alcohols include substituted or
unsubstituted fluorinated alcohols. Suitable unsubstituted
alcohols include methanol, ethanol and propanol, optionally
methanol.

Suitable aprotic organic solvents include, but are not
limited to, substituted or unsubstituted ethers, substituted or
unsubstituted esters, substituted or unsubstituted ketones,

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substituted or unsubstituted aliphatic or aromatic hydrocar-
bons, and combinations thereof, as defined above.

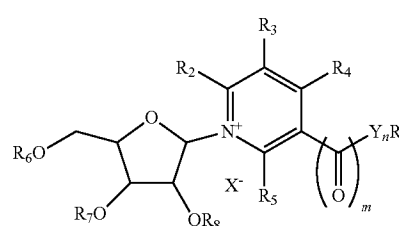
Optionally, the reactants are subjected to mechanical
grinding, further optionally using a ball milling or planetary
ball milling machine.

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.

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



wherein

n, m, Y, R₁-R₈ and X⁻ are as defined above;
with a reducing agent,
an aqueous solution
and an organic solvent
to form a compound of formula (III).

Optionally, X⁻ is selected from ascorbate, glutamate,
aspartate, lactate and acetate.

Suitable organic solvents are as defined above in respect
of the preparation of a compound of formula (I) from
formula (II).

Optionally, when at least two of R₆, R₇ and R₈ comprise
unsubstituted acetyl, the organic solvent is selected from
dichloromethane, 1,2-chloroethane, n-butyl acetate, chloro-
form and ethyl acetate, or a combination thereof, further
optionally ethyl acetate.

Optionally, when at least two of R₂, R₃ and R₄ comprise
unsubstituted benzoyl, the organic solvent is selected from
trichloroethylene, carbon tetrachloride, diisopropyl ether,
toluene, methyl tert-butyl ether, benzene and diethyl ether,
or a combination thereof, further optionally diethyl ether.

Optionally, the reducing agent is selected from sodium
dithionite or sodium borohydride.

Optionally, the method may comprise the simultaneous
addition of the reducing agent, aqueous solution and organic
solvent; or the sequential addition of the reducing agent,
aqueous solution and organic solvent, in any order; or a
combination thereof.

Optionally, the aqueous solution consists essentially of
water.

It will be appreciated that, optionally, the aqueous solu-
tion and the organic solvent form a bi-phasic solution
comprising an aqueous phase and an organic phase.

Optionally, the method comprises the additional steps of
separating the organic phase from the aqueous phase; and
extracting the compound of formula (III) from the organic
solvent.

It will be appreciated by a skilled person that the hydroxyl
protecting groups R₆, R₇ and R₈, are required to be lipophilic

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to the extent that the reduced compound of formula (III), once prepared, migrates into the organic phase of the bi-phasic reaction medium formed by the aqueous solution (aqueous phase) and organic solvent (organic phase).

Optionally, the reactants are subjected to mechanical grinding, further optionally using a ball mill or planetary ball milling machine.

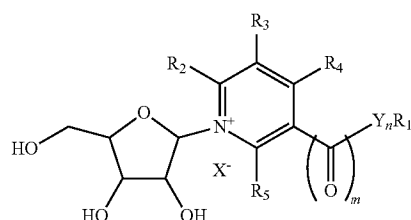
Optionally, in an embodiment of formula (IV), n is 0, m is 1, R_1 is NH_2 , R_2 - R_5 are each H, R_6 - R_8 are each acetyl, and X^- is ^-OTf .

Further optionally, in another embodiment of formula (III), n is 1, Y is O, m is 1, R_1 is ethyl, R_2 - R_5 are each H, R_6 - R_8 are each acetyl, and X^- is ^-OTf .

Still further optionally, in another embodiment of formula (III), n is 0, m is 1, R_1 is NH_2 , R_2 - R_5 are each H, and R_6 - R_8 are each benzoyl, and X^- is ^-OTf .

According to the invention, there are also provided compounds derivable from the methods disclosed herein.

Accordingly to the invention, there is further provided a compound of formula (I)

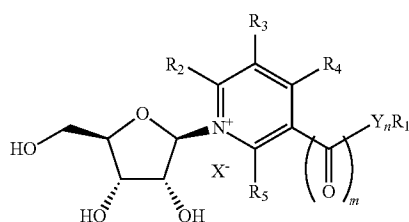


wherein

n , m , Y , R_1 - R_5 and X^- are as defined above.

Optionally, X^- is selected from acetate, formate and trifluoroacetate.

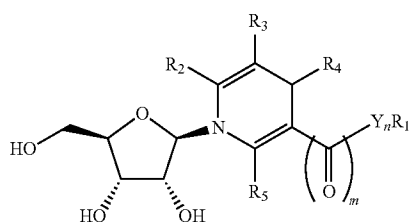
Optionally, the compound of formula (I) has the formula (IA), i.e. is the β -anomer,



wherein

n , m , Y , R_1 - R_5 and X^- are as defined above.

Optionally, the compound of formula (II) has the formula (IIA), i.e. is the β -anomer,

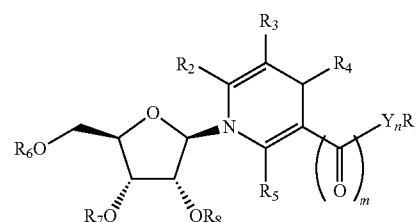


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wherein

n , m , Y and R_1 - R_5 are as defined above.

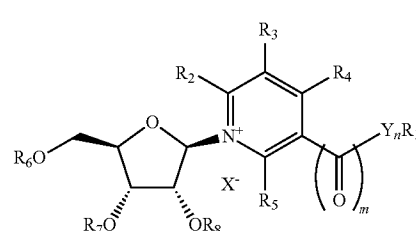
Optionally, the compound of formula (III) has the formula (IIIA), i.e. is the β -anomer,



wherein

n , m , Y and R_1 - R_8 are as defined above.

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



wherein

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

Advantages of the invention include, but are not limited to the following:

(1) The preparation of compounds of formula (I) from compounds of formula (II) provides an efficient method of introducing a counter ion of choice for nicotinamide riboside and its derivatives. Starting from a compound of formula (II), e.g. reduced NRH, a desired counter ion may be introduced. Furthermore, even if the method starts by using compounds of formula (IV) in the form of the triflate salt, the methods of the invention enable the triflate anion to be exchanged during the method in a simple and efficient manner, to a counter ion of choice. Thus, the disclosed methods conveniently enable the preparation of compounds having potential use as nutritional supplements or otherwise.

(2) The invention provides stereoselective methods for the preparation of nicotinamide riboside and derivatives thereof, producing the desired β -anomer. This is in contrast, for example, to Tanimori et al, which is not stereoselective and produces significant amounts of the α -anomer, which is undesirable. Additionally, the methods of the invention are useful, efficient, and can be easily scaled up for industry and commercialisation, and provide for the minimisation of solvent use, purification and reaction time. For example, the methods of the invention for preparing compounds of formula (I) from compounds of formula (II), are conveniently completed in less than 2 hours with quantitative yields. The methods for the preparation of compounds of formula (I) starting from compounds of formula (IV) are also very efficient and produce very good yields. The methods may conveniently be carried out at room temperature.

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(3) The methods described herein are capable of preparing not just nicotinamide riboside but also a whole range of derivatives, which is not disclosed in either Tanimori et al or Franchetti et al. The derivatives include not just derivatives of nicotinamide riboside but also the reduced form of nicotinamide riboside and derivatives thereof. Furthermore, although not described herein, a skilled person will appreciate that, starting from compounds of formula (II), it is possible to easily access the phosphorylated parents of nicotinamide riboside and derivatives thereof, for example nicotinamide mononucleotide and nicotinate mononucleotide.

(4) 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.

(5) The methods described herein conveniently use reactants which enable the compounds of formula (I) to be prepared in a neutral pH range of from about 6 to about 8. For example, in the preparation of the compounds of formula (I) from the compounds of formula (II), this neutral pH range enables both the starting materials (compounds of formula (II)), which are acid labile, and the final products (compounds of formula (I)), which are base labile, to be stable during the reaction.

(6) The inventors have surprisingly found that, the use of a N-containing cation as Z^+ (the proton source), conveniently enables the efficient preparation of compounds of formula (I) from compounds of formula (II) in quantitative yield, and, as mentioned in point (5), in a neutral pH range. Without wishing to be bound by theory, it is proposed that Z^+ , the proton source, must be a conjugated acid of an organic base which is protonated in an equilibrated manner within the neutral pH range. The inventors propose that, by using a N-containing cation as the proton source Z^+ , the N atom of the proton source has a pK_a greater than the pK_a of the N atom of the dihydropyridine of the compound of formula (II). Therefore, in simple terms, due to the relative pK_a values, the N atom of the proton source Z^+ (i.e. $N-H^+$) holds onto the proton H^+ until after the N atom of the dihydropyridine has been oxidised (which oxidation, the inventors propose, is facilitated by the carbon-containing catalyst). It is only after the N atom of the dihydropyridine has been oxidised that it will be protonated by the proton source Z^+ . The inventors propose that if a proton source other than one containing a N atom is used, for example a phosphonium cation containing $P-H^+$ or a sulfonium cation containing $S-H^+$, it is proposed that such proton sources would cause the pH of the reaction medium to fall below the neutral pH range, and the proton sources would release their protons in this lower pH range. It is proposed that this change would cause the N atom of the dihydropyridine to be protonated before oxidation, thereby resulting in the undesirable hydrolysis of a C—N bond of the dihydropyridine. It is also proposed that this resultant instability of the dihydropyridine due to the undesirable breaking of a C—N bond, would also occur using a weak acid (e.g. carboxylic acid) or a strong acid (e.g. hydrochloric acid, phosphoric acid or sulphuric acid). Thus, it is proposed that only a N-containing cation as proposed, is capable of releasing a proton in a pH range (neutral) which

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allows the reaction to proceed as desired to form the compounds of formula (I) from the compounds of formula (II).

THE EXAMPLES

Embodiments of the present invention will now be described, with reference to the accompanying, non-limiting examples and drawings, in which:

FIG. 1 shows the β -anomer forms of nicotinamide riboside, nicotinate riboside, nicotinamide mononucleotide and nicotinate mononucleotide, without counter ions;

FIG. 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; that compounds of formula (III) may be used to prepare compounds of formula (II), as described in Example 2; and that compounds of formula (II) may be used to prepare compounds of formula (I), as described in Example 3; wherein n, m, Y, R_1 - R_8 and X^- are as defined above;

FIG. 3 depicts Scheme B, which is a scheme illustrating, in general terms, that triacetyl nicotinamide riboside, triflate salt may be used to prepare triacetyl-1,4-dihydronicotinamide riboside, as described in Example 1(A), and that triacetyl-1,4-dihydronicotinamide riboside may be used to prepare 1-(β -D-ribofuranosyl)-1,4-dihydronicotinamide, as described in Example 2, and that 1-(β -D-ribofuranosyl)-1,4-dihydronicotinamide may be used to prepare nicotinamide riboside, chloride salt, as described in Examples 3(A), 3(E) and 3(F). The β -anomers of all of the mentioned compounds are shown. It will be appreciated that Scheme B is merely exemplary and is not to be construed as limiting the invention thereto;

FIG. 4 shows the β -anomer forms of triacetyl-1,4-dihydronicotinamide riboside (Example 1(A)), triacetyl O-ethyl-1,4-dihydronicotinamide riboside, (Example 1(B)), tribenzoyl-1,4-dihydronicotinamide riboside (Example 1(C)), and 1-(β -D-ribofuranosyl)-1,4-dihydronicotinamide (Example 2); and

FIG. 5 shows the β -anomer forms of nicotinamide riboside, chloride salt (Examples 3(A), 3(E) and 3(F)), nicotinamide riboside, acetate salt (Example 3(B)), nicotinamide riboside, formate salt (Example 3(C)), and nicotinamide riboside, trifluoroacetate salt (Example 3(D)).

EXAMPLE 1

Compounds of formula (III) were prepared in accordance with the invention as follows. The pH of the reaction media described in the following examples was in the region of about 6-8.

Example 1(A): Preparation of Reduced Triacetyl Nicotinamide Riboside, Namely triacetyl-1,4-dihydronicotinamide riboside, a Compound of Formula (III) (the β -Anomer Form of which is Shown in FIG. 4)

Reduction: All solvents were degassed prior to use by sonication and argon bubbling. Sodium dithionite (0.656 g, 3.76 mmol, 2 eq) and sodium hydrogencarbonate (0.79 g, 9.40 mmol, 5 eq) were added to a clean, dry round bottom flask with a magnetic stirrer and placed under inert atmosphere. A compound of formula (IV), namely triacetyl nicotinamide riboside, triflate ($CF_3SO_3^-$, also known as —OTf) salt (1 g, 1.88 mmol, 1 eq) was then dissolved in a minimum amount of water (<10 ml) and slowly added to the

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reaction vessel. Once the reaction settled, further water was added to the reaction until all of the reactants had dissolved (<10 ml) and was left to stir for 20 minutes. The aqueous solution was then extracted with three half portions of dichloromethane (DCM). The DCM fractions were collected and concentrated under reduced pressure, affording the triacetyl-1,4-dihydronicotinamide riboside derivative (triacetyl-NRHH) with residual amounts of starting material (<5%). The aqueous layer was subjected to the above conditions a second time to increase yields which averaged 65%. Ethyl acetate was also an excellent alternative extraction solvent in place of DCM, yielding a 75% yield.

¹H-NMR (MeOD, 400 MHz) δ 7.15 (s, 1H, H-5), 5.95 (d, 1H, J=7.21 Hz, H-6), 5.25 (d, 1H, J=2.84 Hz) & 5.17 (d, 1H, J=1.80 Hz) (H-8 & H-7), 4.96 (d, 1H, J=7.09 Hz, H-4), 4.87 (ABX, 1H, J_{aa}=8.18 Hz, J_{ab}=3.60 Hz, H-9), 4.26 (d, 2H, J=3.20 Hz, H-10 & H-10) 4.19 (m, 1H, J=3.00 Hz, H-3), 3.13 (m, 2H, J=1.18 Hz, H-2), 2.13 (s, 3H), 2.11 (s, 3H), 2.10 (s, 3H) (H-13, H-15, H-17). ¹³C-NMR (MeOD, 125 MHz) δ 172.80 (C-11), 170.40 (C-12, C-14, C-16), 137.90 (C-5), 125.20 (C-4), 105.12 (C-6), 95.24 (C-3), 83.49 (C-9), 71.18 (C-8), 70.26 (C-7), 61.55 (C-10), 22.16 (C-2), 21.52 (C-13, C-15, C-17). HMRS m/z: 383.1445; Calc. Mass: 383.1454.

The compound of formula (IV), namely triacetyl nicotinamide riboside, triflate (—OTf) salt was prepared as follows. Nicotinamide (10 g, 81.89 mmol, 1 eq) was silylated using TMSCl (15.6 ml, 122.85 mmol, 1.5 eq) in HMDS (100 ml) at 130° C. in quantitative yield, in order to force the β -selectivity via the following Vorbrüggen reaction. Ribose tetraacetate (also known as tetraacetate riboside) was reacted with the resultant silylated nicotinamide in the presence of 5 equivalents of TMSOTf. The reactants were shaken in a 1.5 ml steel vessel with a 5 mm diameter steel ball bearing in a Retsch MM400 mixer mill at 25 Hz for 0.5 h. At this point the formed triacetylated nicotinamide riboside (compound of formula (IV)) could be isolated. It will be appreciated that the triacetyl nicotinamide riboside is not limited to being produced by this exact method, and could, for example, be produced using a conventional Vorbrüggen reaction as described, for example, in International PCT patent publication no. WO 2007/061798 or in T. Yang, N. Y. K. Chan and A. A. Sauve, *Journal of Medicinal Chemistry*, 2007, 50, 6458-6461.

¹H-NMR (MeOD, 400 MHz) δ 9.61 (s, 1H, aromatic), 9.30 (dt, 1H, J=6.3, 1.4 Hz, aromatic), 9.10 (dt, 1H, J=8.2, 1.4 Hz, aromatic), 8.37 (dd, 1H, J=8.2, 6.3 Hz, aromatic), 6.60 (d, 1H, J=3.9 Hz, H-1 (anomeric)), 5.60 (dd, 1H, J=5.6, 3.9 Hz, H-2), 5.46 (t, 1H, J=5.6 Hz, H-3), 4.81-4.84 (m, 1H, H-4), 4.61 (ABX, 1H, J_{aa}=13.1 Hz, J_{ab}=3.5 Hz, H-5), 4.51 (ABX, 1H, J_{aa}=13.0 Hz, J_{ab}=2.8 Hz, H-5'), 2.20 (s, 3H, OAc), 2.17 (s, 3H, OAc), 2.16 (s, 3H, OAc).

¹³C-NMR (MeOD, 125 MHz) δ 172.1, 171.6, 171.2 (3 $\times$ C=OCH₃), 164.9 (C=ONH₂), 147.0, 144.3, 142.3, 136.2, 129.6, (aromatic), 121.6 (q, J=320.2 Hz, CF₃), 99.4 (C-1 (anomeric)), 84.4 (C-4), 77.6 (C-2), 70.7 (C-3), 63.5 (C-5), 20.7 (OAc), 20.3 (OAc), 20.2 (OAc).

¹⁹F-NMR (MeOD, 376 MHz) δ -79.9 (triflate counterion)

Example 1(B): Preparation of Reduced Triacetyl Nicotinate Ester Riboside, Namely Triacetyl O-ethyl-1,4-dihydronicotinamide riboside, a Compound of Formula (III) (the β -Anomer Form of which is Shown in FIG. 4)

Reduction: A compound of formula (IV), namely triacetyl O-ethyl nicotinate riboside, triflate (—OTf) salt (2.30 g, 4.2

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mmol, 1 eq) was dissolved in 20 mL H₂O and a solution of a solution of NaHCO₃ (1.77 g, 21.0 mmol, 5 eq) and sodium dithionite (1.47 g, 8.22 mmol, 2 eq) in 30 mL H₂O was added and stirred for 2 hrs. The yellow solution obtained was then washed with 2 $\times$ ethyl acetate (EtOAc, 40 mL), the organic layer dried over MgSO₄, filtered and concentrated to provide 900 mg (39% yield) of 2,3,5-triacetyl O-ethyl-1,4-dihydronicotinamide riboside (a yellow oil) without further purification. 80% purity based on ¹H-NMR.

¹H-NMR- δ 7.27 (1H, s, H-6), 6.05 (1H, dd, J=8.2, 1.5 Hz, H-7), 5.26 (1H, dd, J=5.8, 2.8 Hz, H-3), 5.23 (1H, dd, J=6.9, 5.8 Hz, H-2), 5.08 (1H, d, J=6.9 Hz, H-1), 4.91 (1H, dt, J=8.3, 3.5 Hz, H-8), 4.24-4.30 (3H, m, H-4, H-5, H-5'), 4.11 (2H, q, J=7.2 Hz, H-11), 3.04-3.06 (2H, m, H-9), 2.16 (3H, s, OAc), 2.12 (3H, s, OAc), 2.09 (3H, s, OAc), 1.25 (3H, t, J=7.2 Hz, H-12).

¹³C-NMR- δ 172.2, 171.5, 171.3, 169.8, (3 $\times$ C=O—CH₃ and C=O—OEt), 139.9 (C-6), 126.3 (C-7), 106.4 (C-8), 101.5 (C-10), 94.2 (C-1), 80.4 (C-4), 72.3 (C-2), 72.1 (C-3), 64.8 (C-5), 61.0 (C-11), 23.4 (C-9), 20.7, 20.5, 20.3 (3 $\times$ C=O—CH₃), 14.8 (C-12).

The compound of formula (IV), namely triacetyl O-ethyl nicotinate riboside, triflate (—OTf) salt was prepared as follows. Ribose tetraacetate (also known as tetraacetate riboside) was reacted with ethyl nicotinate (Sigma Aldrich) using the general ball milling Vorbrüggen procedure described in Example 1(A) above. The reactants, namely leg tetraacetate riboside, leg TMSOTf, leg ethyl nicotinate, were reacted for 30 mins in a 1.5 ml steel vessel with a 1.5 cm diameter steel ball bearing in a Retsch MM400 mixer mill at 25 Hz. The crude reaction mixture (containing some unreacted ethyl nicotinate and starting sugar, <10%) was used for the reduction step (described above) without further purification. It will be appreciated that the triacetyl O-ethyl nicotinate riboside, triflate (—OTf) salt is not limited to being produced by this exact method, and could, for example, be produced using a conventional Vorbrüggen reaction as described, for example, in International PCT patent publication no. WO 2007/061798 or in T. Yang, N. Y. K. Chan and A. A. Sauve, *Journal of Medicinal Chemistry*, 2007, 50, 6458-6461.

¹H-NMR (D₂O, 400 MHz) δ 9.45 (s, 1H, aromatic), 9.14 (d, 1H, J=6.1 Hz, aromatic), 9.02 (d, 1H, J=7.8 Hz, aromatic), 8.18 (t, 1H, J=6.7 Hz, aromatic), 6.51 (d, 1H, J=4.1 Hz, H-1 (anomeric)), 5.47 (t, 1H, J=4.4 Hz, H-2), 5.36 (t, 1H, J=4.7 Hz, H-3), 4.81-4.84 (m, 1H, H-4), 4.45-4.48 (m, 2H, H-5), 4.36 (q, 2H, J=7.0 Hz, C=OCH₂CH₃), 2.04 (s, 3H, OAc), 2.02 (s, 3H, OAc), 1.98 (s, 3H, OAc), 1.25 (t, 3H, J=7.0 Hz, C=OCH₂CH₃).

¹⁹F-NMR (D₂O, 376 MHz) δ -79.0 (triflate counterion)

Example 1(C): Preparation of Reduced Tribenzoyl Nicotinamide Riboside, Namely tribenzoyl-1,4-dihydronicotinamide riboside, a Compound of Formula (III) (the β -Anomer Form of which is Shown in FIG. 4)

Reduction (unoptimised): A compound of formula (IV), namely tribenzoyl nicotinamide riboside, triflate (—OTf) salt was dissolved in minimal methanol and transferred to a round bottomed flask, 10 mL of H₂O was added to the solution and most of the methanol removed via rotary evaporation. The starting material crashed out of solution and 20 mL of diethyl ether (Et₂O) was added until the solids solubilized into a biphasic system. A solution of NaHCO₃ (420 mg, 5 mmol, 5 eq) and sodium dithionite (348 mg, 2 mmol, 2 eq) in 10 mL H₂O was added and stirred for 2 hrs.

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The layers were separated and the ether layer was dried over MgSO_4 and concentrated to provide 428 mg (76% yield) of tribenzoyl-1,4-dihydronicotinamide riboside (yellow solid) without further purification. 80% purity based on ^1H -NMR. Pure material is obtained by Biotage purification.

^1H -NMR- δ 8.01-8.04 (2H, m, OBz), 7.81-7.86 (4H, m, OBz), 7.25-7.55 (9H, m, OBz), 7.13 (1H, s, H-6), 6.01 (1H, dd, $J=8.2, 1.5$ Hz, H-7), 5.68 (1H, dd, $J=6.2, 3.5$ Hz, H-3), 5.57 (1H, dd, $J=6.7, 6.2$ Hz, H-2), 5.29 (1H, d, $J=6.7$ Hz, H-1), 4.61-4.68 (2H, m, H-8, H-5), 4.50-4.55 (2H, m, H-4, H-5'), 3.93-3.94 (2H, m, H-9).

^{13}C -NMR- δ 172.7, 167.6, 166.7, 166.6 ($3\times \text{C}=\text{O}-\text{C}_6\text{H}_5$, $\text{C}=\text{ONH}_2$), 138.1 (C-6), 134.9, 134.8, 134.6, 130.9, 130.8, 130.7, 130.3, 130.0, 129.8, 129.7 ($3\times \text{OBz}$), 125.7 (C-7), 105.9 (C-8), 94.9 (C-1), 80.3 (C-4), 72.9 (C-2), 72.7 (C-3), 65.4 (C-5), 23.6 (C-9).

The compound of formula (IV), namely tribenzoyl nicotinamide riboside, triflate ($-\text{OTf}$) salt was prepared as follows. Ribose tetraacetate (also known as tetraacetate riboside) was reacted with TMS-nicotinamide (trimethylsilyl N-trimethylsilylpyridine-3-carboximidate, available from Sigma-Aldrich) using the general ball milling Vorbrüggen procedure described in Example 1(A) above. The reactants, namely leg 1-acetate-tribenzoate riboside, leg TMSOTf and leg TMS-nicotinamide, were reacted for 30 mins in a 1.5 ml steel vessel with a 1.5 cm diameter steel ball bearing in a Retsch MM400 mixer mill at 25 Hz. 1 eq of DCE (dichloroethylene) was required and the crude reaction mixture (containing some unreacted nicotinamide and starting benzoate sugar, $<10\%$) was used for the reduction step (described above) without further purification. It will be appreciated that the tribenzoyl nicotinamide riboside, triflate ($-\text{OTf}$) salt is not limited to being produced by this exact method, and could, for example, be produced using a conventional Vorbrüggen reaction as described, for example, in International PCT patent publication no. WO 2007/061798 or in T. Yang, N. Y. K. Chan and A. A. Sauve, *Journal of Medicinal Chemistry*, 2007, 50, 6458-6461.

^1H -NMR (MeOD, 400 MHz) $-\delta$ 9.59 (s, 1H, aromatic), 9.31 (d, 1H, $J=6.4$ Hz, aromatic), 8.94 (d, 1H, $J=8.1$ Hz, aromatic), 8.15 (dd, 1H, $J=8.1, 6.4$ Hz, aromatic), 7.90-7.94 (m, 6H, OBz), 7.50-7.54 (m, 3H, OBz), 7.31-7.38 (m, 6H, OBz), 6.79 (d, 1H, $J=3.9$ Hz, H-1 (anomeric)), 5.97 (dd, 1H, $J=5.6, 3.9$ Hz, H-2), 5.87 (t, 1H, $J=5.6$ Hz, H-3), 5.13-5.16 (m, 1H, H-4), 4.83-4.91 (m, 2H, H-5).

^{19}F -NMR (MeOD, 376 MHz) $-\delta$ -79.1 (triflate counterion)

Example 2

A compound of formula (II), namely NRH (reduced nicotinamide riboside, also known as 1-(β -D-ribofuranosyl)-1,4-dihydronicotinamide (the β -anomer form of which is shown in FIG. 4) was prepared as follows. The pH of the reaction medium described in the following example was in the region of about 6-8.

Reduced triacetyl nicotinamide riboside, namely triacetyl-1,4-dihydronicotinamide riboside, a compound of formula (III), prepared in Example 1(A) above, was deprotected using mechanochemical (MeOH, NaOH) processes to remove the acetyl moiety afforded NRH quantitatively. 100 mgs of (III) was dissolved in 0.5 mL of MeOH containing 0.05 g of NaOH. The compounds were reacted for 30 mins in a 1.5 ml steel vessel with a 1.5 cm diameter steel ball bearing in a Retsch MM400 mixer mill at 25 Hz.

^1H -NMR (MeOD, 400 MHz) $-\delta$ 7.18 (s, 1H, H-5), 6.14 (d, 1H, $J=8.28$ Hz, H-6), 4.85 (m, 1H, H-3), 4.76 (d, 1H, $J=5.77$

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Hz, H-4), 4.04 (m, 2H, H-7&H-8), 3.93 (m, 1H, $J=2.76, \text{H-9}$), 3.72 (ABX, 1H, $J_{aa}=12.55$ Hz, $J_{ab}=3.51$ Hz, H-10), 3.65 (ABX, 1H, $J_{aa}=12.55$ Hz, $J_{ab}=4.02$ Hz, H-10), 3.10 (q, 2H, $J=1.51$ Hz H-2). ^{13}C -NMR (MeOD, 125 MHz) $-\delta$ 172.88 (C-11), 137.83 (C-5), 125.29 (C-4), 105.19 (C-6), 95.00 (C-3), 83.54 (C-9), 71.10 (C-8), 70.20 (C-7), 61.61 (C-10), 22.09 (C-2); HRMS m/z : 257.1130; Calc. Mass: 257.1137.

It will be appreciated that the deprotection step as described above may be used to deprotect any other compound of formula (III), including, but not limited to, reduced triacetyl nicotinate ester riboside, namely 2,3,5-triacetyl O-ethyl-1,4-dihydronicotinamide riboside, prepared in Example 1(B), and reduced tribenzoyl nicotinamide riboside, namely tribenzoyl-1,4-dihydronicotinamide riboside, prepared in Example 1(C). The deprotection step may also be modified to suit particular requirements.

Example 3

Compounds of formula (I) were prepared in accordance with the invention as follows. The pH of the reaction media described in the following examples was in the region of about 6-8.

Example 3(A): Preparation of Nicotinamide Riboside, Chloride Salt (the β -Anomer Form of which is Shown in FIG. 5)

A compound of formula (II), namely NRH (reduced nicotinamide riboside, shown in FIG. 2; 50 mg, 0.20 mmol, 1 eq), was dissolved in 5 mL H_2O and then 1 eq (i.e. 0.20 mmol) of ammonium chloride was added in one portion. Activated charcoal (~ 10 mg, i.e. 0.80 mmol) was then added and the mixture stirred at RT for ~ 1 hr and then filtered and freeze-dried to give the chloride salt of nicotinamide riboside, quantitatively, i.e. 100% conversion and pure product.

^1H -NMR (D_2O , 400 MHz) $-\delta$ 9.46 (s, 1H, aromatic), 9.12 (dt, 1H, $J=6.3, 1.4$ Hz, aromatic), 8.83 (dt, 1H, $J=8.2, 1.4$ Hz, aromatic), 8.13 (dd, 1H, $J=8.2, 6.3$ Hz, aromatic), 6.13 (d, 1H, $J=4.3$ Hz, H-1 (anomeric)), 4.37 (t, 1H, $J=4.7$ Hz, H-2), 4.31-4.34 (m, 1H, H-4), 4.21 (t, 1H, $J=4.7$ Hz, H-3), 3.90 (ABX, 1H, $J_{aa}=13.0$ Hz, $J_{ab}=3.5$ Hz, H-5), 3.75 (ABX, 1H, $J_{aa}=13.0$ Hz, $J_{ab}=2.8$ Hz, H-5').

It will be appreciated that the NRH may be that obtained in Example 2, or may be obtained commercially from e.g. Diverchim, 100, rue Louis Blanc, 60 765 Montataire Cedex, France—(CAS Registry Number:19132-12-8) either as a pure product or as a mixture of anomers.

Example 3(B): Preparation of Nicotinamide Riboside, Acetate Salt (the β -Anomer Form of which is Shown in FIG. 5)

The method described in Example 3(A) was carried out, except that 1 eq (i.e. 0.20 mmol) of ammonium acetate was added. The acetate salt of nicotinamide riboside was obtained, quantitatively.

^1H -NMR (D_2O , 400 MHz) $-\delta$ 9.46 (s, 1H, aromatic), 9.12 (d, 1H, $J=6.3$ Hz, aromatic), 8.83 (d, 1H, $J=8.2$ Hz, aromatic), 8.12 (m, 1H, aromatic), 6.09 (d, 1H, $J=4.4$ Hz, H-1 (anomeric)), 4.36 (t, 1H, $J=4.7$ Hz, H-2), 4.32-4.35 (m, 1H, H-4), 4.21 (t, 1H, $J=4.7$ Hz, H-3), 3.91 (ABX, 1H, $J_{aa}=13.1$ Hz, $J_{ab}=2.8$ Hz, H-5), 3.75 (ABX, 1H, $J_{aa}=13.0$ Hz, $J_{ab}=3.5$ Hz, H-5'), 1.79 (s, 3H, OAc).

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Example 3(C): Preparation of Nicotinamide Riboside, Formate Salt (the β -Anomer Form of which is Shown in FIG. 5)

The method described in Example 3(A) was carried out, except that 1 eq (i.e. 0.20 mmol) of ammonium formate (methanoate) was added. The formate salt of nicotinamide riboside was obtained, quantitatively.

$^1\text{H-NMR}$ (D_2O , 400 MHz) δ 9.46 (s, 1H, aromatic), 9.12 (d, 1H, $J=6.3$ Hz, aromatic), 8.83 (d, 1H, $J=8.2$ Hz, aromatic), 8.29 (s, 1H, formate), 8.12 (m, 1H, aromatic), 6.09 (d, 1H, $J=4.4$ Hz, H-1 (anomeric)), 4.36 (t, 1H, $J=4.7$ Hz, H-2), 4.31-4.34 (m, 1H, H-4), 4.21 (t, 1H, $J=4.7$ Hz, H-3), 3.91 (ABX, 1H, $J_{a,a'}=13.1$ Hz, $J_{a,b}=3.5$ Hz, H-5), 3.79 (ABX, 1H, $J_{a,a'}=13.0$ Hz, $J_{a',b}=2.8$ Hz, H-5').

Example 3(D): Preparation of Nicotinamide Riboside, Trifluoroacetate Salt (the β -Anomer Form of which is Shown in FIG. 5)

The method described in Example 3(A) was carried out, except that 1 eq (i.e. 0.20 mmol) of ammonium trifluoroacetate was added. The trifluoroacetate salt of nicotinamide riboside was obtained, quantitatively.

$^1\text{H-NMR}$ (D_2O , 400 MHz) δ 9.46 (s, 1H, aromatic), 9.12 (d, 1H, $J=6.3$ Hz, aromatic), 8.83 (d, 1H, $J=8.2$, aromatic), 8.13 (dd, 1H, $J=8.2$, 6.3 Hz, aromatic), 6.13 (d, 1H, $J=4.3$ Hz, H-1 (anomeric)), 4.35 (t, 1H, $J=4.7$ Hz, H-2), 4.31-4.34 (m, 1H, H-4), 4.20 (t, 1H, $J=4.7$ Hz, H-3), 3.89 (ABX, 1H, $J_{a,a'}=13.0$ Hz, $J_{a,b}=3.6$ Hz, H-5), 3.74 (ABX, 1H, $J_{a,a'}=13.0$ Hz, $J_{a',b}=2.9$ Hz, H-5'). $^{19}\text{F-NMR}$ (D_2O , 376 MHz) δ -75.7 (CF_3COO^-).

Example 3(E): Preparation of Nicotinamide Riboside, Chloride Salt (the β -Anomer Form of which is Shown in FIG. 5)

An alternative method to that described in Example 3(A) was carried out as follows. NRH (reduced nicotinamide riboside, shown in FIG. 4; 50 mg, 0.20 mmol, leg) was dissolved in 5 mL $\text{H}_2\text{O}:\text{EtOAc}$ (1:1) and then 1 eq (i.e. 0.20 mmol) of ammonium chloride was added in one portion. Upon work-up after 1 hr, no oxidation had taken place and the starting materials were fully recovered. The recovered NRH and ammonium chloride were re-suspended in the same solvent system with addition of activated charcoal (~10 mg, i.e. 0.8 mmol) and stirred at RT for 1 hr. Subsequent filtration and freeze-drying afforded the chloride salt of nicotinamide riboside in quantitative yield. Thus it was concluded that a carbon-containing catalyst, e.g. activated charcoal, was essential to the method.

$^1\text{H-NMR}$ (D_2O , 400 MHz) δ 9.46 (s, 1H, aromatic), 9.12 (dt, 1H, $J=6.3$, 1.4 Hz, aromatic), 8.83 (dt, 1H, $J=8.2$, 1.4 Hz, aromatic), 8.13 (dd, 1H, $J=8.2$, 6.3 Hz, aromatic), 6.13 (d, 1H, $J=4.3$ Hz, H-1 (anomeric)), 4.37 (t, 1H, $J=4.7$ Hz, H-2), 4.31-4.34 (m, 1H, H-4), 4.21 (t, 1H, $J=4.7$ Hz, H-3), 3.90 (ABX, 1H, $J_{a,a'}=13.0$ Hz, $J_{a,b}=3.5$ Hz, H-5), 3.75 (ABX, 1H, $J_{a,a'}=13.0$ Hz, $J_{a',b}=2.8$ Hz, H-5').

Example 3(F): Preparation of Nicotinamide Riboside, Chloride Salt (the β -Anomer Form of which is Shown in FIG. 5)

The method described in Example 3(E) was carried out, except that NRH (reduced nicotinamide riboside, shown in FIG. 4; 50 mg, 0.20 mmol, 1 eq) was dissolved in 5 mL $\text{H}_2\text{O}:\text{THF}$ (1:1), instead of $\text{H}_2\text{O}:\text{EtOAc}$ (1:1), and then 1 eq

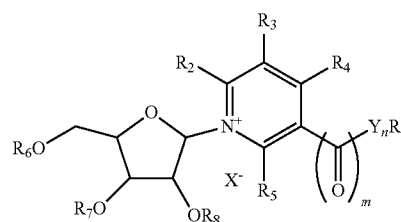
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(i.e. 0.20 mmol) of ammonium chloride was added in one portion. Upon work-up after 1 hr, no oxidation had taken place and the starting materials were fully recovered. The recovered NRH and ammonium chloride were re-suspended in the same solvent system with addition of activated charcoal (~10 mg, i.e. 0.8 mmol) and stirred at RT for 1 hr. Subsequent filtration and freeze-drying afforded the chloride salt of nicotinamide riboside in quantitative yield. Thus it was concluded that a carbon-containing catalyst, e.g. activated charcoal, was essential to the method.

$^1\text{H-NMR}$ (D_2O , 400 MHz) δ 9.46 (s, 1H, aromatic), 9.12 (dt, 1H, $J=6.3$, 1.4 Hz, aromatic), 8.83 (dt, 1H, $J=8.2$, 1.4 Hz, aromatic), 8.13 (dd, 1H, $J=8.2$, 6.3 Hz, aromatic), 6.13 (d, 1H, $J=4.3$ Hz, H-1 (anomeric)), 4.37 (t, 1H, $J=4.7$ Hz, H-2), 4.31-4.34 (m, 1H, H-4), 4.21 (t, 1H, $J=4.7$ Hz, H-3), 3.90 (ABX, 1H, $J_{a,a'}=13.0$ Hz, $J_{a,b}=3.5$ Hz, H-5), 3.75 (ABX, 1H, $J_{a,a'}=13.0$ Hz, $J_{a',b}=2.8$ Hz, H-5').

The invention claimed is:

1. A compound of formula (IV):



or the beta-anomer thereof,

where:

n is 0 and Y is absent;

m is 1;

R_1 is a substituted or unsubstituted primary amino;

R_2 - R_5 are each H;

R_6 , R_7 and R_8 , which may be the same or different, are each independently H or a hydroxyl-protecting group; or wherein R_6 is a phosphate; and

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

2. The compound of claim 1, wherein R_1 is $-\text{NH}_2$.

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.

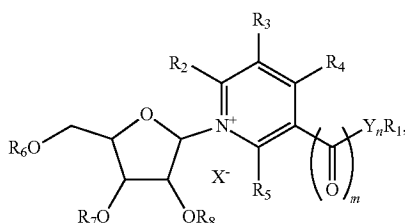
4. The compound of claim 3, wherein X^- is an anion, selected from an anion of an unsubstituted carboxylic acid other than an anion of formic acid, an anion of an unsubstituted phosphate, an anion of an unsubstituted sulfate, an anion of an unsubstituted carbonate, and an anion of an unsubstituted carbamate.

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.

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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;

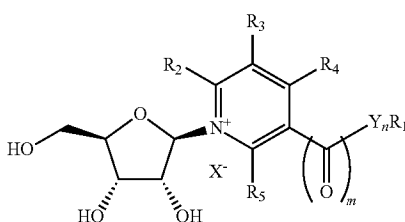
R₂-R₅ are each H;

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.

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

8. The compound of claim 1 of formula:



where:

n is 0 and Y is absent;

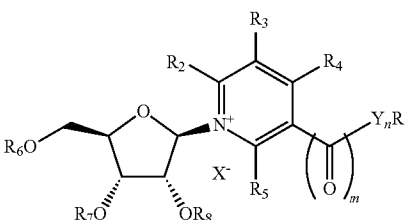
m is 1;

R₁ is —NH₂

R₂-R₅ are each H; and

X⁻ is an anion of a substituted monocarboxylic acid or an anion of an unsubstituted monocarboxylic acid other than formic acid.

9. The compound according to claim 1 of formula:



where:

n is 0 and Y is absent;

m is 1;

R₁ is —NH₂

R₂-R₅ are each H;

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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

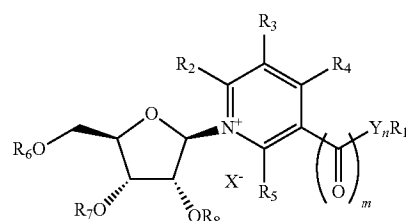
X⁻ is an anion of a substituted monocarboxylic acid, or an anion of an unsubstituted monocarboxylic acid other than formic acid.

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

11. The nutritional supplement composition of claim 10, wherein R₁ is —NH₂ and X⁻ is an anion of a substituted or unsubstituted dicarboxylic acid.

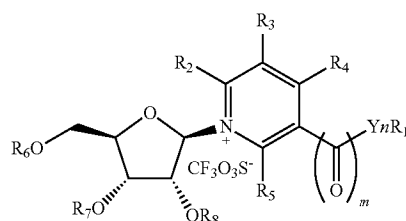
12. The nutritional supplement composition of claim 10, wherein R₁ is —NH₂ and R₆, R₇ and R₈, which may be the same or different, are each independently H or a hydroxyl-protecting group selected from unsubstituted acetyl, and unsubstituted benzoyl.

13. A method of making an isomerically pure compound of formula (IV) having a beta-D-ribofuranosyl configuration:



the method comprising the step of:

introducing the anion X⁻ into a starting isomerically pure trifluoromethanesulfonate compound of formula having a beta-D-ribofuranosyl configuration:



by reacting the starting trifluoromethanesulfonate compound, with a compound of formula Z⁺X⁻, where:

n is 0 or 1;

m is 0 or 1;

Y=O or S;

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 unsubstituted azido;

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;

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

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X^- is an anion selected from an anion of a substituted or unsubstituted carboxylic acid, a halide, a substituted or unsubstituted sulfonate other than trifluoromethanesulfonate, a substituted or unsubstituted phosphate, a substituted or unsubstituted sulfate, a substituted or unsubstituted carbonate, and a substituted or unsubstituted carbamate, and

Z^+ is a nitrogen-containing cation.

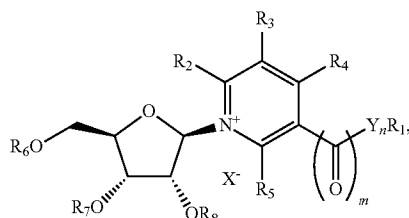
14. The method of claim 13, wherein R_1 is $-\text{NH}_2$.

15. The method of claim 13, wherein R_6 , R_7 and R_8 , which may be the same or different, are each independently H or a hydroxyl-protecting group selected from unsubstituted acetyl, and unsubstituted benzoyl.

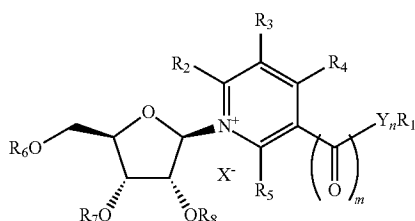
16. The method of claim 13, where the nitrogen containing cation is selected from a substituted or unsubstituted ammonium, a substituted or unsubstituted pyridinium, a substituted or unsubstituted pyrrolidinium, a substituted or unsubstituted imidazolium and a substituted or unsubstituted triazolium.

17. The method of claim 13, where Z^+ is a substituted or unsubstituted ammonium of the formula $\text{N}^+\text{HR}^{\text{I}}\text{R}^{\text{II}}\text{R}^{\text{III}}$, wherein R^{I} , R^{II} and R^{III} , 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.

18. A method of making an isomerically pure compound of formula (IV) having a beta-D-ribofuranosyl configuration:



the method comprising the step of:
introducing the anion X^- into a starting isomerically pure trifluoromethanesulfonate compound of formula having a beta-D-ribofuranosyl configuration:



by reacting the starting trifluoromethanesulfonate compound, with a compound of formula Z^+X^- ,
where:

n is 0 and Y is absent;

m is 1;

$R_1 = \text{NH}_2$;

R_2 - R_5 are each H;

R_6 , R_7 and R_8 , which may be the same or different, are each independently H or a hydroxyl-protecting group; or wherein R_6 is a phosphate;

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X^- is an anion, selected from an anion of a substituted or unsubstituted carboxylic acid, a halide, a substituted or unsubstituted phosphate, a substituted or unsubstituted sulfate, a substituted or unsubstituted carbonate, and a substituted or unsubstituted carbamate; and

Z^+ is a nitrogen-containing cation.

19. The method of claim 18, wherein R_6 , R_7 and R_8 , which may be the same or different, are each independently H or a hydroxyl-protecting group selected from unsubstituted acetyl, and unsubstituted benzoyl; and

X^- is an anion, selected from an anion of a substituted or unsubstituted carboxylic acid and a halide.

20. The method of claim 18, wherein X^- is an anion of a substituted or unsubstituted monocarboxylic acid.

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

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

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

24. The compound of claim 6, wherein the compound is the beta-anomer;

n is 0 and Y is absent;

m is 1;

$R_1 = \text{NH}_2$;

R_2 - R_5 are each H;

R_6 , R_7 and R_8 are each H; and

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

25. The compound of claim 6, wherein the compound is the beta-anomer;

n is 0 and Y is absent;

m is 1;

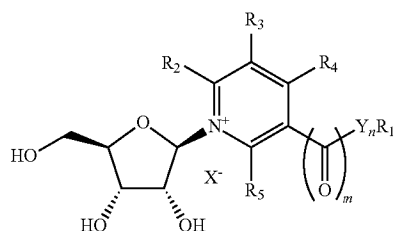
$R_1 = \text{NH}_2$;

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 or unsubstituted aminodicarboxylic acid.

26. The compound of claim 1 of formula:



where:

n is 0 and Y is absent;

m is 1;

$R_1 = \text{NH}_2$;

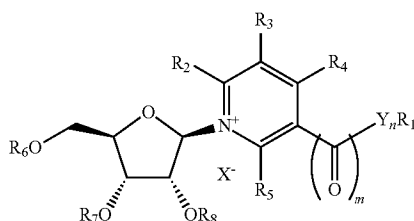
R_2 - R_5 are each H; and

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

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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.

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

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.

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.

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

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.

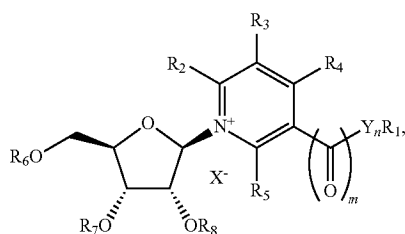
33. The compound of claim 6 that is a beta-anomer; wherein the compound has greater than 90% chemical purity, comprises at least 98% diastereomeric purity of the beta-D-ribofuranosyl configuration; and contains <3000 ppm methanol, under 0.1% (w/w) other solvents and under 0.2% (w/w) water.

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

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

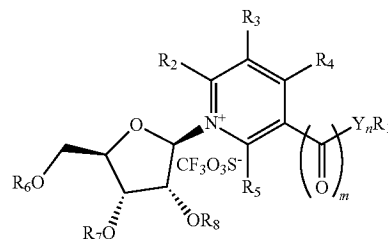
36. The method of claim 18, wherein X⁻ is an anion of a substituted or unsubstituted dicarboxylic acid.

37. A method of making an isomerically pure compound of formula (IV) having a beta-D-ribofuranosyl configuration:

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the method comprising the step of:

introducing the anion X⁻ into a starting isomerically pure trifluoromethanesulfonate compound of formula having a beta-D-ribofuranosyl configuration:



by reacting the starting trifluoromethanesulfonate compound, with a compound of formula Z⁺X⁻, wherein:

n is 0 or 1;

m is 0 or 1;

Y=O or S;

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 unsubstituted azido;

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;

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

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

Z⁺ is a nitrogen-containing cation.

38. The method of claim 13, wherein the compound is a beta-anomer; and wherein the compound has greater than 90% chemical purity, and comprises at least 98% diastereomeric purity of the beta-D-ribofuranosyl configuration.

39. The method of claim 13, wherein the compound is a beta-anomer; and 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.

40. The method of claim 18, wherein the compound is a beta-anomer; and wherein the compound has greater than 90% chemical purity, and comprises at least 98% diastereomeric purity of the beta-D-ribofuranosyl configuration.

41. The method of claim 18, wherein the compound is a beta-anomer; and 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.

42. The method of claim 37, wherein the compound is a beta-anomer; and wherein the compound has greater than 90% chemical purity, and comprises at least 98% diastereomeric purity of the beta-D-ribofuranosyl configuration.

43. The method of claim 37, wherein the compound is a beta-anomer; and 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.

* * * * *

EXHIBIT 2



Patent Assignment Abstract of Title

Search results for Patent #: 12252506

Generated on Tue Apr 28 2026 09:05:23 GMT-0700 (Pacific Daylight Time)

Invention title	Patent number	Application number	Publication number	PCT number
METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF	12252506	18307733	20240101588	N/A
	Issue date	View in PPUBS	View in PPUBS	International number
Inventors	Mar 18, 2025	Filing date	Publication date	N/A
Marie MIGAUD , Philip REDPATH, Kerri CROSSEY, Mark DOHERTY		Apr 26, 2023	Mar 28, 2024	

Assignment 1

Reel/ Frame

[68081/0169](#)

Pages

22

Conveyance

ASSIGNMENT OF
ASSIGNOR'S INTEREST

Documents

[View documents](#)

Recorded

Jul 25, 2024

Assignors & execution date

[MIGAUD, MARIE](#)

May 2, 2017

[REDPATH, PHILIP](#)

Feb 14, 2017

[CROSSEY, KERRI](#)

Feb 14, 2017

[View more](#)

Assignee

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BOULDER, CO 80301

Attorney docket number

339362 : 4-16C US

EXHIBIT 3

Amazon Patent Evaluation Express Agreement

This Amazon Patent Evaluation Express (APEX) Agreement (“Agreement”) is between the Patent Owner (or Patent Owner’s authorized representative) listed in Exhibit 1 and the Seller or Sellers (or their authorized representative(s)) listed in Exhibit 2 (collectively, “Participants”).

Amazon.com, Inc. (“Amazon”) has developed the APEX Procedure (“Procedure”) for owners of United States utility patents to obtain an evaluation of their patent infringement claims against products offered by third-party sellers on amazon.com (“Evaluation”). By executing this agreement, the Patent Owner represents and warrants that it owns or has the right to enforce the patent identified in Exhibit 1 (“Patent”), and asserts that listings identified by the Amazon Standard Identification Numbers (“ASINs”) in Exhibit 1 (“Products”) infringe the patent claim identified in Exhibit 1.

By respectively executing Exhibits 1 and 2, Patent Owner and Seller agree as follows:

- 1. Following the Evaluation Procedure.** Patent Owner and Seller have reviewed and agree to comply with the Procedure, which is incorporated herein by reference. Patent Owner agrees to accurately complete Exhibit 1, and Seller agrees to accurately complete Exhibit 2. Both Exhibits 1 and 2 are incorporated herein by reference.
- 2. Confidentiality; No Discovery.** Participants agree not to disclose to third parties information or documents learned from other Participants, Amazon, or Evaluator in the Evaluation, except to their respective affiliates, legal counsel or as required by law; provided, however, that the fact that an Accused Product and ASIN (identified in Exhibit 1) was either removed or not as a result of an Evaluation, and the identity of the patent claim in that Evaluation, shall not be considered confidential. Participants agree that receipt or disclosure of any information relating to patents in APEX may not be used in court or any agency proceeding to establish notice of patent infringement, knowledge of any patent, or to establish damages. Participants agree not to seek discovery from other Participants, Amazon, or Evaluator relating to the Evaluation in any litigation, arbitration, or agency proceeding.
- 3. Waiver of Claims.** Participants acknowledge and agree that neither Amazon nor Evaluator shall be liable for any claims arising out of the Procedure or Evaluation, and Participants hereby waive any claims (including claims that are unknown or are based on activities that have not yet occurred) against Amazon or Evaluator relating to the Procedure or Evaluation; provided that, the foregoing shall not be deemed to waive any rights or claims of a Participant to receive a refund of amounts paid by a Participant that should be returned to a Participant pursuant to the rules of the Procedure. Participants agree that Amazon’s liability to any Participant relating to the Evaluation is limited to any payment made by that Participant to the Evaluator. Participants agree not to sue Amazon or its affiliates for infringement of the Patent with respect to the ASINs listed on Exhibit 1 or materially identical products. Nothing in this Agreement shall limit a Participant’s ability to sue any Seller or other third party for infringement of the Patent.
- 4. Updating Participant’s Information.** Contact during the Evaluation will occur through the email addresses listed in Exhibits 1 and 2. It is each Participant’s responsibility to ensure that its email address and other information in Exhibits 1 and 2 remain accurate and current.
- 5. General Matters.** This Agreement shall be governed by the laws of the state of Washington, USA, and Participants agree to the jurisdiction and venue of the federal and state courts located in King County, Seattle, Washington. Any dispute regarding this Agreement may be submitted to the Evaluator, and if not resolved by the Evaluator may only be resolved by Amazon, in its sole discretion. Participants may not assign their rights or obligations under this Agreement. This Agreement does not create any partnership or any fiduciary relationship between or among the Participants, the Evaluator and Amazon. No third party is intended to be a beneficiary of this Agreement, except that the parties agree and acknowledge that the Evaluator and Amazon are third- party beneficiaries of Sections 2 and 3 of this Agreement. This Agreement and the APEX Procedure are the entire agreement for the Evaluation and supersede any prior agreements related to the Evaluation.

Exhibit 1: Patent Owner-Supplied Information

Patent Owner name: [ChromaDex, Inc. is the owner of the patent pursuant to an assignment from The Queens Belfast \(Great Britan\) dated December 16, 2025](#)

Patent Owner physical address: [ChromaDex, Inc.10900, Wilshire Blvd., Suite 600, Los Angeles, California 90024](#)

Names of any corporate parents, subsidiaries, or other entities related to Patent Owner:

[ChromaDex, Inc. is a wholly owned subsidiary of Niagen Bioscience, Inc.](#)

Name of individual contact for Patent Owner or Patent Owner's authorized representative:

[Carlos Lopez, SVP, General Counsel, ChromaDex, Inc.](#)

Is Patent Owner registered in Amazon's Brand Registry? If yes, please identify the brand(s) registered in Brand Registry: [Yes. Tru Niagen](#)

Email Address for contact (this email address will be used by the Evaluator and Amazon for communications related to the Evaluation): carlos.lopez@niagenbio.com

United States utility patent number ("Asserted Patent") for Evaluation: [Claim 1](#)

Patent Claim number for Evaluation: [US Patent No. 12,252,506](#)

Amazon Standard Identification Numbers (ASINs) of Accused Products:

B097Z5387H	B0F6LGQCQ7	B0FFSRQ3QR		
B08WPXPTD8	B0DKVD9PBX	B0C35GXZSP		
B0F5BQ86B8	B0F5PZ49FP			
B0DXZYN2BR	B0B14F9PSR			

Signed by:

Signature:



8059C6EE53FA45A...

Name:

[Carlos Lopez](#)

Title:

[SVP, General Counsel](#)

Date:

[04/07/2026](#)

Exhibit 2: Seller-Supplied Information

Seller name:

Seller physical address:

Names of any corporate parents, subsidiaries, or other entities related to Seller:

Name of individual contact for Seller or Seller's authorized representative:

Email Address for contact (this email address will be used by the Evaluator and Amazon for communications related to the Evaluation):

Amazon Standard Identification Numbers (ASINs) of Accused Products for which Seller will participate in the Evaluation:

Signature: _____

Name: _____

Title: _____

Date: _____

EXHIBIT 4



NEWS RELEASE

Niagen Bioscience Acquires Existing Core Nicotinamide Riboside (NR) Patent Portfolio from Queen's University Belfast

2025-12-22

This acquisition establishes Niagen Bioscience as the sole owner of the most comprehensive and defensible intellectual property portfolio in the NAD+ industry

LOS ANGELES--(BUSINESS WIRE)-- **Niagen Bioscience, Inc.** (NASDAQ: NAGE), the global authority on NAD+ (nicotinamide adenine dinucleotide) with a focus on the science of healthy aging, today announced that it has acquired a comprehensive portfolio of existing patents covering nicotinamide riboside (NR) and its salt forms from Queen's University Belfast (QUB), further strengthening the Company's long-standing leadership and ownership position in NAD+ precursor intellectual property.

The acquired portfolio comprises the core body of patents underpinning the production, composition, and commercial use of NR, encompassing foundational composition-of-matter patents covering crystal morphologies, methods of making NR and other NAD+ precursors, and global patent rights spanning multiple jurisdictions. Prior to this transaction, Niagen Bioscience previously held exclusive rights to these patents through long-standing licensing and joint ownership arrangements with QUB. With this acquisition, Niagen Bioscience now becomes the sole owner of this critical IP portfolio.

"This transaction consolidates the most important intellectual property underlying our NR business into Niagen Bioscience outright," said Rob Fried, Chief Executive Officer of Niagen Bioscience. "Composition of matter patents are the strongest form of IP protection, and owning this portfolio further protects Niagen Bioscience shareholders against infringers of all known forms of the greatest precursor to NAD, NR."

The acquired patents include those previously **disclosed** by the Company in March 2025, including U.S. Patent No. **12,252,506**, which covers the composition of matter for multiple NR salt forms—such as NR Malate and NR Tartrate—as well as other NR derivatives. Composition-of-matter patents are widely regarded as the strongest form of intellectual property protection because they cover the patented molecule itself and its defined forms, regardless of specific manufacturing pathways or methods of use.

With the acquisition of this portfolio, Niagen Bioscience gains enhanced financial, strategic and operational flexibility, greater control over the molecules it advances across current and future applications, including the ones that the Company plans to use for pharmaceutical applications. This also represents increased optionality in how the intellectual property is developed, partnered, or licensed. The Company's intellectual property estate includes more than 90 issued and pending patents worldwide across NR and other NAD⁺ precursors, including over 50 issued and pending patents focused solely on NR, reflecting decades of leadership in NAD⁺ science and innovation.

Niagen Bioscience continuously evaluates next-generation NAD⁺ precursors while maintaining the category's most robust and defensible IP position.

For additional information on the IP and clinical research behind Niagen, visit www.niagenbioscience.com.

About Niagen Bioscience:

Niagen Bioscience, Inc. (NASDAQ: NAGE), formerly ChromaDex Corp., is the global leader in NAD⁺ (nicotinamide adenine dinucleotide) science and healthy-aging research. As a trusted pioneer of NAD⁺ discoveries, Niagen Bioscience[™] is dedicated to advancing healthspan through precision science and innovative NAD⁺-boosting solutions.

The Niagen Bioscience team, composed of world-renowned scientists, works with independent investigators from esteemed universities and research institutions around the globe to uncover the full potential of NAD⁺. A vital coenzyme found in every cell of the human body, NAD⁺ declines with age and exposure to everyday lifestyle stressors. NAD⁺ depletion is a key contributor to age-related changes in health and vitality.

Distinguished by state-of-the-art laboratories, rigorous scientific and quality protocols, and collaborations with leading research institutions worldwide, Niagen Bioscience sets the gold standard for research, quality, and innovation. There's a better way to age.

At the heart of its clinically proven product portfolio is Niagen[®] (patented nicotinamide riboside, or NR), the most efficient, well-researched, high-quality, and legal NAD⁺ booster available. Niagen powers the Company's consumer supplement, Tru Niagen[®], the number one NAD⁺ boosting oral supplement in the United States[†] (available at

www.truniagen.com), and Niagen Plus™, featuring pharmaceutical-grade intravenous (IV) and injectable Niagen products (www.niagenplus.com). Pharmaceutical-grade Niagen IV and injections are compounded and distributed by U.S. FDA-registered 503B outsourcing facilities and are available exclusively at clinics with a prescription.

Niagen Bioscience's robust patent portfolio protects NR and other NAD+ precursors. Niagen Bioscience maintains a website at www.niagenbioscience.com, where copies of press releases, news, and financial information are regularly published.

† Based on the top-selling dietary supplement brands by revenue per the largest U.S. e-commerce marketplace (as of 1/1/2024 - 12/31/2024).

Forward Looking Statements:

This release contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, and Section 21E of the Securities Exchange Act of 1934. Statements that are not a description of historical facts constitute forward-looking statements and may often, but not always, be identified by the use of such words as "expects," "anticipates," "intends" "estimates," "plans," "potential," "possible," "probable," "believes" "seeks," "may," "will," "should," "could," "predicts," "projects," "continue," "would" or the negative of such terms or other similar expressions.

Forward-looking statements are based on current expectations and assumptions and are subject to risks and uncertainties that could cause actual results to differ materially from those described. These risks and uncertainties include, but are not limited to, inflationary conditions and adverse economic conditions; our history of operating losses; the growth and profitability of our product sales; our ability to maintain and grow sales, marketing and distribution capabilities; changing consumer perceptions of our products; our reliance on a single or limited number of third-party suppliers; risks of conducting business in China; including unanticipated developments in and risks related to the Company's ability to secure adequate quantities of pharmaceutical-grade Niagen in a timely manner; the Company's ability to obtain appropriate contracts and arrangements with U.S. FDA-registered 503B outsourcing facilities required to compound and distribute pharmaceutical-grade Niagen to clinics; the Company's ability to remain on the U.S. FDA Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act Category 1 list; the Company's ability to maintain and enforce the Company's existing intellectual property and obtain new patents; whether the potential benefits of NRC can be further supported; further research and development and the results of clinical trials possibly being unsuccessful or insufficient to meet applicable regulatory standards or warrant continued development; the ability to enroll sufficient numbers of subjects in clinical trials; determinations made by the FDA and other governmental authorities, including with respect to products seeking to compete in our market; economic and market instability, including as a result of tariffs or trade conflicts; and the risks and uncertainties associated with our business and

financial condition in general, described in our filings with the Securities and Exchange Commission (SEC), including, without limitation, our most recent Annual Report on Form 10-K and Quarterly Report on Form 10-Q as filed with the SEC.

Readers are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof, and actual results may differ materially from those suggested by these forward-looking statements. All forward-looking statements are qualified in their entirety by this cautionary statement and Niagen Bioscience undertakes no obligation to revise or update this release to reflect events or circumstances after the date hereof.

Niagen Bioscience Media Contact:

Kendall Knysch, Senior Director of Media Relations & Partnerships

310.405.5227

kendall.knysch@niagenbio.com

Niagen Bioscience Investor Relations Contact:

Valter Pinto, Managing Director

KCSA Strategic Communications

212.896.1254

Niagen@kcsa.com

Source: Niagen Bioscience, Inc

EXHIBIT 5

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

☒ ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2025

or

☐ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934.

For the transition period from _____ to _____.

Commission file number 001-37752

NIAGEN BIOSCIENCE, INC.

(Exact name of Registrant as specified in its Charter)

Delaware

26-2940963

(State or other jurisdiction of incorporation)

(I.R.S. Employer Identification No.)

10900 Wilshire Blvd. Suite 600, Los Angeles, CA 90024

(Address of Principal Executive Offices and Zip Code)

Registrant's telephone number, including area code (310) 388-6706

Securities registered pursuant to Section 12(b) of the Act:

<u>Title of each class</u>	<u>Trading Symbol</u>	<u>Name of each exchange on which registered</u>
Common Stock, \$0.001 par value per share	NAGE	The Nasdaq Capital Market

Securities registered pursuant to Section 12(g) of the Act: **None.**

[Table of Contents](#)**Patents, Trademarks, Licenses, or Royalty Agreements, Including Duration**

We currently protect our intellectual property through patents, trademarks, designs and copyrights on our products and services. We have used and, to a limited extent, continue to use intellectual property to create new proprietary ingredients. We aim to develop and commercialize these proprietary ingredients ourselves as well as grant licenses to external companies for their commercialization.

The following table sets forth our existing patents and those to which we have licensed rights:

Patent Number	Title	Filing Date	Issued Date	Expires	Licensor
8,106,184	Nicotinyl Riboside Compositions and Methods of Use	11/17/2006	1/31/2012	9/20/2027	Licensed from Cornell University
9,000,147	Nicotyl riboside compositions and methods of use	1/17/2012	4/7/2015	11/17/2026	Licensed from Cornell University
9,321,797	Nicotyl riboside compositions and methods of use	11/17/2014	4/26/2016	11/17/2026	Licensed from Cornell University
9,975,915	Crystalline forms of nicotinoyl ribosides, modified derivatives thereof, and phosphorylated analogs thereof, and methods of preparation thereof	11/10/2017	5/22/2018	11/10/2037	Owned by Niagen Bioscience
10,000,519	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof	7/24/2014	6/19/2018	7/24/2034	Owned by Niagen Bioscience
10,000,520	B-vitamin and amino acid conjugates of nicotinoyl ribosides and reduced nicotinoyl ribosides, derivatives thereof, and methods of preparation thereof	3/16/2017	6/19/2018	3/16/2037	Owned by Niagen Bioscience
10,183,036	Use of nicotinic acid riboside or nicotinamide riboside derivatives, and reduced derivatives thereof, as NAD ⁺ increasing precursors	4/20/2017	1/22/2019	4/20/2037	Owned by Niagen Bioscience
10,280,190	Nicotinic acid riboside or nicotinamide riboside compositions, reduced derivatives thereof, and the use thereof to enhance skin permeation in treating skin conditions	3/16/2016	5/7/2019	5/31/2036	Owned by Niagen Bioscience
10,688,118	Nicotinamide riboside compositions for topical use in treating skin conditions	10/30/2014	6/23/2020	4/6/2035	Owned by Niagen Bioscience
10,689,411	Efficient and scalable syntheses of nicotinoyl ribosides and reduced nicotinoyl ribosides, modified derivatives thereof, phosphorylated analogs thereof, adenylyl dinucleotide conjugates thereof, and novel crystalline forms thereof	11/10/2017	6/23/2020	11/10/2037	Owned by Niagen Bioscience
10,815,262	Methods of preparing nicotinamide riboside and derivatives thereof	2/27/2018	10/27/2020	7/24/2034	Owned by Niagen Bioscience
10,857,172	Use of nicotinamide riboside, nicotinic acid riboside, and nicotinamide mononucleotide, reduced nicotinyl compounds, and nicotinoyl compound derivatives in infant formula for healthy development	4/14/2017	12/8/2020	4/14/2037	Owned by Niagen Bioscience
10,934,322	B-vitamin and amino acid conjugates of nicotinoyl ribosides and reduced nicotinoyl ribosides, derivatives thereof, and methods of preparation thereof	5/11/2018	3/2/2021	3/16/2037	Owned by Niagen Bioscience
11,033,568	Nicotinamide riboside compositions for topical use in treating skin conditions	6/3/2020	6/15/2021	10/30/2034	Owned by Niagen Bioscience
11,071,747	Use of NAD precursors for breast enhancement	11/29/2017	7/27/2021	11/29/2037	Licensed from University of Iowa
11,214,589	Crystalline forms of nicotinoyl ribosides and derivatives thereof, and methods of preparation thereof	12/10/2019	1/4/2022	8/16/2040	Owned by Niagen Bioscience

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Patent Number	Title	Filing Date	Issued Date	Expires	Licensor
11,242,364	Efficient and scalable syntheses of nicotinoyl ribosides and reduced nicotinoyl ribosides, modified derivatives thereof, phosphorylated analogs thereof, adenylyl dinucleotide conjugates thereof, and novel crystalline forms thereof	5/18/2021	2/8/2022	11/10/2037	Owned by Niagen Bioscience
11,274,117	Efficient and scalable syntheses of nicotinoyl ribosides and reduced nicotinoyl ribosides, modified derivatives thereof, phosphorylated analogs thereof, adenylyl dinucleotide conjugates thereof, and novel crystalline forms thereof	4/30/2021	3/15/2022	11/10/2037	Owned by Niagen Bioscience
11,345,720	Efficient and scalable syntheses of nicotinoyl ribosides and reduced nicotinoyl ribosides, modified derivatives thereof, phosphorylated analogs thereof, adenylyl dinucleotide conjugates thereof, and novel crystalline forms thereof	12/15/2021	5/31/2022	11/10/2037	Owned by Niagen Bioscience
11,524,022	Use of nicotinamide riboside, nicotinic acid riboside, and nicotinamide mononucleotide, reduced nicotinyl compounds, and nicotinoyl compound derivatives in infant formula for healthy development	4/14/2017	12/13/2022	4/14/2037	Owned by Niagen Bioscience
11,571,413	Nicotinamide riboside treatments of domesticated meat animals	6/26/2020	2/7/2023	9/27/2039	Licensed from Kansas State University
11,584,770	Methods of preparing nicotinamide riboside and derivatives thereof	5/4/2022	2/21/2023	7/24/2034	Owned by Niagen Bioscience
11,633,421	Use of NAD precursors for improving maternal health and/or offspring health	11/29/2017	4/25/2023	6/19/2039	Licensed from University of Iowa
11,746,123	Efficient and scalable syntheses of nicotinoyl ribosides and reduced nicotinoyl ribosides, modified derivatives thereof, phosphorylated analogs thereof, adenylyl dinucleotide conjugates thereof, and novel crystalline forms thereof	6/22/2020	9/05/2023	11/10/2037	Owned by Niagen Bioscience
11,981,698	Methods of Preparing reduced Nicotinamide Riboside and Derivatives Thereof	5/4/2022	5/14/2024	7/24/2034	Owned by Niagen Bioscience
12,195,494	Efficient and scalable syntheses of nicotinoyl ribosides and reduced nicotinoyl ribosides, modified derivatives thereof, phosphorylated analogs thereof, adenylyl dinucleotide conjugates thereof, and novel crystalline forms thereof	8/24/2023	1/14/2025	11/10/2037	Owned by Niagen Bioscience
12,252,506	Methods of Preparing reduced Nicotinamide Riboside and Derivatives Thereof	4/26/2023	3/18/2025	7/24/2034	Owned by Niagen Bioscience
12,433,908	Use of nicotinamide riboside, nicotinic acid riboside, and nicotinamide mononucleotide, reduced nicotinyl compounds, and nicotinoyl compound derivatives in infant formula for healthy development	11/30/2022	10/7/2025	4/14/2037	Owned by Niagen Bioscience
12,485,134	Use of nicotinamide riboside, nicotinic acid riboside, reduced nicotinyl riboside compounds, and nicotinyl riboside compound derivatives in formulations	2/21/2020	12/2/2025	10/8/2041	Owned by Niagen Bioscience

EXHIBIT 6

Amazon Patent Evaluation Express Procedure

To efficiently resolve claims that third-party product listings infringe utility patents, Amazon offers a simple, low-cost procedure called Amazon Patent Evaluation Express (APEX). APEX is voluntary, confidential, and allows owners of U.S. utility patents or their authorized representatives, such as attorneys or exclusive licensees ("Patent Owner") to obtain a fast evaluation of patent infringement claims against products ("Accused Products"), identified by Amazon Standard Identification Number, listed by third-party sellers ("Sellers") on amazon.com ("Evaluation"). In APEX, a neutral evaluator reviews a patent infringement claim against third-party product listings on amazon.com. The evaluator will make a yes/no decision about whether the patent covers the product listings. The evaluator may decide that the patent does not cover the product listings because: they do not infringe (i.e., include all elements of the asserted claim); a court has found the patent invalid or unenforceable; or the accused products (or physically identical products) were on sale more than one year before the earliest effective filing date of the patent. Amazon will comply with the evaluator's decision pending any litigation or settlement between the patent owner and Sellers, or other legal proceedings that may impact the patent. If there is litigation pending on a patent subject to a proposed or pending Evaluation, Amazon may decide not to initiate or suspend an Evaluation until the completion of that litigation.

If an evaluator concludes that an Accused Product is covered by a patent, Amazon will remove that Accused Product from www.amazon.com. The cost of the Evaluation is \$4,000 and covers the Evaluator's expenses; Amazon will not retain any portion of the cost. The cost will be paid by the participant(s) losing the Evaluation in the event an Evaluation actually occurs.

1. Starting an Evaluation. To request an Evaluation, a Patent Owner submits an APEX Agreement ("Agreement") to Amazon, with all information requested in its Exhibit 1. Amazon then sends that Agreement to each Seller listing Accused Products and gives each the option of: (i) executing and returning the Agreement within three weeks, with all information requested in its Exhibit 2; or (ii) having their listings on Accused Products removed from www.amazon.com. If a Seller does not participate in the Evaluation or does not comply with the Agreement, Amazon intends to remove its listings of Accused Products along with any materially identical variants. After receiving a completed Agreement from one or more Sellers, Amazon will use the information in Exhibits 1 and 2 of the Agreement to select a neutral individual from a list of attorneys experienced in U.S. patent disputes ("Evaluator"). It is critical that each of Exhibits 1 and 2 be filled out completely, including with the full corporate names of each Participant, as well as all of their related companies, so that Amazon can select a neutral evaluator.

2. Payment and Schedule. Once an Evaluator is selected, Amazon will contact the Patent Owner and each Seller with instructions to wire \$4,000 to the Evaluator. When wiring the \$4,000, a party should identify in the wire transmittal the evaluation number and the name of the Participant in the evaluation for which the payment is being made. Each Participant should also email the Evaluator with the confirmation number for the wire once it has been sent. If the Patent Owner does not submit \$4,000 to the Evaluator within one week, no Evaluation will occur and any money submitted by Sellers will be returned. If a Seller does not submit \$4,000 within one week, the Evaluator will notify Amazon, who will then remove that Seller's listings of Accused Products. If no Seller submits \$4,000, Amazon will remove all Sellers' listings of the Accused Products and the Evaluator will return the Patent Owner's payment.

3. Submission of Written Arguments. After the Patent Owner and a Seller have timely submitted \$4,000, the Evaluator will set a schedule for submission of written arguments ("Schedule"). In general, the Schedule will

provide: (i) the Patent Owner with 14 days for its initial arguments; (ii) Sellers with 14 days to respond; and (iii)

the Patent Owner with 7 days to reply. Modifications to the schedule can be requested for good cause only. The Patent Owner may use a total of 20 double-spaced 8.5 x 11" pages between its two submissions. Each Seller may use 15 double-spaced pages in its response. Claim charts and exhibits are not counted against page limits. Each submission must be in English and emailed to the Evaluator and to the opposing Participants in the same email; physical exhibits cannot be submitted. Failure to timely make a submission by a Participant will generally result in a finding by the Evaluator against that Participant and forfeiture of its payment, except that the Patent Owner may waive reply. In appropriate circumstances, the Evaluator may request that the Participants answer discrete questions that will aid the Evaluator in the Evaluator's determination, and the Evaluator may extend the schedule and briefing limits modestly to enable the Participants to answer such questions.

4. Evaluation is a Limited Procedure. To make the Evaluation fast, efficient, and relatively low-cost, it is limited to one claim from one unexpired U.S. utility patent. Design, non-U.S., and expired patents are not eligible. The Patent Owner may include up to 10 ASINs in an Evaluation. If a Patent Owner lists more than 10 ASINs in Exhibit 1 to the Agreement, Amazon may in its sole discretion reduce the Patent Owner's list to 10 ASINs.

Amazon or the Evaluator may exclude ASINs of Accused Products not physically identical for purposes of the Evaluation. When excluding ASINs, the Evaluator will notify Amazon as well as the Patent Owner and implicated Sellers of the excluded ASINs, while also giving the Patent Owner and the implicated Sellers a time deadline and parameters for submitting their respective arguments for and against inclusion of the excluded ASINs. Each of the Patent Owner and Sellers have the option, in their sole discretion, whether or not to submit their respective arguments. The Evaluator will consider submitted arguments, if any, in deciding finally on excluding the ASINs. The Evaluator will communicate to the Participants whether any ASINs have been excluded and if so, which ones.

If Evaluator's exclusion of ASINs results in any of the Sellers having no remaining products in the Evaluation, the Evaluator will return those Sellers' \$4000 payments, those Sellers will no longer be Participants in the Evaluation, and the Evaluator will not consider those Sellers' respective responsive arguments, if any.

The Evaluation will address only Accused Products sold solely by third-party sellers on www.amazon.com. The Evaluator will consider whether a Product likely infringes. The process is intended to evaluate the Accused Products in the listings on the date ("Complaint Date") that the Patent Owner executed the Evaluation Agreement. Any manipulation of the Accused Products, or any manipulation of the listings on amazon.com for Accused Products, after the Complaint Date by a participating Seller will be grounds for the Evaluator to find for the Patent Owner and/or for Amazon to remove the listing of that Seller. Any Seller making such a change may lose all (or part, if there is more than one losing Seller) of its \$4,000 in accordance with Section 6, below.

Amazon reserves the right to terminate an Evaluation at any time, if Amazon determines that a participant has acted improperly in connection with that Evaluation. Such conduct may include: failure to follow this Procedure; failure to abide by the terms of the Agreement; incorrectly filling out an Agreement; providing false information to Amazon or the Evaluator; or any other action that Amazon determines is fraudulent or a misuse of the Evaluation procedure. In addition to terminating an Evaluation for such conduct, Amazon may take down ASINs, prohibit future sales of products, prohibit future filings of Evaluations, and encourage an Evaluator to enter a decision against that participant.

If more than four Sellers opt in and make the required \$4,000 deposit in a single Evaluation case, the Evaluator will give the Patent Owner the option of: (i) limiting the Evaluation so that it applies to no more than four Sellers; or (ii) making one or more additional payments to the Evaluator so that multiple concurrent Evaluations can take

place, each with no more than four Sellers. If the Patent Owner decides to limit the Evaluation to four Sellers and not to proceed in concurrent evaluations against the remaining sellers that opted in and made timely deposits, the Evaluator will return the \$4,000 payments to those Sellers who have not been chosen by the Patent Owner to continue in the Evaluation. The Evaluation will then proceed with four sellers. At the completion of the Evaluation, the Patent Owner may institute one or more additional Evaluations against the other Sellers that opted in, which Amazon intends to have proceed with the same Evaluator as the first Evaluation to minimize the chances of inconsistent results. If the Patent Owner decides to conduct Evaluations against more than four Sellers, the Patent Owner must pay to the Evaluator \$4,000 for each additional Evaluation that will be conducted. Once those payments have been made, the Evaluations will be conducted generally in parallel, with the Evaluator setting a schedule for each and limiting communications for each Evaluation to the Patent Owner and the Sellers involved in that Evaluation. If the Patent Owner does not make an election within one week of notice from the Evaluator that more than four sellers have opted in of whether to proceed against only four Sellers or to conduct multiple Evaluations, no Evaluation will proceed and the Evaluator will return the payments of all parties.

Only two defenses other than non-infringement based on failure to meet one or more claim limitations will be considered by the Evaluator. First, Sellers can defend on the basis of invalidity and/or unenforceability of the asserted patent claim by providing a finding by a court of competent jurisdiction, or by the U.S. Patent Office or U.S. International Trade Commission ("ITC"), that the asserted patent claim is invalid or unenforceable. Arguments regarding, for example, invalidating prior art will not be accepted; the only way Sellers can show invalidity/unenforceability is by presenting a court, Patent Office, or ITC order finding an asserted patent claim invalid or unenforceable. Second, Sellers may show that the Accused Products (or physically identical products) were on sale one year or more before the asserted patent's earliest effective filing date, only by using credible evidence that the Evaluator can independently observe (such as a date of sale on amazon.com, or on the Wayback Machine). The Evaluator will not accept affidavits, declarations, or mere arguments about the date of a sale; the Seller must come forward with independently verifiable objective evidence that the Evaluator can confirm.

The Evaluator will consider infringement under the doctrine of equivalents only if the Patent Owner argues for infringement under the doctrine in its opening brief. Doctrine of equivalents arguments made for the first time in a reply brief will not be considered by the Evaluator.

No discovery (*e.g.*, depositions, document requests, etc.) will occur in the Evaluation, nor will there be a trial or hearing. The Patent Owner and Sellers may not contact the Evaluator, unless by email in response to an inquiry from the Evaluator, while copying the other parties. The Evaluator may consider any information submitted, giving any weight to that information the Evaluator believes appropriate.

5. Decision. Within 14 days of the reply date, the Evaluator will announce a decision, choosing between: (i) the Patent Owner is likely to prove that the Accused Product infringes the asserted claim; or (ii) the Patent Owner is not likely to prove that the Accused Product infringes the asserted claim. The Evaluator will not provide reasoning if the Evaluator decides that the Patent Owner is likely to prove that the Accused Product infringes the asserted claim, although the Evaluator may provide a brief explanation of how certain claim terms were construed where appropriate. If the Evaluator decides that Patent Owner is not likely to prove that the Accused Product infringes, the Evaluator shall provide a brief explanation of why the Patent Owner is unlikely to prove infringement. The Participants will not contact or question the Evaluator regarding his or her decision. There is no process for

reconsideration of the Evaluator's decision, though either side may appeal to Amazon by providing a court order that conflicts with the Evaluator's decision concerning invalidity or infringement.

6. Disposition of Payments Following Evaluation. If the Evaluator decides the Patent Owner is likely to prove that all Accused Products infringe, the Evaluator will return the Patent Owner's \$4,000 and retain a total of \$4,000 divided evenly among the participating Sellers. If more than one Seller has participated and is found to infringe, the Evaluator will give any amount of money deposited from losing Sellers in excess of \$4,000 to an Internal Revenue Code Section 501(c)(3) charitable organization chosen by the Patent Owner. If the Evaluator decides the Patent Owner is not likely to prove that any Accused Product infringes, the Evaluator will return participating Sellers' payments and retain the Patent Owner's \$4,000. If the Evaluator decides the Patent Owner is likely to prove that some Accused Products infringe and not likely to prove that other Accused Products infringe, the Evaluator will: (i) retain \$2,000 from the Patent Owner's payment and return the remainder; (ii) return in full payments of participating Sellers whose Accused Products were found not to infringe; and (iii) retain \$2,000, divided evenly among participating Sellers of Accused Products found to infringe. Any excess funds from Sellers of Accused Products found to infringe shall be given to a 501(c)(3) organization chosen by the Patent Owner. In no case may the Evaluator retain more than \$4,000 after making a merits decision in an Evaluation.

If the Patent Owner and a Seller reach a settlement after Seller's listings have been taken down in connection with an Evaluation, and Patent Owner has agreed to reinstatement of the listings, the Participants may contact Amazon at patent-evaluation@amazon.com for information about the reinstatement process

7. Settlement or Patent Owner Retraction. If the Patent Owner and a Seller notify the Evaluator they have settled their dispute prior to the date of Patent Owner's reply, the Evaluator will terminate the Evaluation as to that Seller, or terminate the Evaluation entirely if there is only one participating Seller. The Evaluator may retain up to \$1,000 to cover the Evaluator's efforts, equally divided from the Participants' payments when settlement results in termination of the entire Evaluation. If the settlement occurs after the Patent Owner's reply but before the Evaluation is completed, the Evaluator may retain up to \$2,000, \$1,000 from the Patent Owner and a total of \$1,000 from the participating Sellers, if the Evaluation is terminated in its entirety. The Evaluator will return the remainder of each Participant's payment to that Participant. If the Patent Owner retracts or withdraws its claims of infringement against one or more Participants such that the retraction or withdrawal of claims by the Patent Owner results in no further claims of infringement to evaluate, the Evaluator will terminate the Evaluation. If the Patent Owner retracts or withdraws its claims of infringement such that the Evaluation is terminated pursuant to the preceding sentence before briefing begins, the Evaluator may retain \$500 from the Patent Owner; the Evaluator must return the remainder of the Patent Owner's deposit and all Seller deposits. If the Patent Owner retracts or withdraws its claims of infringement such that no claims remain to be evaluated during briefing, the Evaluator may retain \$1,000 from the Patent Owner; the Evaluator must return the remainder of the Patent Owner's deposit and all Seller deposits. If the Patent Owner retracts or withdraws its claims of infringement such that no claims remain to be evaluated after briefing has completed but before the Evaluator has announced a decision, the Evaluator may retain \$2,000 from the Patent Owner; the Evaluator must return the remainder of the Patent Owner's deposit and all Seller deposits.

8. Effect of Evaluation. If the Evaluator finds the Patent Owner is likely to prove that an Accused Product infringes, Amazon will remove that Accused Product from www.amazon.com as soon as practicable, but generally within 10 business days of Amazon's receipt of the decision. If the Evaluator finds that the Patent Owner is not likely to prove that an Accused Product infringes, Amazon will have no obligation to take any action as a

result of the Evaluation. No other action is contemplated or required as a result of the Evaluation and no damages, attorney's fees or costs may be awarded.

If any Participant obtains a judgment or order in litigation or an arbitration that an Accused Product does not infringe or that the Patent is invalid or unenforceable, that Participant may submit it to Amazon, and Amazon may allow relisting of the Accused Product, in accordance with Amazon's policies and procedures. When a patent expires or is found invalid or unenforceable, Amazon may restore a removed listing. If the Evaluator finds that the Patent Owner is not likely to prove an Accused Product infringes, and the Patent Owner subsequently obtains an order or judgment finding that the Accused Product infringes, the Patent Owner may submit that judgment or order to Amazon, and Amazon will remove the Accused Product, in accordance with Amazon's policies and procedures. Amazon reserves the right to use and disclose the results of an Evaluation in connection with actual or proposed Evaluations, requests for takedown of ASINs, in response to statements of others about an Evaluation, or otherwise in connection with Amazon's business.

If the Patent Owner and a Seller reach a settlement after Seller's listings have been taken down in connection with an Evaluation, and Patent Owner has agreed to reinstatement of the listings, the Participants may contact Amazon at patent-evaluation@amazon.com for information about the reinstatement process.

EXHIBIT 7



Service Account Account Health <accounthealth@pattern.com>

RE:[CASE 19892191061] Notice: Amazon Patent Evaluation Express Program - Action Required

patent-evaluation@amazon.com <patent-evaluation@amazon.com>

Fri, Apr 10, 2026 at 8:09 AM

Reply-To: "[CASE 19892191061] patent-evaluation@amazon.com" <patent-evaluation+d207de95-d3ea-4cdb-953b-4f377e1ad728@amazon.com>

To: marketplaces@pattern.com

Hello,

We received a report from a patent owner who believes the items listed at the end of this email infringe their U.S. Patent No. 12,252,506.

If you wish to continue selling the items listed at the end of the email, you have two choices.

First, you can choose to resolve your claim with the patent owner directly within the next three weeks. If we receive a retraction from the patent owner within the next three weeks, we will allow you to continue selling the items listed at the end of this email. The patent owner's contact information is as follows:

ChromaDex Inc

carlos.lopez@niagenbio.com

ChromaDex, Inc.10900, Wilshire Blvd., Suite 600, Los Angeles, California 90024

If the patent owner agrees to retract their complaint, they must send the retraction directly to us at patent-evaluation@amazon.com. Forwarded retractions will not be accepted. Another option is to resolve the claim with the patent owner in a federal district court case. If you are already engaged in a patent lawsuit with the patent owner, or if you file a lawsuit against the patent owner for declaratory judgment of non-infringement of the asserted patent, please provide us with a copy of the relevant complaint within the next three weeks, and you may continue selling the items listed at the end of the email while the lawsuit proceeds.

Second, you can choose to participate in neutral evaluation of the patent owner's claim. Amazon's neutral evaluation procedure is described in the attached document titled "Amazon Patent Evaluation Express Procedure." Please read this document carefully and note that payment of a deposit is required. If you choose to participate in the neutral evaluation, you must agree to the attached Amazon Patent Evaluation Express Agreement, complete Exhibit 2 of the Agreement, "Seller-Supplied Information," and return the completed Agreement to patent-evaluation@amazon.com within three weeks.

Please note that participation in the evaluation process does not guarantee that you will be able to continue to sell the items listed at the end of this email following the evaluation. If the evaluator decides that the items likely infringe, we intend to remove them from Amazon.com. If, however, the evaluator decides the items likely do not infringe, we will not remove your listings from Amazon.com, and your deposit may be refunded in part or in full.

If you do not either resolve your claim with the patent owner directly, or agree to participate in the neutral evaluation process, we will remove the listings at the end of this email along with any materially identical variants from Amazon.com. To learn more about this policy, search for "Intellectual Property Violations" in Seller Central Help.

ASIN: B0B14F9PSR

B097Z5387H

B08WPXPTD8

Infringement type: Patent

Patent Number: 12,252,506

Case ID: 19892191061

You can learn more about your account health in the Performance section of Seller Central (<https://sellercentral.amazon.com/gp/seller-rating/pages/performance-summary.html>).

Neutral Patent Evaluation Team
Amazon.com

--

2 attachments



Amazon Patent Evaluation Express Procedure.pdf
205K



ChromaDex Inc Executed Agreement.pdf
249K

EXHIBIT 8

Account health rating

 sellercentral.amazon.com/help/hub/reference/external/GR786P4BPEVKTBAG

What is the purpose of the Account Health page?

The Account Health page provides an overview of your selling account's adherence to the performance targets and policies required to sell in Amazon Stores. The goal is to allow you to improve your account health before any violations or defects affect your ability to sell in Amazon stores.

To ensure that we are delivering a great experience for our customers, we encourage you to view this page regularly and to address any issues as they arise. For more information about the customer service and shipping performance requirements that is displayed on your Account Health page by viewing the [Order Performance Program Policy](#).

If your selling account has been deactivated, you may be eligible for reinstatement. For more information, go to the [Appeal the Restriction or Removal of Selling Privileges](#) page.

What is the Account Health Rating?

To help you better manage your account health, we've created the Account Health Rating (AHR). The AHR indicates your selling account's risk of deactivation due to non-compliance with certain Amazon selling policies. It's displayed on the seller's [Account Health](#) page for each store that they sell worldwide.

To learn more about the selling policies included in the AHR, go to [Policies included in Account Health Rating](#). For a list of Amazon's selling policies, go to [Program policies](#).

The AHR is a color-coded numerical score that ranges from 0 to 1,000 and provides near real-time status of your account's health, letting you know if your selling account in a particular store is at risk of deactivation. Upon detection of any new policy violations associated with your selling account, you lose points. You gain points when you successfully address those violations.

To ensure that your account health is evaluated in the context of the size of your business, points are also granted when a minimum number of orders are filled. All new sellers start with a score of 200, and over time, sellers will see a score that accurately reflects their account health based on policy adherence and selling activities over the last 180 days.

If your AHR is green ("Healthy," based on a score of 200-1,000), your account isn't at risk of deactivation based on the policies comprising the score. If your AHR is yellow ("At Risk," based on a score of 100-199), your account is at risk of deactivation. When your AHR is red ("Unhealthy,"

based on a score of 99 or lower), your account is either eligible for deactivation or already deactivated.

To obtain and maintain a "Healthy" account, we encourage you to avoid policy violations, and if they happen, to address all violations listed on your Account Health page in a timely manner, prioritizing those with the greatest severity.

Regardless of your AHR score, Amazon may deactivate your account immediately if required by law. We will do so if we suspect fraudulent, deceptive, illegal, or otherwise harmful activity (including any activity that attempts to circumvent Amazon's systems), or if you violate other policies outside of AHR. To protect our customers, our selling partners, and Amazon's Store we will engage in account deactivation.

Which violations does the AHR include?

What are the different severities of policy violations included in the AHR?

The AHR is designed to help you address and prioritize the policy violations that most negatively impact your account health. In case of all violations, we encourage you to address them on an ongoing basis and take action to prevent them from recurring. Violations are categorized as follows:

1. **Critical:** Violations of this severity have a serious and unacceptable impact on customers, or violate certain laws, regulations, or the rights of others. Any single violation with this severity immediately qualifies your account for deactivation.
2. **High:** Given the negative impact these violations have on customers, or the degree to which they may also violate applicable laws or regulations, our tolerances for high severity violations are minimal.
3. **Medium:** Violations of this severity may significantly undermine customer and sellers trust if they continue to occur over time.
4. **Low:** We tolerate infrequent low severity violations because we understand that mistakes happen in the course of doing business.
5. **No Impact:** Violations marked as "No impact" on your Account Health dashboard encourages you to address the issues flagged with listings. However, they don't have an impact on your Account Health Rating now.

The following table provides examples of violations associated with each severity level. We may change the severity of a violation if we observe changes in the degree to which that violation affects customers or other sellers.

**AHR Impact
(Severity)****Examples**

Critical	• Product is counterfeit or pirated as determined via a test buy • Solicitation of product reviews or inclusion of non-compliant inserts • Attempting to damage or abuse another seller • Manipulating search results or sales rankings
----------	--

High	• Rights owner submits valid notice of infringement • Customer reports of infringing or counterfeit products
------	---

Medium	Listings that provide links that prompt users to visit external websites
--------	--

Low	Customer reports that a product they received is expired or in the wrong condition, for example, a used item is listed in new condition
-----	---

- Some violations are determined based on complaints from customers or notices from rights owners, and we go to great lengths to accurately assess the validity of these. If you think there is a mistake, let us know by locating the violation on your [Account Health](#) page and following the guidance under **Next steps**.
- The preceding table doesn't include fraudulent, deceptive, illegal, or otherwise harmful activity. If we suspect that you've engaged in this activity (including any attempt to circumvent Amazon's systems), we may immediately deactivate your account, regardless of your AHR score. This is done to protect customers, other sellers, and Amazon.

How were the different severity levels determined?

When determining severity, we consider factors such as the degree to which the violation jeopardizes the customer experience, applicable laws and regulations, and the number of previous violations for that same policy.

Did any policies change as a result of AHR?

We've expanded our Account Health Rating program policy. For more information, go to [AHR program policy](#). The AHR doesn't change Amazon's existing policies that are included in the AHR, but rather aggregates violations of those policies into a single score that shows your account's risk of deactivation because of those violations. The AHR provides you increased transparency into the status of your account health so you can better manage it. To see a list of policies included in AHR, go to [Policies included in Account Health Rating](#).

What happens if I incur a critical violation?

When we detect a critical violation, we will notify you of the violation via your Account Health page and email. Your AHR will turn red and reflect a numeric score of zero. You will have a three-day grace period to address the violation before account deactivation.

During this time, an Account Health specialist may attempt to call you to help you resolve the issue. We encourage you to ensure that your emergency contact phone number is up to date. To verify that the number listed under Emergency notifications is accurate, go to [Notifications preferences](#).

If you're able to successfully address the violation within the three-day period, your account won't be deactivated and your AHR score will be updated accordingly.

How do repeat violations impact my AHR?

Multiple violations of the same policy impact your account health in two ways. First, the point values associated with violations included in your AHR increase each time that same policy is violated. It means that repeat violations will cause your AHR to degrade faster, with higher severity repeat violations having the most impact. To help you identify and track repeat violations for faster and more systemic resolution, repeat violations are labeled as such in the "Impact" column on your Account Health page.

Second, your account may be at immediate risk of deactivation if you reach the maximum number of repeat violations for a single policy in a 180-day period. The maximum number of repeat violations is five for infringement-related policies and two for restricted products policies.

How are repeat violation thresholds determined?

Repeat violation thresholds are based on violation severity, with more severe violations having lower thresholds than less severe ones. For example, infringement policies typically have a lower repeat violation threshold because they are high-severity violations that violate laws and the intellectual property rights of others. By contrast, listing a used product as new has a higher repeat violation threshold because those are often low-severity violations that can be easily resolved.

When determining repeat violation thresholds, we consider the same factors as when determining the severity of a violation. It includes the degree to which the violation jeopardizes the customer experience, applicable laws, and regulations.

What happens if I reach the maximum number of repeat violations for a particular policy?

When we detect you've reached the maximum number of repeat violations for a given policy, a critical violation will surface on your Account Health page, and we will notify you by email. AHR will turn red and reflect a numeric score of zero. You will have a three-day period to address the critical violation before account deactivation. You can follow instructions in the banner at the top of your Account Health page and appeal through the [Product Policy Compliance Dashboard](#).

During this time, an Account Health specialist may attempt to call you to help you resolve the issue. We encourage you to ensure that your emergency contact phone number is up to date. To verify that the number listed under Emergency Notifications is accurate, go to [Notifications preferences](#).

If you're able to successfully address the critical violation within the three-day period, your account won't be deactivated and your AHR score will be updated accordingly. If you don't address the critical violation within the three-day period, your account will be deactivated until you complete your appeal through the Product Policy Compliance Dashboard.

How do I improve my AHR?

Your AHR will increase as you successfully fulfill orders.

You can also improve your AHR by addressing outstanding policy violations via the [Account Health](#) page in Seller Central, either by appealing them or disputing them if you think we made an error. If there is a successful appeal or dispute, we will reverse the policy violation and its corresponding impact on your account health.

We take errors in our processes seriously and won't only remedy the issue, but also use your feedback to continuously improve our processes.

Does a "Healthy" AHR mean my account won't be deactivated?

If your AHR is "Healthy", your account won't be deactivated due to violations of the policies included in the AHR. However, regardless of your AHR score, Amazon may deactivate your account immediately if required by law. We'll do this if we suspect fraudulent, deceptive, illegal, or otherwise harmful activity (including any activity that attempts to circumvent Amazon's systems); or if you violate other policies outside of AHR. This is done to protect customers, our sellers, and Amazon's Store.

Why is my AHR "At risk" if I've already addressed violations on my Account Health page?

Your AHR is based on the unaddressed violations on your [Account Health](#) page. Once we confirm that violations have been addressed, your AHR will update within a few hours.

However, violations that have been removed from your Account Health page after a successful appeal, where you didn't dispute the activity occurred, may still count toward the maximum threshold for repeat violations within a 180-day period.

How can I get additional support about my AHR?

If you're a professional seller, you can contact the Account Health Support team for additional support with Account Health Rating questions via the **Contact us** or **Call me now** button on the [Account Health](#) page. For more information, refer to the [Account Health Support FAQ](#).

If you are not a professional seller, [Seller University](#) and [Seller Forums](#) are resources available to all Amazon sellers.

If my AHR is "At risk," does that mean my account will be deactivated?

If your AHR says that your account is "At risk," we encourage you to address the violations on your [Account Health](#) page in a timely manner to prevent unnecessary disruption to your selling account. If you don't address these violations and we are unable to reach you to help proactively address these violations, the account will most likely be deactivated.

When will violations be removed from my Account Health page?

Violations are removed from your [Account Health](#) page in scenarios such as:

- You successfully dispute the violation, and we confirm that the violation was an error.
- You successfully appeal the violation, and we determine that while you did violate these policies, it wasn't intentional and the violation must be forgiven.
- You successfully acknowledge a violation and confirmed you don't want to reactivate the listing. This may only apply to specific violation types.
- The relevant rights owner retracts an intellectual property complaint.
- You take the required corrective actions to resolve the violation such as removing infringing content.
- After 180 days from when the violation was added to your Account Health page, violations can be removed.

Note: If your account is deactivated for AHR, all the violations on your account will remain static, meaning that they won't fall out of the Account Health dashboard after 180 days. The violations will all remain in their Account Health page to allow you to address them and improve your score to reinstate your selling privileges.

How to remove a violation from the Account Health dashboard without ASIN reinstatement?

- Policy violations will be removed only on successfully appealing or disputing them. A dispute occurs when sellers provide evidence that the violation was detected in error. An appeal occurs when we determine that while you did violate these policies, it wasn't intentional and the violation must be forgiven. The Account Health page displays all unaddressed violations for 180 days.
- Listings aren't removed from the Account Health page if you change the listing status (such as closing or deleting the listing from your inventory).

What do I do if my account is deactivated due to my AHR?

Your account will be reinstated once your AHR score rises above the threshold of 100 for deactivation. To improve your AHR, you must address the outstanding policy violations via your [Account Health](#) page, either by appealing them or disputing them if you think we made an error.

In there's a successful appeal or dispute, we'll reverse the policy violation and its corresponding impact on your AHR. Once your AHR score returns to 100 or higher, your account will be reinstated.

Will you share the formula of the AHR scores and the exact point values for violations?

To calculate your AHR, all new sellers start with a score of 200. Points are deducted from your AHR score each time we find a new policy violation, and added back when you successfully address that violation. Point values for each violation are based on the severity level and typically range from two to eight. However, critical violations automatically bring your AHR score to zero. Also, if you violate the same policy multiple times, sometimes, negative point values double per repeat violation. To ensure that your AHR is evaluated in the context of the size of your business, you also gain four points for every 200 successful orders you fulfilled over the last 180 days.

We haven't displayed the exact point values in the Account Health dashboard now as we focus on learning and inspecting these new features to ensure the AHR offers sellers a best-in-class solution to manage their account health. Our formula and point values may change in future based on your feedback. We'll let you know if they do and make sure you have the support you need from us to continue maintaining a healthy account.

Why did my AHR score increase or decrease when I didn't incur additional violations, make an appeal, or dispute actions?

The AHR score accurately reflects your account health based on policy adherence and selling activities over the last 180 days. You may see your AHR score increase as points associated with violations move out of the 180-day period and your AHR score may decrease as orders fulfilled move out of the 180-day period. For more information on which violations are contributing to your AHR, go to the [Account Health](#) page. To learn more about the policies included in AHR, go to [Policies included in Account Health Rating](#).

EXHIBIT 9

What is Amazon Account Health?

7 ave7lift.ai/glossary/amazon-account-health



Table of Contents

[What is Amazon Account Health?SummaryKey Takeaways](#)

Amazon Account Health is a dashboard that monitors your compliance with selling policies and performance metrics using a color-coded rating system. It acts as an early warning tool, enabling you to proactively resolve violations to maintain your selling privileges and prevent account deactivation.

This is a feature that helps sellers monitor their adherence to Amazon's performance targets and selling policies. Rather than a simple pass/fail metric, it is a holistic overview designed to:

- **Measure Compliance:** Tracks policy violations (such as intellectual property issues) and customer experience metrics (like Order Defect Rate).
- **Prevent Deactivation:** Acts as an early warning system, allowing sellers to fix issues before they result in a suspended account.
- **Gauge Risk:** Classifies the account status into three simple color-coded tiers (Healthy, At Risk, Unhealthy).

What does Amazon Health do?

The system functions primarily as a risk management tool. [Its main purposes are:](#)

- **Proactive Resolution:** It highlights specific violations, allowing you to appeal or address them to restore your standing.
- **Support Access:** For Professional sellers, it provides a direct link ("Call Me Now") to speak with specialists who can help resolve critical issues.
- **Privilege Maintenance:** Keeping this metric "Healthy" ensures uninterrupted access to selling privileges, listing creation, and funds disbursement.

What is the Amazon Health Dashboard?

The Dashboard is the central interface within Seller Central where all performance data is visualized. It serves as the "control center" containing:

- **The Account Health Rating (AHR):** Your numerical score (0–1,000).
- **Policy Compliance Section:** A list of specific violations categorized by severity (e.g., Suspected IP Violations, Authenticity Complaints).
- **Shipping Performance:** Metrics regarding shipping times, valid tracking rates, and cancellation rates.

How is Amazon Account Health calculated?

The rating is determined by a formula that accounts for your history over the last 180 days. It is not an average, but a cumulative score calculated as follows:

- **Baseline:** All new sellers begin with a score of **200**.
- **Plus (+):** Points are added for every 200 successful orders fulfilled. This ensures the score scales relative to the size of your business.
- **Minus (-):** Points are deducted for policy violations. The amount deducted depends on the severity:
 - **Critical:** Massive impact; can immediately drop the score to 0 or trigger deactivation.
 - **High/Medium/Low:** Varying point deductions based on the violation's impact on the customer experience.
 - **No Impact:** Flags an issue for review but does not currently deduct points.

What is a good Amazon Account Health rating?

A "good" rating is defined as maintaining a **Green** status. The tiers are broken down as follows:

- **Green (200–1,000):** "Healthy." The account is not at risk of deactivation.
- **Yellow (100–199):** "At Risk." The account has fallen below the baseline, warning of potential suspension if issues aren't resolved.
- **Red (0–99):** "Unhealthy." The account is either already deactivated or eligible for immediate removal of selling privileges.

What is an Amazon Health Check?

While not an official Amazon term, this refers to the routine manual review a seller performs on their Dashboard. An effective "check" involves:

1. **Daily Review:** Checking the dashboard for new "flags" or policy warnings.
2. **Metric Analysis:** Ensuring the Order Defect Rate (ODR) stays under 1%, Cancellation Rate under 2.5%, and Late Shipment Rate under 4%.
3. **Listing Review:** Identifying "suppressed" listings that may be flagged for quality issues, even if they haven't yet caused a policy violation

Tired of checking Seller Central every day? [Ave7LIFT](#) AI monitors account health signals for you and alerts you before issues escalate. Join the waitlist to get proactive alerts and "fix-it" guidance.

How to increase your Amazon Account Health?

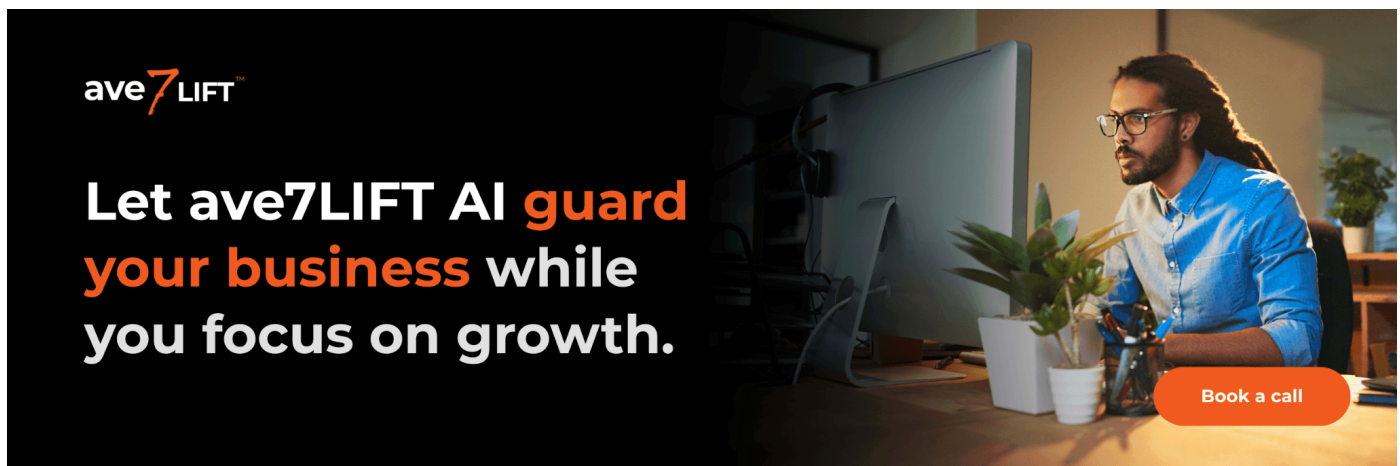
Improving the score requires a two-pronged approach: fixing negatives and increasing positives.

- **Address Violations:** Successfully appealing or removing a violation adds the deducted points back to your score. Prioritize "Critical" and "High" severity issues first.
- **Increase Sales:** Because points are awarded for filled orders, increasing sales volume (without incurring new defects) will naturally raise your baseline score over time.
- **Sustain Performance:** Avoid non-compliance by ensuring products are authentic, listings are accurate, and intellectual property rights are respected.

Does Amazon Account Health affect sales?

Yes, there is a direct correlation between this metric and your revenue.

- **Buy Box Eligibility:** A poor rating or high Order Defect Rate dramatically reduces (or eliminates) your chances of winning the Buy Box (the "Add to Cart" button), causing sales to plummet.
- **Search Visibility:** Good health contributes to better search rankings, while poor health can lead to listing suppression, making your products invisible to customers.
- **Campaign Restrictions:** If the account falls into "At Risk," Amazon may restrict your ability to run advertising campaigns, further stifling growth.



Summary

Amazon Account Health is a Seller Central dashboard that tracks a seller's compliance with Amazon policies and performance standards using a color-coded rating system and a numerical Account Health Rating (0–1,000). It works as an early warning system, highlighting policy violations, customer experience risks, and shipping issues before they lead to suspension or deactivation. By monitoring metrics like Order Defect Rate, cancellations, and late shipments, sellers can proactively resolve issues, protect selling privileges, and maintain visibility, Buy Box eligibility, and uninterrupted sales.

Key Takeaways

- Amazon Account Health provides a holistic view of policy compliance and performance, not just a pass/fail status.
- The Account Health Rating is calculated over the last 180 days, starting at 200, increasing with successful orders and decreasing with violations.
- Green (200–1,000) is healthy, Yellow (100–199) signals risk, and Red (0–99) indicates an unhealthy or deactivated account.

- Resolving violations restores lost points, while higher sales volume (without defects) improves the score over time.
- Poor Account Health directly impacts Buy Box eligibility, search visibility, advertising access, and revenue.
- Regular monitoring and fast issue resolution are essential to avoid suspensions and ensure long-term account stability.

Frequently Asked Questions

Q1. What is the Amazon Account Health rating 1000?

Having a score near 1,000 provides a significant "safety net," as a minor violation will deduct points but is unlikely to drop the score into the Yellow "At Risk" zone.

Q2. What are the different types of Amazon Accounts?

Individual Plan:**Access:** Limited. Individual sellers can view their Health Dashboard and score, but generally lack access to instant phone support or the AHA protection program.

EXHIBIT 10

US 20160168184A1

(19) **United States**(12) **Patent Application Publication**
MIGAUD et al.(10) **Pub. No.: US 2016/0168184 A1**(43) **Pub. Date: Jun. 16, 2016**(54) **METHODS OF PREPARING NICOTINAMIDE
RIBOSIDE AND DERIVATIVES THEREOF**(71) Applicant: **THE QUEEN'S UNIVERSITY OF
BELFAST**, Belfast Antrim (GB)(72) Inventors: **Marie MIGAUD**, Lurgan Armagh (GB);
Philip REDPATH, Portadown, Armagh
(GB); **Kerri CROSSEY**, Magherafelt,
County Derry (GB); **Mark DOHERTY**,
Newtownabbey, County Antrim (GB)(21) Appl. No.: **14/908,831**(22) PCT Filed: **Jul. 24, 2014**(86) PCT No.: **PCT/EP2014/065971**

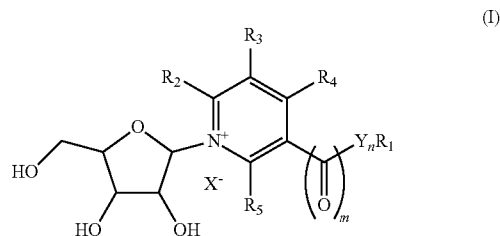
§ 371 (c)(1),

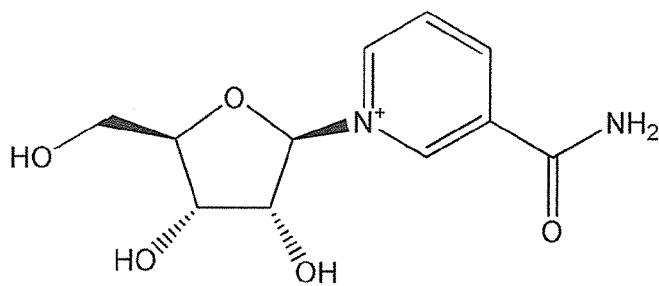
(2) Date: **Jan. 29, 2016**(30) **Foreign Application Priority Data**

Jul. 29, 2013 (GB) 1313465.5

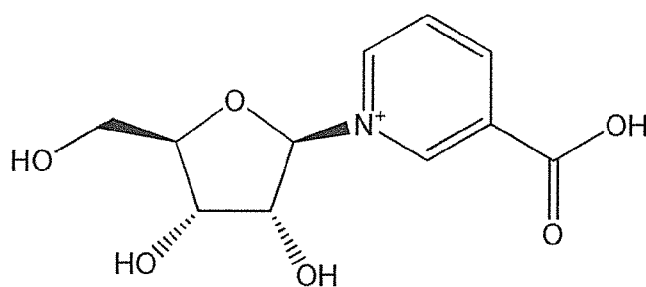
Publication Classification(51) **Int. Cl.****C07H 19/048** (2006.01)**C07H 1/06** (2006.01)(52) **U.S. Cl.**CPC **C07H 19/048** (2013.01); **C07H 1/06**
(2013.01)(57) **ABSTRACT**

The invention relates to methods of preparing nicotinamide riboside and derivatives thereof. In an aspect, the invention relates to a method of preparing a compound of formula (I), wherein n is 0 or 1; m is 0 or 1; Y is O or S; 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; R₂-R₅, which may be the same or different, are each independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl, and substituted or unsubstituted aryl; and 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.

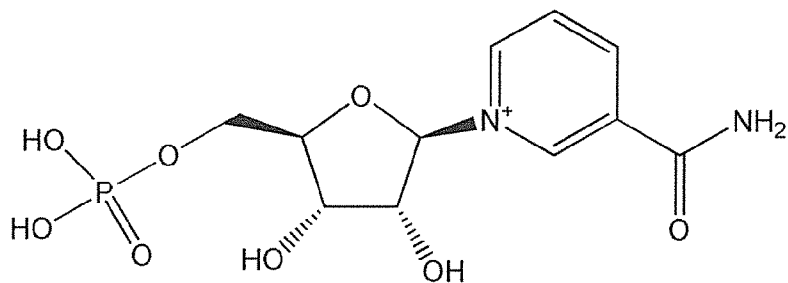




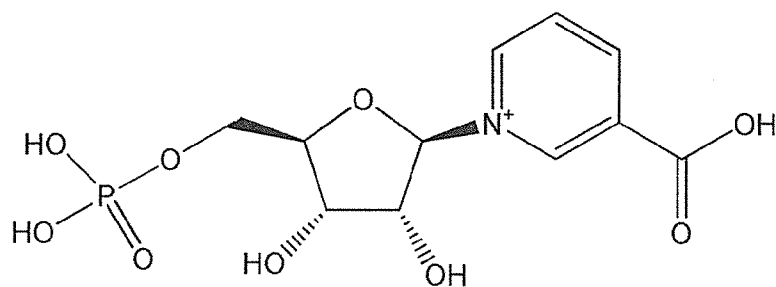
Nicotinamide riboside



Nicotinate riboside

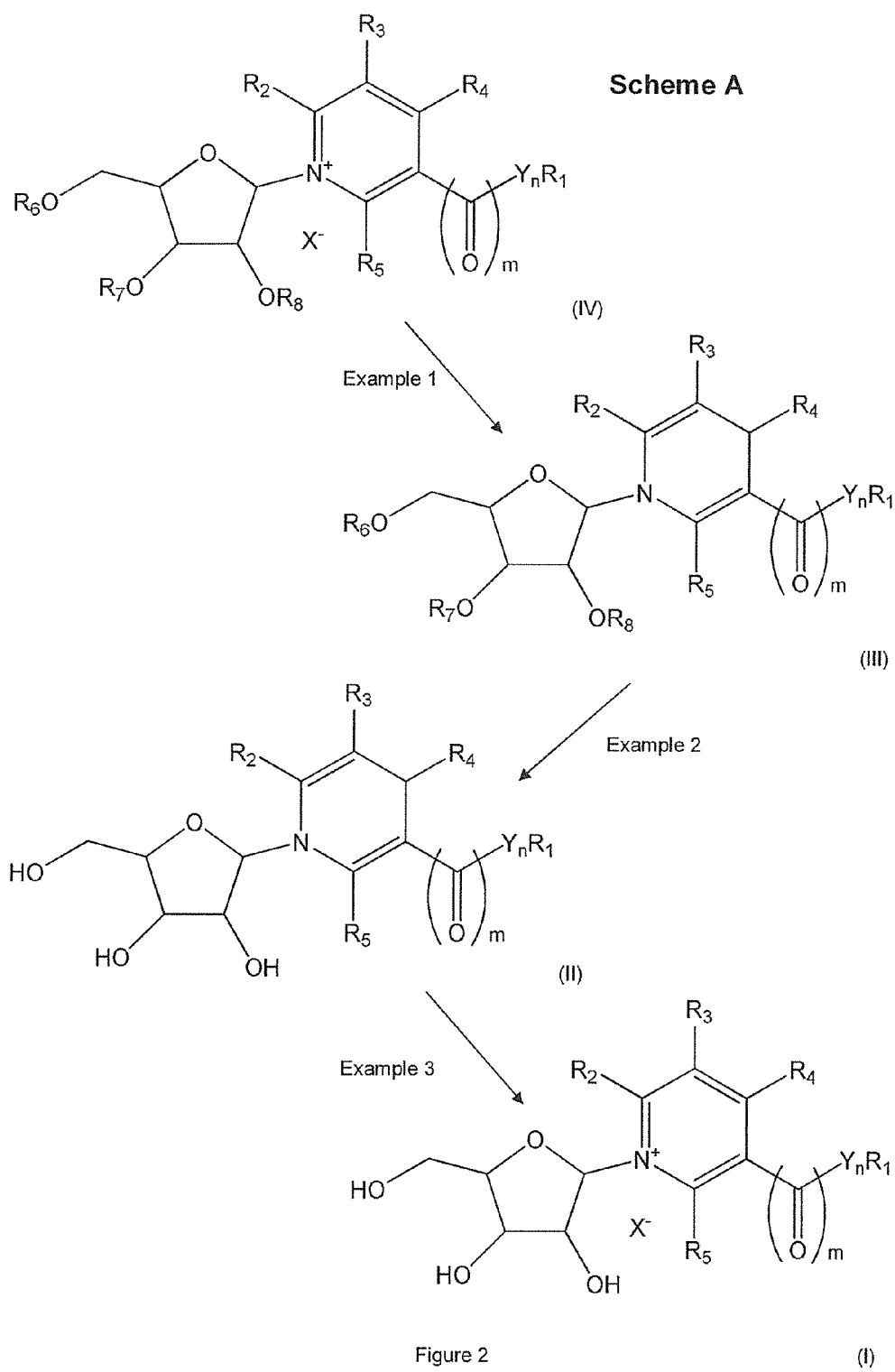


Nicotinamide mononucleotide



Nicotinate mononucleotide

Figure 1



Scheme B

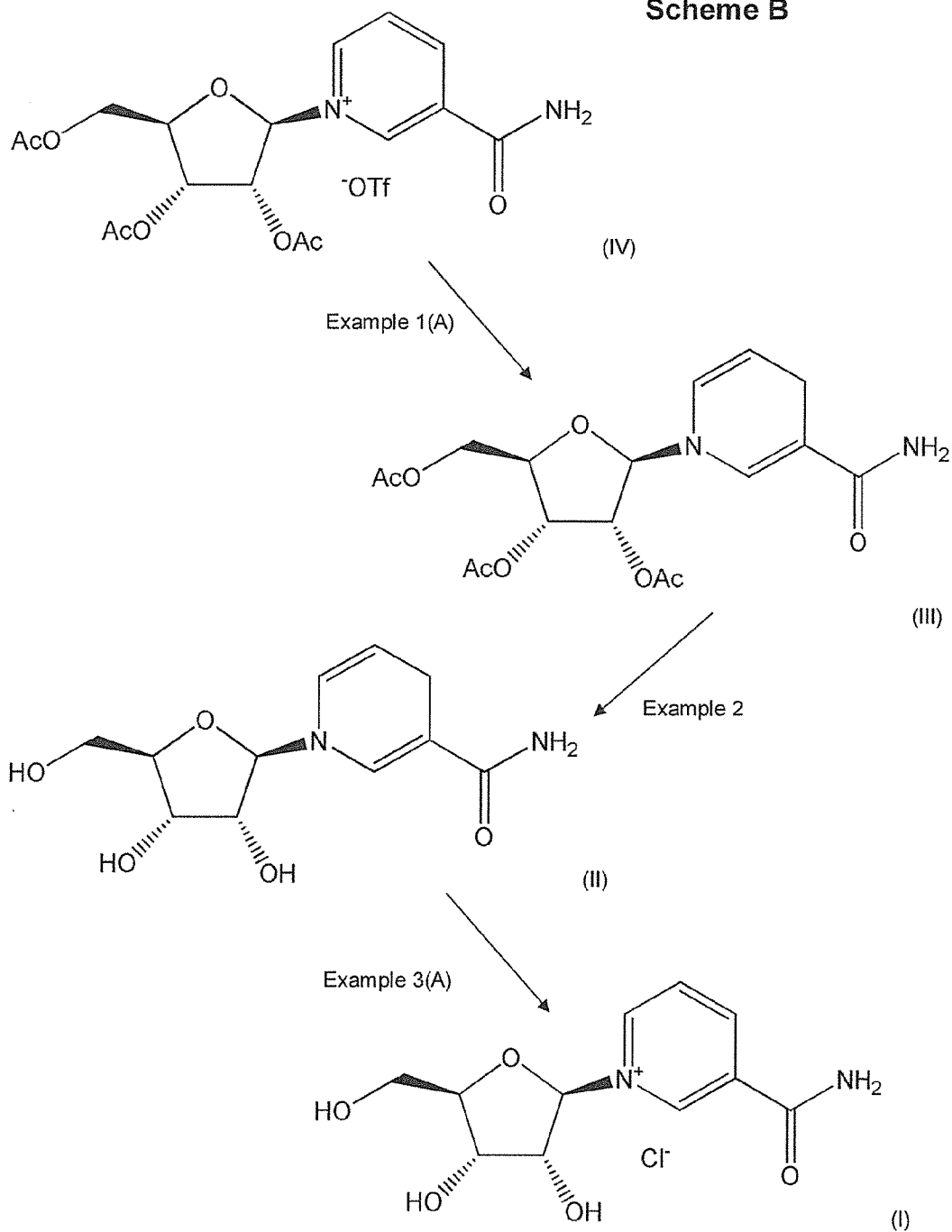
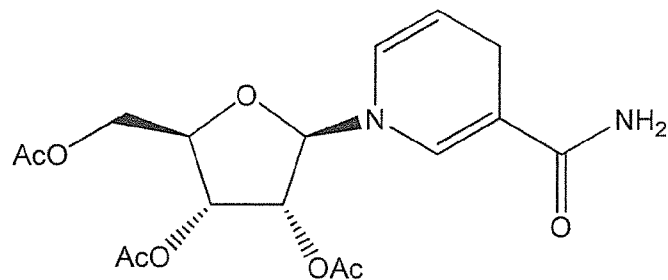
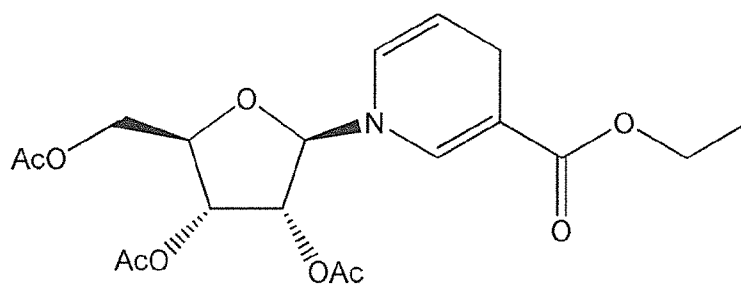


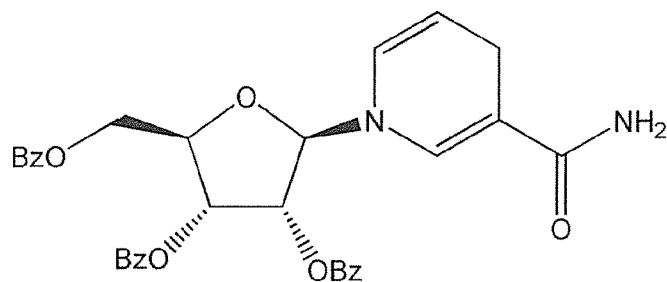
Figure 3



triacetyl-1,4-dihydronicotinamide riboside



triacetyl O-ethyl-1,4-dihydronicotinate riboside



tribenzoyl-1,4-dihydronicotinamide riboside

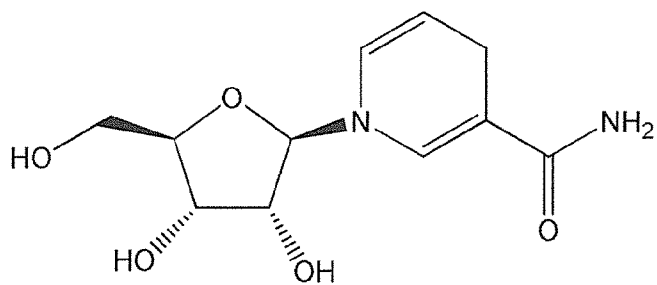
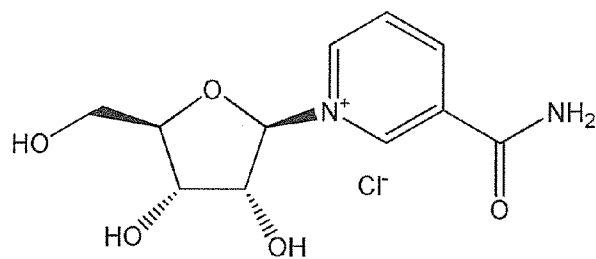
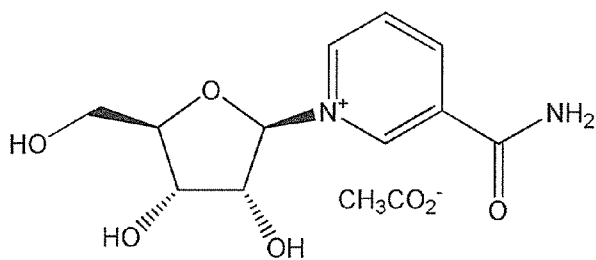
reduced nicotinamide riboside
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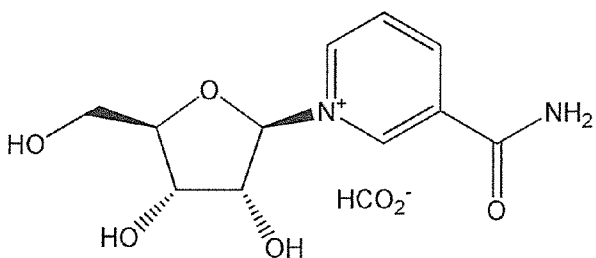
Figure 4



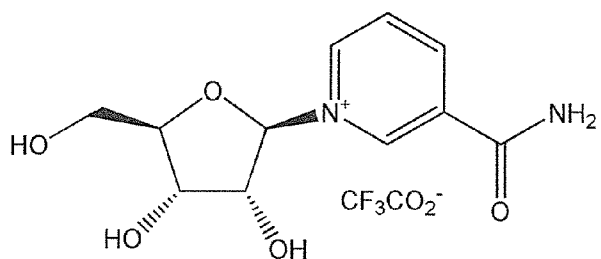
nicotinamide riboside, chloride salt



nicotinamide riboside, acetate salt



nicotinamide riboside, formate salt



nicotinamide riboside, trifluoroacetate salt

Figure 5

US 2016/0168184 A1

Jun. 16, 2016

1

METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF

FIELD OF THE INVENTION

[0001] The invention relates to methods of preparing nicotinamide riboside and derivatives thereof.

BACKGROUND TO THE INVENTION

[0002] Nicotinamide riboside and derivatives thereof, including nicotinate riboside, nicotinamide mononucleotide and nicotinate mononucleotide, are metabolites of nicotinamide adenine dinucleotide (NAD⁺). The β -anomer forms of nicotinamide riboside, nicotinate riboside, nicotinamide mononucleotide and nicotinate mononucleotide are shown, without counter ions, in FIG. 1. As a NAD⁺ precursor, nicotinamide riboside has been shown in mice to enhance oxidative metabolism and protect against high-fat diet induced obesity, which has resulted in significant interest in nicotinamide riboside and its derivatives. Since nicotinamide riboside is a naturally occurring compound, nicotinamide riboside and its derivatives have great potential as natural, nutritional supplements, which may provide health benefits without causing side effects. One limitation in the commercial exploitation of nicotinamide riboside and derivatives thereof, as nutritional supplements, or otherwise, is that known synthetic protocols for preparing nicotinamide riboside and derivatives thereof have disadvantages, rendering them unsuitable for scaling up for commercial or industrial use.

[0003] WO 2007/061798 describes a method for the preparation of nicotinamide riboside and derivatives thereof. However, the disclosed method has a number of disadvantages. For example, trimethylsilyl trifluoromethanesulfonate (TMSOTf) is used as the catalyst in the disclosed method, and results in the prepared compounds inevitably being in the form of their triflate (OTf) salts. The triflate salt form of nicotinamide riboside, or derivatives thereof, is not suitable for use as a nutritional supplement, because of its associated toxicity. Thus, the compounds produced by the disclosed method are not suitable for use as they are prepared, and require an additional step to exchange the triflate anion for an anion that would be pharmaceutically acceptable and therefore suitable for commercialisation, utilizing for example, reverse phase liquid chromatography as disclosed. Additionally, nicotinamide riboside is chemically labile, in particular under the chromatographic conditions used in the disclosed method. It is therefore proposed that the chromatographic conditions used could result in batches of less than optimum purity and, within the batches, great variability in terms of the side products produced. Another disadvantage is that careful control of the temperature of the reaction is necessary to minimise decomposition in the final stages of the synthesis of nicotinamide riboside, yet the disclosed method is exothermic and is therefore prone to microenvironment thermal fluctuation, especially in the event of large scale production set up.

[0004] Tanimori et al (S. Tanimori, T. Ohta and M. Kirihaata, *Bioorganic & Medicinal Chemistry Letters*, 2002, 12, 1135-1137) and Franchetti et al (P. Franchetti, M. Pasqualini, R. Petrelli, M. Ricciutelli, P. Vita and L. Cappellacci, *Bioorganic & Medicinal Chemistry Letters*, 2004, 14, 4655-4658) also describe methods for the preparation of nicotinamide riboside. However, these methods also have the disadvantage of

inevitably resulting in the preparation of the triflate salt by virtue of using TMSOTf as catalyst.

[0005] In summary, the disclosed methods have disadvantages which present obstacles to the scaling up of the method for commercial or industrial use, and which, therefore, greatly limit the commercial opportunities for the methods and the resultant compounds.

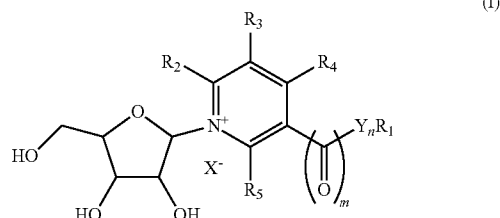
[0006] It is therefore an object of the invention to avoid or mitigate the disadvantages of the prior art.

[0007] It is also an object of the invention to provide a novel, useful and efficient method for the preparation of nicotinamide riboside and derivatives thereof.

[0008] It is also an object of the invention to provide a method for the preparation of nicotinamide riboside and derivatives thereof, whereby the method may be used to introduce a counter ion of choice to the prepared compounds, thereby producing compounds suitable for use as nutritional supplements or otherwise.

SUMMARY OF THE INVENTION

[0009] According to the present invention, there is provided a method of preparing a compound of formula (I)



[0010] wherein

[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

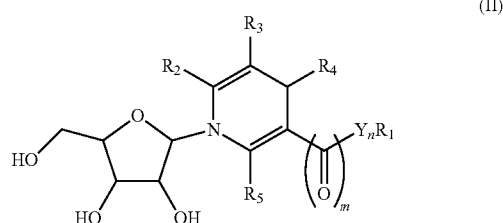
[0016] X⁻ is an anion, selected from an anion of a substituted or unsubstituted carboxylic acid, a halide, a substituted or unsubstituted sulfonate, a substituted or unsubstituted phosphate, a substituted or unsubstituted sulfate, a substituted or unsubstituted carbonate, and a substituted or unsubstituted carbamate;

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[0017] comprising reacting a compound of formula (II)



[0018] wherein n, m, Y and R₁-R₅ are as defined above;

[0019] with a compound of the formula Z⁺X⁻,

[0020] wherein X⁻ is as defined above, and

[0021] wherein Z⁺ is a N-containing cation;

[0022] in the presence of an aqueous solution and a carbon-containing catalyst;

[0023] to form the compound of formula (I).

[0024] Optionally, Z⁺ is selected from a substituted or unsubstituted ammonium, a substituted or unsubstituted pyridinium, a substituted or unsubstituted pyrrolidinium, a substituted or unsubstituted imidazolium and a substituted or unsubstituted triazolium.

[0025] Optionally, Z⁺ is a substituted or unsubstituted ammonium of the formula N⁺HR^IR^{II}R^{III}, wherein R^I, R^{II} and R^{III}, 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.

[0026] Optionally, Z⁺ is an unsubstituted ammonium of the formula NH₄⁺.

[0027] Optionally, 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.

[0028] Optionally, X⁻ is an anion of a substituted monocarboxylic acid, further optionally an anion of a substituted propanoic acid or an anion of a substituted acetic acid. Optionally, X⁻ is an anion of substituted propanoic acid, further optionally an anion of a hydroxy propanoic acid, still further optionally an anion of 2-hydroxypropanoic acid, being lactic acid, the anion of lactic acid being lactate. Optionally, X⁻ is an anion of a substituted acetic acid, being a substituted acetate, further optionally a trihaloacetate selected from trichloroacetate, tribromoacetate and trifluoroacetate. Still further optionally, the trihaloacetate is trifluoroacetate.

[0029] Optionally, 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.

[0030] Optionally, X⁻ is an anion of a substituted or unsubstituted amino-monocarboxylic acid or an anion of a substituted or unsubstituted amino-dicarboxylic acid. Further optionally, X⁻ is an anion of an amino-dicarboxylic acid, optionally selected from glutamic acid and aspartic acid, being glutamate and aspartate, respectively.

[0031] Optionally, X⁻ is an anion of ascorbic acid, being ascorbate.

[0032] Optionally, X⁻ is a halide selected from chloride, bromide, fluoride and iodide, further optionally chloride or bromide.

[0033] Optionally, X⁻ is a substituted or unsubstituted sulfonate. Further optionally, X⁻ is a trihalomethanesulfonate selected from trifluoromethanesulfonate, tribromomethanesulfonate and trichloromethanesulfonate. Still further optionally, the trihalomethanesulfonate is trifluoromethanesulfonate.

[0034] Optionally, X⁻ is a substituted or unsubstituted carbonate, further optionally hydrogen carbonate.

[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.

[0036] Optionally, the compound of the formula Z⁺X⁻ is selected from ammonium chloride, ammonium acetate, ammonium formate, ammonium trifluoroacetate, ammonium ascorbate, ammonium aspartate, ammonium glutamate and ammonium lactate. Further optionally, the compound of the formula Z⁺X⁻ is selected from ammonium chloride, ammonium acetate, ammonium formate and ammonium trifluoroacetate.

[0037] Optionally, the compound of formula (II) and the carbon-containing catalyst are present in a respective molar ratio of from about 10:1 to about 1:10, optionally from about 5:1 to about 1:5, further optionally from about 4:1 to about 1:4, still further optionally about 1:1 or 1:2 or 1:3 or 1:4.

[0038] Suitable carbon-containing catalysts include, but are not limited to, activated charcoal or graphite.

[0039] As used herein, the term "activated charcoal" is intended to mean a carbon containing material processed to be highly porous thereby increasing the surface area of the material. The term "activated charcoal" is intended to be synonymous with the term "activated carbon". The activated charcoal may be in the form of powders and/or fibres and/or granules and/or pellets. Optionally, the activated charcoal may act as a support for a metal. Suitable metals include, but are not limited to, transition metals. Suitable transition metals include, but are not limited to the platinum group metals, optionally selected from ruthenium, rhodium, palladium, osmium, iridium, and platinum, or a combination thereof.

[0040] Optionally, the aqueous solution consists essentially of water.

[0041] Optionally, the aqueous solution comprises, in addition to water, an organic solvent.

[0042] Suitable organic solvents include, but are not limited to, substituted or unsubstituted ethers, substituted or unsubstituted esters, substituted or unsubstituted ketones, substituted or unsubstituted aliphatic or aromatic hydrocarbons, and combinations thereof.

[0043] Optionally, the organic solvent, when present, comprises an ether selected from diethyl ether, methyl tert-butyl ether, ethyl tert-butyl ether, di-tert-butyl ether, diisopropyl ether, dimethoxymethane, tetrahydrofuran, 2-methyltetrahydrofuran, and tetrahydropyran, or a combination thereof.

[0044] Optionally, the organic solvent, when present, comprises an ester selected from methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, isobutyl acetate and n-butyl acetate, or a combination thereof.

[0045] Optionally, the organic solvent, when present, comprises a ketone selected from methyl isobutyl ketone and methyl isopropyl ketone, or a combination thereof.

[0046] Optionally, the organic solvent, when present, comprises an unsubstituted aliphatic hydrocarbon solvent selected from pentane, hexane, cyclohexane and heptane, or a combination thereof.

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[0047] Optionally, the organic solvent, when present, comprises a substituted aliphatic hydrocarbon solvent, optionally a halogenated aliphatic hydrocarbon solvent, further optionally a chlorinated aliphatic hydrocarbon solvent selected from dichloromethane, trichloromethane, tetrachloromethane, 1,2-chloroethane, 1,1,1-trichloroethane and trichloroethylene, or a combination thereof.

[0048] Optionally the organic solvent, when present, comprises an aromatic hydrocarbon solvent selected from benzene, toluene, ethylbenzene and xylene, or a combination thereof.

[0049] Optionally, the aqueous solution comprises water and organic solvent in a respective ratio by volume of from about 1:5 to about 5:1, optionally from about 1:3 to about 3:1, further optionally from about 1:2 to about 2:1, still further optionally about 1:1.

[0050] Optionally, the reaction is carried out in a pH range of from about 6 to about 8, optionally from about 6.5 to about 7.5.

[0051] Optionally, the reaction is carried out at a temperature of from about 10° C. to about 40° C., optionally from about 15° C. to about 35° C., further optionally from about 15° C. to about 30° C., still further optionally from about 15° C. to about 20° C., even further optionally from about 20° C. to about 25° C., even further optionally at a temperature of about 20° C. or 21° C. or 22° C. or 23° C. or 24° C. or 25° C.

[0052] Optionally, the reaction is carried out for a period of time of from about 1 minute to about 180 minutes, optionally, from about 2 minutes to about 120 minutes, further optionally from about 5 minutes to about 120 minutes, still further optionally from about 10 minutes to about 120 minutes, even further optionally from about 20 minutes to about 120 minutes, even further optionally from about 30 minutes to about 120 minutes, still further optionally from about 60 minutes to about 120 minutes, even further optionally from about 60 minutes to about 90 minutes, still further optionally about 60 minutes or 70 minutes or 80 minutes.

[0053] Optionally, the method further comprises a filtration step to remove the carbon-containing catalyst from the prepared compound of formula (I). Suitable filtration means for use in the filtration step include, but are not limited to, syringe filters and/or paper filters, and/or any inert, insoluble substance capable of acting as a filter, e.g. alumina and/or silica and/or diatomaceous earth. It will be appreciated any other suitable filtration means may be used.

[0054] As used herein, the term “substituted” is intended to mean that any one or more hydrogen atoms is replaced with any suitable substituent, provided that the normal valency is not exceeded and the replacement results in a stable compound. Suitable substituents include, but are not limited to, alkyl, alkylaryl, aryl, heteroaryl, halide, hydroxyl, carboxylate, carbonyl (including alkylcarbonyl and arylcarbonyl), phosphate, amino (including alkylamino, dialkylamino, hydroxylamino, dihydroxylamino, alkyl hydroxylamino, arylamino, diarylamino and alkylaryl amino), thiol (including alkylthiol, arylthiol and thiocarboxylate), sulfate, nitro, cyano and azido.

[0055] As used herein, the term “alkyl” is intended to mean a substituted or unsubstituted, saturated or unsaturated, optionally saturated, linear, branched or cyclic, aliphatic hydrocarbon, having from 1 to 12 carbon atoms, optionally from 1 to 10 carbon atoms, further optionally from 1 to 8 carbon atoms, still further optionally from 1 to 6 carbon atoms, even still further optionally 1 or 2 or 3 or 4 or 5 carbon

atoms. Suitable alkyls include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, iso-pentyl, n-hexyl, iso-hexyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Optionally, when Y is O, n is 1, and m is 1, ethyl is preferred.

[0056] As used herein, the term “alkenyl” is intended to mean a substituted or unsubstituted, linear, branched or cyclic, aliphatic hydrocarbon, having at least one carbon-carbon double bond, and having from 2 to 12 carbon atoms, optionally from 2 to 10 carbon atoms, further optionally from 2 to 8 carbon atoms, still further optionally from 2 to 6 carbon atoms, even still further optionally 2 or 3 or 4 or 5 carbon atoms. Suitable alkenyl groups include, but are not limited to, ethenyl, propenyl and butenyl.

[0057] As used herein, the term “alkynyl” is intended to mean a substituted or unsubstituted, linear, branched or cyclic, aliphatic hydrocarbon, having at least one carbon-carbon triple bond, and having from 2 to 12 carbon atoms, optionally from 2 to 10 carbon atoms, further optionally from 2 to 8 carbon atoms, still further optionally from 2 to 6 carbon atoms, even still further optionally 2 or 3 or 4 or 5 carbon atoms. Suitable alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, and the like.

[0058] As used herein, the term “aryl” is intended to mean a substituted, unsubstituted, monocyclic or polycyclic, aromatic hydrocarbon. Suitable aryls include, but are not limited to, substituted or unsubstituted phenyl, and substituted or unsubstituted heteroaryl.

[0059] Optionally, the substituted or unsubstituted primary or secondary amino is selected from substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted hydroxylamino, substituted or unsubstituted dihydroxylamino, and substituted or unsubstituted alkyl hydroxylamino.

[0060] Optionally, the substituted or unsubstituted azido is selected from substituted or unsubstituted alkyl azido and substituted or unsubstituted aryl azido.

[0061] It will be appreciated that, when n is 0 and m is 0, R₁ is directly attached to the pyridine ring or to the pyridinium ring, as appropriate.

[0062] Optionally, in an embodiment of formula (I), n is 0, m is 1, R₁ is NH₂, R₂-R₅ are each H, and X⁻ is selected from chloride, acetate, formate and trifluoroacetate.

[0063] Optionally, in an embodiment of formula (II), n is 0, m is 1, R₁ is NH₂, and R₂-R₅ are each H.

[0064] Optionally, the compound of formula (II) and the compound of the formula Z⁺X⁻ are present in a respective molar ratio of from about 1:5 to about 5:1, optionally from about 1:3 to about 3:1, further optionally from about 1:2 to about 2:1, still further optionally about 1:1.

[0065] Optionally, the method comprises stirring the reactants, optionally using a magnetic or mechanical stirrer, further optionally an overhead mechanical stirrer.

[0066] In an embodiment, the carbon-containing catalyst used in the preparation of a compound of formula (I) may be provided in the form of an activated charcoal column, for example an activated charcoal material such as those supplied by Sigma Aldrich under the trade names NORIT (Trade Mark) or DARCO (Trade Mark), or from CarboChem, W Lancaster Ave, Ardmore, Pa. 19003, USA, or a carbon supported catalyst in a CatCart Packer (Trade Mark) column from ThalesNano, Graphisoft Park, Záhony u. 7. H-1031 Budapest, Hungary. In this embodiment, the activated charcoal column may be used as part of any suitable liquid chro-

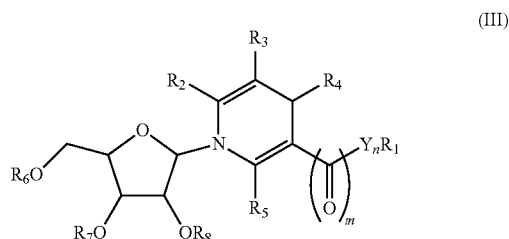
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matography system, including, but not limited to, a fast protein liquid chromatography (FPLC) or a high performance liquid chromatography (HPLC) system, or a flow chemistry system, such as the ThalesNano (Trade Mark) H-cube systems and related flow reactors, available from ThalesNano, details provided above. In this case, the reactants would be recirculated onto the column in a continuous manner until the compound of formula (II) is no longer detected by UV at 340 nm.

[0067] Optionally, the compound of formula (II) is prepared by reacting a compound of formula (III)



[0068] wherein

[0069] n, m, Y and R₁-R₅ are as defined above; and

[0070] R₆, R₇ and R₈, which may be the same or different, are each independently a hydroxyl-protecting group;

[0071] with a deprotecting agent;

[0072] to form the compound of formula (II).

[0073] Suitable R₆, R₇ and R₈ moieties include, but are not limited to, ester-type protecting groups, ether-type protecting groups, and silyl-type protecting groups.

[0074] As used herein, the term "ester-type protecting group" is intended to mean a protecting group that forms an ester bond for the purpose of hydroxyl protection and which may be substituted or unsubstituted. Suitable ester-type protecting groups include, but are not limited to, acetyl, propionyl, isopropionyl, benzoyl, and trihaloacetyl, optionally trifluoroacetyl or trichloroacetyl.

[0075] As used herein, the term "ether-type protecting group" is intended to mean a protecting group that forms an ether bond for the purpose of hydroxyl protection and which may be substituted or unsubstituted. Suitable ether-type protecting groups include, but are not limited to, benzyl, p-methoxybenzyl, methoxymethyl and allyl ethers.

[0076] As used herein, the term "silyl-type protecting group" refers to a protecting group that forms a silyloxy bond for the purpose of hydroxyl protection. Examples thereof from trimethylsilyl, triethylsilyl, triisopropylsilyl, 2-(trimethylsilyl)ethoxymethyl, tert-butyldimethylsilyl, tert-butyl-diphenylsilyl and tetraisopropylsilyl.

[0077] Optionally, the R₆, R₇ and R₈ moieties are selected from substituted and unsubstituted acetyl, and substituted and unsubstituted benzoyl.

[0078] Optionally, at least two of R₆, R₇ and R₈ are selected from unsubstituted acetyl or unsubstituted benzoyl.

[0079] Optionally the deprotecting agent is an acid or a base. Deprotection can also be achieved by catalytic hydrogenation (Pd/C; H₂) for the aromatic ether protecting groups and by fluoride-catalysed chemistry (e.f. TBAF in THF) for all the silyl ethers. Optionally, when R₆, R₇ and R₈ each comprise unsubstituted acetyl or unsubstituted benzoyl, the deprotecting agent is a base, optionally selected from NH₃,

Na₂CO₃ and NaOH. It will be appreciated by a skilled person that any other conventional deprotecting agent may be used.

[0080] Optionally, the reaction is carried out in the presence of a protic or aprotic solvent or a combination thereof.

[0081] Suitable protic solvents include, but are not limited to, water, substituted or unsubstituted alcohol, or a combination thereof. Suitable substituted alcohols include substituted or unsubstituted fluorinated alcohols. Suitable unsubstituted alcohols include methanol, ethanol and propanol, optionally methanol.

[0082] Suitable aprotic organic solvents include, but are not limited to, substituted or unsubstituted ethers, substituted or unsubstituted esters, substituted or unsubstituted ketones, substituted or unsubstituted aliphatic or aromatic hydrocarbons, and combinations thereof, as defined above.

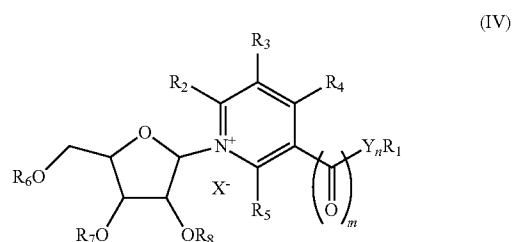
[0083] Optionally, the reactants are subjected to mechanical grinding, further optionally using a ball milling or planetary ball milling machine.

[0084] 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.

[0085] Further optionally, in another embodiment of formula (III), n is 1, Y is 0, m is 1, R₁ is ethyl, R₂-R₅ are each H, and R₆-R₈ are each acetyl.

[0086] 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.

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



[0088] wherein

[0089] n, m, Y, R₁-R₈ and X⁻ are as defined above;

[0090] with a reducing agent,

[0091] an aqueous solution

[0092] and an organic solvent

[0093] to form a compound of formula (III).

[0094] Optionally, X— is selected from ascorbate, glutamate, aspartate, lactate and acetate.

[0095] Suitable organic solvents are as defined above in respect of the preparation of a compound of formula (I) from formula (II).

[0096] Optionally, when at least two of R₆, R₇ and R₈ comprise unsubstituted acetyl, the organic solvent is selected from dichloromethane, 1,2-chloroethane, n-butyl acetate, chloroform and ethyl acetate, or a combination thereof, further optionally ethyl acetate.

[0097] Optionally, when at least two of R₂, R₃ and R₄ comprise unsubstituted benzoyl, the organic solvent is selected from trichloroethylene, carbon tetrachloride, diisopropyl ether, toluene, methyl tert-butyl ether, benzene and diethyl ether, or a combination thereof, further optionally diethyl ether.

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[0098] Optionally, the reducing agent is selected from sodium dithionite or sodium borohydride.

[0099] Optionally, the method may comprise the simultaneous addition of the reducing agent, aqueous solution and organic solvent; or the sequential addition of the reducing agent, aqueous solution and organic solvent, in any order; or a combination thereof.

[0100] Optionally, the aqueous solution consists essentially of water.

[0101] It will be appreciated that, optionally, the aqueous solution and the organic solvent form a bi-phasic solution comprising an aqueous phase and an organic phase.

[0102] Optionally, the method comprises the additional steps of

[0103] separating the organic phase from the aqueous phase; and

[0104] extracting the compound of formula (III) from the organic solvent.

[0105] It will be appreciated by a skilled person that the hydroxyl protecting groups R_6 , R_7 and R_8 , are required to be lipophilic to the extent that the reduced compound of formula (III), once prepared, migrates into the organic phase of the bi-phasic reaction medium formed by the aqueous solution (aqueous phase) and organic solvent (organic phase).

[0106] Optionally, the reactants are subjected to mechanical grinding, further optionally using a ball mill or planetary ball milling machine.

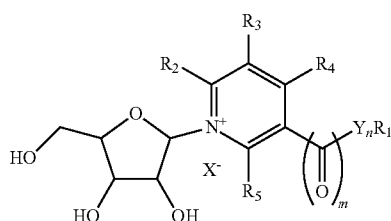
[0107] Optionally, in an embodiment of formula (IV), n is 0, m is 1, R_1 is NH_2 , R_2 - R_5 are each H, R_6 - R_8 are each acetyl, and X^- is ^-OTf .

[0108] Further optionally, in another embodiment of formula (III), n is 1, Y is O, m is 1, R_1 is ethyl, R_2 - R_5 are each H, R_6 - R_8 are each acetyl, and k is ^-OTf .

[0109] Still further optionally, in another embodiment of formula (III), n is 0, m is 1, R_1 is NH_2 , R_2 - R_5 are each H, and R_6 - R_8 are each benzoyl, and X^- is ^-OTf .

[0110] According to the invention, there are also provided compounds derivable from the methods disclosed herein.

[0111] Accordingly to the invention, there is further provided a compound of formula (I)



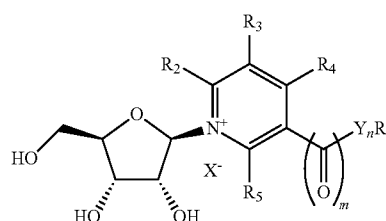
(I)

[0112] wherein

[0113] n , m , Y , R_1 - R_5 and X^- are as defined above.

[0114] Optionally, X^- is selected from acetate, formate and trifluoroacetate.

[0115] Optionally, the compound of formula (I) has the formula (IA), i.e. is the β -anomer,

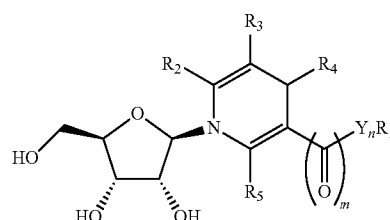


(IA)

[0116] wherein

[0117] n , m , Y , R_1 - R_5 and X^- are as defined above.

[0118] Optionally, the compound of formula (II) has the formula (IIA), i.e. is the β -anomer,

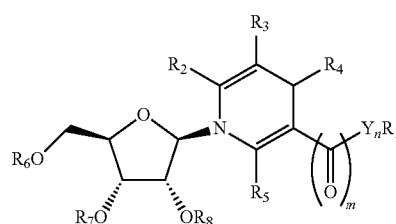


(IIA)

[0119] wherein

[0120] n , m , Y and R_1 - R_5 are as defined above.

[0121] Optionally, the compound of formula (III) has the formula (IIIA), i.e. is the β -anomer,

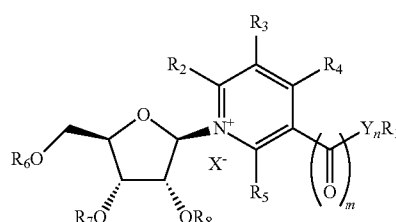


(IIIA)

[0122] wherein

[0123] n , m , Y and R_1 - R_8 are as defined above.

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



(IVA)

[0125] wherein

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

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[0127] Advantages of the invention include, but are not limited to the following:

[0128] (1) The preparation of compounds of formula (I) from compounds of formula (II) provides an efficient method of introducing a counter ion of choice for nicotinamide riboside and its derivatives. Starting from a compound of formula (II), e.g. reduced NRH, a desired counter ion may be introduced. Furthermore, even if the method starts by using compounds of formula (IV) in the form of the triflate salt, the methods of the invention enable the triflate anion to be exchanged during the method in a simple and efficient manner, to a counter ion of choice. Thus, the disclosed methods conveniently enable the preparation of compounds having potential use as nutritional supplements or otherwise.

[0129] (2) The invention provides stereoselective methods for the preparation of nicotinamide riboside and derivatives thereof, producing the desired β -anomer. This is in contrast, for example, to Tanimori et al, which is not stereoselective and produces significant amounts of the α -anomer, which is undesirable. Additionally, the methods of the invention are useful, efficient, and can be easily scaled up for industry and commercialisation, and provide for the minimisation of solvent use, purification and reaction time. For example, the methods of the invention for preparing compounds of formula (I) from compounds of formula (II), are conveniently completed in less than 2 hours with quantitative yields. The methods for the preparation of compounds of formula (I) starting from compounds of formula (IV) are also very efficient and produce very good yields. The methods may conveniently be carried out at room temperature.

[0130] (3) The methods described herein are capable of preparing not just nicotinamide riboside but also a whole range of derivatives, which is not disclosed in either Tanimori et al or Franchetti et al. The derivatives include not just derivatives of nicotinamide riboside but also the reduced form of nicotinamide riboside and derivatives thereof. Furthermore, although not described herein, a skilled person will appreciate that, starting from compounds of formula (II), it is possible to easily access the phosphorylated parents of nicotinamide riboside and derivatives thereof, for example nicotinamide mononucleotide and nicotinate mononucleotide.

[0131] (4) 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.

[0132] (5) The methods described herein conveniently use reactants which enable the compounds of formula (I) to be prepared in a neutral pH range of from about 6 to about 8. For example, in the preparation of the compounds of formula (I) from the compounds of formula (II), this neutral pH range enables both the starting materials (compounds of formula (II)), which are acid labile, and the final products (compounds of formula (I)), which are base labile, to be stable during the reaction.

[0133] (6) The inventors have surprisingly found that, the use of a N-containing cation as Z^+ (the proton source), conveniently enables the efficient preparation of compounds of formula (I) from compounds of formula (II) in quantitative yield, and, as mentioned in point

(5), in a neutral pH range. Without wishing to be bound by theory, it is proposed that Z^+ , the proton source, must be a conjugated acid of an organic base which is protonated in an equilibrated manner within the neutral pH range. The inventors propose that, by using a N-containing cation as the proton source Z^+ , the N atom of the proton source has a pKa greater than the pKa of the N atom of the dihydropyridine of the compound of formula (II). Therefore, in simple terms, due to the relative pKa values, the N atom of the proton source Z^+ (i.e. $N-H^+$) holds onto the proton H^+ until after the N atom of the dihydropyridine has been oxidised (which oxidation, the inventors propose, is facilitated by the carbon-containing catalyst). It is only after the N atom of the dihydropyridine has been oxidised that it will be protonated by the proton source Z^+ . The inventors propose that if a proton source other than one containing a N atom is used, for example a phosphonium cation containing $P-H^+$ or a sulfonium cation containing $S-H^+$, it is proposed that such proton sources would cause the pH of the reaction medium to fall below the neutral pH range, and the proton sources would release their protons in this lower pH range. It is proposed that this change would cause the N atom of the dihydropyridine to be protonated before oxidation, thereby resulting in the undesirable hydrolysis of a C—N bond of the dihydropyridine. It is also proposed that this resultant instability of the dihydropyridine due to the undesirable breaking of a C—N bond, would also occur using a weak acid (e.g. carboxylic acid) or a strong acid (e.g. hydrochloric acid, phosphoric acid or sulphuric acid). Thus, it is proposed that only a N-containing cation as proposed, is capable of releasing a proton in a pH range (neutral) which allows the reaction to proceed as desired to form the compounds of formula (I) from the compounds of formula (II).

EXAMPLES

[0134] Embodiments of the present invention will now be described, with reference to the accompanying, non-limiting examples and drawings, in which:

[0135] FIG. 1 shows the β -anomer forms of nicotinamide riboside, nicotinate riboside, nicotinamide mononucleotide and nicotinate mononucleotide, without counter ions;

[0136] FIG. 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; that compounds of formula (III) may be used to prepare compounds of formula (II), as described in Example 2; and that compounds of formula (II) may be used to prepare compounds of formula (I), as described in Example 3; wherein n, m, Y, R_1-R_8 and X^- are as defined above;

[0137] FIG. 3 depicts Scheme B, which is a scheme illustrating, in general terms, that triacetyl nicotinamide riboside, triflate salt may be used to prepare triacetyl-1,4-dihydronicotinamide riboside, as described in Example 1(A), and that triacetyl-1,4-dihydronicotinamide riboside may be used to prepare 1-(β -D-ribofuranosyl)-1,4-dihydronicotinamide, as described in Example 2, and that 1-(β -D-ribofuranosyl)-1,4-dihydronicotinamide may be used to prepare nicotinamide riboside, chloride salt, as described in Examples 3(A), 3(E) and 3(F). The β -anomers of all of the mentioned

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compounds are shown. It will be appreciated that Scheme B is merely exemplary and is not to be construed as limiting the invention thereto;

[0138] FIG. 4 shows the β -anomer forms of triacetyl-1,4-dihydronicotinamide riboside (Example 1(A)), triacetyl O-ethyl-1, 4-dihydronicotinamide riboside, (Example 1(B)), tribenzoyl-1,4-dihydronicotinamide riboside (Example 1(C)), and 1-(β -D-ribofuranosyl)-1,4-dihydronicotinamide (Example 2); and

[0139] FIG. 5 shows the β -anomer forms of nicotinamide riboside, chloride salt (Examples 3(A), 3(E) and 3(F)), nicotinamide riboside, acetate salt (Example 3(B)), nicotinamide riboside, formate salt (Example 3(C)), and nicotinamide riboside, trifluoroacetate salt (Example 3(D)).

EXAMPLE 1

[0140] Compounds of formula (III) were prepared in accordance with the invention as follows. The pH of the reaction media described in the following examples was in the region of about 6-8.

Example 1(A)

Preparation of Reduced Triacetyl Nicotinamide Riboside, Namely Triacetyl-1,4-dihydronicotinamide riboside, a Compound of Formula (III) (the β -anomer Form of which is Shown in FIG. 4)

[0141] Reduction: All solvents were degassed prior to use by sonication and argon bubbling. Sodium dithionite (0.656 g, 3.76 mmol, 2 eq) and sodium hydrogencarbonate (0.79 g, 9.40 mmol, 5 eq) were added to a clean, dry round bottom flask with a magnetic stirrer and placed under inert atmosphere. A compound of formula (IV), namely triacetyl nicotinamide riboside, triflate (CF_3SO_3^- , also known as —OTf) salt (1 g, 1.88 mmol, 1 eq) was then dissolved in a minimum amount of water (<10 ml) and slowly added to the reaction vessel. Once the reaction settled, further water was added to the reaction until all of the reactants had dissolved (<10 ml) and was left to stir for 20 minutes. The aqueous solution was then extracted with three half portions of dichloromethane (DCM). The DCM fractions were collected and concentrated under reduced pressure, affording the triacetyl-1,4-dihydronicotinamide riboside derivative (triacetyl-NRH) with residual amounts of starting material (<5%). The aqueous layer was subjected to the above conditions a second time to increase yields which averaged 65%. Ethyl acetate was also an excellent alternative extraction solvent in place of DCM, yielding a 75% yield.

[0142] $^1\text{H-NMR}$ (MeOD, 400 MHz)- δ 7.15 (s, 1H, H-5), 5.95 (d, 1H, J=7.21 Hz, H-6), 5.25 (d, 1H, J=2.84 Hz) & 5.17 (d, 1H, J=1.80 Hz) (H-8 & H-7), 4.96 (d, 1H, J=7.09 Hz, H-4), 4.87 (ABX, 1H, $J_{a,a'}=8.18$ Hz, $J_{a,b}=3.60$ Hz, H-9), 4.26 (d, 2H, J=3.20 Hz, H-10 & H-10'), 4.19 (m, 1H, J=3.00 Hz, H-3), 3.13 (m, 2H, J=1.18 Hz, H-2), 2.13 (s, 3H), 2.11 (s, 3H), 2.10 (s, 3H) (H-13, H-15, H-17). $^{13}\text{C-NMR}$ (MeOD, 125 MHz)- δ 172.80 (C-11), 170.40 (C-12, C-14, C-16), 137.90 (C-5), 125.20 (C-4), 105.12 (C-6), 95.24 (C-3), 83.49 (C-9), 71.18 (C-8), 70.26 (C-7), 61.55 (C-10), 22.16 (C-2), 21.52 (C-13, C-15, C-17). HMRS m/z: 383.1445; Calc. Mass: 383.1454.

[0143] The compound of formula (IV), namely triacetyl nicotinamide riboside, triflate (—OTf) salt was prepared as follows. Nicotinamide (10 g, 81.89 mmol, 1 eq) was silylated using TMSCl (15.6 ml, 122.85 mmol, 1.5 eq) in HMDS (100

ml) at 130° C. in quantitative yield, in order to force the β -selectivity via the following Vorbrüggen reaction. Ribose tetraacetate (also known as tetraacetate riboside) was reacted with the resultant silylated nicotinamide in the presence of 5 equivalents of TMSOTf. The reactants were shaken in a 1.5 ml steel vessel with a 5 mm diameter steel ball bearing in a Retsch MM400 mixer mill at 25 Hz for 0.5 h. At this point the formed triacetylated nicotinamide riboside (compound of formula (IV)) could be isolated. It will be appreciated that the triacetyl nicotinamide riboside is not limited to being produced by this exact method, and could, for example, be produced using a conventional Vorbrüggen reaction as described, for example, in International PCT patent publication no. WO 2007/061798 or in T. Yang, N. Y. K. Chan and A. A. Sauve, *Journal of Medicinal Chemistry*, 2007, 50, 6458-6461.

[0144] $^1\text{H-NMR}$ (MeOD, 400 MHz)- δ 9.61 (s, 1H, aromatic), 9.30 (dt, 1H, J=6.3, 1.4 Hz, aromatic), 9.10 (dt, 1H, J=8.2, 1.4 Hz, aromatic), 8.37 (dd, 1H, J=8.2, 6.3 Hz, aromatic), 6.60 (d, 1H, J=3.9 Hz, H-1 (anomeric)), 5.60 (dd, 1H, J=5.6, 3.9 Hz, H-2), 5.46 (t, 1H, J=5.6 Hz, H-3), 4.81-4.84 (m, 1H, H-4), 4.61 (ABX, 1H, $J_{a,a'}=13.1$ Hz, $J_{a,b}=3.5$ Hz, H-5), 4.51 (ABX, 1H, $J_{a,a'}=13.0$ Hz, $J_{a,b}=2.8$ Hz, H-5'), 2.20 (s, 3H, OAc), 2.17 (s, 3H, OAc), 2.16 (s, 3H, OAc).

[0145] $^{13}\text{C-NMR}$ (MeOD, 125 MHz)- δ 172.1, 171.6, 171.2 ($3\times\text{C}=\text{OCH}_3$), 164.9 ($\text{C}=\text{ONH}_2$), 147.0, 144.3, 142.3, 136.2, 129.6, (aromatic), 121.6 (q, J=320.2 Hz, CF_3), 99.4 (C-1 (anomeric)), 84.4 (C-4), 77.6 (C-2), 70.7 (C-3), 63.5 (C-5), 20.7 (OAc), 20.3 (OAc), 20.2 (OAc).

[0146] $^{19}\text{F-NMR}$ (MeOD, 376 MHz)- δ -79.9 (triflate counterion)

Example 1(B)

Preparation of Reduced Triacetyl Nicotinate Ester Riboside, Namely Triacetyl O-ethyl-1,4-dihydronicotinamide riboside, a Compound of Formula (III) (the β -anomer Form of which is Shown in FIG. 4)

[0147] Reduction: A compound of formula (IV), namely triacetyl O-ethyl nicotinate riboside, triflate (—OTf) salt (2.30 g, 4.2 mmol, 1 eq) was dissolved in 20 mL H_2O and a solution of a solution of NaHCO_3 (1.77 g, 21.0 mmol, 5 eq) and sodium dithionite (1.47 g, 8.22 mmol, 2 eq) in 30 mL H_2O was added and stirred for 2 hrs. The yellow solution obtained was then washed with 2x ethyl acetate (EtOAc, 40 mL), the organic layer dried over MgSO_4 , filtered and concentrated to provide 900 mg (39% yield) of 2,3,5-triacetyl O-ethyl-1,4-dihydronicotinamide riboside (a yellow oil) without further purification. 80% purity based on $^1\text{H-NMR}$.

[0148] $^1\text{H-NMR}$ - δ 7.27 (1H, s, H-6), 6.05 (1H, dd, J=8.2, 1.5 Hz, H-7), 5.26 (1H, dd, J=5.8, 2.8 Hz, H-3), 5.23 (1H, dd, J=6.9, 5.8 Hz, H-2), 5.08 (1H, d, J=6.9 Hz, H-1), 4.81 (1H, dt, J=8.3, 3.5 Hz, H-8), 4.24-4.30 (3H, m, H-4, H-5, H-5'), 4.11 (2H, q, J=7.2 Hz, H-11), 3.04-3.06 (2H, m, H-9), 2.16 (3H, s, OAc), 2.12 (3H, s, OAc), 2.09 (3H, s, OAc), 1.25 (3H, t, J=7.2 Hz, H-12).

[0149] $^{13}\text{C-NMR}$ - δ 172.2, 171.5, 171.3, 169.8, ($3\times\text{C}=\text{O}-\text{CH}_3$ and $\text{C}=\text{O}-\text{OEt}$), 139.9 (C-6), 126.3 (C-7), 106.4 (C-8), 101.5 (C-10), 94.2 (C-1), 80.4 (C-4), 72.3 (C-2), 72.1 (C-3), 64.8 (C-5), 61.0 (C-11), 23.4 (C-9), 20.7, 20.5, 20.3 ($3\times\text{C}=\text{O}-\text{CH}_3$), 14.8 (C-12).

[0150] The compound of formula (IV), namely triacetyl O-ethyl nicotinate riboside, triflate (—OTf) salt was prepared as follows. Ribose tetraacetate (also known as tetraac-

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etate riboside) was reacted with ethyl nicotinate (Sigma Aldrich) using the general ball milling Vorbrüggen procedure described in Example 1(A) above. The reactants, namely 1 eq tetraacetate riboside, 1 eq TMSOTf, 1 eq ethyl nicotinate, were reacted for 30 mins in a 1.5 ml steel vessel with a 1.5 cm diameter steel ball bearing in a Retsch MM400 mixer mill at 25 Hz. The crude reaction mixture (containing some unreacted ethyl nicotinate and starting sugar, <10%) was used for the reduction step (described above) without further purification. It will be appreciated that the triacetyl O-ethyl nicotinate riboside, triflate (—OTf) salt is not limited to being produced by this exact method, and could, for example, be produced using a conventional Vorbrüggen reaction as described, for example, in International PCT patent publication no. WO 2007/061798 or in T. Yang, N. Y. K. Chan and A. A. Sauve, *Journal of Medicinal Chemistry*, 2007, 50, 6458-6461.

[0151] ¹H-NMR (D₂O, 400 MHz)-δ 9.45 (s, 1H, aromatic), 9.14 (d, 1H, J=6.1 Hz, aromatic), 9.02 (d, 1H, J=7.8 Hz, aromatic), 8.18 (t, 1H, J=6.7 Hz, aromatic), 6.51 (d, 1H, J=4.1 Hz, H-1 (anomeric)), 5.47 (t, 1H, J=4.4 Hz, H-2), 5.36 (t, 1H, J=4.7 Hz, H-3), 4.81-4.84 (m, 1H, H-4), 4.45-4.48 (m, 2H, H-5), 4.36 (q, 2H, J=7.0 Hz, C=OCH₂CH₃), 2.04 (s, 3H, OAc), 2.02 (s, 3H, OAc), 1.98 (s, 3H, OAc), 1.25 (t, 3H, J=7.0 Hz, C=OCH₂CH₃).

[0152] ¹³F-NMR (D₂O, 376 MHz)-δ -79.0 (triflate counterion)

Example 1(C)

Preparation of Reduced Tribenzoyl Nicotinamide Riboside, Namely

Tribenzoyl-1,4-dihydronicotinamide riboside, a Compound of Formula (III) (the β-anomer Form of which is Shown in FIG. 4)

[0153] Reduction (unoptimised): A compound of formula (IV), namely tribenzoyl nicotinamide riboside, triflate (—OTf) salt was dissolved in minimal methanol and transferred to a round bottomed flask, 10 mL of H₂O was added to the solution and most of the methanol removed via rotary evaporation. The starting material crashed out of solution and 20 mL of diethyl ether (Et₂O) was added until the solids solubilized into a biphasic system. A solution of NaHCO₃ (420 mg, 5 mmol, 5 eq) and sodium dithionite (348 mg, 2 mmol, 2 eq) in 10 mL H₂O was added and stirred for 2 hrs. The layers were separated and the ether layer was dried over MgSO₄ and concentrated to provide 428 mg (76% yield) of tribenzoyl-1,4-dihydronicotinamide riboside (yellow solid) without further purification. 80% purity based on ¹H-NMR. Pure material is obtained by Biotage purification.

[0154] ¹H-NMR-δ 8.01-8.04 (2H, m, OBz), 7.81-7.86 (4H, m, OBz), 7.25-7.55 (9H, m, OBz), 7.13 (1H, s, H-6), 6.01 (1H, dd, J=8.2, 1.5 Hz, H-7), 5.68 (1H, dd, J=6.2, 3.5 Hz, H-3), 5.57 (1H, dd, J=6.7, 6.2 Hz, H-2), 5.29 (1H, d, J=6.7 Hz, H-1), 4.61-4.68 (2H, m, H-8, H-5), 4.50-4.55 (2H, m, H-4, H-5'), 3.93-3.94 (2H, m, H-9). ¹³C-NMR-δ 172.7, 167.6, 166.7, 166.6 (3× C=O—C₆H₅, C=ONH₂), 138.1 (C-6), 134.9, 134.8, 134.6, 130.9, 130.8, 130.7, 130.3, 130.0, 129.8, 129.7 (3× OBz), 125.7 (C-7), 105.9 (C-8), 94.9 (C-1), 80.3 (C-4), 72.9 (C-2), 72.7 (C-3), 65.4 (C-5), 23.6 (C-9).

[0155] The compound of formula (IV), namely tribenzoyl nicotinamide riboside, triflate (—OTf) salt was prepared as follows. Ribose tetraacetate (also known as tetraacetate riboside) was reacted with TMS-nicotinamide (trimethylsilyl N-trimethylsilyl(pyridine-3-carboximidate, available from

Sigma-Aldrich) using the general ball milling Vorbrüggen procedure described in Example 1(A) above. The reactants, namely 1 eq 1-acetate-tribenzoate riboside, 1 eq TMSOTf and 1 eq TMS-nicotinamide, were reacted for 30 mins in a 1.5 ml steel vessel with a 1.5 cm diameter steel ball bearing in a Retsch MM400 mixer mill at 25 Hz. 1 eq of DCE (dichloroethylene) was required and the crude reaction mixture (containing some unreacted nicotinamide and starting benzoate sugar, <10%) was used for the reduction step (described above) without further purification. It will be appreciated that the tribenzoyl nicotinamide riboside, triflate (—OTf) salt is not limited to being produced by this exact method, and could, for example, be produced using a conventional Vorbrüggen reaction as described, for example, in International PCT patent publication no. WO 2007/061798 or in T. Yang, N.Y. K. Chan and A. A. Sauve, *Journal of Medicinal Chemistry*, 2007, 50, 6458-6461.

[0156] ¹H-NMR (MeOD, 400 MHz)-δ 9.59 (s, 1H, aromatic), 9.31 (d, 1H, J=6.4 Hz, aromatic), 8.94 (d, 1H, J=8.1 Hz, aromatic), 8.15 (dd, 1H, J=8.1, 6.4 Hz, aromatic), 7.90-7.94 (m, 6H, OBz), 7.50-7.54 (m, 3H, OBz), 7.31-7.38 (m, 6H, OBz), 6.79 (d, 1H, J=3.9 Hz, H-1 (anomeric)), 5.97 (dd, 1H, J=5.6, 3.9 Hz, H-2), 5.87 (t, 1H, J=5.6 Hz, H-3), 5.13-5.16 (m, 1H, H-4), 4.83-4.91 (m, 2H, H-5).

[0157] ¹⁹F-NMR (MeOD, 376 MHz)-δ -79.1 (triflate counterion)

EXAMPLE 2

[0158] A compound of formula (II), namely NRH (reduced nicotinamide riboside, also known as 1-(β-D-ribofuranosyl)-1,4-dihydronicotinamide (the β-anomer form of which is shown in FIG. 4) was prepared as follows. The pH of the reaction medium described in the following example was in the region of about 6-8.

[0159] Reduced triacetyl nicotinamide riboside, namely triacetyl-1,4-dihydronicotinamide riboside, a compound of formula (III), prepared in Example 1(A) above, was deprotected using mechanochemical (MeOH, NaOH) processes to remove the acetyl moiety afforded NRH quantitatively. 100 mgs of (III) was dissolved in 0.5 mL of MeOH containing 0.05 g of NaOH. The compounds were reacted for 30 mins in a 1.5 ml steel vessel with a 1.5 cm diameter steel ball bearing in a Retsch MM400 mixer mill at 25 Hz.

[0160] ¹H-NMR (MeOD, 400 MHz)-δ 7.18 (s, 1H, H-5), 0.14(d, 1H, J=8.28 Hz, H-6), 4.85 (m, 1H, H-3), 4.76 (d, 1H, J=5.77 Hz, H-4), 4.04 (m, 2H, H-7&H-8), 3.93 (m, 1H, J=2.76, H-9), 3.72 (ABX, 1H, J_{aa}=12.55 Hz, J_{ab}=3.51 Hz, H-10), 3.65 (ABX, 1H, J_{aa}=12.55 Hz, J_{ab}=4.02 Hz, H-10'), 3.10 (q, 2H, J=1.51 Hz H-2). ¹³C-NMR (MeOD, 125 MHz)-δ 172.88 (C-11), 137.83 (C-5), 125.29 (C-4), 105.19 (C-6), 95.00 (C-3), 83.54 (C-9), 71.10 (C-8), 70.20 (C-7), 61.61 (C-10), 22.09 (C-2); HRMS m/z: 257.1130; Calc. Mass: 257.1137.

[0161] It will be appreciated that the deprotection step as described above may be used to deprotect any other compound of formula (III), including, but not limited to, reduced triacetyl nicotinate ester riboside, namely 2,3,5-triacetyl O-ethyl-1,4-dihydronicotinamide riboside, prepared in Example 1(B), and reduced tribenzoyl nicotinamide riboside, namely tribenzoyl-1,4-dihydronicotinamide riboside, prepared in Example 1(C). The deprotection step may also be modified to suit particular requirements.

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EXAMPLE 3

[0162] Compounds of formula (I) were prepared in accordance with the invention as follows. The pH of the reaction media described in the following examples was in the region of about 6-8.

Example 3(A)

Preparation of Nicotinamide Riboside, Chloride Salt (the β -anomer Form of which is Shown in FIG. 5).

[0163] A compound of formula (II), namely NRH (reduced nicotinamide riboside, shown in FIG. 2; 50 mg, 0.20 mmol, 1 eq), was dissolved in 5 mL H₂O and then 1 eq (i.e. 0.20 mmol) of ammonium chloride was added in one portion. Activated charcoal (~10 mg, i.e. 0.80 mmol) was then added and the mixture stirred at RT for ~1 hr and then filtered and freeze-dried to give the chloride salt of nicotinamide riboside, quantitatively, i.e. 100% conversion and pure product.

[0164] ¹H-NMR (D₂O, 400 MHz)- δ 9.46 (s, 1H, aromatic), 9.12 (dt, 1H, J=6.3, 1.4 Hz, aromatic), 8.83 (dt, 1H, J=8.2, 1.4 Hz, aromatic), 8.13 (dd, 1H, J=8.2, 6.3 Hz, aromatic), 6.13 (d, 1H, J=4.3 Hz, H-1 (anomeric)), 4.37 (t, 1H, J=4.7 Hz, H-2), 4.31-4.34 (m, 1H, H-4), 4.21 (t, 1H, J=4.7 Hz, H-3), 3.90 (ABX, 1H, J_{a,a'}=13.0 Hz, J_{a,b}=3.5 Hz, H-5), 3.75 (ABX, 1H, J_{a,a'}=13.0 Hz, J_{a',b}=2.8 Hz, H-5').

[0165] It will be appreciated that the NRH may be that obtained in Example 2, or may be obtained commercially from e.g. Diverchim, 100, rue Louis Blanc, 60765 Montataire Cedex, France—(CAS Registry Number: 19132-12-8) either as a pure product or as a mixture of anomers.

Example 3(B)

Preparation of Nicotinamide Riboside, Acetate Salt (the β -anomer Form of which is Shown in FIG. 5)

[0166] The method described in Example 3(A) was carried out, except that leg (i.e. 0.20 mmol) of ammonium acetate was added. The acetate salt of nicotinamide riboside was obtained, quantitatively.

[0167] ¹H-NMR (D₂O, 400 MHz)- δ 9.46 (s, 1H, aromatic), 9.12 (d, 1H, J=6.3 Hz, aromatic), 8.83 (d, 1H, J=8.2 Hz, aromatic), 8.12 (m, 1H, aromatic), 6.09 (d, 1H, J=4.4 Hz, H-1 (anomeric)), 4.36 (t, 1H, J=4.7 Hz, H-2), 4.32-4.35 (m, 1H, H-4), 4.21 (t, 1H, J=4.7 Hz, H-3), 3.91 (ABX, 1H, J_{a,a'}=13.1 Hz, J_{a,b}=2.8 Hz, H-5), 3.75 (ABX, 1H, J_{a,a'}=13.0 Hz, J_{a',b}=3.5 Hz, H-5), 1.79 (s, 3H, OAc).

Example 3(C)

Preparation of Nicotinamide Riboside, Formate Salt (the β -anomer Form of which is Shown in FIG. 5)

[0168] The method described in Example 3(A) was carried out, except that 1 eq (i.e. 0.20 mmol) of ammonium formate (methanoate) was added. The formate salt of nicotinamide riboside was obtained, quantitatively.

[0169] ¹H-NMR (D₂O, 400 MHz)- δ 9.46 (s, 1H, aromatic), 9.12 (d, 1H, J=6.3 Hz, aromatic), 8.83 (d, 1H, J=8.2 Hz, aromatic), 8.29 (s, 1H, formate), 8.12 (m, 1H, aromatic), 6.09 (d, 1H, J=4.4 Hz, H-1 (anomeric)), 4.36 (t, 1H, J=4.7 Hz, H-2), 4.31-4.34 (m, 1H, H-4), 4.21 (t, 1H, J=4.7 Hz, H-3), 3.91 (ABX, J_{a,a'}=13.1 Hz, J_{a,b}=3.5 Hz, H-5), 3.79 (ABX, 1H, J_{a,a'}=13.0 Hz, J_{a',b}=2.8 Hz, H-5').

Example 3(D)

Preparation of Nicotinamide Riboside, trifluoroacetate Salt (the β -anomer Form of which is Shown in FIG. 5)

[0170] The method described in Example 3(A) was carried out, except that 1 eq (i.e. 0.20 mmol) of ammonium trifluoroacetate was added. The trifluoroacetate salt of nicotinamide riboside was obtained, quantitatively.

[0171] ¹H-NMR (D₂O, 400 MHz)- δ 9.46 (s, 1H, aromatic), 9.12 (d, 1H, J=6.3 Hz, aromatic), 8.83 (d, 1H, J=8.2, aromatic), 8.13 (dd, 1H, J=8.2, 6.3 Hz, aromatic), 6.13 (d, 1H, J=4.3 Hz, H-1 (anomeric)), 4.35 (t, 1H, J=4.7 Hz, H-2), 4.31-4.34 (m, 1H, H-4), 4.20 (t, 1H, J=4.7 Hz, H-3), 3.89 (ABX, 1H, J_{a,a'}=13.0 Hz, J_{a,b}=3.6 Hz, H-5), 3.74 (ABX, 1H, J_{a,a'}=13.0 Hz, J_{a',b}=2.9 Hz, H-5'). ¹⁹F-NMR (D₂O, 376 MHz)- δ -75.7 (CF₃COO⁻).

Example 3(E)

Preparation of Nicotinamide Riboside, Chloride Salt (the β -anomer form of which is Shown in FIG. 5)

[0172] An alternative method to that described in Example 3(A) was carried out as follows. NRH (reduced nicotinamide riboside, shown in FIG. 4; 50 mg, 0.20 mmol, 1 eq) was dissolved in 5 mL H₂O:EtOAc (1:1) and then 1 eq (i.e. 0.20 mmol) of ammonium chloride was added in one portion. Upon work-up after 1 hr, no oxidation had taken place and the starting materials were fully recovered. The recovered NRH and ammonium chloride were re-suspended in the same solvent system with addition of activated charcoal (~10 mg, i.e. 0.8 mmol) and stirred at RT for 1 hr. Subsequent filtration and freeze-drying afforded the chloride salt of nicotinamide riboside in quantitative yield. Thus it was concluded that a carbon-containing catalyst, e.g. activated charcoal, was essential to the method.

[0173] ¹H-NMR (D₂O, 400 MHz)- δ 9.46 (s, 1H, aromatic), 9.12 (dt, 1H, J=6.3, 1.4 Hz, aromatic), 8.83 (dt, 1H, J=8.2, 1.4 Hz, aromatic), 8.13 (dd, 1H, J=8.2, 6.3 Hz, aromatic), 6.13 (d, 1H, J=4.3 Hz, H-1 (anomeric)), 4.37 (t, 1H, J=4.7 Hz, H-2), 4.31-4.34 (m, 1H, H-4), 4.21 (t, 1H, J=4.7 Hz, H-3), 3.90 (ABX, 1H, J_{a,a'}=13.0 Hz, J_{a,b}=3.5 Hz, H-5), 3.75 (ABX, 1H, J_{a,a'}=13.0 Hz, J_{a',b}=2.8 Hz, H-5').

Example 3(F)

Preparation of Nicotinamide Riboside, Chloride Salt (the β -anomer Form of which is Shown in FIG. 5)

[0174] The method described in Example 3(E) was carried out, except that NRH (reduced nicotinamide riboside, shown in FIG. 4; 50 mg, 0.20 mmol, 1 eq) was dissolved in 5 mL H₂O:THF (1:1), instead of H₂O:EtOAc (1:1), and then 1 eq (i.e. 0.20 mmol) of ammonium chloride was added in one portion. Upon work-up after 1 hr, no oxidation had taken place and the starting materials were fully recovered. The recovered NRH and ammonium chloride were re-suspended in the same solvent system with addition of activated charcoal (~10 mg, i.e. 0.8 mmol) and stirred at RT for 1 hr. Subsequent filtration and freeze-drying afforded the chloride salt of nicotinamide riboside in quantitative yield. Thus it was concluded that a carbon-containing catalyst, e.g. activated charcoal, was essential to the method.

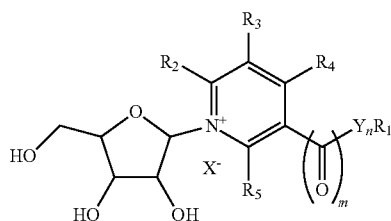
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[0175] $^1\text{H-NMR}$ (D_2O , 400 MHz)- δ 9.46 (s, 1H, aromatic), 9.12 (dt, 1H, $J=6.3$, 1.4 Hz, aromatic), 8.83 (dt, 1H, $J=8.2$, 1.4 Hz, aromatic), 8.13 (dd, 1H, $J=8.2$, 6.3 Hz, aromatic), 6.13 (d, 1H, $J=4.3$ Hz, H-1 (anomeric)), 4.37 (t, 1H, $J=4.7$ Hz, H-2), 4.31-4.34 (m, 1H, H-4), 4.21 (t, 1H, $J=4.7$ Hz, H-3), 3.90 (ABX, 1H, $J_{a,a'}=13.0$ Hz, $J_{a,b}=3.5$ Hz, H-5), 3.75 (ABX, 1H, $J_{a,a'}=13.0$ Hz, $J_{a',b}=2.8$ Hz, H-5').

1. A method of preparing a compound of formula (I)



wherein

n is 0 or 1;

m is 0 or 1;

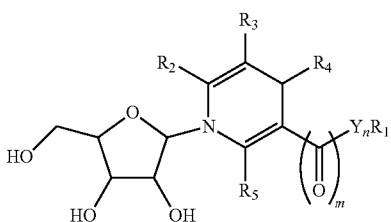
Y is O or S;

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;

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

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;

comprising reacting a compound of formula (II)



wherein n , m , Y and R_1 - R_5 are as defined above;

with a compound of the formula Z^+X^- ,

wherein X^- is as defined above, and

wherein Z^+ is a N-containing cation;

in the presence of an aqueous solution and a carbon-containing catalyst;

to form the compound of formula (I).

2. A method according to claim 1, wherein Z^+ is selected from a substituted or unsubstituted ammonium, a substituted or unsubstituted pyridinium, a substituted or unsubstituted

pyrrolidinium, a substituted or unsubstituted imidazolium and a substituted or unsubstituted triazolium.

3. A method according to claim 1 or claim 2, wherein Z^+ is a substituted or unsubstituted ammonium of the formula $N^+HR^I R^II R^III$, wherein R^I , R^II and R^III , 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.

4. A method according to any one of claims 1 to 3, wherein Z^+ is an unsubstituted ammonium of the formula NH_4^+ .

5. A method according to any preceding claim, wherein the aqueous solution comprises, in addition to water, an organic solvent.

6. A method according to claim 5, wherein the aqueous solution comprises water and organic solvent in a respective ratio by volume of from about 1:5 to about 5:1, optionally from about 1:3 to about 3:1, further optionally from about 1:2 to about 2:1, still further optionally about 1:1.

7. A method according to claim 5 or claim 6, wherein the organic solvent is selected from a substituted or unsubstituted ether, a substituted or unsubstituted ester, a substituted or unsubstituted ketone, a substituted or unsubstituted aliphatic or aromatic hydrocarbon, or a combination thereof.

8. A method according to any one of claims 5 to 7, wherein the organic solvent comprises an ether selected from diethyl ether, methyl tert-butyl ether, ethyl tert-butyl ether, di-tert-butyl ether, diisopropyl ether, dimethoxymethane, tetrahydrofuran, 2-methyltetrahydrofuran, and tetrahydropyran, or a combination thereof.

9. A method according to any one of claims 5 to 8, wherein the organic solvent comprises an ester selected from methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, isobutyl acetate and n-butyl acetate, or a combination thereof.

10. A method according to any one of claims 5 to 9, wherein the organic solvent comprises a ketone selected from methyl isobutyl ketone and methyl isopropyl ketone, or a combination thereof.

11. A method according to any one of claims 5 to 10, wherein the organic solvent comprises an unsubstituted aliphatic hydrocarbon solvent selected from pentane, hexane, cyclohexane and heptane, or a combination thereof.

12. A method according to any one of claims 5 to 11, wherein the organic solvent comprises a substituted aliphatic hydrocarbon solvent, optionally a halogenated aliphatic hydrocarbon solvent, further optionally a chlorinated aliphatic hydrocarbon solvent selected from dichloromethane, trichloromethane, tetrachloromethane, 1,2-chloroethane, 1,1,1-trichloroethane and trichloroethylene, or a combination thereof.

13. A method according to any one of claims 5 to 12, wherein the organic solvent comprises an aromatic hydrocarbon solvent selected from benzene, toluene, ethylbenzene and xylene, or a combination thereof.

14. A method according to any preceding claim, wherein the compound of formula (II) and the compound of the formula Z^+X^- are present in a respective molar ratio of from about 1:5 to about 5:1, 35 optionally from about 1:3 to about 3:1, further optionally from about 1:2 to about 2:1, still further optionally about 1:1.

15. A method according to any preceding claim, wherein the compound of formula (II) and the carbon-containing catalyst are present in a respective molar ratio of from about 10:1

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to about 1:10, optionally from about 5:1 to about 1:5, further optionally from about 4:1 to about 1:4, still further optionally about 1:1 or 1:2 or 1:3 or 1:4.

16. A method according to any preceding claim, wherein the reaction is carried out in a pH range of from about 6 to about 8, optionally from about 6.5 to about 7.5.

17. A method according to any preceding claim, wherein the reaction is carried out at a temperature of from about 10° C. to about 40° C., optionally from about 15° C. to about 35° C., further optionally from about 15° C. to about 30° C., still further optionally from about 15° C. to about 20° C., even further optionally from about 20° C. to about 25° C., even further optionally at a temperature of about 20° C. or 21° C. or 22° C. or 23° C. or 24° C. or 25° C.

18. A method according to any preceding claim, wherein the reaction is carried out for a period of time of from about 1 minute to about 180 minutes, optionally from about 2 minutes to about 120 minutes, further optionally from about 5 minutes to about 120 minutes, still further optionally from about 10 minutes to about 120 minutes, even further optionally from about 20 minutes to about 120 minutes, even further optionally from about 30 minutes to about 120 minutes, still further optionally from about 60 minutes to about 120 minutes, even further optionally from about 60 minutes to about 90 minutes, still further optionally about 60 minutes or 70 minutes or 80 minutes.

19. A method according to any preceding claim, wherein 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.

20. A method according to claim 19, wherein X^- is an anion of a substituted monocarboxylic acid, optionally an anion of a substituted propanoic acid or an anion of a substituted acetic acid.

21. A method according to claim 20, wherein X^- is an anion of a substituted propanoic acid, optionally an anion of a hydroxy propanoic acid, further optionally an anion of 2-hydroxypropanoic acid, being lactate.

22. A method according to claim 20, wherein X^- is an anion of a substituted acetic acid, being a substituted acetate, optionally a trihaloacetate selected from trichloroacetate, tribromoacetate and trifluoroacetate, further optionally trifluoroacetate.

23. A method according to claim 19, wherein 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.

24. A method according to claim 19, wherein X^- is an anion of a substituted or unsubstituted amino-monocarboxylic acid or an anion of a substituted or unsubstituted amino-dicarboxylic acid, wherein, optionally, X^- is an anion of an amino-dicarboxylic acid, further optionally selected from glutamic acid and aspartic acid, being glutamate and aspartate, respectively.

25. A method according to claim 19, wherein X^- is an anion of ascorbic acid, being ascorbate.

26. A method according to any one of claims 1 to 18, wherein X^- is a halide selected from chloride, bromide, fluoride and iodide, optionally chloride or bromide.

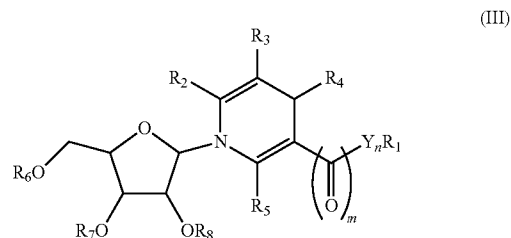
27. A method according to any one of claims 1 to 18, wherein X^- is selected from chloride, acetate, formate, trifluoroacetate, ascorbate, aspartate, glutamate and lactate, optionally selected from chloride, acetate, formate and trifluoroacetate.

28. A method according to any one of claims 1 to 18, wherein the compound of the formula Z^+X^- is selected from ammonium chloride, ammonium acetate, ammonium formate, ammonium trifluoroacetate, ammonium ascorbate, ammonium aspartate, ammonium glutamate and ammonium lactate, optionally selected from ammonium chloride, ammonium acetate, ammonium formate and ammonium trifluoroacetate.

29. A method according to any preceding claim, wherein the method further comprises a filtration step to remove the carbon-containing catalyst from the compound of formula (I).

30. A method according to any one of claims 1 to 18, wherein, in the compound of formula (I), n is 0, m is 1, R_1 is NH_2 , R_2 - R_5 are each H, and X^- is selected from chloride, acetate, formate and trifluoroacetate.

31. A method according to any preceding claim, wherein the compound of formula (II) is prepared by reacting a compound of formula (III)



wherein

n , m , Y and R_1 - R_5 are as defined in the preceding claims; and

R_6 , R_7 and R_8 , which may be the same or different, are each independently a hydroxyl-protecting group;

with a deprotecting agent;

to form the compound of formula (II).

32. A method according to claim 31, wherein R_6 , R_7 and R_8 are each independently an ester-type protecting group, an ether-type protecting group, or a silyl-type protecting group.

33. A method according to claim 32, wherein an ester-type protecting group is a protecting group selected from acetyl, propionyl, isopropionyl, benzoyl, and trihaloacetyl, optionally trifluoroacetyl or trichloroacetyl.

34. A method according to claim 32, wherein an ether-type protecting group is a protecting group selected from benzyl, p-methoxybenzyl, methoxymethyl and allyl ethers.

35. A method according to claim 32, wherein a silyl-type protecting group is a protecting group selected from trimethylsilyl, triethylsilyl, triisopropylsilyl, 2-(trimethylsilyl)ethoxymethyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl and tetraisopropylsilyl.

36. A method according to any one of claims 31 to 33, wherein the R_6 , R_7 and R_8 moieties are selected from substituted and unsubstituted acetyl, and substituted and unsubstituted benzoyl.

37. A method according to claim 36, wherein least two of R_6 , R_7 and R_8 are selected from unsubstituted acetyl or unsubstituted benzoyl.

38. A method according to any one of claims 31 to 37, wherein the deprotecting agent is an acid or a base.

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39. A method according to claim 37, wherein R_6 , R_7 and R_8 each comprise unsubstituted acetyl or unsubstituted benzoyl and the deprotecting agent is a base, optionally selected from NH_3 , Na_2CO_3 and $NaOH$.

40. A method according to any one of claims 31 to 39, wherein the reaction is carried out in the presence of a protic or aprotic solvent or a combination thereof.

41. A method according to claim 41, wherein the reaction is carried out in the presence of a protic solvent selected from water, substituted or unsubstituted alcohol, or a combination thereof.

42. A method according to claim 42, wherein the reaction is carried out in the presence of methanol.

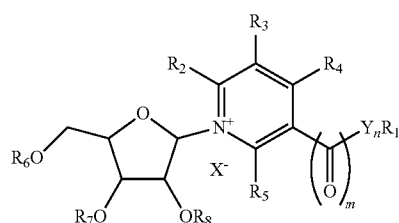
43. A method according to any one of claims 31 to 42, wherein the reactants are subjected to mechanical grinding, optionally using a ball milling or planetary ball milling machine.

44. A method according to any one of claims 31 to 43, wherein, in the compound of formula (III), n is 0, m is 1, R_1 is NH_2 , R_2 - R_5 are each H, and R_6 - R_8 are each acetyl.

45. A method according to any one of claims 31 to 43, wherein, in the compound of formula (III), n is 1, Y is O, m is 1, R_1 is ethyl, R_2 - R_5 are each H, and R_6 - R_8 are each acetyl.

46. A method according to any one of claims 31 to 43, wherein, in the compound of formula (III), n is 0, m is 1, R_1 is NH_2 , R_2 - R_5 are each H, and R_6 - R_8 are each benzoyl.

47. A method according to any one of claims 31 to 46, wherein the compound of formula (III) is prepared by reacting a compound of formula (IV)



(IV)

wherein

n , m , Y , R_1 - R_8 and X^- are as defined in the preceding claims;

with a reducing agent,

an aqueous solution,

and an organic solvent,

to form a compound of formula (III).

48. A method according to claim 47, wherein the organic solvent is as defined in any one of claims 7 to 13.

49. A method according to claim 47 or claim 48, wherein when at least two of R_6 , R_7 and R_8 comprise unsubstituted acetyl, the organic solvent is selected from dichloromethane, 1,2-chloroethane, n -butyl acetate, chloroform and ethyl acetate, or a combination thereof, further optionally ethyl acetate.

50. A method according to claim 47 or claim 48, wherein when at least two of R_2 , R_3 and R_4 comprise unsubstituted benzoyl, the organic solvent is selected from trichloroethylene, carbon tetrachloride, diisopropyl ether, toluene, methyl tert-butyl ether, benzene and diethyl ether, or a combination thereof, further optionally diethyl ether.

51. A method according to any one of claims 47 to 50, wherein the reducing agent is selected from sodium dithionite or sodium borohydride.

52. A method according to any one of claims 47 to 51, wherein the method comprises the additional steps of separating the organic phase from the aqueous phase; and extracting the compound of formula (III) from the organic solvent.

53. A method according to any one of claims 47 to 52, wherein the reactants are subjected to mechanical grinding, optionally using a ball mill or planetary ball milling machine.

54. A method according to any one of claims 47 to 53, wherein, in the compound of formula (IV), n is 0, m is 1, R_1 is NH_2 , R_2 - R_5 are each H, R_6 - R_8 are each acetyl, and X^- is $-OTf$.

55. A method according to any one of claims 47 to 53, wherein, in the compound of formula (IV), n is 1, Y is O, m is 1, R_1 is ethyl, R_2 - R_5 are each H, R_6 - R_8 are each acetyl, and X^- is $-OTf$.

56. A method according to any one of claims 47 to 53, wherein, in the compound of formula (IV), n is 0, m is 1, R_1 is NH_2 , R_2 - R_5 are each H, and R_6 - R_8 are each benzoyl, and X^- is $-OTf$.

* * * * *

EXHIBIT B

**THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF SOUTH CAROLINA
CHARLESTON DIVISION**

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

Plaintiffs

V.

NIAGEN BIOSCIENCE, INC., and
CHROMADEx, INC., and THE QUEEN'S
UNIVERSITY OF BELFAST

Defendants.

C.A. No. 2:26-cv-01758-RMG

DEMAND FOR JURY TRIAL

AMENDED COMPLAINT FOR DECLARATORY JUDGMENT

Plaintiffs Thorne Research, Inc. (“Thorne Research”) and Thorne HealthTech, Inc. (“Thorne HealthTech”) (collectively, “Thorne”) allege as follows for their Complaint against Defendants Niagen Bioscience, Inc. (“Niagen”), ChromaDex, Inc. (“ChromaDex”), and the Queen’s University of Belfast (“University of Belfast”) (collectively, “Defendants”):

NATURE OF THE ACTION

1. This is an action for declaratory judgment of noninfringement and invalidity of U.S. Patent No. 12,252,506 (the “’506 Patent”) arising under the Declaratory Judgment Act (28 U.S.C. §§ 2201–2202) and the patent laws of the United States (35 U.S.C. § 1, *et seq.*); tortious interference with a contract; intentional interference with prospective contractual relations; and unfair competition pursuant to the South Carolina Unfair Trade Practices Act (S.C. Code § 39-5-10, *et seq.*).

2. This action arises from Defendants' campaign to unlawfully restrain Thorne's ability to sell its products. Defendants sent letters demanding that Thorne remove its products

from the marketplace, made allegations of patent infringement, and filed a complaint through Amazon's Patent Evaluation Express ("APEX") procedure seeking removal of Thorne's product listings. Defendants' allegations are without merit. Thorne brings this action to obtain a judicial declaration that its products do not infringe any valid and enforceable claim of the '506 Patent.

THE PARTIES

3. Thorne Research is a South Carolina corporation with its principal place of business at 620 Omni Industrial Blvd., Summerville, South Carolina 29486.

4. Thorne HealthTech is a Delaware corporation with its principal place of business at 620 Omni Industrial Blvd., Summerville, South Carolina 29486. Thorne Research is a wholly owned subsidiary of Thorne HealthTech.

5. Founded in 1984, Thorne is a science-driven wellness company developing innovative solutions for a personalized approach to health and wellness. Thorne seeks to bring the scientific rigor of biopharmaceuticals to the prevention space to help people live longer, healthier lives. Thorne offers unique, vertically-integrated brands to provide personalized data, products and services that empower individuals to take a proactive approach to improve and maintain their health over their lifetime. By combining its proprietary multi-omics database, artificial intelligence and digital health content with its science-backed nutritional supplements, Thorne delivers a total system for wellness. Thorne has spent millions of dollars researching and developing novel products to improve the health and wellness of people.

6. On information and belief, Niagen is a Delaware corporation with its principal place of business at 10900 Wilshire Boulevard, Suite 600, Los Angeles, California 90024.

7. On information and belief, ChromaDex is a California corporation with its principal place of business at 10900 Wilshire Boulevard, Suite 600, Los Angeles, California 90024. On information and belief, ChromaDex is a wholly owned subsidiary of Niagen.

8. On information and belief, the University of Belfast is a public research university in Belfast, Northern Ireland, United Kingdom, whose address is University Road, Belfast BT7 1NN, United Kingdom.

BACKGROUND

9. On information and belief, Defendants' baseless allegations that the Thorne NR Products infringe the '506 Patent are a continuation of Defendants' harassment of Thorne that spans several years.

A. Defendants' Unsuccessful Prior Attacks on Thorne

10. In prior litigation, ChromaDex accused Thorne of infringing U.S. Pat. Nos. 8,197,807 (the "'807 Patent") and 8,383,086 (the "'086 Patent")—patents it licensed from Dartmouth College. Like the '506 Patent, the '807 and '086 Patents are directed to compositions of nicotinamide riboside ("NR"). *ChromaDex, Inc. v. Thorne Rsch., Inc.*, No. 1:21-cv-04241-ER (S.D.N.Y.) (hereinafter, "Failed ChromaDex Litigation"). Now, ChromaDex—in concert with the other Defendants—is attacking one of the same Thorne products (NiaCel[®] 400) that it attacked in the Failed ChromaDex Litigation. *ChromaDex, Inc., et al. v. Thorne Rsch., Inc.*, No. 1:21-cv-04241-ER, D.I. 1, ¶ 13 (S.D.N.Y. May 12, 2021).

11. The Failed ChromaDex Litigation ended because both of ChromaDex's patents were invalidated. The relevant claims of the '086 Patent were found unpatentable by the Patent Trial and Appeal Board, and a District Court (affirmed by the Federal Circuit Court of Appeals) found the relevant claims of the '807 Patent invalid.¹ *Thorne Rsch., Inc. v. Trustees of Dartmouth College*, IPR2021-00268, Paper No. 63 at 41 (PTAB May 31, 2022); *ChromaDex, Inc. v. Elysium*

¹ ChromaDex asserted the '807 Patent against another competitor in a separate action. *ChromaDex, Inc. v. Elysium Health, Inc.*, C.A. No. 18-1434-CFC-JLH (D. Del.).

Health, Inc., 59 F.4th 1280, 1286 (Fed. Cir. 2023). In view of that invalidation, the litigation against Thorne was dismissed. *ChromaDex, Inc., et al. v. Thorne Rsch., Inc.*, No. 1:21-cv-04241-ER, D.I. 31 (S.D.N.Y. Jan. 4, 2024).

B. The '506 Patent

12. The '506 Patent is entitled “Methods of Preparing Nicotinamide Riboside and Derivates Thereof,” and was issued by the United States Patent and Trademark Office (“USPTO”) on March 18, 2025. A true and correct copy of the '506 Patent is attached hereto as Exhibit 1.

13. The University of Belfast, Niagen, and ChromaDex have each held themselves out to be the owner of the '506 Patent.

14. On its face, the '506 Patent is assigned to the University of Belfast.

15. The USPTO Assignment Database indicates that the '506 Patent is assigned to the University of Belfast. Ex. 2.

16. In a signed exhibit to Amazon’s APEX Agreement, Defendants asserted “ChromaDex, Inc. is the owner of the ['506] patent pursuant to an assignment from The Queens Belfast (Great Britain) dated December 16, 2025.” Ex. 3 (the “APEX Agreement”) at 2.

17. That APEX Agreement is signed by “Carlos Lopez, SVP, General Counsel, ChromaDex, Inc.” *Id.*

18. That APEX Agreement states that Carlos Lopez’s email address is carlos.lopez@niagenbio.com. *Id.*

19. On its face, the website niagenbio.com concerns Defendant Niagen, not Defendant ChromaDex.

20. Niagen has publicly stated that it is the assignee and owner of the '506 Patent.

21. For example, on December 22, 2025, Niagen stated in a press release that Niagen

had “acquired a comprehensive portfolio of existing patents covering nicotinamide riboside (NR) and its salt forms from Queen’s University Belfast[.]” Ex. 4 at 1. The press release also stated “[t]his 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[.]” *Id.* at 1-2.

22. Niagen’s 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[.]” Ex. 5 at 9-10.

23. On information and belief, the University of Belfast, Niagen, and ChromaDex are operating in concert to threaten Thorne with enforcement of the ’506 Patent.

C. ChromaDex’s Cease and Desist Letters to Thorne

24. On September 20, 2024, ChromaDex sent a letter to Thorne asserting that “Thorne’s use of NR Malate in its nutritional supplement products infringes upon the rights of ChromaDex[.]” including certain claims of U.S. Pat. No. 11,242,364 (the “’364 Patent”).

25. Thorne responded on October 25, 2024, stating that “Thorne’s use of NR Malate in its products does not fall within the scope of any of the claims of the ’364 patent.”

26. On May 13, 2025, ChromaDex sent Thorne another letter seeking details of the confidential manufacturing process for the NR Malate in Thorne’s products. In this letter, ChromaDex further stated that it was “provid[ing] Thorne notice of the recent issuance of [the ’506 Patent][,]” that “ChromaDex holds exclusive rights to the ’506 [sic] Patent[.]”² and “request[ed] that Thorne reconsider discussing . . . cooperation between the two companies.”

² Niagen announced it had acquired the ’506 Patent seven months later. *Supra*, ¶ 21.

27. Thorne responded on July 17, 2025, stating that ChromaDex’s “notice” of the ’506 Patent was without context, and requesting further explanation if ChromaDex sought a response.

28. On July 22, 2025, ChromaDex sent Thorne another letter alleging that its prior “notice” of the ’506 Patent was instead a cease and desist demand. Specifically, ChromaDex stated:

We informed you that claims 1 and 26 of the ‘506 [sic] patent claim the NR malate compound. You had previously acknowledged that Thorne sells products containing NR malate (for example, its Niacel product), and understand that 35 U.S.C. §271(a) prohibits, inter alia, the sale of any patented invention during the term of the patent. That the sale of Niacel and any other Thorne product containing NR malate infringes the ’506 patent is a tautology.

[...]

It remains ChromaDex’s preference that the parties directly discuss an amicable resolution to this matter. If Thorne declines this invitation, we ask that it . . . confirm that it will cease all sales of Niacel and any other product containing NR malate (including sales by partners such as the Mayo Clinic, which we observe is selling the Niacel product on its website) and destroy all existing NR malate product and inventory in its possession or control.

29. ChromaDex did not further communicate with Thorne regarding the ’506 Patent after the July 22, 2025 letter.

D. Defendants Initiate an APEX Evaluation Against Thorne

30. Amazon.com, Inc. (“Amazon”) offers the APEX procedure “[t]o efficiently resolve claims that third-party product listings [on Amazon] infringe utility patents[.]” Ex. 6 at 1.

31. An APEX evaluation is initiated when a U.S. utility patent owner submits an APEX agreement to Amazon identifying a patent and Amazon Standard Identification Number (“ASIN”) of the products sold by third parties on Amazon that the patent owner alleges infringe the patent. Ex. 3 at 1, 2. Amazon then sends the patent owner-completed APEX agreement to the product seller and provides three options to continue selling the accused products on Amazon: (1) resolve the claim with the patent owner directly; (2) show that the product seller and patent owner are

already in patent litigation, or that the product seller filed a declaratory judgment claim for noninfringement of the patent; or (3) opt in to the APEX evaluation by executing and returning the APEX agreement. Ex. 7 at 1. If the product seller does not respond consistent with one of these three options within three weeks, the listings for the products identified by the patent owner are removed from Amazon. *Id.*

32. On information and belief, when an APEX agreement is submitted to Amazon, Amazon does not take any steps to confirm the submitter is the patent owner.

33. On information and belief, an infringement complaint on Amazon—such as initiation of an APEX evaluation—negatively impacts the “health score” of seller accounts. *E.g.*, Ex. 8 at 2-4, 6. On information and belief, there is a direct correlation between said “health score” and seller revenue, for example, by impacting search visibility (a lower health score leads to lower search visibility, meaning fewer sales). *E.g.*, Ex. 9 at 3-5.

34. Thorne has a contractual relationship with Pattern Inc. (“Pattern”) relating to the sale of its products on Amazon.

35. On April 10, 2026—after almost nine months of silence from ChromaDex—Pattern received notice that ChromaDex initiated an APEX evaluation regarding Thorne’s products. Ex. 7. Pattern sent that notice to Thorne. The notice stated that ChromaDex claimed that ten ASINs sold on Amazon infringed the ’506 Patent. Ex. 3 at 2. Three of the ASINs were associated with Thorne products. Ex. 7 at 1.

E. Thorne’s NR Products

36. The April 10, 2026 APEX Notice Email identified three Thorne products which include nicotinamide riboside: (1) ResveraCel® (ASIN B097Z5387H); (2) SynaQuell® (ASIN B0B14F9PSR); and (3) NiaCel® 400 (ASIN B08WPXPTD8). *Id.* at 1. Each of these Thorne

products is manufactured and sold from Thorne's facilities in South Carolina.

37. ResveraCel® is a dietary supplement designed to promote healthy aging, support cellular metabolism, and enhance NAD⁺ production to boost cellular energy and metabolism.

38. SynaQuell® is a brain health supplement designed to enhance cellular energy production and promote a healthy balance of inflammatory cytokines, particularly for individuals involved in contact sports.

39. NiaCel® 400 is a dietary supplement containing nicotinamide riboside and betaine anhydrous to support healthy aging and optimize vitality.

40. Thorne sells ResveraCel®, SynaQuell®, and NiaCel® 400 direct to consumers on its website, www.thorne.com. Thorne has a contractual relationship with Pattern relating to the sale of these products on Amazon.

41. Thorne sells additional products containing nicotinamide riboside that are not the subject of Defendants' APEX notice. Together with ResveraCel®, SynaQuell®, and NiaCel® 400, all Thorne products that contain nicotinamide riboside malate are the "Thorne NR Products."

JURISDICTION, VENUE, AND JOINDER

42. Thorne incorporates by reference the preceding paragraphs as if fully set forth herein.

43. This Court has subject matter jurisdiction over Thorne's claims pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202, as well as the patent laws of the United States, 35 U.S.C. § 1, *et seq.*

44. This Court has supplemental jurisdiction over Thorne's claims arising under the laws of South Carolina pursuant to 28 U.S.C. § 1367 because Thorne's state law claims are so related to Thorne's federal law claims such that they form part of the same case or controversy and derive from a common nucleus of operative facts.

45. This Court has personal jurisdiction over Niagen because it purposefully directed enforcement activities relating to the '506 Patent to Thorne Research in South Carolina in an improper attempt to block sales of Thorne's products from South Carolina. Thorne Research is a South Carolina entity with headquarters and manufacturing facilities in Summerville, South Carolina, who markets and sells the Thorne NR Products in and from South Carolina. Niagen purposefully acted in concert with ChromaDex and the University of Belfast to direct communications at Thorne levying threats to enforce the '506 Patent—a patent Niagen asserts that it owns—against Thorne and acted in concert with ChromaDex to initiate the APEX evaluation attacking Thorne's ResveraCel[®], SynaQuell[®], and NiaCel[®] 400 products alleging infringement of the '506 Patent. Venue is proper for Niagen in this District pursuant to 28 U.S.C. § 1391 for the same reason.

46. This Court has personal jurisdiction over ChromaDex because it purposefully directed enforcement activities relating to the '506 Patent to Thorne Research in South Carolina in an improper attempt to block sales of Thorne's products from South Carolina. Thorne Research is a South Carolina entity with headquarters and manufacturing facilities in Summerville, South Carolina, who markets and sells the Thorne NR Products in and from South Carolina. ChromaDex purposefully acted in concert with Niagen and the University of Belfast to direct communications at Thorne levying threats to enforce the '506 Patent—a patent ChromaDex also asserts that it owns—against Thorne and initiate the APEX evaluation attacking Thorne's ResveraCel[®], SynaQuell[®], and NiaCel[®] 400 products based on the patent. Venue is proper for ChromaDex in this District pursuant to 28 U.S.C. § 1391 for the same reason.

47. This Court has personal jurisdiction over the University of Belfast under Fed. R. Civ. P. 4(k)(2). This is because: (a) the claims in this action arise under federal law; (b) the

University of Belfast is not subject to the jurisdiction to any state's courts of general jurisdiction; and (c) exercising jurisdiction over the University of Belfast is consistent with the U.S. Constitution. This Court also has personal jurisdiction over the University of Belfast because it purposefully directed enforcement activities relating to the '506 Patent to Thorne Research in South Carolina in an improper attempt to block sales of Thorne's products from South Carolina. Thorne Research is a South Carolina entity with headquarters and manufacturing facilities in Summerville, South Carolina, who markets and sells the Thorne NR Products in and from South Carolina. On information and belief, the University of Belfast purposefully acted in concert with Niagen and ChromaDex to direct communications at Thorne levying threats to enforce the '506 Patent—a patent assigned on its face and in the USPTO Assignment Database to the University of Belfast—against Thorne and acted in concert with ChromaDex to initiate the APEX evaluation attacking Thorne's ResveraCel[®], SynaQuell[®], and NiaCel[®] 400 products based on the '506 Patent. Venue is proper for the University of Belfast in this District pursuant to 28 U.S.C. § 1391 for the same reason. Venue is also proper for the University of Belfast in this District pursuant to 28 U.S.C. § 1391(c)(3) because the University of Belfast is a foreign entity and may be sued in any judicial district.

48. Joinder of the Defendants is proper pursuant to Rules 19 and/or 20 of the Federal Rules of Civil Procedure and 35 U.S.C. § 299 because the conduct alleged herein raises an immediate, real, substantial, and justiciable controversy between Thorne and Defendants as to whether Thorne is infringing or has infringed the '506 Patent ~~and~~, whether the '506 Patent is invalid, arises out of the same transaction, occurrence, or series of transactions or occurrences relating to enforcement of the '506 Patent against Thorne, and poses questions of fact common to all Defendants.

CLAIMS FOR RELIEF

COUNT I: Declaratory Judgment of Noninfringement

49. Thorne incorporates by reference the preceding paragraphs as if fully set forth herein.

50. On information and belief, the '506 Patent is owned by one or more of the Defendants.

51. Defendants have asserted that the Thorne NR Products infringe the '506 Patent, both in cease and desist letters and in initiating an APEX evaluation.

52. The Thorne NR Products do not infringe, directly or indirectly, any valid and enforceable claim of the '506 Patent.

53. Each and every claim of the '506 Patent requires “[a] compound of formula (IV)” or “[a] method of making an isomerically pure compound of formula (IV).” Ex. 1 at Claims. The specification definition of formula (IV) requires that R₆, R₇, and R₈ must be “each independently a hydroxyl-protecting group.” *Id.* at 7:14-15, 8:16-30 (compound of formula (IV) defining R₁–R₈ “as defined above”, and wherein R₆, R₇, and R₈ “are each independently a hydroxyl-protecting group”). The Thorne NR Products do not contain a compound of formula IV where each of R₆, R₇, and R₈ are a hydroxyl-protecting group. Therefore, the Thorne NR Products, and the method of making them, do not infringe any claim of the '506 Patent.

54. An actual, substantial, and continuing controversy exists between Thorne and the Defendants with respect to whether Thorne infringes any valid and enforceable claim of the '506 Patent, warranting the issuance of a declaratory judgment of noninfringement.

55. Thorne seeks a declaration that it does not infringe any valid and enforceable claim of the '506 Patent. Without a declaratory judgment of noninfringement, Thorne has and will continue to suffer uncertainty and unquantifiable financial and business risks because of

Defendants' allegations that the Thorne NR Products infringe the '506 Patent.

COUNT II: Tortious Interference with a Contract

56. Thorne incorporates by reference the preceding paragraphs as if fully set forth herein.

57. Defendants have engaged in tortious interference with a contract in violation of the common law.

58. Specifically, Thorne has contractual relationships with Pattern to distribute the Thorne NR Products sold on Amazon. On information and belief, Defendants each knew, or should have known, about Thorne's contractual relationship with Pattern. On information and belief, Defendants acted in concert to improperly allege infringement of the '506 patent and initiate the APEX evaluation, which was designed to cause a breach of the contract between Pattern and Thorne, without justification.

59. Defendants have caused, and will continue to cause, immediate and irreparable injury to Thorne, including injury to its business, reputation, and goodwill, for which there is no adequate remedy at law. Therefore, Thorne is entitled to an injunction restraining Defendants from engaging in any further acts and requiring Defendants to withdraw the meritless APEX evaluation.

60. Thorne is entitled to the damages it incurred as a result of Defendants' tortious interference with Thorne's contract with Pattern including, but not limited to, the attorney and filing fees incurred in filing this suit to respond to Defendants' meritless APEX evaluation. Thorne also seeks punitive damages for Defendants' tortious interference with Thorne's contract with Pattern.

COUNT III: Intentional Interference with Prospective Contractual Relations

61. Thorne incorporates by reference the preceding paragraphs as if fully set forth herein.

62. Defendants have engaged in tortious interference with prospective contractual relations in violation of the common law.

63. Specifically, Thorne has economic relationships with Amazon, Pattern, and end-user consumers with respect to the sale of the Thorne NR Products, as described herein. These relationships provided Thorne with the probability of future economic benefit and reasonable expectation of prospective contracts for sales of the Thorne NR Products. Defendants, working in concert through ChromaDex, improperly initiated an APEX evaluation, alleging ResveraCel[®], SynaQuell[®], and NiaCel[®] 400 infringe the '506 Patent. Defendants did so for the improper purpose of harming Thorne's sales.

64. By initiating an improper, meritless APEX evaluation against the ResveraCel[®], SynaQuell[®], and NiaCel[®] 400 products, Defendants intentionally interfered with Thorne's potential future contracts regarding the Thorne NR Products with Amazon, Pattern, and end-user consumers, causing injury to Thorne. On information and belief, Defendants also negatively impacted Thorne's Amazon account health rating, lowering, among other things, the search visibility of Thorne's products on Amazon, thereby interfering with said future economic benefits, causing injury to Thorne in the form of lost sales.

65. Thorne also has economic relationships with authorized resellers and end-user consumers (who purchase directly from thorne.com) with respect to the sale of the Thorne NR Products. These relationships provided Thorne with the probability of future economic benefit in the form of prospective contracts for sales of the Thorne NR Products. Defendants improperly initiated an APEX evaluation, alleging ResveraCel[®], SynaQuell[®], and NiaCel[®] 400 infringe the '506 Patent. Defendants did so for the improper purpose of harming Thorne's sales.

66. By initiating an improper, meritless APEX evaluation against the ResveraCel[®],

SynaQuell®, and NiaCel® 400 products, Defendants intentionally interfered with Thorne's potential future contracts regarding the Thorne NR Products with authorized resellers and end-user consumers (who purchase directly from thorne.com), causing injury to Thorne.

67. Defendants have caused, and will continue to cause, immediate and irreparable injury to Thorne, including injury to its business, reputation, and goodwill, for which there is no adequate remedy at law. Therefore, Thorne is entitled to an injunction restraining Defendants from engaging in any further acts and requiring Defendants to withdraw the meritless APEX evaluation.

68. Thorne is entitled to the damages it incurred as a result of Defendants' intentional interference with Thorne's prospective contractual relations with Amazon, Pattern, authorized resellers, and end-user consumers including, but not limited to, the attorney and filing fees incurred in filing this suit to respond to Defendants' meritless APEX evaluation. Thorne also seeks punitive damages for Defendants' intentional interference with Thorne's prospective contractual relations with Amazon, Pattern, authorized resellers, and end-user consumers.

COUNT IV: Unfair Competition (S.C. Code § 39-5-10)

69. Thorne incorporates by reference the preceding paragraphs as if fully set forth herein.

70. Defendants have engaged in unfair competition in violation of the South Carolina Unfair Trade Practices Act (S.C. Code § 39-5-10, *et seq.*) ("SCUTPA").

71. Defendants, working in concert, engaged in an unfair act in the conduct of trade or commerce to initiate an unfounded APEX evaluation targeting Thorne's ResveraCel®, SynaQuell®, and NiaCel® 400 products for the improper reason of harming Thorne's existing and potential business relations, and sales. Initiating a meritless APEX evaluation impacts the public interest, for example, as it improperly restrains and impedes legitimate marketplace competition. Thorne suffered monetary loss in the form of attorney and filing fees related to the institution of

this action, as well as potential lost sales as a result of Defendants' baseless APEX evaluation, as discussed herein.

72. Defendants knew, or in the exercise of reasonable care should have known, that their actions were in violation of SCUTPA, but willfully proceeded with the meritless APEX evaluation. Thorne is therefore entitled to recover treble damages.

73. Defendants have caused, and will continue to cause, immediate and irreparable injury to Thorne, including injury to its business, reputation, and goodwill, for which there is no adequate remedy at law. Therefore, Thorne is entitled to an injunction restraining Defendants from engaging in any further acts and requiring Defendants to withdraw the meritless APEX evaluation. Such an injunction would be in the public interest.

COUNT V: Declaratory Judgment of Invalidity

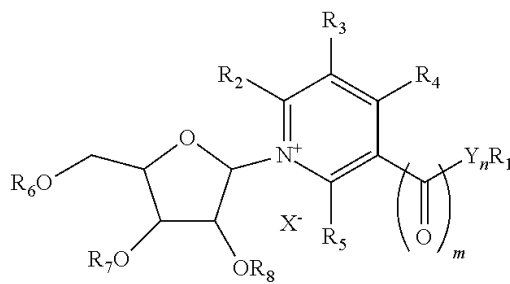
74. Thorne incorporates by reference the preceding paragraphs as if fully set forth herein.

75. The claims of the '506 Patent are invalid because they fail to meet one or more conditions of patentability set forth in Title 35 of the U.S. Code, including, but not limited to, 35 U.S.C. §§ 101, 102, 103, and/or 112.

76. Nicotinamide riboside is an oral supplement that is a precursor for nicotinamide adenine dinucleotide (NAD⁺), a vitamin B3 derivative produced naturally by the body.

77. The title of the '506 Patent is "Methods of Preparing Nicotinamide Riboside and Derivatives Thereof[.]"

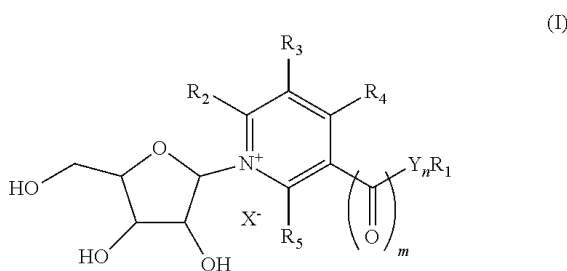
78. Independent claim 1 of the '506 Patent recites "[a] compound of formula (IV)" having the following structure:



79. Independent claim 1 of the '506 Patent recites 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[.]”

80. Asserted claims 2, 3, 10-12, and 26 depend from claim 1 and thus, recite each and every element of claim 1.

81. The specification of the '506 Patent describes a method of preparing nicotinamide riboside (“NR⁺”) salts of formula (I):



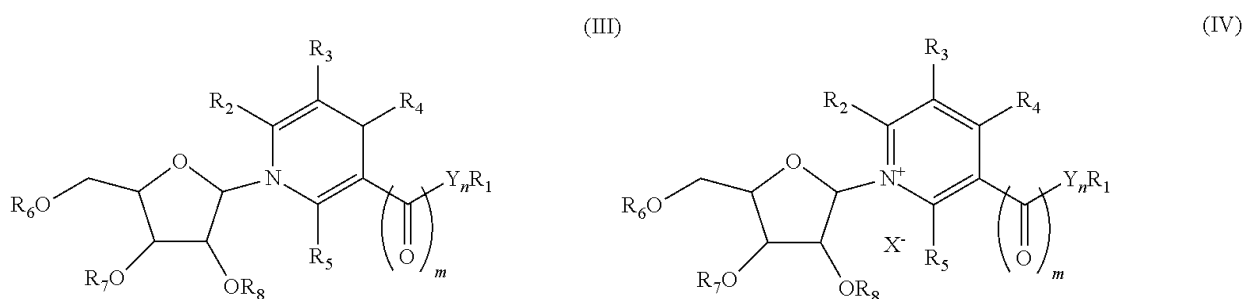
82. The specification of the '506 Patent states that the compound of formula (IV) is used as a precursor molecule to prepare the compound of formula (III) to produce the compound of formula (I):

a) “FIG. 2 depicts Scheme A, which is a scheme illustrating . . . that compounds of formula (IV) may be used to prepare compounds of formula (III), . . . ; that compounds of formula (III) may be used to prepare compounds of formula (II), . . . ; and that compounds of formula (II) may be used to prepare compounds of formula (I) . . . ” (id. at 12:13-20);

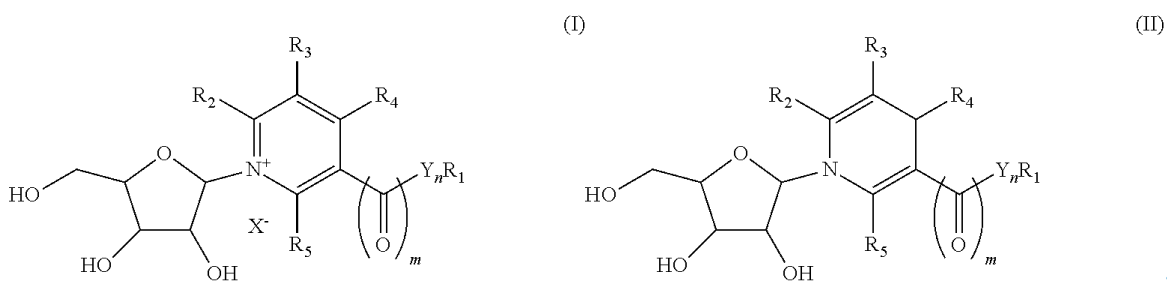
b) “[T]he compound of formula (III) is prepared by reacting a compound of formula (IV)” (*id.* at 8:14-15); and

c) “The methods for the preparation of compounds of formula (I) starting from compounds of formula (IV) are also very efficient and produce very good yields[.]” (*id.* at 10:63-65).

83. The specification of the ’506 Patent states that the compounds of formula (III) and formula (IV) have R-groups R_6 , R_7 and R_8 :



84. The specification of the ’506 Patent states that the compounds of formula (I) and formula (II) have the following structures:



85. The specification of the ’506 Patent states that the compounds of formula (I) and formula (II) do not contain R-groups R_6 , R_7 or R_8 .

86. The specification of the ’506 Patent does not state that the compound of formula (I) is an example of the compound of formula (IV).

87. The specification of the ’506 Patent does not state that the compound of formula (II) is an example of the compound of formula (IV).

88. The specification of the '506 Patent describes the compound of formula (IV) as having “hydroxyl protecting groups R₆, R₇ and R₈[.]” *Id.* at 8:66-67.

89. Hydrogen is not a hydroxyl protecting group.

90. The '506 Patent does not teach or disclose that hydrogen is a hydroxyl protecting group.

91. If R₆ is a hydrogen in the compound of formula (IV), then R₆ is not a hydroxyl protecting group.

92. If R₇ is a hydrogen in the compound of formula (IV), then R₇ is not a hydroxyl protecting group.

93. If R₈ is a hydrogen in the compound of formula (IV), then R₈ is not a hydroxyl protecting group.

94. The specification of the '506 Patent states that the “hydroxyl protecting groups R₆, R₇ and R₈, are required to be lipophilic” in the compound of formula (IV). *Id.* at 8:66-67.

95. The specification of the '506 Patent states “[t]he 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.” *Id.* at 11:14-19.

96. The specification of the '506 Patent describes the compound of formula (IV) where “at least two of R₆, R₇ and R₈ comprise unsubstituted acetyl[.]” *Id.* at 8:40-44.

97. The specification of the '506 Patent exemplifies the compound of formula (IV) where “n is 0, m is 1, R₁ is NH₂, R₂-R₅ are each H, R₆-R₈ are each acetyl, and X⁻ is ⁻OTf.” *Id.* at 9:8-10.

98. The specification of the '506 Patent describes the compound of formula (IV) "in the form of the triflate salt[]" (*id.* at 10:42-44) and exemplifies: (A) "triacetyl nicotinamide riboside, triflate (CF_3SO_3^- , also known as —OTf) salt" (*id.* at 12:64-66); (B) "triacetyl O-ethyl nicotinate riboside, triflate (—OTf) salt" (*id.* at 13:66-67); and (C) "tribenzoyl nicotinamide riboside, triflate (—OTf) salt" (*id.* at 14:58-60).

99. The specification of the '506 Patent does not contain any working examples of the compound of formula (IV) where R_6 , R_7 or R_8 is a hydrogen.

100. The specification of the '506 Patent does not describe the compound of formula (IV) where R_6 is not a hydroxyl protecting group.

101. The specification of the '506 Patent does not describe the compound of formula (IV) where R_7 is not a hydroxyl protecting group.

102. The specification of the '506 Patent does not describe the compound of formula (IV) where R_8 is not a hydroxyl protecting group.

103. The specification of the '506 Patent does not describe the compound of formula (IV) where R_6 is a hydrogen.

104. The specification of the '506 Patent does not describe the compound of formula (IV) where R_7 is a hydrogen.

105. The specification of the '506 Patent does not describe the compound of formula (IV) where R_8 is a hydrogen.

106. Claim 1's recitation that " R_6 , R_7 and R_8 , which may be the same or different, are each independently H" in the compound of formula (IV) is not described in the specification of the '506 Patent.

107. Claim 1 of the '506 Patent lacks written description and is invalid under 35 U.S.C.

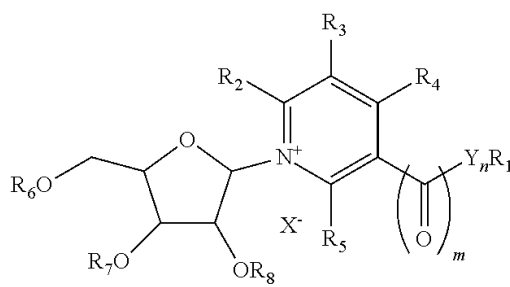
§ 112.

108. Claim 1 of the '506 Patent lacks enablement and is invalid under 35 U.S.C. § 112.

109. Claims 2-3, 10-12, and 26 depend from claim 1 and thus, recite each and every element of claim 1. Therefore, claims 2-3, 10-12, and 26 of the '506 Patent also lack written description and enablement, and are invalid under 35 U.S.C. § 112.

110. The '506 Patent was filed on April 26, 2023 as U.S. Application No. 18/307,733 (“’733 Application”).

111. Claim 1 filed on April 26, 2023 in the '733 Application recites “[a] compound of formula (IV):



... where: ... R₆, R₇ and R₈, which may be the same or different, are each independently H.”

112. The compound of formula (IV) having R₆, R₇ and R₈ as hydrogen appeared for the first time, at the earliest, with the April 26, 2023 filing date of the '733 Application that issued as the '506 Patent.

113. The '506 Patent claims are entitled to priority no earlier than April 26, 2023.

114. U.S. Patent Application Publication No. 2016/0168184 (“’184 Publication”) published on June 16, 2016. Ex. 10.

115. The '184 Publication is prior art to the asserted claims in the '506 Patent.

116. The '184 Publication anticipates the asserted claims in the '506 Patent for the reasons described in IPR2026-00400; thus, the asserted claims in the '506 Patent are invalid under

35 U.S.C. § 102.

117. The asserted claims in the '506 Patent are obvious variations that are conventional in light of the prior art available for the reasons described in IPR2026-00400; thus, the asserted claims in the '506 Patent are invalid under 35 U.S.C. § 103.

~~73.~~118. Thorne is entitled to a judicial declaration that the claims of the '506 Patent are invalid.

PRAYER FOR RELIEF

WHEREFORE, Thorne respectfully requests that the Court enter judgment in its favor and against the Defendants as follows:

- (a) Declaring that Thorne has not infringed, induced others to infringe, or contributed to the infringement of any claim of the '506 Patent, directly or indirectly, literally or under the doctrine of equivalents;
- (b) A permanent injunction enjoining Defendants and their officers, directors, owners, members, partners, employees, agents, attorneys, successors, assigns, and all persons acting in concert or in participation with them, from:
 - (1) Asserting, threatening to assert, or causing to be asserted any claim of the '506 Patent against Thorne or any of Thorne's customers, suppliers, distributors, or partners;
 - (2) Representing, stating, or implying in any manner—whether orally, in writing, or through any other medium—that the Thorne NR Products infringe any valid and enforceable claim of the '506 Patent;
 - (3) Initiating, maintaining, or threatening any action, suit, or proceeding alleging infringement of the '506 Patent by Thorne or any party in privity with Thorne; and

- (4) Otherwise interfering with Thorne's right to make, use, sell, offer for sale, or import its products and services free from claims of infringement of the '506 Patent;

(c) Declaring that pursuant to 28 U.S.C. §§ 2201 and 2202, one or more claims of U.S. Patent No. 12,252,506 (the "'506 Patent"), including but not limited to claims 1–3, 10–12, and 26, are invalid for failure to comply with one or more requirements of Title 35 of the United States Code, including without limitation 35 U.S.C. §§ 101, 102, 103, and 112;

(d) Declaring that the asserted claims of the '506 Patent are invalid for lack of written description and/or lack of enablement under 35 U.S.C. § 112(a);

(e) Declaring that the asserted claims of the '506 Patent are invalid as indefinite under 35 U.S.C. § 112(b);

(f) Declaring that the asserted claims of the '506 Patent are invalid as anticipated and/or obvious under 35 U.S.C. §§ 102 and/or 103 in view of the prior art;

~~(e)~~(g) Adjudging this to be an exceptional case under 35 U.S.C. § 285, and awarding to Thorne its reasonable attorneys' fees, costs, and expenses;

~~(d)~~(h) An award of compensatory damages in an amount to be proven at trial, including damages for lost contractual benefits, lost revenues, and harm to Thorne's existing contractual relationships with its commercial partners;

~~(e)~~(i) A finding that Defendants' interference was intentional and unjustified, and an award of punitive damages in an amount sufficient to punish Defendants for their conduct and to deter similar conduct in the future;

~~(f)~~(j) A permanent injunction enjoining Defendants and their officers, directors, owners,

members, partners, employees, agents, attorneys, successors, assigns, and all persons acting in concert or participation with them, from taking any action intended or reasonably likely to interfere with, disrupt, or cause the breach of any existing contractual relationship between Thorne and any commercial partner;

~~(g)~~(k) An award of compensatory damages in an amount to be proven at trial, including damages for lost prospective business relationships, lost sales, and harm to Thorne's business reputation and goodwill;

~~(h)~~(l) A finding that Defendants acted with actual malice or with a willful and wanton disregard for Thorne's rights, and an award of punitive damages in an amount sufficient to punish Defendants for their conduct and to deter similar conduct in the future;

~~(i)~~(m) A permanent injunction enjoining Defendants and their officers, directors, owners, members, partners, employees, agents, attorneys, successors, assigns, and all persons acting in concert or participation with them, from making any further false, misleading, or disparaging statements or representations regarding Thorne or the Thorne NR Products to any existing or prospective end-user consumers, resellers, or commercial partners;

~~(j)~~(n) A finding that Defendants engaged in unfair and deceptive acts and practices in violation of S.C. Code § 39-5-20;

~~(k)~~(o) An award of actual damages in an amount to be proven at trial;

~~(l)~~(p) A finding that Defendants' violations were willful and knowing, and an award of three times Thorne's actual damages pursuant to S.C. Code § 39-5-140(a);

~~(m)~~(q) A permanent injunction enjoining Defendants and their officers, directors, owners,

members, partners, employees, agents, attorneys, successors, assigns, and all persons acting in concert or participation with them, from engaging in any further unfair or deceptive acts or practices directed at Thorne, Thorne's products, or Thorne's end-user consumers, resellers, and commercial partners;

~~(r)~~(r) An award of reasonable attorneys' fees and costs pursuant to S.C. Code § 39-5-140(a);

~~(s)~~ An award to Thorne of its costs of suit incurred herein, pursuant to 28 U.S.C. § 1920 and Fed. R. Civ. P. 54(d);

~~(t)~~(t) Pre- and post-judgment interest at the maximum rate allowed by law; and

~~(u)~~(u) Granting to Thorne any further relief this Court may deem just, proper, or equitable.

Respectfully submitted,

OF COUNSEL:

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Kristina M. Hanson
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*Attorneys for Plaintiffs Thorne Research, Inc.
and Thorne HealthTech, Inc.*

Dated: ~~April 28~~October 7, 2026

EXHIBIT C

From: Stephen Baskin <sbaskin@kslaw.com>
Sent: Tuesday, September 29, 2026 10:12 PM
To: Devine, Wendy; Tyler Boyce; Hanson, Tina; Mark Zambarda; Kyle Sampson; Joseph Eng; Nicholas Sieger; Klett III, William
Cc: aries; Cheryl Bona; WSGR - Thorne/ChromaDex DJ (505); Stephen Baskin
Subject: RE: Thorne et al. v. Niagen et al., QUB and Niagen Motion to Dismiss

EXT - sbaskin@kslaw.com

Wendy-

For efficiency, I'll respond directly to your email. Your approach on this issue, rather than being reasonable, ignores and is contrary to basic principles of patent law as well as the Federal Rules of Civil Procedure. And, as we have seen in prior communications and filings, misleads and misstates basic facts . . . simply, there is no manipulation of the pleadings. The undeniable fact is that Chromadex has the exclusive rights to the '506 patent. Also, as you are well aware, any settlement of this matter will be directly with Chromadex and Niagen (who is in this case due to Thorne asserting claims against Niagen in the Declaratory Judgment Complaint). Nonetheless, there is real interest from Niagen in engaging and having meaningful settlement discussions, and the hope is that Thorne will similarly engage.

With respect to the issue at hand, our proposal to dismiss or amend the counter-counter claims to only be directed to Chromadex remains and believe that is the prudent and most efficient way to proceed.

Regards,
Steve

From: Devine, Wendy <wdevine@wsgr.com>
Sent: Tuesday, September 29, 2026 4:33 PM
To: Tyler Boyce <TBoyce@kslaw.com>; Hanson, Tina <thanson@wsgr.com>; Mark Zambarda <MZambarda@KSLAW.com>; Stephen Baskin <sbaskin@kslaw.com>; Kyle Sampson <KSampson@KSLAW.com>; Joseph Eng <jeng@kslaw.com>; Nicholas Sieger <NSieger@KSLAW.com>; Klett III, William <wklett@burr.com>
Cc: aries <aries@smithlaw.com>; Cheryl Bona <cbona@smithlaw.com>; WSGR - Thorne/ChromaDex DJ (505) <thornechromadex505@wsgr.com>
Subject: RE: Thorne et al. v. Niagen et al., QUB and Niagen Motion to Dismiss

CAUTION: MAIL FROM OUTSIDE THE FIRM

Hi Tyler,

We understand that you have rejected our reasonable suggestion and that Defendants are maintaining their attempt to manipulate the pleadings by only asserting infringement on behalf of Chromadex. That choice is particularly odd given that we just received a settlement offer regarding the allegation of patent infringement from both Chromadex and Niagen on Friday.

We will proceed with an opposed motion to amend and will inform the Court of our offer and your response.

Best, Wendy

From: Tyler Boyce <TBoyce@kslaw.com>

Sent: Tuesday, September 29, 2026 1:27 PM

To: Hanson, Tina <thanson@wsgr.com>; Mark Zambarda <MZambarda@KSLAW.com>; Stephen Baskin <sbaskin@kslaw.com>; Kyle Sampson <KSampson@KSLAW.com>; Joseph Eng <jeng@kslaw.com>; Nicholas Sieger <NSieger@KSLAW.com>; Klett III, William <wklett@burr.com>

Cc: Devine, Wendy <wdevine@wsgr.com>; aries <aries@smithlaw.com>; Cheryl Bona <cbona@smithlaw.com>; WSGR - Thorne/ChromaDex DJ (505) <thornechromadex505@wsgr.com>

Subject: RE: Thorne et al. v. Niagen et al., QUB and Niagen Motion to Dismiss

EXT - tboyce@kslaw.com

Tina,

We propose a more straightforward third option—removing QUB and Niagen as defendants to the invalidity claims either through voluntarily dismissing or amending the counter-counterclaims. That comports with the fact that only ChromaDex claimed for infringement and therefore is the only properly named defendant in a counterclaim.

Thanks,

J. Tyler Boyce

Associate

T: +1 713 276 7324 | M: +1 985 264 9284 | tboyce@kslaw.com | [Bio](#) | [vCard](#)

From: Hanson, Tina <thanson@wsgr.com>

Sent: Thursday, September 24, 2026 4:16 PM

To: Mark Zambarda <MZambarda@KSLAW.com>; Stephen Baskin <sbaskin@kslaw.com>; Kyle Sampson <KSampson@KSLAW.com>; Joseph Eng <jeng@kslaw.com>; Tyler Boyce <TBoyce@kslaw.com>; Nicholas Sieger <NSieger@KSLAW.com>; Klett III, William <wklett@burr.com>

Cc: wdevine <wdevine@wsgr.com>; aries <aries@smithlaw.com>; Cheryl Bona <cbona@smithlaw.com>; WSGR - Thorne/ChromaDex DJ (505) <thornechromadex505@wsgr.com>

Subject: Thorne et al. v. Niagen et al., QUB and Niagen Motion to Dismiss

CAUTION: MAIL FROM OUTSIDE THE FIRM

Counsel,

We write regarding Defendants' Motion to Strike and Dismiss. We don't think continued motion practice on this issue serves either side or the Court, and we propose the following as a more efficient path forward.

QUB's Motion: QUB's motion raises the same subject-matter jurisdiction arguments already pending in QUB's first motion to dismiss. Rather than re-brief the identical issue, we propose the parties stipulate that the briefing already of record applies to the second motion.

Niagen's Motion: Niagen's objection can be resolved by Thorne amending the Complaint to assert the invalidity declaratory judgment claim against all three Defendants. That would involve restarting pleadings and burdening the court with multiple filings that do not substantively impact the issues being litigated. So that may be avoided, please let us know if Niagen will withdraw its motion.

If Defendants choose not to withdraw Niagen's motion, please confirm that Defendants consent to Thorne amending the Complaint to assert the invalidity declaratory judgment claim against all three Defendants. We would prefer to avoid burdening the Court with a motion for leave to amend (which we note is likely to be granted given the applicable standard, the stage of the case, and the underlying facts), however, if Defendants refuse to consent, we will file an opposed motion for leave.

Please let us know Defendants' position.

Best,
Tina

**WILSON
SONSINI**

Tina Hanson (she/her) | Wilson Sonsini Goodrich & Rosati

One Market | Spear Tower | San Francisco, CA | 94105-1126 | direct: 415.947.2048 | thanson@wsgr.com



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**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF SOUTH CAROLINA
CHARLESTON DIVISION**

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

Plaintiffs,

v.

NIAGEN BIOSCIENCE, INC., CHROMADEx,
INC., and THE QUEEN’S UNIVERSITY OF
BELFAST,

Defendants.

CASE NO.: 2:26-cv-01758-RMG

DECLARATION OF WENDY L. DEVINE

I, Wendy L. Devine, hereby declare as follows:

1. I am a partner at the law firm of Wilson Sonsini Goodrich & Rosati P.C. I am counsel for plaintiffs Thorne Research, Inc. and Thorne Healthtech, Inc. (collectively “Thorne”) in the above-captioned action.

2. I am fully familiar with the matters set forth herein. The following facts are true to my personal knowledge, and if called and sworn as a witness, I could competently testify to them.

3. I represent Thorne in the above-captioned action against defendants Niagen Bioscience, Inc. (“Niagen”), ChromaDex, Inc. (“ChromaDex”), and The Queen’s University of Belfast (“QUB”) seeking a declaratory judgement for non-infringement of U.S. Patent No. 12,252,506 (“’506 Patent”), and damages for tortious interference with a contract, intentional interference with prospective contractual relations, and unfair competition pursuant to the South Carolina Unfair Trade Practices Act.

4. Thorne initiated this suit after it received letters from ChromaDex demanding it remove its products from the marketplace with allegations of infringement of the ’506 Patent and an

APEX submission with allegations of infringement of the '506 Patent originating from a Niagen email address. Thorne seeks declaratory judgment of non-infringement of the '506 Patent against each defendant that has held itself out as the owner of, or maintaining some rights in, the '506 Patent. In response, only ChromaDex counterclaimed for infringement against Thorne.

5. I submit this declaration solely to establish the fact, date, and source of the communication below. I do not offer it to prove or disprove the validity or amount of any claim in this action. Fed. R. Evid. 408.

6. On September 25, 2026, I received a letter from defendants' counsel sent "[o]n behalf of Niagen Bioscience, Inc. and ChromaDex, Inc." that "propose[d] terms to resolve [this litigation]." The letter offered settlement terms concerning rights related to the '506 Patent on behalf of both ChromaDex and Niagen.

I declare under penalty of perjury that, to the best of my knowledge, the foregoing statements are true and correct. Executed this 7 day of October, 2026, in San Francisco, California.



Wendy L. Devine