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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/905,922	02/27/2018	Marie MIGAUD	335040: 4-16A US

CONFIRMATION NO. 1061

23713
Leydig, Voit & Mayer, Ltd. (GS BOULDER)
4940 Pearl East Circle
Suite 200
Boulder, CO 80301

POWER OF ATTORNEY NOTICE

OC000000108438579

Date Mailed: 06/26/2026

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/06/2026.

- The Power of Attorney to you in this application has been revoked by the applicant. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/sejordan/

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15/905,922	02/27/2018	Marie MIGAUD	335040: 4-16A US

CONFIRMATION NO. 1061

51079
AMIN WASSERMAN GURNANI LLP
230 W. Monroe Street
Suite 1405
CHICAGO, IL 60606

POA ACCEPTANCE LETTER

OC000000108438430

Date Mailed: 06/26/2026

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/06/2026.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/sejordan/

Docusign Envelope ID: 74F62959-4F11-8747-835A-E8A1330801CA

PTO/AIA/80 (07-17)
Approved for use through 09/30/2025. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

[X] Practitioners associated with Customer Number: 51079

OR

[ ] Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

[X] The address associated with Customer Number: 51079

OR

[ ]

Firm or individual name		
Address		
City	State	Zip
Country		
Telephone	Email	

Assignee name and address: CHROMADEX INC.
10900 Wilshire Boulevard
Los Angeles, CA 90024

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of the practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee.

Signature Signed by: 8059C6EE53FA45A...	Date 5/5/2026
Name Carlos Lopez	Telephone
Title SVP, General Counsel	

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0035. Public burden for this form is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.** If filing this completed form by mail, send to: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013). https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to: 1) law enforcement, in the event that the system of records indicates a violation or potential violation of law; 2) a Federal, state, local, or international agency, in response to its request; 3) a contractor of the USPTO having need for the information in order to perform a contract; 4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record; 5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record; 6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations; 7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals; 8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)); 9) the Office of Personnel Management (OPM) for personnel research purposes; and 9) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

PTO/AIA/96 (11-23)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)

First Named Inventor/Patent Owner: ChromaDex Inc.

Application No./Patent No.: 10,815,262 Filed/Issue Date: October 27, 2020

Titled: METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF

ChromaDex Inc., a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached*.

B. ☑ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Marie MIGAUD, Philip REDPATH, Kerri CROSSEY, and Mark DOHERTY To: The Queen's University of Belfast

The document was recorded in the United States Patent and Trademark Office at

Reel 45047, Frame 0562, or for which a copy thereof is attached*.

2. From: The Queen's University of Belfast To: ChromaDex Inc.

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached*.

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0031. Public burden for this form is estimated to average 15 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/96 (11-23)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached*.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached*.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached*.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached*.

☑ Additional documents in the chain of title are listed on a supplemental sheet(s).

☑ *As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/George M. Carrera, Jr./	May 6, 2026
Signature	Date
George M. Carrera, Jr.	50317
Printed or Typed Name	Title or Registration Number

PATENT ASSIGNMENT COVER SHEET

Assignment ID: 1675559

Electronic Version v1.1
Stylesheet Version v1.2

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	**Execution Date**
QUEEN'S UNIVERSITY BELFAST	12/16/2025

RECEIVING PARTY DATA

Name:	CHROMADEX INC.
Street Address:	10900 Wilshire Boulevard
City:	Los Angeles
State/Country:	CALIFORNIA UNITED STATES
Postal Code:	90024

PROPERTY NUMBERS Total:18

Property Type	**Number**
Patent Number:	10280190
Patent Number:	10689411
Patent Number:	10934322
Patent Number:	11242364
Patent Number:	11274117
Patent Number:	11345720
Patent Number:	11746123
Patent Number:	12195494
Patent Number:	10000519
Patent Number:	10815262
Patent Number:	11584770
Patent Number:	11981698
Patent Number:	12252506
Application Number:	18598617
PCT Number:	US1622682
PCT Number:	US1722779

PCT Number:	US1761154
Application Number:	19382895

CORRESPONDENCE DATA

Phone:	3124661033
Email:	patent@awglaw.com,seberle@awglaw.com

Correspondence will be sent to the e-mail address first; if that is unsuccessful, it will be sent using a fax number, if provided; if that is unsuccessful, it will be sent via US Mail.

Correspondent Name:	George M. Carrera Jr.
Address Line 1:	AMIN WASSERMAN GURNANI LLP
Address Line 2:	230 W. Monroe Street, Suite 1405
Address Line 4:	Chicago , ILLINOIS 60606

ATTORNEY DOCKET NUMBER:	CHROM/QUB
NAME OF SUBMITTER:	Samantha Eberle
Signature:	/Samantha Eberle/
Date:	03/17/2026

TOTAL ATTACHMENTS: 1
source= QUB-ChromaDex Assignment.pdf

CONFIDENTIAL

ASSIGNMENT

THIS ASSIGNMENT is made December 16, 2025

BETWEEN:

(1) **QUEEN'S UNIVERSITY BELFAST**, having its principal offices at University Road, Belfast BT7 1NN (the "Assignor");

and

(2) **CHROMADEX, INC.**, whose address is at 10900 Wilshire Boulevard, Los Angeles, CA 90024. USA (the "Lead")

(each a "Party" and collectively the "Parties").

Certain capitalized terms used herein are defined on Schedule 1 hereto.

WHEREAS:

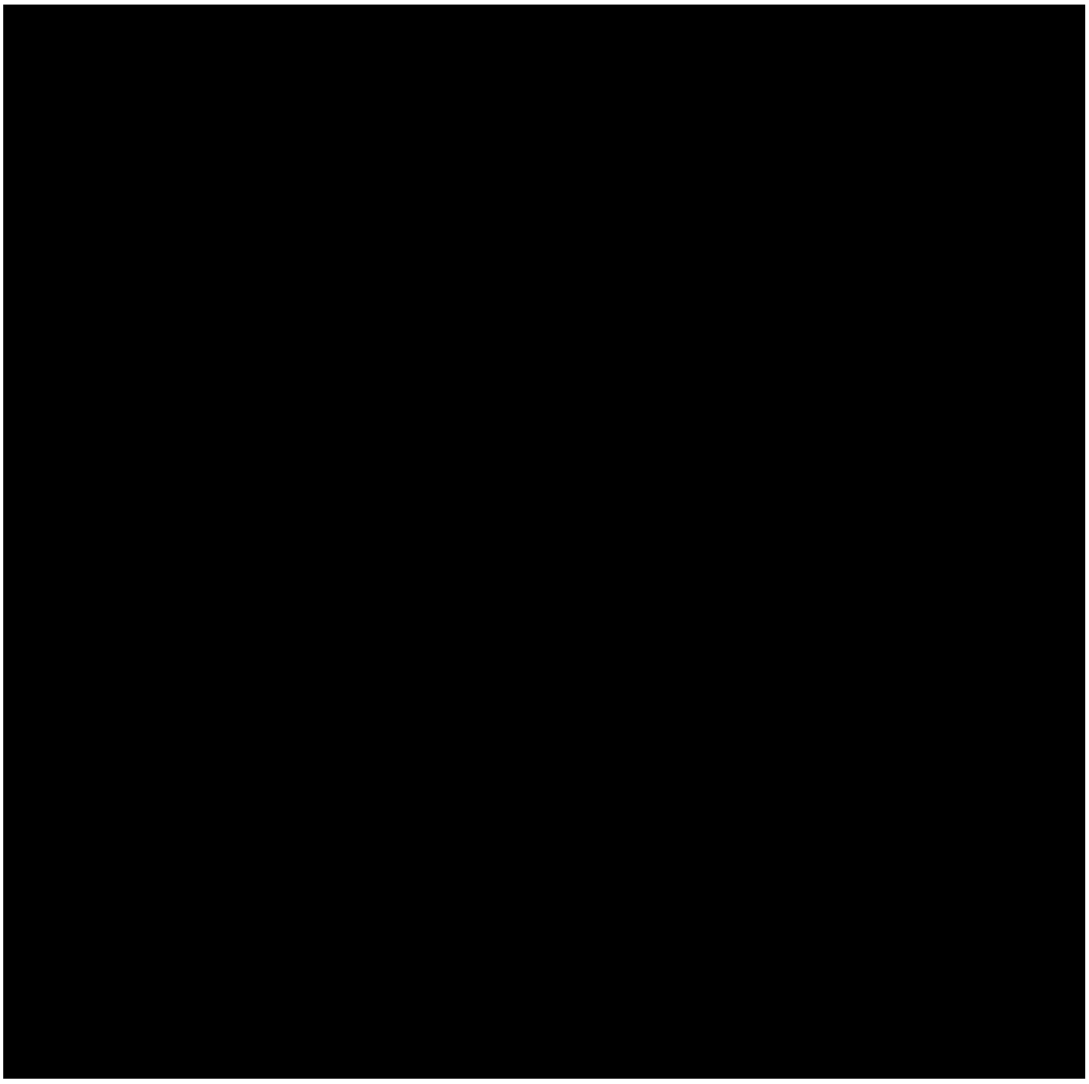
A. The Lead and the Assignor jointly own in equal shares the Patents set forth on Schedule 2.A in respect of which they have entered into a Joint Ownership and Management Agreement dated 09 October 2015, as amended on 10 March 2025 (the "JOMA").

B. The Assignor solely owns the Patents set forth on Schedule 2.B, which are exclusively licensed from the Assignor to the Lead in accordance with a License Agreement dated 23 November 2015 (the "License Agreement").

[redacted]

NOW IT IS AGREED as follows:

[redacted]



2. **ASSIGNMENT**

2.1 In consideration of the payments set out in clause 5 of this Assignment and other good and valuable consideration (receipt and sufficiency of which is hereby acknowledged by Assignor), the Assignor hereby assigns and transfers to the Lead absolutely with full title guarantee all of its right, title and interest, throughout the world (including the United States of America, its territories and all foreign countries) in and to the Patents, any priority applications thereof, and any application that is based in whole or in part on such patent applications, including any divisional, continuing, substitute, renewal, reissue, reexamination and other patent applications, for example that claim priority to the Patents. The foregoing assignment includes:

2.1.1 the right to file the Patents in or in respect of any country or territory in the world;

2.1.2 in respect of any and each patent application comprised within the Patents:

(i) the right to claim priority from, and to prosecute and obtain grant of patent on, such Patent; and

(ii) the right to file divisional applications based thereon and to prosecute and obtain grant of patent on each and any such divisional application;

(iii) the right to extend to or register in, or in respect of, any country or territory in the world each and any of the Patents, and any patents granted on any such Patents or any divisionals thereof;

(iv) the right to extend the term of any patents granted on any Patents or any divisionals thereof;

(v) the absolute entitlement to any patents granted pursuant to any of the Patents or any divisionals thereof; and

(vi) the right to elect to reject or submit to the competence of the Unitary Patent Court in respect of any patent granted pursuant to any Patent Application pursuant to Article 83(3) of the Agreement on a Unified Patent Court (2013/C 175/01) or to validate any such patent as a patent that has unitary effect by virtue of Regulation (EU) No 1257/2012; and

2.1.3 all royalties, fees, income, payments, and other proceeds now or hereafter due or payable to the Assignor with respect to any of the foregoing (except for the payment obligations of the Lead expressly set forth in clause 5 of this Assignment);

2.1.4 all rights to bring or defend any claims, actions or proceedings (and to retain any damages recovered), and/or to appeal any award or judgements issued, in respect of any infringement or challenge to validity or entitlement, or any other cause of action arising from ownership, of the Patents or any patents granted pursuant to such Patents or any divisionals thereof, whether occurring before, on or after the date of this Assignment; and

2.1.5 all other rights, privileges, and protections of any kind whatsoever of the Assignor accruing under any of the foregoing provided by any applicable law, treaty, or other international convention throughout the world.

2.2 From and after the date hereof, the Assignor shall provide to the Lead (promptly on the Lead's request) all information and documentation and give such assistance and take such actions (including executing and delivering documents or procuring execution and delivery of documents by the Named Inventors or other third parties) as the Lead may require, at the additional expense of the Lead solely for reasonable, documented, out-of-pocket costs, for the purpose of giving full effect to this Assignment, including:

2.2.1 to secure the vesting solely in the Lead on the Assignment Effective Date of all rights in the Patents;

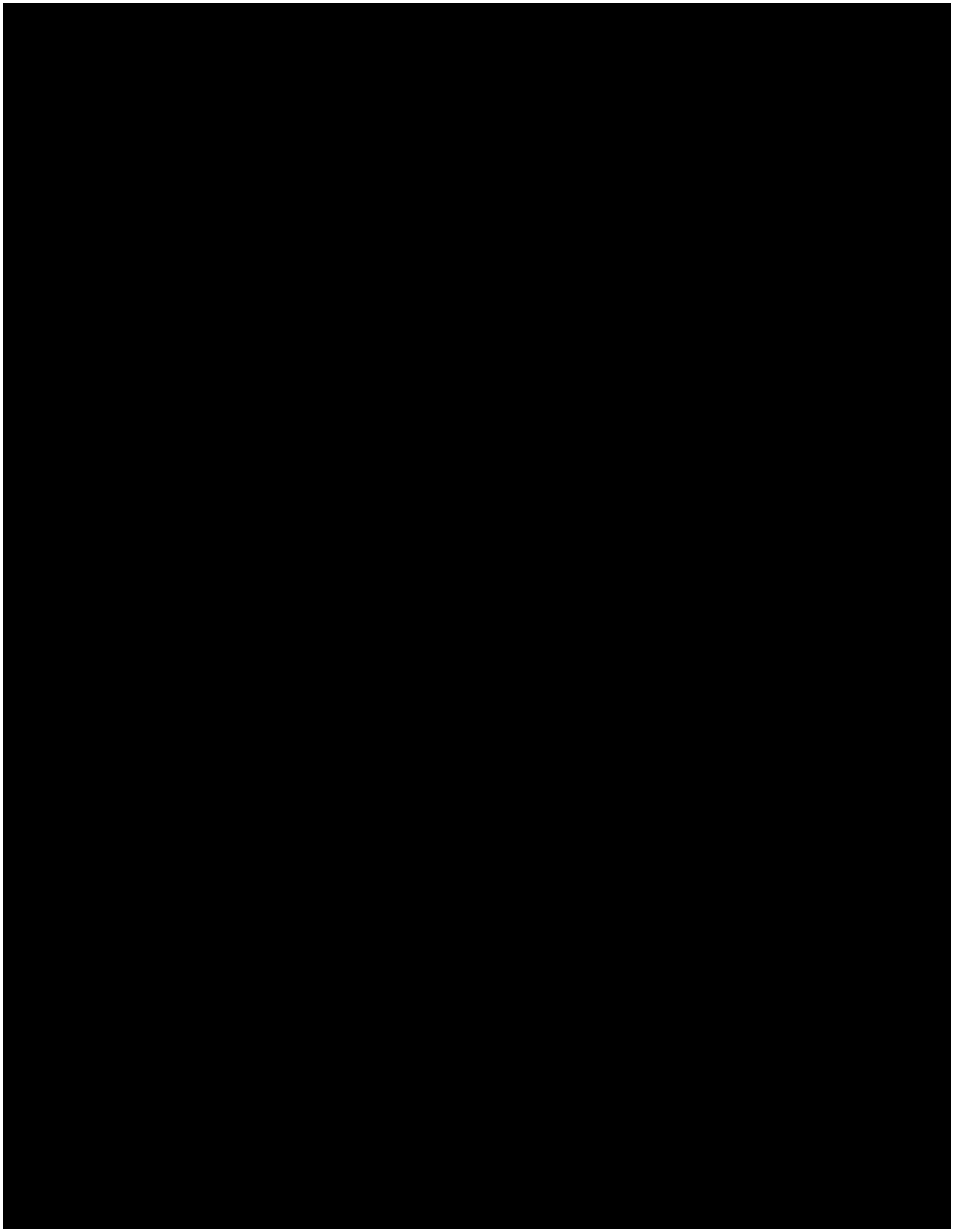
2.2.2 to record the conveyance of rights in the Patents hereunder in a form reasonably satisfactory to the Lead and suitable for filing with the United States Patent and Trademark Office and the registries and other recording governmental authorities in all applicable jurisdictions;

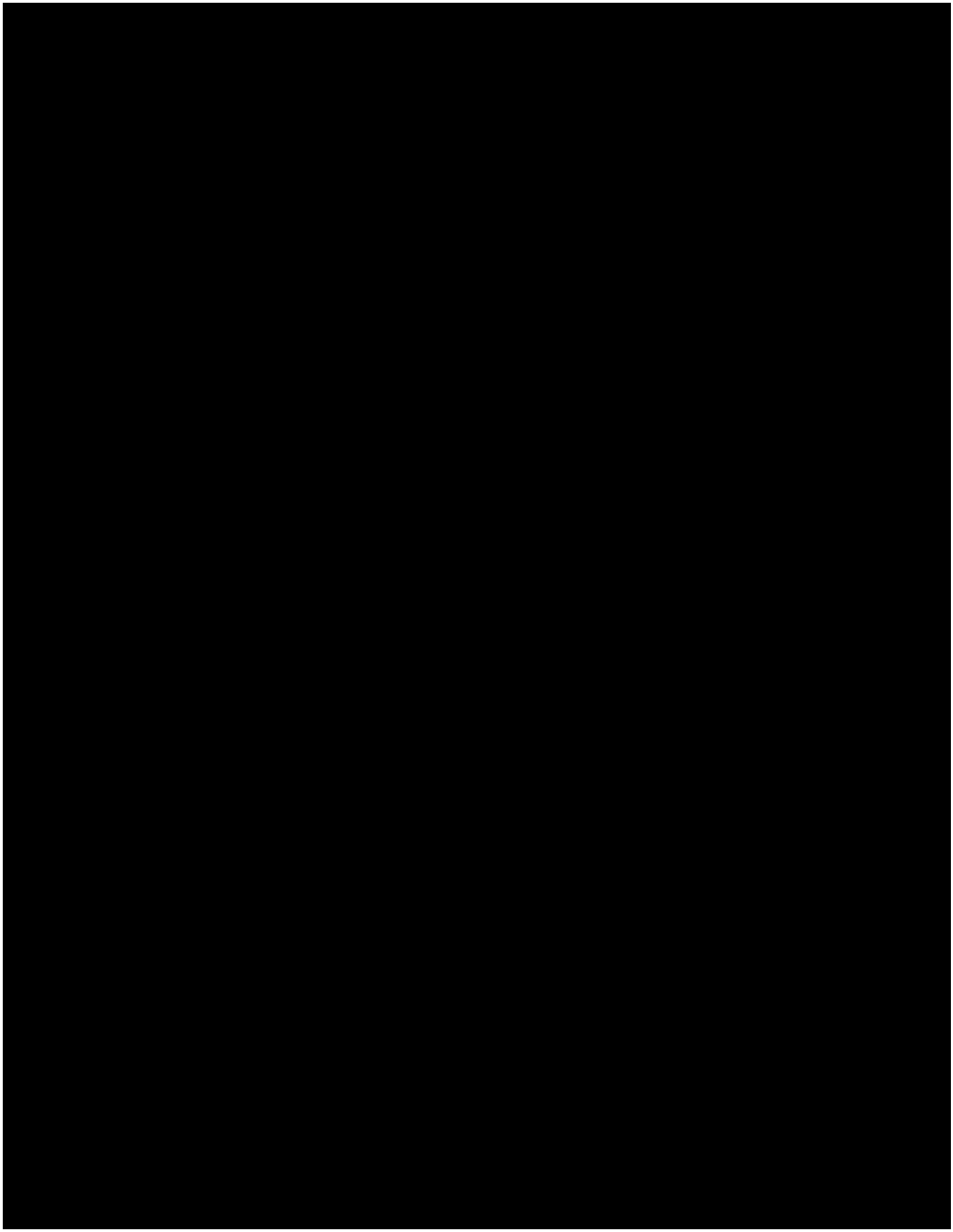
2.2.3 to uphold the Lead's sole ownership of all rights in the Patents; and

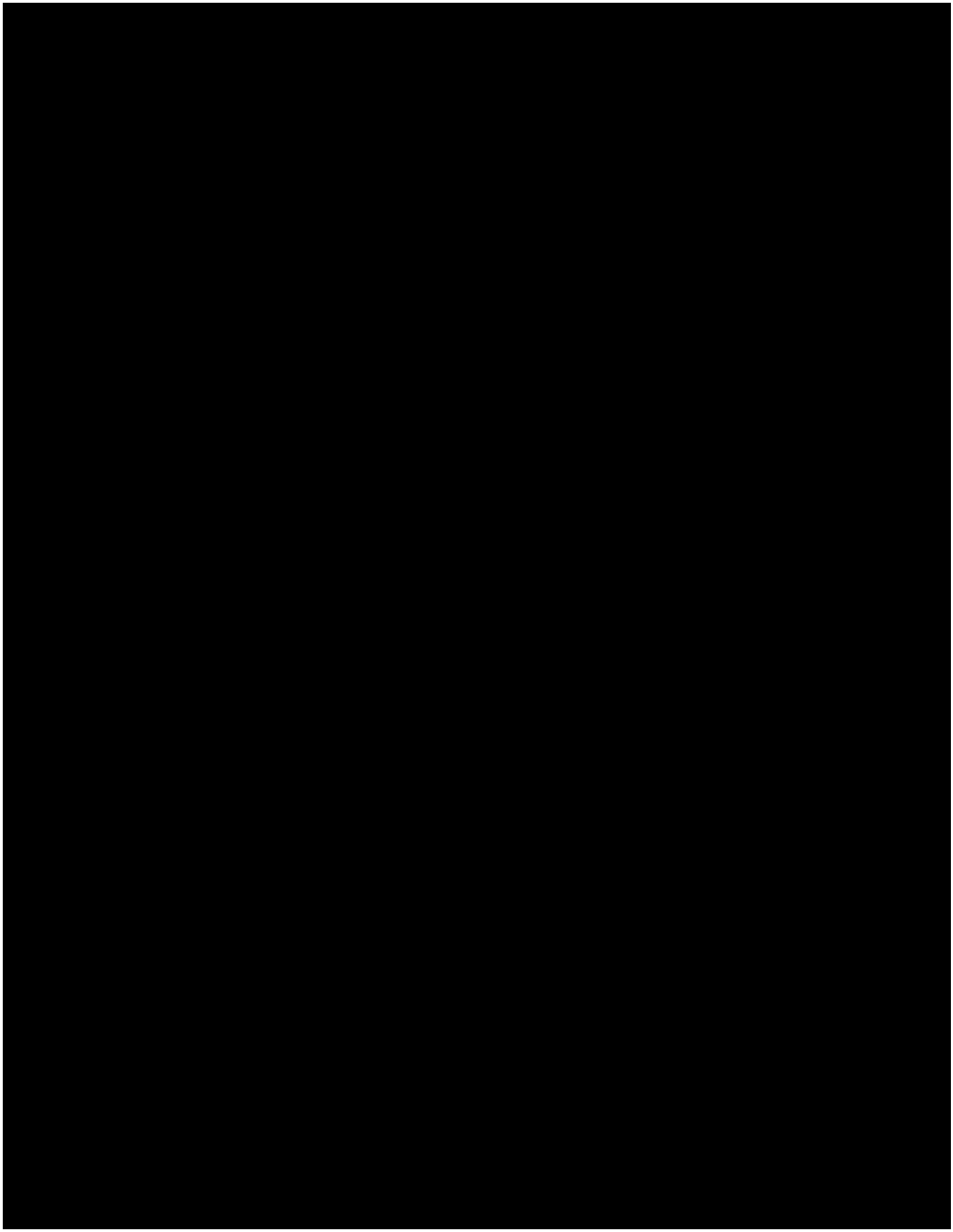
2.2.4 to prosecute, bring, make, oppose or defend any claims, actions or challenge to the entitlement, validity or ownership of, and to resolve any questions concerning, the Patents.

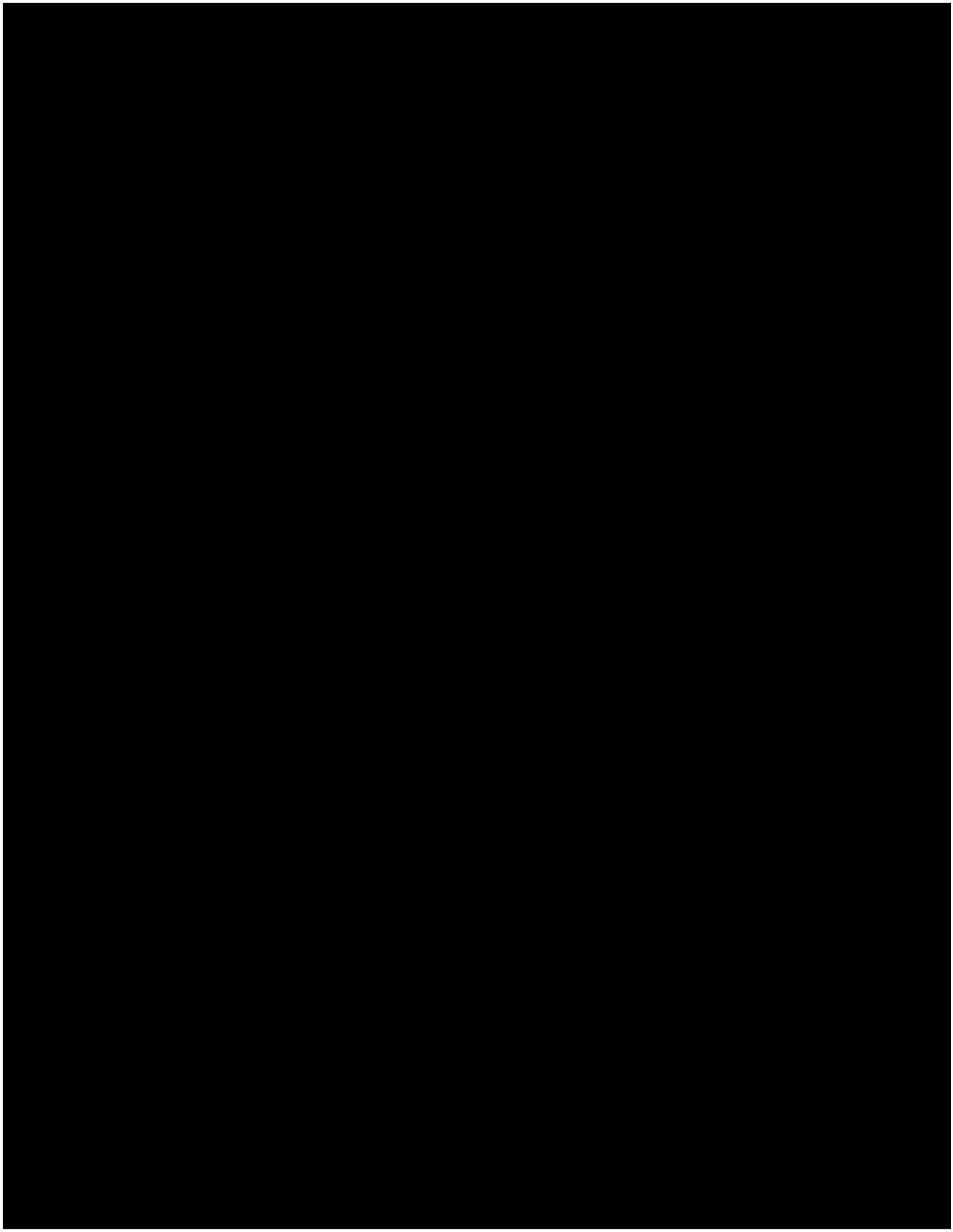
2.3 As between the Assignor and the Lead, the Lead shall be responsible, and shall have the right, to file this Assignment and other documents, certificates, and instruments of conveyance with the applicable governmental authorities.

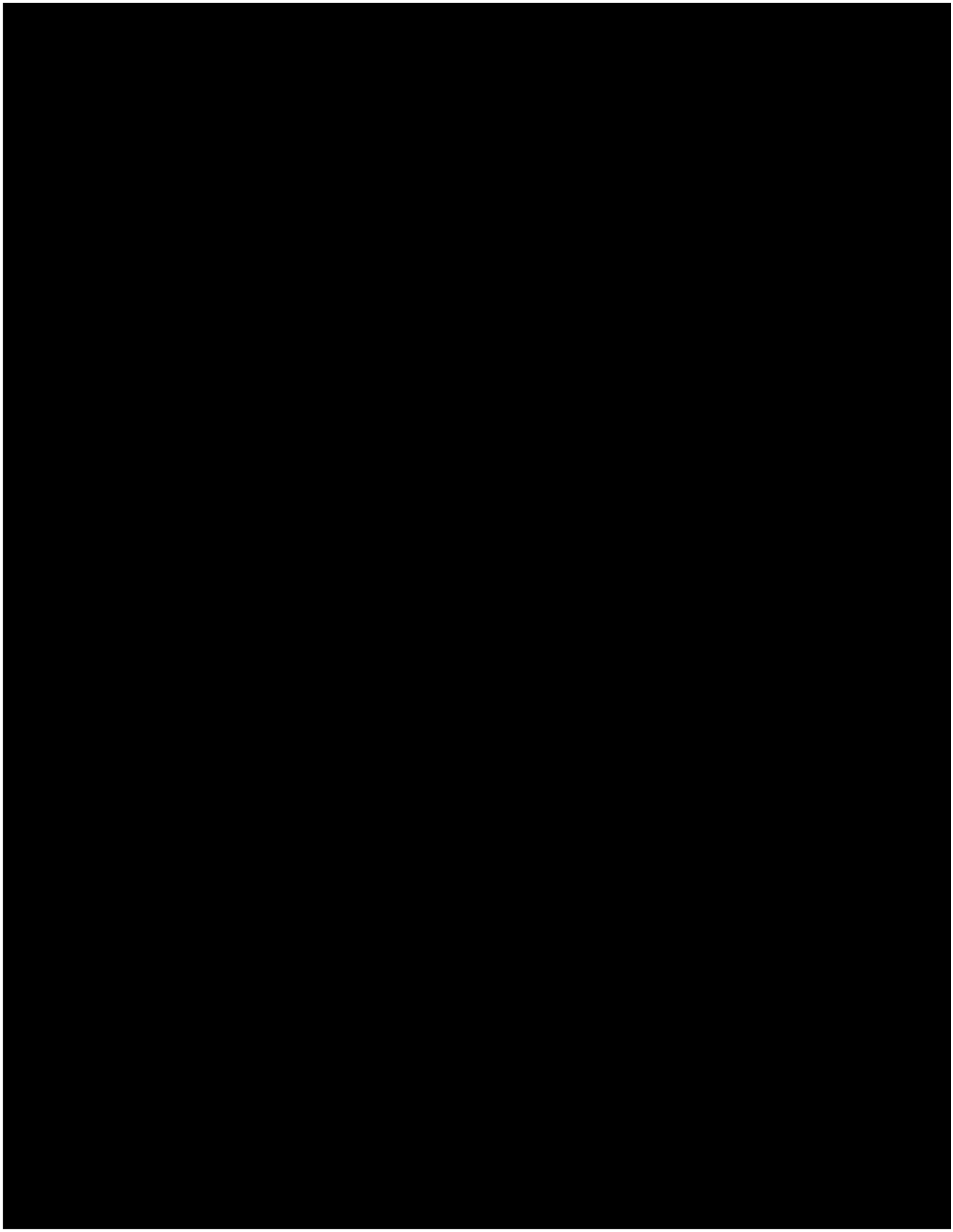
[redacted]

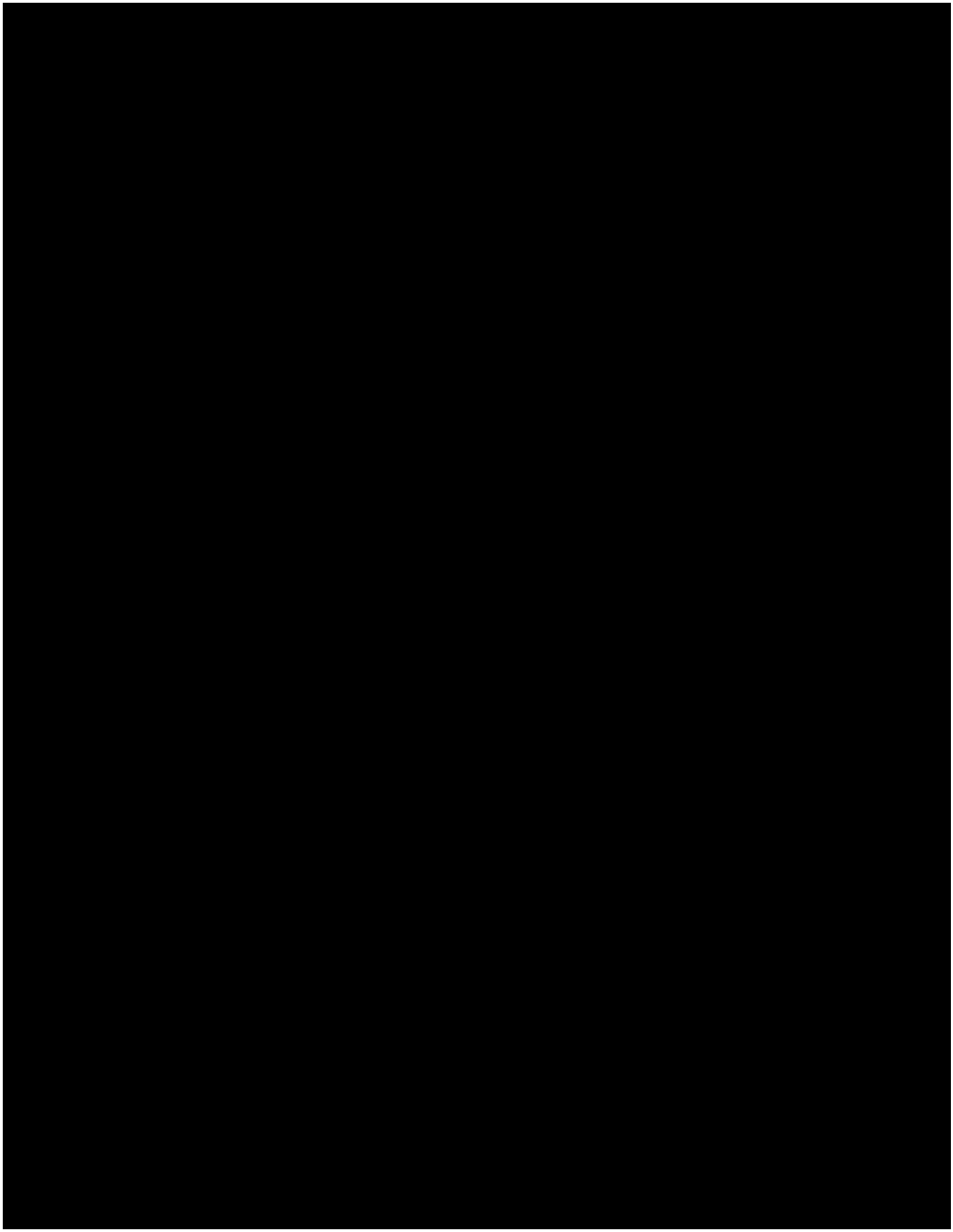


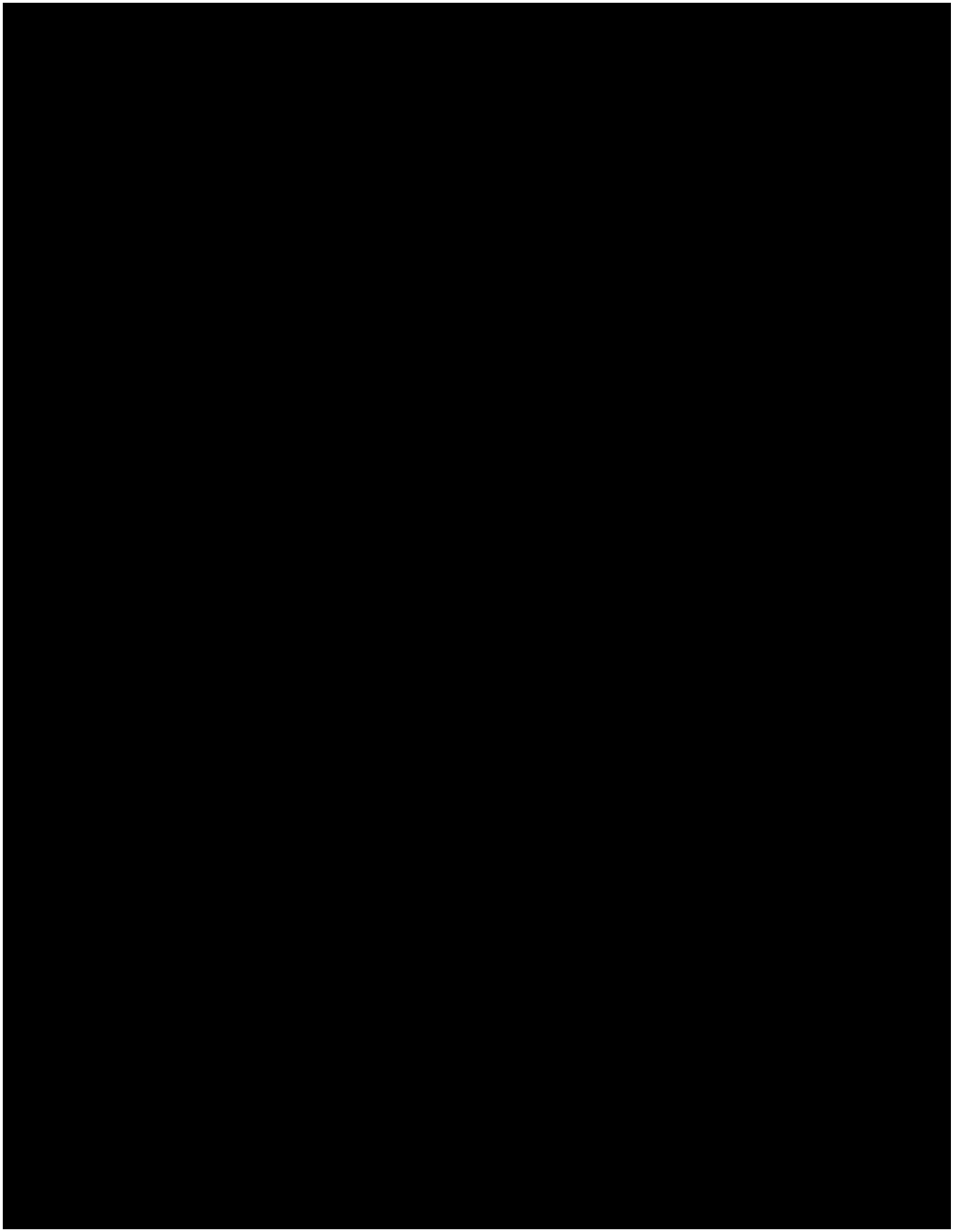












SCHEDULE 2

SPECIFIC ITEMS OF INTELLECTUAL PROPERTY OR OTHER PROPERTY

A. LEAD AND ASSIGNOR JOINTLY-OWNED PATENTS:

Tech ID	Title	Country	Priority Date	File Date	Serial No./Patent No.
1718-084	Crystalline forms of nicotinoyl ribosides, modified derivatives thereof, and phosphorylated analogs	USA	Nov. 11, 2016	Nov. 10, 2017	US 9,975,915 (appl. no. 15/809,731)
14-008	B-vitamin and amino acid conjugates of nicotinoyl ribosides and reduced nicotinoyl ribosides, derivatives thereof, and methods of preparation thereof	WIPO	Mar. 16, 2016	Mar. 16, 2017	WO2017161165A1 (Application No. PCT/US2017/022779)
14-008 (US)	B-vitamin and amino acid conjugates of nicotinoyl ribosides and reduced nicotinoyl ribosides, derivatives thereof, and methods of preparation thereof	USA	Mar. 16, 2016	Mar. 16, 2017	US 10,000,520
14-008 (US)	B-vitamin and amino acid conjugates of nicotinoyl ribosides and reduced nicotinoyl ribosides, derivatives thereof, and methods of preparation thereof	USA	Mar. 16, 2016	Mar. 16, 2017	US 10,000,528C1
1415-017	Nicotinic acid riboside or nicotinamide riboside compositions, reduced derivatives thereof, and the use thereof	WIPO	Mar. 16, 2015	Mar. 16, 2016	WO2016149395A1 (Application No. PCT/US2016/022682)
1415-017 (US)	Nicotinic acid riboside or nicotinamide riboside compositions, reduced derivatives thereof, and the use thereof	USA	Mar. 16, 2015	Mar. 16, 2016	US 10,280,190

1718-083	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	WIPO	Nov. 11, 2016	Nov. 11, 2017	WO2018089830A1 (Application No. PCT/US2017/061154)
1718-083 (US PRI)	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	USA	Nov. 11, 2016	Jun. 23, 2020	US 10,689,411
14-008 (US CON)	B-vitamin and amino acid conjugates of nicotinoyl ribosides and reduced nicotinoyl ribosides, derivatives thereof, and methods of preparation thereof	USA	Mar. 16, 2016	May 11, 2018	US 10,934,322
1718-083 (US CON3)	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	USA	Nov. 11, 2016	May 18, 2021	US 11,242,364
1718-083 (US CON2)	Efficient and scalable syntheses of nicotinoyl ribosides and reduced nicotinoyl ribosides, modified derivatives thereof, phosphorylated analogs thereof, adenylyl dinucleotide conjugates thereof,	USA	Nov. 11, 2016	Apr. 30, 2021	US 11,274,117

	and novel crystalline forms thereof				
1718-083 (US CON4)	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	USA	Nov. 11, 2016	Dec. 15, 2021	US 11,345,720
1718-083 (US CON)	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	USA	Nov. 11, 2016	Jun. 22, 2020	US 11,746,123
1718-083	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	USA	Nov. 11, 2016	Aug. 24, 2023	US 12,195,494
1718-083	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	USA	Nov. 11, 2016	Jan 9, 2025	US 2025/0163093A1 (appl. no. 19/015,302)
1415-017 (AU)	Nicotinic acid riboside or nicotinamide riboside	Australia	Mar. 16, 2015	Mar. 16, 2016	AU2016233247B2

	compositions, reduced derivatives thereof, and the use thereof				
14-008 (AU)	B-vitamin and amino acid conjugates of nicotinoyl ribosides and reduced nicotinoyl ribosides, derivatives thereof, and methods of preparation thereof	Australia		Mar. 16, 2017	AU2017232930B2
1718-084 (AU)	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	Australia	Nov. 11, 2016	Nov. 10, 2017	AU2017356475B2
1718-083	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	Australia	Nov. 11, 2016	Dec. 19, 2023	AU2023285716B2
1718-083	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	Australia	Nov. 11, 2016	May 15, 2024	AU2024203216B2
1718-083	Efficient and scalable syntheses of nicotinoyl ribosides and reduced nicotinoyl ribosides, modified derivatives thereof,	Australia	Nov. 11, 2016	Nov. 8, 2024	AU2024259832B2

	phosphorylated analogs thereof, adenylyl dinucleotide conjugates thereof, and novel crystalline forms thereof				
1718-083	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	Australia	Nov. 11, 2016	Mar. 10, 2025	AU2025201710A1
1415-017(CA)	Nicotinic acid riboside or nicotinamide riboside compositions, reduced derivatives thereof, and the use thereof	Canada	Mar. 16, 2015	Mar. 16, 2016	CA2979057C
14-008(CA)	B-vitamin and amino acid conjugates of nicotinoyl ribosides and reduced nicotinoyl ribosides, derivatives thereof, and methods of preparation thereof	Canada		Mar. 16, 2017	CA3017254C
1718-084(CA)	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	Canada	Nov. 11, 2016	Nov. 10, 2017	CA3045876A1
1415-017(CN)	Nicotinic acid riboside or nicotinamide riboside compositions, reduced derivatives thereof, and the use thereof	China	Mar. 16, 2015	Mar. 16, 2016	CN107531738B
1415-017(CN2)	Nicotinic acid riboside or nicotinamide riboside	China	Mar. 16, 2015	Mar. 16, 2016	CN111643512A

	compositions, reduced derivatives thereof, and the use thereof				
1718-084(CN)	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	China	Nov. 11, 2016	Nov. 10, 2017	CN110662542B
-1718-083	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	China	Nov. 11, 2016	Nov. 10, 2017	CN120383644A
-1718-083	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	China	Nov. 11, 2016	Nov. 10, 2017	CN120463761A
-1718-083	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	China	Nov. 11, 2016	Nov. 10, 2017	CN119320417A

1718-084(EP)	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	Europe	Nov. 11, 2016	Nov. 10, 2017	EP3538099A1
1718-083/4(EP)	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	Europe	Nov. 11, 2016	Nov. 10, 2017	EP3538099A4
1415-017(EP)	Nicotinic acid riboside or nicotinamide riboside compositions, reduced derivatives thereof, and the use thereof	Europe	Mar. 16, 2015	Mar. 16, 2016	EP3271370B1
1718-083(HK)	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	Europe	Nov. 11, 2016	Apr. 29, 2020	HK40017093B
1415-017(HK)	Nicotinic acid riboside or nicotinamide riboside compositions, reduced derivatives thereof, and the use thereof	Hong Kong	Mar. 16, 2015	Jun. 15, 2018	HK1248240B
1415-017(HK2)	Nicotinic acid riboside or nicotinamide riboside compositions,	Hong Kong	Mar. 16, 2015	Dec. 8, 2020	HK40017093A

	reduced derivatives thereof, and the use thereof				
1415-017(HK)	Nicotinic acid riboside or nicotinamide riboside compositions, reduced derivatives thereof, and the use thereof	Indonesia	Mar. 16, 2015	Mar. 16, 2016	IDP0000710097B
1415-017	Nicotinic acid riboside or nicotinamide riboside compositions, reduced derivatives thereof, and the use thereof	Indonesia	Mar 16 2015	May 2020	IDP000088349
1415-017(IN)	Nicotinic acid riboside or nicotinamide riboside compositions, reduced derivatives thereof, and the use thereof	India	Mar. 16, 2015	Oct 7, 2017	IN476255B
1718-084(IN)	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	India	Nov. 11, 2016	Jun. 10, 2019	IN480678B
1415-017(JP)	Nicotinic acid riboside or nicotinamide riboside compositions, reduced derivatives thereof, and the use thereof	Japan	Mar. 16, 2015	Mar. 16, 2016	JP7244163B2
1415-017(JP DIV)	Nicotinic acid riboside or nicotinamide riboside compositions, reduced derivatives thereof, and the use thereof	Japan	Mar. 16, 2015	Oct. 22, 2020	JP2021020934A
1415-017(SK)	Nicotinic acid riboside or nicotinamide riboside compositions, reduced derivatives	Korea	Mar. 16, 2015	Mar. 16, 2016	KR102426320B1

	thereof, and the use thereof				
1415-017(MX)	Nicotinic acid riboside or nicotinamide riboside compositions, reduced derivatives thereof, and the use thereof	Mexico	Mar. 16, 2015	Mar. 16, 2016	MX390185B
1415-017(NZ)	Nicotinic acid riboside or nicotinamide riboside compositions, reduced derivatives thereof, and the use thereof	New Zealand	Mar. 16, 2015	Mar. 16, 2016	NZ735411A
1718-084 (NZ)	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	New Zealand	Nov. 11, 2016	Nov. 10, 2017	NZ753674B2
-1718-084	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	New Zealand	Nov. 11, 2016	Nov. 10, 2017	NZ803738A
1415-017(ZA)	Nicotinic acid riboside or nicotinamide riboside compositions, reduced derivatives thereof, and the use thereof	South Africa	Mar. 16, 2015	Mar. 16, 2016	ZA201706918B
1718-083 (ZA)	Efficient and scalable syntheses of nicotinoyl ribosides and reduced nicotinoyl ribosides, modified derivatives thereof, phosphorylated	South Africa	Nov. 11, 2016		ZA201903654

	analogs thereof, adenylyl dinucleotide conjugates thereof, and novel crystalline forms thereof				

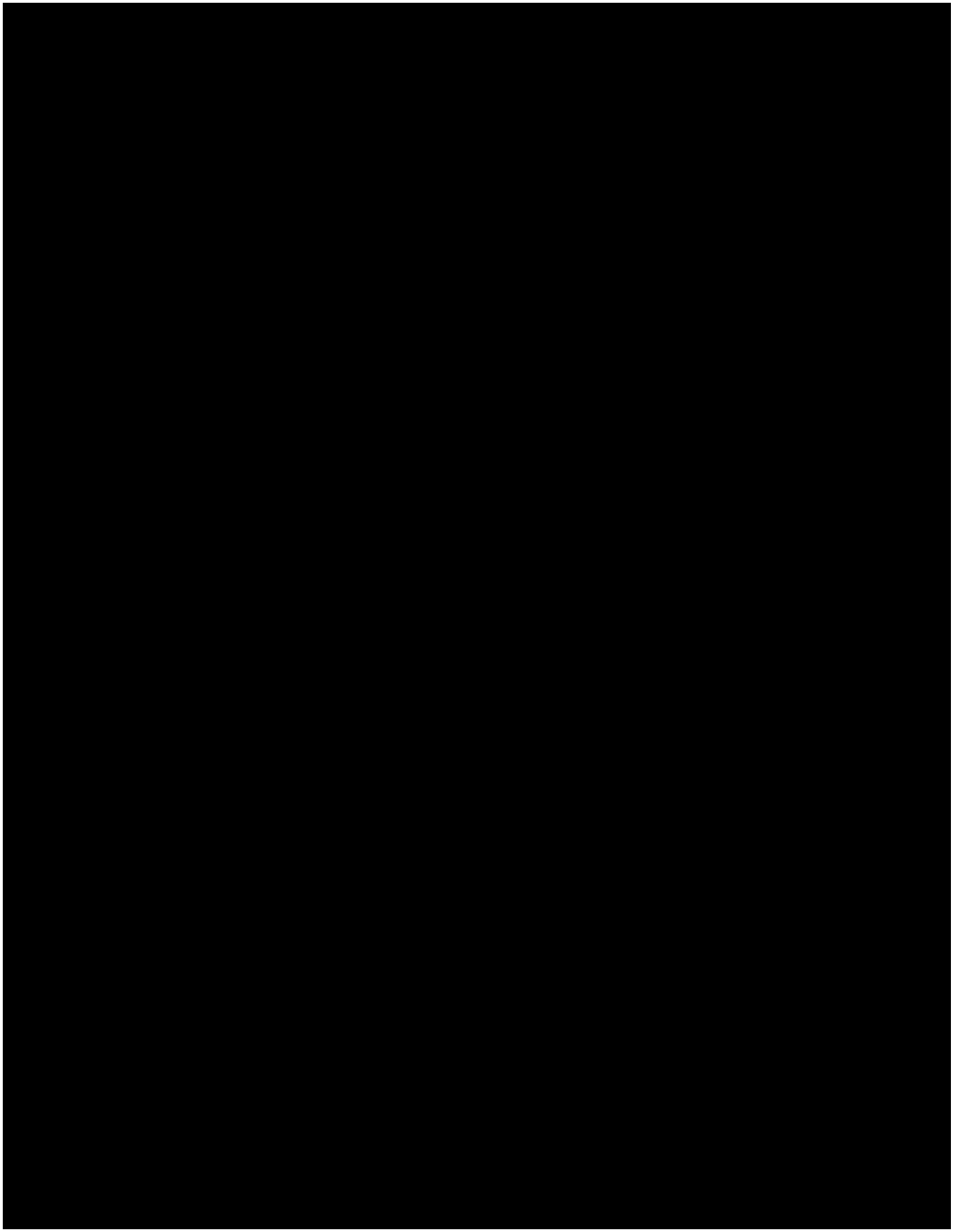
B. ASSIGNOR SOLEY OWNED PATENTS:

Tech ID	Title	Country	Priority Date	File Date	Serial No./Patent No.
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF	WIPO	Jul. 29, 2013	Jul. 24, 2014	WO2015014722A1
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF	USA	Jul. 29, 2013	Jul. 24, 2014	US 10,000,519
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF	USA	Jul. 29, 2013	Feb. 27, 2018	US 10,815,262
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF	USA	Jul. 29, 2013	May 29, 2020	US 11,584,770
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF	USA	Jul. 29, 2013	May 4, 2022	US 11,981,698
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF	USA	Jul. 29, 2013	Apr. 26, 2023	US 12,252,506
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF	USA	Jul. 29, 2013	Mar. 7, 2024	US20240239831A1 (appl. no. 18/598,617)
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND		Jul. 29, 2013	Jul. 24, 2014	AU2014298629B2

	DERIVATIVES THEREOF				
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF		Jul. 29, 2013	Jul. 24, 2014	AU2020201254B2
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF		Jul. 29, 2013	Jul. 24, 2014	AU2022203196B2
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF		Jul. 29, 2013	Jul. 24, 2014	BR112016001774B1
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF		Jul. 29, 2013	Jul. 24, 2014	CA2918955C
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF		Jul. 29, 2013	Jul. 24, 2014	CA3192957A1
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF		Jul. 29, 2013	Jul. 24, 2014	CN105636973B
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF		Jul. 29, 2013	Jul. 24, 2014	CN108707174A
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF		Jul. 29, 2013	Jul. 24, 2014	EP3027635B1
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND		Jul. 29, 2013	Jul. 24, 2014	EP3321274A1

	DERIVATIVES THEREOF				
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF		Jul. 29, 2013	Jul. 24, 2014	HK1218918B
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF		Jul. 29, 2013	Jul. 24, 2014	HK1255037A1
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF		Jul. 29, 2013	Jul. 24, 2014	IDP000067409B
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF		Jul. 29, 2013	Jul. 24, 2014	IN364502B
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF		Jul. 29, 2013	Jul. 24, 2014	JP6208352B2
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF		Jul. 29, 2013	Jul. 24, 2014	KR102303966B1
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF		Jul. 29, 2013	Jul. 24, 2014	KR102414886B1
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF		Jul. 29, 2013	Jul. 24, 2014	MX349969B
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND		Jul. 29, 2013	Jul. 24, 2014	NZ716277A

	DERIVATIVES THEREOF				
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF		Jul. 29, 2013	Jul. 24, 2014	ZA201600908
12-001	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF		Jul. 29, 2013	Jul. 24, 2014	ZA201802315B



This Assignment has been executed and takes effect on the date stated at the beginning of it.

For and on behalf of	For and on behalf of
LEAD: **CHROMADEX, INC.**	**ASSIGNOR:** **QUEEN'S UNIVERSITY BELFAST**
Signed by: Ozan Pamir Signed	DocuSigned by: Matthew Wilson Signed
Ozan Pamir Print name	Matthew Wilson Print name
CFO Title	Commercial Development Manager Title
12/18/2025 Date	12/17/2025 Date

UNITED STATES PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
15/905,922	**05/06/2026 04:53:19 PM Z ET**	**335040: 4-16A US**

Title of Invention

Methods of Preparing Nicotinamide Riboside and Derivatives Thereof

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	10815262
CONFIRMATION #	1061	FILED BY	Samantha Eberle
PATENT CENTER #	75938435	FILING DATE	02/27/2018
CUSTOMER #	23713	FIRST NAMED INVENTOR	Marie MIGAUD
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	GEORGE CARRERA

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
POA_aia_0080.pdf	2	Power of Attorney	551 KB
Warning: The PDF file has been signed with a digital signature and the legal effect of the document will be based on the contents of the file not the digital signature.			
37CFR373c_CHROM-151-US-CON.pdf	30	Assignee showing of ownership per 37 CFR 3.73	3300 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
POA_aia_0080.pdf	60392E406B57E51C5590CE6DA4C3E630CF3424BD5F06B0270 23D1E459187350D989E185D5C9E70DFD900F35E5718A4ACD0

E89AF1B71154CF1D8967A134CB6324

37CFR373c_CHROM-151-US-CON.pdf	FEF906D7AA36D35879EDBD27999C4ABC5B43AD84E69AF28B0733363967289160C67F2E9DDC41E6910AA5E7160A44C75DE827D120AA2CD4C43FA734D1B9DAB1BB

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/905,922	10/27/2020	10815262	335040: 4-16A US	1061

23713 7590 10/07/2020

Leydig, Voit & Mayer, Ltd. (GS BOULDER)
4940 Pearl East Circle
Suite 200
Boulder, CO 80301

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Marie MIGAUD, Lurgan, UNITED KINGDOM;
The Queen's University of Belfast, Belfast Antrim, UNITED KINGDOM;
Philip REDPATH, Portadown, UNITED KINGDOM;
Kerri CROSSEY, Magherafelt, UNITED KINGDOM;
Mark DOHERTY, Newtownabbey, UNITED KINGDOM;

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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/905,922	02/27/2018	Marie MIGAUD	335040: 4-16A US	1061

23713 7590 09/25/2020

Leydig, Voit & Mayer, Ltd. (GS BOULDER)
4940 Pearl East Circle
Suite 200
Boulder, CO 80301

EXAMINER
LEWIS, PATRICK T

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
09/25/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

chgpatent@leydig.com

Response to Rule 312 Communication	Application No.	Applicant(s)	
	15/905,922	MIGAUD et al.	
	Examiner	Art Unit	AIA (FITF) Status
	PATRICK T LEWIS	1623	Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

1. ☑ The amendment filed on 11 September 2020 under 37 CFR 1.312 has been considered, and has been:
   a) ☑ entered.
   b) ☐ entered as directed to matters of form not affecting the scope of the invention.
   c) ☐ disapproved because the amendment was filed after the payment of the issue fee.
      Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.
   d) ☐ disapproved. See explanation below.
   e) ☐ entered in part. See explanation below.

/PATRICK T LEWIS/
Primary Examiner, Art Unit 1623

OK TO ENTER: /P.T.L/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

US Application No.	: 15/905,922	Confirmation No. 1061
Date of Filing	: February 27, 2018	
Applicant	: The Queen's University of Belfast	
Inventors	: Marie MIGAUD, et al.	
For	: Methods of Preparing Nicotinamide Riboside and Derivatives Thereof	
Art Unit	: 1623	
Examiner	: Patrick T. Lewis	
Docket No.	: 335040: 4-16A US	
Customer No.	: 23713	

CERTIFICATE OF EFS-WEB FILING
I hereby certify that this correspondence is being filed with the USPTO EFS-WEB system.

September 11, 2020 (Date) /cathynelson/ (Cathy Nelson)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AFTER NOTICE OF ALLOWANCE (UNDER 37 CFR 1.312)
SUBMITTED WITH PAYMENT OF THE ISSUE FEE

Sir:

Please enter the following amendment after allowance under 37 CFR §1.312 of the claims. This amendment is submitted with payment of the issue fee.

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 7 of this paper.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

US Application No.	: 15/905,922	Confirmation No. 1061
Date of Filing	: February 27, 2018	
Applicant	: The Queen's University of Belfast	
Inventors	: Marie MIGAUD, et al.	
For	: Methods of Preparing Nicotinamide Riboside and Derivatives Thereof	
Art Unit	: 1623	
Examiner	: Patrick T. Lewis	
Docket No.	: 335040: 4-16A US	
Customer No.	: 23713	

CERTIFICATE OF EFS-WEB FILING
I hereby certify that this correspondence is being filed with the USPTO EFS-WEB system.

September 11, 2020 (Date) /cathynelson/ (Cathy Nelson)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AFTER NOTICE OF ALLOWANCE (UNDER 37 CFR 1.312)
SUBMITTED WITH PAYMENT OF THE ISSUE FEE

Sir:

Please enter the following amendment after allowance under 37 CFR §1.312 of the claims. This amendment is submitted with payment of the issue fee.

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 7 of this paper.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23713 7590 06/12/2020

Leydig, Voit & Mayer, Ltd. (GS BOULDER)
4940 Pearl East Circle
Suite 200
Boulder, CO 80301

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

Cathy Nelson	(Typed or printed name)
/cathynelson/	(Signature)
September 11, 2020	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/905,922	02/27/2018	Marie MIGAUD	335040: 4-16A US	1061

TITLE OF INVENTION: Methods of Preparing Nicotinamide Riboside and Derivatives Thereof

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$500	$0.00	$0.00	$500	09/14/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
LEWIS, PATRICK T	1623	536-028100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Leydig, Voit & Mayer, Ltd.
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE	(B) RESIDENCE: (CITY and STATE OR COUNTRY)
THE QUEEN'S UNIVERSITY OF BELFAST	BELFAST ANTRIM, GREAT BRITAIN

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☑ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☑ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☑ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 12-1216

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /sallyasullivan/ Date September 11, 2020

Typed or printed name Sally A. Sullivan Registration No. 32,064

PTOL-85 Part B (08-18) Approved for use through 01/31/2020 OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

IPR2026-00400
Exhibit 2008 Page 42

Electronic Patent Application Fee Transmittal

Application Number:	15905922
Filing Date:	27-Feb-2018
Title of Invention:	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof
First Named Inventor/Applicant Name:	Marie MIGAUD
Filer:	Sally A. Sullivan/Cathy Nelson
Attorney Docket Number:	335040: 4-16A US

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
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Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	2501	1	500	500

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**500**

Electronic Acknowledgement Receipt	
EFS ID:	40531021
Application Number:	15905922
International Application Number:	
Confirmation Number:	1061
Title of Invention:	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof
First Named Inventor/Applicant Name:	Marie MIGAUD
Customer Number:	23713
Filer:	Sally A. Sullivan/Cathy Nelson
Filer Authorized By:	Sally A. Sullivan
Attorney Docket Number:	335040: 4-16A US
Receipt Date:	11-SEP-2020
Filing Date:	27-FEB-2018
Time Stamp:	12:38:10
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$500
RAM confirmation Number	E20209AC38364144
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	4-16A_US_efsCert.pdf	67892 3d91729ebbfe1028de7bc500e7f754af60357bd9	no	1
Warnings:					
Information:					
2		4-16A_US_312_amend.pdf	224911 c225ff5d55f650174969723 0e0c118f3ecf208c5	yes	7

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Applicant Arguments/Remarks Made in an Amendment	7	7
	Claims	2	6
	Amendment after Notice of Allowance (Rule 312)	1	1

Warnings:					
Information:					
3	Issue Fee Payment (PTO-85B)	4-16A_US_PartB_Fee_Transmittal-asfiled.pdf	1614745 515ecbb2316fab291875367bdcde316116574233	no	1
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30543 c0e80b784120a9a37399c3d627afee94841cb6a3	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1938091		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

CERTIFICATE OF EFS-WEB FILING

Application No.	:	15/905,922 Confirmation No. 1061
Filing Date	:	February 27, 2018
Applicant	:	The Queen's University of Belfast
First Named Inventor:	:	Marie MIGAUD
For	:	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof
Group Art Unit	:	1623
Examiner	:	Patrick T. Lewis
Docket No.	:	335040: 4-16A US
Customer No.	:	23713

I hereby certify that the following, along with any other document(s) referenced to as being attached or enclosed:

1. **This Certificate of EFS-WEB Filing – 1 page**
2. **Amendment after Notice of Allowance Submitted with Payment of Issue Fee – 7 pages**
3. **Part B Fee Transmittal – 1 page**

are being submitted electronically through the United States Patent Office EFS-WEB System, to be directed to:

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

On **September 11, 2020**

Cathy Nelson
(Person Filing Correspondence)

/cathynelson/
(Signature of Person Filing Correspondence)

REMARKS

A Notice of Allowance was mailed June 12, 2020 for the referenced application.

Claim 1 is amended to correct the double word “is”. This is the correction of an obvious clerical error.

No new matter has been added.

Claims 1-2, 4-10, 12, 14 and 18-26 are allowed.

Conclusion

This response is accompanied by payment of the issue fee in the amount of $500 for small entity. If the amount paid by EFS web is not correct, please deduct any fees required for timely submission, or credit any overpayment, to deposit account 12-1216.

Respectfully submitted,

/sallyasullivan/

Sally A. Sullivan
Reg. No. 32,064

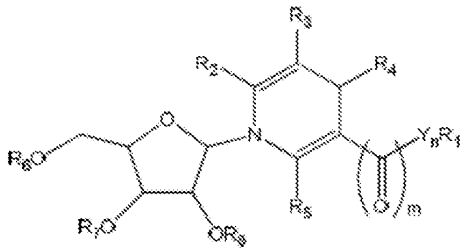
LEYDIG, VOIT & MAYER, Ltd.
4940 Pearl East Circle, Suite 200
Boulder, CO 80301
Telephone: (720) 795-7976
Facsimile: (312) 616-5700
Email: chgpatent@leydig.com

Claim Amendments

This listing of the claims replaces all previous such listings:

Listing of the Claims

1. (Currently amended) A compound of formula (III)



(III)

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

R_6, R_7 and R_8, which may be the same or different, are each independently a hydroxyl protecting group or are each H, provided that when n is 1, m is 1, Y is O, R_1 [[is]] is methyl, and R_2 – R_5 are each H, then R_6, R_7, and R_8 are not all simultaneously H or unsubstituted acetyl; further provided that when n is 1, m is 1, Y is O, R_1 is methyl, R_3 and R_4 are methyl, and R_2 and R_5 are each H, then R_6, R_7, and R_8 are not all simultaneously H or unsubstituted acetyl; and yet further provided that when n is 0, m is 1, R_1 is NH_2, and R_2 – R_5 are each H, then R_6, R_7, and R_8 are not all simultaneously H or unsubstituted benzoyl.

2. (Original) A compound of claim 1, wherein R_6, R_7 and R_8 are each H.

3. (Cancelled)

4. (Original) A compound according to claim 1, 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.

5. (Original) A compound according to claim 4, wherein the R_6, R_7 and R_8 moieties are selected from substituted and unsubstituted acetyl, and substituted and unsubstituted benzoyl.

6. (Original) A compound according to claim 4, wherein the ester-type protecting group is a protecting group selected from acetyl, propionyl, isopropionyl, benzoyl, and trihaloacetyl.

7. (Original) A compound according to claim 6, wherein the R_6, R_7 and R_8 moieties are selected from substituted and unsubstituted acetyl, and substituted and unsubstituted benzoyl.

8. (Previously presented) A compound according to claim 4, wherein the ester-type protecting group is a protecting group selected from trifluoroacetyl or trichloroacetyl, and provided that when n is 0 and m is 1, R_1 is not NH_2.

9. (Original) A compound according to claim 4, wherein the ether-type protecting group is a protecting group selected from benzyl, p-methoxybenzyl, methoxymethyl and allyl ethers.

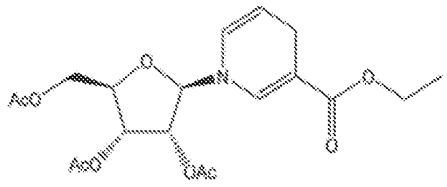
10. (Original) A compound according to claim 4, wherein the silyl-type protecting group is a protecting group selected from trimethylsilyl, triethylsilyl, triisopropylsilyl, 2-(trimethylsilyl)ethoxymethyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl and tetraisopropyldisilyl.

11. (Cancelled)

12. (Previously presented) A compound of claim 1, wherein at least two of R_6, R_7 and R_8 are selected from unsubstituted acetyl or unsubstituted benzoyl.

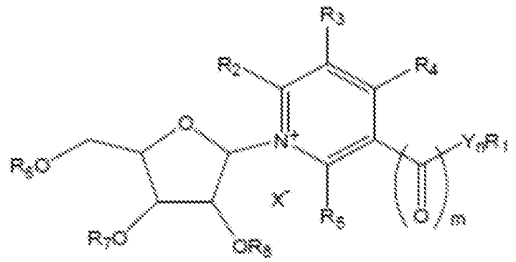
13. (Cancelled)

14. (Previously presented) A compound according to claim 1, which is triacetyl O-ethyl-1,4-dihydronicotinate riboside:



15. -17. (Cancelled)

18. (Previously presented) A compound of formula (IV)



(IV)

wherein

n is 1;

m is 1;

Y is O;

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;

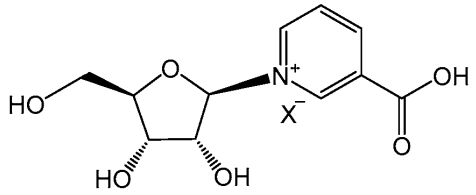
R_2 – R_5 are each H; and

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

provided that when n is 1, m is 1, Y is O, R_1 is H or NH_2, R_2 – R_5 are each H, and X^- is a substituted sulfonate, then R_6, R_7, and R_8 are not all simultaneously H or unsubstituted acetyl or unsubstituted benzoyl.

19. (Previously presented) A compound of formula:



wherein 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, provided that X^- is not trifluoromethylsulfonate.

20. (Previously presented) A compound of claim 1, wherein:

Y_nR_1 is NH_2 or $–OCH_2CH_3$; and

R_2-R_5 are all hydrogens.

21. (Previously presented) The compound of claim 20, wherein R_6, R_7 and R_8, are each the same group.

22. (Previously presented) A compound of claim 12, wherein at least two of R_6, R_7 and R_8 are selected from unsubstituted acetyl or unsubstituted benzoyl and provided that when n is 0 and m is 1, R_1 is not NH_2.

23. (Previously presented) The compound of claim 18, wherein X^- is an anion selected from an anion of a substituted or unsubstituted carboxylic acid, a substituted or unsubstituted phosphate, a substituted or unsubstituted sulfate, a substituted or unsubstituted carbonate, and a substituted or unsubstituted carbamate.

24. (Previously presented) The compound of claim 18, wherein X^- is an anion selected from acetate, formate, trifluoroacetate, glutamate, lactate, and aspartate.

25. (Previously presented) The compound of claim 19, wherein 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.

26. (Previously presented) The compound of claim 19, wherein X^- is an anion selected from acetate, formate, trifluoroacetate, glutamate, lactate and aspartate.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/905,922	02/27/2018	Marie MIGAUD	335040: 4-16A US	1061

23713 7590 09/01/2020

Leydig, Voit & Mayer, Ltd. (GS BOULDER)
4940 Pearl East Circle
Suite 200
Boulder, CO 80301

EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
09/01/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

chgpatent@leydig.com

Response to Rule 312 Communication	Application No. 15/905,922	Applicant(s)
	Examiner	Art Unit

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

1. ☒ The amendment filed on *August 21, 2020* under 37 CFR 1.312 has been considered, and has been:

a) ☒ entered.

b) ☐ entered as directed to matters of form not affecting the scope of the invention.

c) ☐ disapproved because the amendment was filed after the payment of the issue fee.
Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.

d) ☐ disapproved. See explanation below.

e) ☐ entered in part. See explanation below.

Publishing Division

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	15/905,922 Confirmation No. 1061
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Group Art Unit	:	1623
Examiner	:	Patrick T. Lewis
Docket No.	:	335040: 4-16A US
Customer No.	:	23713

CERTIFICATE OF EFS-WEB FILING

I hereby certify that this correspondence is being filed with the USPTO EFS-WEB system.

August 21, 2020 (Date) cathynelson/ (Cathy Nelson)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NOTICE TO FILE CORRECTED APPLICATION PAPERS

Sir,

In response to the Notice to File Corrected Application Papers mailed July 31, 2020, please enter the following:

Amendments to the Specification begins on page 2 of this paper.

Remarks begin on page 3 of this paper.

This response is accompanied by a **Substitute Specification-Marked-up** showing corrections (23 pages) and a **Clean copy of the Substitute Specification** (23 pages)

Methods of preparing nicotinamide riboside and derivatives thereof

Cross-reference to Related Applications

This application is a continuation of U.S. application 14/908,831, filed January 29, 2016 which is a U.S. National Stage under 35 U.S.C. 371 of PCT/EP14/065971, filed July 24, 2014. 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 p-anomer forms of nicotinamide riboside, nicotinate riboside, nicotinamide mononucleotide and nicotinate mononucleotide are shown, without counter ions, in Figure 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 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. Kirihata, *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.

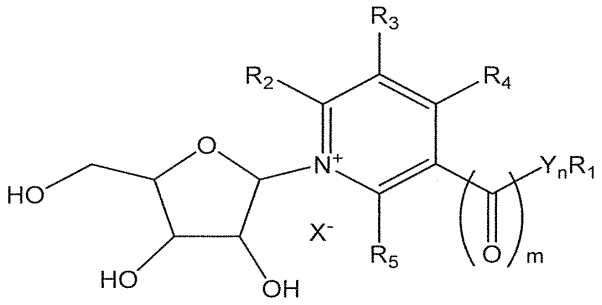
It is therefore an object of the invention to avoid or mitigate the disadvantages of the prior art.

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)



(I)

wherein

n is 0 or 1;

m is 0 or 1;

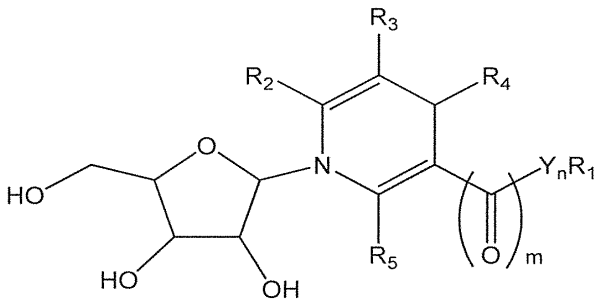
Y is O or S;

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)



(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).

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 $N^+HR^{I}R^{II}R^{III}$, 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.

Optionally, Z^+ is an unsubstituted ammonium of the formula NH_4^+.

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 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.

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 catalystare 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, 1,2-dichloroethane, 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 alkylarylamino), 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 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, R_1 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, R_1 is NH_2, R_2 – R_5 are each H, and X^- is selected from chloride, acetate, formate and trifluoroacetate.

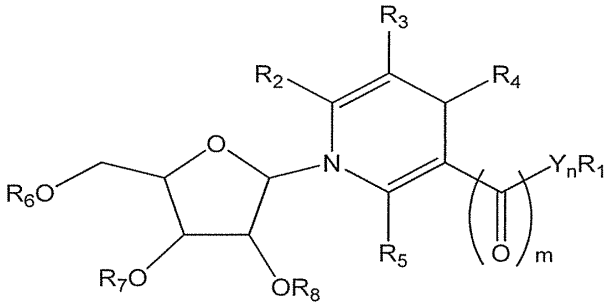
Optionally, in an embodiment of formula (II), n is 0, m is 1, R_1 is NH_2, and R_2 – R_5 are each H.

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 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 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 340nm.

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



(III)

wherein

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

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

with a deprotecting agent;

to form the compound of formula (II).

Suitable R_6, R_7 and R_8 moieties include, but are not limited to, ester-type protecting groups, ether-type protecting groups, and silyl-type protecting groups.

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

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

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

Optionally, the R_6, R_7 and R_8 moieties are selected from substituted and unsubstituted acetyl, and substituted and unsubstituted benzoyl.

Optionally, at least two of R_6, R_7 and R_8 are selected from unsubstituted acetyl or unsubstituted benzoyl.

Optionally the deprotecting agent is an acid or a base. Deprotection can also be achieved by catalytic hydrogenation (Pd/C; H_2) for the aromatic ether protecting groups and by fluoride-catalysed chemistry (e.f. TBAF in THF) for all the silyl ethers. Optionally, when R_6, R_7 and R_8 each comprise unsubstituted acetyl or unsubstituted benzoyl, the deprotecting agent is a base, optionally selected

from NH_3, Na_2CO_3 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, substituted or unsubstituted aliphatic or aromatic hydrocarbons, and combinations thereof, as defined above.

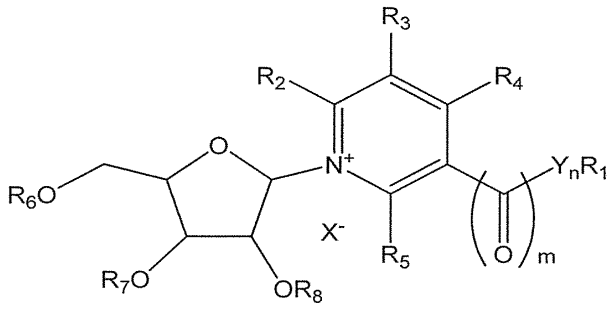
Optionally, the reactants are subjected to mechanical grinding, further optionally using a ball milling or planetary ball milling machine.

Optionally, in an embodiment of formula (III), n is 0, m is 1, R_1 is NH_2, R_2 – R_5 are each H, and R_6 – R_8 are each acetyl.

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

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

Optionally, 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 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 R_6, R_7 and R_8 comprise unsubstituted acetyl, the organic solvent is selected from dichloromethane, 1,2-dichloroethane, n-butyl acetate, chloroform and ethyl acetate, or a combination thereof, further optionally ethyl acetate.

Optionally, when at least two of R_6, R_7 and R_8 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 solution 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 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).

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

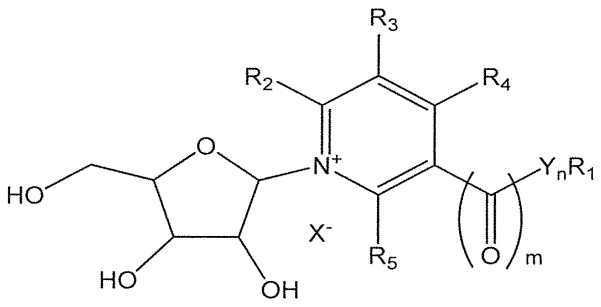
Optionally, in an embodiment of formula (IV), n is 0, m is 1, R_1 is NH_2, $R_2 – R_5$ are each H, $R_6 – R_8$ are each acetyl, and X^- is ^-OTf.

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)



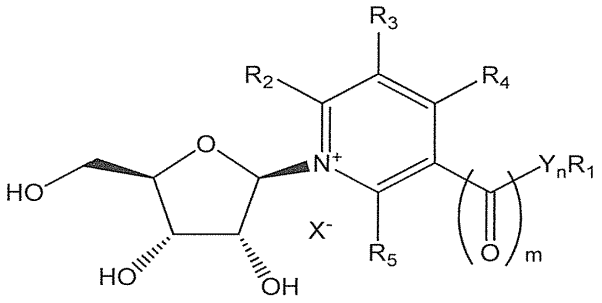
(I)

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,

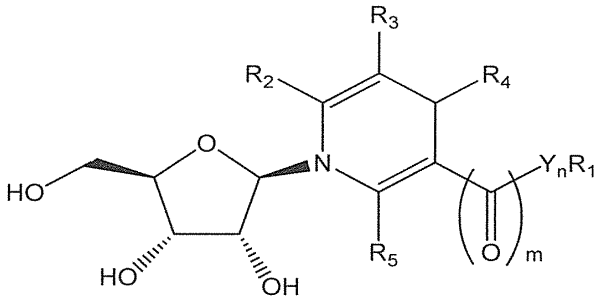


(IA)

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,

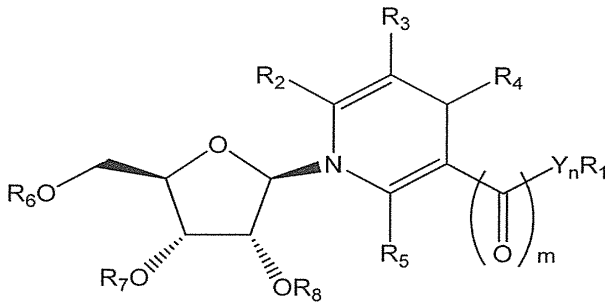


(IIA)

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,

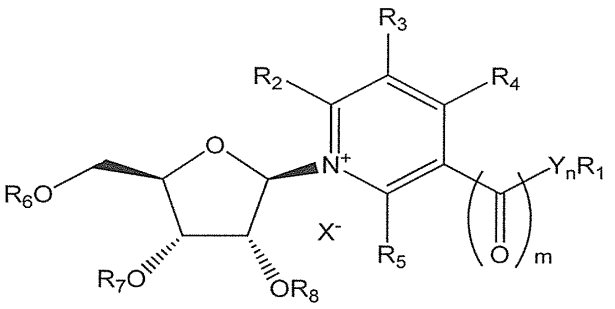


(IIIA)

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,



(IVA)

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.

(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 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 $P\text{-}H^+$ or a sulfonium cation containing SH^+, 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).

Brief Description of the Drawings

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

Figure 2 depicts Scheme A, which is a scheme illustrating, in general terms, that compounds of formula (IV) may be used to prepare compounds of formula (III), as described in Example 1; 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;

Figure 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-(beta-D-ribofuranosyl)-1,4-dihydronicotinamide, as described in Example 2, and that 1-(beta-D-ribofuranosyi)-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;

Figure 4 shows the (3-anomer forms of triacetyl-1,4-dihydronicotinamide riboside (Example 1(A)), triacetyl O-ethyl-1, 4-dihydronicotinate riboside, (Example 1(B)), tribenzoyl-1, 4-dihydronicotinamide riboside (Example 1(C)), and 1-(beta-D-ribofuranosyl)-1,4-dihydronicotinamide (Example 2); and

Figure 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)).

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

The Examples

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 B-anomer form of which is shown in Figure 4).

Reduction: All solvents were degassed prior to use by sonication and argon bubbling. Sodium dithionite (0.656g, 3.76 mmol, 2 eq) and sodium hydrogencarbonate (0.79g, 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 (1g, 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.
^{1}H-NMR (MeOD, 400MHz) - δ7.15 (s, 1H, H-5), 5.95 (d, 1H, J= 7.21 Hz, H-6), 5.25 (d, 1H, J=2.84Hz) & 5.17 (d, 1H, J=1.80Hz) (H-8 & H-7), 4.96 (d, 1H, J=7.09Hz, H-4), 4.87 (ABX, 1H, Jaa=8.18Hz, Jab=3.60Hz, H-9), 4.26 (d, 2H, J=3.20Hz, H-10 & H-10') 4.19 (m, 1H, J=3.00Hz, H-3), 3.13 (m, 2H, J=1.18Hz, H-2), 2.13 (s, 3H), 2.11 (s, 3H), 2.10 (s, 3H) (H-13, H-15, H-17). ^{13}C-NMR (MeOD,125MHz) - δ172.80 (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 (10g, 81.89 mmol, 1eq) was silylated using TMSCI (15.6 ml,122.85 mmol, 1.5 eq) in HMDS (100 ml) at 13Q°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.

^{1}H-NMR (MeOD, 400MHz) - 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, 3.9Hz, 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).

^{13}C-NMR (MeOD, 125MHz) - δ 172.1, 171.6, 171.2 (3x C=OCH_3), 164.9 (C=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).

^{19}F-NMR (MeOD, 376MHz) – δ -79.9 (triflate counterion)

Example 1(B): Preparation of reduced triacetyl nicotinate ester riboside, namely triacetyl O-ethyl-1, 4-dihydronicotinate riboside, a compound of formula (III) (the β-anomer form of which is shown in Figure 4).

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

^{1}H-NMR-δ 7.27 (1H, s, H-6), 6.05 (1H, dd, *J*= 8.2, 1.5Hz, H-7), 5.26 (1H, dd, *J*= 5.8, 2.8Hz, H-3), 5.23 (1H, dd, *J*= 6.9, 5.8Hz, H-2), 5.08 (1H, d, *J*= 6.9Hz, H-1), 4.91 (1H, dt, *J*= 8.3, 3.5Hz, H-8), 4.24-4.30 (3H, m, H-4, H-5, H-5'), 4.11 (2H, q, *J*= 7.2Hz, 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*= 7.2Hz, H-12).

^{13}C-NMR- δ 172.2, 171.5, 171.3, 169.8, (3x C=O-CH_3 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 (3x C=O-CH_3), 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 1eq tetraacetate riboside, 1eq TMSOTf, 1eq ethyl nicotinate, were reacted for 30mins in a 1.5 ml steel vessel with a 1.5cm 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.

^{1}H-NMR (D_2O, 400MHz) - 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=OC<u>H</u>$_2$CH$_3$), 2.04 (s, 3H, OAc), 2.02 (s, 3H, OAc), 1.98 (s, 3H, OAc), 1.25 (t, 3H, *J*=7.0 Hz, C=OCH$_2$C<u>H</u>$_3$).

^{19}F-NMR (D_2O, 376MHz) – δ -79.0 (triflate counterion)

<u>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 Figure 4).</u>

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, 10mL of H_2O was added to the solution and most of the methanol removed *via* rotary evaporation. The starting material crashed out of solution and 20mL of diethyl ether (Et_2O) was added until the solids solubilized into a biphasic system. A solution of $NaHCO_3$ (420mg, 5mmol, 5eq) and sodium dithionite (348mg, 2mmol, 2eq) in 10mL H_2O was added and stirred for 2hrs. The layers were separated and the ether layer was dried over $MgSO_4$ and concentrated to provide 428mg (76% yield) of tribenzoyl-1, 4-dihydronicotinamide riboside (yellow solid) without further purification. 80% purity based on ^{1}H-NMR. Pure material is obtained by Biotage purification.

^{1}H-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, 1.5Hz, H-7), 5.68 (1H, dd, *J*= 6.2, 3.5Hz, H-3), 5.57 (1H, dd, *J*= 6.7, 6.2Hz, H-2), 5.29 (1H, d, *J*= 6.7Hz, 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 (3x <u>C</u>=O-C_6H_5, <u>C</u>=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 (3x 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 (-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 1eq 1-acetate-tribenzoate riboside, 1eq TMSOTf and 1eq TMS-nicotinamide, were reacted for 30mins in a 1.5 ml steel vessel with a 1.5cm diameter steel ball bearing in a Retsch MM400 mixer mill at 25 Hz. 1eq 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.

^{1}H-NMR (MeOD, 400MHz) - 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, 3.9Hz, 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, 376MHz) – δ -79.1 (triflate counterion)

Example 2

A compound of formula (II), namely NRH (reduced nicotinamide riboside, also known as 1-(beta-D-ribofuranosyl)-1,4-dihydronicotinamide (the β-anomer form of which is shown in Figure 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. 100mgs of (III) was dissolved in 0.5mL of MeOH containing 0.05g of NaOH. The compounds were reacted for 30mins in a 1.5 ml steel vessel with a 1.5cm diameter steel ball bearing in a Retsch MM400 mixer mill at 25 Hz.
1H-NMR (MeOD, 400MHz) – δ7.18 (s, 1H, H-5), 6.14 (d, 1H, J= 8.28Hz, H-6), 4.85 (m, 1H, H-3), 4.76 (d, 1H, J= 5.77Hz, H-4), 4.04 (m, 2H, H-7&H-8), 3.93 (m, 1H, J=2.76, H-9), 3.72 (ABX, 1H, Jaa=12.55Hz, Jab=3.51Hz, H-10), 3.65 (ABX, 1H, Jaa=12.55Hz, Jab=4.02Hz, H-10'), 3.10 (q, 2H, J=1.51Hz H-2). 13C-NMR (MeOD, 125MHz) – δ172.88 (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-dihydronicotinate 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 Figure 5).

A compound of formula (II), namely NRH (reduced nicotinamide riboside, shown in Figure 2; 50mg, 0.20mmol, 1eq), was dissolved in 5mL H_2O and then 1eq (i.e. 0.20mmol) of ammonium chloride was added in one portion. Activated charcoal (~10mg, i.e. 0.80mmol) was then added and the mixture stirred at RT for ~1hr and then filtered and freeze-dried to give the chloride salt of nicotinamide riboside, quantitatively, i.e. 100% conversion and pure product.
^{1}H-NMR (D_2O, 400MHz) - 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*=4.7Hz, H-2), 4.31-4.34 (m, 1H, H-4), 4.21 (t, 1H, *J*=4.7Hz, 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').

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 Figure 5).

The method described in Example 3(A) was carried out, except that 1eq (i.e. 0.20mmol) of ammonium acetate was added. The acetate salt of nicotinamide riboside was obtained, quantitatively.
^{1}H-NMR (D_2O, 400MHz) - 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*=4.7Hz, H-2), 4.32-4.35 (m, 1H, H-4), 4.21 (t, 1H, *J*=4.7Hz, 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 Figure 5).

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

^{1}H-NMR (D_2O, 400MHz) - 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*=4.7Hz, H-2), 4.31-4.34 (m, 1H, H-4), 4.21 (t, 1H, *J*=4.7Hz, 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 Figure 5).

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

^{1}H-NMR (D_2O, 400MHz) - δ 9.46 (s, 1H, aromatic), 9.12 (d, 1H, *J*=6.3Hz, 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*=4.7Hz, H-2), 4.31-4.34 (m, 1H, H-4), 4.20 (t, 1H, *J*=4.7Hz, 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}F-NMR (D_2O, 376MHz)- δ -75.7 (CF_3COO^-).

Example 3(E): Preparation of nicotinamide riboside, chloride salt (the β-anomer form of which is shown in Figure 5).

An alternative method to that described in Example 3(A) was carried out as follows. NRH (reduced nicotinamide riboside, shown in Figure 4; 50mg, 0.20mmol, 1eq) was dissolved in 5mL H_2O:EtOAc (1:1) and then 1eq. (i.e. 0.20mmol) 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 (~10mg, i.e. 0.8mmol) 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}H-NMR (D_2O, 400MHz) - 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*=4.7Hz, H-2), 4.31-4.34 (m, 1H, H-4), 4.21 (t, 1H, *J*=4.7Hz, 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 Figure 5).

The method described in Example 3(E) was carried out, except that NRH (reduced nicotinamide riboside, shown in Figure 4; 50mg, 0.20mmol, 1eq) was dissolved in 5mL H_2O:THF (1:1),

instead of H_2O:EtOAc (1:1), and then 1eq (i.e. 0.20mmol) 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 (~10mg, i.e. 0.8mmol) 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}H-NMR ($D_2$0, 400MHZ) - 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*=4.7Hz, H-2), 4.31-4.34 (m, 1H, H-4), 4.21 (t, 1H, *J*=4.7Hz, 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).

Methods of preparing nicotinamide riboside and derivatives thereof

Cross-reference to Related Applications

This application is a continuation of U.S. application 14/908,831, filed January 29, 2016 which is a U.S. National Stage under 35 U.S.C. 371 of PCT/EP14/065971, filed July 24, 2014. 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 p-anomer forms of nicotinamide riboside, nicotinate riboside, nicotinamide mononucleotide and nicotinate mononucleotide are shown, without counter ions, in Figure 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 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. Kirihata, *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.

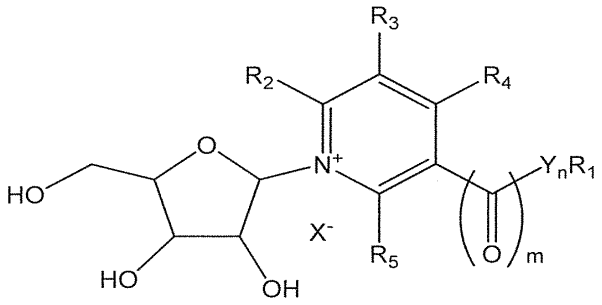
It is therefore an object of the invention to avoid or mitigate the disadvantages of the prior art.

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)



(I)

wherein

n is 0 or 1;

m is 0 or 1;

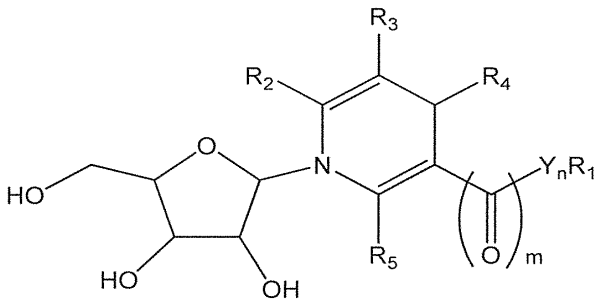
Y is O or S;

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)



(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).

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 $N^+HR^{I}R^{II}R^{III}$, 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.

Optionally, Z^+ is an unsubstituted ammonium of the formula NH_4^+.

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 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.

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 catalystare 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, 1,2-dichloroethane, 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 alkylarylamino), 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 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, R_1 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, R_1 is NH_2, R_2 – R_5 are each H, and X^- is selected from chloride, acetate, formate and trifluoroacetate.

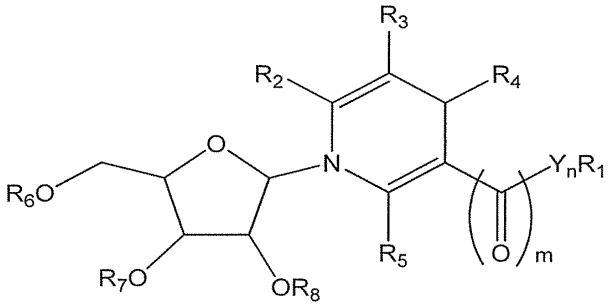
Optionally, in an embodiment of formula (II), n is 0, m is 1, R_1 is NH_2, and R_2 – R_5 are each H.

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 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 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 340nm.

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



(III)

wherein

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

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

with a deprotecting agent;

to form the compound of formula (II).

Suitable R_6, R_7 and R_8 moieties include, but are not limited to, ester-type protecting groups, ether-type protecting groups, and silyl-type protecting groups.

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

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

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

Optionally, the R_6, R_7 and R_8 moieties are selected from substituted and unsubstituted acetyl, and substituted and unsubstituted benzoyl.

Optionally, at least two of R_6, R_7 and R_8 are selected from unsubstituted acetyl or unsubstituted benzoyl.

Optionally the deprotecting agent is an acid or a base. Deprotection can also be achieved by catalytic hydrogenation (Pd/C; H_2) for the aromatic ether protecting groups and by fluoride-catalysed chemistry (e.f. TBAF in THF) for all the silyl ethers. Optionally, when R_6, R_7 and R_8 each comprise unsubstituted acetyl or unsubstituted benzoyl, the deprotecting agent is a base, optionally selected

from NH_3, Na_2CO_3 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, substituted or unsubstituted aliphatic or aromatic hydrocarbons, and combinations thereof, as defined above.

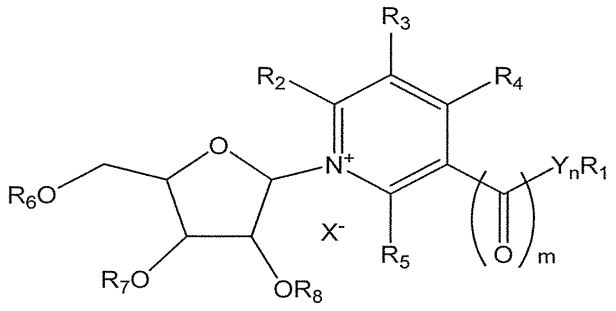
Optionally, the reactants are subjected to mechanical grinding, further optionally using a ball milling or planetary ball milling machine.

Optionally, in an embodiment of formula (III), n is 0, m is 1, R_1 is NH_2, R_2 – R_5 are each H, and R_6 – R_8 are each acetyl.

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

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

Optionally, 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 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 R_6, R_7 and R_8 comprise unsubstituted acetyl, the organic solvent is selected from dichloromethane, 1,2-dichloroethane, n-butyl acetate, chloroform and ethyl acetate, or a combination thereof, further optionally ethyl acetate.

Optionally, when at least two of R_6, R_7 and R_8 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 solution 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 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).

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

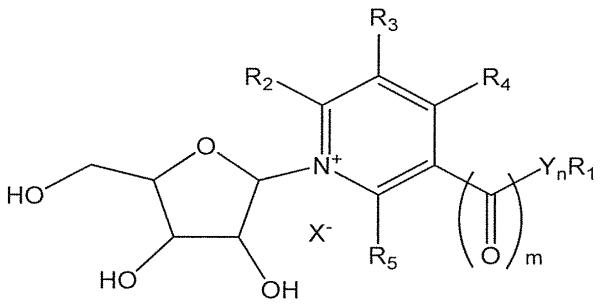
Optionally, in an embodiment of formula (IV), n is 0, m is 1, R_1 is NH_2, $R_2 – R_5$ are each H, $R_6 – R_8$ are each acetyl, and X^- is ^-OTf.

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)



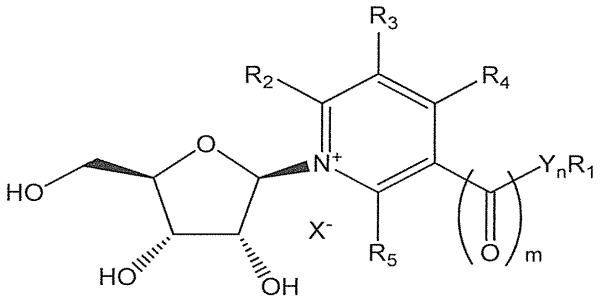
(I)

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,

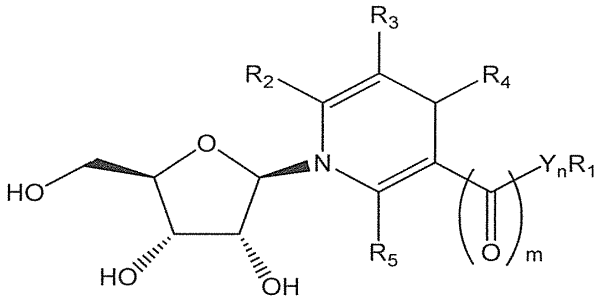


(IA)

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,

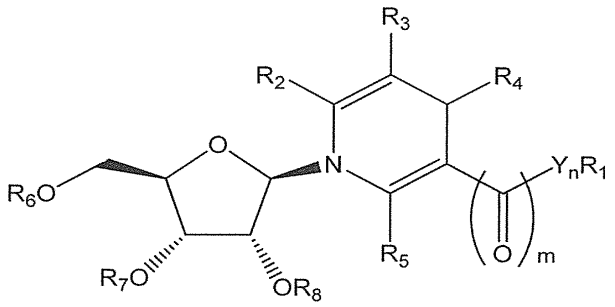


(IIA)

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,

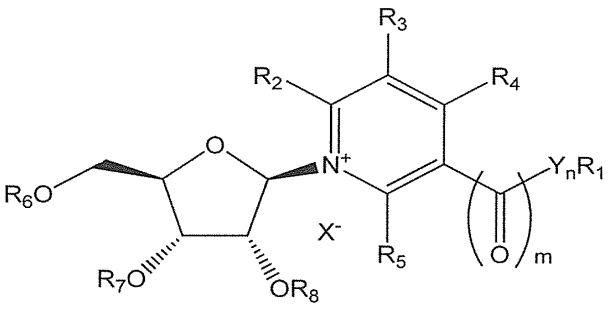


(IIIA)

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,



(IVA)

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.

(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 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 $P\text{-}H^+$ or a sulfonium cation containing SH^+, 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).

Brief Description of the Drawings

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

Figure 2 depicts Scheme A, which is a scheme illustrating, in general terms, that compounds of formula (IV) may be used to prepare compounds of formula (III), as described in Example 1; 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;

Figure 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-(beta-D-ribofuranosyl)-1,4-dihydronicotinamide, as described in Example 2, and that 1-(beta-D-ribofuranosyi)-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;

Figure 4 shows the (3-anomer forms of triacetyl-1,4-dihydronicotinamide riboside (Example 1(A)), triacetyl O-ethyl-1, 4-dihydronicotinate riboside, (Example 1(B)), tribenzoyl-1, 4-dihydronicotinamide riboside (Example 1(C)), and 1-(beta-D-ribofuranosyl)-1,4-dihydronicotinamide (Example 2); and

Figure 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)).

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

The Examples

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 B-anomer form of which is shown in Figure 4).

Reduction: All solvents were degassed prior to use by sonication and argon bubbling. Sodium dithionite (0.656g, 3.76 mmol, 2 eq) and sodium hydrogencarbonate (0.79g, 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 (1g, 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.
^{1}H-NMR (MeOD, 400MHz) - δ7.15 (s, 1H, H-5), 5.95 (d, 1H, J= 7.21 Hz, H-6), 5.25 (d, 1H, J=2.84Hz) & 5.17 (d, 1H, J=1.80Hz) (H-8 & H-7), 4.96 (d, 1H, J=7.09Hz, H-4), 4.87 (ABX, 1H, Jaa=8.18Hz, Jab=3.60Hz, H-9), 4.26 (d, 2H, J=3.20Hz, H-10 & H-10') 4.19 (m, 1H, J=3.00Hz, H-3), 3.13 (m, 2H, J=1.18Hz, H-2), 2.13 (s, 3H), 2.11 (s, 3H), 2.10 (s, 3H) (H-13, H-15, H-17). ^{13}C-NMR (MeOD,125MHz) - δ172.80 (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 (10g, 81.89 mmol, 1eq) was silylated using TMSCl (15.6 ml,122.85 mmol, 1.5 eq) in HMDS (100 ml) at 13Q°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.

^{1}H-NMR (MeOD, 400MHz) - 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, 3.9Hz, 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).

^{13}C-NMR (MeOD, 125MHz) - δ 172.1, 171.6, 171.2 (3x C=OCH_3), 164.9 (C=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).

^{19}F-NMR (MeOD, 376MHz) – δ -79.9 (triflate counterion)

Example 1(B): Preparation of reduced triacetyl nicotinate ester riboside, namely triacetyl O-ethyl-1, 4-dihydronicotinate riboside, a compound of formula (III) (the β-anomer form of which is shown in Figure 4).

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

^{1}H-NMR-δ 7.27 (1H, s, H-6), 6.05 (1H, dd, *J*= 8.2, 1.5Hz, H-7), 5.26 (1H, dd, *J*= 5.8, 2.8Hz, H-3), 5.23 (1H, dd, *J*= 6.9, 5.8Hz, H-2), 5.08 (1H, d, *J*= 6.9Hz, H-1), 4.91 (1H, dt, *J*= 8.3, 3.5Hz, H-8), 4.24-4.30 (3H, m, H-4, H-5, H-5'), 4.11 (2H, q, *J*= 7.2Hz, 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*= 7.2Hz, H-12).

^{13}C-NMR- δ 172.2, 171.5, 171.3, 169.8, (3x C=O-CH_3 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 (3x C=O-CH_3), 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 1eq tetraacetate riboside, 1eq TMSOTf, 1eq ethyl nicotinate, were reacted for 30mins in a 1.5 ml steel vessel with a 1.5cm 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.

^{1}H-NMR (D_2O, 400MHz) - 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=OC$\underline{H_2}$CH$_3$), 2.04 (s, 3H, OAc), 2.02 (s, 3H, OAc), 1.98 (s, 3H, OAc), 1.25 (t, 3H, *J*=7.0 Hz, C=OCH$_2$C$\underline{H_3}$).

^{19}F-NMR (D_2O, 376MHz) – 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 Figure 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, 10mL of H_2O was added to the solution and most of the methanol removed *via* rotary evaporation. The starting material crashed out of solution and 20mL of diethyl ether (Et_2O) was added until the solids solubilized into a biphasic system. A solution of $NaHCO_3$ (420mg, 5mmol, 5eq) and sodium dithionite (348mg, 2mmol, 2eq) in 10mL H_2O was added and stirred for 2hrs. The layers were separated and the ether layer was dried over $MgSO_4$ and concentrated to provide 428mg (76% yield) of tribenzoyl-1, 4-dihydronicotinamide riboside (yellow solid) without further purification. 80% purity based on ^{1}H-NMR. Pure material is obtained by Biotage purification.

^{1}H-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, 1.5Hz, H-7), 5.68 (1H, dd, *J*= 6.2, 3.5Hz, H-3), 5.57 (1H, dd, *J*= 6.7, 6.2Hz, H-2), 5.29 (1H, d, *J*= 6.7Hz, 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 (3x $\underline{C}$=O-C$_6$H$_5$, $\underline{C}$=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 (3x 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 (-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 1eq 1-acetate-tribenzoate riboside, 1eq TMSOTf and 1eq TMS-nicotinamide, were reacted for 30mins in a 1.5 ml steel vessel with a 1.5cm diameter steel ball bearing in a Retsch MM400 mixer mill at 25 Hz. 1eq 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.

^{1}H-NMR (MeOD, 400MHz) - 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, 3.9Hz, 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, 376MHz) – δ -79.1 (triflate counterion)

Example 2

A compound of formula (II), namely NRH (reduced nicotinamide riboside, also known as 1-(beta-D-ribofuranosyl)-1,4-dihydronicotinamide (the β-anomer form of which is shown in Figure 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. 100mgs of (III) was dissolved in 0.5mL of MeOH containing 0.05g of NaOH. The compounds were reacted for 30mins in a 1.5 ml steel vessel with a 1.5cm diameter steel ball bearing in a Retsch MM400 mixer mill at 25 Hz.
1H-NMR (MeOD, 400MHz) – δ7.18 (s, 1H, H-5), 6.14 (d, 1H, J= 8.28Hz, H-6), 4.85 (m, 1H, H-3), 4.76 (d, 1H, J= 5.77Hz, H-4), 4.04 (m, 2H, H-7&H-8), 3.93 (m, 1H, J=2.76, H-9), 3.72 (ABX, 1H, Jaa=12.55Hz, Jab=3.51Hz, H-10), 3.65 (ABX, 1H, Jaa=12.55Hz, Jab=4.02Hz, H-10'), 3.10 (q, 2H, J=1.51Hz H-2). 13C-NMR (MeOD, 125MHz) – δ172.88 (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-dihydronicotinate 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 Figure 5).

A compound of formula (II), namely NRH (reduced nicotinamide riboside, shown in Figure 2; 50mg, 0.20mmol, 1eq), was dissolved in 5mL H_2O and then 1eq (i.e. 0.20mmol) of ammonium chloride was added in one portion. Activated charcoal (~10mg, i.e. 0.80mmol) was then added and the mixture stirred at RT for ~1hr and then filtered and freeze-dried to give the chloride salt of nicotinamide riboside, quantitatively, i.e. 100% conversion and pure product.
^{1}H-NMR (D_2O, 400MHz) - 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*=4.7Hz, H-2), 4.31-4.34 (m, 1H, H-4), 4.21 (t, 1H, *J*=4.7Hz, 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').

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 Figure 5).

The method described in Example 3(A) was carried out, except that 1eq (i.e. 0.20mmol) of ammonium acetate was added. The acetate salt of nicotinamide riboside was obtained, quantitatively.
^{1}H-NMR (D_2O, 400MHz) - 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*=4.7Hz, H-2), 4.32-4.35 (m, 1H, H-4), 4.21 (t, 1H, *J*=4.7Hz, 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 Figure 5).

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

^{1}H-NMR (D_2O, 400MHz) - 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*=4.7Hz, H-2), 4.31-4.34 (m, 1H, H-4), 4.21 (t, 1H, *J*=4.7Hz, 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 Figure 5).

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

^{1}H-NMR (D_2O, 400MHz) - δ 9.46 (s, 1H, aromatic), 9.12 (d, 1H, *J*=6.3Hz, 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*=4.7Hz, H-2), 4.31-4.34 (m, 1H, H-4), 4.20 (t, 1H, *J*=4.7Hz, 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}F-NMR (D_2O, 376MHz)- δ -75.7 (CF_3COO^-).

Example 3(E): Preparation of nicotinamide riboside, chloride salt (the β-anomer form of which is shown in Figure 5).

An alternative method to that described in Example 3(A) was carried out as follows. NRH (reduced nicotinamide riboside, shown in Figure 4; 50mg, 0.20mmol, 1eq) was dissolved in 5mL H_2O:EtOAc (1:1) and then 1eq. (i.e. 0.20mmol) 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 (~10mg, i.e. 0.8mmol) 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}H-NMR (D_2O, 400MHz) - 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*=4.7Hz, H-2), 4.31-4.34 (m, 1H, H-4), 4.21 (t, 1H, *J*=4.7Hz, 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 Figure 5).

The method described in Example 3(E) was carried out, except that NRH (reduced nicotinamide riboside, shown in Figure 4; 50mg, 0.20mmol, 1eq) was dissolved in 5mL H_2O:THF (1:1),

instead of H_2O:EtOAc (1:1), and then 1eq (i.e. 0.20mmol) 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 (~10mg, i.e. 0.8mmol) 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}H-NMR (D_20, 400MHZ) - 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*=4.7Hz, H-2), 4.31-4.34 (m, 1H, H-4), 4.21 (t, 1H, *J*=4.7Hz, 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).

Electronic Acknowledgement Receipt	
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Application Number:	15905922
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Confirmation Number:	1061
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Application No.	:	15/905,922 Confirmation No. 1061
Filing Date	:	February 27, 2018
Applicant	:	The Queen's University of Belfast
First Named Inventor:	:	Marie MIGAUD
For	:	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof
Group Art Unit	:	1623
Examiner	:	Patrick T. Lewis
Docket No.	:	335040: 4-16A US
Customer No.	:	23713

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1. **This Certificate of EFS-WEB Filing – 1 page**
2. **Response to Notice to File Corrected Application Papers – 3 pages**
3. **Substitute Specification-Clean Copy – 23 pages**
4. **Substitute Specification-Marked-Up Copy – 23 pages**

are being submitted electronically through the United States Patent Office EFS-WEB System, to be directed to:

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

On **August 21, 2020**

Cathy Nelson
(Person Filing Correspondence)

/cathynelson/
(Signature of Person Filing Correspondence)

REMARKS

In response to the Notice to File Corrected Application Papers of July 31, 2020, a substitute specification is submitted. Text on page 23 of the specification was inadvertently omitted. A marked-up copy of the specification showing the added text on page 23 is submitted herewith.

The present application is a continuation of U.S. application 14/908,831, filed January 29, 2016 which is a U.S. National Stage under 35 U.S.C. 371 of PCT/EP14/065971, filed July 24, 2014. Both of these applications are incorporated by reference herein. The text on page 23 that was inadvertently omitted on filing of this application is found on page 23 of the listed applications and is matter that was intended to be incorporated by reference in this application as filed.

No new matter has been added with the substitute specification submitted herewith.

It is believed that no fees are due with this submission. If this is incorrect, or if other fees are due for timely submission, the undersigned authorizes the Office to charge any required fees, and credit any overpayment, to deposit account no. 12-1216.

Respectfully submitted,
/sallyasullivan/
Sally A. Sullivan
Reg. No. 32,064

LEYDIG, VOIT & MAYER, Ltd.
4940 Pearl East Circle, Suite 200
Boulder, CO 80301
Telephone: (720) 795-7976
Facsimile: (312) 616-5700
Email: chgpatent@leydig.com

Amendments to the Specification:

Please replace the original specification as filed with the attached substitute specification. A marked-up copy of the specification is included showing changes. A clean copy of the specification is also submitted. The last page of the specification, page 23, was inadvertently omitted in the specification as filed. The substitute specification includes missing page 23. No new matter is added.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/905,922	02/27/2018	Marie MIGAUD	335040: 4-16A US	1061

23713 7590 07/31/2020

Leydig, Voit & Mayer, Ltd. (GS BOULDER)
4940 Pearl East Circle
Suite 200
Boulder, CO 80301

EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
07/31/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

chgpatent@leydig.com

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Application No. : 15905922
Applicant : Migaud
Filing Date : 02/27/2018
Date Mailed : 07/31/2020

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Notice of Allowance Mailed

This application has been accorded an Allowance Date and is being prepared for issuance. The application, however, is incomplete for the reasons below.

Applicant is given two (2) months from the mail date of this Notice within which to respond. This time period for reply is extendable under 37 CFR 1.136(a) for only TWO additional MONTHS.

The informalities requiring correction are indicated in the attachment(s). If the informality pertains to the abstract, specification (including claims) or drawings, the informality must be corrected with an amendment in compliance with 37 CFR 1.121 (or, if the application is a reissue application, 37 CFR 1.173). Such an amendment may be filed after payment of the issue fee if limited to correction of informalities noted herein. See Waiver of 37 CFR 1.312 for Documents Required by the Office of Patent Publication, 1280 Off. Gaz. Patent Office 918 (March 23, 2004). In addition, if the informality is not corrected until after payment of the issue fee, for purposes of 35 U.S.C. 154(b)(1)(iv), "all outstanding requirements" will be considered to have been satisfied when the informality has been corrected. A failure to respond within the above-identified time period will result in the application being ABANDONED.

See attachment(s).

A copy of this notice MUST be returned with the reply. Please address response to "Mail Stop Issue Fee, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450".

/Joanna Black/
Publication Branch
Office of Data Management
(571) 272-4200

Application No. 15905922

IDENTIFICATION OF APPLICATION DEFICIENCIES
IN APPLICATION FILED ON OR AFTER SEPTEMBER 16, 2012

☐ Applicant must provide legible text for the following item(s).

- ☐ Specification filed , page(s) .
- ☐ Claims filed , claim(s) .
- ☐ Other: .

☒ Applicant must provide missing information on the following page(s) of the specification by amending the specification to add the missing text. No new matter may be added.
Page/line no(s). End of page 22 appears to be missing data

☐ The specification refers to one or more applications by attorney docket number and does not show the U.S. application number(s). Applicant must supply the U.S. application number in place of each attorney docket number.
Page/line no(s).

☐ Applicant must provide an Abstract of the Disclosure.

☐ The Application Data Sheet (ADS dated) does not supply the inventor's city and/or does not supply the inventor's U.S. state and/or does not supply the inventor's country. Applicant must submit a signed, in accordance with 37 CFR 1.76(e) and 1.33(b), application data sheet that corrects this deficiency. To be in compliance with 37 CFR 1.76, the corrected application data sheet must identify the information being changed by using underlining for additions and strikethroughs or brackets for deletions.

☐ Other:

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www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

23713 7590 06/12/2020

Leydig, Voit & Mayer, Ltd. (GS BOULDER)
4940 Pearl East Circle
Suite 200
Boulder, CO 80301

EXAMINER	
LEWIS, PATRICK T	
ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 06/12/2020

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/905,922	02/27/2018	Marie MIGAUD	335040: 4-16A US	1061

TITLE OF INVENTION: Methods of Preparing Nicotinamide Riboside and Derivatives Thereof

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$500	$0.00	$0.00	$500	09/14/2020

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23713 7590 06/12/2020
Leydig, Voit & Mayer, Ltd. (GS BOULDER)
4940 Pearl East Circle
Suite 200
Boulder, CO 80301

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/905,922	02/27/2018	Marie MIGAUD	335040: 4-16A US	1061

TITLE OF INVENTION: Methods of Preparing Nicotinamide Riboside and Derivatives Thereof

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$500	$0.00	$0.00	$500	09/14/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
LEWIS, PATRICK T	1623	536-028100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1_____
2_____
3_____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required) ❑Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

IPR2026-00400
Exhibit 2008 Page 113

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/905,922	02/27/2018	Marie MIGAUD	335040: 4-16A US	1061

23713 7590 06/12/2020

Leydig, Voit & Mayer, Ltd. (GS BOULDER)
4940 Pearl East Circle
Suite 200
Boulder, CO 80301

EXAMINER	
LEWIS, PATRICK T	
ART UNIT	**PAPER NUMBER**
1623	

DATE MAILED: 06/12/2020

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 02/11)

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 15/905,922	Applicant(s) MIGAUD et al.	
	Examiner PATRICK T LEWIS	Art Unit 1623	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to Amendment dated May 27, 2020.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☑ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☑ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☑ Certified copies of the priority documents have been received in Application No. 14/908,831 .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☑ Other PTO-2323.

/PATRICK T LEWIS/
Primary Examiner, Art Unit 1623

Continuation of 3. The allowed claim(s) is/are: 1-2,4-10,12,14 and 18-26

AFCP 2.0 Decision	Application No.	Applicant(s)	
	15/905,922	MIGAUD et al.	
	Examiner	Art Unit	AIA (FITF) Status
	PATRICK T LEWIS	1623	Yes

This is in response to the After Final Consideration Pilot request filed 27 May 2020.

1. **Improper Request** – The AFCP 2.0 request is improper for the following reason(s) and the after final amendment submitted with the request will be treated under pre-pilot procedure.

   ☐ An AFCP 2.0 request form PTO/SB/434 (or equivalent document) was not submitted.

   ☐ A non-broadening amendment to at least one independent claim was not submitted.

   ☐ The request is not the first proper AFCP 2.0 request submitted in response to the most recent final rejection.

   ☐ Other: _____

2. **Proper Request**

   A. After final amendment submitted with the request will not be treated under AFCP 2.0.
   The after final amendment cannot be reviewed and a search conducted within the guidelines of the pilot program.

   ☐ The after final amendment will be treated under pre-pilot procedure.

   B. Updated search and/or completed additional consideration.
   The examiner performed an updated search and/or completed additional consideration of the after final amendment within the time authorized for the pilot program. The result(s) of the updated search and/or completed additional consideration are:

   ☑ 1. All of the rejections in the most recent final Office action are overcome and a Notice of Allowance is issued herewith.

   ☐ 2. The after final amendment would not overcome all of the rejections in the most recent final Office action . See attached interview summary for further details.

   ☐ 3. The after final amendment was reviewed, and it raises a new issue(s). See attached interview summary for further details.

   ☐ 4. The after final amendment raises new issues, but would overcome all of the rejections in the most recent final Office action. A decision on determining allowability could not be made within the guidelines of the pilot. See attached interview summary for further details, including any newly discovered prior art.

   ☐ 5. Other: _____

   Examiner Note: Please attach an interview summary when necessary as described above.

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/905,922	MIGAUD et al.
	Examiner	**Art Unit**
	PATRICK T LEWIS	1623

CPC								
Symbol							**Type**	**Version**
C07H	/	19	/	048			F	2013-01-01
C07H	/	1	/	00			I	2013-01-01
C07H	/	1	/	06			I	2013-01-01
C07H	/	19	/	04			A	2013-01-01
Y02P	/	20	/	582			A	2015-11-01

CPC Combination Sets								
Symbol							**Type**	**Set**	**Ranking**	**Version**
	/		/							

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	20	
/PATRICK T LEWIS/ Primary Examiner, Art Unit 1623	08 June 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20200608

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/905,922	MIGAUD et al.
	Examiner	**Art Unit**
	PATRICK T LEWIS	1623

INTERNATIONAL CLASSIFICATION					
CLAIMED					
C07H	/	19	/	00	
C07H	/	19	/	048	

NON-CLAIMED					
	/		/		

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**
536	28.1

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					
536	25.3					
514	43					

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	20	
/PATRICK T LEWIS/ Primary Examiner, Art Unit 1623	08 June 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20200608

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/905,922	MIGAUD et al.
	Examiner	**Art Unit**
	PATRICK T LEWIS	1623

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		10		19										
	2		11		20										
	3		12		21										
	4		13		22										
	5		14		23										
	6		15		24										
	7		16		25										
	8		17		26										
	9		18												

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	20	
/PATRICK T LEWIS/ Primary Examiner, Art Unit 1623	08 June 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20200608

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/905,922	MIGAUD et al.
	Examiner	Art Unit
	PATRICK T LEWIS	1623

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Inventor, REGISTRY, CAPLUS, MEDLINE (see attached)	04/24/2019	/PL/
Inventor, REGISTRY, CAPLUS, MEDLINE (see attached)	01/24/2020	/PL/
Inventor, Updated REGISTRY, CAPLUS, MEDLINE searches	06/08/2020	/PL/

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
536	25.3, 28.1	06/08/2020	/PL/
514	43	06/08/2020	/PL/
C07H	19/04, 19/048, 1/00, 1/06	06/08/2020	/PL/
Y02P	20/582	06/08/2020	/PL/

/PATRICK T LEWIS/ Primary Examiner, Art Unit 1623	

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/905,922	MIGAUD et al.
	Examiner	Art Unit
	PATRICK T LEWIS	1623

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	04/24/2019	01/24/2020	06/08/2020						
	1	✓	✓	=						
	2	✓	✓	=						
	3	✓	✓	-						
	4	✓	✓	=						
	5	✓	✓	=						
	6	✓	✓	=						
	7	✓	✓	=						
	8	✓	✓	=						
	9	✓	✓	=						
	10	✓	✓	=						
	11	✓	✓	-						
	12	✓	✓	=						
	13	✓	✓	-						
	14	✓	✓	=						
	15	✓	-	-						
	16	✓	✓	-						
	17	✓	✓	-						
	18	✓	✓	=						
	19	✓	✓	=						
	20		✓	=						
	21		✓	=						
	21			=						
	22			=						
	23			=						
	24			=						
	25			=						
	26			=						

WEST Search History

Hide Items | Restore | Clear | Close

DATE: Monday, June 08, 2020

Hide?	Set Name	Query	Hit Count
Interference			
DB=PGPB,USPT; PLUR=YES; OP=ADJ			
☐	L10	L8 and (acetyl or benzoyl)	46
☐	L9	L8 and silyl	14
☐	L8	L7 and salt	66
☐	L7	L5 and (protecting group or protect or protection)	69
☐	L6	L5 and hydroxyl protecting group	7
☐	L5	L4 and reduced	82
☐	L4	L3 and nicotinamide riboside	95
☐	L3	L2 and nicotinamide	390
☐	L2	L1 SPACE~or ((C07H1/00 | C07H19/048 | C07H1/06 | C07H19/04 | Y02P20/582).CPC.)	17036
☐	L1	(514/43 or 536/28.1 or 536/25.3)![CCLS]	4696

END OF SEARCH HISTORY

IPR2026-00400
Exhibit 2008 Page 124

OK TO ENTER: /P.T.L/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

US Application No.	: 15/905,922	Confirmation No. 1061
Date of Filing	: February 27, 2018	
Applicant	: The Queen's University of Belfast	
Inventors	: Marie MIGAUD, et al.	
For	: Methods of Preparing Nicotinamide Riboside and Derivatives Thereof	
Art Unit	: 1623	
Examiner	: Patrick T. Lewis	
Docket No.	: 335040: 4-16A US	
Customer No.	: 23713	

CERTIFICATE OF EFS-WEB FILING
I hereby certify that this correspondence is being filed with the USPTO EFS-WEB system.
May 27, 2020 (Date) /sallyasullivan/ (Sally A. Sullivan)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO FINAL OFFICE ACTION

Sir:

Please enter the following response to the Final Office Action mailed January 30, 2020. Applicant Requests After Final Consideration of the Amendment Presented herein. This response is accompanied by a Petition for Extension of Time of One Month with appropriate fees.

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 8 of this paper.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 1061

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
15/905,922	02/27/2018	536	1623	335040: 4-16A US

APPLICANTS
The Queen's University of Belfast, Belfast Antrim, UNITED KINGDOM;

INVENTORS
Marie MIGAUD, Lurgan, UNITED KINGDOM;
Philip REDPATH, Portadown, UNITED KINGDOM;
Kerri CROSSEY, Magherafelt, UNITED KINGDOM;
Mark DOHERTY, Newtownabbey, UNITED KINGDOM;

**** CONTINUING DATA **************************
This application is a CON of 14/908,831 01/29/2016 PAT 10000519
which is a 371 of PCT/EP2014/065971 07/24/2014

**** FOREIGN APPLICATIONS **************************
UNITED KINGDOM 1313465.5 07/29/2013

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
03/22/2018

Foreign Priority claimed ☑ Yes ☐ No 35 USC 119(a-d) conditions met ☑ Yes ☐ No Verified and Acknowledged /PATRICK T LEWIS/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		UNITED KINGDOM	5	19	3

ADDRESS

Leydig, Voit & Mayer, Ltd. (GS BOULDER)
4940 Pearl East Circle
Suite 200
Boulder, CO 80301
UNITED STATES

TITLE

Methods of Preparing Nicotinamide Riboside and Derivatives Thereof

FILING FEE RECEIVED		
785	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

BIB (Rev. 05/07).

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

US Application No.	: 15/905,922	Confirmation No. 1061
Date of Filing	: February 27, 2018	
Applicant	: The Queen's University of Belfast	
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Examiner	: Patrick T. Lewis	
Docket No.	: 335040: 4-16A US	
Customer No.	: 23713	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF EFS-WEB FILING
I hereby certify that this correspondence is being filed with the USPTO EFS-WEB system.
May 27, 2020 (Date) /sallyasullivan/ (Sally A. Sullivan)

AMENDMENT AND RESPONSE TO FINAL OFFICE ACTION

Sir:

Please enter the following response to the Final Office Action mailed January 30, 2020. Applicant Requests After Final Consideration of the Amendment Presented herein. This response is accompanied by a Petition for Extension of Time of One Month with appropriate fees.

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 8 of this paper.

Doc Code: A.NE.AFCP
Document Description: After Final Consideration Pilot Program Request

PTO/SB/434 (05-13)

CERTIFICATION AND REQUEST FOR CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0

Practitioner Docket No.:	Application No.:	Filing Date:
335040: 4-16A US	15/905,922	February 27, 2018
First Named Inventor:	**Title:**	
Marie MIGAUD	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof	

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0 (AFCP 2.0) OF THE ACCOMPANYING RESPONSE UNDER 37 CFR 1.116.

1. The above-identified application is (i) an original utility, plant, or design nonprovisional application filed under 35 U.S.C. 111(a) [a continuing application (*e.g.*, a continuation or divisional application) is filed under 35 U.S.C. 111(a) and is eligible under (i)], or (ii) an international application that has entered the national stage in compliance with 35 U.S.C. 371(c).
2. The above-identified application contains an outstanding final rejection.
3. Submitted herewith is a response under 37 CFR 1.116 to the outstanding final rejection. The response includes an amendment to at least one independent claim, and the amendment does not broaden the scope of the independent claim in any aspect.
4. This certification and request for consideration under AFCP 2.0 is the only AFCP 2.0 certification and request filed in response to the outstanding final rejection.
5. Applicant is willing and available to participate in any interview requested by the examiner concerning the present response.
6. This certification and request is being filed electronically using the Office's electronic filing system (EFS-Web).
7. Any fees that would be necessary consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, extension of time fees, are being concurrently filed herewith. [There is no additional fee required to request consideration under AFCP 2.0.]
8. By filing this certification and request, applicant acknowledges the following:

- Reissue applications and reexamination proceedings are not eligible to participate in AFCP 2.0.
- The examiner will verify that the AFCP 2.0 submission is compliant, *i.e.*, that the requirements of the program have been met (see items 1 to 7 above). For compliant submissions:
  - The examiner will review the response under 37 CFR 1.116 to determine if additional search and/or consideration (i) is necessitated by the amendment and (ii) could be completed within the time allotted under AFCP 2.0. If additional search and/or consideration is required but cannot be completed within the allotted time, the examiner will process the submission consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, by mailing an advisory action.
  - If the examiner determines that the amendment does not necessitate additional search and/or consideration, or if the examiner determines that additional search and/or consideration is required and could be completed within the allotted time, then the examiner will consider whether the amendment places the application in condition for allowance (after completing the additional search and/or consideration, if required). If the examiner determines that the amendment does not place the application in condition for allowance, then the examiner will contact the applicant and request an interview.
    - The interview will be conducted by the examiner, and if the examiner does not have negotiation authority, a primary examiner and/or supervisory patent examiner will also participate.
    - If the applicant declines the interview, or if the interview cannot be scheduled within ten (10) calendar days from the date that the examiner first contacts the applicant, then the examiner will proceed consistent with current practice concerning responses after final rejection under 37 CFR 1.116.

Signature	Date
/sallyasullivan/	May 27, 2020
Name (Print/Typed) Sally A. Sullivan	**Practitioner Registration No.** 32064

***Note**: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.*

☐ * Total of _____ forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	15/905,922 Confirmation No. 1061
Filing Date	:	February 27, 2018
Applicant	:	The Queen's University of Belfast
First Named Inventor:	:	Marie MIGAUD
For	:	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof
Group Art Unit	:	1623
Examiner	:	Patrick T. Lewis
Docket No.	:	335040: 4-16A US
Customer No.	:	23713

CERTIFICATE OF EFS-WEB FILING

I hereby certify that this correspondence is being filed with the USPTO EFS-WEB system.

May 27, 2020 (Date) /sallyasullivan/ Sally A. Sullivan

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION FOR EXTENSION OF TIME UNDER 37 C.F.R. §1.136(a)

Sir,

Applicant hereby petitions for the minimum extension of time necessary so that the accompanying Amendment and Response to Final Office Action is timely filed.

It is believed that an extension of one month is required. Although payment may be effected via the EFS-Web system, authorization is hereby given, if necessary, to charge Deposit Account 121216 in the amount of $100 (small entity status) for the extension of time fee for a small entity. If this amount is incorrect, or if necessary, please charge any required fees and credit any overpayments accordingly.

Respectfully submitted,

/sallyasullivan/

Sally A. Sullivan
Reg. No. 32,064

LEYDIG, VOIT & MAYER, Ltd.
4940 Pearl East Circle, Suite 200
Boulder, CO 80301
Telephone: (720) 795-7976
Facsimile: (312) 616-5700
Email: chgpatent@leydig.com

CERTIFICATE OF EFS-WEB FILING

Application No.	:	15/905,922 Confirmation No. 1061
Filing Date	:	February 27, 2018
Applicant	:	The Queen's University of Belfast
First Named Inventor:	:	Marie MIGAUD
For	:	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof
Group Art Unit	:	1623
Examiner	:	Patrick T. Lewis
Docket No.	:	335040: 4-16A US
Customer No.	:	23713

I hereby certify that the following, along with any other document(s) referenced to as being attached or enclosed:

1. **This Certificate of EFS-WEB Filing – 1 page**
2. **Amendment and Response to Office Action – 13 pages**
3. **Petition for Extension of Time – 1 page**
4. **Certification And Request For Consideration Under The After Final Consideration Pilot Program 2.0 – 2 pages**

are being submitted electronically through the United States Patent Office EFS-WEB System, to be directed to:

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

On **May 27, 2020**

Sally A. Sullivan
(Person Filing Correspondence)

/sallyasullivan/
(Signature of Person Filing Correspondence)

Electronic Patent Application Fee Transmittal					
Application Number:	15905922				
Filing Date:	27-Feb-2018				
Title of Invention:	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof				
First Named Inventor/Applicant Name:	Marie MIGAUD				
Filer:	Sally A. Sullivan				
Attorney Docket Number:	335040: 4-16A US				
Filed as Small Entity					
Filing Fees for Utility under 35 USC 111(a)					
Description		**Fee Code**	**Quantity**	**Amount**	**Sub-Total in USD($)**
Basic Filing:					
Pages:					
Claims:					
Miscellaneous-Filing:					
Petition:					
Patent-Appeals-and-Interference:					
Post-Allowance-and-Post-Issuance:					
Extension-of-Time:					

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 1 month with $0 paid	2251	1	100	100
Miscellaneous:				
		Total in USD ($)		**100**

Electronic Acknowledgement Receipt	
EFS ID:	39554730
Application Number:	15905922
International Application Number:	
Confirmation Number:	1061
Title of Invention:	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof
First Named Inventor/Applicant Name:	Marie MIGAUD
Customer Number:	23713
Filer:	Sally A. Sullivan
Filer Authorized By:	
Attorney Docket Number:	335040: 4-16A US
Receipt Date:	27-MAY-2020
Filing Date:	27-FEB-2018
Time Stamp:	18:12:54
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$100
RAM confirmation Number	E20205QI13185087
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		4-16A_US_RFOA_of_1-30-20_final_as_filed.pdf	289210 f035e3a1fd51caebb15f6c27691171091861cd0a	yes	13
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Applicant Arguments/Remarks Made in an Amendment		8	13	
	Claims		2	7	
	Response After Final Action		1	1	
Warnings:					
Information:					
2	After Final Consideration Program Request	4-16A_US_REG_CERT_AFTER_FINAL_PILOT_PROGRAM_5_27_2020.pdf	226145 453ec2c405b2cbd3821fe6962575eccf84f12052	no	2
Warnings:					
Information:					
3	Extension of Time	4-16A_US_extension_5_27_2020.pdf	69842 5276ad2a319162158c794091fa6305de26cc2571	no	1
Warnings:					
Information:					
4	Miscellaneous Incoming Letter	4-16A_US_efsCert_RFOA_5_27_2020.pdf	68890 632d480ba37c19dae20723dde8145229050ee354	no	1
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	30707 ae2a027d4aeaedf32d1b1832fb3a830831c73fe9	no	2

Warnings:	
Information:	
Total Files Size (in bytes):	684794

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

REMARKS

Claims 1-14 and 16-21 are pending in this application. This amendment cancels claims 3, 11, 13, 16 and 17 without prejudiced to the subject matter therein and adds new claims 22-26. Applicant has cancelled 5 claims and added 5 new claims. On entrance of this amendment, claims 1, 2, 4-10, 12, 14, and 18-26 will be pending in this application.

Applicant respectfully requests entrance of this amendment after final because it is believed to place all of the remaining claims in condition for allowance. Applicant believes that no new issues are raised with the amendments presented. New claims 22-26 are all dependent claims. The claims from which new claims 22-26 depend are believed to be in condition for allowance on entrance of this amendment.

Request for After Final Consideration

A certification and request for consideration under the after final consideration pilot program 2.0 is submitted herewith.

Telephone Interview with Examiner

The undersigned attorney thanks Examine Lewis for the courtesy of a telephone interview on May 15, 2020 to discuss this amendment and response. Each claim amendment and each rejection were discussed. From this discussion, the undersigned attorney understood that the amendments presented would be entered and would place the claims in condition for allowance. The undersigned had indicated to the Examiner that clams 3, 11, 13, 16 and 17 would be cancelled without prejudice.

Amendments to the Claims

Claims 3, 11, 13, 16 and 17 are cancelled without prejudice.

Claim 1 is amended to delete the phrase “optionally wherein the hydroxyl protecting group is substituted or unsubstituted acetyl, or substituted or unsubstituted benzoyl” in

the definition of R_6-R_8, which is believed to be redundant and which was objected to. This amendment is made to improve clarity.

Claim 1 is further amended to recite "further provided that when n is 1, m is 1, Y is O, R_1 is methyl, R_3 and R_4 are methyl, and R_2 and R_5 are each H, then R_6, R_7, and R_8 are not all simultaneously H or unsubstituted acetyl." Support for this amendment is found in the instant published application US 2018-0186824 at paragraphs [0010-0014, 0016, 0055 and 0077-0078].

Claim 1 is also amended to replace "R_1 is unsubstituted alkyl wherein alkyl is methyl," with the simplified phrase "R_1 is methyl." This amendment is believed to improve clarity.

Claim 12 is amended to depend from claim 1, in view of the cancellation of claim 11.

Claim 14 is amended to depend from claim 1.

Claim 18 is amended to include the recitations of claim 16 (as previously amended) and claim 17 and written in independent form. Claims 16 and 17 are now cancelled without prejudice. The recitation from claim 17 that "R_2 – R_5 are each H," and the recitation from claim 18 that "m is 1, n is 1, and Y is O," are both incorporated in the definitions in the body of the claim.

Claim 19 is amended to replace the formula therein to include the counterion X^- and to recite specific counterions. Support for this amendment is found in the instant published application US 2018-0186824 at paragraphs [0028-0036, and 0088-0089].

New claims 22-26 are added which depend variously from claims 12, 18 or 19. These new claims are fully supported in the alternatives of the claims as filed.

No new matter has been added.

Claim Rejections under Section 112

1. Claims 1, 16-18, and 20-21 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

Applicant notes that claims 16 and 17 have been cancelled without prejudice.

The rejection objects to the phrase "optionally wherein the hydroxyl protecting group is substituted or unsubstituted acetyl, or substituted or unsubstituted benzoyl" in the definition of R_6-R_8. This phrase has been deleted from claims 1, which is believed to obviate the rejection. This phrase has not been added or retained in any claim.

2. Claim 3 is rejected under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4th, paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends. Claim 3 is cancelled obviating the rejection.

All of the rejections under Section 112 should be withdrawn.

Claim Rejections under Section 102

1. Claims 1-2, 4-7 and 9-12 were rejected as anticipated by Tietze et al. The claims had previously been amended so that the claims would clearly not read on the compounds described in Tietze as **8Bg** and **9Bg.** The Office Action now refers to compounds **8Bf** and **9Bf** in Tietze.

Claim 1 has now been amended to recite "further provided that when n is 1, m is 1, Y is O, R_1 is methyl, R_3 and R_4 are methyl, and R_2 and R_5 are each H, then R_6, R_7, and R_8 are not all simultaneously H or unsubstituted acetyl." The claims as now amended clearly do not read on compounds **8Bf** and **9Bf** in Tietze. The amendment obviates the rejection.

New claim 22 depends ultimately from claim 1 and should be considered allowable.

2. Claim 19 is rejected under 35 U.S.C. 102(a)(1) as being anticipated by Franchetti et al. Bioorganic & Medicinal Chemistry Letters (2004), Vol. 14, pages 4655-4658.

Claim 19 has been amended to include recitation of counterions X^-. The counterions recited in claim 19 as amended do not include trifluoromethylsulfonate. Franchetti teaches TMSOTf-mediated glycosylation and that the species TMSOTf, with the trifluoromethylsulfonate anion, is critical to success of the synthesis. Franchetti does not teach or suggest any counterion as is now claimed in claim 19. The amendment obviates the rejection.

New claims 25 and 26 depend from claim 19 and should be considered allowable.

3. Claim(s) 16-17 are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Jarman et al. J. Chem. Soc. (C), 1969, pages 199-203 (Jarman). Claims 16 and 17 have been cancelled without prejudice obviating this rejection.

All of the rejections under Section 102 should be withdrawn.

Claim Rejections under Section 103

Claims 8 and 13 are rejected as unpatentable over Yatvin et al. ("Yatvin") in view of Orain et al. ("Orian", J. Combin. Chem. (2002) vol. 4, 1-16) and Takatani et al. ("Takatani", Carbohyd. Res. (2003) vol. 338, 1073-1081).

Claim 13 is cancelled without prejudice obviating the rejection with respect to this claim.

Claim 8 is amended to recite the proviso "that when n is 0 and m is 1, R_1 is not NH_2." Claim 8 as amended does not read on a compound where the group $-(CO)_mY_n-R_1$ is

–CO-NH_2. Yatvin does not teach or suggest any compound as now claimed in amended claim 8. Further, the combination of references does not teach or suggest the compounds of claim 8 as amended. The amendment of claim 8 obviates this rejection.

The rejection under Section 103 should be withdrawn.

Claims Not Rejected Over the Prior Art of Record

Applicant notes that claims 14, 18, 20 and 21 were not rejected over the prior art cited in the rejections herein and are thus believed to be free of this prior art and allowable over this prior art.

Claim 14 now depends from claim 1 and in view of the amendment of claim 1 should now be allowable.

Claim 18 has been rewritten in independent form including the recitations in previously pending claims 16 and 17. The phrase objected to in the 112, second paragraph rejection has not been retained in claim 18. Claim 18 should now be allowable. New claims 23 and 24 depend from claim 18 and should now be considered allowable.

Claims 20 and 21 were rejected under Section 112, second paragraph. These claims depend from claim 1 as amended and should now be considered allowable.

New Claims 22-29

New claims 22-26 depend variously from claims 12, 18 or 19. For the reasons given above, each of claims 12, 16 and 19 should now be allowable and in turn new dependent claims 22-26 should also be allowable.

Nonstatutory Double Patenting

Claims 1-14 and 16-21 are rejected on the ground of nonstatutory double patenting over claims 1-29 of U.S. Patent 10,000,519 B2.

The present application is commonly owned and has inventors in common with U.S. Patent 10,000, 519 B2. The filing of a terminal disclaimer will overcome this rejection.

Applicant has submitted an electronic Terminal Disclaimer with appropriate fee by EFS-Web submission concurrent with the filing of this response. This submission is believed to obviate this rejection.

Conclusion

All pending claims appearing to be in condition for allowance, passage to issuance is respectfully requested. This response is accompanied by an Extension of Time of one Month with appropriate fee. No additional fees are believe to be due. If the amount paid by EFS web is not correct, please deduct any fees required for timely submission, or credit any overpayment, to deposit account 121216.

Respectfully submitted

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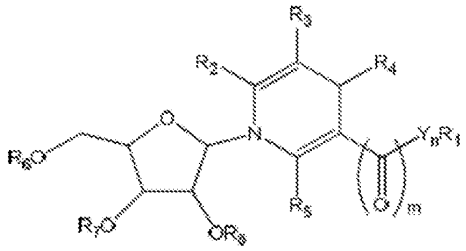
/sallyasullivan/
Sally A. Sullivan
Reg. No.: 32064

Claim Amendments

This listing of the claims replaces all previous such listings:

Listing of the Claims

1. (Currently amended) A compound of formula (III)



(III)

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

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

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

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

2. (Original) A compound of claim 1, wherein R_6, R_7 and R_8 are each H.

3. (Cancelled)

4. (Original) A compound according to claim 1, 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.

5. (Original) A compound according to claim 4, wherein the R_6, R_7 and R_8 moieties are selected from substituted and unsubstituted acetyl, and substituted and unsubstituted benzoyl.

6. (Original) A compound according to claim 4, wherein the ester-type protecting group is a protecting group selected from acetyl, propionyl, isopropionyl, benzoyl, and trihaloacetyl.

7. (Original) A compound according to claim 6, wherein the R_6, R_7 and R_8 moieties are selected from substituted and unsubstituted acetyl, and substituted and unsubstituted benzoyl.

8. (Currently amended) A compound according to claim 4, wherein the ester-type protecting group is a protecting group selected from trifluoroacetyl or trichloroacetyl, and provided that when n is 0 and m is 1, R_1 is not NH_2.

9. (Original) A compound according to claim 4, wherein the ether-type protecting group is a protecting group selected from benzyl, p-methoxybenzyl, methoxymethyl and allyl ethers.

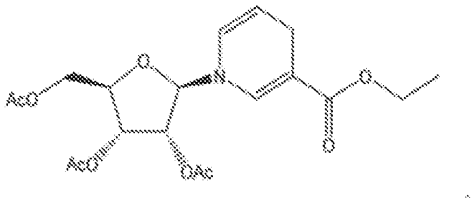
10. (Original) A compound according to claim 4, wherein the silyl-type protecting group is a protecting group selected from trimethylsilyl, triethylsilyl, triisopropylsilyl, 2-(trimethylsilyl)ethoxymethyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl and tetraisopropyldisilyl.

11. (Cancelled)

12. (Currently amended) A compound of claim 1~~claim 11~~, wherein at least two of R_6, R_7 and R_8 are selected from unsubstituted acetyl or unsubstituted benzoyl.

13. (Cancelled)

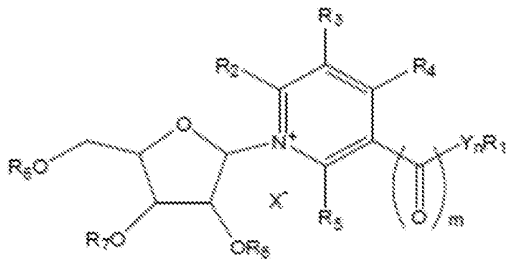
14. (Currently amended) A compound according to ~~claim 12~~ claim 1, which is triacetyl O-ethyl-1,4-dihydronicotinate riboside:



15. (Canceled)

16. -17. (Cancelled)

18. (Currently amended) ~~A compound of claim 17~~ A compound of formula (IV)



(IV)

wherein

n is 1;

m is 1;

Y is O;

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;

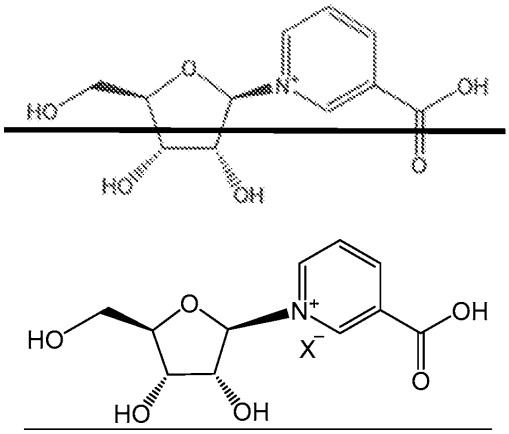
R_2 – R_5 are each H; and

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

provided that when n is 1, m is 1, Y is O, R_1 is H or NH_2, R_2 – R_5 are each H, and X^- is a substituted sulfonate, then R_6, R_7, and R_8 are not all simultaneously H or unsubstituted acetyl or unsubstituted benzoyl~~, wherein m is 1, n is 1, and Y is O~~.

19. (Currently amended) A compound of formula:



wherein 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, provided that X^- is not trifluoromethylsulfonate.

20. (Previously presented) A compound of claim 1, wherein:
Y_nR_1 is NH_2 or $–OCH_2CH_3$; and
R_2-R_5 are all hydrogens.

21. (Previously presented) The compound of claim 20, wherein R_6, R_7 and R_8, are each the same group.

22. (New) A compound of claim 12, wherein at least two of R_6, R_7 and R_8 are selected from unsubstituted acetyl or unsubstituted benzoyl and provided that when n is 0 and m is 1, R_1 is not NH_2.

23. (New) The compound of claim 18, wherein X^- is an anion selected from an anion of a substituted or unsubstituted carboxylic acid, a substituted or unsubstituted phosphate, a substituted or unsubstituted sulfate, a substituted or unsubstituted carbonate, and a substituted or unsubstituted carbamate.

24. (New) The compound of claim 18, wherein X^- is an anion selected from acetate, formate, trifluoroacetate, glutamate, lactate, and aspartate.

25. (New) The compound of claim 19, wherein 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.

26. (New) The compound of claim 19, wherein X^- is an anion selected from acetate, formate, trifluoroacetate, glutamate, lactate and aspartate.

Doc Code: DIST.E.FILE **Document Description: Electronic Terminal Disclaimer - Filed**	PTO/SB/26 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT**
Application Number	15905922
Filing Date	27-Feb-2018
First Named Inventor	Marie MIGAUD
Attorney Docket Number	335040: 4-16A US
Title of Invention	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
The Queen's University of Belfast	100%

The owner(s) with percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s)

10000519

as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:
- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

◉ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

○ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.	
Applicant claims the following fee status: ◉ Small Entity ○ Micro Entity ○ Regular Undiscounted I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.	
THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES I certify, in accordance with 37 CFR 1.4(d)(4) that I am: ◉ An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application Registration Number 32064 ○ A sole inventor ○ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application ○ A joint inventor; all of whom are signing this request	
Signature	/sallyasullivan/
Name	Sally A. Sullivan

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	15905922
Filing Date:	27-Feb-2018
Title of Invention:	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof
First Named Inventor/Applicant Name:	Marie MIGAUD
Filer:	Sally A. Sullivan
Attorney Docket Number:	335040: 4-16A US

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
STATUTORY OR TERMINAL DISCLAIMER	2814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**160**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 15905922

Filing Date: 27-Feb-2018

Applicant/Patent under Reexamination: MIGAUD

Electronic Terminal Disclaimer filed on May 27, 2020

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt	
EFS ID:	39554579
Application Number:	15905922
International Application Number:	
Confirmation Number:	1061
Title of Invention:	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof
First Named Inventor/Applicant Name:	Marie MIGAUD
Customer Number:	23713
Filer:	Sally A. Sullivan
Filer Authorized By:	
Attorney Docket Number:	335040: 4-16A US
Receipt Date:	27-MAY-2020
Filing Date:	27-FEB-2018
Time Stamp:	18:01:45
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$160
RAM confirmation Number	E20205QI01434910
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Terminal Disclaimer-Filed (Electronic)	eTerminal-Disclaimer.pdf	33514 837d8662e7275650bbbde9366c551b3725 1121e2	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30702 8ea163f0fbf39f3e8fc6bdcae8717d5264507 f52	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	64216		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/905,922	Filing Date 02/27/2018	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $230 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	05/27/2020	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 20	Minus	** 20	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	*** 3	= 0		x $230 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/CORALIA BETANCOURT/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/905,922	02/27/2018	Marie MIGAUD	335040: 4-16A US	1061

23713 7590 05/21/2020

Leydig, Voit & Mayer, Ltd. (GS BOULDER)
4940 Pearl East Circle
Suite 200
Boulder, CO 80301

EXAMINER
LEWIS, PATRICK T

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
05/21/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

chgpatent@leydig.com

Applicant-Initiated Interview Summary	**Application No.** 15/905,922	**Applicant(s)** MIGAUD et al.	
	Examiner PATRICK T LEWIS	**Art Unit** 1623	**AIA (FITF) Status** Yes

All participants (applicant, applicants representative, PTO personnel):

(1) PATRICK T. LEWIS. (3) _____.

(2) Sally Sullivan. (4) _____.

Date of Interview: 15 May 2020.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☑ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☑112 ☑102 ☑103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 1-2,4-10,12,14 and 16-26.

Identification of prior art discussed: Tietze, Franchetti, Jarman, and Yatvin (all of record).

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

The examiner and Ms. Sullivan discussed the informal submission attached. The examiner indicated by the proposed amendments would likely overcome the rejections under 112, 102, and 103 of record; however, the examiner noted that further search and/or consideration would be required to determine if a rejection of claims 16 and 17 under 103 would be required. The examiner noted that Jarman teaches that acetylated nicotinamide glucoside has been obtained from nicotinamide and 2,3,4-tri-O-acetyl-D-glucopyranosyl chloride (page 199).

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/PATRICK T LEWIS/ Primary Examiner, Art Unit 1623	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

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The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

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1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
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7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

INFORMAL SUBMISSION FOR DISCUSSION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

US Application No.	: 15/905,922	Confirmation No. 1061
Date of Filing	: February 27, 2018	
Applicant	: The Queen's University of Belfast	
Inventors	: Marie MIGAUD, et al.	
For	: Methods of Preparing Nicotinamide Riboside and Derivatives Thereof	
Art Unit	: 1623	
Examiner	: Patrick T. Lewis	
Docket No.	: 335040: 4-16A US	
Customer No.	: 23713	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO FINAL OFFICE ACTION

Sir:

Please enter the following response to the Final Office Action mailed April 29, 2019. Applicant Requests After Final Consideration of the Amendment Presented herein.

Amendments to the Claims begin on page 2 of this paper.

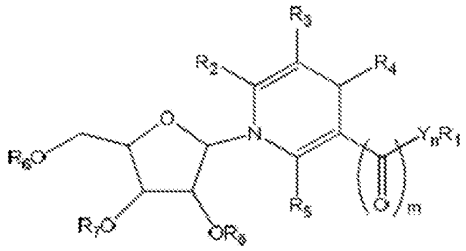
Remarks begin on page 8 of this paper.

Claim Amendments

This listing of the claims replaces all previous such listings:

Listing of the Claims

1. (Currently amended) A compound of formula (III)



(III)

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

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

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

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

2. (Original) A compound of claim 1, wherein R_6, R_7 and R_8 are each H.

3. (Cancelled)

4. (Original) A compound according to claim 1, 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.

5. (Original) A compound according to claim 4, wherein the R_6, R_7 and R_8 moieties are selected from substituted and unsubstituted acetyl, and substituted and unsubstituted benzoyl.

6. (Original) A compound according to claim 4, wherein the ester-type protecting group is a protecting group selected from acetyl, propionyl, isopropionyl, benzoyl, and trihaloacetyl.

7. (Original) A compound according to claim 6, wherein the R_6, R_7 and R_8 moieties are selected from substituted and unsubstituted acetyl, and substituted and unsubstituted benzoyl.

8. (Currently amended) A compound according to claim 4, wherein the ester-type protecting group is a protecting group selected from trifluoroacetyl or trichloroacetyl, and provided that when n is 0 and m is 1, R_1 is not NH_2.

9. (Original) A compound according to claim 4, wherein the ether-type protecting group is a protecting group selected from benzyl, p-methoxybenzyl, methoxymethyl and allyl ethers.

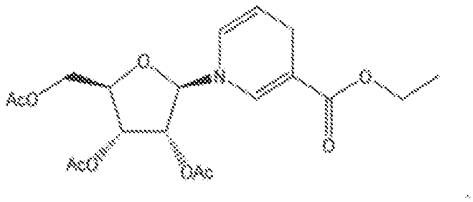
10. (Original) A compound according to claim 4, wherein the silyl-type protecting group is a protecting group selected from trimethylsilyl, triethylsilyl, triisopropylsilyl, 2-(trimethylsilyl)ethoxymethyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl and tetraisopropyldisilyl.

11. (Cancelled)

12. (Currently amended) A compound of claim 1~~claim 11~~, wherein at least two of R_6, R_7 and R_8 are selected from unsubstituted acetyl or unsubstituted benzoyl.

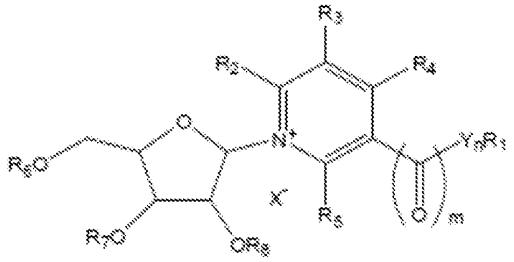
13. (Cancelled)

14. (Currently amended) A compound according to ~~claim 12~~ claim 1, which is triacetyl O-ethyl-1,4-dihydronicotinate riboside:



15. (Canceled)

16. (Currently amended) A compound of formula (IV)



(IV)

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

R_6, R_7 and R_8, which may be the same or different, are each independently a hydroxyl protecting group~~, optionally wherein the hydroxyl protecting group is substituted or unsubstituted acetyl, or substituted or unsubstituted benzoyl~~; 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;

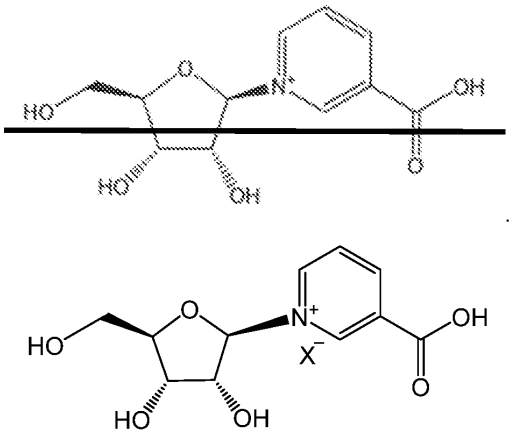
provided that X^- is not trifluorosulfonate; and

provided that when n is 0 or 1, m is 1, Y is O, R_1 is ~~H or~~ NH_2, R_2 – R_5 are each H, and X^- is a halide ~~a substituted sulfonate~~, then R_6, R_7, and R_8 are not all simultaneously ~~H or unsubstituted acetyl or~~ unsubstituted benzoyl.

17. (Previously presented) A compound of claim 16, wherein R_2 – R_5 are each H.

18. (Previously presented) A compound of claim 17, wherein m is 1, n is 1, and Y is O.

19. (Currently amended) A compound of formula:



wherein 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, provided that X^- is not trifluoromethylsulfonate.

20. (Previously presented) A compound of claim 1, wherein:
Y_nR_1 is NH_2 or $–OCH_2CH_3$; and
R_2-R_5 are all hydrogens.

21. (Previously presented) The compound of claim 20, wherein R_6, R_7 and R_8, are each the same group.

22. (New) A compound of claim 12, wherein at least two of R_6, R_7 and R_8 are selected from unsubstituted acetyl or unsubstituted benzoyl and provided that when n is 0 and m is 1, R_1 is not NH_2.

23. (New) The compound of claim 16, wherein X^- is an anion selected from an anion of a substituted or unsubstituted carboxylic acid, a substituted or unsubstituted phosphate, a substituted or unsubstituted sulfate, a substituted or unsubstituted carbonate, and a substituted or unsubstituted carbamate.

24. (New) The compound of claim 16, wherein X^- is an anion selected from acetate, formate, trifluoroacetate, glutamate, lactate, and aspartate.

25. (New) The compound of claim 19, wherein 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.

26. (New) The compound of claim 19, wherein X^- is an anion selected from acetate, formate or trifluoroacetate.

REMARKS

Claims 1-14 and 16-21 are pending in this application. This amendment cancels claims 3, 11 and 13 without prejudiced to the subject matter therein and adds new claims 22-26. On entrance of this amendment, claims 1, 2, 4-10, 12, 14, and 16-26 will be pending in this application.

Applicant respectfully requests entrance of this amendment after final because it is believed to place all of the remaining claims in condition for allowance. New claims 22-26 are all dependent claims. The claims from which new claims 22-26 depend are believed to be in condition for allowance on entrance of this amendment,

Amendments to the Claims

Claims 3, 11 and 13 are cancelled without prejudice.

Claims 1 and 16 are amended to delete the phrase "optionally wherein the hydroxyl protecting group is substituted or unsubstituted acetyl, or substituted or unsubstituted benzoyl" in the definition of R_6-R_8 which is believed to be redundant and which was objected to. This amendment is made to improve clarity.

Claim 1 is further amended to recite "further provided that when n is 1, m is 1, Y is O, R_1 is methyl, R_3 and R_4 are methyl, and R_2 and R_5 are each H, then R_6, R_7, and R_8 are not all simultaneously H or unsubstituted acetyl." Support for this amendment is found in the instant published application US 2018-0186824 at paragraphs [0010-0014, 0016, 0055 and 0077-0078].

Claim 1 is also amended to replace "R_1 is unsubstituted alkyl wherein alkyl is methyl," with the simplified phrase "R_1 is methyl." This amendment is believed to improve clarity.

Claim 12 is amended to depend from claim 1 in view of the cancellation of claim 11.

Claim 14 is amended to depend from claim 1.

Clam 16 is further amended to recite "provided that X^- is not trifluorosulfonate," and "provided that when n is 0 or 1, m is 1, Y is O, R_1 is NH_2, R_2 – R_5 are each H, and X^- is a halide, then R_6, R_7, and R_8 are not all simultaneously unsubstituted benzoyl." Support for this amendment is found in the instant published application US 2018-0186824 at paragraphs [0010-0016, 0034, 0077-0078, 0084, 0086, and 0106].

Claim 19 is amended to replace the formula therein to include the counterion X^- and to recite specific counterions. Support for this amendment is found in the instant published application US 2018-0186824 at paragraphs [0028-0036, and 0088-0089].

New claims 22-26 are added which depend variously from claims 12, 16 or 19. These new claims are fully supported in the alternatives of the claims as filed.

No new matter has been added.

Claim Rejections under Section 112

Claims 1, 16-18, and 20-21 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

The rejection objects to the phrase "optionally wherein the hydroxyl protecting group is substituted or unsubstituted acetyl, or substituted or unsubstituted benzoyl" in the definition of R_6-R_8. This phrase has been deleted from claims 1 and 16, which is believed to obviate the rejection.

Claim 3 is rejected under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4th, paragraph, as being of improper dependent form for failing to further limit the subject matter of the

claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends. Claim 3 is cancelled obviating the rejection.

The rejections under Section 112 should be withdrawn.

Claim Rejections under Section 102

Claims 1-2, 4-7 and 9-12 were rejected as anticipated by Tietze et al. The claims had previously been amended so that the claims would clearly not read on the compounds described in Tietze as **8Bg** and **9Bg.** The Office Action now refers to compounds **8Bf** and **9Bf** in Tietze.

Claim 1 has now been amended to recite "further provided that when n is 1, m is 1, Y is O, R_1 is methyl, R_3 and R_4 are methyl, and R_2 and R_5 are each H, then R_6, R_7, and R_8 are not all simultaneously H or unsubstituted acetyl." The claims as now amended clearly do not read on compounds **8Bf** and **9Bf** in Tietze. The amendment obviates the rejection.

Claim 19 is rejected under 35 U.S.C. 102(a)(1) as being anticipated by Franchetti et al. Bioorganic & Medicinal Chemistry Letters (2004), Vol. 14, pages 4655-4658.

Claim 19 has been amended to include recitation of counter ions X^-. The counterions recited in claim 19 as amended do not include trifluoromethylsulfonate. Franchetti does not teach or suggest any counterion as is now claimed in claim 19. The amendment obviates the rejection.

Claim(s) 16-17 are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Jarman et al. J. Chem. Soc. (C), 1969, pages 199-203 (Jarman). Jarman is characterized as disclosing nicotinamide ribosides and benzyl-protected derivatives thereof of formulae I and II. The compound(s) of Jarman are alleged to be embraced by

instant formula (IV) wherein n is 0; m is 1; R_1 is NH_2; R_2, R_3, and R_5 are H; R_4 is H or methyl; R_6, R_7, and R_8 are H or Bz; and X' is Br or Cl.

Claim 16 is amended to recite "that when n is 0 or 1, m is 1, Y is O, R_1 is H or NH_2, R_{2-5} are each H, and X^- is a halide, then R_6, R_7, and R_8 are not all simultaneously unsubstituted benzoyl." The compounds of claim 16 as amended do not read on the compounds of Jarman. Jarman does not teach and does not suggest the compounds as now claimed in claim 16 and claim 17 which depends from claim 16. The amendment of claim 16 obviates this rejection.

The rejections under Section 102 should be withdrawn.

Claim Rejections under Section 103

Claims 8 and 13 are rejected as unpatentable over Yatvin et al. ("Yatvin") in view of Orain et al. ("Orian", J. Combin. Chem. (2002) vol. 4, 1-16) and Takatani et al. ("Takatani", Carbohyd. Res. (2003) vol. 338, 1073-1081).

Claim 13 is cancelled without prejudice obviating the rejection with respect to this claim.

Claim 8 is amended to recite the proviso "that when n is 0 and m is 1, R_1 is not NH_2." Claim 8 as amended does not read on a compound where the group $-(CO)_mY_n-R_1$ is $-CO-NH_2$. Yatvin does not teach or suggest any compound as now claimed in amended claim 8. Further, the combination of references does not teach or suggest the compounds of claim 8 as amended.

The amendment of claim 8 obviates this rejection.

The rejection under Section 103 should be withdrawn.

New Claims 22-29

New claims 22-26 variously from claims 12, 16 or 19. For the reasons given above, each of claims 12, 16 and 19 should now be allowable and in turn new claims 22-26 should also be allowable.

Nonstatutory Double Patenting

Claims 1-14 and 16-21 are rejected on the ground of nonstatutory double patenting over claims 1-29 of U.S. Patent 10,000, 519 B2.

The present application is commonly owned and has inventors in common with U.S. Patent 10,000, 519 B2. The filing of a terminal disclaimer will overcome this rejection.

No claims in the present application have as yet been indicated to be allowable. Applicant respectfully requests the filing of a terminal disclaimer be postponed until the full scope of allowable subject matter in this application is determined.

Claims Not Rejected Over the Prior Art of Record

Applicant notes that claim 14 is not rejected over the prior art cited in the rejections herein and are thus believed to be free of this prior art and allowable over this prior art.

Conclusion

If the amount paid by EFS web is not correct, please deduct any fees required for timely submission, or credit any overpayment, to deposit account 121216.

DRAFT SUBMISSION

LEYDIG, VOIT & MAYER, Ltd.
4940 Pearl East Circle, Suite 200
Boulder, CO 80301
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UNITED STATES PATENT AND TRADEMARK OFFICE

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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/905,922	02/27/2018	Marie MIGAUD	335040: 4-16A US	1061

23713 7590 02/14/2020

Leydig, Voit & Mayer, Ltd. (GS BOULDER)
4940 Pearl East Circle
Suite 200
Boulder, CO 80301

EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
02/14/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

chgpatent@leydig.com

Applicant-Initiated Interview Summary	**Application No.** 15/905,922	**Applicant(s)** MIGAUD et al.	
	Examiner PATRICK T LEWIS	**Art Unit** 1623	**AIA (FITF) Status** Yes

All participants (applicant, applicants representative, PTO personnel):

(1) PATRICK T. LEWIS. (3) _____.

(2) Sally Sullivan. (4) _____.

Date of Interview: 11 February 2020.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☑ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☑102 ☐103 ☑Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 1 and 14.

Identification of prior art discussed: Prior art of record cited in the Last Office Action.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Ms. Sullivan requested clarification regarding the last Office Action which was provided by the examiner. No agreements were reached regarding patentability..

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/PATRICK T LEWIS/ Primary Examiner, Art Unit 1623	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

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The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

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1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/905,922	02/27/2018	Marie MIGAUD	335040: 4-16A US	1061

23713 7590 01/30/2020

Leydig, Voit & Mayer, Ltd. (GS BOULDER)
4940 Pearl East Circle
Suite 200
Boulder, CO 80301

EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
01/30/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

chgpatent@leydig.com

PTOL-90A (Rev. 04/07)

Office Action Summary	**Application No.** 15/905,922	**Applicant(s)** MIGAUD et al.	
	Examiner PATRICK T LEWIS	**Art Unit** 1623	**AIA (FITF) Status** Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 29 October 2019.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-14 and 16-21 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-14 and 16-21 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 27 February 2018 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☑ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☑ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☑ Certified copies of the priority documents have been received in Application No. 14/908,831.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Applicant's Response Dated October 29, 2019

2. In the Response dated October 29, 2019, claims 1 and 16-18 were amended; claim 15 was canceled; and claims 20-21 were added. Claims 1-14 and 16-21 are pending. An action on the merits of claims 1-14 and 16-21 is contained herein.

3. The rejection of claims 1-14 and 16-19 on the ground of nonstatutory double patenting as being unpatentable over claims 1-29 of U.S. Patent No. 10,000,519 B2 is maintained for the reasons of record as set forth in the Office Action dated April 29, 2019. Newly added claims 20 and 21 are also rejected on the ground of nonstatutory double patenting as being unpatentable over claim 16 of U.S. Patent No. 10,000,519 B2 for the reasons of record as set forth in the Office Action dated April 29, 2019 and is not repeated separately.

4. The rejection of claims 17-18 under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, has been rendered moot in view of Applicant's Amendment dated October 29, 2019.

5. The rejection of claims 1-2, 4-7, and 9-12 under 35 U.S.C. 102(a)(1) as being anticipated by Tietze et al. Angewandte Chemie / Angew. Chem. (1985), Vol. 97, pages 135-136 (Tietze) is maintained for the reasons set forth herein below.

6. The rejection of claims 16-18 under 35 U.S.C. 102(a)(1) as being anticipated by Franchetti et al. Bioorganic & Medicinal Chemistry Letters (2004), Vol. 14, pages 4655-4658 (Franchetti) has been rendered moot in view of Applicant's Amendment dated October 29, 2019.

7. The rejection of claim 19 under 35 U.S.C. 102(a)(1) as being anticipated by Franchetti et al. Bioorganic & Medicinal Chemistry Letters (2004), Vol. 14, pages 4655-4658 (Franchetti) is maintained for the reasons of record as set forth in the Office Action dated April 29, 2019.

8. The rejection of claims 1-2, 4-7, and 9-12 under 35 U.S.C. 102(a)(1) and 102(a)(2) as being anticipated by Yatvin et al. US 6,689,760 B1 (Yatvin) has been rendered moot in view of Applicant's Amendment dated October 29, 2019.

9. The rejection of claim 3 under 35 U.S.C. 102(a)(1) and 102(a)(2) as being anticipated by Yatvin et al. US 6,689,760 B1 (Yatvin) is maintained for the reasons of record as set forth in the Office Action dated April 29, 2019.

10. The rejection of claims 8 and 13 under 35 U.S.C. 103 as being unpatentable over Yatvin et al. US 6,689,760 B1 (Yatvin); Orain et al. Journal of Combinatorial Chemistry (2002), Vol. 4, pages 1-16 (Orain); and Takatani et al. Carbohydrate Research (2003), Vol. 338, pages 1073-1081 (Takatani) in combination is maintained for the reasons of record as set forth in the Office Action dated April 29, 2019.

Rejections of Record Set Forth in the Office Action Dated April 29, 2019

11. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

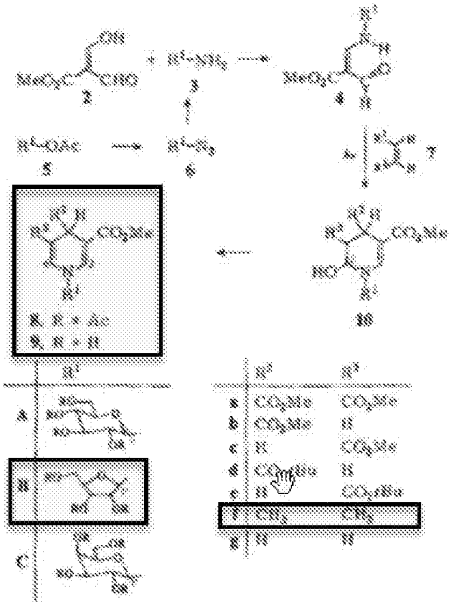
12. Claims 1-14 and 16-21 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-29 of U.S. Patent No. 10,000,519 B2.

13. No arguments were set forth by Applicant. Thus, the rejection is maintained.

14. Claim(s) 1-2, 4-7, and 9-12 is/are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Tietze et al. Angewandte Chemie / Angew. Chem. (1985), Vol. 97, pages 135-136 (Tietze).

15. Applicant's arguments filed October 29, 2019 have been fully considered but they are not persuasive. Claim 1 has been amended to recite ", optionally wherein the hydroxyl protecting group is substituted or unsubstituted acetyl, or substituted or unsubstituted benzoyl; provided that when n is 1, m is 1, Y is 0, R_1 is unsubstituted alkyl wherein alkyl is methyl, and R_2 - R_5 are each H, then R_6, R_7, and R_8 are not all simultaneously H or unsubstituted acetyl." Accordingly, applicant argues that the compounds described in Tietze as **8Bg** and **9Bg** do not fall within the genus of amended claim 1.

Applicant's amendment has been duly considered; however, the rejection of record is made over the teachings of Tietze in toto. Although compounds **8Bg** and **9Bg** do not fall within the genus of amended claim 1, compounds **8Bf** and **9Bf** are embraced by instant formula (III) wherein n is 1; m is 1; Y is O; R_1 is methyl; R_2 and R_5 is H; R_3 and R_4 is methyl; and R_6, R_7, and R_8 is H or Ac (see figure).



Thus, the rejection of claims 1-2, 4-7, and 9-12 is maintained.

16. Claim(s) 19 is/are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Franchetti et al. Bioorganic & Medicinal Chemistry Letters (2004), Vol. 14, pages 4655-4658 (Franchetti).

17. Applicant's arguments filed October 29, 2019 have been fully considered but they are not persuasive. Claim 16 has been amended to recite ", optionally wherein the hydroxyl protecting group is substituted or unsubstituted acetyl, or substituted or unsubstituted benzoyl; and provided that when n is 0 or 1, m is 1, Y is 0, R_1 is H or NH_2, R_2 - R_5 are each H, and X^- is a substituted sulfonate, then R_6, R_7, and R_8 are not all simultaneously H or unsubstituted acetyl or unsubstituted benzoyl." Accordingly, applicant argues that the compounds described in Franchetti et al. as Compounds **1**, **2** and **9**-**12** do not fall within the genus of amended claim 16. Applicant contends that claim 19 ultimately depends from claim 1 and is therefore not anticipated.

Applicant's amendment has been duly considered; however, claim 19 is an independent claim and has not been amended. Thus, the rejection of claim 19 is maintained.

18. Claim(s) 3 is/are rejected under 35 U.S.C. 102(a)(1) and 102(a)(2) as being anticipated by Yatvin et al. US 6,689,760 B1 (Yatvin).

19. Applicant's arguments filed October 29, 2019 have been fully considered but they are not persuasive. Claim 1 has been amended to recite ", optionally wherein the hydroxyl protecting group is substituted or unsubstituted acetyl, or substituted or unsubstituted benzoyl; and further provided that when n is 0, m is 1, R_1 is NH_2, and R_2 - R_5 are each H, then R_6, R_7, and R_8 are not all simultaneously H or unsubstituted benzoyl." Accordingly, applicant argues that the compounds described in Yatvin et al. as beta-C5-ribose and beta-C5-Tribenzoate do not fall within the genus of amended claim 1. Applicant further contends that claims 2-7 and 9-12, which all ultimately depend from claim 1, are not anticipated.

Applicant's amendment has been duly considered; however, claim 3 explicitly claims 1-(β-B-ribofuranosyl)-1,4-dihydronicotinamde which is explicitly disclosed by Yatvin. Thus, the rejection of claim 3 is maintained.

20. Claims 8 and 13 are rejected under 35 U.S.C. 103 as being unpatentable over Yatvin et al. US 6,689,760 B1 (Yatvin); Orain et al. Journal of Combinatorial Chemistry (2002), Vol. 4, pages 1-16 (Orain); and Takatani et al. Carbohydrate Research (2003), Vol. 338, pages 1073-1081 (Takatani) in combination.

21. Applicant's arguments filed October 29, 2019 have been fully considered but they are not persuasive. Applicant argues that the combination of references does not provide

a reasonable expectation of success in making the claimed compounds. Applicant contends that Orain is directed exclusively to solid-phase organic synthesis, a specialized technique which is not employed in the claimed invention. Applicant argues that it is well known to a skilled artisan that solid phase synthesis would be problematic in the preparation of ribose-based compounds, i.e., carbohydrates, much less ribosides or ribonucleosides. Applicant argues that Orain does not list any examples for preparation of pyridyl- substituted ribose compounds, as claimed. Applicant further argues that Takatani cannot cure the deficiency of either Yatvin or Orain. Applicant contends that the fact that Takatani is directed to a very specific series of oligomannosides clearly demonstrates the difficulty of even simple protecting group transformations in carbohydrate synthesis, much less ribose-based compounds, even more so pyridine-substituted ribose compounds as claimed. Applicant contends that without more, a skilled person would not have had a reasonable expectation that the claimed compounds could be obtained by combining the teachings of Yatvin with Orain and Takatani.

The examiner respectfully disagrees.

The differences between the prior art and the claims pointed out by applicant have been fully considered; however, as set forth in the last Office Action, in determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); Schenck v. Nortron Corp., 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983).

Obviousness does not require absolute predictability. The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. In the instant case, one of ordinary skill in the art would have had a reasonable expectation of success in substituting the Bz protecting groups (hydroxyl protecting groups) of C5-tribenzoate with another known hydroxyl protecting group such as TBDMS (claim 8), TBDPS (claim 8), allyl (claim 8), TFA (claim 8), or acetyl (claim 13) in view of the teachings of Orain and Takatani. As evidenced by Orain and Takatani, the use of acetyl and trifluoroacetyl groups for protecting hydroxyl moieties was known at the time of the instant filing.

Thus, the rejection of claims 8 and 13 is maintained in view of the preponderance of the evidence.

Claim Rejections - 35 USC § 112

22. The following is a quotation of 35 U.S.C. 112(b):

> (b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

23. Claims 1, 16-18, and 20-21 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

The text "optionally wherein the hydroxyl protecting group is substituted or unsubstituted acetyl, or substituted or unsubstituted benzoyl" renders claims reading

upon said text indefinite as one of ordinary skill in the art at the time of filing would not have been apprised of the metes and bounds of variables R_6, R_7, and R_8. It is unclear whether applicant intends for "the hydroxyl protecting group", when present, to be limited to 1) substituted or unsubstituted acetyl or 2) substituted or unsubstituted benzoyl. The examiner notes, for example, that claim 4 reads upon a protected group outside to scope of what's recited in claim 1.

24. The following is a quotation of 35 U.S.C. 112(d):

> (d) REFERENCE IN DEPENDENT FORMS.—Subject to subsection (e), a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

The following is a quotation of pre-AIA 35 U.S.C. 112, fourth paragraph:

> Subject to the following paragraph [i.e., the fifth paragraph of pre-AIA 35 U.S.C. 112], a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

25. Claim 3 is rejected under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends. Claim 3 reads upon 1-(β-B-ribofuranosyl)-1,4-dihydronicotinamde which is explicitly excluded by proviso in claim 1, upon which claim 3 ultimately depends. Applicant may cancel the claim(s), amend the claim(s) to place the claim(s) in proper dependent form, rewrite the claim(s) in independent form, or present a sufficient showing that the dependent claim(s) complies with the statutory requirements.

Claim Rejections - 35 USC § 102

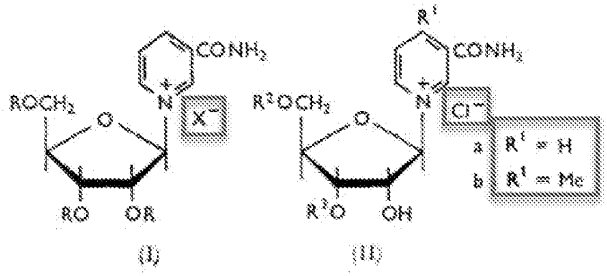
26. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

27. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale or otherwise available to the public before the effective filing date of the claimed invention.

28. Claim(s) 16-17 is/are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Jarman et al. J. Chem. Soc. (C), 1969, pages 199-203 (Jarman).

Jarman discloses nicotinamide ribosides and benzyl-protected derivatives thereof of formulae I and II.



The compound(s) of Jarman embraced by instant formula (IV) wherein n is 0; m is 1; R_1 is NH_2; R_2, R_3, and R_5 is H; R_4 is H or methyl; R_6, R_7, and R_8 is H or Bz; and X^- is Br^- or Cl^-. Thus, claims 16-17 are anticipated.

Conclusion

29. Claims 1-14 and 16-21 are pending. Claims 1-14 and 16-21 are rejected. No claims are allowed.

30. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contacts

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to PATRICK T LEWIS whose telephone number is (571)272-0655. The examiner can normally be reached on Monday to Friday, 10 AM to 4 PM EST (Maxi Flex).

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an

interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on (571) 272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/PATRICK T LEWIS/
Primary Examiner, Art Unit 1623

/PL/

Notice of References Cited	Application/Control No. 15/905,922	Applicant(s)/Patent Under Reexamination MIGAUD et al.	
	Examiner PATRICK T LEWIS	Art Unit 1623	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A					
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Jarman et al. J. Chem. Soc. (C), 1969, pages 199-203.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/905,922	MIGAUD et al.
	Examiner	Art Unit
	PATRICK T LEWIS	1623

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Inventor, REGISTRY, CAPLUS, MEDLINE (see attached)	04/24/2019	/PL/
Inventor, REGISTRY, CAPLUS, MEDLINE (see attached)	01/24/2020	/PL/

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/PATRICK T LEWIS/ Primary Examiner, Art Unit 1623	

IPR2026-00400
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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/905,922	MIGAUD et al.
	Examiner	Art Unit
	PATRICK T LEWIS	1623

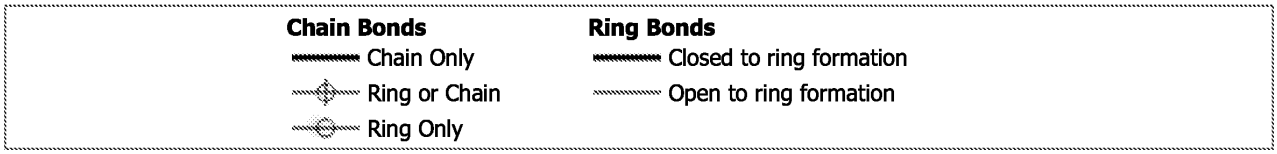
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=	Allowed	÷	Restricted	I	Interference	O	Objected

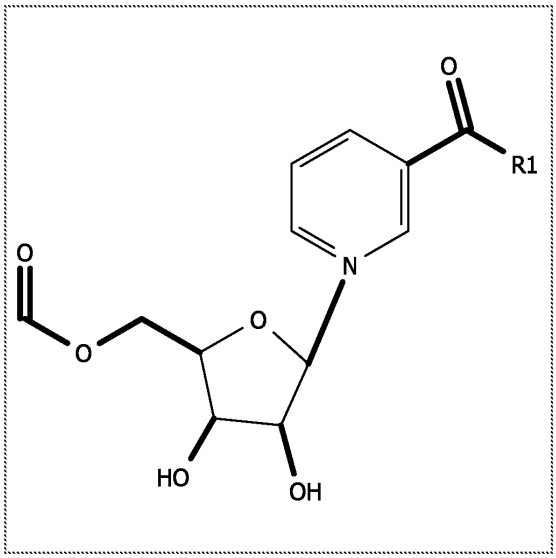
CLAIMS

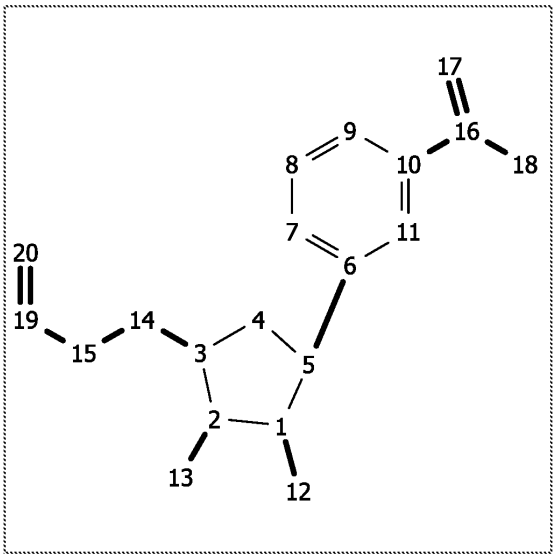
☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	04/24/2019	01/24/2020							
	1	✓	✓							
	2	✓	✓							
	3	✓	✓							
	4	✓	✓							
	5	✓	✓							
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	13	✓	✓							
	14	✓	✓							
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	16	✓	✓							
	17	✓	✓							
	18	✓	✓							
	19	✓	✓							
	20		✓							
	21		✓							

Structure Details (15905922-str2)







R-group Definitions

R-group	Values
R1	O, S, NH2, OH, OEt, OPr-n, OPr-i, OBu-n, OBu-i, OBu-t

Node Attributes

Only nodes with attributes changed from the default value of 'Any' are included in this table.
Nodes which do not support these attributes (R-groups, shortcuts and VAP center points) are not included in this table.

Node	Type	H Count	Non H Count	Mass	Valency
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11	Ring				
14, 15, 16, 17, 19, 20	Chain				

Bond Attributes

Bond	Type	Value
6-7, 7-8, 8-9, 9-10, 10-11, 11-6	Ring	Normalized
1-2, 2-3, 3-4, 4-5, 5-1	Ring	Exact/Normalized
1-12, 2-13, 3-14, 6-5, 10-16, 14-15, 15-19, 16-17, 16-18, 19-20	Chain	Exact/Normalized

Markush Attributes

Nodes which do not support these attributes (R-groups and VAP center points) are not included in this table.

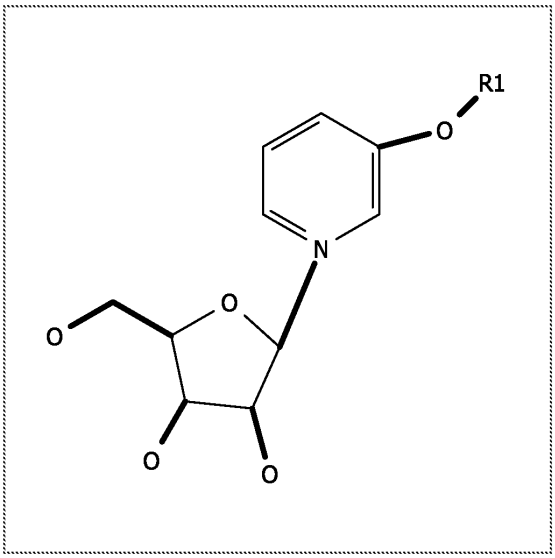
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1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11	Atom	Limited
12, 13, 14, 15, 16, 17, 19, 20	Class	Limited

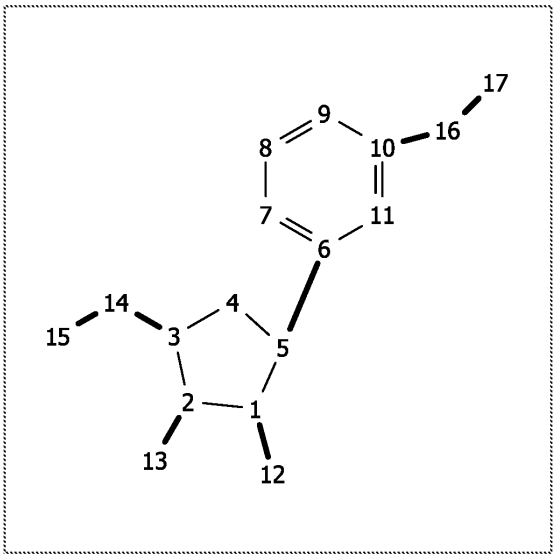
/

Structure Details (15905922-str1)

Chain Bonds
- Chain Only
- Ring or Chain
- Ring Only

Ring Bonds
- Closed to ring formation
- Open to ring formation





R-group Definitions

R-group	Values
R1	Cb, Ak

Node Attributes

Only nodes with attributes changed from the default value of 'Any' are included in this table.
Nodes which do not support these attributes (R-groups, shortcuts and VAP center points) are not included in this table.

Node	Type	H Count	Non H Count	Mass	Valency
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11	Ring				
12, 13, 14, 15, 16	Chain				

Bond Attributes

Bond	Type	Value
6-7, 7-8, 8-9, 9-10, 10-11, 11-6	Ring	Normalized
1-2, 2-3, 3-4, 4-5, 5-1	Ring	Exact/Normalized
1-12, 2-13, 3-14, 6-5, 10-16, 14-15, 16-17	Chain	Exact/Normalized

Markush Attributes

Nodes which do not support these attributes (R-groups and VAP center points) are not included in this table.

Node	Match Level	Element Count Level
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11	Atom	Limited
12, 13, 14, 15, 16	Class	Limited

/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 1061

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
15/905,922	02/27/2018	536	1623	335040: 4-16A US

APPLICANTS
The Queen's University of Belfast, Belfast Antrim, UNITED KINGDOM;

INVENTORS
Marie MIGAUD, Lurgan, UNITED KINGDOM;
Philip REDPATH, Portadown, UNITED KINGDOM;
Kerri CROSSEY, Magherafelt, UNITED KINGDOM;
Mark DOHERTY, Newtownabbey, UNITED KINGDOM;

**** CONTINUING DATA **************************
This application is a CON of 14/908,831 01/29/2016 PAT 10000519
which is a 371 of PCT/EP2014/065971 07/24/2014

**** FOREIGN APPLICATIONS **************************
UNITED KINGDOM 1313465.5 07/29/2013

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
03/22/2018

Foreign Priority claimed ☑ Yes ☐ No 35 USC 119(a-d) conditions met ☑ Yes ☐ No Verified and Acknowledged /PATRICK T LEWIS/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		UNITED KINGDOM	5	19	3

ADDRESS

Leydig, Voit & Mayer, Ltd. (GS BOULDER)
4940 Pearl East Circle
Suite 200
Boulder, CO 80301
UNITED STATES

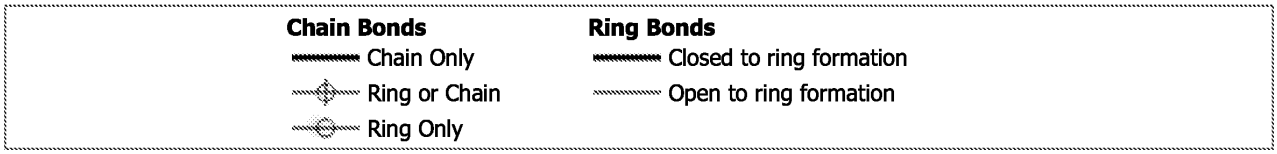
TITLE

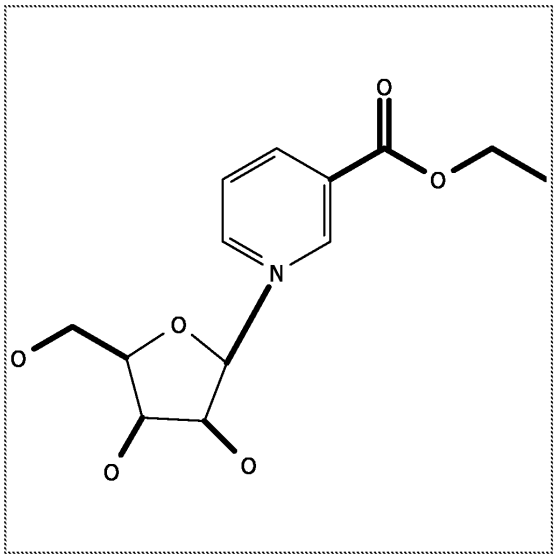
Methods of Preparing Nicotinamide Riboside and Derivatives Thereof

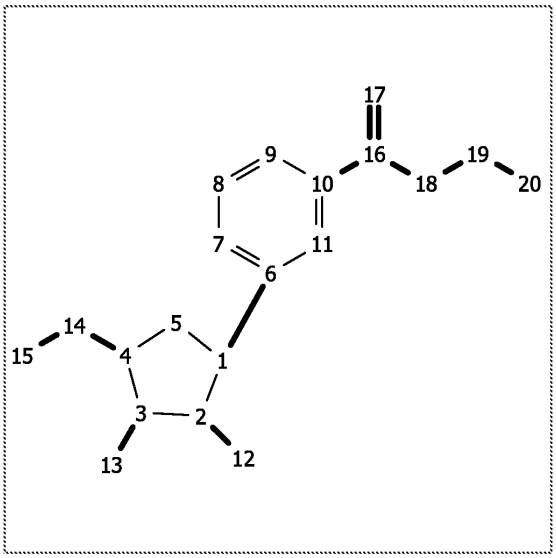
FILING FEE RECEIVED		
785	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

BIB (Rev. 05/07).

Structure Details







Node Attributes

Only nodes with attributes changed from the default value of 'Any' are included in this table.
Nodes which do not support these attributes (R-groups, shortcuts and VAP center points) are not included in this table.

Node	Type	H Count	Non H Count	Mass	Valency
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11	Ring				
12, 13, 14, 15, 16, 17, 18, 19, 20	Chain				

Bond Attributes

Bond	Type	Value
6-7, 7-8, 8-9, 9-10, 10-11, 11-6	Ring	Normalized
1-2, 2-3, 3-4, 4-5, 5-1	Ring	Exact/Normalized
4-14, 10-16, 19-20	Chain	Exact
2-12, 3-13, 6-1, 14-15, 16-18, 16-17, 18-19	Chain	Exact/Normalized

Markush Attributes

Nodes which do not support these attributes (R-groups and VAP center points) are not included in this table.

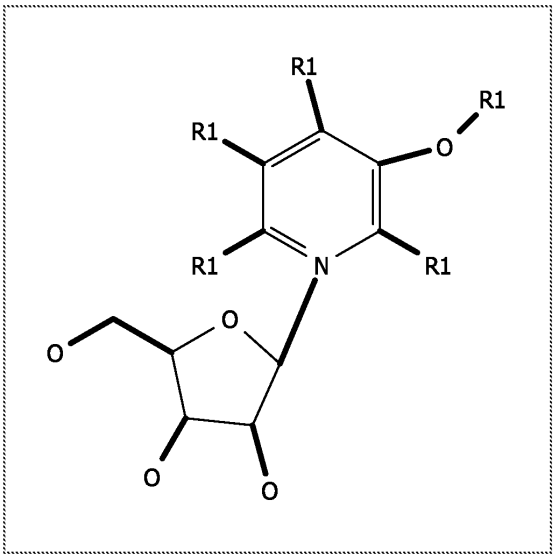
Node	Match Level	Element Count Level
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11	Atom	Limited
12, 13, 14, 15, 16, 17, 18, 19, 20	Class	Limited

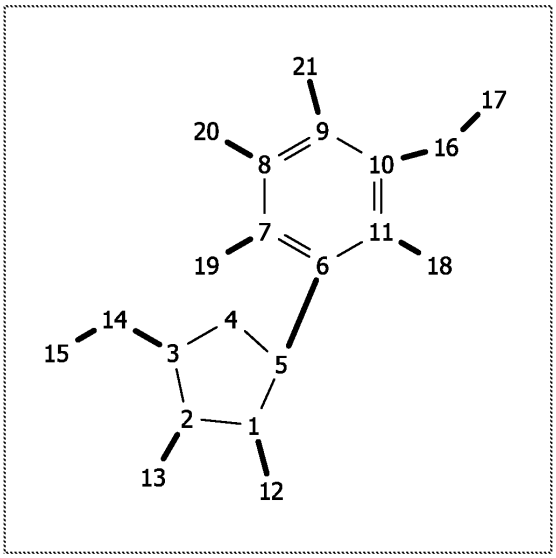
/

Structure Details

Chain Bonds
- Chain Only
- Ring or Chain
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Ring Bonds
- Closed to ring formation
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R-group Definitions

R-group	Values
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Node Attributes

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Node	Type	H Count	Non H Count	Mass	Valency
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11	Ring				
12, 13, 14, 15, 16	Chain				

Bond Attributes

Bond	Type	Value
6-7, 7-8, 8-9, 9-10, 10-11, 11-6	Ring	Normalized
1-2, 2-3, 3-4, 4-5, 5-1	Ring	Exact/Normalized
1-12, 2-13, 3-14, 6-5, 7-19, 8-20, 9-21, 10-16, 11-18, 14-15, 16-17	Chain	Exact/Normalized

Markush Attributes

Nodes which do not support these attributes (R-groups and VAP center points) are not included in this table.

Node	Match Level	Element Count Level
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11	Atom	Limited
12, 13, 14, 15, 16	Class	Limited

/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

US Application No.	: 15/905,922	Confirmation No. 1061
Date of Filing	: February 27, 2018	
Applicant	: The Queen's University of Belfast	
Inventors	: Marie MIGAUD, et al.	
For	: Methods of Preparing Nicotinamide Riboside and Derivatives Thereof	
Art Unit	: 1623	
Examiner	: Patrick T. Lewis	
Docket No.	: 335040: 4-16A US	
Customer No.	: 23713	

CERTIFICATE OF EFS-WEB FILING

I hereby certify that this correspondence is being filed with the USPTO EFS-WEB system.

October 29, 2019 (Date) /cathynelson/ (Cathy Nelson)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO NON-FINAL OFFICE ACTION

Sir:

Please enter the following response to the Office Action mailed April 29, 2019.

Amendments to the Claims begin on page 2 of this paper.

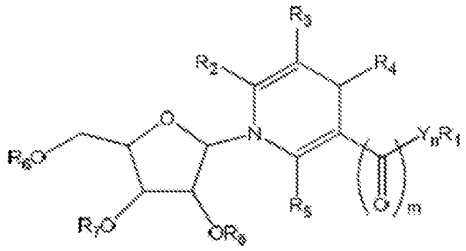
Remarks begin on page 8 of this paper.

Claim Amendments

This listing of the claims replaces all previous such listings:

Listing of the Claims

1. (Currently amended) A compound of formula (III)



(III)

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;

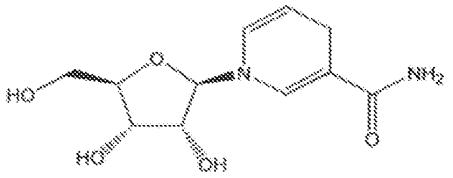
R_2 – R_5, which may be the same or different, are each independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, and substituted or unsubstituted aryl; and

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

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

2. (Original) A compound of claim 1, wherein R_6, R_7 and R_8 are each H.

3. (Original) A compound of claim 2 which is 1-(β-D-ribofuranosyl)-1,4-dihydronicotinamide:



4. (Original) A compound according to claim 1, 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.

5. (Original) A compound according to claim 4, wherein the R_6, R_7 and R_8 moieties are selected from substituted and unsubstituted acetyl, and substituted and unsubstituted benzoyl.

6. (Original) A compound according to claim 4, wherein the ester-type protecting group is a protecting group selected from acetyl, propionyl, isopropionyl, benzoyl, and trihaloacetyl.

7. (Original) A compound according to claim 6, wherein the R_6, R_7 and R_8 moieties are selected from substituted and unsubstituted acetyl, and substituted and unsubstituted benzoyl.

8. (Original) A compound according to claim 4, wherein the ester-type protecting group is a protecting group selected from trifluoroacetyl or trichloroacetyl.

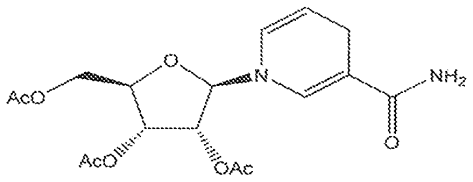
9. (Original) A compound according to claim 4, wherein the ether-type protecting group is a protecting group selected from benzyl, p-methoxybenzyl, methoxymethyl and allyl ethers.

10. (Original) A compound according to claim 4, wherein the silyl-type protecting group is a protecting group selected from trimethylsilyl, triethylsilyl, triisopropylsilyl, 2-(trimethylsilyl)ethoxymethyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl and tetraisopropyldisilyl.

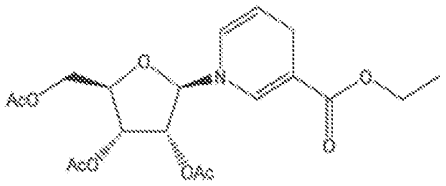
11. (Original) A compound according to claim 1, wherein the R_6, R_7 and R_8 moieties are selected from substituted and unsubstituted acetyl, and substituted and unsubstituted benzoyl.

12. (Original) A compound of claim 11, wherein at least two of R_6, R_7 and R_8 are selected from unsubstituted acetyl or unsubstituted benzoyl.

13. (Original) A compound of claim 12, which is triacetyl-1,4-dihydronicotinamide riboside:

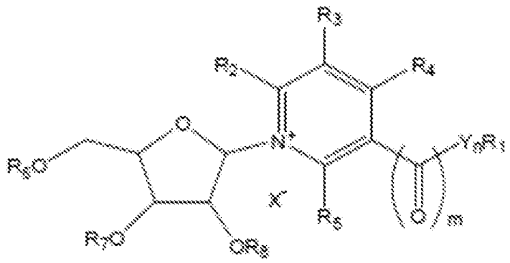


14. (Original) A compound according to claim 12, which is triacetyl O-ethyl-1,4-dihydronicotinate riboside:



15. (Canceled)

16. (Currently amended) A compound of formula (IV)



(IV)

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

R_6, R_7 and R_8, which may be the same or different, are each independently a hydroxyl protecting group, optionally wherein the hydroxyl protecting group is substituted or unsubstituted acetyl, or substituted or unsubstituted benzoyl; and

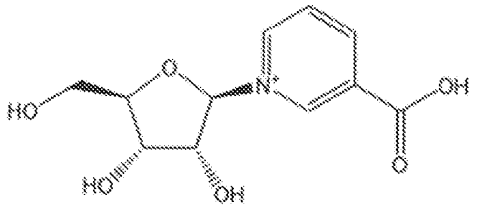
X^- is an anion selected from an anion of a substituted or unsubstituted carboxylic acid, a halide, a substituted or unsubstituted sulfonate, a substituted or unsubstituted phosphate, a substituted or unsubstituted sulfate, a substituted or unsubstituted carbonate, and a substituted or unsubstituted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

provided that when n is 0 or 1, m is 1, Y is O, R_1 is H or NH_2, R_2 – R_5 are each H, and X^- is a substituted sulfonate, then R_6, R_7, and R_8 are not all simultaneously H or unsubstituted acetyl or unsubstituted benzoyl.

17. (Currently amended) A compound of ~~formula~~ claim 16, wherein R_2 – R_5 are each H.

18. (Currently amended) A compound of ~~formula~~ claim 17, wherein m is 1, n is 1, and Y is O.

19. (Original) A compound of formula:



20. (New) A compound of claim 1, wherein:
Y_nR_1 is NH_2 or $–OCH_2CH_3$; and
R_2-R_5 are all hydrogens.

21. (New) The compound of claim 20, wherein R_6, R_7 and R_8, are each the same group.

REMARKS

Claims 1-19 were pending in this application. The response amends the claims as indicated below and cancels claim 15, both without prejudice. New claims 20 and 21 are added. On entrance of this amendment, claims 1-14 and 16-21 are pending in this application.

Amendments to the Claims

Claims 1-19 were pending. Claim 15 is hereby canceled without prejudice. New claims 20 and 21 are added.

Claim 1 is amended to recite ", optionally wherein the hydroxyl protecting group is substituted or unsubstituted acetyl, or substituted or unsubstituted benzoyl; provided that when n is 1, m is 1, Y is O, R_1 is unsubstituted alkyl wherein alkyl is methyl, and R_2 – R_5 are each H, then R_6, R_7, and R_8 are not all simultaneously H or unsubstituted acetyl; further provided that when n is 0, m is 1, R_1 is NH_2, and R_2 – R_5 are each H, then R_6, R_7, and R_8 are not all simultaneously H or unsubstituted benzoyl." Support for this amendment is found in the instant published application US 2018-0186824 at paragraphs [0010-0014, 0016, 0055 and 0077-0078].

Claim 16 is amended to recite ", optionally wherein the hydroxyl protecting group is substituted or unsubstituted acetyl, or substituted or unsubstituted benzoyl; and provided that when n is 0 or 1, m is 1, Y is O, R_1 is H or NH_2, R_2 – R_5 are each H, and X^- is a substituted sulfonate, then R_6, R_7, and R_8 are not all simultaneously H or unsubstituted acetyl or unsubstituted benzoyl." Support for this amendment is found in the instant published application US 2018-0186824 at paragraphs [0010-0016, 0034, 0077-0078 and 0106].

Claims 17 and 18 are amended merely to correct an inadvertent typographical error in order to replace the term "formula" with the term "claim" thus establishing proper antecedent basis.

New claim 20 is added. This claim is fully supported by the alternatives of claim 1, as filed, particularly in view of claims 3 and 14.

New claim 21 depends from claim 20 and is fully supported by the alternatives of claim 1, as filed.

No new matter has been added.

Claim Rejections under Section 112

Claims 17-18 were rejected as being indefinite. Claims 17-18 have been amended as suggested by the Examiner to recite the term "claim" to replace the incorrect term "formula." These amendments obviate the rejection.

Claim Rejections under Section 102

Claims 1-2, 4-7 and 9-12 were rejected as anticipated by Tietze et al. In order to advance prosecution, claim 1 has been amended to recite ", optionally wherein the hydroxyl protecting group is substituted or unsubstituted acetyl, or substituted or unsubstituted benzoyl; provided that when n is 1, m is 1, Y is O, R_1 is unsubstituted alkyl wherein alkyl is methyl, and R_2 – R_5 are each H, then R_6, R_7, and R_8 are not all simultaneously H or unsubstituted acetyl." Accordingly, the compounds described in Tietze as **8Bg** and **9Bg** do not fall within the genus of amended claim 1. Thus, as amended, claim 1 is not anticipated by Tietze et al. Further, claims 2, 4-7 and 9-12 which all ultimately depend from claim 1, are not anticipated. Reconsideration and withdrawal of this rejection is respectfully requested.

Claims 16-19 were rejected as anticipated by Franchetti et al. In order to advance prosecution, claim 16 has been amended to recite ", optionally wherein the hydroxyl protecting group is substituted or unsubstituted acetyl, or substituted or unsubstituted benzoyl; and provided that when n is 0 or 1, m is 1, Y is O, R_1 is H or NH_2, R_2 – R_5 are

each H, and X^- is a substituted sulfonate, then R_6, R_7, and R_8 are not all simultaneously H or unsubstituted acetyl or unsubstituted benzoyl." Accordingly, the compounds described in Franchetti et al. as **Compounds 1, 2 and 9-12** do not fall within the genus of amended claim 16. Thus, as amended, claim 16 is not anticipated by Franchetti et al. Further, claims 17-19 which all ultimately depend from claim 1, are not anticipated. Reconsideration and withdrawal of this rejection is respectfully requested.

Claims 1-7, 9-12 and 15 were rejected as anticipated by Yatvin et al. ("Yatvin"). Claim 15 has been deleted. In order to advance prosecution, Claim 1 has been amended to recite ", optionally wherein the hydroxyl protecting group is substituted or unsubstituted acetyl, or substituted or unsubstituted benzoyl; and further provided that when n is 0, m is 1, R_1 is NH_2, and R_2 – R_5 are each H, then R_6, R_7, and R_8 are not all simultaneously H or unsubstituted benzoyl." Accordingly, the compounds described in Yatvin et al. as **beta-C5-ribose** and **beta-C5-Tribenzoate** do not fall within the genus of amended claim 1. Thus, as amended, claim 1 is not anticipated by Yatvin et al. Further, claims 2-7 and 9-12, which all ultimately depend from claim 1, are not anticipated. Reconsideration and withdrawal of this rejection is respectfully requested.

Claim Rejections under Section 103

Claims 8 and 13 are rejected as unpatentable over Yatvin et al. ("Yatvin") in view of Orain et al. ("Orian", J. Combin. Chem. (2002) vol. 4, 1-16) and Takatani et al. ("Takatani", Carbohyd. Res. (2003) vol. 338, 1073-1081). No other claims are recited in this rejection.

As stated by the Examiner, Yatvin does not teach R_6, R_7, and R_8 as independently selected protecting group moieties, with the exception of simultaneous **benzoyl substitution** – therefore Claim 1 was amended as discussed above. Applicants traverse this rejection since the combination of references does not provide a reasonable expectation of success in making the claimed compounds.

Examiner also states that the compound of Claim 13 is not taught in Yatvin. Applicants agree. Furthermore, the compound of Claim 13 has been specifically exemplified, isolated and characterized. Orain cannot cure the deficiency of Yatvin in teaching claim 13 or claim 8. Orain is directed exclusively to solid-phase organic synthesis, a specialized technique which is not employed in the claimed invention. It is well known to a skilled artisan that solid phase synthesis would be problematic in the preparation of ribose-based compounds, i.e., carbohydrates, much less ribosides or ribonucleosides. Further, Orain does not list any examples for preparation of pyridyl-substituted ribose compounds, as claimed. Therefore, it would not have been obvious, at the time of the invention, to employ the teachings of Orain, in combination with Yatvin to arrive at the claimed compounds.

Further, Takatani cannot cure the deficiency of either Yatvin or Orain. The fact that Takatani is directed to a very specific series of oligomannosides clearly demonstrates the difficulty of even simple protecting group transformations in carbohydrate synthesis, much less ribose-based compounds, even more so pyridine-substituted ribose compounds as claimed. Without more, a skilled person would not have had a reasonable expectation that the claimed compounds could be obtained by combining the teachings of Yatvin with Orain and Takatani. In conclusion, it is not generally the case that protecting group substitutions are either simple or predictable in this field of endeavor. Therefore, the Office action has not established a prima facie case of obviousness, and this rejection should be withdrawn.

Nonstatutory Double Patenting

Claims 1-19 are rejected on the ground of nonstatutory double patenting over claims 1-29 of U.S. Patent 10,000, 519 B2.

The present application is commonly owned and has inventors in common with U.S. Patent 10,000, 519 B2. The filing of a terminal disclaimer would overcome this rejection.

No claims in the present application have been indicated to be allowable. Applicant respectfully requests the filing of a terminal disclaimer be postponed until the full scope of allowable subject matter in this application is determined.

Claims Not Rejected Over the Prior Art of Record

Applicant notes that claims 3 and 14 are not rejected over the prior art cited in the rejections herein and are thus believed to be free of this prior art and allowable over this prior art. New claims 20 and 21 include certain limitations of claims 3 and 14 and are believed to also be free of this prior art and allowable over this prior art.

Conclusion

This response is accompanied by a Petition for Extension of Time of three months with the appropriate fee ($700). No excess claim fees are due. If the amount paid by EFS web is not correct, please deduct any fees required for timely submission, or credit any overpayment, to deposit account 121216.

Respectfully submitted,

/sallyasullivan/

Sally A. Sullivan
Reg. No. 32,064

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Email: chgpatent@leydig.com

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	15/905,922 Confirmation No. 1061
Filing Date	:	February 27, 2018
Applicant	:	The Queen's University of Belfast
First Named Inventor:	:	Marie MIGAUD
For	:	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof
Group Art Unit	:	1623
Examiner	:	Patrick T. Lewis
Docket No.	:	335040: 4-16A US
Customer No.	:	23713

CERTIFICATE OF EFS-WEB FILING

I hereby certify that this correspondence is being filed with the USPTO EFS-WEB system.

October 29, 2019 /cathynelson/
Date Cathy Nelson

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION FOR EXTENSION OF TIME UNDER 37 C.F.R. §1.136(a)

Sir,

Applicant hereby petitions for the minimum extension of time necessary so that the accompanying Amendment and Response to Non-Final Office Action is timely filed.

It is believed that an extension of three months is required. Although payment may be effected via the EFS-Web system, authorization is hereby given if necessary to charge Deposit Account 121216 in the amount of $700 (small entity status) for the extension of time fee for a small entity. If this amount is incorrect, or if necessary, please charge any required fees and credit any overpayments accordingly.

Respectfully submitted,

/sallyasullivan/

Sally A. Sullivan
Reg. No. 32,064

LEYDIG, VOIT & MAYER, Ltd.
4940 Pearl East Circle, Suite 200
Boulder, CO 80301
Telephone: (720) 795-7976
Facsimile: (312) 616-5700
Email: chgpatent@leydig.com

Electronic Patent Application Fee Transmittal	
Application Number:	15905922
Filing Date:	27-Feb-2018
Title of Invention:	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof
First Named Inventor/Applicant Name:	Marie MIGAUD
Filer:	Sally A. Sullivan/Cathy Nelson
Attorney Docket Number:	335040: 4-16A US
Filed as Small Entity	
Filing Fees for Utility under 35 USC 111(a)	

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	2253	1	700	700
Miscellaneous:				
		Total in USD ($)		**700**

Electronic Acknowledgement Receipt	
EFS ID:	37591075
Application Number:	15905922
International Application Number:	
Confirmation Number:	1061
Title of Invention:	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof
First Named Inventor/Applicant Name:	Marie MIGAUD
Customer Number:	23713
Filer:	Sally A. Sullivan/Cathy Nelson
Filer Authorized By:	Sally A. Sullivan
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	4-16A_US_efsCert.pdf	67480 53c0aa1d9f1b629016096ab3f04443faccc63c77	no	1
Warnings:					
Information:					
2		4-16A_US_RTOA_of_4-29-19_FINAL.pdf	327442 ef85964515172a57d9798b4520a7c1a25d426488	yes	12
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	7	
	Applicant Arguments/Remarks Made in an Amendment		8	12	
Warnings:					
Information:					
3	Extension of Time	4-16A_US_extension.pdf	69772 a00df9d934febebcf4d8fb4c53db21d4f42919f5	no	1
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30856 e26858dc6e11bd130ecad4c5b4177409772ef902	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	495550		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

CERTIFICATE OF EFS-WEB FILING

Application No.	:	15/905,922 Confirmation No. 1061
Filing Date	:	February 27, 2018
Applicant	:	The Queen's University of Belfast
First Named Inventor:	:	Marie MIGAUD
For	:	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof
Group Art Unit	:	1623
Examiner	:	Patrick T. Lewis
Docket No.	:	335040: 4-16A US
Customer No.	:	23713

I hereby certify that the following, along with any other document(s) referenced to as being attached or enclosed:

1. **This Certificate of EFS-WEB Filing – 1 page**
2. **Amendment and Response to Office Action – 12 pages**
3. **Petition for Extension of Time – 1 page**

are being submitted electronically through the United States Patent Office EFS-WEB System, to be directed to:

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

On **October 29, 2019**

Cathy Nelson Filing Correspondence)

/cathynelson/
(Signature of Person Filing Correspondence)

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/905,922	Filing Date 02/27/2018	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $230 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	10/29/2019	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 20	Minus	** 20	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	*** 3	= 0		x $230 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/MARSHA R RICHARDS/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/905,922	02/27/2018	Marie MIGAUD	335040: 4-16A US	1061

23713 7590 04/29/2019

Leydig, Voit & Mayer, Ltd. (GS BOULDER)
4940 Pearl East Circle
Suite 200
Boulder, CO 80301

EXAMINER
LEWIS, PATRICK T

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
04/29/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

chgpatent@leydig.com

PTOL-90A (Rev. 04/07)

Office Action Summary	**Application No.** 15/905,922	**Applicant(s)** MIGAUD et al.	
	Examiner PATRICK T LEWIS	**Art Unit** 1623	**AIA (FITF) Status** Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b)☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☑ Claim(s) 1-19 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☑ Claim(s) 1-19 is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 27 February 2018 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☑ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☑ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☑ Certified copies of the priority documents have been received in Application No. 14/908,831.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 10012018.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities

undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

3. Claims 1-19 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-29 of U.S. Patent No. 10,000,519 B2. Although the claims at issue are not identical, they are not patentably distinct from each other because the instantly claimed compound(s) are employed/produced by the method(s) of the ‘519 patent. Claims 1-29 read upon the instantly claimed elements. Thus, claims 1-19 would have been anticipated by claims 1-29 of U.S. Patent No. 10,000,519 B2.

Claim Rejections - 35 USC § 112

4. The following is a quotation of 35 U.S.C. 112(b):

> (b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 17-18 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

The terms “formula 16” and “formula 17” are not defined by the claims or specification. Thus, one of ordinary skill in the art would not have been apprised of the metes and bounds of the claimed compound(s). It appears that the term “formula” was a typo, and applicant intended to recite the term “claim”; thus, claim 17 has been interpreted as a “compound of claim 16”, and claim 18 has been interpreted as a “compound of claim 17”.

Claim Rejections - 35 USC § 102

6. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

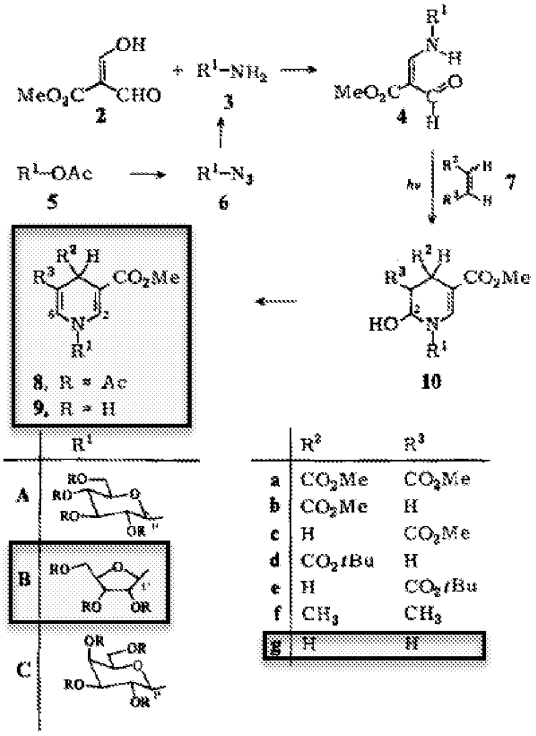
7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale or otherwise available to the public before the effective filing date of the claimed invention.
>
> (a)(2) the claimed invention was described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b), in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention.

8. Claim(s) 1-2, 4-7, and 9-12 is/are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Tietze et al. Angewandte Chemie / Angew. Chem. (1985), Vol. 97, pages 135-136 (Tietze).

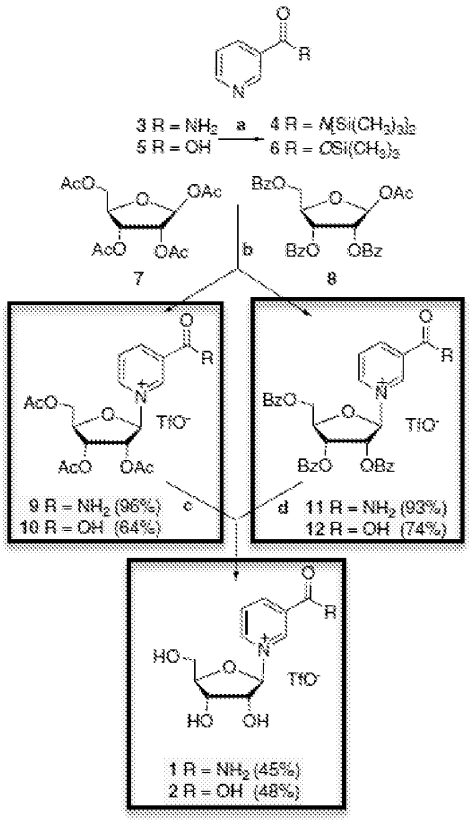
Tietze teaches compounds **8Bg** and **9Bg** which are embraced by instant formula (III) wherein n is 1; m is 1; Y is O; R_1 is methyl; R_2-R_5 is H; and R_6, R_7, and R_8 is H or Ac (see figure). Thus, claims 1-2, 4-7, and 11-12 are anticipated.



9. Claim(s) 16-19 is/are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Franchetti et al. Bioorganic & Medicinal Chemistry Letters (2004), Vol. 14, pages 4655-4658 (Franchetti).

Franchetti teaches that the **β-anomers of** N-ribofuranosylnicotine-3-carboxamide (**β-NAR**) and its nicotinic acid analog (**β-NaR**) were obtained by stereoselective synthesis via glycosylation of the presilylated bases under Vorbruggen's protocol (Abstract). Nicotinamide riboside (β-NAR) is an intermediate in one biosynthetic pathway by which nicotinamide is converted into NAD (page 4655, Introduction). In fact, nicotinamide or nicotinamide riboside derived from degradation of NAD can be reused by nicotinamide phosphoribosyl transferase or ribosylnicotinamide kinase, respectively, to form the ribotide NMN that is adenylated to NAD by nicotinamide mononucleotide adenylyltransferase (NMNAT). Franchetti teaches that there is evidence that hNMNAT is weakly expressed in tumor cells, determining thus interest in the enzyme as a target for anticancer drugs. In this respect, some **nicotinamide riboside analogs** have been described as **antitumor agents** involving their metabolic conversion to NAD analogs by NMNAT activity. Kinetic and structural studies of both human and bacterial NMNAT require the β-anomer of nicotinamide monoribotide as a substrate and of nicotinamide riboside as a product of the NAD degradation pathway.

Compounds **1**, **2**, and **9-12** are embraced by instant formula (IV) wherein n is 0 or 1; m is 1; Y is O; R_1 is H or NH_2; R_2-R_5 is H; and R_6, R_7, and R_8 is H, Ac, or Bz (see Scheme 1). Thus, claims 16-19 are anticipated.



Scheme 1. Reagents and conditions: (a) TMSCl, HMDS, 120 °C, 5h; (b) TMSOTf, $ClCH_2CH_2Cl$ anhydrous, 45°C, 2h; (c) NH_3/CH_3OH, −5°C, 6h; (d) NH_3/CH_3OH, −5°C, 48h.

10. Claim(s) 1-7, 9-12, and 15 is/are rejected under 35 U.S.C. 102(a)(1) and 102(a)(2) as being anticipated by Yatvin et al. US 6,689,760 B1 (Yatvin).

Yatvin teaches **β-C5-ribose** and **β-C5-Tribenzoate** which are embraced by instant formula (III) wherein n is 0; m is 1; R_1 is NH_2; R_2-R_5 is H; and R_6, R_7, and R_8 is H or Bz (Fig. 4I; column 13, lines 34-50). Thus, claims 1-7, 11-12, and 15 are anticipated.

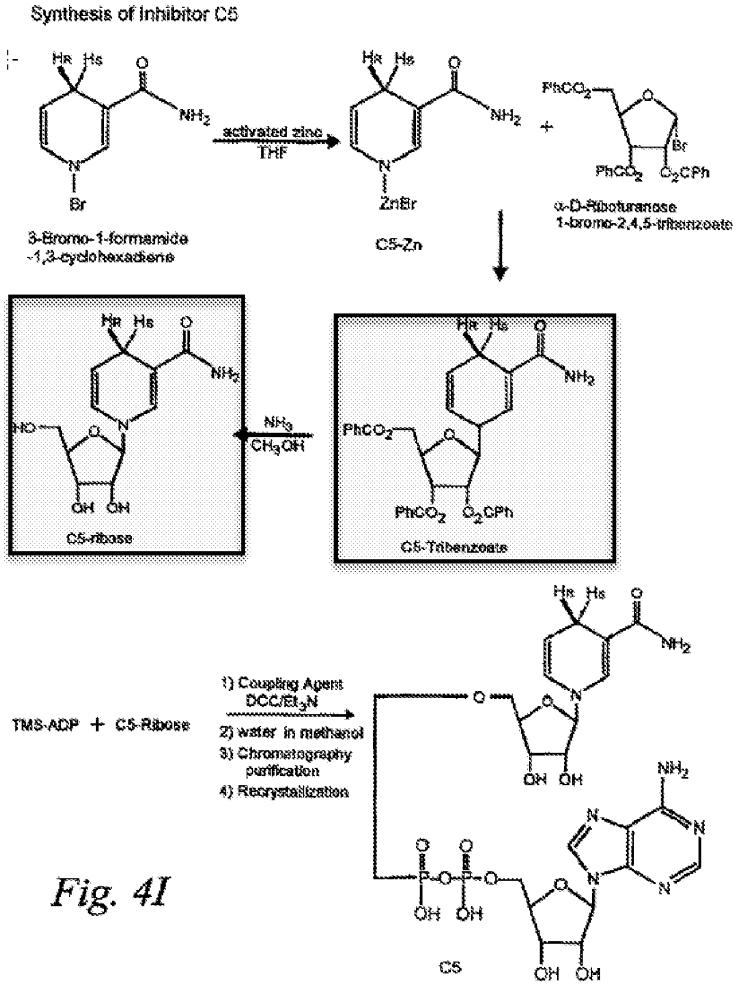


Fig. 4I

Claim Rejections - 35 USC § 103

11. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

12. The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

13. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

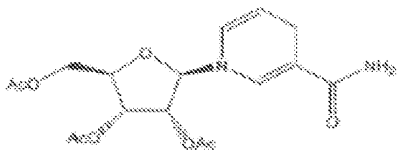
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

15. Claims 8 and 13 is/are rejected under 35 U.S.C. 103 as being unpatentable over Yatvin et al. US 6,689,760 B1 (Yatvin) as applied to claims 1-7, 9-12, and 15 above, and

further in view of Orain et al. Journal of Combinatorial Chemistry (2002), Vol. 4, pages 1-16 (Orain) and Takatani et al. Carbohydrate Research (2003), Vol. 338, pages 1073-1081 (Takatani).

Yatvin differs from the instantly claimed invention in that 1) Yatvin does not teach a compound wherein corresponding moieties R_6, R_7, and R_8 are each independently an ether-type protecting group, a silyl-type protecting group, trifluoroacetyl, or trichloroacetyl (claim 8) and 2) Yatvin does not teach triacetyl-1,4-dihydronicotinamide riboside:



(claim 13).

However, these deficiencies would have been obvious in view of the teachings of Orain and Takatani.

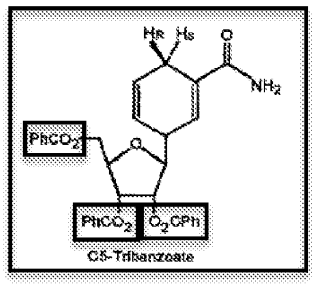
Orain relates to protecting groups employed in solid-phase organic chemistry. Orain teaches that by far the most common base-labile group used for the **protection of hydroxyl groups** is the **acetyl group** (**Ac**) (page 7). Other hydroxyl protecting groups include **benzoyl** (**Bz**) (page 7), **silyl protecting groups** (page 8) such as TBDMS, TBDPS, TMS, or TIPS, and **allyl** (page 8).

Takatani teaches that **trifluoroacetyl** (**TFA**) esters were demonstrated to be useful temporary **hydroxyl group protection** in facile oligosaccharide synthesis (Abstract).

In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); Schenck v. Nortron Corp., 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983).

In the instant case, the references may be combined to show obviousness because Yatvin, Orain, and Takatani are each drawn to hydroxyl group protection. They are from the same field of endeavor, and/or are reasonably pertinent to a compound of instant formula (III).

In the absence of unexpected results, it would have been obvious to one of ordinary skill in the art at the time of filing to substitute the Bz protecting groups (hydroxyl protecting groups) of C5-tribenzoate with another known hydroxyl protecting group such as TBDMS (claim 8), TBDPS (claim 8), allyl (claim 8), TFA (claim 8), or acetyl (claim 13) in view of the teachings of Orain and Takatani as set forth supra.



The simple substitution of one known element (e.g., hydroxyl protecting group) for another to obtain predictable results is prima facie obvious.

To reject a claim based on this rationale, Office personnel must resolve the Graham factual inquiries. Then, Office personnel must articulate the following:

(1) a finding that the prior art contained a device (method, product, etc.) which differed from the claimed device by the substitution of some components (step, element, etc.) with other components;

(2) a finding that the substituted components and their functions were known in the art;

(3) a finding that one of ordinary skill in the art could have substituted one known element for another, and the results of the substitution would have been predictable; and

(4) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

The rationale to support a conclusion that the claim would have been obvious is that the substitution of one known element for another yields predictable results to one of ordinary skill in the art.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

All of the instant limitations are taught by the combination of Yatvin, Orain, and Takatasni. A person of ordinary skill in the art would have had a reason to combine the teachings of Yatvin, Orain, and Takatasni. A person of ordinary skill in the art would have had a reasonable expectation of success in combining the teachings of Yatvin, Orain, and

Takatasni. Thus, claims 8 and 13 would have been obvious based on the preponderance of the evidence.

Conclusion

16. Claims 1-19 are pending. Claims 1-19 are rejected. No claims are allowed.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PATRICK T LEWIS whose telephone number is (571)272-0655. The examiner can normally be reached on Monday to Friday, 10 AM to 4 PM EST (Maxi Flex).

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on (571) 272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on

access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/PATRICK T LEWIS/
Primary Examiner, Art Unit 1623

/PL/

Notice of References Cited	Application/Control No. 15/905,922	Applicant(s)/Patent Under Reexamination MIGAUD et al.	
	Examiner PATRICK T LEWIS	Art Unit 1623	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-6689760-B1	02-2004	Yatvin; Milton B.	C07H21/00	514/45
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Tietze et al. Angewandte Chemie / Angew. Chem. (1985), Vol. 97, pages 135-136.
	V	Franchetti et al. Bioorganic & Medicinal Chemistry Letters (2004), Vol. 14, pages 4655-4658.
	W	Orain et al. Journal of Combinatorial Chemistry (2002), Vol. 4, pages 1-16.
	X	Takatani et al. Carbohydrate Research (2003), Vol. 338, pages 1073-1081.

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/905,922	MIGAUD et al.
	Examiner	Art Unit
	PATRICK T LEWIS	1623

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Inventor, REGISTRY, CAPLUS, MEDLINE (see attached)	04/24/2019	/PL/

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/PATRICK T LEWIS/ Primary Examiner, Art Unit 1623	

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/905,922	MIGAUD et al.
	Examiner	Art Unit
	PATRICK T LEWIS	1623

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS										
☐ Claims renumbered in the same order as presented by applicant			☐ CPA		☐ T.D.		☐ R.1.47			
CLAIM		DATE								
Final	Original	04/24/2019								
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	17	✓								
	18	✓								
	19	✓								

IPR2026-00400
Exhibit 2008 Page 233

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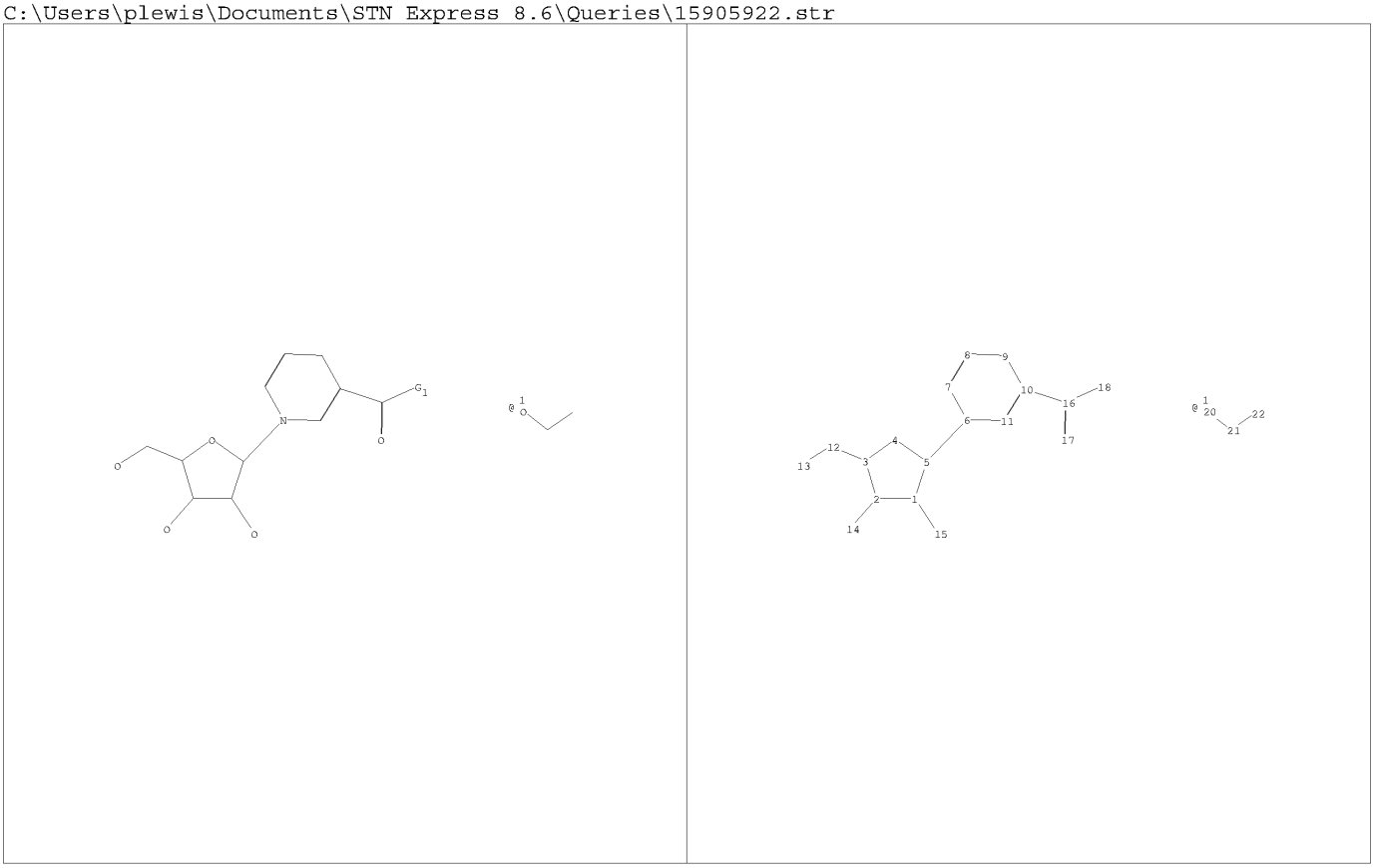
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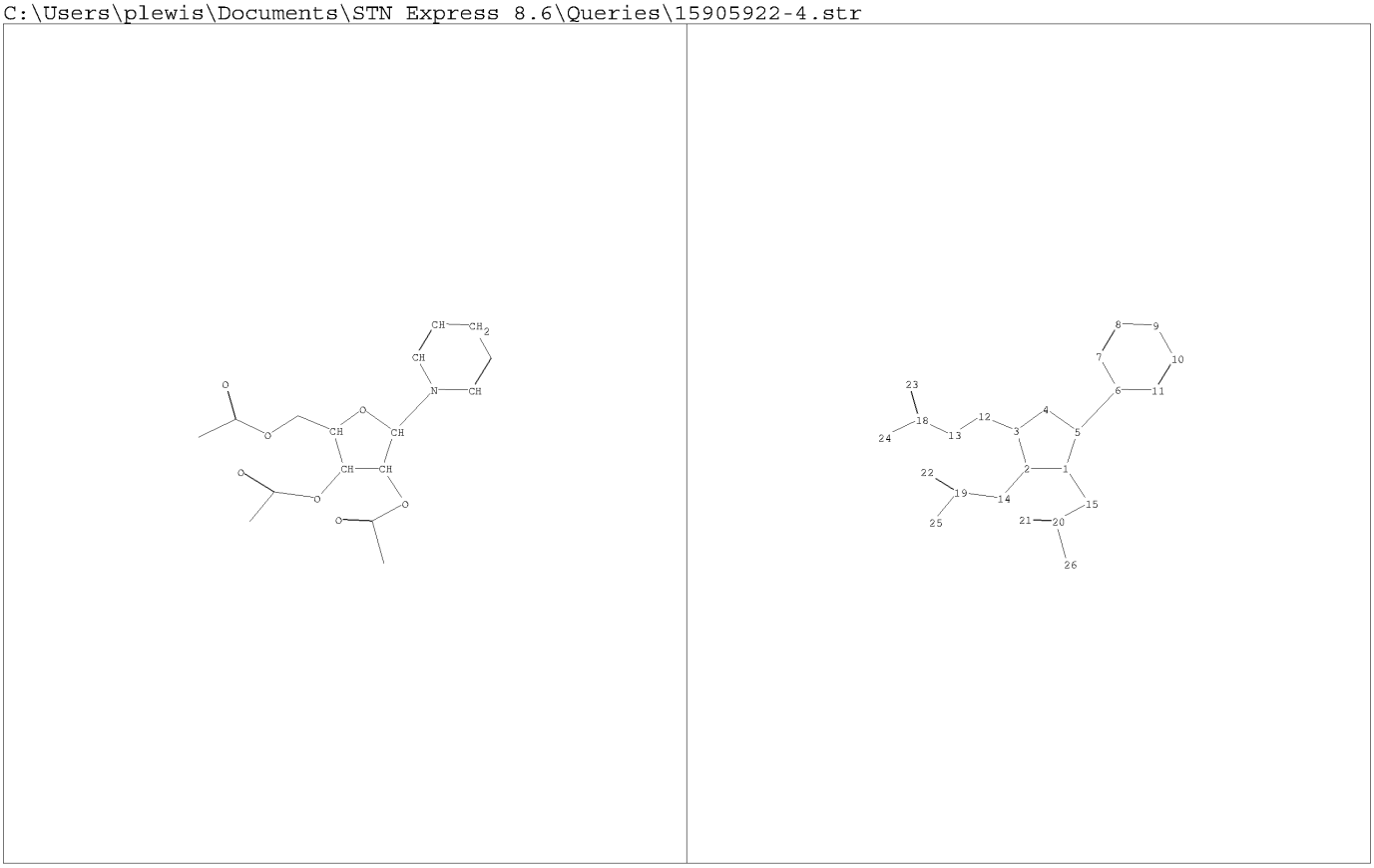


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12 13 14 15 16 17 18 20 21 22
ring nodes :
1 2 3 4 5 6 7 8 9 10 11
chain bonds :
1-15 2-14 3-12 5-6 10-16 12-13 16-17 16-18 20-21 21-22
ring bonds :
1-2 1-5 2-3 3-4 4-5 6-7 6-11 7-8 8-9 9-10 10-11
exact/norm bonds :
1-2 1-5 1-15 2-3 2-14 3-4 4-5 5-6 6-7 6-11 7-8 8-9 9-10 10-11 12-13 16-17 16-18
20-21
exact bonds :
3-12 10-16 21-22

G1:OH,NH2,[@1]

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom
12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS 20:CLASS 21:CLASS
22:CLASS

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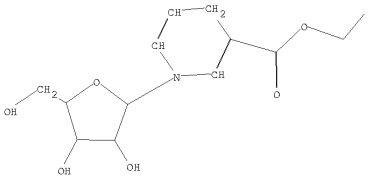
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ring nodes :
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chain bonds :
    1-15  2-14  3-12  5-6  12-13  13-18  14-19  15-20  18-23  18-24  19-22  19-25  20-21  20-26
ring bonds :
    1-2  1-5  2-3  3-4  4-5  6-7  6-11  7-8  8-9  9-10  10-11
exact/norm bonds :
    1-2  1-5  1-15  2-3  2-14  3-4  4-5  5-6  6-7  6-11  7-8  8-9  9-10  10-11  12-13  13-18  14-19
    15-20  18-23  19-22  20-21
exact bonds :
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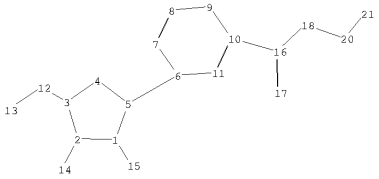

G1:OH,NH2

G2:H

Match level :
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    23:CLASS  24:CLASS  25:CLASS  26:CLASS
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chain nodes :
12 13 14 15 16 17 18 20 21
ring nodes :
1 2 3 4 5 6 7 8 9 10 11
chain bonds :
1-15 2-14 3-12 5-6 10-16 12-13 16-17 16-18 18-20 20-21
ring bonds :
1-2 1-5 2-3 3-4 4-5 6-7 6-11 7-8 8-9 9-10 10-11
exact/norm bonds :
1-2 1-5 1-15 2-3 2-14 3-4 4-5 5-6 6-7 6-11 7-8 8-9 9-10 10-11 16-17 16-18 18-20
exact bonds :
3-12 10-16 12-13 20-21

G1:Cb,Ak

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom
12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS 20:CLASS 21:CLASS

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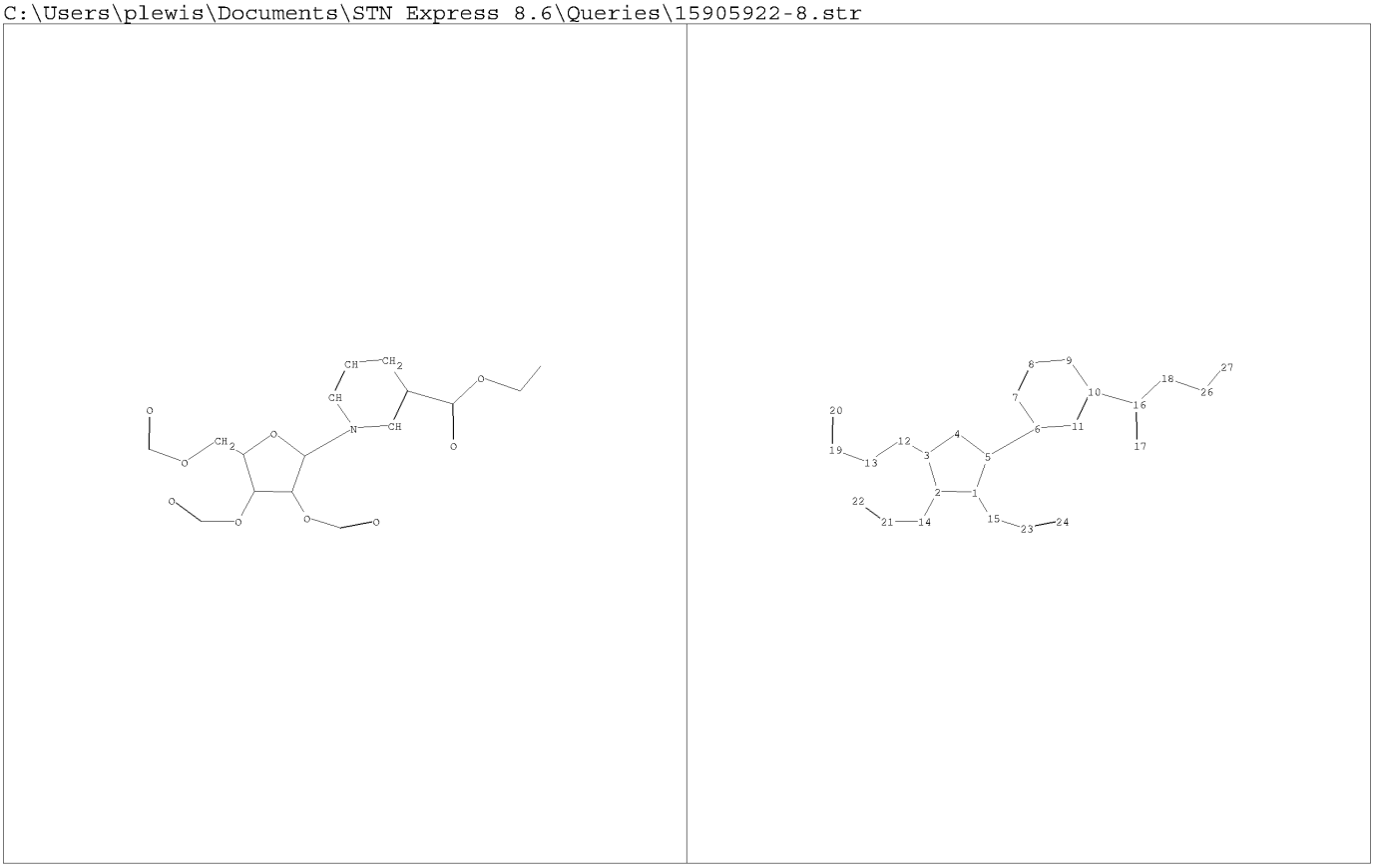
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L5              STRUCTURE UPLOADED
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L7           20 S L5 SSS FULL

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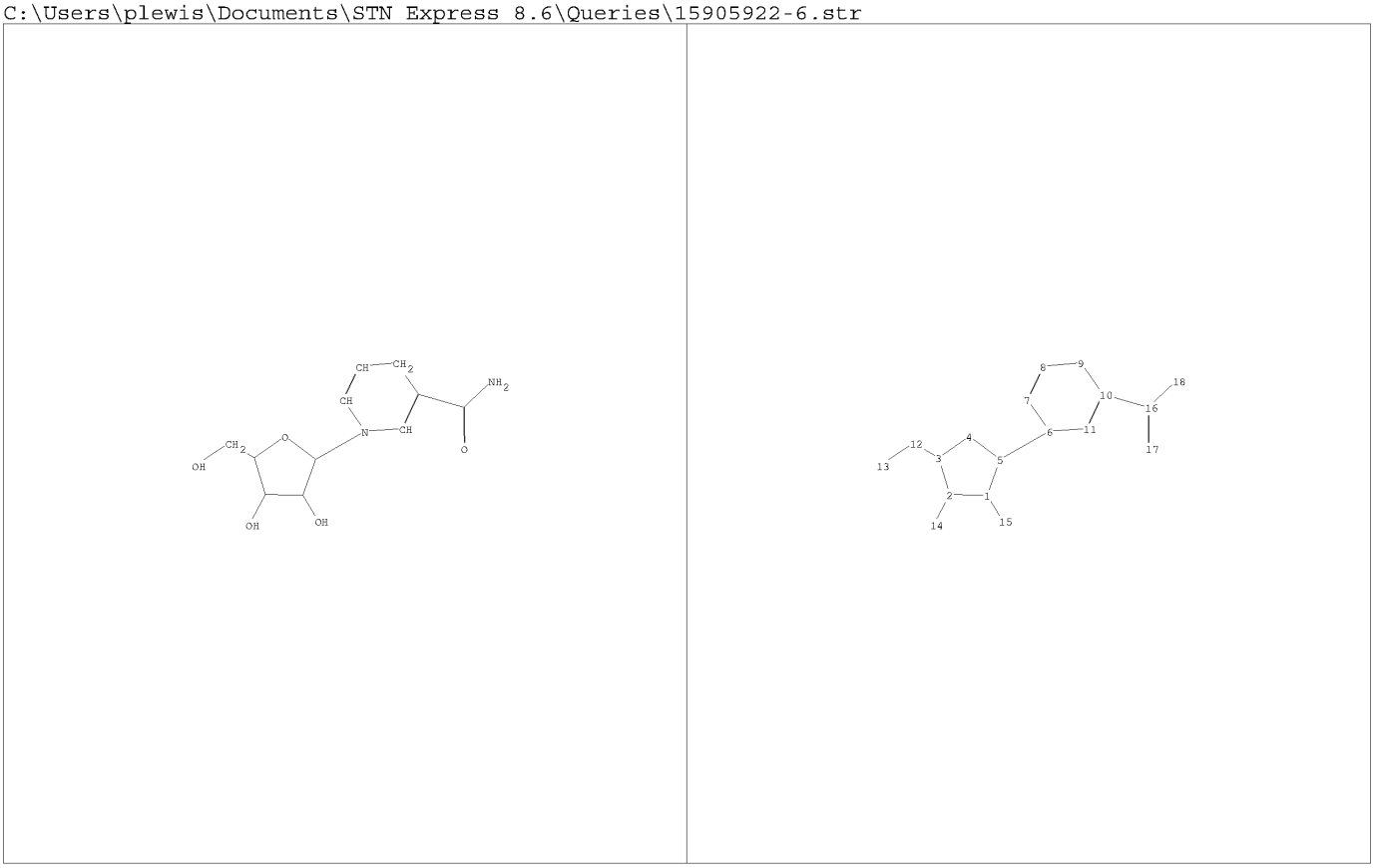


chain nodes :
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ring nodes :
1 2 3 4 5 6 7 8 9 10 11
chain bonds :
1-15 2-14 3-12 5-6 10-16 12-13 13-19 14-21 15-23 16-17 16-18 18-26 19-20 21-22
23-24 26-27
ring bonds :
1-2 1-5 2-3 3-4 4-5 6-7 6-11 7-8 8-9 9-10 10-11
exact/norm bonds :
1-2 1-5 1-15 2-3 2-14 3-4 4-5 5-6 6-7 6-11 7-8 8-9 9-10 10-11 13-19 14-21 15-23
16-17 16-18 18-26 19-20 21-22 23-24
exact bonds :
3-12 10-16 12-13 26-27

G1:Cb,Ak

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom
12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS 19:CLASS 20:CLASS
21:CLASS 22:CLASS 23:CLASS 24:CLASS 26:CLASS 27:CLASS

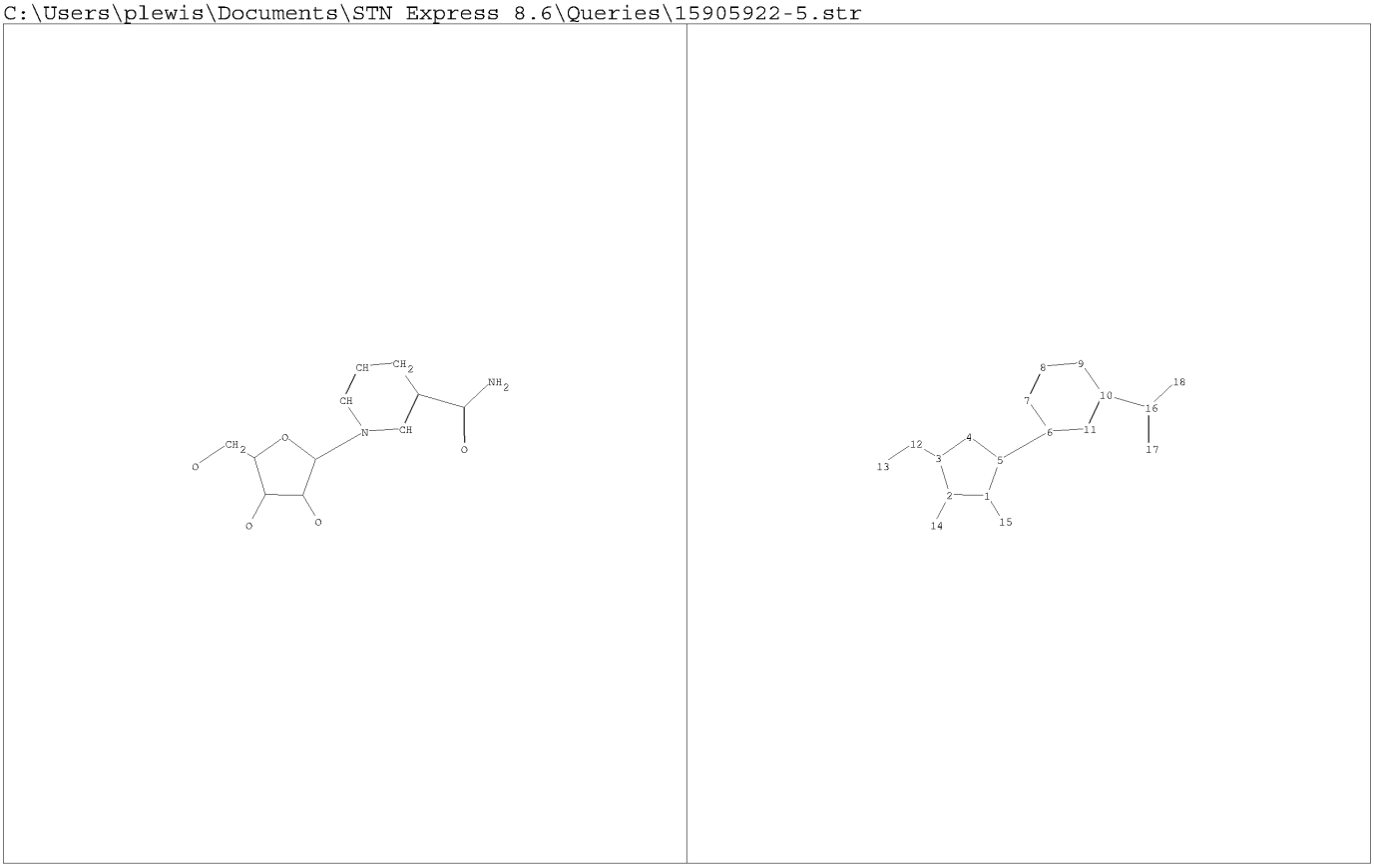
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chain nodes :
    12 13 14 15 16 17 18
ring nodes :
    1 2 3 4 5 6 7 8 9 10 11
chain bonds :
    1-15 2-14 3-12 5-6 10-16 12-13 16-17 16-18
ring bonds :
    1-2 1-5 2-3 3-4 4-5 6-7 6-11 7-8 8-9 9-10 10-11
exact/norm bonds :
    1-2 1-5 1-15 2-3 2-14 3-4 4-5 5-6 6-7 6-11 7-8 8-9 9-10 10-11 16-17 16-18
exact bonds :
    3-12 10-16 12-13

Match level :
    1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom
    12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS

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chain nodes :
    12 13 14 15 16 17 18
ring nodes :
    1 2 3 4 5 6 7 8 9 10 11
chain bonds :
    1-15 2-14 3-12 5-6 10-16 12-13 16-17 16-18
ring bonds :
    1-2 1-5 2-3 3-4 4-5 6-7 6-11 7-8 8-9 9-10 10-11
exact/norm bonds :
    1-2 1-5 1-15 2-3 2-14 3-4 4-5 5-6 6-7 6-11 7-8 8-9 9-10 10-11 16-17 16-18
exact bonds :
    3-12 10-16 12-13

Match level :
    1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom
    12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS

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L2           50 S L1 SSS SAM
L3         2148 S L1 SSS FULL

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L4       101078 S L3

     FILE 'REGISTRY' ENTERED AT 18:33:55 ON 23 APR 2019
L5              STRUCTURE UPLOADED
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L7           20 S L5 SSS FULL

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L8           46 S L7

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L16          14 S L15

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Substitute for form 1449/PTO, based on PTO/SB/08A and 08B		
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Application Number	**15/905,922**
	Filing Date	**February 27, 2018**
	First Named Inventor	**Marie MIGAUD**
	Art Unit	**1673**
	Examiner Name	**Patrick T. Lewis**
	Attorney Docket Number	**335040: 4-16A US**

Confirmation No. 1061 9/28/2018

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number	Issue Date (MM-DD-YYYY)	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number	Publication Date (MM-DD-YYYY)	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.[1]	Foreign Patent Document Number (include WIPO country code)	Publication Date (MM-DD-YYYY)	Name	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear (or entire document unless noted otherwise)	T[2]
	1	WO 2011/081942	07-11-2011	Sauve et al.		
	2	WO 2007/061798	05-31-2007	Sauve et al.		
	3	WO 2002/04478	01-17.2002	Yatvin et al.		
	4	WO 1993/08288	04-29-1993	Anlezark et al.		

NON-PATENT LITERATURE DOCUMENTS

Examiner Initial*	Cite No.	REFERENCE Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	5	International Search Report and Written Opinion corresponding to International Application No. PCT/EP2014/065971, mailed April 9, 2014, 10 pages	
	6	International Preliminary Report on Patentability corresponding to International Application No. PCT/EP2014/065971, issued February 2, 2016	
	7	Extended European Search Report, EP Application No. 17191481.5, issued March 1, 2018, 17 pages.	
	8	M. R. Atkinson et al., "98. Synthesis of glycosylpyridinium compounds from glycosylamines and from glycosyl halides," Journal of the Chemical Society, pages 610-615, January 1, 1965	
	9	Franchetti et al., Stereoselective synthesis of nicotinamide ß-riboside and nucleoside analogs, Bioorganic & Medicinal Chemistry Letters 14:4655-4658, 2004	
	10	E. J. Freyne et al., "Stereospecific synthesis of a novel series of pyridine nucleosides," Carbohydrate Research 78(2):235-242, January 15, 1980	

Examiner Signature	/PATRICK T LEWIS/	Date Considered	04/23/2019

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2]Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5]Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L/

Substitute for form 1449/PTO, based on PTO/SB/08A and 08B		
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Application Number	**15/905,922**
	Filing Date	**February 27, 2018**
	First Named Inventor	**Marie MIGAUD**
	Art Unit	**1673**
	Examiner Name	**Patrick T. Lewis**
	Attorney Docket Number	**335040: 4-16A US**

Confirmation No. 1061 9/28/2018

Examiner Initial*	Cite No.	REFERENCE Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	11	L. J. Haynes et al., "Codehydrogenases, Part II. A synthesis of nicotinamide nucleotide," Journal Chemical Society, pages 3727-3732, January 1, 1957	
	12	R. J. Knox et al., "Virtual cofactors for an Escherichia Coli nitroreductase enzyme: Relevance to reductively activated prodrugs in antibody directed enzyme prodrug therapy (adept)," Biochemical Pharmacology 49(11):1647-1647, January 1, 1995	
	13	S. Ladame et al., "Selective inhibition of trypanosoma cruzi GAPDH by "bi-substrate" analogues," Organic & Biomolecular Chemistry 3(11):2070-2072, January 1, 2005	
	14	J. Lee et al., "A chemical synthesis of nicotinamide adenine dinucleotide (NAD+)," Chemical Communications 8, January 1, 1999, pages 729-730	
	15	N. L. Lifshits et al., "Synthesis and properties of nicotinic acid derivatives containing 2,2,6,6-tetramethylpiperidin-1-oxyl residue," Chemical Abstracts Database, Database accession no. 85-177804, January 1, 1976	
	16	I. A. Mikhailopulo et al., "Synthesis of glycosides of nicotinamide and nicotinamide mononucleotide," Synthesis 1981(5):388-389, January 1, 1981	
	17	N. J. Oppenheimer, "Synthesis of nicotinamide furanosides. Proton NMR study of the solution conformation of .alpha. and .beta., oxidized and reduced nicotinamide xylosides," Journal of Carbohydrates, Nucleosides, Nucleotides 5(3):251-260, January 1, 1978	
	18	R. Riemschneider et al., "The effects of nonphysiological compounds on metabolism, IV. Nicotinylamino acid esters and nucleoside derivatives," pages 99-106, January 1, 1976	
	19	M. L. Sinnott et al., "Preparation and conformation of [alpha]-1-arabinofuranosyl-pyridinium salts, and hydrolysis of the 4-bromoisoquinolinium compound," Carbohydrate Research 136:357-368, February 1, 1985	
	20	Tanimori et al., "An efficient chemical synthesis of nicotinamide riboside (NAR) and analogues", Bioorganic & Medicinal Chemistry Letters 12(8):1135-1137, 2002	
	21	L. F. Tietze et al., "Synthese von 1,4-dihydropyridinnucleosiden durch photochemische cycloaddition," Angew. Chemie 97(2):135-136, February 1, 1985, with English Abstract	
	22	Yang et al., "Syntheses of nicotinamide riboside and derivatives: Effective agents for increasing nicotinamide adenine dinucleotide concentrations in mammalian cells," Journal of Medicinal Chemistry 50:6458-6461, 2007	

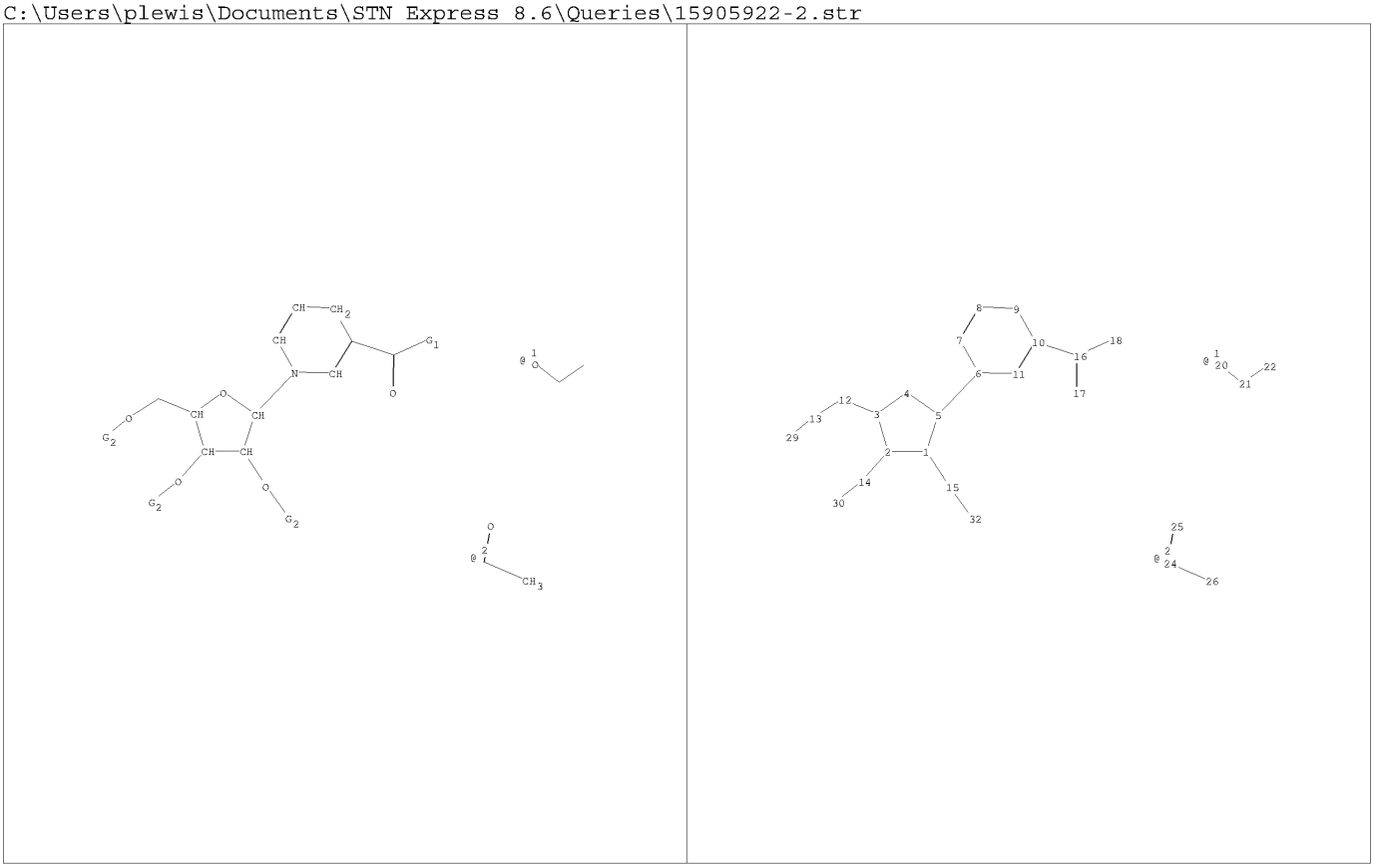
Examiner Signature	/PATRICK T LEWIS/	Date Considered	04/23/2019

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2]Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5]Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L/

C:\Users\plewis\Documents\STN Express 8.6\Queries\15905922-2.str



chain nodes :
12 13 14 15 16 17 18 20 21 22 24 25 26 29 30 32
ring nodes :
1 2 3 4 5 6 7 8 9 10 11
chain bonds :
1-15 2-14 3-12 5-6 10-16 12-13 13-29 14-30 15-32 16-17 16-18 20-21 21-22 24-25
24-26
ring bonds :
1-2 1-5 2-3 3-4 4-5 6-7 6-11 7-8 8-9 9-10 10-11
exact/norm bonds :
1-2 1-5 1-15 2-3 2-14 3-4 4-5 5-6 6-7 6-11 7-8 8-9 9-10 10-11 12-13 13-29 14-30
15-32 16-17 16-18 20-21 24-25
exact bonds :
3-12 10-16 21-22 24-26

G1:OH,NH2,[@1]

G2:H,[@2]

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom
12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS 20:CLASS 21:CLASS
22:CLASS 24:CLASS 25:CLASS 26:CLASS 29:CLASS 30:CLASS 32:CLASS

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L3          292 S L1 SSS FULL

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L4        36810 S L3

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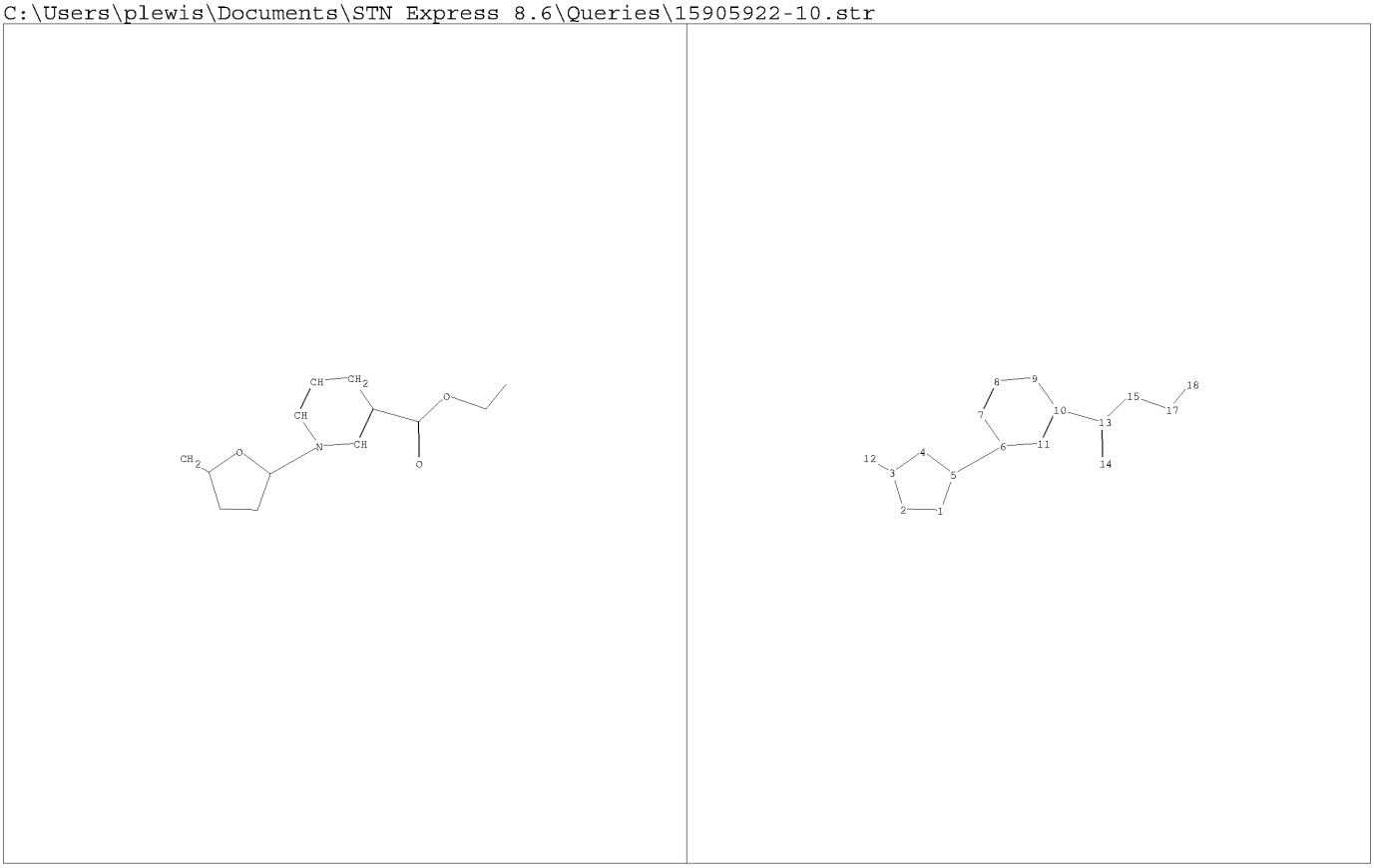
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L13          13 S L12
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ring nodes :
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chain bonds :
    3-12 5-6 10-13 13-14 13-15 15-17 17-18
ring bonds :
    1-2 1-5 2-3 3-4 4-5 6-7 6-11 7-8 8-9 9-10 10-11
exact/norm bonds :
    1-2 1-5 2-3 3-4 4-5 5-6 6-7 6-11 7-8 8-9 9-10 10-11 13-14 13-15 15-17
exact bonds :
    3-12 10-13 17-18

G1:Cb,Ak

Match level :
    1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom
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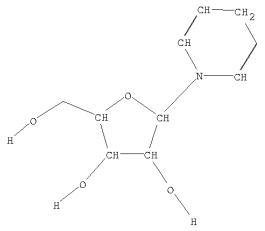
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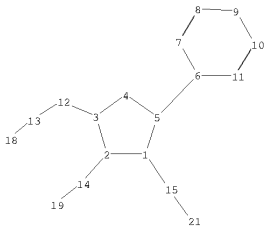
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L3           21 S L1 SSS FULL

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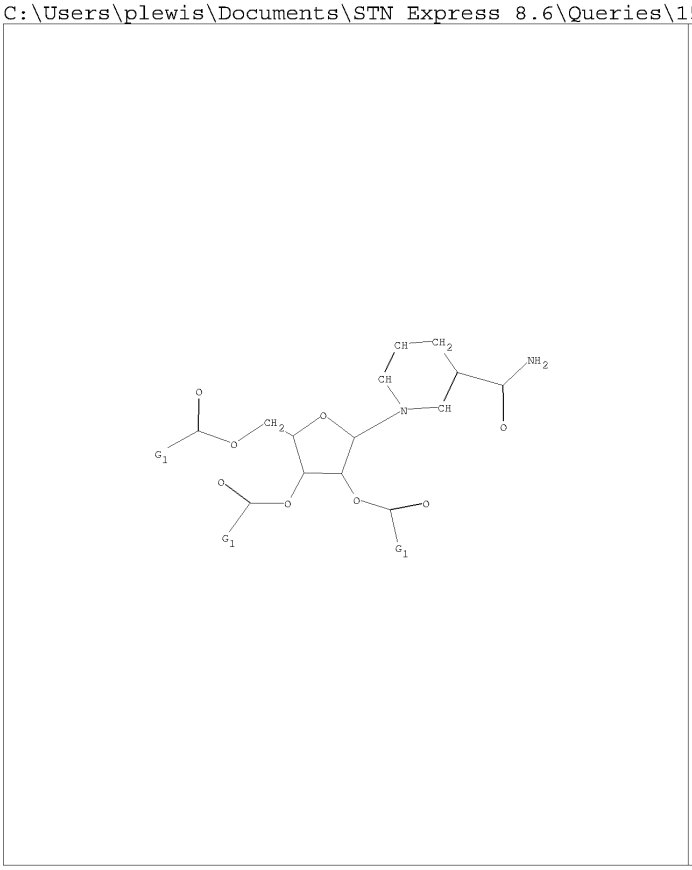
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ring nodes :
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chain bonds :
    1-15  2-14  3-12  5-6  12-13  13-18  14-19  15-21
ring bonds :
    1-2  1-5  2-3  3-4  4-5  6-7  6-11  7-8  8-9  9-10  10-11
exact/norm bonds :
    1-2  1-5  1-15  2-3  2-14  3-4  4-5  5-6  6-7  6-11  7-8  8-9  9-10  10-11  12-13
exact bonds :
    3-12  13-18  14-19  15-21

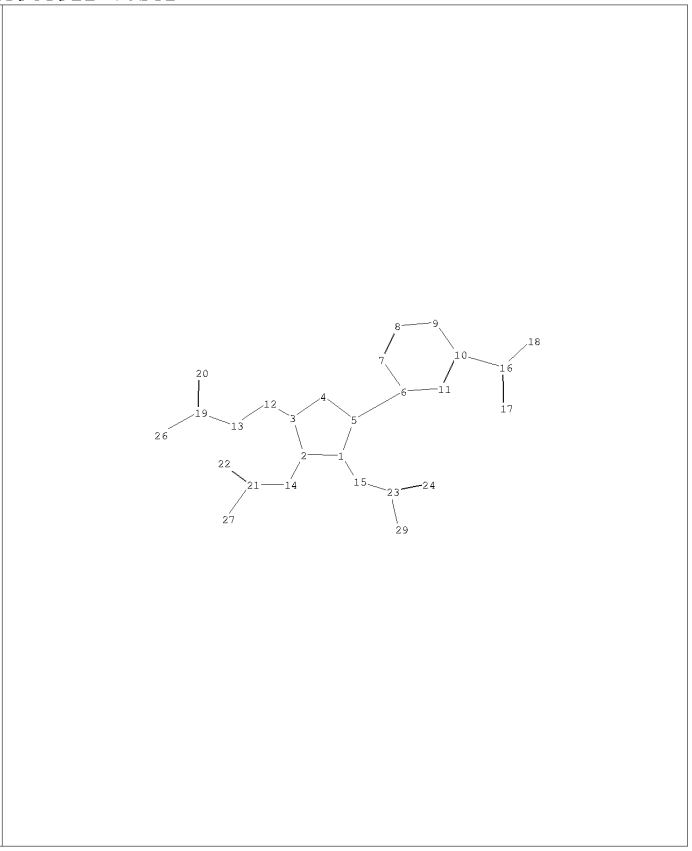

G1:OH,NH2

G2:H

Match level :
    1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:Atom  11:Atom
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C:\Users\plewis\Documents\STN Express 8.6\Queries\15905922-7.str





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chain nodes :
    12  13  14  15  16  17  18  19  20  21  22  23  24  26  27  29
ring nodes :
    1  2  3  4  5  6  7  8  9  10  11
chain bonds :
    1-15  2-14  3-12  5-6  10-16  12-13  13-19  14-21  15-23  16-17  16-18  19-20  19-26  21-22
    21-27  23-24  23-29
ring bonds :
    1-2  1-5  2-3  3-4  4-5  6-7  6-11  7-8  8-9  9-10  10-11
exact/norm bonds :
    1-2  1-5  1-15  2-3  2-14  3-4  4-5  5-6  6-7  6-11  7-8  8-9  9-10  10-11  13-19  14-21  15-23
    16-17  16-18  19-20  19-26  21-22  21-27  23-24  23-29
exact bonds :
    3-12  10-16  12-13


G1:Cb,Ak

Match level :
    1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:Atom  11:Atom
    12:CLASS  13:CLASS  14:CLASS  15:CLASS  16:CLASS  17:CLASS  18:CLASS  19:CLASS  20:CLASS
    21:CLASS  22:CLASS  23:CLASS  24:CLASS  26:CLASS  27:CLASS  29:CLASS
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PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/905,922	Filing Date 02/27/2018	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	12/14/2018	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 10	Minus	** 20	= 0	X $50 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $230 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
DIANE FLOYD

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Substitute for form 1449/PTO, based on PTO/SB/08A and 08B		
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Application Number	**15/905,922**
	Filing Date	**February 27, 2018**
	First Named Inventor	**Marie MIGAUD**
	Art Unit	**1673**
	Examiner Name	**Patrick T. Lewis**
	Attorney Docket Number	**335040: 4-16A US**

Confirmation No. 1061 9/28/2018

U.S. PATENT DOCUMENTS

Examiner Initial*	Cite No.	Patent Number	Issue Date (MM-DD-YYYY)	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No.	Publication Number	Publication Date (MM-DD-YYYY)	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No.[1]	Foreign Patent Document Number (include WIPO country code)	Publication Date (MM-DD-YYYY)	Name	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear (or entire document unless noted otherwise)	T [2]
	1	WO 2011/081942	07-11-2011	Sauve et al.		
	2	WO 2007/061798	05-31-2007	Sauve et al.		
	3	WO 2002/04478	01-17.2002	Yatvin et al.		
	4	WO 1993/08288	04-29-1993	Anlezark et al.		

NON-PATENT LITERATURE DOCUMENTS

Examiner Initial*	Cite No.	REFERENCE Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	5	International Search Report and Written Opinion corresponding to International Application No. PCT/EP2014/065971, mailed April 9, 2014, 10 pages	
	6	International Preliminary Report on Patentability corresponding to International Application No. PCT/EP2014/065971, issued February 2, 2016	
	7	Extended European Search Report, EP Application No. 17191481.5, issued March 1, 2018, 17 pages.	
	8	M. R. Atkinson et al., "98. Synthesis of glycosylpyridinium compounds from glycosylamines and from glycosyl halides," Journal of the Chemical Society, pages 610-615, January 1, 1965	
	9	Franchetti et al., Stereoselective synthesis of nicotinamide ß-riboside and nucleoside analogs, Bioorganic & Medicinal Chemistry Letters 14:4655-4658, 2004	
	10	E. J. Freyne et al., "Stereospecific synthesis of a novel series of pyridine nucleosides," Carbohydrate Research 78(2):235-242, January 15, 1980	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2]Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5]Applicant is to place a check mark here if English language translation is attached.

Substitute for form 1449/PTO, based on PTO/SB/08A and 08B		
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Application Number	**15/905,922**
	Filing Date	**February 27, 2018**
	First Named Inventor	**Marie MIGAUD**
	Art Unit	**1673**
	Examiner Name	**Patrick T. Lewis**
	Attorney Docket Number	**335040: 4-16A US**

Confirmation No. 1061 9/28/2018

Examiner Initial*	Cite No.	REFERENCE Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	11	L. J. Haynes et al., "Codehydrogenases, Part II. A synthesis of nicotinamide nucleotide," Journal Chemical Society, pages 3727-3732, January 1, 1957	
	12	R. J. Knox et al., "Virtual cofactors for an Escherichia Coli nitroreductase enzyme: Relevance to reductively activated prodrugs in antibody directed enzyme prodrug therapy (adept)," Biochemical Pharmacology 49(11):1647-1647, January 1, 1995	
	13	S. Ladame et al., "Selective inhibition of trypanosoma cruzi GAPDH by "bi-substrate" analogues," Organic & Biomolecular Chemistry 3(11):2070-2072, January 1, 2005	
	14	J. Lee et al., "A chemical synthesis of nicotinamide adenine dinucleotide (NAD+)," Chemical Communications 8, January 1, 1999, pages 729-730	
	15	N. L. Lifshits et al., "Synthesis and properties of nicotinic acid derivatives containing 2,2,6,6-tetramethylpiperidin-1-oxyl residue," Chemical Abstracts Database, Database accession no. 85-177804, January 1, 1976	
	16	I. A. Mikhailopulo et al., "Synthesis of glycosides of nicotinamide and nicotinamide mononucleotide," Synthesis 1981(5):388-389, January 1, 1981	
	17	N. J. Oppenheimer, "Synthesis of nicotinamide furanosides. Proton NMR study of the solution conformation of .alpha. and .beta., oxidized and reduced nicotinamide xylosides," Journal of Carbohydrates, Nucleosides, Nucleotides 5(3):251-260, January 1, 1978	
	18	R. Riemschneider et al., "The effects of nonphysiological compounds on metabolism, IV. Nicotinylamino acid esters and nucleoside derivatives," pages 99-106, January 1, 1976	
	19	M. L. Sinnott et al., "Preparation and conformation of [alpha]-1-arabinofuranosyl-pyridinium salts, and hydrolysis of the 4-bromoisoquinolinium compound," Carbohydrate Research 136:357-368, February 1, 1985	
	20	Tanimori et al., "An efficient chemical synthesis of nicotinamide riboside (NAR) and analogues", Bioorganic & Medicinal Chemistry Letters 12(8):1135-1137, 2002	
	21	L. F. Tietze et al., "Synthese von 1,4-dihydropyridinnucleosiden durch photochemische cycloaddition," Angew. Chemie 97(2):135-136, February 1, 1985, with English Abstract	
	22	Yang et al., "Syntheses of nicotinamide riboside and derivatives: Effective agents for increasing nicotinamide adenine dinucleotide concentrations in mammalian cells," Journal of Medicinal Chemistry 50:6458-6461, 2007	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2]Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5]Applicant is to place a check mark here if English language translation is attached.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	15/905,922 Confirmation No. 1061
Filing Date	:	February 27, 2018
Applicant	:	The Queen's University of Belfast
First Named Inventor:	:	Marie MIGAUD
For	:	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof
Group Art Unit	:	1673
Examiner	:	Patrick T. Lewis
Docket No.	:	335040: 4-16A US
Customer No.	:	23713

CERTIFICATE OF EFS-WEB FILING

I hereby certify that this correspondence is being filed with the USPTO EFS-WEB system.

October 1, 2018 /sallyasullivan/
Date Sally A. Sullivan

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

The Examiner is respectfully requested to consider the references which may qualify as prior art. For the Examiner's convenience, the references are listed on the attached form prepared by Applicants; this form is generally based on Patent and Trademark Office form PTO/SB/08, but is not a USPTO form.

This application is a continuation of U.S. Patent Application No. 14/908,831, filed January 29, 2016, now Patent No. 10,000,519, issued June 19, 2018, which is a U.S. National Stage Application under 35 U.S.C. §371 of International Application No. PCT/EP2014/065971, filed July 24, 2014, which claims priority from United Kingdom Patent Application No. 1313465.5, filed on July 29, 2013.

The Examiner is advised that references listed on the substitute form 1449 have been submitted or made of record in U.S. Application No. 14/908,831, of which the present application is a division. In accordance with 37 CFR 1.98(d), as these references are of record in the parent case, copies of the cited references are not attached hereto, but will be provided upon request. Applicant, however, includes a copy of the International Preliminary Report on Patentability (IPRP) issued in PCT/EP2014/065971 with this submission. The Examiner is further directed to the file history of parent Application No. 14/908,831, which may be relevant to this application.

This information is cited in a spirit of forthrightness and cooperation to enable the applicants to obtain that measure of protection for the invention to which there is entitlement. However, no representation is made that the listed art actually qualifies as prior art under the patent statute and the mere use of any accompanying form, whether such form is generated by Applicant or is a USPTO form, is not an admission that all listed references are prior art. No representation is made that Applicants know of the best art.

It is believed that this submission does not require the payment of a fee. If this is not correct, please charge any required fee to deposit account no. 12-1216

Respectfully submitted,

/sallyasullivan/

Sally A. Sullivan
Reg. No. 32,064

LEYDIG, VOIT & MAYER, Ltd.
4875 Pearl East Circle, Suite 301
Boulder, CO 80301
Telephone: (720) 795-7976
Facsimile: (312) 616-5700
Email: chgpatent@leydig.com

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference P108531PC00	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/EP2014/065971	International filing date *(day/month/year)* 24 July 2014 (24.07.2014)	Priority date *(day/month/year)* 29 July 2013 (29.07.2013)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant THE QUEEN'S UNIVERSITY OF BELFAST		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 02 February 2016 (02.02.2016)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Agnès Wittmann-Regis e-mail: pt06.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2014/065971	24.07.2014	29.07.2013

International Patent Classification (IPC) or both national classification and IPC
INV. C07H19/048

Applicant
THE QUEEN'S UNIVERSITY OF BELFAST

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Nikolai, Joachim Telephone No. +49 89 2399-2832

Form PCT/ISA/237 (Cover Sheet) (July 2009)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-56
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-56
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-56
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

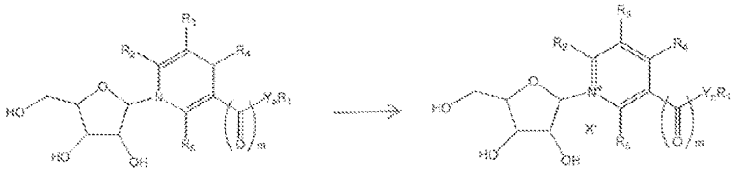
D1 WO 2007/061798 A2 (CORNELL RES FOUNDATION INC [US]; SAUVE ANTHONY ANDREW [US]; YANG TIANL) 31 May 2007 (2007-05-31)cited in the application

D2 FRANCHETTI P ET AL: "Stereoselective synthesis of nicotinamide beta-riboside and nucleoside analogs", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 14, no. 18, 20 September 2004 (2004-09-20), pages 4655-4658, XP027347993, ISSN: 0960-894X [retrieved on 2004-08-20] cited in the application

D3 SHINJI TANIMORI ET AL: "An efficient chemical synthesis of nicotinamide riboside (NAR) and analogues", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 12, no. 8, 1 April 2002 (2002-04-01), pages 1135-1137, XP55103511, ISSN: 0960-894X, DOI: 10.1016/S0960-894X(02)00125-7 cited in the application

1 **Novelty**(Art. 33(1) and 33(2) PCT)

1.1 The present claim 1 relates to a process for the preparation of a compound of formula (I) from a compound of formula (II).



(II) (I)

The claimed subject-matter differs from cited prior art on account of the use of a compound of formula (II) as the starting material which is not disclosed in the cited prior art: the processes for the synthesis of nicotinamide riboside derivatives disclosed in D1-D3 all use a glycosylation reaction under Vorbrüggen conditions (D1, figure 1; D2 scheme 1; D3 scheme 1).

In light of the cited prior art the subject-matter of claim 1 and claims 2-56, which are all dependent on claim 1, is considered to be novel.

2 **Inventive Step**(Art. 33(1) and 33(3) PCT)

D1 (figure 1) discloses the synthesis of nicotinamide riboside derivatives using a glycosylation reaction under Vorbrüggen conditions (cf. figure 1: compounds 1 + 2 →3).

The process according to the current claim 1 also relates to the synthesis of nicotinamide riboside derivatives of formula (I).

D1 is considered as the closest prior art.

The process according to the current claim 1 differs from D1 on account of the use of a compound of formula (II) as the starting material.

The problem to be solved is therefore seen as the provision of an alternative process for the synthesis of nicotinamide riboside derivatives.

With regard to the examples the problem is considered to be solved.

Having regard to the D1 alone or in combination with D2 and D3, the person skilled in the art has no incentive to provide a process according to the current claim 1 in order to solve the problem underlying the invention.

The subject-matter of claim 1 and claims 2-56, which are all dependent on claim 1, is therefore considered to be non-obvious and to involve an inventive step.

3 **Industrial Applicability**(Art. 33(1) and 33(4) PCT)

The invention appears to be industrially applicable.

Re Item VIII

Certain observations on the international application

Having regard to examples 3E and 3F (pages 22/23) it can be seen that activated charcoal needs to be present in order to achieve the synthesis of (I) from (II).

The technical features of a claim to an activity are the physical steps which define such activity. Consequently, in a claim relating to a process for the production of a chemical entity the physical steps of said activity are those process steps which specify the reactions conditions and/or the reagents necessary for producing the final product.

IPR2026-00400
Exhibit 2008 Page 261

From the examples it appears that the use of activated charcoal as the "carbon-containing catalyst" in the process according to current claim 1 is essential for the conversion of compound (II) to compound (I).

The description provides no teaching which other "carbon-containing catalyst" could be used to achieve the desired synthesis of compound (II) from compound (I).

Therefore, as the current claim 1 does not define the "carbon-containing catalyst" as activated charcoal, claim 1 does not encompass the essential technical features needed to define the invention.

Claim 1 does not satisfy Art. 6 PCT.

CERTIFICATE OF EFS-WEB FILING

Application No.	:	15/905,922 Confirmation No. 1061
Filing Date	:	February 27, 2018
Applicant	:	The Queen's University of Belfast
First Named Inventor:	:	Marie MIGAUD
For	:	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof
Group Art Unit	:	1673
Examiner	:	Patrick T. Lewis
Docket No.	:	335040: 4-16A US
Customer No.	:	23713

I hereby certify that the following, along with any other document(s) referenced to as being attached or enclosed:

1. **This Certificate of EFS-WEB Filing – 1 page**
2. **Information Disclosure Statement Transmittal - 2 pages**
3. **Substitute 1449 for SB/08 - 2 pages**
4. **Copy of International Preliminary Report on Patentability (IPRP) issued in PCT/EP2014/065971- 7 pages**

are being submitted electronically through the United States Patent Office EFS-WEB System, to be directed to:

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

On **October 1, 2018**

Sally A. Sullivan
(Name of Person Filing Correspondence)

/sallyasullivan/
(Signature of Person Filing Correspondence)

Electronic Acknowledgement Receipt	
EFS ID:	33884695
Application Number:	15905922
International Application Number:	
Confirmation Number:	1061
Title of Invention:	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof
First Named Inventor/Applicant Name:	Marie MIGAUD
Customer Number:	23713
Filer:	Sally A. Sullivan
Filer Authorized By:	
Attorney Docket Number:	335040: 4-16A US
Receipt Date:	01-OCT-2018
Filing Date:	27-FEB-2018
Time Stamp:	17:12:59
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	4-16A_US_1449.pdf	35176 2862eae6846bf248903fb82373d123f4a8219cc4	no	2
Warnings:					

Information:					
This is not an USPTO supplied IDS fillable form					
2	Transmittal Letter	4-16A_US_ids_transmittal.pdf	19124 ff7372134bda25fdb700e409fe1ed5b03993d422	no	2
Warnings:					
Information:					
3	Other Reference-Patent/App/Search documents	IPRP_PCT_EP_2014_065971.pdf	760286 34e11eda37ae1911002da64b0f32e06ecbd39fba	no	7
Warnings:					
Information:					
4	Miscellaneous Incoming Letter	4-16A_US_efsCert-ids.pdf	16122 79fc505ff6f77f6782756c12ab916c6a1de2ec68	no	1
Warnings:					
Information:					
		Total Files Size (in bytes):	830708		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/905,922	02/27/2018	Marie MIGAUD	599341: 4-16A US

CONFIRMATION NO. 1061

23713
Leydig, Voit & Mayer, Ltd.
4875 Pearl East Circle
Suite 301
Boulder, CO 80301

PUBLICATION NOTICE

OC000000100753504

Title: Methods of Preparing Nicotinamide Riboside and Derivatives Thereof

Publication No.US-2018-0186824-A1
Publication Date:07/05/2018

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 15/905,922

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	75		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	330		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	380		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	19 minus 20 =	*	x 50 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*	x 230 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	785		TOTAL	

APPLICATION AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/905,922	02/27/2018	1629	785	599341: 4-16A US	19	3

CONFIRMATION NO. 1061

FILING RECEIPT

23713
Lathrop Gage LLP (GS)
2440 Junction Place
Suite 300
Boulder, CO 80301

OC000000098248642

Date Mailed: 03/26/2018

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Marie MIGAUD, Lurgan, UNITED KINGDOM;
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Kerri CROSSEY, Magherafelt, UNITED KINGDOM;
Mark DOHERTY, Newtownabbey, UNITED KINGDOM;

Applicant(s)

The Queen's University of Belfast, Belfast Antrim, UNITED KINGDOM;

Power of Attorney: The patent practitioners associated with Customer Number 23713

Domestic Priority data as claimed by applicant

This application is a CON of 14/908,831 01/29/2016
which is a 371 of PCT/EP2014/065971 07/24/2014

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)
UNITED KINGDOM 1313465.5 07/29/2013 No Access Code Provided

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 03/22/2018

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/905,922**

Projected Publication Date: 07/05/2018

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

Methods of Preparing Nicotinamide Riboside and Derivatives Thereof

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

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NOT GRANTED

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DocCode – SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: 15905922 Document Date: 02/27/2018

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

- Drawing

At the time of document entry (noted above):

- USPTO employees may access SCORE content via eDAN using the Supplemental Content tab, or via the SCORE web page.
- External customers may access SCORE content via PAIR using the Supplemental Content tab.

Form Revision Date: August 26, 2013

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
Approved for use through 11/30/2014 OMB 0651-0051
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Under the Paperwork Reduction Act of 1995 no persons are required to respond to a collection of information unless it displays a valid OMB control number

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date
14/908,831	January 29, 2016

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 23713

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☐ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

THE QUEEN'S UNIVERSITY OF BELFAST

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	13 - Feb - 17
Name	Dermot Tierney		
Title	IP manager		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number PCT/EP2014/065971 filed on July 24, 2014.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Marie MIGAUD Date (Optional): 2/5/2017

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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LEGAL NAME OF INVENTOR

Inventor: Philip REDPATH Date (Optional): 14/2/17

Signature: Philip Redpath

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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As the below named inventor, I hereby declare that:

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■ United States application or PCT international application number PCT/EP2014/065971 filed on July 24, 2014.

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LEGAL NAME OF INVENTOR

Inventor: Kerri CROSSEY Date (Optional): 14/2/17

Signature: Kerri Crossey

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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☐ The attached application, or

☒ United States application or PCT international application number PCT/EP2014/065971 filed on JULY 24, 2014.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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LEGAL NAME OF INVENTOR

Inventor: Mark DOHERTY Date (Optional): 15TH FEB 2017

Signature: M. D

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF
First Named Inventor/Applicant Name:	Marie MIGAUD
Filer:	Sally A. Sullivan/Cathy Nelson
Attorney Docket Number:	599341: 4-16A US

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY FILING FEE (ELECTRONIC FILING)	4011	1	75	75
UTILITY SEARCH FEE	2111	1	330	330
UTILITY EXAMINATION FEE	2311	1	380	380
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**785**

Electronic Acknowledgement Receipt	
EFS ID:	31895983
Application Number:	15905922
International Application Number:	
Confirmation Number:	1061
Title of Invention:	METHODS OF PREPARING NICOTINAMIDE RIBOSIDE AND DERIVATIVES THEREOF
First Named Inventor/Applicant Name:	Marie MIGAUD
Customer Number:	23713
Filer:	Sally A. Sullivan/Cathy Nelson
Filer Authorized By:	Sally A. Sullivan
Attorney Docket Number:	599341: 4-16A US
Receipt Date:	27-FEB-2018
Filing Date:	
Time Stamp:	10:16:37
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$785
RAM confirmation Number	022718INTEFSW00009384120600
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	4-16A_US_efsCert-appln.pdf	13928 9ae1859f88e97cb175752ea1e235b67c1a83cd4b	no	1
Warnings:					
Information:					
2	Transmittal of New Application	4-16A_US_utility_transmittal-asfiled.pdf	126536 1b607bf524a35aeff9a22a62f4e68a588fdb3f15	no	1
Warnings:					
Information:					
3	Application Data Sheet	4-16A_US_ads.pdf	1823578 c77e2b6a8efad32b46f58c6852783dd5d094403c	no	9
Warnings:					
Information:					
4		4-16A_US_spec-asfiled.PDF	1618410 1370ca59ace5f86ad810352a007d12774c87b8c4	yes	27

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	22
	Claims	23	26
	Abstract	27	27

Warnings:					
Information:					
5	Drawings-other than black and white line drawings	4-16A_US_drawings_asfiled.pdf	336995 58d417c746eab66db162296360ead9b170f70942	no	5

Warnings:					
Information:					
6	Power of Attorney	4-16_US_exec_poa.PDF	140573 4e06287630ada3b27af335ebbb1168bb761af497	no	1
Warnings:					
Information:					
7	Oath or Declaration filed	4-16_US_exec_inv_declns.PDF	314941 7998c942aa3103c42fb6e488981 4f673851752a9	no	4
Warnings:					
Information:					
8	Fee Worksheet (SB06)	fee-info.pdf	35208 cdec32a45142986f8a8ec5aabe598a7dba982320	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	4410169		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

CERTIFICATE OF EFS-WEB FILING

Application No.	:	To Be Assigned
Filing Date	:	February 27, 2018
Applicant	:	The Queen's University of Belfast
Inventors	:	Marie MIGAUD et al.
For	:	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof
Group Art Unit	:	To Be Assigned
Examiner	:	To Be Assigned
Docket No.	:	599341: 4-16A US
Customer No.	:	23713

I hereby certify that the following correspondence for filing a patent application, along with any other document(s) referenced to as being attached or enclosed:

1. **This Certificate of EFS-Web Filing - 1 page**
2. **Utility Patent Application Transmittal – 1 page**
3. **Application Data Sheet – 9 pages**
4. **Specification – 27 total (Description – 22 pgs., Claims – 4 pgs., Abstract – 1 pg.)**
5. **Drawings – 5 sheets**
6. **Executed Power of Attorney by Applicant from parent application – 1 page**
7. **Executed Declarations for Utility Application from parent application – 4 pages**

is/are being submitted electronically through the United States Patent Office EFS-WEB System, to be directed to:

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

On **February 27, 2018**

Cathy Nelson
(Name of Person Filing Correspondence)

/cathynelson/
(Signature of Person Filing Correspondence)

PTO/AIA/15 (03-13)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	599341: 4-16A US
First Named Inventor	Marie MIGAUD
Title	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof
Express Mail Label No.	Submitted via EFS Web

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. [ ] **Fee Transmittal Form** (PTO/SB/17 or equivalent)
2. [✓] **Applicant asserts small entity status.** See 37 CFR 1.27
3. [ ] **Applicant certifies micro entity status.** See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. [✓] **Specification** [*Total Pages* 27] Both the claims and abstract must start on a new page. *(See MPEP § 608.01(a) for information on the preferred arrangement)*
5. [✓] **Drawing(s)** (35 U.S.C. 113) [*Total Sheets* 5]
6. **Inventor's Oath or Declaration** [*Total Pages* 4] *(including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))*
   a. [ ] Newly executed (original or copy)
   b. [✓] A copy from a prior application (37 CFR 1.63(d))
7. [✓] **Application Data Sheet** ** See note below.* See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
8. **CD-ROM or CD-R** in duplicate, large table, or Computer Program (*Appendix*)
   [ ] Landscape Table on CD
9. **Nucleotide and/or Amino Acid Sequence Submission** (*if applicable, items a. – c. are required*)
   a. [ ] Computer Readable Form (CRF)
   b. [ ] Specification Sequence Listing on:
      i. [ ] CD-ROM or CD-R (2 copies); or
      ii. [ ] Paper
   c. [ ] Statements verifying identity of above copies

ADDRESS TO:

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ACCOMPANYING APPLICATION PAPERS

10. [ ] **Assignment Papers** (cover sheet & document(s))
    Name of Assignee _____
11. [ ] **37 CFR 3.73(c) Statement** (*when there is an assignee*) [✓] **Power of Attorney**
12. [ ] **English Translation Document** (*if applicable*)
13. [ ] **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    [ ] Copies of citations attached
14. [ ] **Preliminary Amendment**
15. [ ] **Return Receipt Postcard** (*MPEP § 503*) (*Should be specifically itemized*)
16. [ ] **Certified Copy of Priority Document(s)** (*if foreign priority is claimed*)
17. [ ] **Nonpublication Request** Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
18. [✓] **Other:** Certificate of Electronic Filing

***Note:** (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must** be included in an Application Data Sheet (ADS).
(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS

[✓] The address associated with Customer Number: 23713 **OR** [ ] Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	/sallyasullivan/	Date	February 27, 2018
Name (Print/Type)	SALLY A. SULLIVAN	Registration No. (Attorney/Agent)	32,064

This collection of information is required by 37 CFR 1.53(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	599341: 4-16A US
	Application Number	
Title of Invention	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Marie		MIGAUD	

Residence Information (Select One) US Residency ● Non US Residency Active US Military Service

City	Lurgan, County Armagh	Country of Residence [i]	GB

Mailing Address of Inventor:

Address 1	41 Banbridge Road
Address 2	

City	Lurgan, County Armagh	State/Province	
Postal Code	BT66 7HG	Country [i]	GB

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Philip		REDPATH	

Residence Information (Select One) US Residency ◉ Non US Residency Active US Military Service

City	Portadown, County Armagh	Country of Residence [i]	GB

Mailing Address of Inventor:

Address 1	55 Oakdene Park, Bleary
Address 2	

City	Portadown, County Armagh	State/Province	
Postal Code	BT63 5SB	Country [i]	GB

Inventor 3 Remove

Legal Name

PTO/AIA/14 (11-15)
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	Application Number	
Title of Invention	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof	

Prefix	Given Name	Middle Name	Family Name	Suffix
	Kerri		CROSSEY	

Residence Information (Select One) US Residency ◉ Non US Residency Active US Military Service

City	Magherafelt, County Derry	Country of Residence [i]	GB

Mailing Address of Inventor:

Address 1	306 Hillhead Road		
Address 2	Knockloughrim		
City	Magherafelt, County Derry	State/Province	
Postal Code	BT45 8QT	Country [i]	GB

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Mark		DOHERTY	

Residence Information (Select One) US Residency ◉ Non US Residency Active US Military Service

City	Newtownabbey, County Antrim	Country of Residence [i]	GB

Mailing Address of Inventor:

Address 1	91 Church Crescent		
Address 2			
City	Newtownabbey, County Antrim	State/Province	
Postal Code	BT36 6ET	Country [i]	GB

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	23713		
Email Address	BoulderIP@lathropgage.com	Add Email	Remove Email

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	599341: 4-16A US
	Application Number	
Title of Invention	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof	

Application Information:

Title of the Invention	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof		
Attorney Docket Number	599341: 4-16A US	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	5	**Suggested Figure for Publication (if any)**	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	● Customer Number	US Patent Practitioner	◯ Limited Recognition (37 CFR 11.9)
Customer Number	23713		

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	599341: 4-16A US
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Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	14908831	2016-01-29
Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14908831	a 371 of international	PCT/EP2014/065971	2014-07-24

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
1313465.5	GB	2013-07-29	

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	599341: 4-16A US
	Application Number	
Title of Invention	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	599341: 4-16A US
	Application Number	
Title of Invention	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 — Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

● Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	The Queen's University of Belfast		
Mailing Address Information For Applicant:			
Address 1	University Road		
Address 2			
City	Belfast Antrim	**State/Province**	
Country	GB	Postal Code	BT7 1NN
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	599341: 4-16A US
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Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/sallyasullivan/			Date (YYYY-MM-DD)	2018-02-27
First Name	Sally A.	Last Name	Sullivan	Registration Number	32064

Additional Signature may be generated within this form by selecting the Add button. Add

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	599341: 4-16A US
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Title of Invention	Methods of Preparing Nicotinamide Riboside and Derivatives Thereof	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Methods of preparing nicotinamide riboside and derivatives thereof

Cross-reference to Related Applications

This application is a continuation of U.S. application 14/908,831, filed January 29, 2016 which is a U.S. National Stage under 35 U.S.C. 371 of PCT/EP14/065971, filed July 24, 2014. 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 p-anomer forms of nicotinamide riboside, nicotinate riboside, nicotinamide mononucleotide and nicotinate mononucleotide are shown, without counter ions, in Figure 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 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. Kirihata, *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.

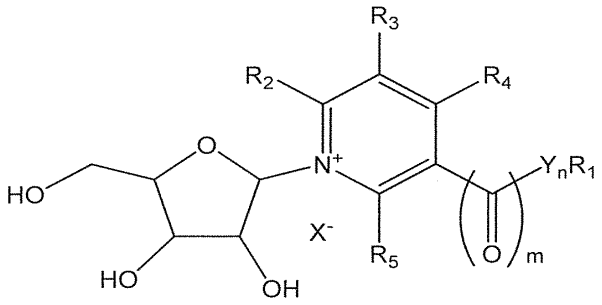
It is therefore an object of the invention to avoid or mitigate the disadvantages of the prior art.

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)



(I)

wherein

n is 0 or 1;

m is 0 or 1;

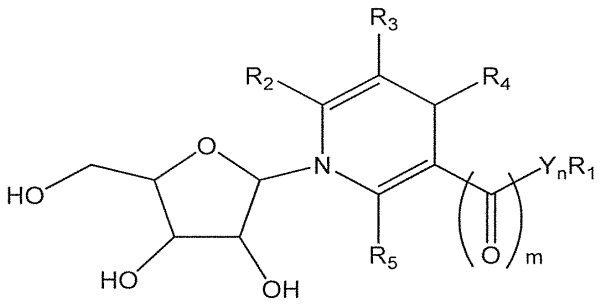
Y is O or S;

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)



(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).

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 NH_4^+.

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 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.

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 catalystare 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, 1,2-dichloroethane, 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 alkylarylamino), 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 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, R_1 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, R_1 is NH_2, R_2 – R_5 are each H, and X^- is selected from chloride, acetate, formate and trifluoroacetate.

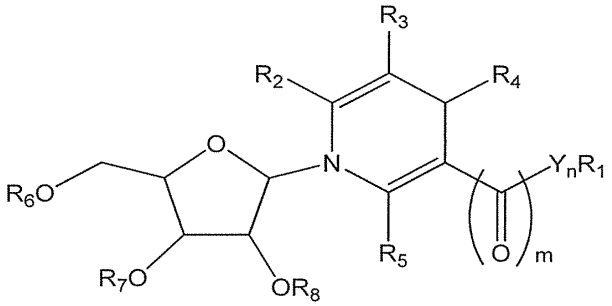
Optionally, in an embodiment of formula (II), n is 0, m is 1, R_1 is NH_2, and R_2 – R_5 are each H.

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 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 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 340nm.

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



(III)

wherein

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

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

with a deprotecting agent;

to form the compound of formula (II).

Suitable R_6, R_7 and R_8 moieties include, but are not limited to, ester-type protecting groups, ether-type protecting groups, and silyl-type protecting groups.

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

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

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

Optionally, the R_6, R_7 and R_8 moieties are selected from substituted and unsubstituted acetyl, and substituted and unsubstituted benzoyl.

Optionally, at least two of R_6, R_7 and R_8 are selected from unsubstituted acetyl or unsubstituted benzoyl.

Optionally the deprotecting agent is an acid or a base. Deprotection can also be achieved by catalytic hydrogenation (Pd/C; H_2) for the aromatic ether protecting groups and by fluoride-catalysed chemistry (e.f. TBAF in THF) for all the silyl ethers. Optionally, when R_6, R_7 and R_8 each comprise unsubstituted acetyl or unsubstituted benzoyl, the deprotecting agent is a base, optionally selected

from NH_3, Na_2CO_3 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, substituted or unsubstituted aliphatic or aromatic hydrocarbons, and combinations thereof, as defined above.

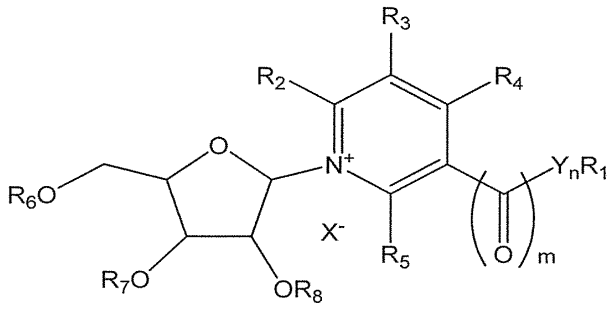
Optionally, the reactants are subjected to mechanical grinding, further optionally using a ball milling or planetary ball milling machine.

Optionally, in an embodiment of formula (III), n is 0, m is 1, R_1 is NH_2, $R_2 – R_5$ are each H, and $R_6 – R_8$ are each acetyl.

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

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

Optionally, 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 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 R_6, R_7 and R_8 comprise unsubstituted acetyl, the organic solvent is selected from dichloromethane, 1,2-dichloroethane, n-butyl acetate, chloroform and ethyl acetate, or a combination thereof, further optionally ethyl acetate.

Optionally, when at least two of R_6, R_7 and R_8 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 solution 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 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).

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

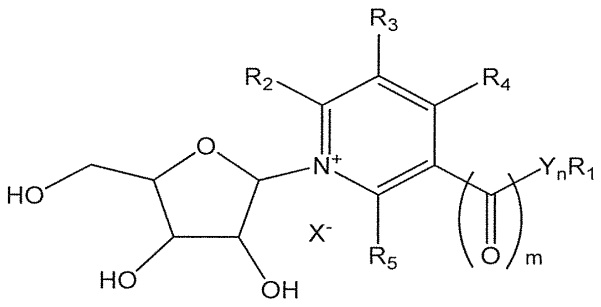
Optionally, in an embodiment of formula (IV), n is 0, m is 1, R_1 is NH_2, R_2 – R_5 are each H, R_6 – R_8 are each acetyl, and X^- is ^-OTf.

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)



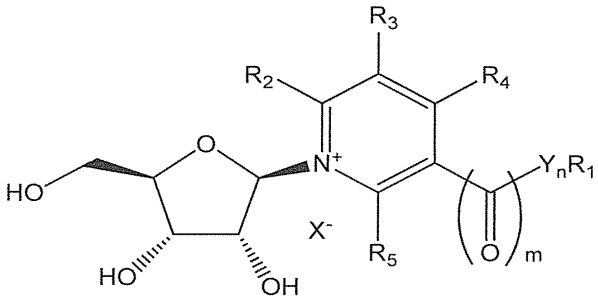
(I)

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,

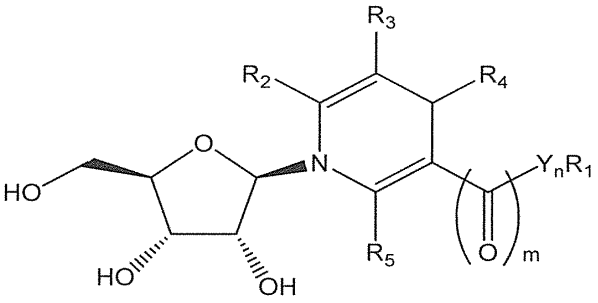


(IA)

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,

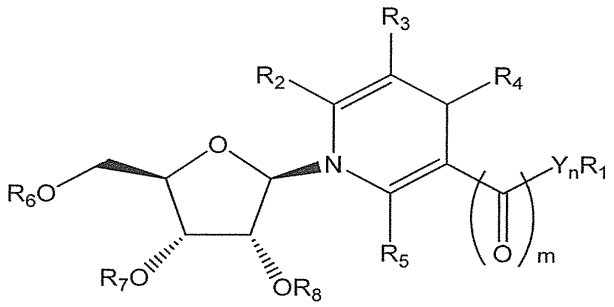


(IIA)

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,

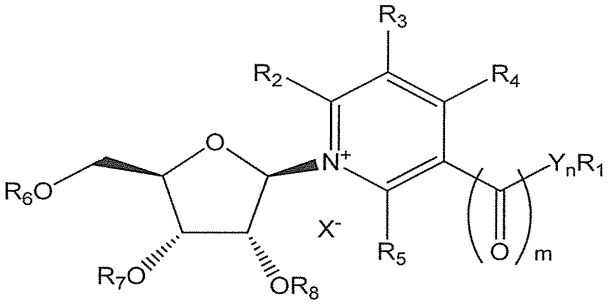


(IIIA)

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,



(IVA)

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.

(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 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 $P\text{-}H^+$ or a sulfonium cation containing SH^+, 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).

Brief Description of the Drawings

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

Figure 2 depicts Scheme A, which is a scheme illustrating, in general terms, that compounds of formula (IV) may be used to prepare compounds of formula (III), as described in Example 1; 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;

Figure 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-(beta-D-ribofuranosyl)-1,4-dihydronicotinamide, as described in Example 2, and that 1-(beta-D-ribofuranosyi)-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;

Figure 4 shows the (3-anomer forms of triacetyl-1,4-dihydronicotinamide riboside (Example 1(A)), triacetyl O-ethyl-1, 4-dihydronicotinate riboside, (Example 1(B)), tribenzoyl-1, 4-dihydronicotinamide riboside (Example 1(C)), and 1-(beta-D-ribofuranosyl)-1,4-dihydronicotinamide (Example 2); and

Figure 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)).

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

The Examples

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 B-anomer form of which is shown in Figure 4).

Reduction: All solvents were degassed prior to use by sonication and argon bubbling. Sodium dithionite (0.656g, 3.76 mmol, 2 eq) and sodium hydrogencarbonate (0.79g, 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 (1g, 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.
^{1}H-NMR (MeOD, 400MHz) - δ7.15 (s, 1H, H-5), 5.95 (d, 1H, J= 7.21 Hz, H-6), 5.25 (d, 1H, J=2.84Hz) & 5.17 (d, 1H, J=1.80Hz) (H-8 & H-7), 4.96 (d, 1H, J=7.09Hz, H-4), 4.87 (ABX, 1H, Jaa=8.18Hz, Jab=3.60Hz, H-9), 4.26 (d, 2H, J=3.20Hz, H-10 & H-10') 4.19 (m, 1H, J=3.00Hz, H-3), 3.13 (m, 2H, J=1.18Hz, H-2), 2.13 (s, 3H), 2.11 (s, 3H), 2.10 (s, 3H) (H-13, H-15, H-17). ^{13}C-NMR (MeOD,125MHz) - δ172.80 (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 (10g, 81.89 mmol, 1eq) was silylated using TMSCl (15.6 ml,122.85 mmol, 1.5 eq) in HMDS (100 ml) at 13Q°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.

^{1}H-NMR (MeOD, 400MHz) - 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, 3.9Hz, 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).

^{13}C-NMR (MeOD, 125MHz) - δ 172.1, 171.6, 171.2 (3x C=OCH_3), 164.9 (C=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).

^{19}F-NMR (MeOD, 376MHz) – δ -79.9 (triflate counterion)

Example 1(B): Preparation of reduced triacetyl nicotinate ester riboside, namely triacetyl O-ethyl-1, 4-dihydronicotinate riboside, a compound of formula (III) (the β-anomer form of which is shown in Figure 4).

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

^{1}H-NMR-δ 7.27 (1H, s, H-6), 6.05 (1H, dd, *J*= 8.2, 1.5Hz, H-7), 5.26 (1H, dd, *J*= 5.8, 2.8Hz, H-3), 5.23 (1H, dd, *J*= 6.9, 5.8Hz, H-2), 5.08 (1H, d, *J*= 6.9Hz, H-1), 4.91 (1H, dt, *J*= 8.3, 3.5Hz, H-8), 4.24-4.30 (3H, m, H-4, H-5, H-5'), 4.11 (2H, q, *J*= 7.2Hz, 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*= 7.2Hz, H-12).

^{13}C-NMR- δ 172.2, 171.5, 171.3, 169.8, (3x C=O-CH_3 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 (3x C=O-CH_3), 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 1eq tetraacetate riboside, 1eq TMSOTf, 1eq ethyl nicotinate, were reacted for 30mins in a 1.5 ml steel vessel with a 1.5cm 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.

^{1}H-NMR (D_2O, 400MHz) - 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=OC<u>H$_2$</u>CH$_3$), 2.04 (s, 3H, OAc), 2.02 (s, 3H, OAc), 1.98 (s, 3H, OAc), 1.25 (t, 3H, *J*=7.0 Hz, C=OCH$_2$C<u>H$_3$</u>).

^{19}F-NMR (D_2O, 376MHz) – δ -79.0 (triflate counterion)

<u>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 Figure 4).</u>

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, 10mL of H_2O was added to the solution and most of the methanol removed *via* rotary evaporation. The starting material crashed out of solution and 20mL of diethyl ether (Et_2O) was added until the solids solubilized into a biphasic system. A solution of $NaHCO_3$ (420mg, 5mmol, 5eq) and sodium dithionite (348mg, 2mmol, 2eq) in 10mL H_2O was added and stirred for 2hrs. The layers were separated and the ether layer was dried over $MgSO_4$ and concentrated to provide 428mg (76% yield) of tribenzoyl-1, 4-dihydronicotinamide riboside (yellow solid) without further purification. 80% purity based on ^{1}H-NMR. Pure material is obtained by Biotage purification.

^{1}H-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, 1.5Hz, H-7), 5.68 (1H, dd, *J*= 6.2, 3.5Hz, H-3), 5.57 (1H, dd, *J*= 6.7, 6.2Hz, H-2), 5.29 (1H, d, *J*= 6.7Hz, 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 (3x <u>C</u>=O-C_6H_5, <u>C</u>=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 (3x 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 (-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 1eq 1-acetate-tribenzoate riboside, 1eq TMSOTf and 1eq TMS-nicotinamide, were reacted for 30mins in a 1.5 ml steel vessel with a 1.5cm diameter steel ball bearing in a Retsch MM400 mixer mill at 25 Hz. 1eq 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.

^{1}H-NMR (MeOD, 400MHz) - 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, 3.9Hz, 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, 376MHz) – δ -79.1 (triflate counterion)

Example 2

A compound of formula (II), namely NRH (reduced nicotinamide riboside, also known as 1-(beta-D-ribofuranosyl)-1,4-dihydronicotinamide (the β-anomer form of which is shown in Figure 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. 100mgs of (III) was dissolved in 0.5mL of MeOH containing 0.05g of NaOH. The compounds were reacted for 30mins in a 1.5 ml steel vessel with a 1.5cm diameter steel ball bearing in a Retsch MM400 mixer mill at 25 Hz.
1H-NMR (MeOD, 400MHz) – δ7.18 (s, 1H, H-5), 6.14 (d, 1H, J= 8.28Hz, H-6), 4.85 (m, 1H, H-3), 4.76 (d, 1H, J= 5.77Hz, H-4), 4.04 (m, 2H, H-7&H-8), 3.93 (m, 1H, J=2.76, H-9), 3.72 (ABX, 1H, Jaa=12.55Hz, Jab=3.51Hz, H-10), 3.65 (ABX, 1H, Jaa=12.55Hz, Jab=4.02Hz, H-10'), 3.10 (q, 2H, J=1.51Hz H-2). 13C-NMR (MeOD, 125MHz) – δ172.88 (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-dihydronicotinate 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 Figure 5).

A compound of formula (II), namely NRH (reduced nicotinamide riboside, shown in Figure 2; 50mg, 0.20mmol, 1eq), was dissolved in 5mL H_2O and then 1eq (i.e. 0.20mmol) of ammonium chloride was added in one portion. Activated charcoal (~10mg, i.e. 0.80mmol) was then added and the mixture stirred at RT for ~1hr and then filtered and freeze-dried to give the chloride salt of nicotinamide riboside, quantitatively, i.e. 100% conversion and pure product.
^{1}H-NMR (D_2O, 400MHz) - 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*=4.7Hz, H-2), 4.31-4.34 (m, 1H, H-4), 4.21 (t, 1H, *J*=4.7Hz, 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').

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 Figure 5).

The method described in Example 3(A) was carried out, except that 1eq (i.e. 0.20mmol) of ammonium acetate was added. The acetate salt of nicotinamide riboside was obtained, quantitatively.
^{1}H-NMR (D_2O, 400MHz) - 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*=4.7Hz, H-2), 4.32-4.35 (m, 1H, H-4), 4.21 (t, 1H, *J*=4.7Hz, 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 Figure 5).

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

^{1}H-NMR (D_2O, 400MHz) - 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*=4.7Hz, H-2), 4.31-4.34 (m, 1H, H-4), 4.21 (t, 1H, *J*=4.7Hz, 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 Figure 5).

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

^{1}H-NMR (D_2O, 400MHz) - δ 9.46 (s, 1H, aromatic), 9.12 (d, 1H, *J*=6.3Hz, 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*=4.7Hz, H-2), 4.31-4.34 (m, 1H, H-4), 4.20 (t, 1H, *J*=4.7Hz, 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}F-NMR (D_2O, 376MHz)- δ -75.7 (CF_3COO^-).

Example 3(E): Preparation of nicotinamide riboside, chloride salt (the β-anomer form of which is shown in Figure 5).

An alternative method to that described in Example 3(A) was carried out as follows. NRH (reduced nicotinamide riboside, shown in Figure 4; 50mg, 0.20mmol, 1eq) was dissolved in 5mL H_2O:EtOAc (1:1) and then 1eq. (i.e. 0.20mmol) 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 (~10mg, i.e. 0.8mmol) 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.

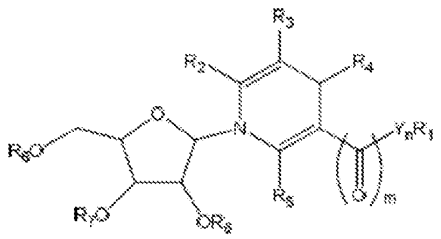
^{1}H-NMR (D_2O, 400MHz) - δ 9.46 (s, 1H, aromatic), 9.12 (dt, 1H, *J*=6.3, 1.4 Hz, aromatic), 8.83 (dt, 1H, *J*=8.2, 1.4 Hz, aromatic), 8.13 (dd, 1H, *J*=8.2, 6.3 Hz, aromatic), 6.13 (d, 1H, *J*=4.3 Hz, H-1 (anomeric)), 4.37 (t, 1H, *J*=4.7Hz, H-2), 4.31-4.34 (m, 1H, H-4), 4.21 (t, 1H, *J*=4.7Hz, H-3), 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 Figure 5).

The method described in Example 3(E) was carried out, except that NRH (reduced nicotinamide riboside, shown in Figure 4; 50mg, 0.20mmol, 1eq) was dissolved in 5mL H_2O:THF (1:1),

The Claims

1. A compound of formula (III)



(III)

wherein:

n is 0 or 1;

m is 0 or 1;

Y is O or S;

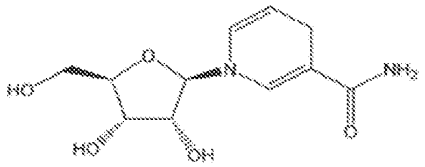
R_1 is selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted primary or secondary amino, and substituted or unsubstituted azido;

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

R_6, R_7 and R_8, which may be the same or different, are each independently a hydroxylprotecting group or are each H.

2. A compound of claim 1, wherein R_6, R_7 and R_8 are each H.

3. A compound of claim 2 which is 1-(β-D-ribofuranosyl)-1,4-dihydronicotinamide:



4. A compound according to claim 1, 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.

5. A compound according to claim 4, wherein the R_6, R_7 and R_8 moieties are selected from substituted and unsubstituted acetyl, and substituted and unsubstituted benzoyl.

6. A compound according to claim 4, wherein the ester-type protecting group is a protecting group selected from acetyl, propionyl, isopropionyl, benzoyl, and trihaloacetyl.

7. A compound according to claim 6, wherein the R_6, R_7 and R_8 moieties are selected from substituted and unsubstituted acetyl, and substituted and unsubstituted benzoyl.

8. A compound according to claim 4, wherein the ester-type protecting group is a protecting group selected from trifluoroacetyl or trichloroacetyl.

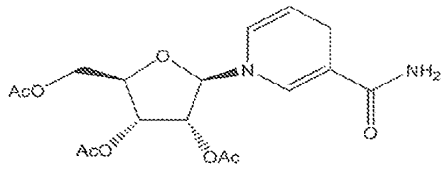
9. A compound according to claim 4, wherein the ether-type protecting group is a protecting group selected from benzyl, p-methoxybenzyl, methoxymethyl and allyl ethers.

10. A compound according to claim 4, wherein the silyl-type protecting group is a protecting group selected from trimethylsilyl, triethylsilyl, triisopropylsilyl, 2-(trimethylsilyl)ethoxymethyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl and tetraisopropyldisilyl.

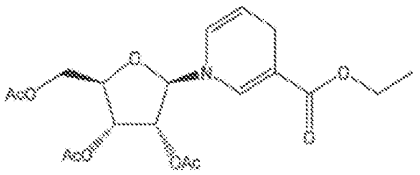
11. A compound according to claim 1, wherein the R_6, R_7 and R_8 moieties are selected from substituted and unsubstituted acetyl, and substituted and unsubstituted benzoyl.

12. A compound of claim 11, wherein at least two of R_6, R_7 and R_8 are selected from unsubstituted acetyl or unsubstituted benzoyl.

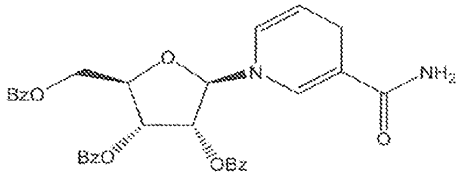
13. A compound of claim 12, which is triacetyl-1,4-dihydronicotinamide riboside:



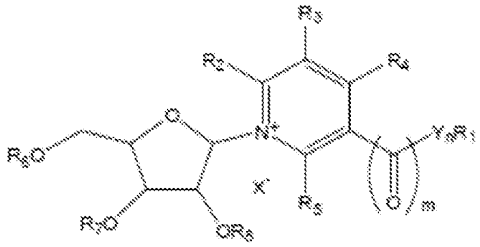
14. A compound according to claim 12, which is triacetyl O-ethyl-1,4-dihydronicotinate riboside:



15. A compound according to claim 11, wherein the compound is tribenzoyl-1,4-dihydronicotinamide riboside:



16. A compound of formula (IV)



(IV)

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

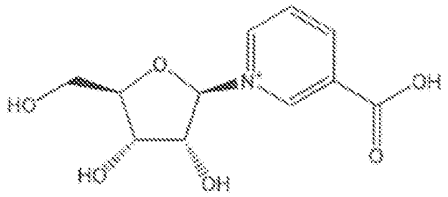
R_6, R_7 and R_8, which may be the same or different, are each independently a hydroxylprotecting group; and

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.

17. A compound of formula 16, wherein R_2 – R_5 are each H.

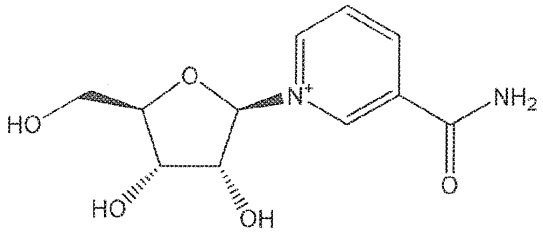
18. A compound of formula 17, wherein m is 1, n is 1, and Y is O.

19. A compound of formula:

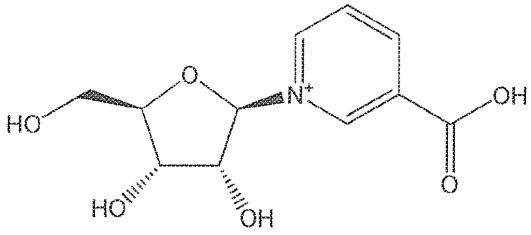

HO
O
N+
OH
HO
OH
O

Abstract

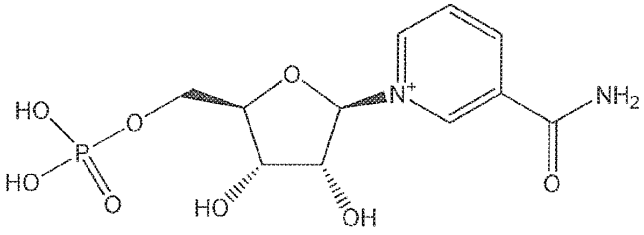
The invention relates to methods of preparing nicotinamide riboside and derivatives thereof. In an aspect, the invention relates to a method of preparing a compound of formula (I), wherein n is 0 or 1; m is 0 or 1; Y is O or S; R_1 is selected from H, substituted or unsubstituted alkyl, substituted or 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.



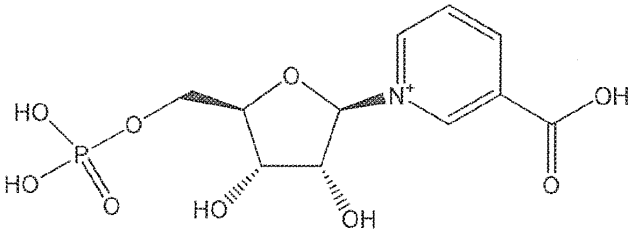
Nicotinamide riboside



Nicotinate riboside



Nicotinamide mononucleotide



Nicotinate mononucleotide

FIG. 1

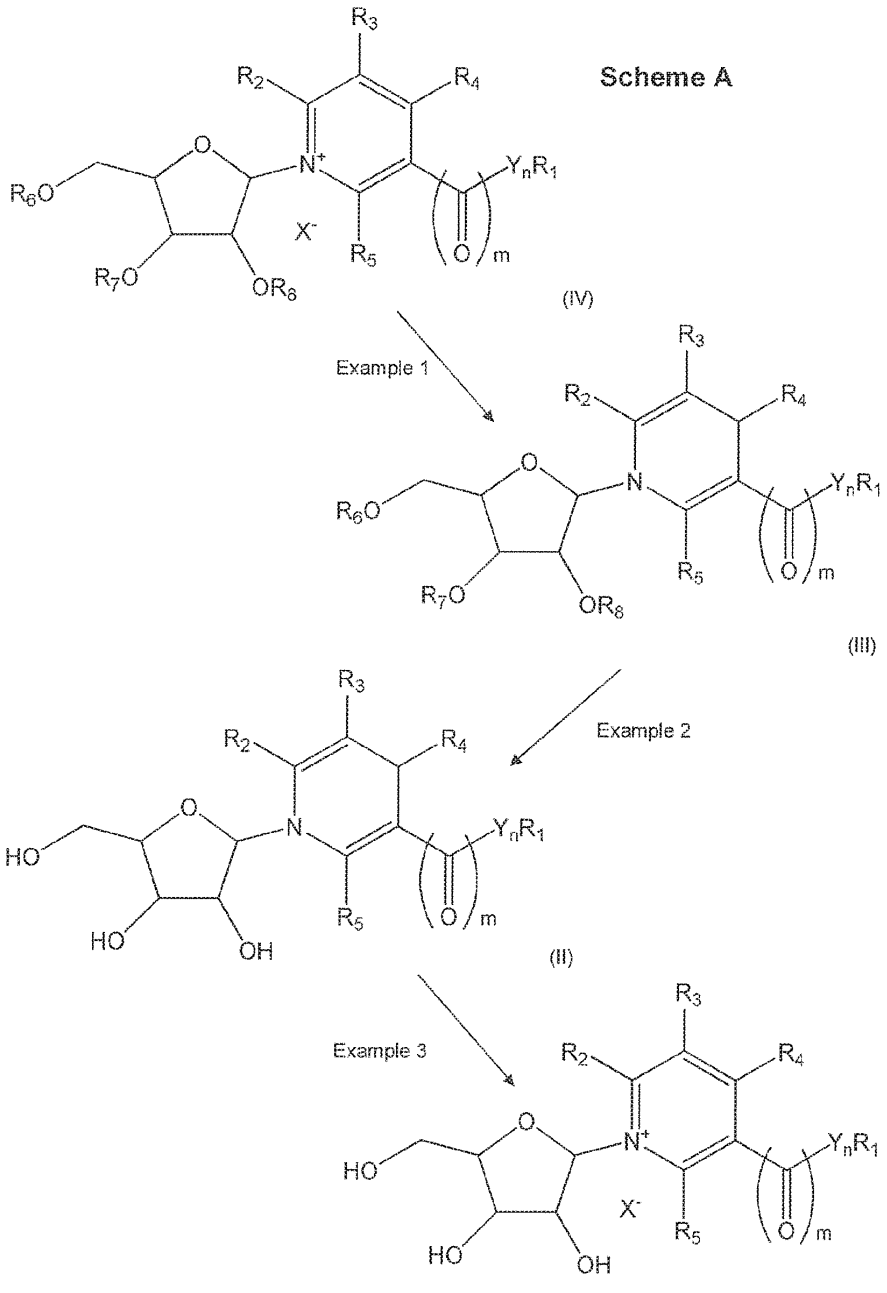


FIG. 2

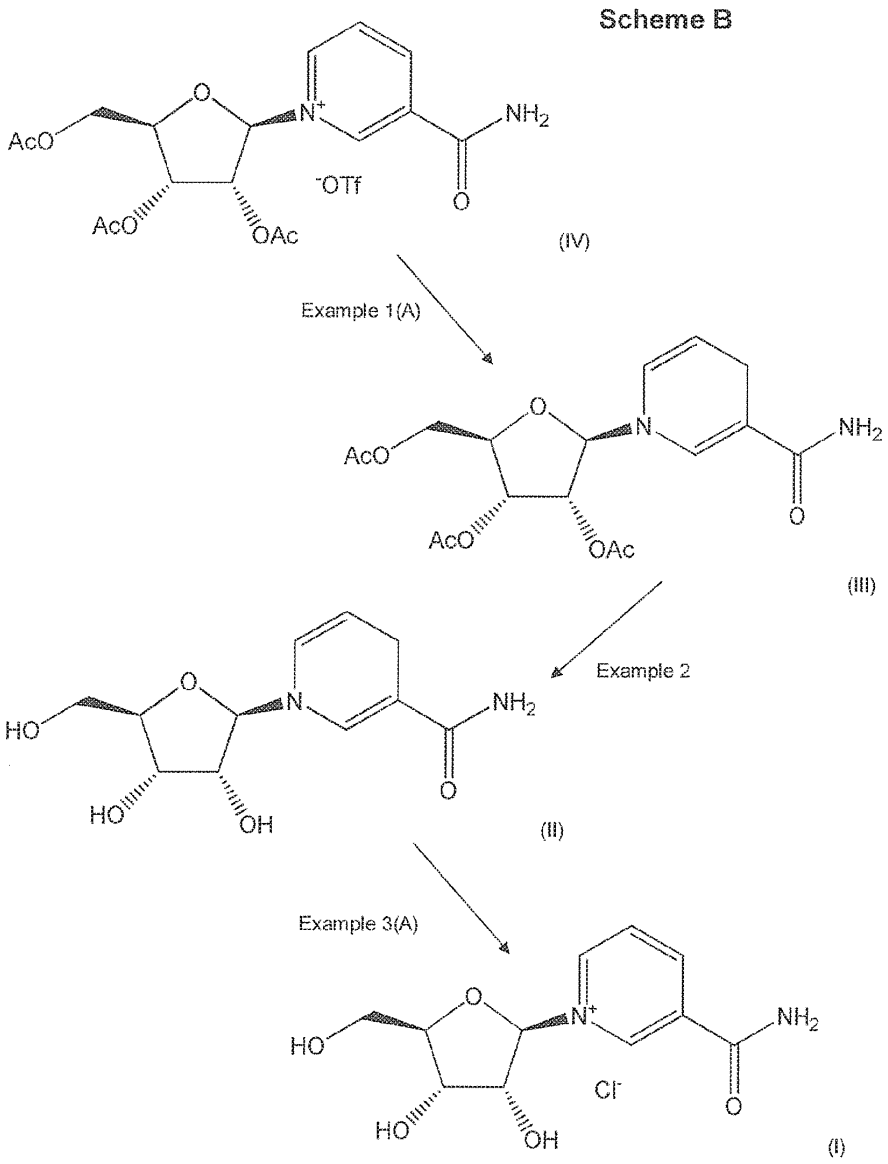
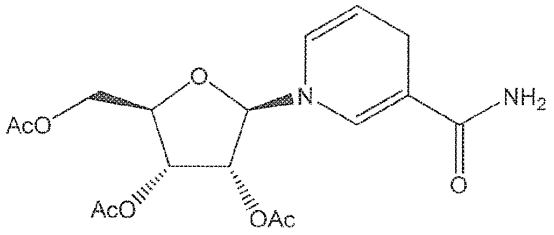
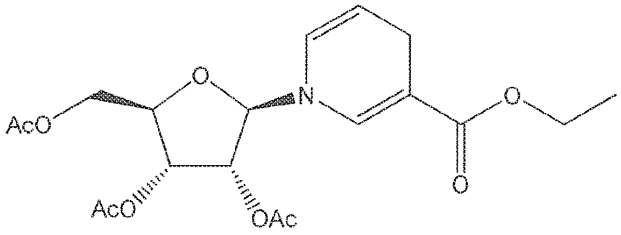

Scheme B
AcO
AcO
OAc
$^-$OTf
NH_2
O
(IV)
Example 1(A)
(III)
Example 2
HO
HO
OH
(II)
Example 3(A)
Cl^-
(I)

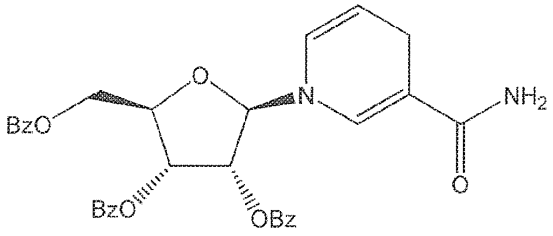
FIG. 3



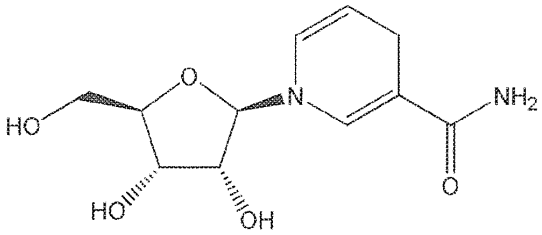
triacetyl-1,4-dihydronicotinamide riboside



triacetyl O-ethyl-1,4-dihydronicotinate riboside

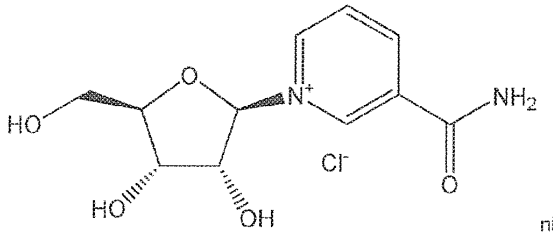


tribenzoyl-1,4-dihydronicotinamide riboside

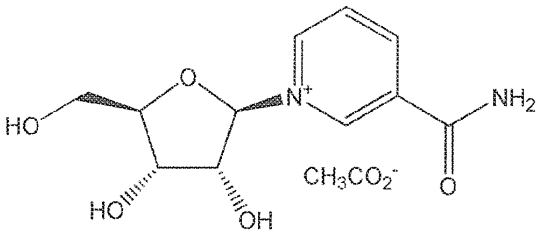


reduced nicotinamide riboside
(1-(beta-D-ribofuranosyl)-1,4-dihydronicotinamide)

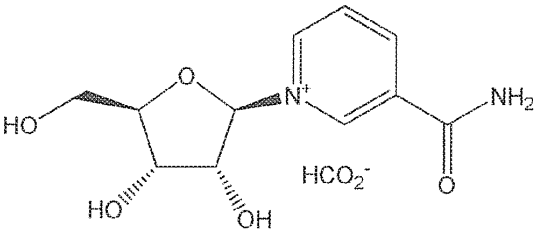
FIG. 4



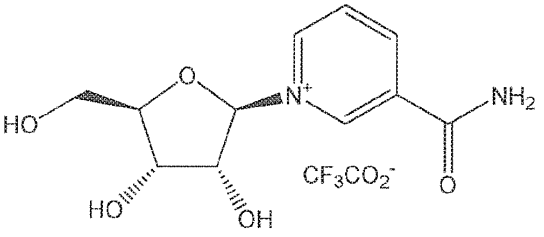
nicotinamide riboside, chloride salt



nicotinamide riboside, acetate salt



nicotinamide riboside, formate salt



nicotinamide riboside, trifluoroacetate salt

FIG. 5