

EXHIBIT 1002

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 12,138,276 B2
APPLICATION NO. : 18/655793
DATED : November 12, 2024
INVENTOR(S) : Jillian M. Hagel and Peter J. Facchini

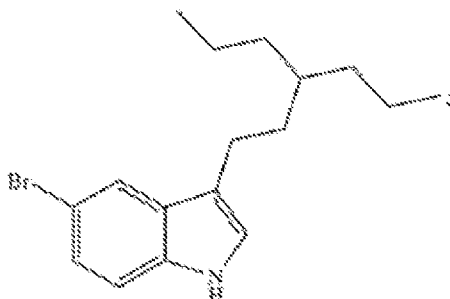
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

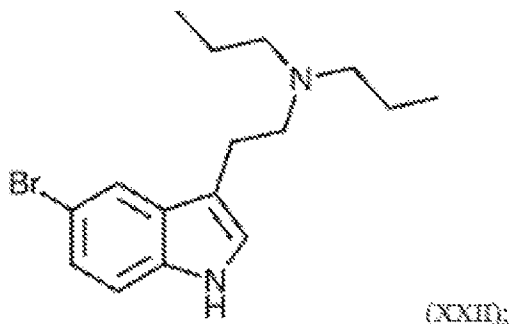
In the Claims

Claim 27, Column 224, Lines 5-10 replace "Formula (XXII)":

(XXII):



With:



Signed and Sealed this
Twenty-second Day of April, 2025

Coke Morgan Stewart
Acting Director of the United States Patent and Trademark Office



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.
18/655,793	05/06/2024	Jillian M. Hagel	29664-P62051US03	4842
1059	7590	04/22/2025		
SMART & BIGGAR LP 40 KING STREET WEST 40TH FLOOR TORONTO, ONTARIO M5H 3Y2 CANADA			EXAMINER RAO, SAVITHA M	
			ART UNIT	PAPER NUMBER
			1629	
			NOTIFICATION DATE	DELIVERY MODE
			04/22/2025	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):

us.mail@smartbiggar.ca

APPLICATION NO.	ISSUE DATE	PATENT NO.
18/655,793	22-Apr-2025	12138276

SMART & BIGGAR LP
40 KING STREET WEST
TORONTO, ON M5H 3Y2
CANADA

ELECTRONIC CERTIFICATE OF CORRECTION NOTIFICATION

Your electronic certificate of correction is now available, and can be accessed via Patent Center at <https://patentcenter.uspto.gov>.

The electronic certificate of correction is the official certificate of correction under 35 U.S.C. 254 or 255. For more information, please visit <https://www.uspto.gov/electronicgrants>.

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PATENT AND TRADEMARK OFFICEP.O. Box 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
18/655,793RECEIPT DATE / TIME
03/24/2025 01:31:42 PM Z ETATTORNEY DOCKET #
29664-P62051US03

Title of Invention

HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # 12138276

CONFIRMATION # 4842

FILED BY Giselle Augurusa

PATENT CENTER # 69705144

FILING DATE 05/06/2024

CUSTOMER # 1059

FIRST NAMED
INVENTOR Jillian M. HagelCORRESPONDENCE
ADDRESS -

AUTHORIZED BY Michael Fenwick

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
P62051US03__RequestForCertificateOfCorrection_2025-03-24.pdf	2	Request for Certificate of Correction	309 KB
P62051US03__CertificateOfCorrection_2025-03-24.pdf	2	Request for Certificate of Correction	210 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
P62051US03__RequestForCertificateOfCorrection_2025-03-24.pdf	B25064C0D7676264A712B3E68C6E9DADDCB999EA0181C6B59A0098F2C63F500E1AE6FEA9D624387FAF698E73BF62638DD ED83E61F6F2CA599E305DBD3E444478

P62051US03__CertificateOfCor
rection_2025-03-24.pdf

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DAC16795F0285DA85C6FF9145BC421EB

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

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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 CERTIFICATE OF CORRECTION

Page 1 of 1

PATENT NO. : 12138,276

APPLICATION NO.: 18,655,793

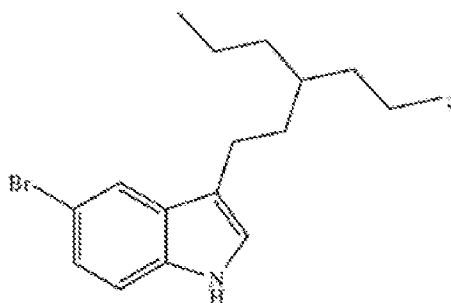
ISSUE DATE : November 12, 2024

INVENTOR(S) : Jillian M. Hagel and Peter J. Facchini

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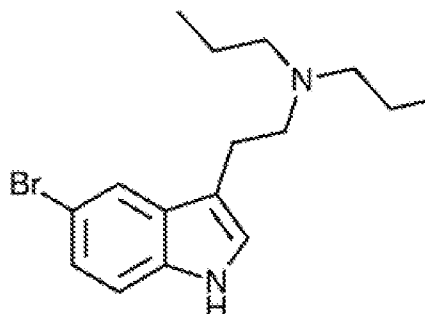
Claim 27, Column 224, lines 5-10 replace "Formula (XXII)" in patent (shown below) with "Formula (XXII)" in final response (shown below).

From Issued Patent



From response

(XXII):



(XXII):

MAILING ADDRESS OF SENDER (Please do not use Customer Number below):

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40 King Street, 40 Floor
Toronto, Ontario, M5H 3Y2, Canada

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 0651-0033. Public burden for this form is estimated to average 80 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 10) 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.

Confirmation No: 4842

Patent. No. : 12,138,276
Applicant : Enveric Biosciences Canada, Inc.
Filed : May 6, 2024
Title : HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS
OF USING
TC./A.U. : 1629
Examiner : SAVITHA M. RAO
Docket No. : 29664-P62051US03
Customer No. : 1059

By Electronic Filing

Honorable Commissioner for Patents
P. O. Box 1450
Alexandria, Virginia 22313 – 1450

Dated: March 24, 2025

REQUEST FOR CERTIFICATE OF CORRECTION

Commissioner:

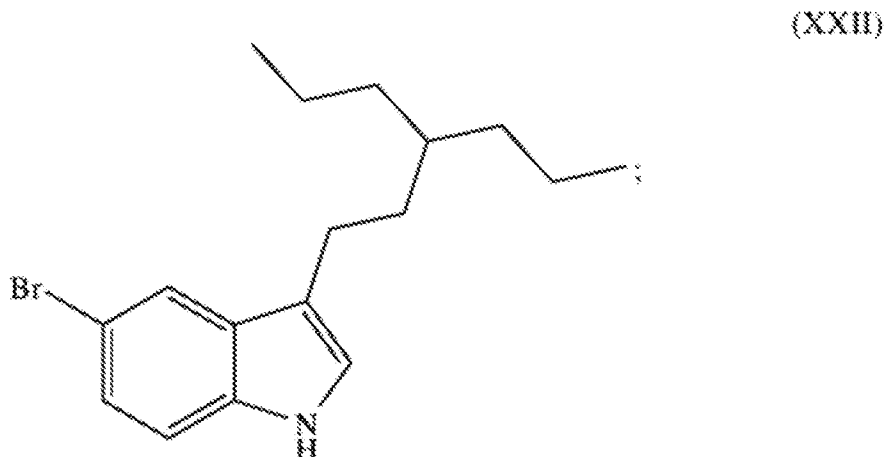
This is in regards to the Response to the Request for Certificate of Correction dated March 11, 2025, in which the Certificate of Correction submitted on February 24, 2025 was rejected as graphics entered were illegible and unclear. Accordingly, Applicant is resubmitting the request for Certificate of Correction to clearly set out the graphics to be corrected

The Applicant respectfully requests that a Certificate of Correction be issued for this patent. Attached is PCT/SB44 in a form suitable for printing. It is submitted that these errors occurred with the USPTO, not the Applicant, and correction under 37 CFR 1.322 is respectfully requested.

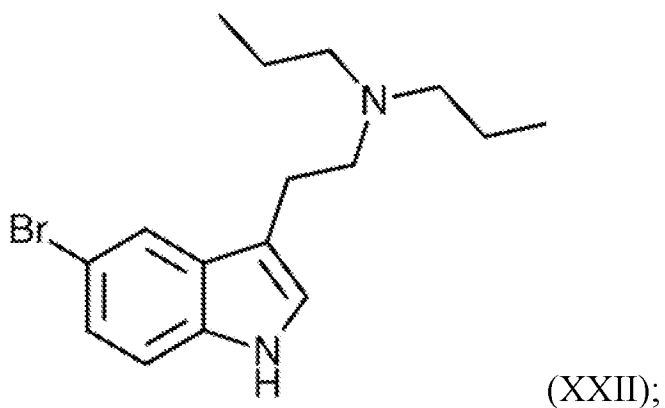
The location of the errors and the corrections that are required are as follows:

At claim 27, column 224, line 5-10 “Formula (XXII)” in the patent.

From the Issue Patent



Should read as set out in response:



Any questions regarding this submission or this patent should be directed to the undersigned.

Respectfully submitted,

SMART & BIGGAR LP
Agent for the Applicant

By: /mfenwick/
Mike Fenwick
Reg. No. 61773
Tel: 416-957-1665



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/655,793	05/06/2024	Jillian M. Hagel	29664-P62051US03	4842
1059	7590	03/11/2025		
SMART & BIGGAR LP 40 KING STREET WEST 40TH FLOOR TORONTO, ONTARIO M5H 3Y2 CANADA			EXAMINER RAO, SAVITHA M	
			ART UNIT	PAPER NUMBER
			1629	
			NOTIFICATION DATE	DELIVERY MODE
			03/11/2025	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):

us.mail@smartbiggar.ca

Response to the Request for Certificate of Correction

Patent No.

12138276

Applicant(s)

Hagel et al.

Issue Date

11/12/2024

Docket No.

29664-P62051US03

This is in response to the request for a Certificate of Correction filed 24 February 2025

☒ **Request Denied** - Consideration has been given to your request for the issuance of a Certificate of Correction under the provisions of 37 CFR 1.322 and/or 37 CFR 1.323. The Request is improper and denied for the reason(s) below:

1. ☐ Assignees' names and addresses (assignment data) printed in a patent, are based solely on information supplied in the appropriate space for identifying the assignment data on the Issue Fee Transmittal Form (PTOL-85b). Any request for a patent to be corrected to state the name of the assignee, must state that the assignment was submitted for recordation as set forth in 37 CFR 3.11 before issuance of the patent. Petition under 3.81 is to be filed for consideration of correction to assignee. The petition fee set forth in 37 CFR 1.17(i)(1) (currently \$140, \$70, \$35 for large, small and micro entities, respectively).
2. ☐ The alleged error in _____, is in fact an Amendment and/or Change made by the examiner and considered to be in accordance with the permissible amendments enumerated in the Manual of Patent Examining Procedure (MPEP) Section 1302.04. Applicant did not file objection or amendment under 37 CFR 1.312 prior to payment of the issue fee.
3. ☐ A petition under CFR 1.182 is required to correct the alleged errors in spelling or order of inventor's names, since inventor's names are printed solely in accordance with the type-written names, and in the order of the type-written names on the Application Data Sheet (ADS). The required fee currently under rule 1.17(f) (small entity \$200, large entity \$400, micro entity fee \$100).
4. ☐ With respect to the alleged error in changing the inventor name on the patent due to clerical error in ADS/OATH of related patents. The inventors name is printed in accordance with the OATH/ADS submitted at the time of filing the application. However, your attention is directed to C.F.R. 1.324, wherein a request is being made to change, add or delete inventor(s), after issuance of the patent.
5. ☐ With respect to the alleged error in _____, comparison of the printed patent with the corresponding location in the application file reveals that there is no discrepancy.
6. ☐ With respect to 37 CFR 1.72, the title should be brief but technically accurate and descriptive and should contain fewer than 500 characters. Inasmuch as the words "new," "improved," "improvement of," and "improvement in" are not considered as part of the title of an invention, these words should not be included at the beginning of the title of the invention and will be deleted when the Office enters the title into the Offices computer records, and when any patent issues.
7. ☐ The fee for correction under 37 CFR 1.323 is set forth in 37 CFR 1.20(a). ☐ Partial fee ☐ No fee was received with your request. Full fee payment is required before further action is taken on this request.
8. ☐ With respect to the request for corrected Letters Patent (Grant), corrections to the original Letters Patent are made under the provisions of Rule 1.322(b), not Rule 1.323, unless a petition is granted.
9. ☒ Other Comments: See Continuation Sheet

Further correspondence concerning this matter should be filed and directed to the Certificates of Correction Branch.

Legal Instrument Examiner: /JACQUELYN L WILLIAMS/
LIE, ODM

Phone: (571)272-1640

Certificates of Correction Branch email: CustomerServiceCoC@uspto.gov

CoC Central Phone Number: (703)756-1814

If applicable, information regarding a petition under 37 CFR 1.183 should be directed to the attention of the Commissioner for Patents using the FAX number (571) 273-8300

Continuation of Other Comments: Please submit a new SB44 (1050) form reflecting the images and graphics that require correction. The office determined the images and graphics entered on the SB44 (1050) form are illegible and unclear.

UNITED STATES
PATENT AND TRADEMARK OFFICEP.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov**ELECTRONIC ACKNOWLEDGEMENT RECEIPT**APPLICATION #
18/655,793RECEIPT DATE / TIME
02/24/2025 10:07:52 PM Z ETATTORNEY DOCKET #
29664-P62051US03**Title of Invention**

HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING

Application InformationAPPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # 12138276

CONFIRMATION # 4842

FILED BY Giselle Augurusa

PATENT CENTER # 69317398

FILING DATE 05/06/2024

CUSTOMER # 1059

FIRST NAMED
INVENTOR Jillian M. HagelCORRESPONDENCE
ADDRESS -

AUTHORIZED BY Michael Fenwick

Documents**TOTAL DOCUMENTS: 2**

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
P62051US03_RequestForCertificateOfCorrection.pdf	2	Miscellaneous Incoming Letter	222 KB
P62051US03_Certificate_Of_Correction.pdf	2	Request for Certificate of Correction	816 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
P62051US03_RequestForCertificateOfCorrection.pdf	44633D861B63DD9A6390F393BE5BE5C80D2E7FFB6000BC830 ECAEFB9D2EFFC25AA2845BFA3DA4BF89F89F72A50C7FFEB EF7C32D0E53FCB276AC016A0BE23358D
P62051US03_Certificate_Of_C	FF4067D5879DEF49C7B5AC43B2DE5C44C2ADF507216A77A9

orrection.pdf

E1365803516708409CF8518596B68E7E42FD64B74C23AD9F53
BE086DBDD08D6659AE9D673FB9C665

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New International Application Filed with the USPTO as a Receiving Office

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Patent. No. : 12,138,276
Applicant : Enveric Biosciences Canada, Inc.
Filed : May 6, 2024
Title : HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS
OF USING
TC./A.U. : 1629
Examiner : SAVITHA M. RAO
Docket No. : 29664-P62051US03
Customer No. : 1059

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Alexandria, Virginia 22313 – 1450

REQUEST FOR CERTIFICATE OF CORRECTION

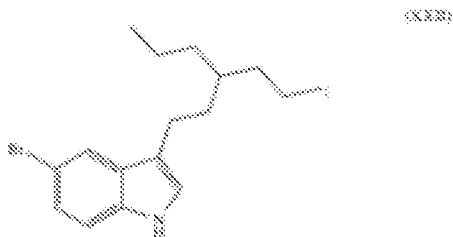
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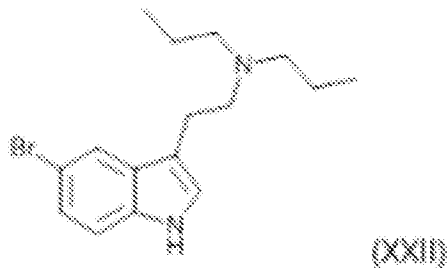
At claim 27, column 224, line 5-10 “Formula (XXII)” in the patent

From Issued Patent



should read:

From response



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Respectfully submitted,

SMART & BIGGAR LP
Agent for the Applicant

By: /mfenwick/
Mike Fenwick
Reg. No. 61773
Tel: 416-957-1665

UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

Page 1 of 1

PATENT NO. : 12138,276

APPLICATION NO.: 18,655,793

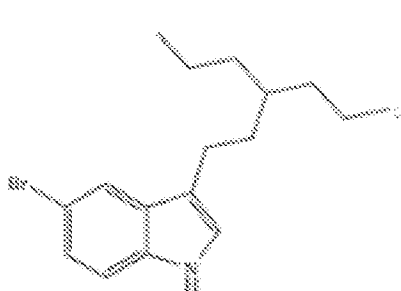
ISSUE DATE : November 12, 2024

INVENTOR(S) : Jillian M. Hagel and Peter J. Facchini

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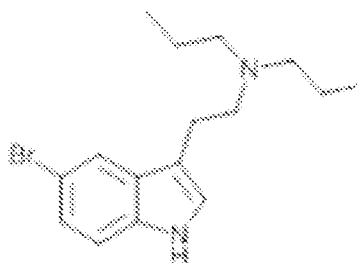
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From Issued Patent



(XXI)

From response



(XXII)

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Toronto, Ontario, M5H 3Y2, Canada

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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 10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

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United States Patent and Trademark Office
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SMART & BIGGAR LP 40 KING STREET WEST 40TH FLOOR TORONTO, ONTARIO M5H 3Y2 CANADA			EXAMINER RAO, SAVITHA M	
			ART UNIT	PAPER NUMBER
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ipprocessingcentre@bereskinparr.com

APPLICATION NO.	ISSUE DATE	PATENT NO.
18/655,793	12-Nov-2024	12138276

SMART & BIGGAR LP
40 KING STREET WEST
TORONTO, ON M5H 3Y2
CANADA

EGRANT NOTIFICATION

Your electronic patent grant (eGrant) is now available, which can be accessed via Patent Center at <https://patentcenter.uspto.gov>

The electronic patent grant is the official patent grant under 35 U.S.C. 153. For more information, please visit <https://www.uspto.gov/electronicgrants>



UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/655,793	11/12/2024	12138276	29664-P62051US03	4842

1059 7590 10/23/2024
SMART & BIGGAR LP
40 KING STREET WEST
40TH FLOOR
TORONTO, ONTARIO M5H 3Y2
CANADA

ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at <https://patentcenter.uspto.gov/>. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

The USPTO is implementing electronic patent issuance with a transition period, during which period the USPTO will mail a ceremonial paper copy of the electronic patent grant to the correspondence address of record. Additional copies of the patent (i.e., certified and presentation copies) may be ordered for a fee from the USPTO's Certified Copy Center at <https://certifiedcopycenter.uspto.gov/index.html>. The Certified Copy Center may be reached at (800)972-6382.

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 Center (<https://patentcenter.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 Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PATENT CENTER site <https://patentcenter.uspto.gov> for additional inventors):

Jillian M. Hagel, Calgary, CANADA;

Peter J. Facchini, Calgary, CANADA;

APPLICANT(s) (Please see PATENT CENTER site <https://patentcenter.uspto.gov> for additional applicants):

Enveric Biosciences Canada Inc., Calgary, CANADA;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit [SelectUSA.gov](https://selectusa.gov).

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

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 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. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

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

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 the USPTO patent electronic filing system 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.
18/655,793	05/06/2024	Jillian M. Hagel	29664-P62051US03	4842

TITLE OF INVENTION: HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0.00	\$0.00	\$480	11/21/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
RAO, SAVITHA M	1629	514-080000

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/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 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 SMART & BIGGAR LP

2 Michael Fenwick

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)

Enveric Biosciences Canada Inc.

Calgary, AB, CA

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)

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

☒ Electronic Payment via the USPTO patent electronic filing system ☐ 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 /mfenwick/

Date 2024-10-08

Typed or printed name Michael Fenwick

Registration No. 61773

UNITED STATES
PATENT AND TRADEMARK OFFICEP.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
18/655,793RECEIPT DATE / TIME
10/08/2024 03:45:09 PM Z ETATTORNEY DOCKET #
29664-P62051US03

Title of Invention

HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 4842

FILED BY Lindsay Earnshaw

PATENT CENTER # 67484145

FILING DATE 05/06/2024

CUSTOMER # 1059

FIRST NAMED
INVENTOR Jillian M. HagelCORRESPONDENCE
ADDRESS -

AUTHORIZED BY Michael Fenwick

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
P62051US03 IF Payment.pdf	1	Issue Fee Payment (PTO-85B)	128 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
P62051US03 IF Payment.pdf	DF3AA418E48B34177D3936EFBCBE00D969496484A0A3C6868 C047E164704E7FC7E27E7508F680CE3A8CB599750BA40CD44 3F3574D27A00ECA48725AD0EE895EC

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.

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.

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Alexandria, VA 22313 - 1450
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ELECTRONIC PAYMENT RECEIPT

APPLICATION #
18/655,793RECEIPT DATE / TIME
10/08/2024 03:45:09 PM Z ETATTORNEY DOCKET #
29664-P62051US03

Title of Invention

HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 4842

FILED BY Lindsay Earnshaw

PATENT CENTER # 67484145

AUTHORIZED BY Michael Fenwick

CUSTOMER # 1059

FILING DATE 05/06/2024

CORRESPONDENCE
ADDRESS -FIRST NAMED
INVENTOR Jillian M. Hagel

Payment Information

PAYMENT METHOD
CARD / 8979PAYMENT TRANSACTION ID
E202408F45257420PAYMENT AUTHORIZED BY
Lindsay Earnshaw

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
2501	UTILITY ISSUE FEE	480.00	1	480.00
TOTAL AMOUNT:				\$480.00

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.



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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
18/655,793	05/06/2024	Jillian M. Hagel	29664-P62051US03

CONFIRMATION NO. 4842

1059

BERESKIN & PARR LLP/S.E.N.C.R.L., s.r.l.
40 KING STREET WEST
40TH FLOOR
TORONTO, ON M5H 3Y2
CANADA

PUBLICATION NOTICE



OC00000077816142

Date Mailed: 09/12/2024

Title:HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING

Publication No.US-2024-0299427-A1

Publication Date:09/12/2024

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 viewed using the USPTO's publicly available Searchable Databases via the Patent Public Search tool at www.uspto.gov. The direct link to access the Patent Public Search tool is currently <https://ppubs.uspto.gov/pubwebapp/static/pages/ppubsbasic.html>.

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 Patent Center, the USPTO's electronic patent application filing and management system. The direct link to access this status information is currently <https://patentcenter.uspto.gov/>. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of Patent Center.

Further assistance in electronically accessing the publication, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101



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www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

1059 7590 08/21/2024
BERESKIN & PARR LLP/S.E.N.C.R.L., s.r.l.
40 KING STREET WEST
40TH FLOOR
TORONTO, ONTARIO M5H 3Y2
CANADA

EXAMINER

RAO, SAVITHA M

ART UNIT

PAPER NUMBER

1629

DATE MAILED: 08/21/2024

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/655,793	05/06/2024	Jillian M. Hagel	29664-P62051US03	4842

TITLE OF INVENTION: HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0.00	\$0.00	\$480	11/21/2024

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 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted 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. 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 the USPTO patent electronic filing system.

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 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. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

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

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 the USPTO patent electronic filing system 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.
18/655,793	05/06/2024	Jillian M. Hagel	29664-P62051US03	4842

TITLE OF INVENTION: HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0.00	\$0.00	\$480	11/21/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
RAO, SAVITHA M	1629	514-080000

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/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 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,

1 _____

(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.

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)

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

☐ Electronic Payment via the USPTO patent electronic filing system ☐ 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. _____



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/655,793	05/06/2024	Jillian M. Hagel	29664-P62051US03	4842
1059	7590	08/21/2024	EXAMINER	
BERESKIN & PARR LLP/S.E.N.C.R.L., s.r.l. 40 KING STREET WEST 40TH FLOOR TORONTO, ONTARIO M5H 3Y2 CANADA			RAO, SAVITHA M	
			ART UNIT	PAPER NUMBER
			1629	
DATE MAILED: 08/21/2024				

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.

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. 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
- 10) 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.

Notice of Allowability	Application No. 18/655,793	Applicant(s) Hagel et al.	
	Examiner SAVITHA M RAO	Art Unit 1629	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 07/25/2024.
☐ 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 1-29. 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. _____.

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 <u>07/16/2024</u> . 3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____. 4. ☒ Interview Summary (PTO-413), Paper No./Mail Date. <u>08/06/2024</u> .	5. ☒ Examiner's Amendment/Comment 6. ☒ Examiner's Statement of Reasons for Allowance 7. ☐ Other _____.
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Notice of Pre-AIA or AIA Status

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

DETAILED ACTION

Claims 1-30 are pending in the instant application.

In the interest of compact prosecution, examiner contacted the applicants with a proposal to file terminal disclaimer over the parent patents to overcome the ODP rejection, which would have been the only rejection on file. Please see the attached interview summary for details.

Information Disclosure Statement

The information disclosure statement (IDS) dated 07/16/2024 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, it has been placed in the application file and the information therein has been considered as to the merits.

Terminal disclaimer

The terminal disclaimer filed on 08/14/2024 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of **US Patent 11,998,557 and 11,918,594** been reviewed and is accepted. The terminal disclaimer has been recorded.

EXAMINER'S AMENDMENT

Art Unit: 1629

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

This application is in condition for allowance except for the presence of claim 30 drawn to method of treating a psychiatric disorder, non-elected without traverse as per applicants response to restriction dated 07/25/2024 Accordingly, claims 30 is cancelled.

Claims are amended as follows for allowance

Examiner's amendment for allowance

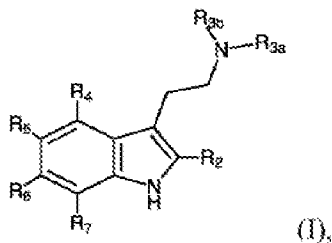
In the claims:

Cancel withdrawn claims 30

REASONS FOR ALLOWANCE

In view of the applicants terminal disclaimer filed on 08/14/2024, the examiner's amendment above and the following examiners statement of reasons for allowance, claims 1-29 are found to be allowable.

Following a diligent search it was determined that the prior art neither teaches nor provides adequate motivation to arrive at the instantly claimed Chemical compound or salts thereof having the formula (I):



wherein, at least one of R₂, R₄, R₅, R₆ or R₇ is a halogen atom, wherein each non- halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom or an alkyl group or 0-alkyl group, wherein R₄ when it is not halogenated is a phosphate group, a hydrogen atom or an alkyl group or 0-alkyl group, and wherein R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group.

Closest prior art is Pratuangdejkul et al (Current Medicinal Chemistry, 2005, 12, 2393-2410). On page 2395-392 art presents Table 1 which teaches various 5-HT analogs. The presented compounds, where X = N, have the same core structure as the currently claimed compounds, however, the substitution pattern of groups R₁-R₇ is not within the scope of the claimed compound. The limited scope of substituents presented in the art does not provide motivation to alter the substitution pattern of the art's compound in a manner that would produce the claimed compound.

Conclusion

Claims 1-29 are allowed.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Art Unit: 1629

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7.00 am to 4.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached on (571) 272-5541. 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.

/SAVITHA M RAO/
Primary Examiner, Art Unit 1629

<i>Examiner-Initiated Interview Summary</i>	Application No. 18/655,793	Applicant(s) Hagel et al.		
	Examiner SAVITHA M RAO	Art Unit 1629	AIA (First Inventor to File) Status Yes	Page 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	Title	Type
SAVITHA M RAO	Primary Examiner	Telephonic
Micheal Fenwick	Attorney of Record	

Date of Interview: 06 August 2024

Issues Discussed:

Proposed Amendment(s)

Examiner proposed to the applicants that they file terminal disclaimer over the parent patents to overcome the ODP rejection, which would have been the only rejection on file to which they agreed

/SAVITHA M RAO/ Primary Examiner, Art Unit 1629	
<p>Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04</p> <p>Please further see: MPEP 713.04 Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b) 37 CFR § 1.2 Business to be transacted in writing</p>	

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of 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.

<i>Notice of References Cited</i>	Application/Control No. 18/655,793	Applicant(s)/Patent Under Reexamination Hagel et al.	
	Examiner SAVITHA M RAO	Art Unit 1629	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date YYYY-MM-DD	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 YYYY-MM-DD	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	Pratuangdejkul et al (Current Medicinal Chemistry, 2005, 12, 2393-2410 (Year: 2005)
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in YYYY-MM-DD format are publication dates. Classifications may be US or foreign.

Issue Classification 	Application/Control No. 18/655,793	Applicant(s)/Patent Under Reexamination Hagel et al.
	Examiner SAVITHA M RAO	Art Unit 1629

CPC						
Symbol					Type	Version
A61K	/	31	/	675	F	2013-01-01
A61K	/	31	/	4045	I	2013-01-01
C12N	/	9	/	0083	I	2013-01-01
C12N	/	9	/	1007	I	2013-01-01
C12N	/	9	/	1205	I	2013-01-01
C12N	/	15	/	52	I	2013-01-01
C12P	/	17	/	10	I	2013-01-01

CPC Combination Sets				
Symbol		Type	Set	Version
	/			

NONE	Total Claims Allowed:	
(Assistant Examiner)	(Date)	29
/SAVITHA M RAO/ Primary Examiner, Art Unit 1629	14 August 2024	O.G. Print Claim(s)
(Primary Examiner)	(Date)	1

Issue Classification 	Application/Control No. 18/655,793	Applicant(s)/Patent Under Reexamination Hagel et al.
	Examiner SAVITHA M RAO	Art Unit 1629

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K31/675	/	31	/	675
A61K31/4045	/	31	/	4045
C12N9/02	/	9	/	02
C12N9/10	/	9	/	10
C12N9/12	/	9	/	12
C12N15/52	/	15	/	52
C12P17/10	/	17	/	10
NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	29	
/SAVITHA M RAO/ Primary Examiner, Art Unit 1629 (Primary Examiner)	14 August 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 1

Issue Classification 	Application/Control No. 18/655,793	Applicant(s)/Patent Under Reexamination Hagel et al.
	Examiner SAVITHA M RAO	Art Unit 1629

☒ 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

NONE	Total Claims Allowed:	
(Assistant Examiner)	(Date)	29
/SAVITHA M RAO/ Primary Examiner, Art Unit 1629	14 August 2024	O.G. Print Claim(s)
(Primary Examiner)	(Date)	1
		O.G. Print Figure
		1

<i>Search Notes</i> 	Application/Control No. 18/655,793	Applicant(s)/Patent Under Reexamination Hagel et al.
	Examiner SAVITHA M RAO	Art Unit 1629

CPC - Searched*		
Symbol	Date	Examiner
A61K31/4045 OR A61K31/675 OR C07D209/16 OR C07F9/5728 OR C07K2319/21 OR C07K2319/40 OR C07K2319/41 OR C07K2319/42 OR C07K2319/43 OR C12N15/52 OR C12N9/0071 OR C12N9/0083 OR C12N9/1007 OR C12N9/1029 OR C12N9/1205 OR C12N9/88 OR C12P17/10 OR C12Y402/0102	08/14/2024	SR

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
PE2E search	08/14/2024	SR
Inventor search in PE2E	08/14/2024	SR
STN search (parent application)	08/14/2024	SR
NPL search in google scholar	08/14/2024	SR

/SAVITHA M RAO/ Primary Examiner, Art Unit 1629	
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<i>Search Notes</i> 	Application/Control No. 18/655,793	Applicant(s)/Patent Under Reexamination Hagel et al.
	Examiner SAVITHA M RAO	Art Unit 1629

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
A61K	A61K31/4045 OR A61K31/675	08/14/2024	SR
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C12P	C12P17/10	08/14/2024	SR
C12Y	C12Y402/0102	08/14/2024	SR

/SAVITHA M RAO/ Primary Examiner, Art Unit 1629	
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Bibliographic Data

Application No: 18/655,793

Foreign Priority claimed: ☐ Yes ☒ No

35 USC 119 (a-d) conditions met: ☐ Yes ☒ No ☐ Met After Allowance

Verified and Acknowledged: /SAVITHA M RAO/

Examiner's Signature

Initials

Title:

HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
05/06/2024	514	1629	29664-P62051US03
RULE			

APPLICANTS

Enveric Biosciences Canada Inc., Calgary, AB, CANADA

INVENTORS

Jillian M. Hagel, Calgary, CANADA

Peter J. Facchini, Calgary, CANADA

CONTINUING DATA

This application is a CON of 17903080 09/06/2022 PAT 11998557

17903080 is a CON of PCT/CA2021/051209 09/01/2021

PCT/CA2021/051209 has PRO of 63073104 09/01/2020

FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

05/21/2024

** SMALL ENTITY **

STATE OR COUNTRY

CANADA

ADDRESS

BERESKIN & PARR LLP/S.E.N.C.R.L., s.r.l.

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40TH FLOOR

TORONTO, ON M5H 3Y2

CANADA

FILING FEE RECEIVED

\$3,128

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
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L49	1	("20230270768").pn.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/14 08:33 PM
L50	7	"5,6-dibromotryptamine"	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/14 08:33 PM
L51	5	L15 AND acyl	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/14 08:33 PM
L52	67	((("HAGEL") near3 ("Jillian")) OR (("FACCHINI") near3 ("Peter"))).INV.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2024/08/14 08:33 PM
L53	4	("20080171779" OR "20090093513" OR "20200397752" OR "5688807").pn.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/14 08:33 PM
L54	1	((US-20230293558- A1).did. AND PGPB.dbnm.)	(US-PGPUB)	OR	ON	ON	2024/08/14 08:33 PM
L55	24784	(A61K31/4045 OR A61K31/675 OR C07D209/16 OR C07F9/5728 OR C07K2319/21 OR C07K2319/40 OR C07K2319/41 OR C07K2319/42 OR C07K2319/43 OR C12N15/52 OR C12N9/0071 OR C12N9/0083 OR C12N9/1007 OR C12N9/1029 OR C12N9/1205 OR C12N9/88 OR C12P17/10 OR C12Y402/0102).cpc.	(US-PGPUB)	OR	ON	ON	2024/08/14 08:33 PM
L56	31	L1 AND psilocybin	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/14 08:33 PM
L57	3618	L2and psilocybin	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/14 08:33 PM
L58	1	L2 AND psilocybin	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/14 08:33 PM
L59	516	L4 AND psilocybin	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/14 08:33 PM

L60	104	L8 AND fluorine	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/14 08:33 PM
L61	0	("2023/0293558").urpn. AND (PGPB USPT USOC).dbnm.	(US-PGPUB; USPAT; USOCR)	OR	ON	ON	2024/08/14 08:33 PM
L62	20	L5 AND halogenated	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/14 08:33 PM
L63	268	L6 AND halogenated	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/14 08:33 PM
L64	2	"halogenated psilocybin"	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/14 08:33 PM
L65	1	("20230270768").pn.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/14 08:33 PM
L66	7	"5,6-dibromotryptamine"	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/14 08:33 PM
L67	5	L15 AND acyl	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/14 08:33 PM
L68	67	((("HAGEL") near3 ("Jillian")) OR ("FACCHINI") near3 ("Peter"))).INV.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2024/08/14 08:33 PM
L69	31	L33 AND Psilocybin	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/14 08:33 PM
L70	20	L34 AND halogenated	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/14 08:33 PM

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N1	40875	(A61K31/4045 OR A61K31/675 OR C07D209/16 OR C07F9/5728 OR C07K2319/21 OR C07K2319/40 OR C07K2319/41 OR C07K2319/42 OR C07K2319/43 OR C12N15/52 OR C12N9/0071 OR C12N9/0083 OR C12N9/1007 OR C12N9/1029 OR C12N9/1205 OR C12N9/88 OR C12P17/10 OR C12Y402/0102).cpc.	(US-PGPUB; USPAT)	OR	ON	ON	2024/01/23 10:03 AM
N2	402	N1 AND psilocybin	(US-PGPUB; USPAT)	OR	ON	ON	2024/01/23 10:05 AM
N3	78	N2 AND fluorine	(US-PGPUB; USPAT)	OR	ON	ON	2024/01/23 10:06 AM
N4	21	n3 AND halogenated	(US-PGPUB; USPAT)	OR	ON	ON	2024/01/23

N5	21	N3 AND halogenated	(US-PGPUB; USPAT)	OR	ON	ON	10:06 AM 2024/01/23 10:07 AM
N6	42286	(A61K31/4045 OR A61K31/675 OR C07D209/16 OR C07F9/5728 OR C07K2319/21 OR C07K2319/40 OR C07K2319/41 OR C07K2319/42 OR C07K2319/43 OR C12N15/52 OR C12N9/0071 OR C12N9/0083 OR C12N9/1007 OR C12N9/1029 OR C12N9/1205 OR C12N9/88 OR C12P17/10 OR C12Y402/0102).cpc.	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/14 08:33 PM
N7	516	N1 AND psilocybin	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/14 08:33 PM
N8	104	N2 AND fluorine	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/14 08:33 PM
N9	27	n3 AND halogenated	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/14 08:33 PM
N10	27	N3 AND halogenated	(US-PGPUB; USPAT)	OR	ON	ON	2024/08/14 08:33 PM

PE2E SEARCH - Search History (Similarity Search)

No Similarity Results available

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18655793	
	Filing Date		2024-05-06	
	First Named Inventor	Jillian M. Hagel		
	Art Unit	1629		
	Examiner Name	SAVITHA M RAO		
	Attorney Docket Number	29664-P62051US03		

U.S.PATENTS Remove						
Examiner Initial*	Cite No	Patent Number	Kind Code ¹	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5688807	A	1997-11-18	Audia et al.	

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	1	20200397752	A1	2020-12-24	Perez Castillo et al.	
	2	20090093513	A1	2009-04-09	Hamann et al.	
	3	20080171779	A1	2008-07-17	De Bruin et al.	

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	1	2004000845	WO	A1	2003-12-31	Suven Pharmaceuticals Ltd.	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18655793	
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	Examiner Name	SAVITHA M RAO		
	Attorney Docket Number	29664-P62051US03		

	2	2021011913	WO	A1	2021-01-21	Arvinas Operations, Inc.		☐
	3	2021108911	WO	A1	2021-06-10	Neomind Biosciences Inc.		☐
	4	2021168082	WO	A1	2021-08-26	Gilgamesh Pharmaceuticals Inc.		☐
	5	2019173797	WO	A1	2019-09-12	New Atlas Biotechnologies LLC		☐
	6	2018064465	WO	A1	2018-04-05	The Regents Of The University of California		☐
	7	2022051670	WO	A1	2022-03-10	Gilgamesh Pharmaceuticals Inc.		☐

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	1	Daniel, J. et al. Clinical potential of psilocybin as a treatment for mental health conditions. Mental Health Clin/, 2017;7 (1): 24-28	☐
	2	Grob, C. et al. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancerArch. Gen. Psychiatry, 2011, 68(1) 71-78	☐
	3	Cathart-Harris, R.L. et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry, 2016, 3: 619-627	☐

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	Attorney Docket Number	29664-P62051US03	

4	Needleman and Wunsch. A general method applicable to the search for similarities in the amino acid sequence of two proteins J. Mol. Biol., 1970, 48: 443	☐
5	Smith and Waterman. Adv. Appl. Math., 1981, 2: 482	☐
6	Carillo and Lipton. SIAM J. Applied Math., 1988, 48:1073	☐
7	Romeo, B. et al. Clinical and biological predictors of psychedelic response in the treatment of psychiatric and addictive disorders: A systematic review. J Psychiatr Res 137: 273, 2021	☐
8	Devereux et al., A comprehensive set of sequence analysis programs for the VAX. Nucleic Acids Res., 1984, 12: 387	☐
9	Altschul et al., J. Mol. Biol., 1990:215:403	☐
10	Thompson, J D, Higgines, D G and Gibson T J, 1994, Nucleic Acid Res 22(22): 4673-4680	☐
11	S. Kawai et al., Transformation of Saccharomyces cerevisiae and other fungi: methods and possible underlying mechanism. Bioeng Bugs. 2010 Nov-Dec;1(6):395-403	☐
12	Henikoff S & Henikoff, J G, 1992, Proc. Natl. Acad. Sci. USA 89: 10915-10919	☐
13	Roy A.D. et al. Development of fluorescent aryltryptophans by Pd mediated cross-coupling of unprotected halotryptophans in water. Chem Commun (Camb). 2008 Oct 21;(39):4831-3	☐
14	Corr M.J. et al. Sonogashira diversification of unprotected halotryptophans, halotryptophan containing tripeptides; and generation of a new to nature bromo-natural product and its diversification in water Chem Sci. 2017 Mar 1;8 (3):2039-2046	☐

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Attorney Docket Number	29664-P62051US03

15	Finnin, B. and Morgan, T.M., Transdermal penetration enhancers: applications, limitations, and potential J Pharm Sci. 1999 Oct;88(10):955-8	☐
16	Ross, S. et al. Acute and Sustained Reductions in Loss of Meaning and Suicidal Ideation Following Psilocybin-Assisted Psychotherapy for Psychiatric and Existential Distress in Life-Threatening Cancer. ACS Pharmacol Transl Sci. 2021 Apr 9; 4(2): 553–562.	☐
17	Schnepel C. et al. Enzymatic Halogenation: A Timely Strategy for Regioselective C-H Activation. Chemistry. 2017 Sep 7;23(50):12064-12086	☐
18	Durak L.J. et al. Late-Stage Diversification of Biologically Active Molecules via Chemoenzymatic C-H Functionalization ACS Catal. 2016 Mar 4; 6(3): 1451–1454	☐
19	Runguphan W. et al. Diversification of monoterpene indole alkaloid analogs through cross-coupling. Org Lett. 2013 Jun 7;15(11):2850-3	☐
20	Ding, L. et al. Discovery and Structure-Based Optimization of 6-Bromotryptamine Derivatives as Potential 5-HT2A Receptor Antagonists. Molecules, 2015, 20:17675-17683	☐
21	Shoubhye, J. et al. Hybrid molecules inhibiting myeloperoxidase activity and serotonin reuptake: a possible new approach of major depressive disorders with inflammatory syndrome. Royal Pharmaceutical Society, Journal of Pharmacy and Pharmacology, 2014, 66, pp. 1122–1132	☐
22	Cregg et al., Recombinant protein expression in Pichia pastoris. Mol Biotechnol. (2000) 16(1): 23-52	☐
23	Mattanovich et al., Recombinant protein production in yeasts. Methods Mol. Biol., 2012, 824:329-58	☐
24	Romanos et al., Foreign gene expression in yeast: a review. Yeast. 1992 Jun;8(6):423-88	☐
25	Andorfer M.C., et al. Directed Evolution of RebH for Catalyst-Controlled Halogenation of Indole C-H Bonds. (2016) Chem. Sci. 7: 3720	☐

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26	Andorfer M.C., et al. Directed Evolution of RebH for Catalyst-Controlled Halogenation of Indole C-H Bonds. (2016) Chem. Sci. 7: 3720	☐
27	Glenn W.S., et al. Reengineering a tryptophan halogenase to preferentially chlorinate a direct alkaloid precursor (2011) J. Am. Chem. Soc. 133: 19346	☐
28	Campos et al. A general synthesis of substituted indoles from cyclic enol ethers and enol lactones 2004, Org. Lett 6: 79-82	☐
29	Dastmalchi et al., 2019, Nat. Chem Biol. 15: 384-390	☐
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32	Jones et al. ePathOptimize: A Combinatorial Approach for Transcriptional Balancing of Metabolic Pathways. 2015, Sci Rep. 5: 11301	☐
33	Pyrgiotakis G. et al., 2009, Ann. Biomed. Eng. 37: 1464-1473	☐
34	Rickli A. et al., 2016, Europ. Neuropsychopharmacol., 26: 1326-1337	☐
35	Lombardo et al. A tandem isomerization/prins strategy: iridium(III)/Brønsted acid cooperative catalysis 2013, Angew. Chem. Int. Ed. 52: 12910-12914	☐
36	Go et al. Amino derivatives of indole as potent inhibitors of isoprenylcysteine carboxyl methyltransferase 2010, J. Med. Chem. 53: 6838-6850	☐

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	Attorney Docket Number	29664-P62051US03	

	37	Pratuangdejkul et al (Current Medicinal Chemistry, 2005, 12, 2393-2410 (Year: 2005)	☐
	38	Winkelblech et al.(Organic and Biomolecular Chemistry, 2016, 14, 9883-9895) (Year: 2016)	☐
	39	Williams et al. (Foye's Principles of Medicinal chemistry, fifth edition, 2002) (Year: 2002)	☐
	40	Patani et al. (Chem. Rev.1996, 96, 3147-3176) (Year: 1996)	☐

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EXAMINER SIGNATURE

Examiner Signature	/SAVITHA M RAO/	Date Considered	08/09/2024
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Application Number	18655793
Filing Date	2024-05-06
First Named Inventor	Jillian M. Hagel
Art Unit	1629
Examiner Name	SAVITHA M RAO
Attorney Docket Number	29664-P62051US03

CERTIFICATION STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

- ☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).
- OR**
- ☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).
- ☐ See attached certification statement.
- ☒ A certification statement is not submitted herewith.

FEE

- ☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

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- ☒ An identification of an earlier application pursuant to 37 CFR 1.98 (d) (1) is attached.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/mfenwick/	Date (YYYY-MM-DD)	2024-07-16
Name/Print	Michael Fenwick	Registration Number	61773

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APPLICATION #	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET #
18655793	05/06/2024	Jillian Hagel	29664-P62051US03

Title of Invention

HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING



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Enveric Biosciences Canada Inc.	100%
Total	100%

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APPROVAL LETTER

APPLICATION #
18/655,793

FILING DATE
05/06/2024

APPLICANT/PATENT UNDER REEXAMINATION
Jillian Hagel

Title of Invention

HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING

Electronic terminal disclaimer filed on 08/14/2024



Approved

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
18/655,793RECEIPT DATE / TIME
08/14/2024 11:56:33 AM Z ETATTORNEY DOCKET #
29664-P62051US03

Title of Invention

HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 4842

FILED BY Giselle Augurusa

PATENT CENTER # 66780313

FILING DATE 05/06/2024

CUSTOMER # 1059

FIRST NAMED
INVENTOR Jillian M. HagelCORRESPONDENCE
ADDRESS -

AUTHORIZED BY Michael Fenwick

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
petition-request.pdf	3	Terminal Disclaimer-Filed (Electronic)	44 KB
grantLetter.pdf	1	Terminal Disclaimer-Electronic- Approved	18 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
petition-request.pdf	1BC7610BED232F97E90205F77FE4044BEF04D02A05E1D859A A52742CE83C1D4C04A9C0AAEBE48882B15644588C85A228A9 566B949622FC8384F3FA074B44D434
grantLetter.pdf	4797EA4408F6BCC55A6962A1A914DAEFEAFAFEAF7A7A580C9E

E8A126246E814083CD8AEACEE0A1C542334148566B7FFBE37
7D5EC71A7A8DBA6E3B17A2F72B614AA

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<i>Application Number</i> * 18/655,793 *	Application/Control No. 18/655,793	Applicant(s)/Patent under Reexamination Hagel et al.	
	Examiner RAO, SAVITHA M	Art Unit 1629	
Document Code - DISQ		Internal Document - DO NOT MAIL	

TERMINAL DISCLAIMER	☐ APPROVED	☒ DISAPPROVED
Date Filed: <u>07 August 2024</u>	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:
/JEAN PROCTOR/ Technology Center: <u>OPLC</u> Telephone: <u>(571)272-1040</u> <u>2 td's wrong filing date on TD should be 5/6/24.</u>

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
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08/07/2024 11:42:20 AM Z ETATTORNEY DOCKET #
29664-P62051US03

Title of Invention

HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4842	FILED BY	Giselle Augurusa
PATENT CENTER #	66686798	FILING DATE	05/06/2024
CUSTOMER #	1059	FIRST NAMED INVENTOR	Jillian M. Hagel
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Michael Fenwick

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
P62051US03_Terminal_Disclaim_11998557.pdf	2	Claims	209 KB
P62051US03_Terminal_Disclaimer_11918594.pdf	2	Claims	212 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
P62051US03_Terminal_Disclaim_11998557.pdf	CB4CF02B21C92FCB80EC0204438AEF2B30853027D9EEAB3C11E7935791332018E74437CB52B3AEC077BBFB8BB524DC8CB2C33F5EBCE8D3AAA52204E287687647
P62051US03_Terminal_Disclaim_11918594.pdf	84657FF29BB3DFC68B886EEE0F36DF66AC83BE274A38860A1

mer_11918594.pdf

BA2543255198333C686E359A546FD6E97292B8C795484F6ED2
EC1FA1828C168B0CFEDDAED3C6FCD

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**TERMINAL DISCLAIMER TO OBIATE A DOUBLE PATENTING
REJECTION OVER A "PRIOR" PATENT**Docket Number (Optional)
29664-P62051US03

In re Application of: Hagel et al.

Application No.: 18/655,793

Filed: 2021-09-01

For: HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING

The owner*, Enveric Biosciences Canada Inc., of 100 percent interest 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** No. 11,998,557 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:

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- is found invalid by a court of competent jurisdiction;
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- has all claims canceled by a reexamination certificate;
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1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

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.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 61,773

/mfenwick/

Signature

August 7, 2024

Date

Michael Fenwick

Typed or printed name

416-957-1665

Telephone Number

- ☒ Terminal disclaimer fee under 37 CFR 1.20(d) included.

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #
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HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING

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APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 4842

FILED BY Giselle Augurusa

PATENT CENTER # 66686798

AUTHORIZED BY Michael Fenwick

CUSTOMER # 1059

FILING DATE 05/06/2024

CORRESPONDENCE
ADDRESS -FIRST NAMED
INVENTOR Jillian M. Hagel

Payment Information

PAYMENT METHOD
CARD / 8979PAYMENT TRANSACTION ID
E202487B43179329PAYMENT AUTHORIZED BY
Giselle AugurusaPRE-AUTHORIZED ACCOUNT
022095PRE-AUTHORIZED CATEGORY
37 CFR 1.16 (National application filing, search, and examination fees); 37
CFR 1.17 (Patent application and reexamination processing fees); 37 CFR
1.19 (Document supply fees); 37 CFR 1.21 (Miscellaneous fees and charges)

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
2814	STATUTORY DISCLAIMER, INCLUDING TERMINAL DISCLAIMER	170.00	2	340.00
TOTAL AMOUNT:				\$340.00

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/mfenwick/

Signature

August 7, 2024

Date

Michael Fenwick

Typed or printed name

416-957-1665

Telephone Number

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Title of Invention

HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING

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APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 4842

FILED BY Giselle Augurusa

PATENT CENTER # 66515307

FILING DATE 05/06/2024

CUSTOMER # 1059

FIRST NAMED INVENTOR
Jillian M. Hagel

CORRESPONDENCE ADDRESS -

AUTHORIZED BY Michael Fenwick

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
P62051US03_ResponseToRestrictionRequirement.pdf	8	Response to Election / Restriction Filed	341 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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Bereskin & Parr

Confirmation No: 4842

Appl. No. : 18/655,793
Applicant : Enveric Biosciences Canada, Inc.
Filed : May 6, 2024
Title : HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS
OF USING
TC./A.U. : 1629
Examiner : SAVITHA M. RAO
Docket No. : 29664-P62051US03
Customer No. : 1059

By Electronic Filing

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RESPONSE TO RESTRICTION REQUIREMENT

Sir:

This is in response to the Office Action dated June 28, 2024.

Amendments to the Claims begin on page 2 of this paper

Remarks begin on page 7 of this paper.



Bereskin & Parr LLP

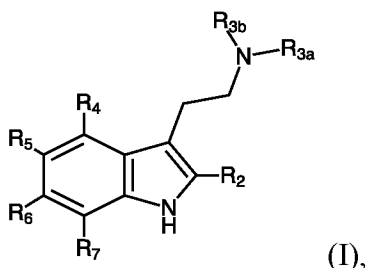
1

Scotia Plaza, 40 King Street West, 40th Floor, Toronto, ON M5H 3Y2 Canada
Tel: 416.364.7311 Fax: 416.361.1398 bereskinparr.com

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. **[Presently amended]** a A chemical compound or salt thereof having the formula (I):



wherein, at least one of R₂, R₄, R₅, R₆ or R₇ is a halogen atom, wherein each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom or an alkyl group or O-alkyl group, wherein R₄ when it is not halogenated is a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group, and wherein R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group.

2. **[Previously presented]** A chemical compound according to claim 1, wherein one or two of R₄, R₅, R₆, or R₇ are a halogen atom, wherein the halogen atom is selected from fluorine (F), chlorine (Cl), and bromine (Br).
3. **[Previously presented]** A chemical compound according to claim 1, wherein one or two of R₄, R₅, or R₆ are halogenated, wherein the halogen atom is selected from fluorine (F), chlorine (Cl), and bromine (Br).
4. **[Previously presented]** A chemical compound according to claim 1, wherein two of R₄, R₅, and R₆ are halogenated, wherein the halogen atom is selected from fluorine (F), chlorine (Cl), and bromine (Br).
5. **[Previously presented]** A chemical compound according to claim 4, wherein R₄ is halogenated, and wherein one of R₅, and R₆ is halogenated.

6. **[Previously presented]** A chemical compound according to claim 4, wherein R₅ is halogenated, and wherein one of R₄, and R₆ is halogenated.
7. **[Previously presented]** A chemical compound according to claim 5, wherein the halogen atoms are fluorine atoms.
8. **[Previously presented]** A chemical compound according to claim 6, wherein the halogen atoms are fluorine atoms.
9. **[Previously presented]** A chemical compound according to claim 2, wherein R₇ is a fluorine atom, and wherein one atom is halogenated.
10. **[Previously presented]** A chemical compound according to claim 7, wherein each non-halogenated R₂, R₄, R₅, R₆, or R₇, is a hydrogen atom.
11. **[Previously presented]** A chemical compound according to claim 8, wherein each non-halogenated R₂, R₄, R₅, R₆, or R₇, is a hydrogen atom.
12. **[Previously presented]** A chemical compound according to claim 9, wherein each non-halogenated R₂, R₄, R₅, R₆, or R₇, is a hydrogen atom.
13. **[Previously presented]** A chemical compound according to claim 3, wherein at least one of the halogen atoms is a chlorine atom.
14. **[Previously presented]** A chemical compound according to claim 3, wherein R₆ is a chlorine atom.
15. **[Previously presented]** A chemical compound according to claim 14, wherein R₅ is a fluorine atom.
16. **[Previously presented]** A chemical compound according to claim 14, wherein each non-halogenated R₂, R₄, R₅, R₆, or R₇, is a hydrogen atom.

17. [Previously presented] A chemical compound according to claim **15**, wherein each non-halogenated R₂, R₄, R₅, R₆, or R₇, is a hydrogen atom.

18. [Previously presented] A chemical compound according to claim **3**, wherein R₅ is a bromine atom, and one atom is halogenated.

19. [Previously presented] A chemical compound according to claim **18**, wherein each non-halogenated R₂, R₄, R₅, R₆, or R₇, is a hydrogen atom.

20. [Previously presented] A chemical compound according to claim **2**, wherein R_{3a} and R_{3b} are each independently selected from a hydrogen atom, a (C₁-C₆)-alkyl group, and a (C₁-C₆)-acyl group.

21. [Previously presented] A chemical compound according to claim **10**, wherein R_{3a} and R_{3b} are, respectively, a hydrogen atom and a (C₁-C₆)-acyl group.

22. [Previously presented] A chemical compound according to claim **11**, wherein R_{3a} and R_{3b} are, respectively, a hydrogen atom and a (C₁-C₆)-acyl group.

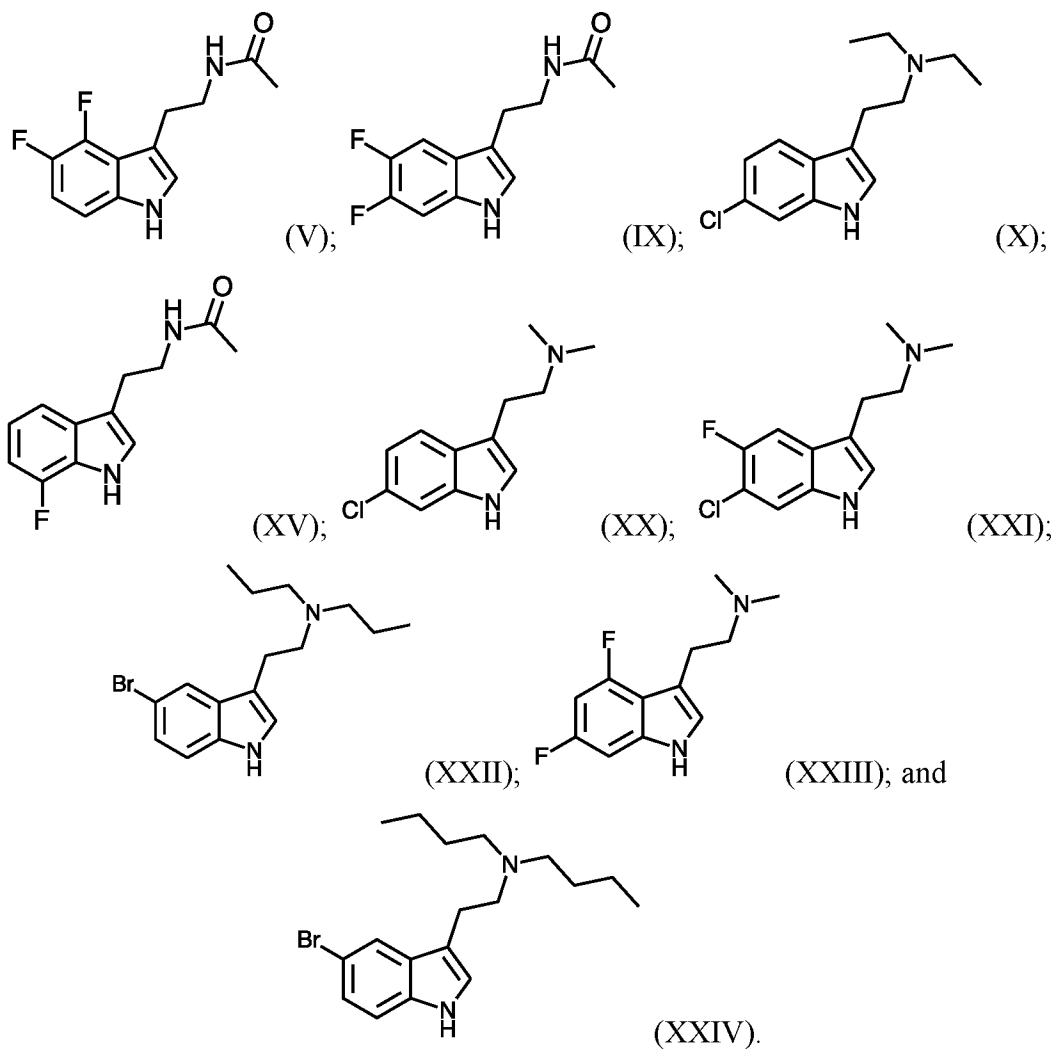
23. [Previously presented] A chemical compound according to claim **12**, wherein R_{3a} and R_{3b} are, respectively, a hydrogen atom and a (C₁-C₆)-acyl group.

24. [Previously presented] A chemical compound according to claim **16**, wherein R_{3a} and R_{3b} are each a (C₁-C₆)-alkyl group.

25. [Previously presented] A chemical compound according to claim **17**, wherein R_{3a} and R_{3b} are each a (C₁-C₆)-alkyl group.

26. [Previously presented] A chemical compound according to claim **19**, wherein R_{3a} and R_{3b} are each a (C₁-C₆)-alkyl group.

27. [Previously presented] A chemical compound according to claim 1, wherein the chemical compound is selected from the group consisting of compounds having formulas (V); (IX); (X); (XV); (XX); (XXI); (XXII); (XXIII); and (XXIV):



28. [Previously presented] A pharmaceutical drug formulation comprising an effective amount of the chemical compound according to claim 1, together with a pharmaceutically acceptable excipient, diluent, or carrier.

29. [Previously presented] A pharmaceutical drug formulation comprising an effective amount of the chemical compound according to claim **27**, together with a pharmaceutically acceptable excipient, diluent, or carrier.

30. [Withdrawn] A method for treating a psychiatric disorder, the method comprising administering to a subject in need thereof a pharmaceutical formulation comprising a chemical compound according to claim **1**, wherein the pharmaceutical formulation is administered in an effective amount to treat the psychiatric disorder in the subject.

REMARKS

The Office Action dated June 28, 2024 has been carefully considered. It is believed that the following election represents a complete response to the Office Action. Reconsideration is respectfully requested.

Claim 1 has been amended to correct a minor typographical error.

Group Election

In the Office Action, the Examiner has indicated that the claims are directed to two different groups of inventions (Group I and Group II), and that Applicant is required to elect one group. In response, Applicant elects Group I, the claims being readable thereon being claims 1 – 29, which are drawn to products of Formula I.

Species Election

The Examiner has further indicated that claims 1 – 29 of Group I are directed to distinct species and that Applicant is required to elect a single disclosed species, notably in particular a single compound from the compounds recited by claim 29. Applicant elects the compound having formula (V). The compound having formula (V) includes the following variable substituents: $R_2, R_6, R_7 = H$; $R_4, R_5 =$ and F; $R_{3a} = -(C=O)CH_3$ ($-(C=O)(C_1-C_6)$ alkyl); and $R_{3b} = H$. This compound is encompassed by claims 1-8, 10, 11, 20, 21, 22, 27, 28 and 29.

The Commissioner is hereby authorized to charge any deficiency in fees (including claim fees) or credit any overpayment to our Deposit Account 02-2095. Should the Examiner wish to discuss this matter, the Examiner is kindly requested to contact Michael Fenwick at 416-957-1665 at the Examiner's convenience.

Appl. No. 18/655,793
Response Dated July 25, 2024
Reply to Office Action dated June 28, 2024

Applicants reserve the right to file one or more continuing applications under 35 U.S.C. §120 on the subject matter of any claims finally held withdrawn from consideration in this application.

Respectfully submitted,

BERESKIN & PARR LLP/S.E.N.C.R.L., s.r.l.
Agent for the Applicant

By: /mfenwick/

Mike Fenwick

Reg. No. 61773

Tel: 416-957-1665

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 18/655,793		Filing Date 05/06/2024		☐ To be Mailed			
ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO											
APPLICATION AS FILED - PART I											
		(Column 1)		(Column 2)							
FOR		NUMBER FILED		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 \$40 =					
INDEPENDENT CLAIMS (37 CFR 1.16(h))		minus 3 = *				x \$ 192 =					
☐ 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	07/25/2024	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR		PRESENT EXTRA		RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	* 30	Minus	** 30	= 0			x \$40 =		0	
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0			x \$ 192 =		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".								/CAROLYN E THOMAS/			
*** 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.**

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
18/655,793	05/06/2024	Jillian M. Hagel	29664-P62051US03

CONFIRMATION NO. 4842

POA ACCEPTANCE LETTER



OC000000075477645

1059
BERESKIN & PARR LLP/S.E.N.C.R.L., s.r.l.
40 KING STREET WEST
40TH FLOOR
TORONTO, ON M5H 3Y2
CANADA

Date Mailed: 07/24/2024

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/16/2024.

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.

/mnguyen/

Confirmation No.: 4842

App. Serial No. : 18/655,793
Inventors : Jillian M. Hagel
Filing Date : May 6, 2024
Entitled : HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF
USING
TC./A.U. : 1629
Examiner : SAVITHA M RAO

Docket No. : 29664-P62051US03
Customer No. : 01059

BY ELECTRONIC FILING

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

July 16, 2024

FILING OF AN INFORMATION DISCLOSURE STATEMENT

In accordance with 37 CFR 1.97 and 1.98, and in recognition of the duty of disclosure set forth in 37 CFR 1.56, the Applicant hereby submits an Information Disclosure Statement on Form PTO-1449 containing a listing of publications of which the Applicant is aware.

In accordance with the provision under 1.98(d), we note that copies of the foreign patent and non-patent literature documents were previously submitted in respect of the parent application no. 17/903,080 now patent no. 11,998,557.

In accordance with the requirements of 1.97 (b)(3), this Information Disclosure Statement is filed before the mailing of a first substantive Office Action on the merits.

The Examiner is requested to indicate consideration of these documents by initialing the appropriate column.

The Applicant reserves the right to contest the applicability of any of these documents as prior art against the subject application. If the Examiner has any questions concerning this Information Disclosure Statement, he/she is requested to contact the undersigned. Entry of the enclosed Information Disclosure Statement is believed to be in order and is respectfully requested.

Respectfully submitted,

BERESKIN & PARR LLP/S.E.N.C.R.L., s.r.l.

By /mfenwick/
Michael Fenwick
Reg. No. 61,773

BERESKIN & PARR LLP/S.E.N.C.R.L., s.r.l.
40 King Street West, 40th Floor
Toronto, Ontario
Canada M5H 3Y2

Tel: 416-957-1665
Fax: 416-361-1398

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA/82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	18/655,793
Filing Date	05/06/2024
First Named Inventor	Hagel
Title	HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING
Art Unit	1629
Examiner Name	SAVITHA M RAO
Attorney Docket Number	29664-P62051US03

SIGNATURE of Applicant or Patent Practitioner

Signature	/mfenwick/	Date (Optional)	
Name	Michael Fenwick	Registration Number	61773
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.



*Total of 1 forms are submitted.

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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
18/655,793	05/06/2024

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☒ 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:

1059

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.)

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I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Enveric Biosciences Canada Inc.

- ☐ 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)

Name

Joseph Tucker

Title

CEO

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.

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
18/655,793

RECEIPT DATE / TIME
07/16/2024 12:20:00 PM Z ET

ATTORNEY DOCKET #
29664-P62051US03

Title of Invention

HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 4842

FILED BY Lindsay Earnshaw

PATENT CENTER # 66384426

FILING DATE 05/06/2024

CUSTOMER # 1059

FIRST NAMED
INVENTOR Jillian M. Hagel

CORRESPONDENCE
ADDRESS -

AUTHORIZED BY Michael Fenwick

Documents

TOTAL DOCUMENTS: 3

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
P62051US03 IDS_Letter.pdf	2	Transmittal Letter	96 KB
P62051US03 Executed PoA.pdf	2	Power of Attorney	1226 KB
P62051US03 IDS.pdf	8	Information Disclosure Statement (IDS) Form (SB08)	1324 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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P62051US03 IDS_Letter.pdf	4C51506C4662D48220B215C07C4E11086D506963C704BAB4B9 78E8F9EDB96095E6C17B3AB8D8E210E25B71579538C3813CD 8E78DB1E95BC21E7C4989EF155EF9
P62051US03 Executed PoA.pdf	B077EEDC4C9706CCB76DFE28EB617A570F1137C1D43A32C0 44776B9D1EE3CB06BCDED2EA84F8533668E0EAE9DCF45013 2FD6DDF84ECEBA3778294C0C6AAD871B
P62051US03 IDS.pdf	30BBC0B21AA4CF2A82811B7ED255FA402E9A6E8E47E3BB988 A759596D1B2203486B092E9E20DDCF54F29699A7B27A0EBA1 529C19CFFE8A7508A83C407BAB40DA

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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 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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18655793	
	Filing Date		2024-05-06	
	First Named Inventor	Jillian M. Hagel		
	Art Unit	1629		
	Examiner Name	SAVITHA M RAO		
	Attorney Docket Number	29664-P62051US03		

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	1	5688807	A	1997-11-18	Audia et al.	

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	1	20200397752	A1	2020-12-24	Perez Castillo et al.	
	2	20090093513	A1	2009-04-09	Hamann et al.	
	3	20080171779	A1	2008-07-17	De Bruin et al.	

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	1	2004000845	WO	A1	2003-12-31	Suven Pharmaceuticals Ltd.		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18655793	
	Filing Date		2024-05-06	
	First Named Inventor	Jillian M. Hagel		
	Art Unit	1629		
	Examiner Name	SAVITHA M RAO		
	Attorney Docket Number	29664-P62051US03		

	2	2021011913	WO	A1	2021-01-21	Arvinas Operations, Inc.		☐
	3	2021108911	WO	A1	2021-06-10	Neomind Biosciences Inc.		☐
	4	2021168082	WO	A1	2021-08-26	Gilgamesh Pharmaceuticals Inc.		☐
	5	2019173797	WO	A1	2019-09-12	New Atlas Biotechnologies LLC		☐
	6	2018064465	WO	A1	2018-04-05	The Regents Of The University of California		☐
	7	2022051670	WO	A1	2022-03-10	Gilgamesh Pharmaceuticals Inc.		☐

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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	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
	1	Daniel, J. et al. Clinical potential of psilocybin as a treatment for mental health conditions. Mental Health Clin/, 2017;7 (1): 24-28	☐
	2	Grob, C. et al. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancerArch. Gen. Psychiatry, 2011, 68(1) 71-78	☐
	3	Cathart-Harris, R.L. et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry, 2016, 3: 619-627	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18655793
Filing Date	2024-05-06
First Named Inventor	Jillian M. Hagel
Art Unit	1629
Examiner Name	SAVITHA M RAO
Attorney Docket Number	29664-P62051US03

4	Needleman and Wunsch. A general method applicable to the search for similarities in the amino acid sequence of two proteins J. Mol. Biol., 1970, 48: 443	☐
5	Smith and Waterman. Adv. Appl. Math., 1981, 2: 482	☐
6	Carillo and Lipton. SIAM J. Applied Math., 1988, 48:1073	☐
7	Romeo, B. et al. Clinical and biological predictors of psychedelic response in the treatment of psychiatric and addictive disorders: A systematic review. J Psychiatr Res 137: 273, 2021	☐
8	Devereux et al., A comprehensive set of sequence analysis programs for the VAX. Nucleic Acids Res., 1984, 12: 387	☐
9	Altschul et al., J. Mol. Biol., 1990:215:403	☐
10	Thompson, J D, Higgines, D G and Gibson T J, 1994, Nucleic Acid Res 22(22): 4673-4680	☐
11	S. Kawai et al., Transformation of Saccharomyces cerevisiae and other fungi: methods and possible underlying mechanism. Bioeng Bugs. 2010 Nov-Dec;1(6):395-403	☐
12	Henikoff S & Henikoff, J G, 1992, Proc. Natl. Acad. Sci. USA 89: 10915-10919	☐
13	Roy A.D. et al. Development of fluorescent aryltryptophans by Pd mediated cross-coupling of unprotected halotryptophans in water. Chem Commun (Camb). 2008 Oct 21;(39):4831-3	☐
14	Corr M.J. et al. Sonogashira diversification of unprotected halotryptophans, halotryptophan containing tripeptides; and generation of a new to nature bromo-natural product and its diversification in water Chem Sci. 2017 Mar 1;8 (3):2039-2046	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18655793
Filing Date	2024-05-06
First Named Inventor	Jillian M. Hagel
Art Unit	1629
Examiner Name	SAVITHA M RAO
Attorney Docket Number	29664-P62051US03

15	Finnin, B. and Morgan, T.M., Transdermal penetration enhancers: applications, limitations, and potential J Pharm Sci. 1999 Oct;88(10):955-8	☐
16	Ross, S. et al. Acute and Sustained Reductions in Loss of Meaning and Suicidal Ideation Following Psilocybin-Assisted Psychotherapy for Psychiatric and Existential Distress in Life-Threatening Cancer. ACS Pharmacol Transl Sci. 2021 Apr 9; 4(2): 553–562.	☐
17	Schnepel C. et al. Enzymatic Halogenation: A Timely Strategy for Regioselective C-H Activation. Chemistry. 2017 Sep 7;23(50):12064-12086	☐
18	Durak L.J. et al. Late-Stage Diversification of Biologically Active Molecules via Chemoenzymatic C-H Functionalization ACS Catal. 2016 Mar 4; 6(3): 1451–1454	☐
19	Runguphan W. et al. Diversification of monoterpene indole alkaloid analogs through cross-coupling. Org Lett. 2013 Jun 7;15(11):2850-3	☐
20	Ding, L. et al. Discovery and Structure-Based Optimization of 6-Bromotryptamine Derivatives as Potential 5-HT2A Receptor Antagonists. Molecules, 2015, 20:17675-17683	☐
21	Shoubhye, J. et al. Hybrid molecules inhibiting myeloperoxidase activity and serotonin reuptake: a possible new approach of major depressive disorders with inflammatory syndrome. Royal Pharmaceutical Society, Journal of Pharmacy and Pharmacology, 2014, 66, pp. 1122–1132	☐
22	Cregg et al., Recombinant protein expression in Pichia pastoris. Mol Biotechnol. (2000) 16(1): 23-52	☐
23	Mattanovich et al., Recombinant protein production in yeasts. Methods Mol. Biol., 2012, 824:329-58	☐
24	Romanos et al., Foreign gene expression in yeast: a review. Yeast. 1992 Jun;8(6):423-88	☐
25	Andorfer M.C., et al. Directed Evolution of RebH for Catalyst-Controlled Halogenation of Indole C-H Bonds. (2016) Chem. Sci. 7: 3720	☐

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18655793
Filing Date	2024-05-06
First Named Inventor	Jillian M. Hagel
Art Unit	1629
Examiner Name	SAVITHA M RAO
Attorney Docket Number	29664-P62051US03

26	Andorfer M.C., et al. Directed Evolution of RebH for Catalyst-Controlled Halogenation of Indole C-H Bonds. (2016) Chem. Sci. 7: 3720	☐
27	Glenn W.S., et al. Reengineering a tryptophan halogenase to preferentially chlorinate a direct alkaloid precursor (2011) J. Am. Chem. Soc. 133: 19346	☐
28	Campos et al. A general synthesis of substituted indoles from cyclic enol ethers and enol lactones 2004, Org. Lett 6: 79-82	☐
29	Dastmalchi et al., 2019, Nat. Chem Biol. 15: 384-390	☐
30	Chen et al., A pathogenesis-related 10 protein catalyzes the final step in thebaine biosynthesis Nat. Chem Biol. 14: 738-743, 2018	☐
31	Chang, L. et al. Isolation and Characterization of O-methyltransferases Involved in the Biosynthesis of Glaucine in Glaucium flavum1. Plant Physiology, October 2015, Vol. 169, pp. 1127–1140,	☐
32	Jones et al. ePathOptimize: A Combinatorial Approach for Transcriptional Balancing of Metabolic Pathways. 2015, Sci Rep. 5: 11301	☐
33	Pyrgiotakis G. et al., 2009, Ann. Biomed. Eng. 37: 1464-1473	☐
34	Rickli A. et al., 2016, Europ. Neuropsychopharmacol., 26: 1326-1337	☐
35	Lombardo et al. A tandem isomerization/prins strategy: iridium(III)/Brønsted acid cooperative catalysis 2013, Angew. Chem. Int. Ed. 52: 12910-12914	☐
36	Go et al. Amino derivatives of indole as potent inhibitors of isoprenylcysteine carboxyl methyltransferase 2010, J. Med. Chem. 53: 6838-6850	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		18655793
	Filing Date		2024-05-06
	First Named Inventor	Jillian M. Hagel	
	Art Unit	1629	
	Examiner Name	SAVITHA M RAO	
	Attorney Docket Number	29664-P62051US03	

	37	Pratuangdejkul et al (Current Medicinal Chemistry, 2005, 12, 2393-2410 (Year: 2005)	☐
	38	Winkelblech et al.(Organic and Biomolecular Chemistry, 2016, 14, 9883-9895) (Year: 2016)	☐
	39	Williams et al. (Foye's Principles of Medicinal chemistry, fifth edition, 2002) (Year: 2002)	☐
	40	Patani et al. (Chem. Rev.1996, 96, 3147-3176) (Year: 1996)	☐

If you wish to add additional non-patent literature document citation information please click the Add button

Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	
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***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.

**INFORMATION DISCLOSURE
STATEMENT BY APPLICANT**
(Not for submission under 37 CFR 1.99)

Application Number	18655793
Filing Date	2024-05-06
First Named Inventor	Jillian M. Hagel
Art Unit	1629
Examiner Name	SAVITHA M RAO
Attorney Docket Number	29664-P62051US03

CERTIFICATION STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

- ☐ See attached certification statement.
- ☒ A certification statement is not submitted herewith.

FEE

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

COPIES

☒ An identification of an earlier application pursuant to 37 CFR 1.98 (d) (1) is attached.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/mfenwick/	Date (YYYY-MM-DD)	2024-07-16
Name/Print	Michael Fenwick	Registration Number	61773

This collection of information is required by 37 CFR 1.97 and 1.98. 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 1 hour 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.**

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 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 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.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/655,793	05/06/2024	Jillian M. Hagel	29664-P62051US03	4842
1059 7590 06/28/2024 BERESKIN & PARR LLP/S.E.N.C.R.L., s.r.l. 40 KING STREET WEST 40TH FLOOR TORONTO, ONTARIO M5H 3Y2 CANADA			EXAMINER RAO, SAVITHA M	
			ART UNIT	PAPER NUMBER
			1629	
			NOTIFICATION DATE	DELIVERY MODE
			06/28/2024	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):

ipprocessingcentre@bereskinparr.com

Notice of Pre-AIA or AIA Status

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

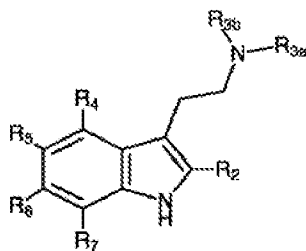
DETAILED ACTION

Claims 1-30 are pending

Restriction to one of the following inventions is required under 35 U.S.C. 121:

Election/Restrictions

- I. Claims 1-29 are drawn to a chemical compound or salts thereof having the formula (I)

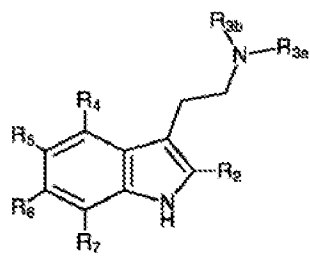


wherein, at least one of R2, R4, R5, R6 or R7 is a halogen atom, wherein each non-halogenated R2, R5, or R7 is a hydrogen atom or an alkyl

group or O-alkyl group, wherein R4 when it is not halogenated is a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group, and wherein R3a and R3b are a hydrogen atom, an alkyl group, an aryl group, or an acyl group..

Classified in CPC C12N9/0083. ; **Further election of species as set forth in specie elections below are required upon electing this invention.**

II. Claims 30 is drawn to a method for treating a psychiatric disorder, the method comprising administering to a subject in need thereof a pharmaceutical formulation comprising the compound of formula (I) shown below



, with variables as defined in instant claim 1, wherein the pharmaceutical formulation is administered in an effective amount to treat the psychiatric disorder in the subject. classified in CPC A61P25/00; **Further election**

of species as set forth in specie elections below are required upon electing this invention.

These inventions are distinct, each from the other because of the following reasons:

These distinct inventions have acquired separate status in the art, will support separate patents, and will require different fields of search for the respective inventions.

Accordingly, restriction for examination purposes as indicated is considered proper; 35 U.S.C. 121; 37 CFR 1.141; 37 CFR 1.142.

Invention I and invention II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the formulation of invention II can be used in materially different processes such as recreational use for its hallucinogenic effect.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

- (a) the inventions have acquired a separate status in the art in view of their different classification;
- (b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;
- (c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);
- (d) the prior art applicable to one invention would not likely be applicable to another invention;
- (e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of an invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention.**

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time

Art Unit: 1629

of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Election of Species

This application contains claims directed to the following patentably distinct species. Applicant is required to elect single disclosed specie from each of the election of specie requirement detailed below.

1. Specie Election 1: This specie election is required upon electing Groups I and II set forth in the above restriction. Applicant is required to elect a single disclosed specie of the compound of formula (I) where each and every variable is specifically defined. For e.g. compound recited in instant claim 21 . Claims 1-29 are generic to this specie.

2. Specie Election 2: This specie election is required upon electing Group II set forth in the above restriction Applicant is required to elect single disclosed specie of the psychiatric disorder being treated . For e.g. depression. Claim 30 is generic to this specie.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species from each of the specie requirement listed above., for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. Accordingly, each specie is patentably distinct and will require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the

Art Unit: 1629

election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Rejoinder paragraph

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder.

Art Unit: 1629

All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA M RAO whose telephone number is (571)270-5315. The examiner can normally be reached on M-F 8.30 am -4.30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached on 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1629

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.

/SAVITHA M RAO/

Primary Examiner, Art Unit 1629



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/655,793	05/06/2024	Jillian M. Hagel	29664-P62051US03	4842
1059	7590	06/13/2024	EXAMINER	
BERESKIN & PARR LLP/S.E.N.C.R.L., s.r.l.			CENTRAL, DOCKET	
40 KING STREET WEST			ART UNIT	
40TH FLOOR			PAPER NUMBER	
TORONTO, ONTARIO M5H 3Y2			OPAP	
CANADA			NOTIFICATION DATE	
			DELIVERY MODE	
			06/13/2024	
			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):

ipprocessingcentre@bereskinparr.com

<i>Decision Granting Request for Prioritized Examination (Track I)</i>	Application No. 18/655,793	Applicant(s) Hagel et al.	
	Examiner FIKIRTE A GEREMEW	Art Unit OMBL	AIA (FITF) Status Yes

1. THE REQUEST FILED 06 May 2024 IS **GRANTED** .

The above-identified application has met the requirements for prioritized examination

A. ☒ for an original nonprovisional application (Track I).

B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;

B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;

C. filing a **request for continued examination** ;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to FIKIRTE GEREMEW at (703) 756-1930. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/FIKIRTE A GEREMEW/ PROGRAM SUPPORT SPECIALIST, OMBL	
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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
18/655,793	05/06/2024		1392	29664-P62051US03	30	1

CONFIRMATION NO. 4842

FILING RECEIPT



0000000072923809

1059

BERESKIN & PARR LLP/S.E.N.C.R.L., s.r.l.
40 KING STREET WEST
40TH FLOOR
TORONTO, ON M5H 3Y2
CANADA

Date Mailed: 05/22/2024

Receipt is acknowledged of this non-provisional utility 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 FIRST INVENTOR, 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 corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction 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 provided that the request is grantable.

Inventor(s)

Jillian M. Hagel, Calgary, CANADA;
Peter J. Facchini, Calgary, CANADA;

Applicant(s)

Enveric Biosciences Canada Inc., Calgary, CANADA;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 17/903,080 09/06/2022 PAT 11,998,557
which is a CON of PCT/CA2021/051209 09/01/2021
which claims benefit of 63/073,104 09/01/2020

Foreign Applications for which priority is claimed (You may be eligible to benefit from the Patent Prosecution Highway program at the USPTO. Please see <http://www.uspto.gov> for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

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: 05/21/2024

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 18/655,793**

Projected Publication Date: 08/29/2024

Non-Publication Request: No

Early Publication Request: No

**** SMALL ENTITY ****

Title

HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING

Preliminary Class

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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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number
18/655,793

APPLICATION AS FILED - PART I

(Column 1)		(Column 2)		SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA		RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	64		N/A	
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A		N/A	280		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	320		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	30	minus 20 =	*	x 40 =	400	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1	minus 3 =	*	x =	0			
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))								
				TOTAL	1232		TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
AMENDMENT A		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	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))							OR		
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
TOTAL ADD'L FEE								OR	TOTAL ADD'L FEE	

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
AMENDMENT B		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	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))							OR		
	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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Under Secretary of Commerce for Intellectual Property and
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A handwritten signature in black ink, reading "Kathi Vidal".

Kathi Vidal

Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

A handwritten signature in black ink, reading "Derrick Brent".

Derrick Brent

Deputy Under Secretary of Commerce for Intellectual Property and
Deputy Director of the United States Patent and Trademark Office

**CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION
UNDER 37 CFR 1.102(e) (Page 1 of 1)**

First Named Inventor:	Jillian M. Hagel	Nonprovisional Application Number (if known):	
Title of Invention:	Halogenated Psilocybin Derivatives and Methods of Using		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently \$0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.
2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.
3. The applicable box is checked below:

I. ☒ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

- i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.
---OR---
(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.
- ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, or the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

- i. A request for continued examination has been filed with, or prior to, this form.
- ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
- iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
- iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
- v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature	/mfenwick/	Date	May 6, 2024
Name (Print/Typed)	Michael Fenwick	Practitioner Registration Number	61773

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.*

☐

*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.
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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.

**DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN
APPLICATION DATA SHEET (37 CFR 1.76)**

**Title of
Invention**

HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING

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/CA2021/051209

filed on September 1, 2021

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 state that I have reviewed and understand the contents of the above identified application, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. 1.56.

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.

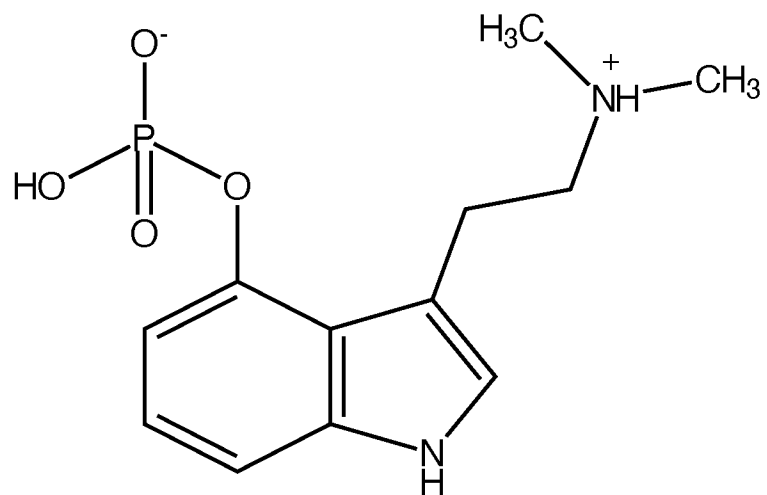
LEGAL NAME OF INVENTOR

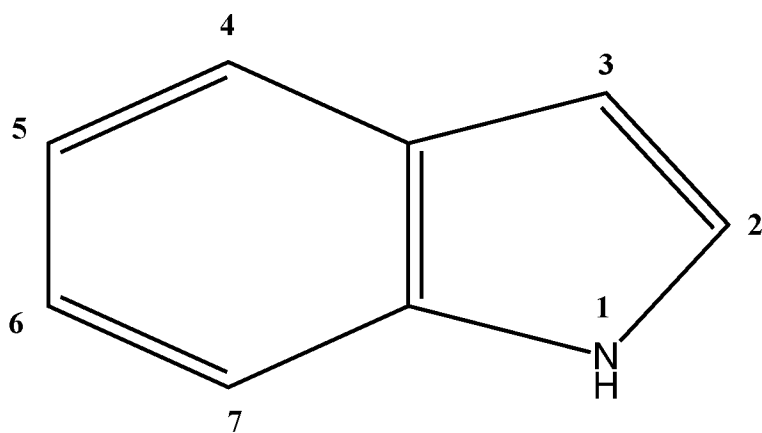
Inventor: Jillian M. HAGEI

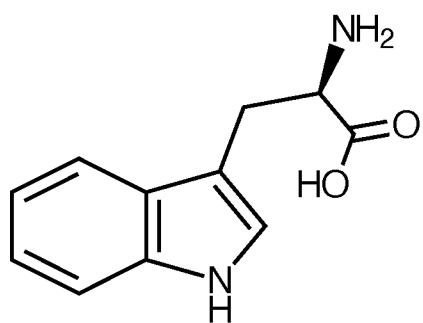
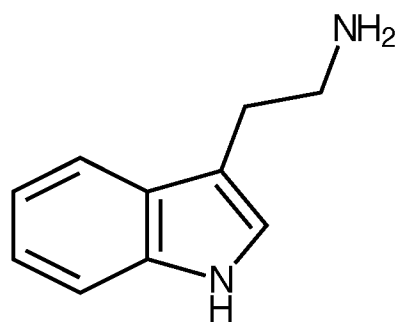
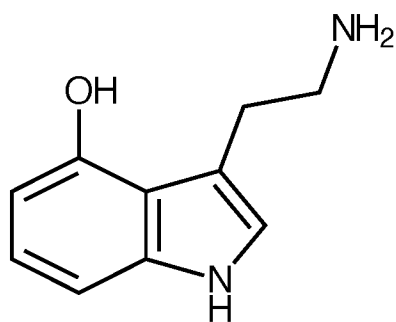
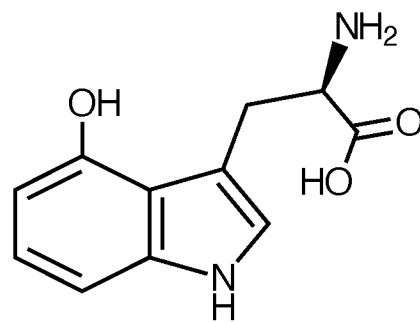
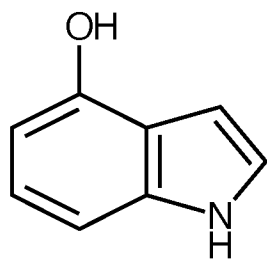
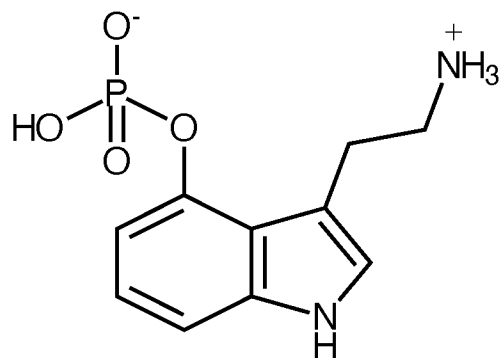
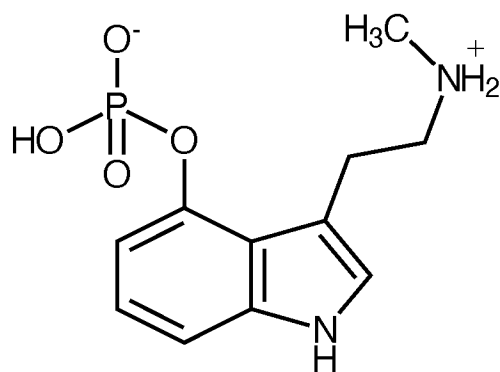
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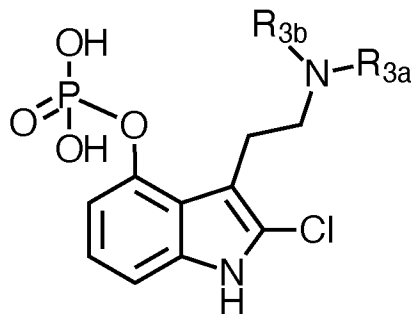
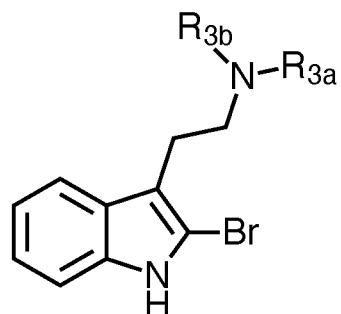
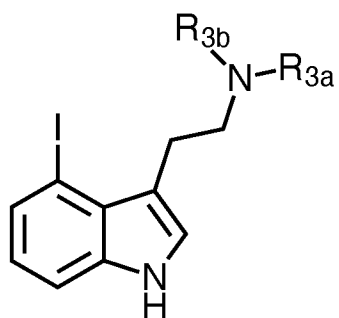
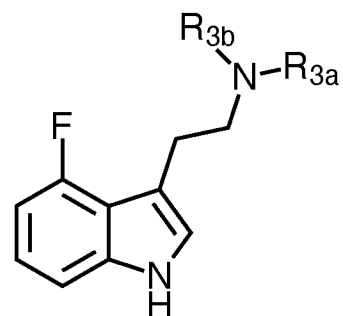
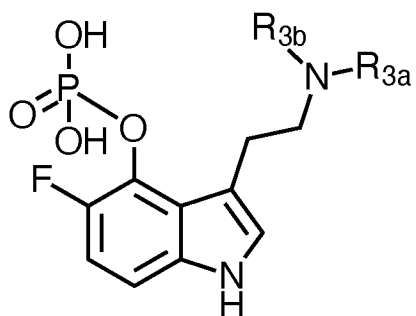
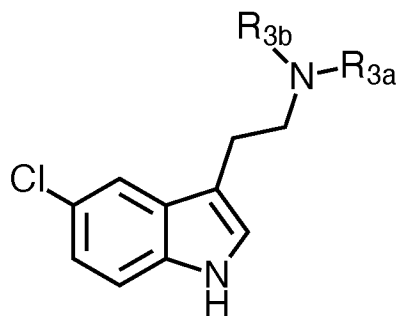
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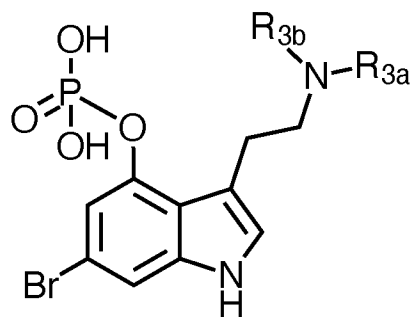
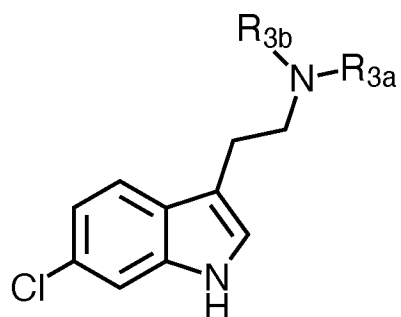
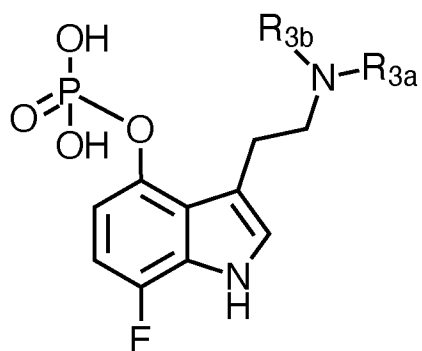
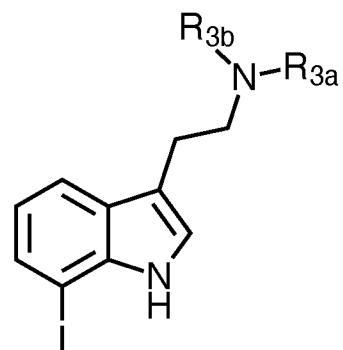
Note: An application data sheet, including naming the entire inventive entity, must accompany this form.
Use an additional form for each additional inventor.

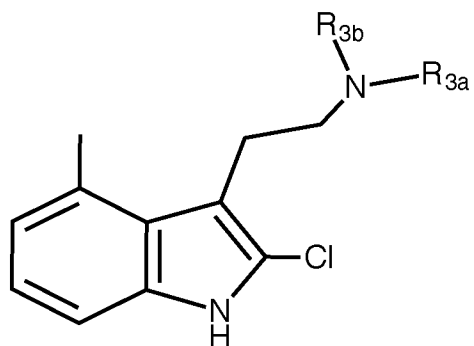
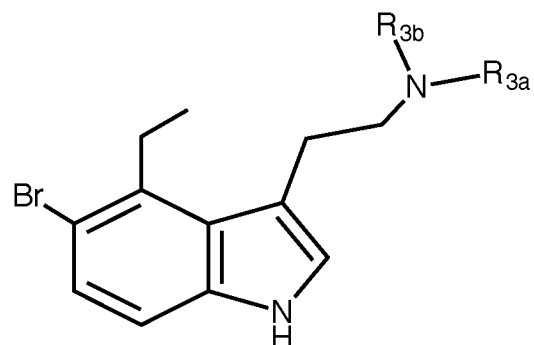
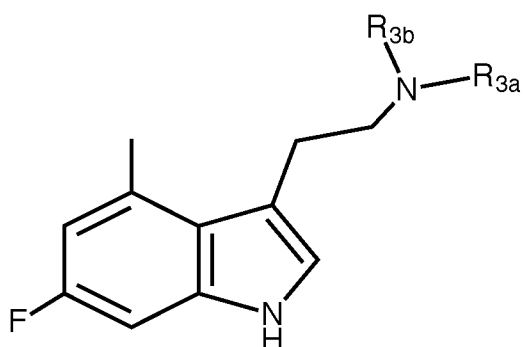
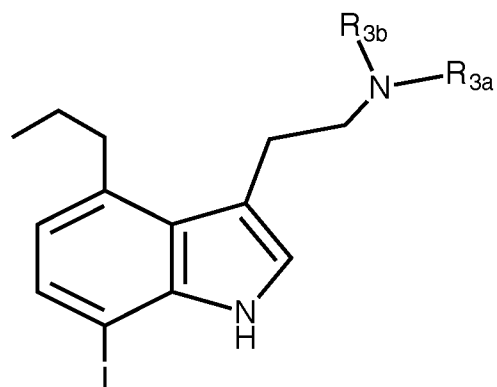
**FIG. 1**

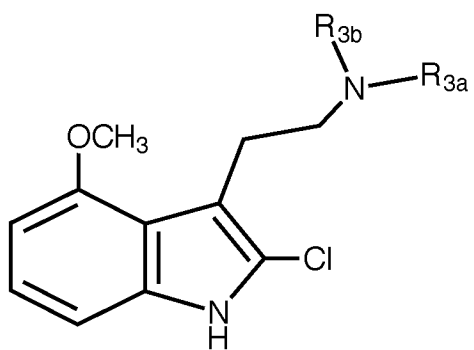
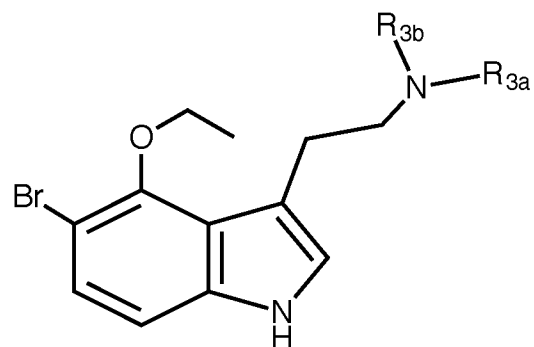
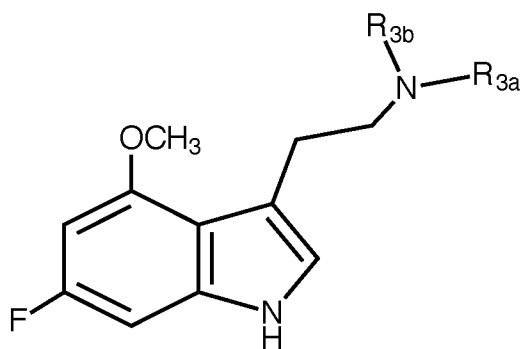
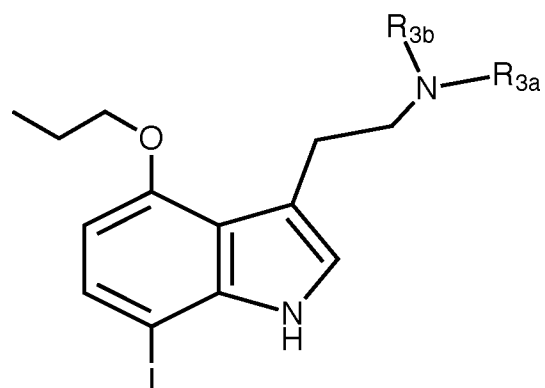
**FIG. 2**

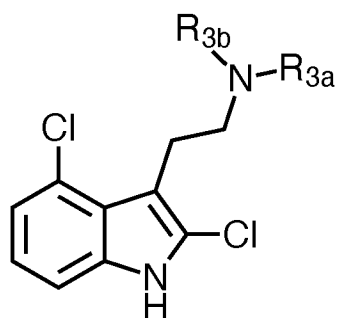
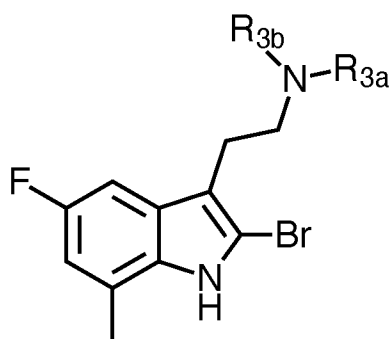
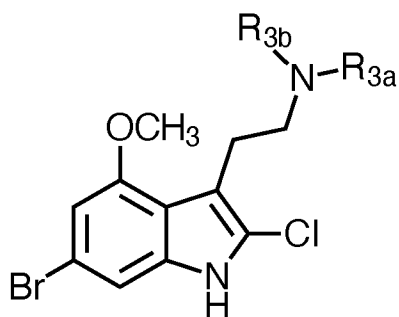
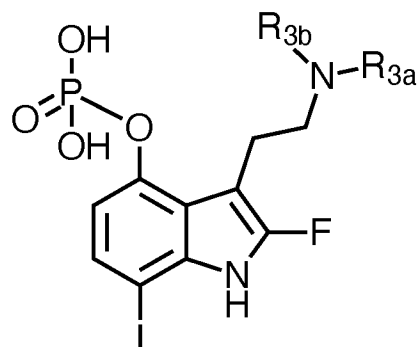
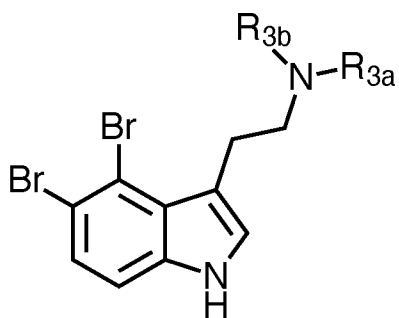
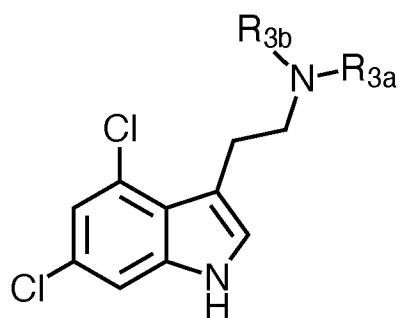
**FIG. 3A****FIG. 3B****FIG. 3C****FIG. 3D****FIG. 3E****FIG. 3F****FIG. 3G**

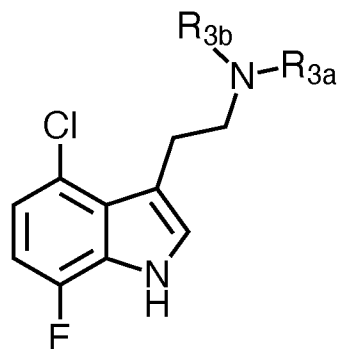
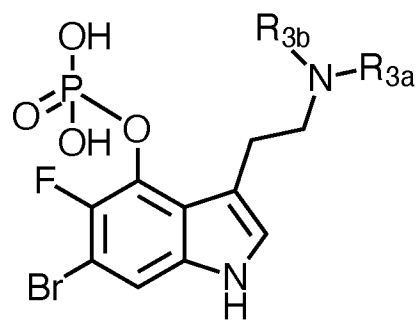
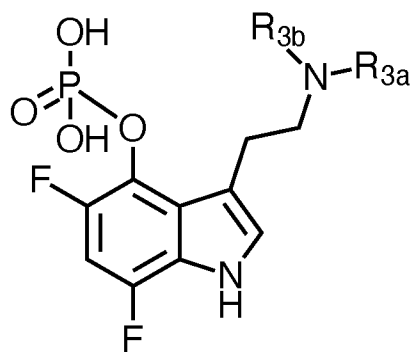
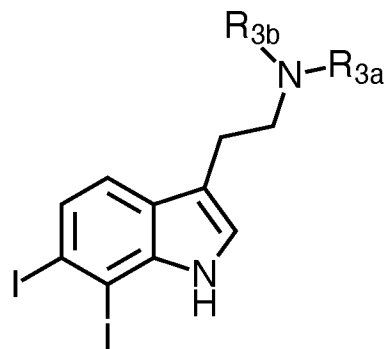
**FIG. 4A****FIG. 4B****FIG. 4C****FIG. 4D****FIG. 4E****FIG. 4F**

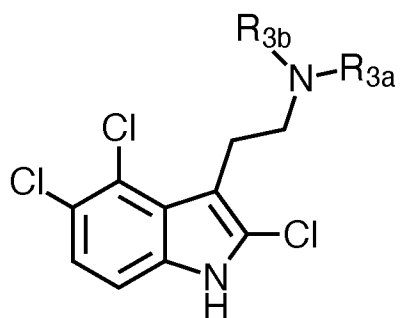
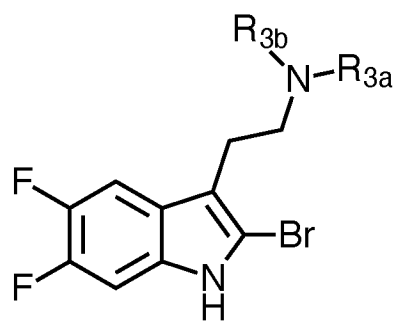
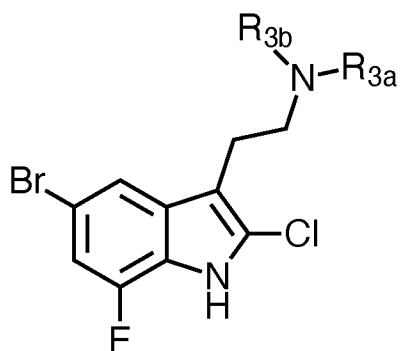
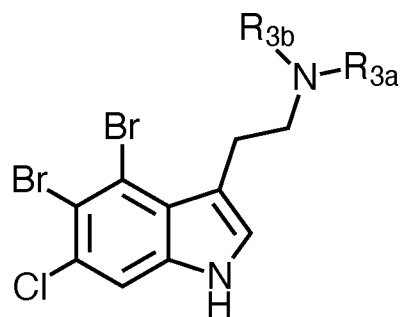
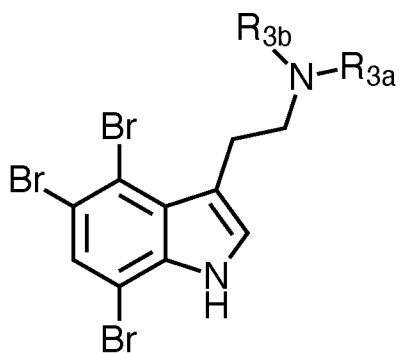
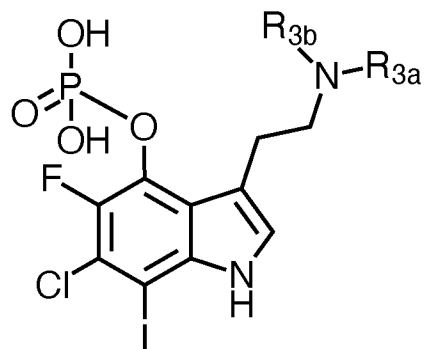
**FIG. 4G****FIG. 4H****FIG. 4I****FIG. 4J**

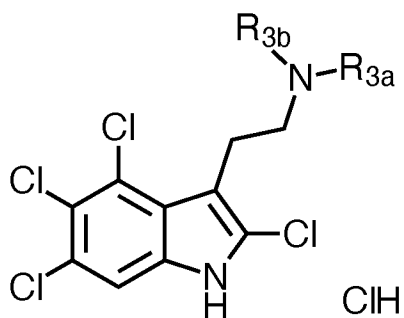
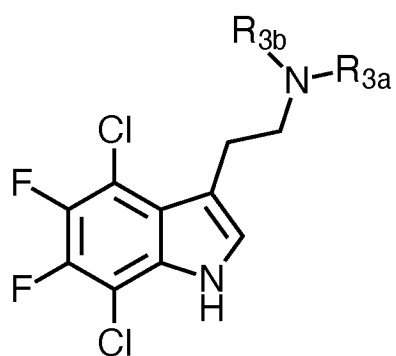
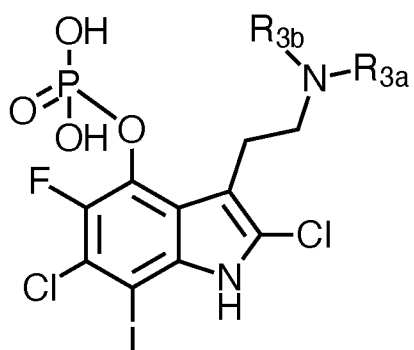
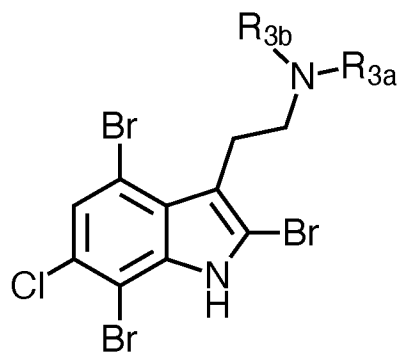
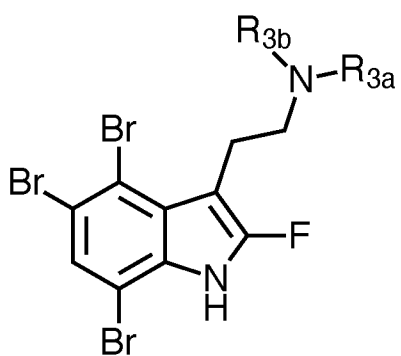
**FIG. 4K****FIG. 4L****FIG. 4M****FIG. 4N**

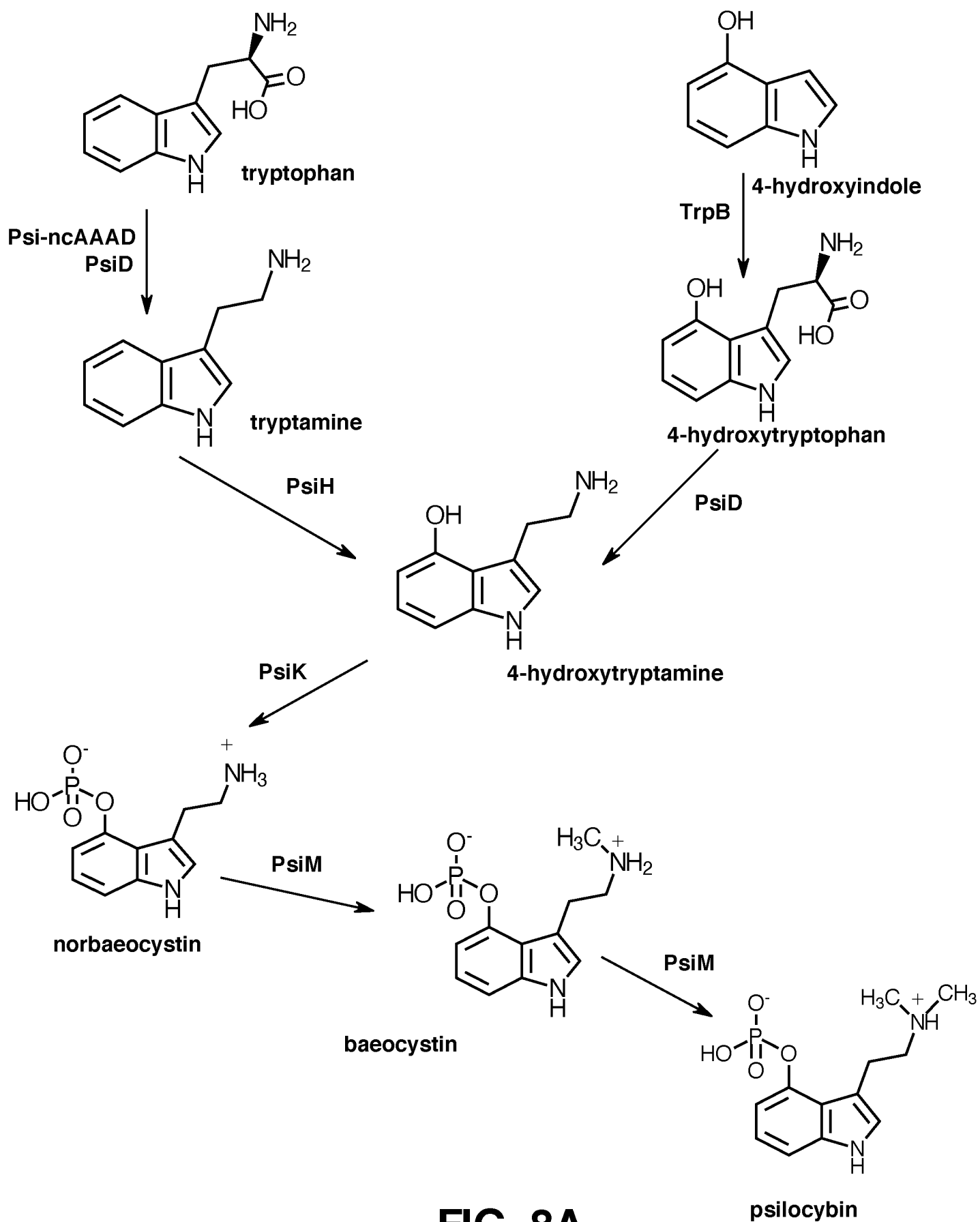
**FIG. 4O****FIG. 4P****FIG. 4Q****FIG. 4R**

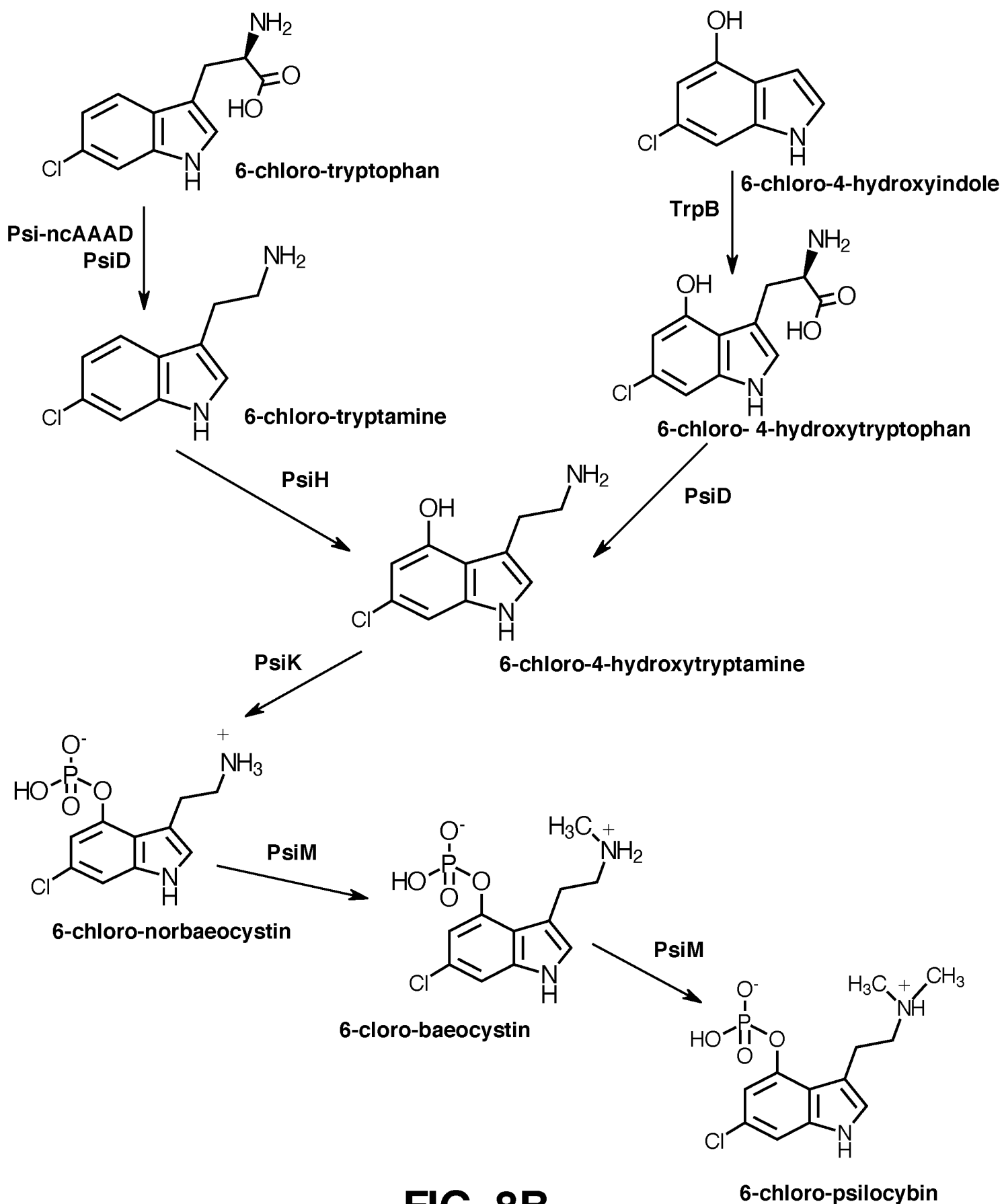
**FIG. 5A****FIG. 5B****FIG. 5C****FIG. 5D****FIG. 5E****FIG. 5F**

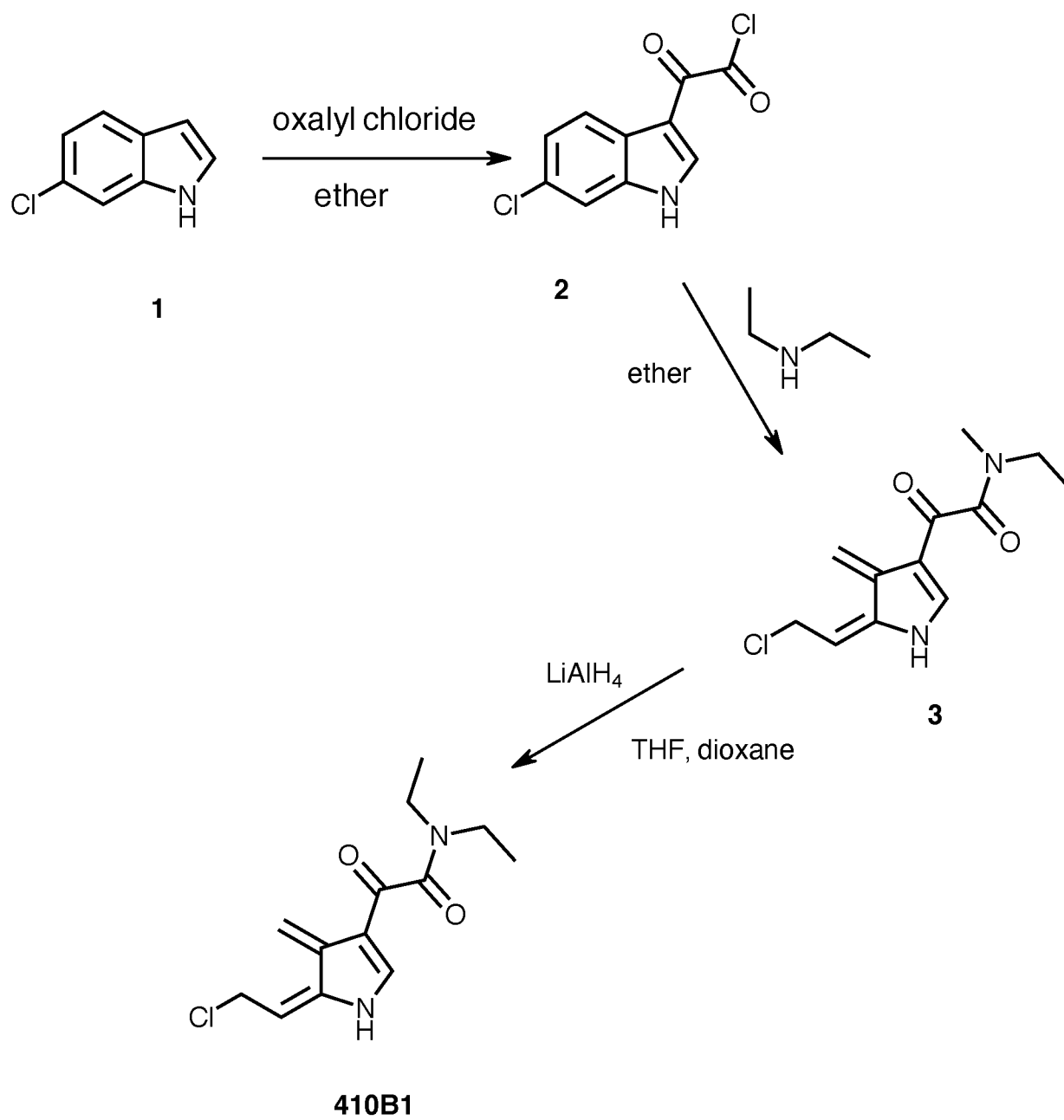
**FIG. 5G****FIG. 5H****FIG. 5I****FIG. 5J**

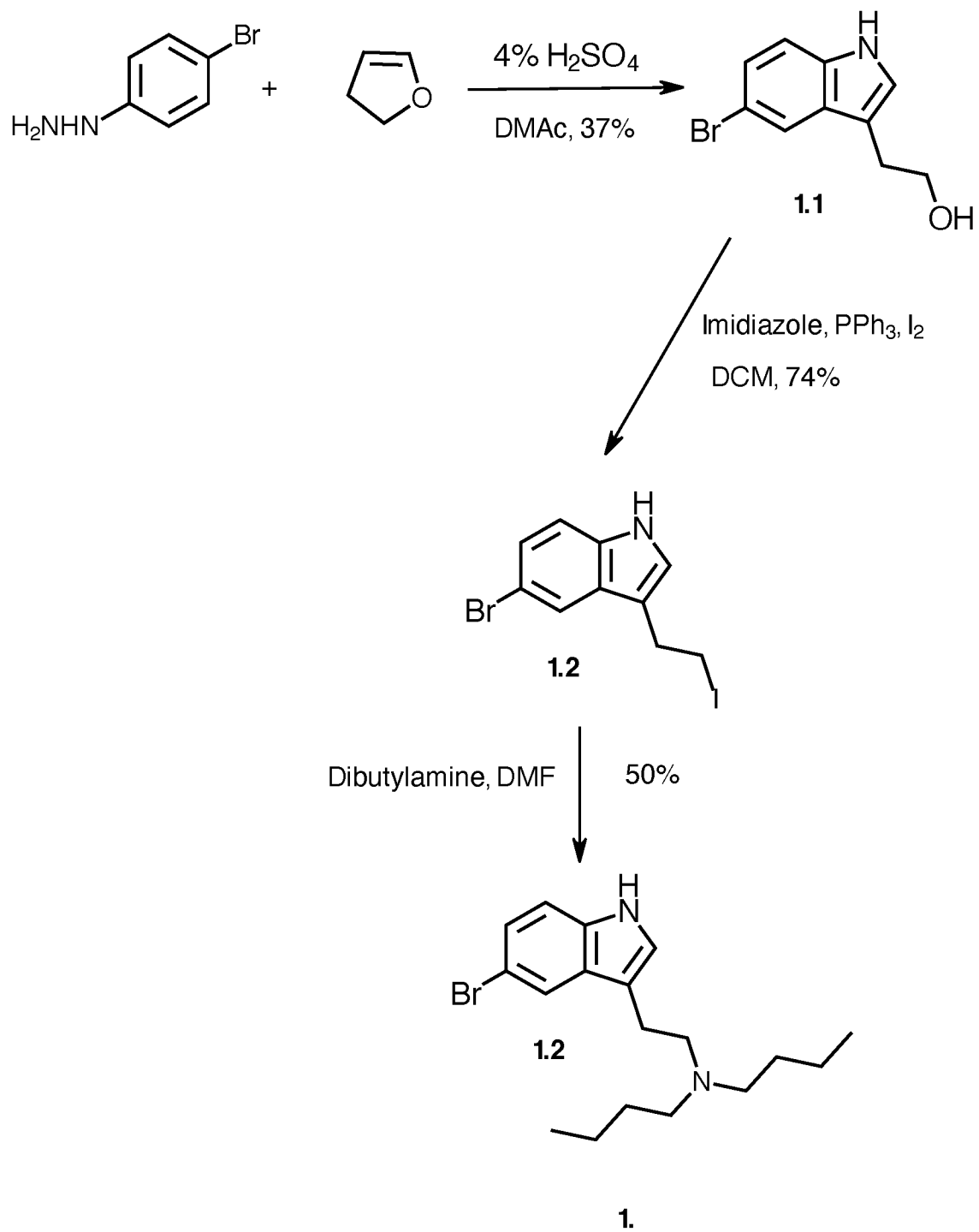
**FIG. 6A****FIG. 6B****FIG. 6C****FIG. 6D****FIG. 6E****FIG. 6F**

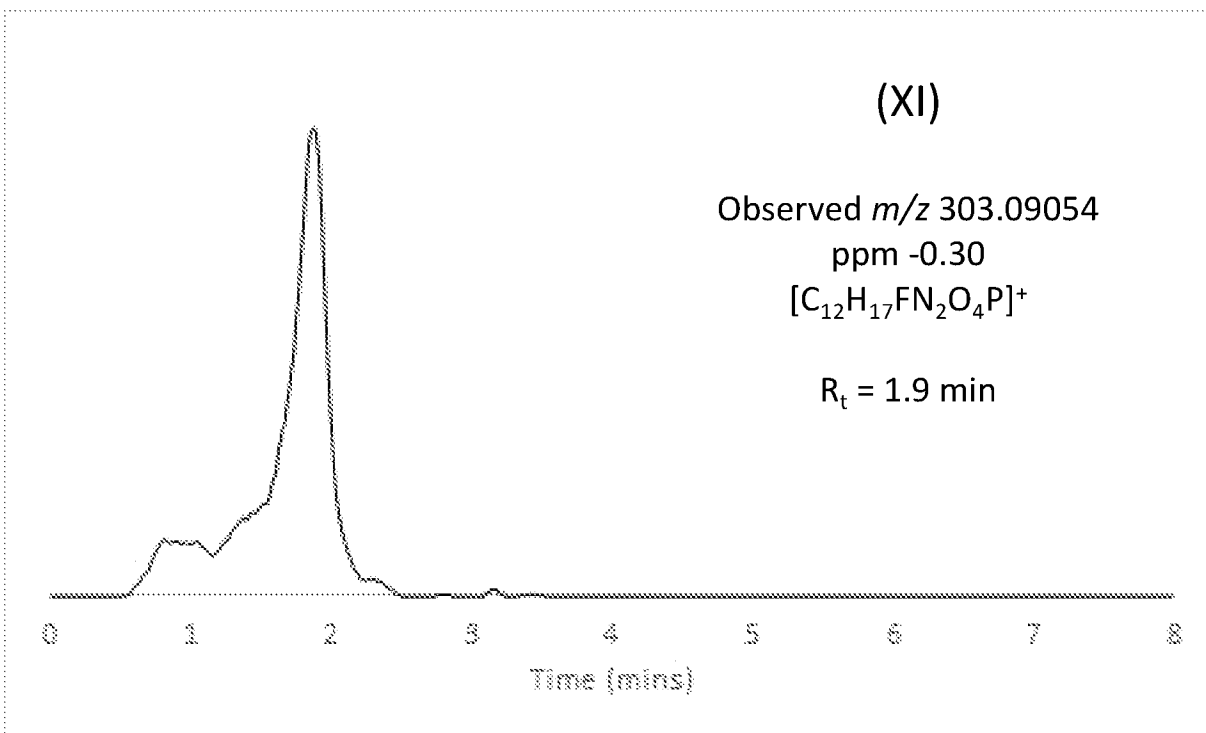
**FIG. 7A****FIG. 7B****FIG. 7C****FIG. 7D****FIG. 7E**

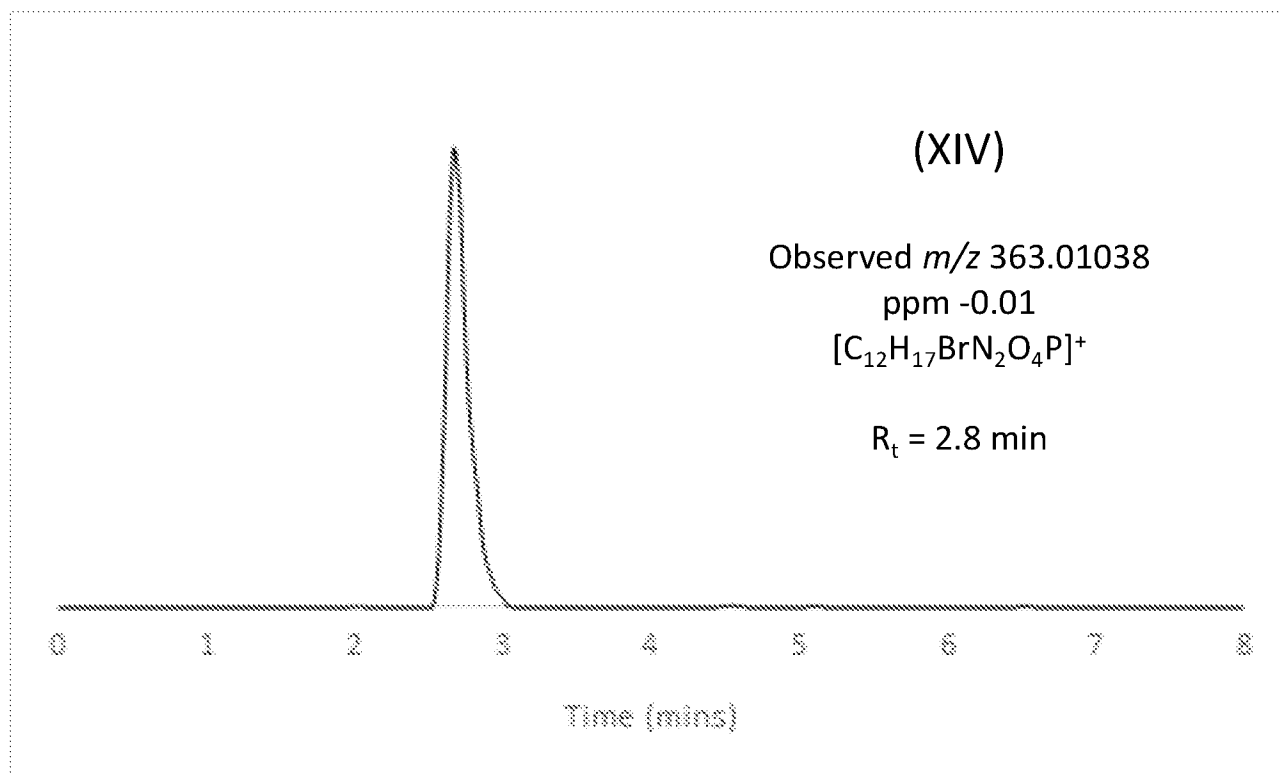
**FIG. 8A**

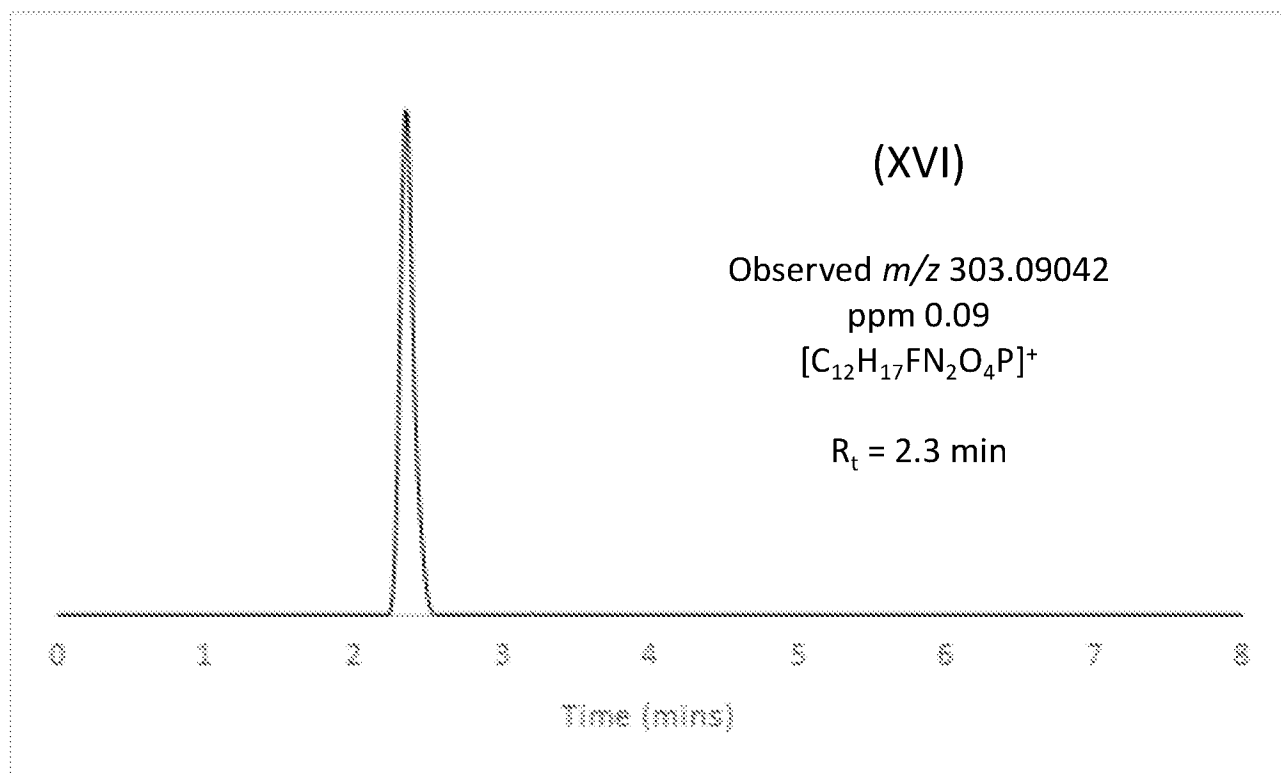


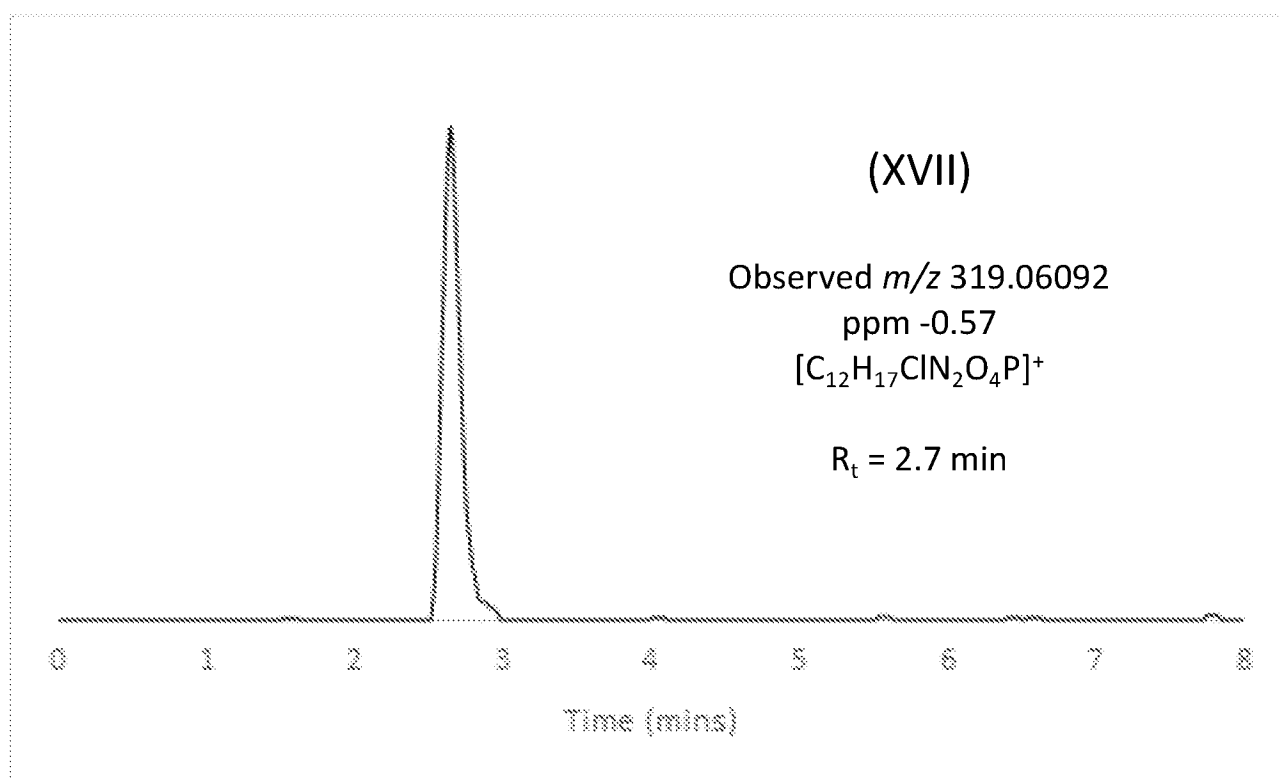
**FIG. 9A**

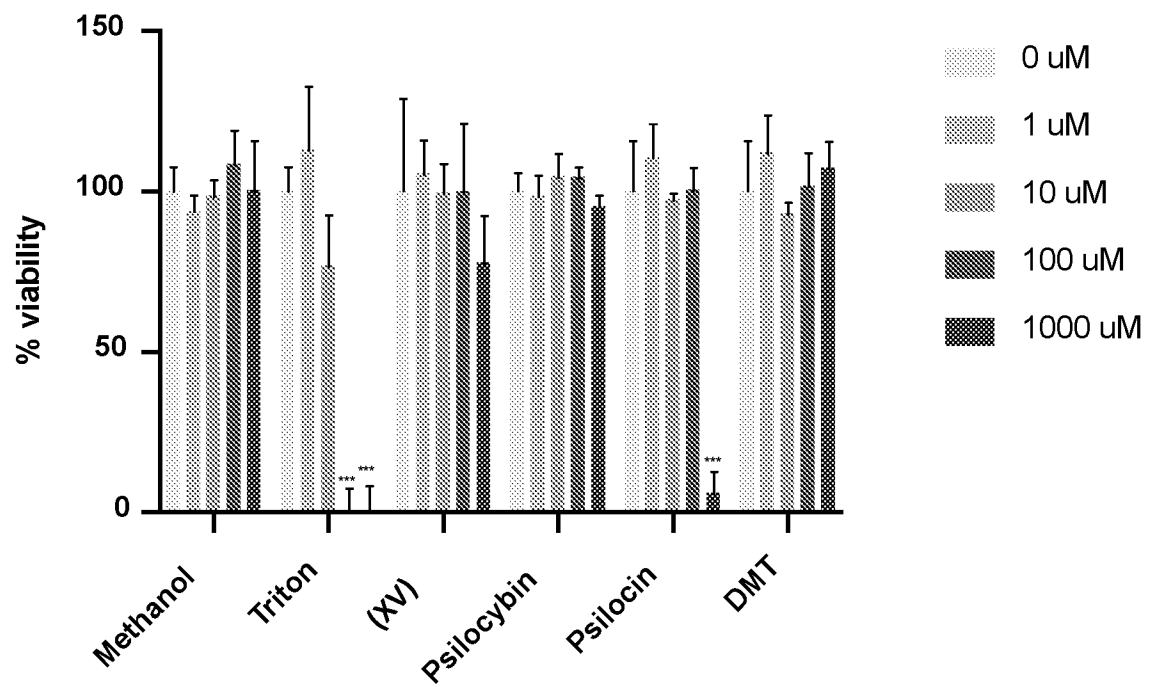
**FIG. 9B**

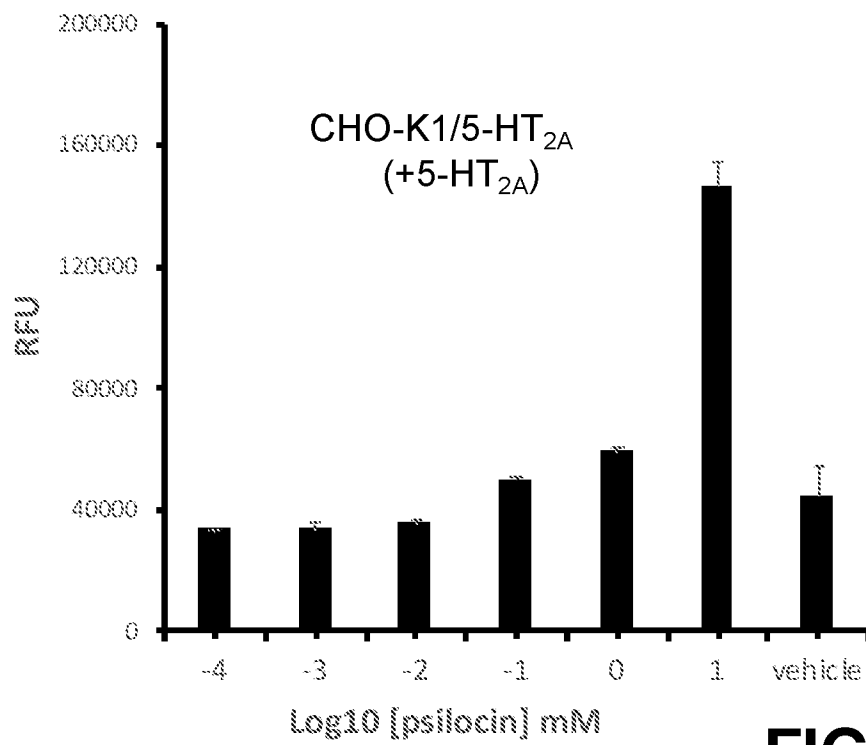
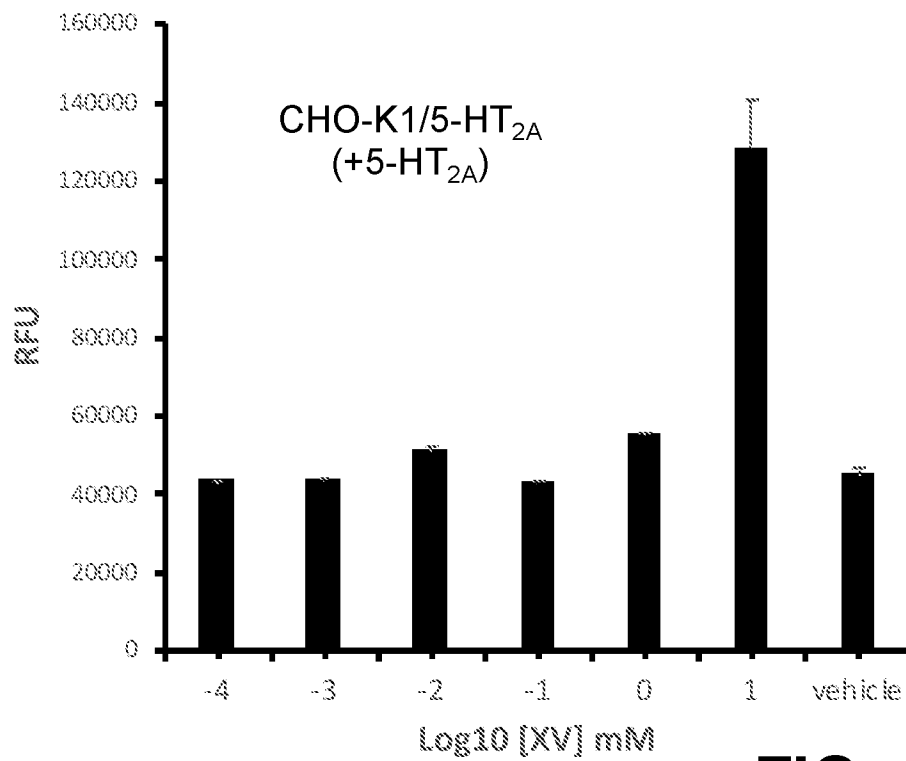
**FIG. 10**

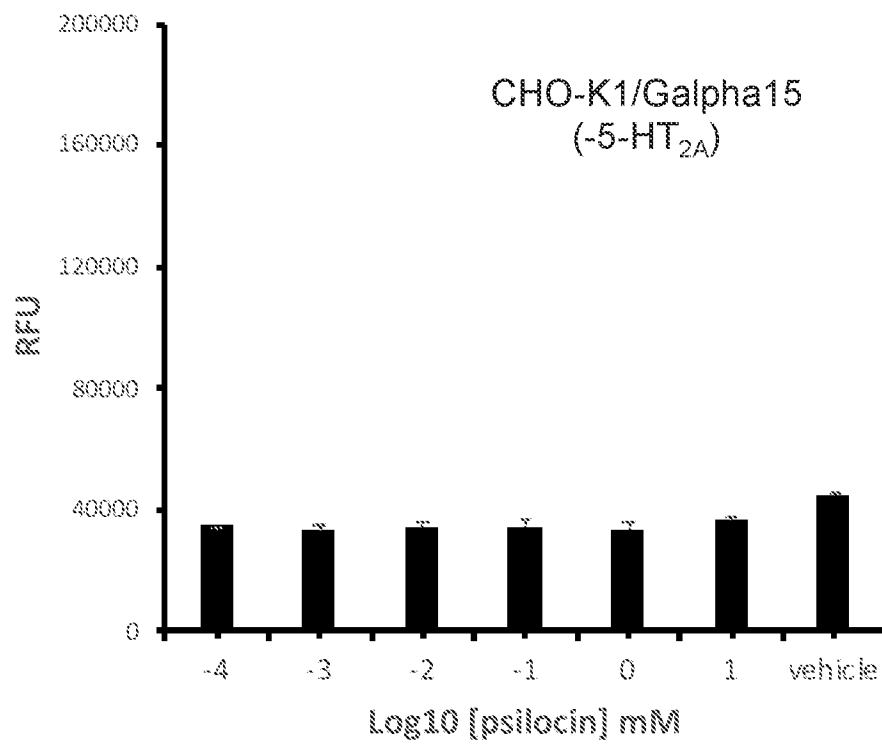
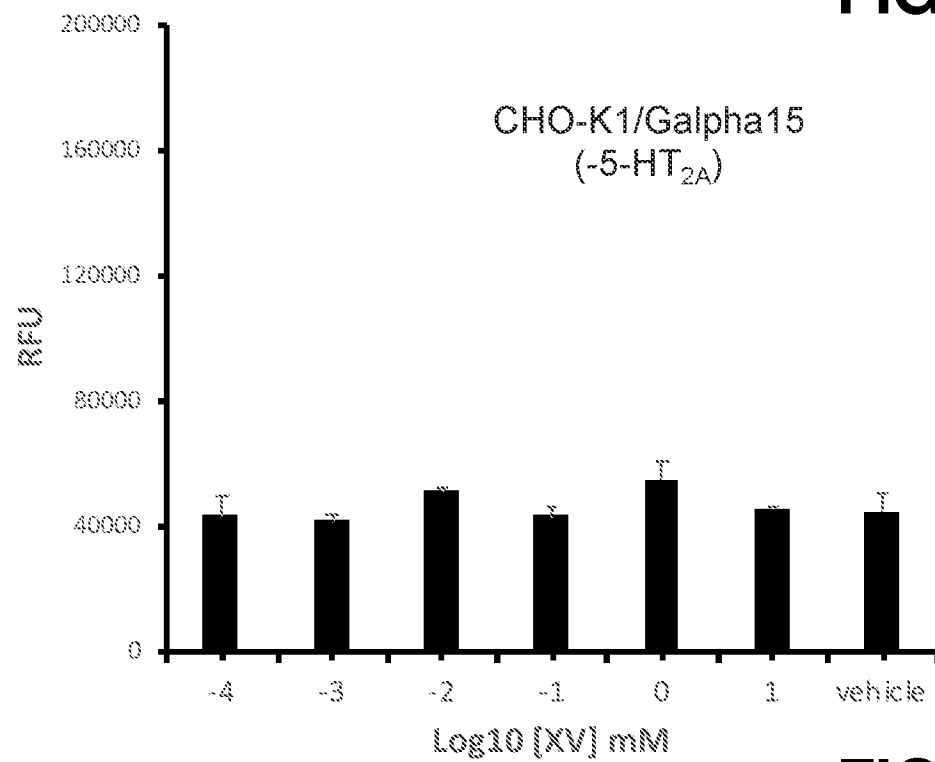
**FIG. 11**

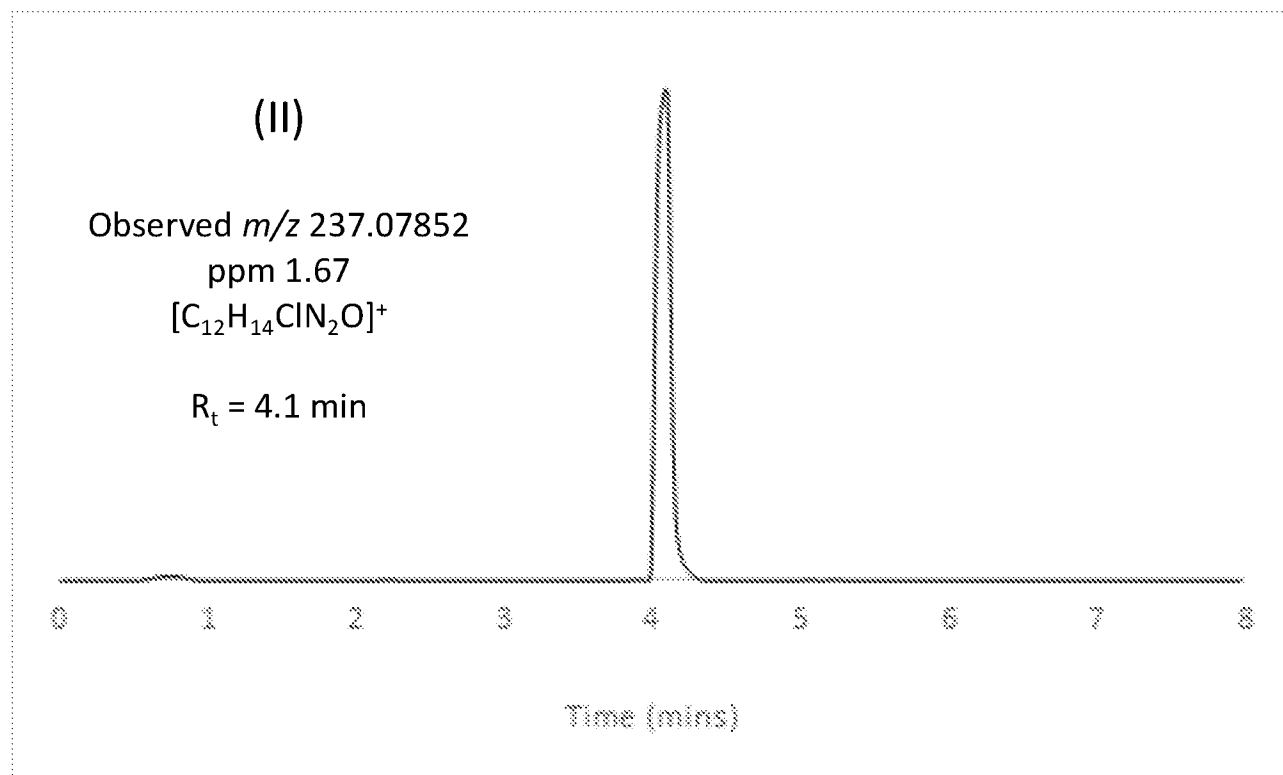
**FIG. 12**

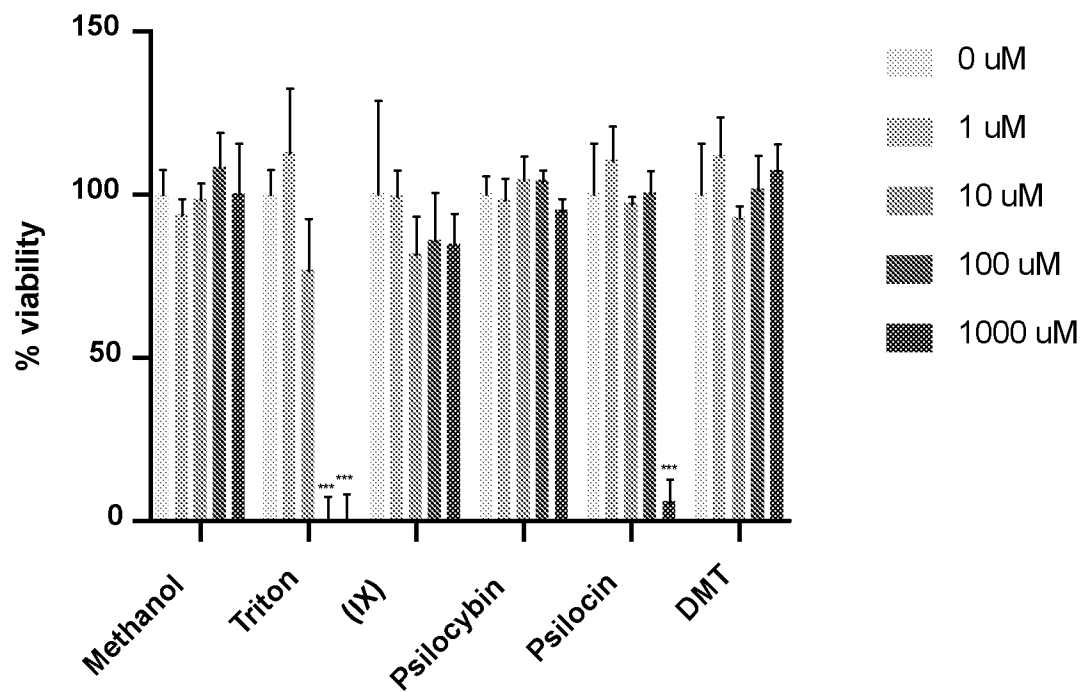
**FIG. 13**

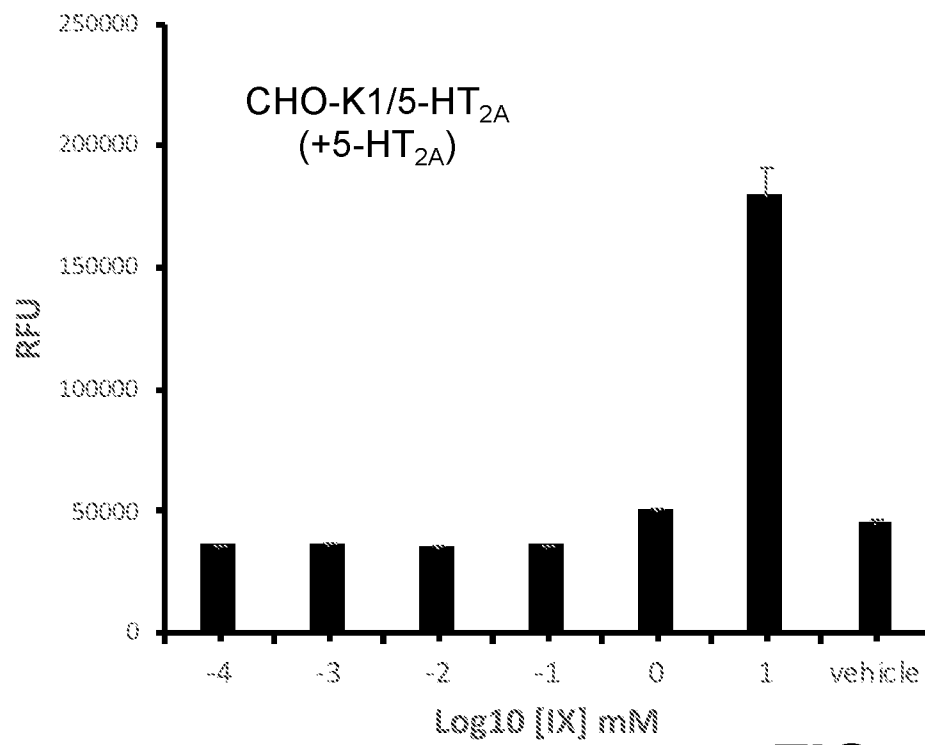
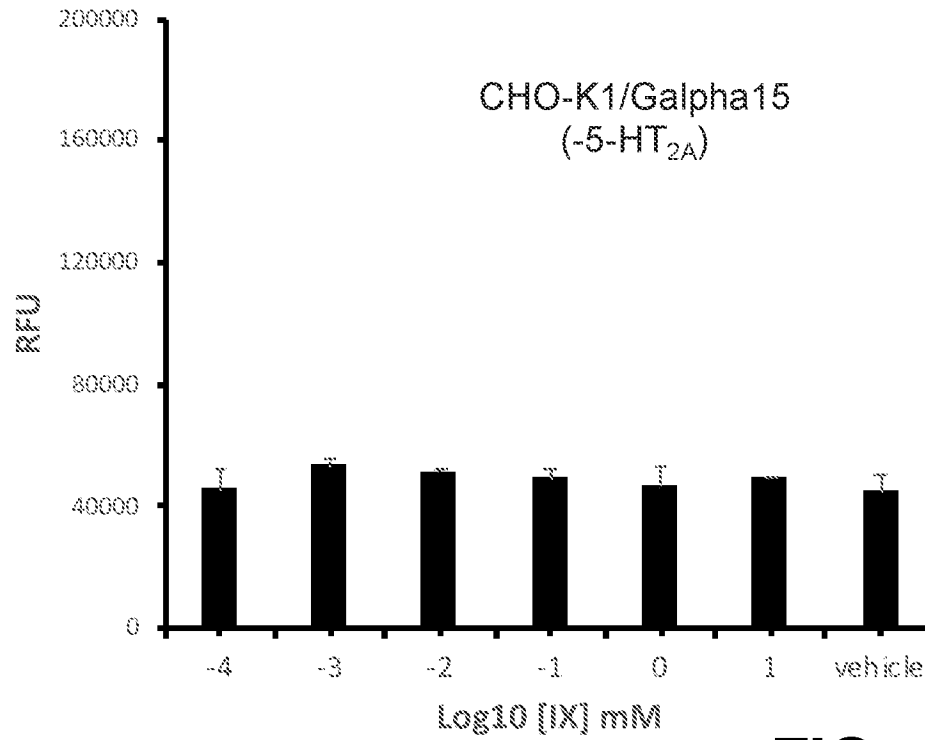
**FIG. 14**

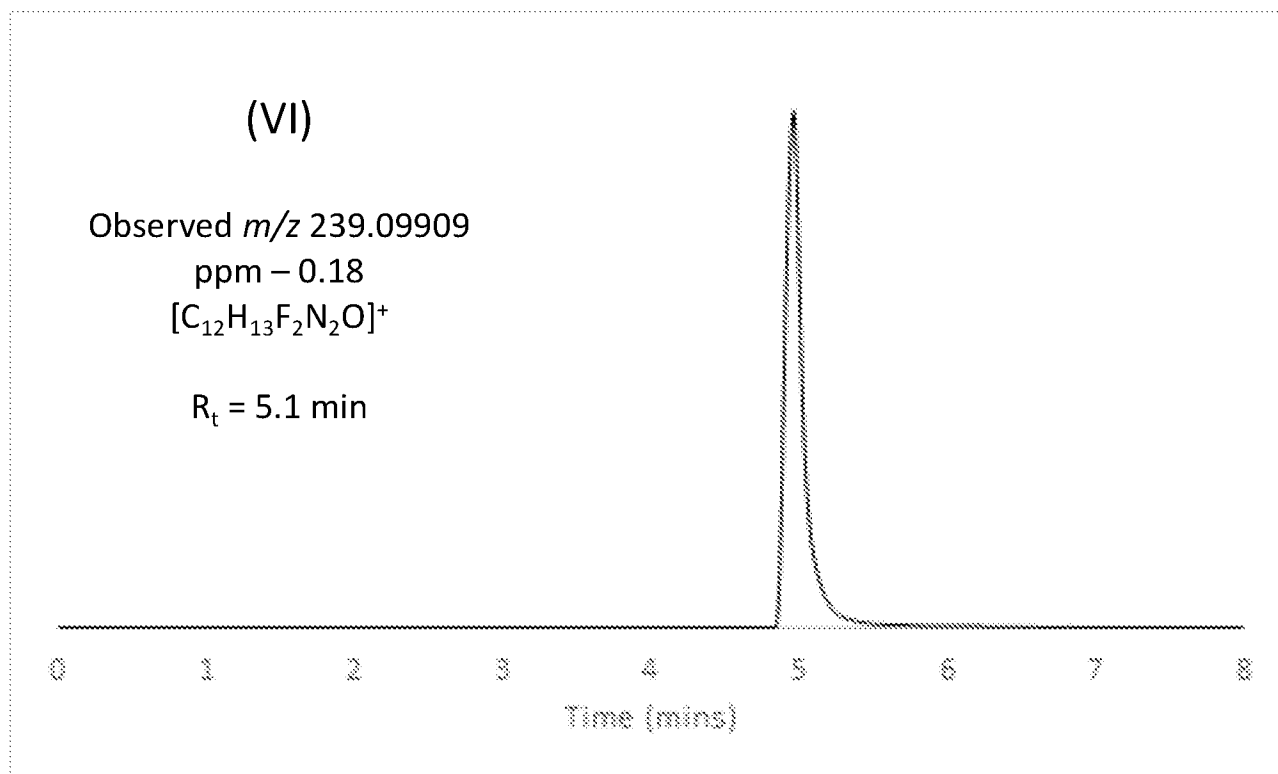
**FIG. 15A****FIG. 15B**

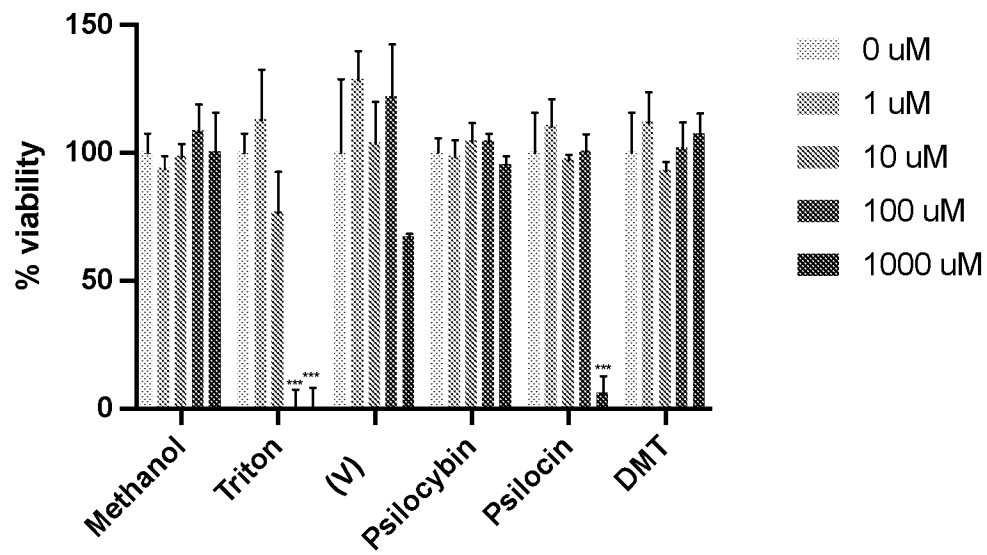
**FIG. 16A****FIG. 16B**

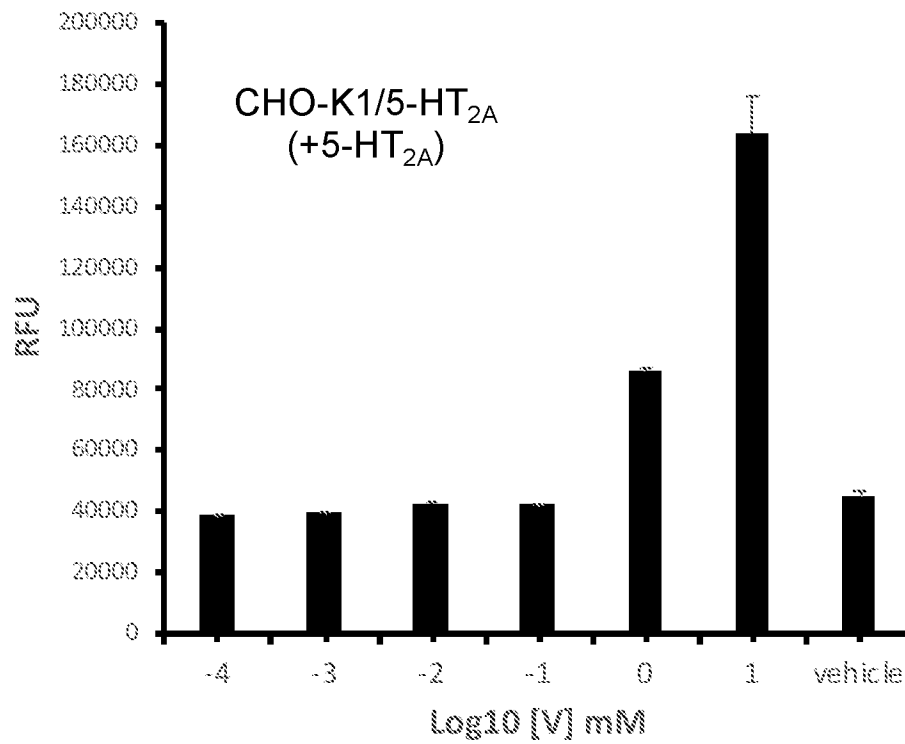
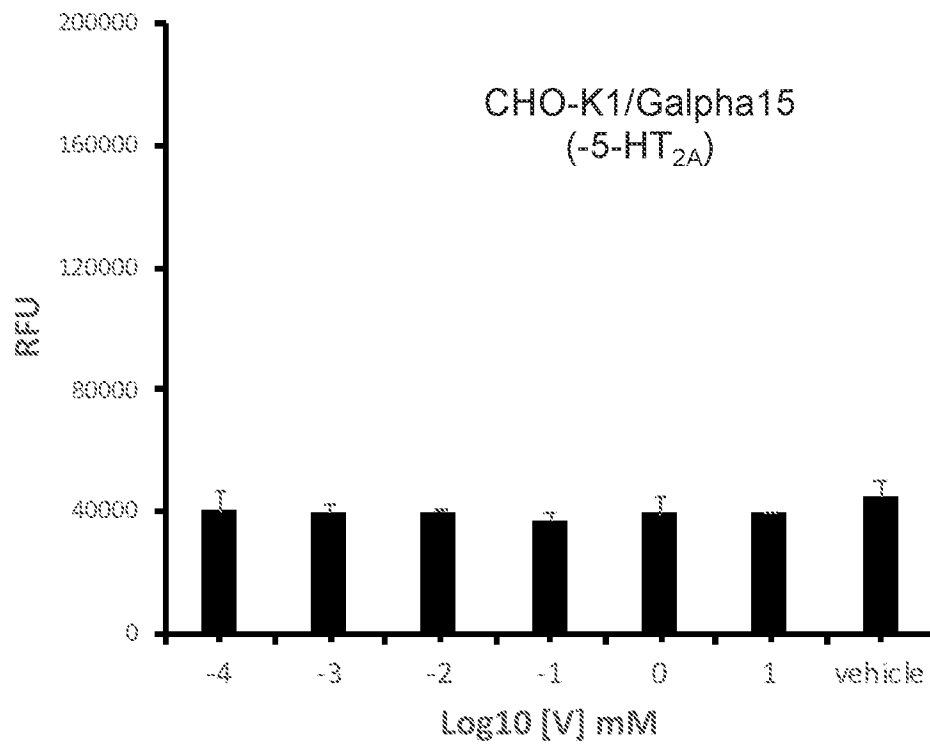
**FIG. 17**

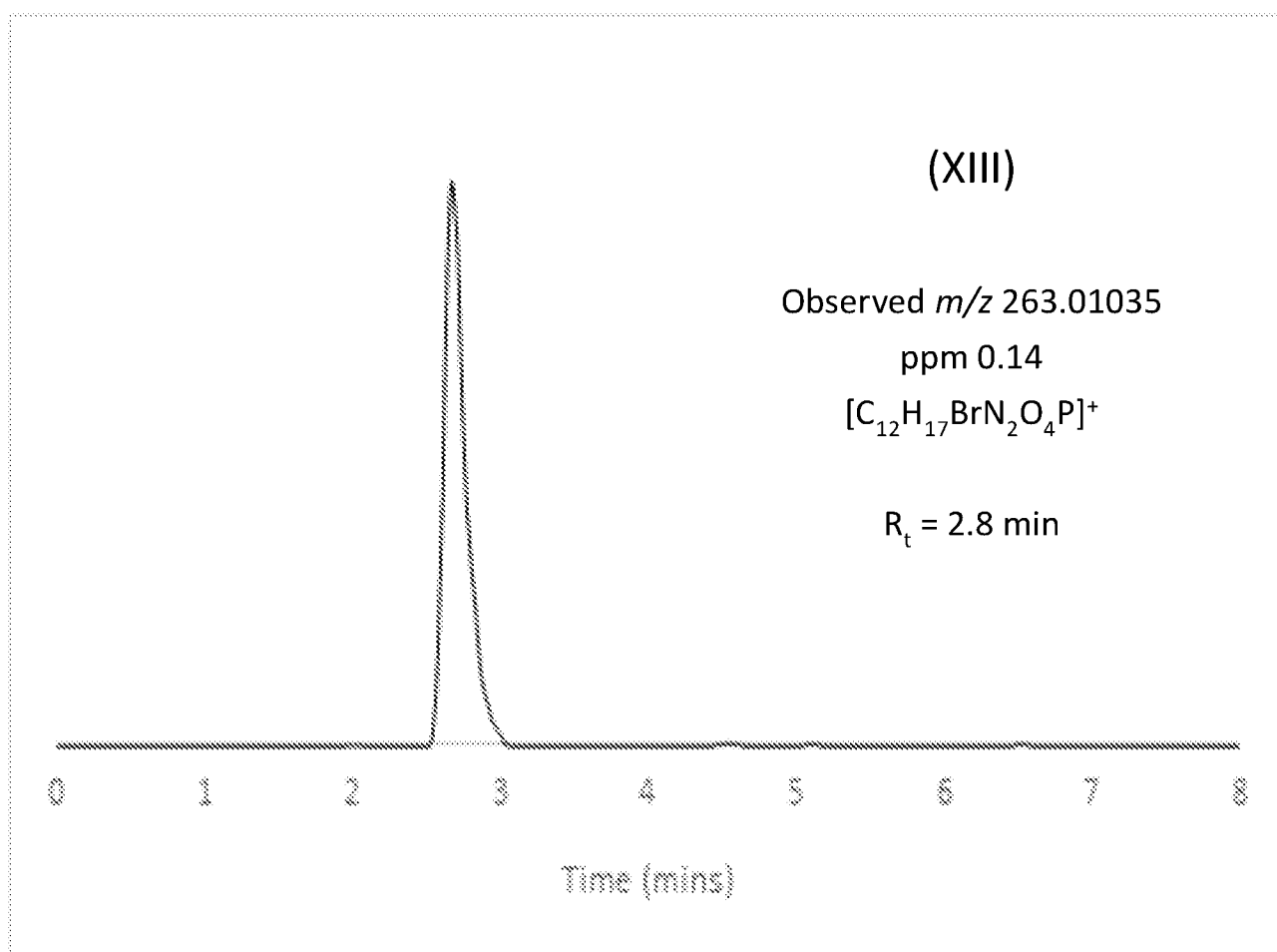
**FIG. 18**

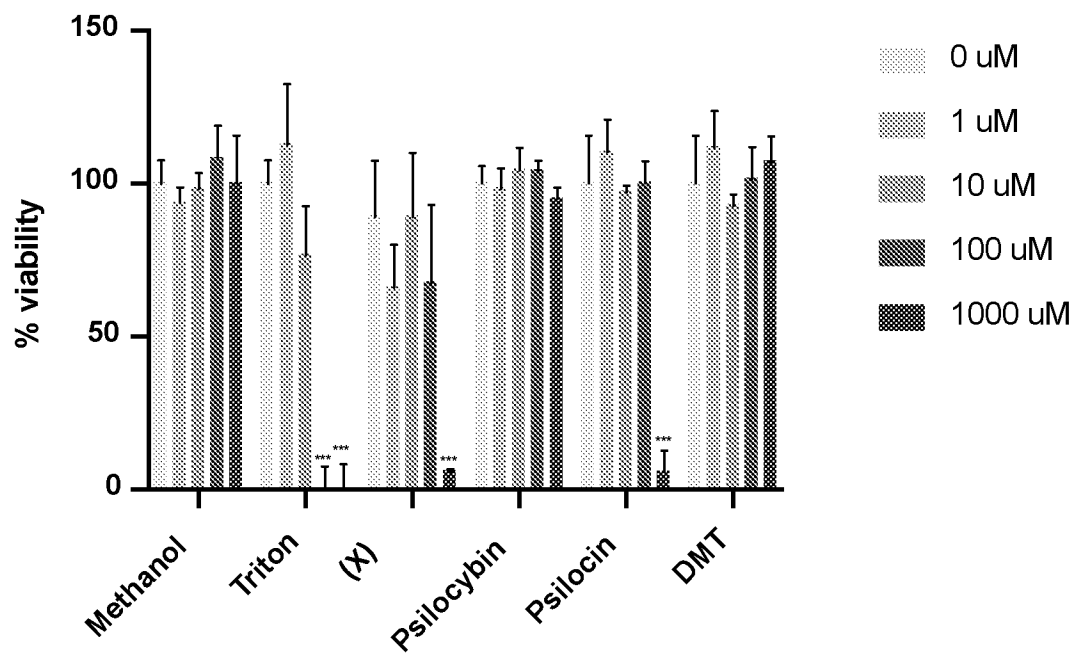
**FIG. 19A****FIG. 19B**

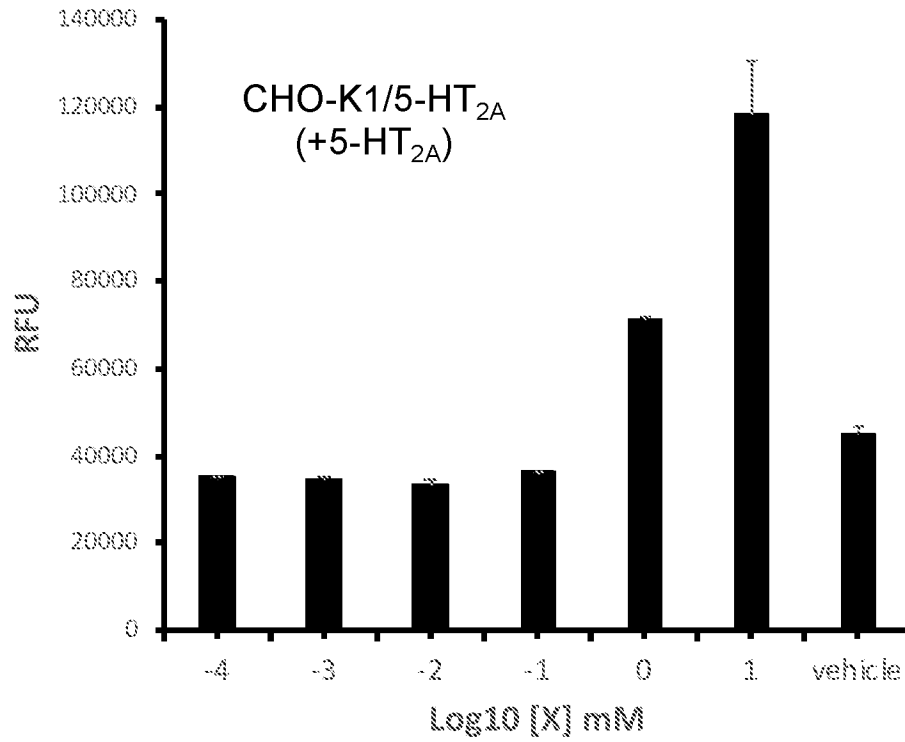
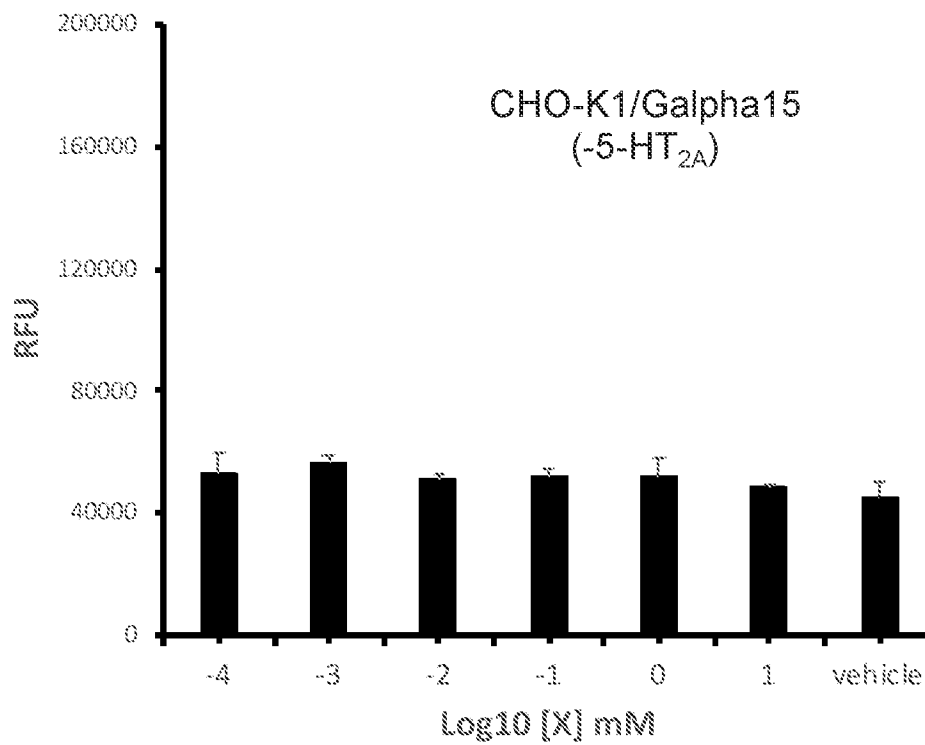
**FIG. 20**

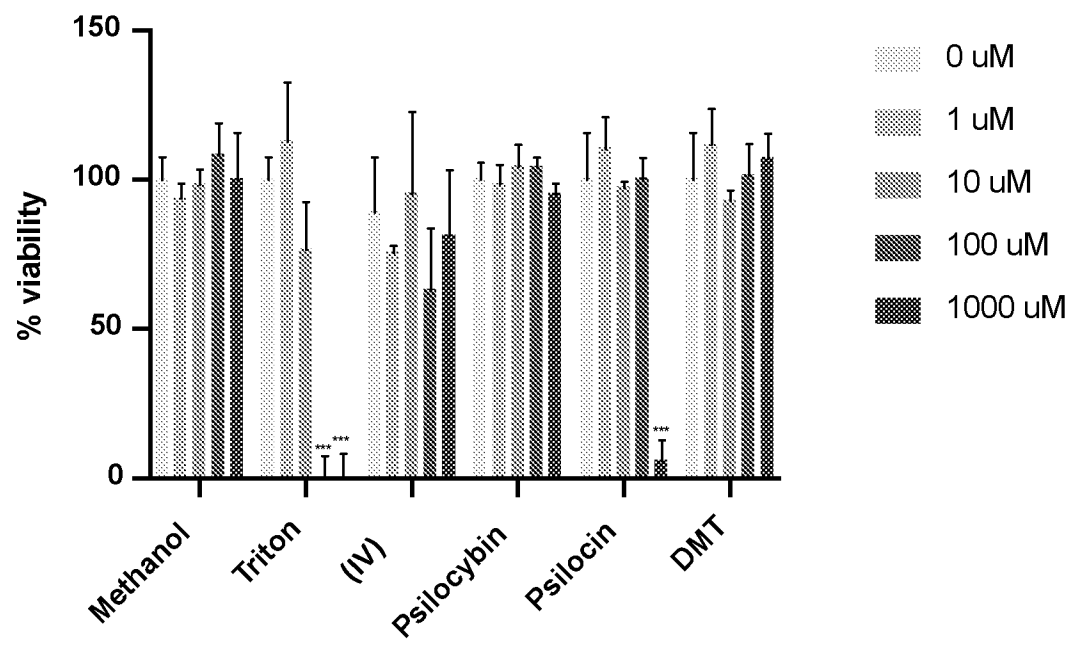
**FIG. 21**

**FIG. 22A****FIG. 22B**

**FIG. 23**

**FIG. 24**

**FIG. 25A****FIG. 25B**

**FIG. 26**

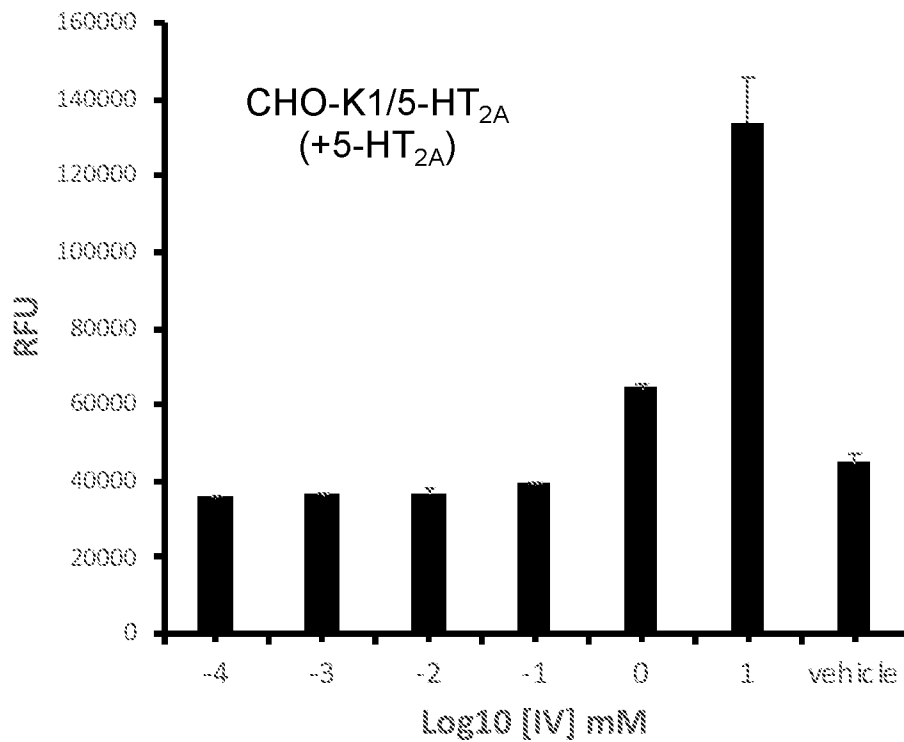


FIG. 27A

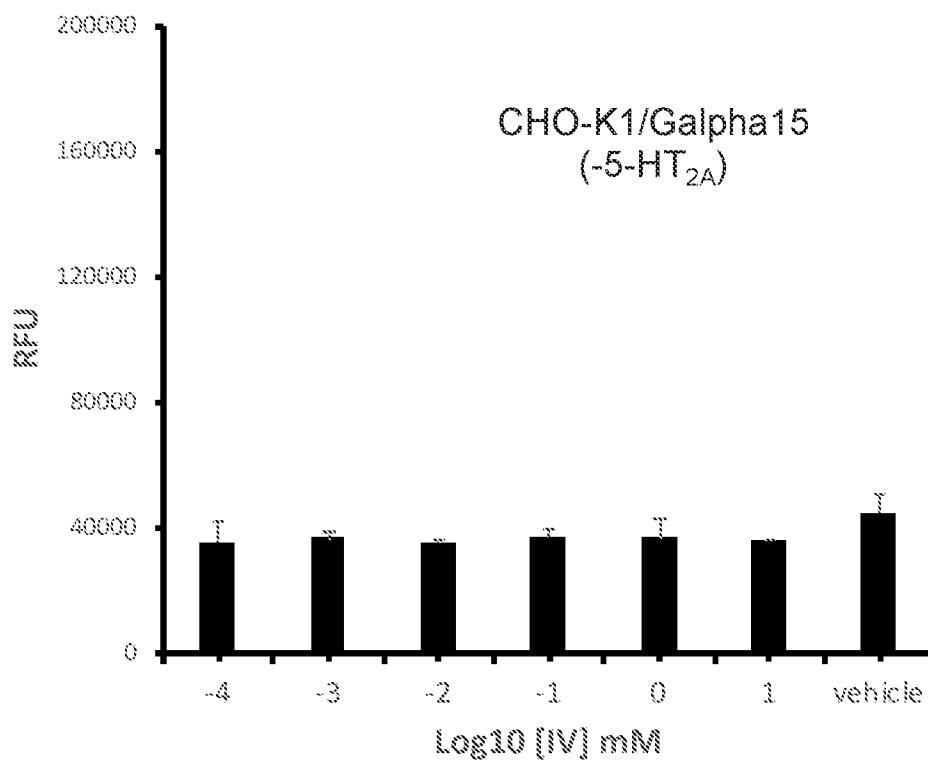
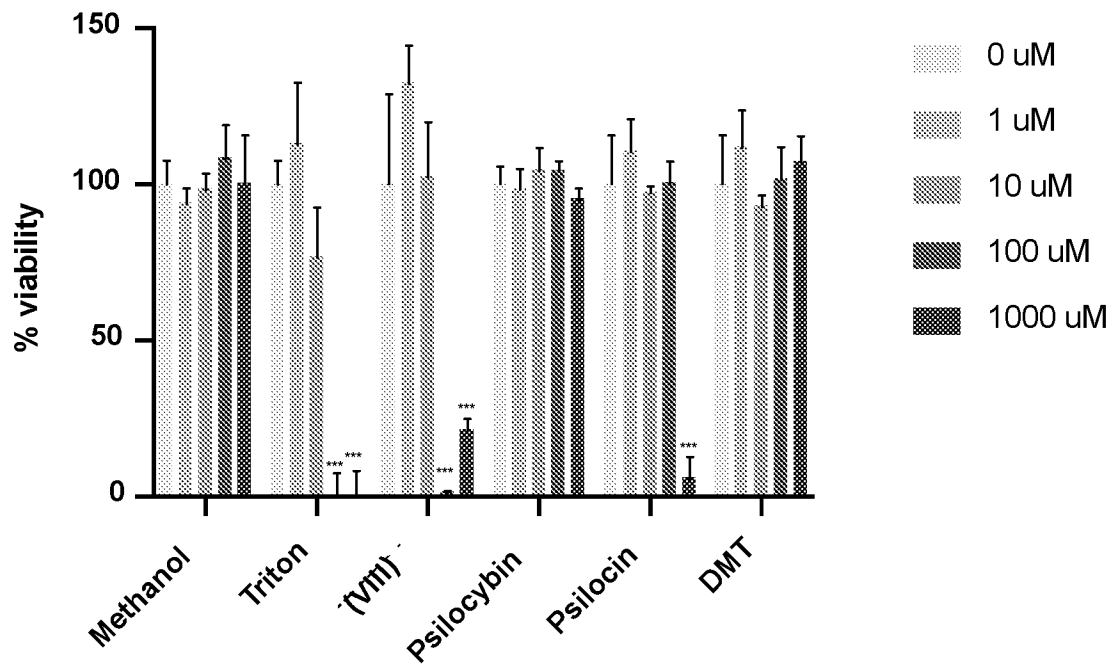
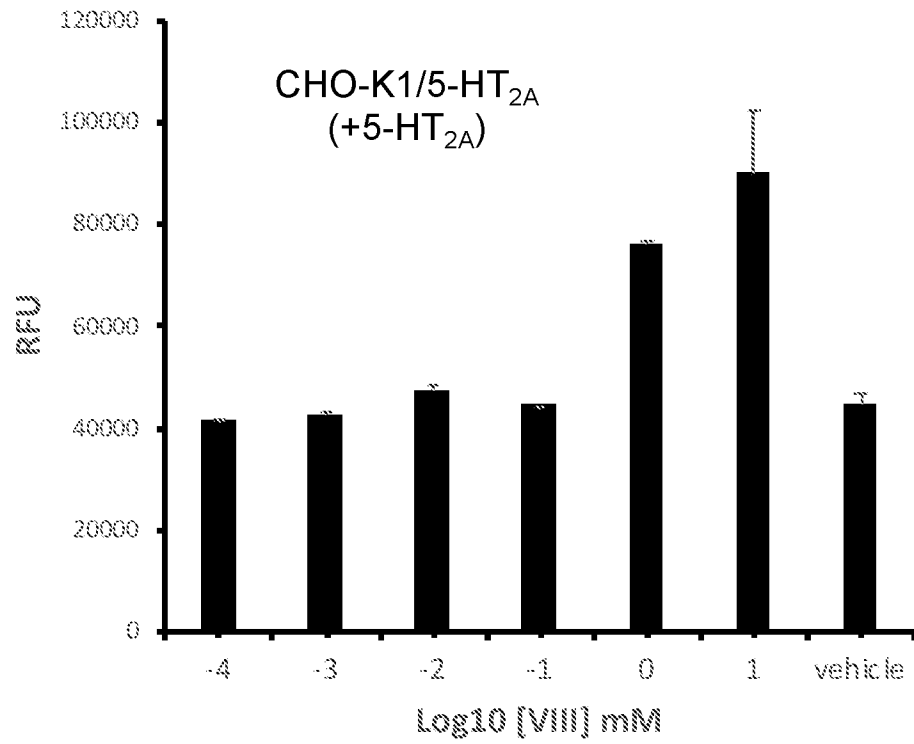
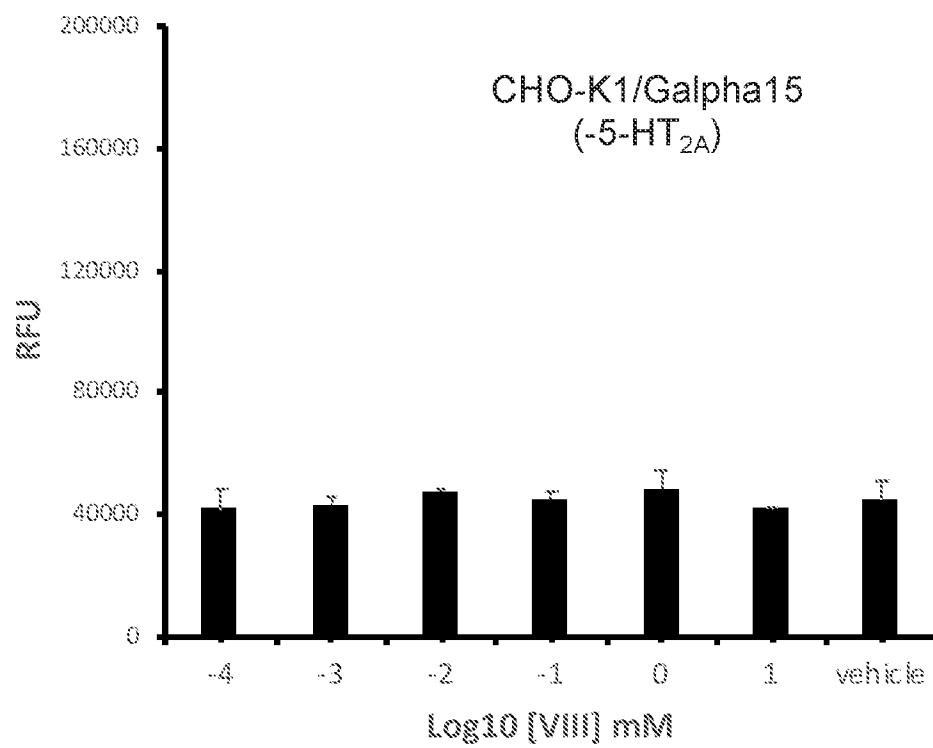
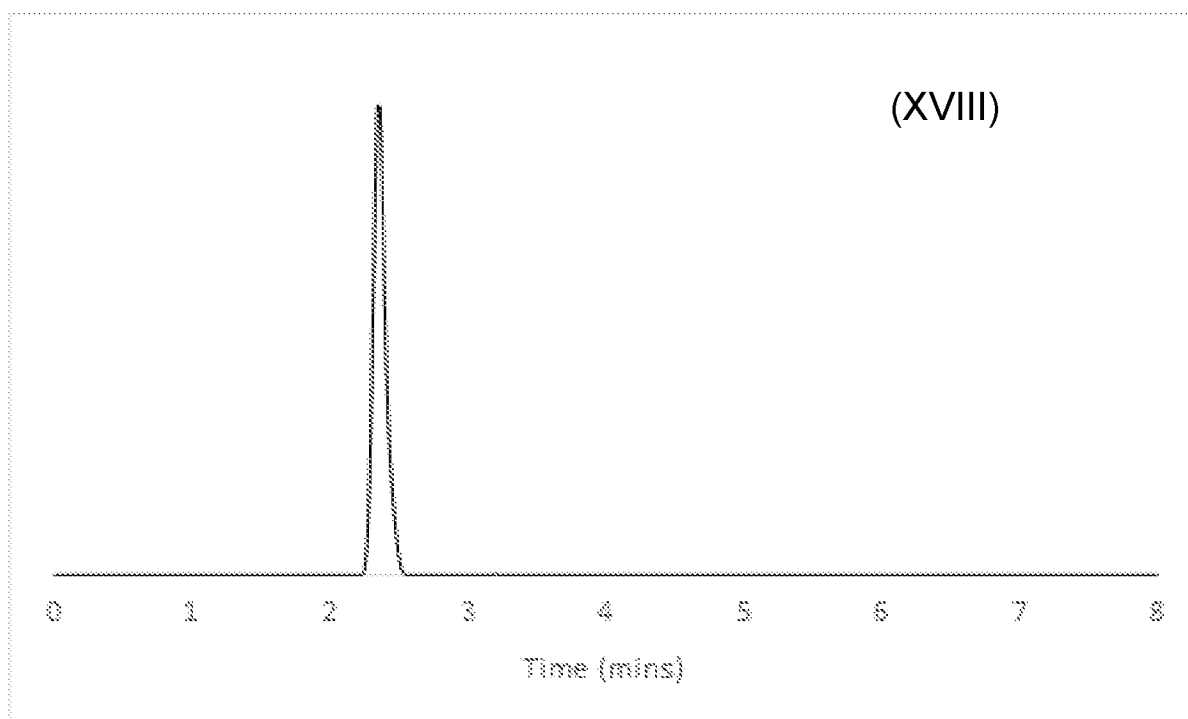


FIG. 27B

**FIG. 28**

**FIG. 29A****FIG. 29B**

**FIG. 30**



ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
18/655,793

RECEIPT DATE / TIME
05/06/2024 03:00:12 PM Z ET

ATTORNEY DOCKET #
29664-P62051US03

Title of Invention

HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 4842

FILED BY Lindsay Earnshaw

PATENT CENTER # 65391713

FILING DATE -

CUSTOMER # 1059

FIRST NAMED INVENTOR Jillian M. Hagel

CORRESPONDENCE ADDRESS -

AUTHORIZED BY Michael Fenwick

Documents

TOTAL DOCUMENTS: 8

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
P62051US03 ADS.pdf	9	Application Data Sheet	2179 KB
P62051US03 Track One Request.pdf	2	Track One Request	153 KB
29664-P62051US03__SequenceListing.xml	-	Sequence Listing Supp (XML File)	211 KB
P62501US02__Figures__1-30.pdf	36	Drawings-only black and white line drawings	1282 KB

Warning: The attached file contains comments or annotations. Comments are not recommended and may cause processing problems with the document.

P62051US03 App Transmittal.pdf	2	Transmittal of New Application	953 KB
P62051US03 Specification.pdf	160	Specification	1269 KB
P62051US02_Hagel_Declaration.pdf	1	Oath or Declaration filed	95 KB
P62051US02_Facchini_Declaration.pdf	1	Oath or Declaration filed	382 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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P62051US02_Hagel_Declaration.pdf	2057933CC748A7FBB4C79D074B07900F33FB2B0CD04D3ED1B3658EE5FE10F7399E4A3DB3EC9D2646AA49863176F6EE1468EE9D17560B8F3A17C9FEF3FC3B598C
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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.

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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.

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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.

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APPLICATION #
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29664-P62051US03

Title of Invention

HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING

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PATENT CENTER # 65391713

AUTHORIZED BY Michael Fenwick

CUSTOMER # 1059

FILING DATE -

CORRESPONDENCE
ADDRESS -FIRST NAMED
INVENTOR Jillian M. Hagel

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37 CFR 1.16 (National application filing, search, and examination fees); 37
CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.19
(Document supply fees); 37 CFR 1.21 (Miscellaneous fees and charges)

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
2830	PROCESSING FEE, EXCEPT IN PROVISIONAL APPLICATIONS	56.00	1	56.00
2817	REQUEST FOR PRIORITIZED EXAMINATION	1680.00	1	1680.00
2111	UTILITY PATENT APPL. SEARCH FEE	280.00	1	280.00
4011	BASIC FILING FEE- UTILITY	64.00	1	64.00

2311	EXAMINATION OF ORIGINAL PATENT APPLICATION	320.00	1	320.00
2054	Non-DOCX Filing Surcharge	160.00	1	160.00
2081	UTILITY APPL. SIZE FEE > THAN 100 PAGES (FEE X PAGES >= 101 IN 50 PAGE INCREMENTS)	168.00	1	168.00
2202	EACH CLAIM IN EXCESS OF 20	40.00	10	400.00

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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	29664-P62051US03
		Application Number	
Title of Invention	HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING		
<p>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.</p> <p>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.</p>			

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	
	Jillian	M.	Hagel		
Residence Information (Select One) ☐ US Residency ☒ Non US Residency ☐ Active US Military Service					
City	Calgary	Country of Residence ⁱ		CA	
Mailing Address of Inventor:					
Address 1		2210-6651 Ranchview Dr. NW			
Address 2					
City	Calgary	State/Province		AB	
Postal Code		T3G 1P3	Country ⁱ	CA	
Inventor 2					Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Peter	J.	Facchini		
Residence Information (Select One) ☐ US Residency ☒ Non US Residency ☐ Active US Military Service					
City	Calgary	Country of Residence ⁱ		CA	
Mailing Address of Inventor:					
Address 1		155 Ranchridge Drive NW			
Address 2					
City	Calgary	State/Province		AB	
Postal Code		T3G 1W1	Country ⁱ	CA	
All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button.					Add

Correspondence Information:

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	29664-P62051US03
		Application Number	
Title of Invention	HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING		

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	1059		
Email Address	mfenwick@bereskinparr.com	<input type="button" value="Add Email"/>	<input type="button" value="Remove Email"/>

Application Information:

Title of the Invention	HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING		
Attorney Docket Number	29664-P62051US03	Small Entity Status Claimed	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	36	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	1059		

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	29664-P62051US03
		Application Number	
Title of Invention	HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING		

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		Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	17903080	2022-09-06
Prior Application Status		Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
17903080	Continuation of	PCT/CA2021/051209	2021-09-01
Prior Application Status		Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/CA2021/051209	Claims benefit of provisional	63073104	2020-09-01
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.			

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).

Application Number	Country ⁱ	Filing Date (YYYY-MM-DD)	Remove
			Access Code ⁱ (if applicable)
Additional Foreign Priority Data may be generated within this form by selecting the Add button.			

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	29664-P62051US03
		Application Number	
Title of Invention	HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING		

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐	<p>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.</p> <p>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.</p>
--------------------------	---

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	29664-P62051US03
	Application Number	
Title of Invention	HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING	

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.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	29664-P62051US03
		Application Number	
Title of Invention	HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING		

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
<p>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.</p>			
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: <input type="text"/>			
If the Applicant is an Organization check here. ☒			
Organization Name	Enveric Biosciences Canada Inc.		
Mailing Address Information For Applicant:			
Address 1	3655-36th Street NW		
Address 2			
City	Calgary	State/Province	AB
Country	CA	Postal Code	T2L 1Y8
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.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	29664-P62051US03
		Application Number	
Title of Invention	HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING		

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	/mfenwick/		Date (YYYY-MM-DD)	2024-05-06	
First Name	Michael	Last Name	Fenwick	Registration Number	61773

Additional Signature may be generated within this form by selecting the Add button.

[Add](#)

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	29664-P62051US03
	Application Number	
Title of Invention	HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING	

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 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 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.

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.

UTILITY PATENT APPLICATION TRANSMITTAL (Only for new nonprovisional applications under 37 CFR 1.53(b))	Attorney Docket No.	29664-P62051US03
	First Named Inventor	Jillian M. Hagel
	Title	HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING
	Priority Mail Express® Label No.	

APPLICATION ELEMENTS <i>See MPEP chapter 600 concerning utility patent application contents.</i>	ADDRESS TO: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450
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1. ☒ Fee Transmittal Form (PTO/SB/17 or equivalent)	ACCOMPANYING APPLICATION PAPERS
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 <u>160</u>] 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 <u>36</u>]	
6. Inventor's Oath or Declaration [Total Pages <u>2</u>] (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	
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: <u>Track One Prioritized Examination Form</u> _____ _____ _____ _____	

***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: <u>1059</u> OR ☐ Correspondence address below				
Name				
Address				
City	State	Zip Code		
Country	Telephone	Email		

Signature	/mfenwick/	Date	May 6, 2024
Name (Print/Type)	Michael Fenwick	Registration No. (Attorney/Agent)	61773

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 0651-0032. Public burden for this form is estimated to average 12 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.

Additional Uses

Additional USPTO uses of the information in this record may include disclosure to: 1) the International Bureau of the World Intellectual Property Organization, if the record is related to an international application filed under the Patent Cooperation Treaty; 2) the public i) after publication of the application pursuant to 35 U.S.C. 122(b), ii) after issuance of a patent pursuant to 35 U.S.C. 151, iii) 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, or iv) without publication of the application or patent under the specific circumstances provided for by 37 CFR 1.14(a)(1)(v)-(vii); and/or 3) the National Archives and Records Administration, for inspection of records.

**DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN
APPLICATION DATA SHEET (37 CFR 1.76)**

Title of
Invention

HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING

As the below named inventor, I hereby declare that:

This declaration ☐ The attached application, or
is directed to:

☒ United States application or PCT international application number PCT/CA2021/051209

filed on September 1, 2021

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 state that I have reviewed and understand the contents of the above identified application, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. 1.56.

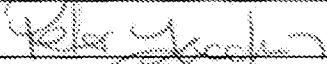
I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

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: Peter J. FAGGIONI Date (Optional): 2021-10-29

Signature: 

Note: An application data sheet, including naming the entire inventive entity, must accompany this form.
Use an additional form for each additional inventor.

TITLE: HALOGENATED PSILOCYBIN DERIVATIVES AND METHODS OF USING

RELATED APPLICATION

[001] This application is a continuation of United States Application No. 17/903,080 filed September 6, 2022 which is a continuation of PCT Application
5 No. PCT/CA2021/051209 filed September 1, 2021, which claims the benefit of United States Provisional Application No. 63/073,104 filed September 1, 2020; the entire contents of which are hereby incorporated by reference.

INCORPORATION OF SEQUENCE LISTING

10 **[002]** A computer readable form of the Sequence Listing "29664-P62051US03_SequenceListing.xml" (216,574 bytes), submitted via Patent Center and created on May 6, 2024, is herein incorporated by reference.

FIELD OF THE DISCLOSURE

15 **[003]** The compositions and methods disclosed herein relate to a chemical compound known as psilocybin. Furthermore, the compositions and methods disclosed herein relate in particular to halogenated forms of psilocybin.

BACKGROUND OF THE DISCLOSURE

20 **[004]** The following paragraphs are provided by way of background to the present disclosure. They are not however an admission that anything discussed therein is prior art or part of the knowledge of a person of skill in the art.

[005] The biochemical pathways in the cells of living organisms may be classified as being part of primary metabolism, or as being part of secondary
25 metabolism. Pathways that are part of a cell's primary metabolism are involved in catabolism for energy production or in anabolism for building block production for the cell. Secondary metabolites, on the other hand, are produced by the cell without having an obvious anabolic or catabolic function. It has long been recognized that secondary metabolites can be useful in many respects, including
30 as therapeutic compounds.

[006] Psilocybin, for example, is a secondary metabolite that is naturally produced by certain mushrooms which taxonomically can be classified as belonging the Basidiomycota division of the fungi kingdom. Mushroom species

which can produce psilocybin include species belonging to the genus *Psilocybe*, such as *Psilocybe azurescens*, *Psilocybe semilanceata*, *Psilocybe serbica*, *Psilocybe mexicana*, and *Psilocybe cyanescens*, for example. The interest of the art in psilocybin is well established. Thus, for example, psilocybin is a psychoactive compound and is therefore used as a recreational drug. Furthermore, psilocybin is used as a research tool in behavioral and neuro-imaging studies in psychotic disorders, and has been evaluated for its clinical potential in the treatment of mental health conditions (Daniel, J. *et al.* *Mental Health Clin*/, 2017;7(1): 24-28), including to treat anxiety in terminal cancer patients (Grob, C. *et al.* *Arch. Gen. Psychiatry*, 2011, 68(1) 71-78) and to alleviate symptoms of treatment-resistant depression (Cathart-Harris, R.L. *et al.* *Lancet Psychiatry*, 2016, 3: 619-627).

[007] Although the toxicity of psilocybin is low, adverse side effects, including, for example, panic attacks, paranoia and psychotic states, sometimes together or individually referred to as “a bad trip”, are not infrequently experienced by recreational psilocybin users.

[008] There exists therefore a need in the art for improved psilocybin compounds.

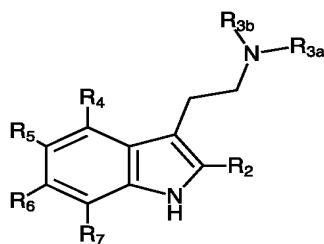
SUMMARY OF THE DISCLOSURE

[009] The following paragraphs are intended to introduce the reader to the more detailed description, not to define or limit the claimed subject matter of the present disclosure.

[0010] In one aspect, the present disclosure relates to psilocybin and derivative compounds.

[0011] In another aspect, the present disclosure relates to halogenated psilocybin derivative compounds and methods of making and using these compounds.

[0012] Accordingly, in one aspect, the present disclosure provides, in accordance with the teachings herein, in at least one embodiment, a chemical compound or salts thereof having the formula (I):



(I),

wherein, at least one of R₂, R₄, R₅, R₆ or R₇ is a halogen atom, wherein each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom or an alkyl group or O-alkyl group, wherein R₄ when it is not halogenated is a phosphate group, hydrogen atom or an alkyl or O-alkyl group, and wherein R_{3A} and R_{3B} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group.

[0013] In at least one embodiment, in an aspect, the halogen atom can be a bromine atom.

[0014] In at least one embodiment, in an aspect, the halogen atom can be a chlorine atom.

[0015] In at least one embodiment, in an aspect, the halogen atom can be a fluorine atom.

[0016] In at least one embodiment, in an aspect, the halogen atom can be an iodine atom.

[0017] In at least one embodiment, in an aspect, R₂ can be a halogen atom and R₅, R₆ and R₇ can each be a hydrogen atom or an alkyl group or O-alkyl group, and R₄ can be a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group.

[0018] In at least one embodiment, in an aspect, R₄ can be a halogen atom and R₂, R₅, R₆ and R₇ can each be a hydrogen atom or an alkyl group or O-alkyl group.

[0019] In at least one embodiment, in an aspect, R₅ can be a halogen atom and R₂, R₆ and R₇ can each be a hydrogen atom or an alkyl group or O-alkyl group, and R₄ can be a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group.

[0020] In at least one embodiment, in an aspect, R₆ can be a halogen atom and R₂, R₅ and R₇ can each be a hydrogen atom or an alkyl group or O-alkyl group, and R₄ can be a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group.

- [0021]** In at least one embodiment, in an aspect, R₇ can be a halogen atom and R₂, R₅ and R₆ can each be a hydrogen atom or an alkyl group or O-alkyl group, and R₄ can be a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group.
- 5 **[0022]** In at least one embodiment, in an aspect, at least two of R₂, R₄, R₅, R₆ or R₇ can be a halogen atom.
- [0023]** In at least one embodiment, in an aspect, the at least of two of R₂, R₄, R₅, R₆ or R₇ that are halogen atoms can be at least two identical halogen atoms.
- 10 **[0024]** In at least one embodiment, in an aspect, the at least of two of R₂, R₄, R₅, R₆ or R₇ that are halogen atoms can at least two non-identical halogen atoms.
- [0025]** In at least one embodiment, in an aspect, R₂ and R₄ can be a halogen atom, and R₅, R₆ and R₇ can be a hydrogen atom or an alkyl group or O-alkyl group.
- 15 **[0026]** In at least one embodiment, in an aspect, R₂ and R₅ can be a halogen atom, R₆ and R₇ can be a hydrogen atom or an alkyl group or O-alkyl group, and R₄ can be a hydrogen atom, a phosphate group or an alkyl group or O-alkyl group.
- 20 **[0027]** In at least one embodiment, in an aspect, R₂ and R₆ can be a halogen atom, R₅ and R₇ can be a hydrogen atom or an alkyl group or O-alkyl group, and R₄ can be a hydrogen atom, a phosphate group or an alkyl group or O-alkyl group.
- [0028]** In at least one embodiment, in an aspect, R₂ and R₇ can be a halogen atom, R₅ and R₆ can be a hydrogen atom or an alkyl group or O-alkyl group, and R₄ can be a hydrogen atom, a phosphate group or an alkyl group or O-alkyl group.
- 25 **[0029]** In at least one embodiment, in an aspect, R₄ and R₅ can be a halogen atom, and R₂, R₆ and R₇ can be a hydrogen atom or an alkyl group or O-alkyl group.
- 30 **[0030]** In at least one embodiment, in an aspect, R₄ and R₆ can be a halogen atom, and R₂, R₅ and R₇ can be a hydrogen atom or an alkyl group or O-alkyl group.

[0031] In at least one embodiment, in an aspect, R₄ and R₇ can be a halogen atom, and R₂, R₅ and R₆ can be a hydrogen atom or an alkyl group or O-alkyl group.

5 **[0032]** In at least one embodiment, in an aspect, R₅ and R₆ can be a halogen atom, R₂ and R₇ can be a hydrogen atom or an alkyl group or O-alkyl group, and R₄ can be a hydrogen atom, a phosphate group or an alkyl group or O-alkyl group.

10 **[0033]** In at least one embodiment, in an aspect, R₅ and R₇ can be a halogen atom, R₂ and R₆ can be a hydrogen atom or an alkyl group or O-alkyl group, and R₄ can be a hydrogen atom, a phosphate group or an alkyl group or O-alkyl group.

15 **[0034]** In at least one embodiment, in an aspect, R₆ and R₇ can be a halogen atom, R₂ and R₅ can be a hydrogen atom or an alkyl group or O-alkyl group, and R₄ can be a hydrogen atom, a phosphate group or an alkyl group or O-alkyl group.

[0035] In at least one embodiment, in an aspect, R₄ when it is not halogenated can be a hydrogen atom.

[0036] In at least one embodiment, in an aspect, R₄ when it is not halogenated can be an alkyl group.

20 **[0037]** In at least one embodiment, in an aspect, R₄ when it is not halogenated can be an O-alkyl group.

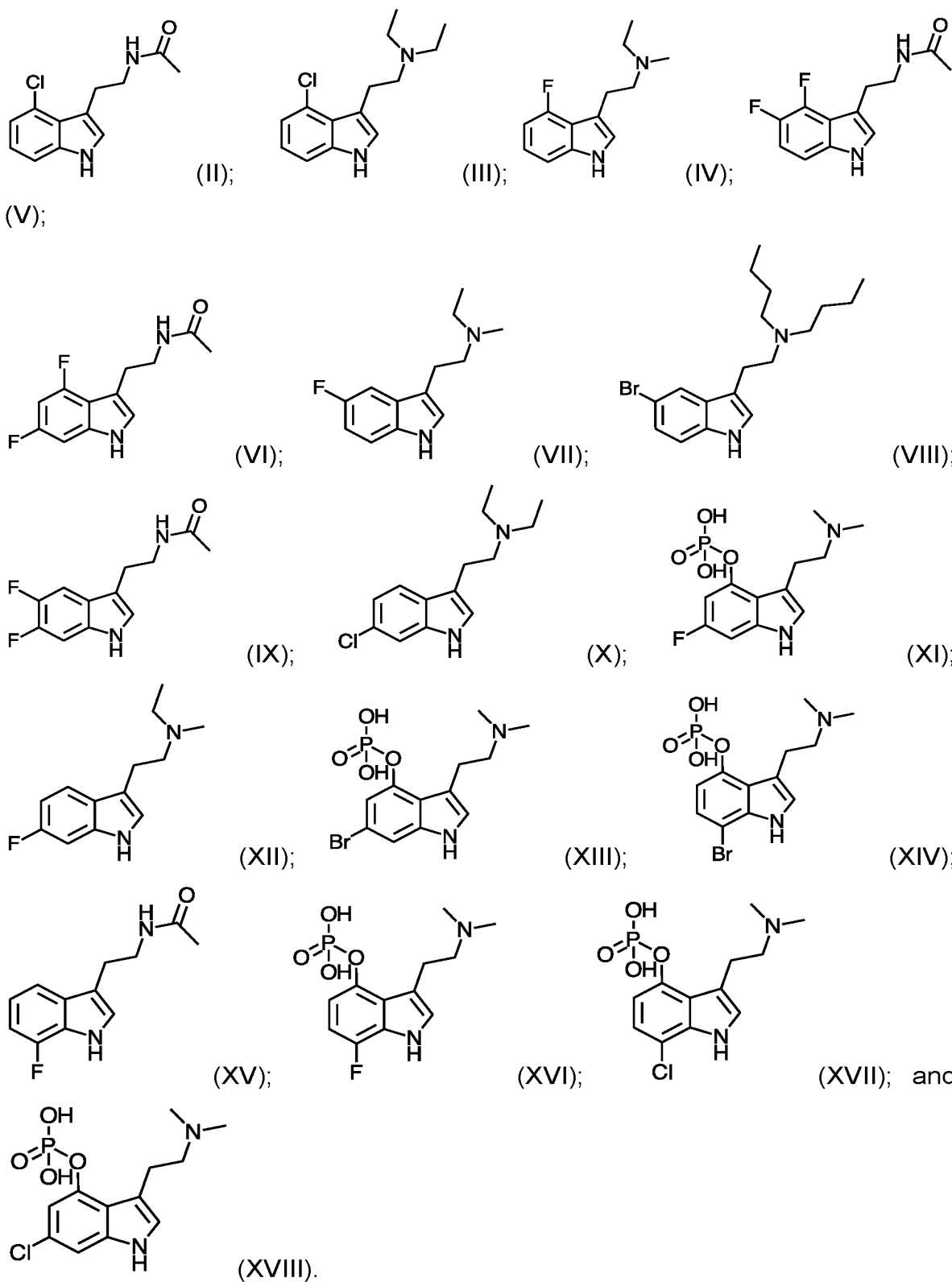
[0038] In at least one embodiment, in an aspect, R₄ when it is not halogenated can be a phosphate group.

25 **[0039]** In at least one embodiment, in an aspect, three, four or all five of R₂, R₄, R₅, R₆ or R₇ can be a halogen atom.

[0040] In at least one embodiment, in an aspect, the three, four, or five of R₂, R₄, R₅, R₆ or R₇ that are halogen atoms can all be identical halogen atoms.

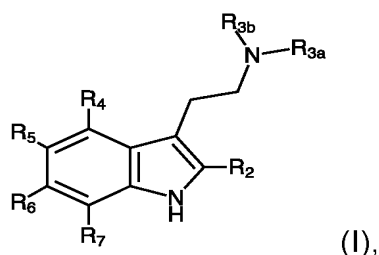
30 **[0041]** In at least one embodiment, in an aspect, the three, four or five of R₂, R₄, R₅, R₆ or R₇ that are halogen atoms, can include at least two non-identical halogen atoms.

[0042] In at least one embodiment, in an aspect, the chemical compound can be selected from the group consisting of compounds having formulas (II); (III); (IV); (V); (VI); (VII); (VIII); (IX); (X); (XI); (XII); (XIII); (XIV); (XV); (XVI); and (XVII):



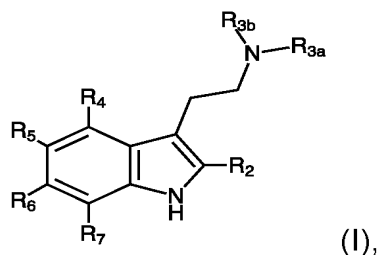
[0043] In at least one embodiment, the chemical compound is at least about 95% (w/w) pure.

[0044] In another aspect, the present disclosure relates to pharmaceutical and recreational drug formulations comprising halogenated psilocybin derivatives. Accordingly, in one aspect, the present disclosure provides in at least one aspect, a pharmaceutical or recreational drug formulation comprising an effective amount of a chemical compound or salts thereof having the formula (I):



wherein, at least one of R₂, R₄, R₅, R₆ or R₇ is a halogen atom, wherein each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom or an alkyl group or O-alkyl group, wherein R₄ when it is not halogenated is a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group, and wherein R_{3A} and R_{3B} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group, together with a pharmaceutically acceptable excipient, diluent or carrier.

[0045] In another aspect, the present disclosure relates to methods of treatment of psychiatric disorders. Accordingly, the present disclosure further provide a method for treating a psychiatric disorder, the method comprising administering to a subject in need thereof a pharmaceutical formulation comprising a chemical compound or salts thereof having the formula (I):



wherein, at least one of R₂, R₄, R₅, R₆ or R₇ is a halogen atom, wherein each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom or an alkyl group or O-alkyl group, wherein R₄ when it is not halogenated is a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group, and wherein R_{3A} and R_{3B} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group, wherein the pharmaceutical

formulation is administered in an effective amount to treat the psychiatric disorder in the subject.

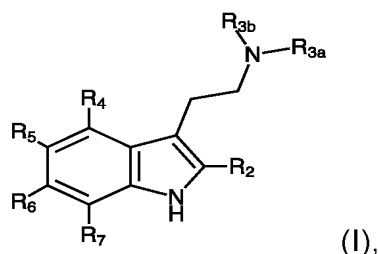
[0046] In at least one embodiment, in an aspect the disorder can be a 5-HT_{2A} receptor mediated disorder.

5 **[0047]** In at least one embodiment, in an aspect, a dose can be administered of about 0.001 mg to about 5,000 mg.

[0048] In another aspect, the present disclosure relates to methods of making halogenated psilocybin derivatives. Accordingly, in one aspect, the present disclosure provides in at least one aspect, a method of making a halogenated
10 psilocybin derivative the method comprising:

- (a) contacting a halogenated psilocybin precursor compound with a host cell comprising a psilocybin biosynthetic enzyme complement; and
- (b) growing the host cell to produce a halogenated psilocybin derivative or salts thereof having the formula (I):

15



wherein, at least one of R₂, R₄, R₅, R₆ or R₇ is a halogen atom, wherein each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom or an alkyl group or O-alkyl group, wherein R₄ when it is not halogenated is a phosphate group,
20 a hydrogen atom or an alkyl group or O-alkyl group, and wherein R_{3A} and R_{3B} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group.

[0049] In at least one embodiment, in an aspect, the halogenated psilocybin precursor compound can be contacted with the host cell by including the psilocybin precursor compound in a growth medium for the host cell.

25 **[0050]** In at least one embodiment, in an aspect, the halogenated psilocybin precursor compound can be formed by contacting the host cell with a non-halogenated psilocybin precursor compound and a halogen, the host cell further comprising a halogenase capable of halogenating the non-halogenated psilocybin compound and forming the halogenated psilocybin precursor compound.

[0051] In at least one embodiment, in an aspect, R₂ can be a halogen atom and R₅, R₆ and R₇ can each be a hydrogen atom, and R₄ can be a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group.

5 **[0052]** In at least one embodiment, in an aspect, R₄ can be a halogen atom and R₂, R₅, R₆ and R₇ can each be a hydrogen atom or an alkyl group or O-alkyl group.

10 **[0053]** In at least one embodiment, in an aspect, R₅ can be a halogen atom and R₂, R₆ and R₇ can each be a hydrogen atom or an alkyl group or O-alkyl group, and R₄ can be a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group.

[0054] In at least one embodiment, in an aspect, R₆ can be a halogen atom and R₂, R₅ and R₇ can each be a hydrogen atom or an alkyl group or O-alkyl group, and R₄ can be a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group.

15 **[0055]** In at least one embodiment, in an aspect, R₇ can be a halogen atom and R₂, R₅ and R₆ can each be a hydrogen atom or an alkyl group or O-alkyl group, and R₄ can be a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group.

20 **[0056]** In at least one embodiment, in an aspect, at least two of R₂, R₄, R₅, R₆ or R₇ can be a halogen atom.

[0057] In at least one embodiment, in an aspect, the at least of two of R₂, R₄, R₅, R₆ or R₇ that are halogen atoms can be two identical halogen atoms.

[0058] In at least one embodiment, in an aspect, the at least of two of R₂, R₄, R₅, R₆ or R₇ that are halogen atoms can be two non-identical halogen atoms.

25 **[0059]** In at least one embodiment, in an aspect, R₂ and R₄ can be a halogen atom, and R₅, R₆ and R₇ can be a hydrogen atom or an alkyl group or O-alkyl group.

30 **[0060]** In at least one embodiment, in an aspect, R₂ and R₅ can be a halogen atom, R₆ and R₇ can be a hydrogen atom or an alkyl group or O-alkyl group, and R₄ can be a hydrogen atom, an alkyl group or O-alkyl group or a phosphate group.

[0061] In at least one embodiment, in an aspect, R₂ and R₆ can be a halogen atom, R₅ and R₇ can be a hydrogen atom or an alkyl group or O-alkyl

group, and R₄ can be a hydrogen atom, an alkyl group or O-alkyl group or a phosphate group.

5 **[0062]** In at least one embodiment, in an aspect, R₂ and R₇ can be a halogen atom, R₅ and R₆ can be a hydrogen atom or an alkyl group or O-alkyl group, and R₄ can be a hydrogen atom, an alkyl group or O-alkyl group or a phosphate group.

[0063] In at least one embodiment, in an aspect, R₄ and R₅ can be a halogen atom, and R₂, R₆ and R₇ can be a hydrogen atom or an alkyl group or O-alkyl group.

10 **[0064]** In at least one embodiment, in an aspect, R₄ and R₆ can be a halogen atom, and R₂, R₅ and R₇ can be a hydrogen atom or an alkyl group or O-alkyl group.

15 **[0065]** In at least one embodiment, in an aspect, R₄ and R₇ can be a halogen atom, and R₂, R₅ and R₆ can be a hydrogen atom or an alkyl group or O-alkyl group.

[0066] In at least one embodiment, in an aspect, R₅ and R₆ can be a halogen atom, R₂ and R₇ can be a hydrogen atom or an alkyl group or O-alkyl group, and R₄ can be a hydrogen atom, an alkyl group or O-alkyl group or a phosphate group.

20 **[0067]** In at least one embodiment, in an aspect, R₅ and R₇ can be a halogen atom, R₂ and R₆ can be a hydrogen atom or an alkyl group or O-alkyl group, and R₄ can be a hydrogen atom, an alkyl group or O-alkyl group or a phosphate group.

25 **[0068]** In at least one embodiment, in an aspect, R₆ and R₇ can be a halogen atom, R₂ and R₅ can be a hydrogen atom or an alkyl group or O-alkyl group, and R₄ can be a hydrogen atom, an alkyl group or O-alkyl group or a phosphate group.

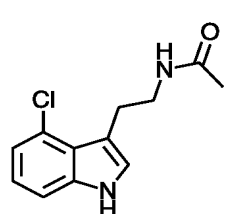
[0069] In at least one embodiment, in an aspect, R₄ when it is not halogenated can be a hydrogen atom.

30 **[0070]** In at least one embodiment, in an aspect, R₄ when it is not halogenated can be an alkyl group.

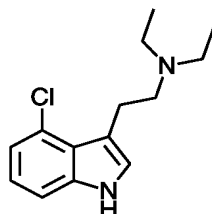
[0071] In at least one embodiment, in an aspect, R₄ when it is not halogenated can be an O-alkyl group.

[0072] In at least one embodiment, in an aspect, R₄ when it is not halogenated can be a phosphate group.

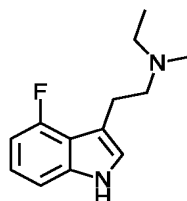
[0073] In at least one embodiment, in an aspect, the halogenated psilocybin derivative can be a derivative selected from the group consisting of derivatives having formulas (II); (III); (IV); (V); (VI); (VII); (VIII); (IX); (X); (XI); (XII); (XIII); (XIV); (XV); (XVI); and (XVII):



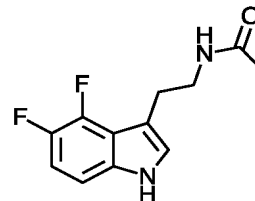
(II);



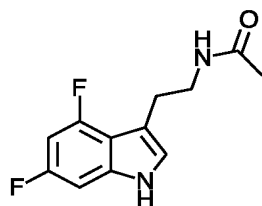
(III);



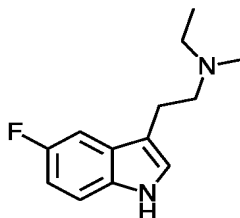
(IV);



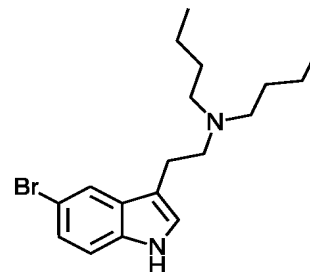
(V);



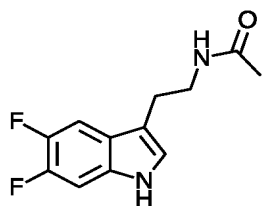
(VI);



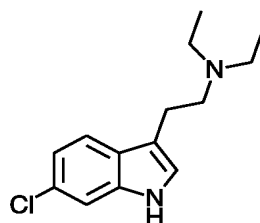
(VII);



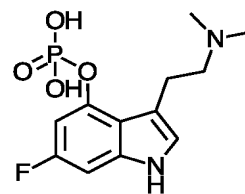
(VIII);



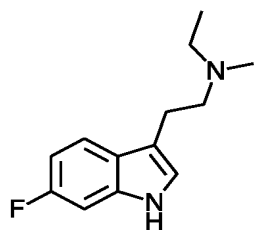
(IX);



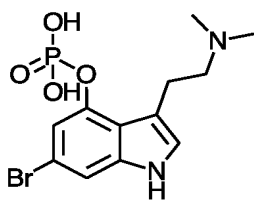
(X);



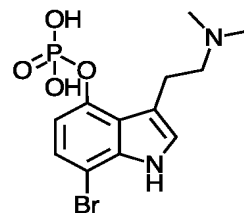
(XI);



(XII);

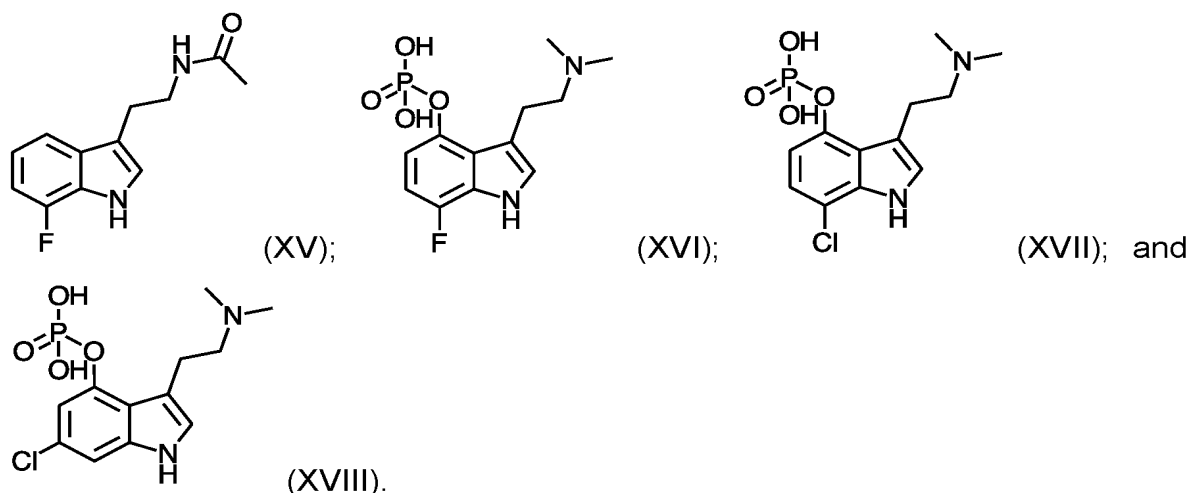


(XIII);



(XIV);

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[0074] In at least one embodiment, in an aspect, the halogenated psilocybin precursor compound can be selected from the group of halogenated compounds consisting of halogenated tryptophan, halogenated tryptamine, halogenated 4-hydroxytryptamine, halogenated 4-hydroxy-indole, halogenated 4-hydroxytryptophan, halogenated norbaeocystin, and halogenated baeocystin.

[0075] In at least one embodiment, in an aspect, the psilocybin biosynthetic enzyme complement can comprise at least one enzyme encoded by a nucleic acid selected from:

(a) SEQ.ID NO: 1, SEQ.ID NO: 3, SEQ.ID NO: 5, SEQ.ID NO: 7, SEQ.ID NO: 9, SEQ.ID NO 11, SEQ.ID NO: 36, SEQ.ID NO: 38, SEQ.ID NO: 40, SEQ. ID NO: 42, SEQ.ID NO: 44, SEQ.ID NO: 46, SEQ.ID NO: 48, SEQ.ID NO: 50, SEQ.ID NO: 52, SEQ.ID NO: 54, SEQ. ID NO: 56, SEQ.ID NO: 58, SEQ.ID NO: 60, SEQ.ID NO: 64, SEQ.ID NO: 66, SEQ.ID NO: 68, SEQ. ID NO: 70, and SEQ.ID NO: 72;

(b) a nucleic acid sequence that is substantially identical to any one of the nucleic acid sequences of (a);

(c) a nucleic acid sequence that is substantially identical to any one of the nucleic acid sequences of (a) but for the degeneration of the genetic code;

(d) a nucleic acid sequence that is complementary to any one of the nucleic acid sequences of (a);

(e) a nucleic acid sequence encoding a polypeptide having any one of the amino acid sequences set forth in SEQ.ID NO: 2, SEQ.ID NO: 4, SEQ.ID NO: 6, SEQ.ID NO: 8, SEQ.ID NO: 10, SEQ.ID NO 12, SEQ.ID NO:

37, SEQ.ID NO: 39, SEQ.ID NO: 41, SEQ. ID NO: 43, SEQ.ID NO: 45, SEQ.ID NO: 47, SEQ.ID NO: 49, SEQ.ID NO: 51, SEQ.ID NO: 53, SEQ.ID NO: 55, SEQ. ID NO: 57, SEQ.ID NO: 59, SEQ.ID NO: 61, SEQ.ID NO: 65, SEQ.ID NO: 67, SEQ.ID NO: 69, SEQ. ID NO: 71, and SEQ.ID NO: 73;

- 5 (f) a nucleic acid sequence that encodes a functional variant of any one of the amino acid sequences set forth in SEQ.ID NO: 2, SEQ.ID NO: 4, SEQ.ID NO: 6, SEQ.ID NO: 8, SEQ.ID NO: 10, SEQ.ID NO 12, SEQ.ID NO: 37, SEQ.ID NO: 39, SEQ.ID NO: 41, SEQ. ID NO: 43, SEQ.ID NO: 45, SEQ.ID NO: 47, SEQ.ID NO: 49, SEQ.ID NO: 51, SEQ.ID NO: 53, SEQ.ID NO: 55, SEQ. ID NO: 57, SEQ.ID NO: 59, SEQ.ID NO: 61, SEQ.ID NO: 65, SEQ.ID NO: 67, SEQ.ID NO: 69, SEQ. ID NO: 71, and SEQ.ID NO: 73; and
- 10 (g) a nucleic acid sequence that hybridizes under stringent conditions to any one of the nucleic acid sequences set forth in (a), (b), (c), (d), (e) or (f).

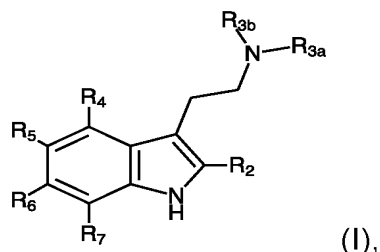
[0076] In at least one embodiment, in an aspect, the halogenase can be encoded by a nucleic acid selected from:

- 15 (a) SEQ.ID NO: 13, SEQ.ID NO: 15, SEQ. ID NO: 17, SEQ.ID NO: 19, SEQ. ID NO: 21, SEQ.ID NO: 23, SEQ.ID NO: 25, and SEQ.ID NO: 27;
- (b) a nucleic acid sequence that is substantially identical to any one of the nucleic acid sequences of (a);
- 20 (c) a nucleic acid sequence that is substantially identical to any one of the nucleic acid sequences of (a) but for the degeneration of the genetic code;
- (d) a nucleic acid sequence that is complementary to any one of the nucleic acid sequences of (a);
- 25 (e) a nucleic acid sequence encoding a polypeptide having any one of the amino acid sequences set forth in SEQ.ID NO: 14, SEQ.ID NO: 16, SEQ. ID NO: 18, SEQ.ID NO: 20, SEQ. ID NO: 22, SEQ.ID NO: 24, SEQ.ID NO: 26, SEQ.ID NO: 28, SEQ.ID NO: 29, SEQ.ID NO: 30, SEQ.ID NO: 31, SEQ.ID NO: 32. SEQ.ID NO: 33, SEQ.ID NO: 34, and SEQ.ID NO: 35;
- 30 (f) a nucleic acid sequence that encodes a functional variant of any one of the amino acid sequences set forth in SEQ.ID NO: 14, SEQ.ID NO: 16, SEQ. ID NO: 18, SEQ.ID NO: 20, SEQ. ID NO: 22, SEQ.ID NO: 24, SEQ.ID NO: 26, SEQ.ID NO: 28, SEQ.ID NO: 29, SEQ.ID NO: 30, SEQ.ID NO: 31, SEQ.ID NO: 32. SEQ.ID NO: 33, SEQ.ID NO: 34, and SEQ.ID NO: 35; and

(g) a nucleic acid sequence that hybridizes under stringent conditions to any one of the nucleic acid sequences set forth in (a), (b), (c), (d), (e) or (f).

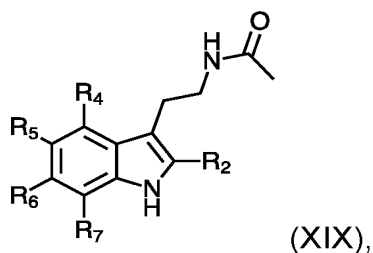
[0077] In at least one embodiment, in an aspect, the host cell can further comprise an acetyl transferase capable of acetylating R_{3a} or R_{3b}, wherein the cell

5 comprises a compound having chemical formula (I):



wherein, at least one of R₂, R₄, R₅, R₆ or R₇ is a halogen atom, wherein each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom or an alkyl group or O-alkyl group, wherein R₄ when it is not halogenated is a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group, and wherein at least

10 one of R_{3A} and R_{3B} is a hydrogen atom,
to form a compound having the chemical formula (XIX):



wherein, at least one of R₂, R₄, R₅, R₆ or R₇ is a halogen atom, wherein each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom or an alkyl group or O-alkyl group, wherein R₄ when it is not halogenated is a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group.

[0078] In at least one embodiment, the acetylase can be encoded by a nucleic acid selected from:

- 20 (a) SEQ.ID NO: 62;
- (b) a nucleic acid sequence that is substantially identical the nucleic acid sequence of (a);
- (c) a nucleic acid sequence that is substantially identical to the nucleic acid sequence of (a) but for the degeneration of the genetic code;

(d) a nucleic acid sequence that is complementary to the nucleic acid sequence of (a);

(e) a nucleic acid sequence encoding a polypeptide having an amino acid sequences set forth in SEQ.ID NO: 63;

5 (f) a nucleic acid sequence that encodes a functional variant of the amino acid sequence set forth in SEQ.ID NO: 63; and

(g) a nucleic acid sequence that hybridizes under stringent conditions to any one of the nucleic acid sequences set forth in (a), (b), (c), (d), (e) or (f).

[0079] In at least one embodiment, in an aspect,

10 (a) the halogenated psilocybin precursor compound can be a halogenated indole, and the a psilocybin biosynthetic enzyme complement can comprise

(i) a nucleic acid encoding TrpB selected from SEQ.ID NO: 12, SEQ.ID NO: 65, SEQ.ID NO: 67, SEQ.ID NO: 69, SEQ.ID NO: 71, and SEQ.ID NO: 73, or a nucleic acid sequence encoding a polypeptide sequence substantially

15 similar thereto; (ii) a nucleic acid encoding PsiD selected from SEQ.ID NO: 2, SEQ.ID NO: 10, SEQ.ID NO: 37, SEQ.ID NO: 39, SEQ.ID NO: 41, SEQ.ID NO: 43, SEQ.ID NO: 45, SEQ.ID NO: 47, SEQ.ID NO: 49, SEQ.ID NO: 51, SEQ.ID NO: 53, SEQ.ID NO: 55, and SEQ.ID NO: 57, or a nucleic acid sequence encoding a polypeptide sequence substantially similar

20 thereto; (iii) a nucleic acid encoding PsiK encoded by SEQ.ID NO: 6, or a nucleic acid sequence encoding a polypeptide sequence substantially similar thereto; and (iv) a nucleic acid encoding PsiM selected from SEQ.ID NO: 8, SEQ.ID NO: 59 and SEQ.ID NO: 61 or a nucleic acid sequence encoding a polypeptide sequence substantially similar thereto; or

25 (b) the halogenated psilocybin precursor compound can be a halogenated tryptophan, and the psilocybin biosynthetic enzyme complement can comprise (i) a nucleic acid encoding PsiD selected from SEQ.ID NO: 2, SEQ.ID NO: 10, SEQ.ID NO: 37, SEQ.ID NO: 39, SEQ.ID NO: 41, SEQ.ID NO: 43, SEQ.ID NO: 45, SEQ.ID NO: 47, SEQ.ID NO: 49, SEQ.ID NO: 51, SEQ.ID NO: 53, SEQ.ID NO: 55, and SEQ.ID NO: 57, or a nucleic acid

30 sequence encoding a polypeptide sequence substantially similar thereto; (ii) a nucleic acid encoding PsiK encoded by SEQ.ID NO: 6, or a nucleic acid sequence encoding a polypeptide sequence substantially similar thereto; and (iii) a nucleic acid encoding PsiM selected from SEQ.ID NO: 8,

SEQ.ID NO: 59 and SEQ.ID NO: 61 or a nucleic acid sequence encoding a polypeptide sequence substantially similar thereto; or

(c) the halogenated psilocybin precursor compound can be a halogenated tryptamine, and the psilocybin biosynthetic enzyme complement can comprise (i) a nucleic acid encoding PsiK encoded by SEQ.ID NO: 6, or a nucleic acid sequence encoding a polypeptide sequence substantially similar thereto; and (ii) and a nucleic acid encoding PsiM selected from SEQ.ID NO: 8, SEQ.ID NO: 59 and SEQ.ID NO: 61 or a nucleic acid sequence encoding a polypeptide sequence substantially similar thereto; or

(d) the halogenated psilocybin precursor compound can be a halogenated norbaeocystin or a halogenated baeocystin and the psilocybin biosynthetic enzyme complement can comprise a nucleic acid encoding PsiM selected from SEQ.ID NO: 8, SEQ.ID NO: 59 and SEQ.ID NO: 61 or a nucleic acid sequence encoding a polypeptide sequence substantially similar thereto; or

(e) the halogenated psilocybin precursor compound can be a halogenated tryptophan, and the psilocybin biosynthetic enzyme complement can comprise (i) a nucleic acid encoding PsiD selected from SEQ.ID NO: 2, SEQ.ID NO: 10, SEQ.ID NO: 37, SEQ.ID NO: 39, SEQ.ID NO: 41, SEQ.ID NO: 43, SEQ.ID NO: 45, SEQ.ID NO: 47, SEQ.ID NO: 49, SEQ.ID NO: 51, SEQ.ID NO: 53, SEQ.ID NO: 55, and SEQ.ID NO: 57, or a nucleic acid sequence encoding a polypeptide sequence substantially similar thereto;

(ii) a nucleic acid encoding PsiH encoded by SEQ.ID NO: 4, or a nucleic acid sequence encoding a polypeptide sequence substantially similar thereto; (iii) a nucleic acid encoding PsiK encoded by SEQ.ID NO: 6, or a nucleic acid sequence encoding a polypeptide sequence substantially similar thereto; and (iv) and a nucleic acid encoding PsiM selected from SEQ.ID NO: 8, SEQ.ID NO: 59 and SEQ.ID NO: 61 or a nucleic acid sequence encoding a polypeptide sequence substantially similar thereto; or

(f) the halogenated psilocybin precursor compound can be, a halogenated tryptamine, and psilocybin biosynthetic enzyme complement can comprise (i) a nucleic acid encoding PsiH encoded by SEQ.ID NO: 4, or a nucleic acid sequence encoding a polypeptide sequence substantially similar thereto; (ii) a nucleic acid encoding PsiK encoded by SEQ.ID NO: 6, or a nucleic acid sequence encoding a polypeptide sequence substantially

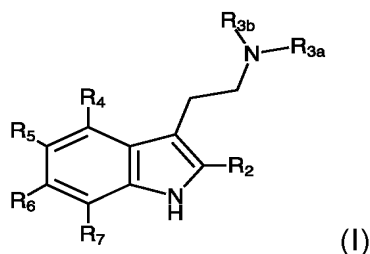
similar thereto; and (iii) and a nucleic acid encoding PsiM selected from SEQ.ID NO: 8, SEQ.ID NO: 59 and SEQ.ID NO: 61 or a nucleic acid sequence encoding a polypeptide sequence substantially similar thereto.

5 **[0080]** In at least one embodiment, in an aspect, the method can further include a step comprising isolating the halogenated psilocybin derivative.

[0081] In at least one embodiment, in an aspect, the host cell can be a microbial cell.

[0082] In at least one embodiment, in an aspect, the host cell can be a bacterial cell or a yeast cell.

10 **[0083]** In another aspect, the present disclosure provides, in at least one embodiment, a method for modulating a 5-HT_{2A} receptor, the method comprising contacting a 5-HT_{2A} receptor with a chemical compound or salts thereof having the formula (I):

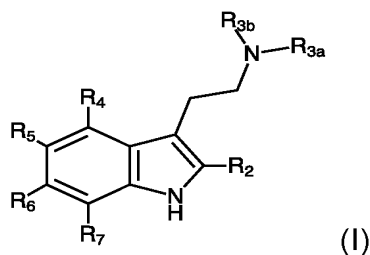


15 wherein, at least one of R₂, R₄, R₅, R₆ or R₇ is a halogen atom, wherein each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom or an alkyl group or O-alkyl group, wherein R₄ when it is not halogenated is a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group, and wherein R_{3A} and R_{3B} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group under reaction conditions
20 sufficient to thereby modulate receptor activity.

[0084] In at least one embodiment, in an aspect, the reaction conditions can be *in vitro* reaction conditions.

25 **[0085]** In at least one embodiment, in an aspect, the reaction conditions can be *in vivo* reaction conditions.

[0086] In another aspect, the present disclosure provides, in at least one embodiment, a use of a chemical compound or salts thereof having the formula (I):

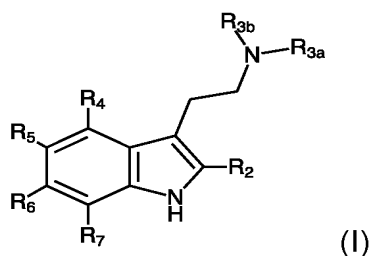


wherein, at least one of R₂, R₄, R₅, R₆ or R₇ is a halogen atom, wherein each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom or an alkyl group or O-alkyl group, wherein R₄ when it is not halogenated is a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group, and wherein R_{3A} and R_{3B} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group in the manufacture of a pharmaceutical or recreational drug formulation.

[0087] In at least one embodiment, in an aspect, the manufacture of a pharmaceutical or recreational drug formulation can comprise formulating the chemical compound with an excipient, diluent or carrier.

[0088] In at least one embodiment, the manufacture of a pharmaceutical or recreational drug formulation can comprise derivatizing the chemical compound having the formula (I) by substituting the halogen atom with another atom or chemical group.

[0089] In another aspect, the present disclosure provides, in at least one embodiment, a use of a chemical compound or salts thereof having the formula (I):



wherein, at least one of R₂, R₄, R₅, R₆ or R₇ is a halogen atom, wherein each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom or an alkyl group or O-alkyl group, wherein R₄ when it is not halogenated is a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group, and wherein R_{3A} and R_{3B} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group together with a diluent, carrier or excipient, as a pharmaceutical or recreational drug formulation.

[0090] Other features and advantages will become apparent from the following detailed description. It should be understood, however, that the detailed description, while indicating preferred implementations of the disclosure, are given by way of illustration only, since various changes and modifications within the spirit and scope of the disclosure will become apparent to those of skill in the art from the detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0091] The disclosure is in the hereinafter provided paragraphs described, by way of example, in relation to the attached figures. The figures provided herein are provided for a better understanding of the example embodiments and to show more clearly how the various embodiments may be carried into effect. The figures are not intended to limit the present disclosure.

[0092] **FIG. 1** depicts the chemical structure of psilocybin.

[0093] **FIG. 2** depicts a certain prototype structure of a psilocybin precursor compound, namely an indole. Certain carbon and nitrogen atoms may be referred herein by reference to their position within the indole structure, *i.e.* N₁, C₂, C₃ *etc.* The pertinent atom numbering is shown.

[0094] **FIGS. 3A, 3B, 3C, 3D, 3E, 3F and 3G** depict the chemical structures of example psilocybin precursor compounds, notably L-tryptophan (**FIG. 3A**), tryptamine (**FIG. 3B**), 4-hydroxytryptamine (**FIG. 3C**), L-4-hydroxytryptophan (**FIG. 3D**), 4-hydroxyindole (**FIG. 3E**), norbaeocystin (**FIG. 3F**), and baecocystin (**FIG. 3G**).

[0095] **FIGS. 4A, 4B, 4C, 4D, 4E, 4F, 4G, 4H, 4I, 4J, 4K, 4L, 4M, 4N, 4O, 4P, 4Q and 4R** depict the chemical structures of certain example halogenated psilocybin derivative compounds, notably a 2-chloro-4-phospho psilocybin derivative (**FIG. 4A**); a 2-bromo psilocybin derivative (**FIG. 4B**); a 4-iodo psilocybin derivative (**FIG. 4C**); a 4-fluoro psilocybin derivative (**FIG. 4D**); a 4-phospho-5-fluoro psilocybin derivative (**FIG. 4E**); a 5-chloro psilocybin derivative (**FIG. 4F**); a 4-phospho-6-bromo psilocybin derivative (**FIG. 4G**); a 6-chloro psilocybin derivative (**FIG. 4H**); a 4-phospho-7-fluoro psilocybin derivative (**FIG. 4I**); a 7-iodo psilocybin derivative (**FIG. 4J**); a 2-chloro-4-methyl psilocybin derivative (**FIG. 4K**); a 4-ethyl-5-bromo psilocybin derivative (**FIG. 4L**); a 4-methyl-6-fluoro psilocybin derivative (**FIG. 4M**); a 4-propyl-7-iodo psilocybin derivative (**FIG. 4N**); a 2-chloro-

4-O-methyl psilocybin derivative (**FIG. 4K**); a 4-O-ethyl-5-bromo psilocybin derivative (**FIG. 4L**); a 4-O-methyl-6-fluoro psilocybin derivative (**FIG. 4M**); and a 4-O-propyl-7-iodo psilocybin derivative (**FIG. 4N**). It is noted that in each of **FIGS. 4A, 4B, 4C, 4D, 4E, 4F, 4G, 4H, 4I, 4J, 4K, 4L, 4M, 4N, 4O, 4P, 4Q** and **4R** R_{3a} and R_{3b} can be a hydrogen atom, an alkyl group, an aryl group, or an acyl group.

[0096] **FIGS. 5A, 5B, 5C, 5D, 5E, 5F, 5G, 5H, 5I** and **5J** depict the chemical structures of certain example halogenated psilocybin derivative compounds, notably a 2,4-di-chloro psilocybin derivative (**FIG. 5A**); a 2-bromo-5-fluoro-7-methyl psilocybin derivative (**FIG. 5B**); a 2-chloro-O-methyl-6-bromo psilocybin derivative (**FIG. 5C**); a 2-fluoro-4-phospho-7-iodo psilocybin derivative (**FIG. 5D**); a 4,5-di-bromo psilocybin derivative (**FIG. 5E**); a 4,6-di-chloro psilocybin derivative (**FIG. 5F**); a 4-chloro-5-fluoro psilocybin derivative (**FIG. 5G**); a 4-phospho-5-fluoro-6-bromo psilocybin derivative (**FIG. 5H**) a 4-phospho-5,7-di-fluoro psilocybin derivative (**FIG. 5I**); and a 6,7-di-iodo psilocybin derivative (**FIG. 5J**). It is noted that in each of **FIGS. 5A, 5B, 5C, 5D, 5E, 5F, 5G, 5H, 5I** and **5J** R_{3a} and R_{3b} can be a hydrogen atom, an alkyl group, an aryl group, or an acyl group.

[0097] **FIGS. 6A, 6B, 6C, 6D, 6E,** and **6F** depict the chemical structures of certain example halogenated psilocybin derivative compounds, notably a 2,4,5-tri-chloro psilocybin derivative (**FIG. 6A**); a 2-bromo-5,6-di-fluoro psilocybin derivative (**FIG. 6B**); a 2-chloro-5-bromo-7-fluoro psilocybin derivative (**FIG. 6C**); a 4,5-di-bromo-6-chloro psilocybin derivative (**FIG. 6D**); a 4,5,7-tri-bromo psilocybin derivative (**FIG. 6E**); and a 4-phospho-5-fluoro-6-chloro-7-iodo psilocybin derivative (**FIG. 6F**). It is noted that in each of **FIGS. 6A, 6B, 6C, 6D, 6E,** and **6F** R_{3a} and R_{3b} can be a hydrogen atom, an alkyl group, an aryl group, or an acyl group.

[0098] **FIGS. 7A, 7B, 7C, 7D,** and **7E** depict the chemical structures of certain example halogenated psilocybin derivative compounds, notably a 2,4,5,6-tetra-chloro psilocybin derivative (**FIG. 7A**); a 4,7-di-chloro-5,6-di-fluoro psilocybin derivative (**FIG. 7B**); a 2-chloro-4-phospho-5-fluoro-6-chloro-7-iodo psilocybin derivative (**FIG. 7C**); a 2,4,7-tri-bromo-6-chloro psilocybin derivative (**FIG. 7D**); and a 2-fluoro-4,5,7-tri-bromo psilocybin derivative (**FIG. 7E**). It is noted that in each of **FIGS. 7A, 7B, 7C, 7D,** and **7E** R_{3a} and R_{3b} can be a hydrogen atom, an alkyl group, an aryl group, or an acyl group.

[0099] **FIGS. 8A and 8B** depict example biosynthesis pathway relating to the synthesis of a halogenated psilocybin derivatives.

[00100] **FIGS. 9A and 9B** depict example chemical synthesis processes for the synthesis of certain example halogenated psilocybin derivatives, notably the compound denoted as **410B01 (FIG. 9A)** and corresponding with a halogenated psilocybin derivative compound having the chemical formula (IV) set forth herein, and the compound denoted as **1 (FIG. 9B)** and corresponding with a halogenated psilocybin derivative compound having the chemical formula (VIII) set forth herein.

[00101] **FIG. 10** depicts a representation of mass spectrometry data in the form of a chromatogram, notably a chromatogram obtained in the performance of an experiment to synthesize an example halogenated psilocybin derivative compound having the chemical formula (XI) set forth herein.

[00102] **FIG. 11** depicts a representation of mass spectrometry data in the form of a chromatogram, notably a chromatogram obtained in the performance of an experiment to synthesize an example halogenated psilocybin derivative compound having the chemical formula (XIV) set forth herein.

[00103] **FIG. 12** depicts a representation of mass spectrometry data in the form of a chromatogram, notably a chromatogram obtained in the performance of an experiment to synthesize an example halogenated psilocybin derivative compound having the chemical formula (XVI) set forth herein.

[00104] **FIG. 13** depicts a representation of mass spectrometry data in the form of a chromatogram, notably a chromatogram obtained in the performance of an experiment to synthesize an example halogenated psilocybin derivative compound having the chemical formula (XVII) set forth herein.

[00105] **FIG. 14** depicts a graph obtained in the performance of an experimental assay to evaluate the efficacy of an example halogenated psilocybin derivative, notably a cell viability assay involving an example halogenated psilocybin derivative compound having the chemical formula (XV) set forth herein.

[00106] **FIGS. 15A and 15B** depict graphs obtained in the performance of an experimental assay to evaluate the efficacy of an example halogenated psilocybin derivative, notably a 5-HT_{2a} receptor modulation assay involving +5-HT_{2A} cells and an example halogenated psilocybin derivative compound having

the chemical formula (XV) set forth herein (**FIG. 15B**) and a control (psilocin) (**FIG. 15A**).

[00107] FIGS. 16A and 16B depict graphs obtained in the performance of an experimental assay to evaluate the efficacy of an example halogenated psilocybin derivative, notably a 5-HT_{2a} receptor modulation assay involving -5-HT_{2A} cells and an example halogenated psilocybin derivative compound having the chemical formula (XV) set forth herein (**FIG. 16B**) and a control (psilocin) (**FIG. 16A**).

[00108] FIG. 17 depicts a representation of mass spectrometry data in the form of a chromatogram, notably a chromatogram obtained in the performance of an experiment to synthesize an example halogenated psilocybin derivative compound having the chemical formula (II) set forth herein.

[00109] FIG. 18 depicts a graph obtained in the performance of an experimental assay to evaluate the efficacy of an example halogenated psilocybin derivative, notably a cell viability assay involving an example halogenated psilocybin derivative compound having the chemical formula (IX) set forth herein.

[00110] FIGS. 19A and 19B depict graphs obtained in the performance of an experimental assay to evaluate the efficacy of an example halogenated psilocybin derivative, notably a 5-HT_{2a} receptor modulation assay involving +5-HT_{2A} cells (**FIG. 19A**) and -5-HT_{2A} cells (**FIG. 19B**) and an example halogenated psilocybin derivative compound having the chemical formula (IX) set forth herein.

[00111] FIG. 20 depicts a representation of mass spectrometry data in the form of a chromatogram, notably a chromatogram obtained in the performance of an experiment to synthesize an example halogenated psilocybin derivative compound having the chemical formula (VI) set forth herein.

[00112] FIG. 21 depicts a graph obtained in the performance of an experimental assay to evaluate the efficacy of an example halogenated psilocybin derivative, notably a cell viability assay involving an example halogenated psilocybin derivative compound having the chemical formula (V) set forth herein.

[00113] FIGS. 22A and 22B depict graphs obtained in the performance of an experimental assay to evaluate the efficacy of an example halogenated psilocybin derivative, notably a 5-HT_{2a} receptor modulation assay involving +5-HT_{2A} cells (**FIG. 22A**) and -5-HT_{2A} cells (**FIG. 22B**), and an example halogenated psilocybin derivative compound having the chemical formula (V) set forth herein.

[00114] **FIG. 23** depicts a representation of mass spectrometry data in the form of a chromatogram, notably a chromatogram obtained in the performance of an experiment to synthesize an example halogenated psilocybin derivative compound having the chemical formula (XIII) set forth herein.

5 **[00115]** **FIG. 24** depicts a graph obtained in the performance of an experimental assay to evaluate the efficacy of an example halogenated psilocybin derivative, notably a cell viability assay involving an example halogenated psilocybin derivative compound having the chemical formula (X) set forth herein.

10 **[00116]** **FIGS. 25A** and **25B** depict graphs obtained in the performance of an experimental assay to evaluate the efficacy of an example halogenated psilocybin derivative, notably a 5-HT_{2a} receptor modulation assay involving +5-HT_{2A} cells (**FIG. 25A**) and -5-HT_{2A} cells (**FIG. 25B**), and an example halogenated psilocybin derivative compound having the chemical formula (X) set forth herein.

15 **[00117]** **FIG. 26** depicts a graph obtained in the performance of an experimental assay to evaluate the efficacy of an example halogenated psilocybin derivative, notably a cell viability assay involving an example halogenated psilocybin derivative compound having the chemical formula (IV) set forth herein.

20 **[00118]** **FIGS. 27A** and **27B** depict graphs obtained in the performance of an experimental assay to evaluate the efficacy of an example halogenated psilocybin derivative, notably a 5-HT_{2a} receptor modulation assay involving +5-HT_{2A} cells (**FIG. 27A**) and -5-HT_{2A} cells (**FIG. 27B**), and an example halogenated psilocybin derivative compound having the chemical formula (IV) set forth herein.

25 **[00119]** **FIG. 28** depicts a graph obtained in the performance of an experimental assay to evaluate the efficacy of an example halogenated psilocybin derivative, notably a cell viability assay involving an example halogenated psilocybin derivative compound having the chemical formula (VIII) set forth herein.

30 **[00120]** **FIGS. 29A** and **29B** depict graphs obtained in the performance of an experimental assay to evaluate the efficacy of an example halogenated psilocybin derivative, notably a 5-HT_{2a} receptor modulation assay involving +5-HT_{2A} cells (**FIG. 29A**) and -5-HT_{2A} cells (**FIG. 29B**), and an example halogenated psilocybin derivative compound having the chemical formula (VIII) set forth herein.

[00121] **FIG. 30** depicts a representation of mass spectrometry data in the form of a chromatogram, notably a chromatogram obtained in the performance of

an experiment to synthesize an example halogenated psilocybin derivative compound having the chemical formula (XVIII) set forth herein.

5 **[00122]** The figures together with the following detailed description make apparent to those skilled in the art how the disclosure may be implemented in practice.

DETAILED DESCRIPTION

10 **[00123]** Various compositions, systems or processes will be described below to provide an example of an embodiment of each claimed subject matter. No embodiment described below limits any claimed subject matter and any claimed subject matter may cover processes, compositions or systems that differ from those described below. The claimed subject matter is not limited to compositions, processes or systems having all of the features of any one composition, system or process described below or to features common to multiple or all of the compositions, systems or processes described below. It is possible that a composition, system or process described below is not an embodiment of any claimed subject matter. Any subject matter disclosed in a composition, system or process described below that is not claimed in this document may be the subject matter of another protective instrument, for example, a continuing patent application, and the applicant(s), inventor(s) or owner(s) do not intend to abandon, disclaim or dedicate to the public any such subject matter by its disclosure in this document.

25 **[00124]** As used herein and in the claims, the singular forms, such “a”, “an” and “the” include the plural reference and vice versa unless the context clearly indicates otherwise. Throughout this specification, unless otherwise indicated, “comprise,” “comprises” and “comprising” are used inclusively rather than exclusively, so that a stated integer or group of integers may include one or more other non-stated integers or groups of integers.

30 **[00125]** Various compositions, systems or processes will be described below to provide an example of an embodiment of each claimed subject matter. No embodiment described below limits any claimed subject matter and any claimed subject matter may cover processes, compositions or systems that differ from those described below. The claimed subject matter is not limited to compositions, processes or systems having all of the features of any one

composition, system or process described below or to features common to multiple or all of the compositions, systems or processes described below. It is possible that a composition, system or process described below is not an embodiment of any claimed subject matter. Any subject matter disclosed in a composition, system or process described below that is not claimed in this document may be the subject matter of another protective instrument, for example, a continuing patent application, and the applicant(s), inventor(s) or owner(s) do not intend to abandon, disclaim or dedicate to the public any such subject matter by its disclosure in this document.

[00126] When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and sub-combinations of ranges and specific embodiments therein are intended to be included. Other than in the operating examples, or where otherwise indicated, all numbers expressing quantities of ingredients or reaction conditions used herein should be understood as modified in all instances by the term "about." The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary between 1% and 15% of the stated number or numerical range, as will be readily recognized by context. Furthermore any range of values described herein is intended to specifically include the limiting values of the range, and any intermediate value or sub-range within the given range, and all such intermediate values and sub-ranges are individually and specifically disclosed (e.g. a range of 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.90, 4, and 5). Similarly, other terms of degree such as "substantially" and "approximately" as used herein mean a reasonable amount of deviation of the modified term such that the end result is not significantly changed. These terms of degree should be construed as including a deviation of the modified term if this deviation would not negate the meaning of the term it modifies.

[00127] Unless otherwise defined, scientific and technical terms used in connection with the formulations described herein shall have the meanings that are commonly understood by those of ordinary skill in the art. The terminology used herein is for the purpose of describing particular embodiments only, and is

not intended to limit the scope of the present invention, which is defined solely by the claims.

[00128] All publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

Terms and definitions

[00129] The term “psilocybin”, as used herein, refers to a chemical compound having the structure set forth in **FIG. 1**, and further includes salts, thereof, such as a sodium salt, a potassium salt, *etc.*

[00130] The term “psilocybin precursor compound”, as used herein, refers to a chemical compound that may serve as a precursor compound in the synthesis or biosynthesis of psilocybin, and includes compounds comprising an indole prototype structure, including, for example, tryptophan, tryptamine, 4-hydroxyindole, 4-hydroxytryptophan, 4-hydroxytryptamine, norbaeocystin, and baeocystin, and further includes halogenated derivatives and salts of any of the foregoing.

[00131] The term “indole prototype structure”, as used herein, refers to the chemical structure shown in **FIG. 2**. It is noted that specific carbon atoms and a nitrogen atom in the indole prototype structure are numbered. Reference may be made to these carbon and nitrogen numbers herein, for example C₂, C₄, N₁, and so forth. Furthermore, reference may be made to chemical groups attached to the indole prototype structure in accordance with the same numbering, for example R₄ and R₆ reference chemical groups attached to the C₄ and C₆ atom, respectively. In addition, R_{3A} and R_{3B}, in this respect, reference chemical groups extending from the ethyl-amino group extending in turn from the C₃ atom of the prototype indole structure.

[00132] The term “tryptophan”, as used herein, refers to a chemical compound having the structure set forth in **FIG. 3A** and further includes its D-enantiomeric form (not shown).

[00133] The term “tryptamine”, as used herein, refers to a chemical compound having the structure set forth in **FIG. 3B**.

[00134] The term “4-hydroxytryptamine”, as used herein, refers to a chemical compound having the structure set forth in **FIG. 3C**.

[00135] The term “4-hydroxytryptophan”, as used herein, refers to a chemical compound having the structure set forth in **FIG. 3D** and further includes its D-enantiomeric form (not shown).

5 **[00136]** The term “4-hydroxyindole”, as used herein, refers to a chemical compound having the structure set forth in **FIG. 3E**.

[00137] The term “norbaeocystin”, as used herein, refers to a chemical compound having the structure set forth in **FIG. 3F**.

[00138] The term “baeocystin”, as used herein, refers to a chemical compound having the structure set forth in **FIG. 3G**.

10 **[00139]** The term “phosphate group”, as used herein, is a molecule containing one atom of phosphorus, covalently bound to four oxygen atoms (three single bonds and one double bond). Of the four oxygen atoms one oxygen atom may be a hydroxy group, and one of the non-hydroxylated oxygen atom may be chemically bonded to another entity.

15 **[00140]** The terms “hydroxy group”, and “hydroxy”, as used herein, refers to a molecule containing one atom of oxygen bonded to one atom of hydrogen, and having the formula -OH. A hydroxy group through its oxygen atom may be chemically bonded to another entity.

20 **[00141]** The terms “halogen”, “halogenated” and “halo-”, as used herein, refer to the class of chemical elements consisting of fluorine (F), chlorine (Cl), bromine (Br), and iodine (I). Accordingly, halogenated compounds can refer to “fluorinated”, “chlorinated”, “brominated”, or “iodinated” compounds.

25 **[00142]** The term “halogenated psilocybin derivative”, as used herein, refers to a psilocybin derivative in which a halogen been bonded to psilocybin, or a derivative thereof. Reference may be made to specific carbon atoms of the psilocybin derivative which may be halogenated, for example, 7-halo-psilocybin refers to a halogenated psilocybin in which carbon atom number 7 (as identified in the indole prototype structure) is halogenated, or, similarly, 2-bromo-psilocybin refers to a brominated psilocybin in which carbon atom number 2 (as identified in
30 the indole prototype structure) is brominated, and so on. The term further includes salts of halogenated psilocybin derivatives, such as sodium salt, potassium salt, or a chlorine salt, for example. Salts may be formed by virtue of a charged atom or group included in the psilocybin derivative, notably a charged nitrogen atom, and/or a charged phosphate group.

[00143] The term “halogenated psilocybin precursor compound”, as used herein, refers to a psilocybin precursor compound possessing a halogen. Reference may be made to specific carbon atoms of the psilocybin precursor compound which may be halogenated, for example, 6-halo-baeocystin refers to a halogenated baeocystin in which carbon atom number 6 (as identified in the indole prototype structure) is halogenated, or, similarly, 2-chloro-4-hydroxytryptamine refers to a chlorinated 4-hydroxytryptamine in which carbon atom number 2 (as identified in the indole prototype structure) is chlorinated. Furthermore, halogenated psilocybin precursor compounds include, without limitation, halogenated tryptophan, e.g. 7-bromo tryptophan, 6-chloro tryptophan, 5,6-difluoro tryptophan, halogenated 4-hydroxy indole e.g. 4-hydroxy-7-bromo indole, 4-hydroxy-5-chloro indole, 6,7-di-fluoro-indole

[00144] The term “alkyl”, as used herein, refers to a straight and/or branched chain, saturated alkyl radical containing from one to “p” carbon atoms (“C₁-C_p-alkyl”) and includes, depending on the identity of “p”, methyl, ethyl, propyl, isopropyl, n-butyl, s-butyl, isobutyl, t-butyl, 2,2-dimethylbutyl, n-pentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, n-hexyl and the like, where the variable p is an integer representing the largest number of carbon atoms in the alkyl radical. Alkyl groups further include hydrocarbon groups arranged in a chain having the chemical formula -C_nH_{2n+1}, including, without limitation, methyl groups (-CH₃), ethyl groups (-C₂H₅), propyl groups (-C₃H₇), and butyl groups (-C₄H₉).

[00145] The term “O-alkyl”, as used herein, refers to a hydrocarbon group arranged in a chain having the chemical formula -O-C_nH_{2n+1}. O-alkyl groups include, without limitation, O-methyl groups (-O-CH₃), O-ethyl groups (-O-C₂H₅), O-propyl groups (-O-C₃H₇) and O-butyl groups (-O-C₄H₉).

[00146] The term “acyl”, as used herein, refers to a carbon atom double bonded to an oxygen and single bonded to an alkyl group. The carbon atom further can be bonded to another entity. An acyl group can be described by the chemical formula: -C(=O)-C_nH_{2n+1}.

[00147] The term “aryl”, as used herein, refers to a monocyclic, bicyclic or tricyclic aromatic ring system containing, depending on the number of atoms in the rings, for example, from 6 to 14 carbon atoms (C₆-C₁₄-aryl) or from 6 to 10 carbons (C₆-C₁₀-aryl), and at least 1 aromatic ring and includes phenyl, naphthyl,

anthracenyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, fluorenyl, phenanthrenyl, biphenylenyl, indanyl, indenyl and the like.

[00148] The term “5-HT_{2A} receptor”, as used herein, refers to a subclass of a family of receptors for the neurotransmitter and peripheral signal mediator serotonin. 5-HT_{2A} receptors can mediate a plurality of central and peripheral physiologic functions of serotonin. Central nervous system effects can include mediation of hallucinogenic effects of hallucinogenic compounds.

[00149] The term “modulating 5-HT_{2A} receptors”, as used herein, refers to the ability of a compound disclosed herein to alter the function of 5-HT_{2A} receptors.

A 5-HT_{2A} receptor modulator may activate the activity of a 5-HT_{2A} receptor, may activate or inhibit the activity of a 5-HT_{2A} receptor depending on the concentration of the compound exposed to the 5-HT_{2A} receptor, or may inhibit the activity of a 5-HT_{2A} receptor. Such activation or inhibition may be contingent on the occurrence of a specific event, such as activation of a signal transduction pathway, and/or maybe manifest only in particular cell types. The term “modulating 5-HT_{2A} receptors,” also refers to altering the function of a 5-HT_{2A} receptor by increasing or decreasing the probability that a complex forms between a 5-HT_{2A} receptor and a natural binding partner to form a multimer. A 5-HT_{2A} receptor modulator may increase the probability that such a complex forms between the 5-HT_{2A} receptor and the natural binding partner, may increase or decrease the probability that a complex forms between the 5-HT_{2A} receptor and the natural binding partner depending on the concentration of the compound exposed to the 5-HT_{2A} receptor, and or may decrease the probability that a complex forms between the 5-HT_{2A} receptor and the natural binding partner. Furthermore, the term includes allosteric modulation of the receptor 5-HT_{2A}, *i.e.* modulation of the 5-HT_{2A} receptor through interaction with the 5-HT_{2A} receptor that is topographically different than the orthosteric site recognized by the cell’s endogenous agonist, such modulation further including positive allosteric modulation (PAM), negative allosteric modulation (NAM) and silent allosteric modulation (SAM).

[00150] The term “5-HT_{2A} receptor-mediated disorder”, as used herein, refers to a disorder that is characterized by abnormal 5-HT_{2A} receptor activity. A 5-HT_{2A} receptor-mediated disorder may be completely or partially mediated by modulating 5-HT_{2A} receptors. In particular, a 5-HT_{2A} receptor-mediated disorder is one in which modulation of 5-HT_{2A} receptors results in some effect on the

underlying disorder e.g., administration of a 5-HT_{2A} receptor modulator results in some improvement in at least some of the subjects being treated.

[00151] The term “pharmaceutical formulation”, as used herein, refers to a preparation in a form which allows an active ingredient, including a psychoactive ingredient, contained therein to provide effective treatment, and which does not contain any other ingredients which cause excessive toxicity, an allergic response, irritation, or other adverse response commensurate with a reasonable risk/benefit ratio. The pharmaceutical formulation may contain other pharmaceutical ingredients such as excipients, carriers, diluents, or auxiliary agents.

[00152] The term “recreational drug formulation”, as used herein, refers to a preparation in a form which allows a psychoactive ingredient contained therein to be effective for administration as a recreational drug, and which does not contain any other ingredients which cause excessive toxicity, an allergic response, irritation, or other adverse response commensurate with a reasonable risk/benefit ratio. The recreational drug formulation may contain other ingredients such as excipients, carriers, diluents, or auxiliary agents.

[00153] The term “effective for administration as a recreational drug”, as used herein, refers to a preparation in a form which allows a subject to voluntarily induce a psychoactive effect for non-medical purposes upon administration, generally in the form of self-administration. The effect may include an altered state of consciousness, satisfaction, pleasure, euphoria, perceptual distortion, or hallucination.

[00154] The term “effective amount”, as used herein, refers to an amount of an active agent, pharmaceutical formulation or recreational drug formulation, sufficient to induce a desired biological or therapeutic effect, including a prophylactic effect, and further including a psychoactive effect. Such effect can include an effect with respect to the signs, symptoms or causes of a disorder, or disease or any other desired alteration of a biological system. The effective amount can vary depending, for example, on the health condition, injury stage, disorder stage, or disease stage, weight, or sex of a subject being treated, timing of the administration, manner of the administration, age of the subject, and the like, all of which can be determined by those of skill in the art.

[00155] The terms “treating” and “treatment”, and the like, as used herein, are intended to mean obtaining a desirable physiological, pharmacological, or

biological effect, and includes prophylactic and therapeutic treatment. The effect may result in the inhibition, attenuation, amelioration, or reversal of a sign, symptom or cause of a disorder, or disease, attributable to the disorder, or disease, which includes mental and psychiatric diseases and disorders. Clinical evidence
5 of the prevention or treatment may vary with the disorder, or disease, the subject and the selected treatment.

[00156] The term “pharmaceutically acceptable”, as used herein, refers to materials, including excipients, carriers, diluents, or auxiliary agents, that are compatible with other materials in a pharmaceutical or recreational drug
10 formulation and within the scope of reasonable medical judgement suitable for use in contact with a subject without excessive toxicity, allergic response, irritation, or other adverse response commensurate with a reasonable risk/benefit ratio.

[00157] The term “psilocybin biosynthetic enzyme complement”, as used herein, refers to one or more polypeptides which alone or together are capable of
15 facilitating the chemical conversion of a psilocybin precursor compound and form another psilocybin precursor compound or psilocybin or a halogenated form thereof. A psilocybin biosynthetic enzyme complement can include, for example, PsiD, PsiH, PsiK, PsiM, Psi-ncAAAD and TrpB.

[00158] The term “PsiD” as used herein, refers to any and all enzymes
20 comprising a sequence of amino acid residues which is (i) substantially identical to the amino acid sequences constituting any PsiD polypeptide set forth herein, including, for example, SEQ.ID NO: 2, SEQ.ID NO: 37, SEQ.ID NO: 39, SEQ.ID NO: 41, SEQ.ID NO: 43, SEQ.ID NO: 45, SEQ.ID NO: 47, SEQ.ID NO: 49, SEQ.ID NO: 51, SEQ.ID NO: 53, SEQ.ID NO: 55, and SEQ.ID NO: 57 or (ii) encoded by a
25 nucleic acid sequence capable of hybridizing under at least moderately stringent conditions to any nucleic acid sequence encoding any PsiD set forth herein, but for the use of synonymous codons.

[00159] The term “PsiH” as used herein, refers to any and all enzymes
30 comprising a sequence of amino acid residues which is (i) substantially identical to the amino acid sequences constituting any PsiH polypeptide set forth herein, including, for example, SEQ.ID NO: 4, or (ii) encoded by a nucleic acid sequence capable of hybridizing under at least moderately stringent conditions to any nucleic acid sequence encoding any PsiH set forth herein, but for the use of synonymous codons.

[00160] The term “PsiK” as used herein, refers to any and all enzymes comprising a sequence of amino acid residues which is (i) substantially identical to the amino acid sequences constituting any PsiK polypeptide set forth herein, including, for example, SEQ.ID NO: 6, or (ii) encoded by a nucleic acid sequence capable of hybridizing under at least moderately stringent conditions to any nucleic acid sequence encoding any PsiK set forth herein, but for the use of synonymous codons.

[00161] The term “PsiM” as used herein, refers to any and all enzymes comprising a sequence of amino acid residues which is (i) substantially identical to the amino acid sequences constituting any PsiM polypeptide set forth herein, including, for example, SEQ.ID NO: 8, and SEQ.ID NO: 59 or (ii) encoded by a nucleic acid sequence capable of hybridizing under at least moderately stringent conditions to any nucleic acid sequence encoding any PsiM set forth herein, but for the use of synonymous codons.

[00162] The term “Psi-ncAAAD” as used herein, refers to any and all enzymes comprising a sequence of amino acid residues which is (i) substantially identical to the amino acid sequences constituting any Psi-ncAAAD polypeptide set forth herein, including, for example, SEQ.ID NO: 10, or (ii) encoded by a nucleic acid sequence capable of hybridizing under at least moderately stringent conditions to any nucleic acid sequence encoding any Psi-ncAAAD set forth herein, but for the use of synonymous codons.

[00163] The term “TrpB” as used herein, refers to any and all enzymes comprising a sequence of amino acid residues which is (i) substantially identical to the amino acid sequences constituting any TrpB polypeptide set forth herein, including, for example, SEQ.ID NO: 12, SEQ.ID NO: 65, SEQ.ID NO: 67, SEQ.ID NO: 69, SEQ.ID NO: 71, and SEQ.ID NO: 73, or (ii) encoded by a nucleic acid sequence capable of hybridizing under at least moderately stringent conditions to any nucleic acid sequence encoding any TrpB set forth herein, but for the use of synonymous codons.

[00164] The term “halogenase”, as used herein, refers to any and all enzymes comprising a sequence of amino acid residues which is (i) substantially identical to the amino acid sequences constituting any halogenase polypeptide set forth herein, including, for example, SEQ.ID NO: 14, or (ii) encoded by a nucleic acid sequence capable of hybridizing under at least moderately stringent

conditions to any nucleic acid sequence encoding any halogenase set forth herein, but for the use of synonymous codons.

[00165] The term “acetyl transferase”, as used herein, refers to any and all enzymes comprising a sequence of amino acid residues which is (i) substantially identical to the amino acid sequences constituting any acetyl transferase polypeptide set forth herein, including, for example, SEQ.ID NO: 63, or (ii) encoded by a nucleic acid sequence capable of hybridizing under at least moderately stringent conditions to any nucleic acid sequence encoding any acetyl transferase set forth herein, but for the use of synonymous codons.

[00166] The terms “nucleic acid sequence encoding PsiD”, and “nucleic acid sequence encoding a PsiD polypeptide”, as may be used interchangeably herein, refer to any and all nucleic acid sequences encoding a PsiD polypeptide, including, for example, SEQ.ID NO: 1, SEQ.ID NO: 36, SEQ.ID NO: 38, SEQ.ID NO: 40, SEQ.ID NO: 42, SEQ.ID NO: 44, SEQ.ID NO: 46, SEQ.ID NO: 48, SEQ.ID NO: 50, SEQ.ID NO: 52, SEQ.ID NO: 54, and SEQ.ID NO: 56. Nucleic acid sequences encoding a PsiD polypeptide further include any and all nucleic acid sequences which (i) encode polypeptides that are substantially identical to the PsiD polypeptide sequences set forth herein; or (ii) hybridize to any PsiD nucleic acid sequences set forth herein under at least moderately stringent hybridization conditions or which would hybridize thereto under at least moderately stringent conditions but for the use of synonymous codons.

[00167] The terms “nucleic acid sequence encoding PsiH”, and “nucleic acid sequence encoding a PsiH polypeptide”, as may be used interchangeably herein, refer to any and all nucleic acid sequences encoding a PsiH polypeptide, including, for example, SEQ.ID NO: 3. Nucleic acid sequences encoding a PsiH polypeptide further include any and all nucleic acid sequences which (i) encode polypeptides that are substantially identical to the PsiH polypeptide sequences set forth herein; or (ii) hybridize to any PsiH nucleic acid sequences set forth herein under at least moderately stringent hybridization conditions or which would hybridize thereto under at least moderately stringent conditions but for the use of synonymous codons.

[00168] The terms “nucleic acid sequence encoding PsiK”, and “nucleic acid sequence encoding a PsiK polypeptide”, as may be used interchangeably herein, refer to any and all nucleic acid sequences encoding a PsiK polypeptide, including,

for example, SEQ.ID NO: 5. Nucleic acid sequences encoding a PsiK polypeptide further include any and all nucleic acid sequences which (i) encode polypeptides that are substantially identical to the PsiK polypeptide sequences set forth herein; or (ii) hybridize to any PsiK nucleic acid sequences set forth herein under at least moderately stringent hybridization conditions or which would hybridize thereto under at least moderately stringent conditions but for the use of synonymous codons.

[00169] The terms “nucleic acid sequence encoding PsiM”, and “nucleic acid sequence encoding a PsiM polypeptide”, as may be used interchangeably herein, refer to any and all nucleic acid sequences encoding a PsiD polypeptide, including, for example, SEQ.ID NO: 7 SEQ.ID NO: 58 and SEQ.ID NO: 61. Nucleic acid sequences encoding a PsiM polypeptide further include any and all nucleic acid sequences which (i) encode polypeptides that are substantially identical to the PsiM polypeptide sequences set forth herein; or (ii) hybridize to any PsiM nucleic acid sequences set forth herein under at least moderately stringent hybridization conditions or which would hybridize thereto under at least moderately stringent conditions but for the use of synonymous codons.

[00170] The terms “nucleic acid sequence encoding Psi-ncAAAD”, and “nucleic acid sequence encoding a Psi-ncAAAD polypeptide”, as may be used interchangeably herein, refer to any and all nucleic acid sequences encoding a PsiD polypeptide, including, for example, SEQ.ID NO: 9. Nucleic acid sequences encoding a Psi-ncAAAD polypeptide further include any and all nucleic acid sequences which (i) encode polypeptides that are substantially identical to the Psi-ncAAAD polypeptide sequences set forth herein; or (ii) hybridize to any Psi-ncAAAD nucleic acid sequences set forth herein under at least moderately stringent hybridization conditions or which would hybridize thereto under at least moderately stringent conditions but for the use of synonymous codons.

[00171] The terms “nucleic acid sequence encoding TrpB”, and “nucleic acid sequence encoding a TrpB polypeptide”, as may be used interchangeably herein, refer to any and all nucleic acid sequences encoding a TrpB polypeptide, including, for example, SEQ.ID NO: 11, SEQ.ID NO: 64, SEQ.ID NO: 66, SEQ.ID NO: 68, SEQ.ID NO: 70, and SEQ.ID NO: 72. Nucleic acid sequences encoding a TrpB polypeptide further include any and all nucleic acid sequences which (i) encode polypeptides that are substantially identical to the TrpB polypeptide sequences set

forth herein; or (ii) hybridize to any TrpB nucleic acid sequences set forth herein under at least moderately stringent hybridization conditions or which would hybridize thereto under at least moderately stringent conditions but for the use of synonymous codons.

5 **[00172]** The terms “nucleic acid sequence encoding a halogenase”, and “nucleic acid sequence encoding a halogenase polypeptide”, as may be used interchangeably herein, refer to any and all nucleic acid sequences encoding a halogenase polypeptide, including, for example, SEQ.ID NO: 13. Nucleic acid sequences encoding a halogenase polypeptide further include any and all nucleic acid sequences which (i) encode polypeptides that are substantially identical to the halogenase polypeptide sequences set forth herein; or (ii) hybridize to any halogenase nucleic acid sequences set forth herein under at least moderately stringent hybridization conditions or which would hybridize thereto under at least moderately stringent conditions but for the use of synonymous codons.

10 **[00173]** The terms “nucleic acid sequence encoding an acetyl transferase”, and “nucleic acid sequence encoding an acetyl transferase polypeptide”, as may be used interchangeably herein, refer to any and all nucleic acid sequences encoding an acetyl transferase polypeptide, including, for example, SEQ.ID NO: 62. Nucleic acid sequences encoding an acetyl transferase polypeptide further include any and all nucleic acid sequences which (i) encode polypeptides that are substantially identical to the acetyl transferase polypeptide sequences set forth herein; or (ii) hybridize to any acetyl transferase nucleic acid sequences set forth herein under at least moderately stringent hybridization conditions or which would hybridize thereto under at least moderately stringent conditions but for the use of synonymous codons.

15 **[00174]** The terms “nucleic acid”, or “nucleic acid sequence”, as used herein, refer to a sequence of nucleoside or nucleotide monomers, consisting of naturally occurring bases, sugars and intersugar (backbone) linkages. The term also includes modified or substituted sequences comprising non-naturally occurring monomers or portions thereof. The nucleic acids of the present disclosure may be deoxyribonucleic acids (DNA) or ribonucleic acids (RNA) and may include naturally occurring bases including adenine, guanine, cytosine, thymidine and uracil. The nucleic acids may also contain modified bases. Examples of such modified bases include aza and deaza adenine, guanine, cytosine, thymidine and

uracil, and xanthine and hypoxanthine. A sequence of nucleotide or nucleoside monomers may be referred to as a polynucleotide sequence, nucleic acid sequence, a nucleotide sequence or a nucleoside sequence.

[00175] The term “polypeptide”, as used herein in conjunction with a reference SEQ.ID NO, refers to any and all polypeptides comprising a sequence of amino acid residues which is (i) substantially identical to the amino acid sequence constituting the polypeptide having such reference SEQ.ID NO, or (ii) encoded by a nucleic acid sequence capable of hybridizing under at least moderately stringent conditions to any nucleic acid sequence encoding the polypeptide having such reference SEQ.ID NO, but for the use of synonymous codons. A sequence of amino acid residues may be referred to as an amino acid sequence, or polypeptide sequence.

[00176] The term “nucleic acid sequence encoding a polypeptide”, as used herein in conjunction with a reference SEQ.ID NO, refers to any and all nucleic acid sequences encoding a polypeptide having such reference SEQ.ID NO. Nucleic acid sequences encoding a polypeptide, in conjunction with a reference SEQ.ID NO, further include any and all nucleic acid sequences which (i) encode polypeptides that are substantially identical to the polypeptide having such reference SEQ.ID NO; or (ii) hybridize to any nucleic acid sequences encoding polypeptides having such reference SEQ.ID NO under at least moderately stringent hybridization conditions or which would hybridize thereto under at least moderately stringent conditions but for the use of synonymous codons.

[00177] By the term “substantially identical” it is meant that two amino acid sequences preferably are at least 70% identical, and more preferably are at least 85% identical and most preferably at least 95% identical, for example 96%, 97%, 98% or 99% identical. In order to determine the percentage of identity between two amino acid sequences the amino acid sequences of such two sequences are aligned, using for example the alignment method of Needleman and Wunsch (J. Mol. Biol., 1970, 48: 443), as revised by Smith and Waterman (Adv. Appl. Math., 1981, 2: 482) so that the highest order match is obtained between the two sequences and the number of identical amino acids is determined between the two sequences. Methods to calculate the percentage identity between two amino acid sequences are generally art recognized and include, for example, those described by Carillo and Lipton (SIAM J. Applied Math., 1988, 48:1073) and those

described in Computational Molecular Biology, Lesk, e.d. Oxford University Press, New York, 1988, Biocomputing: Informatics and Genomics Projects. Generally, computer programs will be employed for such calculations. Computer programs that may be used in this regard include, but are not limited to, GCG (Devereux *et al.*, Nucleic Acids Res., 1984, 12: 387) BLASTP, BLASTN and FASTA (Altschul *et al.*, J. Mol. Biol., 1990:215:403). A particularly preferred method for determining the percentage identity between two polypeptides involves the Clustal W algorithm (Thompson, J D, Higgins, D G and Gibson T J, 1994, Nucleic Acid Res 22(22): 4673-4680 together with the BLOSUM 62 scoring matrix (Henikoff S & Henikoff, J G, 1992, Proc. Natl. Acad. Sci. USA 89: 10915-10919 using a gap opening penalty of 10 and a gap extension penalty of 0.1, so that the highest order match obtained between two sequences wherein at least 50% of the total length of one of the two sequences is involved in the alignment.

[00178] By "at least moderately stringent hybridization conditions" it is meant that conditions are selected which promote selective hybridization between two complementary nucleic acid molecules in solution. Hybridization may occur to all or a portion of a nucleic acid sequence molecule. The hybridizing portion is typically at least 15 (*e.g.* 20, 25, 30, 40 or 50) nucleotides in length. Those skilled in the art will recognize that the stability of a nucleic acid duplex, or hybrids, is determined by the T_m , which in sodium containing buffers is a function of the sodium ion concentration and temperature ($T_m = 81.5^\circ \text{C} - 16.6 (\text{Log}_{10} [\text{Na}^+]) + 0.41(\% (\text{G} + \text{C}) - 600/\text{l})$, or similar equation). Accordingly, the parameters in the wash conditions that determine hybrid stability are sodium ion concentration and temperature. In order to identify molecules that are similar, but not identical, to a known nucleic acid molecule a 1% mismatch may be assumed to result in about a 1°C . decrease in T_m , for example if nucleic acid molecules are sought that have a >95% identity, the final wash temperature will be reduced by about 5°C . Based on these considerations those skilled in the art will be able to readily select appropriate hybridization conditions. In preferred embodiments, stringent hybridization conditions are selected. By way of example the following conditions may be employed to achieve stringent hybridization: hybridization at $5\times$ sodium chloride/sodium citrate (SSC)/ $5\times$ Denhardt's solution/1.0% SDS at T_m (based on the above equation) -5°C , followed by a wash of $0.2\times \text{SSC}/0.1\% \text{SDS}$ at 60°C . Moderately stringent hybridization conditions include a washing step in $3\times \text{SSC}$ at

42° C. It is understood however that equivalent stringencies may be achieved using alternative buffers, salts and temperatures. Additional guidance regarding hybridization conditions may be found in: Current Protocols in Molecular Biology, John Wiley & Sons, N.Y., 1989, 6.3.1.-6.3.6 and in: Sambrook *et al.*, Molecular Cloning, a Laboratory Manual, Cold Spring Harbor Laboratory Press, 1989, Vol. 3.

[00179] The term “functional variant”, as used herein in reference to polynucleotides or polypeptides, refers to polynucleotides or polypeptides capable of performing the same function as a noted reference polynucleotide or polypeptide. Thus, for example, a functional variant of the polypeptide set forth in SEQ.ID NO: 2, refers to a polypeptide capable of performing the same function as the polypeptide set forth in SEQ.ID NO: 2. Functional variants include modified a polypeptide wherein, relative to a noted reference polypeptide, the modification includes a substitution, deletion or addition of one or more amino acids. In some embodiments, substitutions are those that result in a replacement of one amino acid with an amino acid having similar characteristics. Such substitutions include, without limitation (i) glutamic acid and aspartic acid; (ii) alanine, serine, and threonine; (iii) isoleucine, leucine and valine, (iv) asparagine and glutamine, and (v) tryptophan, tyrosine and phenylalanine. Functional variants further include polypeptides having retained or exhibiting an enhanced psilocybin biosynthetic bioactivity.

[00180] The term “chimeric”, as used herein in the context of nucleic acids, refers to at least two linked nucleic acids which are not naturally linked. Chimeric nucleic acids include linked nucleic acids of different natural origins. For example, a nucleic acid constituting a microbial promoter linked to a nucleic acid encoding a plant polypeptide is considered chimeric. Chimeric nucleic acids also may comprise nucleic acids of the same natural origin, provided they are not naturally linked. For example a nucleic acid constituting a promoter obtained from a particular cell-type may be linked to a nucleic acid encoding a polypeptide obtained from that same cell-type, but not normally linked to the nucleic acid constituting the promoter. Chimeric nucleic acids also include nucleic acids comprising any naturally occurring nucleic acids linked to any non-naturally occurring nucleic acids.

[00181] The terms “substantially pure” and “isolated”, as used herein, as may be used interchangeably herein describe a compound, e.g., a secondary

metabolite, psilocybin or a psilocybin derivative, polynucleotide or a polypeptide, which has been separated from components that naturally accompany it. Typically, a compound is substantially pure when at least 60%, more preferably at least 75%, more preferably at least 90%, 95%, 96%, 97%, or 98%, and most preferably at least 99% of the total material (by volume, by wet or dry weight, or by mole percent or mole fraction) in a sample is the compound of interest. Purity can be measured by any appropriate method, e.g., in the case of polypeptides, by chromatography, gel electrophoresis or HPLC analysis.

[00182] The term “recovered” as used herein in association with an enzyme, protein, a secondary metabolite or a chemical compound, refers to a more or less pure form of the enzyme, protein, secondary metabolite, or chemical compound.

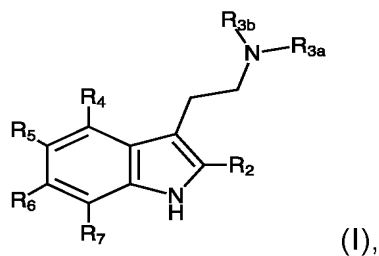
General Implementation

[00183] As hereinbefore mentioned, the present disclosure relates to psilocybin derivatives. In particular, the present disclosure provides novel halogenated psilocybin derivatives. In general, the herein provided compositions exhibit functional properties which deviate from the functional properties of psilocybin. Thus, for example, the psilocybin derivatives, can exhibit pharmacological properties which deviate from psilocybin. The halogenated psilocybin derivatives in this respect are useful in the formulation of pharmaceutical and recreation drug formulations. Furthermore, the halogenated psilocybin derivatives of the present disclosure may be used as a feedstock material for deriving further psilocybin derivatives. In one embodiment, the halogenated psilocybin derivatives of the present disclosure can conveniently be biosynthetically produced. The practice of this method avoids the extraction of psilocybin from mushrooms and the performance of subsequent chemical reactions to achieve halogenation. Furthermore, the growth of mushrooms can be avoided thus limiting the dependence on climate and weather, and potential legal and social challenges associated with the cultivation of mushrooms containing psychoactive compounds. The method can efficiently yield substantial quantities of halogenated psilocybin derivatives.

[00184] In what follows selected embodiments are described with reference to the drawings.

[00185] Initially various halogenated psilocybin derivatives will be described. Thereafter methods example methods of using and making the halogenated psilocybin derivatives will be described

[00186] In at least one aspect, and in at least one example embodiment, the present disclosure provides a chemical compound or salts thereof having the formula (I):



wherein, at least one of R₂, R₄, R₅, R₆ or R₇ is a halogen atom, wherein each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom, wherein R₄ when it is not halogenated is a phosphate group or a hydrogen atom, and wherein R_{3A} and R_{3B} are a hydrogen atom, an alkyl group, an aryl group or an acyl group.

[00187] It is noted that in reference to the indole prototype structure shown in **FIG. 2** carbon atoms C₂, C₄, C₅, C₆ and C₇ are bonded to R₂, R₄, R₅, R₆ and R₇, respectively. Furthermore, R_{3A} and R_{3B} reference chemical groups extending from the ethyl-amino group extending in turn from carbon atom C₃ of the prototype indole structure.

[00188] Referring to the chemical compound having formula (I), In one embodiment, one of R₂, R₄, R₅, R₆ and R₇ can be a halogen atom. Thus, in one embodiment, R₂ can be a bromine, chlorine, fluorine or iodine atom, each of R₅, R₆ and R₇ can be a hydrogen atom or an alkyl group or O-alkyl group, and R₄, when it is not a halogen atom, can be a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivatives shown in **FIG. 4A** (R₂ is chlorine; R₄ is a phosphate group; R₅, R₆ and R₇ are each a hydrogen atom; R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group); **FIG. 4B** (R₂ is bromine; R₄, R₅, R₆ and R₇ are each a hydrogen atom; R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group); **FIG. 4K** (R₂ is chlorine; R₄ is a methyl group; R₅, R₆ and R₇ are each a hydrogen atom; R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group,

or an acyl group); and **FIG. 4O** (R_2 is chlorine; R_4 is an O-methyl group; R_5 , R_6 and R_7 are each a hydrogen atom; R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group)).

[00189] Continuing to refer to the chemical compound having formula (I), in

5 one embodiment, R_4 can be a bromine, chlorine, fluorine or iodine atom, and each of R_2 , R_5 , R_6 and R_7 can be a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivatives shown in **FIG. 4C** (R_4 is iodine; R_2 , R_5 , R_6 and R_7 are each a hydrogen atom; R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group); **FIG. 4D** (R_4 is fluorine; R_2 , R_5 , R_6 and R_7 are each a hydrogen atom; R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group))

[00190] Continuing to refer to the chemical compound having formula (I), in

one embodiment, R_5 can be a bromine, chlorine, fluorine or iodine atom, and each of R_2 , R_6 and R_7 can be a hydrogen atom or an alkyl group or O-alkyl group, and R_4 can be a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivatives shown in **FIG. 4E** (R_5 is fluorine; R_4 is a phosphate group; R_2 , R_6 and R_7 are each a hydrogen atom; R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group); **FIG. 4F** (R_5 is chlorine; R_2 , R_4 , R_6 and R_7 are each a hydrogen atom; R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group); **FIG. 4L** (R_5 is bromine; R_4 is an ethyl group; R_2 , R_6 and R_7 are each a hydrogen atom; R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group); and **FIG. 4P** (R_5 is bromine; R_2 , R_6 and R_7 are each a hydrogen atom; R_4 is an O-ethyl group; R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group)).

[00191] Continuing to refer to the chemical compound having formula (I), in

one embodiment, R_6 can be a bromine, chlorine, fluorine or iodine atom, and each of R_2 , R_5 and R_7 can be a hydrogen atom or an alkyl group or O-alkyl group, and R_4 can be a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivatives shown in **FIG. 4G** (R_6 is bromine; R_4 is a phosphate group; R_2 , R_5 and R_7 are each a hydrogen atom; R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group); **FIG. 4H** (R_6 is chlorine; R_2 , R_4 , R_5 and R_7 are each a hydrogen atom; R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group); **FIG. 4M** (R_6 is

fluorine; R₄ is a methyl group; R₂, R₅ and R₇ are each a hydrogen atom; R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group); and **FIG. 4Q** (R₆ is fluorine; R₂, R₅ and R₇ are each a hydrogen atom; R₄ is an O-methyl group; R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group)).

[00192] Continuing to refer to the chemical compound having formula (I), in one embodiment, R₇ can be a bromine, chlorine, fluorine or iodine atom, and each of R₂, R₅ and R₆ can be a hydrogen atom or an alkyl group or O-alkyl group, and R₄ can be a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivatives shown in **FIG. 4I** (R₇ is fluorine; R₄ is a phosphate group; R₂, R₅ and R₆ are each a hydrogen atom R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group); **FIG. 4J** (R₇ is iodine; R₂, R₄, R₅ and R₆ are each a hydrogen atom; R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group); **FIG. 4N** (R₇ is iodine; R₄ is a propyl group; R₂, R₅ and R₆ are each a hydrogen atom R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group); and **FIG. 4R** (R₇ is iodine; R₂, R₅ and R₆ are each a hydrogen atom; R₄ is an O-propyl group; R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group)).

[00193] Still, continuing to refer to the chemical compound having formula (I), in one embodiment, two of R₂, R₄, R₅, R₆ and R₇ can be a halogen atom, wherein the halogen atoms are independently selected from a bromine, chlorine fluorine or iodine atom, and wherein each non-halogenated R₂, R₅, R₆ and R₇ is a hydrogen atom or an alkyl group or O-alkyl group, and wherein R₄, when it is not a halogen atom, is a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group.

[00194] Thus, continuing to refer to the chemical compound having formula (I), in one embodiment, R₂ and R₄ can be halogen atoms, wherein the halogen atoms are independently selected from a bromine, chlorine fluorine or iodine atom, and R₅, R₆ and R₇ can be a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivative shown in **FIG. 5A** (R₂ is a chlorine atom; R₄ is a chlorine atom; R₅, R₆ and R₇ are each a hydrogen atom; and R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group)).

[00195] Continuing to refer to the chemical compound having formula (I), in one embodiment, R₂ and R₅ can be halogen atoms, wherein the halogen atoms

are independently selected from a bromine, chlorine fluorine or iodine atom, and R₆ and R₇ can be a hydrogen atom or an alkyl group or O-alkyl group and R₄ can be a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivative shown in **FIG. 5B** (R₂ is a bromine atom; R₅ is a fluorine atom; R₄, and R₆ are each a hydrogen atom and R₇ is a methyl group; and R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group)).

[00196] Continuing to refer to the chemical compound having formula (I), in one embodiment, R₂ and R₆ can be halogen atoms, wherein the halogen atoms are independently selected from a bromine, chlorine fluorine or iodine atom, and R₅ and R₇ can be a hydrogen atom or an alkyl group or O-alkyl group, and R₄ can be a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivative shown in **FIG. 5C** (R₂ is a chlorine atom; R₆ is a bromine atom; R₅ and R₇ are each a hydrogen atom; R₄ is an O-methyl group; and R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group)).

[00197] Continuing to refer to the chemical compound having formula (I), in one embodiment, R₂ and R₇ can be halogen atoms, wherein the halogen atoms are independently selected from a bromine, chlorine fluorine or iodine atom, and R₅ and R₆ can be a hydrogen atom or an alkyl group or O-alkyl group and R₄ can be a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivative shown in **FIG. 5D** (R₂ is a fluorine atom; R₇ is an iodine atom; R₄ is a phosphate, R₅ and R₆ are each a hydrogen atom; and R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group)).

[00198] Continuing to refer to the chemical compound having formula (I), in one embodiment, R₄ and R₅ can be halogen atoms, wherein the halogen atoms are independently selected from a bromine, chlorine fluorine or iodine atom, and R₂, R₆ and R₇ can be a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivative shown in **FIG. 5E** (R₄ and R₅ are each bromine atoms; R₂, R₆ and R₇ are each a hydrogen atom; and R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group)).

[00199] Continuing to refer to the chemical compound having formula (I), in one embodiment, R₄ and R₆ can be halogen atoms, wherein the halogen atoms

are independently selected from a bromine, chlorine fluorine or iodine atom, and R₂, R₅ and R₇ can be a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivative shown in **FIG. 5F** (R₄ and R₆ are each chlorine atoms; R₂, R₅ and R₇ are each a hydrogen atom; and R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group)).

[00200] Continuing to refer to the chemical compound having formula (I), in one embodiment, R₄ and R₇ can be halogen atoms, wherein the halogen atoms are independently selected from a bromine, chlorine fluorine or iodine atom, and R₂, R₅ and R₆ can be a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivative shown in **FIG. 5G** (R₄ is a chlorine atom; R₇ is a fluorine atom; R₂, R₅ and R₆ are each a hydrogen atom; and R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group)).

[00201] Continuing to refer to the chemical compound having formula (I), in one embodiment, R₅ and R₆ can be halogen atoms, wherein the halogen atoms are independently selected from a bromine, chlorine fluorine or iodine atom, and R₂ and R₇ can be a hydrogen atom or an alkyl group or O-alkyl group and R₄ can be a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivative shown in **FIG. 5H** (R₅ is a fluorine atom; R₆ is a bromine atom; R₄ is a phosphate group, R₂ and R₇ are each a hydrogen atom; and R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group)).

[00202] Continuing to refer to the chemical compound having formula (I), in one embodiment, R₅ and R₇ can be halogen atoms, wherein the halogen atoms are independently selected from a bromine, chlorine fluorine or iodine atom, and R₂ and R₆ can be a hydrogen atom or an alkyl group or O-alkyl group and R₄ can be a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivative shown in **FIG. 5I** (R₅ and R₇ are each fluorine atoms; R₄ is a phosphate group, R₂ and R₆ are each a hydrogen atom; and R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group)).

[00203] Continuing to refer to the chemical compound having formula (I), in one embodiment, R₆ and R₇ can be halogen atoms, wherein the halogen atoms are independently selected from a bromine, chlorine fluorine or iodine atom, and R₂ and R₅ can be a hydrogen atom or an alkyl group or O-alkyl group and R₄ can

be a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivative shown in **FIG. 5J** (R₆ and R₇ are each iodine atoms; R₂, R₄ and R₅ are each a hydrogen atom; and R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group)).

5 **[00204]** In one embodiment, two of R₂, R₄, R₅, R₆ and R₇ can be a halogen atom, and the halogen atoms are identical, the remaining of R₂, R₅, R₆, and R₇ being a hydrogen atom or an alkyl group or O-alkyl group, and R₄ when it is not a halogen atom, being a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group (see: e.g. the halogenated psilocybin derivatives shown in **FIGS. 5A**,
10 **5E**, **5F**, **5I** and **5J**).

[00205] In one embodiment, two of R₂, R₄, R₅, R₆ and R₇ can be a halogen atom, and the halogen atoms are non-identical, the remaining of R₂, R₅, R₆, and R₇ being a hydrogen atom or an alkyl group or O-alkyl group, and R₄ when it is not a halogen atom, being a phosphate, a hydrogen atom or an alkyl group or O-alkyl
15 group (see: e.g. the halogenated psilocybin derivatives shown in **FIGS. 5B**, **5C**, **5D**, **5G** and **5H**).

[00206] Still continuing to refer to the chemical compound having formula (I), In one further embodiment, three of R₂, R₄, R₅, R₆ and R₇ can be a halogen atom, wherein the halogen atoms are independently selected from a bromine, chlorine fluorine or iodine atom, and wherein the non-halogenated R₂, R₅, R₆, or
20 R₇ is a hydrogen atom or an alkyl group or O-alkyl group, and wherein R₄, when it is not a halogen atom, is a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group.

[00207] Thus, continuing to refer to the chemical compound having formula (I), in one embodiment R₂, R₄, and R₅ can be halogen atom, wherein the halogen atoms are independently selected from a bromine, chlorine fluorine or iodine atom, and R₆ and R₇ can be a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivative shown in **FIG. 6A** (R₂, R₄ and R₅
25 are each chlorine atoms; R₆ and R₇ are each a hydrogen atom; and R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group)).

[00208] Continuing to refer to the chemical compound having formula (I), in one embodiment R₂, R₅, and R₆ can be halogen atom, wherein the halogen atoms are independently selected from a bromine, chlorine fluorine or iodine atom and R₇ can be a hydrogen atom or an alkyl group or O-alkyl group, and R₄ can a

phosphate group, a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivative shown in **FIG. 6B** (R_2 is a bromine atom, R_5 and R_6 are each fluorine atoms; R_4 and R_7 are each a hydrogen atom; and R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group))).

[00209] Continuing to refer to the chemical compound having formula (I), in one embodiment R_2 , R_5 , and R_7 can be halogen atom, wherein the halogen atoms are independently selected from a bromine, chlorine fluorine or iodine atom and R_6 can be a hydrogen atom or an alkyl group or O-alkyl group, and R_4 can a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivative shown in **FIG. 6C** (R_2 is a chlorine atom, R_5 is a bromine atom, and R_7 is a fluorine atoms; R_4 and R_6 are each a hydrogen atom; and R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group))).

[00210] Continuing to refer to the chemical compound having formula (I), in one embodiment R_4 , R_5 , and R_6 can be halogen atom, wherein the halogen atoms are independently selected from a bromine, chlorine fluorine or iodine atom, and R_2 and R_7 can be a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivative shown in **FIG. 6D** (R_4 and R_5 are each a bromine atom, R_6 is a chlorine atom; R_2 and R_7 are each a hydrogen atom; and R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group))).

[00211] Continuing to refer to the chemical compound having formula (I), in one embodiment R_4 , R_5 , and R_7 can be halogen atom, wherein the halogen atoms are independently selected from a bromine, chlorine fluorine or iodine atom, and R_2 and R_6 can be a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivative shown in **FIG. 6E** (R_4 , R_5 and R_7 are each a bromine atom; R_2 and R_6 are each a hydrogen atom; and R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group))).

[00212] Continuing to refer to the chemical compound having formula (I), in one embodiment R_5 , R_6 , and R_7 can be halogen atom, wherein the halogen atoms are independently selected from a bromine, chlorine fluorine or iodine atom and R_2 can be a hydrogen atom or an alkyl group or O-alkyl group, and R_4 can be a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivative shown in **FIG. 6F** (R_5 is a fluorine atom,

R₆ is a chlorine atom, and R₇ is an iodine atom; R₄ is a phosphate group; R₂ is a hydrogen atom; and R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group)).

5 **[00213]** In one embodiment, three of R₂, R₄, R₅, R₆ and R₇ can be a halogen atom, wherein at least two halogen atoms are identical, the remaining R₂, R₅, R₆, and R₇ being a hydrogen atom or an alkyl group or O-alkyl group, and R₄ when it is not a halogen atom, being a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group (see: e.g. the halogenated psilocybin derivatives shown in **FIGS. 6A, 6B and 6E**).

10 **[00214]** In one embodiment, three of R₂, R₄, R₅, R₆ and R₇ can be a halogen atom, and at least two halogen atoms are non-identical, the remaining R₂, R₅, R₆, and R₇ being a hydrogen atom or an alkyl group or O-alkyl group, and R₄ when it is not a halogen atom, being a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group (see: e.g. the halogenated psilocybin derivatives shown in **FIGS.**
15 **6B, 6C, 6D and 6F**).

[00215] In one embodiment, three of R₂, R₄, R₅, R₆ and R₇ can be a halogen atom, and all three halogen atoms are identical, the remaining R₂, R₅, R₆, or R₇ being a hydrogen atom or an alkyl group or O-alkyl group, and R₄ when it is not a
20 alkyl group (see: e.g. the halogenated psilocybin derivatives shown in **FIGS. 6A and 6E**).

[00216] Still continuing to refer to the chemical compound having formula (I), in one embodiment, four of R₂, R₄, R₅, R₆ and R₇ can be a halogen atom, wherein the halogen atoms are independently selected from a bromine, chlorine fluorine or
25 iodine atom, and wherein the non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom or an alkyl group or O-alkyl group, and wherein R₄, when it is not a halogen, is a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group.

[00217] Thus, continuing to refer to the chemical compound having formula (I), in one embodiment R₂, R₄, R₅ and R₆ can be halogen atom, wherein the
30 halogen atoms are independently selected from a bromine, chlorine fluorine or iodine atom, and R₇ can be a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivative shown in **FIG. 7A** (R₂, R₄, R₅ and R₆ are each chlorine atoms; R₇ is a hydrogen atom; and R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group)).

[00218] Continuing to refer to the chemical compound having formula (I), in one embodiment R₄, R₅, R₆ and R₇ can be halogen atom, wherein the halogen atoms are independently selected from a bromine, chlorine fluorine or iodine atom and R₂ can be a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivative shown in **FIG. 7B** (R₄ and R₇ are chlorine atoms, R₅ and R₆ are each fluorine atoms; R₂ is a hydrogen atom; and R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group)).

[00219] Continuing to refer to the chemical compound having formula (I), in one embodiment R₂, R₅, R₆ and R₇ can be halogen atom, wherein the halogen atoms are independently selected from a bromine, chlorine fluorine or iodine atom and R₄ can be a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivative shown in **FIG. 7C** (R₂ and R₆ are each chlorine atoms, R₅ is a fluorine atom, R₇ is an iodine atom, R₄ is a phosphate group; and R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group)).

[00220] Continuing to refer to the chemical compound having formula (I), in one embodiment R₂, R₄, R₆ and R₇ can be halogen atom, wherein the halogen atoms are independently selected from a bromine, chlorine fluorine or iodine atom and R₅ can be a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivative shown in **FIG. 7D** (R₂, R₄ and R₇ are each bromine atoms, R₆ is a chlorine atom, R₅ is a hydrogen atom; and R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group)).

[00221] In one embodiment R₂, R₄, R₅ and R₇ can be halogen atom, wherein the halogen atoms are independently selected from a bromine, chlorine fluorine or iodine atom and R₆ can be a hydrogen atom or an alkyl group or O-alkyl group (see: the example halogenated psilocybin derivative shown in **FIG. 7E** (R₄, R₅ and R₇ are each bromine atoms, R₂ is a fluorine atom, R₆ is a hydrogen atom; and R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group)).

[00222] In one embodiment, four of R₂, R₄, R₅, R₆ and R₇ can be a halogen atom, wherein at least two halogen atoms are identical, the remaining R₂, R₅, R₆, and R₇ being a hydrogen atom or an alkyl group or O-alkyl group, and R₄ when it is not a halogen atom, being a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group (see: e.g. the halogenated psilocybin derivatives shown in **FIGS. 7A, 7B, 7C, 7D and 7E**).

[00223] In one embodiment, four of R₂, R₄, R₅, R₆ and R₇ can be a halogen atom, and at least two halogen atoms are non-identical, the remaining R₂, R₅, R₆, and R₇ being a hydrogen atom or an alkyl group or O-alkyl group, and R₄ when it is not a halogen atom, being a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group (see: e.g. the halogenated psilocybin derivatives shown in **FIGS. 7B, 7C, 7D** and **7E**).

[00224] In one embodiment, four of R₂, R₄, R₅, R₆ and R₇ can be a halogen atom, and all four halogen atoms are identical, the remaining R₂, R₅, R₆, or R₇ being a hydrogen atom or an alkyl group or O-alkyl group, and R₄ when it is not a halogen atom, being a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group (see: e.g. the halogenated psilocybin derivative shown in **FIGS. 7A**).

[00225] Still continuing to refer to the chemical compound having formula (I), In one embodiment, all five of R₂, R₄, R₅, R₆ and R₇ can be a halogen atom, the halogen selected from bromine, chlorine, fluorine or iodine.

[00226] In one embodiment, all five of R₂, R₄, R₅, R₆ and R₇ can be a halogen atom, and at least two halogen atoms are identical.

[00227] In one embodiment, all five of R₂, R₄, R₅, R₆ and R₇ can be a halogen atom, and at least three halogen atoms are identical.

[00228] In one embodiment, all five of R₂, R₄, R₅, R₆ and R₇ can be a halogen atom, and at least four halogen atoms are identical.

[00229] In one embodiment, all five of R₂, R₄, R₅, R₆ and R₇ can be a halogen atom, and all five halogen atoms are identical.

[00230] In one embodiment, all five of R₂, R₄, R₅, R₆ and R₇ can be a halogen atom, and the chemical compound comprises at least two non-identical halogen atoms.

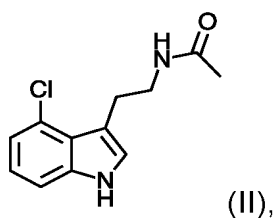
[00231] In one embodiment, all five of R₂, R₄, R₅, R₆ and R₇ can be a halogen atom, and the chemical compound comprises at least three non-identical halogen atoms.

[00232] In one embodiment, all five of R₂, R₄, R₅, R₆ and R₇ can be a halogen atom, and four halogen atoms are non-identical.

[00233] Still continuing to refer to the chemical compound having formula (I), it is noted that, in a further aspect hereof, R_{3A} and R_{3B} can be a hydrogen atom, an alkyl group, an aryl group or an acyl group. Thus, for example, R_{3A} and R_{3B} can each be a hydrogen atom, or R_{3A} and R_{3B} can each be an alkyl group, such as a

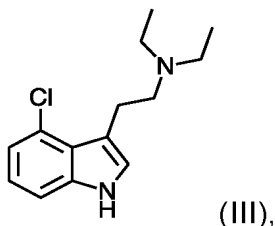
5 methyl group, ethyl group, propyl group, or longer chain alkyl group, or R_{3A} and R_{3B} can each be an aryl group, such as a phenyl group or a naphthyl group, or R_{3A} and R_{3B} can each be an acyl group, such as an acetyl group. Furthermore, one of R_{3A} and R_{3B} can be a hydrogen atom, and one of R_{3A} and R_{3B} can be an alkyl group, and aryl group, or an acyl group. Furthermore, R_{3A} and R_{3B} can be an aryl group and an alkyl group, an aryl group and an acyl group, or an alkyl group and an acyl group.

10 **[00234]** Furthermore, in one embodiment, a psilocybin derivative according to the present disclosure can be a chemical compound having the formula (II):



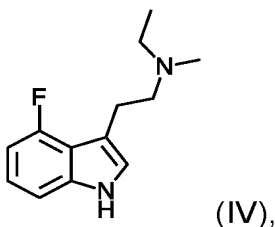
or, a chemical compound having the formula (II), wherein the chlorine is substituted for a bromine, fluorine or iodine.

15 **[00235]** Furthermore, in one embodiment, a psilocybin derivative according to the present disclosure can be a chemical compound having the formula (III):



or, a chemical compound having the formula (III), wherein the chlorine is substituted for a bromine, fluorine or iodine.

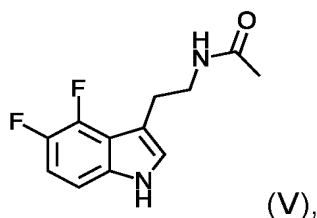
20 **[00236]** Furthermore, in one embodiment, a psilocybin derivative according to the present disclosure can be a chemical compound having the formula (IV):



or, a chemical compound having the formula (IV), wherein the fluorine is substituted for a bromine, chlorine or iodine.

[00237] Furthermore, in one embodiment, a psilocybin derivative according to the present disclosure can be a chemical compound having the formula (V):

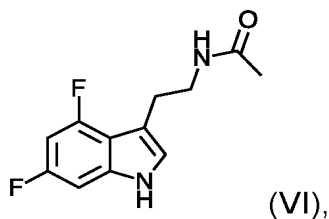
5



or, a chemical compound having the formula (V), wherein one or both of the fluorines are substituted for a bromine, chlorine or iodine.

[00238] Furthermore, in one embodiment, a psilocybin derivative according to the present disclosure can be a chemical compound having the formula (VI):

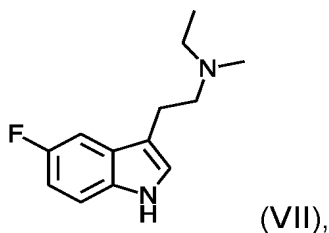
10



or, a chemical compound having the formula (VI), wherein one or both of the fluorines are substituted for a bromine, chlorine or iodine.

[00239] Furthermore, in one embodiment, a psilocybin derivative according to the present disclosure can be a chemical compound having the formula (VII):

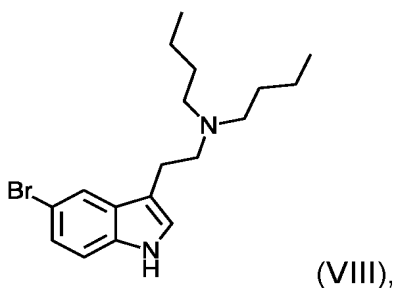
15



or, a chemical compound having the formula (VII), wherein the fluorine is substituted for a bromine, chlorine or iodine.

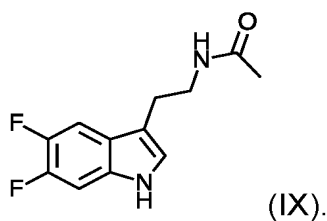
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[00240] Furthermore, in one embodiment, a psilocybin derivative according to the present disclosure can be a chemical compound having the formula (VIII):



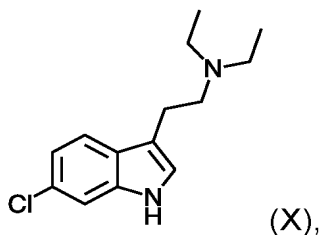
or, a chemical compound having the formula (VIII), wherein the bromine is substituted for a, chlorine, fluorine or iodine.

[00241] Furthermore, in one embodiment, a psilocybin derivative according to the present disclosure can be a chemical compound having the formula (IX):



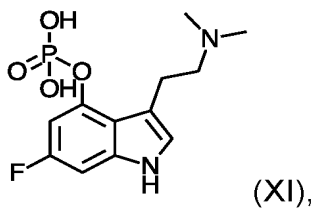
or, a chemical compound having the formula (IX), wherein one or both of the fluorines are substituted for a bromine, chlorine or iodine.

[00242] Furthermore, in one embodiment, a psilocybin derivative according to the present disclosure can be a chemical compound having the formula (X):



or, a chemical compound having the formula (X), wherein the chlorine is substituted for a bromine, chlorine or iodine.

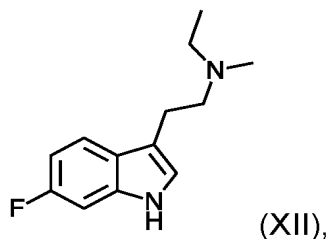
[00243] Furthermore, in one embodiment, a psilocybin derivative according to the present disclosure can be a chemical compound having the formula (XI):



or, a chemical compound having the formula (XI), wherein the fluorine is substituted for a bromine, chlorine or iodine.

[00244] Furthermore, in one embodiment, a psilocybin derivative according to the present disclosure can be a chemical compound having the formula (XII):

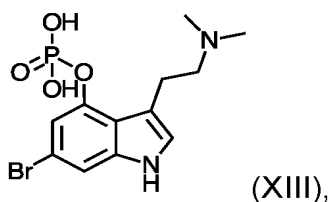
5



or, a chemical compound having the formula (XII), wherein the fluorine is substituted for a bromine, chlorine or iodine.

[00245] Furthermore, in one embodiment, a psilocybin derivative according to the present disclosure can be a chemical compound having the formula (XIII):

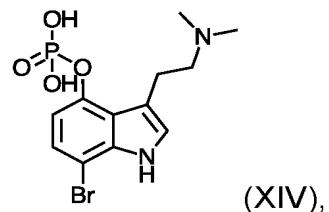
10



or, a chemical compound having the formula (XIII), wherein the bromine is substituted for a chlorine, fluorine or iodine.

[00246] Furthermore, in one embodiment, a psilocybin derivative according to the present disclosure can be a chemical compound having the formula (XIV):

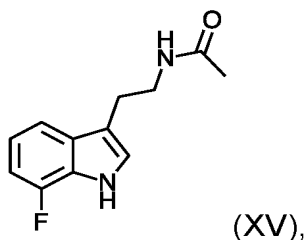
15



or, a chemical compound having the formula (XIV), wherein the bromine is substituted for a chlorine, fluorine or iodine.

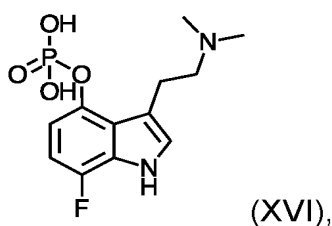
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[00247] Furthermore, in one embodiment, a psilocybin derivative according to the present disclosure can be a chemical compound having the formula (XV):



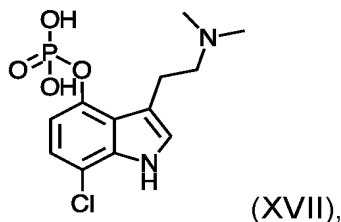
or, a chemical compound having the formula (XV), wherein the fluorine is substituted for a bromine, chlorine or iodine.

[00248] Furthermore, in one embodiment, a psilocybin derivative according to the present disclosure can be a chemical compound having the formula (XVI):



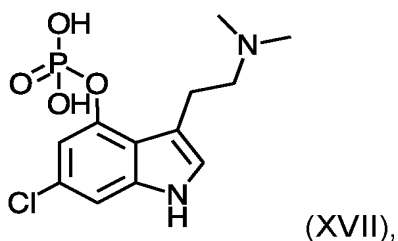
or, a chemical compound having the formula (XV), wherein the fluorine is substituted for a bromine, chlorine or iodine.

[00249] Furthermore, in one embodiment, a psilocybin derivative according to the present disclosure can be a chemical compound having the formula (XVII):



or, a chemical compound having the formula (XVII), wherein the fluorine is substituted for a bromine, chlorine or iodine.

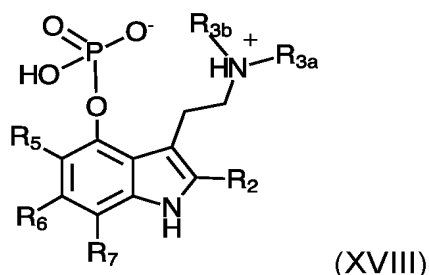
[00250] Furthermore, in one embodiment, a psilocybin derivative according to the present disclosure can be a chemical compound having the formula (XVII):



or, a chemical compound having the formula (XVII), wherein the fluorine is substituted for a bromine, chlorine or iodine.

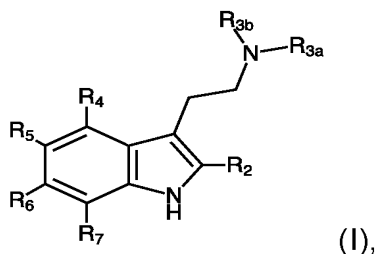
[00251] Furthermore, it is noted that the halogenated psilocybin derivatives of the present disclosure include salts thereof. Thus, the nitrogen atom of the ethyl-amino group extending in turn from the C₃ atom may be protonated, and the positive charge may be balanced by, for example, chloride or sulfate ions, to thereby form a chloride salt or a sulfate salt. Furthermore, in compounds wherein R₄ is a phosphate group, the phosphate group may be de-protonated, and the negative charge may be balanced by, for example, sodium ions or potassium ions, to thereby form a sodium salt or a potassium salt.

[00252] Furthermore, it is noted that when R₄ is a phosphate group, the term halogenated psilocybin derivative also includes compounds having the formula (XVIII):



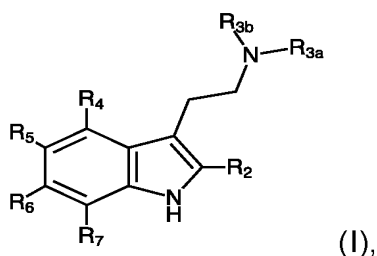
wherein, at least one of R₂, R₅, R₆, or R₇ is a halogen atom or an alkyl group or O-alkyl group, and wherein any R₂, R₅, R₆, or R₇ which are not a halogen is a hydrogen atom, and wherein R_{3A} and R_{3B} are a hydrogen atom, an alkyl group, and aryl group or an acyl group. The term further includes salts, including pharmaceutically acceptable salts, of halogenated psilocybins having the formula (XVIII), such as a sodium salt, a potassium salt *etc.*

[00253] Thus, to briefly recap, the present disclosure provides halogenated psilocybin derivatives. The disclosure provides, in particular, a chemical compound or salts thereof having formula (I):



wherein in an aspect, at least one of R₂, R₄, R₅, R₆, or R₇ is a halogen atom. In an aspect, in formula (I), each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom or an alkyl group or O-alkyl group. In a further aspect, in formula (I), R₄ when it is not halogenated is a hydrogen atom, an alkyl group or O-alkyl group, a hydroxy group, or a phosphate group. Yet in a further aspect, R_{3A} and R_{3B} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group.

[00254] In one embodiment of the disclosure, a chemical compound or salts thereof having formula (I) is included:



wherein at least one of R₂, R₄, R₅, R₆, or R₇ is a halogen atom, and wherein each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom or an alkyl group or O-alkyl group, wherein R₄ when it is not halogenated is a hydrogen atom, alkyl group or O-alkyl group, a hydroxy group, or a phosphate group, and wherein R_{3A} and R_{3B} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group.

[00255] In one embodiment, at least one of R₂, R₄, R₅, R₆, or R₇ is a halogen atom, and wherein each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom or a (C₁-C₂₀)-alkyl group or (C₁-C₂₀)-O-alkyl group. In another embodiment, each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom, a methyl group, ethyl group, a propyl group, an O-methyl group, an O-ethyl group, or an O-propyl group.

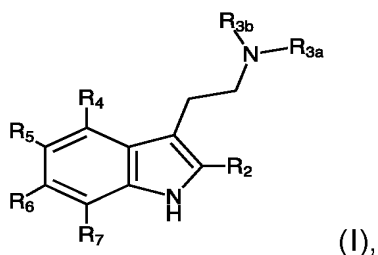
[00256] In another embodiment, each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom or a (C₁-C₁₀)-alkyl group or (C₁-C₁₀)-O-alkyl group. In another embodiment, each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom, a methyl group, ethyl group, a propyl group, an O-methyl group, an O-ethyl group, or an O-propyl group.

[00257] In another embodiment, each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom or a (C₁-C₆)-alkyl group or (C₁-C₆)-O-alkyl group. In another embodiment, each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom, a methyl group, ethyl group, a propyl group, an O-methyl group, an O-ethyl group, or an O-propyl group.

[00258] In another embodiment, when R₄ is not halogenated, R₄ is a hydrogen atom, a (C₁-C₂₀)-alkyl group or (C₁-C₂₀)-O-alkyl group, a hydroxy group, or a phosphate group. In another embodiment, when R₄ is not halogenated, R₄ is a hydrogen atom, a (C₁-C₁₀)-alkyl group or (C₁-C₁₀)-O-alkyl group, a hydroxy group, or a phosphate group. In another embodiment, when R₄ is not halogenated, R₄ is a hydrogen atom, a (C₁-C₆)-alkyl group or (C₁-C₆)-O-alkyl group, a hydroxy group, or a phosphate group. In another embodiment, when R₄ is not halogenated, R₄ is a hydrogen atom, a methyl group, an ethyl group, a propyl group, a phosphate group, an O-methyl group, an O-ethyl group, or an O-propyl group.

[00259] In another embodiment, R_{3A} and R_{3B} are a hydrogen atom, a (C₁-C₂₀)-alkyl group, a (C₆-C₁₄)-aryl group, or a -C(=O)(C₁-C₂₀)-alkyl group. In another embodiment, R_{3A} and R_{3B} are a hydrogen atom, a (C₁-C₁₀)-alkyl group, a (C₆-C₁₀)-aryl group, or a -C(=O)(C₁-C₁₀)-alkyl group. In another embodiment, R_{3A} and R_{3B} are a hydrogen atom, a (C₁-C₆)-alkyl group, a phenyl group, or a -C(=O)(C₁-C₆)-alkyl group. In another embodiment, R_{3A} and R_{3B} are a hydrogen atom, a methyl group, an ethyl group, a propyl group, a phenyl group, -C(=O)-CH₃, -C(=O)-CH₂CH₃, or -C(=O)-CH₂CH₂CH₃.

[00260] In one embodiment of the disclosure, a chemical compound or salts thereof having formula (I) is included:



wherein

R₂, R₅, R₆, and R₇ are independently or simultaneously H, an alkyl group or O-alkyl group or a halogen atom, R_{3A} and R_{3B} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group; and R₄ is hydrogen atom, alkyl group or O-alkyl group, a halogen, a hydroxy group, or a phosphate group; wherein at least one of R₂, R₄, R₅, R₆, and R₇ is a halogen.

[00261] In one embodiment, R₂, R₅, R₆, and R₇ are independently or simultaneously H, (C₁-C₂₀)-alkyl group or (C₁-C₂₀)-O-alkyl group or a halogen atom. In one embodiment, R₂, R₅, R₆, and R₇ are independently or simultaneously

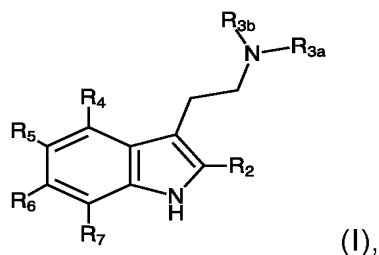
H, (C₁-C₁₀)-alkyl group or (C₁-C₁₀)-O-alkyl group or a halogen atom. In one embodiment, R₂, R₅, R₆, and R₇ are independently or simultaneously H, (C₁-C₆)-alkyl group or (C₁-C₆)-O-alkyl group or a halogen atom. In one embodiment, R₂, R₅, R₆, and R₇ are independently or simultaneously H, methyl, ethyl, propyl, O-methyl, O-ethyl, O-propyl, or a halogen atom.

[00262] In one embodiment, R₄ is H, (C₁-C₂₀)-alkyl group or (C₁-C₂₀)-O-alkyl group, a halogen atom or a phosphate group. In one embodiment, R₄ is H, (C₁-C₁₀)-alkyl group or (C₁-C₁₀)-O-alkyl group, a halogen atom or a phosphate group. In one embodiment, R₄ is H, (C₁-C₆)-alkyl group or (C₁-C₆)-O-alkyl group, a halogen atom, a hydroxy group, or a phosphate group. In one embodiment, R₄ is H, methyl, ethyl, propyl, O-methyl, O-ethyl, O-propyl, a halogen atom, a hydroxy group, or a phosphate group.

[00263] In another embodiment, R_{3A} and R_{3B} are a hydrogen atom independently or simultaneously a (C₁-C₂₀)-alkyl group, a (C₆-C₁₄)-aryl group, or a -C(=O)(C₁-C₂₀)-alkyl group. In another embodiment, R_{3A} and R_{3B} are independently or simultaneously a hydrogen atom, a (C₁-C₁₀)-alkyl group, a (C₆-C₁₀)-aryl group, or a -C(=O)(C₁-C₁₀)-alkyl group or O-alkyl group. In another embodiment, R_{3A} and R_{3B} are independently or simultaneously a hydrogen atom, a (C₁-C₆)-alkyl group, a phenyl group, or a -C(=O)(C₁-C₆)-alkyl group. In another embodiment, R_{3A} and R_{3B} are independently or simultaneously a hydrogen atom, a methyl group, an ethyl group, a propyl group, a butyl group, a phenyl group, -C(=O)-CH₃, -C(=O)-CH₂CH₃, or -C(=O)-CH₂CH₂CH₃.

[00264] The halogenated psilocybin derivatives of the present disclosure may be used to prepare a pharmaceutical or recreational drug formulation. Thus in one embodiment, the present disclosure further provides in another aspect, pharmaceutical and recreational drug formulations comprising halogenated psilocybin derivatives. Accordingly, in one aspect, the present disclosure provides in a further embodiment a pharmaceutical or recreational drug formulation comprising a chemical compound or salts thereof having the formula (I):

30



wherein, at least one of R₂, R₄, R₅, R₆ or R₇ is a halogen atom, wherein each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom or an alkyl group or O-alkyl group, wherein R₄ when it is not halogenated is a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group, and wherein R_{3A} and R_{3B} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group, together with a diluent, carrier or excipient. The pharmaceutical or recreational drug formulations may be prepared as liquids, tablets, capsules, microcapsules, nanocapsules, trans-dermal patches, gels, foams, oils, aerosols, nanoparticulates, powders, creams, emulsions, micellar systems, films, sprays, ovules, infusions, teas, decoctions, suppositories, *etc.* and include a pharmaceutically acceptable salt or solvate of the halogenated psilocybin compound together with an excipient. The term “excipient” as used herein means any ingredient other than the chemical compound of the disclosure. As will readily be appreciated by those of skill in art, the selection of excipient may depend on factors such as the particular mode of administration, the effect of the excipient on solubility of the chemical compounds of the present disclosure and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in “Remington's Pharmaceutical Sciences”, 22nd Edition (Pharmaceutical Press and Philadelphia College of Pharmacy at the University of the Sciences, 2012).

[00265] The dose when using the compounds of the present disclosure can vary within wide limits, and as is customary and is known to those of skill in the art, the dose can be tailored to the individual conditions in each individual case. The dose depends, for example, on the nature and severity of the illness to be treated, on the condition of the patient, on the compound employed or on whether an acute or chronic disease state is treated or prophylaxis is conducted, on the mode of delivery of the compound, or on whether further active compounds are administered in addition to the compounds of the present disclosure.

Representative doses of the present disclosure include, but are not limited to, about 0.001 mg to about 5000 mg, about 0.001 mg to about 2500 mg, about 0.001 mg to about 1000 mg, about 0.001 mg to about 500 mg, about 0.001 mg to about 250 mg, about 0.001 mg to about 100 mg, about 0.001 mg to about 50 mg, and
5 about 0.001 mg to about 25 mg. Representative doses of the present disclosure include, but are not limited to, about 0.0001 to about 1,000 mg, about 10 to about 160 mg, about 10 mg, about 20 mg, about 40 mg, about 80 mg, or about 160 mg. Multiple doses may be administered during the day, especially when relatively large amounts are deemed to be needed, for example 2, 3 or 4, doses. Depending
10 on the subject and as deemed appropriate from the patient's physician or care giver it may be necessary to deviate upward or downward from the doses described herein.

[00266] The pharmaceutical and drug formulations comprising the halogenated psilocybin derivatives of the present disclosure may be administered
15 orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth. Formulations suitable for oral administration include both solid and liquid formulations.

20 **[00267]** Solid formulations include tablets, capsules (containing particulates, liquids, microcapsules, or powders), lozenges (including liquid-filled lozenges), chews, multi- and nano-particulates, gels, solid solutions, liposomal preparations, microencapsulated preparations, creams, films, ovules, suppositories and sprays.

[00268] Liquid formulations include suspensions, solutions, syrups and
25 elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

30 **[00269]** Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose.

[00270] Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

5 **[00271]** Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80. When present, surface active agents may comprise from 0.2% (w/w) to 5% (w/w) of the tablet.

[00272] Tablets may further contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of
10 magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25% (w/w) to 10% (w/w), from 0.5% (w/w) to 3% (w/w) of the tablet.

[00273] In addition to the halogenated psilocybin derivative, tablets may contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose
15 sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 % (w/w) to 25% (w/w) or from 5% (w/w) to 20% (w/w) of the dosage form.

[00274] Other possible auxiliary ingredients include anti-oxidants,
20 colourants, flavouring agents, preservatives and taste-masking agents.

[00275] For tablet dosage forms, depending on the desired effective amount of the chemical compound, the chemical compound of the present disclosure may make up from 1% (w/w) to 80 % (w/w) of the dosage form, more typically from 5% (w/w) to 60% (w/w) of the dosage form.

25 **[00276]** Exemplary tablets contain up to about 80% (w/w) of the chemical compound, from about 10% (w/w) to about 90% (w/w) binder, from about 0% (w/w) to about 85% (w/w) diluent, from about 2% (w/w) to about 10% (w/w) disintegrant, and from about 0.25% (w/w) to about 10% (w/w) lubricant.

[00277] The formulation of tablets is discussed in "Pharmaceutical Dosage
30 Forms: Tablets", Vol. 1 – Vol. 3, by CRC Press (2008).

[00278] The pharmaceutical and recreational drug formulations comprising the halogenated psilocybin derivatives of the present disclosure may also be administered directly into the blood stream, into muscle, or into an internal organ. Thus, the pharmaceutical and recreational drug formulations can be administered

parenterally (for example, by subcutaneous, intravenous, intraarterial, intrathecal, intraventricular, intracranial, intramuscular, or intraperitoneal injection). Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (in one embodiment, to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile water.

[00279] Formulations comprising the halogenated psilocybin derivatives of the present disclosure for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus the chemical compounds of the disclosure may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and poly(DL-lactic-co-glycolic) acid (PLGA) microspheres.

[00280] The pharmaceutical or recreational drug formulations of the present disclosure also may be administered topically to the skin or mucosa, *i.e.* dermally or transdermally. Example pharmaceutical and recreational drug formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, cosmetics, oils, eye drops, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Example carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated (see: for example, Finnin, B. and Morgan, T.M., 1999 J. Pharm. Sci, 88 (10), 955-958).

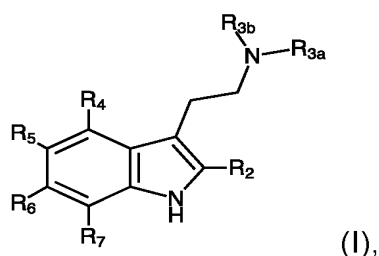
[00281] Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (e.g., Powderject™, Bioject™, etc.) injection.

[00282] Pharmaceutical and recreational drug formulations for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid pharmaceutical compositions can contain suitable pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical compositions are administered by the oral or nasal respiratory route for local or systemic effect.

Pharmaceutical compositions in pharmaceutically acceptable solvents can be nebulized by use of inert gases. Nebulized solutions can be inhaled directly from the nebulizing device or the nebulizing device can be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder pharmaceutical compositions can be administered, e.g., orally or nasally, from devices that deliver the formulation in an appropriate manner.

[00283] In further embodiments, in which the halogenated psilocybin compounds of present disclosure are used as a recreational drug, the compounds may be included in compositions such as food or food product, a beverage, a food seasoning, a personal care product, such as a cosmetic, perfume or bath oil, or oils (both for topical administration as massage oil, or to be burned or aerosolized). The chemical compounds of the present disclosure may also be included in a “vape” product, which may also include other drugs, such as nicotine, and flavorings.

[00284] The pharmaceutical formulations comprising the chemical compounds of the present disclosure may be used to treat a subject, and in particular to treat a psychiatric disorder in a subject. Accordingly, the present disclosure includes in a further embodiment, a method for treating a psychiatric disorder, the method comprising administering to a subject in need thereof a pharmaceutical formulation comprising a chemical compound or salts thereof having the formula (I):



wherein, at least one of R₂, R₄, R₅, R₆ or R₇ is a halogen atom, wherein each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom or an alkyl group or O-alkyl group, wherein R₄ when it is not halogenated is a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group, and wherein R_{3A} and R_{3B} are a hydrogen atom, or an alkyl group, an aryl group, or an acyl group, wherein the pharmaceutical formulation is administered in an effective amount to treat the psychiatric disorder in the subject.

[00285] Psychiatric disorders that may be treated include, for example, neurodevelopmental disorders such as intellectual disability, global development delay, communication disorders, autism spectrum disorder, and attention-deficit hyperactivity disorder (ADHD); bipolar and related disorders, such as mania, and
5 depressive episodes; anxiety disorder, such as generalized anxiety disorder (GAD), agoraphobia, social anxiety disorder, specific phobias (natural events, medical, animal, situational, for example), panic disorder, and separation anxiety disorder; stress disorders, such as acute stress disorder, adjustment disorders, post-traumatic stress disorder (PTSD), and reactive attachment disorder;
10 dissociative disorders, such as dissociative amnesia, dissociative identity disorder, and depersonalization/derealization disorder; somatoform disorders, such as somatic symptom disorders, illness anxiety disorder, conversion disorder, and factitious disorder; eating disorders, such as anorexia nervosa, bulimia nervosa, rumination disorder, pica, and binge-eating disorder; sleep disorders, such as
15 narcolepsy, insomnia disorder, hypersomnolence, breathing-related sleep disorders, parasomnias, and restless legs syndrome; disruptive disorders, such as kleptomania, pyromania, intermittent explosive disorder, conduct disorder, and oppositional defiant disorder; depressive disorders, such as disruptive mood dysregulation disorder, major depressive disorder, persistent depressive disorder
20 (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, postpartum depression, and depressive disorder caused by another medical condition, for example, psychiatric and existential distress within life-threatening cancer situations (ACS Pharmacol Transl Sci 4: 553-562; J Psychiatr Res 137: 273); substance-related disorders, such as alcohol-related
25 disorders, cannabis related disorders, inhalant-use related disorders, stimulant use disorders, and tobacco use disorders; neurocognitive disorders, such as delirium; schizophrenia; compulsive disorders, such as obsessive compulsive disorders (OCD), body dysmorphic disorder, hoarding disorder, trichotillomania disorder, excoriation disorder, substance/medication induced obsessive-
30 compulsive disorder, and obsessive-compulsive disorder related to another medical condition; and personality disorders, such as antisocial personality disorder, avoidant personality disorder, borderline personality disorder, dependent personality disorder, histrionic personality disorder, narcissistic personality

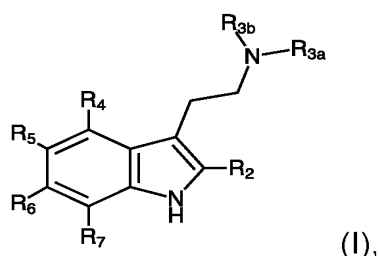
disorder, obsessive-compulsive personality disorder, paranoid personality disorder, schizoid personality disorder, schizotypal personality disorder.

[00286] In an aspect, the compounds of the present disclosure may be used to be contacted with a 5-HT_{2A} receptor to thereby modulate the 5-HT_{2A} receptor.

5 Such contacting includes bringing a compound of the present disclosure and 5-HT_{2A} receptor together under *in vitro* conditions, for example, by introducing the compounds in a sample containing a 5-HT_{2A} receptor, for example, a sample containing purified 5-HT_{2A} receptors, or a sample containing cells comprising 5-HT_{2A} receptors. *In vitro* conditions further include the conditions described in
10 Example 3 hereof. Contacting further includes bringing a compound of the present disclosure and 5-HT_{2A} receptor together under *in vivo* conditions. Such *in vivo* conditions include the administration to an animal or human subject, for example, of a pharmaceutically effective amount of the compound of the present disclosure, when the compound is formulated together with a pharmaceutically active carrier,
15 diluent or excipient, as hereinbefore described, to thereby treat the subject. Upon having contacted the 5-HT_{2A} receptor, the compound may activate the 5-HT_{2A} receptor or inhibit the 5-HT_{2A} receptor.

[00287] Thus, in a further aspect, the condition that may be treated in accordance herewith can be any 5-HT_{2A} receptor mediated disorder. Such
20 disorders include, but are not limited to schizophrenia, psychotic disorder, attention deficit hyperactivity disorder, autism, and bipolar disorder.

[00288] The chemical compounds of the present disclosure may also be used as a feedstock material for other psilocybin derivatives. Thus in one embodiment, the chemical compounds of the present disclosure may be in used
25 manufacture of a pharmaceutical or recreational drug formulation, wherein the manufacture may comprise derivatizing a chemical compound or salts thereof having the formula (I):



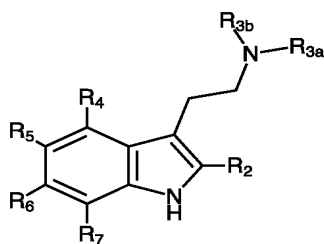
wherein, at least one of R₂, R₄, R₅, R₆ or R₇ is a halogen atom, wherein each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom or an alkyl group or O-alkyl group, wherein R₄ when it is not halogenated is a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group, and wherein R_{3A} and R_{3B} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group.

[00289] In order to use the compound having formula (I) as a feedstock, one or more halogen atoms may be replaced by any atoms or groups, for example hydrocarbon groups. Those of skill in the art will be generally familiar with methods that may be used to substitute halogen groups. In this respect, guidance may be found in Schnepel C. *et al.* (2017) Chem. Eur. J. 23:12064-12086; Durak L.J. *et al.* (2016) ACS Catal. 6: 1451; Runguphan W. *et al.* (2013) Org Lett 15: 2850; Corr M.J. *et al.* (2017) Chem. Sci. 8: 2039; and Roy A.D. *et al.* Chem. Comm. 4831.

[00290] Turning now to methods of making the halogenated psilocybin derivatives, it is noted that the psilocybin compounds of the present disclosure may be prepared in any suitable manner, including any organic chemical synthesis methods, biosynthetic methods, or a combination thereof. Synthesis generally may involve selecting a psilocybin precursor compound, and modifying the psilocybin precursor compound to form a halogenated psilocybin derivative. In this respect, it is noted that a non-halogenated psilocybin derivative may be selected and modified to form psilocybin, which subsequently may be halogenated, or, alternatively, a halogenated psilocybin derivative may be selected to subsequently form a halogenated psilocybin. Suitable psilocybin precursor compounds include compounds comprising an indole prototype structure (see: **FIG. 2**), including, for example tryptophan, tryptamine, 4-hydroxyindole, 4-hydroxytryptophan, 4-hydroxytryptamine, norbaeocystin and baeocystin, and halogenated forms thereof, notably, with respect to the indole prototype structure, 2-, 5-, 6-, 7-halogenated forms thereof. The halogenated psilocybin precursor compounds may be provided in a more or less chemically pure form, for example, in the form of a psilocybin precursor preparation having a purity of at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or at least 99.9%. The psilocybin precursor compounds may be chemically synthesized, or obtained from a fine chemical manufacturer.

[00291] In one embodiment of the present disclosure the halogenated psilocybin derivatives may be formed biosynthetically. Accordingly, the present disclosure further includes in one embodiment, a method of making a halogenated psilocybin derivative the method comprising:

- 5 (a) contacting a halogenated psilocybin precursor compound with a host cell comprising a psilocybin biosynthetic enzyme complement; and
(b) growing the host cell to produce a halogenated psilocybin compound or salts thereof having the formula (I):



10 wherein, at least one of R₂, R₄, R₅, R₆ or R₇ is a halogen atom, wherein each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom or an alkyl group or O-alkyl group, wherein R₄ when it is not halogenated is a phosphate group, hydrogen atom or an alkyl group or O-alkyl group, and wherein R_{3A} and R_{3B}
15 are a hydrogen atom, or an alkyl group, an aryl group, or an acyl group of the chemical compound.

[00292] Implementation of the foregoing example embodiment initially involves providing halogenated psilocybin precursor compounds and host cells having a psilocybin biosynthetic enzyme complement. Accordingly, next,
20 exemplary halogenated psilocybin precursor compounds and example host cells that may be selected and used in accordance with the present disclosure will be described. Thereafter, example methodologies and techniques will be described to contact and use the halogenated psilocybin precursor compounds and cells to produce example halogenated psilocybin compounds.

25 **[00293]** A variety of halogenated psilocybin precursor compounds may be selected, prepared and used. In some embodiments, for example, the halogenated psilocybin precursor compound is a compound comprising a halogenated indole prototype structure. Examples of such compounds are halogenated tryptophan, halogenated tryptamine, halogenated 4-hydroxyindole, halogenated 4-

hydroxytryptophan, halogenated 4-hydroxytryptamine, halogenated norbaeocystin, and halogenated baeocystin, and in particular the 2-halogenated, 5-halogenated, 6-halogenated and 7-halogenated forms (with respect to the indole prototype structure) of any of the foregoing.

5 **[00294]** Turning now to the host cells that can be used in accordance with the present disclosure, it is initially noted that a variety of host cells may be selected in accordance with the present disclosure, including microorganism host cells, plant host cells, and animal host cells.

10 **[00295]** In accordance herewith the host cell includes a psilocybin biosynthetic enzyme complement. Such cells can be obtained in at least two ways. First, in some embodiments, host cells may be selected in which a psilocybin biosynthetic enzyme complement is naturally present. Generally cells naturally producing psilocybin for example, cells of fungal species belonging to the genus *psilocybe*, are suitable in this respect. Second, in some embodiments, a host cell
15 that not naturally produces psilocybin may be modulated to produce a psilocybin biosynthetic enzyme complement. Thus, for example, a nucleic acid sequence encoding a psilocybin biosynthetic enzyme complement may be introduced into a host cell, and upon cell growth the host cells can make the psilocybin biosynthetic enzyme complement.

20 **[00296]** Typically a nucleic acid sequence encoding one or more enzymes constituting a psilocybin biosynthetic enzyme complement further includes one or more additional nucleic acid sequences, for example, a nucleic acid sequences controlling expression of the one or more enzymes, and these one or more additional nucleic acid sequences together with the nucleic acid sequence
25 encoding the one or more enzymes can be said to form a chimeric nucleic acid sequence.

30 **[00297]** A host cell which upon cultivation expresses the chimeric nucleic acid can be selected and used in accordance with the present disclosure. Suitable host cells in this respect include, for example, microbial cells, such as bacterial cells, yeast cells, for example, and algal cells or plant cells. A variety of techniques and methodologies to manipulate host cells to introduce nucleic acid sequences in cells and attain expression exists and are well known to the skilled artisan. These methods include, for example, cation based methods, for example, lithium ion or calcium ion based methods, electroporation, biolistics, and glass beads

based methods. As will be known to those of skill in the art, depending on the host cell selected, the methodology to introduce nucleic acid material in the host cell may vary, and, furthermore, methodologies may be optimized for uptake of nucleic acid material by the host cell, for example, by comparing uptake of nucleic acid material using different conditions. Detailed guidance can be found, for example, in Sambrook *et al.*, Molecular Cloning, a Laboratory Manual, Cold Spring Harbor Laboratory Press, 2012, Fourth Ed. It is noted that the chimeric nucleic acid is a non-naturally occurring chimeric nucleic acid sequence and can be said to be heterologous to the host cell.

10 **[00298]** In some embodiments, the one or more enzymes constituting a psilocybin enzyme complement can be selected from by a nucleic acid sequence selected from the nucleic acid sequences consisting of:

15 (a) SEQ.ID NO: 1, SEQ.ID NO: 3, SEQ.ID NO: 5, SEQ.ID NO: 7, SEQ.ID NO: 9, SEQ.ID NO 11, SEQ.ID NO: 36, SEQ.ID NO: 38, SEQ.ID NO: 40, SEQ. ID NO: 42, SEQ.ID NO: 44, SEQ.ID NO: 46, SEQ.ID NO: 48, SEQ.ID NO: 50, SEQ.ID NO: 52, SEQ.ID NO: 54, SEQ. ID NO: 56, SEQ.ID NO: 58, SEQ.ID NO: 60, SEQ.ID NO: 64, SEQ.ID NO: 66, SEQ.ID NO: 68, SEQ. ID NO: 70, and SEQ.ID NO: 72;

20 (b) a nucleic acid sequence that is substantially identical to any one of the nucleic acid sequences of (a);

(c) a nucleic acid sequence that is substantially identical to any one of the nucleic acid sequences of (a) but for the degeneration of the genetic code;

25 (d) a nucleic acid sequence that is complementary to any one of the nucleic acid sequences of (a);

30 (e) a nucleic acid sequence encoding a polypeptide having any one of the amino acid sequences set forth in SEQ.ID NO: 2, SEQ.ID NO: 4, SEQ.ID NO: 6, SEQ.ID NO: 8, SEQ.ID NO: 10, SEQ.ID NO 12, SEQ.ID NO: 37, SEQ.ID NO: 39, SEQ.ID NO: 41, SEQ. ID NO: 43, SEQ.ID NO: 45, SEQ.ID NO: 47, SEQ.ID NO: 49, SEQ.ID NO: 51, SEQ.ID NO: 53, SEQ.ID NO: 55, SEQ. ID NO: 57, SEQ.ID NO: 59, SEQ.ID NO: 61, SEQ.ID NO: 63, SEQ.ID NO: 65, SEQ.ID NO: 67, SEQ.ID NO: 69, SEQ. ID NO: 71, and SEQ.ID NO: 73;

(f) a nucleic acid sequence that encodes a functional variant of any one of the amino acid sequences set forth in SEQ.ID NO: 2, SEQ.ID NO: 4, SEQ.ID NO: 6, SEQ.ID NO: 8, SEQ.ID NO: 10, SEQ.ID NO 12, SEQ.ID NO: 37, SEQ.ID NO: 39, SEQ.ID NO: 41, SEQ. ID NO: 43, SEQ.ID NO: 45, SEQ.ID NO: 47, SEQ.ID NO: 49, SEQ.ID NO: 51, SEQ.ID NO: 53, SEQ.ID NO: 55, SEQ. ID NO: 57, SEQ.ID NO: 59, SEQ.ID NO: 61, SEQ.ID NO: 63, SEQ.ID NO: 65, SEQ.ID NO: 67, SEQ.ID NO: 69, SEQ. ID NO: 71, and SEQ.ID NO: 73; and

(g) a nucleic acid sequence that hybridizes under stringent conditions to any one of the nucleic acid sequences set forth in (a), (b), (c), (d), (e) or (f).

[00299] Thus any of the nucleic acid sequence set forth in (a), (b), (c), (d), (e), (f) or (g) may be selected and introduced into a host cell. In general, however the nucleic acid sequence is selected in conjunction with the selected psilocybin precursor compound, as hereinafter further discussed in reference to **FIGS. 8A** and **8B**.

[00300] One example host cell that conveniently may be used is *Escherichia coli*. The preparation of the *E. coli* vectors may be accomplished using commonly known techniques such as restriction digestion, ligation, gel electrophoresis, DNA sequencing, the polymerase chain reaction (PCR) and other methodologies. A wide variety of cloning vectors is available to perform the necessary steps required to prepare a recombinant expression vector. Among the vectors with a replication system functional in *E. coli*, are vectors such as pBR322, the pUC series of vectors, the M13 mp series of vectors, pBluescript *etc.* Suitable promoter sequences for use in *E. coli* include, for example, the T7 promoter, the T5 promoter, tryptophan (trp) promoter, lactose (lac) promoter, tryptophan/lactose (tac) promoter, lipoprotein (lpp) promoter, and λ phage PL promoter. Typically, cloning vectors contain a marker, for example, an antibiotic resistance marker, such as ampicillin or kanamycin resistance marker, allowing selection of transformed cells. Nucleic acid sequences may be introduced in these vectors, and the vectors may be introduced in *E. coli* by preparing competent cells, electroporation or using other well known methodologies to a person of skill in the art. *E. coli* may be grown in an appropriate medium, such as Luria-Broth medium and harvested. Recombinant expression vectors may readily be recovered from cells upon harvesting and lysing of the cells.

[00301] Another example host cell that may be conveniently used is a yeast cell. Example yeast host cells that can be used are yeast cells belonging to the genus *Candida*, *Kluyveromyces*, *Saccharomyces*, *Schizosaccharomyces*, *Pichia*, *Hansenula*, and *Yarrowia*. In specific example embodiments, the yeast cell can be

[00302] A number of vectors exist for the expression of recombinant proteins in yeast host cells. Examples of vectors that may be used in yeast host cells include, for example, Yip type vectors, YE_p type vectors, YR_p type vectors, YC_p type vectors, pGPD-2, pAO815, pGAPZ, pGAPZ α , pHIL-D2, pHIL-S1, pPIC3.5K, pPIC9K, pPICZ, pPICZ α , pPIC3K, pHWO10, pPUZZLE and 2 μ m plasmids. Such vectors are known to the art and are, for example, described in Cregg *et al.*, Mol Biotechnol. (2000) 16(1): 23-52. Suitable promoter sequences for use in yeast host cells are also known and described, for example, in Mattanovich *et al.*, Methods Mol. Biol., 2012, 824:329-58, and in Romanos *et al.*, 1992, Yeast 8: 423-488. Examples of suitable promoters for use in yeast host cells include promoters of glycolytic enzymes, like triosephosphate isomerase (TPI), phosphoglycerate kinase (PGK), glyceraldehyde-3-phosphate dehydrogenase (GAPDH or GAP) and variants thereof, lactase (LAC) and galactosidase (GAL), *P. pastoris* glucose-6-phosphate isomerase promoter (PPGI), the 3-phosphoglycerate kinase promoter (PPGK), the glycerol aldehyde phosphate dehydrogenase promoter (PGAP), translation elongation factor promoter (PTEF), *S. cerevisiae* enolase (ENO-1), *S. cerevisiae* galactokinase (GAL1), *S. cerevisiae* alcohol dehydrogenase/glyceraldehyde-3-phosphate dehydrogenase (ADH1, ADH2/GAP), *S. cerevisiae* triose phosphate isomerase (TPI), *S. cerevisiae* metallothionein (CUP1), and *S. cerevisiae* 3-phosphoglycerate kinase (PGK), and the maltase gene promoter (MAL). Marker genes suitable for use in yeast host cells are also known to the art. Thus, antibiotic resistance markers, such as ampicillin resistance markers, can be used in yeast, as well as marker genes providing genetic functions for essential nutrients, for example, leucine (LEU2), tryptophan (TRP1 and TRP2), uracil (URA3, URA5, URA6), histidine (HIS3), and the like. Methods for introducing vectors into yeast host cells can, for example, be found in S. Kawai *et al.*, 2010, Bioeng. Bugs 1(6): 395-403.

[00303] Further, guidance with respect to the preparation of expression vectors and introduction thereof into host cells, including in *E. coli* cells, yeast cells,

and other host cells, may be found in, for example: Sambrook *et al.*, Molecular Cloning, a Laboratory Manual, Cold Spring Harbor Laboratory Press, 2012, Fourth Ed.

5 **[00304]** Thus, to briefly recap, a host cell comprising a chimeric nucleic acid comprising (i) a nucleic acid sequence controlling expression in a host cell and (ii) a nucleic acid sequence encoding a psilocybin biosynthetic enzyme complement, can be prepared in accordance with the present disclosure.

10 **[00305]** In accordance herewith, host cells are grown to multiply and to express a chimeric nucleic acid. Expression of the chimeric nucleic acid results in the biosynthetic production in the host cell of a psilocybin biosynthetic enzyme complement. Growth media and growth conditions can vary depending on the host cell that is selected, as will be readily appreciated to those of ordinary skill in the art. Growth media typically contain a carbon source, one or several nitrogen sources, essential salts including salts of potassium, sodium, magnesium, phosphate and sulphate, trace metals, water soluble vitamins, and process aids including but not limited to antifoam agents, protease inhibitors, stabilizers, ligands and inducers. Example carbon sources are e.g. mono- or disaccharides. Example nitrogen sources are, e.g. ammonia, urea, amino acids, yeast extract, corn steep liquor and fully or partially hydrolyzed proteins. Example trace metals are e.g. Fe, Zn, Mn, Cu, Mo and H₃BO₃. Example water soluble vitamins are e.g. biotin, pantothenate, niacin, thiamine, p- aminobenzoic acid, choline, pyridoxine, folic acid, riboflavin and ascorbic acid. Further, specific example media include liquid culture media for the growth of yeast cells and bacterial cells including, Luria-Bertani (LB) broth for bacterial cell cultivation, and yeast extract peptone dextrose (YEPD or YPD), for yeast cell cultivation. Further media and growth conditions can be found in Sambrook *et al.*, Molecular Cloning, a Laboratory Manual, Cold Spring Harbor Laboratory Press, 2012, Fourth Ed.

25 **[00306]** In order for the host cells to produce the halogenated psilocybin compound, the cells are provided with a psilocybin precursor compound. Thus in accordance herewith, host cells may be contacted with a psilocybin precursor compound. In some embodiments, a psilocybin precursor compound can be exogenously supplied, for example, by including a psilocybin precursor compound in the growth medium of the host cells, and growing the host cells in a medium including the psilocybin precursor compound.

[00307] Referring next to **FIGS. 8A** and **8B**, shown therein is an example natural biosynthetic pathway showing the conversion of example psilocybin precursor compounds to form psilocybin (**FIG. 8A**). Thus, as can be appreciated from **FIG. 8A**, various psilocybin precursor compounds may be selected and prepared in halogenated form, in conjunction with a psilocybin biosynthetic enzyme complement.

[00308] Thus, by way of example, referring to **FIG. 8B**, a chlorinated psilocybin precursor compound, for example, 6-chloro-4-hydroxy indole may be selected and contacted with a host cell comprising a psilocybin biosynthetic enzyme complement comprising PsiD, (e.g. SEQ.ID NO: 2) PsiH (e.g. SEQ.ID NO: 4), PsiK (e.g. SEQ.ID NO: 6) and PsiM (e.g. SEQ.ID NO: 8), and upon growth of the cells 6-chloro-psilocybin can be formed. Or by way of another example, 6-chloro-tryptophan may be selected and contacted with a host cell comprising a psilocybin biosynthetic enzyme complement comprising TrpB (SEQ.ID NO: 12) PsiD, (e.g. SEQ.ID NO: 2), PsiK (e.g. SEQ.ID NO: 6) and PsiM (e.g. SEQ.ID NO: 8), and upon growth of the cells 6-chloro-psilocybin can be formed. It will be clear to those of skill in the art that by referring to **FIGS. 8A** and **8B**, other halogenated psilocybin precursors may be selected (e.g. 2-chloro tryptophan, 4-chloro-tryptophan, 5-chloro-tryptophan, 7-chlorotryptophan; 6-bromo-tryptophan, 6-fluoro-tryptophan, 6-iodotryptophan; and 6-chlorotryptamine, 6-chloro-4-hydroxytryptophan, 6-hydroxy-4-chloro-tryptamine, 6-chloro-norbaeocystin or 6-chloro-baeocystin), and contacted with a host cell comprising an appropriate psilocybin biosynthetic enzyme complement to produce a halogenated psilocybin derivative.

[00309] Thus, in one further example embodiment, a halogenated indole, such as 6-chloro-4-hydroxy indole, for example (see: **FIG. 8B**), may be selected and contacted with a host cell comprising a psilocybin biosynthetic enzyme complement comprising (i) a nucleic acid encoding TrpB selected from SEQ.ID NO: 12, SEQ.ID NO: 65, SEQ.ID NO: 67, SEQ.ID NO: 69, SEQ.ID NO: 71, and SEQ.ID NO: 73, or a nucleic acid sequence encoding a polypeptide sequence substantially similar to any of the aforementioned sequences; (ii) a nucleic acid encoding PsiD selected from SEQ.ID NO: 2, SEQ.ID NO: 10, SEQ.ID NO: 37, SEQ.ID NO: 39, SEQ.ID NO: 41, SEQ.ID NO: 43, SEQ.ID NO: 45, SEQ.ID NO: 47, SEQ.ID NO: 49, SEQ.ID NO: 51, SEQ.ID NO: 53, SEQ.ID NO: 55, and SEQ.ID

NO: 57, or a nucleic acid sequence encoding a polypeptide sequence substantially similar to any of the aforementioned sequences; (iii) a nucleic acid encoding PsiK encoded by SEQ.ID NO: 6, or a nucleic acid sequence encoding a polypeptide sequence substantially similar thereto; and (iv) a nucleic acid encoding PsiM selected from SEQ.ID NO: 8, SEQ.ID NO: 59 and SEQ.ID NO: 61 or a nucleic acid sequence encoding a polypeptide sequence substantially similar to any of the aforementioned sequences to produce a halogenated psilocybin derivative.

[00310] Thus, in one further example embodiment, a halogenated tryptophan, such as 6-chloro-4-hydroxy tryptophan, for example (see: **FIG. 8B**), may be selected and contacted with a host cell comprising a psilocybin biosynthetic enzyme complement comprising (i) a nucleic acid encoding PsiD selected from SEQ.ID NO: 2, SEQ.ID NO: 10, SEQ.ID NO: 37, SEQ.ID NO: 39, SEQ.ID NO: 41, SEQ.ID NO: 43, SEQ.ID NO: 45, SEQ.ID NO: 47, SEQ.ID NO: 49, SEQ.ID NO: 51, SEQ.ID NO: 53, SEQ.ID NO: 55, and SEQ.ID NO: 57, or a nucleic acid sequence encoding a polypeptide sequence substantially similar to any of the aforementioned sequences; (ii) a nucleic acid encoding PsiK encoded by SEQ.ID NO: 6, or a nucleic acid sequence encoding a polypeptide sequence substantially similar thereto; and (iii) a nucleic acid encoding PsiM selected from SEQ.ID NO: 8, SEQ.ID NO: 59 and SEQ.ID NO: 61 or a nucleic acid sequence encoding a polypeptide sequence substantially similar to any of the aforementioned sequences to produce a halogenated psilocybin derivative.

[00311] Thus, in one further example embodiment, a halogenated tryptamine, such as 6-chloro-4-hydroxy tryptamine, for example (see: **FIG. 8B**), may be selected and contacted with a host cell comprising a psilocybin biosynthetic enzyme complement comprising (i) a nucleic acid encoding PsiK encoded by SEQ.ID NO: 6, or a nucleic acid sequence encoding a polypeptide sequence substantially similar thereto; and (ii) and a nucleic acid encoding PsiM selected from SEQ.ID NO: 8, SEQ.ID NO: 59 and SEQ.ID NO: 61 or a nucleic acid sequence encoding a polypeptide sequence substantially similar to any of the aforementioned sequences to produce a halogenated psilocybin derivative.

[00312] Thus, in one further example embodiment, a halogenated norbaeocystin, such as 6-chloro-norbaeocystin, or a halogenated baeocystin may, such as 6-chlorobaecocystin, for example (see: **FIG. 8B**), may be selected and contacted with a host cell comprising a psilocybin biosynthetic enzyme

complement comprising a nucleic acid encoding PsiM selected from SEQ.ID NO: 8, SEQ.ID NO: 59 and SEQ.ID NO: 61 or a nucleic acid sequence encoding a polypeptide sequence substantially similar to any of the aforementioned sequences to produce a halogenated psilocybin derivative.

5 **[00313]** Thus, in one further example embodiment, a halogenated tryptophan, such as 6-chloro-4-hydroxy tryptophan, for example (see: **FIG. 8B**), may be selected and contacted with a host cell comprising a psilocybin biosynthetic enzyme complement comprising (i) a nucleic acid encoding PsiD selected from SEQ.ID NO: 2, SEQ.ID NO: 10, SEQ.ID NO: 37, SEQ.ID NO: 39,
10 SEQ.ID NO: 41, SEQ.ID NO: 43, SEQ.ID NO: 45, SEQ.ID NO: 47, SEQ.ID NO: 49, SEQ.ID NO: 51, SEQ.ID NO: 53, SEQ.ID NO: 55, and SEQ.ID NO: 57, or a nucleic acid sequence encoding a polypeptide sequence substantially similar to any of the aforementioned sequences; (ii) a nucleic acid encoding PsiH encoded by SEQ.ID NO: 4, or a nucleic acid sequence encoding a polypeptide sequence
15 substantially similar thereto; (iii) a nucleic acid encoding PsiK encoded by SEQ.ID NO: 6, or a nucleic acid sequence encoding a polypeptide sequence substantially similar thereto; and (iv) and a nucleic acid encoding PsiM selected from SEQ.ID NO: 8, SEQ.ID NO: 59 and SEQ.ID NO: 61 or a nucleic acid sequence encoding a polypeptide sequence substantially similar to any of the aforementioned
20 sequences to produce a halogenated psilocybin derivative.

[00314] Thus, in one further example embodiment, a halogenated tryptamine, such as 6-chloro-tryptamine, for example (see: **FIG. 8B**), may be selected and contacted with a host cell comprising a psilocybin biosynthetic enzyme complement comprising (i) a nucleic acid encoding PsiH encoded by
25 SEQ.ID NO: 4, or a nucleic acid sequence encoding a polypeptide sequence substantially similar thereto; (ii) a nucleic acid encoding PsiK encoded by SEQ.ID NO: 6, or a nucleic acid sequence encoding a polypeptide sequence substantially similar thereto; and (iii) and a nucleic acid encoding PsiM selected from SEQ.ID NO: 8, SEQ.ID NO: 59 and SEQ.ID NO: 61 or a nucleic acid sequence encoding
30 a polypeptide sequence substantially similar to any of the aforementioned sequences to produce a halogenated psilocybin derivative.

[00315] In some embodiments, the psilocybin can be a halogenated psilocybin precursor compound which is exogenously supplied to a host cell, for example by inclusion in the host cell's growth medium. Thus, for example, referring

to **FIG. 8**, it will be understood that in accordance herewith, for example, 6-chloro-tryptophan or 6-chloro-4-hydroxy indole, may be included in the growth medium of a host cell comprising a psilocybin biosynthetic enzyme complement.

[00316] It is noted that in some embodiments, the host cells may in addition to the psilocybin biosynthetic enzyme complement include a halogenase. In such embodiments the cell may be contacted with a non-halogenated psilocybin precursor compound, and halogenation may occur *in vivo* in the host cells. Thus, referring again to **FIG. 8**, by way of example, non-halogenated tryptophan may be selected and contacted with a host cell comprising a psilocybin biosynthetic enzyme complement comprising PsiD, (e.g. SEQ.ID NO: 2) PsiH (e.g. SEQ.ID NO: 4), PsiK (e.g. SEQ.ID NO: 6) and PsiM (e.g. SEQ.ID NO: 8), the host cells further including a halogenase, and upon growth of the host cells in the presence of a halogen, for example in the form of a halogen salt, sodium chloride (NaCl) or sodium bromide (NaBr) halogenated psilocybin derivatives can be formed.

[00317] Suitable halogenases that may be used in accordance herewith include, for example, a PyrH halogenase of *Streptomyces rugosporus* (SEQ.ID NO: 13; SEQ.ID NO: 14), which may, for example, be contacted with non-halogenated tryptophan to form 5-halo-tryptophan; a KtZR halogenase of *Kutzneria* sp. 744 (SEQ.ID NO: 15; SEQ.ID NO: 16), which may be contacted with non-halogenated tryptophan to form 6-halo-tryptophan; a SstH halogenase of *Streptomyces toxytricini* (SEQ.ID NO: 17; SEQ.ID NO: 18), which may be contacted with non-halogenated tryptophan to form 6-halo-tryptophan; a Thal halogenase of *Streptomyces albogriseolus* (SEQ.ID NO: 19; SEQ.ID NO: 20), which may be contacted with non-halogenated tryptophan to form 6-halo-tryptophan; a BorH halogenase (see: SEQ.ID NO: 21; SEQ.ID NO: 22), which may be contacted with non-halogenated tryptophan to form 6-halo-tryptophan; a KtzQ halogenase of *Kutzneria* sp. 744 (SEQ.ID NO: 23; SEQ.ID NO: 24), which may be contacted with non-halogenated tryptophan to form 7-halo-tryptophan; a PrnA halogenase of *Pseudomonas fluorescens* (SEQ.ID NO: 25; SEQ.ID NO: 26), which may be contacted with non-halogenated tryptophan and other psilocybin precursor compounds to form 7-halo-tryptophan or 2-halo-tryptophan and other 7-halo or 2-halo psilocybin precursor compounds; a RebH halogenase of *Lentzea aerocolonigenes* (SEQ.ID NO: 27; SEQ.ID NO: 28), which may be contacted with non-halogenated tryptophan to form 7-halo-tryptophan; and a SatH halogenase of

Streptomyces albus (SEQ.ID NO: 29), which may be contacted with non-halogenated tryptophan to form 6-halo-tryptophan.

[00318] It is noted that halogenases comprising amino acid sequences substantially similar to any of the aforementioned halogenase sequences may be prepared and used to modulate the substrate specificity and/or the enzyme's catalytic efficiency. Thus, for example, halogenases comprising amino acid sequences substantially similar to SEQ.ID NO: 14; SEQ.ID NO: 16; SEQ.ID NO: 18; SEQ.ID NO: 20; SEQ.ID NO: 22; SEQ.ID NO: 24; SEQ.ID NO: 26; SEQ.ID NO: 28, and SEQ.ID NO: 29, may be prepared and used to obtain 2-halo, 5-halo, 6-halo or 7-halo tryptophan, or halogenases comprising amino acid sequences substantially similar to SEQ.ID NO: 14; SEQ.ID NO: 16; SEQ.ID NO: 18; SEQ.ID NO: 20; SEQ.ID NO: 22; SEQ.ID NO: 24; SEQ.ID NO: 26; SEQ.ID NO: 28, and SEQ.ID NO: 29 may be prepared and used to halogenate other non-halogenated psilocybin precursor compounds, such as tryptamine, 4-hydroxyindole, 4-hydroxytryptophan, 4-hydroxytryptamine, norbaeocystin, and baeocystin, for example, to form halogenated forms thereof.

[00319] Thus, for example, the native polypeptide sequence of a RebH halogenase *Lentzea aerocolonigenes* (SEQ.ID NO: 27; SEQ.ID NO: 28) may be modulated to thereby modulate the substrate specificity. Thus, for example, a modulated *Lentzea aerocolonigenes* RebH halogenase, which may be referred to as a RebH-Y455W mutant, set forth in SEQ.ID NO: 30 prefers tryptamine over tryptophan as a substrate and when contacted with tryptamine forms 7-halo-tryptamine.

[00320] By way of a further example, a modulated *Lentzea aerocolonigenes* RebH halogenase, which may be referred to as a RebH-N470S mutant, set forth in SEQ.ID NO: 31 prefers tryptamine over tryptophan as a substrate and when contacted with tryptamine forms 7-halo-tryptamine.

[00321] By way of a further example, a modulated *Lentzea aerocolonigenes* RebH halogenase, which may be referred to as a RebH-8F mutant, set forth in SEQ.ID NO: 32 prefers tryptamine over tryptophan as a substrate and when contacted with tryptamine forms 6-halo-tryptamine.

[00322] By way of a further example, a modulated *Lentzea aerocolonigenes* RebH halogenase, which may be referred to as a RebH-10F mutant, set forth in

SEQ.ID NO: 33 prefers tryptamine over tryptophan as a substrate and when contacted with tryptamine forms 5-halo-tryptamine.

[00323] By way of a further example, a modulated *Lentzea aerocolonigenes* RebH halogenase, which may be referred to as a RebH-3SS mutant, set forth in SEQ.ID NO: 34 has an altered substrate acceptance profile and converts tricyclic tryptoline derivatives.

[00324] By way of yet a further example, a modulated *Lentzea aerocolonigenes* RebH halogenase, which may be referred to as a RebH-3SS mutant set forth in SEQ.ID NO: 35 has an altered substrate acceptance profile and converts a broad range of large indoles and carbazoles.

[00325] The foregoing examples of halogenases exhibiting modulated substrate specificity and/or catalytic efficiency are known to the art and are documented in, for example, Andorfer M.C., *et al.* (2016) Chem. Sci. 7: 3720; Andorfer M.C. *et al.* (2017) Catalysis 7: 1897; Glenn W.S., *et al.* (2011) J. Am. Chem. Soc. 133: 19346; and Payne J.T. *et al.* (2015) Angew. Chem. Int. Ed. 54: 4226.

[00326] Accordingly, in one embodiment the halogenase can be encoded by a nucleic acid selected from:

(a) SEQ.ID NO: 13, SEQ.ID NO: 15, SEQ. ID NO: 17, SEQ.ID NO: 19, SEQ. ID NO: 21, SEQ.ID NO: 23, SEQ.ID NO: 25, and SEQ.ID NO: 27;

(b) a nucleic acid sequence that is substantially identical to any one of the nucleic acid sequences of (a);

(c) a nucleic acid sequence that is substantially identical to any one of the nucleic acid sequences of (a) but for the degeneration of the genetic code;

(d) a nucleic acid sequence that is complementary to any one of the nucleic acid sequences of (a);

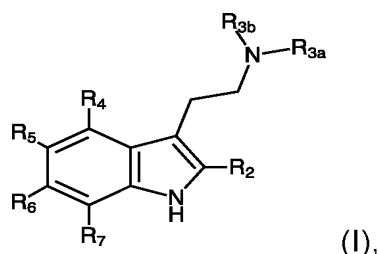
(e) a nucleic acid sequence encoding a polypeptide having any one of the amino acid sequences set forth in SEQ.ID NO: 14, SEQ.ID NO: 16, SEQ. ID NO: 18, SEQ.ID NO: 20, SEQ. ID NO: 22, SEQ.ID NO: 24, SEQ.ID NO: 26, SEQ.ID NO: 28, SEQ.ID NO: 29, SEQ.ID NO: 30, SEQ.ID NO: 31, SEQ.ID NO: 32, SEQ.ID NO: 33, SEQ.ID NO: 34, and SEQ.ID NO: 35;

(f) a nucleic acid sequence that encodes a functional variant of any one of the amino acid sequences set forth in SEQ.ID NO: 14, SEQ.ID NO: 16,

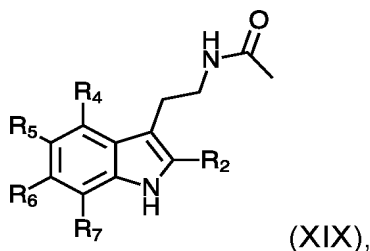
SEQ. ID NO: 18, SEQ.ID NO: 20, SEQ. ID NO: 22, SEQ.ID NO: 24, SEQ.ID NO: 26, SEQ.ID NO: 28, SEQ.ID NO: 29, SEQ.ID NO: 30, SEQ.ID NO: 31, SEQ.ID NO: 32. SEQ.ID NO: 33, SEQ.ID NO: 34, and SEQ.ID NO: 35; and

- (g) a nucleic acid sequence that hybridizes under stringent conditions to any one of the nucleic acid sequences set forth in (a), (b), (c), (d), (e) or (f).

[00327] In one further embodiment, the host cell can comprise an acetyl transferase capable of acetylating R_{3a} or R_{3b}, wherein the cell comprises a compound having chemical formula (I):



- wherein, at least one of R₂, R₄, R₅, R₆ or R₇ is a halogen atom, wherein each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom or an alkyl group or O-alkyl group, wherein R₄ when it is not halogenated is a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group, and wherein at least one of R_{3A} and R_{3B} is a hydrogen atom,
- to form a compound having the chemical formula (XIX):



- wherein, at least one of R₂, R₄, R₅, R₆ or R₇ is a halogen atom, wherein each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom or an alkyl group or O-alkyl group, wherein R₄ when it is not halogenated is a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group.

[00328] In some embodiments, R_{3a} and R_{3b} are each a hydrogen atom.

[00329] Suitable acyl transferases that may be used in accordance herewith include a PsmF acetyl transferase obtained from *Streptomyces griseofuscus*, including a PsmF N-acetyltransferase comprising polypeptide sequence SEQ.ID

NO: 63 set forth herein, and further including a PsmF polypeptide encoded by a nucleic acid selected from:

- (a) SEQ.ID NO: 62;
- (b) a nucleic acid sequence that is substantially identical the nucleic acid sequence of (a);
- (c) a nucleic acid sequence that is substantially identical to the nucleic acid sequence of (a) but for the degeneration of the genetic code;
- (d) a nucleic acid sequence that is complementary to the nucleic acid sequence of (a);
- (e) a nucleic acid sequence encoding a polypeptide having an amino acid sequences set forth in SEQ.ID NO: 63;
- (f) a nucleic acid sequence that encodes a functional variant of the amino acid sequence set forth in SEQ.ID NO: 63; and
- (g) a nucleic acid sequence that hybridizes under stringent conditions to any one of the nucleic acid sequences set forth in (a), (b), (c), (d), (e) or (f).

[00330] It will be clear to those of skill in the art that a significant variety of different halogenated and non-halogenated psilocybin precursor compounds may be selected. **FIGS. 8A** and **8B** in this respect provide guidance and allow a person of skill in the art to select appropriate psilocybin precursor compounds and a matching a psilocybin biosynthetic enzyme complement.

[00331] Upon production by the host cells of the halogenated psilocybin compounds in accordance with the methods of the present disclosure, the halogenated psilocybin compounds may be extracted from the host cell suspension, and separated from other constituents within the host cell suspension, such as media constituents and cellular debris. Separation techniques will be known to those of skill in the art and include, for example, solvent extraction (e.g. butane, chloroform, ethanol), column chromatography based techniques, high-performance liquid chromatography (HPLC), for example, and/or countercurrent separation (CCS) based systems. The recovered halogenated psilocybin compounds may be obtained in a more or less pure form, for example, a preparation of halogenated psilocybin compounds of at least about 60% (w/w), about 70% (w/w), about 80% (w/w), about 90% (w/w), about 95% (w/w), about 96% (w/w), about 97% (w/w), about 98% (w/w) or about 99% (w/w) purity may be

obtained. Thus, in this manner, halogenated psilocybin derivatives in more or less pure form may be prepared.

[00332] Similarly, other methods of making the halogenated psilocybin compounds that may be used in accordance herewith may yield preparations of
5 halogenated compounds of at least about 60% (w/w), about 70% (w/w), about 80% (w/w), about 90% (w/w), about 95% (w/w), about 96% (w/w), about 97% (w/w), about 98% (w/w), or about 99% (w/w) purity.

[00333] It will now be clear from the foregoing that novel halogenated psilocybin derivatives are disclosed herein. The halogenated psilocybin
10 compounds may be formulated for use as a pharmaceutical drug or recreational drug., The halogenated psilocybin compounds may also be used as a feedstock to produce other psilocybin derivatives.

SUMMARY OF SEQUENCES

15

[00334] SEQ.ID NO: 1 sets forth a *Psilocybe cubensis* nucleic acid sequence encoding a PsiD polypeptide.

[00335] SEQ.ID NO: 2 sets forth a deduced amino acid sequence of a *Psilocybe cubensis* PsiD polypeptide.

20 **[00336]** SEQ.ID NO: 3 sets forth a *Psilocybe cubensis* nucleic acid sequence encoding a PsiH polypeptide.

[00337] SEQ.ID NO: 4 sets forth a deduced amino acid sequence of a *Psilocybe cubensis* PsiH polypeptide.

25 **[00338]** SEQ.ID NO: 5 sets forth a *Psilocybe cubensis* nucleic acid sequence encoding a PsiK polypeptide.

[00339] SEQ.ID NO: 6 sets forth a deduced amino acid sequence of a *Psilocybe cubensis* PsiK polypeptide.

[00340] SEQ.ID NO: 7 sets forth a *Psilocybe cubensis* nucleic acid sequence encoding a PsiM polypeptide.

30 **[00341]** SEQ.ID NO: 8 sets forth a deduced amino acid sequence of a *Psilocybe cubensis* PsiM polypeptide.

[00342] SEQ.ID NO: 9 sets forth a *Psilocybe cubensis* nucleic acid sequence encoding a Psi-ncAAAD polypeptide.

- [00343]** SEQ.ID NO: 10 sets forth a deduced amino acid sequence of a *Psilocybe cubensis* Psi-ncAAAD polypeptide.
- [00344]** SEQ.ID NO: 11 sets forth a *Psilocybe cubensis* nucleic acid sequence encoding a TrpB polypeptide.
- 5 **[00345]** SEQ.ID NO: 12 sets forth a deduced amino acid sequence of a *Psilocybe cubensis* TrpB polypeptide.
- [00346]** SEQ.ID NO: 13 sets forth a *Streptomyces rugosporus* nucleic acid sequence encoding a PyrH halogenase polypeptide.
- [00347]** SEQ.ID NO: 14 sets forth a deduced amino acid sequence of a
- 10 *Streptomyces rugosporus* PyrH halogenase polypeptide.
- [00348]** SEQ.ID NO: 15 sets forth a *Kutzneria* sp. 744 nucleic acid sequence encoding a KtzR halogenase polypeptide.
- [00349]** SEQ.ID NO: 16 sets forth a deduced amino acid sequence of a *Kutzneria* sp. 744 KtzR halogenase polypeptide.
- 15 **[00350]** SEQ.ID NO: 17 sets forth a *Streptomyces toxytrinici* nucleic acid sequence encoding a SttH halogenase polypeptide.
- [00351]** SEQ.ID NO: 18 sets forth a deduced amino acid sequence of a *Streptomyces toxytrinici* SttH halogenase polypeptide.
- [00352]** SEQ.ID NO: 19 sets forth a *Streptomyces albogriseolus* nucleic acid
- 20 sequence encoding a Thal halogenase polypeptide.
- [00353]** SEQ.ID NO: 20 sets forth a deduced amino acid sequence of a *Streptomyces albogriseolus* Thal halogenase polypeptide.
- [00354]** SEQ.ID NO: 21 sets forth a nucleic acid sequence encoding a BorH halogenase polypeptide of an unidentified soil bacterium.
- 25 **[00355]** SEQ.ID NO: 22 sets forth a deduced amino acid sequence of a BorH halogenase polypeptide of an unidentified soil bacterium.
- [00356]** SEQ.ID NO: 23 sets forth a *Kutzneria* sp. 744 nucleic acid sequence encoding a KtzQ halogenase polypeptide.
- [00357]** SEQ.ID NO: 24 sets forth a deduced amino acid sequence of a
- 30 *Kutzneria* sp. 744 KtzQ halogenase polypeptide.
- [00358]** SEQ.ID NO: 25 sets forth a *Pseudomonas fluorescens* nucleic acid sequence encoding a PrnA halogenase polypeptide.
- [00359]** SEQ.ID NO: 26 sets forth a deduced amino acid sequence of a *Pseudomonas fluorescens* PrnA halogenase polypeptide.

- [00360]** SEQ.ID NO: 27 sets forth a nucleic acid sequence encoding a *Lentzea areocolonigenes* RebH halogenase polypeptide.
- [00361]** SEQ.ID NO: 28 sets forth a deduced amino acid sequence of a *Lentzea aerocoliginenes* RebH halogenase polypeptide.
- 5 **[00362]** SEQ.ID NO: 29 sets forth a deduced amino acid sequence of a *Streptomyces albus* SatH halogenase polypeptide.
- [00363]** SEQ.ID NO: 30 sets forth a deduced amino acid sequence of a mutated *Lentzea aerocoliginenes* RebH halogenase polypeptide.
- [00364]** SEQ.ID NO: 31 sets forth a deduced amino acid sequence of another
10 mutated *Lentzea aerocoliginenes* RebH halogenase polypeptide.
- [00365]** SEQ.ID NO: 32 sets forth a deduced amino acid sequence of another mutated *Lentzea aerocoliginenes* RebH halogenase polypeptide.
- [00366]** SEQ.ID NO: 33 sets forth a deduced amino acid sequence of another mutated *Lentzea aerocoliginenes* RebH halogenase polypeptide.
- 15 **[00367]** SEQ.ID NO: 34 sets forth a deduced amino acid sequence of another mutated *Lentzea aerocoliginenes* RebH halogenase polypeptide.
- [00368]** SEQ.ID NO: 35 sets forth a deduced amino acid sequence of another mutated *Lentzea aerocoliginenes* RebH halogenase polypeptide.
- [00369]** SEQ.ID NO: 36 sets forth a nucleic acid sequence encoding a
20 *Bacillus atrophaeus* BaTDC tryptophan decarboxylase polypeptide.
- [00370]** SEQ.ID NO: 37 sets forth a deduced amino acid sequence of a *Bacillus atrophaeus* BaTDC tryptophan decarboxylase polypeptide.
- [00371]** SEQ.ID NO: 38 sets forth a nucleic acid sequence encoding a *Ruminococcus gnavus* RgnTDC tryptophan decarboxylase polypeptide.
- 25 **[00372]** SEQ.ID NO: 39 sets forth a deduced amino acid sequence of a *Ruminococcus gnavus* RgnTDC tryptophan decarboxylase polypeptide.
- [00373]** SEQ.ID NO: 40 sets forth a nucleic acid sequence encoding a *Streptomyces griseofuscus* SgTDC tryptophan decarboxylase polypeptide.
- [00374]** SEQ.ID NO: 41 sets forth a deduced amino acid sequence of a
30 *Streptomyces griseofuscus* SgTDC tryptophan decarboxylase polypeptide.
- [00375]** SEQ.ID NO: 42 sets forth a nucleic acid sequence encoding a *Ceriporiopsis subvermispora* CsTDC tryptophan decarboxylase polypeptide.
- [00376]** SEQ.ID NO: 43 sets forth a deduced amino acid sequence of a *Ceriporiopsis subvermispora* CsTDC tryptophan decarboxylase polypeptide.

- [00377]** SEQ.ID NO: 44 sets forth a nucleic acid sequence encoding a *Clostridium sporogenes* ClostSporTDC tryptophan decarboxylase polypeptide.
- [00378]** SEQ.ID NO: 45 sets forth a deduced amino acid sequence of a *Clostridium sporogenes* ClostSporTDC tryptophan decarboxylase polypeptide.
- 5 **[00379]** SEQ.ID NO: 46 sets forth a nucleic acid sequence encoding a *Homo sapiens* HsDDC DOPA decarboxylase polypeptide.
- [00380]** SEQ.ID NO: 47 sets forth a deduced amino acid sequence of a *Homo sapiens* HsDDC DOPA decarboxylase polypeptide.
- [00381]** SEQ.ID NO: 48 sets forth a nucleic acid sequence encoding an
- 10 *Ophiorrhiza pumila* OpTDC tryptophan decarboxylase polypeptide.
- [00382]** SEQ.ID NO: 49 sets forth a deduced amino acid sequence of an *Ophiorrhiza pumila* OpTDC tryptophan decarboxylase polypeptide.
- [00383]** SEQ.ID NO: 50 sets forth a nucleic acid sequence encoding an *Oryza sativa* OsTDC1 tryptophan decarboxylase polypeptide.
- 15 **[00384]** SEQ.ID NO: 51 sets forth a deduced amino acid sequence of an *Oryza sativa* OsTDC1 tryptophan decarboxylase polypeptide.
- [00385]** SEQ.ID NO: 52 sets forth a nucleic acid sequence encoding another *Oryza sativa* OsTDC2 tryptophan decarboxylase polypeptide.
- [00386]** SEQ.ID NO: 53 sets forth a deduced amino acid sequence of another
- 20 *Oryza sativa* OsTDC2 tryptophan decarboxylase polypeptide.
- [00387]** SEQ.ID NO: 54 sets forth a nucleic acid sequence encoding a *Xenorhabdus doucetiae* XdTDC decarboxylase polypeptide.
- [00388]** SEQ.ID NO: 55 sets forth a deduced amino acid sequence of a *Xenorhabdus doucetiae* XdTDC decarboxylase polypeptide.
- 25 **[00389]** SEQ.ID NO: 56 sets forth a nucleic acid sequence encoding a *Camptotheca acuminata* CaTDC tryptophan decarboxylase polypeptide.
- [00390]** SEQ.ID NO: 57 sets forth a deduced amino acid sequence of a *Camptotheca acuminata* CaTDC tryptophan decarboxylase polypeptide.
- [00391]** SEQ.ID NO: 58 sets forth a nucleic acid sequence encoding an
- 30 *Oryctolagus cuniculus* OcINMT indolethylamine N-methyltransferase polypeptide.
- [00392]** SEQ.ID NO: 59 sets forth a deduced amino acid sequence of an *Oryctolagus cuniculus* OcINMT indolethylamine N-methyltransferase polypeptide.
- [00393]** SEQ.ID NO: 60 sets forth a nucleic acid sequence encoding a *Hordeum vulgare* HvNMT N-methyltransferase polypeptide.

- [00394]** SEQ.ID NO: 61 sets forth a deduced amino acid sequence of a *Hordeum vulgare* HvNMT N-methyltransferase polypeptide.
- [00395]** SEQ.ID NO: 62 sets forth a nucleic acid sequence encoding a *Streptomyces griseofuscus* PsmF N-acetyltransferase polypeptide.
- 5 **[00396]** SEQ.ID NO: 63 sets forth a deduced amino acid sequence of a *Streptomyces griseofuscus* PsmF N-acetyltransferase polypeptide.
- [00397]** SEQ.ID NO: 64 sets forth a nucleic acid sequence encoding a mutated *Thermotoga maritima* TmTrpB-2F3 tryptophan synthase subunit B polypeptide.
- 10 **[00398]** SEQ.ID NO: 65 sets forth a deduced amino acid sequence of a mutated *Thermotoga maritima* TmTrpB-2F3 tryptophan synthase subunit B polypeptide.
- [00399]** SEQ.ID NO: 66 sets forth a nucleic acid sequence encoding a mutated *Pyrococcus furiosus* PfTrpB-0A9 tryptophan synthase subunit B
- 15 polypeptide.
- [00400]** SEQ.ID NO: 67 sets forth a deduced amino acid sequence of a mutated *Pyrococcus furiosus* PfTrpB-0A9 tryptophan synthase subunit B polypeptide.
- [00401]** SEQ.ID NO: 68 sets forth a nucleic acid sequence encoding another
- 20 mutated *Pyrococcus furiosus* PfTrpB-2A6 tryptophan synthase subunit B polypeptide.
- [00402]** SEQ.ID NO: 69 sets forth a deduced amino acid sequence of a mutated *Pyrococcus furiosus* PfTrpB-2A6 tryptophan synthase subunit B polypeptide.
- 25 **[00403]** SEQ.ID NO: 70 sets forth a nucleic acid sequence encoding another mutated *Pyrococcus furiosus* PfTrpB-7E6 tryptophan synthase subunit B polypeptide.
- [00404]** SEQ.ID NO: 71 sets forth a deduced amino acid sequence of a mutated *Pyrococcus furiosus* PfTrpB-7E6 tryptophan synthase subunit B
- 30 polypeptide.
- [00405]** SEQ.ID NO: 72 sets forth a nucleic acid sequence encoding another mutated *Pyrococcus furiosus* PfTrpB-Quat tryptophan synthase subunit B polypeptide.

- [00406]** SEQ.ID NO: 73 sets forth a deduced amino acid sequence of a mutated *Pyrococcus furiosus* PfTrpB-Quat tryptophan synthase subunit B polypeptide.
- 5 **[00407]** SEQ.ID NO: 74 sets forth a nucleic acid sequence used as integration cassette XII-4::TADH1-PsiH-HA-PPGK1-PTDH3-CPR-c-myc-TCYC1 for homologous recombination-based genome editing of *Saccharomyces cerevisiae* strain Sc-1.
- 10 **[00408]** SEQ.ID NO: 75 sets forth a nucleic acid sequence used as integration cassette XII-5::TADH1-PsiK-V5-PPGK1-PTDH3-PsiM-FLAG-TCYC1 for homologous recombination-based genome editing of *Saccharomyces cerevisiae* strain Sc-1.
- 15 **[00409]** SEQ.ID NO: 76 sets forth a nucleic acid sequence of modified pMM1 vector pMM1-PTDH3-ClostrSporTDC-His-TCYC1 for engineering of *Saccharomyces cerevisiae* strain Sc-1.
- [00410]** SEQ.ID NO: 77 sets forth a nucleic acid sequence for *Saccharomyces cerevisiae* promoter PGK1.
- [00411]** SEQ.ID NO: 78 sets forth a nucleic acid sequence for *Saccharomyces cerevisiae* promoter TDH3.
- 20 **[00412]** SEQ.ID NO: 79 sets forth a nucleic acid sequence for *Saccharomyces cerevisiae* promoter CLN1.
- [00413]** SEQ.ID NO: 80 sets forth a nucleic acid sequence for *Saccharomyces cerevisiae* promoter UGA1.
- [00414]** SEQ.ID NO: 81 sets forth a nucleic acid sequence encoding a synthetic HA epitope tag polypeptide
- 25 **[00415]** SEQ.ID NO: 82 sets forth deduced amino acid sequence of a synthetic HA epitope tag polypeptide
- [00416]** SEQ.ID NO: 83 sets forth a nucleic acid sequence encoding a synthetic c-MYC epitope tag polypeptide
- 30 **[00417]** SEQ.ID NO: 84 sets forth deduced amino acid sequence of a synthetic c-MYC epitope tag polypeptide
- [00418]** SEQ.ID NO: 85 sets forth a nucleic acid sequence encoding a synthetic FLAG epitope tag polypeptide
- [00419]** SEQ.ID NO: 86 sets forth deduced amino acid sequence of a synthetic FLAG epitope tag polypeptide

- [00420]** SEQ.ID NO: 87 sets forth a nucleic acid sequence encoding a synthetic V5 epitope tag polypeptide
- [00421]** SEQ.ID NO: 88 sets forth deduced amino acid sequence of a synthetic V5 epitope tag polypeptide
- 5 **[00422]** SEQ.ID NO: 89 sets forth a nucleic acid sequence encoding a synthetic HIS epitope tag polypeptide
- [00423]** SEQ.ID NO: 90 sets forth deduced amino acid sequence of a synthetic HIS epitope tag polypeptide
- [00424]** SEQ.ID NO: 91 sets forth a nucleic acid sequence of pMM1 vector
- 10 **[00425]** SEQ.ID NO: 92 sets forth a nucleic acid sequence of pCDM4 vector
- [00426]** SEQ.ID NO: 93 sets forth a nucleic acid sequence of pETM6 vector
- [00427]** SEQ.ID NO: 94 sets forth a nucleic acid sequence of pET28a(+) vector
- [00428]** SEQ.ID NO: 95 sets forth a nucleic acid sequence encoding a
- 15 *Psilocybe cubensis* PcCPR cytochrome P450 reductase polypeptide.
- [00429]** SEQ.ID NO: 96 sets forth a deduced amino acid sequence of a *Psilocybe cubensis* PcCPR cytochrome P450 reductase polypeptide.
- [00430]** SEQ.ID NO: 97 sets forth a nucleic acid sequence of pETM6-H10 vector.
- 20 **[00431]** SEQ.ID NO: 98 sets forth a nucleic acid sequence of pRSM3 vector.

SEQUENCE LISTING

- 25 **[00432]** SEQ.ID NO: 1
- ATGCAGGTGATACCCGCGTGCAACTCGGCAGCAATAAGATCACTATGTCCTACTCCCGA
 GTCTTTTAGAAACATGGGATGGCTCTCTGTCAGCGATGCGGTCTACAGCGAGTTCATAG
 GAGAGTTGGCTACCCGCGCTTCCAATCGAAATTACTCCAACGAGTTCGGCCTCATGCAA
 CCTATCCAGGAATTCAAGGCTTTTCATTGAAAGCGACCCGGTGGTGCACCAAGAATTTAT
 30 TGACATGTTTCGAGGGCATTTCAGGACTCTCCAAGGAATTATCAGGAACTATGTAATATGT
 TCAACGATATCTTTCGCAAAGCTCCCGTCTACGGAGACCTTGGCCCTCCCGTTTATATG
 ATTATGGCCAAATTAATGAACACCCGAGCGGGCTTCTCTGCATTTCACGAGACAAAGGTT
 GAACCTTCACTTCAAAAACTTTTCGATACCTGGGGATTGTTCTGTCTTCGAAAGATT
 CTCGAAATGTTCTTGTGGCCGACCAGTTCGACGACAGACATTGCGGCTGGTTGAACGAG
 35 CGGGCCTTGTCTGCTATGGTTAAACATTACAATGGACGCGCATTTGATGAAGTCTTCCT
 CTGCGATAAAAATGCCCCATACTACGGCTTCAACTCTTACGACGACTTCTTTAATCGCA
 GATTTTCGAAACCGAGATATCGACCGACCTGTAGTCGGTGGAGTTAACAACACCACCTC
 ATTTCTGCTGCTTGCGAATCACTTTCTTACAACGTCTCTTATGACGTCCAGTCTCTCGA
 CACTTTAGTTTTTCAAAGGAGAGACTTATTCGCTTAAGCATTTGCTGAATAATGACCCTT
 40 TCACCCCACAATTCGAGCATGGGAGTATTCTACAAGGATTCTTGAACGTCAACCGCTTAC

CACCGATGGCACGCACCCGTCAATGGGACAATCGTCAAAATCATCAACGTTCCAGGTAC
CTACTTTGCGCAAGCCCCGAGCACGATTGGCGACCCTATCCCGGATAACGATTACGACC
CACCTCCTTACCTTAAGTCTCTTGTCTACTTCTCTAATATTGCCGCAAGGCAAATTATG
5 TTTATTGAAGCCGACAACAAGGAAATTGGCCTCATTTTCCTTGTGTTTCATCGGCATGAC
CGAAATCTCGACATGTGAAGCCACGGTGTCCGAAGGTCAACACGTCAATCGTGGCGATG
ACTTGGGAATGTTCCATTTTCGGTGGTTCTTCGTTTCGCGCTTGGTCTGAGGAAGGATTGC
AGGGCAGAGATCGTTGAAAAGTTCACCGAACCCGGAACAGTGATCAGAATCAACGAAGT
CGTCGCTGCTCTAAAGGCTTAG

10 **[00433]** SEQ.ID NO: 2

MQVIPACNSAAIRSLCPTPESFRNMGWLSVSDAVYSEFIGELATRASNRNYSNEFGLMQ
PIQEFKAFIESDPVVHQEFIDMFEGIQDSPRNYQELCNMFNDIFRKAPVYGD LGPPVYM
15 IMAKLMNTRAGFSAFTRQRLNLHFKKLFDTWGLFLSSKDSRNVLVADQFDDRHCWLN
RALSAMVKHYNGRAFDEVFLCDKNAPYYGFNSYDDFFNRRFRNRDIDRPVVGVNNTTL
ISAACESLSYNVSYDVQSLDTLVFKGETYSLKHLLNNDPFTPQFEHGSILQGFLNVTAY
HRWHAPVNGTIVKIIINVPGTYFAQAPSTIGDPIPDNDYDPPPYLKSLVYFSNIAARQIM
FIEADNKEIGLIFLVFIGMTEISTCEATVSEGHVNRGDDLGMFHFGGSSFALGLRKDC
RAEIVEKFTEPGTVIRINEVVAALKA

20 **[00434]** SEQ.ID NO: 3

ATGATCGCTGTACTATTCTCCTTCGTCAATTGCAGGATGCATATACTACATCGTTTCTCG
TAGAGTGAGGCGGTTCGCGCTTGCCACCAGGGCCGCTGGCATTCCCTATTCCCTTCATTG
25 GGAACATGTTTGATATGCCTGAAGAATCTCCATGGTTAACATTTCTACAATGGGGACGG
GATTACAGTCTGTCTTGCCGCGTTGACTTCTAATATATGAACAGCTAATATATTGTCAG
ACACCGATATTCTCTACGTGGATGCTGGAGGGACAGAAATGGTTATTCTTAACACGTTG
GAGACCATTACCGATCTATTAGAAAAGCGAGGGTCCATTTATTCTGGCCGGTGAGCTGA
TGTTGAGTTTTTTGCAATTGAATTTGTGGTCACACGTTTCCAGACTTGAGAGTACAATG
30 GTCAACGAACTTATGGGGTGGGAGTTTGACTTAGGGTTCATCACATACGGCGACAGGTG
GCGCGAAGAAAGGCGCATGTTTCGCCAAGGAGTTCAGTGAGAAGGGCATCAAGCAATTTT
GCCATGCTCAAGTGAAAGCTGCCCATCAGCTTGTCCAACAGCTTACCAAACGCCAGAC
CGCTGGGCACAACATATTCGCCAGTAAGTACTACTTGAGGAAAATAGCGTACGCTTCGC
TGACCGGTCCGTACATCAAAGTCAGATAGCGGCAATGTCACTGGATATTGGTTATGGAA
35 TTGATCTTGCAGAAGACGACCCTTGGCTGGAAGCGACCCATTTGGCTAATGAAGGCCTC
GCCATAGCATCAGTGCCGGGCAAATTTTGGGTGATTTCGTTCCCTTCTCGTGAGCATCC
TTCTTCTATGTAGGAAGGGAAGGAGTCTAACAAGTGTTAGTAAAATACCTTCCTGCTTG
GTTCCCAGGTGCTGTCTTCAAGCGCAAAGCGAAGGTCTGGCGAGAAGCCGCCGACCATA
TGTTTGACATGCCTTATGAAACTATGAGGAAATTAGCAGTTAGTCAAATGCGTTCTCCC
40 CGTATTTTTTTCAATACTCTAACTTCAGCTCACAGCCTCAAGGATTGACTCGTCCGTCTGT
ATGCTTCAGCTCGTCTGCAAGCCATGGATCTCAACGGTGACCTTGAGCATCAAGAACAC
GTAATCAAGAACACAGCCGCAGAGGTTAATGTGCGTAAGTCAAAGCGTCCGTCCGGCAA
TTCAAATTCAGGCGCTAAAGTGGGTCTTCTCACCAAGGTGGAGGCGATACTGTAAGGA
TTTCTCAATCGTTAGAGTATAAGTGTTCTAATGCAGTACATACTCCACCAACCAGACTG
45 TCTCTGCTATGTCTGCGTTCATCTTGGCCATGGTGAAGTACCCTGAGGTCCAGCGAAAG
GTTCAAGCGGAGCTTGATGCTCTGACCAATAACGGCCAAATTCCTGACTATGACGAAGA
AGATGACTCCTTGCCATACCTCACCGCATGTATCAAGGAGCTTTTCCGGTGGAATCAAA
TCGCACCCCTCGCTATACCGCACAAATTAATGAAGGACGACGTGTACCGCGGGTATCTG
ATTCCCAAGAACACTCTAGTCTTCGCAAACACCTGGTGAGGCTGTCCATTTCATTCTAG
50 TACATCCGTTGCCCCACTAATAGCATCTTGATAACAGGGCAGTATTAAACGATCCAGAA
GTCTATCCAGATCCCTCTGTGTTCCGCCAGAAAGATATCTTGGTCCTGACGGGAAGCC

5 TGATAACACTGTACGCGACCCACGTAAAGCGGCATTTGGCTATGGACGACGAAATTGGT
AAGTGC GCTTTCAGAACCCCCCTTCCGTTGACTAGTGCCATGCGCGCATACAATATCG
CTATTGATCTGATATAACTTCCCTGCGGCATTTATTTTGGCATTCCCTTTAGTCCCGGAA
TTCATCTAGCGCAGTCGACGGTTTGGATTGCAGGGGCAACCCTCTTATCAGCGTTCAAT
ATCGAGCGACCTGTGATCAGAATGGGAAGCCCATTGACATACCGGCTGATTTTACTAC
AGGATTCTTCAGGTAGCTAATTTCCGTCTTTGTGTGCATAAATACCCCTAACGACGCACG
TTTACCTTTTTGTAAAGACACCCAGTGCCTTTCCAGTGCAGGTTTGTTCCTCGAACAGA
GCAAGTCTCACAGTCGGTATCCGGACCCTGA

10 **[00435]** SEQ.ID NO: 4

15 MIAVLFSFVIAGCIYYIVSRRVRRSRLPPGPPGIPIPIFIGNMFDMPPEESPWLTFLQWGR
DYNTDILYVDAGGTEMVILNTLETITDLLEKRGSIYSGRLESTMVNELMGWEFDLGFIT
YGDRWREERRMFAKEFSEKGIKQFRHAQVKAHQLVQQLTKTPDRWAQHIRHQIAAMSL
DIGYGIDLAEDDPWLEATHLANEGLAIASVPGKFWVDSFPSLKYLPAWFPGAVFKRKAK
VWREAADHMDMPYETMRKLAPQGLTRPSYASARLQAMDNLNGDLEHQEHVIKNTAAEVN
VGGGDTTVSAMSAFILAMVKYPEVQRKVQAEALDALTNNQIPDYDEEDDSLPLYLTACIK
ELFRWNQIAPLAI PHKLMKDDVYRGYLI PKNTLVFANTWAVLNDPEVYPDPSPVFRPERY
LGPDGKPDNTVRDPRKAAFYGRNCPGIHLAQSTVWIAGATLLSAFNIERPVDQNGKP
20 IDIPADFTTGFFRHPVPFQCRFVPRTEQVSQSVSGP

[00436] SEQ.ID NO: 5

25 ATGGCGTTTCGATCTCAAGACTGAAGACGGCCTCATCACATATCTCACTAAACATCTTTC
TTTGGACGTCGACACGAGCGGAGTGAAGCGCCTTAGCGGAGGCTTTGTCAATGTAACCT
GGCGCATTAAAGCTCAATGCTCCTTATCAAGGTCATACGAGCATCATCCTGAAGCATGCT
CAGCCGCACATGTCTACGGATGAGGATTTTAAGATAGGTGTAGAACGTTTCGGTTTACGA
ATACCAGGCTATCAAGCTCATGATGGCCAATCGGGAGGTTCTGGGAGGCGTGGATGGCA
30 TAGTTTCTGTGCCAGAAGGCCTGAACTACGACTTAGAGAATAATGCATTGATCATGCAA
GATGTCGGGAAGATGAAGACCCTTTTAGATTATGTCAACGCCAAACCGCCACTTGCGAC
GGATATAGCCCGCCTTGTTGGGACAGAAATTGGGGGGTTCGTTGCCAGACTCCATAACA
TAGGCCGCGAGAGGCGAGACGATCCTGAGTTCAAATTCTTCTCTGGAAATATTGTCGGA
AGGACGACTTCAGACCAGCTGTATCAAACCATCATACCCAACGCAGCGAAATATGGCGT
CGATGACCCCTTGCTGCCTACTGTGGTTAAGGACCTTGTGGACGATGTCATGCACAGCG
35 AAGAGACCCTTGTCATGGCGGACCTGTGGAGTGGAAATATTCTTCTCCAGTTGGAGGAG
GGAAACCCATCGAAGCTGCAGAAGATATATATCCTGGATTGGGAACTTTGCAAGTACGG
CCCAGCGTCGTTGGACCTGGGCTATTTCTTGGGTGACTGCTATTTGATATCCCGCTTTC
AAGACGAGCAGGTCGGTACGACGATGCGGCAAGCCTACTTGCAAAGCTATGCGCGTACG
AGCAAGCATTTCGATCAACTACGCCAAAGTCACTGCAGGTATTGCTGCTCATATTGTGAT
40 GTGGACCGACTTTATGCAGTGGGGGAGCGAGGAAGAAAGGATAAATTTTGTGAAAAGG
GGGTAGCTGCCTTTCACGACGCCAGGGGCAACAACGACAATGGGGAAATTACGTCTACC
TTACTGAAGGAATCATCCACTGCGTAA

45 **[00437]** SEQ.ID NO: 6

50 MHIRNPYRTPIDYQALSEAFPPLKPFVSVNADGTSSVDLTIP EAQRAFTAALLHRDFGL
TMTIPEDRLCPTVPNRLNYVLWIEDIFNYTNKTLGLSDDRPIKGV DIGTGASAIYPMLA
CARFKAWSMVGTEVERKCIDTARLNVVANNLQDRLSILETSIDGPILVPIFEATEEY EY
EFTMCNPPFYDGAADMQTS DAAKGFGFGV GAPHSGTVIEMSTEGGESAFVAQMVRESLK
LRTRCRWYTSNLGKLKSLKEIVGLLKELEISNYAINEYVQGSTRRYAVAWSFTDIQLPE
ELSRPSNPELSSLF

[00438] SEQ.ID NO: 7

5 ATGCATATCAGAAATCCTTACCGTACACCAATTGACTATCAAGCACTTTTCAGAGGCCTT
CCCTCCCCTCAAGCCATTTGTGTCTGTCAATGCAGATGGTACCAGTTCTGTTGACCTCA
CTATCCCAGAAGCCCAGAGGGCGTTCACGGCCGCTCTTCTTCATCGTGACTTCGGGCTC
10 ACCATGACCATAACCAGAAGACCGTCTGTGCCCAACAGTCCCCAATAGGTTGAACTACGT
TCTGTGGATTGAAGATATTTTCAACTACACGAACAAAACCTCGGCCTGTCGGATGACC
GTCCTATTAAAGGCGTTGATATTGGTACAGGAGCCTCCGCAATTTATCCTATGCTTGCC
TGTGCTCGGTTCAAGGCATGGTCTATGGTTGGAACAGAGGTCGAGAGGAAGTGCATTGA
CACGGCCCGCCTCAATGTCGTCGCGAACAACTCTCCAAGACCGTCTCTCGATATTAGAGA
15 CATCCATTGATGGTCCTATTCTCGTCCCCATTTTCGAGGCGACTGAAGAATACGAATAC
GAGTTTACTATGTGTAACCTCCATTCTACGACGGTGTGCGGATATGCAGACTTCGGA
TGCTGCCAAAGGATTTGGATTTGGCGTGGGCGCTCCCCATTCTGGAACAGTCATCGAAA
TGTCGACTGAGGGAGGTGAATCGGCTTTCTGTCGCTCAGATGGTCCGTGAGAGCTTGAAG
CTTCGAACACGATGCAGATGGTACACGAGTAACCTGGGAAAGCTGAAATCCTTGAAAGA
AATAGTGGGGCTGCTGAAAGAACTTGAGATAAGCAACTATGCCATTAACGAATACGTTT
20 AGGGGTCCACACGTCGTTATGCCGTTGCGTGGTCTTTCACTGATATTCAACTGCCTGAG
GAGCTTTCTCGTCCCTCTAACCCCGAGCTCAGCTCTCTTTTCTAG

[00439] SEQ.ID NO: 8

25 MHIRNPYRTPIDYQALSEAFPPLKPFVSVNADGTSSVDLTIP EAQRAFTAALLHRDFGL
TMTIPEDRLCPTVPNRLNYVLWIEDIFNYTNKTLGLSDDRPIKGV DIGTGASAIYPMLA
CARFKAWSMVGTEVERKCIDTARLNVVANNLQDRLSILETSIDGPILVPIFEATEEY EY
EFTMCNPPFYDGAADMQTS DAAKGFGFGVGAPHSGTVIEMSTEGGESAFVAQMVRESLK
30 LRTRCRWYTSNLGKLKSLKEIVGLLKELEISNYAINEYVQGST RRYAVAWSFTDIQLPE
ELSRPSNP ELSSLF

[00440] SEQ.ID NO: 9

35 ATGCCTTCCAGTCACCCTCACATTACTCATCGCTATCGGGTTCCTTCGAGTGACGACCA
TGAACGTATATCTGCTCTGTTCTTGGGTCCCAAAGCAGAAAATGCCGCATTTCTCCAGC
AATGGTTGACCACGGTCGTCGCACAGCAAAAGGCTGCCCGCGATGCATACTTCCCGGAT
GACAATGCTTTTATTACTACAGACATGCAAACCTTCCCCCGCCTTTGCTCAGACTACTAA
AGTAATCGCCTCCAATCTCACCGAATTATTGACTGCACTCGGTGAAAGGTCGATTCCCTT
TCTTCTCACCTCGGTACAGCGGCCATATGTCTGTGGACCAAAGTCTACCTGCCATTCTC
40 GGATTCTTATCGACCACATTTTATAATCCTAACAATGTTGCCTTCGAGGCTAGTCCATT
CACGACCCTCATCGAGGAAGAAGTTGGCTTGCAACTCTCTGAAATGCTGGGTTATAATC
GGCTAAATAACACCGAGAAACCTCTCGCCTGGGGACATATTGCATCAGGTGGAACGTGT
GCAAACCTTGGAAGCGATGTGGGCGGCGCGAAACCTCAAGTTTTACCCTCTCTCACTCCG
TGATGCTTCAGCCGAAGGCGCAGAGATGGAATTCATTCTGACACATTCTCCGTCAAAA
45 CCTGTGTTGGTGACAAAAAATTATTAAAGGATTGCAGCCCATGGGAACTCCTCAATTTG
CATGTTTCTACTATCTTAGACATGCCCCGACCGTCTGCACGACGAGTACAATATTTACC
TCAGTTCCTCGAAAAGGTTATGCGAAAGTATATCATCCAGTCTACCAACAAAGACACGT
TGATGCAGCGTTGGGGACTTACCCAACAACCTGTCGTTTTATCCCCGAGCACAACCAT
TATTCCTGGCCAAAGGCTGCAGCTGTGCTCGGTATTGGCTCAGACAACCTTCGCAACGT
50 CCCAGTAGACATCCAAGCCCACATGGACATAAACGAACTCGATCGTATGTTAAAAATTT
GCTTGACGAGGAGACGCCAGTATATCAAGTAGTTGCTGTTATCGGTACCACCGAAGAG

5 GCGGTGTCGATCGCATTACGGAGATCCTGAAGCTGCGCCAAAAGTATGAAGCTTTGGG
 GCTGTCTTTTGCCATCCATGCAGATGCTGCTTGGGGAGGCTATTTTGCAACCATGCTAC
 CCAAAGATACATTGGGTTCGAAACCGGACTAGGCTTCCCAAAGAGGACACTACCTCGGGC
 TTTGTCCCTCACGTGCGTCTGCGCGAGGAGAGCGCGTTACAACCTCAGCCATATAAAGTA
 10 TGCCGATTCTATTACTATCGACCCGCACAAGGCAGGCTATGTTCCCTTACCCCGCTGGGG
 CACTCTGTTATCGCGACGGAAGAATGAGGTACCTGCTTACATGGTCCGCGCCCTACCTT
 GCCCAAGGCAACGAGGGCCAAAGTATCGGAATATACGGGATCGAAGGAAGCAAACCTGG
 TGCAGCAGCATCCGCGGTATTTCATGGCGCACGAAACCATTGGCCTGACTCCTTCTGGAT
 ACGGGAACCTTCTTGGCCAGGCAATGTTTACATGTCGCCGATACGCTGCTCACTGGTCT
 15 GCAATGTCAACGGATACTACCAGTTTCACTGTCACCCCGTTCAATCCTATCCCTGCTGA
 CATCGACCCCAACGCTGACCCCGCAAAGGTTCGAAGAGCAAAAACAGTTCATCAGAGATC
 GTATCTTGTTCAAATCGAACGAGGAAATATACAACGATTCTGAGGCTATGGAACCTTG
 CACCAACTTGGGTCCGATCTCAATATCAACGTTTTTCGCATGCAACTTCCGCGACCGCGA
 TAATAATCTCAACACCGACGTCGAGGAAGCCAACTGGCTCAATAACCGTATTTTCCAAC
 20 GCTTTTCTGTTACAAGTGCTGAGGAGAACCATTGGAAACGCCATTCTTCCTCAGCTCA
 ACTACATTGAAACAATCCGAATACGGCGTCTGCGCAACCGAAGTAAAGAGACGCATGGG
 ACTTGTTGGTGACCAGGATGTTATAGTCCTGAGGAACGTCGTTATGTCTCCATTTACTA
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 GTCGAGTATGCACGGATCCGCAACGATATGAAACCTAGCATTACACACCTTCCTTCTTCA
 25 TGGTTCAGGAGAGCAATACTATCTTGTCCACACCCCAACGATCCATATGGCCAGCGGCC
 GTCGCCAAATCATCCTTTTCAGTAAATGTTGAAGGCCAAGTTCGGCAGGCGATACATGCC
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 CGTTGACGGAGGATCATTTGACGGCATACTCACCATCGGAAAGAGGAAAAGTATTTCA
 AAGTGAAGATTTCAAACATTAAAGTAGTCAAGAAGCGCTCTCTGATGACTGAGGACCTG
 30 GAATCTGCGTACCCATCGTTGATGCCATTCTATTTCTACGGGACTCAAGGACACGCTCA
 TCTCGACCATGTCATTACTGTCGTTTCTAACATCCATCTGAGTGCTGGCGAAATACAGT
 ACAAATTCGACGACGAGGTGTCAAGCGAGGACCTCGCCAAGGGCCTCATTGTTGTTGCT
 GAGAACGTACACGAGGCATCCATGCAGCCCTTCCCGCTCATGAAAGATTTCAAGATCAC
 CAACCAATTCTTCTTCAGCTCCGGGCAAATACTCCGCGTCAAAGTGACAGAGATCCAT
 35 ACCCGGCATCGACAATGGATCCCATCCCTCTCCACGACATCAAGAACCAGCCCGTCGTG
 ACACAAGGCACCATCACGCTCGTCGGAAATATTTACGTCGATTCTGATGCGCTCAACGT
 CGCTTCCGAGCCTACTGCCGACGAAGACGCGGCGCATGTTCCCTCACGCTCGCAACATGT
 ACGGCGAGATGACCGCTGGAACGATCAAAGGCTGGCAAACGCTGTTTCGTCATTTCCAC
 AACAAATTGGAGACTGTTGCTCCGACGAAGTAG

35

[00441] SEQ.ID NO: 10

40 MPSSHPHITHRYRVPSSDDHERISALFLGPKAENAAFLQQWLTTVVAQQKAARDAYFPD
 DNAFITTTDMQTSFAFAQTTKVIASNLTELLTALGERSIPFFSPRYSGHMSVDQSLPAIL
 GFLSTTFYNPNNVAFEASPFTTLIEEEVGLQLSEMLGYNRLNNTTEKPLAWGHIASGGTV
 ANLEAMWAARNLKFYPLSLRDASAEGAEMEFIRDTSVKTCTVGDKKLLKDCSPWELLNL
 HVSTILDMPDRLHDEYNISPFLEKVMRKYIIQSTNKDTLMQRWGLTQQPVVLS PSTNH
 YSWPKAAAVLGIGSDNLRNVPVDIQAHDINELDRMLKICLDEETPVYQVVAVIGTTEE
 45 GGVDRITEILKLQKYEALGLSFAIHADAAGGYFATMLPKDTLGRNRTRLPKEDTTSG
 FVPHVGLREESALQLSHIKYADSITIDPHKAGYVPYPAGALCYRDGRMRYLLTWSAPYL
 AQGNEGQSIGIYGIEGSKPGAAASAVFMAHETIGLTPSGYGNLLGQAMFTCRRYAAHWS
 AMSTDTSFTVTPFNPIPADIDPNADPAKVEEQKQFIRDRI LFKSNEEIYNDSEAMELL
 HQLGSDLNINVFACNFRDRDNNLNTDVEEANWLNRI FQRF SVTSAEENPLETPFFLSS
 50 TTLKQSEYGVCATEVKRRMGLVGDQDVIVLRNVMSPTTTNDFVGTLANTFQKIVEEEE
 VEYARIRNDMKPSIHTFLLHGSGEQYYLVHTPTIHMASGRRQIILSVNVEGQVRQAIHA
 HERVEAVIVHNTVPLRLDEIVDGGGFDGILTIGKRKTSFKVKISNIKVVKKRSLMTEDL

ESAYPSLMPFYFYGTQGHABLDHVITVVPNIHLSAGEIQYKFDDEVSSSEDLAKGLIVVA
ENVHEASMOPFPLMKDFKITNQFFFSSGQILRVKVYRDPYPASTMDPIPLHDIKNQPVV
TQGTITLVGNIYVDS DALNVASEPTADEDAAHVPHARNMYGEMTAGTIKGWQNAVRHFH
NKLETVAPTK

5

[00442] SEQ.ID NO: 11

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GACCTTTGTTACTGCAGGATATCCTCGTCCCGAAGATACTGTTCCCATCTTGCTGGCCA
10 TGGAGGCCGGTGGTGTGATATCATCGAGCTTGGTATGCCATTTTCAGACCCAATTGCA
GATGGTCCTGTCATCCAGGAAACGAACACAATCGCCGTTGCAAACCAGGTAGATTATAC
CACTGTTCTCGGACAACTTCGGGAAGCCCGCAAACAAGGGCTCAAGGCACCCGTTCTTC
TGATGGGATATTATAACCCCATATTGGCTTACGGAGAAGACAGATCTATTCAAGATGCG
GCTGAAGCTGGAGCCAATGGGTTTTATTATGGTCGACCTTCCACCCGAGGAGGCTGTGCG
15 TTTTCGAGAGAAATGTATCAAATCCAACCTCTCATATGTTCCCTCTAATTGCACCCTCAA
CGACTCTGTGCGGTATAAAGTTCCCTCTCAACAATTGCAGACACGTTTCATCTATGTCGTG
TCTAAATGGGAACCACCGGATCCTCAGAGAAGGTTGCCATGAATAACGCCCTTCCCAC
CATCATCGATCGTATTTCGCGAGTACGCTGAAGTTCCTTTAGCAGTCGGATTTGGAGTCG
CCACTCGGGCTCACTTCAACTACGTCGCCGATTCCGGTGTGATGGTGTGCTTATTGGC
20 ACCAACTCGTTAACGTTATTAAAGAGTCACCGCAAGGGGAAGCACCCAAAAATGTTGA
GGCATACTGCCGTGAGATGAGCCAAAAGGGAGAAACAAATCGCGTCAAATCTCCACCAA
CTGCCCGTGTGCCAGCTCCGAATCAATTCCTGTTGTTGTTTCCTTCTGTTCTCCCCGCA
CGTTTTCGGAGAATTTCGGAGGACAATACGTTCCCGAAGCTCTTGTCGATTGTCTGGTTGA
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25 CGCATGCCGGATATGCAAATCGTCTTTCACAAATATACCTCGCCGAAAATCTCACCAAG
GATGCTGGGGGTGCAAATATTTGGTTGAAACGTGAAGATTTGAACCACACAGGTTCCCA
CAAAATCAATAACGCTTTGGGACAAATTCCTGCTTGCCCGGAGAATCGGAAAGACCAGAA
TTATCGCAGAAACAGGTGCCGGCCAGCATGGTGTGCAACAGCGACTGTTTGCGCTAAG
TTTGGAATGGAATGTGTTATCTACATGGGCGCAGAAGATGTGCGACGGCAAGCTCTAAA
30 TGTATTTCAGGATTGAGATGCTAGGAGCAAAAGTTGTTCCCTGTTACTTCAGGATCATGCA
CATTGAAGGACGCTGTAAACGAGGCCTTCCGTGACTGGGTGACAAACCTTTCTACGACG
CATTATTTGGTTGGCTCTGTAATTGGACCTCATCCCTTCCCCACCATTTGTCCGAGATTT
CCAAAAGGTCATTGGTCAAGAGATCAAGGCTCAGATGTTGGCCGCCCGCGGCAAACTTC
CTGATGTCGTCGTCGCTTGTGTTGGTGGAGGAAGCAATGCTATCGGTACGTTCTATGAT
35 TTTATTGGCGACAAGAGTGTACGTCTAGTTGGGGTGAAGCAGGAGGAGAAGGTATTGA
CGGAGACCGACATAGCGCCACACTTTCGATGGGGCAACCGGGAGTACTTCACGGTGTTA
GAACATATATTCTACAAGACAAGGCCGGTCAAATCATCGAGACGCACTCAATCAGCGCT
GGATTGGATTATCCCGGCGTTGGACCAGAACATGCTTGGCTAAAGGACTCTAAAAGAGC
AGAATATGTTGTCGCCACAGACGAAGAAGCACTTCGCGGTTTCCGTATGCTAACACAAA
40 GGGAGGGAATTATTCTGCCCCGTTGAATCTTCCCATGCGATCTGGGAGGCTGTCAGGATT
GCCCCGACCATGTGCAAGGACCAGGATCTTGTGTTGTGTTTGTCTGGCCGAGGTGATAA
AGACGTTGAGCAAATTTCTCAACTTCTTCCCAAGTGGGCGGATATTCTAGACTGGCATG
TTTCTTCCCATGCCGTTGGACACACAACAAATTTCTAA

45

[00443] SEQ.ID NO: 12

MEAIKKVFENKKAEGIPVLVTFVVTAGYPRPEDTVPILLAMEAGGADI IELGMPFSDPIA
DGPVIQETNTI AVANQVDYTTVLGQLREARKQGLKAPVLLMGYYNPILAYGEDRSIQDA
AEAGANGFIMVDLPPEEAVAFREKCIKSNLSYVPLIAPSTTSLRIKFLSTIADTFIYVV
50 SKMGTTSSEKVMNNALPTIIDRIREYAEVPLAVGFGVATRAHFNYVADSGADGVVIG
TKLVNVIKESPOGEAPKNVEAYCREMSQKGETNRVKSPTARAASSESI PVVVP SVLPA

RFGEFGGQYVPEALVDCLVELEEAHKSAMADPEFQKELOSHAGYANRPSQIYLAENLTK
DAGGANIWLKREDLNHTGSHKINNALGQILLARRIGKTRI IAETGAGQHGVATATVCAK
FGMECVIYMGAEDVRRQALNVFRIEMLGAKVVPVTS GSCTLKDAVNEAFRDWVTNLSTT
HYLVGSGVIGPHFPPTIVRDFQKVI GQE IKAQMLAARGKLPDVVVACVGGGSNAIGTFYD
5 FIGDKSVRLVGVEAGGEGIDGRHSATLSMGQPGVLHGVRTYI LQDKAGQIIETHSISA
GLDYPGVGPEHAWLKDSKRAEYVVATDEEALRGFRMLTQREGI I PALESSHAIWEAVRI
ARTMSKDQDLVVCLSGRGDKDVEQISQLLPKWADILDWHVSSHAVGHTTKF

[00444] SEQ.ID NO: 13

10 ATGGAAAGGCGGAAGCGTGAGCGTCTTGGCTCACTCGGCCGACCGACCAAAAAGGAGCT
CCGCATGATCCGATCTGTGGTGATCGTGGGTGGTGGCACGGCGGGCTGGATGACCGCCT
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GTCAGGCGGATCGGGGTCGGCGAAGCGACCTTCAGCACGGTCCGCCACTTCTTCGACTA
15 CCTGGGCCTCGACGAGCGCGAGTGGCTGCCCCGCTGCGCCGGCGGCTACAAGCTCGGCA
TCCGCTTCGAGAACTGGAGCGAGCCGGGCGAGTACTTCTACCACCCGTTTCGAGCGCCTG
CGCGTCGTCGACGGCTTCAACATGGCCGAGTGGTGGCTCGCGGTTCGGCGACCGCAGGAC
GTCCTTCAGCGAGGCCTGCTATCTCACGCACCGGCTGTGCGAGGCCAAGCGGGCGCCCC
GCATGCTCGACGGCTCGCTCTTCGCCTCCCAGGTGGACGAGTCGCTCGGCCGCTCGACC
20 CTGGCCGAGCAGCGCGCCAGTTCCCGTACGCCTACCACTTCGACGCCGACGAGGTTCG
CCGCTACCTGTCGGAGTACGCCATCGCCCGCGGCGTCCGCCACGTGGTTCGACGACGTGC
AGCACGTTCGGCCAGGACGAGCGCGGCTGGATCAGCGGCGTCCACACCAAGCAGCACGGC
GAGATCAGCGGCGACCTGTTTCGTCGACTGCACCGGCTTCCGCGGCCTGCTCATCAACCA
GACGCTGGGCGGCAGGTTCCAGTCTTCTCCGACGTGCTGCCCAACAACCGGGCGGTCG
25 CGCTGCGCGTCCCGCGGGGAGAACGACGAGGACATGCGGCCGTACACGACGGCGACCGCG
ATGAGCGCCGGCTGGATGTGGACGATCCCGCTGTTCAAGCGCGACGGCAACGGCTACGT
CTACTCCGACGAGTTCATCTCGCCGGAGGAGGCCGAGCGCGAGCTGCGGTCCACCGTCG
CCCCCGGCCGCGACGACCTGGAGGCCAACACATCCAGATGCGGATCGGCAGGAACGAG
CGCACCTGGATCAACAACCTGCGTCGCCGTCGGCCTGTCCGCCGCCTTCGTCGAGCCGCT
30 GGAGTCGACCGGCATCTTCTTCATCCAGCACGCCATCGAGCAGCTCGTGAAGCACTTCC
CCGGCGAGCGCTGGGACCCGGTGTGATCAGCGCGTACAACGAGCGCATGGCGCACATG
GTCGACGGGGTCAAGGAGTTCCTCGTCTCCACTACAAGGGCGCCCAGCGCGAGGACAC
CCCCTACTGGAAGGCCGCCAAGACCAGGGCCATGCCCGACGGCCTCGCCCGCAAGCTGG
AGCTGTCCGCCTCCACCTGCTGGACGAGCAGACGATCTACCCCTACTACCACGGCTTC
35 GAGACCTATTCTGTGGATCACCATGAACCTCGGTCTCGGCATCGTGCCCGAGCGGCCGCG
TCCCGCGCTCCTGCACATGGACCCGGCGCCCGCGCTGGCCGAGTTTGAACGGCTCAGGC
GCGAGGGCGACGAGCTGATCGCCGCCCTGCCAGCTGCTACGAGTACCTCGCCAGCATC
CAATGA

40 [00445] SEQ.ID NO: 14

MERRKRERLGS LGRPTKKELRMIRSVVIVGGGTAGWMTASYLKAAFDDRIDVTLVESGN
VRRIGVGEATFSTVRHFFDYLG LDEREWLPRCAGGYKLGIRFENWSEPGEYFYHPFERL
RVVDGFNMAEWLAVGDRRTSFSEACYLTHRLCEAKRAPRMLDGS LFA SQVDES LGRST
45 LAEQRAQFPYAYHFD ADEVARYLSEYAIARGVRHVVDVQHV GQDERGWISGVHTKQHG
EISGDLFVDCTGFRGLLINQTLGGRFQS FSDVLPNNRAVALRVPRENDEDMRPYTTATA
MSAGWMWTIPLFKRDGNGYVYSDEFISPEEAERELRSTVAPGRDDLEANHIQMRIGRNE
RTWINNCVAVGLSAAFVEPLESTGIFFIQHAIEQLVKHFPGERWDPVLI SAYNERMAHM
VDGVKEFLVLHYKGAQREDTPYWKAAKTRAMPDGLARKLELSASHLLDEQTIYPYHGF
50 ETYSWITMNLGLGIVPERPRPALLHMDPAPALAEFERLRREGDELIAALPSCYEYLASI
Q

[00446] SEQ.ID NO: 15

5 ATGACCGCCGCCTACCTGAAGACCGCGTTTCGGCGACCGGCTTTCGATCACCGTCGTGGA
ATCGAGCAGAATCGGGACCATCGGCGTCGGTGAGGCGACCTTCAGCGACATCCAGCACT
TCTTCCAGTTCTCAACCTCCGGGAACAGGACTGGATGCCGGCCTGCAACGCCACCTAC
AAGCTGGGCATCCGCTTCGAGAACTGGCGGCATGTCGGCCATCATTTCTACCAGCCGTT
CGAGCAGATCCGCCCCTGCTACGGCTTTCGCTGACCGACTGGTGGCTGCACGACGCGC
10 CGACCGACCGCTTCGACACCGACTGCTTCGTTCATGCCCAACCTGTGCGAGGCGGGCGC
AGCCCGCGCCACCTCGACGGCACGCTGGCCGACGAGGACTTCGTGGAGGAGGGCGACGA
GCTCGCCAACCGCACCATGTCCGAGCACAGGGCAAGTCGCAGTTCCCGTACGCCTACC
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GAGCACGTCGTTCGACGACGTCTGGACGTGCGGCTGGACCAGCGCGGGTGGATCGAGCA
15 CGTGGTCACCGCCGAGCACGGCGAGATCCACGGCGACCTGTTTCGTTCGACTGCACCGGTT
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CTGCCCAACGACAGCGCGGTTCGCCCTCCAGGTCCCGCTGGACATGCAGCGGCGCGGCAT
CGTGCCGAACACCACGGCCACCGCGCGGGAGGCCGGCTGGATCTGGACCATCCCGCTGT
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20 GAGCGCACGCTGCGCGAGTTCGTTCGGCCGCGCGGCCGCGGACGTGGAGGCCAACCACAT
CCGCATGCGGATCGGCCGACAGGAGTCTGGCGGAACAACGCGTGGCCATCGGCC
TGTCCAGCGGCTTCGTTCGAGCCGCTGGAGTCGACCGGGATCTTCTTCATCCACCACGCC
ATCGAGCAGCTGGTGAAGCACTTCCCGCGCGCCGACTGGAACCCGAAGTCCCGGGACAT
GTACAACTCCGCGGTTCGCGCACGTGATGGACGGCATCCGCGAGTTCCTGGTGATCCACT
25 ACCGGGGCGCGGCGCGGGCCGACAACCAGTACTGGCGCGACACCAAGACCCGCCGCTG
CCGACGGCCTGGCCGAGCGCATCGAGTGCTGGCAGACGCAGCTGCCGGACACCGAGAC
GATCTACCCGTAATAACACGGGCTGCCGCCCTACTCCTACATGTGCATCCTGATGGGCG
GCGGGGCCATCCGGACGCCGGCCTCGGCCGCGTTGGCCCTGACCGACCAGGGGGCCGCG
CAGAAGGAGTTTCGCCGCCGTCCGGGACCGGGCCGCGCAGCTGCGCGACACGCTGCCCAG
30 CCACTACGAGTACCTCGCGCGGATGCGTGGTCTGGATGTCTGA

[00447] SEQ.ID NO: 16

35 MTAAYLKTAFGDRLSITVVESSRIGTIGVGEATFSDIQHFFQFLNLREQDWMPACNATY
KLGIRFENWRHVHGHFYQPFQIRPVYGFPLTDWWLHDAPTDRFDTD CFVMPNLCEAGR
SPRHLDTLADDEFVEEGDELANRTMSEHQKSGFPYAYHFEEALLAKFLTGYAVDRGV
EHVVDVLDVRLDQRGWIEHVVTAEHGEIHGDLFVDCTGFRGLLLNKGALGVFVSYQDT
LPNDSAVALQVPLDMQRRGIVPNTTATAAREAGWIWTIPLFGRVGTGYVYAKDYLSPEEA
ERTLREFVGPAAADVEANHIRMRIGRSQESWRNNCVAIGLSSGFVEPLESTGIFFIHHA
40 IEQLVKHFPAADWNPKSRDMYNSAVAHVMDGIREFLVIHYRGAARADNQYWRDTKTRPL
PDGLAERIECWQTQLPDTETIYPYHGLPPYSYMCILMGGGAIRTPASAALALTDQGAA
QKEFAAVRDRAAQLRDTLPSHYEYLARMRGLDV

[00448] SEQ.ID NO: 17

45 ATGAACACGAGAAATCCGGACAAGGTCGTTCATCGTCGGCGGGCGGCACGGCGGGATGGAT
GACCGCCTCGTACCTGAAGAAGGCGTTCGGCGAGCGCGTGTCCGTGACCCTCGTCGAAT
CGGGCACCATCGGCACCGTCGGCGTCGGCGAGGCGACCTTCAGCGACATCCGGCACTTC
TTCGAATTCCTCGACCTGCGGGAGGAGGAATGGATGCCGGCCTGCAACGCCACGTACAA
50 GCTGGCCGTCCGCTTCAGGACTGGCAGCGCCCCGGCCACCACTTCTACCACCCGTTTCG
AGCAGATGCGCTCCGTAGACGGGTTCGCCCTGACCGACTGGTGGCTGCAGAACGGGGCCG

ACCGACCGGTTTCGACAGGGACTGCTTCGTGATGGCGTCGCTGTGCGACGCGGGGCGCAG
 CCCGCGCTATCTCAACGGTTCCTGCTGCAGCAGGAGTTCGACGAGCGCGCGGAGGAGC
 CGGCGGGGCTCACCATGTCCGAGCACCAGGGCAAGACGCAGTTCCTTACGCCTACCAC
 5 TTCGAGGCGGGCCCTGCTCGCCGAATTCCTTTCTGGGTACTCCAAGGACCGCGGCGTGAA
 GCACGTGGTTCGACGAGGTGCTGGAGGTGAAGCTCGACGACCGCGGATGGATCAGCCACG
 TTGTCACCAAGGAGCACGGCGACATCGGCGGGCGACCTGTTTCGTGCGACTGCACCGGTTTC
 CGCGGGCTACTGCTGAACCAGGCGCTGGGTGTGCCCTTCGTCTCCTACCAGGACACCCT
 GCCCAATGACAGCGCGGTTCGCCCTCCAGGTGCCGCTCGACATGGAGGCGCGGGGCATCC
 10 CGCCGTACACCCGGGCCACCGCCAAGGAGGCCGGGTGGATCTGGACGATCCCGCTGATC
 GGCCGGATCGGCACCGGGTACGTGTACGCCAAGGACTACTGCTCGCCGGAGGAGGCCGA
 GCGCACCCCTGCGCGAGTTCGTTCGGTCCGGAGGCCGCCGACGTCGAGGCCAACCACATCC
 GCATGCGGATCGGGCGCAGCGAGCAGTCCTGGAAGAACAACCTGCGTCGCGATCGGGCTC
 TCCAGTGGCTTCGTGCAACCCCTCGAGTCGACCGGCATCTTCTTCATCCACCACGCCAT
 15 CGAGCAGTTGGTGAAGCACTTCCCGCGGGCGACTGGCACCCGCAGCTGCGCGCCGGCT
 ACAACTCGGCCGTCGCCAACGTTCATGGACGGGGTCCGGGAGTTCCTCGTCTGCACTAC
 CTGGGCGCCGCGCGCAACGACACCCGGTACTGGAAGGACACCAAGACCCGGGCGGTTCC
 GGATGCCCTGGCGGAGCGCATCGAGCGCTGGAAGGTGCAGCTGCCCCACTCCGAGAACG
 TCTTCCCCTACTACCACGGCCTGCCGCCGTACTCGTACATGGCCATCCTGCTCGGGACC
 GGCGCGATCGGGCTGCGACCGTTCGCCGGCGCTCGCACTGGCCGACCCGGCGGGCGGCGGA
 20 GAAGGAGTTCACCGCGATCCGGGACAGGGCGCGGTTCTTGGTCGACACCCTGCCGAGCC
 AGTACGAGTACTTCGCCGCGATGGGGCAGCGTGTCTGA

[00449] SEQ.ID NO: 18

25 MNTRNPDKVIVGGGTAGWMTASYLKKAFGERSVTLVESGTIGTVGVGEATFSDIRHF
 FEFLDLREEEWMPACNATYKLAVRFQDWQRPGRHHFYHPFEQMRSDVGFPLTDWWLQNGP
 TDRFDRDCFVMASLCDAGRSRYLNGSLAQEFDERAEPAGLTMSEHQGKTQFPYAYH
 FEAALLAEFLSGYSKDRGVKHVVDEVLEVKLDDRGWISHVVTKEHGDIGGDLFVDCTGF
 30 RGVLLNQALGVFPVSYQDTLPNDSAVALQVPLDMEARGIPPYTRATAKEAGWIWTIPLI
 GRIGTGYVYAKDYCSPEEAERTLREFVGPEAADVEANHIRMRIGRSEQSWKNNCVAIGL
 SSGFVEPLESTGIFFIHHAIEQLVKHFHPAGDWHPLRAGYNSAVANVMDGVREFVLVHY
 LGAARNTRYWKDTKTRAVPDALAERIERWKVQLPDSENVFPYYHGLPPYSYMAILLGT
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35 [00450] SEQ.ID NO: 19

ATGGACAATCGAATCAAGACAGTCGTGATCCTGGGCGGCGGCACCGCCGGCTGGATGAC
 TGCGGCGTATCTCGGCAAGGCGCTGCAGAACACGGTGAAGATCGTGGTCTTGAGGGCGC
 CCACCATCCCGCGGATCGGTGTGGGCGAAGCCACCGTCCCCAACCTGCAGCGCGCGTTC
 40 TTCGACTACCTCGGCATCCCCGAGGAGGAGTGGATGCGCGAGTGCAACGCCAGTTACAA
 GATGGCGGTGAAGTTCATCAACTGGCGCACACCGGGGAGGGCAGCCCGGATCCCCGGA
 CGCTCGACGACGGTCACACCGACACCTTCCACCACCCCTTCGGAAGTGTGCCGTCCGCC
 GACCAGATAACCGCTCTCCCACTACTGGGCGGCCAAGCGGCTCCAGGGCGAGACCGACGA
 GAACTTCGACGAGGCGTGTTCGCCGACACCGCGATCATGAACGCCAAGAAGGCGCCCC
 45 GCTTCCTCGACATGCGGCGGGCGACCAACTACGCCTGGCACTTCGACGCCAGCAAGGTC
 GCCGCGTTCCTGCGCAACTTCGCCGTACCAAGCAGGCGGTGAGACGTCGAGGACGA
 GATGACCGAGGTCTCACCGACGAACGGGGCTTCATCACCGCCCTGCGCACCAAGTCCG
 GACGGATCCTGCAGGGTGACCTCTTCGTGCACTGCTCCGGCTTCCGCGGGCTGCTGATC
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 50 GGTGCGCCACGGCCGTACCGCACGACGACGAGAAGAAGGTGTCGAGCCGTACACCTCCT
 CGATCGCCATGGAGGCCGGCTGGACCTGGAAGATTCCCATGCTGGGCGGTTCCGGCAGC

GGTCACGTCTACTCCGACCACTTCGCCACCCAGGACGAGGCCACCCTGGCCTTCTCGAA
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GCAACCGCAGGGCCTGGGTGCGCAACTGCGTCAGCGTCGGCCTCGCGTCGTGCTTCGTG
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5 GCACTTCCCCGACAAGACCTTCGACAAGGTGCTCGTCGACCGGTTCAACCGGGAGATCG
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CAAGGTTCGAGACGTACCGGGCCGGGCTGCCGGTCAACCTGCCGGTCACCGACGAGGGGA
CCTACTACGGCAACTTCGAGGCCGAGTTCCGGAACCTTCTGGACCAACGGCAGCTACTAC
10 TGCATCTTCGCCGGCCTCGGCCTGATGCCGCGCAACCCGCTGCCCGCGCTCGCCTACAA
GCCGCAGTCGATCGCGGAGGCCGAGCTGCTGTTCCCGACGTCAAGCGCAAGGGGGACA
CCCTGGTTCGAGTCGCTGCCGTCGACCTATGACCTGCTGCGTCAGTTGCACGGTGCCTCG
TGA

15 **[00451]** SEQ.ID NO: 20

MDNRIKTVVILGGGTAGWMTAAYLGKALQNTVKIVVLEAPTIPRIGVGEATVPNLQRAF
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DQIPLSHYWAAKRLQGETDENFDEACFADTAIMNAKKAPRFLDMRRATNYAWHFDASKV
20 AAFLRNFAVTKQAVEHVEDEMTEVLTDERGFITALRTKSGRILQGDLFVDCSGFRGLLI
NKAMEEPFIDMSDHLNCNSAVATAVPHDDEKNGVEPYTSSIAMEAGWTWKIPMLGRFGS
GHVYSDHFATQDEATLAFSKLWGLDPDNTEFNHVRFRVGRNRRRAWVRNCVSVGLASC
EPLESSGIYFIYAAIHMLAKHFPDKTFDKVLVDRFNREIEEMFDDTRDFLQAHYYFSPR
VDTPFWRANKELKLADSIKDKVETYRAGLPVNLVPTDEGTYYGNFEEFRNFWTNGSYY
25 CIFAGLGLMPRNPLPALAYKPQSI AEAEELLFADV KRKGDTLVESLPSTYDLLRQLHGAS

[00452] SEQ.ID NO: 21

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30 CGCCTCCTACCTGGCGAAGGCGCTCGGTGACACCGTCACGATCACCTGCTGGAAGCAC
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GACGGCCGTGAAGTTCATCAACTGGCGTACCCCCGGGCGGCGAGGCCAAGGCCCGCA
CGATCGACGGCCGGCCGGACCACTTCTACCACCGTTTCGGGCTGCTGCCCGAGCACGGC
35 CAGGTGCCGCTGTTCGCACTACTGGGCCTACAACCGGGCGGCCGGCACCAACGACGAGCC
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GGCTCGACGGGCGGCCCGCCACCCGGTATGCCTGGCACTTCGACGCCACCTGGTCGCC
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GCAGCAGGTGCTGCGCGACGAGCGGGGCTTCATCACCGCCCTGCGCACGGTCGAGGGCC
40 GGGACCTCGAGGGTGACCTGTTTCATCGACTGCTCCGGCTTCCGCGGCCTGCTGATCAAC
AAGGCCATGGAGGAGCCCTTCATCGACATGAACGACCAGCTGCTGTGCAACCGCGCGGT
GGCCACGGCGATCAAGCACGACGACGACGCGCACGGGTTCGAGCCGTACACCTCGGCGA
TCGCCATGCGGTCCGGCTGGAGCTGGAAGATCCCGATGCTGGGCGGCTTCGGGACCGGC
TACGTCTACTCCAGCCGGTTCGCCGAGAAGGACGAGGCCACCTCGACTTCTGCCGGAT
45 GTGGGGCCTGGACCCGGAGAACACCCCGCTCAACCAGGTGGCCTTCCGGGTTCGGCCGCA
ACCGCCGGGCCTGGGTGAAGAACTGCGTGAGCATCGGCCTGGCGTCGTGCTTCTGGAG
CCACTGGAGTCCACCGGCATCTACTTCATCACCGCGGCCATCTACCAGCTGACTCAGCA
CTTCCCGGACCGCACCTTCGCGCTCGCGTTGAGCGACGCGTTCAACCACGAGATCGAAG
CCATGTTTCGACGACACCCGGGACTTCATCCAGGCGCACTTCTACGTGTGCCGCGCACCC
50 GACACGCCGTTCTGGAAGGCGAACAAGGACCTGCACCTGCCCGAGCAGATGCGCGAGAA
GATCGCGATGTACAAGGCCGGCCTGCCGATCAACGCGCCGGTCACCGACGAGTCGACCT

ACTACGGCAGGTTCGAGGCCGAGTTCGCAACTTCTGGACCAACGGCAGCTACTACTGC
ATCTTCGCGGGCCTCGGGCTGCGCCCGGACAACCCGCTGCCGATGCTGCGACACCGTCC
GGAGCAGGTCCGCGAGGCGCAGGCGCTGTTCCGCGGGGTGAAGGACAAGCAGCGGGAGT
TGGTGGAGACGCTGCCGAGCAACCTGGAGTTCCTGCGCAGCCTGCACGGCAAGTAG

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[00453] SEQ.ID NO: 22

MDNRINRIVILGGGTAGWMTASYLAKALGDTVTTITLEAPAIGRIGVGEATVPNLQRVF
FDFLGLREEEWMPECNAAFKTAVKFINWRTPGPGGEAKARTIDGRPDHIFYHPFGLLPEHG
10 QVPLSHYWAYNRAAGTTDEPFDYACFAETAAMDRAVPKWLDRPATRYAWHFDHLVA
EFLRRHATERLNVEHVQGEMQQVLRDERGFITALRTVEGRDLEGLDFIDCSGFRGLLIN
KAMEEPFIDMNDQLLCNRAVATAIKHDDDAHGVEPYTSAIAMRSGWSWKIPMLGRFGTG
YVYSSRFAEKDEATLDFCRMWGLDPENTPLNQVAFRVGRNRRRAWVKNCVSIGLASCFLE
PLESTGIYFITAAIYQLTQHFPDRTFALALSDAFNHEIEAMFDDTRDFIQAHFYVSPRT
15 DTPFWKANKDLHLPEQMREKIAMYKAGLPINAPVTDESTYYGRFEAEFRNFWTNGSYYC
IFAGLGLRPDNLPLMLRHRPEQVREAQALFAGVKDKQRELVETLPSNLEFLRSLHGK

[00454] SEQ.ID NO: 23

20 ATGGATGACAATCGAATTCGGAGCATCCTTGTCCTTGGCGGGCGGCACGGCCGGCTGGAT
GTCCGCCTGCTACCTGAGCAAGGCGCTCGGGCCCGGCGTCGAGGTCACCGTGCTCGAGG
CGCCCTCCATCTCGCGCATCCGGGTGCGCGAGGCCACCATTCCTAACCTGCACAAGGTC
TTCTTCGACTTCCTGGGCATCGCCGAGGACGAGTGGATGCGGGAGTGCAACGCCAGCTA
CAAGGCCGCGGTCCGGTTCGTCAACTGGCGGACGCCGGGCGACGGCCAGGCCACGCCGC
25 GGCGGGCGTCCGGACGGCCGCCCCGACCACTTCGACCACCTGTTCCGGCCAGCTGCCCGAG
CACGAGAACCTGCCGCTGTGCGAGTACTGGGCGCACCGGCGCCTCAACGGCCTGACCGA
CGAACCTTCGACCGCTCCTGCTACGTGCAGCCGAGCTGCTGGACCGCAAGCTCTCGC
CGAGGTTGATGGACGGCACGAACTGGCCAGCTACGCTGGCACTTCGACGCCGACCTG
GTGGCCGACTTCCTCTGCCGGTTCGCCGTGCAGAAAGCTGAACGTGACCCACGTCCAGGA
30 CGTGTTACGCGATGCCGACCTCGACCAGCGCGGCCACATCACGGCCGTCAACACCGAGT
CCGGCCGCACGCTGGCCGCCGACCTGTTTCATCGACTGCAGCGGCTTCCCGCAGCGTGCTC
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CGCGGTGGCGCTGATGCTCCCGCACGACGACGAGAAGGTGGGCATCGAGCCGTACACCT
CGTCGCTGGCCATGCGGTGCGGCTGGTCTGGAAGATCCCGCTGCTCGGCCGGTTCGGC
35 TCCGGCTACGTCTACTCCAGCCAGTTCACCTCCAGGACGAGGCGGCCGAGGAGCTCTG
CCGCATGTGGGACGTCGACCCGGCGGAGCAGACGTTCAACAACGTCCGGTTCGGGGTCG
GCCGCAGCCGCCGGGCCTGGGTGCGCAACTGCGTCGCCATCGGCGTGTCCGCCATGTTT
GTGGAGCCGCTGGAGTCGACCGGCCTGTACTTCAGTTACGCCTCGCTCTACCAGCTGGT
GAAGCACTTCCCGGACAAGCGGTTCCGGCCGATCCTGGCCGACCGGTTCAACCGCGAGG
40 TGGCGACCATGTACGACGACACCCGCGACTTCCTCCAGGCGCACTTCAGCCTGTCGCCG
CGTGACGACTCCGAGTTCTGGCGGGCCTGCAAGGAGCTGCCGTTCCGGGACGGGTTCGC
CGAGAAGGTCGAGATGTACAGGGCCGGGCTGCCGGTCGAACTGCCGGTCACCATCGACG
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TACTACTGCATCTTCGCCGGGCTCGGTTTCTGCCCGAGCATCCGCTGCCGGTGCTCGA
45 ATTCCGCCCCGGAGGCCGTGATCGCGCGGAGCCGGTGTTCCGCCGCGGTGCGCCGGCGCA
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GGCACGTAG

[00455] SEQ.ID NO: 24

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MDDNRIRSI LVLGGGTAGWMSACYLSKALGPGVEVTVLEAPSI SRIRVGEATIPNLHKV
FFDFLGIAEDEWMRECNASYKAAVRFVNWRTPGDGQATPRRRPDGRPDHFDHLFGQLPE
HENLPLSQYWAHRRNLNGLTDEPFDRSCYVQPELLDRKLSPRLMDGTKLASYAWHFDADL
VADFLCRFAVQKLVNTHVQDVFTHADLDQRGHI TAVNTESGRTLADLFIDCSGFRSVL
5 MGKVMQEPFLDMSKHLLNDRAVALMLPHDDEKVGIEPYTSSLAMRSGWSWKIPLLGFRFG
SGYVYSSQFTSQDEAAEELCRMWDVDPAEQTFNNVRFRVGRSRRRAWVRNCVAIGVSAMF
VEPLESTGLYFSYASLYQLVKHFDPDKRFRPILADRFRNREVATMYDDTRDFLQAHFSLSP
RDDSEFWRACKELPFADGFAEKVEMYRAGLPVELPVTIDDGHYGNGFEAEFRNFWTNSN
10 YYCIFAGLGFLPEHPLPVLEFRPEAVDRAEPVF AAVRRRTEELVATAPTMQAYLRRLHQ
GT

[00456] SEQ.ID NO: 25

ATGAACAAGCCGATCAAGAATATCGTCATCGTGGGCGGCGGTACTGCGGGCTGGATGGC
15 CGCCTCGTACCTCGTCCGGGCCCTCCAACAGCAGGCGAACATTACGCTCATCGAATCTG
CGGCGATCCCTCGGATCGGCGTGGGCGAAGCGACCATCCCAAGTTTGCAGAAGGTGTTT
TTCGATTTCTCTCGGGATACCGGAGCGGGAATGGATGCCCAAGTGAACGGCGCGTTC
GGCCGCGATCAAGTTCGTGAATTGGAGAAAGTCTCCCGACCCCTCGCGCGACGATCACT
TCTACCATTTGTTCGGCAACGTGCCGAACGTGCGACGGCGTGCCGCTTACCCACTACTGG
20 CTGCGCAAGCGCGAACAGGGCTTCCAGCAGCCGATGGAGTACGCGTGCTACCCGCAGCC
CGGGGCACTCGACGGCAAGCTGGCACCGTGCTGTCCGACGGCACCCGCCAGATGTCCC
ACGCGTGGCACTTCGACGCGCACCTGGTGGCCGACTTCTTGAAGCGCTGGGCGTTCGAG
CGCGGGGTGAACCGCGTGGTCGATGAGGTGGTGGACGTTTCGCTGAACAACCGCGGCTA
CATCTCCAACCTGCTCACCAAGGAGGGGCGGACGCTGGAGGCGGACCTGTTTCATCGACT
25 GCTCCGGCATGCGGGGGCTCCTGATCAATCAGGCGCTGAAGGAACCCTTCATCGACATG
TCCGACTACCTGCTGTGCGACAGCGCGGTGCGCCAGCGCCGTGCCAACGACGACGCGCG
CGATGGGGTTCGAGCCGTACACCTCCTCGATCGCCATGAACTCGGGATGGACCTGGAAGA
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GACCAGGCCACCGCCGACTTCTTCAAACCTCTGGGGCCTCTCGGACAATCAGCCGCTCAA
30 CCAGATCAAGTTCGGGGTTCGGGCGCAACAAGCGGGCGTGGGTCAACAACCTGCGTCTCGA
TCGGGCTGTGCTCGTGCTTTTCTGGAGCCCTGGAATCGACGGGGATCTACTTCATCTAC
GCGGCGCTTTTACCAGCTCGTGAAGCACTTCCCCGACACCTCGTTTCGACCCGCGGCTGAG
CGACGCTTTCAACGCCGAGATCGTCCACATGTTTCGACGACTGCCGGGATTTTCGTCCAAG
CGCACTATTTTACCACGTGCGCGGATGACACGCCGTTTCTGGCTCGCGAACCGGCACGAC
35 CTGCGGCTCTCGGACGCCATCAAAGAGAAGGTTTACGCGCTACAAGGCGGGGCTGCCGCT
GACCACCACGTGTTTCGACGATTCCACGTACTACGAGACCTTCGACTACGAATTCAAGA
ATTTCTGGTTGAACGGCAACTACTACTGCATCTTTGCCGGCTTGGGCATGCTGCCCAC
CGGTGCTGCGGCTGTTGCAGCACCGACCGGAGTCGATCGAGAAAGCCGAGGCGATGTT
CGCCAGCATCCGGCGCGAGGCCGAGCGTCTGCGCACCGACCTGCCGACAACTACGACT
40 ACCTGCGGTGCTGCGTGACGGCGACGCGGGGCTGTGCGCGGCCAGCGTGGGCCGAAG
CTCGCAGCGCAGGAAAGCCTGTAG

[00457] SEQ.ID NO: 26

MNKPIKNIVIVGGGTAGWMAASYLVRLQQQANITLIESAAIPRIGVGEATIPSLQKVF
FDFLGIPEREWMPQVNGAFKAAIKFVNWRKSPDPSRDDHFIYHLFGNVPNCDGVPLTHYW
LRKREQGFQQPMYACYPQPGALDGKLAPCLSDGTRQMSHAWHFD AHLVADFLKRWAVE
RGVNRVVDEVVDVRLNNRGYISNLLTKEGRTLEADLFIDCSGMRGLLINQALKEPFIDM
SDYLLCDSAVASAVPND DARDGVEPYTSSIAMNSGWTWKIPMLGRFGSGYVFSSHFTSR
50 DQATADFLKLWGLSDNQPLNQIKFRVGRNKRRAWVNNCVSI GLSSCFLEPLESTGIYFIY
AALYQLVKHFDPDTSFDPRLSDAFNAEIVHMFDDCRDFVQAHYFTTSRDDTPFWLANRHD

LRLSDAIKEKVQRYKAGLPLTTTSFDDSTYYETFDYEFKNFWLNGNYYCIFAGLGMLPD
RSLPLLQHRPESIEKAEAMFASIRREAERLRTSLPTNYDYLRSLRDGDAGLSRGQRGPK
LAAQESL

[00458] SEQ.ID NO: 27

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ATGTCCGGCAAGATTGACAAGATCCTCATCGTCGGCGGGCGGCACCGCCGGATGGATGGC
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TTCGACTTCCTCGGAATCCCCGAGGACGAGTGGATGCGGGAGTGCAACGCGAGCTACAA
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AGCTCGACGGAGGGCCCGACCACTTCTACCACTCCTTCGGTCTGCTCAAGTACCACGAG
CAGATTCCGCTGTCGCACTACTGGTTCGACCGTTCGTACCGGGGGAAGACCGTCGAGCC
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GACTTCCTGCGCCGGTTCGCCACCGAGAAGCTCGGCGTGCGCCACGTCGAGGACCGCGT
CGAGCACGTCCAGCGCGACGCCAACGGCAACATCGAGTCGGTTCGCACGGCAACGGGGC
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AAGGCGATGGAGGAGCCCTTCCTCGACATGAGCGATCACCTGCTCAACGACAGCGCCGT
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TCGCCATGAAGTCGGGCTGGACGTGGAAGATCCCGATGCTCGGCAGGTTCCGCACCGGG
TACGTCTACTCGAGCCGGTTCGCCACCGAGGACGAGGCGGTGCGCGAGTTCTGCGAGAT
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ACCGGCGCGCGTGGGTGCGCAACTGCGTCAGCATCGGCACGTCGTCGTGCTTCGTGGAA
CCACTGGAGTCGACGGGCATCTACTTCGTCTACGCCGCGCTGTACCAGCTGGTGAAGCA
CTTCCCCGACAAGAGCCTCAACCCCGTGCTGACCGCCAGGTTCAACCGCGAGATCGAGA
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GACACCCCGTTCTGGAGGGCCAACAAGGAGCTGCGCCTGGCGGACGGCATGCAGGAGAA
GATCGACATGTACCGCGCGGGCATGGCGATCAACGCGCCCCGCGTCCGACGACGCCCAGC
TCTACTACGGCAACTTCGAGGAGGAGTTCCGCAACTTCTGGAACAACAGCAACTACTAC
TGCGTGCTGGCCGGCCTCGGTCTGGTGCCCGACGCACCCTCACCACGCCTGGCGCACAT
GCCACAGGCGACGGAGTCGGTGGACGAGGTCTTCGGCGCCGTCAAGGACCGGCAGCGGA
ACCTGCTCGAGACCCTGCCGAGCCTCCACGAGTTCCTGAGGCAACAGCACGGCCGCTGA

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[00459] SEQ.ID NO: 28

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MSGKIDKILIVGGGTAGWMAASYLGKALQGTADITLLQAPDIPTLGVGEATIPNLQTAF
FDFLGIPEDWMMRECNASYKVAIKFINWRTAGEGTSEARELDGGPDHIFYHSFGLLYHE
QIPLSHYWFDERSYRGKTVEPFYACYKEPVILDANRSPRRLDGSKVTNYAWHFD AHLVA
DFLRRFATEKLGVRHVEDRVEHVQORDANGNIESVRTATGRVFDADLFVDCSGFRGLLIN
KAMEEPFLDMSDHLNDSAVATQVPHDDANGVEPFTSAIAMKSGWTWKIPMLGRFGTG
YVYSSRFATEDEAVREFCEMWHLDPETQPLNRIRFRVGRNRRRAWVGNCVSI GTSSCFVE
PLESTGIYFVYAALYQLVKHFPDKSLNPVLTARFNREIETMFDDTRDFIQAHFYFSPRT
DTPFWRANKELRLADGMQEKIDMYRAGMAINAPASDDAQLYGNFEEEFNFWNNSNYY
CVLAGLGLVPDAPSPRLAHMPQATESVDEVFGAVKDRQRNLLETLP SLHEFLRQQHGR

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[00460] SEQ.ID NO: 29

MLNNVVIVGGGTAGWMTASYFKAAFGERINITLVESGNIGAVGVGEATFSDIRHFFDFL
GLKEKDWMPACNATYKLAVRFENWREEGHYFYHPFEQMRVNGFPLADWWLREKPTDRF
DKDCFVMPSIIDAGLSPRHLDGSLIDQPFVEGAEMOGLTMSEHQGKTQFPYAYQFEAA
LLAKYLTTYSVERGVKHIVDDVQQVNLDERGWIRNVTTAEHGEIGGDLFIDCTGFRGLL

50

LNKALEEPFISFQDTLPNDSAVALQVPMDMERRGILPCTTATAQDAGWIWTIPLMGRVG
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VEPLESTGIFFIHHAEIQLAKNFPGEDWNPVQRNLYNDSVAHVMDGVREFLVLYHVA
5 RSDTQYWRDTKTRKIPDALAERIEKWKTQLPDTETVFPYYHGLPPYSYHCVLLGMGGID
VKPSPALALGDSAAAEREFAEIREKTRHLTSVLPKAYDYFSRMR

[00461] SEQ.ID NO: 30

MSGKIDKILIVGGGTAGWMAASYLGKALQGTADITLLQAPDIPTLGVGEATIPNLQTAF
FDFLGIPEDWWMRECNASYKVAIKFINWRTAGEGTSEARELDGGPDHIFYHSFGLLKYHE
10 QIPLSHYWFDRSYRGKTVEPFYACYKEPVILDANRSPRRLDGSKVTNYAWHFD AHLVA
DFLRRFATEKLGVRHVEDRVEHVQORDANGNIESVRTATGRVFDADLFVDCSGFRGLLIN
KAMEEPFLDMSDHLNDSAVATQVPHDDANGVEPFTSAIAMKSGWTWKIPMLGRFGTG
YVYSSRFATEDEAVREFCEMWHLDPETQPLNRIRFRVGRNRRRAWVGNCVSIGTSSCFVE
PLESTGIYFVYAALYQLVKHFDPKSLNPVLTARFNREIETMFDDTRDFIQAHFYFSPRT
15 DTPFWRANKELRLADGMQEKIDMYRAGMAINAPASDDAQLYWGNFEEEFNFWNNSSYY
CVLAGLGLVPDAPSPRLAHMPQATESVDEVFGAVKDRQRNLLETLP SLHEFLRQQHGR

[00462] SEQ.ID NO: 31

MSGKIDKILIVGGGTAGWMAASYLGKALQGTADITLLQAPDIPTLGVGEATIPNLQTAF
FDFLGIPEDWWMRECNASYKVAIKFINWRTAGEGTSEARELDGGPDHIFYHSFGLLKYHE
20 QIPLSHYWFDRSYRGKTVEPFYACYKEPVILDANRSPRRLDGSKVTNYAWHFD AHLVA
DFLRRFATEKLGVRHVEDRVEHVQORDANGNIESVRTATGRVFDADLFVDCSGFRGLLIN
KAMEEPFLDMSDHLNDSAVATQVPHDDANGVEPFTSAIAMKSGWTWKIPMLGRFGTG
YVYSSRFATEDEAVREFCEMWHLDPETQPLNRIRFRVGRNRRRAWVGNCVSIGTSSCFVE
25 PLESTGIYFVYAALYQLVKHFDPKSLNPVLTARFNREIETMFDDTRDFIQAHFYFSPRT
DTPFWRANKELRLADGMQEKIDMYRAGMAINAPASDDAQLYGNFEEEFNFWNNSSYY
CVLAGLGLVPDAPSPRLAHMPQATESVDEVFGAVKDRQRNLLETLP SLHEFLRQQHGR

[00463] SEQ.ID NO: 32

MSGKIDKILIVGGGTAGWMAASYLGKALQGTADITLLQAPDIPTLGVGEATMPNLQTAF
FDFLGIPEDWWMRECNASYKVAIKFINWRTAGEGTSEARELDGGPDHIFYHFPGLLKYHE
30 QIPLSHYWFDRLYRGKTVEPFYACYKEPVILDANRSPRRLDGSKVTSYAWHFD AHLVA
DFLRRFATEKLGVRHVEDRVEHVQORDANGNIESVRTATGRVFDADLFVDCSGFRGLLIN
KAMEEPFLDMSDHLNDSAVATQVPHDDANGVEPFTSAIAMKSGWTWKIPMLGRFGTG
35 YVYSSRFATEDEAVREFCEMWHLDPETQPLNRIRFRVGRNRRRAWVGNCVSIGTSSCFVE
PLESTGIYFVYAALYQLVKHFDPKSFNPVLTARFNREIETMFDDTRDFIQAHFYFSPRT
DTPFWRANKELRLADGMQEKIDMYRAGMAINAPAPDDAQLYWGNFEEEFNFWNNSSYY
CVLAGLGLVPDAPSPRLAHMPRATESVDEVFGAVKDQQRNLLETLP SLHEFLRQQHGR

40 **[00464] SEQ.ID NO: 33**

MSGKIDKILIVGGGTAGWMAASYLGKALQGTADITLLQAPDIPTLGVGEATHPNLQTAF
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QIPLSHYWFDRSYRGKTVEPFYACYKEPVILDANRSPRRLDGSKVTNYAWHFD AHLVA
DFLRRFATEKLGVRHVEDRVEHVQORDANGNIESVRTATGRVFDADLFVDCSGFRGLLIN
45 KAMEEPFLDMSDHLNDSAVATQVPHDDANGVEPFTSAIAMKSGWTWKIPMLGRFGTG
YVYSSRFATEDEAVREFCEMWHLDPETQPLNRIRFRVGRNRRRAWVGNCVSIGTSSCFVE
PLESTGIYFVYAALYQLVKHFDPKSFNPVLTARFNREIETMFDDTRDFIQAHFYFSPRT

DTPFWRANKELRLADGMQEKIDMYRAGMAINAPASDDAQLYYGNFEEEFRCNCWNNSSYY
CVLAGLGLVPDAPSPRLAHMPRATESVDEVFGAVKDQQRNLLETLP SLHEFLRQQHGR

[00465] SEQ.ID NO: 34

5 MSGKIDKILIVGGGTAGWMAASYLGKALQGTADITLLQAPDIPTLGVGEATIPNLQTAF
FDFLGIPEDWMMRECNASYKVAIKFINWRTAGEGTSEARELDGGPDHIFYHSFSLKYHE
QIPLSHYWFDRSYRGKTVEPFYACYKEPVILDANRSPRRLDGSKVTNYAWHFD AHLVA
DFLRRFATEKLGVRHVEDRVEHVQORDANGNIESVRTATGRVFDADLFVDCSGFRGLLIN
KAMEEPFLDMSDHLLNDSAVATQVPHDDDANGVEPFTSAIAMKSGWTWKIPMLGRFGTG
10 YVYSSRFATEDEAVREFCEMWHLDPETQPLNRIRFRVGRNRRRAWVGNCVSI GTSSCFVE
PLESTGIYFVYAALYQLVKHFDPDKSLNPVLTARFNREIETMFDDTRDFIQA HFYFSPRT
DTPFWRANKELRLADGMQEKIDMYRAGMAINAPASDDAQLYYGNFEEEFRCNFWNNSSYY
CVLAGLGLVPDAPSPRLAHMPQATESVDEVFGAVKDRQRNLLETLP SLHEFLRQQHGR

15 **[00466] SEQ.ID NO: 35**

MSGKIDKILIVGGGTAGWMAASYLGKALQGTADITLLQAPDIPTLGVGEATIPNLQTAF
FDFLGIPEDWMMRECNASYKVAIKFINWRTAGEGTSEARELDGGPDHIFYHSFGLKYHE
QIPLSHYWFDRSYRGKTVEPFYACYKEPVILDANRSPRRLDGSKVTNYAWHFD AHLVA
DFLRRFATEKLGVRHVEDRVEHVQORDANGNIESVRTATGRVFDADLFVDCSGFRGLLIN
20 KAMEEPFLDMSDHLLNDSAVATQVPHDDDANGVEPFTSAIAMKSGWTWKIPMLGRFGTG
YVYSSRFATEDEAVREFCEMWHLDPETQPLNRIRFRVGRNRRRAWVGNCVSI GTSSCFVE
PLESTGIYFVYAALYQLVKHFDPDKSLNPVLTARFNREIETMFDDTRDFIQA HFYFSPRT
DTPFWRANKELRLADGMQEKIDMYRAGMVINAPASDDAQLYYGNFEEEFRCNFWNNSSYY
CVLAGLGLVPDAPSPRLAHMPQATESVDEVFGAVKDRQRNLLETLP SLHEFLRQQHGR

25 **[00467] SEQ.ID NO: 36**

ATGATGTCTGAAAATTTGCAATTGTCAGCTGAAGAAATGAGACAATTGGGTTACCAAGC
AGTTGATTTGATCATCGATCACATGAACCATTTGAAGTCTAAGCCAGTTTCAGAAACAA
TCGATTCTGATATCTTGAGAAATAAGTTGACTGAATCTATCCCAGAAAATGGTTCAGAT
30 CCAAAGGAATTGTTGCATTTCTTGAACAGAAACGTTTTTAATCAAATTACACATGTTGA
TCATCCACATTTCTTGGCTTTTGTTCAGGTCCAAATAATTACGTTGGTGTGTTGCAG
ATTTCTTGGCTTCTGGTTTTAATGTTTTTCCAACCTGCATGGATTGCTGGTGCAGGTGCT
GAACAAATCGAATTGACTACAATTAATTGGTTGAAATCTATGTTGGGTTTTCCAGATTC
AGCTGAAGGTTTATTTGTTTCTGGTGGTTCAATGGCAAATTTGACAGCTTTGACTGTTG
35 CAAGACAGGCTAAGTTGAACAACGATATCGAAAATGCTGTTGTTTACTTCTCTGATCAA
ACACATTTCTCAGTTGATAGAGCATTGAAGGTTTTAGGTTTTTAAACATCATCAAATCTG
TAGAATCGAAACAGATGAACATTTGAGAATCTCTGTTTCAGCTTTGAAGAAACAAATTA
AAGAAGATAGAACTAAGGGTAAAAAGCCATTCTGTGTTATTGCAAATGCTGGTACTACA
AATTGTGGTGCTGTTGATTCTTTGAACGAATTAGCAGATTTGTGTAACGATGAAGATGT
40 TTGGTTGCATGCTGATGGTTCTTATGGTGCTCCAGCTATCTTGTCTGAAAAGGGTTCAG
CTATGTTGCAAGGTATTCATAGAGCAGATTCTTTGACTTTAGATCCACATAAGTGTTG
TTCCAACCATACGATGTTGGTTGTGTTTTGATCAGAACTCTCAATATTTGTCAAAGAC
TTTTAGAATGATGCCAGAATACATCAAGGATTCAGAACTAACGTTGAAGGTGAAATTA
ATTTCCGGTGAATGTGGTATCGAATTGTCAAGAAGATTCAGAGCTTTGAAGGTTTGGTTG
45 TCTTTTAAAGTTTTTCGGTGTTGCTGCTTTTTAGACAAGCAATCGATCATGGTATCATGTT
AGCAGAACAAGTTGAAGCATTTTTGGGTAAAGCAAAAGATTGGGAAGTTGTTACACCAG
CTCAATTGGGTATCGTTACTTTTAGATACATTCCATCTGAATTGGCATCAACAGATACT
ATTAATGAAATTAATAAGAAATTGGTTAAGGAAATCACACATAGAGGTTTCGCTATGTT

ATCTACTACAGAATTGAAGGAAAAGGTTGTTATTAGATTGTGTTCAATTAATCCAAGAA
CTACAACCTGAAGAAATGTTGCAAATCATGATGAAGATTAAAGCATTGGCTGAAGAAGTT
TCTATTTTCATACCCATGTGTTGCTGAATAA

5 **[00468]** SEQ.ID NO: 37

MMSENLQLSAEEMRQLGYQAVDLIIDHMHNLKSKPVSETIDSDILRNKLTESIPENGSD
PKELLHFLNRNVFNQITHVDHPHFLAFVPGPNYVGVVADFLASGFNVFPTAWIAGAGA
EQIELTTINWLKSMGLGFPDSAEGLFVSGGSMANLTALTVARQAKLNNDIENAVVYFSDQ
THFSVDRALKVLGFKHHQICRIETDEHLRISVSALKKQIKEDRTKGKKPFCVIANAGTT
10 NCGAVDSLNELADLCNDEDVWLHADGSYGAPAILSEKGSAMLQGIHRADSLTLDPHKWL
FQPYDVGCVLIRNSQYLSKTFRMMPEYIKDSETNVEGEINFGECGIELSRRFRALKVWL
SFKVFGVAAFRQAIDHGIMLAEQVEAFLGKAKDWEVVTPAQLGIVTFRYIPSELASTDT
INEINKKLVEITHRGFAMLSSTELKEKVIRLCSINPRTTTEEMLQIMMKIKALAEV
SISYPCVAE

15

[00469] SEQ.ID NO: 38

ATGTCTCAAGTGATCAAAAAAAGAGAAACACTTTCATGATCGGTACCGAATATATATT
GAACTCTACCCAATTAGAAGAGGCTATTAAATCTTTCGTCCATGATTTCTGTGCCGAAA
AGCACGAAATTCACGACCAACCAGTTGTCGTTGAAGCTAAGGAACACCAAGAAGATAAG
20 ATTAAGCAAATCAAAATTCAGAAAAGGGTCGTCCAGTCAATGAAGTTGTTTCTGAAAT
GATGAACGAAGTCTACAGATACAGAGGTGATGCCAACCATCCAAGATTCTTCTCTTTCG
TTCCAGGTCCAGCTTCCTCTGTCTCCTGGTTGGGTGACATCATGACTTCTGCTTACAAC
ATCCACGCTGGTGGTTCTAAATTGGCCCCAATGGTTAACTGTATCGAACAAGAAGTCTT
GAAATGGCTCGCAAAGCAAGTTGGTTTCACCGAAAACCCTGGTGGTGTTCGTTTCCG
25 GTGGTTCTATGGCTAACATTACTGCTTTGACAGCCGCTAGAGACAACAAGCTTACCGAT
ATTAACCTTGCACTTGGGTACTGCTTACATTTCCGACCAAACCCACTCTTCAGTTGCTAA
GGGTTTACGTATCATTGGTATCACTGACTCCAGAATCAGAAGAATTCCAACCTAATCCC
ACTTCCAAATGGACACCACTAAGTTGGAAGAAGCTATCGAAACCGACAAGAAGTCCGGT
TACATCCCATTTGTTGTTATCGGTACTGCCGGTACCACCAACACTGGTTCCATTGACCC
30 ATTGACTGAAATTTCCGCTTTTGTGTAAGAAGCATGACATGTGGTTCCACATTGATGGTG
CCTACGGTGCTTCAGTTTTGTTGTCTCCAAAGTACAAGTCTTTGTTAACAGGTACCGGT
TTGGCTGACTCTATCTCTTGGGATGCTCACAAGTGGTTATTTCAAACCTTACGGTTGTGC
TATGGTTTTTGGTCAAGGATATTAGAACTTGTTTCATTCCTTCCACGTCAATCCAGAAT
ACTTGAAGGATCTGGAAAACGACATCGATAACGTTAACACCTGGGACATCGGCATGGAA
35 TTGACCAGACCAGCCAGAGGTTTGAAGTTGTGGTTGACTTTGCAAGTTCTAGGTTCTGA
TCTTATTGGTTCTGCCATTGAACACGGTTTCCAATTGGCTGTCTGGGCTGAAGAAGCCT
TGAATCCAAAGAAGGACTGGGAAATTGTCTCTCCTGCTCAAATGGCTATGATCAACTTC
AGATATGCTCCAAAGGACTTGACCAAGGAAGAACAAGATATCTTGAACGAAAAGATCTC
TCACCGTATTTTGGAAATCCGGTTACGCTGCTATCTTCACTACCGTCCTAAACGGTAAGA
40 CTGTCTTGAGAATCTGCGCTATTCACCCAGAAGCTACTCAAGAAGACATGCAACACACC
ATTGATTTGTTGGACCAATACGGTAGAGAAATCTACACTGAAATGAAGAAGGCTTAG

[00470] SEQ.ID NO: 39

MSQVIKKRNTFMIGTEYIILNSTQLEEAIKSFVHDFCAEKHEIHDQPVVVEAKEHQEDK
45 IKQIKIPEKGRPVNEVVSEMMNEVYRYRGDANHPRFFSFVPGPASSVSWLGDIMTSAYN
IHAGGSKLAPMVNCIEQEVLKWLAKQVGFTENPGGVFVSGGSMANITALTAARDNKLTD
INLHLGTAYISDQTHSSVAKGLRIIGITDSRIRRIPTNSHFQMDTTKLEEAIEYTDKKS
YIPFVVIGTAGTTNTGSIDPLTEISALCKKHDMWFHIDGAYGASVLLSPKYKSLTGTG

LADSI SWDAHKWLFQTYGCAMVLVKDIRNLFHSHFVNPEY LKDLENDIDNVNTWDIGME
LTRPARGLKLWLTLQVLGSDLIGSAIEHGFQLAVWAEELNPKKDWEIVSPAQMAMINF
RYAPKDLTKEEQDILNEKISHRILESGYAAI FTTVLNGKTVLRICAIHPEATQEDMQHT
IDLDDQYGREIYTEMKKA

5 **[00471]** SEQ.ID NO: 40

ATGAAGCCAGCTGAAGCTAAACCACCTCACATGGACCATGATACTTTCAGATCCTTGGG
TCACCAAGCTATTGACTGGATTGCTGATTACTGGCAACACTTGGCTGACAGACCAGTTG
CTCCATTGGTTGAACCAGGTACTGTTAGAGCCCAATTGCCTACCACTCCACCAGAGTAC
GGTGAAGACTTCCCAGCTTTGTTATCTGACTTGGAAAGAATTGTCTTGCCAGGCTTGTT
10 GCACTGGCAACACCCAAGATTCTTCGGTTACTTCCCAGCTAACGCTTCCGGTCCAGCCG
TTTTAGCTGAATTATTATCTGCTGGTCTAGGTGTCCAAGGTATGAACTGGAACACTTCT
CCAGCTTGTACCGAAGTTGAACAACAAATGTTGGACTGGTTCGTTCAATTTGTTAGGGTT
GCCAGAACTTCAGAGGTGGTGGTGTATCCAAGACACTGCCTCCTCCGCCGTTTTTG
TCGCTCTATTGACTGCTTTGCACAGAGCTTCTGCTGGTAGAACCAGAGATCACGGTACT
15 GGTGAATGTGGTTACAGGGTTTACCTAACCGCTGAACTCACTCCGCTGCTAGAAAGGC
TGCCGTCATCACCGGTTTGGGTTTGCCTGCTGTTTGTGAAGTCGCAACTGATGCTGACG
GTGCTATGGATGCCGCTGACTTGGCCGCTCGTATTCAAGCCGATTTGGCTGCCGGTTTG
ACCCCATTTGATGGTTGTTGCTACCCGTGGTACCACCTCTGATTTGTCCTTCGATCCATT
GGAAGACATCGGTCCAGTCTGTAGAAGACATGGTGTCTGGTTACACGTTGACGCTGCTT
20 ATGCTGGTGTTGCTGCAGTGTGCGATGAATTGCATTGGGTTAATGATGGTGTTAGATAC
GCTGATTCTTACTGTACTAACCCACACAAGTGGTTGTTGACCAACTTCGACTGTGATTT
ATTATGGGTTGCCGACCCAGAAGCTTTGGTCAACGCTTTGTCCGTTTTGCCTGCTTACT
TGAGAAACCCAGCTTCTGAATCAGGTAGAGTTACTGACTACAGACACTGGCAAGTTCCA
TTGGGCAGAAGATTCAGAGCCTTGAAGTTGTGGTCTGTCTTAAGATGGTACGGTGCCGA
25 AGGTTTGGAGATCTCACATCAGAAGTGGTGTGACACACGCCAGATTGTTTCGCTGACCTGG
TCAGAGAAGATGACCGTTTCACCTTGTGCGCCAGCTACTTTGGGTTTGGTCACTTTC
CGTCACGCTGGTCTGACACCGACAACAGAACTTGTGACGCTATCAACGCCGAAGG
TACAACTTTTTTAACTCATAGTGAAAAGAACGGTACCTTTTTCTTGAGATTTGCTACCG
GTGGTACCCACACTGAAGACCATCACGTCCACGAAGCTTGGAGAGCTGTCCAAAATGCC
30 GTCCAAAACGCCGTCCCAAGAGCCCAACATGCCACCGATGGTACTGCCGATGCTTTGAA
CGGTTAA

[00472] SEQ.ID NO: 41

MKPAAKPPHMDHDTFRSLGHQAIDWIADYWQHLADRPVAPLVEPGTVRAQLPTTPPEY
35 GEDFPALLSDLERIVLPGLLHWQHPRFFGYFPANASGPAVLAE LLSAGLGVQGMNWN
PACTEVEQQMLDWFVHLLGLPEHFRGGGVIQDTASSAVLVALLTALHRASAGRTRDHGT
GECGYRVYLTAETHSAARKAAVITGLGLRAVCEVATDADGAMDAADLAARIQADLAAGL
TPLMVVATRGTTS DLSFDPLEDIGPVCRRHGVWLHVDAAYAGVAAVCDLHWVNDGVRY
ADSYCTNPHKWL LTNFDCDLLWVADPEALVNALSVLPAYLRNPASESGRVTDYRHWQVP
40 LGRRFRALKLWSVLRWYGAEGLRSHIRTGVRHARLFADLVREDDRFTLLAPATLGLVTF
RHAGSDTDNRNLLHAINAEGTTFLTHSEKNGTFFLR FATGGTHTEDHHVHEAWRAVQNA
VQNAVPRAQHATDGTADALNG

[00473] SEQ.ID NO: 42

45 ATGGATATTGAAGCTTTTAGAAAAGCAGGTACCAAGCTATCGATAGAATTTGTGACTA
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ATGCATTACCAGATTCTCCACCAGAACAAGGTGAAGATTTCACTGTTATTGCTGATGAT
TACCAAAAGTACATCTTGCCAGGTTTGACACATTGGCAACATCCATCTTTCTTGCATA

CTTTCCAACAGCTTGTACTTTTGAAGGTATTTTGGGTGACTTGTATTCTACATCAACTG
 CAAATCCAGGTTTTAATTGGTTGGCTTCTCCAGCATGTACTGAATTAGAAATGGTTGTT
 ATGGATTGGTCTGCTAAGTTGTTAGGTTTGTGAGAACATTTCTTGCATTCTTCAGGTAA
 AGGTGGTGGTGTATTCAAACACAGCATCAGAATTGGCTTTAGTTGTTGTTGTTGCTG
 5 CAAGAGAAAGATACTTGAGAATTCATCCAGATGCTAAGGCAGATGAATTGGTTATATAT
 ACTACAACACAAACACATTCTTTGGGTGTTAAAGCTGGTTTAGTTTTTGGTATGGAATG
 TAGAGCATTGGAAGTTAAAGCTGAAGATGCTTACGCATTAAGAGGTGCAACTTTGAAGT
 CAGCTTTAGAAGAAGATGAAAAGAGAGGTAAAAGACCTTTTATTTTGGTTGCAACAGTT
 GGTACAACCTTCTTCAGGTGCTATTGATAGATTGGATGAAATTGGTCAAGTTTCTGAAGA
 10 TTATCCATCATTATGGATTGATGCTGCATGGGCAGGTGTTACTTTGGCTTGTC
 CAGAATACAGAGGTACAGCTCAATTAGAAAACATCAACGCTTATGCAACATCTTTCGGT
 ACTAACTTCCATAAGTGGGGTTTGGTTAACTTTGATGCTGCATTGTTGTGGGTTAAGGA
 TAGAAAGGATTTGACAGATGCTTTAGATGTTACTCCAGAATTCTTGAGAACAAAACAAG
 GTGACGCTGGTGCAGTTGTTGATTTTAGAAATTGGCATTGTTGGGTTTGGGTAGAAGATTC
 15 AGATCTTTGAAGGTTTGGTTCGTTTTGAGATCATACGGTGTGAAGGTTTGAAGACTA
 CATCAGACAAGGTATTAAATTGAATGAACATTTTACTTCTTTAATTAGAGCTTCTTTGG
 ATTTTTTCATTAGTTACAGCACCATCATTCGCTTTGACAGTTTTTAGATTGACTCCAGCT
 GGTGCATCTTTGACTGGTTCAGAATTGAACGAATTAAACAGAGCTTTCTACGCAAGATT
 ATCTTCAAGACATGATATCATGTTGACACAACTGTTTTGAACGGTGTTCCTGTATCA
 20 GATTTGCAGTTGGTGCTGCAAGAACTCAACAAGAACATATTGATACAGCTTGGGATTTG
 TTACAACAAGAAGGTGCTGTTGCAGTTCAAGAATACATGCAAAAGATTTCTAAGGATGT
 TCAATAA

[00474] SEQ.ID NO: 43

25 MDIEAFRKAGYQAIDRICDYYSYLQNRPVVPSVQPGYLLDALPDSPEQGEDFTVIADD
 YQKYILPGLTHWQHPSFFAYFPTACTFEGILGDLYSTSTANPGFNWLASPACTELEMVV
 MDWSAKLLGLSEHFLHSSGKGGGVIQTTASELALVVVVAARERYLRHPDAKADELVIY
 TTTQTHSLGVKAGLVFGMECRALEVKAEDAYALRGATLKSAALEDEKRGKRPFILVATV
 GTTSSGAIDRLDEIGQVSEDPYPSLWIHVDAAWAGVTLACPEYRGTAQLENINAYATSFG
 30 TNFHKWGLVNFDAALLWVKDRKDLTDALDVTPEFLRTKQGDAGAVVDFRNWHLGLGRRF
 RSLKVWFVLRSGVEGFRNYIRQGIKLNEHFTSLIRASLDFSLVTAPS FALT VFRLTPA
 GASLTGSELNELNRAFYARLSSRHDIMLTQTVLNGVFCIRFAVGAARTQQEHIDTAWDL
 LQQEGAVAVQEYMQKISKDVQ

35 [00475] SEQ.ID NO: 44

ATGAAGTTCTGGAGAAAGTACACACAACAAGAAATGGATGAAAAGATTACTGAATCTTT
 GGAAAAGACTTTGAACTACGATAACACTAAGACAATCGGTATTCCAGGTACTAAGTTGG
 ATGATACAGTTTTCTATGATGATCATTCTTTGTTAAGCATTACCATACTTGAGAAT
 TTTATTCAAACCCAAACCATATCGGTTGTCATACTTATGATAAGGCTGATATCTTGTT
 40 CGGTGGTACATTCGATATCGAAAGAGAATTAATCCAATTGTTAGCAATCGATGTTTTGA
 ACGGTAACGATGAAGAATTTGATGGTTACGTTACTCAAGGTGGTACAGAAGCTAACATC
 CAAGCAATGTGGGTTTACAGAACTACTTCAAGAAAGAAAGAAAGGCTAAGCATGAAGA
 AATCGCTATCATCACTTCAGCAGATACACATTACTCTGCATACAAAGGTTTCAGATTTGT
 TGAACATCGATATTATTAAGGTTCCAGTTGATTTTTATTCAAGAAAAATTCAAGAAAAT
 45 ACATTGGATTCAATTGTTAAAGAAGCTAAAGAAATTGGTAAAAAGTACTTCATCGTTAT
 CTCTAACATGGGTACTACAATGTTTGGTTCAGTTGATGATCCAGATTTGTACGCTAACA
 TCTTCGATAAGTACAATTTGGAATACAAAATTCATGTTGATGGTGCATTTGGTGGTTTT
 ATATATCCAATTGATAATAAGGAATGTAAAACCTGATTTCTCTAATAAGAACGTTTCTTC
 AATCACATTAGATGGTCATAAGATGTTGCAAGCTCCATACGGTACTGGTATCTTCGTTT

CAAGAAAGAATTTGATCCATAACACTTTGACAAAGGAAGCAACTTACATCGAAAATTTG
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AGCTTCTTATGGTCCATACGGTTGGATGGAAAAGATTAATAAGTTGAGAAATAGAACTA
AATGGTTGTGTAAGCAATTGAACGATATGAGAATTAAATATTACAAAGAAGATTCAATG
5 AATATTGTTACAATTGAAGAACAATATGTTAATAAGGAAATCGCTGAAAAGTACTTTTT
AGTTCCAGAAGTTTCATAACCCAACTAACAACCTGGTACAAGATCGTTGTTATGGAACATG
TTGAATTGGATATCTTGAACCTTTGGTTTACGATTTGAGAAAGTTTAATAAGGAACAT
TTGAAGGCAATGTAA

10 **[00476]** SEQ.ID NO: 45

MKFWRKYTQQEMDEKITESLEKTLNYDNKTIGIPGTKLDDTVFYDDHSFVKHSPYLRT
FIQNPNHIGCHTYDKADILFGGTFDIERELIQLLAIDVLNGNDEEFDGYVTQGGTEANI
QAMWVYRNYFKKERKAKHEEIAIITSADTHYSAYKGSDDLNIIDIKVPVDFYSRKIQEN
15 TLDSIVKEAKEIGKKYFIVISNMGTTMFGSVDDPDLYANIFDKYNLEYKIHVDGAFGGF
IYPIDNKECKTDFSNKNVSSITLDGHKMLQAPYGTGIFVSRKNLIHNTLTKEATYIENL
DVTLSGSRSGSNAVAIWMVLASYGPYGWMEKINKLRNRTKWLCKQLNDMRIKYYKEDSM
NIVTIEEQYVNKEIAEKYFLVPEVHNPTNNWYKIVVMEHVELDILNSLVYDLRKFNKEH
LKAM

20 **[00477]** SEQ.ID NO: 46

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CATGGAAGGTATTGAAGGTAGACAAGTTTATCCAGATGTTGAACCAGGTTACTTGAGAC
CATTAATTCAGCTGCAGCTCCACAAGAACCAGATACATTTGAAGATATTATTAACGAT
GTTGAAAAGATTATCATGCCAGGTGTTACACATTGGCATTACCATATTTCTTTGCATA
25 CTTTCCAACCTGCTTCTTCATATCCAGCAATGTTGGCTGATATGTTATGTGGTGCAATTG
GTTGTATTGGTTTTTCTTGGGCAGCTTCACCAGCTTGTACAGAATTGGAACTGTTATG
ATGGATTGGTTAGGTAAAATGTTGGAATTACCAAAGGCATTTTTGAACGAAAAGGCTGG
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CAGCTAGAACTAAAGTTATTCATAGATTGCAAGCAGCTTCTCCAGAATTAACACAAGCA
30 GCTATCATGGAAAAATTGGTTGCATATTCTTCAGATCAAGCTCATTCTTCAGTTGAAAG
AGCTGGTTTGATCGGTGGTGTAAAGTTGAAGGCAATCCCATCTGATGGTAATTTTGCTA
TGAGAGCATCAGCTTTGCAAGAAGCATTAGAAAGAGATAAAGCAGCTGGTTTGATTCCA
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35 GTTCAGCTTTTTATTTGTCCAGAATTCAGACATTTGTTGAACGGTGTTGAATTCGCTGAT
TCTTTTAATTTCAATCCACATAAATGGTTGTTAGTTAACTTCGATTGTTTCAGCAATGTG
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40 GCAAGCTTACATCAGAAAGCATGTTCAATTGTCTCATGAATTCGAATCATTAGTTAGAC
AAGATCCAAGATTCGAAATCTGTGTTGAAGTTATTTGGGTTTAGTTTGTTTCAGATTG
AAGGGTTCTAATAAGGTAAACGAAGCATTGTTGCAAAGAATTAATTCAGCTAAGAAAAT
TCATTTGGTTCCATGTCATTTGCGTGATAAGTTGTTTTGAGATTTCGCTATTTGTTCAA
GAACCTGTTGAATCAGCACATGTTCAAAGAGCTTGGAACATATCAAGGAATTGGCAGCT
45 GATGTTTTGAGAGCTGAAAGAGAATAA

[00478] SEQ.ID NO: 47

[00481] SEQ.ID NO: 50

ATGGGGTTCATTAGATACAAATCCAACTGCTTTTTCTGCATTTCCAGCTGGTGAAGGTGA
AACTTTTCAACCATTTGAACGCAGATGATGTTAGATCATATTTGCATAAGGCTGTTGATT
TCATCTCTGATTACTACAAATCAGTTGAATCTATGCCAGTTTTGCCAAACGTTAAGCCA
5 GGTATTTGCAAGATGAATTAAGAGCATCACCACCAACTTACTCTGCTCCATTTCGATGT
TACAATGAAGGAATTGAGATCTTCAGTTGTTCTGGTATGACTCATTGGGCATCTCCAA
ATTTCTTTGCTTTCTTTCCATCAACAAATCTGCTGCAGCTATTGCTGGTGACTTGATT
GCATCAGCTATGAATACAGTTGGTTTTACTTTGGCAAGCTTCTCCAGCAGCTACTGAAAT
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10 ACAGAACTGGTGAAGGTAGAGGTACTGGTGGTGGTGTATTTTTGGGTACTACATCTGAA
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TGGTGTTCAGGTTTGCATAGATTAGCTGTTTATGCAGCTGATCAAACACATTCAACTT
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15 TGCTGATGCAGGTTTAGTTCCAACATACGTTTGTGCAACTGTTGGTACTACATCTTCAA
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20 ACTAACCCAGAATACTTGAAAAATCATGCTTCAGATTCTGGTGAAGTTACAGATTTGAA
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GAACTTATGGTGTGCTAAGTTGCAAGAACATATCAGATCAGATGTTGCTATGGCAAAA
GTTTTTGAAGATTTGGTTAGAGGTGACGATAGATTGGAAGTTGTTGTTCCAAGAACTT
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25 ATGCAGATGAAGCTAACAGAGAATTGATGAAAGATTGAATAAGACTGGTAAAGCATAC
GTTGCTCATAACAGTTGTTGGTGGTAGATTTGTTTTGAGATTTGCAGTTGGTTCCTTCATT
ACAAGAAGAACATCATGTTAGATCTGCTTGGGAATTGATTAAGAAAACCTACAACGAAA
TGATGAACTAA

30 [00482] SEQ.ID NO: 51

MGSLDTNPTAFSAFPAGEGETFQPLNADDVRSYLHKAVD FISDYYKSVESMPVLPNVKP
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ASAMNTVGF TWQASPAATEMEVLALDWLAQMLNLPTSFMNRTGEGRGTTGGGVILGTTSE
35 AMLVTLVAARDAALRRSGSDGVAGLHRLAVYAADQTHSTFFKACRLAGFDPANIRSIPT
GAETDYGLD PARLLEAMQADADAGLVPTYVCATVGTSSNAVDPVGAVADVAARFAAWV
HVDAAAYAGSACICPEFRHHLDGVERVDSISMSPHKWLMTCLDCTCLYVRDTHRLTGSLE
TNPEYLKNHASDSGEVTDLKDMQVGVGRFRGLKLWMMVRTYGVAKLQEHIRSDVAMAK
VFEDLVRGDDRFEVVVPRNFALVCFRIRAGAGAAAATEEDADEANRELMERLNKTGKAY
40 VAHTVVGGRFVLRFAVGSSSLQEEHHVRS AWELIKTTTEMN

[00483] SEQ.ID NO: 52

ATGGAAGGTGTTGGTGGTGGTGGTGGTGGTGAAGAATGGTTGAGACCAATGGATGCAGA
ACAATTAAGAGAATGTGGTCATAGAATGGTTGATTTGTTGCAGATTACTACAAGTCAA
45 TCGAAGCTTTTCCAGTTTTGTCTCAAGTTCAACCAGGTTATTTGAAAGAAGTTTTGCCA
GATTCAGCTCCAAGACAACCAGATACTTTAGATTCTTTGTTTCGATGATATCCAACAAAA
GATTATCCCAGGTGTTACACATTGGCAATCACCAACTACTTCGCATACTACCCATCTA
ATTCTTCTACTGCTGGTTTTCTTGGGTGAAATGTTGTCTGCTGCTTTTAATATCGTTGGT

TTTTCATGGATCACTTCTCCAGCTGCAACAGAATTGGAAGTTATTGTTTTAGATTGGTT
 CGCAAAGATGTTGCAATTGCCATCACAATTCTTATCTACTGCTTTGGGTGGTGGTGGTTA
 TTCAAGGTACAGCTTCAGAAGCAGTTTTTGGTTGCATTGTTAGCTGCAAGAGATAGAGCT
 TTGAAGAAACATGGTAAACATTCTTTAGAAAAATTGGTTGTTTACGCATCAGATCAAAC
 5 TCATTCTGCTTTACAAAAAGCATGTCAAATCGCTGGTATTTTCTCTGAAAACGTTAGAG
 TTGTTATTGCTGATTGTAATAAGAACTACGCTGTTGCACCAGAAGCAGTTTCAGAAGCT
 TTGTCTATCGATTTGTCTTCAGGTTTGATCCCATTTTTTCATTTGTGCAACAGTTGGTAC
 TACATCTTCATCTGCTGTTGATCCATTACCAGAATTGGGTCAAATCGCTAAGTCAAACG
 ATATGTGGTTCCATATCGATGCTGCTTATGCTGGTTCTGCATGTATTTGTCCAGAATAC
 10 AGACATCATTTGAATGGTGGTTGAAGAAGCAGATTCTTTTAATATGAATGCTCATAAGTG
 GTTCTTGACTAACTTCGATTGTTTCATTGTTGTGGGTAAAGGATAGATCATTTTTTGATCC
 AATCATTATCTACAAATCCAGAATTCTTGAAAAATAAGGCTTCACAAGCAAACCTCTGTT
 GTTGATTTCAAGGATTGGCAAATCCCATTTGGGTAGAAGATTCAGATCATTGAAGTTGTG
 GATGGTTTTGAGATTGTACGGTGTGATAATTTGCAATCTTACATCAGAAAGCATATCC
 15 ATTTGGCTGAACATTTTCGAACAATTGTTGTTGTGATTCAGATTCGAAGTTGTTACT
 CCAAGAACATTTTCATTGGTTTGTTCAGATTAGTTCCACCAACTTCTGATCATGAAAA
 CGGTAGAAAGTTGAACTACGATATGATGGATGGTGTAAATTCATCTGGTAAAATTTTCT
 TGTCACATACAGTTTTGTCTGGTAAATTCGTTTTGAGATTTGCTGTTGGTGCACCATTA
 ACTGAAGAAAGACATGTTGATGCTGCATGGAAGTTGTTGAGAGATGAAGCTACAAAGGT
 20 TTTAGGTAAAATGGTTTAA

[00484] SEQ.ID NO: 53

MEGVGGGGGGGEEWLRPMDAEQLRECGHRMVDVADYYKSI EAFPVLSQVQPGYLKEVLP
 DSAPRQPDTLDSLFDIQQKIIPGVTHWQSPNYFAYYPSNSSTAGFLGEMLSAAFNIVG
 25 FSWITSPAATELEVIVLDWFAKMLQLPSQFLSTALGGGVIQGTASEAVLVALLAARDRA
 LKKHGHKSLEKLVVYASDQTHSALQKACQIAGIFSENVRVVIADCNKNYAVAPEAVSEA
 LSIDLSSGLIPFFICATVGTSSSAVDPLPELGQIAKSNDMWFHIDAAYAGSACICPEY
 RHHLNGVEEADS FNMNAHKWFLTNFDCSLLWVKDRSFLIQSLSTNPEFLKNKASQANSV
 VDFKDWQIPLGRRFRSLKLWMVLRLYGVDNLQSYIRKHIHLAEHFEQLLLSDSRFEVVT
 30 PRTFSLVCFRLVPPTSDHENGRLKLNMDMGVNSSGKIFLSHTVLSGKFVLRFAVGAPL
 TEERHVDAAWKLLRDEATKVLGKMV

[00485] SEQ.ID NO: 54

ATGACAAAGCCATTCCATCCAAATTTGAACGTTGATGCATTGTTTTTAGGTCCAAAGTC
 35 TGAAAACGCTGTTTTCTTTAGAGAAATGATGGATTATGCAGTTTCTGAACACATGCATT
 GGAGATCAGGTTTTTCATCCAGAAGATTCTACATTGGTTACTTCAGTTGATAGATACGAA
 CATAACTACAGAGAAACATTGTACAGAAGTGAAGGTATTTTGAATCAATTATCTGCTAA
 GTTGAAAAATTCTTCAATCCCATTTTTCTCTCCAAGATACTTAGGTCAATTTCTTCAG
 ATACTTTGATGGTTTCTAATTTGGCTTATGTTATGGCTATGATGTACAACCCAAACAAC
 40 TGTCTTATGAAGCTTCACCAACTACAACGAATTGGAATTAGAATCTGGTTTGGATTT
 GTGTAGAATGTTCCGTTACAATCCACAACAATCTTGGGGTCATATTACATCAGGTGGTA
 CTGTTGCAAATTACGAAGGTTTGTGGGTTGCTAGAAATTTGAAGACATTGTCTTTCGCA
 ATCTCACACATCCAAAGGCTAAGGATTTGATCGAACATAAGACTCCAAAGCAATTGAA
 AAATATGCCAACATCTGAATTGTTAGATTTGATCACTGAATTACAAAAGAGAGGTTTGT
 45 TCGAAGAAATCAGAGATATGACATGTAGAGGTACTGGTGTAAAGGCTCAAATTTTAGGT
 AAATTGTTAGTTCCACAATCTAAGCATTATTCATGGATGAAAGCTGCAGATATCTTCGG
 TATCGGTCAAGAAAACATCATCCCATTTGCCAGTTAATGATCATTACCAAACAGATGTTG
 CTCAAATGAGAAAGATCACTTTCGGTTTGATTGAACAAGGTGAACCAATTTTAGCAATG
 ATTGCTGTTGTTGGTACAACGAAGTTGGTGCAATCGATAGAATCGATGAAGTTATTGC

TTTAAGAAAAGAATGTGAAGAAAGATACGGTGAATCTTTCTACATCCATGTTGATGCTG
 CTTATGCTGGTTACGCTTGTTCAATGTTGTTGAACGAACAGGGTGAATTCGTTGAATAC
 GATGAATTGGCAAACCTACCATAGATCTGCTGGTATTATGCCAGAAAATATTTTCATGGCC
 AAAACCAGAAGTTTACCAATCTTTTAAAGCTTTGAAAGATGTTGATTCAATTACAGTTG
 5 ATCCACATAAGGTTGGTTTTATTCAATATGCTGCAGGTGCAATTTGTATGAAGGATAAG
 AGAATTTTGAATTAATTTCTTCACATGCTGCATACGTTTTTGAAGGTCATGCTGATAA
 GACATCTACTAAAAATAGAGGTATTTTGGGTTCTTCAATTATGGAAGGTTCTAAATCAG
 GTGCAACAGCTGCAGCTTTGTGGGCAGCTCATAGATTGTTACCATTGAACATCAACGGT
 TACGGTAAAGTTATTGCAGCTGGTATCGTTACTGCACAATCTTTGTTGAATAAGTTGGC
 10 TAATTTGCCACCAATCGAAATCGGTAAACATAGATTCTGAAGTTCATATTTTTCCATCAC
 CAGATTTCCACATGATCAACTTCACTTTTAAAGAAGTTGGTAACGAATCTTTGTCAAAC
 CATAACGCTTTGAATAAGAGATTGTATGAATTATGTTCTTACTCAGCAGGTAGAGCTTA
 CACAAATGATTTCTTGACATCTTCAACTATTTTAGATTACAAGGAATACGGTGACACTC
 CTTGGCATCATGCTCAAAAATGTGGTTTTTCAAGATCAGAATGGGAAAAAGTTAGAAAC
 15 ATCTATGTTTTGAGAGCAGCTGTTATGACATACTGTTTGAGAGATGAAGAACATTTCTGA
 AGAATTCTGGGAACAATTGCAAGCTATCTTCGTTAAGAAATTGACTCAAATCGTTGATG
 AAGAAGATAAGAAAGCAAGATTGAGATTAGAACCAGATGTTCTTTTTATTGGTTAA

[00486] SEQ.ID NO: 55

20 MTKPFHPNLNVDALFLGPKESENAVFFREMMDYAVSEHMHWRSGFHPEDSTLVTSVDRYE
 HNYRETLYRTEGILNQLSAKLKNSSIPFFSPRYLGHISSDTLMVSNLAYVMAMMYNPNN
 CSYEASPTTTELELESGLDLCRMFGYNPQQSWGHTSGGTVANYEGLWVARNLKTL SFA
 ISQHPKAKDLIEHKTPKQLKNMPTSELDDLITELQKRGLFEEIRDMTCRGTGVKAQILG
 KLLVPQSKHYSWMKAADIFGIGQENI IPLPVNDHYQTDVAQMRKITFGLIEQGEPI LAM
 25 IAVVGTTEVGAI DRIDEVIALRKECEERYGESFYIHVDAAYAGYACSM LLNEQGEFVEY
 DELANYHRSAGIMPENISWPKEVYQSFKALKDVDSITVDPHKVGF IQYAAGAI CMKDK
 RILELISSHAAYVFEGHADKTSTKNRGILGSSIMEGSKSGATAAALWAAHRLPLNING
 YGKVIAAGIVTAQSLNKLANLPPIEIGKHFVEVHIFPSPDFHMINFTFKEVGNESLSN
 HNALNKRLYELCSYSAGRAYTNDFLTSS TILDYKEYGDTPWHAQKCGFSRSEWEKVRN
 30 IYVLRAAVMTYCLRDEEHFEEFWEQLOAI FVKKLTQIVDEEDKKARLRLEPDVPF IG

[00487] SEQ.ID NO: 56

ATGGGTTCTTTGGATTCAAACCTACGATACTGAATCTCCAGCTTCAGTTGGTCAATTCAA
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 35 ATTACTACAAGAACATTGAATCTTATCCAGTTTTGT CACAAGTTGATCCAGGTTACAGA
 CATTCAAGATTGGGTAAAAATGCTCCATACAGATCTGAACCATTCTGAATCAATCTTGAA
 GGATGTTCAAAAAGGATATCATCCCTGGTATGACTCATTGGATGTCTCCAAATTTCTTTG
 CTCATTTTCCAGCAACTGTTTCTTCAGCTGCATTTGTTGGTGAAATGTTGTGTACATGT
 TTCAACTCTGTTGGTTTTAATTGGTTAGCATCACCAGCTGCAACAGAATTGGAAATGGT
 40 TGTTATTGATTGGTTAGCTAACATGTTGAAGTTGCCAAAGTCTTTTATGTTTT CAGGTA
 CTGGTGGTGGTGT TTTGCAAGGTACTACATCTGAAGCTATCTTGTGTACATTGATTGCT
 GCATCACCAATGCATTTGAAATCGTTGGTGTTAAGACTTCTACATCATTCTGTTGTTTA
 TGGTTCTGATCAAACCTATTCAACATACGCTAAAGCATGTAAATTAGCAGGTATTTTGC
 CATGTAACATCAGATCTATTCCAACCTACAGCTGATTCAAACCTCTCTGTTT CACCATTG
 45 TTGTTGAGAAGAGCTATTGAAGCAGATAAAGCTGCAGGTATGGTTCCATTGTATATTTG
 TGCTACAGTTGGTACTACATCTACTACAGCAATTGATCCATTATCTTCATTGGCTGATG
 TTGCAATGATTATGGTGT TTTGGTTTCATGTTGATGCTGCATACGCTGGTTCTGCATGT
 ATTTGTCCAGAATTCAGACATTATTTGGATGGTATCGAAAGAGCAGATTCTTTGT CATT
 GTCTCCACATAAGTGGTTGTTGTCTTACTTAGATTGTTGTTGTTTGTGGGTAAAGTCAC

CATCTTTATTGGTTAAGGCTTTATCAACTGATCCAGAATATTTGAAAAATCAACCATCA
GAATCTAAGTCAGTTGTTGATTACAAGGATTGGCAAGTTGGTACAGGTAGAAGATTCAA
AGCTTTGAGATTGTGGTTCGTTATGAGATCTTATGGTGTTGCAAATTTGCAATCACATA
TCAGAACTGATGTTCAAATGGCTAAGATGTTCGAAGGTTTCGTTAAGTCTGATCCAAGA
5 TTCGAAATTTTGGTTCCAAGAGTTTTCTCTTTGGTTTGTTCAGATTGAACCCAATCTC
TGGTTCAGATCCAACCTGGTACAGAAGCTTTGAACAGAAAGTTATTGGATTGGGTTAATT
CTACAGGTAGAGTTTATATGACTCATAACAAAAGTTGGTGGTATCTATATGTTGAGATTT
GCTGTTGGTGCAACTTTAACAGAAAAGAGACATGTTTCTTCAGCTTGGAAGTTGATTAA
AGAAGGTGCAGATGTTTTGTTGAAGGAAGATTAA

10

[00488] SEQ.ID NO: 57

MGSLDSNYDTESPASVGQFNPLDPEEFRKQAHCIVDIFIADYYKNIESYPVLSQVDPGYR
HSRLGKNAPYRSEPFESILKDVQKDIIPGMTHWMSPNFFAHFPATVSSAAFVGEMLCTC
FNSVGFNWLASPAATELEMVVIDWLANMLKLPKSFMFSGTGGGVLQGTTSEAILCTLIA
15 ASPMHFEIVGVKTSTS FVVYGS DQTHSTYAKACKLAGILPCNIRSIPTTADSNFSVSPL
LLRRAIEADKAAGMVPLYICATVGTSTTAIDPLSSLADVANDYGVWFHVDAAAYAGSAC
ICPEFRHYLDGIERADSLSLSPHKWLLSYLDCCCLWVKSPSLLVKALSTDPEYLNQPS
ESKSVVDYKDWQVGTGRRFKALRLWFVMRSYGVANLQSHIRTDVQMAKMFEGFVKSDPR
FEILVPRVFSVLVCFRLNPISGSDPTGTEALNRKLLDWNSTGRVYMTHTKVGGIYMLRF
20 AVGATLLEKRVHSSAWKLIKEGADVLLKED

20

[00489] SEQ.ID NO: 58

ATGGAAGGTGGTTTTACTGGTGGTGACGAATACCAAAGCATTCTTGCCAAGAGATTA
CTTAAACACATACTACTCATTTCCAATCTGGTCCATCACCAGAAGCTGAAATGTTGAAGT
25 TTAATTTGGAATGTTTGCATAAGACTTTCTGGTCCAGGTGGTTTGCAAGGTGACACTTTA
ATTGATATTGGTCTCTGGTCCAACAATCTATCAAGTTTTGGCTGCATGTGAATCTTTTAA
AGATATCACTTTGTGAGATTTTACAGATAGAAATAGAGAAGAATTGGCTAAATGGTTGA
AGAAAGAACCAGGTGCATACGATTGGACTCCAGCTTTGAAGTTCGCATGTGAATTAGAA
GGCAACTCTGGTAGATGGCAAGAAAAAGCTGAAAAGTTGAGAGCAACAGTTAAGAGAGT
30 TTTGAAGTGTGATGCTAATTTGTCAAATCCATTAACCTCAGTTGTTTTGCCACCAGCAG
ATTGTGTTTTTGACATTGTTAGCTATGGAATGTGCATGTTGTTCTTTGGATGCTTATAGA
GCTGCATTGAGAAATTTGGCATCATTTGTTAAACCAGGTGGTCATTTGGTTACTACAGT
TACTTTGCAATTATCTTCATACATGGTTGGTGAAAGAGAATTTTCTTGTTGTTGCTTTGG
AAAAAGAAGAAGTTGAACAAGCTGTTTTAGATGCAGGTTTCGATATCGAACAATTGTTG
35 TACTCTCCACAATCTTACTCAGCTTCTACAGCACCAAATAGAGGTGTTTGTCTTGGT
TGCTAGAAAGAAACCAGGTTTCATAA

35

[00490] SEQ.ID NO: 59

MEGGFTGGDEYQKHFLPRDYLNITYYSFQSGPSPEAEMLKFNLECLHKTFGPGGLQGDTL
40 IDIGSGPTIYQVLAACESFKDITLSDFDTRNREELAKWLKKEPGAYDWTPALKFACELE
GNSGRWQEKAEKLRA TVKRVLKCDANLSNPLTPVVLPPADCVLTL LAMECACCSLDAYR
AALRNLASLLKPGGHLVTTVT LQLSSYMGVEREFSCVALEKEEVEQAVLDAGFDIEQLL
YSPQSYSASTAPNRGVCFLVARKKPGS

40

[00491] SEQ.ID NO: 60

ATGGATAAGATCTCTGCACCATTTTTCTCTGGTACTTCACCAGCTGCAGCTTCAGTTGC
TGGTGTGATGAAGATGATAGATTGTGTTTCCAAGCTCAAGAATTGATGTTGCATACA

45

ACATCTCTATGGTTTTGAGAGCAGCTATTCAATTAGGTTTGTAGATGCTTTGTCAGCA
GCTGGTGGTAAAGCATTGACTCCAAACGAATTAGTTGAAAACGTTGAAACATCTTCAA
TAAGGCTGAAGCAGCTGCAGCTGTTGATAGAATTTTGAGATATTTGTCTTGTTCACG
5 TTGTTACTTGTTCCTTCAGAAGCAGCTGGTCCAGATGGTACATTAGTTAGAAGATACACT
ACAGGTCCATTGTGTAGATGGTTAACTAAAGATAGAGGTGACGGTACATTATCTCCATT
TGCTGTTTTTGTGTTGATCCAGATCATTGTTTCCTTGGCATCATATTGCAGAAGCTG
TTACTGCTGGTGGTCCATCAGCATTGAAAGAACACAAAAGTGGCCATACTACGAATAC
ATGGGTAAAAATCAAAGATTGGGTACTTTGTTTCGATAACGCAATGGCTCAACATTCTGT
TATTTTGGTTACAAAGATGTTAGAAAGATTCAAAGGTTTTGATGGTGTTCAAAGATTAG
10 TTGATGTTGGTGGTGGTACTGGTTCTACATTGGGTATGATCACTTCAAAGTACAAGCAC
ATGACAGGTATTAATTACGATTTGCCACATGTTATTGCTCAAGGTTTGGCATTACCAGG
TGTTGAACATGTTGCAGGTGACATGTACGAATCTATTCCAAGTGGTGACGCTGTTTTGT
TACAATGGATTACATTGATGTTGAACGATGATGAATTCGTTAAGATCTTGTCAAATTGT
CATAATGCTTTGCCAAAAGATGGTAAAGTTATTGTTGTTGATGGTATTTTACCAGAAAA
15 CCCAGATTCTTCATTGACTGCAAGAGATGCTTTTACATTAGATATCATCATGTTCTGTTT
TGTTTAAAGGTGCAAAGCAAAGAACTGAAAAGGAATTTCGCAAGATTAGCTAAGCAAGCA
GGTTTTACTGGTGGTATTAAGAAAACCTTATATTTTCTTTAATTTTACGCTTTGGAATT
CACTAAATAA

20 **[00492]** SEQ.ID NO: 61

MDKISAPFFSGTSPAAASVAGVDEDDRLCFQAQELMFAYNISMVLRAAIQLGLLDALSA
AGGKALTPNELVENVETSSNKAEEAAAVDRLRYLSCFNVVTCSSAAGPDGTLVRRYT
TGPLCRWLTKDRGDGTLSPFAVFVDPDHLFPWHHIAEAVTAGGPSAFERTQKWPYYEY
MGKNQRLGTLFDNAMAQHSVILVTKMLERFKGFDGVQRLVDVGGGTGSTLGMITSKYKH
25 MTGINYDLPHVIAQGLPLPGVEHVAGDMYESIPTGDAVLLQWITLMLNDDEFVKILSNC
HNALPKDGKVIIVVDGILPENPDSSLTARDAFTLDIIMFVLFKGAKQRTEKEFARLAKQA
GFTGGIKKTYIFFNFYALEFTK

30 **[00493]** SEQ.ID NO: 62

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GGAAGCCTTCGCAACTGATCCACCCACGCAGTGGGTGTTCCCCGACGGTACTGCCGCCG
TCAGCAGGTTCTTTACACATGTTGCAGATAGGGTTCACACGGCCGGTGGTATTGTTGAG
CTACTACCAGACAGAGCCGCCATGATTGCATTGCCACCACACGTGAGGCTGCCAGGAGA
AGCTGCCGACGGAAGGCAGGCGGAAATTCAGAGAAGGCTGGCAGACAGGCACCCGCTGA
35 CACCTCACTACTACCTGCTGTTTTACGGAGTTAGAACGGCACACCAGGGTTCGGGATTG
GGCGGAAGAATGCTGGCCAGATTAAGTAGCAGAGCTGATAGGGACAGGGTGGGTACATA
TACTGAGGCATCCACCTGGCGTGGCGCTAGACTGATGCTGAGACATGGATTCCATGCTA
CAAGGCCACTAAGATTGCCAGATGGACCCAGCATGTTTCCACTTTGGAGAGATCCAATC
CATGATCATTCTGATTAG

40 **[00494]** SEQ.ID NO: 63

MNTFRTATARDIPDVAATLTEAFATDPPTQWVFPDGTAAVSRFFTHVADRVHTAGGIVE
LLPDRAAMIALPPHVRLPGEAADGRQAEIQRRILADRHPLTPHYLLFYGVRTAHQGSGL
GGRMLARLTSRADRDVGTYTEASTWRGARLMLRHGFHATRPLRLPDGSPMFPLWRDPI
45 HDHSD

[00495] SEQ.ID NO: 64

ATGAAAGGATATTTTCGGACCATACGGTGGCCAGTACGTACCAGAAATATTAATGGGTGC
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 AGTTCAACGATCTACTGAGGGATTACGCAGGCAGACCAACGCCATTGTACTTTGCCAGG
 AGATTGTCTGAGAAGTACGGCGCCCGTGTCTTACTTGAAGCGTGAGGATCTGCTGCACAC
 5 TGGAGCACACAAGATAAATAACGCTATCGGACAGGTTTTATTGGCCAAATTAATGGGGA
 AGACACGTATCATAGCCGAGACGGGAGCTGGGCAGCATGGAGTCGCTACTGCTACCGCT
 GCTGCCCTGTTTCGGAATGGAATGTGTGATCTACATGGGTGAAGAGGACACAATCAGACA
 GAAGTTGAACGTGGAGCGTATGAAATTATTAGGGGGCTAAAGTTGTCCCTGTAAAGTCTG
 GCAGTAGGACCTTGAAGGATGCGATAGACGAGGCTTTGAGAGACTGGATTACTAATTTA
 10 CAGACAACATATTATGTTATCGGATCTGTTGTTGGTCCCCACCCTTACCCAATTATCGT
 AAGGAATTTCCAGAAGGTTATCGGTGAGGAGACCAAGAAGCAAATACCAGAAAAGGAAG
 GTCGTTTGCCAGACTATATAGTTGCCTGCGTAGGCGGCGGTAGCAATGCCGCAGGTATA
 TTTTACCCATTTCATAGACTCTGGAGTAAAGCTGATAGGTGTTGAGGCAGGTGGCGAGGG
 ATTGGAGACAGGTAAACACGCAGCCTCGTTATTAAAGGGTAAAATTGGCTATTTACATG
 15 GATCGAAGACCTTTGTTCTACAAGATGACTGGGGTCAAGTCCAAGTGAGCCATTCGGTG
 TCAGCTGGTCTTGACTATTCAGGAGTAGGACCTGAGCATGCTTATTGGAGAGAGACAGG
 GAAGGTTCTGTACGACGCAGTGACTGACGAAGAGGCTTTGGACGCATTTATAGAGTTAT
 CAAGACTAGAGGGCATTATACCCGCTTTAGAGTCATCGCATGCTCTAGCATATTTGAAG
 AAGATAAATATAAAAGGTAAGGTTGTGGTGGTCAACCTATCAGGGAGAGGGGATAAAGA
 20 CCTGGAGTCAGTCTTAAACCATCCATACGTGAGAGAAAGAATTAGATGA

[00496] SEQ.ID NO: 65

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 RLSEKYGARVYLKREDLLHTGAHKINNAIGQVLLAKLMGKTRIIAETGAGQHGVATATA
 25 AALFGMECVIYMGEEDTIRQKLNVERMKLLGAKVVPVKSGSRTLKDAIDEALRDWITNL
 QTTYVIGSVVGPYPPIIVRNFAQKVI GEETKKQIPEKEGRLPDYIVACVGGGSNAAGI
 FYPFIDSGVKLIGVEAGGEGLTGKHAASLLKGKIGYLHGSKTFVLQDDWGQVQVSHSV
 SAGLDYSGVGPEHAYWRETGKVLVDAVTDEEALDAFIELSRLEGIIPALESSHALAYLK
 KINIKGKVVVNLSGRGDKDLESVLNHPYVRERIR

30

[00497] SEQ.ID NO: 66

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 GGAATTGGAAAAGGCATATAAAAGGTTCAAGGACGATGAGGAGTTCAACAGGCAACTAA
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 35 ACTGAAAAGATTGGCGGCGCGAAAGTGTATCTGAAAAGAGAAGACCTAGTTCATGGTGG
 AGCACACAAGACAAATAATGCCATTGGACAAGCACTATTGGCAAAGCTAATGGGTAAAA
 CTAGATTGATAGCTGAGACAGGAGCGGGTCAACATGGGGTCGCGACAGCGATGGCTGGT
 GCACTACTGGGGATGAAGGTAGATATTTACATGGGTGCTGAGGACGTTGAGCGTCAGAA
 ACTAAATGTCTTCAGGATGAAGCTATTAGGTGCCAATGTTATACCTGTAAATTCTGGCT
 40 CAAGAACACTAAAGGACGCCTTCGACGAGGCTCTTAGAGACTGGGTGGCACTTTTCGAG
 TATACTCATTACTTGATCGGTTCAAGTGGTGGACCACATCCATACCCAACCATCGTTAG
 GGACTTTTCAGAGCGTGATTGGTAGAGAGGCTAAGGCACAGATCTTAGAAGCAGAGGGAC
 AGCTACCTGACGTCATAGTTGCCTGCGTCGGCGGTGGCTCTAACGCAATGGGTATATTC
 TATCCATTTCGTTAATGACAAGAAGGTTAAATTAGTAGGAGTCGAAGCTGGCGGAAAGGG
 45 GTTAGAGTCGGGTAAACACTCAGCAAGCTTAAATGCAGGACAGGTAGGGGTGTCCACG
 GCATGTTGTCGTATTTCTTGCAAGACGAGGAAGGTCAGATAAAGCCAAGTCATTCAATT
 GCTCCAGGCCTTGACCACCCCGGTGTTGGTCCAGAGCACGCTTACTTAAAGAAGATTCA
 AAGGGCCGAGTACGTCGCTGTAACAGACGAAGAGGCATTGAAAGCTTTCCATGAGCTAT
 CCAGAACTGAGGGGATTATACCCGCCCTTGAGTCTGCCCATGCTGTGGCGTACGCCATG

AAGTTAGCTAAAGAGATGTCCCGTGACGAAATCATCATTGTAAATCTATCAGGGAGAGG
AGACAAGGATTTGGACATTGTATTGAAGGCAAGCGGAAATGTTTGA

[00498] SEQ.ID NO: 67

5 MWFGEFGGQYVPETLVGPLKELEKAYKRFDDEEFNRQLNYYLKTWAGRPTPLYAKRL
TEKIGGAKVYLKREDLVHGGAHKTNNAI GQALLAKLMGKTRLIAETGAGQHGVATAMAG
ALLGMKVDIYMGAEDVERQKLN VFRMKLLGANV I PVNSGSRTLKDAFDEALRDWVATFE
YTHYLIGSVVGPHPYPTIVRDFQSVIGREAKAQILEAEGQLPDVIVACVGGGSNAMGI F
YPFVNDKKVKLVGVEAGGKGLES GKHSASLNAGQVGVSHGMLS YFLQDEEGQIKPSHS I
10 APGLDHPGVGPEHAYLKKI QRAEYVAVTDEEALKAFHEL SRTEGI I PALESAHAVAYAM
KLAKEMSRDEI I I VNLSGRGDKDL DIVLKASGNV

[00499] SEQ.ID NO: 68

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15 GGAGCTTGAGAAAGCTTACAAAAGATTTAAGGACGACGAGGAGTTTAATAGGCAATTAA
ACTATTACTTGAAGACTTGGGCAGGTAGACCAACACCACTTTATTACGCGAAGAGACTT
ACAGAGAAGATCGGTGGCGCTAAGGTTTATTTGAAGCGTGAGGATTTGGTTCATGGTGG
AGCACATAAGACAAACAATGCCATCGGGCAAGCCTTGTTGGCCAAATTGATGGGTAAAG
CTAGGTTGATAGCTGGCACAGGTGCCGCCAGCATGGCGTTGCAACAGCAATGGCTGGT
20 GCTCTTTTAGGGATGAAGGTGGATATCTATATGGGCGCCGAGGACGTTGAAAGACAAAA
GCTTAACGTATTCAGAATGAAGTTATTAGGTGCGAATGTTATTCCAGTGAATTCAGGTT
CCAGGACGCTGAAGGACGCAATAGACGAAGCCTTGAGAGACTGGGTTGCTACTTTTGGAG
TACACACATTATTTGATTGGTTCCGTGGTTGGACCCACCCGTACCCTACAATAGTTAG
AGATTTTCAATCTGTTATCGGTAGAGAGGCGAAGGCTCAAATTCAGAGGCCGAGGGAC
25 AGCTACCCGATGTTATAGTCGCCTGCGTTGGAGGAGGATCAAATGCGATGGGAATCTTC
TACCCTTTTGTAATGATAAGAAAGTTAAGTTAGTCGGAGTTGAGGCCGGTGGTAAAGG
GCTAGAAAGCGGCAAACACTCGGCATCTCTTAATGCCGGTCAAGTAGGAGTAAGTCACG
GGATGTTATCTTACTTCTTGCAGGATGAGGAAGGTCAAATTAAGCCATCTCATTCTATA
GCCCCAGGATTAGACTATCCCGGTGTTGGGCCTGAGCACGCTTATCTGAAGAAGATACA
30 GCGTGCTGAGTACGTTGCAGTAAGTGAAGAGGCTTTGAAGGCTTTTCACGAGTTAT
CAAGAACTGAGGGAATAATTCCTGCCTTGGAATCGGCACATGCGGTTGCCTACGCCATG
AAGCTTGCTAAGGAAATGTCAAGAGACGAAATCATTATAGTGAATTTATCGGGAAGGGG
CGATAAGGACTTGGACATTGTTTTAAAGCAAGTGGCAATGTATAA

35 **[00500] SEQ.ID NO: 69**

MWFGEFGGQYVPETLVGPLKELEKAYKRFDDEEFNRQLNYYLKTWAGRPTPLYAKRL
TEKIGGAKVYLKREDLVHGGAHKTNNAI GQALLAKLMGKTRLIAGTGAGQHGVATAMAG
ALLGMKVDIYMGAEDVERQKLN VFRMKLLGANV I PVNSGSRTLKDAIDEALRDWVATFE
YTHYLIGSVVGPHPYPTIVRDFQSVIGREAKAQIPEAEGQLPDVIVACVGGGSNAMGI F
40 YPFVNDKKVKLVGVEAGGKGLES GKHSASLNAGQVGVSHGMLS YFLQDEEGQIKPSHS I
APGLDYPGVGPEHAYLKKI QRAEYVAVTDEEALKAFHEL SRTEGI I PALESAHAVAYAM
KLAKEMSRDEI I I VNLSGRGDKDL DIVLKASGNV

[00501] SEQ.ID NO: 70

45 ATGTGGTTTGGTGAGTTTGGTGGTCAGTATGTGCCTGAGACGCTAGTTGGGCCACTGAA
GGAGTTAGAGAAAGCGTACAAGAGATTCAAAGATGACGAGGAGTTTAACCGTCAGTTGA
ATTATTATCTTAAGACGTGGGCTGGTAGGCCGACCCCTCTATACTACGCTAAGCGTTTA

ACCGAAAAGATAGGTGGCGCCAAGATCTATCTGAAGAGAGAGGACCTAGTCCACGGCGG
 GGCTCACAAAACATAACAACGCAATTGGTCAGGCACCATTAGCAAAGTTAATGGGCAAAA
 CACGTCTAATTGCCGAAACTGGTGCTGGTCAACATGGAGTTGCTACGGCAATGGCGGGC
 GCACTGTTAGGTATGAAAGTGGATATCTATATGGGAGCAGAAGACGTGGAGAGACAGAA
 5 GATGAACGTGTTCCGTATGAAACTATTGGGAGCTAATGTTATCCCGGTTAACTCTGGCT
 CAAGAACTGCAAAGGACGCCATAAACGAAGCTTTGAGGGATTGGGAAGCCACATTCGAG
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 TGACTTCCAGAGTGTTATTGGCCGTGAGGCCAAGGCACAGATCTTGGAAGCTGAAGGTC
 AATTGCCTGACGTAATAGTTGCATGTGTGGGTGGCGGTTCTAACGCTATGGGTATATTC
 10 TACCCCTTCGTGAACGATAAGAAAGTAAAGCTAGTTGGAGTGGAAGCAGGTGGCAAAGG
 GTTGGAGTCGGGCAAGCACTCAGCCTCATTAACGCAGGTCAGGTAGGCGTTCTGCACG
 GTATGTTATCCTATTTCTTACAGGACGAGGAAGGCCAAATCAAACCATCGCACTCAATC
 GCACCTGGTTTATAGATTACCCAGGAGTCGGTCCCGAGCACGCATATTTAAAGAAAATCCA
 GAGAGCAGAGTACGTCACGGTGACGGATGAGGAAGCCCTTAAAGCGTTTCACGAGCTGT
 15 CGAGGACCGAGGGCATAATACCTGCTCTTGAAAGTGCCACGCAGTTGCCTATGCTATG
 AAGTTGGCCAAGGAGATGAGTAGAGACGAGATTATCATAGTAAATCTGTCAGGCAGAGG
 TGACAAGGATCTTGACATAGTCCTTAAGGCGAGCGGTAATGTTTTGGAGTAA

[00502] SEQ.ID NO: 71

20 MWFGEFGGQYVPETLVGPLKELEKAYKRFDDEEFNRQLNYYLKTWAGRPTPLYAKRL
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 ALLGMKVDIYMGAEDVERQKMNVFRMKLLGANVIVPNSGSRTAKDAINEALRDWEATFE
 YTHYLIGSVVGPYPYPTIVRDFQSVIGREAKAQILEAEGQLPDVIVACVGGGSNAMGIF
 YPFVNDKKVKLVGVEAGGKGLES GKHSASLNAGQVGV LHGMLS YFLQDEEGQIKPSHSI
 25 APGLDYPGVGPEHAYLKKI QRAEYVTVTDEEALKAFHEL SRTEGI I PALESAHAVAYAM
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[00503] SEQ.ID NO: 72

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[00504] SEQ.ID NO: 73

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[00505] SEQ.ID NO: 74

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[00506] SEQ.ID NO: 75

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[00507] SEQ.ID NO: 76

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30

[00523] SEQ.ID NO: 92

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[00524] SEQ.ID NO: 93

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[00525] SEQ.ID NO: 94

[illegible]

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30 **[00526]** SEQ.ID NO: 95

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20 **[00527]** SEQ.ID NO: 96

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35 **[00528]** SEQ.ID NO: 97

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25 **[00529] SEQ.ID NO: 98**

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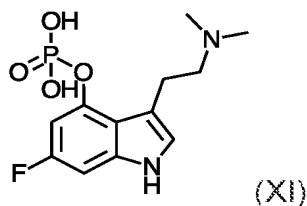
[00530] Hereinafter are provided examples of specific implementations for
 performing the methods of the present disclosure, as well as implementations
 45 representing the compositions of the present disclosure. The examples are
 provided for illustrative purposes only, and are not intended to limit the scope of
 the present disclosure in any way.

EXAMPLES

Example 1 – Process for making a first halogenated psilocybin derivative from halogenated tryptophan feedstock.

[00531] Yeast (*Saccharomyces cerevisiae*) was genetically engineered to enable bioconversion of commercially obtained, halogenated, simple indole, tryptophan, or tryptamine feedstock to generate final product. The parent yeast (*Saccharomyces cerevisiae*) strain was CEN.PK with genotype *Mat α* ; *ura3-52*; *trp1-289*; *leu2-3,112*; *his3 Δ 1*; *MAL2-8C*; *SUC2*. The parent strain was engineered to include three enzymatic steps through chromosomal homologous recombination of integration cassettes as described previously (Dastmalchi *et al.*, 2019, Nat. Chem Biol. 15: 384-390; Chen *et al.*, 2018, Nat. Chem Biol. 14: 738-743). The three steps were comprised of PsiH (SEQ.ID NO: 4), PsiK (SEQ.ID NO: 6) and PsiM (SEQ.ID NO: 8), encoded by SEQ.ID NO: 3, SEQ.ID NO: 5 and SEQ.ID NO: 7, respectively, with addition of in-frame, C-terminal HA (SEQ.ID NO: 81, SEQ.ID NO: 82), V5 (SEQ.ID NO: 87, SEQ.ID NO: 88), and FLAG (SEQ.ID NO: 85, SEQ.ID NO: 86) epitope tags, respectively. DNA (SEQ.ID NO: 95) encoding a fifth enzyme, PcCPR (SEQ.ID NO: 96) was also integrated following PCR-based, C-terminal, in-frame addition of epitope tag c-MYC (SEQ.ID NO: 83, SEQ.ID NO: 84) to support functionality of PsiH. Integration cassettes were built using yeast promoter sequences amplified from *S. cerevisiae* genomic DNA as described (Dastmalchi et al. 2019; Chen et al. 2018) enabling constitutive gene expression. Amplified promoters included *PGK1* (SEQ.ID NO: 77), *TDH3* (SEQ.ID NO: 78), *CLN1* (SEQ.ID NO: 79), and *UGA1* (SEQ.ID NO: 80). Two integration cassettes were assembled: the first (SEQ.ID NO: 74) harbored tagged PsiH and PcCPR, and the second (SEQ.ID NO: 75) harbored tagged PsiK and PsiM. Successive genomic integration of these cassettes was performed as described previously (Chen et al. 2018). Following stable integration of these two cassettes, the strain was further manipulated by transformation with a yeast episomal vector encoding a promiscuous decarboxylase, ClostSporTDC (pMM1-pTDH3-ClostSporTDC-His-tCYC1) (SEQ.ID NO: 76) enabling efficient decarboxylation of halogenated tryptophan intermediates and/or feedstocks. For

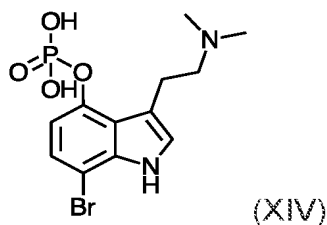
this Example, heterologous expression of a non-native or engineered TrpB gene was not necessary, as endogenous tryptophan synthase activity proved sufficient. The final engineered strain was called Sc-1. For scaled-up production of halogenated product, culturing was performed as follows. Seed cultures were inoculated in SD-drop-out medium overnight. The overnight culture was then divided into two flasks containing 500 ml each of SD-drop-out medium containing 2% (w/v) glucose, 0.3%(w/v) KH₂PO₄, 0.05% (w/v) MgSO₄.7H₂O, 0.5% (w/v) (NH₄)₂SO₄ plus 500 µM 6-fluorotryptophan (ThermoFisher Scientific) for conversion by Sc-1. Yeast cultures were grown for 48 h. Cultures were then centrifuged (10,000g x 5 minutes) to remove cellular content, and culture broth containing secreted halogenated product was stored at -80°C until further processing. To determine successful biosynthesis of 6-fluoro-psilocybin (compound with formula (XI)), culture broth was analyzed using high-resolution LC-HESI-LTQ-Orbitrap-XL MS (Thermo Fisher Scientific), employing a modified version of a method described previously (Chang *et al.*, 2015, Plant Physiol. 169: 1127-1140), with the exception that liquid chromatography was carried out using an UltiMate 3000 HPLC (Thermo Fisher Scientific) equipped with a Poroshell 120 SB-C18 column (Agilent Technologies) instead of an Accela HPLC system (Thermo Fisher Scientific) equipped with a Zorbax C18 column (Agilent Technologies). Briefly, 10 microliters of sample was injected at a flow rate of 0.5 mL/min and a gradient of solvent A (water with 0.1 % of formic Acid) and solvent B (ACN with 0.1% formic Acid) as follows: 100% to 0% (v/v) solvent A over 5 min; isocratic at 0% (v/v) for 1 min; 0% to 100% (v/v) over 0.1 min; and isocratic at 100% (v/v) for 1.9 min. Total run time was 8 minutes. Heated ESI source and interface conditions were operated in positive ion mode as follows: vaporizer temperature, 400°C; source voltage, 3 kV; sheath gas, 60 au, auxiliary gas, 20 au; capillary temperature, 380°C; capillary voltage, 6 V; tube lens, 45 V. Instrumentation was performed as a single, HR scan event using Orbitrap detection of *m/z* in the range of 100-500 *m/z*. Ion injection time was 300 ms with scan time of 1 s. External and internal calibration procedures ensured <2 ppm error to facilitate elemental formulae predictions. Singly protonated product with exact *m/z* and expected elemental formula matching 6-fluoro-psilocybin having chemical formula (XI):



eluted at 1.9 minutes (EIC, see: FIG. 10).

5 Example 2 – Process for making a second halogenated psilocybin derivative from halogenated tryptophan feedstock.

[00532] The same yeast strain (Sc-1) and procedures described in Example 1 were used to biosynthesize a halogenated psilocybin derivative with chemical formula (XIV), with the following exception: in place of 6-fluorotryptophan, 500 μ M 7-bromotryptophan (Combi-Blocks, www.combi-blocks.com) was supplied as feedstock for bioconversion. Singly protonated product with exact m/z and expected elemental formula matching 7-bromo-psilocybin having chemical formula (XIV):

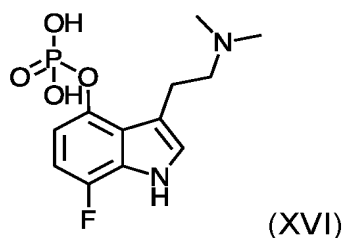


eluted at 2.8 minutes (EIC, see: FIG. 11).

20 Example 3 – Process for making a third halogenated psilocybin derivative from halogenated indole feedstock.

[00533] The same yeast strain (Sc-1) and procedures described in Example 1 were used to biosynthesize a halogenated psilocybin derivative with chemical formula (XVI), with the following exception: in place of 6-fluorotryptophan, 500 μ M 7-fluoroindole (Combi-Blocks, www.combi-blocks.com) was supplied as feedstock for bioconversion. Singly protonated product with exact m/z and expected

elemental formula matching 7-fluoro-psilocybin compound having chemical formula (XVI):



5

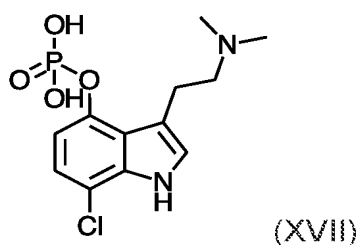
eluted at 2.3 minutes (EIC, see: **FIG. 12**).

Example 4 – Process for making a fourth halogenated psilocybin derivative from halogenated indole feedstock.

10

[00534] The same yeast strain (Sc-1) and procedures described in Example 1 were used to biosynthesize a halogenated psilocybin derivative with formula (XVII), with the following exception: in place of 6-fluorotryptophan, 500 μ M 7-chloroindole (Combi-Blocks, www.combi-blocks.com) was supplied as feedstock for bioconversion. Singly protonated product with exact m/z and expected elemental formula matching 7-chloro-psilocybin having formula (XVII):

15



eluted at 2.7 minutes (EIC, see: **FIG. 13**).

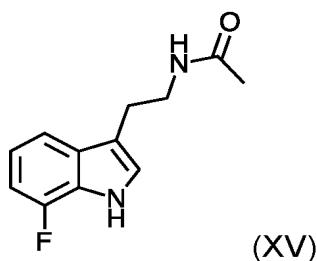
Example 5 – Process for making a fifth halogenated psilocybin derivative from halogenated indole feedstock.

20

[00535] *E. coli* strain Ec-1 was constructed as follows. For plasmid cloning, Top10 or XL1-blue strains were used depending on antibiotic markers. Standard LB media was used for culturing. For gene expression and feeding experiments, the parent host strain employed was BL21 (DE3). For this Example, heterologous

25

expression of a non-native or engineered TrpB gene was not necessary, as endogenous tryptophan synthase activity proved sufficient. An in frame, C-terminally His-tagged (SEQ.ID NO: 89, SEQ.ID NO: 90) BaTDC (SEQ.ID NO: 36, SEQ.ID NO: 37) was generated by PCR, followed by cloning into the *NdeI* and *XhoI* sites of the plasmid pCDM4 (SEQ.ID NO: 92) where the expression of the gene was driven by a T7 promoter. In a second plasmid, an in-frame, C-terminally His-tagged (SEQ.ID NO: 89, SEQ.ID NO: 90) PsmF (SEQ.ID NO: 62, SEQ.ID NO: 63) was cloned into the *NdeI* and *XhoI* sites of pET28a(+) (SEQ.ID NO: 94) where the expression of the gene was also driven by a T7 promoter. The *E. coli* host strain BL21 (DE3) was transformed with both plasmids and selected for using streptomycin and kanamycin antibiotics. This strain (Ec-1, F– *ompT hsdSB* (rB–, mB–) *gal dcm* (DE3), pCDM4-BaTDC-His, pET28a(+)-PsmF-His) enabled production of *N*-acetylated products from modified indole feedstock. Further, the use of promiscuous BaTDC (SEQ.ID NO: 36, SEQ.ID NO: 37) allowed decarboxylation of a wide variety of halogenated tryptophan intermediates. Scaled-up culturing of engineered *E. coli* was conducted as follows: seed cultures were inoculated in AMM (Jones *et al.*, 2015, Sci. Rep. 5: 11301) medium overnight. The overnight culture was then divided into two flasks containing 500 mL each of AMM medium additionally containing 0.5% (w/v) serine, 1M IPTG, 50ug/L kanamycin and streptomycin, and 100 mg/L 7-fluoroindole (Combi-Blocks, www.combi-blocks.com) for conversion by the *E. coli* strain. Cultures were grown for 24 h. Cultures were then centrifuged (10,000g x 5 minutes) to remove cellular content, and culture broth containing secreted derivative was stored at -80C until further processing. The *N*-(2-(7-difluoro-1*H*-indol-3-yl)ethyl)acetamide product having chemical formula (XV):



[00536] contained in 1 L of *E. coli* culture was extracted by ethyl acetate (3×300 ml). The organic layer was dried over Na₂SO₄, followed by concentration under reduced pressure. The residue was purified by column chromatography on

silica gel using ethyl acetate – hexane (50 → 80 %) as eluent to give the compound as a light yellow solid (22 mg). Following purification, high-resolution MS (HRMS), ¹H NMR, and selective ¹³C NMR were performed to assess purity, estimate total quantity, and confirm molecular structure. ¹H NMR (400 MHz, CDCl₃): δ = 1.96 (s, 3H), 2.97 (t, *J* = 6.8 Hz, 2H), 3.59 (dt, *J* = 6.7, 6.1 Hz, 2H), 5.7 (br, s, 1H), 6.91 (dd, *J* = 11.2, 7.8 Hz, 1H), 7.03 (m, 2H), 7.35 (d, *J* = 7.9 Hz, 1H), 8.6 (br, s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 23.3, 25.3, 39.8, 106.9 (d, *J*_{C,F} = 16.1 Hz), 113.7, 114.4 (d, *J*_{C,F} = 3.4 Hz), 119.6 (d, *J*_{C,F} = 6.1 Hz), 122.8, 124.7, 131.1 (d, *J*_{C,F} = 5.3 Hz), 149.7 (d, *J*_{C,F} = 244.2 Hz), 170.3. HRMS (ESI) *m/z*: calcd. for C₁₂H₁₃FN₂O [M+H]⁺ 221.1090, found 221.1087. The compound having chemical formula (XV) was 95% (w/w) pure. It is noted that the acetyl group of the compound having chemical formula (XV) is included therein by virtue of the acetyl transferase having SEQ.ID NO: 63 in *Escherichia coli* strain Ec-1.

[00537] *Cell lines for pharmacology assays.* CHO-K1/Galpha15 (GenScript, M00257) (-5-HT_{2A}) and CHO-K1/5-HT_{2A} (GenScript, M00250) (+5-HT_{2A}) cells lines were used in both toxicology/growth inhibition (MTT) and calcium release assays. Briefly, CHO-K1/Galpha15 is a control cell line that constitutively expresses Galpha15 which is a promiscuous Gq protein. It is engineered as a host cell, allowing transfected receptor(s) to signal through the Gq signal transduction pathway and mobilize intracellular calcium from the endoplasmic reticulum (ER). These control cells lack any transgene encoding 5-HT_{2A} receptors, thus preventing calcium mobilization in response to 5-HT_{2A} activation. Conversely, CHO-K1/5-HT_{2A} cells stably express 5-HT_{2A} receptor in the CHO-K1 host background. This design enables Gq-11 expressed in CHO-K1 cells to mobilize intracellular calcium changes when 5-HT_{2A} receptors are activated by ligands.

[00538] Cell lines were maintained in Ham's F12 media plus 10% FBS in the presence of 100 ug/ml hygromycin for CHO-K1/Ga15 or 400 ug/ml G418 for CHO-K1/5-HT_{2A} unless indicated otherwise for specific assays. Cell maintenance was carried out as recommended by the cell supplier. Briefly, vials with cells were removed from the liquid nitrogen and thawed quickly in 37°C water bath. Just before cells were completely thawed, vial exteriors were decontaminated with 70% ethanol spray. Cell suspension was then retrieved from the vial and added to warm (37°C), 'complete' (non-dropout) growth media, and centrifuged at 1,000 rpm for 5

minutes. The supernatant was discarded and the cell pellet was then resuspended in another 10 ml of complete growth media, and added to a 10 cm cell culture dish (Greiner Bio-One #664160). The media was changed every third day until the cells reached ~90% confluence. The ~90% confluent cells were then split 10:1, and used either for maintenance or pharmacological study.

[00539] *Assessment of cell viability upon treatment of glycosylated psilocybin derivatives.* To establish suitable ligand concentrations for the calcium release assays, MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium) assays were first performed. Results of these assays were conducted using both control ligands (e.g. psilocybin, psilocin, DMT) and novel derivatives, in part as a pre-screen for any remarkable toxic effects on cell cultures up to concentrations of 1 mM. A known cellular toxin (Triton X-100, Pyrgiotakis G. *et al.*, 2009, Ann. Biomed. Eng. 37: 1464-1473) was included as a general marker of toxicity. Modified Chinese Hamster Ovary cells (CHO-K1/Ga15) were cultured using standard procedures using the manufacture's protocols (Genscript, M00257). Briefly, cells were cultured in Ham's F12 medium supplemented with 10% fetal bovine serum and 100 mg/ml Hygromycin B, and grown at 37°C in the presence of 5% CO₂. To test the various compounds with the cell line, cells were seeded in a clear 96-well culture plate at 10,000 cells per well. After allowing cells to attach and grow for 24 hours, assay compounds were added at 1 µM, 10 µM, 100 µM, and 1 mM final concentrations. Methanol concentrations used are 0.001, 0.01, 0.1, and 1%. Triton concentrations used are 0.0001, 0.001, 0.01 and 0.1%. Cells were incubated with compounds for 48 hours before accessing cell viability with the MTT assay following the manufacture's protocol (MTT Cell Growth Assay Kit; Millipore Sigma, CT02). MTT reagent was added to cells and allowed to incubate for 4 hours before solubilization with isopropanol plus 0.04 N HCl. Absorbance readings were performed at 570 nm with the reference at 630 nm on a SpectraMax iD3 plate reader. Non-treated cells were assigned 100% viability. Results of the cell viability assays are shown in **FIG. 14**. Bar graphs show the mean +/- SD (n=3). Significance (P<0.0001), as indicated by (***) was determined using 2-way ANOVA with Dunnett's multiple comparisons test. The results using compound with formula (XV) are indicated as "(XV)" on the x-axis.

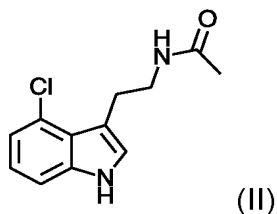
[00540] *Increase in cytosolic calcium concentration by 5-HT_{2A} activation.* Changes in intracellular calcium concentration due to the treatment with assay

compounds was measured using Fluo-8 dye (Abcam, #ab112129) according to the manufacturer's instructions. Briefly, CHO-K1 cells stably expressing 5-HT_{2A} (Genscript # M00250) (+5-HT_{2A}) or lacking 5-HT_{2A} (Genscript, M00257) (-5-HT_{2A}) were seeded on black walled clear bottom 96-well plates (Thermo Scientific #NUNC165305), allowing 70,000 cells/well in 100 ul media (HAM's F12, GIBCO #11765-047) with 1% FBS (Thermo Scientific #12483020). Cultures were maintained in a humidified incubator at 37°C and 5% CO₂. Fluo-8 dye was loaded into the cultures for 30 min at 37°C, followed by 30 min additional incubation at room temperature. Next, different dilutions of novel molecules and controls were prepared in serum-free culture media and added to the cells. Fluorescence (ex 490 nm / em 525 nm) obtained after the addition of molecules was expressed relative to values obtained before addition of the molecules (relative Fluo-8 fluorescence = F_{max}/ F₀, where F_{max}=maximum fluorescence and F₀=baseline fluorescence). Fluorescence intensities were measured using a Spectramax ID3 plate reader (www.moleculardevices.com). Relative fluorescence (RFU) at increasing concentrations of compound was determined, illustrating concentration-dependent calcium flux. Psilocin, a known agonist with binding activity at 5-HT_{2A} (Rickli A. *et al.*, 2016, *Europ. Neuropsychopharmacol.*, 26: 1326-1337) was used as a positive control to establish assay functionality. The Example compound (XV) was then evaluated. Results are shown in **FIGS. 15A – 15B** and **16A – 16B**. The results using different concentrations of psilocin and compound with formula (XV) (indicated as "(XV)") in +5-HT_{2A} cell cultures are shown in **FIG. 15A** and **FIG. 15B**, respectively. The results using different concentrations of psilocin and compound with formula (XV) (indicated as "(XV)") in -5-HT_{2A} cell cultures are shown in **FIG. 16A** and **FIG. 16B**, respectively. Results for negative control treatment with vehicle containing neither psilocin nor derivative are shown in **FIGS. 15A – 15B** and **16A – 16B**. Error bars show +/- SD about the mean (n=3).

Example 6 – Process for making a sixth halogenated psilocybin derivative from halogenated indole feedstock.

[00541] *Escherichia coli* strain Ec-1 was used to biosynthesize halogenated tryptamine derivative having chemical formula (II) from halogenated indole

feedstock. The construction of Ec-1 is described in Example 5. Scaled-up culturing and material storage of engineered *E.coli* was conducted as described in Example 5, except that 4-chloroindole (Combi-Blocks, www.combi-blocks.com) was used in place of 7-fluoroindole. To assess product, high-resolution LC-HESI-LTQ-Orbitrap-XL MS analysis was conducted as described in Example 1. Singly protonated product with exact m/z and expected elemental formula matching 4-chloro-N-acetyltryptamine having chemical formula (II):

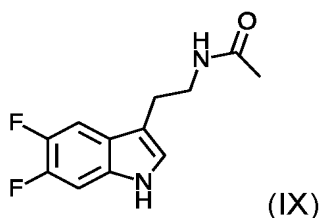


Eluted at 4.1 minutes (EIC, see: **FIG. 17**). It is noted that the acetyl group of the compound having chemical formula (II) is included therein by virtue of the acetyl transferase having SEQ.ID NO: 63 in *Escherichia coli* strain Ec-1.

Example 7 – Process for making a seventh halogenated psilocybin derivative from halogenated indole feedstock.

15

[00542] *Escherichia coli* strain Ec-1 was used to biosynthesize halogenated tryptamine derivative having chemical formula (IX) from halogenated indole feedstock. The construction of Ec-1 is described in Example 5. Scaled-up culturing and material storage of engineered *E.coli* was conducted as described in Example 5, except that 5,6-difluoroindole (Combi-Blocks, www.combi-blocks.com) was used in place of 7-fluoroindole. N-(2-(5,6-difluoro-1H-indol-3-yl)ethyl)acetamide product having Chemical formula (IX):



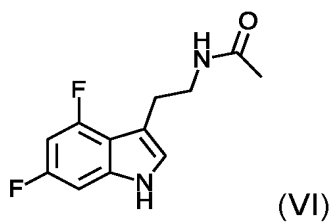
[00543] contained in 0.55 L of *E.coli* culture was extracted by ethyl acetate (3×300 ml). The organic layer was dried over Na₂SO₄, followed by concentration under reduced pressure. The residue was purified by column chromatography on

silica gel using ethyl acetate – hexane (50 → 80 %) as eluent to give the compound as a light yellow solid (11 mg). Following purification, high-resolution MS (HRMS), ¹H NMR, and selective ¹³C NMR were performed to assess purity, estimate total quantity, and confirm molecular structure. ¹H NMR (400 MHz, CDCl₃): δ = 1.70-1.79 (m, 1H), 1.99-2.06 (m, 1H), 2.29 (s, 6H), 2.33-2.38 (m, 1H), 2.40-2.48 (m, 1H), 3.22 (t, 1H, *J* = 8.0 Hz), 3.28-3.36 (m, 1H), 3.68 (t, 1H, *J* = 8.4 Hz), 3.94 (br, 1H), 6.65 (d, 1H, *J* = 8.4 Hz), 6.74 (t, 1H, *J* = 7.6 Hz), 7.05 (t, 1H, *J* = 7.6 Hz), 7.11 (d, 1H, *J* = 7.6 Hz). ¹³C NMR (100 MHz, CDCl₃): δ = 23.4, 25.2, 39.7, 99.1 (d, *J*_{C, F} = 21.7 Hz), 105.4 ((d, *J*_{C, F} = 20.0 Hz), 123.3 (d, *J*_{C, F} = 3.7 Hz), 150.6 (dd, *J*_{C, F} = 237.4, 17.2 Hz), 148.9 (dd, *J*_{C, F} = 238.3, 18.1 Hz), 170.1. HRMS (ESI) calcd. for C₁₂H₁₂F₂N₂O 239.0996 [M+H]⁺, found 239.0989. The compound having chemical formula (IX) was 95% (w/w) pure. It is noted that the acetyl group of the compound having chemical formula (IX) is included therein by virtue of the acetyl transferase having SEQ.ID NO: 63 in *Escherichia coli* strain Ec-1.

[00544] Efficacy testing was carried out as described in Example 5. MTT assay results are shown in **FIG. 18**, and calcium mobility assay results are shown in **FIG. 19A** (+5-HT_{2A} cells) and **FIG. 19B** (-5-HT_{2A} cells). In both cases, the example compound having the chemical formula (IX) is shown as “(IX)”.

Example 8 – Process for making an eighth halogenated psilocybin derivative from halogenated indole feedstock.

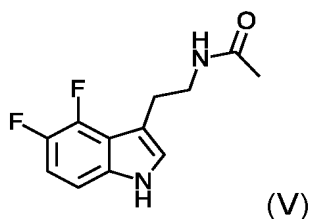
[00545] *Escherichia coli* strain Ec-1 was used to biosynthesize halogenated tryptamine derivative having chemical formula (VI) from halogenated indole feedstock. The construction of Ec-1 is described in Example 5. Scaled-up culturing and material storage of engineered *E. coli* was conducted as described in Example 5, except that 4,6-difluoroindole (Combi-Blocks, www.combi-blocks.com) was used in place of 7-fluoroindole. To assess product, high-resolution LC-HESI-LTQ-Orbitrap-XL MS analysis was conducted as described in Example 1. Singly protonated product with exact *m/z* and expected elemental formula matching 4,6-difluoro-N-acetyltryptamine having chemical formula (VI):



eluted at 5.1 minutes (EIC, see: **FIG. 20**).

Example 9 – Process for making a ninth halogenated psilocybin derivative from halogenated indole feedstock.

[00546] *Escherichia coli* strain Ec-1 was used to biosynthesize halogenated tryptamine derivative having chemical formula (V) from halogenated indole feedstock. The construction of Ec-1 is described in Example 5. Scaled-up culturing and material storage of engineered *E.coli* was conducted as described in Example 5, except that 4,5-difluoroindole (Combi-Blocks, www.combi-blocks.com) was used in place of 7-fluoroindole. *N*-(2-(4,5-difluoro-1*H*-indol-3-yl)ethyl)acetamide product having chemical formula (V):



[00547] contained in 1 L of *E.coli* culture was extracted by ethyl acetate (3×600 ml). The organic layer was dried over Na₂SO₄, followed by concentration under reduced pressure. The residue was purified by flash chromatography on silica gel using ethyl acetate – hexane (50 → 80 %) as eluent, followed by crystallization from EtOAc/Hexane to give the compound as a white solid (20 mg). Following purification, high-resolution MS (HRMS), ¹H NMR, and selective ¹³C NMR were performed to assess purity, estimate total quantity, and confirm molecular structure. ¹H NMR (400 MHz, CDCl₃): δ = 1.96 (s, 3H), 3.04 (t, *J* = 6.9 Hz, 2H), 3.60 (dt, *J* = 6.6, 6.4 Hz, 2H), 5.64 (br, s, 1H), 7.01 (m, 3H), 8.41 (br, s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 23.4, 26.3, 40.5 (d, *J*_{C, F} = 2.0 Hz), 106.6 (dd, *J*_{C, F} = 7.7, 4.2 Hz), 111.7 (d, *J*_{C, F} = 21.7 Hz), 124.0, 143.9 (dd, *J*_{C, F} = 246.4, 14.5 Hz), 143.8 (dd, *J*_{C, F} = 246.4, 14.5 Hz), 170.2. HRMS (ESI) *m/z*: calcd. for C₁₂H₁₂F₂N₂O [M+H]⁺ 239.0996, found 239.0989. The compound having chemical

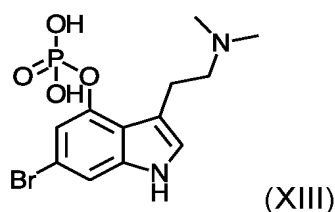
formula (V) was 95% (w/w) pure. It is noted that the acetyl group of the compound having chemical formula (II) is included therein by virtue of the acetyl transferase having SEQ.ID NO: 63 in *Escherichia coli* strain Ec-1.

5 **[00548]** Efficacy testing was carried out as described in Example 5. MTT assay results are shown in **FIG. 21**, and calcium mobility assay results are shown in **FIGS. 22A** and **22B**. In both cases, the example compound having the chemical formula (V) is shown as “(V)”.

10 **Example 10 – Process for making a tenth halogenated psilocybin derivative from halogenated indole feedstock.**

[00549] *E. coli* strain Ec-2 was constructed as follows. For plasmid cloning, Top10 or XL1-blue strains were used depending on antibiotic markers. Standard LB media was used for culturing. For gene expression and feeding experiments,
15 the parent host strain employed was BL21 (DE3). For this Example, heterologous expression of a non-native or engineered TrpB gene was not necessary, as endogenous tryptophan synthase activity proved sufficient. From plasmid pCDM4 (SEQ.ID NO: 92), the plasmid pCDM4-PsiD-FLAG was created by inserting an in-frame, C-terminally FLAG-tagged (SEQ.ID NO: 85) PsiD gene (SEQ.ID NO: 1) into
20 the *Nde*II/*Xho*I site of pCDM4. The plasmid pETM6-H10-PsiK-V5-PsiM-FLAG was created by first cloning the in-frame, C-terminally V5-tagged (SEQ.ID NO: 87) PsiK (SEQ.ID NO: 5) into the *Nde*II/*Xho*I site of pETM6-H10 (SEQ.ID NO: 97) to create pETM6-H10-PsiK-V5. This intermediate plasmid was digested with *Spe*I and *Sal*I, and in-frame, C-terminally FLAG tagged (SEQ.ID NO: 85) PsiM (SEQ.ID NO: 7)
25 was cloned into the site with *Xba*I and *Sal*I, nullifying the *Spe*I restriction site. In this setup, the T7 polymerase was able to drive the expression of the polycistronic DNA containing both PsiK and PsiM. The two target plasmids pCDM4-PsiD-FLAG and pETM6-H10-PsiK-V5-PsiM-FLAG were transformed into BL21 (DE3) cells, and antibiotics ampicillin plus streptomycin were used to select for the correct
30 clones containing both plasmids. Scaled-up culturing of engineered *E.coli* was conducted as follows: seed cultures were inoculated in AMM (Jones *et al.* 2015, Sci Rep. 5: 11301) medium overnight. The overnight culture was then divided into two flasks containing 500 mL each of AMM medium additionally containing 0.5% (w/v) serine, 1M IPTG, 50ug/L ampicillin and streptomycin, and 100 mg/L 4-

hydroxy-6-bromoindole (BLDPharm, www.bldpharm.com) for conversion by Ec-2. Cultures were grown for 24 h. Cultures were then centrifuged (10,000g x 5 minutes) to remove cellular content, and culture broth containing secreted derivative was stored at -80C until further processing. To assess product, high-
5 resolution LC-HESI-LTQ-Orbitrap-XL MS analysis was conducted as described in Example 1. Singly protonated product with exact *m/z* and expected elemental formula matching 6-bromo-psilocybin having chemical formula (XIII):



10

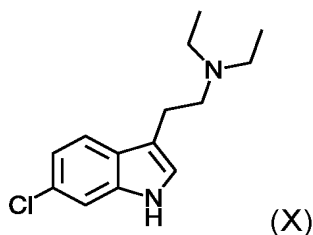
eluted at 2.8 minutes (EIC, see: FIG. 23).

Example 11 – Process for making an eleventh halogenated psilocybin derivative from halogenated indole feedstock.

15

[00550] In a flame-dried round bottom flask under argon, 6-chloroindole (**compound 1**, see: **FIG. 9A**) (210 mg, 1.39 mmol, 1.00 eq) was dissolved in diethyl ether (4.0 mL) and cooled to 0 °C. To this solution, oxalyl chloride (369 mg, 2.91 mmol, 2.10 eq) in diethyl ether (2.0 mL) was added dropwise over a period of
20 10 minutes. The reaction mixture was allowed to stir at room temperature for 4 hours. Additional ether (5.0 mL) was added to the reaction mixture which was then cooled to 0 °C and subsequently vacuum-filtered to yield a bright yellow solid (**compound 2**) (211 mg, 0.872 mmol, 63%). **Compound 2** (see: **FIG. 9A**) was washed with cold ether (10 mL) and allowed to briefly dry before being
25 resuspended in diethyl ether (3.0 mL) and cooled to 0 °C. Diethylamine (510 mg, 6.97 mmol, 8.00 eq) was diluted with diethyl ether (3.0 mL) and added dropwise to the reaction flask, immediately precipitating out a white solid. This mixture was allowed to stir for 10 minutes at 0 °C, warmed to room temperature, and stirred for an additional 1.5 hours. The visible precipitate was vacuum filtered to yield a solid
30 which was washed with cold diethyl ether (10 mL). This solid was suspended in

deionized water (50 mL), stirred for 10 minutes, vacuum-filtered, and allowed to dry overnight, yielding **compound 3** (see: **FIG. 9A**) as a white powder (124 mg, 0.445 mmol, 51%). No further purification was required. ¹H NMR (400 MHz, CDCl₃): δ (ppm) = 9.56 (s, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 7.74 (d, *J* = 3.0 Hz, 1H), 7.36 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.28 (d, *J* = 1.8 Hz, 1H), 3.54 (q, *J* = 7.1 Hz, 2H), 3.36 (q, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H). A THF solution of lithium aluminum hydride (2.20 mL, 2.22 mmol, 5.00 eq, 1.0 M) was added to a 3-neck, flame-dried, round-bottom flask under argon. Anhydrous dioxane (3.0 mL) was added to the reaction mixture. In a separate vial, **compound 3** (124 mg, 0.445 mmol) was dissolved in a THF (2.0 mL)/dioxane (1.0 mL) solution and added dropwise to the reaction vessel. This mixture was then allowed to reflux at 95 °C for 1.5 hours. The reaction mixture was cooled to 0 °C and quenched through dropwise addition of a water (1.0 mL)/THF (2.0 mL) solution, yielding a flocculent precipitate. This precipitate was removed through vacuum-filtration and the filter-cake was washed with diethyl ether (20 mL). The filtrate was collected, dried with MgSO₄, and solvent removed to yield a pale-yellow oil. Purification through column chromatography on silica gel (2% MeOH/DCM + 1% NEt₃) yielded compound **410B01** (see: **FIG. 9A**), corresponding to compound with formula (X):



as a clear, colourless oil (34 mg, 0.136 mmol, 30%). ¹H NMR (400 MHz, CDCl₃): δ (ppm) = 8.37 (s, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.30 (d, *J* = 1.8 Hz, 1H), 7.07 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.98 (dd, *J* = 2.5, 1.1 Hz, 1H), 2.90 (high order m, 2H), 2.79 (high order m, 2H), 2.74 – 2.62 (q, *J* = 7.1 Hz, 4H), 1.15 – 1.04 (t, *J* = 7.1 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) = 136.6, 127.8, 126.2, 122.2, 119.9, 119.7, 114.8, 111.0, 70.5, 53.5, 46.9, 22.8, 11.7. The compound having chemical formula (IX) was 95% (w/w) pure.

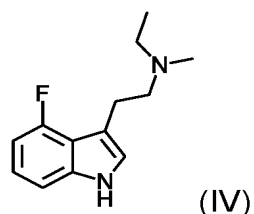
[00551] Efficacy testing was carried out as described in Example 5. MTT assay results are shown in **FIG. 24**, and calcium mobility assay results are shown

in **FIGS. 25A** and **25B**. In both cases, the example compound having chemical formula (X) is shown as “(X)”.

Example 12 – Process for making a twelfth halogenated psilocybin derivative from halogenated indole feedstock.

[00552] A similar process as illustrated in **FIG. 9A** (Example 11) was followed. In a flame-dried round bottom flask under argon, 4-fluoroindole (**compound 1**) (200 mg, 1.48 mmol, 1.00 eq) was dissolved in diethyl ether (4.0 mL) and cooled to 0 °C. To this solution, oxalyl chloride (394 mg, 3.11 mmol, 2.10 eq) in diethyl ether (2.0 mL) was added dropwise over a period of 10 minutes. The reaction mixture was allowed to stir at room temperature for 4 hours. Additional ether (5.0 mL) was added to the reaction mixture which was then cooled to 0 °C and subsequently vacuum-filtered to yield a bright yellow solid (**compound 2**) (264 mg, 1.17 mmol, 79%). **Compound 2** was washed with cold ether (10 mL) and allowed to briefly dry before being resuspended in diethyl ether (3.0 mL) and cooled to 0 °C. N-Methylethylamine (574 mg, 9.72 mmol, 8.00 eq) was diluted with diethyl ether (3.0 mL) and added dropwise to the reaction flask. This mixture was allowed to stir for 10 minutes at 0 °C, warmed to room temperature, and stirred for an additional 1.5 hours, yielding a suspension of light-pink gooey solid. The diethyl ether was decanted, and the solid dissolved in dichloromethane (10 mL) and washed with water (3 x 10 mL). The organic phase was dried with MgSO₄ and solvent removed to yield a pale-pink glassy solid (128 mg, 0.516 mmol, 43%). ¹H NMR (400 MHz, CDCl₃): δ (ppm) = 10.72 (s, 1H), 7.72 (d, *J* = 3.8 Hz, 1H), 7.10 – 7.00 (m, 2H), 6.84 (ddd, *J* = 11.1, 7.2, 1.6 Hz, 1H), 3.55 (q, *J* = 7.2 Hz, 1H), 3.35 (q, *J* = 7.1 Hz, 1H), 3.05 (s, 2H), 2.98 (s, 1H), 1.23 (t, *J* = 7.2 Hz, 1H), 1.15 (t, *J* = 7.1 Hz, 2H). A THF solution of lithium aluminum hydride (2.58 mL, 2.58 mmol, 5.00 eq, 1.0 M) was added to a 3-neck, flame-dried, round-bottom flask under argon. Anhydrous dioxane (3.0 mL) was added to the reaction mixture. In a separate vial, **compound 3** (128 mg, 0.516 mmol) was dissolved in an anhydrous THF (2.0 mL)/dioxane (1.0 mL) solution and added dropwise to the reaction vessel. This mixture was then allowed to reflux at 95 °C for 2.5 hours. The reaction mixture was cooled to 0 °C and quenched through dropwise addition of a water (1 mL)/THF (2 mL) solution, yielding a flocculent precipitate. This precipitate was removed

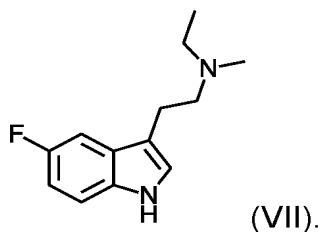
through vacuum-filtration and the filter-cake was washed with diethyl ether (20 mL). The filtrate was collected, dried with MgSO₄, and solvent removed to yield a pale-orange oil. Purification through column chromatography on silica gel (1% MeOH/CH₂Cl₂ + 1% NEt₃) yielded compound **456B01**, corresponding to
5 compound having chemical formula (IV):



as clear, colourless oily crystal (86 mg, 0.390 mmol, 76%). ¹H NMR (400 MHz, CDCl₃): δ (ppm) = 8.68 (s, 1H), 7.12 – 6.99 (m, 2H), 6.91 (d, *J* = 2.3 Hz, 1H), 6.73 (ddd, *J* = 11.2, 6.9, 1.6 Hz, 1H), 3.04 (high order m, 2H), 2.75 (high order m, 2H),
10 2.57 (q, *J* = 7.2 Hz, 2H), 2.38 (s, 3H), 1.12 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) = 157.2 (d, *J*_{C-F} = 245.6 Hz), 139.2 (d, *J*_{C-F} = 11.8 Hz), 122.2 (d, *J*_{C-F} = 8.2 Hz), 121.9, 107.2 (d, *J*_{C-F} = 3.6 Hz), 104.2 (d, *J*_{C-F} = 19.7 Hz), 58.5, 51.2, 41.5, 24.1, 12.1. The compound having chemical formula (IV) was 95% (w/w) pure.
[00553] Efficacy testing was carried out as described in Example 5. MTT
15 assay results are shown in **FIG. 26**, and calcium mobility assay results are shown in **FIG. 27A** and **FIG. 27B**. In both cases, the example compound having the chemical formula (IV) is shown as “(IV)”.

20 **Example 13 – Process for making a thirteenth halogenated psilocybin derivative from halogenated indole feedstock.**

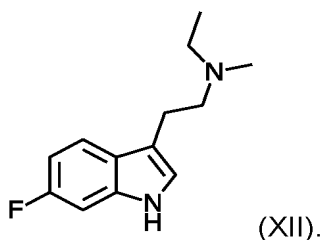
[00554] A thirteenth halogenated psilocybin derivative compound was synthesized according to the method of Example 11, except using 5-fluoroindole and N-methylethylamine as starting materials. Analysis indicated the isolation of a
25 compound having chemical formula (VII):



¹H NMR (400 MHz, CDCl₃): δ (ppm) = 8.09 (s, 1H), 7.29 – 7.20 (m, 2H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.96 – 6.87 (m, 1H), 2.93 – 2.86 (m, 2H), 2.72 – 2.64 (m, 2H), 2.53 (q, *J* = 7.2 Hz, 2H), 2.35 (s, 3H), 1.11 (t, *J* = 7.2 Hz, 3H).

Example 14 – Process for making a fourteenth halogenated psilocybin derivative from halogenated indole feedstock.

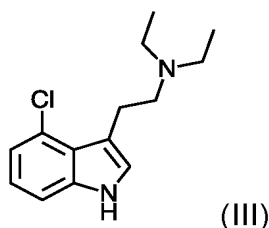
10 **[00555]** A fourteenth halogenated psilocybin derivative was synthesized according to the method of Example 11, except using 6-fluoroindole and N-methylethylamine as starting materials. Analysis indicated the isolation of a compound having chemical formula (XII):



15 ¹H NMR (400 MHz, CDCl₃): δ (ppm) = 8.05 (s, 1H), 7.50 (ddt, *J* = 8.7, 5.3, 0.6 Hz, 1H), 7.02 (ddd, *J* = 9.7, 2.3, 0.5 Hz, 1H), 7.00 – 6.97 (m, 1H), 6.88 (ddd, *J* = 9.6, 8.6, 2.3 Hz, 1H), 2.96 – 2.89 (m, 2H), 2.74 – 2.66 (m, 2H), 2.53 (q, *J* = 7.2 Hz, 2H), 2.35 (s, 3H), 1.11 (t, *J* = 7.2 Hz, 3H).

20 **Example 15 – Process for making a fifteenth halogenated psilocybin derivative from halogenated indole feedstock.**

25 **[00556]** A fifteenth halogenated psilocybin derivative was synthesized according to the method of Example 11, except using 4-chloroindole as starting material. Analysis indicated the isolation of a compound having chemical formula (III):

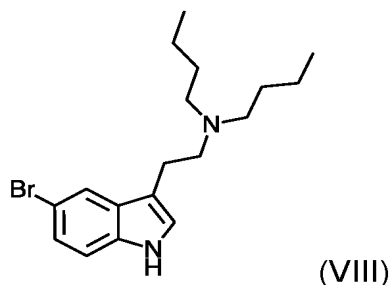


¹H NMR (400 MHz, CDCl₃): δ (ppm) = 8.28 (s, 1H), 7.26 – 7.19 (m, 1H), 7.08 – 7.01 (m, 3H), 3.18 – 3.10 (m, 2H), 2.86 – 2.77 (m, 2H), 2.67 (q, *J* = 7.1 Hz, 4H),
 5 1.09 (t, *J* = 7.1 Hz, 6H).

Example 16 – Process for making a sixteenth halogenated psilocybin derivative from halogenated indole feedstock.

10 **[00557]** The initial reaction to generate **compound 1.1** (see: **FIG. 9B**) followed a previously reported procedure with modifications (Campos *et al.* 2004, Org. Lett 6: 79-82). To a solution of 4-bromophenylhydrazine hydrochloride (300 mg, 1.34 mmol) in a mixture of *N,N*-dimethylacetamide (1.9 mL) and 4% H₂SO₄ (1.9 mL), was added 2,3-dihydrofuran (0.10 mL, 1.33 mmol). The reaction mixture
 15 was heated at 100°C for 16 hours. Once the mixture was cooled to room temperature, ethyl acetate (15 mL) was added, and the organic solution was washed with water (2 × 6 mL), and dried over anhydrous MgSO₄. The organic solvent was removed *in vacuo*. The product (**compound 1.1**, (see: **FIG. 9B**)) was purified by flash chromatography on silica gel (eluted with a gradient of hexanes-EtOAc, 100:0 to 0:100) to afford an orange oil. Yield: 37%. The characterization of
 20 this first product agreed with previously reported procedure (Go *et al.* 2010, J. Med. Chem. 53: 6838-6850). ¹H NMR (400 MHz, CDCl₃) δ 8.13 (bs, 1H), 7.74 (d, *J* = 1.7 Hz, 1H), 7.28 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 1H), 7.08 (d, *J* = 2.3 Hz, 1H), 3.89 (t, *J* = 6.3 Hz, 2H), 2.98 (t, *J* = 6.4 Hz, 2H). The second reaction
 25 (see: **FIG. 9B**) followed a previously reported procedure (Lombardo *et al.* 2013, Angew. Chem. Int. Ed. 52: 12910-12914). Imidazole (73 mg, 1.1 mmol), triphenyl phosphine (140 mg, 0.54 mmol), and iodine (140 mg, 0.54 mmol) were added to a solution of **compound 1.1** (see: **FIG. 9B**) (119 mg, 0.49 mmol) in anhydrous dichloromethane (5.0 mL) cooled in an ice-water bath. The reaction was stirred at
 30 room temperature for 6 hours. The mixture was quenched with saturated sodium

thiosulfate (10 mL), extracted in dichloromethane (3 × 10 mL), and the combined organic solution was dried over anhydrous MgSO₄, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluted with a gradient of hexanes-EtOAc, 100:0 to 50:50) to afford an orange oil. Yield of **compound 1.2** (see: **FIG. 9B**): 74%. ¹H NMR (400 MHz, CDCl₃) δ 8.07 (s, 1H), 7.71–7.69 (m, 1H), 7.29 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.25 (d, *J* = 8.6 Hz, 1H), 7.10 (d, *J* = 2.4 Hz, 1H), 3.44–3.39 (m, 2H), 3.30 (t, *J* = 7.0 Hz, 2H). To a solution of **compound 1.2** (129 mg, 0.37 mmol) in anhydrous DMF (1.0 mL) was added di-*n*-butylamine (0.25 mL, 1.48 mmol). The reaction mixture was heated at 60°C for 16 hours. The reaction was quenched with saturated sodium bicarbonate solution, extracted in ethyl acetate (3 × 20 mL), and the combined organic solution was washed with water (2 × 40 mL), brine (2 × 40 mL), dried over anhydrous MgSO₄ and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography on silica gel (eluted with a gradient of hexanes-EtOAc, 100:0 to 0:100) to afford an orange oil. Yield of **compound 1**, with structure as indicated by compound (VIII):



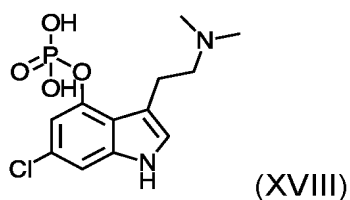
50%. ¹H NMR (400 MHz, CDCl₃) δ 8.16 (s, 1H), 7.72 (s, 1H), 7.28 – 7.22 (m, 1H), 7.22–7.18 (m, 1H), 7.03–6.99 (m, 1H), 2.89–2.82 (m, 2H), 2.81–2.73 (m, 2H), 2.54 (t, *J* = 7.6 Hz, 4H), 1.52–1.43 (m, 5H), 1.33 (h, *J* = 7.0 Hz, 4H), 0.93 (t, *J* = 7.4 Hz, 6H) (Figure X, NMR). ¹³C NMR (100 MHz, CDCl₃) δ 134.95, 129.58, 124.81, 122.83, 121.65, 114.83, 112.62, 112.57, 54.75, 54.01, 29.42, 22.87, 20.95, 14.27. HRMS (ESI, positive) *m/z* for C₁₈H₂₈BrN₂[M+H]⁺ calcd. 351.1430, found 351.1427. The compound having chemical formula (VIII) was 95% (w/w) pure.

[00558] Efficacy testing was carried out as described in Example 5. MTT assay results are shown in **FIG. 28**, and calcium mobility assay results are shown

in **FIGS. 29A** and **29B**. In both cases, the example compound having the chemical formula (VIII) is shown as “(VIII)”.

Example 17 – Process for making a seventeenth halogenated psilocybin derivative from halogenated indole feedstock.

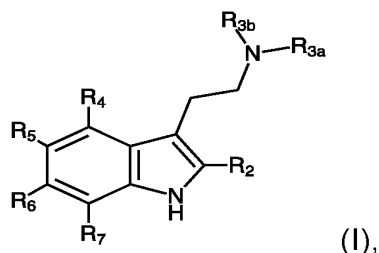
[00559] *E. coli* strain Ec-3 was constructed as follows. For plasmid cloning, Top10 or XL1-blue strains were used depending on antibiotic markers. Standard LB media was used for culturing. For gene expression and feeding experiments, the parent host strain employed was BL21 (DE3). For this Example, heterologous expression of a non-native or engineered TrpB gene was not necessary, as endogenous tryptophan synthase activity proved sufficient. Plasmids pCDM4-PsiD-FLAG and pETM6-H10-PsiK-V5-PsiM-FLAG are described in Example 10. A third plasmid, pRSM3-Thal-HIS, was created by cloning an in-frame, C-terminally HIS-tagged (SEQ.ID NO: 89) Thal gene (SEQ.ID NO: 19), encoding a halogenase having SEQ.ID NO: 20, into the *NdeI/XhoI* site of pRSM3 (SEQ.ID NO: 98). The three target plasmids pCDM4-PsiD-FLAG, pETM6-H10-PsiK-V5-PsiM-FLAG, and pRSM3-Thal-HIS were transformed into BL21 (DE3) cells and antibiotics ampicillin plus streptomycin plus kanamycin were used to select for the correct clones containing all three plasmids. Scaled-up culturing of engineered *E.coli* was conducted as described in Example 10. To assess product, high-resolution LC-HESI-LTQ-Orbitrap-XL MS analysis was conducted as described in Example 1. Singly protonated product with exact *m/z* and expected elemental formula matching 6-chloro-psilocybin having chemical formula (XVIII):



eluted at 2.3 minutes (EIC, see: **FIG. 30**).

CLAIMS

1. a chemical compound or salt thereof having the formula (I):

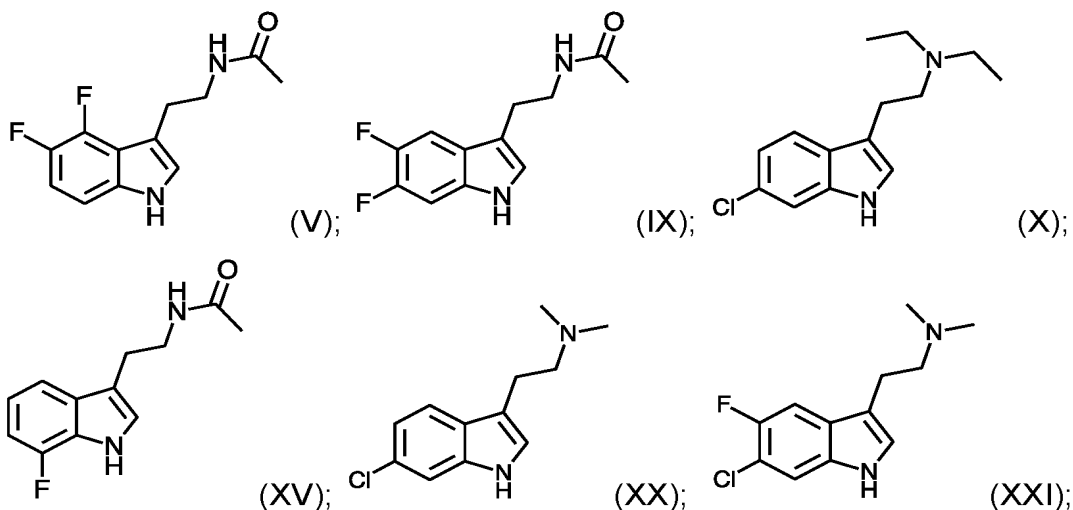


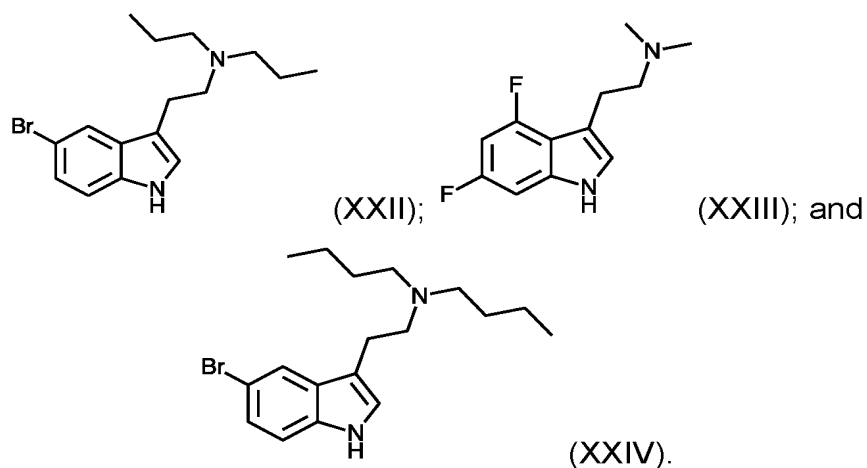
wherein, at least one of R₂, R₄, R₅, R₆ or R₇ is a halogen atom, wherein each non-halogenated R₂, R₅, R₆, or R₇ is a hydrogen atom or an alkyl group or O-alkyl group, wherein R₄ when it is not halogenated is a phosphate group, a hydrogen atom or an alkyl group or O-alkyl group, and wherein R_{3a} and R_{3b} are a hydrogen atom, an alkyl group, an aryl group, or an acyl group.

2. A chemical compound according to claim 1, wherein one or two of R₄, R₅, R₆, or R₇ are a halogen atom, wherein the halogen atom is selected from fluorine (F), chlorine (Cl), and bromine (Br).
3. A chemical compound according to claim 1, wherein one or two of R₄, R₅, or R₆ are halogenated, wherein the halogen atom is selected from fluorine (F), chlorine (Cl), and bromine (Br).
4. A chemical compound according to claim 1, wherein two of R₄, R₅, and R₆ are halogenated, wherein the halogen atom is selected from fluorine (F), chlorine (Cl), and bromine (Br).
5. A chemical compound according to claim 4, wherein R₄ is halogenated, and wherein one of R₅, and R₆ is halogenated.
6. A chemical compound according to claim 4, wherein R₅ is halogenated, and wherein one of R₄, and R₆ is halogenated.
7. A chemical compound according to claim 5, wherein the halogen atoms are fluorine atoms.

- 8.** A chemical compound according to claim **6**, wherein the halogen atoms are fluorine atoms.
- 9.** A chemical compound according to claim **2**, wherein R_7 is a fluorine atom, and wherein one atom is halogenated.
- 10.** A chemical compound according to claim **7**, wherein each non-halogenated R_2 , R_4 , R_5 , R_6 , or R_7 , is a hydrogen atom.
- 11.** A chemical compound according to claim **8**, wherein each non-halogenated R_2 , R_4 , R_5 , R_6 , or R_7 , is a hydrogen atom.
- 12.** A chemical compound according to claim **9**, wherein each non-halogenated R_2 , R_4 , R_5 , R_6 , or R_7 , is a hydrogen atom.
- 13.** A chemical compound according to claim **3**, wherein at least one of the halogen atoms is a chlorine atom.
- 14.** A chemical compound according to claim **3**, wherein R_6 is a chlorine atom.
- 15.** A chemical compound according to claim **14**, wherein R_5 is a fluorine atom.
- 16.** A chemical compound according to claim **14**, wherein each non-halogenated R_2 , R_4 , R_5 , R_6 , or R_7 , is a hydrogen atom.
- 17.** A chemical compound according to claim **15**, wherein each non-halogenated R_2 , R_4 , R_5 , R_6 , or R_7 , is a hydrogen atom.
- 18.** A chemical compound according to claim **3**, wherein R_5 is a bromine atom, and one atom is halogenated.
- 19.** A chemical compound according to claim **18**, wherein each non-halogenated R_2 , R_4 , R_5 , R_6 , or R_7 , is a hydrogen atom.

- 20.** A chemical compound according to claim **2**, wherein R_{3a} and R_{3b} are each independently selected from a hydrogen atom, a (C₁-C₆)-alkyl group, and a (C₁-C₆)-acyl group.
- 21.** A chemical compound according to claim **10**, wherein R_{3a} and R_{3b} are, respectively, a hydrogen atom and a (C₁-C₆)-acyl group.
- 22.** A chemical compound according to claim **11**, wherein R_{3a} and R_{3b} are, respectively, a hydrogen atom and a (C₁-C₆)-acyl group.
- 23.** A chemical compound according to claim **12**, wherein R_{3a} and R_{3b} are, respectively, a hydrogen atom and a (C₁-C₆)-acyl group.
- 24.** A chemical compound according to claim **16**, wherein R_{3a} and R_{3b} are each a (C₁-C₆)-alkyl group.
- 25.** A chemical compound according to claim **17**, wherein R_{3a} and R_{3b} are each a (C₁-C₆)-alkyl group.
- 26.** A chemical compound according to claim **19**, wherein R_{3a} and R_{3b} are each a (C₁-C₆)-alkyl group.
- 27.** A chemical compound according to claim **1**, wherein the chemical compound is selected from the group consisting of compounds having formulas (V); (IX); (X); (XV); (XX); (XXI); (XXII); (XXIII); and (XXIV):





- 28.** A pharmaceutical drug formulation comprising an effective amount of the chemical compound according to claim **1**, together with a pharmaceutically acceptable excipient, diluent, or carrier.
- 29.** A pharmaceutical drug formulation comprising an effective amount of the chemical compound according to claim **27**, together with a pharmaceutically acceptable excipient, diluent, or carrier.
- 30.** A method for treating a psychiatric disorder, the method comprising administering to a subject in need thereof a pharmaceutical formulation comprising a chemical compound according to claim **1**, wherein the pharmaceutical formulation is administered in an effective amount to treat the psychiatric disorder in the subject.

ABSTRACT

Disclosed are novel halogenated psilocybin derivative compounds and pharmaceutical and recreational drug formulations containing the same. The compounds may be produced using a biosynthetic system which comprises cells comprising a psilocybin biosynthetic enzyme complement.

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Application Number: 18655793

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Validated By CRFValidator v 2.3.0

Application No: 18655793 Version No: 1.1

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Application Number: 18655793

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