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PTO/AIA/01 (06-12)
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	GLP-1R Agonist and Therapeutic Method Thereof

As the below named inventor, I hereby declare that:

This declaration is directed to:

- [x] The attached application, or
- [ ] United States application or PCT international application number _____ filed on _____.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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

WARNING:

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LEGAL NAME OF INVENTOR

Inventor: Bailing Yang Date (Optional): 2024.09.06

Signature: 签署人: Yang Bailing FB1D7D35DE43430

Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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Additional Uses

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PTO/AIA/80 (07-17)
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POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

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

I hereby appoint:

[X] Practitioners associated with Customer Number: 83682

OR

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

Name	Registration Number

Name	Registration Number

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

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

[X] The address associated with Customer Number: 83682

OR

[ ]

Firm or individual name		
Address		
City	State	Zip
Country		
Telephone	Email	

Assignee name and address: Ascletis Pharma (China) Co., Limited
Room 1903, 19/F, Lee Garden One, 33 Hysan Avenue, Causeway Bay
Hong Kong
China

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

SIGNATURE of Assignee of Record

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

Signature DocuSigned by: Jinzi Jason Wu 060F881ABSE84SF	Date 2024.09.06
Name Jinzi Jason Wu	Telephone
Title CEO	

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Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (11-23)

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

First Named Inventor:	Bin Liang	Nonprovisional Application Number (if known):	
Title of Invention:	GLP-1R Agonist and Therapeutic Method Thereof		

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 USPTO patent electronic filing system.

---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 USPTO patent electronic filing system.
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 /Daniel J. Nevrivy/	Date September 13, 2024
Name (Print/Typed) Daniel J. Nevrivy	Practitioner Registration Number 59,118

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 1 forms are submitted.

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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;

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As the below named inventor, I hereby declare that:

This declaration is directed to:

- [x] The attached application, or
- [ ] United States application or PCT international application number _____ filed on _____.

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LEGAL NAME OF INVENTOR

Inventor: Bin Liang Date (Optional): 2024.09.06

Signature: 簽署人： Bin Liang 29C0788CE03F42E...

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LEGAL NAME OF INVENTOR

Inventor: Jinzi Jason Wu Date (Optional): 2024.09.06

Signature: DocuSigned by: [signature] 06F881AB5F84BF...

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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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Liang *et al.*	Confirmation No.:	To Be Assigned
Application No.:	To Be Assigned	Art Unit:	To Be Assigned
Filing Date:	To Be Assigned	Examiner:	To Be Assigned
Title:	**GLP-1R Agonist and Therapeutic Method Thereof**	Attorney Docket No.:	HRT-030US1

Authorization to Treat a Reply as Incorporating an Extension of Time Under 37 C.F.R. § 1.136(a)(3)

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

Madam:

The U.S. Patent and Trademark Office is hereby authorized to treat a concurrent or future reply that requires a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for an extension of time for the appropriate length of time. The U.S. Patent and Trademark Office is hereby authorized to charge all required extensions of time fees to our Deposit Account No. 60-2104, if such fees are not otherwise provided for in such reply.

Respectfully submitted,

NEVRIVY PATENT LAW GROUP P.L.L.C.

/DANIEL J. NEVRIVY/

_____

Daniel J. Nevrivy
Registration No. 59,118

Dated: September 13, 2024
Customer No. 83682
202.713.0843

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HRT-030US1
	Application Number	
Title of Invention	GLP-1R Agonist and Therapeutic Method Thereof	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Bin		Liang	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Hong Kong	Country of Residence	CN

Mailing Address of Inventor:

Address 1	Room 1903, 19/F, Lee Garden One, 33 Hysan Avenue		
Address 2	Causeway Bay		
City	Hong Kong	**State/Province**	
Postal Code	999077	**Country**	CN

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Jinzi	Jason	Wu	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Hong Kong	Country of Residence	CN

Mailing Address of Inventor:

Address 1	Room 1903, 19/F, Lee Garden One, 33 Hysan Avenue		
Address 2	Causeway Bay		
City	Hong Kong	**State/Province**	
Postal Code	999077	**Country**	CN

Inventor 3 Remove

Legal Name

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HRT-030US1
	Application Number	
Title of Invention	GLP-1R Agonist and Therapeutic Method Thereof	

Prefix	Given Name	Middle Name	Family Name	Suffix
	Bailing		Yang	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Hong Kong	Country of Residence [i]	CN

Mailing Address of Inventor:

Address 1	Room 1903, 19/F, Lee Garden One, 33 Hysan Avenue		
Address 2	Causeway Bay		
City	Hong Kong	**State/Province**	
Postal Code	999077	**Country** [i]	CN

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	83682		
Email Address	dnevrivy@nevrivylaw.com	Add Email	Remove Email

Application Information:

Title of the Invention	GLP-1R Agonist and Therapeutic Method Thereof		
Attorney Docket Number	HRT-030US1	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		**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).

[i]

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HRT-030US1
	Application Number	
Title of Invention	GLP-1R Agonist and Therapeutic Method Thereof	

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	83682		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Claims benefit of provisional	63603854	2023-11-29
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Claims benefit of provisional	63673461	2024-07-19

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HRT-030US1
	Application Number	
Title of Invention	GLP-1R Agonist and Therapeutic Method Thereof	

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove			
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
202311582240.2	CN	2023-11-24	921B
Remove			
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
202311686034.6	CN	2023-12-08	AF8F
Remove			
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
202410142451.2	CN	2024-01-31	151D
Remove			
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
202410202078.5	CN	2024-02-22	2F87
Remove			
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
202410398964.X	CN	2024-04-02	6C5B
Remove			
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
202410584679.7	CN	2024-05-11	B096
Remove			
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
202410906296.7	CN	2024-07-05	2A04
Remove			
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
202411237013.0	CN	2024-09-04	A954

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

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

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HRT-030US1
	Application Number	
Title of Invention	GLP-1R Agonist and Therapeutic Method Thereof	

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HRT-030US1
	Application Number	
Title of Invention	GLP-1R Agonist and Therapeutic Method Thereof	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HRT-030US1
	Application Number	
Title of Invention	GLP-1R Agonist and Therapeutic Method Thereof	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Ascletis Pharma (China) Co., Limited		
Mailing Address Information For Applicant:			
Address 1	Room 1903, 19/F, Lee Garden One, 33 Hysan Avenue		
Address 2	Causeway Bay		
City	Hong Kong	**State/Province**	
Country	CN	Postal Code	999077
Phone Number		Fax Number	
Email Address			

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

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HRT-030US1
	Application Number	
Title of Invention	GLP-1R Agonist and Therapeutic Method Thereof	

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	/Daniel Nevrivy/			Date (YYYY-MM-DD)	2024-09-13
First Name	Daniel	Last Name	Nevrivy	Registration Number	59118

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

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	HRT-030US1
	Application Number	
Title of Invention	GLP-1R Agonist and Therapeutic Method Thereof	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

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

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

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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STATEMENT UNDER 37 CFR 3.73(c)

First Named Inventor/Patent Owner: Bin Liang

Application No./Patent No.: _____ Filed/Issue Date: _____

Titled: GLP-1R Agonist and Therapeutic Method Thereof

Ascletis Pharma (China) Co., Limited, a Corporation

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

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

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

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

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

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

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

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

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

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

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

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

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

   1. From: _____ To: _____

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

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

   2. From: _____ To: _____

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

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

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0031. Public burden for this form is estimated to average 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. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

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

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

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

/Daniel J. Nevrivy/	September 13, 2024
Signature	Date
Daniel J. Nevrivy	59,118
Printed or Typed Name	Title or Registration Number

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9) the Office of Personnel Management (OPM) for personnel research purposes; and

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ASSIGNMENT

In consideration of the sum of One Dollar ($1.00) or equivalent and other good and valuable consideration paid to the undersigned inventors: Bin Liang, Jinzi Jason Wu and Bailing Yang, hereby sell and assign to Ascletis Pharma (China) Co., Limited, whose mailing address is Room 1903, 19/F, Lee Garden One, 33 Hysan Avenue, Causeway Bay, Hong Kong, China (hereafter referred to as the Assignee), his/her entire right, title and interest, including the right to sue for past infringement and to collect for all past, present and future damages, for the United States of America (as defined in 35 U.S.C. § 100), and throughout the world,

(a) in the invention(s) known as GLP-1R Agonist and Therapeutic Method Thereof for which a U.S. Non-provisional Patent Application was filed _____ (also known as U.S. Appl. No. _____), and which claims the benefit or priority to U.S. Provisional Applications and Chinese National Applications in the table shown below, and in any and all Letters Patent(s) granted from such applications,

Application No.	Filing Date
CN Appl. No.: 202311582240.2	November 24, 2023
CN Appl. No.: 202311686034.6	December 8, 2023
CN Appl. No.: 202410142451.2	January 31, 2024
CN Appl. No.: 202410202078.5	February 22, 2024
CN Appl. No.: 202410398964.X	April 2, 2024
CN Appl. No.: 202410584679.7	May 11, 2024
CN Appl. No.: 202410906296.7	July 5, 2024
CN Appl. No.: 202411237013.0	September 4, 2024
U.S. Appl. No.: 63/603,854	November 29, 2023
U.S. Appl. No.: 63/673,461	July 19, 2024

(b) in any and all applications that claim the benefit or priority of the patent application listed above in part (a), including non-provisional applications, international or foreign applications, continuing (continuation, divisional, or continuation-in-part) applications, reissues, extensions, renewals and reexaminations of the patent applications or Letters Patents therefor, to the full extent of the term or terms for which Letters Patents issue, and

(c) in any and all inventions described in the patent application listed above in part (a), and in any and all forms of intellectual and industrial property protection derivable from such patent applications, and that are derivable from any and all continuing applications, reissues, extensions, renewals and reexaminations of such patent applications, including, without limitation, patents, applications, utility models, inventor's certificates, and designs together with the right to file applications therefor; and including the right to claim the same priority rights from any previously filed applications under the International Agreement for the Protection of Industrial Property, or any other international agreement, or the domestic laws of the country in which any such application is filed, as may be applicable;

all such rights, title and interest to be held and enjoyed by the above-named Assignee, its successors, legal representatives and assigns to the same extent as all such rights, title and interest would have been held and enjoyed by the Assignors had this assignment and sale not been made.

The undersigned inventors agree to execute all papers necessary in connection with the application(s) and any non-provisional, continuing (continuation, divisional, or continuation-in-part), reissue, reexamination or corresponding application(s) thereof and also to execute separate assignments in connection with such application(s) as the Assignee may deem necessary or expedient.

The undersigned inventors agree to execute all papers necessary in connection with any post-grant proceeding or patent enforcement action (judicial or otherwise) related to the application(s) or any non-provisional, continuing (continuation, divisional, or continuation-in-part), reissue or reexamination application(s) thereof and to cooperate with the Assignee in every way possible in obtaining evidence and going forward with such post-grant proceeding or patent enforcement action.

The undersigned inventors hereby represent that he/she has full right to convey the entire interest herein assigned, and that he/she has not executed, and will not execute, any agreement in conflict therewith.

The undersigned inventors hereby grant the patent practitioner Daniel J. Nevrivy, Registration No. 59,118, the power to insert in this assignment any further identification that may be necessary or desirable in order to comply with the rules of the United States Patent and Trademark Office for recordation of this document.

IN WITNESS WHEREOF, executed by the undersigned inventors on the date opposite his/her name.

Date: 2024. 09. 06 Signature of Inventor: 签署人：Bin Liang 29C0780CE66F42E...

Bin Liang

Date: 2024. 09. 06 Signature of Inventor: DocuSigned by: 06BF881AB5F64BF...

Jinzi Jason Wu

Date: 2024. 09. 06 Signature of Inventor: 签署人：Yang Bailing FB1D7DB5DE43430...

Bailing Yang

Agreed and Accepted:

Date: 2024. 09. 06 Signature of Assignee: DocuSigned by: 06BF881AB5F64BF...

Name: Jinzi Jason Wu
Title: CEO
Ascletis Pharma (China) Co., Limited

PTO/AIA/15 (10-17)
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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	HRT-030US1
First Named Inventor	Bin Liang
Title	GLP-1R Agonist and Therapeutic Method Thereof
Priority Mail Express® Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. [✓] **Fee Transmittal Form** (PTO/SB/17 or equivalent)
2. [✓] **Applicant asserts small entity status.** See 37 CFR 1.27
3. [ ] **Applicant certifies micro entity status.** See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. [✓] **Specification** [*Total Pages* 88] 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* ____]
6. **Inventor's Oath or Declaration** [*Total Pages* 6] *(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
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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:** Authorization to Treat a Reply as Incorporating an Extension of Time
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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: 83682 **OR** [ ] Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	/Daniel J. Nevrivy/	Date	September 13, 2024
Name (Print/Type)	Daniel J. Nevrivy	Registration No. (Attorney/Agent)	59,118

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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.

GLP-1R Agonist and Therapeutic Method Thereof

Cross-reference to related applications

The present disclosure claims the benefits of the Chinese patent application No. 202311582240.2 entitled "GLP-1R Agonist and Therapeutic Method Thereof" filed November 24, 2023 with the China National Intellectual Property Administration, the U.S. provisional application No. 63/603,854 entitled "GLP-1R Agonist and Therapeutic Method Thereof" filed November 29, 2023 with the U.S. Patent and Trademark Office, the Chinese patent application No. 202311686034.6 entitled "GLP-1R Agonist and Therapeutic Method Thereof" filed December 8, 2023, No. 202410142451.2 entitled "GLP-1R Agonist and Therapeutic Method Thereof" filed January 31, 2024, No. 202410202078.5 entitled "GLP-1R Agonist and Therapeutic Method Thereof" filed February 22, 2024, No. 202410398964.X entitled "GLP-1R Agonist and Therapeutic Method Thereof" filed April 2, 2024, No. 202410584679.7 entitled "GLP-1R Agonist and Therapeutic Method Thereof" filed May 11, 2024, No. 202410906296.7 entitled "GLP-1R Agonist and Therapeutic Method Thereof" filed July 5,2024 with the China National Intellectual Property Administration, and the U.S. provisional application No. 63/673,461 entitled "GLP-1R Agonist and Therapeutic Method Thereof" filed July 19, 2024 with the U.S. Patent and Trademark Office, the Chinese patent application No. 202411237013.0 entitled "GLP-1R Agonist and Therapeutic Method Thereof" filed September 4, 2024 with the China National Intellectual Property Administration, which are incorporated herein by their entireties.

FIELD

The present disclosure generally relates to compounds that bind to and act as agonists or modulators of the glucagon-like peptide-1 receptor (GLP-1R), as well as the use of such compounds for the treatment and/or prevention of GLP-1R-mediated diseases and conditions.

BACKGROUND

Glucagon-like peptide-1 (GLP-1) is a peptide hormone that is secreted from the enteroendocrine cells in the gut in response to a meal. GLP-1 is believed to play a role in the regulation of post-prandial glycemia via directly augmenting meal-induced insulin secretion from the pancreatic beta-cells, as well as in promoting satiety by delaying the transit of food through the gut. GLP-1 mediates intracellular signaling via the GLP-1 receptor (GLP-1R) which belongs to a family of G-protein coupled receptors that are present on the cell

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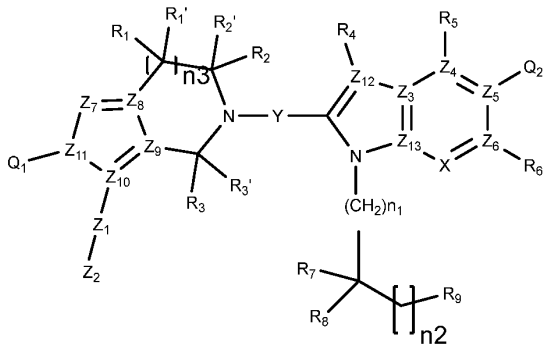
membrane and can result in the accumulation of the secondary messenger cyclic adenosine monophosphate (cAMP) upon activation. Non-alcoholic steatohepatitis (NASH) can be associated with features of metabolic syndrome, including obesity, type 2 diabetes, insulin resistance and cardiovascular disease.

GLP-1R agonists are currently being investigated in connection with diabetes, obesity, and NASH. GLP-1R agonists include peptides, such as exenatide, liraglutide, and dulaglutide, which have been approved for the management of type 2 diabetes. Such peptides are predominantly administered by subcutaneous injection. Oral GLP-1 agonists are also under investigation for treatment of type 2 diabetes. Some GLP-1R agonists, such as liraglutide, dulaglutide, and exenatide, are resistant to rapid degradation by dipeptidyl peptidase 4, resulting in longer half-lives than endogenous GLP-1.

There remains a need for compounds, such as agonists of GLP-1R, with desirable therapeutic properties, metabolic properties, and/or easy administration in the treatment of GLP-1R-mediated diseases and conditions.

SUMMARY

One aspect of the present disclosure provides a compound of Formula (I), a stereoisomer, a pharmaceutically acceptable salt, or a deuterated compound thereof:



Formula (I)

wherein:

X is selected from the group consisting of N and -CR^a; wherein R^a is selected from the group consisting of hydrogen, halogen, and C_{1-6} alkyl;

Y is -C(=O)-;

each of Z_3, Z_4, Z_5, Z_6, Z_7, Z_8, Z_9, Z_{10}, Z_{11}, Z_{12} and Z_{13} is independently selected from the group consisting of N and C;

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wherein Q_1 is selected from the group consisting of C_{6-10} aryl and 5- to 10-membered heteroaryl, wherein C_{6-10} aryl or 5- to 10- membered heteroaryl is optionally substituted with one to five substituents independently selected from the group consisting of halogen and C_{3-8} cycloalkyl;

wherein Q_2 is selected from the group consisting of 3- to 12-membered heterocyclic, and 5- to 10-membered heteroaryl, wherein 3- to 12-membered heterocyclic, or 5- to 10-membered heteroaryl is optionally substituted by 1-3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and $-NR^{Qa}R^{Qb}$, wherein two C_{1-6} alkyl groups optionally together with the carbon atoms to which they are attached form C_{3-8} carbocyclic ring ; wherein R^{Qa} and R^{Qb} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl and (C_{1-6} alkyl) carbonyl;

wherein each of R_1, R_2, R_3, R_1', R_2' and R_3' is independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cycloalkyl and heterocycloalkyl; wherein C_{1-6} alkyl, cycloalkyl or heterocycloalkyl is optionally substituted by one or more substituents independently selected from the group consisting of halogen, C_{1-6} alkoxy and hydroxyl; or

wherein R_2 and R_3 together with the carbon atom to which they are attached form 4- to 8-membered heterocycloalkyl;

each of R_4, R_5 and R_6 is independently selected from the group consisting of hydrogen, halogen and C_{1-6} alkyl;

each of R_7 and R_8 is independently selected from the group consisting of hydrogen and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen and C_{3-15} cycloalkyl;

or R_7 and R_8 together with the carbon atom to which they are attached form C_{3-15} carbocyclic ring, wherein the C_{3-15} carbocyclic ring is optionally substituted by one to three C_{1-6} alkyl, wherein each C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from the group consisting of halogen, hydroxyl, $-NR^{7a}R^{7b}$, C_{1-6} alkoxy and 3- to 12-membered heterocyclic, and R^{7a} and R^{7b} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl; and any two C_{1-6} alkyl optionally together with the carbon atom to which they are attached form C_{3-15} carbocyclic ring;

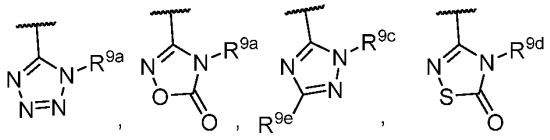
n1 is 0, 1, 2 or 3;

n2 is 0, 1, 2, 3, 4 or 5;

n3 is 0 or 1;

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R_9 is selected from the group consisting of:



, $-CO_2R^{9f}$ and $-C(=O)-NR^{9g}R^{9h}$; and each of R^{9a}, R^{9b}, R^{9c}, R^{9d} and R^{9g} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl, wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen and C_{1-6} alkoxy;

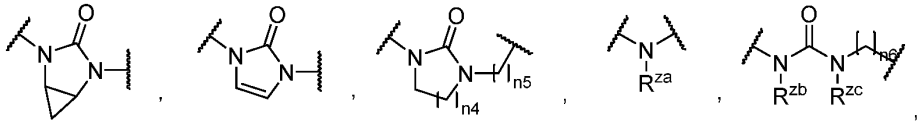
R^{9e} is selected from the group consisting of hydrogen and C_{1-6} alkyl optionally substituted with one or more halogen;

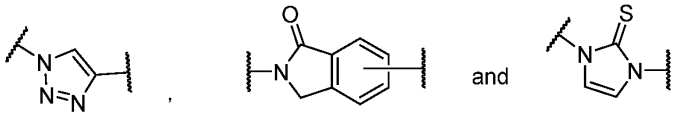
R^{9f} is selected from the group consisting of hydrogen and C_{1-6} alkyl;

R^{9h} is selected from the group consisting of hydrogen, C_{1-6} alkyl, (C_{1-6} alkyl) carbonyl, cyano and $-S(=O)_{n9}-R^{9i}$; n9 is 0, 1 or 2;

R^{9i} is C_{1-6} alkyl;

Z_1 is selected from the group consisting of:





wherein R^{za} is selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl, and each of R^{zb} and R^{zc} is independently selected from the group consisting of hydrogen and C_{1-6} alkyl;

n4 is 1, 2 or 3;

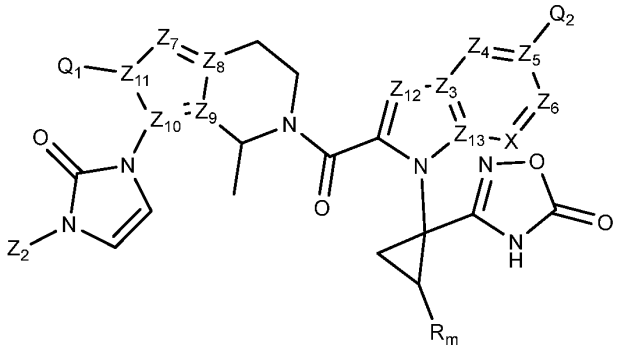
each of n5 and n6 is independently an integer selected from 0 to 10;

Z_2 is 5- to 10- membered heteroaryl, and Z_2 is substituted with one halogen and one of C_3-C_{15} cycloalkyl and C_1-C_6 alkyl-C_3-C_{15} cycloalkyl; wherein the cycloalkyl or alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, oxo, C_{1-6} alkyl, C_{1-6} alkoxy and (C_{1-6} alkyl) carbonyl, wherein each of alkyl and alkoxy is optionally substituted with halogen.

Another aspect of the present disclosure provides a compound of Formula (II), a

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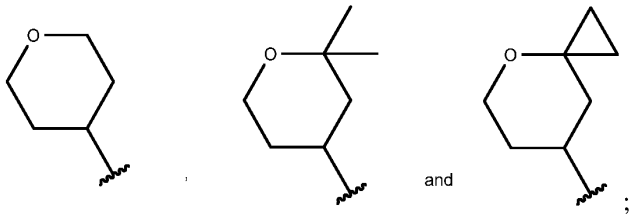
stereoisomer, a pharmaceutically acceptable salt, or a deuterated compound thereof:



Formula (II)

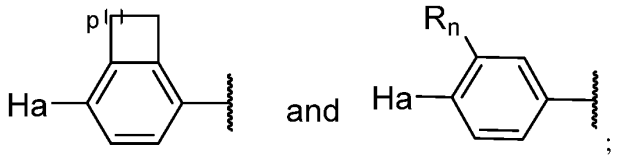
wherein:

Q_2 is selected from the group consisting of



;

Q_1 is selected from the group consisting of



;

p is 0, 1, 2 or 3;

R_n is C_{3-8} cycloalkyl;

Ha is selected from the group consisting of F, Cl, Br and I;

each of Z_3, Z_4, Z_5, Z_6, Z_7, Z_8, Z_9, Z_{10}, Z_{11}, Z_{12} and Z_{13} is independently selected from the group consisting of N and C;

X is selected from the group consisting of N and $-CR^a$; wherein R^a is selected from the group consisting of hydrogen, halogen and C_{1-6} alkyl;

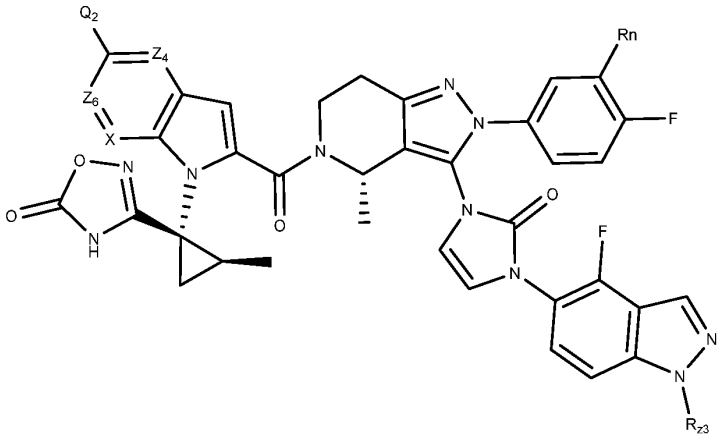
R_m is C_{1-6} alkyl;

Z_2 is 5- to 10- membered heteroaryl; and Z_2 is substituted with one Halogen and one of C_3-C_{15} cycloalkyl and C_1-C_6 alkyl-C_3-C_{15} cycloalkyl; wherein the cycloalkyl or alkyl is optionally substituted with one or more substituents independently selected from the group

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consisting of halogen, oxo, C_{1-6} alkyl, C_{1-6} alkoxy and (C_{1-6} alkyl) carbonyl, wherein each of alkyl and alkoxy is optionally substituted with halogen.

Still another aspect of the present disclosure provides a compound of Formula (III), a stereoisomer, a pharmaceutically acceptable salt, or a deuterated compound thereof:



Formula (III)

wherein:

each of X, Z_4 and Z_6 is independently selected from the group consisting of N and CH;

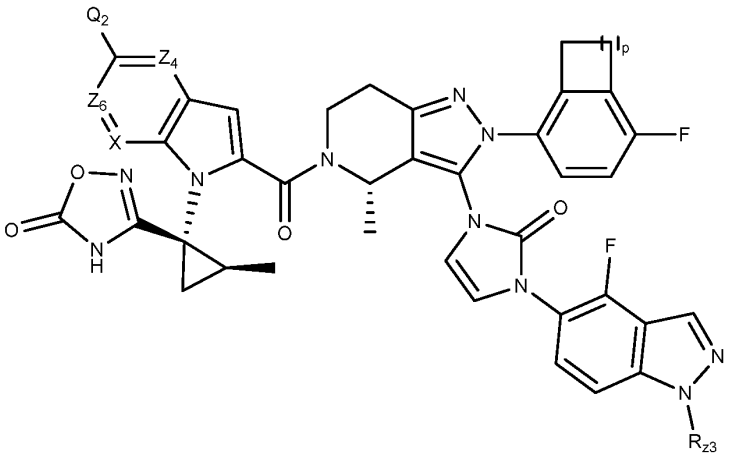
R_n is C_{3-8} cycloalkyl;

Q_2 is selected from the group consisting of 3- to 12-membered heterocyclic, and 5- to 10-membered heteroaryl, wherein 3- to 12-membered heterocyclic, or 5- to 10-membered heteroaryl is optionally substituted by 1-3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and $-NR^{Qa}R^{Qb}$, wherein two C_{1-6} alkyl groups;

R_{z3} is selected from the group consisting of C_3-C_8 cycloalkyl and C_1-C_6 alkyl-C_3-C_8 cycloalkyl.

Yet still another aspect of the present disclosure provides a compound of Formula (IV), a stereoisomer, a pharmaceutically acceptable salt, or a deuterated compound thereof:

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Formula (IV)

wherein:

each of X, Z_4 and Z_6 is independently selected from the group consisting of N and CH;

p is 0, 1, 2, or 3;

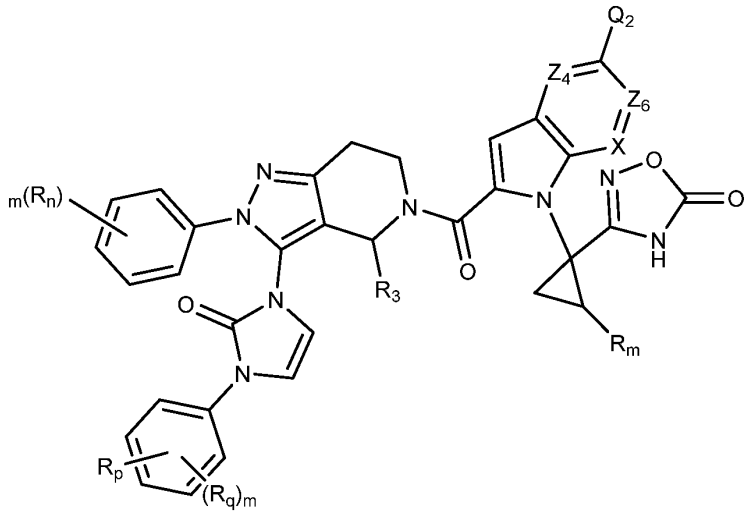
R_{z3} is selected from the group consisting of C_{1-6} alkyl, C_3-C_8 cycloalkyl and C_1-C_6 alkyl-C_3-C_8 cycloalkyl; R_{z3} is optionally substituted with substituents independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkyl and C_{1-6} alkoxy;

Q_2 is selected from the group consisting of 3- to 12-membered heterocyclic, and 5- to 10-membered heteroaryl, wherein 3- to 12-membered heterocyclic, or 5- to 10-membered heteroaryl is optionally substituted by 1-3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and $-NR^{Qa}R^{Qb}$, wherein two C_{1-6} alkyl groups optionally together with the carbon atoms to which they are attached form C_{3-8} carbocyclic ring ;

wherein R^{Qa} and R^{Qb} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl and (C_{1-6} alkyl) carbonyl.

Yet still another aspect of the present disclosure provides a compound of Formula (V), a stereoisomer, a pharmaceutically acceptable salt, or a deuterated compound thereof:

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Formula (V)

wherein:

each of X, Z_4 and Z_6 is independently selected from the group consisting of N and CH;

m is 0, 1, 2 or 3;

R_p is selected from the group consisting of $-CH_2-P(=O)R^{zm}R^{zn}$ and $-P(=O)OR^{zm}OR^{zn}$;

R_q is selected from the group consisting of halogen, -NH-C_{1-6} alkyl, C_{1-6} alkyl, -O- C_{1-6} alkyl, 3- to 12-membered heterocyclyl, C_3-C_{15} cycloalkyl and C_1-C_6 alkyl-C_3-C_{15} cycloalkyl;

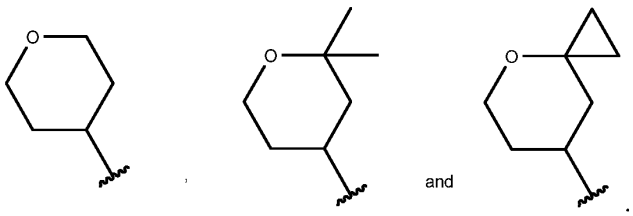
wherein each of R^{zm} and R^{zn} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl and C_{6-10} aryl; or R^{zm} and R^{zn} together with the phosphorous atom to which they are attached form 5- to 8- membered heterocycloalkyl, wherein the heterocycloalkyl is optionally substituted with 1-3 C_{1-6} alkyl;

R_m is selected from the group consisting of H and C_{1-6} alkyl, the C_{1-6} alkyl is optionally substituted with halogen;

R_n is selected from the group consisting of halogen and C_{3-8} cycloalkyl;

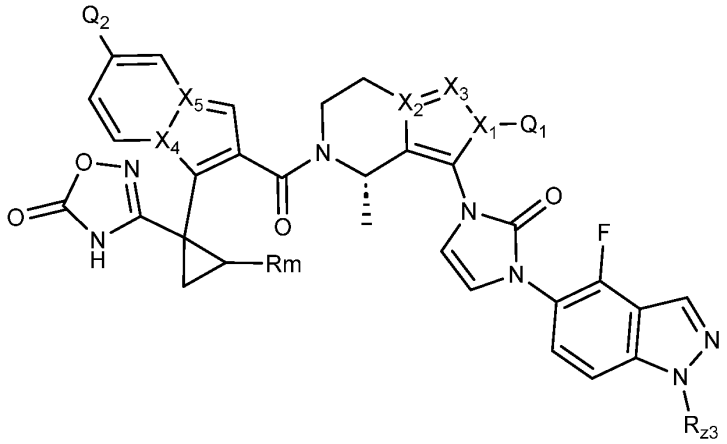
R_3 is selected from the group consisting of H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl and C_{1-6} alkoxy;

Q_2 is selected from the group consisting of



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Yet still another aspect of the present disclosure provides a compound of Formula (VI), a stereoisomer, a pharmaceutically acceptable salt, or a deuterated compound thereof:



Formula (VI)

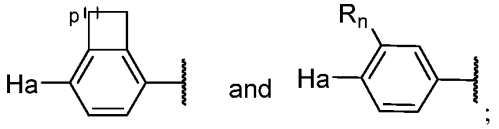
wherein:

X_1, X_2, and X_3 are independently selected from the group consisting of N and C;

X_4, and X_5 are independently selected from the group consisting of N and C;

R_m is selected from the group consisting of H and C_{1-6} alkyl, the C_{1-6} alkyl is optionally substituted with halogen;

Q_1 is selected from the group consisting of

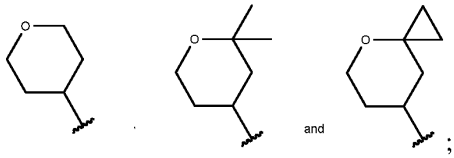


p is 0, 1, 2 and 3;

R_n is C_{3-8} cycloalkyl;

Ha is selected from the group consisting of F, Cl, Br and I;

Q_2 is selected from the group consisting of

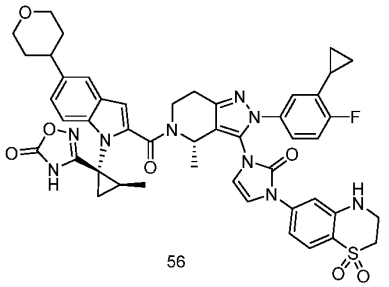


R_{z3} is selected from the group consisting of C_3-C_{15} cycloalkyl and C_1-C_6 alkyl-C_3-C_{15} cycloalkyl.

Yet still another aspect of the present disclosure provides a compound, a stereoisomer, a pharmaceutically acceptable salt, or a deuterated compound thereof, wherein the compound is

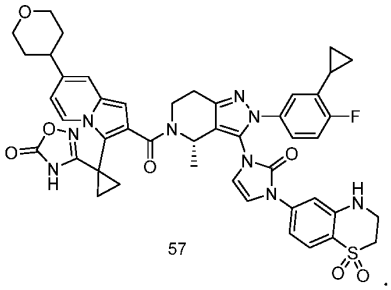
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selected from the group consisting of



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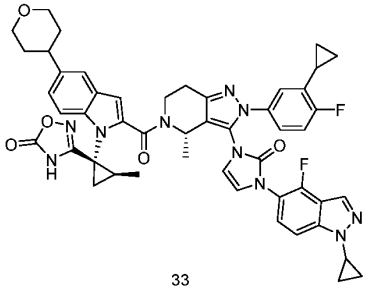
and



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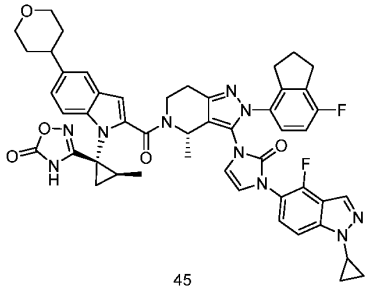
.

Yet still another aspect of the present disclosure provides a compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:



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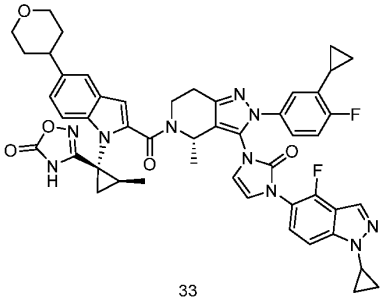
and



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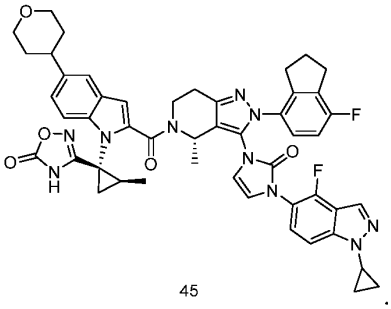
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Yet still another aspect of the present disclosure provides a compound, selected from the group consisting of:



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and



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Yet still another aspect of the present disclosure relates to a composition comprising the compound, the stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof of the present disclosure, and a pharmaceutically acceptable excipient.

Yet still another aspect of the present disclosure provides a method for treating GLP-1R mediated diseases or conditions, comprising administering to a subject in need thereof a therapeutically effective amount of the compound, the stereoisomer, the pharmaceutically

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acceptable salt, or the deuterated compound thereof, or a pharmaceutical composition of the present disclosure.

DETAILED DESCRIPTION

In the following description, certain specific details are included to provide a comprehensive understanding of the various disclosed embodiments. However, those skilled in the art will recognise that embodiments may be achieved without the use of one or more of these specific details and with the use of other methods, components, materials, etc.

Unless otherwise required in this disclosure, throughout the specification and subsequent claims, the words "including" and "comprising" are to be interpreted in an open-ended, inclusive sense, i.e., "including, without limitation".

As used in this disclosure and in the appended claims, singular referents without indication of quantity include plural referents unless the context clearly indicates otherwise.

Throughout this specification, references to "an embodiment" or "embodiments" or "in another embodiment" or "in some embodiments" means to include in at least one embodiment a specific reference element, structure or feature related to that embodiment as described in that embodiment. Accordingly, the phrases "in an embodiment" or "in an embodiment" or "in another embodiment" or "in certain embodiments" appearing at various places throughout the specification are intended to mean that at least one embodiment includes a specific reference element or feature related to that embodiment as described therein. "In some embodiments" need not all refer to the same embodiment. In addition, specific elements, structures, or features may be combined in one or more embodiments in any suitable manner.

It should be understood that the singular form of the article "one" (corresponding to the English words "a", "an", and "the") is used in the specification of the present disclosure and the appended claims. "The" are used in the claims in the singular form to include objects in the plural unless the context explicitly states otherwise. Thus, for example, reference to an extended-release tablet comprising "pharmaceutically acceptable excipients" includes one pharmaceutically acceptable excipient or two or more pharmaceutically acceptable excipients.

It should be understood that the singular form of the article "a" (corresponding to the English "a", "an", and "the") used in this disclosure and the accompanying claims includes plural objects unless otherwise explicitly stated in the text. Therefore, for example, a sustained-release tablet containing "pharmaceutically acceptable excipients" includes one

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pharmaceutically acceptable excipient or two or more pharmaceutically acceptable excipients.

Definition

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. A dash at the front or end of a chemical group is a matter of convenience to indicate the point of attachment to a parent moiety; chemical groups may be depicted with or without one or more dashes without losing their ordinary meaning. A prefix such as "C_{u-v}" or "C_u-C_v" indicates that the following group has from u to v carbon atoms, where u and v are integers. For example, "C_{1-6} alkyl" or "C_1-C_6 alkyl" indicates that the alkyl group has from 1 to 6 carbon atoms. "C_3-C_{10} cycloalkyl" describes a cycloalkyl group having a total of 3 to 10 carbon atoms.

The terms "and/or" are used in this disclosure to denote "and" or "or" unless otherwise indicated.

"Substituted" as used herein refers to wherein one or more hydrogen atoms of the group are independently replaced by one or more substituents (e.g., 1, 2, 3, or 4 or more) as indicated. The substituent is selected from the following substituents, but are not limited to: alkyl, cycloalkyl, aryl, heteroaryl, heteroaryl, hydroxy, protected hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylsulfanyl, cyano, halogenated, carbonyl, thiocarbonyl, O-carbamoyl, N-carbamoyl O-thiocarbamoyl, N-thiocarbamoyl, C-acylamino, N-acylamino, S-sulfinylamino, N-sulfinylamino, C-carboxylic, protected C-carboxylic, O-carboxylic, isocyanatocarbonyl, cyanothiocyanatocarbonyl, isothiocyanatocarbonyl, nitro, methyldimethylsilanyl, trihalomethanesulfonyl, -NR' R" (R' and R" are alkyl groups as defined in this disclosure) or a protected amino group.

"Alkyl" is a monovalent or divalent linear or branched saturated hydrocarbon radical. For example, an alkyl group can have 1 to 10 carbon atoms (i.e., C_{1-10} alkyl) or 1 to 8 carbon atoms (i.e., C_{1-8} alkyl) or 1 to 6 carbon atoms (i.e., C_{1-6} alkyl) or 1 to 4 carbon atoms (i.e., C_{1-4} alkyl). Examples of alkyl groups include, but are not limited to, methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (*n*-Pr, *n*-propyl, $-CH_2CH_2CH_3$), 2-propyl (*i*-Pr, *i*-Propyl, $-CH(CH_3)_2$), 1-butyl (*n*-Bu, *n*-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (*i*-Bu, *i*-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (*s*-Bu, *s*-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (*t*-Bu, *t*-butyl, $-C(CH_3)_3$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl (-

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$CH_2CH(CH_3)CH_2CH_3$), 1-hexyl (-$CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl (-$CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl (-$CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl (-$C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl (-$CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl (-$CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl (-$C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl (-$CH(CH_2CH_3)CH(CH_3)_2$), 2, 3-dimethyl-2-butyl (-$C(CH_3)_2CH(CH_3)_2$), 3, 3-dimethyl-2-butyl (-$CH(CH_3)C(CH_3)_3$, and octyl (-$(CH_2)_7CH_3$). Alkyl groups can be unsubstituted or substituted.

The alkyl group may be optionally substituted, i.e., substituted or unsubstituted. When substituted, the substituent group is individually and independently selected from one or more of the following: cycloalkyl, aryl, heteroaryl, heteroaryl, hydroxy, alkoxy, aryloxy, thiol, alkylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, O-carbamoyl, N-carbamoyl, O-thiocarbamoyl, N-thiocarbamoyl, C-acylamino, N-acyl amino, S-sulfinylamino, N-sulfinylamino, C-carboxyl, O-carboxyl, isocyanato, cyanothio, isothiocyanato, nitro, methylsilyl, trihalomethanesulfonyl, -NR'R" (R' and R" are alkyl groups as defined in the present disclosure) or amino groups including mono- and di-substituted amino groups, and protected derivatives thereof.

In some embodiments, exemplary examples of alkyl groups that can be used in the present disclosure include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, and hexyl. Whenever a substituent is described as being "optionally substituted", the substituent may be substituted with one of the above substituents.

"Alkoxy" refers to the group -O-alkyl, where alkyl is as defined above. For example, C_{1-4} alkoxy refers to an -O-alkyl group having 1 to 4 carbons. Alkoxy groups can be unsubstituted or substituted.

"Alkoxyalkyl" is an alkoxy group attached to an alkyl as defined above, such that the alkyl is divalent. For example, C_{2-6} alkoxyalkyl includes -CH_2-OMe, -CH_2-O-*i*Pr, -CH_2-CH_2-OMe, -CH_2-CH_2-O-CH_2-CH_3, and -CH_2-CH_2-O-*t*Bu. Alkoxyalkyl groups can be unsubstituted or substituted.

"Alkenyl" is a monovalent or divalent linear or branched hydrocarbon radical with at least one carbon-carbon double bond. For example, an alkenyl group can have 2 to 8 carbon atoms (i.e., C_{2-8} alkenyl) or 2 to 6 carbon atoms (i.e., C_{2-6} alkenyl) or 2 to 4 carbon atoms (i.e., C_{2-4} alkenyl). Examples of alkenyl groups include, but are not limited to, ethenyl (-$CH=CH_2$), allyl (-$CH_2CH=CH_2$), and -CH_2-CH=CH-CH_3. Alkenyl groups can be unsubstituted or substituted.

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"Alkynyl" is a monovalent or divalent linear or branched hydrocarbon radical with at least one carbon-carbon triple bond. For example, an alkynyl group can have 2 to 8 carbon atoms (i.e., C_{2-8} alkynyl) or 2 to 6 carbon atoms (i.e., C_{2-6} alkynyl) or 2 to 4 carbon atoms (i.e., C_{2-4} alkynyl). Examples of alkynyl groups include, but are not limited to, acetylenyl (-C≡CH), propargyl (-CH_2C≡CH), and -CH_2-C≡C-CH_3. Alkynyl groups can be unsubstituted or substituted.

"Oxo" as used herein refers to =O.

"Halogen" or "halo" refers to fluoro (-F), chloro (-Cl), bromo (-Br) and iodo (-I).

"Haloalkyl" is an alkyl as defined herein, wherein one or more hydrogen atoms of the alkyl are independently replaced by a halogen, which may be the same or different, such that the alkyl is divalent. The alkyl group and the halogen can be any of those described above. In some embodiments, the haloalkyl defines the number of carbon atoms in the alkyl portion, e.g., C_{1-4} haloalkyl includes CF_3, CH_2F, CHF_2, CH_2CF_3, $CH_2CH_2CF_3$, $CCl_2CH_2CH_2CH_3$, and $C(CH_3)_2(CF_2H)$. Haloalkyl groups can be unsubstituted or substituted.

"Haloalkoxy" is an alkoxy as defined herein, wherein one or more hydrogen atoms of the alkyl in the alkyoxy are independently replaced by a halogen, which may be the same or different, such that the alkyl is divalent. The alkoxy group and the halogen can be any of those described above. In some embodiments, the haloalkoxy defines the number of carbon atoms in the alkyl portion, e.g., C_{1-4} haloalkoxy includes OCF_3, OCH_2F, OCH_2CF_3, $OCH_2CH_2CF_3$, $OCCl_2CH_2CH_2CH_3$, and $OC(CH_3)_2(CF_2H)$. Haloalkoxy groups can be unsubstituted or substituted.

"Cycloalkyl" is a monovalent or divalent single all carbon ring or a multiple condensed all carbon ring system wherein the ring in each instance is a non-aromatic saturated or unsaturated ring. For example, in some embodiments, a cycloalkyl group has 3 to 12 carbon atoms, 3 to 10 carbon atoms, 3 to 8 carbon atoms, 3 to 6 carbon atoms, 3 to 5 carbon atoms, or 3 to 4 carbon atoms. Exemplary single ring cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, and cyclooctyl. Cycloalkyl also includes multiple condensed ring systems (e.g., ring systems comprising 2 rings) having about 7 to 12 carbon atoms. The rings of the multiple condensed ring system can be connected to each other via fused, spiro, or bridged bonds when allowed by valency requirements. Exemplary multiple ring cycloalkyl groups include octahydropentalene, bicyclo[2. 2. 1]heptane, bicyclo[2. 2. 2]octane, bicyclo[2. 2. 2]oct-2-ene, and spiro[2. 5]octane. Cycloalkyl groups can be unsubstituted or substituted.

The term "cycloalkyl" is intended to include a cycloalkyl group as defined above

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optionally substituted by one or more groups selected from the following substituents: cycloalkyl, aryl, heteroaryl, heteroaliphatic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, thio carbonyl, isocyanate, cyanothionyl, isothiocyanate, nitro, -NR'R " (R' and R" are alkyl groups as defined in the present disclosure) or amino groups including mono- and di-substituted amino groups, and protected derivatives thereof.

In some embodiments, "C_{3-6} cycloalkyl" refers to a cycloalkyl group as defined above having three to six carbon atoms. C_{3-6} cycloalkyl groups may be optionally substituted as defined above for cycloalkyl.

In some embodiments, "C_{3-8} cycloalkyl" refers to a cycloalkyl group having from three to eight carbon atoms as defined above. C_{3-8} cycloalkyl groups may be optionally substituted as defined above for cycloalkyl.

In some embodiments, the term "C_{3-15} cycloalkyl" refers to a cycloalkyl group as defined above having from three to twelve carbon atoms. C_{3-15} cycloalkyl groups may be optionally substituted as defined above for cycloalkyl.

"Aryl" as used herein refers to a monovalent or divalent single all carbon aromatic ring or a multiple condensed all carbon ring system wherein the ring is aromatic. For example, in some embodiments, an aryl group has 6 to 20 carbon atoms, 6 to 14 carbon atoms, 6 to 12 carbon atoms, or 6 to 10 carbon atoms. Aryl includes a phenyl radical. Aryl also includes multiple condensed ring systems (e.g., ring systems comprising 2, 3 or 4 rings) having about 9 to 20 carbon atoms in which multiple rings are aromatic. The rings of the multiple condensed ring system can be connected to each other via fused bonds when allowed by valency requirements. It is also understood that when reference is made to a certain atom-range membered aryl (e.g., 6-10 membered aryl), the atom range is for the total ring atoms of the aryl. For example, a 6-membered aryl would include phenyl and a 10-membered aryl would include naphthyl. Non-limiting examples of aryl groups include, but are not limited to, phenyl, naphthyl, anthracenyl, and the like. Aryl groups can be unsubstituted or substituted.

"Heterocyclyl" or "heterocycle" or "heterocycloalkyl" or "heterocyclic" or "heterocyclic ring" as used herein refers to a single saturated or partially unsaturated non-aromatic ring or a non-aromatic multiple ring system that has at least one heteroatom in the ring (i.e., at least one annular (i.e., ring-shaped) heteroatom selected from oxygen, nitrogen, and sulfur). Unless otherwise specified, a heterocyclyl group has from 3 to about 20 annular atoms, for example from 3 to 12 annular atoms, for example from 4 to 12 annular atoms, 4 to 10 annular atoms, or 3 to 8 annular atoms, or 3 to 6 annular atoms, or 3 to 5 annular atoms, or 4 to 6 annular atoms, or 4 to 5 annular atoms. Thus, the term includes single saturated or partially

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unsaturated rings (e.g., 3, 4, 5, 6 or 7- membered rings) having from about 1 to 6 annular carbon atoms and from about 1 to 3 annular heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur in the ring. The rings of the multiple condensed ring (e.g. bicyclic heterocyclyl) system can be connected to each other via fused, spiro and bridged bonds when allowed by valency requirements. Heterocycles include, but are not limited to, azetidine, aziridine, imidazolidine, morpholine, oxirane(epoxide), oxetane, thietane, piperazine, piperidine, pyrazolidine, piperidine, pyrrolidine, pyrrolidinone, tetrahydrofuran, tetrahydrothiophene, dihydropyridine, tetrahydropyridine, quinuclidine,2-oxa-6-azaspiro[3. 3]heptan-6-yl, 6-oxa-1-azaspiro[3. 3]heptan-1-yl, 2-thia-6-azaspiro[3. 3]heptan-6-yl, 2, 6-diazaspiro[3. 3]heptan-2-yl, 2-azabicyclo[3. 1. 0]hexan-2-yl, 3-azabicyclo[3. 1. 0]hexanyl, 2-azabicyclo[2. 1. 1]hexanyl, 2-azabicyclo[2. 2. 1]heptan-2-yl, 4-azaspiro[2. 4]heptanyl, 5-azaspiro[2. 4]heptanyl, and the like. Heterocyclyl groups can be unsubstituted or substituted.

"5-10 membered heteroaryl" refers to an aromatic ring that has at least one atom other than carbon in the ring, wherein the atom is selected from the group consisting of oxygen, nitrogen and sulfur; "5-10 membered heteroaryl" also includes multiple condensed ring systems that have at least one such aromatic ring, which multiple condensed ring systems are further described below. Thus, "5-10 membered heteroaryl" includes single aromatic rings of from about 1 to 6 carbon atoms and about 1-4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur. The sulfur and nitrogen atoms may also be present in an oxidized form provided the ring is aromatic. Exemplary 5-10 membered heteroaryl ring systems include but are not limited to pyridyl, pyrimidinyl, oxazolyl or furyl. "5-10 membered heteroaryl" also includes multiple condensed ring systems (e.g., ring systems comprising 2, 3 or 4 rings) wherein a 5-10 membered heteroaryl group, as defined above, is condensed with one or more rings selected from 5-10 membered heteroaryls (to form for example 1, 8-naphthyridinyl) and aryls (to form, for example, benzimidazolyl or indazolyl) to form the multiple condensed ring system. Thus, a 5-10 membered heteroaryl (a single aromatic ring or multiple condensed ring system) can have about 1-20 carbon atoms and about 1-6 heteroatoms within the 5-10 membered heteroaryl ring. For example, tetrazolyl has 1 carbon atom and 4 nitrogen heteroatoms within the ring. The rings of the multiple condensed ring system can be connected to each other via fused bonds when allowed by valency requirements. It is to be understood that the individual rings of the multiple condensed ring system may be connected in any order relative to one another. It is to be understood that the point of attachment for a 5-10 membered heteroaryl or 5-10 membered heteroaryl multiple condensed ring system can be at any suitable atom of the 5-10 membered

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heteroaryl or 5-10 membered heteroaryl multiple condensed ring system including a carbon atom and a heteroatom (e.g., a nitrogen). It also to be understood that when a reference is made to a certain atom-range membered (e.g., a 5-10 membered heteroaryl), the atom range is for the total ring atoms of the 5-10 membered heteroaryl and includes carbon atoms and heteroatoms. It is also to be understood that the rings of the multiple condensed ring system may include an aryl ring fused to a heterocyclic ring with saturated or partially unsaturated bonds (e.g., 3, 4, 5, 6 or 7-membered rings) having from about 1 to 6 annular carbon atoms and from about 1 to 3 annular heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur in the ring. For example, a 5-10 membered heteroaryl includes thiazolyl and a 5-10 membered heteroaryl includes quinolinyl. Exemplary 5-10 membered heteroaryls include but are not limited to pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, thienyl, indolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, furyl, oxadiazolyl, thiadiazolyl, quinolyl, isoquinolyl, benzothiazolyl, benzoxazolyl, indazolyl, quinoxalyl, quinazolyl, benzofuranyl, benzimidazolyl, thianaphthenyl, pyrrolo[2, 3-b]pyridinyl, quinazolinyl-4(3H)-one, triazolyl, and tetrazolyl. 5-10 membered heteroaryl groups can be unsubstituted or substituted.

The term "5-10 membered heteroaryl" is intended to include an aromatic ring group as defined above optionally substituted by one or more groups selected from the following substituents: cycloalkyl, aryl, heteroaryl, heteroaliphatic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, thio carbonyl, isocyanate, cyanothionyl, isothiocyanate, nitro, -NR'R " (R' and R" are alkyl groups as defined in the present disclosure) or amino groups including mono- and di-substituted amino groups, and protected derivatives thereof.

"(C_{1-6} alkyl)carbonyl" means the group: (C_{1-6} alkyl)-C(O)- group, wherein alkyl is defined as mentioned above. The carbonyl refers to the C(O)- group, which is a carbon atom double-bonded to an oxygen atom. Examples include methyl carbonyl (acetyl), ethyl carbonyl (propionyl), n-propyl carbonyl, isopropyl carbonyl, n-butyl carbonyl, isobutyl carbonyl, sec-butyl carbonyl, tert-butyl carbonyl, 1-methylpropyl carbonyl, n-amyl carbonyl, isoamyl carbonyl, 2-methylbutyl carbonyl, 1,1-dimethylpropyl carbonyl, 1-ethylpropyl carbonyl, n-hexyl carbonyl, 4-methylpentyl carbonyl, and 2-ethylbutyl carbonyl. Carbonyl ethylpentane, 4-methylpentylcarbonyl, and 2-ethylbutylcarbonyl.

A "compound of the present disclosure" includes compound disclosed herein, for example a compound of the present disclosure includes compound of Formula (I), (II), (III), (IV), (V), (VI), (Ia), (Ib), and (Ic), but also includes the compound of the examples.

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"Pharmaceutically acceptable excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

"Therapeutically effective amount" or "effective amount" as used herein refers to an amount that is effective to elicit the desired biological or medical response, including the amount of a compound that, when administered to a subject for treating a disease, is sufficient to affect such treatment for the disease. The effective amount will vary depending on the compound, the disease, and its severity and the age, weight, etc., of the subject to be treated. The effective amount can include a range of amounts. As is understood in the art, an effective amount may be in one or more doses, i.e., a single dose or multiple doses may be required to achieve the desired treatment endpoint. An effective amount may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable or beneficial result may be or is achieved. Suitable doses of any co-administered compounds may optionally be lowered due to the combined action (e.g., additive or synergistic effects) of the compounds.

"Co-administration" as used herein refers to administration of unit dosages of the compounds disclosed herein before or after administration of unit dosages of one or more additional therapeutic agents, for example, administration of the compound disclosed herein within seconds, minutes, or hours of the administration of one or more additional therapeutic agents. For example, in some embodiments, a unit dose of a compound of the present disclosure is administered first, followed within seconds or minutes by administration of a unit dose of one or more additional therapeutic agents. Alternatively, in other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed by administration of a unit dose of a compound of the present disclosure within seconds or minutes. In some embodiments, a unit dose of a compound of the present disclosure is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more additional therapeutic agents. In other embodiments, a unit dose of one or more additional therapeutic agents is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound of the present disclosure. Co-administration of a compound disclosed herein with one or more additional therapeutic agents generally refers to simultaneous or sequential administration of a

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compound disclosed herein and one or more additional therapeutic agents, such that therapeutically effective amounts of each agent are present in the body of the subject.

Provided are also pharmaceutically acceptable salts, hydrates, solvates, tautomeric forms, polymorphs, and prodrugs of the compounds described herein.

"Pharmaceutically acceptable" refers to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

The compounds described herein may be prepared and/or formulated as pharmaceutically acceptable salts or when appropriate as a free base. Pharmaceutically acceptable salts are non-toxic salts of a free base form of a compound that possesses the desired pharmacological activity of the free base. These salts may be derived from inorganic or organic acids or bases. For example, a compound that contains a basic nitrogen may be prepared as a pharmaceutically acceptable salt by contacting the compound with an inorganic or organic acid. Non-limiting examples of pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogen-phosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1, 4-dioates, hexyne-1, 6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, methylsulfonates, propylsulfonates, besylates, xylenesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ-hydroxybutyrates, glycolates, tartrates, and mandelates. Lists of other suitable pharmaceutically acceptable salts are found in Remington: The Science and Practice of Pharmacy, 21st Edition, Lippincott Wiliams and Wilkins, Philadelphia, Pa., 2006.

Examples of "pharmaceutically acceptable salts" of the compounds disclosed herein also include salts derived from an appropriate base, such as an alkali metal (for example, sodium, potassium), an alkaline earth metal (for example, magnesium), ammonium and $N(C_1\text{-}C_4\ alkyl)_4^+$. Also included are base addition salts, such as sodium or potassium salts.

Provided are also compounds described herein or pharmaceutically acceptable salts, isomers, or a mixture thereof, in which from 1 to n hydrogen atoms attached to a carbon atom may be replaced by a deuterium atom or D, in which n is the number of hydrogen atoms in the molecule. As known in the art, the deuterium atom is a non-radioactive isotope of the hydrogen atom. Such compounds may increase resistance to metabolism, and thus may be

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useful for increasing the half-life of the compounds described herein or pharmaceutically acceptable salts, isomer, or a mixture thereof when administered to a mammal. See, e.g., Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism", Trends Pharmacol. Sci., 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogen atoms have been replaced by deuterium.

Examples of isotopes that can be incorporated into the disclosed compounds also include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of Formula I can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

The compounds of the embodiments disclosed herein, or their pharmaceutically acceptable salts may contain one or more asymmetric centers and may thus give rise to enantiomers, tautomer, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids, as well as deuterated analogs thereof. The chemical formula shown in the present disclosure is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (R)- and (S)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included. Where compounds are represented in their chiral form, it is understood that the embodiment encompasses, but is not limited to, the specific diastereomerically or enantiomerically enriched form. Where chirality is not specified but is present, it is understood that the embodiment is directed to either the specific diastereomerically or enantiomerically enriched

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form; or a racemic or scalemic mixture of such compound(s). As used herein, "scalemic mixture" is a mixture of stereoisomers at a ratio other than 1:1.

"Stereoisomer" as used herein refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present disclosure contemplates various stereoisomers and mixtures thereof and includes "enantiomers", which refers to two stereoisomers whose molecules are non-superimposable mirror images of one another.

"Tautomer" as used herein refers to a proton shift from one atom of a molecule to another atom of the same molecule. In some embodiments, the present disclosure includes tautomers of said compounds.

"Prevention" or "preventing" means any treatment of a disease or condition that causes the clinical symptoms of the disease or condition not to develop. Compounds may, in some embodiments, be administered to a subject (including a human) who is at risk or has a family history of the disease or condition.

"Prodrug" as used herein refers to a derivative of a drug that upon administration to the human body is converted to the parent drug according to some chemical or enzymatic pathway. In some embodiments, a prodrug is a biologically inactive derivative of a drug that upon administration to the human body is converted to the biologically active parent drug according to some chemical or enzymatic pathway.

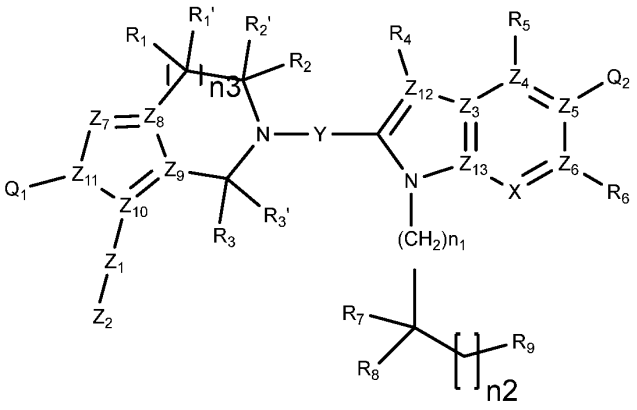
"Treatment" or "treat" or "treating" as used herein refers to an approach for obtaining beneficial or desired results. For purposes of the present disclosure, beneficial or desired results include, but are not limited to, alleviation of a symptom and/or diminishment of the extent of a symptom and/or preventing a worsening of a symptom associated with a disease or condition. In one embodiment, "treatment" or "treating" includes one or more of the following: a) inhibiting the disease or condition (e.g., decreasing one or more symptoms resulting from the disease or condition, and/or diminishing the extent of the disease or condition); b) slowing or arresting the development of one or more symptoms associated with the disease or condition (e.g., stabilizing the disease or condition, delaying the worsening or progression of the disease or condition); and c) relieving the disease or condition, e.g., causing the regression of clinical symptoms, ameliorating the disease state, delaying the progression of the disease, increasing the quality of life, and/or prolonging survival. "At risk individual" as used herein refers to an individual who is at risk of developing a condition to be treated. An individual "at risk" may or may not have detectable disease or condition, and may or may not have displayed detectable disease prior to the treatment of methods described

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herein. “At risk” denotes that an individual has one or more so-called risk factors, which are measurable parameters that correlate with development of a disease or condition and are known in the art. An individual having one or more of these risk factors has a higher probability of developing the disease or condition than an individual without these risk factor(s).

Compound

One aspect of the present disclosure provides a compound of Formula (I), a stereoisomer, a pharmaceutically acceptable salt, or a deuterated compound thereof:



Formula (I)

wherein,

X is selected from the group consisting of N and -CR^a; and R^a is selected from the group consisting of hydrogen, halogen, and C_{1-6} alkyl;

Y is -C(=O)-;

each of Z_3, Z_4, Z_5, Z_6, Z_7, Z_8, Z_9, Z_{10}, Z_{11}, Z_{12} and Z_{13} is independently selected from the group consisting of N and C;

wherein Q_1 is selected from the group consisting of C_{6-10} aryl and 5- to 10-membered heteroaryl, wherein C_{6-10} aryl or 5- to 10- membered heteroaryl is optionally substituted with one to five substituents independently selected from the group consisting of halogen and C_{3-8} cycloalkyl;

wherein Q_2 is selected from the group consisting of 3- to 12-membered heterocyclic, and 5- to 10-membered heteroaryl, wherein 3- to 12-membered heterocyclic or5- to 10-membered heteroaryl is optionally substituted by 1-3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and -$NR^{Qa}R^{Qb}$, wherein two C_{1-6} alkyl groups optionally together with the carbon atoms to which they are attached form C_{3-8}

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carbocyclic ring ; wherein R^{Qa} and R^{Qb} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl and (C_{1-6} alkyl) carbonyl;

wherein each of R_1, R_2, R_3, R_1', R_2' and R_3' is independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cycloalkyl and heterocycloalkyl; wherein C_{1-6} alkyl, cycloalkyl or heterocycloalkyl is optionally substituted by one or more substituents independently selected from the group consisting of halogen, C_{1-6} alkoxy and hydroxyl; or

wherein R_2 and R_3 together with the carbon atom to which they are attached form 4- to 8-membered heterocycloalkyl;

each of R_4, R_5 and R_6 is independently selected from the group consisting of hydrogen, halogen and C_{1-6} alkyl;

each of R_7 and R_8 is independently selected from the group consisting of hydrogen and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen and C_{3-15} cycloalkyl;

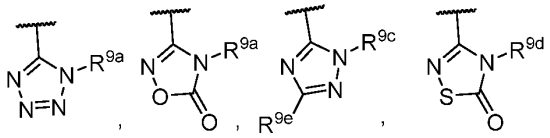
or R_7 and R_8 together with the carbon atom to which they are attached form C_{3-15} carbocyclic ring, wherein the C_{3-15} carbocyclic ring is optionally substituted with one to three C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, $-NR^{7a}R^{7b}$, C_{1-6} alkoxy and 3- to 12-membered heterocyclic, and R^{7a} and R^{7b} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl; and any two C_{1-6} alkyl optionally together with the carbon atom to which they are attached form C_{3-15} carbocyclic ring;

n1 is 0, 1, 2 or 3;

n2 is 0, 1, 2, 3, 4 or 5;

n3 is 0 or 1;

R_9 is selected from the group consisting of:



, $-CO_2R^{9f}$ and $-C(=O)-NR^{9g}R^{9h}$; and

each of R^{9a}, R^{9b}, R^{9c}, R^{9d} and R^{9g} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl, wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen and C_{1-6} alkoxy;

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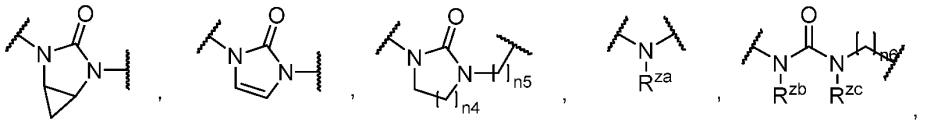
R^{9e} is selected from the group consisting of hydrogen and C_{1-6} alkyl optionally substituted with one or more halogen;

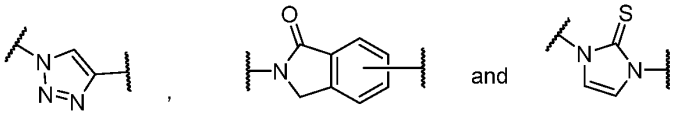
R^{9f} is selected from the group consisting of hydrogen and C_{1-6} alkyl;

R^{9h} is selected from the group consisting of hydrogen, C_{1-6} alkyl, (C_{1-6} alkyl) carbonyl, cyano and $-S(=O)_{n9}-R^{9i}$; n9 is 0, 1 or 2;

R^{9i} is C_{1-6} alkyl;

Z_1 is selected from the group consisting of:





wherein R^{za} is selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl, and each of R^{zb} and R^{zc} is independently selected from the group consisting of hydrogen and C_{1-6} alkyl;

n4 is 1, 2 or 3;

each of n5 and n6 is independently an integer selected from 0 to 10;

Z_2 is 5- to 10- membered heteroaryl; and Z_2 is substituted with one halogen and one of C_3-C_{15} cycloalkyl and C_1-C_6 alkyl-C_3-C_{15} cycloalkyl; wherein the cycloalkyl or alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, oxo, C_{1-6} alkyl, C_{1-6} alkoxy and (C_{1-6} alkyl) carbonyl, wherein each of alkyl and alkoxy is optionally substituted with halogen.

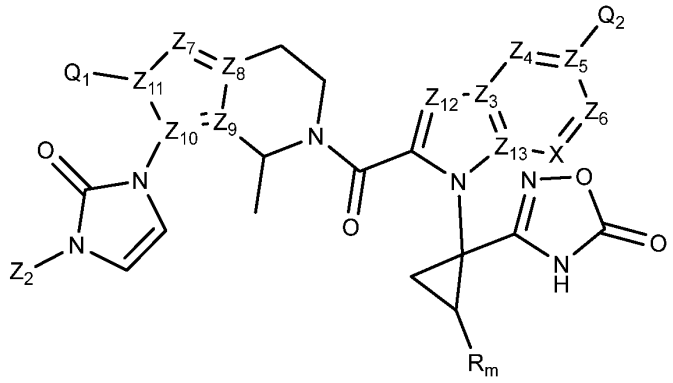
In some embodiments, in the compound of Formula (I), the stereoisomer, the pharmaceutically acceptable salt or the deuterated compound thereof, Q_1 is selected from the group consisting of C_{6-10} aryl and 5- to 10-membered heteroaryl, wherein C_{6-10} aryl or 5- to 10- membered heteroaryl is substituted by at least one C_{3-8} cycloalkyl and optionally by one to four halogens.

In some embodiments, in the compound of Formula (I), the stereoisomer, the pharmaceutically acceptable salt or the deuterated compound thereof, wherein Q_1 is optionally substituted with two C_{1-6} alkyl, wherein the C_{1-6} alkyl together with the carbon atoms, to which they are attached, form C_{3-8} carbocyclic ring or 4- to 10- membered heterocyclyl.In some embodiments, in the compound of Formula (I), the stereoisomer, the

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pharmaceutically acceptable salt or the deuterated compound thereof, Q_1 is selected from the group consisting of C_{6-10} aryl and 5- to 10-membered heteroaryl, wherein C_{6-10} aryl or 5- to 10- membered heteroaryl is optionally substituted with at least one C_{3-8} cycloalkyl and optionally with one to four halogen; the C_{3-8} cycloalkyl is selected from the group consisting of optionally substituted cyclopropyl, cyclobutyl, and cyclopentyl.

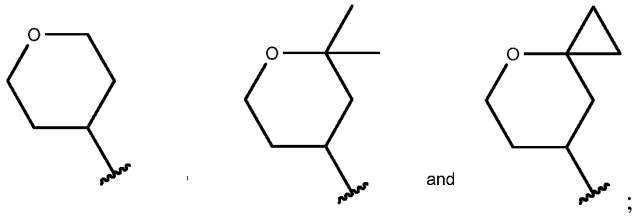
Another aspect of the present disclosure provides a compound of Formula (II), a stereoisomer, a pharmaceutically acceptable salt, or a deuterated compound thereof:



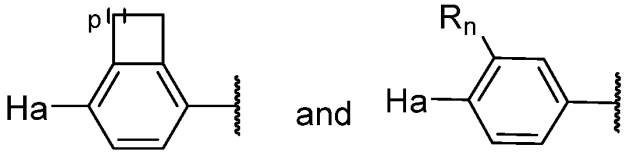
Formula (II)

wherein:

Q_2 is selected from the group consisting of



Q_1 is selected from the group consisting of



p is 0, 1, 2 or 3;

R_n is C_{3-8} cycloalkyl;

Ha is selected from the group consisting of F, Cl, Br and I;

each of Z_3, Z_4, Z_5, Z_6, Z_7, Z_8, Z_9, Z_{10}, Z_{11}, Z_{12} and Z_{13} is independently selected from the group consisting of N and C;

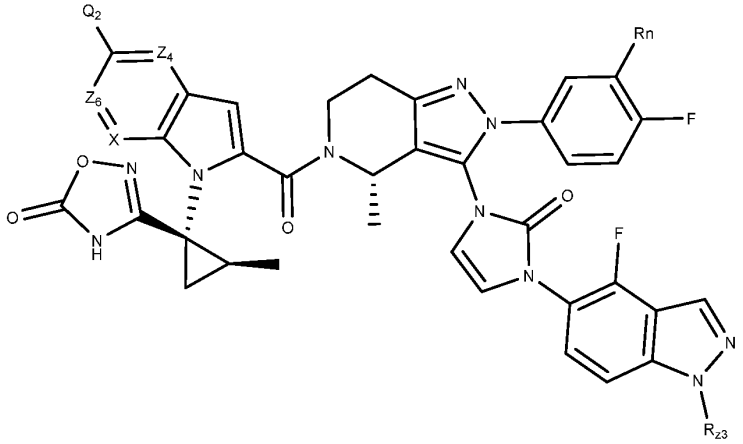
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X is selected from the group consisting of N and -CR^a; wherein R^a is selected from the group consisting of hydrogen, halogen and C_{1-6} alkyl;

R_m is C_{1-6} alkyl;

Z_2 is 5- to 10- membered heteroaryl; and Z_2 is substituted with one halogen and one of C_3-C_{15} cycloalkyl and C_1-C_6 alkyl-C_3-C_{15} cycloalkyl; wherein the cycloalkyl or alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, oxo, C_{1-6} alkyl, C_{1-6} alkoxy and (C_{1-6} alkyl) carbonyl, wherein each of alkyl and alkoxy is optionally substituted with halogen.

Still another aspect of the present disclosure provides a compound of Formula (III), a stereoisomer, a pharmaceutically acceptable salt, or a deuterated compound thereof:



Formula (III)

wherein:

each of X, Z_4 and Z_6 is independently selected from the group consisting of N and CH;

R_n is C_{3-8} cycloalkyl.

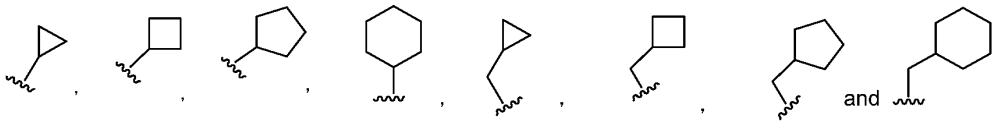
Q_2 is selected from the group consisting of 3- to 12-membered heterocyclic, and 5- to 10-membered heteroaryl, wherein 3- to 12-membered heterocyclic, or 5- to 10-membered heteroaryl is optionally substituted by 1-3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and -$NR^{Qa}R^{Qb}$, wherein two C_{1-6} alkyl groups optionally together with the carbon atoms to which they are attached form C_{3-8} carbocyclic ring ; wherein R^{Qa} and R^{Qb} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl and (C_{1-6} alkyl) carbonyl;

R_{z3} is selected from the group consisting of C_3-C_8 cycloalkyl and C_1-C_6 alkyl-C_3-C_8 cycloalkyl.

In some embodiments, in the compound of Formula (III), othe stereoisomer, the

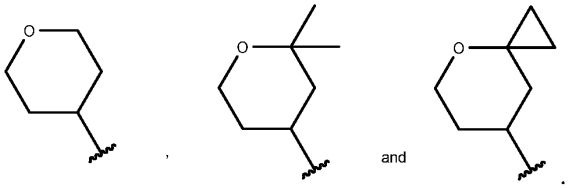
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pharmaceutically acceptable salt or the deuterated compound thereof, R_{Z3} is selected from the group consisting of



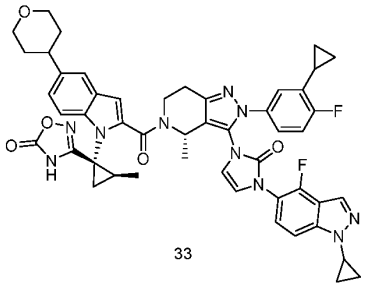
;

Q_2 is selected from the group consisting of

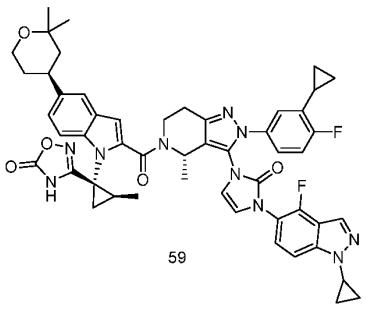


In some embodiments, in the compound of Formula (III), the stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof, the compound is selected from:

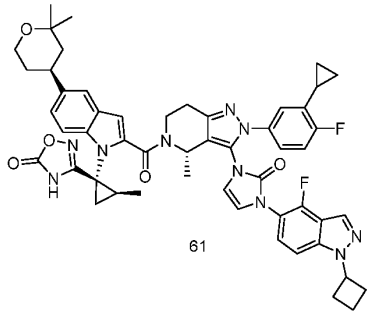
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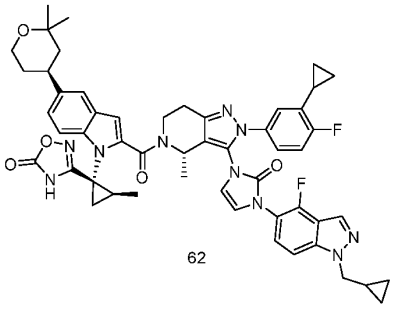
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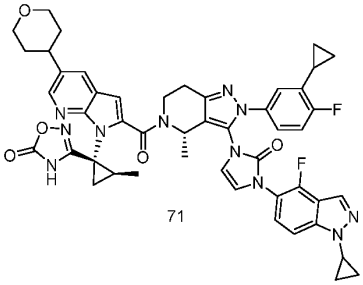
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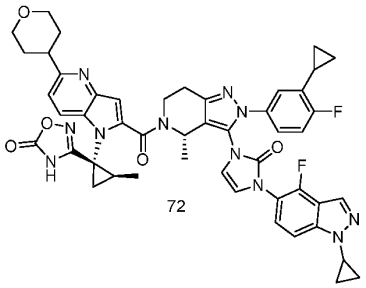
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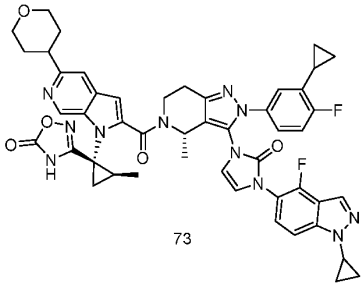
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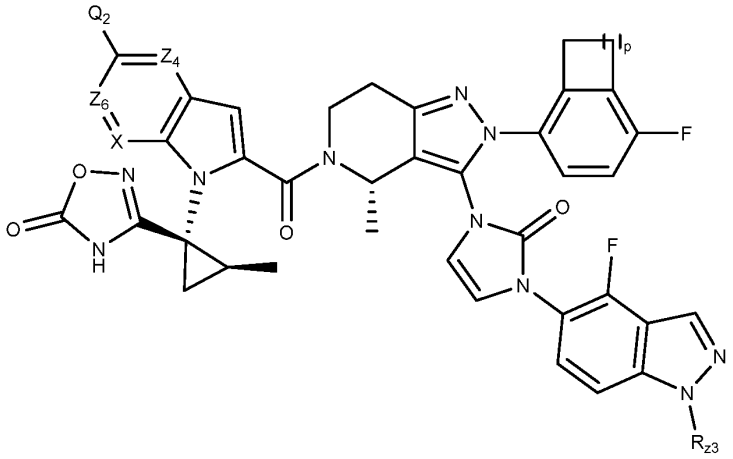


73

and

Yet still another aspect of the present disclosure provides a compound of Formula (IV), a stereoisomer, a pharmaceutically acceptable salt, or a deuterated compound thereof:

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Formula (IV)

wherein:

each of X, Z_4 and Z_6 is independently selected from the group consisting of N and CH;

p is 0, 1, 2, or 3;

R_{Z3} is selected from the group consisting of C_{1-6} alkyl, C_3-C_8 cycloalkyl and C_1-C_6 alkyl-C_3-C_8 cycloalkyl; R_{Z3} is optionally substituted with substituents independently selected from the group consisting of halogen, hydroxyl, C_{1-6} alkyl and C_{1-6} alkoxy.

Q_2 is selected from the group consisting of 3- to 12-membered heterocyclic, and 5- to 10-membered heteroaryl, wherein 3- to 12-membered heterocyclic, or 5- to 10-membered heteroaryl is optionally substituted by 1-3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and $-NR^{Qa}R^{Qb}$, wherein two C_{1-6} alkyl groups optionally together with the carbon atoms to which they are attached form C_{3-8} carbocyclic ring ; wherein R^{Qa} and R^{Qb} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl and (C_{1-6} alkyl) carbonyl..

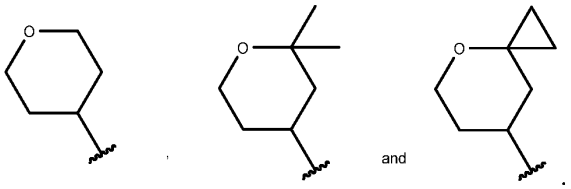
In some embodiments, in the compound of Formula (IV), the stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof, R_{Z3} is selected from the group consisting of



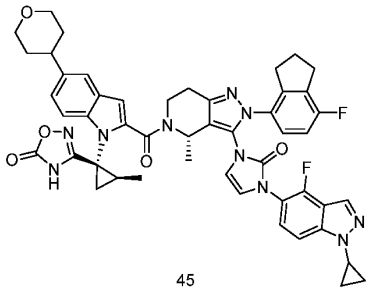
;

Q_2 is selected from the group consisting of

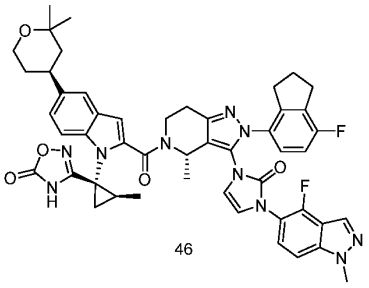
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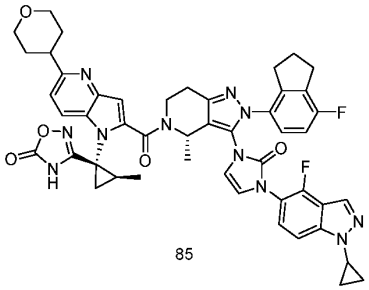
In some embodiments, in the compound of Formula (IV), the stereoisomer, the pharmaceutically acceptable salt or the deuterated compound thereof, the compound is selected from the group consisting of:



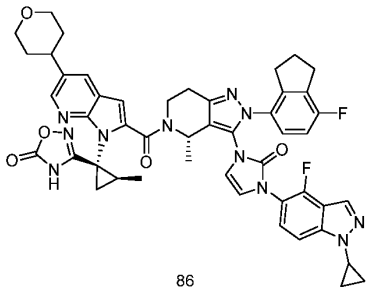
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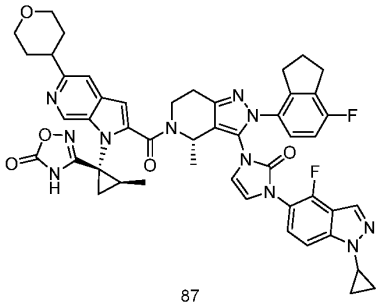


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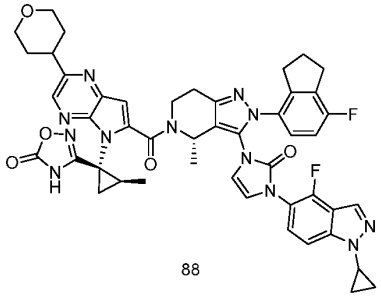


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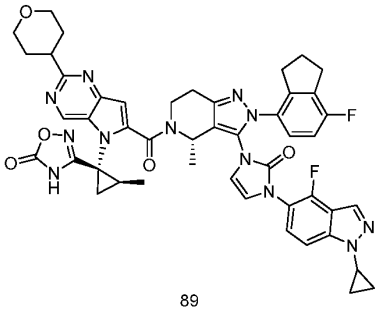
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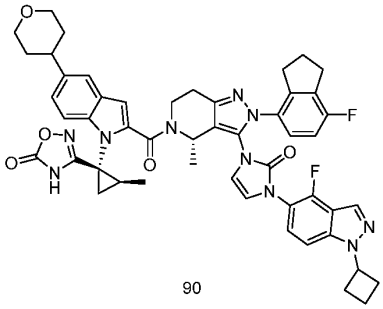
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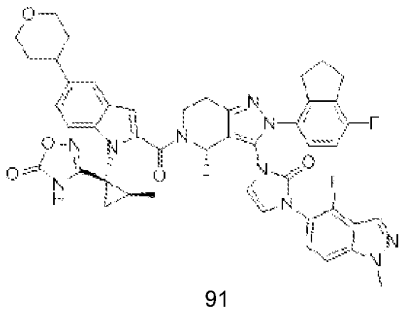
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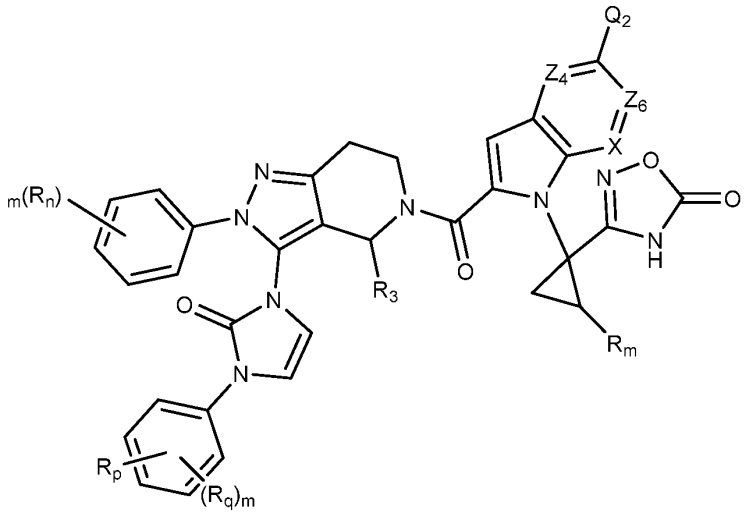
90



and 91 .

Yet still another aspect of the present disclosure provides a compound of Formula (V), a stereoisomer, a pharmaceutically acceptable salt, or a deuterated compound thereof:

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Formula (V)

wherein:

each of X, Z_4 and Z_6 is independently selected from the group consisting of N and CH;

m is 0, 1, 2 or 3;

R_p is selected from the group consisting of $-CH_2-P(=O)R^{zm}R^{zn}$ and $-P(=O)OR^{zm}OR^{zn}$;

R_q is selected from the group consisting of halogen, -NH-C_{1-6} alkyl, C_{1-6} alkyl, -O- C_{1-6} alkyl, 3- to 12-membered heterocyclyl, C_3-C_{15} cycloalkyl and C_1-C_6 alkyl-C_3-C_{15} cycloalkyl;

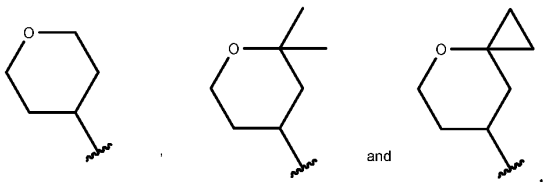
wherein each of R^{zm} and R^{zn} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl and C_{6-10} aryl; or R^{zm} and R^{zn} together with the phosphorous atom to which they are attached form 5- to 8- membered heterocycloalkyl, wherein the heterocycloalkyl is optionally substituted with 1-3 C_{1-6} alkly;

R_m is selected from the group consisting of H and C_{1-6} alkyl, the C_{1-6} alkyl is optionally substituted with halogen;

R_n is selected from the group consisting of halogen and C_{3-8} cycloalkyl;

R_3 is selected from the group consisting of H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl and C_{1-6} alkoxy;

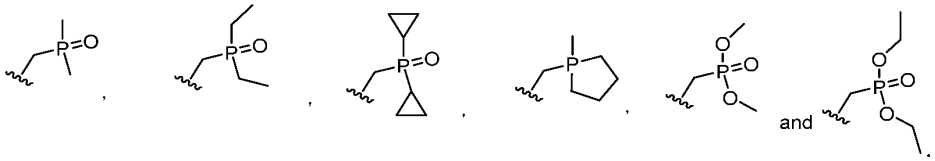
Q_2 is selected from the group consisting of



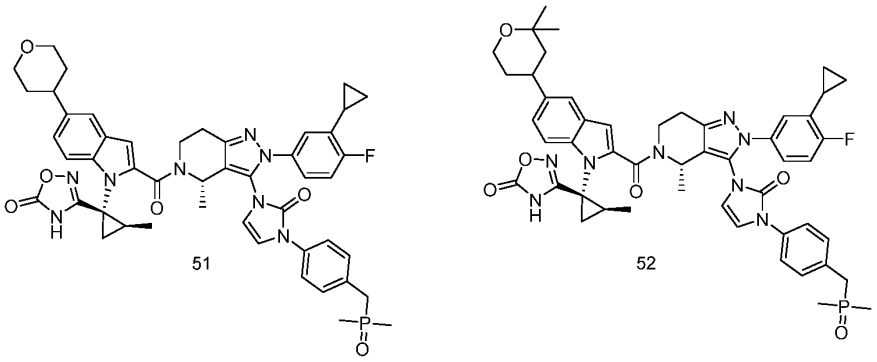
In some embodiments, in the compound of Formula (V), the stereoisomer, the

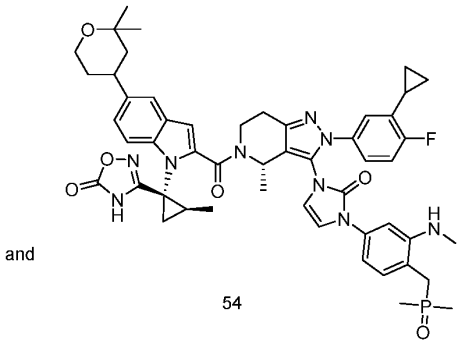
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pharmaceutically acceptable salt or the deuterated compound thereof, R_p is selected from the group consisting of



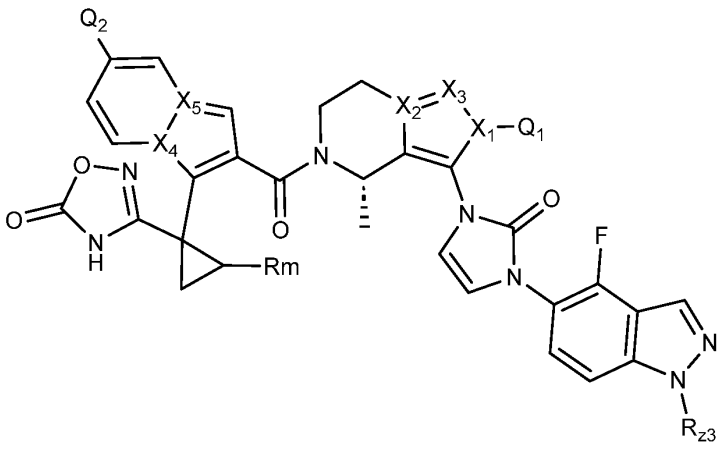
In some embodiments, the compound of Formula (V), the stereoisomer, the pharmaceutically acceptable salt or the deuterated compound thereof, the compound is selected from the group consisting of:





Yet still another aspect of the present disclosure provides a compound of Formula (VI), a stereoisomer, a pharmaceutically acceptable salt, or a deuterated compound thereof:

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Formula (VI)

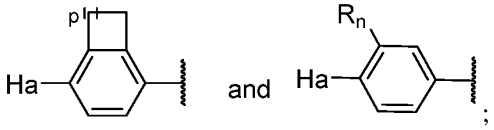
wherein:

X_1, X_2, and X_3 are independently selected from the group consisting of N and C;

X_4, and X_5 are independently selected from the group consisting of N and C;

R_m is selected from the group consisting of H and C_{1-6} alkyl, the C_{1-6} alkyl is optionally substituted with halogen;

Q_1 is selected from the group consisting of

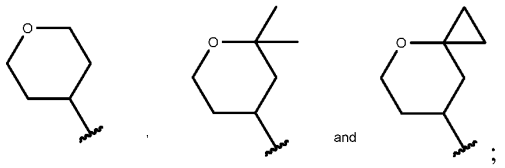


p is 0, 1, 2 and 3;

R_n is C_{3-8} cycloalkyl;

Ha is selected from the group consisting of F, Cl, Br and I;

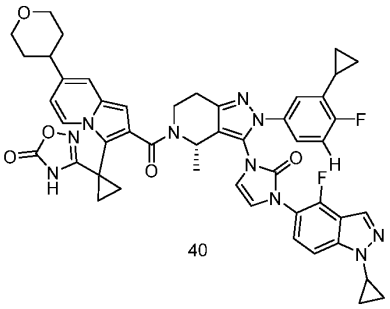
Q_2 is selected from the group consisting of



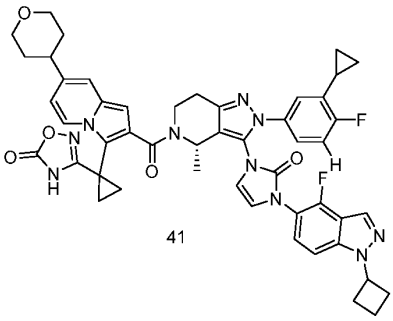
R_{z3} is selected from the group consisting of C_3-C_{15} cycloalkyl and C_1-C_6 alkyl-C_3-C_{15} cycloalkyl.

In some embodiments, in the compound of Formula (VI), the stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof, the compound is selected from the group consisting of

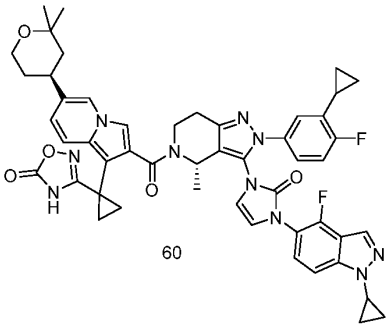
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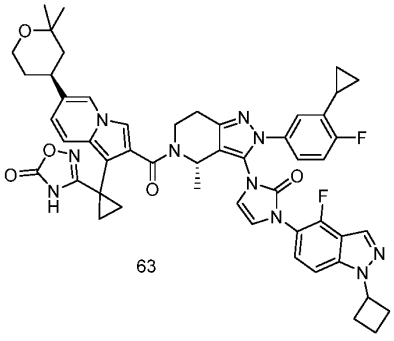
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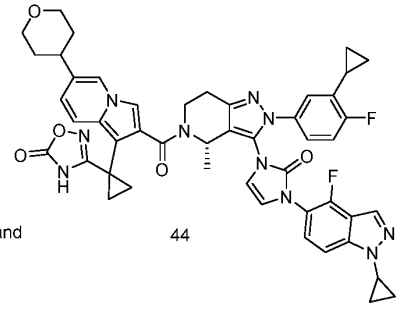
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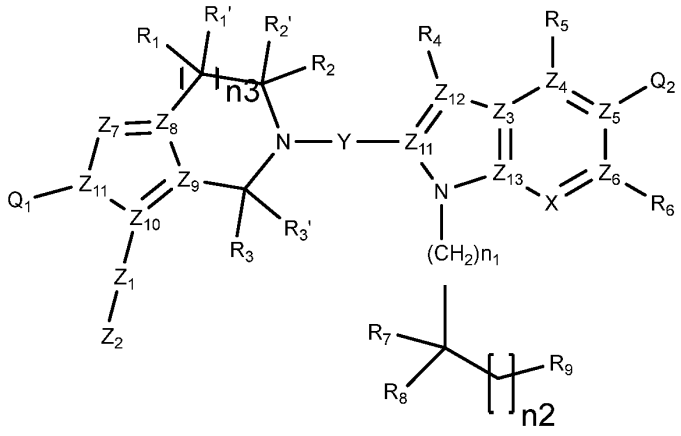


63



and 44

Yet still another aspect of the present disclosure provides a compound of Formula (Ia), a stereoisomer, a pharmaceutically acceptable salt, or a deuterated compound thereof:



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Formula (Ia)

wherein:

X is selected from the group consisting of N and -CR^a; wherein R^a is selected from the group consisting of hydrogen, halogen and C_{1-6} alkyl;

wherein Y is -C(=O)-;

wherein each of Z_3, Z_4, Z_5, Z_6, Z_7, Z_8, Z_9, Z_{10}, Z_{11}, Z_{12} and Z_{13} is independently selected from the group consisting of N and C;

wherein Q_1 is selected from the group consisting of C_{6-10} aryl and C_{5-10} heteroaryl, wherein C_{6-10} aryl or C_{5-10} heteroaryl is optionally substituted by one to five substituents independently selected from the group consisting of halogen and C_{3-8} cycloalkyl;

wherein Q_2 is selected from the group consisting of 3- to 12-membered heterocyclic, bridged, spiro and 5- to 10-membered heteroaryl, wherein 3- to 12-membered heterocyclic, bridged, spiro and 5- to 10-membered heteroaryl are optionally substituted by 1-3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy and -$NR^{Qa}R^{Qb}$, wherein two C_{1-6} alkyl groups together with the carbon atoms to which they are attached form C_{3-8} carbocyclic ring; wherein R^{Qa} and R^{Qb} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl and (C_{1-6} alkyl) carbonyl;

wherein each of R_1, R_2, R_3, R_1', R_2' and R_3' is independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cycloalkyl and heterocycloalkyl; wherein C_{1-6} alkyl, cycloalkyl or heterocycloalkyl is optionally substituted by one or more substituents independently selected from the group consisting of halogen, C_{1-6} alkoxy and hydroxyl;

wherein R_2 and R_3 together with the carbon atom to which they are attached form 4- to 8-membered heterocyclic alkyl;

wherein R_1 and R_1' optionally together with the carbon atom to which they are attached form C_{3-8} cycloalkyl, and R_2 and R_2' optionally together with the carbon atom to which they are attached form C_{3-8} cycloalkyl ; and R_3 and R_3' optionally together with the carbon atom to which they are attached form C_{3-8} cycloalkyl;

each of R_4, R_5 and R_6 is independently selected from the group consisting of hydrogen, halogen and C_{1-6} alkyl;

each of R_7 and R_8 is independently selected from the group consisting of hydrogen and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen and C_{3-15} cycloalkyl;

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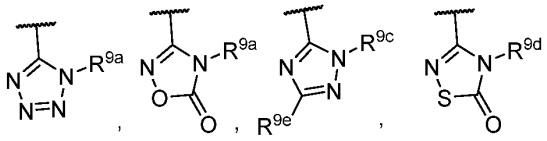
or R_7 and R_8 together with the carbon atom to which they are attached form C_{3-15} carbocyclic ring, wherein the C_{3-15} carbocyclic ring is optionally substituted by one to three C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from halogen, hydroxyl, $-NR^{7a}R^{7b}$, C_{1-6} alkoxy and 3- to 12-membered heterocyclic, and R^{7a} and R^{7b} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl groups and (C_{1-6} alkyl) carbonyl; and any two C_{1-6} alkyl groups optionally form C_{3-15} carbon ring together with the carbon atom to which they are attached;

n_1 is 0, 1, 2 or 3;

n2 is 0, 1, 2, 3, 4 or 5;

n3 is 0, 1 or 2;

R_9 is selected from the group consisting of:



, $-CO_2R^{9f}$ and $-C(=O)-NR^{9g}R^{9h}$; and

each of R^{9a}, R^{9b}, R^{9c}, R^{9d} and R^{9g} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl, wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen and C_{1-6} alkoxy;

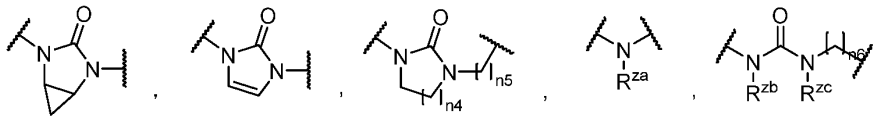
R^{9e} is selected from the group consisting of hydrogen and C_{1-6} alkyl optionally substituted by one or more halogen;

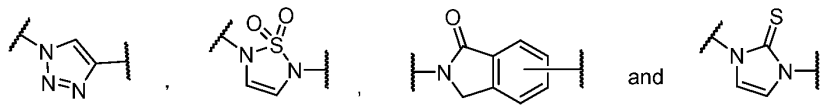
R^{9f} is selected from the group consisting of hydrogen and C_{1-6} alkyl;

R^{9h} is selected from the group consisting of hydrogen, C_{1-6} alkyl, (C_{1-6} alkyl) carbonyl, cyano and $-S(=O)_{n9}-R^{9i}$; n9 is 0, 1, or 2;

R^{9i} is C_{1-6} alkyl;

Z_1 is selected from the group consisting of:





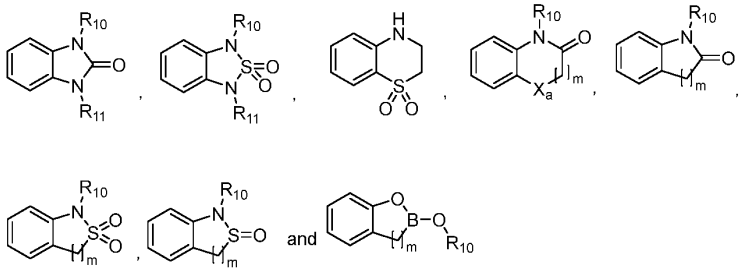
wherein R^{za} is selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl)

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carbonyl, and each of R^{zb} and R^{zc} is independently selected from the group consisting of hydrogen and C_{1-6} alkyl;

n4 is 1, 2 or 3; each of n5 and n6 is independently integers from 0 to 10;

Z_2 is selected from the group consisting of C_{1-6} alkyl, C_{3-15} cycloalkyl, 3 to 12-membered heterocyclic, C_{6-10} aryl, 5 to 10-membered heteroaryl,



;

wherein Z_2 is independently optionally substituted with one to five G's; and m is 1, 2, 3;

wherein each of R_{11} and R_{10} is independently selected from the group consisting of H, C_{1-6} alkyl, (C_{1-6} alkyl) aryl, C_{1-6} haloalkyl, C_3-C_{15} cycloalkyl and C_1-C_6 alkyl-C_3-C_{15} cycloalkyl;

wherein G' is selected from the group consisting of:

a. oxo;

b. halogen;

c. cyano;

d. $-NR^{zd}R^{ze}$; wherein R^{zd} and R^{ze} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl; wherein C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from the group consisting of hydroxyl, halogen and C_{1-6} alkoxy;

e. $-C(=O)-NR^{zf}R^{zg}$; wherein R^{zf} and R^{zg} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl; wherein C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from the group consisting of hydroxyl, halogen and C_{1-6} alkoxy;

f. $-S(=O)_{n7}-R^{zh}$; wherein n7 is 0, 1 or 2; R^{zh} is selected from the group consisting of hydrogen and C_{1-6} alkyl;

g. C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, $-NR^{zi}R^{zj}$, C_{1-6} alkoxy, C_{1-6} alkoxy and 3- to 12-membered heterocyclic groups; wherein each of R^{zi} and R^{zj} is independently selected from the group consisting of hydrogen and C_{1-6} alkyl, wherein the 3-

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to 12-membered heterocyclic groups are optionally substituted with one or more substituents selected from the group consisting of cyano, C_{1-6} alkyl and 3 to 12-membered heterocyclic;

h. C_{1-6} alkoxy; wherein C_{1-6} alkoxy is optionally substituted by one or more substituents of hydroxyl, halogen and C_{1-6} alkoxy;

i. 3 to 12-membered heterocyclic; wherein 3 to 12-membered heterocyclic is optionally substituted by one or more substituents independently selected from C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl;

j. C_{6-10} aryl; wherein C_{6-10} aryl is optionally substituted by one or more (C_{1-6} alkyl) carbonyl;

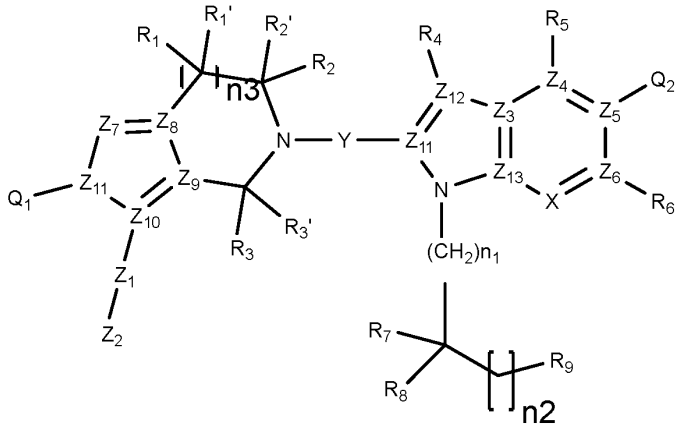
k. 5- to 10-membered heteroaryl; wherein the 5- to 10-membered heteroaryl is optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^{zk}R^{zl}$, and 3- to 12-membered heterocyclic; wherein R^{zk} and R^{zl} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and (C_{1-6} alkyl)carbonyl and wherein the 3- to 12-membered heterocyclic is optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6} alkyl, and C_{1-6} alkoxy;

l. $-C_3$-C_{15} cycloalkyl or $-C_1$-C_6 alkyl-C_3-C_{15} cycloalkyl; wherein $-C_3$-C_{15} cycloalkyl or $-C_1$-C_6 alkyl-C_3-C_{15} cycloalkyl is optionally substituted by one or more substituents independently selected from the group consisting of halogen, oxo, C_{1-6} alkyl, C_{1-6} alkoxy and (C_{1-6} alkyl) carbonyl, wherein each of C_{1-6} alkyl, C_{1-6} alkoxy and (C_{1-6} alkyl) carbonyl is optionally substituted by halogen; and

m. $-P(=O)R^{zm}R^{zn}$, $-(CH_2)_{n8}$-$P(=O)R^{zm}R^{zn}$, $NR^{zm}S(=O)R^{zn}$ and $NR^{zm}S(=O)_2R^{zn}$, wherein R^{zm} and R^{zn} are independently selected from the group consisting of H, C_{1-6} alkyl and C_{6-10} aryl, n8 is 1 or 2;wherein C_{1-6} alkyl is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo; wherein C_{3-6} cycloalkyl is optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo; wherein C_{6-10} aryl is optionally substituted with 1-3 independently selected from C_{1-3} alkyl; or R^{zm} and R^{zn} taken together with the phosphorous atom to which each is attached form a ring including from 5-8 ring atoms, wherein 0-2 ring atoms (in addition to the phosphorous attached to R^{zm} and R^{zn}) are heteroatoms each independently selected from the group consisting of: O, S, and N, wherein the ring is optionally substituted with 1-3 independently selected from C_{1-6} alkyl.

Yet still another aspect of the present disclosure provides a compound of Formula (Ib), a stereoisomer, a pharmaceutically acceptable salt, or a deuterated compound thereof:

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Formula (Ib)

wherein:

X is selected from the group consisting of N and -CR^a; wherein R^a is selected from the group consisting of hydrogen, halogen and C_{1-6} alkyl;

Y is -C(=O)-;

each of Z_3, Z_4, Z_5, Z_6, Z_7, Z_8, Z_9, Z_{10}, Z_{11}, Z_{12} and Z_{13} is independently selected from the group consisting of N and C;

Q_1 is selected from the group consisting of C_{6-10} aryl and C_{5-10} heteroaryl, wherein C_{6-10} aryl or C_{5-10} heteroaryl is optionally substituted by one to five substituents independently selected from the group consisting of halogen and C_{3-8} cycloalkyl;

Q_2 is selected from the group consisting of 3- to 12-membered heterocyclic, bridged, spiro and 5- to 10-membered heteroaryl, wherein 3- to 12-membered heterocyclic, bridged, spiro and 5- to 10-membered heteroaryl are optionally substituted by 1-3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy and -$NR^{Qa}R^{Qb}$, wherein two C_{1-6} alkyl groups together with the carbon atoms to which they are attached form C_{3-8} carbocyclic ring; wherein R^{Qa} and R^{Qb} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl and (C_{1-6} alkyl) carbonyl;

each of R_1, R_2, R_3, R_1', R_2' and R_3' is independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cycloalkyl and heterocycloalkyl; wherein C_{1-6} alkyl, cycloalkyl or heterocycloalkyl is optionally substituted by one or more substituents independently selected from the group consisting of halogen, C_{1-6} alkoxy and hydroxyl;

R_2 and R_3 together with the carbon atom to which they are attached form 4- to 8-membered heterocyclic alkyl;

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R_1 and R_1' optionally together with the carbon atom to which they are attached form C_{3-8} cycloalkyl, and R_2 and R_2' optionally together with the carbon atom to which they are attached form C_{3-8} cycloalkyl ; and R_3 and R_3' optionally together with the carbon atom to which they are attached form C_{3-8} cycloalkyl;

each of R_4, R_5 and R_6 is independently selected from the group consisting of hydrogen, halogen and C_{1-6} alkyl;

each of R_7 and R_8 is independently selected from the group consisting of hydrogen and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen and C_{3-15} cycloalkyl;

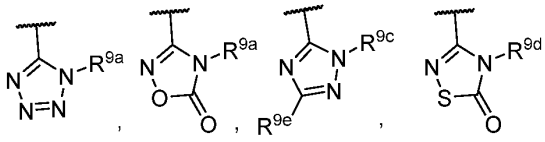
or R_7 and R_8 together with the carbon atom to which they are attached form C_{3-15} carbocyclic ring, wherein the C_{3-15} carbocyclic ring is optionally substituted by one to three C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from halogen, hydroxyl, $-NR^{7a}R^{7b}$, C_{1-6} alkoxy and 3- to 12-membered heterocyclic, and R^{7a} and R^{7b} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl groups and (C_{1-6} alkyl) carbonyl; and any two C_{1-6} alkyl groups optionally form C_{3-15} carbon ring together with the carbon atom to which they are attached;

n1 is 0, 1, 2 or 3;

n2 is 0, 1, 2, 3, 4 or 5;

n3 is 0, 1 or 2;

R_9 is selected from the group consisting of:



, $-CO_2R^{9f}$ and $-C(=O)-NR^{9g}R^{9h}$; and

each of R^{9a}, R^{9b}, R^{9c}, R^{9d} and R^{9g} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl, wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen and C_{1-6} alkoxy;

R^{9e} is selected from the group consisting of hydrogen and C_{1-6} alkyl optionally substituted by one or more halogen atoms;

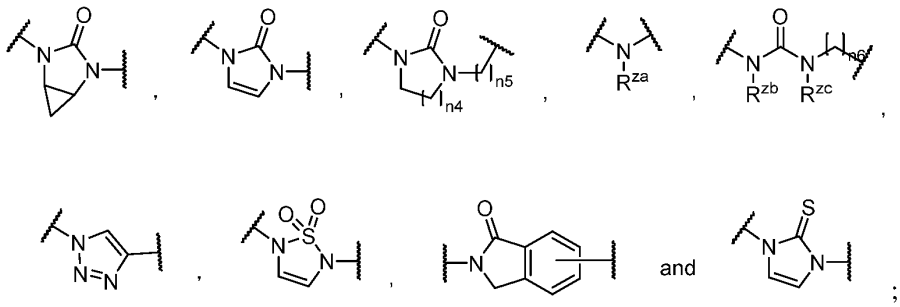
R^{9f} is selected from the group consisting of hydrogen and C_{1-6} alkyl;

R^{9h} is selected from the group consisting of hydrogen, C_{1-6} alkyl, (C_{1-6} alkyl) carbonyl, cyano and $-S(=O)_{n9}-R^{9i}$; n9 is 0, 1, or 2;

R^{9i} is C_{1-6} alkyl;

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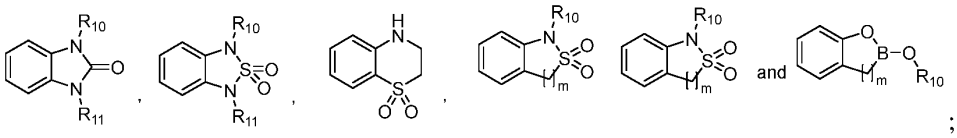
Z_1 is selected from the group consisting of:



wherein R^{za} is selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl, and each of R^{zb} and R^{zc} is independently selected from the group consisting of hydrogen and C_{1-6} alkyl;

n4 is 1, 2 or 3; each of n5 and n6 is independently an integer from 0 to 10;

Z_2 is selected from the group consisting of C_{1-6} alkyl, C_{3-15} cycloalkyl, 3 to 12-membered heterocyclic, C_{6-10} aryl, 5 to 10-membered heteroaryl,



wherein Z_2 is independently optionally substituted with one to five G's; and m is 1, 2, 3;

wherein each of R_{11} and R_{10} is independently selected from the group consisting of H, C_{1-6} alkyl, (C_{1-6} alkyl) aryl, C_{1-6} haloalkyl, C_3-C_{15} cycloalkyl and C_1-C_6 alkyl-C_3-C_{15} cycloalkyl;

wherein G' is selected from the group consisting of:

a. oxo;

b. halogen;

c. cyano;

d. $-NR^{zd}R^{ze}$; wherein R^{zd} and R^{ze} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl; wherein C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from the group consisting of hydroxyl, halogen and C_{1-6} alkoxy;

e. $-C(=O)-NR^{zf}R^{zg}$; wherein R^{zf} and R^{zg} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl; wherein C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from the group consisting of hydroxyl, halogen and C_{1-6} alkoxy;

f. $-S(=O)_{n7}-R^{zh}$; wherein n7 is 0, 1 or 2; R^{zh} is selected from the group consisting of

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hydrogen and C_{1-6} alkyl;

g. C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, $-NR^{zi}R^{zj}$, C_{1-6} alkoxy, C_{1-6} alkoxy and 3- to 12-membered heterocyclic groups; wherein each of R^{zi} and R^{zj} is independently selected from the group consisting of hydrogen and C_{1-6} alkyl, wherein the 3- to 12-membered heterocyclic groups are optionally substituted with one or more substituents selected from the group consisting of cyano, C_{1-6} alkyl and 3 to 12-membered heterocyclic;

h. C_{1-6} alkoxy; wherein C_{1-6} alkoxy is optionally substituted by one or more substituents of hydroxyl, halogen and C_{1-6} alkoxy;

i. 3 to 12-membered heterocyclic; wherein 3 to 12-membered heterocyclic is optionally substituted by one or more substituents independently selected from C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl;

j. C_{6-10} aryl; wherein C_{6-10} aryl is optionally substituted by one or more (C_{1-6} alkyl) carbonyl;

k. 5- to 10-membered heteroaryl; wherein the 5- to 10-membered heteroaryl is optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, $-NR^{zk}R^{zl}$, and 3- to 12-membered heterocyclic; wherein R^{zk} and R^{zl} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and (C_{1-6} alkyl)carbonyl and wherein the 3- to 12-membered heterocyclic is optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6} alkyl, and C_{1-6} alkoxy;

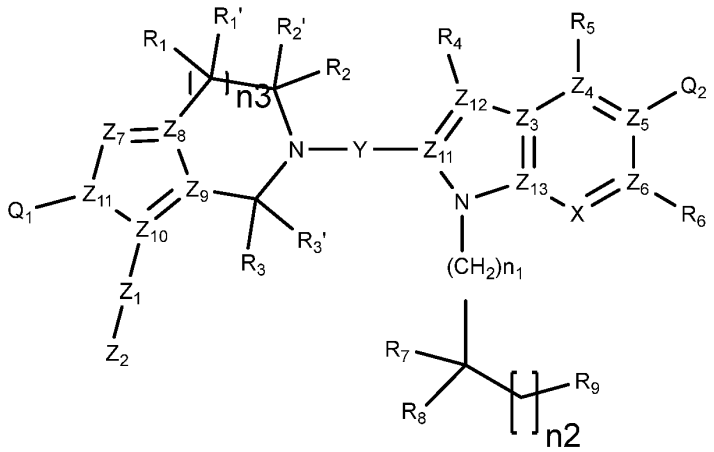
l. $-C_3$-C_{15} cycloalkyl or $-C_1$-C_6 alkyl-C_3-C_{15} cycloalkyl; wherein $-C_3$-C_{15} cycloalkyl or $-C_1$-C_6 alkyl-C_3-C_{15} cycloalkyl is optionally substituted by one or more substituents independently selected from the group consisting of halogen, oxo, C_{1-6} alkyl, C_{1-6} alkoxy and (C_{1-6} alkyl) carbonyl, wherein each of C_{1-6} alkyl, C_{1-6} alkoxy and (C_{1-6} alkyl) carbonyl is optionally substituted by halogen; and

m. $-P(=O)R^{zm}R^{zn}$, $-(CH_2)_{n8}-P(=O)R^{zm}R^{zn}$, $NR^{zm}S(=O)R^{zn}$ and $NR^{zm}S(=O)_2R^{zn}$, wherein R^{zm} and R^{zn} are independently selected from the group consisting of H, C_{1-6} alkyl and C_{6-10} aryl, n8 is 1 or 2;wherein C_{1-6} alkyl is optionally substituted with 1-6 substituents each independently selected from the group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo; wherein C_{3-6} cycloalkyl is optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo; wherein C_{6-10} aryl is optionally substituted with 1-3 independently selected from C_{1-3} alkyl; or R^{zm} and R^{zn} taken together with the phosphorous atom to which each is attached form a ring including from 5-8 ring

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atoms, wherein 0-2 ring atoms (in addition to the phosphorous attached to R^{zm} and R^{zm}) are heteroatoms each independently selected from the group consisting of: O, S, and N, wherein the ring is optionally substituted with 1-3 independently selected from C_{1-6} alkyl.

Yet still another aspect of the present disclosure provides a compound of Formula (Ic), a stereoisomer, a pharmaceutically acceptable salt, or a deuterated compound thereof:



Formula (Ic)

wherein:

X is selected from the group consisting of N and -CR^a; wherein R^a is selected from the group consisting of hydrogen, halogen and C_{1-6} alkyl;

Y is -C(=O)-;

each of Z_3, Z_4, Z_5, Z_6, Z_7, Z_8, Z_9, Z_{10}, Z_{11}, Z_{12} and Z_{13} is independently selected from the group consisting of N and C;

Q_1 is selected from the group consisting of C_{6-10} aryl and C_{5-10} heteroaryl, wherein C_{6-10} aryl or C_{5-10} heteroaryl is optionally substituted by one to five substituents independently selected from the group consisting of halogen and C_{3-8} cycloalkyl;

Q_2 is selected from the group consisting of 3- to 12-membered heterocyclic, bridged, spiro and 5- to 10-membered heteroaryl, wherein 3- to 12-membered heterocyclic, bridged, spiro and 5- to 10-membered heteroaryl are optionally substituted by 1-3 substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy and -$NR^{Qa}R^{Qb}$, wherein two C_{1-6} alkyl groups together with the carbon atoms to which they are attached form C_{3-8} carbocyclic ring; wherein R^{Qa} and R^{Qb} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl and (C_{1-6} alkyl) carbonyl;

each of R_1, R_2, R_3, R_1', R_2' and R_3' is independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cycloalkyl and

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heterocycloalkyl; wherein C_{1-6} alkyl, cycloalkyl or heterocycloalkyl is optionally substituted by one or more substituents independently selected from the group consisting of halogen, C_{1-6} alkoxy and hydroxyl;

R_2 and R_3 together with the carbon atom to which they are attached form 4- to 8-membered heterocyclic alkyl;

R_1 and R_1' optionally together with the carbon atom to which they are attached form C_{3-8} cycloalkyl, and R_2 and R_2' optionally together with the carbon atom to which they are attached form C_{3-8} cycloalkyl ; and R_3 and R_3' optionally together with the carbon atom to which they are attached form C_{3-8} cycloalkyl;

each of R_4, R_5 and R_6 is independently selected from the group consisting of hydrogen, halogen and C_{1-6} alkyl;

each of R_7 and R_8 is independently selected from the group consisting of hydrogen and C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen and C_{3-15} cycloalkyl;

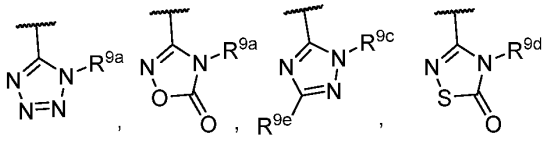
or R_7 and R_8 together with the carbon atom to which they are attached form C_{3-15} carbocyclic ring, wherein the C_{3-15} carbocyclic ring is optionally substituted by one to three C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from halogen, hydroxyl, $-NR^{7a}R^{7b}$, C_{1-6} alkoxy and 3- to 12-membered heterocyclic, and R^{7a} and R^{7b} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl groups and (C_{1-6} alkyl) carbonyl; and any two C_{1-6} alkyl groups optionally form C_{3-15} carbon ring together with the carbon atom to which they are attached;

n1 is 0, 1, 2 or 3;

n2 is 0, 1, 2, 3, 4 or 5;

n3 is 0, 1 or 2;

R_9 is selected from the group consisting of:



, $-CO_2R^{9f}$ and $-C(=O)-NR^{9g}R^{9h}$; and

each of R^{9a}, R^{9b}, R^{9c}, R^{9d} and R^{9g} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl, wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen and C_{1-6} alkoxy;

R^{9e} is selected from the group consisting of hydrogen and C_{1-6} alkyl optionally

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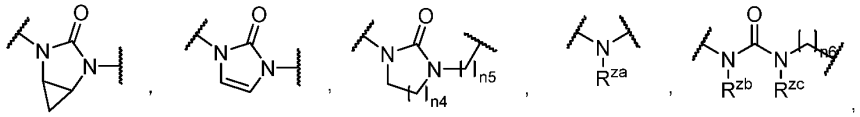
substituted by one or more halogen atoms;

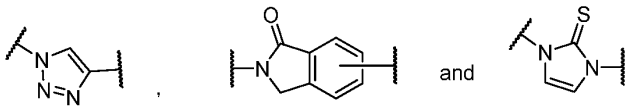
R^{9f} is selected from the group consisting of hydrogen and C_{1-6} alkyl;

R^{9h} is selected from the group consisting of hydrogen, C_{1-6} alkyl, (C_{1-6} alkyl) carbonyl, cyano and $-S(=O)_{n9}-R^{9i}$; n9 is 0, 1, or 2;

R^{9i} is C_{1-6} alkyl;

Z_1 is selected from the group consisting of:

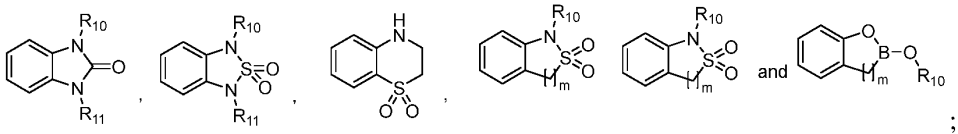




wherein R^{za} is selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl, and each of R^{zb} and R^{zc} is independently selected from the group consisting of hydrogen and C_{1-6} alkyl;

n4 is 1, 2 or 3; each of n5 and n6 is independently integers from 0 to 10;

Z_2 is selected from the group consisting of C_{1-6} alkyl, C_{3-15} cycloalkyl, 3 to 12-membered heterocyclic, C_{6-10} aryl, 5 to 10-membered heteroaryl,



;

wherein Z_2 is independently optionally substituted with one to five G's; and m is 1, 2, 3;

wherein each of R_{11} and R_{10} is independently selected from the group consisting of H, C_{1-6} alkyl, (C_{1-6} alkyl) aryl, C_{1-6} haloalkyl, C_3-C_{15} cycloalkyl and C_1-C_6 alkyl-C_3-C_{15} cycloalkyl;

wherein G' is selected from the group consisting of:

a. oxo;

b. halogen;

c. cyano;

d. $-NR^{zd}R^{ze}$; wherein R^{zd} and R^{ze} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl; wherein C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from the group consisting of hydroxyl, halogen and C_{1-6} alkoxy;

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e. -C(=O)-$NR^{zf}R^{zg}$; wherein R^{zf} and R^{zg} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl; wherein C_{1-6} alkyl is optionally substituted by one or more substituents independently selected from the group consisting of hydroxyl, halogen and C_{1-6} alkoxy;

f. -$S(=O)_{n7}$-R^{zh}; wherein n7 is 0, 1 or 2; R^{zh} is selected from the group consisting of hydrogen and C_{1-6} alkyl;

g. C_{1-6} alkyl; wherein C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, -$NR^{zi}R^{zj}$, C_{1-6} alkoxy, C_{1-6} alkoxy and 3- to 12-membered heterocyclic groups; wherein each of R^{zi} and R^{zj} is independently selected from the group consisting of hydrogen and C_{1-6} alkyl, wherein the 3- to 12-membered heterocyclic groups are optionally substituted with one or more substituents selected from the group consisting of cyano, C_{1-6} alkyl and 3 to 12-membered heterocyclic;

h. C_{1-6} alkoxy; wherein C_{1-6} alkoxy is optionally substituted by one or more substituents of hydroxyl, halogen and C_{1-6} alkoxy;

i. 3 to 12-membered heterocyclic; wherein 3 to 12-membered heterocyclic is optionally substituted by one or more substituents independently selected from C_{1-6} alkyl and (C_{1-6} alkyl) carbonyl;

j. C_{6-10} aryl; wherein C_{6-10} aryl is optionally substituted by one or more (C_{1-6} alkyl) carbonyl;

k. 5- to 10-membered heteroaryl; wherein the 5- to 10-membered heteroaryl is optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, -$NR^{zk}R^{zl}$, and 3- to 12-membered heterocyclic; wherein R^{zk} and R^{zl} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and (C_{1-6} alkyl)carbonyl and wherein the 3- to 12-membered heterocyclic is optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6} alkyl, and C_{1-6} alkoxy;

l. -C_3-C_{15} cycloalkyl or -C_1-C_6 alkyl-C_3-C_{15} cycloalkyl; wherein -C_3-C_{15} cycloalkyl or -C_1-C_6 alkyl-C_3-C_{15} cycloalkyl is optionally substituted by one or more substituents independently selected from the group consisting of halogen, oxo, C_{1-6} alkyl, C_{1-6} alkoxy and (C_{1-6} alkyl) carbonyl, wherein each of C_{1-6} alkyl, C_{1-6} alkoxy and (C_{1-6} alkyl) carbonyl is optionally substituted by halogen; and

m. -$P(=O)R^{zm}R^{zn}$, $NR^{zm}S(=O)R^{zn}$ and $NR^{zm}S(=O)_2R^{zn}$, wherein R^{zm} and R^{zn} are independently selected from the group consisting of H, C_{1-6} alkyl and C_{6-10} aryl;wherein C_{1-6} alkyl is optionally substituted with 1-6 substituents each independently selected from the

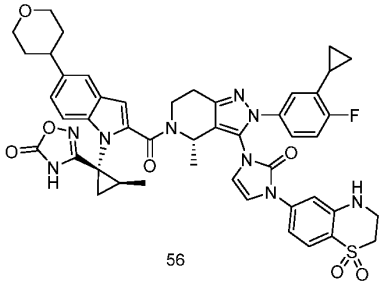
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group consisting of C_{1-6} alkoxy, C_{3-6} cycloalkyl, and halo; wherein C_{3-6} cycloalkyl is optionally substituted with 1-3 substituents each independently selected from the group consisting of C_{1-3} alkyl and halo; wherein C_{6-10} aryl is optionally substituted with 1-3 independently selected from C_{1-3} alkyl; or R^{zm} and R^{zn} taken together with the phosphorous atom to which each is attached form a ring including from 5-8 ring atoms, wherein 0-2 ring atoms (in addition to the phosphorous attached to R^{zm} and R^{zn}) are heteroatoms each independently selected from the group consisting of: O, S, and N, wherein the ring is optionally substituted with 1-3 independently selected from C_{1-6} alkyl.

In some embodiments, in the compound of Formula (Ia), (Ib), or (Ic), the stereoisomer, the pharmaceutically acceptable salt or the deuterated compound thereof, Q_1 is substituted by at least one C_{3-8} cycloalkyl and optionally by one to four halogen.

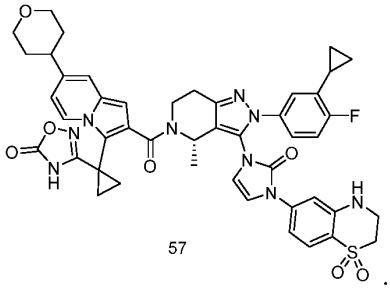
In some embodiments, in the compound of Formula (Ia), (Ib), or (Ic), the stereoisomer, the pharmaceutically acceptable salt or the deuterated compound thereof, Q_1 is optionally substituted with two C1-6 alkyl, wherein the C_{1-6} alkyl together with the carbon atoms, to which they are attached form C_{3-8} carbocyclic ring or 4- to 10- membered heterocyclyl ring.

Yet still another aspect of the present disclosure provides a compound, a stereoisomer, a pharmaceutically acceptable salt, or a deuterated compound thereof, the compound is selected from the group consisting of



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and



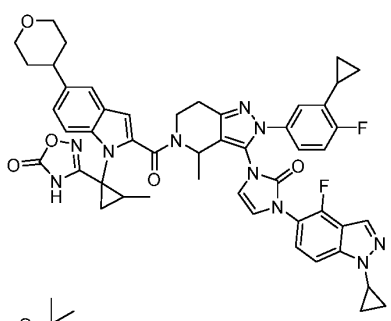
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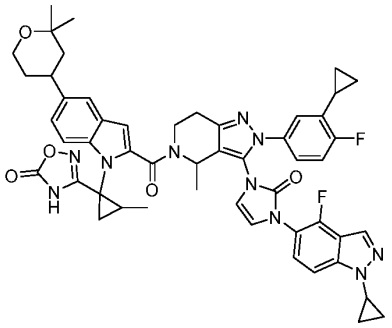
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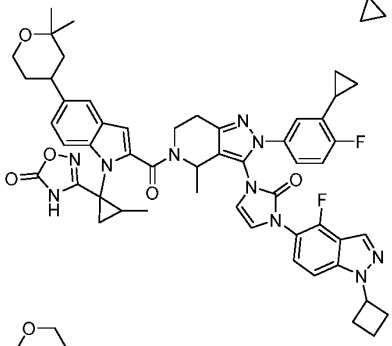
In some embodiments, the pharmaceutically acceptable salt of the present disclosure, selected from the group consisting of, a sodium salt, a calcium salt, a potassium salt, a magnesium salt and a lithium salt.

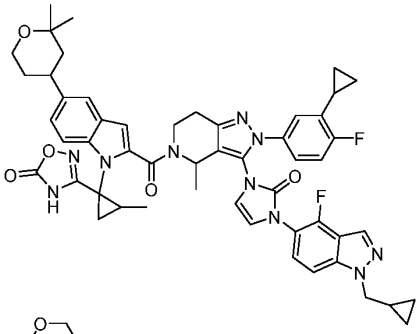
In some embodiments, in the compound the stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof of the present disclosure, the compound is selected from the group consisting of

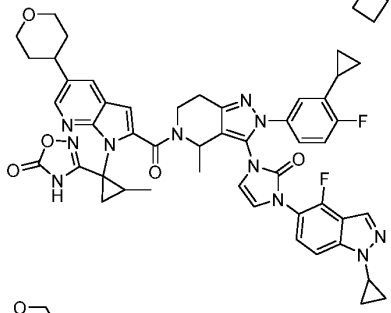
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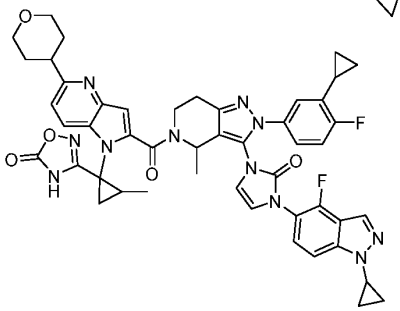


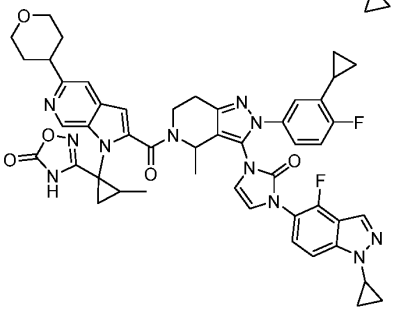




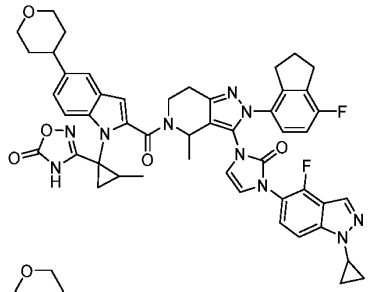


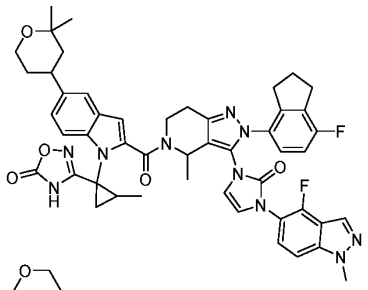


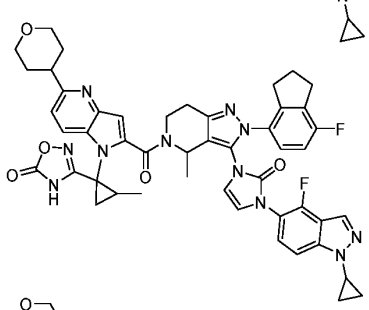


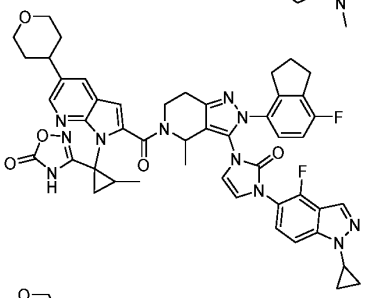


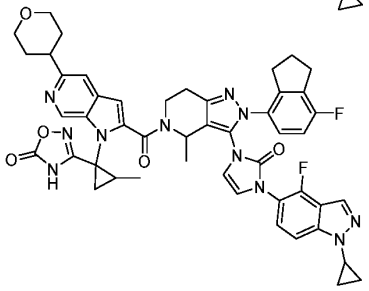
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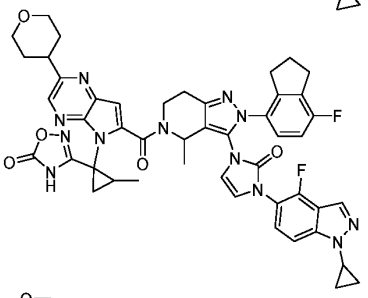


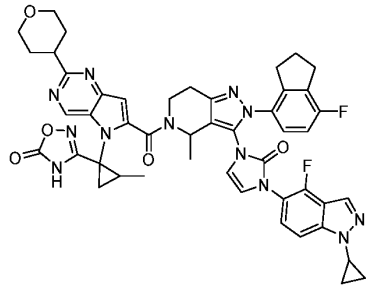


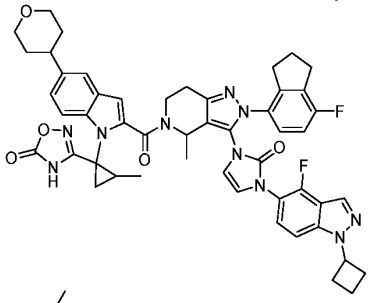


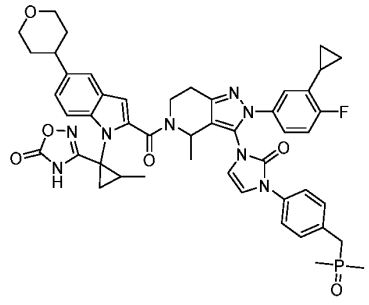


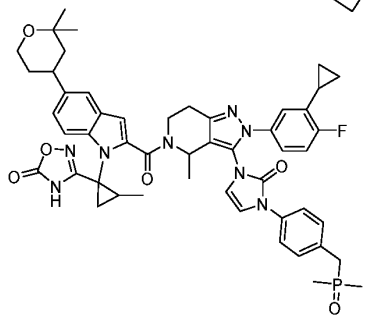




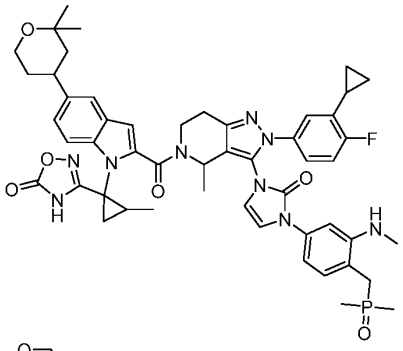


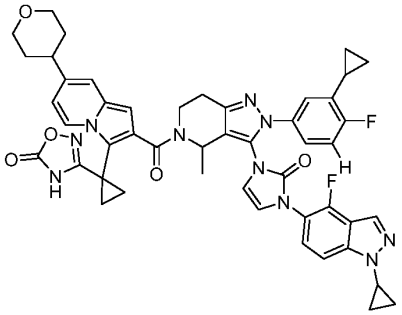


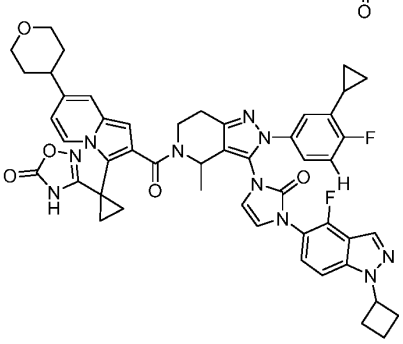


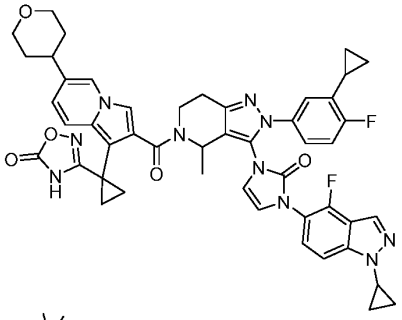


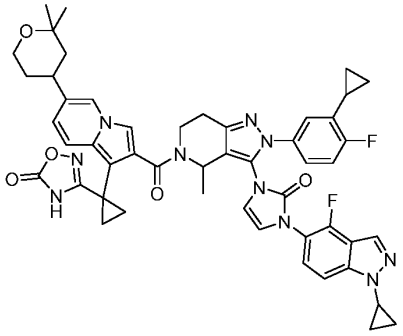
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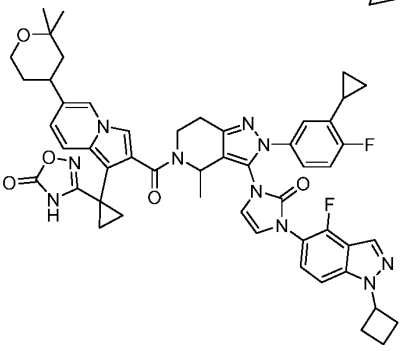






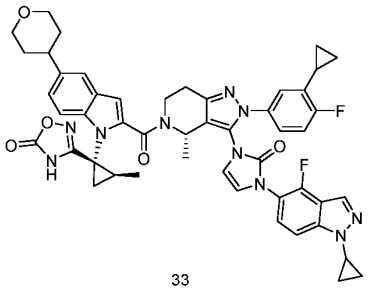


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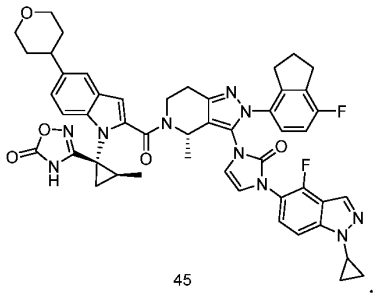


.

Yet still another aspect of the present disclosure provides a compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of



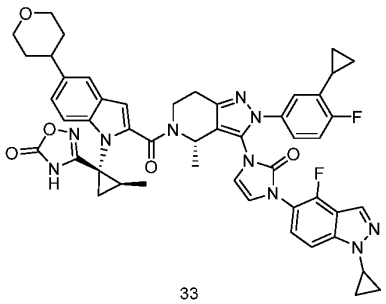
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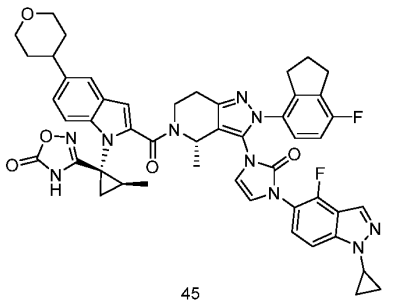
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Yet still another aspect of the present disclosure provides a compound, selected from the group consisting of



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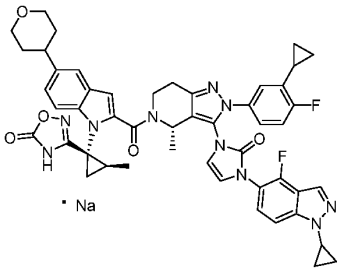
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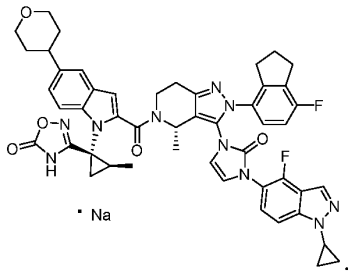
In some embodiments, in the compound or the pharmaceutically acceptable salt thereof of the present disclosure, wherein pharmaceutically acceptable salt is selected from the group consisting of a sodium salt, a calcium salt, a potassium salt, a magnesium salt and a lithium salt.

In some embodiments, the pharmaceutically acceptable salt of the compound of the present disclosure is selected from the group consisting of



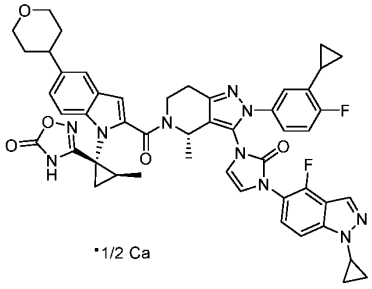
• Na

and



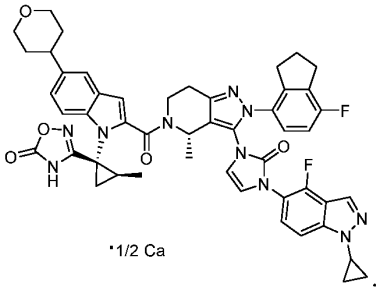
• Na.

In some embodiments, the pharmaceutically acceptable salt of the compound of the present disclosure is selected from the group consisting of



•1/2 Ca

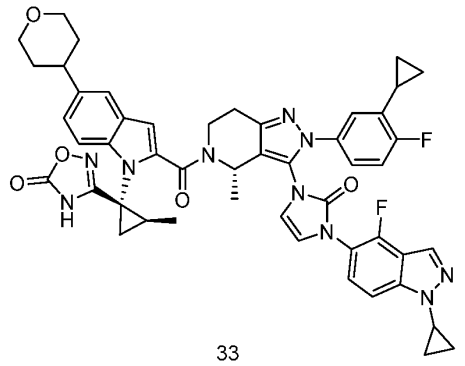
and



•1/2 Ca.

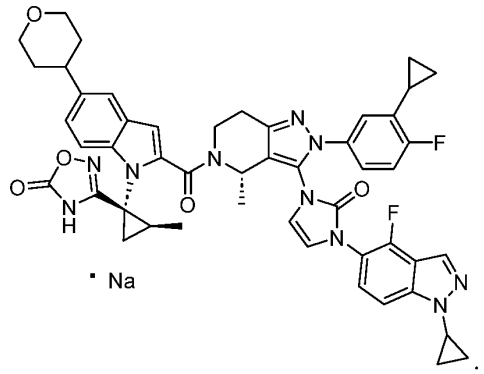
In some embodiments, the compound of the present disclosure is

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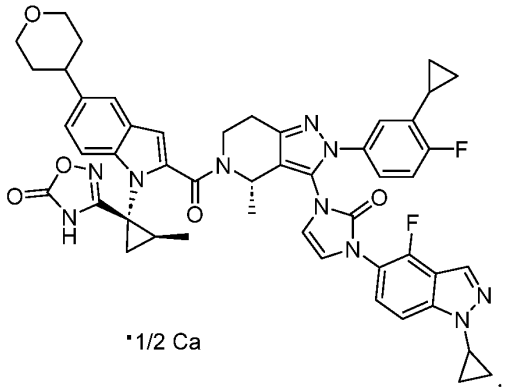
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In some embodiments, the pharmaceutically acceptable salt of the compound of the present disclosure is



· Na

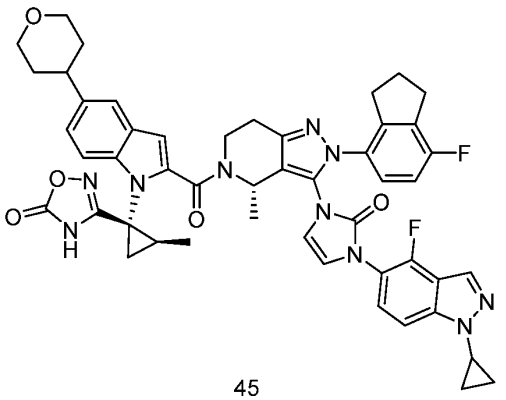
In some embodiments, the pharmaceutically acceptable salt of the compound of the present disclosure is



·1/2 Ca

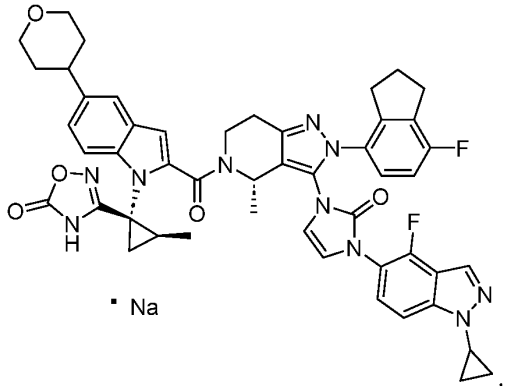
In some embodiments, the compound of the present disclosure is

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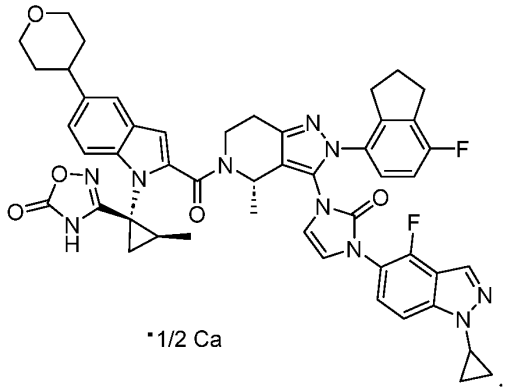
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In some embodiments, the pharmaceutically acceptable salt of the compound of the present disclosure is



· Na

In some embodiments, the pharmaceutically acceptable salt of the compound of the present disclosure is



·1/2 Ca

Pharmaceutical composition

Another aspect of the present disclosure provides a pharmaceutical composition that

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comprise the compound, the stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof of the present disclosure, and a pharmaceutically acceptable excipient.

In some embodiments, the pharmaceutical composition comprising the compound, the stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof of the present disclosure may be prepared with one or more pharmaceutically acceptable excipients, the excipients may be selected in accordance with conventional practice. Tablets may contain excipients, including flow aids, fillers, binders, and the like. Aqueous compositions may be prepared in a sterile form and may generally be isotonic when intended to be delivered by means other than oral administration. In some embodiments, the compositions may comprise excipients, such as those set forth in Rowe et al, Handbook of Pharmaceutical Excipients, 6th edition, American Pharmacists Association, 2009. Excipients may include ascorbic acid and other antioxidants, chelating agents such as ethylenediaminetetraacetic acid, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid, and the like. In some embodiments, the compositions are provided in solid dosage forms, including solid oral dosage forms.

The pharmaceutical composition may be prepared by any of the methods well-known in the art of pharmacy, including oral administration. Such methods include the step of bringing into association the active ingredient (*e.g.*, a compound of the present disclosure or a pharmaceutical salt thereof) with one or more pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical compositions are prepared by uniformly and intimately bringing into association the active ingredient with liquid excipients or finely divided solid excipients or both, and then, if desired, shaping the product. Techniques and formulations generally are found in Remington: The Science and Practice of Pharmacy, 21st Edition, Lippincott Wiliams and Wilkins, Philadelphia, Pa., 2006.

In some embodiments, the pharmaceutical compositions of the present disclosure are presented in unit dosage form, including but not limited to capsules, sachets or tablets each containing a predetermined amount of the active ingredient. In some embodiment, the pharmaceutical composition is a tablet.

The pharmaceutical compositions disclosed herein comprise one or more of the compound, the stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof of the present disclosure, as well as pharmaceutically acceptable excipients and optionally other therapeutic agents. The pharmaceutical compositions containing the active ingredient may be in any form suitable for the intended method of administration.

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When intended for oral use, for example, tablets, lozenges, ingots, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions, and such compositions may contain one or more excipients, including sweeteners, flavoring agents, coloring agents, and preservatives, in order to provide palatable formulations. Tablets containing the active ingredient with a non-toxic pharmaceutically acceptable excipient are acceptable and said excipient is suitable for the production of tablets. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques, including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

The amount of active ingredients that may be combined with the inactive ingredients to produce a dosage form may vary depending upon the intended treatment subject and the mode of administration. For example, in some embodiments, a dosage form for oral administration to humans may contain approximately 1 to 1000 mg of active material formulated with an appropriate and convenient amount of a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutically acceptable excipient varies from about 5% to about 95% of the total compositions (weight: weight).

In some embodiments, the pharmaceutical composition of the present disclosure does not contain an agent that affects the rate at which the active ingredient is metabolized. Thus, it is understood that pharmaceutical compositions comprising a compound of the present disclosure in one aspect do not comprise an agent that would affect (e.g., slow, hinder or retard) the metabolism of a compound of the present disclosure or any other active ingredient administered separately, sequentially or simultaneously with a compound of the present disclosure. It is also understood that any of the methods, kits, articles of manufacture and the like detailed herein in one aspect do not comprise an agent that would affect (e.g., slow, hinder or retard) the metabolism of a compound of the present disclosure or any other active ingredient administered separately, sequentially or simultaneously with a compound of the present disclosure.

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In some embodiments, the above-described pharmaceutical compositions are for use in humans or animals.

The present disclosure also includes the compound of the present disclosure which is administered as a single active ingredient of a pharmaceutically acceptable composition which may be prepared by conventional methods known in the art, for example, by combining the active ingredient to a pharmaceutically acceptable, therapeutically inert organic and/or inorganic carrier or excipient, or by mixing therewith.

The present disclosure provided herein are uses of the compound of the present disclosure as a second or other active ingredient, said second or other active ingredient being synergistic with other active ingredients in known drugs, or the compounds of the present disclosure being administered with such drugs.

The compound of the present disclosure may also be used in the form of a prodrug or other suitably modified form that releases the active ingredient in vivo.

Method of treatment

Another aspect of the present disclosure provides a method for treating a GLP-1R-mediated disease or condition, comprising administering to a subject in need thereof a therapeutically effective amount of the compound, the stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof of the present disclosure, or a pharmaceutical composition of the present disclosure.

In some embodiments, the GLP-1R-mediated disease or condition is selected from the group consisting of T1D (type 1 diabetes), T2DM (type 2 diabetes mellitus), pre-diabetes, idiopathic T1D (idiopathic type 1 diabetes), LADA (latent autoimmune diabetes in adults), EOD (early onset diabetes), YOAD (young onset adult diabetes), MODY (maturity onset diabetes of the young), malnutrition-related diabetes, gestational diabetes, hyperglycemia, insulin resistance, hepatic insulin resistance, impaired glucose tolerance, diabetic neuropathy, diabetic nephropathy, kidney disease, diabetic retinopathy, adipocyte dysfunction, visceral adipose deposition, sleep apnea, obesity, eating disorders, weight gain from use of other agents, excessive sugar craving, dyslipidemia, hyperinsulinemia, NAFLD (non-alcoholic fatty liver disease), NASH, fibrosis, cirrhosis, hepatocellular carcinoma, cardiovascular disease, atherosclerosis, coronary artery disease, peripheral vascular disease, hypertension, endothelial dysfunction, impaired vascular compliance, congestive heart failure, myocardial infarction, stroke, hemorrhagic stroke, ischemic stroke, traumatic brain injury, pulmonary hypertension, restenosis after angioplasty, intermittent claudication, post-prandial lipemia,

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metabolic acidosis, ketosis, arthritis, osteoporosis, parkinson's disease, left ventricular hypertrophy, peripheral arterial disease, macular degeneration, cataract, glomerulosclerosis, chronic renal failure, metabolic syndrome, syndrome X, premenstrual syndrome, angina pectoris, thrombosis, atherosclerosis, transient ischemic attacks, vascular restenosis, impaired glucose metabolism, conditions of impaired fasting plasma glucose, hyperuricemia, gout, erectile dysfunction, skin and connective tissue disorders, psoriasis, foot ulcerations, ulcerative colitis, hyper apo B lipoproteinemia, alzheimer's disease, schizophrenia, impaired cognition, inflammatory bowel disease, short bowel syndrome, crohn's disease, colitis, irritable bowel syndrome, polycystic ovary syndrome and substance addiction.

In some embodiments, the GLP-1R-mediated disease or condition is selected from the group consisting of weight management, chronic weight management, chronic kidney disease, atherosclerotic cardiovascular disease, heart failure, heart failure with reduced ejection fraction; heart failure with preserved ejection fraction; diabetes prevention, obstructive sleep apnea.

The compound of the present disclosure (also referred to herein as the active ingredients) or the pharmaceutical composition of the present disclosure can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intratumoral, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with, for example the condition of the recipient. An advantage of certain compound disclosed herein is that they are orally bioavailable and can be dosed orally.

A compound of the present disclosure may be administered to an individual in accordance with an effective dosing regimen for a desired period of time or duration, such as at least about one month, at least about 2 months, at least about 3 months, at least about 6 months, or at least about 12 months or longer. In one variation, the compound is administered on a daily or intermittent schedule for the duration of the individual's life.

The dosage or dosing frequency of a compound of the present disclosure may be adjusted over the course of the treatment based on the judgment of the administering physician.

The compound may be administered to an individual (e.g., a human) in an effective amount. In some embodiments, the compound is administered once daily.

The compound can be administered by any useful route and means, such as by oral or parenteral (e.g., intravenous) administration. Therapeutically effective amounts of the

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compound may include from about 0. 00001 mg/kg body weight per day to about 10 mg/kg body weight per day, such as from about 0. 0001 mg/kg body weight per day to about 10 mg/kg body weight per day, or such as from about 0. 001 mg/kg body weight per day to about 1 mg/kg body weight per day, or such as from about 0. 01 mg/kg body weight per day to about 1 mg/kg body weight per day, or such as from about 0. 05 mg/kg body weight per day to about 0. 5 mg/kg body weight per day, or such as from about 0. 3 mg to about 30 mg per day, or such as from about 30 mg to about 300 mg per day.

A compound of the present disclosure may be combined with one or more additional therapeutic agents in any dosage amount of the compound of the present disclosure (e.g., from 1 mg to 1000 mg of the compound). Therapeutically effective amounts may include from about 1 mg per dose to about 1000 mg per dose, such as from about 50 mg per dose to about 500 mg per dose, or such as from about 100 mg per dose to about 400 mg per dose, or such as from about 150 mg per dose to about 350 mg per dose, or such as from about 200 mg per dose to about 300 mg per dose. Other therapeutically effective amounts of the compound of the present disclosure are about 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, or about 500 mg per dose. Other therapeutically effective amounts of the compound of the present disclosure are about 100 mg per dose, or about 125, 150, 175, 200, 225, 250, 275, 300, 350, 400, 450, or about 500 mg per dose. A single dose can be administered hourly, daily, or weekly. For example, a single dose can be administered once every 1 hour, 2, 3, 4, 6, 8, 12, 16 or once every 24 hours. A single dose can also be administered once every 1 day, 2, 3, 4, 5, 6, or once every 7 days. A single dose can also be administered once every 1 week, 2, 3, or once every 4 weeks. In some embodiments, a single dose can be administered once every week. A single dose can also be administered once every month.

Kits that comprise the compound, the stereoisomers, the pharmaceutically acceptable salts, or the deuterated compound thereof are also included in the present disclosure.

In some embodiments, a kit further includes a label and/or instructions for the use of the compound in the treatment of the indications, such as the diseases or conditions described herein. In one embodiment, the kit comprises a compound of the present disclosure, or pharmaceutically acceptable salt thereof, in combination with one or more (e.g., one, two, three, four, one or two, or one to three, or one to four) additional therapeutic agents.

EXAMPLES

Example 1 Synthesis

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The compounds of the disclosure may be prepared using methods disclosed herein and routine modifications thereof which will be apparent given the disclosure herein and methods well known in the art. Conventional and well-known synthetic methods may be used in addition to the teachings herein.

The synthesis of typical compounds of Formula (I), (II), (III), (IV), (V), (VI), (Ia), (Ib), and (Ic), or a pharmaceutically acceptable salt thereof, e.g., compounds having structures described by one or more of Formula (I), (II), (III), (IV), (V), (VI), (Ia), (Ib), and (Ic), or other formulas or compounds disclosed herein, may be accomplished as described in the following examples.

General Syntheses

Typical embodiments of compounds in accordance with the present disclosure may be synthesized using the general reaction schemes and/or examples described below. It will be apparent, given the description herein, that the general schemes may be altered by substitution of the starting materials with other materials having similar structures to result in products that are correspondingly different. Descriptions of syntheses follow to provide numerous examples of how the starting materials may vary to provide corresponding products. Starting materials are typically obtained from commercial sources or synthesized using published methods for synthesizing compounds, which are embodiments of the present disclosure, inspection of the structure of the compound to be synthesized will provide the identity of each substituent group. The identity of the final product will generally render apparent the identity of the necessary starting materials by a simple process of inspection, given the examples herein. Group labels (e.g., R1, R2) used in the reaction schemes herein are for illustrative purposes only, and, unless otherwise specified, do not necessarily match by name or function the labels used elsewhere to describe compounds of Formula (I), (II), (III), (IV), (V), (VI), (Ia), (Ib), and (Ic), or aspects or fragments thereof.

Synthetic Reaction Parameters

The compounds of this disclosure can be prepared from readily available starting materials using, for example, the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given; other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting

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groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups, as well as suitable conditions for protecting and deprotecting particular functional groups are well known in the art. For example, numerous protecting groups are described in T. W. Greene and G. M. Wuts (1999) Protecting Groups in Organic Synthesis, 3rd Edition, Wiley, New York, and references cited therein.

Furthermore, the compounds of the present disclosure may contain one or more chiral centers. Accordingly, if desired, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of this disclosure unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents, and the like.

The starting materials for the following reactions are generally known compounds or can be prepared by known procedures or obvious modifications thereof. For example, many of the starting materials are available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA). Others may be prepared by procedures or obvious modifications thereof, described in standard reference texts such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley, and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-5, and Supplemental (Elsevier Science Publishers, 1989) organic Reactions, Volumes 1-40 (John Wiley, and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley, and Sons, 5thEdition, 2001), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

The terms “solvent” or “inert organic solvent” or “inert solvent” refer to a solvent inert under the conditions of the reaction being described in conjunction therewith (including, for example, benzene, toluene, acetonitrile, tetrahydrofuran (“THF”), N, N-dimethylformamide (“DMF”), chloroform, methylene chloride (or dichloromethane), diethyl ether, methanol, pyridine and the like). Unless specified to the contrary, the solvents used in the reactions of the present disclosure are inert organic solvents, and the reactions are carried out under an inert gas, preferably nitrogen.

The term “q.s.” means adding a quantity sufficient to achieve a stated function, e.g., to bring a solution to the desired volume (i.e., 100%).

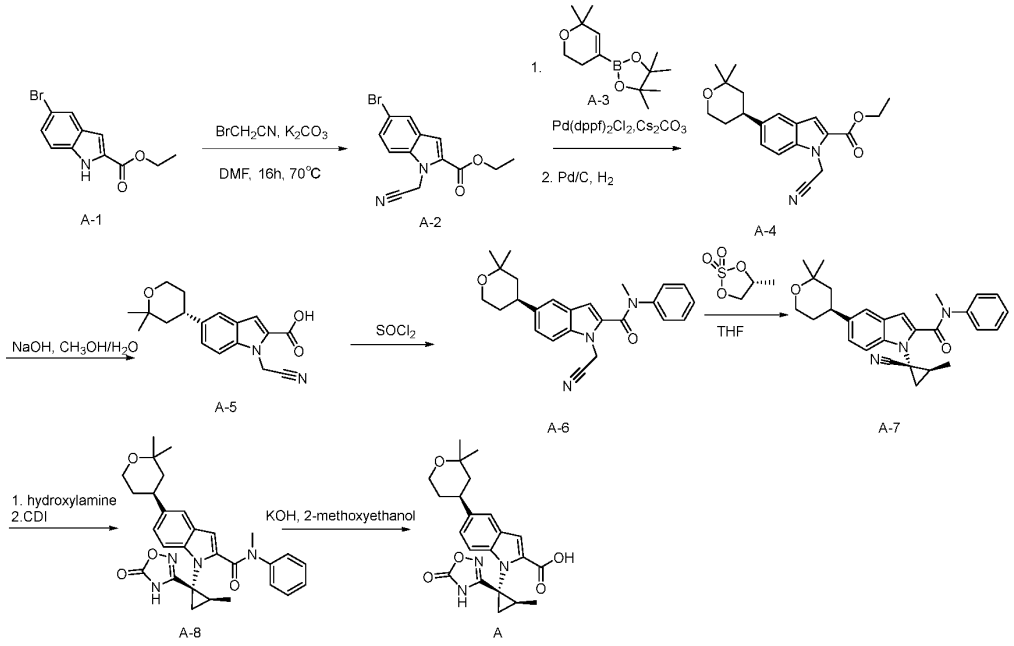
Compounds as provided herein may be synthesized according to the general schemes

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provided below. In the Schemes below, it should be appreciated that each of the compounds shown therein may have protecting groups as required present at any step. Standard protecting groups are well within the pervue of one skilled in the art.

Intermediate preparation:

Preparation of intermediate A



To a solution of **A-1** (5 g, 18.65 mmol), potassium carbonate (5.16 g, 37.3 mmol) and sodium iodide (0.28 g, 1.86 mmol) in DMF (30 mL), was added dropwise bromoacetonitrile (3.36 g, 28.0 mmol). The mixture was heated to 70°C and stirred for 16 hours. Then the mixture was cooled down to room temperature. Water (60 mL) was added into the mixture to get a suspension. The suspension was filtered to obtain a brown solid, 4 g, with a yield of 49.0%.

A suspension of **A-2** (2.0 g, 6.51 mmol), **A-3** (1.71 g, 7.16 mmol), cesium carbonate (3.18 g, 9.77 mmol) and $Pd(dppf)_2Cl_2$ (0.5 g, 0.6 mmol) in dioxane (20 mL) was heated to 100 °C under N_2. The mixture was stirred for 8 hours. The reaction solution was cooled to room temperature, and water (30 mL) and ethyl acetate (30 mL) were added to extract an organic phase. The organic phase was concentrated under vacuum and then purified by column chromatography to obtain 1.2 g of white solid. The solid was dissolved in methanol. Pd/C (0.12 g, 30% wt.) was added into the mixture. The mixture was stirred overnight at room temperature under hydrogen. The mixture was filtered to get a filtrate. The filtrate was

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collected to concentrate to afford a solid. The solid was prepared by chiral Pre-HPLC to obtain **A-4**, 0.6 g, with a yield of 27.3%.

To a solution of **A-4** (0.6 g, 1.76 mmol) in methanol/water (4 mL/2 mL), was added sodium hydroxide (0.28 g, 7.05 mmol) at room temperature. The mixture was stirred for 4 hours. The mixture was adjusted to pH 5.0 with dilute hydrochloric acid. Ethyl acetate (5 mL) was added into the mixture to extract an organic phase. The organic phase was concentrate under vacuum to afford solid **A-5**, 0.53 g, with a yield of 96.3%.

To a solution of **A-5** (300 mg, 1.1 mmol) in dichloromethane (10 mL), was added thionyl dichloride (520 mg, 4.4 mmol) and 1 drop of DMF at room temperature. The mixture was stirred for 6 hours. The mixture was concentrated to obtain an oil. To a solution of oil in dichloromethane (5 mL), was added a solution of *N*- methylaniline (180 mg, 1.65 mmol) and triethylamine (222 mg, 2.2 mmol) in dichloromethane (10 mL) at ice bath. Then warm the mixture to room temperature, and the mixture was stirred for 1 hour. Water (10 mL) was added into the mixture to extract an organic phase. The organic phase was concentrated under vacuum to afford **A-6**, 350 mg, 87.9%.

To a solution of **A-6** (100 mg, 0.25 mmol) and (4R)-4- methyl-1, 3, 2-dioxolane 2, 2-dioxide (103.6 g, 0.75 mmol) in THF (5 mL), was added dropwise lithium bis (trimethylsilylamine) (1 mL, 1M in THF) at -20°C. Then the mixture was warm to room temperature, and stirred for 24 hours. Water (5 mL) was added dropwise into the mixture to quench the reaction. Then ethyl acetate (10 mL) was added into the mixture to extract an organic phase. The organic phase was concentrated under vacuum to obtain an oil. The oil was purified by column chromatography to obtain **A-7**, 40 mg with a yield of 36.4%.

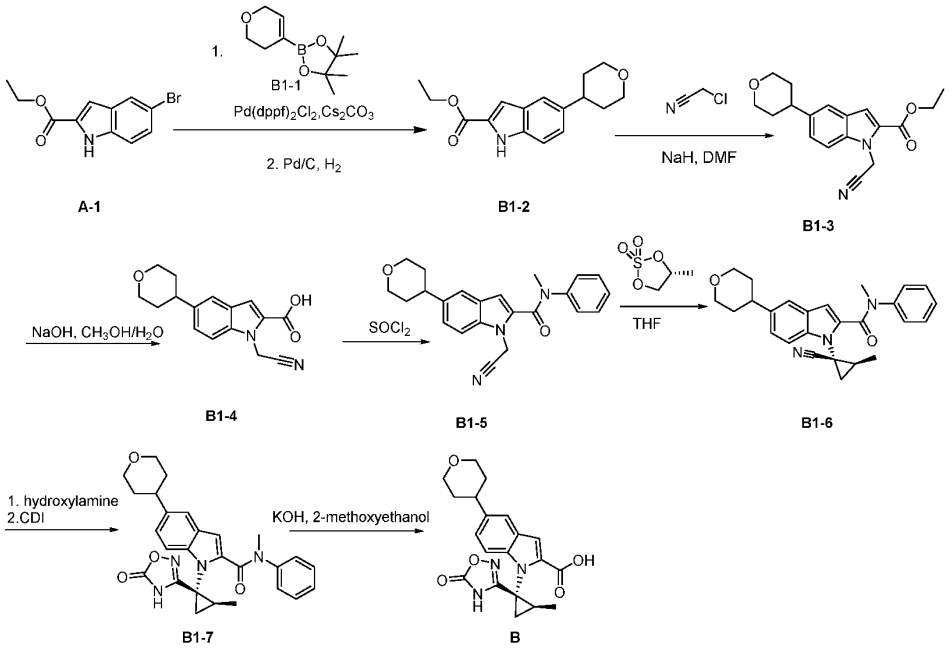
To a solution of **A-7** (10 mg, 0.023 mmol) in DMSO (2 mL), was added hydroxylamine aqueous solution (0.6 mL, 50%) at room temperature. The mixture was stirred for 16 hours. Water (10 mL) and ethyl acetate (10 mL) were added into the mixture for extraction to get an organic phase. The organic phase was concentrated under vacuum to obtain an oil. The oil was dissolved in DMSO (3 mL), followed adding CDI (10 mg, 0.062 mmol) and DBU (10 mg, 0.066 mmol). The mixture was stirred at room temperature for 6 hours. Water (10 mL) and ethyl acetate (10 mL) were added into the mixture to extract to get an organic phase. The organic phase was concentrated under vacuum to obtain **A-8**, 10 mg, with a yield of 88.2%.

To a solution of **A-8** (220 mg, 0.44 mmol) in ethylene glycol methyl ether (3 mL), was added potassium hydroxide (494 mg, 8.8 mmol). The mixture was heated to 130°C and stirred for 5 hours. After cooling down the mixture to room temperature, the mixture was

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adjusted to pH 5.0 with hydrochloric acid (6 N). Ethyl acetate (10 mL) was added into the mixture for extraction to afford an organic phase. The organic phase was dried with anhydrous sodium sulfate, and concentrated under vacuum to obtain intermediate **A**, 180 mg, with a yield of 99.0%.

Preparation of intermediate B



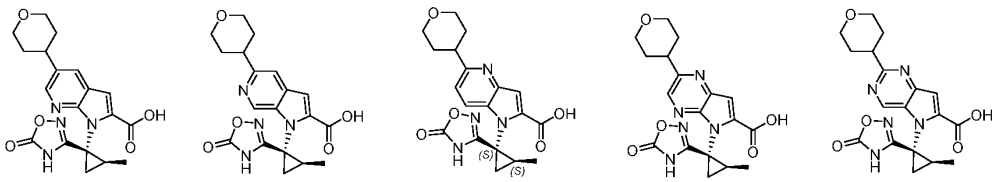
To a solution of **A-1** (120 g, 447.58 mmol) and **B1-1** (103.43 g, 492.34 mmol) in a mixture solution of dioxane (1200 mL) and H_2O (300 mL), was added Cs_2CO_3 (123.72 g, 895.16 mmol) and $Pd(dppf)_2Cl_2$ (18.28 g, 22.38 mmol). The mixture was stirred for 12 hours at 90°C. After cooling down the mixture, saturated NH_4Cl (500 mL) solution and ethyl acetate was added and extracted to obtain an organic phase. The organic phase was concentrated and purified by column chromatography to afford a white solid. The solid was dissolved in THF (1000 mL). Then Pd/C (12 g, 50% wt.) was added into the mixture. The mixture was stirred for 4 hours under H_2. The mixture was filtrated and concentrated to afford **B1-2**, 120 g.

To a solution of **B1-2** (80 g, 292.69 mmol) in DMF (1000 mL), was added NaH (23.42 g, 585.38 mmol, 60%) at 0 °C. The mixture was stirred for 30 mins. Then chloroacetonitrile was added dropwise into the mixture and stirred for 3 hours at room temperature. A saturated NH_4Cl solution (500 mL) was added dropwise into the mixture. The solution was stirred for 10 mins, and a solid was precipitated. The mixture was filtrated to afford **B1-3**, 75 g.

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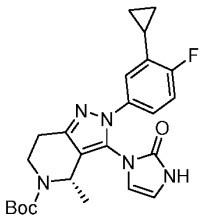
For the subsequent reactions, the preparation of intermediate **A** can be referred to in order to obtain **B**.

Following the preparation methods of intermediate **A** and **B**, the following intermediates can be prepared:

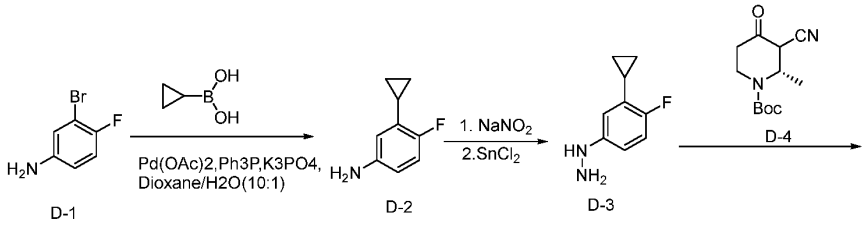


A1 A2 A3 A4 A5

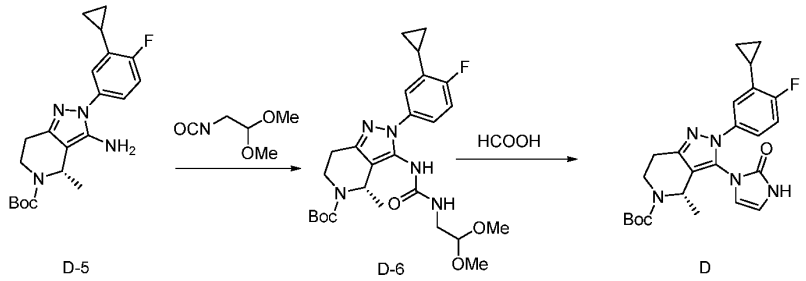
Preparation of intermediate D



D



D-1 D-2 D-3 D-4



D-5 D-6 D

To a solution of **D-1** (30 g, 158 mmol) in dioxane (400 mL), was added cyclopropylboronic acid (20.37 g, 236 mmol), $Pd(AcO)_2$, Ph_3P (4.14 g, 15.8mmol), K_3PO_4 (100 g, 471mmol) and H_2O (40 mL). The mixture was stirred for 8 hours at 100°C under N_2. After cooling down, the mixture was poured into water, and extracted by ethyl acetate to afford an organic phase. The organic phase was concentrated. The residue was dissolved into

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ethanol (200 mL), and the zinc chloride (10 g) was added into the solution, resulting in the precipitation of a large amount of yellow solid. After stirring for more than 8 hours, the mixture was filtrated to afford a solid. The solid was poured into water, and the pH was adjusted to 7.0 with a 2 M aqueous solution of sodium hydroxide. Subsequently, the aqueous phase was extracted with ethyl acetate. After drying the organic phase with anhydrous sodium sulfate (Na_2SO_4), the solution was concentrated under vacuum to afford **D-1**, 20 g of brown oily liquid.

The **D-2** (15 g, 99 mmol) was poured into a mixed solution of water (60 mL) and hydrochloric acid (37%, 60 mL). While stirring, the mixture was cooled to -5 °C, and a solution of sodium nitrite (7.53 g, 109 mmol) in water (10 mL) was slowly added dropwise. After the addition was complete, the reaction was maintained at below 0 °C for 1 hour. The temperature of the reaction was lowered to about -5 °C, and a concentrated hydrochloric acid solution of tin (II) chloride (37.67 g, 199 mmol, 56 mL) was slowly added dropwise to the reaction mixture. After the mixture was stirred for 3 hours at 0~5 °C, the pH was slowly adjusted to 8 with a sodium hydroxide aqueous solution (1.0 M). The organic phase was extracted with dichloromethane. The organic phase, after drying with anhydrous sodium sulfate, was concentrated under vacuum to yield 12 g. The crude product was used directly for the next step without purification.

To a solution of **D-3** (12 g, 72.3 mmol) and **D-4** (16.33 g, 72.3 mmol) in ethanol (100 mL), was added hydrochloride salt of pyridine (840 mg, 7.2 mmol). The mixture was heated to 85 °C and reacted for 3 hours. After cooling down to room temperature, a significant amount of ethanol solvent was removed under vacuum, and the residue was poured into water. The mixture was extracted with ethyl acetate (150 mL) to get an organic phase. The organic phase, after being dried with anhydrous sodium sulfate, was concentrated under vacuum to get a crude. The crude product was purified by silica gel column chromatography (with a petroleum ether to ethyl acetate ratio of 1:1) to afford **D-5**, 21 g.

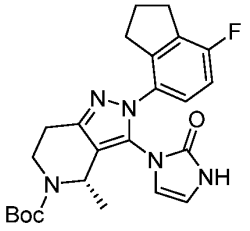
To a solution of phosgene (4.66 g, 38.9 mmol) in dichloromethane (250 mL), was slowly added a solution of **D-5** (15 g, 38.9 mmol) in DCM (80 mL). After the addition was complete, another solution of phosgene (1.16 g, 3.9 mmol) in DCM (20 mL) was added into the mixture, and the mixture was continued with stirring for another 30 minutes. Triethylamine (11.8 g, 116.6 mmol) was slowly added to the reaction mixture over 10 minutes, and the reaction was continued stirring for an additional 20 minutes. Aminomethyl ethanediol (12.24 g, 116.6 mmol) was slowly added to the reaction mixture over 10 minutes, and the reaction was continued with stirring for 1 hour. The reaction mixture was quenched

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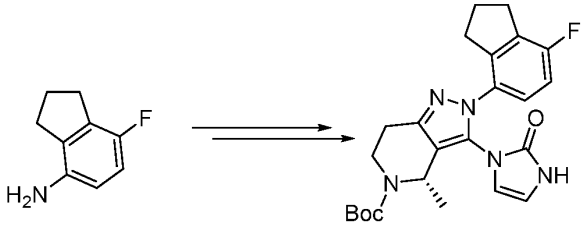
by the addition of water (100 mL). a organic layer was extracted from the mixture. The organic layer was collected and concentrated under vacuum to afford the compound **D-6**, 19.6 g.

To a solution of **D-6** (19.6 g, 37.9 mmol) in tetrahydrofuran (400 mL), was added methanesulfonic acid (4 g, 41.7 mmol). The mixture was heated to 60 °C and reacted for 3 hours. After cooling to room temperature, the reaction was quenched with a saturated solution of sodium bicarbonate. The mixture was extracted with ethyl acetate (200 mL) to get an organic layer. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and then concentrated under vacuum to afford a crude. The crude was purified by silica gel column chromatography (with a petroleum ether to ethyl acetate ratio of 1:1) to yield 9 g of a pale yellow solid **D**.

Preparation of intermediate E



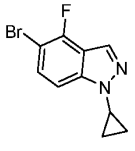
E



E-1 E

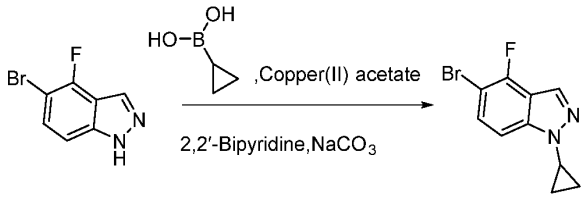
Based on the preparation method of intermediate **D**, starting from **E-1** as the raw material, **E** can be synthesized.

Preparation of intermediate I



I

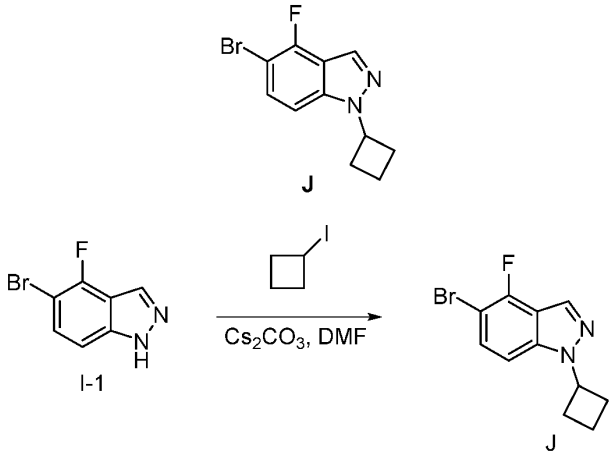
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I-1 I

Compound **I-1** (5 g, 23.3 mmol), cyclopropylboronic acid (3.99 g, 46.5 mmol), copper acetate (3.48 g, 23.2 mmol), 2, 2' bipyridine (3.9 g, 23.3 mmol) and sodium carbonate (4.9 g, 46.5 mmol) were added into dichloroethane. The mixture was stirred over night at 70°C. After cooling down the mixture, the mixture was filtered. The filtrate was extracted with water and dichloromethane to separate an organic phase. The organic phase was concentrated under vacuum and then purified by column chromatography to obtain **I**, 3.6 g, with a yield of 61%.

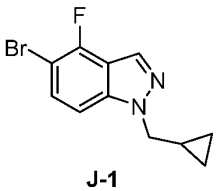
Preparation of intermediate J



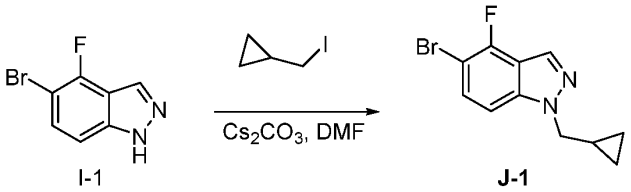
To a solution of **I-1** (2.0 g, 9.3 mmol) in DMF (20 mL), was added iodocyclobutane (1.78 g, 9.8 mmol) and Cs_2CO_3 (4.55 g, 13.9 mmol). The mixture was stirred 6 hours at 50-60 °C. The mixture was added dropwise to water (50 mL), and then a solid precipitated. The suspension was filtrated to afford **J**, 1.6 g, yield: 63.9%.

Preparation of intermediate J-1:

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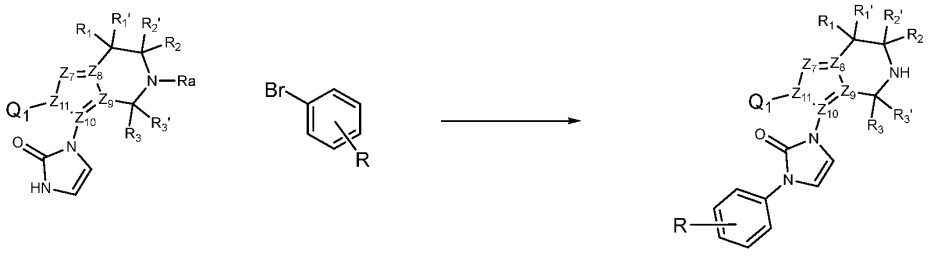
J-1



I-1 J-1

To a solution of **I-1** (1.0 g, 4.65 mmol) in DMF (10 mL), was added (iodomethyl) cyclopropane (0.89 g, 4.9 mmol) and Cs_2CO_3 (2.27 g, 6.98 mmol). The mixture was stirred 4 hours at 50-60 °C. The mixture was added dropwise to water (50 mL), and then a solid precipitated. The suspension was filtrated to afford **J-1**, 0.87 g, yield: 69.51%.

Preparation of intermediate O

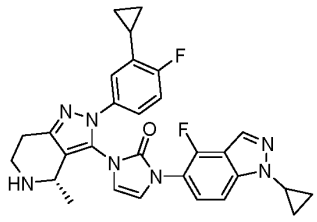


O-1 O

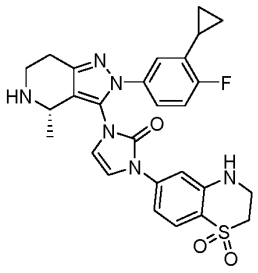
O-1 (1 eq.) and (1R, 2R)-(-)-N, N'- dimethyl -1, 2- cyclohexanediamine (0.5 eq.), CuI (0.5 eq.), bromide (1.5 eq.) and potassium carbonate (3 eq.) were added to NMP. The mixture was stirred overnight at 100~110 °C. After cooling down, the mixture was filtered to get a filtrate. Water (10 V) and ethyl acetate (10 V) was added into the filtrate. The mixture was extracted to separate out an organic phase. The organic phase was concentrated under vacuum, and the residue was purified by column chromatography to obtain the target compound.

The following compounds can be prepared by this method:

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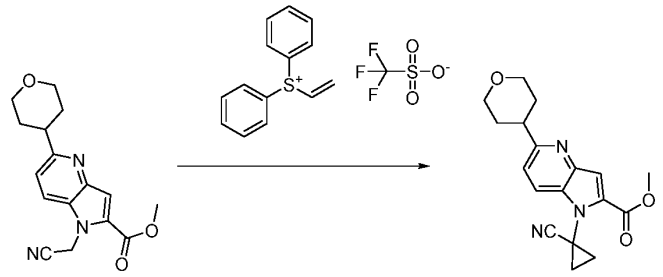


O-1



O-2

Preparation of intermediate AF

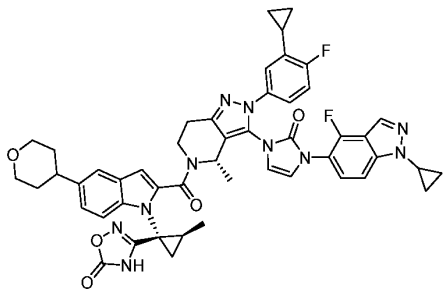


AF-1

AF

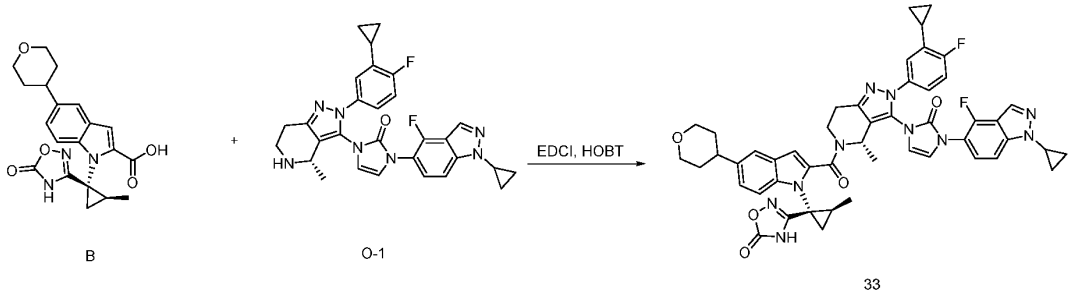
To a solution of **AF-1** (300 mg, 1.00 mmol) in DMSO (10 mL), was added diphenyl(vinyl) sulfonium triflate (0.40 g, 1.1 mmol) and DBU (0.46 g, 3 mmol). The mixture was stirred 2 hours at room temperature. Ethyl acetate (50 mL) and water (20 mL) were added dropwise into the reaction mixture, and an organic phase was extracted. The organic phase was washed with brine, dried over anhydrous sodium sulfate, and then concentrated under vacuum. The residue was purified by column chromatography to yield **AF**, 154 mg, with a yield of 47.22%.

Preparation of compound 33



33

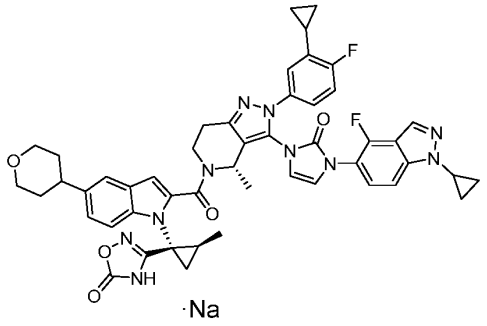
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B O-1 33

Compound **B** (3.36 g, 6.3 mmol), **O-1** (3.66 g, 9.4 mmol), HOBT (1.29 g, 9.4 mmol), and DIEA (2.47 g, 18.9 mmol) were added into DMA (15 mL) at 0 °C. EDCI (1.84 g, 9.4 mmol) was added into the mixture. The reaction mixture was stirred overnight at room temperature. The reaction mixture was then poured into water, and extracted with ethyl acetate (100 mL) to afford an organic phase. The organic phase was washed with a saturated sodium chloride solution and then dried over anhydrous sodium sulfate. The solution was concentrated under vacuum. The residue was purified by column chromatography (with a petroleum ether to ethyl acetate ratio of 1:2) to yield the target compound **33**, 2.587 g, with a yield of 97%.

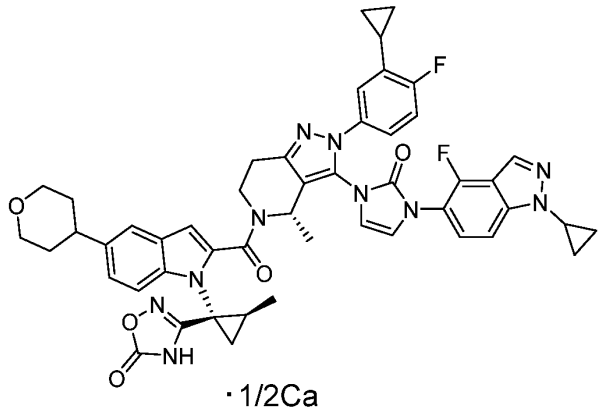
Preparation of the sodium salt of compound 33



To a solution of compound **33** (2 g, 2.24 mmol) in a mixture of dichloromethane (5 mL) and methanol (5 mL) at room temperature, was added dropwise a solution of NaOH (94 mg, 2.35 mmol) in methanol (1 mL). The mixture was stirred overnight. The reaction mixture was concentrated under vacuum. The residue was slurry washed with diethyl ether to afford the sodium salt of compound **33**, 1.95 g with a yield of 95%.

Preparation of the calcium salt of compound 33

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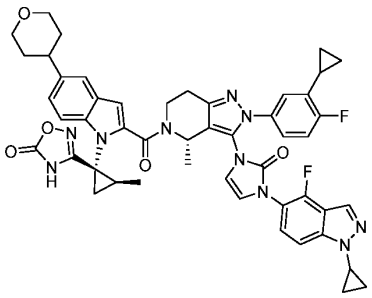
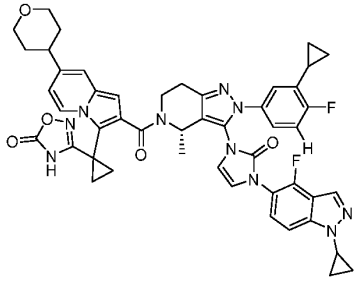
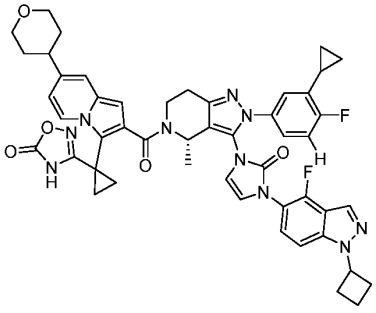


To a solution of the sodium salt of compound **33** (1 g, 1.09 mmol) in THF (5 mL), was added calcium acetate (181 mg, 1.15 mmol). The mixture was stirred for 8 hours. Then the mixture was concentrated under vacuum. The residue was slurry washed with a mixture of dichloromethane (1 mL) and diethyl ether (10 mL) to afford a white solid, 0.85 g, with a yield of 85.3%.

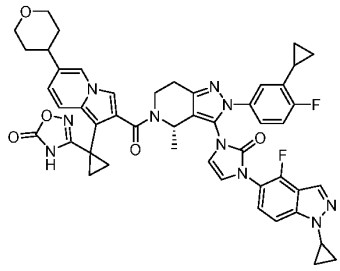
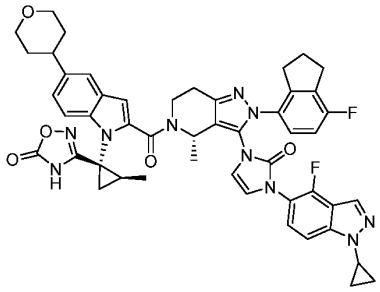
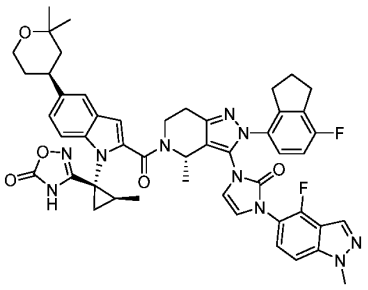
According to the preparation method described in this paper, the following compounds were prepared by using appropriate starting materials and intermediates and, if necessary, appropriate protective group chemistry. The structures were confirmed by MS and ^{1}HNMR in Table 1.

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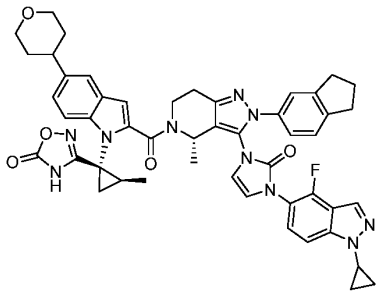
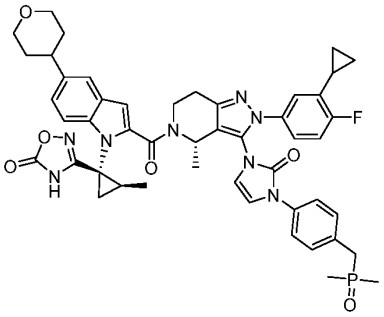
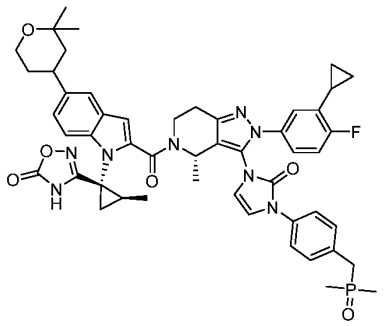
Table 1 The MS and 1HNMR of the compounds

Compounds	Structures	MS	^1HNMR
33		893.37	^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.29 (d, *J* = 21.0 Hz, 1H), 8.02 (d, *J* = 38.0 Hz, 1H), 7.62 – 7.44 (m, 5H), 7.32 – 7.26 (m, 1H), 7.07-7.01 (m, 2H), 6.70 (d, *J* = 6.9 Hz, 1H), 6.61-6.59 (m, 1H), 6.29 (d, *J* = 3.1 Hz, 1H), 5.77-5.75 (m, 1H), 4.46 (dd, *J* = 13.6, 5.0 Hz, 1H), 4.15 – 4.02 (m, 3H), 3.58-3.53 (m, 5H), 3.14-3.11 (m, 1H), 3.07 – 2.78 (m, 3H), 2.16 – 2.01 (m, 1H), 1.93 – 1.75 (m, 7H), 1.65 (d, *J* = 6.7 Hz, 3H), 1.54-1.52 (m, 6H), 1.10 – 0.93 (m, 4H), 0.93 – 0.75 (m, 2H).
40		879.35	1H NMR (500 MHz, DMSO-*d*6) δ 11.16 (s, 1H), 8.42 – 8.37 (m, 3H), 7.91 – 7.81 (m, 1H), 7.65 – 7.54 (m, 2H), 7.45 – 7.36 (m, 2H), 7.12 – 7.09 (m, 1H), 6.51 – 6.46 (m, 2H), 5.33 – 5.23 (m, 1H), 4.61 – 4.49 (m, 1H), 4.15 – 3.85 (m, 2H), 3.67 – 3.47 (m, 4H), 3.09 – 2.91 (m, 3H), 2.42 – 2.29 (m, 4H), 2.18 – 2.11 (m, 2H), 1.92 – 1.82 (m, 2H), 1.42 – 1.25 (m, 9H), 1.13 – 1.07 (m, 3H).
41		893.37	^{1}H NMR (500 MHz, DMSO-*d*6) δ 11.16 (s, 1H), 8.42 – 8.37 (m, 3H), 7.91 – 7.81 (m, 1H), 7.65 – 7.54 (m, 2H), 7.45 – 7.36 (m, 2H), 7.12 – 7.09 (m, 1H), 6.51 – 6.46 (m, 2H), 5.33 – 5.23 (m, 1H), 4.61 – 4.49 (m, 1H), 4.15 – 3.85 (m, 2H), 3.67 – 3.47 (m, 4H), 3.09 – 2.91 (m, 3H), 2.42 – 2.29 (m, 4H), 2.18 – 2.04 (m, 4H), 1.92 – 1.82 (m, 2H), 1.41 – 1.25 (m, 7H), 1.20 – 1.01 (m, 5H).

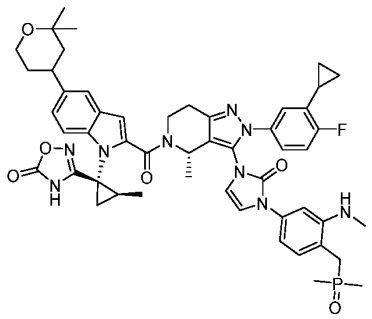
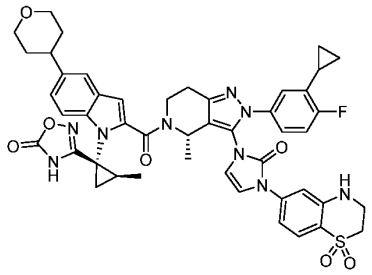
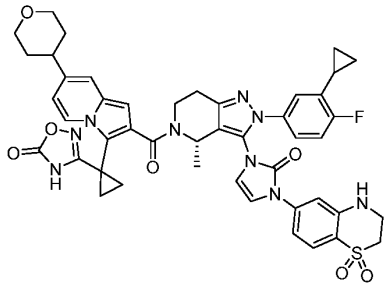
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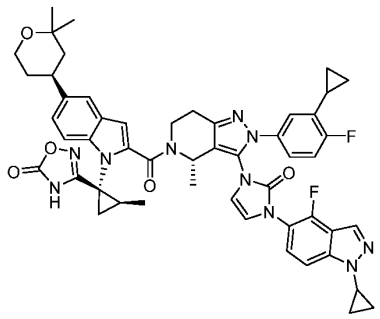
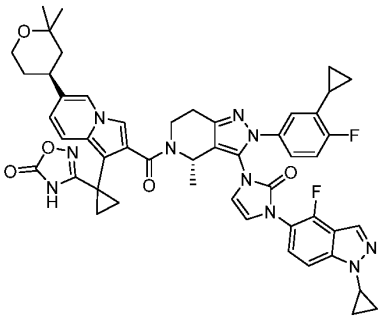
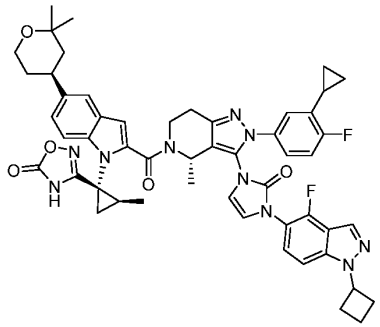
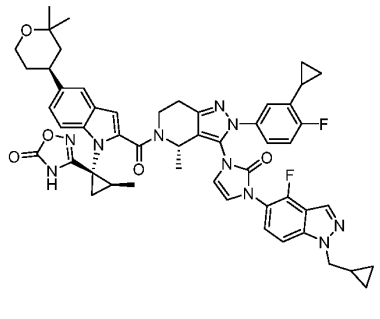
Compounds	Structures	MS	^1HNMR
44		879.35	^{1}H NMR (500 MHz, DMSO-*d*6) δ 11.18 (s, 1H), 8.44 – 8.38 (m, 3H), 7.89 – 7.79 (m, 2H), 7.65 – 7.62 (m, 2H), 7.55 – 7.45 (m, 2H), 6.75 – 6.55 (m, 1H), 6.46 – 6.36 (m, 1H), 5.34 – 5.25 (m, 1H), 4.66 – 4.56 (m, 1H), 4.29 – 3.98 (m, 2H), 3.75 – 3.69 (m, 4H), 3.14 – 2.94 (m, 3H), 2.45 – 2.35 (m, 7H), 2.28 – 2.18 (m, 2H), 1.95 – 1.85 (m, 2H), 1.41 – 1.23 (m, 10H), 1.13 – 1.08 (m, 6H).
45		893.37	^{1}H NMR (500 MHz, DMSO-*d*6) δ 11.20 (s, 1H), 8.43 – 8.33 (m, 2H), 7.95 – 7.87 (m, 1H), 7.69 – 7.59 (m, 2H), 7.48 – 7.39 (m, 3H), 7.22 (d, *J* = 2.0 Hz, 1H), 7.13 – 7.09 (m, 1H), 6.43 – 6.40 (m, 1H), 5.35 – 5.25 (m, 1H), 4.68 – 4.58 (m, 1H), 4.33 – 3.95 (m, 2H), 3.77 – 3.67 (m, 4H), 3.16 – 2.96 (m, 3H), 2.48 – 2.38 (m, 7H), 2.26 – 2.16 (m, 5H), 1.97 – 1.87 (m, 2H), 1.43 – 1.24 (m, 7H), 1.12 – 1.08 (m, 6H).
46		895.38	^{1}H NMR (500 MHz, DMSO-*d*6) δ 11.19 (s, 1H), 8.44 – 8.34 (m, 2H), 7.94 – 7.86 (m, 1H), 7.67 – 7.57 (m, 2H), 7.47 – 7.38 (m, 3H), 7.23 (d, *J* = 2.0 Hz, 1H), 7.12 – 7.09 (m, 1H), 6.45 – 6.40 (m, 1H), 5.35 – 5.25 (m, 1H), 4.68 – 4.58 (m, 1H), 4.33 – 3.95 (m, 2H), 3.77 – 3.67 (m, 2H), 3.16 – 2.96 (m, 5H), 2.48 – 2.38 (m, 7H), 2.26 – 2.16 (m, 5H), 1.97 – 1.87 (m, 2H), 1.43 – 1.24 (m, 3H), 1.12 – 1.08 (m, 12H).

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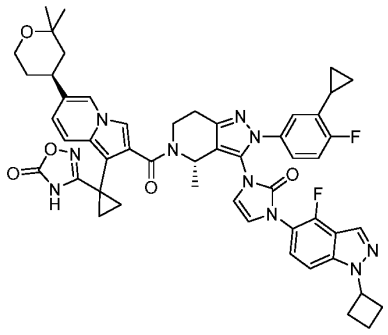
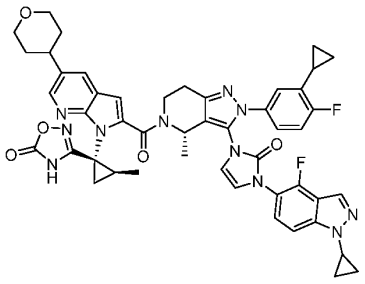
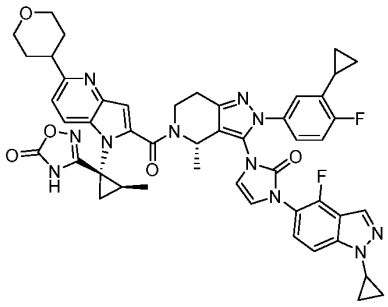
Compounds	Structures	MS	^1HNMR
47		875.37	^{1}H NMR (500 MHz, DMSO-*d*6) δ 11.21 (s, 1H), 8.47 – 8.37 (m, 2H), 7.97 – 7.87 (m, 1H), 7.69 – 7.59 (m, 2H), 7.49 – 7.39 (m, 3H), 7.21 (d, *J* = 2.0 Hz, 1H), 7.14 – 7.12 (m, 1H), 6.48 – 6.44 (m, 1H), 5.36 – 5.26 (m, 1H), 4.71 – 4.62 (m, 1H), 4.36 – 3.95 (m, 2H), 3.79 – 3.68 (m, 4H), 3.12 – 2.96 (m, 3H), 2.45 – 2.38 (m, 7H), 2.25 – 2.16 (m, 5H), 1.95 – 1.87 (m, 2H), 1.45 – 1.24 (m, 7H), 1.11 – 1.08 (m, 6H).
51		885.36	^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.73 (s, 1H), 8.33 – 8.29 (m, 2H), 8.21 – 8.15 (m, 1H), 7.89 – 7.82 (m, 1H), 7.62 – 7.56 (m, 2H), 7.51 – 7.45 (m, 4H), 7.25 – 7.21 (m, 1H), 7.11 – 7.04 (m, 1H), 5.24 – 5.14 (m, 1H), 4.57 – 4.49 (m, 1H), 4.14 – 4.05 (m, 1H), 3.35(s, 2H), 3.86 – 3.61 (m, 2H), 3.08 – 2.90 (m, 3H), 2.49 – 2.32 (m, 3H), 2.26 – 2.23 (m, 6H), 2.08 – 1.91 (m, 2H), 1.86 – 1.69 (m, 2H), 1.61 – 1.57 (m, 5H), 1.39 – 1.31 (m, 2H), 1.01 – 0.98 (m, 3H).
52		913.39	^{1}H NMR (500 MHz, Chloroform-*d*) δ 11.09 (s, 1H), 8.33 – 8.29 (m, 2H), 8.21 – 8.15 (m, 1H), 7.89 – 7.82 (m, 1H), 7.62 – 7.56 (m, 2H), 7.51 – 7.45 (m, 4H), 7.25 – 7.21 (m, 1H), 7.11 – 7.04 (m, 1H), 5.24 – 5.14 (m, 1H), 4.57 – 4.49 (m, 1H), 4.14 – 4.05 (m, 1H), 3.35(s, 2H), 3.86 – 3.61 (m, 2H), 3.08 – 2.90 (m, 3H), 2.49 – 2.32 (m, 3H), 2.26 – 2.23 (m, 6H), 2.08 – 1.91 (m, 2H), 1.86 – 1.69 (m, 2H), 1.61 – 1.57 (m, 9H), 1.39 – 1.31 (m, 2H), 1.19-1.14 (m, 4H), 1.01 – 0.98 (m, 3H).

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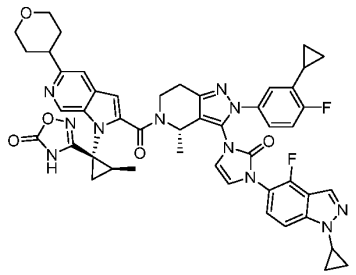
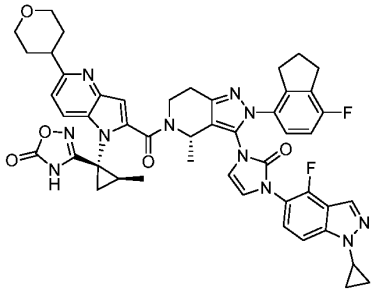
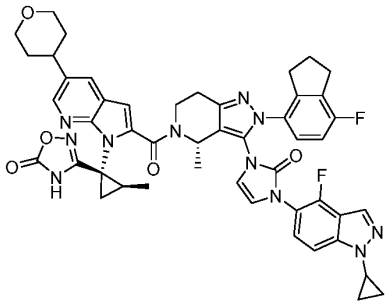
Compounds	Structures	MS	^1HNMR
54		942.42	^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.94 (s, 1H), 8.37 – 8.29 (m, 2H), 8.21 – 8.14 (m, 1H), 7.89 – 7.82 (m, 1H), 7.62 – 7.56 (m, 2H), 7.51 – 7.41 (m, 4H), 7.25 – 7.20 (m, 1H), 7.11 – 7.04 (m, 1H), 5.24 – 5.14 (m, 1H), 4.57 – 4.49 (m, 1H), 4.14 – 4.05 (m, 1H), 3.35(s, 2H), 3.86 – 3.61 (m, 3H), 3.08 – 2.90 (m, 6H), 2.49 – 2.32 (m, 3H), 2.26 – 2.23 (m, 6H), 2.08 – 1.91 (m, 2H), 1.86 – 1.69 (m, 2H), 1.61 – 1.57 (m, 9H), 1.39 – 1.31 (m, 2H), 1.19-1.13 (m, 3H), 1.01 – 0.98 (m, 3H).
56		900.32	1H NMR (500 MHz, DMSO-*d*6) δ 11.15 (s, 1H), 8.42 – 8.38 (m, 3H), 7.90 – 7.82 (m, 1H), 7.65 – 7.56 (m, 2H), 7.44 – 7.41 (m, 2H), 7.13 – 7.09 (m, 1H), 6.54-6.53(m, 1H), 6.51 – 6.46 (m, 2H), 5.33 – 5.23 (m, 1H), 4.61 – 4.49 (m, 1H), 4.15 – 3.85 (m, 2H), 3.67 – 3.47 (m, 8H), 3.09 – 2.91 (m, 3H), 2.42 – 2.29 (m, 4H), 2.18 – 2.11 (m, 2H), 1.92 – 1.82 (m, 2H), 1.42 – 1.25 (m, 4H), 1.13 – 1.07 (m, 6H).
57		886.31	1H NMR (500 MHz, DMSO-*d*6) δ 11.13 (s, 1H), 8.42 – 8.38 (m, 3H), 7.91 – 7.82 (m, 1H), 7.65 – 7.56 (m, 2H), 7.45 – 7.39 (m, 2H), 7.12 – 7.09 (m, 1H), 6.54(s, 1H), 6.51 – 6.46 (m, 2H), 5.33 – 5.23 (m, 1H), 4.61 – 4.49 (m, 1H), 4.15 – 3.85 (m, 2H), 3.67 – 3.47 (m, 8H), 3.09 – 2.91 (m, 3H), 2.42 – 2.29 (m, 4H), 2.18 – 2.11 (m, 2H), 1.92 – 1.82 (m, 3H), 1.42 – 1.25 (m, 4H), 1.13 – 1.07 (m, 3H).

Compounds	Structures	MS	^1HNMR
59		921.39	^{1}H NMR (500 MHz, DMSO-*d*6) δ 11.75 (s, 1H), 8.39 – 8.29 (m, 3H), 7.93 – 7.83 (m, 1H), 7.69 – 7.58 (m, 2H), 7.49 – 7.36 (m, 3H), 7.20 (s, 1H), 7.11 – 7.06 (m, 1H), 5.23 – 5.13 (m, 1H), 4.55 – 4.49 (m, 1H), 4.13 – 3.85 (m, 2H), 3.57 – 3.47 (m, 4H), 3.05 – 2.88 (m, 3H), 2.40 – 2.27 (m, 4H), 2.16 – 2.09 (m, 2H), 1.58 (d, *J* = 8.0 Hz, 3H), 1.40 – 1.22 (m, 8H), 1.11 – 1.05 (m, 9H).
60		907.38	^{1}H NMR (500 MHz, DMSO-*d*6) δ 11.72 (s, 1H), 8.44 – 8.38 (m, 3H), 7.89 – 7.79 (m, 2H), 7.65 – 7.62 (m, 2H), 7.55 – 7.45 (m, 2H), 6.75 – 6.55 (m, 1H), 6.46 – 6.36 (m, 1H), 5.34 – 5.25 (m, 1H), 4.66 – 4.56 (m, 1H), 4.29 – 3.98 (m, 2H), 3.75 – 3.69 (m, 4H), 3.14 – 2.94 (m, 3H), 2.45 – 2.35 (m, 7H), 2.28 – 2.18 (m, 2H), 1.41 – 1.23 (m, 10H), 1.13 – 1.08 (m, 12H).
61		935.41	^{1}H NMR (500 MHz, DMSO-*d*6) δ 11.74(s, 1H), 8.39 – 8.29 (m, 3H), 7.93 – 7.83 (m, 1H), 7.69 – 7.58 (m, 2H), 7.49 – 7.36 (m, 3H), 7.20 (s, 1H), 7.11 – 7.06 (m, 1H), 5.23 – 5.13 (m, 1H), 4.55 – 4.49 (m, 1H), 4.13 – 3.85 (m, 2H), 3.57 – 3.47 (m, 4H), 3.05 – 2.88 (m, 3H), 2.40 – 2.27 (m, 4H), 2.16 – 2.09 (m, 2H), 1.58 (d, *J* = 8.0 Hz, 3H), 1.40 – 1.22 (m, 9H), 1.11 – 1.05 (m, 10H).
62		935.41	^{1}H NMR (500 MHz, DMSO-*d*6) δ 11.75(s, 1H), 8.39 – 8.29 (m, 3H), 7.93 – 7.83 (m, 1H), 7.69 – 7.58 (m, 2H), 7.49 – 7.36 (m, 3H), 7.20 (s, 1H), 7.11 – 7.06 (m, 1H), 5.23 – 5.13 (m, 1H), 4.55 – 4.49 (m, 1H), 4.13 – 3.85 (m, 2H), 3.57 – 3.47 (m, 4H), 3.05 – 2.88 (m, 3H), 2.40 – 2.27 (m, 4H), 2.16 – 2.09 (m, 2H), 1.58 (d, *J* = 8.0 Hz, 3H), 1.40 – 1.22 (m, 8H), 1.11 – 1.05 (m, 11H).

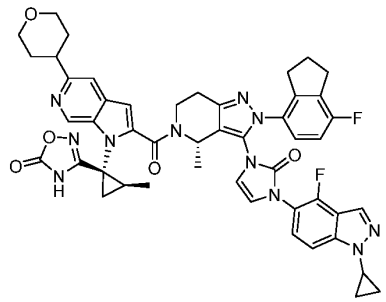
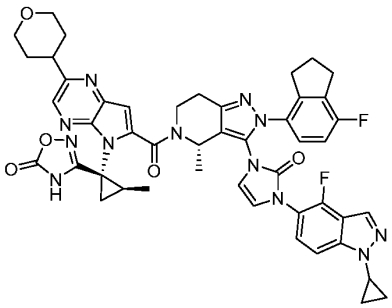
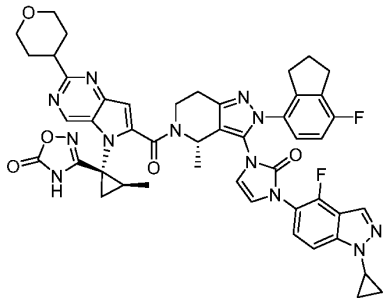
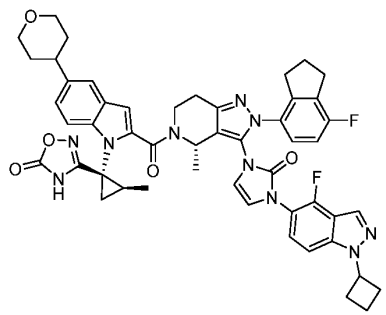
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Compounds	Structures	MS	^1HNMR
63		921.39	^{1}H NMR (500 MHz, DMSO-*d*6) δ 11.78 (s, 1H), 8.44 – 8.38 (m, 3H), 7.89 – 7.79 (m, 2H), 7.65 – 7.62 (m, 2H), 7.55 – 7.45 (m, 2H), 6.75 – 6.55 (m, 1H), 6.46 – 6.36 (m, 1H), 5.34 – 5.25 (m, 1H), 4.66 – 4.56 (m, 1H), 4.29 – 3.98 (m, 2H), 3.75 – 3.69 (m, 4H), 3.14 – 2.94 (m, 3H), 2.45 – 2.35 (m, 7H), 2.28 – 2.18 (m, 2H), 1.41 – 1.23 (m, 12H), 1.13 – 1.08 (m, 12H).
71		894.36	^{1}H NMR (500 MHz, DMSO-*d*6) δ 11.76 (s, 1H), 8.40 – 8.28 (m, 3H), 7.96 – 7.86 (m, 1H), 7.67 – 7.58 (m, 2H), 7.47 – 7.36 (m, 2H), 7.21 (d, *J* = 2.0 Hz, 1H), 7.09 – 7.03 (m, 1H), 5.23 – 5.13 (m, 1H), 4.56 – 4.49 (m, 1H), 4.12 – 3.85 (m, 2H), 3.59 – 3.47 (m, 4H), 3.04 – 2.88 (m, 3H), 2.73-2.68(m, 1H), 2.39 – 2.27 (m, 3H), 2.14 – 2.08 (m, 2H), 1.88 – 1.79 (m, 2H), 1.60 (d, *J* = 8.0 Hz, 3H), 1.39 – 1.20 (m, 4H), 1.01 – 0.89 (m, 7H).
72		894.36	^{1}H NMR (500 MHz, DMSO-*d*6) δ 11.72 (s, 1H), 8.40 – 8.28 (m, 3H), 7.96 – 7.86 (m, 1H), 7.60 – 7.58 (m, 1H), 7.47 – 7.36 (m, 3H), 7.21 (d, *J* = 2.0 Hz, 1H), 7.09 – 7.03 (m, 1H), 5.23 – 5.13 (m, 1H), 4.56 – 4.49 (m, 1H), 4.12 – 3.85 (m, 2H), 3.59 – 3.47 (m, 4H), 3.04 – 2.88 (m, 3H), 2.73-2.68(m, 1H), 2.39 – 2.27 (m, 3H), 2.14 – 2.08 (m, 2H), 1.88 – 1.79 (m, 2H), 1.60 (d, *J* = 8.0 Hz, 3H), 1.39 – 1.20 (m, 4H), 1.01 – 0.89 (m, 7H).

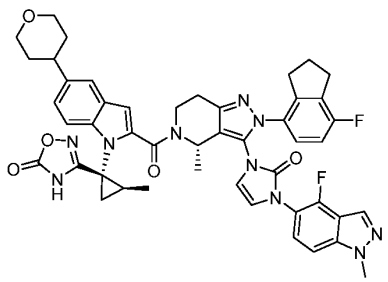
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Compounds	Structures	MS	^1HNMR
73		894.36	^{1}H NMR (500 MHz, DMSO-*d*6) δ 11.62 (s, 1H), 8.40 – 8.28 (m, 3H), 7.96 – 7.86 (m, 1H), 7.62 – 7.58 (m, 2H), 7.47 – 7.33 (m, 2H), 7.21 (d, *J* = 2.0 Hz, 1H), 7.09 – 7.03 (m, 1H), 5.23 – 5.13 (m, 1H), 4.56 – 4.49 (m, 1H), 4.12 – 3.85 (m, 2H), 3.59 – 3.47 (m, 4H), 3.04 – 2.88 (m, 3H), 2.73-2.68(m, 1H), 2.39 – 2.27 (m, 3H), 2.14 – 2.08 (m, 2H), 1.88 – 1.79 (m, 2H), 1.60 (d, *J* = 8.0 Hz, 3H), 1.39 – 1.20 (m, 4H), 1.01 – 0.89 (m, 7H).
85		894.36	^{1}H NMR (500 MHz, DMSO-*d*6) δ 11.20 (s, 1H), 8.43 – 8.33 (m, 2H), 7.61 – 7.59 (m, 2H), 7.48 – 7.39 (m, 2H), 7.27-7.25(m, 1H), 7.22 (d, *J* = 2.0 Hz, 1H), 7.13 – 7.09 (m, 1H), 6.43 – 6.40 (m, 1H), 5.35 – 5.25 (m, 1H), 4.68 – 4.58 (m, 1H), 4.33 – 3.95 (m, 2H), 3.77 – 3.67 (m, 4H), 3.16 – 2.96 (m, 3H), 2.48 – 2.38 (m, 7H), 2.26 – 2.16 (m, 5H), 1.97 – 1.87 (m, 2H), 1.43 – 1.24 (m, 7H), 1.12 – 1.08 (m, 6H).
86		894.36	^{1}H NMR (500 MHz, DMSO-*d*6) δ 11.20 (s, 1H), 8.43 – 8.33 (m, 2H), 7.61 – 7.59 (m, 2H), 7.48 – 7.39 (m, 3H), 7.22 (d, *J* = 2.0 Hz, 1H), 7.13 – 7.09 (m, 1H), 6.43 – 6.40 (m, 1H), 5.35 – 5.25 (m, 1H), 4.68 – 4.58 (m, 1H), 4.33 – 3.95 (m, 2H), 3.77 – 3.67 (m, 4H), 3.16 – 2.96 (m, 3H), 2.48 – 2.38 (m, 7H), 2.26 – 2.16 (m, 5H), 1.97 – 1.87 (m, 2H), 1.43 – 1.24 (m, 7H), 1.12 – 1.08 (m, 6H).

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Compounds	Structures	MS	^1HNMR
87		894.36	^{1}H NMR (500 MHz, DMSO-*d*6) δ 11.20 (s, 1H), 8.33 (s,1H), 7.70 (s, 1H), 7.69 – 7.59 (m, 2H), 7.48 – 7.39 (m, 3H), 7.22 (d, *J* = 2.0 Hz, 1H), 7.13 – 7.09 (m, 1H), 6.43 – 6.40 (m, 1H), 5.35 – 5.25 (m, 1H), 4.68 – 4.58 (m, 1H), 4.33 – 3.95 (m, 2H), 3.77 – 3.67 (m, 4H), 3.16 – 2.96 (m, 3H), 2.48 – 2.38 (m, 7H), 2.26 – 2.16 (m, 5H), 1.97 – 1.87 (m, 2H), 1.43 – 1.24 (m, 7H), 1.12 – 1.08 (m, 6H).
88		895.35	^{1}H NMR (500 MHz, DMSO-*d*6) δ 11.20 (s, 1H), 8.33 (s,1H), 7.69 – 7.59 (m, 2H), 7.48 – 7.39 (m, 3H), 7.22 (d, *J* = 2.0 Hz, 1H), 7.13 – 7.09 (m, 1H), 6.43 – 6.40 (m, 1H), 5.35 – 5.25 (m, 1H), 4.68 – 4.58 (m, 1H), 4.33 – 3.95 (m, 2H), 3.77 – 3.67 (m, 4H), 3.16 – 2.96 (m, 3H), 2.48 – 2.38 (m, 7H), 2.26 – 2.16 (m, 5H), 1.97 – 1.87 (m, 2H), 1.43 – 1.24 (m, 7H), 1.12 – 1.08 (m, 6H).
89		895.35	^{1}H NMR (500 MHz, DMSO-*d*6) δ 11.20 (s, 1H), 7.71 (m, 1H), 7.69 – 7.59 (m, 2H), 7.51(s,1H), 7.48 – 7.39 (m, 2H), 7.22 (d, *J* = 2.0 Hz, 1H), 7.13 – 7.09 (m, 1H), 6.43 – 6.40 (m, 1H), 5.35 – 5.25 (m, 1H), 4.68 – 4.58 (m, 1H), 4.33 – 3.95 (m, 2H), 3.77 – 3.67 (m, 4H), 3.16 – 2.96 (m, 3H), 2.48 – 2.38 (m, 7H), 2.26 – 2.16 (m, 5H), 1.97 – 1.87 (m, 2H), 1.43 – 1.24 (m, 7H), 1.12 – 1.08 (m, 6H).
90		907.38	^{1}H NMR (500 MHz, DMSO-*d*6) δ 11.20 (s, 1H), 8.43 – 8.33 (m, 2H), 7.95 – 7.87 (m, 1H), 7.69 – 7.59 (m, 2H), 7.48 – 7.39 (m, 3H), 7.22 (d, *J* = 2.0 Hz, 1H), 7.13 – 7.09 (m, 1H), 6.43 – 6.40 (m, 1H), 5.35 – 5.25 (m, 1H), 4.68 – 4.58 (m, 1H), 4.33 – 3.95 (m, 2H), 3.77 – 3.67 (m, 4H), 3.16 – 2.96 (m, 3H), 2.48 – 2.38 (m, 7H), 2.26 – 2.16 (m, 5H), 1.97 – 1.87 (m, 2H), 1.43 – 1.24 (m, 7H), 1.12 – 1.08 (m, 8H).

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Compounds	Structures	MS	^1HNMR
91		867.35	^{1}H NMR (500 MHz, DMSO-*d*6) δ 11.20 (s, 1H), 8.43 – 8.33 (m, 2H), 7.95 – 7.87 (m, 1H), 7.69 – 7.59 (m, 2H), 7.48 – 7.39 (m, 3H), 7.22 (d, *J* = 2.0 Hz, 1H), 7.13 – 7.09 (m, 1H), 6.43 – 6.40 (m, 1H), 5.35 – 5.25 (m, 1H), 4.68 – 4.58 (m, 1H), 4.33 – 3.95 (m, 2H), 3.91(s, 3H), 3.77 – 3.67 (m, 3H), 3.16 – 2.96 (m, 3H), 2.48 – 2.38 (m, 7H), 2.26 – 2.16 (m, 5H), 1.97 – 1.87 (m, 2H), 1.43 – 1.24 (m, 5H), 1.12 – 1.08 (m, 4H).

Example 2 *In vitro* activity evaluation

hGLP-1R cAMP Assay

1. Cell line and reagent preparation

1) Cell line: Flp-In-293-GLP1R

2) Medium: DMEM + 10% FBS + 1 X Penicillin-Streptomycin + 200 μg/mL HB

3) Test buffer: 1 X HBSS + 20 mM HEPES + 0.1%BSA + 500 μM IBMX

2. Agonist test

a) Flpin-293-GLP1R cells were incubated in a 384-well assay plate (6007680-50, PE) using complete medium with 2,000 cells per well.

b) Prepared a 4 X complex working solution with assay buffer.

c) Added 5 μL of 4 X Compound Working Solution to the cell plate and incubated at 37°C for 30 minutes.

d) Diluted Eu-cAMP tracer (1/50) with lysis buffer and added 10 μl/well to the assay plate.

e) Diluted Ulight-anti-cAMP (1/150) with lysis buffer and added 10 μl/well to the assay plate.

f) Incubated at constant temperature for 1 hour.

g) Read the plate on Envision 2105 plate reader at 665 nM and 615 nM.

3. Data Analysis

3.1 The formula for calculating % Activity was as follows

% Activity =100-(Signal$_{cmpd}$-Signal$_{Ave_PC}$)/(Signal$_{Ave_VC}$-Signal$_{Ave_PC}$)×100.

3.2 Calculate EC50 and plot the effect-dose curve for cmpds:

Y=Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope))

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X: logarithm of agonist concentration; Y: percentage activity.

Table 2 shows the biological activity of the compounds in the GLP-1R agonist cAMP stimulation assay as follows.

Table 2: Bioactivity of compounds in hGLP-1R agonist cAMP stimulation assay

Compounds	hGLP-1R cAMP: EC_{50} (nM)
33	0.02
45	0.015
51	0.028

Example 3 Pharmacokinetic studies

Single-dose oral administration pharmacokinetic (PK) studies in Sprague-Dawley (SD) rats

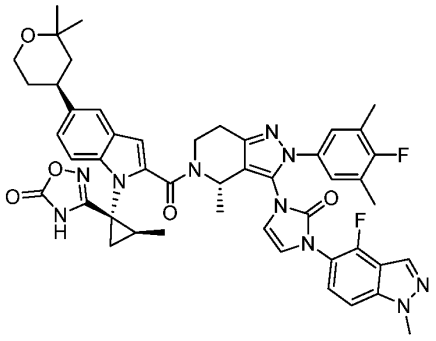
Pharmacokinetic (PK) studies after a single-dose oral administration for compounds. Protocol: Animals: Male Sprague-Dawley (SD) rats; Solvent: Solutol: PEG400: Tween80: Saline = 10:40:2:48 (v/v/v/v); Dose: 5mg/kg; Dosing concentration: 0.5mg/mL in the solvent; Dosing volume: 10 mL/kg. Sample Collection: At each time point, approximately 0.15 mL of blood was drawn from the jugular vein sinus, and the collected whole blood was placed in an anticoagulant tube containing EDTA-K2. After collecting blood samples, they were processed with protein precipitation and then analyzed by LC-MS/MS. Pharmacokinetic parameters were calculated by Phoenix WinNonlin 8.0 and summarized in Table 3.

Table 3. Pharmacokinetic parameters of different compounds after a single-dose oral administration

Compounds	Dosing route	Dose, mg/kg	C_{max}*, ng/mL	AUC_{0-t}*, ng.h/mL
33**	Oral	5	5,607	71,191
45**	Oral	5	3,210	29,577
Orforglipron**	Oral	5	799	7,222

*: C_{max} refers to the maximum plasma concentration of a drug after administration; AUC_{0-t} was an important pharmacokinetic parameter, representing the area under the curve from 0 hour to the study endpoint time t hours, which indicates the drug exposure in the body during that time period. The longer the study time (sampling time points), the higher the relative exposure may.
**: The pharmacokinetic study sampling time points for compounds 33 and 45 were: pre-dose, 0.25, 0.5, 1, 2, 3, 4, 8, 12, 18, 24 hours. The AUC_{0-t} for compounds 33 and 45 in the table refers to the drug exposure over 0-24 hours. The sampling time points for orforglipron were: pre-dose, 0.25, 0.5, 1, 2, 3, 4, 8, 12, 18, 24, 32, 40, 48 hours. The AUC_{0-t} for orforglipron in the table refers to the drug exposure over 0-48 hours. The drug exposure over 0-24 hours for orforglipron was also calculated as 6,725 ng.h/mL.

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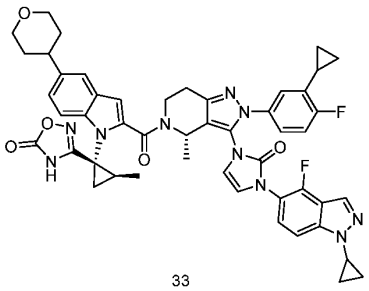


The structure of orforglipron is shown above.

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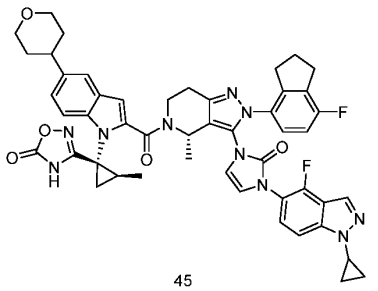
WHAT IS CLAIMED IS:

1. A compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:



33

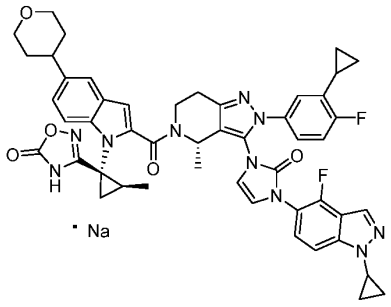
and



45

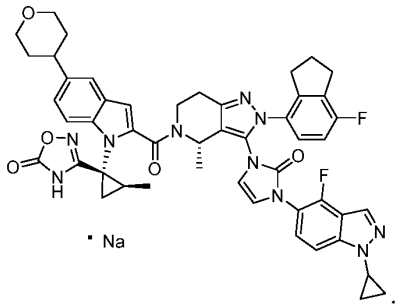
2. The compound, or the pharmaceutically acceptable salt thereof of claim 1, wherein the pharmaceutically acceptable salt is selected from the group consisting of a sodium salt, a calcium salt, a potassium salt, a magnesium salt and a lithium salt.

3. The compound, or the pharmaceutically acceptable salt thereof of claim 1, wherein the pharmaceutically acceptable salt is selected from the group consisting of:



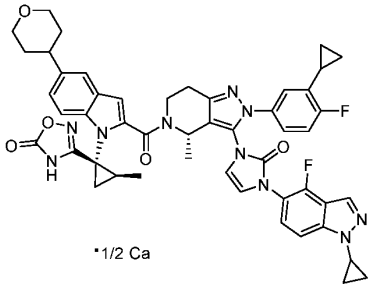
· Na

and



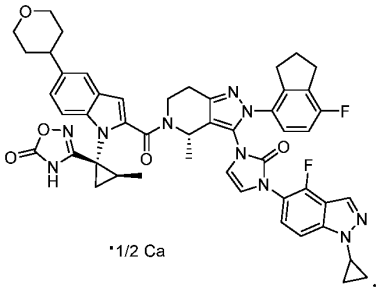
· Na

4. The compound, or the pharmaceutically acceptable salt thereof of claim 1, wherein the pharmaceutically acceptable salt is selected from the group consisting of:



·1/2 Ca

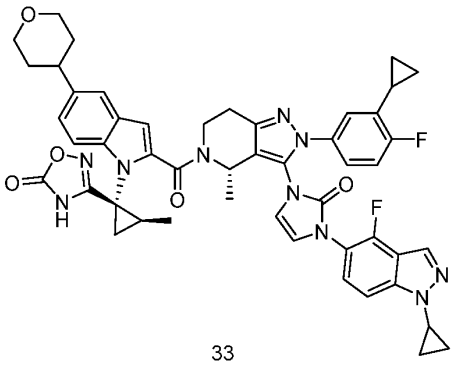
and



·1/2 Ca

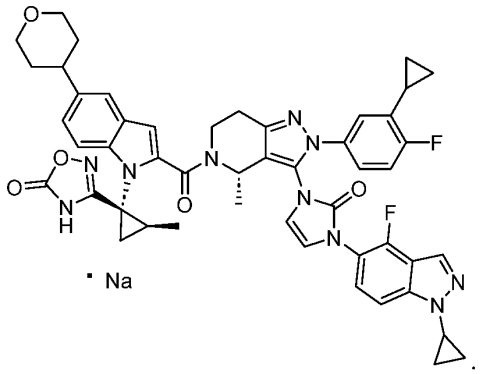
5. The compound or the pharmaceutically acceptable salt thereof of claim 1, wherein the compound is

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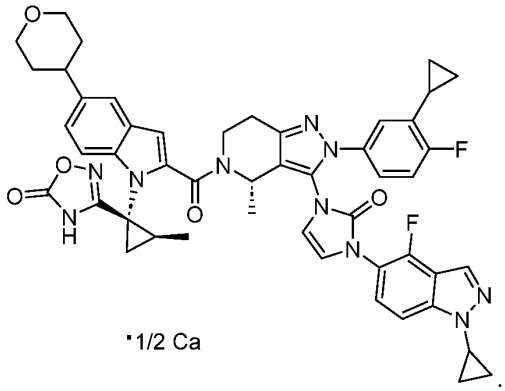
33

6. The compound or the pharmaceutically acceptable salt thereof of claim 1, wherein the pharmaceutically acceptable salt is



· Na

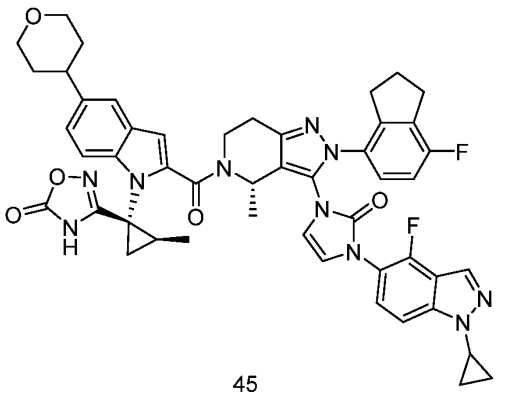
7. The compound or the pharmaceutically acceptable salt thereof of claim 1, wherein the pharmaceutically acceptable salt is



·1/2 Ca

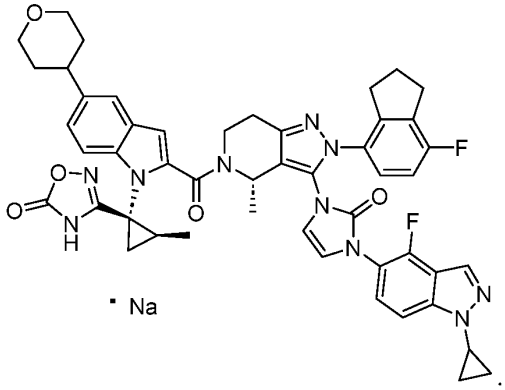
8. The compound or the pharmaceutically acceptable salt thereof of claim 1, wherein the compound is

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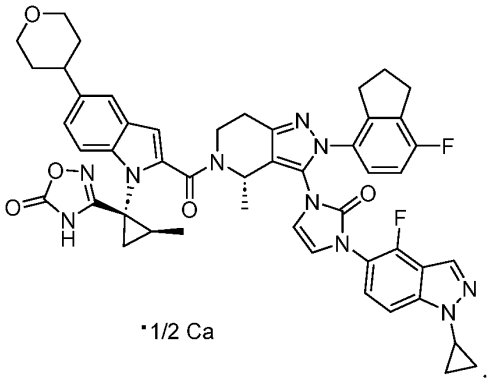
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9. The compound or the pharmaceutically acceptable salt thereof of claim 1, wherein the pharmaceutically acceptable salt is



• Na

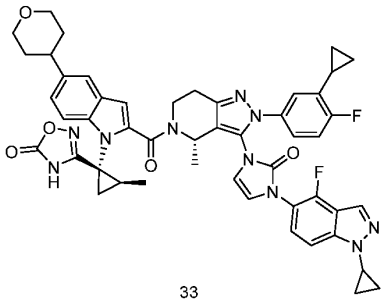
10. The compound or the pharmaceutically acceptable salt thereof of claim 1, wherein the pharmaceutically acceptable salt is



•1/2 Ca

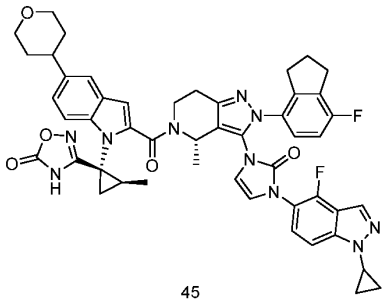
11. A compound, selected from the group consisting of:

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33

and



45

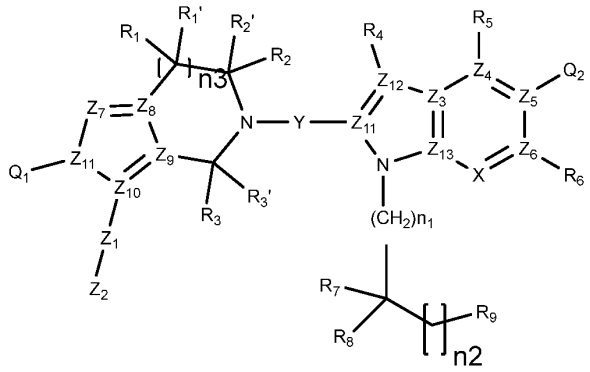
12. A pharmaceutical composition, comprising the compound, or the pharmaceutically acceptable salt thereof of claim 1, and a pharmaceutically acceptable excipient.

13. A pharmaceutical composition, comprising the compound of claim 11, and a pharmaceutically acceptable excipient.

Ascletis EX2003
Page 116 of 555

ABSTRACT

The present disclosure describes GLP-1R modulating compounds that are useful for treating GLP-1R-mediated diseases or conditions.



Formula (I)

Ascletis EX2003
Page 117 of 555

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/885,065	**09/13/2024 04:41:46 PM Z ET**	**HRT-030US1**

Title of Invention

GLP-1R Agonist and Therapeutic Method Thereof

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4802	FILED BY	Daniel Nevrivy
PATENT CENTER #	67167601	FILING DATE	-
CUSTOMER #	83682	FIRST NAMED INVENTOR	Bin Liang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 12

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
ADS.pdf		10	Application Data Sheet	2174 KB
EOT_pleading.pdf		1	Authorization for Extension of Time all replies	20 KB
Declaration_Liang_signed.pdf		2	Oath or Declaration filed	177 KB
Declaration_Yang_signed.pdf		2	Oath or Declaration filed	178 KB
Declaration_Wu_Signed.pdf		2	Oath or Declaration filed	178 KB
poa_signed.pdf		2	Power of Attorney	189 KB
track1.pdf		2	Track One Request	174 KB
application_filed.pdf		88	-	835 KB
application_filed-SPEC.pdf	(1-83)	83	Specification	788 KB

application_filed-CLM.pdf	(84-87)	4	Claims	52 KB
application_filed-ABST.pdf	(88-88)	1	Abstract	23 KB
TRANSMITTAL.pdf		2	Transmittal of New Application	375 KB
373c_merged_.pdf		6	Transmittal Letter	289 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
ADS.pdf	FA94577E75030DEEC7FE32910005B86A3E40D053AC9AC89B DB92CF9B6EC4BAC34E538D6D0E9587C4102A363F26B1B474 35824C6C53FB34527E923A2A236E3F09
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Declaration_Liang_signed.pdf	AA2300ED501E355F440BE34A4310CFDCCFEB54666E60CC66 58D31411F8282C5EC386991326A455D3902EFE55A68E46B42F F76DAECBB74F4079AA11D33AAC1FF1
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Declaration_Wu_Signed.pdf	69AB2116C80BF7C7004B8CDA19AEB479400D5C5BDF49107B 759EF701D08775D64AFFE98E70A8A89876F991EC5B79730105 90CABE79C6781054025B84B93024A6
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application_filed-ABST.pdf	FA6056EDC01E7AF4D7844CB366985A7109A544268C9CFAA51 67BB20492B33DC22BAD9C2EF11A6AB680BD253B161C2A162 1F3897C6E211686AFA3CB906FA99F77
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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/885,065	**09/13/2024 04:41:46 PM Z ET**	**HRT-030US1**

Title of Invention

GLP-1R Agonist and Therapeutic Method Thereof

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4802	FILED BY	Daniel Nevrivy
PATENT CENTER #	67167601	AUTHORIZED BY	-
CUSTOMER #	83682	FILING DATE	-
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Bin Liang

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 7980	**E20249CG50306524**	**Daniel Nevrivy**

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
			TOTAL AMOUNT:	**$2,560.00**

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New Applications Under 35 U.S.C. 111

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

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New International Application Filed with the USPTO as a Receiving Office

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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
18/885,065	09/13/2024		824	HRT-030US1	13	2

CONFIRMATION NO. 4802

83682
Nevrivy Patent Law Group P.L.L.C.
1101 30th Street, NW
Suite 500
Washington, DC 20007

FILING RECEIPT



Date Mailed: 10/01/2024

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.

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Inventor(s)

Bin Liang, Hong Kong, CHINA;
Jinzi Jason Wu, Hong Kong, CHINA;
Bailing Yang, Hong Kong, CHINA;

Applicant(s)

Ascletis Pharma (China) Co., Limited, Hong Kong, CHINA;

Power of Attorney: The patent practitioners associated with Customer Number 83682

Domestic Priority data as claimed by applicant

This appln claims benefit of 63/603,854 11/29/2023
and claims benefit of 63/673,461 07/19/2024

Foreign Applications (You may be eligible to benefit from the Patent Prosecution Highway program at the USPTO. Please see http://www.uspto.gov for more information.)
CHINA 202311582240.2 11/24/2023 Access Code Provided
CHINA 202311686034.6 12/08/2023 Access Code Provided
CHINA 202410142451.2 01/31/2024 Access Code Provided
CHINA 202410202078.5 02/22/2024 Access Code Provided
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CHINA 202410906296.7 07/05/2024 Access Code Provided
CHINA 202411237013.0 09/04/2024 Access Code Provided

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The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 18/885,065**

Projected Publication Date: 05/29/2025

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

GLP-1R Agonist and Therapeutic Method Thereof

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 18/885,065

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	64		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), 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))	13 minus 20 =	* 0	x =	0	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 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).			0			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	664		TOTAL	

APPLICATION AS AMENDED - PART II

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

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

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
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Kathi Vidal

Kathi Vidal
Under Secretary of Commerce for Intellectual Property and
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/885,065	09/13/2024	Bin Liang	HRT-030US1	4802

83682 7590 10/24/2024

Nevrivy Patent Law Group P.L.L.C.
1101 30th Street, NW
Suite 500
Washington, DC 20007

EXAMINER
CENTRAL, DOCKET

ART UNIT	PAPER NUMBER
OPAP	

NOTIFICATION DATE	DELIVERY MODE
10/24/2024	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):

bcastro@nevrivylaw.com
dnevrivy@nevrivylaw.com
eofficeaction@appcoll.com

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 18/885,065	**Applicant(s)** Liang et al.	
	Examiner CHERYL P GIBSON BAYLOR	**Art Unit** OPET	**AIA (FITF) Status** Yes

1. THE REQUEST FILED 13 September 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 CHERYL GIBSON BAYLOR at (571)272-3213. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/CHERYL GIBSON BAYLOR/ Paralegal Specialist, OPET	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Liang *et al.*	Confirmation No.: 4802
Appl. No.: 18/885,065	Art Unit: 1693
Filed: September 13, 2024	Examiner: HOI YAN NMN LEE
For: **GLP-1R Agonist and Therapeutic Method Thereof**	Atty. Docket: HRT-030US1

Information Disclosure Statement Under 37 C.F.R. § 1.97(b)

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

Madam:

Listed on accompanying IDS Form PTO/SB/08a are document(s) that may be considered material to the patentability of this application as defined in 37 C.F.R. § 1.56, and in compliance with the duty of disclosure requirements of 37 C.F.R. § 1.97 and 1.98.

Where the date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicant has listed dates on the attached IDS Forms based on information presently available to the undersigned. However, the listed dates should not be construed as an admission that the information was actually published on the date indicated.

Documents FP1, FP15-FP18, FP32 and FP46 are in a foreign language.

Below are English language abstracts of FP1, FP15-FP17, FP32 and FP46 that are provided to provide a concise statement of the relevance thereof.

Document FP1 Abstract: To provide pharmaceutical compositions which have the same action as GLP-1 peptide as a GLP-1 receptor agonist, are capable of noninvasive administration, and contain a compound having improved activity, metabolic stability, and bioavailability or a salt thereof or a solvate thereof; and to provide methods for preventing or treating non-insulin-dependent diabetes mellitus (type 2 diabetes mellitus) or obesity using the pharmaceutical composition. SOLUTION: The present invention provides a pharmaceutical composition which contains as active ingredient a compound having a base skeleton represented by formula (I) in which an indole ring and a pyrazolopyridine skeleton are linked via a substituent, or a salt thereof or a solvate thereof, and is used in the prevention and treatment of diabetes mellitus non-insulin-dependent (type 2 diabetes mellitus) or obesity.

Document FP15 Abstract: The invention provides a GLP-1 inhibitor. The inhibitor has a structure shown in the specification. The GLP-1 inhibitor has the advantages of good activity and low toxicity.

Document FP16 Abstract: The invention discloses a compound as shown in a formula I, or pharmaceutically acceptable salt, isomer, metabolite, prodrug, solvate or hydrate, pharmaceutical composition and application thereof. The compound shown in the formula I has a good treatment effect on non-insulin-dependent diabetes mellitus (type 2 diabetes mellitus), obesity and the like.

Document FP17 Abstract: The invention discloses a compound as shown in a formula I, or pharmaceutically acceptable salt, isomer, metabolite, prodrug, solvate or hydrate, pharmaceutical composition and application thereof. The compound shown in the formula I has a good treatment effect on non-insulin-dependent diabetes mellitus (type 2 diabetes mellitus), obesity and the like.

Document FP18 Abstract: The invention belongs to the technical field of chemical synthesis of medicines, and particularly relates to a preparation method of a GLP-1 receptor agonist Orforglipron (LY3502970). The synthesis method comprises the following reaction steps: carrying out ring closing on a dihydropyridine compound (1) containing different protecting groups and (4-fluoro-3, 5-dimethylphenyl) hydrazine (8) to obtain a key intermediate (2), carrying out addition, ring closing, Buchwald coupling, amino protecting group removal and salifying to obtain a compound (6), and finally reacting with a compound (11) to obtain the target compound Orforglipron (LY3502970).

Document FP32 Abstract: The present disclosure discloses various salt forms of Compound I and Compound II represented by the following structural formula, and their corresponding pharmaceutical compositions. The present disclosure describes specific single crystalline forms of a 1: 1 compound ITris salt, a 1: 1 compound II Tris salt, and a 1: 1 compound II citrate salt with various properties and physical measurements. Also disclosed are methods of making specific crystalline forms. The present disclosure simultaneously provides methods of treating type 2 diabetes, pre-diabetes, obesity, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, and cardiovascular disease in an individual.

Document FP46 Abstract: Disclosed are novel compounds of Chemical Formula 1, optical isomers of the compounds, and pharmaceutically acceptable salts of the compounds or the optical isomers. The compounds, isomers, and salts exhibit excellent activity as GLP-1 receptor agonists. In particular, they, as GLP-1 receptor agonists, exhibit excellent glucose tolerance, thus having a great potential to be used as therapeutic agents for metabolic diseases. Moreover, they exhibit excellent pharmacological safety for cardiovascular systems.

Applicant reserves the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith.

Respectfully submitted,

NEVRIVY PATENT LAW GROUP P.L.L.C.

/Daniel J. Nevrivy/

Daniel J. Nevrivy
Registration No. 59,118

Date: November 2, 2024

1101 30th St., NW
Suite 500
Washington, D.C. 20007
(202) 713-0843

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 June 2021 (17.06.2021)

WIPO | PCT

(10) International Publication Number
WO 2021/116874 A1

(51) International Patent Classification:
C07C 215/12 (2006.01) *C07D 405/14* (2006.01)
A61P 3/00 (2006.01) *A61K 31/4545* (2006.01)
A61P 5/00 (2006.01) *A61P 25/00* (2006.01)

(21) International Application Number:
PCT/IB2020/061585

(22) International Filing Date:
07 December 2020 (07.12.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/946,084 10 December 2019 (10.12.2019) US

(71) Applicant: **PFIZER INC.** [US/US]; 235 East 42nd Street, New York, New York 10017 (US).

(72) Inventors: **ASPNES, Gary E.**; c/o Pfizer Inc., 445 Eastern Point Road, Bldg. 98, Groton, Connecticut 06340 (US). **BAGLEY, Scott W.**; c/o Pfizer Inc., 445 Eastern Point Road, Bldg. 98, Groton, Connecticut 06340 (US). **CLARK, Wesley Dewitt**; c/o Pfizer Inc., 445 Eastern Point Road, Bldg. 98, Groton, Connecticut 06340 (US). **CURTO, John M.**; c/o Pfizer Inc., 445 Eastern Point Road, Bldg. 98, Groton, Connecticut 06340 (US). **EDMONDS, David James**; c/o Pfizer Inc., 610 Main Street, Cambridge, Massachusetts 02139 (US). **FLANAGAN, Mark E.**; c/o Pfizer Inc., 445 Eastern Point Road, Bldg. 98, Groton, Connecticut 06340 (US). **FUTATSUGI, Kentaro**; c/o Pfizer Inc., 610 Main Street, Cambridge, Massachusetts 02139 (US). **GRIFFITH, David Andrew**; c/o Pfizer Inc., 610 Main Street, Cambridge, Massachusetts 02139 (US). **HUARD, Kim**; 2139 Spaulding Avenue, Berkeley, California 94703 (US). **LIAN, Yajing**; c/o Pfizer Inc., 445 Eastern Point Road, Bldg. 98, Groton, Connecticut 06340 (US). **LIMBERAKIS, Chris**; c/o Pfizer Inc., 445 Eastern Point Road, Bldg. 98, Groton, Connecticut 06340 (US). **LONDREGAN, Allyn T.**; c/o Pfizer Inc., 445 Eastern Point Road, Bldg. 98, Groton, Connecticut 06340 (US). **MATHIOWETZ, Alan M.**; c/o Pfizer Inc., 610 Main Street, Cambridge, Massachusetts 02139 (US). **PIOTROWSKI, David Walter**; c/o Pfizer Inc., 445 Eastern Point Road, Bldg. 98, Groton, Connecticut 06340 (US). **RUGGERI, Roger B.**; 53 Twin Lakes Drive, Waterford, Connecticut 06385 (US).

(74) Agent: **ZIELINSKI, Bryan C.**; PFIZER INC., 235 East 42nd Street, MS 235/9/86, New York, New York 10017 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *with international search report (Art. 21(3))*

(54) **Title:** SOLID FORMS OF 2-((4-((S)-2-(5-CHLOROPYRIDIN-2-YL)-2-METHYLBENZO[D] [1,3]DIOXOL-4-YL)PIPERIDIN-1-YL)METHYL)-1-(((S)-OXETAN-2-YL)METHYL)-1H-BENZO[D] IMIDAZOLE-6-CARBOXYLIC ACID, 1,3-DIHYDROXY-2-(HYDROXYMETHYL)PROPAN-2-AMINE SALT

(57) **Abstract:** The invention provides solid forms of 2-((4-((S)-2-(5-chloropyridin-2-yl)-2-methylbenzo[d][1,3]dioxol-4-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-amine salt for example, a hydrate (e.g. a monohydrate) crystalline form (e.g. Form 2 or Form 3) or an amorphous form; as well as pharmaceutical compositions, and the uses thereof in treating diseases, conditions or disorders modulated by GLP-1R in a mammal, such as a human.

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Solid Forms of 2-((4-((*S*)-2-(5-Chloropyridin-2-yl)-2-methylbenzo[*d*][1,3]dioxol-4-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid, 1,3-Dihydroxy-2-(hydroxymethyl)propan-2-amine Salt

FIELD OF INVENTION

The invention provides solid forms (e.g. crystalline forms) of 2-((4-((*S*)-2-(5-chloropyridin-2-yl)-2-methylbenzo[*d*][1,3]dioxol-4-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-amine salt; processes for preparing thereof; pharmaceutical compositions, dosage forms, and uses thereof in treating diseases, conditions or disorders modulated by GLP-1R in a mammal such as a human.

BACKGROUND OF THE INVENTION

Diabetes is a major public health concern because of its increasing prevalence and associated health risks. The disease is characterized by high levels of blood glucose resulting from defects in insulin production, insulin action, or both. Two major forms of diabetes are recognized, Type 1 and Type 2. Type 1 diabetes (T1D) develops when the body's immune system destroys pancreatic beta cells, the only cells in the body that make the hormone insulin that regulates blood glucose. To survive, people with Type 1 diabetes must have insulin administered by injection or a pump. Type 2 diabetes mellitus (referred to generally as T2DM) usually begins with either insulin resistance or when there is insufficient production of insulin to maintain an acceptable glucose level.

Currently, various pharmacological approaches are available for treating hyperglycemia and subsequently, T2DM (Hampp, C. et al. *Use of Antidiabetic Drugs in the U.S.*, 2003-2012, *Diabetes Care* 2014, 37, 1367-1374). These may be grouped into six major classes, each acting through a different primary mechanism: (A) Insulin secretogogues, including sulphonyl-ureas (e.g., glipizide, glimepiride, glyburide), meglitinides (e.g., nateglidine, repaglinide), dipeptidyl peptidase IV (DPP-IV) inhibitors (e.g., sitagliptin, vildagliptin, alogliptin, dutogliptin, linagliptin, saxogliptin), and glucagon-like peptide-1 receptor (GLP-1R) agonists (e.g., liraglutide, albiglutide, exenatide, lixisenatide, dulaglutide, semaglutide), which enhance secretion of insulin by acting on the pancreatic beta-cells. Sulphonyl-ureas and meglitinides have limited efficacy and tolerability, cause weight gain and often induce hypoglycemia. DPP-IV inhibitors have limited efficacy. Marketed GLP-1R agonists are peptides administered by subcutaneous injection. Liraglutide is additionally approved for the treatment of obesity. (B) Biguanides (e.g., metformin) are thought to act primarily by decreasing hepatic glucose production. Biguanides often cause gastrointestinal disturbances and lactic acidosis, further limiting their use. (C) Inhibitors of alpha-glucosidase (e.g., acarbose) decrease intestinal glucose absorption. These agents often cause gastrointestinal disturbances. (D) Thiazolidinediones (e.g., pioglitazone, rosiglitazone) act on a specific receptor (peroxisome

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proliferator-activated receptor-gamma) in the liver, muscle and fat tissues. They regulate lipid metabolism subsequently enhancing the response of these tissues to the actions of insulin. Frequent use of these drugs may lead to weight gain and may induce edema and anemia. (E) Insulin is used in more severe cases, either alone or in combination with the above agents, and frequent use may also lead to weight gain and carries a risk of hypoglycemia. (F) sodium-glucose linked transporter cotransporter 2 (SGLT2) inhibitors (e.g., dapagliflozin, empagliflozin, canagliflozin, ertugliflozin) inhibit reabsorption of glucose in the kidneys and thereby lower glucose levels in the blood. This emerging class of drugs may be associated with ketoacidosis and urinary tract infections.

However, with the exception of GLP-1R agonists and SGLT2 inhibitors, the drugs have limited efficacy and do not address the most important problems, the declining β-cell function and the associated obesity.

Obesity is a chronic disease that is highly prevalent in modern society and is associated with numerous medical problems including hypertension, hypercholesterolemia, and coronary heart disease. It is further highly correlated with T2DM and insulin resistance, the latter of which is generally accompanied by hyperinsulinemia or hyperglycemia, or both. In addition, T2DM is associated with a two to fourfold increased risk of coronary artery disease. Presently, the only treatment that eliminates obesity with high efficacy is bariatric surgery, but this treatment is costly and risky. Pharmacological intervention is generally less efficacious and associated with side effects. There is therefore an obvious need for more efficacious pharmacological intervention with fewer side effects and convenient administration.

Although T2DM is most commonly associated with hyperglycemia and insulin resistance, other diseases associated with T2DM include hepatic insulin resistance, impaired glucose tolerance, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, obesity, dyslipidemia, hypertension, hyperinsulinemia, and nonalcoholic fatty liver disease (NAFLD).

NAFLD is the hepatic manifestation of metabolic syndrome, and is a spectrum of hepatic conditions encompassing steatosis, non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis and ultimately hepatocellular carcinoma. NAFLD and NASH are considered the primary fatty liver diseases as they account for the greatest proportion of individuals with elevated hepatic lipids. The severity of NAFLD/NASH is based on the presence of lipid, inflammatory cell infiltrate, hepatocyte ballooning, and the degree of fibrosis. Although not all individuals with steatosis progress to NASH, a substantial portion does.

GLP-1 is a 30 amino acid long incretin hormone secreted by the L-cells in the intestine in response to ingestion of food. GLP-1 has been shown to stimulate insulin secretion in a physiological and glucose-dependent manner, decrease glucagon secretion, inhibit gastric emptying, decrease appetite, and stimulate proliferation of beta-cells. In non-clinical experiments GLP-1 promotes continued beta-cell competence by stimulating transcription of

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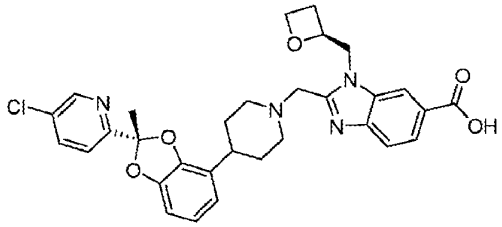
genes important for glucose-dependent insulin secretion and by promoting beta-cell neogenesis (Meier, et al. *Biodrugs*. 2003; 17 (2): 93-102).

In a healthy individual, GLP-1 plays an important role regulating post-prandial blood glucose levels by stimulating glucose-dependent insulin secretion by the pancreas resulting in increased glucose absorption in the periphery. GLP-1 also suppresses glucagon secretion, leading to reduced hepatic glucose output. In addition, GLP-1 delays gastric emptying and slows small bowel motility delaying food absorption. In people with T2DM, the normal post-prandial rise in GLP-1 is absent or reduced (Vilsboll T, et al. *Diabetes*. 2001. 50; 609-613).

Holst (*Physiol. Rev.* 2007, 87, 1409) and Meier (*Nat. Rev. Endocrinol.* 2012, 8, 728) describe that GLP-1 receptor agonists, such as GLP-1, liraglutide and exendin-4, have 3 major pharmacological activities to improve glycemic control in patients with T2DM by reducing fasting and postprandial glucose (FPG and PPG): (i) increased glucose-dependent insulin secretion (improved first- and second-phase), (ii) glucagon suppressing activity under hyperglycemic conditions, (iii) delay of gastric emptying rate resulting in retarded absorption of meal-derived glucose.

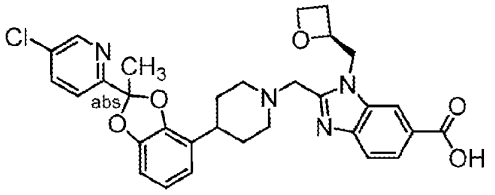
There remains a need for an easily-administered prevention and/or treatment for cardiometabolic and associated diseases.

2-((4-((*S*)-2-(5-Chloropyridin-2-yl)-2-methylbenzo[*d*][1,3]dioxol-4-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid (referred to herein as "Compound 1") is a GLP1 agonist.



Compound 1

Compound 1 (both in the forms the free acid and as its tris salt) was prepared in Example 10 of US Patent Application No. 16/436,311 filed June 10, 2019 and of International Application No. PCT/IB2019/054867 filed June 11, 2019, each of which is hereby incorporated herein by reference in its entirety. There, Compound 1 was designated as 2-({4-[2-(5-chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2:



DIAST-X2,

wherein the chiral center on the left part of the compound structure is marked as "abs" to indicate that chiral center has only one stereo-configuration (i.e., not a racemate with respect to that chiral center).

In addition, US Patent Application No. 16/436,311 and International Application No. PCT/IB2019/054867 reported an anhydrous crystalline form (designed as Form A) of the tris salt of Compound 1.

It is well known that a solid form, for example a crystalline form of a particular drug (including, e.g., anhydrate, hydrate, solvate, etc.) is often an important determinant of the drug's ease of preparation, stability, solubility, storage stability, ease of formulation, ease of handling, and *in vivo* pharmacology and/or efficacy. Different crystalline forms occur where the same composition of matter crystallizes in a different lattice arrangement resulting in different thermodynamic properties and stabilities specific to the particular polymorph form. In cases where two or more crystalline forms can be produced, it is desirable to have a method to make each of the crystalline forms in pure form. In deciding which crystalline form is preferable, the numerous properties of the crystal forms must be compared and the preferred crystal form chosen based on the many physical property variables. It is entirely possible that one crystalline form can be preferable in some circumstances where certain aspects such as ease of preparation, stability, etc. are deemed to be critical. In other situations, a different crystalline form maybe preferred for greater solubility and/or superior pharmacokinetics. Moreover, because of the potential advantages associated with one pure crystalline form, it is desirable to prevent or minimize polymorphic conversion (i.e., conversion of one crystal form to another; or conversion between one crystal form and amorphous form) when two or more crystalline forms of one substance can exist. Such polymorphic conversion can occur during both the preparation of formulations containing the crystalline form, and during storage of a pharmaceutical dosage form containing a crystal form. Because improved drug formulations showing, for example, better bioavailability or better stability are consistently sought, there is an ongoing need for new or purer solid (e.g. crystalline) forms of existing drug molecules. The novel solid (e.g. crystalline) forms of tris salt of Compond 1 described herein are directed toward this and other important ends.

SUMMARY OF THE INVENTION

The present invention provides a solid form, for example a hydrate (e.g. a monohydrate) crystalline form of 2-((4-((*S*)-2-(5-Chloropyridin-2-yl)-2-methylbenzo[*d*][1,3]dioxol-4-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid, tris salt (e.g. Form 2 or Form 3) or an amorphous form, characterized according to the powder X-ray diffraction data, ^{13}C solid state NMR data, and/or optionally single crystal spectrum data provided herein.

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The present invention further provides compositions containing a hydrate (e.g. a monohydrate) crystalline form of the invention (e.g. Form 2 or Form 3).

The present invention further provides a method for preparing a hydrate (e.g. a monohydrate) crystalline form of the invention (e.g. Form 2 or Form 3), for example, a method for preparing Form 3 comprising slurrying an anhydrous crystalline form (e.g. Form A) of tris salt of Compound 1 in a mixed solvent to form the monohydrate crystalline form, wherein the mixed solvent comprises water and acetonitrile.

The present invention further provides a method for treating a disease or disorder comprising administering to a mammal in need of such treatment a therapeutically effective amount of a hydrate (e.g. a monohydrate) crystalline form of the invention (e.g. Form 2 or Form 3), wherein the disease or disorder is selected from the group consisting of T1D, T2DM, pre-diabetes, idiopathic T1D, LADA, EOD, YOAD, MODY, malnutrition-related diabetes, gestational diabetes, hyperglycemia, insulin resistance, hepatic insulin resistance, impaired glucose tolerance, diabetic neuropathy, diabetic nephropathy, kidney disease, diabetic retinopathy, adipocyte dysfunction, visceral adipose deposition, sleep apnea, obesity, eating disorders, weight gain from use of other agents, excessive sugar craving, dyslipidemia, hyperinsulinemia, NAFLD, NASH, fibrosis, NASH with fibrosis, cirrhosis, hepatocellular carcinoma,a cardiovascular disease, atherosclerosis, coronary artery disease, peripheral vascular disease, hypertension, endothelial dysfunction, impaired vascular compliance, congestive heart failure, myocardial infarction, stroke, hemorrhagic stroke, ischemic stroke, traumatic brain injury, pulmonary hypertension, restenosis after angioplasty, intermittent claudication, post-prandial lipemia, metabolic acidosis, ketosis, arthritis, osteoporosis, Parkinson's Disease, left ventricular hypertrophy, peripheral arterial disease, macular degeneration, cataract, glomerulosclerosis, chronic renal failure, metabolic syndrome, syndrome X, premenstrual syndrome, angina pectoris, thrombosis, atherosclerosis, transient ischemic attacks, vascular restenosis, impaired glucose metabolism, conditions of impaired fasting plasma glucose, hyperuricemia, gout, erectile dysfunction, skin and connective tissue disorders, psoriasis, foot ulcerations, ulcerative colitis, hyper apo B lipoproteinemia, Alzheimer's Disease, schizophrenia, impaired cognition, inflammatory bowel disease, short bowel syndrome, Crohn's disease, colitis, irritable bowel syndrome, Polycystic Ovary Syndrome, and addiction.

The present invention further provides an amorphous form of 2-((4-((*S*)-2-(5-Chloropyridin-2-yl)-2-methylbenzo[*d*][1,3]dioxol-4-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid, tris salt, a pharmaceutical composition thereof, and use thereof in treating a disease or disorder modulated by GLP-1R.

BRIEF DESCRIPTION OF FIGURES

FIG. 1 shows an observed powder X-ray diffraction pattern for an anhydrous crystalline form (Form A) of tris salt of Compound 1 carried out on a Bruker AXS D8 Endeavor diffractometer equipped with a Cu radiation source.

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FIG. 2 shows an observed ^{13}C ssNMR pattern of Form A of tris salt of Compound 1 conducted on a Bruker-BioSpin CPMAS probe positioned into a Bruker-BioSpin Avance III 500 MHz (^{1}H frequency) NMR spectrometer. The peaks marked by hashed marks and the gray shaded box are spinning sidebands.

FIG. 3 shows an illustrative single crystal structure of a monohydrate crystalline form (Form 2) of tris salt of Compound 1.

FIG. 4 shows a calculated/simulated PXRD pattern of Form 2 of tris salt of Compound 1 based on the information from its single crystal X-ray data analysis.

FIG. 5 shows an illustrative single crystal structure of a monohydrate crystalline form (Form 3) of tris salt of Compound 1.

FIG. 6 shows an observed powder X-ray diffraction pattern for Form 3 of tris salt of Compound 1 carried out on a Bruker AXS D8 Endeavor diffractometer equipped with a Cu radiation source.

FIG. 7 shows an observed ^{13}C ssNMR pattern of Form 3 of tris salt of Compound 1 conducted on a Bruker-BioSpin CPMAS probe positioned into a Bruker-BioSpin Avance III 500 MHz (^{1}H frequency) NMR spectrometer. The peaks marked by hashed marks and the gray shaded box are spinning sidebands.

DETAILED DESCRIPTION OF THE INVENTION

In a first aspect, the present invention provides a hydrate (e.g. a monohydrate) cystalline form of tris salt of Compound 1, which can be identified by its unique solid state signatures with respect to, for example, single crystal X-ray data, powder X-ray diffraction pattern (PXRD), and other solid state methods such as solid state NMR. A hydrate crystalline form of tris salt of Compound 1 disclosed herein refers to a crystalline material/complex that includes both tris salt of Compond 1 and water (hydrate water) in the crystal lattice of the crystalline material/complex.

In a second aspect, the present invention provides a monohydrate cystalline form of tris salt of Compound 1, designated as Form 2 herein. The monohydrate cystalline form of tris salt of Compound 1 (Form 2) can be identified by its unique solid state signatures with respect to, for example, single crystal X-ray data, powder X-ray diffraction pattern (PXRD), and other solid state methods.

Form 2 can be prepared by slow solvent evaporation of a solution of tris salt of Compound 1 in a solvent to precipitate Form 2, wherein the solvent is about 3% to about 10% (e.g. about 2% to about 5%, or about 3% to about 4%, v/v) water in a protic organic solvent (that is miscible with water), for example, an alcohol such as methanol or ethanol. In some embodiments, Form 2 is prepared by slow solvent evaporation of a solution of tris salt of Compound 1 in a solvent, wherein the solvent is about 2% to about 5% (e.g. or about 3% to about 4%, v/v) water in methanol. In some embodiments, the solution of the tris salt of Compound 1 is generated in situ, for example, by mixing a solution of Compound 1 in a protic

organic solvent that is miscible with water (e.g. an alcohol such as methonal) with an aqueous solution of tris.

Form 2 has a calculated/simulated PXRD pattern substantially the same as that shown in FIG. 4. Simulated peak locations and intensities for the PXRD pattern in FIG. 4 are provided in Table E2-5. Some characteristic PXRD peaks of Form 2, expressed as 2Θ ± 0.2° 2Θ are at 7.1, 7.6, 10.7, and 19.4 (diffraction angles). In some embodiments, Form 2 has a powder X-ray diffraction pattern (PXRD) comprising at least one peak, in terms of 2θ ± 0.2° 2Θ, at 7.1, 7.6, 10.7, and 19.4. In some embodiments, Form 2 has a PXRD comprising at least two peaks, in terms of 2θ ± 0.2° 2Θ, at 7.1, 7.6, 10.7, and 19.4. In some embodiments, Form 2 has a PXRD comprising at least two peaks, in terms of 2θ ± 0.2° 2Θ, at 7.1 and 10.7. In some embodiments, Form 2 has a PXRD comprising at least two peaks, in terms of 2θ ± 0.2° 2Θ, at 7.1 and 7.6. In some embodiments, Form 2 has a PXRD comprising at least three peaks, in terms of 2θ ± 0.2° 2Θ, at 7.1, 7.6, and 10.7. In some embodiments, Form 2 has a PXRD comprising at least three peaks, in terms of 2θ ± 0.2° 2Θ, at 7.1, 7.6, and 19.4. In some embodiments, Form 2 has a PXRD comprising at least four peaks, in terms of 2θ ± 0.2° 2Θ, at 7.1, 7.6, 10.7, and 19.4.

In a third aspect, the present invention provides a monohydrate cystalline form of tris salt of Compound 1, designated as Form 3 herein. The monohydrate cystalline form of tris salt of Compound 1 (Form 3) can be identified by its unique solid state signatures with respect to, for example, single crystal X-ray data, PXRD, ^{13}C ssNMR, and other solid state methods.

Form 3 can be prepared by slurry to slurry conversion. A slurry of Form A (an anhydrous form of tris salt of Compound 1) in a solvent sytem is stirred for a period suffiently long to convert Form A to Form 3, wherein the solvent system includes an aprotic organic solvent (e.g. acetonitrile or tetrahydrofuran) and water. In some embodiments, the solvent system includes acetonitrile and water, and the ratio of water to acetonitrile in the solvent system is from about 2:98 to about 15:85 (e.g. about 8:92 v/v). In some embodiments, the ratio of the solvent system (in mL) to Form A (in gram) is about 10:1 to about 40:1, for exampe, about 15:1 to about 30:1, or about 25:1 to about 35:1. The slurry to slurry conversion can be carried out at room temperature with suffient mixing/stirring. Preparation of the starting material Form A (and its physical characteristic property) is shown in Example 1. The conversion of Form A to Form 3 can be monitored/assessed by PXRD.

Alternatively, Form 3 can be prepared by vapor diffusion of acetonitrile into a concentrated (e.g. saturated) solution of tris salt of Compound 1 in a solvent system, wherein the solvent system is a mixture of acetonitrile and water, and the percentage of water in the solvent system is more than about 10% by volume, for example about 15%. In some embodiment, the tris salt of Compound 1 in the saturated solution can the concentrated (e.g. saturated) solution can be generated in situ, for example, by mixing a solution of Compound 1 in acetonitrile with an aqueous solution of tris (for example, about 1:1 molar ratio). Alternatively,

acetonitrile can be substituted by another aprotic organic solvent that is miscible with water (e.g. tetrahydrofuran) in the vapor diffusion method described herein [i.e., Form 3 can be prepared by vapor diffusion of an aprotic solvent into a concentrated (e.g. saturated) solution of tris salt of Compound 1 in a solvent system, wherein the solvent system is a mixture of the aprotic organic solvent and water].

Form 3 has a PXRD pattern substantially the same as that shown in FIG. 6. Peak locations and intensities for the PXRD pattern in FIG. 6 are provided in Table E3-5. Some characteristic PXRD peaks of Form 3, expressed as 2Θ ± 0.2° 2Θ are at 3.7, 7.4, 9.9, 14.8, and 20.6 (diffraction angles). In some embodiments, Form 3 has a PXRD comprising at least one, two, three, or four peaks, in terms of 2θ ± 0.2° 2Θ, at 3.7, 7.4, 9.9, 14.8, and 20.6. In some embodiments, Form 3 has a PXRD comprising at least two or three peaks, in terms of 2θ ± 0.2° 2Θ, at 3.7, 7.4, 9.9, 14.8, and 20.6. In some embodiments, Form 3 has a PXRD comprising two peaks, in terms of 2θ ± 0.2° 2Θ, at 7.4 and 14.8. In some embodiments, Form 3 has a PXRD comprising three peaks, in terms of 2θ ± 0.2° 2Θ, at 3.7, 7.4, and 14.8. In some embodiments, Form 3 has a PXRD comprising four peaks, in terms of 2θ ± 0.2° 2Θ, at 3.7, 7.4, 14.8, and 20.6. In some embodiments, Form 3 has a PXRD comprising five peaks, in terms of 2θ ± 0.2° 2Θ, at 3.7, 7.4, 9.9, 14.8, and 20.6. In some embodiments, Form 3 has a PXRD comprising peaks, in terms of 2θ ± 0.2° 2Θ, at 3.7, 7.4, 9.9, 11.1, 14.8, 18.2, 20.6, 23.5, 24.3, and 24.6.

Form 3 has a ^{13}C ssNMR spectrum substantially the same as that shown in FIG. 7. ^{13}C Chemical shifts (± 0.2 ppm) of Form 3 as shown in FIG. 7 are listed in Table E3-6. Some characteristic ^{13}C ssNMR chemical shifts of Form 3, expressed as ppm, are at 42.8, 54.7, 128.2, 138.4 and 156.6 ± 0.2 ppm.

In some embodiments, Form 3 has a ^{13}C ssNMR spectrum comprising chemical shifts at 54.7 and 138.4 ± 0.2 ppm. In some embodiments, Form 3 has a ^{13}C ssNMR spectrum comprising chemical shifts at 54.7, 138.4 and 156.6 ppm ± 0.2 ppm.

In a fourth aspect, the present invention further provides an amorphous form of tris salt of Compound 1. The amorphous form of tris salt of Compound 1 does not give distinctive powder X-ray diffraction patterns (i.e., it PXRD does not have sharp peaks as in a PXRD for Form A or Form 3). The amorphous form of tris salt of Compound 1 can be prepared, for example, by a lyophilization process (starting from a solution of tris salt of Compound 1).

Any solid form of the present invention can be substantially pure. As used herein, the term "substantially pure" with reference to a particular solid form (e.g. a crystalline form) means that the particular solid form (e.g. the crystalline form) includes less than 15%, less than 10%, less than 5%, less than 3%, or less than 1% by weight of any other physical form of tris salt of Compound 1.

The term "substantially the same" when used to describe X-ray powder diffraction patterns is meant to include patterns in which peaks are within a standard deviation of +/- 0.2° 2Θ.

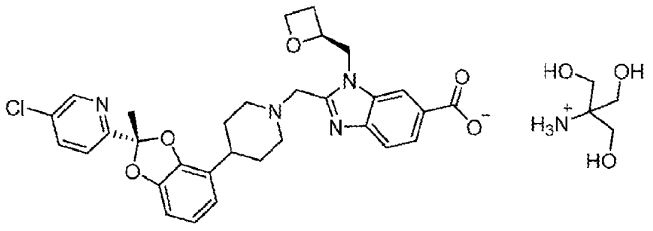
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The term "substantially the same" when used to describe ^{13}C ssNMR spectrum meant to include ^{13}C ssNMR spectra in which chemical shifts are within a standard deviation of +/- 0.2 ppm.

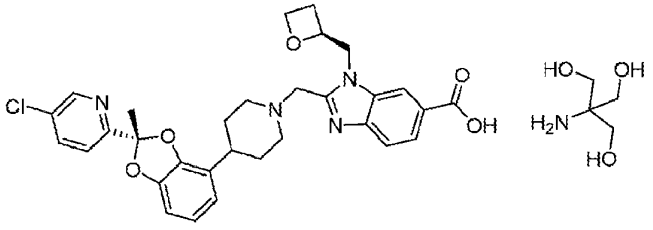
The term "about" generally means within 10%, preferably within 5%, and more preferably within 1% of a given value or range. Alternatively, the term "about" means within an acceptable standard error of the mean, when considered by one skilled in the art.

The term "tris" means 1,3-dihydroxy-2-(hydroxymethyl)propan-2-amine, also known as THAM, tromethamine, or 2-amino-2-(hydroxymethyl)propane-1,3-diol.

Tris salt of Compound 1 means a salt of Compound 1 made using 1,3-dihydroxy-2-(hydroxymethyl)propan-2-amine. The tris is associated with the carboxylic acid moiety of Compound 1. Unless otherwise stated, when referencing the tris salt of Compound 1, the counterion and Compound 1 are in a stoichiometric ratio of about 1:1 (i.e. from 0.9:1.0 to 1.0:0.9, for example, from 0.95:1.00 to 1.00:0.95). Another chemical name for tris salt of Compound 1 is 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium 2-((4-((*S*)-2-(5-Chloropyridin-2-yl)-2-methylbenzo[*d*][1,3]dioxol-4-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylate, which can also be represented, for example, by one of the following structures.



or



Those skilled in the art would readily understand that multiple nomenclatures can be used to name a same compound (including a same salt).

The term "monohydrate" when used to describe a crystalline form of a compound (or a salt) means that the stoichiometric ratio of the hydrate water to the compound (or salt) is about 1 : 1 (for example, from 0.9 :1.0 to 1.1 : 1.0).

In another embodiment, the invention provides a pharmaceutical composition comprising a crystalline form of the invention (e.g. Form 3), in admixture with at least one pharmaceutically acceptable excipient. This would include a pharmaceutical composition

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comprising a crystalline form of the invention (e.g. Form 3), as defined in any of the embodiments described herein, in admixture with at least one pharmaceutically acceptable excipient and one or more other therapeutic agent discussed herein.

In another embodiment, the invention provides a pharmaceutical composition comprising an amorphous form of the invention, in admixture with at least one pharmaceutically acceptable excipient. This would include a pharmaceutical composition comprising an amorphous form of the invention, in admixture with at least one pharmaceutically acceptable excipient and one or more other therapeutic agent discussed herein.

In another embodiment, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of tris salt of Compound 1 and a pharmaceutically acceptable carrier, wherein at least 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 98%, or 99% of the tris salt of Compound 1 is present as one of solid forms of the invention (e.g., Form 2, Form 3, or amorphous form).

In another embodiment, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of tris salt of Compound 1 and a pharmaceutically acceptable carrier, wherein the tris salt of Compound 1 is present as at least two solid forms, for example, a crystalline form and an amorphous form.

In another embodiment, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of tris salt of Compound 1 and a pharmaceutically acceptable carrier, wherein the tris salt of Compound 1 is present as at least two solid forms, for example, a crystalline form of the invention (e.g., Form 2 or Form 3) and an amorphous form. In a further embodiment, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of tris salt of Compound 1 and a pharmaceutically acceptable carrier, wherein the tris salt of Compound 1 is present in two solid forms, one of which is an amorphous form and other is Form 3.

In another embodiment, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of tris salt of Compound 1 and a pharmaceutically acceptable carrier, wherein the tris salt of Compound 1 is present in two solid forms, one of which is amorphous and other is Form 2.

In another embodiment, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of tris salt of Compound 1 and a pharmaceutically acceptable carrier, wherein the tris salt of Compound 1 is present in two solid forms, one of which is Form A and other is Form 3.

The invention also includes the following embodiments:

a solid form of the invention (e.g. Form 2, Form 3, or amorphous form), as defined in any of the embodiments described herein, for use as a medicament;

a solid form of the invention (e.g. Form 2, Form 3, or amorphous form), as defined in any of the embodiments described herein, for use in the prevention and/or treatment of

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cardiometabolic and associated diseases discussed herein, including T2DM, pre-diabetes, obesity, NASH (e.g. NASH with fibrosis), NAFLD, and cardiovascular disease;

a method of treating a disease for which an agonist of GLP-1R is indicated, in a subject in need of such prevention and/or treatment, comprising administering to the subject a therapeutically effective amount of a solid form of the invention (e.g. Form 2, Form 3, or amorphous form), as defined in any of the embodiments described herein;

the use of a solid form of the invention (e.g. Form 2, Form 3, or amorphous form), as defined in any of the embodiments described herein, for the manufacture of a medicament for treating a disease or condition for which an agonist of the GLP-1R is indicated;

a solid form of the invention (e.g. Form 2, Form 3, or amorphous form), as defined in any of the embodiments described herein, for use in the treatment of a disease or condition for which an agonist of GLP-1R is indicated; or

a pharmaceutical composition for the treatment of a disease or condition for which an agonist of the GLP-1R is indicated, comprising a solid form of the invention (e.g. Form 2, Form 3, or amorphous form), as defined in any of the embodiments described herein.

The invention also includes the following embodiments:

a crystalline form of the invention (e.g. Form 3), as defined in any of the embodiments described herein, for use as a medicament;

a crystalline form of the invention (e.g. Form 3), as defined in any of the embodiments described herein, for use in the prevention and/or treatment of cardiometabolic and associated diseases discussed herein, including T2DM, pre-diabetes, obesity, NASH (e.g. NASH with fibrosis), NAFLD, and cardiovascular disease;

a method of treating a disease for which an agonist of GLP-1R is indicated, in a subject in need of such prevention and/or treatment, comprising administering to the subject a therapeutically effective amount of a crystalline form of the invention (e.g. Form 3), as defined in any of the embodiments described herein;

the use of a crystalline form of the invention (e.g. Form 3), as defined in any of the embodiments described herein, for the manufacture of a medicament for treating a disease or condition for which an agonist of the GLP-1R is indicated;

a crystalline form of the invention (e.g. Form 3), as defined in any of the embodiments described herein, for use in the treatment of a disease or condition for which an agonist of GLP-1R is indicated; or

a pharmaceutical composition for the treatment of a disease or condition for which an agonist of the GLP-1R is indicated, comprising a crystalline form of the invention (e.g. Form 3), as defined in any of the embodiments described herein.

Every example of solid forms of the invention may be claimed individually or grouped together in any combination with any number of each and every embodiment described herein.

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The invention also relates to a pharmaceutical composition comprising a solid form of the invention (e.g. Form 2, Form 3, or amorphous form), as defined in any of the embodiments described herein, for use in the treatment and/or prevention of cardiometabolic and associated diseases discussed herein, including T2DM, pre-diabetes, obesity, NASH (e.g. NASH with fibrosis), NAFLD, and cardiovascular disease.

The invention also relates to a pharmaceutical composition comprising a crystalline form of the invention (e.g. Form 3), as defined in any of the embodiments described herein, for use in the treatment and/or prevention of cardiometabolic and associated diseases discussed herein, including T2DM, pre-diabetes, obesity, NASH (e.g. NASH with fibrosis), NAFLD, and cardiovascular disease.

Another embodiment of the invention concerns a solid form of the invention (e.g. Form 2, Form 3, or amorphous form), for example a crystalline form of the invention (e.g. Form 3), as defined in any of the embodiments described herein, for use in the treatment and/or prevention of diseases and/or disorders for which a GLP-1R agonist is indicated including, diabetes (T1D and/or T2DM, including pre-diabetes), idiopathic T1D (Type 1b), latent autoimmune diabetes in adults (LADA), early-onset T2DM (EOD), youth-onset atypical diabetes (YOAD), maturity onset diabetes of the young (MODY), malnutrition-related diabetes, gestational diabetes, hyperglycemia, insulin resistance, hepatic insulin resistance, impaired glucose tolerance, diabetic neuropathy, diabetic nephropathy, kidney disease (e.g., acute kidney disorder, tubular dysfunction, proinflammatory changes to the proximal tubules), diabetic retinopathy, adipocyte dysfunction, visceral adipose deposition, sleep apnea, obesity (including hypothalamic obesity and monogenic obesity) and related comorbidities (e.g., osteoarthritis and urine incontinence), eating disorders (including binge eating syndrome, bulimia nervosa, and syndromic obesity such as Prader-Willi and Bardet-Biedl syndromes), weight gain from use of other agents (e.g., from use of steroids and antipsychotics), excessive sugar craving, dyslipidemia (including hyperlipidemia, hypertriglyceridemia, increased total cholesterol, high LDL cholesterol, and low HDL cholesterol), hyperinsulinemia, NAFLD (including related diseases such as steatosis, NASH, fibrosis, NASH with fibrosis, cirrhosis, and hepatocellular carcinoma),cardiovascular disease, atherosclerosis (including coronary artery disease), peripheral vascular disease, hypertension, endothelial dysfunction, impaired vascular compliance, congestive heart failure, myocardial infarction (e.g. necrosis and apoptosis), stroke, hemorrhagic stroke, ischemic stroke, traumatic brain injury, pulmonary hypertension, restenosis after angioplasty, intermittent claudication, post-prandial lipemia, metabolic acidosis, ketosis, arthritis, osteoporosis, Parkinson's Disease, left ventricular hypertrophy, peripheral arterial disease, macular degeneration, cataract, glomerulosclerosis, chronic renal failure, metabolic syndrome, syndrome X, premenstrual syndrome, angina pectoris, thrombosis, atherosclerosis, transient ischemic attacks, vascular restenosis, impaired glucose metabolism, conditions of impaired fasting plasma glucose, hyperuricemia, gout, erectile dysfunction, skin and connective tissue

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disorders, psoriasis, foot ulcerations, ulcerative colitis, hyper apo B lipoproteinemia, Alzheimer's Disease, schizophrenia, impaired cognition, inflammatory bowel disease, short bowel syndrome, Crohn's disease, colitis, irritable bowel syndrome, Polycystic Ovary Syndrome, and addiction (e.g., alcohol and/or drug abuse).

Room temperature: RT (15 to 25 °C).

Methanol: MeOH.

Ethanol: EtOH.

Isopropanol: iPrOH.

Ethyl acetate: EtOAc.

Tetrahydrofuran: THF.

Toluene: $PhCH_3$.

Cesium carbonate: Cs_2CO_3.

Lithium bis(trimethylsilyl)amide: LiHMDS.

Sodium t-butoxide: NaOtBu.

Potassium t-butoxide: KOtBu.

Lithium diisopropylamide: LDA.

Triethylamine: NEt_3.

N,N-diisopropylethyl amine: DIPEA.

Potassium carbonate: K_2CO_3.

Dimethyl formamide: DMF.

Dimethyl acetamide: DMAc.

Dimethyl sulfoxide: DMSO.

N-Methyl-2-pyrrolidinone: NMP.

Sodium hydride: NaH.

Trifluoroacetic acid: TFA.

Trifluoroacetic anhydride: TFAA.

Acetic anhydride: Ac_2O.

Dichloromethane: DCM.

1,2-Dichloroethane: DCE.

Hydrochloric acid: HCl.

1,8-Diazabicyclo[5.4.0]undec-7-ene: DBU.

Borane-dimethylsulfide complex: BH_3-DMS.

Borane-tetrahydrofuran complex: BH_3-THF.

Lithium aluminum hydride: LAH.

Acetic acid: AcOH.

Acetonitrile: MeCN.

p-Toluenesulfonic acid: pTSA.

Dibenzylidine acetone: DBA.

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2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene: BINAP.

1,1′-Ferrocenediyl-bis(diphenylphosphine): dppf.

1,3-Bis(diphenylphosphino)propane: DPPP.

3-Chloroperbenzoic acid: m-CPBA.

Tert-Butyl methyl ether: MTBE.

Methanesulfonyl: Ms.

N-Methylpyrrolidinone: NMP.

Thin layer chromatography: TLC.

Supercritical fluid chromatography: SFC.

4-(Dimethylamino)pyridine: DMAP.

Tert-Butyloxycarbonyl: Boc.

Triphenylphospine: Ph_3P.

1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate: HATU.

Petroleum ether: PE.

2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate: HBTU.

2-Amino-2-(hydroxymethyl)propane-1,3-diol: tris.

tris(dibenzylideneacetone)dipalladium: $Pd_2(dba)_3$

^1H Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million relative to the residual proton signal in the deuterated solvent ($CHCl_3$ at 7.27 ppm; CD_2HOD at 3.31 ppm; MeCN at 1.94 ppm; DMSO at 2.50 ppm) and are reported using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The symbol ^ denotes that the ^1H NMR peak area was assumed because the peak was partially obscured by water peak. The symbol ^^ denotes that the ^1H NMR peak area was assumed because the peak was partially obscured by solvent peak.

The compounds and intermediates described below were named using the naming convention provided with ACD/ChemSketch 2012, ChemDraw, File Version C10H41, Build 69045 (Advanced Chemistry Development, Inc., Toronto, Ontario, Canada). The naming convention provided with ACD/ChemSketch 2012 is well known by those skilled in the art and it is believed that the naming convention provided with ACD/ChemSketch 2012 generally comports with the IUPAC (International Union for Pure and Applied Chemistry) recommendations on Nomenclature of Organic Chemistry and the CAS Index rules. One will note that the chemical names may have only parentheses or may have parentheses and brackets. The stereochemical descriptors may also be placed at different locations within the name itself, depending on the naming convention. One of ordinary skill in the art will recognize these formatting variations and understand they provide the same chemical structure.

Pharmaceutically acceptable salts include acid addition and base salts.

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Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulfate/sulfate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulfate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate, 1,5-naphathalenedisulfonic acid and xinafoate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, bis(2-hydroxyethyl)amine (diolamine), glycine, lysine, magnesium, meglumine, 2-aminoethanol (olamine), potassium, sodium, 2-Amino-2-(hydroxymethyl)propane-1,3-diol (tris or tromethamine) and zinc salts.

Hemisalts of acids and bases may also be formed, for example, hemisulfate and hemicalcium salts. For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, 2002).

Pharmaceutically acceptable salts may be prepared by one or more of three methods:

(i) by reacting a compound with the desired acid or base;

(ii) by removing an acid- or base-labile protecting group from a suitable precursor of a compound or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or

(iii) by converting one salt of a compound to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

Compounds and pharmaceutically acceptable salts, may exist in unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising a compound or its salt, and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water. For example, a hydrate crystalline form of tris salt of Compound 1 disclosed herein refers to a crystalline material/complex that includes both tris salt of Compond 1 and water (hydrate water) in the crystal lattice of the crystalline material/complex.

A currently accepted classification system for organic hydrates is one that defines isolated site, channel, or metal-ion coordinated hydrates - see Polymorphism in Pharmaceutical Solids by K. R. Morris (Ed. H. G. Brittain, Marcel Dekker, 1995). Isolated site hydrates are ones in which the water molecules are isolated from direct contact with each other by intervening organic molecules. In channel hydrates, the water molecules lie in lattice channels where they

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are next to other water molecules. In metal-ion coordinated hydrates, the water molecules are bonded to the metal ion.

When the solvent or water is tightly bound, the complex may have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and hygroscopic compounds, the water/solvent content may be dependent on humidity and drying conditions. In such cases, non-stoichiometry will be the norm.

Also included within the scope of the invention are multi-component complexes (other than salts and solvates) wherein the drug and at least one other component are present in stoichiometric or non-stoichiometric amounts. Complexes of this type include clathrates (drug-host inclusion complexes) and co-crystals. The latter are typically defined as crystalline complexes of neutral molecular constituents which are bound together through non-covalent interactions, but could also be a complex of a neutral molecule with a salt. Co-crystals may be prepared by melt crystallisation, by recrystallisation from solvents, or by physically grinding the components together - see Chem Commun, 17, 1889-1896, by O. Almarsson and M. J. Zaworotko (2004). For a general review of multi-component complexes, see J Pharm Sci, 64 (8), 1269-1288, by Haleblian (August 1975).

The compounds of the invention may exist in a continuum of solid states ranging from fully amorphous to fully crystalline. The term 'amorphous' refers to a state in which the material lacks long range order at the molecular level and, depending upon temperature, may exhibit the physical properties of a solid or a liquid. Typically such materials do not give distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterised by a change of state, typically second order ('glass transition'). The term 'crystalline' refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such materials when heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterised by a phase change, typically first order ('melting point').

A compound may also exist in a mesomorphic state (mesophase or liquid crystal) when subjected to suitable conditions. The mesomorphic state is intermediate between the true crystalline state and the true liquid state (either melt or solution). Mesomorphism arising as the result of a change in temperature is described as 'thermotropic' and that resulting from the addition of a second component, such as water or another solvent, is described as 'lyotropic'. Compounds that have the potential to form lyotropic mesophases are described as 'amphiphilic' and consist of molecules which possess an ionic (such as $-COO^-Na^+$, $-COO^-K^+$, or $-SO_3^-Na^+$) or non-ionic (such as $-N^+(CH_3)_3$) polar head group. For more information, see Crystals and the Polarizing Microscope by N. H. Hartshorne and A. Stuart, 4th Edition (Edward Arnold, 1970).

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Some compounds may exhibit polymorphism and/or one or more kinds of isomerism (e.g. optical, geometric or tautomeric isomerism). The crystalline forms of the invnetions may also be isotopically labelled. Such variation is implicit to Compound 1 or its salt defined as they are by reference to their structural features and therefore within the scope of the invention.

Compounds containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound contains an alkenyl or alkenylene group, geometric cis/trans (or Z/E) isomers are possible. Where structural isomers are interconvertible via a low energy barrier, tautomeric isomerism ('tautomerism') can occur. This can take the form of proton tautomerism in compounds containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds which contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

Certain pharmaceutically acceptable salts of Compound 1 may also contain a counterion which is optically active (e.g. d-lactate or l-lysine) or racemic (e.g. dl-tartrate or dl-arginine).

Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). Alternatively, a racemic precursor containing a chiral ester may be separated by enzymatic resolution (see, for example, Int J Mol Sci 29682-29716 by A. C. L. M. Carvaho et. al. (2015)). In the case where a compound contains an acidic or basic moiety, a salt may be formed with an optically pure base or acid such as 1-phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be separated by fractional crystallization and one or both of the diastereomeric salts converted to the corresponding pure enantiomer(s) by means well known to a skilled person. Alternatively, the racemate (or a racemic precursor) may be covalently reacted with a suitable optically active compound, for example, an alcohol, amine or benzylic chloride. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization by means well known to a skilled person to give the separated diastereomers as single enantiomers with 2 or more chiral centers. Chiral compounds (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2% to 20%, and from 0 to 5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture. Chiral chromatography using sub-and supercritical fluids may be employed. Methods for chiral chromatography useful in some embodiments of the present invention are known in the art (see, for example, Smith, Roger M., Loughborough University, Loughborough, UK; Chromatographic Science Series

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(1998), 75 (SFC with Packed Columns), pp. 223-249 and references cited therein). In some relevant examples herein, columns were obtained from Chiral Technologies, Inc, West Chester, Pennsylvania, USA, a subsidiary of *Daicel® Chemical Industries, Ltd., Tokyo, Japan.*

When any racemate crystallises, crystals of two different types are possible. The first type is the racemic compound (true racemate) referred to above wherein one homogeneous form of crystal is produced containing both enantiomers in equimolar amounts. The second type is the racemic mixture or conglomerate wherein two forms of crystal are produced in equimolar amounts each comprising a single enantiomer. While both of the crystal forms present in a racemic mixture have identical physical properties, they may have different physical properties compared to the true racemate. Racemic mixtures may be separated by conventional techniques known to those skilled in the art - see, for example, *Stereochemistry of Organic Compounds* by E. L. Eliel and S. H. Wilen (Wiley, 1994).

It must be emphasised that Compound 1 and its salts have been drawn herein in a single tautomeric form, all possible tautomeric forms are included within the scope of the invention.

The present invention includes all pharmaceutically acceptable isotopically-labeled Compound 1 or a salt thereof wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, nitrogen, such as ^{13}N and ^{15}N, and oxygen, such as ^{15}O, ^{17}O and ^{18}O.

Certain isotopically-labelled Compound 1 or a salt thereof, for example those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^{3}H, and carbon-14, i.e. ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, i.e. ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. D_2O, d_6-acetone, d_6-DMSO.

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Administration and Dosing

Typically, a compound (in a crystalline form) of the invention is administered in an amount effective to treat a condition as described herein. The compounds of the invention can be administered as compound per se, or alternatively, as a pharmaceutically acceptable salt. For administration and dosing purposes, the compound per se or pharmaceutically acceptable salt thereof will simply be referred to as the compounds of the invention.

The compounds of the invention are administered by any suitable route in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds of the invention may be administered orally, rectally, vaginally, parenterally, or topically.

The compounds of the invention may be administered 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 bloodstream directly from the mouth.

In another embodiment, the compounds of the invention may also be administered directly into the bloodstream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

In another embodiment, the compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. In another embodiment, the compounds of the invention can also be administered intranasally or by inhalation. In another embodiment, the compounds of the invention may be administered rectally or vaginally. In another embodiment, the compounds of the invention may also be administered directly to the eye or ear.

The dosage regimen for the compounds of the invention and/or compositions containing said compounds is based on a variety of factors, including the type, age, weight, sex and medical condition of the patient; the severity of the condition; the route of administration; and the activity of the particular compound employed. Thus the dosage regimen may vary widely. In one embodiment, the total daily dose of a compound of the invention is typically from about 0.001 to about 100 mg/kg (i.e., mg compound of the invention per kg body weight) for the treatment of the indicated conditions discussed herein. In another embodiment, total daily dose of the compound of the invention is from about 0.01 to about 30 mg/kg, and in another embodiment, from about 0.03 to about 10 mg/kg, and in yet another embodiment, from about 0.1 to about 3. It is not uncommon that the administration of the compounds of the invention

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will be repeated a plurality of times in a day (typically no greater than 4 times). Multiple doses per day typically may be used to increase the total daily dose, if desired.

For oral administration, the compositions may be provided in the form of tablets containing 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 30.0 50.0, 75.0, 100, 125, 150, 175, 200, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, or in another embodiment, from about 1 mg to about 100 mg of active ingredient. Intravenously, doses may range from about 0.01 to about 10 mg/kg/minute during a constant rate infusion.

Suitable subjects according to the invention include mammalian subjects. In one embodiment, humans are suitable subjects. Human subjects may be of either gender and at any stage of development.

Pharmaceutical Compositions

In another embodiment, the invention comprises pharmaceutical compositions. Such pharmaceutical compositions comprise a compound of the invention presented with a pharmaceutically acceptable carrier. Other pharmacologically active substances can also be present. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Examples of pharmaceutically acceptable carriers include one or more of water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof, and may include isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol, or sorbitol in the composition. Pharmaceutically acceptable substances such as wetting agents or minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the antibody or antibody portion.

The compositions of this invention may be in a variety of forms. These include, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions (e.g., injectable and infusible solutions), dispersions or suspensions, tablets, pills, powders, liposomes and suppositories. The form depends on the intended mode of administration and therapeutic application.

Typical compositions are in the form of injectable or infusible solutions, such as compositions similar to those used for passive immunization of humans with antibodies in general. One mode of administration is parenteral (e.g. intravenous, subcutaneous, intraperitoneal, intramuscular). In another embodiment, the antibody is administered by intravenous infusion or injection. In yet another embodiment, the antibody is administered by intramuscular or subcutaneous injection.

Oral administration of a solid dose form may be, for example, presented in discrete units, such as hard or soft capsules, pills, cachets, lozenges, or tablets, each containing a

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predetermined amount of at least one compound of the invention. In another embodiment, the oral administration may be in a powder or granule form. In another embodiment, the oral dose form is sub-lingual, such as, for example, a lozenge. In such solid dosage forms, the compounds of the invention are ordinarily combined with one or more adjuvants. Such capsules or tablets may contain a controlled release formulation. In the case of capsules, tablets, and pills, the dosage forms also may comprise buffering agents or may be prepared with enteric coatings.

In another embodiment, oral administration may be in a liquid dose form. Liquid dosage forms for oral administration include, for example, pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art (e.g., water). Such compositions also may comprise adjuvants, such as wetting, emulsifying, suspending, flavoring (e.g., sweetening), and/or perfuming agents.

In another embodiment, the invention comprises a parenteral dose form. "Parenteral administration" includes, for example, subcutaneous injections, intravenous injections, intraperitoneally, intramuscular injections, intrasternal injections, and infusion. Injectable preparations (i.e., sterile injectable aqueous or oleaginous suspensions) may be formulated according to the known art using suitable dispersing, wetting agents, and/or suspending agents.

In another embodiment, the invention comprises a topical dose form. "Topical administration" includes, for example, transdermal administration, such as via transdermal patches or iontophoresis devices, intraocular administration, or intranasal or inhalation administration. Compositions for topical administration also include, for example, topical gels, sprays, ointments, and creams. A topical formulation may include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. When the compounds of this invention are administered by a transdermal device, administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, B. C. Finnin and T. M. Morgan, J. Pharm. Sci., vol. 88, pp. 955-958, 1999.

Formulations suitable for topical administration to the eye include, for example, eye drops wherein the compound of this invention is dissolved or suspended in a suitable carrier. A typical formulation suitable for ocular or aural administration may be in the form of drops of a micronized suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (i.e., absorbable gel sponges, collagen) and non-biodegradable (i.e., silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed

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linked polyacrylic acid, polyvinyl alcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methylcellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

For intranasal administration or administration by inhalation, the compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant. Formulations suitable for intranasal administration are typically administered in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurized container, pump, spray, atomizer (preferably an atomizer using electrohydrodynamics to produce a fine mist), or nebulizer, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

In another embodiment, the invention comprises a rectal dose form. Such rectal dose form may be in the form of, for example, a suppository. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Other carrier materials and modes of administration known in the pharmaceutical art may also be used. Pharmaceutical compositions of the invention may be prepared by any of the well-known techniques of pharmacy, such as effective formulation and administration procedures. The above considerations in regard to effective formulations and administration procedures are well known in the art and are described in standard textbooks. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania, 1975; Liberman et al., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Kibbe et al., Eds., Handbook of Pharmaceutical Excipients (3rd Ed.), American Pharmaceutical Association, Washington, 1999.

Co-administration

The compounds of the invention can be used alone, or in combination with other therapeutic agents. The invention provides any of the uses, methods or compositions as defined herein wherein the compound of any embodiment herein, or pharmaceutically acceptable salt thereof, or pharmaceutically acceptable solvate of said compound or salt, is used in combination with one or more other therapeutic agent discussed herein. This would include a pharmaceutical composition for the treatment of a disease or condition for which an agonist of the GLP-1R is indicated, comprising a crystalline form of the invention, as defined in

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any of the embodiments described herein, and one or more other therapeutic agent discussed herein.

The administration of two or more compounds "in combination" means that all of the compounds are administered closely enough in time that each may generate a biological effect in the same time frame. The presence of one agent may alter the biological effects of the other compound(s). The two or more compounds may be administered simultaneously, concurrently or sequentially. Additionally, simultaneous administration may be carried out by mixing the compounds prior to administration or by administering the compounds at the same point in time but as separate dosage forms at the same or different site of administration.

The phrases "concurrent administration," "co-administration," "simultaneous administration," and "administered simultaneously" mean that the compounds are administered in combination.

In another embodiment, the invention provides methods of treatment that include administering compounds of the present invention in combination with one or more other pharmaceutical agents, wherein the one or more other pharmaceutical agents may be selected from the agents discussed herein.

In one embodiment, the compounds of this invention are administered with an anti-diabetic agent including but not limited to a biguanide (e.g., metformin), a sulfonylurea (e.g., tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide,glyclopyramide, glimepiride, or glipizide), a thiazolidinedione (e.g., pioglitazone, rosiglitazone, or lobeglitazone), a glitazar (e.g., saroglitazar, aleglitazar, muraglitazar or tesaglitazar), a meglitinide (e.g., nateglinide, repaglinide), a dipeptidyl peptidase 4 (DPP-4) inhibitor (e.g., sitagliptin, vildagliptin, saxagliptin, linagliptin, gemigliptin, anagliptin, teneligliptin, alogliptin, trelagliptin, dutogliptin, or omarigliptin), a glitazone (e.g., pioglitazone, rosiglitazone, balaglitazone, rivoglitazone, or lobeglitazone), a sodium-glucose linked transporter 2 (SGLT2) inhibitor (e.g., empagliflozin, canagliflozin, dapagliflozin, ipragliflozin, lpragliflozin, tofogliflozin, sergliflozin etabonate, remogliflozin etabonate, or ertugliflozin), an SGLTL1 inhibitor, a GPR40 agonist (FFAR1/FFA1 agonist, e.g. fasiglifam), glucose-dependent insulinotropic peptide (GIP) and analogues thereof, an alpha glucosidase inhibitor (e.g. voglibose, acarbose, or miglitol), or an insulin or an insulin analogue, including the pharmaceutically acceptable salts of the specifically named agents and the pharmaceutically acceptable solvates of said agents and salts.

In another embodiment, the compounds of this invention are administered with an anti-obesity agent including but not limited to peptide YY or an analogue thereof, a neuropeptide Y receptor type 2 (NPYR2) agonist, a NPYR1 or NPYR5 antagonist, a cannabinoid receptor type 1 (CB1R) antagonist, a lipase inhibitor (e.g., orlistat), a human proislet peptide (HIP), a melanocortin receptor 4 agonist (e.g., setmelanotide), a melanin concentrating hormone receptor 1 antagonist, a farnesoid X receptor (FXR) agonist (e.g. obeticholic acid), zonisamide,

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phentermine (alone or in combination with topiramate), a norepinephrine/dopamine reuptake inhibitor (e.g., buproprion), an opioid receptor antagonist (e.g., naltrexone), a combination of norepinephrine/dopamine reuptake inhibitor and opioid receptor antagonist (e.g., a combination of bupropion and naltrexone), a GDF-15 analog, sibutramine, a cholecystokinin agonist, amylin and analogues therof (e.g., pramlintide), leptin and analogues thereof (e.g., metroleptin), a serotonergic agent (e.g., lorcaserin), a methionine aminopeptidase 2 (MetAP2) inhibitor (e.g., beloranib or ZGN-1061), phendimetrazine, diethylpropion, benzphetamine, an SGLT2 inhibitor (e.g., empagliflozin, canagliflozin, dapagliflozin, ipragliflozin, lpragliflozin, tofogliflozin, sergliflozin etabonate, remogliflozin etabonate, or ertugliflozin), an SGLTL1 inhibitor, a dual SGLT2/SGLT1 inhibitor, a fibroblast growth factor receptor (FGFR) modulator, an AMP-activated protein kinase (AMPK) activator, biotin, a MAS receptor modulator, or a glucagon receptor agonist (alone or in combination with another GLP-1R agonist, e.g., liraglutide, exenatide, dulaglutide, albiglutide, lixisenatide, or semaglutide), including the pharmaceutically acceptable salts of the specifically named agents and the pharmaceutically acceptable solvates of said agents and salts.

In another embodiment, the compounds of this invention are administered in combination with one or more of the following: an agent to treat NASH including but not limited to PF-05221304, an FXR agonist (e.g., obeticholic acid), a PPAR α/δ agonist (e.g., elafibranor), a synthetic fatty acid−bile acid conjugate (e.g., aramchol), a caspase inhibitor (e.g., emricasan), an anti-lysyl oxidase homologue 2 (LOXL2) monoclonal antibody (e.g., simtuzumab), a galectin 3 inhibitor (e.g., GR-MD-02), a MAPK5 inhibitor (e.g., GS-4997), a dual antagonist of chemokine receptor 2 (CCR2) and CCR5 (e.g., cenicriviroc), a fibroblast growth factor 21 (FGF21) agonist (e.g., BMS-986036), a leukotriene D4 (LTD4) receptor antagonist (e.g., tipelukast), a niacin analogue (e.g., ARI 3037MO), an ASBT inhibitor (e.g., volixibat), an acetyl-CoA carboxylase (ACC) inhibitor (e.g., NDI 010976 or PF-05221304), a ketohexokinase (KHK) inhibitor, a diacylglyceryl acyltransferase 2 (DGAT2) inhibitor, a CB1 receptor antagonist, an anti-CB1R antibody, or an apoptosis signal-regulating kinase 1 (ASK1) inhibitor, including the pharmaceutically acceptable salts of the specifically named agents and the pharmaceutically acceptable solvates of said agents and salts.

Some specific compounds that can be used in combination with the compounds of the present invention for treating diseases or disorders described herein (e.g. NASH) include:

4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid, which is an example of a selective ACC inhibitor and was prepared as the free acid in Example 9 of U.S. Patent No. 8,859,577, which is the U.S. national phase of International Application No. PCT/IB2011/054119, the disclosures of which are hereby incorporated herein by reference in their entireties for all purposes. Crystal forms of 4-(4-(1-Isopropyl-7-oxo-1,4,6,7-tetrahydrospiro[indazole-5,4'-piperidine]-1'-carbonyl)-6-methoxypyridin-2-yl)benzoic acid, including an anhydrous mono-tris form (Form 1) and a trihydrate of the mono-

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tris salt (Form 2), are described in International PCT Application No. PCT/IB2018/058966, the disclosure of which is hereby incorporated herein by reference in its entirety for all purposes;

(S)-2-(5-((3-Ethoxypyridin-2-yl)oxy)pyridin-3-yl)-N-(tetrahydrofuran-3-yl)pyrimidine-5-carboxamide, or a pharmaceutically acceptable salt thereof, and its crystalline solid forms (Form 1 and Form 2) is an example of a DGAT2 inhibitor described in Example 1 of U.S. Patent No. 10,071,992, the disclosure of which is hereby incorporated herein by reference in its entirety for all purposes;

[(1R,5S,6R)-3-{2-[(2S)-2-methylazetidin-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}-3-azabicyclo[3.1.0]hex-6-yl]acetic acid, or a pharmaceutically acceptable salt thereof, (including a crystalline free acid form thereof) is an example of a ketohexokinase inhibitor and is described in Example 4 of U.S. Patent No. 9,809,579, the disclosure of which is hereby incorporated herein by reference in its entirety for all purposes; and

the FXR agonist Tropifexor or a pharmaceutically acceptable salt thereof is described in Example 1-1B of U.S. Patent No. 9,150,568, the disclosure of which is hereby incorporated herein by reference in its entirety for all purposes.

These agents and compounds of the invention can be combined with pharmaceutically acceptable vehicles such as saline, Ringer's solution, dextrose solution, and the like. The particular dosage regimen, i.e., dose, timing and repetition, will depend on the particular individual and that individual's medical history.

Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and may comprise buffers such as phosphate, citrate, and other organic acids; salts such as sodium chloride; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens, such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or Igs; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

Liposomes containing these agents and/or compounds of the invention are prepared by methods known in the art, such as described in U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Patent No. 5,013,556. Particularly useful liposomes can be generated by the reverse phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol and PEG-derivatized

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phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter.

These agents and/or the compounds of the invention may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington, The Science and Practice of Pharmacy, 20th Ed., Mack Publishing (2000).

Sustained-release preparations may be used. Suitable examples of sustained-release preparations include semi-permeable matrices of solid hydrophobic polymers containing the compound of Formulas I, II, III, IV, or V, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or 'poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and 7 ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as those used in LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), sucrose acetate isobutyrate, and poly-D-(-)-3-hydroxybutyric acid.

The formulations to be used for intravenous administration must be sterile. This is readily accomplished by, for example, filtration through sterile filtration membranes. Compounds of the invention are generally placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Suitable emulsions may be prepared using commercially available fat emulsions, such as Intralipid™, Liposyn™, Infonutrol™, Lipofundin™ and Lipiphysan™. The active ingredient may be either dissolved in a pre-mixed emulsion composition or alternatively it may be dissolved in an oil (e.g., soybean oil, safflower oil, cottonseed oil, sesame oil, corn oil or almond oil) and an emulsion formed upon mixing with a phospholipid (e.g., egg phospholipids, soybean phospholipids or soybean lecithin) and water. It will be appreciated that other ingredients may be added, for example glycerol or glucose, to adjust the tonicity of the emulsion. Suitable emulsions will typically contain up to 20% oil, for example, between 5 and 20%. The fat emulsion can comprise fat droplets between 0.1 and 1.0 μm, particularly 0.1 and 0.5 μm, and have a pH in the range of 5.5 to 8.0.

The emulsion compositions can be those prepared by mixing a compound of the invention with Intralipid™ or the components thereof (soybean oil, egg phospholipids, glycerol and water).

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders.

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The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

KITS

Another aspect of the invention provides kits comprising a solid form of the invention (e.g. a crystalline form such as Form 3) or pharmaceutical compositions comprising a solid form of the invention (e.g. a crystalline form such as Form 3). A kit may include, in addition to a solid form of the invention (e.g. a crystalline form such as Form 3) or pharmaceutical composition thereof, diagnostic or therapeutic agents. A kit may also include instructions for use in a diagnostic or therapeutic method. In some embodiments, the kit includes a crystalline form of the invention and a diagnostic agent. In other embodiments, the kit includes a crystalline form of the invention, or a pharmaceutical composition thereof.

In yet another embodiment, the invention comprises kits that are suitable for use in performing the methods of treatment described herein. In one embodiment, the kit contains a first dosage form comprising one or more of solid forms of the invention (e.g. a crystalline form such as Form 3) in quantities sufficient to carry out the methods of the invention. In another embodiment, the kit comprises one or more solid forms of the invention (e.g. a crystalline form such as Form 3) in quantities sufficient to carry out the methods of the invention and a container for the dosage and a container for the dosage.

PREPARATION

Compound 1, tris salt thereof, and crystalline forms of tris salt of Compound 1, may be prepared by the general and specific methods described below, using the common general knowledge of one skilled in the art of synthetic organic chemistry. Such common general knowledge can be found in standard reference books such as Comprehensive Organic Chemistry, Ed. Barton and Ollis, Elsevier; Comprehensive Organic Transformations: A Guide to Functional Group Preparations, Larock, John Wiley and Sons; and Compendium of Organic Synthetic Methods, Vol. I-XII (published by Wiley-Interscience). The starting materials used herein are commercially available or may be prepared by routine methods known in the art.

In the preparation of the compounds, salts, and crystalline forms of the invention, it is noted that some of the preparation methods described herein may require protection of remote functionality (e.g., primary amine, secondary amine, carboxyl in precursors). The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. The need for such protection is readily determined by one skilled in the

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art. The use of such protection/deprotection methods is also within the skill in the art. For a general description of protecting groups and their use, see T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

For example, certain compounds contain primary amines or carboxylic acid functionalities which may interfere with reactions at other sites of the molecule if left unprotected. Accordingly, such functionalities may be protected by an appropriate protecting group which may be removed in a subsequent step. Suitable protecting groups for amine and carboxylic acid protection include those protecting groups commonly used in peptide synthesis (such as N-t-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), and 9-fluorenylmethylenoxycarbonyl (Fmoc) for amines and lower alkyl or benzyl esters for carboxylic acids) which are generally not chemically reactive under the reaction conditions described and can typically be removed without chemically altering other functionality in the compounds.

The Schemes described below are intended to provide a general description of the methodology employed in the preparation of the compounds of the present invention. Some of the compounds of the present invention may contain single or multiple chiral centers with the stereochemical designation (R) or (S). It will be apparent to one skilled in the art that all of the synthetic transformations can be conducted in a similar manner whether the materials are enantioenriched or racemic. Moreover the resolution to the desired optically active material may take place at any desired point in the sequence using well known methods such as described herein and in the chemistry literature. For example, intermediates and finals may be separated using chiral chromatographic methods. Alternatively, chiral salts may be utilized to isolate enantiomerically enriched intermediates and final compounds.

EXAMPLES

The following illustrate the synthesis of non-limiting compounds (including solid forms thereof) of the present invention.

Experiments were generally carried out under inert atmosphere (nitrogen or argon), particularly in cases where oxygen- or moisture-sensitive reagents or intermediates were employed. Commercial solvents and reagents were generally used without further purification. Anhydrous solvents were employed where appropriate, generally AcroSeal® products from Acros Organics, Aldrich® Sure/Seal™ from Sigma-Aldrich, or DriSolv® products from EMD Chemicals. In other cases, commercial solvents were passed through columns packed with 4Å molecular sieves, until the following QC standards for water were attained: a) <100 ppm for dichloromethane, toluene, *N,N*-dimethylformamide, and tetrahydrofuran; b) <180 ppm for methanol, ethanol, 1,4-dioxane, and diisopropylamine. For very sensitive reactions, solvents were further treated with metallic sodium, calcium hydride, or molecular sieves, and distilled just prior to use. Products were generally dried under vacuum before being carried on to further reactions or submitted for biological testing. Mass spectrometry data is reported from either liquid chromatography-mass spectrometry (LCMS), atmospheric pressure chemical ionization

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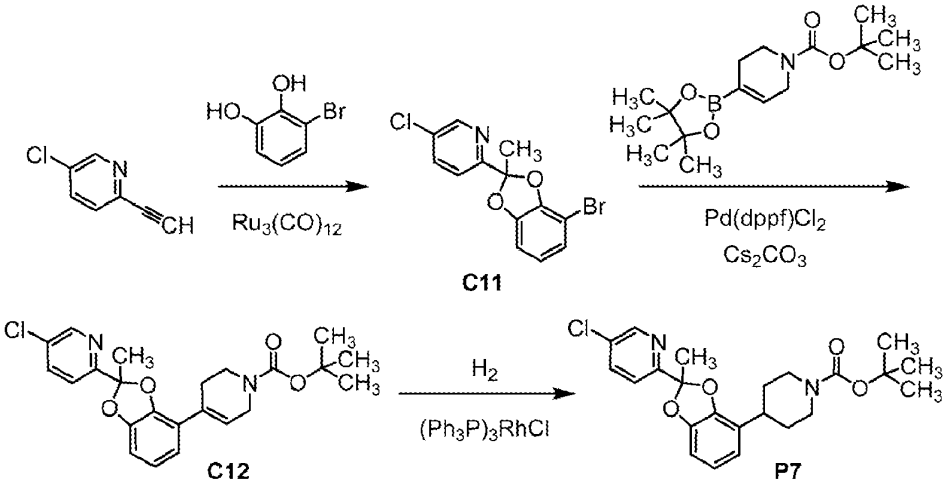
(APCI) or gas chromatography-mass spectrometry (GCMS) instrumentation. The symbol ♦ denotes that the chlorine isotope pattern was observed in the mass spectrum.

Chiral separations were used to separate enantiomers or diastereomers of some intermediates during the preparation of the compounds of the invention. When chiral separation was done, the separated enantiomers were designated as ENT-1 or ENT-2 (or DIAST-1 or DIAST-2), according to their order of elution. In some embodiments, enantiomers designated as ENT-1 or ENT-2 can be used as starting materials to prepare other enantiomers or diastereomers. In such situations, the resulting enantiomers prepared are designated as ENT-X1 and ENT-X2, respectively, according to their starting materials; similarly, the diastereomers prepared are designated as DIAST-X1 and DIAST-X2, respectively, (or DIAST-according to their starting materials. DIAST-Y and DIAST-Z nomenclature is used similarly, in syntheses employing multiple intermediates.

Reactions proceeding through detectable intermediates were generally followed by LCMS, and allowed to proceed to full conversion prior to addition of subsequent reagents. For syntheses referencing procedures in other Examples or Methods, reaction conditions (reaction time and temperature) may vary. In general, reactions were followed by thin-layer chromatography or mass spectrometry, and subjected to work-up when appropriate. Purifications may vary between experiments: in general, solvents and the solvent ratios used for eluents/gradients were chosen to provide appropriate R_fs or retention times. All starting materials in these Preparations and Examples are either commercially available or can be prepared by methods known in the art or as described herein.

Preparation P7

*tert-Butyl 4-[2-(5-chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidine-1-carboxylate (**P7**)*



*Step 1. Synthesis of 2-(4-bromo-2-methyl-1,3-benzodioxol-2-yl)-5-chloropyridine (**C11**).*

A mixture of 5-chloro-2-ethynylpyridine (1.80 g, 13.1 mmol), 3-bromobenzene-1,2-diol (2.47 g, 13.1 mmol), and triruthenium dodecacarbonyl (167 mg, 0.261 mmol) in toluene (25 mL)

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was degassed for 1 minute and then heated at 100 °C for 16 hours. The reaction mixture was diluted with ethyl acetate (30 mL) and filtered through a pad of diatomaceous earth; the filtrate was concentrated *in vacuo* and purified using silica gel chromatography (Gradient: 0% to 1% ethyl acetate in petroleum ether) to provide **C11** as a yellow oil. Yield: 1.73 g, 5.30 mmol, 40%. LCMS *m/z* 325.6 (bromine-chlorine isotope pattern observed) $[M+H]^+$. ^1H NMR (400 MHz, chloroform-*d*) δ 8.63 (dd, *J* = 2.4, 0.7 Hz, 1H), 7.71 (dd, component of ABX pattern, *J* = 8.4, 2.4 Hz, 1H), 7.60 (dd, component of ABX pattern, *J* = 8.4, 0.7 Hz, 1H), 6.97 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.76 (dd, component of ABX pattern, *J* = 7.8, 1.4 Hz, 1H), 6.72 (dd, component of ABX pattern, *J* = 8.0, 7.8 Hz, 1H), 2.10 (s, 3H).

Step 2. Synthesis of tert-*butyl 4-[2-(5-chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]-3,6-dihydropyridine-1(2*H*)-carboxylate (**C12**).*

[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (388 mg, 0.530 mmol) was added to a suspension of **C11** (1.73 g, 5.30 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (1.64 g, 5.30 mmol), and cesium carbonate (5.18 g, 15.9 mmol) in 1,4-dioxane (35 mL) and water (6 mL). The reaction mixture was stirred at 90 °C for 4 hours, whereupon it was diluted with ethyl acetate (30 mL) and water (5 mL). The organic layer was concentrated *in vacuo* and the residue was subjected to silica gel chromatography (Gradient: 0% to 5% ethyl acetate in petroleum ether), affording **C12** as a yellow gum. Yield: 1.85 g, 4.31 mmol, 81%. LCMS *m/z* 451.0♦ $[M+Na^+]$. ^1H NMR (400 MHz, chloroform-*d*) δ 8.62 (dd, *J* = 2.5, 0.8 Hz, 1H), 7.69 (dd, component of ABX pattern, *J* = 8.4, 2.4 Hz, 1H), 7.57 (dd, component of ABX pattern, *J* = 8.4, 0.8 Hz, 1H), 6.84 – 6.79 (m, 2H), 6.78 – 6.73 (m, 1H), 6.39 – 6.33 (br m, 1H), 4.13 – 4.07 (m, 2H), 3.68 – 3.58 (m, 2H), 2.60 – 2.51 (br m, 2H), 2.07 (s, 3H), 1.49 (s, 9H).

Step 3. Synthesis of tert-*butyl 4-[2-(5-chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidine-1-carboxylate (**P7**).*

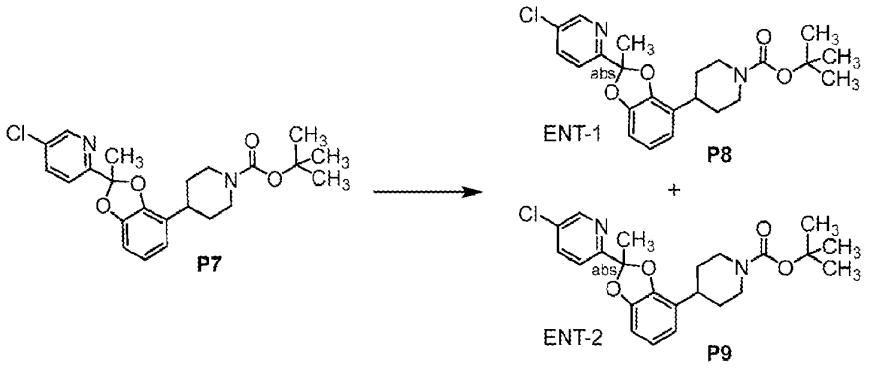
A solution of **C12** (2.61 g, 6.08 mmol) and tris(triphenylphosphine)rhodium(I) chloride (Wilkinson's catalyst; 563 mg, 0.608 mmol) in methanol (100 mL) was degassed under vacuum and then purged with hydrogen; this evacuation-purge cycle was carried out a total of three times. The reaction mixture was then stirred at 60 °C under hydrogen (50 psi) for 16 hours, whereupon it was filtered. The filtrate was concentrated *in vacuo*, and the residue was purified using silica gel chromatography (Gradient: 0% to 10% ethyl acetate in petroleum ether); the resulting material was combined with material from a similar hydrogenation carried out on **C12** (110 mg, 0.256 mmol) to provide **P7** as a light-yellow gum. Combined yield: 2.05 g, 4.76 mmol, 75%. LCMS *m/z* 431.3♦ $[M+H]^+$. ^1H NMR (400 MHz, chloroform-*d*) δ 8.62 (d, *J* = 2.3 Hz, 1H), 7.69 (dd, component of ABX pattern, *J* = 8.4, 2.4 Hz, 1H), 7.57 (d, half of AB quartet, *J* = 8.4 Hz, 1H), 6.79 (dd, component of ABC pattern, *J* = 7.8, 7.7 Hz, 1H), 6.72 (dd, component of ABC

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pattern, J = 7.8, 1.3 Hz, 1H), 6.68 (br d, component of ABC pattern, J = 7.9 Hz, 1H), 4.32 – 4.12 (br m, 2H), 2.91 – 2.73 (m, 3H), 2.05 (s, 3H), 1.90 – 1.62 (m, 4H), 1.48 (s, 9H).

Preparations P8 and P9

*tert-Butyl 4-[2-(5-chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidine-1-carboxylate, ENT-1 (**P8**) and* tert*-Butyl 4-[2-(5-chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidine-1-carboxylate, ENT-2 (**P9**)*



Separation of **P7** (500 mg, 1.16 mmol) into its component enantiomers was effected using SFC {Column: Phenomenex Lux Amylose-1, 5 µm; Mobile phase: 9:1 carbon dioxide / [2-propanol containing 0.2% (7 M ammonia in methanol)]}. The first-eluting enantiomer was designated as ENT-1 (**P8**), and the second-eluting enantiomer as ENT-2 (**P9**).

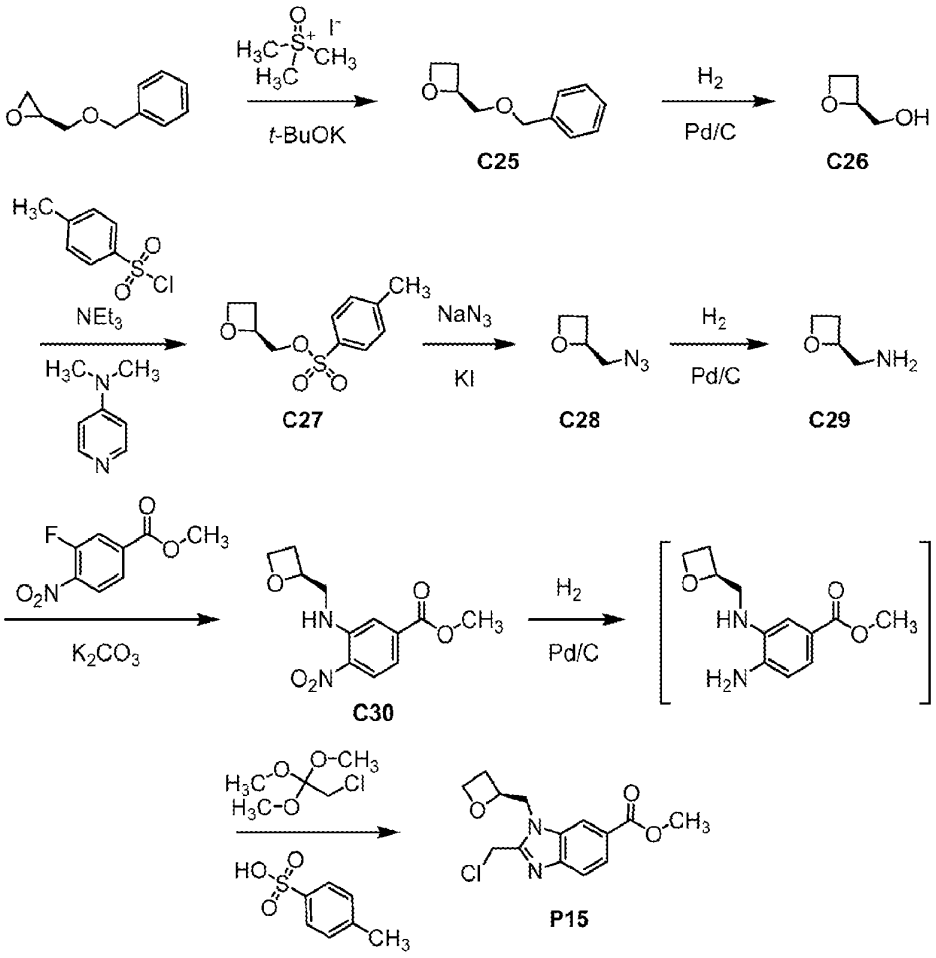
P8 Yield: 228 mg, 0.529 mmol, 46%. Retention time 4.00 minutes {Column: Phenomenex Lux Amylose-1, 4.6 x 250 mm, 5 µm; Mobile phase A: carbon dioxide; Mobile phase B: [2-propanol containing 0.2% (7 M ammonia in methanol)]; Gradient: 5% B for 1.00 minute, then 5% to 60% B over 8.00 minutes; Flow rate: 3.0 mL/minute; Back pressure: 120 bar}.

P9 Yield: 229 mg, 0.531 mmol, 46%. Retention time 4.50 minutes (Analytical conditions identical to those used for **P8**).

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Preparation P15

*Methyl 2-(chloromethyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylate (**P15**)*



This entire sequence was carried out on large scale. In general, before reactions, as well as after addition of reagents, reactors were evacuated to −0.08 to −0.05 MPa and then filled with nitrogen to normal pressure. This process was generally repeated 3 times, and then oxygen content was assessed to ensure that it was ≤1.0%. For the processes of extraction and washing of organic layers, mixtures were generally stirred for 15 to 60 minutes and then allowed to settle for 15 to 60 minutes before separation of layers.

*Step 1. Synthesis of (2S)-2-[(benzyloxy)methyl]oxetane (**C25**).*

This reaction was carried out in three batches of approximately the same scale. A 2000 L glass-lined reactor was charged with 2-methylpropan-2-ol (774.7 kg). Potassium *tert*-butoxide (157.3 kg, 1402 mol) was added via a solid addition funnel, and the mixture was stirred for 30 minutes. Trimethylsulfoxonium iodide (308.2 kg, 1400 mol) was then added in the same

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manner, and the reaction mixture was heated at 55 °C to 65 °C for 2 to 3 hours, whereupon (2*S*)-2-[(benzyloxy)methyl]oxirane (92.1 kg, 561 mol) was added at a rate of 5 to 20 kg/hour. After the reaction mixture had been maintained at 55 °C to 65 °C for 25 hours, it was cooled to 25 °C to 35 °C, and filtered through diatomaceous earth (18.4 kg). The filter cake was rinsed with *tert*-butyl methyl ether (3 x 340 kg), and the combined filtrates were transferred to a 5000 L reactor, treated with purified water (921 kg), and stirred for 15 to 30 minutes at 15 °C to 30 °C. The organic layer was then washed twice using a solution of sodium chloride (230.4 kg) in purified water (920.5 kg), and concentrated under reduced pressure (≤ −0.08 MPa) at ≤45 °C. *n*-Heptane (187 kg) was added, and the resulting mixture was concentrated under reduced pressure (≤ −0.08 MPa) at ≤45 °C; the organic phase was purified using silica gel chromatography (280 kg), with sodium chloride (18.5 kg) on top of the column. The crude material was loaded onto the column using *n*-heptane (513 kg), and then eluted with a mixture of *n*-heptane (688.7 kg) and ethyl acetate (64.4 kg). The three batches were combined, providing **C25** as an 85% pure light yellow oil (189.7 kg, 906 mmol, 54%). ^{1}H NMR (400 MHz, chloroform-*d*), **C25** peaks only: δ 7.40 – 7.32 (m, 4H), 7.32 – 7.27 (m, 1H), 4.98 (dddd, *J* = 8.1, 6.7, 4.9, 3.7 Hz, 1H), 4.72 – 4.55 (m, 4H), 3.67 (dd, component of ABX pattern, *J* = 11.0, 4.9 Hz, 1H), 3.62 (dd, component of ABX pattern, *J* = 11.0, 3.7 Hz, 1H), 2.72 – 2.53 (m, 2H).

*Step 2. Synthesis of (2S)-oxetan-2-ylmethanol (**C26**).*

10% Palladium on carbon (30.7 kg) was added through an addition funnel to a 10 °C to 30 °C solution of 85% pure **C25** (from previous step; 185.3 kg, 884.8 mol) in tetrahydrofuran (1270 kg) in a 3000 L stainless steel autoclave reactor. The addition funnel was rinsed with purified water and tetrahydrofuran (143 kg), and the rinses were added to the reaction mixture. After the reactor contents had been purged with nitrogen, they were similarly purged with hydrogen, increasing the pressure to 0.3 to 0.5 MPa and then venting to 0.05 MPa. This hydrogen purge was repeated 5 times, whereupon the hydrogen pressure was increased to 0.3 to 0.4 MPa. The reaction mixture was then heated to 35 °C to 45 °C. After 13 hours, during which the hydrogen pressure was maintained at 0.3 to 0.5 MPa, the mixture was vented to 0.05 MPa, and purged five times with nitrogen, via increasing the pressure to 0.15 to 0.2 MPa and then venting to 0.05 MPa. After the mixture had been cooled to 10 °C to 25 °C, it was filtered, and the reactor was rinsed with tetrahydrofuran (2 x 321 kg). The filter cake was soaked twice with this rinsing liquor and then filtered; concentration at reduced pressure (≤ −0.06 MPa) was carried out at ≤40 °C, affording **C26** (62.2 kg, 706 mol, 80%) in tetrahydrofuran (251 kg)

*Step 3. Synthesis of (2S)-oxetan-2-ylmethyl 4-methylbenzenesulfonate (**C27**).*

4-(Dimethylamino)pyridine (17.5 kg, 143 mol) was added to a 10 °C to 25 °C solution of **C26** (from the previous step; 62.2 kg, 706 mol) in tetrahydrofuran (251 kg) and triethylamine (92.7 kg, 916 mol) in dichloromethane (1240 kg). After 30 minutes, *p*-toluenesulfonyl chloride

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(174.8 kg, 916.9 mol) was added in portions at intervals of 20 to 40 minutes, and the reaction mixture was stirred at 15 °C to 25 °C for 16 hours and 20 minutes. Purified water (190 kg) was added; after stirring, the organic layer was washed with aqueous sodium bicarbonate solution (prepared using 53.8 kg of sodium bicarbonate and 622 kg of purified water), and then washed with aqueous ammonium chloride solution (prepared using 230 kg of ammonium chloride and 624 kg of purified water). After a final wash with purified water (311 kg), the organic layer was filtered through a stainless steel Nutsche filter that had been preloaded with silica gel (60.2 kg). The filter cake was soaked with dichloromethane (311 kg) for 20 minutes, and then filtered; the combined filtrates were concentrated at reduced pressure (≤ −0.05 MPa) and ≤40 °C until 330 to 400 L remained. Tetrahydrofuran (311 kg) was then added, at 15 °C to 30 °C, and the mixture was concentrated in the same manner, to a final volume of 330 to 400 L. The tetrahydrofuran addition and concentration was repeated, again to a volume of 330 to 400 L, affording a light yellow solution of **C27** (167.6 kg, 692 mmol, 98%) in tetrahydrofuran (251.8 kg). ^{1}H NMR (400 MHz, chloroform-*d*), **C27** peaks only: δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 4.91 (ddt, *J* = 8.0, 6.7, 3.9 Hz, 1H), 4.62 – 4.55 (m, 1H), 4.53 – 4.45 (m, 1H), 4.14 (d, *J* = 3.9 Hz, 2H), 2.75 – 2.63 (m, 1H), 2.60 – 2.49 (m, 1H), 2.44 (s, 3H).

*Step 4. Synthesis of (2S)-2-(azidomethyl)oxetane (**C28**).*

N,N-Dimethylformamide (473 kg), sodium azide (34.7 kg, 534 mol), and potassium iodide (5.2 kg, 31 mol) were combined in a 3000 L glass-lined reactor at 10 °C to 25 °C. After addition of **C27** (83.5 kg, 344.6 mol) in tetrahydrofuran (125.4 kg), the reaction mixture was heated to 55 °C to 65 °C for 17 hours and 40 minutes, whereupon it was cooled to 25 °C to 35 °C, and nitrogen was bubbled from the bottom valve for 15 minutes. *tert*-Butyl methyl ether (623 kg) and purified water (840 kg) were then added, and the resulting aqueous layer was extracted twice with *tert*-butyl methyl ether (312 kg and 294 kg). The combined organic layers were washed with purified water (2 x 419 kg) while maintaining the temperature at 10 °C to 25 °C, affording **C28** (31.2 kg, 276 mol, 80%) in a solution of the above organic layer (1236.8 kg).

*Step 5. Synthesis of 1-[(2S)-oxetan-2-yl]methanamine (**C29**).*

10% Palladium on carbon (3.7 kg) was added through an addition funnel to a 10 °C to 30 °C solution of **C28** [from the previous step; 1264 kg (31.1 kg of **C28**, 275 mol)] in tetrahydrofuran (328 kg) in a 3000 L stainless steel autoclave reactor. The addition funnel was rinsed with tetrahydrofuran (32 kg), and the rinse was added to the reaction mixture. After the reactor contents had been purged with nitrogen, they were similarly purged with hydrogen, increasing the pressure to 0.05 to 0.15 MPa and then venting to 0.03 to 0.04 MPa. This hydrogen purge was repeated 5 times, whereupon the hydrogen pressure was increased to 0.05 to 0.07 MPa. The reaction temperature was increased to 25 °C to 33 °C, and the hydrogen pressure was maintained at 0.05 to 0.15 MPa for 22 hours, while exchanging the hydrogen

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every 3 to 5 hours. The mixture was then purged five times with nitrogen, via increasing the pressure to 0.15 to 0.2 MPa and then venting to 0.05 MPa. After filtration, tetrahydrofuran (92 kg and 93 kg) was used to wash the reactor and then soak the filter cake. The combined filtrates were concentrated at reduced pressure (≤ −0.07 MPa) and ≤45 °C, affording **C29** (18.0 kg, 207 mol, 75%) in tetrahydrofuran (57.8 kg). ^{1}H NMR (400 MHz, DMSO-d_6), **C29** peaks only: δ 4.62 (ddt, *J* = 7.6, 6.6, 5.1 Hz, 1H), 4.49 (ddd, *J* = 8.6, 7.3, 5.6 Hz, 1H), 4.37 (dt, *J* = 9.1, 5.9 Hz, 1H), 2.69 (d, *J* = 5.1 Hz, 2H), 2.55 – 2.49 (m, 1H), 2.39 (m, 1H).

*Step 6. Synthesis of methyl 4-nitro-3-{[(2S)-oxetan-2-ylmethyl]amino}benzoate (**C30**).*

Potassium carbonate (58.1 kg, 420 mol) was added to a solution of methyl 3-fluoro-4-nitrobenzoate (54.8 kg, 275 mol) in tetrahydrofuran (148 kg) in a 100 L glass-lined reactor, and the mixture was stirred for 10 minutes. A solution of **C29** (29.3 kg, 336 mol) in tetrahydrofuran (212.9 kg) was added, and the reaction mixture was stirred at 20 °C to 30 °C for 12 hours, whereupon ethyl acetate (151 kg) was added, and the mixture was filtered through silica gel (29 kg). The filter cake was rinsed with ethyl acetate (150 kg and 151 kg), and the combined filtrates were concentrated at reduced pressure (≤ −0.08 MPa) and ≤45 °C to a volume of 222 to 281 L. After the mixture had been cooled to 10 °C to 30 °C, *n*-heptane (189 kg) was added, stirring was carried out for 20 minutes, and the mixture was concentrated at reduced pressure (≤ −0.08 MPa) and ≤45 °C to a volume of 222 L. *n*-Heptane (181 kg) was again added into the mixture at a reference rate of 100 to 300 kg/hour, and stirring was continued for 20 minutes. The mixture was sampled until residual tetrahydrofuran was ≤5% and residual ethyl acetate was 10% to 13%. The mixture was heated to 40 °C to 45 °C and stirred for 1 hour, whereupon it was cooled to 15 °C to 25 °C at a rate of 5 °C to 10 °C per hour, and then stirred at 15 °C to 25 °C for 1 hour. Filtration using a stainless steel centrifuge provided a filter cake, which was rinsed with a mixture of ethyl acetate (5.0 kg) and *n*-heptane (34 kg), and then stirred with tetrahydrofuran (724 kg) at 10 °C to 30 °C for 15 minutes; filtration provided a yellow solid largely composed of **C30** (57.3 kg, 210 mol, 76%). ^{1}H NMR (400 MHz, DMSO-d_6) 8.34 (t, *J* = 5.8 Hz, 1H), 8.14 (d, *J* = 8.9 Hz, 1H), 7.63 (d, *J* = 1.7 Hz, 1H), 7.13 (dd, *J* = 8.9, 1.8 Hz, 1H), 4.99 (dddd, *J* = 7.7, 6.7, 5.3, 4.1 Hz, 1H), 4.55 (ddd, *J* = 8.6, 7.3, 5.8 Hz, 1H), 4.43 (dt, *J* = 9.1, 6.0 Hz, 1H), 3.87 (s, 3H), 3.67 – 3.61 (m, 2H), 2.67 (dddd, *J* = 11.1, 8.6, 7.7, 6.2 Hz, 1H), 2.57 – 2.47 (m, 1H).

*Step 7. Synthesis of methyl 2-(chloromethyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylate (**P15**).*

A solution of **C30** (from the previous step; 51.8 kg, 190 mol) in tetrahydrofuran (678 kg), in a 3000 L autoclave reactor, was treated with 10% palladium on carbon (5.2 kg) at 10 °C to 30 °C. The addition pipe was rinsed with tetrahydrofuran (46 kg) and the rinse was added to the reaction mixture. After the reactor contents had been purged with nitrogen, they were similarly

purged with hydrogen, increasing the pressure to 0.1 to 0.2 MPa and then venting to 0.02 to 0.05 MPa. This hydrogen purge was repeated 5 times, whereupon the hydrogen pressure was increased to 0.1 to 0.25 MPa. The reaction mixture was stirred at 20 °C to 30 °C, and every 2 to 3 hours, the mixture was purged with nitrogen three times, and then purged with hydrogen five times; after each final hydrogen exchange, the hydrogen pressure was increased to 0.1 to 0.25 MPa. After 11.25 hours total reaction time, the reaction mixture was vented to normal pressure, and purged five times with nitrogen, via increasing the pressure to 0.15 to 0.2 MPa and then venting to 0.05 MPa. It was then filtered, and the filter cake was rinsed twice with tetrahydrofuran (64 kg and 63 kg); the combined rinse and filtrate were concentrated under reduced pressure (≤ −0.08 MPa) and ≤40 °C to a volume of 128 to 160 L. Tetrahydrofuran (169 kg) was added, and the mixture was again concentrated to a volume of 128 to 160 L; this process was repeated a total of 4 times, affording a solution of the intermediate methyl 4-amino-3-{[(2*S*)-oxetan-2-ylmethyl]amino}benzoate.

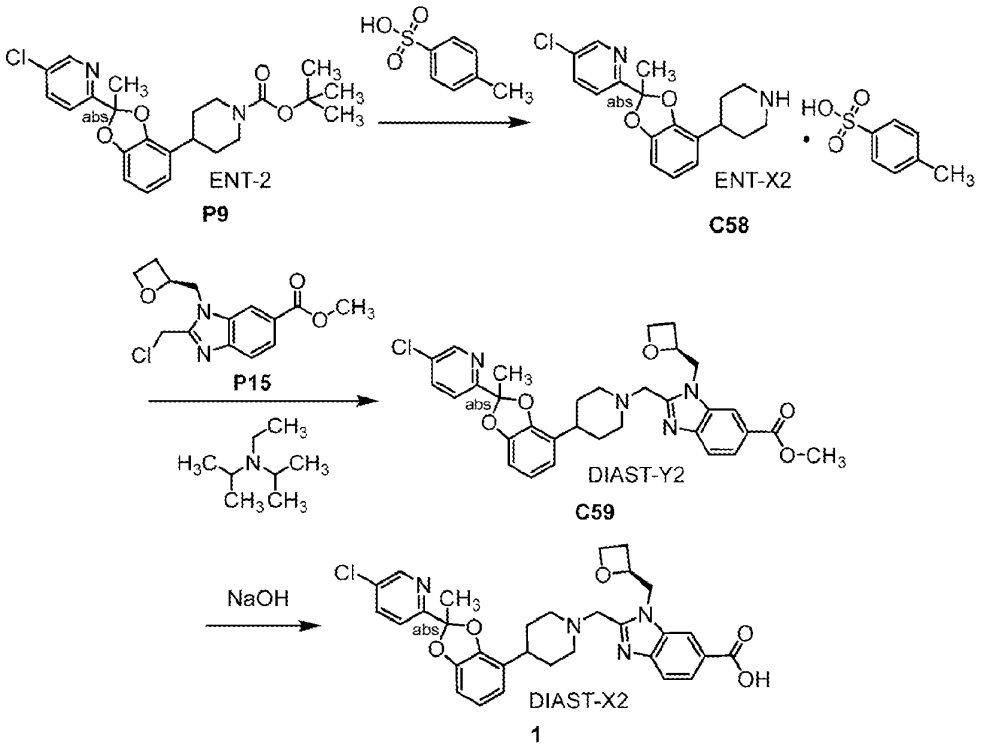
Tetrahydrofuran (150 kg) was added to this solution, followed by 2-chloro-1,1,1-trimethoxyethane (35.1 kg, 227 mol) and *p*-toluenesulfonic acid monohydrate (1.8 kg, 9.5 mol). After the reaction mixture had been stirred for 25 minutes, it was heated at 40 °C to 45 °C for 5 hours, whereupon it was concentrated under reduced pressure to a volume of 135 to 181 L. 2-Propanol (142 kg) was added, and the mixture was again concentrated to a volume of 135 to 181 L, whereupon 2-propanol (36.5 kg) and purified water (90 kg) were added, and stirring was continued until a solution was obtained. This was filtered with an in-line liquid filter, and then treated with purified water (447 kg) at a reference rate of 150 to 400 kg/hour at 20 °C to 40 °C. After the mixture had been cooled to 20 °C to 30 °C, it was stirred for 2 hours, and the solid was collected via filtration with a centrifuge. The filter cake was rinsed with a solution of 2-propanol (20.5 kg) and purified water (154 kg); after drying, **P15** was obtained as a white solid (32.1 kg, 109 mol, 57%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.14 – 8.11 (m, 1H), 8.01 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.79 (br d, *J* = 8.6 Hz, 1H), 5.26 – 5.18 (m, 1H), 5.04 (s, 2H), 4.66 – 4.58 (m, 2H), 4.53 (dd, component of ABX pattern, *J* = 15.7, 2.7 Hz, 1H), 4.34 (dt, *J* = 9.1, 6.0 Hz, 1H), 3.96 (s, 3H), 2.82 – 2.71 (m, 1H), 2.48 – 2.37 (m, 1H).

Alternatively, **P15** can be prepared using the methods described in US Patent No. 10,208,019 (see Intermediate 23 at Column 58 of the patent), which is hereby incorporated by reference in its entirety.

Example 1

2-({4-[2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2 (***Compound 1****) [from* ***P9****]*

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*Step 1. Synthesis of 5-chloro-2-[2-methyl-4-(piperidin-4-yl)-1,3-benzodioxol-2-yl]pyridine, ENT-X2, p-toluenesulfonate salt (**C58**) [from **P9**].*

A solution of **P9** (228 mg, 0.529 mmol) in ethyl acetate (2.7 mL) was treated with *p*-toluenesulfonic acid monohydrate (116 mg, 0.610 mmol), and the reaction mixture was heated at 50 °C for 16 hours. It was then allowed to stir at room temperature overnight, whereupon the precipitate was collected via filtration and rinsed with a mixture of ethyl acetate and heptane (1:1, 2 x 20 mL) to provide **C58** as a white solid. Yield: 227 mg, 0.451 mmol, 85%. LCMS *m/z* 331.0♦ $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.73 (d, *J* = 2.4 Hz, 1H), 8.61 – 8.46 (br m, 1H), 8.35 – 8.18 (br m, 1H), 8.02 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.47 (d, *J* = 7.8, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.89 – 6.81 (m, 2H), 6.72 (pentet, *J* = 4.0 Hz, 1H), 3.45 – 3.27 (m, 2H, assumed; partially obscured by water peak), 3.10 – 2.91 (m, 3H), 2.28 (s, 3H), 2.02 (s, 3H), 1.97 – 1.80 (m, 4H).

*Step 2. Synthesis of methyl 2-({4-[2-(5-chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylate, DIAST-Y2 (**C59**) [from **P9**].*

N,N-Diisopropylethylamine (0.234 mL, 1.34 mmol) was added to a solution of **C58** (225 mg, 0.447 mmol) in acetonitrile (2.2 mL). After this mixture had been stirred for 5 minutes at 45 °C, **P15** (120 mg, 0.407 mmol) was added, and stirring was continued at 45 °C for 16 hours,

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whereupon **P15** (11 mg, 37 μmol) was again added. After an additional 3 hours of stirring, the reaction mixture was treated with water (2.5 mL) and allowed to cool to room temperature. More water (5 mL) was added, and the resulting slurry was stirred for 2 hours, whereupon the solid was collected via filtration and washed with a mixture of acetonitrile and water (15:85, 3 x 5 mL) to afford **C59** as an off-white solid (252 mg). This material contained some *N,N*-diisopropylethylamine by ^{1}H NMR analysis, and was taken directly to the following step. LCMS *m/z* 589.1♦ [M+H]$^+$. ^{1}H NMR (400 MHz, chloroform-*d*) 8.61 (d, *J* = 2.3 Hz, 1H), 8.18 (d, *J* = 1.5 Hz, 1H), 7.96 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.67 (dd, component of ABX pattern, *J* = 8.4, 2.4 Hz, 1H), 7.59 – 7.51 (m, 1H), 6.82 – 6.75 (m, 1H), 6.74 – 6.66 (m, 2H), 5.28 – 5.19 (m, 1H), 4.75 (dd, component of ABX pattern, *J* = 15.3, 6.0 Hz, 1H), 4.68 (dd, component of ABX pattern, *J* = 15.3, 3.4 Hz, 1H), 4.67 – 4.58 (m, 1H), 4.41 (ddd, *J* = 9.1, 5.9, 5.9 Hz, 1H), 3.95 (s, 2H), 3.95 (s, 3H), 3.07 – 2.89 (m, 2H), 2.81 – 2.69 (m, 2H), 2.53 – 2.41 (m, 1H), 2.37 – 2.22 (m, 2H), 2.05 (s, 3H), 1.93 – 1.74 (m, 4H).

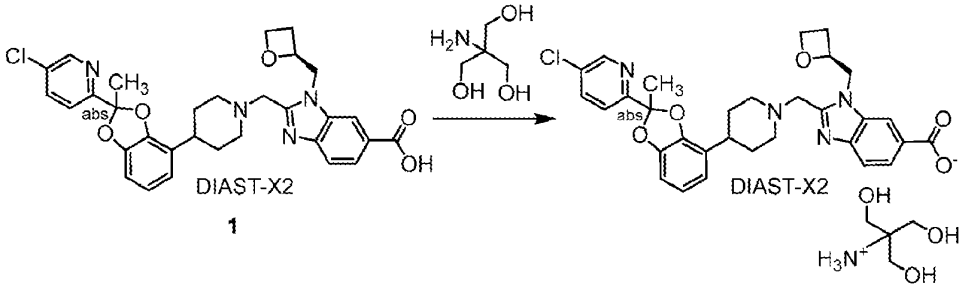
*Step 3. Synthesis of 2-({4-[2-(5-chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylic acid, DIAST-X2 (**Compound 1**) [from **P9**].*

A suspension of **C59** (from the previous step; 250 mg, ≤0.407 mmol) in methanol (2 mL) was heated to 40 °C, whereupon aqueous sodium hydroxide solution (1 M; 0.81 mL, 0.81 mmol) was added. After 17 hours, the reaction mixture was allowed to cool to room temperature, and the pH was adjusted to 5 to 6 with 1 M aqueous citric acid solution. The resulting mixture was diluted with water (2 mL), stirred for 2 hours, and extracted with ethyl acetate (3 x 5 mL); the combined organic layers were washed with saturated aqueous sodium chloride solution (5 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide a foamy solid. This material was taken up in a mixture of ethyl acetate and heptane (1:1, 4 mL), heated to 50 °C, and then allowed to cool and stir overnight. Filtration afforded ***Compound 1*** as a white solid. Yield: 179 mg, 0.311 mmol, 76% over 2 steps. LCMS *m/z* 575.1♦ [M+H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.73 (br s, 1H), 8.71 (d, *J* = 2.5 Hz, 1H), 8.27 (d, *J* = 1.5 Hz, 1H), 8.00 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.80 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 6.83 – 6.72 (m, 3H), 5.14 – 5.06 (m, 1H), 4.77 (dd, component of ABX pattern, *J* = 15.2, 7.2 Hz, 1H), 4.63 (dd, component of ABX pattern, *J* = 15.2, 2.8 Hz, 1H), 4.50 – 4.42 (m, 1H), 4.37 (ddd, *J* = 9.0, 5.9, 5.9 Hz, 1H), 3.85 (AB quartet, J_{AB} = 13.6 Hz, $\Delta\nu_{AB}$ = 71.5 Hz, 2H), 3.01 (br d, *J* = 11.2 Hz, 1H), 2.85 (br d, *J* = 11.2 Hz, 1H), 2.74 – 2.57 (m, 2H), 2.47 – 2.38 (m, 1H), 2.29 – 2.10 (m, 2H), 2.01 (s, 3H), 1.81 – 1.64 (m, 4H).

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Synthesis 1S-1. Synthesis of Compound 1, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt

*Synthesis of 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium 2-({4-[2-(5-chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylate, DIAST-X2 (**Compound 1, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt**) [from **P9**].*



1, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt

A mixture of **Compound 1** (1.54 g, 2.68 mmol) in tetrahydrofuran (10 mL) was treated with an aqueous solution of 2-amino-2-(hydroxymethyl)propane-1,3-diol (Tris, 1.0 M; 2.81 mL, 2.81 mmol). After 24 hours, the reaction mixture was concentrated *in vacuo* with ethanol (2 x 50 mL). The residue was treated with ethanol (15 mL). After stirring for 20 hours, the solid was collected via filtration and washed with cold ethanol (5 mL) to afford **Compound 1, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt** as a white solid. Yield: 1.41 g, 2.03 mmol, 76%. LCMS *m/z* 575.3♦ $[M+H]^+$. ^1H NMR (600 MHz, DMSO-d_6) δ 8.71 (d, *J* = 2.5 Hz, 1H), 8.21 (br s, 1H), 8.00 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.79 (br d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 6.82 – 6.73 (m, 3H), 5.13 – 5.07 (m, 1H), 4.74 (dd, *J* = 15.3, 7.2 Hz, 1H), 4.61 (dd, *J* = 15.3, 2.9 Hz, 1H), 4.49 – 4.43 (m, 1H), 4.37 (ddd, *J* = 9.0, 5.9, 5.9 Hz, 1H), 3.93 (d, *J* = 13.6 Hz, 1H), 3.75 (d, *J* = 13.5 Hz, 1H), 3.01 (br d, *J* = 11.3 Hz, 1H), 2.86 (br d, *J* = 11.4 Hz, 1H), 2.73 – 2.59 (m, 2H), 2.48 – 2.37 (m, 1H), 2.27 – 2.20 (m, 1H), 2.19 – 2.12 (m, 1H), 2.01 (s, 3H), 1.82 – 1.66 (m, 4H). mp = 184 °C to 190 °C.

Synthesis 1S-2. Alternative synthesis of Compound 1, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt

A mixture of **Compound 1** (8.80 gm, 15.3 mmol) in 2-methyltetrahydrofuran (90 ml) was concentrated in vacuo on a rotary evaporator, in a 37°C water bath, to reduce the total volume to ~54 ml. Isopropanol (90ml) was added to the mixture and then again concentrate the resulting mixture to a volume of ~54 ml. Isopropanol (135 ml) was added to the mixture, followed by addition of aqueous tris amine (3M; 5.0ml, 0.98 equiv). The resulting mixture/solution was stirred at ambient temperature; and a solid precipitate began to form within ~15min. The mixture was then stirred at ambient temperature for additional 5 hr. The resulting

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mixture/slurry was cooled to 0°C and the cooled slurry was stirred for about another 2 hr. The slurry was filtered and washed with cold isopropanol (3 x 15 ml). The solid collected was allowed to Air dry on the collection funnel for about 90min and then transfer to the vacuum oven for overnight drying. After ~16 hr at 50°C/23inHg vacuum (with a slight nitrogen bleed) 8.66 gm of **Compound 1, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt** was obtained as white solid; 99.8 area % by UPLC (yield:12.5 mmol, 81%). LCMS and ^{1}H NMR data were obtained, which are substantially the same as those in Synthesis **1S-1** shown above.

Acquisition of Powder X-ray Diffraction (PXRD) Data for Form A of Compound 1, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt (also known as Form A of anhydrous tris salt of Compound 1)

The white solid of the tris salt of Compound 1 (from both **Synthesis 1S-1** and **Synthesis 1S-2**) was submitted for PXRD analysis and found to be a crystalline material (which is designated as Form A). Powder X-ray diffraction analysis was conducted using a Bruker AXS D8 Endeavor diffractometer equipped with a Cu radiation source. The divergence slit was set at 15 mm continuous illumination. Diffracted radiation was detected by a PSD-Lynx Eye detector, with the detector PSD opening set at 2.99 degrees. The X-ray tube voltage and amperage were set to 40 kV and 40 mA respectively. Data was collected at the Cu wavelength (CuK_δ = 1.5418 λ) in the Theta-Theta goniometer from 3.0 to 40.0 degrees 2-Theta using a step size of 0.01 degrees and a step time of 1.0 second. The antiscatter screen was set to a fixed distance of 1.5 mm. Samples were rotated during data collection. Samples were prepared by placing them in a silicon low background sample holder and rotated during collection. Data were collected using Bruker DIFFRAC Plus software and analysis was performed by EVA diffract plus software. The PXRD data file was not processed prior to peak searching. Using the peak search algorithm in the EVA software, peaks selected with a threshold value of 1 were used to make preliminary peak assignments. To ensure validity, adjustments were manually made; the output of automated assignments was visually checked, and peak positions were adjusted to the peak maximum. Peaks with relative intensity of ≥ 3% were generally chosen. Typically, the peaks which were not resolved or were consistent with noise were not selected. A typical error associated with the peak position from PXRD stated in USP up to +/- 0.2° 2-Theta (USP-941). A list of diffraction peaks expressed in terms of the degree 2θ and relative intensities with a relative intensity of ≥ 3.0% of a PXRD from a sample of Form A obtained by Synthesis 1S-2 is provided above in Table E1-1.

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Table E1-1

Angle (2 theta) +/- 0.2°	Relative Intensity (%)
3.9	18.4
7.7	36.3
8.1	10.4
8.7	3.4
10.2	4.1
14.6	5.8
15.2	30.1
15.7	45.5
16.0	31.3
16.8	8.7
17.6	86.0
19.2	46.6
19.5	25.4
19.8	31.4
20.2	25.0
21.1	100.0
21.4	40.2
22.2	37.0
23.0	19.8
24.3	43.0
25.0	9.9
26.0	15.8
27.3	35.3
28.2	14.1
29.3	19.7
29.8	11.7
31.6	9.3
32.8	6.0
34.0	14.4
34.5	12.1
35.4	3.0
36.5	4.1

The anhydrous (anhydrate) crystalline form of tris salt of Compound 1 obtained by the methods described herein is designated as Form A. Form A can be identified by its unique

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solid state signatures with respect to, for example, powder X-ray diffraction pattern (PXRD), and other solid state methods such as ^{13}C solid state NMR.

In some embodiments, Form A exhibits a powder X-ray diffraction pattern comprising at least two characteristic peaks, in terms of 2θ, selected from at 7.7 ± 0.2°; 15.2 ± 0.2°; 15.7 ± 0.2°; and 17.6 ± 0.2°. In some embodiments, Form A exhibits a powder X-ray diffraction pattern comprising at least three characteristic peaks, in terms of 2θ, selected from at 7.7 ± 0.2°; 15.2 ± 0.2°; 15.7 ± 0.2°; and 17.6 ± 0.2°. In some embodiments, Form A exhibits a powder X-ray diffraction pattern comprising characteristic peaks, in terms of 2θ, selected from at 7.7 ± 0.2°; 15.2 ± 0.2°; 15.7± 0.2°; and 17.6± 0.2°.

In some embodiments, Form A exhibits a powder X-ray diffraction pattern comprising characteristic peaks, in terms of 2θ, at 7.7 ± 0.2° and 17.6 ± 0.2°.

In some embodiments, Form A exhibits a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 7.7 ± 0.2°; 15.2 ± 0.2°; and 17.6 ± 0.2°.

In some embodiments, Form A exhibits a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 7.7 ± 0.2°; 15.2 ± 0.2°; and 15.7 ± 0.2°.

In some embodiments, Form A exhibits a powder X-ray diffraction pattern comprising peaks, in terms of 2θ, at 7.7 ± 0.2°; 15.2 ± 0.2°; 15.7 ± 0.2°; and 17.6 ± 0.2°.

In some embodiments, Form A exhibits a powder X-ray diffraction pattern substantially as shown in FiG. 1.

Solid State NMR Analysis of Form A of
1,3-Dihydroxy-2-(hydroxymethyl)propan-2-aminium Salt of Compound 1

Solid state NMR (ssNMR) analysis was conducted on a CPMAS probe positioned into a Bruker-BioSpin Avance III 500 MHz (^{1}H frequency) NMR spectrometer. A sample of Form A of *1,3-Dihydroxy-2-(hydroxymethyl)propan-2-aminium Salt of Compound 1* was packed into a 4 mm rotor. A magic angle spinning rate of 15.0 kHz was used.

^{13}C ssNMR spectrum was collected using a proton decoupled cross-polarization magic angle spinning (CPMAS) experiment. A phase modulated proton decoupling field of 80-90 kHz was applied during spectral acquisition. The cross-polarization contact time was set to 2 ms and the recycle delay of 3-8 seconds. The number of scans was adjusted to obtain an adequate signal to noise ratio, with 2048 scans being collected for each API. The ^{13}C chemical shift scale was referenced using a ^{13}C CPMAS experiment on an external standard of crystalline adamantane, setting its up-field resonance to 29.5 ppm.

Automatic peak picking was performed using Bruker-BioSpin TopSpin version 3.6 software. Generally, a threshold value of 3% relative intensity was used for preliminary peak selection. The output of the automated peak picking was visually checked to ensure validity and adjustments were manually made if necessary. Although specific solid state NMR peak (ssNMR) values are reported herein there does exist a range for these peak values due to differences in

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instruments, samples, and sample preparation. This is common practice in the art of ssNMR because of the variation inherent in peak positions. A typical variability for a ^{13}C chemical shift x-axis value is on the order of plus or minus 0.2 ppm for a crystalline solid. The ssNMR peak heights reported herein are relative intensities. Solid state NMR intensities can vary depending on the actual setup of the CPMAS experimental parameters and the thermal history of the sample. The chemical shift data is dependent on the testing conditions (i.e. spinning speed and sample holder), reference material, and data processing parameters, among other factors. Typically, the ss-NMR results are accurate to within about ± 0.2 ppm. A representative ^{13}C ssNMR spectrum of Form A was obtained, which is shown in FIG. 2. ^{13}C Chemical Shifts [ppm] ± 0.2 ppm of Form A are listed in Table E1-2.

Table E1-2 Carbon chemical shifts observed.

^{13}C Chemical Shifts [ppm] ± 0.2 ppm	Relative Intensity
22.1	30
23.4	49
25.7	29
29.6	50
33.7	25
34.9	22
40.7	29
41.3	31
47.3	31
47.7	30
52.7	28
53.8	28
56.1	53
57.5	53
59.1	100
61.8	64
69.2	28
70.5	27
80.1	57
105.9	42
112.4	33
112.5	33
115.6	35
118.7	46
121.1	44

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121.4	44
122.3	34
123.0	36
123.4	34
125.6	30
126.0	30
126.8	44
132.4	31
134.1	46
135.2	21
137.1	41
137.6	26
142.6	28
143.1	27
144.0	28
146.7	23
147.9	29
148.5	23
148.9	26
152.5	47
156.1	29
175.3	28
175.6	27

Example 2.

Form 2 of 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt of Compound 1

Preparation of Form 2 of 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt of Compound 1

Compound 1 (49.7 mg) was mixed with methanol (0.828 mL) in a vial and heated to 50°C. A stock solution of Tris (30.25µL, 3M) was then added and the resultant mixture was cooled to room temperature slowly. The mixture was then allowed to slowly evaporate at room temperature (the vial was placed in a fume hood and the cap slightly cracked to allow for solvent evaporation). Crystals of tris salt of Compound 1 formed by slow evaporation in the methanol/water mixed solvent (and this crystalline form is designated as Form 2).

Single Crystal X-Ray Analysis.

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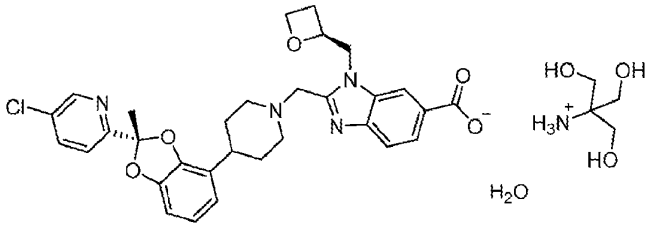
A sample of Form 2 of tris salt of Compound 1 was tested for single crystal analysis. Data collection was performed on a Bruker D8 Venture diffractometer at room temperature. Data collection consisted of omega and phi scans.

The structure was solved by intrinsic phasing using SHELX software suite in the Monoclinic class space group $P2_1$. The structure was subsequently refined by the full-matrix least squares method. All non-hydrogen atoms were found and refined using anisotropic displacement parameters.

Terminal ring (C1-C2-C3-C4-C5—Cl1) was disordered. A disorder model was tested for this group, but did not refine satisfactorily. CIF_Check module generated level "A" based on above mentioned segment.

The hydrogen atoms located on nitrogen and oxygen were found from the Fourier difference map and refined with distances restrained. The remaining hydrogen atoms were placed in calculated positions and were allowed to ride on their carrier atoms. The final refinement included isotropic displacement parameters for all hydrogen atoms.

TRIS salt was confirmed because of proton transfer from O5 to N5. Additionally, the structure contained one water molecule (and thus monohydrate). Analysis of the absolute structure using likelihood methods (Hooft 2008) was performed using PLATON (Spek 2010), with the known stereochemistry information of C22 (and thus, the stereochemistry information of C6 was determined). The refined structure was plotted using the SHELXTL plotting package (FIG. 3). According to the refined structure, Form 2 is a monohydrate of tris salt of Compound 1, the structure of which can be represented as shown below:



The final R-index was 6.6%. A final difference Fourier revealed no missing or misplaced electron density.

Pertinent crystal, data collection and refinement are summarized in Table E2-1. Atomic coordinates, bond lengths, bond angles and displacement parameters are listed in tables E2-2 to E2-4.

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Table E2-1. Crystal data and structure refinement for Form 2.

Empirical formula	C35 H44 Cl N5 O9	
Formula weight	714.20	
Temperature	296(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 12.944(4) Å	α= 90°.
	b = 6.1938(16) Å	β= 91.731(16)°.
	c = 24.777(7) Å	γ = 90°.
Volume	1985.5(9) $Å^3$	
Z	2	
Density (calculated)	1.195 Mg/m^3	
Absorption coefficient	1.311 mm^{-1}	
F(000)	756	
Crystal size	0.500 x 0.060 x 0.020 mm^3	
Theta range for data collection	3.416 to 58.358°.	
Index ranges	-14<=h<=14, -6<=k<=6, -25<=l<=26	
Reflections collected	22149	
Independent reflections	5405 [R(int) = 0.0849]	
Completeness to theta = 58.358°	96.9 %	
Absorption correction	Empirical	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5405 / 9 / 476	
Goodness-of-fit on F^2	1.074	
Final R indices [I>2sigma(I)]	R1 = 0.0659, wR2 = 0.1680	
R indices (all data)	R1 = 0.0821, wR2 = 0.1786	
Absolute structure parameter	0.12(6)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.301 and -0.346 $e.Å^{-3}$	

Table E2-2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Form 2. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	2581(4)	11780(30)	6569(4)	378(7)
N(1)	5044(11)	8410(30)	6117(5)	175(5)
C(1)	4152(16)	9050(60)	6370(8)	225(12)
C(2)	3718(14)	10890(60)	6277(12)	219(13)
C(3)	4300(30)	12470(60)	5989(14)	286(17)
C(4)	5186(17)	11870(40)	5789(11)	227(10)
C(5)	5581(10)	9900(20)	5840(5)	126(4)
N(2)	9326(3)	11743(8)	7589(2)	54(1)
N(3)	10176(3)	8565(8)	8754(2)	52(1)
N(4)	8507(3)	8823(7)	8496(2)	47(1)
N(5)	3667(3)	3409(8)	9569(2)	49(1)
O(1)	6700(8)	10298(17)	5094(3)	151(3)
O(2)	7372(5)	10295(14)	5994(2)	122(2)
O(3)	6798(5)	6442(10)	7818(2)	103(2)
O(4)	6517(3)	2465(7)	9413(2)	62(1)
O(5)	7791(3)	641(7)	9848(2)	64(1)
O(6)	3401(3)	5679(7)	8537(2)	75(1)
O(7)	4901(3)	86(6)	9094(2)	62(1)
O(8)	2255(3)	-731(6)	8733(2)	61(1)
C(6)	6593(9)	9250(20)	5626(4)	118(3)
C(7)	6806(13)	6880(20)	5590(7)	167(5)
C(8)	8023(8)	11410(16)	5654(3)	98(3)
C(9)	7637(10)	11460(20)	5116(3)	116(3)
C(10)	8078(12)	12520(30)	4692(4)	142(4)
C(11)	8984(13)	13550(30)	4828(4)	155(5)
C(12)	9410(9)	13510(20)	5362(3)	128(4)
C(13)	8937(7)	12450(16)	5800(3)	96(3)
C(14)	9378(6)	12511(14)	6388(3)	83(2)
C(15)	8732(6)	13879(13)	6775(3)	82(2)
C(16)	9212(6)	13926(11)	7362(3)	75(2)

C(17)	9980(5)	10417(12)	7242(2)	71(2)
C(18)	9549(6)	10275(14)	6651(3)	83(2)
C(19)	9680(4)	11785(10)	8170(2)	58(1)
C(20)	9472(4)	9706(9)	8468(2)	48(1)
C(21)	7527(4)	9701(10)	8270(2)	55(1)
C(22)	7151(4)	8630(12)	7742(2)	65(2)
C(23)	6088(7)	9320(20)	7521(4)	112(3)
C(24)	5793(8)	7010(30)	7585(5)	145(5)
C(25)	8600(4)	6993(9)	8828(2)	46(1)
C(26)	9649(4)	6850(9)	8990(2)	46(1)
C(27)	9995(4)	5194(10)	9341(2)	50(1)
C(28)	9282(4)	3703(10)	9519(2)	48(1)
C(29)	8227(4)	3843(9)	9353(2)	45(1)
C(30)	7881(4)	5488(9)	8998(2)	45(1)
C(31)	7460(4)	2181(9)	9559(2)	46(1)
C(32)	3324(4)	2306(9)	9042(2)	47(1)
C(33)	2752(4)	3898(9)	8662(2)	57(1)
C(34)	4280(4)	1420(9)	8750(2)	52(1)
C(35)	2607(4)	435(10)	9209(2)	54(1)
O(1W)	5386(3)	6086(7)	9518(2)	62(1)

Table E2-3. Bond lengths [Å] and angles [°] for Form 2.

Cl(1)-C(2)	1.75(2)	N(2)-C(16)	1.469(9)
N(1)-C(5)	1.356(17)	N(2)-C(17)	1.473(8)
N(1)-C(1)	1.39(3)	N(2)-C(19)	1.498(7)
C(1)-C(2)	1.29(4)	N(3)-C(20)	1.340(7)
C(1)-H(1)	0.9300	N(3)-C(26)	1.399(7)
C(2)-C(3)	1.43(4)	N(4)-C(20)	1.368(6)
C(3)-C(4)	1.32(3)	N(4)-C(25)	1.403(7)
C(3)-H(3)	0.9300	N(4)-C(21)	1.475(7)
C(4)-C(5)	1.33(2)	N(5)-C(32)	1.528(7)
C(4)-H(4)	0.9300	N(5)-H(5X)	0.97(3)
C(5)-C(6)	1.483(18)	N(5)-H(5Y)	0.98(3)

N(5)-H(5Z)	0.99(3)	C(16)-H(16B)	0.9700
O(1)-C(9)	1.410(14)	C(17)-C(18)	1.554(10)
O(1)-C(6)	1.479(13)	C(17)-H(17A)	0.9700
O(2)-C(8)	1.392(10)	C(17)-H(17B)	0.9700
O(2)-C(6)	1.486(12)	C(18)-H(18A)	0.9700
O(3)-C(22)	1.445(9)	C(18)-H(18B)	0.9700
O(3)-C(24)	1.450(12)	C(19)-C(20)	1.512(8)
O(4)-C(31)	1.274(6)	C(19)-H(19A)	0.9700
O(5)-C(31)	1.261(7)	C(19)-H(19B)	0.9700
O(6)-C(33)	1.426(7)	C(21)-C(22)	1.534(9)
O(6)-H(6Z)	0.99(3)	C(21)-H(21A)	0.9700
O(7)-C(34)	1.420(7)	C(21)-H(21B)	0.9700
O(7)-H(7Z)	0.99(3)	C(22)-C(23)	1.527(10)
O(8)-C(35)	1.445(7)	C(22)-H(22)	0.9800
O(8)-H(8Z)	0.97(3)	C(23)-C(24)	1.493(19)
C(6)-C(7)	1.50(2)	C(23)-H(23A)	0.9700
C(7)-H(7A)	0.9600	C(23)-H(23B)	0.9700
C(7)-H(7B)	0.9600	C(24)-H(24A)	0.9700
C(7)-H(7C)	0.9600	C(24)-H(24B)	0.9700
C(8)-C(13)	1.386(13)	C(25)-C(30)	1.391(7)
C(8)-C(9)	1.410(12)	C(25)-C(26)	1.406(7)
C(9)-C(10)	1.376(16)	C(26)-C(27)	1.410(8)
C(10)-C(11)	1.371(18)	C(27)-C(28)	1.386(8)
C(10)-H(10)	0.9300	C(27)-H(27)	0.9300
C(11)-C(12)	1.418(16)	C(28)-C(29)	1.416(7)
C(11)-H(11)	0.9300	C(28)-H(28)	0.9300
C(12)-C(13)	1.422(12)	C(29)-C(30)	1.411(8)
C(12)-H(12)	0.9300	C(29)-C(31)	1.528(7)
C(13)-C(14)	1.548(11)	C(30)-H(30)	0.9300
C(14)-C(18)	1.544(11)	C(32)-C(33)	1.538(8)
C(14)-C(15)	1.545(10)	C(32)-C(35)	1.549(8)
C(14)-H(14)	0.9800	C(32)-C(34)	1.552(7)
C(15)-C(16)	1.565(10)	C(33)-H(33A)	0.9700
C(15)-H(15A)	0.9700	C(33)-H(33B)	0.9700
C(15)-H(15B)	0.9700	C(34)-H(34A)	0.9700
C(16)-H(16A)	0.9700	C(34)-H(34B)	0.9700

C(35)-H(35A)	0.9700
C(35)-H(35B)	0.9700
O(1W)-H(1WX)	0.99(3)
O(1W)-H(1WY)	1.00(3)
C(5)-N(1)-C(1)	119(2)
C(2)-C(1)-N(1)	122(2)
C(2)-C(1)-H(1)	118.8
N(1)-C(1)-H(1)	118.8
C(1)-C(2)-C(3)	117(2)
C(1)-C(2)-Cl(1)	125(3)
C(3)-C(2)-Cl(1)	117(3)
C(4)-C(3)-C(2)	118(3)
C(4)-C(3)-H(3)	120.8
C(2)-C(3)-H(3)	120.8
C(3)-C(4)-C(5)	124(3)
C(3)-C(4)-H(4)	118.0
C(5)-C(4)-H(4)	118.0
C(4)-C(5)-N(1)	118.2(17)
C(4)-C(5)-C(6)	123.8(15)
N(1)-C(5)-C(6)	118.0(13)
C(16)-N(2)-C(17)	110.1(5)
C(16)-N(2)-C(19)	112.0(5)
C(17)-N(2)-C(19)	113.9(5)
C(20)-N(3)-C(26)	106.8(4)
C(20)-N(4)-C(25)	106.9(4)
C(20)-N(4)-C(21)	127.5(5)
C(25)-N(4)-C(21)	125.3(4)
C(32)-N(5)-H(5X)	118(3)
C(32)-N(5)-H(5Y)	106(3)
H(5X)-N(5)-H(5Y)	107(5)
C(32)-N(5)-H(5Z)	117(4)
H(5X)-N(5)-H(5Z)	90(5)
H(5Y)-N(5)-H(5Z)	118(5)
C(9)-O(1)-C(6)	107.0(7)
C(8)-O(2)-C(6)	104.8(7)
C(22)-O(3)-C(24)	90.2(8)
C(33)-O(6)-H(6Z)	110(5)
C(34)-O(7)-H(7Z)	110(4)
C(35)-O(8)-H(8Z)	113(4)
O(1)-C(6)-C(5)	107.9(9)
O(1)-C(6)-O(2)	106.1(9)
C(5)-C(6)-O(2)	104.7(9)
O(1)-C(6)-C(7)	110.7(11)
C(5)-C(6)-C(7)	116.9(13)
O(2)-C(6)-C(7)	109.8(10)
C(6)-C(7)-H(7A)	109.5
C(6)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5
C(6)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5
H(7B)-C(7)-H(7C)	109.5
C(13)-C(8)-O(2)	126.8(7)
C(13)-C(8)-C(9)	120.9(8)
O(2)-C(8)-C(9)	112.3(9)
C(10)-C(9)-C(8)	126.1(12)
C(10)-C(9)-O(1)	126.1(10)
C(8)-C(9)-O(1)	107.8(8)
C(11)-C(10)-C(9)	113.9(10)
C(11)-C(10)-H(10)	123.0
C(9)-C(10)-H(10)	123.0
C(10)-C(11)-C(12)	121.8(11)
C(10)-C(11)-H(11)	119.1
C(12)-C(11)-H(11)	119.1
C(11)-C(12)-C(13)	123.9(12)
C(11)-C(12)-H(12)	118.1
C(13)-C(12)-H(12)	118.1
C(8)-C(13)-C(12)	113.4(8)
C(8)-C(13)-C(14)	123.1(6)
C(12)-C(13)-C(14)	123.5(9)
C(18)-C(14)-C(15)	107.6(5)
C(18)-C(14)-C(13)	114.8(7)

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C(15)-C(14)-C(13)	114.0(7)	N(4)-C(20)-C(19)	122.8(5)
C(18)-C(14)-H(14)	106.6	N(4)-C(21)-C(22)	114.3(5)
C(15)-C(14)-H(14)	106.6	N(4)-C(21)-H(21A)	108.7
C(13)-C(14)-H(14)	106.6	C(22)-C(21)-H(21A)	108.7
C(14)-C(15)-C(16)	112.4(6)	N(4)-C(21)-H(21B)	108.7
C(14)-C(15)-H(15A)	109.1	C(22)-C(21)-H(21B)	108.7
C(16)-C(15)-H(15A)	109.1	H(21A)-C(21)-H(21B)	107.6
C(14)-C(15)-H(15B)	109.1	O(3)-C(22)-C(23)	91.5(6)
C(16)-C(15)-H(15B)	109.1	O(3)-C(22)-C(21)	112.8(5)
H(15A)-C(15)-H(15B)	107.9	C(23)-C(22)-C(21)	116.3(7)
N(2)-C(16)-C(15)	111.7(6)	O(3)-C(22)-H(22)	111.6
N(2)-C(16)-H(16A)	109.3	C(23)-C(22)-H(22)	111.6
C(15)-C(16)-H(16A)	109.3	C(21)-C(22)-H(22)	111.6
N(2)-C(16)-H(16B)	109.3	C(24)-C(23)-C(22)	85.5(8)
C(15)-C(16)-H(16B)	109.3	C(24)-C(23)-H(23A)	114.4
H(16A)-C(16)-H(16B)	107.9	C(22)-C(23)-H(23A)	114.4
N(2)-C(17)-C(18)	112.6(5)	C(24)-C(23)-H(23B)	114.4
N(2)-C(17)-H(17A)	109.1	C(22)-C(23)-H(23B)	114.4
C(18)-C(17)-H(17A)	109.1	H(23A)-C(23)-H(23B)	111.5
N(2)-C(17)-H(17B)	109.1	O(3)-C(24)-C(23)	92.7(8)
C(18)-C(17)-H(17B)	109.1	O(3)-C(24)-H(24A)	113.2
H(17A)-C(17)-H(17B)	107.8	C(23)-C(24)-H(24A)	113.2
C(14)-C(18)-C(17)	113.0(6)	O(3)-C(24)-H(24B)	113.2
C(14)-C(18)-H(18A)	109.0	C(23)-C(24)-H(24B)	113.2
C(17)-C(18)-H(18A)	109.0	H(24A)-C(24)-H(24B)	110.5
C(14)-C(18)-H(18B)	109.0	C(30)-C(25)-N(4)	132.2(4)
C(17)-C(18)-H(18B)	109.0	C(30)-C(25)-C(26)	121.4(5)
H(18A)-C(18)-H(18B)	107.8	N(4)-C(25)-C(26)	106.4(4)
N(2)-C(19)-C(20)	113.6(5)	N(3)-C(26)-C(25)	108.2(5)
N(2)-C(19)-H(19A)	108.8	N(3)-C(26)-C(27)	131.3(4)
C(20)-C(19)-H(19A)	108.8	C(25)-C(26)-C(27)	120.5(5)
N(2)-C(19)-H(19B)	108.8	C(28)-C(27)-C(26)	118.6(4)
C(20)-C(19)-H(19B)	108.8	C(28)-C(27)-H(27)	120.7
H(19A)-C(19)-H(19B)	107.7	C(26)-C(27)-H(27)	120.7
N(3)-C(20)-N(4)	111.7(5)	C(27)-C(28)-C(29)	120.8(5)
N(3)-C(20)-C(19)	125.4(5)	C(27)-C(28)-H(28)	119.6

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C(29)-C(28)-H(28)	119.6
C(30)-C(29)-C(28)	120.7(5)
C(30)-C(29)-C(31)	119.8(4)
C(28)-C(29)-C(31)	119.5(5)
C(25)-C(30)-C(29)	118.0(4)
C(25)-C(30)-H(30)	121.0
C(29)-C(30)-H(30)	121.0
O(5)-C(31)-O(4)	124.9(5)
O(5)-C(31)-C(29)	119.1(4)
O(4)-C(31)-C(29)	116.0(5)
N(5)-C(32)-C(33)	111.0(4)
N(5)-C(32)-C(35)	105.5(4)
C(33)-C(32)-C(35)	111.2(4)
N(5)-C(32)-C(34)	110.0(4)
C(33)-C(32)-C(34)	108.5(4)
C(35)-C(32)-C(34)	110.7(4)
O(6)-C(33)-C(32)	110.6(4)
O(6)-C(33)-H(33A)	109.5
C(32)-C(33)-H(33A)	109.5
O(6)-C(33)-H(33B)	109.5
C(32)-C(33)-H(33B)	109.5
H(33A)-C(33)-H(33B)	108.1
O(7)-C(34)-C(32)	111.7(4)
O(7)-C(34)-H(34A)	109.3
C(32)-C(34)-H(34A)	109.3
O(7)-C(34)-H(34B)	109.3
C(32)-C(34)-H(34B)	109.3
H(34A)-C(34)-H(34B)	107.9
O(8)-C(35)-C(32)	109.4(4)
O(8)-C(35)-H(35A)	109.8
C(32)-C(35)-H(35A)	109.8
O(8)-C(35)-H(35B)	109.8
C(32)-C(35)-H(35B)	109.8
H(35A)-C(35)-H(35B)	108.2
H(1WX)-O(1W)-H(1WY)	104(6)

Symmetry transformations used to generate equivalent atoms:

Table E2-4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for Form 2. The anisotropic displacement factor exponent takes the form:

$-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	135(3)	610(20)	393(10)	-72(14)	34(5)	33(7)
N(1)	154(10)	208(13)	161(9)	50(10)	-32(8)	-41(10)
C(1)	108(12)	390(40)	175(15)	30(20)	-3(11)	-59(18)
C(2)	99(11)	320(40)	230(20)	-30(20)	-48(12)	48(16)
C(3)	180(20)	280(40)	390(40)	-50(30)	0(30)	60(30)
C(4)	167(16)	169(18)	350(30)	60(20)	34(17)	21(14)
C(5)	127(9)	134(10)	113(7)	39(7)	-32(6)	-16(8)
N(2)	60(3)	46(3)	56(2)	3(2)	10(2)	-2(2)
N(3)	46(2)	56(3)	55(2)	-4(2)	2(2)	-13(2)
N(4)	40(2)	52(3)	51(2)	1(2)	2(2)	-3(2)
N(5)	43(2)	46(3)	58(3)	-5(2)	2(2)	2(2)
O(1)	184(8)	173(8)	92(4)	21(5)	-40(5)	-9(7)
O(2)	115(4)	173(7)	77(3)	35(4)	-21(3)	-36(5)
O(3)	103(4)	95(4)	108(4)	-3(3)	-39(3)	-16(3)
O(4)	38(2)	60(3)	87(3)	6(2)	-1(2)	-8(2)
O(5)	48(2)	64(3)	79(3)	19(2)	3(2)	-6(2)
O(6)	69(3)	48(2)	109(3)	14(2)	17(2)	3(2)
O(7)	44(2)	48(2)	92(3)	-2(2)	-3(2)	4(2)
O(8)	42(2)	52(2)	90(3)	-11(2)	1(2)	-7(2)
C(6)	127(8)	135(10)	91(6)	3(6)	-21(6)	-10(7)
C(7)	185(13)	125(11)	189(13)	22(10)	-43(10)	0(10)
C(8)	122(7)	109(7)	63(4)	27(4)	13(4)	2(6)
C(9)	151(9)	126(8)	70(5)	15(5)	-16(5)	3(7)
C(10)	184(12)	177(12)	65(5)	24(6)	1(6)	4(10)
C(11)	203(13)	186(13)	79(6)	45(7)	33(7)	-10(12)
C(12)	157(9)	158(10)	70(5)	32(6)	16(5)	-10(8)

C(13)	117(7)	106(6)	67(4)	14(4)	24(4)	-3(6)
C(14)	97(5)	92(5)	61(4)	19(4)	13(3)	-7(4)
C(15)	106(5)	58(4)	82(4)	8(4)	5(4)	13(4)
C(16)	92(5)	53(4)	79(4)	0(3)	6(4)	6(4)
C(17)	77(4)	71(4)	67(4)	10(3)	16(3)	17(4)
C(18)	102(5)	84(5)	64(4)	-4(4)	27(3)	23(4)
C(19)	57(3)	55(4)	61(3)	3(3)	2(3)	-9(3)
C(20)	39(3)	55(3)	48(3)	-7(2)	1(2)	-6(2)
C(21)	45(3)	58(4)	61(3)	2(3)	2(2)	4(3)
C(22)	50(3)	82(5)	61(3)	5(3)	-2(3)	-1(3)
C(23)	76(5)	148(10)	110(6)	14(6)	-29(5)	6(6)
C(24)	84(6)	196(14)	152(9)	15(10)	-36(6)	-32(8)
C(25)	40(3)	55(3)	43(2)	-3(2)	2(2)	0(2)
C(26)	37(2)	53(3)	46(2)	-7(3)	2(2)	-3(2)
C(27)	34(2)	63(4)	52(3)	-5(3)	-3(2)	-3(2)
C(28)	44(3)	57(3)	44(2)	1(3)	-4(2)	-4(3)
C(29)	42(3)	53(3)	41(2)	-3(2)	1(2)	-4(2)
C(30)	36(2)	53(3)	47(2)	0(2)	4(2)	-5(2)
C(31)	45(3)	48(3)	46(3)	-1(3)	3(2)	-1(2)
C(32)	36(2)	47(3)	57(3)	0(2)	1(2)	-1(2)
C(33)	48(3)	47(3)	76(3)	1(3)	3(3)	4(3)
C(34)	41(3)	50(3)	66(3)	-5(3)	4(2)	-2(2)
C(35)	42(3)	53(3)	67(3)	-3(3)	5(2)	-4(3)
O(1W)	52(2)	54(2)	80(3)	4(2)	5(2)	-2(2)

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Calculated/simulated PXRD data.

Using the information obtained by Single Crystal X-Ray Analysis herein above, PXRD peak positions and intensity for Form 2 can be caculated/simulated (See FIG. 4, using Bruker DIFFRAC.EVA version 5.0.0.22). A list of caculated/simulated PXRD diffraction peaks expressed in terms of the degree 2θ and relative intensities with a relative intensity of ≥ 3.0% for Form 2 is provided below.

Table E2-5: Calculated PXRD peak positions and intensity for Form 2.

Angle 2-Theta °	Relative Intensity %
3.6	100%
7.1	**96%**
7.6	**69%**
7.8	37%
9.7	22%
10.0	9%
10.7	**11%**
12.5	5%
14.0	18%
14.3	37%
14.7	42%
15.6	18%
16.0	31%
16.2	25%
17.3	57%
17.9	15%
19.0	19%
19.4	**57%**
19.8	42%
20.2	23%
20.6	7%
20.8	10%
21.0	7%
21.3	14%
21.5	6%

22.4	21%
22.9	11%
23.8	24%
24.3	23%
24.8	4%
25.9	9%
26.4	5%
26.6	11%
27.0	10%
28.7	5%
29.1	6%
29.7	4%
30.0	8%
31.5	7%
32.3	3%
34.1	3%
35.8	4%
36.2	4%

Example 3. Form 3 of tris salt of Compound 1

Preparation of Form 3 of Tris salt of Compound 1 (Slurry to Slurry Conversion)

The anhydrous form Form A of tris salt of Compound 1 (1.177grams) was added to a 50 mL EasyMax® reactor. A mixed solvent of acetonitrile and water (27.9 mL acetonitrile and 2.4 mL water) was then added. The resulting mixture (a slurry) was stirred with overhead paddle stirring at room temperature (about 25°C) over two days. The mixture was then cooled to 0°C and stirred for about 1 hour. Then the mixture was filtered by suction filtration through filter paper and the solid collected (cake) was rinsed with 2-3 mL cold acetonitrile (0°C) twice. The resulting cake was air-dried on the funnel for one hour. The cake/funnel was transferred to a vacuum oven for further drying (50°C/~22 in Hg vacuum, with slight nitrogen bleed). After about 5 hours 1.115 gm of white solid was obtained (designed as Form 3).

Altervative Preparation of Form 3 of Compound 1, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt

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Altervatively, single crystals of Form 3 of tris salt of Compound 1 were prepared by vapor diffusion of acetonitrile into a saturated solution of Compound 1, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt in acetonitrile/15% water (v/v).

Single Crystal X-Ray Analysis.

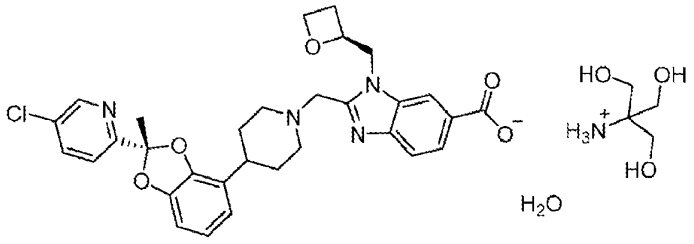
A sample of *Form 3 of tris salt of* Compound 1 was tested for single crystal X-ray analysis. Data collection was performed on a Bruker D8 Venture diffractometer at room temperature on a representative crystal. Data collection consisted of omega and phi scans.

The structure was solved by intrinsic phasing using SHELX software suite (SHELXTL, Version 5.1, Bruker AXS, 1997) in the Monoclinic space group $P2_1$. The structure was subsequently refined by the full-matrix least squares method. All non-hydrogen atoms were found and refined using anisotropic displacement parameters.

The hydrogen atoms located on nitrogen and oxygen were found from the Fourier difference map and refined with distances restrained. The remaining hydrogen atoms were placed in calculated positions and were allowed to ride on their carrier atoms. The final refinement included isotropic displacement parameters for all hydrogen atoms.

Analysis of the absolute structure using likelihood methods (*See* R.W.W. Hooft et al. *J. Appl. Cryst.* (2008). 41. 96-103) was performed using PLATON (*See* A.L. Spek, J. Appl. Cryst. 2003, 36, 7-13). Assuming the sample submitted is enantiopure, the absolute structure (with stereochemistry information on the two chiral centers) was assigned.

The final R-index was 5.1%. A final difference Fourier revealed no missing or misplaced electron density. The refined structure was plotted using the SHELXTL plotting package (SHELXTL, Version 5.1, Bruker AXS, 1997) (FIG. 5). The absolute configuration was determined by the method of Flack (*See* H.D. Flack, *Acta Cryst.* 1983, A39, 867-881). According to the refined structure, Form 3 is a monohydrate of tris salt of Compound 1:



and a chemical name for this hydrate form (including stereochemistry information) is: 2-({4-[(2S)-2-(5-Chloropyridin-2-yl)-2-methyl-1,3-benzodioxol-4-yl]piperidin-1-yl}methyl)-1-[(2S)-oxetan-2-ylmethyl]-1H-benzimidazole-6-carboxylate, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt, monohydrate.

Pertinent crystal, data collection and refinement are summarized in Table E3-1. Atomic coordinates, bond lengths, bond angles and displacement parameters are listed in tables E3-2 to E3-4.

Table E3-1. Crystal data and structure refinement for Form 3.

Empirical formula	C35 H44 Cl N5 O9	
Formula weight	714.20	
Temperature	296(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 12.8892(5) Å	α= 90°.
	b = 6.1536(3) Å	β= 91.835(2)°.
	c = 23.9167(10) Å	γ = 90°.
Volume	1895.98(14) $Å^3$	
Z	2	
Density (calculated)	1.251 Mg/m^3	
Absorption coefficient	1.373 mm^{-1}	
F(000)	756	
Crystal size	0.780 x 0.100 x 0.040 mm^3	
Theta range for data collection	3.431 to 72.528°.	
Index ranges	-12<=h<=15, -7<=k<=7, -29<=l<=29	
Reflections collected	16800	
Independent reflections	6869 [R(int) = 0.0523]	
Completeness to theta = 67.679°	98.0 %	
Absorption correction	Empirical	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6869 / 9 / 476	
Goodness-of-fit on F^2	1.043	
Final R indices [I>2sigma(I)]	R1 = 0.0508, wR2 = 0.1434	
R indices (all data)	R1 = 0.0542, wR2 = 0.1482	
Absolute structure parameter	0.06(3)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.260 and -0.321 $e.Å^{-3}$	

Table E3-2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Form 3. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	2582(2)	9965(16)	6603(2)	325(4)
N(1)	5060(6)	6766(14)	6129(3)	148(2)
N(2)	9316(2)	10129(4)	7585(1)	49(1)
N(3)	10186(2)	6949(4)	8750(1)	48(1)
N(4)	8505(2)	7208(4)	8496(1)	44(1)
N(5)	3669(2)	1786(4)	9568(1)	47(1)
O(1)	6678(4)	8716(10)	5096(2)	131(2)
O(2)	7358(3)	8701(8)	6001(1)	104(1)
O(3)	6794(3)	4812(6)	7825(1)	92(1)
O(4)	6522(2)	848(4)	9422(1)	58(1)
O(5)	7796(2)	-981(4)	9855(1)	60(1)
O(6)	2262(2)	-2325(4)	8721(1)	56(1)
O(7)	3425(2)	4070(4)	8536(1)	69(1)
O(8)	4910(2)	-1536(3)	9093(1)	58(1)
O(1W)	5392(2)	4478(4)	9523(1)	58(1)
C(1)	4178(9)	7380(30)	6380(4)	185(5)
C(2)	3714(8)	9290(40)	6315(6)	190(6)
C(3)	4194(12)	10740(30)	6016(7)	229(7)
C(4)	5148(9)	10270(20)	5778(6)	186(4)
C(5)	5568(5)	8290(13)	5846(2)	113(2)
C(6)	6587(5)	7667(12)	5634(2)	107(2)
C(7)	6794(7)	5276(14)	5590(4)	150(3)
C(8)	8020(4)	9821(9)	5659(2)	87(1)
C(9)	7605(5)	9845(11)	5117(2)	104(2)
C(10)	8072(7)	10888(14)	4692(2)	126(2)
C(11)	8964(7)	11915(15)	4824(2)	131(2)
C(12)	9397(5)	11903(12)	5359(2)	107(2)
C(13)	8917(4)	10851(8)	5804(2)	81(1)
C(14)	9376(3)	10911(7)	6388(2)	73(1)

C(15)	9545(3)	8656(7)	6648(1)	73(1)
C(16)	9983(3)	8811(6)	7242(1)	64(1)
C(17)	9203(3)	12329(6)	7363(2)	68(1)
C(18)	8725(4)	12292(6)	6778(2)	76(1)
C(19)	9678(2)	10173(5)	8169(1)	54(1)
C(20)	9475(2)	8082(5)	8466(1)	46(1)
C(21)	7529(2)	8089(5)	8276(1)	49(1)
C(22)	7147(3)	7018(7)	7745(1)	61(1)
C(23)	6068(3)	7712(11)	7537(2)	94(2)
C(24)	5782(5)	5437(16)	7594(3)	128(2)
C(25)	8603(2)	5376(5)	8831(1)	42(1)
C(26)	9655(2)	5244(5)	8988(1)	43(1)
C(27)	10003(2)	3558(5)	9340(1)	46(1)
C(28)	9287(2)	2076(5)	9519(1)	46(1)
C(29)	8228(2)	2223(5)	9355(1)	42(1)
C(30)	7882(2)	3870(5)	9003(1)	42(1)
C(31)	7462(2)	548(5)	9563(1)	45(1)
C(32)	3329(2)	681(4)	9035(1)	43(1)
C(33)	2609(2)	-1171(5)	9201(1)	51(1)
C(34)	2769(2)	2309(5)	8659(1)	54(1)
C(35)	4294(2)	-179(5)	8747(1)	49(1)

Table E3-3. Bond lengths [Å] and angles [°] for Form 3.

Cl(1)-C(2)	1.684(13)	N(5)-C(32)	1.496(4)
N(1)-C(5)	1.340(10)	N(5)-H(5X)	0.95(2)
N(1)-C(1)	1.355(16)	N(5)-H(5Y)	0.98(2)
N(2)-C(16)	1.454(4)	N(5)-H(5Z)	0.97(2)
N(2)-C(19)	1.458(4)	O(1)-C(9)	1.382(8)
N(2)-C(17)	1.460(4)	O(1)-C(6)	1.446(7)
N(3)-C(20)	1.322(4)	O(2)-C(8)	1.385(6)
N(3)-C(26)	1.385(4)	O(2)-C(6)	1.452(7)
N(4)-C(20)	1.365(4)	O(3)-C(22)	1.446(5)
N(4)-C(25)	1.386(4)	O(3)-C(24)	1.451(7)
N(4)-C(21)	1.454(4)	O(4)-C(31)	1.261(3)

O(5)-C(31)	1.241(4)	C(15)-H(15B)	0.9700
O(6)-C(33)	1.410(4)	C(16)-H(16A)	0.9700
O(6)-H(6Y)	0.95(2)	C(16)-H(16B)	0.9700
O(7)-C(34)	1.411(4)	C(17)-C(18)	1.510(5)
O(7)-H(7Y)	0.96(3)	C(17)-H(17A)	0.9700
O(8)-C(35)	1.405(4)	C(17)-H(17B)	0.9700
O(8)-H(8Y)	0.97(2)	C(18)-H(18A)	0.9700
O(1W)-H(1WX)	0.97(2)	C(18)-H(18B)	0.9700
O(1W)-H(1WY)	0.96(2)	C(19)-C(20)	1.496(4)
C(1)-C(2)	1.33(2)	C(19)-H(19A)	0.9700
C(1)-H(1)	0.9300	C(19)-H(19B)	0.9700
C(2)-C(3)	1.31(2)	C(21)-C(22)	1.500(4)
C(3)-C(4)	1.401(17)	C(21)-H(21A)	0.9700
C(3)-H(3)	0.9300	C(21)-H(21B)	0.9700
C(4)-C(5)	1.343(14)	C(22)-C(23)	1.522(5)
C(4)-H(4)	0.9300	C(22)-H(22)	0.9800
C(5)-C(6)	1.473(10)	C(23)-C(24)	1.455(11)
C(6)-C(7)	1.500(12)	C(23)-H(23A)	0.9700
C(7)-H(7A)	0.9600	C(23)-H(23B)	0.9700
C(7)-H(7B)	0.9600	C(24)-H(24A)	0.9700
C(7)-H(7C)	0.9600	C(24)-H(24B)	0.9700
C(8)-C(13)	1.354(7)	C(25)-C(30)	1.385(4)
C(8)-C(9)	1.387(6)	C(25)-C(26)	1.398(4)
C(9)-C(10)	1.359(9)	C(26)-C(27)	1.400(4)
C(10)-C(11)	1.340(11)	C(27)-C(28)	1.376(4)
C(10)-H(10)	0.9300	C(27)-H(27)	0.9300
C(11)-C(12)	1.379(9)	C(28)-C(29)	1.411(4)
C(11)-H(11)	0.9300	C(28)-H(28)	0.9300
C(12)-C(13)	1.405(6)	C(29)-C(30)	1.384(4)
C(12)-H(12)	0.9300	C(29)-C(31)	1.521(4)
C(13)-C(14)	1.499(6)	C(30)-H(30)	0.9300
C(14)-C(18)	1.532(6)	C(32)-C(34)	1.514(4)
C(14)-C(15)	1.534(6)	C(32)-C(33)	1.530(4)
C(14)-H(14)	0.9800	C(32)-C(35)	1.536(4)
C(15)-C(16)	1.514(5)	C(33)-H(33A)	0.9700
C(15)-H(15A)	0.9700	C(33)-H(33B)	0.9700

C(34)-H(34A)	0.9700	C(5)-C(4)-H(4)	120.3
C(34)-H(34B)	0.9700	C(3)-C(4)-H(4)	120.3
C(35)-H(35A)	0.9700	N(1)-C(5)-C(4)	119.7(9)
C(35)-H(35B)	0.9700	N(1)-C(5)-C(6)	116.6(7)
		C(4)-C(5)-C(6)	123.7(7)
C(5)-N(1)-C(1)	117.3(11)	O(1)-C(6)-O(2)	105.6(5)
C(16)-N(2)-C(19)	111.9(3)	O(1)-C(6)-C(5)	106.8(5)
C(16)-N(2)-C(17)	111.4(3)	O(2)-C(6)-C(5)	106.1(5)
C(19)-N(2)-C(17)	110.9(3)	O(1)-C(6)-C(7)	110.9(7)
C(20)-N(3)-C(26)	105.5(2)	O(2)-C(6)-C(7)	110.6(6)
C(20)-N(4)-C(25)	106.5(2)	C(5)-C(6)-C(7)	116.3(7)
C(20)-N(4)-C(21)	128.1(3)	C(6)-C(7)-H(7A)	109.5
C(25)-N(4)-C(21)	125.1(2)	C(6)-C(7)-H(7B)	109.5
C(32)-N(5)-H(5X)	105(2)	H(7A)-C(7)-H(7B)	109.5
C(32)-N(5)-H(5Y)	112(2)	C(6)-C(7)-H(7C)	109.5
H(5X)-N(5)-H(5Y)	104(3)	H(7A)-C(7)-H(7C)	109.5
C(32)-N(5)-H(5Z)	111(2)	H(7B)-C(7)-H(7C)	109.5
H(5X)-N(5)-H(5Z)	115(3)	C(13)-C(8)-O(2)	128.3(4)
H(5Y)-N(5)-H(5Z)	109(3)	C(13)-C(8)-C(9)	122.4(4)
C(9)-O(1)-C(6)	106.8(4)	O(2)-C(8)-C(9)	109.3(5)
C(8)-O(2)-C(6)	106.5(4)	C(10)-C(9)-O(1)	128.0(5)
C(22)-O(3)-C(24)	89.1(4)	C(10)-C(9)-C(8)	122.5(7)
C(33)-O(6)-H(6Y)	107(2)	O(1)-C(9)-C(8)	109.6(5)
C(34)-O(7)-H(7Y)	105(3)	C(11)-C(10)-C(9)	116.4(6)
C(35)-O(8)-H(8Y)	105(3)	C(11)-C(10)-H(10)	121.8
H(1WX)-O(1W)-H(1WY)	117(3)	C(9)-C(10)-H(10)	121.8
C(2)-C(1)-N(1)	125.3(13)	C(10)-C(11)-C(12)	122.3(6)
C(2)-C(1)-H(1)	117.4	C(10)-C(11)-H(11)	118.8
N(1)-C(1)-H(1)	117.4	C(12)-C(11)-H(11)	118.8
C(3)-C(2)-C(1)	116.5(13)	C(11)-C(12)-C(13)	122.0(7)
C(3)-C(2)-Cl(1)	119.2(17)	C(11)-C(12)-H(12)	119.0
C(1)-C(2)-Cl(1)	124.3(17)	C(13)-C(12)-H(12)	119.0
C(2)-C(3)-C(4)	121.4(16)	C(8)-C(13)-C(12)	114.5(4)
C(2)-C(3)-H(3)	119.3	C(8)-C(13)-C(14)	123.9(3)
C(4)-C(3)-H(3)	119.3	C(12)-C(13)-C(14)	121.6(5)
C(5)-C(4)-C(3)	119.4(13)	C(13)-C(14)-C(18)	112.0(4)

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C(13)-C(14)-C(15)	113.8(4)	N(3)-C(20)-C(19)	124.6(3)
C(18)-C(14)-C(15)	109.1(3)	N(4)-C(20)-C(19)	122.6(3)
C(13)-C(14)-H(14)	107.2	N(4)-C(21)-C(22)	113.6(2)
C(18)-C(14)-H(14)	107.2	N(4)-C(21)-H(21A)	108.8
C(15)-C(14)-H(14)	107.2	C(22)-C(21)-H(21A)	108.8
C(16)-C(15)-C(14)	111.6(3)	N(4)-C(21)-H(21B)	108.8
C(16)-C(15)-H(15A)	109.3	C(22)-C(21)-H(21B)	108.8
C(14)-C(15)-H(15A)	109.3	H(21A)-C(21)-H(21B)	107.7
C(16)-C(15)-H(15B)	109.3	O(3)-C(22)-C(21)	113.4(3)
C(14)-C(15)-H(15B)	109.3	O(3)-C(22)-C(23)	91.1(4)
H(15A)-C(15)-H(15B)	108.0	C(21)-C(22)-C(23)	115.1(3)
N(2)-C(16)-C(15)	110.8(3)	O(3)-C(22)-H(22)	111.9
N(2)-C(16)-H(16A)	109.5	C(21)-C(22)-H(22)	111.9
C(15)-C(16)-H(16A)	109.5	C(23)-C(22)-H(22)	111.9
N(2)-C(16)-H(16B)	109.5	C(24)-C(23)-C(22)	86.1(4)
C(15)-C(16)-H(16B)	109.5	C(24)-C(23)-H(23A)	114.3
H(16A)-C(16)-H(16B)	108.1	C(22)-C(23)-H(23A)	114.3
N(2)-C(17)-C(18)	110.9(3)	C(24)-C(23)-H(23B)	114.3
N(2)-C(17)-H(17A)	109.5	C(22)-C(23)-H(23B)	114.3
C(18)-C(17)-H(17A)	109.5	H(23A)-C(23)-H(23B)	111.5
N(2)-C(17)-H(17B)	109.5	O(3)-C(24)-C(23)	93.6(4)
C(18)-C(17)-H(17B)	109.5	O(3)-C(24)-H(24A)	113.0
H(17A)-C(17)-H(17B)	108.1	C(23)-C(24)-H(24A)	113.0
C(17)-C(18)-C(14)	111.0(3)	O(3)-C(24)-H(24B)	113.0
C(17)-C(18)-H(18A)	109.4	C(23)-C(24)-H(24B)	113.0
C(14)-C(18)-H(18A)	109.4	H(24A)-C(24)-H(24B)	110.4
C(17)-C(18)-H(18B)	109.4	C(30)-C(25)-N(4)	131.7(2)
C(14)-C(18)-H(18B)	109.4	C(30)-C(25)-C(26)	122.5(2)
H(18A)-C(18)-H(18B)	108.0	N(4)-C(25)-C(26)	105.8(2)
N(2)-C(19)-C(20)	112.5(2)	N(3)-C(26)-C(25)	109.5(2)
N(2)-C(19)-H(19A)	109.1	N(3)-C(26)-C(27)	131.0(2)
C(20)-C(19)-H(19A)	109.1	C(25)-C(26)-C(27)	119.6(2)
N(2)-C(19)-H(19B)	109.1	C(28)-C(27)-C(26)	118.3(2)
C(20)-C(19)-H(19B)	109.1	C(28)-C(27)-H(27)	120.9
H(19A)-C(19)-H(19B)	107.8	C(26)-C(27)-H(27)	120.9
N(3)-C(20)-N(4)	112.7(2)	C(27)-C(28)-C(29)	121.6(3)

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C(27)-C(28)-H(28)	119.2
C(29)-C(28)-H(28)	119.2
C(30)-C(29)-C(28)	120.4(2)
C(30)-C(29)-C(31)	119.7(2)
C(28)-C(29)-C(31)	119.8(2)
C(29)-C(30)-C(25)	117.7(2)
C(29)-C(30)-H(30)	121.2
C(25)-C(30)-H(30)	121.2
O(5)-C(31)-O(4)	125.1(3)
O(5)-C(31)-C(29)	118.7(2)
O(4)-C(31)-C(29)	116.2(2)
N(5)-C(32)-C(34)	109.1(2)
N(5)-C(32)-C(33)	106.4(2)
C(34)-C(32)-C(33)	111.4(2)
N(5)-C(32)-C(35)	108.6(2)
C(34)-C(32)-C(35)	109.8(2)
C(33)-C(32)-C(35)	111.5(2)
O(6)-C(33)-C(32)	110.1(2)
O(6)-C(33)-H(33A)	109.6
C(32)-C(33)-H(33A)	109.6
O(6)-C(33)-H(33B)	109.6
C(32)-C(33)-H(33B)	109.6
H(33A)-C(33)-H(33B)	108.2
O(7)-C(34)-C(32)	110.8(2)
O(7)-C(34)-H(34A)	109.5
C(32)-C(34)-H(34A)	109.5
O(7)-C(34)-H(34B)	109.5
C(32)-C(34)-H(34B)	109.5
H(34A)-C(34)-H(34B)	108.1
O(8)-C(35)-C(32)	113.0(2)
O(8)-C(35)-H(35A)	109.0
C(32)-C(35)-H(35A)	109.0
O(8)-C(35)-H(35B)	109.0
C(32)-C(35)-H(35B)	109.0
H(35A)-C(35)-H(35B)	107.8

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Symmetry transformations used to generate equivalent atoms:

Table E3-4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for Form 3. The anisotropic displacement factor exponent takes the form:

$-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	121(2)	543(11)	312(4)	-88(7)	38(2)	21(4)
N(1)	123(5)	171(6)	147(5)	38(5)	-24(4)	-23(5)
N(2)	56(1)	44(1)	49(1)	0(1)	9(1)	-3(1)
N(3)	38(1)	55(1)	51(1)	-4(1)	1(1)	-8(1)
N(4)	38(1)	48(1)	47(1)	-1(1)	2(1)	-2(1)
N(5)	38(1)	50(1)	54(1)	-6(1)	2(1)	1(1)
O(1)	160(4)	152(4)	77(2)	20(2)	-31(2)	-19(4)
O(2)	101(2)	141(3)	70(2)	29(2)	-13(2)	-25(2)
O(3)	100(2)	84(2)	89(2)	-4(2)	-30(2)	-16(2)
O(4)	37(1)	59(1)	79(1)	6(1)	1(1)	-7(1)
O(5)	45(1)	62(1)	71(1)	19(1)	2(1)	-5(1)
O(6)	38(1)	53(1)	77(1)	-11(1)	2(1)	-7(1)
O(7)	61(1)	48(1)	99(2)	13(1)	14(1)	2(1)
O(8)	42(1)	46(1)	85(1)	-6(1)	-4(1)	3(1)
O(1W)	48(1)	54(1)	72(1)	3(1)	1(1)	-2(1)
C(1)	113(6)	286(17)	154(7)	53(10)	-9(5)	-33(9)
C(2)	95(6)	277(19)	196(10)	-10(11)	-40(6)	5(9)
C(3)	156(10)	233(17)	296(18)	-36(15)	-1(11)	77(12)
C(4)	162(8)	142(8)	258(12)	43(9)	36(8)	6(7)
C(5)	112(4)	126(5)	98(3)	30(3)	-33(3)	-22(4)
C(6)	114(4)	120(4)	85(3)	17(3)	-22(3)	-12(3)
C(7)	167(7)	114(5)	167(7)	21(5)	-30(5)	-7(5)
C(8)	107(3)	98(3)	55(2)	17(2)	5(2)	6(3)
C(9)	140(5)	110(4)	62(2)	9(2)	-8(2)	2(4)
C(10)	172(6)	147(6)	60(2)	18(3)	0(3)	1(5)

C(11)	180(7)	148(6)	68(3)	32(3)	31(3)	-4(6)
C(12)	126(4)	127(4)	71(2)	30(3)	24(3)	-4(4)
C(13)	96(3)	90(3)	59(2)	14(2)	15(2)	4(2)
C(14)	79(2)	83(2)	59(2)	15(2)	14(2)	-5(2)
C(15)	92(3)	76(2)	53(2)	0(2)	20(2)	23(2)
C(16)	68(2)	65(2)	60(2)	7(2)	14(1)	16(2)
C(17)	86(2)	45(2)	72(2)	2(2)	1(2)	2(2)
C(18)	98(3)	55(2)	73(2)	10(2)	0(2)	12(2)
C(19)	54(2)	51(2)	57(1)	-3(1)	3(1)	-10(1)
C(20)	44(1)	50(1)	45(1)	-5(1)	5(1)	-7(1)
C(21)	40(1)	56(2)	52(1)	2(1)	4(1)	5(1)
C(22)	50(2)	78(2)	53(2)	1(2)	-1(1)	1(2)
C(23)	64(2)	132(5)	85(3)	5(3)	-22(2)	11(3)
C(24)	79(3)	170(7)	134(4)	16(5)	-36(3)	-38(4)
C(25)	36(1)	50(1)	40(1)	-2(1)	1(1)	0(1)
C(26)	35(1)	52(1)	41(1)	-8(1)	2(1)	-7(1)
C(27)	31(1)	63(2)	44(1)	-4(1)	-4(1)	-3(1)
C(28)	40(1)	58(2)	38(1)	3(1)	-2(1)	1(1)
C(29)	36(1)	52(1)	38(1)	-3(1)	2(1)	-4(1)
C(30)	31(1)	53(1)	44(1)	1(1)	0(1)	-3(1)
C(31)	36(1)	53(2)	45(1)	-2(1)	3(1)	-3(1)
C(32)	35(1)	44(1)	51(1)	-4(1)	-1(1)	-2(1)
C(33)	39(1)	52(2)	62(2)	0(1)	6(1)	-3(1)
C(34)	43(1)	50(2)	68(2)	0(1)	1(1)	2(1)
C(35)	38(1)	50(2)	58(1)	-7(1)	4(1)	-1(1)

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Acquisition of Powder X-ray Diffraction (PXRD) Data for Form 3 of Compound 1, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium salt (also known as Form 3 of monohydrate of tris salt of Compound 1)

A sample of Form 3 (e.g., the white solid of the tris salt of Compound 1 prepared according to the method described herein) was submitted for PXRD analysis and found to be a crystalline material (which is designated as Form 3).

Powder X-ray diffraction analysis was conducted using a Bruker AXS D8 Endeavor diffractometer equipped with a Cu radiation source (K-α average). The divergence slit was set at 15 mm continuous illumination. Diffracted radiation was detected by a PSD-Lynx Eye detector, with the detector PSD opening set at 2.99 degrees. The X-ray tube voltage and amperage were set to 40 kV and 40 mA respectively. Data was collected in the Theta-Theta goniometer at the Cu wavelength from 3.0 to 40.0 degrees 2-Theta using a step size of 0.00999 degrees and a step time of 1.0 second. The antiscatter screen was set to a fixed distance of 1.5 mm. Samples were rotated at 15/min during collection. Samples were prepared by placing them in a silicon low background sample holder and rotated during collection. Data were collected using Bruker DIFFRAC Plus software and analysis was performed by EVA diffract plus software. The sample holder used in a particular experiment is given by a codename within the filename: DW=Deep well holder, SD=small divot holder and FP=Flat plate holder.

The PXRD data file was not processed prior to peak searching. Using the peak search algorithm in the EVA software, peaks selected with a threshold value of 1 and a width value of 0.3 were used to make preliminary peak assignments. The output of automated assignments was visually checked to ensure validity and adjustments were manually made if necessary. Peaks with relative intensity of ≥ 3% were generally chosen. The peaks which were not resolved or were consistent with noise were not selected. A typical error associated with the peak position from PXRD stated in USP up to +/- 0.2° 2-Theta (USP-941). A list of PXRD diffraction peaks expressed in terms of the degree 2θ and relative intensities with a relative intensity of ≥ 3.0% from a sample of Form 3 is provided below.

Table E3-5. PXRD Peaks and Relative Intensities of Form 3

Degrees 2Θ (Angle) ± 0.2° 2Θ	Relative Intensity
3.7*	**16%**
7.4*	**45%**
7.7	28%

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7.9	10%
9.9*	**11%**
10.2	7%
11.1*	**7%**
12.8	3%
14.1	16%
14.3	20%
14.8*	**49%**
15.8	12%
16.1	27%
16.6	14%
17.4	48%
18.2*	**12%**
18.6	4%
19.6	42%
19.9*	100%
20.0	98%
20.6*	**36%**
21.6	18%
23.1	18%
23.5*	**17%**
24.3*	**39%**
24.6*	**25%**
25.9	5%
26.1	5%
26.6	12%
27.0	11%
27.3	8%
27.7	14%
28.9	7%
30.5	5%
30.9	15%
31.6	8%
34.2	8%

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35.2	4%
35.9	5%
37.2	7%

Solid State NMR Analysis of Form 3 of Tris Salt of Compound 1(monohydrate)

Solid state NMR (ssNMR) analysis was conducted on a CPMAS probe positioned into a Bruker-BioSpin Avance III 500 MHz (^{1}H frequency) NMR spectrometer. A sample of Form 3 of *1,3-Dihydroxy-2-(hydroxymethyl)propan-2-aminium Salt of Compound 1, monohydrate* was packed into a 4 mm rotor. A magic angle spinning rate of 15.0 kHz was used.

^{13}C ssNMR spectrum was collected using a proton decoupled cross-polarization magic angle spinning (CPMAS) experiment. A phase modulated proton decoupling field of 80-90 kHz was applied during spectral acquisition. The cross-polarization contact time was set to 2 ms and the recycle delay of 3-8 seconds. The number of scans was adjusted to obtain an adequate signal to noise ratio, with 2048 scans being collected for each API. The ^{13}C chemical shift scale was referenced using a ^{13}C CPMAS experiment on an external standard of crystalline adamantane, setting its up-field resonance to 29.5 ppm.

Automatic peak picking was performed using Bruker-BioSpin TopSpin version 3.6 software. Generally, a threshold value of 3% relative intensity was used for preliminary peak selection. The output of the automated peak picking was visually checked to ensure validity and adjustments were manually made if necessary. Although specific solid state NMR peak values are reported herein there does exist a range for these peak values due to differences in instruments, samples, and sample preparation. This is common practice in the art of solid state NMR because of the variation inherent in peak positions. A typical variability for a ^{13}C chemical shift x-axis value is on the order of plus or minus 0.2 ppm for a crystalline solid. The solid state NMR peak heights reported herein are relative intensities. Solid state NMR intensities can vary depending on the actual setup of the CPMAS experimental parameters and the thermal history of the sample. The chemical shift data is dependent on the testing conditions (i.e. spinning speed and sample holder), reference material, and data processing parameters, among other factors. Typically, the ss-NMR results are accurate to within about ± 0.2 ppm.

Table E3-6. Carbon chemical shifts observed (Characteristic peaks are starred).

^{13}C Chemical Shifts [ppm] ± 0.2 ppm	Relative Intensity
21.0	75
24.2	67
29.9	71

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32.1	67
42.8 *	85
51.9	59
52.8	72
54.7 *	100
59.3	62
61.2	66
62.3	44
68.2	72
83.2	87
106.0	67
114.8	41
116.2	65
119.9	56
122.4	99
122.7	88
123.8	80
125.5	58
128.2 *	83
132.3	58
133.5	43
137.2	45
138.4 *	63
142.8	55
144.3	54
147.2	79
147.5	89
153.7	58
156.6 *	46
172.6	44

Example AA. CHO GLP-1R Clone H6 - Assay 1

GLP-1R-mediated agonist activity was determined with a cell-based functional assay utilizing an HTRF (Homogeneous Time-Resolved Fluorescence) cAMP detection kit (cAMP HI Range Assay Kit; CisBio cat #62AM6PEJ) that measures cAMP levels in the cell. The method is

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a competitive immunoassay between native cAMP produced by the cells and exogenous cAMP labeled with the dye d2. The tracer binding is visualized by a mAb anti-cAMP labeled with Cryptate. The specific signal (i.e. energy transfer) is inversely proportional to the concentration of cAMP in either standard or experimental sample.

The human GLP-1R coding sequence (NCBI Reference Sequence NP_002053.3, including naturally-occurring variant Gly168Ser) was subcloned into pcDNA3 (Invitrogen) and a cell line stably expressing the receptor was isolated (designated Clone H6). Saturation binding analyses (filtration assay procedure) using ^{125}I-GLP-1$_{7-36}$ (Perkin Elmer) showed that plasma membranes derived from this cell line express a high GLP-1R density (K_d: 0.4 nM, B_{max}: 1900 fmol/mg protein).

Cells were removed from cryopreservation, re-suspended in 40 mL of Dulbecco's Phosphate Buffered Saline (DPBS - Lonza Cat # 17-512Q) and centrifuged at 800 x g for 5 minutes at 22 °C. The cell pellet was then re-suspended in 10 mL of growth medium [DMEM/F12 1:1 Mixture with HEPES, L-Gln, 500 mL (DMEM/F12 Lonza Cat # 12-719F), 10% heat inactivated fetal bovine serum (Gibco Cat # 16140-071), 5 mL of 100X Pen-Strep (Gibco Cat # 15140-122), 5 mL of 100X L-Glutamine (Gibco Cat # 25030-081) and 500 µg/mL Geneticin (G418) (Invitrogen #10131035)]. A 1 mL sample of the cell suspension in growth media was counted on a Becton Dickinson ViCell to determine cell viability and cell count per mL. The remaining cell suspension was then adjusted with growth media to deliver 2000 viable cells per well using a Matrix Combi Multidrop reagent dispenser, and the cells were dispensed into a white 384 well tissue culture treated assay plate (Corning 3570). The assay plate was then incubated for 48 hours at 37 °C in a humidified environment in 5% carbon dioxide.

Varying concentrations of each compound to be tested (in DMSO) were diluted in assay buffer (HBSS with Calcium/Magnesium (Lonza/BioWhittaker cat # 10-527F) /0.1% BSA (Sigma Aldrich cat # A7409-1L)/20 mM HEPES (Lonza/BioWhittaker cat #17-737E) containing 100 µM 3-isobutyl-1-methylxanthin (IBMX; Sigma cat # I5879). The final DMSO concentration is 1%.

After 48 hours, the growth media was removed from the assay plate wells, and the cells were treated with 20 µL of the serially diluted compound in assay buffer for 30 minutes at 37 °C in a humidified environment in 5% carbon dioxide. Following the 30 minute incubation, 10 µL of labeled d2 cAMP and 10 µL of anti-cAMP antibody (both diluted 1:20 in cell lysis buffer; as described in the manufacturer's assay protocol) were added to each well of the assay plate. The plates were then incubated at room temperature and after 60 minutes, changes in the HTRF signal were read with an Envision 2104 multi-label plate reader using excitation of 330 nm and emissions of 615 and 665 nm. Raw data were converted to nM cAMP by interpolation from a cAMP standard curve (as described in the manufacturer's assay protocol) and the percent effect was determined relative to a saturating concentration of the full agonist GLP-1$_{7-36}$

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(1 μM) included on each plate. EC_{50} determinations were made from agonist dose-response curves analyzed with a curve fitting program using a 4-parameter logistic dose response equation.

Example BB. CHO GLP-1R Clone C6 - Assay 2

GLP-1R-mediated agonist activity was determined with a cell-based functional assay utilizing an HTRF (Homogeneous Time-Resolved Fluorescence) cAMP detection kit (cAMP HI Range Assay Kit; Cis Bio cat #62AM6PEJ) that measures cAMP levels in the cell. The method is a competitive immunoassay between native cAMP produced by the cells and exogenous cAMP labeled with the dye d2. The tracer binding is visualized by a mAb anti-cAMP labeled with Cryptate. The specific signal (i.e. energy transfer) is inversely proportional to the concentration of cAMP in either a standard or an experimental sample.

The human GLP-1R coding sequence (NCBI Reference Sequence NP_002053.3, including naturally-occurring variant Leu260Phe) was subcloned into pcDNA5-FRT-TO and a clonal CHO cell line stably expressing a low receptor density was isolated using the Flp-In™ T-Rex™ System, as described by the manufacturer (ThermoFisher). Saturation binding analyses (filtration assay procedure) using ^{125}I-GLP-1 (Perkin Elmer) showed that plasma membranes derived from this cell line (designated clone C6) express a low GLP-1R density (K_d: 0.3 nM, B_{max}: 240 fmol/mg protein), relative to the clone H6 cell line.

Cells were removed from cryopreservation, re-suspended in 40 mL of Dulbecco's Phosphate Buffered Saline (DPBS - Lonza Cat # 17-512Q) and centrifuged at 800 x g for 5 minutes at 22 °C. The DPBS was aspirated, and the cell pellet was re-suspended in 10 mL of complete growth medium (DMEM:F12 1:1Mixture with HEPES, L-Gln, 500 mL (DMEM/F12 Lonza Cat # 12-719F), 10% heat inactivated fetal bovine serum (Gibco Cat # 16140-071), 5 mL of 100X Pen-Strep (Gibco Cat # 15140-122), 5 mL of 100X L-Glutamine (Gibco Cat # 25030-081), 700 μg/mL Hygromycin (Invitrogen Cat # 10687010) and 15 μg/mL Blasticidin (Gibco Cat # R21001). A 1 mL sample of the cell suspension in growth media was counted on a Becton Dickinson ViCell to determine cell viability and cell count per mL. The remaining cell suspension was then adjusted with growth media to deliver 1600 viable cells per well using a Matrix Combi Multidrop reagent dispenser, and the cells were dispensed into a white 384 well tissue culture treated assay plate (Corning 3570). The assay plate was then incubated for 48 hours at 37 °C in a humidified environment (95% O_2, 5% CO_2)

Varying concentrations of each compound to be tested (in DMSO) were diluted in assay buffer [HBSS with Calcium/Magnesium (Lonza/BioWhittaker cat # 10-527F) /0.1% BSA (Sigma Aldrich cat # A7409-1L)/20 mM HEPES (Lonza/BioWhittaker cat #17-737E)] containing 100 μM

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3-isobutyl-1-methylxanthin (IBMX; Sigma cat # I5879). The final DMSO concentration in the compound/assay buffer mixture is 1%.

After 48 hours, the growth media was removed from the assay plate wells, and the cells were treated with 20 µL of the serially diluted compound in assay buffer for 30 minutes at 37 °C in a humidified environment (95% O_2, 5% CO_2). Following the 30 minute incubation, 10 µL of labeled d2 cAMP and 10 µL of anti-cAMP antibody (both diluted 1:20 in cell lysis buffer; as described in the manufacturer's assay protocol) were added to each well of the assay plate. The plates were then incubated at room temperature and after 60 minutes, changes in the HTRF signal were read with an Envision 2104 multi-label plate reader using excitation of 330 nm and emissions of 615 and 665 nm. Raw data were converted to nM cAMP by interpolation from a cAMP standard curve (as described in the manufacturer's assay protocol) and the percent effect was determined relative to a saturating concentration of the full agonist GLP-1 (1 µM) included on each plate. EC_{50} determinations were made from agonist dose response curves analyzed with a curve fitting program using a 4-parameter logistic dose response equation.

In Table X-1, assay data are presented to two (2) significant figures as the geometric mean (EC_{50}s) and arithmetic mean (Emax) based on the number of replicates listed (Number). A blank cell means there was no data for that Example or the Emax was not calculated.

Table X-1. Biological activity for Compound 1.

Compound	Assay 1 EC_{50} (nM)	Assay 1 Emax (%)	Assay 1 Number	Assay 2 EC_{50} (nM)	Assay 2 Emax (%)	Assay 2 Number
Compound 1****	0.96	99	5	17	96	8

****Tested as formate salt and free acid

All patents, patent applications and references referred to herein are hereby incorporated by reference in their entirety.

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WHAT IS CLAIMED IS:

1. A hydrate crystalline form of 2-((4-((*S*)-2-(5-chloropyridin-2-yl)-2-methylbenzo[*d*][1,3]dioxol-4-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-amine salt.

2. The hydrate crystalline form of claim 1 wherein the hydrate crystalline form is a monohydrate crystalline form.

3. The hydrate crystalline form of claim 2, wherein the crystalline form is Form 2, and wherein Form 2 has a powder X-ray diffraction pattern (PXRD) comprising at least two peaks, in terms of 2θ, at 7.1 ± 0.2°, 7.6 ± 0.2°, 10.7 ± 0.2°, and 19.4 ± 0.2°.

4. The monohydrate crystalline form of claim 3, wherein Form 2 has a powder X-ray diffraction pattern (PXRD) comprising at least three peaks, in terms of 2θ, at 7.1 ± 0.2°, 7.6 ± 0.2°, 10.7 ± 0.2°, and 19.4 ± 0.2°.

5. The monohydrate crystalline form of claim 4, wherein Form 2 has a powder X-ray diffraction pattern (PXRD) comprising peaks, in terms of 2θ, at 7.1 ± 0.2°, 7.6 ± 0.2°, 10.7 ± 0.2°, and 19.4 ± 0.2°.

6. A monohydrate crystalline form (Form 3) of 2-((4-((*S*)-2-(5-chloropyridin-2-yl)-2-methylbenzo[*d*][1,3]dioxol-4-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-amine salt, wherein Form 3 has a PXRD comprising at least two peaks, in terms of 2θ, at 3.7 ± 0.2°, 7.4 ± 0.2°, 9.9 ± 0.2°, 14.8 ± 0.2°, and 20.6 ± 0.2°.

7. The monohydrate crystalline form of claim 6, wherein the PXRD comprises peaks, in terms of 2θ, at 3.7 ± 0.2°, 7.4 ± 0.2°, and 14.8 ± 0.2°.

8. The monohydrate crystalline form of claim 6, wherein the PXRD comprises peaks, in terms of 2θ, at 3.7 ± 0.2°, 7.4 ± 0.2°, 14.8 ± 0.2°, and 20.6 ± 0.2°.

9. The monohydrate crystalline form of claim 6, wherein the PXRD comprises peaks, in terms of 2θ, at 3.7 ± 0.2°, 7.4 ± 0.2°, 9.9 ± 0.2°, 14.8 ± 0.2°, and 20.6 ± 0.2°.

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10. The monohydrate crystalline form of any one of claims 6 to 9, wherein the monohydrate crystalline form has a ^{13}C ssNMR spectrum comprising chemical shifts at 54.7 ± 0.2 ppm and 138.4 ± 0.2 ppm.

11. The monohydrate crystalline form of claim 10, wherein the ^{13}C ssNMR spectrum comprises chemical shifts at 54.7 ± 0.2 ppm, 138.4 ± 0.2 ppm, and 156.6 ppm ± 0.2 ppm.

12. The monohydrate crystalline form of claim 10, wherein the ^{13}C ssNMR spectrum comprises chemical shifts at 42.8 ± 0.2 ppm, 54.7 ± 0.2 ppm, 128.2 ± 0.2 ppm, 138.4 ± 0.2 ppm, and 156.6 ± 0.2 ppm.

13. The hydrate crystalline form of any one of claims 1-12, wherein said hydrate crystalline form is substantially pure.

14. A pharmaceutical composition comprising a therapeutically effective amount of the hydrate crystalline form of any one of claims 1-13 and a pharmaceutically acceptable carrier.

15. A pharmaceutical composition comprising a therapeutically effective amount of 2-((4-((*S*)-2-(5-chloropyridin-2-yl)-2-methylbenzo[*d*][1,3]dioxol-4-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-amine salt ("tris salt of Compound 1") and a pharmaceutically acceptable carrier, wherein at least 5% of the tris salt of Compound 1 is present as a hydrate crystalline form of any one of claims 1-13.

16. The pharmaceutical composition of claim 15, wherein at least 10% of the tris salt of Compound 1 is present as a hydrate crystalline form of any one of claims 1-13.

17. The pharmaceutical composition of claim 15, wherein at least 30% of the tris salt of Compound 1 is present as a hydrate crystalline form of any one of claims 1-13.

18. The pharmaceutical composition of claim 15, wherein at least 50% of the tris salt of Compound 1 is present as a hydrate crystalline form of any one of claims 1-13.

19. The pharmaceutical composition of claim 15, wherein at least 80% of the tris salt of Compound 1 is present as a hydrate crystalline form of any one of claims 1-13.

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20. The pharmaceutical composition of claim 15, wherein at least 90% of the tris salt of Compound 1 is present as a hydrate crystalline form of any one of claims 1-13.

21. The pharmaceutical composition of claim 15, wherein at least 95% of the tris salt of Compound 1 is present as a hydrate crystalline form of any one of claims 1-13.

22. An amorphous form of 2-((4-((*S*)-2-(5-chloropyridin-2-yl)-2-methylbenzo[*d*][1,3]dioxol-4-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-amine salt.

23. The amorphous form of claim 22, wherein said amorphous form is substantially pure.

24. A pharmaceutical composition comprising a therapeutically effective amount of an amorphous form of claim 22 or 23 and a pharmaceutically acceptable carrier.

25. A pharmaceutical composition comprising a therapeutically effective amount of 2-((4-((*S*)-2-(5-chloropyridin-2-yl)-2-methylbenzo[*d*][1,3]dioxol-4-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-amine salt ("tris salt of Compound 1") and a pharmaceutically acceptable carrier, wherein at least 5% of the tris salt of Compound 1 is present as an amorphous form of claim 22 or 23.

26. A pharmaceutical composition comprising a therapeutically effective amount of 2-((4-((*S*)-2-(5-chloropyridin-2-yl)-2-methylbenzo[*d*][1,3]dioxol-4-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-amine salt ("tris salt of Compound 1") and a pharmaceutically acceptable carrier, wherein the tris salt of Compound 1 comprises a crystalline form of tris salt of Compound 1 and an amorphous form of tris salt of Compound 1.

27. A pharmaceutical composition comprising a therapeutically effective amount of 2-((4-((*S*)-2-(5-chloropyridin-2-yl)-2-methylbenzo[*d*][1,3]dioxol-4-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid, 1,3-dihydroxy-2-(hydroxymethyl)propan-2-amine salt ("tris salt of Compound 1") and a pharmaceutically acceptable carrier, wherein the tris salt of Compound 1 comprises a hydrate crystalline form of any one of claims 1-13 and an amorphous form of claim 22 or 23.

28. A method for treating a disease or disorder comprising administering to a mammal in need of such treatment a therapeutically effective amount of a hydrate crystalline form of any one of claims 1-13, wherein the disease or disorder is selected from the group consisting of T1D, T2DM, pre-diabetes, idiopathic T1D, LADA, EOD, YOAD, MODY, malnutrition-related diabetes, gestational diabetes, hyperglycemia, insulin resistance, hepatic insulin resistance, impaired glucose tolerance, diabetic neuropathy, diabetic nephropathy, kidney disease, diabetic retinopathy, adipocyte dysfunction, visceral adipose deposition, sleep apnea, obesity, eating disorders, weight gain from use of other agents, excessive sugar craving, dyslipidemia, hyperinsulinemia, NAFLD, NASH, fibrosis, NASH with fibrosis, cirrhosis, hepatocellular carcinoma, cardiovascular disease, atherosclerosis, coronary artery disease, peripheral vascular disease, hypertension, endothelial dysfunction, impaired vascular compliance, congestive heart failure, myocardial infarction, stroke, hemorrhagic stroke, ischemic stroke, traumatic brain injury, pulmonary hypertension, restenosis after angioplasty, intermittent claudication, post-prandial lipemia, metabolic acidosis, ketosis, arthritis, osteoporosis, Parkinson's Disease, left ventricular hypertrophy, peripheral arterial disease, macular degeneration, cataract, glomerulosclerosis, chronic renal failure, metabolic syndrome, syndrome X, premenstrual syndrome, angina pectoris, thrombosis, atherosclerosis, transient ischemic attacks, vascular restenosis, impaired glucose metabolism, conditions of impaired fasting plasma glucose, hyperuricemia, gout, erectile dysfunction, skin and connective tissue disorders, psoriasis, foot ulcerations, ulcerative colitis, hyper apo B lipoproteinemia, Alzheimer's Disease, schizophrenia, impaired cognition, inflammatory bowel disease, short bowel syndrome, Crohn's disease, colitis, irritable bowel syndrome, Polycystic Ovary Syndrome, and addiction.

29. A method for treating a disease or disorder comprising administering to a mammal in need of such treatment a therapeutically effective amount of an amorphous form of claim 22 or 23, wherein the disease or disorder is selected from the group consisting of T1D, T2DM, pre-diabetes, idiopathic T1D, LADA, EOD, YOAD, MODY, malnutrition-related diabetes, gestational diabetes, hyperglycemia, insulin resistance, hepatic insulin resistance, impaired glucose tolerance, diabetic neuropathy, diabetic nephropathy, kidney disease, diabetic retinopathy, adipocyte dysfunction, visceral adipose deposition, sleep apnea, obesity, eating disorders, weight gain from use of other agents, excessive sugar craving, dyslipidemia, hyperinsulinemia, NAFLD, NASH, fibrosis, NASH with fibrosis, cirrhosis, hepatocellular carcinoma, cardiovascular disease, atherosclerosis, coronary artery disease, peripheral vascular disease, hypertension, endothelial dysfunction, impaired vascular compliance, congestive heart failure, myocardial

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infarction, stroke, hemorrhagic stroke, ischemic stroke, traumatic brain injury, pulmonary hypertension, restenosis after angioplasty, intermittent claudication, post-prandial lipemia, metabolic acidosis, ketosis, arthritis, osteoporosis, Parkinson's Disease, left ventricular hypertrophy, peripheral arterial disease, macular degeneration, cataract, glomerulosclerosis, chronic renal failure, metabolic syndrome, syndrome X, premenstrual syndrome, angina pectoris, thrombosis, atherosclerosis, transient ischemic attacks, vascular restenosis, impaired glucose metabolism, conditions of impaired fasting plasma glucose, hyperuricemia, gout, erectile dysfunction, skin and connective tissue disorders, psoriasis, foot ulcerations, ulcerative colitis, hyper apo B lipoproteinemia, Alzheimer's Disease, schizophrenia, impaired cognition, inflammatory bowel disease, short bowel syndrome, Crohn's disease, colitis, irritable bowel syndrome, Polycystic Ovary Syndrome, and addiction.

30. A method for treating a disease or disorder comprising administering to a mammal in need of such treatment a therapeutically effective amount of 1,3-dihydroxy-2-(hydroxymethyl)propan-2-amine salt of 2-((4-((*S*)-2-(5-chloropyridin-2-yl)-2-methylbenzo[*d*][1,3]dioxol-4-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid ("tris salt of Compound 1"), wherein the tris salt of Compound 1 comprises a crystalline form of tris salt of Compound 1 and an amorphous form of tris salt of Compound 1, and wherein the disease or disorder is selected from the group consisting of T1D, T2DM, pre-diabetes, idiopathic T1D, LADA, EOD, YOAD, MODY, malnutrition-related diabetes, gestational diabetes, hyperglycemia, insulin resistance, hepatic insulin resistance, impaired glucose tolerance, diabetic neuropathy, diabetic nephropathy, kidney disease, diabetic retinopathy, adipocyte dysfunction, visceral adipose deposition, sleep apnea, obesity, eating disorders, weight gain from use of other agents, excessive sugar craving, dyslipidemia, hyperinsulinemia, NAFLD, NASH, fibrosis, NASH with fibrosis, cirrhosis, hepatocellular carcinoma, cardiovascular disease, atherosclerosis, coronary artery disease, peripheral vascular disease, hypertension, endothelial dysfunction, impaired vascular compliance, congestive heart failure, myocardial infarction, stroke, hemorrhagic stroke, ischemic stroke, traumatic brain injury, pulmonary hypertension, restenosis after angioplasty, intermittent claudication, post-prandial lipemia, metabolic acidosis, ketosis, arthritis, osteoporosis, Parkinson's Disease, left ventricular hypertrophy, peripheral arterial disease, macular degeneration, cataract, glomerulosclerosis, chronic renal failure, metabolic syndrome, syndrome X, premenstrual syndrome, angina pectoris, thrombosis, atherosclerosis, transient ischemic attacks, vascular restenosis, impaired glucose metabolism, conditions of impaired fasting plasma glucose, hyperuricemia, gout, erectile dysfunction, skin and connective tissue disorders, psoriasis, foot ulcerations, ulcerative colitis, hyper apo B lipoproteinemia, Alzheimer's

Disease, schizophrenia, impaired cognition, inflammatory bowel disease, short bowel syndrome, Crohn's disease, colitis, irritable bowel syndrome, Polycystic Ovary Syndrome, and addiction.

31. A method for treating a disease or disorder comprising administering to a mammal in need of such treatment a therapeutically effective amount of 1,3-dihydroxy-2-(hydroxymethyl)propan-2-amine salt of 2-((4-((*S*)-2-(5-chloropyridin-2-yl)-2-methylbenzo[*d*][1,3]dioxol-4-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid ("tris salt of Compound 1"), wherein the tris salt of Compound 1 comprises a hydrate crystalline form of any one of claims 1-13 and an amorphous form of claim 22 or 23, and wherein the disease or disorder is selected from the group consisting of T1D, T2DM, pre-diabetes, idiopathic T1D, LADA, EOD, YOAD, MODY, malnutrition-related diabetes, gestational diabetes, hyperglycemia, insulin resistance, hepatic insulin resistance, impaired glucose tolerance, diabetic neuropathy, diabetic nephropathy, kidney disease, diabetic retinopathy, adipocyte dysfunction, visceral adipose deposition, sleep apnea, obesity, eating disorders, weight gain from use of other agents, excessive sugar craving, dyslipidemia, hyperinsulinemia, NAFLD, NASH, fibrosis, NASH with fibrosis, cirrhosis, hepatocellular carcinoma, cardiovascular disease, atherosclerosis, coronary artery disease, peripheral vascular disease, hypertension, endothelial dysfunction, impaired vascular compliance, congestive heart failure, myocardial infarction, stroke, hemorrhagic stroke, ischemic stroke, traumatic brain injury, pulmonary hypertension, restenosis after angioplasty, intermittent claudication, post-prandial lipemia, metabolic acidosis, ketosis, arthritis, osteoporosis, Parkinson's Disease, left ventricular hypertrophy, peripheral arterial disease, macular degeneration, cataract, glomerulosclerosis, chronic renal failure, metabolic syndrome, syndrome X, premenstrual syndrome, angina pectoris, thrombosis, atherosclerosis, transient ischemic attacks, vascular restenosis, impaired glucose metabolism, conditions of impaired fasting plasma glucose, hyperuricemia, gout, erectile dysfunction, skin and connective tissue disorders, psoriasis, foot ulcerations, ulcerative colitis, hyper apo B lipoproteinemia, Alzheimer's Disease, schizophrenia, impaired cognition, inflammatory bowel disease, short bowel syndrome, Crohn's disease, colitis, irritable bowel syndrome, Polycystic Ovary Syndrome, and addiction.

32. The method of any one of claims 28 to 31, wherein the disease or disorder is selected from obesity, NAFLD, NASH, NASH with fibrosis, T2D, and a cardiovascular disease.

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FIG. 1

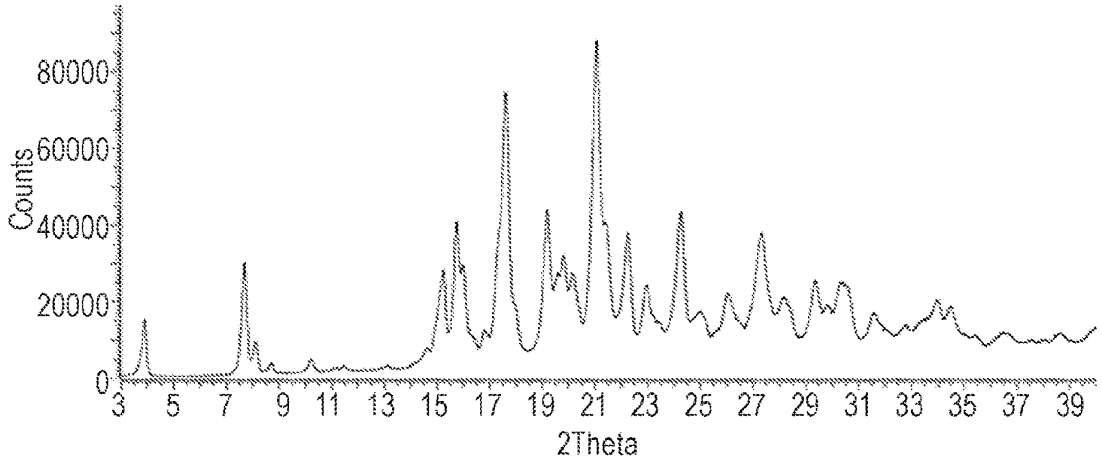
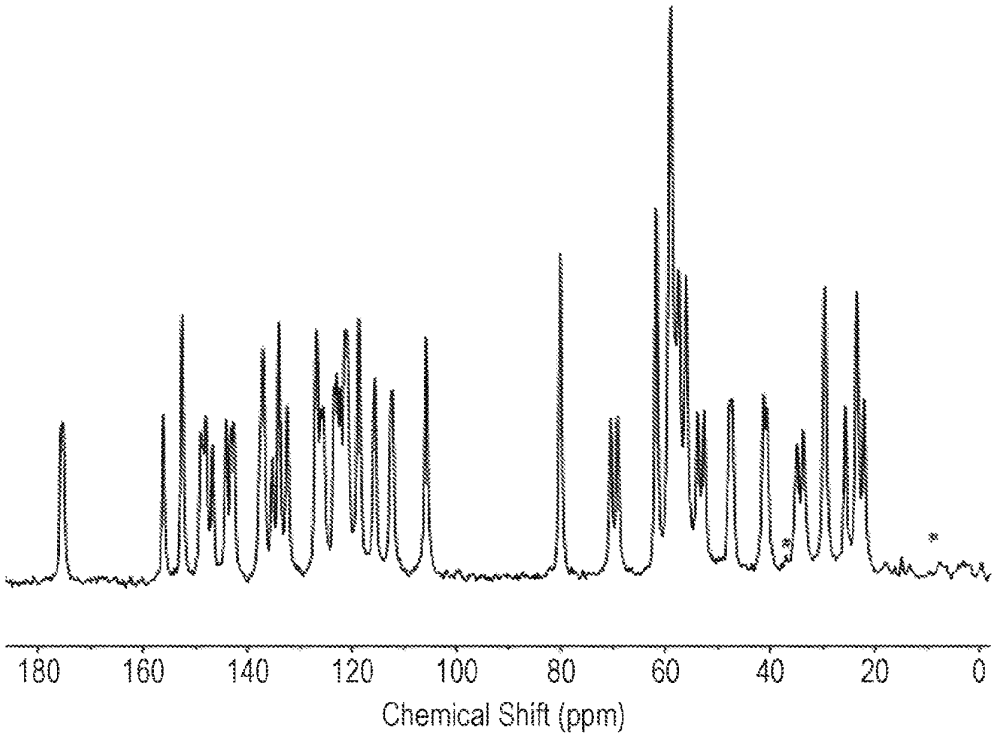
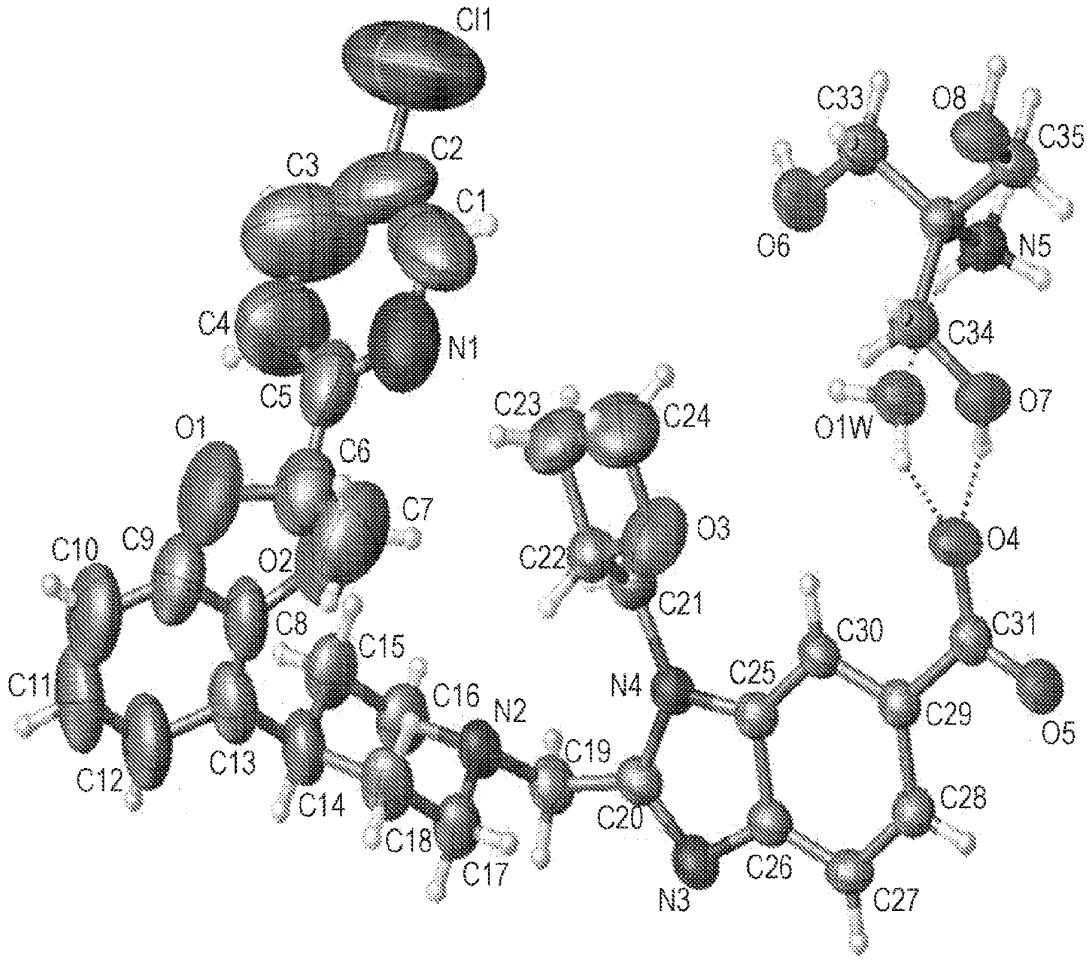

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FIG. 2



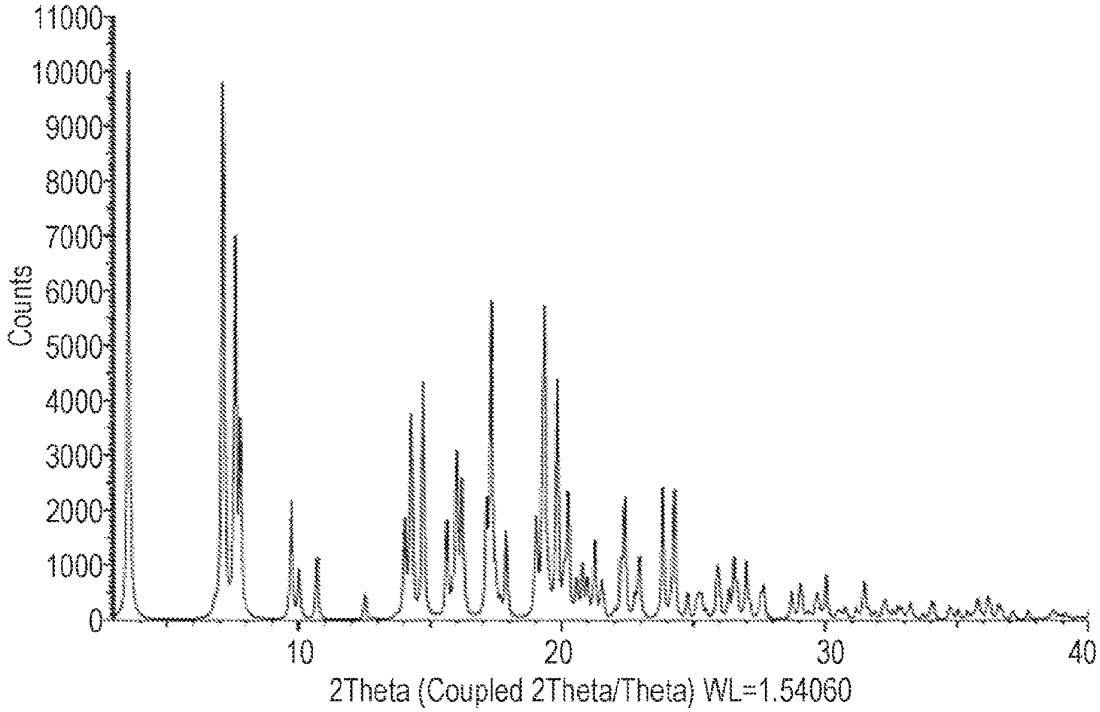
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FIG. 3



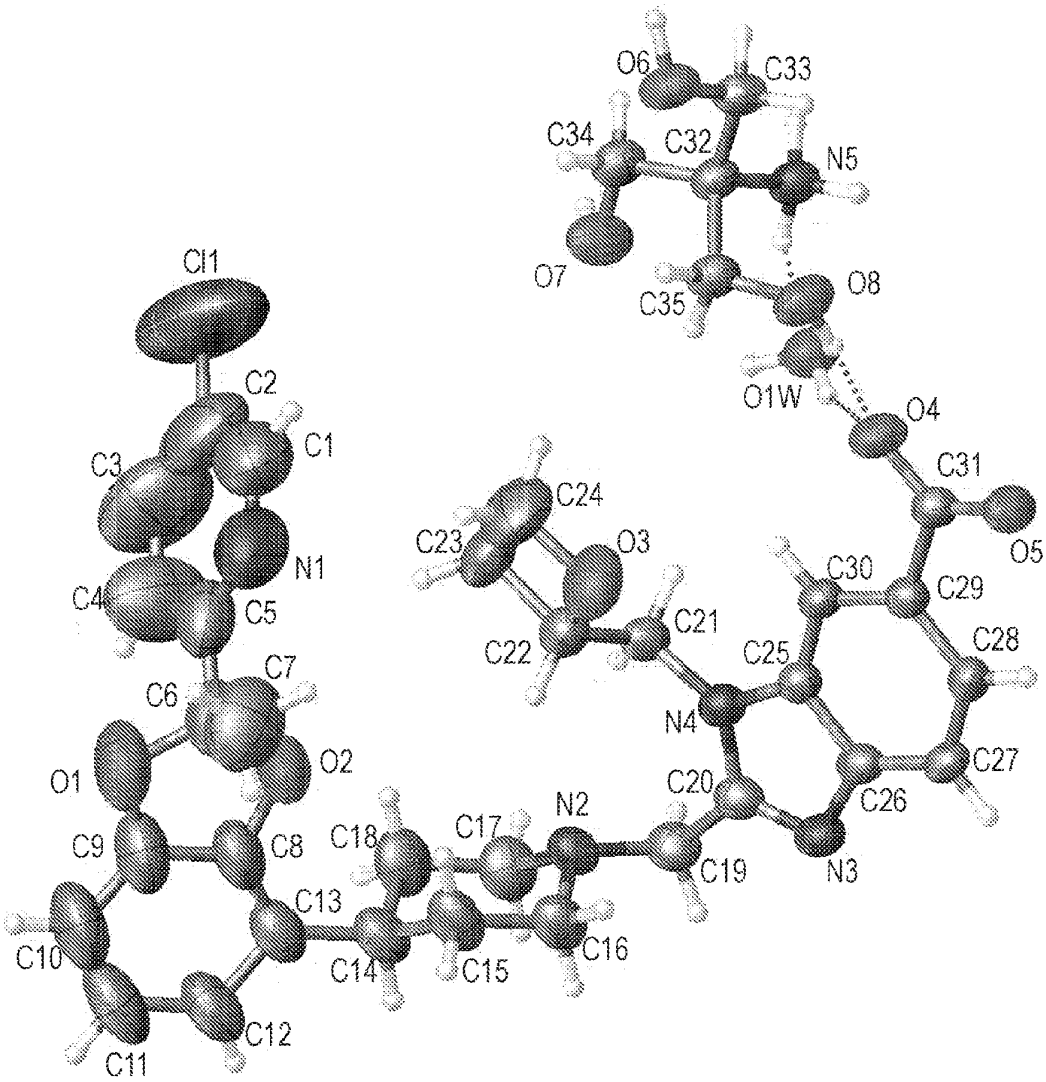
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FIG. 4



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FIG. 5



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FIG. 6

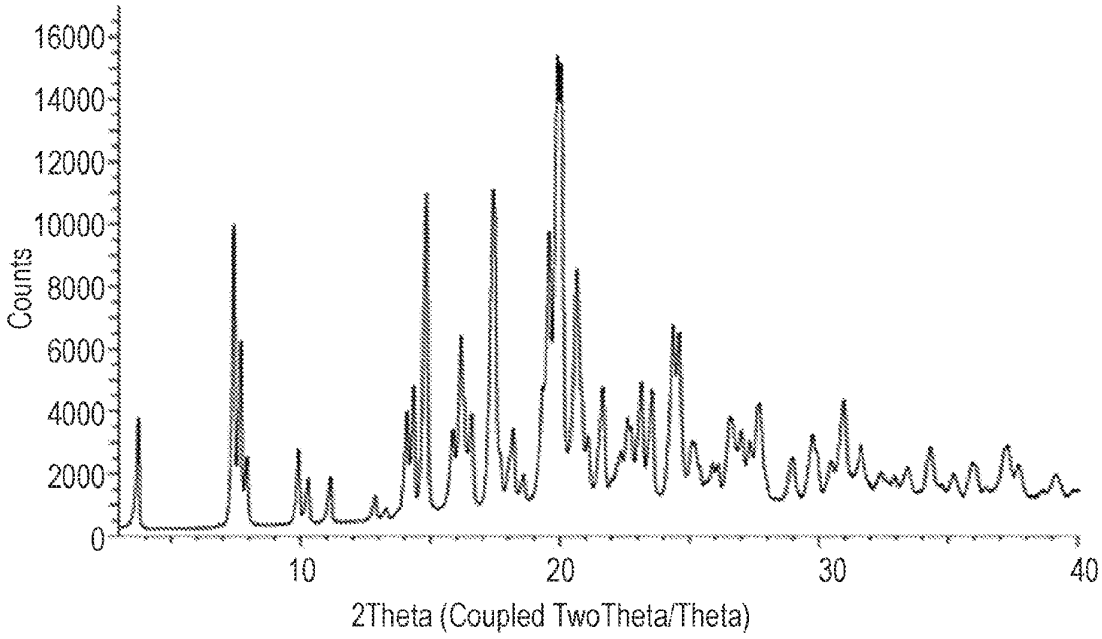
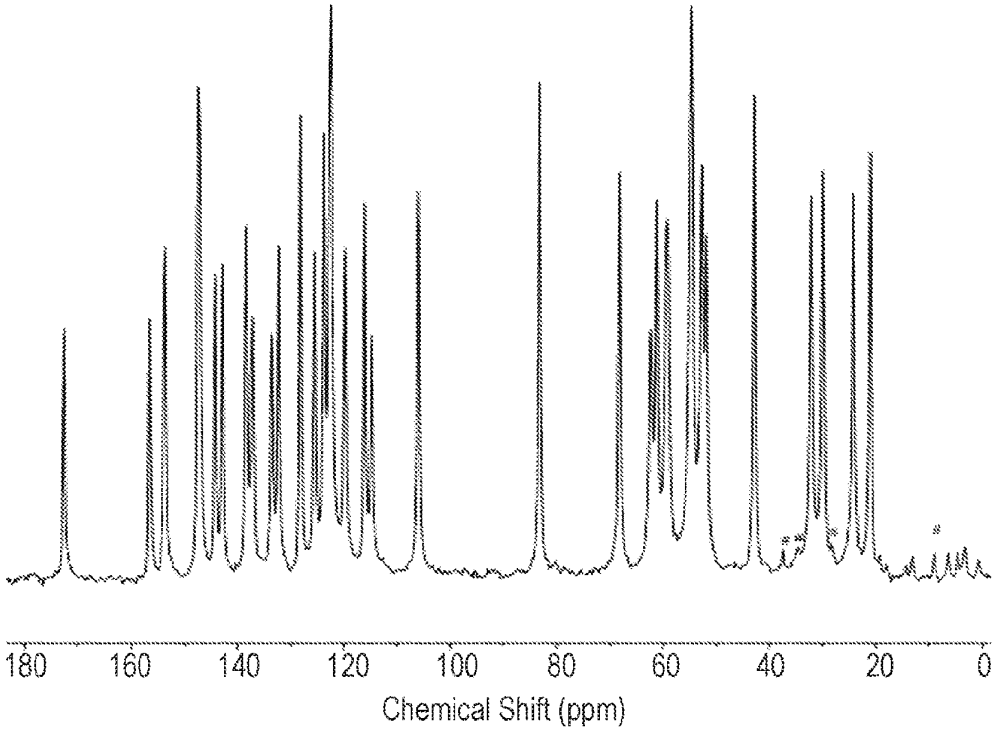

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FIG. 7



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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2020/061585

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C215/12 A61P3/00 A61P5/00 C07D405/14 A61K31/4545
A61P25/00
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According to International Patent Classification (IPC) or to both national classification and IPC

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Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2018/109607 A1 (PFIZER [US]) 21 June 2018 (2018-06-21) cited in the application page 1, paragraph 1; claims 1,9,11,13,23,24; table 9	1-32
A	WO 2008/012623 A1 (PFIZER PROD INC [US]; EFREMOV IVAN VIKTOROVICH [US] ET AL.) 31 January 2008 (2008-01-31) claims 1,34,40; table 7	1-32
X,P	WO 2019/239319 A1 (PFIZER [US]) 19 December 2019 (2019-12-19) cited in the application claims 1,33,42,43; example 10; table X2	1-32

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Information on patent family members

International application No
PCT/IB2020/061585

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	Application Number	18885065
	Filing Date	2024-09-13
	First Named Inventor	Bin Liang
	Art Unit	1693
	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

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	2	2023220109	WO	A1	2023-11-16	Eli Lilly and Company		☐
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	10	2023016546	WO	A1	2023-02-16	GASHERBRUM BIO INC		☐
	11	2023169456	WO	A1	2023-09-14	GASHERBRUM BIO INC		☐
	12	2024125602	WO	A1	2024-06-20	GASHERBRUM BIO INC		☐
	13	2024169952	WO	A1	2024-08-22	GASHERBRUM BIO INC		☐
	14	2022017338	WO	A1	2022-01-27	ECCOGENE SHANGHAI CO LTD		☐

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	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

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	37	2021018023	WO	A1	2021-02-04	THE TITAN LEADING MED TECH INC		☐
	38	2021081207	WO	A1	2021-04-29	GILEAD SCIENCES INC		☐
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	46	TWI786467	TW	B	2022-12-11	ILDONG PHARMACEUTICAL CO LTD		☐
	47	2023182869	WO	A1	2023-09-28	ILDONG PHARMACEUTICAL CO LTD		☐

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	Filing Date	2024-09-13
	First Named Inventor	Bin Liang
	Art Unit	1693
	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

	48	2021112538	WO	A1	2021-06-10	HYUNDAI PHARM CO LTD		☐
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	50	2021219019	WO	A1	2021-11-04	GASHERBRUM BIO INC		☐

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	4	2023138684	WO	A1	2023-07-27	GASHERBRUM BIO INC		☐
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	10	115279750	CN	A	2022-11-01	LG CHEMICAL LTD		☐
	11	2022216094	WO	A1	2022-10-13	LG CHEMICAL LTD		☐
	12	117279904	CN	A	2023-12-22	LG CHEMICAL LTD		☐
	13	2021197464	WO	A1	2021-10-07	JIANGSU HENGRUI MEDICINE CO		☐
	14	113801136	CN	B	2023-04-07	Jiangsu Hengrui Medicine Co., Ltd.		☐

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	15	113816948	CN	B	2023-08-11	Jiangsu Hengrui Medicine Co., Ltd.		☐
	16	2021254470	WO	A1	2021-12-23	JIANGSU HENGRUI MEDICINE CO		☐
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	18	114805336	CN	A	2022-07-29	JIANGSU HENGRUI MEDICINE CO		☐
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	23	113773310	CN	B	2023-12-22	Chongqing Kangding Pharmaceutical Technology Co.		☐
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	26	113831337	CN	B	2023-03-24	Guangzhou Hengnuokang Pharmaceutical Technology Co		☐
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	28	2022040600	WO	A1	2022-02-24	TERNS PHARMACEUTICALS INC		☐
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	32	2022068772	WO	A1	2022-04-07	SHENZHEN SALUBRIS PHARM CO LTD		☐
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	42	2022078152	WO	A1	2022-04-21	HANGZHOU ZHONGMEIHUADONG PHARMACEUTICAL CO LTD		☐
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	46	2022199458	WO	A1	2022-09-29	HANGZHOU ZHONGMEIHUADONG PHARMACEUTICAL CO LTD		☐
	47	2022268152	WO	A1	2022-12-29	HANGZHOU ZHONGMEIHUADONG PHARMACEUTICAL CO LTD		☐

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	48	114478497	CN	A	2022-05-13	HANGZHOU ZHONGMEI EAST CHINA PHARMACY LTD COMPANY		☐
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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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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/885,065	**11/04/2024 03:52:01 PM Z ET**	**HRT-030US1**

Title of Invention

GLP-1R Agonist and Therapeutic Method Thereof

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4802	FILED BY	Daniel Nevrivy
PATENT CENTER #	67828211	FILING DATE	09/13/2024
CUSTOMER #	83682	FIRST NAMED INVENTOR	Bin Liang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 53

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
FP5_compressed.pdf	212	Foreign Reference	11060 KB
FP1_compressed.pdf	286	Foreign Reference	14173 KB
FP4_compressed.pdf	281	Foreign Reference	14885 KB
FP3_compressed-2.pdf	339	Foreign Reference	16586 KB
FP2_-1-.pdf	480	Foreign Reference	18491 KB
FP2_-2-.pdf	430	Foreign Reference	22744 KB
FP7_compressed.pdf	140	Foreign Reference	18019 KB
FP8_compressed-1.pdf	142	Foreign Reference	17510 KB
FP10_compressed-2.pdf	74	Foreign Reference	14425 KB
FP6_compressed.pdf	152	Foreign Reference	20713 KB

FP9.pdf	106	Foreign Reference	23194 KB
FP16.pdf	44	Foreign Reference	10445 KB
FP11_compressed-3.pdf	305	Foreign Reference	12548 KB
FP13.pdf	59	Foreign Reference	13765 KB
FP12.pdf	39	Foreign Reference	16194 KB
FP14.pdf	34	Foreign Reference	17529 KB
FP15.pdf	40	Foreign Reference	21927 KB
FP19.pdf	54	Foreign Reference	10357 KB
FP20.pdf	41	Foreign Reference	8155 KB
FP18.pdf	40	Foreign Reference	17595 KB
FP17_compressed.pdf	149	Foreign Reference	19419 KB
FP26_compressed.pdf	115	Foreign Reference	7993 KB
FP23_compressed.pdf	58	Foreign Reference	8898 KB
FP24.pdf	59	Foreign Reference	15210 KB
FP22.pdf	95	Foreign Reference	16423 KB
FP25.pdf	78	Foreign Reference	16824 KB
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FP30.pdf	132	Foreign Reference	24104 KB
FP36.pdf	49	Foreign Reference	3025 KB
FP35.pdf	25	Foreign Reference	5575 KB
FP38.pdf	17	Foreign Reference	821 KB
FP33.pdf	144	Foreign Reference	7422 KB
FP39.pdf	13	Foreign Reference	714 KB
FP40.pdf	37	Foreign Reference	1741 KB
FP34.pdf	174	Foreign Reference	10864 KB
FP37_compressed.pdf	56	Foreign Reference	10168 KB

FP32_compressed.pdf	219	Foreign Reference	14449 KB
FP31_compressed.pdf	167	Foreign Reference	21224 KB
FP41.pdf	16	Foreign Reference	1030 KB
FP44.pdf	19	Foreign Reference	1092 KB
FP43.pdf	38	Foreign Reference	2154 KB
FP48.pdf	38	Foreign Reference	2154 KB
FP46.pdf	75	Foreign Reference	3497 KB
FP47.pdf	81	Foreign Reference	3838 KB
FP49.pdf	28	Foreign Reference	1592 KB
PleadingIDS2.pdf	12	Transmittal Letter	60 KB
FP45.pdf	90	Foreign Reference	4783 KB
IDS2.pdf	8	Information Disclosure Statement (IDS) Form (SB08)	1317 KB
FP42.pdf	172	Foreign Reference	7593 KB
FP50.pdf	90	Foreign Reference	16831 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Liang *et al.*	Confirmation No.: 4802
Appl. No.: 18/885,065	Art Unit: 1693
Filed: September 13, 2024	Examiner: HOI YAN NMN LEE
For: **GLP-1R Agonist and Therapeutic Method Thereof**	Atty. Docket: HRT-030US1

Information Disclosure Statement Under 37 C.F.R. § 1.97(b)

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

Madam:

Listed on accompanying IDS Form PTO/SB/08a are document(s) that may be considered material to the patentability of this application as defined in 37 C.F.R. § 1.56, and in compliance with the duty of disclosure requirements of 37 C.F.R. § 1.97 and 1.98.

Where the date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicant has listed dates on the attached IDS Forms based on information presently available to the undersigned. However, the listed dates should not be construed as an admission that the information was actually published on the date indicated.

Documents FP9-FP21, FP23-FP27 and FP32-FP50 are in a foreign language.

Below are the translated English language Abstracts of FP9-FP21, FP23-FP27 and FP32-FP50 that are provided to provide a concise statement of the relevance thereof.

Document FP9 Abstract: The present invention relates to a novel compound useful as an agent for treatment or prophylaxis of various metabolic diseases such as obesity or diabetes and hyperlipidemia, by means of excellent GLP-1 agonist activity and an excellent DMPK profile, an isomer thereof or a pharmaceutically acceptable salt thereof, a pharmaceutical composition comprising the compound, and a method for preparing the compound.

Document FP10 Abstract: The present invention relates to a novel compound, an isomer thereof or a pharmaceutically acceptable salt thereof, a pharmaceutical composition comprising the compound, and a method for preparing the compound, the compound is useful as a drug for the treatment or prevention of various metabolic diseases such as obesity or diabetes and hyperlipidemia through excellent GLP-1 agonist activity and excellent DMPK properties.

Document FP11 Abstract: The present invention relates to: a novel compound having excellent GLP-1 agonist activity and an excellent DMPK profile, and thus useful as an agent for treating or preventing obesity or various metabolic diseases such as diabetes and hyperlipidemia; an isomer thereof or a pharmaceutically acceptable salt thereof; a pharmaceutical composition comprising the compound; and a method for preparing the compound.

Document FP12 Abstract: The present invention relates to: a novel compound which has excellent GLP-1 agonist activity and excellent DMPK properties and thus can be used as an agent for treating or preventing obesity or various metabolic diseases such as diabetes and hyperlipidemia; an isomer thereof or a pharmaceutically acceptable salt

thereof; pharmaceutical compositions comprising such compounds; and methods of making the compounds.

Document FP13 Abstract: The present disclosure relates to fused imidazole derivatives, preparation methods and medical use thereof. Specifically, the present disclosure relates to a fused imidazole derivative represented by the general formula (I), the preparation method thereof, and the pharmaceutical composition containing the same, as well as the use as a therapeutic agent, especially as GLP-1 receptor agonists, and the use thereof in the preparation of medicaments for the treatment and/or prevention of diabetes. The substituents of general formula (I) are the same as defined in the specification.

Document FP14 Abstract: The invention relates to an imidazo heteroaryl derivative as well as a preparation method and medical application thereof. Specifically, the invention relates to an imidazo heteroaryl derivative as shown in a general formula (I) defined in the description, a preparation method thereof, a pharmaceutical composition containing the derivative, and application of the derivative as a therapeutic agent, especially an application of the derivative as a GLP-1 receptor agonist and an application of the derivative in preparation of drugs for treating and/or preventing diabetes.

Document FP15 Abstract: The invention relates to a condensed imidazole derivative, a preparation method thereof and application of the condensed imidazole derivative in medicine. Specifically, the invention relates to a condensed imidazole derivative as shown in a general formula (I), a preparation method thereof, a pharmaceutical composition containing the derivative and application of the derivative as

a therapeutic agent, especially application of the derivative as a GLP-1 receptor agonist and application of the derivative in preparation of drugs for treating and/or preventing diabetes.

Document FP16 Abstract: Disclosed are a 6-oxo-3,6-dihydropyridine derivative, and a preparation method therefor and the use thereof in medicine. In particular, the present invention relates to a 6-oxo-3,6-dihydropyridine derivative as shown in general formula (I), and a preparation method therefor, and a pharmaceutical composition containing the derivative, and the use thereof as a therapeutic agent, in particular as a GLP-1 receptor agonist and in the preparation of drugs for the treatment and/or prevention of diabetes.

Document FP17 Abstract: Disclosed are fused imidazole derivatives, preparation methods therefor and medical uses thereof. Specifically, the present disclosure relates to a fused imidazole derivative as shown in general formula (IM), a preparation method therefor, a pharmaceutical composition containing the derivative, and the use of same as a therapeutic agent, in particular the use thereof as a GLP-1 receptor agonist, and the use thereof in the preparation of drugs for the treatment and/or prevention of diabetes.

Document FP18 Abstract: The invention relates to a fused imidazole compound, a preparation method thereof and application of the fused imidazole compound in medicine. Specifically, the invention relates to a condensed imidazole compound as shown in a general formula (I), a preparation method thereof, a pharmaceutical composition containing the compound and application of the compound as a therapeutic agent, especially application of the compound as a GLP-1 receptor agonist and application of the compound in preparation of drugs for treating and/or preventing diabetes.

Document FP19 Abstract: Provided are a pharmaceutically acceptable salt and a crystalline form of a GLP-1 receptor agonist and a preparation method therefor. Specifically, provided are a pharmaceutically acceptable salt and a crystalline form of a compound 2-((4-((S)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4] dioxane-5-yl)piperidin-1-yl)methyl)-1-(((S)-oxetane-2-yl)methyl)-1H-benzo[d]imidazole-6-formic acid.

Document FP20 Abstract: A crystalline form of a GLP-1 receptor agonist and a preparation method therefor. The agonist is a compound 2-((4-((S)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxane-5-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid.

Document FP21 Abstract: A novel five-membered heteroaromatic imidazole compound and use thereof in preparing a medicament for treating related diseases. Specifically, disclosed are a compound as shown in formula (III) and a pharmaceutically acceptable salt thereof.

Document FP23 Abstract: The invention provides a GLP-1 small molecule compound with cardiovascular benefits, which not only can be used for treatment of diabetes mellitus, but also can be independently or jointly applied as a cardiovascular protective agent and has the pharmaceutical application of reducing cardiovascular adverse events or reducing cardiovascular adverse events in type 2 diabetes mellitus. The reduction of cardiovascular adverse events comprises reduction of the incidence rate of myocardial infarction of patients, reduction of the hospitalization frequency caused by heart failure, reduction of the risk of myocardial infarction and stroke of patients, and reduction of the

cardiovascular death risk of heart failure of adults with reduced ejection fraction and the hospitalization risk caused by heart failure (NYHA II-IV level).

Document FP24 Abstract: Provided are a new methyl-substituted benzobisoxazole compound and the use thereof in the preparation of drugs for treating related diseases. Specifically disclosed is a compound represented by formula (P) or a pharmaceutically acceptable salt thereof.

Document FP25 Abstract: series of imidazocyclic compounds and an application thereof, which specifically relate to a compound represented by formula (P) and a pharmaceutically acceptable salt thereof. series of imidazocyclic compounds and an application thereof, which specifically relate to a compound represented by formula (P) and a pharmaceutically acceptable salt thereof.

Document FP26 Abstract: The invention provides a heteroaryl compound as shown in a formula (I) as a GLP-1 receptor agonist, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, tautomer, regioisomer, nitrogen oxide or a mixture thereof, a pharmaceutical composition containing the compound, and application of the compound or the pharmaceutical composition thereof in preparation of medicines for treating cardiovascular metabolic diseases and related diseases of mammals. The compound provided by the invention shows an excellent agonistic effect on a GLP-1 receptor, and has a very good development prospect.

Document FP27 Abstract: The invention belongs to the technical field of medicine. In particular, the invention relates to a compound capable of being used as a GLP-1 receptor agonist, a pharmaceutically acceptable salt or a stereoisomer of the compound, a

pharmaceutical composition and a preparation containing the compound, the pharmaceutically acceptable salt or the stereoisomer of the compound, and application of the compound, the pharmaceutically acceptable salt or the stereoisomer of the compound.

Document FP32 Abstract: A compound related to formula (I), a preparation method therefor, and the use thereof in medicine. Specifically, provided are a compound related to formula (I) or a stereoisomer, a tautomer and a pharmaceutically acceptable salt thereof. The compounds are agonists of glucagon-like peptide-1 receptors (GLP-1R). The present invention also relates to a pharmaceutical composition comprising the compounds and the use of the compounds in drugs for treating diseases such as diabetes.

Document FP33 Abstract: Disclosed are a compound of formula (I), a preparation method therefor, and a medical application thereof. In particular, provided are the compound of formula (I) or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof. These compounds are agonists of a glucagon-like peptide-1 receptor (GLP-1R). The present invention also relates to a pharmaceutical composition containing these compounds and use of the compound in a drug for treating diseases such as diabetes.

Document FP34 Abstract: The invention belongs to the technical field of chemical drugs, and relates to a compound shown in a formula (I), a preparation method thereof and application of the compound in medicine. Specifically, the present invention provides a compound of formula (I) or a stereoisomer, a tautomer, and a pharmaceutically acceptable salt thereof. These compounds are agonists of the glucagon-like peptide-1 receptor (GLP-1R). The invention also relates to a pharmaceutical composition containing the compounds

and application of the compounds in medicines for treating diseases such as diabetes mellitus.

Document FP35 Abstract: Disclosed are salts of a series of GLP-1R agonist compounds, a pharmaceutical composition containing same, and the use of the compounds in drugs for treating diseases such as diabetes.

Document FP36 Abstract: The invention belongs to the technical field of chemical medicines, and relates to a compound as shown in a general formula (I), or a tautomer, a meso-mer, a raceme, an enantiomer, a diastereoisomer, or a mixture form or a medicinal salt thereof, a preparation method and an application of the compound in medicines. These compounds are agonists of the glucagon-like peptide-1 receptor (GLP-1R). The invention also relates to a pharmaceutical composition containing the compounds and application of the compounds in medicines for treating diseases such as diabetes mellitus.

Document FP37 Abstract: The invention belongs to the technical field of chemical drugs, and relates to a compound shown in a formula (I), a preparation method thereof and application of the compound in medicine. Specifically, the present invention provides a compound of formula (I) or a stereoisomer, a tautomer, and a pharmaceutically acceptable salt thereof. These compounds are agonists of the glucagon-like peptide-1 receptor (GLP-1R). The invention also relates to a pharmaceutical composition containing the compounds and application of the compounds in medicines for treating diseases such as diabetes mellitus.

Document FP38 Abstract: The invention belongs to the field of chemical drug preparation, and particularly relates to a polymorphic substance of a GLP-1R agonist compound A-a and a pharmaceutical composition containing the polymorphic substance.

Document FP39 Abstract: The invention belongs to the field of chemical medicine preparation, and particularly relates to an amorphous form of a GLP-1R agonist compound A-a tromethamine salt, a preparation method of the amorphous form and a medicine composition containing the amorphous form.

Document FP40 Abstract: The invention belongs to the field of chemical drug preparation, and particularly relates to a polymorphic substance of a GLP-1R agonist compound A-a tromethamine salt and a pharmaceutical composition containing the polymorphic substance.

Document FP41 Abstract: The invention belongs to the technical field of chemical drugs, and particularly relates to medical application of a glucagon-like peptide-1 (GLP-1) receptor agonist in the aspect of drugs for preventing and/or treating non-alcoholic fatty liver diseases.

Document FP42 Abstract: benzimidazolone GLP-1 receptor agonist and the use thereof.

Document FP43 Abstract: The invention provides a series of aryl alkyl acid GLP-1 receptor agonist compounds as well as a preparation method and pharmaceutical application thereof. The compounds can be used for treating or preventing GLP-1 mediated diseases and related diseases.

Document FP44 Abstract: The invention relates to an imidazopyridine derivative and application thereof, and provides an imidazopyridine-derived GLP-1 receptor agonist compound, namely 2-((4-(6-((4-cyano-2-fluorobenzyl) oxy) pyridine-2-yl) piperidine-1-yl) methyl)-3-(oxetan-2-yl methyl) imidazo [1, 2-a] pyridine-6-formic acid as well as a preparation method and pharmaceutical application of the imidazopyridine-derived GLP-1 receptor agonist compound. The compound can be used for preparing medicines for treating or preventing GLP-1 mediated diseases and related diseases. The invention further provides 2-(hydroxymethyl)-3-(oxetan-2-ylmethyl) imidazo [1, 2-a] pyridine-6-carboxylic acid methyl ester and a preparation method thereof, and the imidazo [1, 2-a] pyridine-6-carboxylic acid methyl ester can also be used as a synthesis intermediate of a medicine

Document FP45 Abstract: The invention provides a series of tricyclic GLP-1 receptor agonist compounds as well as a preparation method and pharmaceutical application thereof. The compounds can be used for preparing medicines for treating or preventing GLP-1 mediated diseases and related diseases.

Document FP46 Abstract: Provided are a series of thiophene GLP-1 receptor agonist compounds, a preparation method therefor and the pharmaceutical use thereof. The compounds can be used for preparing drugs for treating or preventing GLP-1-mediated diseases and related diseases.

Document FP47 Abstract: Provided are a GLP-1 receptor agonist compound and a composition and use thereof. The compound can be used for treating or preventing GLP-1 receptor-mediated diseases or disorders and related diseases or disorders.

Document FP48 Abstract: The invention provides a series of aryl alkyl acid GLP-1 receptor agonist compounds as well as a preparation method and pharmaceutical application thereof. The compounds can be used for treating or preventing GLP-1 mediated diseases and related diseases.

Document FP49 Abstract: The invention provides a GLP-1 receptor agonist and application thereof, and particularly relates to a series of ketal GLP-1 receptor agonist compounds as shown in a formula (I), a preparation method and pharmaceutical application thereof, and the compounds can be used for preparing medicines for treating or preventing GLP-1 mediated diseases and related diseases.

Document FP50 Abstract: Disclosed are a salt-type GLP-1 receptor agonist, a crystal form thereof, a preparation method therefor, a pharmaceutical composition thereof, and the use thereof. Specifically, the GLP-1 receptor agonist is (S)-2-((4-(6-((2-fluoro-4-(oxetane-3-yl)benzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-1-(oxetane-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid.

Applicant reserves the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith.

Respectfully submitted,

NEVRIVY PATENT LAW GROUP P.L.L.C.

/Daniel J. Nevrivy/

Daniel J. Nevrivy
Registration No. 59,118

Date: November 2, 2024

1101 30th St., NW
Suite 500
Washington, D.C. 20007
(202) 713-0843

PTO/SB/08a (01-22)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	18885065
	Filing Date	2024-09-13
	First Named Inventor	Bin Liang
	Art Unit	1693
	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

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	Attorney Docket Number	HRT-030US1

	1	Pending claims in co-pending U.S. Appl. No.: 18/884,965, entitled "GLP-1R Agonist and Therapeutic Method Thereof," filed September 13, 2024.	☐

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	Art Unit	1693
	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

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☒ 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	/Daniel J. Nevrivy/	Date (YYYY-MM-DD)	2024-11-04
Name/Print	Daniel J. Nevrivy	Registration Number	59,118

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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/885,065	**11/04/2024 03:53:36 PM Z ET**	**HRT-030US1**

Title of Invention

GLP-1R Agonist and Therapeutic Method Thereof

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4802	FILED BY	Daniel Nevrivy
PATENT CENTER #	67832763	FILING DATE	09/13/2024
CUSTOMER #	83682	FIRST NAMED INVENTOR	Bin Liang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
NPL1.pdf	14	Non Patent Literature	117 KB
IDS6.pdf	4	Information Disclosure Statement (IDS) Form (SB08)	1316 KB

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	Application Number	18885065
	Filing Date	2024-09-13
	First Named Inventor	Bin Liang
	Art Unit	1693
	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

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	1	118184638	CN	A	2024-06-14	HANGZHOU ZHONGMEI HUADONG PHARMACEUTICAL CO LTD		☐
	2	118184637	CN	A	2024-06-14	HANGZHOU ZHONGMEI HUADONG PHARMACEUTICAL CO LTD		☐
	3	2022116693	WO	A1	2022-06-09	SUZHOU VINCENTAGE PHARMA CO LTD		☐

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	Attorney Docket Number	HRT-030US1

	4	114591296	CN	A	2022-06-07	HEIXIDAE MEDICINE GROUP STOCK LTD COMPANY		☐
	5	114763352	CN	A	2022-07-19	HAISCO PHARMACEUTICAL GROUP INC		☐
	6	2023124824	WO	A1	2023-07-06	HAISCO PHARMACEUTICAL GROUP CO LTD		☐
	7	2023125896	WO	A1	2023-07-06	HAISCO PHARMACEUTICAL GROUP CO LTD		☐
	8	2023130878	WO	A1	2023-07-13	HAISCO PHARMACEUTICAL GROUP CO LTD		☐
	9	2022135572	WO	A1	2022-06-30	SICHUAN HAISCO PHARMACEUTICAL CO LTD		☐
	10	2022165076	WO	A1	2022-08-04	CARMOT THERAPEUTICS INC		☐
	11	2022235717	WO	A1	2022-11-10	CARMOT THERAPEUTICS INC		☐
	12	2024026338	WO	A1	2024-02-01	CARMOT THERAPEUTICS INC		☐
	13	2022184849	WO	A1	2022-09-09	SERVIER LAB		☐
	14	2022202864	WO	A1	2022-09-29	SHIONOGI & CO		☐

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	Attorney Docket Number	HRT-030US1

	15	117377666	CN	A	2024-01-09	SHIONOGI & CO		☐
	16	2024063140	WO	A1	2024-03-28	SHIONOGI & CO		☐
	17	2024063143	WO	A1	2024-03-28	SHIONOGI & CO		☐
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	22	2023011539	WO	A1	2023-02-09	SHANGHAI HANSOH BIOMEDICAL CO LTD		☐
	23	117986264	CN	A	2024-05-07	JIANGSU HANSOH PHARMACEUTICAL GROUP CO LTD		☐
	24	2023001237	WO	A1	2023-01-26	HEPAGENE THERAPEUTICS HK LTD		☐
	25	113480534	CN	B	2022-05-13	Guangzhou Bibet Pharmaceutical Co., Ltd.		☐

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	Attorney Docket Number	HRT-030US1

	26	115703766	CN	A	2023-02-17	TIANDI HENGYI PHARMACEUTICAL CO LTD		☐
	27	2023029380	WO	A1	2023-03-09	MINDRANK AI LTD		☐
	28	117362282	CN	A	2024-01-09	HANGZHOU DERUI PHARMACEUTICAL TECH CO LTD		☐
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	33	2024153041	WO	A1	2024-07-25	MINDRANK AI LTD		☐
	34	115872982	CN	A	2023-03-31	SICHUAN KELUN BOTAI BIOMEDICAL CO LTD		☐
	35	116120296	CN	A	2023-05-16	SICHUAN KELUN BIOTECH BIOPHARMACEUTICAL CO LTD		☐
	36	2023057414	WO	A1	2023-04-13	ASTRAZENECA AB		☐

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	Attorney Docket Number	HRT-030US1

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	40	2023111145	WO	A1	2023-06-22	ASTRAZENECA AB		☐
	41	116003393	CN	A	2023-04-25	CGENE TECH SUZHOU CHINA CO LTD		☐
	42	116354945	CN	A	2023-06-30	CHANGCHUN GENESCIENCE PHARMACEUTICALS CO LTD		☐
	43	2023164358	WO	A1	2023-08-31	ASCLETIS BIOSCIENCE CO LTD		☐
	44	2023169436	WO	A1	2023-09-14	GUANGZHOU UNIRISE PHARMACEUTICAL CO LTD		☐
	45	2024046342	WO	A1	2024-03-07	GUANGZHOU UNIRISE PHARMACEUTICAL CO LTD		☐
	46	2024041609	WO	A1	2024-02-29	GUANGZHOU UNIRISE PHARMACEUTICAL CO LTD		☐
	47	118271299	CN	A	2024-07-02	GUANGZHOU LIANRUI PHARMACEUTICAL CO LTD		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	18885065
	Filing Date	2024-09-13
	First Named Inventor	Bin Liang
	Art Unit	1693
	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

	48	118271300	CN	A	2024-07-02	GUANGZHOU LIANRUI PHARMACEUTICAL CO LTD		☐
	49	114716423	CN	A	2022-07-08	SHANGHAI INST MATERIA MEDICA CAS		☐
	50	116574092	CN	A	2023-08-11	CHENGDU DI AO JIUHONG PHARMACEUTICAL FACTORY		☐

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[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	18885065
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	First Named Inventor	Bin Liang
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	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

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).

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☐ 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	/Daniel J. Nevrivy/	Date (YYYY-MM-DD)	2024-11-02
Name/Print	Daniel J. Nevrivy	Registration Number	59,118

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.**

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Liang *et al.*	Confirmation No.: 4802
Appl. No.: 18/885,065	Art Unit: 1693
Filed: September 13, 2024	Examiner: HOI YAN NMN LEE
For: **GLP-1R Agonist and Therapeutic Method Thereof**	Atty. Docket: HRT-030US1

Information Disclosure Statement Under 37 C.F.R. § 1.97(b)

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

Madam:

Listed on accompanying IDS Form PTO/SB/08a are document(s) that may be considered material to the patentability of this application as defined in 37 C.F.R. § 1.56, and in compliance with the duty of disclosure requirements of 37 C.F.R. § 1.97 and 1.98.

Where the date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicant has listed dates on the attached IDS Forms based on information presently available to the undersigned. However, the listed dates should not be construed as an admission that the information was actually published on the date indicated.

Documents FP1-FP9, FP14-FP17, FP21-FP23, FP25-FP28, FP30-FP35, FP41, FP42, and FP44-FP50 are in a foreign language.

Below are the translated English language abstracts of FP1-FP9, FP14-FP17, FP21-FP23, FP25-FP28, FP30-FP35, FP41, FP42, and FP44-FP50 that are provided to provide a concise statement of the relevance thereof.

Document FP1 Abstract: The invention provides a salt type GLP-1 receptor agonist, a crystal form and a preparation method thereof, and a pharmaceutical composition and application thereof. In particular, the GLP-1 receptor agonist is (S)-2-((4-(6-((2-fluoro-4-(oxetan-3-yl) benzyl) oxy) pyridine-2-yl) piperidine-1-yl) methyl)-1-(oxetan-2-yl methyl)-1H-benzo [d] imidazole-6-formic acid. The invention also relates to a preparation method of the GLP-1 receptor agonist.

Document FP2 Abstract: The invention provides a novel crystal form of a GLP-1 receptor agonist, a preparation method, a pharmaceutical composition and application thereof. Specifically, the GLP-1 receptor agonist is a compound I, namely (S)-2-((4-(6-((2-fluoro-4-(oxetan-3-yl) benzyl) oxy) pyridine-2-yl) piperidin-1-yl) methyl)-1-(oxetan-2-yl methyl)-1H-benzo [d] imidazole-6-formic acid.

Document FP3 Abstract: The present invention relates to a GLP-1R receptor agonist compound and a use thereof. Specifically, the present invention discloses a compound represented by formula (I) or a pharmaceutically acceptable salt thereof. The compound can be used for treating a metabolism-related disease, such as diabetes or nonalcoholic fatty liver disease, by means of activating GLP-1R receptors.

Document FP4 Abstract: The invention relates to a compound with GLP-1R receptor agonistic activity shown in a general formula (I) or (II), or a stereoisomer, a tautomer, a deuterated compound, a solvate, a prodrug, a metabolite, a pharmaceutically acceptable salt or eutectic of the compound, an intermediate and a preparation method of

the compound, and an application of the compound in preparation of related drugs for treating diabetes mellitus.

Document FP5 Abstract: The invention relates to a compound shown in a general formula (I) or a stereoisomer, a tautomer, a deuterated compound, a solvate, a prodrug, a metabolite, pharmaceutically acceptable salt or eutectic of the compound, an intermediate and a preparation method of the compound, and application of the compound in preparation of related drugs for treating diabetes mellitus.

Document FP6 Abstract: The present invention relates to a trihydroxymethyl aminomethane salt of a compound (S)-2-((6-((4-cyano-2-fluorobenzyl)oxy)-3',6'-dihydro-[2,4'-bipyridine]-1'(2'H)-yl)methyl)-1-(oxetane-2-ylmethyl)-1H thieno[2,3-d]imidazole-5-carboxylic acid, amorphous and crystal forms of the salt, a preparation method therefor, and a use thereof in pharmaceutical compositions and medicines.

Document FP7 Abstract: A preparation method for a compound represented by formula (I) and an intermediate thereof. The method has the advantages of mild reaction conditions, simple operation, high reaction yield, high product purity, convenience in post-treatment and suitability for industrial production.

Document FP8 Abstract: Provided are an (S)-2-((6-((4-cyano-2-fluorobenzyl)oxy)-3',6'-dihydro-[2,4'-bipyridyl-1'(2'H)-yl)methyl)-1(oxetan-2-ylmethyl)-1H-thieno[2,3-d]imidazole-5-carboxylic acid compound, a salt or a salt crystal of the compound, a preparation method therefor, the use thereof in a pharmaceutical composition, and the medical use thereof.

Document FP9 Abstract: A compound represented by general formula (I) or a stereoisomer, tautomer, deuterated substance, solvate, prodrug, metabolite,

pharmaceutically acceptable salt or co-crystal thereof, an intermediate thereof, and a preparation method therefor, as well as an application in preparation of a drug for treating diabetes.

Document FP14 Abstract: The present invention relates to: a compound, or a pharmacologically acceptable salt thereof, that has GLP-1 receptor agonist activity and that is useful as an agent for treating or preventing diseases involving the GLP-1 receptors; and a pharmaceutical composition containing the compound or the pharmacologically acceptable salt. Provided is a compound represented by formula (I): (in the formula, A1 is C(R5), etc.; A2 is C(R6), etc.; A3 is C(R7), etc.; R5, R6, and R7 each independently are a hydrogen atom, etc.; R1 is a carboxy, etc.; R2 is a substituted or unsubstituted alkyl, etc.; -X- is -O-, etc.; the ring represented by (AAA) is a ring represented by (BBB) (in the formula, R10 each independently are a halogen, etc.; and s is 0, etc.); R13 each independently are a hydrogen atom, etc.; and R3 is a substituted or unsubstituted aromatic carbocyclic group, etc.), or a pharmacologically acceptable salt thereof.

Document FP15 Abstract: The present invention relates to a compound having GLP-1 receptor agonist activity and useful as a therapeutic or prophylactic agent for diseases in which GLP-1 receptors are involved, or a pharmaceutically acceptable salt thereof, and a pharmaceutical composition containing the same. A compound represented by formula (I) or a pharmaceutically acceptable salt thereof (in the formula, A1 is C (R5) or the like, A2 is C (R6) or the like, A3 is C (R7) or the like, R5, R6 and R7 are each independently a hydrogen atom or the like, R1 is a carboxyl group or the like, R2 is a substituted or unsubstituted alkyl group or the like,-X-is-O-or the like, the ring represented by (AAA) is a ring represented by (BBB) (in the formula, R10 is each independently a

halogen or the like, and s is 0 or the like), R13 is each independently a hydrogen atom or the like, and R7 is each independently a hydrogen atom or the like. And R3 represents a substituted or unsubstituted aromatic carbocyclic group or the like).

Document FP16 Abstract: The present invention relates to a compound represented by formula (I) or a pharmaceutically acceptable salt thereof. (In formula (I), A1 is C(R5) or N, A2 is C(R6) or N, A3 is C(R7) or N, R5, R6, and R7 are each independently a hydrogen atom or the like, R2 is a substituted or unsubstituted alkyl or the like, R3 is a phenyl or the like that may be substituted with a substituent from group F, which includes halogens, cyanos, alkyls, haloalkyls, alkyloxys, and haloalkyloxys, and, in the formulas for -L-, R1 is a hydrogen atom or the like, R8 is a hydrogen atom or the like, each R10 is independently a cyano group or the like, and m is an integer from 1 to 3.)

Document FP17 Abstract: The present invention relates to a compound represented by formula (I) or (II) or a pharmaceutically acceptable salt thereof. Formula (I): [wherein: A1 is C(R1), etc.; R1 is a hydrogen atom, etc.; R8 is a hydrogen atom, etc.; B1 is CH, etc.; R10 is cyano, etc. R3 is a phenyl group optionally substituted with a group of substituents F, etc.; the group of substituents F: halogen, cyano, alkyl, haloalkyl, alkyloxy and haloalkyloxy; Q is a substituted or unsubstituted benzene ring, etc.; R2 is a substituted or unsubstituted alkyl, etc.; and -L- is a group represented by the formula, etc.].

Document FP21 Abstract: Disclosed are a polycyclic derivative modulator, and a preparation method therefor and the use thereof. Specifically, disclosed are a compound as represented by general formula (I-D), a preparation method therefor, a pharmaceutical composition containing same, and the use thereof as a modulator in the preparation of a

drug for treating metabolic diseases and related diseases. Each of the substituents in general formula (I-D) is the same as defined in the description.

Document FP22 Abstract: Provided are a polycyclic derivative regulator, a preparation method therefor, and an application thereof. In particular, provided are a compound represented by general formula (I'), a preparation method therefor, a pharmaceutical composition comprising the compound, and an application thereof as a regulator in the preparation of a drug for treating metabolic diseases and related diseases; the substituents in general formula (I') are the same as those defined in the description.

Document FP23 Abstract: The invention relates to a benzo nitrogen-containing polycyclic derivative regulator as well as a preparation method and application thereof. In particular, the present invention relates to a compound represented by general formula (I), a preparation method thereof, a pharmaceutical composition containing the compound, and an application of the compound as a regulator in the preparation of drugs for treating metabolic diseases and related diseases, each substituent in the general formula (I) being as defined in the specification.

Document FP25 Abstract: The invention discloses a benzimidazole or azabenzimidazole-6-carboxylic acid compound and an application of the benzimidazole or azabenzimidazole-6-carboxylic acid compound. The benzimidazole or azabenzimidazole-6-carboxylic acid compound has a structure as shown in a formula (I). The benzimidazole or azabenzimidazole-6-carboxylic acid compound can effectively activate a GLP-1R downstream signal channel and improve cAMP expression, so that the effects of promoting insulin secretion and treating diabetes mellitus and complications of

diabetes mellitus are achieved, and the benzimidazole or azabenzimidazole-6-carboxylic acid compound has high application value.

Document FP26 Abstract: The present invention provides novel benzimidazole compounds as GLP-1 receptor agonists, as well as methods of making such compounds and methods of administering such compounds to mammals in need thereof. The compound disclosed by the invention shows a relatively strong GLP-1 receptor excitation effect and relatively good metabolic stability, and has relatively strong specificity and medicinal safety on a GLP-1 receptor.

Document FP27 Abstract: The present invention relates to a novel aryl ether substituted heterocyclic compound having GLP1R agonist activity. Specifically, disclosed are a compound as a GLP1R agonist represented by formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, isotope substituent or isomer thereof.

Document FP28 Abstract: The invention relates to a salt form of a GLP-1R agonist compound I as well as a preparation method and application thereof. The salt disclosed by the invention has excellent GLP-1R agonist activity and good bioavailability in animal bodies, and is suitable for preparing preparations for treating metabolic diseases, tumors, autoimmune diseases or metastatic diseases.

Document FP30 Abstract: The invention provides a polymorphic substance of a GLP-1R agonist compound I as well as a preparation method and application of the polymorphic substance. Compared with the amorphous substance of the compound I, the polymorphic substance provided by the invention has higher stability and better processability; and the compound is more suitable for preparing medicines for preventing or treating diseases related to GLP-1R targets and signal channels thereof, such as type 2

diabetes mellitus, prediabetes mellitus, obesity, non-alcoholic fatty liver diseases, non-alcoholic steatohepatitis, nephropathy, gout, hyperhematuria, cardiovascular diseases and the like.

Document FP31 Abstract: The present invention relates to a novel aryl ether substituted heterocyclic compound having GLP1R agonist activity. Specifically disclosed is a compound having a structure as represented by formula (I) as a GLP1R agonist, or a pharmaceutically acceptable salt, solvate, hydrate, isotopic substitute or isomer thereof.

Document FP32 Abstract: Provided are a polymorph of a GLP-1R agonist compound I, a preparation method therefor, and use thereof. Compared with the free state of the compound I, the polymorph has higher stability and better processability, and is more suitable for preparing drugs for preventing or treating diseases related to a GLP-1R target and a signaling pathway thereof, such as type 2 diabetes, prediabetes, obesity, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, nephropathy, gout, hyperhematuria, and cardiovascular diseases.

Document FP33 Abstract: The present invention relates to a method for preparing a GLP-1R agonist compound as represented by formula (I) or a pharmaceutically acceptable salt thereof, and an intermediate. The method of the present invention overcomes defects in the prior art and greatly reduces costs, the obtained product has good purity and a high yield, and the process has high levels of operability and greatly improved safety. Therefore, the preparation method of the present invention and the use thereof are suitable for industrial application.

Document FP34 Abstract: The invention relates to a polycyclic compound, a pharmaceutical composition containing the polycyclic compound, and a preparation

method and application of the polycyclic compound. Specifically, the invention relates to a compound with a structure as shown in a formula I. The compound shows better GLP-1R agonist activity, can be used as an efficient GLP-1R agonist and is used for preventing and/or treating GLP-1R related diseases.

Document FP35 Abstract: The invention relates to a polycyclic compound, a pharmaceutical composition containing the polycyclic compound, and a preparation method and application of the polycyclic compound. Specifically, the invention relates to a compound with a structure as shown in a formula I. The compound shows better GLP-1R agonist activity, can be used as an efficient GLP-1R agonist and is used for preventing and/or treating GLP-1R related diseases.

Document FP41 Abstract: The invention provides a compound as shown in a formula (I) and application thereof. The compound as shown in the formula (I) provided by the invention can be used as an effective glucagon-like peptide-1 (GLP-1) receptor agonist, has excellent GLP-1 receptor agonist activity and obvious blood sugar reducing effect, and has better pharmacokinetic characteristics; more choices are provided for prevention and/or treatment of GLP-1 activity-related diseases, conditions or symptoms, and the GLP-1 has a good clinical application prospect.

Document FP42 Abstract: The invention relates to a condensed imidazole carboxylic acid compound as shown in a formula I, and a preparation method and application thereof, in particular to application in medicine. The invention particularly relates to a condensed imidazole carboxylic acid compound as shown in a general formula I, a preparation method of the compound, a pharmaceutical composition containing the

compound and application of the compound as a GLP-1R agonist in the aspects of treating diabetes or obesity and the like.

Document FP44 Abstract: Disclosed in the present invention are a benzo bicyclic compound, and a preparation method and application thereof. Specifically disclosed is a compound, which is a compound as shown in formula (X), or a stereoisomer, geometric isomer, tautomer, nitrogen oxide, hydrate, solvate, metabolite, pharmaceutically acceptable salt or prodrug of the compound as shown in formula (X).

Document FP45 Abstract: Disclosed are benzo bicyclic compounds and the use thereof in drugs. Specifically, the present invention relates to novel benzo bicyclic compounds and pharmaceutical compositions comprising said compounds. The present invention further relates to a method for preparing the compounds, and the use of the compounds or the pharmaceutical compositions for preparing drugs for treating GLP-1 receptor agonist-mediated diseases and/or disorders, in particular the use for preparing drugs for treating diabetes, non-alcoholic fatty liver disease and obesity.

Document FP46 Abstract: The present invention relates to a benzo bicyclic compound and use thereof in a medicament, and specifically relates to a novel benzo bicyclic compound and a pharmaceutical composition comprising the compound. The present invention also relates to a method for preparing the compound, and use of the compound or the pharmaceutical composition in the preparation of a medicament for treating a GLP-1 receptor agonist-mediated disease and/or disorder, and particularly, to use thereof in the preparation of a medicament for treating diabetes, non-alcoholic fatty liver disease and obesity.

Document FP47 Abstract: The invention discloses a lactam compound and an application of the lactam compound in a medicine, and particularly relates to a novel lactam compound and a medicine composition containing the novel lactam compound. The invention also relates to a method for preparing the compound, and application of the compound or the pharmaceutical composition in preparation of medicines for treating GLP-1 receptor agonist mediated diseases and/or symptoms, in particular to application in preparation of medicines for treating diabetes, non-alcoholic fatty liver diseases and obesity.

Document FP48 Abstract: The invention discloses a lactam compound and an application of the lactam compound in a medicine, and particularly relates to a novel lactam compound and a medicine composition containing the novel lactam compound. The invention also relates to a method for preparing the compound, and application of the compound or the pharmaceutical composition in preparation of medicines for treating GLP-1 receptor agonist mediated diseases and/or symptoms, in particular to application in preparation of medicines for treating diabetes, non-alcoholic fatty liver diseases and obesity.

Document FP49 Abstract: The present invention discloses a 5, 6-dihydro-1, 2, 4-triazine compound and a pharmaceutical use thereof as a GLP-1 receptor agonist, the structure of the 5, 6-dihydro-1, 2, 4-triazine compound is as shown in formula I, and in the formula, the definition of each substituent group is as described in the specification and claims. As a GLP-1 receptor agonist, the compound provided by the invention can be used for treating diabetes mellitus, metabolic syndrome and the like.

Document FP50 Abstract: The invention discloses a benzimidazole or azabenzimidazole compound as well as a preparation method and application thereof. The benzimidazole or azabenzimidazole compound has a structure as shown in a formula (I). Application of compounds and pharmaceutically acceptable salts, stereoisomers, solvates or hydrates thereof in preparation of GLP-1 receptor agonists and application in preparation of drugs for treating and/or preventing metabolic diseases

Applicant reserves the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith.

Respectfully submitted,

NEVRIVY PATENT LAW GROUP P.L.L.C.

/Daniel J. Nevrivy/

Daniel J. Nevrivy
Registration No. 59,118

Date: November 2, 2024

1101 30th St., NW
Suite 500
Washington, D.C. 20007
(202) 713-0843

UNITED STATES
PATENT AND TRADEMARK OFFICE

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

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/885,065	**11/04/2024 03:54:50 PM Z ET**	**HRT-030US1**

Title of Invention

GLP-1R Agonist and Therapeutic Method Thereof

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4802	FILED BY	Daniel Nevrivy
PATENT CENTER #	67829465	FILING DATE	09/13/2024
CUSTOMER #	83682	FIRST NAMED INVENTOR	Bin Liang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 54

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
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FP27.pdf	429	Foreign Reference	13786 KB
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Digest

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	18885065
Filing Date	2024-09-13
First Named Inventor	Bin Liang
Art Unit	1693
Examiner Name	HOI YAN NMN LEE
Attorney Docket Number	HRT-030US1

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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	9120813	B2	2015-09-01	TRANSTECH PHARMA LLC [US]; VTV THERAPEUTICS LLC	
	2	9198901	B2	2015-12-01	TRANSTECH PHARMA LLC	
	3	6482844	B1	2002-11-19	NEUROGEN CORP	

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	1	20110064806	A1	2011-03-17	TRANSTECH PHARMA INC	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	116903588	CN	A	2023-10-20	XIAMEN BORUILAI MEDICINE TECH CO LTD		☐

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	Attorney Docket Number	HRT-030US1

	2	2024028795	WO	A1	2024-02-08	ZYDUS LIFESCIENCES LTD		☐
	3	116102543	CN	A	2023-05-12	TANG CHUNLEI; FAN WEIZHENG		☐
	4	118084936	CN	A	2024-05-28	CSPC ZHONGQI PHARMACEUTICAL TECH SHIJIAZHUANG CO L		☐
	5	116102555	CN	A	2023-05-12	HUAZHONG PHARMACEUTICAL CO LTD		☐
	6	116675680	CN	B	2023-10-20	Yaokang Zhongtuo (Beijing) Pharmaceutical Technolo		☐
	7	117624145	CN	A	2024-03-01	UNIV CHINA PHARMA		☐
	8	118344349	CN	A	2024-07-16	Shanghai Institute of Materia Medica, Chinese Acad		☐
	9	2024149080	WO	A1	2024-07-18	SHANGHAI INST MATERIA MEDICA CAS		☐
	10	2024160271	WO	A1	2024-08-08	JIANGSU HANSOH PHARMACEUTICAL GROUP CO LTD		☐
	11	118420603	CN	A	2024-08-02	Jiangsu Hansoh Pharmaceutical Group Co., Ltd.		☐
	12	118496200	CN	A	2024-08-16	Chengdu Kanghong Pharmaceutical Group Co., Ltd.		☐

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	Attorney Docket Number	HRT-030US1

	13	2024169773	CN	A	2024-08-22	CHENGDU KANGHONG PHARMACEUTICAL CO LTD		☐
	14	102378574	CN	B	2013-11-20	TRANSTECH PHARMA INC		☐
	15	2021242806	WO	A1	2021-12-02	VTV THERAPEUTICS LLC		☐
	16	2022061091	WO	A1	2022-03-24	VTV THERAPEUTICS LLC		☐
	17	2019103060	WO	A1	2019-05-31	DAIICHI SANKYO CO LTD		☐
	18	2021196949	WO	A1	2021-10-07	HANGZHOU ZHONGMEIHUADONG PHARMACEUTICAL CO LTD		☐
	19	115315426	CN	A	2022-11-08	HANGZHOU ZHONGMEI HUADONG PHARMACEUTICAL CO LTD		☐
	20	115697968	CN	B	2022-11-08	HANGZHOU ZHONGMEI HUADONG PHARMACEUTICAL CO LTD		☐
	21	115667219	CN	A	2023-01-31	HANGZHOU ZHONGMEI HUADONG PHARMACEUTICAL CO LTD		☐
	22	115667222	CN	B	2023-09-29	Hangzhou Zhongmei Huadong Pharmaceutical Co., Ltd.		☐
	23	115667268	CN	B	2023-01-31	HANGZHOU ZHONGMEI HUADONG PHARMACEUTICAL CO LTD		☐

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	24	117500789	CN	A	2024-02-02	HANGZHOU ZHONGMEI HUADONG PHARMACEUTICAL CO LTD		☐
	25	117500808	CN	A	2024-02-02	HANGZHOU ZHONGMEI HUADONG PHARMACEUTICAL CO LTD		☐
	26	117897387	CN	A	2024-04-16	HANGZHOU ZHONGMEI HUADONG PHARMACEUTICAL CO LTD		☐
	27	2023051490	WO	A1	2023-04-06	HANGZHOU ZHONGMEIHUADONG PHARMACEUTICAL CO LTD [CN		☐
	28	2022165076	WO	A1	2022-08-04	CARMOT THERAPEUTICS INC		☐
	29	2022235717	WO	A1	2022-11-10	CARMOT THERAPEUTICS INC [US]; GARAI SUMANTA		☐
	30	2024026338	WO	A1	2024-02-01	CARMOT THERAPEUTICS INC		☐
	31	2019183577	WO	A1	2019-09-26	CARMOT THERAPEUTICS INC		☐
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	35	2005056537	WO	A1	2005-06-23	SHANGHAI INST MATERIA MEDICA		☐
	36	101195612	CN	B	2012-08-08	CHINESE ACADEMY OF SCIENCES		☐
	37	113929698	CN	B	2023-08-04	Kunming Institute of Botany, Chinese Academy of Sc		☐
	38	2009129696	WO	A1	2009-10-29	NAT CT FOR DRUG SCREENING		☐
	39	112812077	CN	B	2023-08-22	Shanghai Institute of Materia Medica, Chinese Acad		☐
	40	116444355	CN	A	2023-07-18	KUNMING INST BOTANY CAS		☐
	41	2011094890	WO	A1	2011-08-11	ARGUSINA INC		☐
	42	102946882	CN	B	2016-05-18	ARGUSINA INC		☐
	43	2012076966	WO	A1	2012-06-14	LUPIN LTD		☐
	44	2011122815	WO	A2	2011-10-06	DONG A PHARM CO LTD		☐
	45	104080767	CN	A	2014-10-01	RECEPTOS INC		☐

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	Examiner Name	HOI YAN NMN LEE
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	46	109867630	CN	A	2019-06-11	CELGENE INT II SARL		☐
	47	107074820	CN	B	2021-05-18	Celgene Second International Co., Ltd.		☐
	48	2016094729	WO	A1	2016-06-16	CELGENE INTERNAT II SARL		☐
	49	2018064476	WO	A1	2018-04-05	CELGENE INT II SARL		☐
	50	2018200833	WO	A1	2018-11-01	CELGENE INT II SARL		☐

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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.

PC 6.1.24

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	18885065
	Filing Date	2024-09-13
	First Named Inventor	Bin Liang
	Art Unit	1693
	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

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	/Daniel J. Nevrivy/	Date (YYYY-MM-DD)	2024-11-04
Name/Print	Daniel J. Nevrivy	Registration Number	59,118

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.**

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

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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.

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/885,065	**11/04/2024 03:56:41 PM Z ET**	**HRT-030US1**

Title of Invention

GLP-1R Agonist and Therapeutic Method Thereof

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4802	FILED BY	Daniel Nevrivy
PATENT CENTER #	67831344	FILING DATE	09/13/2024
CUSTOMER #	83682	FIRST NAMED INVENTOR	Bin Liang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 53

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
FP6.pdf	13	Foreign Reference	589 KB
FP5.pdf	19	Foreign Reference	693 KB
FP3.pdf	25	Foreign Reference	1315 KB
FP7.pdf	31	Foreign Reference	1687 KB
FP1.pdf	72	Foreign Reference	3291 KB
FP4.pdf	74	Foreign Reference	4430 KB
FP2.pdf	143	Foreign Reference	4457 KB
FP9.pdf	110	Foreign Reference	5432 KB
FP10.pdf	109	Foreign Reference	4167 KB
FP11.pdf	62	Foreign Reference	3232 KB

FP8.pdf	106	Foreign Reference	6058 KB
FP16.pdf	38	Foreign Reference	5739 KB
FP15.pdf	38	Foreign Reference	5567 KB
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FP21.pdf	1	Foreign Reference	210 KB
FP24.pdf	1	Foreign Reference	178 KB
FP26.pdf	1	Foreign Reference	203 KB
FP23.pdf	1	Foreign Reference	258 KB
FP25.pdf	1	Foreign Reference	230 KB
FP22.pdf	14	Foreign Reference	6745 KB
FP28_2.pdf	289	Foreign Reference	10404 KB
FP29_compressed.pdf	305	Foreign Reference	12548 KB
FP31_compressed.pdf	719	Foreign Reference	10698 KB
FP33.pdf	98	Foreign Reference	5902 KB
FP27.pdf	79	Foreign Reference	20291 KB
FP34.pdf	60	Foreign Reference	3350 KB
FP35.pdf	32	Foreign Reference	2811 KB
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FP36.pdf	44	Foreign Reference	4223 KB
FP38.pdf	75	Foreign Reference	5229 KB
FP40.pdf	15	Foreign Reference	8383 KB

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FP37.pdf	23	Foreign Reference	12284 KB
FP44.pdf	81	Foreign Reference	5095 KB
FP39.pdf	26	Foreign Reference	14558 KB
FP42.pdf	179	Foreign Reference	14195 KB
FP41.pdf	274	Foreign Reference	19277 KB
FP45.pdf	214	Foreign Reference	14887 KB
IDS4_.pdf	8	Information Disclosure Statement (IDS) Form (SB08)	1318 KB
PleadingIDS4.pdf	14	Transmittal Letter	72 KB
FP49.pdf	106	Foreign Reference	6088 KB
FP50.pdf	160	Foreign Reference	6281 KB
FP47_compressed.pdf	157	Foreign Reference	7530 KB
FP46_compressed.pdf	478	Foreign Reference	22963 KB
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Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 4802
Liang *et al.*	Art Unit: 1693
Appl. No.: 18/885,065	Examiner: HOI YAN NMN LEE
Filed: September 13, 2024	Atty. Docket: HRT-030US1
For: **GLP-1R Agonist and Therapeutic Method Thereof**	

Information Disclosure Statement Under 37 C.F.R. § 1.97(b)

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

Madam:

Listed on accompanying IDS Form PTO/SB/08a are document(s) that may be considered material to the patentability of this application as defined in 37 C.F.R. § 1.56, and in compliance with the duty of disclosure requirements of 37 C.F.R. § 1.97 and 1.98.

Where the date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicant has listed dates on the attached IDS Forms based on information presently available to the undersigned. However, the listed dates should not be construed as an admission that the information was actually published on the date indicated.

Documents FP3-FP14, FP17-FP27, FP35-FP40, FP42 and FP45-FP47 are in a foreign language.

Below are translated English language abstracts of FP3-FP14, FP17-FP27, FP35-FP40, FP42 and FP45-FP47 that are provided to provide a concise statement of the relevance thereof.

Document FP3 Abstract: The invention discloses a GLP-1R agonist as well as a synthesis method and application thereof, and belongs to the field of medicines. The structure of the GLP-1R agonist is shown as a formula (I), and the GLP-1R agonist can be used for treating human GLP-1R mediated diseases or symptoms, such as type 2 diabetes mellitus, prediabetes mellitus, obesity, non-alcoholic fatty liver diseases, non-alcoholic steatosis hepatitis and cardiovascular diseases.

Document FP4 Abstract: The invention provides a compound as shown in a formula (I), or a tautomer, a stereoisomer or a pharmaceutically acceptable salt thereof. The compound disclosed by the invention has a relatively strong agonistic effect on GLP-1R, can be used for treating diseases such as diabetes mellitus and the like or has an effect of reducing weight.

Document FP5 Abstract: The invention discloses an imidazo heteroaromatic derivative and application thereof.The imidazo heteroaromatic derivative has the structural general formula shown in the formula I. Compared with a polypeptide agonist, the imidazo heteroaromatic derivative has the advantages that the bioavailability of oral administration of small-molecule drugs is remarkable, and the imidazo heteroaromatic derivative is easier and more convenient to take and is not limited by food or taking time, so that the application range of the imidazo heteroaromatic derivative is widened, and the application range of the imidazo heteroaromatic derivative is widened. In addition, the imidazo

heteroaryl derivative as a small molecule agonist shows a good curative effect on the cellular level, and has a good drug application prospect.

Document FP6 Abstract: The invention provides a deuterated compound as well as a preparation method, a medicine and application thereof. The deuterated compound is a compound shown in a formula I or pharmaceutically acceptable salt thereof, wherein R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23 and R24 are independently H or deuterium, R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23 and R24 are not H at the same time, and n is equal to 2. The deuterated compound can be used as a GLP-1 receptor agonist, and is small in administration dosage and small in toxic and side effects.

Document FP7 Abstract: The invention discloses a selenium-containing compound and application thereof. The compound has a complete GLP-1R-cAMP signal pathway agonist effect (Emax), the GLP-1R-cAMP half effect concentration (EC50) of the compound reaches the nanomole level, the EC50 of part of the compound reaches the picomole level, and the compound is an excellent GLP-1 receptor agonist. Meanwhile, the compound is good in patent medicine property. Therefore, the selenium-containing compound disclosed by the invention can be used for preparing the GLP-1 receptor agonist and preparing the medicine for preventing and/or treating diseases related to agonizing the GLP-1 receptor.

Document FP8 Abstract: The invention discloses a 4-alkoxy benzimidazole-6-carboxylic acid derivative used as a GLP-1 receptor agonist, the structure of the 4-alkoxy benzimidazole-6-carboxylic acid derivative is shown in a general formula (II), and the

definition of each substituent is shown in the description and claims. The compound disclosed by the invention is used as a GLP-1 receptor agonist and can be used for preventing and/or treating diseases or symptoms related to GLP-1 receptor signaling pathway disorder.

Document FP9 Abstract: Disclosed in the present invention is a 4-alkoxy benzimidazole-6-carboxylic acid derivative serving as a GLP-1 receptor agonist. The structure of the 4-alkoxy benzimidazole-6-carboxylic acid derivative is represented by general formula (II), and the definition of each substituent is as recited in the description and the claims. The compound in the present invention serves as a GLP-1 receptor agonist, and can be used to prevent and/or treat diseases or symptoms associated with dysregulation of GLP-1 receptor signaling pathway.

Document FP10 Abstract: A salt and a crystal form of a cycloalkene compound, and a preparation method therefor and the use thereof. Specifically, a salt and a crystal form of a compound as represented by general formula (I), a preparation method, and a pharmaceutical composition comprising a therapeutically effective amount of the salt, and the use thereof as a regulator in the preparation of a drug for treating metabolic diseases and related diseases.

Document FP11 Abstract: The invention relates to a tromethamine salt crystal form of a cycloalkene compound as well as a preparation method and application of the tromethamine salt crystal form. The invention specifically relates to a salt and a crystal form of a compound represented by a general formula (I), a preparation method, a pharmaceutical composition containing a therapeutically effective amount of the salt form,

and an application of the pharmaceutical composition as a regulator in preparation of drugs for treating metabolic diseases and related diseases.

Document FP12 Abstract: The invention relates to an indazolinone GLP1 receptor agonist as shown in a formula I in the specification, wherein the definition of each substituent group is as shown in the specification; the invention also relates to a composition containing the compound or the salt thereof and application of the compound or the salt thereof in preparing a medicine for agonizing the GLP-1 receptor.

Document FP13 Abstract: The present invention relates to an indazolinone GLP1 receptor agonist as represented by formula I, the definitions of substituents being as stated in the present invention, a composition containing the compound or a salt thereof, and a use thereof in the preparation of a drug for GLP-1 receptor agonism.

Document FP14 Abstract: The azoanthracene derivatives that the present invention relates to replace or its pharmacy acceptable salt, it is regulated mankind's GLP-1 acceptor and can be used for the treatment of wherein useful disease, obstacle or the patient's condition of adjusting of mankind GLP-1 acceptor, such as diabetes B.The present invention also relates to comprise the pharmaceutical composition of these compounds, and relate to these compounds and the composition purposes in the adjusting for the treatment of mankind GLP-1 acceptor wherein useful described disease, obstacle or the patient's condition.

Document FP17 Abstract: The present invention addresses the problem of providing a drug to be used to prevent or treat obesity or to prevent or treat type 2 diabetes. The means for solution according to the present invention is a compound represented by general formula (I) or a pharmacologically acceptable salt thereof. [Abbreviated

description of each substituent. For example, R1: phenyl group or the like, R2: hydrogen atom or the like, R3: hydrogen atom or the like, R4: hydrogen atom or the like, R5: methyl group or the like, R6: hydrogen atom or the like, R7: heteroaryl group or the like, X: CH2 or the like, Y: CH2 or the like, Z: CH2 or the like]

Document FP18 Abstract: The present invention relates to a crystalline form A of a GLP-1 receptor agonist and a preparation method therefor, and in particular, to a crystalline form A of (S)-2-(3S,8S)-3-(4-(3,4-dicholorobenzyloxyl)phenyl-7-((S)-1-phenylpropyl)-2,3,6,7,8,9-hexahydro-[1,4]-dioxino[2,3-g]isoquinoline-8-formylamino)-3-(4-(2,3-lutidine-4-yl)phenyl)propanoic acid("OAD2") and a preparation method therefor. The crystalline form A can be used for treating various metabolic-related diseases and disorders, including but not limited to type 2 diabetes.

Document FP19 Abstract: The invention relates to a pharmaceutically acceptable acid salt of a GLP-1 receptor agonist free alkali and a preparation method thereof, in particular to a pharmaceutically acceptable acid salt of (S)-2-(3S, 8S)-3-(4-(3, 4-dichlorobenzyloxy) phenyl-7-((S)-1-phenylpropyl)-2, 3, 6, 7, 8, 9-hexahydro-[1, 4]-dioxacyclohexene [2, 3-g] isoquinoline-8-formylamino)-3-(4-(2, 4-dichlorobenzyloxy)-3-(4-(3, 4-dichlorobenzyloxy) phenyl)-7-((S)-1-phenylpropyl)-2, 3, 6, 7, 8, 9-hexahydro-[1, 4]-dioxacyclohexene [2, 3 The present invention relates to pharmaceutically acceptable acid salts of (2, 3-dimethylpyridin-4-yl) phenyl) propionic acid ("OAD2") and methods of making the same. The pharmaceutically acceptable acid salts of OAD2 are useful in the treatment of various metabolism-related diseases and conditions, including but not limited to type II diabetes.

Document FP20 Abstract: The invention relates to a pharmaceutically acceptable acid salt of a GLP-1 receptor agonist free alkali and a preparation method thereof, in particular to a pharmaceutically acceptable acid salt of (S)-2-(3S, 8S)-3-(4-(3, 4-dichlorobenzyloxy) phenyl-7-((S)-1-phenylpropyl)-2, 3, 6, 7, 8, 9-hexahydro-[1, 4]-dioxacyclohexene [2, 3-g] isoquinoline-8-formylamino)-3-(4-(2, 4-dichlorobenzyloxy)-3-(4-(3, 4-dichlorobenzyloxy) phenyl)-7-((S)-1-phenylpropyl)-2, 3, 6, 7, 8, 9-hexahydro-[1, 4]-dioxacyclohexene [2, 3 The present invention relates to pharmaceutically acceptable acid salts of (2, 3-dimethylpyridin-4-yl) phenyl) propionic acid ("OAD2") and methods of making the same. The pharmaceutically acceptable acid salts of OAD2 are useful in the treatment of various metabolism-related diseases and conditions, including but not limited to type II diabetes.

Document FP21 Abstract: The invention provides a preparation method of a key intermediate (S)-2-amino-3-[4-(2, 3, 4-dichlorobenzyloxy) phenyl-7-((S)-1-phenylpropyl)-2, 3, 6, 7, 8, 9-hexahydro-[1, 4]-dioxacyclohexene [2, 3-g] isoquinoline-8-formylamino)-3-(4-(2, 3-dimethyl pyridine-4-yl) phenyl) propionic acid dihydrochloride, and a preparation method thereof. Compared with the prior art, the method has the advantages that chromatographic column separation and purification are not needed, the cost is low, the yield is high, and the method is more suitable for industrial production.

Document FP22 Abstract: The present invention relates to a method for preparing a GLP-1 receptor agonist, and more particularly, to a method for preparing a GLP-1 receptor agonist (S)-2-(3S, 8S)-3-(4-(3, 4-dichlorobenzyloxy) phenyl-7-((S)-1-phenylpropyl)-2, 3, 6, 7, 8, 9-hexahydro-[1, 4]-dioxacyclohexeno [2, 3-g] isoquinoline-8-formylamino)-3-(4-(2, 4-dichlorobenzyloxy)-3-(4-(3, 4-dichlorobenzyloxy)-7-((S)-1-

phenylpropyl)-2, 3, 6, 7, 8, 9-hexahydro-[1, 4]-dioxacyclohexeno [2, the invention relates to an industrial preparation method of 2, 3-dimethyl pyridine-4-yl) phenyl) propionic acid dihydrochloride (compound I). A compound I is prepared by taking a compound 1 as a raw material through nucleophilic addition, hydrolysis, reductive ammoniation, cyclization, amide condensation, hydrolysis and salt forming reaction. The total yield of the compound I prepared by the method reaches more than 35%, and the purity reaches more than 98%.

Document FP23 Abstract: The invention provides a preparation method of a GLP-1 receptor agonist free alkali, and more particularly provides a preparation method of (S)-2-(3S, 8S)-3-(4-(3, 4-dichlorobenzyloxy) phenyl-7-((S)-1-phenylpropyl)-2, 3, 6, 7, 8, 9-hexahydro-[1, 4]-dioxacyclohexene [2, 3-g] isoquinoline-8-formylamino)-3-(4-(2, 3-dimethyl pyridine-4-yl) phenyl) propionic acid. The preparation method comprises the following steps: firstly, reacting a compound III with a condensing agent to form active ester, so that amino organic acid salt is free in situ and directly participates in an amide condensation reaction; the preparation method comprises the following steps: firstly, dissolving (S)-2-(3S, 8S)-3-(4-(3, 4-dichlorobenzyloxy) phenyl-7-((S)-1-phenylpropyl)-2, 3, 6, 7, 8, 9-hexahydro-[1, 4]-dioxino [2, 3-g] isoquinoline-8-formylamino)-3-(4-(2, 3-dimethyl pyridine-4-yl) phenyl) propionic acid in a proper solvent in a hydrolysis reaction by virtue of an acid-base neutralization post-treatment mode. According to the method, the highest yield of the two-step reaction can reach 80% or above, the purity reaches 98% or above, large-scale preparation can be achieved, and the method can be applied to industrial production.

Document FP24 Abstract: The invention provides a preparation method of 2, 3-dimethyl-4-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxoborane-2-yl) pyridine, which can reduce the dosage of boric acid ester, lower the cost and reduce three wastes, so that the effective content of the product is higher.

Document FP25 Abstract: The invention relates to an anthracene compound as shown in a formula A and a preparation method and medical application thereof. The anthracene compound has the effect of inhibiting growth of tumor cells and has the potential of serving as an anti-tumor drug. The invention also relates to a method for quality control of a sample.

Document FP26 Abstract: The invention provides a preparation method of (S, Z)-3-(2-(4-((3, 4-dichlorobenzyl) oxy) phenyl)-2, 3-dihydrobenzo [b] [1, 4] dioxin-6-yl)-2-hydroxyacrylic acid and (S)-3-((S)-2-(4-((3, 4-dichlorobenzyl) oxy) phenyl)-2, 3-dihydrobenzo [b] [1, 4] dioxin-6-yl)-2-(((S)-1-phenylpropyl) amino) propionic acid, and the preparation method has the advantages of low cost, high yield and controllable quality. The method is more suitable for industrial production.

Document FP27 Abstract: Provided in the present invention is a pharmaceutical composition of a small molecular GLP-1R receptor agonist suitable for oral administration. More specifically, the present invention relates to a pharmaceutical composition containing (S)-2-(3S,8S)-3-(4-(3,4-dichlorobenzyloxy)phenyl-7-((S)-1-phenylpropyl)-2,3,6,7,8,9-hexahydro-[1,4]-dioxino[2,3-g]isoquinoline-8-formylamino)-3-(4-(2,3-dimethylpyridin-4-yl)phenyl)propionic acid ("OAD2") and a pharmaceutically acceptable salt thereof, and a preparation method therefor. The composition may contain a low level of one or more oxidative degradation substances or may contain a low level of

reactive oxygen species. The pharmaceutical composition provided in the present invention has low content of oxidative degradation impurity B and a low total impurity content, so that the composition can be stably stored for 12 months or more under normal temperature and normal humidity. The present invention further relates to a method for treating type II diabetes and indications related to improper blood glucose control using such pharmaceutical compositions.

Document FP35 Abstract: The present invention provides the glucagon-like peptide-1 receptor agonists. It is indicated that the agonists have good binding capability to glucagon-like peptide-1 receptor by pharmacological tests. The present invention also provides the preparation of the agonists.

Document FP36 Abstract: The invention provides a compound with a substituted cyclobutane structure represented as the following formula I or II, a preparation method for the same, and an application of being glucagon-like peptide-1 receptor modulator to prevent and/or treat metabolic disorder (as diabetes, insulin resistance and obesity or the like), cardiovascular disease and neurodegenerative disease (as Alzheimer's) or the like.

Document FP37 Abstract: The invention provides ten novel diaryl heptane dimers shown in a structural formula (I), namely katsumadainol C1-C10 1-10, a pharmaceutical composition with the katsumadainol C1-C10 as an active ingredient, and a preparation method and application of the two , and belongs to the technical field of medicines. Thedimers can significantly promote GLP-1 secretion, has GPa, PTP1B and alpha-glucosidase inhibitory activity, can form a pharmaceutical composition with a pharmaceutically acceptable carrier or excipient, and can be used for preparing hypoglycemic drugs or health food.

Document FP38 Abstract: A kind of substituted five-membered heterocyclic compounds represented by the following formula I, pharmaceutically acceptable salts, esters, salvates, metal complex or prodrug with the same biological activity thereof. The uses of those compounds as GLP-1 receptor signaling transoluction positive modulators, and in the treatment and/or prophylaxis of diseases relating to metabolic diseases (including but not limited to type-2 diabetes, insulin resistance and obesity etc.), cardiovascular disease and neuro degenerative diseases(such as Alzheimer's Disease,AD, also said Alzheimer's dememtia).

Document FP39 Abstract: The invention discloses a benzamide compound, and a preparation method, a pharmaceutical composition and application thereof. The structure of the compound is shown in a general formula I, and R1 and R2 in the formula I are defined in the specification and claims. The compound or pharmaceutically acceptable salt, raceme, R-isomer or S-isomer or a mixture thereof, and a pharmaceutical composition containing the compound can be used as a GLP-1 agonist for treating diabetes mellitus.

Document FP40 Abstract: The invention provides sesquiterpenoids as well as a preparation method and application thereof, and belongs to the technical field of medicines. According to the present invention, seven sesquiterpenoids are separated from alpinia oxyphylla, and comprise 2-O-ethyl-beta-nootkol, alpinoxyphyll A, alpinoxyphyll B, 11-hydroxyisohanalpinone, 6S-hydroxyphyllone H, 6R-hydroxyphyllone H, and 6S-hydroxyphyllone D. The sesquiterpenoids can be adopted as a GLP-1 secretion promoting agent and a PTP1B and alpha-glucosidase inhibitor, can provide a blood sugar reducing effect on a plurality of targets, can be used for preparing the GLP-1 secretion promoting agent, and can be used for preparing the GLP-1 secretion promoting agent, the PTP1B and

the alpha-glucosidase inhibitor, such that the GLP-1 secretion promoting agent, the PTP1B and the alpha- The method has important significance on the application of alpinia oxyphylla and the development of new hypoglycemic drugs or functional foods and health foods.

Document FP42 Abstract: Provided herein is non-peptide GLP-1-1 receptor modulator compounds, non-peptide GLP-1-1 receptor modulator compounds of for example formula I, and the pharmaceutical composition that comprises this compounds, and preparation method thereof. Also provide the method that it is used for the treatment of metabolic disorder.

Document FP45 Abstract: The invention relates to compounds that modulate a glucagon-like peptide 1 (GLP-1) receptor, synthesis methods thereof, and methods thereof for therapeutic and/or prophylactic use. Such compounds are act as modulators or potentiators of GLP-1 receptor on their own, or with receptor ligands including GLP-1 peptides GLP-1(7-36) and GLP-1(9-36), or with peptide-based therapies, such as exenatide and liraglutide, and have the following general structure, wherein "wavy line" represents either or both the R and S form of the compound; and A, B, C, Y1, Y2, Z, R1, R2, R3, R4, R5, W1, n, p and q are as defined herein.

Document FP46 Abstract: The present invention provides compounds are provided that modulate the glucagon-like peptide 1 (GLP-1) receptor, as well as methods of their synthesis, and methods of their therapeutic and/or prophylactic use. Such compounds can act as modulators or potentiators of GLP-1 receptor on their own, or with incretin peptides such as GLP-1(7-36) and GLP-1(9-36), or with peptide-based therapies, such asexenatide and liraglutide, and have the following general structure (where the sign as shown in the

description represents either or both the R and S form of the compound): wherein A, B, C, Y1, Y2, Z,R1, R2, R3, R4, R5, W1, n, p and q are defined in the description.

Document FP47 Abstract: Compounds are provided that modulate the glucagon-like peptide 1 (GLP-1) receptor, as well as methods of their synthesis, and methods of their therapeutic and/or prophylactic use. Such compounds can act as modulators or potentiators of GLP-1 receptor on their own, or with incretin peptides such as GLP-1(7-36), GLP-1(9-36), and oxyntomodulin, or with peptide-based therapies, such as exenatide and liraglutide, and have the following general structure (where " " represents either or both the R and S form of the compound): where A, B, C, R1, R2, R3, R4, R5, n, p and q are as defined herein.

Applicant reserves the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith.

Respectfully submitted,

NEVRIVY PATENT LAW GROUP P.L.L.C.

/Daniel J. Nevrivy/

Daniel J. Nevrivy
Registration No. 59,118

Date: November 4, 2024

1101 30th St., NW
Suite 500
Washington, D.C. 20007
(202) 713-0843

UNITED STATES
PATENT AND TRADEMARK OFFICE

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

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/885,065	**11/04/2024 03:59:59 PM Z ET**	**HRT-030US1**

Title of Invention

GLP-1R Agonist and Therapeutic Method Thereof

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4802	FILED BY	Daniel Nevrivy
PATENT CENTER #	67832437	FILING DATE	09/13/2024
CUSTOMER #	83682	FIRST NAMED INVENTOR	Bin Liang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 30

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
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FP4.pdf	23	Foreign Reference	1611 KB
FP3.pdf	37	Foreign Reference	2112 KB
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FP22.pdf	7E96897D4707782EE168BEDEE211E20F55A3002AD58CDD01 E67EAE05DB0B8B391217D05081E7C87CA42217870DA1D3862 539B10F918AEB639A5A18887C4AF60A
FP27.pdf	35BF1B55B1C8D5B472C9615494837B66E0BE53BC9624469FC 4A385F3E4217B2652B550D6AC7D0D7F8D30C32504C173E66B 08D27F9796659E1F014A04B97DB81B
PleadingIDS5.pdf	906EA36C25ED0D980416373D1E628AAF5966FEC6E21560E75 FBED902C3BAF3862ED5E1656E1ED66D08DC67BB5F7CEF4F B37E3EA2147564F3CD1EEF96D52FA81D
IDS5.pdf	A169726605E043E2B7E813588BD183BB9D845F7039C64CE29 709A35D968DD17DFA467A2EE8E94CEA49224CCD54C768C6D 305F8842F41807467ECD9BA4B8D1EC0
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5A1B48BB2768989B9DD244EDDA73FE

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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

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

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	18885065
Filing Date	2024-09-13
First Named Inventor	Bin Liang
Art Unit	1693
Examiner Name	HOI YAN NMN LEE
Attorney Docket Number	HRT-030US1

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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	9150482	B2	2015-10-06	WU REY-YUH	
	2	10392357	B2	2019-08-27	ACADEMIA SINICA	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	I495464	TW	B	2015-08-11	UNIV NAT TAIWAN		☐
	2	103694195	CN	B	2016-04-06	UNIV EAST CHINA NORMAL		☐

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	Filing Date	2024-09-13
	First Named Inventor	Bin Liang
	Art Unit	1693
	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

	3	201613883	TW	A	2016-04-16	NAT RES INST OF CHINESE MEDICINE MINISTRY OF HEALT		☐
	4	105622687	CN	B	2018-03-23	China Medical Research Institute		☐
	5	2017117556	WO	A1	2017-07-06	UNIV VANDERBILT		☐
	6	2017170826	WO	A1	2017-10-05	AJINOMOTO KK		☐
	7	2022241287	WO	A3	2022-12-29	CARMOT THERAPEUTICS INC		☐
	8	2020110152	WO	A1	2020-06-04	GIRDHAR KHYATI		☐
	9	2020210582	WO	A1	2020-10-15	UNIV OF THE SCIENCES		☐
	10	2021044401	WO	A3	2021-04-22	UNITED ARAB EMIRATES UNIVERSITY		☐
	11	111548311	CN	B	2021-04-23	Shanxi Medical University		☐
	12	116323599	CN	A	2023-06-23	GASHUBLOOM BIOLOGICS INC		☐
	13	2023151575	WO	A1	2023-08-17	GASHERBRUM BIO INC		☐

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	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

	14	2023151574	WO	A1	2023-08-17	GASHERBRUM BIO INC		☐
	15	2022076503	WO	A1	2022-04-14	LILLY CO ELI		☐
	16	2022127868	WO	A1	2022-06-23	UNIV HONG KONG CHINESE		☐
	17	114790160	CN	A	2022-07-26	UNIV SHANXI MEDICAL		☐
	18	115286550	CN	A	2022-11-04	UNIV SHANXI MEDICAL		☐
	19	2022246230	WO	A1	2022-11-24	ENERGESIS PHARMACEUTICALS INC		☐
	20	115536638	CN	A	2022-12-30	UNIV SHANGHAI JIAOTONG		☐
	21	2023106310	WO	A1	2023-06-15	SHIONOGI & CO		☐
	22	2023191408	WO	A1	2023-10-05	LG CHEMICAL LTD		☐
	23	117534668	CN	A	2024-02-09	BEIJING FUYUAN PHARMACEUTICAL CO LTD		☐
	24	116217522	CN	A	2023-06-06	GUANGDONG RAFFLES PHARMATECH CO LTD		☐

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	Attorney Docket Number	HRT-030US1

	25	116804013	CN	A	2023-09-26	WUHAN AIMO JIAHUA BIOTECHNOLOGY CO LTD		☐
	26	2022269439	WO	A1	2022-12-29	ILDONG PHARMACEUTICAL CO LTD		☐
	27	112451515	CN	A	2021-03-09	GUANGZHOU INST BIOMED & HEALTH		☐
	28	2024148104	WO	A1	2024-07-11	BIOAGE LABS INC		☐

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	1		☐

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	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

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

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☐ See attached certification statement.

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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	/Daniel J. Nevrivy/	Date (YYYY-MM-DD)	2024-11-04
Name/Print	Daniel J. Nevrivy	Registration Number	59,118

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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.

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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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	Filing Date	2024-09-13
	First Named Inventor	Bin Liang
	Art Unit	1693
	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	106588749	CN	A	2017-04-26	UNIV ZHEJIANG		☐
	2	2000033839	WO	A1	2000-06-15	AGOURON PHARMA		☐
	3	2000042026	WO	A1	2000-07-20	NOVO NORDISK AS		☐

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	First Named Inventor	Bin Liang
	Art Unit	1693
	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

	4	20180101671	KR	A	2018-09-13	KOREA RESEARCH INSTITUTE OF CHEMICAL TECHNOLOGY		☐

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Signature	/Daniel J. Nevrivy/	Date (YYYY-MM-DD)	2024-11-15
Name/Print	Daniel J. Nevrivy	Registration Number	59,118

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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/885,065	**11/15/2024 05:18:03 PM Z ET**	**HRT-030US1**

Title of Invention

GLP-1R Agonist and Therapeutic Method Thereof

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4802	FILED BY	Daniel Nevrivy
PATENT CENTER #	67989414	FILING DATE	09/13/2024
CUSTOMER #	83682	FIRST NAMED INVENTOR	Bin Liang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 6

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
PleadingIDS7.pdf	3	Transmittal Letter	27 KB
FP4.pdf	27	Foreign Reference	702 KB
IDS7.pdf	4	Information Disclosure Statement (IDS) Form (SB08)	1316 KB
FP1.pdf	38	Foreign Reference	1913 KB
FP2.pdf	87	Foreign Reference	5677 KB
FP3.pdf	194	Foreign Reference	10953 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)

PleadingIDS7.pdf	5D4F0700EBDC511DF34063CD60350B7FBC016E8F2EE3079F F6F464890C249D80EA5D675F1FFAE5B3A6F79DEA55F9CF01 D52D041149FA9B22C5CF031676FE50E4
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IDS7.pdf	12916D41C0CF91E723D3F930B7B3B9AB7A6967FAA59DD5BF 236CACFC8F7154FCE799ECBA47C746FA1A23095422C5EA63 B606A23EBE9C316E01788491DD001955
FP1.pdf	C063F7E9D47261169A948E6FC0748567148BD8034AF339D29A 122CEE4B6E81EFC310690837CFECE35259EFB052221038DE1 EF9D74CCAFCC0C950A7728C23EED9
FP2.pdf	8BAF13015D36AF24365154CC4251B006881B52F96535C5D4D 846094767DEC25D6F808825E28B9A2BB6A6480F4183F5665FE 06059D7E0C335FFDCC2A61C430501
FP3.pdf	2585CD143EEA8ECE7D79093CDFAD5473F390745482470A236 A527F838F533356587993547B53F2C50B99820196BA2B5AC98 6DFDFF1F7F6DB822656B157E2313B

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.

Examiner-Initiated Interview Summary	**Application No.** 18/885,065	**Applicant(s)** Liang et al.		
	Examiner HOI YAN LEE	**Art Unit** 1693	**AIA (First Inventor to File) Status** Yes	**Page** 1 of 2

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
HOI YAN LEE	Examiner	Telephonic
DANIEL NEVRIVY	Attorney	

Date of Interview: 14 November 2024

Issues Discussed:

Proposed Amendment(s)

Applicant has filed an application under special new. After carefully reviewing the application,the examiner proposes the following changes.

Claim 1: Changing numbers "33" and "45" (line 3) below the structures to "(33)" and "(45)".
Claim 3: Replacing ".Na" (line 3) with "(Na salt)".
Claim 4: Replacing ".1/2 Ca" (line 3) with "(1/2 Ca salt)".
Claim 5: changing number "33" (line 3) below the structure to "(33)".
Claim 6: Replacing ".Na" (line 3) with "(Na salt)".
Claim 7: Replacing ".1/2 Ca" (line 3) with "(1/2 Ca salt)".
Claim 8: Changing number "45" (line 3) below the structure to "(45)".
Claim 9: Replacing ".Na" (line 3) with "(Na salt)".
Claim 10: Replacing ".1/2 Ca" (line 3) with "(1/2 Ca salt)".
Claim 11: Changing numbers "33" and "45" (line 3) below the structures to "(33)" and "(45)".

The examiner also notifies Applicant regarding the priority. The disclosure of the prior-filed application, Application No. 63603854 and 63673461, fail to provide adequate support or enablement in the manner provided by 35 U.S.C. 112(a) or pre-AIA 35 U.S.C. 112, first paragraph for one or more claims of this application. The domestic applications 63603854 and 63673461 do not provide support for the limitation of “a lithium salt” that recited in the claim 2; the sodium salts recited in claims 3, 6, and 9; the calcium salts recited in claims 4, 7, and 10.

A call was made to Mr. Nevrivy on November 14, 2024 to discuss the above changes. Mr. Nevrivy consulted with Applicant and called back on November 15, 2024 to give authorization to the examiner for amending the claims.

Examiner-Initiated Interview Summary	**Application No.** 18/885,065	**Applicant(s)** Liang et al.		
	Examiner HOI YAN LEE	**Art Unit** 1693	**AIA (First Inventor to File) Status** Yes	**Page** **2 of 2**

/HOI YAN NMN LEE/ Examiner, Art Unit 1693	/YIH-HORNG SHIAO/ Primary Examiner, Art Unit 1693

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
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

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.

Notice of References Cited	Application/Control No. 18/885,065	Applicant(s)/Patent Under Reexamination Liang et al.	
	Examiner HOI YAN LEE	Art Unit 1693	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	US-20190225604-A1	2019-07-25	YOSHINO; Hitoshi	C07D519/00	1/1
	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	
	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.	Applicant(s)/Patent Under Reexamination
	18/885,065	Liang et al.
	Examiner	**Art Unit**
	HOI YAN LEE	1693

CPC						
Symbol					**Type**	**Version**
C07D	/	471	/	04	F	2013-01-01
A61K	/	31	/	437	I	2013-01-01
C07F	/	9	/	6561	I	2013-01-01
C07D	/	519	/	00	I	2013-01-01
A61K	/	31	/	5415	I	2013-01-01
A61K	/	31	/	519	I	2013-01-01
A61K	/	31	/	4985	I	2013-01-01
A61K	/	31	/	675	I	2013-01-01

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

/HOI YAN NMN LEE/ Examiner, Art Unit 1693	18 November 2024	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	13	
/YIH-HORNG SHIAO/ Primary Examiner, Art Unit 1693	22 November 2024	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office — Part of Paper No.: 20241118

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/885,065	Liang et al.
	Examiner	**Art Unit**
	HOI YAN LEE	1693

INTERNATIONAL CLASSIFICATION				
CLAIMED				
C07D	/	471	/	04
A61K	/	31	/	437
C07F	/	9	/	6561
C07D	/	519	/	00
A61K	/	31	/	5415
A61K	/	31	/	519
A61K	/	31	/	4985
A61K	/	31	/	675

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**
514	303

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

/HOI YAN NMN LEE/ Examiner, Art Unit 1693 (Assistant Examiner)	18 November 2024 (Date)	**Total Claims Allowed:** 13	
/YIH-HORNG SHIAO/ Primary Examiner, Art Unit 1693 (Primary Examiner)	22 November 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure None

U.S. Patent and Trademark Office — Part of Paper No.: 20241118

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/885,065	Liang et al.
	Examiner	**Art Unit**
	HOI YAN LEE	1693

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

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	10	10												
2	2	11	11												
3	3	12	12												
4	4	13	13												
5	5														
6	6														
7	7														
8	8														
9	9														

/HOI YAN NMN LEE/ Examiner, Art Unit 1693 (Assistant Examiner)	18 November 2024 (Date)	**Total Claims Allowed:** 13	
/YIH-HORNG SHIAO/ Primary Examiner, Art Unit 1693 (Primary Examiner)	22 November 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure None

U.S. Patent and Trademark Office Part of Paper No.: 20241118

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/885,065	Liang et al.
	Examiner	Art Unit
	HOI YAN LEE	1693

CPC - Searched*		
Symbol	**Date**	**Examiner**
C07D471/04	11/18/2024	HYL
A61K31/437	11/18/2024	HYL
A61K31/4985	11/18/2024	HYL
A61K31/519	11/18/2024	HYL
A61K31/5415	11/18/2024	HYL
A61K31/675	11/18/2024	HYL
C07D519/00	11/18/2024	HYL
C07F9/6561	11/18/2024	HYL

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.

/H.Y.L./ Examiner, Art Unit 1693	

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/885,065	Liang et al.
	Examiner	**Art Unit**
	HOI YAN LEE	1693

Search Notes		
Search Notes	**Date**	**Examiner**
PE2E Search	11/18/2024	HYL
STN Search 1	11/12/2024	HYL
STN Search 2	11/14/2024	HYL
Search Terms: "GLP" "GLP-1R" "Pharmaceutically acceptable salt" (" sodium salt" OR "calcium salt" OR "potassium salt" OR "magnesium salt" OR "lithium salt")	11/18/2024	HYL
PDP Search	11/18/2024	HYL

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
C07D	471/04	11/18/2024	HYL
A61K	31/437	11/18/2024	HYL
A61K	31/4985	11/18/2024	HYL
A61K	31/519	11/18/2024	HYL
A61K	31/5415	11/18/2024	HYL
A61K	31/675	11/18/2024	HYL
C07D	519/00	11/18/2024	HYL
C07F	9/6561	11/18/2024	HYL

/H.Y.L./ Examiner, Art Unit 1693	

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	0	((("ASCLETIS") near3 ("PHARMA") near3 ("(CHINA)") near3 ("CO") near3 ("LIMITED"))).AS,AANM.	(US-PGPUB; USPAT)	OR	ON	ON	2024/11/18 09:31 PM
L2	264	((("LIANG") near3 ("Bin")) OR (("WU") near3 ("Jinzi")) OR (("YANG") near3 ("Bailing"))).INV.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2024/11/18 09:31 PM
L3	0	((("ASCLETIS") near3 ("PHARMA") near3 ("(CHINA)") near3 ("CO") near3 ("LIMITED"))).AS,AANM.	(US-PGPUB; USPAT)	OR	ON	ON	2024/11/18 09:32 PM
L4	133805	(C07D471/04 OR A61K31/437 OR A61K31/4985 OR A61K31/519 OR A61K31/5415 OR A61K31/675 OR C07D519/00 OR C07F9/6561).cpc.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2024/11/18 09:36 PM
L5	7	L2 AND L4	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2024/11/18 09:37 PM
L6	8	L2 AND "GLP"	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2024/11/18 09:37 PM
L7	3848	L4 AND "GLP"	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2024/11/18 09:43 PM
L8	201	L4 AND "GLP-1R"	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2024/11/18 09:43 PM
L9	164	L8 AND "pharmaceutically acceptable salt"	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2024/11/18 09:46 PM
L10	68	L9 AND ("sodium salt" OR "calcium salt" OR "potassium salt" OR "magnesium salt" OR "lithium salt")	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2024/11/18 09:48 PM

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default	Plurals	British	Time Stamp

				Operator		Equivalents	
N1	76817	(C07D471/04 OR A61K31/437 OR A61K31/4985 OR A61K31/519 OR A61K31/5415 OR A61K31/675 OR C07D519/00 OR C07F9/6561).cpc.	(US-PGPUB; USPAT)	OR	ON	ON	2024/11/18 09:53 PM

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	18885065
	Filing Date	2024-09-13
	First Named Inventor	Bin Liang
	Art Unit	1693
	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2022042691	WO	A1	2022-03-03	GASHERBRUM BIO INC		☐
	2	2022078407	WO	A1	2022-04-21	GASHERBRUM BIO INC		☐
	3	2022078380	WO	A1	2022-04-21	GASHERBRUM BIO INC		☐

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /H.Y.L./

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Attorney Docket Number	HRT-030US1

	4	2023138684	WO	A1	2023-07-27	GASHERBRUM BIO INC		☐
	5	2023179542	WO	A1	2023-09-28	GASHERBRUM BIO INC		☐
	6	2023198140	WO	A1	2023-10-19	GASHERBRUM BIO INC		☐
	7	2024131869	WO	A1	2024-06-27	GASHERBRUM BIO INC		☐
	8	2024138048	WO	A1	2024-06-27	GASHERBRUM BIO INC		☐
	9	2021187886	WO	A1	2021-09-23	LG CHEMICAL LTD		☐
	10	115279750	CN	A	2022-11-01	LG CHEMICAL LTD		☐
	11	2022216094	WO	A1	2022-10-13	LG CHEMICAL LTD		☐
	12	117279904	CN	A	2023-12-22	LG CHEMICAL LTD		☐
	13	2021197464	WO	A1	2021-10-07	JIANGSU HENGRUI MEDICINE CO		☐
	14	113801136	CN	B	2023-04-07	Jiangsu Hengrui Medicine Co., Ltd.		☐

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /H.Y.L./

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	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

	15	113816948	CN	B	2023-08-11	Jiangsu Hengrui Medicine Co., Ltd.		☐
	16	2021254470	WO	A1	2021-12-23	JIANGSU HENGRUI MEDICINE CO		☐
	17	2022007979	WO	A1	2022-01-13	JIANGSU HENGRUI MEDICINE CO		☐
	18	114805336	CN	A	2022-07-29	JIANGSU HENGRUI MEDICINE CO		☐
	19	2023116882	WO	A1	2023-06-29	JIANGSU HENGRUI PHARMACEUTICALS CO LTD		☐
	20	2023116879	WO	A1	2023-06-29	JIANGSU HENGRUI PHARMACEUTICALS CO LTD		☐
	21	2021244645	WO	A1	2021-12-09	SCIWIND BIOSCIENCES CO LTD [CN]; MEDSHINE DISCOVER		☐
	22	2023098852	WO	A1	2023-06-08	HANGZHOU SCIWIND BIOSCIENCES CO LTD		☐
	23	113773310	CN	B	2023-12-22	Chongqing Kangding Pharmaceutical Technology Co.		☐
	24	2021249492	WO	A1	2021-12-16	MEDSHINE DISCOVERY INC		☐
	25	2023025201	WO	A1	2023-03-02	MEDSHINE DISCOVERY INC		☐

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /H.Y.L./

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	Attorney Docket Number	HRT-030US1

	26	113831337	CN	B	2023-03-24	Guangzhou Hengnuokang Pharmaceutical Technology Co		☐
	27	113493447	CN	B	2024-06-11	Xuanzhu (Beijing) Pharmaceutical Technology Co., L		☐
	28	2022040600	WO	A1	2022-02-24	TERNS PHARMACEUTICALS INC		☐
	29	2023049518	WO	A1	2023-03-30	TERNS PHARMACEUTICALS INC		☐
	30	2023076237	WO	A1	2023-05-04	TERNS PHARMACEUTICALS INC		☐
	31	2023164050	WO	A1	2023-08-31	TERNS PHARMACEUTICALS INC		☐
	32	2022068772	WO	A1	2022-04-07	SHENZHEN SALUBRIS PHARM CO LTD		☐
	33	2022111624	WO	A1	2022-06-02	SHENZHEN SALUBRIS PHARM CO LTD		☐
	34	115594669	CN	A	2023-01-13	SHENZHEN SALUBRIS PHARM CO LTD		☐
	35	2023011395	WO	A	2023-01-13	SHENZHEN SALUBRIS PHARM CO LTD		☐
	36	115703792	CN	A	2023-02-17	SHENZHEN SALUBRIS PHARM CO LTD		☐

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /H.Y.L./

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Art Unit	1693
Examiner Name	HOI YAN NMN LEE
Attorney Docket Number	HRT-030US1

	37	116217558	CN	A	2023-06-06	SHENZHEN SALUBRIS PHARM CO LTD		☐
	38	117003749	CN	A	2023-11-07	SHENZHEN SALUBRIS PHARM CO LTD		☐
	39	117003748	CN	A	2023-11-07	SHENZHEN SALUBRIS PHARM CO LTD		☐
	40	117105932	CN	A	2023-11-24	SHENZHEN SALUBRIS PHARM CO LTD		☐
	41	117100752	CN	A	2023-11-24	SHENZHEN SALUBRIS PHARM CO LTD		☐
	42	2022078152	WO	A1	2022-04-21	HANGZHOU ZHONGMEIHUADONG PHARMACEUTICAL CO LTD		☐
	43	114478497	CN	B	2022-05-13	HANGZHOU ZHONGMEI EAST CHINA PHARMACY LTD COMPAN		☐
	44	114634510	CN	A	2022-06-17	HANGZHOU ZHONGMEI EAST CHINA PHARMACY LTD COMPAN		☐
	45	114907351	CN	A	2022-08-16	HANGZHOU ZHONGMEI HUADONG PHARMACEUTICAL CO LTD		☐
	46	2022199458	WO	A1	2022-09-29	HANGZHOU ZHONGMEIHUADONG PHARMACEUTICAL CO LTD		☐
	47	2022268152	WO	A1	2022-12-29	HANGZHOU ZHONGMEIHUADONG PHARMACEUTICAL CO LTD		☐

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /H.Y.L./

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	First Named Inventor	Bin Liang
	Art Unit	1693
	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

	48	114478497	CN	A	2022-05-13	HANGZHOU ZHONGMEI EAST CHINA PHARMACY LTD COMPANY		☐
	49	117586240	CN	A	2024-02-23	HANGZHOU ZHONGMEI HUADONG PHARMACEUTICAL CO LTD		☐
	50	2024125446	WO	A1	2024-06-20	HANGZHOU ZHONGMEIHUADONG PHARMACEUTICAL CO LTD		☐

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	1		☐

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EXAMINER SIGNATURE

Examiner Signature	/HOI YAN NMN LEE/	Date Considered	11/18/2024

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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-22)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	18885065
Filing Date	2024-09-13
First Named Inventor	Bin Liang
Art Unit	1693
Examiner Name	HOI YAN NMN LEE
Attorney Docket Number	HRT-030US1

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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	9120813	B2	2015-09-01	TRANSTECH PHARMA LLC [US]; VTV THERAPEUTICS LLC	
	2	9198901	B2	2015-12-01	TRANSTECH PHARMA LLC	
	3	6482844	B1	2002-11-19	NEUROGEN CORP	

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	1	20110064806	A1	2011-03-17	TRANSTECH PHARMA INC	

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	1	116903588	CN	A	2023-10-20	XIAMEN BORUILAI MEDICINE TECH CO LTD		☐

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	Attorney Docket Number	HRT-030US1

	2	2024028795	WO	A1	2024-02-08	ZYDUS LIFESCIENCES LTD		☐
	3	116102543	CN	A	2023-05-12	TANG CHUNLEI; FAN WEIZHENG		☐
	4	118084936	CN	A	2024-05-28	CSPC ZHONGQI PHARMACEUTICAL TECH SHIJIAZHUANG CO L		☐
	5	116102555	CN	A	2023-05-12	HUAZHONG PHARMACEUTICAL CO LTD		☐
	6	116675680	CN	B	2023-10-20	Yaokang Zhongtuo (Beijing) Pharmaceutical Technolo		☐
	7	117624145	CN	A	2024-03-01	UNIV CHINA PHARMA		☐
	8	118344349	CN	A	2024-07-16	Shanghai Institute of Materia Medica, Chinese Acad		☐
	9	2024149080	WO	A1	2024-07-18	SHANGHAI INST MATERIA MEDICA CAS		☐
	10	2024160271	WO	A1	2024-08-08	JIANGSU HANSOH PHARMACEUTICAL GROUP CO LTD		☐
	11	118420603	CN	A	2024-08-02	Jiangsu Hansoh Pharmaceutical Group Co., Ltd.		☐
	12	118496200	CN	A	2024-08-16	Chengdu Kanghong Pharmaceutical Group Co., Ltd.		☐

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	Attorney Docket Number	HRT-030US1

	13	2024169773	CN	A	2024-08-22	CHENGDU KANGHONG PHARMACEUTICAL CO LTD		☐
	14	102378574	CN	B	2013-11-20	TRANSTECH PHARMA INC		☐
	15	2021242806	WO	A1	2021-12-02	VTV THERAPEUTICS LLC		☐
	16	2022061091	WO	A1	2022-03-24	VTV THERAPEUTICS LLC		☐
	17	2019103060	WO	A1	2019-05-31	DAIICHI SANKYO CO LTD		☐
	18	2021196949	WO	A1	2021-10-07	HANGZHOU ZHONGMEIHUADONG PHARMACEUTICAL CO LTD		☐
	19	115315426	CN	A	2022-11-08	HANGZHOU ZHONGMEI HUADONG PHARMACEUTICAL CO LTD		☐
	20	115697968	CN	B	2022-11-08	HANGZHOU ZHONGMEI HUADONG PHARMACEUTICAL CO LTD		☐
	21	115667219	CN	A	2023-01-31	HANGZHOU ZHONGMEI HUADONG PHARMACEUTICAL CO LTD		☐
	22	115667222	CN	B	2023-09-29	Hangzhou Zhongmei Huadong Pharmaceutical Co., Ltd.		☐
	23	115667268	CN	B	2023-01-31	HANGZHOU ZHONGMEI HUADONG PHARMACEUTICAL CO LTD		☐

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	Attorney Docket Number	HRT-030US1

	24	117500789	CN	A	2024-02-02	HANGZHOU ZHONGMEI HUADONG PHARMACEUTICAL CO LTD		☐
	25	117500808	CN	A	2024-02-02	HANGZHOU ZHONGMEI HUADONG PHARMACEUTICAL CO LTD		☐
	26	117897387	CN	A	2024-04-16	HANGZHOU ZHONGMEI HUADONG PHARMACEUTICAL CO LTD		☐
	27	2023051490	WO	A1	2023-04-06	HANGZHOU ZHONGMEIHUADONG PHARMACEUTICAL CO LTD [CN		☐
	28	2022165076	WO	A1	2022-08-04	CARMOT THERAPEUTICS INC		☐
	29	2022235717	WO	A1	2022-11-10	CARMOT THERAPEUTICS INC [US]; GARAI SUMANTA		☐
	30	2024026338	WO	A1	2024-02-01	CARMOT THERAPEUTICS INC		☐
	31	2019183577	WO	A1	2019-09-26	CARMOT THERAPEUTICS INC		☐
	32	2022241287	WO	A2	2022-11-17	CARMOT THERAPEUTICS INC		☐
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	First Named Inventor	Bin Liang
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	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

	35	2005056537	WO	A1	2005-06-23	SHANGHAI INST MATERIA MEDICA		☐
	36	101195612	CN	B	2012-08-08	CHINESE ACADEMY OF SCIENCES		☐
	37	113929698	CN	B	2023-08-04	Kunming Institute of Botany, Chinese Academy of Sc		☐
	38	2009129696	WO	A1	2009-10-29	NAT CT FOR DRUG SCREENING		☐
	39	112812077	CN	B	2023-08-22	Shanghai Institute of Materia Medica, Chinese Acad		☐
	40	116444355	CN	A	2023-07-18	KUNMING INST BOTANY CAS		☐
	41	2011094890	WO	A1	2011-08-11	ARGUSINA INC		☐
	42	102946882	CN	B	2016-05-18	ARGUSINA INC		☐
	43	2012076966	WO	A1	2012-06-14	LUPIN LTD		☐
	44	2011122815	WO	A2	2011-10-06	DONG A PHARM CO LTD		☐
	45	104080767	CN	A	2014-10-01	RECEPTOS INC		☐

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	Art Unit	1693
	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

	46	109867630	CN	A	2019-06-11	CELGENE INT II SARL		☐
	47	107074820	CN	B	2021-05-18	Celgene Second International Co., Ltd.		☐
	48	2016094729	WO	A1	2016-06-16	CELGENE INTERNAT II SARL		☐
	49	2018064476	WO	A1	2018-04-05	CELGENE INT II SARL		☐
	50	2018200833	WO	A1	2018-11-01	CELGENE INT II SARL		☐

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	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

	1	Pending claims in co-pending U.S. Appl. No.: 18/884,965, entitled "GLP-1R Agonist and Therapeutic Method Thereof," filed September 13, 2024.	☐

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Doc description: Information Disclosure Statement (IDS) Filed

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	1	118184638	CN	A	2024-06-14	HANGZHOU ZHONGMEI HUADONG PHARMACEUTICAL CO LTD		☐
	2	118184637	CN	A	2024-06-14	HANGZHOU ZHONGMEI HUADONG PHARMACEUTICAL CO LTD		☐
	3	2022116693	WO	A1	2022-06-09	SUZHOU VINCENTAGE PHARMA CO LTD		☐

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	Art Unit	1693
	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

	4	114591296	CN	A	2022-06-07	HEIXIDAE MEDICINE GROUP STOCK LTD COMPANY		☐
	5	114763352	CN	A	2022-07-19	HAISCO PHARMACEUTICAL GROUP INC		☐
	6	2023124824	WO	A1	2023-07-06	HAISCO PHARMACEUTICAL GROUP CO LTD		☐
	7	2023125896	WO	A1	2023-07-06	HAISCO PHARMACEUTICAL GROUP CO LTD		☐
	8	2023130878	WO	A1	2023-07-13	HAISCO PHARMACEUTICAL GROUP CO LTD		☐
	9	2022135572	WO	A1	2022-06-30	SICHUAN HAISCO PHARMACEUTICAL CO LTD		☐
	10	2022165076	WO	A1	2022-08-04	CARMOT THERAPEUTICS INC		☐
	11	2022235717	WO	A1	2022-11-10	CARMOT THERAPEUTICS INC		☐
	12	2024026338	WO	A1	2024-02-01	CARMOT THERAPEUTICS INC		☐
	13	2022184849	WO	A1	2022-09-09	SERVIER LAB		☐
	14	2022202864	WO	A1	2022-09-29	SHIONOGI & CO		☐

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	15	117377666	CN	A	2024-01-09	SHIONOGI & CO		☐
	16	2024063140	WO	A1	2024-03-28	SHIONOGI & CO		☐
	17	2024063143	WO	A1	2024-03-28	SHIONOGI & CO		☐
	18	2022199661	WO	A1	2022-09-29	ECCOGENE SHANGHAI CO LTD		☐
	19	2022219495	WO	A1	2022-10-20	NOVARTIS AG		☐
	20	2023152698	WO	A1	2023-08-17	NOVARTIS AG		☐
	21	2022228490	WO	A1	2022-11-03	SHANGHAI HANSOH BIOMEDICAL CO LTD		☐
	22	2023011539	WO	A1	2023-02-09	SHANGHAI HANSOH BIOMEDICAL CO LTD		☐
	23	117986264	CN	A	2024-05-07	JIANGSU HANSOH PHARMACEUTICAL GROUP CO LTD		☐
	24	2023001237	WO	A1	2023-01-26	HEPAGENE THERAPEUTICS HK LTD		☐
	25	113480534	CN	B	2022-05-13	Guangzhou Bibet Pharmaceutical Co., Ltd.		☐

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	26	115703766	CN	A	2023-02-17	TIANDI HENGYI PHARMACEUTICAL CO LTD		☐
	27	2023029380	WO	A1	2023-03-09	MINDRANK AI LTD		☐
	28	117362282	CN	A	2024-01-09	HANGZHOU DERUI PHARMACEUTICAL TECH CO LTD		☐
	29	117417330	CN	A	2024-01-19	DERUI PHARMACEUTICAL SUZHOU NEW DRUG RES AND DEV		☐
	30	117417329	CN	A	2024-01-19	DERUI PHARMACEUTICAL SUZHOU NEW DRUG RES AND DEV		☐
	31	2024051700	WO	A1	2024-03-14	MINDRANK THERAPEUTICS SUZHOU NEW DRUG RES AND DE		☐
	32	2024051749	WO	A1	2024-03-14	MINDRANK THERAPEUTICS SUZHOU NEW DRUG RES AND DEVE		☐
	33	2024153041	WO	A1	2024-07-25	MINDRANK AI LTD		☐
	34	115872982	CN	A	2023-03-31	SICHUAN KELUN BOTAI BIOMEDICAL CO LTD		☐
	35	116120296	CN	A	2023-05-16	SICHUAN KELUN BIOTECH BIOPHARMACEUTICAL CO LTD		☐
	36	2023057414	WO	A1	2023-04-13	ASTRAZENECA AB		☐

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	37	2023057429	WO	A1	2023-04-13	ASTRAZENECA AB		☐
	38	2023057427	WO	A1	2023-04-13	ASTRAZENECA AB		☐
	39	2023111144	WO	A1	2023-06-22	ASTRAZENECA AB		☐
	40	2023111145	WO	A1	2023-06-22	ASTRAZENECA AB		☐
	41	116003393	CN	A	2023-04-25	CGENE TECH SUZHOU CHINA CO LTD		☐
	42	116354945	CN	A	2023-06-30	CHANGCHUN GENESCIENCE PHARMACEUTICALS CO LTD		☐
	43	2023164358	WO	A1	2023-08-31	ASCLETIS BIOSCIENCE CO LTD		☐
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	46	2024041609	WO	A1	2024-02-29	GUANGZHOU UNIRISE PHARMACEUTICAL CO LTD		☐
	47	118271299	CN	A	2024-07-02	GUANGZHOU LIANRUI PHARMACEUTICAL CO LTD		☐

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	Attorney Docket Number	HRT-030US1

	48	118271300	CN	A	2024-07-02	GUANGZHOU LIANRUI PHARMACEUTICAL CO LTD		☐
	49	114716423	CN	A	2022-07-08	SHANGHAI INST MATERIA MEDICA CAS		☐
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Bibliographic Data

Application No: 18/885,065

Foreign Priority claimed: ◉ Yes ○ No

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

Verified and Acknowledged: /HOI YAN NMN LEE/ Examiner's Signature | Initials

Title: GLP-1R Agonist and Therapeutic Method Thereof

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
09/13/2024	514	1693	HRT-030US1
RULE			

APPLICANTS

Ascletis Pharma (China) Co., Limited, Hong Kong, CHINA

INVENTORS

Bin Liang, Hong Kong, CHINA

Jinzi Jason Wu, Hong Kong, CHINA

Bailing Yang, Hong Kong, CHINA

CONTINUING DATA

This application has PRO of 63673461 07/19/2024

This application has PRO of 63603854 11/29/2023

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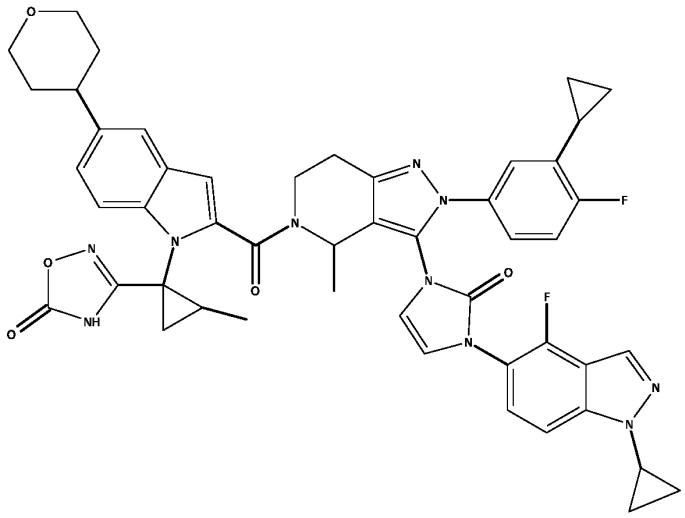
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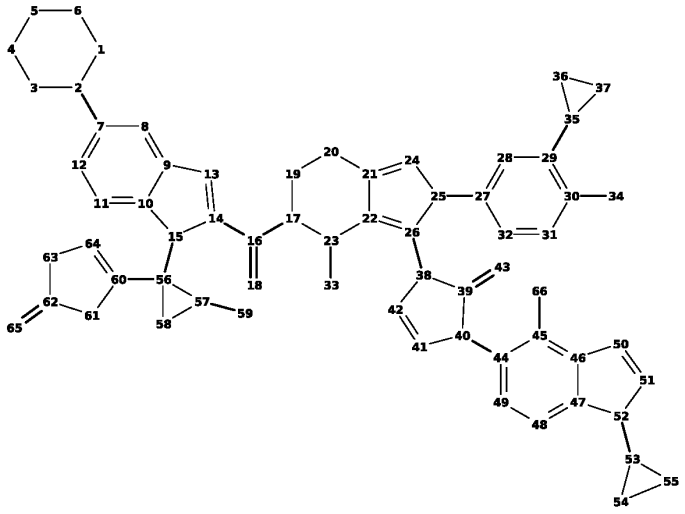
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Uploading structure file: 18885065 S1
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Node Attributes
Ring Nodes : 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 17 19 20 21
22 23 24 25 26 27 28 29 30 31 32 35 36 37 38 39 40 41 42 44
45 46 47 48 49 50 51 52 53 54 55 56 57 58 60 62 63 64
Chain Nodes : 16 18 33 34 43 59 65 66
Bond Attributes
Ring Bonds : 1-2 2-3 3-4 4-5 5-6 6-1 7-8 8-9 9-10 9-13 10-11 11-12
12-7 13-14 14-15 15-10 17-19 19-20 20-21 21-22 21-24 22-23 23-17
24-25 25-26 26-22 27-28 28-29 29-30 30-31 31-32 32-27 35-36 35-37
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48-49 49-44 50-51 51-52 52-47 53-54 53-55 54-55 56-57 56-58 58-57
60-61 61-62 62-63 63-64 64-60
Chain Bonds : 2-7 14-16 15-56 16-17 16-18 23-33 25-27 26-38 29-35 30-34

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39-43  40-44  45-66  52-53  56-60  57-59  62-65
Exact Bonds : 2-7  14-16  23-33  29-35  30-34  45-66  56-60  57-59
Normalized Bonds : 7-8  8-9  9-10  10-11  11-12  12-7  27-28  28-29  29-30
30-31  31-32  32-27  44-45  45-46  46-47  47-48  48-49  49-44
Exact/Normalized Bonds : 1-2  2-3  3-4  4-5  5-6  6-1  9-13  13-14  14-15  15-10
15-56  16-17  16-18  17-19  19-20  20-21  21-22  21-24  22-23  23-17  24-25
25-26  25-27  26-22  26-38  35-36  35-37  36-37  38-39  39-40  39-43  40-41
40-44  41-42  42-38  46-50  50-51  51-52  52-47  52-53  53-54  53-55  54-55
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Markush Attributes
Match Level (ATOM) : 1  2  3  4  5  6  7  8  9  10  11  12  13  14  15  17  19
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42  44  45  46  47  48  49  50  51  52  53  54  55  56  57  58  60  61  62  63
64
Match Level (CLASS) : 16  18  33  34  43  59  65  66
Element Count Level (LIMITED) : 1  2  3  4  5  6  7  8  9  10  11  12  13  14
15  16  17  18  19  20  21  22  23  24  25  26  27  28  29  30  31  32  33  34
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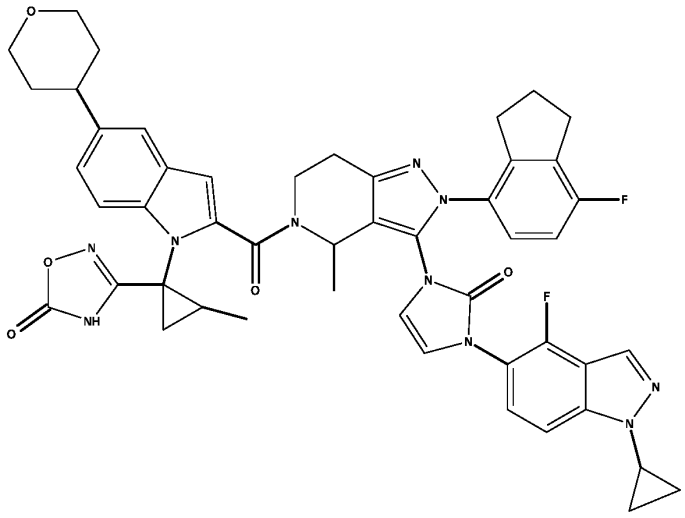
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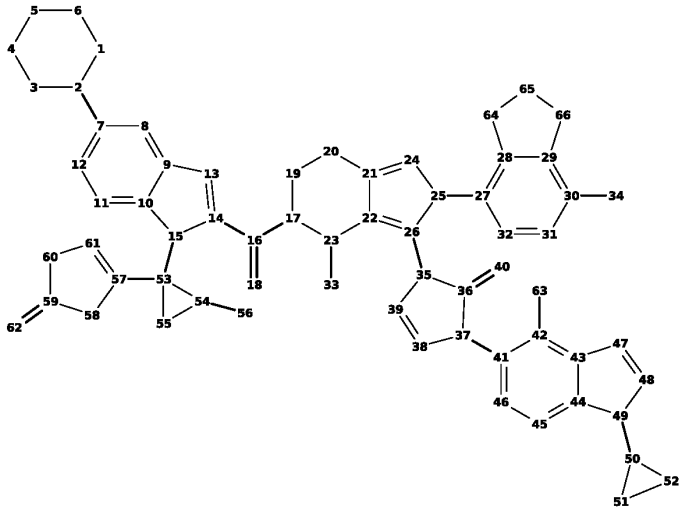
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SEARCH TIME: 00.00.01

L2            0 SEA SSS FUL L1

=>
Uploading structure file: 18885065 S2
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Node Attributes
Ring Nodes : 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 17 19 20 21
22 23 24 25 26 27 28 29 30 31 32 35 36 37 38 39 41 42 43 44
45 46 47 48 49 50 51 52 53 54 55 57 59 60 61 64 65 66
Chain Nodes : 16 18 33 34 40 56 62 63
Bond Attributes
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12-7 13-14 14-15 15-10 17-19 19-20 20-21 21-22 21-24 22-23 23-17
24-25 25-26 26-22 27-28 28-29 28-64 29-30 30-31 31-32 32-27 35-36
36-37 37-38 38-39 39-35 41-42 42-43 43-44 43-47 44-45 45-46 46-41
47-48 48-49 49-44 50-51 50-52 51-52 53-54 53-55 55-54 57-58 58-59
59-60 60-61 61-57 64-65 65-66 66-29
Chain Bonds : 2-7 14-16 15-53 16-17 16-18 23-33 25-27 26-35 30-34 36-40
37-41 42-63 49-50 53-57 54-56 59-62
Exact Bonds : 2-7 14-16 23-33 30-34 42-63 53-57 54-56
Normalized Bonds : 7-8 8-9 9-10 10-11 11-12 12-7 27-28 28-29 29-30
30-31 31-32 32-27 41-42 42-43 43-44 44-45 45-46 46-41
Exact/Normalized Bonds : 1-2 2-3 3-4 4-5 5-6 6-1 9-13 13-14 14-15 15-10
15-53 16-17 16-18 17-19 19-20 20-21 21-22 21-24 22-23 23-17 24-25
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39-35 43-47 47-48 48-49 49-44 49-50 50-51 50-52 51-52 53-54 53-55
55-54 57-58 58-59 59-60 59-62 60-61 61-57 64-65 65-66 66-29
Markush Attributes
Match Level (ATOM) : 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 17 19
20 21 22 23 24 25 26 27 28 29 30 31 32 35 36 37 38 39 41 42
43 44 45 46 47 48 49 50 51 52 53 54 55 57 58 59 60 61 64 65
66
Match Level (CLASS) : 16 18 33 34 40 56 62 63
Element Count Level (LIMITED) : 1 2 3 4 5 6 7 8 9 10 11 12 13 14
15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54
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L3 STRUCTURE UPLOADED

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L4             0 SEA SSS FUL L3

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Doc description: Information Disclosure Statement (IDS) Filed

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(Not for submission under 37 CFR 1.99)

Application Number	18885065
Filing Date	2024-09-13
First Named Inventor	Bin Liang
Art Unit	1693
Examiner Name	HOI YAN NMN LEE
Attorney Docket Number	HRT-030US1

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	2	10392357	B2	2019-08-27	ACADEMIA SINICA	

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	1	I495464	TW	B	2015-08-11	UNIV NAT TAIWAN		☐
	2	103694195	CN	B	2016-04-06	UNIV EAST CHINA NORMAL		☐

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	First Named Inventor	Bin Liang
	Art Unit	1693
	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

	3	201613883	TW	A	2016-04-16	NAT RES INST OF CHINESE MEDICINE MINISTRY OF HEALT		☐
	4	105622687	CN	B	2018-03-23	China Medical Research Institute		☐
	5	2017117556	WO	A1	2017-07-06	UNIV VANDERBILT		☐
	6	2017170826	WO	A1	2017-10-05	AJINOMOTO KK		☐
	7	2022241287	WO	A3	2022-12-29	CARMOT THERAPEUTICS INC		☐
	8	2020110152	WO	A1	2020-06-04	GIRDHAR KHYATI		☐
	9	2020210582	WO	A1	2020-10-15	UNIV OF THE SCIENCES		☐
	10	2021044401	WO	A3	2021-04-22	UNITED ARAB EMIRATES UNIVERSITY		☐
	11	111548311	CN	B	2021-04-23	Shanxi Medical University		☐
	12	116323599	CN	A	2023-06-23	GASHUBLOOM BIOLOGICS INC		☐
	13	2023151575	WO	A1	2023-08-17	GASHERBRUM BIO INC		☐

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	Art Unit	1693
	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

	14	2023151574	WO	A1	2023-08-17	GASHERBRUM BIO INC		☐
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	16	2022127868	WO	A1	2022-06-23	UNIV HONG KONG CHINESE		☐
	17	114790160	CN	A	2022-07-26	UNIV SHANXI MEDICAL		☐
	18	115286550	CN	A	2022-11-04	UNIV SHANXI MEDICAL		☐
	19	2022246230	WO	A1	2022-11-24	ENERGESIS PHARMACEUTICALS INC		☐
	20	115536638	CN	A	2022-12-30	UNIV SHANGHAI JIAOTONG		☐
	21	2023106310	WO	A1	2023-06-15	SHIONOGI & CO		☐
	22	2023191408	WO	A1	2023-10-05	LG CHEMICAL LTD		☐
	23	117534668	CN	A	2024-02-09	BEIJING FUYUAN PHARMACEUTICAL CO LTD		☐
	24	116217522	CN	A	2023-06-06	GUANGDONG RAFFLES PHARMATECH CO LTD		☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	First Named Inventor	Bin Liang
	Art Unit	1693
	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

	25	116804013	CN	A	2023-09-26	WUHAN AIMO JIAHUA BIOTECHNOLOGY CO LTD		☐
	26	2022269439	WO	A1	2022-12-29	ILDONG PHARMACEUTICAL CO LTD		☐
	27	112451515	CN	A	2021-03-09	GUANGZHOU INST BIOMED & HEALTH		☐
	28	2024148104	WO	A1	2024-07-11	BIOAGE LABS INC		☐

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                                                     ENTRY          SESSION
FULL ESTIMATED COST                                   0.35             0.35

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DICTIONARY FILE UPDATES:  11 NOV 2024  HIGHEST RN 3060584-69-9

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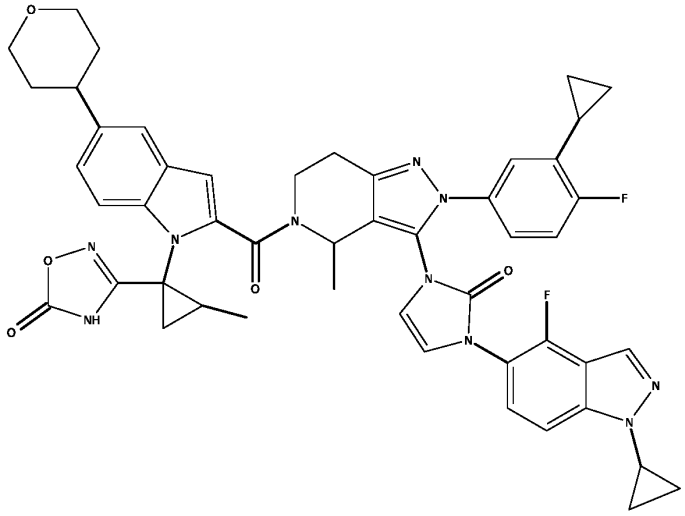
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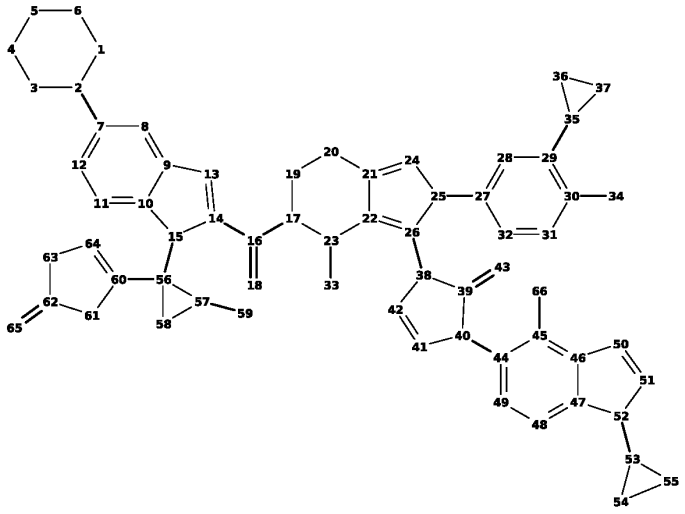
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experimental property data in the original document.  For information
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Node Attributes
Ring Nodes : 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 17 19 20 21
22 23 24 25 26 27 28 29 30 31 32 35 36 37 38 39 40 41 42 44
45 46 47 48 49 50 51 52 53 54 55 56 57 58 60 62 63 64
Chain Nodes : 16 18 33 34 43 59 65 66
Bond Attributes
Ring Bonds : 1-2 2-3 3-4 4-5 5-6 6-1 7-8 8-9 9-10 9-13 10-11 11-12
12-7 13-14 14-15 15-10 17-19 19-20 20-21 21-22 21-24 22-23 23-17
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60-61 61-62 62-63 63-64 64-60
Chain Bonds : 2-7 14-16 15-56 16-17 16-18 23-33 25-27 26-38 29-35 30-34

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39-43  40-44  45-66  52-53  56-60  57-59  62-65
Exact Bonds : 2-7  14-16  23-33  29-35  30-34  45-66  56-60  57-59
Normalized Bonds : 7-8  8-9  9-10  10-11  11-12  12-7  27-28  28-29  29-30
30-31  31-32  32-27  44-45  45-46  46-47  47-48  48-49  49-44
Exact/Normalized Bonds : 1-2  2-3  3-4  4-5  5-6  6-1  9-13  13-14  14-15  15-10
15-56  16-17  16-18  17-19  19-20  20-21  21-22  21-24  22-23  23-17  24-25
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56-57  56-58  58-57  60-61  61-62  62-63  62-65  63-64  64-60
Markush Attributes
Match Level (ATOM) : 1  2  3  4  5  6  7  8  9  10  11  12  13  14  15  17  19
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64
Match Level (CLASS) : 16  18  33  34  43  59  65  66
Element Count Level (LIMITED) : 1  2  3  4  5  6  7  8  9  10  11  12  13  14
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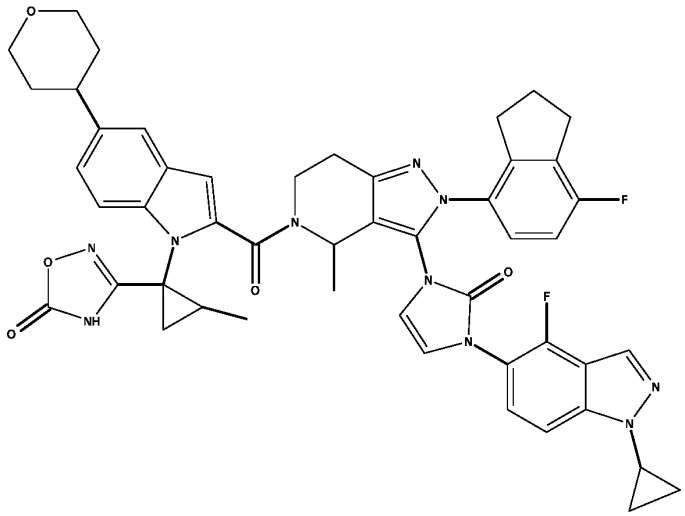
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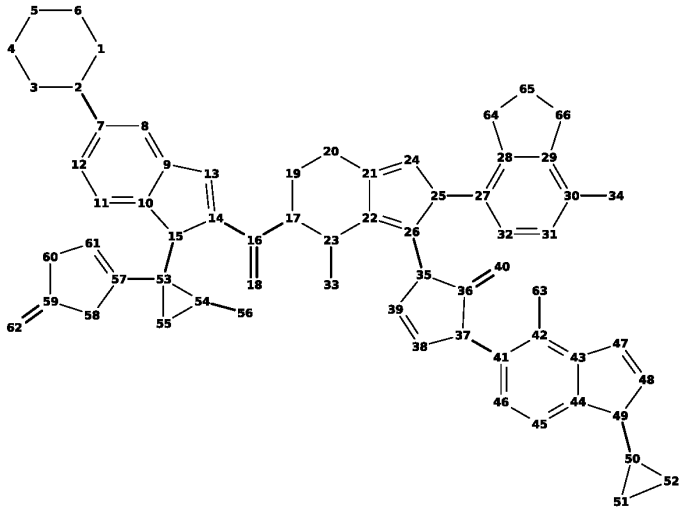
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FULL SCREEN SEARCH COMPLETED -      602 TO ITERATE

100.0% PROCESSED        602 ITERATIONS                                  0 ANSWERS
SEARCH TIME: 00.00.01

L2            0 SEA SSS FUL L1

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Node Attributes
Ring Nodes : 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 17 19 20 21
22 23 24 25 26 27 28 29 30 31 32 35 36 37 38 39 41 42 43 44
45 46 47 48 49 50 51 52 53 54 55 57 59 60 61 64 65 66
Chain Nodes : 16 18 33 34 40 56 62 63
Bond Attributes
Ring Bonds : 1-2 2-3 3-4 4-5 5-6 6-1 7-8 8-9 9-10 9-13 10-11 11-12
12-7 13-14 14-15 15-10 17-19 19-20 20-21 21-22 21-24 22-23 23-17
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Exact/Normalized Bonds : 1-2 2-3 3-4 4-5 5-6 6-1 9-13 13-14 14-15 15-10
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25-26 25-27 26-22 26-35 28-64 35-36 36-37 36-40 37-38 37-41 38-39
39-35 43-47 47-48 48-49 49-44 49-50 50-51 50-52 51-52 53-54 53-55
55-54 57-58 58-59 59-60 59-62 60-61 61-57 64-65 65-66 66-29
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66
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Element Count Level (LIMITED) : 1 2 3 4 5 6 7 8 9 10 11 12 13 14
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55 56 57 58 59 60 61 62 63 64 65 66

L3 STRUCTURE UPLOADED

=> S L3 SSS FULL

FULL SEARCH INITIATED 18:29:15
FULL SCREEN SEARCH COMPLETED - 602 TO ITERATE

100.0% PROCESSED 602 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

L4 0 SEA SSS FUL L3

=> FILE REGISTRY

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.35	0.35

FILE 'REGISTRY' ENTERED AT 11:07:15 ON 14 NOV 2024
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 13 NOV 2024 HIGHEST RN 3060885-98-2
DICTIONARY FILE UPDATES: 13 NOV 2024 HIGHEST RN 3060885-98-2

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy

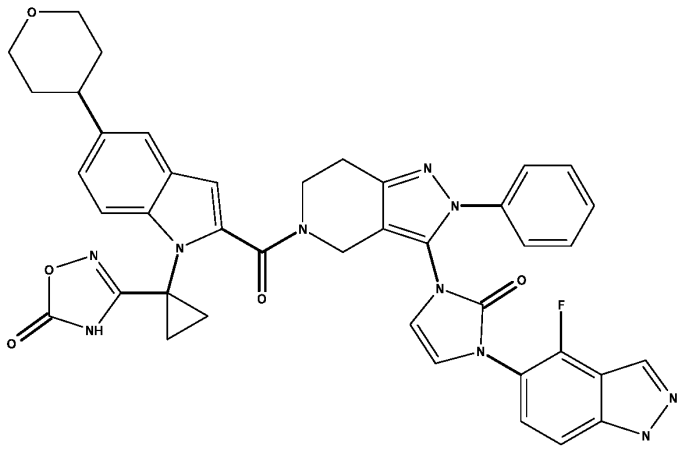
TSCA Inventory information is current through May 2024.

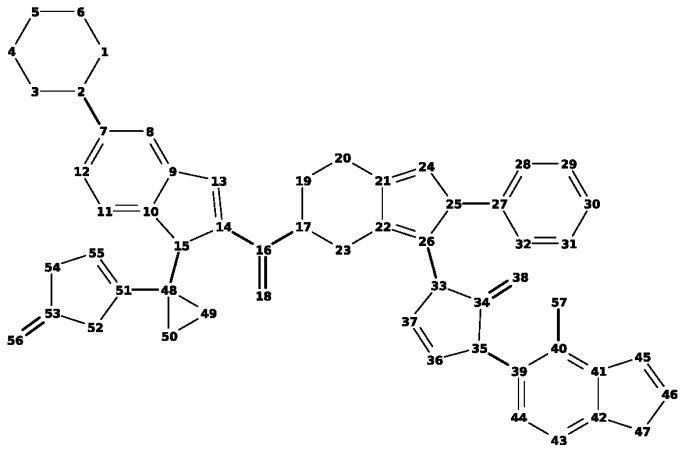
Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/training/stn/database-specific

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54-55  55-51
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Element Count Level (LIMITED) : 1  2  3  4  5  6  7  8  9  10  11  12  13  14
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55  56  57



L1      STRUCTURE UPLOADED

=> S L1 SSS FULL

FULL SEARCH INITIATED 11:07:53
FULL SCREEN SEARCH COMPLETED -      953 TO ITERATE

100.0% PROCESSED        953 ITERATIONS                              42 ANSWERS
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SEARCH TIME: 00.00.01

L2 42 SEA SSS FUL L1

=> FILE CAPLUS

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	883.16	883.51

FILE 'CAPLUS' ENTERED AT 11:07:59 ON 14 NOV 2024
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FILE LAST UPDATED: 13 Nov 2024 (20241113/ED)

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http://www.cas.org/legal/infopolicy

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> S L2

L3 38 L2

=> D L3 1-38 ABS BIB HITSTR

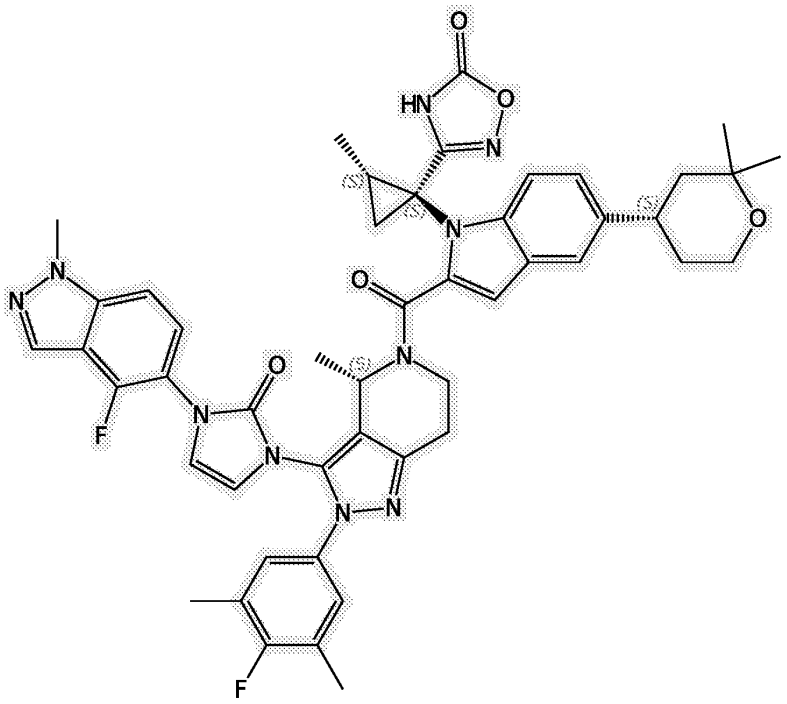
L3 ANSWER 1 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN
AB Disclosed herein are methods of inhibiting ketohexokinase (KHK) in a biol. sample or subject, and of treating or preventing diseases or disorders (e.g., diseases or disorders assocd. with KHK dysregulation), comprising administering to said biol. sample or subject an effective amt. of the title compd. or pharmaceutically acceptable salt thereof. E.g., a multi-step synthesis of 2-[4-[5-methyl-6-(trifluoromethyl)-2-[(2R)-2-(trifluoromethyl)azetidin-1-yl]pyrimidin-4-yl]pyrazol-1-yl]-1-piperazin-1-yl-ethanone, starting from 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]acetic acid and tert-Bu piperazine-1-carboxylate, was described. Exemplified compds. were evaluated for KHK inhibition (data given). Pharmaceutical compn. comprising the title compd. was disclosed.
AN 2024:2237809 CAPLUS Full-text
DN 188:281350
TI Preparation of disubstituted pyrimidine compounds for ketohexokinase inhibition
IN Whitlock, Gavin; Glossop, Paul; Rolph, Timothy P.; Tillman, Erik J.
PA Centennial Therapeutics, LLC, USA
UO CENTENNIAL THERAPEUTICS LLC
UOS CENTENNIAL THERAPEUTICS LLC
SO PCT Int. Appl., 97pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2024216034	A1	20241017	WO 2024-US24273	20240412
PRAI	US 2023-63495649	P	20230412		

PSPI

	PATENT NO.	KIND	STATUS	STATUS DATE
	WO 2024216034	A1	Alive	20241024

IT 2212020-52-3, Orforglipron
RL: SCLM (Substance claimed); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(co-drug; prepn. of disubstituted pyrimidine compds. for ketohexokinase inhibition)
RN 2212020-52-3 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
WO 2024216034 A1	WO 2024-US24273	Register|Global Dossier

L3 ANSWER 2 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN
AB Provided herein are combinations comprising a glucagon-like peptide-1 receptor (GLP-1R) agonist and a thyroid hormone receptor beta (THRβ) agonist and methods comprising administering to a subject in need thereof such combinations.
AN 2024:2168327 CAPLUS Full-text
DN 188:276645
TI Combination comprising a thyroid hormone receptor beta (THRβ) agonist and glucagon-like peptide-1 receptor (GLP-1R) agonist for use in treating a liver disorder or a cardiometabolic disease

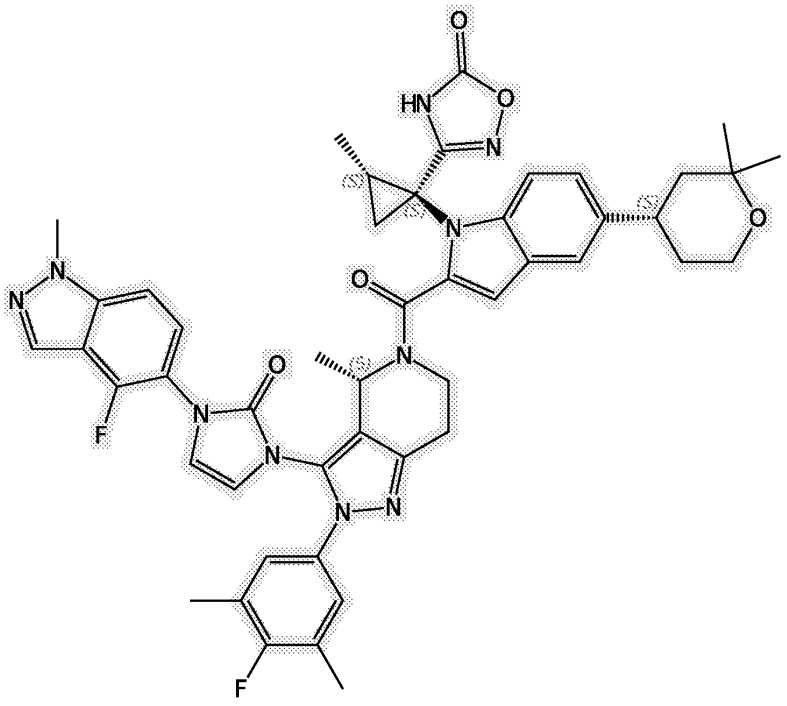
IN Teal, Olivia D.; Quinn, Kevin P.; Jones, Christopher T.; Jasper, Jeffrey R.
PA Terns Pharmaceuticals, Inc., USA
UO TERNS PHARMACEUTICALS INC
UOS Terns Pharmaceuticals
SO PCT Int. Appl., 384pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2024211898	A1	20241010	WO 2024-US23598	20240408
PRAI	US 2023-63495049	P	20230407		
	US 2023-63526362	P	20230712		
	US 2023-63615985	P	20231229		

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2024211898	A1	Alive	20241017

IT 2212020-52-3, Orforglipron
RL: PAC (Pharmacological activity); SCLM (Substance claimed); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination comprising a thyroid hormone receptor beta (THRβ) agonist and glucagon-like peptide-1 receptor (GLP-1R) agonist for use in treating a liver disorder or a cardiometabolic disease)
RN 2212020-52-3 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
WO 2024211898 A1	WO 2024-US23598	Register|Global Dossier

L3 ANSWER 3 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN

AB The present disclosure relates generally to glucagon-like peptide-1 (GLP-1) agonists and pharmaceutical compns. comprising the same, as well as methods for treating a GLP-1 assocd. disease, disorder, or condition.

AN 2024:1791823 CAPLUS Full-text

DN 188:66909

TI Preparation of tetrahydropyrazolopyridine derivatives as GLP-1 agonists

IN Huang, Wei; Lei, Hui; Lu, Chunliang; Zhang, Haizhen

PA Gasherbrum Bio, Inc., USA

UO STRUCTURE THERAPEUTICS INC

UOS Structure Therapeutics

SO PCT Int. Appl., 445pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2024169952	A1	20240822	WO 2024-CN77096	20240209
	US 20240327404	A1	20241003	US 2024-18628545	20240405
PRAI	WO 2023-CN76495	A	20230216		
	WO 2023-CN113565	A	20230817		
	WO 2023-CN141034	A	20231222		
	WO 2024-CN77096	A1	20240209		

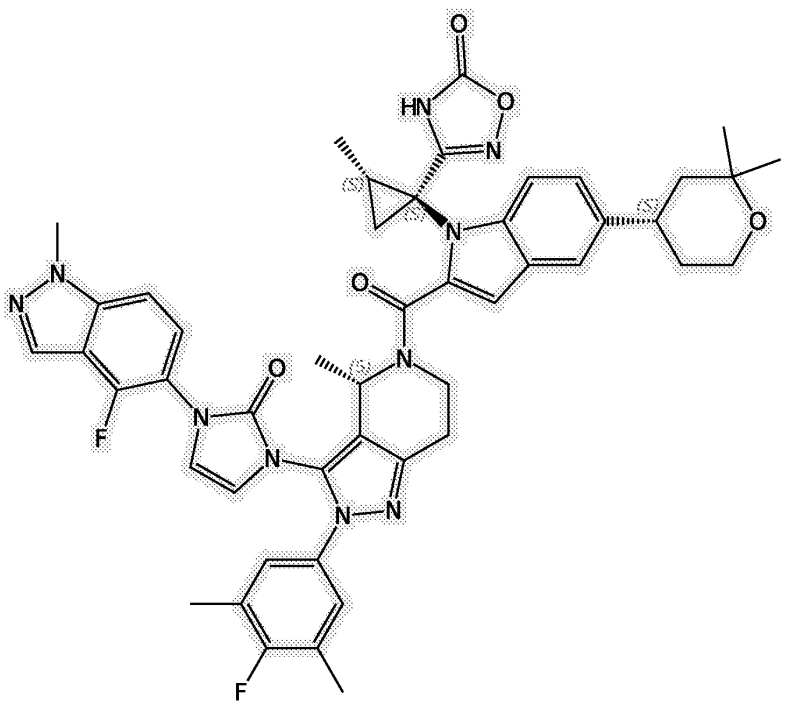
PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2024169952	A1	Alive	20240829
US 20240327404	A1	Transitional	20241024

IT 2212020-52-3 3054166-20-7
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of tetrahydropyrazolopyridine derivs. as GLP-1 agonists)

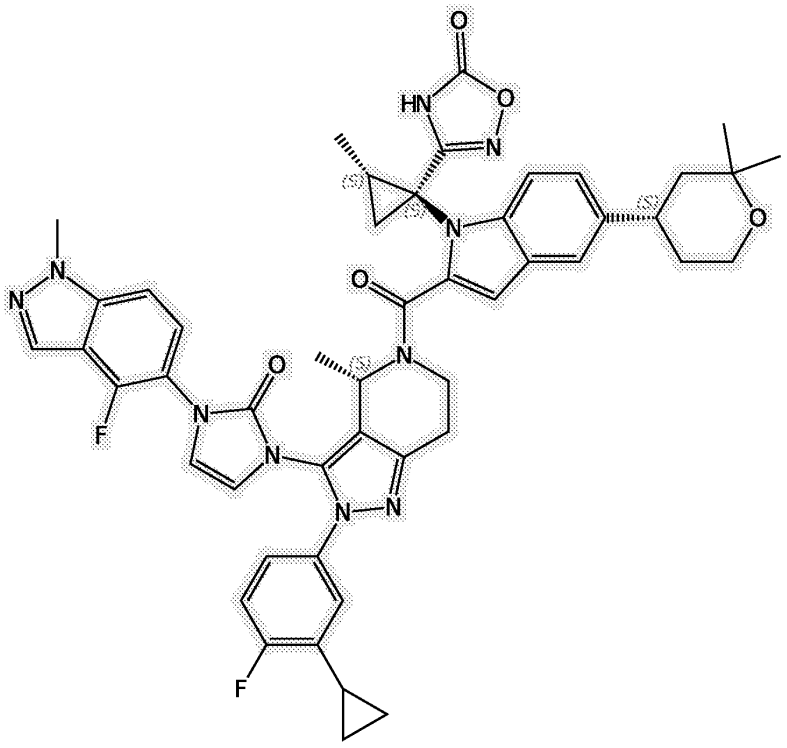
RN 2212020-52-3 CAPLUS

CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

RN 3054166-20-7 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(3-cyclopropyl-4-fluorophenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
US 20240327404 A1	US 2024-18628545	Register|Global Dossier
WO 2024169952 A1	WO 2024-CN77096	Register|Global Dossier

L3 ANSWER 4 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN

AB The present invention provides novel bisindolylmaleimide, indolylmaleimide, triphenylethylene and bisindolylpyrazolone compds. for use in methods of treating fat cell assocd. diseases such as obesity, liposarcoma, and polycystic ovary syndrome (PCOS) by targeting adipocytes to induce adipocyte hypertrophy while minimizing hERG blocker (QTc prolongation) activity. The fluoro substituted secondary amino analogs and prodrugs of the present invention are an effective approach by which properties of these compds. such as drug pharmacokinetics, pharmacodynamics and toxicol. can be modulated. The compds. of the present invention were screened for inhibiting hERG, PKCα, PKCβ1, and PKCβ2 to identify a series of selective PKCβ inhibitors which would shrink fat cells for treating cell assocd. diseases. Thus, tert-Bu 4-[3-(2-methoxy-2-oxoacetyl)indol-1-yl]piperidine-1-carboxylate was cyclocondensed with 2-(1-methylindol-3-yl)acetamide in the presence of potassium tert-butoxide in THF at 45° for 1 h under nitrogen to give 81.0% tert-Bu 4-[3-[4-(1-methylindol-3-yl)-2,5-dioxo-1H-pyrrol-3-yl]indol-1-yl]piperidine-1-carboxylate which was stirred in 4 M HCl/EtOAc at room temp. for 1 h under nitrogen to give 94% 3-(1-methylindol-3-yl)-4-[1-(piperidin-4-yl)indol-3-yl]-1H-pyrrole-2,5-dione hydrochloride (I). The compd. (I) was stirred with 2,2,2-trifluoroethyl trifluoromethanesulfonate in the presence of Et3N in DMF at 75° overnight to give 63.7% 3-(1-methylindol-3-yl)-4-[1-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]indol-3-yl]-1H-pyrrole-2,5-dione (II). The compd. (II) showed IC50 of >30,000, 79.4, 21.8, and 4.16 nM against hERG, PKCα, PKCβ1, and PKCβ2, resp., compared to 21, 0.74, 0.19, and 0.07 nM, resp., for ruboxistaurin (known PKCβ inhibitor).

AN 2024:1667110 CAPLUS Full-text
DN 187:300819
TI Preparation of 3,4-bis(1H-indol-3-yl)-1H-pyrrole-2,5-dione derivatives, macrocyclic derivatives thereof, and related compounds and methods and compositions for treatment of obesity and diseases associated with fat cell enlargement
IN Jagtap, Prakash; Pope, Benjamin D.; Basu, Madhumita; Glieberman, Aaron L.; Truex, Connor; Nnah, Prince
PA MelliCell, Inc., USA
UO MELLICELL
UOS MELLICELL
SO PCT Int. Appl., 112pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

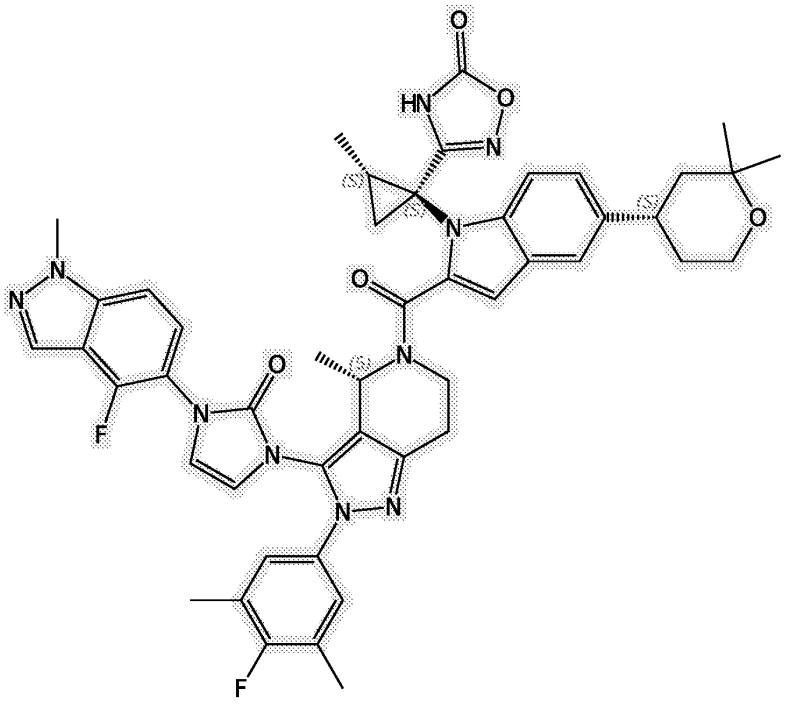
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2024159211	A1	20240802	WO 2024-US13317	20240129
PRAI	US 2023-63441716	P	20230127		

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2024159211	A1	Alive	20240815

OS CASREACT 187:300819
IT 2212020-52-3, Orforglipron
RL: PAC (Pharmacological activity); SCLM (Substance claimed); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use in combination chemotherapy; prepn. of bis(indolyl)pyrroledione derivs., macrocyclic derivs. thereof, and related compds. as inducers of adipocyte hypertrophy for treatment of fat cell assocd. diseases)
RN 2212020-52-3 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylp

henyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
WO 2024159211 A1	WO 2024-US13317	Register|Global Dossier

L3 ANSWER 5 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN

AB Described herein is N-[4-[4-(4-morpholinyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]-4-[[3(R)-[(1-oxo-2-propen-1-yl)amino]-1-piperidinyl]methyl]-2-pyridinecarboxamide (Compd. A) (Formula I), including cryst. forms, solvates, and pharmaceutically acceptable salts thereof. Also disclosed are pharmaceutical compns. or pharmaceutical formulations that include the compd., as well as methods of using the compd., alone or in combination with other therapeutic agents, for the treatment of autoimmune diseases or conditions, heteroimmune diseases or conditions, cancer, including lymphoma, diabetes, and inflammatory diseases or conditions.

AN 2024:1612998 CAPLUS Full-text

DN 187:267325

TI Crystalline forms of N-[4-[4-(4-Morpholinyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]-4-[[3(R)-[(1-oxo-2-propen-1-yl)amino]-1-piperidinyl]methyl]-2-pyridinecarboxamide as a covalent inhibitor of menin-MLL interaction

IN Puppali, Satish Goud; Palmer, James T.; Kirschberg, Thorsten A.; Wong, Angelina Sau Man; Li, Jay; Lin, Ming; Gao, Ming; Li, Shuang; Gu, Yuyao; He, Hongyan; Zheng, Bo; Zhou, Yanjing; You, Mei; Ding, Junlu; Qiu, Yihong; Tan, Heow Meng

PA Biomea Fusion, Inc., USA

UO BIOMEA FUSION, INC

UOS BIOMEA FUSION, INC

SO PCT Int. Appl., 187pp.
CODEN: PIXXD2

DT Patent

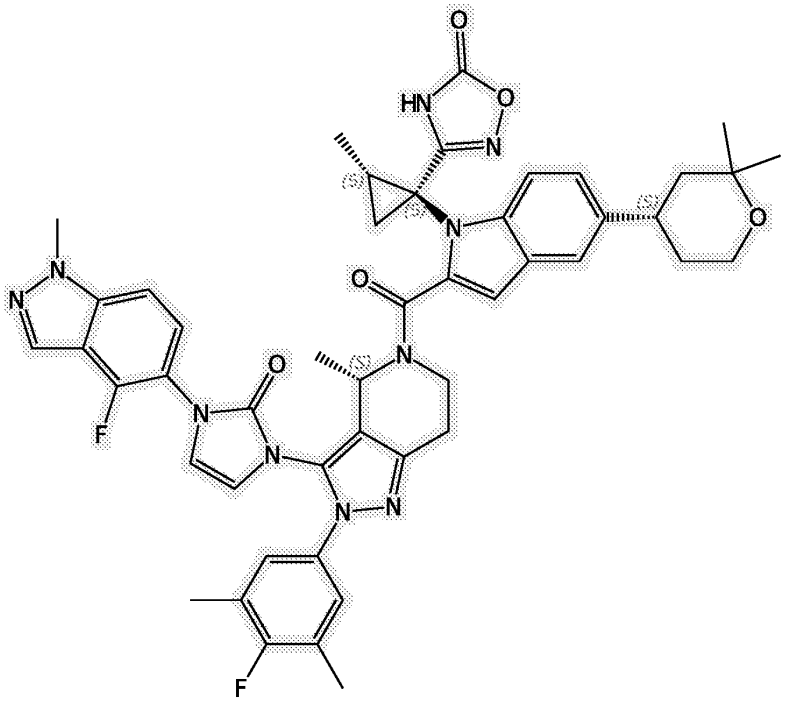
LA English
FAN.CNT 2
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	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2024155719	A1	20240725	WO 2024-US11848	20240117
	US 20240300950	A1	20240912	US 2024-18427226	20240130
PRAI	US 2023-63480443	P	20230118		
	US 2023-63483648	P	20230207		
	US 2023-63486405	P	20230222		
	US 2023-63492404	P	20230327		
	US 2023-63579754	P	20230830		
	WO 2024-US11848	A1	20240117		

PSPI

	PATENT NO.	KIND	STATUS	STATUS DATE
	WO 2024155719	A1	Alive	20240801
	US 20240300950	A1	Alive	20240919

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
IT 2212020-52-3, Orforglipron
RL: SCLM (Substance claimed); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cryst. forms of N-[4-[4-(4-Morpholinyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl]phenyl]-4-[[3(R)-[(1-oxo-2-propen-1-yl)amino]-1-piperidinyl]methyl]-2-pyridinecarboxamide as a covalent inhibitor of menin-MLL interaction)
RN 2212020-52-3 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
US 20240300950 A1	US 2024-18427226	Register|Global Dossier
WO 2024155719 A1	WO 2024-US11848	Register|Global Dossier

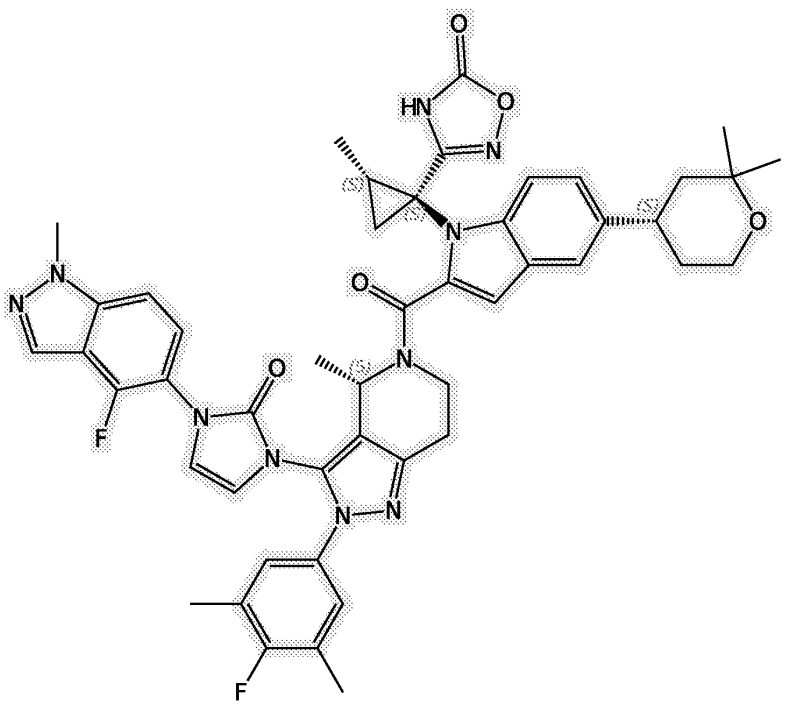
L3 ANSWER 6 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN
AB Described herein is N-[4-[4-(4-morpholinyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl
]phenyl]-4-[[3(R)-[(1-oxo-2-propen-1-yl)amino]-1-piperidinyl]methyl]-2-pyridinec
arboxamide (Compd. A) (Formula I), including cryst. forms,
    solvates, and pharmaceutically acceptable salts thereof. Also disclosed
    are pharmaceutical compns. or pharmaceutical formulations that include the
    compd., as well as methods of using the compd., alone or in combination
    with other therapeutic agents, for the treatment of autoimmune diseases or
    conditions, heteroimmune diseases or conditions, cancer, including
    lymphoma, diabetes, and inflammatory diseases or conditions.
AN 2024:1612964 CAPLUS Full-text
DN 187:241026
TI Crystalline forms of n-[4-[4-(4-morpholinyl)-7h-pyrrolo[2,3-d]pyrimidin-6-
    yl]phenyl]-4-[[3(r)-[(l-oxo-2-propen-1-yl)amino]-1-piperidinyl]methyl]-2-py
ridinecarboxamide and its therapeutic use
IN Puppali, Satish Goud; Palmer, James T.; Kirschberg, Thorsten A.; Wong,
    Angelina Sau Man; Tan, Heow Meng; Li, Jay; Lin, Ming; Gao, Ming; Ding,
    Junlu; Li, Shuang; Gu, Yuyao; He, Hongyan; Zheng, Bo; Zhou, Yanjing; You,
    Mei; Qiu, Yihong
PA Biomea Fusion, Inc., USA
UO BIOMEA FUSION, INC
UOS BIOMEA FUSION, INC
SO PCT Int. Appl., 405pp.
    CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2
PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2024155710	A1	20240725	WO 2024-US11830	20240117
PRAI	US 2023-63480443	P	20230118		
	US 2023-63483648	P	20230207		
	US 2023-63486405	P	20230222		
	US 2023-63492404	P	20230327		
	US 2023-63579754	P	20230830		

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2024155710	A1	Alive	20240801

IT 2212020-52-3, Orforglipron
    RL: PAC (Pharmacological activity); SCLM (Substance claimed); THU
    (Therapeutic use); BIOL (Biological study); USES (Uses)
       (cryst. forms of n-[4-[4-(4-morpholinyl)-7h-pyrrolo[2,3-d]pyrimidin-6-
       yl]phenyl]-4-[[3(r)-[(l-oxo-2-propen-1-yl)amino]-1-piperidinyl]methyl]-2
-pyridinecarboxamide and its therapeutic use)
RN 2212020-52-3 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylp
henyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-
yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)
-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]-
(CA INDEX NAME)



Absolute stereochemistry shown

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
WO 2024155710 A1	WO 2024-US11830	Register|Global Dossier

L3 ANSWER 7 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN

AB Provided are certain GLP-1R agonists of heterocyclic ketones, pharmaceutical compns. thereof, and methods of use thereof. The invention compds. were prepd. by given steps. All the invention compds. were evaluated for their GLP-1R inhibitory activity.

AN 2024:1603652 CAPLUS Full-text
DN 187:252375
TI Heterocyclic ketones as GLP-1R agonists and their preparation, pharmaceutical compositions and use in the treatment of diseases
IN Xu, Hua; Zhou, Chenglin; Zhao, Xingdong; Wang, Weibo
PA Fochon Biosciences, Ltd., Peop. Rep. China
UO SHANGHAI FOSUN PHARMACEUTICAL (GROUP) CO., LTD.
UOS Fosun Pharma
SO PCT Int. Appl., 73pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2024153070	A1	20240725	WO 2024-CN72529	20240116
PRAI	WO 2023-CN72748	A	20230117		
	WO 2023-CN85615	A	20230331		
	WO 2023-CN93742	A	20230512		

PSPI

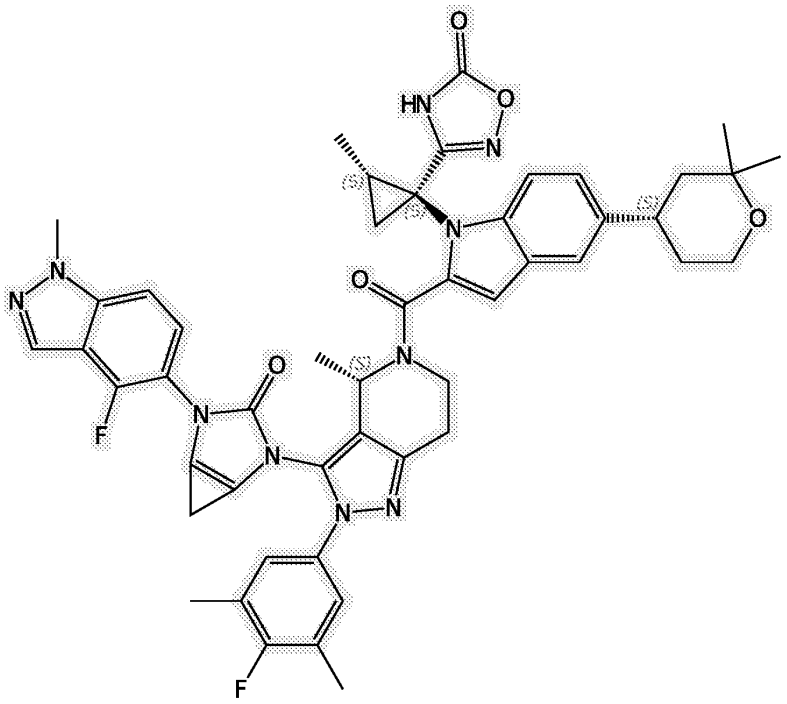
PATENT NO.	KIND	STATUS	STATUS DATE
WO 2024153070	A1	Alive	20240801

IT 3051607-21-4P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of heterocyclic ketones as GLP-1R agonists useful in the treatment of diseases)

RN 3051607-21-4 CAPLUS

CN INDEX NAME NOT YET ASSIGNED



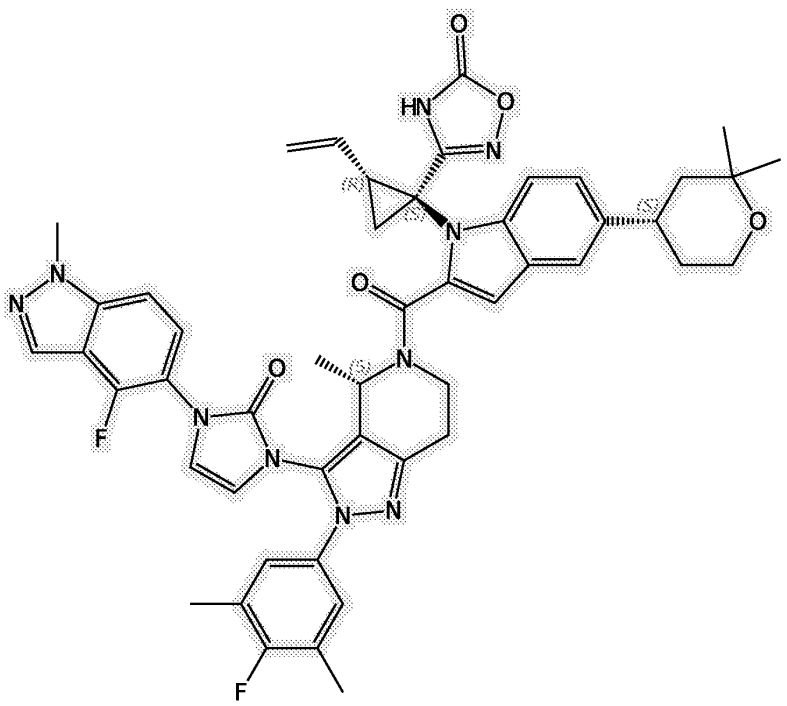
Absolute stereochemistry shown

IT 3051607-47-4P 3051607-50-9P 3051607-53-2P
3051607-59-8P 3051607-65-6P 3051607-68-9P
3051607-70-3P 3051607-72-5P 3051607-74-7P
3051607-77-0P

RL: PAC (Pharmacological activity); SCLM (Substance claimed); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of heterocyclic ketones as GLP-1R agonists useful in the treatment of diseases)

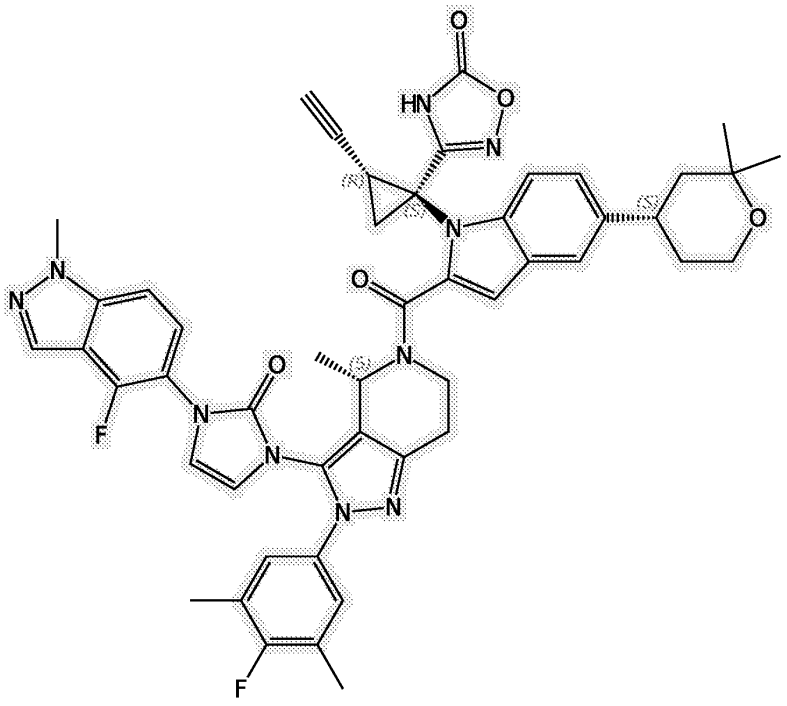
RN 3051607-47-4 CAPLUS

CN INDEX NAME NOT YET ASSIGNED



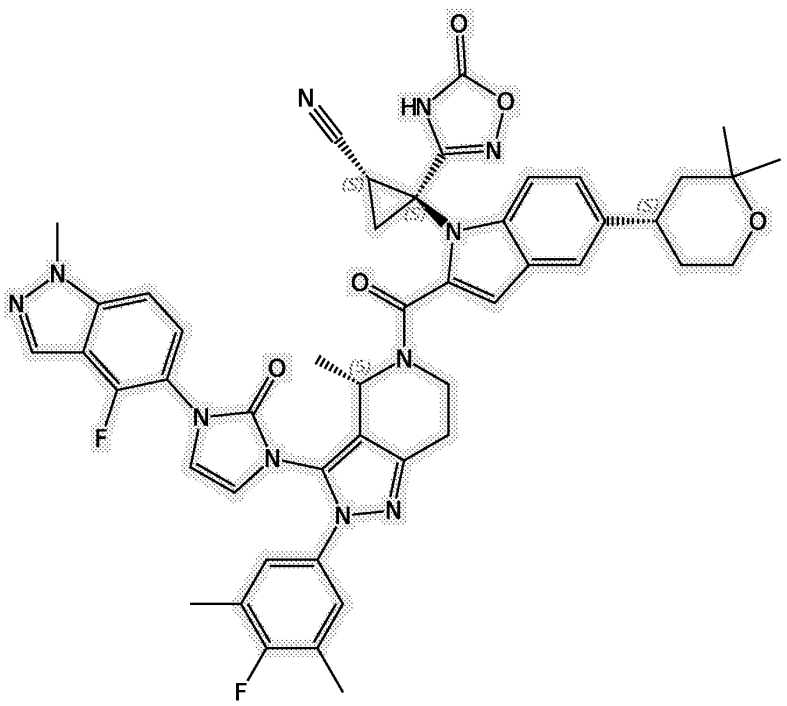
Absolute stereochemistry shown

RN 3051607-50-9 CAPLUS
CN INDEX NAME NOT YET ASSIGNED



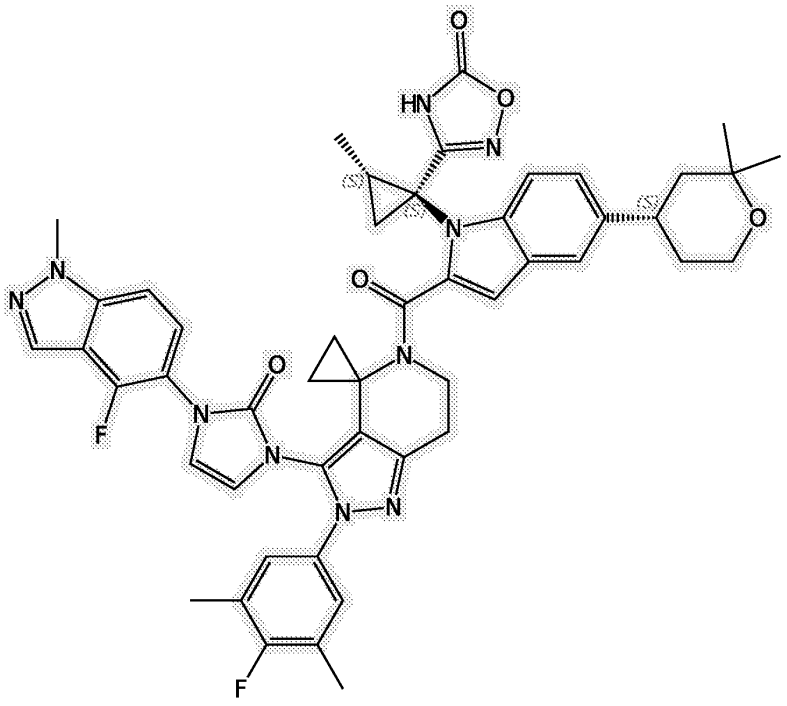
Absolute stereochemistry shown

RN 3051607-53-2 CAPLUS
CN INDEX NAME NOT YET ASSIGNED



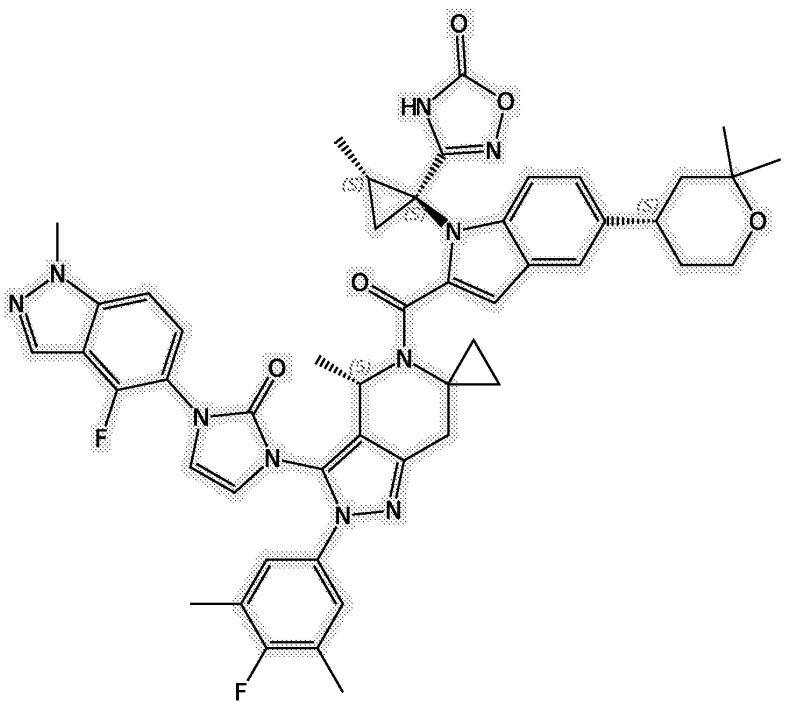
Absolute stereochemistry shown

RN 3051607-59-8 CAPLUS
CN INDEX NAME NOT YET ASSIGNED



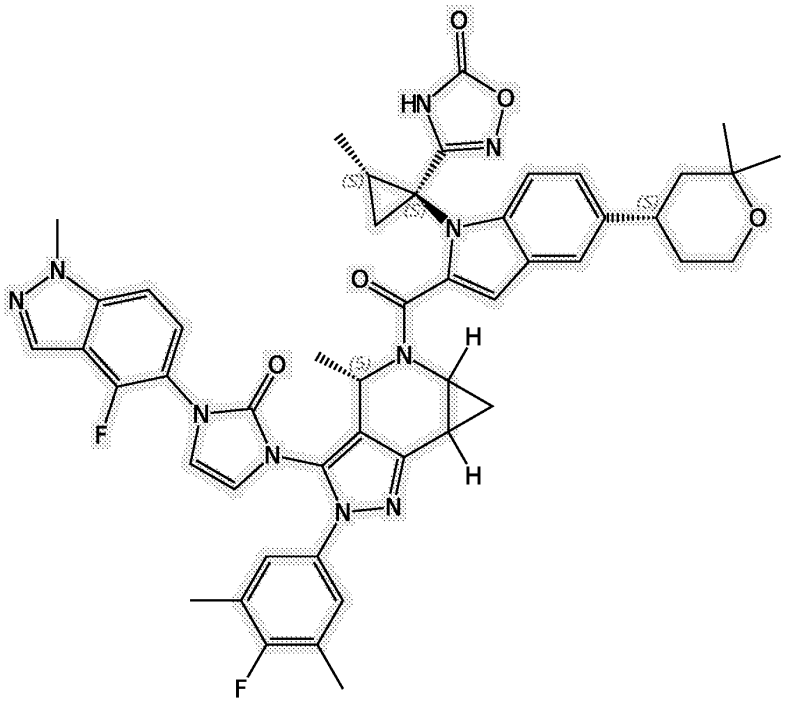
Absolute stereochemistry shown

RN 3051607-65-6 CAPLUS
CN INDEX NAME NOT YET ASSIGNED



Absolute stereochemistry shown

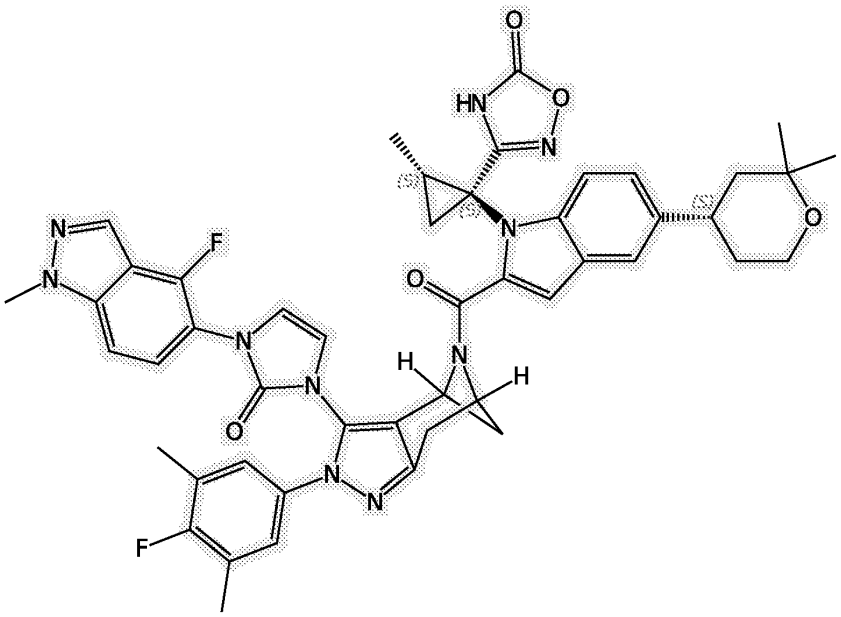
RN 3051607-68-9 CAPLUS
CN INDEX NAME NOT YET ASSIGNED



Absolute stereochemistry shown

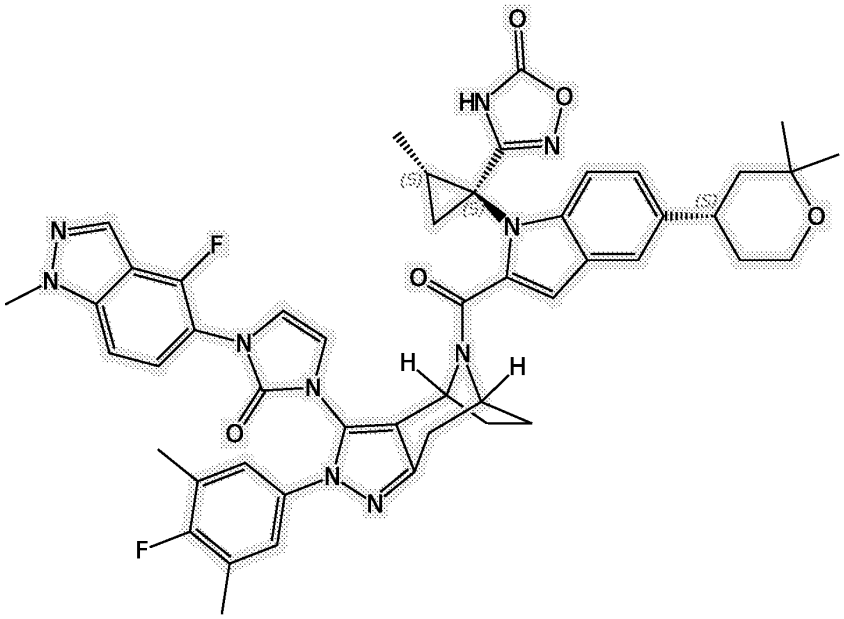
RN 3051607-70-3 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[2-(4-fluoro-3,5-dimethylphenyl

)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2
,4,6,7-tetrahydro-4,6-methano-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-t
etrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA
INDEX NAME)



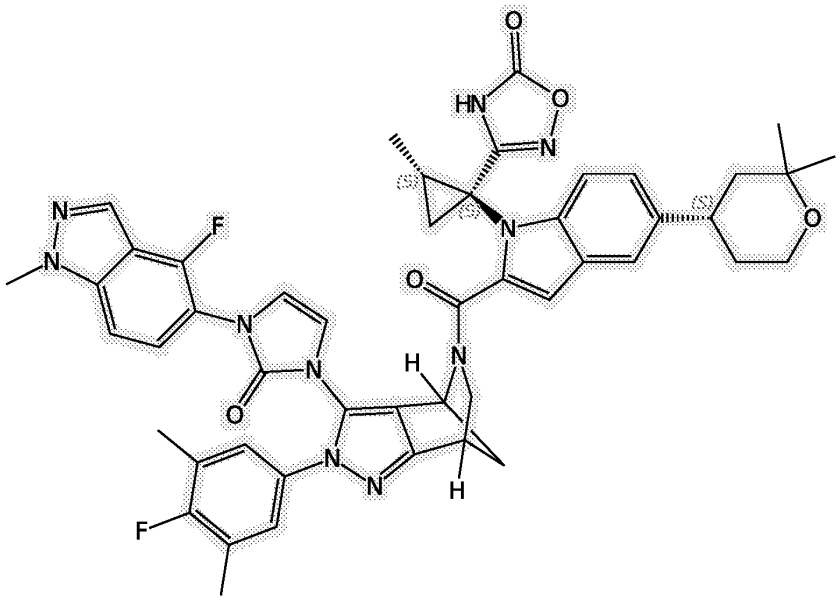
Absolute stereochemistry shown

RN   3051607-72-5 CAPLUS
CN   1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[2-(4-fluoro-3,5-dimethylphenyl
)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2
,4,5,6,7,8-hexahydro-4,7-iminocycloheptapyrazol-9-yl]carbonyl]-5-[(4S)-tetrahydr
o-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX
NAME)



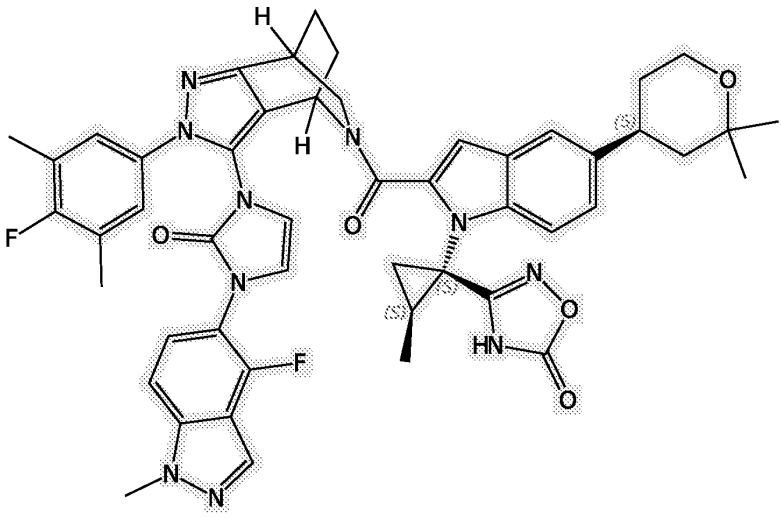
Absolute stereochemistry shown

RN 3051607-74-7 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4,7-methano-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

RN 3051607-77-0 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4,7-ethano-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

LINK INFORMATION
PUBLICATIONS APPLICATIONS REGISTER

WO 2024153070 A1	WO 2024-CN72529	Register|Global Dossier

L3 ANSWER 8 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN

AB This disclosure provides methods for treating a condition or disease assocd. with wt. gain that include coadministration of an apelin receptor agonist and a GLP-1 receptor agonist. Methods for increasing total wt. loss in the subject relative to wt. loss that would be caused by administration of a pre-detd. amt. of a GLP-1 receptor agonist alone are also provided. In some embodiments, the method is for preserving, or maintaining muscle mass, muscle function, and/or muscle strength in a subject undergoing wt. loss therapy.

AN 2024:1509645 CAPLUS Full-text

DN 187:224553

TI Combination therapy of apelin receptor agonist and GLP-1 receptor agonist for treating a disease or condition associated with weight gain

IN Fortney, Kristen Patricia; Morgen, Eric Kim; Rubin, Paul David; Pan, Yong; Wang, Yan; Leong, Peng Khun; Rebo, Justin

PA BioAge Labs, Inc., USA

UO BIOAGE LABS INC

UOS BIOAGE LABS INC

SO PCT Int. Appl., 347pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2024148104	A1	20240711	WO 2024-US10197	20240103
	US 20240366602	A1	20241107	US 2024-18754784	20240626
PRAI	US 2023-63478331	P	20230103		
	US 2023-63514113	P	20230717		
	US 2023-63517587	P	20230803		
	US 2023-63520332	P	20230817		
	US 2023-63520904	P	20230821		
	US 2023-63580336	P	20230901		
	WO 2024-US10197	A1	20240103		

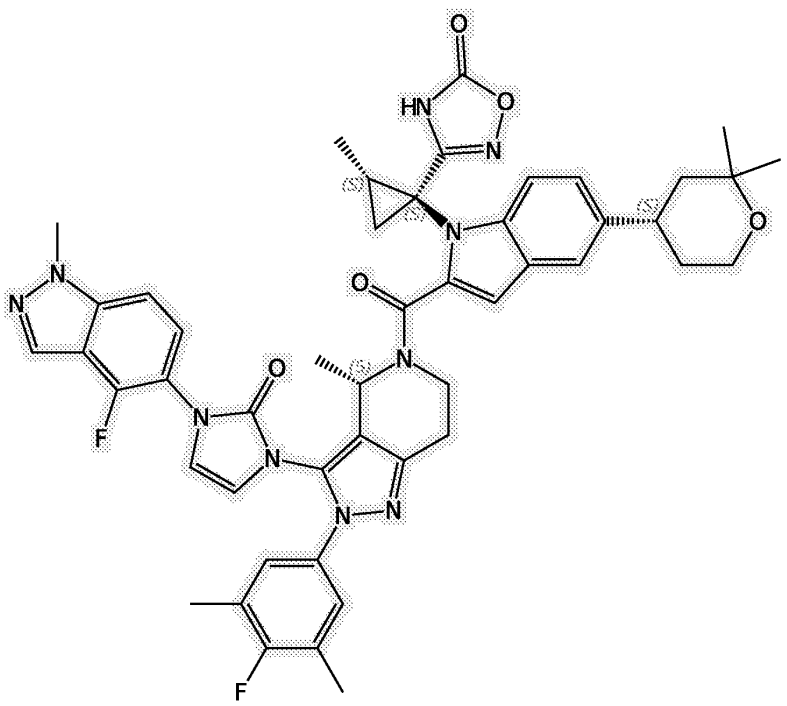
PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2024148104	A1	Alive	20240718

IT 2212020-52-3, Orforglipron 2415797-61-3, LY-3502970
RL: PAC (Pharmacological activity); SCLM (Substance claimed); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy of apelin receptor agonist and GLP-1 receptor agonist for treating a disease or condition assocd. with wt. gain)

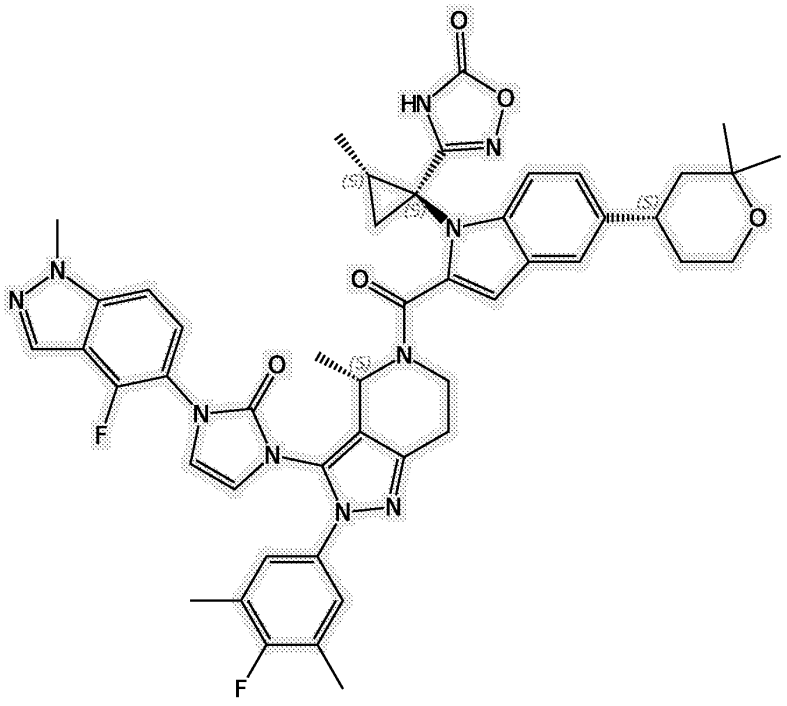
RN 2212020-52-3 CAPLUS

CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

RN 2415797-61-2 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]-, calcium salt (2:1) (CA INDEX NAME)



• 1/2 Ca

Absolute stereochemistry shown

RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
US 20240366602 A1	US 2024-18754784	Register|Global Dossier
WO 2024148104 A1	WO 2024-US10197	Register|Global Dossier

L3 ANSWER 9 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN

AB Cyclic peptides are attracting attention as therapeutic agents due to their potential for oral absorption and easy access to tough intracellular targets. LUNA18, a clin. KRAS inhibitor, was transformed-without scaffold hopping-from the initial hit by using an mRNA display library that met our criteria for drug-likeness. In drug discovery using mRNA display libraries, hit compds. always possess a site linked to an mRNA tag. Here, we describe our examn. of the Structure-Activity Relationship (SAR) using X-ray structures for chem. optimization near the site linked to the mRNA tag, equiv. to the C-terminus. Structural modifications near the C-terminus demonstrated a relatively wide range of tolerance for side chains. Furthermore, we show that a single atom modification is enough to change the pharmacokinetic (PK) profile. Since there are four positions where side chain modification is permissible in terms of activity, it is possible to flexibly adjust the pharmacokinetic profile by structurally optimizing the side chain. The side chain transformation findings demonstrated here may be generally applicable to hits obtained from mRNA display libraries.

AN 2024:1503832 CAPLUS Full-text

TI Structure-activity relationships of middle-size cyclic peptides, KRAS inhibitors derived from an mRNA display

AU Kage, Mirai; Hayashi, Ryuji; Matsuo, Atsushi; Tamiya, Minoru; Kuramoto, Shino; Ohara, Kazuhiro; Irie, Machiko; Chiyoda, Aya; Takano, Koji; Ito, Toshiya; Kotake, Tomoya; Takeyama, Ryuuichi; Ishikawa, Shiho; Nomura, Kenichi; Furuichi, Noriyuki; Morita, Yuya; Hashimoto, Satoshi; Kawada, Hatsuo; Nishimura, Yoshikazu; Nii, Keiji; Sase, Hitoshi; Ohta, Atsushi; Kojima, Tetsuo; Iikura, Hitoshi; Tanada, Mikimasa; Shiraishi, Takuya

CS 216, Totsuka-cho, Research Division, Chugai Pharmaceutical Co. Ltd., Yokohama, Kanagawa, 244-8602, Japan

SO Bioorganic & Medicinal Chemistry (2024), 110, 117830
CODEN: BMECEP; ISSN: 0968-0896

DOI 10.1016/j.bmc.2024.117830

PB Elsevier B.V.

DT Journal; (online computer file)

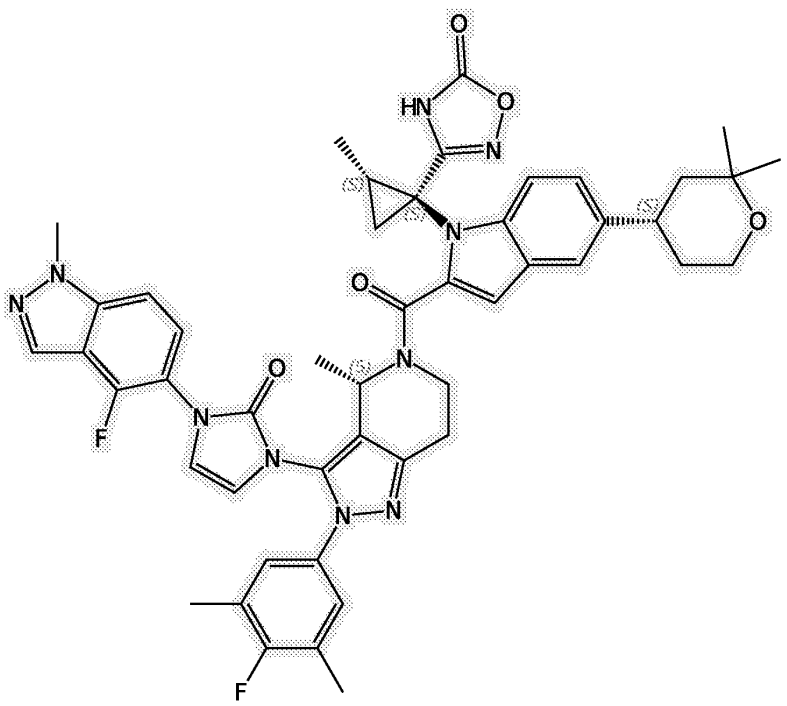
LA English

IT INDEXING IN PROGRESS

IT 2212020-52-3, orforglipron
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Structure-activity relationships of middle-size cyclic peptides, KRAS inhibitors derived from an mRNA display)

RN 2212020-52-3 CAPLUS

CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 10 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN

AB The present invention provides method for increasing the systemic bioavailability of a polypeptide therapeutic agent undergoing oral, orogastric, nasogastric, or intragastric administration, said method comprising administering said polypeptide therapeutic agent together with an alginate oligomer, and optionally a gastrointestinal permeation enhancer, to a stomach of a human or non-human animal as part of one or more dosage forms, wherein said one or more dosage forms do not carry a coating in addn. to the polypeptide therapeutic agent, the alginate oligomer, and the gastrointestinal permeation enhancer if used, which would provide substantive protection from a gastric environment. Such methods allow for systemic treatment or prevention of a disease or condition or complication thereof which is responsive to, or which is prevented by, a polypeptide therapeutic agent via oral, orogastric, nasogastric, or intragastric administration routes. Further provided are compns. for use in such methods comprising alginate oligomers, polypeptide therapeutic agents, and optionally gastrointestinal permeation enhancers.

AN 2024:1469695 CAPLUS Full-text
DN 187:208170

TI Compositions and methods to increase the systemic bioavailability of a polypeptide therapeutic agent undergoing oral administration

IN Rye, Philip Desmond; Aastrand, Ove Alexander Hoegmoen; Mikkelsen, Yngve
PA AlgiPharma AS, Norway; Rowe, Daniel
UO ROWE DANIEL; ALGIPHARMA AS
UOS ROWE DANIEL; ALGIPHARMA AS

SO PCT Int. Appl., 147pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2024141760	A1	20240704	WO 2023-GB53383	20231229
PRAI	GB 2022-19851	A	20221230		

GB 2023-4240 A 20230323

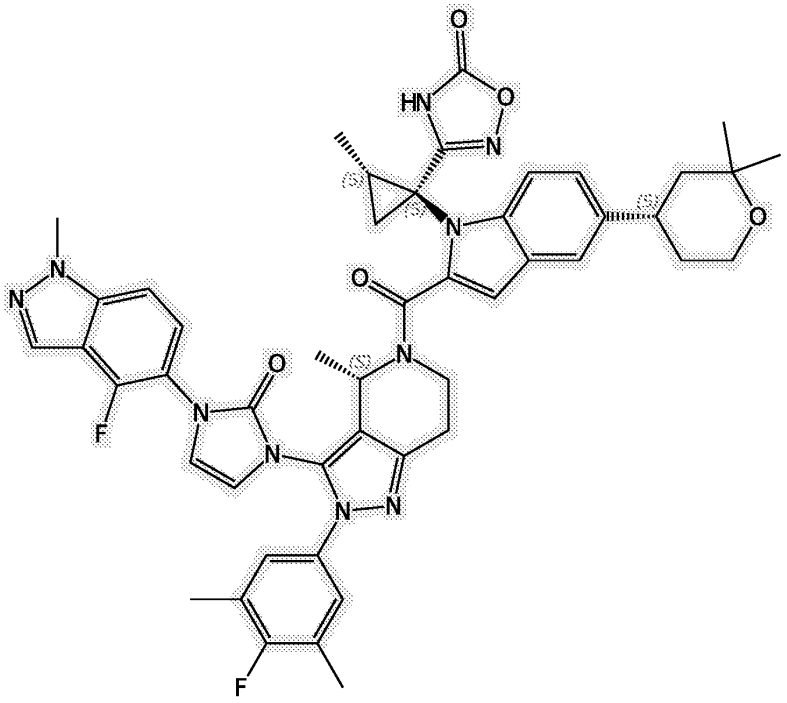
PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2024141760	A1	Alive	20240718

IT 2212020-52-3, LY3502970
RL: SCLM (Substance claimed); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. and methods to increase systemic bioavailability of polypeptide therapeutic agent undergoing oral administration)

RN 2212020-52-3 CAPLUS

CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
WO 2024141760 A1	WO 2023-GB53383	Register|Global Dossier

L3 ANSWER 11 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN

AB The present invention relates to the synthesis of 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one, or a salt thereof, and related synthetic intermediate compds.

AN 2024:1416023 CAPLUS Full-text

DN 187:158766

TI Process to make GLP1RA and intermediates therefor

IN Allian, Ayman D.; Berglund, Kenneth Derek; Cole, Kevin Paul; Davis, Ashlee Jeanette; Hess, Molly; Jemison, Adrianna; Kerr, Mark Steven; Mack, Audrey Grace; Ortiz-Medina, Xavier A.; Remick, David Michael; Starkey, Derek Robert; Vaid, Radhe Krishan; Yang, Qiang

PA Eli Lilly and Company, USA

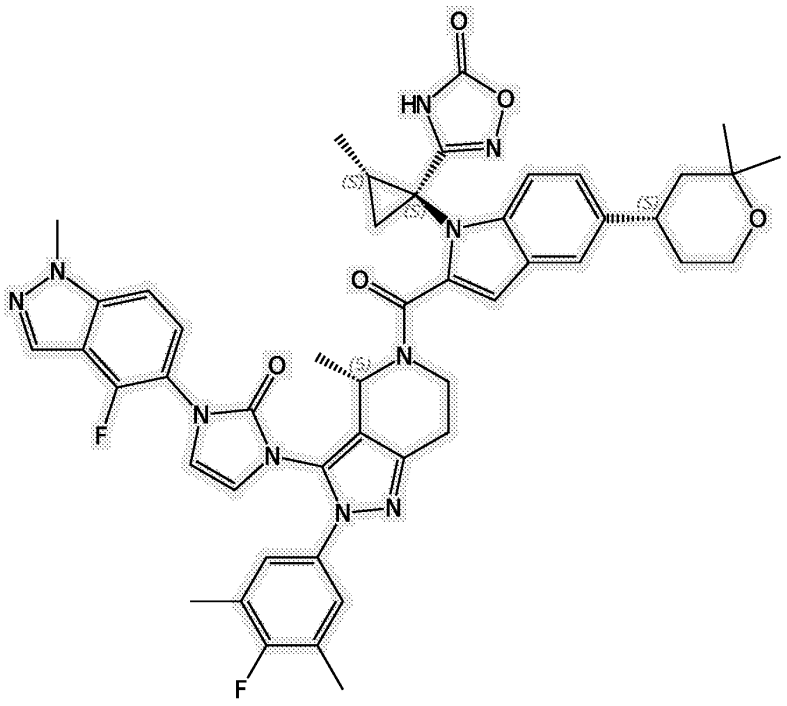
UO ELI LILLY & CO
UOS Eli Lilly
SO PCT Int. Appl., 74pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2024137426	A1	20240627	WO 2023-US84487	20231218
PRAI	US 2022-63433515	P	20221219		

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2024137426	A1	Alive	20240704

OS MARPAT 187:158766
IT 2415797-61-2P
RL: SCLM (Substance claimed); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(GLP1RA; process to make GLP1RA and intermediates therefor)
RN 2415797-61-2 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]-, calcium salt (2:1) (CA INDEX NAME)

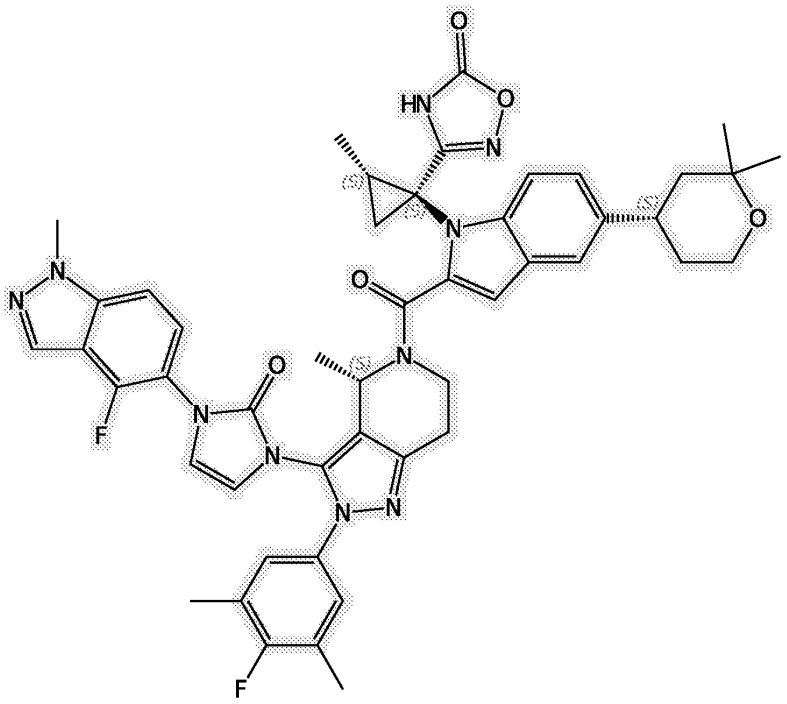


• 1/2 Ca

Absolute stereochemistry shown

IT 2212020-52-3P
RL: RCT (Reactant); SCLM (Substance claimed); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(process to make GLP1RA and intermediates therefor)
RN 2212020-52-3 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylp

henyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
WO 2024137426 A1	WO 2023-US84487	Register|Global Dossier

L3 ANSWER 12 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN

AB A review. Glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) have changed the landscape of type 2 diabetes (T2D) management due to their cardio-renal benefits, their glucose-lowering efficacy and wt. loss (WL) maintenance. However, the response to GLP-1 RA monotherapy is heterogeneous. Addnl., the majority of GLP-1 RAs are injectable treatments. Oral GLP-1 RAs and injectable combinations of GLP-1 with other entero-pancreatic hormones (glucose-dependent insulinotropic polypeptide (GIP), glucagon and amylin) are under development for T2D and obesity management. Areas coveredHerein, we review the data on (i) oral GLP-1 RAs (oral semaglutide 25/50 mg and orforglipron) and (ii) dual/triple agonists (tirzepatide, cagrilintide 2.4 mg/semaglutide 2.4 mg, survodutide, mazdutide, retatrutide) that have recently completed phase 3 trials for T2D or are currently in phase 3 clin. trials. Tirzepatide is the first approved dual agonist (GLP-1/GIP) for T2D and obesity management. Expert opinionWe are in a new era in T2D management where entero-pancreatic hormone-based treatments can result in ≥15% WL and euglycemia for many people with T2D. Multiple mols. with different mechanisms of action are under development for T2D, obesity and other metabolic complications. Data on their cardio-renal benefits, long-term efficacy and safety as well as their cost-effectiveness will better inform their position in treatment algorithms.

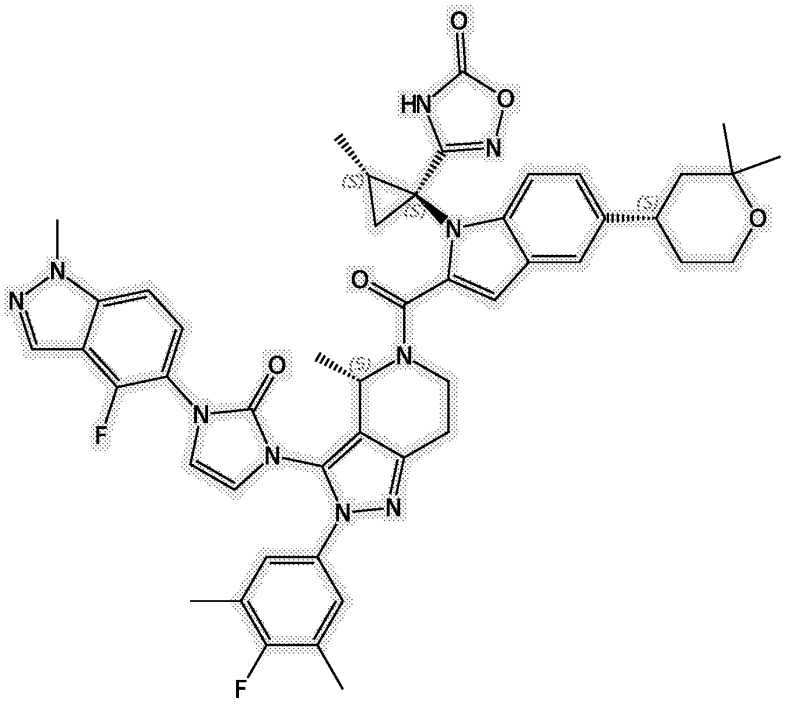
AN 2024:1370256 CAPLUS Full-text

DN 188:98545

TI Oral glucagon-like peptide-1 receptor agonists and combinations of entero-pancreatic hormones as treatments for adults with type 2 diabetes: where are we now?

AU Gogineni, Prathima; Melson, Eka; Papamargaritis, Dimitris; Davies, Melanie

CS Diabetes Research Centre, University of Leicester College of Life Sciences, Leicester, UK
SO Expert Opinion on Pharmacotherapy (2024), 25(7), 801-818
CODEN: EOPHF7; ISSN: 1465-6566
DOI 10.1080/14656566.2024.2356254
PB Taylor & Francis Ltd.
DT Journal; General Review; (online computer file)
LA English
IT 2212020-52-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(review on oral GLP-1RA and combinations of entero-pancreatic hormones as treatments for adults with type 2 diabetes)
RN 2212020-52-3 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

OSC.G 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
RE.CNT 101 THERE ARE 101 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 13 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN
AB The invention relates to a method for treating a subject with T2D, obesity, or overweight with at least one wt. related comorbidity using a glucagon-like peptide-1 (GLP-1) receptor non-peptide agonist (NPA) by oral administration, and the uses of the GLP-1 receptor NPA for the manuf. of a medicament for treating T2D, obesity, or overweight with at least one wt. related comorbidity.
AN 2024:1345182 CAPLUS Full-text
DN 187:129138
TI Composition containing orforglipron and method for treating subject with type 2 diabetes (T2D), obesity, or overweight with at least one weight related comorbidity
IN Bethel, Mary Angelyn; Cox, David Andrew; Keding, Stacy Jo; Konig, Manige; Liu, Rong; Ma, Xiaosu; Pratt, Edward John; Robins, Deborah Ann

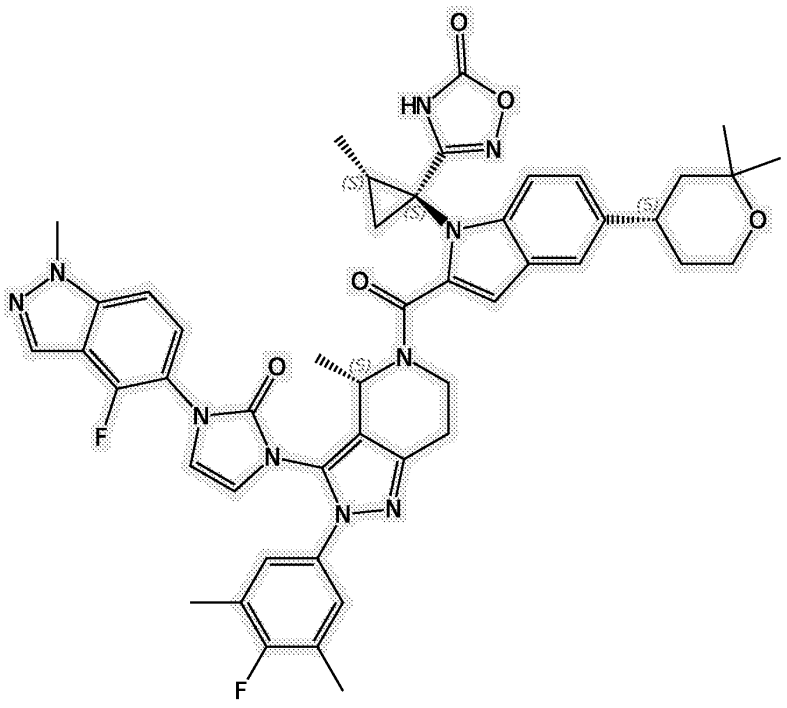
PA Eli Lilly and Company, USA
UO ELI LILLY & CO
UOS Eli Lilly
SO PCT Int. Appl., 95pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2024129676	A1	20240620	WO 2023-US83545	20231212
PRAI	US 2022-63432197	P	20221213		
	US 2023-63499328	P	20230501		

PSPI

	PATENT NO.	KIND	STATUS	STATUS DATE
	WO 2024129676	A1	Alive	20240627

IT 2212020-52-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compn. contg. orforglipron and method for treating subject with type 2 diabetes (T2D), obesity, or overweight with at least one wt. related comorbidity)
RN 2212020-52-3 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
WO 2024129676 A1	WO 2023-US83545	Register|Global Dossier

L3 ANSWER 14 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN
AB This present invention provides a pharmaceutical compn. comprising one or

more acyl-CoA cholesterol acyltransferase (ACAT) inhibitors and one or more Glucagon-like peptide-1 receptor agonists (GLP-1 RAs). It also provides a method for controlling body wt. comprising co-administering to a subject in need one or more ACAT inhibitors and one or more GLP-1RAs.

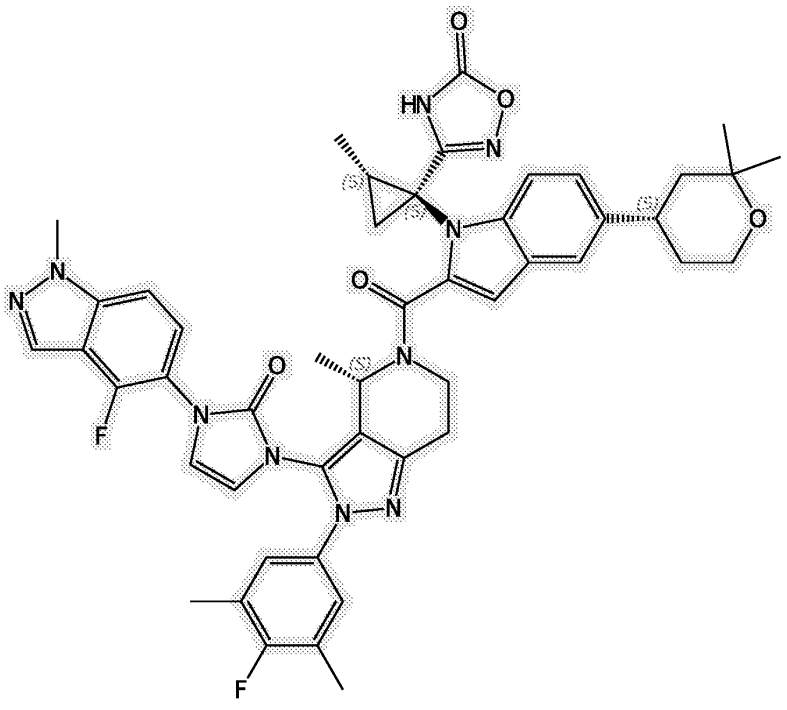
AN 2024:1002431 CAPLUS Full-text
DN 186:346310
TI Composition comprising GLP-1 receptor agonist and ACAT inhibitor for controlling body weight
IN Kim, Jeong-Hoon; Choi, Mu Lim; Kim, Kee-Hong
PA EFIL BioScience Inc., S. Korea; Purdue Research Foundation
UO EFIL BIOSCIENCE
UOS EFIL BIOSCIENCE
SO U.S. Pat. Appl. Publ., 12pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20240148833	A1	20240509	US 2023-18501740	20231103
WO 2024098005	A1	20240510	WO 2023-US78704	20231103
PRAI US 2022-63382287	P	20221103		

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
US 20240148833	A1	Alive	20240516
WO 2024098005	A1	Alive	20240516

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
IT 2212020-52-3, Orforglipron
RL: PAC (Pharmacological activity); SCLM (Substance claimed); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compn. comprising GLP-1 receptor agonist and ACAT inhibitor for controlling body wt.)
RN 2212020-52-3 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
US 20240148833 A1	US 2023-18501740	Register|Global Dossier
WO 2024098005 A1	WO 2023-US78704	Register|Global Dossier

L3 ANSWER 15 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN

AB The present invention relates to the prepn. of GLP-1 receptor agonist orforglipron. In particular, the prepn. comprises of following steps: (1) cyclizing dihydropyridine contg. different protective groups with (4-fluoro-3,5-dimethylphenyl)hydrazine and reacting at 0-120°C for 0-15h to obtain a key intermediate; (2) reacting product from step (1) with 2-isocyanato-1,1-dimethoxyethane at 20-150°C under alk. conditions to obtain tert-butylamino(fluorodimethylphenyl)pyrazolopyridinecarboxylate; (3) cyclizing the product from step (2) under acidic conditions and reacting at 10-140°C for 3-24 h to obtain tert-butyldimethoxyethylureido fluorodimethylphenylpyrazolo pyridinecarboxylate. Further, (4) reacting product from step (3) with 4-fluoro-1-methyl-1H-indazole at 90-120°C for 2-10 h via Buchwald coupling reaction to obtain fluorodimethyl phenyloxodihydroimidazolyl pyrazolopyridinecarboxylic acid tert Bu ester; (5) saltifying product from step (4) with hydrochloric acid and the amino protecting group is removed to obtain fluoromethyl indazoleyl fluorodimethylphenyl pyrazolopyridinyl dihydroimidazoleoxazolone hydrochloride; and (6) reacting product from step (5) with 5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indole-2-carboxylic acid at -40-50°C for 0-24h to obtain orforglipron.

AN 2024:949966 CAPLUS Full-text

DN 186:336228

TI Preparation of GLP-1 receptor agonist orforglipron

IN Liang, Yonghong; Huang, Jianyi

PA Shanghai Sunway Pharmaceutical Technology Co., Ltd., Peop. Rep. China

UO SHANGHAI XIANGHUI MEDICAL TECH

UOS SHANGHAI XIANGHUI MEDICAL TECH

SO Faming Zhuanli Shenqing, 9pp.
CODEN: CNXXEV

DT Patent

LA Chinese

FAN.CNT 1

PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	CN 117964617	A	20240503	CN 2023-11862364	20231229
PRAI	CN 2023-11862364		20231229		

PSPI

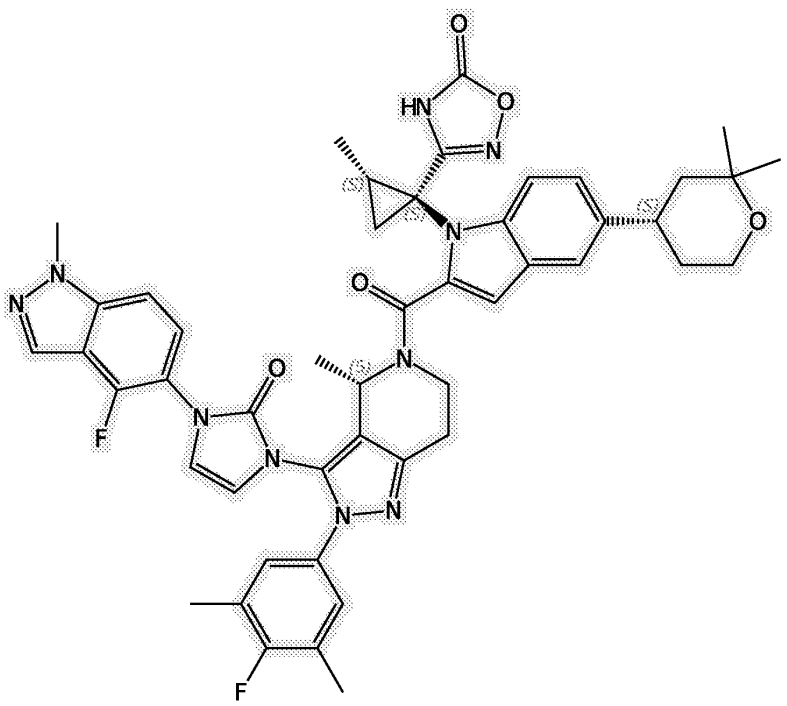
PATENT NO.	KIND	STATUS	STATUS DATE
CN 117964617	A	Alive	20240516

IT 2212020-52-3P

RL: SCLM (Substance claimed); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of GLP-1 receptor agonist orforglipron)

RN 2212020-52-3 CAPLUS

CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 117964617 A	CN 2023-11862364	Register|Global Dossier

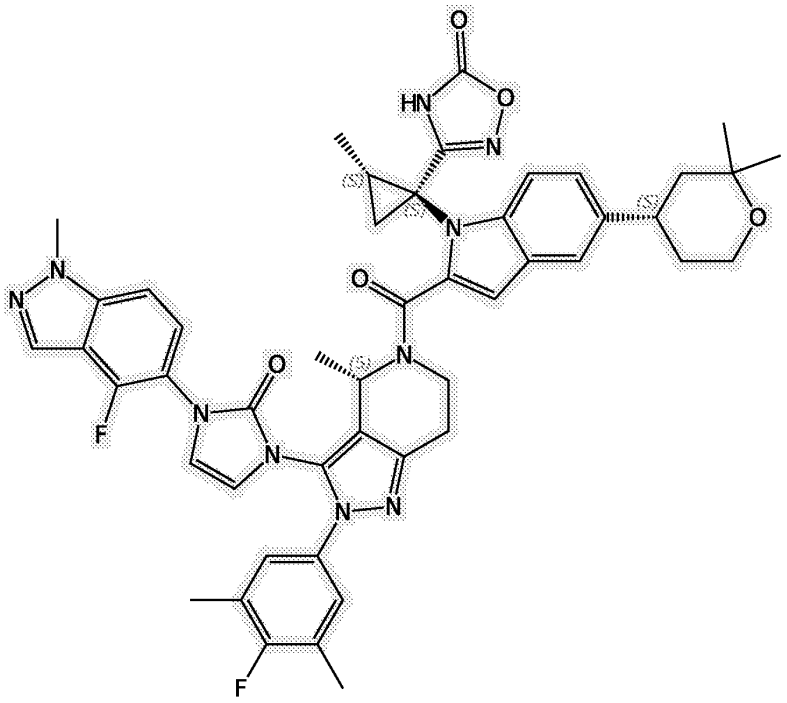
L3 ANSWER 16 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN

AB We assessed the effect of the prandial state on the pharmacokinetics, safety, and tolerability of single and multiple doses of orforglipron (LY3502970), an oral, non-peptide glucagon-like peptide 1 receptor agonist (GLP-1 RA), in two studies (A and B). Study A and study B were phase 1, randomized, crossover studies in healthy adults aged 18-65 years and 21-70 years, resp. Participants received single (3 mg, study A) or multiple (16 mg, study B) oral doses of orforglipron under fasted and fed conditions. Blood samples were collected pre- and postdose to assess area under the concn.-time curve (AUC), max. obsd. drug concn. (Cmax), time of Cmax (tmax), and half-life (t1/2) assocd. with terminal rate const. AUC and Cmax were analyzed using a linear mixed-effects model. Treatment differences were presented as ratios of geometric least squares means (GLSM). Treatment-emergent adverse events (TEAEs), adverse events of special interest, and serious adverse events were assessed. Study A included 12 participants (mean age 45.0 years; male 66.7%); study B included 34 participants (mean age 42.8 years; male 88.2%). GLSM AUC and Cmax were lower by 23.7% and 23.2% in study A, and 17.6% and 20.9% in study B, in the fed vs. fasted states, resp. In both studies, t1/2 and median tmax were comparable between fed and fasted states. The majority of TEAEs in both studies were gastrointestinal tract-related conditions. No serious adverse events or deaths were reported in either study. The obsd. pharmacokinetic differences due to the prandial state are unlikely to contribute to clin. meaningful differences in the efficacy of orforglipron. The safety profile was consistent with the known profiles of other GLP-1 RAs. Given the absence of prandial restrictions, orforglipron may emerge as a convenient oral treatment option for patients with type 2 diabetes or obesity.

AN 2024:473843 CAPLUS Full-text

TI Effect of Food Consumption on the Pharmacokinetics, Safety, and Tolerability of Once-Daily Orally Administered Orforglipron (LY3502970), a Non-peptide GLP-1 Receptor Agonist

AU Ma, Xiaosu; Liu, Rong; Pratt, Edward J.; Benson, Charles T.; Bhattachar, Shobha N.; Sloop, Kyle W.
CS Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN, 46240, USA
SO Diabetes Therapy (2024), 15(4), 819-832
CODEN: DTIHAP; ISSN: 1869-6961
DOI 10.1007/s13300-024-01554-1
PB Springer Healthcare Ltd.
DT Journal; (online computer file)
LA English
IT INDEXING IN PROGRESS
IT 2212020-52-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of food consumption on pharmacokinetics, safety, and tolerability of once-daily orally administered orforglipron (LY3502970), non-peptide GLP-1 receptor agonist)
RN 2212020-52-3 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



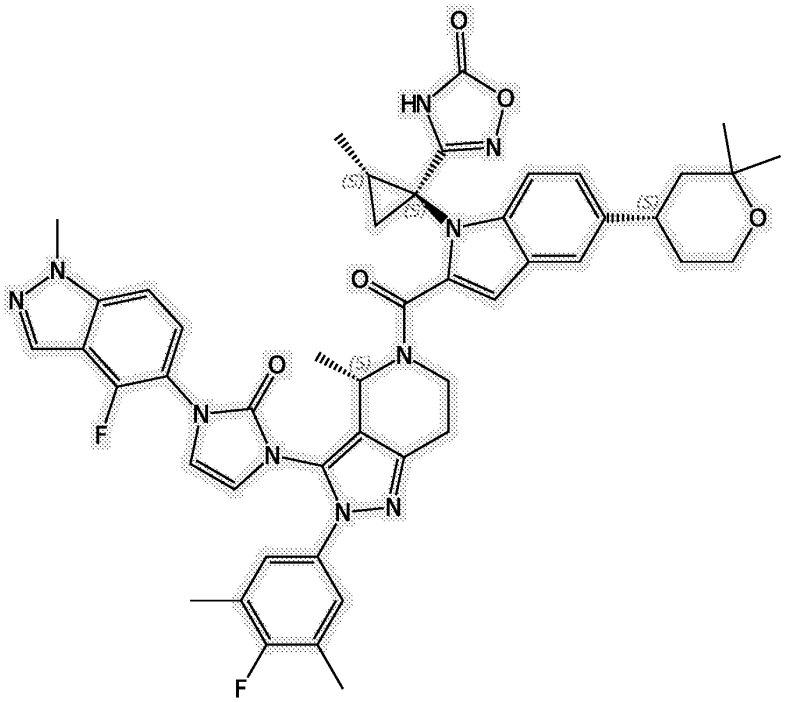
Absolute stereochemistry shown

RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 17 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN
AB GLP-1 receptor agonists (GLP-1RAs) reduce glucagon and glycogen secretion, inhibit appetite and slow gastric empties and have recently been approved to treat obesity. To explore the safety and efficacy of GLP-1RAs in the treatment of obesity and clarify the optimal GLP-1RAs treatment regimen. PubMed, Embase, Web of Science, and Cochrane Library databases were searched for English randomized controlled trials (RCTs) on GLP-1RAs in the treatment and management of obesity published before July 18, 2023. Literature screening and data extn. were performed independently by three researchers. Bayesian random effect model was used to compare the effects of interventions. Continuous variables were expressed as mean difference

with 95% CI, and dichotomous variables were reported as RR with 95% CI. A total of 29 studies with 10,333 participants were included in the present study. The combination of cagrilintide and semaglutide (short for cagrANDsema) was an optimal strategy for wt. loss and glycosylated Hb (HbA1c) redn. Compared to placebo, cagrANDsema reduced wt. by - 14.13 kg (95% CI: -16.49, -11.73) and HbA1c by - 0.33% (95% CI: -0.41, -0.25). Moreover, this study indicated that orforglipron and semaglutide also had relatively good effects on wt. loss. Meta-regression results indicated that higher dose levels might have better effects on wt. loss. CagrANDsema exerts the best effect for wt. loss. In terms of current dose levels, a higher dose gets better wt.-loss effects without increasing the risk of adverse events.

AN 2024:216555 CAPLUS Full-text
DN 186:316906
TI Efficacy and safety of GLP-1RAs for people with obesity: A systematic review based on RCT and Bayesian network meta-analysis
AU Li, Hong; Yu, Guanzheng; Huang, Qi; Yang, Bao; Nie, Juan; Liu, Yinbei; Tu, Xing
CS Chinese Medicinal Materials Products Quality Supervision and Inspection Center in Wuling Mountainous Area, Hubei Minzu University, Hubei, Peop. Rep. China
SO Biomedicine & Pharmacotherapy (2024), 171, 116150
CODEN: BIPHEX; ISSN: 0753-3322
DOI 10.1016/j.biopha.2024.116150
PB Elsevier Masson SAS
DT Journal; (online computer file)
LA English
IT 2212020-52-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(efficacy and safety of GLP1RAs for people with obesity)
RN 2212020-52-3 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

OSC.G 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
RE.CNT 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

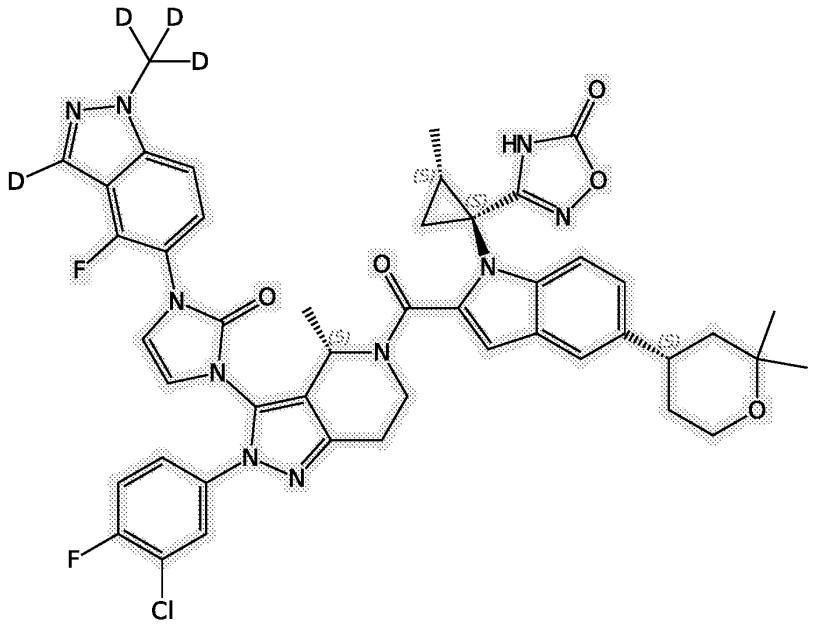
L3 ANSWER 18 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN
AB The present invention discloses compds. of formula I, or pharmaceutically acceptable salts, isomers, metabolites, prodrugs, solvates or hydrates thereof, pharmaceutical compns. and uses thereof. The compd. represented by formula I provided in the present invention can be used as GLP-1 receptor agonist for treating non-dependent diabetes mellitus, hyperglycemia, impaired glucose tolerance and insulin-dependent diabetes mellitus, obesity, complications of diabetes, hypertension, hyperlipidemia, atherosclerosis, coronary heart disease, cerebral infarction, non-alc. steatohepatitis, Parkinson's disease or dementia.
AN 2024:186541 CAPLUS Full-text
DN 186:239317
TI Deuterated indolizine compounds, pharmaceutical compositions and applications
IN Liu, Chunhe; Meng, Xiangjie; Guo, Binghua
PA Yaokang Zhongtuo (Beijing) Pharmaceutical Technology Co., Ltd., Peop. Rep. China
UO YAOKANG ZHONGTUO BEIJING PHARMACEUTICAL TECH
UOS YAOKANG ZHONGTUO BEIJING PHARMACEUTICAL TECH
SO Faming Zhuanli Shenqing, 12pp.
CODEN: CNXXEV
DT Patent
LA Chinese
FAN.CNT 1
PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	CN 117447493	A	20240126	CN 2023-11785556	20231225
PRAI	CN 2023-11785556		20231225		

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
CN 117447493	A	Alive	20240201

OS MARPAT 186:239317
IT 3034115-79-9P
RL: PAC (Pharmacological activity); SCLM (Substance claimed); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of deuterated indolizine deriv. and application as GLP-1 receptor agonist)
RN 3034115-79-9 CAPLUS
CN INDEX NAME NOT YET ASSIGNED



Absolute stereochemistry shown

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 117447493 A	CN 2023-11785556	Register|Global Dossier

L3 ANSWER 19 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN

AB The application relates to a substituted imidazole compd. or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, which modulates the activity of GLP-1 receptor, a pharmaceutical compn. comprising a substituted imidazole compd., and a method of treating or preventing a disease in which GLP-1 receptor plays a role. Example compd. was prepd. by a multistep procedure (procedure given). The invention compds. were evaluated for their GLP-1 receptor modulatory activity. From the assay, it was detd. that the compd. exhibited EC50 value of > 0 nM.

AN 2023:2460554 CAPLUS Full-text

DN 185:30523

TI Preparation of substituted imidazoles as GLP-1 receptor modulators

IN Ren, Zaifang; Sun, Xuefeng; Zhou, Jingye; Xu, Qing

PA Eccogene (Shanghai) Co., Ltd., Peop. Rep. China

UO ECCOGENE INC.

UOS ECCOGENE INC.

SO U.S., 249pp.
CODEN: USXXAM

DT Patent

LA English

FAN.CNT 2

PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	US 11584751	B1	20230221	US 2021-17516932	20211102
	US 20230051320	A1	20230216	US 2021-17380084	20210720
	US 12037339	B2	20240716		
PRAI	WO 2020-CN102955	A	20200720		
	WO 2021-CN70120	A	20210104		
	US 2021-17380084	A1	20210720		

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
US 11584751	B1	Alive	20230302

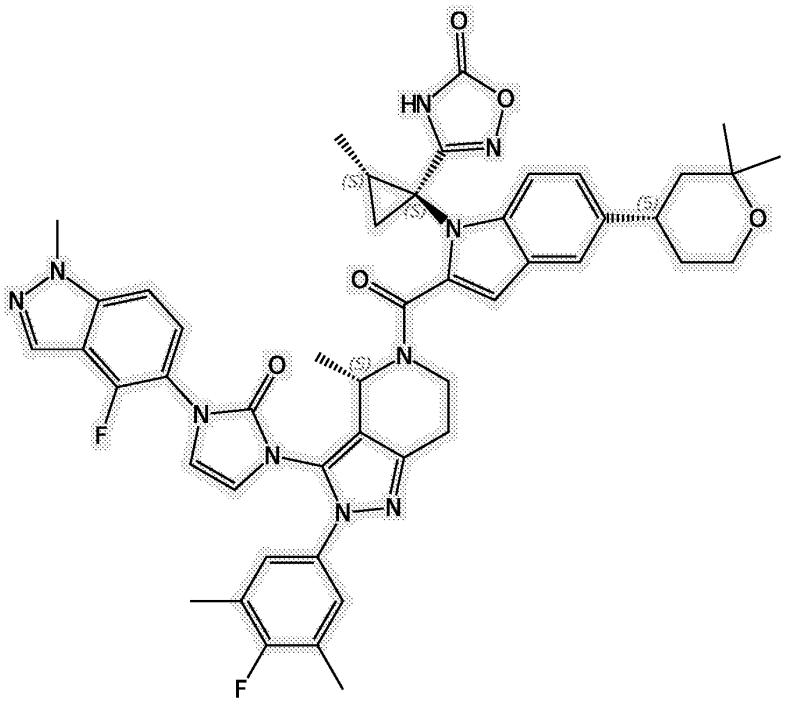
US 20230051320 A1 Alive 20230831
US 12037339 B2 Alive 20230831

OS CASREACT 185:30523; MARPAT 185:30523

IT 2212020-52-3
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of tetrahydropyrazolo-pyrazinyl-dihydroimidazolone and tetrahydropyrazolo-pyridinyl-dihydroimidazolone compds. as GLP-1 receptor modulators)

RN 2212020-52-3 CAPLUS

CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
US 12037339 B2	US 2021-17380084	Register|Global Dossier
US 20230051320 A1	US 2021-17380084	Register|Global Dossier
US 11584751 B1	US 2021-17516932	Register|Global Dossier

L3 ANSWER 20 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN

AB The invention relates to a tablet compn. comprising: spray dried dispersion (SDD) of 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one, or a pharmaceutically acceptable salt thereof; and a pH modifier, wherein the SDD also comprises a polymer to maintain an amorphous state.

AN 2023:2360096 CAPLUS Full-text

DN 184:347210

TI Pharmaceutical tablet composition containing glucagon-like peptide-1 for treating Type 2 diabetes mellitus

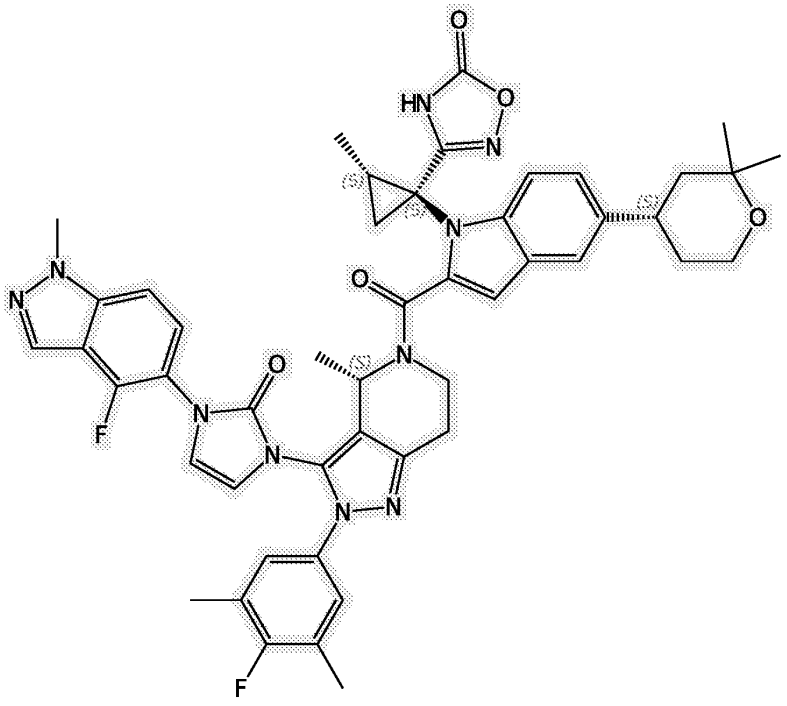
IN Aburub, Aktham; Allgeier, Matthew Carl; Hanson, Joshua M.; Huang, Siyuan
PA Eli Lilly and Company, USA
UO ELI LILLY & CO
UOS Eli Lilly
SO PCT Int. Appl., 65pp.
    CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2023220112	A1	20231116	WO 2023-US21641	20230510
PK 2023000288	A0	20230519	PK 2023-288	20230511

PRAI US 2022-63340595 P 20220511
PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2023220112	A1	Alive	20231123

OS CASFORMULTNS 2023:2360096
IT 2212020-52-3
    RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
       (pharmaceutical tablet compn. contg. glucagon-like peptide-1 for treating Type 2 diabetes mellitus)
RN 2212020-52-3 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
WO 2023220112 A1	WO 2023-US21641	Register|Global Dossier

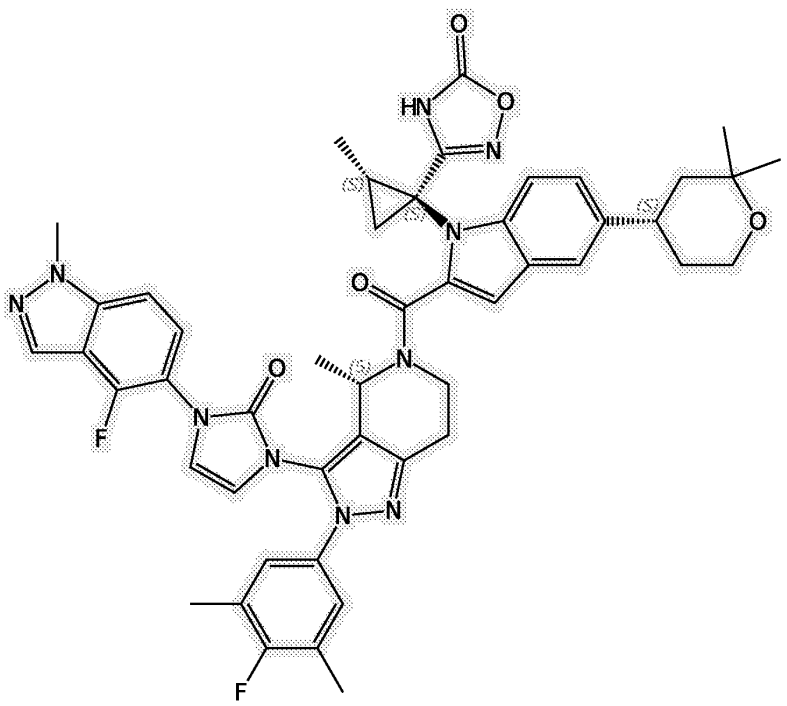
L3 ANSWER 21 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN
AB The present invention relates to an oral capsule compn. comprising 3-[(1S,2S)-1-[5-[(4S)-2,2-dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one,or a pharmaceutically acceptable salt thereof; and a pH modifier.
AN 2023:2360082 CAPLUS Full-text
DN 185:59037
TI Glp1 pharmaceutical compositions
IN Burns, Lee Joseph
PA Eli Lilly and Company, USA
UO ELI LILLY & CO
UOS Eli Lilly
SO PCT Int. Appl., 38pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2023220109	A1	20231116	WO 2023-US21637	20230510
	PK 2023000287	A0	20230519	PK 2023-287	20230511
PRAI	US 2022-63340591	P	20220511		

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2023220109	A1	Alive	20231123

OS CASFORMULTNS 2023:2360082
IT 3008544-96-2
RL: PRP (Properties); RCT (Reactant); SCLM (Substance claimed); RACT (Reactant or reagent)
(Glp1 pharmaceutical compns.)
RN 3008544-96-2 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]-, calcium salt, hydrate (2:1:2) (CA INDEX NAME)

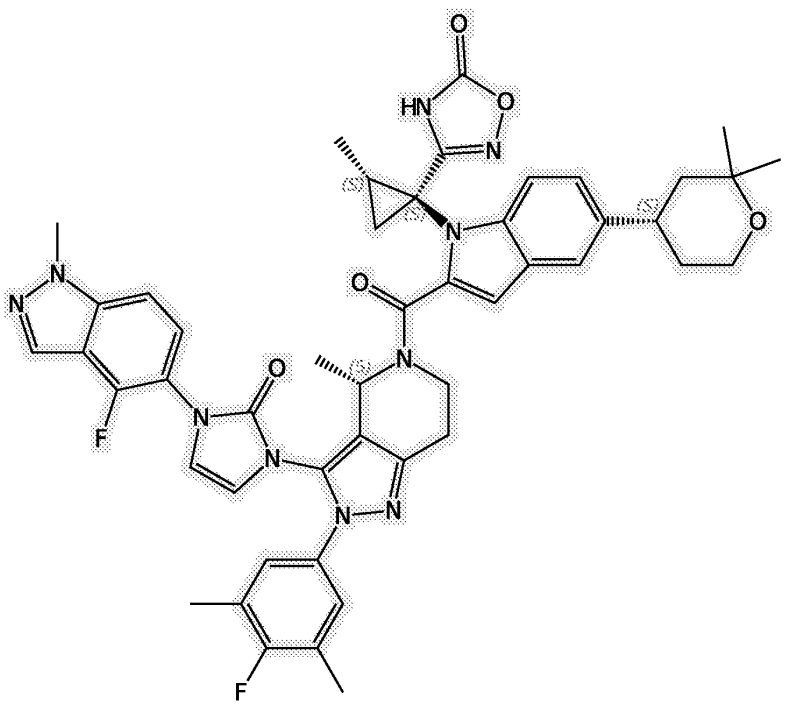


• 1/2 Ca

• H_2O

Absolute stereochemistry shown

IT 2212020-52-3P
RL: PRP (Properties); SCLM (Substance claimed); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(Glp1 pharmaceutical compns.)
RN 2212020-52-3 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
WO 2023220109 A1	WO 2023-US21637	Register|Global Dossier

L3 ANSWER 22 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN

AB The present systematic review aimed to synthesize available data from recently published randomized trials (RCTs) investigating the efficacy and safety of the novel, orally administered, small-mol. glucagon-like peptide 1 receptor agonists (GLP-1RAs) orforglipron and danuglipron for the treatment of type 2 diabetes mellitus (T2DM), obesity or both. Literature search was performed through Medline (via PubMed), Cochrane Library and Scopus until August 16, 2023. Double-independent study selection, data extn. and quality assessment were performed. Evidence was pooled with random effects meta-anal. Totally, 1037 patients among seven RCTs were analyzed. All RCTs had low risk of bias according to the Cochrane Collaboration tool (RoB2). Novel GLP-1RAs led to significant redn. in HbA1c in patients with T2DM compared to controls (MD = -1.03%; 95% CI = [-1.29, -0.77]; P < 0.001). A significantly greater wt. redn. was also noted both in patients with T2DM or obesity compared to controls (MD = -3.26 kg; 95% CI = [-4.79, -1.72]; P < 0.001 and MD = -7.52 kg; 95% CI = [-14.63, -0.41]; P = 0.038, resp.; P for subgroup differences = 0.25). Regarding safety, novel GLP-1RAs showed a neutral effect on the odds of severe hypoglycemia or serious adverse events (OR = 0.34; 95% CI = [0.09, 1.31]; P = 0.11 and OR = 0.95; 95% CI = [0.39, 2.34]; P = 0.91, resp.) and significantly higher odds of gastrointestinal, treatment-emergent adverse events (OR = 2.57; 95% CI = [1.49, 4.42]; P < 0.001) and adverse events leading to discontinuation (OR = 2.89; 95% CI = [1.22, 6.87]; P = 0.016). Preliminary evidence supports that orforglipron and danuglipron are efficient in glycemic control and wt. redn. in T2DM, obesity or both. More longitudinal research is warranted in order to provide deeper insights into their efficacy, safety and tolerability before their potential incorporation in the pharmacol. arsenal against T2DM or obesity.

AN 2023:2160033 CAPLUS Full-text

DN 184:327495

TI Safety and efficacy of the new, oral, small-molecule, GLP-1 receptor agonists orforglipron and danuglipron for the treatment of type 2 diabetes and obesity: systematic review and meta-analysis of randomized controlled trials

AU Karakasis, Paschalis; Patoulias, Dimitrios; Pamporis, Konstantinos; Stachteas, Panagiotis; Bougioukas, Konstantinos I.; Klisic, Aleksandra; Fragakis, Nikolaos; Rizzo, Manfredi

CS Second Department of Cardiology, Aristotle University of Thessaloniki, General Hospital Hippokration, Greece

SO Metabolism, Clinical and Experimental (2023), 149, 155710
CODEN: METAAJ; ISSN: 0026-0495

DOI 10.1016/j.metabol.2023.155710

PB Elsevier Inc.

DT Journal; (online computer file)

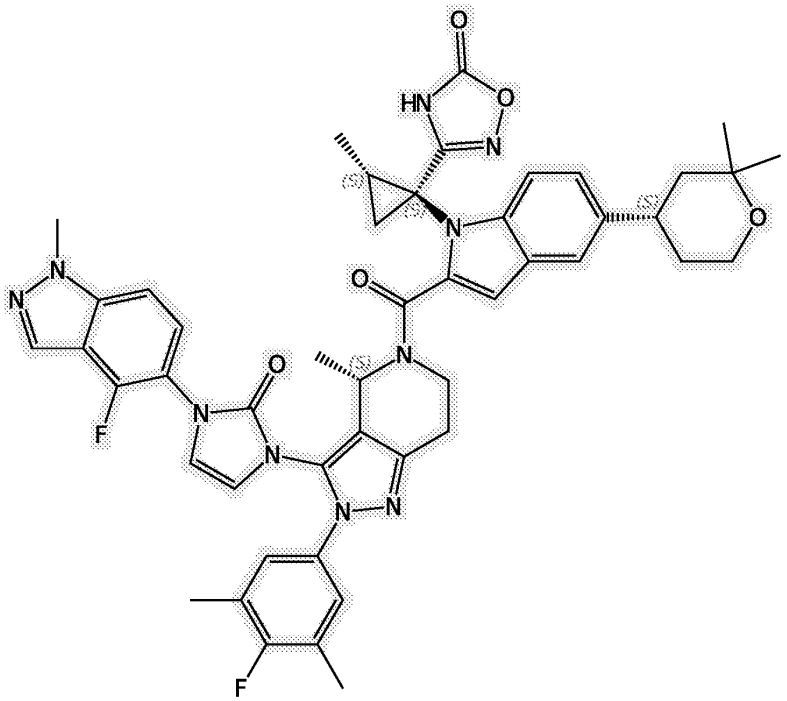
LA English

IT 2212020-52-3

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(safety and efficacy of the new, oral, small-mol., GLP-1 receptor agonists orforglipron and danuglipron for the treatment of type 2 diabetes and obesity)

RN 2212020-52-3 CAPLUS

CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

OSC.G 10 THERE ARE 10 CAPLUS RECORDS THAT CITE THIS RECORD (10 CITINGS)
RE.CNT 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 23 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN

AB Background Obesity is a major risk factor for many leading causes of illness and death worldwide. Data are needed regarding the efficacy and safety of the nonpeptide glucagon-like peptide-1 (GLP-1) receptor agonist orforglipron as a once-daily oral therapy for wt. redn. in adults with obesity. methods In this phase 2, randomized, double-blind trial, we

enrolled adults with obesity, or with overweight plus at least one wt.-related coexisting condition, and without diabetes. Participants were randomly assigned to receive orforglipron at one of four doses (12, 24, 36, or 45 mg) or placebo once daily for 36 wk. The percentage change from baseline in body wt. was assessed at week 26 (primary end point) and at week 36 (secondary end point). results A total of 272 participants underwent randomization. At baseline, the mean body wt. was 108.7 kg, and the mean body-mass index (the wt. in kilograms divided by the square of the height in meters) was 37.9. At week 26, the mean change from baseline in body wt. ranged from -8.6% to -12.6% across the orforglipron dose cohorts and was -2.0% in the placebo group. At week 36, the mean change ranged from -9.4% to -14.7% with orforglipron and was -2.3% with placebo. A wt. redn. of at least 10% by week 36 occurred in 46 to 75% of the participants who received orforglipron, as compared with 9% who received placebo. The use of orforglipron led to improvement in all prespecified wt.-related and cardiometabolic measures. The most common adverse events reported with orforglipron were gastrointestinal events, which were mild to moderate, occurred primarily during dose escalation, and led to discontinuation of orforglipron in 10 to 17% of participants across dose cohorts. The safety profile of orforglipron was consistent with that of the GLP-1 receptor agonist class. conclusions Daily oral orforglipron, a nonpeptide GLP-1 receptor agonist, was assocd. with wt. redn. Adverse events reported with orforglipron were similar to those with injectable GLP-1 receptor agonists.

AN 2023:1886467 CAPLUS Full-text

DN 184:241213

TI Daily oral GLP-1 receptor agonist orforglipron for adults with obesity

AU Wharton, Sean; Blevins, Thomas; Connery, Lisa; Rosenstock, Julio; Raha, Sohini; Liu, Rong; Ma, Xiaosu; Mather, Kieren J.; Haupt, Axel; Robins, Deborah; Pratt, Edward; Kazda, Christof; Konig, Manige

CS The GZGI Investigators, McMaster University, Toronto, ON, Can.

SO New England Journal of Medicine (2023), 389(10), 877-888
CODEN: NEJMAG; ISSN: 1533-4406
URL: http://www.nejm.org/medical-index

DOI 10.1056/nejmoa2302392

PB Massachusetts Medical Society

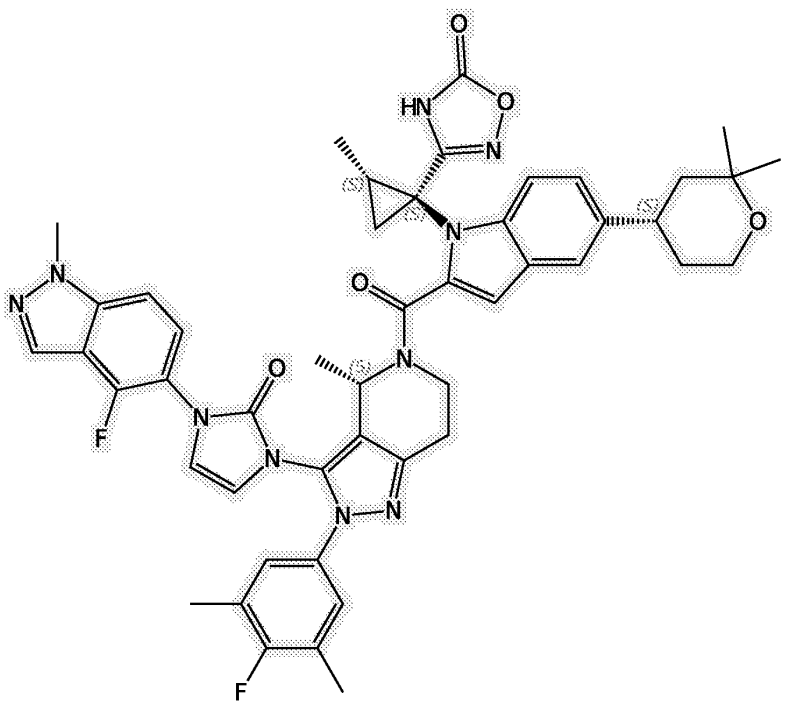
DT Journal; (online computer file)

LA English

IT 2212020-52-3
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(daily oral GLP-1 receptor agonist orforglipron for adults with obesity)

RN 2212020-52-3 CAPLUS

CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

OSC.G 43 THERE ARE 43 CAPLUS RECORDS THAT CITE THIS RECORD (44 CITINGS)
RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 24 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN
AB Orforglipron, an oral, non-peptide glucagon-like peptide-1 (GLP-1) receptor agonist, is in development for type 2 diabetes and obesity. We assessed the efficacy and safety of orforglipron vs. placebo or dulaglutide in participants with type 2 diabetes. In this 26-wk, phase 2, double-blind, randomised, multicentre study, participants were recruited from 45 centers (private clinics, hospitals, and research centers) in the USA, Hungary, Poland, and Slovakia. Adult participants aged 18 years or older with type 2 diabetes treated with diet and exercise, with or without metformin, and with a glycated Hb (HbA1c) of 7.0-10.5%, and stable BMI of 23 kg/m2 or more, were randomly assigned (5:5:5:5:5:3:3:3:3) via an interactive web-response system to placebo, dulaglutide 1.5 mg once per wk, or orforglipron 3 mg, 12 mg, 24 mg, 36 mg (group 1), 36 mg (group 2), 45 mg (group 1), or 45 mg (group 2) once per day with no food or water restrictions. Two different dose escalation regimens were evaluated for each of the 36 mg and 45 mg cohorts. Participants were masked to the study drug, dulaglutide, and placebo. The primary efficacy outcome The primary efficacy outcome was mean change in HbA1c from baseline with orforglipron vs. placebo at week 26. Efficacy was analyzed in all randomly assigned participants who received at least one dose of study drug and excluded data after the permanent discontinuation of study drug or initiation of rescue medication. Safety was analyzed in all participants who received at least one dose of study treatment. This trial is registered at ClinicalTrials.gov (NCT05048719) and is completed. Between Sept 15, 2021, and Sept 30, 2022, 569 participants were screened and 383 were enrolled and randomly assigned to a group. 352 (92%) completed the study and 303 (79%) completed 26 wk of treatment. At baseline, the mean age was 58.9 years, HbA1c was 8.1%, BMI was 35.2 kg/m2, 226 (59%) were men, and 157 (41%) were women. At week 26, mean change in HbA1c with orforglipron was up to -2.10% (-1.67% placebo adjusted), vs. -0.43% with placebo and -1.10% with dulaglutide. HbA1c redn. was statistically superior with orforglipron vs. placebo (estd. treatment difference -0.8% to -1.7%). Change in mean bodyweight at week 26 was up to -10.1 kg (95% CI -11.5 to -8.7; 7.9 kg placebo adjusted [-9.9 to -5.9])

with orforglipron vs. -2.2 kg (-3.6 to -0.7) for placebo and -3.9 kg (-5.3 to -2.4) for dulaglutide. The incidence of treatment-emergent adverse events ranged from 61.8% to 88.9% in orforglipron-treated participants, compared with 61.8% with placebo and 56.0% with dulaglutide. The majority were gastrointestinal events (44.1% to 70.4% with orforglipron, 18.2% with placebo, and 34.0% with dulaglutide) of mild to moderate severity. Three participants receiving orforglipron and one participant receiving dulaglutide had clin. significant (<54 mg/dL [<3 mmol/L]) hypoglycemia and no participants had severe hypoglycemia. One death occurred in the placebo group and was not related to study treatment. In this phase 2 trial the novel, oral, non-peptide GLP-1 receptor agonist orforglipron at doses of 12 mg or greater showed significant redns. in HbA1c and bodyweight compared with placebo or dulaglutide. The adverse event profile was similar to other GLP-1 receptor agonists in similar stage of development. Orforglipron might provide an alternative to injectable GLP-1 receptor agonists and oral semaglutide, with the prospect of less burdensome administration to achieve treatment goals in people with type 2 diabetes.Eli Lilly and Company.

AN 2023:1379711 CAPLUS Full-text

DN 183:320858

TI Efficacy and safety of oral orforglipron in patients with type 2 diabetes: a multicentre, randomised, dose-response, phase 2 study

AU Frias, Juan P.; Hsia, Stanley; Eyde, Sarah; Liu, Rong; Ma, Xiaosu; Konig, Manige; Kazda, Christof; Mather, Kieren J.; Haupt, Axel; Pratt, Edward; Robins, Deborah

CS Velocity Clinical Research, Los Angeles, CA, USA

SO Lancet (2023), 402(10400), 472-483
CODEN: LANCAO; ISSN: 0140-6736

DOI 10.1016/s0140-6736(23)01302-8

PB Elsevier Ltd.

DT Journal; (online computer file)

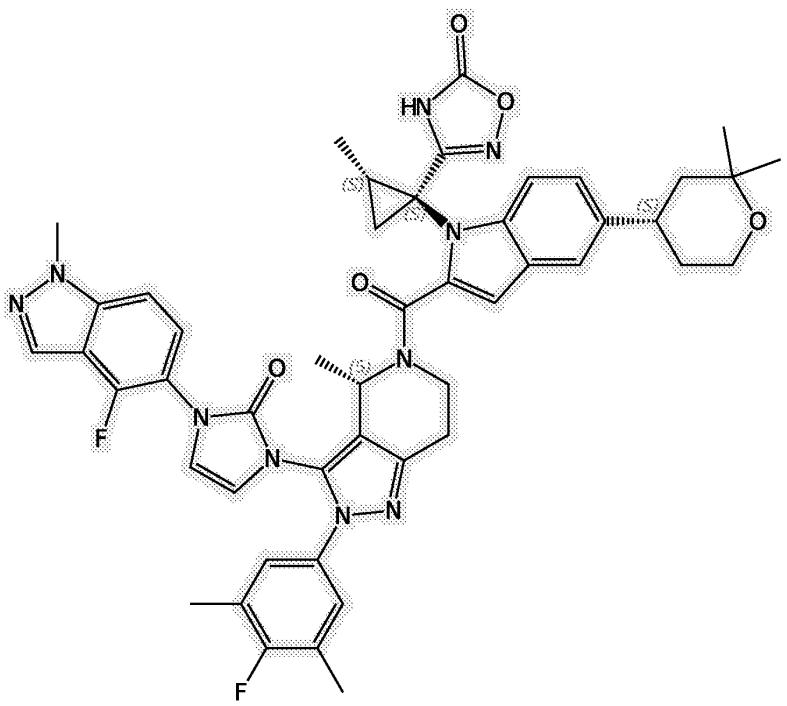
LA English

IT 2212020-52-3

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(efficacy and safety of oral orforglipron in patients with type 2 diabetes)

RN 2212020-52-3 CAPLUS

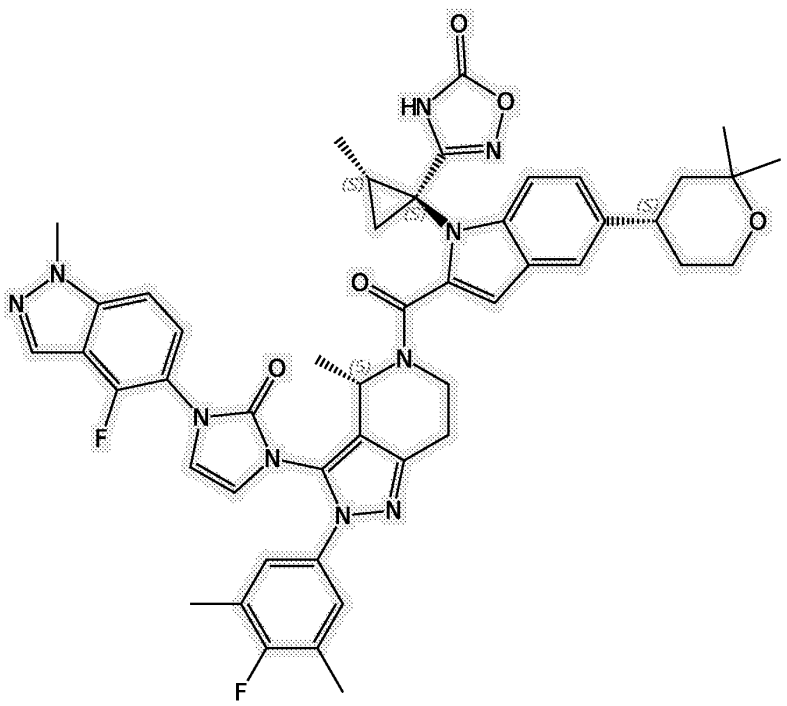
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

OSC.G 20 THERE ARE 20 CAPLUS RECORDS THAT CITE THIS RECORD (20 CITINGS)
RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 25 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN
AB This study was a 26-wk multicentre trial performed in four countries (the USA, Hungary, Poland, and Slovakia). 383 Patients with type 2 diabetes were enrolled and randomly assigned to one of five once-per-day doses of orforglipron (3 mg, 12 mg, 24 mg, 36 mg, or 45 mg), placebo, or the active comparator (dulaglutide 1.5 mg once-per-week; an injectable GLP-1 receptor agonist).
AN 2023:1379710 CAPLUS Full-text
DN 183:320857
TI Non-peptide, once-per-day oral orforglipron to compete with established peptide-based, injectable GLP-1 receptor agonists
AU Nauck, Michael A.; Horowitz, Michael
CS Diabetes, Endocrinology, Metabolism Section, Medical Department I, St Josef Hospital, Katholisches Klinikum Bochum, Ruhr-University Bochum, Bochum, 44791, Germany
SO Lancet (2023), 402(10400), 429-431
CODEN: LANCAO; ISSN: 0140-6736
DOI 10.1016/s0140-6736(23)01201-1
PB Elsevier Ltd.
DT Journal; (online computer file)
LA English
IT 2212020-52-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(non-peptide, once-per-day oral orforglipron to compete with established peptide-based, injectable GLP-1 receptor agonists)
RN 2212020-52-3 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 26 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN

AB To evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of single and multiple doses of orforglipron (LY3502970), an oral, non-peptide glucagon-like peptide-1 receptor agonist (GLP-1RA) in healthy participants. This was a double-blind, placebo-controlled, Phase 1 study. Overtly healthy adults aged 18 to 65 years with body mass index of 20 to 40 kg/m2 and glycated Hb concn. of 47.5 mmol/mol (<6.5%) were eligible. In Part A, participants received single-dose orforglipron, with four cohorts receiving escalating doses (0.3-6 mg). In Part B, participants received 4 wk of daily repeated oral orforglipron with doses escalating weekly to four different final target doses (2-24 mg). Ninety-two participants enrolled and received at least one study drug dose (32 in Part A [mean age 43.4 years] and 60 in Part B [mean age 42.5 years]). The most common adverse events were gastrointestinal tract-related. Pharmacokinetics were approx. dose proportional, and the mean t1/2 was 24.6 to 35.3 h after a single dose (0.3-6 mg). On Day 28, the mean t1/2 was 48.1 to 67.5 h across the dose range (2-24 mg). Substantial redns. in body wt. of up to 5.4 kg were obsd. after 4 wk in orforglipron-treated participants, compared to a redn. of 2.4 kg with placebo ($P < 0.05$). Orforglipron decreased fasting glucose levels across Days 1 to 28, and gastric emptying was delayed on Day 28. Orforglipron's long half-life (25-68 h) allows once-daily oral dosing, without water and food restrictions. Orforglipron had a pharmacodynamic and safety profile similar to that of injectable GLP-1RAs, which supports continued clin. development.

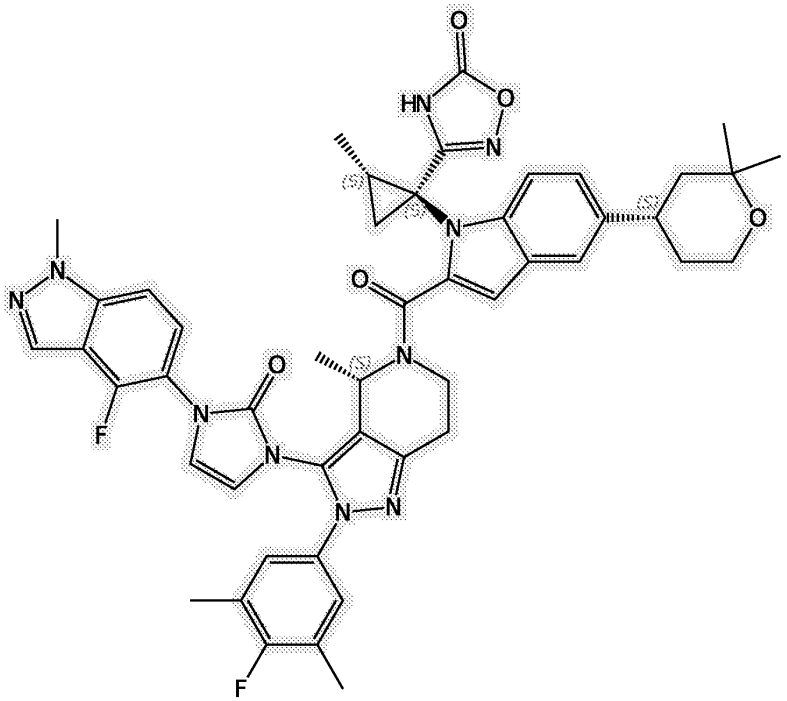
AN 2023:1298430 CAPLUS Full-text
DN 183:258513

TI Orforglipron (LY3502970), a novel, oral non-peptide glucagon-like peptide-1 receptor agonist: A Phase 1a, blinded, placebo-controlled, randomized, single- and multiple-ascending-dose study in healthy participants

AU Pratt, Edward; Ma, Xiaosu; Liu, Rong; Robins, Deborah; Haupt, Axel; Coskun, Tamer; Sloop, Kyle W.; Benson, Charles
CS Lilly Centre for Clinical Pharmacology Pte Ltd, Singapore

SO Diabetes, Obesity and Metabolism (2023), 25(9), 2634-2641

CODEN: DOMEF6; ISSN: 1462-8902
DOI 10.1111/dom.15184
PB Wiley-Blackwell
DT Journal; (online computer file)
LA English
IT 2212020-52-3
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(orforglipron (LY3502970), is novel, oral non-peptide glucagon-like peptide-1 receptor agonist)
RN 2212020-52-3 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

OSC.G 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 27 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN
AB Aim : To report the results of a Phase 1b trial evaluating the safety, pharmacokinetics and pharmacodynamics of orforglipron (LY3502970), an oral, non-peptide glucagon-like peptide-1 receptor agonist (GLP-1RA), in patients with type 2 diabetes (T2D). Materials and Methods : This was a double-blind, placebo-controlled Phase 1 study evaluating five different dosing regimens. The first group established that weekly dose escalation of the daily doses of orforglipron was generally well tolerated. This enabled a parallel-arm design for the four groups following. Participants were randomized 3:1 to daily doses of orforglipron or placebo for 12 wk. Eligible participants with T2D were aged 18 to 70 years and had glycated Hb (HbA1c) levels ≥53.0 mmol/mol (7.0%) and ≤91.3 mmol/mol (10.5%). Results : A total of 51 participants received orforglipron and 17 received placebo. In the placebo and orforglipron groups, resp., baseline HbA1c was 8.1% and 8.0%, and baseline body wt. was 90.3 and 88.4 kg. The most common adverse events were gastrointestinal-related, and

occurred early in treatment, similar to findings with other GLP-1RAs. At Week 12, mean t1/2 ranged from 29 to 49 h. Mean HbA1c change ranged from -1.5% to -1.8% across orforglipron doses, vs. -0.4% with placebo, and body wt. change was -0.24 to -5.8 kg across orforglipron doses, vs. 0.5 kg with placebo. Conclusions : Orforglipron treatment resulted in meaningful redns. in HbA1c and body wt., with an adverse event profile consistent with that of other GLP-1RAs. Orforglipron may provide a safe and effective once-daily oral treatment alternative to injectable GLP-1RAs or peptide oral formulations without water and food restrictions.

AN 2023:1194747 CAPLUS Full-text

DN 183:258556

TI Orforglipron (LY3502970), a novel, oral non-peptide glucagon-like peptide-1 receptor agonist: A Phase 1b, multicentre, blinded, placebo-controlled, randomized, multiple-ascending-dose study in people with type 2 diabetes

AU Pratt, Edward; Ma, Xiaosu; Liu, Rong; Robins, Deborah; Coskun, Tamer; Sloop, Kyle W.; Haupt, Axel; Benson, Charles

CS Lilly Centre for Clinical Pharmacology Pte Ltd, Singapore

SO Diabetes, Obesity and Metabolism (2023), 25(9), 2642-2649
CODEN: DOMEF6; ISSN: 1462-8902

DOI 10.1111/dom.15150

PB Wiley-Blackwell

DT Journal; (online computer file)

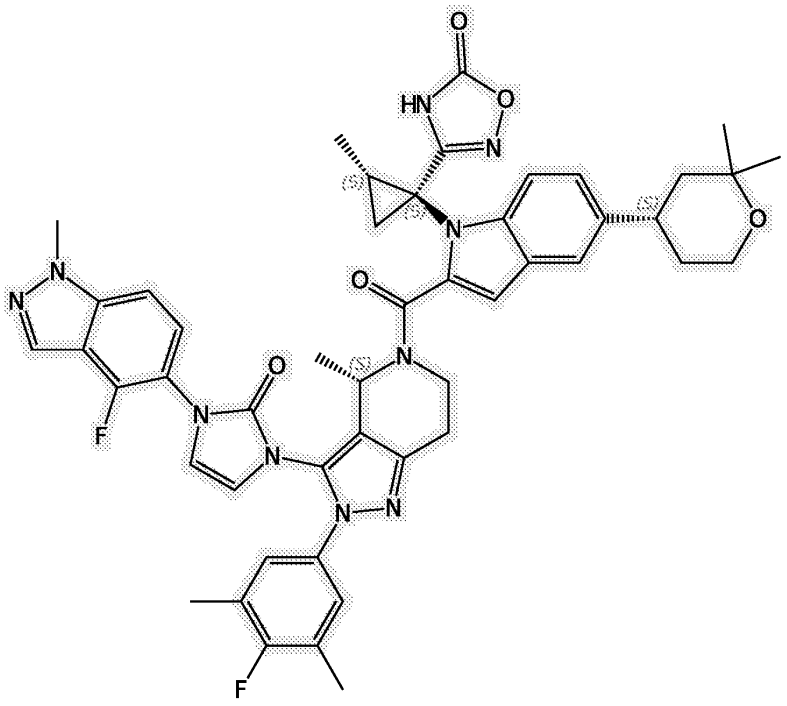
LA English

IT 2212020-52-3

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Orforglipron (LY3502970), novel, oral non-peptide glucagon-like peptide-1 receptor agonist phase 1b, multicentre, blinded, placebo-controlled, people with type 2 diabetes)

RN 2212020-52-3 CAPLUS

CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)

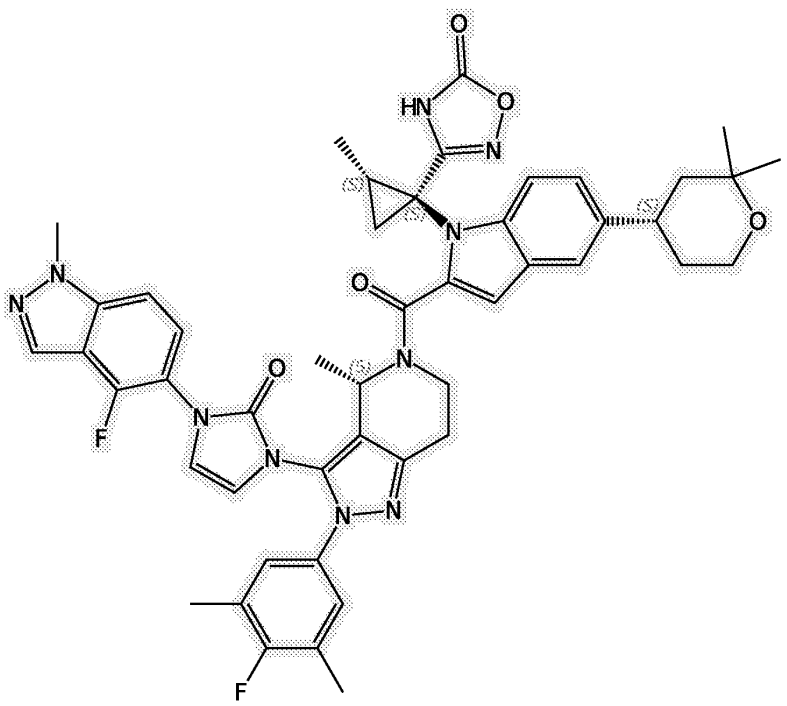


Absolute stereochemistry shown

OSC.G 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)

RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

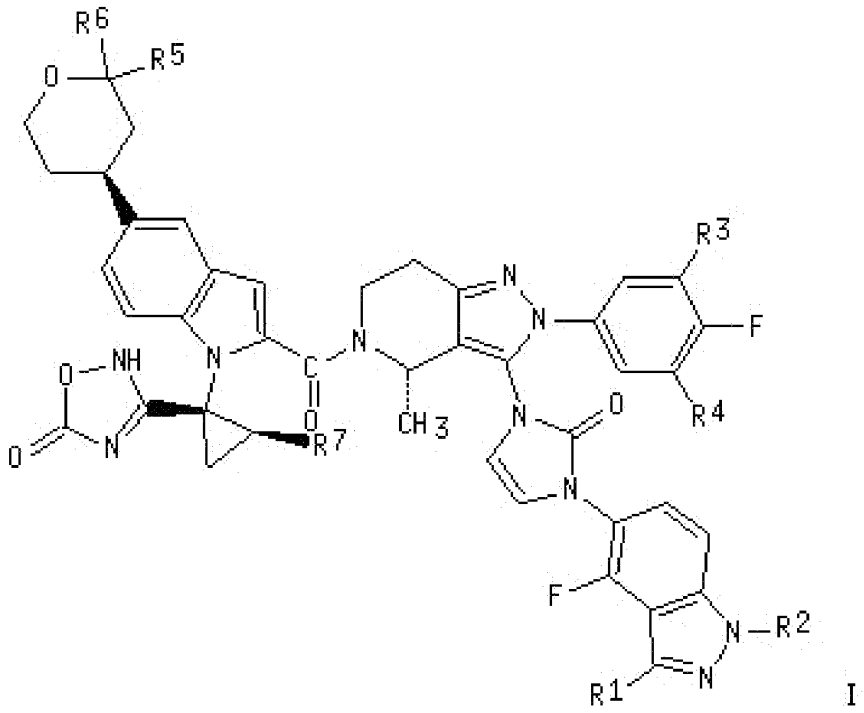
L3 ANSWER 28 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN
AB G protein-coupled receptors (GPCRs) generally accommodate specific ligands in the orthosteric-binding pockets. Ligand binding triggers a receptor allosteric conformational change that leads to the activation of intracellular transducers, G proteins and β-arrestins. Because these signals often induce adverse effects, the selective activation mechanism for each transducer must be elucidated. Thus, many orthosteric-biased agonists have been developed, and intracellular-biased agonists have recently attracted broad interest. These agonists bind within the receptor intracellular cavity and preferentially tune the specific signalling pathway over other signalling pathways, without allosteric rearrangement of the receptor from the extracellular side1-3. However, only antagonist-bound structures are currently available1,4-6, and there is no evidence to support that biased agonist binding occurs within the intracellular cavity. This limits the comprehension of intracellular-biased agonism and potential drug development. Here we report the cryogenic electron microscopy structure of a complex of Gs and the human parathyroid hormone type 1 receptor (PTH1R) bound to a PTH1R agonist, PCO371. PCO371 binds within an intracellular pocket of PTH1R and directly interacts with Gs. The PCO371-binding mode rearranges the intracellular region towards the active conformation without extracellularly induced allosteric signal propagation. PCO371 stabilizes the significantly outward-bent conformation of transmembrane helix 6, which facilitates binding to G proteins rather than β-arrestins. Furthermore, PCO371 binds within the highly conserved intracellular pocket, activating 7 out of the 15 class B1 GPCRs. Our study identifies a new and conserved intracellular agonist-binding pocket and provides evidence of a biased signalling mechanism that targets the receptor-transducer interface.
AN 2023:1177017 CAPLUS Full-text
TI Class B1 GPCR activation by an intracellular agonist
AU Kobayashi, Kazuhiro; Kawakami, Kouki; Kusakizako, Tsukasa; Tomita, Atsuhiro; Nishimura, Michihiro; Sawada, Kazuhiro; Okamoto, Hiroyuki H.; Hiratsuka, Suzune; Nakamura, Gaku; Kuwabara, Riku; Noda, Hiroshi; Muramatsu, Hiroyasu; Shimizu, Masaru; Taguchi, Tomohiko; Inoue, Asuka; Murata, Takeshi; Nureki, Osamu
CS Department of Biological Sciences, Graduate School of Science, The University of Tokyo, Tokyo, Japan
SO Nature (London, United Kingdom) (2023), 618(7967), 1085-1093
CODEN: NATUAS; ISSN: 1476-4687
DOI 10.1038/s41586-023-06169-3
PB Nature Portfolio
DT Journal; (online computer file)
LA English
IT INDEXING IN PROGRESS
IT 2212020-52-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(class B1 GPCR activation by intracellular agonist)
RN 2212020-52-3 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

OSC.G 10 THERE ARE 10 CAPLUS RECORDS THAT CITE THIS RECORD (10 CITINGS)
RE.CNT 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 29 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN
GI



I

AB The present invention relates to the prepn. of deuterated indazole compds. as GLP-1 receptor agonists. In particular, the deuterated indazole compd. I (wherein, R1 = hydrogen or deuterium and R2, R3, R4, R5, R6 and R7 = independently CD3 or CH3; when R1 = hydrogen, at least one of R2, R3, R4, R5, R6 and R7 = CD3) or a pharmaceutically acceptable salt, isomer, metabolite, prodrug, or solvate or hydrates were prepd. The inventive compds. have good therapeutic effects on non-insulin dependent diabetes mellitus (type 2 diabetes), obesity etc.

AN 2023:862780 CAPLUS Full-text

DN 182:380686

TI Preparation of deuterated indazole compounds as GLP-1 receptor agonists

IN Guo, Binghua; Yan, Hailei; Wen, Jie

PA Yaokang Zhongtuo (Beijing) Pharmaceutical Technology Co., Ltd., Peop. Rep. China

UO YAOKANG ZHONGTUO BEIJING PHARMACEUTICAL TECH

UOS YAOKANG ZHONGTUO BEIJING PHARMACEUTICAL TECH

SO Faming Zhuanli Shenqing, 13pp.
CODEN: CNXXEV

DT Patent

LA Chinese

FAN.CNT 1

PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 116003403	A	20230425	CN 2022-11451463	20221120
CN 116003403	B	20240723		
CN 118791482	A	20241018	CN 2024-10776755	20221120

PRAI CN 2022-11451463 A3 20221120

PSPI

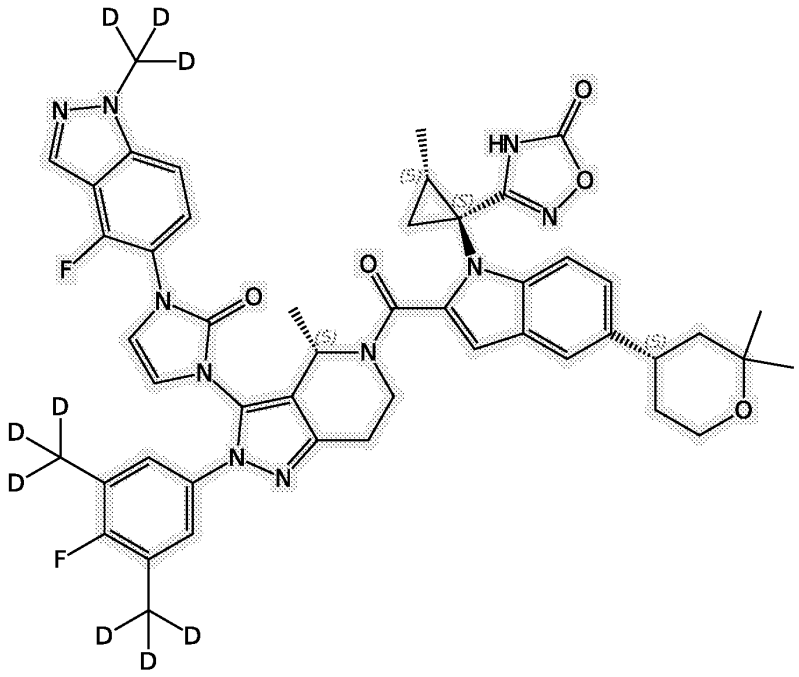
PATENT NO.	KIND	STATUS	STATUS DATE
CN 116003403	A	Alive	20230504
CN 116003403	B	Alive	20230504
CN 118791482	A	Alive	20241024

OS CASREACT 182:380686; MARPAT 182:380686

IT 2923760-27-2
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SCLM (Substance claimed); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of deuterated indazole compds. as GLP-1 receptor agonists)

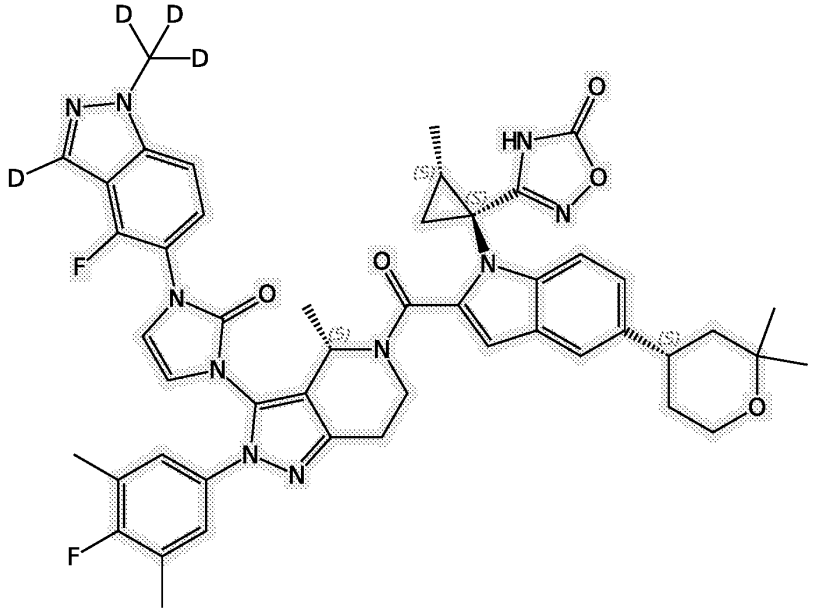
RN 2923760-27-2 CAPLUS

CN INDEX NAME NOT YET ASSIGNED



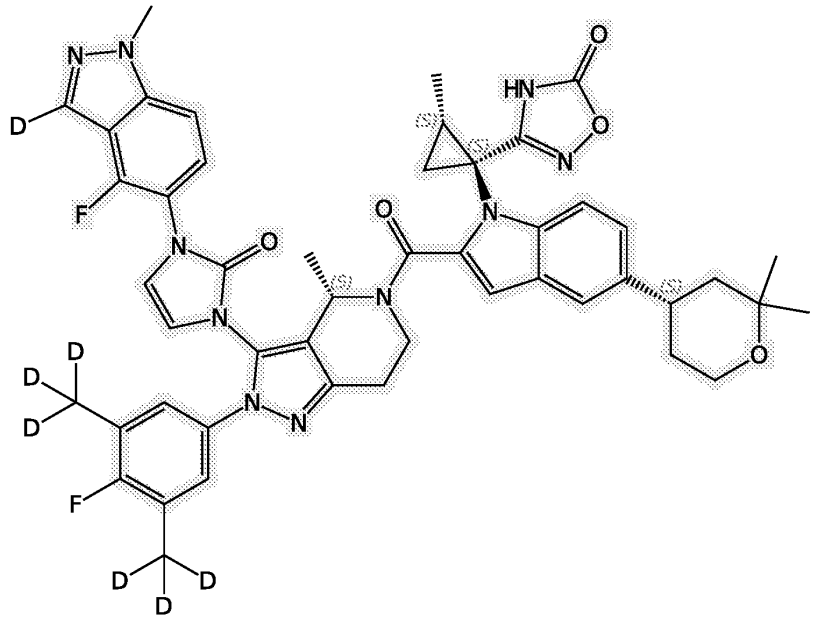
Absolute stereochemistry shown

IT 2923760-29-4P 2923760-31-8P 2923760-33-0P
2923760-36-3P
RL: PAC (Pharmacological activity); SCLM (Substance claimed); SPN
(Synthetic preparation); THU (Therapeutic use); BIOL (Biological study);
PREP (Preparation); USES (Uses)
(prepn. of deuterated indazole compds. as GLP-1 receptor agonists)
RN 2923760-29-4 CAPLUS
CN INDEX NAME NOT YET ASSIGNED



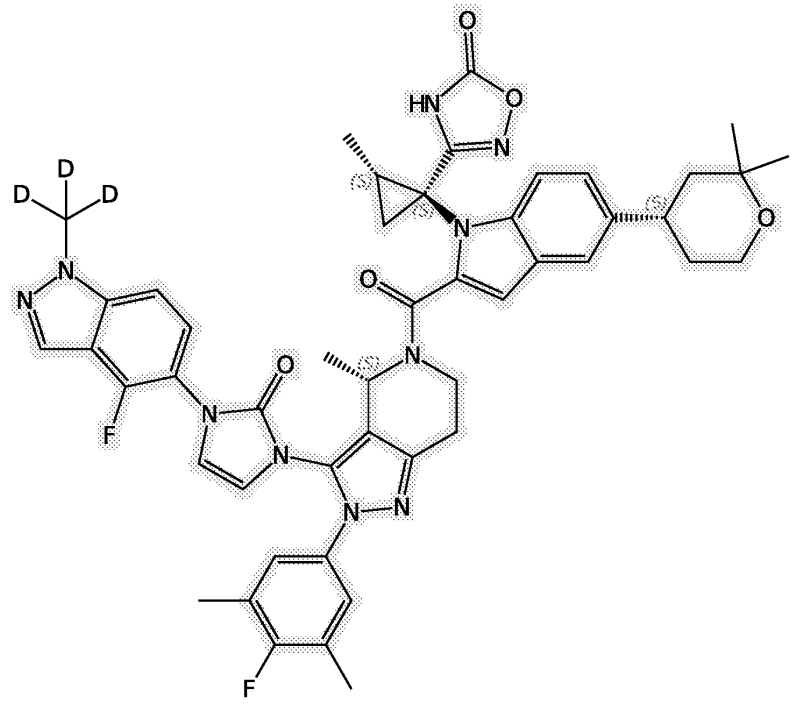
Absolute stereochemistry shown

RN 2923760-31-8 CAPLUS
CN INDEX NAME NOT YET ASSIGNED



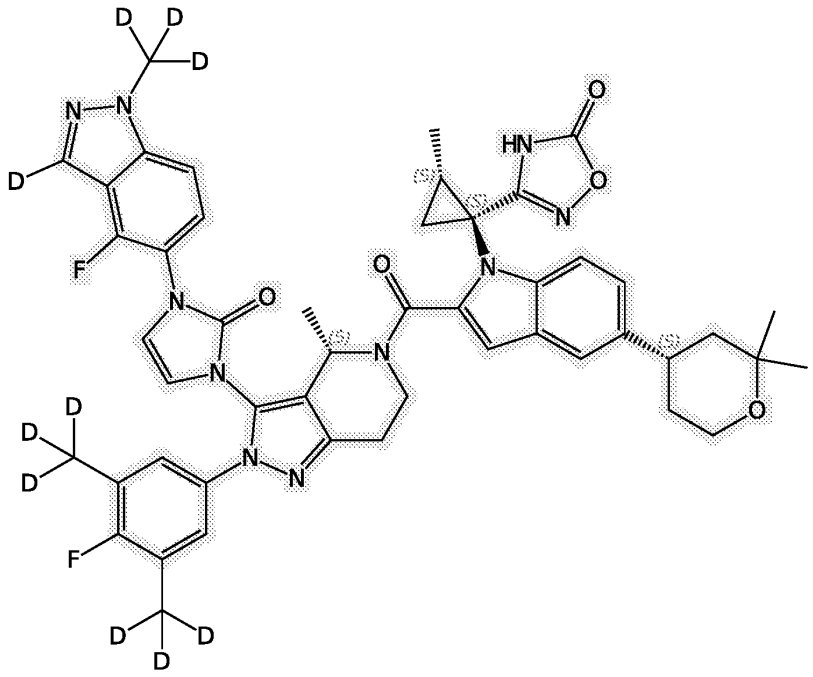
Absolute stereochemistry shown

RN 2923760-33-0 CAPLUS
CN INDEX NAME NOT YET ASSIGNED



Absolute stereochemistry shown

RN 2923760-36-3 CAPLUS
CN INDEX NAME NOT YET ASSIGNED



Absolute stereochemistry shown

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
CN 116003403 A	CN 2022-11451463	Register|Global Dossier
CN 116003403 B	CN 2022-11451463	Register|Global Dossier
CN 118791482 A	CN 2024-10776755	Register|Global Dossier

L3 ANSWER 30 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN

AB The present invention provides a medicine characterized by the combination of: a compd. represented by (A) or a pharmaceutically acceptive salt thereof; and (B) at least one drug selected from the group consisting of drugs having exhibiting anti-obesity activity, drugs for controlling blood sugar level, drugs for controlling blood cholesterol and/or triglycerides, and drugs for controlling blood pressure. The medicine is useful for the prevention and treatment of diseases linked to anti-obesity activity.

AN 2023:528384 CAPLUS Full-text

DN 182:173340

TI Medicine for prevention and treatment of diseases linked to anti-obesity activity

IN Takemoto, Kosuke; Kusumoto, Keisuke

PA Shionogi & Co., Ltd., Japan

UO SHIONOGI & CO LTD

UOS Shionogi & Co

SO PCT Int. Appl., 79pp.
CODEN: PIXXD2

DT Patent

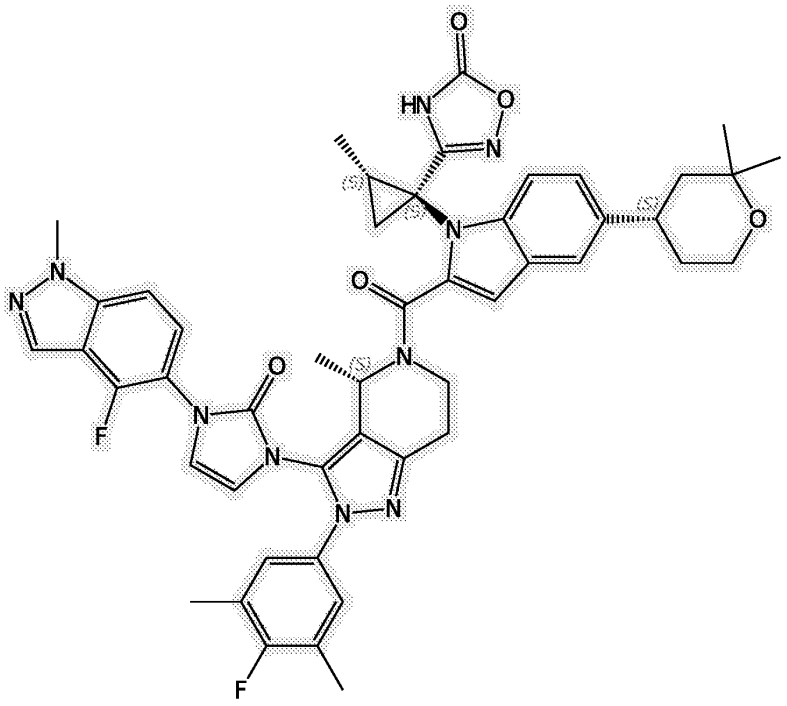
LA Japanese

FAN.CNT 1

PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2023038039	A1	20230316	WO 2022-JP33492	20220907
	CA 3231153	A1	20230316	CA 2022-3231153	20220907
	AU 2022344074	A1	20240229	AU 2022-344074	20220907
	KR 2024056719	A	20240430	KR 2024-7006808	20220907
	CN 118215478	A	20240618	CN 2022-80070367	20220907
	EP 4400105	A1	20240717	EP 2022-867361	20220907
PRAI	JP 2021-146025	A	20210908		

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     WO 2022-JP33492      W    20220907
PSPI
     PATENT NO.           KIND  STATUS          STATUS DATE
     ---------------      ----  -------------   -----------
     WO 2023038039         A1   Alive           20230323
     CA 3231153            A1   Alive           20240321
     AU 2022344074         A1   Alive           20240307
     KR 2024056719         A    Alive           20240516
     CN 118215478          A    Alive           20240627
     EP 4400105            A1   Alive           20240718
OS   MARPAT 182:173340
IT   2212020-52-3, LY-3502970
     RL: PAC (Pharmacological activity); SCLM (Substance claimed); THU
     (Therapeutic use); BIOL (Biological study); USES (Uses)
        (combination drug for prevention and treatment of diseases linked to
        anti-obesity activity)
RN   2212020-52-3  CAPLUS
CN   1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylp
henyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-
yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)
-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]-
(CA INDEX NAME)
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Absolute stereochemistry shown

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RE.CNT  8     THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION
 PUBLICATIONS         APPLICATIONS          REGISTER
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 AU 2022344074 A1     AU 2022-344074        Register
 CA 3231153 A1        CA 2022-3231153       Register
 CN 118215478 A       CN 2022-80070367      Register|Global Dossier
 EP 4400105 A1        EP 2022-867361        Register|Federated Reg.
 KR 2024056719 A      KR 2024-7006808       Register|Global Dossier
 WO 2023038039 A1     WO 2022-JP33492       Register|Global Dossier

L3   ANSWER 31 OF 38  CAPLUS  COPYRIGHT 2024 ACS on STN
AB   The present invention relates to a glucose-dependent insulinotropic
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peptide (GIP) receptor (GIPR) antagonist GIP peptide in combination with a glucagon-like peptide-1 (GLP-1) receptor agonist, such as a GLP-1 peptide, for use in the treatment of obesity and obesity-related disorders, as well as GIPR antagonist GIP peptides for treating a subset of obesity-related disorders.

AN 2022:3104554 CAPLUS Full-text

DN 181:196805

TI Treatment of obesity and obesity-related disorders with glucose-dependent insulinotropic peptide receptor and a glucagon-like peptide-1 receptor agonist

IN Hovard Sparre-Ulrich, Alexander; Rosenkilde, Mette Marie

PA Antag Therapeutics ApS, Den.

UO ANTAG THERAPEUTICS APS

UOS ANTAG THERAPEUTICS APS

SO PCT Int. Appl., 95pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2022258805	A1	20221215	WO 2022-EP65826	20220610
	CA 3221661	A1	20221215	CA 2022-3221661	20220610
	AU 2022289247	A1	20231221	AU 2022-289247	20220610
	SG 11202309107	A	20231229	SG 2023-11202309107	20220610
	IL 309128	A0	20240101	IL 2022-309128	20220610
	KR 2024021212	A	20240216	KR 2024-7000556	20220610
	BR 112023024968	A2	20240220	BR 2023-112023024968	20220610
	CN 117881415	A	20240412	CN 2022-80040922	20220610
	EP 4351630	A1	20240417	EP 2022-733387	20220610
	JP 2024521398	T	20240531	JP 2023-575695	20220610
	US 20240277813	A1	20240822	US 2023-18565984	20231130
	IL 309128	A	20240201	IL 2023-309128	20231206
	IN 202417000428	A	20241018	IN 2024-17000428	20240103
PRAI	EP 2021-178712	A	20210610		
	WO 2022-EP65826	W	20220610		

PSPI

	PATENT NO.	KIND	STATUS	STATUS DATE
	WO 2022258805	A1	Alive	20221222
	CA 3221661	A1	Alive	20231228
	AU 2022289247	A1	Alive	20231228
	KR 2024021212	A	Alive	20240314
	BR 112023024968	A2	Alive	20240418
	CN 117881415	A	Alive	20240418
	EP 4351630	A1	Alive	20240418
	JP 2024521398	T	Alive	20240613
	US 20240277813	A1	Alive	20240829
	IL 309128	A	Alive	20240222

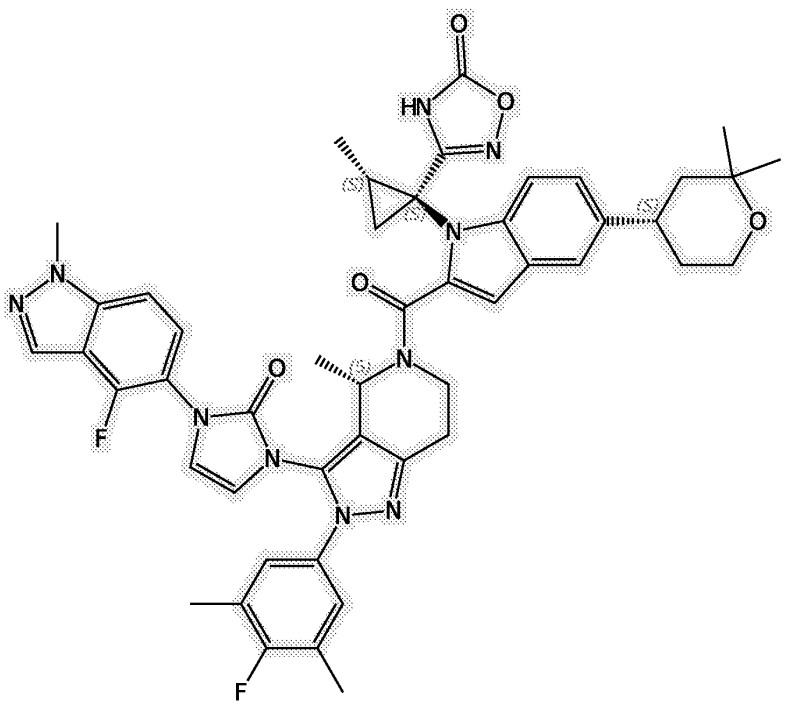
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OS MARPAT 181:196805

IT [illegible], Owl833
RL: PAC (Pharmacological activity); SCLM (Substance claimed); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of obesity and obesity-related disorders with glucose-dependent insulinotropic peptide receptor and a glucagon-like peptide-1 receptor agonist)

RN 2212020-52-3 CAPLUS

CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
AU 2022289247 A1	AU 2022-289247	Register
BR 112023024968 A2	BR 2023-112023024968	Register
CA 3221661 A1	CA 2022-3221661	Register
CN 117881415 A	CN 2022-80040922	Register|Global Dossier
EP 4351630 A1	EP 2022-733387	Register|Federated Reg.
IL 309128 A0	IL 2022-309128	Register
IL 309128 A	IL 2023-309128	Register
IN 202417000428 A	IN 2024-17000428	Register
JP 2024521398 T	JP 2023-575695	Register|Global Dossier
KR 2024021212 A	KR 2024-7000556	Register|Global Dossier
SG 11202309107 A	SG 2023-11202309107	Register
US 20240277813 A1	US 2023-18565984	Register|Global Dossier
WO 2022258805 A1	WO 2022-EP65826	Register|Global Dossier

L3 ANSWER 32 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN
AB This disclosure features compns. and methods for the treatment of metabolic disorders such as diabetes and obesity.
AN 2022:2947018 CAPLUS Full-text
DN 181:95196
TI Methods and compositions for inducing brown adipogenesis
IN Boss, Olivier D.; Freeman, Brian
PA Energesis Pharmaceuticals, Inc., USA
UO ENERGESIS PHARMACEUTICALS
UOS ENERGESIS PHARMACEUTICALS
SO PCT Int. Appl., 69pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

	WO 2022246230	A1	20221124	WO 2022-US30299	20220520
	CA 3218880	A1	20221124	CA 2022-3218880	20220520
	AU 2022276512	A1	20231130	AU 2022-276512	20220520
	CN 117355297	A	20240105	CN 2022-80036497	20220520
	BR 112023024099	A2	20240206	BR 2023-112023024099	20220520
	EP 4340824	A1	20240327	EP 2022-805598	20220520
	JP 2024521091	T	20240528	JP 2023-571654	20220520
	IL 308617	A	20240101	IL 2023-308617	20231116
	US 20240238374	A1	20240718	US 2023-18561769	20231117
	IN 202317082503	A	20240927	IN 2023-17082503	20231204
PRAI	US 2021-63191271	P	20210520		
	WO 2022-US30299	W	20220520		

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2022246230	A1	Alive	20221201
CA 3218880	A1	Alive	20231130
AU 2022276512	A1	Alive	20231207
CN 117355297	A	Alive	20240111
BR 112023024099	A2	Alive	20240307
EP 4340824	A1	Alive	20240328
JP 2024521091	T	Alive	20240606
IL 308617	A	Alive	20240118
US 20240238374	A1	Alive	20240725

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

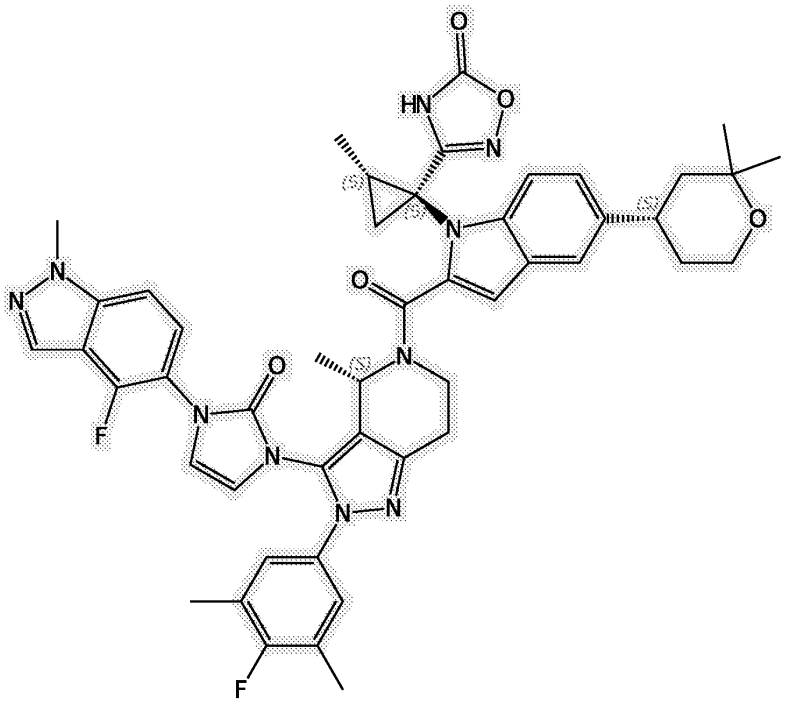
OS CASFORMULTNS 2022:2947018

IT 2212020-52-3

RL: PAC (Pharmacological activity); SCLM (Substance claimed); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods and compns. for inducing brown adipogenesis)

RN 2212020-52-3 CAPLUS

CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

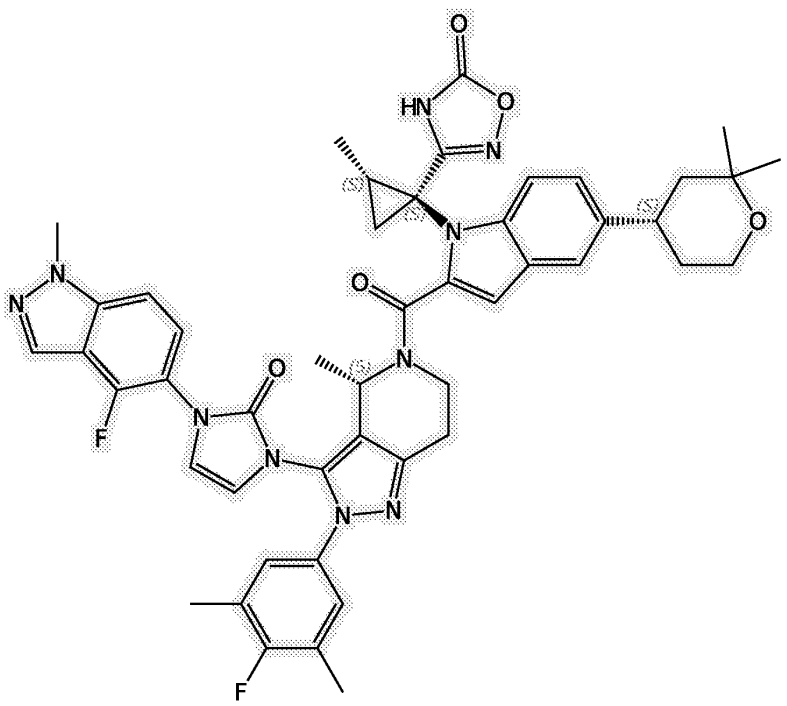
OSC.G 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
AU 2022276512 A1	AU 2022-276512	Register
BR 112023024099 A2	BR 2023-112023024099	Register
CA 3218880 A1	CA 2022-3218880	Register
CN 117355297 A	CN 2022-80036497	Register|Global Dossier
EP 4340824 A1	EP 2022-805598	Register|Federated Reg.
IL 308617 A	IL 2023-308617	Register
IN 202317082503 A	IN 2023-17082503	Register
JP 2024521091 T	JP 2023-571654	Register|Global Dossier
US 20240238374 A1	US 2023-18561769	Register|Global Dossier
WO 2022246230 A1	WO 2022-US30299	Register|Global Dossier

L3 ANSWER 33 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN
AB GLP-1 receptor agonists stimulate GLP-1R to promote insulin secretion, whereas DPP4 inhibitors slow GLP-1 degrdn. Both approaches are incretin-based therapies for T2D. In addn. to GLP-1 analogs, small nonpeptide GLP-1RAs such as LY3502970, TT-OAD2, and PF-06882961 have been considered as possible therapeutic alternatives. Pseudostellaria heterophylla, Linum usitatissimum, and Drymaria diandra are plants rich in cyclopeptides with hypoglycemic effects. Our previous study demonstrated the potential of their cyclopeptides for DPP4 inhibition. Reports of cyclic setmelanotide as an MC4R (GPCR) agonist and cyclic α-conotoxin chimeras as GLP-1RAs led to docking studies of these cyclopeptides with GLP-1R. Heterophyllin B, Pseudostellarin B, Cyclolinopeptide B, Cyclolinopeptide C, Drymarin A, and Diandrine C are abundant in these plants, with binding affinities of -9.5, -10.4, -10.3, -10.6, -11.2, and -11.9 kcal/mol, resp. The configuration they demonstrated established multiple hydrogen bonds with the transmembrane region of GLP-1R. DdC:(cyclo)-GGPYWP showed the most promising docking score. The results suggest that, in addn. to DPP4, GLP-1R may be a hypoglycemic target of these cyclopeptides. This may bring about more discussion of plant cyclopeptides as GLP-1RAs. Moreover, peptides derived from the HB precursor (IFGGLPPP), including IFGGWPPP, IFPGWPPP, IFGGYWPPP, and IFGYGWPPPP, exhibited diverse interactions with GLP-1R and displayed backbones available for further research.
AN 2022:1655947 CAPLUS Full-text
TI Investigating Potential GLP-1 Receptor Agonists in Cyclopeptides from Pseudostellaria heterophylla, Linum usitatissimum, and Drymaria diandra, and Peptides Derived from Heterophyllin B for the Treatment of Type 2 Diabetes: An In Silico Study
AU Liao, Hui-Jun; Tzen, Jason T. C.
CS Graduate Institute of Biotechnology, National Chung Hsing University, Taiwan
SO Metabolites (2022), 12(6), 549
CODEN: METALU; ISSN: 2218-1989
URL: https://www.mdpi.com/journal/metabolites
DOI 10.3390/metabo12060549
PB MDPI AG
DT Journal; (online computer file)
LA English
IT INDEXING IN PROGRESS
IT [illegible]
RL: PRP (Properties)
(potential glp-1 receptor agonists in cyclopeptides from Pseudostellaria heterophylla, Linum usitatissimum and Drymaria diandra, and peptides derived from heterophyllin b for treatment of type 2 diabetes)
RN 2212020-52-3 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

OSC.G 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
RE.CNT 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 34 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN
AB Provided herein are methods to treat brain functional decline during aging, which involve administration of glucagon-like peptide-1 receptor (GLP-1R) agonists (GLP-1RAs) that treat the aging-assocd. changes of the brain. The GLP-1R agonist is exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, semaglutide, taspoglutide, PF-06882961, OWL-833, TTP-273, or any other mol. that activates GLP-1R.
AN 2022:1555619 CAPLUS Full-text
DN 179:153914
TI A method for reversing aging brain functional decline
IN Ko, Ho; Li, Zhonggi; Chen, Xinyi; Vong, Si Long; Zhao, Lei; Mok, Chung Tong Vincent; Huang, Junzhe; Yan, Yik Chun Leo; Lai, Hei Ming
PA The Chinese University of Hong Kong, Peop. Rep. China
UO CHINESE UNIVERSITY OF HONG KONG
UOS Chinese University of Hong Kong
SO PCT Int. Appl., 49pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2022127868	A1	20220623	WO 2021-CN138827	20211216
	AU 2021399517	A1	20230706	AU 2021-399517	20211216
	AU 2021399517	A9	20240620		
	EP 4262873	A1	20231025	EP 2021-905794	20211216
	CN 117320755	A	20231229	CN 2021-80093732	20211216
	JP 2024500410	T	20240109	JP 2023-536878	20211216
	US 20240050531	A1	20240215	US 2023-18257745	20230615
PRAI	US 2020-63126122	P	20201216		
	WO 2021-CN138827	W	20211216		

PSPI

	PATENT NO.	KIND	STATUS	STATUS DATE

WO 2022127868	A1	Alive	20220630
AU 2021399517	A1	Alive	20230713
AU 2021399517	A9	Alive	20230713
EP 4262873	A1	Alive	20231026
CN 117320755	A	Alive	20240111
JP 2024500410	T	Alive	20240118
US 20240050531	A1	Alive	20240222

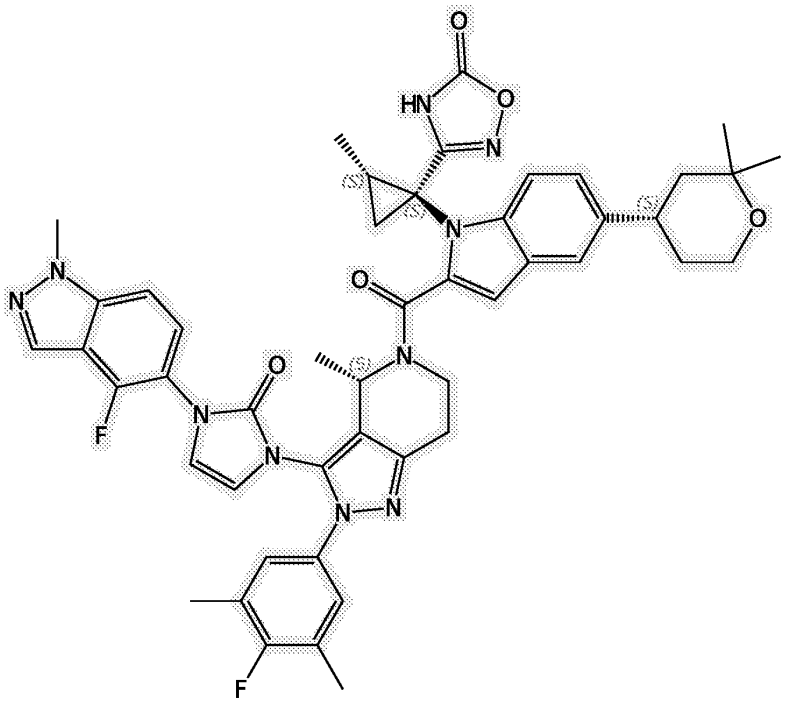
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

IT 2212020-52-3

RL: PAC (Pharmacological activity); SCLM (Substance claimed); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(OWL 833; method for reversing aging brain functional decline)

RN 2212020-52-3 CAPLUS

CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



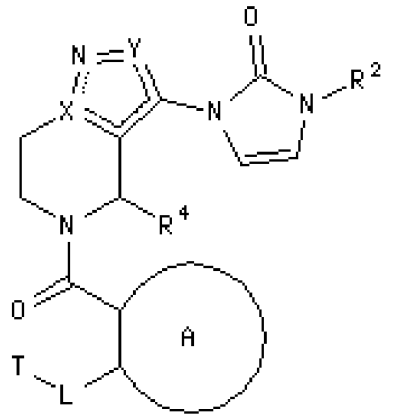
Absolute stereochemistry shown

LINK INFORMATION

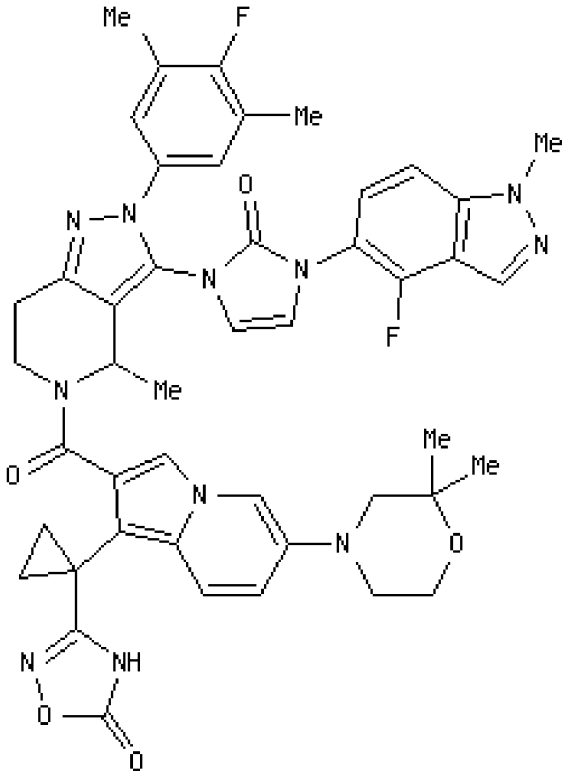
PUBLICATIONS	APPLICATIONS	REGISTER
AU 2021399517 A1	AU 2021-399517	Register
AU 2021399517 A9	AU 2021-399517	Register
CN 117320755 A	CN 2021-80093732	Register|Global Dossier
EP 4262873 A1	EP 2021-905794	Register|Federated Reg.
JP 2024500410 T	JP 2023-536878	Register|Global Dossier
US 20240050531 A1	US 2023-18257745	Register|Global Dossier
WO 2022127868 A1	WO 2021-CN138827	Register|Global Dossier

L3 ANSWER 35 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN

GI



I



II

AB The application relates to a compd. of formula I or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, which modulates the activity of GLP-1 receptor, a pharmaceutical compn. comprising a compd. of formula I, and a method of treating or preventing a disease in which GLP-1 receptor plays a role. Compds. of formula I wherein dashed bond is single and double bond; X is C and N; Y is NR1 and CR1; R1 is (CRcRc)0-2-C3-6 cycloalkyl, (CRcRc)0-2-Ph and (CRcRc)0-2-heteroaryl; each Rc is independently H, C1-3 alkyl and C1-3 haloalkyl; R2 is (un)substituted C3-10 cycloalkyl, (un)substituted Ph and (un)substituted heterocyclyl; ring A is (un)substituted pyrrolopyridine, (un)substituted indole, (un)substituted pyrazolopyridine, etc.; R4 is C1-6 alkyl, C1-6 haloalkyl, C1-6 alkoxy, etc.; L is CR5R6 and (un)substituted phenylenyl; R5 and R6 are independently H, C1-6 alkyl, C1-6 haloalkyl, C16

alkoxy, OH, etc.; T is CO2H, CH2NHSO2-C1-6 alkyl and heteroaryl; and with provisions; and pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, and tautomers thereof, are claimed. Example compd. II was prepd. by a multistep procedure (procedure given). The invention compds. were evaluated for their GLP-1 receptor modulatory activity. From the assay, it was detd. that compd. II exhibited EC50 value of > 0 nM.

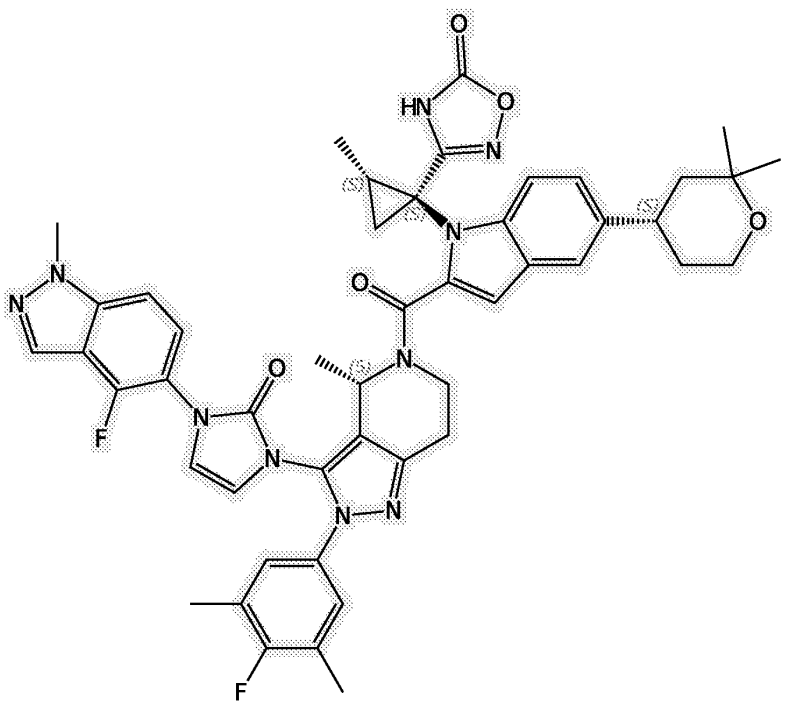
AN 2022:191074 CAPLUS Full-text
DN 177:295250
TI Preparation of tetrahydropyrazolo-pyrazinyl-dihydroimidazolone or tetrahydropyrazolo-pyridinyl-dihydroimidazolone compounds as GLP-1 receptor modulators and methods of using same
IN Ren, Zaifang; Sun, Xuefeng; Zhou, Jingye; Xu, Qing
PA Eccogene (Shanghai) Co., Ltd., Peop. Rep. China
UO ECCOGENE INC.
UOS ECCOGENE INC.
SO PCT Int. Appl., 310 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2
PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	WO 2022017338	A1	20220127	WO 2021-CN107216	20210720
	CA 3186217	A1	20220127	CA 2021-3186217	20210720
	AU 2021311567	A1	20230216	AU 2021-311567	20210720
	SG 11202300100	A	20230228	SG 2023-11202300100	20210720
	KR 2023048056	A	20230410	KR 2023-7005845	20210720
	EP 4182020	A1	20230524	EP 2021-749074	20210720
	PE 2023000854	A1	20230529	PE 2023-103	20210720
	CN 116390926	A	20230704	CN 2021-80063652	20210720
	JP 2023534983	T	20230815	JP 2023-504008	20210720
	JP 7569443	B2	20241017		
	VN 97031	A	20230825	VN 2023-945	20210720
	BR 112023000932	A2	20231003	BR 2023-112023000932	20210720
	IN 202317003213	A	20240412	IN 2023-17003213	20230116
	CO 2023001407	A2	20230216	CO 2023-1407	20230209
PRAI	WO 2020-CN102955	A	20200720		
	WO 2021-CN70120	A	20210104		
	WO 2021-CN107216	W	20210720		

PSPI

	PATENT NO.	KIND	STATUS	STATUS DATE
	WO 2022017338	A1	Alive	20220203
	CA 3186217	A1	Alive	20230330
	AU 2021311567	A1	Alive	20230223
	KR 2023048056	A	Alive	20230427
	EP 4182020	A1	Alive	20230525
	PE 2023000854	A1	Alive	20230720
	CN 116390926	A	Alive	20230713
	JP 2023534983	T	Alive	20230824
	JP 7569443	B2	Alive	20230824
	BR 112023000932	A2	Alive	20231221
	CO 2023001407	A2	Alive	20230223

OS CASREACT 177:295250; MARPAT 177:295250
IT 2212020-52-3
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of tetrahydropyrazolo-pyrazinyl-dihydroimidazolone and tetrahydropyrazolo-pyridinyl-dihydroimidazolone compds. as GLP-1 receptor modulators)
RN 2212020-52-3 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

LINK INFORMATION

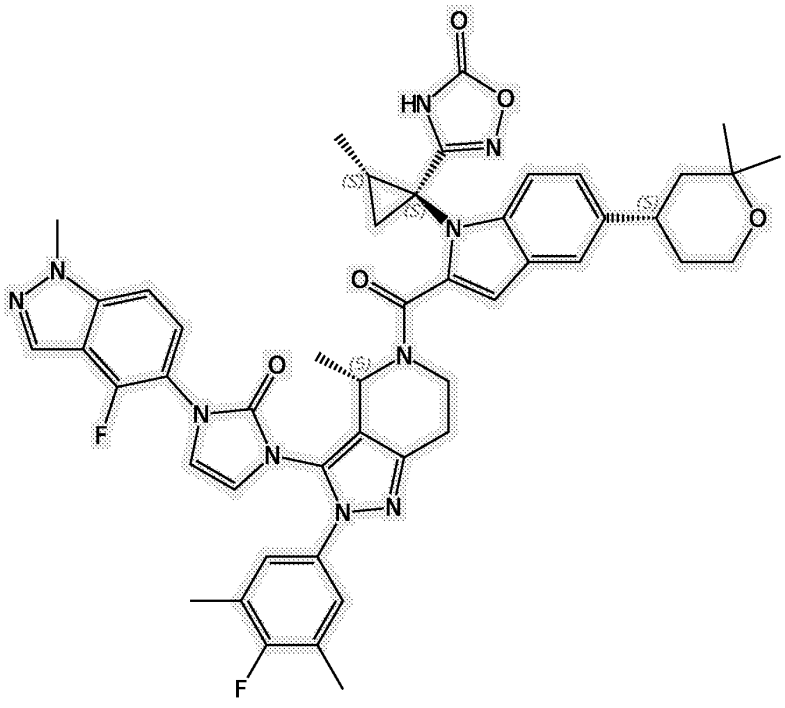
PUBLICATIONS	APPLICATIONS	REGISTER
AU 2021311567 A1	AU 2021-311567	Register
BR 112023000932 A2	BR 2023-112023000932	Register
CA 3186217 A1	CA 2021-3186217	Register
CN 116390926 A	CN 2021-80063652	Register|Global Dossier
CO 2023001407 A2	CO 2023-1407	Register
EP 4182020 A1	EP 2021-749074	Register|Federated Reg.
IN 202317003213 A	IN 2023-17003213	Register
JP 2023534983 T	JP 2023-504008	Register|Global Dossier
JP 7569443 B2	JP 2023-504008	Register|Global Dossier
KR 2023048056 A	KR 2023-7005845	Register|Global Dossier
PE 2023000854 A1	PE 2023-103	Register
SG 11202300100 A	SG 2023-11202300100	Register
VN 97031 A	VN 2023-945	Register
WO 2022017338 A1	WO 2021-CN107216	Register|Global Dossier

L3 ANSWER 36 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN

AB Glucagon-like peptide-1 receptor (GLP-1R) agonists are efficacious antidiabetic medications that work by enhancing glucose-dependent insulin secretion and improving energy balance. Currently approved GLP-1R agonists are peptide based, and it has proven difficult to obtain small-mol. activators possessing optimal pharmaceutical properties. We report the discovery and mechanism of action of LY3502970 (OWL833), a nonpeptide GLP-1R agonist. LY3502970 is a partial agonist, biased toward G protein activation over β-arrestin recruitment at the GLP-1R. The mol. is highly potent and selective against other class B G protein-coupled receptors (GPCRs) with a pharmacokinetic profile favorable for oral administration. A high-resoln. structure of LY3502970 in complex with active-state GLP-1R revealed a unique binding pocket in the upper helical bundle where the compd. is bound by the extracellular domain (ECD), extracellular loop 2, and transmembrane helixes 1, 2, 3, and 7. This mechanism creates a distinct receptor conformation that may explain the partial agonism and biased signaling of the compd. Further,

interaction between LY3502970 and the primate-specific Trp33 of the ECD informs species selective activity for the mol. In efficacy studies, oral administration of LY3502970 resulted in glucose lowering in humanized GLP-1R transgenic mice and insulinotropic and hypophagic effects in nonhuman primates, demonstrating an effect size in both models comparable to injectable exenatide. Together, this work detd. the mol. basis for the activity of an oral agent being developed for the treatment of type 2 diabetes mellitus, offering insights into the activation of class B GPCRs by nonpeptide ligands.

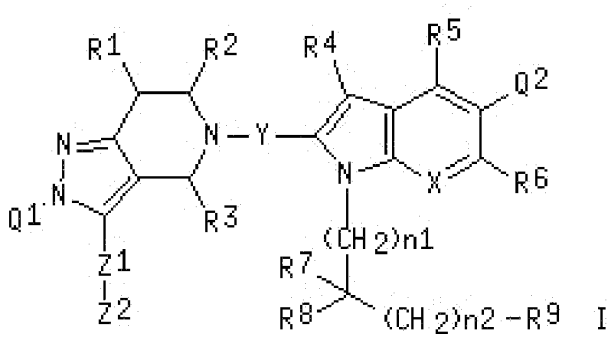
AN 2020:2464056 CAPLUS Full-text
DN 176:205249
TI Structural basis for GLP-1 receptor activation by LY3502970, an orally active nonpeptide agonist
AU Kawai, Takahiro; Sun, Bingfa; Yoshino, Hitoshi; Feng, Dan; Suzuki, Yoshiyuki; Fukazawa, Masanori; Nagao, Shunsuke; Wainscott, David B.; Showalter, Aaron D.; Droz, Brian A.; Kobilka, Tong Sun; Coghlan, Matthew P.; Willard, Francis S.; Kawabe, Yoshiki; Kobilka, Brian K.; Sloop, Kyle W.
CS Research Division, Chugai Pharmaceutical Co., Ltd., Gotemba, Shizuoka, 412-8513, Japan
SO Proceedings of the National Academy of Sciences of the United States of America (2020), 117(47), 29959-29967
CODEN: PNASA6; ISSN: 0027-8424
DOI 10.1073/pnas.2014879117
PB National Academy of Sciences
DT Journal; (online computer file)
LA English
IT 2212020-52-3
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(LY3502970; structural basis for GLP-1 receptor activation by LY3502970, orally active nonpeptide agonist)
RN 2212020-52-3 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

OSC.G 66 THERE ARE 66 CAPLUS RECORDS THAT CITE THIS RECORD (66 CITINGS)
RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 37 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN
GI



I

AB The present invention relates to a pharmaceutical compn. comprising a pyrazolopyridine deriv. compd. having a basic skeleton represented by formula [I; X = N or (un)substituted CH; Y = C(O), C1-66 alkyl-(un)substituted CH2, or S(O)2; Q1 = each (un)substituted C6-10 aryl or 5- to 10-membered heteroaryl; Q2 = each (un)substituted 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl; R1, R2, R3 = each independently H or (un)substituted C1-6 alkyl; R4, R5, R6 = H, halo, or C1-6 alkyl; R7, R8 = each independently H or (un)substituted C1-6 alkyl; or CR7R8 together form (un)substituted C3-15 cycloalkane ring; n1 = 0, 1, 2, or 3; n2 = an integer of 0-5; R9 = each (un)substituted 1,2,3,4-1H-tetrazol-5-yl, 5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl, 2H-1,2,4-triazol-3-yl, or 5-oxo-4,5-dihydro-1,2,4-thiadiazol-3-yl; Z1 = Q3, Q4, Q5, or each N-(un)substituted NH or CHCONH(CH2)n6; n4 = 1, 2, or 3; n5, n6 = each independently an integer of 0-10; Z2 = C1-6 alkyl or each (un)substituted C3-15 cycloalkyl, 3- to 12-membered heterocyclyl, C6-10 aryl, or 5- to 10-membered heteroaryl], salts thereof, or solvates thereof. as an active ingredient. The pharmaceutical compn. is used in the prevention or treatment of non-insulin dependent diabetes mellitus (type-2 diabetes) or obesity. The pharmaceutical compn. has pyrazolopyridine deriv. having the same action as GLP-1 peptide as a GLP-1 receptor agonist, and is capable of non-invasive administration and improving activity, metabolic stability and bioavailability.

AN 2019:1222516 CAPLUS Full-text
DN 171:134236
TI Pharmaceutical composition containing pyrazolopyridine derivative having GLP-1 receptor agonist effect
IN Yoshino, Hitoshi; Tsuchiya, Satoshi; Matsuo, Atsushi; Sato, Tsutomu; Nishimoto, Masahiro; Oguri, Kyoko; Ogawa, Ayako; Nishimura, Yoshikazu; Furuta, Yoshiyuki; Kashiwagi, Hirotaka; Hori, Nobuyuki; Iekado, Takuma; Shiraishi, Takuya; Yoshida, Masanobu; Kawai, Takahiro; Tanida, Satoshi; Aoki, Masahide
PA Chugai Pharmaceutical Co., Ltd., Japan
UO CHUGAI PHARMACEUTICAL LTD
UOS CHUGAI PHARMACEUTICAL LTD
SO Jpn. Kokai Tokkyo Koho, 169pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1
PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	JP 2019099571	A	20190624	JP 2018-223465	20181129
	JP 7461104	B2	20240403		
	JP 2024079762	A	20240611	JP 2024-45935	20240322
PRAI	JP 2017-228661	A	20171129		
	JP 2018-223465	A3	20181129		

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
JP 2019099571	A	Alive	20201121
JP 7461104	B2	Alive	20240411
JP 2024079762	A	Alive	20240627

OS MARPAT 171:134236

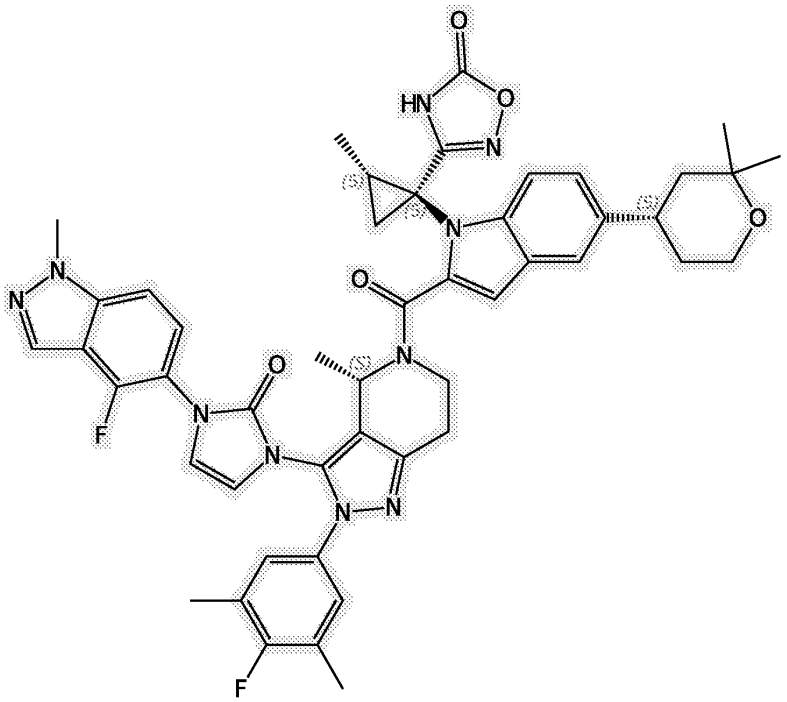
IT [redacted], 3-[(1S,2S)-1-[5-((4S)-2,2-Dimethyloxan-4-yl)-2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(pharmaceutical compn. contg. pyrazolopyridine deriv. having GLP-1 receptor agonist effect)

RN 2212020-52-3 CAPLUS

CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

IT [redacted], 3-[(1S,2S)-1-[2-[[(4S)-2-(4-Fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-(oxan-4-yl)indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one

[redacted], 3-[(1S,2S)-1-[2-[[(4S)-2-(4-Fluoro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-(2,2,2-trifluoroethyl)indazol-5-yl]-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-(oxan-4-yl)indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one [redacted],

3-[(1S,2S)-1-[2-[[(4S)-2-(4-Fluoro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-[(3-methyloxetan-3-yl)methyl]indazol-5-yl]-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-(oxan-4-yl)indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one [redacted]

, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-Fluoro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-(2-hydroxy-2-methylpropyl)indazol-5-yl]-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-(oxan-4-yl)indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one [redacted],

3-[(1S,2S)-1-[5-((4S)-2,2-Dimethyloxan-4-yl)-2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-(2,2,2-trifluoroethyl)indazol-5-yl]-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one

[illegible], 3-[(1S,2S)-1-[5-((4S)-2,2-Dimethyloxan-4-yl)-2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-(2-methoxyethyl)indazol-5-yl]-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one [illegible],

3-[(1S,2S)-1-[5-((4S)-2,2-Dimethyloxan-4-yl)-2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-[(3-methyloxetan-3-yl)methyl]indazol-5-yl]-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one

[illegible], 3-[(1S,2S)-1-[5-((4S)-2,2-Dimethyloxan-4-yl)-2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-(2-hydroxy-2-methylpropyl)indazol-5-yl]-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one [illegible],

3-[(1S,2S)-1-[5-((4S)-2,2-Dimethyloxan-4-yl)-2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-((3S)-oxolan-3-yl)indazol-5-yl]-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one

[illegible], 3-[(1S,2S)-1-[2-[[(4S)-2-(4-Fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-((2S,4S)-methyloxan-4-yl)indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one

[illegible], 3-[(1S,2S)-1-[2-[[(4S)-2-(4-Chloro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-(2,2,2-trifluoroethyl)indazol-5-yl]-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-((4S)-2,2-dimethyloxan-4-yl)indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one [illegible],

3-[(1S,2S)-1-[2-[[(4S)-2-(4-Chloro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-(2-methoxyethyl)indazol-5-yl]-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-((4S)-2,2-dimethyloxan-4-yl)indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one

[illegible], 3-[(1S,2S)-1-[2-[[(4S)-2-(4-Chloro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-(2,2,2-trifluoroethyl)indazol-5-yl]-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-(oxan-4-yl)indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one [illegible],

3-[(1S,2S)-1-[2-[[(4S)-2-(4-Chloro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-(2-methoxyethyl)indazol-5-yl]-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-(oxan-4-yl)indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one [illegible],

3-[(1S,2S)-1-[2-[[(4S)-2-(4-Fluoro-3-methylphenyl)-3-[3-[4-fluoro-1-(2,2,2-trifluoroethyl)indazol-5-yl]-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-(oxan-4-yl)indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one [illegible],

3-[(1S,2S)-1-[2-[[(4S)-3-[3-[4-Fluoro-1-(2-methoxyethyl)indazol-5-yl]-2-oxoimidazol-1-yl]-2-(4-fluoro-3-methylphenyl)-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-(oxan-4-yl)indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one [illegible],

3-[(1S,2S)-1-[5-((4S)-2,2-Dimethyloxan-4-yl)-2-[[(4S)-3-[3-[4-fluoro-1-(2-methoxyethyl)indazol-5-yl]-2-oxoimidazol-1-yl]-2-(4-fluoro-3-methylphenyl)-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]indol-1-yl]-2-methylcyclopropyl]-1,2,4-oxadiazol-5-one [illegible],

3-[(1S,2S)-1-[2-[[(4S)-2-(4-Chloro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-((4S)-2,2-dimethyloxan-4-yl)indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one

[illegible], 3-[(1S,2S)-1-[5-((4S)-2,2-Dimethyloxan-4-yl)-2-[[(4S)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-2-(4-fluoro-3-methylphenyl)-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one

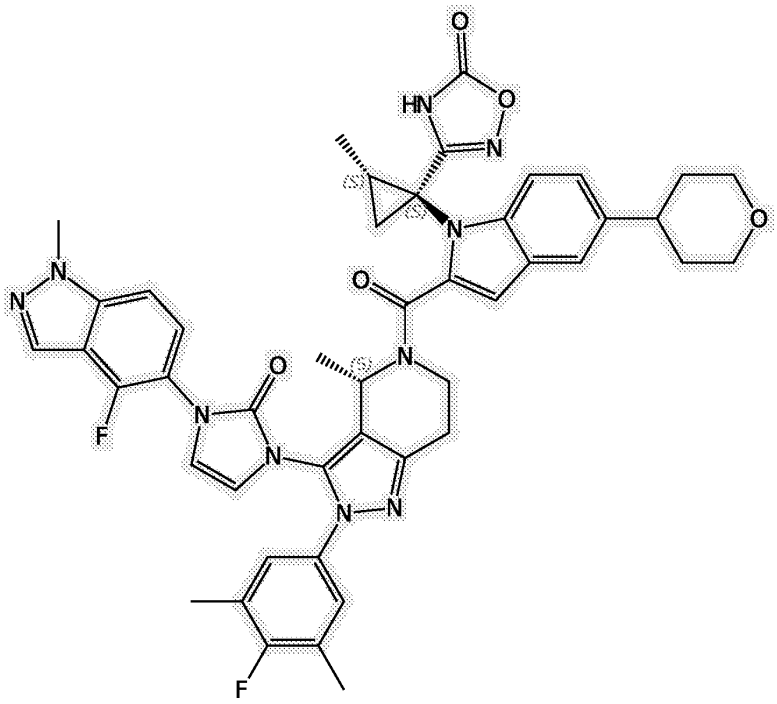
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3-[(1S,2S)-1-[5-((4S)-2,2-Dimethyloxan-4-yl)-2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one sodium salt hydrate

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

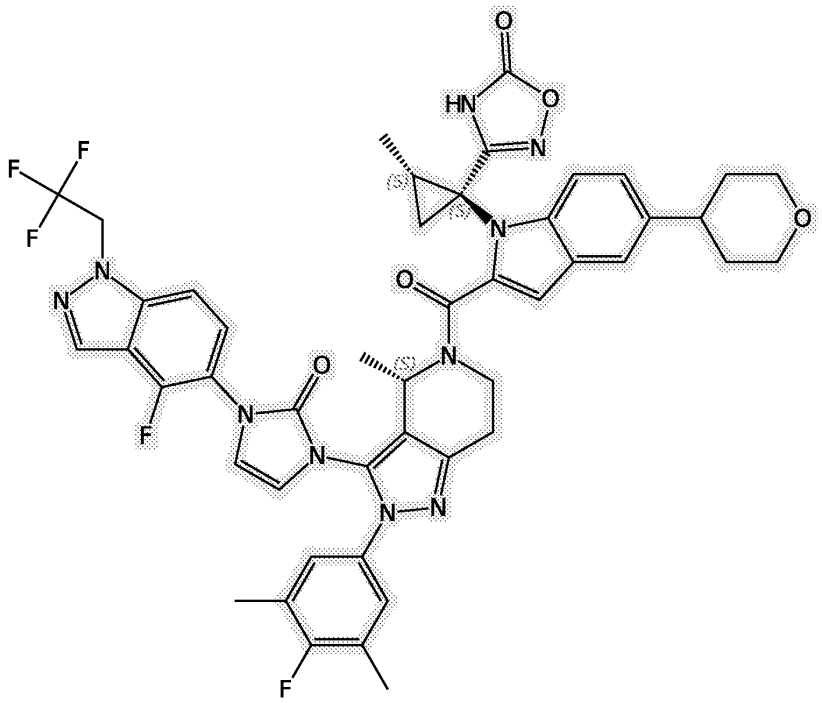
(pharmaceutical compn. contg. pyrazolopyridine deriv. having GLP-1

receptor agonist effect)
RN 2212019-93-5 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-(tetrahydro-2H-pyran-4-yl)-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



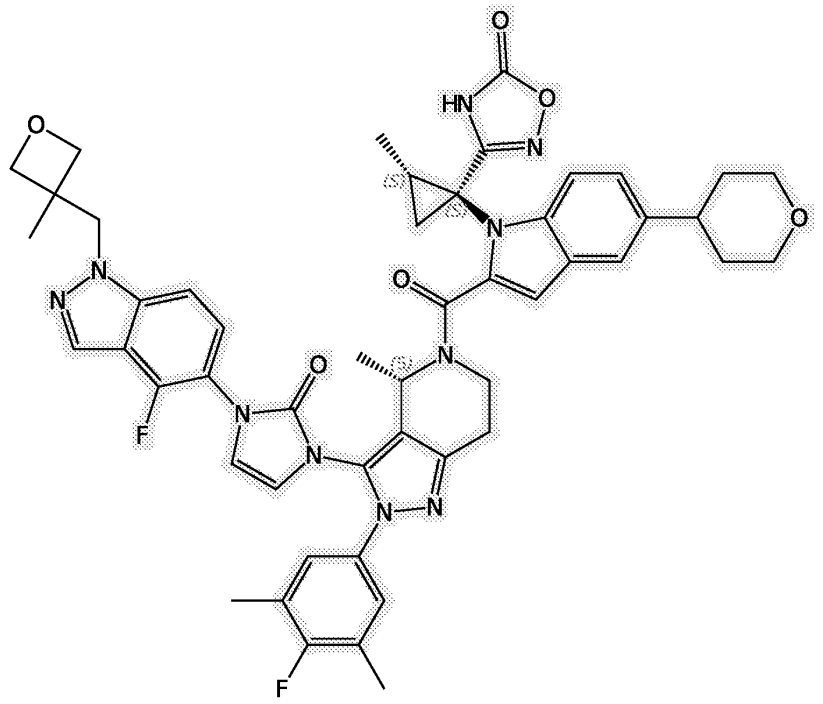
Absolute stereochemistry shown

RN 2212019-98-0 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-(2,2,2-trifluoroethyl)-1H-indazol-5-yl]-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-(tetrahydro-2H-pyran-4-yl)-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



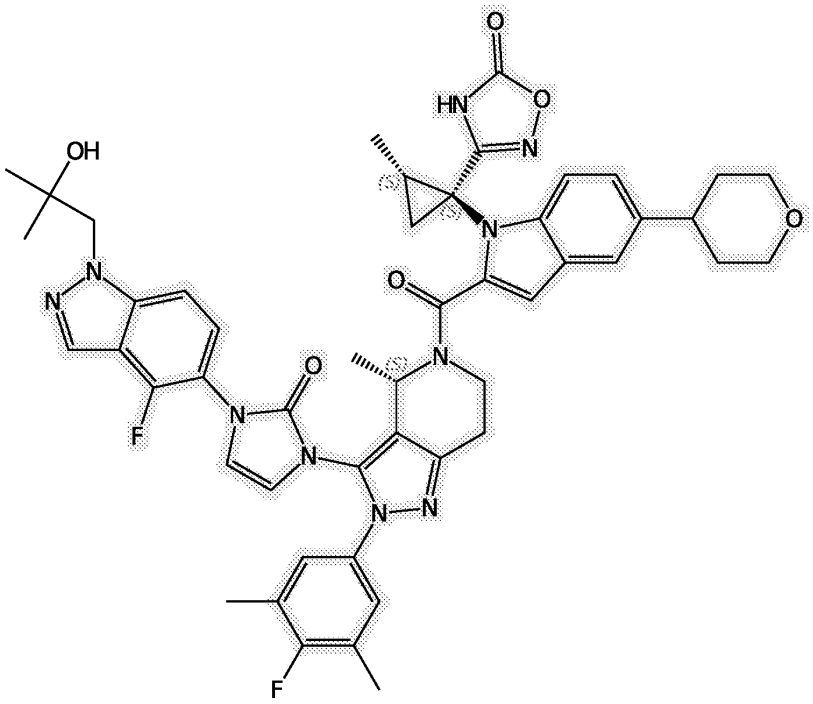
Absolute stereochemistry shown

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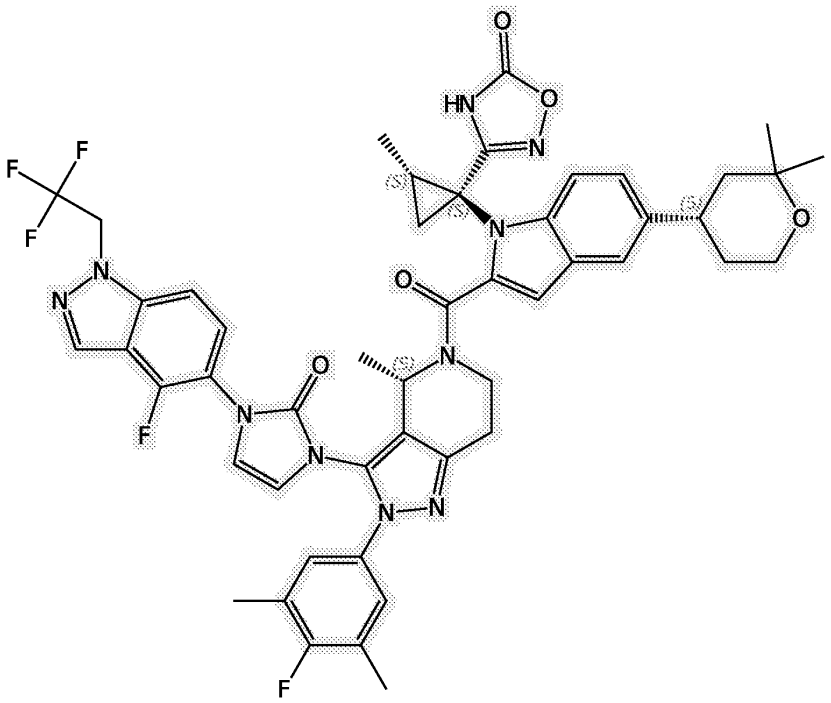
Absolute stereochemistry shown

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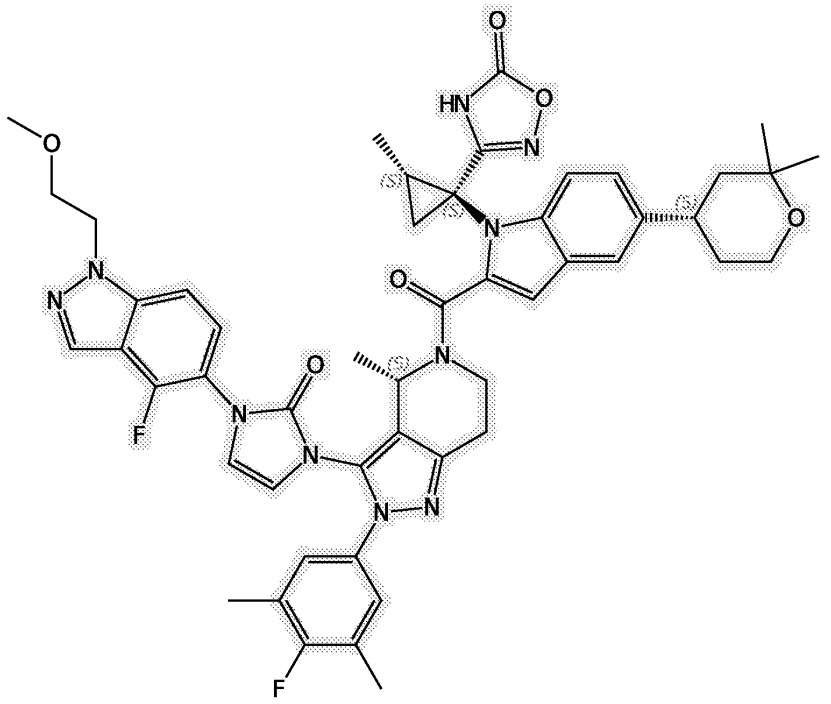
Absolute stereochemistry shown

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CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-(2,2,2-trifluoroethyl)-1H-indazol-5-yl]-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



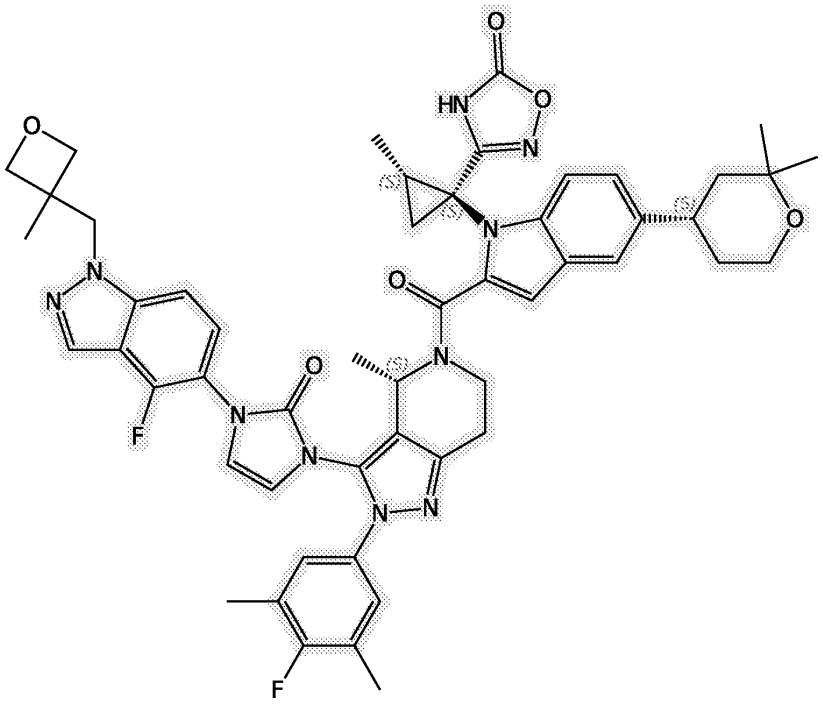
Absolute stereochemistry shown

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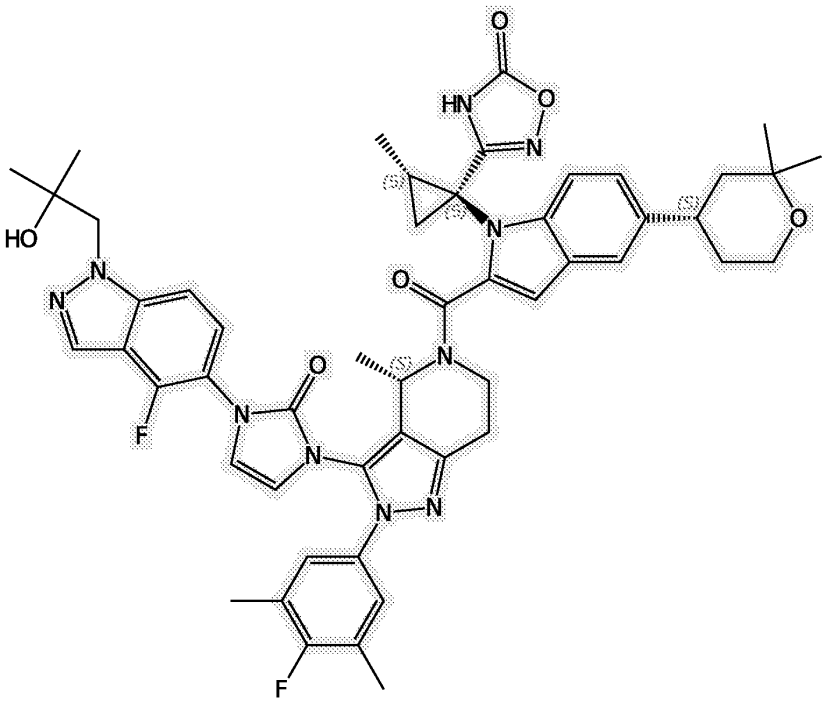
Absolute stereochemistry shown

RN 2212020-07-8 CAPLUS
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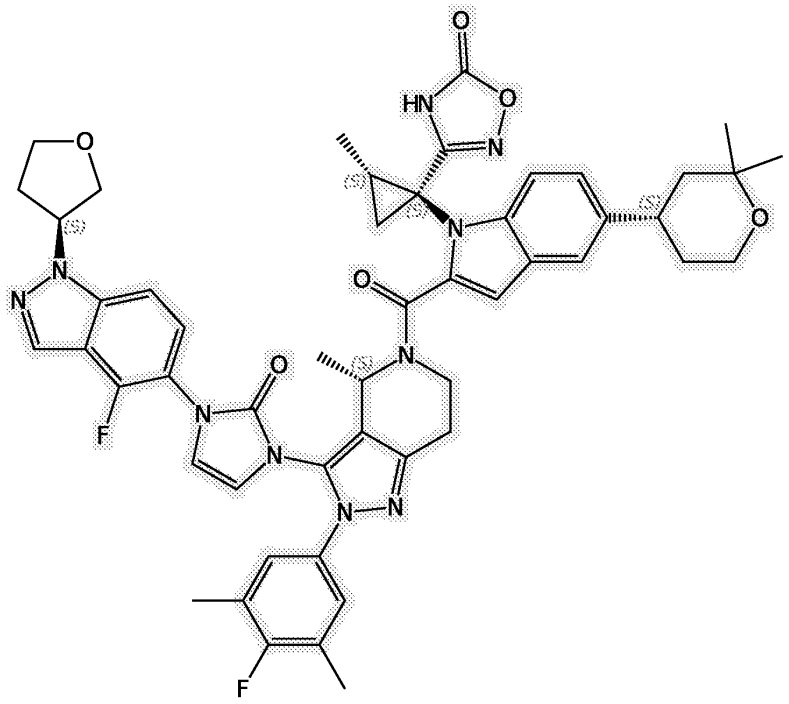
Absolute stereochemistry shown

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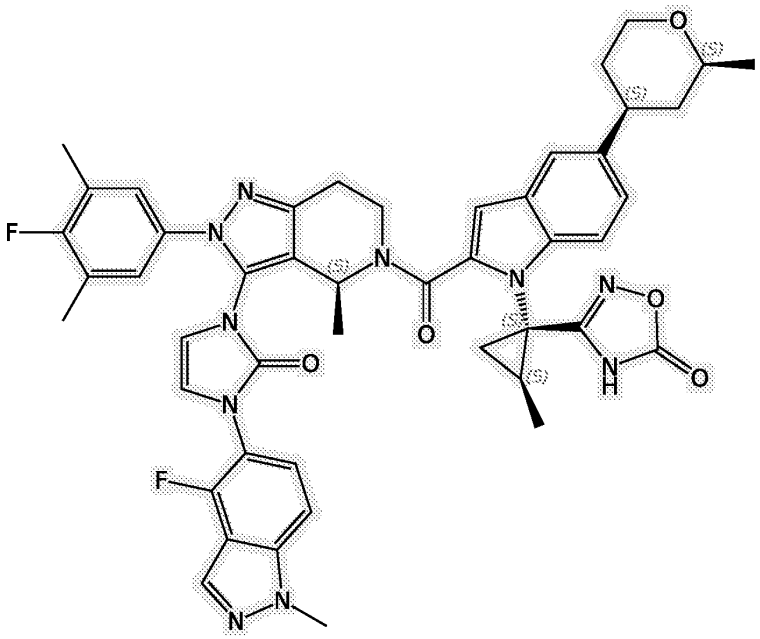
Absolute stereochemistry shown

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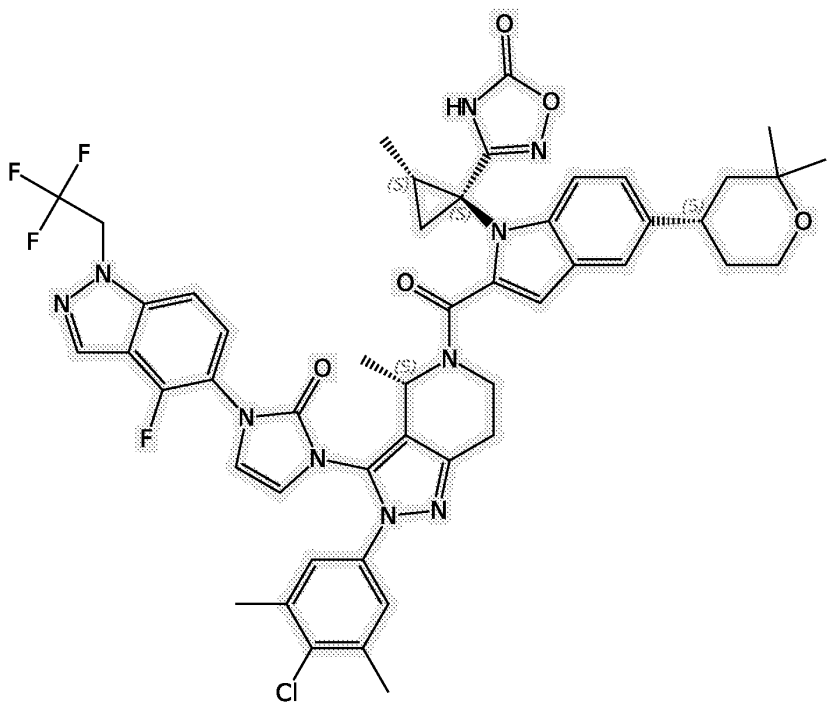
Absolute stereochemistry shown

RN 2212020-11-4 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(2S,4S)-tetrahydro-2-methyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



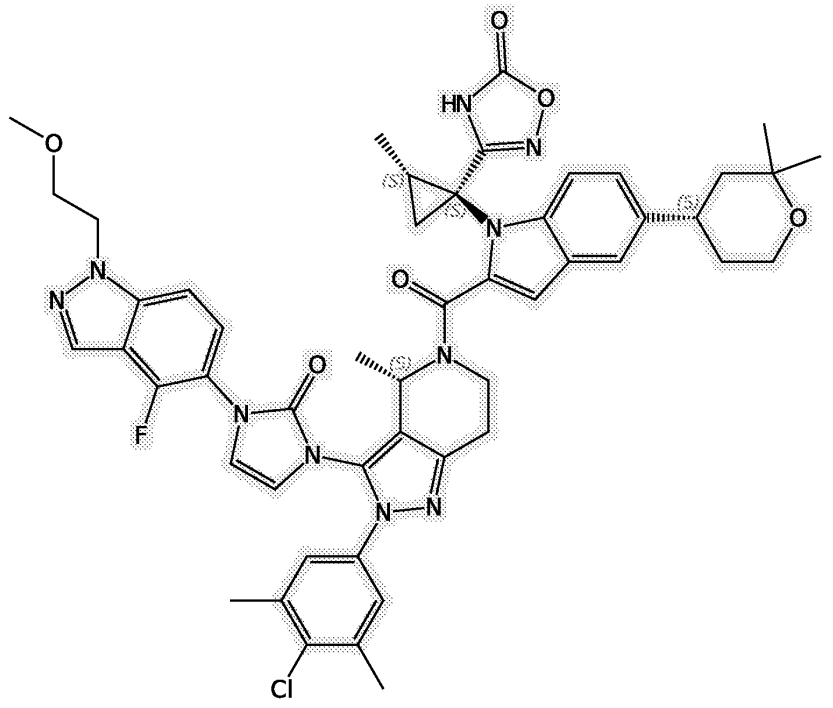
Absolute stereochemistry shown

RN 2212020-12-5 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-chloro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-(2,2,2-trifluoroethyl)-1H-indazol-5-yl]-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



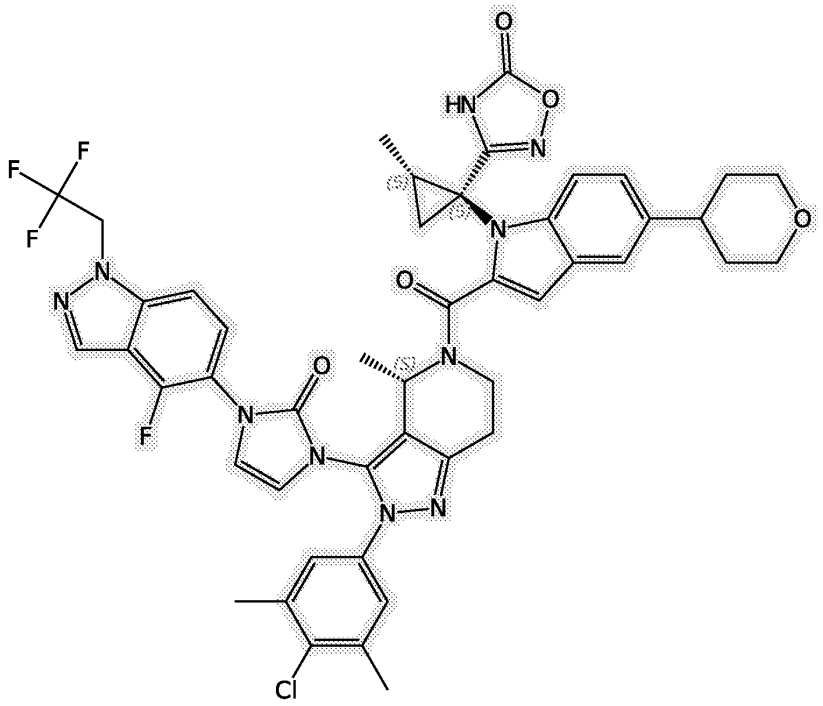
Absolute stereochemistry shown

RN 2212020-13-6 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-chloro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-(2-methoxyethyl)-1H-indazol-5-yl]-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



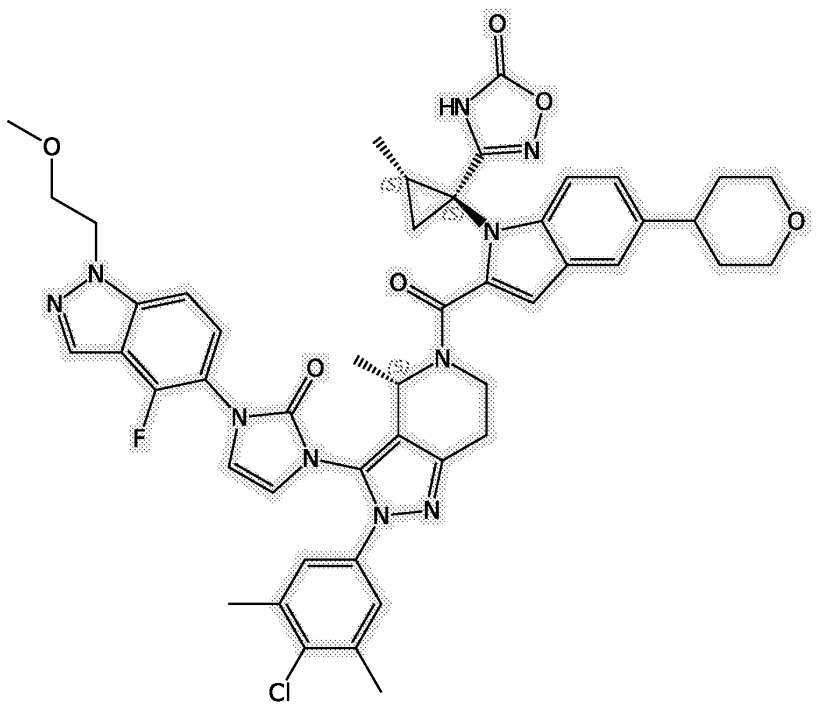
Absolute stereochemistry shown

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CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-chloro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-(2,2,2-trifluoroethyl)-1H-indazol-5-yl]-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-(tetrahydro-2H-pyran-4-yl)-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



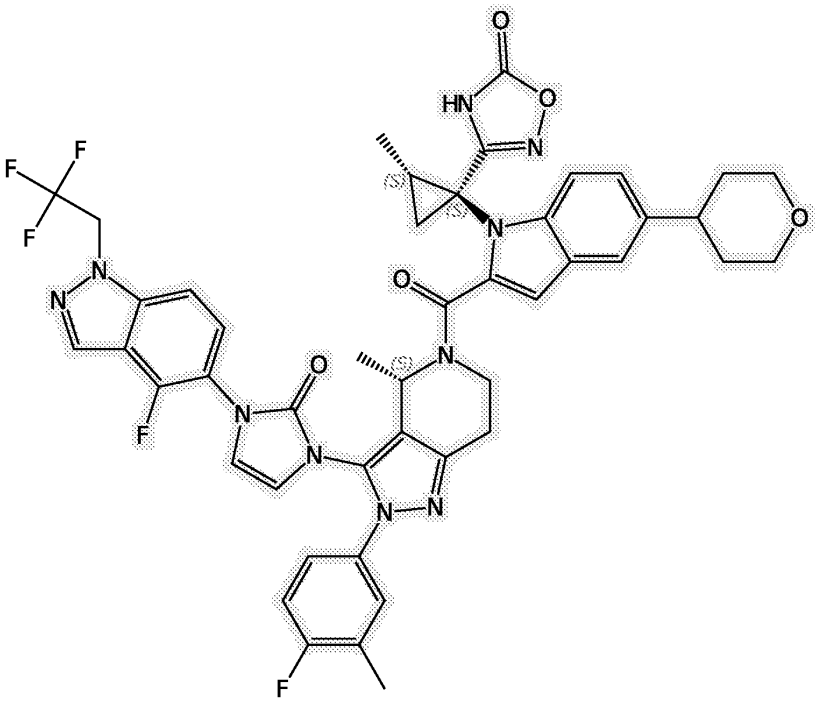
Absolute stereochemistry shown

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CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-chloro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-(2-methoxyethyl)-1H-indazol-5-yl]-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-(tetrahydro-2H-pyran-4-yl)-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



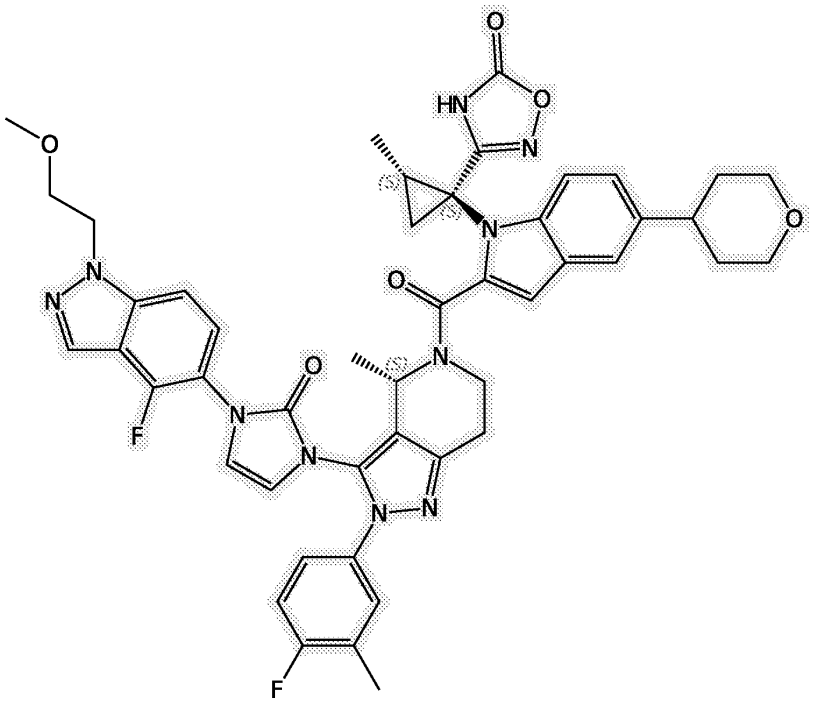
Absolute stereochemistry shown

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CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3-methylphenyl)-3-[3-[4-fluoro-1-(2,2,2-trifluoroethyl)-1H-indazol-5-yl]-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-(tetrahydro-2H-pyran-4-yl)-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



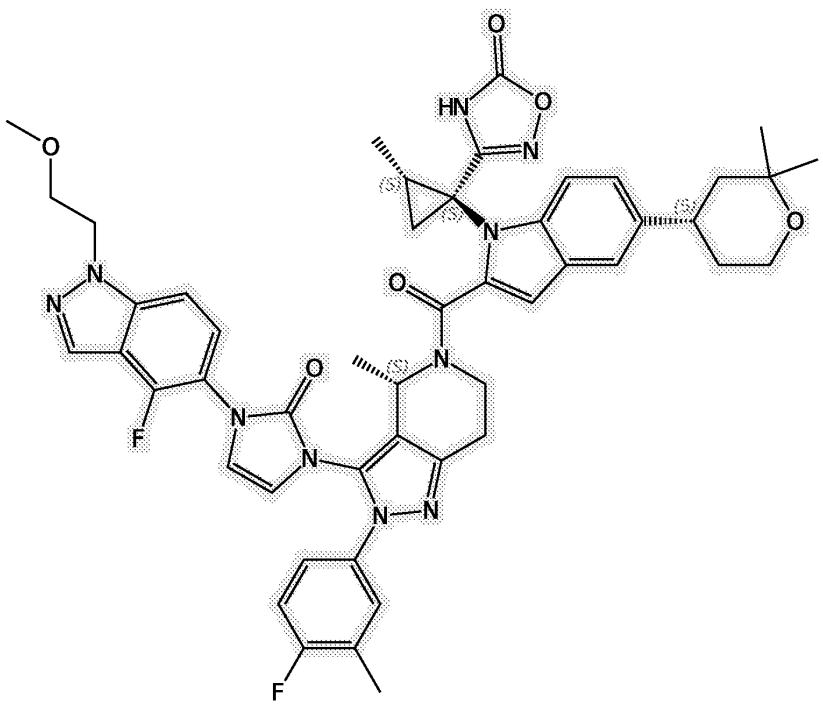
Absolute stereochemistry shown

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CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-3-[3-[4-fluoro-1-(2-metho
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NAME)



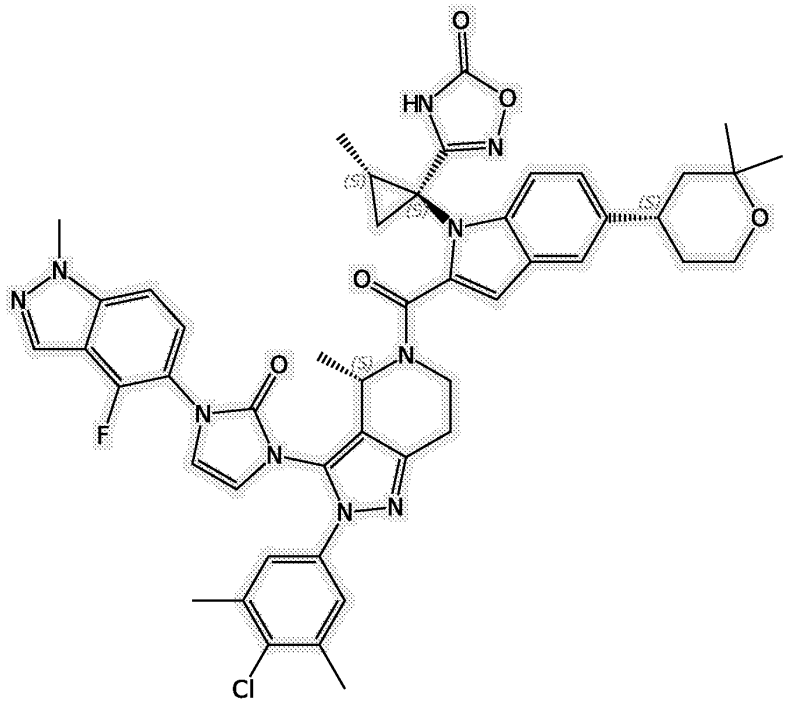
Absolute stereochemistry shown

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CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-3-[3-[4-fluoro-1-(2-metho
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ylphenyl)-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5
-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl
]- (CA INDEX NAME)



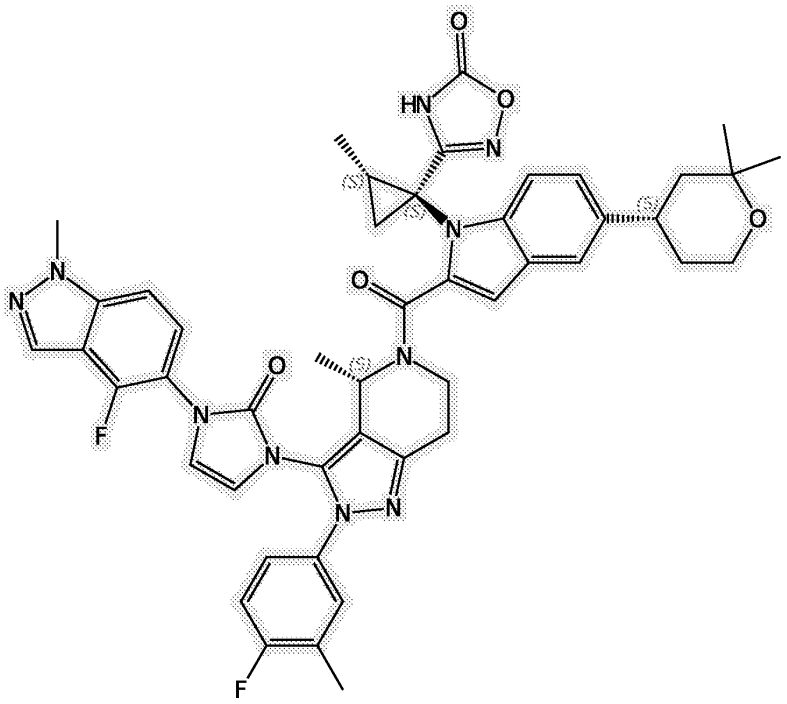
Absolute stereochemistry shown

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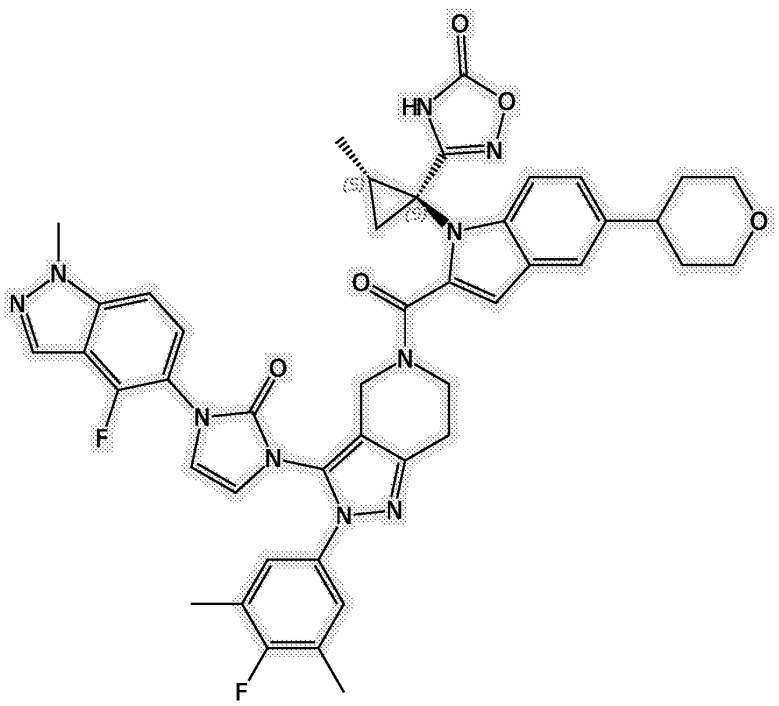
Absolute stereochemistry shown

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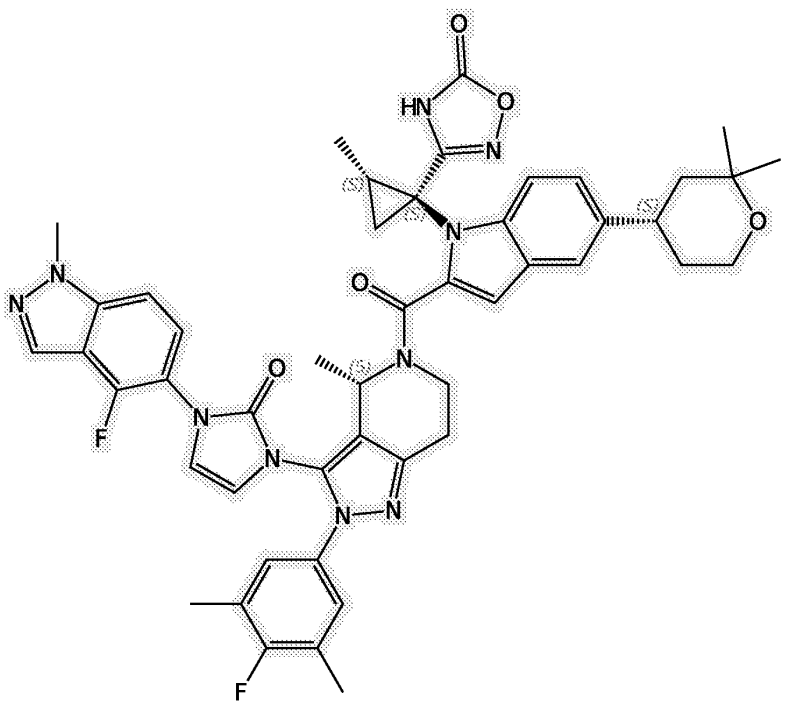
Absolute stereochemistry shown

RN 2212020-74-9 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-(tetrahydro-2H-pyran-4-yl)-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



Absolute stereochemistry shown

RN 2212021-26-4 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]-, sodium salt, hydrate (1:1:1) (CA INDEX NAME)



• Na

• H_2O

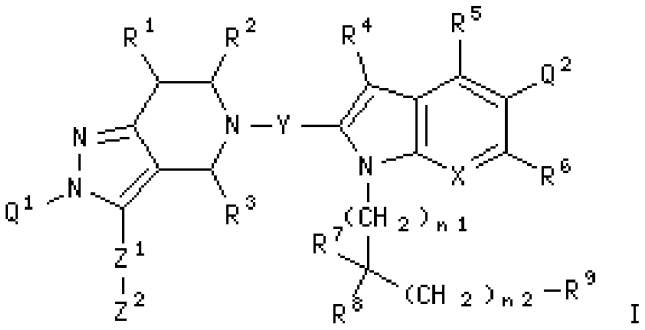
Absolute stereochemistry shown

OSC.G 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

LINK INFORMATION

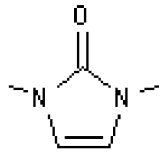
PUBLICATIONS	APPLICATIONS	REGISTER
JP 2019099571 A	JP 2018-223465	Register|Global Dossier
JP 7461104 B2	JP 2018-223465	Register|Global Dossier
JP 2024079762 A	JP 2024-45935	Register|Global Dossier

L3 ANSWER 38 OF 38 CAPLUS COPYRIGHT 2024 ACS on STN
GI

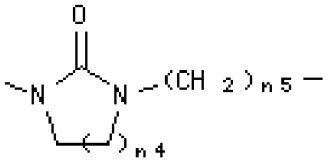


I

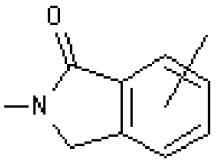
Q^3 =



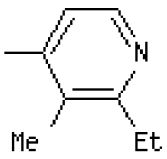
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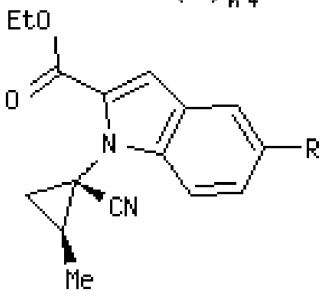


Q^5 =

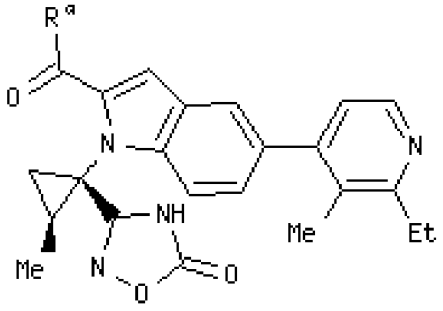


Q^6 =



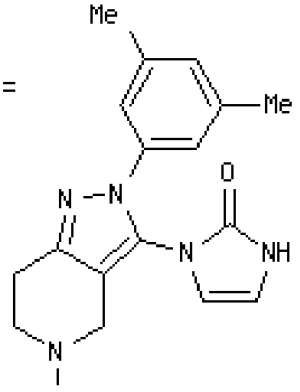


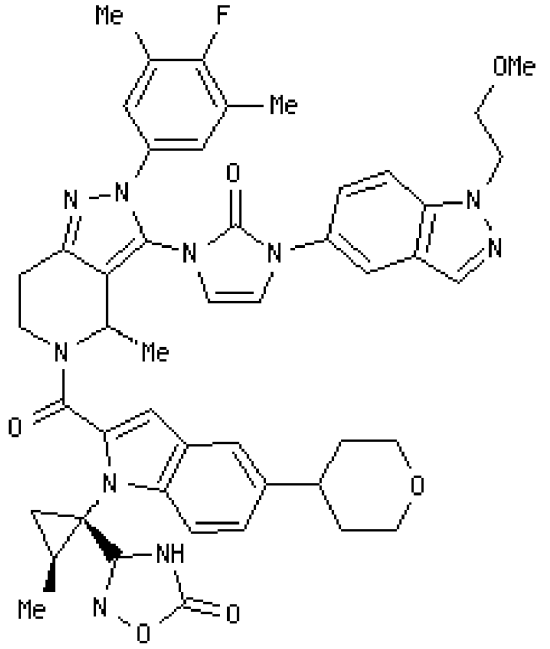
II



III

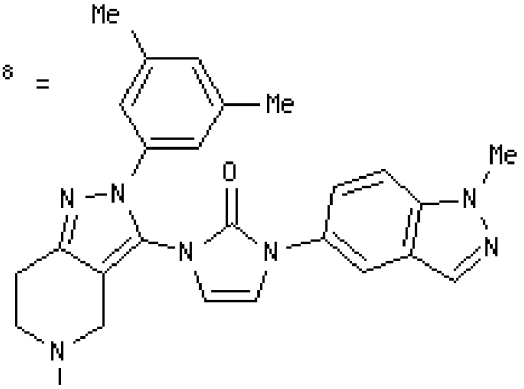
Q^7 =





IV

Q^8 =



AB The present invention provides pyrrolo[2,3-b]pyridine compds. represented by formula I [X = N or (un)substituted CH; Y = C(O), C1-6 alkyl-(un)substituted CH2, or S(O)2; Q1 = each (un)substituted C6-10 aryl or 5- to 10-membered heteroaryl; Q2 = each (un)substituted 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl; R1, R2, R3 = each independently H or (un)substituted C1-6 alkyl; R4, R5, R6 = H, halo, or C1-6 alkyl; R7, R8 = each independently H or (un)substituted C1-6 alkyl; or CR7R8 together form (un)substituted C3-15 cycloalkane ring; n1 = 0, 1, 2, or 3; n2 = an integer of 0-5; R9 = each (un)substituted 1,2,3,4-1H-tetrazol-5-yl, 5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl, 2H-1,2,4-triazol-3-yl, or 5-oxo-4,5-dihydro-1,2,4-thiadiazol-3-yl; Z1 = Q3, Q4, Q5, or each N-(un)substituted NH or CHCONH(CH2)n6; n4 = 1, 2, or 3; n5, n6 = each independently an integer of 0-10; Z2 = C1-6 alkyl or each (un)substituted C3-15 cycloalkyl, 3- to 12-membered heterocyclyl, C6-10 aryl, or 5- to 10-membered heteroaryl], salts thereof, or solvates thereof. The compds. are glucagon-like peptide-1 (GLP-1) receptor agonists and are useful as preventive or therapeutic medications for non-insulin dependent diabetes mellitus (type 2 diabetes), hyperglycemia, impaired glucose tolerance, insulin dependent diabetes mellitus (type 1 diabetes), diabetic complications, obesity, hypertension, dyslipidemia, arteriosclerosis, coronary heart disease, cerebral infarction, nonalcoholic steatohepatitis, Parkinson's disease, or dementia. Thus, stereoselective cyclopropanation of 5-bromo-1-(cyanomethyl)indole-2-carboxylic acid Et ester by (4R)-4-Methyl-1,3,2-dioxathiolane 2,2-dioxide in the presence of potassium bis(trimethylsilyl)amide in N,N'-dimethylpropyleneurea at 0° for 2.5 h gave 42% 5-bromo-1-[(1S,2S)-1-cyano-2-methylcyclopropyl]indole-2-carboxylic acid Et ester (II; R = Br) which underwent one-pot sequential coupling with 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) in the presence of potassium acetate and 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride-CH2Cl2 complex in dioxane at 100° for 3 h and then with 4-bromo-2-ethyl-3-methylpyridine in the presence of sodium acetate in aq. dioxane at 100° for 2 h to give 97% 1-[(1S,2S)-1-cyano-2-methylcyclopropyl]-5-(2-ethyl-3-methylpyridin-4-yl)indole-2-carboxylic acid Et ester II (R = Q6). Addn. reaction of II (R = Q6) with hydroxylamine in aq. DMSO at room temp. for 17 h followed by cyclocondensation reaction with N,N'-carbonyldiimidazole in the presence of 1,8-diazacycloundec-7-ene in DMSO at room temp. for 0.5 h gave 65% 5-(2-Ethyl-3-methylpyridin-4-yl)-1-[(1S,2S)-2-methyl-1-(5-oxo-4H-1.2.4-oxadiazol-3-yl)cyclopropyl]indole-2-carboxylic acid Et ester (III; Ra = EtO). Sapon. of III (Ra = EtO) with a mixt. of 2 M aq. NaOH soln. and DMSO at room temp. for 1.5 h followed by acidification with formic acid gave 100% III (Ra = HO) which underwent amidation with 3-[2-(3,5-dimethylphenyl)-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridin-3-yl]-1H-imidazol-2-one using [dimethylamino(triazolo[4,5-b]pyridin-3-yloxy)methylene]dimethylazanium hexafluorophosphate in the presence of diisopropylethylamine in N,N-dimethylformamide at room temp. for 30 min to give 95% III (Ra = Q7). N-heteroarylation of III (Ra = Q7) with 5-bromo-1-methylindazole in the presence of (1S,2S)-N1,N2-dimethylcyclohexane-1,2-diamine, CuI, and K2CO3 in N-methylpyrrolidone at 130° for 3 h gave 73% III (Ra = Q8). III (Ra = Q8) and 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-[1-(2-methoxyethyl)indazol-5-yl]-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-(oxan-4-yl)indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one (IV) increased the prodn. of cAMP in gGLP1R-HEK293 cell stably expressing human GLP-1 receptor with EC50 of 8.8 and 0.51 nM, resp., relative to the cAMP concn. (100%) when human GLP-1 (7-37) (control) was used.

AN 2018:619220 CAPLUS Full-text

DN 168:377246

TI Preparation of pyrazolopyridines derivatives having glucagon-like peptide-1 (GLP-1) receptor agonist effect

IN Yoshino, Hitoshi; Tsuchiya, Satoshi; Matsuo, Atsushi; Sato, Tsutomu; Nishimoto, Masahiro; Oguri, Kyoko; Ogawa, Hiroko; Nishimura, Yoshikazu; Furuta, Yoshiyuki; Kashiwagi, Hirotaka; Hori, Nobuyuki; Kamon, Takuma; Shiraishi, Takuya; Yoshida, Shoshin; Kawai, Takahiro; Tanida, Satoshi; Aoki, Masahide

PA Chugai Seiyaku Kabushiki Kaisha, Japan

UO ROCHE HOLDING AG; Chugai Pharmaceutical (in: Roche)
UOS Roche; Chugai Pharmaceutical (in: Roche)
SO PCT Int. Appl., 247pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1
PI

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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	JO 2019000060	A1	20190326	JO 2019-60	20170616
	CA 3038479	A1	20180329	CA 2017-3038479	20170926
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	AU 2017330733	A1	20190314	AU 2017-330733	20170926
	AU 2017330733	B2	20200528		
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	KR 2223227	B1	20210308		
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	JP 7280929	B2	20230524		
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	AU 2022205222	A1	20220804	AU 2022-205222	20220713
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	JP 2023100963	A	20230719	JP 2023-79006	20230512
	US 20230382912	A1	20231130	US 2023-18448497	20230811
	US 20240246971	A1	20240725	US 2024-18584672	20240222
	US 20240262824	A1	20240808	US 2024-18584177	20240222
	AU 2024201884	A1	20240411	AU 2024-201884	20240322
PRAI	JP 2016-187605	A	20160926		
	AU 2017-330733	A3	20170926		
	EP 2017-853220	A3	20170926		

IL 2017-264945	A3	20170926	
JP 2018-540344	A3	20170926	
SG 2019-11201901565	A3	20170926	
WO 2017-JP34620	W	20170926	
US 2018-15759872	A1	20180314	
JP 2019-141806	A3	20190731	
AU 2020-223687	A3	20200826	
US 2020-17065122	A1	20201007	
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US 2023-18448497	A1	20230811	

PSPI

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2018056453	A1	Dead	20210527
JO 2019000060	A1	Alive	20210430
CA 3038479	A1	Alive	20201121
CA 3038479	C	Alive	20210708
AU 2017330733	A1	Alive	20201120
AU 2017330733	B2	Alive	20201121
KR 2019039591	A	Alive	20210204
KR 2223227	B1	Alive	20210408
IL 264945	A	Alive	20211125
CN 109790161	A	Alive	20201120
CN 109790161	B	Alive	20220324
UA 125586	C2	Alive	20220519
BR 112019005322	A2	Alive	20201120
EP 3517538	A1	Indeterminate	20240314
EP 3517538	B1	Indeterminate	20240314
MA 46286	A	Alive	20210923
JP 6567778	B2	Alive	20201120
MX 2019003488	A	Alive	20201120
NZ 751725	A	Alive	20210820
EA 37989	B1	Indeterminate	20210729
TW I753946	B	Alive	20220512
EP 4134367	A1	Dead	20240725
EP 4349840	A2	Alive	20240411
EP 4349840	A3	Alive	20240411
RS 65398	B1	Alive	20240516
US 20190225604	A1	Alive	20201121
US 10858356	B2	Alive	20201217
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SA 519401409	B1	Alive	20220908
JP 2019203015	A	Alive	20201121
JP 6957564	B2	Alive	20211124
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AU 2020223687	B2	Alive	20220421
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US 11814381	B2	Alive	20231123
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JP 7280929	B2	Alive	20230601
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US 20240246971	A1	Alive	20240801
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AU 2024201884	A1	Alive	20240425

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

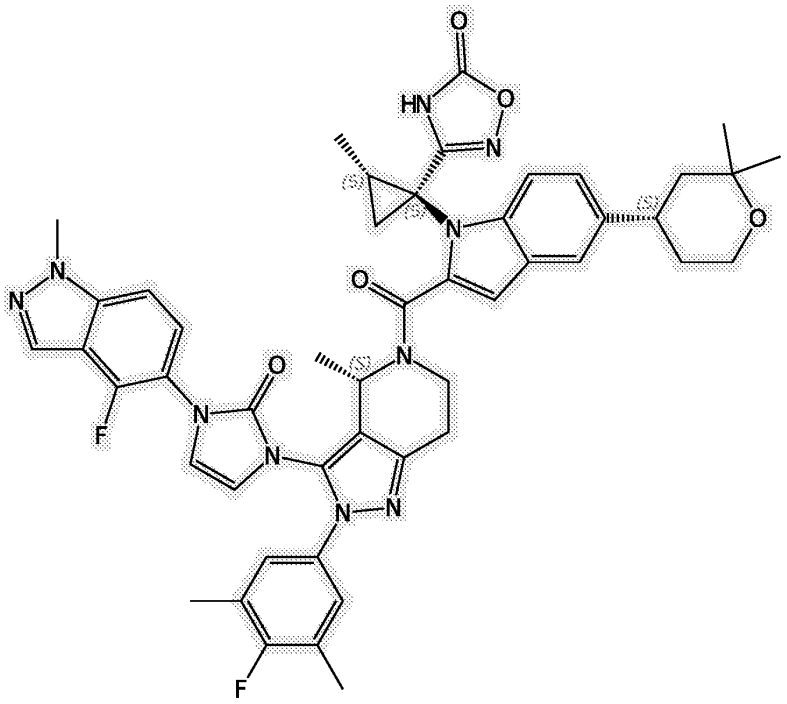
OS CASREACT 168:377246; MARPAT 168:377246; CASFORMULTNS 2018:619220

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RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(prepn. of pyrazolopyridines derivs. as glucagon-like peptide-1 (GLP-1)

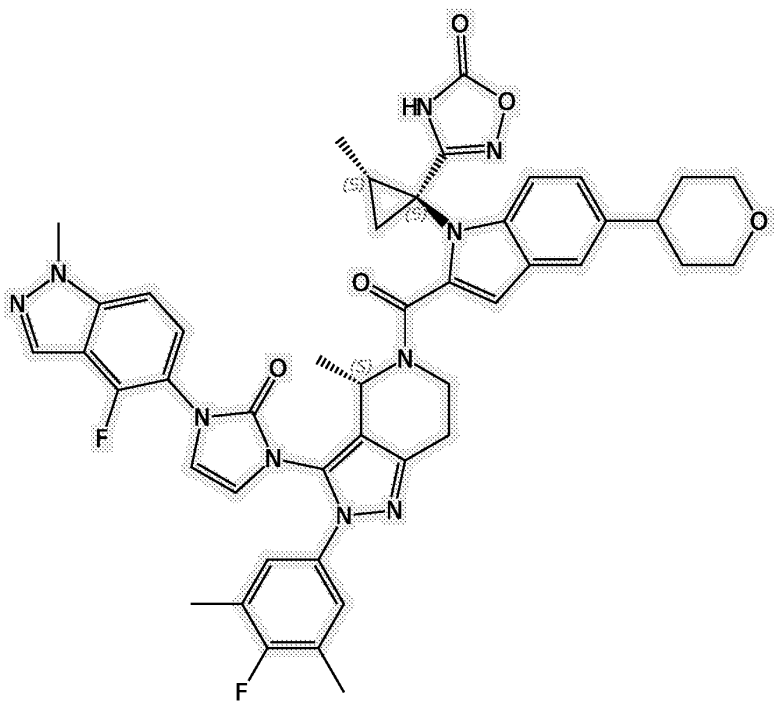
receptor agonists)
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Absolute stereochemistry shown

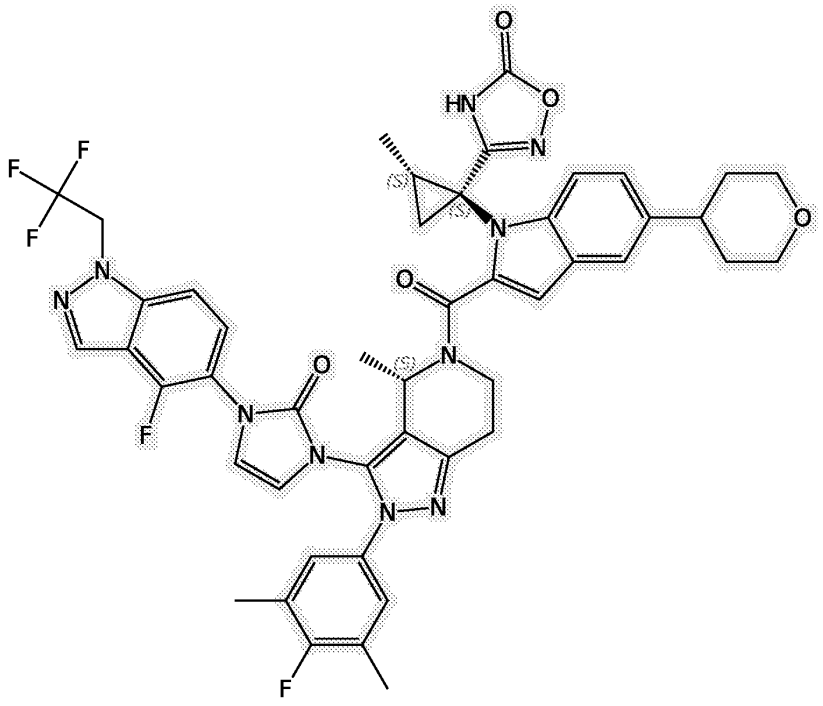
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2212019-98-0P, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-Fluoro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-(2,2,2-trifluoroethyl)indazol-5-yl]-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-(oxan-4-yl)indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one 2212019-99-1P,
3-[(1S,2S)-1-[2-[[(4S)-2-(4-Fluoro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-[(3-methyloxetan-3-yl)methyl]indazol-5-yl]-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-(oxan-4-yl)indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one 2212020-00-1P
, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-Fluoro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-(2-hydroxy-2-methylpropyl)indazol-5-yl]-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-(oxan-4-yl)indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one 2212020-05-6P,
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2212020-06-7P, 3-[(1S,2S)-1-[5-((4S)-2,2-Dimethyloxan-4-yl)-2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-(2-methoxyethyl)indazol-5-yl]-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one 2212020-07-8P,
3-[(1S,2S)-1-[5-((4S)-2,2-Dimethyloxan-4-yl)-2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-[(3-methyloxetan-3-yl)methyl]indazol-5-yl]-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one
2212020-08-9P, 3-[(1S,2S)-1-[5-((4S)-2,2-Dimethyloxan-4-yl)-2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-(2-hydroxy-2-methylpropyl)indazol-5-y

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nyl]indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one 2212020-10-3P,
    3-[(1S,2S)-1-[5-((4S)-2,2-Dimethyloxan-4-yl)-2-[[(4S)-2-(4-fluoro-3,5-dimet
hylphenyl)-3-[3-[4-fluoro-1-((3S)-oxolan-3-yl)indazol-5-yl]-2-oxoimidazol-1-yl]-
4-methyl-6,7-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]indol-1-yl]-2-methy
lcyclopropyl]-4H-1,2,4-oxadiazol-5-one
    2212020-11-4P, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-Fluoro-3,5-dimethylphenyl)-3-[3-
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zolo[4,3-c]pyridin-5-yl]carbonyl]-5-((2S,4S)-methyloxan-4-yl)indol-1-yl]-2-methy
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indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadiazol-5-one 2212020-13-6P,
    3-[(1S,2S)-1-[2-[[(4S)-2-(4-Chloro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-(2-
methoxyethyl)indazol-5-yl]-2-oxoimidazol-1-yl]-4-methyl-6,7-dihydro-4H-pyrazolo[
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hylcyclopropyl]-4H-1,2,4-oxadiazol-5-one 2212020-15-8P,
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4,3-c]pyridin-5-yl]carbonyl]-5-(oxan-4-yl)indol-1-yl]-2-methylcyclopropyl]-4H-1,
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o[4,3-c]pyridin-5-yl]carbonyl]-5-(oxan-4-yl)indol-1-yl]-2-methylcyclopropyl]-4H-
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c]pyridin-5-yl]carbonyl]-5-(oxan-4-yl)indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-
oxadiazol-5-one 2212020-18-1P,
    3-[(1S,2S)-1-[5-((4S)-2,2-Dimethyloxan-4-yl)-2-[[(4S)-3-[3-[4-fluoro-1-(2-m
ethoxyethyl)indazol-5-yl]-2-oxoimidazol-1-yl]-2-(4-fluoro-3-methylphenyl)-4-meth
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propyl]-1,2,4-oxadiazol-5-one 2213020-50-1P,
    3-[(1S,2S)-1-[2-[[(4S)-2-(4-Chloro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-met
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din-5-yl]carbonyl]-5-((4S)-2,2-dimethyloxan-4-yl)indol-1-yl]-2-methylcyclopropyl
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cyclopropyl]-4H-1,2,4-oxadiazol-5-one
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idin-5-yl]carbonyl]-5-(oxan-4-yl)indol-1-yl]-2-methylcyclopropyl]-4H-1,2,4-oxadi
azol-5-one 2212021-26-4P,
    3-[(1S,2S)-1-[5-((4S)-2,2-Dimethyloxan-4-yl)-2-[[(4S)-2-(4-fluoro-3,5-dimet
hylphenyl)-3-[3-(4-fluoro-1-methylindazol-5-yl)-2-oxoimidazol-1-yl]-4-methyl-6,7
-dihydro-4H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]indol-1-yl]-2-methylcyclopropyl
]-4H-1,2,4-oxadiazol-5-one sodium salt hydrate
    RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
    (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
    (Uses)
       (prepn. of pyrazolopyridines derivs. as glucagon-like peptide-1 (GLP-1)
       receptor agonists)
RN 2212019-93-5 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylp
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yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-(tetr
ahydro-2H-pyran-4-yl)-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



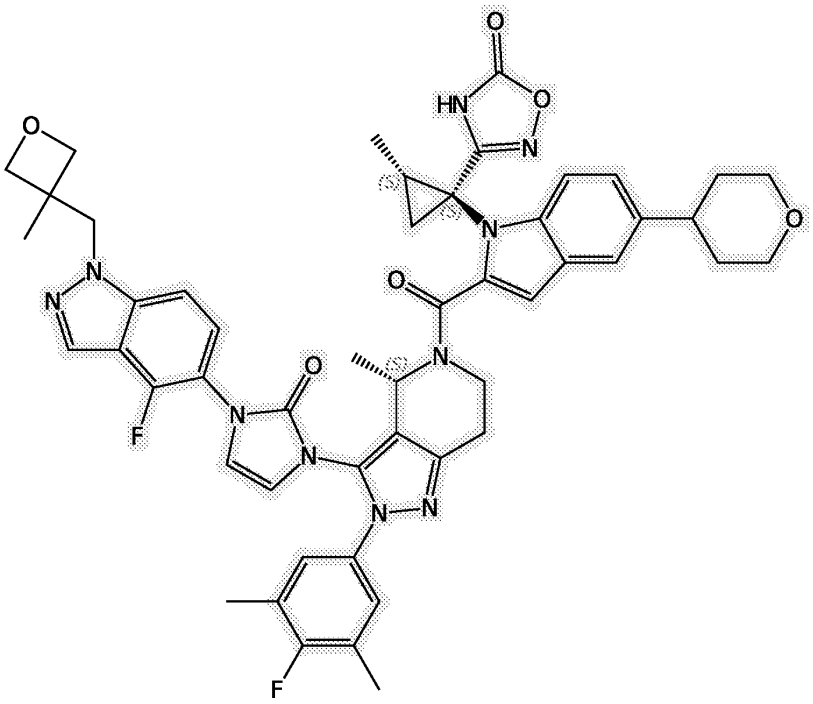
Absolute stereochemistry shown

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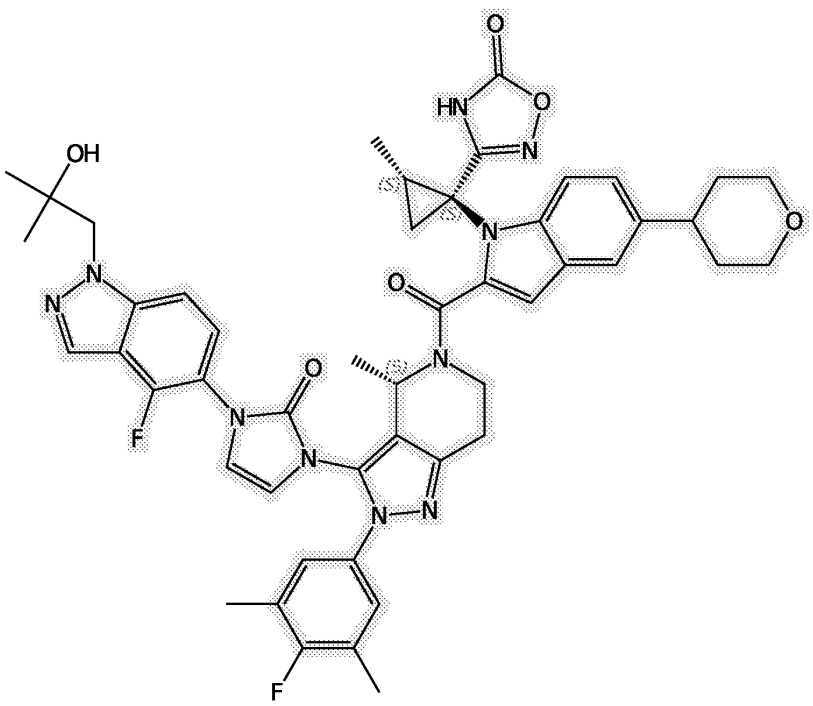
Absolute stereochemistry shown

RN 2212019-99-1 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-[(3-methyl-3-oxetanyl)methyl]-1H-indazol-5-yl]-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-(tetrahydro-2H-pyran-4-yl)-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



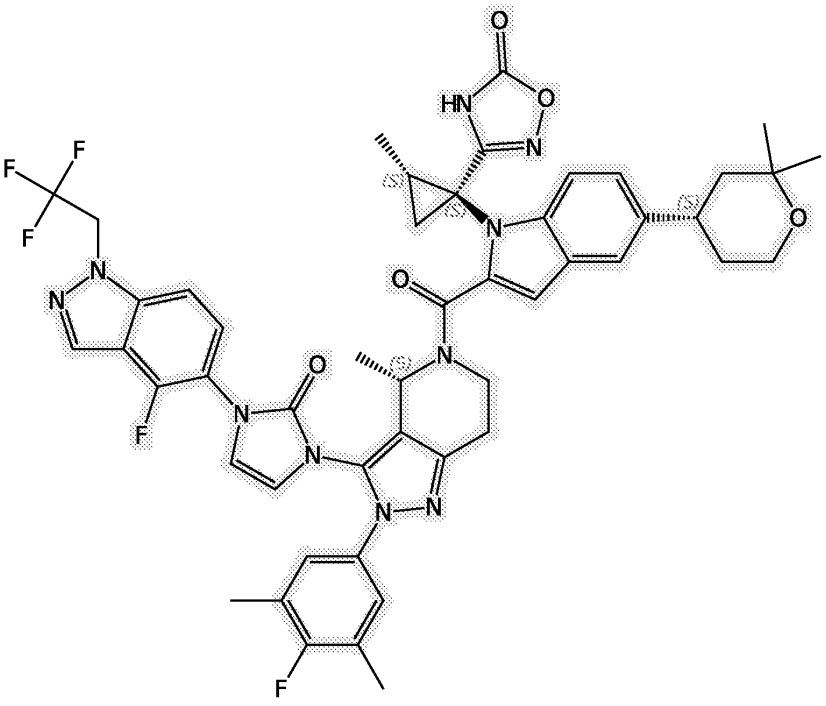
Absolute stereochemistry shown

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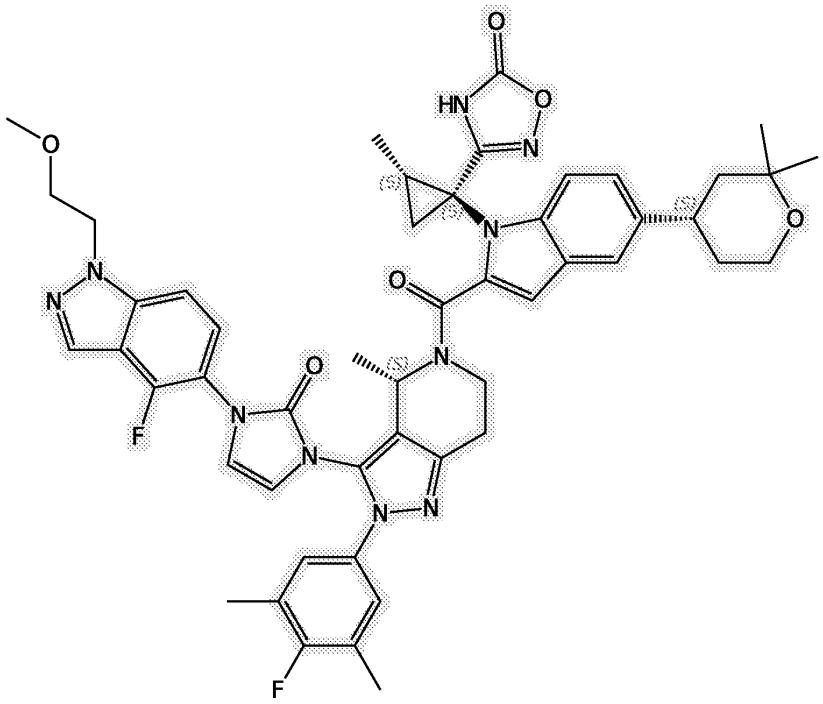
Absolute stereochemistry shown

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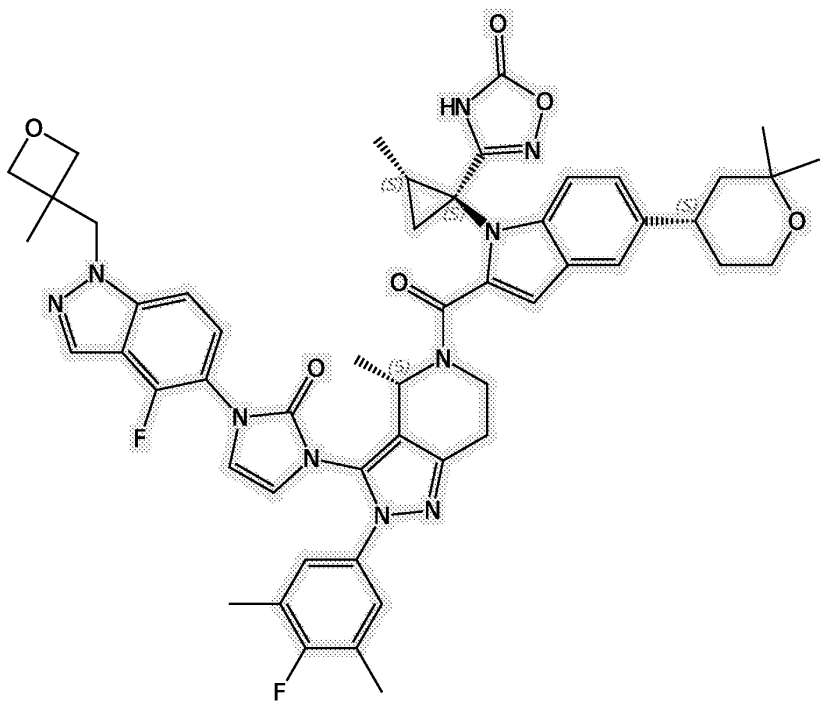
Absolute stereochemistry shown

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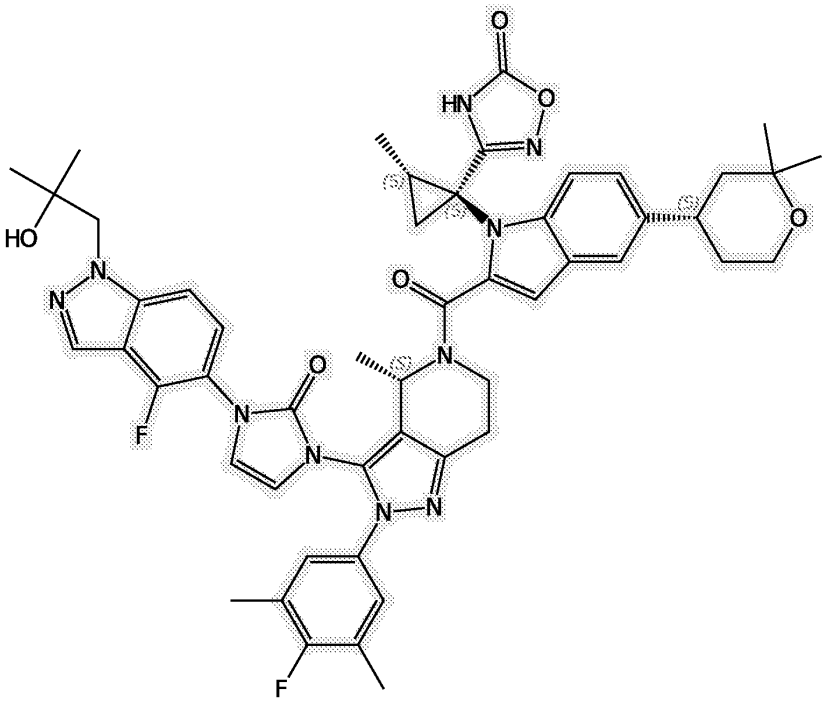
Absolute stereochemistry shown

RN 2212020-07-8 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-[(3-methyl-3-oxetanyl)methyl]-1H-indazol-5-yl]-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



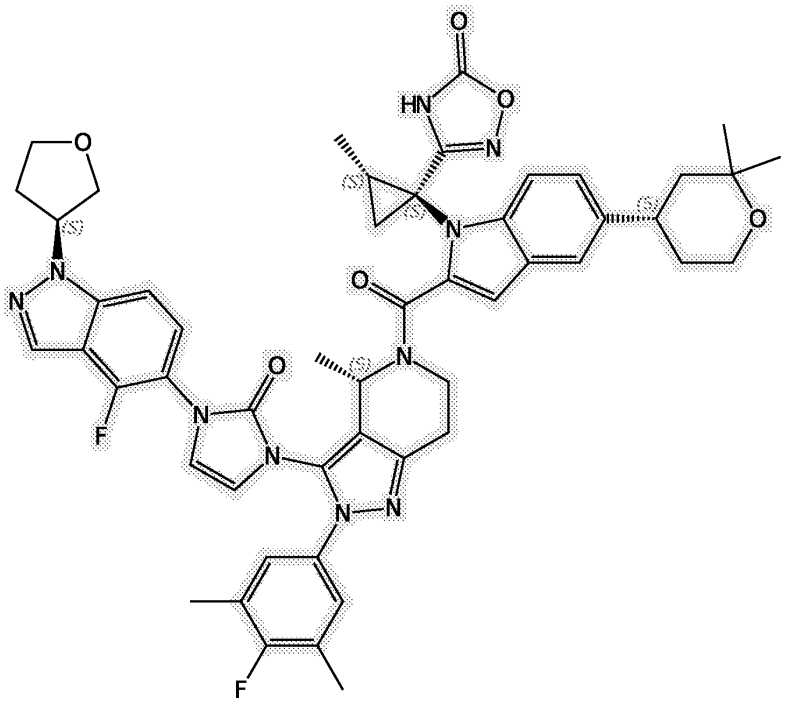
Absolute stereochemistry shown

RN 2212020-08-9 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-[4-fluoro-1-(2-hydroxy-2-methylpropyl)-1H-indazol-5-yl]-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]- (CA INDEX NAME)



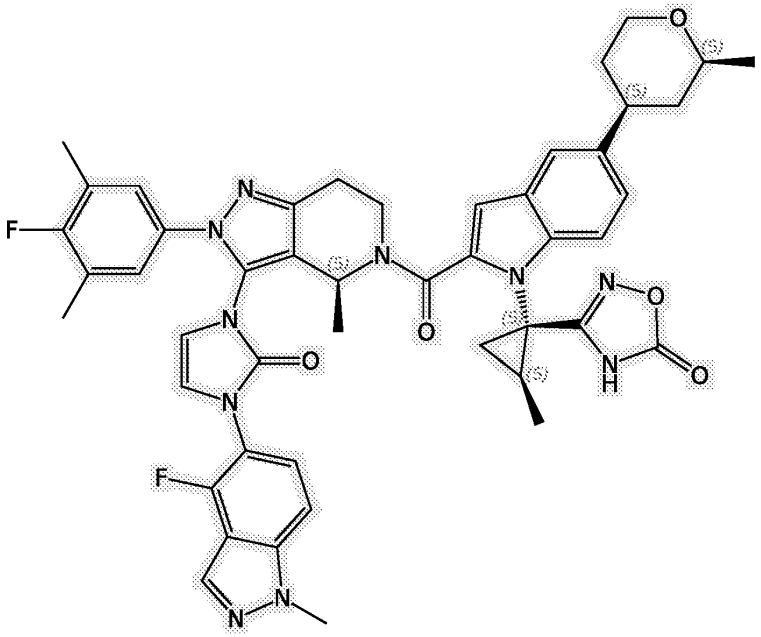
Absolute stereochemistry shown

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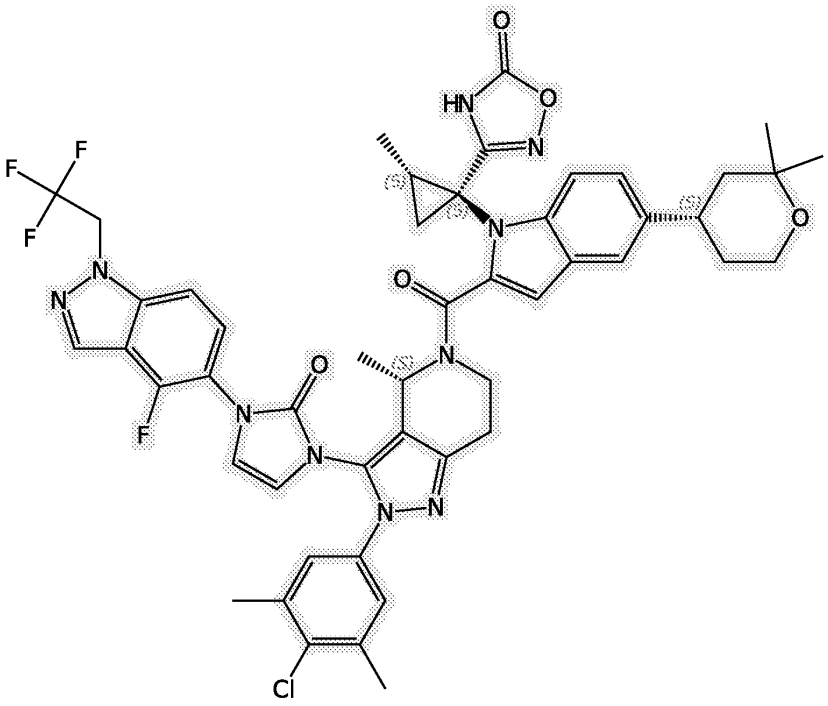
Absolute stereochemistry shown

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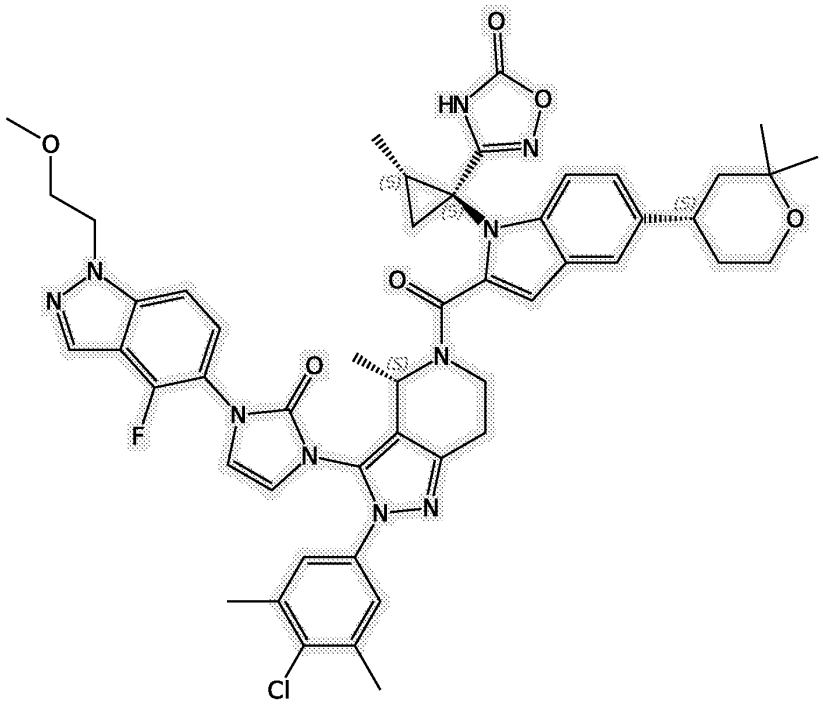
Absolute stereochemistry shown

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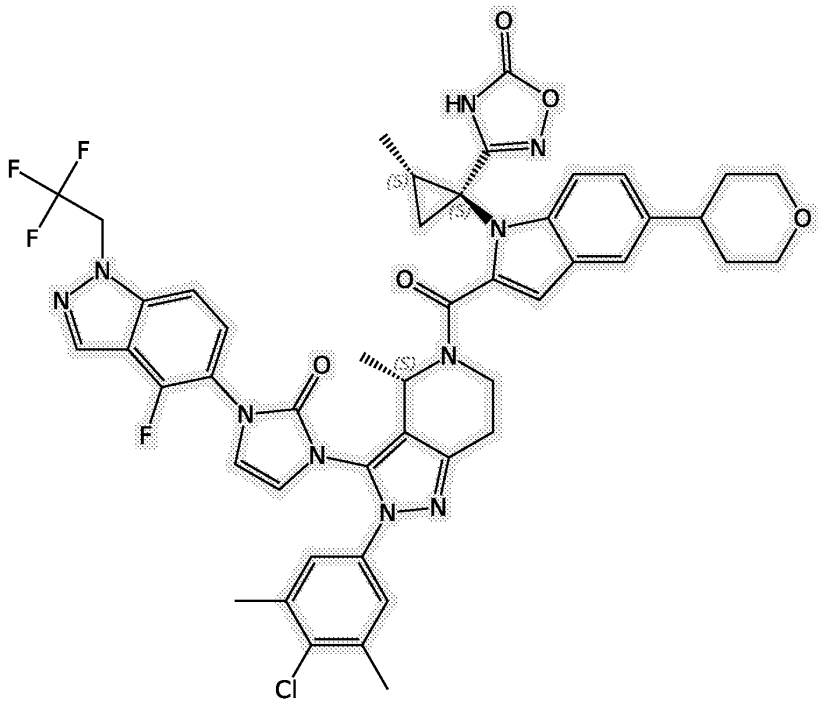
Absolute stereochemistry shown

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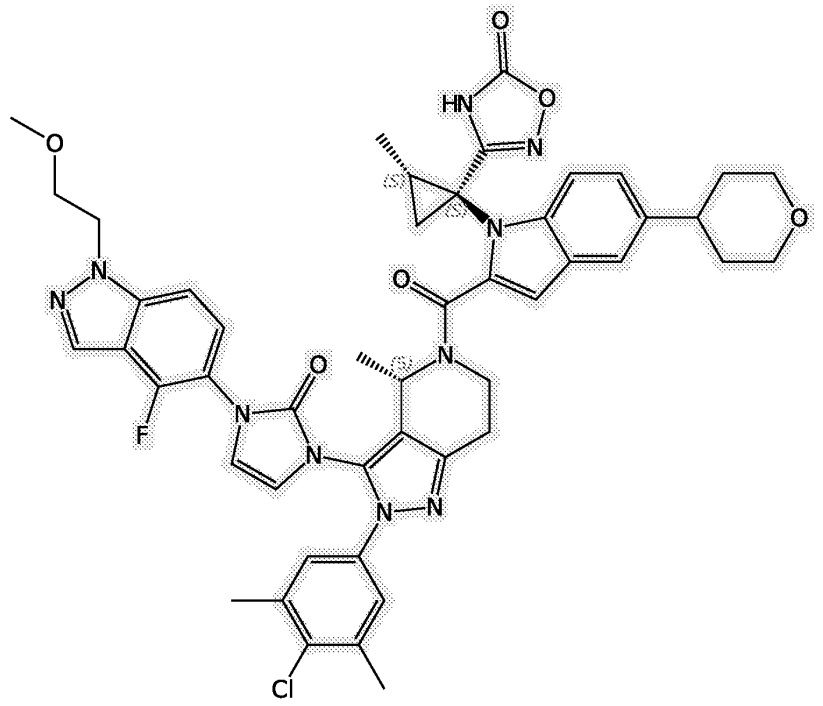
Absolute stereochemistry shown

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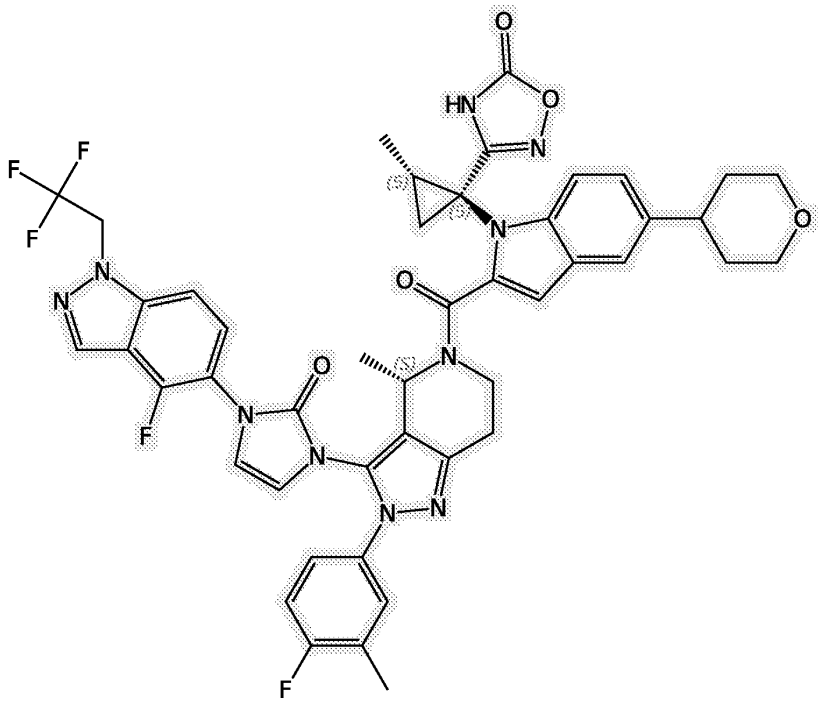
Absolute stereochemistry shown

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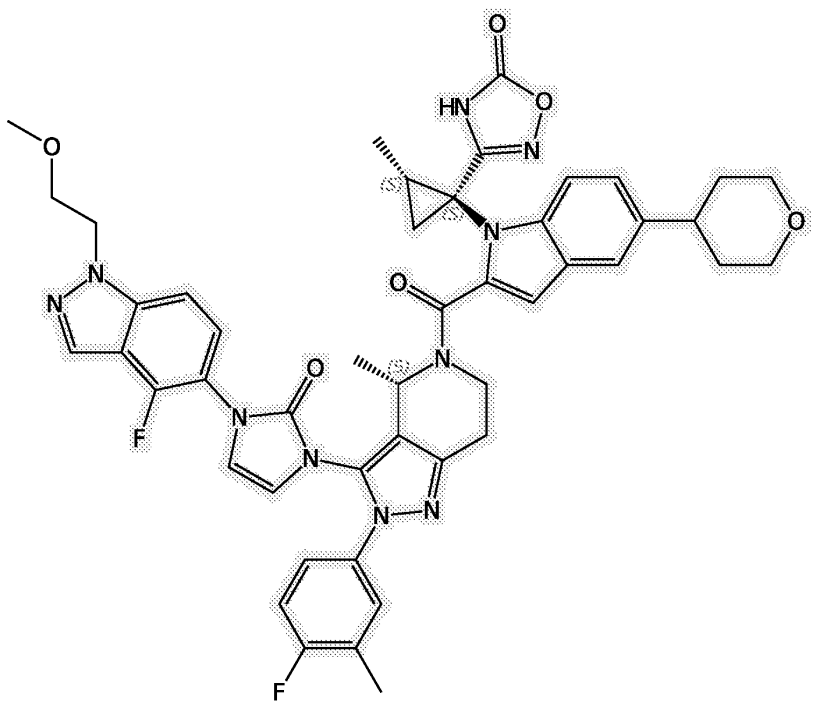
Absolute stereochemistry shown

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INDEX NAME)



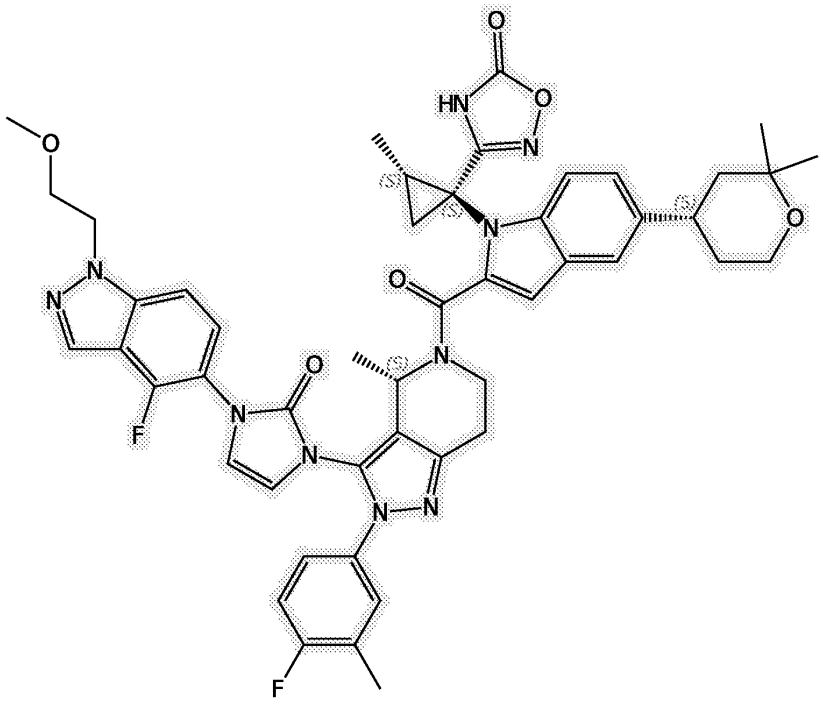
Absolute stereochemistry shown

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ylphenyl)-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5
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NAME)



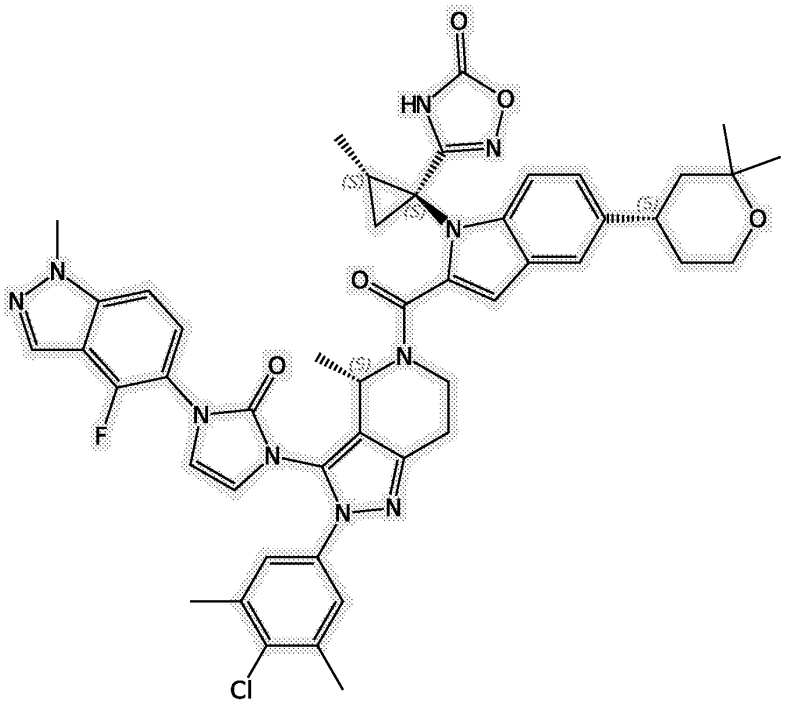
Absolute stereochemistry shown

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ylphenyl)-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5
-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl
]- (CA INDEX NAME)



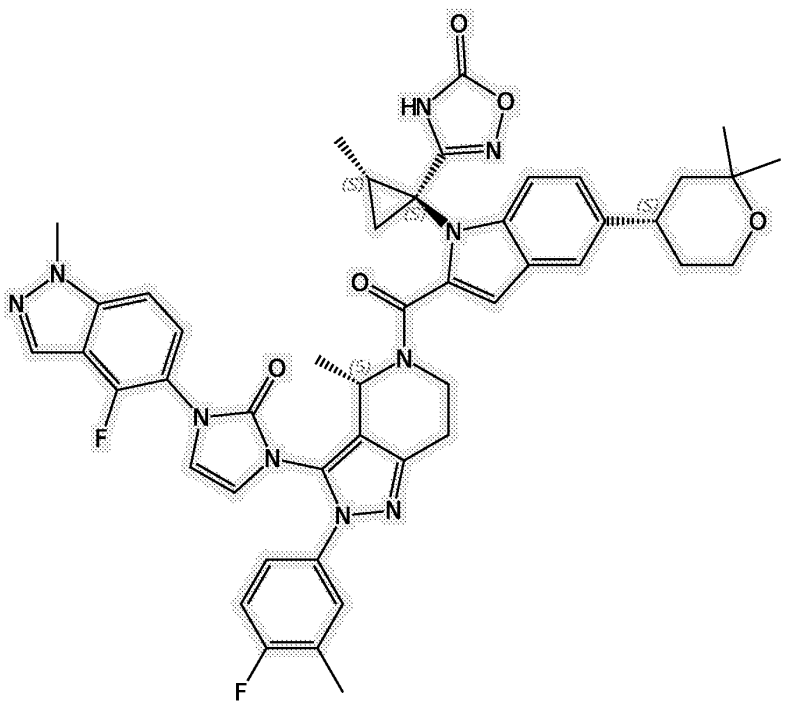
Absolute stereochemistry shown

RN 2212020-50-1 CAPLUS
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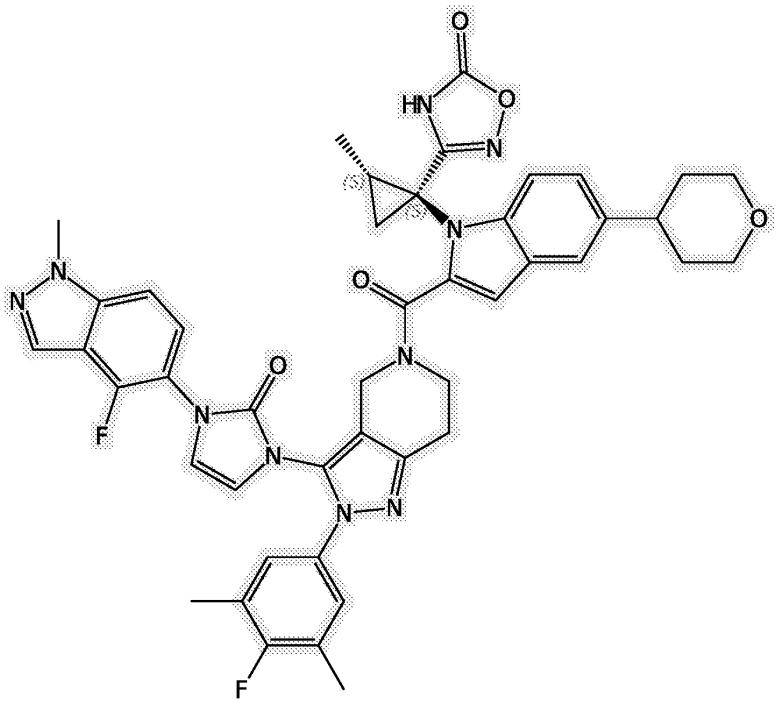
Absolute stereochemistry shown

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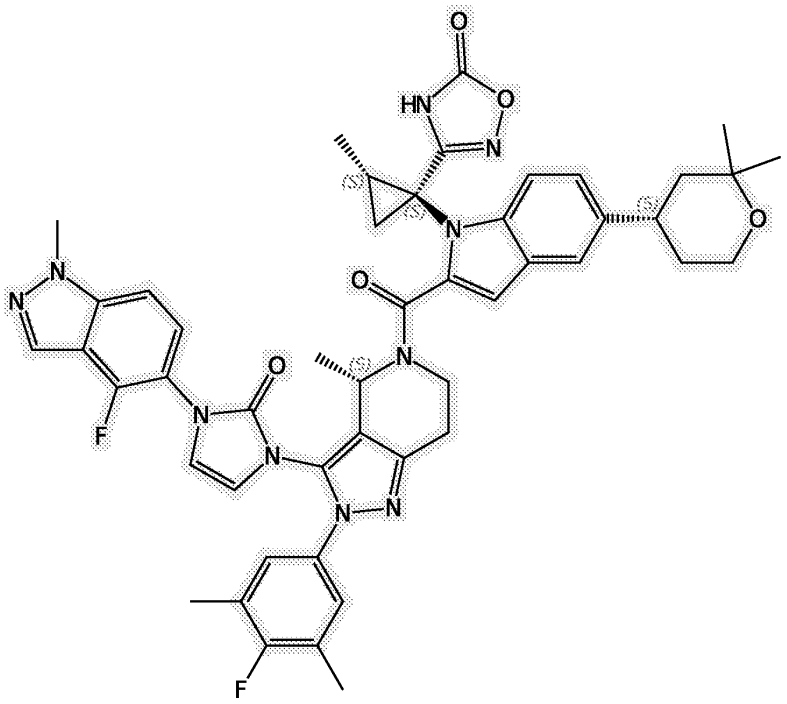
Absolute stereochemistry shown

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Absolute stereochemistry shown

RN 2212021-26-4 CAPLUS
CN 1,2,4-Oxadiazol-5(2H)-one, 3-[(1S,2S)-1-[2-[[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,3-dihydro-2-oxo-1H-imidazol-1-yl]-2,4,6,7-tetrahydro-4-methyl-5H-pyrazolo[4,3-c]pyridin-5-yl]carbonyl]-5-[(4S)-tetrahydro-2,2-dimethyl-2H-pyran-4-yl]-1H-indol-1-yl]-2-methylcyclopropyl]-, sodium salt, hydrate (1:1:1) (CA INDEX NAME)



• Na

• H_2O

Absolute stereochemistry shown

OSC.G 12 THERE ARE 12 CAPLUS RECORDS THAT CITE THIS RECORD (12 CITINGS)

LINK INFORMATION

PUBLICATIONS	APPLICATIONS	REGISTER
AU 2017330733 A1	AU 2017-330733	Register
AU 2017330733 B2	AU 2017-330733	Register
AU 2020223687 A1	AU 2020-223687	Register
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US 20240262824 A1   US 2024-18584177      Register|Global Dossier
US 20240246971 A1   US 2024-18584672      Register|Global Dossier
VN 10036072 B       VN 2019-2091          Register
WO 2018056453 A1    WO 2017-JP34620       Register|Global Dossier

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NOTICE OF ALLOWANCE AND FEE(S) DUE

83682 7590 12/11/2024

Nevrivy Patent Law Group P.L.L.C.
1101 30th Street, NW
Suite 500
Washington, DC 20007

EXAMINER
LEE, HOI YAN NMN

ART UNIT	PAPER NUMBER
1693	

DATE MAILED: 12/11/2024

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/885,065	09/13/2024	Bin Liang	HRT-030US1	4802

TITLE OF INVENTION: GLP-1R Agonist and Therapeutic Method Thereof

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	03/11/2025

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.

PTOL-85 (Rev. 11/23)

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)

83682 7590 12/11/2024
Nevrivy Patent Law Group P.L.L.C.
1101 30th Street, NW
Suite 500
Washington, DC 20007

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.
18/885,065	09/13/2024	Bin Liang	HRT-030US1	4802

TITLE OF INVENTION: GLP-1R Agonist and Therapeutic Method Thereof

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	03/11/2025

EXAMINER	ART UNIT	CLASS-SUBCLASS
LEE, HOI YAN NMN	1693	514-303000

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_____
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
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.

❑ Applicant asserting small entity status. See 37 CFR 1.27
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.

❑ Applicant changing to regular undiscounted fee 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. _____

Ascletis EX2003
Page 489 of 555

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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.
18/885,065	09/13/2024	Bin Liang	HRT-030US1	4802

83682 7590 12/11/2024

Nevrivy Patent Law Group P.L.L.C.
1101 30th Street, NW
Suite 500
Washington, DC 20007

EXAMINER	
LEE, HOI YAN NMN	

ART UNIT	PAPER NUMBER
1693	

DATE MAILED: 12/11/2024

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.

PTOL-85 (Rev. 11/23)

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. 18/885,065	Applicant(s) Liang et al.	
	Examiner HOI YAN LEE	Art Unit 1693	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 the submission filed on September 13, 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 1-13 . 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 11/04/2024 and 11/15/2024.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☑ Interview Summary (PTO-413), Paper No./Mail Date. November 14, 2024.
5. ☑ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/H.Y.L./ Examiner, Art Unit 1693	/YIH-HORNG SHIAO/ Primary Examiner, Art Unit 1693

EXAMINER'S AMENDMENT

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to Applicant, an amendment may 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.

Authorization for this examiner's amendment was given in an interview with Daniel Nevrivy on November 15, 2024.

The application has been amended as follows:

- Claim 1: Changing numbers "33" and "45" (line 3) below the structures to "(33)" and "(45)".
- Claim 3: Replacing "· Na" (line 3) with "(Na salt)".
- Claim 4: Replacing "· ½ Ca" (line 3) with "(½ Ca Salt)".
- Claim 5: Changing number "33" (line 3) below the structure to "(33)".
- Claim 6: Replacing "· Na" (line 3) with "(Na salt)".
- Claim 7: Replacing "· ½ Ca" (line 3) with "(½ Ca Salt)".
- Claim 8: Changing number "45" (line 3) below the structure to "(45)".
- Claim 9: Replacing "· Na" (line 3) with "(Na salt)".
- Claim 10: Replacing "· ½ Ca" (line 3) with "(½ Ca Salt)".
- Claim 11: Changing numbers "33" and "45" (line 3) below the structures to "(33)" and "(45)".

As Notice of Pre-AIA or AIA Status

2. 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

3. Claims 1 – 13 are pending in this application and are allowed herein.

Priority

4. This application is a domestic application, filed September 13, 2024, which claims benefit of provisional application 63/603,854 and 63/673,461, filed November 29, 2023 and July 19, 2024, respectively, and foreign priority document CN202311582240.2, CN202311686034.6, CN202410142451.2, CN202410202078.5, CN202410398964.X, CN202410584679.7, CN202410906296.7, and CN202411237013.0, filed November 24, 2023, December 8, 2023, January 31, 2024, February 22, 2024, April 2, 2024, May 11, 2024, July 5, 2024, and September 4, 2024, respectively. These foreign priority documents are not in English.

Receipt is acknowledged of certified copies of papers required by 37 CFR 1.55. Should Applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a) – (d) prior to declaration of an interference, a certified English translation of the foreign application must be submitted in reply to this action. 37 CFR 41.154(b) and 41.202(e). Failure to provide a certified translation may result in no benefit being accorded for the non-English application.

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, 365(c), or 386(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of 35 U.S.C. 112(a) or the

first paragraph of pre-AIA 35 U.S.C. 112, except for the best mode requirement. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 63/603,854 and 63/673,461, fails to provide adequate support or enablement in the manner provided by 35 U.S.C. 112(a) or pre-AIA 35 U.S.C. 112, first paragraph for one or more claims of this application. The domestic applications 63/603,854 and 63/673,461 does not provide support for the limitations "a lithium salt" that recited in the claim 2; the sodium salts recited in claims 3, 6, and 9; the calcium salts recited in claims 4, 7, and 10. Thus, the priority date of claims 2 – 4, 6 – 7, and 9 – 10 is September 13, 2024.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on 11/04/2024 and 11/15/2024 are being considered by the examiner.

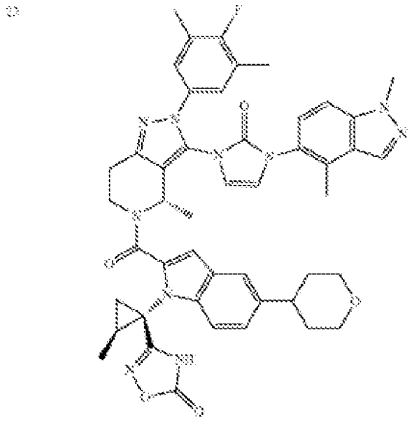
The information disclosure statement filed 11/04/2024 (NPL #4 of 9-page 1449) fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the publication date has been missing. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Reasons for Allowance

6. The following is an examiner's statement of reasons for allowance:

Regarding the claims, the closest prior art is Yoshino et al. (US20190225604A1).

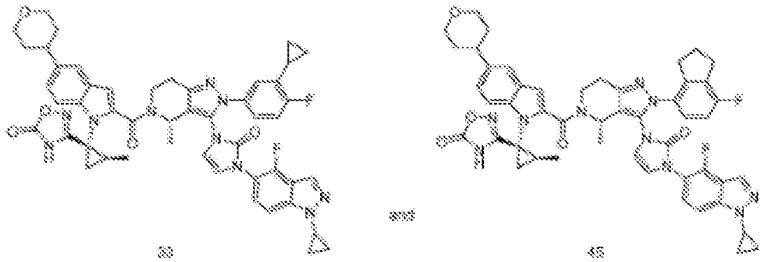
Yoshino et al. teaches a structure of compound 23 (page 36):



,

wherein this compound contains the core structure of the claimed compound 33 and 45.

However, Yoshino et al. does not teach the exact compounds of:



as well as their salts. Claim 1 also limits the compound to be "selected from the group consisting of compounds 33 and 45, which excludes other compounds disclosed in Yoshino et al. Therefore, Yoshino et al. does not teach the claimed compounds, justifying the allowance of the claims.

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".

Allowable Subject Matter

7. Claims 1 – 13 are allowed.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to HOI YAN LEE whose telephone number is 571-270-0265. The examiner can normally be reached Monday - Thursday 7:30 - 17:30.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SHAOJIA JIANG can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/H.Y.L./
Examiner, Art Unit 1693

/YIH-HORNG SHIAO/
Primary Examiner, Art Unit 1693

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/885,065	09/13/2024	Bin Liang	HRT-030US1	4802

83682 7590 01/15/2025

Nevrivy Patent Law Group P.L.L.C.
1101 30th Street, NW
Suite 500
Washington, DC 20007

EXAMINER
LEE, HOI YAN NMN

ART UNIT	PAPER NUMBER
1693	

NOTIFICATION DATE	DELIVERY MODE
01/15/2025	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):

bcastro@nevrivylaw.com
dnevrivy@nevrivylaw.com
eofficeaction@appcoll.com

Corrected ***Notice of Allowability***	**Application No.** 18/885,065	**Applicant(s)** Liang et al.	
	Examiner HOI YAN LEE	**Art Unit** 1693	**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 Applicant-initialed interview and clarification of the examiner's amendment for claims 3 and 4.
   ☐ 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 1-13 . 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 _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☑ Interview Summary (PTO-413), Paper No./Mail Date. 12/20/2024.
5. ☑ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/H.Y.L./ Examiner, Art Unit 1693	/YIH-HORNG SHIAO/ Primary Examiner, Art Unit 1693

EXAMINER'S AMENDMENT

1. 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.

Authorization for this examiner's amendment was given in an interview with Daniel Nevrivy on November 15, 2024.

This application has been amended as of record in the Notice of Allowance mailed on December 11, 2024, below are the amendments further clarified for claims 3 and 4:

- Claim 3: Replacing "· Na" (line 3) with "(Na salt)" immediately below first and second chemical structures.
- Claim 4: Replacing "· ½ Ca" (line 3) with "(½ Ca)" immediately below first and second chemical structures.

Notice of Pre-AIA or AIA Status

2. 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

3. The Corrected Notice of Allowance is prepared in view of the clarification of the examiner's amendment and the Priority as of record in the Notice of Allowance mailed on December 11, 2024.

Claims 1 – 13 are allowed herein, as of record in the Notice of Allowance mailed on December 11, 2024.

Priority

4. As of record in the Notice of Allowance, mailed on December 11, 2024, the examiner states "Should Applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a) – (d) prior to declaration of an interference, a certified English translation of the foreign application must be submitted in reply to this action. 37 CFR 41.154(b) and 41.202(e). Failure to provide a certified translation may result in no benefit being accorded for the non-English application". This statement is pertinent only when the interference arises.

Reasons for Allowance

5. The examiner's statement of reasons for allowance, as of record in the Notice of Allowance mailed on December 11, 2024.

Allowable Subject Matter

6. Claims 1 – 13 are allowed.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to HOI YAN LEE whose telephone number is 571-270-0265. The examiner can normally be reached Monday - Thursday 7:30 - 17:30.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SHAOJIA JIANG can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/H.Y.L./
Examiner, Art Unit 1693

/YIH-HORNG SHIAO/
Primary Examiner, Art Unit 1693

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/885,065	**01/27/2025 06:08:35 PM Z ET**	**HRT-030US1**

Title of Invention

GLP-1R Agonist and Therapeutic Method Thereof

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4802	FILED BY	Daniel Nevrivy
PATENT CENTER #	68921290	AUTHORIZED BY	-
CUSTOMER #	83682	FILING DATE	09/13/2024
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Bin Liang

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 7254	**E20251QI09057220**	**Daniel Nevrivy**

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.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/885,065	**01/27/2025 06:08:35 PM Z ET**	**HRT-030US1**

Title of Invention

GLP-1R Agonist and Therapeutic Method Thereof

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4802	FILED BY	Daniel Nevrivy
PATENT CENTER #	68921290	FILING DATE	09/13/2024
CUSTOMER #	83682	FIRST NAMED INVENTOR	Bin Liang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
issue_fee_pmt.pdf	1	Issue Fee Payment (PTO-85B)	433 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
issue_fee_pmt.pdf	370B5F12849A9EE96ECFA2F11C10F785765EC8414C6C31FAA ECF3745DE2109ADEC3F763F3CC15778DDE23A381819072AC 897F8B976BE8AC5A7993CD5DBD66D4B

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.

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)

83682 7590 12/11/2024
Nevrivy Patent Law Group P.L.L.C.
1101 30th Street, NW
Suite 500
Washington, DC 20007

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.
18/885,065	09/13/2024	Bin Liang	HRT-030US1	4802

TITLE OF INVENTION: GLP-1R Agonist and Therapeutic Method Thereof

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	03/11/2025

EXAMINER	ART UNIT	CLASS-SUBCLASS
LEE, HOI YAN NMN	1693	514-303000

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 Nevrivy Patent Law Group P.L.L.C.
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: Ascletis Pharma (China) Co., Limited

(B) RESIDENCE: (CITY and STATE OR COUNTRY): HONG KONG, CHINA

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. 60-2104

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

☐ Applicant certifying micro entity status. See 37 CFR 1.29
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.

☐ Applicant asserting small entity status. See 37 CFR 1.27
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.

☐ Applicant changing to regular undiscounted fee 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 /Daniel J. Nevrivy/ Date January 27, 2025

Typed or printed name Daniel J. Nevrivy Registration No. 59,118

PTOL-85 Part B (11/23) Approved for use through 03/31/2026 OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	18885065
Filing Date	2024-09-13
First Named Inventor	Bin Liang
Art Unit	1693
Examiner Name	HOI YAN NMN LEE
Attorney Docket Number	HRT-030US1

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	9150482	B2	2015-10-06	WU REY-YUH	
	2	10392357	B2	2019-08-27	Chein et al. ~~ACADEMIA SINICA~~	

Change(s) applied to document. /H.Y.L/ 1/16/2025

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U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	I495464	TW	B	2015-08-11	UNIV NAT TAIWAN		☐
	2	103694195	CN	B	2016-04-06	UNIV EAST CHINA NORMAL		☐

PC 6.1.24

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /H.Y.L./

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	18885065
Filing Date	2024-09-13
First Named Inventor	Bin Liang
Art Unit	1693
Examiner Name	HOI YAN NMN LEE
Attorney Docket Number	HRT-030US1

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
Change(s) applied to document, /P.H./ 1/16/2025	1	9120813	B2	2015-09-01	Mjalli et al. TRANSTECH PHARMA LLC [US]; VTV THERAPEUTICS LLC	
	2	9198901	B2	2015-12-01	Almariego et al. ~~TRANSTECH PHARMA LLC~~	
	3	6482844	B1	2002-11-19	He et al. ~~NEUROGEN CORP~~	

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U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20110064806	A1	2011-03-17	Polisetti et al. ~~TRANSTECH PHARMA INC~~	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	116903588	CN	A	2023-10-20	XIAMEN BORUILAI MEDICINE TECH CO LTD		☐

PC 6.1.24

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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.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/885,065	03/25/2025	12258347	HRT-030US1	4802

83682 7590 03/05/2025

Nevrivy Patent Law Group P.L.L.C.
1101 30th Street, NW
Suite 500
Washington, DC 20007

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):

Bin Liang, Hong Kong, CHINA;
Jinzi Jason Wu, Hong Kong, CHINA;
Bailing Yang, Hong Kong, CHINA;

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

Ascletis Pharma (China) Co., Limited, Hong Kong, CHINA;

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.

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Application Number	18885065
Filing Date	2024-09-13
First Named Inventor	Bin Liang
Art Unit	1693
Examiner Name	HOI YAN NMN LEE
Attorney Docket Number	HRT-030US1

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Inventor of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	1					

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Inventor or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
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If you wish to add additional U.S. Published Application citation information, please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2025006921	WO	A1	2025-01-02	GASHERBRUM BIO INC		☐
	2	2025002250	WO	A1	2025-01-02	WAYNE BIOTECHNOLOGY CO LTD		☐
	3	2025002326	WO	A1	2025-01-02	CHIA TAI TIANQING PHARMACEUTICAL GROUP CO LTD		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT		
	Application Number	18885065
	Filing Date	2024-09-13
	First Named Inventor	Bin Liang
	Art Unit	1693
	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

	4	119306743	CN	A	2025-01-14	Tíbet Hisco Pharmaceutical Co., Ltd.		☐
	5	119372270	CN	A	2025-01-28	Chengdu Ambio Biopharmaceutical Co., Ltd.		☐
	6	2025026270	WO	A1	2025-02-06	SHANGHAI HANSOH BIOMEDICAL CO LTD		☐
	7	119431365	CN	A	2025-02-14	SHANGHAI HANSOH BIOMEDICAL CO LTD		☐
	8	2025026436	WO	A1	2025-02-06	WAYNE BIOTECHNOLOGY CO LTD		☐
	9	119528907	CN	A	2025-02-28	Wayne Biotechnology Co., Ltd.		☐
	10	119552158	CN	A	2025-03-04	Institute of Chemistry, Henan Academy of Sciences		☐
	11	119504764	CN	A	2025-02-25	Standard Pharmacopoeia Standard Material Research		☐
	12	2025045208	WO	A1	2025-03-06	GASHERBRUM BIO INC [US]; HUANG WEI		☐
	13	119285580	CN	A	2025-01-10	Insilicon Intelligence Technology (Shanghai) Co.,		☐
	14	2025007843	WO	A1	2025-01-09	MINDRANK THERAPEUTICS SUZHOU NEW DRUG RES AND DEVE		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT		
	Application Number	18885065
	Filing Date	2024-09-13
	First Named Inventor	Bin Liang
	Art Unit	1693
	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

	15	119330949	CN	A	2025-01-21	CSPC Zhongqi Pharmaceutical Technology Shijiazhua		☐
	16	2025021048	WO	A1	2025-01-30	CSPC ZHONGQI PHARMACEUTICAL TECH SHIJIAZHUANG CO L		☐
	17	119431369	CN	A	2025-02-14	Jiangsu Hausen Pharmaceutical Group Co., Ltd.		☐

If you wish to add additional Foreign Patent Document citation information, please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

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	English Translation of WO 2025/026270 A1 (FP6).	☐

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

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered and 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		
	Application Number	18885065
	Filing Date	2024-09-13
	First Named Inventor	Bin Liang
	Art Unit	1693
	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

TIMING 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 timing statement under 37 CFR 1.97(e).

☐ A timing statement under 37 CFR 1.97(e) is not submitted herewith.

TIMING 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.

SIZE FEE ASSERTION

Please see 37 CFR 1.17(v) and the IDS Auto-Load Instructions for completing this form to make the appropriate selection of an assertion under 37 CFR 1.98. For the information disclosure statement (IDS) submitted herewith, the applicant or patent owner certifies the following with respect to the cumulative number of applicant-provided or patent-owner provided items of information submitted to date including those in the accompanying IDS (select only one):

☐ No IDS size fee is required under 37 CFR 1.17(v) at this time.

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(1).

☐ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(2).

☒ The IDS is accompanied by the IDS size fee under 37 CFR 1.17(v)(3).

SIGNATURE

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 11.18. Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Daniel J. Nevrivy/	Date (YYYY-MM-DD)	2025-03-21
Name/Print	Daniel J. Nevrivy	Registration Number	59,118

PC.1.19.25

INFORMATION DISCLOSURE STATEMENT BY APPLICANT		
	Application Number	18885065
	Filing Date	2024-09-13
	First Named Inventor	Bin Liang
	Art Unit	1693
	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

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.**

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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 record s.

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.

UNITED STATES
PATENT AND TRADEMARK OFFICE

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

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/885,065	**03/21/2025 10:33:26 PM Z ET**	**HRT-030US1**

Title of Invention

GLP-1R Agonist and Therapeutic Method Thereof

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	12258347
CONFIRMATION #	4802	FILED BY	Daniel Nevrivy
PATENT CENTER #	69692974	FILING DATE	09/13/2024
CUSTOMER #	83682	FIRST NAMED INVENTOR	Bin Liang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 26

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
petition-request.pdf	2	ePetition Request Form	29 KB
transmittal.pdf	2	Quick Path Information Disclosure Statement	228 KB
RCE.pdf	3	Request for Continued Examination (RCE)	1628 KB
IDSPleading.pdf	10	Letter specifying the conditions for filing under 37 CFR 1.97	290 KB
IDS.pdf	6	Information Disclosure Statement (IDS) Form (SB08)	1315 KB
FP5.pdf	11	Other reference-Patent/Application/Search Documents	1345 KB

FP1.pdf	92	Other reference-Patent/Application/Search Documents	4132 KB
FP2.pdf	99	Other reference-Patent/Application/Search Documents	4929 KB
FP3.pdf	101	Other reference-Patent/Application/Search Documents	5049 KB
FP4.pdf	52	Other reference-Patent/Application/Search Documents	7205 KB
FP10.pdf	13	Other reference-Patent/Application/Search Documents	852 KB
FP8.pdf	64	Other reference-Patent/Application/Search Documents	2916 KB
FP11.pdf	7	Other reference-Patent/Application/Search Documents	1368 KB
FP7.pdf	246	Other reference-Patent/Application/Search Documents	11281 KB
FP6.pdf	295	Other reference-Patent/Application/Search Documents	16568 KB
FP12.pdf	140	Other reference-Patent/Application/Search Documents	6207 KB
FP14.pdf	184	Other reference-Patent/Application/Search Documents	7096 KB
FP13.pdf	46	Other reference-Patent/Application/Search Documents	9642 KB
FP15.pdf	181	Other reference-Patent/Application/Search Documents	6767 KB
FP9.pdf	65	Other reference-Patent/Application/Search	17689 KB

		Documents	
FP17.pdf	36	Other reference-Patent/Application/Search Documents	4618 KB
FP16.pdf	108	Other reference-Patent/Application/Search Documents	6191 KB
NPL1_p211_252.pdf	42	Other reference-Patent/Application/Search Documents	18069 KB
NPL1_p136_210.pdf	75	Other reference-Patent/Application/Search Documents	17599 KB
NPL1_p64_135.pdf	72	Other reference-Patent/Application/Search Documents	16749 KB
NPL1_p1_63.pdf	63	Other reference-Patent/Application/Search Documents	19466 KB

Digest

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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.

Doc Code: QPIDS.REQ
Document Description: Quick Path Information Disclosure Statement

PTO/SB/09 (01-25)

CERTIFICATION AND REQUEST FOR CONSIDERATION OF AN INFORMATION DISCLOSURE STATEMENT FILED AFTER PAYMENT OF THE ISSUE FEE UNDER THE QPIDS PROGRAM

Non-Provisional Application Number: 18/885,065	Filing Date: 2024-09-13
First Named Inventor: Bin Liang	Title of Invention: GLP-1R Agonist and Therapeutic Method Thereof

THE UNDERSIGNED HEREBY CERTIFIES AND REQUESTS THE FOLLOWING FOR THE ABOVE- IDENTIFIED APPLICATION.

1. Consideration is requested of the information disclosure statement (IDS) submitted herewith, which is being filed after payment of the issue fee.
2. Check one of the following boxes:
   - ☐ Each item of information contained in the IDS 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 IDS. See 37 CFR 1.97(e)(1).
   - ☒ No item of information contained in the IDS 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 IDS was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the IDS. See 37 CFR 1.97(e)(2).
   - ☐ See attached certification statement in compliance with 37 CFR 1.97(e).
3. The IDS size fee written assertion under 37 CFR 1.98 is submitted herewith as (i) part of the PTO/SB/08 – Patent Center IDS, or equivalent, or (ii) an additional IDS paper, such as the form PTO/SB/08c or equivalent.
4. If an IDS size fee is due, the Director is authorized to charge the IDS size fee under 37 CFR 1.17(v) in the amount of $ 800 for the IDS submitted herewith to deposit account 60-2104. (Do not complete if this information is being provided on the form PTO/SB/08c, or equivalent).

   WARNING: Failure to include the assertion and/or an authorization to charge to a deposit account the applicable IDS size fee will result in automatic entry of the RCE and the IDS will be placed in the file but not considered.
5. The Director is authorized to charge the IDS timing fee under 37 CFR 1.17(p) to deposit account 60-2104.
6. A Petition to Withdraw from Issue After Payment of the Issue Fee (37 CFR 1.313(c)(2)), including the petition fee set forth in 37 CFR 1.17(h), is submitted herewith as a **Web-based ePetition**.

   WARNING: Failure to use the Web-based ePetition interface will result in automatic entry of the RCE.
7. A request for continued examination (RCE) under 37 CFR 1.114 and the RCE fee under 37 CFR 1.17(e) are submitted herewith.
8. The RCE for a compliant QPIDS will be treated as a "conditional" RCE. In the event the examiner determines that any item of information contained in the IDS necessitates the reopening of prosecution in the application, the undersigned understands that (i) the RCE will be processed and treated as an RCE under 37 CFR 1.114 and therefore (ii) the IDS fee under 37 CFR 1.17(p) will be returned in accordance with 37 CFR 1.97(b)(4). In the event that no item of information in the IDS necessitates reopening prosecution, the undersigned understands that the RCE will not be processed and the RCE fee under 37 CFR 1.17(e) will be returned.
9. This certification and request is being filed as a **Web-based ePetition** and is not accompanied by an amendment to the application. Inclusion of an amendment will result in automatic entry of the RCE.

Signature /Daniel Nevrivy/	Date March 21, 2025
Name (Print/Typed) Daniel Nevrivy	Practitioner Registration Number (If applicable) 59,118

Note: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. The party signing this form must be a listed fee payer for the above-identified deposit account in the USPTO's online fee payment management tool. Submit multiple forms if more than one signature is required and complete below.*

☑ *Total of 1 forms are submitted.

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

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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.

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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 4802
Liang *et al.*	Art Unit: 1693
Appl. No.: 18/885,065	Examiner: HOI YAN NMN LEE
Filed: September 13, 2024	Atty. Docket: HRT-030US1
For: **GLP-1R Agonist and Therapeutic Method Thereof**	

REQUEST FOR CONSIDERATION OF AN INFORMATION DISCLOSURE STATEMENT FILED AFTER PAYMENT OF THE ISSUE FEE UNDER THE QPIDS PROGRAM

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

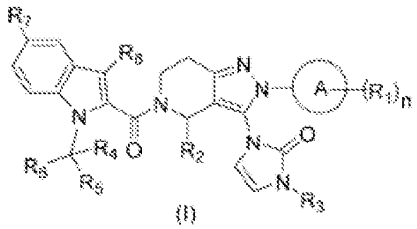
Madam:

Listed on accompanying IDS Form PTO/SB/08a are document(s) that may be considered material to the patentability of this application as defined in 37 C.F.R. § 1.56, and in compliance with the duty of disclosure requirements of 37 C.F.R. § 1.97 and 1.98.

Documents FP2, FP3, FP4, FP5, FP6, FP7, FP8, FP9, FP10, FP11, FP13, FP14, FP15, FP16 and FP17 are in a foreign language.

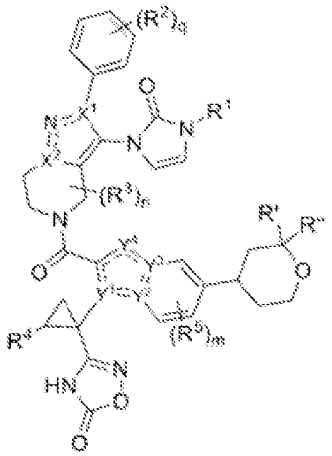
Applicant provides below English language abstracts for FP2, FP3, FP4, FP5, FP6, FP7, FP8, FP9, FP10, FP11, FP13, FP14, FP15, FP16 and FP17 in satisfaction of the requirement for providing a concise statement of relevance. Applicant also provides a WIPO English translation of FP6 as NPL1.

Document FP2 Abstract: Disclosed in the present invention are a GLP-1 receptor agonist, and a preparation method therefor and a use thereof. Specifically, disclosed are a compound represented by formula (I), and a use thereof in preparation of a drug for treating or preventing GLP-1 receptor-mediated diseases.



(I)

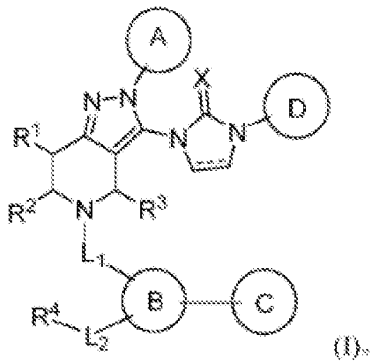
FP3 Abstract: The present invention is in the field of pharmaceutical chemistry, and relates to a compound containing a multi-fused ring structure, specifically to a compound of formula (I), a stereoisomer or pharmaceutically acceptable salt thereof, a preparation method therefor, or a pharmaceutical composition thereof, and a use thereof in the preparation of a drug for treating diabetes or obesity-related diseases.



式（I）

FP4 Abstract: The present invention provides a tetrahydropyridopyrazole derivative and its application in medicine, specifically a compound described by general formula (I) or its stereoisomers, tautomers, deuterated substances, solvates, prodrugs,

metabolites, pharmaceutically acceptable salts or cocrystals, and intermediates and preparation methods thereof, as well as application in preparing drugs for treating diabetes.

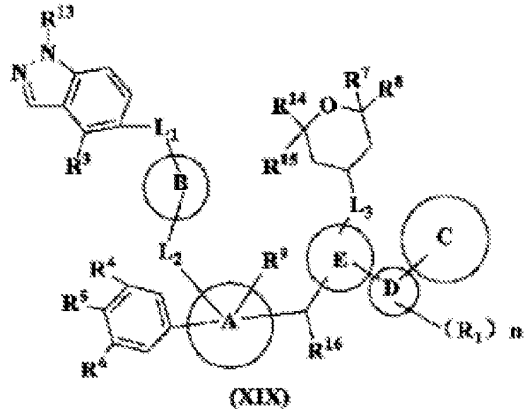


(I),

FP5 Abstract: The invention relates to the technical field of organic synthesis, and in particular to a method for constructing the chirality of an Orforglipron pyran ring by enzyme catalysis. The method comprises the following steps: step S1, taking SM1 and SM2 as raw materials, reacting under the action of a palladium catalyst and a ligand to obtain INT-1; step S2, hydrogenating and reducing double bonds of INT-1 under the catalysis of Pd/C to obtain INT-2; step S3, hydrolyzing and resolving INT-2 under the catalysis of a solvent, a buffer salt system and enzyme to obtain a chiral pure intermediate INT-3; step S4, ring-closing INT-3 to synthesize a lactone intermediate INT-4 through a Grignard reaction; and step S5, reducing INT-4 through Dibal-H, quenching, extracting with dichloromethane, drying with anhydrous sodium sulfate, and then reducing with triethylsilane to obtain a compound with a general formula A. The invention constructs chirality through enzyme catalysis, and when constructing chirality, it is not necessary to separate isomeric impurities through SFC splitting, thereby reducing losses, improving

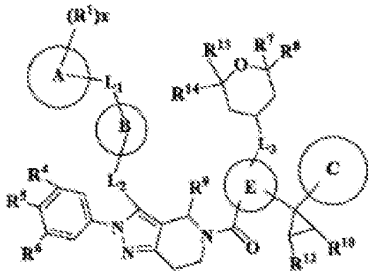
yield, and obtaining the target product with high yield and high chiral selectivity; meanwhile, the cost is relatively reduced, thus saving costs.

FP6 Abstract: A benzo nitrogen-containing heterocyclic derivative regulator, a preparation method therefor and a use thereof. Particularly, the present invention relates to a compound represented by general formula (XIX), a preparation method therefor, a pharmaceutical composition containing the compound, and a use of the compound as a regulator in the preparation of drugs for treating metabolic diseases and related diseases, wherein each substituent in the general formula (XIX) is the same as the definition in the description.



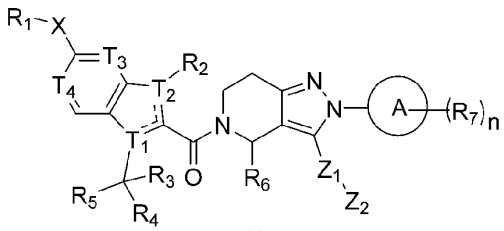
(XIX)

FP7 Abstract: The present invention relates to a phenyl-containing heterocyclic derivative modulator, a preparation method and application thereof. In particular, the present invention relates to a compound represented by general formula (XVI), a preparation method thereof and a pharmaceutical composition containing the compound, and application thereof as a modulator in the preparation of drugs for treating metabolic diseases and related diseases, wherein each substituent in general formula (XVI) has the same definition as in the specification.



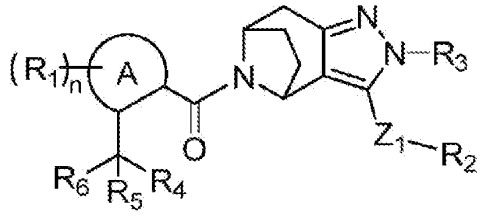
(XVI)

FP8 Abstract: A nitrogen-containing fused ring compound as a GLP-1 receptor agonist, and a preparation method therefor and the use thereof. Specifically, provided are a compound as represented by formula (I), and the use thereof in the preparation of a drug for treating or preventing diseases mediated by GLP-1.



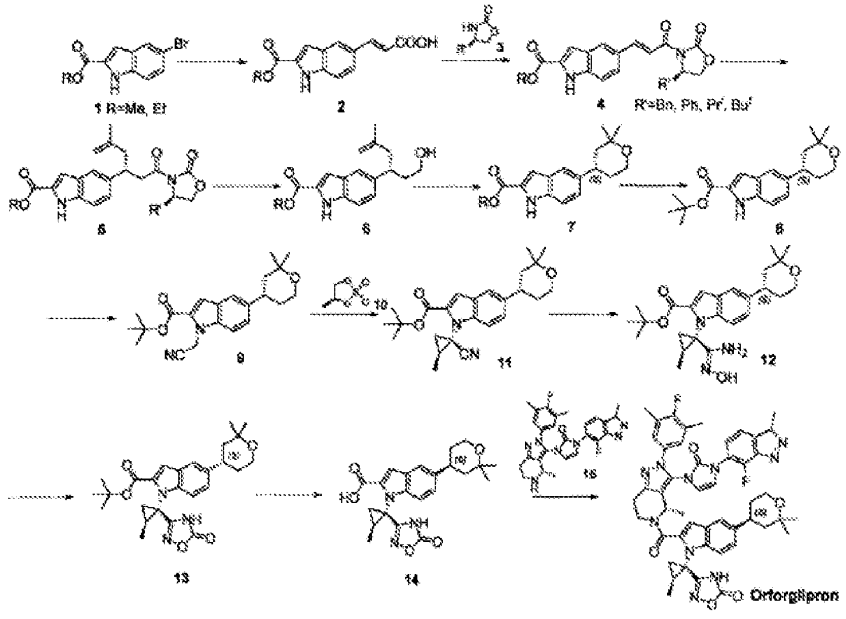
(I)

FP9 Abstract: The present invention discloses a nitrogen-containing bridged ring compound as a GLP-1 receptor agonist, a preparation method and use thereof. Specifically, disclosed is a compound represented by formula (I), and its use in the preparation of a drug for treating or preventing GLP-1-mediated diseases.



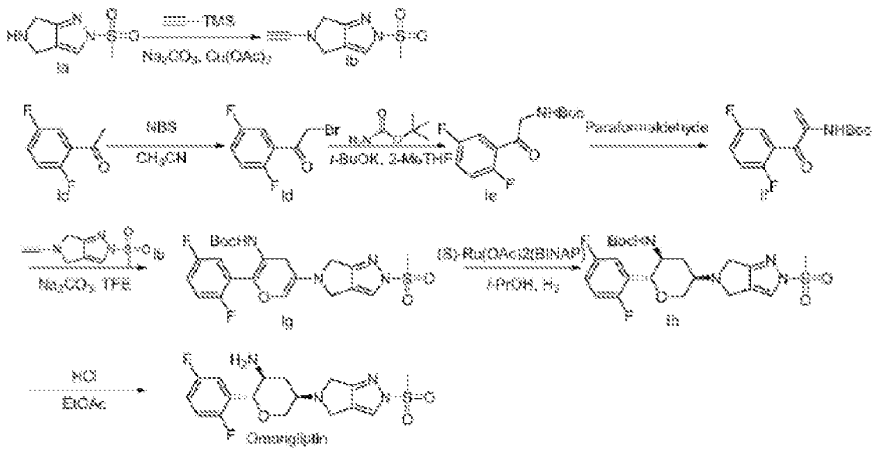
I

FP10 Abstract: The present disclosure relates to a method for synthesizing the GLP-1R agonist Orforglipron, as described in the following formula.

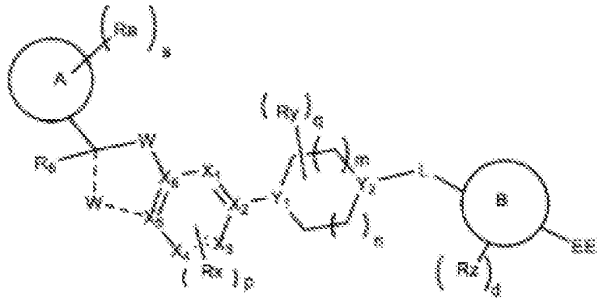


FP11 Abstract: The present invention relates to Omarigliptin, and in particular to a novel method for preparing Istradefylline. The method comprises the following steps: compound Ia undergoes coupling reaction with TMS acetylene to obtain intermediate Ib; intermediate Ic undergoes bromination reaction under the action of NBS to obtain intermediate Id; intermediate Id undergoes substitution reaction with tert-butyl carbamate

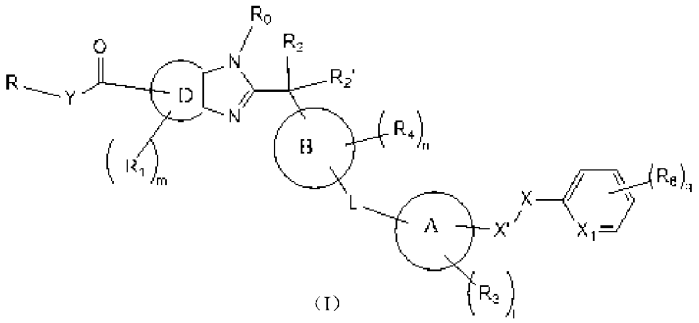
under the action of potassium tert-butoxide to obtain intermediate Ie; intermediate Ie reacts with polyformaldehyde to obtain intermediate If; intermediate If and intermediate Ib undergo cycloaddition reaction to obtain key intermediate Ig; intermediate Ig undergoes asymmetric catalytic hydrogenation reduction to obtain intermediate Ih; intermediate Ih undergoes deprotection in a hydrochloric acid ethyl acetate system to obtain a final product. The invention has a short route, simple operation, mild conditions, high reaction yield, avoids the use of dangerous and highly toxic substances and regulated hazardous chemicals, is environmentally friendly, and is easy for industrial production.



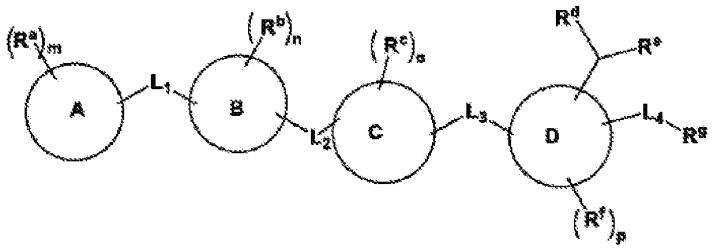
FP13 Abstract: The present invention provides a compound represented by Formula I, or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof. The compounds were shown to be good GLP-1 receptor agonists. In addition, the compound has a simple preparation method and has certain application prospects.



FP14 Abstract: A novel prodrug compound having GLP1R agonist activity. Specifically disclosed is a compound having a structure represented by formula (I) as a GLP1R agonist, or a pharmaceutically acceptable salt, solvate, hydrate, isotopic substituent or isomer thereof.

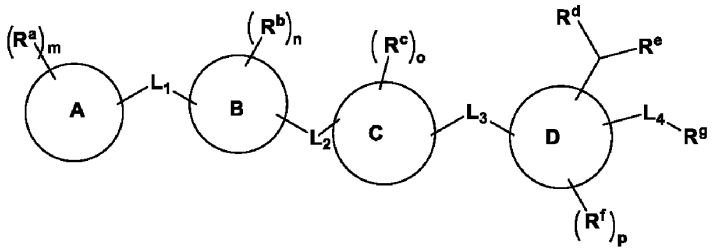


FP15 Abstract: Provided are a compound represented by formula (I'), or a tautomer, stereoisomer or pharmaceutically acceptable salt thereof. The compound represented by formula (I') has a strong agonistic effect on GLP-1R, and can treat diseases such as diabetes, metabolic-associated fatty liver diseases, and Alzheimer's disease, or has a weight loss effect.



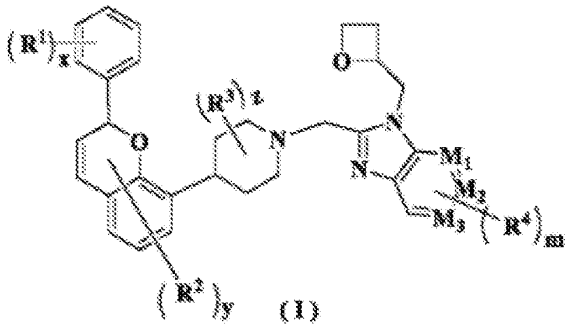
(I')

FP16 Abstract: Provided are a compound represented by formula (I'), or a tautomer, stereoisomer or pharmaceutically acceptable salt thereof. The compound represented by formula (I') has a strong agonistic effect on GLP-1R, and can treat diseases such as diabetes, metabolic-associated fatty liver diseases, and Alzheimer's disease, or has a weight loss effect.



(I')

FP17 Abstract: The invention relates to a nitrogen-containing heteroaromatic ring derivative regulator, a preparation method and application thereof. In particular, the present invention relates to a compound represented by general formula (I), a method for preparing the same, a pharmaceutical composition containing the same, and use of the same as a regulator in the preparation of drugs for treating metabolic diseases and related diseases, wherein each substituent in general formula (I) has the same definition as in the specification.



(I)

Applicant reserves the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith.

Respectfully submitted,

NEVRIVY PATENT LAW GROUP P.L.L.C.

/Daniel J. Nevrivy/

Daniel J. Nevrivy
Registration No. 59,118

Date: March 20, 2025

1101 30th St., NW
Suite 500
Washington, D.C. 20007
(202) 713-0843

UNITED STATES
PATENT AND TRADEMARK OFFICE

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

PETITION TO WITHDRAW AN APPLICATION FROM ISSUE AFTER PAYMENT OF THE ISSUE FEE UNDER 37 CFR 1.313(c)(2) with Assigned Patent Number)

APPLICATION #	ATTORNEY DOCKET #	FILING DATE
18885065	HRT-030US1	09/13/2024

Title of Invention

GLP-1R Agonist and Therapeutic Method Thereof

Application Information

CONFIRMATION #	**4802**	FILING DATE	**09/13/2024**
ART UNIT	**1693**	FIRST NAMED INVENTOR	**Bin Liang**
EXAMINER	**HOI YAN LEE**		

An application may be withdrawn from issue for further action upon petition by the applicant. To request that the Office withdraw an application from issue, applicant must file a petition under this section including the fee set forth in § 1.17(h) and a showing of good and sufficient reasons why withdrawal of the application from issue is necessary.

APPLICANT HEREBY PETITIONS TO WITHDRAW THIS APPLICATION FROM ISSUE UNDER 37 CFR 1.313(c).

A grantable petition requires the following items:

(1) Petition fee; and
(2) One of the following reasons: A grantable petition requires the following items: (a) Unpatentability of one or more claims, which must be accompanied by an unequivocal statement that one or more claims are unpatentable, an amendment to such claim or claims, and an explanation as to how the amendment causes such claim or claims to be patentable;
(b) Consideration of a request for continued examination in compliance with § 1.114 (for a utility or plant application only); or
(c) Express abandonment of the application. Such express abandonment may be in favor of a continuing application, but not a CPA under 37 CFR 1.53(d).

Reason for withdrawal

Consideration of a request for continued examination (Quick Path Information Disclosure Statement) - RCE request,

submission, and fee are attached

Applicant claims the following entity status

Small

Signature

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:
An attorney or agent registered to practice before the Patent and Trademark Office who has been given power of attorney in this application

Signature	Name	Registration #
/Daniel Nevrivy/	Daniel Nevrivy	59118

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PATENT AND TRADEMARK OFFICE

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

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/885,065	**03/21/2025 10:33:26 PM Z ET**	**HRT-030US1**

Title of Invention

GLP-1R Agonist and Therapeutic Method Thereof

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	12258347
CONFIRMATION #	4802	FILED BY	Daniel Nevrivy
PATENT CENTER #	69692974	AUTHORIZED BY	-
CUSTOMER #	83682	FILING DATE	09/13/2024
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Bin Liang

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 602104	**E20253KM35409116**	**Daniel Nevrivy**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2834	FILING AN INFORMATION DISCLOSURE STATEMENT THAT CAUSES THE CUMULATIVE NUMBER OF APPLICANT-PROVIDED ITEMS OF INFORMATION TO EXCEED 200	800.00	1	800.00
2464	PETITIONS REQUIRING THE PETITION FEE SET FORTH IN 37 CFR 1.17(H) (GROUP III)	60.00	1	60.00
2801	REQUEST FOR CONTINUED EXAMINATION (RCE) - 1ST REQUEST (SEE 37 CFR 1.114)	600.00	1	600.00
			TOTAL AMOUNT:	**$1,460.00**

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.

Doc code : PET.DEC.AUTO
Description : ePetition Grant Letter

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Alexandria, VA 22313 - 1450
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GRANT LETTER

APPLICATION #	DECISION DATE	DECISION ON PETITION #	ATTORNEY DOCKET NUMBER
18/885,065	03/21/2025		HRT-030US1

Title of Invention

GLP-1R Agonist and Therapeutic Method Thereof

In re Application of Bin Liang

This is an electronic decision on the petition under , filed March 21, 2025 to withdraw the above-identified application from issue after payment of the issue fee.

The request is **GRANTED.**

Petitioner is advised that the issue fee paid in this application cannot be refunded. If, however, this application is again allowed, petitioner may request that it be applied towards the issue fee required by the new Notice of Allowance.

The application is being referred to Technology Center AU for

Telephone inquired concerning this decision should be directed to the Patent Electronic Business Center (EBC) at 866-217-9197.

Office of Petitions

United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :Terrance Lawrence

Sale Accounting Date:03/24/2025

Sale Item Reference Number	Effective Date
18885065	03/21/2025

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I20253NC56018915	2806	SUBMISSION- INFORMATION DISCLOSURE STMT	$112.00	Deposit Account

United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :Sengpheth Sandara

Refund Accounting Date:04/07/2025

Effective Date	Sale Item Reference Number	Refund Total
04/07/2025	18885065	$600.00

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method	Account Number
I202547050197608	2801	RCE- 1ST REQUEST	$600.00	DA	602104

United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :Sengpheth Sandara

Sale Adjustment Accounting Date:04/07/2025

Effective Date	Sale Accounting Date	Sale Item Reference Number
04/07/2025	04/07/2025	18885065

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I202547050197608	2801	RCE- 1ST REQUEST	$600.00	DA

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08 (01-25)
Approved for use through 11/30/2027. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Application Number	18885065
Filing Date	2024-09-13
First Named Inventor	Bin Liang
Art Unit	1693
Examiner Name	HOI YAN NMN LEE
Attorney Docket Number	HRT-030US1

U.S. PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Inventor of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information, please click the Add button. Add

U.S. PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Inventor or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information, please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2025006921	WO	A1	2025-01-02	GASHERBRUM BIO INC		☐
	2	2025002250	WO	A1	2025-01-02	WAYNE BIOTECHNOLOGY CO LTD		☐
	3	2025002326	WO	A1	2025-01-02	CHIA TAI TIANQING PHARMACEUTICAL GROUP CO LTD		☐

PC.1.19.25

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /H.Y.L./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT		
	Application Number	18885065
	Filing Date	2024-09-13
	First Named Inventor	Bin Liang
	Art Unit	1693
	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

	4	119306743	CN	A	2025-01-14	Tíbet Hisco Pharmaceutical Co., Ltd.		☐
	5	119372270	CN	A	2025-01-28	Chengdu Ambio Biopharmaceutical Co., Ltd.		☐
	6	2025026270	WO	A1	2025-02-06	SHANGHAI HANSOH BIOMEDICAL CO LTD		☐
	7	119431365	CN	A	2025-02-14	SHANGHAI HANSOH BIOMEDICAL CO LTD		☐
	8	2025026436	WO	A1	2025-02-06	WAYNE BIOTECHNOLOGY CO LTD		☐
	9	119528907	CN	A	2025-02-28	Wayne Biotechnology Co., Ltd.		☐
	10	119552158	CN	A	2025-03-04	Institute of Chemistry, Henan Academy of Sciences		☐
	11	119504764	CN	A	2025-02-25	Standard Pharmacopoeia Standard Material Research		☐
	12	2025045208	WO	A1	2025-03-06	GASHERBRUM BIO INC [US]; HUANG WEI		☐
	13	119285580	CN	A	2025-01-10	Insilicon Intelligence Technology (Shanghai) Co.,		☐
	14	2025007843	WO	A1	2025-01-09	MINDRANK THERAPEUTICS SUZHOU NEW DRUG RES AND DEVE		☐

PC.1.19.25

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /H.Y.L./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT		
	Application Number	18885065
	Filing Date	2024-09-13
	First Named Inventor	Bin Liang
	Art Unit	1693
	Examiner Name	HOI YAN NMN LEE
	Attorney Docket Number	HRT-030US1

	15	119330949	CN	A	2025-01-21	CSPC Zhongqi Pharmaceutical Technology Shijiazhua		☐
	16	2025021048	WO	A1	2025-01-30	CSPC ZHONGQI PHARMACEUTICAL TECH SHIJIAZHUANG CO L		☐
	17	119431369	CN	A	2025-02-14	Jiangsu Hausen Pharmaceutical Group Co., Ltd.		☐

If you wish to add additional Foreign Patent Document citation information, please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

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	English Translation of WO 2025/026270 A1 (FP6).	☐

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

EXAMINER SIGNATURE

Examiner Signature	/HOI YAN NMN LEE/	Date Considered	03/31/2025

*EXAMINER: Initial if reference considered and 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.

PC.1.19.25

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /H.Y.L./

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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/885,065	09/13/2024	Bin Liang	HRT-030US1	4802

83682 7590 04/08/2025

Nevrivy Patent Law Group P.L.L.C.
1101 30th Street, NW
Suite 500
Washington, DC 20007

EXAMINER	
LEE, HOI YAN NMN	

ART UNIT	PAPER NUMBER
1693	

NOTIFICATION DATE	DELIVERY MODE
04/08/2025	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):

bcastro@nevrivylaw.com
dnevrivy@nevrivylaw.com
eofficeaction@appcoll.com

CORRECTED ***Notice of Allowability***	**Application No.** 18/885,065	**Applicant(s)** Liang et al.	
	Examiner HOI YAN LEE	**Art Unit** 1693	**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 newly filed information disclosure statement, filed March 21, 2025.
   ☐ 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 1-13 . 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 03/21/2025.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/H.Y.L./ Examiner, Art Unit 1693	/SCARLETT Y GOON/ Supervisory Patent Examiner, Art Unit 1693

Notice of Pre-AIA or AIA Status

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

DETAILED ACTION

2. The Corrected Notice of Allowance is prepared in view of new IDS.

Claims 1 – 13 are allowed herein, as of record in the Notice of Allowance mailed on December 11, 2024.

Priority

3. The priority record, as of record in the Notice of Allowance and Corrected Notice of Allowance mailed on December 11, 2024 and January 15, 2025, respectively.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on 03/21/2025 was filed after the mailing date of the Corrected Notice of Allowance on January 15, 2025. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Reasons for Allowance

5. The examiner's statement of reasons for allowance, as of record in the Notice of Allowance and Corrected Notice of Allowance mailed on December 11, 2024 and January 15, 2025, respectively.

The new reference provided in the IDS does not result in reopening the prosecution as there is no teaching or suggestion that would motivate one skilled in the art to modify the compounds to achieve the claimed invention, justifying the allowance of the claims.

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".

Allowable Subject Matter

6. Claims 1 – 13 are allowed.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to HOI YAN LEE whose telephone number is 571-270-0265. The examiner can normally be reached Monday - Thursday 7:30 - 17:30.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SCARLETT GOON can be reached on 571-270-5241. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC)

at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service

Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/H.Y.L./
Examiner, Art Unit 1693

/SCARLETT Y GOON/
Supervisory Patent Examiner, Art Unit 1693

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UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/885,065	05/06/2025	12291530	HRT-030US1	4802

83682 7590 04/16/2025

Nevrivy Patent Law Group P.L.L.C.
1101 30th Street, NW
Suite 500
Washington, DC 20007

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):

Bin Liang, Hong Kong, CHINA;
Jinzi Jason Wu, Hong Kong, CHINA;
Bailing Yang, Hong Kong, CHINA;

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

Ascletis Pharma (China) Co., Limited, Hong Kong, CHINA;

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.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/885,065	09/13/2024	Bin Liang	HRT-030US1	4802

83682 7590 05/06/2025

Nevrivy Patent Law Group P.L.L.C.
1101 30th Street, NW
Suite 500
Washington, DC 20007

EXAMINER	
LEE, HOI YAN NMN	

ART UNIT	PAPER NUMBER
1693	

NOTIFICATION DATE	DELIVERY MODE
05/06/2025	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):

bcastro@nevrivylaw.com
dnevrivy@nevrivylaw.com
eofficeaction@appcoll.com

APPLICATION NO.	ISSUE DATE	PATENT NO.
18/885,065	06-May-2025	12291530

Nevrivy Patent Law Group P.L.L.C.
1101 30th Street, NW
Washington, DC 20007

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