PTO/AIA/01 (05-12)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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

Title of Invention	CRYSTAL FORM OF OREXIN RECEPTOR ANTAGONIST, PREPARATION METHOD THEREFOR AND USE THEREOF

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number PCT/CN2018/097797 filed on 07/31/2018.

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

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

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

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Minhua Chen Date (Optional) :

Signature: minhua Chen

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

PTO/AIA/01 (06-12)
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LEGAL NAME OF INVENTOR

Inventor: Yanfeng Zhang Date (Optional): _____

Signature: _____

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

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LEGAL NAME OF INVENTOR

Inventor: Chunxiang Huang Date (Optional): _____

Signature: Chunxiang Huang

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

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LEGAL NAME OF INVENTOR

Inventor: Xiaoyu Zhang Date (Optional): _____

Signature: Xiaoyu Zhang

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

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: January 30, 2020
Electronic Signature for Xiaoyuan Ding: /Xiaoyuan Ding/

Docket No.: 134070-01602
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Utility Application of:
Minhua Chen et al.

Application No.: Not Yet Assigned
Continuation of PCT/CN2018/097797

Confirmation No.: N/A

Filed: Concurrently Herewith
Int'l Filing Date: July 31, 2018

Art Unit: N/A

For: CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE THEREOF

Examiner: Not Yet Assigned

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

INFORMATION DISCLOSURE STATEMENT (IDS)

Dear Sir:

Pursuant to 37 C.F.R. §§ 1.56, 1.97, and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is filed together with a continuation application filing as set forth in 37 C.F.R. § 1.491 (37 C.F.R. § 1.97(b)(1)).

In accordance with 37 C.F.R. § 1.98(a)(2)(ii), Applicant has not submitted copies of U.S. patents and U.S. patent applications. Applicant submits herewith copies of foreign patents and non-patent literature in accordance with 37 C.F.R. § 1.98(a)(2).

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed as a representation that a search has been made. In accordance with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

Applicant believes no fee is due with this response.

Dated: January 30, 2020

Respectfully submitted,

Electronic signature: /Xiaoyuan Ding/
Xiaoyuan Ding
Registration No.: 75,354
MCCARTER & ENGLISH, LLP
265 Franklin Street
Boston, Massachusetts 02110
(617) 449-6500
(617) 607-9200 (Fax)
Attorney/Agent For Applicant

PTO/AIA/14 (02-18)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	134070-01602
	Application Number	
Title of Invention	CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE 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
	Minhua		Chen	

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

City	Suzhou	Country of Residence [i]	CN

Mailing Address of Inventor:

Address 1	B4-301, Biobay, 218 Xinghu Street
Address 2	Suzhou Industrial Park

City	Suzhou, Jiangsu	State/Province	
Postal Code	215123	Country [i]	CN

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Yanfeng		Zhang	

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

City	Suzhou	Country of Residence [i]	CN

Mailing Address of Inventor:

Address 1	B4-301, Biobay, 218 Xinghu Street
Address 2	Suzhou Industrial Park

City	Suzhou, Jiangsu	State/Province	
Postal Code	215123	Country [i]	CN

Inventor 3 Remove

Legal Name

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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	134070-01602
	Application Number	
Title of Invention	CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE THEREOF	

Prefix	Given Name	Middle Name	Family Name	Suffix
	Chunxiang		Huang	

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

City	Suzhou	Country of Residence [i]	CN

Mailing Address of Inventor:

Address 1	B4-301, Biobay, 218 Xinghu Street
Address 2	Suzhou Industrial Park

City	Suzhou, Jiangsu	State/Province	
Postal Code	215123	**Country** [i]	CN

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Xiaoyu		Zhang	

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

City	Suzhou	Country of Residence [i]	CN

Mailing Address of Inventor:

Address 1	B4-301, Biobay, 218 Xinghu Street
Address 2	Suzhou Industrial Park

City	Suzhou	State/Province	
Postal Code	215123	**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	86738		
Email Address	docket@mccarter.com	Add Email	Remove Email

PTO/AIA/14 (02-18)
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Application Information:

Title of the Invention	CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE THEREOF		
Attorney Docket Number	134070-01602	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	7	**Suggested Figure for Publication (if any)**	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

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

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	● Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	86738		

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	134070-01602
	Application Number	
Title of Invention	CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE THEREOF	

Domestic Benefit/National Stage Information:

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

Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	PCT/CN2018/097797	2018-07-31

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

Foreign Priority Information:

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

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
201710648135.2	CN	2017-08-01	

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

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

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

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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	134070-01602
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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 Number	
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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	Crystal Pharmaceutical (Suzhou) Co., Ltd.		
Mailing Address Information For Applicant:			
Address 1	B4-301, Biobay, 218 Xinghu Street		
Address 2	Suzhou Industrial Park		
City	Suzhou, Jiangsu	**State/Province**	JS
Country	CN	Postal Code	215123
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 Number	
Title of Invention	CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE 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	/Xiaoyuan Ding/			Date (YYYY-MM-DD)	2020-01-30
First Name	Xiaoyuan	Last Name	Ding	Registration Number	75,354

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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	134070-01602
	Application Number	
Title of Invention	CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE 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.**

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Filing Date:	
Title of Invention:	CRYSTAL FORM OF OREXIN RECEPTOR ANTAGONIST, PREPARATION METHOD THEREFOR AND USE THEREOF
First Named Inventor/Applicant Name:	Minhua Chen
Filer:	Xiaoyuan Ding/Gayle Coy
Attorney Docket Number:	134070-01602

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Filing Fees for Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a)

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UTILITY FILING FEE (ELECTRONIC FILING)	4011	1	75	75
UTILITY SEARCH FEE	2111	1	330	330
UTILITY EXAMINATION FEE	2311	1	380	380
REQUEST FOR PRIORITIZED EXAMINATION	2817	1	2000	2000
Pages:				
Claims:				
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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	2830	1	70	70
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10	Application Data Sheet	134070_01602_ADS.pdf	1256148 a6b001e6582c6e92ea0faee115712db3956188f9	no	9
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(54) **Title**: METHODS AND COMPOUNDS USEFUL IN THE SYNTHESIS OF OREXIN-2 RECEPTOR ANTAGONISTS

(57) **Abstract**: The present disclosure provides compounds and methods that are useful for the preparation of compounds useful as orexin-2 receptor antagonists.

METHODS AND COMPOUNDS USEFUL IN THE SYNTHESIS OF OREXIN-2 RECEPTOR ANTAGONISTS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application No. 61/600,109, filed February 17, 2012, which is incorporated by reference herein in its entirety.

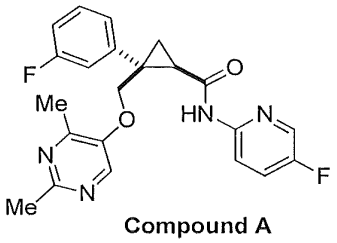
FIELD OF THE INVENTION

The present invention relates to compounds and methods that are useful for the preparation of compounds useful as orexin-2 receptor antagonists.

BACKGROUND OF THE INVENTION

Orexin receptors are G-protein coupled receptors found predominately in the brain. Their endogenous ligands, orexin-A and orexin-B, are expressed by neurons localized in the hypothalamus. Orexin-A is a 33 amino acid peptide; orexin-B consists of 28 amino acids. (Sakurai T. et al., Cell, 1998, 92, 573-585). There are two subtypes of orexin receptors, OX_1 and OX_2; OX_1 binds orexin-A preferentially, while OX_2 binds both orexin-A and -B. Orexins stimulate food consumption in rats, and it has been suggested that orexin signaling could play a role in a central feedback mechanism for regulating feeding behavior (Sakurai et al., *supra*). It has also been observed that orexins control wake-sleep conditions (Chemelli R.M. et al., Cell, 1999, 98, 437-451). Orexins may also play roles in brain changes associated with opioid and nicotine dependence (S.L. Borgland et al., Neuron, 2006, 49, 598-601; C.J. Winrow et al., Neuropharmacology, 2010, 58, 185-194), and ethanol dependence (J.R. Shoblock et al., Psychopharmacology, 2011, 215, 191-203). Orexins have additionally been suggested to play a role in some stress reactions (T. Ida et al., Biochem. Biophys. Res. Commun., 2000, 270, 318-323).

Compounds such as (1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide (Compound A, below) have been found to be potent orexin receptor antagonists, and may be useful in the treatment of sleep disorders such as insomnia, as well as for other therapeutic uses.



Compound A

There is thus a need for synthetic methods and intermediates useful in the preparation of Compound A and related compounds. It is, therefore, an object of the present application to provide such synthetic methods and intermediates.

SUMMARY

Provided herein are compounds and methods that are useful for the preparation of compounds useful as orexin-2 receptor antagonists.

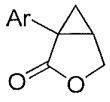
Provided is a process for making a compound of **Formula I**,

I

wherein Ar is an aryl such as phenyl, which aryl may be unsubstituted, or substituted 1-3 times, for example, with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl,

the method comprising one or more of the steps of :

i) providing a composition comprising a compound of **Formula II**:



II

wherein Ar is as given above, and an organic solvent, wherein said composition is at a temperature of from -30 to 40 °C, or from -30 to 30 °C, or from -30 to 10 °C, or from -10 to 0 °C, or from -10 to -5 °C; and

ii) adding to said composition a hydride reducing agent, wherein said agent reduces said compound of **Formula II** into said compound of **Formula I**,

to thereby make said compound of **Formula I**.

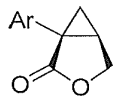
In some embodiments, Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

In some embodiments, the organic solvent is an aromatic hydrocarbon solvent, an aliphatic hydrocarbon solvent, a halogenated hydrocarbon solvent or an ether solvent.

In some embodiments, the process may further include the step of mixing (e.g., by stirring) the composition after said adding step for a time of 12 to 24 hours.

In some embodiments, the process may further include the step of quenching the reduction by adding to said composition a mild aqueous acid (e.g., citric acid, EDTA or tartaric acid).

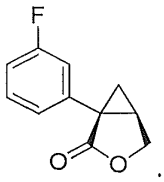
In some embodiments, the compound of **Formula II** has the absolute stereochemistry of **Formula IIa**:



IIa .

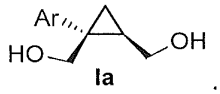
In some embodiments, the compound of **Formula II** has an enantiomeric excess (ee) of the **Formula IIa** stereoisomer of at least 75, 80, 85, 90, 95, 98, 99%, or greater.

In some embodiments, the compound of **Formula II** or **Formula IIa** is the compound:



.

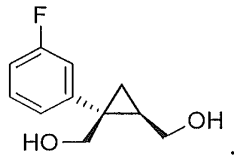
In some embodiments, the compound of **Formula I** has the absolute stereochemistry of **Formula Ia**:



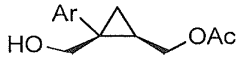
Ia

In some embodiments, the compound of **Formula I** has an enantiomeric excess (ee) of the **Formula Ia** stereoisomer of at least 75, 80, 85, 90, 95, 98, 99%, or greater.

In some embodiments, the compound of **Formula I** or **Formula Ia** is:



Also provided is compound of **Formula III**:

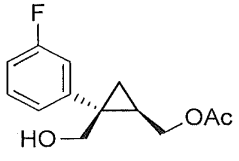


III

wherein Ar is an aryl such as phenyl, which aryl may be unsubstituted, or substituted 1-3 times, for example with substituents independently chosen from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl.

In some embodiments, Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

In some embodiments, the compound is:



Also provided is a process for making a compound of **Formula III**:

III

wherein Ar is aryl such as phenyl, which aryl may be unsubstituted, or substituted 1-3 times, for example with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl,

comprising reacting a mixture of:

i) a compound of **Formula Ia:**

Ia

wherein Ar is as given above,

ii) vinyl acetate,

iii) a lipase, and

iv) an organic solvent

for a time of from 5 to 36 hours, or from 7 to 18 hours,

to thereby make the compound of **Formula III**.

In some embodiments, Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

In some embodiments, the organic solvent is tetrahydrofuran, 2-methyltetrahydrofuran, an ether solvent, acetone, or acetonitrile.

In some embodiments, the lipase is a *Candida Antarctica* lipase, for example, a *Candida Antarctica* B lipase, which may be coupled to solid support such as an acrylic resin.

In some embodiments, the process may further include the step of filtering the mixture after said reacting to produce a filtrate, and may further include concentrating the filtrate to produce a concentrated filtrate. In some embodiments, the process may further include the step of washing the concentrated filtrate with water or water comprising a salt (e.g., a solution of 15-20% NaCl in water).

Also provided is a compound of **Formula IV**:

IV

wherein:

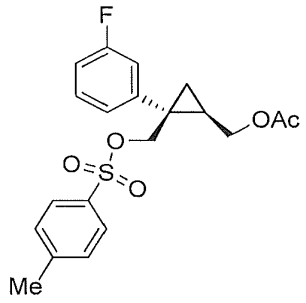
Ar is an aryl such as phenyl, which aryl may be unsubstituted, or substituted 1-3 times, for example with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl; and

R_1 is a leaving group.

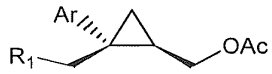
In some embodiments, Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

In some embodiments, the leaving group is a sulfonate ester leaving group selected from the group consisting of: mesylate, tosylate, nosylate, benzene sulfonate, and brosylate.

In some embodiments, the compound is:



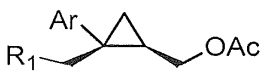
In some embodiments, the compound of **Formula IV** has the absolute stereochemistry of **Formula IVa**:



IVa

In some embodiments, the compound of **Formula IV** has an enantiomeric excess (ee) of the **Formula IVa** stereoisomer of at least 75, 80, 85, 90, 95, 98, 99%, or greater.

Further provided is a process for making a compound of **Formula IV**:

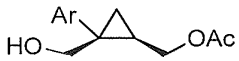


IV

wherein Ar is an aryl such as phenyl, which aryl may be unsubstituted, or substituted 1-3 times, for example with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl; and

R_1 is a sulfonate ester leaving group,

said process comprising reacting a compound of **Formula III**:



III

wherein Ar is as given above,

with a compound selected from the group consisting of: tosyl chloride, mesyl chloride, nosyl chloride, toluenesulfonyl chloride, toluenesulfonic anhydride and methanesulfonic anhydride, wherein said reacting is carried out in an organic solvent in the presence of a base,

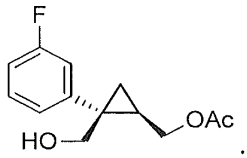
to thereby make said compound of **Formula IV**.

In some embodiments, Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

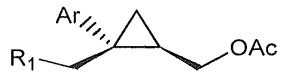
In some embodiments, the reacting is carried out for a time of from 10 minutes to 2 hours.

In some embodiments, the base is an organic amine or potassium carbonate.

In some embodiments, the compound of **Formula III** is:



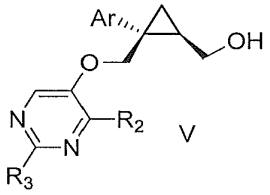
In some embodiments, the compound of **Formula IV** has the absolute stereochemistry of **Formula IVa**:



IVa

In some embodiments, the compound of **Formula IV** has an enantiomeric excess (ee) of the **Formula IVa** stereoisomer of at least 75, 80, 85, 90, 95, 98, 99%, or greater.

Also provided is a process for making a compound of **Formula V**,



V

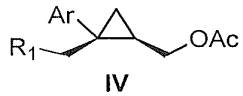
wherein Ar is an aryl such as phenyl, which aryl may be unsubstituted, or substituted 1-3 times, for example with substituents independently selected from the group consisting of: halo, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, and halo$C_{1\text{-}6}$alkyl; and

R_2 and R_3 are each independently selected from the group consisting of: hydrogen, $C_{1\text{-}6}$alkyl, halo$C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$alkoxy, and hydroxy$C_{1\text{-}6}$alkyl,

comprising the steps of:

a) stirring a mixture of:

i) a compound of **Formula IV**:

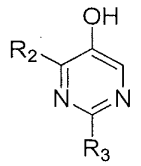


IV

wherein Ar is as given above; and

R_1 is a leaving group,

ii) a substituted pyrimidine of **Formula VI**:



VI ,

wherein R_2 and R_3 are as given above;

iii) a base; and

iv) an organic solvent,

at a temperature of from 65-70 °C, for 1 to 12 hours; and then

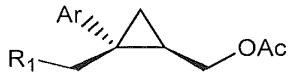
b) reacting the mixture with an aqueous base for a time of from 2 to 20 hours,

to thereby make said compound of **Formula V**.

In some embodiments, Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

In some embodiments, R_2 and R_3 are each independently selected from the group consisting of: hydrogen and C_{1-6}alkyl.

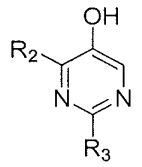
In some embodiments, the compound of **Formula IV** has the absolute stereochemistry of **Formula IVa**:



IVa .

In some embodiments, the compound of **Formula IV** has an enantiomeric excess (ee) of the **Formula IVa** stereoisomer of at least 75, 80, 85, 90, 95, 98, 99%, or greater.

Further provided is a process for making a compound of **Formula VI**:

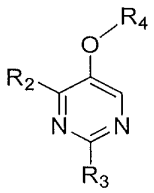


VI

wherein R_2 and R_3 are each independently selected from the group consisting of: hydrogen and C_{1-6} alkyl,

comprising the step of heating a mixture of:

i) a compound of **Formula B**:



B

wherein:

R_2 and R_3 are as given above; and

R_4 is C_{1-6} alkyl,

ii) an alkoxide or hydroxide salt,

iii) a thiol, and

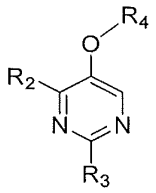
iv) an organic solvent,

to thereby make said compound of **Formula VI**.

In some embodiments, the heating is to a temperature of from 50 °C to 140 °C. In some embodiments, heating comprises boiling or refluxing the mixture.

In some embodiments, the heating is carried out in a time of from 5 to 50 hours.

Also provided is a process for making a compound of **Formula B**:



B

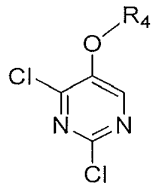
wherein:

R_2 and R_3 are each independently selected from the group consisting of: hydrogen and C_{1-6} alkyl; and

R_4 is C_{1-6} alkyl,

comprising mixing:

i) a compound of **Formula A**:



A

wherein R_4 is as given above,

ii) trimethylaluminum,

iii) a palladium catalyst, and

iv) an organic solvent,

to thereby make said compound of **Formula B**.

In some embodiments, the mixing step is carried out for a time of from 12 to 48 hours.

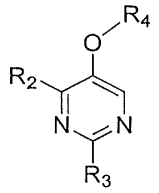
In some embodiments, the mixing step is carried out at a temperature of from 20 °C to 110 °C.

In some embodiments, the process further includes a step of quenching the reaction, e.g., with water comprising a base (e.g., a hydroxide such as sodium hydroxide).

In some embodiments, the process further includes a step of treating said compound of **Formula B** with a solution comprising hydrogen chloride and a solvent such as an alcohol (e.g.,

isopropyl alcohol) to obtain said compound of **Formula B** as a hydrochloride salt. In some embodiments this is done after a quenching step.

Further provided is a process for making a compound of **Formula B**:



B

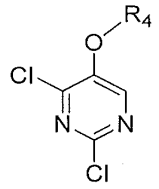
wherein:

R_2 and R_3 are each independently selected from the group consisting of: hydrogen and C_{1-6} alkyl; and

R_4 is C_{1-6} alkyl,

comprising mixing:

i) a compound of **Formula A**:



A

wherein R_4 is as given above,

ii) a nickel catalyst (e.g., $Ni(acac)_2$, $Ni(PPh_3)_2Cl_2$, or $Ni(dppp)Cl_2$),

iii) an alkylmagnesium halide, and

iv) an organic solvent,

to thereby make said compound of **Formula B**.

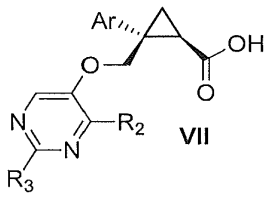
In some embodiments, the mixing is carried out for a time of from 6 to 36 hours.

In some embodiments, the mixing is carried out at a temperature of from 10 °C to 30 °C.

In some embodiments, the process further includes a step of quenching the reaction, e.g., with water comprising an acid (e.g., citric acid). In some embodiments, the process further includes a step of adding ammonium hydroxide after the quenching step.

In some embodiments, the process further includes reacting the compound of **Formula B** with a solution comprising hydrogen chloride and a solvent such as an alcohol (e.g., isopropyl alcohol) to obtain the compound of **Formula B** as a hydrochloride salt.

Also provided is a process for making a compound of **Formula VII**:



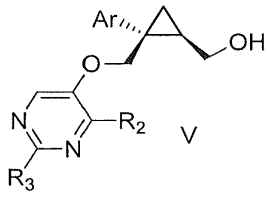
VII

wherein Ar is an aryl such as phenyl, which aryl may be unsubstituted, or substituted 1-3 times, for example with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl; and

R_2 and R_3 are each independently selected from the group consisting of: hydrogen, C_{1-6}alkyl, haloC_{1-6} alkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl,

comprising the steps of :

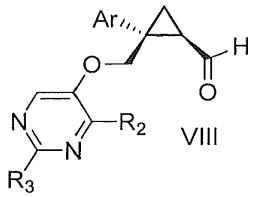
a) oxidizing a compound of **Formula V**:



V

wherein Ar, R_2 and R_3 are as given above,

with a first oxidizing agent, to form an aldehyde of Formula **VIII**:



VIII

wherein Ar, R_2 and R_3 are as given above; and then

b) oxidizing the aldehyde of **Formula VIII** with a second oxidizing agent,

to thereby make said compound of **Formula VII**.

In some embodiments, Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

In some embodiments, R_2 and R_3 are each independently selected from the group consisting of: hydrogen and C_{1-6}alkyl.

In some embodiments, the first oxidizing agent is sodium hypochlorite.

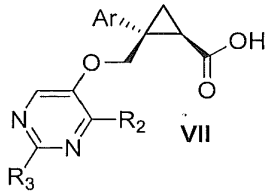
In some embodiments, oxidizing of step a) is catalyzed with an effective amount of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO).

In some embodiments, the second oxidizing agent is sodium chlorite.

In some embodiments, the first oxidizing agent and the second oxidizing agent are the same. In some embodiments, the first oxidizing agent and the second oxidizing agent are different.

In some embodiments, the oxidizing of step a) and/or step b) is carried out in an organic solvent (e.g., dichloromethane, tetrahydrofuran, 2-methyltetrahydrofuran, toluene, acetonitrile, or ethyl acetate).

Further provided is a process for preparing a compound of **Formula VII**:

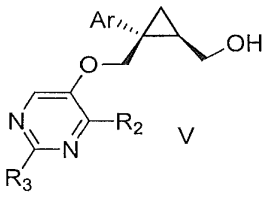


VII

wherein Ar is an aryl such as phenyl, which aryl may be unsubstituted, or substituted 1-3 times, for example with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl; and

R_2 and R_3 are each independently selected from the group consisting of: hydrogen, C_{1-6}alkyl, haloC_{1-6} alkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl,

comprising: oxidizing a compound of **Formula V**:



V

wherein Ar, R_2 and R_3 are as given above,

with sodium hypochlorite and sodium chlorite,

to thereby make said compound of **Formula VII**.

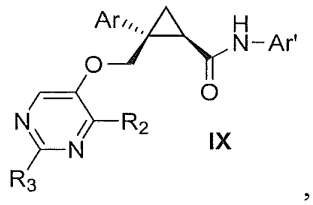
In some embodiments, Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

In some embodiments, R_2 and R_3 are each independently selected from the group consisting of: hydrogen and C_{1-6}alkyl.

In some embodiments, the oxidizing with sodium hypochlorite and sodium chlorite is carried out simultaneously.

In some embodiments, the oxidizing is catalyzed with an effective amount of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO).

Also provided is a process for making a compound of **Formula IX**:



IX

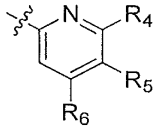
,

wherein:

Ar is an aryl such as phenyl, which aryl may be unsubstituted, or substituted 1-3 times, for example with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl;

R_2 and R_3 are each independently selected from the group consisting of: hydrogen, C_{1-6}alkyl, haloC_{1-6} alkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; and

Ar' is a pyridine group:



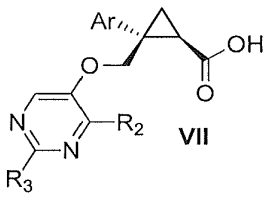
wherein:

R_4 is selected from the group consisting of: hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkoxy, and (C_{1-6}alkoxy)C_{1-6}alkyl;

R_5 is selected from the group consisting of: hydrogen, halo, C_{1-6}alkyl, and haloC_{1-6}alkyl; and

R_6 is selected from the group consisting of: hydrogen, halo, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, (C_{1-6}alkoxy)C_{1-6}alkyl, and cyano;

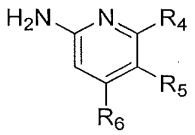
comprising the step of reacting a compound of **Formula VII**:



VII

wherein Ar, R_2 and R_3 are as given above,

with a compound of **Formula X**:



X ;

wherein R_4, R_5, and R_6 are as given above,

said reacting carried out in an organic solvent in the presence of an organic amine and an amide coupling agent,

to thereby make said compound of **Formula IX**.

In some embodiments, Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

In some embodiments, R_2 and R_3 are each independently selected from the group consisting of: hydrogen and C_{1-6}alkyl.

DETAILED DESCRIPTION

All U.S. Patent references are hereby incorporated by reference herein to the extent they are consistent with the present descriptions.

A. Definitions

Compounds of this invention include those described generally above, and are further illustrated by the embodiments, sub-embodiments, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated.

As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. In general, the term "substituted" refers to the replacement of hydrogen in a given structure with a specified substituent. Unless otherwise indicated, a substituted group may have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds.

"Isomers" refer to compounds having the same number and kind of atoms and hence the same molecular weight, but differing with respect to the arrangement or configuration of the atoms.

"Stereoisomers" refer to isomers that differ only in the arrangement of the atoms in space.

"Absolute stereochemistry" refers to the specific spatial arrangement of atoms or groups in a chemical compound about an asymmetric atom. For example, a carbon atom is asymmetric if it is attached to four different types of atoms or groups of atoms.

"Diastereoisomers" refer to stereoisomers that are not mirror images of each other.

"Enantiomers" refers to stereoisomers that are non-superimposable mirror images of one another.

Enantiomers include "enantiomerically pure" isomers that comprise substantially a single enantiomer, for example, greater than or equal to 90%, 92%, 95%, 98%, or 99%, or equal to 100% of a single enantiomer.

"Enantiomerically pure" as used herein means a compound, or composition of a compound, that comprises substantially a single enantiomer, for example, greater than or equal to 90%, 92%, 95%, 98%, or 99%, or equal to 100% of a single enantiomer.

"Stereomerically pure" as used herein means a compound or composition thereof that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound. For example, a stereomerically pure composition of a compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure composition of a compound having two chiral centers will be substantially free of diastereomers, and substantially free of the enantiomer, of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, more preferably greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, even more preferably greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, and most preferably greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound. *See, e.g.,* US Patent No. 7,189,715.

"R" and "S" as terms describing isomers are descriptors of the stereochemical configuration at an asymmetrically substituted carbon atom. The designation of an asymmetrically substituted carbon atom as "R" or "S" is done by application of the Cahn-Ingold-Prelog priority rules, as are well known to those skilled in the art, and described in the

International Union of Pure and Applied Chemistry (IUPAC) Rules for the Nomenclature of Organic Chemistry. Section E, Stereochemistry.

"Enantiomeric excess" (ee) of an enantiomer, when expressed as a percentage, is [(the mole fraction of the major enantiomer) minus (the mole fraction of the minor enantiomer)] x 100.

"Stable" as used herein refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40 °C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

"Refluxing" as used herein refers to a technique in which vapors from a boiling liquid are condensed and returned to the mixture from which it came, typically by boiling the liquid in a vessel attached to a condenser.

"Concentrating" as used herein refers to reducing the volume of solvent in a composition or mixture.

A "filtrate" is the liquid produced after filtering thereof; filtering typically includes the removal of a suspension of solid from the liquid.

An "organic" compound as used herein is a compound that contains carbon. Similarly, an "organic solvent" is a compound containing carbon that is useful as a solvent. Examples of organic solvents include, but are not limited to, acid amides such as N,N-dimethylformamide and N,N-dimethylacetamide; alcohols such as ethanol, methanol, isopropanol, amyl alcohol, ethylene glycol, propylene glycol, 1-butanol, butyl carbitol acetate and glycerin; aliphatic hydrocarbons such as hexane and octane; aromatic hydrocarbons such as toluene, xylenes and benzene; ketones such as acetone, methyl ethyl ketone and cyclohexanone; halogenated hydrocarbons such as methylene chloride, chlorobenzene and chloroform; esters such as ethyl acetate, amyl acetate and butyl acetate; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, tert-butyl methyl ether, diethyl ether and ethylene glycol dimethyl ether; nitriles such as acetonitrile; and sulfoxides such as dimethylsulfoxide.

An "inorganic" compound is a compound not containing carbon.

A "hydrocarbon" is an organic compound consisting of carbon and hydrogen atoms. Examples of hydrocarbons useful as "hydrocarbon solvents" include, but are not limited to, an "aromatic hydrocarbon solvent" such as benzene, toluene, xylenes, etc., and an "aliphatic hydrocarbon solvent" such as pentane, hexane, heptane, etc.

An "amine", "organic amine", "amine base" or "organic amine base" as used herein refers to an organic compound having a basic nitrogen atom (R-NR'R"), and may be a primary (R-NH_2), secondary (R-NHR') or tertiary (R-NR'R") amine. R, R' and R" may be independently selected from the group consisting of alkyl (*e.g.*, cycloalkyl), aryl and heteroaryl, which groups may be optionally substituted, or R and R', R and R" and/or R' and R", when present, may also combine to form cyclic or heteroalicyclic ring. The term heteroalicyclic as used herein refers to mono-, bi- or tricyclic ring or ring systems having one or more heteroatoms (for example, oxygen, nitrogen or sulfur) in at least one of the rings. The ring system may be a "saturated ring", which means that the ring does not contain any alkene or alkyne moieties, or it may also be an "unsaturated ring" which means that it contains at least one alkene or alkyne moiety provided that the ring system is not aromatic. The cyclic or heteroalicyclic group may be unsubstituted or substituted as defined herein.

In some embodiments the amine is aromatic. Examples of aromatic amines include, but are not limited to, pyridine, pyrimidine, quinoline, isoquinolines, purine, pyrrole, imidazole, and indole. The aromatic amines may be substituted or unsubstituted.

The term "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted" and means that a group may be substituted by one or more suitable substituents which may be the same or different. In some embodiments, suitable substituents may be selected from alkyl, cycloalkyl, biaryl, carbocyclic aryl, heteroalicyclic, heteroaryl, acyl, amidino, amido, amino, alkoxyamino, carbamoyl, carboxy, cyano, ether, guanidine, hydroxamoyl, hydroxyl, imino, isocyanato, isothiocyanato, halo, nitro, silyl, sulfonyl, sulfinyl, sulfenyl, sulfonato, sulfamoyl, sulfonamido, thiocarbonyl, thiol, thiocyanato, thiocarbamoyl, thioamido and urea.

Examples include, but are not limited to, triethylamine, pyridine, dimethylaminopyridine, N-methylmorpholine, Hunig's base (N,N-diisopropylethylamine), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

An "amide" as used herein refers to an organic functional group having a carbonyl group (C=O) linked to a nitrogen atom (N).

An "amide coupling agent" is an agent that may be used to couple a nitrogen and carboxyl group to form an amide, typically by activating the carboxyl group. Examples of amide coupling agents include, but are not limited to, carbodiimides such as *N,N'*-dicyclohexylcarbodiimide (DCC), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDC) or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDAC), *N,N'*-diisopropylcarbodiimide (DIC); imidazoliums such as 1,1'-carbonyldiimidazole (CDI), 1,1'-carbonyl-di-(1,2,4-triazole) (CDT); uronium or guanidinium salts such as *O*-(7-azabenzotriazol-

1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU), and *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU); phosphonium salts such as benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP or Castro's reagent), (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP®, Merck KGaA, Germany), 7-azabenxotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyAOP); alkyl phosphonic acid anhydrides such as ®T3P (Archimica, Germany), etc.

"Aqueous" is a solution in which water is the dissolving medium, or solvent. An "aqueous base" is a base in water. An "aqueous acid" is an acid in water.

An "acid" is a compound that can act as a proton donor or electron pair acceptor, and thus can react with a base. The strength of an acid corresponds to its ability or tendency to lose a proton. A "strong acid" is one that completely dissociates in water. Examples of strong acids include, but are not limited to, hydrochloric acid (HCl), hydroiodic acid (HI), hydrobromic acid (HBr), perchloric acid ($HClO_4$), nitric acid (HNO_3), sulfuric acid (H_2SO_4), etc. A "weak" or "mild" acid, by contrast, only partially dissociates, with both the acid and the conjugate base in solution at equilibrium. Examples of mild acids include, but are not limited to, carboxylic acids such as acetic acid, citric acid, formic acid, gluconic acid, lactic acid, oxalic acid, tartaric acid, ethylenediaminetetraacetic acid (EDTA), etc.

A "base" is a compound that can accept a proton (hydrogen ion) or donate an electron pair. A base may be organic (*e.g.*, DBU, cesium carbonate, etc.) or inorganic. A "strong base" as used herein is a compound that is capable of deprotonating very weak acids. Examples of strong bases include, but are not limited to, hydroxides, alkoxides, and ammonia.

A "hydroxide" is the commonly known diatomic anion OH^-, or a salt thereof (typically an alkali metal or alkaline earth metal salt thereof). Examples of hydroxides include, but are not limited to, sodium hydroxide (NaOH), potassium hydroxide (KOH), lithium hydroxide (LiOH), and calcium hydroxide ($Ca(OH)_2$).

An "alkoxide" is RO^-, the conjugate base of an alcohol. Examples include, but are not limited to, methoxide, ethoxide, and propoxide.

An "oxidizing agent" is an agent useful to oxidize a compound, whereby the compound loses electrons or increases its oxidation state. Examples include, but are not limited to, oxygen, ozone, organic peroxides such as hydrogen peroxide, halogens such as fluorine or chlorine, or halogen compounds such as chlorite, chlorate or perchlorate, nitrate compounds such as nitric acid, a sulfuric acid or persulfuric acid, hypohalite compounds such as hypophlorite and sodium

hypochlorite (NaClO), hexavalent chromium compounds such as chromic and dichromic acids and chromium trioxide, pyridinium chlorochromate and chromate/dichromate compounds, permanganate compounds, sodium perborate, nitrous oxide, silver oxide, osmium tetroxide, Tollens' reagent, and 2,2'-dipyridyldisulfide.

A "reducing agent" is an agent useful to reduce a compound, whereby the compound gains electrons or decreases its oxidation state. A "hydride reducing agent" is a reducing agent comprising a hydride. Examples include, but are not limited to, sodium borohydride, lithium borohydride, lithium aluminum hydride, lithium tri-butoxyaluminum hydride, diisobutylaluminum hydride (DIBAH), zinc borohydride (*See, e.g.*, Nakata et al., Tett. Lett., 24, 2653-56, 1983), and lithium triethyl borohydride (Super-Hydride®, Sigma-Aldrich, Saint Louis, Missouri). *See* Seyden-Penne, J. (1997). Reductions by the Alumino- and Borohydrides in Organic Synthesis, 2nd edition. Wiley-VCH.

A "leaving group" is a group or substituent of a compound that can be displaced by another group or substituent in a substitution reaction, such as a nucleophilic substitution reaction. For example, common leaving groups include halo groups; sulfonate ester leaving groups, such as a mesylate (methane sulfonate or -OMs), tosylate (*p*-toluenesulfonate or -OTs), brosylate, nosylate, besylate (benzene sulfonate) and the like; triflates, such as trifluoromethanesulfonate; and acyloxy groups, such as acetoxy, trifluoroacetoxy and the like. *See, e.g.*, US Patent No. 8,101,643.

A "lipase" as used herein is an enzyme capable of acylating a steryl glycoside. Examples include, but are not limited to, *Aspergillus* lipase; *Aspergillus niger* lipase; *Thermomyces lanuginosa* lipase; *Candida Antarctica* lipase A; *Candida Antarctica* lipase B; *Candida cylindracae* lipase; *Candida deformans* lipase; *Candida lipolytica* lipase; *Candida parapsilosis* lipase; *Candida rugosa* lipase; *Corynebacterium acnes* lipase; Cryptococcus spp. S-2 lipase; *Fusarium culmorum* lipase; *Fusarium heterosporum* lipase; *Fusarium oxysporum* lipase; *Mucor javanicus* lipase; *Rhizomucor miehei* lipase; *Rhizomucor delemar* lipase; *Burkholderia (Pseudomonas) cepacia* lipase; *Pseudomonas camembertii* lipase; *Pseudomonas fluorescens* lipase; *Rhizopus* lipase; *Rhizopus arrhizus* lipase; *Staphylococcus aureus* lipase; *Geotrichium candidum* lipase; Hyphozyma sp. lipase; *Klebsiella oxytoca* lipase; and homologs thereof (*e.g.*, variants thereof that have an amino acid sequence that is at least 80%, at least 85%; at least 90%, at least 92%; at least 94%; at least 95%, at least 96%; at least 97%; at least 98% or at least 99% identical to any of those wildtype enzymes). *See* US Patent Application Publication No. 2012/0009659.

A "*Candida Antarctica* lipase" is a lipase originally isolated from *Candida Antarctica* (and now more commonly expressed recombinantly, for example, in an *Aspergillus* species), and may be form A, form B, etc. In some embodiments, the lipase is coupled to a resin (*e.g.*, an acrylic resin). For example, *Candida Antarctica* B lipase is available immobilized on acrylic resin (Novozym® 435, Sigma-Aldrich, Saint Louis, Missouri). In some embodiments, the enzyme is selected from the group consisting of: *Candida Antarctica* lipase A, *Candida Antarctica* lipase B, and homologs thereof (*e.g.*, variants thereof that have an amino acid sequence that is at least 80%, at least 85%; at least 90%, at least 92%; at least 94%; at least 95%, at least 96%; at least 97%; at least 98% or at least 99% identical to any of those wildtype enzymes). *See* US Patent Application Publication No. 2012/0009659.

"Quenching," as known in the art, refers to stopping or substantially stopping a chemical reaction.

"Catalyze" means to accelerate a reaction by acting as a catalyst. A catalyst is a compound or substance that participates in a chemical reaction but is not consumed by the reaction itself.

Addition of one or more compounds or agents "simultaneously" or "concurrently" means that both are used at the same, or overlapping, times. For example, oxidizing with a first and second oxidizing agent in some embodiments may be accomplished by addition to a reaction vessel through multiple ports at the same or overlapping times.

"Ar" or "aryl" refer to an aromatic carbocyclic moiety having one or more closed rings. Examples include, without limitation, phenyl, naphthyl, anthracenyl, phenanthracenyl, biphenyl, and pyrenyl.

"Heteroaryl" refers to a cyclic moiety having one or more closed rings, with one or more heteroatoms (for example, oxygen, nitrogen or sulfur) in at least one of the rings, wherein at least one of the rings is aromatic, and wherein the ring or rings may independently be fused, and/or bridged. Examples include without limitation quinolinyl, isoquinolinyl, indolyl, furyl, thienyl, pyrazolyl, quinoxalinyl, pyrrolyl, indazolyl, thieno[2,3-c]pyrazolyl, benzofuryl, pyrazolo[1,5-a]pyridyl, thiophenylpyrazolyl, benzothienyl, benzothiazolyl, thiazolyl, 2-phenylthiazolyl, and isoxazolyl.

"Alkyl" or "alkyl group," as used herein, means a straight-chain (*i.e.*, unbranched), branched, or cyclic hydrocarbon chain that is completely saturated. In some embodiments, alkyl groups contain 1, 2, or 3, to 4, 5 or 6 carbon atoms (*e.g.*, C_{1-4}, C_{2-4}, C_{3-4}, C_{1-5}, C_{2-5}, C_{3-5}, C_{1-6}, C_{2-6}, C_{3-6}). In some embodiments, alkyl groups contain 3-4 carbon atoms. In certain embodiments, alkyl groups contain 1-3 carbon atoms. In still other embodiments, alkyl groups contain 2-3

carbon atoms, and in yet other embodiments alkyl groups contain 1-2 carbon atoms. In certain embodiments, the term "alkyl" or "alkyl group" refers to a cycloalkyl group, also known as carbocycle. Non-limiting examples of exemplary alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, cyclopropyl and cyclohexyl.

"Alkenyl" or "alkenyl group" as used herein refers to a straight-chain (*i.e.*, unbranched), branched, or cyclic hydrocarbon chain that has one or more double bonds. In certain embodiments, alkenyl groups contain 2-6 carbon atoms. In certain embodiments, alkenyl groups contain 2-4 carbon atoms. In still other embodiments, alkenyl groups contain 3-4 carbon atoms, and in yet other embodiments alkenyl groups contain 2-3 carbon atoms. According to another aspect, the term alkenyl refers to a straight chain hydrocarbon having two double bonds, also referred to as "diene." In other embodiments, the term "alkenyl" or "alkenyl group" refers to a cycloalkenyl group. Non-limiting examples of exemplary alkenyl groups include $-CH=CH_2$, $-CH_2CH=CH_2$ (also referred to as allyl), $-CH=CHCH_3$, $-CH_2CH_2CH=CH_2$, $-CH_2CH=CHCH_3$, $-CH=CH_2CH_2CH_3$, $-CH=CH_2CH=CH_2$, and cyclobutenyl.

"Alkoxy" or "alkylthio" as used herein refers to an alkyl group, as previously defined, attached to the principal carbon chain through an oxygen ("alkoxy") or sulfur ("alkylthio") atom.

"Methylene", "ethylene", and "propylene" as used herein refer to the bivalent moieties $-CH_2-$, $-CH_2CH_2-$, and $-CH_2CH_2CH_2-$, respectively.

"Ethenylene", "propenylene", and "butenylene" as used herein refer to the bivalent moieties $-CH=CH-$, $-CH=CHCH_2-$, $-CH_2CH=CH-$, $-CH=CHCH_2CH_2-$, $-CH_2CH=CH_2CH_2-$, and $-CH_2CH_2CH=CH-$, where each ethenylene, propenylene, and butenylene group can be in the *cis* or *trans* configuration. In certain embodiments, an ethenylene, propenylene, or butenylene group can be in the *trans* configuration.

"Alkylidene" refers to a bivalent hydrocarbon group formed by mono or dialkyl substitution of methylene. In certain embodiments, an alkylidene group has 1-6 carbon atoms. In other embodiments, an alkylidene group has 2-6, 1-5, 2-4, or 1-3 carbon atoms. Such groups include propylidene ($CH_3CH_2CH=$), ethylidene ($CH_3CH=$), and isopropylidene ($CH_3(CH_3)CH=$), and the like.

"Alkenylidene" refers to a bivalent hydrocarbon group having one or more double bonds formed by mono or dialkenyl substitution of methylene. In certain embodiments, an alkenylidene group has 2-6 carbon atoms. In other embodiments, an alkenylidene group has 2-6, 2-5, 2-4, or 2-3 carbon atoms. According to one aspect, an alkenylidene has two double bonds. Exemplary alkenylidene groups include $CH_3CH=C=$, $CH_2=CHCH=$, $CH_2=CHCH_2CH=$, and $CH_2=CHCH_2CH=CHCH=$.

"C_{1-6} alkyl ester or amide" refers to a C_{1-6} alkyl ester or a C_{1-6} alkyl amide where each C_{1-6} alkyl group is as defined above. Such C_{1-6} alkyl ester groups are of the formula (C_{1-6} alkyl)OC(=O)- or (C_{1-6} alkyl)C(=O)O-. Such C_{1-6} alkyl amide groups are of the formula (C_{1-6} alkyl)NHC(=O)- or (C_{1-6} alkyl)C(=O)NH-.

"C_{2-6} alkenyl ester or amide" refers to a C_{2-6} alkenyl ester or a C_{2-6} alkenyl amide where each C_{2-6} alkenyl group is as defined above. Such C_{2-6} alkenyl ester groups are of the formula (C_{2-6} alkenyl)OC(=O)- or (C_{2-6} alkenyl)C(=O)O-. Such C_{2-6} alkenyl amide groups are of the formula (C_{2-6} alkenyl)NHC(=O)- or (C_{2-6} alkenyl)C(=O)NH-.

"Halo" refers to fluoro, chloro, bromo or iodo.

"Haloalkyl" refers to an alkyl group substituted with one or more halo atoms. For example, "fluoromethyl" refers to a methyl group substituted with one or more fluoro atoms (*e.g.,* monofluoromethyl, difluoromethyl, trifluoromethyl).

"Hydroxyalkyl" refers to an alkyl group substituted with a hydroxyl group (-OH).

"Fluoromethoxy" as used herein refers to a fluoromethyl group, as previously defined, attached to the principal carbon chain through an oxygen atom.

"Thiol" refers to an organosulfur compound R-SH, wherein R is an aliphatic group.

"Cyano" refers to the group –C≡N, or –CN.

"Aliphatic" is an acyclic or cylic, non-aromatic carbon compound.

"Protecting group" as used herein, is meant that a particular functional moiety, *e.g.*, O, S, or N, is temporarily blocked so that a reaction can be carried out selectively at another reactive site in a multifunctional compound. For example, in certain embodiments, as detailed herein, certain exemplary oxygen protecting groups are utilized. Oxygen protecting groups include, but are not limited to, groups bonded to the oxygen to form an ether, such as methyl, substituted methyl (*e.g.*, Trt (triphenylmethyl), MOM (methoxymethyl), MTM (methylthiomethyl), BOM (benzyloxymethyl), PMBM or MPM (p-methoxybenzyloxymethyl)), substituted ethyl (*e.g.*, 2-(trimethylsilyl)ethyl), benzyl, substituted benzyl (*e.g.*, para-methoxybenzyl), silyl (*e.g.*, TMS (trimethylsilyl), TES (triethylsilyl), TIPS (triisopropylsilyl), TBDMS (t-butyldimethylsilyl), tribenzylsilyl, TBDPS (t-butyldiphenyl silyl), 2-trimethylsilylprop-2-enyl, t-butyl, tetrahydropyranyl, allyl, etc.

In some embodiments, the compounds described herein may be provided as a salt, such as a pharmaceutically acceptable salt. "Pharmaceutically acceptable salts" are salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects. Specific examples of pharmaceutically acceptable salts include inorganic acid salts (such as sulfates, nitrates, perchlorates, phosphates, carbonates, bicarbonates, hydrofluorides,

hydrochlorides, hydrobromides and hydroiodides), organic carboxylates (such as acetates, oxalates, maleates, tartrates, fumarates and citrates), organic sulfonates (such as methanesulfonates, trifluoromethanesulfonates, ethanesulfonates, benzenesulfonates, toluenesulfonates and camphorsulfonates), amino acid salts (such as aspartates and glutamates), quaternary amine salts, alkali metal salts (such as sodium salts and potassium salts) and alkali earth metal salts (such as magnesium salts and calcium salts).

Unless indicated otherwise, nomenclature used to describe chemical groups or moieties as used herein follow the convention where, reading the name from left to right, the point of attachment to the rest of the molecule is at the right-hand side of the name. For example, the group "(C_{1-3} alkoxy)C_{1-3} alkyl," is attached to the rest of the molecule at the alkyl end. Further examples include methoxyethyl, where the point of attachment is at the ethyl end, and methylamino, where the point of attachment is at the amine end.

Unless indicated otherwise, where a mono or bivalent group is described by its chemical formula, including one or two terminal bond moieties indicated by "-," it will be understood that the attachment is read from left to right.

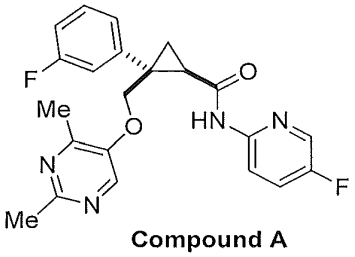
Unless otherwise stated, structures depicted herein are also meant to include all enantiomeric, diastereomeric, and geometric (or conformational) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention.

Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays.

B. Compounds and Chemical Synthesis

Provided herein are compounds (*e.g.*, intermediate compounds) and methods that are useful for the preparation of compounds useful as orexin-2 receptor antagonists, such as (1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide (Compound A, below), which have been found to be potent orexin

receptor antagonists, and may be useful in the treatment of sleep disorders such as insomnia, as well as for other therapeutic uses.



Compound A

However, it will be understood that the compounds and methods herein may also be useful to make similar compounds and/or perform similar chemical syntheses.

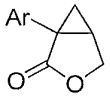
Provided is a process for making a compound of **Formula I**,

I

wherein Ar is an aryl such as phenyl, which aryl may be unsubstituted, or substituted 1-3 times, for example, with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl,

the method comprising one or more of the the steps of :

i) providing a composition comprising a compound of **Formula II**:



II

wherein Ar is as given above, and an organic solvent, wherein said composition is at a temperature of from -30 to 40 °C, or from -30 to 30 °C, or from -30 to 10 °C, or from -10 to 0 °C, or from -10 to -5 °C; and

ii) adding to said composition a hydride reducing agent, wherein said agent reduces said compound of **Formula II** into said compound of **Formula I**,

to thereby make said compound of **Formula I**.

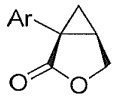
In some embodiments, Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

In some embodiments, the organic solvent is an aromatic hydrocarbon solvent, an aliphatic hydrocarbon solvent, a halogenated hydrocarbon solvent or an ether solvent.

In some embodiments, the process may further include the step of mixing (*e.g.*, by stirring) the composition after said adding step for a time of 12 to 24 hours.

In some embodiments, the process may further include the step of quenching the reduction by adding to said composition a mild aqueous acid (*e.g.*, citric acid, EDTA or tartaric acid).

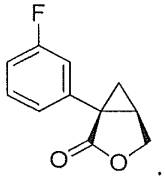
In some embodiments, the compound of **Formula II** has the absolute stereochemistry of **Formula IIa**:



IIa .

In some embodiments, the compound of **Formula II** has an enantiomeric excess (ee) of the **Formula IIa** stereoisomer of at least 75, 80, 85, 90, 95, 98, 99%, or greater.

In some embodiments, the compound of **Formula II** or **Formula IIa** is the compound:



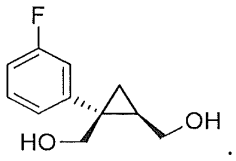
.

In some embodiments, the compound of **Formula I** has the absolute stereochemistry of **Formula Ia**:

Ia .

In some embodiments, the compound of **Formula I** has an enantiomeric excess (ee) of the **Formula Ia** stereoisomer of at least 75, 80, 85, 90, 95, 98, 99%, or greater.

In some embodiments, the compound of **Formula I** or **Formula Ia** is:



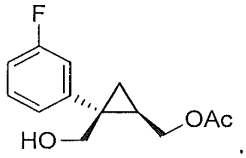
Also provided is compound of **Formula III**:

III

wherein Ar is an aryl such as phenyl, which aryl may be unsubstituted, or substituted 1-3 times, for example with substituents independently chosen from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl.

In some embodiments, Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

In some embodiments, the compound is:



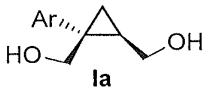
Also provided is a process for making a compound of **Formula III**:

III

wherein Ar is aryl such as phenyl, which aryl may be unsubstituted, or substituted 1-3 times, for example with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl,

comprising reacting a mixture of:

i) a compound of **Formula Ia:**



Ia

wherein Ar is as given above,

ii) vinyl acetate,

iii) a lipase, and

iv) an organic solvent

for a time of from 5 to 36 hours, or from 7 to 18 hours,

to thereby make the compound of **Formula III**.

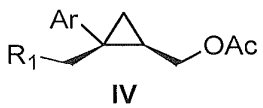
In some embodiments, Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

In some embodiments, the organic solvent is tetrahydrofuran, 2-methyltetrahydrofuran, an ether solvent, acetone, or acetonitrile.

In some embodiments, the lipase is a *Candida Antarctica* lipase, for example, a *Candida Antarctica* B lipase, which may be coupled to solid support such as an acrylic resin.

In some embodiments, the process may further include the step of filtering the mixture after said reacting to produce a filtrate, and may also include concentrating the filtrate to produce a concentrated filtrate. In some embodiments, the process may further include the step of washing the concentrated filtrate with water or water comprising a salt (*e.g.*, a solution of 15-20% NaCl in water).

Also provided is a compound of **Formula IV**:



IV

wherein:

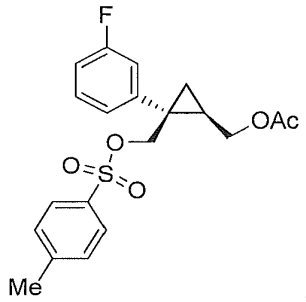
Ar is an aryl such as phenyl, which aryl may be unsubstituted, or substituted 1-3 times, for example with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl; and

R_1 is a leaving group.

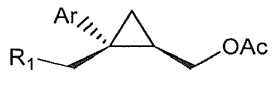
In some embodiments, Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

In some embodiments, the leaving group is a sulfonate ester leaving group selected from the group consisting of: mesylate, tosylate, nosylate, benzene sulfonate, and brosylate.

In some embodiments, the compound is:



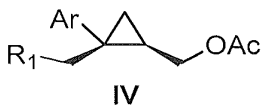
In some embodiments, the compound of **Formula IV** has the absolute stereochemistry of **Formula IVa**:



IVa

In some embodiments, the compound of **Formula IV** has an enantiomeric excess (ee) of the **Formula IVa** stereoisomer of at least 75, 80, 85, 90, 95, 98, 99%, or greater.

Further provided is a process for making a compound of **Formula IV**:



IV

wherein Ar is an aryl such as phenyl, which aryl may be unsubstituted, or substituted 1-3 times, for example with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl; and

R_1 is a sulfonate ester leaving group,

said process comprising reacting a compound of **Formula III**:

III

wherein Ar is as given above,

with a compound selected from the group consisting of: tosyl chloride, mesyl chloride, nosyl chloride, toluenesulfonyl chloride, toluenesulfonic anhydride and methanesulfonic anhydride, wherein said reacting is carried out in an organic solvent in the presence of a base,

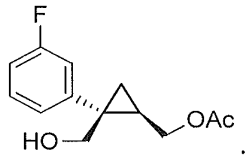
to thereby make said compound of **Formula IV**.

In some embodiments, Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

In some embodiments, the reacting is carried out for a time of from 10 minutes to 2 hours.

In some embodiments, the base is an organic amine or potassium carbonate.

In some embodiments, the compound of **Formula III** is:

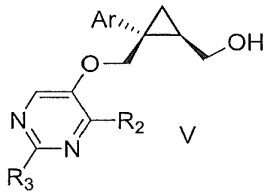


In some embodiments, the compound of **Formula IV** has the absolute stereochemistry of **Formula IVa**:

IVa

In some embodiments, the compound of **Formula IV** has an enantiomeric excess (ee) of the **Formula IVa** stereoisomer of at least 75, 80, 85, 90, 95, 98, 99%, or greater.

Also provided is a process for making a compound of **Formula V**,



V

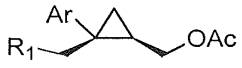
wherein Ar is an aryl such as phenyl, which aryl may be unsubstituted, or substituted 1-3 times, for example with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl; and

R_2 and R_3 are each independently selected from the group consisting of: hydrogen, C_{1-6}alkyl, haloC_{1-6} alkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl,

comprising the steps of:

a) stirring a mixture of:

i) a compound of **Formula IV**:

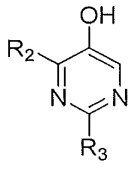


IV

wherein Ar is as given above; and

R_1 is a leaving group,

ii) a substituted pyrimidine of **Formula VI**:



VI ,

wherein R_2 and R_3 are as given above;

iii) a base; and

iv) an organic solvent,

at a temperature of from 65-70 °C, for 1 to 12 hours; and then

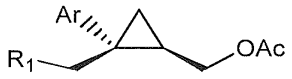
b) reacting the mixture with an aqueous base for a time of from 2 to 20 hours,

to thereby make said compound of **Formula V**.

In some embodiments, Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

In some embodiments, R_2 and R_3 are each independently selected from the group consisting of: hydrogen and C_{1-6}alkyl.

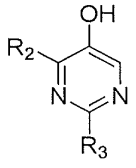
In some embodiments, the compound of **Formula IV** has the absolute stereochemistry of **Formula IVa**:



IVa

In some embodiments, the compound of **Formula IV** has an enantiomeric excess (ee) of the **Formula IVa** stereoisomer of at least 75, 80, 85, 90, 95, 98, 99%, or greater.

Further provided is a process for making a compound of **Formula VI**:

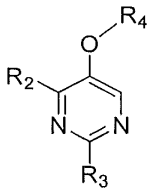


VI

wherein R_2 and R_3 are each independently selected from the group consisting of: hydrogen and C_{1-6} alkyl,

comprising the step of heating a mixture of:

i) a compound of **Formula B**:



B

wherein:

R_2 and R_3 are as given above; and

R_4 is C_{1-6} alkyl,

ii) an alkoxide or hydroxide salt,

iii) a thiol, and

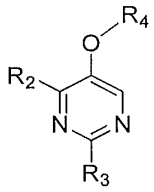
iv) an organic solvent,

to thereby make said compound of **Formula VI**.

In some embodiments, the heating is to a temperature of from 50 to 140 °C. In some embodiments, heating comprises boiling or refluxing the mixture.

In some embodiments, the heating is carried out in a time of from 5 to 50 hours.

Also provided is a process for making a compound of **Formula B**:



B

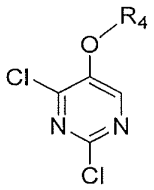
wherein:

R_2 and R_3 are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl; and

R_4 is C_{1-6} alkyl,

comprising mixing:

i) a compound of **Formula A**:



A

wherein R_4 is as given above,

ii) trimethylaluminum,

iii) a palladium catalyst, and

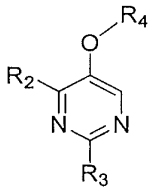
iv) an organic solvent,

to thereby make said compound of **Formula B**.

In some embodiments, the mixing step is carried out for a time of from 12 to 48 hours.

In some embodiments, the mixing step is carried out at a temperature of from 20 to 110 °C.

Further provided is a process for making a compound of **Formula B**:



B

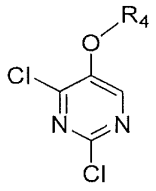
wherein:

R_2 and R_3 are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl; and

R_4 is C_{1-6} alkyl,

comprising mixing:

i) a compound of **Formula A**:



A

wherein R_4 is as given above,

ii) a nickel catalyst (*e.g.*, $Ni(acac)_2$, $Ni(PPh_3)_2Cl_2$, or $Ni(dppp)Cl_2$),

iii) an alkylmagnesium halide, and

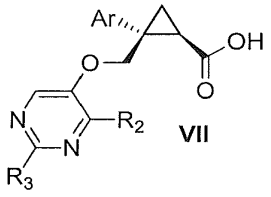
iv) an organic solvent,

to thereby make said compound of **Formula B**.

In some embodiments, the mixing is carried out for a time of from 6 to 36 hours.

In some embodiments, the mixing is carried out at a temperature of from 10 to 30 °C.

Also provided is a process for making a compound of **Formula VII**:



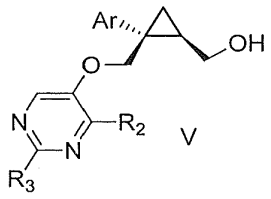
VII

wherein Ar is an aryl such as phenyl, which aryl may be unsubstituted, or substituted 1-3 times, for example with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl; and

R_2 and R_3 are each independently selected from the group consisting of: hydrogen, C_{1-6}alkyl, haloC_{1-6} alkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl,

comprising the steps of :

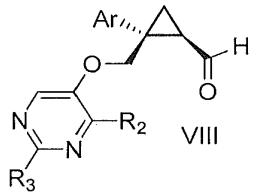
a) oxidizing a compound of **Formula V**:



V

wherein Ar, R_2 and R_3 are as given above,

with a first oxidizing agent, to form an aldehyde of Formula **VIII**:



VIII

wherein Ar, R_2 and R_3 are as given above; and then

b) oxidizing the aldehyde of **Formula VIII** with a second oxidizing agent, to thereby make said compound of **Formula VII**.

In some embodiments, Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

In some embodiments, R_2 and R_3 are each independently selected from the group consisting of: hydrogen and C_{1-6}alkyl.

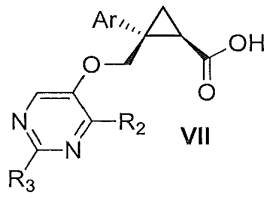
In some embodiments, the first oxidizing agent is sodium hypochlorite.

In some embodiments, oxidizing of step a) is catalyzed with an effective amount of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO).

In some embodiments, the second oxidizing agent is sodium chlorite.

In some embodiments, the first oxidizing agent and the second oxidizing agent are the same. In some embodiments, the first oxidizing agent and the second oxidizing agent are different.

Further provided is a process for preparing a compound of **Formula VII**,

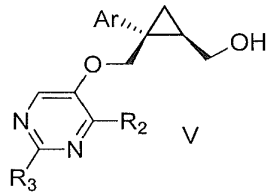


VII

wherein Ar is an aryl such as phenyl, which aryl may be unsubstituted, or substituted 1-3 times, for example with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl; and

R_2 and R_3 are each independently selected from the group consisting of: hydrogen, C_{1-6}alkyl, haloC_{1-6} alkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl,

comprising: oxidizing a compound of **Formula V**:



V

wherein Ar, R_2 and R_3 are as given above,

with sodium hypochlorite and sodium chlorite,

to thereby make said compound of **Formula VII**.

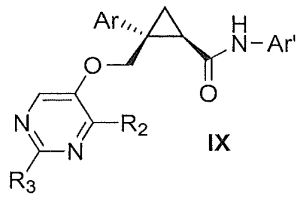
In some embodiments, Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

In some embodiments, R_2 and R_3 are each independently selected from the group consisting of: hydrogen and C_{1-6}alkyl.

In some embodiments, the oxidizing with sodium hypochlorite and sodium chlorite is carried out simultaneously.

In some embodiments, the oxidizing is catalyzed with an effective amount of TEMPO.

Also provided is a process for making a compound of **Formula IX**:



IX

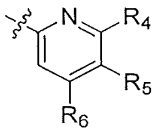
,

wherein:

Ar is an aryl such as phenyl, which aryl may be unsubstituted, or substituted 1-3 times, for example with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl;

R_2 and R_3 are each independently selected from the group consisting of: hydrogen, C_{1-6}alkyl, haloC_{1-6} alkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; and

Ar' is a pyridine group:



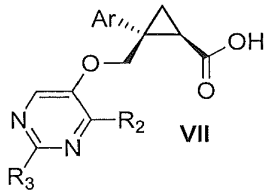
wherein:

R_4 is selected from the group consisting of: hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkoxy, and (C_{1-6}alkoxy)C_{1-6}alkyl;

R_5 is selected from the group consisting of: hydrogen, halo, C_{1-6}alkyl, and haloC_{1-6}alkyl; and

R_6 is selected from the group consisting of: hydrogen, halo, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, (C_{1-6}alkoxy)C_{1-6}alkyl, and cyano;

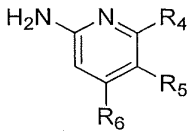
comprising the step of reacting a compound of **Formula VII**:



VII

wherein Ar, R_2 and R_3 are as given above,

with a compound of **Formula X**:



X ;

wherein R_4, R_5, and R_6 are as given above,

said reacting carried out in an organic solvent in the presence of an organic amine and an amide coupling agent,

to prepare said compound of **Formula IX**.

In some embodiments, Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

In some embodiments, R_2 and R_3 are each independently selected from the group consisting of: hydrogen and C_{1-6}alkyl.

It should be understood that any of the compounds listed above and used in the processes disclosed herein may be provided in a stereochemically pure form and are included in the present disclosure. In some embodiments, the stereochemically pure compound has greater than about 75% by weight of one stereoisomer of the compound and less than about 25% by weight of other stereoisomers of the compound, greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, or greater than about 85% by weight of one stereoisomer of the compound and less than about 15% by weight of other stereoisomers of the compound, or greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, or greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, or greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound, or greater than about 98% by weight of one stereoisomer of the compound and less than about 2% by weight of the other stereoisomers of the compound. In some embodiments, the stereochemically pure compound has greater than 99% by weight of one stereoisomer of the compound and less than 1% by weight of the other stereoisomers of the compound.

As noted above, in some embodiments the compounds described herein may be provided as a salt, such as a pharmaceutically acceptable salt.

EXAMPLES

General:

Column chromatography was carried out using a Biotage SP4. Solvent removal was carried out using either a Büchii rotary evaporator or a Genevac centrifugal evaporator. Preparative LC/MS was conducted using a Waters autopurifier and 19 x 100mm XTerra 5 micron MS C18 column under acidic mobile phase conditions. NMR spectra were recorded using either a Varian 400 or 500 MHz spectrometer.

The term "inerted" is used to describe a reactor (*e.g.*, a reaction vessel, flask, glass reactor, and the like) in which the air in the reactor has been replaced with an essentially moisture-free or dry, inert gas (such as nitrogen, argon, and the like). The term "equivalent" (abbreviation: equiv.) as used herein describes the stoichiometry (molar ratio) of a reagent or a reacting compound by comparison to a pre-established starting material. The term "weight" (abbreviation: wt) as used herein corresponds to the ratio of the mass of a substance or a group of substances by comparison to the mass of a particular chemical component of a reaction or purification specifically referenced in the examples below. The ratio is calculated as: g/g, or Kg/Kg. The term "volume" (abbreviation: vol) as used herein corresponds to the ratio of the volume of a given substance or a group of substances to the mass or volume of a pre-established chemical component of a reaction or purification. The units used in the equation involve matching orders of magnitude. For example, a ratio is calculated as: mL/mL, mL/g, L/L or L/Kg.

General methods and experimentals for preparing compounds of the present invention are set forth below. In certain cases, a particular compound is described by way of example. However, it will be appreciated that in each case a series of compounds of the present invention were prepared in accordance with the schemes and experimentals described below.

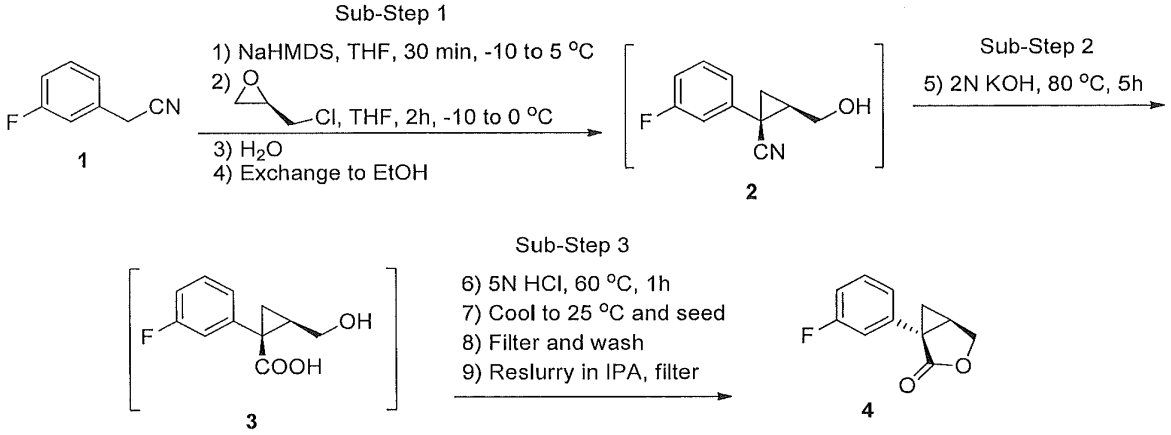
The following abbreviations are used herein:

Abbreviation	Definition
TMS	Trimethylsilyl
TBAF	Tetrabutylammonium fluoride
NaOH	Sodium hydroxide
$Bu_4N\ HSO_4$	Tetrabutylammonium hydrogen sulfate
THF	Tetrahydrofuran
rt	Room temperature

h	Hour(s)
NaCl	Sodium chloride
HCOOH	Formic acid
V	Volumes
equiv.	Equivalent(s)
wt	Weights
CDI	N,N-Carbonyldiimidazole
DCM	Dichloromethane
Aq	Aqueous
Sat.	Saturated
HCl	Hydrochloric acid
HRMS	High Resolution Mass Spectrometry
nBuLi	n-butyl lithium
NH_4Cl	Ammonium chloride
MeOH	Methanol
EtOAc	Ethyl acetate
$NaHCO_3$	Sodium bicarbonate
M	Molar (moles/liter)
T	Temperature
MTBE	Methyl *tert*-butyl ether
TLC	Thin layer chromatography
N	Normal (equivalents per liter)
iPrMgBr	Isopropyl magnesium bromide
LiCl	Lithium chloride
NaOAc	Sodium acetate
NH_4OH	Ammonium hydroxide
HPLC	High performance liquid chromatography
ee	Enantiomeric excess
DMI	1,3-Dimethyl-2-imidazolidinone
UV	Ultraviolet
RRT	Relative retention time
OROT	Optical rotation
Bz	Benzoyl
ACN	Acetonitrile
®T3P (Archimica, Germany)	Tri-n-propyl phosphonic acid anhydride
HATU	*N,N,N',N'*-tetramethyl-*O*-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate

5

A. Preparation of Cyclopropane Compounds of Formula II



(1S,5R)-1-(3-fluorophenyl)-3-oxabicyclo[3.1.0]hexan-2-one (4). 3-fluorophenylacetonitrile (**1**, 200 g, 1.48 mol, 1.0 equiv.) was dissolved in THF (1500 mL) and cooled to -3 °C. To the solution was added dropwise sodium bis(trimethylsilyl)amine (2.0 M solution in THF, 1520 mL, 3.04 mol, 2.05 equiv.), maintaining the internal temperature at less than 7 °C. The mixture was allowed to stir for 29 h at 0 °C after which it was warmed to room temperature and quenched by addition of water (85 mL). The mixture was concentrated to near dryness by rotary evaporation and ethanol (1500 mL) was added followed by aqueous potassium hydroxide solution (2.0 M, 1477 mL). The mixture was heated to 80 °C and aged at this temperature for 5 hours, after which it was cooled to room temperature. Aqueous hydrochloric acid solution (6 M, 944 mL) and water (189 mL) were added. The mixture was heated to 60 °C and aged at this temperature for 2 hours. The mixture was cooled to room temperature and seed crystals of **4** ((1S,5R)-1-(3-fluorophenyl)-3-oxabicyclo[3.1.0]hexan-2-one) were added (1.5 g, 0.005 equiv.). The resulting slurry was allowed to stir overnight and then filtered. The cake was washed with 2:1 water/ethanol solution (2 x 200 mL) followed by water (3 x 400 mL) until the pH of the filtrate was pH=7. The cake was dried under vacuum with a sweep of nitrogen to afford (1S,5R)-1-(3-fluorophenyl)-3-oxabicyclo[3.1.0]hexan-2-one (**4**, 205.31 g, 70% yield, 91% ee) as an off-white crystalline solid.

(1S,5R)-1-(3-fluorophenyl)-3-oxabicyclo[3.1.0]hexan-2-one: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.43 – 7.36 (m, 1H), 7.35 – 7.31 (m, 1H), 7.31 – 7.28 (m, 1H), 7.14 – 7.08 (m, 1H), 4.46 (dd, J = 9.1, 4.6 Hz, 1H), 4.25 (d, J = 9.1 Hz, 1H), 2.80 (dt, J = 8.0, 4.6 Hz, 1H), 1.72 (dd, J = 7.9, 4.8 Hz, 1H), 1.37 (t, J = 4.8 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 175.35, 161.98 (d, J_{CF} = 243.1 Hz), 137.67 (d, J_{CF} = 8.2 Hz), 130.15 (d, J_{CF} = 8.6 Hz), 124.19 (d, J_{CF} = 2.8 Hz), 115.01 (d, J_{CF} = 22.4 Hz), 113.95 (d, J_{CF} = 20.9 Hz), 67.93, 30.70 (d, J_{CF} = 2.4 Hz), 25.57, 19.99.

HRMS Calculated for $C_{11}H_{10}FO_2$ $[M+H]^+$ 193.0665; found 193.0659.

HPLC Method TM-1172 for monitoring of above process step:

Equipment, Reagents, and Mobile Phase:

Equipment:

HPLC column:	Waters SunFire C18, 3.5 um 3 x 150 mm, Waters catalog no. 186002544.
Solvent Delivery System	Agilent 1100 HPLC quaternary pump, low pressure mixing, with an in-line degasser, or equivalent.
Autosampler:	Agilent 1100 autosampler, variable loop, 0.1 to 100 μL range, or equivalent.
Detector:	Agilent 1100 Diode Array Detector or equivalent.
Chromatographic Software:	Agilent ChemStation software version A.09.03 or higher for HPLC, Waters Empower 2 Build 2154, or equivalent.
Volumetric Glassware:	Class A.
Balance:	Analytical balance, capable of weighing ± 0.1 mg.

Reagents:

Water:	HPLC grade, (Baker cat no. 4218-03) or equivalent
Acetonitrile:	HPLC grade, (Baker cat no. 9017-03) or equivalent.
Trifluoroacetic acid (TFA):	Spectrophotometric grade, Aldrich (catalog no. 302131) or equivalent.

Mobile Phase:

Solvent A:	Add 1000 mL of water to an appropriate flask. Add 1.0 mL of trifluouroacetic acid and mix. Degas in-line during use.
Solvent B:	Add 1000 mL of acetonitrile to an appropriate flask. Add 1.0 mL of trifluouroacetic acid and mix. Degas in-line during use.

HPLC Parameters:

Chromatographic Parameters

HPLC column:	Waters SunFire C18, 3.5 um 3 x 150 mm, Waters catalog no. 186002544.		
Temperature:	40 °C		
Flow rate:	0.5 mL/min. Flow rate may be adjusted ± 0.2 mL/min to obtain specified retention times.		
Gradient:	**Time, min**	**%-Solvent A**	**%-Solvent B**
	Initial	95	5

	3	70	30
	20	70	30
	20.1	95	5
	30	95	5
Injection volume:	5 µL		
Detection:	210 nm UV		
Data acquisition time:	20 min		
Run time:	30 min		

TM-1213: Chiral HPLC Assay for 4

Equipment, Reagents, and Mobile Phase:

Equipment:

HPLC column:	AD-H 4.6 x 250 mm 5 µm, Chiral Tech catalog no. 19325 or equivalent.
Solvent Delivery System:	Agilent 1100 HPLC quaternary pump, low pressure mixing with an in-line degasser, or equivalent.
Autosampler:	Agilent 1100 autosampler, 0.1 to 100 µL range, or equivalent.
Detector:	Agilent 1100 variable wavelength detector or equivalent.
Chromatographic Software:	Agilent ChemStation software version A.09.03 or higher for HPLC, Waters Empower 2 Build 2154, or equivalent.
Volumetric Glassware:	Class A.
Volumetric pipette:	Class A.
Balance:	Analytical balance, capable of weighing ± 0.1 mg.

Reagents:

Hexanes:	HPLC grade, EMD (catalog no. HX0296-1) or equivalent.
2-Propanol:	HPLC grade, J.T. Baker (catalog no. 9095-03) or equivalent.

Mobile Phase:

Mobile phase A:
Using appropriate graduated cylinders, add 900 mL of hexanes and 100 mL of 2-propanol to an appropriate flask. Mix well and degas in line during use.

HPLC Parameters:

Chromatographic Parameters:

HPLC column:	AD-H 4.6 x 250 mm 5 µm, Chiral Tech catalog no. 19325 or equivalent.
Temperature:	25 °C

Flow rate:	1.0 mL/min. Flow rate may be adjusted to obtain specified retention times.
Isocratic	Mobile Phase A
Injection volume:	5.0 µL
Detection:	UV detector 213 nm
Acquisition time:	15 min
Re-equilibration time:	N/A
Total run time:	15 min

Calculations:

The system suitability tests must pass all acceptance criteria before analysis of the results from the Sample Analysis section is allowed to proceed.

%-Enantiomeric Excess Calculation:

Calculate the %-enantiomeric excess (%-ee) for each **4** sample preparation using the appropriate peak areas obtained from each sample analysis injection and the following equation:

$$\%\,ee = \frac{(A_4 - A_{19})(100\%)}{(A_4 + A_{19})}$$

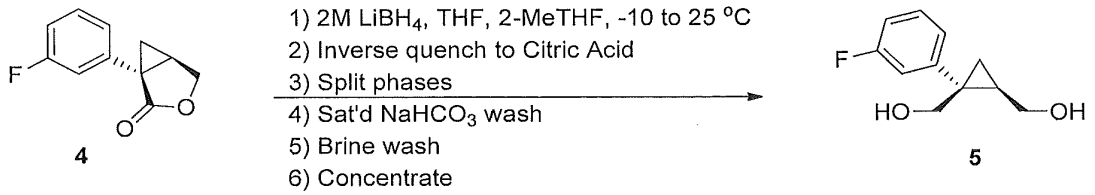
A_4 = Peak area of 4 from each sample solution injection

A_{19} = Peak area of 19 from each sample solution injection

Note: Compound **19** is the enantiomer of compound **4**.

An enantiomeric excess was calculated at 91% for compound **4**.

B. Preparation of Compounds of Formula I



((1S,2R)-1-(3-fluorophenyl)cyclopropane-1,2-diyl)dimethanol (5). (1S,5R)-1-(3-fluorophenyl)-3-oxabicyclo[3.1.0]hexan-2-one (**4**, 10.08 g, 0.052 mol, 1.0 equiv.) was dissolved

in 2-methyl-THF (75.60 mL) under nitrogen. The solution was cooled to -5 to -10 °C, and 2.0 M Lithium tetrahydroborate in THF (39.34 mL, 0.079 mol, 1.5 equiv.) was added to the reaction mixture while maintaining the internal temperature below 0 °C. The reaction was stirred at 20-25 °C for 14-16 hours and monitored by HPLC and TLC (EtOAc/Heptane = 1/1). Once the reaction was completed, the reaction mixture was cooled to 0-5 °C and reverse quenched into a pre-cooled (0-5 °C) 20% aqueous citric acid solution (50.40 mL, 1.67 equiv.) at such a rate as to maintain the internal temperature below 5 °C. Once the quench was complete, the reaction mixture was warmed to 20-25 °C and stirred for at least 20 min. The aqueous layer was back extracted once with 2-methyl-THF (50.40 mL). The organic layers were combined and washed once with saturated aqueous sodium bicarbonate solution (20.16 mL) and once with 20% aqueous NaCl (20.16 mL). The solvent was removed under reduced pressure then azeotroped with 2-methyl-THF until KF is less than 1500 ppm to afford the title compound, ((1S,2R)-1-(3-fluorophenyl)cyclopropane-1,2-diyl)dimethanol; **5** (10.29 g).

((1S,2R)-1-(3-fluorophenyl)cyclopropane-1,2-diyl)dimethanol: ^{1}H NMR (500 MHz, CD_3OD) δ 7.28 (td, J = 8.0, 6.2 Hz, 1H), 7.22 – 7.17 (m, 1H), 7.16 – 7.09 (m, 1H), 6.96 – 6.85 (m, 1H), 3.99 – 3.93 (m, 2H), 3.71 (d, J = 12.0 Hz, 1H), 3.56 (dd, J = 11.9, 9.5 Hz, 1H), 1.52 (tt, J = 9.1, 6.1 Hz, 1H), 1.10 (dd, J = 8.7, 5.1 Hz, 1H), 0.85 (t, J = 5.5 Hz, 1H); ^{13}C NMR (126 MHz, CD_3OD) δ 164.10 (d, J_{CF} = 243.6 Hz), 148.96 (d, J_{CF} = 7.5 Hz), 130.74 (d, J_{CF} = 8.4 Hz), 125.61 (d, J_{CF} = 2.7 Hz), 116.77 (d, J_{CF} = 21.6 Hz), 113.93 (d, J_{CF} = 21.3 Hz), 67.16, 63.31, 33.04, 28.09, 17.44.

HPLC method for monitoring process step B:

Equipment:

HPLC column:	Waters SunFire C18, 3.5 um 3 x 150 mm, Waters catalog no. 186002544.
Solvent Delivery System:	Agilent 1100 HPLC quaternary pump, low pressure mixing, with an in-line degasser, or equivalent.
Autosampler:	Agilent 1100 autosampler, variable loop, 0.1 to 100 μL range, or equivalent.
Detector:	Agilent 1100 Diode Array Detector or equivalent.
Chromatographic Software:	Agilent ChemStation software version A.09.03 or higher for HPLC, Waters Empower 2 Build 2154, or equivalent.
Volumetric Glassware:	Class A.
Balance:	Analytical balance, capable of weighing ± 0.1 mg.

Reagents:

Water:	HPLC grade, (Baker cat no. 4218-03) or equivalent
Acetonitrile:	HPLC grade, (Baker cat no. 9017-03) or equivalent.
Trifluoroacetic acid (TFA):	Spectrophotometric grade, Aldrich (catalog no. 302131) or equivalent.

Mobile Phase:

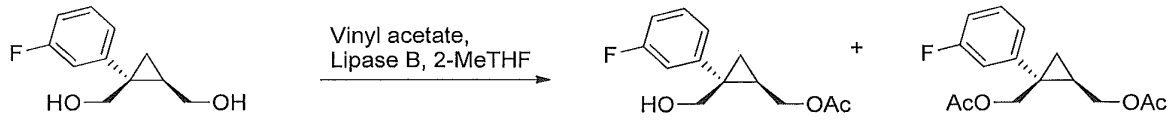
Solvent A:	Add 1000 mL of water to an appropriate flask. Add 1.0 mL of trifluouroacetic acid and mix. Degas in-line during use.
Solvent B:	Add 1000 mL of acetonitrile to an appropriate flask. Add 1.0 mL of trifluouroacetic acid and mix. Degas in-line during use.

HPLC Parameters

Chromatographic Parameters

HPLC column:	Waters SunFire C18, 3.5 um 3 x 150 mm, Waters catalog no. 186002544.		
Temperature:	40 °C		
Flow rate:	0.5 mL/min. Flow rate may be adjusted ± 0.1 mL/min to obtain specified retention times.		
Gradient:	**Time, min**	**%-Solvent A**	**%-Solvent B**
	Initial	95	5
	5	70	30
	9	60	40
	17	0	100
	20	0	100
	20.1	95	5
	30	95	5
Injection volume:	4 µL		
Detection:	220 nm UV		
Data acquisition time:	20 min		
Run time:	30 min		

C. Preparation of Acetates of Formula III



5 6 7

((1R,2S)-2-(3-fluorophenyl)-2-(hydroxymethyl)cyclopropyl)methyl acetate (6). ((1S,2R)-1-

(3-fluorophenyl)cyclopropane-1,2-diyl)dimethanol (**5**, 7.89 g, 0.040 mol, 1.0 equiv.) was dissolved in 2-methyl-THF (23.68 mL), under nitrogen. Lipase acrylic resin (*Candida Antarctica* Lipase B, Sigma-Aldrich, Saint Louis, Missouri) (417.5 mg, 5.0 wt%) was added. Vinyl acetate (5.56 mL, 0.060 mol, 1.5 equiv.) was added, and the reaction mixture was stirred at 20-25 °C while monitoring the ratio of mono-acetate and diacetate (8-9 h) by HPLC and TLC (EtOAc/Heptane = 1/1). Upon reaction completion, the lipase was removed by filtration and rinsed with 2-methyl-THF (71.04 mL). The filtrate and the rinse were combined and washed with 15% NaCl aq. solution (27.63 mL) followed by sat. aqueous NaCl solution (23.68 mL). The solvent was removed under reduced pressure then azeotroped with 2-methyl-THF until KF is less than 1500 ppm to afford the title compound, ((1R,2S)-2-(3-fluorophenyl)-2-(hydroxymethyl)cyclopropyl)methyl acetate, **6** (9.59 g).

((1R,2S)-2-(3-fluorophenyl)-2-(hydroxymethyl)cyclopropyl)methyl acetate: ^{1}H NMR (500 MHz, CD_3OD) δ 7.28 (tt, J = 19.4, 9.7 Hz, 1H), 7.18 – 7.14 (m, 1H), 7.12 – 7.04 (m, 1H), 6.96 – 6.87 (m, 1H), 4.36 (dd, J = 11.9, 7.2 Hz, 1H), 4.25 (dd, J = 11.9, 8.3 Hz, 1H), 3.85 (d, J = 11.9 Hz, 1H), 3.77 (d, J = 11.9 Hz, 1H), 2.09 (s, 3H), 1.58 – 1.49 (m, 1H), 1.15 (dd, J = 8.8, 5.1 Hz, 1H), 0.95 – 0.90 (m, 1H); ^{13}C NMR (126 MHz, CD_3OD) δ 173.03, 164.10 (d, J_{CF} = 243.8 Hz), 148.31 (d, J_{CF} = 7.4 Hz), 130.86 (d, J_{CF} = 8.4 Hz), 125.78 (d, J_{CF} = 2.8 Hz), 116.90 (d, J_{CF} = 21.4 Hz), 114.16 (d, J_{CF} = 21.3 Hz), 66.46, 65.77, 33.39, 24.73, 20.92, 16.79.

HPLC method for monitoring process step B:

Equipment, Reagents, and Mobile Phase:

Equipment:

HPLC column:	Waters SunFire C18, 3.5 um 3 x 150 mm, Waters catalog no. 186002544.
Solvent Delivery System	Agilent 1100 HPLC quaternary pump, low pressure mixing, with an in-line degasser, or equivalent.
Autosampler:	Agilent 1100 autosampler, variable loop, 0.1 to 100 μL range, or equivalent.
Detector:	Agilent 1100 Diode Array Detector or equivalent.
Chromatographic Software:	Agilent ChemStation software version A.09.03 or higher for HPLC, Waters Empower 2 Build 2154, or equivalent.
Volumetric Glassware:	Class A.
Balance:	Analytical balance, capable of weighing ± 0.1 mg.

Reagents:

Water:	HPLC grade, (Baker cat no. 4218-03) or

	equivalent
Acetonitrile:	HPLC grade, (Baker cat no. 9017-03) or equivalent.
Trifluoroacetic acid (TFA):	Spectrophotometric grade, Aldrich (catalog no. 302131) or equivalent.

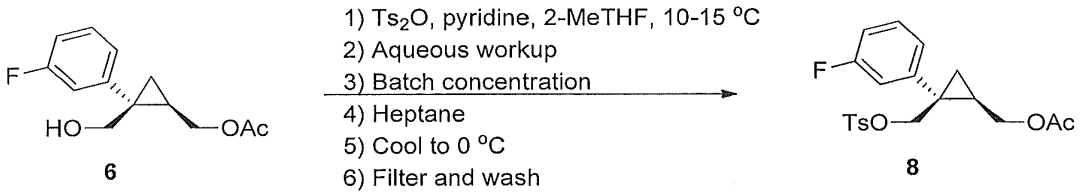
Mobile Phase:

Solvent A:	Add 1000 mL of water to an appropriate flask. Add 1.0 mL of trifluouroacetic acid and mix. Degas in-line during use.
Solvent B:	Add 1000 mL of acetonitrile to an appropriate flask. Add 1.0 mL of trifluouroacetic acid and mix. Degas in-line during use.

HPLC Parameters:

HPLC column:	Waters SunFire C18, 3.5 um 3 x 150 mm, Waters catalog no. 186002544.		
Temperature:	40 °C		
Flow rate:	0.5 mL/min. Flow rate may be adjusted ± 0.1 mL/min to obtain specified retention times.		
Gradient:	**Time, min**	**%-Solvent A**	**%-Solvent B**
	Initial	95	5
	5	70	30
	9	60	40
	17	0	100
	20	0	100
	20.1	95	5
	30	95	5
Injection volume:	4 µL		
Detection:	220 nm UV		
Data acquisition time:	20 min		
Run time:	30 min		

D. Preparation of Compounds of Formula IV



6 **8**

((1R,2S)-2-(3-fluorophenyl)-2-((tosyloxy)methyl)cyclopropyl)methyl acetate (8). ((1R,2S)-2-(3-fluorophenyl)-2-(hydroxymethyl)cyclopropyl)methyl acetate (**6**, 9.59 g, 0.040 mol, 1.0 equiv.) was dissolved in 2-methyl-THF (95.9 mL), under nitrogen. The solution was cooled to 10-15 °C,

and pyridine (11.4 mL, 0.141 mol, 3.5 equiv.) was added to the reaction mixture while maintaining the internal temperature below 15 °C. p-Toluenesulfonic acid anhydride (15.76 g, 0.048 mol, 1.2 equiv.) solid was added to the reaction mixture in portions while maintaining the internal temperature below 15 °C. The reaction was stirred at 10-15 °C for at least 1 hour while being monitored by HPLC and TLC (EtOAc/Heptane = 1/1). Upon completion of the reaction, the reaction mixture was quenched with water (38.4 mL) while maintaining the internal temperature below 25 °C. The organic layer was washed twice with 1 N HCl (38.0 mL each wash) to pH 1-2 (second aqueous wash), and then was washed with saturated aqueous $NaHCO_3$ solution (33.6 mL) to pH $\geq$ 7 followed by sat. aqueous NaCl solution (23.98 mL). The organic layer was separated and concentrated under reduced pressure to approximately 24.0 mL. n-Heptane (86.3 mL) was added slowly with agitation. The suspension was stirred for at least 30 min at 20-22 °C and then stirred for at least 1 h at 0-5 °C. The suspension was filtered and the cake was washed at least two times with n-heptane (14.4 mL used for each wash). The cake was dried under nitrogen and/or vacuum to provide the title compound ((1R,2S)-2-(3-fluorophenyl)-2-((tosyloxy)methyl)cyclopropyl)methyl acetate, (**8**, 11.05 g, 89.3% ee) as an off white to tan solid.

((1R,2S)-2-(3-fluorophenyl)-2-((tosyloxy)methyl)cyclopropyl)methyl acetate: ^{1}H NMR (500 MHz, CD_3OD) δ 7.55 (d, J = 8.3 Hz, 2H), 7.32 – 7.27 (m, 2H), 7.23 (td, J = 8.0, 6.1 Hz, 1H), 7.02 (dd, J = 7.7, 0.9 Hz, 1H), 6.95 – 6.90 (m, 1H), 6.90 – 6.84 (m, 1H), 4.36 (d, J = 10.9 Hz, 1H), 4.32 (dd, J = 12.1, 6.3 Hz, 1H), 4.17 (d, J = 10.9 Hz, 1H), 4.08 (dd, J = 12.1, 9.1 Hz, 1H), 2.42 (s, 3H), 2.09 (s, 3H), 1.68 (tt, J = 9.0, 6.3 Hz, 1H), 1.19 (dd, J = 8.9, 5.5 Hz, 1H), 1.00 (t, J = 5.8 Hz, 1H); ^{13}C NMR (126 MHz, CD_3OD) δ 171.38, 162.58 (d, J_{CF} = 244.6 Hz), 144.92, 144.51 (d, J_{CF} = 7.4 Hz), 132.52, 129.73 (d, J_{CF} = 8.5 Hz), 129.51, 127.36, 124.50 (d, J_{CF} = 2.9 Hz), 115.47 (d, J_{CF} = 21.8 Hz), 113.45 (d, J_{CF} = 21.3 Hz), 74.17, 63.50, 28.94, 23.49, 20.11, 19.49, 15.67.

HRMS Calculated for $C_{20}H_{21}FO_5SNa$ $[M+Na]^+$ 415.0991; found 415.0973.

HPLC method for monitoring process step D:

Mobile Phase:

Solvent A:	1000 mL of water and 1.0 mL of trifluoroacetic acid
Solvent B:	1000 mL of acetonitrile and 1.0 mL of trifluoroacetic acid

HPLC Parameters:

HPLC column:	Waters SunFire C18, 3.5 um 3 x 150 mm, Waters catalog no. 186002544.
Temperature:	40 °C

Flow rate:	0.5 mL/min. Flow rate may be adjusted ± 0.1 mL/min to obtain specified retention times.		
Gradient:	**Time, min**	**%-Solvent A**	**%-Solvent B**
	Initial	95	5
	5	70	30
	9	60	40
	17	0	100
	20	0	100
	20.1	95	5
	30	95	5
Injection volume:	2 μL		
Detection:	215 nm UV		
Data acquisition time:	20 min		
Run time:	30 min		

Chiral HPLC Assay for 8

TM-1257: Chiral HPLC Assay for 8

Equipment, Reagents, and Mobile Phase:

Equipment:

HPLC column:	AD-H 4.6 x 250 mm 5 μm, Chiral Tech catalog no. 19325.
Solvent Delivery System:	Agilent 1100 HPLC quaternary pump, low pressure mixing with an in-line degasser, or equivalent.
Autosampler:	Agilent 1100 autosampler, 0.1 to 100 μL range, or equivalent.
Detector:	Agilent 1100 Diode Array Detector or equivalent.
Chromatographic Software:	Agilent ChemStation software version A.09.03 or higher for HPLC, Waters Empower 2 Build 2154, or equivalent.
Volumetric Glassware:	Class A.
Volumetric pipette:	Class A.
Balance:	Analytical balance, capable of weighing ± 0.1 mg.

Reagents:

Hexanes:	HPLC grade, EMD (catalog no. HX0296-1) or equivalent.
2-Propanol:	HPLC grade, J.T.Baker (catalog no. 9095-03) or equivalent.

Mobile Phase:

Mobile phase A:
Using appropriate graduated cylinders, add 900 mL of hexanes and 100 mL of 2-propanol to an appropriate flask. Mix well and degas in line during use.

HPLC Parameters:

Chromatographic Parameters:

HPLC column:	AD-H, 250 x 4.6 mm, 5 μm, Chiral Tech Catalog no. 19325, or equivalent.
Temperature:	25 °C
Flow rate:	1.0 mL/min. Flow rate may be adjusted to obtain specified retention times.
Isocratic:	Solvent A
Injection volume:	5.0 μL
Detection:	UV detector 217 nm
Acquisition time:	20 min
Re-equilibration time:	Not Applicable
Total run time:	20 min

Calculations:

%-Enantiomeric Excess Calculation:

Calculate the %-enantiomeric excess (%-ee) for **8** using the appropriate peak areas obtained from each sample analysis and the following equation:

$$\%\,ee = \frac{(A_8 - A_9)(100\%)}{(A_8 + A_9)}$$

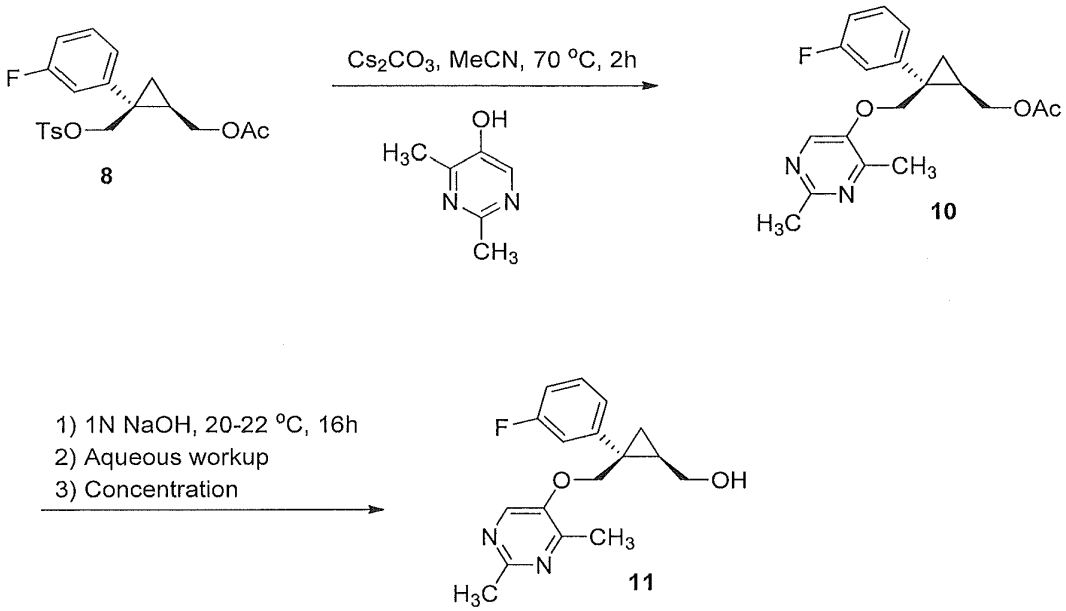
A_8 = Average peak area of 8 for each sample solution

A_9 = Average peak area of 9 for each sample solution

Note: Compound **9** is the enantiomer of compound **8**.

An enantiomeric excess was calculated at 89.3% for compound **8**.

E. Preparation of Compounds of Formula V



((1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)-cyclopropyl) methanol (11). ((1R,2S)-2-(3-fluorophenyl)-2-((tosyloxy)methyl)cyclopropyl)methyl acetate (**8**, 11.05 g, 0.028 mol, 1.0 equiv.), 2,4-dimethylpyrimidin-5-ol (3.74 g, 0.030 mol, 1.07 equiv.), and cesium carbonate (22.94 g, 1.8 equiv.) were dissolved in ACN (110.5 mL), under nitrogen. The solution was stirred vigorously and heated to 65-70 °C for 2-3 hours. The reaction was monitored by HPLC and TLC (EtOAc/Heptane = 1/1). Once complete, aqueous 1 N NaOH solution (71.82 mL) was added to the reaction mixture. The reaction mixture was stirred at 20-25 °C for 10-16 h, and was monitored by HPLC and TLC (EtOAc/Heptane = 1/1). Once the hydrolysis reaction was complete, the reaction mixture was diluted with MTBE (110.50 mL) and stirred for at least 15 min. The aqueous layer was back extracted once with MTBE (55.25 mL). The organic layers were combined and washed once with saturated aqueous NaCl solution (33.15 mL). The solvent was removed under reduced pressure to afford the title compound; ((1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)cyclopropyl)methanol: (**11**, 8.51 g).

((1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)-cyclopropyl)methanol: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.33 (td, J = 8.0, 6.5 Hz, 1H), 7.20 (d, J = 7.9 Hz, 1H), 7.19 – 7.14 (m, 1H), 7.01 (ddd, J = 8.3, 2.6, 1.2 Hz, 1H), 4.63 (t, J = 5.4 Hz, 1H), 4.36 (dd, J = 22.5, 10.5 Hz, 2H), 3.72 – 3.61 (m, 2H), 2.45 (s, 3H), 2.22 (s, 3H), 1.51 – 1.43 (m, 1H), 1.23 (dd, J = 8.9, 5.0 Hz, 1H), 1.01 (dd, J = 6.0, 5.3 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.48 (d, J_{CF} = 243.0 Hz), 158.91, 156.26, 149.51, 147.47 (d, J_{CF} = 7.5 Hz),

139.85, 130.35 (d, J_{CF} = 8.5 Hz), 124.72 (d, J_{CF} = 2.5 Hz), 115.54 (d, J_{CF} = 21.3 Hz), 113.43 (d, J_{CF} = 20.9 Hz), 72.73, 60.70, 29.23, 28.64, 24.94, 18.77, 17.06.

HRMS Calculated for $C_{17}H_{20}FN_2O_2$ $[M+H]^+$ 303.1590; found 303.1517.

HPLC method for monitoring process step E:

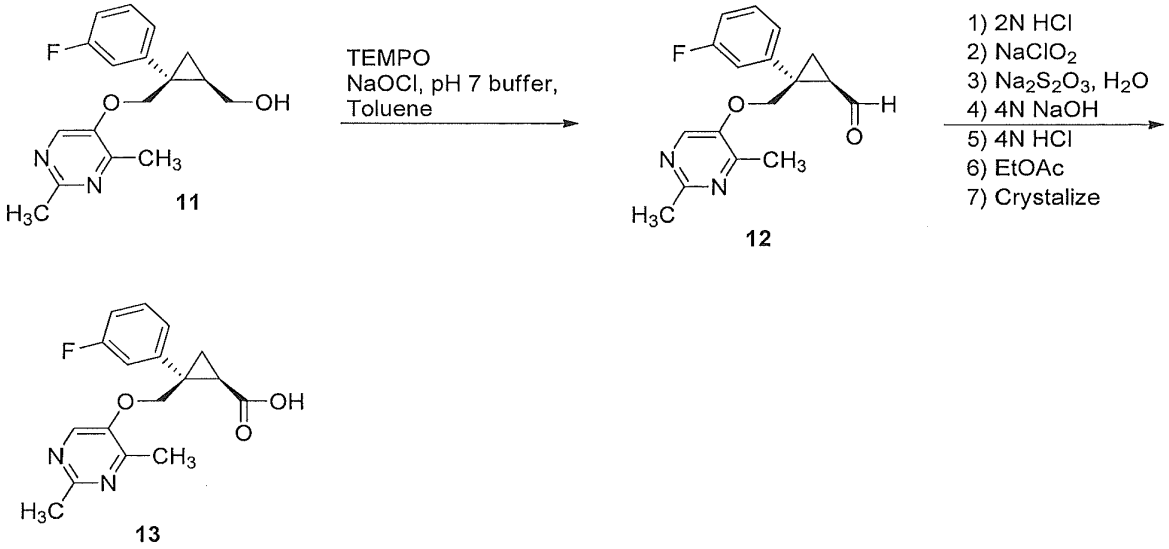
Sample preparation:

Combine reaction mixture (5 μL) with 1 mL acetonitrile, mix and inject.

Summary of chromatography conditions:

HPLC column:	Waters SunFire C18, 3.5 um 3 x 150 mm, Waters catalog no. 186002544.		
Temperature:	40 °C		
Flow rate:	0.5 mL/min. Flow rate may be adjusted ± 0.1 mL/min to obtain specified retention times.		
Mobile Phase A	1000 mL water and 1 mL trifluoroacetic acid		
Mobile Phase B	1000 mL acetonitrile and 1 mL trifluoroacetic acid		
Gradient:	**Time, min**	**%-Solvent A**	**%-Solvent B**
	Initial	95	5
	5	70	30
	9	60	40
	17	0	100
	20	0	100
	20.1	95	5
	30	95	5
Injection volume:	3 μL		
Detection:	215 nm UV		
Data acquisition time:	20 min		
Run time:	30 min		
18 Retention time:	3.0 min ± 10%		
11 Retention time:	10.2 min ± 10%		
10 Retention time:	13.5 min ± 10%		
8 Retention time:	17.2 min ± 10%		

F. Preparation of Compounds of Formula VII



(1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)cyclopropane-carboxylic acid (13). ((1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)cyclopropyl)methanol (**11**, 87.5 g, 290 mmol, 1.0 equiv.) was dissolved in toluene (390 mL). To the mixture was added pH 7 buffer (107 g, prepared from 4.46 g of sodium phosphate dibasic and 7.79 g of sodium phosphate monobasic in 94.4 mL of water) and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) (0.93 g, 5.9 mmol, 0.02 equiv.). The mixture was cooled to 0 °C and sodium hypochlorite solution (5% active chlorine, 383 mL, 304 mmol, 1.05 equiv.) was added dropwise, maintaining the internal temperature below 9 °C. The mixture was allowed to warm to room temperature and stirred for 2 h. To the mixture was added aqueous hydrochloric acid (2.0 M, 8.73 mL, 0.05 equiv.) followed by a solution of sodium chlorite (36.0 g, 318 mmol, 1.1 equiv.) in water (87 mL), maintaining the internal temperature below 26 °C. The mixture was stirred at room temperature for 4 h, and then cooled to 10 °C. A solution of sodium thiosulfate (92 g, 579 mmol, 2.0 equiv.) in water (177 mL) was added, maintaining the internal temperature below 20 °C. The mixture was stirred for 20 min, and then aqueous sodium hydroxide solution (4 N, 87 mL, 348 mmol, 1.2 equiv.) was added to achieve ca. pH = 13. The mixture was heated to 80 °C for 4 hours, then cooled to room temperature. Stirring was halted and the phases allowed to split. The lower aqueous phase was collected and the upper organic phase was washed once with 4 N sodium hydroxide solution (17 mL). The combined aqueous phases were acidified with aqueous hydrochloric acid solution (4 N, 17 mL) to pH = 4 and extracted with ethyl acetate

(2 x 470 mL). The combined organic phases were washed with ca. 20% aqueous NaCl solution (175 mL). The organic phases were concentrated by rotary evaporation to yield 96.84 g of crude oil. A portion (74 g) of this crude oil was dissolved in acetonitrile (400 mL) and concentrated to dryness by rotary evaporation. Another portion of acetonitrile (400 mL) was added and the mixture was again concentrated to dryness. To the residue was added acetonitrile (370 mL). The mixture was heated to 65 °C resulting in a clear solution. The mixture was cooled to room temperature, then to 0 °C and held at this temperature for 6 h. The mixture was filtered and the wet cake was washed with acetonitrile (2 x 74 mL). The cake was dried under vacuum with a nitrogen sweep, then in a vacuum oven at 20 torr and 40 °C to afford (1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)cyclopropanecarboxylic acid (**13**, 56.9 g, 80% yield) as an off-white crystalline solid.

(1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)-cyclopropanecarboxylic acid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.47 (s, 1H), 8.17 (s, 1H), 7.39 (td, J = 8.0, 6.4 Hz, 1H), 7.29 (d, J = 7.9 Hz, 1H), 7.27 – 7.22 (m, 1H), 7.10 (td, J = 8.3, 2.1 Hz, 1H), 4.63 (d, J = 10.2 Hz, 1H), 4.30 (d, J = 10.2 Hz, 1H), 2.46 (s, 3H), 2.26 (s, 3H), 2.13 (dd, J = 7.7, 6.6 Hz, 1H), 1.63 – 1.54 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.65, 162.48 (d, J_{CF} = 243.6 Hz), 159.08, 156.24, 149.45, 145.15 (d, J_{CF} = 7.5 Hz), 139.60, 130.71 (d, J_{CF} = 8.5 Hz), 124.79 (d, J_{CF} = 2.6 Hz), 115.60 (d, J_{CF} = 21.8 Hz), 114.32 (d, J_{CF} = 20.8 Hz), 71.15, 33.92 (d, J_{CF} = 2.0 Hz), 26.46, 24.96, 19.72, 18.70.

HRMS Calculated for $C_{17}H_{18}FN_2O_3$ $[M+H]^+$ 317.1301; found 317.1298.

Sample preparation:

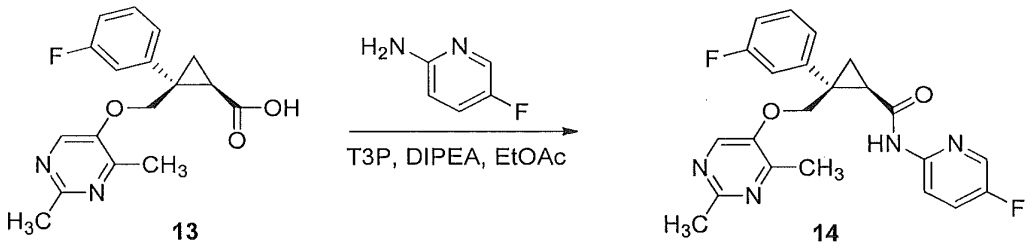
Transfer 10 μL of reaction mixture to an HPLC vial containing 1 mL diluting solution, and mix by vortexing. Transfer 100 μL of this solution to an HPLC vial containing 1 mL diluting solution, and mix by vortexing. This is the sample solution.

Summary of chromatography conditions:

HPLC column:	Waters SunFire C18, 3.5 um 3 x 150 mm, Waters catalog no. 186002544.
Temperature:	40 °C
Flow rate:	0.5 mL/min. Flow rate may be adjusted ± 0.1 mL/min to obtain specified retention times.
Mobile Phase A	1000 mL water and 1 mL trifluoroacetic acid
Mobile Phase B	1000 mL acetonitrile and 1 mL trifluoroacetic acid

Gradient:	**Time, min**	**%-Solvent A**	**%-Solvent B**
	Initial	95	5
	5	70	30
	9	60	40
	17	0	100
	20	0	100
	20.1	95	5
	30	95	5
Injection volume:	3 μL		
Detection:	220 nm UV		
Data acquisition time:	20 min		
Run time:	30 min		
11 Retention time:	10.2 min ± 10%		
12 Retention time:	11.7 min ± 10%		
13 Retention time:	10.6 min ± 10%		

G. Preparation of Compounds of Formula IX



(1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide (14). (1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)-cyclopropanecarboxylic acid (**13**, 12.80 g, 0.040 mol, 1.0 equiv.), and 2-amino-5-fluoropyridine (4.76 g, 0.0425 mol, 1.05 equiv.) were dissolved in ethyl acetate (102.4 mL), under nitrogen. The solution was cooled to 0-5 °C, and *N,N*-diisopropylethylamine (14.10 mL, 0.081 mol, 2.0 equiv.) was added to the reaction mixture while maintaining the internal temperature at 0-15 °C. The reaction mixture was stirred at 0-10 °C for 20-30 minutes. n-Propylphosphonic anhydride (T3P; 50% w/w solution in ethyl acetate, 36.1 g, 1.4 equiv.) was added to the reaction mixture while maintaining the internal temperature

at 0-15 °C. The reaction was stirred at 20-25 °C for at least 20-24 hour and monitored by HPLC and TLC (EtOAc/Heptane = 1/1). Upon completion of the reaction, the reaction mixture was cooled to 0-5 °C and then was quenched with water (64.0 mL) while maintaining the internal temperature below 10-15 °C. The aqueous layer was back extracted once with MTBE (76.8 mL). The organic layers were combined and washed once with saturated aqueous $NaHCO_3$ solution (38.4 mL) and once with water (38.4 mL). The organic layer was polish filtered and the filter rinsed with MTBE (12.8 mL). The organic layer was then concentrated under reduced pressure to a minimum stirrable volume. Ethyl acetate (60.8 mL) was added to the reaction mixture and the mixture was heated to no more than 50 °C to achieve a clear solution. n-Heptane (86.3 mL) was added slowly with agitation. The reaction mixture was cooled to 20-25 °C, and the suspension was stirred for at least 1 h at 20-25 °C and then stirred at least for 1 h at 0-5 °C. The suspension was filtered and the cake was washed two times with 5:1 heptane/ethyl acetate (2 x 12.8 mL). The cake was dried under nitrogen and/or vacuum to provide the title compound, (1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide, (**14**, 12.54 g, >99% ee) as a white to off white solid.

(1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.19 (s, 1H), 8.31 (d, J = 3.0 Hz, 1H), 8.12 (s, 1H), 7.94 – 7.85 (m, 1H), 7.62 (tt, J = 8.7, 3.1 Hz, 1H), 7.44 (dd, J = 10.6, 1.5 Hz, 1H), 7.41 – 7.40 (m, 1H), 7.39 (s, 1H), 7.14 – 7.06 (m, 1H), 4.67 (d, J = 10.2 Hz, 1H), 4.29 (t, J = 9.9 Hz, 1H), 2.63 (t, J = 7.0 Hz, 1H), 2.38 (s, 3H), 2.03 (s, 3H), 1.76 – 1.64 (m, 1H), 1.49 (dd, J = 8.0, 4.8 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.68, 161.98 (d, J_{CF} = 242.3 Hz), 158.46, 155.15, 155.38 (d, J_{CF} = 247.9 Hz), 148.90, 148.51, 145.00 (d, J_{CF} = 7.7 Hz), 139.37, 135.15 (d, J_{CF} = 24.9 Hz), 130.06 (d, J_{CF} = 8.4 Hz), 125.05 (d, J_{CF} = 19.5 Hz), 124.70 (d, J_{CF} = 2.6 Hz), 115.71 (d, J_{CF} = 21.7 Hz), 114.20 (d, J_{CF} = 4.1 Hz), 113.70 (d, J_{CF} = 20.9 Hz), 70.80, 34.09 (d, J_{CF} = 1.9 Hz), 26.90, 24.38, 18.37, 17.78.

HRMS Calculated for $C_{22}H_{21}F_2N_4O_2$ $[M+H]^+$ 411.1627; found 411.1632.

Sample preparation:

Transfer 500 µL of reaction mixture to an HPLC vial containing 500 µL acetonitrile, and mix by vortexing.

Summary of chromatography conditions:

HPLC column:	Waters SunFire C18, 3.5 um 3 x 150 mm, Waters catalog no. 186002544.		
Temperature:	40 °C		
Flow rate:	0.5 mL/min. Flow rate may be adjusted ± 0.1 mL/min to obtain specified retention times.		
Mobile Phase A	1000 mL water and 1 mL trifluoroacetic acid		
Mobile Phase B	1000 mL acetonitrile and 1 mL trifluoroacetic acid		
Gradient:	**Time, min**	**%-Solvent A**	**%-Solvent B**
	Initial	95	5
	5	70	30
	9	60	40
	17	0	100
	20	0	100
	20.1	95	5
	30	95	5
Injection volume:	2 µL		
Detection:	220 nm UV		
Data acquisition time:	20 min		
Run time:	30 min		
Retention times:	**13**	10.6 min ± 10%	
	14	13.2 min ± 10%	
	Ethyl acetate	7.5 min ± 10%	

Chiral HPLC Assay for (1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide (14)

TM-1186: Chiral HPLC Assay for Compound 14

Equipment, Reagents, and Mobile Phase:

Equipment:

HPLC column:	CHIRALPAK AD-H, 250 x 4.6 mm, 5 µm, Chiral Technologies catalog no. 19325, or equivalent.
Solvent Delivery System:	Agilent 1100 HPLC quaternary pump, low pressure mixing with an in-line degasser, or equivalent.
Autosampler:	Agilent 1100 autosampler, 0.1 to 100 µL range, or equivalent.
Detector:	Agilent 1100 variable wavelength detector or equivalent.
Chromatographic Software:	Agilent ChemStation software version A.09.03 or higher for HPLC, Waters Empower 2 Build 2154, or equivalent.

Volumetric Glassware:	Class A.
Volumetric pipette:	Class A.
Balance:	Analytical balance, capable of weighing ± 0.1 mg.

Reagents:

Heptane:	HPLC grade, EMD (catalog no. HX0078-1) or equivalent.
2-Propanol:	HPLC grade, EMD (catalog no. PX1838-1) or equivalent.

Mobile Phase:

Mobile phase A: Add 1000 mL of heptane to an appropriate flask. Mix well and degas in line during use.

Mobile phase B: Add 1000 mL of 2-propanol to an appropriate flask. Mix well and degas in line during use.

HPLC Parameters:

Chromatographic Parameters:

HPLC column:	CHIRALPAK AD-H, 250 x 4.6 mm, 5 μm, Chiral Technologies catalog no. 19325, or equivalent.
Temperature:	35 °C
Flow rate*:	1.0 mL/min. Flow rate may be adjusted to obtain specified retention times.
Gradient:	Isocratic, 80/20 (vol/vol) mobile phase A/mobile phase B
Injection volume:	5.0 μL
Detection:	UV detector 282 nm
Acquisition time:	15 min
Re-equilibration time:	N/A
Total run time:	15 min

Calculations:

%-Enantiomeric Excess Calculation:

Calculate the %-enantiomeric excess (%-ee) for **14** using the appropriate peak areas obtained from each sample analysis and the following equation:

$$\% \text{ ee} = \frac{(A_{14} - A_{15})(100\%)}{(A_{14} + A_{15})}$$

A_{14} = Average peak area of 14 for each sample solution

A_{15} = Average peak area of 15 for each sample solution

Note: The enantiomer of compound **14** is compound **15**.

An enantiomeric excess was calculated at >99% for compound **14**.

Alternate Procedure for Preparation of Compounds of Formula IX

(1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide (14).

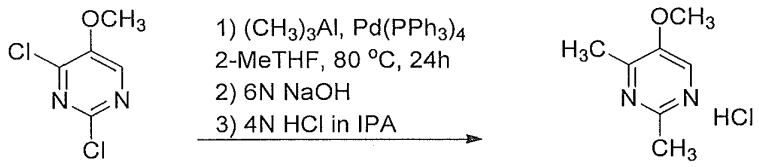
(1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)cyclopropane-carboxylic acid (**13**, 12.80 g, 0.040 mol, 1.0 equiv.), 2-amino-5-fluoropyridine (4.76 g, 0.0425 mol, 1.05 equiv.), and *N,N,N',N'*-tetramethyl-*O*-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (HATU; 16.16 g, 0.0425 mol, 1.05 equiv.) were dissolved in DMF (64.0 mL), under nitrogen. The solution was cooled to 0-5 °C, and *N,N*-diisopropylethylamine (14.10 mL, 0.081 mol, 2.0 equiv.) was added to the reaction mixture while maintaining the internal temperature below 10 °C. The reaction was stirred at 20-25 °C for at least 20-24 hour and monitored by HPLC and TLC (EtOAc/Heptane = 1/1). If (1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)cyclopropane-carboxylic acid was > 2%, additional *N,N,N',N'*-tetramethyl-*O*-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate was added (based on the conversion) at 20-25 °C, and then *N,N*-diisopropylethylamine (based on the conversion) was added to the reaction mixture while maintaining the internal temperature below 10 °C. If (1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)cyclopropane-carboxylic acid was ≤ 2%, but the conversion to the titled compound from the intermediate was < 97%, additional 2-amino-5-fluoropyridine (based on the conversion) was added to the reaction mixture at 20-25 °C. Upon completion of the reaction, the reaction mixture was diluted with MTBE (51.2 mL) and was cooled to 0-5 °C. It was quenched with water (64.0 mL) while maintaining the internal temperature below 10-15 °C. The reaction mixture was warmed up to

20-25 °C, and MTBE (76.8 mL) was added. The aqueous layer was back extracted once with MTBE (128.0 mL) and once with toluene (102.4 mL). The organic layers were combined and washed once with saturated aqueous $NaHCO_3$ solution (38.4 mL) and with 18% aq. NaCl solution (2 x 32.0 mL). The HATU by product in the organic layer was analyzed: if it was > 0.2%, additional 18% aq. NaCl solution washes were needed. The organic layer was polish filtered and the filter rinsed with MTBE (12.8 mL). It was then concentrated under reduced pressure to a minimum stirrable volume. The residual toluene in the residue was ≤ 10%. Ethyl acetate (60.8 mL) was added to the reaction mixture and the mixture was heated to no more than 50 °C to achieve a clear solution. The solution was cooled to 20-25 °C, and n-heptane (86.3 mL) was added slowly with agitation. The suspension was stirred for at least 30 min at 20-25 °C and then stirred at least for 1 h at 0-5 °C. The suspension was filtered and the cake was washed with 5:1 heptane/ethyl acetate (2 x 12.8 mL). The cake was dried under nitrogen and/or vacuum to provide the title compound, (1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide, (**14**, 11.65 g) as a white to off white solid.

(1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.19 (s, 1H), 8.31 (d, J = 3.0 Hz, 1H), 8.12 (s, 1H), 7.94 – 7.85 (m, 1H), 7.62 (tt, J = 8.7, 3.1 Hz, 1H), 7.44 (dd, J = 10.6, 1.5 Hz, 1H), 7.41 – 7.40 (m, 1H), 7.39 (s, 1H), 7.14 – 7.06 (m, 1H), 4.67 (d, J = 10.2 Hz, 1H), 4.29 (t, J = 9.9 Hz, 1H), 2.63 (t, J = 7.0 Hz, 1H), 2.38 (s, 3H), 2.03 (s, 3H), 1.76 – 1.64 (m, 1H), 1.49 (dd, J = 8.0, 4.8 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.68, 161.98 (d, J_{CF} = 242.3 Hz), 158.46, 155.15, 155.38 (d, J_{CF} = 247.9 Hz), 148.90, 148.51, 145.00 (d, J_{CF} = 7.7 Hz), 139.37, 135.15 (d, J_{CF} = 24.9 Hz), 130.06 (d, J_{CF} = 8.4 Hz), 125.05 (d, J_{CF} = 19.5 Hz), 124.70 (d, J_{CF} = 2.6 Hz), 115.71 (d, J_{CF} = 21.7 Hz), 114.20 (d, J_{CF} = 4.1 Hz), 113.70 (d, J_{CF} = 20.9 Hz), 70.80, 34.09 (d, J_{CF} = 1.9 Hz), 26.90, 24.38, 18.37, 17.78.

HRMS Calculated for $C_{22}H_{21}F_2N_4O_2$ $[M+H]^+$ 411.1627; found 411.1632.

H. Preparation of Compounds of Formula VI

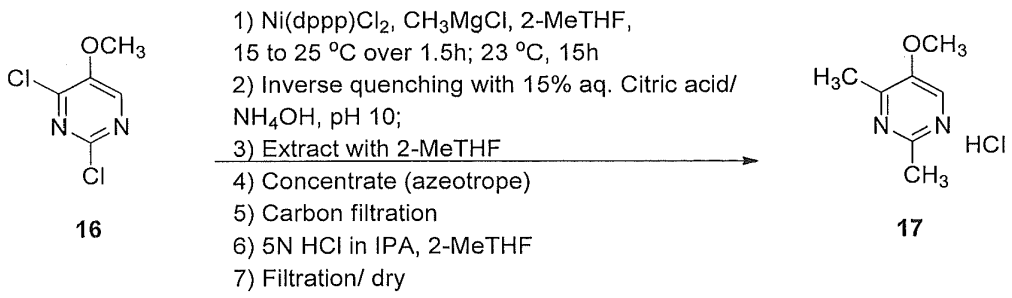


16 17

5-methoxy-2,6-dimethylpyrimidin-1-ium chloride (17). 2,4-Dichloro-5-methoxypyrimidine (**16**, 400 g, 2.23 mol, 1.0 equiv) was dissolved in 2-methyltetrahydrofuran (4.0 L). To this mixture was charged trimethylaluminum (2.0 M in heptane, 2200 mL, 2.0 equiv.), maintaining the internal temperature below 35 °C. Tetrakis(triphenylphosphine)palladium(0) (25.8 g, 0.022 mol, 0.01 equiv.) was added and the mixture was heated to 80 °C. The mixture was stirred for 24 h at 80 °C, cooled to room temperature and added slowly to a cold (5-10 °C) aqueous sodium hydroxide solution (6 N, 4.0 L), maintaining the internal temperature of the quench solution below 15 °C (Caution: methane gas evolution). The mixture was warmed to room temperature and allowed to stir for 30 min after which stirring was halted and the phases allowed to split. The phases were separated. The upper organic phase was filtered through a pre-packed charcoal column (200 g) with aid of additional 2-methyltetrahydrofuran (1.0 L). The solution was concentrated to 2/3 volume. The mixture was diluted with fresh 2-methyltetrahydrofuran (4.0 L) and then concentrated under vacuum until 4.0 L of distillate had been collected. To the remaining solution was slowly added a solution of hydrogen chloride in isopropyl alcohol (5 M, 670 mL, 3.35 mol, 1.5 equiv.) resulting in the precipitation of a crystalline solid. The slurry was stirred for 1 h, and filtered. The wet cake was washed with 2-methyltetrahydrofuran (800 mL) and then dried under vacuum with a nitrogen sweep to afford 5-methoxy-2,6-dimethylpyrimidin-1-ium chloride (**17**, 279 g, 70% yield) as a pale yellow solid.

5-methoxy-2,6-dimethylpyrimidin-1-ium chloride: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.60 (s, 1H), 3.97 (s, 3H), 2.68 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.14, 155.22, 150.35, 134.89, 57.02, 21.80, 18.46.

HRMS Calculated for $C_7H_{11}N_2O$ $[M+H]^+$ 139.0871; found 139.0874.

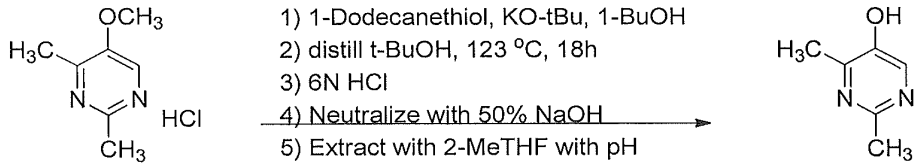


5-methoxy-2,6-dimethylpyrimidin-1-ium chloride (17). A three-neck round bottom flask, fitted with a mechanical stirrer, an additional funnel, a temperature probe and N_2 inlet was charged sequentially with 2-MeTHF (330 mL, 10.5 vol, water content: <300ppm), 2,4-dichloro-5-methoxy-pyrimidine (**16**, 30.0 g, 0.164 mol) (FWD Chem, Shanghai, China, or Amfinecom, Inc., St. Petersburg, VA), and $NiCl_2$(dppp) (1.4 g, 2.6 mmol, 1.6 mol%). The resulting mixture was degassed by evacuation with a reduced pressure followed by purging with nitrogen gas (3 times at room temperature). The resulting mixture was cooled to 15 °C and a solution of 3 M Methyl magnesium chloride in THF (125 mL, 2.25 equiv.) was added via a dropping funnel maintaining the internal temperature at 15-25 °C over a period of 1.5 h (Note: first 6 mL of MeMgCl was added slowly at 15–20 °C, and aged for 15 min to activate the catalyst). The dropping funnel was rinsed with 2-MeTHF (15 mL). After addition of the MeMgCl, the reaction was warmed to room temperature over 1 h with the aid of a cooling water-bath. The reaction was stirred for 13 h at room temperature with water-bath cooling (At this point, HPLC indicated the reaction was complete. Magnesium salt was precipitated as a golden yellow colored slurry). The resulting slurry was transferred into the pre-cooled (10 °C) 15% aqueous citric acid solution (300 mL) via cannula at such a rate to maintain the temperature below 30 °C, and the biphasic mixture was vigorously stirred for 15 min. The reaction flask was rinsed with 2-MeTHF (60 mL). After stirring for 15 min, ammonium hydroxide (28%, 150 mL) was added keeping the temperature below 30 °C (the pH of the aq. Layer: ~10). The biphasic mixture was stirred for an additional 15 min. At this point, sodium chloride (83 g) was added and allowed to dissolve (~20 min). After phase separation, the aqueous layer was back-extracted with 2-MeTHF (300 mL). After a phase-cut, the organic layers were combined, concentrated and azeotropically dried (below 40 °C) by 2-MeTHF flush (300 mL). The precipitated inorganic salt was filtered through an in-line CUNO-filter, and rinsed with 120 mL of 2-MeTHF. The rinse was combined with the initial filtrate.

Salt formation and Isolation: The crude pyrimidine in 2-MeTHF (total volume 270 mL) was treated with 5 N HCl in 2-isopropanol (33 mL, 0.165 mol) at 10 °C. The slurry was cooled to -10 ~ -15 °C over 30 min, and aged for an additional 30 min at this temperature. The resulting slurry was filtered, and rinsed with pre-cooled 2-MeTHF (45 mL, -15 °C). The wet cake was dried under vacuum with a nitrogen sweep overnight to give 22.2 g (77.4%) of 2,4-dimethyl-5-methoxy-pyrimidine HCl salt, **17**, as a yellow to orange colored crystalline solid.

5-methoxy-2,6-dimethylpyrimidin-1-ium chloride: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.60 (s, 1H), 3.97 (s, 3H), 2.68 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.14, 155.22, 150.35, 134.89, 57.02, 21.80, 18.46.

HRMS Calculated for $C_7H_{11}N_2O$ $[M+H]^+$ 139.0871; found 139.0874.

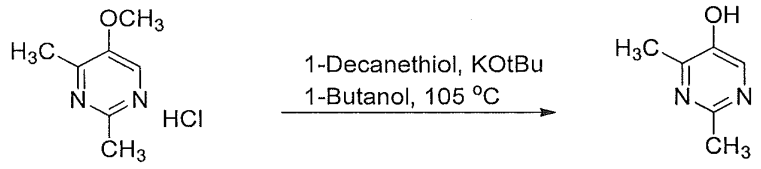


2,4-Dimethylpyrimidin-5-ol (18). 1-Butanol (158 mL) was added into the reaction flask which was fitted with a mechanical stirrer, a temperature probe, nitrogen inlet, and distillation equipment. The solvent was cooled to 10-15 °C and potassium *t*-butoxide (33.7 g, 0.3 mol) was charged in 3 portions maintaining an internal temperature less than 40 °C. 1-Dodecanethiol (43.2 mL, 0.18 mol) was added to the resulting suspension, and was agitated at 20-25 °C for 30 min. 1-Dodecanethiol (43.2 mL, 0.18 mol) was added to the suspension and the mixture was stirred at room temperature for an additional 30 min. Next, 5-methoxy-2,6-dimethylpyrimidin-1-ium chloride, **17**, (21 g, 0.12 mol) was added in 3 portions with efficient agitation, and the inlet was rinsed with 1-butanol (10 mL). The reaction flask was degassed with vacuum and purged with nitrogen (3X) and then maintained under a nitrogen atmosphere. The reaction mixture was heated to 117~120 °C, and volitile tert-butanol (~30 mL) was collected. Then, the reaction was aged at reflux temperature (120-125 °C) for 20 h (conversion was 99.5%). The reaction mixture was cooled to 10-15 °C, and 6 N HCl (90 mL) charged at 10-15 °C. Deionized water was added (63 mL), and the reaction was aged for 20 min at room temperature. Heptane (126 mL) was

added, agitated for 15 min, and allowed to split for 15 min. The product containing lower aqueous layer was drained to a suitable vessel. The upper organic layer was extracted with a combined solution of water (84 mL), 6 N HCl (21 mL) and MeOH (42 mL). The organic layer was back-extracted with water (42 mL). The aqueous layers were combined, and cooled to 10-15 °C. The pH of the aqueous layer was adjusted to 6.8-7.2 with 50% sodium hydroxide (26 mL). Sodium chloride (37.8 g) was added, and the reaction was agitated for 30 min. 2-MeTHF (140 mL) was charged, agitated for 15 min, and allowed to split. The aqueous layer was back-extracted twice with 2-MeTHF (140 mL) with pH adjustment of the aqueous layer after each extraction (0.5 mL of 6 N HCl, desired pH in aqueous layer is 6.8 ~ 7.2). Note: The pH of the aqueous layer went up slightly after each extraction, and it should be adjusted accordingly (with 0.25 mL of 6 N HCl). The organic layers were combined and concentrated at reduced pressure to a minimum stirrable volume maintaining the internal temperature below 40 °C. The concentrated solution was dried azeotropically with 2-MeTHF (3 x 65 mL), and then 2-MeTHF was charged to adjust the final solvent volume to 100 mL (any product on the wall of the reactor should be dissolved). Insoluble inorganic material was filtered off using a sintered glass funnel. The reactor and filter pot were rinsed with 2-MeTHF (40 mL). The filtrate was concentrated under a reduced pressure maintianing the internal temperature below 40 °C to ca. 60 mL of total batch volume. The reaction was next chased with heptane (4 x 80 mL) and the final batch volume was adjusted to a total volume of 65 mL. Then, the slurry mixture was cooled to 0-5 °C over 30 min, and aged for 1h at this temperature. The resulting slurry was filtered, and the wet cake was rinsed with pre-cooled (0-5 °C) heptane (63 mL). The wet cake was dried under vacuum with a nitrogen flush at room temperature for 24 h to afford 11.6 g of 2,4-dimethylpyrimidin-5-ol, (**18**, 78~ 85% yield).

2,4-Dimethylpyrimidin-5-ol: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.05 (s, 1H), 2.43 (s, 1H), 2.28 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.24, 153.71, 147.60, 141.80, 24.39, 18.33.

HRMS Calculated for $C_6H_9N_2O$ $[M+H]^+$ 125.0715; found 125.0720.



17 18

Alternate Preparation of 2,4-Dimethylpyrimidin-5-ol (18). To a 22-Liter round bottomed flask was charged potassium tert-butoxide (1200 g, 11 mol, 3.5 equiv.) and 1–butanol (2700 mL). The mixture was stirred for 40 mins and then 1-decanethiol (1300 mL, 6.1 mol, 2.0 equiv.) was added. To the resulting slurry was added portionwise, 5-methoxy-2,6-dimethylpyrimidin-1-ium chloride (**17**, 532 g, 3.05 mol, 1.0 equiv.), using a minimal amount of 1-butanol for rinses as needed. The mixture was heated to 105-110 °C and stirred for 24 hours at this temperature. The mixture was cooled to room temperature and aqueous hydrochloric acid solution (6 N, 2000 mL) was added slowly, maintaining the internal temperature below 35 °C. Heptane (2700 mL) was added and the mixture stirred for 10 mins. Stirring was halted and the phases were separated. The upper organic phase was backwashed with additional 6 N HCl solution (1000 mL). The aqueous phases were combined and neutralized by addition of aqueous sodium hydroxide solution (50% w/w, 789 mL) to pH = 7-8, then extracted with 2-methyltetrahydrofuran (2 x 3000 mL). The 2-methyltetrahydrofuran was removed by vacuum distillation and replaced with heptane (3000 mL). The mixture was concentrated to near dryness and heptane (1300 mL was added). The resulting slurry was filtered and the wet cake was washed with heptane (3 x 400 mL). The cake was dried under vacuum with a nitrogen sweep to afford 2,4-dimethylpyrimidin-5-ol (**18**, 281 g, 74% yield) as an off-white solid.

2,4-Dimethylpyrimidin-5-ol: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.05 (s, 1H), 2.43 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.24, 153.71, 147.60, 141.80, 24.39, 18.33.

HRMS Calculated for $C_6H_9N_2O$ $[M+H]^+$ 125.0715; found 125.0720.

That which is claimed is:

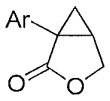
1. A process for making a compound of **Formula I**,

I

wherein Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl,

comprising the steps of :

i) providing a composition comprising a compound of **Formula II**:



II

wherein Ar is as given above, and an organic solvent, wherein said composition is at a temperature of from -30 to 40 °C; and

ii) adding to said composition a hydride reducing agent, wherein said agent reduces said compound of **Formula II** into said compound of **Formula I**,

to thereby make said compound of **Formula I**.

2. The process of claim 1, wherein Ar is unsubstituted or substituted 1 – 3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

3. The process of claim 1 or claim 2, wherein said composition is provided at a temperature of from -30 to 30 °C.

4. The process of claim 1 or claim 2, wherein said composition is provided at a temperature of from -30 to 10 °C.

5. The process of claim 1 or claim 2, wherein said composition is provided at a temperature of from -10 to 0 °C.

6. The process of claim 1 or claim 2, wherein said composition is provided at a temperature of from -10 to -5 °C.

7. The process of any of claims 1-6, wherein the organic solvent is an aromatic hydrocarbon solvent, an aliphatic hydrocarbon solvent, a halogenated hydrocarbon solvent or an ether solvent.

8. The process of any of claims 1-6, wherein the organic solvent is tetrahydrofuran or toluene.

9. The process of any of claims 1-6, wherein the organic solvent is a mixture of tetrahydrofuran and 2-methyltetrahydrofuran.

10. The process of any of claims 1-9, wherein the hydride reducing agent is selected from the group consisting of: sodium borohydride, lithium borohydride, lithium aluminum hydride, lithium tributoxy aluminum hydride, diisobutylaluminum hydride, zinc borohydride, and lithium triethyl borohydride.

11. The process of any of claims 1-9, wherein the hydride reducing agent is lithium borohydride or lithium triethyl borohydride.

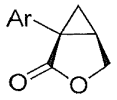
12. The process of any of claims 1-11, further comprising the step of mixing the composition after said adding step for a time of 12 to 24 hours.

13. The process of claim 11, further comprising the step of quenching the reduction by adding to said composition a mild aqueous acid.

14. The process of claim 13, wherein said mild aqueous acid is citric acid, EDTA or tartaric acid.

15. The process of claim 13, wherein said mild aqueous acid is citric acid.

16. The process of any of claims 1-15, wherein the compound of **Formula II** has the absolute stereochemistry of **Formula IIa**:



IIa

17. The process of claim 16, wherein the compound has an enantiomeric excess (ee) of the **Formula IIa** stereoisomer of at least 80%.

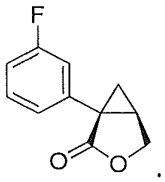
18. The process of claim 16, wherein the compound has an enantiomeric excess (ee) of the **Formula IIa** stereoisomer of at least 85%.

19. The process of claim 16, wherein the compound has an enantiomeric excess (ee) of the **Formula IIa** stereoisomer of at least 90%.

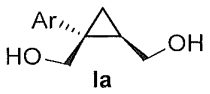
20. The process of claim 16, wherein the compound has an enantiomeric excess (ee) of the **Formula IIa** stereoisomer of at least 95%.

21. The process of claim 16, wherein the compound has an enantiomeric excess (ee) of the **Formula IIa** stereoisomer of at least 98%.

22. The process of any of claims 1-16, wherein the compound of **Formula II** is the compound:



23. The process of any of claims 1-22, wherein the compound of **Formula I** has the absolute stereochemistry of **Formula Ia**:



Ia

24. The process of claim 23, wherein the compound has an enantiomeric excess (ee) of the **Formula Ia** stereoisomer of at least 80%.

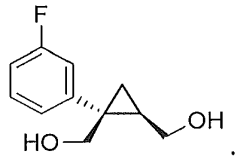
25. The process of claim 23, wherein the compound has an enantiomeric excess (ee) of the **Formula Ia** stereoisomer of at least 85%.

26. The process of claim 23, wherein the compound has an enantiomeric excess (ee) of the **Formula Ia** stereoisomer of at least 90%.

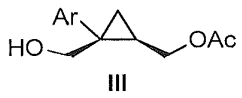
27. The process of claim 23, wherein the compound has an enantiomeric excess (ee) of the **Formula Ia** stereoisomer of at least 95%.

28. The process of claim 23, wherein the compound has an enantiomeric excess (ee) of the **Formula Ia** stereoisomer of at least 98%.

29. The process of any of claims 1-28, wherein the compound of **Formula I** is:



30. A compound of **Formula III**:

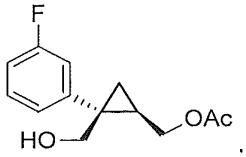


III

wherein Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with substituents independently chosen from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl.

31. The compound of claim 30, wherein Ar is unsubstituted or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

32. The compound of claim 30, wherein said compound is:



33. A process for making a compound of **Formula III**:

III

wherein Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl,

comprising reacting a mixture of:

i) a compound of **Formula Ia:**

Ia

wherein Ar is as given above,

ii) vinyl acetate,

iii) a lipase, and

iv) an organic solvent

for a time of from 5 to 36 hours,

to thereby make the compound of **Formula III**.

34. The process of claim 33, wherein Ar is unsubstituted or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

35. The process of claim 33 or claim 34, wherein the organic solvent is tetrahydrofuran, 2-methyltetrahydrofuran, an ether solvent, acetone, or acetonitrile.

36. The process of any of claims 33-35, wherein the reacting step is carried out for a time of from 7 to 18 hours.

37. The process of any of claims 33-36, wherein said lipase is a *Candida Antarctica* lipase.

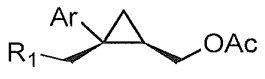
38. The process of any of claims 33-36, wherein said lipase is a *Candida Antarctica* B lipase coupled to an acrylic resin.

39. The process of any of claims 33-38, further comprising the step of filtering the mixture after said reacting to produce a filtrate, and concentrating the filtrate to produce a concentrated filtrate.

40. The process of claim 39, further comprising the step of washing the concentrated filtrate with water or water comprising a salt.

41. The process of claim 39, further comprising the step of washing the concentrated filtrate with a solution of 15-20% NaCl in water.

42. A compound of **Formula IV**:



IV

wherein:

Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl; and

R_1 is a leaving group.

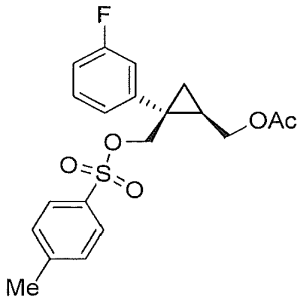
43. The compound of claim 42, wherein Ar is unsubstituted or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

44. The compound of claim 42 or claim 43, wherein the leaving group is a sulfonate ester leaving group selected from the group consisting of: mesylate, tosylate, nosylate, benzene sulfonate, and brosylate.

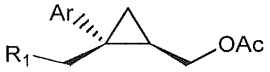
45. The compound of claim 42 or claim 43, wherein the leaving group is mesylate.

46. The compound of claim 42 or claim 43, wherein the leaving group is tosylate.

47. The compound of claim 42, wherein said compound is:



48. The compound of any of claims 42-47, wherein the compound of **Formula IV** has the absolute stereochemistry of **Formula IVa**:



IVa

49. The compound of claim 48, wherein the compound has an enantiomeric excess (ee) of the **Formula IVa** stereoisomer of at least 80%.

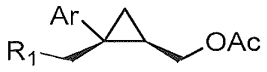
50. The compound of claim 48, wherein the compound has an enantiomeric excess (ee) of the **Formula IVa** stereoisomer of at least 85%.

51. The compound of claim 48, wherein the compound has an enantiomeric excess (ee) of the **Formula IVa** stereoisomer of at least 90%.

52. The compound of claim 48, wherein the compound has an enantiomeric excess (ee) of the **Formula IVa** stereoisomer of at least 95%.

53. The compound of claim 48, wherein the compound has an enantiomeric excess (ee) of the **Formula IVa** stereoisomer of at least 98%.

54. A process for making a compound of **Formula IV**:



IV

wherein Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl; and

R_1 is a sulfonate ester leaving group,

said process comprising reacting a compound of **Formula III**:

III

wherein Ar is as given above,

with a compound selected from the group consisting of: tosyl chloride, mesyl chloride, nosyl chloride, toluenesulfonyl chloride, toluenesulfonic anhydride and methanesulfonic anhydride, wherein said reacting is carried out in an organic solvent in the presence of a base,

to thereby make said compound of **Formula IV**.

55. The process of claim 54, wherein Ar is unsubstituted or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

56. The process of claim 54 or claim 55, where said reacting is carried out for a time of from 10 minutes to 2 hours.

57. The process of any of claims 54-56 wherein the base is an organic amine or potassium carbonate.

58. The process of any of claims 54-56, wherein the base is an organic amine selected from the group consisting of: triethylamine, diisopropylethylamine, and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene).

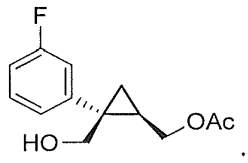
59. The process of any of claims 54-56, wherein the base is pyridine.

60. The process of any of claims 54-59, wherein the organic solvent is selected from the group consisting of: dichloromethane, tetrahydrofuran, 2-methyltetrahydrofuran, toluene, acetonitrile, and ethyl acetate.

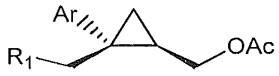
61. The process of any of claims 54-59, wherein the organic solvent is dichloromethane.

62. The process of any of claims 54-59, wherein the organic solvent is 2-methyltetrahydrofuran.

63. The process of any of claims 54-62, wherein said compound of **Formula III** is:



64. The process of any of claims 54-63, wherein the compound of **Formula IV** has the absolute stereochemistry of **Formula IVa**:



IVa

65. The process of claim 64, wherein the compound has an enantiomeric excess (ee) of the **Formula IVa** stereoisomer of at least 80%.

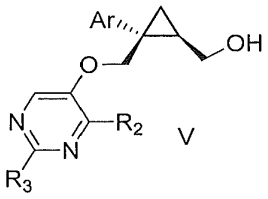
66. The process of claim 64, wherein the compound has an enantiomeric excess (ee) of the **Formula IVa** stereoisomer of at least 85%.

67. The process of claim 64, wherein the compound has an enantiomeric excess (ee) of the **Formula IVa** stereoisomer of at least 90%.

68. The process of claim 64, wherein the compound has an enantiomeric excess (ee) of the **Formula IVa** stereoisomer of at least 95%.

69. The process of claim 64, wherein the compound has an enantiomeric excess (ee) of the **Formula IVa** stereoisomer of at least 98%.

70. A process for making a compound of **Formula V**,



V

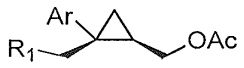
wherein Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl; and

R_2 and R_3 are each independently selected from the group consisting of: hydrogen, C_{1-6}alkyl, haloC_{1-6} alkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl,

comprising the steps of:

a) stirring a mixture of:

i) a compound of **Formula IV**:

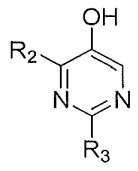


IV

wherein Ar is as given above; and

R_1 is a leaving group,

ii) a substituted pyrimidine of **Formula VI**:



VI ,

wherein R_2 and R_3 are as given above;

iii) a base; and

iv) an organic solvent,

at a temperature of from 65-70 °C, for 1 to 12 hours; and then

b) reacting the mixture with an aqueous base for a time of from 2 to 20 hours,

to thereby make said compound of **Formula V**.

71. The process of claim 70, wherein Ar is unsubstituted or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

72. The process of claim 70 or claim 71, wherein R_2 and R_3 are each independently selected from the group consisting of: hydrogen and C_{1-6}alkyl.

73. The process of any of claims 70-72, wherein the base of step a) is cesium carbonate or DBU (1,8-diazabicyclo[5.4.0]undec-7-ene).

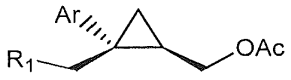
74. The process of any of claims 70-73, wherein the aqueous base of step b) is an aqueous hydroxide or carbonate.

75. The process of any of claims 70-73, wherein the aqueous base of step b) is aqueous sodium hydroxide.

76. The process of any of claims 70-73, wherein the aqueous base of step b) is aqueous potassium hydroxide.

77. The process of any of claims 70-76, wherein the organic solvent is selected from the group consisting of: acetonitrile, acetone, ethyl acetate and tetrahydrofuran.

78. The process of any of claims 70-77, wherein the compound of **Formula IV** has the absolute stereochemistry of **Formula IVa**:



IVa

79. The process of claim 78, wherein the compound has an enantiomeric excess (ee) of the **Formula IVa** stereoisomer of at least 80%.

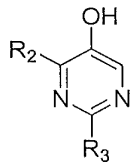
80. The process of claim 78, wherein the compound has an enantiomeric excess (ee) of the **Formula IVa** stereoisomer of at least 85%.

81. The process of claim 78, wherein the compound has an enantiomeric excess (ee) of the **Formula IVa** stereoisomer of at least 90%.

82. The process of claim 78, wherein the compound has an enantiomeric excess (ee) of the **Formula IVa** stereoisomer of at least 95%.

83. The process of claim 78, wherein the compound has an enantiomeric excess (ee) of the **Formula IVa** stereoisomer of at least 98%.

84. A process for making a compound of **Formula VI**:

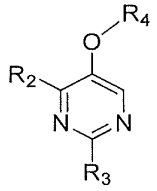


VI

wherein R_2 and R_3 are each independently selected from the group consisting of: hydrogen and C_{1-6} alkyl,

comprising the step of heating a mixture of:

i) a compound of **Formula B**:



B

wherein:

R_2 and R_3 are as given above; and

R_4 is C_{1-6} alkyl,

ii) an alkoxide or hydroxide salt,

iii) a thiol, and

iv) an organic solvent,

to thereby make said compound of **Formula VI**.

85. The process of claim 84, wherein said heating is to a temperature of from 50 to 140 °C.

86. The process of claim 84, wherein said heating comprises boiling said mixture.

87. The process of claim 84, wherein said heating comprises refluxing said mixture.

88. The process of any of claims 84-87, wherein said heating is carried out in a time of from 5 to 50 hours.

89. The process of any of claims 84-88, wherein said alkoxide salt is an ethoxide, *t*-butoxide, 3-methyl-3-pentoxide, or 7-amyloxide salt.

90. The process of any of claims 84-88, wherein said alkoxide salt is a *t*-butoxide salt.

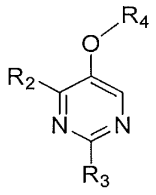
91. The process of any of claims 84-88, wherein said alkoxide is potassium *t*-butoxide.

92. The process of any of claims 84-91, wherein said thiol is 1-decanethiol or 1-dodecanethiol.

93. The process of any of claims 84-92, wherein said organic solvent is, *N,N*-Dimethylformamide, *N,N*-Dimethylacetamide, *N*-Methylpyrrolidone, 1-butanol, 2-butanol, *tert*-butanol, *iso*-butanol.

94. The process of any of claims 84-92, wherein said organic solvent is 1-butanol.

95. A process for making a compound of **Formula B**:



B

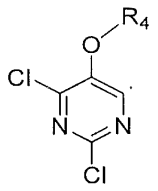
wherein:

R_2 and R_3 are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl; and

R_4 is C_{1-6} alkyl,

comprising mixing:

i) a compound of **Formula A**:



A

wherein R_4 is as given above,

ii) trimethylaluminum,

iii) a palladium catalyst, and

iv) an organic solvent,

to thereby make said compound of **Formula B**.

96. The process of claim 95, wherein said palladium catalyst is tetrakis-(triphenylphosphine)palladium(0).

97. The process of claim 95 or claim 96, wherein said organic solvent is tetrahydrofuran or 2-methyltetrahydrofuran.

98. The process of any of claims 95-97, wherein said mixing step is carried out for a time of from 12 to 48 hours.

99. The process of any of claims 95-98, wherein said mixing step is carried out at a temperature of from 20 to 110 °C.

100. The process of any of claims 95-99, further comprising the step of quenching the reaction with water comprising a base.

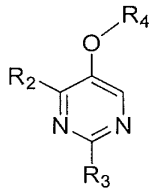
101. The process of claim 100, wherein said base is sodium hydroxide.

102. The process of any of claims 95-101, further comprising the step of treating said compound of **Formula B** with a solution comprising hydrogen chloride and an alcohol to obtain said compound of **Formula B** as a hydrochloride salt.

103. The process of claim 102, wherein said alcohol is selected from the group consisting of methanol, ethanol, n-propanol, isopropyl alcohol, n-butanol, amyl alcohol, ethylene glycol, propylene glycol, butyl carbitol acetate, glycerin and a combination thereof.

104. The process of claim 102, wherein said alcohol is isopropyl alcohol.

105. A process for making a compound of **Formula B**:



B

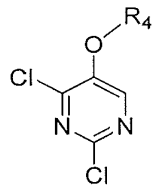
wherein:

R_2 and R_3 are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl; and

R_4 is C_{1-6} alkyl;

comprising mixing:

i) a compound of **Formula A**:



A

wherein R_4 is as given above,

ii) a nickel catalyst,

iii) an alkylmagnesium halide, and

iv) an organic solvent,

to thereby make said compound of **Formula B**.

106. The process of claim 105, wherein said nickel catalyst is selected from the group consisting of: $Ni(acac)_2$, $Ni(PPh_3)_2Cl_2$, or $Ni(dppp)Cl_2$.

107. The process of claim 105, wherein said nickel catalyst is $Ni(dppp)Cl_2$.

108. The process of any of claims 105-107, wherein said alkylmagnesium halide is methyl magnesium chloride.

109. The process of any of claims 105-108, wherein said organic solvent is tetrahydrofuran or 2-methyltetrahydrofuran.

110. The process of any of claims 105-109, wherein said mixing is carried out for a time of from 6 to 36 hours.

111. The process of any of claims 105-110, wherein said mixing is carried out at a temperature of from 10 to 30 °C.

112. The process of any of claims 105-111, further comprising the step of quenching the reaction with water comprising an acid.

113. The process of claim 112, wherein said acid is citric acid.

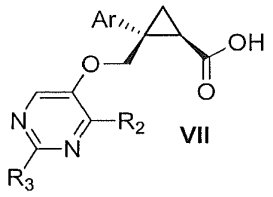
114. The process of claim 112 or claim 113, further comprising the step of adding ammonium hydroxide after said quenching step.

115. The process of any of claims 105-114, wherein said process further comprises reacting the compound of **Formula B** with a solution comprising hydrogen chloride and an alcohol to obtain said compound of **Formula B** as a hydrochloride salt.

116. The process of claim 115, wherein said alcohol is selected from the group consisting of methanol, ethanol, n-propanol, isopropyl alcohol, n-butanol, amyl alcohol, ethylene glycol, propylene glycol, butyl carbitol acetate, glycerin and a combination thereof.

117. The process of claim 115, wherein said alcohol is isopropyl alcohol.

118. A process for making a compound of **Formula VII**:



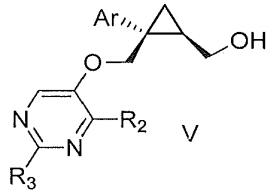
VII

wherein Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl; and

R_2 and R_3 are each independently selected from the group consisting of: hydrogen, C_{1-6}alkyl, haloC_{1-6} alkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl,

comprising the steps of :

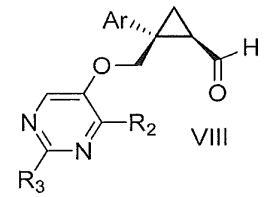
a) oxidizing a compound of **Formula V**:



V

wherein Ar, R_2 and R_3 are as given above,

with a first oxidizing agent, to form an aldehyde of Formula **VIII**:



VIII

wherein Ar, R_2 and R_3 are as given above; and then

b) oxidizing the aldehyde of **Formula VIII** with a second oxidizing agent, to thereby make said compound of **Formula VII**.

119. The process of claim 118, wherein Ar is unsubstituted or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

120. The process of claim 118 or claim 119, wherein R_2 and R_3 are each independently selected from the group consisting of: hydrogen and C_{1-6}alkyl.

121. The process of any of claims 118-120, wherein the first oxidizing agent is sodium hypochlorite.

122. The process of claim 121, wherein said oxidizing of step a) is catalyzed with an effective amount of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO).

123. The process of any of claims 118-122, wherein the second oxidizing agent is sodium chlorite.

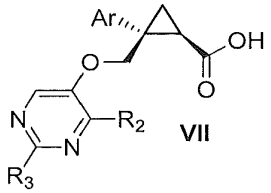
124. The process of any of claims 118-122, wherein the first oxidizing agent and the second oxidizing agent are the same.

125. The process of any of claims 118-122, wherein the first oxidizing agent and the second oxidizing agent are different.

126. The process of any of claims 118-125, wherein said oxidizing of step a) and/or step b) is carried out in an organic solvent selected from the group consisting of dichloromethane, tetrahydrofuran, 2-methyltetrahydrofuran, toluene, acetonitrile, and ethyl acetate.

127. The process of claim 126, wherein said organic solvent is toluene.

128. A process for preparing a compound of **Formula VII**,

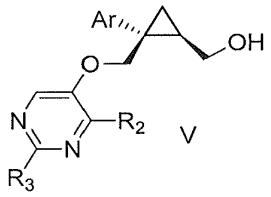


VII

wherein Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl; and

R_2 and R_3 are each independently selected from the group consisting of: hydrogen, C_{1-6}alkyl, haloC_{1-6} alkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl,

comprising: oxidizing a compound of **Formula V**:



V

wherein Ar, R_2 and R_3 are as given above,

with sodium hypochlorite and sodium chlorite,

to thereby make said compound of **Formula VII**.

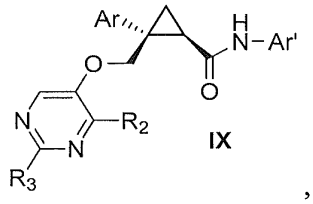
129. The process of claim 128, wherein Ar is unsubstituted or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

130. The process of claim 128 or claim 129, wherein R_2 and R_3 are each independently selected from the group consisting of: hydrogen and C_{1-6}alkyl.

131. The process of any of claims 128-130, wherein said oxidizing with sodium hypochlorite and sodium chlorite is carried out simultaneously.

132. The process of any of claims 128-131, wherein said oxidizing is catalyzed with an effective amount of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO).

133. A process for making a compound of **Formula IX**:



IX

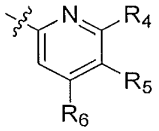
,

wherein:

Ar is phenyl, which phenyl may be unsubstituted, or substituted 1-3 times with substituents independently selected from the group consisting of: halo, C_{1-6}alkyl, C_{1-6}alkoxy, and haloC_{1-6}alkyl;

R_2 and R_3 are each independently selected from the group consisting of: hydrogen, C_{1-6}alkyl, haloC_{1-6} alkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; and

Ar' is a pyridine group:



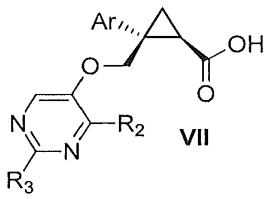
wherein:

R_4 is selected from the group consisting of: hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkoxy, and (C_{1-6}alkoxy)C_{1-6}alkyl;

R_5 is selected from the group consisting of: hydrogen, halo, C_{1-6}alkyl, and haloC_{1-6}alkyl; and

R_6 is selected from the group consisting of: hydrogen, halo, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, (C_{1-6}alkoxy)C_{1-6}alkyl, and cyano;

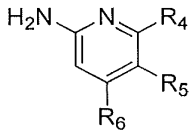
comprising the step of reacting a compound of **Formula VII**:



VII

wherein Ar, R_2 and R_3 are as given above,

with a compound of **Formula X**:



X ;

wherein R_4, R_5, and R_6 are as given above,

said reacting carried out in an organic solvent in the presence of an organic amine and an amide coupling agent,
to prepare said compound of **Formula IX**.

134. The process of claim 133, wherein Ar is unsubstituted or substituted 1-3 times with a halo independently selected from the group consisting of: chloro, fluoro, bromo, and iodo.

135. The process of claim 133 or claim 134, wherein R_2 and R_3 are each independently selected from the group consisting of: hydrogen and C_{1-6}alkyl.

136. The process of any of claims 133-135, wherein said organic solvent is selected from the group consisting of: *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide (DMA), *N*-methyl-2-pyrrolidone (NMP), acetone, toluene, acetonitrile, and dichloromethane.

137. The process of any of claims 133-136, wherein said amide coupling agent is an alkyl phosphonic anhydride.

138. The process of any of claims 133-136, wherein said amide coupling agent is a propyl phosphonic anhydride.

139. The process of any of claims 133-136, wherein said amide coupling agent is tri-n-propyl phosphonic anhydride.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/026204

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C29/147 C07C303/28 C07D239/28 C12P41/00 C07C33/50
C07C309/70 C07D239/34 C07D401/12
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C C07D C12P

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, 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.
X	KAZUYA YAMAGUCHI ET AL: "Construction of a cis-Cyclopropane via Reductive Radical Decarboxylation. Enantioselective Synthesis of cis- and trans-1-Arylpiperazyl-2-phenylcyclopropane s Designed as Antidopaminergic Agents", JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY, vol. 68, no. 24, 11 June 2003 (2003-06-11) , pages 9255-9262, XP002512742, DOI: 10.1021/JO0302206 [retrieved on 2003-11-06] scheme 2 page 9260, column 1, paragraph 3 ----- -/--	1

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 April 2013	25/04/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Delanghe, Patrick

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/026204

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/057575 A2 (DOV PHARMACEUTICAL INC [US]; SKOLNICK PHIL [US]; CHEN ZHENGMING [US];) 15 May 2008 (2008-05-15) page 97, line 15 - page 99, line 12	1
X	VALGIMIGLI L ET AL: "THE EFFECT OF RING NITROGEN ATOMS ON THE HOMOLYTIC REACTIVITY OF PHENOLIC COMPOUNDS: UNDERSTANDING THE RADICAL-SCAVENGING ABILITY OF 5-PYRIMIDINOLS", CHEMISTRY - A EUROPEAN JOURNAL, WILEY - V C H VERLAG GMBH & CO. KGAA, WEINHEIM, DE, vol. 9, no. 20, 17 October 2003 (2003-10-17), pages 4997-5010, XP009062482, ISSN: 0947-6539, DOI: 10.1002/CHEM.200304960 page 4998, column 1, last 4 lines to column 2, first 2 lines page 5007, column 1, paragraph 4	84
A	WO 2008/150364 A1 (MERCK & CO INC [US]; COLEMAN PAUL J [US]; MERCER SWATI P [US]; ROECKER) 11 December 2008 (2008-12-11) the whole document	1-139

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2013/026204

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008057575 A2	15-05-2008	CA 2705457 A1	15-05-2008
		EP 2086328 A2	12-08-2009
		JP 2010509334 A	25-03-2010
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(54) **Title**: COMPOSITIONS AND METHODS FOR TREATING INSOMNIA

(57) **Abstract**: In the present invention, compound such as (lR,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl) cyclopropanecarboxamide have been found to be potent orexin receptor antagonists, and may be useful in the treatment of sleep disorders such as insomnia, as well as for other therapeutic uses.

DESCRIPTION

COMPOSITIONS AND METHODS FOR TREATING INSOMNIA

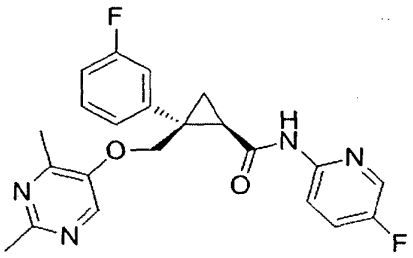
FIELD OF THE INVENTION

[0001] The present invention is directed to compositions and methods for treating insomnia. The present application claims priority on the basis of US Patent Application No. 62/067,443, filed in the United States on October 23, 2014, the contents of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] Orexin receptors are G-protein coupled receptors found predominately in the brain. Their endogenous ligands, orexin-A and orexin-B, are expressed by neurons localized in the hypothalamus. Orexin-A is a 33 amino acid peptide; orexin-B consists of 28 amino acids (Sakurai T. et al., Cell, 1998, 92 573-585). There are two subtypes of orexin receptors, orexin receptor 1 (hereinafter referred to as OX1) and orexin receptor 2 (hereinafter referred to as OX2); OX1 binds orexin-A preferentially, while OX2 binds both orexin-A and -B. Orexins stimulate food consumption in rats, and it has been suggested that orexin signaling could play a role in a central feedback mechanism for regulating feeding behavior (Sakurai et al., supra). It has also been observed that orexins control wake-sleep conditions (Chemelli R.M. et al., Cell, 1999, 98, 437-451). Orexins may also play roles in brain changes associated with opioid and nicotine dependence (S.L. Borgland et al., Neuron, 2006, 49, 598-601; C.J. Winrow et al., Neuropharmacology, 2010, 58, 185-194), and ethanol dependence (J.R. Shoblock et al., Psychopharmacology, 2011, 215, 191-203). Orexins have additionally been suggested to play a role in some stress reactions (T. Ida et al., Biochem. Biophys. Res. Commun., 2000, 270, 318-323). Compound such as
(1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl) cyclopropanecarboxamide (hereinafter referred to as Compound A) have been found to be potent orexin receptor antagonists, and may be useful in the treatment of sleep disorders such as insomnia, as well as for other therapeutic uses.

[0003] The Formula of Compound A



[0004] Regarding the hypnotic agent, when an active pharmaceutical ingredient (hereinafter referred to as API) in a pharmaceutical formulation to be taken a once-a-night dosing is too high a dose, it has the potential to cause the next-day residual sleepiness, while the single insufficient dose may cause the patient to wake up during normal sleep period even if the patients are able to fall sleep with the hypnotic. Therefore, it is difficult to set the proper dose with considering the sensitive balance between easy of sleep onset and the avoidance of the residual sleepiness, as compared with the considering only the balance between side effects and efficacy. Furthermore, even if the dose of a certain drug for insomnia, the physiochemical properties of the API and the pharmacokinetic (hereinafter referred to as PK) profile after administration of the drug were known, such information would not be applicable to other APIs for insomnia because it would be likely effected by a number of factors, including the mechanism of action, the route of administration, the rate of absorption, the physiochemical property such as the solubility and the stability in plasma or other factors of each API. Indeed, the relationship between the residual sleepiness and the characteristics of the hypnotic agents is not always consistent (CNS Drugs 2004; 18 (5): 297-328). The relation between PK profile and the sleepiness effect such as the sleep onset or the residual sleepiness has been unknown yet for compound A.

[0005] There exists a need in the art for more effective methods of treating insomnia to achieve rapid sleep onset as well as sleep maintenance, throughout the sleep period, but avoid residual sleepiness and/or the next-day impairment, comprising administrating orally a solid dosage form of a hypnotic agent. Further, there exists a need in the art for a pharmaceutical composition comprising a hypnotic agent and at least one pharmaceutically acceptable excipient for the treatment of insomnia to achieve rapid sleep onset as well as sleep maintenance, throughout the sleep period, but avoid residual sleepiness and/or next-day impairment.

SUMMARY OF THE INVENTION

[0006] It is an object of the present invention to provide methods of treating insomnia comprising administrating orally a solid dosage form of the drug compound A.

[0007] It is further an object of the present invention to provide a pharmaceutical composition, comprising a therapeutically effective amount of compound A

[0008] In certain embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose ranging from about 1 mg to about 15 mg.

[0009] In certain embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose ranging from about 2 mg to about 15 mg.

[0010] In certain embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose ranging from about 2 mg to about 10 mg.

[0011] In certain embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose chosen from about 2, 2.5, 4, 5, 8, 10, or 15 mg.

[0012] In certain embodiment, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose providing a mean maximum plasma concentration (Cmax) of from about 3.0 ng/ml to about 7.2 ng/ml for each 1 mg of compound A, after single dose administration to human subjects.

[0013] In certain embodiment, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose ranging from about 1 mg to about 15 mg, and wherein said single daily dose achieves a mean maximum plasma concentration (Cmax) of from about 3.0 ng/ml to about 7.2 ng/ml for each 1 mg of compound A, after single dose administration to human subjects.

[0014] In certain embodiment, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single dose achieves a mean

maximum plasma concentration (Cmax) within the range of about 80% to about 125% of 5.3 ng/ml, after single dose administration to human subjects.

[0015] In certain embodiment, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves a mean maximum plasma concentration (Cmax) within the range of about 80% to about 125% of 16 ng/ml, after single dose administration to human subjects.

[0016] In certain embodiment, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said single daily dose achieves a mean maximum plasma concentration (Cmax) of within the range of about 80% to about 125% of 23 ng/ml, after single dose administration to human subjects.

[0017] In certain embodiment, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves a mean maximum plasma concentration (Cmax) within the range of about 80% to about 125% of 36 ng/ml, after single dose administration to human subjects.

[0018] In further embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose to achieve a mean AUC(0-24) of from about 15.9 ng*hr/ml to about 23.8 ng*hr/ml for each 1 mg of compound A, after single dose administration to human subjects.

[0019] In further embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-24) within the range of about 80% to about 125% of 17 ng*hr/ml, after single dose administration to human subjects.

[0020] In further embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves a

mean AUC(0-24) within the range of about 80% to about 125% of 57 ng*hr/ml, after single dose administration to human subjects.

[0021] In further embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-24) within the range of about 80% to about 125% of 95 ng*hr/ml, after single dose administration to human subjects.

[0022] In further embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-24) within the range of about 80% to about 125% of 159 ng*hr/ml, after single dose administration to human subjects.

[0023] In further embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose to achieve a mean AUC(0-t) of from about 19.1 ng*hr/ml to about 51.1 ng*hr/ml for each 1 mg of compound A, after single dose administration to human subjects.

[0024] In further embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-t) within the range of about 80% to about 125% of 19 ng*hr/ml, after single dose administration to human subjects.

[0025] In further embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-t) within the range of about 80% to about 125% of 80 ng*hr/ml, after single dose administration to human subjects.

[0026] In further embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said single daily dose achieves a

mean AUC(0-t) within the range of about 80% to about 125% of 128 ng*hr/ml, after single dose administration to human subjects.

[0027] In further embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-t) within the range of about 80% to about 125% of 284 ng*hr/ml, after single dose administration to human subjects.

[0028] In further embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose to achieve a mean AUC(0-inf) of from about 19.8 ng*hr/ml to about 53.1 ng*hr/ml for each 1 mg of compound A, after single dose administration to human subjects.

[0029] In further embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-inf) within the range of about 80% to about 125% of 20 ng*hr/ml, after single dose administration to human subjects.

[0030] In further embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-inf) within the range of about 80% to about 125% of 80 ng*hr/ml, after single dose administration to human subjects.

[0031] In further embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-inf) within the range of about 80% to about 125% of 149 ng*hr/ml, after single dose administration to human subjects.

[0032] In further embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves a

mean AUC(0-inf) within the range of about 80% to about 125% of 311 ng*hr/ml, after single dose administration to human subjects.

[0033] In certain embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose ranging from about 1 mg to about 15 mg, and wherein said single daily dose provides a mean plasma compound A concentration of about 20 ng/ml or less at from 8 to 10 hours after single dose administration to human subjects.

[0034] In another embodiment, the present invention provides an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single daily dose ranging from about 1 mg to about 15 mg.

[0035] In another embodiment, the present invention provides an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single daily dose to achieve a mean maximum plasma concentration (Cmax) of from about 3.0 ng/ml to about 7.2 ng/ml for each 1 mg of the drug, after single dose administration to human subjects.

[0036] In another embodiment, the present invention provides an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves a mean maximum plasma concentration (Cmax) within the range of about 80% to about 125% of 5.3 ng/ml, after single dose administration to human subjects.

[0037] In another embodiment, the present invention provides an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves a mean maximum plasma concentration (Cmax) within the range of about 80% to about 125% of 16 ng/ml, after single dose administration to human subjects.

[0038] In another embodiment, the present invention provides an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said single daily dose achieves a mean maximum plasma concentration (Cmax) within the range of about

80% to about 125% of 23 ng/ml, after single dose administration to human subjects.

[0039] In another embodiment, the present invention provides an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves a mean maximum plasma concentration (Cmax) within the range of about 80% to about 125% of 36 ng/ml, after single dose administration to human subjects.

[0040] In further embodiments, the present invention provides an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single daily dose providing a mean AUC(0-24) of from about 15.9 ng*hr/ml to about 23.8 ng*hr/ml for each 1 mg of the drug, after single dose administration to human subjects.

[0041] In further embodiments, the present invention provides an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-24) within the range of about 80% to about 125% of 17 ng*hr/ml, after single dose administration to human subjects.

[0042] In further embodiments, the present invention provides an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-24) within the range of about 80% to about 125% of 57 ng*hr/ml, after single dose administration to human subjects.

[0043] In further embodiments, the present invention provides an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-24) within the range of about 80% to about 125% of 95 ng*hr/ml, after single dose administration to human subjects.

[0044] In further embodiments, the present invention provides an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-24) within the range of about 80% to about 125%

of 159ng*hr/ml, after single dose administration to human subjects.

[0045] In further embodiments, the present invention provides an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single daily dose providing a mean AUC(0-t) of from about 19.1 ng*hr/ml to about 51.1 ng*hr/ml for each 1 mg of the drug, after single dose administration to human subjects.

[0046] In further embodiments, the present invention provides an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-t) within the range of about 80% to about 125% of 19 ng*hr/ml, after single dose administration to human subjects.

[0047] In further embodiments, the present invention provides an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-t) within the range of about 80% to about 125% of 80 ng*hr/ml, after single dose administration to human subjects.

[0048] In further embodiments, the present invention provides an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-t) within the range of about 80% to about 125% of 128 ng*hr/ml, after single dose administration to human subjects.

[0049] In further embodiments, the present invention provides an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-t) within the range of about 80% to about 125% of 284 ng*hr/ml, after single dose administration to human subjects.

[0050] In further embodiments, the present invention provides an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single daily dose providing a mean AUC(0-inf) of from about 19.8 ng*hr/ml to about 53.1 ng*hr/ml for each 1 mg of the drug, after single

dose administration to human subjects.

[0051] In further embodiments, the present invention provides an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-inf) within the range of about 80% to about 125% of 20 ng*hr/ml, after single dose administration to human subjects.

[0052] In further embodiments, the present invention provides an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-inf) within the range of about 80% to about 125% of 80 ng*hr/ml, after single dose administration to human subjects.

[0053] In further embodiments, the present invention provides an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-inf) within the range of about 80% to about 125% of 149 ng*hr/ml, after single dose administration to human subjects.

[0054] In further embodiments, the present invention provides an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-inf) within the range of about 80% to about 125% of 311 ng*hr/ml, after single dose administration to human subjects.

[0055] In certain embodiments, the present invention to provide an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single daily dose ranging from about 1 mg to about 15 mg, and wherein said single daily dose provides a mean plasma compound A concentration of about 20 ng/ml or less at from 8 to 10 hours after single dose administration to human subjects.

[0056] In certain embodiments, the present invention is directed to an oral pharmaceutical dosage form comprising a pharmaceutically acceptable excipient and an effective amount of compound A for treating insomnia, the dosage form providing an dissolution rate of 85 % or more in dissolution medium (0.1

mol/L hydrochloric acid containing 0.5% polysorbate 80, 900 mL, 37 ± 0.5°C) within 30 minutes from the onset of dissolution study using the Apparatus 2 (Paddle Apparatus, paddle speed; 75 rpm) according to the procedure for immediate-release dosage form in 6.10 Dissolution test of JP16 or <711> Dissolution of USP37.

[0057] In certain embodiments, the present invention is directed to an oral pharmaceutical dosage form comprising a pharmaceutically acceptable excipient and an effective amount of compound A for treating insomnia, the dosage form providing an dissolution rate of 85 % or more in dissolution medium (0.1 mol/L hydrochloric acid, 900 mL, 37 ± 0.5°C) within 15 minutes from the onset of dissolution study using the Apparatus 2 (Paddle Apparatus, paddle speed; 50 rpm) according to the procedure for immediate-release dosage form in 6.10 Dissolution test of JP16 or <711> Dissolution of USP37.

[0058] In certain embodiments, the present invention is directed to an oral pharmaceutical dosage form comprising lactose as pharmaceutically acceptable excipient.

[0059] In certain embodiments, the present invention is directed to an oral pharmaceutical dosage form comprising low-substituted hydroxypropyl cellulose as pharmaceutically acceptable excipient.

[0060] In certain embodiments, the present invention is directed to an oral pharmaceutical dosage form comprising lactose and low-substituted hydroxypropyl cellulose as pharmaceutically acceptable excipient.

[0061] The method according to the present invention has a potential use of the treatment of insomnia with easy of sleepiness onset, but the avoidance of residual sleepiness and/or the next-day impairment.

[0062] The pharmaceutical composition according to the present invention has a potential use of an oral solid dosage for the treatment of insomnia.

DETAILED DESCRIPTION

I. Definitions

[0063] In order the invention described herein may be more fully understood, the following definitions are provided for the purposes of the disclosure:

[0064] The term "effective amount" means an amount of drug of compound A that is capable of achieving a therapeutic effect in a human subjective in need thereof.

[0065]The term "drug of compound A" shall mean (1R, 2S)-2-(((2,4-dimetylpyrimidin-5-yl)oxy)

methyl)-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, free-base or any combination thereof.

[0066] The term "human subject" shall mean a normal healthy male or female volunteers and/or any individual that presents with clinical signs and symptoms of insomnia or any disease or disorder that causes insomnia.

[0067] The term "insomnia" as used herein shall mean all of the description as delineated in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (2013) (hereafter referred to as DSM-V), published by the American Psychiatric Association. The DSM-V lists the diagnostic criteria for insomnia as follows:

A. A predominant complaint is dissatisfaction with sleep quantity or quality, associated with one (or more) of the following symptoms:
   1. Difficulty initiating sleep. (In children, this may manifest as difficulty initiating sleep without caregiver intervention.)
   2. Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings. (In children, this may manifest as difficulty returning to sleep without caregiver intervention.)
   3. Early-morning awakening with inability to return to sleep.
B. The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning.
C. The sleep difficulty occurs at least 3 nights per week
D. The sleep difficulty is present for at least 3 months.
E. The sleep difficulty occurs despite adequate opportunity for sleep.
F. The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder (e.g, narcolepsy, breathing-related sleep disorder, circadian rhythm sleep-wake disorder, a parasomnia.).
G. The insomnia is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication).
H. Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia.

[0068] Insomnia shall mean a sleep disorder characterized by symptoms including, without limitation, difficulty in falling asleep, difficulty in staying asleep, intermittent wakefulness, and/or waking up too early. The term also encompasses daytime symptoms such as sleepiness, anxiety, impaired concentration, impaired memory, and irritability. Types of insomnia suitable for treatment with the compositions of the

present invention include, without limitation, short-term, and chronic insomnia. The term "short-term insomnia" refers to insomnia lasting for about two to about four weeks. The term "chronic insomnia" refers to insomnia lasting for at least one month or longer.

[0069] The expression "bioequivalent" or "bioequivalence" is a term of art and is intended to be defined in accordance with Approved Drug Products with Therapeutic Equivalence Evaluations, 34th Edition, which is published by the U.S Department of Health and Human Services, and is commonly known as the "Orange Book". Bioequivalence of different formulation of the same drug substance involves equivalence with respect to the rate and extent of drug absorption. The extent and rate of absorption of the test formulation is compared to a reference formulation in order to determine whether the two formulations are bioequivalent. The standard bioequivalence study is conducted in crossover fashion by extensive testing which includes administering single doses of the test and reference drugs to a number of volunteers, usually 12 to 24 healthy normal adults, and then measuring the blood or plasma levels of the drug over time. Detailed guidelines for establishing the bioequivalence of a formulation with a reference formulation have been published by the FDA Office of Generic Drugs, Division of Bioequivalence.

[0070] Two formulations whose PK parameters such as Cmax, AUC, or Tmax differ by -20%/+25% or less are generally considered to be "bioequivalent". Another approach for average bioequivalence involves the calculation of a 90% confidence interval for the ratio of the averages (population geometric means) of the measures for the test and reference products. To establish BE, the calculated confidence interval should fall within usually 80-125% for the ratio of the product averages. In addition to this general approach, the others approach, including (1) logarithmic transformation of pharmacokinetic data, (2) methods to evaluate sequence effects and (3) methods to evaluate outlier data, may be useful for the establishment of bioequivalence. For example, in the above (1) the confidence interval should fall within usually 80-125% for the difference in the mean value of the logarithmic converted PK parameter.

[0071] The term "sleep time" refers to the time that a subject spends sleeping. Sleep time can be continuous or discontinuous.

[0072] "Sleep efficiency" refers to the total sleep time a subject receives during their time in bed. Sleep efficiency is measured by the following equation: 100*(total sleep time (TST)/total time in bed).

[0073] The phrase "residual sleepiness" refers to a patient's subjective feeling of sleepiness or sedation upon awakening, usually in the next morning after administration the hypnotic on the evening before. "The next-day impairment" refers to a patient's behavior to impair activities that require alertness, including driving, which occurs when they are awake in the next morning, but levels of the insomnia

medicine in their blood remain high enough. The Karolinska sleepiness scale (KSS) is one of a number of tools used for evaluating subjective sleepiness. The KSS was originally developed to constitute a one-dimensional scale of sleepiness and was validated against alpha and theta electroencephalographic (EEG) activity as well as slow eye movement electrooculographic (EOG) activity (Åkerstedt and Gillberg, 1990). Other subjective tests for evaluating residual sleepiness or the next day impairment effect include a Epworth Sleepiness Scale (ESS), a Stanford Sleepiness Scale (SSS), and a Sleep-Wake Activity Inventory (SWAI). Their effects also can be evaluated using one or more of a number of tests to human subjects by those of skill in the art to explore their memory, their attention, information processing and psychomotor performance, including, for example, a Digit Symbol Substitution Test (DSST), a Psychomotor Vigilance Test (PVT), a Choice Reaction Time test (CRT), a Sleep Latency Test (SLT), a Visual Analog Test (VAT), a Symbol Copying Test (SCT), a Critical Flicker Fusion threshold test (CFF), a Simple Reaction time test (visual or auditory; SRT), a Word Learning Test (WLT), a Critical Tracking Test (CTT), a Divided Attention Test (DAT), a digit or letter cancellation test, sleep staging through polysomnographic (PSG) measurements, Continuous Performance Task test (CPT), Multiple Sleep Latency Test (MSLT), a Rapid Visual Information Processing test (RVIP) and others.

[0074] The term "dosage form(s)" or "pharmaceutical dosage form(s)" shall mean the means to administer the drug substance (active pharmaceutical ingredient (API)), or to facilitate dosing, administration, and delivery of the medicine to the patient and other mammals. Dosage forms are classified in terms of administration routes and application sites, including, for example, oral, topical, rectal, vaginal, intravenous, subcutaneous, intramuscular, ophthalmic, nasal, otic and inhalation administration. Alternatively, dosage forms are classified in terms of physical form such as solid, semi-solid or liquid. Furthermore, dosage forms are subdivided based on their form, functions and characteristics, including, without limited, tablet, capsule or injection as described in monograph of Japanese Pharmacopoeia 16 edition (JP16) or General Chapter <1151> Pharmaceutical Dosage Forms of U.S. Pharmacopoeia-NF (37)(USP37).

[0075] The terms "excipient" shall mean a typically inactive ingredient used as a vehicle (for example, water, capsule shell etc.), a diluent, or a component to constitute a dosage form or pharmaceutical composition comprising a drug such as a therapeutic agent. The term also encompasses a typically inactive ingredient that imparts cohesive function (i.e. binder), disintegrating function (i.e. disintegrator), lubricant function (lubricating agent), and/or the other function (i.e. solvent, surfactant etc.) to the composition.

[0076] The term “a mean” refers to a geometric mean. The pharmacokinetic parameters such as “a mean Cmax” or “a mean AUC” refers to the geometric mean value of a Cmax or an AUC.

[0077] The list of the abbreviations and definitions of the terms used in this application is presented the following.

AUC: Area under the plasma concentration-time curve
AUC(0-x): Area under the plasma concentration-time curve from time zero to x hours after dosing
AUC(0-t): Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
AUC(0-inf): Area under the plasma concentration-time curve from time zero to infinity
ANCOVA: Analysis of covariance
CI: Confidence interval
Cmax: Maximum drug concentration
Cx: plasma concentration at x hours after dosing
CV: Coefficient of variation
DSST: Digit Symbol Substitution Test
ECG: Electrocardiogram
EEG: Electroencephalogram
EMG: Electromyogram
EOG: Electrooculogram
KSS: Karolinska Sleepiness Scale
LC-MS/MS: Lipid chromatography-mass spectrometry/mass spectrometry
LPS: Latency to persistent sleep, Duration of time measured from lights off to the first 30 seconds of PSG recording (epoch) of 20 consecutive epochs of non-wake
LS: Least square
MAD: Multiple ascending dose
MTD: Maximum tolerated dose
PD: Pharmacodynamics
PK: Pharmacokinetic(s)
PSG: Polysomnogram, polysomnography
PVT: Psychomotor Vigilance Test
REM: Rapid eye movement
RT: Reaction time
SE: Sleep efficiency, TST divided by the time in bed (min) multiplied by 100
SAD: Single ascending dose
SD: Standard deviation
t1/2: Terminal elimination half-life

tmax: Time to reach maximum (peak) concentration following drug administration
TST: Total sleep time, Duration of rapid eye movement (REM) + non-REM (NREM) sleep during Time in Bed (TIB)
WASO: Wake after sleep onset, Duration of wakefulness from onset of persistent sleep (LPS) to lights-on

BRIEF DESCRIPTION OF THE FIGURES

[0078] Fig.1 shows Dissolution Profiles of compound A 1 mg and 50 mg Capsules

[0079] Fig.2 shows Dissolution Profiles of compound A 1 mg, 2.5 mg, 5 mg, 10 mg and 25 mg Tablets

[0080] Fig.3 shows Comparative Dissolution Profiles between Compound A Capsules and Tablets Obtained in Condition I

II. Description of the Embodiments

[0081] In certain embodiments, the present invention is directed to a method of treating insomnia, comprising orally administering a single daily dose of compound A in an amount from about 1 mg to about 15 mg, and wherein said single dose provides easy sleep onset, but avoids residual sleepiness and/or the next-day impairment.

[0082] In certain embodiments, the present invention is directed to a method of treating insomnia, comprising orally administering a single daily dose of compound A in an amount from about 1 mg to about 15 mg to achieve a mean maximum plasma concentration (Cmax) of from about 3.0 ng/ml to about 108 ng/ml. Administration of the single daily dose achieves a mean AUC(0-24) of from about 15.9 ng*hr/ml to about 356.4 ng*hr/ml; a mean AUC(0-t) of from about 19.1 ng*hr/ml to about 766.5 ng*hr/ml; a mean AUC(0-inf) of from about 19.8 ng*hr/ml to about 796.5 ng*hr/ml; a mean t1/2 of from about 12.7 to about 60 hours; and a mean time to reach maximum plasma concentration (tmax) from about 1 to about 3.25 hours are achieved.

[0083] In another embodiment, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose to achieve a mean maximum plasma concentration (Cmax) of from about 3.0 ng/ml to about 7.2 ng/ml for each 1 mg of compound A. Administration of the single daily dose achieves a mean AUC(0-24) of from about 15.9 ng*hr/ml to about 23.8 ng*hr/ml for each 1 mg of compound A; a mean AUC(0-t) of from about 19.1 ng*hr/ml to about 51.1 ng*hr/ml for each 1 mg of compound A; a mean AUC(0-inf) of from about 19.8 ng*hr/ml to about 53.1 ng*hr/ml for each 1 mg of compound A are achieved.

[0084] When a single 1 mg daily dose of compound A is administered to a human subject, a mean maximum plasma concentration (Cmax) of about 5.3 ng/ml; a mean AUC(0-24) of about 17.2 ng*hr/ml; a mean AUC(0-t) of about 19.1 ng*hr/ml; a mean AUC(0-inf) of about 19.8 ng*hr/ml ; a mean t1/2 of about 12.7 hours; and a mean time to maximum plasma concentration (tmax) of about 1 hours are achieved.

[0085] When a single 2.5 mg daily dose of compound A is administered to a human subject, a mean maximum plasma concentration (Cmax) of from about 10 ng/ml to about 18 ng/ml; a mean AUC(0-24) of about 57 ng*hr/ml to about 60 ng*hr/ml; a mean AUC(0-t) of from about 80 ng*hr/ml to about 95 ng*hr/ml; a mean AUC(0-inf) of from about 80 ng*hr/ml to about 103 ng*hr/ml; a mean t1/2 of from about 30 to about 37 hours; and a mean time to maximum plasma concentration (tmax) of from about 1 to 2 hours are achieved.

[0086] When a single 5 mg daily dose of compound A is administered to a human subject, a mean maximum plasma concentration (Cmax) of from about 19 ng/ml to about 23 ng/ml; a mean AUC(0-24) of from about 95 ng*hr/ml to about 110 ng*hr/ml; a mean AUC(0-t) of about 128 ng*hr/ml; a mean AUC(0-inf) of about 150 ng*hr/ml; a mean t1/2 of about 31 hours; and a mean time to maximum plasma concentration (tmax) of from about 1 to about 2 are achieved.

[0087] When a single 10 mg daily dose of compound A is administered to a human subject, a mean maximum plasma concentration (Cmax) of from about 30 ng/ml to about 58 ng/ml,; a mean AUC(0-24) of from about 160 ng*hr/ml to about 190 ng*hr/ml; a mean AUC(0-t) of from about 280ng*hr/ml to about 510 ng*hr/ml; a mean AUC(0-inf) of from about 310 ng*hr/ml to about 530 ng*hr/ml; a mean t1/2 of from about 56 to about 60 hours; and a mean time to maximum plasma concentration (tmax) of from about 1 to about 3.25 hours are achieved.

[0088] In certain embodiment, when a single 1 mg daily dose of compound A is administered to a human subject, (1) a mean maximum plasma concentration (Cmax) within the range of about 80% to about 125% of 5.3 ng/ml; (2) a mean AUC(0-24) within the range of about 80% to about 125% of 17 ng*hr/ml;(3) a mean AUC(0-t) within the range of about 80% to about 125% of 19 ng*hr/ml; (4) a mean AUC(0-inf) within the range of about 80% to about 125% of 19 ng*hr/ml ; and/or (5) a mean time to maximum plasma concentration (tmax) within the range of about 80% to about 125% of 1.0 hour is/are achieved.

[0089] In another embodiment, when a single 2.5 mg daily dose of compound A is administered to a human subject, (1) a mean maximum plasma concentration (Cmax) within the range of about 80% to

about 125% of 16 ng/ml; (2) a mean AUC(0-24) within the range of about 80% to about 125% of 57 ng*hr/ml; (3) a mean AUC(0-t) within the range of about 80% to about 125% of 80 ng*hr/ml; (4) a mean AUC(0-inf) within the range of about 80% to about 125% of 80 ng*hr/ml ; and/or (5) a mean time to maximum plasma concentration (tmax) within the range of about 80% to about 125% of 1.0 hour is/are achieved.

[0090] In another embodiment, when a single 5 mg daily dose of compound A is administered to a human subject, (1) a mean maximum plasma concentration (Cmax) within the range of about 80% to about 125% of 23 ng/ml; (2) a mean AUC(0-24) within the range of about 80% to about 125% of 95 ng*hr/ml; (3) a mean AUC(0-t) within the range of about 80% to about 125% of 128 ng*hr/ml; (4) a mean AUC(0-inf) within the range of about 80% to about 125% of 149 ng*hr/ml ; and/or (5) a mean time to maximum plasma concentration (tmax) within the range of about 80% to about 125% of 1.6 hours is/are achieved.

[0091] In another embodiment, when a single 10 mg daily dose of compound A is administered to a human subject, (1) a mean maximum plasma concentration (Cmax) within the range of about 80% to about 125% of 36 ng/ml; (2) a mean AUC(0-24) within the range of about 80% to about 125% of 159 ng*hr/ml; (3) a mean AUC(0-t) within the range of about 80% to about 125% of 284 ng*hr/ml; (4) a mean AUC(0-inf) within the range of about 80% to about 125% of 311 ng*hr/ml ; and/or (5) a mean time to maximum plasma concentration (tmax) within the range of about 80% to about 125% of 1.0 hour is/are achieved.

[0092] In certain embodiments, when a single 2.5 mg daily dose is administered over a period of about 14 days, a mean maximum plasma concentration (Cmax) of about 15 ng/ml; a mean AUC(0-24) of about 120 ng*hr/ml; a mean t1/2 of about 44 hours; and a mean time to maximum plasma concentration (tmax) of about 2 hours are achieved.

[0093] In certain embodiments, when a single 5 mg daily dose is administered over a period of about 14 days, a mean maximum plasma concentration (Cmax) of about 24 ng/ml; a mean AUC(0-24) of about 190 ng*hr/ml; a mean t1/2 of about 46 hours; and a mean time to maximum plasma concentration (tmax) of about 1 hour are achieved.

[0094] In certain embodiments, when a single 10 mg daily dose is administered over a period of about 14 days, a mean maximum plasma concentration (Cmax) of about 47 ng/ml; a mean AUC(0-24) of about 360 ng*hr/ml; a mean t1/2 of about 55 hours; and a mean time to maximum plasma concentration (tmax) of about 2 hours are achieved.

[0095] In certain embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose to provide a mean plasma compound A concentration of about 20 ng/ml or less, at from 8 to 10 hours after single dose administration to human subjects.

[0096] In certain embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose to provide a mean plasma compound A concentration of about 18 ng/ml or less, at from 8 to 10 hours after single dose administration to human subjects.

[0097] In certain embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose to provide a mean plasma compound A concentration of about 15 ng/ml or less, at from 8 to 10 hours after single dose administration to human subjects.

[0098] In certain embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose to provide a mean plasma compound A concentration of about 9.0 ng/ml or less, at from 8 to 10 hours after single dose administration to human subjects.

[0099] In certain embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose to achieve a mean plasma compound A concentration of from about 0.4 ng/ml to about 9.0 ng/ml, at from 8 to 10 hours after single dose administration to human subjects.

[0100] In certain embodiments, the present invention to provide methods of treating insomnia, comprises administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose ranging from about 2.5 mg to about 10 mg, and wherein said single daily dose achieves a mean plasma compound A concentration of from about 1.8 ng /ml to about 9.0 ng /ml at 8 hours, or from about 1.5 ng /ml to about 5.0 ng /ml at 9 hours, or from about 2.0 ng /ml to about 8.0 ng /ml at 10 hours, after single dose administration to human subjects.

[0101] In certain embodiments, the present invention provides an oral dosage form for treating insomnia, comprising therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is a single dose ranging from about 1 mg to about

15 mg, and wherein said single dose provides easy sleep onset, but avoids residual sleepiness and/or the next-day impairment.

[0102] The dosage form of the present invention achieves: 1) a mean maximum plasma concentration (Cmax) of from about 3.0 ng/ml to about 108 ng/ml ; 2) a mean AUC(0-24) of from about 15.9 ng*hr/ml to about 356.4 ng*hr/ml; 3) a mean t1/2 of from about 12.7 to about 60 hours; and 4) a mean time to maximum plasma concentration (tmax) of from about 1 to about 3.25 hours, after single dose administration to a human subjects.

[0103] In certain embodiments, the dosage form provides a mean maximum plasma concentration (Cmax) of from about 3.0 ng/ml to about 7.2 ng/ml for each 1 mg of compound A, after single dose administration to human subjects.

[0104] In certain embodiments, the dosage form comprises 1 mg of compound A and provides a mean maximum plasma concentration (Cmax) of about 5.3 ng/ml after single dose administration to human subject.

[0105] In certain embodiments, the dosage form comprises 2.5 mg of compound A and provides a mean maximum plasma concentration (Cmax) of from about 10 ng/ml to about 18 ng/ml after single dose administration to human subject.

[0106] In certain embodiments, the dosage form comprises 5 mg of compound A and provides a mean maximum plasma concentration (Cmax) of from about 19 ng/ml to about 23 ng/ml after single dose administration to human subject.

[0107] In certain embodiments, the dosage form comprises 10 mg of compound A and provides a mean maximum plasma concentration (Cmax) of from about 30 ng/ml to about 58 ng/ml after single dose administration to human subject.

[0108] In certain embodiments, the dosage form provides a mean AUC(0-24) of from about 15.9 ng*hr/ml to about 23.8 ng*hr/ml for each 1 mg of compound A, after single dose administration to human subjects.

[0109] In certain embodiments, the dosage form comprises 1 mg of compound A and provides a mean AUC(0-24) of about 17 ng*hr/ml, after single dose administration to human subjects.

[0110] In certain embodiments, the dosage form comprises 2.5 mg of compound A and provides a mean AUC(0-24) of about 57 ng*hr/ml to about 60 ng*hr/ml, after single dose administration to human subjects.

[0111] In certain embodiments, the dosage form comprises 5 mg of compound A and provides a mean AUC(0-24) of about 95 ng*hr/ml to about 110 ng*hr/ml, after single dose administration to human subjects.

[0112] In certain embodiments, the dosage form comprises 10 mg of compound A and provides a mean AUC(0-24) of about 160 ng*hr/ml to about 190 ng*hr/ml, after single dose administration to human subjects.

[0113] In further embodiments, the dosage form provides a mean AUC(0-t) of from about 19.1 ng*hr/ml to about 766.5 ng*hr/ml, after single dose administration to human subjects.

[0114] In further embodiments, the dosage form comprises from 1 mg to 15 mg of compound A and provides a mean AUC(0-t) of from about 19.1 ng*hr/ml to about 766.5 ng*hr/ml, after single dose administration to human subjects.

[0115] In certain embodiments, the dosage form provides a mean AUC(0-t) of from about 19.1 ng*hr/ml to about 51.1 ng*hr/ml for each 1 mg of compound A, after single dose administration to human subjects.

[0116] In certain embodiments, the dosage form comprises 1 mg of compound A and provides a mean AUC(0-t) of about 19 ng*hr/ml, after single dose administration to human subjects.

[0117] In certain embodiments, the dosage form comprises 2.5 mg of compound A and provides a mean AUC(0-t) of from about 80 ng*hr/ml to about 95 ng*hr/ml, after single dose administration to human subjects.

[0118] In certain embodiments, the dosage form comprises 5 mg of compound A and provides a mean AUC(0-t) of about 128 ng*hr/ml, after single dose administration to human subjects.

[0119] In certain embodiments, the dosage form comprises 10 mg of compound A and provides a mean AUC(0-t) of from about 280 ng*hr/ml to about 510 ng*hr/ml, after single dose administration to human subjects.

[0120] In further embodiments, the dosage form provides a mean AUC(0-inf) of from about 19.8 ng*hr/ml to about 796.5 ng*hr/ml, after single dose administration to human subjects.

[0121] In certain embodiments, the dosage form comprises from about 1 mg to about 15 mg of compound A and provides a mean AUC(0-inf) of from about 19.8 ng*hr/ml to about 796.5 ng*hr/ml, after single dose administration to human subjects.

[0122] In certain embodiments, the dosage form provides a mean AUC(0-inf) of from about 19.8 ng*hr/ml to about 53.1 ng*hr/ml for each 1 mg of compound A, after single dose administration to human subjects.

[0123] In certain embodiments, the dosage form comprises 1 mg of compound A and provides a mean AUC(0-inf) of about 19.8 ng*hr/ml, after single dose administration to human subjects.

[0124] In certain embodiments, the dosage form comprises 2.5 mg of compound A and provides a mean AUC(0-inf) of from about 80 ng*hr/ml to about 103 ng*hr/ml, after single dose administration to human subjects.

[0125] In ceratin embodiments, the dosage form comprises 5 mg of compound A and provides a mean AUC(0-inf) of about 150 ng*hr/ml, after single dose administration to human subjects.

[0126] In certain embodiments, the dosage form comprises 10 mg of compound A and provides a mean AUC(0-inf) of from about 310 ng*hr/ml to about 530 ng*hr/ml, after single dose administration to human subjects.

[0127] In certain embodiments, the dosage form provides a mean plasma compound A concentration of about 20 ng /ml or less, at from 8 to 10 hours after single dose administration to human subjects.

[0128] In certain embodiments, the dosage form provides a mean plasma compound A concentration of about 18 ng /ml or less, at from 8 to 10 hours after single dose administration to human subjects.

[0129] In certain embodiments, the dosage form provides a mean plasma compound A concentration of about 15 ng /ml or less, at from 8 to 10 hours after single dose administration to human subjects.

[0130] In certain embodiments, the dosage form provides a mean plasma compound A concentration of about 9.0 ng /ml or less, at from 8 to 10 hours after single dose administration to human subjects.

[0131] In certain embodiments, the dosage form provides a mean plasma compound A concentration of from about 0.4 ng /ml to about 9.0 ng /ml, at from 8 to 10 hours after single dose administration to human subjects.

[0132] In further embodiments, the dosage form comprises a therapeutically effective amount of compound A and at least one pharmaceutically acceptable carrier or excipient, wherein said therapeutically effective amount is single daily dose ranging from about 2.5 mg to about 10 mg, and wherein said single dose achieves a mean plasma compound A concentration of from about 1.8 ng /ml to about 9.0 ng /ml at 8 hours, or from about 1.5 ng /ml to about 5.0 ng /ml at 9 hours, or from about 2.0 ng /ml to about 8.0 ng /ml at 10 hours, after single dose administration to human subjects.

[0133] In certain embodiments, the dosage form comprises 1 mg of compound A and provides an elimination half-life (t1/2) of about 12.7 hours after single dose administration to human subjects.

[0134] In certain embodiments, the dosage form comprises 2.5 mg of compound A and provides an elimination half-life (t1/2) of from about 30 to 37 hours after single dose administration to human subjects.

[0135] In certain embodiments, the dosage form comprises 5 mg of compound A and provides an elimination half-life (t1/2) of about 31 hours after single dose administration to human subjects.

[0136] In certain embodiments, the dosage form comprises 10 mg of compound A and provides an elimination half-life (t1/2) of from about 56 to 60 hours after single dose administration to human subjects.

[0137] In certain embodiments, the dosage form comprises 1 mg of compound A and provides a mean time to maximum plasma concentration (tmax) of about 1 hour after single dose administration to human subjects.

[0138] In certain embodiments, the dosage form comprises 2.5 mg of compound A and provides a mean time to maximum plasma concentration (tmax) of from about 1 to about 2 hours after single dose administration to human subjects.

[0139] In certain embodiments, the dosage form comprises 5 mg of compound A and provides a mean time to maximum plasma concentration (tmax) of from about 1 to about 2 hours after single dose

administration to human subjects.

[0140] In certain embodiments, the dosage form comprises 10 mg of compound A and provides a mean time to maximum plasma concentration (tmax) of from about 1 to about 3.25 hours after single dose administration to human subjects.

[0141] In certain embodiment, the present invention provides an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves (1) a mean maximum plasma concentration (Cmax) within the range of about 80% to about 125% of 5.3 ng/ml; (2) a mean AUC(0-24) within the range of about 80% to about 125% of 17 ng*hr/ml; (3) a mean AUC(0-t) within the range of about 80% to about 125% of 19 ng*hr/ml; (4) a mean AUC(0-inf) within the range of about 80% to about 125% of 19 ng*hr/ml ; and/or (5) a mean time to maximum plasma concentration (tmax) within the range of about 80% to about 125% of 1.0 hour.

[0142] In another embodiment, the present invention provides an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves (1) a mean maximum plasma concentration (Cmax) within the range of about 80% to about 125% of 16 ng/ml; (2) a mean AUC(0-24) within the range of about 80% to about 125% of 57 ng*hr/ml; (3) a mean AUC(0-t) within the range of about 80% to about 125% of 80 ng*hr/ml; (4) a mean AUC(0-inf) within the range of about 80% to about 125% of 80 ng*hr/ml ; and/or (5) a mean time to maximum plasma concentration (tmax) within the range of about 80% to about 125% of 1.0 hour.

[0143] In another embodiment, the present invention provides an oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said single daily dose achieves (1) a mean maximum plasma concentration (Cmax) within the range of about 80% to about 125% of 23 ng/ml; (2) a mean AUC(0-24) within the range of about 80% to about 125% of 95 ng*hr/ml; (3) a mean AUC(0-t) within the range of about 80% to about 125% of 128 ng*hr/ml; (4) a mean AUC(0-inf) within the range of about 80% to about 125% of 149 ng*hr/ml ; and/or (5) a mean time to maximum plasma concentration (tmax) within the range of about 80% to about 125% of 1.6 hours.

[0144] In another embodiment, the present invention provides an oral dosage form for treating insomnia

comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves (1) a mean maximum plasma concentration (Cmax) within the range of about 80% to about 125% of 36 ng/ml; (2) a mean AUC(0-24) within the range of about 80% to about 125% of 159 ng*hr/ml; (3) a mean AUC(0-t) within the range of about 80% to about 125% of 284 ng*hr/ml; (4) a mean AUC(0-inf) within the range of about 80% to about 125% of 311 ng*hr/ml ; and/or (5) a mean time to maximum plasma concentration (tmax) within the range of about 80% to about 125% of 1.0 hour.

[0145] In certain embodiments, the present invention is directed to an oral pharmaceutical dosage form comprising a pharmaceutically acceptable excipient and an effective amount of compound A for treating insomnia, wherein the dosage form provides an dissolution rate of 85 % or more within 45 minutes from the onset of dissolution study using the Apparatus 2 (Paddle Apparatus) according to the procedure for immediate-release dosage form in 6.10 Dissolution test of JP16 or <711> Dissolution of USP37. The dissolution medium (900 mL, 37 ± 0.5°C) is chosen from 0.1 mol/L hydrochloric acid or 0.1 mol/L hydrochloric acid containing 0.5% polysorbate 80. The paddle speed is chosen from 50 rpm or 75 rpm.

[0146] In certain embodiments, the present invention is directed to an oral pharmaceutical dosage form comprising a pharmaceutically acceptable excipient and an effective amount of compound A for treating insomnia, wherein the dosage form provides an dissolution rate of 85 % or more within 30 minutes from the onset of dissolution study using the Apparatus 2 (Paddle Apparatus) according to the procedure for immediate-release dosage form in 6.10 Dissolution test of JP16 or <711> Dissolution of USP37. The dissolution medium (900 mL, 37 ± 0.5°C) is chosen from 0.1 mol/L hydrochloric acid or 0.1 mol/L hydrochloric acid containing 0.5% polysorbate 80. The paddle speed is chosen from 50 rpm or 75 rpm.

[0147] In certain embodiments, the present invention is directed to an oral pharmaceutical dosage form comprising a pharmaceutically acceptable excipient and an effective amount of compound A for treating insomnia, wherein the dosage form provides an dissolution rate of 85 % or more within 15 minutes from the onset of dissolution study using the Apparatus 2 (Paddle Apparatus) according to the procedure for immediate-release dosage form in 6.10 Dissolution test of JP16 or <711> Dissolution of USP37. The dissolution medium (900 mL, 37 ± 0.5°C) is chosen from 0.1 mol/L hydrochloric acid or 0.1 mol/L hydrochloric acid containing 0.5% polysorbate 80. The paddle speed is chosen from 50 rpm or 75 rpm.

[0148] In certain embodiments, the present invention is directed to an oral pharmaceutical dosage form comprising a pharmaceutically acceptable excipient and an effective amount of compound A for treating insomnia, wherein the dosage form provides an dissolution rate of 85 % or more in dissolution medium

(pH1.2, 900 mL, 37 ± 0.5°C) within 15 minutes from the onset of dissolution study using the Apparatus 2 (Paddle Apparatus, paddle speed;50 rpm) according to the procedure for immediate-release dosage form in 6.10 Dissolution test of JP16 or <711> Dissolution of USP37.

[0149] In certain embodiments, the present invention is directed to an oral pharmaceutical dosage form comprising lactose as pharmaceutically acceptable excipient.

[0150] In certain embodiments, the present invention is directed to an oral pharmaceutical dosage form comprising low-substituted hydroxypropyl cellulose as pharmaceutically acceptable excipient.

[0151] In certain embodiments, the present invention is directed to an oral pharmaceutical dosage form comprising lactose and low-substituted hydroxypropyl cellulose as pharmaceutically acceptable excipient.

[0152] In the present invention, compound A may be in the form of free base, a pharmaceutically acceptable salt, hydrate, solvate, polymorph or any combination of the foregoing.

[0153] Pharmaceutically acceptable salts may include, but are not limited to,
inorganic acid salts (for example, a sulfate, a nitrate, a perchlorate, a phosphate, a carbonate, a bicarbonate, a hydrofluoride, a hydrochloride, a hydrobromide, a hydroiodide); organic carboxylates (for example, an acetate, an oxalate, a maleate, a tartrate, a fumarate, a citrate); organic sulfonates (for example, a methanesulfonate, a trifluoromethanesulfonate, an ethanesulfonate, a benzenesulfonate, a toluenesulfonate, a camphorsulfonate); amino acid salts (for example, an aspartate, a glutamate); quaternary amine salts; alkaline metal salts (for example, a sodium salt, a potassium salt); and alkaline-earth metal salts (for example, a magnesium salt, a calcium salt).

[0154] Methods of treating insomnia of the present invention contain compound A in a therapeutically effective amount for treatment of insomnia when administered in accordance with the teachings of the present invention. The effective amount is single daily dose, ranging from 0.5 mg to 100 mg, from 1 mg to 15 mg, from 2 mg to 15 mg, or from 2 mg to 10 mg.

Formulations

[0155] Dosage forms of the present invention contain compound A in a therapeutically effective amount for treatment of insomnia when administered in accordance with the teachings of the present invention. Unit dose of the effective amount in a dosage form is from 0.5 mg to 100 mg, from 1 mg to 15 mg, from 2 mg to 15mg, or chosen from 2 mg, 2.5 mg, 4 mg, 5 mg, 8 mg, 10 mg, or 15 mg. Unit dose is not limited by the type of the dosage form or the number of dosage forms for single dose.

[0156] A dosage form in the present invention may constitute one or more pharmaceutical composition comprising compound A together with pharmaceutically acceptable excipients.

[0157] The term "composition" used herein includes a product comprising a particular ingredient in a particular amount and any product directly or indirectly brought about by the combination of particular ingredients in particular amounts. Such a term related to the pharmaceutical composition is intended to include a product comprising an active ingredient and an inert ingredient constituting a carrier and include every product directly or indirectly brought about by the combination, complexation or aggregation of any two or more ingredients or the dissociation, other kinds of reactions or interaction of one or more ingredients. Thus, the pharmaceutical composition of the present invention includes every composition prepared by mixing the compound of the present invention with a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable" is used to mean that a carrier, a diluent or a vehicle must be compatible with other ingredients of a preparation and must be nontoxic to a taker.

[0158] A dosage form is not limited to as previous said, preferably a solid dosage form; more preferably an oral solid dosage form; furthermore preferably an immediate release oral dosage form.

[0159] The dissolution rate of compound A from the dosage form is over 85% within 45 minutes, preferably within 30 minutes, more preferably within 15 minutes, from the onset of dissolution study using the Apparatus 2 (Paddle Apparatus, paddle speed) according to the procedure for immediate-release dosage form in 6.10 Dissolution test of JP16 or <711> Dissolution of USP37. The dissolution medium (900 mL, 37 ± 0.5°C) is chosen from 0.1 mol/L hydrochloric acid or 0.1 mol/L hydrochloric acid containing 0.5% polysorbate 80. The paddle speed is chose from 50 rpm or 75 rpm.

[0160] The term "immediate release" in this invention shall mean a dissolution profile that the dissolution rate of compound A from the dosage form is over 80%, preferably over 85% in dissolution medium (pH1.2, 900 mL, 37 ± 0.5°C) within 15 minutes from the onset of dissolution study using the Apparatus 2 (Paddle Apparatus, paddle speed; 50 rpm) according to the procedure for immediate-release dosage form in 6.10 Dissolution test of JP16 or <711> Dissolution of USP37.

[0161] Solid dosage forms include capsules, granules, lozenges, pellets, pills, powders, suspensions, tablets, preferably capsules, granules, pellets, pills, tablets.

[0162] The pharmaceutical composition of the invention may be prepared, using standard techniques and manufacturing processes generally known in the art. See, e.g. the monograph of Japanese Pharmacopoeia

16 edition or General Chapter <1151> Pharmaceutical Dosage Forms of U.S. Pharmacopoeia-NF (37).

[0163] The pharmaceutical composition for solid dosage form of the invention may be prepared, for example, powders is prepared by dry blending the components. For example, Compound A, one or more diluents, one or more optional excipients (e.g., binders and/or disintegrants, as well as other additional optional excipients) are blended together. The components of the blend prior to blending, or the blend itself, may be passed through a mesh screen, for example a 400-700 μm mesh screen. A lubricant, which may also be screened, is then added to the blend and blending is continued until a homogeneous mixture is obtained as granules. The mixture is then compressed into tablets. Alternatively, a wet granulation technique can be employed. For example, the active agent and excipient(s) are blended together, for example by using a granulator, and the powder blend is granulated with a small volume of purified water. The resultant wet granule is dried and passed through a mill to obtain as granules. Furthermore, a disintegrator and a lubricant are added to the milled granules and after blending the resultant homogeneous mixture is compressed into tablets. Alternatively, a vehicle such as capsule shells is filled with powders or granules to obtain as capsules. It will be appreciated that modifications of the dry blending and wet granulation techniques, including the order of addition of the components and their screening and blending prior to compression into tablets, may be carried out according to principles well known in the art.

[0164] In the case of production of tablets or granules, it may be coated with a water-based film, for example by spray-coating, if necessary.

[0165] Examples of diluents used herein include lactose, corn starch and crystalline cellulose etc. Examples of binders used herein include hydroxypropyl cellulose, hypromellose etc. Examples of disintegrators used herein include low-substituted hydroxypropyl cellulose, calcium carboxymethyl cellulose, sodium croscarmellose etc. Examples of lubricants used herein include magnesium stearate, calcium stearate etc. Examples of coloring agents used herein include titanium oxide etc. Examples of coating agents used herein include hydroxypropyl cellulose, hypromellose, methyl cellulose etc. However, needless to say, examples of above agents are not limited thereto.

Detailed Description of the Preferred Embodiments

EXAMPLES

[0166] The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

Example 1

Single Dose Study (001 Study)

[0167] This was a randomized, double-blind, placebo-and active-controlled, sequential, single-dose study. The study consisted of two parts, Part A (healthy subjects) and Part B (otherwise healthy subjects with primary insomnia).

[0168] The primary objective in this study was to evaluate the safety and tolerability of single oral doses of compound A administered in the morning to healthy subjects, and to evaluate selected pharmacodynamic (PD) parameters (e.g., polysomnographically defined sleep measures) with regard to dose response in subjects with primary insomnia following single oral dosing of compound A in the evening approximately 30 minutes prior to the sleep period, compared with 10 mg zolpidem and placebo.

[0169] The secondary objective was to evaluate the safety and tolerability of single oral doses of compound A in otherwise healthy subjects with primary insomnia, and to assess the pharmacokinetics (PK) of compound A following administration of single oral doses in healthy subjects and subjects with primary insomnia.

[0170] Both parts of the study had two phases, the Prerandomization Phase and the Randomization Phase. The Prerandomization Phase lasted up to 21 days and consisted of a screening period (Day–21 to Day–3) and a baseline period (Day –2 to Day –1) during which each subject's study eligibility was determined and baseline assessments were conducted on Day–2. In the Randomization Phase, subjects were randomized to receive a single oral dose of either compound A or compound A matching placebo (Part A), and/or zolpidem, or zolpidem-matched placebo (Part B).

[0171] It was planned to screen approximately 160 healthy subjects and 250 otherwise healthy subjects with primary insomnia in order to enroll 64 and 60 subjects specifically for Part A and Part B, respectively. 160 healthy subjects and 281 otherwise healthy subjects with primary insomnia were actually screened to enroll 64 and 58 subjects into Parts A and B, respectively.

[0172] For Part A, 64 healthy subjects were enrolled into cohorts sequentially in a gradual dose escalation manner, to receive either compound A or placebo, and stratified by gender. Each cohort comprised six compound A- and two placebo-treated subjects. All study drugs were administered as single doses using one or more compound A-capsules or compound A-matched placebo capsules due to the test dose. After screening, subjects underwent baseline procedures and randomization on Day –2. Subjects were dosed on Day 1 in the morning after an overnight fast, 1 hour after lights-on. PK blood samples were collected at prespecified timepoints, and PD assessments were performed. Subjects were administered assessments on Day 1 predose and every 2 hours from 2 to 12 hours postdose, and each morning on Days 2 to 6.

[0173] These assessments included the Karolinska Sleepiness Scale (KSS), Digit Symbol Substitution Test (DSST), and Psychomotor Vigilance Test (PVT) in order to assess daytime sleepiness, level of alertness, and ability to concentrate. Waketime Questionnaires were administered after PD assessments each morning on Days 1 to Day 6. Time and duration of naps was recorded on Days 1 and 2. Safety was monitored throughout the study.

[0174] Doses for Part A were 1 mg, 2.5 mg, 5 mg, 10 mg, 25 mg, 50 mg, 100 mg, and 200 mg of compound A. Escalation to the next higher dose level did not occur until: 1) the safety, tolerability (including laboratory and electrocardiogram [ECG]), and available PK data from the latest completed cohort were reviewed in a blinded manner and 2) the available data supported the increase to the next dose.

[0175] For Part B, 58 otherwise healthy subjects with primary insomnia were randomized across three cohorts, and stratified by gender. Part B also included an active control (zolpidem) and matching placebo. In each cohort, there were approximately 12 subjects in the compound A/zolpidem-matched placebo group, approximately four subjects in the zolpidem/compound A-matched placebo group, and approximately four subjects in the compound A-matched placebo/zolpidem-matched placebo group. Part B dosing occurred in the evening, 30 minutes prior to the sleep period. The starting dose for Part B was 3 dose levels that determined to be safe and well tolerated in Part A. Subsequent dose levels in Part B were determined based on the PD results of the first cohort in Part B and PD and safety results from at least 3 completed higher dose cohorts in Part A. Each cohort in Part B was divided into at least two groups, with dosing of each group staggered by a minimum of 2 days.

[0176] After the initial Screening visit, eligible subjects were scheduled to return to the clinic for 2 days during the Screening Period to conduct screening/baseline PSGs. These two days occurred at least 3 days after the initial Screening visit and within a window from Day -7 to Day -6 (± 2 days). The first PSG was used to screen for sleep apnea and periodic limb movements in sleep (PLMS) and serve as the first baseline PSG. The second PSG was used as the second baseline PSG. Specific PSG variables were used to determine whether subjects met PSG inclusion criteria, and the average of PSG variables from these two PSGs was used as Baseline for this PD measure. Subjects who had met PSG inclusion criteria returned to the clinic on Day –1 for additional baseline procedures and randomization. Subjects were not allowed to nap on Day 1. On the evening of Day 1, after fasting a minimum of 3 hours, study drug was administered 30 minutes prior to the subject's habitual bedtime (lights-out), as calculated from the sleep diary for the first PSG during the Screening Period. PK blood samples were collected at prespecified timepoints, and PD assessments were performed. PSG was recorded on Day 1, postdose. Subjects were

administered additional PD assessments each morning on Day 1 through Day 6. These assessments included the KSS, DSST, and PVT, in order to assess daytime sleepiness, level of alertness, and ability to concentrate. The KSS and DSST were also administered 5 minutes predose and 25 minutes postdose on Day 1, just prior to lights-out. Waketime Questionnaires were administered after the PD assessments within 15 minutes of lights-on, on Day 1 to Day 6. Time and duration of naps was recorded on Day 2.

Pharmacokinetic:

[0177] For subjects in Part A, Blood samples for determination of plasma concentrations of compound A were collected on Day 1 predose and at 0.25 (15 minutes), 0.5 (30 minutes), 1, 2, 3, 4, 5, 6, 9, 12, 24, 48, 72, 96, 120, 168, and 240 hours after oral administration of compound A, but collected up to 72 hours in the first three cohorts (1, 2.5 and 5 mg compound A groups). PK samples were collected preferentially via an indwelling venous catheter for the first 12 hours and by direct venipuncture thereafter.

[0178] For subjects in Part B, blood samples for measurements of plasma concentrations of compound A were obtained by direct venipuncture on Day 1 predose and at 0.5, 9, 12, 24, 36, 60, 84, 108, 156, and 228 hours postdose.

[0179] The noncompartmental plasma PK parameters that were calculated for compound A (as data permitted) included, but were not limited to: Cmax (maximum drug concentration); tmax (time to reach maximum (peak) concentration following drug administration); AUC(0-24h) (area under the concentration x time curve from time zero to time 24 hours); AUC(0-t) (area under the concentration x time curve from time zero to time of last measurable concentration); AUC(0-inf) (area under the concentration x time curve from time zero to infinity); t1/2 (terminal elimination half-life); CL/F (apparent total body clearance of the drug from after extravascular administration); and V/F (apparent volume of distribution).

[0180] Plasma concentrations of compound A were measured using a validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) assay.

[0181] PK parameters of compound A for subjects in Part A were summarized in Table 1. In Part B, the concentration-time profiles were approximately similar to their corresponding dose groups in Part A.

[0182] Table 1 PK parameters of compound A for subjects in Part A

		1mg	2.5mg	5mg	10mg	25mg	50mg	100mg	200mg
AUC(0-24) (ng*h/mL)	N	6	6	6	6	6	6	6	6
	Mean(SD)	17.2(3.06)	56.8(21.1)	94.6(18.8)	159(61.9)	654(97.6)	1110(321)	1930(588)	4080(1040)
Cmax (ng/mL)	N	6	6	6	6	6	6	6	6
	Mean(SD)	5.29(1.25)	15.9(5.73)	22.7(4.39)	36.0(18.7)	108(22.0)	168(48.7)	264(128)	431(51.1)
AUC(0-t) (ng*h/mL)	N	6	6	6	6	6	6	6	6
	Mean(SD)	19.1(6.18)	80.2(32.2)	128(26.5)	284(80.7)	1450(455)	2080(775)	4490(1300)	9840(3510)
AUC(0-inf) (ng*h/mL)	N	5	4	5	6	6	6	6	6
	Mean(SD)	19.8(4.01)	79.7(42.0)	149(34.3)	311(90.1)	1540(518)	2150(834)	4740(1420)	10500(3690)
tmax (h)	N	6	6	6	6	6	6	6	6
	Median	1.00	1.01	1.55	1.00	2.01	2.53	3.00	3.00
t1/2 (h)	N	6	6	6	6	6	6	6	6
	Median	12.70	30.10	31.35	56.15	65.50	51.85	59.75	65.20
C9 (ng/mL)	N	6	6	6	6	6	6	6	6
	Mean(SD)	0.384(0.0726)	1.54(0.711)	2.68(0.942)	4.60(1.39)	21.9(4.19)	39.3(14.6)	86.0(47.5)	199(119)

Pharmacodynamic:

[0183] Part A Subjects were administered the KSS, DSST, and PVT starting 30 minutes predose on Day 1, then every 2 hours for 12 hours postdose and on Days 2 to 6 starting 30 minutes after lights-on. Waketime Questionnaires were administered on the mornings of Days 1 to 6 following the PD assessments.

[0184] In Part A, measures of sleepiness (KSS, DSST, PVT) indicated a general dose-response relationship. Pharmacodynamic response on these measures was generally maximal at 2 hours postdose, coinciding with Cmax. Duration of effect correlated with dose, i.e., the effects were longer with higher doses.

[0185] Part B subjects were administered the KSS, DSST, and PVT within 15 minutes after lights-on specifically in that order, on each morning from Day 1 through Day 6, followed by the Waketime Questionnaire. The KSS and DSST were also administered 5 minutes predose and 25 minutes postdose on Day 1 (just prior to lights-out).

[0186] In addition, PSG was performed during the Screening Period at Days -7 and -6 (±2 days), and postdose on Day 1. An 8-hour diagnostic PSG consisting of electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), ECGs, leg electrodes, and measures of respiratory function (airflow, respiratory effort, and oxygen saturation) were performed starting at the subject's habitual bedtime as determined from the sleep diary for the 3 nights immediately prior to the first PSG on Day –7 (±2 days). PSG variables from this night were used to screen for sleep apnea and PLMS. On Day -6 (±2) and postdose on Day1, standard PSGs (i.e., not including leg electrodes or measures of respiratory function other than oxygen saturation) were performed. Specified PSG variables from these two PSGs conducted during the Screening Period were used to determine whether subjects met PSG inclusion criteria. The average of PSG variables from these two PSGs conducted during the Screening Period were

used as baseline PSG values. The key PD parameters such as PSG LPS, TST, SE, and WASO have been obtained from all PSG recordings.

[0187] Polysomnography results indicated preliminary efficacy of compound A. At 2.5 and 10 mg doses, LPS was reduced by almost 30 minutes and at 25 mg, LPS was reduced by approximately 45 minutes relative to Baseline. At 2.5- and 10-mg doses, WASO was reduced by approximately 30 minutes and at 25 mg, WASO was reduced by more than 45 minutes relative to Baseline. Relative to zolpidem, the 2.5- and 10- mg doses of compound A showed a similar magnitude of effect on LPS and WASO. Relative to Baseline, SE was improved by 11% for the 2.5-mg dose of compound A, by 13% for the 10-mg dose, and by 18% for the 25-mg dose. This compared to a change from Baseline in SE of 3% for placebo treatment and 13% for zolpidem. After a single dose of 25 mg of compound A, SE was increased to approximately 90%. However, PD assessments indicated that some individuals at this dose exhibited increases from baseline on measures of next-day residual sleepiness.

[0188] There were no clinically significant next day effects of any dose of compound A, zolpidem, or placebo on KSS, DSST, or PVT.

Example 2

Multiple Ascending Dose Study (002 Study)

[0189] This was a single-center, randomized, double-blind, placebo-controlled, sequential, multiple -dose study.

[0190] Primary objective of this study was to evaluate the safety, tolerability, and pharmacokinetics (PK) of compound A after multiple doses administered orally, once daily in the evening for 14 days in healthy adult subjects. In addition, the objective of this study is to identify the maximum tolerated dose (MTD) or a sufficiently high tolerated dose of compound A to provide a safety margin relative to anticipated therapeutic dose.

[0191] A total of 48 healthy adult subjects (18 to 55 years) were to be enrolled into 1 of 6 cohorts sequentially in a gradual dose escalation manner, and randomized to receive either compound A or compound A-matched placebo in the evening 30 minutes before habitual bedtime, and after 3 hours fasting, for 14 days. Each cohort was to comprise 6 compound A- treated subjects and 2 placebo-treated subjects. Blood samples were collected for PK analysis at prespecified timepoints, and PD assessments were conducted.

[0192] The study had two phases, the Prerandomization Phase and the Randomization Phase. The

Prerandomization Phase lasted up to 21 days and consisted of a screening period (Day-21 to Day-3) and a baseline period (Day -2 to Day -1) during which each subject's study eligibility was determined and baseline assessments were conducted on Day–2. The Randomization Phase (Days 1–28) consisted of 3 periods: Treatment (Days 1–14) during which subjects were randomized and received daily oral doses of either compound A or compound A-matched placebo, Inpatient Follow-up (Days 15-19), and Outpatient Follow-up (Days 20–28) during which PK and safety assessments were conducted.

[0193] All subjects were administered PD assessments, including the Karolinska Sleepiness Scale (KSS), Digit Symbol Substitution Test (DSST), and Psychomotor Vigilance Test (PVT) in order to assess acute sleepiness in the interval between dosing and bedtime, as well as next-day residual sleepiness and the level of alertness and ability to concentrate. In addition, a Waketime Questionnaire was administered daily in order to assess quality of sleep on the previous night.

[0194] The starting dose for this study was based on the results in the study of Example 1. Escalation to the next higher dose level did not occur until the safety, tolerability (including laboratory and electrocardiogram [ECG]), and available PK data from the latest completed cohort and if the available data supported the increase to the next dose.

[0195] Blood samples for determination of plasma concentrations of compound A were collected at Day 1 predose and postdose 0.5 (30 minutes), 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 hours; Days 2 to 13: predose; Day 14: predose and postdose 0.5 (30 minutes), 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 hours; Day 15: 24 hours after Day 14 dose; Days 16 to 19: 36, 60, 84, and 108 hours after Day 14 dose; Day 21, 24, 26, 28: As close as possible to 156, 228, 276, and 324 hours after Day 14 dose. Plasma concentrations of compound A were measured in the same manner as described in Example 1 and the above noncompartmental plasma PK parameters were calculated for compound A.

[0196] PD effects were assessed by evaluating postdose and next-day functioning on the KSS, DSST, and the PVT, and by self-report of sleep quality on the Waketime Questionnaire. The KSS, DSST, and PVT were performed starting Day –1 at 15 minutes before habitual bedtime; on Days 1 to 15 within 15 minutes after habitual waketime, and at 1, 2, 4, 8, and 12 hours after habitual waketime, and on Days 1 to 14 at 15 minutes predose and 15 minutes postdose. 24-hour Holter recordings were started 30 minutes before bedtime on Day –2 and just prior to dosing on Day 14. Extractions from these recordings were used to conduct ECG analyses, including the HPQT analysis. Waketime Questionnaires were administered on Day 1 to Day 19.

[0197] The KSS, PVT, and DSST were administered on each treatment day in the evening predose and

postdose to assess the acute effect of compound A on sleepiness. For these timepoints, the daily 15 minutes predose values on the KSS, DSST, and PVT served as a baseline for that day's 15 minutes postdose value (daily baseline). The KSS, PVT, and DSST were also administered throughout the daytime hours subsequent to each dosing evening to assess the effect of compound A on next-day residual sleepiness. For these timepoints, the assessments taken at Day 1, 15 minutes and 1, 2, 4, 8, and 12 hours after habitual waketime served as the baseline for the assessments taken at the corresponding times after habitual waketime on Day 2 to Day 15 (time-matched baseline). Waketime Questionnaires were administered on Day 1 through Day 19 in the morning hours. The predose value on Day 1 was used as the baseline. The difference between placebo and each dose of compound A in change from baseline at each timepoint was calculated along with 95% confidence intervals (CIs). Potential dose-response and time trend were explored as data allowed.

[0198] Compound A capsules and compound A-matched placebo capsules were available in strengths of 2.5 mg, 10 mg, and 50 mg. All study drugs were administered as daily doses using one or more compound A-capsules or compound A-matched placebo capsules due to the test dose.

Pharmacokinetic

[0199] PK parameters on Day1 and Day14 were summarized in Table 2 and Table 3 respectively.

[0200] Table 2 PK parameters on Day1

		2.5mg	5mg	10mg	25mg	50mg	75mg
AUC(0-24)	N	6	6	6	6	5	6
(ng*h/mL)	Mean(SD)	59.4(17.5)	108(34.9)	187(47.9)	549(104)	931(253)	1260(301)
Cmax	N	6	6	6	6	5	6
(ng/mL)	Mean(SD)	10.1(4.26)	19.4(7.91)	30.4(13.1)	92.0(24.0)	199(81.2)	223(103)
tmax (h)	N	6	6	6	6	5	6
	Median	2.015	1.250	3.250	1.500	2.000	3.000
C8 (ng/mL)	N	6	6	6	6	5	6
	Mean(SD)	2.33(0.967)	4.40(1.73)	8.51(2.89)	24.1(9.26)	38.1(11.0)	54.5(21.7)
C10 (ng/mL)	N	6	6	6	6	5	6
	Mean(SD)	2.04(0.769)	3.63(1.23)	7.72(4.13)	19.8(7.11)	32.9(10.2)	44.2(13.4)

[0201] Table 3 PK parameters on Day14

		2.5mg	5mg	10mg	25mg	50mg	75mg
AUC(0-24)	N	6	6	6	5	5	5
(ng*h/mL)	Mean(SD)	120(38.0)	186(87.5)	357(193)	1100(387)	2300(758)	3790(857)
Cmax	N	6	6	6	5	5	5
(ng/mL)	Mean(SD)	15.4(4.73)	24.0(10.7)	46.9(14.5)	107(38.9)	220(33.5)	420(140)
tmax (h)	N	6	6	6	5	5	5
	Median	2.000	1.000	1.750	3.000	2.020	2.000
t1/2 (h)	N	6	6	6	5	5	5
	Mean(SD)	43.8(13.1)	45.6(16.6)	55.0(23.8)	50.6(10.7)	55.5(21.3)	56.2(20.1)

[0202] Based on graphical assessment of dose-normalized data, Cmax increased slightly less than in proportion to dose for both Day 1 and Day 14 assessments. Based on dose-normalized data, AUC(0-24h) increased slightly less than in proportion to dose on Day 1 but increased in approximate proportion to dose based on Day 14 assessments. The terminal half-life for the 2.5-and 5-mg doses were similar, averaging approximately 45 hours. At doses of 10 mg and higher, the mean terminal half-life was approximately 55 hours following the last day of Day 14 dosing. Accumulation was lower than predicted by the terminal half-life. Based on accumulation, the effective half-life was ranged from 16.9 to 24.7 hours for doses ranging from 2.5 to 25 mg, and 28.0 and 39.3 hours for the 50- and 75-mg doses, respectively.

Pharmacodynamics

[0203] Next-day residual sleepiness effect: There were dose-related increases in both the magnitude and duration of next day residual sleepiness as measured by the KSS, PVT, and DSST. In the 2.5-mg and 5-mg dose groups, there was no meaningful difference from placebo indicative of an increase in next-day residual sleepiness groups on any assessment at any time relative to waketime on any treatment day. Slight differences from placebo were observed in the 10-mg dose group at timepoints within 2 hours after waketime on the KSS on Day 2 through Day 4. In the 25-mg dose group, the increase in next-day residual sleepiness was more consistent and slightly larger than in the 10-mg dose group. The effect was again, limited to timepoints within 2 hours after waketime, but was observed on the KSS and to some extent on PVT Lapses and PVT Mean RRT. The differences from placebo were most consistent and larger on Day 2 and Day 15, compared with all other treatment days. In the 50-mg and 75-mg dose groups, there were consistent and relatively large differences from placebo on all assessments of sleepiness. These differences were of greater magnitude at timepoints within 2 hours after waketime, but were still observed at 4 hours and 8 hours after waketime, particularly on the PVT Mean RRT. By 12 hours after waketime, there were no differences from placebo on any measures of sleepiness in any dose group on any day. For

dose groups in which next-day residual sleepiness was observed (ie, 10 mg and higher), sleepiness was relatively greater on Days 2 to 4 vs Days 5 to 15. This pattern of lessening sleepiness across treatment days was generally observed, despite accumulation of compound A in plasma.

[0204] None of the items on the Waketime Questionnaire indicated a systematic pattern of changes in nighttime sleep in any dose group or the placebo group, with the exception that the Quality of Sleep scale showed a trend for more subjects in both the placebo and compound A groups to report "restless" or "very restless" sleep on Day 2 and especially on Day 15, relative to other days.

Pharmacokinetic-Pharmacodynamics

[0205] For the PK-PD exploratory analysis of next-day residual sleepiness, population PK model-derived compound A plasma concentrations at 8, 9, and 10 hours following administration on the evening of Day 1 were related to change from baseline on the KSS, PVT Lapses, and DSST at 15 minutes, 1 hour, and 2 hours after waketime on the morning of Day 2, respectively. At all timepoints, both KSS and the PVT Lapses were observed to increase more from baseline with increasing compound A concentrations. Concentrations below 30 ng/mL (which occur at doses below 25 mg) after 9-10 hours postdose, which correspond to the 1-2 hours after morning awakening, were associated with minimal or no change from baseline on the KSS, PVT Lapses, or DSST.

Example 3

Crossover Study of Ralative Bioavailability of Tablet versus Capsule Formulation (005 Study)

[0206] Single-center, open-label, randomized crossover study was conducted to evaluate, in healthy adult subjects, the bioavailability of single solid oral doses of compound A in tablet formulation relative to single oral doses of compound A in capsule formulation at 2.5, 10, and 25 mg. Another objective of the study was to evaluate the safety and tolerability of tablet formulations of compound A at 2.5, 10, and 25 mg in healthy adult subjects. Approximately 36 subjects were randomly assigned to one of three cohorts (approximately 12 subjects per cohort) and received both a single dose of compound A as a capsule formulation and a single dose of compound A as a tablet formulation, in random sequence, in a 1:1 ratio. The doses were 2.5 mg, 10 mg, and 25 mg.

[0207] The study had two phases: Prerandomization and Randomization. The Prerandomization Phase lasted for up to 21 days and included a Screening Period and Baseline Period A, during which eligibility was established and baseline assessments before dosing of the first formulation occurred. The Randomization Phase consisted of two Treatment Periods (A and B), separated by Baseline Period B. On the first day of Treatment Period A, subjects received a single oral dose of the first formulation. After the

first formulation dose, pharmacokinetic (PK) and safety assessments were obtained throughout Treatment Period A, and subjects completed a 20-day washout. Before dosing of the second formulation, subjects completed Baseline Period B assessments. Subjects then proceeded to Treatment Period B and received a single oral dose of the second formulation. Pharmacokinetic and safety assessments were obtained throughout Treatment Period B.

[0208] Blood samples for the determination of plasma concentrations of compound A were collected at the following times: Treatment Period A (Day 1 to Day 15): before and after dosing at 0.5 (30 minutes), 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 120, 168, 240, and 336 hours; Treatment Period B (Day 22 to Day 36): before and after dosing at 0.5 (30 minutes), 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 120, 168, 240, and 336 hours.

[0209] Plasma concentrations of compound A were measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay.

[0210] Noncompartmental methods were used to calculate the following plasma PK parameters for compound A: area under the plasma concentration-time curve from time zero to 8 hours after dosing (AUC(0-8)), area under the plasma concentration-time curve from time zero to 72 hours after dosing (AUC(0-72)), area under the plasma concentration-time curve from time zero to time of the last quantifiable concentration (AUC(0-t)), area under the plasma concentration-time curve from time zero extrapolated to time infinity (AUC(0-inf)), maximum observed plasma drug concentration (Cmax), terminal elimination half-life (t1/2), absorption lag time (tlag), and time to reach the maximum (peak) plasma concentration after drug administration (tmax). The primary PK parameters were AUC(0-inf) and Cmax. The individual PK parameters of compound A were presented in the data listings by formulation (tablet or capsule) and dose (2.5, 10, or 25 mg). The PK parameters except tmax and tlag were summarized by formulation and dose using descriptive statistics: number of subjects, mean, SD, coefficient of variation, geometric mean, median, minimum, and maximum. The parameters tmax and tlag were summarized by formulation and dose using the following descriptive statistics: median, minimum, maximum, and the 90% confidence interval (CI) of the median point estimate. The natural log (ln)-transformed PK parameters for compound A (AUC(0-inf), Cmax, AUC(0-8), AUC(0-72), and AUC(0-t)) were compared separately by dose with a mixed-effects model with sequence, treatment period, and formulation as fixed effects and subjects nested within sequence as a random effect. The ratio of geometric least squares (LS) means (tablet formulation as test/capsule formulation as reference) and corresponding 90% CI were computed by exponentiation of the LS mean difference and corresponding 90% CI.

[0211] PK parameters of compound A were summarized in Table 4.

[0212] Table 4 PK parameters of compound A (Tablet versus Capsule)

	2.5mg		10mg		25mg	
	Tablet	Capsule	Tablet	Capsule	Tablet	Capsule
N	12	12	12	12	15	13
AUC(0-8) (ng*h/mL) Mean(SD)	47.1(16.3)	45.5(14.8)	178(62.2)	164(44.3)	386(67.0)	358(88.7)
AUC(0-72) (ng*h/mL) Mean(SD)	84.3(30.8)	85.1(27.4)	341(135)	372(114)	795(199)	803(234)
AUC(0-t) (ng*h/mL) Mean(SD)	93.2(40.0)	94.9(34.6)	455(214)	511(222)	1070(350)	1080(368)
AUC(0-inf) (ng*h/mL) Mean(SD)	101(42.9)	103(39.3)	472(222)	531(234)	1100(366)	1110(379)
Cmax (ng/mL) Mean(SD)	18.0(7.50)	15.9(5.93)	58.1(24.0)	49.0(16.5)	120(26.7)	105(33.0)
tmax (h) (median)	1.00	1.00	1.00	1.50	1.00	1.50
t1/2 (h) Mean(SD)	35.1(14.6)	36.8(17.2)	59.5(19.0)	57.0(22.0)	57.6(18.7)	57.4(20.5)
C8 (ng/mL) Mean(SD)	1.75(0.610)	1.84(0.618)	7.44(3.23)	8.90(2.70)	17.6(6.11)	19.9(7.62)

[0213] Differences between formulations (Treatment A [tablet] compared to Treatment B [capsule]) in AUC(0-8), AUC(0-72), AUC(0-t), and AUC(0-inf) across all dose levels were each less than 13%. Differences between the tablet and capsule formulations in Cmax across all dose levels were each less than 16%. The median tmax was observed at 1 to 1.5 hours after administration of both the tablet and capsule formulations across all dose levels. A trend of a 30-minute delay in median tmax for the capsule formulation (Treatment B) compared to the tablet formulation (Treatment A) was observed at higher doses. There was no observed absorption lag in either formulation at any dose level.

[0214] Overall, the results indicate that both the rate and extent of compound A absorption after tablet administration are comparable to the reference capsule for all strengths tested. Variability in the derived PK parameters was also similar for the tablet compared to capsule treatments. These results support the conclusion that the relative bioavailability of the tablet at strengths of 2.5, 10, and 25 mg is similar to corresponding strengths of the capsule. Thus, clinical transition to the tablet formulation can be made

without dose adjustment relative to the capsule.

Example 4 (201 Study)

[0215] This was a multi-center, randomized, double-blind, adaptive design, dose-response study in subjects with insomnia. Subjects were randomized to 1 of 6 doses of compound A (1 mg, 2.5 mg, 5 mg, 10 mg, 15 mg and 25 mg) or placebo.

[0216] The primary objectives of the study were to:

1. Identify a dose or doses of compound A that maximize efficacy and minimize next-day residual sleepiness in subjects with chronic insomnia at the beginning of treatment by comparing the effect of 6 doses of compound A with placebo using a composite utility function incorporating change from baseline on sleep efficiency (SE) and change from baseline on the Karolinska Sleepiness Scale (KSS) at 1 hour after morning waketime after dosing on Day 2 and Day 3.
2. Compare the effect of 6 doses of compound A with placebo on the KSS at 1 hour after morning waketime on Day 15 and Day 16 in subjects with chronic insomnia, in order to confirm that the dose or doses that maximize efficacy and minimize next-day residual sleepiness at the beginning of treatment are not associated with treatment unacceptable levels of next-day residual sleepiness at the end of treatment.

[0217] The additional objectives of the study were to evaluate:

1. Efficacy at beginning of treatment:

Overall: Compare each dose level of compound A with placebo on change from mean SE at baseline to mean SE after dosing on Day 1 and Day 2

Sleep induction: Compare each dose level of compound A with placebo on change from mean latency to persistent sleep (LPS) at baseline to mean LPS after dosing on Day 1 and Day 2

Sleep maintenance: Compare each dose level of compound A with placebo on change from mean wakefulness after sleep onset (WASO) at baseline to mean WASO after dosing on Day 1 and Day 2

2. Efficacy at end of treatment: Overall: Compare each dose level of compound A with placebo on change from mean SE at baseline to mean SE after dosing on Day 14 and Day 15

Sleep induction: Compare each dose level of compound A with placebo on change from mean LPS at baseline to mean LPS after dosing on Day 14 and Day 15

Sleep maintenance: Compare each dose level of compound A with placebo on change from mean WASO at baseline to mean WASO after dosing on Day 14 and Day 15

3. Potential habituation of efficacy from beginning to end of treatment:

Overall: Compare each dose level of compound A with placebo on change from mean SE at baseline to mean SE after dosing on Day 1 and Day 2 versus change from mean SE at baseline to mean SE after dosing on Day 14 and Day 15

Sleep induction: Compare each dose level of compound A with placebo on change from mean LPS at baseline to mean LPS after dosing on Day 1 and Day 2 versus change from mean LPS at baseline to mean LPS after dosing on Day 14 and Day 15
Sleep maintenance: Compare each dose level of compound A with placebo on change from mean WASO at baseline to mean WASO after dosing on Day 1 and Day 2 versus change from mean WASO at baseline to mean WASO after dosing on Day 14 and Day 15

[0218] A total of 616 subjects were screened, and 291 of these subjects were randomized to the study; 56 to placebo, 32 to 1 mg, 27 to 2.5 mg, 38 to 5 mg, 32 to 10 mg, 56 to 15 mg and 50 to 25 mg. 291 subjects were contained in the Full Analysis Set, Safety Analysis Set, and PD Analysis Set. There were 222 subjects in the active dose groups (roughly equal over all doses, 90 to 100%) and 51 (91.1%) in the placebo group who completed the planned treatment regimen.

[0219] The study had 2 phases: Prerandomization and Randomization. The Prerandomization Phase lasted up to 21 days and consisted of a Screening Period (Days –21 to –2) and a Baseline Period (Day –1). After the Baseline Period, all eligible subjects were randomized in a double-blind manner to receive compound A or placebo for 15 nights during the Treatment Period (Days 1 to 15). All subjects then received placebo in a single-blind manner, for 2 nights (Days 16 to 17) during the Rebound Insomnia Assessment Period (Days 16 to 18). Subjects did not receive study drug during the Follow-up Period (Days 19 to 30). All subjects came to the clinic for screening procedures. During the Screening Period, subjects completed the Sleep Diary each day. Polysomnographic sleep was measured during the Screening Period on 2 consecutive nights between Day –9 and Day –3. The 8-hour polysomnograms (PSGs) were started at the median habitual bedtime calculated from responses on the Sleep Diary, which were completed for 7 days before the first PSG night. These recordings served as both eligibility screening PSGs and as Baseline PSGs. Subjects could leave the clinic between the screening/Baseline PSG nights.

[0220] All subjects returned to the clinic on Day –1 for Baseline Period procedures. They remained in the clinic until Day 3. Morning assessments on Day 1 provided the Baseline values for the KSS, the Digit Symbol Substitution Test (DSST), and the Reaction Time Index (RTI). Assessments at 6 hours after waketime provided the Baseline values for the Waking Function Battery (WFB), and the Profile of Mood States-Brief (POMS-B). Subjects were then randomized to receive 1 of 6 doses of compound A or placebo for the next 15 days. Study drugs were tablets containing compound A-matched placebo or compound A of 1 mg, 2.5 mg, 5 mg, or 10 mg and to be ingested 30 minutes before the median habitual bedtime calculated from their Sleep Diary responses during the Screening Period. An 8-hour PSG, starting at the same bedtime as used for the screening and Baseline PSG nights, was recorded on the first 2 treatment nights (Days 1 and 2). The Sleep Diary continued to be completed each day in the clinic, and

assessments of insomnia severity (ISI), next-day residual effects (KSS, DSST, and RTI) were conducted while subjects were in the clinic. On specified study days, plasma concentrations of compound A were assessed while subjects were in the clinic in the morning after awakening and at trough just before dosing.

[0221] Subjects continued to take compound A or placebo 30 minutes before their anticipated, self-selected bedtime and continued to complete the Sleep Diary each day while at home during the Treatment Period. On Day 14 of the Treatment Period, subjects returned to the clinic. They remained in the clinic for 4 nights and the intervening days until Day 18. Eight-hour PSGs were recorded each night in the clinic, to start at the median habitual bedtime calculated from responses on the Sleep Diary completed on Days 3 to 13. The Sleep Diary continued to be completed each day in the clinic, and the ISI, KSS, DSST, RTI, were administered at prespecified time points during the daytime hours.

[0222] After the Treatment Period ended, all subjects received placebo in a single-blind manner on the final 2 nights spent in the clinic (Days 16 and 17). On these 2 nights, 8-hour PSGs starting on the same bedtime as Days 14 and 15 were recorded to assess for rebound insomnia (Rebound Insomnia Assessment Period).

[0223] During the Treatment period, blood samples for plasma concentrations of compound A were obtained within 30 minutes predose each night (except on Day 1) in the clinic and within 1 hour of morning waketime following each night spent in the clinic. Plasma concentrations of compound A were measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay.

[0224] The KSS was used to measure next-day residual effects at prespecified timepoints. In this test, subjects rate their sleepiness using the KSS, a 9-point verbally anchored scale. Categories and scores range from "extremely alert" (score = l), "alert" (3), "neither alert nor sleepy" (5), "sleepy-but no difficulty remaining awake" (7), to "extremely sleepy-fighting sleep" (9). The key outcome parameter for the KSS was the score from 1 to 9.

[0225] All statistical tests were based on the 5% level of significance, except for the Bayesian methods used for the primary endpoint. Details of statistical methods and analyses were specified in the Statistical Analysis Plan (SAP) and body of the clinical study report.

[0226] The Safety Analysis Set was the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment. The Full Analysis Set (FAS) was the group of randomized subjects who received at least 1 dose of study drug and had at least 1 postdose primary efficacy measurement. The PK Analysis Set was the group of randomized subjects who received at least 1 dose of

compound A and had at least 1 quantifiable compound A concentration. The PD Analysis Set was the group of subjects who had sufficient PD data to derive at least 1 PD parameter. The PK/PD Analysis Set was the group of randomized subjects who received at least 1 dose of compound A or placebo, and had at least 1 quantifiable concentration of compound A concentration (active subjects), and at least 1 postdose PD assessment.

[0227] A difference from placebo of at least 6% in the change from baseline of mean SE at Day 1 and Day 2 was considered the minimum clinically significant difference (CSD).

[0228] Each dose was assessed for next-day residual sleepiness using the KSS. A mean difference of change from baseline in KSS at 1 hour after waketime on Day 2 and Day 3 of less than 4 units was incorporated into the utility function. A dose of compound A was considered to have an acceptable KSS at Day 15 and Day 16 if the mean difference of change from baseline in KSS at 1 hour after waketime on Day 15 and Day 16 at this dose relative to placebo was less than 4 units. Operationally, acceptable KSS for Day15 and Day 16 was defined as the lower boundary of a 90% confidence interval (CI) being less than 4 units (of the mean difference of change from baseline in KSS at 1 hour after waketime at this dose relative to placebo).

[0229] Utility Function: The utility at a dose was a function of both SE and KSS, constructed by specifying the 1-dimensional component for each endpoint and then combining them multiplicatively. Sufficient utility was defined as a Pr(Utility >1).

[0230] Maximum Utility Dose (dUmax): The dose that produced the maximum utility score, ie, the best combination of efficacy and residual sleepiness as judged by the utility above.

[0231] The PK/PD Analysis Set was used to evaluate relationships between compound A concentrations and selected PD parameters. The relationships between exposure to compound A and selected PD endpoints (eg. KSS, DSST, RTI) were explored graphically and could be followed by population PK/PD modeling. The relationship between plasma concentrations of compound A at predose (trough), and within 1 hour after morning waketime, and selected PD parameters, was analyzed using Nonmem version 7.2 or later.

Results

[0232] The summary statistics for change from baseline in SE are presented in Table 5. All compound All doses were statistically significant against placebo for the change from baseline of Mean of Days 1/2. Doses compound A 2.5 mg and above were statistically significant against placebo for the change from

baseline of Mean of Days 14/15. There was no statistical evidence of an increase or decrease in SE for the change from baseline of the mean of Days 1/2 compared to Days 14/15, indicating no loss of treatment effect.

[0233] In Table 5, "Baseline" was defined as the mean of the screening PSG 1 and 2, within -9 to -3 days of randomization. "LS Means Diff" refers to the differences between LS Means of Placebo and each compound A dose, "95% CI" means to 95% CI of LS Means Diff. "p-value" was analyzed using analysis of covariance (ANCOVA) with baseline as a covariate.

[0234] Table 5 Summary Statistics for Change from Baseline in SE (%)

	Placebo	Compound A					
		1 mg	2.5 mg	5 mg	10 mg	15 mg	25 mg
Baseline							
N	56	32	27	38	32	56	50
Mean	66.5	61.7	61.3	63.1	65.1	65.1	66.6
SD	9.25	12.30	14.7	12.48	11.75	12.19	10.94
(A) Change from Baseline of Mean of Days 1 & 2							
N	56	32	27	38	32	56	50
Mean	12.6	21.1	21.3	21.2	21.9	23.8	22.7
SD	12.18	11.21	14.1	13.20	11.92	12.22	10.98
LS Means Diff		4.57	4.44	5.74	8.09	10.06	10.13
95% CI		1.19, 7.94	0.86, 8.01	2.54, 8.93	4.73, 11.45	7.20, 12.93	7.18, 13.08
p-value		0.0083	0.0151	0.0005	<0.0001	<0.0001	<0.0001
(B) Change from Baseline of Mean of Days 14 & 15							
N	52	31	27	37	31	54	46
Mean	12.3	17.5	20.7	21.0	21.7	21.2	21.4
SD	10.53	13.62	14.66	15.43	13.37	12.92	9.96
LS Means Diff		0.34	3.94	5.76	7.78	7.89	8.87
95% CI		-3.22, 3.90	0.22, 7.66	2.40, 9.12	4.24, 11.32	4.86, 10.92	5.72, 12.02
p-value		0.8505	0.038	0.0008	<0.0001	<0.0001	<0.0001
(B)-(A) (Potential Habituation Effect)							
N	52	31	27	37	31	54	46
Mean	-0.1	-4.0	-0.5	0.1	-0.7	-2.3	-2.1
SD	7.19	8.19	10.51	6.89	6.88	6.60	5.39
LS Means Diff		-3.3	0.3	1.0	0.3	-1.3	-1.1
95% CI		-6.5, 0.0	-3.1, 3.7	-2.1, 4.0	-3.0, 3.5	-4.1, 1.4	-4.0, 1.8
p-value		0.0506	0.8790	0.5441	0.8651	0.3438	0.4493

[0235] The summary statistics for change from baseline in KSS at 1 hour post waketime are presented in Table 6. The LS mean differences between placebo and compound A 1 mg to 15 mg were not statistically significant on the Mean of Days 2/3. Only the LS mean difference between placebo and compound A 25 mg was statistically significant on the Mean of Days 2/3 (LS mean difference 0.47; P = 0.0393), indicating that subjects rated themselves worse than placebo subjects. This result was similar for the

mean of Days 15/16 at 1 hour post waketime. The 2 hour post waketime assessments for both the mean of Days 2/3 showed statistical significance for compound A 15 mg and 25 mg, while the mean of Days 15/16 was statistically significant for compound A 25 mg. No statistically significant differences were seen at the 15 min post waketime timepoints.

[0236] In Table 6, "Baseline" was defined as the time-matched value on Day 1. "LS Means Diff" refers to the differences between LS Means of Placebo and each compound A dose, "95% CI" means to 95% CI of LS Means Diff. "p-value" was analyzed using analysis of covariance (ANCOVA) with baseline as a covariate.

[0237] Table 6 Summary Statistics for Change from Baseline in KSS, 1 hour post waketime

	Placebo	Compound A					
		1 mg	2.5 mg	5 mg	10 mg	15 mg	25 mg
Baseline							
N	55	32	27	38	32	56	50
Mean	4.0	4.0	4.0	4.3	3.8	4.1	3.7
SD	2.01	1.82	1.59	1.61	1.77	1.91	1.76
Median	4.0	4.0	4.0	4.0	3.5	4.0	3.0
Min, Max	1.0, 9.0	1.0, 8.0	1.0, 8.0	2.0, 8.0	1.0, 8.0	1.0, 8.0	1.0, 8.0
(A) Change from Baseline of Mean of Days 2 & 3							
N	55	32	27	38	32	56	50
Mean	-0.2	-0.2	-0.3	-0.1	0.0	0.1	0.4
SD	1.27	0.97	1.00	1.54	1.51	1.59	1.36
LS Means Diff		0.02	-0.06	0.20	0.16	0.32	0.47
95% CI		-0.49, 0.54	-0.61, 0.48	-0.29, 0.68	-0.36, 0.67	-0.11, 0.76	0.02, 0.93
p-value		0.9290	0.8177	0.4304	0.5485	0.1471	0.0393
(B) Change from Baseline of Mean of Days 15 & 16							
N	51	31	27	37	31	54	46
Mean	-0.2	0.3	-0.1	0.1	-0.1	0.1	0.6
SD	1.43	1.22	1.12	1.39	1.57	1.72	1.51
LS Means Diff		0.51	0.13	0.43	0.01	0.38	0.68
95% CI		-0.03, 1.06	-0.44, 0.70	-0.09, 0.94	-0.54, 0.55	-0.08, 0.85	0.19, 1.17
p-value		0.0651	0.6490	0.1059	0.9818	0.1071	0.0063

[0238] The summary statistics for change from baseline in LPS are presented in Table 7. As a result of a non-normal distribution, the data were log–transformed and analyzed using ANCOVA as pre-specified. The geometric mean ratio between placebo and compound A 1 mg was not statistically significant for the change from baseline of Mean of Days 1/2. The geometric mean ratios between placebo and all other active compound A showed evidence of statistical significance for the change from baseline of Mean of Days 1/2. Similar results were shown for the change from baseline of Mean of Days 14/15.
Compound A 10 mg showed a statistical difference of change from baseline of the mean of Days 1/2 compared to Days 14/15, showing further improvement in LPS over time. On all other doses except compound A 10 mg, there was no other statistical evidence of an increase or decrease in LPS for the change from baseline of the mean of Days 1/2 compared to Days 14/15.

[0239] In Table 7, "Baseline" was defined as the mean of the screening PSG 1 and 2, within -9 to -3 days of randomization. "p-value" was analyzed using analysis of covariance (ANCOVA) with baseline as a covariate.

[0240] Table 7 Summary Statistics for Change from Baseline in LPS (min)

	Placebo	Compound A					
		1 mg	2.5 mg	5 mg	10 mg	15 mg	25 mg
Baseline							
N	56	32	27	38	32	56	50
Mean	58.8	69.9	73.0	70.4	67.9	72.5	64.3
SD	30.58	39.09	50.94	42.66	52.43	36.12	45.91
Median	55.8	68.60	68.5	61.4	52.3	68.9	52.1
Min, Max	7.3, 150.3	17.0, 160.8	3.3, 187.8	5.8, 164.3	11.3, 218.0	5.5, 188.3	2.8, 217.3
(A) Change from Baseline of Mean of Days 1 & 2							
N	56	32	27	38	32	56	50
Mean	-22.9	-42.9	-52.7	-47.7	-46.8	-51.6	-50.2
SD	44.46	41.86	50.15	39.39	46.11	36.73	43.14
Median	-29.9	-42.0	-47.8	-37.4	-26.5	-49.1	-42.6
Min, Max	-126.3, 174.8	-136.0, 71.0	-173.3, 18.3	-140.5, 13.3	-200.5, 3.0	-176.0, 26.8	-199.0, 18.8
Geometric Mean Ratio (compound A/placebo)		0.77	0.55	0.60	0.54	0.52	0.39
95% CI		0.54, 1.09	0.38, 0.80	0.43, 0.83	0.38, 0.76	0.38, 0.70	0.29, 0.54
p-value		0.1407	0.0018	0.0025	0.0006	<0.0001	<0.0001
(B) Change from Baseline of Mean of Days 14 & 15							
N	52	31	27	37	31	54	46
Mean	-22.4	-41.2	-54.2	-51.7	-56.1	-51.6	-50.8
SD	29.04	34.62	44.92	41.99	45.55	36.73	40.16
Median	-23.9	-34.3	-48.5	-47.3	-39.5	-49.1	-41.6
Min, Max	-79.0, 75.3	-107.0, 27.8	-165.0, -1.0	-130.8, 28.5	-178.5, 2.3	-176.0, 26.8	-200.0, 1.3
Geometric Mean Ratio (compound A /placebo)		0.73	0.49	0.47	0.32	0.41	0.34
95% CI		0.49, 1.08	0.33, 0.75	0.32, 0.69	0.21, 0.47	0.29, 0.57	0.24, 0.48
p-value		0.1158	0.001	0.0001	<0.0001	<0.0001	<0.0001
(B)-(A) (Potential Habituation Effect)							
N	52	31	27	37	31	54	46
Mean	0.57	2.7	-1.5	-4.6	-7.9	-1.1	1.4
SD	40.85	24.33	22.12	22.34	17.41	24.57	12.05
Median	3.6	4.0	-0.8	-3.8	-5.5	-3.60	-0.5
Min, Max	-234.0, 66.8	-43.3, 68.0	-41.3, 62.5	-90.0, 38.8	-75.8, 22.0	-49.5, 74.8	-32.0, 35.5
Geometric Mean Ratio (compound A/placebo)		0.93	0.90	0.77	0.60	0.76	0.89
95% CI		0.60, 1.44	0.57, 1.41	0.51, 1.17	0.39, 0.93	0.52, 1.10	0.60, 1.31
p-value		0.7491	0.6354	0.2245	0.0216	0.1450	0.5493

[0241] The summary statistics for change from baseline in WASO are presented in Table 8. All compound A doses of 10 mg and above were statistically significant against placebo for the change from baseline of the mean of Days 1/2. Doses compound A 15 mg and above were statistically significant against placebo for the change from baseline of the mean of Days 14/15. There was no statistical evidence of an increase or decrease in WASO between the change from baseline of the mean of Days 1/2 compared to Days 14/15.

[0242] In Table 8, "Baseline" was defined as the mean of the screening PSG 1 and 2, within -9 to -3 days of randomization. "LS Means Diff" refers to the differences between LS Means of Placebo and each compound A dose, "95% CI" means to 95% CI of LS Means Diff. "p-value" was analyzed using analysis of covariance (ANCOVA) with baseline as a covariate.

[0243] Table 8 Summary Statistics for Change from Baseline in WASO (min)

	Placebo	Compound A					
		1 mg	2.5 mg	5 mg	10 mg	15 mg	25 mg
Baseline							
N	56	32	27	38	32	56	50
Mean	108.9	121.2	119.8	113.7	103.5	103.3	103.0
SD	37.52	49.59	51.18	47.96	34.35	42.90	42.55
(A) Change from Baseline of Mean of Days 1 & 2							
N	56	32	27	38	32	56	50
Mean	-40.8	-60.9	-51.1	-55.6	-56.7	-66.1	-62.3
SD	46.18	36.69	46.37	52.28	35.45	44.25	41.18
LS Means Diff		-11.1	-2.3	-11.3	-19.8	-29.3	-25.8
95% CI		-24.5, 2.3	-16.5, 11.9	-23.9, 1.4	-33.2, -6.4	-40.8, -17.9	-37.6, -14.1
p-value		0.1050	0.7501	0.0818	0.0038	<0.0001	<0.0001
(B) Change from Baseline of Mean of Days 14 & 15							
N	52	31	27	37	31	54	46
Mean	-38.2	-43.6	-48.9	-52.2	-48.5	-53.4	-53.9
SD	45.35	54.27	55.86	59.22	40.17	46.97	42.51
LS Means Diff		5.7	-2.3	-10.7	-14.7	-20.8	-21.5
95% CI		-9.6, 21.0	-18.3, 13.6	-25.1, 3.8	-30.0, 0.5	-33.9,-7.7	-35.1, -7.9
p-value		0.4642	0.7754	0.1461	0.0581	0.0019	0.0020
(B)-(A) (Potential Habituation Effect)							
N	52	31	27	37	31	54	46
Mean	6.0	18.0	2.2	2.7	9.3	11.8	9.3
SD	31.42	34.30	44.05	29.73	25.89	26.19	23.12
LS Means Diff		13.2	-2.9	-2.9	2.8	5.2	2.7
95% CI		-0.3, 26.7	-17.0, 11.2	-15.7, 9.8	-10.6, 16.3	-6.4, 16.7	-9.3, 14.7
p-value		0.0547	0.6852	0.6498	0.6796	0.3792	0.6635

[0244] The PK of compound A was best described by a 2-compartment model with elimination from the central compartment. Apparent clearance of compound A was independent of dose and time, indicating linearity in PK. Measures of the PD effects of compound A included KSS, RTI, DSST, the WFB (RTI, Rapid Visual Processing [RVP], and Spatial Span [SSP]), POMS, melatonin levels, and the DLMO. Due to high variability and non-normal distribution in change from baseline of LPS, it was not possible to reliably model the concentration-response relationship between compound A PK parameters and LPS. Nonetheless, higher plasma concentrations of compound A were associated with larger decreases in LPS, up to approximately 10 ng/mL. This finding was consistent with the efficacy results, where LPS was decreased at doses of 2.5 mg and higher. Above this concentration, the relationship appeared to reach an asymptote, suggesting that there was no apparent additional benefit of higher compound A concentrations with regard to sleep onset . When modeled, WASO data were best described by log-linear relationships with the maximum observed concentration (Cmax). The exposure-response relationship for WASO showed a log-linear relationship with Cmax, such that higher concentrations of compound A at Cmax were associated with larger decreases in WASO. PK/PD analyses for next-day residual sleepiness assessments (KSS, DSST, and RTI) did not show any apparent relationship with time-matched compound A plasma concentrations. However, subjects whose compound A plasma concentrations were greater than 20 ng/mL at 1 hour after waking had slightly greater increases on the KSS and a higher incidence of AEs of somnolence. This concentration is predicted to be achieved by most subjects receiving doses greater than 10 mg.

Example 5 (Formulation)

[0245] Capsules used for Example 1, 2, and 3 consist of size 2 hypromellose capsules containing 1 mg, 2.5 mg, 10mg, or 50mg each of compound A drug substance. Compound A 25 mg capsules which consist of size 2 hypromellose capsules containing 25 mg compound A drug substance are also prepared only for the dissolution evaluation. The placebo consists of size 2 hypromellose capsules containing 10 mg of microcrystalline cellulose.

[0246] The components and compositions of tablets used for Examples 3 and 4 are shown in Table 9

[0247] Table 9 Components and Compositions of Compound A Tablets

Component	Strength				
	1mg	2.5mg	5mg	10mg	25mg
Core tablet					
(Internal phase)					
compound A	1.0	2.5	5.0	10.0	25.0
Lactose monohydrate	97.88	96.38	93.88	88.88	222.2
Low-substituted hydroxypropyl cellulose	10.8	10.8	10.8	10.8	27.0
Hydroxypropyl cellulose	3.6	3.6	3.6	3.6	9.0
(External phase)					
Low-substituted hydroxypropyl cellulose	6.0	6.0	6.0	6.0	15.0
Magnesium stearate	0.72	0.72	0.72	0.72	1.8
Film-coated tablet					
Opadry RED	9.0	9.0	9.0	9.0	15.0
Total Weight (mg)	129	129	129	129	315

[0248] Conventional wet granulation method was used for the manufacturing for compound A film-coated tablets. The compound A film-coated tablets were manufactured through mixing, wet-granulation, drying, sizing, lubrication, tableting and film-coating process. Compound A, lactose monohydrate and low-substituted hydroxypropyl cellulose were mixed using mixer. The mixture was wet-granulated using mixer with gradually adding appropriate amount of the aqueous solution of hydroxypropyl cellulose. The wet granules were dried using a dryer. The dried granules are passed through a 1.0 mm screen using a screening mill. Low-substituted hydroxypropyl cellulose and magnesium stearate are weighed depending on the yield of granules. The granules, low-substituted hydroxypropyl cellulose and magnesium stearate are lubricated together in a mixer. The lubricated granules equivalent to one tablet were compressed into bi-convex tablets using a tablet press. The core tablets were coated using a coating machine with spraying the aqueous suspension of Opadry RED.

Test Example

[0249] The dissolution test for the compound A capsules and tablets prepared in the Example 5 was executed using Apparatus 2 (paddle apparatus) according to JP 6.10, USP <711>, and Ph.Eur. 2.9.3. The capsules and tablets were tested in 900 mL of 0.1 mol/L hydrochloric acid containing 0.5% polysorbate 80 at the paddle rotation speed of 75 rpm (Condition I). In addition, the tablets were tested in 900 mL of 0.1 mol/L hydrochloric acid at the paddle rotation speed of 50 rpm (Condition II). A helical wire sinker was used in the tests for capsules. Aliquots of media were withdrawn through a filter (pore size: 0.45 μm) at the prescribed time point to make sample solutions. The standard solutions were prepared to have

compound A concentrations corresponding to those of the sample solutions at nominal concentration level. The amount of compound A released was determined chromatographically compared to the standard solution. The dissolution conditions and HPLC conditions are provided in Table10. Testing was carried out on 6 capsules/tablets and their average value was indicated in each case. Dissolution profiles of compound A 1 mg and 50 mg capsules obtained in Condition I are presented in Fig.1 and Table 11. Dissolution profiles of compound A 1 mg, 2.5 mg, 5 mg, 10 mg and 25 mg tablets obtained in Condition II are presented in Fig.2 and Table 12. Comparative dissolution profiles between compound A capsules and tablets obtained in Condition I are presented in Fig 3 and Table 13. The difference between capsules and tablets was observed in the dissolution profiles, which was caused by the lag time for the disintegration of capsules.

[0250] Table 10 Dissolution Conditions and HPLC Conditions

Dissolution Conditions		
Parameter	**Condition I**	**Condition II**
Apparatus	Apparatus 2 (paddle apparatus) in accordance with JP 6.10, USP <711>, and Ph. Eur. 2.9.3	
Paddle rotation speed	75 rpm	50 rpm
Dissolution medium	0.1 mol/L hydrochloric acid containing 0.5% polysorbate 80	0.1 mol/L hydrochloric acid
Medium volume	900 mL	
Medium temperature	37 °C	
Sinker	Compound A capsules: helical wire sinkers Compound A tablets: N/A	
Sampling time	Compound A capsules:5, 10, 15, 30, 45 and 60 minutes Compound A tablets: "5, 10, 15, and 30 minutes" or "5, 10, 15, 30, and 45 minutes"	
HPLC Conditions		
Parameter	**Condition I**	**Condition II**
Detection Wavelength	283 nm	
Column	4.6-mm × 7.5-cm column that contains 3.5-μm packing L1 (USP)	4.6-mm × 7.5-cm column that contains 3-μm packing L1 (USP)
Column temperature	A constant temperature of about 40 °C	
Mobile phase	A: Water/70% perchloric acid (1000:1, v/v) B: Acetonitrile/70% perchloric acid (1000:1, v/v) Isocratic flow: A=60% B=40%	Water/acetonitrile/70% perchloric acid (550:450:1, v/v/v)
Flow rate	1.0 mL/min	1.2 mL/min
Injection volume	10 μL	50 μL
Sample cooler temperature	25 °C	
Measurement time	5 minutes after injection	

[0251] Table 11 Dissolution Rates of Compound A 1 mg and 50 mg Capsules Obtained in Condition I

Samples	Dissolution rate (%)					
	5 min	10 min	15 min	30 min	45 min	60 min
Compound A 1 mg capsules	0.0	50.0	86.0	96.4	96.0	95.9
Compound A 50 mg capsules	0.0	1.4	10.6	69.2	94.3	96.9

[0252] Table 12 Dissolution Rates of Compound A 1 mg, 2.5 mg, 5 mg, 10 mg, and 25 mg Tablets Obtained in Condition II

Samples	Dissolution rate (%)					
	5 min	10 min	15 min	30 min	45 min	60 min
Compound A 1 mg tablets	77.0	99.7	100.5	100.6	100.4	
Compound A 2.5 mg tablets	66.1	100.2	101.7	101.9	102.0	
Compound A 5 mg tablets	58.0	96.1	99.7	100.3	100.2	
Compound A 10 mg tablets	52.2	96.2	100.6	100.9	100.9	
Compound A 25 mg tablets	51.7	89.0	97.5	100.4	100.5	

[0253] Table 13 Dissolution Rates of Compound A Capsules and Tablets Obtained in Condition I

Samples	Dissolution rate (%)					
	5 min	10 min	15 min	30 min	45 min	60 min
Compound A 1 mg capsules	0.0	50.0	86.0	96.4	96.0	95.9
Compound A 2.5 mg capsules	0.0	54.6	88.5	98.4	98.8	98.5
Compound A 10 mg capsules	0.0	41.4	80.7	96.2	96.6	96.5
Compound A 25 mg capsules	0.1	50.7	87.7	99.0	99.2	99.3
Compound A 50 mg capsules	0.0	1.4	10.6	69.2	94.3	96.9
Compound A 1 mg tablets	87.7	97.7	99.7	99.9		
Compound A 25 mg tablets	83.3	100.0	102.0	102.3		

CLAIMS

What is claimed is;

1. A method of treating insomnia, comprising administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose to achieve a mean Cmax of from about 3.0 ng/ml to about 7.2 ng/ml for each 1 mg of compound A after administration to human subjects.

2. The method of claim 1, wherein said single daily dose ranges from about 1 mg to about 15 mg.

3. The method of claim 1, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves a mean Cmax within the range of about 80% to about 125% of 5.3 ng/ml.

4. The method of claim 1, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves a mean Cmax within the range of about 80% to about 125% of 16 ng/ml.

5. The method of claim 1, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said single daily dose achieves a mean Cmax within the range of about 80% to about 125% of 23 ng/ml.

6. The method of claim 1, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves a mean maximum Cmax within the range of about 80% to about 125% of 36 ng/ml.

7. The method of claim 1, wherein said therapeutically effective amount is single daily dose to achieve a mean AUC(0-24) of from about 15.9 ng*hr/ml to about 23.8 ng*hr/ml for each 1 mg of compound A.

8. The method of claim 1, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-24) within the range of about 80% to about 125% of 17 ng*hr/ml.

9. The method of claim 1, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said daily single dose achieves a mean AUC(0-24) within the range of about 80% to about 125%

of 57 ng*hr/ml.

10. The method of claim 1, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said daily single dose achieves a mean AUC(0-24) within the range of about 80% to about 125% of 95 ng*hr/ml.

11. The method of claim 1, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-24) within the range of about 80% to about 125% of 159 ng*hr/ml.

12. The method of claim 1, wherein said therapeutically effective amount is single daily dose to achieve a mean AUC(0-t) of from about 19.1 ng*hr/ml to about 51.1 ng*hr/ml for each 1 mg of compound A.

13. The method of claim 1, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-t) within the range of about 80% to about 125% of 19 ng*hr/ml.

14. The method of claim 1, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-t) within the range of about 80% to about 125% of 80 ng*hr/ml.

15. The method of claim 1, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-t) within the range of about 80% to about 125% of 128 ng*hr/ml.

16. The method of claim 1, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-t) within the range of about 80% to about 125% of 284 ng*hr/ml.

17. The method of claim 1, wherein said therapeutically effective amount is single daily dose to achieve a mean AUC(0-inf) of from about 19.8 ng*hr/ml to about 53.1 ng*hr/ml for each 1 mg of compound A.

18. The method of claim 1, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-inf) within the range of about 80% to about 125% of 20 ng*hr/ml.

19. The method of claim 1, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-inf) within the range of about 80% to about 125% of 80 ng*hr/ml.

20. The method of claim 1, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-inf) within the range of about 80% to about 125% of 149 ng*hr/ml.

21. The method of claim 1, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-inf) within the range of about 80% to about 125% of 311 ng*hr/ml.

22. The method of claim 1, wherein said single daily dose provides a mean plasma compound A concentration of about 20 ng/ml or less at from 8 to 10 hours after single dose administration to human subjects.

23. An oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single daily dose to achieve a mean Cmax of from about 3.0 ng/ml to about 7.2 ng/ml for each 1 mg of compound A after administration to human subjects.

24. The dosage form of claim 23, wherein said single daily dose ranges from about 1 mg to about 15 mg.

25. The dosage form of claim 23, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves a mean Cmax within the range of about 80% to about 125% of 5.3 ng/ml.

26. The dosage form of claim 23, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves a mean Cmax within the range of about 80% to about 125% of 16 ng/ml.

27. The dosage form of claim 23, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said single dose achieves a mean Cmax within the range of about 80% to about 125% of 23 ng/ml.

28. The dosage form of claim 23, wherein said therapeutically effective amount is single 10 mg daily dose,

and wherein said single daily dose achieves a mean Cmax within the range of about 80% to about 125% of 36 ng/ml.

29. The dosage form of claim 23, wherein said therapeutically effective amount is single daily dose to achieve a mean AUC(0-24) of from about 15.9 ng*hr/ml to about 23.8 ng*hr/ml for each 1 mg of compound A.

30. The dosage form of claim 23, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-24) within the range of about 80% to about 125% of 17 ng*hr/ml.

31. The dosage form of claim 23, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-24) within the range of about 80% to about 125% of 57 ng*hr/ml.

32. The dosage form of claim 23, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-24) within the range of about 80% to about 125% of 95 ng*hr/ml.

33. The dosage form of claim 23, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-24) within the range of about 80% to about 125% of 159 ng*hr/ml.

34. The dosage form of claim 23, wherein said therapeutically effective amount is single daily dose to achieve a mean AUC(0-t) of from about 19.1 ng*hr/ml to about 51.1 ng*hr/ml for each 1 mg of compound A.

35. The dosage form of claim 23, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-t) within the range of about 80% to about 125% of 19 ng*hr/ml.

36. The dosage form of claim 23, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-t) within the range of about 80% to about 125% of 80 ng*hr/ml.

37. The dosage form of claim 23, wherein said therapeutically effective amount is single 5 mg daily dose,

and wherein said single daily dose achieves a mean AUC(0-t) within the range of about 80% to about 125% of 128 ng*hr/ml.

38. The dosage form of claim 23, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-t) within the range of about 80% to about 125% of 284 ng*hr/ml.

39. The dosage form of claim 23, wherein said therapeutically effective amount is single daily dose to achieve a mean AUC(0-inf) of from about 19.8 ng*hr/ml to about 53.1 ng*hr/ml for each 1 mg of compound A.

40. The dosage form of claim 23, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-inf) within the range of about 80% to about 125% of 20 ng*hr/ml.

41. The dosage form of claim 23, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-inf) within the range of about 80% to about 125% of 80 ng*hr/ml.

42. The dosage form of claim 23, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-inf) within the range of about 80% to about 125% of 149 ng*hr/ml.

43. The dosage form of claim 23, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-inf) within the range of about 80% to about 125% of 311 ng*hr/ml.

44. The dosage form of claim 23, wherein said daily dose provides a mean plasma compound A concentration of about 20 ng/ml or less at from 8 to 10 hours after single dose administration to human subjects.

45. The dosage form of claim 23, wherein said dosage form provides an dissolution rate of 85 % or more in dissolution medium (0.1 mol/L hydrochloric acid containing 0.5% polysorbate 80, 900 mL, 37 ± 0.5°C) within 30 minutes from the onset of dissolution study using the Apparatus 2 (Paddle Apparatus, paddle speed; 75 rpm) according to the procedure for immediate-release dosage form in 6.10 Dissolution test of JP16 or <711> Dissolution of USP37.

46. The dosage form of claim 23, wherein said dosage form provides an dissolution rate of 85 % or more in dissolution medium (0.1 mol/L hydrochloric acid, 900 mL, 37 ± 0.5°C) within 15 minutes from the onset of dissolution study using the Apparatus 2 (Paddle Apparatus, paddle speed; 50 rpm) according to the procedure for immediate-release dosage form in 6.10 Dissolution test of JP16 or <711> Dissolution of USP37.

47. The dosage form of claim 23, wherein said dosage form comprises lactose as pharmaceutically acceptable excipient.

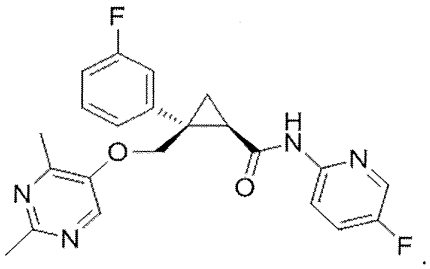
48. The dosage form of claim 23, wherein said dosage form comprises low-substituted hydroxypropyl cellulose as pharmaceutically acceptable excipient.

49. The dosage form of claim 23, wherein said dosage form comprises lactose and low-substituted hydroxypropyl cellulose as pharmaceutically acceptable excipient.

AMENDED CLAIMS
received by the International Bureau on 10 March 2016 (10.03.2016)

What is claimed is;

1. (Amended) A method of treating insomnia, comprising administrating orally a dosage form with a therapeutically effective amount of compound A, wherein said therapeutically effective amount is single daily dose to achieve a mean Cmax of from about 3.0 ng/ml to about 7.2 ng/ml for each 1 mg of compound A after administration to human subjects, and said compound A is (1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl) cyclopropanecarboxamide represented by a following formula:



2. The method of claim 1, wherein said single daily dose ranges from about 1 mg to about 15 mg.

3. The method of claim 1, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves a mean Cmax within the range of about 80% to about 125% of 5.3 ng/ml.

4. The method of claim 1, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves a mean Cmax within the range of about 80% to about 125% of 16 ng/ml.

5. The method of claim 1, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said single daily dose achieves a mean Cmax within the range of about 80% to about 125% of 23 ng/ml.

6. The method of claim 1, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves a mean maximum Cmax within the range of about 80% to about 125% of 36 ng/ml.

AMENDED SHEET (ARTICLE 19)

7. The method of claim 1, wherein said therapeutically effective amount is single daily dose to achieve a mean AUC(0-24) of from about 15.9 ng*hr/ml to about 23.8 ng*hr/ml for each 1 mg of compound A.

8. The method of claim 1, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-24) within the range of about 80% to about 125% of 17 ng*hr/ml.

9. The method of claim 1, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said daily single dose achieves a mean AUC(0-24) within the range of about 80% to about 125% of 57 ng*hr/ml.

10. The method of claim 1, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said daily single dose achieves a mean AUC(0-24) within the range of about 80% to about 125% of 95 ng*hr/ml.

11. The method of claim 1, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-24) within the range of about 80% to about 125% of 159 ng*hr/ml.

12. The method of claim 1, wherein said therapeutically effective amount is single daily dose to achieve a mean AUC(0-t) of from about 19.1 ng*hr/ml to about 51.1 ng*hr/ml for each 1 mg of compound A.

13. The method of claim 1, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-t) within the range of about 80% to about 125% of 19 ng*hr/ml.

14. The method of claim 1, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-t) within the range of about 80% to about 125% of 80 ng*hr/ml.

15. The method of claim 1, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-t) within the range of about 80% to about 125% of 128 ng*hr/ml.

16. The method of claim 1, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-t) within the range of about 80% to about 125%

of 284 ng*hr/ml.

17. The method of claim 1, wherein said therapeutically effective amount is single daily dose to achieve a mean AUC(0-inf) of from about 19.8 ng*hr/ml to about 53.1 ng*hr/ml for each 1 mg of compound A.

18. The method of claim 1, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-inf) within the range of about 80% to about 125% of 20 ng*hr/ml.

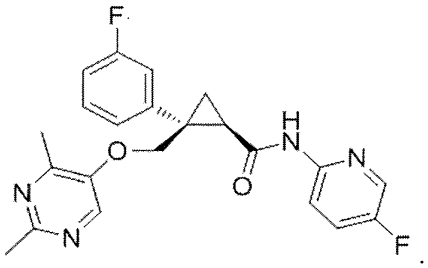
19. The method of claim 1, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-inf) within the range of about 80% to about 125% of 80 ng*hr/ml.

20. The method of claim 1, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-inf) within the range of about 80% to about 125% of 149 ng*hr/ml.

21. The method of claim 1, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-inf) within the range of about 80% to about 125% of 311 ng*hr/ml.

22. The method of claim 1, wherein said single daily dose provides a mean plasma compound A concentration of about 20 ng/ml or less at from 8 to 10 hours after single dose administration to human subjects.

23. (Amended) An oral dosage form for treating insomnia comprising a therapeutically effective amount of compound A and at least one pharmaceutically acceptable excipient, wherein said therapeutically effective amount is single daily dose to achieve a mean Cmax of from about 3.0 ng/ml to about 7.2 ng/ml for each 1 mg of compound A after administration to human subjects, and said compound A is (1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl) cyclopropanecarboxamide represented by a following formula:



24. The dosage form of claim 23, wherein said single daily dose ranges from about 1 mg to about 15 mg.

25. The dosage form of claim 23, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves a mean Cmax within the range of about 80% to about 125% of 5.3 ng/ml.

26. The dosage form of claim 23, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves a mean Cmax within the range of about 80% to about 125% of 16 ng/ml.

27. The dosage form of claim 23, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said single dose achieves a mean Cmax within the range of about 80% to about 125% of 23 ng/ml.

28. The dosage form of claim 23, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves a mean Cmax within the range of about 80% to about 125% of 36 ng/ml.

29. The dosage form of claim 23, wherein said therapeutically effective amount is single daily dose to achieve a mean AUC(0-24) of from about 15.9 ng*hr/ml to about 23.8 ng*hr/ml for each 1 mg of compound A.

30. The dosage form of claim 23, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-24) within the range of about 80% to about 125% of 17 ng*hr/ml.

31. The dosage form of claim 23, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-24) within the range of about 80% to

about 125% of 57 ng*hr/ml.

32. The dosage form of claim 23, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-24) within the range of about 80% to about 125% of 95 ng*hr/ml.

33. The dosage form of claim 23, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-24) within the range of about 80% to about 125% of 159 ng*hr/ml.

34. The dosage form of claim 23, wherein said therapeutically effective amount is single daily dose to achieve a mean AUC(0-t) of from about 19.1 ng*hr/ml to about 51.1 ng*hr/ml for each 1 mg of compound A.

35. The dosage form of claim 23, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-t) within the range of about 80% to about 125% of 19 ng*hr/ml.

36. The dosage form of claim 23, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-t) within the range of about 80% to about 125% of 80 ng*hr/ml.

37. The dosage form of claim 23, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-t) within the range of about 80% to about 125% of 128 ng*hr/ml.

38. The dosage form of claim 23, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-t) within the range of about 80% to about 125% of 284 ng*hr/ml.

39. The dosage form of claim 23, wherein said therapeutically effective amount is single daily dose to achieve a mean AUC(0-inf) of from about 19.8 ng*hr/ml to about 53.1 ng*hr/ml for each 1 mg of compound A.

40. The dosage form of claim 23, wherein said therapeutically effective amount is single 1 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-inf) within the range of about 80% to about

125% of 20 ng*hr/ml.

41. The dosage form of claim 23, wherein said therapeutically effective amount is single 2.5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-inf) within the range of about 80% to about 125% of 80 ng*hr/ml.

42. The dosage form of claim 23, wherein said therapeutically effective amount is single 5 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-inf) within the range of about 80% to about 125% of 149 ng*hr/ml.

43. The dosage form of claim 23, wherein said therapeutically effective amount is single 10 mg daily dose, and wherein said single daily dose achieves a mean AUC(0-inf) within the range of about 80% to about 125% of 311 ng*hr/ml.

44. The dosage form of claim 23, wherein said daily dose provides a mean plasma compound A concentration of about 20 ng/ml or less at from 8 to 10 hours after single dose administration to human subjects.

45. The dosage form of claim 23, wherein said dosage form provides an dissolution rate of 85 % or more in dissolution medium (0.1 mol/L hydrochloric acid containing 0.5% polysorbate 80, 900 mL, 37 ± 0.5°C) within 30 minutes from the onset of dissolution study using the Apparatus 2 (Paddle Apparatus, paddle speed; 75 rpm) according to the procedure for immediate-release dosage form in 6.10 Dissolution test of JP16 or <711> Dissolution of USP37.

46. The dosage form of claim 23, wherein said dosage form provides an dissolution rate of 85 % or more in dissolution medium (0.1 mol/L hydrochloric acid, 900 mL, 37 ± 0.5°C) within 15 minutes from the onset of dissolution study using the Apparatus 2 (Paddle Apparatus, paddle speed; 50 rpm) according to the procedure for immediate-release dosage form in 6.10 Dissolution test of JP16 or <711> Dissolution of USP37.

47. The dosage form of claim 23, wherein said dosage form comprises lactose as pharmaceutically acceptable excipient.

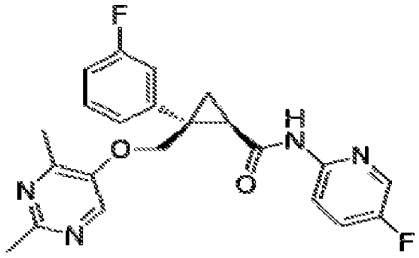
48. The dosage form of claim 23, wherein said dosage form comprises low-substituted hydroxypropyl cellulose as pharmaceutically acceptable excipient.

AMENDED SHEET (ARTICLE 19)

49. The dosage form of claim 23, wherein said dosage form comprises lactose and low-substituted hydroxypropyl cellulose as pharmaceutically acceptable excipient.

Statement under Article 19(1)

The description “, and said compound A is (1R,2S)-2-(((2,4-dimethylpyrimidin-5-yl)oxy)methyl)-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl) cyclopropanecarboxamide represented by a following formula:



” has been inserted to the end portion of claims 1 and 23.

This description is based on paragraphs [0002] and [0003] of the specification.

Claims 1 and 23 have been clarified by this amendment.

Fig. 1

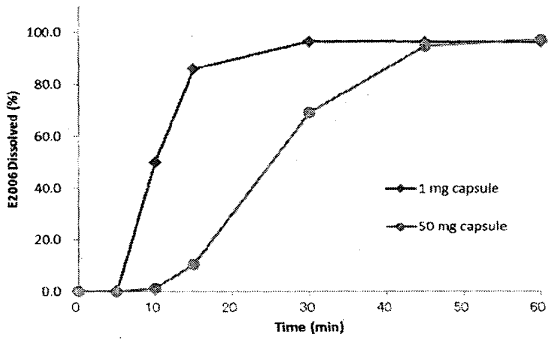


Fig. 2

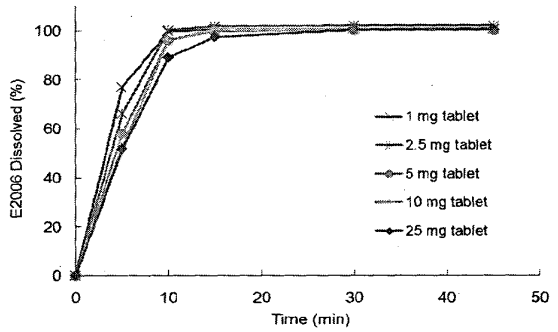
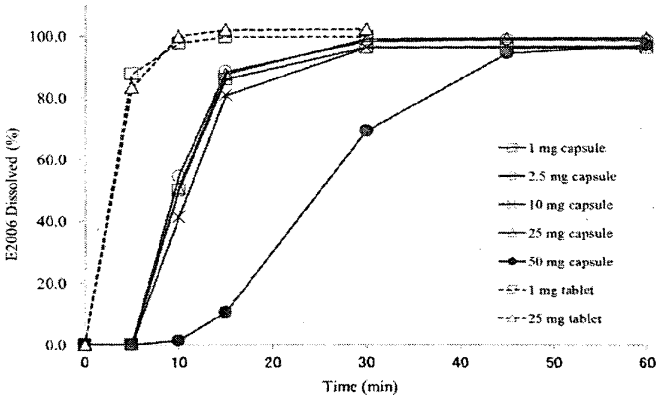


Fig. 3



INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2015/080304

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl. A61K31/506(2006.01)i, A61P25/20(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl. A61K31/506, A61P25/20

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Published examined utility model applications of Japan 1922-1996
Published unexamined utility model applications of Japan 1971-2016
Registered utility model specifications of Japan 1996-2016
Published registered utility model applications of Japan 1994-2016

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAplus/REGISTRY (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2012/0095031 A1 (EISAI R&D MANAGEMENT CO., LTD.) 2012.04.19, Claims, [0463]-[0470],[0477],[0996]-[1002], Ex.95 & WO 2012/039371 A1 & EP 2626350 A1 & CN 103153963 A & KR 10-2013-0097776 A	1-49
Y	YAMADERA, Hiroshi, Recent progress in development of hypnotic drugs, Japanese Journal of Clinical Medicine, 1998.02.01, Vol.56, No.2, p.245-250, whole text, especially p.248 '2.clinical study'	1-49

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15.01.2016	26.01.2016

Name and mailing address of the ISA/JP	Authorized officer	
Japan Patent Office 3-4-3, Kasumigaseki, Chiyoda-ku, Tokyo 100-8915, Japan	IMAMURA, Akiko Telephone No. +81-3-3581-1101 Ext. 3452	4C 3847

Form PCT/ISA/210 (second sheet) (January 2015)

Range to be covered by this search:

The inventions of claims 1-49 relate to 'compound A'; however there is no definition of 'compound A' in the claims. Therefore the term 'compound A' in the claims is considered as unclear.

On the other hand, in the description of the present application, compound A is defined as (1R,2S)-2-{[(2,4-dimethylpyrimidin-5-yl)oxy]methyl}-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide([0002],[0003]).

Consequently, this international search was carried out on the basis of the interpretation that 'compound A' means (1R,2S)-2-{[(2,4-dimethylpyrimidin-5-yl)oxy]methyl}-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2018/097797

A. CLASSIFICATION OF SUBJECT MATTER

C07D 239/34(2006.01)i; A61K 31/506(2006.01)i; A61P 25/20(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D239/-,A61K31/-,A61P25/-

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)

CNPAT, CNKI, WPI, EPODOC, STN, E-2006, lemborexant, 离子液体, 结晶, 晶型, 晶体, ionic liquid, crystal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 104114524 A (EISAI R&D MANAGEMENT CO., LTD.) 22 October 2014 (2014-10-22) description, paragraphs 3-4 and 217	1-4, 7-9
Y	CN 104114524 A (EISAI R&D MANAGEMENT CO., LTD.) 22 October 2014 (2014-10-22) description, paragraphs 3-4 and 217	4-6
Y	CN 104592184 A (YUNNAN INSTITUTE OF MATERIA MEDICA; HLK PHARMACIN LLC) 06 May 2015 (2015-05-06) description, paragraph 7	4-6
A	CN 103153963 A (EISAI R&D MANAGEMENT CO., LTD.) 12 June 2013 (2013-06-12) description, paragraphs 659-662 and embodiment 95, and claims 1-20	1-9
A	WO 2016063995 A1 (EISAI R&D MAN CO., LTD.) 28 April 2016 (2016-04-28) description, paragraphs 1-253	1-9

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 October 2018	**31 October 2018**

Name and mailing address of the ISA/CN	Authorized officer
State Intellectual Property Office of the P. R. China **No. 6, Xitucheng Road, Jimenqiao Haidian District, Beijing** **100088** **China**	
Facsimile No. **(86-10)62019451**	Telephone No.

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2018/097797

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
CN	104114524	A	22 October 2014	IL	232949	D0	03 August 2014
				WO	2013123240	A1	22 August 2013
				MX	352881	B	13 December 2017
				US	2016318858	A1	03 November 2016
				US	2018044285	A1	15 February 2018
				US	9828336	B2	28 November 2017
				IL	232949	A	31 August 2016
				US	2015025237	A1	22 January 2015
				JP	2015509939	A	02 April 2015
				RU	2617696	C2	26 April 2017
				MX	2014009917	A	13 November 2014
				JP	6147279	B2	14 June 2017
				US	9416109	B2	16 August 2016
				SG	11201403216U	A	30 December 2014
				EP	2814798	A1	24 December 2014
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CN	104592184	A	06 May 2015	WO	2016095702	A1	23 June 2016
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				US	2017368019	A1	28 December 2017
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CN	103153963	A	12 June 2013	MY	160969	A	31 March 2017
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				KR	101458007	B1	04 November 2014
				TW	I516484	B	11 January 2016
				ES	2540851	T3	14 July 2015
				DK	2626350	T3	29 June 2015
				CN	103153963	B	24 December 2014
				AU	2011304285	B2	29 January 2015
				US	8268848	B2	18 September 2012
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				CL	2013000784	A1	05 July 2013
				CA	2811895	A1	29 March 2012
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				EP	2626350	A4	12 February 2014
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				IL	225437	D0	27 June 2013
				AU	2011304285	A1	16 May 2013
				MA	34609	B1	02 October 2013
				JP	WO2012039371	A1	03 February 2014
				KR	20130097776	A	03 September 2013
				AR	083060	A1	30 January 2013
				IL	225437	A	31 May 2015
				PT	2626350	E	03 August 2015

Form PCT/ISA/210 (patent family annex) (January 2015)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2018/097797

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
		SG	188585	A1	30 April 2013
		TW	201305129	A	01 February 2013
		SI	EP2626350	T1	30 September 2015
		UA	108510	C2	12 May 2015
		EP	2626350	B1	15 April 2015
		WO	2012039371	A1	29 March 2012
		BR	112013006594	A2	21 June 2016
		RU	2013117464	A	27 October 2014
		US	2012095031	A1	19 April 2012
WO 2016063995 A1	28 April 2016	IL	251759	D0	29 June 2017
		KR	20170068478	A	19 June 2017
		AU	2015336463	A1	04 May 2017
		EP	3209298	A1	30 August 2017
		CA	2964504	A1	28 April 2016
		CN	107810006	A	16 March 2018
		BR	112017007063	A2	14 February 2018
		JP	2017531683	A	26 October 2017
		SG	11201703064W	A	30 May 2017
		US	2017252342	A1	07 September 2017
		MX	2017004950	A	16 January 2018
		EP	3209298	A4	20 June 2018

国际检索报告

国际申请号 PCT/CN2018/097797

A. 主题的分类

C07D 239/34(2006.01)i；A61K 31/506(2006.01)i；A61P 25/20(2006.01)i

按照国际专利分类(IPC)或者同时按照国家分类和IPC两种分类

B. 检索领域

检索的最低限度文献(标明分类系统和分类号)

C07D239/-,A61K31/-,A61P25/-

包含在检索领域中的除最低限度文献以外的检索文献

在国际检索时查阅的电子数据库(数据库的名称，和使用的检索词（如使用））

CNPAT,CNKI,WPI,EPODOC,STN,E-2006，lemborexant,离子液体，结晶，晶型，晶体，ionic liquid,crystal

C. 相关文件

类 型*	引用文件，必要时，指明相关段落	相关的权利要求
X	CN 104114524 A（卫材R&D管理有限公司）2014年 10月 22日（2014-10-22） 说明书第3-4段，217段	1-4，7-9
Y	CN 104114524 A（卫材R&D管理有限公司）2014年 10月 22日（2014-10-22） 说明书第3-4段，217段	4-6
Y	CN 104592184 A（云南省药物研究所 深圳市华力康生物医药有限公司）2015年 5月 6日（2015-05-06） 说明书第7段	4-6
A	CN 103153963 A（卫材R&D管理有限公司）2013年 6月 12日（2013-06-12） 说明书第659-662段，实施例95，权利要求1-20	1-9
A	WO 2016063995 A1（EISAI R&D MAN CO LTD.）2016年 4月 28日（2016-04-28） 说明书第1-253段	1-9

☐ 其余文件在C栏的续页中列出。

☑ 见同族专利附件。

* 引用文件的具体类型：

“A” 认为不特别相关的表示了现有技术一般状态的文件

“E” 在国际申请日的当天或之后公布的在先申请或专利

“L” 可能对优先权要求构成怀疑的文件，或为确定另一篇引用文件的公布日而引用的或者因其他特殊理由而引用的文件（如具体说明的）

“O” 涉及口头公开、使用、展览或其他方式公开的文件

“P” 公布日先于国际申请日但迟于所要求的优先权日的文件

“T” 在申请日或优先权日之后公布，与申请不相抵触，但为了理解发明之理论或原理的在后文件

“X” 特别相关的文件，单独考虑该文件，认定要求保护的发明不是新颖的或不具有创造性

“Y” 特别相关的文件，当该文件与另一篇或者多篇该类文件结合并且这种结合对于本领域技术人员为显而易见时，要求保护的发明不具有创造性

“&” 同族专利的文件

国际检索实际完成的日期	国际检索报告邮寄日期
2018年 10月 15日	2018年 10月 31日

ISA/CN的名称和邮寄地址	受权官员
中华人民共和国国家知识产权局(ISA/CN) 中国北京市海淀区蓟门桥西土城路6号 100088	李敏
传真号 (86-10)62019451	电话号码 86-(010)-53962148

表 PCT/ISA/210（第2页）（2015年1月）

国际检索报告
关于同族专利的信息

国际申请号
PCT/CN2018/097797

检索报告引用的专利文件			公布日（年/月/日）	同族专利			公布日（年/月/日）
CN	104114524	A	2014年 10月 22日	IL	232949	D0	2014年 8月 3日
				WO	2013123240	A1	2013年 8月 22日
				MX	352881	B	2017年 12月 13日
				US	2016318858	A1	2016年 11月 3日
				US	2018044285	A1	2018年 2月 15日
				US	9828336	B2	2017年 11月 28日
				IL	232949	A	2016年 8月 31日
				US	2015025237	A1	2015年 1月 22日
				JP	2015509939	A	2015年 4月 2日
				RU	2617696	C2	2017年 4月 26日
				MX	2014009917	A	2014年 11月 13日
				JP	6147279	B2	2017年 6月 14日
				US	9416109	B2	2016年 8月 16日
				SG	11201403216U	A	2014年 12月 30日
				EP	2814798	A1	2014年 12月 24日
				RU	2014137470	A	2016年 4月 10日
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CN	103153963	A	2013年 6月 12日	MY	160969	A	2017年 3月 31日
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				KR	101458007	B1	2014年 11月 4日
				TW	I516484	B	2016年 1月 11日
				ES	2540851	T3	2015年 7月 14日
				DK	2626350	T3	2015年 6月 29日
				CN	103153963	B	2014年 12月 24日
				AU	2011304285	B2	2015年 1月 29日
				US	8268848	B2	2012年 9月 18日
				NZ	609313	A	2014年 5月 30日
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				EP	2626350	A1	2013年 8月 14日
				CL	2013000784	A1	2013年 7月 5日
				CA	2811895	A1	2012年 3月 29日
				JP	4944286	B1	2012年 5月 30日
				CA	2811895	C	2015年 12月 8日
				PE	11622013	A1	2013年 10月 19日
				EP	2626350	A4	2014年 2月 12日
				RU	2571414	C2	2015年 12月 20日
				IL	225437	D0	2013年 6月 27日
				AU	2011304285	A1	2013年 5月 16日
				MA	34609	B1	2013年 10月 2日
				JP	WO2012039371	A1	2014年 2月 3日
				KR	20130097776	A	2013年 9月 3日
				AR	083060	A1	2013年 1月 30日
				IL	225437	A	2015年 5月 31日
				PT	2626350	E	2015年 8月 3日

表 PCT/ISA/210（同族专利附件）（2015年1月）

国际检索报告
关于同族专利的信息

国际申请号
PCT/CN2018/097797

检索报告引用的专利文件			公布日（年/月/日）	同族专利			公布日（年/月/日）
				SG	188585	A1	2013年 4月 30日
				TW	201305129	A	2013年 2月 1日
				SI	EP2626350	T1	2015年 9月 30日
				UA	108510	C2	2015年 5月 12日
				EP	2626350	B1	2015年 4月 15日
				WO	2012039371	A1	2012年 3月 29日
				BR	112013006594	A2	2016年 6月 21日
				RU	2013117464	A	2014年 10月 27日
				US	2012095031	A1	2012年 4月 19日
WO	2016063995	A1	2016年 4月 28日	IL	251759	D0	2017年 6月 29日
				KR	20170068478	A	2017年 6月 19日
				AU	2015336463	A1	2017年 5月 4日
				EP	3209298	A1	2017年 8月 30日
				CA	2964504	A1	2016年 4月 28日
				CN	107810006	A	2018年 3月 16日
				BR	112017007063	A2	2018年 2月 14日
				JP	2017531683	A	2017年 10月 26日
				SG	11201703064W	A	2017年 5月 30日
				US	2017252342	A1	2017年 9月 7日
				MX	2017004950	A	2018年 1月 16日
				EP	3209298	A4	2018年 6月 20日

表 PCT/ISA/210（同族专利附件）（2015年1月）

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	
First Named Inventor	Minhua Chen
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	134070-01602

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	8268848	B2	2012-09-18	Terauchi et al.	
	2	10172824	B2	2019-01-08	Wang et al.	

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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	2013/123240	WO	A1	2013-08-22	Eisai R&D Management Co., Ltd.		
	2	2016/063995	WO	A1	2016-04-28	Eisai R&D Management Co., Ltd.		

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	
	First Named Inventor	Minhua Chen
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	134070-01602

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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	International Search Report for Application No. PCT/CN2018/097797, dated October 31, 2018, 6 pages.	X

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	
	First Named Inventor	Minhua Chen
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	134070-01602

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 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.

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

☒ A certification statement is not submitted herewith.

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	/Xiaoyuan Ding/	Date (YYYY-MM-DD)	2020-01-30
Name/Print	Xiaoyuan Ding	Registration Number	75,354

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

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

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

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

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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.

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

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

First Named Inventor:	Minhua Chen	Nonprovisional Application Number (if known):	Not Yet Assigned
Title of Invention:	CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE 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. [X] **Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)**

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. [ ] **Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)**

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

Signature	/Xiaoyuan Ding/	Date	January 30, 2020
Name (Print/Typed)	Xiaoyuan Ding	Practitioner Registration Number	75,354

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.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: January 30, 2020 Electronic Signature for Xiaoyuan Ding: /Xiaoyuan Ding/

(12) 按照专利合作条约所公布的国际申请

(19) 世界知识产权组织
国 际 局

(43) 国际公布日
2019 年 2 月 7 日 (07.02.2019)

WIPO | PCT

(10) 国际公布号
WO 2019/024845 A1

(51) 国际专利分类号:
C07D 239/34 (2006.01) *A61P 25/20* (2006.01)
A61K 31/506 (2006.01)

(21) 国际申请号: PCT/CN2018/097797

(22) 国际申请日: 2018 年 7 月 31 日 (31.07.2018)

(25) 申请语言: 中文

(26) 公布语言: 中文

(30) 优先权:
201710648135.2 2017年8月1日 (01.08.2017) CN

(71) 申请人: 苏州科睿思制药有限公司(CRYSTAL PHARMACEUTICAL (SUZHOU) CO., LTD.) [CN/CN]; 中国江苏省苏州市工业园区星湖街218号生物纳米园B4-301赵林林, Jiangsu 215123 (CN)。

(72) 发明人: 陈敏华 (CHEN, Minhua); 中国江苏省苏州市工业园区星湖街218号生物纳米园B4-301赵林林, Jiangsu 215123 (CN)。 张炎锋 (ZHANG, Yanfeng); 中国江苏省苏州市工业园区星湖街218号生物纳米园B4-301赵林林, Jiangsu 215123 (CN)。 黄春香 (HUANG, Chunxiang); 中国江苏省苏州市工业园区星湖街218号生物纳米园B4-301赵林林, Jiangsu 215123 (CN)。 张晓宇 (ZHANG, Xiaoyu); 中国江苏省苏州市工业园区星湖街218号生物纳米园B4-301赵林林, Jiangsu 215123 (CN)。

(81) 指定国(除另有指明，要求每一种可提供的国家保护): 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, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK,

(54) **Title:** CRYSTAL FORM OF OREXIN RECEPTOR ANTAGONIST, PREPARATION METHOD THEREFOR AND USE THEREOF

(54) **发明名称:** 一种食欲素受体拮抗剂的晶型及其制备方法和用途

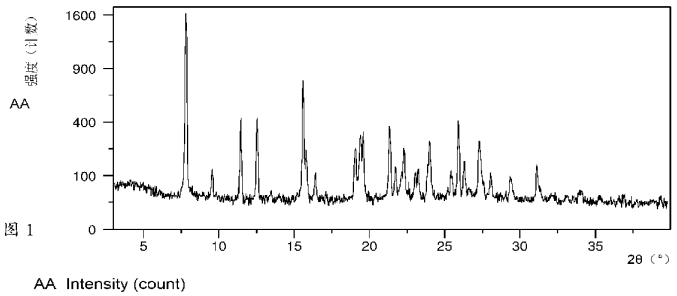
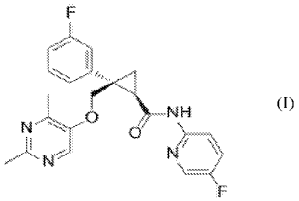


图 1



(I)

(57) **Abstract:** A crystal form of a compound Lemborexant, a preparation method therefor, a pharmaceutical composition comprising the crystal form, and use of the crystal form in the preparation of an orexin receptor antagonist and of a pharmaceutical formulation for treating insomnia and irregular sleep-wake rhythm disorder. The crystal form of the compound Lemborexant provided by the present invention has one or more improved properties with respect to the prior art, having great value for the optimization and development of this medicament in the future.

[见续页]

WO 2019/024845 A1

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, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW。

(84) **指定国**(除另有指明，要求每一种可提供的地区保护)：ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), 欧亚 (AM, AZ, BY, KG, KZ, RU, TJ, TM), 欧洲 (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)。

本国际公布:

— 包括国际检索报告(条约第21条(3))。

(57) 摘要：一种化合物Lemborexant的晶型及其制备方法，含有该晶型的药物组合物，以及该晶型在制备食欲素受体拮抗剂、治疗失眠症和不规则睡眠-觉醒节律障碍药物制剂中的用途。提供的化合物Lemborexant的晶型比现有技术具有一种或多种改进的特性，对未来该药物的优化和开发具有重要价值。

一种食欲素受体拮抗剂的晶型及其制备方法和用途

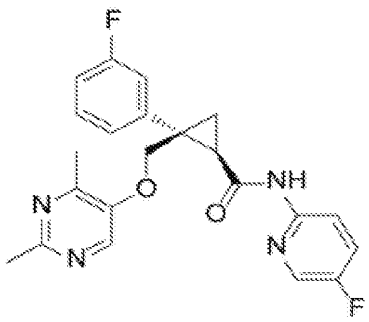
技术领域

本发明涉及药物化学领域。具体而言，涉及食欲素受体拮抗剂的晶型及其制备方法和用途。

背景技术

E-2006 (Lemborexant)由卫材公司研发，临床用于治疗失眠症。研究表明，食欲素系统是睡眠-觉醒周期的关键调节剂，食欲素受体拮抗剂具有阻碍不适当的定时夜间觉醒、并促进正常的睡眠-觉醒周期的潜力。E-2006 是一种食欲素受体拮抗剂，在临床试验中，E-2006 能显著改善失眠患者的睡眠效率，包括入睡更快，夜间醒来的时间更短。此外，E-2006 在治疗阿尔茨海默病患者的不规则睡眠-觉醒节律障碍方面也显示巨大的潜力，不规则睡眠-觉醒节律障碍不同于一般的失眠，该领域存在着未获满足的医疗需求。

E-2006的化学名称为：(1R, 2S)-2-{[(2, 4-二甲基嘧啶-5-基)氧基]甲基}-2-(3-氟苯基)-N-(5-氟吡啶-2-基)环丙烷甲酰胺（以下称为“化合物(I)”），其结构式如下：



化合物(I)

目前无化合物(I)的晶型信息公开。专利CN103153963B公开了化合物(I)的结构和制备方法，发明人根据该公开的制备方法得到了化合物(I)的无定形固体。与本发明的晶型相比，该无定形固体稳定性差，具有较低的密度和较差的流动性，不利于制剂的制备。此外，无定形是热力学最不稳定的固体形态，易发生转变或降解等，导致化合物的化学纯度降低。并且无定形的制备通常是一个快速的动力学固体析出的过程，容易导致残留溶剂超标，且其颗粒属性很难通过工艺进行控制。

本发明人发现了性质优良的化合物(I)的晶型CS2，其在稳定性、熔点、溶解度、体内外溶出、引湿性、生物有效性、黏附性、可压性、流动性以及加工性能、提纯作用、制剂生产等方面中的至少一方面上存在优势，特别是稳定性好、引湿性低、制剂可加工性强、体外溶出度和溶出速率高，为含化合物(I)的药物开发提供了新的更好的选择，具有非常重要的意义。

发明内容

本发明的主要目的是提供化合物(I)的晶型及其制备方法和用途。

根据本发明的目的，本发明提供化合物（I）的晶型 CS2（以下称作“晶型 CS2”）。

一方面，使用 Cu-Kα 辐射，所述晶型 CS2 的 X 射线粉末衍射在衍射角 2θ 值为 7.8°±0.2°、15.6°±0.2°、11.4°±0.2°处有特征峰。

进一步地，所述晶型 CS2 的 X 射线粉末衍射在衍射角 2θ 值为 12.5°±0.2°、21.3°±0.2°、27.3°±0.2°中的 1 处、或 2 处、或 3 处有特征峰；优选地，所述晶型 CS2 的 X 射线粉末衍射在衍射角 2θ 为 12.5°±0.2°、21.3°±0.2°、27.3°±0.2°中的 3 处有特征峰。

进一步地，所述晶型 CS2 的 X 射线粉末衍射在衍射角 2θ 值为 24.0°±0.2°、19.4°±0.2°、22.3°±0.2°中的 1 处、或 2 处、或 3 处有特征峰；优选地，所述晶型 CS2 的 X 射线粉末衍射在衍射角 2θ 为 24.0°±0.2°、19.4°±0.2°、22.3°±0.2°中的 3 处有特征峰。

另一方面，所述晶型 CS2 的 X 射线粉末衍射在衍射角 2θ 值为 7.8°±0.2°、15.6°±0.2°、11.4°±0.2°、12.5°±0.2°、21.3°±0.2°、27.3°±0.2°、24.0°±0.2°、19.1°±0.2°、19.4°±0.2°、22.3°±0.2°、25.9°±0.2°中的任意 3 处、或 4 处、或 5 处、或 6 处、或 7 处、或 8 处、或 9 处、或 10 处、或 11 处有特征峰。

非限制性地，晶型 CS2 的 X 射线粉末衍射谱图如图 1 或图 5 所示。

根据本发明的目的，本发明还提供所述晶型 CS2 的制备方法，所述制备方法包括:

(1) 将化合物(I)原料溶解在正溶剂中，配成含化合物(I)的溶液，后将反溶剂缓慢滴加到正溶剂溶液中，搅拌析晶得到；或

(2) 将化合物(I)原料溶解在酮类溶剂中，缓慢挥发得到；或

(3) 将化合物(I)原料溶解在腈类溶剂中，加入离子液体诱导，后缓慢挥发得到。

进一步地，方法(1)中所述正溶剂优选为醇类溶剂，所述反溶剂优选为水；

更进一步地，方法(1)中所述醇类溶剂优选为甲醇。

进一步地，方法(2)中所述酮类溶剂优选为丙酮。

进一步地，方法(3)中所述腈类溶剂优选为乙腈，所述离子液体优选为 1-乙基-3-甲基咪唑硫酸甲酯盐、1-乙基-3-甲基咪唑六氟锑酸盐或 1,3-二甲基咪唑磷酸二甲酯盐。

根据本发明的目的，本发明还提供一种药物组合物，所述药物组合物包含有效治疗量的晶型CS2及药学上可接受的载体、稀释剂或赋形剂。

进一步地，本发明提的晶型 CS2 在制备食欲素受体拮抗剂药物制剂中的用途。

更进一步地，本发明提供的晶型 CS2 在制备治疗失眠症和/或不规则睡眠-觉醒节律障碍药物制剂中的用途。

本发明提供的晶型 CS2 具有以下有益效果：

（1）本发明晶型 CS2 具有更低的引湿性。实验表明，晶型 CS2 在 80%相对湿度条件下的增重为 0.21%，属于略有引湿性，且 DVS 前后本发明晶型未发生改变，在 0%-95%相对湿度条件范围内具有良好的物理稳定性。

引湿性会影响药物的稳定性、加工时的流动性和均匀性等，最终影响药物制剂的质量。引湿性会影响药物的制备、储存与后处理工艺。低引湿性晶型对储存条件要求不苛刻，降低了物料储存以及质量控制成本，具有很强的经济价值。

（2）本发明提供的晶型具有良好的稳定性。

本发明提供的晶型原料药在不同的储存条件下具有良好的物理、化学稳定。本发明提供的晶型 CS2 在 25°C /60%相对湿度和 40°C /75%相对湿度下敞口放置，至少放置 10 个月晶型保持不变，优选的可至少放置 1 年晶型保持不变。在 60°C /75%相对湿度条件下至少放置 2 周晶型未发生变化。本发明晶型的化学纯度在 99%以上，更优选的在 99.5%以上，且在放置过程中化学纯度基本保持不变。

本发明提供的晶型原料药在研磨条件下具有良好的物理稳定性。制剂加工过程中常需要原料药的研磨粉碎，研磨条件下良好的物理稳定性能够减小制剂加工过程中发生原料药晶型结晶度改变和转晶的风险。

本发明提供的晶型在制剂中具有良好的物理、化学稳定性。本发明晶型 CS2 与辅料混合做成药物制剂后，在 25℃/60%相对湿度和 40℃/75%相对湿度下至少放置 1 个月，制剂中本发明的晶型保持不变，且制剂中晶型的化学纯度基本保持不变。

晶型原料药和制剂具有良好的物理、化学稳定性。在存储和制剂工艺过程中，晶型 CS2 不会转变成其它晶型，且在储存过程中，晶型 CS2 的化学纯度基本保持不变，从而保证原料药和制剂的质量一致可控。

（3）本发明晶型 CS2 具有良好的体外溶出度与体外溶出速率。本发明的晶型 CS2 在 0.1mol/L 的盐酸水溶液介质中，60min 时已完全溶出。良好的体外溶出有利于其在体内的良好吸收，达到理想的生物利用度。

溶出是吸收的前提条件，良好的体外溶出度使得药物的吸收程度较高，在体内暴露特性更好，从而提高生物利用度，提高药物的疗效；高的体外溶出速率使得药物在给药后药物在血浆中能够很快达到最高浓度值，进而确保药物快速起效。

进一步地，本发明提供的晶型 CS2 还具有以下有益效果：

（1）本发明提供的晶型 CS2 具有良好的可压性。晶型 CS2 良好的可压性可以有效改善原料药加工过程中的硬度/脆碎度不合格等问题，降低对前续产品工艺处理的要求，使制剂工

艺更为稳健，改善产品外观，提升产品质量。

（2）与现有技术相比，本发明提供的晶型 CS2 具有更大的密度。实验结果表明：本发明晶型 CS2 的松密度与振实密度均优于现有技术固体。晶型 CS2 的密度较大，有利于大规模生产，更大的密度可减少粉尘，同时又能降低职业危害，减少安全隐患，保障生产安全。

（3）与现有技术相比，本发明晶型 CS2 具有更好的流动性。流动性评价结果表明，晶型 CS2 流动性较好，而现有技术固体流动性较差。晶型 CS2 更好的流动性可以有效提升压片和充填的生产速度，提升生产效率；晶型 CS2 更好的流动性能保证制剂的混合均匀度及含量均匀度、降低剂型的重量差异，提升产品质量。

（4）本发明晶型 CS2 具有优良的黏附性。黏附性评价结果表明，晶型 CS2 的吸附量较低，具有低的黏附性。低的黏附性可有效改善或者避免干法制粒和片剂压片等环节引起的黏轮、黏冲等现象，有利于改善产品外观、重量差异等。此外，低的黏附性还能有效减少原料的团聚现象，减少物料和器具之间的吸附，利于原料的分散及与其他辅料的混合，增加物料混合时的混合均匀度及最终产品的含量均匀度。

（5）本发明晶型 CS2 几乎没有溶剂残留，符合药用要求，而现有技术固体溶剂残留量超标，不能直接作为药用原料药。很多有机溶剂对环境、人体有一定危害，因此，为保障药物的用药安全，控制产品质量，需要严格对药物原料药的有机溶剂残留量进行要求和控制。

本发明中所述“挥发”，采用本领域的常规方法完成，例如缓慢挥发是将容器封上封口膜，扎孔，静置挥发；快速挥发是将容器敞口放置挥发。

本发明中，“晶体”或“多晶型”指被 X 射线粉末衍射图表征证实的。本领域技术人员能够理解，这里所讨论的理化性质可以被表征，其中的实验误差取决于仪器的条件、样品的准备和样品的纯度。特别是，本领域技术人员公知，X 射线衍射图通常会随着仪器的条件而有所改变。特别需要指出的是，X 射线粉末衍射图的相对强度也可能随着实验条件的变化而变化，所以峰强度的顺序不能作为唯一或决定性因素。事实上，XRPD 图谱中衍射峰的相对强度与晶体的择优取向有关，本文所示的峰强度为说明性而非用于绝对比较。另外，峰角度的实验误差通常在 5%或更少，这些角度的误差也应该被考虑进去，通常允许有±0.2°的误差。另外，由于样品厚度等实验因素的影响，会造成峰角度的整体偏移，通常允许一定的偏移。因而，本领域技术人员可以理解的是，本发明中一个晶型的 X 射线粉末衍射图不必和这里所指的实施例中的 X 射线粉末衍射图完全一致，本文所述“XRPD 图相同”并非指绝对相同，相同峰位置可相差±0.2°且峰强度允许一定可变性。任何具有和这些图谱中的

特征峰相同或相似的图的晶型均属于本发明的范畴之内。本领域技术人员能够将本发明所列的图谱和一个未知晶型的图谱相比较，以证实这两组图谱反映的是相同还是不同的晶型。

在一些实施方案中，本发明的晶型CS2是纯的、单一的，基本没有混合任何其他晶型。本发明中，“基本没有”当用来指新晶型时指这个晶型含有少于20%（重量）的其他晶型，尤其指少于10%（重量）的其他晶型，更指少于5%（重量）的其他晶型，更指少于1%（重量）的其他晶型。

需要说明的是，本发明中提及的数值及数值范围不应被狭隘地理解为数值或数值范围本身，本领域技术人员应当理解其可以根据具体技术环境的不同，在不背离本发明精神和原则的基础上围绕具体数值有所浮动，本发明中，这种本领域技术人员可预见的浮动范围多以术语“约”来表示。

附图说明

图1为实施例1所得晶型CS2的XRPD图。

图2为实施例1所得晶型CS2的DSC图。

图3为实施例1所得晶型CS2的TGA图。

图4为实施例1所得晶型CS2的^{1}HNMR图。

图5为实施例2所得晶型CS2的XRPD图。

图6为实施例2所得晶型CS2的DSC图。

图7为实施例2所得晶型CS2的TGA图。

图8为实施例2所得晶型CS2的^{1}HNMR图。

图9为本发明晶型CS2在25℃/60%相对湿度下放置前后的XRPD图（上图为放置前，下图为放置后）。

图10为本发明晶型CS2在40℃/75%相对湿度下放置前后的XRPD图（上图为放置前，下图为放置后）。

图11为本发明晶型CS2在60℃/75%相对湿度下放置前后的XRPD图（上图为放置前，下图为放置后）。

图12为本发明晶型CS2研磨前后的XRPD图（上图为研磨前，下图为研磨后）。

图13为本发明晶型CS2的DVS图。

图14为本发明晶型CS2在DVS前后的XRPD图（上图为DVS前，下图为DVS后）。

图15为本发明晶型CS2的体外溶出曲线。

具体实施方式

本发明进一步参考以下实施例限定，所述实施例详细描述本发明的晶型的制备和使用

方法。对本领域技术人员显而易见的是，对于材料和方法两者的许多改变可在不脱离本发明范围的情况下实施。

本发明中所用到的缩写的解释如下：

XRPD：X 射线粉末衍射

DSC：差示扫描量热

TGA：热重分析

DVS：动态水分吸附

^{1}H NMR：液态核磁氢谱

采集数据所用的仪器及方法：

本发明所述的 X 射线粉末衍射图在 Bruker D2 PHASER X 射线粉末衍射仪上采集。本发明所述的 X 射线粉末衍射的方法参数如下：

X 射线反射参数：

X 射线光源：Cu, Kα

Kα1 (Å)：1.54060；Kα2 (Å)：1.54439

Kα2/Kα1 强度比例：0.50

电压：30 仟伏特（kV)

电流：10 毫安培（mA)

扫描范围：自 3.0 至 40.0 度

本发明所述的差示扫描量热分析（DSC）图在 TA Q2000 上采集。本发明所述的 DSC 的方法参数如下：

扫描速率：10 °C/min

保护气体：氮气

本发明所述的热重分析（TGA）图在 TA Q500 上采集。本发明所述的 TGA 的方法参数如下：

扫描速率：10 °C /min

保护气体：氮气

本发明所述动态水分吸附（DVS）图在由 SMS 公司（Surface Measurement Systems Ltd.）生产的 Intrinsic 动态水分吸附仪上采集。所述的动态水分吸附仪的方法参数如下：

温度：25 °C

载气，流速：N_2, 200 毫升/分钟

单位时间质量变化：0.002%/分钟

相对湿度范围：0%RH-95%RH

本发明中高效液相色谱(HPLC)数据采自于安捷伦 1260，所用检测器为二极管阵列检测器(DAD)，方法参数如下：

色谱柱：ZORBAX Eclipse C18，100×4.6 mm, 3.5 μm

流动相： A：乙腈：水：三氟乙酸=50:950:1（体积比）

B：0.1%的三氟乙酸乙腈溶液

洗脱梯度如下：

时间 (min)	%B
0.0	0
0.5	0
30.0	90
35.0	90
35.1	0
40.0	0

流速：1.0 ml/min

进样量：2 μl

检测波长：220 nm

柱温：40 ℃

稀释剂：乙腈

核磁共振氢谱数据 (^{1}HNMR) 采自于 Bruker Avance II DMX 400M HZ 核磁共振波谱仪。称量 1-5mg 样品，用 0.5 mL 氘代二甲亚砜溶解，配成 2-10 mg/mL 的溶液。

除非特殊说明，以下实施例均在室温条件下操作。所述“室温”不是精确的温度值，是指10-30°C温度范围。

根据本发明，作为原料的所述化合物(I)指其固体（晶体或无定形）、半固体、蜡或油形式。优选地，作为原料的化合物（I）为固体粉末形式。

以下实施例中所使用到的 E-2006 是根据现有技术制备得到，例如根据 CN103153963B 中公开的制备方法得到。

具体实施方式

实施例 1：挥发法制备晶型 CS2

称取约 199.6 mg 的化合物(I)原料，溶解于 3.0mL 的丙酮中，过滤后在室温下缓慢挥发得到固体。经检测，所得固体为晶型 CS2，其 X 射线粉末衍射数据如图 1，表 1 所示。

本实施例所得晶型CS2的DSC如附图2所示，加热至177℃附近开始出现一个吸热峰，该吸热峰为CS2的熔化吸热峰。

本实施例所得晶型CS2的TGA如附图3所示，加热至170℃附近时具有约0.6%的质量损失。

本实施例所得晶型CS2的核磁共振氢谱如图4所示，数据为：^{1}H NMR (400 MHz, DMSO) δ 11.22 (s, 1H), 8.33 (d, J = 3.0 Hz, 1H), 8.13 (s, 1H), 7.89 (dd, J = 9.1, 4.1 Hz, 1H), 7.64 (td, J = 8.7, 3.1 Hz, 1H), 7.48-7.35 (m, 3H), 7.11 (ddd, J = 11.5, 6.0, 3.0 Hz, 1H), 4.68 (d, J = 10.2 Hz, 1H), 4.29 (d, J = 10.3 Hz, 1H), 2.64 (dd, J = 15.7, 8.8 Hz, 1H), 2.36 (d, J = 21.5 Hz, 3H), 2.03 (s, 3H), 1.74-1.67 (m, 1H), 1.50 (dd, J = 8.0, 4.8 Hz, 1H)。

表 1

衍射角 2θ	d 值	强度%
7.81	11.32	100.00
9.55	9.26	5.68
11.44	7.73	23.41
12.53	7.07	25.17
15.58	5.69	46.96
15.78	5.62	11.77
16.40	5.41	4.67
19.05	4.66	12.69
19.38	4.58	17.51
19.57	4.54	18.50
21.32	4.17	21.23
21.73	4.09	6.60
22.27	3.99	11.54
23.03	3.86	5.32
23.23	3.83	6.23
23.99	3.71	15.14
25.42	3.50	4.70
25.89	3.44	23.53
26.28	3.39	7.86
27.26	3.27	15.44
28.04	3.18	5.25
29.36	3.04	3.75
31.09	2.88	5.99

33.99	2.64	1.25

实施例 2：反溶剂添加法制备晶型 CS2

称取约 1026.0 mg 的化合物(I)原料，溶解于 10.0 mL 的甲醇中。过滤后搅拌，同时加入约 10.0 mL 的反溶剂水，继续搅拌约 4 小时有大量沉淀析出。抽滤，并于 40 °C 条件下真空干燥约 18 小时得到固体。经检测，所得固体为晶型 CS2，其 X 射线粉末衍射数据如图 5，表 2 所示。

本实施例所得晶型 CS2 的 DSC 如图 6 所示，加热至 176℃附近时开始出现一个吸热峰，该吸热峰为晶型 CS2 的融化吸热峰。

本实施例所得晶型 CS2 的 TGA 如图 7 所示，加热至 170℃附近时具有约 0.5%的失重。

本实施例所得晶型 CS2 的 ^{1}H NMR 图如图 8 所示，数据为：^{1}H NMR (400 MHz, DMSO) δ 11.21 (s, 1H), 8.33 (d, J = 3.0 Hz, 1H), 8.13 (s, 1H), 7.89 (dd, J = 9.2, 4.2 Hz, 1H), 7.64 (td, J = 8.8, 3.1 Hz, 1H), 7.49–7.34 (m, 3H), 7.16–7.05 (m, 1H), 4.68 (d, J = 10.2 Hz, 1H), 4.29 (d, J = 10.3 Hz, 1H), 2.67–2.57 (m, 1H), 2.38 (s, 3H), 2.03 (s, 3H), 1.74 - 1.66 (m, 1H), 1.50 (dd, J = 8.0, 4.8 Hz, 1H)。

表 2

衍射角 2θ	d 值	强度%
7.84	11.27	100.00
9.59	9.22	6.98
11.49	7.70	13.05
12.56	7.05	35.00
15.61	5.68	59.13
15.82	5.60	9.92
16.44	5.39	9.29
19.07	4.65	19.61
19.41	4.57	19.56
19.60	4.53	20.52
21.36	4.16	22.18
21.77	4.08	10.04
22.31	3.98	29.55
23.07	3.86	9.34
23.89	3.72	14.02
24.00	3.71	11.54
25.46	3.50	6.67

25.93	3.44	17.57
26.31	3.39	16.60
27.33	3.26	16.63
28.06	3.18	9.34
29.37	3.04	7.28
31.15	2.87	3.40
31.38	2.85	4.42
29.37	3.04	7.28
31.15	2.87	3.40

实施例 3~5：离子液体诱导挥发法制备晶型 CS2

称取约 31.5 mg 的化合物(I)原料，加入 1.0 mL 的乙腈溶剂溶解过滤，加入少量如表 3 中所示的离子液体，于室温下缓慢挥发得到固体。实施例 3~5 所得固体分别标记为样品 3~5，经检测，样品 3~5 均为晶型 CS2。

表 3

实施例	离子液体	样品标记
3	1-乙基-3-甲基咪唑硫酸甲酯盐	样品 3
4	1-乙基-3-甲基咪唑六氟锑酸盐	样品 4
5	1,3-二甲基咪唑磷酸二甲酯盐	样品 5

实施例 6：晶型 CS2 的稳定性

称取本发明的晶型 CS2，分别在 25℃/60%相对湿度、40℃/75%相对湿度、60℃/75%相对湿度条件下敞口放置，采用 HPLC 和 XRPD 测定晶型与化学纯度的变化，结果如表 4 所示。

表 4

起始晶型	起始纯度	放置条件	放置时间	放置后晶型	放置后纯度
晶型 CS2（图 9 上图）	99.67%	25°C /60%相对湿度	10 个月	晶型 CS2（图 9 下图）	99.63%
晶型 CS2（图 10 上图）	99.67%	40°C /75%相对湿度	10 个月	晶型 CS2（图 10 下图）	99.67%
晶型 CS2	99.67%	60°C /75%	2 周	晶型 CS2	99.70%

（图 11 上图）		相对湿度		（如图 11 下图）	

结果表明，晶型 CS2 在 25℃/60%相对湿度和 40℃/75%相对湿度条件下至少可稳定 10 个月，在 60℃/75%相对湿度条件下放置至少可稳定 2 周，且放置前后晶型 CS2 的化学纯度基本保持不变。可见，晶型 CS2 具有良好的物理、化学稳定性。

实施例 7：晶型 CS2 的研磨稳定性

将晶型 CS2 置于研钵中，手动研磨 5 分钟，研磨前后的 XRPD 图如图 12 所示（上图为研磨前，下图为研磨后）。结果表明，研磨前后晶型 CS2 未发生变化，具有良好的研磨稳定性。

实施例 8：晶型 CS2 的引湿性

称取本发明晶型 CS2 约 10 mg 采用动态水分吸附(DVS) 仪测试其引湿性，在 0-95%-0 相对湿度下循环一次，记录每个湿度下的质量变化，DVS 图如图 13 所示，实验结果如表 5 所示。测试 DVS 前后晶型的 XRPD 图，结果如图 14 所示（上图为 DVS 前，下图为 DVS 后）。结果表明，晶型 CS2 的引湿性低，在 80%相对湿度的增重量为 0.21%，属于略有引湿性，且 DVS 前后晶型未发生改变，在 0%-95%相对湿度条件范围内具有良好的物理稳定性。

表 5

相对湿度 / 增重(%)	80%相对湿度的增重	引湿性
晶型 CS2	0.21%	略有引湿性

关于引湿性特征描述与引湿性增重的界定（中国药典 2015 年版通则 9103 药物引湿性试验指导原则，实验条件：25°C±1°C，80%相对湿度）：

潮解：吸收足量水分形成液体

极具引湿性：引湿增重不小于 15.0%

有引湿性：引湿增重小于 15.0%但不小于 2.0%

略有引湿性：引湿增重小于 2.0%但不小于 0.2%

无或几乎无引湿性：引湿增重小于 0.2%

实施例 9：晶型 CS2 和现有技术固体的流动性对比

制剂工艺过程中，通常可采用压缩性来评价粉体或中间体颗粒的流动性，即压缩度（c）。压缩度是指将一定量的粉体轻轻装入量筒后测量最初松体积；采用轻敲法使粉体处于最紧

状态，测量最终的体积；计算松密度 ρ_0 与振实密度 ρ_f；根据公式 $c=(\rho_f-\rho_0)/\rho_f$ 计算压缩度。压缩度又称为可压性系数（Compressibility index）或卡尔系数（Carr Index），是评价流动性的重要指标。

可压性系数的测试方法如下：在测定出晶型 CS2 和无定形固体样品堆密度 ρ_0 和振实密度 ρ_f 的基础上，通过公式 $c=(\rho_f-\rho_0)/\rho_f*100\%$ 计算样品可压性系数。可压性系数对粉体流动性的界定标准详见表 6。

表 6

可压性系数（%）	流动性
≦10	极好
11-15	好
16-20	一般
21-25	可接受
26-31	差
32-37	很差
>38	极差

重复现有专利 CN103153963B 中的制备方法得到无定形固体，晶型 CS2 和该无定形固体的流动性评价结果见表 7，结果表明晶型 CS2 的流动性优于现有无定形固体。

表 7

晶型	松密度 (ρ_0, g/mL)	振实密度 (ρ_f, g/mL)	可压性指数 (%)	流动性
无定形固体	0.196	0.274	28	差
晶型 CS2	0.263	0.351	25	可接受

实施例 10：晶型 CS2 的黏附性

将 30 mg 晶型 CS2 置于直径为 8mm 圆形平冲中，采用 10 kN 的压力进行压片处理，压片后停留约半分钟，称量冲头吸附的粉末量。采用该方法连续压制两次后，记录冲头累计的最终吸附量、压制过程中的最高吸附量和平均吸附量，实验结果如表 8 所示。

表 8

晶型	最高吸附量(mg)	平均吸附量(mg)	累计的最终吸附量(mg)
晶型 CS2	0.74	0.22	0.44

实施例 11：晶型 CS2 的可压性

将 80 mg 晶型 CS2 样品置于直径为 6mm 圆形平冲中，在 10 kN 压力下压制成圆形片剂，放置于干燥器中 24 h，待完全弹性复原后采用片剂硬度测定仪测试其径向破碎力（硬度，H）。采用游标卡尺测量片剂的直径（D）和厚度（L），利用公式 T=2H/πDL 计算出不同硬度下粉体的抗张强度。在一定的压力下，抗张强度越大的，表示其可压性越好。测试结果如下表 9 所示。

表 9

晶型	厚度(mm)	直径(mm)	硬度(N)	抗张强度(MPa)
CS2	2.40	6.06	8.4	0.37

实施例 12：晶型 CS2 和现有技术固体的溶剂残留

重复现有专利 CN103153963B 中的制备方法得到无定形固体，分别测试本发明晶型 CS2 和无定形固体的溶剂残留量。测试结果表明，本发明晶型 CS2 无溶剂残留，而无定形固体中正庚烷的溶剂残留量为 46596.16 ppm，乙酸乙酯的溶剂残留量为 1260.01 ppm。根据国际协调会（ICH）关于残留溶剂的指导原则，正庚烷和乙酸乙酯均属于第三类溶剂，溶剂残留量不得超过 5000 ppm。可见无定形固体中正庚烷溶剂的残留量远超过 ICH 规定的限度，不适合直接作为药用原料药。

实施例 13：晶型 CS2 的制剂

1. 化合物(I)片剂的制备：

将晶型 CS2 与表 10 所示的内加辅料混合均匀，用直径为 20mm 的单冲手动压片机压片，压力为 5±0.5 KN，片剂片重为 500 mg。将上述片剂碾碎，过 20 目筛，并与表 10 所示的外加辅料混合均匀，用直径为 7mm 的单冲手动压片机压片，压力为 5±0.5 KN，片剂片重为 120.0 mg 。

表 10

成分		质量(毫克/片)	质量比(%)
E-2006 (晶型 CS2)		10.00	8.3
内加辅料	一水乳糖	88.88	74.1
	羟丙基纤维素	3.60	3.0
	低取代羟丙基纤维素	10.80	9.0
	硬脂酸镁	0.36	0.3
小计		113.64	94.7
外加辅料	低取代羟丙基纤维素	6.00	5.0

	硬脂酸镁	0.36	0.3
总计		120.00	100.0

2. 晶型 CS2 在制剂中的稳定性

上述制备的片剂用 35cc HDPE 瓶包装（每瓶一片），每瓶含有 1g 干燥剂，用封口机封口。在 25℃/60%相对湿度和 40℃/75%相对湿度条件下放置 1 个月，经检测，在含晶型 CS2 的片剂中，晶型未发生变化，且在放置过程中晶型 CS2 的单杂和总杂基本保持不变。结果如下表 11 和表 12 所示，说明晶型 CS2 在制剂中具有好的物理、化学稳定性。

表 11 晶型 CS2 在制剂中的物理稳定性

样品	放置条件	放置时间	放置后 API 晶型
含晶型 CS2 的片剂	25℃/60%相对湿度	1 个月	晶型 CS2
	40℃/75%相对湿度	1 个月	晶型 CS2

表 12 晶型 CS2 在制剂中的化学稳定性

放置条件	放置时间	起始最大单杂（%）	放置后最大单杂（%）	起始总杂（%）	放置后总杂（%）	单杂变化量（%）	总杂变化量（%）
25℃/60%相对湿度	1 个月	0.08	0.09	0.17	0.21	0.01	0.04
40℃/75%相对湿度	1 个月	0.08	0.08	0.17	0.20	0	0.03

实施例 14：晶型 CS2 的体外溶出度与体外溶出速率

对实施例 12 获得的含 CS2 的片剂测试体外溶出情况，溶出度的测定按照中国药典 2015 年版 0931 溶出度与释放度测定法，条件如下：

溶出介质： 0.1mol/L 的盐酸水溶液

溶出方法：桨法

介质体积：900 mL

转速：50 rpm

介质温度：37 ℃

晶型 CS2 的体外溶出情况如下表 13，图 15 所示。

表 13

累积溶出度（%） / 时间（min）	晶型 CS2
0	0.0

5	55.2
10	73.1
15	81.0
20	86.2
30	92.1
45	96.9
60	100.5

结果表明，采用晶型 CS2 制备的制剂样品，在 0.1mol/L 的盐酸水溶液介质中的体外溶出完全，且溶出速率高，有利于其在体内达到良好的生物利用度。

上述实施例只为说明本发明的技术构思及特点，其目的在于让熟悉此项技术的人士能够了解本发明的内容并据以实施，并不能以此限制本发明的保护范围。凡根据本发明精神实质所作的等效变化或修饰，都应涵盖在本发明的保护范围之内。

权 利 要 求 书

1. 一种 E-2006 的晶型 CS2，其特征在于，其 X 射线粉末衍射图在 2θ 值为 7.8°±0.2°、15.6°±0.2°、11.4°±0.2°处具有特征峰。

2. 根据权利要求 1 所述的晶型 CS2，其特征在于，其 X 射线粉末衍射图在 2θ 值为 12.5°±0.2°、21.3°±0.2°、27.3°±0.2°中的 1 处或 2 处或 3 处具有特征峰。

3. 根据权利要求 1 所述的晶型 CS2，其特征在于，其 X 射线粉末衍射图在 2θ 值为 24.0°±0.2°、19.4°±0.2°、22.3°±0.2°中的 1 处或 2 处或 3 处具有特征峰。

4. 一种权利要求 1 所述的 E-2006 晶型 CS2 的制备方法，其特征在于所述方法包括：

(1) 将化合物(I)原料溶解在正溶剂中，配成含化合物(I)的溶液，后将反溶剂缓慢滴加到该溶液中，搅拌析晶得到；或

(2) 将化合物(I)原料溶解在酮类溶剂中，缓慢挥发得到；或

(3) 将化合物(I)原料溶解在腈类溶剂中，加入离子液体诱导，后缓慢挥发得到。

5. 根据权利要求 4 所述的制备方法，方法(1)中所述正溶剂为醇类溶剂，所述反溶剂为水；方法(2)中所述酮类溶剂为丙酮；方法(3)中所述腈类溶剂为乙腈，所述离子液体为 1-乙基-3-甲基咪唑硫酸甲酯盐、或 1-乙基-3-甲基咪唑六氟锑酸盐、或 1,3-二甲基咪唑磷酸二甲酯盐。

6. 根据权利要求 5 所述的制备方法，方法(1)中所述醇类溶剂为甲醇。

7. 一种药物组合物，所述药物组合物包含有效治疗量的权利要求 1 中所述的晶型 CS2 及药学上可接受的载体、稀释剂或赋形剂。

8. 权利要求 1 中所述的晶型 CS2 在制备食欲素受体拮抗剂药物中的用途。

9. 权利要求 1 中所述的晶型 CS2 在制备治疗失眠症和/或不规则睡眠-觉醒节律障碍药物中的用途。

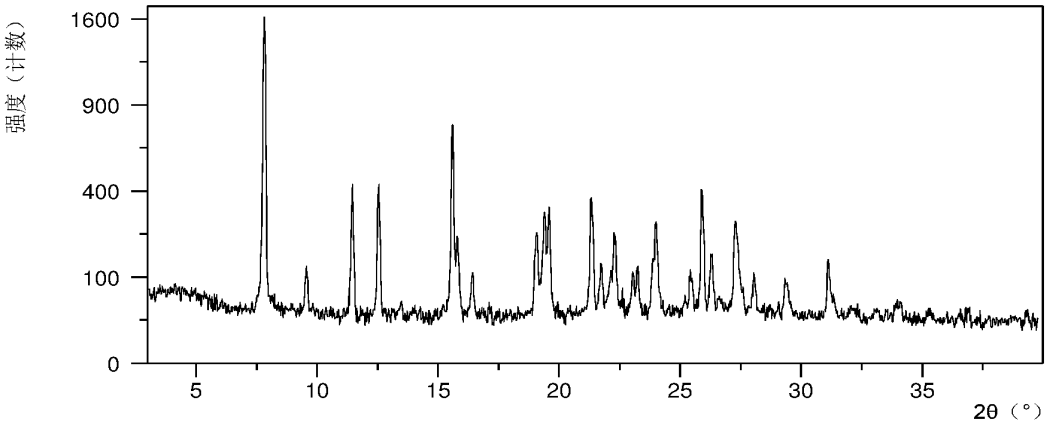

强度（计数）
1600
900
400
100
0
5
10
15
20
25
30
35
2θ（°）

图 1

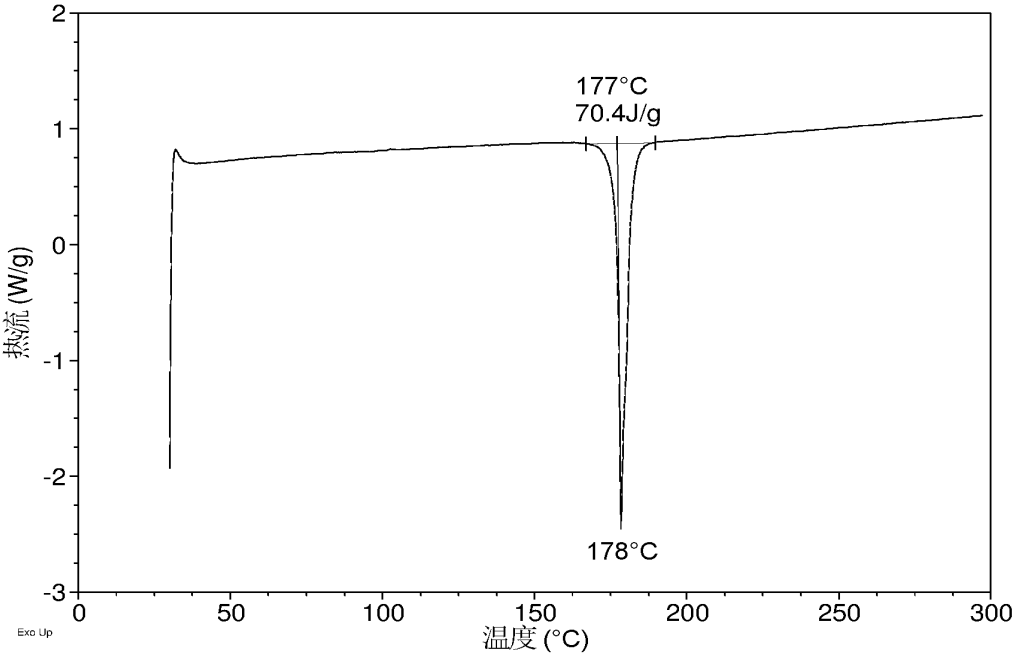

177°C
70.4J/g
178°C
热流 (W/g)
Exo Up
温度 (°C)
2
1
0
-1
-2
-3
0
50
100
150
200
250
300

图 2

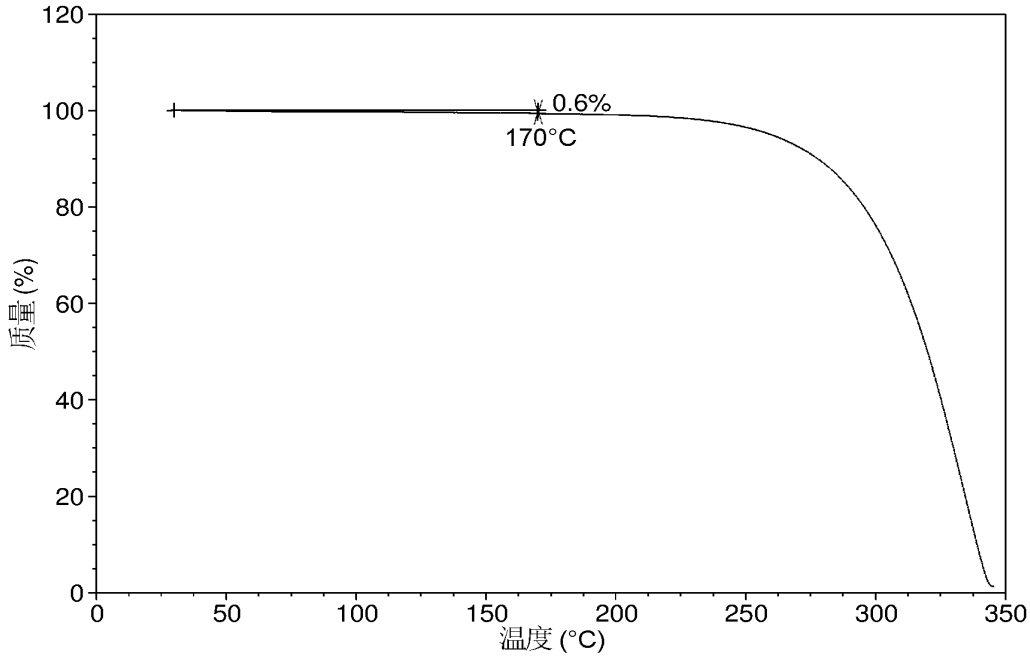

120
100
80
60
40
20
0
质量 (%)
0.6%
170°C
0
50
100
150
200
250
300
350
温度 (°C)

图 3

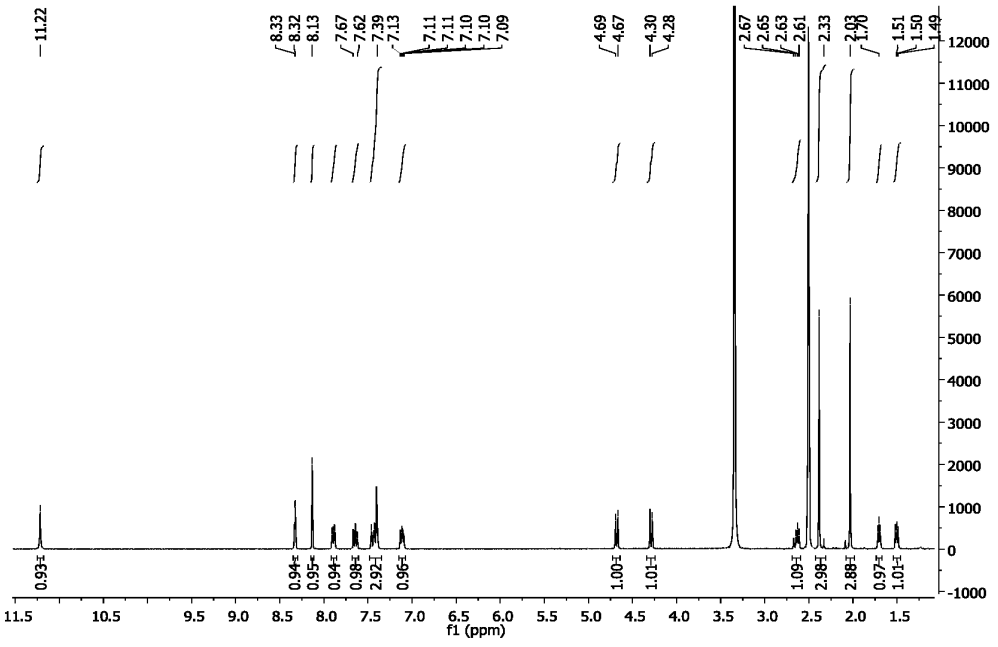

11.22
8.33
8.32
8.13
7.67
7.62
7.39
7.13
7.11
7.11
7.10
7.10
7.09
4.69
4.67
4.30
4.28
2.67
2.65
2.63
2.61
2.33
2.03
1.90
1.51
1.50
1.49
0.93
0.94
0.95
0.94
0.98
2.92
0.96
1.00
1.01
1.09
2.98
2.88
0.97
1.01
f1 (ppm)

图 4

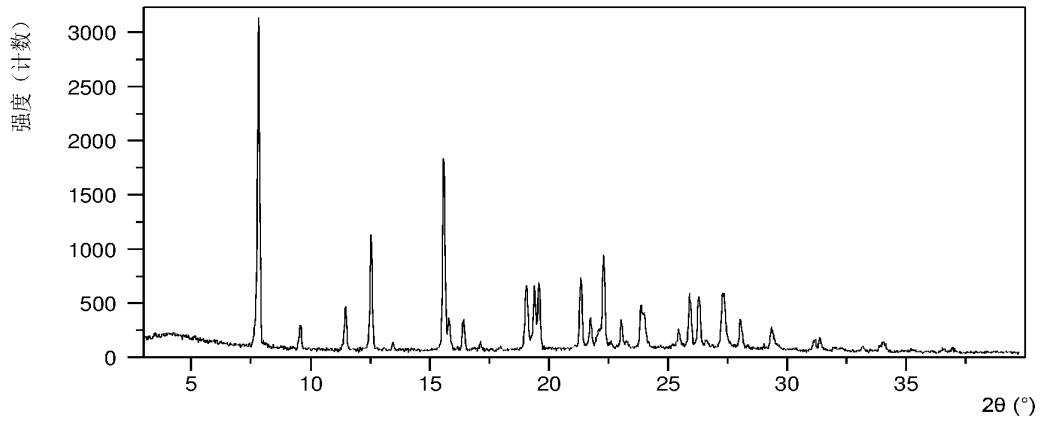

强度（计数）
3000
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
2θ (°)

图 5

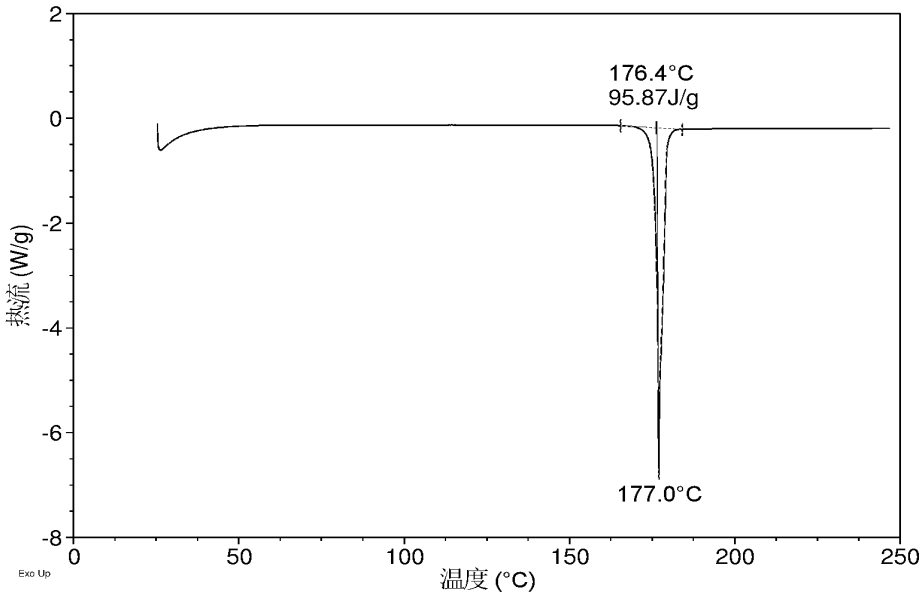

176.4°C
95.87J/g
177.0°C
热流 (W/g)
2
0
-2
-4
-6
-8
0
50
100
150
200
250
Exo Up
温度 (°C)

图 6

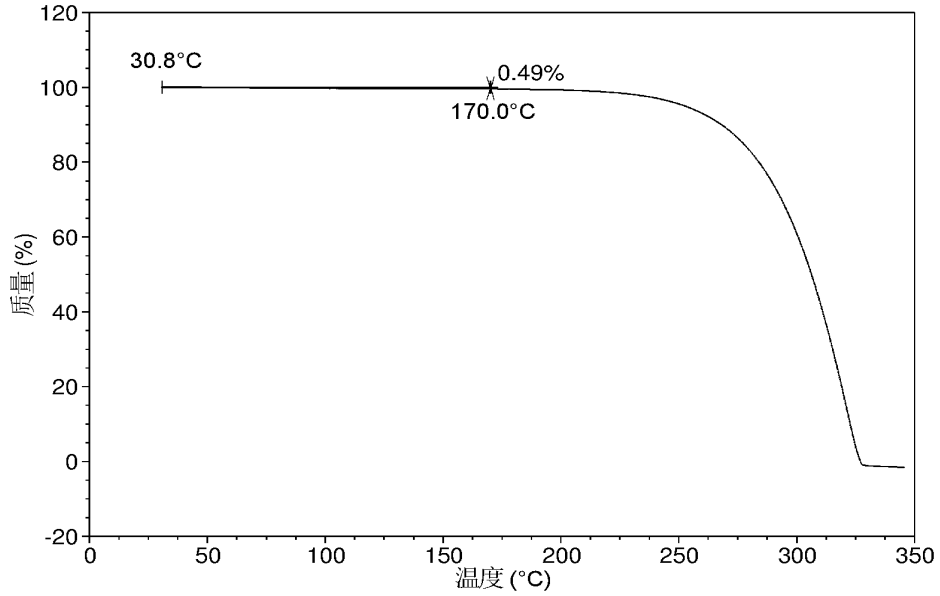


图 7

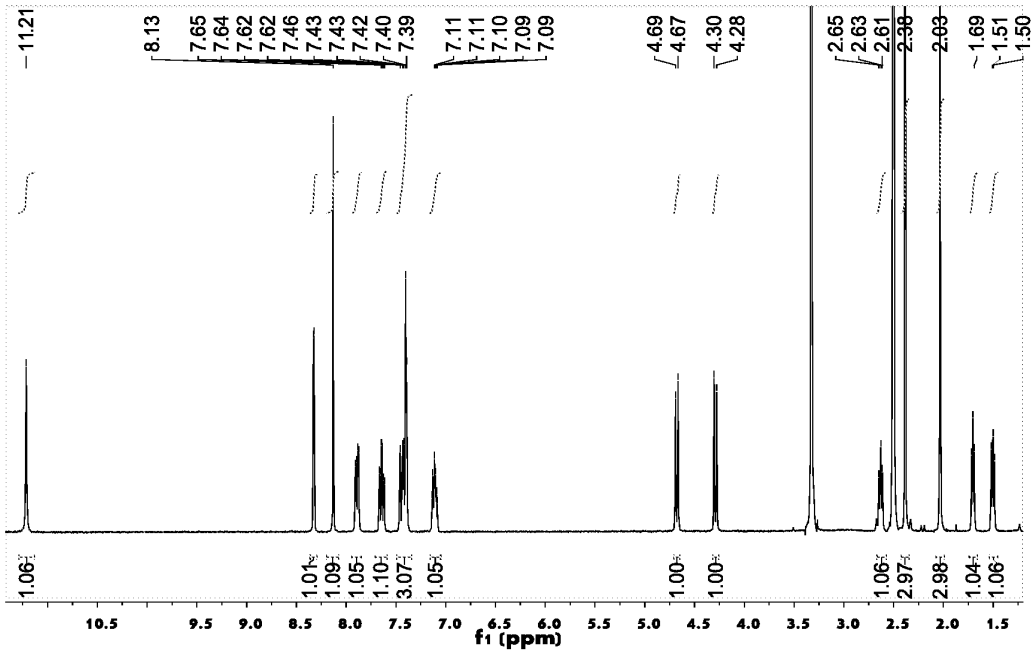


图 8

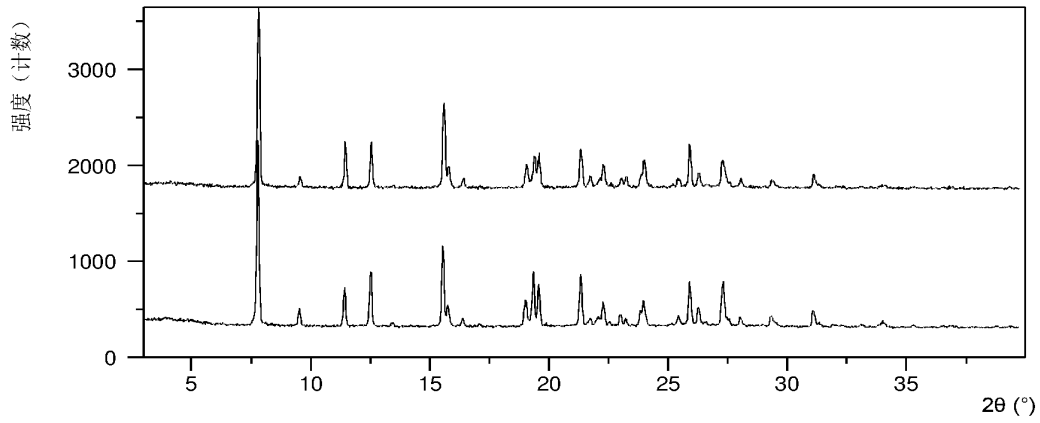

强度（计数）
3000
2000
1000
0
5
10
15
20
25
30
35
2θ (°)

图 9

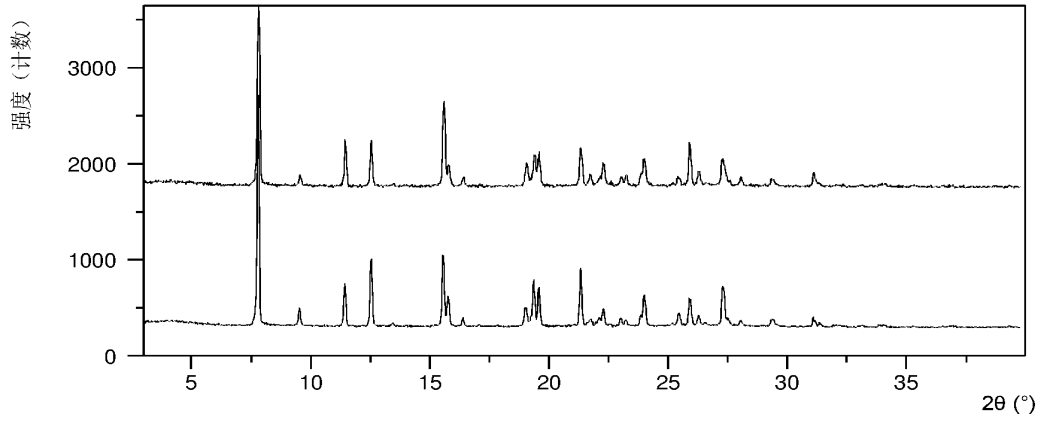

强度（计数）
3000
2000
1000
0
5
10
15
20
25
30
35
2θ (°)

图 10

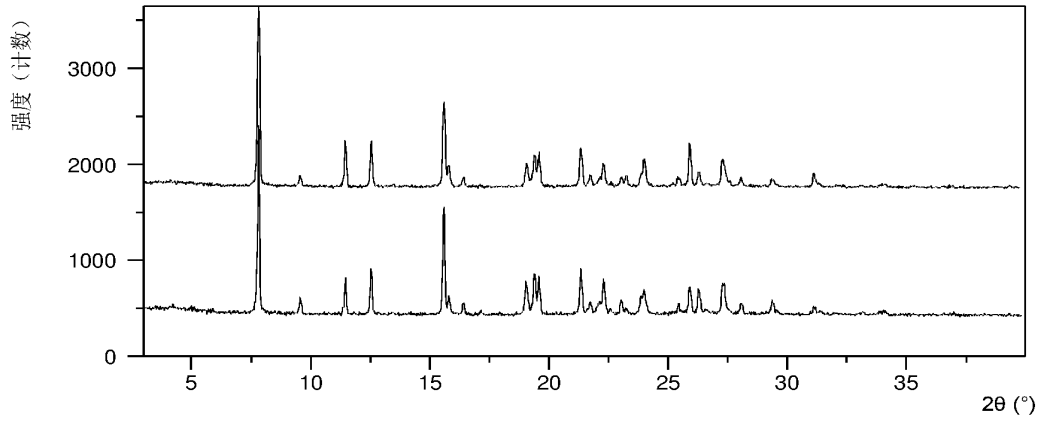

强度（计数）
3000
2000
1000
0
5
10
15
20
25
30
35
2θ (°)

图 11

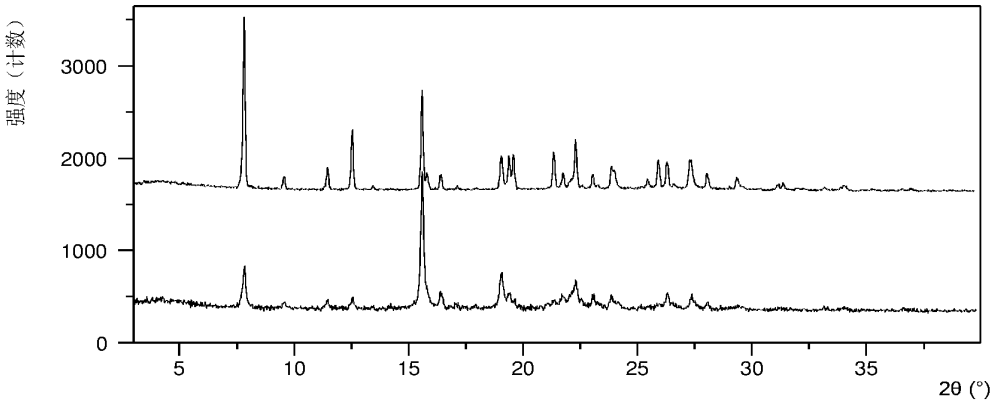

强度（计数）
3000
2000
1000
0
5
10
15
20
25
30
35
2θ (°)

图 12

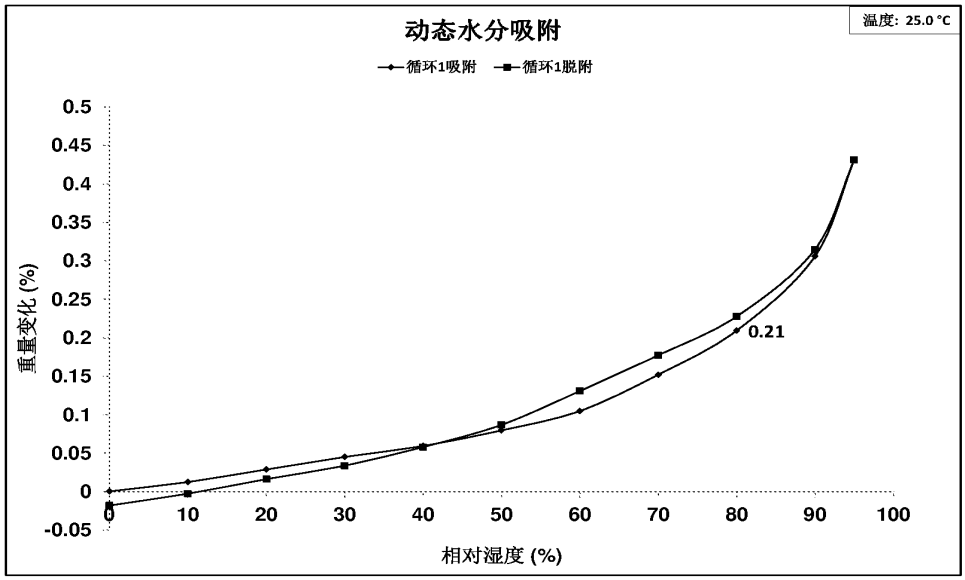

动态水分吸附
温度: 25.0 °C
循环1吸附
循环1脱附
重量变化 (%)
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
-0.05
0.21
0
10
20
30
40
50
60
70
80
90
100
相对湿度 (%)

图 13

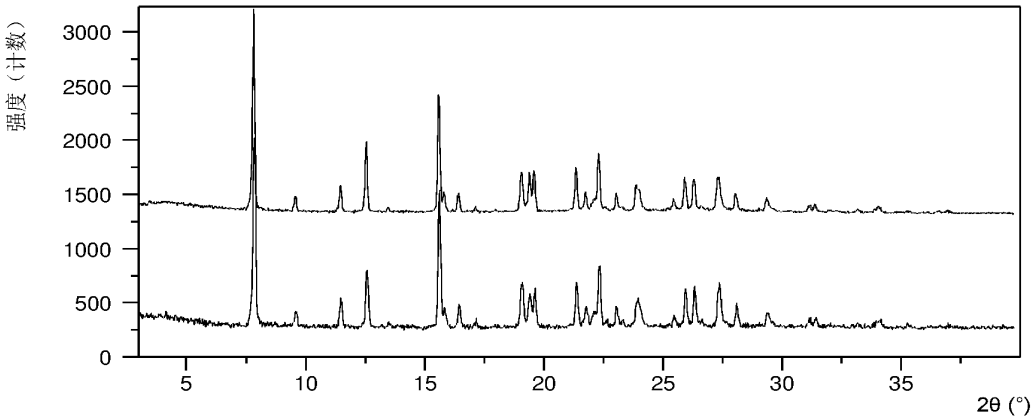

强度（计数）
3000
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
2θ (°)

图 14

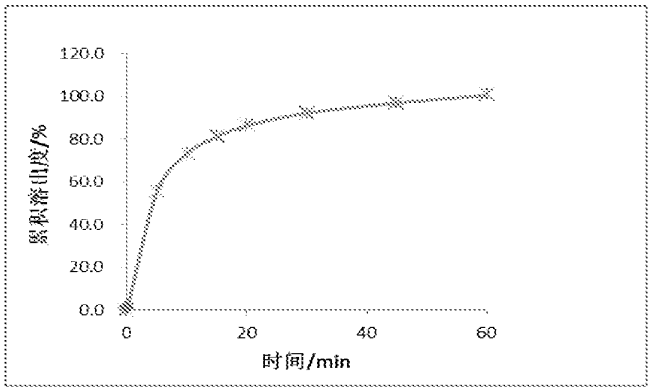


图 15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2018/097797

A. CLASSIFICATION OF SUBJECT MATTER

C07D 239/34(2006.01)i; A61K 31/506(2006.01)i; A61P 25/20(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D239/-,A61K31/-,A61P25/-

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)

CNPAT, CNKI, WPI, EPODOC, STN, E-2006, lemborexant, 离子液体, 结晶, 晶型, 晶体, ionic liquid, crystal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 104114524 A (EISAI R&D MANAGEMENT CO., LTD.) 22 October 2014 (2014-10-22) description, paragraphs 3-4 and 217	1-4, 7-9
Y	CN 104114524 A (EISAI R&D MANAGEMENT CO., LTD.) 22 October 2014 (2014-10-22) description, paragraphs 3-4 and 217	4-6
Y	CN 104592184 A (YUNNAN INSTITUTE OF MATERIA MEDICA; HLK PHARMACIN LLC) 06 May 2015 (2015-05-06) description, paragraph 7	4-6
A	CN 103153963 A (EISAI R&D MANAGEMENT CO., LTD.) 12 June 2013 (2013-06-12) description, paragraphs 659-662 and embodiment 95, and claims 1-20	1-9
A	WO 2016063995 A1 (EISAI R&D MAN CO., LTD.) 28 April 2016 (2016-04-28) description, paragraphs 1-253	1-9

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 October 2018	**31 October 2018**

Name and mailing address of the ISA/CN	Authorized officer
State Intellectual Property Office of the P. R. China **No. 6, Xitucheng Road, Jimenqiao Haidian District, Beijing** **100088** **China**	
Facsimile No. **(86-10)62019451**	Telephone No.

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2018/097797

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
CN	104114524	A	22 October 2014	IL	232949	D0	03 August 2014
				WO	2013123240	A1	22 August 2013
				MX	352881	B	13 December 2017
				US	2016318858	A1	03 November 2016
				US	2018044285	A1	15 February 2018
				US	9828336	B2	28 November 2017
				IL	232949	A	31 August 2016
				US	2015025237	A1	22 January 2015
				JP	2015509939	A	02 April 2015
				RU	2617696	C2	26 April 2017
				MX	2014009917	A	13 November 2014
				JP	6147279	B2	14 June 2017
				US	9416109	B2	16 August 2016
				SG	11201403216U	A	30 December 2014
				EP	2814798	A1	24 December 2014
				RU	2014137470	A	10 April 2016
				CA	2861493	A1	22 August 2013
				CN	104114524	B	17 August 2016
CN	104592184	A	06 May 2015	WO	2016095702	A1	23 June 2016
				CN	104592184	B	29 September 2017
				US	2017368019	A1	28 December 2017
				CN	107501223	A	22 December 2017
CN	103153963	A	12 June 2013	MY	160969	A	31 March 2017
				MX	2013003218	A	28 June 2013
				RS	54101	B1	30 October 2015
				KR	101458007	B1	04 November 2014
				TW	I516484	B	11 January 2016
				ES	2540851	T3	14 July 2015
				DK	2626350	T3	29 June 2015
				CN	103153963	B	24 December 2014
				AU	2011304285	B2	29 January 2015
				US	8268848	B2	18 September 2012
				NZ	609313	A	30 May 2014
				SI	2626350	T1	30 September 2015
				EP	2626350	A1	14 August 2013
				CL	2013000784	A1	05 July 2013
				CA	2811895	A1	29 March 2012
				JP	4944286	B1	30 May 2012
				CA	2811895	C	08 December 2015
				PE	11622013	A1	19 October 2013
				EP	2626350	A4	12 February 2014
				RU	2571414	C2	20 December 2015
				IL	225437	D0	27 June 2013
				AU	2011304285	A1	16 May 2013
				MA	34609	B1	02 October 2013
				JP	WO2012039371	A1	03 February 2014
				KR	20130097776	A	03 September 2013
				AR	083060	A1	30 January 2013
				IL	225437	A	31 May 2015
				PT	2626350	E	03 August 2015

Form PCT/ISA/210 (patent family annex) (January 2015)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2018/097797

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
		SG	188585	A1	30 April 2013
		TW	201305129	A	01 February 2013
		SI	EP2626350	T1	30 September 2015
		UA	108510	C2	12 May 2015
		EP	2626350	B1	15 April 2015
		WO	2012039371	A1	29 March 2012
		BR	112013006594	A2	21 June 2016
		RU	2013117464	A	27 October 2014
		US	2012095031	A1	19 April 2012
WO 2016063995 A1	28 April 2016	IL	251759	D0	29 June 2017
		KR	20170068478	A	19 June 2017
		AU	2015336463	A1	04 May 2017
		EP	3209298	A1	30 August 2017
		CA	2964504	A1	28 April 2016
		CN	107810006	A	16 March 2018
		BR	112017007063	A2	14 February 2018
		JP	2017531683	A	26 October 2017
		SG	11201703064W	A	30 May 2017
		US	2017252342	A1	07 September 2017
		MX	2017004950	A	16 January 2018
		EP	3209298	A4	20 June 2018

Form PCT/ISA/210 (patent family annex) (January 2015)

国际检索报告

国际申请号 PCT/CN2018/097797

A. 主题的分类

C07D 239/34(2006.01)i；A61K 31/506(2006.01)i；A61P 25/20(2006.01)i

按照国际专利分类(IPC)或者同时按照国家分类和IPC两种分类

B. 检索领域

检索的最低限度文献(标明分类系统和分类号)

C07D239/-,A61K31/-,A61P25/-

包含在检索领域中的除最低限度文献以外的检索文献

在国际检索时查阅的电子数据库(数据库的名称，和使用的检索词（如使用））

CNPAT,CNKI,WPI,EPODOC,STN,E-2006，lemborexant,离子液体，结晶，晶型，晶体，ionic liquid,crystal

C. 相关文件

类 型*	引用文件，必要时，指明相关段落	相关的权利要求
X	CN 104114524 A（卫材R&D管理有限公司）2014年 10月 22日（2014-10-22） 说明书第3-4段，217段	1-4，7-9
Y	CN 104114524 A（卫材R&D管理有限公司）2014年 10月 22日（2014-10-22） 说明书第3-4段，217段	4-6
Y	CN 104592184 A（云南省药物研究所 深圳市华力康生物医药有限公司）2015年 5月 6日（2015-05-06） 说明书第7段	4-6
A	CN 103153963 A（卫材R&D管理有限公司）2013年 6月 12日（2013-06-12） 说明书第659-662段，实施例95，权利要求1-20	1-9
A	WO 2016063995 A1（EISAI R&D MAN CO LTD.）2016年 4月 28日（2016-04-28） 说明书第1-253段	1-9

☐ 其余文件在C栏的续页中列出。

☑ 见同族专利附件。

* 引用文件的具体类型：

“A” 认为不特别相关的表示了现有技术一般状态的文件

“E” 在国际申请日的当天或之后公布的在先申请或专利

“L” 可能对优先权要求构成怀疑的文件，或为确定另一篇引用文件的公布日而引用的或者因其他特殊理由而引用的文件（如具体说明的）

“O” 涉及口头公开、使用、展览或其他方式公开的文件

“P” 公布日先于国际申请日但迟于所要求的优先权日的文件

“T” 在申请日或优先权日之后公布，与申请不相抵触，但为了理解发明之理论或原理的在后文件

“X” 特别相关的文件，单独考虑该文件，认定要求保护的发明不是新颖的或不具有创造性

“Y” 特别相关的文件，当该文件与另一篇或者多篇该类文件结合并且这种结合对于本领域技术人员为显而易见时，要求保护的发明不具有创造性

“&” 同族专利的文件

国际检索实际完成的日期	国际检索报告邮寄日期
2018年 10月 15日	2018年 10月 31日
ISA/CN的名称和邮寄地址 中华人民共和国国家知识产权局(ISA/CN) 中国北京市海淀区蓟门桥西土城路6号 100088 传真号 (86-10)62019451	受权官员 李敏 电话号码 86-(010)-53962148

表 PCT/ISA/210（第2页）（2015年1月）

国际检索报告
关于同族专利的信息

国际申请号
PCT/CN2018/097797

检索报告引用的专利文件			公布日（年/月/日）	同族专利			公布日（年/月/日）
CN	104114524	A	2014年 10月 22日	IL	232949	D0	2014年 8月 3日
				WO	2013123240	A1	2013年 8月 22日
				MX	352881	B	2017年 12月 13日
				US	2016318858	A1	2016年 11月 3日
				US	2018044285	A1	2018年 2月 15日
				US	9828336	B2	2017年 11月 28日
				IL	232949	A	2016年 8月 31日
				US	2015025237	A1	2015年 1月 22日
				JP	2015509939	A	2015年 4月 2日
				RU	2617696	C2	2017年 4月 26日
				MX	2014009917	A	2014年 11月 13日
				JP	6147279	B2	2017年 6月 14日
				US	9416109	B2	2016年 8月 16日
				SG	11201403216U	A	2014年 12月 30日
				EP	2814798	A1	2014年 12月 24日
				RU	2014137470	A	2016年 4月 10日
				CA	2861493	A1	2013年 8月 22日
				CN	104114524	B	2016年 8月 17日
CN	104592184	A	2015年 5月 6日	WO	2016095702	A1	2016年 6月 23日
				CN	104592184	B	2017年 9月 29日
				US	2017368019	A1	2017年 12月 28日
				CN	107501223	A	2017年 12月 22日
CN	103153963	A	2013年 6月 12日	MY	160969	A	2017年 3月 31日
				MX	2013003218	A	2013年 6月 28日
				RS	54101	B1	2015年 10月 30日
				KR	101458007	B1	2014年 11月 4日
				TW	I516484	B	2016年 1月 11日
				ES	2540851	T3	2015年 7月 14日
				DK	2626350	T3	2015年 6月 29日
				CN	103153963	B	2014年 12月 24日
				AU	2011304285	B2	2015年 1月 29日
				US	8268848	B2	2012年 9月 18日
				NZ	609313	A	2014年 5月 30日
				SI	2626350	T1	2015年 9月 30日
				EP	2626350	A1	2013年 8月 14日
				CL	2013000784	A1	2013年 7月 5日
				CA	2811895	A1	2012年 3月 29日
				JP	4944286	B1	2012年 5月 30日
				CA	2811895	C	2015年 12月 8日
				PE	11622013	A1	2013年 10月 19日
				EP	2626350	A4	2014年 2月 12日
				RU	2571414	C2	2015年 12月 20日
				IL	225437	D0	2013年 6月 27日
				AU	2011304285	A1	2013年 5月 16日
				MA	34609	B1	2013年 10月 2日
				JP	WO2012039371	A1	2014年 2月 3日
				KR	20130097776	A	2013年 9月 3日
				AR	083060	A1	2013年 1月 30日
				IL	225437	A	2015年 5月 31日
				PT	2626350	E	2015年 8月 3日

表 PCT/ISA/210（同族专利附件）（2015年1月）

国际检索报告
关于同族专利的信息

国际申请号
PCT/CN2018/097797

检索报告引用的专利文件			公布日（年/月/日）	同族专利			公布日（年/月/日）
				SG	188585	A1	2013年 4月 30日
				TW	201305129	A	2013年 2月 1日
				SI	EP2626350	T1	2015年 9月 30日
				UA	108510	C2	2015年 5月 12日
				EP	2626350	B1	2015年 4月 15日
				WO	2012039371	A1	2012年 3月 29日
				BR	112013006594	A2	2016年 6月 21日
				RU	2013117464	A	2014年 10月 27日
				US	2012095031	A1	2012年 4月 19日
WO	2016063995	A1	2016年 4月 28日	IL	251759	D0	2017年 6月 29日
				KR	20170068478	A	2017年 6月 19日
				AU	2015336463	A1	2017年 5月 4日
				EP	3209298	A1	2017年 8月 30日
				CA	2964504	A1	2016年 4月 28日
				CN	107810006	A	2018年 3月 16日
				BR	112017007063	A2	2018年 2月 14日
				JP	2017531683	A	2017年 10月 26日
				SG	11201703064W	A	2017年 5月 30日
				US	2017252342	A1	2017年 9月 7日
				MX	2017004950	A	2018年 1月 16日
				EP	3209298	A4	2018年 6月 20日

表 PCT/ISA/210（同族专利附件）（2015年1月）

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: January 30, 2020

Docket No.: 134070-01602
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Utility Application of:
Minhua Chen et al.

Application No.: Not Yet Assigned
Continuation of PCT/CN2018/097797

Confirmation No.: N/A

Filed: Concurrently Herewith
Int'l Filing Date: July 31, 2018

Art Unit: N/A

For: CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE THEREOF

Examiner: Not Yet Assigned

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

PRELIMINARY AMENDMENT

Dear Sir:

Prior to examination on the merits, please amend the above-identified U.S. patent application as follows:

Amendments to the Specification begin at page 2 of this paper.

Amendments to the Claims begin at page 4 of this paper.

Remarks/Arguments begin at page 6 of this paper.

AMENDMENTS TO THE SPECIFICATION

Please amend the title as follows:

~~CRYSTAL FORM OF OREXIN RECEPTOR ANTAGONIST, PREPARATION METHOD THEREFOR AND USE THEREOF~~

CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE THEREOF

Please add the following paragraph at page 1 right below the application title:

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of International Application No. PCT/CN2018/097797, filed on July 31, 2018, which claims the benefit of foreign priority of Chinese Patent Application No.: 201710648135.2, filed on August 1, 2017. The entire contents of the aforementioned applications are incorporated herein by reference.

Please amend the paragraph at page 2, lines 19-20, as follows:

According to one aspect of the present disclosure, the X-ray powder diffraction pattern of Form CS2 shows characteristic peaks at 2theta values of 7.8°±0.2°, 15.6°±0.2° and 11.4°±0.2° using CuKα radiation.

Please amend the paragraph at page 2, line 29 through page 3, line 2 as follows:

According to another aspect of the present disclosure, the X-ray powder diffraction pattern of Form CS2 shows three or four or five or six or seven or eight or nine or ten or eleven characteristic peaks at 2theta values of 7.8°±0.2°, 15.6°±0.2°, 11.4°±0.2°, 12.5°±0.2°, 21.3°±0.2°, 27.3°±0.2°, 24.0°±0.2°, 19.1°±0.2°, 19.4°±0.2°, 22.3°±0.2°, 25.9°±0.2° using CuKα radiation.

AMENDMENTS TO THE CLAIMS

1. (Currently Amended) A crystalline form CS2 of E-2006, wherein the X-ray powder diffraction pattern shows characteristic peaks at 2theta values of 7.8°±0.2°, 15.6°±0.2° and 11.4°±0.2° using CuKα radiation.

2. (Currently Amended) The crystalline form CS2 according to claim 1, wherein the X-ray powder diffraction pattern shows one or two or three characteristic peaks at 2theta values of 12.5°±0.2°, 21.3°±0.2° and 27.3°±0.2° using CuKα radiation.

3. (Currently Amended) The crystalline form CS2 according to claim 1, wherein the X-ray powder diffraction pattern shows one or two or three characteristic peaks at 2theta values of 24.0°±0.2°, 19.4°±0.2° and 22.3°±0.2° using CuKα radiation.

4. (Original) A process for preparing crystalline form CS2 according to claim 1, wherein the process comprises:

(1) Dissolving compound (I) in a solvent to get a solution containing compound (I), then adding an anti-solvent to the solution slowly, stirring and crystallization to obtain crystalline form CS2; or

(2) Dissolving compound (I) in ketones and slowly evaporating to obtain crystalline form CS2; or

(3) Dissolving compound (I) in nitriles, adding an ionic liquid, then slowly evaporating to obtain crystalline form CS2.

5. (Original) The process for preparing crystalline form CS2 according to claim 4, wherein in method (1), said solvent is alcohol, said anti-solvent is water; in method (2), said ketone is acetone; in method (3), said nitrile is acetonitrile, said ionic liquid is 1-ethyl-3-methylimidazolium methyl sulfate, or 1-ethyl-3-methylimidazolium hexafluoroantimonate, or 1,3-dimethylimidazolium dimethyl phosphate.

6. (Original) The process for preparing crystalline form CS2 according to claim 5, wherein

in method (1) said alcohol is methanol.

7. (Original) A pharmaceutical composition, said pharmaceutical composition comprises a therapeutically effective amount of crystalline form CS2 according to claim 1 and pharmaceutically acceptable carriers, diluents or excipients.

8. (Cancelled)

9. (Currently Amended) ~~Crystalline form CS2 according to claim 1 for the use of preparing drugs~~ A method of treating insomnia and/or irregular sleep-wake rhythm disorder, comprising administering to a patient in need thereof a therapeutically effective amount of crystalline form CS2 according to claim 1.

REMARKS

Applicant has amended the Title and added the "cross-reference to related applications" section to the Specification.

Furthermore, Applicant has amended the Specification at pages 2-3 and claims 1-3 to include the phrase "using CuKα radiation". Support for these amendments appears in the Specification at page 8, line 15.

Claim 8 has been cancelled without prejudice or disclaimer.

Claim 9 has been rewritten into method of treatment claim format to conform to U.S. practice.

Upon entry of the claim amendments as set forth above, claims 1-7 and 9 will be pending.

No new matter has been introduced by the amendments to the specification and the claims.

Applicant respectively requests favorable consideration of the present application.

Dated: January 30, 2020

Respectfully submitted,

Electronic signature: /Xiaoyuan Ding/
Xiaoyuan Ding
Registration No.: 75,354
MCCARTER & ENGLISH, LLP
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Boston, Massachusetts 02110
(617) 449-6500
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Attorney/Agent For Applicant

CRYSTAL FORM OF OREXIN RECEPTOR ANTAGONIST, PREPARATION METHOD THEREFOR AND USE THEREOF

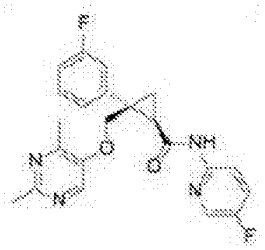
TECHNICAL FIELD

The present disclosure relates to the field of pharmaceutical chemistry, particularly relates to a novel crystalline forms of orexin receptor antagonist, processes for preparation and use thereof.

BACKGROUND

E-2006 (Lemborexant) was developed by Eisai and clinically used to treat insomnia. Studies have shown that the orexin system is a key regulator of the sleep-wake cycle, and thus orexin receptor antagonists have the potential to counteract inappropriate nighttime wakefulness and promote a regular sleep-wake cycle. E-2006 is an orexin receptor antagonist. In clinical trials, E-2006 can significantly improve sleep efficiency in patients with insomnia, including falling asleep fast and shorter time spent awake at night. In addition, E-2006 also shows great potential in the treatment of Alzheimer's patients with Irregular Sleep-Wake Rhythm Disorder (ISWRD). ISWRD is different from common insomnia, and has unmet clinical needs.

The chemical name of E-2006 is (1R, 2S)-2-{[(2, 4-dimethylpyrimidin-5-yl)oxy]methyl}-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide (hereinafter referred to as "Compound (I)"), and the structure is shown as follows:



Compound (I)

Currently, no crystalline forms of compound (I) was disclosed. CN103153963B disclosed the structure of compound (I) and the process for preparing compound (I). The inventors of the present disclosure have repeated the preparation method in CN103153963B and amorphous solid was obtained. Compared with the crystalline form of the present disclosure, the

amorphous solid has lower stability, lower density and poorer flowability, which is not suitable for the preparation of drug product. In addition, amorphous is the thermodynamically most unstable solid form, which is prone to crystal transformation or chemical degradation, resulting in a decrease in the purity of the compound. The preparation of amorphous is usually a rapid precipitation process to produce kinetically stable solid, which easily leads to excessive residual solvent. The particle property control in the preparation process is difficult.

The inventors of the present disclosure discovered excellent crystalline form CS2 of compound (I), which has advantages in at least one aspect of stability, melting point, solubility, in vitro and in vivo dissolution, hygroscopicity, bioavailability, adhesiveness, compressibility, flowability, processability, purification ability, formulation production, etc. Particularly, crystalline form CS2 has good stability, low hygroscopicity, good formulation processability, high in vitro dissolution and dissolution rate, which provides a new and better choice for the development of drug containing compound (I) and is of great significance.

SUMMARY

The main objective of the present disclosure is to provide a novel crystalline form of compound (I), processes for preparation and use thereof.

According to the objective of the present disclosure, crystalline form CS2 of compound (I) is provided (hereinafter referred to as Form CS2).

According to one aspect of the present disclosure, the X-ray powder diffraction pattern of Form CS2 shows characteristic peaks at 2theta values of 7.8°±0.2°, 15.6°±0.2° and 11.4°±0.2°.

Furthermore, the X-ray powder diffraction pattern of Form CS2 shows one or two or three characteristic peaks at 2theta values of 12.5°±0.2°, 21.3°±0.2°, 27.3°±0.2°. Preferably, the X-ray powder diffraction pattern of Form CS2 shows three characteristic peaks at 2theta values of 12.5°±0.2°, 21.3°±0.2°, 27.3°±0.2°.

Furthermore, the X-ray powder diffraction pattern of Form CS2 shows one or two or three characteristic peaks at 2theta values of 24.0°±0.2°, 19.4°±0.2° and 22.3°±0.2°. Preferably, the X-ray powder diffraction pattern of Form CSI shows three characteristic peaks at 2theta values of 24.0°±0.2°, 19.4°±0.2°, 22.3°±0.2°.

According to another aspect of the present disclosure, the X-ray powder diffraction pattern of Form CS2 shows three or four or five or six or seven or eight or nine or ten or eleven

characteristic peaks at 2theta values of 7.8°±0.2°, 15.6°±0.2°, 11.4°±0.2°, 12.5°±0.2°, 21.3°±0.2°, 27.3°±0.2°, 24.0°±0.2°, 19.1°±0.2°, 19.4°±0.2°, 22.3°±0.2°, 25.9°±0.2°.

Without any limitation being implied, the X-ray powder diffraction pattern of Form CS2 is substantially as depicted in Figure 1 or 5.

According to the objective of the present disclosure, a process for preparing Form CS2 is also provided. The process comprises:

(1) Dissolving compound (I) in a solvent to get a solution containing compound (I), then adding an anti-solvent to the solution slowly, stirring and crystallizing to obtain Form CS2; or

(2) Dissolving compound (I) in ketones and slowly evaporating to obtain Form CS2; or

(3) Dissolving compound (I) in nitriles, adding an ionic liquid, then slowly evaporating to obtain Form CS2.

Furthermore, in method (1) said solvent is alcohol, said anti-solvent is water;

Furthermore, in method (1) said alcohol is methanol.

Furthermore, in method (2) said ketone is preferably acetone.

Furthermore, in method (3) said nitrile is preferably acetonitrile, said ionic liquid is preferably 1-ethyl-3-methylimidazolium methyl sulfate, or 1-ethyl-3-methylimidazolium hexafluoroantimonate or 1,3-dimethylimidazolium dimethyl phosphate.

According to the objective of the present disclosure, a pharmaceutical composition is provided, said pharmaceutical composition comprises a therapeutically effective amount of Form CS2 and pharmaceutically acceptable carriers, diluents or excipients.

Furthermore, Form CS2 can be used for preparing orexin receptor antagonist drugs.

Furthermore, Form CS2 can be used for preparing drugs treating insomnia and/or irregular sleep-wake rhythm disorder.

Form CS2 of the present disclosure has the following advantages:

(1) Form CS2 of the present disclosure has lower hygroscopicity. The test results show that the weight gain of Form CS2 at 80% RH (Relative Humidity) is 0.21%. Form CS2 is slightly hygroscopic. The crystalline form does not change after DVS, Form CS2 has good physical stability at 0-95% RH.

Hygroscopicity affects the stability of drug substances, flowability and uniformity during the formulation process, thus affecting the quality of drug products. Hygroscopicity affects the preparation, storage and post-treatment of the drug. The crystalline form with low hygroscopicity is not demanding on storage conditions, which reduces the cost of storage and quality control, and has strong economic value.

(2) The crystalline form provided by the present disclosure has good stability.

Drug substance Form CS2 of the present disclosure has good physical and chemical stability in different storage conditions. The crystalline form of Form CS2 of the present disclosure remained unchanged for at least 10 months when stored in open dishes under the conditions of 25 °C/60% RH and 40 °C/75% RH, preferably for at least one year. The crystalline form of Form CS2 doesn't change for at least 2 weeks when stored under the condition of 60 °C/75% RH. The chemical purity of Form CS2 of the present disclosure is above 99%, preferably above 99.5%, and remained substantially unchanged during storage.

Form CS2 of the present disclosure has good physical stability after grinding. Grinding and pulverization are often required in drug manufacturing process. Good physical stability of the drug substance can reduce the risk of crystallinity decrease and crystal transformation during the drug production process.

Form CS2 of the present disclosure has good physical and chemical stability in drug product. Drug product is prepared with excipient and stored under the conditions of 25 °C/60% RH and 40 °C/75% RH for at least one month. The crystalline form of Form CS2 remained unchanged and chemical purity remained substantially unchanged in drug product.

Drug substance and drug product has good physical and chemical stability. During the storage and formulation process, Form CS2 does not convert to other crystalline forms, and the chemical purity of Form CS2 remained substantially unchanged during storage, thus ensuring consistent and controllable quality of drug substance and drug product.

(3) Form CS2 has good in vitro dissolution and dissolution rate. Form CS2 of the present disclosure in drug product underwent 100% dissolution in 60 minutes in 0.1 mol/L aqueous hydrochloric acid solution. Good in vitro dissolution leads to higher in vivo absorption, thereby achieving ideal bioavailability.

Dissolution is the prerequisite for absorption. Good in vitro dissolution leads to higher in vivo absorption and better in vivo exposure, thereby improving drug's bioavailability and efficacy.

High dissolution rate is beneficial for the drug to achieve peak plasma concentration quickly after administration, thus ensuring rapid drug action.

Furthermore, Form CS2 of the present disclosure also has the following advantages:

(1) Form CS2 of the present disclosure has good compressibility. Failure in hardness/friability test issue can be avoided in the tableting process due to better compressibility of Form CS2, thus reducing the requirements for pretreatment process, making the preparation process more reliable and improving product appearance and product quality.

(2) Compared with prior art, Form CS2 of the present disclosure has higher density. Test results indicate that the bulk density and tapped density of Form CS2 are remarkably higher than that of prior art solid. Higher density of Form CS2 is beneficial to large scale production. High density of Form CS2 can also reduce dust, reduce occupational hazard, reduce security risks and ensure production safety.

(3) Compared with prior art, Form CS2 of the present disclosure has better flowability. Flowability evaluation results indicate that the flowability of Form CS2 is good, while the flowability of prior art form is poor. Better flowability can effectively increase the speed of tableting and filling and increase manufacturing efficiency. Better flowability of Form CS2 ensures the blend uniformity and content uniformity of the drug product, and reduces the weight variation of the drug product and improves product quality.

(4) Compared with prior art, Form CS2 of the present disclosure shows superior adhesiveness. Adhesiveness evaluation results indicate that Form CS2 has low adhesiveness amount and low adhesiveness. Due to low adhesiveness of Form CS2, adhesion to roller and tooling during dry-granulation and compression process can be reduced, which is also beneficial to improve product appearance and weight variation. In addition, low adhesiveness of Form CS2 can reduce the agglomeration of drug substance, which is beneficial to the dispersion of drug substance and reduce the adhesion between drug substance and other excipients, and improve the blend uniformity and content uniformity of drug product.

(5) Form CS2 of the present disclosure has almost no residual solvent and meets the requirements of drug substance, while the residual solvent of the prior art exceeds the standard and cannot be used as a drug substance directly. Many organic solvents are harmful to human and environment. Therefore, in order to ensure drug safety and product quality, it is necessary to control the residual organic solvent of drug substance.

In the present disclosure, said "evaporating" is accomplished by using a conventional method in the field such as slow evaporation or rapid evaporation. Slow evaporation is accomplished in a container covered by sealing film with pinholes. Rapid evaporation is accomplished in an open container.

In the present disclosure, "crystal" or "crystalline form" refers to the crystal or the crystalline form being identified by the X-ray diffraction pattern shown herein. Those skilled in the art are able to understand that physicochemical properties discussed herein can be characterized. The experimental errors depend on the instrument conditions, the sampling processes and the purity of samples. In particular, those skilled in the art generally know that the X-ray diffraction pattern typically varies with the experimental conditions. It is necessary to point out that, the relative intensity of the diffraction peaks in the X-ray diffraction pattern may also vary with the experimental conditions; therefore, the order of the diffraction peak intensities cannot be regarded as the sole or decisive factor. In fact, the relative intensity of the diffraction peaks in the X-ray powder diffraction pattern is related to the preferred orientation of the crystals, and the diffraction peak intensities shown herein are illustrative and identical diffraction peak intensities are not required. In addition, the experimental error of the diffraction peak position is usually 5% or less, and the error of these positions should also be taken into account. An error of ±0.2° is usually allowed. In addition, due to experimental factors such as sample thickness, the overall offset of the diffraction peak is caused, and a certain offset is usually allowed. Thus, it will be understood by those skilled in the art that a crystalline form of the present disclosure is not necessarily to have the exactly same X-ray diffraction pattern of the example shown herein. As used herein, "the same XRPD pattern" does not mean absolutely the same, the same peak positions may differ by ±0.2° and the peak intensity allows for some variability. Any crystalline forms whose X-ray diffraction patterns have the same or similar characteristic peaks should be within the scope of the present disclosure. Those skilled in the art can compare the patterns shown in the present disclosure with that of an unknown crystalline form in order to identify whether these two groups of patterns reflect the same or different crystalline forms.

In some embodiments, Form CS2 of the present disclosure is pure and substantially free of any other crystalline forms. In the present disclosure, the term "substantially free" when used to describe a novel crystalline form, it means that the content of other crystalline forms in the novel crystalline form is less than 20% (w/w), specifically less than 10% (w/w), more specifically less than 5% (w/w) and further more specifically less than 1% (w/w).

It should be noted that the number and the number range should not be understood as the number or number range themselves only. It should be understood by those skilled in the art that the specific number can be shifted at specific technical environment without departing from the spirit and principle of the present disclosure. In the present disclosure, the number of shift ranges expected by one of skilled in the art is represented by the term "about".

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows an XRPD pattern of Form CS2 in Example 1.

Figure 2 shows a DSC curve of Form CS2 in Example 1.

Figure 3 shows a TGA curve of Form CS2 in Example 1.

Figure 4 shows a ^{1}H NMR spectrum of Form CS2 in Example 1.

Figure 5 shows an XRPD pattern of Form CS2 in Example 2.

Figure 6 shows a DSC curve of Form CS2 in Example 2.

Figure 7 shows a TGA curve of Form CS2 in Example 2.

Figure 8 shows a ^{1}H NMR spectrum of Form CS2 in Example 2.

Figure 9 shows an XRPD pattern overlay of Form CS2 before and after stored at 25 ℃/60% RH (top: before storage, bottom: after storage).

Figure 10 shows an XRPD pattern overlay of Form CS2 before and after stored at 40 ℃/75% RH (top: before storage, bottom: after storage).

Figure 11 shows an XRPD pattern overlay of Form CS2 before and after stored at 60 ℃/75% RH (top: before storage, bottom: after storage).

Figure 12 shows an XRPD curve of Form CS2 before and after grinding (top: XRPD pattern before grinding; bottom: XRPD pattern after grinding).

Figure 13 shows a DSC curve of Form CS2.

Figure 14 shows an XRPD pattern overlay of Form CS2 before and after DVS test (top: XRPD pattern before DVS; bottom: XRPD pattern after DVS).

Figure 15 shows an in vitro dissolution profile of Form CS2.

DETAILED DESCRIPTION

The present disclosure is further illustrated by the following examples which describe the preparation and use of the crystalline form of the present disclosure in detail. It is obvious to those skilled in the art that many changes in the materials and methods can be accomplished without departing from the scope of the present disclosure.

The abbreviations used in the present disclosure are explained as follows:

XRPD: X-ray Powder Diffraction

DSC: Differential Scanning Calorimetry

TGA: Thermo Gravimetric Analysis

DVS: Dynamic Vapor Sorption

^{1}H NMR: Proton Nuclear Magnetic Resonance

Instruments and methods used for data collection:

X-ray powder diffraction patterns in the present disclosure were acquired by a Bruker D2 PHASER X-ray powder diffractometer. The parameters of the X-ray powder diffraction method of the present disclosure were as follows:

X-ray Reflection: Cu, Kα

Kα1 (Å): 1.54060; Kα2 (Å): 1.54439

Kα2/Kα1 intensity ratio: 0.50

Voltage: 30 (kV)

Current: 10 (mA)

Scan range: from 3.0 degree to 40.0 degree

Differential scanning calorimetry (DSC) data in the present disclosure were acquired by a TA Q2000. The parameters of the DSC method of the present disclosure are as follows:

Heating rate: 10 °C/min

Purge gas: nitrogen

Thermo gravimetric analysis (TGA) data in the present disclosure were acquired by a TA Q500. The parameters of the TGA method of the present disclosure were as follows:

Heating rate: 10 °C/ min

Purge gas: nitrogen

Dynamic Vapor Sorption (DVS) is measured via a SMS (Surface Measurement Systems Ltd.) intrinsic DVS instrument. Typical Parameters for DVS test are as follows:

Temperature: 25 °C

Gas and flow rate: N_2, 200 mL/min

dm/dt: 0.002%/min

RH range: 0% RH to 95% RH

High Performance Liquid Chromatography (HPLC) data in the present disclosure were collected from an Agilent 1260 with Diode Array Detector (DAD).

The HPLC method parameters in the present disclosure are as follows:

Column: ZORBAX Eclipse C18, 100×4.6mm, 5 μm

Mobile Phase: A: Acetonitrile: Water: Trifluoroacetic acid =50:950:1 (Volume ratio)

B: 0.1% Trifluoroacetic acid in acetonitrile

Gradient:

Time (min)	%B
0.0	0
0.5	0
30.0	90
35.0	90
35.1	0
40.0	0

Flow rate: 1.0 mL/min

Injection Volume: 2 μL

Detection wavelength: 220 nm

Column Temperature: 40 °C

Diluent: Acetonitrile

Proton nuclear magnetic resonance spectrum data (^{1}H NMR) were collected from a Bruker

Avance II DMX 400M HZ NMR spectrometer. 1-5 mg of sample was weighed, and dissolved in 0.5 mL of deuterated dimethyl sulfoxide to obtain a solution with a concentration of 2-10 mg/mL.

Unless otherwise specified, the following examples were conducted at room temperature. Said "room temperature" is not a specific value, and refers to 10-30 ℃.

According to the present disclosure, compound (I) used as a raw material is solid (crystalline or amorphous), semisolid, wax or oil. Preferably, said compound (I) used as a raw material is a solid.

Raw materials of E-2006 used in the following examples were prepared by known methods in the prior art, for example, the method disclosed in CN103153963B.

DETAILED DESCRIPTION

Example 1 Preparation of Form CS2:

Approximately 199.6 mg of compound (I) was weighted and dissolved in 3.0 mL of acetone, followed by filtration and slowly evaporation to obtain a solid at room temperature. The obtained solid was confirmed to be Form CS2. The XRPD pattern is substantially as depicted in Figure 1, and the XRPD data are listed in Table 1.

The DSC curve of Form CS2 in this example is substantially as depicted in Figure 2. When heated to 177 ℃, an endothermic peak appears, which corresponds to the melting endothermic peak of Form CS2.

The TGA curve of Form CS2 in this example shows about 0.6% weight loss when heated to 170 ℃, which is substantially as depicted in Figure 3.

The ^{1}H NMR spectrum of Form CS2 is substantially as depicted in Figure 4, and the corresponding data are: ^{1}H NMR (400 MHz, DMSO) δ11.22 (s, 1H), 8.33 (d, J = 3.0 Hz, 1H), 8.13 (s, 1H), 7.89 (dd, J = 9.1, 4.1 Hz, 1H), 7.64 (td, J = 8.7, 3.1 Hz, 1H), 7.48-7.35 (m, 3H), 7.11 (ddd, J = 11.5, 6.0, 3.0 Hz, 1H), 4.68 (d, J = 10.2 Hz, 1H), 4.29 (d, J = 10.3 Hz, 1H), 2.64 (dd, J = 15.7, 8.8 Hz, 1H), 2.36 (d, J = 21.5 Hz, 3H), 2.03 (s, 3H), 1.74-1.67 (m, 1H), 1.50 (dd, J = 8.0, 4.8 Hz, 1H)。

Table 1

2θ	d spacing	Intensity %
7.81	11.32	100.00
9.55	9.26	5.68
11.44	7.73	23.41

12.53	7.07	25.17
15.58	5.69	46.96
15.78	5.62	11.77
16.40	5.41	4.67
19.05	4.66	12.69
19.38	4.58	17.51
19.57	4.54	18.50
21.32	4.17	21.23
21.73	4.09	6.60
22.27	3.99	11.54
23.03	3.86	5.32
23.23	3.83	6.23
23.99	3.71	15.14
25.42	3.50	4.70
25.89	3.44	23.53
26.28	3.39	7.86
27.26	3.27	15.44
28.04	3.18	5.25
29.36	3.04	3.75
31.09	2.88	5.99
33.99	2.64	1.25

Example 2 Preparation of Form CS2 by anti-solvent addition method

Approximately 1026.0 mg of compound (I) was weighted and dissolved in 10.0 mL of methanol. The solution was filtered and stirred while adding about 10.0 mL of water as an anti-solvent. After stirred for about 4 hours, a large amount of solid precipitated out. The precipitation collected by suction filtration and dried under vacuum at 40 °C for about 18 hours to obtain solids. The obtained solid was confirmed to be Form CS2. The XRPD pattern is substantially as depicted in Figure 5, and the XRPD data are listed in Table 2.

The DSC curve of Form CS2 in this example is substantially as depicted in Figure 6. When heated to 176 °C, an endothermic peak appears, which corresponds to the melting endothermic peak of Form CS2.

The TGA curve of Form CS2 in this example shows about 0.5% weight loss when heated to 170 °C, which is substantially as depicted in Figure 7.

The ^{1}H NMR spectrum of Form CS2 is substantially as depicted in Figure 8, and the corresponding data are: ^{1}H NMR (400 MHz, DMSO) δ11.21 (s, 1H), 8.33 (d, J = 3.0 Hz, 1H), 8.13 (s, 1H), 7.89 (dd, J = 9.2, 4.2 Hz, 1H), 7.64 (td, J = 8.8, 3.1 Hz, 1H), 7.49-7.34 (m, 3H), 7.16-7.05 (m, 1H), 4.68 (d, J = 10.2 Hz, 1H), 4.29 (d, J = 10.3 Hz, 1H), 2.67-2.57 (m, 1H), 2.38 (s, 3H), 2.03 (s, 3H), 1.74-1.66 (m, 1H), 1.50 (dd, J = 8.0, 4.8 Hz, 1H)。

Table 2

2θ	d spacing	Intensity %
7.84	11.27	100.00
9.59	9.22	6.98
11.49	7.70	13.05
12.56	7.05	35.00
15.61	5.68	59.13
15.82	5.60	9.92
16.44	5.39	9.29
19.07	4.65	19.61
19.41	4.57	19.56
19.60	4.53	20.52
21.36	4.16	22.18
21.77	4.08	10.04
22.31	3.98	29.55
23.07	3.86	9.34
23.89	3.72	14.02
24.00	3.71	11.54
25.46	3.50	6.67
25.93	3.44	17.57
26.31	3.39	16.60
27.33	3.26	16.63
28.06	3.18	9.34
29.37	3.04	7.28
31.15	2.87	3.40
31.38	2.85	4.42
29.37	3.04	7.28
31.15	2.87	3.40

Example 3-5 Preparation of Form CS2 by ionic liquid induced evaporation

Approximately 31.5 mg of compound (I) was dissolved in 1.0 mL of acetonitrile and filtered. A small amount of ionic liquid as shown in Table 3 was added, and the solution was slowly evaporated at room temperature to obtain solid. The solid obtained in example 3-5 were labeled as samples 3-5 and confirmed to be Form CS2.

Table 3

Example	Ionic liquid	Sample
3	1-ethyl-3-methylimidazolium methyl sulfate	Sample 3
4	1-ethyl-3-methylimidazolium hexafluoroantimonate	Sample 4
5	1,3-dimethylimidazolium dimethyl phosphate	Sample 5

Example 6 Stability of Form CS2

Form CS2 of the present disclosure were weighed and stored under conditions of 25 ℃/60% RH, 40 ℃/75% RH, 60 ℃/75% RH and 80 ℃ in open dishes. Crystalline form and chemical impurity were checked by XRPD and HPLC, respectively. The results are shown in Table 4.

Table 4

Initial crystalline form	Initial purity	Storage condition	Storage time	Crystalline form after storage	Purity after storage
Form CS2 (top of Figure 9)	99.67%	25°C /60% RH	10 months	Form CS2 (bottom of Figure 9)	99.63%
Form CS2 (top of Figure 10)	99.67%	40°C /75% RH	10 months	Form CS2 (bottom of Figure 10)	99.67%
Form CS2 (top of Figure 11)	99.67%	60°C /75% RH	2 weeks	Form CS2 (bottom of Figure 11)	99.70%

The results show that Form CS2 keeps stable for at least 10 months at 25 ℃/60% RH and 40 ℃/75% RH. Form CS2 keeps stable for at least 2 weeks at 60 ℃/75% RH, the purity of Form

CS2 remained substantially unchanged. It can be seen that Form CS2 has good physical and chemical stability.

Example 7 Grinding stability of Form CS2

Form CS2 was ground manually for 5 minutes in a mortar. The XRPD pattern of the solids before and after grinding are presented in Figure 12 (top: XRPD pattern before grinding; bottom: XRPD pattern after grinding). The results show that the crystalline form of Form CS2 does not change after grinding. Form CS2 has good grinding stability.

Example 8 Hygroscopicity of Form CS2

Dynamic vapor sorption (DVS) was applied to measure hygroscopicity of Form CS2 with about 10 mg of samples. The weight gains at each relative humidity were recorded in a cycle of 0-95%-0 RH. DVS is substantially as depicted in Figure 13, and the experimental results are shown in Table 5. The XRPD pattern overlay of Form CS2 before and after DVS test is presented in Figure 14 (top: XRPD pattern before DVS; bottom: XRPD pattern after DVS). The results show that the hygroscopicity of Form CS2 is low. The weight gain under 80% RH is 0.21%. Form CS2 is slightly hygroscopic. The crystalline form of Form CS2 does not change after DVS, which indicates that Form CS2 is physically stable at 0% - 95% RH.

Table 5

Relative Humidity / Weight Gain (%)	Weight gain under 80% Relative Humidity	Hygroscopicity
Form CS2	0.21%	Slightly hygroscopic

Description and definition of hygroscopicity (Chinese Pharmacopoeia 2015 edition appendix Drug hygroscopic test guidelines, test at 25 °C±1 °C, 80% RH.).

—deliquescent: Sufficient water is absorbed to form a liquid;

—very hygroscopic: Increase in mass is equal to or greater than 15 percent;

—hygroscopic: Increase in mass is less than 15 percent and equal to or greater than 2 percent;

—slightly hygroscopic: Increase in mass is less than 2 percent and equal to or greater than 0.2 percent.

—non hygroscopic or almost non hygroscopic: Increase in mass is less than 0.2%.

Example 9 Flowability comparison of Form CS2 and the prior art solid

Compressibility, also known as compressibility index is usually used to evaluate the flowability of powder and granular intermediates during the formulation process. A certain amount of powder was added into a measuring cylinder and bulk volume was recorded. Then the measuring cylinder was tapped to make the powder in the tightest state and the tapped volume was recorded. The bulk density (ρ_0), tapped density (ρ_f) were calculated, and compressibility index was calculated according to $c=(\rho_f-\rho_0)/\rho_f$. Compressibility index or Carr Index is an important indicator for evaluating the flowability of powder.

Compressibility index test method is as follows: Compressibility index was calculated according to bulk density ρ_0 and tapped density ρ_f of Form CS2 and the amorphous solid of the prior art with $c=(\rho_f-\rho_0)/\rho_f*100\%$. Criteria of flowability is shown in Table 6.

Table 6

Compressibility index (%)	Flowability
≦10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	poor
32-37	Very poor
>38	Very, very poor

Amorphous solid was obtained by repeating the preparation method disclosed in CN103153963B. Flowability evaluation results of Form CS2 and the amorphous solid are presented in table 7, which indicate that the flowability of Form CS2 is remarkably superior to that of the amorphous solid in the prior art.

Table 7

Form	Bulk density (ρ_0, g/mL)	Tapped density (ρ_f, g/mL)	Compressibility index (%)	Flowability
Amorphous solid	0.196	0.274	28	Poor
Form CS2	0.263	0.351	25	Passable

Example 10 Adhesiveness of Form CS2

30 mg of Form CS2 was weighed and added into the dies of φ8mm round tooling, tableted at 10 KN and held for 30s. The amount of material sticking to the punch was weighed. The

compression was repeated twice and the cumulative amount, maximum amount and average amount of material sticking to the punch during the compression process were recorded. Detailed experimental results are shown in Table 8.

Table 8

Crystalline Form	Maximum amount (mg)	Average amount (mg)	Cumulative amount (mg)
CS2	0.74	0.22	0.44

Example 11 Compressibility of CS2

80mg of Form CS2 was weighted and added into the dies of φ6mm round tooling, compressed at 10 KN. The round tablet was stored in a desiccator for 24 hours until complete elastic recovery. Hardness (H) was tested with a tablet hardness tester. Diameter (D) and thickness (L) were tested with caliper. Tensile strength of the powder was calculated with the following formula: $T=2H/\pi DL$. Under a certain force, the greater the tensile strength, the better the compressibility. The results are presented in Table 9.

Table 9

Form	Thickness(mm)	Diameter (mm)	Hardness(N)	Tensile strength (MPa)
CS2	2.40	6.06	8.4	0.37

Example 12 Residual solvents of Form CS2 and the prior art solid

Amorphous solid was obtained by repeating the preparation method disclosed in CN103153963B. Residual solvents of Form CS2 and the amorphous solid were tested. The results show that Form CS2 has no residual solvents, while the -heptane and ethyl acetate residue in the amorphous solid is 46596.16 ppm and 1260.01 pm, respectively. According to the guideline of the International Council for Harmonization (ICH) on residual solvents, both n-heptane and ethyl acetate belong to Class 3 solvents, and the residual solvent must not exceed 5000 ppm. It can be seen that the residue of n-heptane in the amorphous solid is much higher than the limits of ICH, and the amorphous not suitable for drug substance.

Example 13 CS2 drug product

1. Preparation of compound (I) tablets

Form CS2 and intragranular excipients in Table 10 were blended according to formulation and the blend was compressed with the target weight of 500 mg using a φ20 mm single punch manual press at 5±0.5 KN pressure. The above tablets were crushed, passed through a 20 mesh sieve, then blended uniformly with the extragranular excipients shown in Table 10, and

the blend was compressed with a target weight of 120.0 mg using a φ7 mm single punch manual press at 5±0.5 KN pressure.

Table 10

Component		Quantity (mg/unit)	Mass ratio (%)
E-2006 (Form CS2)		10.00	8.3
Intragranular excipients	Lactose monohydrate	88.88	74.1
	Hydroxypropyl cellulose	3.60	3.0
	Low substituted hydroxypropyl cellulose	10.80	9.0
	Magnesium stearate	0.36	0.3
Total		113.64	94.7
Extragranular excipients	Low substituted hydroxypropyl cellulose	6.00	5.0
	Magnesium stearate	0.36	0.3
Total		120.00	100.0

2. Stability of Form CS2 in drug product

The tablets prepared above were packed in 35 cc HDPE bottles (one tablet per bottle) with 1 g desiccant. The bottles were sealed with a sealer. The bottles were stored under conditions of 25 ℃/60% RH and 40 ℃/75% RH for 1 month. Crystalline form of Form CS2 tablet was tested and the results show that the crystalline form of Form CS2 does not change. In addition, single and total impurity of Form CS2 remained substantially unchanged in storage. The results presented in Table 11 and 12 indicate that Form CS2 keeps physically and chemically stable in drug product.

Table 11 Physical stability of Form CS2 in drug product

Sample	Condition	Time	API crystalline Form after storage
Tablet contains Form CS2	25 ℃/60% RH	1 month	Form CS2
	40 ℃/75% RH	1 month	Form CS2

Table 12 Chemical stability of Form CS2 in drug product

Condition	Time	Initial largest single impurity (%)	Largest single impurity after storage (%)	Initial total impurity (%)	Total impurity after storage (%)	Single impurity change (%)	Total impurity change (%)
25 ℃/60% RH	1 month	0.08	0.09	0.17	0.21	0.01	0.04
40 ℃/75% RH	1 month	0.08	0.08	0.17	0.20	0	0.03

Example 14 In vitro dissolution and dissolution rate of Form CS2

In vitro dissolution test was performed on Form CS2 tablet obtained from example 12. Dissolution method according to Chinese Pharmacopoeia 2015<0931> was used. The conditions are as follows:

Medium: 0.1 mol/L aqueous solution of hydrochloric acid

Method: Paddle

Volume: 900 mL

Speed: 50 rpm

Temperature: 37 ℃

In vitro dissolution of Form CS2 are presented in Table 13 and Figure 15.

Table 13

Cumulative drug release (%) / Time (minute)	Form CS2
0	0.0
5	55.2
10	73.1
15	81.0
20	86.2
30	92.1
45	96.9
60	100.5

The results showed that Form CS2 drug product can undergo 100% dissolution in 0.1 mol/L

aqueous hydrochloric acid, and the dissolution rate is high, which is favorable for achieving good in vivo bioavailability.

The examples described above are only for illustrating the technical concepts and features of the present disclosure, and intended to make those skilled in the art being able to understand the present disclosure and thereby implement it, and should not be concluded to limit the protective scope of this disclosure. Any equivalent variations or modifications according to the spirit of the present disclosure should be covered by the protective scope of the present disclosure.

CLAIMS

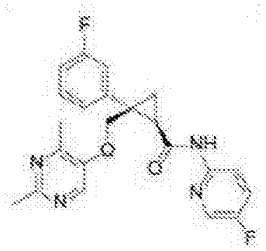
What is claimed is:

1. A crystalline form CS2 of E-2006, wherein the X-ray powder diffraction pattern shows characteristic peaks at 2theta values of 7.8°±0.2°, 15.6°±0.2° and 11.4°±0.2°.
2. The crystalline form CS2 according to claim 1, wherein the X-ray powder diffraction pattern shows one or two or three characteristic peaks at 2theta values of 12.5°±0.2°, 21.3°±0.2° and 27.3°±0.2°.
3. The crystalline form CS2 according to claim 1, wherein the X-ray powder diffraction pattern shows one or two or three characteristic peaks at 2theta values of 24.0°±0.2°, 19.4°±0.2° and 22.3°±0.2°.
4. A process for preparing crystalline form CS2 according to claim 1, wherein the process comprises:
   (1) Dissolving compound (I) in a solvent to get a solution containing compound (I), then adding an anti-solvent to the solution slowly, stirring and crystallization to obtain crystalline form CS2; or
   (2) Dissolving compound (I) in ketones and slowly evaporating to obtain crystalline form CS2; or
   (3) Dissolving compound (I) in nitriles, adding an ionic liquid, then slowly evaporating to obtain crystalline form CS2.
5. The process for preparing crystalline form CS2 according to claim 4, wherein in method (1), said solvent is alcohol, said anti-solvent is water; in method (2), said ketone is acetone; in method (3), said nitrile is acetonitrile, said ionic liquid is 1-ethyl-3-methylimidazolium methyl sulfate, or 1- ethyl-3-methylimidazolium hexafluoroantimonate, or 1,3-dimethylimidazolium dimethyl phosphate.
6. The process for preparing crystalline form CS2 according to claim 5, wherein in method (1) said alcohol is methanol.
7. A pharmaceutical composition, said pharmaceutical composition comprises a therapeutically effective amount of crystalline form CS2 according to claim 1 and pharmaceutically acceptable carriers, diluents or excipients.
8. Crystalline form CS2 according to claim 1 for the use of preparing orexin receptor antagonist drugs.
9. Crystalline form CS2 according to claim 1 for the use of preparing drugs treating insomnia

and/or irregular sleep-wake rhythm disorder.

ABSTRACT

The present disclosure provides a novel crystalline form of Lemborexant and processes for preparation thereof. Pharmaceutical composition containing Lemborexant, and use of Lemborexant for preparing orexin receptor antagonist drug, and use of Lemborexant for preparing drugs treating insomnia and irregular sleep-wake rhythm disorder are also provided. The crystalline form of the present disclosure have one or more improved properties compared with crystalline forms of prior arts, and has significant values for future drug optimization and development.



Compound (I)

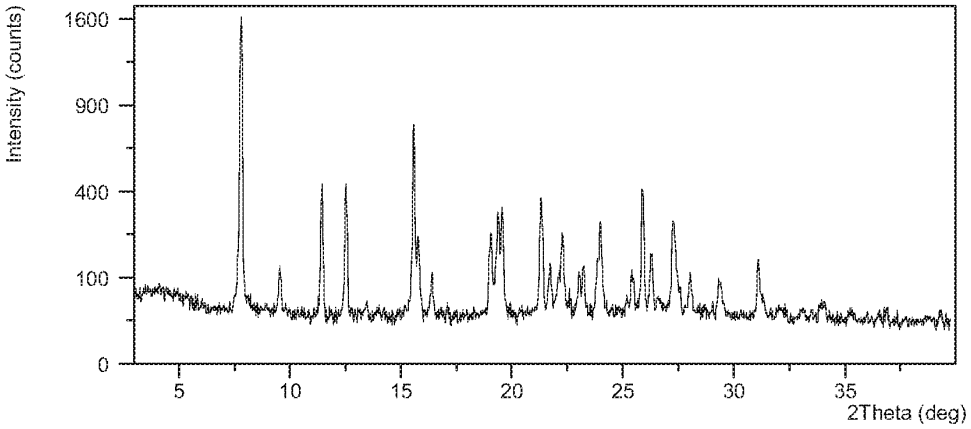

Intensity (counts)
1600
900
400
100
0
5
10
15
20
25
30
35
2Theta (deg)

FIG. 1

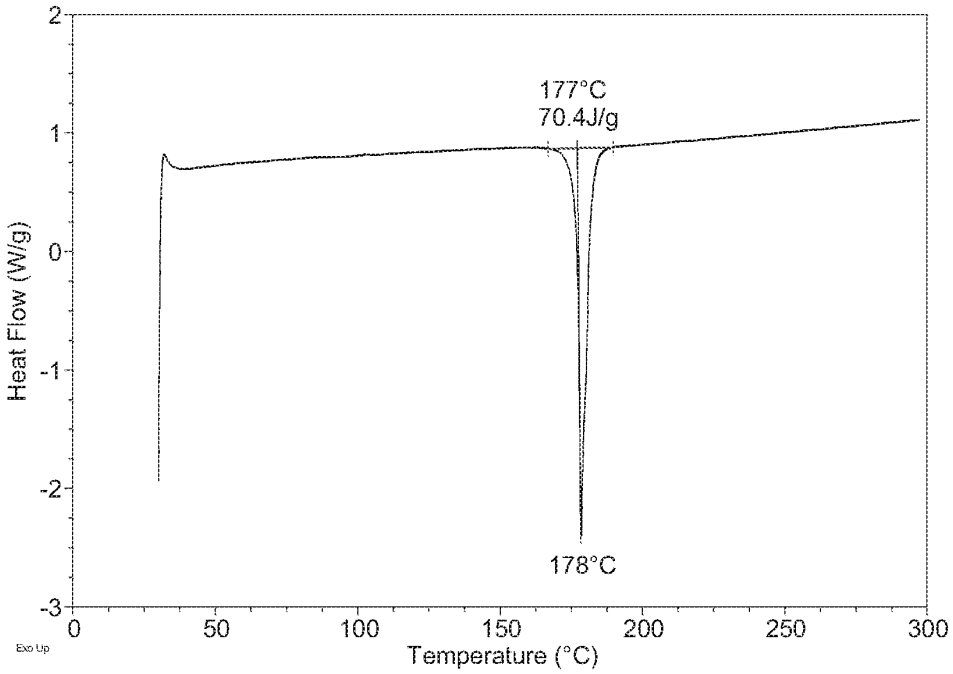

177°C
70.4J/g
178°C
Heat Flow (W/g)
2
1
0
-1
-2
-3
0
50
100
150
200
250
300
Temperature (°C)
Exo Up

FIG. 2

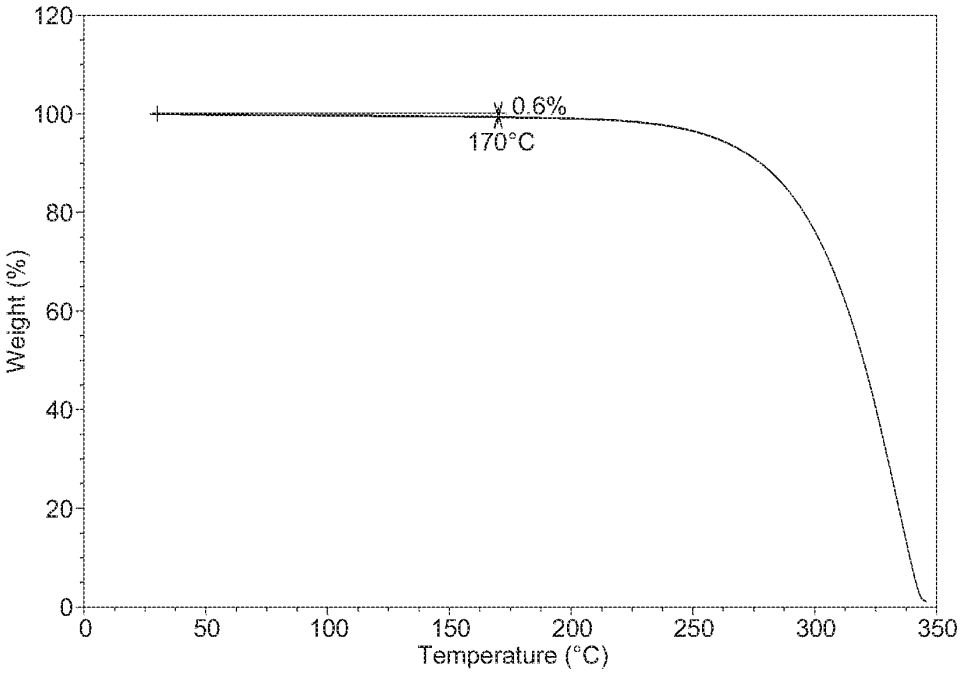

120
100
80
60
40
20
0
Weight (%)
0.6%
170°C
0
50
100
150
200
250
300
350
Temperature (°C)

FIG. 3

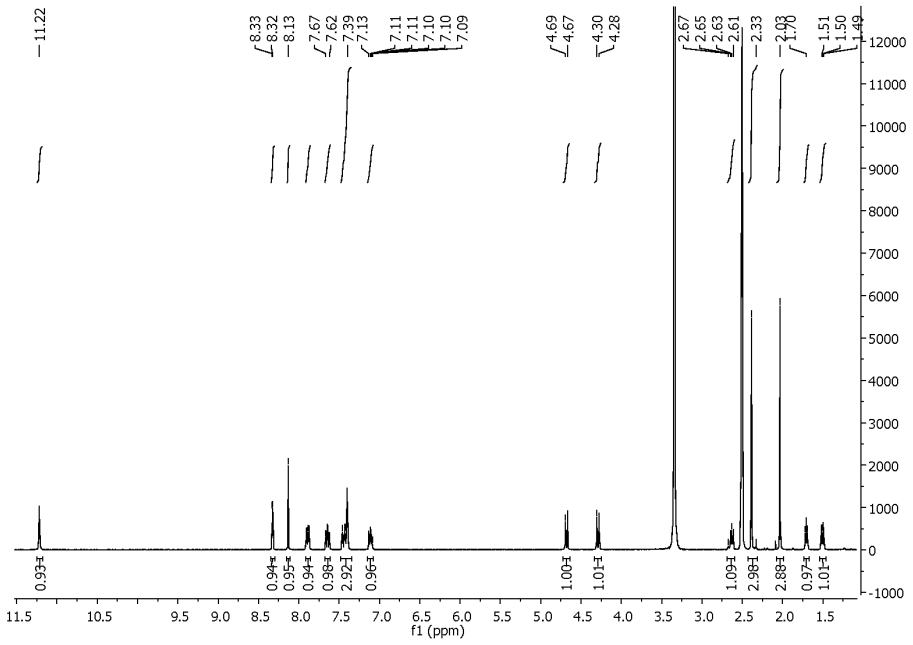
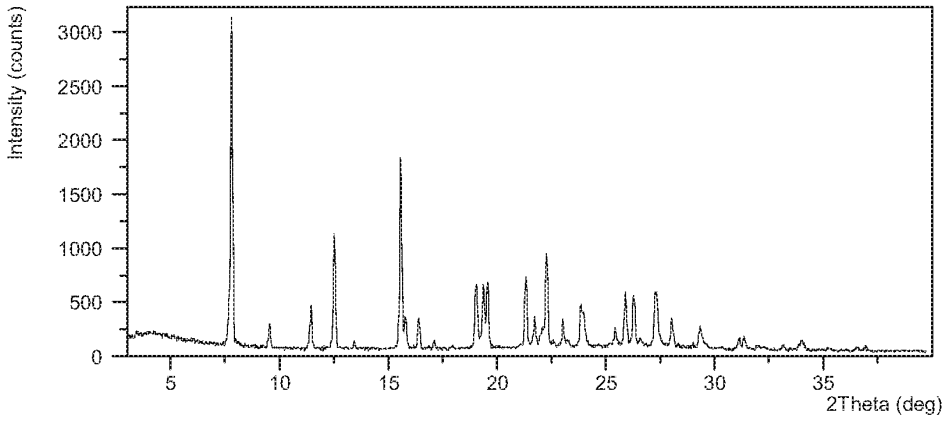

11.22
8.33
8.32
8.13
7.67
7.62
7.39
7.13
7.11
7.11
7.10
7.10
7.09
4.69
4.67
4.30
4.28
2.67
2.65
2.63
2.61
2.33
2.08
1.70
1.51
1.50
1.49
0.93
0.94
0.95
0.94
0.98
2.92
0.96
1.00
1.01
1.09
2.98
2.88
0.97
1.01
f1 (ppm)

FIG. 4


Intensity (counts)
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2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
2Theta (deg)

FIG. 5

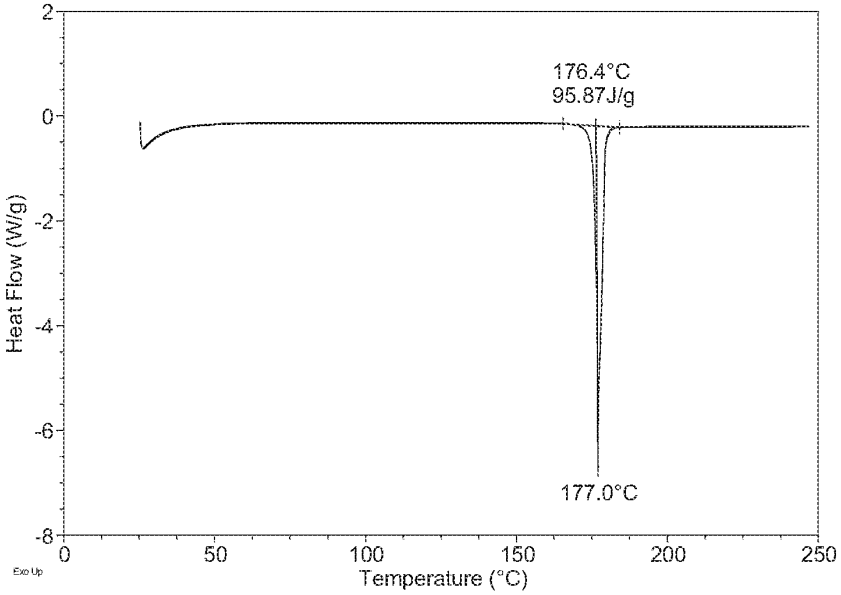

176.4°C
95.87J/g
177.0°C
Heat Flow (W/g)
2
0
-2
-4
-6
-8
0
50
100
150
200
250
Temperature (°C)
Exo Up

FIG. 6

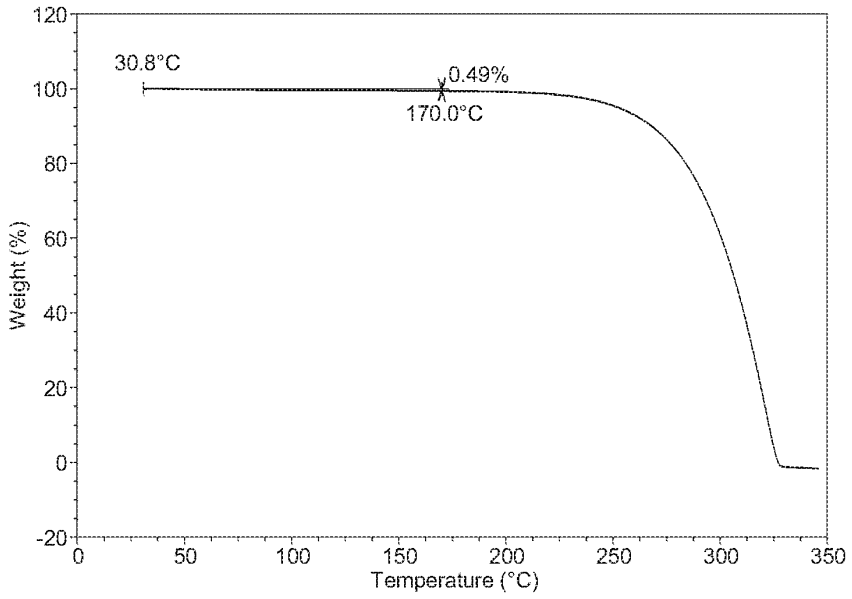
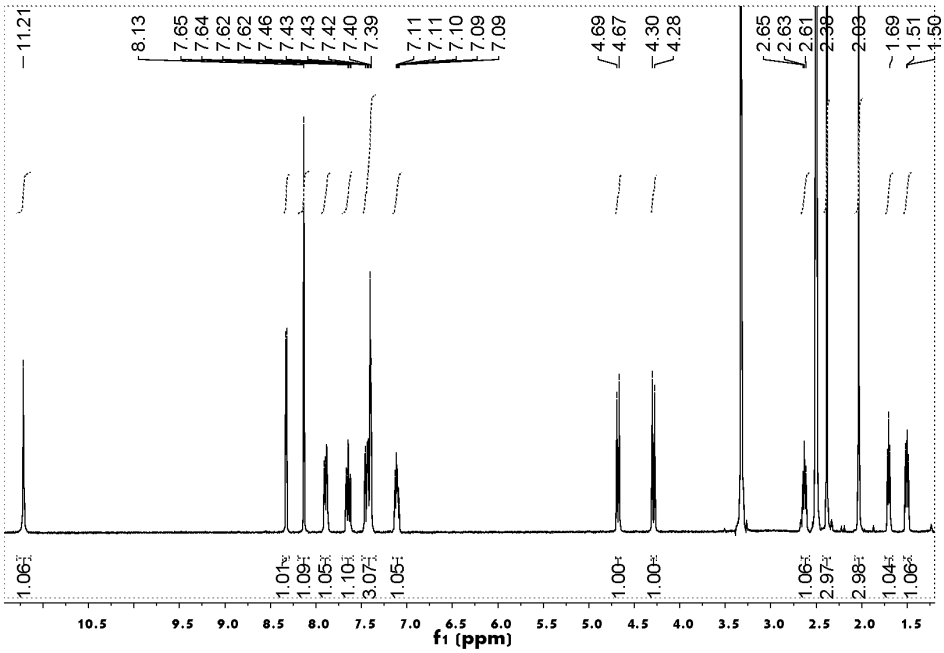

30.8°C
0.49%
170.0°C
Weight (%)
Temperature (°C)

FIG. 7


11.21
8.13
7.65
7.64
7.62
7.62
7.46
7.43
7.43
7.42
7.40
7.39
7.11
7.11
7.10
7.09
7.09
4.69
4.67
4.30
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2.63
2.61
2.38
2.03
1.69
1.51
1.50
f1 (ppm)

FIG. 8

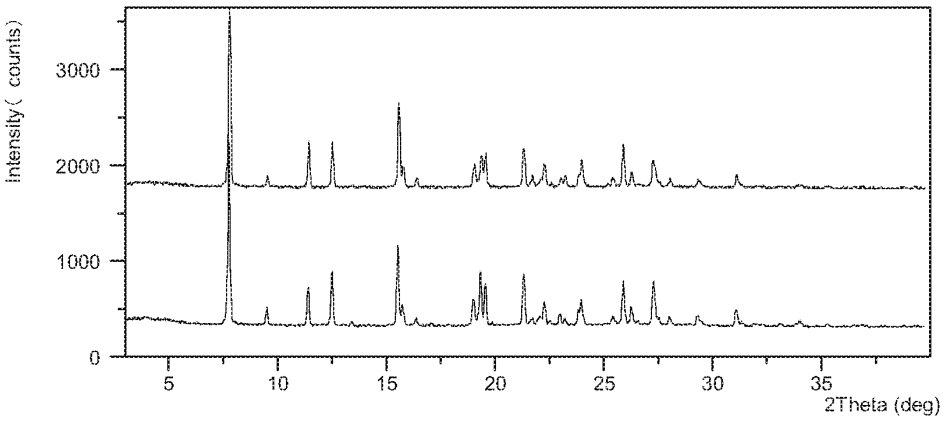


FIG. 9

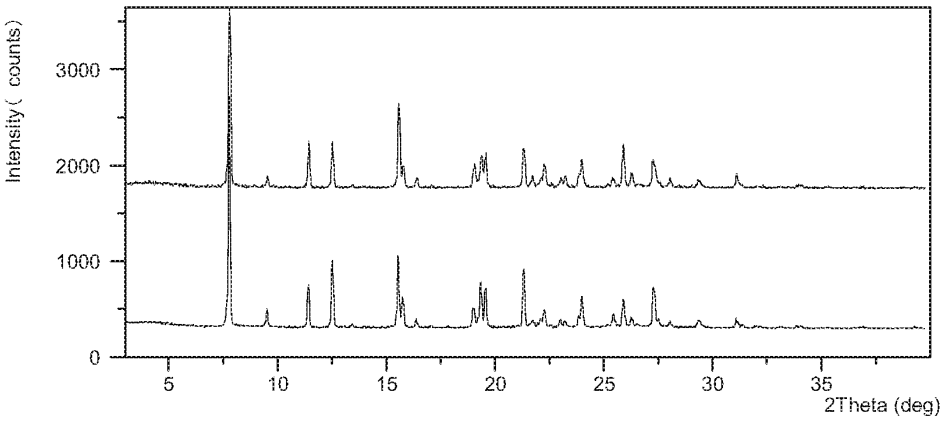


FIG. 10

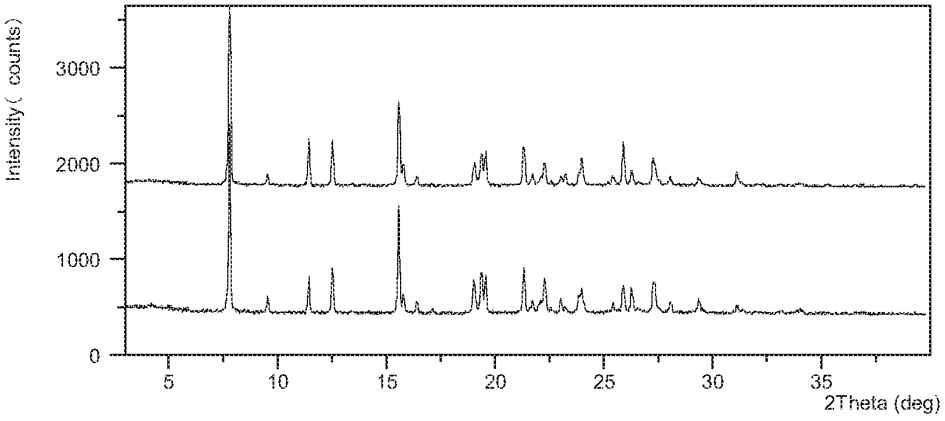
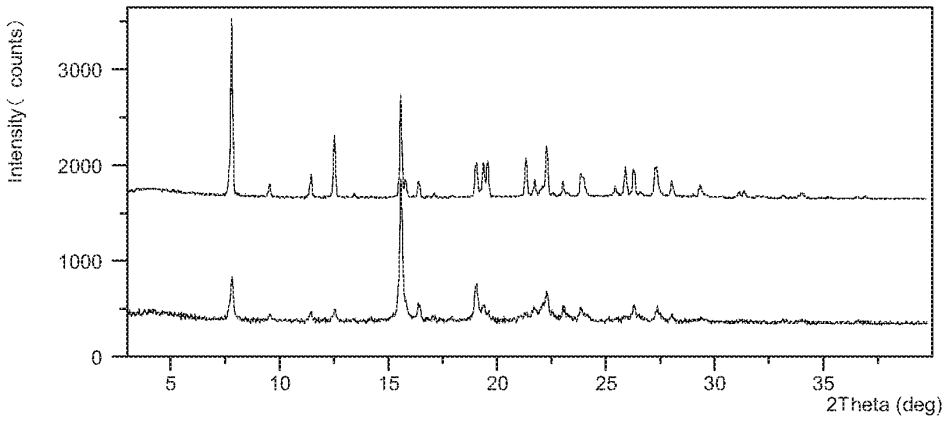


FIG. 11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1000
0
5
10
15
20
25
30
35
2Theta (deg)

FIG. 12

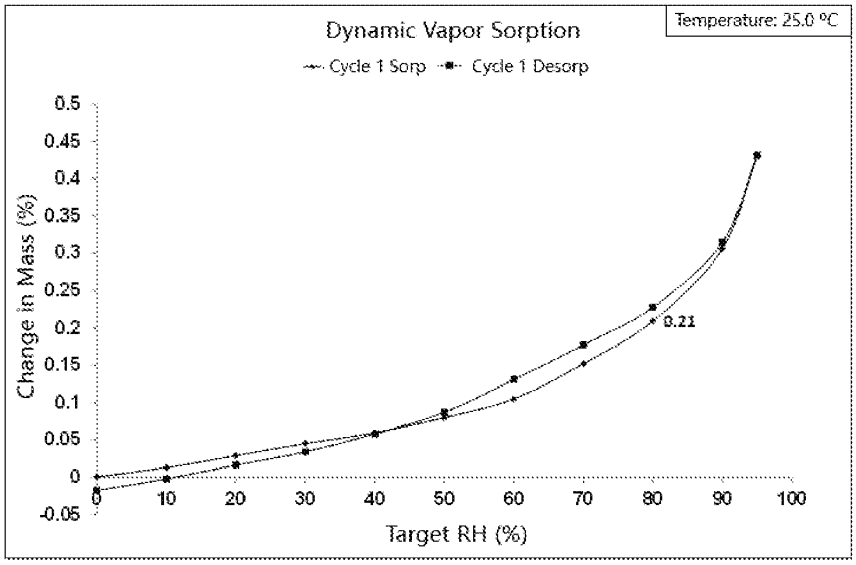
Dynamic Vapor Sorption
Temperature: 25.0 °C
Cycle 1 Sorp
Cycle 1 Desorp
Change in Mass (%)
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
-0.05
0.21
0
10
20
30
40
50
60
70
80
90
100
Target RH (%)

FIG. 13

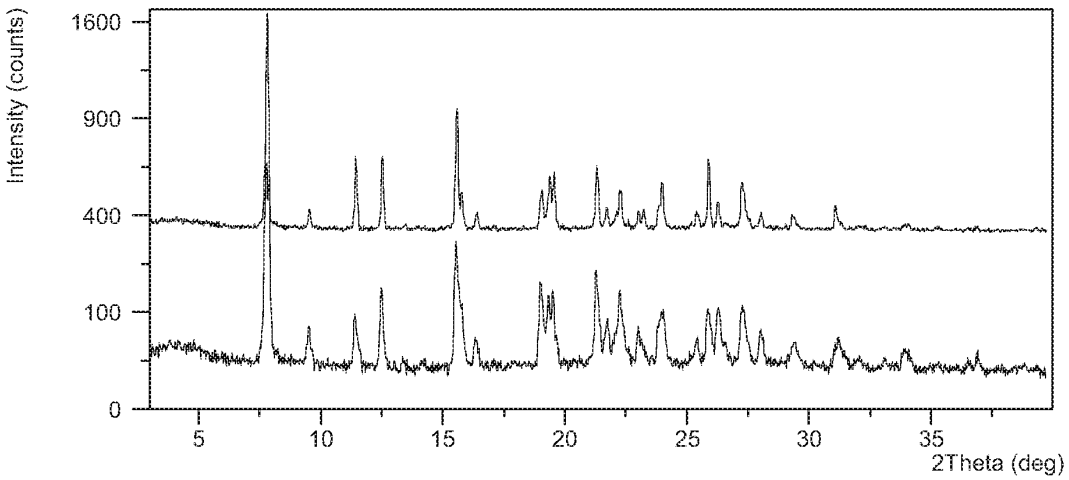
Intensity (counts)
1600
900
400
100
0
5
10
15
20
25
30
35
2Theta (deg)

FIG. 14

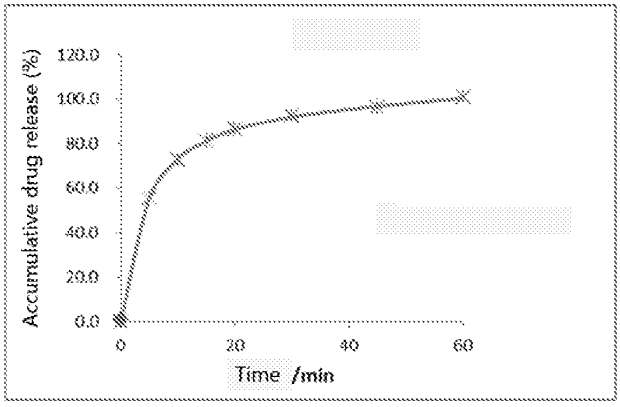
Accumulative drug release (%)
120.0
100.0
80.0
60.0
40.0
20.0
0.0
0
20
40
60
Time /min

FIG. 15

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
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Application Number	16/777,121
Filing Date	January 30, 2020
First Named Inventor	Minhua Chen
Title	CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE THEREOF
Art Unit	1629
Examiner Name	Not Yet Assigned
Attorney Docket Number	134070-01602

SIGNATURE of Applicant or Patent Practitioner

Signature	/Xiaoyuan Ding/	Date (Optional)	January 31, 2020
Name	Xiaoyuan Ding	Registration Number	75,354
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

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

☐ *Total of 1 forms are submitted.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: January 31, 2020 Electronic Signature for Xiaoyuan Ding: /Xiaoyuan Ding/

ME1 32542660v.1

Doc Code: PA.
Document Description: Power of Attorney

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I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

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OR

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Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

[X] The address associated with the above-mentioned Customer Number

OR

[ ] The address associated with Customer Number:

OR

[ ] Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

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

Crystal Pharmaceutical (Suzhou) Co., Ltd.

[ ] Inventor or Joint Inventor (title not required below)

[ ] Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

[X] Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

[ ] Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	Minhua Chen	Date (Optional)	Minhua Chen DEC 14, 2018
Name	Minhua Chen		
Title	CEO		

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

[ ] Total of 1 forms are submitted.

MF1:2677161.82v.1

Electronic Acknowledgement Receipt	
EFS ID:	38460705
Application Number:	16777121
International Application Number:	
Confirmation Number:	1029
Title of Invention:	CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE THEREOF
First Named Inventor/Applicant Name:	Minhua Chen
Customer Number:	86738
Filer:	Xiaoyuan Ding
Filer Authorized By:	
Attorney Docket Number:	134070-01602
Receipt Date:	31-JAN-2020
Filing Date:	
Time Stamp:	14:59:12
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	134070_01602_POA_Transmittal.pdf	17373 7d7f9a79294f8ac81ddb5830e26b47acf17f62b6	no	1
Warnings:					

Information:					
2	Power of Attorney	134070_01602_Executed_POA.PDF	115494 9b03bf83cdb2b9ae1d0419cd11fcaa50aa4f8795	no	1
Warnings:					
Information:					
			Total Files Size (in bytes):	132867	

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

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

New International Application Filed with the USPTO as a Receiving Office

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

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United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/777,121	01/30/2020	1629	785	134070-01602	8	1

CONFIRMATION NO. 1029

86738
MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

FILING RECEIPT

OC000000114762512

Date Mailed: 02/19/2020

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Minhua Chen, Suzhou, CHINA;
Yanfeng Zhang, Suzhou, CHINA;
Chunxiang Huang, Suzhou, CHINA;
Xiaoyu Zhang, Suzhou, CHINA;

Applicant(s)

Crystal Pharmaceutical (Suzhou) Co., Ltd., Suzhou, CHINA;

Power of Attorney: The patent practitioners associated with Customer Number 86738

Domestic Priority data as claimed by applicant

This application is a CON of PCT/CN2018/097797 07/31/2018

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 201710648135.2 08/01/2017 No Access Code Provided

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Projected Publication Date: To Be Determined - pending completion of Corrected Papers
Non-Publication Request: No
Early Publication Request: No
**** SMALL ENTITY ****
Title

CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE THEREOF

Preliminary Class

514

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

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Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/777,121	01/30/2020	Minhua Chen	134070-01602

CONFIRMATION NO. 1029

86738
MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

FORMALITIES LETTER

OC000000114762513

Date Mailed: 02/19/2020

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given **TWO MONTHS** from the date of this Notice within which to correct the informalities indicated below. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

The required item(s) identified below must be timely submitted to avoid abandonment:

- A substitute specification excluding claims in compliance with 37 CFR 1.52, 1.121(b)(3), and 1.125 is required. The substitute specification must be submitted with markings and be accompanied by a clean version (without markings) as set forth in 37 CFR 1.125(c) and a statement that the substitute specification contains no new matter (see 37 CFR 1.125(b)). Since a preliminary amendment was present on the filing date of the application and such amendment is part of the original disclosure of the application, the substitute specification must include all of the desired changes made in the preliminary amendment. See 37 CFR 1.115 and 1.215.

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

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Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

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

/eruga/

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/777,121

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	75		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	330		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	380		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	8 minus 20 =	*	x 50 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*	x 230 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	785		TOTAL	

APPLICATION AS AMENDED - PART II

		(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".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: February 25, 2020
Electronic Signature for Xiaoyuan Ding: /Xiaoyuan Ding/

Docket No.: 134070-01602
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Utility Application of:
Minhua Chen et al.

Application No.: 16/777,121 Confirmation No.: 1029

Filed: January 30, 2020 Art Unit: 1629

For: CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE THEREOF

Examiner: Not Yet Assigned

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

RESPONSE TO NOTICE TO FILE CORRECTED APPLICATION PAPERS

Dear Sir:

This paper is filed in response to the Notice to File Corrected Application Papers dated February 19, 2020.

Applicant submits herewith a substitute specification in both marked-up and clean versions under 37 C.F.R. § 1.52, 1.121(b)(3) and 1.125(c). Specifically, per the Office's request, the substitute specification has included all of the changes presented in the Preliminary Amendment filed on January 30, 2020.

No new matter has been introduced by the aforementioned amendments. Applicant respectfully requests the entry of the substitute specification to replace the original specification.

It is believed that no additional fees are due with this response. However, if an additional fee is due, please charge our Deposit Account No. 50-4876, under Order No. 134070-01602 from which the undersigned is authorized to draw.

Dated: February 25, 2020

Respectfully submitted,

Electronic signature: /Xiaoyuan Ding/
Xiaoyuan Ding
Registration No.: 75,354
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(617) 449-6500
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Attorney/Agent For Applicant

~~CRYSTAL FORM OF OREXIN RECEPTOR ANTAGONIST, PREPARATION METHOD THEREFOR AND USE THEREOF~~

CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of International Application No. PCT/CN2018/097797, filed on July 31, 2018, which claims the benefit of foreign priority of Chinese Patent Application No.: 201710648135.2, filed on August 1, 2017. The entire contents of the aforementioned applications are incorporated herein by reference.

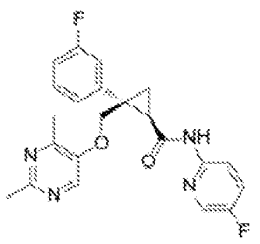
TECHNICAL FIELD

The present disclosure relates to the field of pharmaceutical chemistry, particularly relates to a novel crystalline forms of orexin receptor antagonist, processes for preparation and use thereof.

BACKGROUND

E-2006 (Lemborexant) was developed by Eisai and clinically used to treat insomnia. Studies have shown that the orexin system is a key regulator of the sleep-wake cycle, and thus orexin receptor antagonists have the potential to counteract inappropriate nighttime wakefulness and promote a regular sleep-wake cycle. E-2006 is an orexin receptor antagonist. In clinical trials, E-2006 can significantly improve sleep efficiency in patients with insomnia, including falling asleep fast and shorter time spent awake at night. In addition, E-2006 also shows great potential in the treatment of Alzheimer's patients with Irregular Sleep-Wake Rhythm Disorder (ISWRD). ISWRD is different from common insomnia, and has unmet clinical needs.

The chemical name of E-2006 is (1R, 2S)-2-{[(2, 4-dimethylpyrimidin-5-yl)oxy]methyl}-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide (hereinafter referred to as “Compound (I)”), and the structure is shown as follows:



Compound (I)

Currently, no crystalline forms of compound (I) was disclosed. CN103153963B disclosed the structure of compound (I) and the process for preparing compound (I). The inventors of the present disclosure have repeated the preparation method in CN103153963B and amorphous solid was obtained. Compared with the crystalline form of the present disclosure, the amorphous solid has lower stability, lower density and poorer flowability, which is not suitable for the preparation of drug product. In addition, amorphous is the thermodynamically most unstable solid form, which is prone to crystal transformation or chemical degradation, resulting in a decrease in the purity of the compound. The preparation of amorphous is usually a rapid precipitation process to produce kinetically stable solid, which easily leads to excessive residual solvent. The particle property control in the preparation process is difficult.

The inventors of the present disclosure discovered excellent crystalline form CS2 of compound (I), which has advantages in at least one aspect of stability, melting point, solubility, in vitro and in vivo dissolution, hygroscopicity, bioavailability, adhesiveness, compressibility, flowability, processability, purification ability, formulation production, etc. Particularly, crystalline form CS2 has good stability, low hygroscopicity, good formulation processability, high in vitro dissolution and dissolution rate, which provides a new and better choice for the development of drug containing compound (I) and is of great significance.

SUMMARY

The main objective of the present disclosure is to provide a novel crystalline form of compound (I), processes for preparation and use thereof.

According to the objective of the present disclosure, crystalline form CS2 of compound (I) is provided (hereinafter referred to as Form CS2).

According to one aspect of the present disclosure, the X-ray powder diffraction pattern of Form

CS2 shows characteristic peaks at 2theta values of 7.8°±0.2°, 15.6°±0.2° and 11.4°±0.2° using CuKα radiation.

Furthermore, the X-ray powder diffraction pattern of Form CS2 shows one or two or three characteristic peaks at 2theta values of 12.5°±0.2°, 21.3°±0.2°, 27.3°±0.2°. Preferably, the X-ray powder diffraction pattern of Form CS2 shows three characteristic peaks at 2theta values of 12.5°±0.2°, 21.3°±0.2°, 27.3°±0.2°.

Furthermore, the X-ray powder diffraction pattern of Form CS2 shows one or two or three characteristic peaks at 2theta values of 24.0°±0.2°, 19.4°±0.2° and 22.3°±0.2°. Preferably, the X-ray powder diffraction pattern of Form CSI shows three characteristic peaks at 2theta values of 24.0°±0.2°, 19.4°±0.2°, 22.3°±0.2°.

According to another aspect of the present disclosure, the X-ray powder diffraction pattern of Form CS2 shows three or four or five or six or seven or eight or nine or ten or eleven characteristic peaks at 2theta values of 7.8°±0.2°, 15.6°±0.2°, 11.4°±0.2°, 12.5°±0.2°, 21.3°±0.2°, 27.3°±0.2°, 24.0°±0.2°, 19.1°±0.2°, 19.4°±0.2°, 22.3°±0.2°, 25.9°±0.2° using CuKα radiation.

Without any limitation being implied, the X-ray powder diffraction pattern of Form CS2 is substantially as depicted in Figure 1 or 5.

According to the objective of the present disclosure, a process for preparing Form CS2 is also provided. The process comprises:

(1) Dissolving compound (I) in a solvent to get a solution containing compound (I), then adding an anti-solvent to the solution slowly, stirring and crystallizing to obtain Form CS2; or

(2) Dissolving compound (I) in ketones and slowly evaporating to obtain Form CS2; or

(3) Dissolving compound (I) in nitriles, adding an ionic liquid, then slowly evaporating to obtain Form CS2.

Furthermore, in method (1) said solvent is alcohol, said anti-solvent is water;

Furthermore, in method (1) said alcohol is methanol.

Furthermore, in method (2) said ketone is preferably acetone.

Furthermore, in method (3) said nitrile is preferably acetonitrile, said ionic liquid is preferably

1-ethyl-3-methylimidazolium methyl sulfate, or 1-ethyl-3-methylimidazolium hexafluoroantimonate or 1,3-dimethylimidazolium dimethyl phosphate.

According to the objective of the present disclosure, a pharmaceutical composition is provided, said pharmaceutical composition comprises a therapeutically effective amount of Form CS2 and pharmaceutically acceptable carriers, diluents or excipients.

Furthermore, Form CS2 can be used for preparing orexin receptor antagonist drugs.

Furthermore, Form CS2 can be used for preparing drugs treating insomnia and/or irregular sleep-wake rhythm disorder.

Form CS2 of the present disclosure has the following advantages:

(1) Form CS2 of the present disclosure has lower hygroscopicity. The test results show that the weight gain of Form CS2 at 80% RH (Relative Humidity) is 0.21%. Form CS2 is slightly hygroscopic. The crystalline form does not change after DVS, Form CS2 has good physical stability at 0-95% RH.

Hygroscopicity affects the stability of drug substances, flowability and uniformity during the formulation process, thus affecting the quality of drug products. Hygroscopicity affects the preparation, storage and post-treatment of the drug. The crystalline form with low hygroscopicity is not demanding on storage conditions, which reduces the cost of storage and quality control, and has strong economic value.

(2) The crystalline form provided by the present disclosure has good stability.

Drug substance Form CS2 of the present disclosure has good physical and chemical stability in different storage conditions. The crystalline form of Form CS2 of the present disclosure remained unchanged for at least 10 months when stored in open dishes under the conditions of 25 °C/60% RH and 40 °C/75% RH, preferably for at least one year. The crystalline form of Form CS2 doesn't change for at least 2 weeks when stored under the condition of 60 °C/75% RH. The chemical purity of Form CS2 of the present disclosure is above 99%, preferably above 99.5%, and remained substantially unchanged during storage.

Form CS2 of the present disclosure has good physical stability after grinding. Grinding and pulverization are often required in drug manufacturing process. Good physical stability of the drug substance can reduce the risk of crystallinity decrease and crystal transformation during

the drug production process.

Form CS2 of the present disclosure has good physical and chemical stability in drug product. Drug product is prepared with excipient and stored under the conditions of 25 °C/60% RH and 40 °C/75% RH for at least one month. The crystalline form of Form CS2 remained unchanged and chemical purity remained substantially unchanged in drug product.

Drug substance and drug product has good physical and chemical stability. During the storage and formulation process, Form CS2 does not convert to other crystalline forms, and the chemical purity of Form CS2 remained substantially unchanged during storage, thus ensuring consistent and controllable quality of drug substance and drug product.

(3) Form CS2 has good in vitro dissolution and dissolution rate. Form CS2 of the present disclosure in drug product underwent 100% dissolution in 60 minutes in 0.1 mol/L aqueous hydrochloric acid solution. Good in vitro dissolution leads to higher in vivo absorption, thereby achieving ideal bioavailability.

Dissolution is the prerequisite for absorption. Good in vitro dissolution leads to higher in vivo absorption and better in vivo exposure, thereby improving drug's bioavailability and efficacy. High dissolution rate is beneficial for the drug to achieve peak plasma concentration quickly after administration, thus ensuring rapid drug action.

Furthermore, Form CS2 of the present disclosure also has the following advantages:

(1) Form CS2 of the present disclosure has good compressibility. Failure in hardness/friability test issue can be avoided in the tableting process due to better compressibility of Form CS2, thus reducing the requirements for pretreatment process, making the preparation process more reliable and improving product appearance and product quality.

(2) Compared with prior art, Form CS2 of the present disclosure has higher density. Test results indicate that the bulk density and tapped density of Form CS2 are remarkably higher than that of prior art solid. Higher density of Form CS2 is beneficial to large scale production. High density of Form CS2 can also reduce dust, reduce occupational hazard, reduce security risks and ensure production safety.

(3) Compared with prior art, Form CS2 of the present disclosure has better flowability. Flowability evaluation results indicate that the flowability of Form CS2 is good, while the flowability of prior art form is poor. Better flowability can effectively increase the speed of

tableting and filling and increase manufacturing efficiency. Better flowability of Form CS2 ensures the blend uniformity and content uniformity of the drug product, and reduces the weight variation of the drug product and improves product quality.

(4) Compared with prior art, Form CS2 of the present disclosure shows superior adhesiveness. Adhesiveness evaluation results indicate that Form CS2 has low adhesiveness amount and low adhesiveness. Due to low adhesiveness of Form CS2, adhesion to roller and tooling during dry-granulation and compression process can be reduced, which is also beneficial to improve product appearance and weight variation. In addition, low adhesiveness of Form CS2 can reduce the agglomeration of drug substance, which is beneficial to the dispersion of drug substance and reduce the adhesion between drug substance and other excipients, and improve the blend uniformity and content uniformity of drug product.

(5) Form CS2 of the present disclosure has almost no residual solvent and meets the requirements of drug substance, while the residual solvent of the prior art exceeds the standard and cannot be used as a drug substance directly. Many organic solvents are harmful to human and environment. Therefore, in order to ensure drug safety and product quality, it is necessary to control the residual organic solvent of drug substance.

In the present disclosure, said "evaporating" is accomplished by using a conventional method in the field such as slow evaporation or rapid evaporation. Slow evaporation is accomplished in a container covered by sealing film with pinholes. Rapid evaporation is accomplished in an open container.

In the present disclosure, "crystal" or "crystalline form" refers to the crystal or the crystalline form being identified by the X-ray diffraction pattern shown herein. Those skilled in the art are able to understand that physicochemical properties discussed herein can be characterized. The experimental errors depend on the instrument conditions, the sampling processes and the purity of samples. In particular, those skilled in the art generally know that the X-ray diffraction pattern typically varies with the experimental conditions. It is necessary to point out that, the relative intensity of the diffraction peaks in the X-ray diffraction pattern may also vary with the experimental conditions; therefore, the order of the diffraction peak intensities cannot be regarded as the sole or decisive factor. In fact, the relative intensity of the diffraction peaks in the X-ray powder diffraction pattern is related to the preferred orientation of the crystals, and the diffraction peak intensities shown herein are illustrative and identical diffraction peak

intensities are not required. In addition, the experimental error of the diffraction peak position is usually 5% or less, and the error of these positions should also be taken into account. An error of ±0.2° is usually allowed. In addition, due to experimental factors such as sample thickness, the overall offset of the diffraction peak is caused, and a certain offset is usually allowed. Thus, it will be understood by those skilled in the art that a crystalline form of the present disclosure is not necessarily to have the exactly same X-ray diffraction pattern of the example shown herein. As used herein, "the same XRPD pattern" does not mean absolutely the same, the same peak positions may differ by ±0.2° and the peak intensity allows for some variability. Any crystalline forms whose X-ray diffraction patterns have the same or similar characteristic peaks should be within the scope of the present disclosure. Those skilled in the art can compare the patterns shown in the present disclosure with that of an unknown crystalline form in order to identify whether these two groups of patterns reflect the same or different crystalline forms.

In some embodiments, Form CS2 of the present disclosure is pure and substantially free of any other crystalline forms. In the present disclosure, the term "substantially free" when used to describe a novel crystalline form, it means that the content of other crystalline forms in the novel crystalline form is less than 20% (w/w), specifically less than 10% (w/w), more specifically less than 5% (w/w) and further more specifically less than 1% (w/w).

It should be noted that the number and the number range should not be understood as the number or number range themselves only. It should be understood by those skilled in the art that the specific number can be shifted at specific technical environment without departing from the spirit and principle of the present disclosure. In the present disclosure, the number of shift ranges expected by one of skilled in the art is represented by the term "about".

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows an XRPD pattern of Form CS2 in Example 1.

Figure 2 shows a DSC curve of Form CS2 in Example 1.

Figure 3 shows a TGA curve of Form CS2 in Example 1.

Figure 4 shows a ^{1}H NMR spectrum of Form CS2 in Example 1.

Figure 5 shows an XRPD pattern of Form CS2 in Example 2.

Figure 6 shows a DSC curve of Form CS2 in Example 2.

Figure 7 shows a TGA curve of Form CS2 in Example 2.

Figure 8 shows a ^{1}H NMR spectrum of Form CS2 in Example 2.

Figure 9 shows an XRPD pattern overlay of Form CS2 before and after stored at 25 ℃/60% RH (top: before storage, bottom: after storage).

Figure 10 shows an XRPD pattern overlay of Form CS2 before and after stored at 40 ℃/75% RH (top: before storage, bottom: after storage).

Figure 11 shows an XRPD pattern overlay of Form CS2 before and after stored at 60 ℃/75% RH (top: before storage, bottom: after storage).

Figure 12 shows an XRPD curve of Form CS2 before and after grinding (top: XRPD pattern before grinding; bottom: XRPD pattern after grinding).

Figure 13 shows a DSC curve of Form CS2.

Figure 14 shows an XRPD pattern overlay of Form CS2 before and after DVS test (top: XRPD pattern before DVS; bottom: XRPD pattern after DVS).

Figure 15 shows an in vitro dissolution profile of Form CS2.

DETAILED DESCRIPTION

The present disclosure is further illustrated by the following examples which describe the preparation and use of the crystalline form of the present disclosure in detail. It is obvious to those skilled in the art that many changes in the materials and methods can be accomplished without departing from the scope of the present disclosure.

The abbreviations used in the present disclosure are explained as follows:

XRPD: X-ray Powder Diffraction

DSC: Differential Scanning Calorimetry

TGA: Thermo Gravimetric Analysis

DVS: Dynamic Vapor Sorption

^{1}H NMR: Proton Nuclear Magnetic Resonance

Instruments and methods used for data collection:

X-ray powder diffraction patterns in the present disclosure were acquired by a Bruker D2 PHASER X-ray powder diffractometer. The parameters of the X-ray powder diffraction method of the present disclosure were as follows:

X-ray Reflection: Cu, Kα

Kα1 (Å): 1.54060; Kα2 (Å): 1.54439

Kα2/Kα1 intensity ratio: 0.50

Voltage: 30 (kV)

Current: 10 (mA)

Scan range: from 3.0 degree to 40.0 degree

Differential scanning calorimetry (DSC) data in the present disclosure were acquired by a TA Q2000. The parameters of the DSC method of the present disclosure are as follows:

Heating rate: 10 ℃/min

Purge gas: nitrogen

Thermo gravimetric analysis (TGA) data in the present disclosure were acquired by a TA Q500. The parameters of the TGA method of the present disclosure were as follows:

Heating rate: 10 ℃/ min

Purge gas: nitrogen

Dynamic Vapor Sorption (DVS) is measured via a SMS (Surface Measurement Systems Ltd.) intrinsic DVS instrument. Typical Parameters for DVS test are as follows:

Temperature: 25 ℃

Gas and flow rate: N_2, 200 mL/min

dm/dt: 0.002%/min

RH range: 0% RH to 95% RH

High Performance Liquid Chromatography (HPLC) data in the present disclosure were collected from an Agilent 1260 with Diode Array Detector (DAD).

The HPLC method parameters in the present disclosure are as follows:

Column: ZORBAX Eclipse C18, 100×4.6mm, 5 μm

Mobile Phase: A: Acetonitrile: Water: Trifluoroacetic acid =50:950:1 (Volume ratio)

B: 0.1% Trifluoroacetic acid in acetonitrile

Gradient:

Time (min)	%B
0.0	0
0.5	0
30.0	90
35.0	90
35.1	0
40.0	0

Flow rate: 1.0 mL/min

Injection Volume: 2 μL

Detection wavelength: 220 nm

Column Temperature: 40 ℃

Diluent: Acetonitrile

Proton nuclear magnetic resonance spectrum data (^{1}H NMR) were collected from a Bruker Avance II DMX 400M HZ NMR spectrometer. 1-5 mg of sample was weighed, and dissolved in 0.5 mL of deuterated dimethyl sulfoxide to obtain a solution with a concentration of 2-10 mg/mL.

Unless otherwise specified, the following examples were conducted at room temperature. Said "room temperature" is not a specific value, and refers to 10-30 ℃.

According to the present disclosure, compound (I) used as a raw material is solid (crystalline or amorphous), semisolid, wax or oil. Preferably, said compound (I) used as a raw material is a solid.

Raw materials of E-2006 used in the following examples were prepared by known methods in the prior art, for example, the method disclosed in CN103153963B.

DETAILED DESCRIPTION

Example 1 Preparation of Form CS2:

Approximately 199.6 mg of compound (I) was weighted and dissolved in 3.0 mL of acetone, followed by filtration and slowly evaporation to obtain a solid at room temperature. The obtained solid was confirmed to be Form CS2. The XRPD pattern is substantially as depicted in Figure 1, and the XRPD data are listed in Table 1.

The DSC curve of Form CS2 in this example is substantially as depicted in Figure 2. When heated to 177 ℃, an endothermic peak appears, which corresponds to the melting endothermic peak of Form CS2.

The TGA curve of Form CS2 in this example shows about 0.6% weight loss when heated to 170 ℃, which is substantially as depicted in Figure 3.

The ^{1}H NMR spectrum of Form CS2 is substantially as depicted in Figure 4, and the corresponding data are: ^{1}H NMR (400 MHz, DMSO) δ11.22 (s, 1H), 8.33 (d, J = 3.0 Hz, 1H), 8.13 (s, 1H), 7.89 (dd, J = 9.1, 4.1 Hz, 1H), 7.64 (td, J = 8.7, 3.1 Hz, 1H), 7.48-7.35 (m, 3H), 7.11 (ddd, J = 11.5, 6.0, 3.0 Hz, 1H), 4.68 (d, J = 10.2 Hz, 1H), 4.29 (d, J = 10.3 Hz, 1H), 2.64 (dd, J = 15.7, 8.8 Hz, 1H), 2.36 (d, J = 21.5 Hz, 3H), 2.03 (s, 3H), 1.74-1.67 (m, 1H), 1.50 (dd, J = 8.0, 4.8 Hz, 1H)。

Table 1

2θ	d spacing	Intensity %
7.81	11.32	100.00
9.55	9.26	5.68
11.44	7.73	23.41
12.53	7.07	25.17
15.58	5.69	46.96
15.78	5.62	11.77
16.40	5.41	4.67
19.05	4.66	12.69
19.38	4.58	17.51
19.57	4.54	18.50
21.32	4.17	21.23
21.73	4.09	6.60
22.27	3.99	11.54
23.03	3.86	5.32
23.23	3.83	6.23

23.99	3.71	15.14
25.42	3.50	4.70
25.89	3.44	23.53
26.28	3.39	7.86
27.26	3.27	15.44
28.04	3.18	5.25
29.36	3.04	3.75
31.09	2.88	5.99
33.99	2.64	1.25

Example 2 Preparation of Form CS2 by anti-solvent addition method

Approximately 1026.0 mg of compound (I) was weighted and dissolved in 10.0 mL of methanol. The solution was filtered and stirred while adding about 10.0 mL of water as an anti-solvent. After stirred for about 4 hours, a large amount of solid precipitated out. The precipitation collected by suction filtration and dried under vacuum at 40 °C for about 18 hours to obtain solids. The obtained solid was confirmed to be Form CS2. The XRPD pattern is substantially as depicted in Figure 5, and the XRPD data are listed in Table 2.

The DSC curve of Form CS2 in this example is substantially as depicted in Figure 6. When heated to 176 ℃, an endothermic peak appears, which corresponds to the melting endothermic peak of Form CS2.

The TGA curve of Form CS2 in this example shows about 0.5% weight loss when heated to 170 ℃, which is substantially as depicted in Figure 7.

The ^{1}H NMR spectrum of Form CS2 is substantially as depicted in Figure 8, and the corresponding data are: ^{1}H NMR (400 MHz, DMSO) δ11.21 (s, 1H), 8.33 (d, J = 3.0 Hz, 1H), 8.13 (s, 1H), 7.89 (dd, J = 9.2, 4.2 Hz, 1H), 7.64 (td, J = 8.8, 3.1 Hz, 1H), 7.49-7.34 (m, 3H), 7.16-7.05 (m, 1H), 4.68 (d, J = 10.2 Hz, 1H), 4.29 (d, J = 10.3 Hz, 1H), 2.67-2.57 (m, 1H), 2.38 (s, 3H), 2.03 (s, 3H), 1.74-1.66 (m, 1H), 1.50 (dd, J = 8.0, 4.8 Hz, 1H)。

Table 2

2θ	d spacing	Intensity %
7.84	11.27	100.00
9.59	9.22	6.98
11.49	7.70	13.05

12.56	7.05	35.00
15.61	5.68	59.13
15.82	5.60	9.92
16.44	5.39	9.29
19.07	4.65	19.61
19.41	4.57	19.56
19.60	4.53	20.52
21.36	4.16	22.18
21.77	4.08	10.04
22.31	3.98	29.55
23.07	3.86	9.34
23.89	3.72	14.02
24.00	3.71	11.54
25.46	3.50	6.67
25.93	3.44	17.57
26.31	3.39	16.60
27.33	3.26	16.63
28.06	3.18	9.34
29.37	3.04	7.28
31.15	2.87	3.40
31.38	2.85	4.42
29.37	3.04	7.28
31.15	2.87	3.40

Example 3-5 Preparation of Form CS2 by ionic liquid induced evaporation

Approximately 31.5 mg of compound (I) was dissolved in 1.0 mL of acetonitrile and filtered. A small amount of ionic liquid as shown in Table 3 was added, and the solution was slowly evaporated at room temperature to obtain solid. The solid obtained in example 3-5 were labeled as samples 3-5 and confirmed to be Form CS2.

Table 3

Example	Ionic liquid	Sample
3	1-ethyl-3-methylimidazolium methyl sulfate	Sample 3
4	1-ethyl-3-methylimidazolium	Sample 4

	hexafluoroantimonate	
5	1,3-dimethylimidazolium dimethyl phosphate	Sample 5

Example 6 Stability of Form CS2

Form CS2 of the present disclosure were weighed and stored under conditions of 25 ℃/60% RH, 40 ℃/75% RH, 60 ℃/75% RH and 80 ℃ in open dishes. Crystalline form and chemical impurity were checked by XRPD and HPLC, respectively. The results are shown in Table 4.

Table 4

Initial crystalline form	Initial purity	Storage condition	Storage time	Crystalline form after storage	Purity after storage
Form CS2 (top of Figure 9)	99.67%	25°C /60% RH	10 months	Form CS2 (bottom of Figure 9)	99.63%
Form CS2 (top of Figure 10)	99.67%	40°C /75% RH	10 months	Form CS2 (bottom of Figure 10)	99.67%
Form CS2 (top of Figure 11)	99.67%	60°C /75% RH	2 weeks	Form CS2 (bottom of Figure 11)	99.70%

The results show that Form CS2 keeps stable for at least 10 months at 25 ℃/60% RH and 40 ℃/75% RH. Form CS2 keeps stable for at least 2 weeks at 60 ℃/75% RH, the purity of Form CS2 remained substantially unchanged. It can be seen that Form CS2 has good physical and chemical stability.

Example 7 Grinding stability of Form CS2

Form CS2 was ground manually for 5 minutes in a mortar. The XRPD pattern of the solids before and after grinding are presented in Figure 12 (top: XRPD pattern before grinding; bottom: XRPD pattern after grinding). The results show that the crystalline form of Form CS2 does not change after grinding. Form CS2 has good grinding stability.

Example 8 Hygroscopicity of Form CS2

Dynamic vapor sorption (DVS) was applied to measure hygroscopicity of Form CS2 with

about 10 mg of samples. The weight gains at each relative humidity were recorded in a cycle of 0-95%-0 RH. DVS is substantially as depicted in Figure 13, and the experimental results are shown in Table 5. The XRPD pattern overlay of Form CS2 before and after DVS test is presented in Figure 14 (top: XRPD pattern before DVS; bottom: XRPD pattern after DVS). The results show that the hygroscopicity of Form CS2 is low. The weight gain under 80% RH is 0.21%. Form CS2 is slightly hygroscopic. The crystalline form of Form CS2 does not change after DVS, which indicates that Form CS2 is physically stable at 0% - 95% RH.

Table 5

Relative Humidity / Weight Gain (%)	Weight gain under 80% Relative Humidity	Hygroscopicity
Form CS2	0.21%	Slightly hygroscopic

Description and definition of hygroscopicity (Chinese Pharmacopoeia 2015 edition appendix Drug hygroscopic test guidelines, test at 25 ºC±1 ºC, 80% RH.).

—deliquescent: Sufficient water is absorbed to form a liquid;

—very hygroscopic: Increase in mass is equal to or greater than 15 percent;

—hygroscopic: Increase in mass is less than 15 percent and equal to or greater than 2 percent;

—slightly hygroscopic: Increase in mass is less than 2 percent and equal to or greater than 0.2 percent.

—non hygroscopic or almost non hygroscopic: Increase in mass is less than 0.2%.

Example 9 Flowability comparison of Form CS2 and the prior art solid

Compressibility, also known as compressibility index is usually used to evaluate the flowability of powder and granular intermediates during the formulation process. A certain amount of powder was added into a measuring cylinder and bulk volume was recorded. Then the measuring cylinder was tapped to make the powder in the tightest state and the tapped volume was recorded. The bulk density (ρ_0), tapped density (ρ_f) were calculated, and compressibility index was calculated according to $c=(\rho_f-\rho_0)/\rho_f$. Compressibility index or Carr Index is an important indicator for evaluating the flowability of powder.

Compressibility index test method is as follows: Compressibility index was calculated according to bulk density ρ_0 and tapped density ρ_f of Form CS2 and the amorphous solid of the prior art with $c=(\rho_f-\rho_0)/\rho_f *100\%$. Criteria of flowability is shown in Table 6.

Table 6

Compressibility index (%)	Flowability
≦10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	poor
32-37	Very poor
>38	Very, very poor

Amorphous solid was obtained by repeating the preparation method disclosed in CN103153963B. Flowability evaluation results of Form CS2 and the amorphous solid are presented in table 7, which indicate that the flowability of Form CS2 is remarkably superior to that of the amorphous solid in the prior art.

Table 7

Form	Bulk density (ρ_0, g/mL)	Tapped density (ρ_f, g/mL)	Compressibility index (%)	Flowability
Amorphous solid	0.196	0.274	28	Poor
Form CS2	0.263	0.351	25	Passable

Example 10 Adhesiveness of Form CS2

30 mg of Form CS2 was weighed and added into the dies of φ8mm round tooling, tableted at 10 KN and held for 30s. The amount of material sticking to the punch was weighed. The compression was repeated twice and the cumulative amount, maximum amount and average amount of material sticking to the punch during the compression process were recorded. Detailed experimental results are shown in Table 8.

Table 8

Crystalline Form	Maximum amount (mg)	Average amount (mg)	Cumulative amount (mg)
CS2	0.74	0.22	0.44

Example 11 Compressibility of CS2

80mg of Form CS2 was weighted and added into the dies of φ6mm round tooling, compressed at 10 KN. The round tablet was stored in a desiccator for 24 hours until complete elastic recovery. Hardness (H) was tested with a tablet hardness tester. Diameter (D) and thickness (L) were tested with caliper. Tensile strength of the powder was calculated with the following formula: $T=2H/\pi DL$. Under a certain force, the greater the tensile strength, the better the compressibility. The results are presented in Table 9.

Table 9

Form	Thickness(mm)	Diameter (mm)	Hardness(N)	Tensile strength (MPa)
CS2	2.40	6.06	8.4	0.37

Example 12 Residual solvents of Form CS2 and the prior art solid

Amorphous solid was obtained by repeating the preparation method disclosed in CN103153963B. Residual solvents of Form CS2 and the amorphous solid were tested. The results show that Form CS2 has no residual solvents, while the -heptane and ethyl acetate residue in the amorphous solid is 46596.16 ppm and 1260.01 pm, respectively. According to the guideline of the International Council for Harmonization (ICH) on residual solvents, both n-heptane and ethyl acetate belong to Class 3 solvents, and the residual solvent must not exceed 5000 ppm. It can be seen that the residue of n-heptane in the amorphous solid is much higher than the limits of ICH, and the amorphous not suitable for drug substance.

Example 13 CS2 drug product

1. Preparation of compound (I) tablets

Form CS2 and intragranular excipients in Table 10 were blended according to formulation and the blend was compressed with the target weight of 500 mg using a φ20 mm single punch manual press at 5±0.5 KN pressure. The above tablets were crushed, passed through a 20 mesh sieve, then blended uniformly with the extragranular excipients shown in Table 10, and the blend was compressed with a target weight of 120.0 mg using a φ7 mm single punch manual press at 5±0.5 KN pressure.

Table 10

Component	**Quantity (mg/unit)**	**Mass ratio (%)**
E-2006 (Form CS2)	10.00	8.3

Intragranular excipients	Lactose monohydrate	88.88	74.1
	Hydroxypropyl cellulose	3.60	3.0
	Low substituted hydroxypropyl cellulose	10.80	9.0
	Magnesium stearate	0.36	0.3
Total		113.64	94.7
Extragranular excipients	Low substituted hydroxypropyl cellulose	6.00	5.0
	Magnesium stearate	0.36	0.3
Total		120.00	100.0

2. Stability of Form CS2 in drug product

The tablets prepared above were packed in 35 cc HDPE bottles (one tablet per bottle) with 1 g desiccant. The bottles were sealed with a sealer. The bottles were stored under conditions of 25 ℃/60% RH and 40 ℃/75% RH for 1 month. Crystalline form of Form CS2 tablet was tested and the results show that the crystalline form of Form CS2 does not change. In addition, single and total impurity of Form CS2 remained substantially unchanged in storage. The results presented in Table 11 and 12 indicate that Form CS2 keeps physically and chemically stable in drug product.

Table 11 Physical stability of Form CS2 in drug product

Sample	Condition	Time	API crystalline Form after storage
Tablet contains Form CS2	25 ℃/60% RH	1 month	Form CS2
	40 ℃/75% RH	1 month	Form CS2

Table 12 Chemical stability of Form CS2 in drug product

Condition	Time	Initial largest single impurity (%)	Largest single impurity after storage	Initial total impurity (%)	Total impurity after storage (%)	Single impurity change (%)	Total impurity change (%)

			(%)				
25 ℃/60% RH	1 month	0.08	0.09	0.17	0.21	0.01	0.04
40 ℃/75% RH	1 month	0.08	0.08	0.17	0.20	0	0.03

Example 14 In vitro dissolution and dissolution rate of Form CS2

In vitro dissolution test was performed on Form CS2 tablet obtained from example 12. Dissolution method according to Chinese Pharmacopoeia 2015<0931> was used. The conditions are as follows:

Medium: 0.1 mol/L aqueous solution of hydrochloric acid

Method: Paddle

Volume: 900 mL

Speed: 50 rpm

Temperature: 37 ℃

In vitro dissolution of Form CS2 are presented in Table 13 and Figure 15.

Table 13

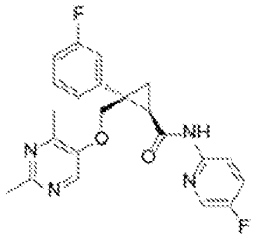
Cumulative drug release (%) / Time (minute)	Form CS2
0	0.0
5	55.2
10	73.1
15	81.0
20	86.2
30	92.1
45	96.9
60	100.5

The results showed that Form CS2 drug product can undergo 100% dissolution in 0.1 mol/L aqueous hydrochloric acid, and the dissolution rate is high, which is favorable for achieving good in vivo bioavailability.

The examples described above are only for illustrating the technical concepts and features of the present disclosure, and intended to make those skilled in the art being able to understand the present disclosure and thereby implement it, and should not be concluded to limit the protective scope of this disclosure. Any equivalent variations or modifications according to the spirit of the present disclosure should be covered by the protective scope of the present disclosure.

ABSTRACT

The present disclosure provides a novel crystalline form of Lemborexant and processes for preparation thereof. Pharmaceutical composition containing Lemborexant, and use of Lemborexant for preparing orexin receptor antagonist drug, and use of Lemborexant for preparing drugs treating insomnia and irregular sleep-wake rhythm disorder are also provided. The crystalline form of the present disclosure have one or more improved properties compared with crystalline forms of prior arts, and has significant values for future drug optimization and development.



Compound (I)

Electronic Acknowledgement Receipt	
EFS ID:	38681294
Application Number:	16777121
International Application Number:	
Confirmation Number:	1029
Title of Invention:	CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE THEREOF
First Named Inventor/Applicant Name:	Minhua Chen
Customer Number:	86738
Filer:	Xiaoyuan Ding
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant Response to Pre-Exam Formalities Notice	134070_01602_Response_to_Notice_to_File_Corrected_Appln_Papers.PDF	7352 af7dd017e4cdac4754ce786c319473bee61d3831	no	2
Warnings:					

Information:					
2	Miscellaneous Incoming Letter	134070_01602_Substitute_Specification_clean.PDF	161214 5042ee9fee0090bf60ca66616f3e4d5c0db52e13	no	21
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CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of International Application No. PCT/CN2018/097797, filed on July 31, 2018, which claims the benefit of foreign priority of Chinese Patent Application No.: 201710648135.2, filed on August 1, 2017. The entire contents of the aforementioned applications are incorporated herein by reference.

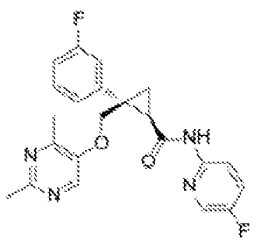
TECHNICAL FIELD

The present disclosure relates to the field of pharmaceutical chemistry, particularly relates to a novel crystalline forms of orexin receptor antagonist, processes for preparation and use thereof.

BACKGROUND

E-2006 (Lemborexant) was developed by Eisai and clinically used to treat insomnia. Studies have shown that the orexin system is a key regulator of the sleep-wake cycle, and thus orexin receptor antagonists have the potential to counteract inappropriate nighttime wakefulness and promote a regular sleep-wake cycle. E-2006 is an orexin receptor antagonist. In clinical trials, E-2006 can significantly improve sleep efficiency in patients with insomnia, including falling asleep fast and shorter time spent awake at night. In addition, E-2006 also shows great potential in the treatment of Alzheimer's patients with Irregular Sleep-Wake Rhythm Disorder (ISWRD). ISWRD is different from common insomnia, and has unmet clinical needs.

The chemical name of E-2006 is (1R, 2S)-2-{[(2, 4-dimethylpyrimidin-5-yl)oxy]methyl}-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl)cyclopropanecarboxamide (hereinafter referred to as “Compound (I)”), and the structure is shown as follows:



Compound (I)

Currently, no crystalline forms of compound (I) was disclosed. CN103153963B disclosed the structure of compound (I) and the process for preparing compound (I). The inventors of the present disclosure have repeated the preparation method in CN103153963B and amorphous solid was obtained. Compared with the crystalline form of the present disclosure, the amorphous solid has lower stability, lower density and poorer flowability, which is not suitable for the preparation of drug product. In addition, amorphous is the thermodynamically most unstable solid form, which is prone to crystal transformation or chemical degradation, resulting in a decrease in the purity of the compound. The preparation of amorphous is usually a rapid precipitation process to produce kinetically stable solid, which easily leads to excessive residual solvent. The particle property control in the preparation process is difficult.

The inventors of the present disclosure discovered excellent crystalline form CS2 of compound (I), which has advantages in at least one aspect of stability, melting point, solubility, in vitro and in vivo dissolution, hygroscopicity, bioavailability, adhesiveness, compressibility, flowability, processability, purification ability, formulation production, etc. Particularly, crystalline form CS2 has good stability, low hygroscopicity, good formulation processability, high in vitro dissolution and dissolution rate, which provides a new and better choice for the development of drug containing compound (I) and is of great significance.

SUMMARY

The main objective of the present disclosure is to provide a novel crystalline form of compound (I), processes for preparation and use thereof.

According to the objective of the present disclosure, crystalline form CS2 of compound (I) is provided (hereinafter referred to as Form CS2).

According to one aspect of the present disclosure, the X-ray powder diffraction pattern of Form

CS2 shows characteristic peaks at 2theta values of 7.8°±0.2°, 15.6°±0.2° and 11.4°±0.2° using CuKα radiation.

Furthermore, the X-ray powder diffraction pattern of Form CS2 shows one or two or three characteristic peaks at 2theta values of 12.5°±0.2°, 21.3°±0.2°, 27.3°±0.2°. Preferably, the X-ray powder diffraction pattern of Form CS2 shows three characteristic peaks at 2theta values of 12.5°±0.2°, 21.3°±0.2°, 27.3°±0.2°.

Furthermore, the X-ray powder diffraction pattern of Form CS2 shows one or two or three characteristic peaks at 2theta values of 24.0°±0.2°, 19.4°±0.2° and 22.3°±0.2°. Preferably, the X-ray powder diffraction pattern of Form CSI shows three characteristic peaks at 2theta values of 24.0°±0.2°, 19.4°±0.2°, 22.3°±0.2°.

According to another aspect of the present disclosure, the X-ray powder diffraction pattern of Form CS2 shows three or four or five or six or seven or eight or nine or ten or eleven characteristic peaks at 2theta values of 7.8°±0.2°, 15.6°±0.2°, 11.4°±0.2°, 12.5°±0.2°, 21.3°±0.2°, 27.3°±0.2°, 24.0°±0.2°, 19.1°±0.2°, 19.4°±0.2°, 22.3°±0.2°, 25.9°±0.2° using CuKα radiation.

Without any limitation being implied, the X-ray powder diffraction pattern of Form CS2 is substantially as depicted in Figure 1 or 5.

According to the objective of the present disclosure, a process for preparing Form CS2 is also provided. The process comprises:

(1) Dissolving compound (I) in a solvent to get a solution containing compound (I), then adding an anti-solvent to the solution slowly, stirring and crystallizing to obtain Form CS2; or

(2) Dissolving compound (I) in ketones and slowly evaporating to obtain Form CS2; or

(3) Dissolving compound (I) in nitriles, adding an ionic liquid, then slowly evaporating to obtain Form CS2.

Furthermore, in method (1) said solvent is alcohol, said anti-solvent is water;

Furthermore, in method (1) said alcohol is methanol.

Furthermore, in method (2) said ketone is preferably acetone.

Furthermore, in method (3) said nitrile is preferably acetonitrile, said ionic liquid is preferably

1-ethyl-3-methylimidazolium methyl sulfate, or 1-ethyl-3-methylimidazolium hexafluoroantimonate or 1,3-dimethylimidazolium dimethyl phosphate.

According to the objective of the present disclosure, a pharmaceutical composition is provided, said pharmaceutical composition comprises a therapeutically effective amount of Form CS2 and pharmaceutically acceptable carriers, diluents or excipients.

Furthermore, Form CS2 can be used for preparing orexin receptor antagonist drugs.

Furthermore, Form CS2 can be used for preparing drugs treating insomnia and/or irregular sleep-wake rhythm disorder.

Form CS2 of the present disclosure has the following advantages:

(1) Form CS2 of the present disclosure has lower hygroscopicity. The test results show that the weight gain of Form CS2 at 80% RH (Relative Humidity) is 0.21%. Form CS2 is slightly hygroscopic. The crystalline form does not change after DVS, Form CS2 has good physical stability at 0-95% RH.

Hygroscopicity affects the stability of drug substances, flowability and uniformity during the formulation process, thus affecting the quality of drug products. Hygroscopicity affects the preparation, storage and post-treatment of the drug. The crystalline form with low hygroscopicity is not demanding on storage conditions, which reduces the cost of storage and quality control, and has strong economic value.

(2) The crystalline form provided by the present disclosure has good stability.

Drug substance Form CS2 of the present disclosure has good physical and chemical stability in different storage conditions. The crystalline form of Form CS2 of the present disclosure remained unchanged for at least 10 months when stored in open dishes under the conditions of 25 °C/60% RH and 40 °C/75% RH, preferably for at least one year. The crystalline form of Form CS2 doesn't change for at least 2 weeks when stored under the condition of 60 °C/75% RH. The chemical purity of Form CS2 of the present disclosure is above 99%, preferably above 99.5%, and remained substantially unchanged during storage.

Form CS2 of the present disclosure has good physical stability after grinding. Grinding and pulverization are often required in drug manufacturing process. Good physical stability of the drug substance can reduce the risk of crystallinity decrease and crystal transformation during

the drug production process.

Form CS2 of the present disclosure has good physical and chemical stability in drug product. Drug product is prepared with excipient and stored under the conditions of 25 °C/60% RH and 40 °C/75% RH for at least one month. The crystalline form of Form CS2 remained unchanged and chemical purity remained substantially unchanged in drug product.

Drug substance and drug product has good physical and chemical stability. During the storage and formulation process, Form CS2 does not convert to other crystalline forms, and the chemical purity of Form CS2 remained substantially unchanged during storage, thus ensuring consistent and controllable quality of drug substance and drug product.

(3) Form CS2 has good in vitro dissolution and dissolution rate. Form CS2 of the present disclosure in drug product underwent 100% dissolution in 60 minutes in 0.1 mol/L aqueous hydrochloric acid solution. Good in vitro dissolution leads to higher in vivo absorption, thereby achieving ideal bioavailability.

Dissolution is the prerequisite for absorption. Good in vitro dissolution leads to higher in vivo absorption and better in vivo exposure, thereby improving drug's bioavailability and efficacy. High dissolution rate is beneficial for the drug to achieve peak plasma concentration quickly after administration, thus ensuring rapid drug action.

Furthermore, Form CS2 of the present disclosure also has the following advantages:

(1) Form CS2 of the present disclosure has good compressibility. Failure in hardness/friability test issue can be avoided in the tableting process due to better compressibility of Form CS2, thus reducing the requirements for pretreatment process, making the preparation process more reliable and improving product appearance and product quality.

(2) Compared with prior art, Form CS2 of the present disclosure has higher density. Test results indicate that the bulk density and tapped density of Form CS2 are remarkably higher than that of prior art solid. Higher density of Form CS2 is beneficial to large scale production. High density of Form CS2 can also reduce dust, reduce occupational hazard, reduce security risks and ensure production safety.

(3) Compared with prior art, Form CS2 of the present disclosure has better flowability. Flowability evaluation results indicate that the flowability of Form CS2 is good, while the flowability of prior art form is poor. Better flowability can effectively increase the speed of

tableting and filling and increase manufacturing efficiency. Better flowability of Form CS2 ensures the blend uniformity and content uniformity of the drug product, and reduces the weight variation of the drug product and improves product quality.

(4) Compared with prior art, Form CS2 of the present disclosure shows superior adhesiveness. Adhesiveness evaluation results indicate that Form CS2 has low adhesiveness amount and low adhesiveness. Due to low adhesiveness of Form CS2, adhesion to roller and tooling during dry-granulation and compression process can be reduced, which is also beneficial to improve product appearance and weight variation. In addition, low adhesiveness of Form CS2 can reduce the agglomeration of drug substance, which is beneficial to the dispersion of drug substance and reduce the adhesion between drug substance and other excipients, and improve the blend uniformity and content uniformity of drug product.

(5) Form CS2 of the present disclosure has almost no residual solvent and meets the requirements of drug substance, while the residual solvent of the prior art exceeds the standard and cannot be used as a drug substance directly. Many organic solvents are harmful to human and environment. Therefore, in order to ensure drug safety and product quality, it is necessary to control the residual organic solvent of drug substance.

In the present disclosure, said "evaporating" is accomplished by using a conventional method in the field such as slow evaporation or rapid evaporation. Slow evaporation is accomplished in a container covered by sealing film with pinholes. Rapid evaporation is accomplished in an open container.

In the present disclosure, "crystal" or "crystalline form" refers to the crystal or the crystalline form being identified by the X-ray diffraction pattern shown herein. Those skilled in the art are able to understand that physicochemical properties discussed herein can be characterized. The experimental errors depend on the instrument conditions, the sampling processes and the purity of samples. In particular, those skilled in the art generally know that the X-ray diffraction pattern typically varies with the experimental conditions. It is necessary to point out that, the relative intensity of the diffraction peaks in the X-ray diffraction pattern may also vary with the experimental conditions; therefore, the order of the diffraction peak intensities cannot be regarded as the sole or decisive factor. In fact, the relative intensity of the diffraction peaks in the X-ray powder diffraction pattern is related to the preferred orientation of the crystals, and the diffraction peak intensities shown herein are illustrative and identical diffraction peak

intensities are not required. In addition, the experimental error of the diffraction peak position is usually 5% or less, and the error of these positions should also be taken into account. An error of ±0.2° is usually allowed. In addition, due to experimental factors such as sample thickness, the overall offset of the diffraction peak is caused, and a certain offset is usually allowed. Thus, it will be understood by those skilled in the art that a crystalline form of the present disclosure is not necessarily to have the exactly same X-ray diffraction pattern of the example shown herein. As used herein, "the same XRPD pattern" does not mean absolutely the same, the same peak positions may differ by ±0.2° and the peak intensity allows for some variability. Any crystalline forms whose X-ray diffraction patterns have the same or similar characteristic peaks should be within the scope of the present disclosure. Those skilled in the art can compare the patterns shown in the present disclosure with that of an unknown crystalline form in order to identify whether these two groups of patterns reflect the same or different crystalline forms.

In some embodiments, Form CS2 of the present disclosure is pure and substantially free of any other crystalline forms. In the present disclosure, the term "substantially free" when used to describe a novel crystalline form, it means that the content of other crystalline forms in the novel crystalline form is less than 20% (w/w), specifically less than 10% (w/w), more specifically less than 5% (w/w) and further more specifically less than 1% (w/w).

It should be noted that the number and the number range should not be understood as the number or number range themselves only. It should be understood by those skilled in the art that the specific number can be shifted at specific technical environment without departing from the spirit and principle of the present disclosure. In the present disclosure, the number of shift ranges expected by one of skilled in the art is represented by the term "about".

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows an XRPD pattern of Form CS2 in Example 1.

Figure 2 shows a DSC curve of Form CS2 in Example 1.

Figure 3 shows a TGA curve of Form CS2 in Example 1.

Figure 4 shows a ^{1}H NMR spectrum of Form CS2 in Example 1.

Figure 5 shows an XRPD pattern of Form CS2 in Example 2.

Figure 6 shows a DSC curve of Form CS2 in Example 2.

Figure 7 shows a TGA curve of Form CS2 in Example 2.

Figure 8 shows a ^{1}H NMR spectrum of Form CS2 in Example 2.

Figure 9 shows an XRPD pattern overlay of Form CS2 before and after stored at 25 ℃/60% RH (top: before storage, bottom: after storage).

Figure 10 shows an XRPD pattern overlay of Form CS2 before and after stored at 40 ℃/75% RH (top: before storage, bottom: after storage).

Figure 11 shows an XRPD pattern overlay of Form CS2 before and after stored at 60 ℃/75% RH (top: before storage, bottom: after storage).

Figure 12 shows an XRPD curve of Form CS2 before and after grinding (top: XRPD pattern before grinding; bottom: XRPD pattern after grinding).

Figure 13 shows a DSC curve of Form CS2.

Figure 14 shows an XRPD pattern overlay of Form CS2 before and after DVS test (top: XRPD pattern before DVS; bottom: XRPD pattern after DVS).

Figure 15 shows an in vitro dissolution profile of Form CS2.

DETAILED DESCRIPTION

The present disclosure is further illustrated by the following examples which describe the preparation and use of the crystalline form of the present disclosure in detail. It is obvious to those skilled in the art that many changes in the materials and methods can be accomplished without departing from the scope of the present disclosure.

The abbreviations used in the present disclosure are explained as follows:

XRPD: X-ray Powder Diffraction

DSC: Differential Scanning Calorimetry

TGA: Thermo Gravimetric Analysis

DVS: Dynamic Vapor Sorption

^{1}H NMR: Proton Nuclear Magnetic Resonance

Instruments and methods used for data collection:

X-ray powder diffraction patterns in the present disclosure were acquired by a Bruker D2 PHASER X-ray powder diffractometer. The parameters of the X-ray powder diffraction method of the present disclosure were as follows:

X-ray Reflection: Cu, Kα

Kα1 (Å): 1.54060; Kα2 (Å): 1.54439

Kα2/Kα1 intensity ratio: 0.50

Voltage: 30 (kV)

Current: 10 (mA)

Scan range: from 3.0 degree to 40.0 degree

Differential scanning calorimetry (DSC) data in the present disclosure were acquired by a TA Q2000. The parameters of the DSC method of the present disclosure are as follows:

Heating rate: 10 ℃/min

Purge gas: nitrogen

Thermo gravimetric analysis (TGA) data in the present disclosure were acquired by a TA Q500. The parameters of the TGA method of the present disclosure were as follows:

Heating rate: 10 ℃/ min

Purge gas: nitrogen

Dynamic Vapor Sorption (DVS) is measured via a SMS (Surface Measurement Systems Ltd.) intrinsic DVS instrument. Typical Parameters for DVS test are as follows:

Temperature: 25 °C

Gas and flow rate: N_2, 200 mL/min

dm/dt: 0.002%/min

RH range: 0% RH to 95% RH

High Performance Liquid Chromatography (HPLC) data in the present disclosure were

collected from an Agilent 1260 with Diode Array Detector (DAD).

The HPLC method parameters in the present disclosure are as follows:

Column: ZORBAX Eclipse C18, 100×4.6mm, 5 μm

Mobile Phase: A: Acetonitrile: Water: Trifluoroacetic acid =50:950:1 (Volume ratio)

B: 0.1% Trifluoroacetic acid in acetonitrile

Gradient:

Time (min)	%B
0.0	0
0.5	0
30.0	90
35.0	90
35.1	0
40.0	0

Flow rate: 1.0 mL/min

Injection Volume: 2 μL

Detection wavelength: 220 nm

Column Temperature: 40 ℃

Diluent: Acetonitrile

Proton nuclear magnetic resonance spectrum data (^{1}H NMR) were collected from a Bruker Avance II DMX 400M HZ NMR spectrometer. 1-5 mg of sample was weighed, and dissolved in 0.5 mL of deuterated dimethyl sulfoxide to obtain a solution with a concentration of 2-10 mg/mL.

Unless otherwise specified, the following examples were conducted at room temperature. Said "room temperature" is not a specific value, and refers to 10-30 ℃.

According to the present disclosure, compound (I) used as a raw material is solid (crystalline or amorphous), semisolid, wax or oil. Preferably, said compound (I) used as a raw material is a solid.

Raw materials of E-2006 used in the following examples were prepared by known methods in the prior art, for example, the method disclosed in CN103153963B.

DETAILED DESCRIPTION

Example 1 Preparation of Form CS2:

Approximately 199.6 mg of compound (I) was weighted and dissolved in 3.0 mL of acetone, followed by filtration and slowly evaporation to obtain a solid at room temperature. The obtained solid was confirmed to be Form CS2. The XRPD pattern is substantially as depicted in Figure 1, and the XRPD data are listed in Table 1.

The DSC curve of Form CS2 in this example is substantially as depicted in Figure 2. When heated to 177 ℃, an endothermic peak appears, which corresponds to the melting endothermic peak of Form CS2.

The TGA curve of Form CS2 in this example shows about 0.6% weight loss when heated to 170 ℃, which is substantially as depicted in Figure 3.

The ^{1}H NMR spectrum of Form CS2 is substantially as depicted in Figure 4, and the corresponding data are: ^{1}H NMR (400 MHz, DMSO) δ11.22 (s, 1H), 8.33 (d, J = 3.0 Hz, 1H), 8.13 (s, 1H), 7.89 (dd, J = 9.1, 4.1 Hz, 1H), 7.64 (td, J = 8.7, 3.1 Hz, 1H), 7.48-7.35 (m, 3H), 7.11 (ddd, J = 11.5, 6.0, 3.0 Hz, 1H), 4.68 (d, J = 10.2 Hz, 1H), 4.29 (d, J = 10.3 Hz, 1H), 2.64 (dd, J = 15.7, 8.8 Hz, 1H), 2.36 (d, J = 21.5 Hz, 3H), 2.03 (s, 3H), 1.74-1.67 (m, 1H), 1.50 (dd, J = 8.0, 4.8 Hz, 1H)。

Table 1

2θ	d spacing	Intensity %
7.81	11.32	100.00
9.55	9.26	5.68
11.44	7.73	23.41
12.53	7.07	25.17
15.58	5.69	46.96
15.78	5.62	11.77
16.40	5.41	4.67
19.05	4.66	12.69
19.38	4.58	17.51
19.57	4.54	18.50
21.32	4.17	21.23
21.73	4.09	6.60
22.27	3.99	11.54
23.03	3.86	5.32

23.23	3.83	6.23
23.99	3.71	15.14
25.42	3.50	4.70
25.89	3.44	23.53
26.28	3.39	7.86
27.26	3.27	15.44
28.04	3.18	5.25
29.36	3.04	3.75
31.09	2.88	5.99
33.99	2.64	1.25

Example 2 Preparation of Form CS2 by anti-solvent addition method

Approximately 1026.0 mg of compound (I) was weighted and dissolved in 10.0 mL of methanol. The solution was filtered and stirred while adding about 10.0 mL of water as an anti-solvent. After stirred for about 4 hours, a large amount of solid precipitated out. The precipitation collected by suction filtration and dried under vacuum at 40 °C for about 18 hours to obtain solids. The obtained solid was confirmed to be Form CS2. The XRPD pattern is substantially as depicted in Figure 5, and the XRPD data are listed in Table 2.

The DSC curve of Form CS2 in this example is substantially as depicted in Figure 6. When heated to 176 ℃, an endothermic peak appears, which corresponds to the melting endothermic peak of Form CS2.

The TGA curve of Form CS2 in this example shows about 0.5% weight loss when heated to 170 ℃, which is substantially as depicted in Figure 7.

The ^{1}H NMR spectrum of Form CS2 is substantially as depicted in Figure 8, and the corresponding data are: ^{1}H NMR (400 MHz, DMSO) δ11.21 (s, 1H), 8.33 (d, J = 3.0 Hz, 1H), 8.13 (s, 1H), 7.89 (dd, J = 9.2, 4.2 Hz, 1H), 7.64 (td, J = 8.8, 3.1 Hz, 1H), 7.49-7.34 (m, 3H), 7.16-7.05 (m, 1H), 4.68 (d, J = 10.2 Hz, 1H), 4.29 (d, J = 10.3 Hz, 1H), 2.67-2.57 (m, 1H), 2.38 (s, 3H), 2.03 (s, 3H), 1.74-1.66 (m, 1H), 1.50 (dd, J = 8.0, 4.8 Hz, 1H)。

Table 2

2θ	d spacing	Intensity %
7.84	11.27	100.00
9.59	9.22	6.98

11.49	7.70	13.05
12.56	7.05	35.00
15.61	5.68	59.13
15.82	5.60	9.92
16.44	5.39	9.29
19.07	4.65	19.61
19.41	4.57	19.56
19.60	4.53	20.52
21.36	4.16	22.18
21.77	4.08	10.04
22.31	3.98	29.55
23.07	3.86	9.34
23.89	3.72	14.02
24.00	3.71	11.54
25.46	3.50	6.67
25.93	3.44	17.57
26.31	3.39	16.60
27.33	3.26	16.63
28.06	3.18	9.34
29.37	3.04	7.28
31.15	2.87	3.40
31.38	2.85	4.42
29.37	3.04	7.28
31.15	2.87	3.40

Example 3-5 Preparation of Form CS2 by ionic liquid induced evaporation

Approximately 31.5 mg of compound (I) was dissolved in 1.0 mL of acetonitrile and filtered. A small amount of ionic liquid as shown in Table 3 was added, and the solution was slowly evaporated at room temperature to obtain solid. The solid obtained in example 3-5 were labeled as samples 3-5 and confirmed to be Form CS2.

Table 3

Example	Ionic liquid	Sample
3	1-ethyl-3-methylimidazolium methyl sulfate	Sample 3

4	1-ethyl-3-methylimidazolium hexafluoroantimonate	Sample 4
5	1,3-dimethylimidazolium dimethyl phosphate	Sample 5

Example 6 Stability of Form CS2

Form CS2 of the present disclosure were weighed and stored under conditions of 25 ℃/60% RH, 40 ℃/75% RH, 60 ℃/75% RH and 80 ℃ in open dishes. Crystalline form and chemical impurity were checked by XRPD and HPLC, respectively. The results are shown in Table 4.

Table 4

Initial crystalline form	Initial purity	Storage condition	Storage time	Crystalline form after storage	Purity after storage
Form CS2 (top of Figure 9)	99.67%	25°C /60% RH	10 months	Form CS2 (bottom of Figure 9)	99.63%
Form CS2 (top of Figure 10)	99.67%	40°C /75% RH	10 months	Form CS2 (bottom of Figure 10)	99.67%
Form CS2 (top of Figure 11)	99.67%	60°C /75% RH	2 weeks	Form CS2 (bottom of Figure 11)	99.70%

The results show that Form CS2 keeps stable for at least 10 months at 25 ℃/60% RH and 40 ℃/75% RH. Form CS2 keeps stable for at least 2 weeks at 60 ℃/75% RH, the purity of Form CS2 remained substantially unchanged. It can be seen that Form CS2 has good physical and chemical stability.

Example 7 Grinding stability of Form CS2

Form CS2 was ground manually for 5 minutes in a mortar. The XRPD pattern of the solids before and after grinding are presented in Figure 12 (top: XRPD pattern before grinding; bottom: XRPD pattern after grinding). The results show that the crystalline form of Form CS2 does not change after grinding. Form CS2 has good grinding stability.

Example 8 Hygroscopicity of Form CS2

Dynamic vapor sorption (DVS) was applied to measure hygroscopicity of Form CS2 with about 10 mg of samples. The weight gains at each relative humidity were recorded in a cycle of 0-95%-0 RH. DVS is substantially as depicted in Figure 13, and the experimental results are shown in Table 5. The XRPD pattern overlay of Form CS2 before and after DVS test is presented in Figure 14 (top: XRPD pattern before DVS; bottom: XRPD pattern after DVS). The results show that the hygroscopicity of Form CS2 is low. The weight gain under 80% RH is 0.21%. Form CS2 is slightly hygroscopic. The crystalline form of Form CS2 does not change after DVS, which indicates that Form CS2 is physically stable at 0% - 95% RH.

Table 5

Relative Humidity / Weight Gain (%)	Weight gain under 80% Relative Humidity	Hygroscopicity
Form CS2	0.21%	Slightly hygroscopic

Description and definition of hygroscopicity (Chinese Pharmacopoeia 2015 edition appendix Drug hygroscopic test guidelines, test at 25 ℃±1 ℃, 80% RH.).

—deliquescent: Sufficient water is absorbed to form a liquid;

—very hygroscopic: Increase in mass is equal to or greater than 15 percent;

—hygroscopic: Increase in mass is less than 15 percent and equal to or greater than 2 percent;

—slightly hygroscopic: Increase in mass is less than 2 percent and equal to or greater than 0.2 percent.

—non hygroscopic or almost non hygroscopic: Increase in mass is less than 0.2%.

Example 9 Flowability comparison of Form CS2 and the prior art solid

Compressibility, also known as compressibility index is usually used to evaluate the flowability of powder and granular intermediates during the formulation process. A certain amount of powder was added into a measuring cylinder and bulk volume was recorded. Then the measuring cylinder was tapped to make the powder in the tightest state and the tapped volume was recorded. The bulk density (ρ_0), tapped density (ρ_f) were calculated, and compressibility index was calculated according to $c=(\rho_f-\rho_0)/\rho_f$. Compressibility index or Carr Index is an

important indicator for evaluating the flowability of powder.

Compressibility index test method is as follows: Compressibility index was calculated according to bulk density ρ_0 and tapped density ρ_f of Form CS2 and the amorphous solid of the prior art with $c=(\rho_f-\rho_0)/\rho_f *100\%$. Criteria of flowability is shown in Table 6.

Table 6

Compressibility index (%)	Flowability
≦10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	poor
32-37	Very poor
>38	Very, very poor

Amorphous solid was obtained by repeating the preparation method disclosed in CN103153963B. Flowability evaluation results of Form CS2 and the amorphous solid are presented in table 7, which indicate that the flowability of Form CS2 is remarkably superior to that of the amorphous solid in the prior art.

Table 7

Form	Bulk density (ρ_0, g/mL)	Tapped density (ρ_f, g/mL)	Compressibility index (%)	Flowability
Amorphous solid	0.196	0.274	28	Poor
Form CS2	0.263	0.351	25	Passable

Example 10 Adhesiveness of Form CS2

30 mg of Form CS2 was weighed and added into the dies of φ8mm round tooling, tableted at 10 KN and held for 30s. The amount of material sticking to the punch was weighed. The compression was repeated twice and the cumulative amount, maximum amount and average amount of material sticking to the punch during the compression process were recorded. Detailed experimental results are shown in Table 8.

Table 8

Crystalline Form	Maximum amount (mg)	Average amount (mg)	Cumulative amount (mg)

CS2	0.74	0.22	0.44

Example 11 Compressibility of CS2

80mg of Form CS2 was weighted and added into the dies of φ6mm round tooling, compressed at 10 KN. The round tablet was stored in a desiccator for 24 hours until complete elastic recovery. Hardness (H) was tested with a tablet hardness tester. Diameter (D) and thickness (L) were tested with caliper. Tensile strength of the powder was calculated with the following formula: $T=2H/\pi DL$. Under a certain force, the greater the tensile strength, the better the compressibility. The results are presented in Table 9.

Table 9

Form	Thickness(mm)	Diameter (mm)	Hardness(N)	Tensile strength (MPa)
CS2	2.40	6.06	8.4	0.37

Example 12 Residual solvents of Form CS2 and the prior art solid

Amorphous solid was obtained by repeating the preparation method disclosed in CN103153963B. Residual solvents of Form CS2 and the amorphous solid were tested. The results show that Form CS2 has no residual solvents, while the -heptane and ethyl acetate residue in the amorphous solid is 46596.16 ppm and 1260.01 pm, respectively. According to the guideline of the International Council for Harmonization (ICH) on residual solvents, both n-heptane and ethyl acetate belong to Class 3 solvents, and the residual solvent must not exceed 5000 ppm. It can be seen that the residue of n-heptane in the amorphous solid is much higher than the limits of ICH, and the amorphous not suitable for drug substance.

Example 13 CS2 drug product

1. Preparation of compound (I) tablets

Form CS2 and intragranular excipients in Table 10 were blended according to formulation and the blend was compressed with the target weight of 500 mg using a φ20 mm single punch manual press at 5±0.5 KN pressure. The above tablets were crushed, passed through a 20 mesh sieve, then blended uniformly with the extragranular excipients shown in Table 10, and the blend was compressed with a target weight of 120.0 mg using a φ7 mm single punch manual press at 5±0.5 KN pressure.

Table 10

Component	**Quantity**	**Mass**

		(mg/unit)	ratio (%)
E-2006 (Form CS2)		10.00	8.3
Intragranular excipients	Lactose monohydrate	88.88	74.1
	Hydroxypropyl cellulose	3.60	3.0
	Low substituted hydroxypropyl cellulose	10.80	9.0
	Magnesium stearate	0.36	0.3
Total		113.64	94.7
Extragranular excipients	Low substituted hydroxypropyl cellulose	6.00	5.0
	Magnesium stearate	0.36	0.3
Total		120.00	100.0

2. Stability of Form CS2 in drug product

The tablets prepared above were packed in 35 cc HDPE bottles (one tablet per bottle) with 1 g desiccant. The bottles were sealed with a sealer. The bottles were stored under conditions of 25 ℃/60% RH and 40 ℃/75% RH for 1 month. Crystalline form of Form CS2 tablet was tested and the results show that the crystalline form of Form CS2 does not change. In addition, single and total impurity of Form CS2 remained substantially unchanged in storage. The results presented in Table 11 and 12 indicate that Form CS2 keeps physically and chemically stable in drug product.

Table 11 Physical stability of Form CS2 in drug product

Sample	Condition	Time	API crystalline Form after storage
Tablet contains Form CS2	25 ℃/60% RH	1 month	Form CS2
	40 ℃/75% RH	1 month	Form CS2

Table 12 Chemical stability of Form CS2 in drug product

Condition	Time	Initial largest single	Largest single impurity	Initial total impurity	Total impurity after	Single impurity change	Total impurity change

		impurity (%)	after storage (%)	(%)	storage (%)	(%)	(%)
25 ℃/60% RH	1 month	0.08	0.09	0.17	0.21	0.01	0.04
40 ℃/75% RH	1 month	0.08	0.08	0.17	0.20	0	0.03

Example 14 In vitro dissolution and dissolution rate of Form CS2

In vitro dissolution test was performed on Form CS2 tablet obtained from example 12. Dissolution method according to Chinese Pharmacopoeia 2015<0931> was used. The conditions are as follows:

Medium: 0.1 mol/L aqueous solution of hydrochloric acid

Method: Paddle

Volume: 900 mL

Speed: 50 rpm

Temperature: 37 ℃

In vitro dissolution of Form CS2 are presented in Table 13 and Figure 15.

Table 13

Cumulative drug release (%) / Time (minute)	Form CS2
0	0.0
5	55.2
10	73.1
15	81.0
20	86.2
30	92.1
45	96.9
60	100.5

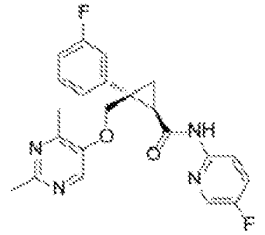
The results showed that Form CS2 drug product can undergo 100% dissolution in 0.1 mol/L aqueous hydrochloric acid, and the dissolution rate is high, which is favorable for achieving

good in vivo bioavailability.

The examples described above are only for illustrating the technical concepts and features of the present disclosure, and intended to make those skilled in the art being able to understand the present disclosure and thereby implement it, and should not be concluded to limit the protective scope of this disclosure. Any equivalent variations or modifications according to the spirit of the present disclosure should be covered by the protective scope of the present disclosure.

ABSTRACT

The present disclosure provides a novel crystalline form of Lemborexant and processes for preparation thereof. Pharmaceutical composition containing Lemborexant, and use of Lemborexant for preparing orexin receptor antagonist drug, and use of Lemborexant for preparing drugs treating insomnia and irregular sleep-wake rhythm disorder are also provided. The crystalline form of the present disclosure have one or more improved properties compared with crystalline forms of prior arts, and has significant values for future drug optimization and development.



Compound (I)

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Title

CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE THEREOF

Preliminary Class

514

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

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

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Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/777,121

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	75		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	330		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	380		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	8 minus 20 =	*	x 50 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*	x 230 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	785		TOTAL	

APPLICATION AS AMENDED - PART II

		(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".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

Doc Code: PD.REQ.RETR
Document Description: Request for USPTO to retrieve priority docs

PTO/SB/38 (09-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Request to Retrieve Electronic Priority Application(s)

Send completed form to: Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

COMPLETE IF KNOWN	
Application Number	16/777,121
Filing Date	January 30, 2020
First Named Inventor	Minhua Chen
Art Unit	1629
Examiner Name	Not yet assigned
Attorney Docket Number	134070-01602

Pursuant to 37 CFR 1.55(i), the undersigned hereby requests that the USPTO retrieve an electronic copy of each of the following foreign applications for which priority has been claimed under 35 U.S.C. 119(a)-(d) from a foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement. This Request must be submitted:

- within the later of sixteen months from the filing date of the prior foreign application or four months from the actual filing date of an application under 35 U.S.C. 111(a),
- within four months from the later of the date of commencement (37 CFR 1.491(a)) or the date of the initial submission under 35 U.S.C. 371 of an application entering the national stage under 35 U.S.C. 371, or
- with a petition under 37 CFR 1.55(e) or (f).

☐ **OPTION A**

Please retrieve the priority application identified in Column C, a certified copy of which is contained in the EP or JP application identified in Columns A and B:

	A	B			C	
	Code for Participating Office (EP or JP only)	Application containing the non-participating priority application			Non-participating priority application to be retrieved	
		App. No.	Filing Date	Access Code (for JP only)	Country Code	App. No.
1						

☒ **OPTION B**

This Request may be used for the infrequent circumstance when a claim for priority to an application filed in a participating foreign intellectual property office was made prior to that foreign intellectual property office becoming a participating foreign intellectual property office.

Please retrieve the priority application identified in Columns A and B:

	A	B		
	Code for Participating Office (e.g., EP, KR) or WIPO DAS Depositing Office (e.g., AU, BR, CN, DK, EA, EE, ES, FI, GB, IB, IN, JP, MA, NL, NZ, SE)	Application to be retrieved		
		App. No.	Filing Date	Access Code (for WIPO DAS Depositing Office)
1	CN	201710648135.2	08/01/2017	F26C
2				

The USPTO will not attempt to retrieve the identified priority application(s) unless an identical claim for foreign priority to the application identified above is made pursuant to 37 CFR 1.55(d) or a petition is granted under 37 CFR 1.55(e) or (f). Applicants are advised to consult Private PAIR (accessed through www.uspto.gov) to assure that the retrieval has been successful. The 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 set forth in 37 CFR 1.55(g)(1).

I hereby declare that I have the authority to grant access to the above-identified foreign application(s).

/Wei Song/	March 5, 2020
Signature	Date
Wei Song	(617) 449-6589
Printed or Typed Name	Telephone Number
Attorney for Applicant(s)	64,320
Title	Registration Number, if applicable

Electronic Acknowledgement Receipt	
EFS ID:	38786289
Application Number:	16777121
International Application Number:	
Confirmation Number:	1029
Title of Invention:	CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE THEREOF
First Named Inventor/Applicant Name:	Minhua Chen
Customer Number:	86738
Filer:	Wei Song
Filer Authorized By:	
Attorney Docket Number:	134070-01602
Receipt Date:	05-MAR-2020
Filing Date:	30-JAN-2020
Time Stamp:	22:14:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for USPTO to retrieve priority docs	32803021_1.pdf	23445 982049d8320c7890a2a53f0ba79156a340af41fe	no	1

Warnings:

Information:	
Total Files Size (in bytes):	23445

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

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

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 NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/777,121	01/30/2020	1629	785	134070-01602	8	1

CONFIRMATION NO. 1029

REPLACEMENT FILING RECEIPT

86738
MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

OC000000015259248

Date Mailed: 03/09/2020

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Minhua Chen, Suzhou, CHINA;
Yanfeng Zhang, Suzhou, CHINA;
Chunxiang Huang, Suzhou, CHINA;
Xiaoyu Zhang, Suzhou, CHINA;

Applicant(s)

Crystal Pharmaceutical (Suzhou) Co., Ltd., Suzhou, CHINA;

Power of Attorney: The patent practitioners associated with Customer Number 86738

Domestic Priority data as claimed by applicant

This application is a CON of PCT/CN2018/097797 07/31/2018

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 201710648135.2 08/01/2017 Access Code Provided

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

Request to Retrieve - This application either claims priority to one or more applications filed in an intellectual property Office that participates in the Priority Document Exchange (PDX) program or contains a proper **Request to Retrieve Electronic Priority Application(s)** (PTO/SB/38 or its equivalent). Consequently, the USPTO will attempt to electronically retrieve these priority documents.

If Required, Foreign Filing License Granted: 03/06/2020

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/777,121**

Projected Publication Date: 06/18/2020

Non-Publication Request: No

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

CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE THEREOF

Preliminary Class

514

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

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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Title 35, United States Code, Section 184

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community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

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Application number: 2017106481352

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国家知识产权局

NATIONAL INTELLECTUAL PROPERTY ADMINISTRATION, PRC

证　　明

本证明之附件是向本局提交的下列专利申请文件副本。

申　　请　　号：201710648135.2

申　请　类　型：发明专利

发明 创造 名称：一种食欲素受体拮抗剂的晶型及其制备方法和用途

申　　请　　日：2017 年 08 月 01 日

申　　请　　人：苏州科睿思制药有限公司

发明人或设计人：陈敏华、张炎锋、黄春香、张晓宇

局长

申长雨

2020 年 03 月 05 日

权 利 要 求 书

1. 一种 E-2006 的晶型 CS2，其特征在于，其 X 射线粉末衍射在衍射角 2θ 值为 7.8°±0.2°、15.6°±0.2°、11.4°±0.2°处有特征峰。

2. 根据权利要求 1 所述的晶型 CS2，其特征还在于，其 X 射线粉末衍射在衍射角 2θ 值为 12.5°±0.2°、21.3°±0.2°、27.3°±0.2°中的一处或多处有特征峰。

3. 根据权利要求 1 所述的晶型 CS2，其特征还在于，其 X 射线粉末衍射在衍射角 2θ 值为 24.0°±0.2°、19.4°±0.2°、22.3°±0.2°中的一处或多处有特征峰。

4. 一种 E-2006 的晶型 CS2 的制备方法，其特征在于，所述方法为：

(1) 将 E-2006 溶解在酮类、卤代烃类或酰胺类溶剂体系中，缓慢挥发得到；或

(2) 将 E-2006 溶解在腈类溶剂体系中，加入离子液体诱导，后缓慢挥发得到；或

(3) 将 E-2006 溶解在正溶剂体系中，配成含 E-2006 的溶液，后将反溶剂缓慢滴加到正溶剂溶液中或者将正溶剂溶液滴加到反溶剂体系中，搅拌析晶得到；或

(4) 将 E-2006 溶解在酮类溶剂、酮类与水的混合溶剂体系、酮类与正庚烷的混合溶剂体系、环醚类与水的混合溶剂体系或卤代烃类溶剂体系中，加热快速挥发得到。

5. 根据权利要求 4 所述的制备方法，方法(1)中所述酮类溶剂为丙酮，所述卤代烃类溶剂为氯仿，所述酰胺类溶剂为二甲基甲酰胺或二甲基乙酰胺；方法(2)中所述腈类溶剂为乙腈，所述离子液体为 1-乙基-3-甲基咪唑硫酸甲酯盐、1-乙基-3-甲基咪唑六氟锑酸盐或 1, 3-二甲基咪唑磷酸二甲酯盐；方法(3)中当反溶剂为正庚烷时，正溶剂为卤代烷烃类或芳香烃类溶剂，当反溶剂为水时，正溶剂为醇类或酰胺类溶剂；方法(4)中所述酮类溶剂为丁酮，所述酮类与水的混合溶剂为

权 利 要 求 书

丙酮与水的混合溶剂，所述酮类与正庚烷的混合溶剂为丙酮与正庚烷的混合溶剂，所述环醚类与水混合溶剂为四氢呋喃与水的混合溶剂，所述卤代烃类溶剂为二氯甲烷，所述加热温度为 40°C~100°C。

6. 根据权利要求 5 所述的制备方法，方法(3)中所述卤代烷烃类溶剂为二氯甲烷，所述芳香烃类溶剂为甲苯；所述醇类溶剂为甲醇，所述酰胺类溶剂为二甲基甲酰胺；方法(4)中所述丙酮与水、丙酮与正庚烷、四氢呋喃与水的体积比(v:v)均为 1:1，所述加热温度为 100°C。

7. 一种药物组合物，所述药物组合物包含有效治疗量的权利要求 1 中所述的晶型 CS2 及药学上可接受的载体、稀释剂或赋形剂。

8. 权利要求 1 中所述的晶型 CS2 在生产用于制备食欲素受体拮抗剂药物制剂中的用途。

9. 权利要求 1 中所述的晶型 CS2 在生产用于制备预防和治疗失眠和/或睡眠障碍和/或不规则睡眠-觉醒节律障碍的药物制剂中的用途。

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说 明 书

一种食欲素受体拮抗剂的晶型及其制备方法和用途

技术领域

本发明涉及药物晶体技术领域。具体而言，涉及一种食欲素受体拮抗剂的晶型及其制备方法和用途。

背景技术

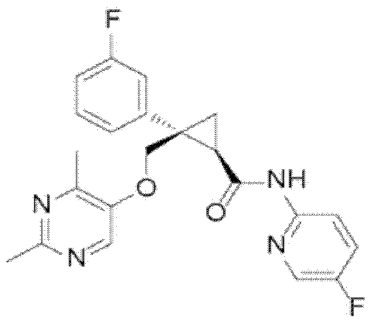
多晶型或者多晶现象是某些分子和分子组合物的特有性质，相同的分子可能因不同的排列形式而形成不同的晶型，而这些晶型具有不同的晶体结构和物理性质，如溶解度、稳定性、流动性、热性质、机械性质、纯化能力、X射线衍射图、红外吸收图谱、拉曼光谱和固态核磁等(参见*P. Di Martino etal, J. Thermal Anal., 48 :447-458 (1997)*)。一种或多种分析检测方式可用于区分同一分子或分子组合物的不同晶型。

固体化学药物晶型不同，可造成其溶解度、稳定性、流动性和压缩性等不同，从而影响含有该化合物的药物产品的安全性和有效性(参见*K. Knapman, Modern Drug Discovery, 3, 53-54, 57, 2000.*)，导致临床药效的差异。发现药物活性成分新的晶型（包括无水物、水合物、溶剂化物等）可能会产生更具加工优势或提供具有更好理化特性的物质，比如更好的生物利用度、储存稳定性、易加工处理、易提纯或作为促进转化为其它晶型的中间体晶型。药学上化合物的新晶型可以帮助改善药物的性能，扩大制剂学上可选用的原料型态。

E-2006 (Lemborexant)由卫材公司研发，临床用于治疗失眠症。失眠症是难以入睡和睡眠维持困难为特征的一种常见的睡眠障碍。研究表明，食欲素系统是睡眠-觉醒周期的关键调节剂，食欲素受体拮抗剂具有阻碍不适当的定时夜间觉醒、并促进正常的睡眠-觉醒周期的潜力。E-2006 是一种食欲素受体拮抗剂，

在临床试验中，E-2006 能显著改善失眠患者的睡眠效率，包括入睡更快，夜间醒来的时间更短。此外，E-2006 在治疗阿尔茨海默病患者的不规则睡眠-觉醒节律障碍（ISWRD）方面也显示巨大的潜力，不规则睡眠-觉醒节律障碍（ISWRD）不同于一般的失眠，该领域存在着未获满足的医疗需求。

E-2006 的化学名称为：(1R, 2S)-2-{[(2, 4-二甲基嘧啶-5-基)氧基]甲基}-2-(3-氟苯基)-N-(5-氟吡啶-2-基)环丙烷甲酰胺，其结构式如式(I)所示：



式(I)

专利CN103153963B公开了E-2006的制备方法，但未公开E-2006的晶型信息，目前尚无E-2006的晶型信息公开。因此，本领域需要系统全面的开发式(I)所示E-2006的晶型，从而实现其药物学上的发展并释放其潜能，并促进含该活性药物成分的更好配方的制备。

经研究，本发明人发现了E-2006的晶型CS2。本发明E-2006的晶型CS2具有良好的稳定性和低的引湿性。此外，其在溶解度、熔点、溶出度、生物有效性以及加工性能、提纯作用等方面中的至少一方面上存在优势，为含E-2006的晶型CS2的药物制剂的制备提供了新的更好的选择，对于药物开发具有非常重要的意义。

发明内容

针对现有技术的空白，本发明的主要目的是提供 E-2006 的晶型及其制备

方法和用途。

根据本发明的目的，本发明提供式(I)所示化合物的晶型 CS2（以下称作“晶型 CS2”）。

使用 Cu-Kα 辐射，所述晶型 CS2 的 X 射线粉末衍射在衍射角 2θ 值为 7.8°±0.2°、15.6°±0.2°、11.4°±0.2°处有特征峰。

进一步的，所述晶型 CS2 的 X 射线粉末衍射在衍射角 2θ 值为 12.5°±0.2°、21.3°±0.2°、27.3°±0.2°中的一处或多处有特征峰。优选的，所述晶型 CS2 的 X 射线粉末衍射在衍射角 2θ 值为 12.5°±0.2°、21.3°±0.2°、27.3°±0.2°处均有特征峰。

进一步的，所述晶型 CS2 的 X 射线粉末衍射在衍射角 2θ 值为 24.0°±0.2°、19.4°±0.2°、22.3°±0.2°中的一处或多处有特征峰。优选的，所述晶型 CS2 的 X 射线粉末衍射在衍射角 2θ 值为 24.0°±0.2°、19.4°±0.2°、22.3°±0.2°处均有特征峰。

在一个优选的实施方案中，所述晶型 CS2 的 X 射线粉末衍射在衍射角 2θ 值为 7.8°±0.2°、15.6°±0.2°、11.4°±0.2°、12.5°±0.2°、21.3°±0.2°、27.3°±0.2°、24.0°±0.2°、19.4°±0.2°、22.3°±0.2°处有特征峰。

非限制性地，在本发明的一个具体实施方案中，晶型 CS2 的 X 射线粉末衍射谱图如附图 1 所示。

根据本发明的目的，本发明还提供晶型 CS2 的制备方法，其特征在于，所述方法包括：

(1) 将 E-2006 溶解在酮类、卤代烃类或酰胺类溶剂体系中，缓慢挥发得到；或

(2) 将E-2006溶解在腈类溶剂体系中，加入离子液体诱导，后缓慢挥发得到；或

(3) 将E-2006溶解在正溶剂体系中，配成含E-2006的溶液，后将反溶剂缓慢滴加到正溶剂溶液中或者将正溶剂溶液滴加到反溶剂体系中，搅拌析晶得到；或

(4) 将E-2006溶解在酮类溶剂、酮类与水的混合溶剂体系、酮类与正庚烷的混合溶剂体系、环醚类与水的混合溶剂体系或卤代烃类溶剂体系中，加热快速挥发得到。

进一步的，方法(1)中所述酮类溶剂包含丙酮，所述卤代烃类溶剂包含氯仿，所述酰胺类溶剂包含二甲基甲酰胺和二甲基乙酰胺。

进一步的，方法(2)中所述腈类溶剂包含乙腈，所述离子液体包含1-乙基-3-甲基咪唑硫酸甲酯盐、1-乙基-3-甲基咪唑六氟锑酸盐和1,3-二甲基咪唑磷酸二甲酯盐。

进一步的，方法(3)中当反溶剂为正庚烷时，正溶剂为卤代烷烃类或芳香烃类溶剂；当反溶剂为水时，正溶剂为醇类或酰胺类溶剂；

更进一步的，方法(3)中所述卤代烷烃类溶剂包含二氯甲烷，所述芳香烃类溶剂包含甲苯；所述醇类溶剂包含甲醇，所述酰胺类溶剂包含二甲基甲酰胺。

进一步的，方法(4)中所述酮类溶剂包含丁酮，所述酮类与水的混合溶剂包含丙酮与水的混合溶剂，所述酮类与正庚烷的混合溶剂包含丙酮与正庚烷的混合溶剂，所述环醚类与水混合溶剂包含四氢呋喃与水的混合溶剂，所述卤代烃类溶剂包含二氯甲烷，所述加热温度为40°C~100°C；

更进一步的，方法(4)中所述丙酮与水、丙酮与正庚烷、四氢呋喃与水的体积比(v:v)均为1:1，所述加热温度为100°C。

说 明 书

药物稳定性至关重要的，尤其在市售有效期内保持较好的稳定性，能够避免药物由于晶型变化而导致药物溶出速率及生物利度改变，对保证药物疗效和安全性具有重要意义。并且，更稳定的晶型在结晶工艺过程中更加可控，不容易出现混晶；在制剂工艺及储存过程中，不容易转变成其它晶型，从而保证样品的质量一致可控，并确保制剂产品的溶出曲线不会随着储存的时间变化而发生改变。本发明通过提供 E-2006 的晶型 CS2 具有良好的稳定性，在 25°C/60%相对湿度和 40°C/75%相对湿度条件下放置 1 个月，在 60°C /75%相对湿度下放置 2 周后晶型保持不变。

引湿性是药物晶型的关键性质之一，引湿性高的药物晶型因吸附较多水分导致重量发生变化，使原料晶型组份含量不易确定。此外，原料药晶型因引湿性高而吸水结块，从而影响制剂工艺中样品的粒径分布和原料药在制剂中的均一度，进而影响样品的溶出及生物利用度。引湿性高的原料药对包装和贮存条件要求苛刻，导致药品的生产成本增加。因此，制备低引湿性的药物晶型对药物生产至关重要。本发明提供的晶型 CS2 具有较低的引湿性，在 80%相对湿度下平衡后，相较于起始相对湿度，增重约 0.10%，属于几乎无引湿性，解决上述药物晶型高引湿性带来的问题。

此外，晶型 CS2 还具有选自以下至少一项的有利性质：溶解度高，制备简单且所用溶剂毒性低，结晶度好，好的颗粒形态、更好的流动性、更好的表观密度。

在本发明的晶型 CS2 的制备方法中：

所述“挥发”，采用本领域的常规方法完成，例如缓慢挥发是将容器封上封口膜，扎孔，静置挥发；快速挥发是将容器敞口放置挥发。

根据本发明，作为原料的所述 E-2006 指其固体（晶型或无定形）、半固体、

蜡或油形式。优选地，作为原料的所述式（I）化合物为固体粉末形式。

本发明中，“晶体”或“多晶型”指的是被所示的X射线衍射图表征所证实的。本领域技术人员能够理解，这里所讨论的理化性质可以被表征，其中的实验误差取决于仪器的条件、样品的准备和样品的纯度。特别是，本领域技术人员公知，X射线衍射图通常会随着仪器的条件而有所改变。特别需要指出的是，X射线衍射图的相对强度也可能随着实验条件的变化而变化，所以峰强度的顺序不能作为唯一或决定性因素。事实上，XRPD图谱中衍射峰的相对强度与晶体的择优取向有关，本文所示的峰强度为说明性而非用于绝对比较。另外，峰角度的实验误差通常在5%或更少，这些角度的误差也应该被考虑进去，通常允许有±0.2°的误差。另外，由于样品高度等实验因素的影响，会造成峰角度的整体偏移，通常允许一定的偏移。因而，本领域技术人员可以理解的是，本发明中一个晶型的X射线衍射图不必和这里所指的例子中的X射线衍射图完全一致，本文所述“XRPD图相同”并非指绝对相同，相同峰位置可相差±0.2°且峰强度允许一定可变性。任何具有和这些图谱中的特征峰相同或相似的图的晶型均属于本发明的范畴之内。本领域技术人员能够将本发明所列的图谱和一个未知晶型的图谱相比较，以证实这两组图谱反映的是相同还是不同的晶型。

“晶型”和“多晶型”以及其他相关词汇在本发明中指的是固体化合物在晶体结构中以特定的晶型状态存在。多晶型理化性质的不同可以体现在储存稳定性、可压缩性、密度、溶出速度等方面。在极端的情况下，溶解度或溶出速度的不同可以造成药物低效，甚至毒性。

需要说明的是，本发明中提及的数值及数值范围不应被狭隘地理解为数值或数值范围本身，本领域技术人员应当理解其可以根据具体技术环境的不同，

在不背离本发明精神和原则的基础上围绕具体数值有所浮动，本发明中，这种本领域技术人员可预见的浮动范围多以术语“约”来表示。

此外，本发明提供一种药物组合物，所述药物组合物包含治疗和/或预防有效量的本发明的晶型CS2，以及至少一种药学上可接受的载体、稀释剂或赋形剂。

进一步地，本发明提的晶型 CS2 在制备食欲素受体拮抗剂药物制剂中的用途。

更进一步地，本发明提供的晶型 CS2 在制备用于预防和治疗失眠和/或睡眠障碍和/或不规则睡眠-觉醒节律障碍的药物制剂中的用途。

附图说明

图 1 为根据本发明实施例 1 所得晶型 CS2 的 XRPD 图。

图 2 为根据本发明实施例 1 所得晶型 CS2 的 DSC 图。

图 3 为根据本发明实施例 1 所得晶型 CS2 的 TGA 图。

图 4 为根据本发明实施例 1 所得晶型 CS2 的 ^{1}H NMR 谱图。

图 5 为根据本发明实施例 7 所得晶型 CS2 的 XRPD 图。

图 6 为根据本发明实施例 8 所得晶型 CS2 的 XRPD 图。

图 7 为根据本发明实施例 17 所得晶型 CS2 的 XRPD 图。

图 8 为本发明晶型 CS2 的 DVS 图。

图 9 为 DVS 前后晶型 CS2 的 XRPD 图（上图为 DVS 前的 XRPD 图，下图为 DVS 后的 XRPD 图）。

图 10 为晶型 CS2 在 25°C/60%相对湿度条件下放置 1 个月前后的 XRPD 对比图（下图为放置前的 XRPD 图，上图为放置后的 XRPD 图）。

图 11 为晶型 CS2 在 40°C/75%相对湿度条件下放置 1 个月前后的 XRPD 对比图（下图为放置前的 XRPD 图，上图为放置后的 XRPD 图）。

图 12 为晶型 CS2 在 60°C/75%相对湿度条件下放置 2 周前后的 XRPD 对比图（下图为放置前的 XRPD 图，上图为放置后的 XRPD 图）。

具体实施方式

本发明进一步参考以下实施例限定，所述实施例详细描述本发明的晶型的制备和使用方法。对本领域技术人员显而易见的是，对于材料和方法两者的许多改变可在不脱离本发明范围的情况下实施。

采集数据所用的仪器及方法：

本发明所述的 X 射线粉末衍射图在 Bruker D2 PHASER X 射线粉末衍射仪上采集。本发明所述的 X 射线粉末衍射的方法参数如下：

X 射线反射参数：Cu, Kα

Kα1 (Å)：1.54060；Kα2 (Å)：1.54439

Kα2/Kα1 强度比例：0.50

电压：30 仟伏特（kV)

电流：10 毫安培（mA)

扫描范围：自 3.0 至 40.0 度

本发明所述的差示扫描量热分析（DSC）图在 TA Q2000 上采集。本发明所述的差示扫描量热分析（DSC）的方法参数如下：

扫描速率：如无特别说明为 10℃/min

保护气体：N_2

本发明所述的热重分析（TGA）图在 TA Q500 上采集。本发明所述的热重分析（TGA）的方法参数如下：

扫描速率：10℃/min

保护气体：N_2

本发明所述动态水分吸附（DVS）图在由 SMS 公司（Surface Measurement Systems Ltd.）生产的 Intrinsic 动态水分吸附仪上采集。所述的动态水分吸附仪的方法参数如下：

温度：25 °C

载气，流速：N_2, 200 毫升/分钟

单位时间质量变化：0.002%/分钟

相对湿度范围：0%RH-95%RH

缩写解释：

XRPD：X 射线粉末衍射

DSC：差示扫描量热分析

TGA：热重分析

DVS：动态水分吸附

^{1}H NMR：核磁共振氢谱

除非特殊说明，以下实施例均在室温条件下操作。

以下实施例中所使用到的 E-2006 是根据现有技术制备得到，例如根据 CN103153963B 中公开的制备方法得到。

实施例 1~2：缓慢挥发法制备晶型 CS2

称取一定质量的 E-2006 原料，溶解于如表 1 所示的一定体积的溶剂中，过滤后在室温下缓慢挥发得到固体。实施例 1~4 所得的固体分别标记为样品 1~4，经检测样品 1~4 均为晶型 CS2。选取样品 1 进行测试表征，其 X 射线粉末衍射数据如图 1，表 2 所示。

实施例 1 所得晶型 CS2 的 DSC 如附图 2 所示，加热至 177℃附近开始出现一个吸热峰，该吸热峰为 CS2 的熔化吸热峰。

实施例 1 所得晶型 CS2 的 TGA 如附图 3 所示，加热至 170℃附近时具有约 0.6%的质量损失。

实施例 1 所得晶型 CS2 的核磁共振氢谱如图 4 所示，数据为：^{1}H NMR (400 MHz, DMSO) δ 11.22 (s, 1H), 8.33 (d, J = 3.0 Hz, 1H), 8.13 (s, 1H), 7.89 (dd, J = 9.1, 4.1 Hz, 1H), 7.64 (td, J = 8.7, 3.1 Hz, 1H), 7.48-7.35 (m, 3H), 7.11 (ddd, J = 11.5, 6.0, 3.0 Hz, 1H), 4.68 (d, J = 10.2 Hz, 1H), 4.29 (d, J = 10.3 Hz, 1H), 2.64 (dd, J = 15.7, 8.8 Hz, 1H), 2.36 (d, J = 21.5 Hz, 3H), 2.03 (s, 3H), 1.74-1.67 (m, 1H), 1.50 (dd, J = 8.0, 4.8 Hz, 1H)。

表 1

实施例	原料质量(mg)	溶剂	溶剂体积(mL)	样品标记
1	199.6	丙酮	3.0	样品 1
2	29.7	氯仿	1.0	样品 2
3	29.8	二甲基甲酰胺	1.0	样品 3
4	30.5	二甲基乙酰胺	1.0	样品 4

表 2

衍射角 2θ	d 值	强度%
7.81	11.32	100.00
9.55	9.26	5.68
11.44	7.73	23.41
12.53	7.07	25.17
15.58	5.69	46.96
15.78	5.62	11.77
16.40	5.41	4.67
19.05	4.66	12.69
19.38	4.58	17.51
19.57	4.54	18.50
21.32	4.17	21.23

21.73	4.09	6.60
22.27	3.99	11.54
23.03	3.86	5.32
23.23	3.83	6.23
23.99	3.71	15.14
25.42	3.50	4.70
25.89	3.44	23.53
26.28	3.39	7.86
27.26	3.27	15.44
28.04	3.18	5.25
29.36	3.04	3.75
31.09	2.88	5.99
33.99	2.64	1.25

实施例 5~7：离子液体诱导挥发法制备晶型 CS2

称取约 31.5 mg 的 E-2006 原料，加入 1.0 mL 的乙腈溶剂溶解过滤，加入少量如表 3 中所示的离子液体，于室温下缓慢挥发得到固体。实施例 5~7 所得固体分别标记为样品 5~7，经检测，样品 5~7 均为晶型 CS2。选取样品 7 进行测试表征，其 X 射线粉末衍射数据如图 5，表 4 所示。

表 3

实施例	离子液体	样品标记
5	1-乙基-3-甲基咪唑硫酸甲酯盐	样品 5
6	1-乙基-3-甲基咪唑六氟锑酸盐	样品 6
7	1,3-二甲基咪唑磷酸二甲酯盐	样品 7

表 4

衍射角 2θ	d 值	强度%
7.80	11.34	100.00
9.56	9.25	5.51
11.48	7.71	7.42
12.53	7.07	4.38
12.68	6.98	3.66

15.66	5.66	27.20
16.41	5.40	4.61
19.13	4.64	6.25
19.38	4.58	19.17
19.60	4.53	7.08
21.33	4.17	16.08
22.31	3.99	5.95
22.48	3.96	5.95
23.17	3.84	3.53
23.97	3.71	11.16
25.97	3.43	7.64
26.34	3.38	3.46
27.30	3.27	6.10
29.37	3.04	3.89
31.12	2.87	2.49
34.04	2.63	1.07

实施例 8~11：反溶剂添加或反向反溶剂添加法制备晶型 CS2

称取一定质量的 E-2006 原料，溶解于如表 5 和表 6 中所示的一定体积的正溶剂中，过滤后得到含 E-2006 的正溶剂溶液。向正溶剂溶液中滴加反溶剂（反溶剂添加法）或者将正溶剂溶液滴加至反溶剂中（反向反溶剂添加法），后继续搅拌至有大量固体析出，离心收集并干燥得到固体。实施例 8~15 所得的固体分别标记为样品 8~15，经检测，样品 8~15 均为晶型 CS2。选取样品 8 进行测试表征，其 X 射线粉末衍射数据如图 6，表 7 所示。

表 5：反溶剂添加法制备晶型 CS2

实施例	原料质量(mg)	正溶剂	正溶剂积(mL)	反溶剂	反溶剂体积(mL)	样品标记
8	20.2	二氯甲烷	0.5	正庚烷	1.0	8
9	19.6	甲苯	1.0	正庚烷	2.0	9
10	20.5	甲醇	0.5	水	0.2	10
11	20.5	二甲基甲酰胺	0.5	水	0.3	11

表 6：反向反溶剂添加法制备晶型 CS2

实施例	原料质量(mg)	正溶剂	正溶剂积(mL)	反溶剂	反溶剂体积(mL)	样品标记*
12	20.2	二氯甲烷	0.5	正庚烷	2.0	12
13	19.6	甲苯	1.0	正庚烷	2.0	13
14	20.5	甲醇	0.5	水	2.0	14
15	20.5	二甲基甲酰胺	0.5	水	2.0	15

表 7

衍射角 2θ	d 值	强度%
7.81	11.32	63.88
9.55	9.26	10.90
11.45	7.73	12.09
12.53	7.06	18.46
15.57	5.69	100.00
15.78	5.61	13.33
16.39	5.41	12.10
19.03	4.66	26.50
19.38	4.58	27.60
19.56	4.54	10.34
21.33	4.17	13.37
21.73	4.09	9.02
22.27	3.99	28.94
23.02	3.86	14.73
23.84	3.73	12.42
25.40	3.51	4.20
25.89	3.44	8.56
26.27	3.39	16.25
26.58	3.35	4.78
27.34	3.26	17.28
28.03	3.18	7.02
29.33	3.04	6.82
31.25	2.86	2.28
33.96	2.64	2.27

实施例 16~20：快速挥发法制备晶型 CS2

称取一定质量的 E-2006 原料，溶解于如表 8 中所示的一定体积的溶剂中，过滤后于 100℃下敞口快速挥发得到固体。实施例 16~20 所得固体分别标记为样品 16~20，经检测，样品 16~20 均为晶型 CS2。选取样品 17 进行测试表征，其 X 射线粉末衍射数据如图 7，表 9 所示。

表 8

实施例	原料 质量(mg)	溶剂	溶剂 体积(mL)	样品标记
16	10.4	二氯甲烷	0.3	16
17	11.4	丁酮	0.3	17
18	9.9	正庚烷/丙酮 v:v=1:1	0.3	18
19	11.4	水/丙酮 v:v=1:1	0.4	19
20	10.8	四氢呋喃/水 v:v=1:1	0.4	20

表 9

衍射角 2θ	d 值	强度%
7.81	11.32	100.00
9.54	9.27	10.27
11.44	7.73	19.94
12.53	7.07	37.37
13.44	6.59	2.60
15.56	5.69	29.09
15.78	5.62	15.16
16.39	5.41	4.93
19.02	4.67	15.13
19.37	4.58	28.72
19.57	4.54	24.95
21.36	4.16	48.39
21.72	4.09	4.45
22.28	3.99	13.25
23.00	3.87	6.53
23.99	3.71	12.06
25.42	3.50	6.08

25.90	3.44	20.50
26.27	3.39	8.51
27.30	3.27	19.40
28.05	3.18	4.50
29.37	3.04	5.26
31.18	2.87	2.42
33.99	2.64	2.39

实施例 21：引湿性研究

引湿性是药物晶型的关键性质之一，引湿性高的药物晶型因吸附较多水分导致重量发生变化，使原料晶型组份含量不易确定。此外，原料药晶型因引湿性高而吸水结块，从而影响制剂工艺中样品的粒径分布和原料药在制剂中的均一度，进而影响样品的溶出及生物利用度。引湿性高的原料药对包装和贮存条件要求苛刻，导致药品的生产成本增加。因此，制备低引湿性的药物晶型对药物生产至关重要。

基于引湿性的重要性，发明人在25℃条件下，取本发明的晶型CS2约15 mg进行动态水分吸附（DVS）测试其引湿性。结果表明：

晶型CS2在80%相对湿度下平衡后，相较于起始相对湿度，增重约0.10%，属于几乎无引湿性，解决上述药物晶型高引湿性带来的问题，方便长期贮存放置，大大降低物料储存以及质量控制成本，具有很强的经济价值。晶型 CS2 的 DVS 图如图 8 所示。此外，DVS 实验前后分别检测晶型 CS2 的 XRPD 图，结果如图 9（上图为 DVS 前的 XRPD 图，下图为 DVS 后的 XRPD 图）所示，表明 DVS 前后晶型 CS2 没有发生变化。

关于引湿性特征描述与引湿性增重的界定（中国药典 2015 年版通则 9103 药物引湿性试验指导原则，实验条件：25℃±1℃，80%相对湿度）：

潮解：吸收足量水分形成液体

极具引湿性：引湿增重不小于 15%

有引湿性：引湿增重小于 15%但不小于 2%

略有引湿性：引湿增重小于 2%但不小于 0.2%

无或几乎无引湿性：引湿增重小于 0.2%

实施例 22：稳定性研究

将本发明制备得到的晶型 CS2 分别置于 25℃/60%相对湿度、40℃/75%相对湿度条件下敞口放置 1 个月，置于 60°C /75%相对湿度下放置 2 周，结果如表 10 所示。

表 10

起始晶型	起始纯度	放置条件	放置时间	放置后晶型	放置后纯度	纯度变化量
晶型 CS2 (图 10 下图)	99.85%	25°C/60% 相对湿度	1 个月	晶型 CS2 (图 10 上图)	99.69%	0.16%
晶型 CS2 (图 11 下图)	99.85%	40°C/75% 相对湿度	1 个月	晶型 CS2 (图 11 上图)	99.67%	0.18%
晶型 CS2 (图 12 下图)	99.85%	60°C/75% 相对湿度	2 周	晶型 CS2 (图 12 上图)	99.70%	0.15%

本领域技术人员均知药物化学稳定性与其纯度及杂质有直接关系。药物晶型的纯度对于保证药物的疗效和安全性，防止药物不良反应的发生具有重要意义。同时，晶型纯度越高，相对来说收率越稳定，易于工业化生产。并且，药物晶型中含有的杂质是影响纯度的主要因素，如含有超过限量的杂质，就有可能使理化常数变动，外观性状产生变异，影响药物的化学稳定性；杂质增多也使药物含量明显偏低或活性降低，毒副作用显著增加。

结果表明，晶型 CS2 敞口裸露在 25℃/60%相对湿度、40℃/75%相对湿度、60°C/75%相对湿度的条件下，放置后晶型保持不变且纯度几乎不变，说明 CS2 具有非常好的稳定性，能够避免药物由于晶型变化而导致药物溶出速率及生物

利度改变，对保证药物疗效和安全性具有重要意义。

实施例 23：纯度测试

采用 HPLC 测定本发明的晶型 CS2 的纯度，纯度测试结果为 99.85%，表明，本申请的晶型 CS2 具有较好的纯度，适合药用。

实施例 24：动态溶解度研究

具体为：

参照《中国药典》附录中溶解度测定法；结合生物体内不同器官部位的 pH 值变化。根据上述两种参考依据，本发明设置了 1.2~7.5 等 4 个 pH 值的溶媒系统。具体为：pH 为 1.8 的 SGF(模拟胃液)，pH 为 5.0 的 FeSSIF(模拟进食状态下人工肠液)，pH 为 6.5 的 FaSSIF(模拟空腹状态下人工肠液)以及水。

精密称取 5 mg 的本发明的晶型 CS2，分别置于小瓶中，分别用 pH 为 1.8 的 SGF(模拟胃液)，pH 为 5.0 的 FeSSIF(模拟进食状态下人工肠液)，pH 为 6.5 的 FaSSIF(模拟空腹状态下人工肠液)以及水进行混合。在旋转器上以 25 转/分钟的速率旋转，并分别于 1 小时、4 小时和 24 小时取样，在使用 0.45μm 聚四氟乙烯（PTFE）过滤器离心分离后，收集滤液进行 HPLC 分析。

实施例 25：提纯效果

取一定量的 E-2006 粗品，采用本发明所述晶型 CS2 的结晶方法对此粗品进行纯化。结果表明，本申请的晶型 CS2 具有较好的提纯效果，具有良好的产业化价值。

实施例 26：形态测试

对本发明的晶型 CS2 进行偏光显微镜拍摄，偏光显微镜的拍摄图表明，本发明晶型 CS2 的形貌适合药物制剂的开发。

实施例 27：粒径分布测试

取 10-30mg 本发明的晶型 CS2，加入 10mL Isopar G(含有 0.2%卵磷脂)，将待测样品充分混合均匀后加入 SDC 进样系统中，使样品量指示图达到合适位置，开始实验，进行粒径分布的测试，从而得到按照体积计算的平均粒径、粒径分布中（体积分布）占 10% 所对应的粒径、粒径分布中（体积分布）占 50%所对应的粒径。粒径分布中（体积分布）占 90% 所对应的粒径以及晶型粒度分布图。

实验结果可以看出，本发明获得的晶型 CS2 有着较窄的粒径分布。

实施例 28：流动性评估测试

按照 USP<1174>通过可压性系数对本发明的晶型 CS2 进行评估，测定它们的堆密度和振实密度后，根据下面的公式计算可压性系数。

可压性系数(%)=(振实密度–堆密度)/振实密度×100%

可压性指数（%）	流动性
≦10	极好
11-15	好
16-20	一般
21-25	可接受
26-31	差
32-37	很差
>38	极差

结果表明，本发明晶型 CS2 的流动性较好。

上述实施例只为说明本发明的技术构思及特点，其目的在于让熟悉此项技术的人士能够了解本发明的内容并据以实施，并不能以此限制本发明的保护范围。凡根据本发明精神实质所作的等效变化或修饰，都应涵盖在本发明的保护范围之内。

说 明 书 附 图

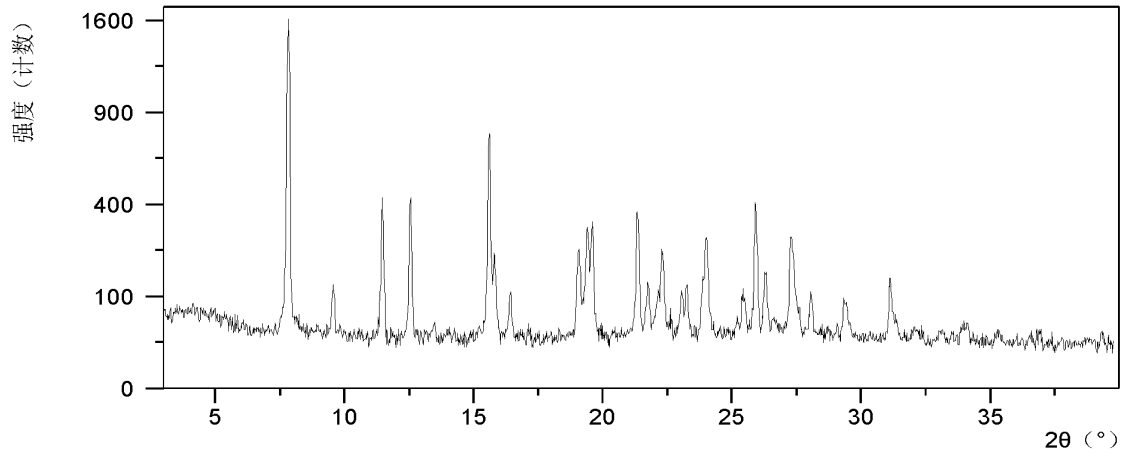

强度（计数）
1600
900
400
100
0
5
10
15
20
25
30
35
2θ（°）

图 1

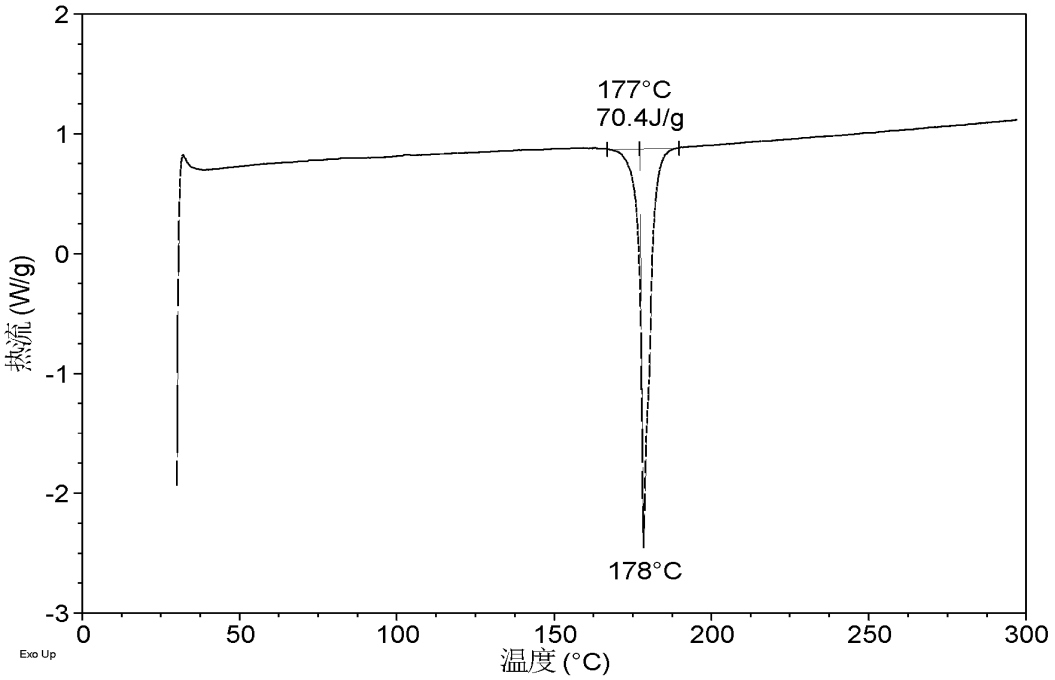

177°C
70.4J/g
178°C
热流 (W/g)
Exo Up
温度 (°C)
2
1
0
-1
-2
-3
0
50
100
150
200
250
300

图 2

说 明 书 附 图

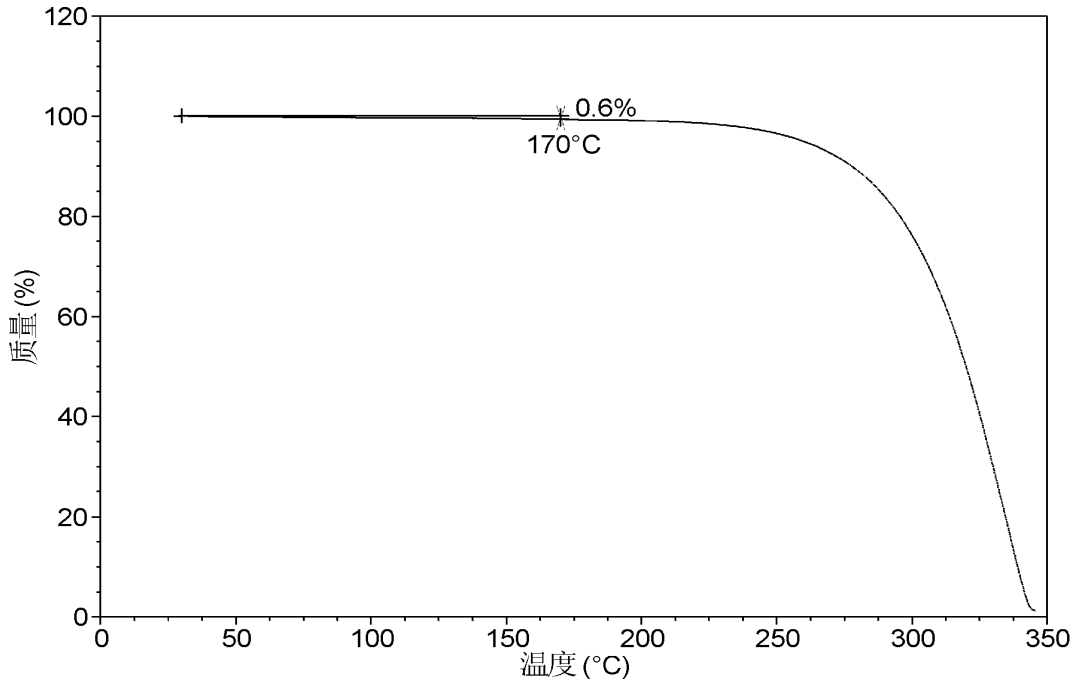

120
100
80
60
40
20
0
质量(%)
0.6%
170°C
0
50
100
150
200
250
300
350
温度(°C)

图 3

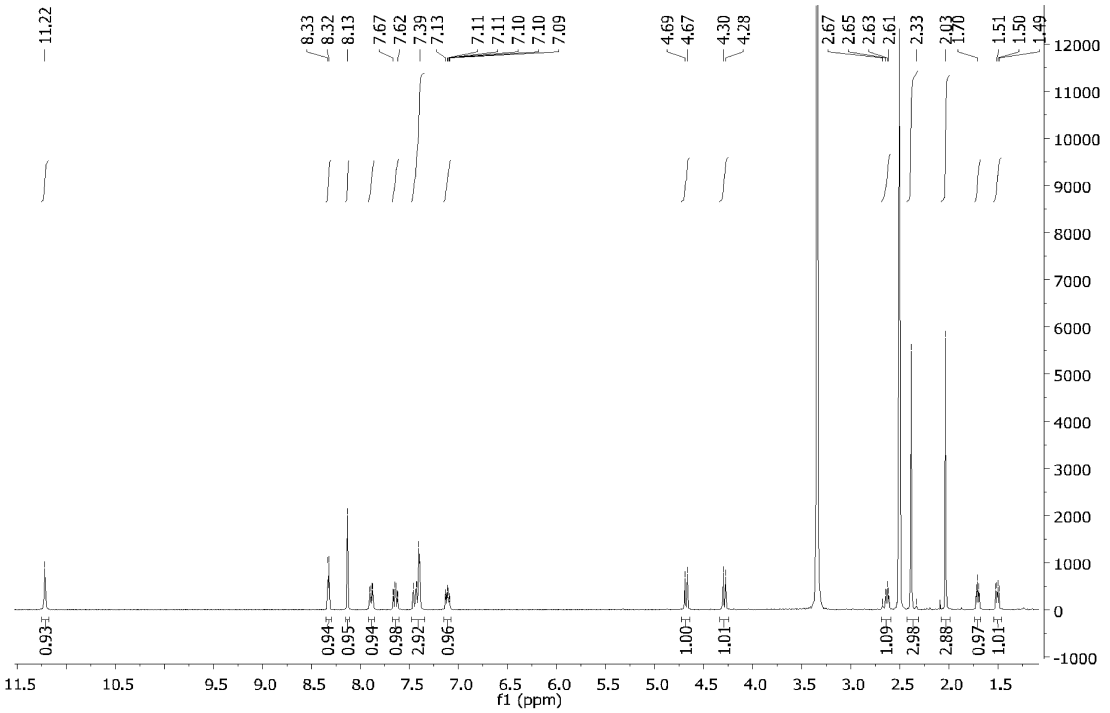

11.22
8.33
8.32
8.13
7.67
7.62
7.39
7.13
7.11
7.11
7.10
7.10
7.09
4.69
4.67
4.30
4.28
2.67
2.65
2.63
2.61
2.33
2.03
1.70
1.51
1.50
1.49
0.93
0.94
0.95
0.94
0.98
2.92
0.96
1.00
1.01
1.09
2.98
2.88
0.97
1.01
f1 (ppm)

图 4

说 明 书 附 图

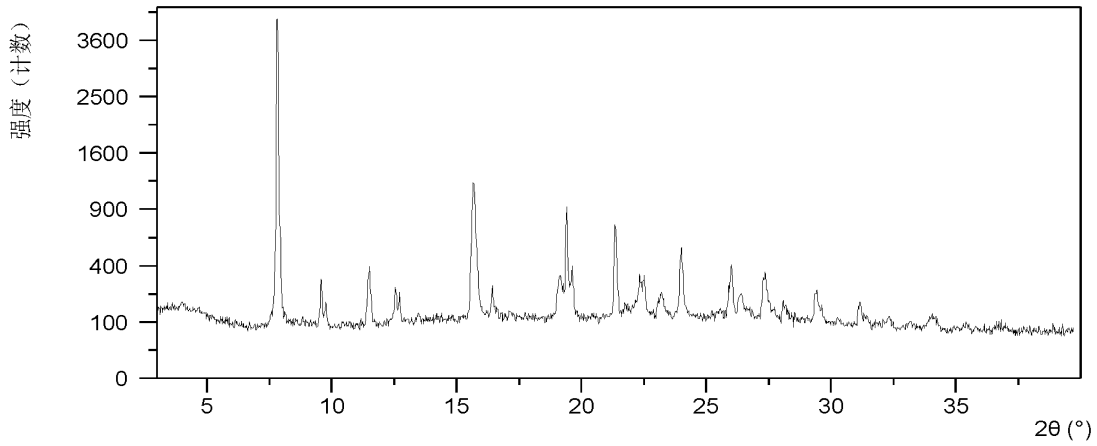


图 5

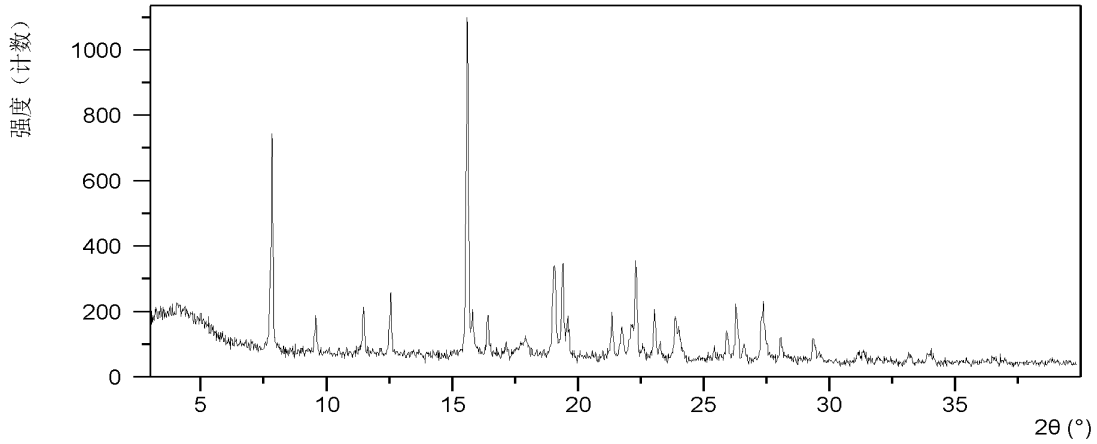


图 6

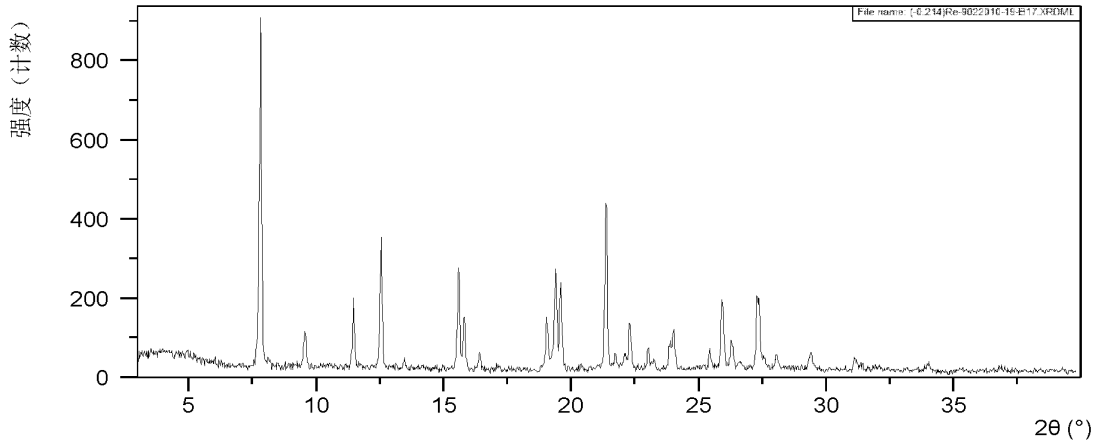


图 7

说 明 书 附 图

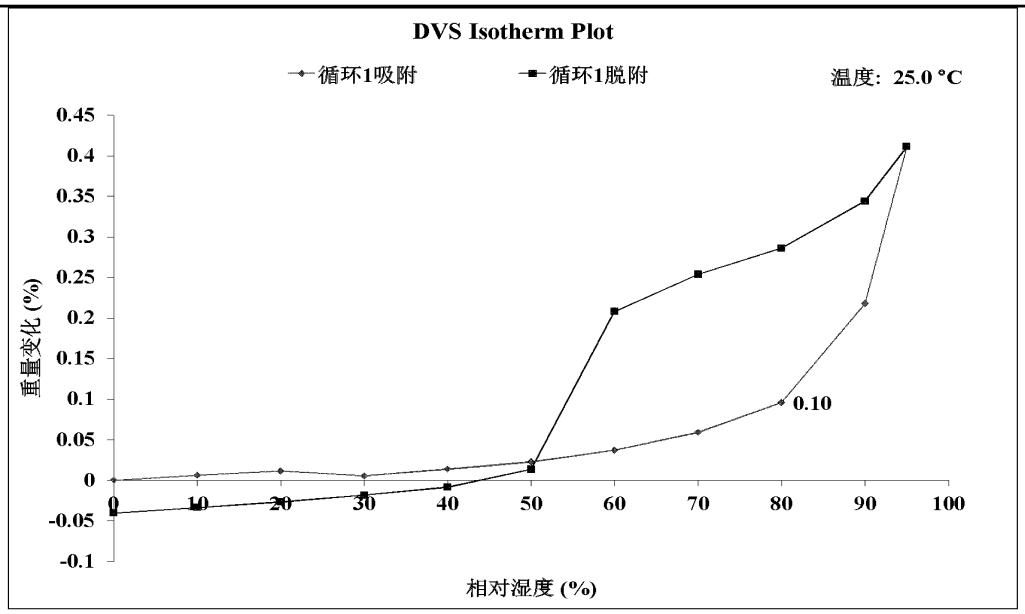

DVS Isotherm Plot
循环1吸附
循环1脱附
温度: 25.0 °C
重量变化 (%)
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
-0.05
-0.1
0.10
0
10
20
30
40
50
60
70
80
90
100
相对湿度 (%)

图 8

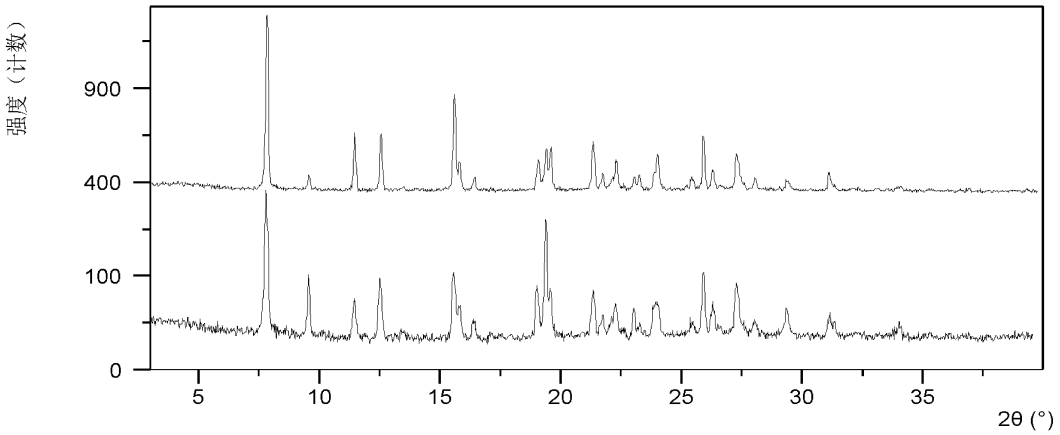

强度（计数）
900
400
100
0
5
10
15
20
25
30
35
2θ (°)

图 9

说 明 书 附 图

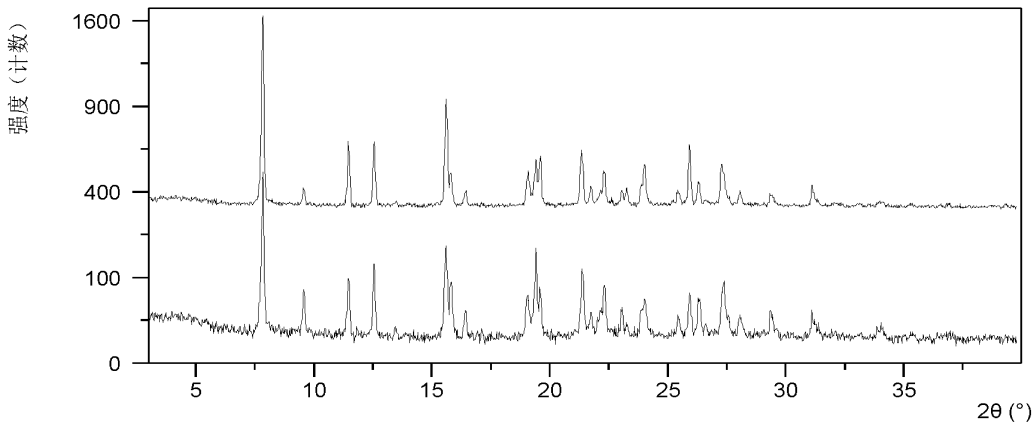


图 10

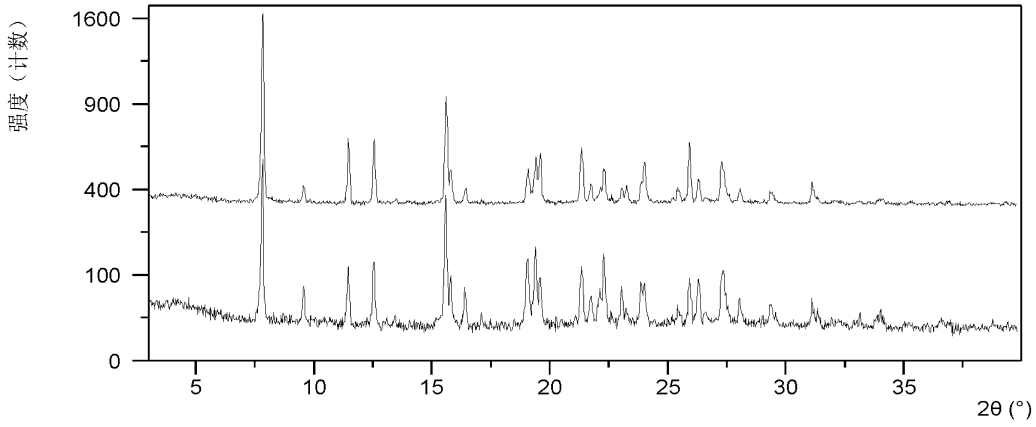


图 11

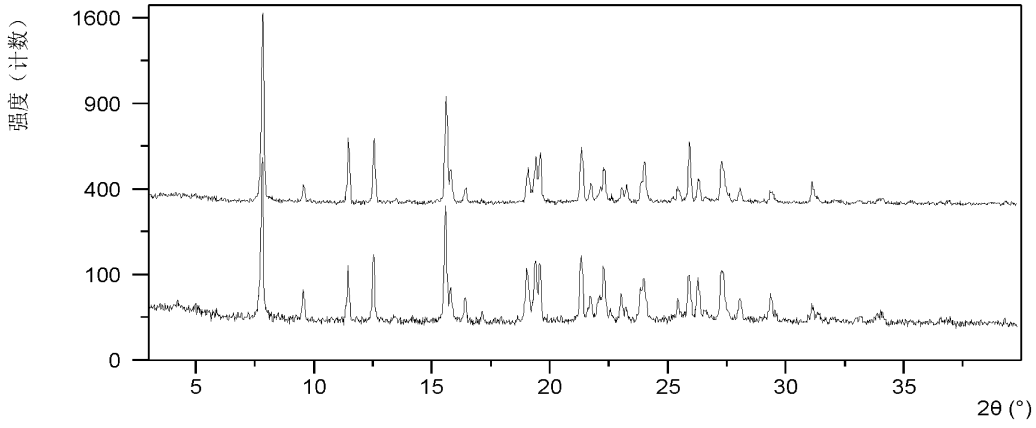


图 12

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/777,121	01/30/2020	Minhua Chen	134070-01602	1029

86738 7590 03/20/2020

MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

EXAMINER	
ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
03/20/2020	ELECTRONIC

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

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

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

docket@mccarter.com

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 16/777,121	**Applicant(s)** Chen et al.	
	Examiner DIANE C GOODWYN	**Art Unit** OPET	**AIA (FITF) Status** Yes

1. THE REQUEST FILED 30 January 2020 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 DIANE GOODWYN at (571) 272-6735. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/DIANE C GOODWYN/ Paralegal Specialist, OPET	

UNITED STATES PATENT AND TRADEMARK OFFICE

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NOTICE OF ALLOWANCE AND FEE(S) DUE

86738 7590 04/28/2020
MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

EXAMINER	
WARD, PAUL V	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 04/28/2020

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/777,121	01/30/2020	Minhua Chen	134070-01602	1029

TITLE OF INVENTION: CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$500	$0.00	$0.00	$500	07/28/2020

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

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

HOW TO REPLY TO THIS NOTICE:

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

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

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

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

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

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

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

PART B - FEE(S) TRANSMITTAL

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

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

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

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

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

86738 7590 04/28/2020
MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

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

Certificate of Mailing or Transmission

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

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/777,121	01/30/2020	Minhua Chen	134070-01602	1029

TITLE OF INVENTION: CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$500	$0.00	$0.00	$500	07/28/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
WARD, PAUL V	1624	514-269000

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

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

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

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

1_____
2_____
3_____

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

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

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

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

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

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

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

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

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

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

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

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

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/777,121	01/30/2020	Minhua Chen	134070-01602	1029

86738 7590 04/28/2020

MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

EXAMINER	
WARD, PAUL V	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 04/28/2020

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

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

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

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

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

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

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

Privacy Act Statement

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

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

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

Notice of Allowability	Application No. 16/777,121	Applicant(s) Chen et al.	
	Examiner PAUL V WARD	Art Unit 1624	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 1/30/20.
   ☐ 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 1-7 and 9 . 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 1/30/20.
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 _____.

/PAUL V WARD/
Primary Examiner, Art Unit 1624

Notice of Pre-AIA or AIA Status

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

DETAILED ACTION

Allowable Subject Matter

The following is a statement of reasons for the indication of allowable subject matter: The compounds, composition and method in claims 1-7 and 9 were not found to be obvious or anticipated by the prior art of record. The prior art (i.e., CN104114524 and CN104592184) does not teach or suggest the methods, composition and crystalline compounds encompassing the XRPD patterns in the manner claimed by the Applicant. Therefore, these claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL V WARD whose telephone number is (571)272-2909. The examiner can normally be reached on M-F 9am to 5pm.

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, Mark Shibuya can be reached on (571)272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/PAUL V WARD/
Primary Examiner, Art Unit 1624

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/777,121	Chen et al.
	Examiner	Art Unit
	PAUL V WARD	1624

CPC - Searched*		
Symbol	Date	Examiner
C07D 401/12	04/04/2020	pvw

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

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

Search Notes		
Search Notes	Date	Examiner
STN, East & Inventor	04/04/2020	pvw

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
Under Searched	Under Searched	04/04/2020	pvw

/PAUL V WARD/ Primary Examiner, Art Unit 1624	

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/777,121	Chen et al.
	Examiner	**Art Unit**
	PAUL V WARD	1624

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

CLAIMS

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

CLAIM		DATE								
Final	Original	04/04/2020								
	1	=								
	2	=								
	3	=								
	4	=								
	5	=								
	6	=								
	7	=								
	8									
	9	=								

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/777,121	Chen et al.
	Examiner	**Art Unit**
	PAUL V WARD	1624

CPC							
Symbol						**Type**	**Version**
C07D	/	401	/	12		F	2013-01-01
C07B	/	2200	/	13		A	2013-01-01

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

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	8	
/PAUL V WARD/ Primary Examiner, Art Unit 1624	16 April 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20200404

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/777,121	Chen et al.
	Examiner	**Art Unit**
	PAUL V WARD	1624

INTERNATIONAL CLASSIFICATION				
CLAIMED				
C07D	/	401	/	12

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

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

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 8	
/PAUL V WARD/ Primary Examiner, Art Unit 1624 (Primary Examiner)	16 April 2020 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20200404

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/777,121	Chen et al.
	Examiner	**Art Unit**
	PAUL V WARD	1624

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

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	8	
/PAUL V WARD/ Primary Examiner, Art Unit 1624	16 April 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20200404

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16/777,121
Filing Date	
First Named Inventor	Minhua Chen
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	134070-01602

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	8268848	B2	2012-09-18	Terauchi et al.	
	2	10172824	B2	2019-01-08	Wang et al.	

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 Patentee 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] 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	2013/123240	WO	A1	2013-08-22	Eisai R&D Management Co., Ltd.		
	2	2016/063995	WO	A1	2016-04-28	Eisai R&D Management Co., Ltd.		

/PAUL V WARD/ (04/04/2020)

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.V.W/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16/777,121
	Filing Date	
	First Named Inventor	Minhua Chen
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	134070-01602

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	International Search Report for Application No. PCT/CN2018/097797, dated October 31, 2018, 6 pages.	X

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

EXAMINER SIGNATURE

Examiner Signature	/PAUL V WARD/ (04/04/2020)	Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.V.W/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16/777,121
	Filing Date	
	First Named Inventor	Minhua Chen
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	134070-01602

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 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.

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

☒ A certification statement is not submitted herewith.

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	/Xiaoyuan Ding/	Date (YYYY-MM-DD)	2020-01-30
Name/Print	Xiaoyuan Ding	Registration Number	75,354

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:

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

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

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

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

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

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

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

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

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United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 1029

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
16/777,121	01/30/2020	514	1624	134070-01602

APPLICANTS
Crystal Pharmaceutical (Suzhou) Co., Ltd., Suzhou, CHINA;

INVENTORS
Minhua Chen, Suzhou, CHINA;
Yanfeng Zhang, Suzhou, CHINA;
Chunxiang Huang, Suzhou, CHINA;
Xiaoyu Zhang, Suzhou, CHINA;

**** CONTINUING DATA ************************
This application is a CON of PCT/CN2018/097797 07/31/2018

**** FOREIGN APPLICATIONS ************************
CHINA 201710648135.2 08/01/2017

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
03/06/2020

Foreign Priority claimed ☑ Yes ☐ No 35 USC 119(a-d) conditions met ☑ Yes ☐ No Verified and Acknowledged /PAUL V WARD/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		CHINA	7	8	1

ADDRESS
MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110
UNITED STATES

TITLE
CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE THEREOF

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

BIB (Rev. 05/07).

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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 NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/777,121	01/30/2020	Minhua Chen	134070-01602

CONFIRMATION NO. 1029

86738
MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

PUBLICATION NOTICE

Title:CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE THEREOF

Publication No.US-2020-0190060-A1
Publication Date:06/18/2020

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

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

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

PART B–FEE(S) TRANSMITTAL

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

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

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

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

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

MCCARTER & ENGLISH, LLP
265 Franklin Street
Boston, Massachusetts 02110

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

Certificate of Mailing or Transmission

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

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

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
16/777,121	01/30/2020	Minhua Chen	134070-01602	1029

TITLE OF INVENTION: CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE THEREOF

APPLN: TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$500.00			$500.00	07/28/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
P. V. Ward	1624	

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

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

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

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1. McCarter & English, LLP
2. Steven G. Davis, Ph.D.
3. Wei Song

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: Crystal Pharmaceutical (Suzhou) Co., Ltd.

(B) RESIDENCE: (CITY and STATE or COUNTRY): Suzhou, 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) ☐ Advance Order - # of Copies _____

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

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

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 50-4876

5. Change of 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 as a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status. NOTE: Checking this box will be taken as 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 /Wei Song/ Date July 27, 2020

Typed or printed name Wei Song Registration No. 64,320

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

ME1 33915596v.1

Electronic Patent Application Fee Transmittal

Application Number:	16777121
Filing Date:	30-Jan-2020
Title of Invention:	CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE THEREOF
First Named Inventor/Applicant Name:	Minhua Chen
Filer:	Wei Song/Erin Shea
Attorney Docket Number:	134070-01602

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

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

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

Electronic Acknowledgement Receipt	
EFS ID:	40109965
Application Number:	16777121
International Application Number:	
Confirmation Number:	1029
Title of Invention:	CRYSTALLINE FORM OF OREXIN RECEPTOR ANTAGONIST, PROCESSES FOR PREPARATION THEREOF AND USE THEREOF
First Named Inventor/Applicant Name:	Minhua Chen
Customer Number:	86738
Filer:	Wei Song
Filer Authorized By:	
Attorney Docket Number:	134070-01602
Receipt Date:	27-JUL-2020
Filing Date:	30-JAN-2020
Time Stamp:	13:15:25
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$500
RAM confirmation Number	E20207QD15433453
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	Issue_Fee_Transmittal.pdf	36320 edb4284a368ea0133dc4014fe3b1177852d16668	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30212 4a1aa0d6d345d6d600a1a5b1b1aff6c1c71b406f	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	66532		

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

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

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United States Patent and Trademark Office
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/777,121	09/01/2020	10759779	134070-01602	1029

86738 7590 08/12/2020

MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

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

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

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

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

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

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

Minhua Chen, Suzhou, CHINA;
Crystal Pharmaceutical (Suzhou) Co., Ltd., Suzhou, CHINA;
Yanfeng Zhang, Suzhou, CHINA;
Chunxiang Huang, Suzhou, CHINA;
Xiaoyu Zhang, Suzhou, CHINA;

IR103 (Rev. 10/09)