

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

UTILITY PATENT APPLICATION TRANSMITTAL (Only for new nonprovisional applications under 37 CFR 1.53(b))	Attorney Docket No.	1258.19CT
	First Named Inventor	Fionn Hurley
	Title	Compositions comprising (R)-2-amino-3-phenylpropyl carbonates and uses thereof
	Priority Mail Express® Label No.	

APPLICATION ELEMENTS See MPEP chapter 600 concerning utility patent application contents. 1. ☐ Fee Transmittal Form (PTO/SB/17 or equivalent) 2. ☐ Applicant asserts small entity status. See 37 CFR 1.27 3. ☐ Applicant certifies micro entity status. See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent. 4. ☒ Specification [Total Pages 20] Both the claims and abstract must start on a new page. (See MPEP § 608.01(a) for information on the preferred arrangement) 5. ☒ Drawing(s) (35 U.S.C. 113) [Total Sheets 5] 6. ☒ Inventor's Oath or Declaration [Total Pages 1] (including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e)) a. ☐ Newly executed (original or copy) b. ☒ A copy from a prior application (37 CFR 1.63(d)) 7. ☒ Application Data Sheet * See note below. See 37 CFR 1.76 (PTO/AIA/14 or equivalent) 8. ☐ CD-ROM or CD-R in duplicate, large table, or Computer Program (Appendix) ☐ Landscape Table on CD 9. Nucleotide and/or Amino Acid Sequence Submission (if applicable, items a. – c. are required) a. ☐ Computer Readable Form (CRF) b. ☐ Specification Sequence Listing on: i. ☐ CD-ROM or CD-R (2 copies); or ii. ☐ Paper c. ☐ Statements verifying identity of above copies	ADDRESS TO: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450 ACCOMPANYING APPLICATION PAPERS 10. ☐ Assignment Papers (cover sheet & document(s)) Name of Assignee _____ 11. ☐ 37 CFR 3.73(c) Statement ☒ Power of Attorney (when there is an assignee) 12. ☐ English Translation Document (if applicable) 13. ☒ Information Disclosure Statement (PTO/SB/08 or PTO-1449) ☐ Copies of citations attached 14. ☒ Preliminary Amendment 15. ☐ Return Receipt Postcard (MPEP § 503) (Should be specifically itemized) 16. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed) 17. ☐ Nonpublication Request Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent. 18. ☐ Other: _____ _____ _____ _____ _____
---	---

***Note:** (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must** be included in an Application Data Sheet (ADS).
(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS				
☐ The address associated with Customer Number: 129932 OR ☐ Correspondence address below				
Name				
Address				
City	State	Zip Code		
Country	Telephone	Email		

Signature	/Robert A. Schwartzman/	Date	November 6, 2020
Name (Print/Type)	Robert A. Schwartzman, Ph.D.	Registration No. (Attorney/Agent)	50,211

This collection of information is required by 37 CFR 1.53(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

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

Application Number	To Be Assigned
Filing Date	Concurrently Herewith
First Named Inventor	Fionn Hurley
Title	Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses thereof
Art Unit	
Examiner Name	
Attorney Docket Number	1258.19CT

SIGNATURE of Applicant or Patent Practitioner

Signature	/Robert A. Schwartzman/	Date (Optional)	November 6, 2020
Name	Robert A. Schwartzman, Ph.D.	Registration Number	50,211
Title (if Applicant is a juristic entity)	Attorney for Applicant		
Applicant Name (if Applicant is a juristic entity)	Jazz Pharmaceuticals Ireland Limited		

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.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☒ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above:

OR

129932

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☒ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

Firm or Individual Name				
Address				
City		State		Zip
Country				
Telephone		Email		

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

Jazz Pharmaceuticals International III Limited

- ☐ Inventor or Joint Inventor (title not required below)
- ☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)
- ☒ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)
- ☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	JANUARY 21, 2016
Name	KEVIN INSLEY		
Title	PRESIDENT		

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 _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 36 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1480, Alexandria, VA 22313-1480. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS, SEND TO: Commissioner for Patents, P.O. Box 1480, Alexandria, VA 22313-1480.

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

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

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

Application Number	To Be Assigned
Filing Date	Concurrently Herewith
First Named Inventor	Fionn Hurley
Title	Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses thereof
Art Unit	
Examiner Name	
Attorney Docket Number	1258.19CT

SIGNATURE of Applicant or Patent Practitioner

Signature	/Robert A. Schwartzman/	Date (Optional)	November 6, 2020
Name	Robert A. Schwartzman, Ph.D.	Registration Number	50,211
Title (if Applicant is a juristic entity)	Attorney for Applicant		
Applicant Name (if Applicant is a juristic entity)		SK Biopharmaceuticals Co., Ltd.	

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.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☒ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above:

129932

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☒ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

Firm or Individual Name				
Address				
City		State		Zip
Country				
Telephone		Email		

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

SK Biopharmaceuticals Co., Ltd.

- ☐ Inventor or Joint Inventor (title not required below)
- ☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)
- ☒ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)
- ☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	<i>Jaegu Shim</i>	Date (Optional)	Dec. 4, 2015
Name	JAEGU SHIM		
Title	2P group leader		

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 _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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

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	1258.19CT
		Application Number	
Title of Invention	Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses 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
	Fionn		Hurley	
Residence Information (Select One) ☐ US Residency ☒ Non US Residency ☐ Active US Military Service				
City	Baldoyle, Dublin	Country of Residence ⁱ	IE	
Mailing Address of Inventor:				
Address 1	6 Turnberry Square			
Address 2				
City	Baldoyle, Dublin	State/Province		
Postal Code	13	Country ⁱ	IE	
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	129932		
Email Address		Add Email	Remove Email

Application Information:

Title of the Invention	Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses thereof		
Attorney Docket Number	1258.19CT	Small Entity Status Claimed ☐	
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	5	Suggested Figure for Publication (if any)	

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	1258.19CT
		Application Number	
Title of Invention	Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses thereof		

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	129932		

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		Patented		Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
	Continuation of	16331069	2019-03-06	10829443	2020-11-10

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	1258.19CT
		Application Number	
Title of Invention	Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses thereof		
Prior Application Status	Expired	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
16331069	a 371 of international	PCTUS2017050233	2017-09-06
Prior Application Status	Expired	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCTUS2017050233	Claims benefit of provisional	62383822	2016-09-06
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.			

Foreign Priority Information:

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

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

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	1258.19CT
		Application Number	
Title of Invention	Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses thereof		

Authorization or Opt-Out of Authorization to Permit Access:

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

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

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

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

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

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

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

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

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

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

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

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	1258.19CT
		Application Number	
Title of Invention	Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses thereof		

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.			
Applicant 1			
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	
☐ 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	Jazz Pharmaceuticals Ireland Limited		
Mailing Address Information For Applicant:			
Address 1	Waterloo Exchange, Waterloo Road		
Address 2			
City	Dublin	State/Province	
Country	IE	Postal Code	4
Phone Number		Fax Number	
Email Address			
Additional Applicant Data may be generated within this form by selecting the Add button.			

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	1258.19CT
		Application Number	
Title of Invention	Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses thereof		

Applicant 2			
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	
☐ 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	SK Biopharmaceuticals Co., Ltd.		
Mailing Address Information For Applicant:			
Address 1	221 Pangyoyeok-ro, Bundang-gu		
Address 2			
City	Seongnam-si, Gyeonggi-do	State/Province	
Country	KR	Postal Code	13494
Phone Number		Fax Number	
Email Address			
Additional Applicant Data may be generated within this form by selecting the Add button.			

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.

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.
If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

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	1258.19CT
		Application Number	
Title of Invention	Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses thereof		

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		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.

Signature:

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	/Robert A. Schwartzman/		Date (YYYY-MM-DD)	2020-11-06
First Name	Robert A.	Last Name	Schwartzman, Ph.D.	Registration Number
				50211

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

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.**

Attorney Docket No. 1258.19CT
In re: Hurley
Application No.: To Be Assigned

REMARKS

The claims have been amended to place the application in condition for examination.
No new matter has been added.

Applicant respectfully requests entry of the amendments and requests substantive examination on the merits.

It is not believed that any additional fee(s) are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, the Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-0220.

Respectfully submitted,



Robert A. Schwartzman, Ph.D.
Registration No. 50,211
Attorney for Applicant

Customer Number 129932

Myers Bigel, P.A.
P. O. Box 37428
Raleigh, North Carolina 27627
Telephone: (919) 854-1400
Facsimile: (919) 854-1401

#2691442

CERTIFICATION OF TRANSMISSION

I hereby certify that this correspondence is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4) to the U.S. Patent and Trademark Office on November 6, 2020.

Signature: /Betty-Lou Medlin/
Name: Betty-Lou Medlin

Amendment to the Claims

The following list of claims will replace all prior versions and listings of claims in the application.

1-19. (Canceled)

20. (Currently Amended) A composition comprising (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride and 2-chloropropane, wherein the composition comprises ~~comprising~~ less than about 5 ppm 2-chloropropane.

21. (Original) The composition of claim 20, wherein the composition comprises less than about 1 ppm 2-chloropropane (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride is ~~prepared by the method of any one of claims 16-19.~~

22. (Currently Amended) The composition of claim 20 ~~or 21~~, wherein the composition is a dosage form.

23. (Original) The composition of claim 22, wherein the composition is an immediate release oral dosage form.

24. (Original) The composition of claim 23, wherein the composition is a tablet or a capsule.

25. (Currently Amended) A method of treating narcolepsy, cataplexy, excessive daytime sleepiness, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, or obesity in a subject in need thereof, or promoting smoking cessation in a subject in need thereof, comprising administering to the subject the composition of claim 20 ~~any one of claims 20-24~~.

26. (Original) The method of claim 25, wherein the tablet is administered once per day.

27. (Original) The method of claim 25, wherein the tablet is administered more than once per day.

Attorney Docket No. 1258.19CT
In re: Hurley
Application No.: To Be Assigned

Amendment to the Specification

Replace the title with the following title.

Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses thereof

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Hurley

Application No.: To Be Assigned

Filing Date: Concurrently Herewith

For: Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses thereof

November 6, 2020

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Prior to the examination of the above-referenced application, please enter the following amendments and consider the following remarks.

Amendments to the Specification begin on Page 2 of this paper.

Amendments to the Claims begin on Page 3 of this paper.

Remarks begin on Page 4 of this paper.

Abstract

Solvate Form of (*R*)-2-amino-3-phenylpropyl carbamate

The present invention relates to a newly identified solvate form of (*R*)-2-amino-3-phenylpropyl carbamate (APC) hydrochloride, a method of preparing APC hydrochloride, and methods of using the same to treat disorders. The invention further relates to methods of producing APC hydrochloride with increased purity.

What is Claimed is:

1. A solvate form of (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride characterized by a powder x-ray diffraction pattern substantially the same as that shown in Figure 1 Form B and/or a powder x-ray diffraction pattern having peaks at about 7.0, 13.6, 16.2, 17.4, 17.8, 18.5, 21.0, 21.7, 22.7, 23.0, 24.0, and 27.3 ± 0.2 °2 θ .
2. The solvate form of claim 1, further characterized by differential scanning calorimetry as having a broad endotherm with onset at 69.1°C and peak at 71.7°C and a sharp endotherm with onset at 182.5°C and peak at 183.6°C.
3. The solvate form of claim 1 or 2, wherein the solvate form is a hemihydrate.
4. The solvate form of any one of claims 1-3, further characterized as being produced by slurrying (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride in acetonitrile/water (95%/5% v/v).
5. A process of preparing a solvate form of (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride, comprising slurrying (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride in acetonitrile/water (95%/5% v/v) and collecting the solvate by vacuum filtration.
6. The process of claim 5, wherein the slurrying is performed at about room temperature.
7. The process of claim 5 or 6, wherein the slurrying is performed at for at least about 20 hours.
8. A composition comprising (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride, wherein at least 30% of the (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride is the solvate form of any one of claims 1-4.
9. A composition comprising (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride, wherein less than 10% of the (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride is the solvate form of any one of claims 1-4.

10. The composition of claim 8 or 9, wherein the composition is a dosage form.
11. The composition of claim 10, wherein the composition is an immediate release oral dosage form.
12. The composition of claim 11, wherein the composition is a tablet or a capsule.
13. A method of treating narcolepsy, cataplexy, excessive daytime sleepiness, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, or obesity in a subject in need thereof, or promoting smoking cessation in a subject in need thereof, comprising administering to the subject the composition of any one of claims 8-11.
14. The method of claim 13, wherein the tablet is administered once per day.
15. The method of claim 13, wherein the tablet is administered more than once per day.
16. A method of preparing (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride while minimizing contamination with 2-chloropropane, the method comprising crystallizing (*R*)-2-amino-3-phenylpropyl carbamate in the presence of aqueous HCl, thereby producing crystals of (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride.
17. The method of claim 16, wherein the crystallizing is performed at a temperature of about 25°C to about 30°C.
18. The method of claim 16 or 17, further comprising drying the crystals of (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride at a temperature of about 35°C or less.
19. The method of any one of claims 16-18, wherein the amount of 2-chloropropane in the (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride is less than about 5 ppm.
20. A composition comprising (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride, the composition comprising less than about 5 ppm 2-chloropropane.

21. The composition of claim 20, wherein the (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride is prepared by the method of any one of claims 16-19.
22. The composition of claim 20 or 21, wherein the composition is a dosage form.
23. The composition of claim 22, wherein the composition is an immediate release oral dosage form.
24. The composition of claim 23, wherein the composition is a tablet or a capsule.
25. A method of treating narcolepsy, cataplexy, excessive daytime sleepiness, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, or obesity in a subject in need thereof, or promoting smoking cessation in a subject in need thereof, comprising administering to the subject the composition of any one of claims 20-24.
26. The method of claim 25, wherein the tablet is administered once per day.
27. The method of claim 25, wherein the tablet is administered more than once per day.

Solvate Form of (*R*)-2-amino-3-phenylpropyl carbamate

Statement Of Priority

[0001] This application is a continuation of U.S. Patent Application No. 16/331,069, filed March 6, 2019, now U.S. Patent No. 10,829,443, which is a 35 U.S.C. § 371 national phase application of PCT Application PCT/US2017/050233 filed September 6, 2017, which claims the benefit, under 35 U.S.C. § 119(e), of U.S. Provisional Application No. 62/383,822, filed September 6, 2016; the entire contents of each of which are incorporated by reference herein in its entirety.

Field of the Invention

[0002] The present invention relates to a newly identified solvate form of (*R*)-2-amino-3-phenylpropyl carbamate (APC) hydrochloride, a method of preparing APC hydrochloride, and methods of using the same to treat disorders. The invention further relates to methods of producing APC hydrochloride with increased purity.

Background of the Invention

[0003] APC is a phenylalanine analog that has been demonstrated to be useful in the treatment of a variety of disorders, including excessive daytime sleepiness, cataplexy, narcolepsy, fatigue, depression, bipolar disorder, fibromyalgia, and others. See, for example, US Patent Nos. 8,232,315; 8,440,715; 8,552,060; 8,623,913; 8,729,120; 8,741,950; 8,895,609; 8,927,602; 9,226,910; and 9,359,290; and U.S. Publication Nos. 2012/0004300 and 2015/0018414. Methods for producing APC (which also has other names) and related compounds can be found in US Patent Nos. 5,955,499; 5,705,640; 6,140,532 and 5,756,817. All of the above patents and applications are hereby incorporated herein by reference in their entireties for all purposes.

[0004] The present invention overcomes shortcomings in the art by providing a new solvate form of APC and a method of preparing APC with minimal contaminants.

Summary of the Invention

[0005] The present invention relates to the identification of a novel solvate form of APC which is a hemihydrate form. The invention further relates to a method of preparing APC

with minimal contaminants. The invention additionally relates to the use of the new solvate form and/or the APC with increased purity for the treatment of disorders responsive to APC.

[0006] Accordingly, the invention relates to a solvate form of APC hydrochloride characterized by a powder x-ray diffraction pattern substantially the same as that shown in Figure 1 and/or a powder x-ray diffraction pattern having peaks at about 7.0, 13.6, 16.2, 17.4, 17.8, 18.5, 21.0, 21.7, 22.7, 23.0, 24.0, and $27.3 \pm 0.2^\circ 2\theta$.

[0007] The invention further relates to a process of preparing a solvate form of APC hydrochloride, comprising slurrying APC hydrochloride in acetonitrile/water (95%/5% v/v) and collecting the solvate by vacuum filtration.

[0008] The invention further relates to a composition comprising APC, wherein less than about 10% of the APC in the composition is the solvate form of the invention.

[0009] The invention also relates to a composition comprising APC, wherein at least about 30% of the APC in the composition is the solvate form of the invention.

[0010] The invention additionally relates to a method of treating a disorder amenable to treatment with APC, *e.g.*, narcolepsy, cataplexy, excessive daytime sleepiness, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, or obesity in a subject in need thereof, or promoting smoking cessation in a subject in need thereof, comprising administering to the subject a dosage form comprising the solvate form of the invention.

[0011] The invention also relates to a method of preparing APC hydrochloride while minimizing contamination with 2-chloropropane, the method comprising crystallizing APC in the presence of aqueous HCl, thereby producing crystals of APC hydrochloride.

[0012] The invention further relates to a composition comprising APC with increased purity as prepared by the method of the invention.

[0013] The invention additionally relates to a method of treating a disorder amenable to treatment with APC, *e.g.*, narcolepsy, cataplexy, excessive daytime sleepiness, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, or obesity in a subject in need thereof, or promoting smoking cessation in a subject in need thereof, comprising administering to the subject a dosage form comprising APC with increased purity as prepared by the method of the invention.

[0014] The present invention is explained in greater detail in the drawings herein and the specification set forth below.

Brief Description of the Drawings

- [0015] Figure 1 shows the X-ray pattern diffraction (XRPD) of crystalline forms of APC.
- [0016] Figure 2 shows the differential scanning calorimetry (DSC) thermogram of hemihydrate Form B of APC.
- [0017] Figure 3 shows a comparison of the DSC thermograms of Forms A and B of APC.
- [0018] Figure 4 shows a comparison of the thermogravimetric (TG) thermograms of Forms A and B of APC.
- [0019] Figure 5 shows XRPD patterns of the conversion of Form A to Form B of APC.

Detailed Description of the Invention

[0020] The present invention can be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art. For example, features illustrated with respect to one embodiment can be incorporated into other embodiments, and features illustrated with respect to a particular embodiment can be deleted from that embodiment. In addition, numerous variations and additions to the embodiments suggested herein will be apparent to those skilled in the art in light of the instant disclosure, which do not depart from the instant invention.

[0021] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The terminology used in the description of the invention herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention.

[0022] Unless the context indicates otherwise, it is specifically intended that the various features of the invention described herein can be used in any combination.

[0023] Moreover, the present invention also contemplates that in some embodiments of the invention, any feature or combination of features set forth herein can be excluded or omitted.

[0024] To illustrate, if the specification states that a complex comprises components A, B and C, it is specifically intended that any of A, B or C, or a combination thereof, can be omitted and disclaimed singularly or in any combination.

[0025] All publications, patent applications, patents, and other references mentioned herein are incorporated by reference herein in their entirety for all purposes.

[0026] As used herein, “a,” “an,” or “the” can mean one or more than one. For example, “a” cell can mean a single cell or a multiplicity of cells.

[0027] Also as used herein, “and/or” refers to and encompasses any and all possible combinations of one or more of the associated listed items, as well as the lack of combinations when interpreted in the alternative (“or”).

[0028] Furthermore, the term “about,” as used herein when referring to a measurable value such as an amount of a compound or agent of this invention, dose, time, temperature, and the like, is meant to encompass variations of $\pm 10\%$, $\pm 5\%$, $\pm 1\%$, $\pm 0.5\%$, or even $\pm 0.1\%$ of the specified amount.

[0029] The term “consists essentially of” (and grammatical variants), as applied to the compositions of this invention, means the composition can contain additional components as long as the additional components do not materially alter the composition. The term “materially altered,” as applied to a composition, refers to an increase or decrease in the therapeutic effectiveness of the composition of at least about 20% or more as compared to the effectiveness of a composition consisting of the recited components.

[0030] The term “therapeutically effective amount” or “effective amount,” as used herein, refers to the amount of a composition, compound, or agent of this invention that imparts a modulating effect, which, for example, can be a beneficial effect, to a subject afflicted with a disorder, disease or illness, including improvement in the condition of the subject (*e.g.*, in one or more symptoms), delay or reduction in the progression of the condition, delay of the onset of the disorder, and/or change in clinical parameters, disease or illness, *etc.*, as would be well known in the art. For example, a therapeutically effective amount or effective amount can refer to the amount of a composition, compound, or agent that improves a condition in a subject by at least 5%, *e.g.*, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 100%.

[0031] “Treat” or “treating” or “treatment” refers to any type of action that imparts a modulating effect, which, for example, can be a beneficial effect, to a subject afflicted with a disorder, disease or illness, including improvement in the condition of the subject (*e.g.*, in one or more symptoms), delay or reduction in the progression of the condition, and/or change in clinical parameters, disease or illness, *etc.*, as would be well known in the art.

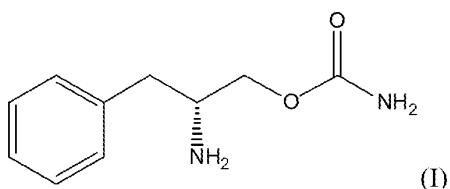
[0032] A “disorder amenable to treatment with APC” refers to any disorder in which administration of APC to a subject results in the treatment of one or more symptoms of the disorder in the subject. Examples of such disorders include, without limitation, narcolepsy, cataplexy, excessive daytime sleepiness, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, or obesity.

[0033] “Pharmaceutically acceptable,” as used herein, means a material that is not biologically or otherwise undesirable, *i.e.*, the material can be administered to an individual along with the compositions of this invention, without causing substantial deleterious biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. The material would naturally be selected to minimize any degradation of the active ingredient and to minimize any adverse side effects in the subject, as would be well known to one of skill in the art (see, *e.g.*, *Remington's Pharmaceutical Science*; 21st ed. 2005).

[0034] “Concurrently” means sufficiently close in time to produce a combined effect (that is, concurrently can be simultaneously, or it can be two or more events occurring within a short time period before or after each other). In some embodiments, the administration of two or more compounds “concurrently” means that the two compounds are administered closely enough in time that the presence of one alters the biological effects of the other. The two compounds can be administered in the same or different formulations or sequentially. Concurrent administration can be carried out by mixing the compounds prior to administration, or by administering the compounds in two different formulations, for example, at the same point in time but at different anatomic sites or using different routes of administration.

[0035] The present invention relates to the identification and characterization of a new solvate form of APC hydrochloride, called Form B. The solvate form is a hemihydrate form and is the more stable form of the compound at higher humidity levels compared to the anhydrous Form A.

[0036] The structure of APC free base is given below as formula I.



[0037] Thus, one aspect of the invention relates to a solvate form of APC hydrochloride characterized by a powder x-ray diffraction pattern substantially the same as that shown in Figure 1 for solvate Form B and/or a powder x-ray diffraction pattern having peaks at about 7.0, 13.6, 16.2, 17.4, 17.8, 18.5, 21.0, 21.7, 22.7, 23.0, 24.0, and 27.3 ± 0.2 °2 θ . In some embodiments, the solvate is further characterized by differential scanning calorimetry as having a broad endotherm with onset at 69.1°C and peak at 71.7°C and a sharp endotherm with onset at 182.5°C and peak at 183.6°C. In some embodiments, the solvate is further characterized by having a solubility in buffer solution of about 700-750 mg/ml at pH 1-6.5. In certain embodiments, the solvate form is a hemihydrate.

[0038] In some embodiments, the solvate form is further characterized as being produced by slurring APC in acetonitrile/water (95%/5% v/v).

[0039] As used herein, the term “hemihydrate,” refers to a hydrate in which one molecule of water is associated with two molecules of APC.

[0040] As used herein, the term “crystalline” refers to a material that contains a specific compound, which may be hydrated and/or solvated, and has sufficient crystal content to exhibit a discernible diffraction pattern by XRPD or other diffraction techniques.

[0041] The solvate form may be prepared by a method comprising slurring APC hydrochloride in a suitable solvent system (*e.g.*, acetonitrile/water (95%/5% v/v)) and collecting the solvate crystals using a suitable technique, *e.g.*, vacuum filtration. In some embodiments, the process is carried out at about room temperature, *e.g.*, about 20°C to about 28°C and in about 5-15 (*e.g.*, 10) volumes of solvent. In some embodiments, the slurring step is carried out for a sufficient length of time for the solvate to form, *e.g.*, at least about 10 hours, *e.g.*, at least about 10, 15, 20, 25, 50, 75, or 100 hours or more.

[0042] In some embodiments, the process is carried out at a temperature of about 20°C and in about 5 volumes of solvent. In some embodiments, the slurring step is carried out for a sufficient length of time for the solvate to form, *e.g.*, about 1-2 hours.

[0043] The wet Form B prepared by the methods described herein may be dried by any method suitable for maintaining Form B and limiting dehydration to Form A. In some

embodiments, the drying is carried out at a temperature of about 20°C to about 25°C. In some embodiments, the drying is carried out at reduced pressure, *e.g.*, about 600-950 mbar *e.g.*, about 700-750 mbar. In some embodiments, the drying is carried out for a suitable length of time to achieve complete dryness, *e.g.*, about 4-40 hours, *e.g.*, about 10-24 hours. In some embodiments, the drying is carried out at high humidity, *e.g.*, about 80-100% relative humidity.

[0044] Another aspect of the invention relates to a composition, *e.g.*, a dosage form, comprising APC, wherein less than about 10% of the APC in the composition is solvate Form B. In some embodiments, less than about 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, or 1% of the APC is in solvate Form B. In some embodiments, the dosage form is an oral dosage form, *e.g.*, a tablet or a capsule, including, *e.g.*, an immediate release dosage form.

[0045] A further aspect of the invention relates to a composition, *e.g.*, a dosage form, comprising APC, wherein at least about 30% of the APC in the composition is solvate Form B, *e.g.*, about 30% to about 99% or more. In some embodiments, at least about 40%, 50%, 60%, 70%, 80%, or 90% of the APC is solvate Form B. In some embodiments, the dosage form is an oral dosage form, *e.g.*, a tablet or a capsule, including, *e.g.*, an immediate release dosage form.

[0046] In some embodiments, the dosage form is an immediate release dosage form that releases at least 85%, *e.g.*, at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%, of the APC HCl contained therein within a period of less than 15 minutes after administration of the tablet to a subject. Such immediate release dosage forms are disclosed, for example, US Provisional Application No. 62/383,818, incorporated herein by reference in its entirety.

[0047] Formulations of APC, including immediate release formulations, may be processed into unit dosage forms suitable for oral administration, such as for example, filled capsules, compressed tablets or caplets, or other dosage form suitable for oral administration using conventional techniques. Immediate release dosage forms prepared as described may be adapted for oral administration, so as to attain and maintain a therapeutic level of APC over a preselected interval. In certain embodiments, an immediate release dosage form as described herein may comprise a solid oral dosage form of any desired shape and size including round, oval, oblong cylindrical, or polygonal. In one such embodiment, the surfaces of the immediate release dosage form may be flat, round, concave, or convex.

[0048] In particular, when the immediate release formulations are prepared as a tablet, the immediate release tablets contain a relatively large percentage and absolute amount of APC

and so are expected to improve patient compliance and convenience by replacing the need to ingest large amounts of liquids or liquid/solid suspensions. One or more immediate release tablets as described herein can be administered, by oral ingestion, *e.g.*, closely spaced, in order to provide a therapeutically effective dose of APC to the subject in a relatively short period of time.

[0049] Where desired or necessary, the outer surface of an immediate release dosage form may be coated, *e.g.*, with a color coat or with a moisture barrier layer using materials and methods known in the art.

[0050] The dosage form may contain any amount of APC or a pharmaceutically acceptable salt thereof suitable for administration as a unit dosage form. In some embodiments, the dosage form contains about 1 mg to about 1000 mg of the drug or any range or value therein, *e.g.*, about 10 mg to about 500 mg, *e.g.*, about 37.5 mg, about 75 mg, about 150 mg, or about 300 mg.

[0051] APC or a pharmaceutically acceptable salt thereof may be obtained or synthesized by methods known in the art and as described herein. Details of reaction schemes for synthesizing APC have been described in U.S. Patent Nos. 5,705,640; 5,756,817; 5,955,499; and 6,140,532, all incorporated herein by reference in their entirety.

[0052] During the development of manufacturing processes for APC, it was found that unacceptable levels of the impurity 2-chloropropane (*i.e.*, isopropyl chloride) could appear during the crystallization of APC hydrochloride. It is desirable to minimize 2-chloropropane as it is a potential genotoxic impurity. Thus, one aspect of the invention relates to an improved method of preparing APC hydrochloride in which contamination with 2-chloropropane is minimized. With this improved method, the level of 2-chloropropane in the final product may be less than about 10 ppm, *e.g.*, less than about 9, 8, 7, 6, 5, 4, 3, 2, or 1 ppm.

[0053] Thus, one aspect of the invention relates to a method of preparing APC hydrochloride while minimizing contamination with 2-chloropropane, the method comprising crystallizing APC in the presence of aqueous HCl, thereby producing crystals of APC hydrochloride. The crystallization may be carried out with the free base of APC in a suitable solvent, *e.g.*, isopropanol.

[0054] In some embodiments, the aqueous HCl is 37% aqueous HCl. In some embodiments, the crystallization is carried out at a temperature of about 15°C to about 40°C, *e.g.*, about 25°C to about 35°C, followed by cooling to a temperature of less than 0°C, *e.g.*, about -5°C to about -25°C, *e.g.*, about -15°C. In some embodiments, the crystals are dried at

a temperature less than about 45°C, *e.g.*, less than about 40°C, 35°C, or 30°C. In some embodiments, the crystallization is carried out in the presence of about 1 to about 1.2 molar equivalents (*e.g.*, about 1.05 molar equivalents) of 37% aqueous HCl at a temperature of about 25°C to about 35°C followed by a temperature of about -15°C.

[0055] Methods are disclosed herein to treat conditions amenable to treatment by APC, by administering an effective amount of one or more dosage forms as described herein. For example, the present dosage forms can be administered to treat a subject in need of treatment for narcolepsy, cataplexy, excessive daytime sleepiness, drug addiction, sexual dysfunction, fatigue, fibromyalgia, attention deficit/hyperactivity disorder, restless legs syndrome, depression, bipolar disorder, or obesity, or to promoting smoking cessation in a subject in need thereof. *See, e.g.*, US Patent Nos. 8,232,315; 8,440,715; 8,552,060; 8,623,913; 8,729,120; 8,741,950; 8,895,609; 8,927,602; 9,226,910; and 9,359,290; and U.S. Publication Nos. 2012/0004300 and 2015/0018414; each of which is incorporated by reference in its entirety with respect to the disorder to be treated.

[0056] The dosage forms disclosed herein can also be provided as a kit comprising, for example, a container comprising a plurality of immediate release tablets or capsules, which tablets or capsules can be individually packaged, as in foil envelopes or in a blister pack. The tablets or capsules can be packaged in many conformations with or without desiccants or other materials to prevent ingress of water. Instruction materials or means, such as printed labeling, can also be included for their administration, *e.g.*, sequentially over a preselected time period and/or at preselected intervals, to yield the desired levels of APC *in vivo* for preselected periods of time, to treat a preselected condition.

[0057] A daily dose of about 1 to about 2000 mg of APC or a pharmaceutically acceptable salt thereof may be administered to accomplish the therapeutic results disclosed herein. For example, a daily dosage of about 10-1000 mg, *e.g.*, about 20-500 mg, in single or divided doses, is administered. In some embodiments, the daily dose may be about 0.01 to about 150 mg/kg body weight, *e.g.*, about 0.2 to about 18 mg/kg body weight.

[0058] In one embodiment of the invention, APC is administered to the subject as needed to treat a disorder. The compound can be administered continuously or intermittently. In one embodiment, the compound is administered to the subject more than once a day, *e.g.*, 2, 3, or 4 times per day, or once every 1, 2, 3, 4, 5, 6, or 7 days. In another embodiment, the compound is administered to the subject no more than once a week, *e.g.*, no more than once every two weeks, once a month, once every two months, once every three months, once every four months, once every five months, once every six months, or longer. In a further

embodiment, the compound is administered using two or more different schedules, *e.g.*, more frequently initially (for example to build up to a certain level, *e.g.*, once a day or more) and then less frequently (*e.g.*, once a week or less). In other embodiments, the compound can be administered by any discontinuous administration regimen. In one example, the compound can be administered not more than once every three days, every four days, every five days, every six days, every seven days, every eight days, every nine days, or every ten days, or longer. The administration can continue for one, two, three, or four weeks or one, two, or three months, or longer. Optionally, after a period of rest, the compound can be administered under the same or a different schedule. The period of rest can be one, two, three, or four weeks, or longer, according to the pharmacodynamic effects of the compound on the subject. In another embodiment, the compound can be administered to build up to a certain level, then maintained at a constant level and then a tailing dosage.

[0059] In one aspect of the invention, APC is delivered to a subject concurrently with an additional therapeutic agent. The additional therapeutic agent can be delivered in the same composition as the compound or in a separate composition. The additional therapeutic agent can be delivered to the subject on a different schedule or by a different route as compared to the compound. The additional therapeutic agent can be any agent that provides a benefit to the subject. Further agents include, without limitation, stimulants, anti-psychotics, anti-depressants, agents for neurological disorders, and chemotherapeutic agents. One therapeutic agent that can be administered during the same period is Xyrem®, sold commercially by Jazz Pharmaceuticals, which is used to treat narcolepsy and cataplexy. See U.S. Patent Nos. 8,952,062 and 9,050,302.

[0060] The present invention finds use in research as well as veterinary and medical applications. Suitable subjects are generally mammalian subjects. The term “mammal” as used herein includes, but is not limited to, humans, non-human primates, cattle, sheep, goats, pigs, horses, cats, dog, rabbits, rodents (*e.g.*, rats or mice), *etc.* Human subjects include neonates, infants, juveniles, adults and geriatric subjects.

[0061] In particular embodiments, the subject is a human subject that has a disorder amenable to treatment with APC. In other embodiments, the subject used in the methods of the invention is an animal model of a disorder amenable to treatment with APC.

[0062] The subject can be a subject “in need of” the methods of the present invention, *e.g.*, in need of the therapeutic effects of the inventive methods. For example, the subject can be a subject that is experiencing a disorder amenable to treatment with APC, is suspected of having a disorder amenable to treatment with APC, and/or is anticipated to experience a

disorder amenable to treatment with APC, and the methods and compositions of the invention are used for therapeutic and/or prophylactic treatment.

[0063] The present invention is explained in greater detail in the following non-limiting Examples.

EXAMPLE 1

Solvate form of (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride

[0064] A polymorph and solvate screen of APC was conducted to evaluate its propensity to exist in various solid forms and determine the stable form of the compound. Four lots of APC were partially characterized. All lots were found to be the same anhydrous, crystalline material, and the material was designated Form A.

[0065] The polymorph and solvate screen of APC was conducted using different crystallization techniques to vary conditions of nucleation and growth investigating both thermodynamic and kinetic conditions. Solvent systems with varying chemical properties were used, and selected experiments focused specifically on process solvents. Selected experiments were also conducted via salt formation experiments using the free base and targeting the monohydrochloride salt.

[0066] A crystalline hemihydrate form was identified and named Form B. Form B was prepared from a slurry in acetonitrile:water (95%:5% v:v) at room temperature. Form B was also produced from a slurry in *p*-dioxane:water (95%:5% v:v) at subambient temperature. Form B was also observed as mixtures with Form A or other crystalline materials from various experiments such as evaporations and crash precipitations in ethanol, hexafluoroisopropanol, methanol, and/or water. Partial conversion to Form B was also observed after stressing of Form A at approximately 75% humidity (RH).

[0067] The XRPD pattern of Form B is shown in **FIG. 1**. The differential scanning calorimetry (DSC) thermogram of Form B exhibited a broad endotherm at 69.1°C (onset), 71.7°C (peak max) (**FIG. 2**). The endotherm is associated with a corresponding weight loss of 3.5% on the TG thermogram, which calculates to approximately 0.5 moles of water. These events are likely due to dehydration. A sharp endotherm is observed at 182.5 °C (onset), 183.6°C (peak max) followed by an exotherm at 185.2°C (peak max) possibly due to a recrystallization event. This was followed by an endotherm at 190.1°C (peak max). DSC and thermogravimetry (TG) thermogram comparisons of Form B and Form A are shown in **FIG. 3** and **FIG. 4**.

[0068] Karl Fischer analysis indicated Form B contained ~3.71 wt% water or approximately 0.5 moles. This data was consistent with the weight loss observed in the TG thermogram.

[0069] Microscopy images were taken of Form B and showed elongated plates (~50-100 μm) and smaller fragments.

[0070] The aqueous solubility of Form B was measured at over 700 mg/ml in different pH buffers as shown in Table 1.

Table 1

Solvent	pH (buffer) measured starting conditions	pH (buffered sample)	Solubility (mg/ml mean of triplicates)
Buffer solution pH 1.2	1.2	4.5	732.26
Buffer solution pH 4.5	4.5	5.7	733.04
Buffer solution pH 5.5	5.5	6.0	741.79
Buffer solution pH 7.4	7.4	6.4	746.41

[0071] Crystals of APC were submitted for single crystal structure analysis. The structure was determined by single crystal X-ray diffraction. The monoclinic cell parameters and calculated volume are: $a = 15.9491(8) \text{ \AA}$; $b = 5.8431(6) \text{ \AA}$; $c = 12.7663(12) \text{ \AA}$; $\beta = 94.404(5)^\circ$ ($\alpha = \gamma = 90^\circ$); $V = 1186.21(18) \text{ \AA}^3$. The formula weight of the asymmetric unit in the crystal structure of APC Form B is $239.70 \text{ g mol}^{-1}$ with $Z = 4$, resulting in a calculated density of 1.342 g cm^{-3} . The space group was determined to be $C2$ (no. 5). The space group and unit cell parameters are in agreement with those obtained previously from XRPD indexing for Form B.

[0072] When adequate relative RH is achieved Form A converts to Form B. Interconversion slurry experiments conducted with Form A and Form B suggest that Form B is the more stable form at approximately 50% RH or greater at room temperature.

[0073] Slurry experiments were performed with various water activities starting with Form A only and also by conducting interconversion slurries or pre-saturating solutions with APC and then adding equal amounts of Form A and Form B. When slurrying Form A only, conversion to Form B at room temperature occurred at 67% RH, and 40% RH at 2-8°C. With

the interconversion slurries, Form B was isolated from all experiments with relative humidities ranging from 50% to 70%.

[0074] Two small scale experiments were conducted in acetonitrile:water (95%:5% v:v) to evaluate whether an overnight conversion of Form A to Form B was possible. Experiments were conducted at approximately 98 mg/ml and approximately 51 mg/ml. Both experiments resulted in Form B after slurrying for approximately 24 hours indicating that kinetics of conversion of Form A to Form B can occur within 24 hours (**FIG. 5**).

[0075] Drying studies were performed on Form B. The drying experiments were performed under various temperatures with and without vacuum. Additionally, milling, storage under desiccant, and low RH stressing were conducted. In all experiments, Form B partially or fully dehydrated to Form A. Partial conversion to Form A occurred after vacuum drying at ambient temperature for 1 day, heating at 40°C for 1 day, storage under desiccant for 1 day, and stressing at 33% RH for 2 weeks. Full dehydration to Form A occurred after vacuum drying at 50°C for 1 day, heating at 80°C for 1 day, and milling. The results of the drying studies of Form B suggest that Form B is not stable under low RH or at elevated temperature.

[0076] A scaled-up method for producing Form B was developed. APC was slurried in acetonitrile:water (95%:5% v:v) while maintaining the temperature at 22°C. Subsamples of the slurry were taken periodically, vacuum filtered, and analyzed by XRPD. It was found that mixtures of Form B with trace amounts of Form A were observed from approximately 20 to 28.5 hours. Compared to the subsample taken at 20 hours, an increase in Form A was observed in the subsample taken at 24 hours. This may be due to dehydration caused by vacuum filtration and low atmospheric humidity. The slurry was stirred for an additional 3 days and another subsample was taken. XRPD analysis indicated that a subsample taken at approximately 91 hours was Form B. The slurry was isolated by vacuum filtration after slurrying of approximately 121.5 hours, and the wet cake was washed with two filter cake volumes of acetonitrile:water (95%:5% v:v). XRPD analysis indicated the wet cake was composed of Form B. The wet cake was dried under vacuum at ambient temperature for approximately 16 hours. XRPD analysis indicated the dried material dehydrated slightly to Form A, with approximately 5% Form A in the mixture. The dehydration may be avoided by drying without vacuum or drying under high RH (approximately 75%).

[0077] The mixture of Form B with a trace amount of Form A was additionally characterized by Karl Fischer for water content determination and solution ¹H NMR for an estimation of solvent content. Karl Fischer analysis indicated the mixture contained approximately 3.52% water or 0.47 moles of water per mole of APC. The ¹H NMR spectrum

was consistent with the structure of APC. Water and a trace amount of acetonitrile (0.003 moles per mole of APC) were also observed in the spectrum.

[0078] An additional scaled-up method for producing Form B was developed that reduced reaction time and volume and increased yield. Isolation of Form B from Form A was carried out in 5 volumes of solvent (acetonitrile:water (95%:5% v:v)) at about 20°C for about 1-2 hours. The drying process was carried out at an oven temperature of 20-25°C and low vacuum (700-750 mbar). Under these drying conditions Form B was stable and no detectable Form A was formed. This method was used on a 4.5 kg batch of APC and produced Form B with a yield of 93.7%.

EXAMPLE 2

Synthesis of (*R*)-2-amino-3-phenylpropyl carbamate hydrochloride with minimal 2-chloropropane

[0079] Initially, large scale preparation of APC hydrochloride from the free base was carried out as follows. APC free base solution in isopropyl alcohol was diluted with isopropyl alcohol to a final concentration of 19% w/w. Water (37 g/mol) was added, and the solution was heated to 70°C. Gaseous HCl (about 2 equivalents) was added in the headspace above the solution through a flow meter. As HCl dissolved the temperature increased to 75-80°C. The clear supersaturated solution was seeded quickly within the 15 minutes following the addition. APC hydrochloride crystallized. The suspension was stirred at 78°C, then cooled to 40°C in 10 hours. The suspension was further cooled to 20°C, then to 3°C in 2 hours, and stirred at this temperature for 1 hour. The solid was recovered by filtration and washed with isopropyl alcohol. The wet cake was dried under reduced pressure for at least 16 hours.

[0080] This method produced unacceptable levels of the potential genotoxic impurity 2-chloropropane (2-CP), which is preferentially at a level of no more than 5 ppm. The levels were likely due to the harsh crystallization conditions (HCl charging close to the boiling point of the reaction mixture, stirring 1 hour at 78°C, then cooling to 40°C in 10 hours, then progressively cooling to 3°C). Drying the crystals, even at elevated temperatures, did not reduce the amount of 2-CP. Reslurrying the crystals also was ineffective.

[0081] Given the difficulty of removing 2-CP once it was formed, it was necessary to revise the crystallization conditions to avoid the formation of 2-CP. Starting with APC free base in isopropyl acetate prevented formation of 2-CP but the crystallization was poorly controlled, resulting in the formation of a thick crust in the reactor, and produced very small crystals, so

the conditions were not suitable. Charging the HCl gas at a lower temperature (30-35°C) controlled formation of 2-CP but the crystallization was poorly controlled, resulting in the formation of a thick crust in the reactor, and produced a less crystalline material, so the conditions were not suitable.

[0082] Because the charging of HCl in gas form caused unwanted spontaneous crystallization in the conditions evaluated, adding HCl in the form of a 37% aqueous solution was tested. This protocol increases the total amount of water 1.76-fold from 37 g/mol to 65 g/mol so the resulting suspension has to be cooled to a lower temperature to maximize the yield. However, the larger amount of water combined with the lower molar excess of acid (1.05 molar equivalents compared to 2 molar equivalents) and the lower temperature contributes to minimizing the rate of formation of 2-CP.

[0083] The following general protocol was developed. APC free base solution in isopropyl alcohol was diluted with isopropyl alcohol to a final concentration of 19% w/w. The clear solution was warmed up to 25°C (20-30°C). 37% aqueous HCl was slowly added to the clear solution. The temperature was allowed to rise to 30°C. Seeding was applied soon afterwards (within 15 minute). The clear solution was stirred for 15 minutes at 30°C, whereby APC hydrochloride slowly started crystallizing. 37% aqueous HCl was further added to the suspension. The mixture was stirred at 30°C for 1 hour, then cooled to -15°C in 2 hours, and stirred at this temperature for 1 hour. The product was recovered as a white crystalline solid and washed with isopropyl alcohol. The wet product was dried at 35°C (30-40°C) under a nitrogen stream.

[0084] In one example, a solution of APC free base (16.9 g, 0.0871 mol) was diluted with isopropyl alcohol (43.8 g) and warmed to 30°C. 37% aqueous HCl (4.51 g, 0.0458 mol, 0.525. mol equiv) was added dropwise, keeping the temperature $\leq$ 35°C. APC hydrochloride (22 mg) was added to the clear solution. The solution became turbid almost immediately. After 15 minutes a suspension was obtained. No crystallization around the reactor walls occurred. Further 37% aqueous HCl (4.51 g, 0.0458 mol, 0.525. mol equiv) was added dropwise, keeping the temperature $\leq$ 35°C. After charging the suspension was stirred at 30°C for 1 hour, cooled to -15°C in 2 hours and stirred 2 hours at this temperature. The product was recovered by filtration, washed with IPA (16.7 g) and dried at 35°C, 30-50 mbar for 17 hours under air flow. 16.87 g product was recovered (yield 83.96%). The crystallization occurred very smoothly. The product was a white crystalline powder. No 2-CP was detected.

[0085] Two additional batches were prepared using the same protocol. In both batches 2-CP levels in the product were less than 1 ppm.

[0086] The foregoing is illustrative of the present invention, and is not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein. All publications, patent applications, patents, patent publications, and any other references cited herein are incorporated by reference in their entireties for the teachings relevant to the sentence and/or paragraph in which the reference is presented.

1/5

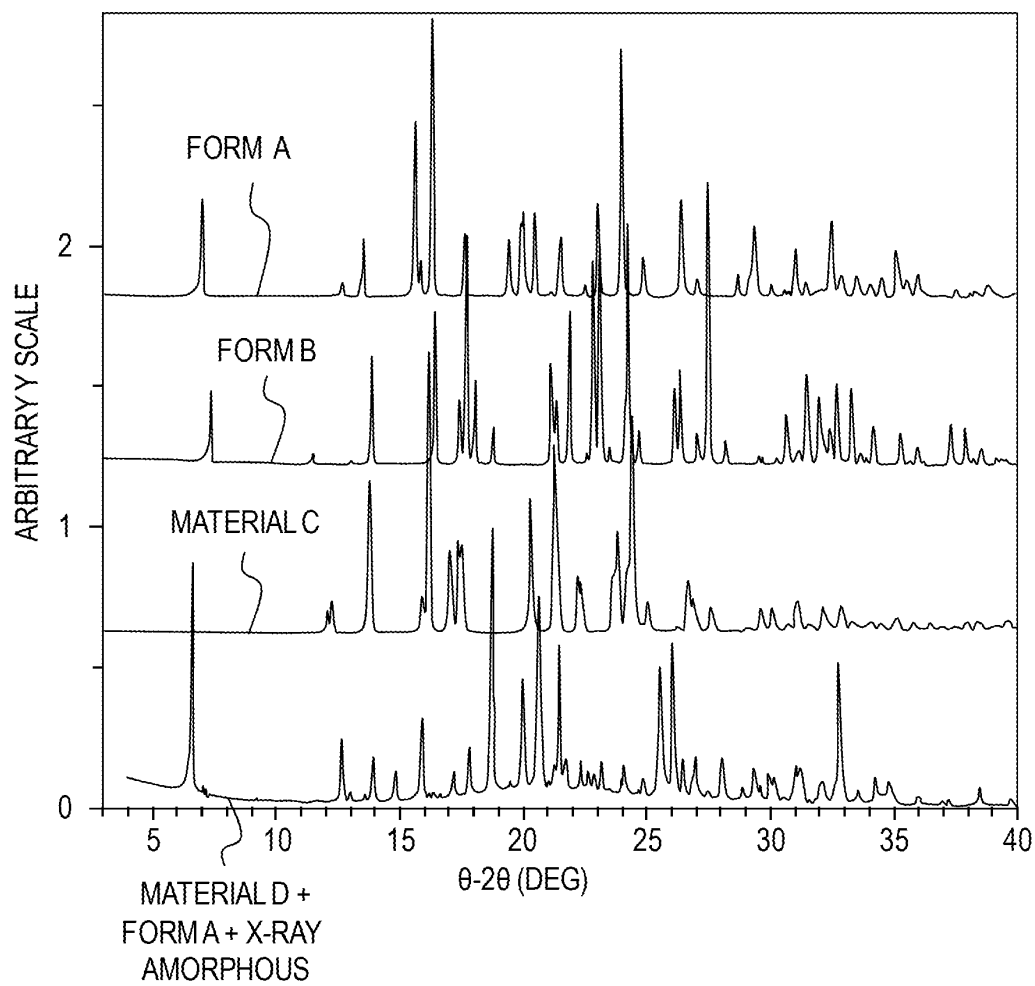


FIG. 1

2/5

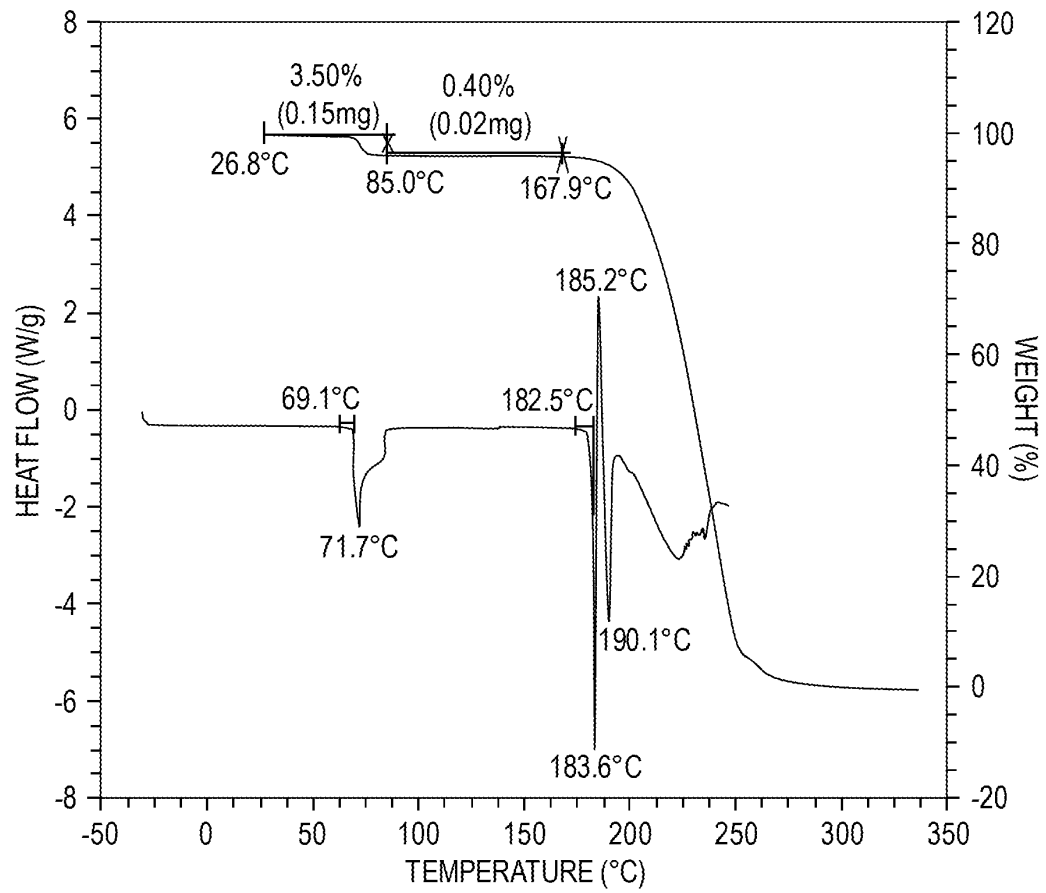


FIG. 2

3/5

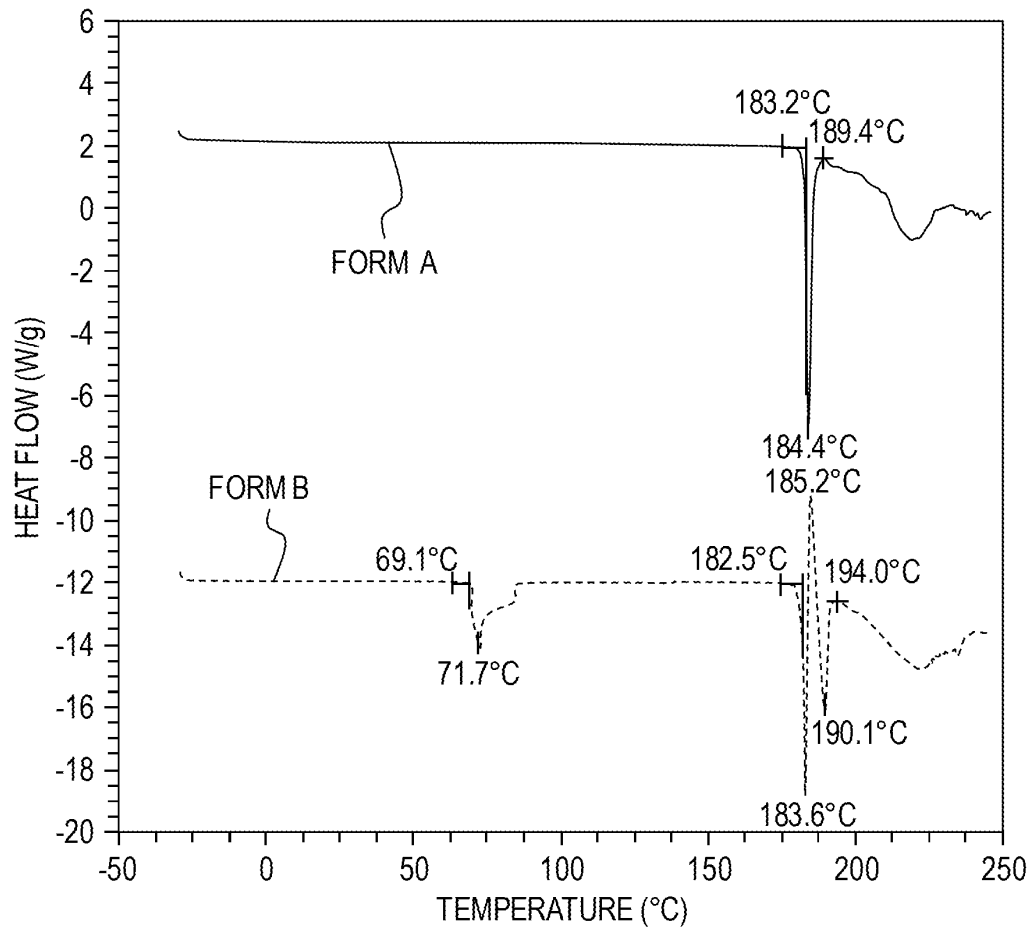


FIG. 3

4/5

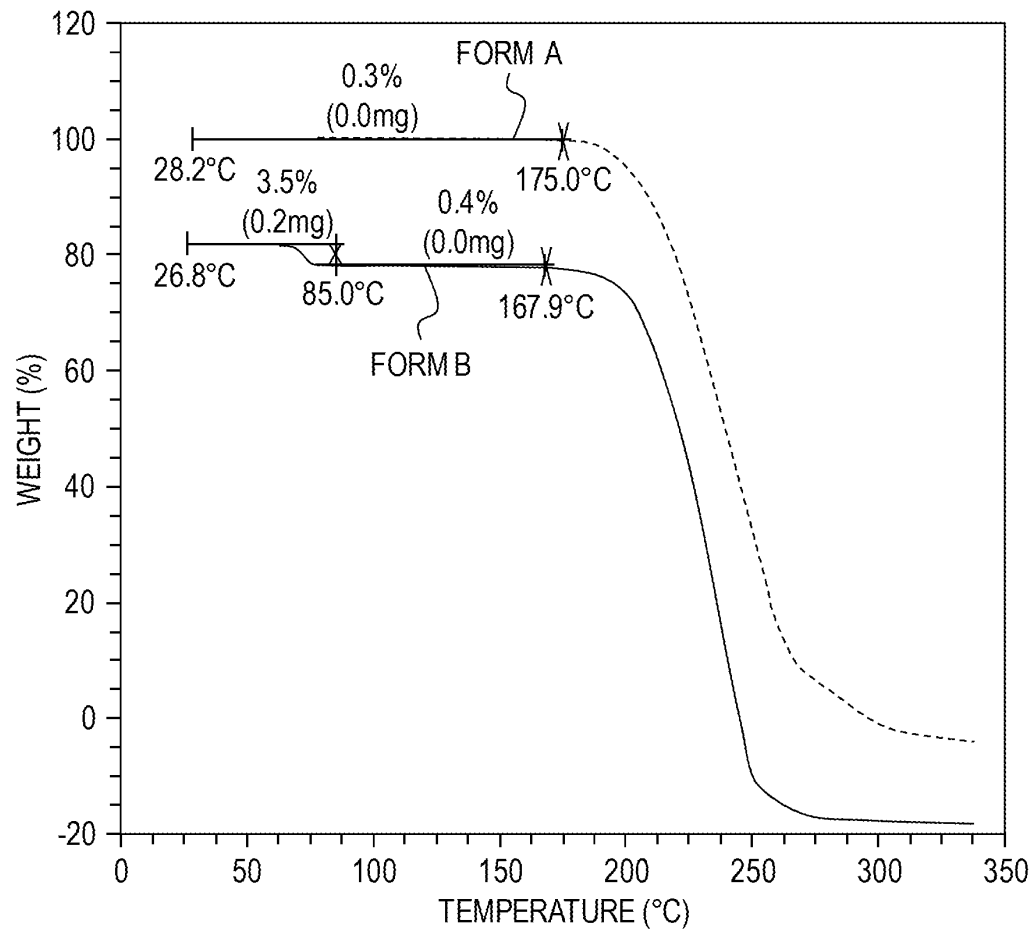
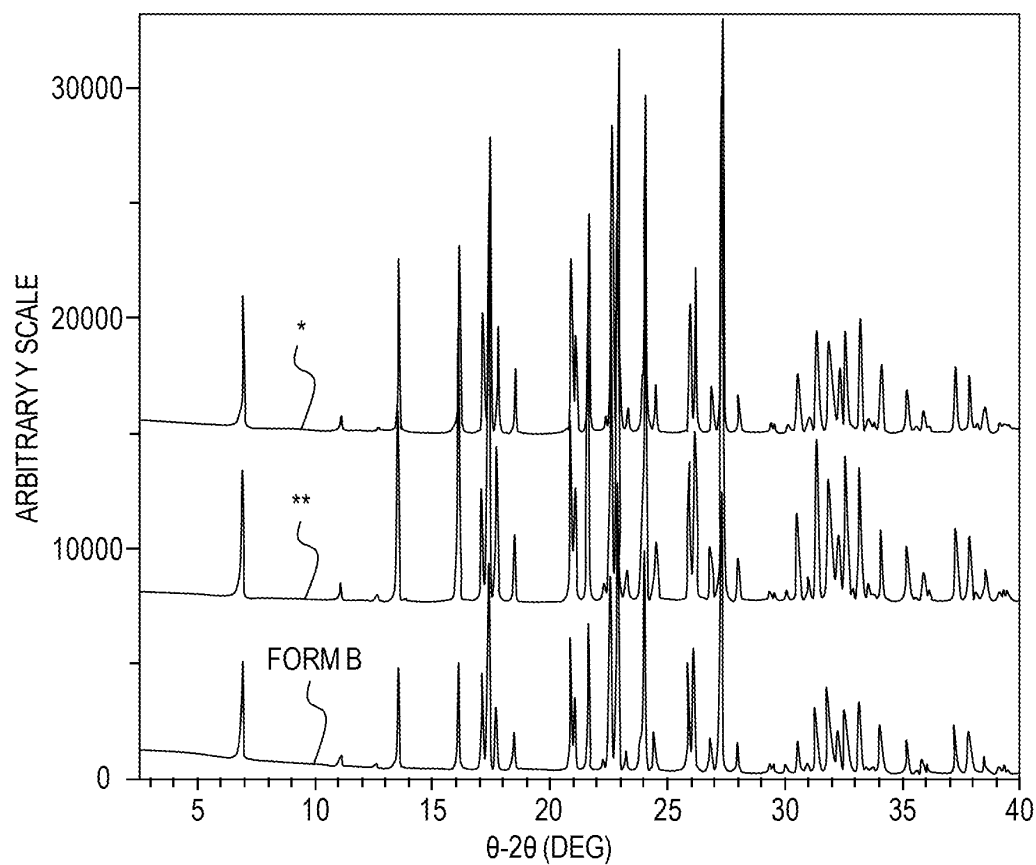


FIG. 4

5/5



*ISOLATED FROM 24 HOUR SLURRY IN WATER:
ACN (5:95 V:V), CONCENTRATION ~98 mg/ml

**ISOLATED FROM 24 HOUR SLURRY IN WATER:
ACN (5:95 V:V), CONCENTRATION ~51 mg/ml

FIG. 5

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.

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

Title of Invention	Solvate Form of (R)-2-amino-3-phenylpropyl carbamate
-------------------------------	--

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/US2017/050233
filed on September 6, 2017.

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: Fionn Hurley Date (Optional) : _____
Signature: *Fionn Hurley*

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

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

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

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		
	Filing Date		
	First Named Inventor	Fionn Hurley	
	Art Unit		
	Examiner Name		
	Attorney Docket Number	1258.19CT	

U.S.PATENTS						
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	5955499		1999-09-21	CHOI, et al.	
	2	6350596		2002-02-26	IOMANTAS YURGIS ANTA, et al.	
	3	9403761		2016-08-02	KANG YOUNG-SOON, et al.	
	4	9604917		2017-03-28	AHNAOU ABDALLAH, et al.	
	5	9649291		2017-05-16	KHAYRALLAH, et al.	

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS						
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	20050080268		2005-04-14	CHOI, et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		
	Filing Date		
	First Named Inventor	Fionn Hurley	
	Art Unit		
	Examiner Name		
	Attorney Docket Number	1258.19CT	

	2	20100331332		2010-12-30	LEE SUNG JAMES, et al.	
	3	20140350098		2014-11-27	AHNAOU ABDALLAH, et al.	
	4	20150246874		2015-09-03	KANG YOUNG-SOON, et al.	
	5	20160081970		2016-03-24	KHAYRALLAH, et al.	

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ²	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T ⁵
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
	1	"Extended European Search Report corresponding to European Application No. 17849432.4 dated April 9, 2020"	☐
	2	"International Preliminary Report on Patentability corresponding to International Application No. PCT/US2017/050233 mailed March 21, 2019"	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		
	Filing Date		
	First Named Inventor	Fionn Hurley	
	Art Unit		
	Examiner Name		
	Attorney Docket Number	1258.19CT	

	3	"International Search Report and Written Opinion corresponding to International Application No. PCT/US2017/050233 mailed November 13, 2017"	☒
	4	"International Search Report corresponding to Singapore Application No. 11201901998W dated May 2, 2020"	☐
	5	"Written Opinion corresponding to Singapore Application No. 11201901998W dated May 6, 2020"	☐
	6	Phenprobamate, Wikipedia, https://en.wikipedia.org/wiki/Phenprobamate , last edited April 2, 2016, accessed September 24, 2019	☐

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

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.

Attorney Docket No. 1258.19CT

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Fionn Hurley

Application No.: To Be Assigned

Filing Date: Concurrently Herewith

For: Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses thereof

Date: November 6, 2020

Commissioner for Patents
Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT COVER LETTER

Sir:

Attached is an Information Disclosure Statement listing of documents previously of record in parent Application No. 16/331,069 filed on March 6, 2019. As the benefit of this application is claimed under 35 U.S.C. § 120, no copies need to be furnished in accordance with 37 C.F.R. § 1.98(d); however, copies will be furnished on request.

- ☒ In accordance with **37 CFR 1.97(b)**, the information disclosure statement is being filed:
- ☐ (1) within three months of the filing date of a national application other than a continued prosecution application under §1.53(d);
 - ☐ (2) within three months of the date of entry of the national stage as set forth in §1.491 in an international application;
 - ☒ (3) before the mailing of a first Office Action on the merits; or
 - ☐ (4) before the mailing of a first Office Action after the filing of a request for continued examination under §1.114.

☐ In accordance with **37 CFR 1.97(c)**, the information disclosure statement is being filed after the period specified in 37 CFR 1.97(b) above, but before the mailing date of any of a final action under §1.113, a notice of allowance under §1.311, or an action that otherwise closes prosecution in the application, and is accompanied by one of the following:

- ☐ (1) The statement specified under **37 CFR 1.97(e)**, as follows:
- ☐ 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; or
 - ☐ 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 §1.56(c) more than three months prior to the filing of the information disclosure statement; or
- ☐ (2) The fee set forth in §1.17(p);

In re: Fionn Hurley
Application No.: To Be Assigned
Filing Date: Concurrently Herewith
Page 2 of 2

☐ In accordance with **37 CFR 1.97(d)**, the information disclosure statement is being filed after the period specified in 37 CFR 1.97(c) above, but on or before payment of the issue fee, and is accompanied by **both** of the following:

☐ (1) The statement specified under **37 CFR 1.97(e)**, as follows:

☐ 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; **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 §1.56(c) more than three months prior to the filing of the information disclosure statement; **and**

☐ (2) The fee set forth in §1.17(p);

In accordance with **37 CFR 1.97(g)**, the information disclosure statement shall not be construed as a representation that a search has been made.

In accordance with **37 CFR 1.97(h)**, the information disclosure statement shall not be construed to be an admission that the information cited in the statement is, or is considered to be, material to patentability as defined in §1.56(b).

☐ The Director is hereby authorized to charge the fee specified in 37 C.F.R. § 1.17(p), and any fee deficiency or credit any overpayment, to Deposit Account No. 50-0220; **or**

☒ No fee is believed due. However, the Director is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-0220.

Respectfully submitted,



Robert A. Schwartzman, Ph.D.
Registration No. 50,211
Attorney for Applicant(s)

Customer Number 129932

Myers Bigel, P.A.
P.O. Box 37428, Raleigh, NC 27627
919-854-1400
919-854-1401 (Fax)

CERTIFICATION OF TRANSMISSION

I hereby certify that this correspondence is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4) to the U.S. Patent and Trademark Office on November 6, 2020.

Signature: /Betty-Lou Medlin/
Name: Betty-Lou Medlin

Electronic Patent Application Fee Transmittal				
Application Number:				
Filing Date:				
Title of Invention:		Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses thereof		
First Named Inventor/Applicant Name:		Fionn Hurley		
Filer:		Robert Andrew Schwartzman/Betty-Lou Medlin		
Attorney Docket Number:		1258.19CT		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	320	320
UTILITY SEARCH FEE	1111	1	700	700
UTILITY EXAMINATION FEE	1311	1	800	800
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				1820

Electronic Acknowledgement Receipt	
EFS ID:	41056045
Application Number:	17091222
International Application Number:	
Confirmation Number:	6803
Title of Invention:	Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses thereof
First Named Inventor/Applicant Name:	Fionn Hurley
Customer Number:	129932
Filer:	Robert Andrew Schwartzman/Betty-Lou Medlin
Filer Authorized By:	Robert Andrew Schwartzman
Attorney Docket Number:	1258.19CT
Receipt Date:	06-NOV-2020
Filing Date:	
Time Stamp:	13:06:13
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$1820
RAM confirmation Number	E2020A6D06445368
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	Transmittal of New Application	1258-19CT_Transmittal.pdf	336520	no	1
			09a2d68107aacef7564470d367690ba47e291863		
Warnings:					
Information:					
2	Power of Attorney	1258-19CT_Jazz_POA.pdf	661614	no	2
			84cb2cf0f12465112e57ca1f9cd21e5534cf2bab		
Warnings:					
Information:					
3	Power of Attorney	1258-19CT_SK_POA.pdf	382913	no	2
			56eb6269598ea26909fb854a4c2118728efe4e6e		
Warnings:					
Information:					
4	Application Data Sheet	1258-19CT_ADS.pdf	1438261	no	7
			40ef295fef0265bc6a93333489269f5523be4498		
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
5		1258-19CT_PreliminaryAmendment.pdf	951287	yes	4
			6cd3e94051ff916c82231823d8b402325b77b914		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Applicant Arguments/Remarks Made in an Amendment		4	4	
	Claims		3	3	

	Specification		2	2	
	Preliminary Amendment		1	1	
Warnings:					
Information:					
6		1258-19CT_Specification.pdf	6313609 466be93d952b54c783ec82e72930a58fcd4bb9f2	yes	20
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Abstract		20	20	
	Claims		17	19	
	Specification		1	16	
Warnings:					
Information:					
7	Drawings-only black and white line drawings	1258-19CT_Figs.pdf	590743 d816fca82e30b7e147e74f43e17abc2a3db10e9d	no	5
Warnings:					
Information:					
8	Oath or Declaration filed	1258-19CT_Declaration.pdf	363434 4715fdd52c03011592f7f709d3ef7207aefe533c	no	1
Warnings:					
Information:					
9		1258-19CT_IDS.pdf	1169743 73f2661736c4c7618fcd216498dd2b6cf953470	yes	5
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Information Disclosure Statement (IDS) Form (SB08)		3	5	
	Transmittal Letter		1	2	

Warnings:					
Information:					
10	Fee Worksheet (SB06)	fee-info.pdf	35527	no	2
			3afb7dbcbfd8e7f0c51fe86c817f446df60c34de		
Warnings:					
Information:					
Total Files Size (in bytes):			12243651		
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. <u>New Applications Under 35 U.S.C. 111</u> 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. <u>National Stage of an International Application under 35 U.S.C. 371</u> 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. <u>New International Application Filed with the USPTO as a Receiving Office</u> 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
17/091,222	11/06/2020	1629	1820	1258.19CT	8	1

CONFIRMATION NO. 6803

129932

Myers Bigel, P.A.
P.O. Box 37428
Raleigh, NC 27627

FILING RECEIPT



0000000121403098

Date Mailed: 11/18/2020

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)

Fionn Hurley, Baldoyle, IRELAND;

Applicant(s)

Jazz Pharmaceuticals Ireland Limited, Dublin, IRELAND;
SK Biopharmaceuticals Co., Ltd., Seongnam-si, KOREA, REPUBLIC OF;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 16/331,069 03/06/2019 PAT 10829443
which is a 371 of PCT/US2017/050233 09/06/2017
which claims benefit of 62/383,822 09/06/2016

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

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

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 11/17/2020

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 17/091,222**

Projected Publication Date: 02/25/2021

Non-Publication Request: No

Early Publication Request: No
Title

Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses thereof

Preliminary Class

514

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

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific

page 2 of 4

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 Assets Control, 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).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor 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.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875						Application or Docket Number 17/091,222				
APPLICATION AS FILED - PART I										
(Column 1)		(Column 2)		SMALL ENTITY		OTHER THAN SMALL ENTITY				
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)			
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	320			
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	700			
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	800			
TOTAL CLAIMS (37 CFR 1.16(j))	8	minus 20 = *			OR	x 100 =	0.00			
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1	minus 3 = *			OR	x 480 =	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		TOTAL	1820			
APPLICATION AS AMENDED - PART II										
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OTHER THAN SMALL ENTITY		
AMENDMENT A		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=	x	=	OR	x	=
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x	=	OR	x	=
	Application Size Fee (37 CFR 1.16(s))							OR		
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
TOTAL ADD'L FEE								OR	TOTAL ADD'L FEE	
AMENDMENT B		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=	x	=	OR	x	=
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x	=	OR	x	=
	Application Size Fee (37 CFR 1.16(s))							OR		
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
TOTAL ADD'L FEE								OR	TOTAL ADD'L FEE	
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3. ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.										



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	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/091,222	11/06/2020	Fionn Hurley	1258.19CT

129932
Myers Bigel, P.A.
P.O. Box 37428
Raleigh, NC 27627

CONFIRMATION NO. 6803
IMPROPER CPOA LETTER



Date Mailed: 11/18/2020

NOTICE REGARDING POWER OF ATTORNEY

This is in response to the power of attorney filed 11/06/2020. The power of attorney in this application is not accepted for the reason(s) listed below:

- The power of attorney has not been accepted because the party who is giving power has not been identified. Power of attorney may only be signed by the applicant for patent (37 CFR 1.42) or the patent owner. A party who is not the applicant must become the applicant in accordance with 37 CFR 1.46(c) and appoint any power of attorney in compliance with 37 CFR 3.71 and 3.73. For a reissue application, reexamination proceeding, or supplemental examination proceeding, a patent owner who was not the applicant under 37 CFR 1.46 must appoint any power of attorney in compliance with 37 CFR 3.71 and 3.73. See 37 CFR 1.32(b)(4).

/ckhambay/

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



TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

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

Application Number	17/091,222
Filing Date	11/06/2020
First Named Inventor	Jennifer Leigh Nelson
Title	Solvate Form of (R)-2-amino-3-phenylpropyl carbamate
Art Unit	1629
Examiner Name	
Attorney Docket Number	1258.19CT

SIGNATURE of Applicant or Patent Practitioner

Signature	/Robert A. Schwartzman/	Date (Optional)	November 24, 2020
Name	Robert A. Schwartzman, Ph.D.	Registration Number	50,211
Title (if Applicant is a juristic entity)	Attorney for Applicant		
Applicant Name (if Applicant is a juristic entity)	SK Biopharmaceuticals Co., Ltd.		

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.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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

Doc Code: PA..

Document Description: Power of Attorney

PTO/AIA/82B (07-13)

Approved for use through 11/30/2014. OMB 0651-0051

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

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☒ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above:

129932

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☒ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

Firm or Individual Name				
Address				
City		State		Zip
Country				
Telephone		Email		

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

SK Biopharmaceuticals Co., Ltd.

- ☐ Inventor or Joint Inventor (title not required below)
- ☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)
- ☒ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)
- ☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	<i>Jaegu Shim</i>	Date (Optional)	Dec. 4, 2015
Name	JAEGU SHIM		
Title	2P group leader		

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 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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

Electronic Acknowledgement Receipt	
EFS ID:	41218853
Application Number:	17091222
International Application Number:	
Confirmation Number:	6803
Title of Invention:	Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses thereof
First Named Inventor/Applicant Name:	Fionn Hurley
Customer Number:	129932
Filer:	Robert Andrew Schwartzman/Betty-Lou Medlin
Filer Authorized By:	Robert Andrew Schwartzman
Attorney Docket Number:	1258.19CT
Receipt Date:	24-NOV-2020
Filing Date:	06-NOV-2020
Time Stamp:	18:19:04
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	1258-19CT_JazzPOA.pdf	201600	no	2
			df68418bc0f60e9707403142ab7f33ae23ba4faa		

Warnings:

Information:					
2	Power of Attorney	1258-19CT_SK_POA.pdf	181942	no	2
			de46fdee505c61d7c355be83b65ef167f8cd b9e1		
Warnings:					
Information:					
Total Files Size (in bytes):			383542		
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. <u>New Applications Under 35 U.S.C. 111</u> 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. <u>National Stage of an International Application under 35 U.S.C. 371</u> 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. <u>New International Application Filed with the USPTO as a Receiving Office</u> 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.					

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

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

Application Number	17/091,222
Filing Date	11/06/2020
First Named Inventor	Jennifer Leigh Nelson
Title	Solvate Form of (R)-2-amino-3-phenylpropyl carbamate
Art Unit	1629
Examiner Name	
Attorney Docket Number	1258.19CT

SIGNATURE of Applicant or Patent Practitioner

Signature	/Robert A. Schwartzman/	Date (Optional)	November 24, 2020
Name	Robert A. Schwartzman, Ph.D.	Registration Number	50,211
Title (if Applicant is a juristic entity)	Attorney for Applicant		
Applicant Name (if Applicant is a juristic entity)	Jazz Pharmaceuticals Ireland Limited		

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.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

- ☒ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 129932
- OR
- ☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

- ☒ The address associated with the above-mentioned Customer Number
- OR
- ☐ The address associated with Customer Number:
- OR

Firm or Individual Name				
Address				
City		State		Zip
Country				
Telephone		Email		

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

Jazz Pharmaceuticals Ireland Limited

- ☐ Inventor or Joint Inventor (title not required below)
- ☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)
- ☒ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)
- ☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	<u>Bridget O'Brien</u>	Date (Optional)	<u>4 MARCH 2020</u>
Name	<u>BRIDGET O'BRIEN</u>		
Title	<u>DIRECTOR</u>		

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

☒ Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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



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	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/091,222	11/06/2020	Fionn Hurley	1258.19CT

CONFIRMATION NO. 6803

POA ACCEPTANCE LETTER

129932
Myers Bigel, P.A.
P.O. Box 37428
Raleigh, NC 27627



Date Mailed: 11/30/2020

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 11/24/2020.

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

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

/tnguyen/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		17091222	
	Filing Date		2020-11-06	
	First Named Inventor	Fionn Hurley		
	Art Unit	1629		
	Examiner Name			
	Attorney Docket Number	1258.19CT		

U.S. PATENTS						
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					

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S. PATENT APPLICATION PUBLICATIONS						
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.

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ²	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T ⁵
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		17091222
	Filing Date		2020-11-06
	First Named Inventor	Fionn Hurley	
	Art Unit	1629	
	Examiner Name		
	Attorney Docket Number	1258.19CT	

1	"Office Action corresponding to Indian Application No. 201917009658 mailed November 24, 2020"	☒
If you wish to add additional non-patent literature document citation information please click the Add button		
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.		

Electronic Acknowledgement Receipt	
EFS ID:	41591665
Application Number:	17091222
International Application Number:	
Confirmation Number:	6803
Title of Invention:	Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses thereof
First Named Inventor/Applicant Name:	Fionn Hurley
Customer Number:	129932
Filer:	Robert Andrew Schwartzman/Betty-Lou Medlin
Filer Authorized By:	Robert Andrew Schwartzman
Attorney Docket Number:	1258.19CT
Receipt Date:	08-JAN-2021
Filing Date:	06-NOV-2020
Time Stamp:	12:34:22
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		1258-19CT_IDS.pdf	103782	yes	4
			1cecf0aedfb1303ecfa183e0169401604964e30		

	Multipart Description/PDF files in .zip description								
	Document Description		Start	End					
	Transmittal Letter		1	2					
	Information Disclosure Statement (IDS) Form (SB08)		3	4					
Warnings:									
Information:									
2	Other Reference-Patent/App/Search documents	1258-19IN_112420_OA.pdf	152612	no	6				
			fa57861e1165132b702fd999f1babf067c3533fe						
Warnings:									
Information:									
Total Files Size (in bytes):			256394						
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. <u>New Applications Under 35 U.S.C. 111</u> 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. <u>National Stage of an International Application under 35 U.S.C. 371</u> 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. <u>New International Application Filed with the USPTO as a Receiving Office</u> 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.									

Attorney Docket No. 1258.19CT

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Fionn Hurley

Confirmation No.: 6803

Application No.: 17/091,222

Group Art Unit: 1629

Filing Date: November 6, 2020

For: Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses thereof

Date: January 8, 2021

Commissioner for Patents
Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT COVER LETTER

Sir:

Attached is an Information Disclosure Statement listing of documents, together with a copy of any listed foreign patent document and/or non-patent literature. A copy of any listed U.S. patent and/or U.S. patent application publication is not provided herewith in accordance with 37 C.F.R. § 1.98(a)(2)(ii).

- ☒ In accordance with **37 CFR 1.97(b)**, the information disclosure statement is being filed:
- ☐ (1) within three months of the filing date of a national application other than a continued prosecution application under §1.53(d);
 - ☐ (2) within three months of the date of entry of the national stage as set forth in §1.491 in an international application;
 - ☒ (3) before the mailing of a first Office Action on the merits; or
 - ☐ (4) before the mailing of a first Office Action after the filing of a request for continued examination under §1.114.

☐ In accordance with **37 CFR 1.97(c)**, the information disclosure statement is being filed after the period specified in 37 CFR 1.97(b) above, but before the mailing date of any of a final action under §1.113, a notice of allowance under §1.311, or an action that otherwise closes prosecution in the application, and is accompanied by one of the following:

- ☐ (1) The statement specified under **37 CFR 1.97(e)**, as follows:
- ☐ 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; or
 - ☐ 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 §1.56(c) more than three months prior to the filing of the information disclosure statement; or
- ☐ (2) The fee set forth in §1.17(p);

☐ In accordance with **37 CFR 1.97(d)**, the information disclosure statement is being filed after the period specified in 37 CFR 1.97(c) above, but on or before payment of the issue fee, and is accompanied by **both** of the following:

☐ (1) The statement specified under **37 CFR 1.97(e)**, as follows:

☐ 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; **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 §1.56(c) more than three months prior to the filing of the information disclosure statement; **and**

☐ (2) The fee set forth in §1.17(p);

In accordance with **37 CFR 1.97(g)**, the information disclosure statement shall not be construed as a representation that a search has been made.

In accordance with **37 CFR 1.97(h)**, the information disclosure statement shall not be construed to be an admission that the information cited in the statement is, or is considered to be, material to patentability as defined in §1.56(b).

☐ The Director is hereby authorized to charge the fee specified in 37 C.F.R. § 1.17(p), and any fee deficiency or credit any overpayment, to Deposit Account No. 50-0220; **or**

☒ No fee is believed due. However, the Director is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-0220.

Respectfully submitted,



Robert A. Schwartzman, Ph.D.
Registration No. 50,211
Attorney for Applicant(s)

Customer Number 129932
Myers Bigel, P.A.
P.O. Box 37428, Raleigh, NC 27627
919-854-1400
919-854-1401 (Fax)

CERTIFICATION OF TRANSMISSION

I hereby certify that this correspondence is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4) to the U.S. Patent and Trademark Office on January 8, 2021.

Signature: /Betty-Lou Medlin/
Name: Betty-Lou Medlin



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	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/091,222	11/06/2020	Fionn Hurley	1258.19CT

CONFIRMATION NO. 6803

129932
Myers Bigel, P.A.
P.O. Box 37428
Raleigh, NC 27627

PUBLICATION NOTICE



OC000000123658015

Title:Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses thereof

Publication No.US-2021-0053912-A1

Publication Date:02/25/2021

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		17091222	
	Filing Date		2020-11-06	
	First Named Inventor	Fionn Hurley		
	Art Unit	1629		
	Examiner Name			
	Attorney Docket Number	1258.19CT		

U.S. PATENTS						
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					

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S. PATENT APPLICATION PUBLICATIONS						
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.

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ²	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T ⁵
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		17091222
	Filing Date		2020-11-06
	First Named Inventor	Fionn Hurley	
	Art Unit	1629	
	Examiner Name		
	Attorney Docket Number	1258.19CT	

1	"Office Action corresponding to Indonesian Application No. PID201902732 March 18, 2021"	☐
If you wish to add additional non-patent literature document citation information please click the Add button		
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.		

Electronic Acknowledgement Receipt	
EFS ID:	42348427
Application Number:	17091222
International Application Number:	
Confirmation Number:	6803
Title of Invention:	Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses thereof
First Named Inventor/Applicant Name:	Fionn Hurley
Customer Number:	129932
Filer:	Robert Andrew Schwartzman/Betty-Lou Medlin
Filer Authorized By:	Robert Andrew Schwartzman
Attorney Docket Number:	1258.19CT
Receipt Date:	01-APR-2021
Filing Date:	06-NOV-2020
Time Stamp:	17:35:14
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		1258-19CT_IDS.pdf	103364	yes	4
			4e26732a267518e4a20b26bb30d7dfbafb0c7c22		

	Multipart Description/PDF files in .zip description								
	Document Description		Start	End					
	Transmittal Letter		1	2					
	Information Disclosure Statement (IDS) Form (SB08)		3	4					
Warnings:									
Information:									
2	Other Reference-Patent/App/Search documents	1258-19ID_031821-OA.pdf	131889	no	3				
			95dec9bc06c09407e80736cc56a36dc1531908d9						
Warnings:									
Information:									
Total Files Size (in bytes):			235253						
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. <u>New Applications Under 35 U.S.C. 111</u> 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. <u>National Stage of an International Application under 35 U.S.C. 371</u> 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. <u>New International Application Filed with the USPTO as a Receiving Office</u> 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.									

Attorney Docket No. 1258.19CT

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Fionn Hurley

Confirmation No.: 6803

Application No.: 17/091,222

Group Art Unit: 1629

Filing Date: November 6, 2020

For: Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses thereof

Date: April 1, 2021

Commissioner for Patents
Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT COVER LETTER

Sir:

Attached is an Information Disclosure Statement listing of documents, together with a copy of any listed foreign patent document and/or non-patent literature. A copy of any listed U.S. patent and/or U.S. patent application publication is not provided herewith in accordance with 37 C.F.R. § 1.98(a)(2)(ii).

☒ In accordance with **37 CFR 1.97(b)**, the information disclosure statement is being filed:

- ☐ (1) within three months of the filing date of a national application other than a continued prosecution application under §1.53(d);
- ☐ (2) within three months of the date of entry of the national stage as set forth in §1.491 in an international application;
- ☒ (3) before the mailing of a first Office Action on the merits; or
- ☐ (4) before the mailing of a first Office Action after the filing of a request for continued examination under §1.114.

☐ In accordance with **37 CFR 1.97(c)**, the information disclosure statement is being filed after the period specified in 37 CFR 1.97(b) above, but before the mailing date of any of a final action under §1.113, a notice of allowance under §1.311, or an action that otherwise closes prosecution in the application, and is accompanied by one of the following:

☐ (1) The statement specified under **37 CFR 1.97(e)**, as follows:

☐ 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; or

☐ 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 §1.56(c) more than three months prior to the filing of the information disclosure statement; or

☐ (2) The fee set forth in §1.17(p);

☐ In accordance with **37 CFR 1.97(d)**, the information disclosure statement is being filed after the period specified in 37 CFR 1.97(c) above, but on or before payment of the issue fee, and is accompanied by **both** of the following:

☐ (1) The statement specified under **37 CFR 1.97(e)**, as follows:

☐ 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; **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 §1.56(c) more than three months prior to the filing of the information disclosure statement; **and**

☐ (2) The fee set forth in §1.17(p);

In accordance with **37 CFR 1.97(g)**, the information disclosure statement shall not be construed as a representation that a search has been made.

In accordance with **37 CFR 1.97(h)**, the information disclosure statement shall not be construed to be an admission that the information cited in the statement is, or is considered to be, material to patentability as defined in §1.56(b).

☐ The Director is hereby authorized to charge the fee specified in 37 C.F.R. § 1.17(p), and any fee deficiency or credit any overpayment, to Deposit Account No. 50-0220; **or**

☒ No fee is believed due. However, the Director is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-0220.

Respectfully submitted,



Robert A. Schwartzman, Ph.D.
Registration No. 50,211
Attorney for Applicant(s)

Customer Number 129932
Myers Bigel, P.A.
P.O. Box 37428, Raleigh, NC 27627
919-854-1400
919-854-1401 (Fax)

CERTIFICATION OF TRANSMISSION

I hereby certify that this correspondence is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4) to the U.S. Patent and Trademark Office on April 1, 2021.

Signature: /Betty-Lou Medlin/
Name: Betty-Lou Medlin

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		17091222	
	Filing Date		2020-11-06	
	First Named Inventor	Fionn Hurley		
	Art Unit	1629		
	Examiner Name			
	Attorney Docket Number	1258.19CT		

U.S. PATENTS								
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							
If you wish to add additional U.S. Patent citation information please click the Add button.								
U.S. PATENT APPLICATION PUBLICATIONS								
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.								
FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ²	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T ⁵
	1							☐
If you wish to add additional Foreign Patent Document citation information please click the Add button								
NON-PATENT LITERATURE DOCUMENTS								
Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.						T ⁵

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		17091222
	Filing Date		2020-11-06
	First Named Inventor	Fionn Hurley	
	Art Unit	1629	
	Examiner Name		
	Attorney Docket Number	1258.19CT	

1	"Examination Report corresponding to European Application No. 17849432.4 dated May 11, 2021"	☐
If you wish to add additional non-patent literature document citation information please click the Add button		
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.		

Attorney Docket No. 1258.19CT

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Fionn Hurley

Confirmation No.: 6803

Application No.: 17/091,222

Group Art Unit: 1629

Filing Date: November 6, 2020

For: Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses thereof

Date: May 18, 2021

Commissioner for Patents
Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT COVER LETTER

Sir:

Attached is an Information Disclosure Statement listing of documents, together with a copy of any listed foreign patent document and/or non-patent literature. A copy of any listed U.S. patent and/or U.S. patent application publication is not provided herewith in accordance with 37 C.F.R. § 1.98(a)(2)(ii).

☒ In accordance with **37 CFR 1.97(b)**, the information disclosure statement is being filed:

- ☐ (1) within three months of the filing date of a national application other than a continued prosecution application under §1.53(d);
- ☐ (2) within three months of the date of entry of the national stage as set forth in §1.491 in an international application;
- ☒ (3) before the mailing of a first Office Action on the merits; or
- ☐ (4) before the mailing of a first Office Action after the filing of a request for continued examination under §1.114.

☐ In accordance with **37 CFR 1.97(c)**, the information disclosure statement is being filed after the period specified in 37 CFR 1.97(b) above, but before the mailing date of any of a final action under §1.113, a notice of allowance under §1.311, or an action that otherwise closes prosecution in the application, and is accompanied by one of the following:

☐ (1) The statement specified under **37 CFR 1.97(e)**, as follows:

☐ 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; or

☐ 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 §1.56(c) more than three months prior to the filing of the information disclosure statement; or

☐ (2) The fee set forth in §1.17(p);

☐ In accordance with **37 CFR 1.97(d)**, the information disclosure statement is being filed after the period specified in 37 CFR 1.97(c) above, but on or before payment of the issue fee, and is accompanied by **both** of the following:

☐ (1) The statement specified under **37 CFR 1.97(e)**, as follows:

☐ 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; **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 §1.56(c) more than three months prior to the filing of the information disclosure statement; **and**

☐ (2) The fee set forth in §1.17(p);

In accordance with **37 CFR 1.97(g)**, the information disclosure statement shall not be construed as a representation that a search has been made.

In accordance with **37 CFR 1.97(h)**, the information disclosure statement shall not be construed to be an admission that the information cited in the statement is, or is considered to be, material to patentability as defined in §1.56(b).

☐ The Director is hereby authorized to charge the fee specified in 37 C.F.R. § 1.17(p), and any fee deficiency or credit any overpayment, to Deposit Account No. 50-0220; **or**

☒ No fee is believed due. However, the Director is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-0220.

Respectfully submitted,



Robert A. Schwartzman, Ph.D.
Registration No. 50,211
Attorney for Applicant(s)

Customer Number 129932
Myers Bigel, P.A.
P.O. Box 37428, Raleigh, NC 27627
919-854-1400
919-854-1401 (Fax)

CERTIFICATION OF TRANSMISSION

I hereby certify that this correspondence is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4) to the U.S. Patent and Trademark Office on May 18, 2021.

Signature: /Betty-Lou Medlin/
Name: Betty-Lou Medlin

Electronic Acknowledgement Receipt	
EFS ID:	42750561
Application Number:	17091222
International Application Number:	
Confirmation Number:	6803
Title of Invention:	Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses thereof
First Named Inventor/Applicant Name:	Fionn Hurley
Customer Number:	129932
Filer:	Robert Andrew Schwartzman/Betty-Lou Medlin
Filer Authorized By:	Robert Andrew Schwartzman
Attorney Docket Number:	1258.19CT
Receipt Date:	18-MAY-2021
Filing Date:	06-NOV-2020
Time Stamp:	17:44:08
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		1258-19CT_IDS.pdf	103834	yes	4
			c/4898323aacdacea69f561d19285e5f68a5a38c1		

	Multipart Description/PDF files in .zip description								
	Document Description		Start	End					
	Information Disclosure Statement (IDS) Form (SB08)		3	4					
	Transmittal Letter		1	2					
Warnings:									
Information:									
2	Other Reference-Patent/App/Search documents	1258-19EP_051121-OA.pdf	199887	no	6				
			3cf0b4562a33c410c0304663128a640e730bc0c						
Warnings:									
Information:									
Total Files Size (in bytes):			303721						
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. <u>New Applications Under 35 U.S.C. 111</u> 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. <u>National Stage of an International Application under 35 U.S.C. 371</u> 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. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.									

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		17091222	
	Filing Date		2020-11-06	
	First Named Inventor	Fionn Hurley		
	Art Unit	1629		
	Examiner Name			
	Attorney Docket Number	1258.19CT		

U.S. PATENTS								
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							
If you wish to add additional U.S. Patent citation information please click the Add button.								
U.S. PATENT APPLICATION PUBLICATIONS								
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	2015025136	A1	2015-01-22	KHAYRALLAH, et al.			
If you wish to add additional U.S. Published Application citation information please click the Add button.								
FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number ³	Country Code ²	Kind Code ⁴	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T ⁵
	1	9607637	WO	A1	1996-03-14	YUKONG LIMITED		☐
	2	H09503231	JP	A	1997-03-31			☐
	3	2005033064	WO	A1	2005-04-14	SK CORPORATION		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		17091222	
	Filing Date		2020-11-06	
	First Named Inventor	Fionn Hurley		
	Art Unit	1629		
	Examiner Name			
	Attorney Docket Number	1258.19CT		

	4	2007001841	WO	A1	2007-01-04	JANSSEN PHARMACEUTICA, N.V.		☐
	5	2007508293	JP	A	2007-04-05			☐
	6	2008546778	JP	A	2008-12-25			☐
	7	2016532679	JP	A	2016-10-20	Jazz Pharmaceuticals International Limited		☐
	8	2017512211	JP	A	2017-05-18			☐
	9	2017140778	WO	A1	2017-08-24	THE UNIVERSITY OF QUEENSLAND; THE PROVOST, FELLOWS		☐
	10	2019512009	JP	A	2019-05-09			☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T ⁵
	1	"Office Action corresponding to Japanese Application No. 2019-512895 mailed June 28, 2021"	☒
	2	"Written Opinion corresponding to Singapore Application No. 11201901998W dated June 29, 2021"	☐

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		17091222
	Filing Date		2020-11-06
	First Named Inventor	Fionn Hurley	
	Art Unit	1629	
	Examiner Name		
	Attorney Docket Number	1258.19CT	

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.			

Attorney Docket No. 1258.19CT

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Fionn Hurley

Confirmation No.: 6803

Application No.: 17/091,222

Group Art Unit: 1629

Filing Date: November 6, 2020

For: Compositions comprising (R)-2-amino-3-phenylpropyl carbamate and uses thereof

Date: July 8, 2021

Commissioner for Patents
Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT COVER LETTER

Sir:

Attached is an Information Disclosure Statement listing of documents, together with a copy of any listed foreign patent document and/or non-patent literature. A copy of any listed U.S. patent and/or U.S. patent application publication is not provided herewith in accordance with 37 C.F.R. § 1.98(a)(2)(ii).

- ☒ In accordance with **37 CFR 1.97(b)**, the information disclosure statement is being filed:
- ☐ (1) within three months of the filing date of a national application other than a continued prosecution application under §1.53(d);
 - ☐ (2) within three months of the date of entry of the national stage as set forth in §1.491 in an international application;
 - ☒ (3) before the mailing of a first Office Action on the merits; or
 - ☐ (4) before the mailing of a first Office Action after the filing of a request for continued examination under §1.114.

☐ In accordance with **37 CFR 1.97(c)**, the information disclosure statement is being filed after the period specified in 37 CFR 1.97(b) above, but before the mailing date of any of a final action under §1.113, a notice of allowance under §1.311, or an action that otherwise closes prosecution in the application, and is accompanied by one of the following:

- ☐ (1) The statement specified under **37 CFR 1.97(e)**, as follows:
- ☐ 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; or
 - ☐ 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 §1.56(c) more than three months prior to the filing of the information disclosure statement; or
- ☐ (2) The fee set forth in §1.17(p);

☐ In accordance with **37 CFR 1.97(d)**, the information disclosure statement is being filed after the period specified in 37 CFR 1.97(c) above, but on or before payment of the issue fee, and is accompanied by **both** of the following:

☐ (1) The statement specified under **37 CFR 1.97(e)**, as follows:

☐ 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; 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 §1.56(c) more than three months prior to the filing of the information disclosure statement; and

☐ (2) The fee set forth in §1.17(p);

In accordance with **37 CFR 1.97(g)**, the information disclosure statement shall not be construed as a representation that a search has been made.

In accordance with **37 CFR 1.97(h)**, the information disclosure statement shall not be construed to be an admission that the information cited in the statement is, or is considered to be, material to patentability as defined in §1.56(b).

☐ The Director is hereby authorized to charge the fee specified in 37 C.F.R. § 1.17(p), and any fee deficiency or credit any overpayment, to Deposit Account No. 50-0220; or

☒ No fee is believed due. However, the Director is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-0220.

Respectfully submitted,



Robert A. Schwartzman, Ph.D.
Registration No. 50,211
Attorney for Applicant(s)

Customer Number 129932
Myers Bigel, P.A.
P.O. Box 37428, Raleigh, NC 27627
919-854-1400
919-854-1401 (Fax)

CERTIFICATION OF TRANSMISSION

I hereby certify that this correspondence is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4) to the U.S. Patent and Trademark Office on July 8, 2021.

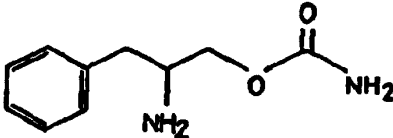
Signature: /Betty-Lou Medlin/
Name: Betty-Lou Medlin

PCT

WORLD INTELLECTUAL PR
International

INTERNATIONAL APPLICATION PUBLISHED UN

WO 9607637A1

(51) International Patent Classification ⁶ : C07C 271/20, 269/00		A1	(11) International Publication Number: WO 96/07637
			(43) International Publication Date: 14 March 1996 (14.03.96)
(21) International Application Number: PCT/KR95/00114 (22) International Filing Date: 6 September 1995 (06.09.95) (30) Priority Data: 1994/22798 9 September 1994 (09.09.94) KR (71) Applicant (for all designated States except US): YUKONG LIMITED [KR/KR]; 26-4, Yoido-dong, Yongdungpo-ku, Seoul 150-010 (KR). (72) Inventors; and (75) Inventors/Applicants (for US only): CHOI, Yong, Moon [US/US]; 2 Van Dyne Court, Towaco, NJ 07082 (US). BYUN, Jai, Kook [KR/KR]; 4-102, Hyosung Villa, Banpo-dong, Suhcho-ku, Seoul 137-040 (KR). (74) Agents: LEE, Chul et al.; 600-71, Kuro-dong, Kuro-Ku, Seoul 152-050 (KR).		(81) Designated States: AU, CA, CN, JP, RU, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report.	
(54) Title: NOVEL PHENYLALKYLAMINOALCOHOL CARBAMATES AND PROCESS FOR PREPARING THE SAME			
(57) Abstract O-carbamoyl-(D/L)-phenylalaninol represented by structural formula (I) is pharmaceutically useful to treat diseases of the central nervous system, which is prepared by a characteristic process comprising the steps of: treating phenylalaninol with benzyl chloroformate in a basic aqueous solution medium, to give N-benzyloxycarbonyl-phenylalaninol; subjecting this intermediate to reaction with phosgene and then, to the treatment with excess of concentrated ammonium hydroxide aqueous solution, to provide O-carbamoyl-N-benzyloxycarbonyl-phenylalaninol; deprotecting it through hydrogenolysis reaction.  (I)			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

NOVEL PHENYLALKYLAMINOALCOHOL CARBAMATES AND PROCESS
FOR PREPARING THE SAME

BACKGROUND OF THE INVENTION

5

Field of the invention

The present invention relates, in general, to
pharmaceutically novel and useful organic compounds and,
more particularly, to O-carbamoylphenylalaninol compounds
10 including their racemates and enantiomers and the
pharmaceutically acceptable salts thereof, useful to treat
the diseases of the central nervous system, especially for
depression. Also, the present invention is concerned
with a process for preparing the same.

15

Description of the Prior Art

Organic alkyl carbamates have been effectively used
for controlling various central nervous system (CNS)
disorders. For example, U.S. Pat. Nos. 2,884,444,
20 2,937,119 and 3,313,697 disclose function of carbamate in
CNS disorders, especially as antiepileptic and centrally
acting muscle relaxant.

Phenylethylamine derivatives, one important class of
therapeutical medicines useful for managing CNS diseases,
25 have been used mainly to treat obesity, narcolepsy,
minimal brain dysfunction and mild depression.

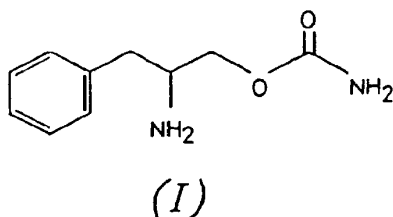
Recent design of pharmacologically useful compounds

has been based on amino acids or the derivatives thereof, which is mainly attributable to the fact that many of the compounds found in biological systems come from amino acids or the derivatives thereof. In addition, in most cases, the function of a pharmaceutically useful compound is effected after it binds to an enzyme or receptor, which may trigger the regulatory mechanisms of the enzyme or receptor.

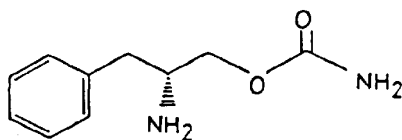
SUMMARY OF THE INVENTION

As a result of intensive and thorough research, the present inventors found that O-carbamoyl derivatives from (D/L)-phenylalaninol, (D)-phenylalaninol and (L)-phenylalaninol are pharmaceutically useful for CNS disorders, especially for depression.

Accordingly, it is a principal object of the present invention to provide novel phenylalkylaminoalcohol carbamate compounds, represented by the following structural formulas I, II and III:

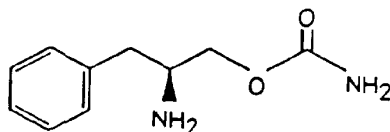


3



(II)

5



(III)

10 and pharmaceutically acceptable salts thereof.

It is another object of the present invention to provide a method for preparing the O-carbamoyl derivatives from (D/L)-phenylalaninol, (D)-phenylalaninol and (L)-phenylalaninol, represented by the structural formulas I, 15 II and III.

DETAILED DESCRIPTION OF THE INVENTION

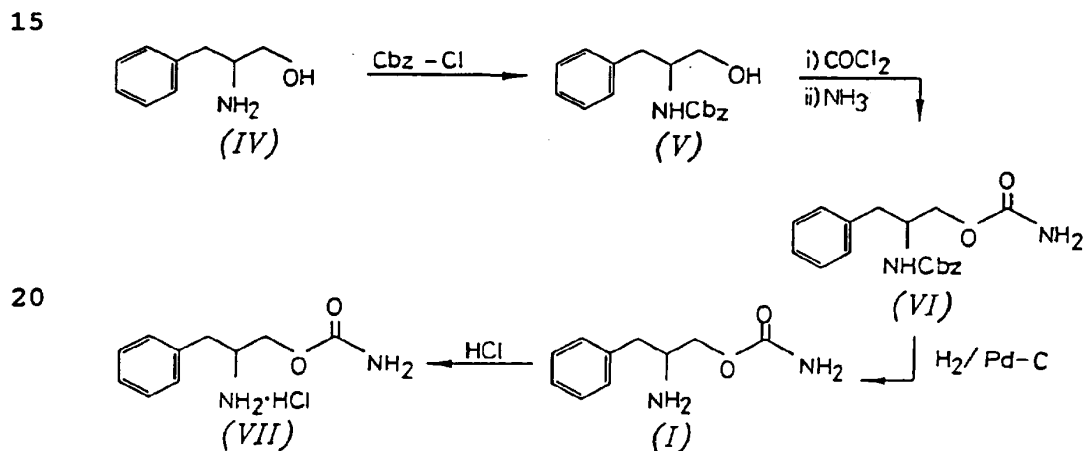
By virtue of the basic nitrogen atom, the novel 20 compounds of the present invention form into pharmaceutically acceptable acid addition salts with organic or inorganic acids. Concrete examples of the acids suitable for the formation of pharmaceutically acceptable salts include hydrochloric, sulfuric, 25 phosphoric, acetic, benzoic, citric, malonic, salicylic, malic, fumaric, oxalic, succinic, tartaric, lactic, gluconic, ascorbic, maleic, aspartic, benzenesulfonic,

methanesulfonic, ethanesulfonic, hydroxymethanesulfonic, and hydroxyethanesulfonic and the like. Additional acids can refer to "Pharmaceutical Salts", J. Pharm. Sci., 1977; 66(1): 1-19.

5 In accordance with the present invention, the compounds of Structural Formulas I, II and III are prepared as set forth in the following Reaction Schemes I, II and III, respectively. Following is of the preparation of the novel compounds in conjunction with the
10 reaction schemes.

The compound of Structural Formula I is prepared as shown in Reaction Scheme I below.

REACTION SCHEME I



In Reaction Scheme I, first, phenylalaninol (IV) is converted to N-benzyloxycarbonylphenylalaninol (V) by

reaction with benzyl chloroformate in a basic aqueous solution, which is subjected to carbamoylation with phosgene, followed by the ammonolysis with excess of concentrated ammonium hydroxide aqueous solution, to afford O-carbamoyl-N-benzyloxycarbonylphenylalaninol (VI). Removal of the benzyloxycarbonyl group, a nitrogen protecting group, by hydrogenolysis gives O-carbamoylphenylalaninol (I), which is, then, treated with ethereal hydrogen chloride provides O-carbamoylphenylalaninol hydrochloride salt (VII).

Details of the reaction conditions described in Reaction Scheme I is as follows. In the first step, the concentration of the starting material (IV) is between 0.1 and 3 molar and benzyl chloroformate is used at 1 to 2 equivalents. The basic aqueous solution has a pH value between 7 and 14 and the conversion reaction is carried out at temperatures ranging from -10 to 70 °C.

For the conversion of compound (V) to (VI), 1 to 2 molar equivalent of phosgene, either neat or as solution in toluene, is used at 0.05 to 2 molar concentration of the compound (V). Halogenated alkane such as methylene chloride, ethereal solvents such as tetrahydrofuran, aromatic solvents such as toluene or the mixtures thereof can be used as a solvent. Use of a base as acid scavenger is recommended while the reaction can be completed in the absence of a base. Typically, a tertiary amine, such as triethylamine, diisopropylethylamine, triisopropylamine,

DBU(1,6-diazabicyclo[5.4.0]undec-7-ene), DBN(1,5-diazabicyclo[4.3.0]non-5-ene), antipyrine and dimethylphenylamine, can be used for this purpose. The reacting ammonia can be used as neat or as solution in
5 water or lower alkyl alcohol such as methanol, ethanol, n-propanol or isopropanol, and 1 to 1,000 molar equivalent is used. The reaction temperature is between -30 and 60 °C.

As for the step of preparing compound (I) from (VI),
10 an ethereal solvent such as THF, an alcoholic solvent such as methanol, water, an aromatic solvent such as toluene, benzene, or xylene, an ester solvent such as ethyl acetate or any compositional mixture thereof is used as the reaction medium, and the hydrogenation reaction is carried
15 out at a temperature of -10 to 150 °C under a 1 to 100 atm hydrogen pressure in the presence of a catalyst such as palladium (0.1% to 10 % on charcoal, alumina or other supporting materials), platinum, platinum oxide, rhodium, iridium or yttrium. Typical substrate concentration of
20 compound (VI) is between 0.05 and 5 molar.

To prepare the salt (VII) from the free base (I), an ethereal solvent such as THF, an alcoholic solvent such as methanol, an ester solvent such as ethyl acetate, an aromatic solvent or any compositional mixture thereof can
25 be used. For the precipitation, a nonpolar organic solvent is used, such as dialkyl ether where the alkyl typically represents a lower alkyl of C1 to C6, either

7

straight or branched. The concentration of the substrate (I) in the initial solution is on the order of 0.05 to 5 molar.

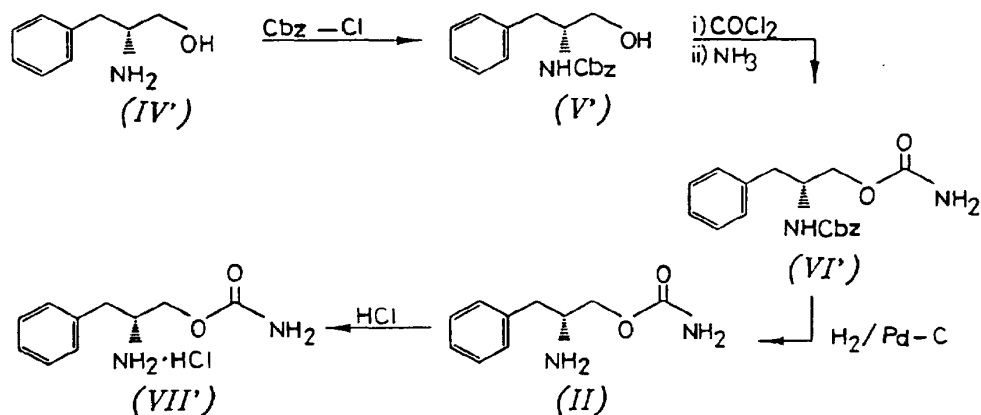
The compound of Structural Formula II is prepared as shown in Reaction Scheme II below.

10

REACTION SCHEME II

15

20



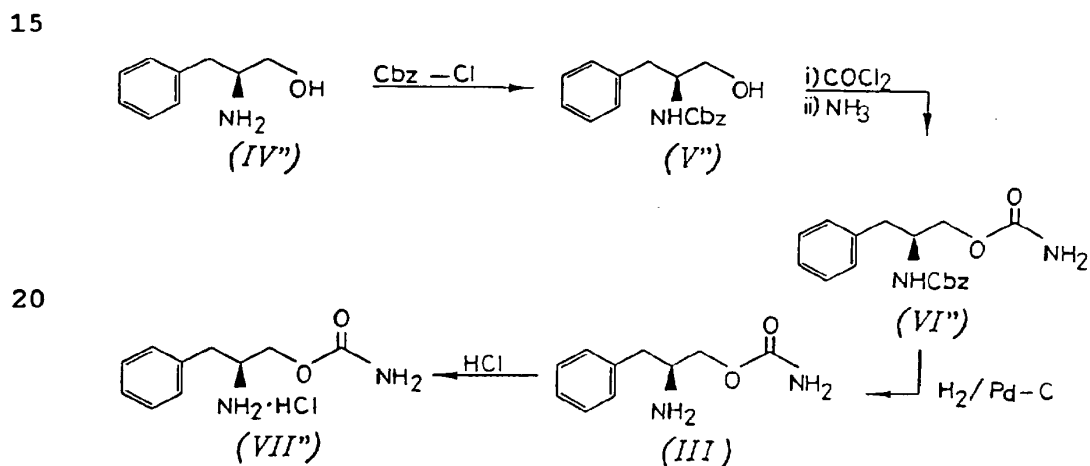
In Reaction Scheme II, (D)-phenylalaninol (IV') is converted to N-benzyloxycarbonylphenylalaninol (V') by reaction with benzyl chloroformate in a basic aqueous solution. Carbamoylation of compound (V') with phosgene followed by the ammonolysis of the chloroformate intermediate affords (D)-O-carbamoyl-N-

benzyloxycarbonylphenylalaninol (VI'). Removal of benzyloxy-carbonyl group, a nitrogen protecting group, by hydrogenolysis gives (D)-O-carbamoylphenylalaninol (II). Treatment of compound (II) with ethereal hydrogen chloride provides (D)-O-carbamoylphenylalaninol hydrochloride salt (VII').

The reaction steps described in Reaction Scheme II are undertaken under the same conditions as those in Reaction Scheme I.

The compound of Structural Formula III is prepared as shown in Reaction Scheme III below.

REACTION SCHEME III



In Reaction Scheme III, first, (L)-phenylalaninol (IV'') is converted through the reaction with benzyl

chloroformate in a basic aqueous solution to N-benzyloxycarbonylphenylalaninol (V") which is subsequently subjected to carbamoylation with phosgene, followed by ammonolysis, to afford (L)-O-carbamoyl-N-benzyloxycarbonylphenylalaninol (VI"). Removal of the benzyloxycarbonyl group, a nitrogen protecting group, by hydrogenolysis gives (L)-O-carbamoylphenylalaninol (III), the treatment of which with ethereal hydrogen chloride provides (L)-O-carbamoylphenylalaninol hydrochloride salt (VII").

The reaction steps described in Reaction Scheme III are undertaken under the same conditions as those in Reaction Scheme I.

In therapeutic use as agents for various central nervous system (CNS) disorders, especially for depression, the compounds of the present invention are administered to patients at a dosage of from 0.7 to 7,000 mg per day. For a normal human adult with a body weight of approximately 70 kg, the administration amount is translated into a daily dose of 0.01 to 100 mg per kg of body weight. The specific dosage employed, however, may vary depending upon the requirements of the patient, the severity of patient's condition and the activity of the compound. The determination of optimum dosages for a particular situation is within the skill of the art.

In utilizing the compounds of the present invention for the central nervous system, particularly to treat

depression, it is preferred to administer the compounds orally. Since the compounds absorb well orally, it usually will not be necessary to resort to parenteral administration. For oral administration, the present
5 phenylalkylaminoalcohol carbamate compounds are preferably combined with a pharmaceutical carrier. The ratio of the carrier to the phenylalkylaminoalcohol carbamate compounds is not critical to express the effects of the medicine on the central nervous system, and they can vary considerably
10 depending on whether the composition is to be filled into capsules or formed into tablets. In tableting, it is usually desirable to employ at least as much pharmaceutical carrier as the pharmaceutically active ingredients. Various edible pharmaceutical carriers or
15 the mixture thereof can be used. A suitable carriers, for example, are a mixture of lactose, dibasic calcium phosphate and cornstarch. Other pharmaceutically acceptable ingredients can be further added, including lubricants such as magnesium stearate.

20 The therapeutic effect of the compounds according to the present invention in treating depression has been proved by "Forced Swimming Test", a well known pharmacological screening methods for depression and the results are shown in the following Table 1.

25

11

Table 1

(Oral administration in mice (1 hr))

5	Treatment	Dose(mg/kg)	Immobility time		Inhibition
			(sec)	(mean)	(%)
	Control	0	132		-
	Compound II	30	50		62
10	Control	0	105		-
	Compound III	30	132.5		n.s.*
	Control	0	154		-
	Compound I	30	77		30

15 * n.s.: statistically not significant

As shown in Table 1, compound II exhibits the most potency against the forced swimming model for depression.

20 Compound III, an optical antipode of compound II, showed no activity at 30 mg/kg dose level for this particular model. It is not surprising to find that compound I, which is the racemic mixture of compound II and compound III, has shown half the potency of the pharmacologically active component, compound II.

25 A better understanding of the present invention may be obtained in light of following examples which are set forth to illustrate, but are not to be construed to limit, the present invention.

30

EXAMPLE I

Preparation of N-Benzyloxycarbonyl-D-phenylalaninol

In a 500 mL RB flask equipped with a mechanical
5 stirrer and a dropping funnel, D-phenylalaninol (45.4 g,
300 mmol) was dissolved in 220 mL of distilled water, and
cooled in an ice-bath. The pH of the solution was
adjusted with 50 % sodium hydroxide to 14. Benzyl
chloroformate (49.3 mL, 345 mmol) was charged into the
10 dropping funnel and added slowly to the well stirred
solution over 0.5 hr. After the completion of the
addition, the reaction mixture was stirred for 1 hr. at
0 °C. The product precipitated from the reaction mixture
as a white solid. It was collected by filtration and
15 washed completely with distilled water. After being dried
in vacuo, the solid thus obtained weighed 104 grams
without any further purification: 99.8% Yield.

Melting point = 90 - 92 °C

$[\alpha]_D^{20} = + 43.4$ (c = 1.0, EtOH)

20 Analysis calc.: C, 71.56; H, 6.71; N, 4.91

Found: C, 71.35; H, 6.71; N, 4.91

EXAMPLE II

Preparation of N-Benzyloxycarbonyl-D-phenylalaninol
25 carbamate

In a 500 mL RB flask, N-benzyloxycarbonyl-D-

phenylalaninol (13.56 g, 50 mmol) was charged with antipyrine (11.29 g, 60 mmol) in 250 mL of dry THF under a nitrogen atmosphere. The reaction mixture was cooled in an ice-bath and phosgene (30.3 mL of 1.93 M solution in toluene, 58.5 mmol) was added quickly while vigorously stirring. After stirring for 1 hr., the formation of a corresponding chloroformate from the starting material was monitored by TLC. The chloroformate solution thus prepared, was slowly added to a well stirred and ice-chilled aqueous ammonium hydroxide solution (75 mL, 28-30 %, 1,190 mmol) via cannula over 0.5 hr. The resulting reaction mixture was stirred for an extra 0.5 hr. The organic phase separated was collected. The aqueous phase was extracted twice with methylene chloride (100 mL). The combined organic phase was washed with brine (50 mL), dried over sodium sulfate, and concentrated to yield 17.8 g (113%) of foamy solid. It was purified a flash column chromatography to give 14.8 g of the title compound, white solid: 94% Yield.

Melting point = 121 - 125 °C

$[\alpha]_D^{20} = + 28.6$ (c = 2.0, EtOH)

Analysis calc.: C, 65.84; H, 6.14; N, 8.53

Found: C, 66.68; H, 6.21; N, 7.80

25

EXAMPLE III

Preparation of D-Phenylalaninol carbamate hydrochloric acid salt

14

In a 160 mL Parr reactor, N-benzyloxycarbonyl-D-phenylalaninol carbamate (9.43 g) was added with 75 mL of anhydrous methanol and 10 % palladium on charcoal (0.32 g). Then, the reactor was closed and purged with hydrogen
5 for 1 min. The reaction was completed in 2 hrs. under 40 psi pressure of hydrogen at 45 °C. The catalyst was filtered off. Thereafter, the organic layer was concentrated into 5.97 g (102 %) of pale yellow thick liquid. The liquid was poured in 50 mL of anhydrous THF
10 and cooled to 0 °C. Anhydrous hydrogen chloride gas was then purged through the solution with slowly stirring for 0.5 hr. 50 mL of anhydrous ether was added, to give a precipitate. Filtration with THF-ether (1:1) mixture provided 6.1 g of the title compound as a white solid: 88
15 % Yield.

Melting point = 172 - 174 °C

$[\alpha]_D^{20} = -12.9$ (c = 2.0, H₂O)

Analysis calc.: C, 52.60; H, 6.55; N, 12.14; Cl,
15.37

20 Found: C, 51.90; H, 6.60; N, 12.15; Cl,
15.52

EXAMPLE IV

Preparation of N-benzyloxycarbonyl-L-Phenylalaninol

25

The title compound was prepared in the same manner as that of Example I, except that (L)-phenylalaninol was

15

used as the starting material.

Melting point = 90 - 92 °C

$[\alpha]_D^{20} = -42.0$ (c = 1.0, EtOH)

Analysis calc.: C, 71.56; H, 6.71; N, 4.91

5 Found: C, 70.98; H, 6.67; N, 4.95

EXAMPLE V

Preparation of N-benzyloxycarbonyl-L-Phenylalaninol
carbamate

10

The title compound was prepared in the same manner as that of Example II, except that N-benzyloxycarbonyl-L-phenylalaninol was used as the starting material.

Melting point = 121 - 128 °C

15 $[\alpha]_D^{20} = -28.9$ (c = 2.0, EtOH)

Analysis calc.: C, 65.84; H, 6.14; N, 8.53

Found: C, 65.45; H, 6.15; N, 8.32

EXAMPLE VI

20 Preparation of L-Phenylalaninol carbamate hydrochloric
acid salt

The title compound was prepared in the same manner as that of Example III, except that N-benzyloxycarbonyl-L-phenylalaninol carbamate was used as the starting
25 material.

Melting point = 175 - 177 °C

16

$$[\alpha]_D^{20} = + 13.1 \text{ (c = 1.0, H}_2\text{O)}$$

Analysis calc.: C, 52.60; H, 6.55; N, 12.14; Cl,
15.37

Found: C, 51.95; H, 6.58; N, 12.09; Cl,

5 15.37

EXAMPLE VII

Preparation of N-benzyloxycarbonyl-D,L-Phenylalaninol

10 The title compound was prepared in the same manner
as that of Example I, except that (D,L)-phenylalaninol was
used as the starting material.

Melting point = 72 - 75 °C

Analysis calc.: C, 71.56; H, 6.71; N, 4.91

15 Found: C, 71.37; H, 6.74; N, 4.84

EXAMPLE VIII

Preparation of N-benzyloxycarbonyl-D,L-Phenylalaninol carbamate

20

The title compound was prepared in the same manner
as that of Example II, except that N-benzyloxycarbonyl-
D,L-phenylalaninol was used as the starting material.

Melting point = 130 - 133 °C

25 Analysis calc.: C, 65.84; H, 6.14; N, 8.53

Found: C, 65.85; H, 6.14; N, 8.49

17

EXAMPLE IX

Preparation of D,L-Phenylalaninol carbamate hydrochloric
acid salt

5 The title compound was prepared in the same manner
as that of Example III, except that N-benzyloxycarbonyl-
D,L-phenylalaninol carbamate was used as the starting
material.

Melting point = 163 - 165 °C

10 Analysis calc.: C, 52.60; H, 6.55; N, 12.14; Cl,
15.37

Found: C, 51.92; H, 6.56; N, 11.95; Cl,
15.82

Other features, advantages and embodiments of the
15 present invention disclosed herein will be readily
apparent to those exercising ordinary skill after reading
the foregoing disclosures. In this regard, while specific
embodiments of the invention have been described in
considerable detail, variations and modifications of these
20 embodiments can be effected without departing from the
spirit and scope of the invention as described and
claimed.

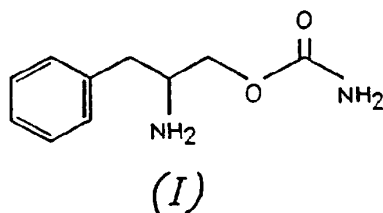
25

18

WHAT IS CLAIMED IS:

1. O-Carbamoyl-(D/L)-phenylalaninol, represented by the following structural formula I:

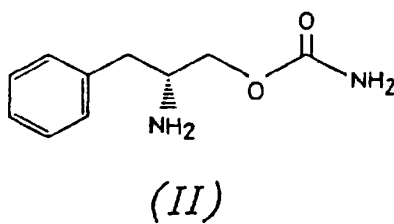
5



10 and the pharmaceutically acceptable salts thereof.

2. O-Carbamoyl-(D)-phenylalaninol, represented by the following structural formula II:

15

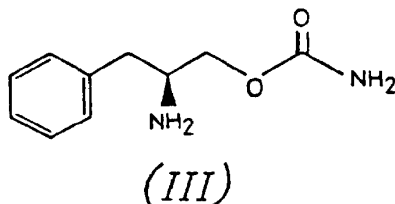


and the pharmaceutically acceptable salts thereof.

20

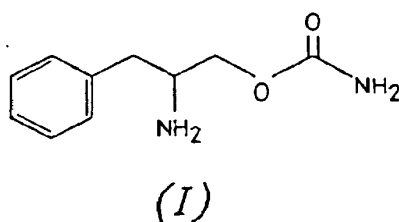
3. O-Carbamoyl-(L)-phenylalaninol, represented by the following structural formula III:

25



and the pharmaceutically acceptable salts thereof.

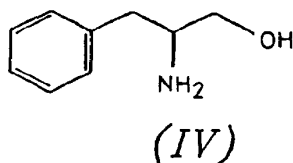
4. A process for preparing O-carbamoyl-(D/L)-phenylalaninol represented by the following structural
5 formula I:



10

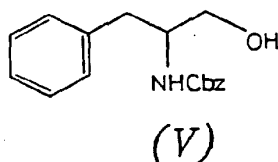
comprising the steps of:

treating (D/L)-phenylalaninol represented by the
following structural formula IV:



15

with benzyl chloroformate in a basic aqueous solution
20 medium, to give N-benzyloxycarbonyl-(D/L)-phenylalaninol
represented by the following structural formula V:

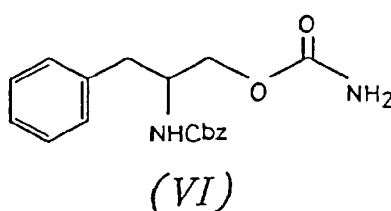


25

subjecting the compound of the structural formula V

20

to reaction with phosgene and then, to the treatment with excess of concentrated ammonium hydroxide aqueous solution, to provide O-carbamoyl-N-benzyloxycarbonyl-(D/L)-phenylalaninol represented by the following structural formula VI:

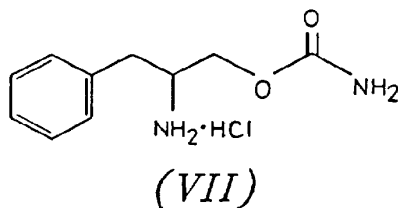


deprotecting the compound of the structural formula VI through hydrogenolysis reaction, to give O-carbamoyl-(D/L)-phenylalaninol represented by the structural formula I.

15

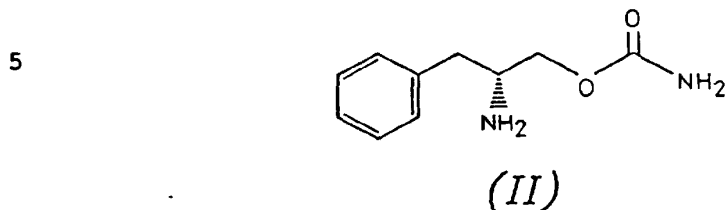
5. A process in accordance with claim 4, further comprising the steps of treating the compound of the structural formula I with anhydrous hydrochloric acid in an ethereal solution, subsequent to the deprotecting step, to give O-carbamoyl-(D/L)-phenylalaninol hydrochloric acid salt represented by the following structural formula VII, a pharmaceutically acceptable salt:

25



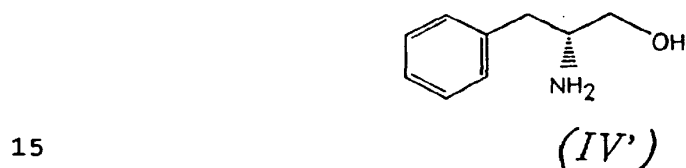
21

6. A process for preparing O-carbamoyl-(D)-phenylalaninol represented by the following structural formula II:

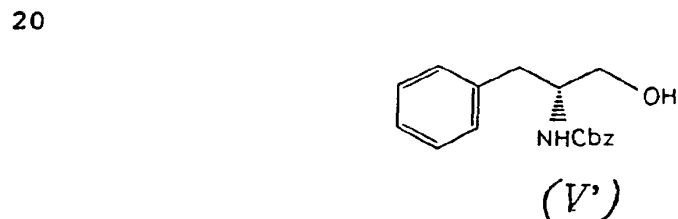


comprising the steps of:

10 treating (D)-phenylalaninol represented by the following structural formula IV':

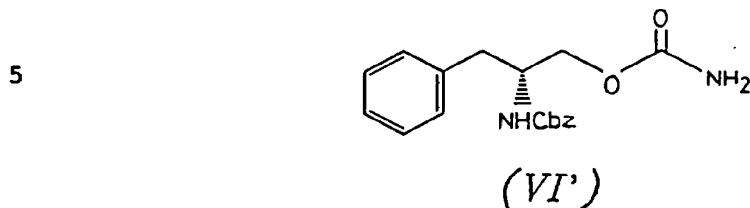


with benzyl chloroformate in a basic aqueous solution medium, to give N-benzyloxycarbonyl-(D)-phenylalaninol represented by the following structural formula V':



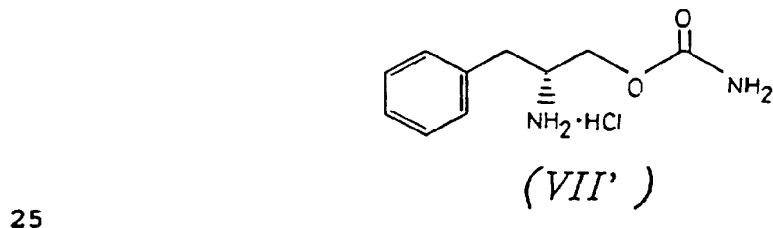
25 subjecting the compound of the structural formula V' to reaction with phosgene and then, to the treatment with excess of concentrated ammonium hydroxide aqueous

solution, to provide O-carbamoyl-N-benzyloxycarbonyl-(D)-phenylalaninol represented by the following structural formula VI':



deprotecting the compound of the structural formula VI' through hydrogenolysis reaction, to give O-carbamoyl-(D)-phenylalaninol represented by the structural formula II.

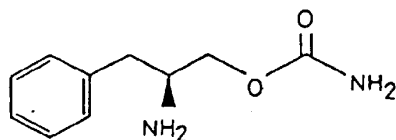
7. A process in accordance with claim 6, further comprising the steps of treating the compound of the structural formula II with anhydrous hydrochloric acid in an ethereal solution subsequent to the deprotecting step, to give O-carbamoyl-(D)-phenylalaninol hydrochloric acid salt represented by the following structural formula VII', a pharmaceutically acceptable salt:



8. A process for preparing O-carbamoyl-(L)-phenylalaninol represented by the following structural

23

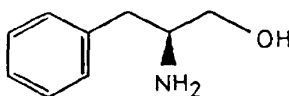
formula III:



(III)

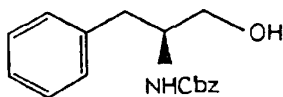
comprising the steps of:

treating (L)-phenylalaninol represented by the following structural formula IV":



(IV")

15 with benzyl chloroformate in a basic aqueous solution medium, to give N-benzyloxycarbonyl-(L)-phenylalaninol represented by the following structural formula V":

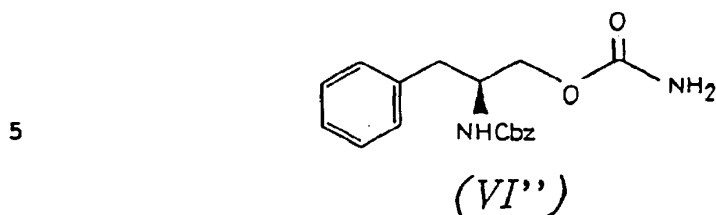


(V")

subjecting the compound of the structural formula V"
25 to reaction with phosgene and then, to the treatment with excess of concentrated ammonium hydroxide aqueous solution, to provide O-carbamoyl-N-benzyloxycarbonyl-(L)-

24

phenylalaninol represented by the following structural formula VI":



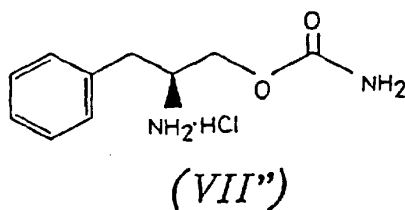
deprotecting the compound of the structural formula VI" through hydrogenolysis reaction, to give O-carbamoyl-(L)-phenylalaninol represented by the structural formula III.

10

9. A process in accordance with claim 8, further comprising the steps of treating the compound of the structural formula III with anhydrous hydrochloric acid in an ethereal solution, subsequent to the deprotecting step, to give O-carbamoyl-(L)-phenylalaninol hydrochloric acid salt represented by the following structural formula VII", a pharmaceutically acceptable salt:

15

20



25

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 95/00114

A. CLASSIFICATION OF SUBJECT MATTER IPC ⁶ : C 07 C 271/20, 269/00 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) IPC ⁶ : C 07 C 271/20, 269/00 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) QUESTEL - G-DARC		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 1 434 826 A (ANTONIO GALLARDO) 05 May 1976 (05.05.76), claims 5,11-14. ----- -	1,4-9
☐ 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 document 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 05 December 1995 (05.12.95)		Date of mailing of the international search report 18 December 1995 (18.12.95)
Name and mailing address of the ISA/ AT AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna Facsimile No. 1/53424/535		Authorized officer Hofbauer e.h. Telephone No. 1/53424/225

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/KR 95/00114

In Recherchenbericht angeführtes Patentedokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
GB A 1434826	05-05-76	ES A1 432131	01-03-77



Espacenet

Bibliographic data: JPH09503231 (A) — 1997-03-31

NOVEL PHENYLALKYLAMINOALCOHOL CARBAMATES AND PROCESS FOR PREPARING THE SAME

Inventor(s):

Applicant(s):

Classification: - international: A61K31/27; A61P25/00; A61P25/08; A61P25/20; A61P25/24; A61P25/26; A61P25/28; C07C269/00; C07C271/12; C07C271/20; (IPC1-7): C07C269/00; C07C271/12
 - cooperative: A61P25/00 (EP); A61P25/08 (EP); A61P25/20 (EP); A61P25/24 (EP); A61P25/26 (EP); A61P25/28 (EP); C07C271/12 (EP); C07C271/20 (KR); Y02P20/55 (EP)

Application number: JP19960509386 19950906

Priority number(s): KR19940022798 19940909

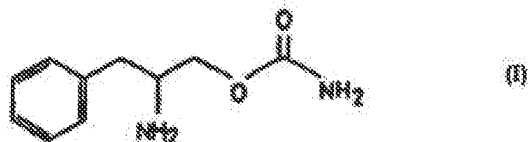
Also published as: AU3485695 (A) AU700544 (B2) CA2176012 (A1) CA2176012 (C) CN1069635 (C) CN1135209 (A) DE69513140 (T2) EP0728129 (A1) EP0728129 (B1) ES2140703 (T3) JP2680478 (B2) KR100197892 (B1) KR960010617 (A) RU2104266 (C1) US5955499 (A) WO9607637 (A1) less

Abstract not available for JPH09503231 (A)

Abstract of corresponding document: WO9607637 (A1)

O-carbamoyl-(D/L)-phenylalaninol represented by structural formula (I) is pharmaceutically useful to treat diseases of the central nervous system, which is prepared by a characteristic process

comprising the steps of: treating phenylalaninol with benzyl chloroformate in a basic aqueous solution medium, to give N-benzyloxycarbonyl-phenylalaninol; subjecting this intermediate to reaction with phosgene and then, to the treatment with excess of concentrated ammonium hydroxide aqueous solution, to provide O-carbamoyl-N-benzyloxycarbonyl-phenylalaninol; deprotecting it through hydrogenolysis reaction.



(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
14 April 2005 (14.04.2005)

PCT

(10) International Publication Number
WO 2005/033064 A1

(51) International Patent Classification: **C07C 237/10**

(21) International Application Number:
PCT/KR2004/002571

(22) International Filing Date: 8 October 2004 (08.10.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/680,979 8 October 2003 (08.10.2003) US

(71) Applicant (for all designated States except US): **SK CORPORATION** [KR/KR]; 99 Seorin-dong, Jongro-ku, Seoul 110-110 (KR).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **CHOI, Yong-Moon** [US/US]; 101 Windsor Drive, Pine Brook, NJ 07058 (US). **KIM, Min-Woo** [KR/US]; 2 Tiffany Court, Montville, NJ 07045 (US).

(74) Agent: **C & S PATENT AND LAW OFFICE**; C-2306 Daelim Acrotel, 467-6 Dogok-dong, Kangnam-gu, Seoul 135-971 (KR).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS OF PREPARING O-CARBAMOYL COMPOUNDS IN THE PRESENCE OF ACTIVE AMINE GROUP

(57) Abstract: A process for preparing O-carbamoyl aminoalcohols represented by Formula(I) wherein: n is an integer from 0 and 5; R₁, R₂, R₃ and R₄ are individually selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted or unsubstituted aryl and arylalkyl the aryl portion of which may be unsubstituted or substituted; R₅ and R₆ are individually selected from the group consisting of hydrogen, alkyl or arylalkyl the aryl portion of which may be unsubstituted or substituted; or R₁ and R₅ together with the carbon and nitrogen to which they are attached may form an unfused or fused heterocyclic ring having from 4 to 10 members, comprising reacting an aminoalcohol represented by Formula (II) wherein n, R₁, R₂, R₃, R₄, R₅ and R₆ are as defined; with a cyanate and an excess of an acid in an organic solvent medium.

PROCESS OF PREPARING O-CARBAMOYL COMPOUNDS IN THE PRESENCE OF ACTIVE AMINE GROUP

FIELD OF INVENTION

5

The present invention relates to a novel process for preparing O-carbamoyl aminoalcohols.

BACKGROUND OF THE INVENTION

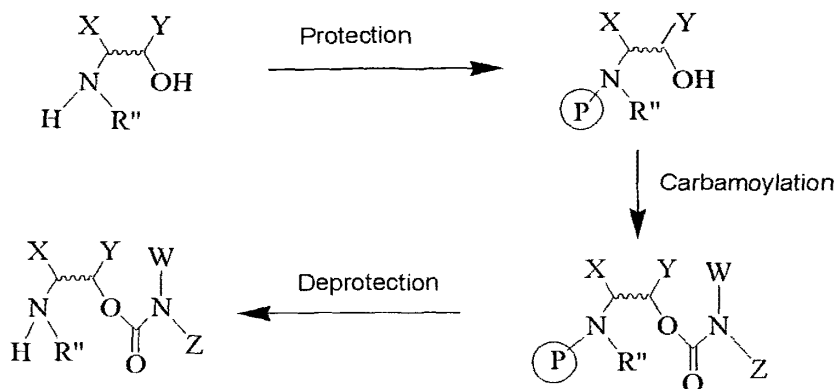
10

O-carbamoyl aminoalcohols comprise a new class of pharmaceutically useful compounds. For instance, O-carbamoyl-(D)-phenylalaninol hydrochloride and O-carbamoyl-(L)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride are being developed for the treatment of central nervous system (CNS) disorders, particularly as
15 antidepressants.

Due to the generally higher reactivity of amines in comparison to hydroxyl groups, when the O-carbamoylated product of an aminoalcohol is synthesized, the amine moieties need to be protected prior to the carbamylation reaction. Hence, a lengthy sequence of (1) protection, (2) carbamylation reaction and (3) deprotection is
20 typically required for the transformation as described in Scheme 1.

An example of the reaction in accordance with Scheme 1 would be the reaction of an aminoalcohol with benzyl chloroformate to form the protected N-benzyloxycarbonyl aminoalcohol. Carbamylation of this protected aminoalcohol with phosgene followed by reaction with an amine yields the O-carbamoyl-N-protected
25 aminoalcohol. The deprotection of this N-protected compound is achieved by hydrogenation.

Scheme 1



wherein W, X, Y and Z are individually selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl or arylalkyl; and,

5 R'' is selected from the group consisting of hydrogen, alkyl or arylalkyl.

This process has been advantageously simplified in accordance with the present invention.

10 SUMMARY OF THE INVENTION

The present invention provides a novel process for preparing O-carbamoyl aminoalcohols via chemoselective carbamoylation of hydroxyl groups therein in a single step using a cyanate and an excess of acid in an organic medium. Particularly, the present invention involves the use of sodium cyanate and methanesulfonic acid in the single step preparation of O-carbamoyl aminoalcohols. Both small-scale laboratory preparations and large-scale industrial preparations are disclosed. The process is particularly advantageous for the preparation of O-carbamoyl-D-phenylalaninol, O-carbamoyl-(L)-oxymethyl-1,2,3,4-tetrahydroisoquinoline, and carbamic acid 2-((4-fluorobenzoyl)piperidin-1-yl)-1-phenylethyl ester.

DETAILED DESCRIPTION OF THE INVENTION

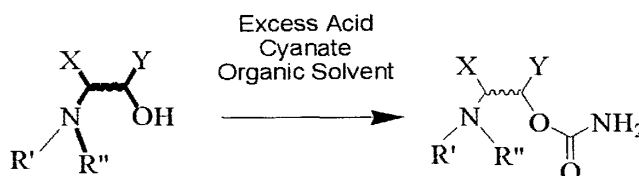
The present invention provides a novel process for preparing O-carbamoyl

aminoalcohols. The process is more efficient in introducing the carbamoyl moiety into the starting aminoalcohol than that previously known, which is shown above in Scheme

1. As such, the present invention can be illustrated by Scheme 2:

5

Scheme 2



wherein

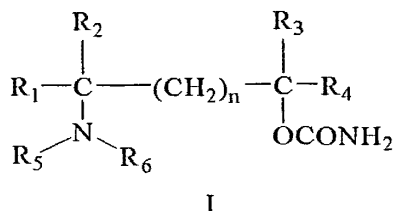
X and Y are individually selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl or arylalkyl; wherein the aryl portion may be substituted or

10 unsubstituted by (X')_m as defined below; and,

R' and R'' are selected from the group consisting of hydrogen, alkyl or arylalkyl, wherein the aryl portion may be substituted or unsubstituted by (X')_m as defined below.

It is quite surprising that the process described in the present invention, which
 15 employs an organic solvent system as the reaction medium, selectively produces the O-carbamoylated species as the dominant product. It should be noted that the reaction of aminoalcohols in aqueous acidic medium with a cyanate produces the *N*-carbamoylated product as the major product.

The present invention provides a novel process that is particularly advantageous
 20 for the preparation of O-carbamoyl aminoalcohols represented by Formula I



I

wherein:

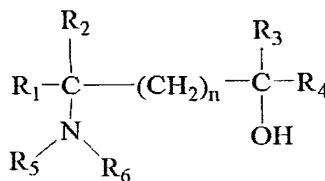
n is an integer from 0 to 5;

R₁, R₂, R₃ and R₄ are individually selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted or unsubstituted aryl and arylalkyl wherein the aryl portion may be unsubstituted or substituted by (X')_m, wherein m is an integer from 0 to 4 and X' is selected from the group consisting of hydrogen, alkyl, alkoxy, alkylthio, halogen, hydroxy, nitro and trifluoromethyl;

R₅ and R₆ are individually selected from the group consisting of hydrogen, alkyl or arylalkyl wherein the aryl portion may be substituted or unsubstituted by (X')_m, wherein m and X' are as defined; or

R₁ and R₅ together with the carbon and nitrogen to which they are attached form an unfused or fused heterocyclic ring having from 4 to 10 members.

The process comprises reacting an aminoalcohol represented by Formula II



II

wherein R₁ through R₆ and n are as defined above, with a cyanate and an excess of acid, in an organic solvent medium.

The starting aminoalcohol represented by the general structural Formula II may be chiral or achiral. The process described in the present invention can be used to prepare both the racemate and optically active forms of the desired O-carbamoyl aminoalcohol.

While specific reaction conditions may vary for individual starting aminoalcohol, the following description is of general conditions for the preparatory process of the present invention.

In accordance with the present invention, an excess of the acid is required for the protonation of the amine moieties present in the starting alcohol prior to the desired

reaction. Typically, the amount of the acid is between about one and about ten molar equivalents in excess of amount required to react with the total number of amine groups present in the starting aminoalcohol represented by formula II. Hence, if one amine group is present, about two to about eleven equivalents of an acid are typically used, however, the presence of additional equivalents of acid does not hinder the reaction.

The acid utilized in the process of the present invention can be an organic or inorganic acid such as, for example, hydrochloric acid, sulfuric acid, phosphoric acid, acetic acid, halogenated acetic acids, arylsulfonic acids, alkylsulfonic acids and halogenated alkylsulfonic acids. Hydrochloric acid, halogenated acetic acids, arylsulfonic acids and alkylsulfonic acids are preferred for the subject synthesis. Particularly preferred acids include hydrochloric acid, trifluoroacetic acid, trichloroacetic acid, benzenesulfonic acid, toluenesulfonic acid, methanesulfonic acid, ethanesulfonic acid, and trifluoromethanesulfonic acid.

The present invention utilizes a cyanate to produce a cyanic acid in situ. Typically, the cyanate is used in about one to about ten mole equivalents of the starting aminoalcohol for the present invention. Useful cyanates for the present invention include, but are not limited to, alkali metal cyanates, such as sodium cyanate, potassium cyanate, and ammonium cyanate, alkaline earth cyanates, such as magnesium cyanate, calcium cyanate, and the like. Alternatively, rather than producing cyanic acid from a cyanate, purified cyanic acid may be employed which would also produce the desired product.

The carbamation reaction described in the present invention can be executed in various organic solvents. Halogenated alkanes such as dichloromethane; etheral solvents, such as tetrahydrofuran; nitrile solvents, such as acetonitrile; and aromatic solvents, such as toluene; or mixtures thereof can be used as the reaction solvent. Preferred solvents are selected from the group consisting of dichloromethane, chloroform, 1,2-dichloroethane, 1,1,1-trichloroethane, tetrahydrofuran, 1,2-dimethoxyethane, diethyl ether, acetonitrile, propionitrile, benzene, toluene, xylene and mixtures thereof. Halogenated alkanes and nitrile solvents including dichloromethane, 1,2-dichloroethane, 1,1,1-trichloroethane and acetonitrile are particularly preferred solvents.

The weight to volume ratio for the amount of the aminoalcohol represented by Formula II to the amount of the organic solvent medium is within the range from about 1:3 to about 1:100. For example, when one gram of aminoalcohol is employed, between about three and about one hundred milliliters of solvent would be utilized for the

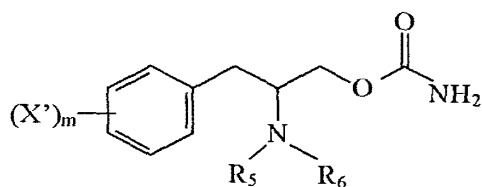
5 reaction.

The subject reaction is carried out at a temperature ranging from about -80° to about 80°C , depending upon the solvent employed. Typically, the reaction is carried out at temperatures ranging from about -10°C to about 60°C . The reaction temperature will vary within the ranges given depending on the starting aminoalcohol.

10 In a typical reaction in accordance with the present invention, the starting aminoalcohol is placed in a reaction vessel followed by addition of the reaction solvent. The order of subsequent addition of the cyanate and the acid employed typically does not produce any significantly different result. Preferably, the reagent addition steps are carried out at temperatures ranging from about -10°C to about 5°C .

15

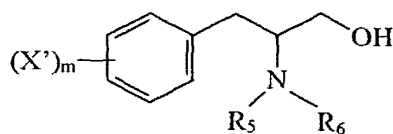
A preferred embodiment of this invention provides a novel process for preparing O-carbamoyl aminoalcohol represented by Formula III



III

20 wherein X' , m , R_5 and R_6 are as defined;

The process comprises reacting an aminoalcohol represented by Formula IV



7

IV

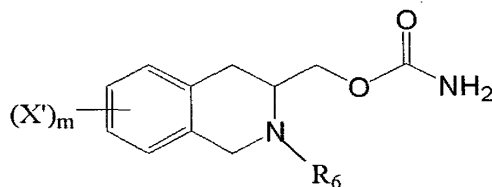
wherein X', m, R₅ and R₆ are as defined;

with a cyanate selected from the group consisting of sodium cyanate, potassium cyanate, ammonium cyanate, magnesium cyanate, and calcium cyanate;

5 and an excess of an acid selected from the group consisting of hydrochloric acid, acetic acid, trifluoroacetic acid, trichloroacetic acid, benzenesulfonic acid, toluenesulfonic acid, methanesulfonic acid, ethanesulfonic acid, and trifluoromethanesulfonic acid;
in an organic solvent medium selected from the group consisting of dichloromethane, chloroform, 1,2-dichloroethane, 1,1,1-trichloroethane, tetrahydrofuran, 1,2-
10 dimethoxyethane, diethyl ether, acetonitrile, propionitrile, benzene, toluene, xylene, and mixtures thereof.

Another preferred embodiment of this invention provides a novel process for preparing an O-carbamoyl aminoalcohol represented by Formula V

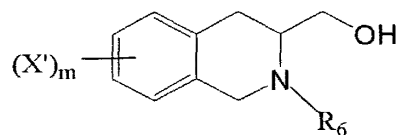
15



V

20 wherein X', m, and R₆ are as defined.

The process comprises reacting an aminoalcohol represented by Formula VI



VI

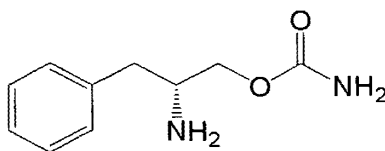
wherein X', m, and R₆ are as defined;

with a cyanate selected from the group consisting of sodium cyanate, potassium cyanate, ammonium cyanate, magnesium cyanate, and calcium cyanate;

and an excess of an acid selected from the group consisting of hydrochloric acid, acetic acid, trifluoroacetic acid, trichloroacetic acid, benzenesulfonic acid, toluenesulfonic acid, methanesulfonic acid, ethanesulfonic acid, and trifluoromethanesulfonic acid;

in an organic solvent medium selected from a group consisting of dichloromethane, chloroform, 1,2-dichloroethane, 1,1,1-trichloroethane, tetrahydrofuran, 1,2-dimethoxyethane, diethyl ether, acetonitrile, propionitrile, benzene, toluene, xylene, and mixtures thereof.

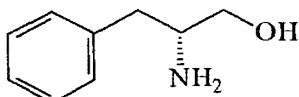
Still another preferred embodiment of the present invention provides a novel process for preparing O-carbamoyl-D-phenylalaninol represented by Formula VII



VII

which comprises reacting D-phenylalaninol represented by Formula VIII

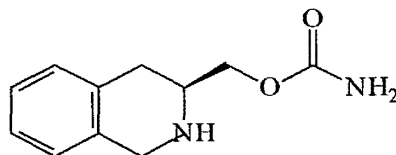
9



VIII

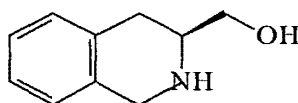
with a cyanate selected from the group consisting of sodium cyanate, potassium
 5 cyanate, ammonium cyanate, magnesium cyanate, and calcium cyanate;
 and an excess of an acid selected from the group consisting of hydrochloric acid, acetic
 acid, trifluoroacetic acid, trichloroacetic acid, benzenesulfonic acid, toluenesulfonic
 acid, methanesulfonic acid, ethanesulfonic acid, and trifluoromethanesulfonic acid;
 in an organic solvent medium selected from the group consisting of dichloromethane,
 10 chloroform, 1,2-dichloroethane, 1,1,1-trichloroethane, tetrahydrofuran, 1,2-
 dimethoxyethane, diethyl ether, acetonitrile, propionitrile, benzene, toluene, xylene,
 and mixtures thereof.

Still another preferred embodiment of the present invention provides a novel
 15 process for preparing O-carbamoyl-(L)-oxymethyl-1,2,3,4-tetrahydroisoquinoline
 represented by Formula IX



IX

20 which comprises reacting (L)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline
 represented by Formula X



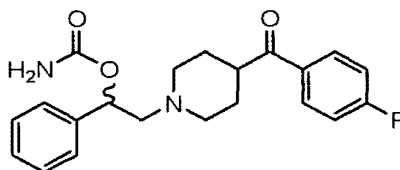
X

25

with a cyanate selected from the group consisting of sodium cyanate, potassium
 cyanate, ammonium cyanate, magnesium cyanate, and calcium cyanate;

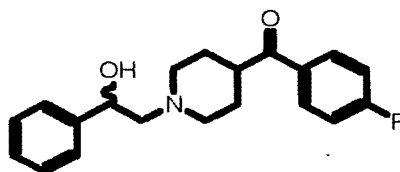
and an excess of an acid selected from the group consisting of hydrochloric acid, acetic acid, trifluoroacetic acid, trichloroacetic acid, benzenesulfonic acid, toluenesulfonic acid, methanesulfonic acid, ethanesulfonic acid, and trifluoromethanesulfonic acid; in an organic solvent medium selected from a group consisting of dichloromethane, chloroform, 1,2-dichloroethane, 1,1,1-trichloroethane, tetrahydrofuran, 1,2-dimethoxyethane, diethyl ether, acetonitrile, propionitrile, benzene, toluene, xylene and mixtures thereof.

Yet still another embodiment of the present invention provides a novel process for preparing carbamic acid 2-((4-fluorobenzoyl)piperidin-1-yl)-1-phenylethyl ester represented by Formula XI:



XI

which comprises reacting 2-(4-fluorobenzoyl)piperidin-1-yl)-1-phenylethanol represented by Formula XII



XII

with a cyanate selected from the group consisting of sodium cyanate, potassium cyanate, ammonium cyanate, magnesium cyanate, and calcium cyanate; and an excess of an acid selected from the group consisting of hydrochloric acid, acetic acid, trifluoroacetic acid, trichloroacetic acid, benzenesulfonic acid, toluenesulfonic

acid, methanesulfonic acid, ethanesulfonic acid, and trifluoromethanesulfonic acid;
in an organic solvent medium selected from a group consisting of dichloromethane,
chloroform, 1,2-dichloroethane, 1,1,1-trichloroethane, tetrahydrofuran, 1,2-
dimethoxyethane, diethyl ether, acetonitrile, propionitrile, benzene, toluene, xylene
5 and mixtures thereof.

Set forth below are definitions of the radicals covered by Formulae I to VI.
As utilized herein, the term "alkyl" means a straight- or branched-chain hydrocarbon
radical having from one to eight carbon atoms and includes, but is not limited to, methyl,
10 ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, and
the like, except where specifically stated otherwise.

The term "halogen" includes fluorine, chlorine, bromine, and iodine with fluorine
and chlorine being preferred.

The term "alkoxy" refers to an alkyl radical attached to the remainder of the
15 molecule by oxygen; this includes, but is not limited to, methoxy, ethoxy, and propoxy
groups.

The term "alkylthio" refers to an alkyl radical attached to the remainder of the
molecule by sulfur; this includes, but is not limited to, methylthio, ethylthio, and
propylthio groups.

20 The term "cycloalkyl" refers to a cyclic group of from three to six carbon atoms;
preferred cycloalkyl groups are cyclopentyl and cyclohexyl.

The term "aryl" refers to aromatic hydrocarbons such as phenyl, naphthyl, and
the like which may be unsubstituted or substituted with radicals selected from alkyl,
such as methyl or ethyl, alkoxy, such as methoxy or ethoxy, alkylthio, such as
25 methylthio, halogen, hydroxy, nitro and trifluoromethyl.

The term "arylalkyl" is as defined above for alkyl and for aryl. Such groups
include, but are not limited to, benzyl.

The following examples serve to illustrate certain embodiments of the invention,
30 without limiting the invention to these particular embodiments. Those skilled in the art
will recognize that the invention covers all alternatives, modifications and equivalents as
may be included within the scope of the appended claims.

Example 1. Preparation of O-Carbamoyl-(D)-phenylalaninol

In a dry 2L three-neck round bottomed flask equipped with a mechanical stirrer,
5 thermometer and 250mL addition funnel, 838mL of dichloromethane was charged
followed by D-phenylalaninol (100g, 0.66mole) and sodium cyanate (85g, 0.92mole).
The mixture was stirred in an ice-bath. The addition funnel was charged with
methanesulfonic acid (222.3g, 2.31mol) which was slowly added to the reaction mixture
so as to maintain the temperature below 5 °C. The reaction mixture thickened after the
10 completion of the addition. The ice-bath was removed and the reaction mixture was
stirred until D-phenylalaninol was no longer detected by TLC analysis. To the reaction
mixture, 80 grams of ice was added and the reaction mixture was cooled in an ice bath,
and a 20% aqueous solution of sodium hydroxide was added at such a rate as to maintain
the temperature below 5°C until the pH of the aqueous phase was between 10 and 11 as
15 measured by using pH paper. The mixture was transferred to a separatory funnel and the
organic phase was separated. The aqueous phase was extracted with two 500mL
portions of dichloromethane, and the combined organic phase was washed with brine
(350mL) and dried over sodium sulfate (50g) overnight. After removal of sodium
sulfate by filtration, the organic phase was concentrated in vacuo to yield 115g (89%) of
20 the free base form of the desired product O-Carbamoyl-(D)-phenylalaninol as an oil.

O-Carbamoyl-(D)-phenylalaninol hydrochloride was prepared as follows. The
crude reaction product O-Carbamoyl-(D)-phenylalaninol (115g) was dissolved in 120mL
of isopropanol and was transferred to three-neck round bottom flask equipped with a
mechanical stirrer. The mixture was chilled in an ice bath and the dropping funnel was
25 charged with 100mL of saturated HCl solution in isopropanol (6.5M). The HCl solution
was slowly added to the free base solution so as to maintain the temperature below 5 °C.
During the addition, precipitation of the desired product in HCl form was observed.
After the complete addition the mixture was stirred for another hour and 660mL of
acetone was added. The mixture was stirred for another hour and the white precipitate
30 was collected by filtration. The product was washed thoroughly with ice-chilled
isopropanol-acetone (1/3, v/v), and dried in vacuo. The product O-Carbamoyl-(D)-
phenylalaninol hydrochloride weighed 110gram (71.5%) and was a white solid.

Example 2. Preparation of O-Carbamoyl-(D)-3,4-dichlorophenylalaninol

In a dry 2L three-neck round bottomed flask equipped with a mechanical stirrer,
5 thermometer and 250mL addition funnel, 75mL of dichloromethane was charged
followed by (D)-3,4-dichlorophenylalaninol (4.00g, 0.018mole) and sodium cyanate
(1.87g, 0.027mole). The mixture was stirred in an ice-bath. The addition funnel was
charged with methanesulfonic acid (4.37g, 0.045mol) which was slowly added to the
reaction mixture so as to maintain the temperature below 5 °C. The reaction mixture
10 thickened after the completion of the addition. The ice-bath was removed and the
reaction mixture was stirred until (D)-3,4-dichlorophenylalaninol was no longer detected
by TLC analysis. A saturated aqueous solution of sodium bicarbonate was added to the
reaction mixture at such a rate as to maintain the temperature below 5°C until the pH of
the aqueous phase was between 9 and 10. The mixture was transferred to a separatory
15 funnel and the organic phase was separated. The aqueous phase was extracted with two
25mL portions of dichloromethane, and the combined organic phase was washed with
brine (30mL) and dried over sodium sulfate (5g) overnight. After removal of sodium
sulfate by filtration, the organic phase was concentrated in vacuo to yield 4.38g (91%) of
the free base form of the desired product O-Carbamoyl- (D)-3,4-dichlorophenylalaninol
20 as an oil.

O-Carbamoyl-(D)-3,4-dichlorophenylalaninol hydrochloride was prepared as
follows. The crude reaction product O-Carbamoyl-(D)-3,4-dichlorophenylalaninol
(3.27g) was dissolved in 10mL of tetrahydrofuran and was transferred to three-neck
round bottom flask equipped with a mechanical stirrer. The mixture was chilled in an ice
25 bath and the dropping funnel was charged with 13.7mL of 1N HCl solution in ethyl ether
(0.0137M). The HCl solution was slowly added to the free base solution so as to
maintain the temperature below 5 °C. During the addition, precipitation of the desired
product in HCl form was observed. The white precipitate was collected by filtration.
The product was washed thoroughly with ethyl ether, and dried in vacuo. The product
30 O-Carbamoyl-(D)-3,4-dichlorophenylalaninol hydrochloride weighed 3.68gram (99%)
and was a white solid.

Example 3. Preparation of O-Carbamoyl-(L)-3-oxymethyl-1,2,3,4-tetrahydroisoquinoline

(L)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (194g) was suspended in
5 dichloromethane (1.5L) and the mixture was chilled in an ice-bath. To the resulting
mixture, sodium cyanate (100.4g) was added followed by dropwise addition of
methanesulfonic acid (277.4mL) so as to maintain the reaction temperature below 5°C.
The addition took about 2 hours. The reaction mixture was stirred at room temperature
until the reaction was complete. 1.5 Liters of deionized water was added to the reaction
10 mixture. The aqueous phase was isolated and chilled in an ice-bath. The pH of the
aqueous phase was adjusted to between 10 and 11 by adding 20% aqueous solution of
sodium hydroxide. The resulting mixture was chilled in an ice-bath for about an hour
and the product was filtered and washed with two 100mL portions of deionized water.
The product was dried under vacuum to yield 221.6g (90.4%) of the desired product.

15

Example 4. Large-scale preparation of O-Carbamoyl-(D)-phenylalaninol

Eighteen kilogram (18.0kg) of D-phenylalaninol and 477.4kg of dichloromethane
were charged into a 300-gallon glass-lined reactor (Pfaudler, model R-01) blanketed
20 with nitrogen. The solution was cooled to 4.8°C. Sodium cyanate (10.8kg) was then
added. To this mixture methanesulfonic acid (39.0kg) was slowly charged over 2 hours
and 42 minutes while maintaining the temperature below 5°C. After the addition was
complete, the mixture was allowed to warm to 22.4°C over 2 hours and 3 minutes, and
agitated at ambient temperature for 16 hours and 50 minutes, at which time a sample was
25 submitted to quality control for analysis by HPLC and the amount of D-phenylalaninol
was less than 1.0%. The reactor contents were cooled to 4.1°C, and 100L of a 10%
solution of sodium hydroxide (prepared by dissolving 12.0kg sodium hydroxide in 108L
water) was added while maintaining the reactor contents at less than 5°C, so that the pH
was raised from pH 1.4 to pH 10.5. The two layers were separated. The upper aqueous
30 was further extracted two times by dichloromethane (133.4kg each), and the three
organic layers were combined. The product containing dichloromethane was washed
with 100L of a 1% solution of sodium hydroxide (prepared by dissolving 1.2 kg of

sodium hydroxide in 108L of water), and analyzed by HPLC. The level of late eluting impurities was less than 0.3%. The organic layer was washed with 50L of a 10% brine solution (prepared from dissolving 5 kg sodium chloride in 50L water), then with water (50L), and dried by adding anhydrous sodium sulfate (19kg) and allowing the mixture to stand for 18 hours. The sodium sulfate was removed by vacuum filtration on a 45cm Nutch funnel (Baxter filter paper grade 615-20). The filter cake was washed with dichloromethane (25kg), and the filtrate was concentrated to approximately 100L on a rotary evaporator at 25-30°C. The material was transferred to glass trays, dried in a vacuum oven at 40°C until a constant weight was achieved.

10

Example 5. Large-scale preparation of O-Carbamoyl-(L)-3-oxymethyl-1,2,3,4-tetrahydroisoquinoline

A 300-gallon reactor was charged with acetonitrile (236kg) and THIC-alcohol (15kg). The reaction mixture was cooled to less than 5°C and methanesulfonic acid (39.9kg) and sodium cyanate (17.8kg) were added. The reaction mixture was allowed to warm to about 20°C and held at this temperature for about 2 hours. HPLC analysis of the reaction mixture was performed to indicate that the reaction had gone to completion. The reaction mixture was diluted with toluene (104kg) and cooled to less than 5°C for 1 hour. The solid was isolated by filtration and the cake was washed with about 30L of toluene. The wet cake was added back to a 100-gallon reactor containing 10.1 kg of concentrated HCl in 150L of water. An in-process HPLC analysis showed that the reaction mixture contained no impurities greater than 1%. The reaction mixture was filtered to remove particulate matter. Then the upper toluene layer was removed and discarded. The aqueous layer was cooled to less than 5°C and the pH adjusted to 10.5 by carefully adding 20% aqueous sodium hydroxide. The mixture was stirred for 1 hour then the solid was collected by filtration. The wet cake was slurry washed with water (50L) and refiltered. The product was dried *in vacuo* at 40°C to yield 14.79kg of product, which was found to be 98.77% pure by HPLC assay.

30

Example 6. Large-scale preparation of carbamic acid 2-((4-fluorobenzoyl)piperidin-1-yl)-1-phenylethyl ester

A 100-gallon reactor was charged with dichloromethane (210.1kg) and 2-(4-fluorobenzoyl)piperidin-1-yl)-1-phenylethanol (15.9kg). The mixture was stirred at 100rpm and cooled to $5^{\circ}\text{C} \pm 5^{\circ}\text{C}$. Methanesulfonic acid (9.4kg) was added to the solution over a twenty-minute period while maintaining the temperature below 10°C . Stirring was continued for 1 hour at $5^{\circ}\text{C} \pm 5^{\circ}\text{C}$. Sodium cyanate was charged in five portions (total 6.4kg) every five minutes while maintaining the temperature under 10°C . The reaction mixture was stirred for thirty minutes at this temperature, then stirred overnight at $25^{\circ}\text{C} \pm 5^{\circ}\text{C}$. At one point, upon warming, the temperature of the reaction mixture briefly rose to 30.7°C . Another 0.7kg of sodium cyanate and 1.1kg of methanesulfonic acid were added to the reaction mixture and stirred at $25^{\circ}\text{C} \pm 5^{\circ}\text{C}$ overnight. An in-process HPLC test indicated that the reaction had not gone to completion ($<5\%$ starting material). Thus, additional sodium cyanate (1.3kg) and methanesulfonic acid (2.6kg) were added to the reactor and stirred continuously for 8 hours. At this time the reaction mixture was found to contain only 3.2% starting material. The solid was collected by filtration. The filter cake was washed with two portions (23.0kg, 22.5kg) of dichloromethane. The wet cake was held overnight under a nitrogen atmosphere. The crude product was charged back to a 100-gallon reactor containing 140L of deionized water. The mixture was stirred at 90 rpm and cooled to $5^{\circ}\text{C} \pm 5^{\circ}\text{C}$. A 50% solution of sodium hydroxide (7.6kg) was added to the reactor while maintaining the temperature below 10°C . The mixture was stirred at this temperature for one hour then the solid was isolated by filtration. The filter cake was washed with 49L of deionized water. The solid was charged back into a reactor containing 52.5kg of heptane. The mixture was stirred for 15 minutes then the solid was isolated by filtration. The solid was washed with heptane (2.3kg) and then dried overnight *in vacuo* (27mm) at 25°C .

The dried material (16.8kg) was charged back to a reactor containing 464.1kg of dichloromethane. The mixture was heated to reflux (40°C) for one hour. The slurry was cooled to $34^{\circ}\text{C} \pm 5^{\circ}\text{C}$ and passed through a Cuno Filter into a clean reactor. The filter was rinsed with two portions (22.3kg each) of warm (31°C) dichloromethane. The

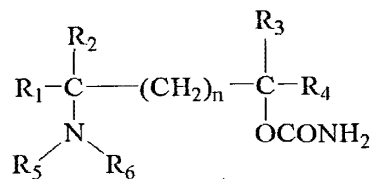
combined filtrate was reduced in volume to approximately 240L. The slurry was cooled to $3^{\circ}\text{C} \pm 5^{\circ}\text{C}$ for 2 hours and the solid was then collected by filtration. The filter cake was washed with 29.5kg of dichloromethane. The solid was dried in vacuo in a rotary cone drier at 28°C for 46.5 hours. The product so obtained weighted 12.2kg,
5 representing a 67.9% yield.

It is understood that various other embodiments and modifications in the practice of the invention will be apparent to, and can be readily made by, those skilled in the art without departing from the scope of the invention described above. Accordingly, it is not
10 intended that the scope of the claims appended hereto be limited to the exact description set forth above, but rather that the claims be construed as encompassing all of the features of patentable novelty which reside in the present invention, including all the features and embodiments which would be treated as equivalents thereof by those skilled in the art to which the invention pertains.

15

What is claimed is:

1. A process for preparing an O-carbamoyl aminoalcohol represented by Formula I



I

wherein:

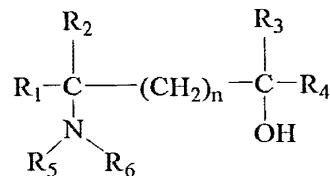
n is an integer from 0 and 5;

R₁, R₂, R₃ and R₄ are individually selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted or unsubstituted aryl and arylalkyl wherein the aryl portion of which may be unsubstituted or substituted by (X')_m, wherein m is an integer from 0 to 4 and X' is selected from the group consisting of hydrogen, alkyl, alkoxy, alkylthio, halogen, hydroxy, nitro and trifluoromethyl;

R₅ and R₆ are individually selected from a group consisting of hydrogen, alkyl and arylalkyl wherein the aryl portion may be substituted or unsubstituted by (X')_m, wherein m and X' are as defined; or

R₁ and R₅ together with the carbon and nitrogen to which they are attached may form an unfused or fused heterocyclic ring having from 4 to 10 members;

the process comprising reacting an aminoalcohol represented by Formula II

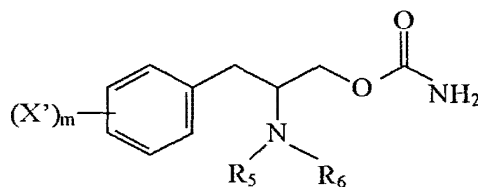


II

wherein n, R₁, R₂, R₃, R₄, R₅ and R₆ are as defined;

with a cyanate and an excess of an acid in an organic solvent medium.

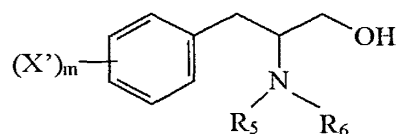
2. A process according to claim 1, wherein the cyanate is an alkali cyanate or alkaline earth cyanate.
3. A process according to claim 2, wherein the cyanate is selected from the group
5 consisting of sodium cyanate, potassium cyanate, ammonium cyanate, magnesium cyanate, and calcium cyanate.
4. A process according to claim 1, wherein the acid is selected from the group
10 consisting of hydrochloric acid, sulfuric acid, phosphoric acid, acetic acid, halogenated acetic acids, arylsulfonic acids, alkylsulfonic acids and halogenated alkylsulfonic acids.
5. A process according to claim 1, wherein the organic solvent medium is selected
15 from the group consisting of halogenated alkanes solvents, ethereal solvents, nitrile solvents, aromatic solvents; and mixtures thereof.
6. A process according to claim 1, wherein the cyanate is sodium cyanate and the acid is methanesulfonic acid.
- 20 7. A process according to claim 6, wherein the organic solvent medium is dichloromethane or acetonitrile.
8. A process according to claim 1, wherein the O-carbamoyl aminoalcohol is represented by Formula III



III

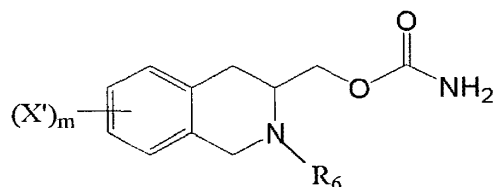
wherein X' , m , R_5 and R_6 are as defined;

the process comprising reacting an aminoalcohol represented by Formula IV



IV

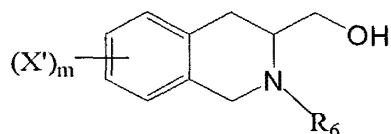
- 5 wherein X', m, R₅ and R₆ are as defined;
with a cyanate and an excess of an acid in an organic solvent medium.
9. A process according to claim 1, wherein the O-carbamoyl aminoalcohol is represented by Formula V



V

wherein X', m, and R₆ are as defined; :

the process comprising reacting an aminoalcohol represented by Formula VI

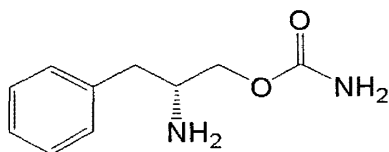


VI

wherein X', m, and R₆ are as defined;

with a cyanate and an excess of an acid in an organic solvent medium.

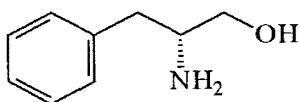
10. A process according to claim 1, wherein the O-carbamoyl aminoalcohol is represented by Formula VII



VII

5

the process comprising reacting D-phenylalaninol represented by Formula VIII



VIII

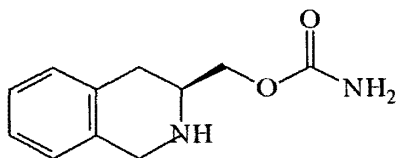
10

with a cyanate and an excess of an acid in an organic solvent medium.

11. A process according to claim 10, wherein the cyanate is selected from the group consisting of sodium cyanate, potassium cyanate, ammonium cyanate, magnesium cyanate, and calcium cyanate; the acid is selected from the group consisting of hydrochloric acid, acetic acid, trifluoroacetic acid, trichloroacetic acid, benzenesulfonic acid, toluenesulfonic acid, methanesulfonic acid, ethanesulfonic acid, and trifluoromethanesulfonic acid; and the organic solvent medium is selected from the group consisting of dichloromethane, chloroform, 1,2-dichloroethane, 1,1,1-trichloroethane, tetrahydrofuran, 1,2-dimethoxyethane, diethyl ether, acetonitrile, propionitrile, benzene, toluene, xylene, and mixtures thereof.
12. A process according to claim 10, wherein the cyanate is sodium cyanate and the acid is methanesulfonic acid.
13. A process according to claim 12, wherein the organic solvent medium is dichloromethane.

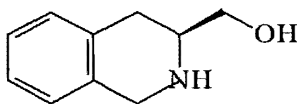
25

14. A process according to claim 1, wherein the O-carbamoyl aminoalcohol is O-carbamoyl-(L)-oxymethyl-1,2,3,4-tetrahydroisoquinoline represented by Formula IX



IX

the process comprising reacting (L)-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline represented by Formula X



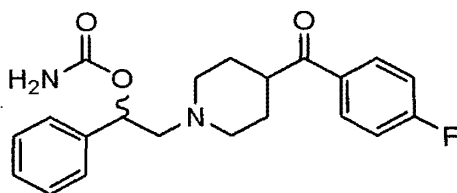
X

with a cyanate and an excess of an acid in an organic solvent medium.

15. A process according to claim 14, wherein the cyanate is selected from the group consisting of sodium cyanate, potassium cyanate, ammonium cyanate, magnesium cyanate, and calcium cyanate; the acid is selected from the group consisting of hydrochloric acid, acetic acid, trifluoroacetic acid, trichloroacetic acid, benzenesulfonic acid, toluenesulfonic acid, methanesulfonic acid, ethanesulfonic acid, and trifluoromethanesulfonic acid; and the organic solvent medium is selected from the group consisting of dichloromethane, chloroform, 1,2-dichloroethane, 1,1,1-trichloroethane, tetrahydrofuran, 1,2-dimethoxyethane, diethyl ether, acetonitrile, propionitrile, benzene, toluene, xylene, and mixtures thereof.
16. A process according to claim 14, wherein the cyanate is sodium cyanate and the acid is methanesulfonic acid.
17. A process according to claim 16, wherein the organic solvent medium is dichloromethane.

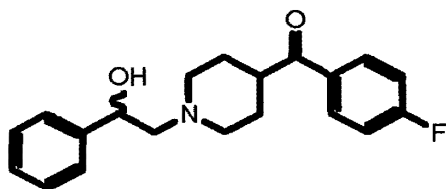
18. A process according to claim 16, wherein the organic solvent medium is acetonitrile.

19. A process according to claim 1, wherein the O-carbamoyl aminoalcohol is carbamic acid 2-((4-fluorobenzoyl)piperidin-1-yl)-1-phenylethyl ester represented by Formula XI:



XI

the process comprising reacting 2-(4-fluorobenzoyl)piperidin-1-yl)-1-phenylethanol represented by Formula XII



XII

with a cyanate and an excess of an acid in an organic solvent medium.

20. A process according to claim 19, wherein the cyanate is selected from the group consisting of sodium cyanate, potassium cyanate, ammonium cyanate, magnesium cyanate, and calcium cyanate; the acid is selected from the group consisting of hydrochloric acid, acetic acid, trifluoroacetic acid, trichloroacetic acid, benzenesulfonic acid, toluenesulfonic acid, methanesulfonic acid, ethanesulfonic acid, and trifluoromethanesulfonic acid; and the organic solvent medium is selected from the group consisting of dichloromethane, chloroform, 1,2-dichloroethane, 1,1,1-trichloroethane, tetrahydrofuran, 1,2-dimethoxyethane, diethyl ether, acetonitrile, propionitrile, benzene, toluene, xylene, and mixtures thereof.

21. A process according to claim 19, wherein the cyanate is sodium cyanate and the acid is methanesulfonic acid.
22. A process according to claim 21, wherein the organic solvent medium is
5 dichloromethane.
23. A process according to claim 1, wherein the amount of the acid is between about one to about ten molar equivalents in excess of the total number of amine groups in the aminoalcohol represented by Formula II.
10
24. A process according to claim 1, wherein the molar ratio of cyanate to aminoalcohol represented by Formula II is between about one to about ten.
25. A process according to claim 1, wherein the weight to volume ratio of the amount of
15 the aminoalcohol represented by Formula II to the amount of the organic solvent medium is within the range of from about 1:3 to about 1:100.
26. A process according to claim 1, wherein the reaction is carried out at a temperature ranging from about -80°C to about 80°C.
20
27. A process according to claim 25, wherein the reaction is carried out at a temperature ranging from about -10°C to about 60°C.
28. A process according to claim 1, wherein the O-carbamoyl aminoalcohol represented
25 by Formula I and aminoalcohol represented by Formula II are in the racemic form.
29. A process according to claim 1, wherein the O-carbamoyl aminoalcohol represented by Formula I and aminoalcohol represented by Formula II are in optically active form.
30

30. A process according to claim 1, wherein the O-carbamoyl aminoalcohol represented by Formula I and aminoalcohol represented by Formula II are in are in the S-form.
31. A process according to claim 1, wherein the O-carbamoyl aminoalcohol represented
5 by Formula I and aminoalcohol represented by Formula II are in the R-form.

INTERNATIONAL SEARCH REPORT

 International application No.
PCT/KR2004/002571
A. CLASSIFICATION OF SUBJECT MATTER**IPC7 C07C 237/10**

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)

IPC7 C07C, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean Patents and Applications for Inventions since 1975Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS on line**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98/15526 A1 (YUKONG LTD.) 16 APR. 1998 See the whole document	1-31
A	WO 96/32375 A1 (YUKONG LTD.) 17 OCT. 1996 See the whole document	1-31
A	WO 96/07636 A1 (YUKONG LTD.) 15 JUN. 1996 See the whole document	1-31
A	DE 1961599 A (CHINOIN GYOGYSZER) 18 JUN. 1970 See the whole document -----End of documents-----	1-31

☐ 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 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

17 JANUARY 2005 (17.01.2005)

Date of mailing of the international search report

18 JANUARY 2005 (18.01.2005)

Name and mailing address of the ISA/KR


 Korean Intellectual Property Office
920 Dunsan-dong, Seo-gu, Daejeon 302-701,
Republic of Korea

Facsimile No. 82-42-472-7140

Authorized officer

KIM, YONG

Telephone No. 82-42-481-8148



Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2004/002571

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 98/15526 A1	16 APR. 1998	CA 2240060 AA EP 873308 B1 CN 1076016 B JP 2000-502364 T2	1998.04.16 2002.01.02 2001.12.12 2000.02.29
WO 96/32375 A1	17 OCT. 1996	KR 173863 B1 US 6140532 A EP 820438 B1 JP 11503447 T2	1999.04.01 2000.10.31 2001.06.20 1999.03.26
WO 96/07636 A1	15 JUN. 1996	KR 197892 B1 CA 2176012 C EP 728129 B1 JP 09503231 T2 US 5955499 A	1999.06.15 1999.01.05 1999.11.03 1997.03.31 1999.09.21
DE 1961599 A	18 JUN. 1970	FR 2025991 A5 ES 374449 A1 AT 297016 B	1970.09.10 1972.01.01 1972.03.10

Form PCT/ISA/210 (patent family annex) (January 2004)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
4 January 2007 (04.01.2007)

PCT

(10) International Publication Number
WO 2007/001841 A1(51) International Patent Classification:
A61P 15/10 (2006.01) *A61K 31/165* (2006.01)(74) Agent: **JOHNSON, Philip, S.**; JOHNSON & JOHNSON,
One Johnson & Johnson Plaza, New Brunswick, NJ 08901-
7003 (US).(21) International Application Number:
PCT/US2006/023068(81) Designated States (*unless otherwise indicated, for every
kind of national protection available*): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV,
LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI,
NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE,
SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG,
US, UZ, VC, VN, ZA, ZM, ZW.

(22) International Filing Date: 13 June 2006 (13.06.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/692,809 22 June 2005 (22.06.2005) US(84) Designated States (*unless otherwise indicated, for every
kind of regional protection available*): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT,
RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG).(71) Applicant (*for all designated States except US*):
JANSSEN PHARMACEUTICA, N.V. [BE/BE];
Turnhoutseweg 30, B-2340 Beerse (BE).

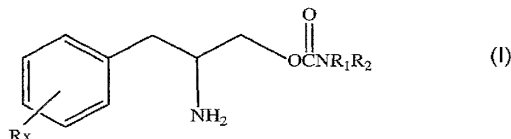
(71) Applicants and

(72) Inventors: **PALUMBO, Joseph** [US/US]; 616 Brookside
Avenue, St. Davids, PA 19087 (US). **SPORN, Johathan**
[US/US]; 103 Mercer Street, Princeton, NJ 08540 (US).
STECKLER, Thomas [DE/BE]; Stokt 112, B-2400
Mol/milligem (BE). **CHOI, Yong** [US/US]; 101 Windsor
Drive, Pine Brook, NJ 07058 (US). **LEE, James, S.**
[US/US]; 15 Anysley Court, Montville, NJ 007045 (US).**Published:**

— with international search report

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: TREATMENT OF SEXUAL DYSFUNCTION

(57) **Abstract:** This invention is directed to a method of treating sexual dysfunction in a subject, comprising the step of administer-
ing a therapeutically effective amount of a compound of Formula (I): or a pharmaceutically acceptable salt or ester thereof wherein
Rx is a member selected from the group consisting of hydrogen, lower alkyl of 1 to 8 carbon atoms, halogen selected from F, Cl, Br
and I, alkoxy containing 1 to 3 carbon atoms, nitro, hydroxy, trifluoromethyl, and thioalkoxy containing 1 to 3 carbon atoms; x is an
integer of 1 to 3, with the proviso that R may be the same or different when x is 2 or 3; R₁ and R₂ can be the same or different from
each other and are independently selected from the group consisting of hydrogen, lower alkyl of 1 to 8 carbon atoms, aryl, arylalkyl,
cycloalkyl of 3 to 7 carbon atoms; R₁ and R₂ can be joined to form a 5 to 7-membered heterocycle substituted with a member selected
from the group consisting of hydrogen, alkyl, and aryl groups, wherein the cyclic compound can comprise 1 to 2 nitrogen atoms and
O to 1 oxygen atom, wherein the nitrogen atoms are not directly connected with each other or with the oxygen atom.

WO 2007/001841 A1

METHODS FOR TREATING SEXUAL DYSFUNCTION**BACKGROUND OF THE INVENTION****FIELD OF INVENTION**

The present invention relates generally to the fields of pharmacology, urology and psychiatry and to methods of treating sexual dysfunction. More specifically, this invention provides methods for the use of certain carbamate compounds for use alone or in combination with other medications for the treatment of sexual dysfunction in human females or males

DESCRIPTION OF RELATED ART

Masters and Johnson defined sexual dysfunction as "the persistent impairment of normal or usual patterns of sexual interest and/or response" (Masters et al., Human Sexual Response, Boston, Mass.: Little, Brown and Co. 1966). The problem came to national attention when the results of the National Health and Societal Life Survey were published in 1999. Interviews with over 3000 American men and women aged 18-59 revealed that 31% of men and 43% of women (about 40 million) experienced some degree of sexual dysfunction. The scope of the problem was such that it was said to "warrant recognition as a significant public health concern." See Laumann et al., "Sexual Dysfunction in the United States: prevalence and predictors," JAMA 281:537 (1999). Although sexual dysfunction rarely threatens physical health, it can take a heavy psychological toll, bringing on depression, anxiety, and debilitating feelings of inadequacy.

Sexual dysfunction (SD) is a significant clinical problem that can affect both males and females. The causes of SD may be both organic as well as psychological. Organic aspects of SD are typically caused by underlying vascular diseases, such as those associated with hypertension or diabetes mellitus, by

prescription medication and/or by psychiatric disease such as depression. Physiological factors include fear, performance anxiety and interpersonal conflict. SD impairs sexual performance, diminishes self-esteem and disrupts personal relationships thereby inducing personal distress. In the clinic, SD disorders have been divided into female sexual dysfunction (FSD) disorders and male sexual dysfunction (MSD) disorders (Melman et al 1999 J. Urology 161, 5-11). FSD is best defined as the difficulty or inability of a woman to find satisfaction in sexual expression.

Male sexual dysfunction (MSD) is generally associated with either erectile dysfunction, also known as male erectile dysfunction (MED) and/or ejaculatory disorders such as premature ejaculation or rapid ejaculation (PED), anorgasmia (unable to achieve orgasm) or male orgasmic disorder (MOD) or desire disorders such as hypoactive sexual desire disorder (lack of interest in sex) (HSDD) and can result from a variety of causes, including physical illness, depression, hormonal abnormality or medications that affect libido or performance.

Recent studies suggest that, at least, 43% of woman have some form of sexual dysfunction (See above, Lauman et al. JAMA, 281:537, 1999). These can be categorized into four main areas: 1) sexual desire disorders, namely hypoactive sexual desire or sexual aversion disorder; 2) sexual arousal disorders; 3) orgasmic disorders; and 4) sexual pain disorders which include dyspareunia and vaginismus.

The dominant category of female sexual dysfunction (FSD) is female sexual arousal disorder (FSAD), which affects up to 75% of women diagnosed with FSD.

The categories of female sexual dysfunction (FSD) are best defined by contrasting them to the phases of normal female sexual response: desire, arousal and orgasm (see S R Leiblum, (1998), Definition and Classification of Female Sexual Disorders, Int. J. Impotence Res., 10, S104-S106). Sexual desire or libido is the drive for sexual expression. Its manifestations include sexual thoughts and fantasies. Arousal includes the vascular response to sexual

stimulation, an important component of which is genital engorgement and increased vaginal lubrication, elongation of the vagina and increased genital sensation/sensitivity and a subjective excitement response. Orgasm is the release of sexual tension that has culminated during arousal. Hence, Female Sexual Disorder (FSD) occurs when a woman has an absent, inadequate or unsatisfactory response in any one or more of these phases, usually desire, arousal or orgasm.

The American Psychiatric Association classifies female sexual dysfunction (FSD) into four classes: FSAD, hypoactive sexual desire disorder (HSDD), female orgasmic disorder (FOD), and sexual pain disorders (e.g. dyspareunia and vaginismus) [see the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)].

DSM-IV defines the four classes as follows:

HSDD--Persistently or recurrently deficient (or absent) sexual fantasies and desire for sexual activity that causes marked distress or interpersonal difficulties. The judgement of deficiency or absence is made by the clinician, taking into account factors that affect functioning, such as age and the context of the person's life.

FSAD--Persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate lubrication-swelling response of sexual excitement

FOD--Persistent or recurrent delay in, or absence of, orgasm following a normal sexual excitement phase. Women exhibit wide variability in the type or intensity of stimulation that triggers orgasm. The diagnosis of FOD should be based on the clinician's judgement that the woman's orgasmic capacity is less than would be reasonable for her age, sexual experience, and the adequacy of the sexual stimulation she receives.

Sexual Pain Disorders such as Dyspareunia and Vaginismus. Dyspareunia is the recurrent or persistent genital pain associated with sexual intercourse. Vaginismus is the recurrent or persistent involuntary spasm of the

musculature of the outer third of the vagina that interferes with sexual intercourse.

The American Foundation for Urologic Disease has also developed definitions using the same four classes (see The Journal of Urology, 2000, Vol 163, page 888-893). The definitions are very similar to those of the DSM-IV:

1) HSDD is the persistent or recurrent deficiency (or absence) of sexual fantasies/thoughts, and/or desire for or receptivity to sexual activity, which causes personal distress.

HSDD is present if a woman has no or little desire to be sexual, and has no or few sexual thoughts or fantasies. This type of FSD can be caused by low testosterone levels, due either to natural menopause or to surgical menopause. Other causes in both pre-menopausal woman (i.e. woman who are pre-menopausal and who have not have hysterectomies) as well as post menopausal women include illness, medications, fatigue, depression and/or anxiety. Factors having a potential (conscious or sub-conscious) psychological impact such as relationship difficulties or religious factors may be related to the presence of/development of HSDD in females.

The term significant HSDD means a level of HSDD which causes some degree of personal distress to the female subject. Preferably significant HSDD means a level of HSDD which causes some degree of distress and is measurable, for example, through evaluation by a clinician using a semi-structured questionnaire.

2) FSAD is the persistent or recurrent inability to attain or maintain sufficient sexual excitement, causing personal distress, which may be expressed as a lack of subjective excitement, or genital (lubrication/swelling) or other somatic responses.

FSAD is a highly prevalent sexual disorder affecting pre-, peri-, and post menopausal women. It is associated with concomitant disorders such as depression, cardiovascular diseases, diabetes and UG disorders. FSAD is characterized by inadequate genital response to sexual stimulation. The genitalia do not undergo the engorgement that characterizes normal sexual arousal. The

vaginal walls are poorly lubricated, so that intercourse is painful. Orgasms may be impeded. FSAD can be caused by reduced estrogen at menopause or after childbirth and during lactation, as well as by illnesses, with vascular components such as diabetes and arteriosclerosis. Other causes result from treatment with diuretics, antihistamines, antidepressants e.g. selective serotonin reuptake inhibitors or antihypertensive agents.

3) FOD is the persistent or recurrent difficulty, delay in or absence of attaining orgasm following sufficient sexual stimulation and arousal, which causes personal distress.

4) Sexual pain disorders: Dyspareunia is the recurrent or persistent genital pain associated with sexual intercourse. Vaginismus is the recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with vaginal penetration, which causes personal distress. Dyspareunia and vaginismus are characterised by pain resulting from penetration and sexual activity and may be caused by medications which reduce lubrication, endometriosis, pelvic inflammatory disease, inflammatory bowel disease or urinary tract problems.

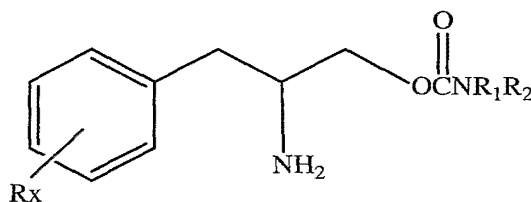
The etiology of sexual dysfunction, in both men and women, may include vascular/endothelial disease such as hypertension, neurological disorders, and hormonal disorders, such as decreased levels of estrogen and/or testosterone. Sexual dysfunction in both men and women can also be caused, or exacerbated, by medication such as antidepressants, antihypertensive and many other classes of commonly used medication. Given the extensive use of these medication by all ages and both sexes it is especially important to develop means of treating medication induced sexual dysfunction.

Clearly FSD especially, is a complex disorder with more active clinical issues than the corresponding male disorder, penile erectile dysfunction (MED). Hence it is not surprising that to date there has been little success in treating FSD, and use of treatments that are successful in treating MED, such as sildenafil, have shown only limited success in ameliorating FSD. It may be that a different spectrum of activities, mechanisms, dosing regimens and duration of

action of agents is needed when devising treatments for women, relative to approaches taken with men. But treatments for sexual dysfunction of all types in both men and women, with the partial exception of MED, is inadequate and thus there is a great clinical need for such treatments.

SUMMARY OF THE INVENTION

The present invention is directed to methods of treating sexual dysfunction in a subject, comprising the step of the administration, to a subject in need of such treatment, of a therapeutically effective amount a compound of the Formula (1):



(I)

or a pharmaceutically acceptable salt or ester thereof;
wherein

R_x is a member selected from the group consisting of hydrogen, lower alkyl of 1 to 8 carbon atoms, halogen selected from F, Cl, Br and I, alkoxy containing 1 to 3 carbon atoms, nitro, hydroxy, trifluoromethyl, and thioalkoxy containing 1 to 3 carbon atoms;

x is an integer of 1 to 3, with the proviso that R may be the same or different when x is 2 or 3;

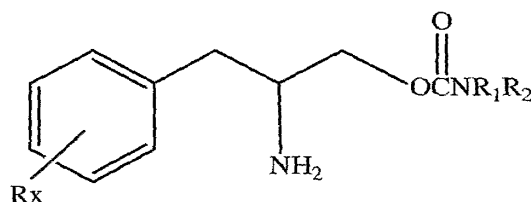
R₁ and R₂ can be the same or different from each other and are independently selected from the group consisting of hydrogen, lower alkyl of 1 to 8 carbon atoms, aryl, arylalkyl, cycloalkyl of 3 to 7 carbon atoms;

R₁ and R₂ can be joined to form a 5 to 7-membered heterocycle substituted with a member selected from the group consisting of hydrogen, alkyl, and aryl groups,

wherein the cyclic compound can comprise 1 to 2 nitrogen atoms and 0 to 1 oxygen atom,

wherein the nitrogen atoms are not directly connected with each other or with the oxygen atom.

Embodiments of the invention include methods of treating sexual dysfunction in a subject, comprising the step of the administration, to a subject in need of such treatment, of a therapeutically effective amount of an enantiomer of Formula 1 substantially free of other enantiomers or an enantiomeric mixture wherein one enantiomer of Formula 1 predominates;



(I)

or a pharmaceutically acceptable salt or ester thereof;

wherein

R_x is a member selected from the group consisting of hydrogen, lower alkyl of 1 to 8 carbon atoms, halogen selected from F, Cl, Br and I, alkoxy containing 1 to 3 carbon atoms, nitro, hydroxy, trifluoromethyl, and thioalkoxy containing 1 to 3 carbon atoms;

x is an integer of 1 to 3, with the proviso that R may be the same or different when x is 2 or 3;

R₁ and R₂ can be the same or different from each other and are independently selected from the group consisting of hydrogen, lower alkyl of 1 to 8 carbon atoms, aryl, arylalkyl, cycloalkyl of 3 to 7 carbon atoms;

R₁ and R₂ can be joined to form a 5 to 7-membered heterocycle substituted with a member selected from the group consisting of hydrogen, alkyl, and aryl groups,

wherein the cyclic compound can comprise 1 to 2 nitrogen atoms and 0 to 1 oxygen atom,

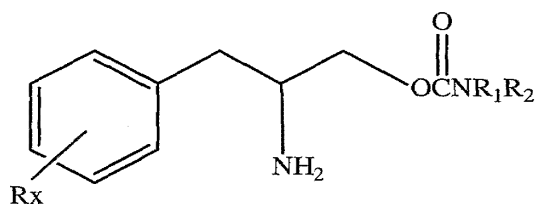
wherein the nitrogen atoms are not directly connected with each other or with the oxygen atom.

Preferably, wherein Rx, R1 and R2 are all selected from hydrogen.

Preferably wherein one enantiomer selected from the group consisting of Formula 1 predominates to the extent of about 90% or greater.

More preferably, wherein one enantiomer selected from the group consisting of Formula 1 predominates to the extent of about 98% or greater.

Embodiments of the invention include a method for using the enantiomer selected from the group consisting of Formula 1 for the preparation of a medicament for the treatment of sexual dysfunction,



(I)

or a pharmaceutically acceptable salt or ester thereof
wherein

Rx is a member selected from the group consisting of hydrogen, lower alkyl of 1 to 8 carbon atoms, halogen selected from F, Cl, Br and I, alkoxy containing 1 to 3 carbon atoms, nitro, hydroxy, trifluoromethyl, and thioalkoxy containing 1 to 3 carbon atoms;

x is an integer of 1 to 3, with the proviso that R may be the same or different when x is 2 or 3;

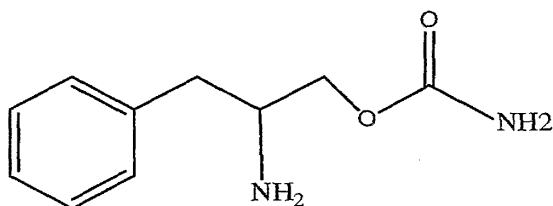
R₁ and R₂ can be the same or different from each other and are independently selected from the group consisting of hydrogen, lower alkyl of 1 to 8 carbon atoms, aryl, arylalkyl, cycloalkyl of 3 to 7 carbon atoms;

R₁ and R₂ can be joined to form a 5 to 7-membered heterocycle substituted with a member selected from the group consisting of hydrogen, alkyl, and aryl groups,

wherein the cyclic compound can comprise 1 to 2 nitrogen atoms and 0 to 1 oxygen atom,

wherein the nitrogen atoms are not directly connected with each other or with the oxygen atom.

Embodiments of the invention include a method for using the enantiomer of Formula 1 substantially free of other enantiomers that is the enantiomer of Formula 1b or an enantiomeric mixture wherein the enantiomer of Formula 1b predominates. (note: in the structural formula of Formula 1b below the amino group attached to the beta carbon projects into the plane of the paper. This is the dextrorotary (D) enantiomer that is of absolute configuration (R))



Formula 1b

wherein

the enantiomer of Formula 1b predominates to the extent of about 90% or greater.

More preferably, wherein an enantiomer of Formula 1b predominates to the extent of about 98% or greater.

Embodiments of the invention also include methods wherein the carbamate compounds of the invention are administered concomitantly with other medications that may themselves cause sexual dysfunction in order to prevent, reverse or minimizes this unwanted side effect.

Such other medications include but are not limited to; conventional antidepressants and other psychiatric medications that include but are not limited to; selective serotonin reuptake inhibitors (SSRI's); selective serotonin and norepinephrine reuptake inhibitors (SNRI's); older tricyclic antidepressants

(TCAs); monoamine oxidase inhibitors (MAO-inhibitors), reversible inhibitors of monoamine oxidase (RIMAs), tertiary amine tricyclics and secondary amine tricyclic antidepressants, antipsychotics, anticonvulsants, lithium carbonate, and including but not limited to fluoxetine, duloxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine, sertraline, 5- MCA-NAT, lithium carbonate (LiCO₃), isocarboxazid, phenelzine, tranylcypromine, selegiline, moclobemide, amitriptyline, clomipramine, doxepin, imipramine, trimipramine, amoxapine, desipramine, maprotiline, nortriptyline and protriptyline, kappa opioid receptor antagonists; selective neurokinin antagonists, corticotropin releasing factor (CRF) antagonists, antagonists of tachykinins, α - adrenoreceptor antagonists., and other types of medications such as; antihypertensive medications, cardiac medications such as calcium channel blockers, ACE inhibitors, statins, etc and pharmaceutically acceptable salts thereof and wherein the therapeutically effective amount of enantiomer is from about 0.01 mg/kg/dose to about 300 mg/kg/dose.

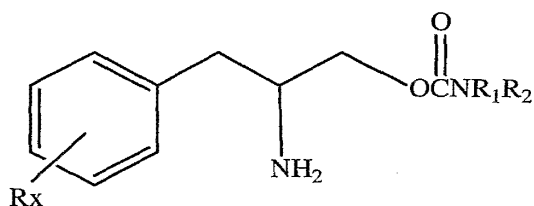
BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows the effect of increasing doses of test compound on the lordotic response in female rats as compared to vehicle and the active control quinelorane.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a method of treatment of sexual dysfunction. The method comprising, administering to a subject in need thereof a therapeutically effective amount of a compound selected from the group consisting of phenylalkylamino carbamates.

The invention features compounds of Formula 1:



Formula 1

or enantiomers, diastereomers, racemates or mixtures thereof, or hydrates, solvates and pharmaceutically acceptable salts, esters and amides thereof: wherein;

R_x is a member selected from the group consisting of hydrogen, lower alkyl of 1 to 8 carbon atoms, halogen selected from F, Cl, Br and I, alkoxy containing 1 to 3 carbon atoms, nitro, hydroxy, trifluoromethyl, and thioalkoxy containing 1 to 3 carbon atoms;

x is an integer of 1 to 3, with the proviso that R may be the same or different when x is 2 or 3;

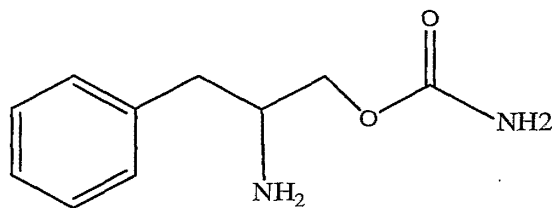
R₁ and R₂ can be the same or different from each other and are independently selected from the group consisting of hydrogen, lower alkyl of 1 to 8 carbon atoms, aryl, arylalkyl, cycloalkyl of 3 to 7 carbon atoms;

R₁ and R₂ can be joined to form a 5 to 7-membered heterocycle substituted with a member selected from the group consisting of hydrogen, alkyl, and aryl groups,

wherein the cyclic compound can comprise 0 to 2 nitrogen atoms and 0 to 1 oxygen atoms,

wherein the nitrogen atoms are not directly connected with each other or with the oxygen atom and the pharmaceutically acceptable salts and esters thereof.

The present method also includes the use of a compound selected from the group consisting Formula 1 wherein R_x, R₁ and R₂ are preferably selected from hydrogen, this is Formula 1a below;



Formula 1a

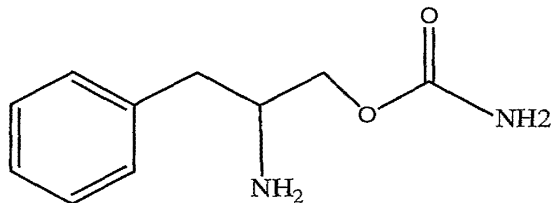
The present method also preferably includes the use of the D (or dextrorotary) enantiomer (of absolute configuration R) selected from the group consisting of Formula 1 or an enantiomeric mixture thereof:

wherein:

the D enantiomer selected from the group consisting of Formula 1a predominates and:

Rx, R1 and R2 are preferably selected from hydrogen,

this is O-carbamoyl-(D)-phenylalaninol, this compound can also be named (R)-(beta-amino-benzenepropyl) carbamate monohydrochloric acid, Formula 1b below; also referred to herein as "test compound"



Formula 1b

(note: in the structural formula of Formula 1b above (test compound), the amino group attached to the beta carbon projects into the plane of the paper. This is the dextrorotary (D) enantiomer that is of absolute configuration (R))

For enantiomeric mixtures wherein one enantiomer selected from the group consisting of Formula 1 predominates, preferably, an enantiomer selected from the group consisting of Formula 1 predominates to the extent of about 90% or greater.

More preferably, an enantiomer selected from the group consisting of Formula 1 predominates to the extent of about 98% or greater.

The compounds of Formula 1 can be synthesized by methods known to a skilled artisan. Some reaction schemes for synthesizing compounds of Formula (I) have been described in published; US Patent No. 5705640, US Patent No. 5756817, US Patent No. 5955499, and US Patent No. 6140532.

Details of the above reactions schemes as well as representative examples on the preparation of specific compounds have been described in published; US Patent No. 5705640, US Patent No. 5756817, US Patent No. 5955499, US Patent No. 6140532, all incorporated herein by reference in their entirety.

The salts and esters of the compounds of Formula (I) can be produced by treating the compound with an acid (HX) in suitable solvent or by means well known to those of skill in the art.

From Formula 1 it is evident that some of the compounds of the invention have at least one and possibly more asymmetric carbon atoms. It is intended that the present invention include within its scope the stereochemically pure isomeric forms of the compounds as well as their racemates. Stereochemically pure isomeric forms may be obtained by the application of art known principles. Diastereoisomers may be separated by physical separation methods such as fractional crystallization and chromatographic techniques, and enantiomers may be separated from each other by the selective crystallization of the diastereomeric salts with optically active acids or bases or by chiral chromatography. Pure stereoisomers may also be prepared synthetically from appropriate stereochemically pure starting materials, or by using stereoselective reactions.

During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, Third

Edition, John Wiley & Sons, 1999. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The present invention is based in part on the discovery that phenylalkylamino carbamates of Formula 1 discussed above have novel and unique pharmacological properties. These compounds have been shown in both an animal model and by signals seen in the side effects reported in clinical studies in humans to have the ability to treat sexual dysfunction in both male and females.

Although the precise mechanism of action is not completely understood it is known that these compounds do not work by the same mechanisms as most other known treatments for sexual dysfunction. For these reasons the compounds of Formula 1 are especially suitable for use as sole or adjunctive treatment for sexual dysfunction or in combination with other medications that are known to produce sexual dysfunction as a side effect so as to minimize or eliminate this side effect.

Thus, these compounds can be safely used alone or in combination with other useful medications to provide enhanced efficacy and reduced side effects because of the smaller doses of each drug that can be used.

In one aspect, this invention relates to methods to treat a female or a male suffering from sexual dysfunction; the method comprising delivering to the subject a therapeutically effective amount of one or more of the carbamate compounds of the invention or a pharmaceutically acceptable salt or ester thereof and a pharmaceutically acceptable carrier, diluent or excipient.

In a further aspect, the present invention relates to methods to eliminate, reduce or counter the sexual dysfunction produced by other medications by means of co administration. Therefore, embodiments of the invention also include methods wherein the carbamate compounds of the invention are administered concomitantly or sequentially with other medications that may

themselves cause sexual dysfunction in order to prevent, reverse or minimizes this unwanted side effect.

Therefore in the methods of this invention these carbamate compounds can be added or combined in a regimen with one or more other medications including antidepressants or other medications to produce a combination with decreased sexual dysfunction side effects. This may allow the patient to tolerate higher doses of the required medication and so result in increased therapeutic efficacy and/or improved quality of life for the patient.

Thus, in some embodiments of this invention, the subject or patient is already stabilized on the antidepressant or other medication but may be showing significant sexual dysfunction as a side effect. In this embodiment, the compound of Formula 1 is added to the existing regimen in doses of 1.0mg to 100.00mg/day increments until the sexual dysfunction induced by the first medication is reduced or eliminated. One of skill in the art can assess reduction in side effects through clinical interviews or questionnaires that measure symptoms.

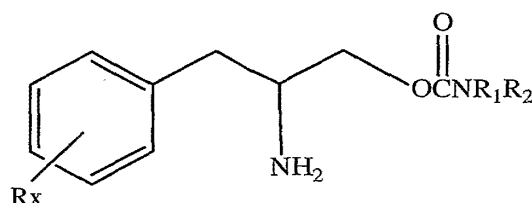
In other embodiments, the antidepressant or other medication is started simultaneously with the compound of Formula 1; this is concomitant administration. In this embodiment the intention would be to provide a prophylactically effective amount of a compound of Formula 1 in order to prevent the development of sexual dysfunction due to the conventional antidepressant or other medication. In embodiments in which both medications are started simultaneously the prophylactically effective doses of compounds of Formula 1 would be determined by side effects and response. Typically, prophylactically effective doses of a compound of Formula 1 would start at 25-50mg/day and increase in increments of about 25 - 50 mg./day per week until side effects intervene or an adequate response is obtained. One of skill in the art could readily determine appropriate doses of the antidepressant or other medication from the manufactures recommendations and the response and side effects experienced by the patient.

Compounds of the present invention (compounds of Formula 1) or enantiomers, diastereomers, racemates or mixtures thereof, or hydrates, solvates and pharmaceutically acceptable salts, esters and amides thereof may be used to provide treatment, either prophylactically or after their development, for the serious adverse side effect of sexual dysfunction in both males and females for many medications.

Such medications include but are not limited to; conventional antidepressants and other psychiatric medications that include but are not limited to; selective serotonin reuptake inhibitors (SSRI's); selective serotonin and norepinephrine reuptake inhibitors (SNRI's); older tricyclic antidepressants (TCAs); monoamine oxidase inhibitors (MAO-inhibitors), reversible inhibitors of monoamine oxidase (RIMAs), tertiary amine tricyclics and secondary amine tricyclic antidepressants, antipsychotics, anticonvulsants, lithium carbonate, and including but not limited to fluoxetine, duloxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine, sertraline, 5- MCA-NAT, lithium carbonate (LiCO_3), isocarboxazid, phenelzine, tranylcypromine, selegiline, moclobemide, amitriptyline, clomipramine, doxepin, imipramine, trimipramine, amoxapine, desipramine, maprotiline, nortriptyline and protriptyline, kappa opioid receptor antagonists; selective neurokinin antagonists, corticotropin releasing factor (CRF) antagonists, antagonists of tachykinins, α - adrenoreceptor antagonists., and other types of medications such as; antihypertensive medications, cardiac medications such as calcium channel blockers, ACE inhibitors, statins, etc and pharmaceutically acceptable salts or esters thereof.

The Test Compound

One compound of Formula 1, (referred to herein as the "test compound"), is (R)-(beta-amino-benzenepropyl) carbamate monohydrochloric acid also called O-carbamoyl-(D)-phenylalaninol.



wherein Rx=R1=R2=hydrogen.

(note: in the structural formula above (test compound), the amino group attached to the beta carbon projects into the plane of the paper. This is the dextrorotary (D) enantiomer that is of absolute configuration (R)

This compound has been tested in animal models and in humans and has demonstrated effects that strongly support the value of this group of compounds in treating sexual dysfunction, as discussed below.

In humans, the test compound has shown a significant signal in the trial conducted to assess the compounds antidepressant effects. This was a large placebo controlled study where the test compound was compared with a conventional SSRI antidepressant (Paroxetine). An analysis of the post trial questionnaires shows an effect of increasing interest in sex and in ability to have an orgasm mostly in males with the peak effect occurring at a dose of 400mg per day. This study was not designed to see or evaluate this property of the compound and so future studies directed specifically to assess this property of test compound in humans will be performed.

Test compound has also shown activity in an animal model that would support the use of the compounds of the invention as treatments for sexual dysfunction (See below).

EXAMPLE 1

In rats and mice, the test compound has antidepressant effects and at higher dose stimulant-like effects on locomotor activity. Although the mechanism of action of test compound is unknown, this pharmacological profile may involve activation of central catecholaminergic pathways. In addition to antidepressant effects, increased central catecholaminergic activity is also known to increase

sexual behavior in laboratory animals and patients (See, Foreman MM and Hall JL, "Effects of D₂-dopaminergic receptor stimulation on the lordotic response of female rats." Psychopharmacology 91:96-100, 1987 and Foreman MM: "Disorders of sexual response: Pioneering new pharmaceutical and therapeutic opportunities." Exp. Opin. Invest. Drugs 4:621-636, 1995.).

For initial preclinical evaluation of the effects on sexual behavior, the following study was conducted to evaluate the effects of test compound on lordotic response in the ovariectomized estrogen treated rat.

MATERIALS AND METHODS

Animals: Long-Evans hooded female rats (100-125 g) male Sprague-Dawley rats (150-175 g) were obtained from Charles River Breeding laboratories.

Chemicals: Progesterone (Cat. # P-0130; Lot 128H0456) and estrone (Cat # E-9750; Lot 28H0372) were purchased from Sigma Chemical Company and quinelorane Cat # Q-110; Lot PRF-694A) and bupropion (Cat # B-102; BS-11-10) were purchased from Research Biochemicals Incorporated. Test compound (Lot # D5-91B) was synthesized at SK Biopharmaceutical Center, Fairfield, NJ. Estrone and progesterone were dissolved in propylene glycol (Fisher Scientific P355-1; Lot # 992032). test compound, quinelorane and bupropion were dissolved in sterile saline (0.9% NaCl, Abbott Laboratories Lot #25-270-DK).

Protocol for ovariectomy: Female rats (108-120 g) were anesthetized with 100 mg/kg s.c. ketamine (Ketaset 100mg/ml, Ford Dodge Laboratories, lot #440339) and 7 mg/kg s.c. xylazine (Rompun 20 mg/ml, Bayer Corporation, lot #26050E). A midline incision (1 cm) on the ventral surface was made starting approximately 0.5-1 cm from the genitalia. A second incision (1 cm) was through the linea alba connecting fascia for abdominal muscles. The body of the uterus was located near the pubic bone and retracted through the abdominal incision. The uterine horns with ovaries were retracted through the abdominal wall. Each uterine horn was ligated near the uterine body bisected and removed. The abdominal wall was closed with 2 sutures and the skin incision was closed with

either wound clips or sutures. The rats were kept warm until they recovered from the anesthesia. OVX=ovariectomized.

Accelerated light cycle (10:14): Lights were on from 1 am to 11 am. During dark phase, the room was kept dark except for lighting from red lights needed to observe the behaviors.

Behavior observation arenas: Side walls (45 X 60 cm) and top (60 X 60 cm) with hole (15 X15 cm) were constructed of clear Lucite plastic and bonded together with adhesive. The base was made from stainless steel grating and was placed over bedding material. Arenas and base were washed between experiments.

Protocol for female sexual behavior: At least 2-3 hours into the dark phase of the lighting cycle, male rats are placed into the behavior arenas and allowed to acclimate for 15 minutes prior to testing. Prior to the testing of experimental animals, the males are exposed to sexually receptive, OVX rats treated with estrone 0.25 mg s.c. 48 hours prior to test and progesterone 1 mg s.c. 6 hours prior to test. When active mating occurs, the receptive females are removed. The test female (OVX treated only with estrone 0.25 mg 48 hours prior to test) is added to the arena with the activated male. The number of lordosis responses for 15 mounts is recorded (lordosis is defined as a downward arching of the back to expose genitalia).

During this first test period, only female rats with a L/M of 4/15 or lower were treated with test drug and 90 minutes later the rats were retested as previously for 15 mounts. This exclusion criterion is used to lower the variance due to rats that become overly receptive to estrone. The index of change is the change in L/M between test 2 and test 1. Statistical comparisons of the treatment groups were made using ANOVA followed by a Dunnett's test for multiple treatment group designs and a Student's t test for single control and treatment designs with the minimum level of significance set at $p < 0.05$.

RESULTS

Test compound produced dose-related increases in lordotic behavior in the female rat at doses of 10, 30 and 100 mg/kg s.c. (Table 1) (See also Figure

1) test compound at 30 and 100 mg/kg produced significantly greater lordotic response than vehicle treatment. For reference, some of these animals were subsequently treated with either quinelorane (25 µg/kg s.c.) or bupropion (30 mg/kg s.c.). Both quinelorane and bupropion produced significant increases in lordotic response compared to vehicle treatment.

Table 1: Effects of test compound (TC) on Lordotic Response

Treatment	Number of Rats	Change in Lordotic Response
Vehicle (saline)	22	0.201 +/- 0.042
TC 10 mg/kg s.c.	23	0.338 +/- 0.049
TC 10A 30 mg/kg s.c.	15	0.476 +/- 0.049 *
TC 10A 100 mg/kg s.c.	14	0.559 +/- 0.059 *

*= significantly different from vehicle control by ANOVA, Dunnett's test.

Table 2: Effects of Quinelorane on Lordotic Response

Treatment	Number of Rats	Change in Lordotic Response
Vehicle (saline)	9	0.174 +/- 0.062
Quinelorane 25 µg/kg s.c.	9	0.593 +/- 0.056 *

*= significantly different from vehicle control by Student's test.

Table 3: Effects of Bupropion on Lordotic Response

Treatment	Number of Rats	Change in Lordotic Response
Vehicle (saline)	9	0.174 +/- 0.066
Bupropion 30 mg/kg s.c.	9	0.478 +/- 0.073 *

*= significantly different from vehicle control by Student's test.

DISCUSSION

One of the potential clinical indications of test compound is for the treatment of depression. (See, Foreman MM: "Disorders of Sexual Response: Pioneering new pharmaceutical and therapeutic opportunities." Exp. Opin. Invest. Drugs 4:621-636, 1995)

Since many antidepressants are known to suppress sexual response, the preceding studies serve as an evaluation of this potential side effect. In the current studies, treatment with test compound produced dose-related increases in lordotic responses to mounting. The magnitude of these effects were similar to quinelorane and bupropion, which are known to augment sexual response in patients. (See, Foreman MM: "Disorders of sexual response: Pioneering new pharmaceutical and therapeutic opportunities." Exp. Opin. Invest. Drugs 4:621-636, 1995)

These studies provide preliminary evidence that test compound will not suppress sexual responses, but may augment sexual response. Since the responses observed are similar to two compounds that augment sexual responses in clinical trials, test compound could be used for the treatment of sexual disorders.

SUMMARY

- Test compound produced dose-related increases in lordotic response in the ovariectomized, estrogen treated rat with statistical significance at 30 and 100 mg/kg s.c.
- The magnitude of effects (efficacy) of test compound was similar to that observed with quinelorane and bupropion, compounds that reportedly increase sexual response in patients.
- These findings provide preliminary evidence that test compound will not suppress sexual response and that test compound could be useful for the treatment of sexual disorders.

USE OF COMPOUNDS OF INVENTION TO TREAT SEXUAL DYSFUNCTION SIDE EFFECTS OF OTHER MEDICATIONS

As used herein the term "antidepressant" shall mean any compound known to possess antidepressant action in mammals that can be used in combination with the carbamate compounds of the present invention. Many of the most commonly used antidepressants produce the serious, adverse side effect of sexual dysfunction in both males and females. Thus, the term includes but is not limited to: selective serotonin reuptake inhibitors (SSRI's); selective serotonin and norepinephrine reuptake inhibitors (SNRI's); older tricyclic antidepressants; bupropion and MAO inhibitors.

Selective serotonin reuptake inhibitors (SSRI's) and selective serotonin and norepinephrine reuptake inhibitors (SNRI's) include, but are not limited to:

Fluoxetine, N-methyl-3-(p-trifluoromethylphenoxy)-3-phenylpropylamine, is marketed in the hydrochloride salt form, and as the racemic mixture of its two enantiomers. U.S. Pat. No. 4,314,081 is an early reference on the compound. Robertson et al., J. Med. Chem, 31, 1412 (1988), taught the separation of the R and S enantiomers of fluoxetine and showed that their activity as serotonin uptake inhibitors is similar to each other. In this document, the word "fluoxetine" will be used to mean any acid addition salt or the free base, and to include either the racemic mixture or either of the R and S enantiomers.

Duloxetine, N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine, is usually administered as the hydrochloride salt and as the (+) enantiomer. It was first taught by U.S. Pat. No. 4,956,388, which shows its high potency. The word "duloxetine" will be used here to refer to any acid addition salt or the free base of the molecule;

Venlafaxine is known in the literature, and U.S. Pat No. 4,761,501 teaches its method of synthesis and its activity as an inhibitor of serotonin and norepinephrine uptake. Venlafaxine is identified as compound A in that patent;

Milnacipran (N,N-diethyl-2-aminomethyl-1-phenylcyclopropanecarboxamide) is taught by U.S. Pat. No. 4,478,836, which prepared milnacipran as its Example 4. The patent describes its compounds as antidepressants. Moret et al., *Neuropharmacology* 24, 1211-19 (1985), describe its pharmacological activities as an inhibitor of serotonin and norepinephrine reuptake;

Citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, is disclosed in U. S. Pat. No. 4,136,193 as a serotonin reuptake inhibitor. Its pharmacology was disclosed by Christensen et al., *Eur. J Pharmacol.* 41, 153 (1977), and reports of its clinical effectiveness in depression may be found in Dufour et al., *Int. Clin. Psychopharmacol.* 2, 225 (1987), and Timmerman et al., *ibid.*, 239;

Fluvoxamine, 5-methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone O-(2-aminoethyl)oxime, is taught by U.S. Pat. No. 4,085,225. Scientific articles about the drug have been published by Claassen et al., *Brit. J. Pharmacol.* 60, 505 (1977); and De Wilde et al., *J. Affective Disord.* 4, 249 (1982); and Benfield et al., *Drugs* 32, 313 (1986);

Paroxetine, trans-(-)-3-[(1,3-benzodioxol-5-yl)oxy)methyl]-4-(4-fluorophenyl)piperidine, may be found in U.S. Pat. Nos. 3,912,743 and 4,007,196. Reports of the drug's activity are in Lassen, *Eur. J. Pharmacol.* 47, 351 (1978); Hassan et al., *Brit J. Clin. Pharmacol.* 19, 705 (1985); Laursen et al., *Acta Psychiat. Scand.* 71, 249 (1985); and Battegay et al., *Neuropsychobiology* 13, 31 (1985); and

Sertraline, (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine hydrochloride, is a serotonin reuptake inhibitor that is marketed as an antidepressant. It is disclosed by U.S. Pat. No. 4,536,518.

Carbamate compounds of the present invention may also be used in combination with other classes of antidepressants and other therapeutically

effective agents including but not limited to, for example; 5- MCA-NAT (e.g., U.S. Pat. No. 6,562,858); lithium carbonate (LiCO_3), monoamine oxidase inhibitors (MAO-inhibitors), suitable monoamine oxidase inhibitors include: isocarboxazid, phenelzine, tranylcypromine and selegiline, and pharmaceutically acceptable salts thereof; reversible inhibitors of monoamine oxidase (RIMAs), suitable reversible inhibitors of monoamine oxidase include: moclobemide, and pharmaceutically acceptable salts thereof; antiepileptic drugs (AEDs) including but not limited to kappa opioid receptor antagonists (e.g., U.S. Pat. No. 6,528,518); selective neurokinin antagonists (e.g., U.S. Pat. No. 6,436,928) corticotropin releasing factor (CRF) antagonists, suitable CRF antagonists include those compounds described in International Patent Specification Nos. WO 94/13643, WO 94/13644, WO 94/13661, WO 94/13676 and WO 94/13677.; antagonists of tachykinins (e.g., U.S. Pat. No. 6,518,273) and α - adrenoreceptor antagonists.

In addition, the compounds of the present invention can be used to reverse or reduce the sexual dysfunction caused by older antidepressants that are primarily norepinephrine reuptake inhibitors. Such drugs include norepinephrine reuptake inhibitors, include tertiary amine tricyclics and secondary amine tricyclics. Suitable examples of tertiary amine tricyclics include: amitriptyline, clomipramine, doxepin, imipramine and trimipramine, and pharmaceutically acceptable salts thereof.

Suitable examples of secondary amine tricyclics include: amoxapine, desipramine, maprotiline, nortriptyline and protriptyline, and pharmaceutically acceptable salts thereof.

Suitable serotonin and noradrenaline reuptake inhibitors of use in the present invention include: venlafaxine, and pharmaceutically acceptable salts thereof.

Combined use of one or more of the compounds of the invention with any of the above described antidepressants may reduce, lessen or eliminate the serious, adverse side effect of sexual dysfunction produced by these drugs in both males and females.

All of the U.S. patents that have been mentioned above in connection with compounds used in the present invention are incorporated herein by reference.

Definitions

For convenience, certain terms employed in the specification, examples, and appended claims are collected here.

It is to be understood that this invention is not limited to the particular methodology, protocols, animal species or genera, and reagents described, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention that will be limited only by the appended claims.

As used herein the term "subject", refers to an animal, preferably a mammal, and most preferably a human both male and female, who has been the object of treatment, observation or experiment.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of one or more of the signs or symptoms of the disease or disorder being treated.

The term "prophylactically effective amount" is intended to mean that amount of a pharmaceutical drug that will prevent or reduce the risk of occurrence of the biological or medical event that is sought to be prevented of a tissue, a system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

The term "pharmaceutically acceptable salts or esters" shall mean non-toxic salts or esters of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base. Examples of such salts include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide,

calcium, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, potassium, salicylate, sodium, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, valerate.

Therefore, the term “a patient in need of treatment” as used herein will refer to any subject or patient who currently has or may develop any of the above syndromes or disorders, including any mood disorder which can be treated by antidepressant medication, or any other disorder in which the patient’s present clinical condition or prognosis could benefit from the administration of one or more compounds of Formula (I) alone or in combination with another therapeutic intervention including but not limited to another medication.

The term “treating” or “treatment” as used herein, refers to any indicia of success in the prevention or amelioration of an injury, pathology or condition such as sexual dysfunction, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology, or condition more tolerable to the patient; slowing in the rate of degeneration or decline or worsening of the illness; making the final point of worsening less debilitating; or improving a subject’s physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neurological examination, and/or psychiatric evaluations. Accordingly, the term “treating” or “treatment” includes the administration of the compounds or agents of the present invention for treatment of any form of sexual dysfunction in both males and females. In some instances, treatment with the compounds of the present invention will be done in combination with other compounds to prevent, inhibit, or arrest the progression of the mood disorder.

The term "therapeutic effect" as used herein, refers to the effective improvement in or reduction of symptoms of sexual dysfunction.

The term "a therapeutically effective amount" as used herein means a sufficient amount of one or more of the compounds of the invention to produce a therapeutic effect, as defined above, in a subject or patient in need of such neuroprotection treatment.

The terms "subject" or "patient" are used herein interchangeably and as used herein mean any mammal including but not limited to human beings including a human patient or subject to which the compositions of the invention can be administered. The term mammals include human patients, both male and female and non-human primates, as well as experimental animals such as rabbits, rats, and mice, and other animals.

Methods are known in the art for determining therapeutically and prophylactically effective doses for the instant pharmaceutical composition. For example the compound can be employed at a daily dose in the range of about 0.1 mg to 400 mg usually on a regimen of 1 to 2 times per day, for an average adult human. The effective amount, however, may be varied depending upon the particular compound used, the mode of administration, the strength of the preparation, the mode of administration, and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient age, weight, diet and time of administration, will result in the need to adjust dosages.

The compound may be administered to a subject by any conventional route of administration, including, but not limited to, intravenous, oral, subcutaneous, intramuscular, intradermal and parenteral. Depending on the route of administration, compounds of Formula (1) can be constituted into any form. For example, forms suitable for oral administration include solid forms, such as pills, gelcaps, tablets, caplets, capsules (each including immediate release, timed release and sustained release formulations), granules, and powders. Forms suitable for oral administration also include liquid forms, such as solutions, syrups, elixirs, emulsions, and suspensions. In addition, forms

useful for parenteral administration include sterile solutions, emulsions and suspensions.

To prepare the pharmaceutical compositions of this invention, one or more compounds of formula (1) or salt thereof as the active ingredient is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. Carriers are necessary and inert pharmaceutical excipients, including, but not limited to, binders, suspending agents, lubricants, flavorings, sweeteners, preservatives, dyes, and coatings. In preparing compositions in oral dosage form, any of the usual pharmaceutical carriers may be employed. For example, for liquid oral preparations, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. For parenteral use, the carrier will usually comprise sterile water, though other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed.

Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. Suppositories may be prepared, in which case cocoa butter could be used as the carrier. The tablets or pills can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pills can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer, which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of material can be used for such enteric layers or coatings, such materials

including a number of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The active drug can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Active drug may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. Active drug may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinyl- pyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxy-ethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, active drug may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories, for oral parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation.

Alternatively, the composition may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection.

The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful, suppository and the like, an amount of the active ingredient necessary to deliver an effective dose as described above. For example, the pharmaceutical compositions herein can

contain, per unit dosage unit, from about 25 to about 400 mg of the active ingredient. Preferably, the range is from about 50 to about 200 mg of the active ingredient.

In some embodiments of the present invention carbamate compounds suitable for use in the practice of this invention will be administered either singly or concomitantly with at least one or more other compounds or therapeutic agents. In these embodiments, the present invention provides methods to treat or prevent sexual dysfunction in a patient. The method includes the step of; administering to a patient in need of treatment, an effective amount of one of the carbamate compounds disclosed herein in combination with an effective amount of one or more other compounds or therapeutic agents that may either cause or them selves have the ability to treat sexual dysfunction or the ability to augment the sexual dysfunction treatment effects of the compounds of the invention.

As used herein the term "concomitant administration" or "combination administration" of a compound, therapeutic agent or known drug with a compound of the present invention means administration of the one or more compounds of the invention at such time that the other therapeutic agent, that may cause sexual dysfunction, is being administered so that the combination will have reduced tendency to cause sexual dysfunction. Such concomitant administration can involve concurrent (i.e. at the same time), prior, or subsequent administration of the other therapeutic agent with respect to the administration of a compound of the present invention. A person of ordinary skill in the art, would have no difficulty determining the appropriate timing, sequence and dosages of administration for particular drugs and compounds of the present invention.

In addition, in some embodiments, the compounds of this invention will be used, either alone or in combination with each other or in combination with one or more other therapeutic medications as described above, or their salts or esters, for manufacturing a medicament for the purpose of providing treatment of sexual dysfunction to a patient or subject in need thereof.

"C₁-C₄ alkyl" as used herein refers to substituted or unsubstituted aliphatic hydrocarbons having from 1 to 4 carbon atoms. Specifically included within the

definition of "alkyl" are those aliphatic hydrocarbons that are optionally substituted. In a preferred embodiment of the present invention, the C₁-C₄ alkyl is either unsubstituted or substituted with phenyl.

The term "phenyl", as used herein, whether used alone or as part of another group, is defined as a substituted or unsubstituted aromatic hydrocarbon ring group having 6 carbon atoms. Specifically included within the definition of "phenyl" are those phenyl groups that are optionally substituted. For example, in a preferred embodiment of the present invention, the, "phenyl" group is either unsubstituted or substituted with halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, amino, nitro, or cyano.

It is understood that substituents and substitution patterns on the compounds of the present invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as the methods provided herein.

Representative 2-phenyl-1, 2-ethanediol monocarbomates and dicarbamates include, for example, the following compounds:

The present invention includes the use of isolated enantiomers of Formula 1. In one preferred embodiment, a pharmaceutical composition comprising the isolated S-enantiomer of Formula 1 is used to provide adjuvant antidepressant efficacy in a subject. In another preferred embodiment, a pharmaceutical composition comprising the isolated R-enantiomer of Formula 1 is used to provide adjuvant antidepressant efficacy a subject

The present invention also includes the use of mixtures of enantiomers of Formula 1. In one aspect of the present invention, one enantiomer will predominate. An enantiomer that predominates in the mixture is one that is present in the mixture in an amount greater than any of the other enantiomers present in the mixture, e.g., in an amount greater than 50%. In one aspect, one enantiomer will predominate to the extent of 90% or to the extent of 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% or greater. In one preferred

embodiment, the enantiomer that predominates in a composition comprising a compound of Formula 1 is the S-enantiomer of Formula 1.

The present invention provides methods of using enantiomers and enantiomeric mixtures of compounds represented by Formula 1. A carbamate enantiomer of Formula 1 contains an asymmetric chiral carbon at the benzylic position, which is the second aliphatic carbon adjacent to the phenyl ring.

An enantiomer that is isolated is one that is substantially free of the corresponding enantiomer. Thus, an isolated enantiomer refers to a compound that is separated via separation techniques or prepared free of the corresponding enantiomer. The term "substantially free," as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In preferred embodiments, the compound includes at least about 90% by weight of a preferred enantiomer. In other embodiments of the invention, the compound includes at least about 99% by weight of a preferred enantiomer. Preferred enantiomers can be isolated from racemic mixtures by any method known to those skilled in the art, including high performance liquid chromatography (HPLC) and the formation and crystallization of chiral salts, or preferred enantiomers can be prepared by methods described herein.

Carbamate Compounds as Pharmaceuticals:

The present invention provides racemic mixtures, enantiomeric mixtures and isolated enantiomers of Formula 1 as pharmaceuticals. The carbamate compounds are formulated as pharmaceuticals to provide adjuvant antidepressant action in a subject.

In general, the carbamate compounds of the present invention can be administered as pharmaceutical compositions by any method known in the art for administering therapeutic drugs including oral, buccal, topical, systemic (e.g., transdermal, intranasal, or by suppository), or parenteral (e.g., intramuscular, subcutaneous, or intravenous injection.) Administration of the compounds directly to the nervous system can include, for example, administration to intracerebral, intraventricular, intracerebroventricular, intrathecal, intracisternal,

intraspinal or peri-spinal routes of administration by delivery via intracranial or intravertebral needles or catheters with or without pump devices.

Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, emulsions, syrups, elixirs, aerosols, or any other appropriate compositions; and comprise at least one compound of this invention in combination with at least one pharmaceutically acceptable excipient. Suitable excipients are well known to persons of ordinary skill in the art, and they, and the methods of formulating the compositions, can be found in such standard references as Alfonso AR: Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton PA, 1985, the disclosure of which is incorporated herein by reference in its entirety and for all purposes. Suitable liquid carriers, especially for injectable solutions, include water, aqueous saline solution, aqueous dextrose solution, and glycols.

The carbamate compounds can be provided as aqueous suspensions. Aqueous suspensions of the invention can contain a carbamate compound in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients can include, for example, a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethylene oxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol (e.g., polyoxyethylene sorbitol mono-oleate), or a condensation product of ethylene oxide with a partial ester derived from fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan mono-oleate).

The aqueous suspension can also contain one or more preservatives such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such

as sucrose, aspartame or saccharin. Formulations can be adjusted for osmolality.

Oil suspensions for use in the present methods can be formulated by suspending a carbamate compound in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin; or a mixture of these. The oil suspensions can contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents can be added to provide a palatable oral preparation, such as glycerol, sorbitol or sucrose. These formulations can be preserved by the addition of an antioxidant such as ascorbic acid. As an example of an injectable oil vehicle, see Minto, J. Pharmacol. Exp. Ther. 281:93-102, 1997. The pharmaceutical formulations of the invention can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil, described above, or a mixture of these.

Suitable emulsifying agents include naturally occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan mono-oleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan mono-oleate. The emulsion can also contain sweetening agents and flavoring agents, as in the formulation of syrups and elixirs. Such formulations can also contain a demulcent, a preservative, or a coloring agent.

The compound of choice, alone or in combination with other suitable components can be made into aerosol formulations (i.e., they can be "nebulized") to be administered via inhalation. Aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like.

Formulations of the present invention suitable for parenteral administration, such as, for example, by intraarticular (in the joints), intravenous, intramuscular, intradermal, intraperitoneal, and subcutaneous routes, can include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation

isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. Among the acceptable vehicles and solvents that can be employed are water and Ringer's solution, an isotonic sodium chloride. In addition, sterile fixed oils can conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can likewise be used in the preparation of injectables. These solutions are sterile and generally free of undesirable matter.

Where the compounds are sufficiently soluble they can be dissolved directly in normal saline with or without the use of suitable organic solvents, such as propylene glycol or polyethylene glycol. Dispersions of the finely divided compounds can be made-up in aqueous starch or sodium carboxymethyl cellulose solution, or in suitable oil, such as arachis oil. These formulations can be sterilized by conventional, well-known sterilization techniques. The formulations can contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, toxicity adjusting agents, e.g., sodium acetate, sodium chloride, potassium chloride, calcium chloride, sodium lactate and the like.

The concentration of a carbamate compound in these formulations can vary widely, and will be selected primarily based on fluid volumes, viscosities, body weight, and the like, in accordance with the particular mode of administration selected and the patient's needs. For IV administration, the formulation can be a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluents or solvent, such as a solution of 1,3-butanediol. The formulations of compounds can be presented in unit-dose or multi-dose sealed containers, such as ampoules

and vials. Injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

A carbamate compound suitable for use in the practice of this invention can be and is preferably administered orally. The amount of a compound of the present invention in the composition can vary widely depending on the type of composition, size of a unit dosage, kind of excipients, and other factors well known to those of ordinary skill in the art. In general, the final composition can comprise, for example, from 0.000001 percent by weight (% w) to 50 % w of the carbamate compound, preferably 0.00001 % w to 25% w, with the remainder being the excipient or excipients.

Pharmaceutical formulations for oral administration can be formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical formulations to be formulated in unit dosage forms as tablets, pills, powder, dragees, capsules, liquids, lozenges, gels, syrups, slurries, suspensions, etc. suitable for ingestion by the patient.

Formulations suitable for oral administration can consist of (a) liquid solutions, such as an effective amount of the pharmaceutical formulation suspended in a diluents, such as water, saline or PEG 400; (b) capsules, sachets or tablets, each containing a predetermined amount of the active ingredient, as liquids, solids, granules or gelatin; (c) suspensions in an appropriate liquid; and (d) suitable emulsions.

Pharmaceutical preparations for oral use can be obtained through combination of the compounds of the present invention with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable additional compounds, if desired, to obtain tablets or dragee cores. Suitable solid excipients are carbohydrate or protein fillers and include, but are not limited to sugars, including lactose, sucrose, mannitol, or sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose such as methyl cellulose, hydroxymethyl cellulose, hydroxypropylmethyl-cellulose or sodium

carboxymethylcellulose; and gums including arabic and tragacanth; as well as proteins such as gelatin and collagen.

If desired, disintegrating or solubilizing agents can be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate. Tablet forms can include one or more of lactose, sucrose, mannitol, sorbitol, calcium phosphates, corn starch, potato starch, microcrystalline cellulose, gelatin, colloidal silicon dioxide, talc, magnesium stearate, stearic acid, and other excipients, colorants, fillers, binders, diluents, buffering agents, moistening agents, preservatives, flavoring agents, dyes, disintegrating agents, and pharmaceutically compatible carriers. Lozenge forms can comprise the active ingredient in a flavor, e.g., sucrose, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin or sucrose and acacia emulsions, gels, and the like containing, in addition to the active ingredient, carriers known in the art.

The compounds of the present invention can also be administered in the form of suppositories for rectal administration of the drug. These formulations can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperatures and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

The compounds of the present invention can also be administered by intranasal, intraocular, intravaginal, and intrarectal routes including suppositories, insufflation, powders and aerosol formulations (for examples of steroid inhalants, see Rohatagi, J. Clin. Pharmacol. 35:1187-1193, 1995; Tjwa, Ann. Allergy Asthma Immunol. 75:107-111, 1995).

The compounds of the present invention can be delivered transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

Encapsulating materials can also be employed with the compounds of the present invention and the term "composition" can include the active

ingredient in combination with an encapsulating material as a formulation, with or without other carriers. For example, the compounds of the present invention can also be delivered as microspheres for slow release in the body. In one embodiment, microspheres can be administered via intradermal injection of drug (e.g., mifepristone)-containing microspheres, which slowly release subcutaneously (see Rao, J. Biomater Sci. Polym. Ed. 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao, Pharm. Res. 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, J. Pharm. Pharmacol. 49:669-674, 1997). Both transdermal and intradermal routes afford constant delivery for weeks or months. Cachets can also be used in the delivery of the compounds of the present invention.

In another embodiment, the compounds of the present invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, i.e., by employing ligands attached to the liposome that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the carbamate compound into target cells in vivo. (See, e.g., Al-Muhammed, J. Microencapsul. 13:293-306, 1996; Chonn, Curr. Opin. Biotechnol. 6:698-708, 1995; Ostro, Am. J. Hosp. Pharm. 46:1576-1587, 1989).

The pharmaceutical formulations of the invention can be provided as a salt and can be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms. In other cases, the preferred preparation can be a lyophilized powder which can contain, for example, any or all of the following: 1 mM-50 mM histidine, 0.1%-2% sucrose, 2%-7% mannitol, at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

Pharmaceutically acceptable salts and esters refer to salts and esters that are pharmaceutically acceptable and have the desired pharmacological properties. Such salts include salts that may be formed where

acidic protons present in the compounds are capable of reacting with inorganic or organic bases. Suitable inorganic salts include those formed with the alkali metals, e.g. sodium and potassium, magnesium, calcium, and aluminum. Suitable organic salts include those formed with organic bases such as the amine bases, e.g. ethanolamine, diethanolamine, triethanolamine, tromethamine, N methylglucamine, and the like. Pharmaceutically acceptable salts can also include acid addition salts formed from the reaction of amine moieties in the parent compound with inorganic acids (e.g. hydrochloric and hydrobromic acids) and organic acids (e.g. acetic acid, citric acid, maleic acid, and the alkane- and arene-sulfonic acids such as methanesulfonic acid and benzenesulfonic acid). Pharmaceutically acceptable esters include esters formed from carboxy, sulfonyloxy, and phosphonoxy groups present in the compounds. When there are two acidic groups present, a pharmaceutically acceptable salt or ester may be a mono-acid-mono-salt or ester or a di-salt or ester; and similarly where there are more than two acidic groups present, some or all of such groups can be salified or esterified.

Compounds named in this invention can be present in unsalified or unesterified form, or in salified and/or esterified form, and the naming of such compounds is intended to include both the original (unsalified and unesterified) compound and its pharmaceutically acceptable salts and esters. The present invention includes pharmaceutically acceptable salt and ester forms of Formula (1). More than one crystal form of an enantiomer of Formula 1 can exist and as such are also included in the present invention.

A pharmaceutical composition of the invention can optionally contain, in addition to a carbamate compound, at least one other therapeutic agent useful in the treatment of sexual dysfunction. For example the carbamate compounds of Formula 1 can be combined physically with other sexual dysfunction treatments in fixed dose combinations to simplify their administration.

Methods of formulating pharmaceutical compositions have been described in numerous publications such as Pharmaceutical Dosage Forms: Tablets, Second Edition. Revised and Expanded. Volumes 1-3, edited by

Lieberman et al; Pharmaceutical Dosage Forms: Parenteral Medications. Volumes 1-2, edited by Avis et al; and Pharmaceutical Dosage Forms: Disperse Systems. Volumes 1-2, edited by Lieberman et al; published by Marcel Dekker, Inc, the disclosure of which are herein incorporated by reference in their entireties and for all purposes.

The pharmaceutical compositions are generally formulated as sterile, substantially isotonic and in full compliance with all Good Manufacturing Practice (GMP) regulations of the U.S. Food and Drug Administration.

Dosage Regimens

The present invention provides methods of providing adjuvant antidepressant action in a mammal using carbamate compounds. The amount of the carbamate compound necessary to reduce or prevent sexual dysfunction is defined as a therapeutically or a pharmaceutically effective dose. The dosage schedule and amounts effective for this use, i.e., the dosing or dosage regimen will depend on a variety of factors including the stage of the disease, the patient's physical status, age and the like. In calculating the dosage regimen for a patient, the mode of administration is also taken into account.

A person of ordinary skill in the art will be able without undue experimentation, having regard to that skill and this disclosure, to determine a therapeutically effective amount of a particular substituted carbamate compound for practice of this invention (see, e.g., Lieberman, Pharmaceutical Dosage Forms (Vols. 1-3, 1992); Lloyd, 1999, The art, Science and Technology of Pharmaceutical Compounding; and Pickar, 1999, Dosage Calculations). A therapeutically effective dose is also one in which any toxic or detrimental side effects of the active agent is outweighed in clinical terms by therapeutically beneficial effects. It is to be further noted that for each particular subject, specific dosage regimens should be evaluated and adjusted over time according to the individual need and professional judgment of the person administering or supervising the administration of the compounds.

For treatment purposes, the compositions or compounds disclosed herein can be administered to the subject in a single bolus delivery, via continuous delivery over an extended time period, or in a repeated administration protocol (e.g., by an hourly, daily or weekly, repeated administration protocol). The pharmaceutical formulations of the present invention can be administered, for example, one or more times daily, 3 times per week, or weekly. In one embodiment of the present invention, the pharmaceutical formulations of the present invention are orally administered once or twice daily.

In this context, a therapeutically effective dosage of the biologically active agent(s) can include repeated doses within a prolonged treatment regimen that will yield clinically significant results to provide antidepressant action. Determination of effective dosages in this context is typically based on animal model studies followed up by human clinical trials and is guided by determining effective dosages and administration protocols that significantly reduce the occurrence or severity of targeted exposure symptoms or conditions in the subject. Suitable models in this regard include, for example, murine, rat, porcine, feline, non-human primate, and other accepted animal model subjects known in the art. Alternatively, effective dosages can be determined using in vitro models (e.g., immunologic and histopathologic assays). Using such models, only ordinary calculations and adjustments are typically required to determine an appropriate concentration and dose to administer a therapeutically effective amount of the biologically active agent(s) (e.g., amounts that are intranasally effective, transdermally effective, intravenously effective, or intramuscularly effective to elicit a desired response).

In an exemplary embodiment of the present invention, unit dosage forms of the compounds are prepared for standard administration regimens. In this way, the composition can be subdivided readily into smaller doses at the physician's direction. For example, unit dosages can be made up in packeted powders, vials or ampoules and preferably in capsule or tablet form.

The active compound present in these unit dosage forms of the composition can be present in an amount of, for example, from about 10 mg. to

about one gram or more, for single or multiple daily administration, according to the particular need of the patient. By initiating the treatment regimen with a minimal daily dose of about one gram, the blood levels of the carbamate compounds can be used to determine whether a larger or smaller dose is indicated.

Effective administration of the carbamate compounds of this invention can be administered, for example, at an oral or parenteral dose of from about 0.01 mg/kg/dose to about 150 mg/kg/dose. Preferably, administration will be from about 0.1 /mg/kg/dose to about 25 mg/kg/dose, more preferably from about 0.2 to about 18 mg/kg/dose. Therefore, the therapeutically effective amount of the active ingredient contained per dosage unit as described herein can be, for example, from about 1 mg/day to about 7000 mg/day for a subject having, for example, an average weight of 70 kg.

The methods of this invention also provide for kits for use in providing treatment of sexual dysfunction. After a pharmaceutical composition comprising one or more carbamate compounds of this invention, with the possible addition of one or more other compounds of therapeutic benefit, has been formulated in a suitable carrier, it can be placed in an appropriate container and labeled for providing adjuvant antidepressant action. Additionally, another pharmaceutical comprising at least one other therapeutic agent useful in the provide antidepressant action can be placed in the container as well and labeled for treatment of the indicated disease. Such labeling can include, for example, instructions concerning the amount, frequency and method of administration of each pharmaceutical.

Although the foregoing invention has been described in detail by way of example for purposes of clarity of understanding, it will be apparent to the artisan that certain changes and modifications are comprehended by the disclosure and may be practiced without undue experimentation within the scope of the appended claims, which are presented by way of illustration not limitation. The following examples are provided to illustrate specific aspects of the invention and are not meant to be limitations.

References cited

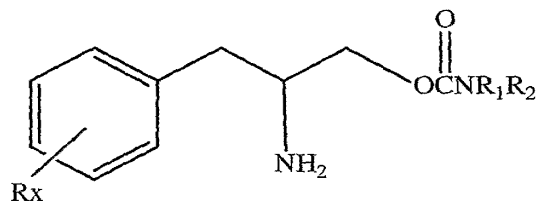
All references cited herein are incorporated herein by reference in their entirety and for all purposes to the same extent as if each individual publication or patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

The discussion of references herein is intended merely to summarize the assertions made by their authors and no admission is made that any reference constitutes prior art. Applicants reserve the right to challenge the accuracy and pertinence of the cited references.

The present invention is not to be limited in terms of the particular embodiments described in this application, which are intended as single illustrations of individual aspects of the invention. Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. Functionally equivalent methods and apparatus within the scope of the invention, in addition to those enumerated herein will be apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications and variations are intended to fall within the scope of the appended claims. The present invention is to be limited only by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled.

WHAT IS CLAIMED IS:

1. A method of treating sexual dysfunction in a subject, comprising the step of the administration, to a subject in need of such treatment, of a therapeutically effective amount of a compound of the Formula (1):



(I)

or a pharmaceutically acceptable salt or ester thereof:

wherein

R is a member selected from the group consisting of hydrogen, lower alkyl of 1 to 8 carbon atoms, halogen selected from F, Cl, Br and I, alkoxy containing 1 to 3 carbon atoms, nitro, hydroxy, trifluoromethyl, and thioalkoxy containing 1 to 3 carbon atoms;

x is an integer of 1 to 3, with the proviso that R may be the same or different when x is 2 or 3;

R₁ and R₂ can be the same or different from each other and are independently selected from the group consisting of hydrogen, lower alkyl of 1 to 8 carbon atoms, aryl, arylalkyl, cycloalkyl of 3 to 7 carbon atoms;

R₁ and R₂ can be joined to form a 5 to 7-membered heterocycle substituted with a member selected from the group consisting of hydrogen, alkyl, and aryl groups,

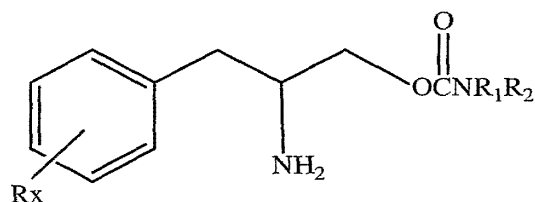
wherein the cyclic compound can comprise 1 to 2 nitrogen atoms and 0 to 1 oxygen atom,

wherein the nitrogen atoms are not directly connected with each other or with the oxygen atom.

2. The method of claim 1 wherein R is hydrogen and x=1

3. The method of claim 1 wherein R, R₁ and R₂ are all selected from hydrogen and x=1

4. A method of treating sexual dysfunction in a subject, comprising the step of the administration, to a subject in need of such treatment, of a therapeutically effective amount of an enantiomer of Formula 1 substantially free of other enantiomers or an enantiomeric mixture wherein one enantiomer of Formula 1 predominates;



(I)

or a pharmaceutically acceptable salt or ester thereof;
wherein;

R is a member selected from the group consisting of hydrogen, lower alkyl of 1 to 8 carbon atoms, halogen selected from F, Cl, Br and I, alkoxy containing 1 to 3 carbon atoms, nitro, hydroxy, trifluoromethyl, and thioalkoxy containing 1 to 3 carbon atoms;

x is an integer of 1 to 3, with the proviso that R may be the same or different when x is 2 or 3;

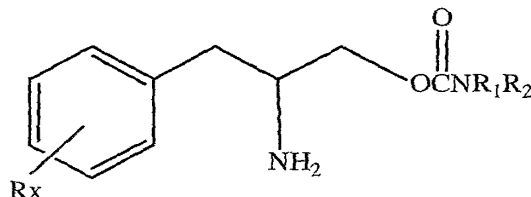
R₁ and R₂ can be the same or different from each other and are independently selected from the group consisting of hydrogen, lower alkyl of 1 to 8 carbon atoms, aryl, arylalkyl, cycloalkyl of 3 to 7 carbon atoms;

R₁ and R₂ can be joined to form a 5 to 7-membered heterocycle substituted with a member selected from the group consisting of hydrogen, alkyl, and aryl groups,

wherein the cyclic compound can comprise 1 to 2 nitrogen atoms and 0 to 1 oxygen atom,

wherein the nitrogen atoms are not directly connected with each other or with the oxygen atom.

5. The method of claim 4 wherein Rx is hydrogen
6. The method of claim 4 wherein Rx, R₁ and R₂ are all selected from hydrogen
7. The method of claim 4 wherein one enantiomer selected from the group consisting of Formula 1 predominates to the extent of about 90% or greater.
8. The method of claim 4 wherein one enantiomer selected from the group consisting of Formula 1 predominates to the extent of about 98% or greater.
9. The method of claim 4 wherein the enantiomer selected from the group consisting of Formula 1 is an enantiomer selected from the group consisting of Formula 1a; (note: in the structural formula of Formula 1a below the amino group attached to the beta carbon projects into the plane of the paper)



or a pharmaceutically acceptable salt or ester thereof;
wherein;

R_x is a member selected from the group consisting of hydrogen, lower alkyl of 1 to 8 carbon atoms, halogen selected from F, Cl, Br and I, alkoxy containing 1 to 3 carbon atoms, nitro, hydroxy, trifluoromethyl, and thioalkoxy containing 1 to 3 carbon atoms;

x is an integer of 1 to 3, with the proviso that R may be the same or different when x is 2 or 3;

R₁ and R₂ can be the same or different from each other and are independently selected from the group consisting of hydrogen, lower alkyl of 1 to 8 carbon atoms, aryl, arylalkyl, cycloalkyl of 3 to 7 carbon atoms;

R₁ and R₂ can be joined to form a 5 to 7-membered heterocycle substituted with a member selected from the group consisting of hydrogen, alkyl, and aryl groups,

wherein the cyclic compound can comprise 0 to 2 nitrogen atoms and 0 to 1 oxygen atoms,

wherein the nitrogen atoms are not directly connected with each other or with the oxygen atom.

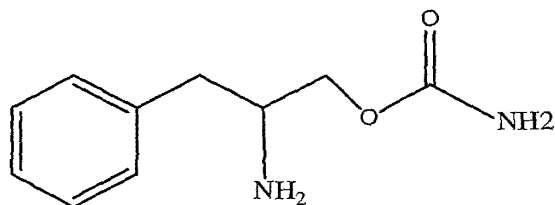
10. The method of claim 9 wherein R is hydrogen and $x=1$

11. The method of claim 9 wherein R, R1 and R2 are all selected from hydrogen and $x=1$

12. The method of claim 9 wherein one enantiomer selected from the group consisting of Formula 1a predominates to the extent of about 90% or greater.

13. The method of claim 4 wherein one enantiomer selected from the group consisting of Formula 1a predominates to the extent of about 98% or greater.

14. The method of claim 4 wherein the enantiomer of Formula 1a substantially free of other enantiomers is an enantiomer of Formula 1b or an enantiomeric mixture wherein the enantiomer of Formula 1b predominates. This is O-carbamoyl-(D)-phenylalaninol, this compound can also be named (R)-(beta-amino-benzenepropyl) carbamate monohydrochloric acid.



Formula 1b

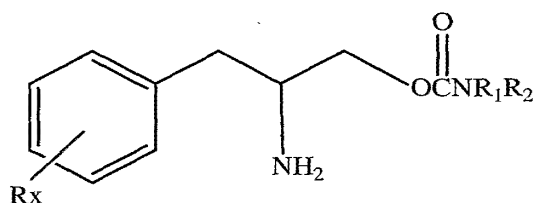
(note: in the structural formula of Formula 1b above (test compound), the amino group attached to the beta carbon projects into the plane of the paper. This is the dextrorotary (D) enantiomer that is of absolute configuration (R))

15. The method of claim 14 wherein the enantiomer of Formula 1b predominates to the extent of about 90% or greater.

16. The method of claim 14 wherein the enantiomer of Formula 1b predominates to the extent of about 98% or greater.

17. The method of claim 14 wherein the therapeutically effective amount of enantiomer is from about 0.01 mg/kg/dose to about 300 mg/kg/dose.

18. A method of treating sexual dysfunction in a subject, comprising the step of the concomitant administration, to a subject in need of such treatment, of a therapeutic agent that may cause sexual dysfunction and a therapeutically effective amount of an enantiomer of Formula 1 substantially free of other enantiomers or an enantiomeric mixture wherein one enantiomer of Formula 1 predominates;



(I)

or a pharmaceutically acceptable salt or ester thereof;

wherein;

R is a member selected from the group consisting of hydrogen, lower alkyl of 1 to 8 carbon atoms, halogen selected from F, Cl, Br and I, alkoxy containing 1 to 3 carbon atoms, nitro, hydroxy, trifluoromethyl, and thioalkoxy containing 1 to 3 carbon atoms;

x is an integer of 1 to 3, with the proviso that R may be the same or different when x is 2 or 3;

R_1 and R_2 can be the same or different from each other and are independently selected from the group consisting of hydrogen, lower alkyl of 1 to 8 carbon atoms, aryl, arylalkyl, cycloalkyl of 3 to 7 carbon atoms;

R_1 and R_2 can be joined to form a 5 to 7-membered heterocycle substituted with a member selected from the group consisting of hydrogen, alkyl, and aryl groups,

wherein the cyclic compound can comprise 1 to 2 nitrogen atoms and 0 to 1 oxygen atom,

wherein the nitrogen atoms are not directly connected with each other or with the oxygen atom.

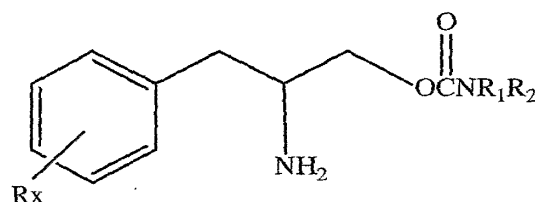
19. The method of claim 18 wherein R_x is hydrogen

20. The method of claim 18 wherein Rx, R₁ and R₂ are all selected from hydrogen

21. The method of claim 18 wherein one enantiomer selected from the group consisting of Formula 1 predominates to the extent of about 90% or greater.

22. The method of claim 18 wherein one enantiomer selected from the group consisting of Formula 1 predominates to the extent of about 98% or greater.

23. The method of claim 18 wherein the enantiomer selected from the group consisting of Formula 1 is an enantiomer selected from the group consisting of Formula 1;



(I)

or a pharmaceutically acceptable salt or ester thereof;
wherein;

R_x is a member selected from the group consisting of hydrogen, lower alkyl of 1 to 8 carbon atoms, halogen selected from F, Cl, Br and I, alkoxy containing 1 to 3 carbon atoms, nitro, hydroxy, trifluoromethyl, and thioalkoxy containing 1 to 3 carbon atoms;

x is an integer of 1 to 3, with the proviso that R may be the same or different when x is 2 or 3;

R₁ and R₂ can be the same or different from each other and are independently selected from the group consisting of hydrogen, lower alkyl of 1 to 8 carbon atoms, aryl, arylalkyl, cycloalkyl of 3 to 7 carbon atoms;

R₁ and R₂ can be joined to form a 5 to 7-membered heterocycle substituted with a member selected from the group consisting of hydrogen, alkyl, and aryl groups,

wherein the cyclic compound can comprise 0 to 2 nitrogen atoms and 0 to 1 oxygen atoms,

wherein the nitrogen atoms are not directly connected with each other or with the oxygen atom.

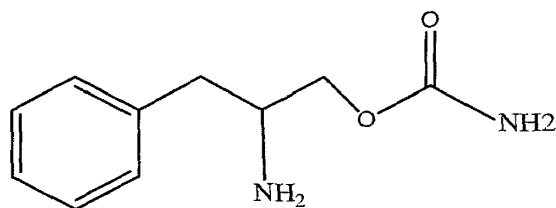
24. The method of claim 23 wherein R is hydrogen and $x=1$

25. The method of claim 23 wherein R, R1 and R2 are all selected from hydrogen and $x=1$

26. The method of claim 23 wherein one enantiomer selected from the group consisting of Formula 1 predominates to the extent of about 90% or greater.

27. The method of claim 23 wherein one enantiomer selected from the group consisting of Formula 1 predominates to the extent of about 98% or greater.

28. The method of claim 18 wherein the enantiomer of Formula 1 substantially free of other enantiomers is an enantiomer of Formula 1b or an enantiomeric mixture wherein the enantiomer of Formula 1b predominates. This is O-carbamoyl-(D)-phenylalaninol, this compound can also be named (R)-(beta-amino-benzenepropyl) carbamate monohydrochloric acid.



Formula 1b

(note: in the structural formula of Formula 1b above (test compound), the amino group attached to the beta carbon projects into the plane of the paper. This is the dextrorotary (D) enantiomer that is of absolute configuration (R))

29. The method of claim 28 wherein the enantiomer of Formula 1b predominates to the extent of about 90% or greater.

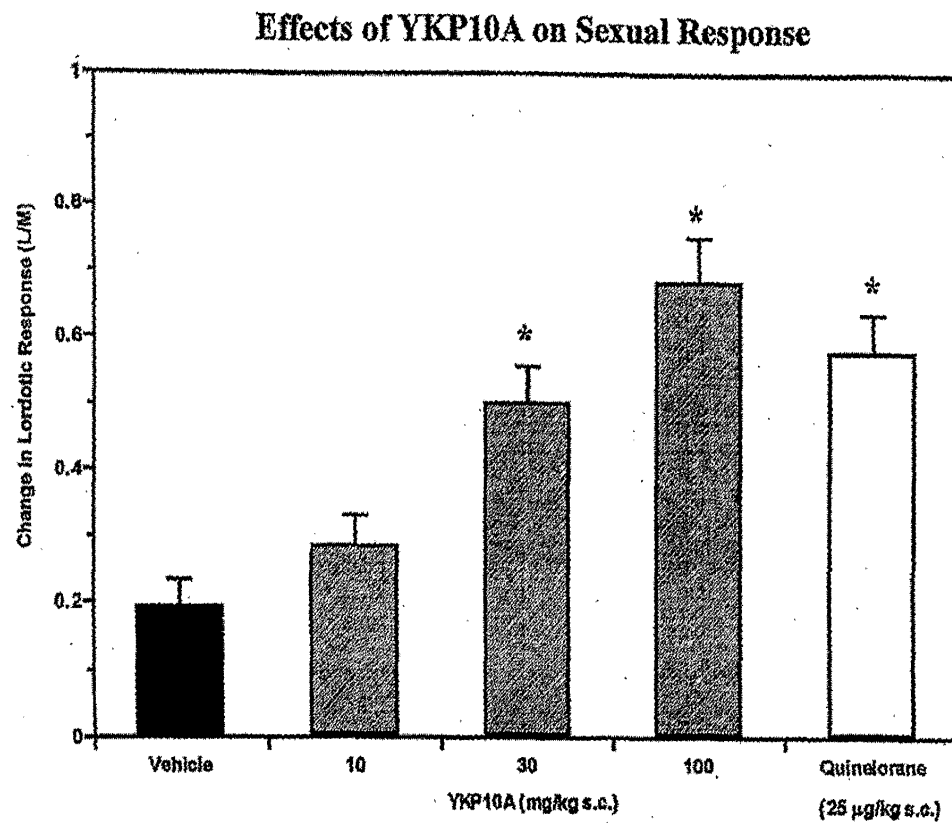
30. The method of claim 28 wherein the enantiomer of Formula 1b predominates to the extent of about 98% or greater.

31. The method of claim 28 wherein the other therapeutic agent is chosen from the group consisting of; selective serotonin reuptake inhibitors (SSRI's);

selective serotonin and norepinephrine reuptake inhibitors (SNRI's); older tricyclic antidepressants (TCAs); monoamine oxidase inhibitors (MAO-inhibitors), reversible inhibitors of monoamine oxidase (RIMAs), tertiary amine tricyclics and secondary amine tricyclic antidepressants

32. The method of claim 28 wherein the other therapeutic agent is chosen from the group consisting of; fluoxetine, duloxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine, sertraline, 5- MCA-NAT , lithium carbonate (LiCO_3), isocarboxazid, phenelzine, tranylcypromine, selegiline, moclobemide, kappa opioid receptor antagonists; selective neurokinin antagonists, corticotropin releasing factor (CRF) antagonists, antagonists of tachykinins , α -adrenoreceptor antagonists. amitriptyline, clomipramine, doxepin, imipramine, : venlafaxine, trimipramine, amoxapine, desipramine, maprotiline, nortriptyline and protriptyline, and pharmaceutically acceptable salts thereof.

33. The method of claim 28 wherein the therapeutically effective amount of enantiomer is from about 0.01 mg/kg/dose to about 300 mg/kg/dose.



Unlike most antidepressants, YKP10A augments sexual response
YKP10A may also have utility as an agent to treat disorders of sexual response



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/023068

A. CLASSIFICATION OF SUBJECT MATTER INV. A61P15/10 A61K31/165		
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) A61K		
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 practical, search terms used) EPO-Internal, CHEM ABS Data, WPI Data, MEDLINE, BIOSIS, EMBASE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96/24577 A (YUKONG LTD [KR]) 15 August 1996 (1996-08-15) cited in the application claim 1 page 3, paragraph 1	1-33
A	EP 0 633 023 A2 (LILLY CO ELI [US]) 11 January 1995 (1995-01-11) page 11, lines 10-24 page 10; table IV	1-33
P, X	WO 2006/050037 A (JANSSEN PHARMACEUTICA NV [BE]; SPORN JONATHAN [US]) 11 May 2006 (2006-05-11) paragraph [0013] claim 1	1-33
☐ 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 document 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 12 October 2006		Date of mailing of the international search report 20/10/2006
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Strack, Eberhard

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/023068

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-33 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2006/023068

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9624577	A	15-08-1996	CA 2212326 A1	15-08-1996
			CN 1173863 A	18-02-1998
			DE 69615668 D1	08-11-2001
			DE 69615668 T2	11-07-2002
			DK 815074 T3	28-01-2002
			EP 0815074 A1	07-01-1998
			ES 2165485 T3	16-03-2002
			JP 11501617 T	09-02-1999
			KR 173862 B1	01-04-1999
			PT 815074 T	28-03-2002
			US 5705640 A	06-01-1998
EP 0633023	A2	11-01-1995	AU 677317 B2	17-04-1997
			AU 6460794 A	15-12-1994
			CA 2125088 A1	11-12-1994
			CN 1342457 A	03-04-2002
			CN 1100634 A	29-03-1995
			CZ 9401354 A3	15-12-1994
			CZ 285829 B6	17-11-1999
			HK 1043322 A1	03-06-2005
			HU 71464 A2	28-11-1995
			IL 109872 A	06-12-2000
			JP 7048254 A	21-02-1995
			NO 942143 A	12-12-1994
			NO 991551 A	12-12-1994
			NO 993461 A	12-12-1994
			NO 20015806 A	12-12-1994
			NZ 260667 A	26-05-1997
			NZ 314570 A	24-11-2000
			RU 2154476 C2	20-08-2000
			US 5703112 A	30-12-1997
			ZA 9403862 A	04-12-1995
WO 2006050037	A	11-05-2006	NONE	

Form PCT/ISA/210 (patent family annex) (April 2005)



Espacenet

Bibliographic data: JP2007508293 (A) — 2007-04-05
PROCESS OF PREPARING O-CARBAMOYL COMPOUNDS IN THE PRESENCE OF ACTIVE AMINE GROUP
Inventor(s):
Applicant(s):

Classification: - international: C07C269/00; C07C271/20; C07D211/32; C07D211/62; C07D217/16; C07C271/12
 - cooperative: C07C269/00 (EP); C07D211/32 (EP); C07D217/16 (EP); C07B2200/07 (EP) more

Application number: JP20060532099 20041008 [Global Dossier](#)

Priority number(s): [US20030680979 20031008](#) ; [WO2004KR02571 20041008](#)

Also published as: [AR045868 \(A1\)](#) [AU2004277479 \(A1\)](#) [CA2541303 \(A1\)](#) [CN1867542 \(A\)](#) [EP1689701 \(A1\)](#) [KR20060126965 \(A\)](#) [RU2006115520 \(A\)](#) [TW200524848 \(A\)](#) [US2005080268 \(A1\)](#) [US2006058548 \(A1\)](#) [WO2005033064 \(A1\)](#) less

Abstract not available for JP2007508293 (A)

Abstract of corresponding document: WO2005033064 (A1)

A process for preparing O-carbamoyl aminoalcohols represented by Formula(I) wherein: n is an integer from 0 and 5; R1, R2, R3 and R4 are individually selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted or unsubstituted aryl and arylalkyl the aryl portion of which may be unsubstituted or substituted; R5 and R6 are individually selected from the group consisting of hydrogen, alkyl or arylalkyl the aryl portion of which may be unsubstituted or substituted; or R1 and R5 together with the carbon and nitrogen to which they are attached may form an unfused or fused heterocyclic ring having from 4 to 10 members, comprising reacting an aminoalcohol represented by Formula (II) wherein n, R1, R2, R3, R4, R5 and R6 are as defined; with a cyanate and an excess of an acid in an organic solvent medium.

(19) 日本国特許庁 (JP)

(12) 公表特許公報(A)

(11) 特許出願公表番号

特表2007-508293

(P2007-508293A)

(43) 公表日 平成19年4月5日 (2007. 4. 5)

(51) Int. Cl.	F I	テーマコード (参考)
C O 7 C 269/00 (2006. 01)	C O 7 C 269/00	4 C O 3 4
C O 7 C 271/20 (2006. 01)	C O 7 C 271/20	4 C O 5 4
C O 7 D 217/16 (2006. 01)	C O 7 D 217/16	4 H O O 6
C O 7 D 211/62 (2006. 01)	C O 7 D 211/62	
審査請求 未請求 予備審査請求 未請求 (全 20 頁)		

(21) 出願番号	特願2006-532099 (P2006-532099)	(71) 出願人	303024622
(86) (22) 出願日	平成16年10月8日 (2004. 10. 8)		エスケー コーポレーション
(85) 翻訳文提出日	平成18年6月7日 (2006. 6. 7)		大韓民国、ソウル、ゾンロック、ソリン-
(86) 国際出願番号	PCT/KR2004/002571		ドン、99
(87) 国際公開番号	W02005/033064	(74) 代理人	100068618
(87) 国際公開日	平成17年4月14日 (2005. 4. 14)		弁理士 粂 経夫
(31) 優先権主張番号	10/680, 979	(74) 代理人	100104145
(32) 優先日	平成15年10月8日 (2003. 10. 8)		弁理士 官崎 嘉夫
(33) 優先権主張国	米国 (US)	(74) 代理人	100080908
			弁理士 館石 光雄
		(74) 代理人	100093193
			弁理士 中村 壽夫
		(74) 代理人	100104385
			弁理士 加藤 勉
		最終頁に続く	

(54) 【発明の名称】 活性アミン基の存在下におけるO-カルバモイル化合物の製造方法

(57) 【要約】

【課題】 活性アミン基の存在下におけるO-カルバモイル化合物の製造方法の提供。

【解決手段】 式 I (式中、nは、0ないし5の整数を表わし；

R₁、R₂、R₃及びR₄は、個々に、水素原子、アルキル基、シクロアルキル基、置換された又は未置換のアリール基及びアリールアルキル基 [ここで、アリール基部分は、未置換であり得るか又は置換され得る。] からなる群から選択され；

R₅及びR₆は、個々に、水素原子、アルキル基又はアリールアルキル基 [ここで、アリール基部分は、未置換であり得るか又は置換され得る。] からなる群から選択されるか；又は、

R₁及びR₅が、それらが結合する炭素原子及び窒素原子と一緒にあって、4ないし10員を有する非縮合又は縮合複素環を形成し得る。) で表わされるO-カルバモイルアミノアルコールの製造方法であって、

該方法は、式 I I (式中、n、R₁、R₂、R₃、R₄、R₅及びR₆は、上記で定義した通りである。) で表わされるアミノアルコールとシアネート及び過剰量の酸を有機溶剤中で反応させることからなる方法

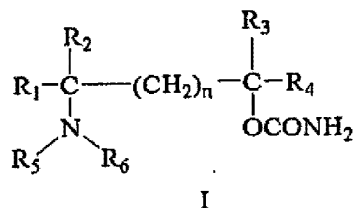
【選択図】 なし

【特許請求の範囲】

【請求項1】

式 I

【化1】



〔式中、

nは、0ないし5の整数を表わし；

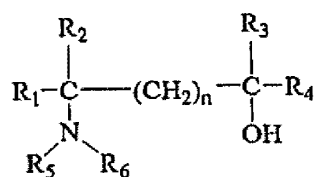
R₁、R₂、R₃及びR₄は、個々に、水素原子、アルキル基、シクロアルキル基、置換された又は未置換のアリール基及びアリールアルキル基〔ここで、アリール基部分は、未置換であり得るか又は(X')_m (式中、mは、0ないし4の整数を表わし、X'は、水素原子、アルキル基、アルコキシ基、アルキルチオ基、ハロゲン原子、ヒドロキシ基、ニトロ基及びトリフルオロメチル基からなる群から選択される。)によって置換され得る。〕からなる群から選択され；

R₅及びR₆は、個々に、水素原子、アルキル基及びアリールアルキル基〔ここで、アリール基部分は、未置換であり得るか又は(X')_m (式中、m及びX'は、上記で定義した通りである。)によって置換され得る。〕からなる群から選択されるか；又は、

R₁及びR₅が、それらが結合する炭素原子及び窒素原子と一緒に、4ないし10員を有する非縮合又は縮合複素環を形成し得る。〕で表わされるO-カルバモイルアミノアルコールの製造方法であって、

該方法は、式 I I

【化2】



II

(式中、n、R₁、R₂、R₃、R₄、R₅及びR₆は、上記で定義した通りである。)で表わされるアミノアルコールとシアネート及び過剰量の酸を有機溶媒中で反応させることからなる方法。

【請求項2】

前記シアネートが、アルカリシアネート又はアルカリ土類シアネートである請求項1記載の方法。

【請求項3】

前記シアネートが、シアン酸ナトリウム、シアン酸カリウム、シアン酸アンモニウム、シアン酸マグネシウム及びシアン酸カルシウムからなる群から選択される請求項2記載の方法。

【請求項4】

前記酸が、塩酸、硫酸、リン酸、酢酸、ハロゲン化酢酸、アリールスルホン酸、アルキルスルホン酸及びハロゲン化アルキルスルホン酸からなる群から選択される請求項1記載の方法。

【請求項5】

前記有機溶媒が、ハロゲン化アルカン溶媒、エーテル溶媒、ニトリル溶媒、芳香族溶媒及びそれらの混合物からなる群から選択される請求項1記載の方法。

【請求項6】

前記シアネートがシアン酸ナトリウムであり、かつ前記酸がメタンスルホン酸である請求項1記載の方法。

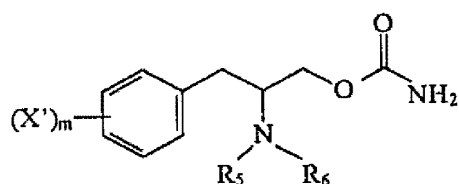
【請求項7】

前記有機溶媒が、ジクロロメタン又はアセトニトリルである請求項6記載の方法。

【請求項8】

前記O-カルバモイルアミノアルコールが、式I I I

【化3】

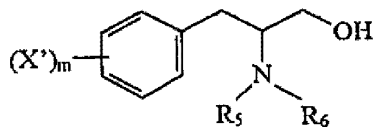


III

(式中、X'、m、R₅及びR₆は、請求項1で定義した通りである。)で表わされる請求項1記載の方法であって、

該方法は、式I V

【化4】



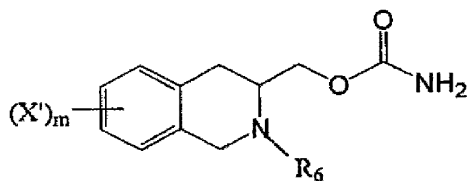
IV

(式中、X'、m、R₅及びR₆は、請求項1で定義した通りである。)で表わされるアミノアルコールとシアネート及び過剰量の酸を有機溶媒中で反応させることからなる方法。

【請求項9】

前記O-カルバモイルアミノアルコールが、式V

【化5】

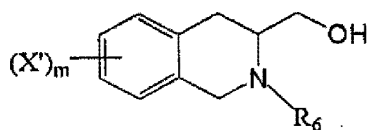


V

(式中、X'、m及びR₆は、請求項1で定義した通りである。)で表わされる請求項1記載の方法であって、

該方法は、式V I

【化6】



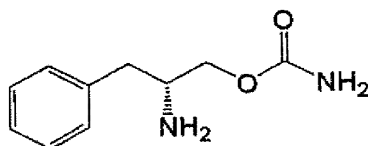
VI

(式中、X'、m及びR₆は、請求項1で定義した通りである。)で表わされるアミノアルコールとシアネート及び過剰量の酸を有機溶媒中で反応させることからなる方法。

【請求項10】

前記O-カルバモイルアミノアルコールが、式V I I

【化7】

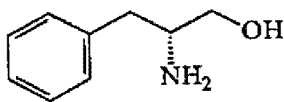


VII

で表わされる請求項1記載の方法であって、

該方法は、式V I I I

【化8】



VIII

で表わされるD-フェニルアラニノールとシアネート及び過剰量の酸を有機溶媒中で反応させることからなる方法。

【請求項11】

前記シアネートがシアン酸ナトリウム、シアン酸カリウム、シアン酸アンモニウム、シアン酸マグネシウム及びシアン酸カルシウムからなる群から選択され、前記酸が塩酸、酢酸、トリフルオロ酢酸、トリクロロ酢酸、ベンゼンスルホン酸、トルエンスルホン酸、メタンスルホン酸、エタンスルホン酸及びトリフルオロメタンスルホン酸からなる群から選択され、前記有機溶媒がジクロロメタン、クロロホルム、1, 2-ジクロロエタン、1, 1, 1-トリクロロエタン、テトラヒドロフラン、1, 2-ジメトキシエタン、ジエチルエーテル、アセトニトリル、プロピオニトリル、ベンゼン、トルエン、キシレン及びそれらの混合物からなる群から選択される請求項10記載の方法。

【請求項12】

前記シアネートがシアン酸ナトリウムであり、かつ前記酸がメタンスルホン酸である請求項10記載の方法。

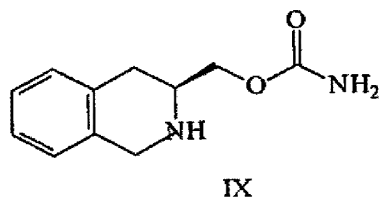
【請求項13】

前記有機溶媒がジクロロメタンである請求項12記載の方法。

【請求項14】

前記O-カルバモイルアミノアルコールが、式I X

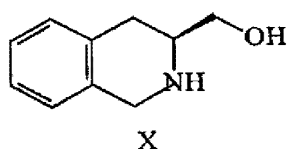
【化9】



で表わされるO-カルバモイル-L-オキシメチル-1, 2, 3, 4-テトラヒドロイソキノリンである請求項1記載の方法であって、

該方法は、式X

【化10】



で表わされる(L)-ヒドロキシメチル-1, 2, 3, 4-テトラヒドロイソキノリンとシアネート及び過剰量の酸を有機溶媒中で反応させることからなる方法。

【請求項15】

前記シアネートがシアン酸ナトリウム、シアン酸カリウム、シアン酸アンモニウム、シアン酸マグネシウム及びシアン酸カルシウムからなる群から選択され、前記酸が塩酸、酢酸、トリフルオロ酢酸、トリクロロ酢酸、ベンゼンスルホン酸、トルエンスルホン酸、メタンスルホン酸、エタンスルホン酸及びトリフルオロメタンスルホン酸からなる群から選択され、前記有機溶媒がジクロロメタン、クロロホルム、1, 2-ジクロロエタン、1, 1, 1-トリクロロエタン、テトラヒドロフラン、1, 2-ジメトキシエタン、ジエチルエーテル、アセトニトリル、プロピオニトリル、ベンゼン、トルエン、キシレン及びそれらの混合物からなる群から選択される請求項14記載の方法。

【請求項16】

前記シアネートがシアン酸ナトリウムであり、かつ前記酸がメタンスルホン酸である請求項14記載の方法。

【請求項17】

前記有機溶媒がジクロロメタンである請求項16記載の方法。

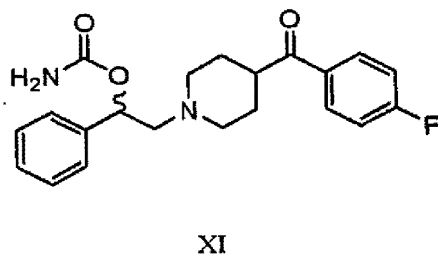
【請求項18】

前記有機溶媒がアセトニトリルである請求項16記載の方法。

【請求項19】

前記O-カルバモイルアミノアルコールが、式XI

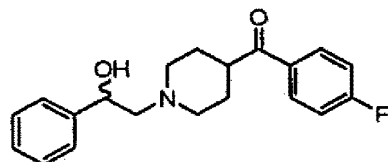
【化11】



で表わされるカルバミン酸2-((4-フルオロベンゾイル)ピペリジン-1-イル)-1-フェニルエチルエステルである請求項1記載の方法であって、

該方法は、式XII

【化12】



XII

で表わされる 2-(4-フルオロベンゾイル)ピペリジニ-1-イル)-1-フェニルエタノールとシアネート及び過剰量の酸を有機溶媒中で反応させることからなる方法。

【請求項20】

前記シアネートがシアン酸ナトリウム、シアン酸カリウム、シアン酸アンモニウム、シアン酸マグネシウム及びシアン酸カルシウムからなる群から選択され、前記酸が塩酸、酢酸、トリフルオロ酢酸、トリクロロ酢酸、ベンゼンスルホン酸、トルエンスルホン酸、メタンスルホン酸、エタンスルホン酸及びトリフルオロメタンスルホン酸からなる群から選択され、前記有機溶媒がジクロロメタン、クロロホルム、1, 2-ジクロロエタン、1, 1, 1-トリクロロエタン、テトラヒドロフラン、1, 2-ジメトキシエタン、ジエチルエーテル、アセトニトリル、プロピオニトリル、ベンゼン、トルエン、キシレン及びそれらの混合物からなる群から選択される請求項19記載の方法。

【請求項21】

前記シアネートがシアン酸ナトリウムであり、かつ前記酸がメタンスルホン酸である請求項19記載の方法。

【請求項22】

前記有機溶媒がジクロロメタンである請求項21記載の方法。

【請求項23】

前記酸の量が、請求項1記載の式Iで表わされるアミノアルコール中のアミン基の総数より約1ないし約10モル当量多い請求項1記載の方法。

【請求項24】

前記シアネートの請求項1記載の式Iで表わされるアミノアルコールに対するモル比が約1ないし10である請求項1記載の方法。

【請求項25】

請求項1記載の式Iで表わされるアミノアルコールの量と前記有機溶媒の量の質量体積比が約1:3ないし約1:100の範囲内である請求項1記載の方法。

【請求項26】

前記反応が、約-80℃ないし約80℃の範囲内の温度で行われる請求項1記載の方法。

【請求項27】

前記反応が、約-10℃ないし約60℃の範囲内の温度で行われる請求項25記載の方法。

【請求項28】

請求項1記載の式Iで表わされるO-カルバモイルアミノアルコール及び請求項1記載の式Iで表わされるアミノアルコールがラセミ体である請求項1記載の方法。

【請求項29】

請求項1記載の式Iで表わされるO-カルバモイルアミノアルコール及び請求項1記載の式Iで表わされるアミノアルコールが光学活性体である請求項1記載の方法。

【請求項30】

請求項1記載の式Iで表わされるO-カルバモイルアミノアルコール及び請求項1記載の式Iで表わされるアミノアルコールがS体である請求項1記載の方法。

【請求項31】

請求項1記載の式Iで表わされるO-カルバモイルアミノアルコール及び請求項1記載の式I Iで表わされるアミノアルコールがR体である請求項1記載の方法。

【発明の詳細な説明】

【技術分野】

【0001】

本発明は、O-カルバモイルアミノアルコールの新規製造方法に関する。

【背景技術】

【0002】

O-カルバモイルアミノアルコールは、医薬的に有用な新規化合物を含む。例えば、O-カルバモイル-(D)-フェニルアラニノール塩酸塩及びO-カルバモイル-(L)-3-ヒドロキシメチル-1, 2, 3, 4-テトラヒドロイソキノリン塩酸塩が、中枢神経系(CNS)疾患の治療のために、特に抗うつ剤として開発されている。

【発明の開示】

【発明が解決しようとする課題】

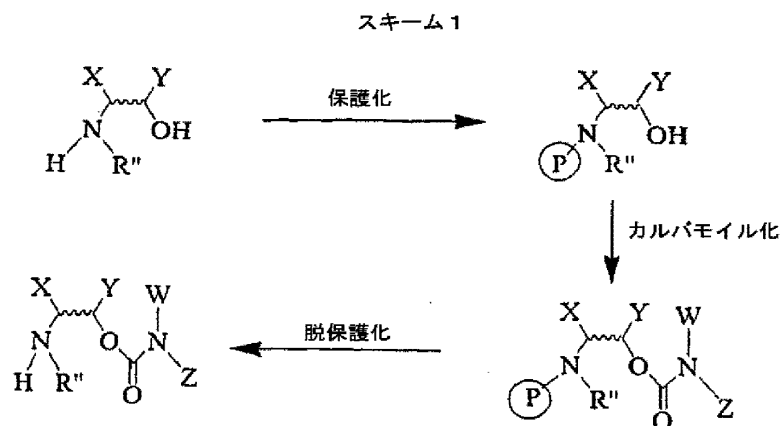
【0003】

アミン基はヒドロキシ基と比べて一般的に反応性が高いため、アミノアルコールのO-カルバモイル化生成物を合成する場合、カルバモイル化反応の前に、アミン部分を保護する必要がある。それ故、スキーム1に記載されるように、(1)保護、(2)カルバモイル化反応及び(3)脱保護の長い手順が、典型的には、転換のために必要とされる。

【0004】

スキーム1に従った反応の例は、保護化N-ベンジルオキシカルボニルアミノアルコールを形成するためのアミノアルコールとベンジルクロロホルメートの反応であり得る。該保護化アミノアルコールをホスゲンと反応させた後、アミンとの反応でカルバモイル化することにより、O-カルバモイル-N-保護化アミノアルコールが得られる。このN-保護化化合物の脱保護は、水素化によってなされる。

【化1】



(式中、W、X、Y及びZは、個々に、水素原子、アルキル基、シクロアルキル基、アリール基又はアリーラルキル基からなる群から選択され、

R' 'は、水素原子、アルキル基又はアリーラルキル基からなる群から選択される。)

この方法は、本発明に従って有益に単純化される。

【課題を解決するための手段】

【0005】

発明の概要

本発明は、有機溶媒中でシアネート及び過剰量の酸を使用した単工程でのヒドロキシル

基の化学選択的カルバモイル化によるO-カルバモイルアミノアルコールの新規製造方法を提供する。特に、本発明は、O-カルバモイルアミノアルコールの単工程製造におけるシアン酸ナトリウム及びメタンスルホン酸の使用を含む。少規模な実験室での製造及び大規模な工業製造の双方が開示される。該方法は、特に、O-カルバモイル-D-フェニルアラニノール、O-カルバモイル-(L)-オキシメチル-1, 2, 3, 4-テトラヒドロイソキノリン及びカルバミン酸2-((4-フルオロベンゾイル)ピペリジニ-1-イル)-1-フェニルエチルエステルの製造において有益である。

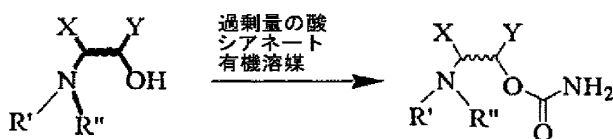
【0006】

発明の詳細な説明

本発明は、O-カルバモイルアミノアルコールの新規製造方法を提供する。該方法は、出発アミノアルコール中にカルバモイル部分を導入することにより、上記スキーム1で示した既知の方法よりも効率が良い。そのようなものとして、本発明は、スキーム2

【化2】

スキーム2



【式中、

X及びYは、個々に、水素原子、アルキル基、シクロアルキル基、アリール基又はアリールアルキル基（ここで、アリール基部分は、未置換であり得るか又は下記で定義する（X'）_mによって置換され得る。）からなる群から選択され；

R'及びR''は、水素原子、アルキル基又はアリールアルキル基（ここで、アリール基部分は、未置換であり得るか又は下記で定義する（X'）_mによって置換され得る。）からなる群から選択される。】で図解され得る。

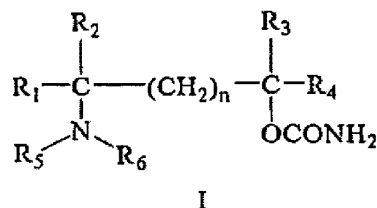
【0007】

本発明に記載される方法が反応溶媒として有機溶媒系を使用し、独占的な生成物として、O-カルバモイル化種を選択的に生成することは、非常に驚くべきことである。酸性水溶液中でのアミノアルコールとシアネートの反応が、主生成物としてN-カルバモイル化生成物を生成することは注目すべきである。

【0008】

本発明は、式I

【化3】



【式中、

nは、0ないし5の整数を表わし；

R₁、R₂、R₃及びR₄は、個々に、水素原子、アルキル基、シクロアルキル基、置換された又は未置換のアリール基及びアリールアルキル基〔ここで、アリール基部分は、未置換であり得るか又は（X'）_m（式中、mは、0ないし4の整数を表わし、X'は、水素原子、アルキル基、アルコキシ基、アルキルチオ基、ハロゲン原子、ヒドロキシ基、ニトロ基及びトリフルオロメチル基からなる群から選択される。）によって置換され得る。〕

からなる群から選択され；

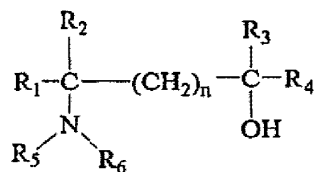
R_5 及び R_6 は、個々に、水素原子、アルキル基又はアリールアルキル基〔ここで、アリール基部分は、未置換であり得るか又は $(X')_m$ (式中、 m 及び X' は、上記で定義した通りである。) によって置換され得る。〕からなる群から選択されるか；又は、

R_1 及び R_5 が、それらが結合する炭素原子及び窒素原子と一緒に、4ないし10員を有する非縮合又は縮合複素環を形成する。〕で表わされるO-カルバモイルアミノアルコールを製造するために特に有益な新規方法を提供する。

【0009】

該方法は、式 I I

【化4】



II

(式中、 R_1 ないし R_6 及び n は、上記で定義した通りである。) で表わされるアミノアルコールとシアネート及び過剰量の酸を有機溶媒中で反応させることからなる。

【0010】

一般構造式 I I で表わされる出発アミノアルコールは、キラル又はアキラルであり得る。本発明に記載される方法は、ラセミ体及び光学活性体の所望のO-カルバモイルアミノアルコールを製造するために使用され得る。

【0011】

特定の反応条件は個々の出発アミノアルコールにより変化し得るが、本発明の製造方法の一般条件は下記の通りである。

【0012】

本発明に従って、所望の反応の前に、過剰量の酸が、出発アルコール中に存在するアミン部分のプロトン化のために必要とされる。典型的には、酸の量は、式 I I で表わされる出発アミノアルコール中に存在するアミン基の総数と反応するために必要とされる量よりも約1ないし約10モル当量多い。それ故、1つのアミン基が存在する場合、約2ないし約11当量の酸が典型的には使用されるが、更なる当量の酸の存在は反応を妨げない。

【0013】

本発明の方法において利用される酸は、例えば、塩酸、硫酸、リン酸、酢酸、ハロゲン化酢酸、アリールスルホン酸、アルキルスルホン酸及びハロゲン化アルキルスルホン酸等の有機又は無機酸であり得る。塩酸、ハロゲン化酢酸、アリールスルホン酸及びアルキルスルホン酸が、対象物の合成のために好ましい。特に好ましい酸は、塩酸、トリフルオロ酢酸、トリクロロ酢酸、ベンゼンスルホン酸、トルエンスルホン酸、メタンスルホン酸、エタンスルホン酸及びトリフルオロメタンスルホン酸を含む。

【0014】

本発明は、シアネートを利用して、系中でシアン酸を生成する。典型的には、シアネートは、本発明における出発アミノアルコールの約1ないし約10モル当量で使用される。本発明のために有用なシアネートは、シアン酸ナトリウム、シアン酸カリウム及びシアン酸アンモニウム等のアルカリ金属シアネート、シアン酸マグネシウム、シアン酸カルシウム等のアルカリ土類シアネート等を含むが、これらに制限されない。さもないれば、シアネートからシアン酸を生成するよりはむしろ、所望生成物も生成し得る精製シアン酸を使用し得る。

【0015】

本発明に記載されるカルバメート化反応は、様々な有機溶媒中で行われ得る。ジクロロメタン等のハロゲン化アルカン、テトラヒドロフラン等のエーテル溶媒、アセトニトリル等のニトリル溶媒及びトルエン等の芳香族溶媒又はこれらの混合物が、反応溶媒として使用され得る。好ましい溶媒は、ジクロロメタン、クロロホルム、1, 2-ジクロロエタン、1, 1, 1-トリクロロエタン、テトラヒドロフラン、1, 2-ジメトキシエタン、ジエチルエーテル、アセトニトリル、プロピオニトリル、ベンゼン、トルエン、キシレン及びそれらの混合物からなる群から選択される。ジクロロメタン、1, 2-ジクロロエタン、1, 1, 1-トリクロロエタン及びアセトニトリルを含むハロゲン化アルカン及びニトリル溶媒が特に好ましい溶媒である。

【0016】

式 I I で表わされるアミノアルコールの量と有機溶媒の量の質量体積比は、約 1 : 3 ないし約 1 : 100 の範囲内である。例えば、1 g のアミノアルコールが使用される場合、約 3 ないし約 100 mL の溶媒が、反応のために利用され得る。

【0017】

対象物の反応は、使用する溶媒に依存して、約 -80℃ ないし約 80℃ の範囲内の温度で行われる。典型的には、反応は、約 -10℃ ないし約 60℃ の範囲内の温度で行われる。反応温度は、出発アミノアルコールに依存して、上記範囲内で変化し得る。

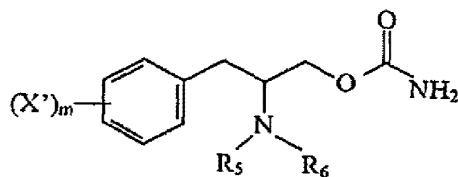
【0018】

本発明に従った典型的な反応では、出発アミノアルコールを反応容器中に置き、その後、反応溶媒を添加する。その後の、使用するシアネート及び酸の添加順序は、典型的には、いかなる著しく異なる結果ももたらさない。好ましくは、試薬の添加工程は、約 -10℃ ないし約 5℃ の範囲内の温度で行われる。

【0019】

本発明の好ましい態様は、式 I I I

【化5】



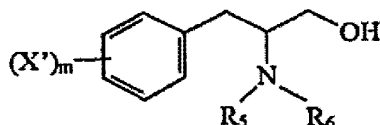
III

(式中、X'、m、R₅ 及び R₆ は、上記で定義した通りである。) で表わされる O-カルバモイルアミノアルコールの新規製造方法を提供する。

【0020】

該方法は、式 I V

【化6】



IV

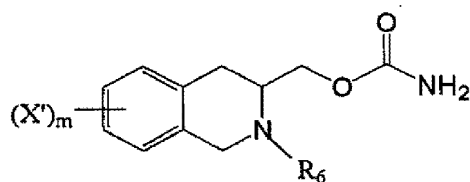
(式中、X'、m、R₅ 及び R₆ は、上記で定義した通りである。) で表わされるアミノアルコールとシアネートナトリウム、シアネートカリウム、シアネートアンモニウム、シアネートマグネシウム及びシアネートカルシウムからなる群から選択されるシアネート及び過剰量の、塩酸、酢酸、トリフルオロ酢酸、トリクロロ酢酸、ベンゼンスルホン酸、トルエンスルホン酸、メタンスルホン酸、エタンスルホン酸及びトリフルオロメタンスルホン酸からなる

群から選択される酸を、ジクロロメタン、クロロホルム、1, 2-ジクロロエタン、1, 1, 1-トリクロロエタン、テトラヒドロフラン、1, 2-ジメトキシエタン、ジエチルエーテル、アセトニトリル、プロピオニトリル、ベンゼン、トルエン、キシレン及びそれらの混合物からなる群から選択される有機溶媒中で反応させることからなる。

【0021】

本発明の他の好ましい態様は、式V

【化7】



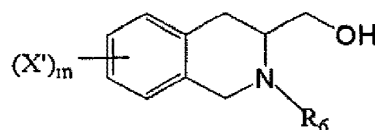
V

(式中、X'、m及びR₆は、上記で定義した通りである。)で表わされるO-カルバモイルアミノアルコールの新規製造方法を提供する。

【0022】

該方法は、式V I

【化8】



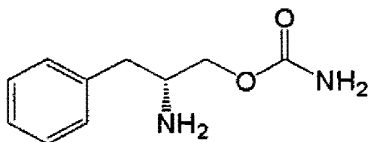
VI

(式中、X'、m及びR₆は、上記で定義した通りである。)で表わされるアミノアルコールとシアン酸ナトリウム、シアン酸カリウム、シアン酸アンモニウム、シアン酸マグネシウム及びシアン酸カルシウムからなる群から選択されるシアネート及び過剰量の、塩酸、酢酸、トリフルオロ酢酸、トリクロロ酢酸、ベンゼンスルホン酸、トルエンスルホン酸、メタンスルホン酸、エタンスルホン酸及びトリフルオロメタンスルホン酸からなる群から選択される酸を、ジクロロメタン、クロロホルム、1, 2-ジクロロエタン、1, 1, 1-トリクロロエタン、テトラヒドロフラン、1, 2-ジメトキシエタン、ジエチルエーテル、アセトニトリル、プロピオニトリル、ベンゼン、トルエン、キシレン及びそれらの混合物からなる群から選択される有機溶媒中で反応させることからなる。

【0023】

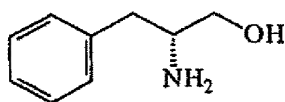
本発明の更なる他の好ましい態様は、式V I I

【化9】



VII

【化10】



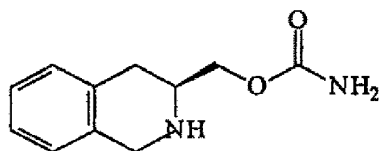
VIII

で表わされるD-フェニルアラニノールとシアン酸ナトリウム、シアン酸カリウム、シアン酸アンモニウム、シアン酸マグネシウム及びシアン酸カルシウムからなる群から選択されるシアネート及び過剰量の、塩酸、酢酸、トリフルオロ酢酸、トリクロロ酢酸、ベンゼンスルホン酸、トルエンスルホン酸、メタンスルホン酸、エタンスルホン酸及びトリフルオロメタンスルホン酸からなる群から選択される酸を、ジクロロメタン、クロロホルム、1, 2-ジクロロエタン、1, 1, 1-トリクロロエタン、テトラヒドロフラン、1, 2-ジメトキシエタン、ジエチルエーテル、アセトニトリル、プロピオニトリル、ベンゼン、トルエン、キシレン及びそれらの混合物からなる群から選択される有機溶媒中で反応させることからなる方法を提供する。

【0024】

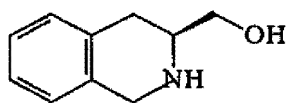
本発明の更なる他の好ましい態様は、式IX

【化11】



IX

【化12】



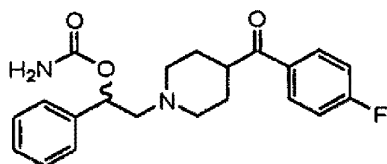
X

で表わされる(L)-3-ヒドロキシメチル-1, 2, 3, 4-テトラヒドロイソキノリンとシアン酸ナトリウム、シアン酸カリウム、シアン酸アンモニウム、シアン酸マグネシウム及びシアン酸カルシウムからなる群から選択されるシアネート及び過剰量の、塩酸、酢酸、トリフルオロ酢酸、トリクロロ酢酸、ベンゼンスルホン酸、トルエンスルホン酸、メタンスルホン酸、エタンスルホン酸及びトリフルオロメタンスルホン酸からなる群から選択される酸を、ジクロロメタン、クロロホルム、1, 2-ジクロロエタン、1, 1, 1-トリクロロエタン、テトラヒドロフラン、1, 2-ジメトキシエタン、ジエチルエーテル、アセトニトリル、プロピオニトリル、ベンゼン、トルエン、キシレン及びそれらの混合物からなる群から選択される有機溶媒中で反応させることからなる方法を提供する。

【0025】

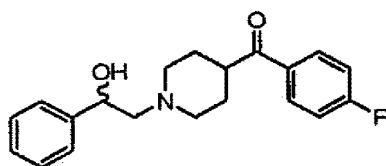
また、本発明の更なる他の態様は、式XI

【化13】



XI

【化14】



XII

で表わされる 2-(4-フルオロベンゾイル)ピペリジニ-1-イル)-1-フェニルエタノールとシアン酸ナトリウム、シアン酸カリウム、シアン酸アンモニウム、シアン酸マグネシウム及びシアン酸カルシウムからなる群から選択されるシアネート及び過剰量の、塩酸、酢酸、トリフルオロ酢酸、トリクロロ酢酸、ベンゼンスルホン酸、トルエンスルホン酸、メタンスルホン酸、エタンスルホン酸及びトリフルオロメタンスルホン酸からなる群から選択される酸を、ジクロロメタン、クロロホルム、1, 2-ジクロロエタン、1, 1-トリクロロエタン、テトラヒドロフラン、1, 2-ジメトキシエタン、ジエチルエーテル、アセトニトリル、プロピオニトリル、ベンゼン、トルエン、キシレン及びそれらの混合物からなる群から選択される有機溶媒中で反応させることからなる方法を提供する。

【0026】

式 I ないし VI に含まれる基の定義を以下に示す。

特に指示がない限りは、本願明細書で利用される用語「アルキル基」は、1ないし 8 個の炭素原子を有する直鎖又は枝分かれ鎖の炭化水素基を意味し、そして、メチル基、エチル基、n-プロピル基、イソプロピル基、n-ブチル基、第二ブチル基、イソブチル基、第三ブチル基、n-ペンチル基、n-ヘキシル基等を含むが、これらに制限されない。

【0027】

用語「ハロゲン原子」は、フッ素原子、塩素原子、臭素原子及びヨウ素原子を含み、フッ素原子及び塩素原子が好ましい。

【0028】

用語「アルコキシ基」は、酸素原子によって分子の残りに結合されたアルキル基を言及する。これは、メトキシ基、エトキシ基及びプロポキシ基を含むが、これらに制限されない。

【0029】

用語「アルキルチオ基」は、硫黄原子によって分子の残りに結合されたアルキル基を言及する。これは、メチルチオ基、エチルチオ基及びプロピルチオ基を含むが、これらに制限されない。

【0030】

用語「シクロアルキル基」は、3ないし 6 個の炭素原子の環式基を言及する。好ましいシクロアルキル基は、シクロペンチル基及びシクロヘキシル基である。

【0031】

用語「アリール基」は、未置換であり得るか、又はメチル基又はエチル基等のアルキル基、メトキシ基又はエトキシ基等のアルコキシ基、メチルチオ基等のアルキルチオ基、ハロゲン原子、ヒドロキシ基、ニトロ基及びトリフルオロメチル基から選択される基で置換され得る、フェニル基、ナフチル基等の芳香族炭化水素基を言及する。

【0032】

用語「アリールアルキル基」は、アルキル基及びアリール基において上記で定義した通りである。該基は、ベンジル基を含むが、これに制限されない。

【0033】

以下の実施例は、本発明の特定の態様を説明するためのものであり、本発明は、これらの特定の態様に制限されない。当業者ならば、本発明が添付した特許請求の範囲内に含まれ得る全ての代替案、変更案及び同等案を含むことを分り得る。

【実施例】

【0034】

実施例1. O-カルバモイル-(D)-フェニルアラニノールの製造

機械攪拌機、温度計及び250mL滴下漏斗を備えた乾燥2L三つ口丸底フラスコ中に、ジクロロメタン838mLを添加し、その後、D-フェニルアラニノール(100g、0.66mol)及びシアン酸ナトリウム(85g、0.92mol)を添加した。混合物を氷浴中で攪拌した。滴下漏斗にメタンスルホン(222.3g、2.31mol)を添加し、そして、5℃以下の温度を維持するために、それをゆっくりと反応混合物へ添加した。添加が完了した後、反応混合物は粘性が高くなった。氷浴を取り除き、D-フェニルアラニノールがTLC分析によって検出されなくなるまで、反応混合物を攪拌した。氷80gを反応混合物へ添加し、反応混合物を氷浴中で冷却し、pH紙を使用することによって測定した水相のpHが1.0ないし1.1になるまで、20%水酸化ナトリウム水溶液を、5℃以下の温度を維持するような速度において添加した。混合物を分液漏斗に移し、有機相を分離した。水相をジクロロメタン500mLで2度抽出し、1つにまとめた有機相を、塩水(350mL)で洗浄し、硫酸ナトリウム(50g)上で一晩乾燥させた。濾過によって硫酸ナトリウムを除去した後、有機相を真空中で濃縮し、オイルとして、遊離塩基形態の所望の生成物、O-カルバモイル-(D)-フェニルアラニノールを115g(89%)得た。

O-カルバモイル-(D)-フェニルアラニノール塩酸塩を以下のように製造した。粗反応生成物、O-カルバモイル-(D)-フェニルアラニノール(115g)をイソプロパノール120mL中に溶解し、機械攪拌機を備えた三つ口丸底フラスコへ移した。混合物を氷浴中で冷却し、滴下漏斗にイソプロパノール中飽和HCl溶液100L(6.5M)を添加した。5℃以下の温度を維持するために、HCl溶液をゆっくりと遊離塩基溶液へ添加した。添加中、HCl形態の所望の生成物の沈殿が観察された。添加が完了した後、混合物を更に1時間攪拌し、アセトン660mLを添加した。混合物を、更に1時間攪拌し、白色沈殿を、濾過によって収集した。生成物を、氷冷イソプロパノール-アセトン(1/3、v/v)で十分に洗浄し、真空中で乾燥させた。生成物、O-カルバモイル-(D)-フェニルアラニノール塩酸塩の質量は110g(71.5%)であり、白色固体であった。

【0035】

実施例2. O-カルバモイル-(D)-3,4-ジクロロフェニルアラニノールの製造

機械攪拌機、温度計及び250mL滴下漏斗を備えた乾燥2L三つ口丸底フラスコ中に、ジクロロメタン75mLを添加し、その後、(D)-3,4-ジクロロフェニルアラニノール(4.00g、0.018mol)及びシアン酸ナトリウム(1.87g、0.027mol)を添加した。混合物を氷浴中で攪拌した。滴下漏斗にメタンスルホン(4.37g、0.045mol)を添加し、そして、5℃以下の温度を維持するために、それをゆっくりと反応混合物へ添加した。添加が完了した後、反応混合物は粘性が高くなった。氷浴を取り除き、(D)-3,4-ジクロロフェニルアラニノールがTLC分析によ

て検出されなくなるまで、反応混合物を撹拌した。水相のpHが9ないし10になるまで、重炭酸ナトリウムの飽和水溶液を、5℃以下の温度を維持するような速度において、反応混合物へ添加した。混合物を分液漏斗に移し、有機相を分離した。水相をジクロロメタン25 mLで2度抽出し、1つにまとめた有機相を、塩水(30 mL)で洗浄し、硫酸ナトリウム(5 g)上で一晚乾燥させた。濾過によって硫酸ナトリウムを除去した後、有機相を真空中で濃縮し、オイルとして、遊離塩基形態の所望の生成物、O-カルバモイル-(D)-3, 4-ジクロロフェニルアラニノールを4.38 g(91%)得た。

O-カルバモイル-(D)-3, 4-ジクロロフェニルアラニノール塩酸塩を以下のように製造した。粗反応生成物、O-カルバモイル-(D)-3, 4-ジクロロフェニルアラニノール(3.27 g)をテトラヒドロフラン10 mL中に溶解し、機械撹拌機を備えた三口丸底フラスコへ移した。混合物を氷浴中で冷却し、滴下漏斗にエチルエーテル中1N HCl溶液13.7 mL(0.0137M)を添加した。5℃以下の温度を維持するために、HCl溶液をゆっくりと遊離塩基溶液へ添加した。添加中、HCl形態の所望の生成物の沈殿が観察された。白色沈殿を、濾過によって収集した。生成物を、エチルエーテルで十分に洗浄し、真空中で乾燥させた。生成物、O-カルバモイル-(D)-3, 4-ジクロロフェニルアラニノール塩酸塩の質量は3.68 g(99%)であり、白色固体であった。

【0036】

実施例3. O-カルバモイル-(L)-3-オキシメチル-1, 2, 3, 4-テトラヒドロイソキノリンの製造

(L)-3-ヒドロキシメチル-1, 2, 3, 4-テトラヒドロイソキノリン(194 g)をジクロロメタン(1.5 L)中に懸濁させ、混合物を氷浴中で冷却した。5℃以下の反応温度を維持するために、混合物にシアン酸ナトリウム(100.4 g)を添加し、その後、メタンスルホン酸(277.4 mL)を滴下添加した。添加は約2時間かかった。反応が完了するまで、反応混合物を室温で撹拌した。脱イオン水1.5 Lを反応混合物に添加した。水相を単離し、氷浴中で冷却した。水相のpHを、20%水酸化ナトリウム水溶液を添加することによって、10ないし11に調整した。混合物を氷浴中で約1時間冷却し、生成物を濾過し、脱イオン水100 mLで2度洗浄した。生成物を真空下で乾燥させ、所望の生成物を221.6 g(90.4%)得た。

【0037】

実施例4. O-カルバモイル-(D)-フェニルアラニノールの大規模製造

D-フェニルアラニノール18.0 kg及びジクロロメタン477.4 kgを、窒素でガスシールした300ガロンのガラス内張反応器(プファウドラ、R-01型)中に添加した。溶液を4.8℃まで冷却した。その後、シアン酸ナトリウム(10.8 kg)を添加した。5℃以下の温度に維持する間に、この混合物にメタンスルホン酸(39.0 kg)を2時間42分かけてゆっくりと添加した。添加が完了した後、混合物を、2時間3分かけて22.4℃まで温め、室温で16時間50分撹拌した。該時間において、試料に、HPLCによる分析のための品質試験を受けさせたところ、D-フェニルアラニノールの量は1.0%未満であった。反応器の内容物を4.1℃まで冷却し、反応器の内容物を5℃未満で維持する間に、pHを1.4から10.5に上げるために、(水108 L中に水酸化ナトリウム12.0 kgを溶解することによって製造した)10%水酸化ナトリウム溶液100 Lを添加した。2つの層を分離した。上部の水層を、更に、ジクロロメタンで2度抽出し(それぞれ、133.4 kg)、3つの有機層を1つにまとめた。ジクロロメタンを含む生成物を(水108 L中に水酸化ナトリウム1.2 kgを溶解することによって製造した)1%水酸化ナトリウム溶液100 Lで洗浄し、HPLCで分析した。遅く溶離する不純物の量は、0.3%未満であった。有機層を、(水50 L中に塩化ナトリウム5 kgを溶解することによって製造した)10%塩水溶液50 Lで洗浄し、その後、水(50 L)で洗浄し、無水硫酸ナトリウム(19 kg)を添加することによって乾燥させ、混合物を18時間放置した。硫酸ナトリウムを、45 cmナッチ漏斗(Nutche funnel)(バクスター濾紙等級 615-20)上で真空濾過によって除去した。濾

過ケーキをジクロロメタン(25kg)で洗浄し、母液を、回転エバポレーター上で25-30℃において、約100Lまで濃縮した。材料をガラストレイへ移し、恒量に達するまで、真空オーブン中で400℃で乾燥させた。

【0038】

実施例5. O-カルバモイル-(L)-3-オキシメチル-1, 2, 3, 4-テトラヒドロイソキノリンの大規模製造

アセトニトリル(236kg)及びTHIC-アルコール(15kg)を、300ガロンの反応器に添加した。反応混合物を5℃未満まで冷却し、メタンスルホン酸(39.9kg)及びシアン酸ナトリウム(17.8kg)を添加した。反応混合物を約20℃まで温め、この温度において約2時間維持した。反応が完了したことを確認するため、反応混合物のHPLC分析を行った。反応混合物をトルエン(104kg)で希釈し、5℃未満まで1時間冷却した。固体を母液によって分離し、そのケーキをトルエン約30Lで洗浄した。湿潤ケーキを、水150L中濃HCl 10.1kgを含む100ガロンの反応器へ添加した。工程内のHPLC分析は、反応混合物が1%以上の不純物を含まないことを示した。反応混合物を母液し、特定の物質を除去した。その後、上部のトルエン層を除去し、処分した。水層を5℃未満まで冷却し、pHを、20%水酸化ナトリウム水溶液を注意深く添加することによって、10.5に調整した。混合物を1時間攪拌し、その後、固体を母液によって収集した。湿潤ケーキを、水(50L)でスラリー洗浄し、再母液した。生成物を40℃において真空中で乾燥させ、生成物を14.79kg得、HPLC分析によって、該生成物の純度は98.77%であることが分かった。

【0039】

実施例6. カルバミン酸2-(4-フルオロベンゾイル)ピペリジニ-1-イル)-1-フェニルエチルエステルの大規模製造

ジクロロメタン(210.1kg)及び2-(4-フルオロベンゾイル)ピペリジニ-1-イル)-1-フェニルエタノール(15.9kg)を100ガロンの反応器に添加した。混合物を100rpmにおいて攪拌し、5℃±5℃まで冷却した。温度を10℃以下に維持する間に、メタンスルホン酸(9.4kg)を20分かけて溶液に添加した。攪拌を5℃±5℃において1時間続けた。温度を10℃以下に維持する間に、シアン酸ナトリウムを5分間おきに5度添加した(合計6.4kg)。反応混合物を、この温度で30分間攪拌し、その後、25℃±5℃において一晩攪拌した。ある時点において、温度上昇に依存して、反応混合物の温度は、一時的に30.7℃まで上昇した。更なるシアン酸ナトリウム0.7kg及びメタンスルホン酸1.1kgを反応混合物へ添加し、25℃±5℃において一晩攪拌した。工程内のHPLC試験は、反応が完了していないこと(<5%出発材料)を示した。そのため、更なるシアン酸ナトリウム(1.3kg)及びメタンスルホン酸(2.6kg)を反応器へ添加し、引続き8時間攪拌した。この時点において、反応混合物は、出発材料を3.2%しか含まないことを示した。固体を母液によって収集した。母液ケーキをジクロロメタンで2度洗浄した(23.0kg、22.5kg)。湿潤ケーキを窒素雰囲気下で一晩維持した。粗生成物を、脱イオン水140Lを含む100ガロンの反応器へ再度添加した。混合物を、90rpmにおいて攪拌し、5℃±5℃まで冷却した。温度を10℃以下に維持する間に、50%水酸化ナトリウム溶液(7.6kg)を反応器へ添加した。混合物を、この温度において1時間攪拌し、その後、固体を母液によって分離した。母液ケーキを、脱イオン水49Lで洗浄した。固体をヘプタン52.5kg含む反応器へ再度添加した。混合物を15分間攪拌し、その後、固体を母液によって分離した。固体をヘプタン(2.3kg)で洗浄し、その後、25℃において真空中(27mm)で一晩乾燥させた。

乾燥物質(16.8kg)を、ジクロロメタン464.1kg含む反応器へ再度添加した。混合物を、1時間、還流(40℃)で加熱した。スラリーを、34℃±5℃まで冷却し、クノ母液器(Cuno Filter)を通してきれいな反応器中に入れた。母液器は、中温(31℃)ジクロロメタンで2度(それぞれ、22.3kg)すすいだ。1つにまとめた母液を、約240Lまで、体積を減少させた。スラリーを、3℃±5℃まで2時

間冷却し、その後、固体を濾過によって収集した。濾過ケーキをジクロロメタン 29.5 kg で洗浄した。固体を、回転コーン乾燥機 (rotary cone drier) を用いて、28℃において真空中で、46.5 時間乾燥させた。得られた生成物の質量は、12.2 kg であり、67.9% の収率を示した。

【0040】

上記した本発明の範囲から外れることなく、本発明の実施における多様な他の態様及び変更は、当業者には明白であり、容易になされ得る。従って、添付された特許請求範囲は、上記した詳細な説明に制限されず、むしろ、本発明に関する当業者によって同一なものとみなされ得る全ての特徴及び態様を含む本発明が有する特許可能な全ての特徴を含むと理解される。

INTERNATIONAL SEARCH REPORT		International application No. PCT/KR2004/002571
A. CLASSIFICATION OF SUBJECT MATTER IPC7 C07C 237/10 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) IPC7 C07C, A61K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Korean Patents and Applications for Inventions since 1975 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAS on line		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98/15526 A1 (YUKONG LTD.) 16 APR. 1998 See the whole document	1-31
A	WO 96/32375 A1 (YUKONG LTD.) 17 OCT. 1996 See the whole document	1-31
A	WO 96/07636 A1 (YUKONG LTD.) 15 JUN. 1996 See the whole document	1-31
A	DE 1961599 A (CHINOIN GYOGYSZER) 18 JUN. 1970 See the whole document -----End of documents-----	1-31
☐ 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 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" Inter 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 17 JANUARY 2005 (17.01.2005)		Date of mailing of the international search report 18 JANUARY 2005 (18.01.2005)
Name and mailing address of the ISA/KR  Korean Intellectual Property Office 920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140		Authorized officer KIM, YONG Telephone No. 82-42-481-8148 

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR2004/002571

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 98/15526 A1	16 APR. 1998	CA 2240060 AA EP 873308 B1 CN 1076016 B JP 2000-502364 T2	1998.04.16 2002.01.02 2001.12.12 2000.02.29
WO 96/32375 A1	17 OCT. 1996	KR 173863 B1 US 6140532 A EP 820438 B1 JP 11503447 T2	1999.04.01 2000.10.31 2001.06.20 1999.03.26
WO 96/07636 A1	15 JUN. 1996	KR 197892 B1 CA 2176012 C EP 728129 B1 JP 09503231 T2 US 5955499 A	1999.06.15 1999.01.05 1999.11.03 1997.03.31 1999.09.21
DE 1961599 A	18 JUN. 1970	FR 2025991 A5 ES 374449 A1 AT 297016 B	1970.09.10 1972.01.01 1972.03.10

Form PCT/ISA/210 (patent family annex) (January 2004)

(81)指定国 AP(BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), EA(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), EP(AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OA(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG), AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

(74)代理人 100109690

弁理士 小野塚 薫

(74)代理人 100131266

弁理士 ▲高▼ 昌宏

(74)代理人 100093414

弁理士 村越 祐輔

(72)発明者 チョイ, ヨンムン

アメリカ合衆国, 07058 ニュージャージー州, バインブルック, ウィンザー ドライブ
101

(72)発明者 キム, ミンウー

アメリカ合衆国, 07045 ニュージャージー州, モントビレ, ティファニー コート 2

Fターム(参考) 4C034 AH01

4C054 AA02 CC07 DD01 EE01 FF14

4H006 AA02 AC56 BB12 BE90 RA14 RB08



Espacenet

Bibliographic data: JP2008546778 (A) — 2008-12-25

TREATMENT OF SEXUAL DYSFUNCTION

Inventor(s):

Applicant(s):

Classification: - international: A61K31/27; A61P15/08; A61P15/10
 - cooperative: A61K31/165 (EP); A61P15/00 (EP); A61P15/08 (EP);
A61P15/10 (EP)

Application number: JP20080518221 20060613 Global Dossier

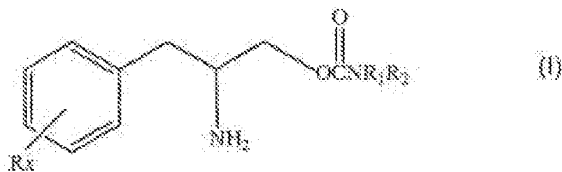
Priority number(s): US20050692809P 20050622 ; WO2006US23068 20060613

Also published as: AR054790 (A1) AT459393 (T) CA2612672 (A1) CA2612672 (C)
EP1893291 (A1) EP1893291 (B1) ES2344469 (T3)
JP5298334 (B2) KR101335942 (B1) KR20080028445 (A)
MY145066 (A) TW200727893 (A) TWI387452 (B)
US2009221553 (A1) US8552060 (B2) WO2007001841 (A1) less

Abstract not available for JP2008546778 (A)

Abstract of corresponding document: WO2007001841 (A1)

This invention is directed to a method of treating sexual dysfunction in a subject, comprising the step of administering a therapeutically effective amount of a compound of Formula (I): or a pharmaceutically acceptable salt or ester thereof wherein Rx is a member selected from the group consisting of hydrogen, lower alkyl of 1 to 8 carbon atoms, halogen selected from F, Cl, Br and I, alkoxy containing 1 to 3 carbon atoms, nitro, hydroxy, trifluoromethyl, and thioalkoxy containing 1 to 3 carbon atoms; x is an integer of 1 to 3, with the proviso that R may be the same or different when x is 2 or 3; R1 and R2 can be the same or different from each other and are independently selected from the group consisting of hydrogen, lower alkyl of 1 to 8 carbon atoms, aryl, arylalkyl, cycloalkyl of 3 to 7 carbon atoms; R1 and R2 can be joined to form a 5 to 7-membered heterocycle substituted with a member selected from the group consisting of hydrogen, alkyl, and aryl groups, wherein the cyclic compound can comprise 1 to 2 nitrogen atoms and 0 to 1 oxygen atom, wherein the nitrogen atoms are not directly connected with each other or with the oxygen atom.



(19) 日本国特許庁 (JP)

(12) 公表特許公報 (A)

(11) 特許出願公表番号

特表2008-546778

(P2008-546778A)

(43) 公表日 平成20年12月25日 (2008. 12. 25)

(51) Int. Cl.	F I	テーマコード (参考)
A 6 1 K 31/27 (2006. 01)	A 6 1 K 31/27	4 C 2 0 6
A 6 1 P 15/10 (2006. 01)	A 6 1 P 15/10	
A 6 1 P 15/08 (2006. 01)	A 6 1 P 15/08	

審査請求 未請求 予備審査請求 未請求 (全 38 頁)	
(21) 出願番号	特願2008-518221 (P2008-518221)
(86) (22) 出願日	平成18年6月13日 (2006. 6. 13)
(85) 翻訳文提出日	平成20年2月25日 (2008. 2. 25)
(86) 国際出願番号	PCT/US2006/023068
(87) 国際公開番号	W02007/001841
(87) 国際公開日	平成19年1月4日 (2007. 1. 4)
(31) 優先権主張番号	60/692, 809
(32) 優先日	平成17年6月22日 (2005. 6. 22)
(33) 優先権主張国	米国 (US)
(71) 出願人	303024622 エスケー ホルディングス カンパニー リミテッド 大韓民国、ソウル、ゾンロック、ソリン ドン、99
(71) 出願人	308035416 パルンボ ジョセフ アメリカ合衆国、19087 ペンシルベ ニア州、セント デービッツ、ブルークサ イド アベニュー 616
(71) 出願人	308035427 スポーン ジョナサン アメリカ合衆国、08540 ニュージャ ージー州、プリンストン、マーサー スト リート 103

最終頁に続く

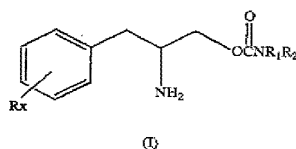
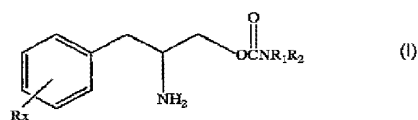
(54) 【発明の名称】 性機能障害を治療する方法

(57) 【要約】

【課題】 本発明は、被験者の性機能障害を治療する方法に関する。

【解決手段】

【化6】



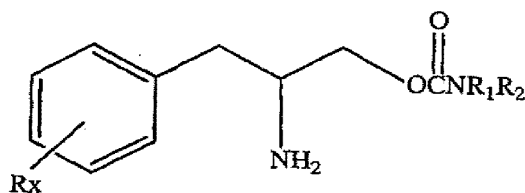
式 (1) で表される化合物又はその医薬品として許容できるその塩又はエステルの治療有効量を、投与する工程を含み、前記式中、 R_x は、水素原子、炭素原子数 1 ないし 8 の低級アルキル基、F、Cl、Br 及び I より選ばれたハロゲン原子、1 ないし 3 個の炭素原子を有するアルコキシ基、ニトロ基、ヒドロキシ基、トリフルオロメチル基、及び炭素原子 1 ないし 3 個の炭素原子を有するチオアルコキシ基からなる群から選択された一つを表し； x は、1 ないし 3 の整数を表し、ただし、 x が 2 又は 3 のとき、 R は同じでも異なっても良い； R_1

【特許請求の範囲】

【請求項1】

被験者の性機能障害を治療する方法であって、式(1)：

【化1】



(I)

(式中、

R は、水素原子、炭素原子数1ないし8の低級アルキル基、F、Cl、Br及びIより選ばれたハロゲン原子、1ないし3個の炭素原子を有するアルコキシ基、ニトロ基、ヒドロキシ基、トリフルオロメチル基、及び1ないし3個の炭素原子を有するチオアルコキシ基からなる群から選択された一つを表し；

x は、1ないし3の整数を表し、ただし、 x が2又は3のとき、 R は同じでも異なっても良い；

R_1 及び R_2 は互いに同じでも異なってもよく、それぞれ独立して、水素原子、炭素原子数1ないし8の低級アルキル基、アリール基、アリールアルキル基、炭素原子数3ないし7のシクロアルキル基からなる群より選ばれ；

R_1 及び R_2 は、一緒になって、水素原子、アルキル基及びアリール基からなる群から選択された一つで置換された5ないし7員の複素環を形成し得；

ここで、環状化合物は1ないし2個の窒素原子及び0ないし1個の酸素原子を含み得；

ここで、前記窒素原子は互いに又は前記酸素原子と直接結合しない。)

で表される化合物又はその医薬品として許容できる塩又はエステルの治療有効量を、治療を必要とする被験者に投与する工程を含む方法。

【請求項2】

R は水素原子を表し、 $x=1$ である、請求項1に記載の方法。

【請求項3】

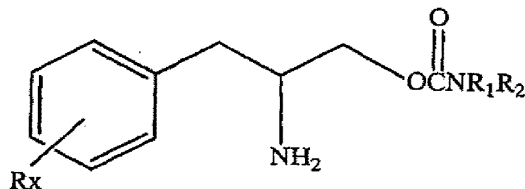
R 、 R_1 及び R_2 が全て水素原子から選択され、 $x=1$ である、請求項1に記載の方法。

【請求項4】

被験者の性機能障害を治療する方法であって、

実質的に他の光学異性体を含まない式1：

【化2】



(I)

(式中、

R は、水素原子、炭素原子数1ないし8の低級アルキル基、F、Cl、Br及びIより選ばれたハロゲン原子、1ないし3個の炭素原子を有するアルコキシ基、ニトロ基、ヒドロキシ基、トリフルオロメチル基、及び1ないし3個の炭素原子を有するチオアルコキシ基からなる群から選択された一つを表し；

xは、1ないし3の整数を表し、ただし、xが2又は3のとき、Rは同じでも異なっても良い；

R₁及びR₂は互いに同じでも異なってもよく、それぞれ独立して、水素原子、炭素原子数1ないし8の低級アルキル基、アリール基、アリールアルキル基、炭素原子数3ないし7のシクロアルキル基からなる群より選ばれ；

R₁及びR₂は、一緒になって、水素原子、アルキル基及びアリール基からなる群から選択される一つで置換された5ないし7員の複素環を形成し得；

ここで、環状化合物は1ないし2個の窒素原子及び0ないし1個の酸素原子を含み得；

ここで、前記窒素原子は互いに又は前記酸素原子と直接結合しない。）

で表される光学異性体又は式1で表される光学異性体の一つが優勢である光学異性体の混合物又はその医薬品として許容できる塩又はエステルの治療有効量を、前記治療を必要とする被験者に投与する工程を含む方法。

【請求項5】

R_xは水素原子を表す、請求項4に記載の方法。

【請求項6】

R_x、R₁及びR₂が全て水素原子から選択された、請求項4に記載の方法。

【請求項7】

式1からなる群より選択されるひとつの光学異性体が約90%以上の範囲で優勢である、請求項4に記載の方法。

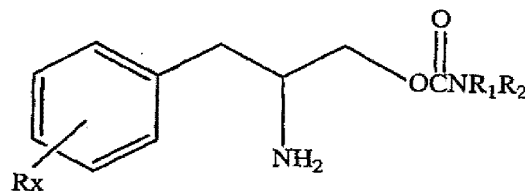
【請求項8】

式1からなる群より選択されたひとつの光学異性体が約98%以上の範囲で優勢である、請求項4に記載の方法。

【請求項9】

式1からなる群から選ばれた1つの光学異性体が式1a：

【化3】



(I)

(式中、

R_xは、水素原子、炭素原子数1ないし8の低級アルキル基、F、Cl、Br及びIより選ばれたハロゲン原子、1ないし3個の炭素原子を有するアルコキシ基、ニトロ基、ヒドロキシ基、トリフルオロメチル基、及び1ないし3個の炭素原子を有するチオアルコキシ基からなる群より選択された一つを表し；

xは、1ないし3の整数を表し、ただし、xが2又は3のとき、Rは同じでも異なっても良い；

R₁及びR₂は互いに同じでも異なってもよく、それぞれ独立して、水素原子、炭素原子数1ないし8の低級アルキル基、アリール基、アリールアルキル基、炭素原子数3ないし7のシクロアルキル基からなる群より選ばれ；

R₁及びR₂は、一緒になって、水素原子、アルキル基及びアリール基からなる群から選択された一つで置換された5ないし7員の複素環を形成し得；

ここで、環状化合物は1ないし2個の窒素原子及び0ないし1個の酸素原子を含み得；

ここで、前記窒素原子は互いに又は前記酸素原子と直接結合しない。）

からなる群より選ばれた光学異性体（注：上記の式1aの化学構造中、ベータ炭素に結合したアミノ基は、紙面の平面へ突き出ている。）又はその医薬品として許容できる塩又は

エステルである、請求項4に記載の方法。

【請求項10】

Rは水素原子を表し、 $x = 1$ である、請求項9に記載の方法。

【請求項11】

R、R₁及びR₂が全て水素原子から選択され、 $x = 1$ である、請求項9に記載の方法。

【請求項12】

式1 aからなる群より選択されたひとつの光学異性体が約90%以上の範囲まで優勢である、請求項9に記載の方法。

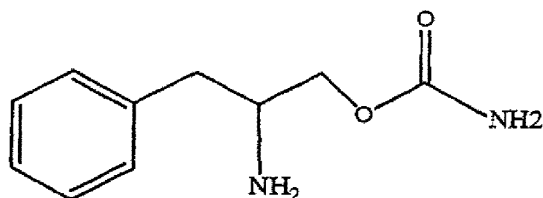
【請求項13】

式1 aからなる群より選択されたひとつの光学異性体が約98%以上の範囲まで優勢である、請求項4に記載の方法。

【請求項14】

実質的に他の光学異性体を実質的に含まない式1 aで表される化合物が、式1 bで表される光学異性体又は式1 bで表される光学異性体が優勢である光学異性体の混合物であり、これがO-カルバモイル-(D)-フェニルアラニノールであり；この化合物は(R)- (ベータ-アミノ-ベンゼンプロピル) カルバメート 一塩酸とも命名されるものであり、

【化4】



式 1b

(注：上記の式1 bで表される化学構造(試験化合物)中、ベータ炭素に結合したアミノ基は、紙面の平面へ突き出ている。)であり；これは絶対配置が(R)の右旋性(D)の光学異性体であるところの請求項4に記載の方法。

【請求項15】

式1 bで表される光学異性体が約90%以上の範囲で優勢である、請求項14に記載の方法。

【請求項16】

式1 bで表される光学異性体が約98%以上の範囲で優勢である、請求項14に記載の方法。

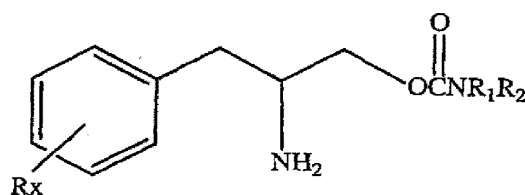
【請求項17】

光学異性体の治療有効量が約0.01mg/kg/投与から約300mg/kg/投与である、請求項14に記載の方法。

【請求項18】

被験者の性機能障害を治療する方法であって、
性機能障害の原因となり得る治療薬、及び実質的に他の光学異性体を含まない式1：

【化5】



(I)

(式中、

Rは、水素原子、炭素原子数1ないし8の低級アルキル基、F、Cl、Br及びIより選ばれたハロゲン原子、1ないし3個の炭素原子を有するアルコキシ基、ニトロ基、ヒドロキシ基、トリフルオロメチル基、及び1ないし3個の炭素原子を有するチオアルコキシ基からなる群から選択された一つを表し；

xは、1ないし3の整数を表し、ただし、xが2又は3のとき、Rは同じでも異なっても良い；

R₁及びR₂は互いに同じでも異なってもよく、それぞれ独立して、水素原子、炭素原子数1ないし8の低級アルキル基、アリール基、アリールアルキル基、炭素原子数3ないし7のシクロアルキル基からなる群より選ばれ；

R₁及びR₂は、一緒になって、水素原子、アルキル基及びアリール基からなる群から選択された一つで置換された5ないし7員の複素環を形成し得；

ここで、環状化合物は1ないし2の窒素原子及び0ないし1の酸素原子を含み得；

ここで、前記窒素原子は互いに又は前記酸素原子と直接結合しない。))

で表される光学異性体又は式1で表される光学異性体のひとつが優勢である光学異性体の混合物又はその医薬品として許容できる塩又はエステルの治療有効量を、前記治療を必要とする被験者に同時投与する工程を含む方法。

【請求項19】

Rは水素原子を表す、請求項18に記載の方法。

【請求項20】

Rx、R₁及びR₂が全て水素原子から選択される、請求項18に記載の方法。

【請求項21】

式1からなる群より選択されたひとつの光学異性体が約90%以上の範囲で優勢である、請求項18に記載の方法。

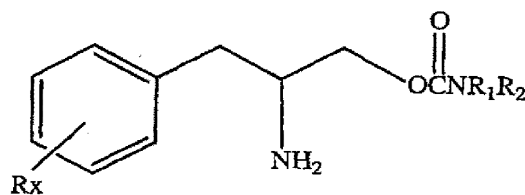
【請求項22】

式1からなる群より選択されるひとつの光学異性体が約98%以上の範囲で優勢である、請求項18に記載の方法。

【請求項23】

式1で表される群から選ばれた1つの光学異性体が式1：

【化6】



(I)

(式中、

Rは、水素原子、炭素原子数1ないし8の低級アルキル基、F、Cl、Br及びIより

選ばれたハロゲン原子、1ないし3個の炭素原子を有するアルコキシ基、ニトロ基、ヒドロキシ基、トリフルオロメチル基、及び1ないし3個の炭素原子を有するチオアルコキシ基からなる群から選択された一つを表し；

xは、1ないし3の整数を表し、ただし、xが2又は3のとき、Rは同じでも異なっても良い；

R₁及びR₂は互いに同じでも異なってもよく、それぞれ独立して、水素原子、炭素原子数1ないし8の低級アルキル基、アリール基、アリールアルキル基、炭素原子数3ないし7のシクロアルキル基からなる群より選ばれ；

R₁及びR₂は、一緒になって、水素原子、アルキル基及びアリール基からなる群から選択された一つで置換された5ないし7員の複素環を形成し得；

ここで、環状化合物は1ないし2個の窒素原子及び0ないし1個の酸素原子を含み得；

ここで、前記窒素原子は互いに又は前記酸素原子と直接結合しない。）

からなる群より選ばれた光学異性体又はその医薬品として適用可能な塩又はエステルである、請求項18に記載の方法。

【請求項24】

Rは水素原子を表し、x=1である、請求項23に記載の方法。

【請求項25】

R、R₁及びR₂が全て水素原子から選択され、x=1である、請求項23に記載の方法。

。

【請求項26】

式1からなる群より選択されたひとつの光学異性体が約90%以上の範囲で優勢である、請求項23に記載の方法。

【請求項27】

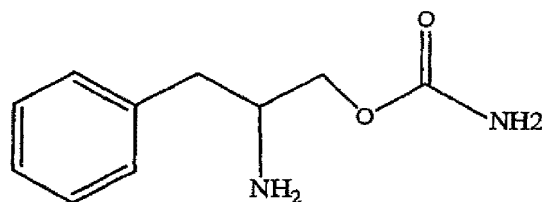
式1からなる群より選択されたひとつの光学異性体が約98%以上の範囲で優勢である、請求項23に記載の方法。

【請求項28】

実質的に他の光学異性体を含まない式1で表される化合物が、

式1bで表される光学異性体又は式1bで表される光学異性体が優勢である光学異性体の混合物であり、これがO-カルバモイル-(D)-フェニルアラニノールであり；この化合物は(R)-(ベータ-アミノベンゼンプロピル)カルバメート一塩酸とも命名されるものであり、

【化7】



式 1b

(注：上記の式1bの化学構造(試験化合物)中、ベータ炭素に結合するアミノ基は、紙面の平面へ突き出ている。)であり；これは絶対配置が(R)の右旋性(D)の光学異性体であるところの請求項18に記載の方法。

【請求項29】

式1bで表される光学異性体が約90%以上の範囲で優勢である、請求項28に記載の方法。

【請求項30】

式1bで表される光学異性体が約98%以上の範囲で優勢である、請求項28に記載の方法。

【請求項31】

前記その他の治療薬が、選択的セロトニン再取り込み阻害剤 (SSRI's) ; 選択的セロトニン及びノルエピネフリン再取り込み阻害剤 (SNRI's) ; 慣用の三環系抗うつ薬 (TCAs) ; モノアミンオキシダーゼ阻害剤 (MAO-阻害剤)、モノアミンオキシダーゼの可逆的阻害剤 (RIMAs)、第三級アミン三環系及び第二級アミン三環系抗うつ薬、からなる群より選択される、請求項28に記載の方法。

【請求項32】

前記その他の治療薬が、フルオキセチン、デュロキセチン、ベンラファクシン、ミルナシプラン、シタロプラム、フルボキサミン、パロキセチン、セルトラリン、5-MCA-NAT、炭酸リチウム (LiCO₃)、イソカルボキサジド、フェネルジン、トラニルシプロミン、セレジリン、モクロベミド、カップーオピオイドレセプターアンタゴニスト ; 選択的ニューロキニンアンタゴニスト、コルチコトロピン放出因子 (CRF) アンタゴニスト、タキキニンアンタゴニスト、 α -アドレノレセプターアンタゴニスト、アミトリプチリン、クロミプラミン、ドクセピン、イミプラミン、ベンラファクシン、トリミプラミン、アモキサピン、デシプラミン、マプロチリン、ノルトリプチリン及びプロトリプチリン、及びその医薬品として許容できる塩類からなる群より選択される、請求項28に記載の方法。

【請求項33】

光学異性体の治療有効量が約0.01mg/kg/投与から約300mg/kg/投与である、請求項28に記載の方法。

【発明の詳細な説明】

【技術分野】

【0001】

本発明は、一般的に薬理学、泌尿器学、精神医学の分野に関し、また性機能障害を治療する方法に関する。より詳細には、本発明は、特定のカルバメート化合物を、ヒトの女性又は男性の性機能障害の治療用に単独又は他の医薬と併用して使用する為の、使用方法を提供する。

【背景技術】

【0002】

Masters及びJohnsonは性機能障害を「性的興味及び/又は反応の健常又は通常のパターンの持続性の機能的障害」として定義した (Masters等、Human Sexual Response、Boston, Mass.: Little, Brown and Co. 1996年)。この問題は、National Health and Societal Life Surveyの結果が1999年に発行された時に国民的注目に及んだ。3000人以上の18ないし59歳の米国男性及び女性へのインタビューは、31%の男性及び43%の女性 (約4千万人) が何らかの程度の性機能障害を経験したという事を明らかにした。この問題の範囲は、“有意な公衆衛生の関心事としての認識は当然である”といわれる程のものであった。Laumann等、“Sexual Dysfunction in the United States: prevalence and predictor” JAMA、281巻、537頁 (1999年) 参照。性機能障害は、めったに身体的健康を脅かす事はないが、重篤な精神的障害となり、うつ病、不安、及び消耗性の (機能的) 欠陥をもたらし得る。

【0003】

性機能障害 (SD) は、男性及び女性に影響し得る重大な臨床上的問題である。SDの原因は、器質的なものと並びに精神的なものの両方であり得る。SDの器質的な局面は、典型的には、高血圧又は糖尿病と関連するもののような、根底にある血管系疾患により、処方医薬により及び/又はうつ病の様な精神疾患によりもたらされ得る。精神学的な因子としては、不安、性能不安及び対人的葛藤等が挙げられる。SDは、性的能力を損ない、自尊心を損ない、人間関係を崩壊させ、その結果個人の苦痛を引き起こす。臨床的には、SD障害は女性性機能障害 (FSD) 疾患及び男性性機能障害 (MSD) 疾患に分けられる。

(Melman等、1999年、Urlogy、161巻、5頁-11頁)。FSDは、女性の性表現行為に於ける満足を見出す事への困難性又は不可能性として最も良く定義される。

【0004】

男性性機能障害は、一般的には、男性勃起障害(MED)及び／又は早漏(premature ejaculation又はrapid ejaculation)(PED)などの様な射精障害、無オルガスム症(オルガスムに達する事ができない)又は男性オルガスム障害として知られる男性勃起障害(MED)、又は性的欲求低下障害(性に於ける興味の欠如)(HSDD)などの様な性欲障害と関連し、身体的疾患、うつ病、ホルモン異常又はリビドー又は行動に影響する投薬を含む種々の原因より生じ得る。

【0005】

最近の研究では、少なくとも43%の女性は何らかの形の性機能障害を持つ事が示唆された(上記参照、Lauman等、JAMA、281巻、537頁、1999年)。これらは4つの主たる領域に分類され、即ち1)性的欲求障害、即ち、性的欲求低下又は性的嫌悪障害；2)性的興奮障害；3)オルガスム障害；及び4)性交疼痛症及び膣瘻を含む性疼痛障害である。

【0006】

女性の性機能障害(FSD)の主要な分類は、FSDと診断される女性の75%まで影響している女性性的興奮障害(FSAD)である。

【0007】

女性性機能障害(FSD)の分類は、女性の健常な性的反応；欲求、興奮及びオルガスムの様相と比較する事により最も良く定義される(SR Leiblum(1998年)、Definition and Classification of Female Sexual Disorders(女性性障害の定義及び分類)Int. J. Impotence Res. 10巻、S 104頁-S 106頁参照)。性的欲求又はリビドーは、性表現行為の動因である。その兆候としては性的想像及び空想を含む。興奮は、性器の腫脹及び膣の潤滑増加、膣の伸長及び増大した性器の興奮／感受性及び主観的興奮反応がその重要な要素である、性的刺激への血管反応を含む。オルガスムは、興奮の間頂点に達した性的緊張の放出である。故に、女性性障害(FSD)は、女性がこれらの様相、通常は欲求、興奮又はオルガスムに於けるいずれかの1つ以上の欠如、不十分な又は不満足な応答を持つ場合に起こる。

【0008】

米国精神医学会は、女性の性機能障害(FSD)を4つのクラスに分類しており：FSAD、性的欲求低下障害(HSDD)、女性オルガスム障害(FOD)、性的疼痛障害(即ち、性交疼痛症及び膣瘻)である[American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders(米国精神医学会の精神障害診断及び統計マニュアル)第4版(DSM-IV)参照]。

DSM-IVは、上記4つのクラスを以下の通りに定義する。

【0009】

HSDD——持続性又は再発性のある、著しい苦痛又は人間関係の困難を引き起こす、性活動への空想及び欲望の欠乏(又は欠如)。この欠乏又は欠如の判定は臨床医によって、年齢及び個人の生活の内容等の機能に影響する因子を考慮に入れて行われる。

【0010】

FSAD——持続性又は再発性の、適正な性的興奮の潤滑-腫脹反応である性活動の達成又は完了までの維持の不能。

【0011】

FOD——持続性又は再発性の、健常の性的興奮様相に次ぐオルガスムの遅延又は欠如。女性は、オルガスムの誘因となる刺激の種類又は強度に於いて広く変動を示す。FODの診断は、その女性のオルガスム能力が、年齢、性的経験及び受けた性的刺激の適正さに

対して妥当であったであろうものよりも低いという、臨床医による判定に基づくべきである。

【0012】

性交疼痛症及び膣痙等性疼痛性障害

性交疼痛症は、性交に関連する再発性又は持続性の性器痛である。膣痙は、性交を妨げる持続性又は再発性の膣外端3分の1の筋肉組織の無意識の痙攣である。

【0013】

米国泌尿器疾患財団もまた、同様の4つのクラスを用いた定義を開発した(The Journal of Urology, 2000年、163巻888頁-893頁参照)。この定義はDSM-IVのものと大変近似している：

1) HSDDは、個人の苦痛を引き起こす、持続性又は再発性の、性的空想／想像、及び／又は欲望又は性活動の受容力の欠乏（又は欠如）である。

HSDDは、女性が全く又はほとんど性的である欲望を持たない場合及び、全く又はほとんど性的想像又は空想を持たない場合、存在する。FSDのこのタイプは、低テストステロン量に起因し得、自然閉経か又は外科的閉経が原因である。閉経前の女性（即ち、閉経前及び子宮摘出を受けていない女性）並びに閉経後の女性の両方に於けるその他の原因としては、例えば、疾患、投薬、倦怠感、うつ病、及び／又は不安が挙げられる。関係障害又は宗教的な要因などの精神的影響の可能性（意識的又は潜在意識的）を持つ要因は、女性に於けるHSDDの存在／発生と関係し得る。

【0014】

用語「重篤なHSDD」は、女性被験者へのある程度の個人的苦痛を引き起こすHSDDのレベルを意味する。好ましくは、重篤なHSDDは、ある程度の苦痛を引き起こし、また例えば、半構造的アンケートを用いた臨床医による評価を通じて測定可能な、HSDDのレベルを意味する。

【0015】

2) FSADは、主客観な興奮又は性器の（潤滑／隆起）またはその他の身体反応の欠乏として表し得る、個人の苦痛を引き起こす、十分な性的興奮に達する又は該興奮を維持する事の持続性又は再発性の不能である。

【0016】

FSADは、閉経前、周辺、後の女性に作用する非常に一般的な性障害である。これは、うつ病、循環器疾患、糖尿病及びUG障害等の随伴性疾患と関連付けられる。FSADは、性的興奮に対する不十分な性器の反応によって特徴付けられる。性器は、通常の性的興奮を特徴付ける拡張を起こさない。膣壁はあまり湿潤されないので、性交は苦痛である。オルガスムは阻止され得る。FSADは、糖尿病及び動脈硬化の様な血管成分を伴う疾病によるものと同様に、閉経又は産後及び授乳期に於けるエストロゲン減少により引き起こされ得る。その他の原因は、利尿薬、抗ヒスタミン剤、抗うつ薬、例えば、選択的セロトニン再取り込み阻害剤又は降圧剤の治療に起因する。

【0017】

3) FODは、個人の苦痛を引き起こす、十分な性的刺激及び興奮に次ぐオルガスムの到達の、持続性又は再発性の困難、遅延または欠如である。

【0018】

4) 性的疼痛性障害：性交疼痛症は、性交に関連する再発性又は持続性の性器痛である。膣痙は、個人の苦痛に起因する、膣侵入を妨げる持続性又は再発性の膣外端3分の1の筋肉組織の無意識の痙攣である。性交疼痛症及び膣痙は、侵入及び性活動により生じる疼痛により特徴付けられ、湿潤を減少させる医薬、子宮内膜症、骨盤感染症、炎症性大腸炎又は尿路系障害により引き起こされ得る。

【0019】

【非特許文献1】Masters等、Human Sexual Response、Boston, Mass.: Little, Brown and Co. 1996年。

【非特許文献2】Laumann等、“Sexual Dysfunction in

the United States: prevalence and predictor" JAMA、281巻、537頁(1999年)。

【非特許文献3】Melman等、Urology、161巻、5頁-11頁、1999年。

【非特許文献4】S. R. Leiblum、Definition and Classification of Female Sexual Disorders (女性性障害の定義及び分類) 10巻S104頁-S106頁、1998年。

【非特許文献5】American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (米国精神医学会の精神障害診断及び統計マニュアル) 第4版 (DSM-IV)。

【非特許文献6】The Journal of Urology、163巻888頁-893頁、2000年。

【発明の開示】

【発明が解決しようとする課題】

【0020】

男性及び女性の両方に於ける性機能障害の原因としては、例えば、高血圧の様な血管系/内皮系疾病、神経系疾患、エストロゲン及び/又はテストステロン量の減少の様なホルモン機能障害等が挙げられ得る。男性及び女性の両方に於ける性機能障害はまた、抗うつ薬、降圧剤及びその他多くの種類の一般的に用いられる医薬によって引き起こされ得、又は悪化し得る。全ての年齢及び両性に於けるこれらの医薬の大量使用を考慮して、医薬誘発性機能障害を治療する方法を開発する事は特に重要である。

【0021】

明らかにFSDは特に、該当する男性の障害、陰茎勃起障害(MED)よりもより活発な臨床上的問題を伴う複雑な障害である。ゆえに、FSDの治療に於いて、今日までわずかしき成功がなされおらず、またシルデナフィルの様に、MED治療に於いて成功した治療の使用はFSDの改善に於いて限られた効果しか認められていない事は、驚くべき事ではない。女性用の治療を講じる場合、男性に於いて行われる試みに対して、薬剤の異なる活性の範囲、機構、用量計画及び薬剤の作用の持続時間が必要とされるということであり得る。しかしながら、MEDを部分的に除外するとして、男性及び女性の両方に於ける全ての種類の性機能障害の為の治療は、不十分であり、ゆえに、この様な治療の為の大きな臨床上的必要性がある。

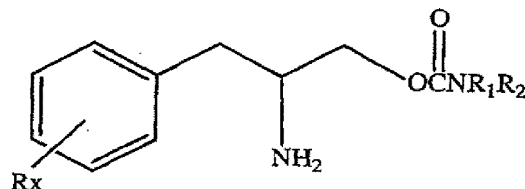
【課題を解決するための手段】

【0022】

発明の概要

本発明は、被験者の性機能障害を治療する方法であって、式(1)：

【化8】



(I)

(式中、

Rxは、水素原子、炭素原子数1ないし8の低級アルキル基、F、Cl、Br及びIより選ばれたハロゲン原子、1ないし3個の炭素原子を有するアルコキシ基、ニトロ基、ヒドロキシ基、トリフルオロメチル基、及び1ないし3個の炭素原子を有するチオアルコキシ基からなる群から選択された一つを表し；

x は、1ないし3の整数を表し、ただし、 x が2又は3のとき、 R は同じでも異なっても良い；

R_1 及び R_2 は互いに同じでも異なってもよく、それぞれ独立して、水素原子、炭素原子数1ないし8の低級アルキル基、アリール基、アリールアルキル基、炭素原子数3ないし7のシクロアルキル基からなる群より選ばれ；

R_1 及び R_2 は、一緒になって、水素原子、アルキル基及びアリール基からなる群から選択された一つで置換された5ないし7員の複素環を形成し得；

ここで、環状化合物は1ないし2個の窒素原子及び0ないし1個の酸素原子を含み得；

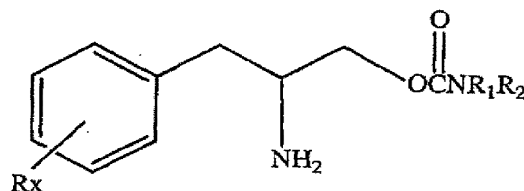
ここで、前記窒素原子は互いに又は前記酸素原子と直接結合しない。）

で表される化合物又はその医薬品として許容できる塩又はエステルの治療有効量を、前記治療を必要とする被験者に投与する工程を含む方法に関する。

【0023】

本発明の実施態様は、被験者の性機能障害を治療する方法であって、実質的に他の光学異性体を含まない式1：

【化9】



(I)

(式中、

R_x は、水素原子、炭素原子数1ないし8の低級アルキル基、F、Cl、Br及びIより選ばれるハロゲン原子、1ないし3個の炭素原子を有するアルコキシ基、ニトロ基、ヒドロキシ基、トリフルオロメチル基、及び1ないし3個の炭素原子を有するチオアルコキシ基からなる群から選択された一つを表し；

x は、1ないし3の整数を表し、ただし、 x が2又は3のとき、 R は同じでも異なっても良い；

R_1 及び R_2 は互いに同じでも異なってもよく、それぞれ独立して、水素原子、炭素原子数1ないし8の低級アルキル基、アリール基、アリールアルキル基、炭素原子数3ないし7のシクロアルキル基からなる群より選ばれ；

R_1 及び R_2 は、一緒になって、水素原子、アルキル基及びアリール基からなる群から選択された一つで置換された5ないし7員の複素環を形成し得；

ここで、環状化合物は1ないし2個の窒素原子及び0ないし1個の酸素原子を含み得；

ここで、前記窒素原子は互いに又は前記酸素原子と直接結合しない。）

の光学異性体又は式1の光学異性体の一つが優勢である光学異性体の混合物又はその医薬品として許容できる塩又はエステルの治療有効量を、前記治療を必要とする被験者に投与する工程を含む、被験者の性機能障害を治療する方法を含む。

【0024】

好ましくは、ここで、 R_x 、 R_1 及び R_2 が全て水素原子から選択される。

【0025】

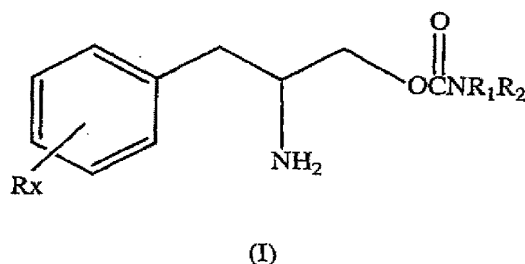
好ましくは、ここで、式1からなる群より選択されたひとつの光学異性体が約90%以上の範囲まで優勢である。

【0026】

より好ましくは、ここで、式1からなる群より選択されたひとつの光学異性体が約98%以上の範囲まで優勢である。

【0027】

本発明の実施態様は、式 1 からなる群より選択された光学異性体又は、その医薬品として許容できる塩又はエステルを性機能障害の治療用医薬の製造に用いる方法を含み、
【化10】



(式中、

R_x は、水素原子、炭素原子数 1 ないし 8 の低級アルキル基、F、Cl、Br 及び I より選ばれたハロゲン原子、1 ないし 3 個の炭素原子を有するアルコキシ基、ニトロ基、ヒドロキシ基、トリフルオロメチル基、及び 1 ないし 3 個の炭素原子を有するチオアルコキシ基からなる群から選択された一つを表し；

x は、1 ないし 3 の整数を表し、ただし、 x が 2 又は 3 のとき、 R は同じでも異なっても良い；

R_1 及び R_2 は互いに同じでも異なってもよく、それぞれ独立して、水素原子、炭素原子数 1 ないし 8 の低級アルキル基、アリール基、アリールアルキル基、炭素原子数 3 ないし 7 のシクロアルキル基からなる群より選ばれ；

R_1 及び R_2 は、一緒になって、水素原子、アルキル基及びアリール基からなる群から選択された一つで置換された 5 ないし 7 員の複素環を形成し得；

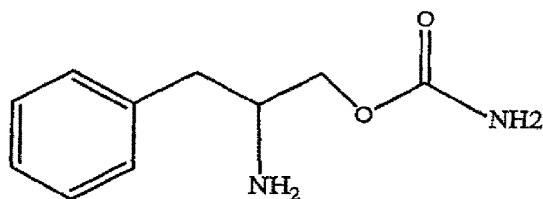
ここで、環状化合物は 1 ないし 2 個の窒素原子及び 0 ないし 1 個の酸素原子を含み得；

ここで、前記窒素原子は互いに又は前記酸素原子と直接結合しない。

【0028】

本発明の実施態様は、式 1 b の光学異性体又は式 1 b の光学異性体が優勢である光学異性体の混合物である、実質的に他の光学異性体を含まない、式 1 の化合物を用いる方法を含む。(注：下記の式 1 b の化学構造中、ベータ炭素に結合するアミノ基は、紙面の平面へ突き出ている。)これは、絶対配置が (R) の右旋性 (D) の光学異性体である。

【化11】



ここで、式 1 b の光学異性体が約 90 % 以上の範囲まで優勢である。

【0029】

より好ましくは、式 1 b の光学異性体が約 98 % 以上の範囲まで優勢である。

【0030】

本発明の実施態様はまた、本発明のカルバメート化合物を、それ自身が性機能障害の原因となり得るその他の医薬とともに、この望ましくない副作用を防止し、逆転させ又は最小にする為に、同時投与する方法を含む。

【0031】

その様な他の医薬には、例えば、慣用の抗うつ薬及び、例えば、選択的セロトニン再取

り込み阻害剤 (SSRI's) ; 選択的セロトニン及びノルエピネフリン再取り込み阻害剤 (SNRI's) ; 慣用の三環系抗うつ薬 (TCAs) ; モノアミンオキシダーゼ阻害剤 (MAO-阻害剤) 、モノアミンオキシダーゼの可逆的阻害剤 (RIMAs) 、第三級アミン三環系及び第二級アミン三環系抗うつ薬、抗精神病薬、抗痙攣剤、炭酸リチウム、が挙げられるがこれに限定されないその他の精神薬が挙げられるがこれに限定されず、フルオキセチン、デュロキセチン、ベンラファクシン、ミルナシプラン、シタロプラム、フルボキサミン、パロキセチン、セルトラリン、5-MCA-NAT、炭酸リチウム (LiCO_3) 、イソカルボキサジド、フェネルジン、トラニルシプロミン、セレジリン、モクロベミド、アミトリプチリン、クロミプラミン、ドクセピン、イミプラミン、トリミプラミン、アモキサピン、デシプラミン、マプロチリン、ノルトリプチリン及びプロトリプチリン、銅-オピオイドレセプターアンタゴニスト ; 選択的ニューロキニンアンタゴニスト、コルチコトロピン放出因子 (CRF) アンタゴニスト、タキキニンアンタゴニスト、 α -アドレノレセプターアンタゴニスト、及び、降圧剤、カルシウムチャネルブロッカー、ACE阻害剤、スタチン等の様な心臓病薬等のその他の種類の医薬であり、及びその医薬品として許容できる塩類を含むがこれらに限定されず、またここで、光学異性体の治療有効量は約 0.01 mg/kg 投与から約 300 mg/kg 投与である。

【0032】

図面の簡単な説明

図1は、雌ラットの前湾反応に於ける様々な用量の試験化合物の効果を、媒体及び活性対照のキネロランと比較した図である。

【発明を実施するための最良の形態】

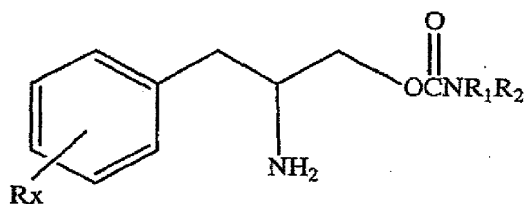
【0033】

本発明は、性機能障害を治療する方法を対象とする。本方法は、フェニルアルキルアミノカルバメート類からなる群より選択された化合物の治療有効量を、それを必要とする被験者に投与することを含む。

【0034】

本発明は、式1：

【化12】



式 1

(式中、

R_x は、水素原子、炭素原子数1ないし8の低級アルキル基、F、Cl、Br及びIより選ばれたハロゲン原子、1ないし3個の炭素原子を有するアルコキシ基、ニトロ基、ヒドロキシ基、トリフルオロメチル基、及び1ないし3個の炭素原子を有するチオアルコキシ基からなる群より選択された一つを表し；

x は、1ないし3の整数を表し、ただし、 x が2又は3のとき、 R は同じでも異なっても良い；

R_1 及び R_2 は互いに同じでも異なってもよく、それぞれ独立して、水素原子、炭素原子数1ないし8の低級アルキル基、アリール基、アリールアルキル基、炭素原子数3ないし7のシクロアルキル基からなる群より選ばれ；

R_1 及び R_2 は、一緒になって、水素原子、アルキル基及びアリール基からなる群から選択された一つで置換された5ないし7員環の複素環を形成してもよく；

ここで、環状化合物は1ないし2の窒素原子及び0ないし1の酸素原子を含んでいてもよく；

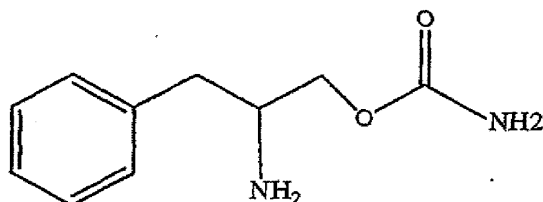
ここで、前記窒素原子は互いに又は前記酸素原子と直接結合しない。)

で表される化合物又はその光学異性体、鏡像異性体、ラセミ体又はそれらの混合物、並びにその水和物、溶媒和物及び医薬品として許容できる塩類、エステル類、及びアミド類を特徴とする。

【0035】

本発明の方法はまた、式1（式中、R_x、R₁及びR₂が好ましくは水素原子から選択される。）からなる群より選択される化合物の使用を含み、これは以下の式1a：

【化13】



式 1a

である。

【0036】

本発明の方法は、好ましくは式1から成る群より選択されるD（又は、右旋性の）光学異性体（又は、絶対配置がR）又はその光学異性体の混合物であり、

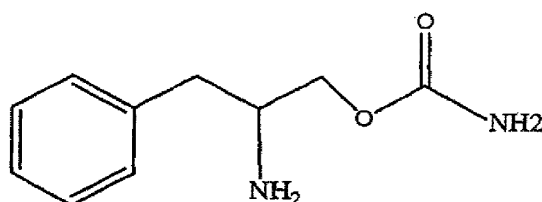
ここで、

式1aからなる群より選択されるD光学異性体が優勢であり、及び、

R_x、R₁及びR₂が好ましくは水素原子から選択され、

これは、O-カルバモイル-(D)-フェニルアラニノールであり、この化合物はまた、(R)-(ベータ-アミノ-ベンゼンプロピル)カルバメート一塩酸と命名され得る下記式1bで表されるものであり；また、本明細書では「試験化合物」とも呼ぶ。

【化14】



式 1b

【0037】

（注：上記の式1b（試験化合物）の化学構造中、ベータ炭素に結合するアミノ基は、紙面の平面へ突き出ている。これは、絶対配置が（R）の右旋性（D）の光学異性体である。

【0038】

光学異性体の混合物に関して、式1からなる群より選択される1つの光学異性体が優勢であり、好ましくは式1からなる群より選択される光学異性体が約90%以上の範囲まで優勢を占める。

【0039】

より好ましくは、式1から成る群から選択される光学異性体は、約98%以上の範囲まで優勢を占める。

【0040】

式1の化合物は、当該技術分野の通常の知識を有する者に知られている方法により合成され得る。式（I）の化合物を合成する幾つかの反応スキームは、発行された米国特許第5705640号公報、米国特許第5756817号公報、米国特許第5955499号

公報及び米国特許第6140532号公報に記載されている。

【0041】

上記反応スキームの詳細、並びに具体的化合物の製造に於ける代表例は、発行された米国特許第5705640号公報、米国特許第5756817号公報、米国特許第5955499号公報及び米国特許第6140532号公報に記載され、これらの内容は全て参照としてここに取り込まれている。

【0042】

式(I)の化合物の塩類及びエステル類は、化合物を適切な溶媒中で酸(HX)によって処理する事により、又は当該技術分野の通常の知識を有する者に知られている方法により製造する事ができる。

【0043】

式1から、本発明の化合物の幾つかは少なくとも1つ又はおそらくそれ以上の不斉炭素原子を有する事が明らかである。本発明は、その範囲に、前記化合物の立体化学的に純粋な異性体の形態並びにそのラセミ体を、含む事を意図する。前記化合物の立体化学的に純粋な異性体の形態は当該技術分野で知られた原理の応用により得られ得る。鏡像異性体類は、分別結晶化及びクロマトグラフ技術などの物理的な分離方法により分離され得、光学異性体類は、光学活性な酸、又は塩基を用いたジアステレオマー塩の選択的結晶化により、またはキラルクロトグラフィーにより、互いに分離され得る。純粋な立体異性体類は、また適切な立体化学的に純粋な出発物質から合成的に製造し得、又は立体選択的な反応により合成的に製造し得る。

【0044】

本発明の化合物の製造のいずれの工程の間においても、関係する分子のあらゆる感受性のある又は反応性のある基を保護する事が必要及び／又は望まれ得る。これは、“Protective Groups in Organic Chemistry”(有機化学に置ける保護基)、J. F. W. McOmie著、Plenum Press, 1973年；及びT. W. Greene及びP. G. M. Wuts, "Protective Groups in Organic Synthesis"(有機合成に於ける保護基)第3版John Wiley & Sons, 1999年等に記載のもののような慣用の保護基を用いて達成し得る。保護基は、当該技術分野に於いて知られる方法を用いて簡便に次のステージで除去され得る。

【0045】

本発明は、上記で論じた式1のフェニルアルキルアミノ カルバメート化合物が新規であり独特の薬理学的特性を有しているとの発見に基づくものである。これらの化合物は、雌雄両方において性機能障害の治療能力を持つと、動物モデルにおいてもまたヒトの臨床試験で報告された副作用にみられた信号によっても示されている。

【0046】

この作用の正確な機構は完全には解明されていないが、これらの化合物は性機能障害のためのその他の既知の治療薬のほとんどと同様の機構により作用するものではない事が知られている。この理由により、式1の化合物は、単独又は補助的に性機能障害の治療に、又は副作用として性機能障害を生じる事が知られているその他の薬剤とともに併用してこの副作用を最小又は解消する為に、使用する事に特に適する。

【0047】

ゆえに、これらの化合物は、各薬剤のより少ない用量が使用し得るので、増強された効果および減少した副作用をもたらす為に単独で又はその他の有用な医薬と併用して安全に使用され得る。

【0048】

ひとつの局面として、本発明は性機能障害に苦しむ女性又は男性を治療する方法に関し；該方法は、1つ以上の本発明のカルバメート化合物又は医薬品として許容できる塩又はエステルの治療上有効量、及び医薬品として許容できる担体、希釈剤又は賦形剤を被験者に送達する事を含む。

【0049】

さらなる局面としては、本発明は、同時投与方法により、その他の医薬により生じた性機能障害を、解消し、低下させ又は対抗する方法に関する。したがって、本発明の実施態様はまた、本発明のカルバメート化合物が、それ自身が性機能障害の原因となり得るその他の医薬と、この望ましくない副作用を防止し、逆転させ又は最小にする為に、同時に又は連続して投与される方法をも含む。

【0050】

従って、本発明の方法に於いて、これらのカルバメート化合物は、性機能障害副作用を減少との組み合わせを形成する様に、抗うつ薬又はその他の薬剤を含む他の薬剤の1つ以上の療法に於いて加えるか組み合わされるべきである。これは、患者が、必要な医薬のより高い用量に耐える余地を与え得、こうして治療上の効果を増し、及び／又は患者のクオリティ・オブ・ライフの改善が得られる。

【0051】

従って、本発明の幾つかの実施態様に於いては、被験者又は患者はすでに抗うつ薬又はその他の医薬により安定化しているが、副作用として重大な性機能障害を示し得る。この実施態様に於いては、式1の化合物は、第一の医薬により誘発された性機能障害が低下するか又は解消するまで、現在の療法に、1.0mgないし100.0mg/日の単位の用量で加える。当業者は、病状を測る臨床的インタビューやアンケートを通して、副作用の減少を判断し得る。

【0052】

その他の態様に於いて、抗うつ薬又はその他の薬剤は、式1の化合物と同時に開始され；これは、同時の投与である。この実施態様に於いては、本発明は、慣用の抗うつ薬又はその他の薬剤に由来する性機能障害の発症を予防する為に、式1の化合物の予防的有効量を、提供する事が意図される。両薬剤を同時に開始する実施態様に於いて、式1の化合物の予防的有効量は副作用と応答性により決定されるであろう。典型的には、式1の化合物の予防的有効量は、25ないし50mg/日から始められ、1週間あたり約25ないし50mg/日の単位で、副作用が生じるか又は十分な効果が得られるまで増加し得る。当業者であれば、製者の推奨及び患者の経験した反応及び副作用から抗うつ薬及びその他の薬物の適切な用量を容易に決定する事ができるであろう。

【0053】

本発明の化合物（式1の化合物）又はそれらの光学異性体、鏡像異性体、ラセミ体又は混合物、又はその水和物類、溶解物類および医薬品として許容できる塩類、エステル類及びアミド類が、治療の提供に用い得、予防的に又はそれらが発症した後のどちらでも、多くの薬剤についての男性及び女性のいずれに於ける性機能障害の深刻な不都合な副作用の為に用い得る。

【0054】

その様な薬物には、例えば、慣用の抗うつ薬、及び選択的セロトニン再取り込み阻害剤（SSRI's）；選択的セロトニン及びノルエピネフリン再取り込み阻害剤（SNRI's）；慣用の三環系抗うつ薬（TCAs）；モノアミンオキシダーゼ阻害剤（MAO阻害剤）、モノアミンオキシダーゼの可逆的阻害剤（RIMAs）、第三級アミン三環系及び第二級アミン三環系抗うつ薬、抗精神病薬、抗痙攣剤、炭酸リチウムが挙げられるがこれに限定されないその他の精神病薬を含むがこれに限定されず、また、フルオキセチン、デュロキセチン、ベンラファクシン、ミルナシプラン、シタロプラム、フルボキサミン、パロキセチン、セルトラリン、5-MCA-NAT、炭酸リチウム（LiCO₃）、イソカルボキサジド、フェネルジン、トラニルシプロミン、セレジリン、モクロベミド、アミトリプチリン、クロミプラミン、ドクセピン、イミプラミン、トリミプラミン、アモキサピン、デシプラミン、マプロチリン、ノルトリプチリン及びプロトリプチリン、カップーオピオイドレセプターアンタゴニスト；選択的ニューロキニンアンタゴニスト、コルチコトロピン放出因子（CRF）アンタゴニスト、タキキニンアンタゴニスト、 α -アドレノレセプターアンタゴニスト、及び、降圧剤、カルシウムチャネルブロッカー、ACE阻

害剤、スタチン等の様な心臓病薬等のその他の種類の薬物であり、並びにその医薬品として許容できる塩類又はエステル類、が挙げられるがこれに限定されない。

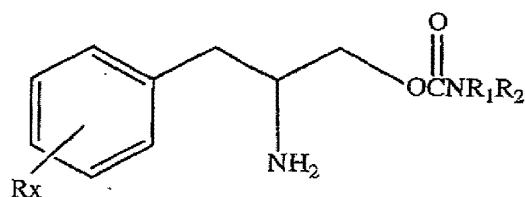
【0055】

試験化合物

式1のひとつの化合物（ここで試験化合物と呼ぶ）は、（R）-（ベータ-アミノ-ベンゼンプロピル）カルバメート-塩酸塩であり、O-カルバモイル-（D）-フェニアラニノールとも呼ばれる。

【0056】

【化15】



ここで $R_x = R_1 = R_2 =$ 水素原子である。

【0057】

（注：上記の試験化合物の化学構造（試験化合物）中、ベータ炭素に結合するアミノ基は、紙面の平面へ突き出ている。）これは、絶対配置が（R）の右旋性（D）の光学異性体である。

【0058】

この化合物は、動物モデル及びヒトに於いて試験され、下記に示す様に、性機能障害の治療に於ける化合物の群の価値を強く支持する効果を実証した。

【0059】

ヒトに於いて、試験化合物の抗うつ効果を評価する為に行われた試験段階で該化合物は有意なシグナルを示した。これは、試験化合物が慣用のSSRI抗うつ薬（パロキセチン）と比較された大きなプラセボ対照試験であった。

試験段階後のアンケートの分析は、主に男性において、400mgの一日用量に於いて現れたピーク効果をもって、性への関心の増加及びオルガスムを持つ能力の効果を示す。この研究は、本化合物のこの特性を理解し評価する為に設計されたものではなかったが、それゆえ、試験化合物の具体的にこの特性の評価に関する更なる研究が行われるであろう。

【0060】

試験化合物は、動物モデルに於いても活性を示し、性機能障害の治療として本発明の化合物の使用を支持し得るものであった（下記参照）。

【0061】

性機能障害を治療するための本発明の化合物の使用

その他の薬物の副作用

ここで用いた用語「抗うつ薬」とは、本発明のカルバメート化合物と併用して用いられ得る、哺乳類の抗うつ作用を有する事が知られている任意の化合物を意味するものとする。多くの最も一般的に用いられている抗うつ薬は、男性及び女性の両方に於いて性機能障害の重篤な、不都合な副作用を生じる。従って、この用語は、選択的セロトニン再取り込み阻害剤（SSRI's）、選択的セロトニン及びノルエピネフリン再取り込み阻害剤（SNRI's）；慣用の三環系抗うつ薬；プロピオン及びMAO阻害剤を含むが、これに限定されるものではない。

【0062】

選択的セロトニン再取り込み阻害剤（SSRI's）及び選択的セロトニン及びノルエピネフリン再取り込み阻害剤（SNRI's）は、例えば以下のものが挙げられるがこれに限定されるものではない。

【0063】

フルオキセチン、N-メチル-3-(p-トリフルオロメチルフェノキシ)-3-フェニルプロピルアミンは、塩酸塩の形態、及び2種の光学異性体のラセミ混合物として販売されている。米国特許第4,314,081号公報は、この化合物についての初期の文献である。Robertson等、J. Med. Chem. 31巻、1412頁(1988年)は、フルオキセチンのR及びS光学異性体の分離を教示し、またそのセロトニン取り込み阻害剤としての活性が互いに類似している事を示した。この文献では、“フルオキセチン”の用語は、いずれの酸付加塩、遊離塩基の形態も指し、及びラセミ混合物か又は、R及びS光学異性体を含み用いられる。

【0064】

デュロキセチン、N-メチル-3-(1-ナフタレニルオキシ)-3-(2-チエニル)プロパンアミンは、通常、塩酸塩及び(+)光学異性体として投与される。米国特許第4,956,388号でその高い可能性を教示したのが最初の教示である。“ジウロキセチン”の用語は、ここでは分子のいかなる酸付加塩又は遊離塩基も指して用いられる。

【0065】

ベンラファキシンは文献中で知られ、米国特許第4,761,501号公報はその合成方法及びセロトニン及びノルエピネフリン取り込み阻害剤としての活性を教示する。ベンラファキシンはこの特許中の化合物Aとして特定される。

【0066】

ミルナシプラン(N,N-ジエチル-2-アミノメチル-1-フェニルシクロプロパンカルボキサミド)は、その実施例4としてミルナシプランを製造した、米国特許第4,478,836号公報に教示されている。この特許はこの化合物を抗うつ薬として記載している。Moret等、Neuropharmacology 24巻、1211-19頁(1985年)はそのセロトニン及びノルエピネフリン再取り込みの阻害剤としての薬理学的活性を記載している。

【0067】

シタロプラム、1-[3-(ジメチルアミノ)プロピル]-1-(4-フルオロフェニル)-1,3-ジヒドロ-5-イソベンゾフランカルボニトリル、は、米国特許第4,136,193号公報にセロトニン再取り込み阻害剤として開示されている。この薬効薬理は、Christensenら、Eur. J. Pharmacol. 41巻153頁(1977年)に開示され、また、そのうつ病に於ける臨床的効能の報告が、Dufour等、Int. J. Clin. Psychopharmacol. 2巻225頁(1987年)に見られ得る。

【0068】

フルボキサミン、5-メトキシ-1-[4-(トリフルオロメチル)フェニル]-1-ペンタノンO-(2-アミノエチル)オキシム、は米国特許第4,085,225号公報に教示されている。この薬物の科学論文は、Claassen等、Brit. J. Pharmacol. 60巻、505頁(1977年)；及びDeWilde等、J. Affective Disord. 4巻、249頁(1982年)；及びBenfield等、Drugs 32巻、313頁(1986年)により刊行されている。

【0069】

パロキセチン、trans-(+)-3-[(1,3-ベンゾジオキサール-5-イルオキシ)メチル]-4-(4-フルオロフェニル)ピペリジン、は米国特許第3,912,743号公報及び第4,007,196号公報に見られ得る。この薬物の活性の報告は、Lassen、Eur. J. Pharmacol. 47巻、351頁(1978年)、Hassan等、Brit. J. Clin. Pharmacol. 19巻、705頁(1985年)、Laursen等、Acta Psychiat. Scand. 71巻、249頁(1985年)、及びBattegay等、Neuropsychobiology 13巻、31頁(1985年)にある。

【0070】

セルトラリン、(1S-cis)-4-(3,4-ジクロロフェニル)-1,2,3,

4-テトラヒドロ-N-メチル-1-ナフチルアミン塩酸塩、は、抗うつ薬として市販されているセロトニン再取り込み阻害剤である。これは米国特許第4, 536, 518号公報に開示されている。

【0071】

本発明のカルバメート化合物は、またその他の種類の抗うつ薬及びその他の治療上有効な薬剤とともに併用して用いられ得、前記その他の治療用有効薬剤には例えば、5-MC A-NAT（例えば、米国特許第6, 562, 858号公報）；炭酸リチウム（L i C O 3）；モノアミノキシダーゼ阻害剤（MAO-阻害剤）（好適なモノアミノキシダーゼ阻害剤は、イソカルボキサジド、フェネルジン、トラニルシプロミン及びセレジリン及びその医薬品として許容できる塩類を含む）、可逆的モノアミノキシダーゼ阻害剤（R I M A s）（好適な可逆的モノアミノキシダーゼ阻害剤は、モクロベミド、及びその医薬品として許容できる塩類を含む）；カップオピオイドレセプターアンタゴニスト（例えば米国特許第6, 528, 518号公報）等が挙げられるがこれに限定されない抗てんかん薬、選択的ニューロキニンアンタゴニスト（例えば、米国特許第6, 436, 928号公報）コルチコトロピン放出因子（CRF）アンタゴニスト（好適なCRFアンタゴニストは、国際公開公報WO94/13643号、WO94/13644号、WO94/13661号、WO94/13676号及びWO94/13677号公報に記載のものを含む）。；タキキニンアンタゴニスト（例えば、米国特許第6, 518, 273号公報）及び α -アデノレセプターアンタゴニスト等が挙げられるが、これに限定されるものではない。

【0072】

さらに、本発明の化合物は、第一次的にノルエピネフリン再取り込み阻害剤である慣用の抗うつ薬により引き起こされた性機能障害を脱却又は軽減する為に用いられ得る。その様な薬物には、第三級アミン三環系化合物及び第二級アミン三環系化合物を含むノルエピネフリン再取り込み阻害剤等が挙げられる。第三級アミン三環系化合物の適切な例としては、例えば、アミトリプチリン、クロミプラミン、ドキセピン、イミプラミン及びトリミプラミンならびにその医薬品として許容できる塩類等が挙げられる。

【0073】

第二級アミン三環系化合物の適切な例としては、アモキサピン、デシプラミン、マプロチリン、ノルトリプチリン、及びプロトリプチリンならびにその医薬品として許容できる塩類等が挙げられる。

【0074】

本発明の使用に於ける適切なセロトニン及びノルアドレナリン再取り込み阻害剤としては、ベンラファクシン、及びその医薬品として許容できる塩類等が挙げられる。

【0075】

一つ以上の本発明の化合物の上記の抗うつ薬のいずれかとの併用は、男性及び女性の両方に於いて、これらの薬物により生じた性機能障害の重篤な不都合な副作用を軽減、和らげ、解消し得る。

【0076】

本発明に用いられる化合物に関連して上述した米国特許全ては、ここへ参照として取り込まれる。

【0077】

定義

便宜上、明細書中、実施例及び添付の特許請求の範囲において用いたいくつかの用語をここに集める。

【0078】

本発明は、特定の метод論、プロトコル、動物の種又は属、及び記載された試薬は変化し得るものなので、それらに限定されるものではない事は理解されるべきである。また、ここに用いた専門用語は、特定の実施態様を記載する目的のみの為のものであり、また、添付の特許請求の範囲によってのみ限定されるべき本発明の範囲を限定する事を意図するものではない事も理解されるべきである。

【0079】

ここに用いた用語「被験者」とは、治療、観察又は実験の対象である動物、好ましくは哺乳類、及び最も好ましくはヒトの男性及び女性のいずれも指す。

【0080】

ここに用いた用語「治療有効量」とは、研究者、獣医、医師又はその他の臨床医によって探求されている、治療されている疾患又は障害の1以上の兆候又は症状の軽減を含む、組織系内、動物又はヒトに生物学的又は医学的反応を誘発する活性化化合物又は医薬品の量を指す。

【0081】

用語「予防的有効量」とは、研究者、獣医、医師又はその他の臨床医によって探求されている、組織、系、動物又はヒトの、予防するよう探求されている、生物学的又は医学的事象の発生のリスクを予防又は減少するであろう医薬品の量を意味する事を意図する。

【0082】

用語「医薬品として許容される塩類又はエステル類」は、遊離酸を適切な有機又は無機塩基と反応させる事により一般的に合成された、本発明で用いられた化合物の無毒性塩類又はエステル類を指すものとする。その様な塩類としては、酢酸塩、ベンゼンスルホン酸塩、安息香酸塩、重炭酸塩、重硫酸塩、酸性酒石酸塩、ホウ酸塩、臭化物、カルシウム、エデト酸カルシウム塩、カルシン酸塩、炭酸塩、塩化物、クラブラン酸塩、クエン酸塩、二塩酸塩、エデト酸塩、エディシレート、エストレート、フマル酸塩、グルセブテート、グルコン酸塩、グルタミン酸塩、グリコイルアルサニレート、ヘキシルレソルシネート、ヒドラバミン、臭化水素酸塩、塩化水素酸塩、ヒドロキシナフトエート、ヨウ化物、イソチオネート、乳酸塩、ラクトビオン酸塩、ラウリン酸塩、リンゴ酸塩、マレイン酸塩、マンデル酸塩、メシル酸塩、メチル臭化物、メチル硝酸塩、メチル硫酸塩、ムケート、ナプシル酸塩、硝酸塩、オレイン酸塩、オキサル酸塩、パマオート (pamaote)、パルミチン酸塩、パントテネート (panthothenate)、リン酸塩/二リン酸塩、ポリガラクトウロン酸塩、カリウム、サリチル酸塩、ナトリウム、ステアリン酸塩、スベセテート (subacetate)、コハク酸塩、タンニン酸塩、酒石酸塩、テオクレート (teoclolate)、トシレート、トリエチオグライド (triethiodide)、甘草酸塩等が挙げられるが、これらに限定されるものではない。

【0083】

従って、ここで用いた用語「治療を必要とする患者」は、抗うつ薬で治療し得る何れかの気分障害を含む上記の何れかの症状又は障害、又は患者の現在の臨床的状態又は予後が式(I)で表される一つ以上の化合物単独の又は別の医薬品を含むがこれに限定されない別の治療的行為と組み合わせた投与から益を得るところの他の何れかの障害、を現在有しているか又は発症し得る何れの被験者又は患者をも指す。

【0084】

ここで用いた用語「治療する」又は「治療」は、軽減；寛解；症状の減少或いは傷害、病状又は状態を患者により耐えられるものとする事；病気の病変若しくは減退又は悪化の速度の減速；悪化の終点をより減弱性でなくすること；又は対象者の身体的及び精神的健康状態を改善することの如何なる客観的又は主観的パラメーターを含む、傷害、病状又は状態の予防又は改善における成功の如何なる兆候をも言及する。症状の治療又は改善は、身体的試験、神経学的試験及び/又は精神医学的評価の結果を含む客観的又は主観的パラメーターに基づき得る。従って、用語「治療する」又は「治療」は、男性及び女性両方に於けるいずれかの形態の性機能障害の為の本発明の化合物又は薬物の投与を含む。場合によっては、本発明の化合物を用いた処置は、気分障害の進行を予防、抑制又は止める為に他の化合物と併用して行われ得る。

【0085】

ここで用いた用語「治療効果」は、性機能障害に於ける症状の効果的な改善又は軽減を指す。

【0086】

ここで用いた用語「治療有効量」は、精神防護作用治療を必要とする被験者又は患者に於ける、上記に挙げた治療効果を生む為の、一つ以上の本発明の化合物の十分な量を意味する。

【0087】

「被験者」又は「患者」の用語は、ここで互換可能に用いられ、ここでは、本発明の組成物が投与され得るヒトの患者又は被験者を含む、ヒトを含むがそれに限定されない任意の哺乳類を指して用いられる。哺乳類の用語は、男性及び女性の両方のヒトの患者及びヒト以外の霊長類並びにウサギ、ラット、及びマウスのような実験動物並びにその他の動物を含む。

【0088】

本発明の医薬品組成物の為の治療及び予防有効用量を決定する方法は、当該技術分野に於いて知られている。例えば、化合物は、一日用量を平均的ヒト成人で約0.1 mgから400 mgの範囲で、1日1ないし2回の処方用い得る。有効量は、しかしながら、使用された特定の化合物、投与方法、製剤の強度、投与方法、及び病状の進展状況により変化し得る。さらに、患者の年齢、体重、食事及び投与時間を含む、治療を受けている特定の患者に関連付けられる要因は、用量を調製する必要を生むであろう。

【0089】

化合物は任意の従来の投与経路で投与され、例えば、静脈内、経口、皮下、筋肉内、皮内及び非経口が挙げられるがこれらに限定されるものではない。投与経路に依存して、式(1)の化合物は、任意の剤形を構成し得る。例えば、経口投与に適した剤形は、ビル、ジェルキャップ、タブレット、カプレット、カプセル(それぞれ、迅速な放出、時間調整した放出及び持続した放出の配合物を含む)、顆粒、及び粉末等の様な固体の剤形が挙げられる。経口投与に適した剤形はまた、溶液、シロップ、エリキシル剤、乳剤、及び懸濁液等の様な液体剤形が挙げられる。さらに、非経口投与に有用な剤形は、滅菌水溶液、乳剤及び懸濁液が挙げられる。

【0090】

本発明の医薬品組成物を製造する為に、活性成分としての一つ以上の式(1)の化合物又はその塩は、従来の医薬品配合技術により、医薬品担体と密に混合する。担体は、必要かつ不活性の医薬品賦形剤であり、例えば、バインダー、懸濁化剤、潤滑剤、香味料、甘味料、防腐剤、色素、及びコート剤が挙げられるがこれらに限定されるものではない。経口剤形の組成物の製造に於いて、任意の通常の医薬品担体を用い得る。例えば、液体経口剤の製造には、適した担体及び添加剤は、例えば、水、グリコール、油、アルコール、香料添加物、防腐剤、着色剤等が含まれ、固体経口剤の製造には、適した担体及び添加剤は、スターチ、糖、希釈剤、造粒剤、潤滑剤、バインダー、崩壊剤等が挙げられる。非経口用途には、担体は通常滅菌水を含むが、その他の成分が、例えば溶解度補助又は防腐のための様な目的で含まれ得る。注射用懸濁液もまた製造し得る、この場合には、適切な液体担体、懸濁化剤等が用い得る。

【0091】

投与の容易さゆえに、タブレット及びカプセルは最も有利な経口用量単位剤形であり、その場合、明らかに、固体医薬品担体を用いられる。必要ならば、タブレットは、標準的な技術により糖衣又は腸溶性コーティングされ得る。坐薬も製造し得、その場合は、ココアバターを担体として用い得る。タブレット及びビルは、延長された作用の有利な効果をもたらす用量剤形を提供するために、コーティングされ得、又はその他配合し得る。例えば、タブレット又はビルは内部の用量及び外部の用量成分を包含し得、後者は、前者の上の包装の形態となる。2種の成分は、胃での分解に抵抗し、内部の成分を無傷で十二指腸を通過させるか又は放出を遅延させるよう腸溶性層により分離し得る。物質の種類は、この様な腸溶性層又はコーティングには多様な物質が用いられ得、該物質は、セラック、セチルアルコール及び酢酸セルロース等の様な物質と共に多数のポリマー酸等が挙げられる。

【0092】

活性薬剤はまた、小単層ベシクル、大単層ベシクル、多層ベシクルの様なりボソーム送達系の形態で投与され得る。リボソームは、コレステロール、ステアシルアミン又ホスファチジルコリンの様な種々のリン脂質から形成し得る。

【0093】

活性薬剤は、化合物分子が連結する個々の担体としてモノクローナル抗体の使用によっても送達し得る。活性薬剤は、標的可能な薬剤担体としての可溶性ポリマーと連結され得る。その様なポリマーとしては、ポリビニルピロリドン、ピラン コポリマー、ポリヒドロキシプロピルメタクリルアミドフェノール、ポリヒドロキシエチルアスパルタミドフェノール、又はパルミトイル残基で置換されたポリエチレンオキシドポリリジンが含まれ得る。さらにまた、活性薬剤は、薬剤の制御された放出を達成するのに有用な生物分解性ポリマーの類、例えば、ポリ乳酸、ポリグリコール酸、ポリ乳酸とポリグリコール酸の共重合体、ポリεピロリドン カプロラクトン、ポリヒドロキシ酪酸、ポリオルトエステル類、ポリアセタール類、ポリジヒドロピラン類、ポリシアノアクリレート類及び架橋した、又は両親媒性ハイドロゲルのブロック共重合体、と連結し得る。

【0094】

好ましくはこれらの組成物は、タブレット、ピル、カプセル、粉末、顆粒、点滴剤又は懸濁液、計測するエアロゾル又は液体スプレー、ドロップ、アンプル、自動注入機又は坐薬、経口、非経口、経鼻投与の、舌下の又は直腸投与の又は吸入剤又は吸入吸送の投与用等の単位用量形態にある。

【0095】

あるいは、組成物は週1回又は月1回の投与に適した剤形で提供され得、例えば、デカン酸塩の様な活性化化合物の不溶性塩は、筋肉内投与の為に持続性調剤の提供に適合され得る。

【0096】

本明細書における医薬品組成物は、用量単位毎、例えば、タブレット、カプセル、粉末、注射液、スプーン1杯分、坐薬等毎に、上記の様な有効用量を送達するのに必要な活性成分の量を含むであろう。例えば、ここでの医薬品組成物は、単位用量単位毎、約25ないし約400mgの活性成分を含み得る。好ましくは、その範囲は、約50ないし約200mgの活性成分である。

【0097】

本発明の幾つかの態様では、本発明の実施に於ける使用に適したカルバメート化合物は、単独でか又は少なくとも一つ以上のその他の化合物又は治療薬と同時に投与されるであろう。これらの実施態様では、本発明は、患者の性機能障害を治療又は予防する方法を提供する。該方法は、治療を必要とする患者に、ここに開示したカルバメート化合物の1つの有効量を、性機能障害の要因となるか又はそれ自身が該障害の治療能力又は本発明の化合物の性機能障害の治療効果を増強能力を持つその他の化合物又は治療薬の少なくとも一つ以上の有効量と併用して投与する工程を含む。

【0098】

ここで用いた、化合物、治療薬又は公知の薬剤の本発明の化合物との「同時投与」又は「併用投与」の用語は、1以上の本発明の化合物の投与を意味し、性機能障害の要因となり得るその他の治療薬が投与されるような時での投与であって、その併用が性機能障害を引き起こす傾向を減少できる投与をいう。その様な同時投与には、本発明の化合物の投与に関して、その他の治療薬を、並行（即ち、同時に）、先行、又はその後に投与する事が含まれ得る。その技術分野に於ける通常の知識を持つ者は、特定の薬剤と本発明の化合物の投与の適切なタイミング、順序、用量を決定する事は、困難ではないであろう。

【0099】

さらに、幾つかの実施態様に於いて、本発明の化合物は、単独又は互いに、又は一つ以上の上記のその他の治療薬剤又はそれらの塩類またはエステル類と併用して、性機能障害の治療を必要とする患者又は被験者へ該治療を提供する目的で薬剤を製造する為に、使用されるであろう。

【0100】

ここで用いた「 C_1-C_4 アルキル基」は、1ないし4個の炭素原子を有する置換または非置換の脂肪族炭化水素を指す。特に「アルキル基」の範囲に具体的に含まれるものは、付加的に所望により置換されている脂肪族炭化水素を指す。本発明の好ましい実施態様では、 C_1-C_4 アルキル基は非置換又はフェニル基で置換されている。

【0101】

ここで用いた用語「フェニル基」は、単独で用いられようとする他の基の部分として用いられようとする置換又は非置換の6個の炭素原子数を有する芳香族炭化水素環基として定義される。「フェニル基」の定義に具体的に含まれるものは、所望により置換されたフェニル基である。例えば、本発明の好ましい実施態様では、「フェニル基」は、非置換か又はハロゲン原子、 C_1-C_4 アルキル基、 C_1-C_4 アルコキシ基、アミノ基、ニトロ基又はシアノ基で置換されている。

【0102】

本発明の化合物の置換基及び置換パターンは、化合物を提供する為に当該技術分野の通常の知識を有する者により選択され得、化学的に安定であり、当該技術分野に於いて知られる技術並びにここに提供した方法により容易に合成され得ると理解される。

【0103】

代表的な2-フェニル-1、2-エタンジオール モノカルバメート及びジカルバメートは、例えば、以下の化合物である。

【0104】

本発明は、式1の分離された光学異性体の使用を含む。一つの好ましい実施態様に於いて、式1の分離されたS-光学異性体を含む医薬品組成物は、被験者に於ける補助抗うつ薬効果をもたらす為に用いられる。その他の好ましい実施態様に於いて、式1の分離されたR-光学異性体を含む医薬品組成物は、被験者に於ける補助抗うつ薬効果をもたらす為に用いられる。

【0105】

本発明はまた、式1の光学異性体の混合物の使用を含む。本発明のひとつの局面には、ひとつの光学異性体が優勢であろう。混合物中の優勢な光学異性体は混合物中に存在するその他のいかなる光学異性体よりも多い量、即ち50%より多くの量で混合物中に存在するものをいう。ひとつの局面に於いて、ひとつの光学異性体は、90%の範囲まで又は91%、92%、93%、94%、95%、96%、97%又は98%又はこれ以上の範囲まで優勢であろう。ひとつの好ましい実施形態に於いて、式1の化合物を含有する組成物中に於いて優勢な光学異性体は、式1のS-光学異性体である。

【0106】

本発明は、式1で表される化合物の光学異性体及び光学異性体の混合物を用いる方法を提供する。式1のカルバメート光学異性体は、フェニル環の隣の2番目の脂肪族炭素であるベンジル位に於いて不斉炭素を含む。

【0107】

分離された光学異性体は、対応する光学異性体を実質的に含まないものである。従って、分離された光学異性体を、分離技術により分離された又は対応する光学異性体を含まず合成された化合物という。ここで用いた用語「実質的に含まず」とは、化合物が、有意に大きい比率のひとつの光学異性体からなるものをいう。好ましい実施態様に於いて、前記化合物は少なくとも質量を基準に約90%の好ましい光学異性体を含む。本発明の他の実施態様に於いて、前記化合物は少なくとも質量を基準に約99%の好ましい光学異性体を含む。好ましい光学異性体は、高速液体クロマトグラフィー（HPLC）及びキラルな塩の生成及び結晶化を含む、当該技術分野のいかなる公知の方法によってもラセミ混合物から分離され得、又は好ましい光学異性体はここに述べた方法によって合成され得る。

【0108】

医薬品としてのカルバメート化合物

本発明は、医薬品として式1のラセミ混合物、光学異性体混合物及び分離された光学異

性体を提供する。カルバメート化合物は、被験者に於ける補助的抗うつ作用をもたらす医薬品として形成される。

【0109】

一般的に、本発明のカルバメート化合物は、経口、口腔内、局部、全身（例えば、経皮、鼻腔内、又は坐薬によって）、又は非経口（例えば、筋肉内、皮下、又は静脈内注射）を含む治療薬の投与の為の当該技術分野に於けるいずれの公知の方法によっても医薬品組成物として投与され得る。直接的な神経系への化合物の投与は、例えば、大脳内、心室内、脳室内、髄腔内（intrathecal）、嚢内、髄腔内（intraspinal）、脊髄周辺（peri-spinal）経路の、ポンプ装置を用いた又は用いない頭蓋内又は脊椎内のニードル又はカテーテルを経る供給による投与が挙げられる。

【0110】

組成物は、タブレット、ピル、カプセル、半固体、粉末、徐放性製剤、溶液、懸濁液、乳剤、シロップ、エリキシル剤、エアロゾル、又はその他の好適な組成物の形態をとり得；及び少なくとも1つの本発明の化合物を、少なくとも1つの医薬品として許容し得る賦形剤と併用して含有し得る。好適な賦形剤は、当該技術分野に於ける通常の知識を有する者によく知られているものであり、それら及び組成物を形成する方法は、Arfonso AR Remington's Pharmaceutical Sciences、17版、Mark Publishing Company、Easton PA、1985年、のような標準的文献に見出し得、前記文献の開示は、ここに全て参照として全ての目的の為に取り込まれている。好適な液体担体、特に注射液用のものとしては、例えば、水、生理食塩液、水性デキストロス溶液、及びグリセロール等が挙げられる。

【0111】

カルバメート化合物は水性懸濁液として提供され得る。本発明の水性懸濁液は、水性懸濁液の製造に好適な賦形剤と混合液してカルバメート化合物を含有し得る。そのような賦形剤としては、例えば、カルボキシメチルセルロース ナトリウム、メチルセルロース、ヒドロキシプロピルメチルセルロース、アルギン酸ナトリウム、ポリビニルピロリドン、トラガカントゴム、アカシアゴム等の様な懸濁化剤、天然リン脂質（例えば、レシチン）、アルキレンオキシドと脂肪酸との縮合生成物（例えば、ポリオキシエチレン ステアレート）、エチレンオキシドと長鎖脂肪アルコールとの縮合生成物（例えば、ヘプタデカエチレン オキシセタノール）、エチレンオキシドと脂肪酸及びヘキシトールから誘導された部分エステルとの縮合生成物（例えば、ポリオキシエチレン ソルビトール モノオレエート）、又はエチレンオキシドと脂肪酸及び無水ヘキシトールから誘導された部分エステル（例えば、ポリオキシエチレン ソルビタン モノオレエート）等の様な分散剤又は湿潤剤が挙げられる。

【0112】

水性懸濁液は、一つ以上のエチル又はn-プロピル-p-ヒドロキシベンゾエートの様な防腐剤、一つ以上の着色剤、一つ以上の香料添加物、及びスクロース、アスパルテーム又はサッカリン等の様な一つ以上の甘味剤を含み得る。配合物はオスモル濃度に合わせ調整され得る。

【0113】

本発明の方法に用いる油懸濁液は、らっかせい油、オリーブ油、ゴマ油、ココナツ油の様な植物油中に、又は流動パラフィンの様な鉱油並びにこれらの混合物中にカルバメート化合物を懸濁させる事により配合し得る。油懸濁液は、蜜ろう、固形パラフィン又はセチルアルコール等の様な増粘剤を含み得る。甘味剤は、口当たりのよい経口製剤を提供する為添加し得、グリセロール、ソルビトール又はスクロース等がある。これらの配合物は、アスコルビン酸の様な酸化防止剤の添加により保存し得る。注射可能な油状媒体の例としては、Minto, J. Pharmacol. Exp. Ther. 281巻93頁-102頁、1997年を参照されたい。本発明の医薬品配合物は、水中油型乳剤の形でもあり得る。油相は、上記の植物油又は鉱油であり得、又はこれらの混合物であり得る。

【0114】

好適な乳化剤としては、アカシアゴム、トラガカントゴム等の様な天然ゴム、大豆レクチンの様な天然リン脂質、ソルビタン モノオレエートの様な脂肪酸と無水ヘキシトールから誘導されたエステル類又は部分エステル類、ポリオキシエチレン ソルビタン モノオレエートの様なこれらの部分エステル類とエチレンオキシドとの縮合生成物が挙げられる。乳剤は、シロップ及びエリキシル剤の配合物におけるのと同様に甘味剤及び香料添加物を含有し得る。その様な配合剤はまた鎮痛剤、防腐剤又は着色剤を含有し得る。

【0115】

選択した化合物は、単独又は他の好適な組成物と併用して、吸入により投与されるエアロゾル配合物（即ち、ネブライザーとし得る）に製造し得る。エアロゾル配合物は、ジクロロジフルオロメタン、プロパン、窒素等の加圧した許容できる推進剤中へ入れられ得る。

【0116】

非経口投与、例えば、関節内投与（関節中へ）、静脈内投与、筋肉内投与、皮内投与、腹腔内投与、及び皮下投与経路等に好適な本発明の配合物は、水性、非水性、等張無菌注射液を含み得、該注射液は酸化防止剤、緩衝液、殺菌剤、及び配合剤を対象とする受容者の血液と等張にする溶質、及び懸濁化剤、可溶化剤、増粘剤、安定剤及び防腐剤を包含し得る水性及び非水性の無菌懸濁液を包含し得る。用い得る許容できる媒体及び溶媒のうちには、水、及びリンガー液、等張塩化ナトリウム溶液がある。さらに、無菌固定油は溶媒又は懸濁媒体として従来から用い得る。この目的の為に、合成モノ又はジグリセリドを含む、いかなる無刺激性の固定油も用い得る。さらに、オレイン酸などの脂肪酸が注射剤の製造に於いて同様に使用し得る。これらの溶液は無菌であり一般的に望ましくない物質を含まない。

【0117】

化合物が十分に可溶性である場合には、これらは、直接、通常の生理食塩水に、プロピレングリコール又はポリエチレングリコールの様な好適な有機溶媒を使用して又は使用せずに溶解し得る。よく分離した化合物の分散液は水溶性でんぷん又はカルボキシメチルセルロース ナトリウム溶液中で、又はらっかせい油の様な好適な油中で製造され得る。これらの配合物は慣用の、よく知られた滅菌技術により滅菌され得る。前記配合物は、pH調製剤、緩衝剤、毒性調製剤、例えば酢酸ナトリウム、塩化ナトリウム、塩化カリウム、塩化カルシウム、乳酸ナトリウムなどの様な医薬品として許容できる補助物質を、生理学的に状態を近似させるために含有し得る。

【0118】

これらの配合物に於けるカルバメート化合物の濃度は広く変化し得、主に液量、粘度、体重等に基づいて、特定の選択された投与形態及び患者の必要性に従い、選択されるであろう。静脈内投与のためには、配合物は、滅菌注射用水性又は油性懸濁液の様な滅菌注射用製剤であり得る。この懸濁液は、それらの好適な分散剤又は湿潤剤及び懸濁化剤を用いて、既知の技術技術に従い配合される。この滅菌注射用製剤はまた、1，3-ブタンジオール溶液の様な、無毒の非経口に於いて許容できる希釈剤又は溶媒中の、滅菌注射用溶液又は懸濁液であり得る。推奨する配合物は、アンプル及びバイアルの様な単位用量又は複数用量のシール容器で提供され得る。注射用溶液及び懸濁液は、先に述べた様な滅菌粉末、顆粒、及びタブレットより製造され得る。

【0119】

本発明の実施に好適に用いられるカルバメート化合物は、経口投与され得、好ましくは経口投与される。組成物中の本発明の化合物量は組成物の種類、単位用量の大きさ、賦形剤の種類、及び当該技術分野の通常の技術を有する者によく知られたその他の因子により広く変化し得る。一般的に、最終組成物は、例えば、0.000001質量パーセント（%W）ないし50%wのカルバメート化合物を、好ましくは0.00001%wないし25%wを含有し得、残余は賦形剤又は賦形剤類である。

【0120】

経口投与の為の医薬品配合物は当該技術分野に於いてよく知られた医薬品として許容で

きる担体を経口投与に好適な用量で用い形成され得る。その様な担体は医薬品配合物が、タブレット、ピル、粉末、糖衣錠、カプセル、液体、トローチ錠、ジェル、シロップ、スラリー、懸濁液等の患者による摂取に好適な単位用量形態で配合されることを可能にする。

【0121】

経口投与に好適な配合物は、(a) 水、生理食塩水又はPEG 400の様な希釈剤中に懸濁させた有効量の医薬品配合物の様な液体溶液；(b) 液体、固体、顆粒又はゼラチンとして活性成分の所定量をそれぞれ含有する、カプセル、小袋又はタブレット；(c) 適切な溶液中の懸濁液；及び(d) 好適な乳剤、から成り得る。

【0122】

経口投与に用いる医薬品製剤は、本発明の化合物と、固体賦形剤を併用し、所望により得られた混合物を粉碎し、そして、タブレット又は糖衣錠のコアを得るために必要に応じて好適な付加化合物を添加した後、顆粒の混合物を加工することを通して得られ得る。好適な固体賦形剤としては、炭水化物又はタンパク質充填剤があり、また、例えば、ラクトース、スクロース、マンニトール、又はソルビトールの様な糖類；例えば、とうもろこし、小麦、米、ジャガイモ、又はその他の植物由来のでんぷん；例えば、メチルセルロース、ヒドロキシメチルセルロース、ヒドロキシプロピルメチルセルロース又はカルボキシメチルセルロースナトリウムの様なセルロース；及び例えば、アラビアゴム及びトラガcantゴムを含むゴム類；同様に、例えば、ゼラチン及びコラーゲンの様なタンパク質が挙げられるがこれらに限定されない。

【0123】

必要であれば、架橋ポリビニルピロリドン、寒天、アルギン酸、又はアルギン酸ナトリウムの様なその塩の様な崩壊剤又は可溶化剤を添加し得る。タブレット剤形は一つ以上のラクトース、スクロース、マンニトール、ソルビトール、リン酸カルシウム、コーンスターチ、ジャガイモでんぷん、ミクロクリスタリンセルロース、ゼラチン、コロイド状二酸化ケイ素、タルク、ステアリン酸マグネシウム、ステアリン酸、及びその他の賦形剤、着色剤、充填剤、バインダー、希釈剤、緩衝剤、湿潤剤、防腐剤、香料添加剤、染料、崩壊剤、及び医薬品として適し得る担体を含有し得る。トローチ剤の剤形は、例えばトローチが、ゼラチン及びグリセリン又はスクロース及びアカシアゴムの乳剤、ジェル、など含有の不活性基剤中に活性種を含有するのと同様に、香味料例えば、スクロース中に活性原料を含有し得、活性原料に加えて、当該技術分野で知られている担体を含有し得る。

【0124】

本発明の化合物はまた、薬剤の直腸投与の為の坐薬の形で投与され得る。これらの配合物は薬剤を、常温で固体であるが直腸温度に於いて液体であり、これゆえ直腸内で溶解して薬剤を放出するところの好適な無刺激賦形剤と薬剤を混合して製造し得る。その様な物質はココアバター及びポリエチレングリコールである。

【0125】

本発明の化合物は、吹送物、粉末及びエアロゾル配合物（ステロイド吸入の例、Rohatagi, J. Clin. Pharmacol. 35巻、1187頁-1193頁、1995年；Tjwa, Ann. Allergy Asthma Immunol.、75巻、107頁-111頁、1995年参照）を含む鼻腔内、眼球内、腔内及び坐薬を含む直腸内経路により、投与され得る。

【0126】

本発明の化合物は、塗布スティック、溶液、懸濁液、乳剤、ジェル、クリーム、軟膏、ペースト、ゼリー、塗料、粉末、及びエアロゾルとして配合された、局所的な経路によって、経皮的に送達され得る。

【0127】

封入材料もまた、本発明の化合物に用い得、「組成物」の用語は、配合物として活性成分を、その他の担体を用いてまたはその他の担体を用いずに、封入材料と共に含み得る。例えば、本発明の化合物はまた、体内で徐々に放出する為のミクロスフェアとして送達さ

れ得る。ひとつの実施態様においては、ミクロスフェアは、皮下に徐々に放出する(Rao, J. Biomater Sci. Polym. Ed. 7巻、623頁-645頁、1995年参照)、生分解性及び注射用ジェルの配合物として(例えば、Gao, Pharm Res. 12巻、669頁-674頁、1997年参照)、又は経口投与用のミクロスフェアとして(例えば、Eyles, J. Pharm. Pharmacol 49巻、669頁-674頁(1997年)参照)、薬剤(例えば、ミフェプリストン)一含有ミクロスフェアの経皮注射液を介して投与され得る。経皮投与及び皮内投与の経路のどちらも、数週間又は数ヶ月の間持続して送達する事ができる。カプセルもまた、本発明の化合物の送達に用い得る。

【0128】

その他の実施態様に於いて、本発明の化合物は、細胞膜で溶解するか又は取り込まれるリボソームの使用により、即ち、細胞の表面膜タンパク質レセプターに結合してエンドサイトーシスを生じる、リボソームに結合したリガンドを用いる事により送達し得る。リボソームを使用する事により、特にリボソーム表面が標的細胞に特異的なリガンドを有するとき、又はそうでなければ特定の臓器に選択的に向けられるとき、生体内で標的臓器へのカルバメート化合物の送達に専念し得る。(Al-Muhammed, J. Microencapsul.、13巻、293頁-306頁、1996年; Chonn, Curr. Opin. Biotechnol.、6巻、698頁-708頁、1995年; Ostror, Am. J. Hosp. Pharm. 46巻、1576頁-1587頁、1989年参照)

【0129】

本発明の医薬品剤形は、塩として提供され得、及び例えば、塩酸、硫酸、酢酸、乳酸、酒石酸、リンゴ酸、コハク酸等が挙げられるがこれに限定されない多くの酸を用いて形成し得る。塩類は、水溶液又は該遊離塩基の形態にあるその他のプロトン性溶媒に、より可溶である傾向にある。その他の場合に於いて、好ましい製剤は、4.5ないし5.5のpH範囲で、例えば、任意の又は全ての以下の：1mM-50mMヒスチジン、0.1%-2%のスクロース、2%-7%のマンニトールの何れか又は全てを含み得る凍結乾燥粉末であり得、該粉末は使用前に緩衝液と混合される。

【0130】

医薬品として許容できる塩類及びエステル類は、医薬品として許容でき、望まれる薬理学的特性を持つ塩類及びエステル類を指す。その様な塩類としては、化合物中に存在する酸性プロトンが無機又は有機塩基類と反応し得る場合に形成し得る塩類が挙げられる。好適な無機塩類としては、アルカリ金属、例えば、ナトリウム、及びカリウム、マグネシウム、カルシウム、及びアルミニウムを用いて形成されたもの等が挙げられる。好適な有機塩類としては、アミン塩基、例えば、エタノールアミン、ジエタノールアミン、トリエタノールアミン、トロメタミン、N-メチルグルカミン等の有機塩基を用いて形成されたもの等が挙げられる。医薬品として許容できる塩類はまた、親化合物中のアミン部分と無機酸(例えば、塩化水素酸、臭化水素酸)との、及び有機酸(例えば、酢酸、クエン酸、マレイン酸、及びメタンスルホン酸及びベンゼンスルホン酸の様なアルカン-及びアレ-ン-スルホン酸)との反応から形成した酸付加塩、等が挙げられる。医薬品として許容できるエステル類としては、化合物中に存在するカルボキシ基、スルホニルオキシ基、及びホスホンオキシ基より生成されたエステル類等が挙げられる。2つの酸性基が存在する場合、医薬品として許容できる塩又はエステルは、モノ-酸-モノ-塩又はエステル(mono-acid-mono-salt or ester)又はジ-塩又はエステル(di-salt or ester)であり得、同様に、2より多くの酸性基が存在する場合、その様な基の幾つか又は全てが塩化又はエステル化し得る。

【0131】

本発明中で名を挙げられた化合物は塩化されていない又はエステル化されていない形態、又は塩化及び/又はエステル化した形態で存在し得、その様な化合物の指定はもとの(塩化されていない及びエステル化されていない)化合物及びその医薬品として許容できる