

Electronic Acknowledgement Receipt	
EFS ID:	35476511
Application Number:	
International Application Number:	PCT/US17/60761
Confirmation Number:	4463
Title of Invention:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF
First Named Inventor/Applicant Name:	IONO PHAMA, LLC
Customer Number:	76447
Correspondence Address:	Susan B. Fentress Veritay Group, IP 20 Dudley St Suite 803 Memphis TN 38103 US 9013716664 eofficeaction@appcoll.com
Filer:	Susan Bennett Fentress
Filer Authorized By:	
Attorney Docket Number:	24050.0001PCT
Receipt Date:	20-MAR-2019
Filing Date:	09-NOV-2017
Time Stamp:	12:12:52
Application Type:	International Application (PCT) for filing in the US receiving office
Patent Number:	

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	Misc. incoming letter from Applicant - IA	letter.pdf	100676	no	1
			548ae6b44a3f70b3a08ffdf59d16985a39969e5e		
Warnings:					
Information:					
2	CHII - Amendmnts to descrpt/drawings - PCT Art. 34	replacmentsheetspec.pdf	138816	no	1
			0d8e50b9e11f07fb5795dd5acdbaed3fe57af36		
Warnings:					
Information:					
3	CHII - Amendment to the claims - PCT Art. 34	replacmentsheetclaimspage18.pdf	80520	no	1
			24d23a62b10431691ff63093e561375f1fa3c10e		
Warnings:					
Information:					
4	CHII - Amendment to the claims - PCT Art. 34	replacmentsheetpage24claims.pdf	82708	no	1
			58b0a96311afb91318e83d0d8448e20fce95f6c2		
Warnings:					
Information:					
Total Files Size (in bytes):			402720		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

20 March 2019 (20.03.2019)

IN THE INTERNATIONAL BUREAU RECEIVING OFFICE

Applicant: Iono Pharma, LLC
International Application No.: PCT/US2017/60761

International Filing Date: 09.11.2017

For: Pharmaceutical Formulation For Sublingual or Buccal Delivery of
Epinephrine or a Pro-Drug Thereof

Attn: Authorized Officer AT INTERNATIONAL BUREAU
Email: pct.infoline@wipo.int
Fax: 41 22 338 82 70

The International Bureau of WIPO
PCT Receiving Section
34, chemin des Colombettes
1211 Geneva 20
Switzerland

LETTER and REQUEST TO PUBLISH REPLACEMENT SHEETS

Applicant hereby files replacement sheets pages 7, 18 and 24 to correct the nomenclature of certain compounds as suggested in Box no VIII of the Preliminary Report on Patentability dated November 13, 2018.

Applicant respectfully requests that the International Bureau published the replacement sheets filed with the Chapter II with the US receiving office on April 20, 2018 and submitted herewith.

Dated: March 19, 2019

Respectfully submitted,

/susan b fentress/

Name: Susan Fentress
Reg no. 31327
Veritay Group IP
20 Dudley Suite 8093
Memphis, TN 38103
USA
901-371-6664
Title: Agent for the Applicant

Electronic Patent Application Fee Transmittal

Application Number:	PCT/US17/60761			
Filing Date:	09-Nov-2017			
Title of Invention:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF			
First Named Inventor/Applicant Name:	IONO PHARMA, LLC			
Filer:	Susan Bennett Fentress			
Attorney Docket Number:	24050.0001PCT			
Filed as Small Entity				
Filing Fees for International Application (PCT) for filing in the US receiving office				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
PRELIMINARY EXAM FEE-US WAS THE ISA	2605	1	300	300
HANDLING FEE	1705	1	205	205
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 (\$)				505

Electronic Acknowledgement Receipt	
EFS ID:	32405186
Application Number:	
International Application Number:	PCT/US17/60761
Confirmation Number:	4463
Title of Invention:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF
First Named Inventor/Applicant Name:	IONO PHARMA, LLC
Customer Number:	76447
Correspondence Address:	Susan B. Fentress Veritay Group, IP 20 Dudley St Suite 803 Memphis TN 38103 US 9013716664 eofficeaction@appcoll.com
Filer:	Susan Bennett Fentress
Filer Authorized By:	
Attorney Docket Number:	24050.0001PCT
Receipt Date:	20-APR-2018
Filing Date:	09-NOV-2017
Time Stamp:	21:03:17
Application Type:	International Application (PCT) for filing in the US receiving office
Patent Number:	

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$505
RAM confirmation Number	042318INTEFSW21085800
Deposit Account	601480
Authorized User	Susan Fentress

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:
PCT Rule 16

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	CHII - Form PCT/IPEA/401 - Demand	chapter2demand.pdf	1265736	no	3
			cd0f916e0f2c9418b65ce65c1ffdcfe223e0ee02		

Warnings:

Information:

2	CHII - Form IPEA/401 Annex	pctfeecalculationsheet.pdf	299054	no	1
			e92762949fe58a7d2852aa0b0af8e22889c7f9f1		

Warnings:

Information:

3	CHII - Misc. communication from Applicant - IA	pctletter.pdf	1796360	no	6
			f0f706915ea8ab90b3415557b5ad9a301480762c		

Warnings:

Information:

4	CHII - Amendmnts to descrpt/drawings - PCT Art. 34	PCTreplacementsheetspec.pdf	6964621	no	17
			43ee6b2b359a4f5a90d70f028a2b8ae115d81205		

Warnings:

Information:

5	CHII - Amendment to the claims - PCT Art. 34	pctreplacementsheetclaims.pdf	1281948 905f0f2f8338f86e1289961bbf671ef5d66bd536	no	7
Warnings:					
Information:					
6	CHII - Amendmnts to descrpt/drawings - PCT Art. 34	replacementsheetabstract.pdf	227761 0b11bcd6d0e30e5d4238cd027bd3a9d4d7b35859	no	1
Warnings:					
Information:					
7	CHII - Amendmnts to descrpt/drawings - PCT Art. 34	figs.pdf	276610 b86f465a16b950de558e1ab14ac926ad13c47bd0	no	9
Warnings:					
Information:					
8	Fee Worksheet (SB06)	fee-info.pdf	31785 6730225fe558dc123bd2c23eb197388e3e90dc00	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			12143875		
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.					

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: SUSAN B. FENTRESS
VERITAY GROUP, IP
20 DUDLEY SUITE 803
MEMPHIS, TN 38103

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
(day/month/year)

25 JAN 2018

Applicant's or agent's file reference
24050.0001PCT

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US 17/60761

International filing date
(day/month/year) **09 November 2017 (09.11.2017)**

Applicant **IONO PHARMA, LLC**

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

How? Directly to the International Bureau of WIPO preferably through ePCT or on paper to, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:**
☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90bis.1 and 90bis.3).

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pot/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Within **22 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45bis.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-8300

Authorized officer

Lee W. Young

PCT Helpdesk: 571-272-4300
Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2014)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 24050.0001PCT	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US 17/60761	International filing date (<i>day/month/year</i>) 09 November 2017 (09.11.2017)	(Earliest) Priority Date (<i>day/month/year</i>) 13 November 2016 (13.11.2016)
Applicant IONO PHARMA, LLC		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed.
☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (see Box No. II).

3. ☐ Unity of invention is lacking (see Box No. III).

4. With regard to the title,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. 2
☒ as suggested by the applicant.
☐ as selected by this Authority, because the applicant failed to suggest a figure.
☐ as selected by this Authority, because this figure better characterizes the invention.
 b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/60761

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/137 (2017.01)

CPC - A61K 9/0056, A61J 7/0053, A61J 1/035, A61K 9/006

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)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y -- A	US 4,145,441 A (BODOR) 20 March 1979 (20.03.1979), entire document, especially: col 5, preferred compound (1) 3,4-dipivaloyloxy-a-[(methylamino)methyl]benzyl alcohol; col 5, preferred compound (7) 3-(trimethylacetoxy)-a-[(methylamino)methyl]benzyl alcohol; col 5, preferred compound (17) 3,4-di-2,5-hexadienoyloxy-a-[(methylamino)methyl]benzyl alcohol; col 1, ln 7-10; col 1, ln 12-21; col 1, ln 34-44; col 4, ln 59-68; col 10, ln 15-17, Claim 40.	1,5,11,13 ----- 2-4,15-16, 18-22 ----- 6-10,12
X -- Y	US 2007/0202163 A1 (RAWAS-QALAJI et al.) 30 August 2007 (30.08.2007), entire document, especially: para [0004]; para [0007]; para [0130]; para [0131]; para [0139].	14,17 ----- 2-4, 15-16,18,20-22
Y	US 2003/0180357 A1 (MARTINO et al.) 25 September 2003 (25.09.2003), entire document, especially: para [0011]; para [0025].	19-22
A	US 4,320,144 A (RESNICK) 16 March 1982 (16.03.1982), entire document, especially: col 3, ln 13-47, 1,5-bis[(3-dichloropropanoyloxyphenyl)oxy] pentane.	6-10,12
A	- PubChem-CID-70464361, Create Date: 01 December 2012 (01.12.2012), pg 3, Fig.	1-22
A	- PubChem-CID-969492, Create Date: 09 July 2005 (09.07.2005), pg 3, Fig.	1-22

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

08 January 2018

Date of mailing of the international search report

25 JAN 2018

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

SEARCH HISTORY

Application Number	PCT/US 17/60761
Search Conducted By	JFK
Search Approved By	SV

IPC/CPC Classifications Searched	IPC(8): A61K 31/137 (2017.01) CPC: A61K 9/0056, A61J 7/0053, A61J 1/035, A61K 9/006
Date Conducted	8 January 2018 (08.01.2018)

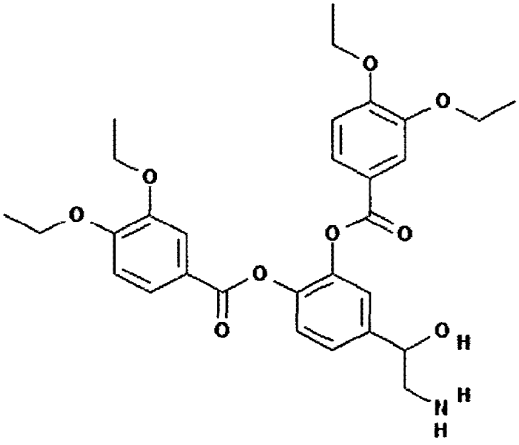
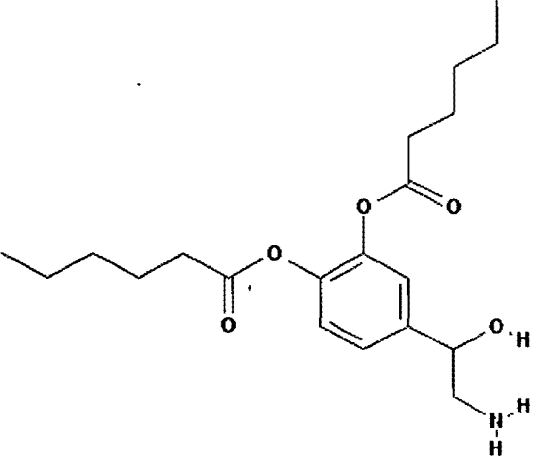
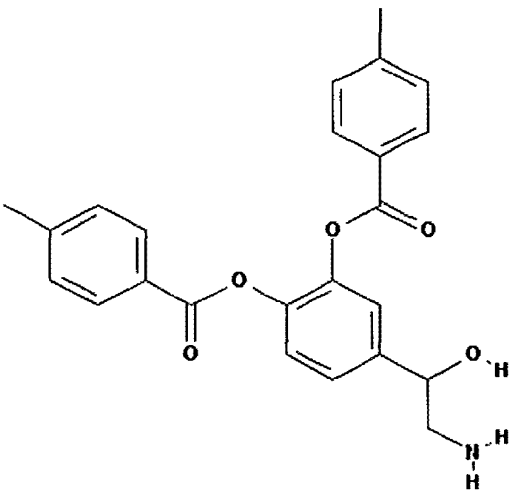
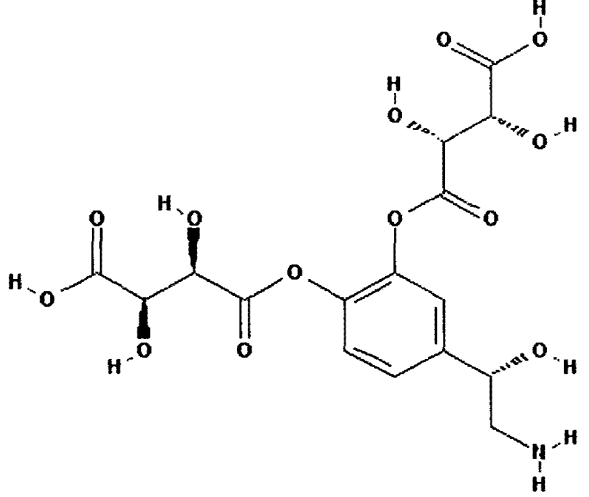
Documentation Searched	USPC: None
Search Terms Used	PatBase; Keyword limited: anaphylaxis/anaphylactic; epinephrine/adrenaline/dipivefrin/isoproterenol/isoprenaline; sublingual/buccal; prodrug/pro-drug
Date Conducted	8 January 2018 (08.01.2018)

Electronic Database Searched	PatBase
Files Searched	Full-text: AU BE BR CA CH CN DE DK EP ES FI FR GB IN JP KR SE TH TW US WO Bibliographic: (Europe) AT BA BE BG CH CS CY CZ DD DK EE ES FI GE GR HR HU IE IS IT LT LU LV MC MD MT NL NO PL PT RO RS SE SI SK SM TR UA YU (Asia) EA GC HK ID IL IN KZ MN MY PH RU SG SU TH TJ TW UZ VN (North America) CA CR CU DO GT HN MX NI PA SV TT (South America) AR BR CL CO EC PE UY (Australasia) AU NZ (Africa) AP DZ EG KE MA MW OA ZA ZM ZW
Date Conducted	8 January 2018 (08.01.2018)
Search Logic: Search 1: IC=(A61K31/137) (Results 7265) Search 2: CPC=(A61K9/0056 or A61J7/0053 or A61J1/035 or A61K9/006) (Results 7486) Search 3: 1 or 2 (Results 14477) Search 4: 3 and FT=(anaphylaxis) (Results 0) Search 4:	

3 and FT=(anaphylaxis) (Results 163)
 Search 5:
 3 and FT=(anaphylactic) (Results 146)
 Search 6:
 4 or 5 (Results 244)
 Search 7:
 6 and FT=(epinephrine) (Results 101)
 Search 8:
 6 and FT=(adrenaline) (Results 48)
 Search 9:
 6 and FT=(dipivefrin) (Results 6)
 Search 10:
 6 and FT=(isoproterenol) (Results 34)
 Search 11:
 6 and FT=(isoprenaline) (Results 13)
 Search 12:
 7 or 8 or 9 or 10 or 11 (Results 114)
 Search 13:
 12 and FT=(sublingual) (Results 55)
 Search 14:
 12 and FT=(buccal) (Results 53)
 Search 15:
 12 and FT=(prodrug) (Results 13)
 Search 16:
 12 and FT=(pro-drug) (Results 1)
 Search 17:
 FT=(anaphylaxis) (Results 11108)
 Search 18:
 FT=(anaphylactic) (Results 8634)
 Search 19:
 17 or 18 (Results 17502)
 Search 20:
 19 and FT=(epinephrine) (Results 1371)
 Search 21:
 19 and FT=(adrenaline) (Results 584)
 Search 22:
 19 and FT=(dipivefrin) (Results 62)
 Search 23:
 19 and FT=(isoproterenol) (Results 480)
 Search 24:
 19 and FT=(isoprenaline) (Results 347)
 Search 25:
 20 or 21 or 22 or 23 or 24 (Results 2089)
 Search 26:
 25 and FT=(sublingual) (Results 674)
 Search 27:
 25 and FT=(buccal) (Results 528)
 Search 28:
 25 and FT=(prodrug) (Results 465)
 Search 29:
 25 and FT=(pro-drug) (Results 66)

Electronic Database Searched	Google
Files Searched	Web (Articles and Patents)
Date Conducted	8 January 2018 (08.01.2018)
Search Logic:	
anaphylaxis 2,460,000 results anaphylactic 5,150,000 results anaphylaxis sublingual epinephrine 54,400 results anaphylactic sublingual epinephrine 47,600 results anaphylaxis buccal epinephrine 37,300 results anaphylactic buccal epinephrine 42,900 results anaphylaxis sublingual adrenaline 24,200 results anaphylactic sublingual adrenaline 31,800 results anaphylaxis buccal adrenaline 18,600 results anaphylactic buccal adrenaline 18,600 results anaphylaxis sublingual dipivefrin 5,900 results anaphylactic sublingual dipivefrin 5,670 results anaphylaxis buccal dipivefrin 3,520 results anaphylactic buccal dipivefrin 3,460 results anaphylaxis sublingual isoprenaline 12,900 results anaphylactic sublingual isoprenaline 11,200 results anaphylaxis buccal isoprenaline 12,500 results anaphylactic buccal isoprenaline 13,100 results anaphylaxis sublingual epinephrine prodrug 7 results anaphylactic sublingual epinephrine prodrug 8,460 results anaphylaxis buccal epinephrine prodrug 5 results anaphylactic buccal epinephrine prodrug 22,800 results anaphylaxis sublingual adrenaline pro-drug 28,100 results anaphylactic sublingual adrenaline pro-drug 40,100 results anaphylaxis buccal adrenaline pro-drug 26,500 results anaphylactic buccal adrenaline pro-drug 25,900 results	

Electronic Database Searched	PubChem Compound
Files Searched	Data Source Categories: Biological Properties, Chemical Vendors, Journal Publishers, NIH Molecular Libraries 68,406,957 records
Date Conducted	8 January 2018 (08.01.2018)
Search Logic:	
CID = chemical ID; SID = substance ID	

53944616 	54121467 
13080819 	493597 

Supplemental

Electronic Database Searched	Google patents
Files Searched	
Date Conducted	8 January 2018 (08.01.2018)
Search Logic:	

dipivefrin isoprenaline

About 214 results (0.34 seconds)

buccal isoprenaline pro-drug epinephrine sublingual anaphylaxis

About 274 results (0.44 seconds)

APPL. NO.: PCT/US2017/060761
APPLICANT: Iono Phama, LLC
FILED: 09 NOV 2017
TITLE: PHARMACEUTICAL FORMULATION FOR
SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG
THEREOF

Mail stop PCT, Commissioner of Patents
PO Box PCT
Alexandria, VA 22313-1450

Dear Sirs:

In response to the invitation to correct defects dated 20 NOV 2017, applicant has submitted a replacement sheet for the title heading the description and replacement drawings to correct the defects.

Respectfully Submitted
/Susan B Fentress/
Susan B. Fentress, Agent of record 31327
Veritay Group, IP
20 Dudley Suite 803
Memphis, TN 38103 USA
Telephone No. 901-371-6664
sfentress@veritaygroup.com
Dated: December 14, 2017

TITLE OF THE INVENTION: PHARMACEUTICAL FORMULATION FOR
SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG
THEREOF

Field of the Invention:

5 [0001] The present invention relates to pharmaceutical compositions for the treatment of
anaphylaxis formulated for rapid sublingual or buccal delivery, *i.e.*, compounds that dissolves
in the oral cavity. In one embodiment, the delivery vehicle is a rapidly dissolving film. The
films contain an epinephrine, or a novel epinephrine pro-drug formulated for the rapid
delivery of the drug to a patient in need of treatment, such as for example, a patient in need of
10 treatment for anaphylaxis.

Description of Related Art Including Information

[0002] Epinephrine is considered the primary choice for the treatment of anaphylaxis
which is a life threatening allergic reaction that might lead to death if untreated especially in
children. A study reported that one in every 10,000 children has an anaphylactic attack per
15 year. Epinephrine is the drug of choice for the treatment of anaphylactic shock in children
and adults. It is highly soluble in water, highly hydrophilic (log P -0.68) and can be oxidized
readily. Based on the current physicochemical properties of epinephrine, the only delivery
available in the market is intramuscular injection. The administration of proper therapeutic
agents, such as, epinephrine must be prompt. This is usually performed through the usage of
20 auto-injectors such as EPIPEN (MYLAN) or TWINJECT (SHIONOGI PHARMA, INC.) that
deliver the required dose in the mid-outer thigh either subcutaneously or intramuscularly.
However, many disadvantages are reported with the usage of these injectors such as high
cost, inaccurate administration, short half-life, patient's fear of needles, accidental injections,
and unavailability of a sufficient number of fixed prefilled doses.

25 [0003] These shortcomings affect greatly the patient compliance and adherence to
these injectors. In addition, it is very challenging to adjust the dose to different children ages
as there are only two premeasured fixed epinephrine doses (0.15 and 0.3 mg). Recent study
showed that only 17% of pediatric patients who have experienced anaphylactic symptoms
have used prescribed auto injectors. Other available delivery systems such as syringes or
30 inhalers are also underused due to their

1/9

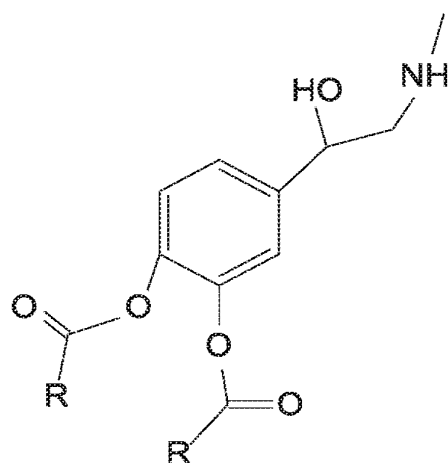


FIG. 1

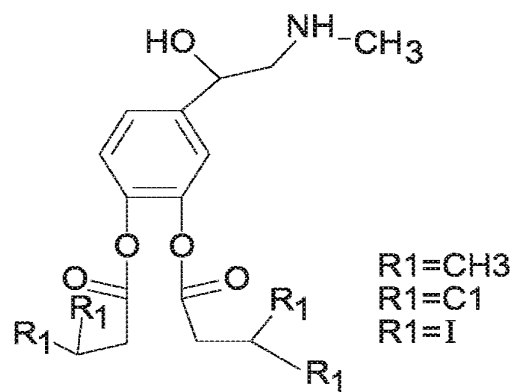
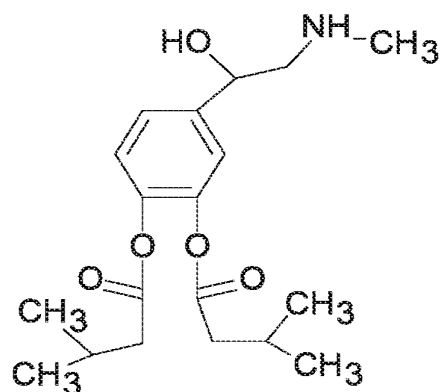


FIG. 2A



4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene
bis(3-methylbutanoate)
CLogP: 2.0114

FIG. 2B

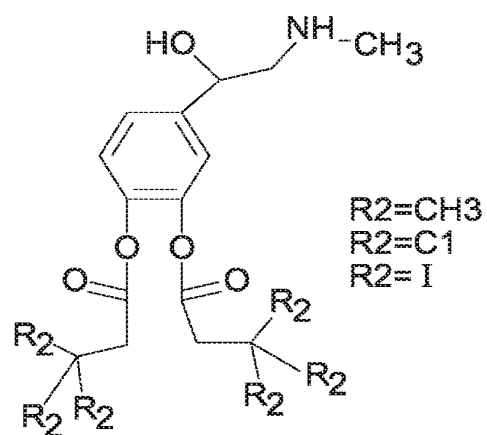
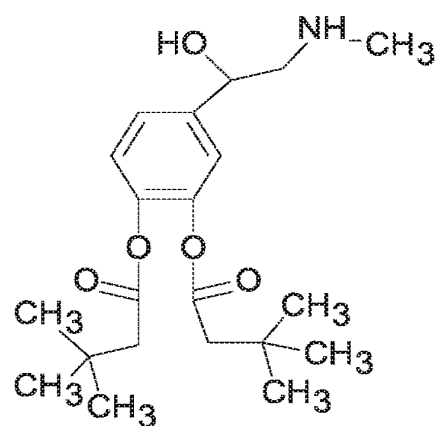


FIG. 2C



4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene
bis(3,3-dimethylbutanoate)
CLogP: 2.8094

FIG. 2D

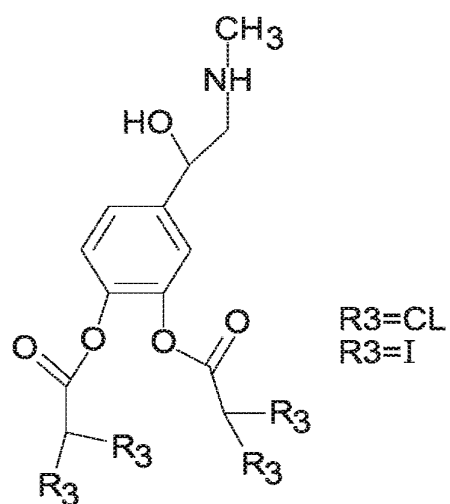
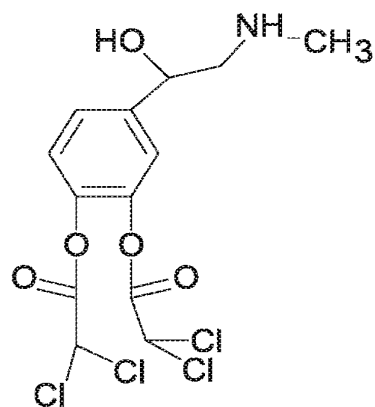


FIG. 3A



4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene
bis(2,2-dichloroacetate)
CLogP: 1.4494

FIG. 3B

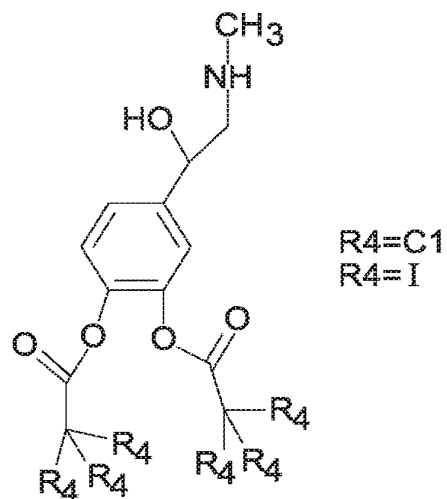
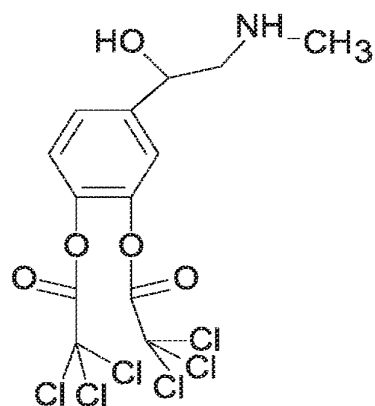


FIG. 3C



4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene
bis(2,2,2-trichloroacetate)
CLogP: 2.8554

FIG. 3D

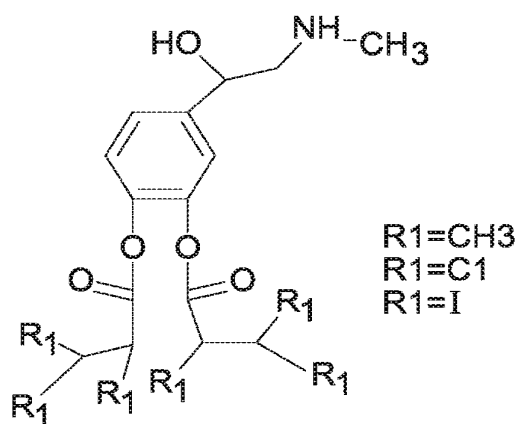
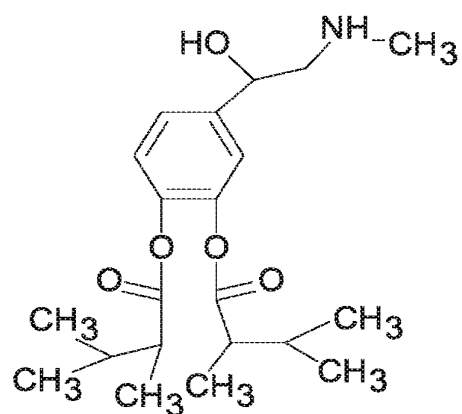


FIG. 4A



4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene
bis(2,3-dimethylbutanoate)
CLogP: 2.6294

FIG. 4B

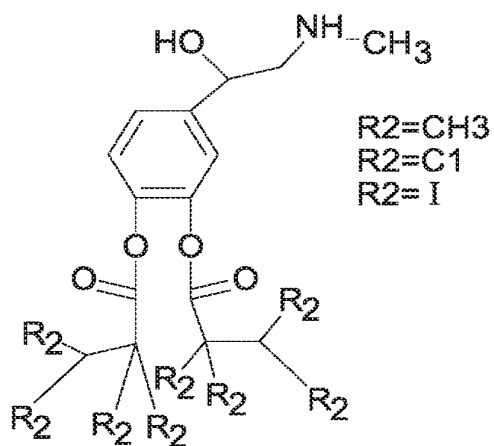
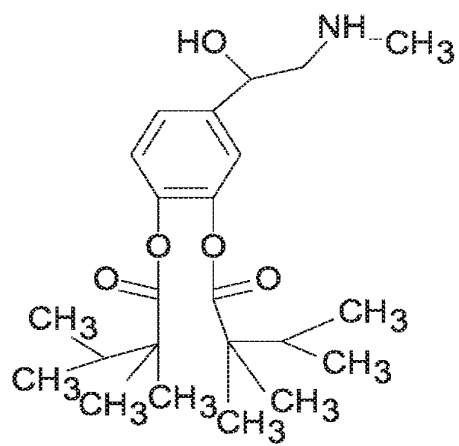


FIG. 4C



4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene
bis(2,3,3-trimethylbutanoate)
CLogP: 3.4274

FIG. 4D

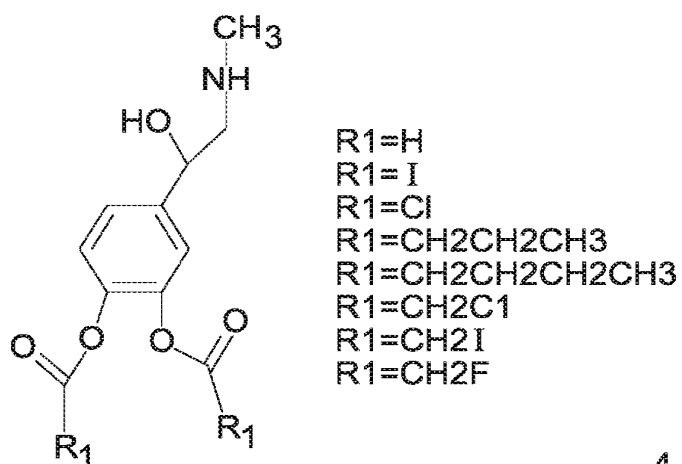
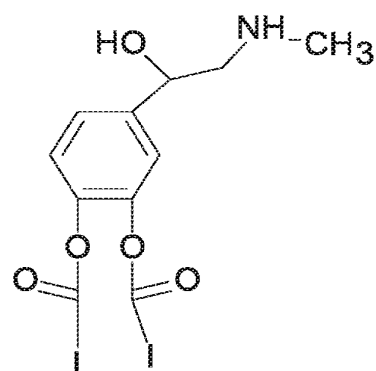
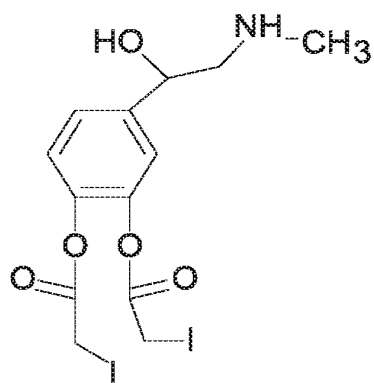


FIG. 5A



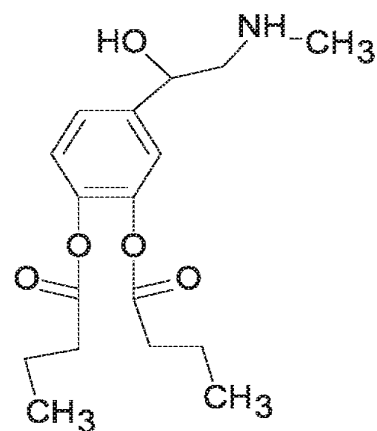
4-(1-hydroxy-2-(methylamino)ethyl)-1,
2-phenylene dicarboxylate
CLogP: 1.0854

FIG. 5B



4-(1-hydroxy-2-(methylamino)ethyl)-1,
2-phenylene bis(2-iodoacetate)
CLogP: 0.3834

FIG. 5C



4-(1-hydroxy-2-(methylamino)ethyl)-1,
2-phenylene dibutyrate
CLogP: 1.2134

FIG. 5D

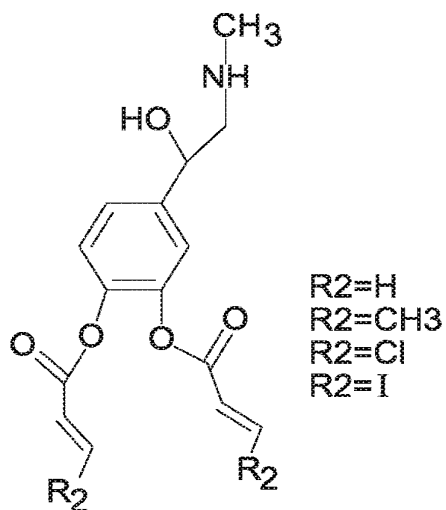
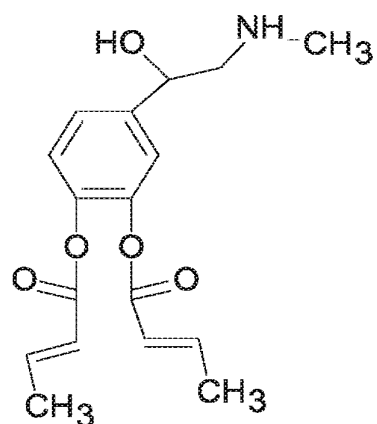


FIG. 6A



4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene
 (2E,2'E)-bis(but-2-enoate)
 CLogP: 1.2054

FIG. 6B

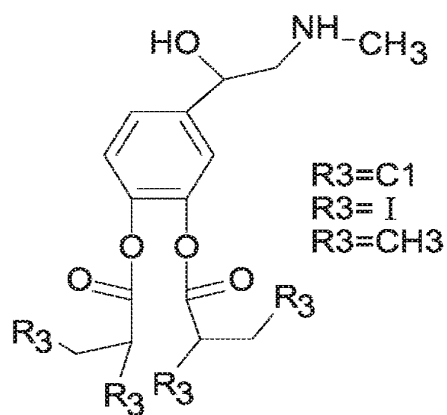
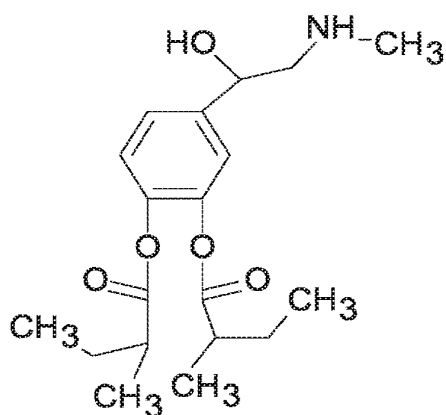
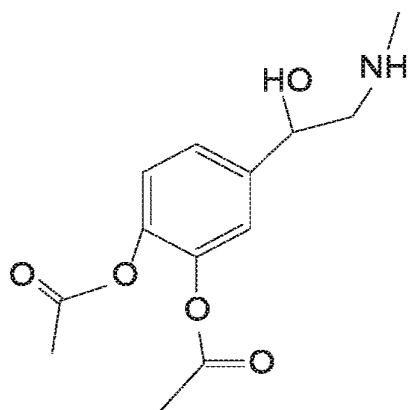


FIG. 6C



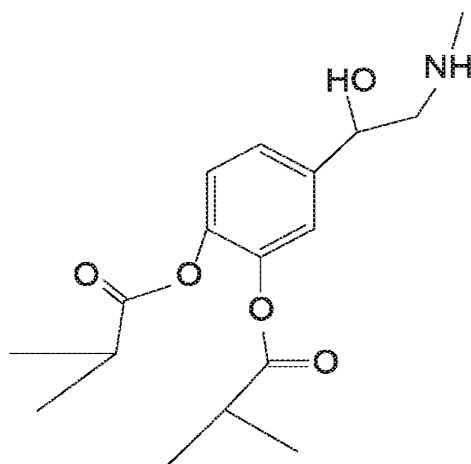
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene
 bis(2-methylbutanoate)
 CLogP: 1.8314

FIG. 6D



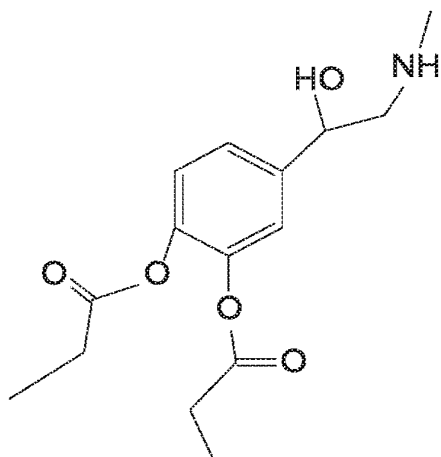
4-(1-hydroxy-2-(methylamino)ethyl)-1,
2-phenylene diacetate
CLogP: -0.9026

FIG. 7A



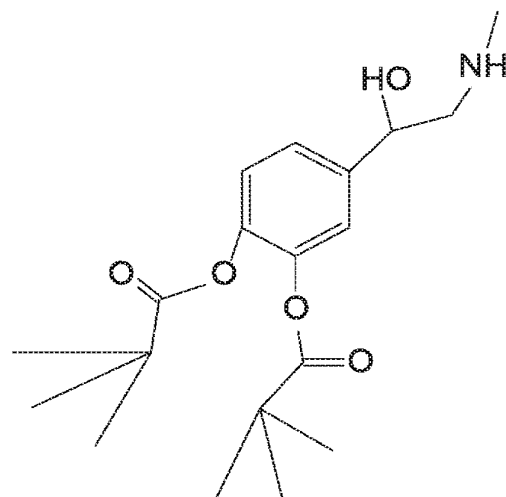
4-(1-hydroxy-2-(methylamino)ethyl)-1,
2-phenylene bis(2-methylpropanoate)
CLogP: 0.7733

FIG. 7B



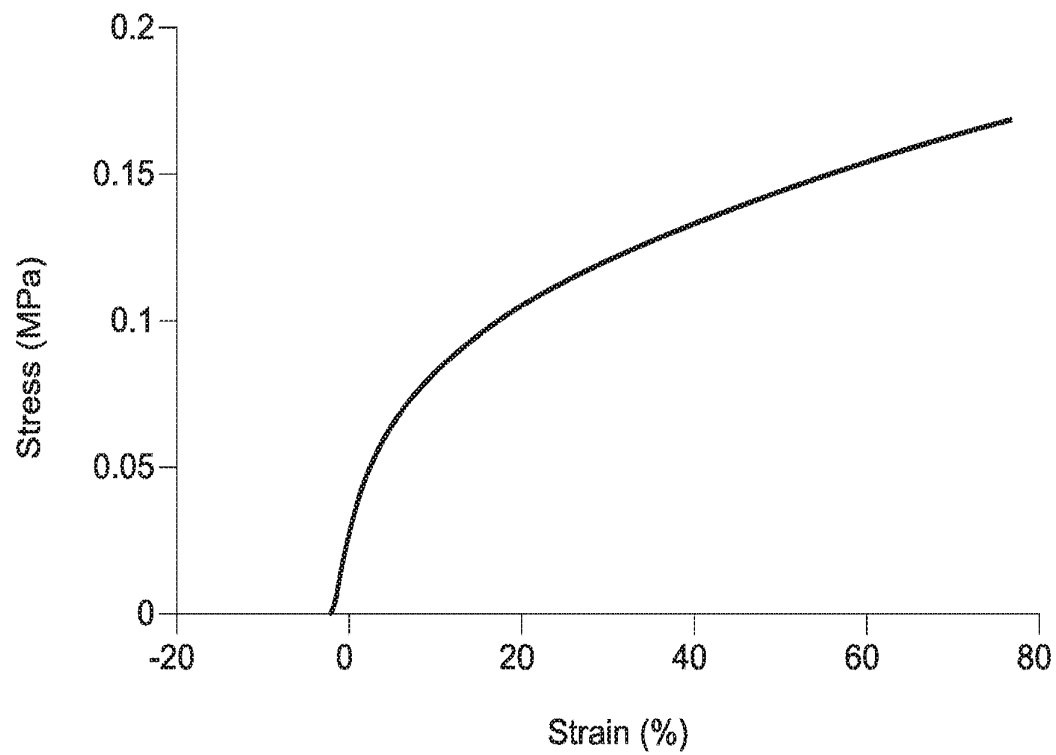
4-(1-hydroxy-2-(methylamino)ethyl)-1,
2-phenylene dipropanoate
CLogP: 0.1554

FIG. 7C



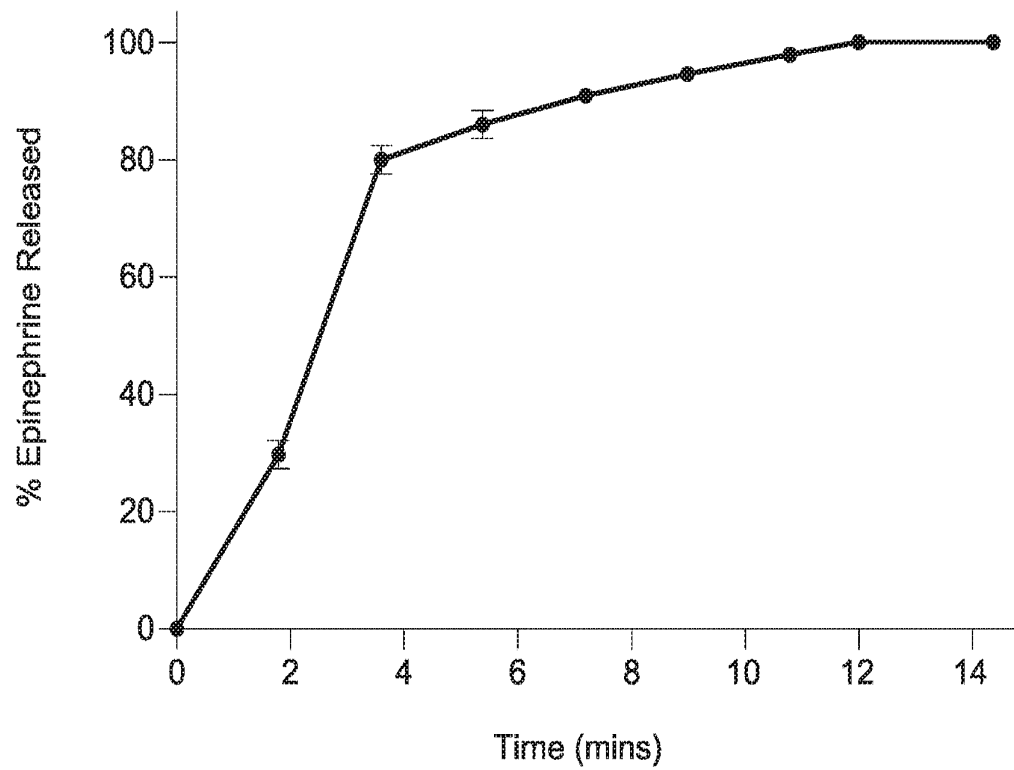
4-(1-hydroxy-2-(methylamino)ethyl)-1,
2-phenylene bis(2,2-dimethylpropanoate)
CLogP: 1.5714

FIG. 7D



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FIG. 8



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FIG. 9

Electronic Acknowledgement Receipt	
EFS ID:	31228370
Application Number:	
International Application Number:	PCT/US17/60761
Confirmation Number:	4463
Title of Invention:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF
First Named Inventor/Applicant Name:	IONO PHARMA, LLC
Customer Number:	76447
Correspondence Address:	Susan B. Fentress Veritay Group, IP 20 Dudley St Suite 803 Memphis TN 38103 US 9013716664 eofficeaction@appcoll.com
Filer:	Susan Bennett Fentress
Filer Authorized By:	
Attorney Docket Number:	24050.0001PCT
Receipt Date:	14-DEC-2017
Filing Date:	09-NOV-2017
Time Stamp:	13:56:28
Application Type:	International Application (PCT) for filing in the US receiving office
Patent Number:	

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	Misc. incoming letter from Applicant - IA	letteroftransmital.pdf	63627	no	1
			3bd1e0f04bbdbab4fd75d8f682e2812eea7f2acc		
Warnings:					
Information:					
2	Specification	replacmentspecpage.pdf	329449	no	1
			069dfc220d72c301157e12f121e15a5542683536		
Warnings:					
Information:					
3	Drawings-only black and white line drawings	ionofigsreplacment.pdf	233988	no	9
			07b575274d4e2a854735cb4d95985c8cb60170c6		
Warnings:					
Information:					
Total Files Size (in bytes):			627064		
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.					

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF RECEIPT OF SEARCH COPY

(PCT Rule 25.1)

To:

SUSAN B. FENTRESS
VERITAY GROUP, IP
20 DUDLEY SUITE 803
MEMPHIS, TENNESSEE 38103

Date of mailing
(day/month/year)

20 Nov 2017

Applicant's or agent's file reference

24050.0001PCT

IMPORTANT NOTIFICATION

International application No.

PCT/US2017/060761

International filing date (day/month/year)

09 Nov 2017

Priority date (day/month/year)

13 Nov 2016

Applicant

IONO PHARMA, LLC

1. Where the International Searching Authority and the receiving Office are not the same Office:

The applicant is hereby notified that the search copy of the international application was received by this International Searching Authority on the date indicated below.

Where the International Searching Authority and the receiving Office are the same Office:

The applicant is hereby notified that the search copy of the international application was received on the date indicated below.

09 Nov 2017

(date of receipt)

2. ☐ The search copy was accompanied by a nucleotide and/or amino acid sequence listing in the form of an Annex C/ST.25 text file under PCT Rule 13^{ter}.1(a) for the purposes of international search only.

3. ☐ The search copy contained a nucleotide and/or amino acid sequence listing in the form of an Annex C/ST.25 text file forming part of the international application as filed.

4. Time limit for establishment of international search report and written opinion of the International Searching Authority

The applicant is informed that the time limit for establishing the international search report and the written opinion of the International Searching Authority is three months from the date of receipt indicated above or nine months from the priority date, whichever time limit expires later (Rules 42.1 and 43^{bis}.1(a)).

A copy of this Notification has been sent to the International Bureau and, where the first sentence of paragraph 1 applies, to the receiving Office.

Name and mailing address of the ISA/

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

Facsimile No. 571-273-8300

Authorized officer

LaShonnah Tyson

Telephone No. 571-272-6628

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

PCT

NOTIFICATION CONCERNING PAYMENT OF PRESCRIBED FEES

(PCT Rules 12bis.1(c), 14, 15 and 16
and Administrative Instructions,
Sections 304, 323(b) and 707)

To: SUSAN B. FENTRESS VERITAY GROUP, IP 20 DUDLEY SUITE 803 MEMPHIS, TENNESSEE 38103		Date of mailing <i>(day/month/year)</i> 20 Nov 2017	
Applicant's or agent's file reference 24050.0001PCT		PAYMENT DUE see item 3 for time limits	
International application No. PCT/US2017/060761	International filing date/Date of receipt <i>(day/month/year)</i> 09 Nov 2017	Priority date <i>(day/month/year)</i> 13 Nov 2016	
Applicant IONO PHARMA, LLC			

1. The applicant is hereby notified that this receiving Office has received:

- ☒ **the payment** of all the prescribed fees, and
 ☐ **an overpayment**, which will be refunded in due course.
- ☐ **no or insufficient payment** of the prescribed fees and the applicant is hereby **invited to pay the balance due**, as summarized under item 2, within the time limit(s) indicated under item 3.

2. Fees and payment calculation:

2,514.00	2,514.00	0.00
Total fees payable	Amount paid	Balance

- ☐ The details of the calculation are given in the Annex.

3. Time limit(s) for payment and amount(s) payable (Rules 14.1, 15.3 and 16.1(f)):

- ☐ within ONE MONTH from the date of receipt of the international application (**for the transmittal fee (if any), the search fee and the international filing fee**). The amount payable for each fee is the amount applicable on the date of receipt of the international application.
- ☐ within 16 MONTHS from the priority date (only for the fee for priority document). The applicant's attention is drawn to the fact that the request made by the applicant under Rule 17.1(b) will be considered not to have been made unless the fee is paid within that time limit.

4. Additional observations *(if necessary)*:

- ☐ The search copy will not be transmitted to the International Searching Authority until the search fee is paid (therefore the start of the international search will be delayed) (Rule 23.1(a) and (b)).

Name and mailing address of the receiving Office Mail Stop PCT, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer LaShonnah Tyson Telephone No. 571-272-6628
---	---

**ANNEX TO FORM PCT/RO/102
CALCULATION OF THE PRESCRIBED FEES**

(If a reduced fee has been applied, the reduced amount is indicated.)

International application No.

PCT/US2017/060761

T Transmittal Fee

Prescribed amount: 120.00 **T**
 Amount paid: 120.00
 Balance: 0.00

☒ correct amount
☐ overpayment
☐ balance due

S Search Fee

Prescribed amount: 1,040.00 **S**
 Amount paid: 1,040.00
 Balance: 0.00

☒ correct amount
☐ overpayment
☐ balance due

I International Filing Fee

Prescribed amount:

Fixed amount for first 30 sheets: 1,264.00 **i1**

$\frac{6}{\text{Number of sheets in excess of 30}} \times \frac{15.00}{\text{Fee per sheet}} = 90.00$ **i2**

(excluding pages referred to in Section 707(a-bis))

Reduction where the international application is filed

(See PCT Fee tables <http://www.wipo.int/pct/en/fees.pdf>):

in electronic form, the request not being in character coded format 0.00 **r**

or

in electronic form, the request being in character coded format 0.00 **r**

or

in electronic form, the request, description, claims and abstract being in character coded format 0.00 **r**

Sub-total: 1,354.00 **i1+i2-r**

Applicants from certain States are entitled to a reduction of 90% of the international filing fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 10% of the sub-total entered at (i1+i2-r); (see Notes to the Fee Calculation Sheet as annexed to the Request Form, PCT/RO/101, for details):

. 1,354.00 **I**
 1,354.00
 0.00

Amount paid:
 Balance:

☒ correct amount
☐ overpayment
☐ balance due

P Fee for Priority Document

Prescribed amount: 0.00 **P**
 Amount paid: 0.00
 Balance: 0.00

☒ correct amount
☐ overpayment
☐ balance due

ES Fee for Earlier Search Documents

Prescribed amount: 0.00 **ES**
 Amount paid: 0.00
 Balance: 0.00

☐ correct amount
☐ overpayment
☐ balance due

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

PCT

To:
SUSAN B. FENTRESS
VERITAY GROUP, IP
20 DUDLEY SUITE 803
MEMPHIS, TENNESSEE 38103

NOTIFICATION OF THE INTERNATIONAL APPLICATION NUMBER AND OF THE INTERNATIONAL FILING DATE

(PCT Rule 20.2(c))

Confirmation No: 4463

Date of mailing
(day/month/year) 20 Nov 2017

Applicant's or agent's file reference
24050.0001PCT

IMPORTANT NOTIFICATION

International application No.
PCT/US2017/060761

International filing date (day/month/year)
09 Nov 2017

Priority date (day/month/year)
13 Nov 2016

Applicant
IONO PHARMA, LLC

Title of the invention
PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE OR A PRO-DRUG THEREOF

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.

2. The applicant is further notified that the record copy of the international application:

- ☒ was transmitted to the International Bureau on 20 Nov 2017 .
- ☐ has not yet been transmitted to the International Bureau for the reason indicated below and a copy of this notification has been sent to the International Bureau*:
- ☐ because the necessary national security clearance has not yet been obtained.
- ☐ because (reason to be specified):

* The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c)).

3. FOREIGN TRANSMITTAL LICENSE INFORMATION

Completed by: LT

- ☐ Additional license for foreign transmittal not required. This subject matter is covered by a license already granted or the equivalent U.S. national application. Refer to that license for information concerning its scope.
- ☐ License for foreign transmittal not required. 37 CFR. 5.11(e)(1) or 37 CFR 5.11(e)(2). However, a license may be required for additional subject matter. See 37 CFR 5.15(b).
- ☒ Foreign transmittal license granted. 35 U.S.C. 184; 37 CFR 5.11 on 17 Nov 2017 :
(date)
- ☐ 37 CFR 5.15(a) ☒ 37 CFR 5.15(b)

Name and mailing address of the receiving Office
Mail Stop PCT, Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450
Facsimile No. 571-273-8300

Authorized officer
LaShonnah Tyson
Telephone No. 571-272-6628

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

PCT

INVITATION TO CORRECT DEFECTS IN THE INTERNATIONAL APPLICATION

(PCT Articles 3(4)(i) and 14(1) and Rule 26)

To: SUSAN B. FENTRESS VERITAY GROUP, IP 20 DUDLEY SUITE 803 MEMPHIS, TENNESSEE 38103	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 2px;">Date of mailing (day/month/year)</td> <td style="width: 50%; padding: 2px;">20 Nov 2017</td> </tr> </table>	Date of mailing (day/month/year)	20 Nov 2017
Date of mailing (day/month/year)	20 Nov 2017		
Applicant's or agent's file reference 24050.0001PCT	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 2px;">REPLY DUE</td> <td style="width: 50%; padding: 2px;">within TWO MONTHS from the above date of mailing</td> </tr> </table>	REPLY DUE	within TWO MONTHS from the above date of mailing
REPLY DUE	within TWO MONTHS from the above date of mailing		
International application No. PCT/US2017/060761	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 2px;">International filing date (day/month/year)</td> <td style="width: 50%; padding: 2px;">09 Nov 2017</td> </tr> </table>	International filing date (day/month/year)	09 Nov 2017
International filing date (day/month/year)	09 Nov 2017		
Applicant IONO PHARMA, LLC			

1. ☒ The applicant is hereby **invited**, within the time limit indicated above, to correct **in the international application as filed**, the defects specified on the attached:

☒ Annex A
☐ Annex B1 (*text matter of the international application as filed*)
☒ Annex C1 (*drawings of the international application as filed*)

2. ☐ The applicant is hereby **invited**, within the time limit indicated above, to correct, **in the translation of the international application** furnished under Rule 12.3 or 12.4, the defects specified on the attached:

☐ Annex A
☐ Annex B2 (*text matter of the translation of the international application*)
☐ Annex C2 (*drawings of the translation of the international application*)

Additional observations (if necessary):

HOW TO CORRECT THE DEFECTS?

Except where the defect is in the request, any correction must be submitted by filing a replacement sheet embodying the correction and a letter accompanying the replacement sheet, which shall draw attention to the difference between the replaced sheet and the replacement sheet. For a defect in the request, a correction may simply be stated in a letter if it is of such nature that the correction can be transferred clearly onto the request record copy (Rule 26.4).

ATTENTION

Failure to correct the defects will result in the international application being considered withdrawn by this receiving Office (see Rule 26.5 for further details).

A copy of this Invitation and any attachments has been sent to the International Bureau

☒ and the International Searching Authority.

Name and mailing address of the receiving Office Mail Stop PCT, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer LaShonnah Tyson Telephone No. 571-272-6628
---	---

The receiving Office has found the following defects in the international application as filed:

1. As to the **signature** of the international application (Rules 4.15, 26.2bis(a) and 90.4), the request:
- ☐ is not signed by the applicant or, if there is more than one applicant, by at least one of them*.
 - ☐ is signed by what appears to be an agent/common representative, but the international application is not accompanied by a power of attorney signed by at least one of the applicants*.
 - ☐ other (*specify*):

* The applicant's attention is drawn to the fact that the national law applied by each designated Office may require, in connection with the processing of the international application in the national phase, that the applicant furnish the confirmation of the international application by the signature of any applicant for the designated State who has not signed the request (Rule 51bis.1(a)(vi)).

2. As to the indications concerning the **applicant*** who is entitled, according to Rule 19.1, to file the international application with the receiving Office, the request (Rules 4.4, 4.5 and 26.2bis(b)):
- ☐ does not properly indicate the applicant's name (*specify*):
 - ☐ does not indicate the applicant's address.
 - ☐ does not properly indicate the applicant's address (*specify*):
 - ☐ does not indicate the applicant's nationality.
 - ☐ does not indicate the applicant's residence.

☐ Further observations about indications concerning other applicants (if applicable):

* Although Rules 4.4 and 4.5 require indications concerning the applicant, or if there are several applicants, of each of them for the purposes of Article 14(1)(a)(ii), if there is more than one applicant, it shall be sufficient that the indications required under Rule 4.5(a)(ii) and (iii) be provided in respect of one of them who is entitled according to Rule 19.1 to file the international application with the receiving Office (Rule 26.2bis(b)).

However, the applicant's attention is drawn to the fact that the national law applied by each designated Office may require, in connection with the processing of the international application in the national phase, that the applicant furnish any missing indication required under Rule 4.5(a)(ii) and (iii) in respect of any applicant for the designated State (Rule 51bis.1(a)(vii)).

3. As to the **language** of certain elements of the international application, other than the description and claims (Rules 12.1(c) and 26.3ter(a) and (c)):
- ☐ the **request** is not in a language of publication accepted by this receiving Office; (the) language(s) accepted by this receiving Office is/are:
 - ☐ the **text matter of the drawings** is not in the language in which the international application is to be published, which is:
 - ☐ the **abstract** is not in the language in which the international application is to be published, which is:

4. The **title** of the invention:
- ☐ is not indicated in Box No. I of the request (Rule 4.1(a)).
 - ☐ is not indicated at the top of the first sheet of the description (Rule 5.1(a)).
 - ☒ as appearing in Box No. I of the request is not identical with the title heading the description (Rule 5.1(a)).

5. As to the **abstract** (Rules 8 and 26.1):
- ☐ the international application does not contain an abstract.

This receiving Office has found that, with regard to the presentation of the **text matter of the international application as filed**, the physical requirements are not complied with to the extent that compliance therewith is necessary for:

1. ☐ reasonably uniform international publication (Rules 11 and 26.3(a)(i)) (*defects to be specified*):

	Request	Description	Claims	Abstract
a. ☐ the sheets do not admit of direct reproduction	☐	☐	☐	☐
b. ☐ the element does not commence on a new sheet	☐	☐	☐	☐
c. ☐ sheets are not free from creases, cracks, folds	☐	☐	☐	☐
d. ☐ sheets are not used in the upright position	☐	☐	☐	☐
e. ☐ one side of the sheets is not left unused	☐	☐	☐	☐
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g. ☐ the sheets are not connected as prescribed (Rule 11.4(b))	☐	☐	☐	☐
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j. ☐ the file reference number indicated on the sheets does not appear in the left-hand corner of the sheets, within 1.5 cm of the top of the sheets		☐	☐	☐
k. ☐ the file reference number exceeds the maximum of 12 characters	☐	☐	☐	☐
l. ☐ the sheets of the description, claims and abstract are not numbered in consecutive Arabic numerals		☐	☐	☐
m. ☐ the sheet numbers are not centered at the top or bottom of the sheets	☐	☐	☐	☐
n. ☐ the sheet numbers are in the margin (see i. above for the size of the margins)		☐	☐	☐
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r. ☐ the text matter on the sheets is not in dark, indelible color	☐	☐	☐	☐
s. ☐ the element contains drawings	☐	☐	☐	☐
t. ☐ the sheets contain alterations/overwritings/interlineations/too many erasures	☐	☐	☐	☐
u. ☐ the sheets contain photocopy marks	☐	☐	☐	☐

2. ☐ satisfactory reproduction (Rules 11 and 26.3(b)(i))

Further observations (*if necessary*):

This receiving Office has found that, with regard to the presentation of the **drawings of the international application as filed**, the physical requirements are not complied with to the extent that compliance therewith is necessary for:

1. ☒ reasonably uniform international publication (Rules 11 and 26.3(a)(i)) (*defects to be specified*):

Sheets containing drawings:

- a. ☐ the sheets do not admit of direct reproduction
- b. ☐ the sheets are not free from creases, cracks, folds
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- d. ☐ the paper of the sheets is not flexible/strong/white/smooth/non-shiny/durable
- e. ☐ the drawings do not commence on a new sheet
- f. ☐ the sheets are not connected as prescribed (Rule 11.4(b))
- g. ☐ the sheets are not A4 size (29.7cm x 21cm)
- h. ☐ the minimum margins on the sheets are not as prescribed (top: 2.5cm; left side: 2.5cm; right side: 1.5cm; bottom: 1cm)
- i. ☐ the file reference number indicated on the sheets does not appear in the left-hand corner of the sheets, within 1.5m of the top of the sheets
- j. ☐ the file reference number exceeds the maximum of 12 characters
- k. ☐ the sheets are not free from frames around usable or used surfaces
- l. ☒ the sheets are not numbered in consecutive Arabic numerals (e.g. 1/3, 2/3, 3/3)
- m. ☐ the sheet numbers are not centered at the top or bottom of the sheets
- n. ☐ the sheet numbers are in the margin (see h. above for the size of the margins)
- o. ☐ the sheets contain alterations/overwritings/interlineations/too many erasures
- p. ☐ the sheets contain photocopy marks

Drawings (Rule 11.13):

- a. ☐ do not admit of direct reproduction
- b. ☐ contain unnecessary text matter
- c. ☐ contain words so placed as to prevent translation without interference with lines thereof
- d. ☒ are not executed in durable black color; the lines are not uniformly thick and well-defined
- e. ☐ contain cross-sections not properly hatched
- f. ☒ would not be properly distinguishable in reduced reproduction
- g. ☐ contain scales not represented graphically
- h. ☒ contain numbers, letters and reference lines lacking simplicity and clarity
- i. ☐ contain lines drafted without the aid of drafting instruments
- j. ☐ contain disproportionate elements of a figure not necessary for clarity
- k. ☒ contain numbers and letters of height less than 0.32 cm
- l. ☐ contain letters not conforming to the Latin, and where customary, Greek alphabets
- m. ☐ contain figures on two or more sheets which form a single complete figure but which are not able to be assembled without concealing parts thereof
- n. ☐ contain figures which are not properly arranged and clearly separated
- o. ☐ contain different figures not numbered in consecutive Arabic numerals
- p. ☐ contain different figures not numbered independently of the numbering of the sheets
- q. ☐ are not restricted to reference signs mentioned in the description
- r. ☐ do not contain reference signs that are mentioned in the description
- s. ☐ contain the same feature denoted by different reference signs
- t. ☐ are not arranged in an upright position, clearly separated from one another
- u. ☐ are not presented sideways with the top of the figures at the left side of the sheets

2. ☐ satisfactory reproduction (Rules 11 and 26.3(b)(i))

Further observations (*if necessary*):

TITLE OF THE INVENTION: PHARMACEUTICAL FORMULATION FOR
SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE

Field of the Invention:

[0001] The present invention relates to pharmaceutical compositions for the treatment
5 of anaphylaxis formulated for rapid sublingual or buccal delivery, *i.e.*, compounds that
dissolves in the oral cavity. In one embodiment, the delivery vehicle is a rapidly dissolving
film. The films contain an epinephrine, or a novel epinephrine pro-drug formulated for the
rapid delivery of the drug to a patient in need of treatment, such as for example, a patient in
need of treatment for anaphylaxis.

10 Description of Related Art Including Information

[0002] Epinephrine is considered the primary choice for the treatment of
anaphylaxis which is a life threatening allergic reaction that might lead to death if
untreated especially in children. A study reported that one in every 10,000 children
has an anaphylactic attack per year. Epinephrine is the drug of choice for the
15 treatment of anaphylactic shock in children and adults. It is highly soluble in water,
highly hydrophilic (log P -0.68) and can be oxidized readily. Based on the current
physicochemical properties of epinephrine, the only delivery available in the market is
intramuscular injection. The administration of proper therapeutic agents, such as,
epinephrine must be prompt. This is usually performed through the usage of auto-
20 injectors such as EPIPEN (MYLAN) or TWINJECT (SHIONOGI PHARMA, INC.)
that deliver the required dose in the mid-outer thigh either subcutaneously or
intramuscularly. However, many disadvantages are reported with the usage of these
injectors such as high cost, inaccurate administration, short half-life, patient's fear of
needles, accidental injections, and unavailability of a sufficient number of fixed
25 prefilled doses.

[0003] These shortcomings affect greatly the patient compliance and adherence
to these injectors. In addition, it is very challenging to adjust the dose to different
children ages as there are only two premeasured fixed epinephrine doses (0.15 and
0.3 mg). Recent study showed that only 17% of pediatric patients who have
30 experienced anaphylactic symptoms have used prescribed auto injectors. Other
available delivery systems such as syringes or inhalers are also underused due to their

lack of rapid and accurate dosing. Therefore, there is growing interest in the development of an alternative non-invasive delivery system that can easily provide accurate doses of epinephrine.

[0004] Anwar A. Hussain and James E. Truelove were granted patents related to the synthesis of novel esters of [(methylamino)methyl] benzyl alcohol which is epinephrine. The purpose of the Hussain's *et. al.* invention was to develop a prodrug of epinephrine HCl with superior lipid solubility to enhance penetration through the cornea of the eye to treat glaucoma. Hussain *et. al.* synthesized four different prodrugs for this purpose (see structures 7A, 7B, 7C, 7D). These four molecules were tested in human, rabbit and horse plasmas and found that 3, 4 - dipivalyl- α -[(methylamino) methyl] benzyl alcohol hydrochloride (structure 7D) shows the best penetration profile into the eye. Hussain's *et. al.* didn't evaluate the log P of these molecules nor did they evaluate the sublingual or buccal permeability or absorption. Their main focus was to develop a prodrug specifically for the eye. Since the initial publishing of Anwar's patents in 1974 and 1975, no one has followed up or even published any new data on structures 7A, 7B, and 7C. Dipivalyl- α -[(methylamino)] benzyl alcohol hydrochloride (7D) was further developed into a drug delivery system for glaucoma (Dipivefrin or Propine). Hussain and Truelove selected this prodrug for further development because of several physicochemical and biological qualities. The first quality was estimating the delay before onset of seizure for this prodrug was about 8-10 minutes, the second quality was the rate of hydrolysis expressed as $t_{1/2}$ in human plasma was about 1,800 seconds and the third quality was the $t_{1/2}$ hydrolysis and oxidation *in vitro* was 700 and 300 days respectively. In a separate publication (Journal of Pharmaceutical Sciences, Vol. 65, No. 10, October 1976, p: 1510-1512), Hussain *et. al.* shared the graphs for the *in vitro* hydrolysis of this particular prodrug using rabbit eye homogenate and compared the hydrolysis among three different plasmas (human, rabbit, rabbit eye homogenate).

[0005] Films that incorporate a pharmaceutically active ingredient are disclosed in U.S. Pat. No. 4,136,145 to Fuchs, *et al.* ("Fuchs"). These films can be formed into a sheet, dried and then cut into individual doses. Examples of specific uses disclosed by Fuchs include application of the films to mucosal membrane areas of the body, including the mouth, rectal, vaginal, nasal and ear areas. A drug delivery vehicle must provide a high level of uniformity with respect to the dosage delivered.

BRIEF SUMMARY OF THE INVENTION

[0006] This invention relates to pharmaceutical compositions made by modifying the physicochemical properties of epinephrine in order to enhance its permeability through biological membranes (sublingual and buccal membranes). Several prodrugs of epinephrine are shown by modifying the two hydroxyl (phenolic) groups in positions 3 and 4 on the benzene ring, by chemically reacting the two groups with several acid moieties to form an ester bond with different alkyl chains. The addition of an alkyl group will enhance the lipophilicity of epinephrine (increase log P) and will consequently increase its permeability through the biological membranes (sublingual and buccal tissues in the oral cavity). The 3 and 4 positions represent meta and para locations with respect to the carbon in position 1 on the phenolic ring of epinephrine. Once the prodrug penetrates biological membranes (sublingual and buccal), the biological enzyme carboxyesterase will degrade the ester bond and release epinephrine for therapeutic activity. A prodrug is a biologically inactive compound that can be metabolized in the body to produce a drug. One characteristic of the selected prodrug compounds is fast hydrolysis in plasma.

[0007] In another embodiment, the subject matter includes a method to deliver epinephrine involving the steps of: providing epinephrine in a unit dosage form formulated for sublingual or buccal administration, wherein the unit dosage form is a rapidly dissolving film and the unit dosage form provides the pharmaceutical pro-drug of epinephrine. More specifically, this method involves providing pharmaceutical pro-drug compositions epinephrine in a unit dosage form to patients in need of anaphylactic treatment.

[0008] The subject matter includes a pharmaceutical formulation made of: a compound as depicted in a formula 2A and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R₁ is selected for the group consisting of: CH₃, CL and I. A pharmaceutical formulation made of: a compound as depicted in a formula 2B and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R₂ is selected for the group consisting of: CL and I. A pharmaceutical formulation made of: a compound as depicted in a formula 3C and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R₄ is selected for the group consisting of: CL and I. A pharmaceutical formulation made of: a compound as depicted in a formula 3D and a pharmaceutically acceptable carrier or a

pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: CH_3 , Cl and I . A pharmaceutical formulation made of: a compound as depicted in a formula 4E and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_2 is selected for the group consisting of: CH_3 , Cl and I . A
5 pharmaceutical formulation made of: a compound as depicted in a formula 4F and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group consisting of: CH_3 , Cl and I . A pharmaceutical formulation made of: a compound as depicted in a formula 5G and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_1 is selected for the group
10 consisting of: H , I , Cl , $CH_2CH_2CH_3$ & $CH_2CH_2CH_2CH_3$, CH_2Cl , CH_2I and CH_2F . A pharmaceutical formulation made of: a compound as depicted in a formula 6H and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R_2 is selected for the group consisting of: H , CH_3 , Cl and I . A pharmaceutical formulation made of: a compound as depicted in a formula 6I and a pharmaceutically
15 acceptable carrier or a pharmaceutically acceptable excipient, wherein R_3 is selected for the group consisting of: Cl , I and CH_3 . The compound is formulated in a unit dosage form as a rapidly dissolving film. The invention further provides use of the pharmaceutical formulation in a patient in need of anaphylactic treatment.

BRIEF DESCRIPTION OF SEVERAL VIEWS OF THE DRAWING(S):

20 [00010] The invention can be best understood by those having ordinary skill in the art by reference to the following detailed description when considered in conjunction with the accompanying drawings in which:

[00011] FIG. 1 shows the generic chemical structure of a biologically inactive compound of this invention.

25 [00012] FIG. 2 shows exemplary compounds of the present invention.

[00013] FIG. 3 shows exemplary compounds of the present invention.

[00014] FIG. 4 shows exemplary compounds of the present invention.

[00015] FIG. 5 shows exemplary compounds of the present invention.

[00016] FIG. 6 shows exemplary compounds of the present invention.

30 [00017] FIG. 7 shows Anwar A. Hussain and James E. Truelove compounds.

[00018] FIG. 8 shows a stress-strain profile of the optimized epinephrine fast dissolving film.

[00019] FIG. 9 shows a release profile of the epinephrine from the optimized fast dissolving film in 500 ml Simulated Saliva at 37 °C.

DETAILED DESCRIPTION OF THE INVENTION:

[00020] The present invention may be understood more readily by reference to the following detailed description of the invention. It is to be understood that this invention is not limited to the specific devices, methods, conditions or parameters described herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of the claimed invention. Also, as used in the specification including the appended claims, the singular forms "a," "an," and "the" include the plural, and reference to a particular numerical value includes at least that particular value, unless the context clearly dictates otherwise. Ranges may be expressed herein as from "about" or "approximately" one particular value and/or to "about" or "approximately" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment.

[00021] These and other aspects, features and advantages of the invention will be understood with reference to the detailed description herein, and will be realized by means of the various elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description of the invention are exemplary and explanatory of preferred embodiments of the inventions, and are not restrictive of the invention as claimed. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Reference will now be made in detail to the presently preferred embodiments of the invention, examples of which are illustrated in the accompanying drawings. Throughout the following detailed description, the same reference numerals refer to the same elements in all figures.

[00022] The present invention provides a novel biologically inactive compound that can be metabolized in the body to produce a drug that has the biological activity of epinephrine. Epinephrine acts on nearly all body tissues. Its actions vary by tissue type and tissue expression of adrenergic receptors. For example, high levels of

epinephrine cause smooth muscle relaxation in the airways but cause contraction of the smooth muscle that lines most arterioles. The present subject matter relates to modifying the physicochemical properties of epinephrine in order to enhance its permeability through biological membranes (sublingual and buccal membranes. FIG. 1 shows the generic chemical structure of a biologically inactive compound of this invention, while Table 1 shows exemplary prodrugs of epinephrine made by modifying the two hydroxyl (phenolic) groups in positions 3 and 4 on the benzene ring along with Log P values or a pharmaceutically acceptable salt thereof. The prodrugs of epinephrine preferably have a Log P value in the range of about 0.5-6.0, and more preferably between 1.0-5.0. This range was listed as a table of marketed sublingual tablets and films in Ashraf et. al "Considerations in developing sublingual tablets-An overview", Pharmaceutical Technology, 2014, 38(11). Log P is the logarithmic value of the ratio of two concentrations of a compound in a mixture of two immiscible liquids such as water and octanol at equilibrium. Log P values can be calculated mathematically by the use of PERCEPTA PLATFORM software (ACD Labs, Toronto, Ontario, Canada).

TABLE 1

R	Log P	R	Log P
R= CHCH ₂	-0.20	R= CH ₂ COCH ₃	-1.44
R= CHCHCH ₃	+0.84	R= CH ₂ COCL	-0.21
R= CHCH ₂ CL	+0.05	R= CH ₂ COI	+1.10
R= CHCH ₂ I	+1.36	R= CH ₂ OCH ₃	-1.29
R= CHCLCH ₂ CL	+0.78	R= CHICH ₃	+1.82
R= CHICH ₂ I	+4.0	R= CCLCLCH ₃	+1.36
R= CHCH ₂ CH ₂ CH ₃	+1.85	R= CH ₂ CHCH ₃ CH ₃	+1.85
R= CH ₂ CCH ₃ CH ₃ CH ₃	+2.55	R= CH ₂ CHCLCL	+1.06
R= CH ₂ CH ₂ CH ₃	+0.8	R= CH ₂ CHII	+4.09
R= CH ₂ CL	-0.51	R= CH ₂ CCLCLCL	+2.97
R= CH ₂ I	+1.12	R= CH ₂ CHII	+7.68
R= CH ₂ F	-0.85	R= CHCLCL	+0.66
R= CHII	+8.13	R= CHII	+4.03
R= CL	+1.24	R= CCH ₃ CH ₃ CHCH ₃ CH ₃	+3.24
R= I	+2.55	R= NHCCCH ₃ CH ₃ CH ₃	+1.63
R= F	+0.72	R= NHCHCH ₃ CH ₃	+1.28
R= CHCH ₃ CHCH ₃ CH ₃	+2.54	R= NHCH ₂ CH ₃	+0.93
R= CHCLCHCLCL	+2.08	R= NHCH ₃	+0.40

R= CHICHII	+7.09	R= SCH ₃	+1.92
R= CHFCHFF	+0.80	R= SCH ₂ CH ₃	+2.45
R= CH ₂ CHCH ₂	+0.07	R= SCHCH ₃ CH ₃	+2.80
R= CCLCLCHCLCL	+4.18	R= SCCH ₃ CH ₃ CH ₃	+3.15
R= CIICHII	+11.29	R= CH ₂ C ₆ H ₅	+2.52
R= CCLCLCL	+2.90	R= C ₆ H ₅	+3.10

[00023] A pro-drug is a derivative of epinephrine selected for fast permeability through sublingual and buccal membranes (ie a compound that dissolves in the oral cavity) and fast hydrolysis (half-life $t_{1/2}$ range from 1-6 minutes) by plasma enzymes to form epinephrine when delivered. These characteristics are physical properties of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film. Now referring to FIG. 2, derivatives of epinephrine are shown. Structure 2A represents di-ester derivatives of epinephrine where the R₁ can be a short alkyl chain of CH₃, CH₂CH₃, CH₂CH₂CH₃, or CH₂CH₂CH₂CH₃, CL or I. A representative molecule of this group compounds is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(3-methylbutanoate) having a CLogP: 2.0114. Structure 2B represents derivatives of epinephrine where R₂ = CH₃, CL or I. A representative molecule of this group of compounds is 4-(1-hydroxy-2-(methylamino) ethyl)-1,2-phenylene bis(3,3-dimethylbutanoate) having a CLogP: 2.8094. Adding H, CH₃, Cl or I change the Log P of the prodrug and adds a non-toxic moiety to the molecule. The rate of hydrolysis of each ester can increase or decrease depending on how the atom in position R₄ influences the ester group

[00024] Now referring to FIG. 3, derivatives of epinephrine are shown. Structure 3C represents a derivative of epinephrine where R₃ = Cl or I. A representative molecule of the group is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dichloroacetate) having a CLogP: 1.4494. Structure 3D represents a derivative of epinephrine where R₄ = Cl or I. A representative molecule of the groups is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2,2-trichloroacetate) having a CLogP: 2.8554. The molecule that shows fast permeability through the sublingual and buccal membranes and fast hydrolysis by the enzyme is a physical property of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film.

[00025] Now referring to FIG. 4 derivatives of epinephrine are shown. Structure 4E represents a derivative of epinephrine where R₁ = CH₃, CL or I. A representative molecule is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,3-

dimethylbutanoate) having a CLogP: 2.6294. Structure 4F represents a derivative of epinephrine where $R_2 = \text{CH}_3$, CL or I. A representative molecule is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2,3-trimethylbutanoate) having a CLogP: 3.4274. The molecule that shows fast permeability through the sublingual and buccal membranes and fast hydrolysis by the enzyme is a physical property of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film.

[00026] Now referring to FIG. 5, derivatives of epinephrine are shown.

Structure G represents a derivative epinephrine where $R_1 = \text{H}$, I, CL, $\text{CH}_2\text{CH}_2\text{CH}_3$ & $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, CH_2Cl , CH_2I or CH_2F . Representative molecules are: 5G 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dicarboniodidate having a Clog: 1.084; 5G' 4-(1-hydroxy-2-(methylamino-ethyl)-1,2-phenylene bis (2-iodoacetate) having a CLogP: 0.3834 and Structure 5G'' 4-(1-hydroxy-2-methylamino)ethyl)-1,2-phenylene dibutyrate) having a CLogP: 1.2134.

[00027] Now referring to FIG. 6, a derivative epinephrine is shown. Structure

H6 represents a derivative of epinephrine where $R_2 = \text{H}$, CH_3 , CL or I. A representative example is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene (2E,2'E)-bis(but-2-enoate) having a CLogP: 1.2054. Structure I6 represents a derivative of epinephrine where $R_3 = \text{CL}$, I or CH_3 . A representative example is: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2-methylbutanoate) having a CLogP: 1.8314.

[00028] Now referring to FIG. 7, the compounds of the invention as shown in US patent 3,809,714 and US patent 3,825,583 hereby incorporated by reference.

Representative molecules include: 7A 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene diacetate having a DLogP: -0.9026. 7B 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate) having a CLogP: 0.773300. 7C 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate having a CLogP: 0.1554. 7D 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate) having a CLogP: 1.5714. If these molecules show fast permeability through the sublingual and buccal membranes and fast hydrolysis by the enzyme (half-life 1-6 minutes) a physical property of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film. The subject matter includes: uses of a pharmaceutical formulation in a patient in need of anaphylactic treatment, wherein the pharmaceutical formulation is made of a compound selected from the group consisting of: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene di-acetate; 4-(1-hydroxy-

2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate), and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient. A pharmaceutical formulation made of a compound selected from the group consisting of: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene di-acetate; 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate), and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

TABLE 2

R	Log P
Structure 7A R= CH ₃	-0.97
Structure 7C R= CH ₂ CH ₃	+0.09
Structure 7B R= CHCH ₃ CH ₃	+0.79
Structure 7D R= CCH ₃ CH ₃ CH ₃	+1.49

[00029] The present invention further provides a pharmaceutical composition made of at least one compound or mixture of compounds of the invention in a pharmaceutically acceptable carrier thereof. The invention features a pharmaceutical composition in unit dosage form formulated for sublingual or buccal administration. The delivery systems include: fast dissolving films, oral dissolving tablets, inhalation, and nasal delivery. In one embodiment, the unit dosage form of the present invention is a film for the delivery of epinephrine hydrochloride, as an anaphylactic treatment in a patient, such as for a pediatric or geriatric patient. A typical rapidly dissolving film is made of a drug, a water-soluble polymer, a plasticizer, a saliva stimulating agent, a surfactant and other fillers such as sweetening agents and flavors in case of bitter taste drugs. *See e.g.* A. Arya, A. Chandra, V. Sharma, and K. Pathak, "Fast dissolving oral films: An innovative drug delivery system and dosage form," *Int. J. ChemTech Res.*, vol. 2, no. 1, pp. 576-583, 2010. D. P. Lettre, "Formulation and Evaluation of Rapidly Disintegrating Film of Levocetirizine Hydrochloride," *Pharmacia*, vol. 2, no. 2, pp. 208-220, 2010.

[00030] For the present invention, the drug is epinephrine, a prodrug of epinephrine or a salt thereof. The typical dose of epinephrine for anaphylactic treatment

is 0.3 to 0.5 mg in adults and 0.01 mg/kg up to a maximum of 0.3 mg in children administered through intramuscular route. In this study, 13mg/9 cm² of epinephrine (5.9 % w/w) are used as the dose size. This quantity is calculated for 6-7-year-old child according to Clark's rule Pediatric dose = Adult dose x (child's weight/150).

5 [000031] A typical dose of 40 mg was based on a study in rabbits that showed a dose bioequivalence between a 40mg epinephrine tablet administered sublingually and 0.3 mg epinephrine administered intramuscularly using Epi pen. Injectors, Rawas-Qalaji et. al. Biopharm Drug Dispos. 27: 427-435 (2006). Furthermore, the time to reach maximum epinephrine concentration after a 0.3 mg EPIPEN (Mylan Specialty L.P.)
10 injection in children is reported at 8±2 minutes. In another study, maximum plasma epinephrine concentration is reached within 34±14 minutes using 0.01 mg/kg dose injection of epinephrine subcutaneously in the deltoid region.

[00032] The polymer and the optimal amount of polymer are selected to obtain a non-sticky and functional film. A film-forming polymer should have good wetting
15 property, high spread ability, good feeling in the mouth and should be safe and non-irritant. Many studies have showed that polymer content of at least 10 -15 % is needed in order to formulate proper film of proper thickness after drying in order to peel the film off from the release line. In one exemplary embodiment, the polymer is a water soluble modified hydroxypropyl starch that is specifically manufactured for
20 aqueous film coating in immediate release solid oral dosage forms.

[00033] A plasticizer is used to form the rapidly dissolving film. The plasticizer enhances the flow of the polymer and improve the tensile strength and elongation of the fill. Several plasticizers are commonly used in rapidly dissolving film preparation such as glycerol, di-butylphthalate, and polyethylene glycols and they are usually used
25 up to 20 % concentration of dry polymer weight.

[00034] The function of the surfactant is to facilitate the solubilization or wetting of the film and subsequently causing the film to disintegrate quickly, releasing the drug to be absorbed through the buccal cavity. Surfactants can include Tween 80, which is a complex mixture of polyoxyethylene ethers used as emulsifiers
30 or dispersing agents in pharmaceuticals.

[00035] A saliva stimulating agent used to facilitate the delivery of the drug using a rapidly dissolving film to the patient. Other fillers, such as sweetening agents and flavors in case of bitter taste drugs and colors are added to the rapidly

dissolving film to facilitate the delivery of the drug using a rapidly dissolving film to the patient. Typically, acids such as citric acid, malic acid, lactic acid and ascorbic acid are used as chemical stimulants of saliva secretion. However, citric acid is the most preferred among them. Xylitol and Tutti Frutti flavor are used for taste masking.

5 Xylitol is an effective sweetening agent which has equal sweetness to sucrose.

[00037] Examples :Four formulations are prepared in this example. Epinephrine is soluble in Lycoat 720 (modified hydroxypropyl starch) water mixture. This hydrophilic polymer solubilizes epinephrine HCl, form a high viscosity gel that spreads well as we cast the film and lead to a non-sticky dry film after water
10 evaporation. This polymer doesn't have any oxyethylene groups that can promote the oxidation of epinephrine nor it has glucose units that promotes water adsorption. The other ingredients added such as tween, glycerin decreased the rigidity of the film and improved elasticity. sodium metabisulfite was added to prevent and long-term oxidation of epinephrine HCl in the film. The citric acid brings the pH of the gel to
15 the maximum stability range for epinephrine. The percentages of the polymer are shown in (Table 3). The polymer percentages are (20, 25, 27 and 30 %) of the total formulation weights. The polymer used in this example is LYCOAT (Ferromet). LYCOAT is a water soluble modified hydroxypropyl starch that is specifically manufactured for aqueous film coating in immediate release solid oral dosage forms.

20 [00038] Table 3: List of the compositions of the four FDFs formulations.

Ingredient (% w/w)	Use	F1	F2	F3	F4
<i>Epinephrine HCl</i>	Drug	5.9	5.9	5.9	5.9
<i>Sodium Metabisulfite</i>	Antioxidant	5.9	5.9	5.9	5.9
<i>Lycoat 720 (hydroxypropyl starch)</i>	Film- forming polymer	20	25	27	30
<i>Glycerin</i>	Plasticizer	3	3	3	3
<i>Tween 80</i>	Surfactant	2	2	2	2
<i>Citric Acid Monohydrate</i>	Buffer; increases absorption	0.5	0.5	0.5	0.5

	in oral cavity				
<i>Sodium Citrate Monobasic</i>	Buffer	0.5	0.5	0.5	0.5
<i>Xylitol</i>	Sweetener	10	10	10	10
<i>Tutti Frutti</i>	Flavor	6	6	6	6
<i>Water</i>		46.2	41.2	39.2	36.2

[00039] Glycerin is used as a plasticizer to provide the proper elasticity for the film (Table 1). A plasticizer imparts a certain level of flexibility to the film by decreasing its brittleness. Films in this example are prepared using 3% glycerol which is equivalent to 10-15 % of the amount of polymer used.

[00040] Tween 80 is used as a surfactant (Table 2). Citric acid is used to adjust the pH and can be used in rapidly dissolving film as a saliva simulating agent to increase the secretion rate of saliva which will further improve the disintegration time of the film. Finally, the addition of an antioxidant is very important for the stability of epinephrine. Prompt oxidation of epinephrine in aqueous solutions results in a colored inactive product which has been reported. Therefore, different types of antioxidants are used in the commercial injectors such as sodium metabisulfite, EDTA and ascorbic acid achieving shelf life of two years. In this exemplary embodiment, the addition of sodium metabisulfite stabilizes the film.

[00041] However, films formed by formulations 1, 2 and 3 are too sticky after drying rendering them unusable. Formulation 4, having 30 % polymer content, formed a smooth, transparent, flexible and uniform film and therefore it is selected for further testing. The difference in stickiness is clearly related to the variation of the polymer content. This comes in agreement with a previous study that showed that using 22.5% of LYCOAT polymer formed a thin and flexible but sticky film at that concentration concluding that a higher percentage of polymer is needed.

[00042] Physical properties of the film prepared by formulation 4 are evaluated such as elastic modulus, thickness, content uniformity and dissolution time. Assessing these parameters is essential to determine the efficiency and usability of the film by patients. Elastic modulus is first studied as it represents a clear measure of the

stiffness level of the film. It is calculated as the ratio of the applied stress over strain on a specific section.

[00043] Elastic's modulus= (Force at corresponding strain/cross section area) $\times$ 1/(corresponding strain).

5 [00044] Now referring to FIG. 8, the profile of the film is illustrated showing a small increase in the applied strain to the film causes a quick increase in stress reaching a value of 0.1 MPa at 20 % strain level. As the strain increases further above 20 %, the increase magnitude in stress decreases gradually until it reaches a semi-plateau at value 0.16 MPa where % stress is 80 %. The value of elastic
10 modulus is determined at 1.325 MPa which is an indication of very good flexibility of the film (Table 3).

[00045] Table 4: List of physical properties of the optimized film

Test	Results
Elastic Modulus	1.325 $\pm$ 0.2 MPa
Thickness	0.29 $\pm$ 0.01 mm
Content Uniformity	93% $\pm$ 10%

15 [00046] The thickness of the film at different locations is measured at 0.29 mm with very small margin of variability which is an indication of the high uniformity of the film (Table 4). A maximum thickness variation of 5 % is permitted in the preparation of the rapidly dissolving film. A uniform thickness across the film as it directly correlates with the accuracy of the dose in the film. Drug content in film is
20 measured at 93 % $\pm$ 10 indicating high level of consistency of epinephrine dose within the film (Table 2), as a limit of 85 -115 % of content uniformity is acceptable according to USP.

[00047] Now referring to FIG. 9, the dissolution profile of epinephrine from the film in terms of rate and extent in simulated saliva is determined on six samples of
25 the optimized film. More than 90 % of epinephrine is released from the film within 7.2 minutes.

[00048] Taste and disintegration time of the optimized film are evaluated on 6 volunteers (Table 3). The disintegration time is the time when the film starts to break

or disintegrates. Volunteers reported 10 -30 seconds disintegration time (Table 3). This complies with the regulations set by United State Pharmacopeia (USP) for disintegration time of oral films (not exceeding 30 seconds). Bitterness of epinephrine is masked efficiently according to volunteer's comments (Table 5). Four volunteers
5 sensed no bitterness of the film while the other two volunteers reported slight to very slight sensation of bitterness. Moreover, no tongue constriction is reported by any of the volunteers. This data presents clear proof of the efficiency of rapidly dissolving film in taste masking the bitterness of epinephrine and an indication of strong potential for using a rapidly dissolving film as a replacement therapy of epinephrine
10 injections for children.

[00049] Table 5: *In vivo* taste and disintegration time evaluation of the optimized epinephrine FDF.

Volunteer	Bitterness	Tongue Constriction	Disintegration Time
1	None	None	~10 seconds
2	None	None	~10 seconds
3	Slight	None	~20 seconds
4	None	None	~30 seconds
5	Very slight	None	~20 seconds
6	None	None	~30 seconds

15 [00050] Materials--Epinephrine hydrochloride, sodium metabisulfite, citric acid monohydrate and sodium citrate monobasic are purchased from Sigma Aldrich (St. Louis, MO). Lycoat® RS720 is obtained from Roquette (Lestrem, France). Glycerin and tween 80 are purchased from Fisher Chemicals (Pittsburg, PA). Xylitol is purchased from Gallipot (St. Paul, MN). Tutti Frutti is obtained from LorAnn Oils
20 (Lansing, MI). Film Preparation--Several rapidly dissolving films are prepared by a solvent casting technique to choose the optimum film formulation. The formulation compositions of the rapidly dissolving film are mentioned in Table 3. LYCOAT and Xylitol are dissolved in warm water. The solution is then placed in a sonicator for

two hours and then the solution is left overnight to ensure the removal of all entrapped air bubbles. Other excipients and Epinephrine HCl are added to the solution on the next day at room temperature. The mixture is then placed again in a sonicator for 40 minutes. The mixture is then spread onto a checkered paper covered by plastic sheet using a stainless-steel bar applicator. The film is left to dry overnight and is cut into 9 mm² small film strips.

[00053] Physical properties-The thickness and elastic modulus of the optimized film is evaluated using Dynamic Mechanical Analyzer (Q800 DMA, TA instruments, New Castle, DE). This is important to evaluate tensile properties of the films. Three strips of the optimized films are tested at 25 °C according to ASTM International Test Method for Thin Plastic Sheeting (D 882-02). Each film is positioned between the grips of the instrument. The preload force is set at 0.01 N and the final force at 15N. The initial grip separation is set to 60 mm and crosshead speed is set to 500 mm/min. The test is terminated when the film breaks. Elastic modulus is determined as the slope of the straight-line part of the stress-strain curve and it is expressed in force per unit area (MPa).

[00054] Drug content uniformity: Specific areas are cut from six different films and weighted to calculate the estimated amount of drug in each area. Films are then dissolved in 100 ml of citric acid buffer. The media are stirred and then filtered using 0.45 um filters (Millipore Corporation, Millipore, Vimodron, Italy) and epinephrine content is assessed using UVmini-1240 UV-Vis Spectrophotometer (Shimadzu, Japan) at wavelength 280 nm. Epinephrine content is determined by calculating the percentage of the measured epinephrine to the estimated amount in each film.

[00055] *In vitro* dissolution test: For the dissolution test, rapidly dissolving film are evaluated using USP dissolution apparatus II, paddle (Distek Evolution 6100, North Brunswick, NJ). Six strips are placed in different 1 L vessels containing 500 ml Simulated Saliva. The temperature of the dissolution media is set to 37 C and rpm is set to 50 rpm. Samples are taken at different time points throughout the time of the experiment (15 mins), and the amount of epinephrine released in the media is determined by UVmini-1240 UV-Vis Spectrophotometer (Shimadzu, Japan) at 280 nm.

[00056] Human taste panel--To evaluate the palatability of optimized epinephrine film, a taste evaluation study is performed on six healthy volunteers. The study is

carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki), and all volunteers are informed in advance of the related details and the goal of the study and their consents are obtained. Volunteers are asked to place the film on the interior surface of their buccal cavity until the film is fully disintegrated. Volunteers then rinsed their mouths with drinking water. Volunteers have to report their findings of the presence of bitterness or not, any tongue restriction and how long it took for full disintegration of the film.

[00057] Equivalent elements can be substituted for the ones set forth above such that they perform in substantially the same manner in substantially the same way for achieving substantially the same result. It is believed that the system and method of the present invention and many of its attendant advantages will be understood by the foregoing description. It is also believed that it will be apparent that various changes may be made in the form, construction and arrangement of the components thereof without departing from the scope and spirit of the invention or without sacrificing all of its material advantages. The form herein before described being merely exemplary and explanatory embodiment thereof. It is the intention of the following claims to encompass and include such changes.

ABSTRACT

The present invention relates to a pharmaceutical composition for the treatment of anaphylaxis formulated for rapid delivery. In one embodiment, the delivery vehicle is a rapidly dissolving film. The films contain an epinephrine or a novel epinephrine pro-drug
5 for the rapid treatment of anaphylaxis in a patient. This invention relates to pharmaceutical compositions made by modifying the physicochemical properties of epinephrine in order to enhance its permeability through biological membranes (sublingual and buccal membranes). Several prodrugs of epinephrine are shown by modifying the two hydroxyl (phenolic) groups in positions 3 and 4 on the benzene
10 ring, by chemically reacting the two groups with several acid moieties to form an ester bond with different alkyl chains. The addition of an alkyl group will enhance the lipophilicity of epinephrine (increase log P) and will consequently increase its permeability through the biological membranes (sublingual and buccal tissues in the oral cavity).

15

FIG. 1

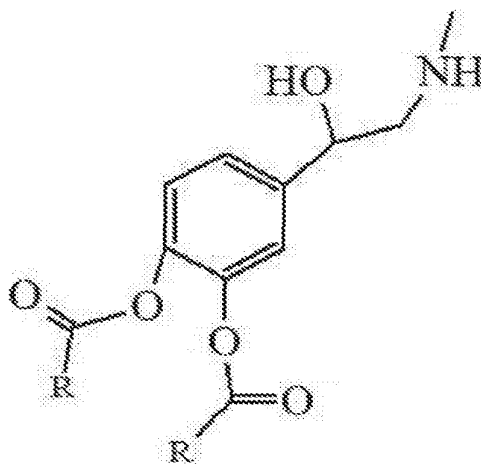


FIG. 2

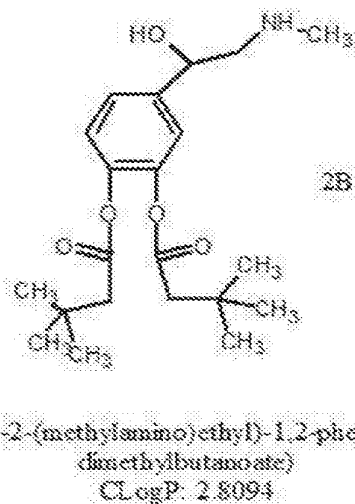
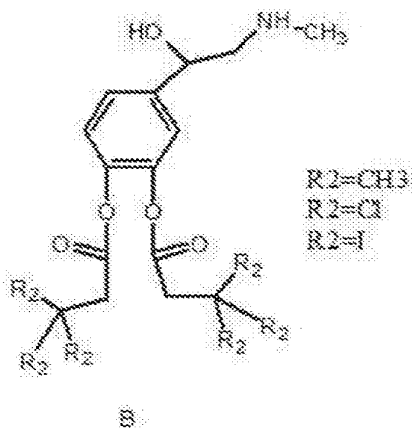
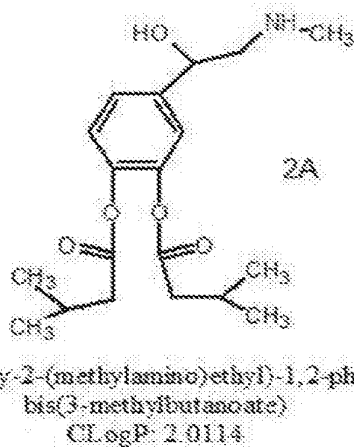
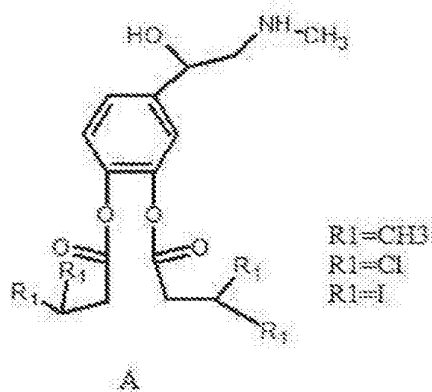
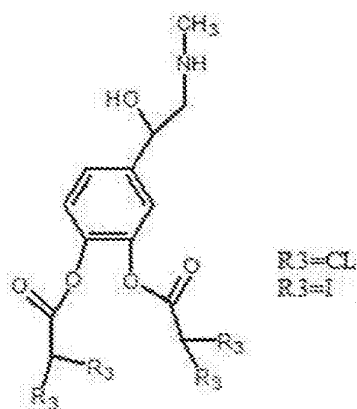
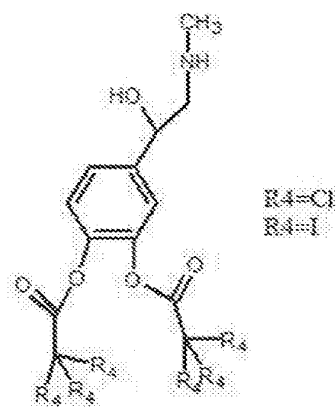
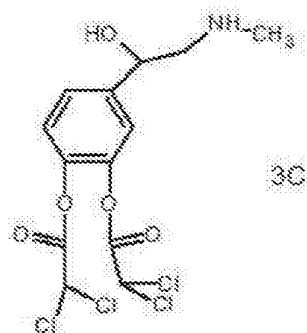


FIG. 3



C

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dichloroacetate)
CLogP: 1.4494



D

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2,2-trichloroacetate)
CLogP: 2.8554

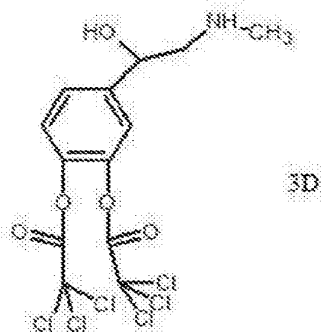
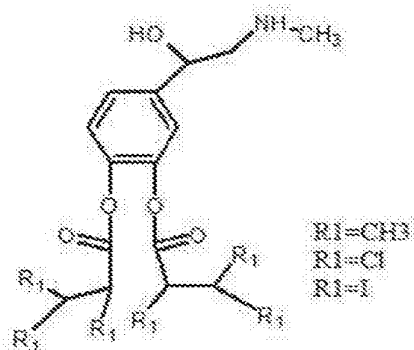
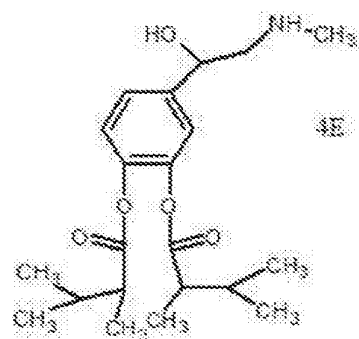


FIG. 4

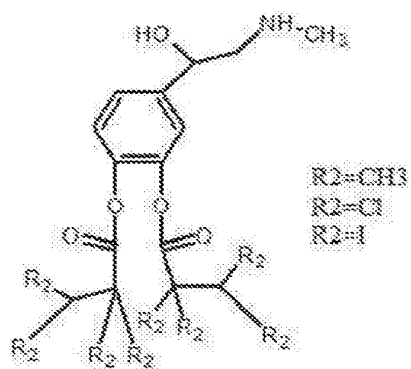


E

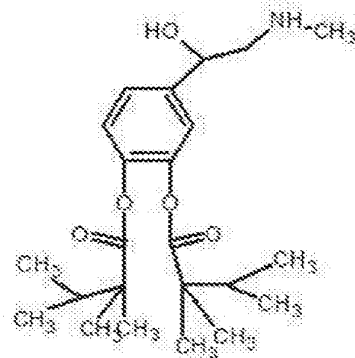


4E

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,3-dimethylbutanoate)
 CLogP: 2.6294



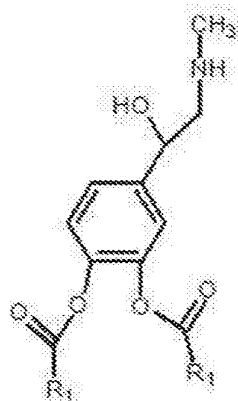
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4F

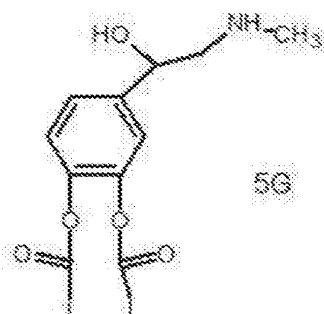
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2,3-trimethylbutanoate)
 CLogP: 3.4274

FIG. 5



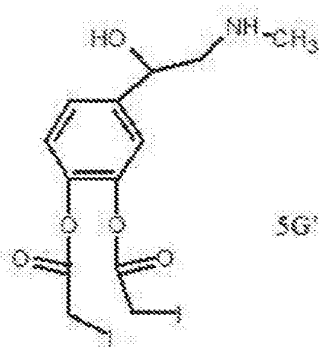
G

R1=H
R1=I
R1=Cl
R1=CH₂CH₂CH₃
R1=CH₂CH₂CH₂CH₃
R1=CH₂Cl
R1=CH₂I
R1=CH₂F



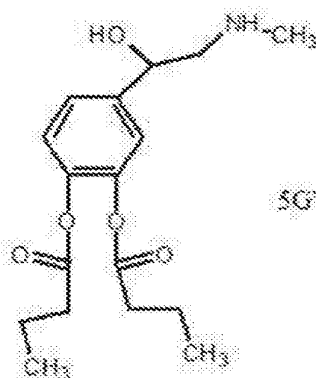
5G

4-(1-hydroxy-2-(methylamino)ethyl)-
1,2-phenylene dicarboniodate
CLogP: 1.0854



5G'

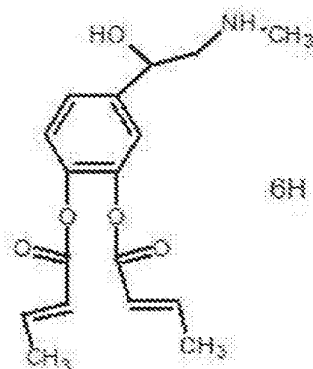
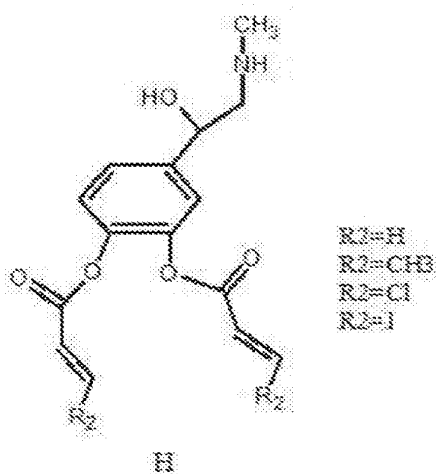
4-(1-hydroxy-2-(methylamino)ethyl)-1,
2-phenylene bis(2-iodoacetate)
CLogP: 0.3834



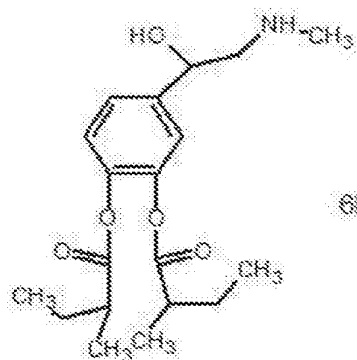
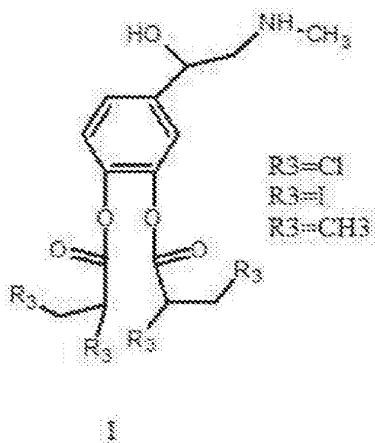
5G''

4-(1-hydroxy-2-(methylamino)ethyl)-1,2-
phenylene dibutyrate
CLogP: 1.2134

FIG. 6

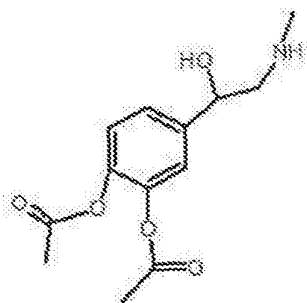


4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene (2*E*,2'*E*)-bis(but-2-enoate)
 CLogP: 1.2054



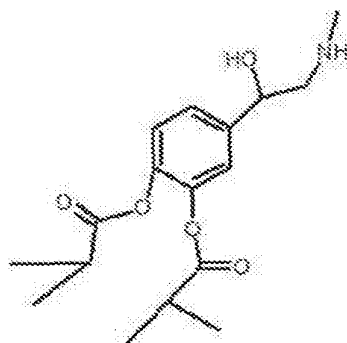
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2-methylbutanoate)
 CLogP: 1.8314

FIG. 7



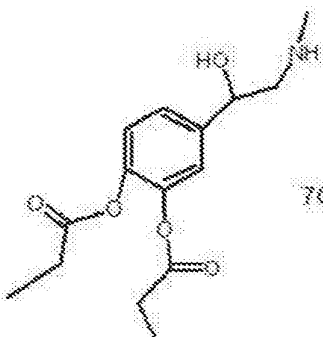
7A

4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate
CLogP: -0.9026



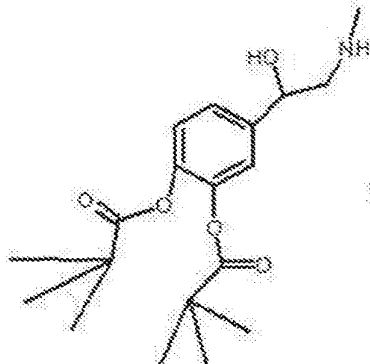
7B

4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene bis(2-methylpropanoate)
CLogP: 0.7733



7C

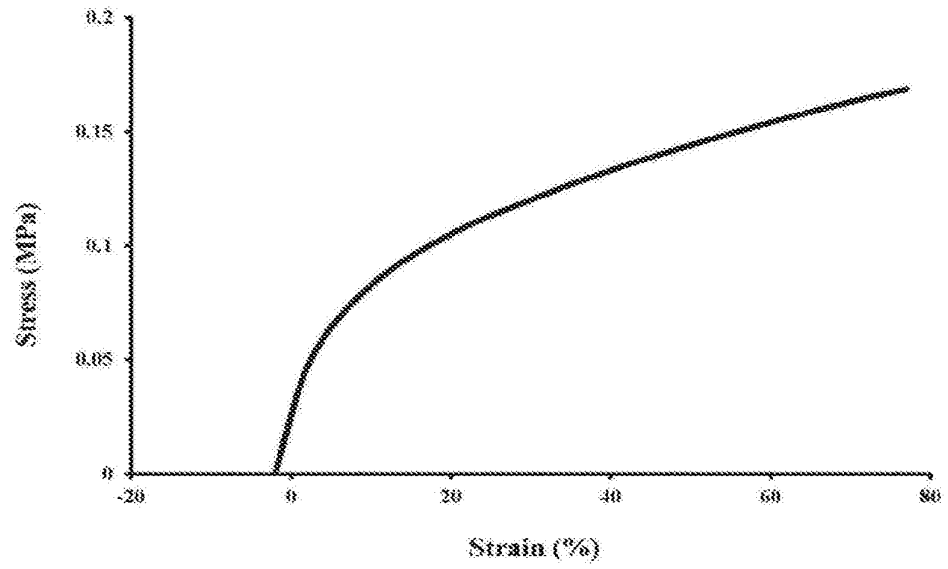
4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropanoate
CLogP: 0.1554

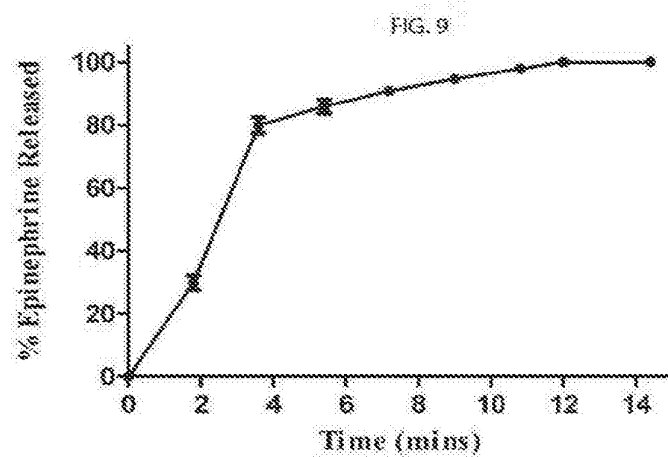


7D

4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene bis(2,2-dimethylpropanoate)
CLogP: 1.5714

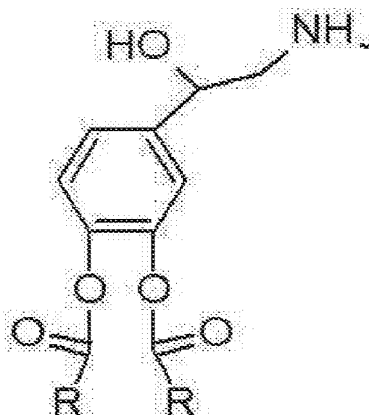
FIG. 8





CLAIMS

1. A compound of a Formula:



wherein R is selected from the group consisting of: H, CHCH₂, CHCHCH₃, CHCH₂CL,
 5 CHCH₂I, CHCLCH₂CL, CHICH₂I, CHCH₃CH₂CH₃, CH₂CCH₃CH₃CH₃, CH₂CH₂CH₃,
 CH₂CL, CH₂I, CH₂F, CL, I, F, CHCH₃CHCH₃CH₃, CHCLCHCLCL, CHICHII,
 CHFCHFF, CH₂CHCH₂, CCLCLCHCLCL, CHCHII, CCLCLCL, CHII, CH₂COCH₃,
 CH₂COCL, CH₂COI, CH₂OCH₃, CHICH₃, CCLCLCH₃, CH₂CHCH₃CH₃, CH₂CHCLCL,
 CH₂CHII, CH₂CCLCLCL, CH₂CHII, CHCLCL, CHII,
 10 CCH₃CH₃CHCH₃CH₃, NHCCH₃CH₃CH₃, NHCHCH₃CH₃, NHCH₂CH₃, NHCH₃, SCH₃,
 SCH₂CH₃, SCHCH₃CH₃, SCCH₃CH₃CH₃, CH₂C₆H₅ and C₆H₅ or a pharmaceutically
 acceptable salt thereof.

2. The compound of claim 1, formulated as a pharmaceutical composition in a unit dosage
 form configured for sublingual or buccal administration.

15 3. The compound of claim 2, wherein the compound is formulated in a unit dosage form as a
 rapidly dissolving film.

4. Use of the pharmaceutical composition of claims 2 or 3 in a patient in need of anaphylactic
 treatment.

5. The compound of claim 1 comprising: a compound as depicted in a formula 2A and a
 20 pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R₁ is
 selected for the group consisting of: CH₂CH₃, CH₂CH₂CH₃, or CH₂CH₂CH₂CH₃, CL or I.

6. The compound of claim 1 comprising: a compound as depicted in a formula 2B and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R₂ is selected for the group consisting of: CL or I.
7. The compound of claim 1 comprising: a compound as depicted in a formula 3C and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R₃ is selected for the group consisting of: CL and I.
8. The compound of claim 1 comprising: a compound as depicted in a formula 3D and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R₄ is selected for the group consisting of: CI and I.
9. The compound of claim 1 comprising: a compound as depicted in a formula 4E and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R₁ is selected for the group consisting of: CI and I.
10. The compound of claim 1 comprising: a compound as depicted in a formula 4F and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R₂ is selected for the group consisting of: CI and I.
11. The compound of claim 1 comprising: a compound as depicted in a formula 5G and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R₁ is selected for the group consisting of: H, I, CI, CH₂CH₂CH₃, CH₂CH₂CH₂CH₃, CH₂Cl, CH₂I and CH₂F.
12. The compound of claim 1 comprising: a compound as depicted in 6H and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R₂ is selected for the group consisting of: H, CH₃, CI and I.
13. The compound of claim 1 comprising: a compound as depicted in a formula 6I and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein R₃ is selected for the group consisting of: CI, I and CH₃.
14. A method to deliver epinephrine or a prodrug of epinephrine comprising: the steps of: providing epinephrine in a unit dosage form, formulated for sublingual or buccal administration, wherein the unit dosage form is a rapidly dissolving film, to a patient in need of treatment thereof.

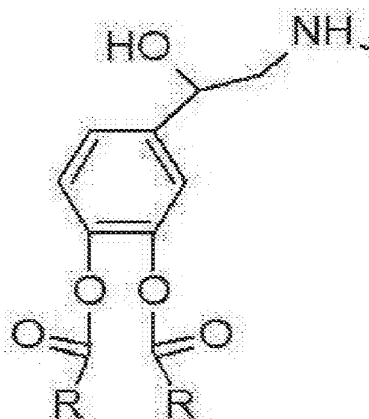
15. The method of claim 14 wherein the prodrugs of epinephrine has a Log P value in the range of about 0.5-6.0.

16. The method of claim 14 wherein the prodrugs of epinephrine has a Log P value in the range of about 1.0-5.0.

5 17. The method of claim 14 further comprising: providing said epinephrine or the prodrug of epinephrine in a unit dosage form to a patient in need of anaphylactic treatment.

18. The method of claim 14 further comprising: providing said prodrug of epinephrine in a unit dosage form to a patient in need of anaphylactic treatment.

19. A compound of a Formula:



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wherein R is selected from the group consisting of: H, CH₃, CH₂CH₃, CHCH₃CH₃ and CCH₃CH₃CH₃, and wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration.

15 20. The compound of claim 19, wherein the compound is selected from the group consisting of: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene di-acetate; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate), and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage
20 form as a rapidly dissolving film.

21. The compound of claim 19, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

22. Use of the pharmaceutical formulation of claim 21 in a patient in need of anaphylactic treatment.

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Electronic Patent Application Fee Transmittal

Application Number:				
Filing Date:				
Title of Invention:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE			
First Named Inventor/Applicant Name:	Iono Pharma, LLC			
Filer:	Susan Bennett Fentress			
Attorney Docket Number:	24050.0001PCT			
Filed as Small Entity				
Filing Fees for International Application (PCT) for filing in the US receiving office				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
TRANSMITTAL FEE	2601	1	120	120
PCT SEARCH FEE- NO PRIOR US APPL FILED	2602	1	1040	1040
Intl Filing first 30pgs EFS without ZIP	1701	1	1264	1264
Suppl. Intl Filing Fee (each page > 30)	1703	6	15	90
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				2514

Electronic Acknowledgement Receipt	
EFS ID:	30900690
Application Number:	
International Application Number:	PCT/US17/60761
Confirmation Number:	4463
Title of Invention:	PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF EPINEPHRINE
First Named Inventor/Applicant Name:	Iono Pharma, LLC
Customer Number:	76447
Correspondence Address:	Susan B Fentress - 20 Dudley St Suite 803 Memphis TN 38103 US 9013716664 sfentress@veritaygroup.com
Filer:	Susan Bennett Fentress
Filer Authorized By:	
Attorney Docket Number:	24050.0001PCT
Receipt Date:	09-NOV-2017
Filing Date:	
Time Stamp:	11:53:53
Application Type:	International Application (PCT) for filing in the US receiving office
Patent Number:	

Payment information:

Submitted with Payment	yes				
Payment Type	CARD				
Payment was successfully received in RAM	\$2514				
RAM confirmation Number	110917INTEFSW11553200				
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	RO/101 - Request form for new IA - Conventional	pctransmital.pdf	2980691	no	7
			8f6a63f3504fb0104a2117bb94464739e64a2b9f		
Warnings:					
Information:					
2	Specification	spec.pdf	5139338	no	16
			1f82efa95b08ebd3c9a9ddac110d9d1c4fca3ffd		
Warnings:					
Information:					
3	Abstract	abstract.pdf	148209	no	1
			e96f779b919bd2721a6dd874e2e9a520e821a9dd		
Warnings:					
Information:					
4	Drawings-only black and white line drawings	ionofinlafigs.pdf	1251584	no	9
			4af8d6239084b6235a7f35a7516c974637aea173		
Warnings:					
Information:					

5	Claims	ionoupdatedclaims.pdf	714229	no	4
			246755c5fc39bab4feef3bccf4237ac21fo0c294		
Warnings:					
Information:					
6	Fee Worksheet (SB06)	fee-info.pdf	36997	no	2
			95413eb24e5a3831c64827033a860b362f384f30		
Warnings:					
Information:					
Total Files Size (in bytes):			10271048		
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.					

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

PCT/US17/60761

International Application No.

09 NOV 2017 (09.11.17)

Date stamp of the receiving Office

Applicant's or agent's
file reference

24050.0001PCT

Applicant

Iono Pharma, LLC

CALCULATION OF PRESCRIBED FEES

(Applicants may be entitled to a reduction of certain fees as indicated in the PCT Fee Tables
(<http://www.wipo.int/pct/en/fees.pdf>))

1. TRANSMITTAL FEE: 206.00 [T]

2. SEARCH FEE: 1040.00 [S]

International search to be carried out by: USPTO

3. INTERNATIONAL FILING FEE

Enter total number of sheets indicated in Box No (X): 36

[1] Fixed amount for the first 30 sheets 1264.00 [1]

[2] 6 x 15 = 90.00 [2]
number of sheets in excess of 30 fee per sheet

Add amounts entered at 11 and 12 and enter total at 1: 1354.00 [T]

(Applicants from certain States are entitled to a reduction of 90% of the international filing fee (see
http://www.wipo.int/pct/en/fees/fee_reduction.pdf). Where the applicant is (or all applicants are) so entitled,
the total to be entered at 1 is 10% of the international filing fee.)

4. FEE FOR PRIORITY DOCUMENT (if applicable): [P]

5. FEE FOR RESTORATION OF THE RIGHT OF PRIORITY (if applicable): [RP]

6. FEE FOR EARLIER SEARCH DOCUMENTS (if applicable): [ES]

7. TOTAL FEES PAYABLE 2600.00

Add amounts entered at T, S, 1, P, RP and ES,
and enter total in the TOTAL box

TOTAL

MODE OF PAYMENT (Not all modes of payment may be available at all receiving Offices)

- ☒ credit card (details should not be included on this sheet) ☐ authorization to charge deposit or current account (see below) ☐ bank transfer ☐ cash
☐ postal money order ☐ check ☐ revenue stamps ☐ other (specify):

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT OR CURRENT ACCOUNT

(This mode of payment may not be available at all receiving Offices)

Receiving Office: RO/ USPTO

Deposit or Current Account No.: 60-1480

Date: Nov 8, 2017

Name: Susan B Fentress

- ☐ Authorization to charge the total fees indicated above.
☒ (This check box may be marked only if the conditions for deposit or current accounts of the receiving Office so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.
☐ Authorization to charge the fee for priority document.

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1052.pdf Page 074

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/US17/60761

International Application No.

09 NOV 2017 (09.11.17)

International Filing Date

PCT INTERNATIONAL APPLICATION
RO/US

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum)

Box No. I TITLE OF INVENTION

PHARMACEUTICAL FORMULATION FOR SUBLINGUAL OR BUCCAL DELIVERY OF
EPINEPHRINE OR A PRO-DRUG THEREOF

Box No. II APPLICANT

☐ This person is also inventor

Name and address: (Family name followed by given name; for a legal entity, full official designation.
The address must include postal code and name of country. The country of the address indicated in this
box is the applicant's State (that is, country of residence if no State of residence is indicated below).)

Iono Pharma, LLC
3133 Hill Lake Drive
Bartlett, TN 38135
USA

Telephone No.

Facsimile No.

Applicant's registration No. with the Office

E-mail authorization: Marking one of the check-boxes below authorizes the receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority to use the e-mail address indicated in this Box to send notifications issued in respect of this international application to that e-mail address if those offices are willing to do so.

☐ as advance copies followed by paper notifications; or

☐ exclusively in electronic form (no paper notifications will be sent).

E-mail address:

State (that is, country) of nationality:

US

State (that is, country) of residence:

US

This person is applicant
for the purposes of:

☒ all designated States

☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf
of the applicant(s) before the competent International Authorities as:

☒ agent

☐ common
representative

Name and address: (Family name followed by given name; for a legal entity, full official designation.
The address must include postal code and name of country.)

Susan B Fentress
Veritay Group, IP
20 Dudley Suite 803
Memphis, TN 38103
USA

Telephone No.

9013716663

Facsimile No.

9018661656

Agent's registration No. with the Office

31327

E-mail authorization: Marking one of the check-boxes below authorizes the receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority to use the e-mail address indicated in this Box to send notifications issued in respect of this international application to that e-mail address if those offices are willing to do so.

☒ as advance copies followed by paper notifications; or

☐ exclusively in electronic form (no paper notifications will be sent).

E-mail address: sfentress@veritaygroup.com

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) Hassan Almoazen 3133 Hill Lake Drive Bartlett, TN 38135 USA		This person is: ☐ applicant only ☐ applicant and inventor ☒ inventor only (If this check-box is marked, do not fill in below.)
Applicant's registration No. with the Office		
State (that is, country) of nationality:	State (that is, country) of residence:	
This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box		
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) Lindsay Haynes 2068 Horizons Dr Ooltewah, TN 37363 USA		This person is: ☐ applicant only ☐ applicant and inventor ☒ inventor only (If this check-box is marked, do not fill in below.)
Applicant's registration No. with the Office		
State (that is, country) of nationality:	State (that is, country) of residence:	
This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box		
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)		This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
Applicant's registration No. with the Office		
State (that is, country) of nationality:	State (that is, country) of residence:	
This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box		
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)		This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
Applicant's registration No. with the Office		
State (that is, country) of nationality:	State (that is, country) of residence:	
This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box		
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)		This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)
Applicant's registration No. with the Office		
State (that is, country) of nationality:	State (that is, country) of residence:	
This person is applicant for the purposes of: ☐ all designated States ☐ the States indicated in the Supplemental Box		
☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.		

Box No. V DESIGNATIONS

The filing of this request constitutes under Rule 4.9(a) the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

- ☐ DE Germany is not designated for any kind of national protection
- ☐ JP Japan is not designated for any kind of national protection
- ☐ KR Republic of Korea is not designated for any kind of national protection

(The check-boxes above may only be used to exclude (irrevocably) the designations concerned if, at the time of filing or subsequently under Rule 26bis.1, the international application contains in Box No. VI a priority claim to an earlier national application filed in the particular State concerned, in order to avoid the ceasing of the effect, under the national law, of this earlier national application.)

Box No. VI PRIORITY CLAIM AND DOCUMENT

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application: regional Office	international application: receiving Office
item (1) 13/11/2016 13 NOV 2016	62/421,316	US		
item (2)				
item (3)				

- ☐ Further priority claims are indicated in the Supplemental Box.

Furnishing the priority document(s):

- ☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application(s) was filed with the receiving Office which, for the purposes of this international application, is the receiving Office) identified above as:

- ☒ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental Box

- ☐ The International Bureau is requested to obtain from a digital library a certified copy of the earlier application(s) identified above, using, where applicable, the access code(s) indicated below (if the earlier application(s) is available to it from a digital library):

- ☐ item (1) access code _____ ☐ item (2) access code _____ ☐ item (3) access code _____ ☐ other, see Supplemental Box

Restore the right of priority: the receiving Office is requested to restore the right of priority for the earlier application(s) identified above or in the Supplemental Box as item(s) (_____). (See also the Notes to Box No. VI: further information must be provided to support a request to restore the right of priority.)

Incorporation by reference: where an element of the international application referred to in Article 11(1)(iii)(3) or (e) or a part of the description, claims or drawings referred to in Rule 20.5(a) is not otherwise contained in this international application but is completely contained in an earlier application whose priority is claimed on the date on which one or more elements referred to in Article 11(1)(iii) were first received by the receiving Office, that element or part is, subject to confirmation under Rule 20.6, incorporated by reference in this international application for the purposes of Rule 20.6.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if more than one International Searching Authority is competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA/ US

AQUESTIVE THERAPEUTICS, INC. EXHIBIT 1052.pdf Page 077

Continuation of Box No. VII USE OF EARLIER SEARCH AND CLASSIFICATION RESULTS		
1. Request by the applicant under Rule 4.12		
1.1 ☐ The ISA indicated in Box No. VII is requested to take into account the results of the earlier search(es) indicated below (see also Notes to Continuation of Box No. VII, item 1; use of results of more than one earlier search) Filing date (day/month/year): Application Number: Country (or regional Office):		
☐ Statement (Rule 4.12(ii)): this international application is the same, or substantially the same, as the application in respect of which the earlier search was carried out except, where applicable, that it is filed in a different language.		
1.2 Submission of the earlier search results, where necessary* ☐ Availability of documents (Rules 12bis.1(c) and (d) and 12bis.2(h)): the following documents are available to the ISA in a form and a manner acceptable to it, and therefore DO NOT need to be submitted by the applicant to the receiving Office, or to the ISA: ☐ a copy of the results of the earlier search; ☐ a copy of the earlier application; ☐ a translation of the earlier application into a language which is accepted by the ISA; ☐ a translation of the results of the earlier search into a language which is accepted by the ISA; ☐ a copy of any document cited in the earlier search results (if known, please indicate below the documents available to the ISA):		
☐ Request from the applicant to the receiving Office to transmit to the ISA a copy of the earlier search results (Rule 12bis.1(b) and (d)): (where the earlier search was not carried out by the ISA indicated in Box No. VII but by the same Office as that which is acting as receiving Office; or where the earlier search results are otherwise available to the receiving Office); the applicant requests the receiving Office to prepare and transmit to the ISA a copy of the earlier search results.		
* The applicant only needs to furnish a copy of the earlier search results to the receiving Office, or the ISA, if none of the scenarios mentioned under item 1 applies. (See item 10 in the check-list and also Notes to Continuation of Box No. VII, item 1).		
☐ Further earlier searches are indicated on a continuation sheet.		
2. Transmission of the earlier search and classification results to the ISA by the receiving Office where the applicant DID NOT make a request under Rule 4.12		
2.1 Where the international application claims priority of an earlier application, subject to Article 30(2)(a) and (3), the receiving Office: -- shall transmit a copy of this earlier search and classification results to the ISA (unless such copy is already available to the ISA), where the earlier application was filed with the same Office as that which is acting as the receiving Office and that Office has carried out the earlier search in respect of the earlier application (Rule 23bis.2(a)); -- may transmit such a copy if the earlier application was filed with a different Office, but where the results of that earlier search and classification are nevertheless available to the receiving Office (Rule 23bis.2(c)).		
However, where the applicant did not request the receiving Office to transmit to the ISA a copy of the earlier search results under Rule 4.12 (see above item 1), in respect of an earlier search carried out on the following earlier application, the priority of which is subsequently claimed in this international application, the applicant may consider (see also Notes to Continuation of Box No. VII, item 2; use of more than one earlier search): Filing date (day/month/year): Application Number: Country (or regional Office):		
2.2 Request not to transmit the earlier search results by the receiving Office to the ISA (Rule 23bis.2(b)) ☐ to request that the receiving Office DOES NOT transmit the results of the earlier search to the ISA (Rule 23bis.2(b)) (may only be checked where the international application is filed with the following receiving Offices: DE, FI and SE)		
2.3 Authorization to transmit the earlier search and classification results by the receiving Office to the ISA (Rule 23bis.2(a) and (c)) ☐ to authorize the receiving Office to transmit the results of the earlier search and classification to the ISA (Rule 23bis.2(c)) (may only be checked where the international application is filed with the following receiving Offices: AU, CH, CZ, FI, HU, IL, JP, NO, SE, SG and US)		
☐ to authorize the receiving Office to transmit the results of the earlier international search and classification to the ISA (Rule 23bis.2(a) and Article 30(2)(a) and (3)) (may only be checked where the earlier search concerns an international application, the priority of which is subsequently claimed in this international application and where the earlier international search was carried out by a different ISA than the ISA chosen in Box No. VII)		
☐ Further earlier searches are indicated on a continuation sheet.		
Box No. VIII DECLARATIONS		
The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):		Number of declarations
☐ Box No. VIII (i)	Declaration as to the identity of the inventor	:
☒ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

Box No. VIII (B) DECLARATION: ENTITLEMENT TO APPLY FOR AND BE GRANTED A PATENT

The declaration must conform to the standardized wording provided for in Section 212; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (B). If this Box is not used, this sheet should not be included in the request.

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:

In relation to this international application Iono Pharma, LLC is entitled to apply for and be granted a patent by virtue of the following assignments: an assignment of Hassan Almoazen dated 13 NOV 2016 and Lindsay Haynes dated 12 OCT 2016.

☐ This declaration is continued on the following sheet, "Continuation of Declaration" **QUESTIVE THERAPEUTICS, INC. EXHIBIT 1052 pdf Page 079**

Box No. IX CHECK LIST for EFS-Web filings - this sheet is only to be used when filing an international application with ROA/US via EFS-Web			
This international application contains the following:	Number of sheets	This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item):	Number of items
(a) request form PCT/RO/101 (including any declarations and supplemental sheets)	6	1. ☐ fee calculation sheet	1
(b) description (excluding any sequence listing part of the description, see (f), below)	16	2. ☐ original separate power of attorney	
(c) claims	4	3. ☐ original general power of attorney	
(d) abstract	1	4. ☐ copy of general power of attorney; reference number:	
(e) drawings (if any)	9	5. ☐ priority document(s) identified in Box No. VI as item(s)	
(f) sequence listing part of the description in the form of an image file (e.g. PDF)		6. ☐ Translation of international application into (language):	
Total number of sheets (including the sequence listing part of the description if filed as an image file)	36	7. ☐ separate indications concerning deposited microorganism or other biological material	
(g) sequence listing part of the description		8. ☐ (only where item (f) is marked in the left column) copy of the sequence listing in electronic form (Annex C/ST.25 text file) not forming part of the international application but furnished only for the purposes of international search under Rule 13ter	
☐ filed in the form of an Annex C/ST.25 text file		9. ☐ (only where item (f) (in the left column) and item 8 (above) are marked) a statement confirming that "the information recorded in electronic form submitted under Rule 13ter is identical to the sequence listing as contained in the international application" as filed via EFS-Web	
☐ WILL BE filed separately on physical data carrier(s), on the same day and in the form of an Annex C/ST.25 text file		10. ☐ copy of results of earlier search(es) (Rule 12bis.1(a))	
Indicate type and number of physical data carrier(s)		11. ☐ other (specify):	
Figure of the drawings which should accompany the abstract:	2	Language of filing of the international application:	ENGLISH
Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).			
/susan b fentress/ Veritay Group, IP 20 Dudley 803 Memphis, TN 38103 US 31327 Agent for Applicant 09-11-2017			
For receiving Office use only			
1. Date of actual receipt of the purported international application:	09 NOV 2017 (09.11.17)		
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	2. Drawings:		
4. Date of timely receipt of the required corrections under PCT Article 11(2):	☐ received:		
5. International Searching Authority (if two or more are competent): ISA / US	☐ not received:		
6. ☐ Transmittal of search copy delayed until search fee is paid.			
For International Bureau use only			
Date of receipt of the record copy by the International Bureau:			