PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 17/170,275	Filing Date 02/08/2021	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $480 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

AMENDMENT	06/30/2021	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 5	Minus	** 20	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $480 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	SLIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/DEIDRE C KING-WOODWARD/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/170,275	02/08/2021	Jo Ann Wilson	224990/10-039C6-US/483214

CONFIRMATION NO. 8006

91684
JONATHAN P. O"BRIEN, PH.D.
HONIGMAN LLP
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402

PUBLICATION NOTICE



Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

Publication No.US-2021-0161885-A1
Publication Date:06/03/2021

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/170,275	02/08/2021	Jo Ann Wilson	224990/10-039C6-US/483214	8006

91684 7590 03/31/2021

JONATHAN P. O''BRIEN, PH.D.
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650 Trade Centre Way
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Kalamazoo, MI 49002-0402

EXAMINER	
SEAMAN, D MARGARET M	

ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
03/31/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

apeters@honigman.com
hberven@honigman.com
patent@honigman.com

Office Action Summary	Application No. 17/170,275	Applicant(s) Wilson et al.	
	Examiner D MARGARET M SEAMAN	Art Unit 1625	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 35-37 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 35-37 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application is being examined under the pre-AIA first to invent provisions.

Claim Rejections - 35 USC § 102

2. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

3. The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 35-37 are rejected under pre-AIA 35 U.S.C. 102(a)(1) as being anticipated by US20120035212. "212 teaches compound IA on page 1 column 2. This anticipates the instant claims.

5. Claims 35-37 are rejected under pre-AIA 35 U.S.C. 102(a)(1) as being anticipated by US20090105299. '299 teaches the instant composition on claim 68, 69 and 71 and the maleic acid on paragraph 278.

6. Claims 35-37 are rejected under pre-AIA 35 U.S.C. 102(a)(1) as being anticipated by US20070054928. '928 teaches the instant composition on page 316 #12 and claim 106 has the pharmaceutical composition.

7. Claims 35-37 are rejected under pre-AIA 35 U.S.C. 102(a)(1) as being anticipated by US7579473. '473 teaches the compound, salt or its pharmaceutical composition on claim 3. Paragraph 312 teaches the salt can be maleic acid salt.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed.

Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

9. Claims 35-37 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims of U.S. Patent No. 9717720, 10123999 and 10543206.

9717720: teaches IB in claims 1-12. 10123999: Makes IA in claim 9. 10543206: Makes a generic formula that encompasses the instant IA and IB and their pharmaceutical compositions.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D MARGARET M SEAMAN whose telephone number is (571)272-0694. The examiner can normally be reached on M-F 8-4 EDT Telework Home.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/D MARGARET M SEAMAN/
Primary Examiner, Art Unit 1625

Notice of References Cited	Application/Control No. 17/170,275	Applicant(s)/Patent Under Reexamination Wilson et al.	
	Examiner D MARGARET M SEAMAN	Art Unit 1625	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-9717720-B2	08-2017	Wilson; Jo Ann	C07D215/233	1/1
*	B	US-10123999-B2	11-2018	Wilson; Jo Ann	A61P35/00	1/1
*	C	US-10543206-B2	01-2020	Wilson; Jo Ann	A61K31/47	1/1
*	D	US-20120035212-A1	02-2012	Brown; Adrian St. Clair	A61P5/14	514/312
*	E	US-20090105299-A1	04-2009	BANNEN; LYNNE CANNE	C07D215/46	514/312
*	F	US-20070054928-A1	03-2007	Bannen; Lynne Canne	A61K31/506	514/266.2
*	G	US-7579473-B2	08-2009	Bannen; Lynne Canne	A61K31/4725	546/153
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

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

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/170,275	Wilson et al.
	Examiner	Art Unit
	D MARGARET M SEAMAN	1625

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	03/26/2021								
	1	-								
	2	-								
	3	-								
	4	-								
	5	-								
	6	-								
	7	-								
	8	-								
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	30	-								
	31	-								
	32	-								
	33	-								
	34	-								
	35	✓								
	36	✓								
	37	✓								

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/170,275	Wilson et al.
	Examiner	Art Unit
	D MARGARET M SEAMAN	1625

CPC - Searched*		
Symbol	Date	Examiner
A61K 31/47	03/26/2021	dms
C07D 215/233	03/26/2021	dms

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Inventor Name Search	03/26/2021	dms
STNext Structure search	03/26/2021	dms

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

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BIB DATA SHEET

CONFIRMATION NO. 8006

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
17/170,275	02/08/2021	514	1625	224990/10-039C6-US/483214

APPLICANTS
Exelixis, Inc., Alameda, CA;

INVENTORS
Jo Ann Wilson, San Francisco, CA;
Khalid Shah, Half Moon Bay, CA;

**** CONTINUING DATA ***************************
This application is a CON of 17/152,394 01/19/2021
which is a CON of 16/706,323 12/06/2019 ABN
which is a DIV of 16/151,653 10/04/2018 PAT 10543206
which is a DIV of 15/348,716 11/10/2016 PAT 10123999
which is a DIV of 13/984,559 03/20/2014 PAT 9717720
which is a 371 of PCT/US2012/024591 02/10/2012
which claims benefit of 61/441,520 02/10/2011
and claims benefit of 61/441,527 02/10/2011

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
02/24/2021

Foreign Priority claimed ❑ Yes ☑ No 35 USC 119(a-d) conditions met ❑ Yes ❑ No Verified and Acknowledged /D M SEAMAN/ Examiner's Signature	❑ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		CA	0	3	1

ADDRESS

JONATHAN P. O"BRIEN, PH.D.
HONIGMAN LLP
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402
UNITED STATES

TITLE

Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

FILING FEE RECEIVED		
1820	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	❑ All Fees ❑ 1.16 Fees (Filing) ❑ 1.17 Fees (Processing Ext. of time) ❑ 1.18 Fees (Issue) ❑ Other _____ ❑ Credit

Last Name: Shah
First Name: Khalid

Examiner: GRAHAM, D MARGARET (1655)

	ASC #		Patent #	Status	Filing Date	Inventor Name	Title
☐	15/566,858	Not Issued	41	10/16/2017	SHAH, Khalid	AGENTS, SYSTEMS AND METHODS FOR TREATING CANCER
☐	15/512,703	10034873	150	06/02/2017	Shah, Khalid	C-Met Modulator Pharmaceutical Compositions
☐	15/706,862	10285993	150	09/15/2017	Shah, Khalid	CRYSTALLINE FORM OF (S)-N-(5-((R)-2-(2,5-DIFLUOROPHENYL)-PYRRO...
☐	15/832,109	10633636	150	12/05/2017	Shah, Khalid	ONCOLYTIC VIRUS THERAPY FOR RESISTANT TUMORS
☐	15/872,782	10172861	150	01/16/2018	Shah, Khalid	CRYSTALLINE FORM OF (S)-N-(5-((R)-2-(2,5-DIFLUOROPHENYL)-PYRRO...
☐	15/918,881	10676515	150	06/21/2018	Shah, Khalid	MULTIMODAL TRAIL MOLECULES EXPRESSED IN T CELLS
☐	16/036,708	10548888	150	07/03/2018	Shah, Khalid	C-MET MODULATOR PHARMACEUTICAL COMPOSITIONS
☐	15/151,653	10543206	150	10/04/2018	Shah, Khalid	Processes for Preparing Quinoline Compounds and Pharmaceutical Co...
☐	16/386,368	10813936	150	03/27/2019	Shah, Khalid	CRYSTALLINE FORM OF (S)-N-(5-((R)-2-(2,5-DIFLUOROPHENYL)-PYRRO...
☐	16/417,352	Not Issued	19	Invalid Date	Shah, Khalid	CRYSTALLINE SOLID FORMS OF SALTS OF N-(4-[(6,7-DIMETHOXYQUIN...
☐	16/520,373	Not Issued	20	12/06/2019	Shah, Khalid	Liquid Dosage Forms to Treat Cancer
☐	16/671,894	10851061	150	11/01/2019	Shah, Khalid	Crystalline Solid Forms of N-(4-[(6,7-Dimethoxyquinolin-4-yl)oxy]phen...
☐	16/708,323	Not Issued	161	12/06/2019	Shah, Khalid	Processes for Preparing Quinoline Compounds and Pharmaceutical Co...
☐	16/715,455	Not Issued	20	12/16/2019	SHAH, Khalid	STEM CELL DELIVERED ONCOLYTIC HERPES SIMPLEX VIRUS AND MET...
☐	16/722,563	Not Issued	30	12/20/2019	Shah, Khalid	C-Met Modulator Pharmaceutical Compositions
☐	16/760,668	Not Issued	20	04/30/2020	SHAH, Khalid	MSC-EXPRESSED IMMUNOMODULATORS IN COMBINATION WITH CA...
☐	17/085,011	Not Issued	19	Invalid Date	SHAH, Khalid	COMPOSITIONS AND METHODS RELATED TO TUMOR CELL KILLERS AN...
☐	17/088,312	Not Issued	20	10/29/2020	Shah, Khalid	Crystalline Solid Forms of N-(4-[(6,7-Dimethoxyquinolin-4-yl)oxy]phen...
☐	17/152,308	Not Issued	19	01/19/2021	Shah, Khalid	Processes for Preparing Quinoline Compounds and Pharmaceutical Co...
☐	17/170,275	Not Issued	37	02/08/2021	Shah, Khalid	Processes for Preparing Quinoline Compounds and Pharmaceutical Co...
☐	61/822,883	Not Issued	159	01/31/2011	Shah, Khalid	MULTIMODAL TRAIL MOLECULES AND USES IN CELLULAR THERAPIES
☐	61/675,613	Not Issued	159	07/24/2012	Shah, Khalid	Methods and Compositions for Treating Cancer
☐	61/694,895	Not Issued	159	08/30/2012	Shah, Khalid	Compositions and methods for treating cancer
☐	61/914,481	Not Issued	159	12/11/2013	Shah, Khalid	Compositions, Cells and Methods for Treating Tumors

☐	61/939,985	Not Issued	159	02/14/2014	Shah, Khalid	Solid forms of N-[4-[[6,7-Dimethoxyquinolin-4-yl]oxy]phenyl]-N'-(4-flu...

Last Name: Wilson
First Name: Jo Ann

Customer Number: 0 Assignment Record

	Appl. #	Patent #	Status	Filing Date	Inventor Name	Title
☐	13/129,183	Not Issued	164	07/24/2012	Wilson, Jo Ann	METHODS OF PREPARING QUINOLINE DERIVATIVES
☐	13/132,859	Not Issued	164	07/24/2012	Wilson, Jo Ann	Methods of Preparing Quinoline Derivatives
☐	13/810,537	9724342	150	08/26/2013	Wilson, Jo Ann	C-Met Modulator Pharmaceutical Compositions
☐	13/810,546	Not Issued	161	08/27/2013	Wilson, Jo Ann	C-Met Modulator Pharmaceutical Compositions
☐	13/984,552	9717720	150	03/20/2014	Wilson, Jo Ann	PROCESSES FOR PREPARING QUINOLINE COMPOUNDS AND PH/
☐	14/355,251	9365516	150	04/21/2014	Wilson, Jo Ann	PROCESS FOR PREPARING QUINOLINE DERIVATIVES
☐	15/133,288	9969692	150	04/20/2016	Wilson, Jo Ann	Process for Preparing Quinoline Derivatives
☐	15/348,716	10123999	150	11/10/2016	Wilson, Jo Ann	Processes for Preparing Quinoline Compounds and Pharmaceut
☐	15/426,806	10039757	150	02/07/2017	Wilson, Jo Ann	C-Met Modulator Pharmaceutical Compositions
☐	15/612,702	10084873	150	06/02/2017	Wilson, Jo Ann	C-Met Modulator Pharmaceutical Compositions
☐	15/955,286	Not Issued	160	04/17/2018	Wilson, Jo Ann	Processes for Preparing Quinoline Derivatives
☐	15/986,298	10548888	150	07/03/2018	Wilson, Jo Ann	C-MET MODULATOR PHARMACEUTICAL COMPOSITIONS
☐	16/151,683	10543206	150	10/04/2018	Wilson, Jo Ann	Processes for Preparing Quinoline Compounds and Pharmaceut
☐	16/706,213	Not Issued	161	12/06/2019	Wilson, Jo Ann	Processes for Preparing Quinoline Compounds and Pharmaceut
☐	16/722,563	Not Issued	30	12/20/2019	Wilson, Jo Ann	C-Met Modulator Pharmaceutical Compositions
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☐	16/663,367	Not Issued	41	10/23/2019	Wilson, Jo Ann Z.	CRYSTALLINE FORMS OF MNK INHIBITORS
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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	2021-02-08
First Named Inventor	Jo Ann Wilson
Art Unit	TBD
Examiner Name	TBD
Attorney Docket Number	224990/10-039C6-US/483214

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	9724342		2017-08-08	WILSON, et al.	
	2	9809549		2017-11-07	BROWN, et al.	
	3	7579473		2009-08-25	EXELIXIS, INC.	
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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.M.S/

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	First Named Inventor	Jo Ann Wilson
	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

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	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

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U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20080161305		2008-07-03	FORSYTH, et al.	
	2	20110077233		2011-03-31	BANNEN, et al.	
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	4	20140066444		2014-03-26	SMITH, et al.	
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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.M.S/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

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	Attorney Docket Number	224990/10-039C6-US/483214

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	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

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	First Named Inventor	Jo Ann Wilson
	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

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	First Named Inventor	Jo Ann Wilson
	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

	50	20140256938		2014-09-11	WISON, et al.	
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	Attorney Docket Number	224990/10-039C6-US/483214

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	65	20180311229		2018-11-01	WILSON, et al.	
	66	20190151302		2019-05-23	AFTAB, et al.	
	67	20190091215		2019-03-28	AFTAB, et al.	
	68	20050049267		2005-03-03	SUTO, et al.	

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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2009136663	WO		2009-11-12	TAKEDA PHARMACEUTICAL COMPANY LIMITED		☐

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.M.S/

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	First Named Inventor	Jo Ann Wilson
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	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

	2	2005030140	WO		2005-04-07	EXELIXIS, INC.		☐
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If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Kurzrock R et al. "379 POSTER A phase I study of XL 184, a MET, VEGFR2, and RET kinase inhibitor, administered orally to patients (pts) with advanced malignancies, including a subgroup of pts with medullary thyroid cancer (MTC)." Eropean journal of cancer. supplement, vol 6, no 12, 2008-10-01, 119.	☐
	2	European Medicines Agency, "Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: chemical substances", May 2000.	☐
	3	Sigma-Aldrich Corporation, "Cabozantinib Material Safety Data Sheet", Version 5.0, October 20, 2014, retrieved from the internet at http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=CDS009101&brand=ALDRICH&PageToGoToURL=http%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Faldrich%2Fcds009101%3Flang%3Den on October 1, 2015.	☐
	4	United States Department of Health and Human Services, "Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products", Revision 2, November 2003, retrieved from the internet at www.fda.gov/downloads/drugs/guidancecomplianceregulatory information/guidances/ucm073369.pdf on October 1, 2015.	☐

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.M.S/

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	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

	5	International Search Report for PCT/US2012/024591, mailed May 25, 2012	☐
	6	KIBBE, A.H. Handbook of Pharmaceutical Excipients, 3rd edition: American Pharmactical Association and Pharmaceutical Press, ISBN 0-85369-381-1, 2000 (pages 110,244,305,143,102,501,534,386,160)	☐

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

EXAMINER SIGNATURE

Examiner Signature	/D MARGARET M SEAMAN/	Date Considered	03/26/2021

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.M.S/

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	First Named Inventor	Jo Ann Wilson
	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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

OR

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

☐ See attached certification statement.

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

☒ A certification statement is not submitted herewith.

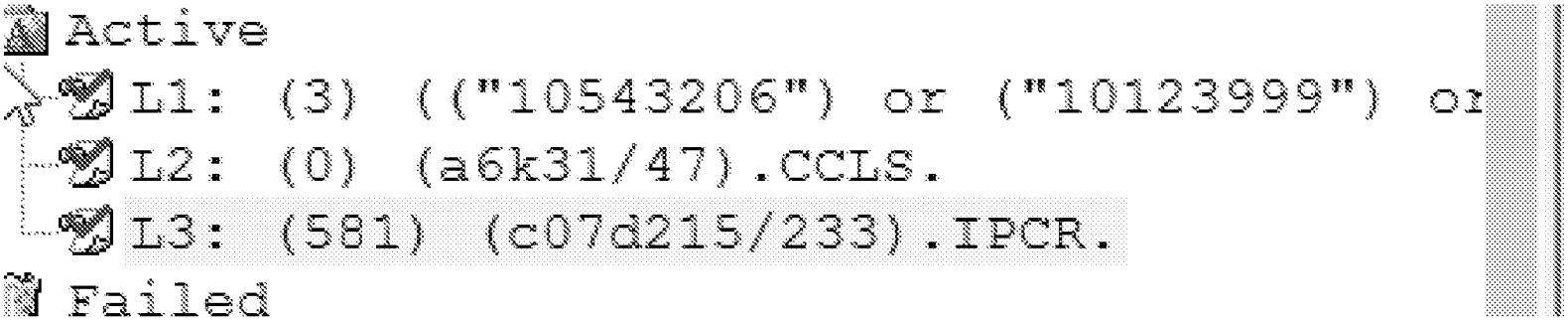
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Signature	/Heidi M. Berven/	Date (YYYY-MM-DD)	2021-02-08
Name/Print	Heidi M. Berven, Ph.D.	Registration Number	48951

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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L2: (0) (a6k31/47).CCLS.
L3: (581) (c07d215/233).IPCR.
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L4 87 S L3 FULL ...

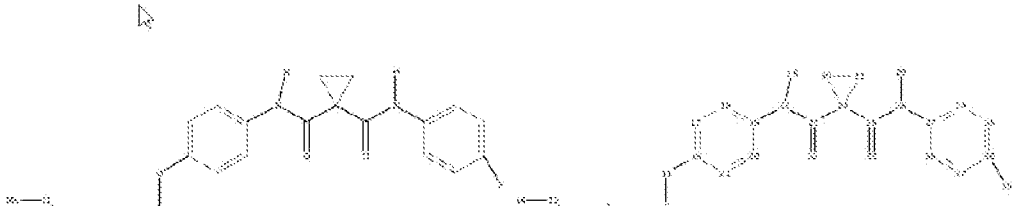
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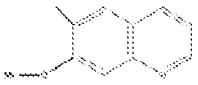
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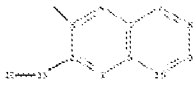
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L7 37 S L6 AND PY<2011 ...

2







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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/170,275	02/08/2021	Jo Ann Wilson	224990/10-039C6-US/483214	8006

91684 7590 03/23/2021

JONATHAN P. O''BRIEN, PH.D.
HONIGMAN LLP
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402

EXAMINER	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
03/23/2021	ELECTRONIC

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The time period for reply, if any, is set in the attached communication.

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In re Application of
WILSON, JO ANN, et al.
Application No.: 17/170,275
Filed: 08 February 2021
Attorney Docket No.: 224990/10-039C6-US/483214
For: PROCESSES FOR PREPARING QUINOLINE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH COMPOUNDS

: DECISION ON REQUEST TO
: PARTICIPATE IN THE PATENT
: PROSECUTION HIGHWAY
: PROGRAM AND PETITION
: TO MAKE SPECIAL UNDER
: 37 CFR 1.102(a)

This is a decision on the request to participate in the Patent Prosecution Highway (PPH) program and the petition under 37 CFR 1.102(a), filed February 08, 2021, to make the above-identified application special.

The request and petition are **GRANTED**.

DISCUSSION

A grantable request to participate in the PPH pilot program and petition to make special require:

1. The U.S. application for which participation in the Global/IP5 PPH pilot program is requested must have the same earliest date, whether this is the priority date or filing date, as that of a corresponding national or regional application filed with another Global/IP5 PPH participating office or a corresponding PCT international application for which one of the Global/IP5 PPH participating offices was the International Searching Authority (ISA) or the International Preliminary Examining Authority (IPEA).

2. Applicant must:

    a. Ensure all the claims in the U.S. application must sufficiently correspond or be amended to sufficiently correspond to the allowable/patentable claim(s) in the corresponding Office of Earlier Examination (OEE) application and
    b. Submit a claims correspondence table in English;

3. Examination of the U.S. application has not begun;

4. Applicant must submit:

a. Documentation of prior office action:
   i. a copy of the office action(s) just prior to the "Decision to Grant a Patent" from each of the Global/IP5 PPH participating office application(s) containing the allowable/patentable claim(s) or
   ii. if the allowable/patentable claims(s) are from a "Notification of Reasons for Refusal" then the Notification of Reasons for Refusal or
   iii. if the Global/IP5 PPH participating office application is a first action allowance then no office action from the Global/IP5 PPH participating office is necessary should be indicated on the request/petition form or
   iv. the latest work product in the international phase of the OEE PCT application;

b. An English language translation of the Global/IP5 PPH participating office action or work product from (4)(a)(i)-(ii) or (iv) above;

5. Applicant must submit:

   a. An IDS listing the documents cited by the Global/IP5 PPH participating office examiner in the Global/IP5 PPH participating office action or work product (unless already submitted in this application);
   b. Copies of the documents except U.S. patents or U.S. patent application publications (unless already submitted in this application).

The request to participate in the PPH pilot program and petition comply with the above requirements. Accordingly, the above-identified application has been accorded "special" status.

Telephone inquiries concerning this decision should be directed to Dale Hall at (571)272-3586.

All other inquiries concerning the examination or status of the application is accessible in the PAIR system at http://portal.uspto.gov.

This application will be forwarded to the examiner for action on the merits commensurate with this decision once this application's formality reviews have been completed.

/Dale A. Hall/
Paralegal Specialist, OPET

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/170,275	02/08/2021	Jo Ann Wilson	224990/10-039C6-US/483214	8006

91684 7590 03/18/2021

JONATHAN P. O''BRIEN, PH.D.
HONIGMAN LLP
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402

EXAMINER	
ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
03/18/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

apeters@honigman.com
hberven@honigman.com
patent@honigman.com

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 17/170,275	**Applicant(s)** Wilson et al.	
	Examiner CHERYL P GIBSON BAYLOR	**Art Unit** OPET	**AIA (FITF) Status** No

1. THE REQUEST FILED 08 February 2021 IS **GRANTED** .

   The above-identified application has met the requirements for prioritized examination
   - A. ☑ for an original nonprovisional application (Track I).
   - B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination**. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:
   - A. filing a **petition for extension of time** to extend the time period for filing a reply;
   - B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims** , or a multiple dependent claim;
   - C. filing a **request for continued examination** ;
   - D. filing a notice of appeal;
   - E. filing a request for suspension of action;
   - F. mailing of a notice of allowance;
   - G. mailing of a final Office action;
   - H. completion of examination as defined in 37 CFR 41.102; or
   - I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to CHERYL GIBSON BAYLOR at (571)272-3213. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/CHERYL GIBSON BAYLOR/ Paralegal Specialist, OPET	

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
17/170,275	02/08/2021	1629	1820	224990/10-039C6-US/483214	3	1

CONFIRMATION NO. 8006

FILING RECEIPT

91684
JONATHAN P. O"BRIEN, PH.D.
HONIGMAN LLP
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402

OC000000123627847

Date Mailed: 02/25/2021

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Jo Ann Wilson, San Francisco, CA;
Khalid Shah, Half Moon Bay, CA;

Applicant(s)

Exelixis, Inc., Alameda, CA;

Power of Attorney: The patent practitioners associated with Customer Number 91684

Domestic Priority data as claimed by applicant

This application is a CON of 17/152,394 01/19/2021
which is a CON of 16/706,323 12/06/2019
which is a DIV of 16/151,653 10/04/2018 PAT 10543206
which is a DIV of 15/348,716 11/10/2016 PAT 10123999
which is a DIV of 13/984,559 03/20/2014 PAT 9717720
which is a 371 of PCT/US2012/024591 02/10/2012
which claims benefit of 61/441,520 02/10/2011
and claims benefit of 61/441,527 02/10/2011

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

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

If Required, Foreign Filing License Granted: 02/24/2021

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 17/170,275**

Projected Publication Date: 06/03/2021

Non-Publication Request: No

Early Publication Request: No

Title

Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

Preliminary Class

514

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

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

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

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

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

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 17/170,275

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	320
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	700
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	800
TOTAL CLAIMS (37 CFR 1.16(i))	3 minus 20 =	*			OR	x 100 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*				x 480 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1820

APPLICATION AS AMENDED - PART II

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

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

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

PTO/AIA/82A (07-13)
Approved for use through 03/31/2021. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	TBD
Filing Date	February 8, 2021
First Named Inventor	Jo Ann Wilson
Title	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
Art Unit	TBD
Examiner Name	TBD
Attorney Docket Number	224990/10-039C6-US/483214

SIGNATURE of Applicant or Patent Practitioner

Signature	/Heidi M. Berven/	Date (Optional)	February 8, 2021
Name	Heidi M. Berven, Ph.D.	Registration Number	48951
Title (if Applicant is a juristic entity)	Attorney for applicant		
Applicant Name (if Applicant is a juristic entity)	Exelixis, Inc.		

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

☑ *Total of 1 forms are submitted.

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

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

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

PTO/AIA/82B (07-13)
Approved for use through 01/31/2018 OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

POWER OF ATTORNEY BY APPLICANT

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

Application Number	Filing Date

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

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 91684

OR

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

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

☑ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

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

Exelixis, Inc.

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

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

Signature		Date (Optional)	9/26/19
Name	Jeffrey Hesseldenz		
Title	Executive Vice President and General Counsel		

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

☐ Total of forms are submitted.

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

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Jo Ann Wilson, et al.	Art Unit:	TBD
Application No.:	TBD	Examiner:	TBD
Filing Date:	February 8, 2021	Conf. No.:	TBD
Atty. Docket No.:	224990/10-039C6-US/483214		

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

CERTIFICATE OF TRANSMISSION UNDER 37 C.F.R. § 1.8(a)

The undersigned hereby certifies that the following documents are being submitted in accordance with 37 C.F.R. § 1.6(a)(4) on the 8th day of February 2021.

1. Cover Letter to the Commissioner;
2. Utility Patent Application Transmittal form (PTO/AIA/15);
3. Application Data Sheet (PTO/AIA/14);
4. Specification, Claims, and Abstract;
5. Preliminary Amendment under 37 C.F.R. § 1.115;
6. Issued Claims of AU 2012214322;
7. Request for Prioritized Examination under 37 C.F.R. § 1.102(e);
8. Request for Participation in the Global/IP5 Patent Prosecution Highway (PPH) Pilot Program in the USPTO (PTO/SB/20GLBL);
9. Information Disclosure Statement by Applicant (PTO/SB/08a);
10. Fee Transmittal (PTO/SB/17);
11. Executed Inventor Declaration (2 sheets)(PTO/AIA/01);
12. Executed Power of Attorney with Transmittal (PTO/AIA/82A&B); and
13. This Certificate of Transmission under 37 C.F.R. § 1.8(a).

/Amy L. Peters/

Amy L. Peters (for Heidi M. Berven, Reg. No. 48,951)

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
First Named Inventor/Applicant Name:	Jo Ann Wilson
Filer:	Heid Marie Berven/Amy Peters
Attorney Docket Number:	224990/10-039C6-US/483214

Filed as Large Entity

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	320	320
UTILITY SEARCH FEE	1111	1	700	700
UTILITY EXAMINATION FEE	1311	1	800	800
REQUEST FOR PRIORITIZED EXAMINATION	1817	1	4200	4200
Pages:				
Claims:				
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**6160**

Electronic Acknowledgement Receipt

EFS ID:	41867064
Application Number:	17170275
International Application Number:	
Confirmation Number:	8006
Title of Invention:	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
First Named Inventor/Applicant Name:	Jo Ann Wilson
Customer Number:	91684
Filer:	Heid Marie Berven/Amy Peters
Filer Authorized By:	Heid Marie Berven
Attorney Docket Number:	224990/10-039C6-US/483214
Receipt Date:	08-FEB-2021
Filing Date:	
Time Stamp:	16:41:46
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$6160
RAM confirmation Number	E202128G43403792
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		2021-02-08_EX10-039C6-US_Application_Filing_Docs.pdf	4374877 a74eee3c19b2224f2ce395253b03a8612761d10b	yes	93

Multipart Description/PDF files in .zip description

Document Description	Start	End
Miscellaneous Incoming Letter	1	2
Transmittal of New Application	3	3
Application Data Sheet	4	11
Specification	12	48
Claims	49	57
Abstract	58	58
Preliminary Amendment	59	59
Claims	60	60
Specification	61	61
Applicant Arguments/Remarks Made in an Amendment	62	68
Petition to make special under Patent Prosecution Hwy	69	72
TrackOne Request	73	73
Petition to make special under Patent Prosecution Hwy	74	75
Information Disclosure Statement (IDS) Form (SB08)	76	87
Transmittal Letter	88	88

	Oath or Declaration filed		89	90	
	Power of Attorney		91	92	
	Miscellaneous Incoming Letter		93	93	
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	40569 ff6fbd647ed86b5cd2fb51f71ad8be3ad81cd2fe	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	4415446		

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.

HONIGMAN

Heidi M. Berven, Ph.D.
Office: 269.337.7710
Mobile: 269.365.8962
hberven@honigman.com

VIA EFS

February 8, 2021

Commissioner for Patents
United States Patent and Trademark Office
P. O. Box 1450
Alexandria, VA 22313

Re: US Patent Application No.: TBD
Inventors: Jo Ann Wilson, et al.
Filing Date: February 8, 2021
Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
Attorney Docket No.: 224990/10-039C6-US/483214

Dear Sir or Madam:

Enclosed for filing please find the following documents:

1. This Cover Letter to the Commissioner;
2. Utility Patent Application Transmittal form (PTO/AIA/15);
3. Application Data Sheet (PTO/AIA/14);
4. Specification, Claims, and Abstract;
5. Preliminary Amendment under 37 C.F.R. § 1.115;
6. Issued Claims of AU 2012214322;
7. Request for Prioritized Examination under 37 C.F.R. § 1.102(e);
8. Request for Participation in the Global/IP5 Patent Prosecution Highway (PPH) Pilot Program in the USPTO (PTO/SB/20GLBL);
9. Information Disclosure Statement by Applicant (PTO/SB/08a);
10. Fee Transmittal (PTO/SB/17);
11. Executed Inventor Declaration (2 sheets)(PTO/AIA/01);
12. Executed Power of Attorney with Transmittal (PTO/AIA/82A&B); and
13. Certificate of Transmission under 37 C.F.R. § 1.8(a).

This application is a continuation application of United States Serial Number 17/152,394 filed January 19, 2021, which is a continuation of United States Application Serial Number 16/706,323, filed December 6, 2019, which is a divisional of United States Application Serial Number 16/151,653, filed October 4, 2018, now United States Patent Number 10,543,206, which is a division of United States Application Serial Number 15/348,716, filed November 10, 2016, now United States Patent Number 10,123,999, which is a divisional of United States Application Serial Number 13/984,559, filed March 20, 2014, now united States Patent Number 9,717,720, which claims priority under 35 U.S.C. § 371 to Patent Cooperation Treaty Application Number

PCT/US2012/024591, filed February 10, 2012, which claims the benefit of United States Provisional Application Number 61/441,520, filed February 10, 2011, and United States Provisional Application Number 61/441,527, filed February 10, 2011, the entire contents of which are incorporated herein by reference.

Included with these filing documents, Applicant also provides its Request for Participation in the Global/IP5 Patent Prosecution Highway (PPH) Pilot Program and petition to make this application special under the PPH Pilot Program. The Applicant notes that the claims set forth in the preliminary amendment are substantially identical to the claims that the Applicant submitted to IP Australian on March 27, 2017, which were subsequently found allowable.

Applicant also provides herewith a Request for Track One prosecution along with the pertinent processing and examination fees.

The Applicant notes that the filing of the enclosed Information Disclosure Statement shall not be construed to be an admission that the information cited in the statement qualifies as prior art under 35 U.S.C. § § 102 or 103, or is considered to be material to patentability as defined in 37 C.F.R. § 1.56(b). It is believed that no fee is due pursuant to 37 C.F.R. § 1.97(b)(3). In accordance with 37 C.F.R. § 1.98(d), copies of the cited references are not provided because they were previously provided to the Office in an earlier application. The Applicant will gladly provide the references to the Examiner, however, upon request.

It is believed that due with this submission is the Basic Utility Application Fee of $320.00 set forth in 37 C.F.R. § 1.16(a), the Utility Search Fee of $700.00 set forth in § 1.16(k), the Utility Examination Fee of $800.00 set forth in § 1.16(o), the processing fee of $140.00 set forth in 37 C.F.R. 1.17(i), and the prioritized examination fee of $4,200.00 set forth in 37 C.F.R. § 1.17(c). The Applicant hereby authorizes the Patent Office to charge this total of $6,160.00 to Deposit Account No. 503145, referencing Attorney Docket Number 224990/10-039C6-US/483214. It is believed that no other fees are due at this time. However, if there are any additional charges for this submission, or any credits, please apply them to Deposit Account Number 503145, referencing Attorney Docket Number 224990/10-039C6-US/483214.

Very truly yours,

HONIGMAN LLP

/Heidi M. Berven/

Heidi M. Berven, Ph.D.
Reg. No. 48,951

HMB/ayp

Enclosures

PTO/SB/20GLBL (04-15)
Approved for use through 04/30/2018. OMB 0651-0058
U.S. Patent and Trademark Office; U.S DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

REQUEST FOR PARTICIPATION IN THE GLOBAL/IP5 PATENT PROSECUTION HIGHWAY (PPH) PILOT PROGRAM IN THE USPTO

Application No.:	TBD	First Named Inventor:	Jo Ann Wilson
Filing Date:	February 8, 2021	Attorney Docket No.:	224990/10-039C6-US/483214
Title of the Invention:	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Comp		

THIS REQUEST FOR PARTICIPATION IN THE PPH PILOT PROGRAM ALONG WITH THE REQUIRED DOCUMENTS MUST BE SUBMITTED VIA EFS-WEB. INFORMATION REGARDING EFS-WEB IS AVAILABLE AT HTTP://WWW.USPTO.GOV/PATENTS-APPLICATION-PROCESS/FILING-ONLINE/ABOUT-EFS-WEB.

APPLICANT HEREBY REQUESTS PARTICIPATION IN THE PATENT PROSECUTION HIGHWAY (PPH) PILOT PROGRAM AND PETITIONS TO MAKE THE ABOVE-IDENTIFIED APPLICATION SPECIAL UNDER THE PPH PILOT PROGRAM.

Office of earlier examination (OEE): Australia (IP Australia)

OEE application number: AU 2012214322

Both the OEE application and the above-identified U.S. application have the following earliest date (filing or priority date): February 10, 2011

Type of OEE work product relied upon: Decision to grant a patent

Mailing date of OEE work product: April 13, 2017

Supporting Documents

One or more of the required documents below may be available electronically from the Dossier Access System or PATENTSCOPE (see https://www.jpo.go.jp/ppph-portal/filewrapper.htm). If the applicant requests the USPTO to attempt to obtain a document electronically and such attempt is unsuccessful, the applicant will be required to supply the document. Accordingly, to avoid dismissal of the initial PPH request and potential denial of participation in the PPH program, the applicant should verify that the document is actually available via the Dossier Access System or PATENTSCOPE before requesting retrieval. If the applicant is unable to verify availability, then the applicant should submit the document with the PPH request.

1. OEE Work Product and Translation

A copy of the OEE work product and translation if not already in English:

☐ Attached ☐ Previously submitted ☐ Not required because the decision to grant a patent was the first office action

☒ Applicant requests the USPTO to attempt to obtain the document(s) from the Dossier Access System or PATENTSCOPE

2. References Cited in OEE Work Product

A listing of references cited in the OEE work product and document copies (except U.S. patents and U.S. published patent applications):

☒ Attached ☐ Previously Submitted ☐ Not required because no references were cited in the OEE work product

☐ Applicant requests the USPTO to attempt to obtain the document(s) from the Dossier Access System or PATENTSCOPE

This collection of information is required by 35 U.S.C. 119, 37 CFR 1.55, and 37 CFR 1.102(d). The information is required to obtain or retain a benefit by the public, which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.

REQUEST FOR PARTICIPATION IN THE GLOBAL/IP5 PPH PILOT PROGRAM IN THE USPTO
(continued)

Application No.:	TBD	First Named Inventor:	Jo Ann Wilson

3. Claims Correspondence Certification Statement

All of the claims in this application sufficiently correspond to the patentable/allowable claims in the OEE application.

4. Claims Correspondence Table

Claims in US Application	Patentable Claims in OEE Application	Explanation regarding the correspondence
1-34		Cancelled
35	1	Substantially Identical
36	3	Substantially Identical
37	4	Substantially Identical

Signature	/Heidi M. Berven/	Date	2021-02-08
Name (Print/Typed)	Heidi M. Berven, Ph.D.	Registration Number	48951

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	2021-02-08
First Named Inventor	Jo Ann Wilson
Art Unit	TBD
Examiner Name	TBD
Attorney Docket Number	224990/10-039C6-US/483214

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	9724342		2017-08-08	WILSON, et al.	
	2	9809549		2017-11-07	BROWN, et al.	
	3	7579473		2009-08-25	EXELIXIS, INC.	
	4	7977345		2011-07-12	EXELIXIS, INC.	
	5	7999006		2011-08-16	EXELIXIS, INC.	
	6	8067436		2011-11-29	EXELIXIS, INC.	
	7	8178532		2012-05-15	EXELIXIS, INC.	
	8	8314232		2012-11-20	EXELIXIS, INC.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
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	First Named Inventor	Jo Ann Wilson
	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

	9	8476298		2013-07-02	EXELIXIS, INC.	
	10	8497284		2013-07-30	EXELIXIS, INC.	
	11	8673912		2014-03-18	EXELIXIS, INC.	
	12	8877776		2014-11-04	EXELIXIS, INC.	
	13	9174947		2015-11-03	EXELIXIS, INC.	
	14	9365516		2016-06-14	EXELIXIS, INC.	
	15	7166722		2007-01-23	MATSUNAGA, et al.	
	16	7169789		2007-01-30	KUBO, et al.	
	17	5358941		1994-10-25	BECHARD, et al.	
	18	9717720		2017-08-01	WILSON, et al.	
	19	9969692		2018-05-15	WILSON, et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	
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	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

	20	10034873		2018-07-31	WILSON, et al.	
	21	10039757		2018-09-08	WILSON, et al.	
	22	10166225		2019-01-01	AFTAB, et al.	
	23	10123999		2018-11-13	WILSON, et al.	

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

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20080161305		2008-07-03	FORSYTH, et al.	
	2	20110077233		2011-03-31	BANNEN, et al.	
	3	20120252840		2012-10-04	AFTAB, et al.	
	4	20140066444		2014-03-26	SMITH, et al.	
	5	20150057310		2015-02-26	BROWN, et al.	

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	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

	6	20150202196		2015-07-23	BANNEN, et al.	
	7	20160000772		2016-01-07	AFTAB, et al.	
	8	20160051532		2016-02-25	AFTAB, et al.	
	9	20160229805		2016-08-11	WILSON, et al.	
	10	20170143689		2017-05-25	WILSON, et al.	
	11	20170266178		2017-09-21	WILSON, et al.	
	12	20170275251		2017-09-28	BROWN, et al.	
	13	20180002289		2018-01-04	BROWN, et al.	
	14	20180037552		2018-02-08	BROWN, et al.	
	15	20090274693		2009-11-05	EXELIXIS, INC.	
	16	20110077233		2011-03-31	EXELIXIS, INC.	

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	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

	17	20120070368		2012-03-22	EXELIXIS, INC.	
	18	20120184523		2012-07-19	EXELIXIS, INC.	
	19	20120252840		2012-10-04	EXELIXIS, INC.	
	20	20120282179		2012-11-08	EXELIXIS, INC.	
	21	20130030172		2013-01-31	EXELIXIS, INC.	
	22	20130142790		2013-01-31	EXELIXIS, INC.	
	23	20130143881		2013-01-31	EXELIXIS, INC.	
	24	20130150363		2013-06-06	EXELIXIS, INC.	
	25	20130197230		2013-06-06	EXELIXIS, INC.	
	26	20130252940		2013-06-13	EXELIXIS, INC.	
	27	20130252956		2013-08-01	EXELIXIS, INC.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

	28	20130330377		2013-09-26	EXELIXIS, INC.	
	29	20130337015		2013-09-26	EXELIXIS, INC.	
	30	20140057943		2013-12-12	EXELIXIS, INC.	
	31	20140057908		2013-12-19	EXELIXIS, INC.	
	32	20140066444		2014-02-27	EXELIXIS, INC.	
	33	20140155396		2014-02-27	EXELIXIS, INC.	
	34	20140179736		2014-03-06	EXELIXIS, INC.	
	35	20070054928		2007-03-08	BANNEN, et al.	
	36	20140200242		2014-06-05	EXELIXIS, INC.	
	37	20140228401		2014-06-26	EXELIXIS, INC.	
	38	20140302012		2014-07-17	EXELIXIS, INC.	

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	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

	39	20140323522		2014-08-14	EXELIXIS, INC.	
	40	20150057310		2014-10-09	EXELIXIS, INC.	
	41	20150196545		2014-10-30	EXELIXIS, INC.	
	42	20150202196		2015-02-26	EXELIXIS, INC.	
	43	20150376133		2015-07-16	EXELIXIS, INC.	
	44	20160000772		2015-07-23	EXELIXIS, INC.	
	45	20160051532		2015-12-31	EXELIXIS, INC.	
	46	20160185725		2016-01-07	EXELIXIS, INC.	
	47	20050209247		2005-09-22	CHIRON CORPORATION	
	48	20070078159		2007-04-05	MATSUSHIMA, et al.	
	49	20110059081		2011-03-10	QUINTILES TRANSNATIONAL CORP.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

	50	20140256938		2014-09-11	WISON, et al.	
	51	20160220554		2016-08-04	SMITH, et al.	
	52	20080004273		2008-01-03	RAEPPEL, et al.	
	53	20140121239		2014-05-01	AFTAB, et al.	
	54	20140221372		2014-08-07	KULKARNI, et al.	
	55	20150133494		2015-05-14	AFTAB, et al.	
	56	20150238477		2015-08-27	AFTAB, Dana T.	
	57	20160031818		2016-02-04	AFTAB, et al.	
	58	20160082019		2016-03-24	SWEENEY, et al.	
	59	20170087143		2017-03-30	AFTAB, et al.	
	60	20090203729		2009-08-13	INOUE, et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
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	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

	61	20190030021		2019-01-31	WILSON, et al.	
	62	20170057921		2017-03-02	WILSON, et al.	
	63	20170355678		2017-12-14	BANNEN, et al.	
	64	20180230100		2018-08-16	WILSON, et al.	
	65	20180311229		2018-11-01	WILSON, et al.	
	66	20190151302		2019-05-23	AFTAB, et al.	
	67	20190091215		2019-03-28	AFTAB, et al.	
	68	20050049267		2005-03-03	SUTO, et al.	

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

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2009136663	WO		2009-11-12	TAKEDA PHARMACEUTICAL COMPANY LIMITED		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
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	Filing Date	2021-02-08
	First Named Inventor	Jo Ann Wilson
	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

	2	2005030140	WO		2005-04-07	EXELIXIS, INC.		☐
	3	2010083414	WO		2010-07-22	EXELIXIS, INC.		☐
	4	2011017639	WO		2011-02-10	EXELIXIS, INC.		☐
	5	2012009722	WO		2012-01-19	EXELIXIS, INC.		☐
	6	2012109510	WO		2012-06-16	WILSON, Jo Ann		☐

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

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Kurzrock R et al. "379 POSTER A phase I study of XL 184, a MET, VEGFR2, and RET kinase inhibitor, administered orally to patients (pts) with advanced malignancies, including a subgroup of pts with medullary thyroid cancer (MTC)." Eropean journal of cancer. supplement, vol 6, no 12, 2008-10-01, 119.	☐
	2	European Medicines Agency, "Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: chemical substances", May 2000.	☐
	3	Sigma-Aldrich Corporation, "Cabozantinib Material Safety Data Sheet", Version 5.0, October 20, 2014, retrieved from the internet at http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=CDS009101&brand=ALDRICH&PageToGoToURL=http%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Faldrich%2Fcds009101%3Flang%3Den on October 1, 2015.	☐
	4	United States Department of Health and Human Services, "Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products", Revision 2, November 2003, retrieved from the internet at www.fda.gov/downloads/drugs/guidancecomplianceregulatory information/guidances/ucm073369.pdf on October 1, 2015.	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
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	Filing Date	2021-02-08
	First Named Inventor	Jo Ann Wilson
	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

	5	International Search Report for PCT/US2012/024591, mailed May 25, 2012	☐
	6	KIBBE, A.H. Handbook of Pharmaceutical Excipients, 3rd edition: American Pharmactical Association and Pharmaceutical Press, ISBN 0-85369-381-1, 2000 (pages 110,244,305,143,102,501,534,386,160)	☐

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

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	
	Filing Date	2021-02-08
	First Named Inventor	Jo Ann Wilson
	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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

OR

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

☐ See attached certification statement.

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

☒ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Heidi M. Berven/	Date (YYYY-MM-DD)	2021-02-08
Name/Print	Heidi M. Berven, Ph.D.	Registration Number	48951

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

PTO/SB/17 (10-20)
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FEE TRANSMITTAL

Complete if known	
Application Number	
Filing Date	February 8, 2021
First Named Inventor	Jo Ann Wilson
Examiner Name	TBD
Art Unit	TBD
Practitioner Docket No.	224990/10-039C6-US/483214

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29. Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

TOTAL AMOUNT OF PAYMENT ($) 6,160.00

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☒ Deposit Account Deposit Account Number: 503145 Deposit Account Name: Honigman LLP

For the above-identified deposit account, the Director is hereby authorized to (check all that apply):

☒ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☒ Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17 ☒ Credit any overpayment of fee(s)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES (U = undiscounted fee; S = small entity fee; M = micro entity fee)

	FILING FEES			SEARCH FEES			EXAMINATION FEES			
Application Type	**U ($)**	**S ($)**	**M ($)**	**U ($)**	**S ($)**	**M ($)**	**U ($)**	**S ($)**	**M ($)**	**Fees Paid ($)**
Utility	320	160*	80	700	350	175	800	400	200	$1,820.00
Design	220	110	55	160	80	40	640	320	160	$0
Plant	220	110	55	440	220	110	660	330	165	$0
Reissue	320	160	80	700	350	175	2,320	1,160	580	$0
Provisional	300	150	75	0	0	0	0	0	0	$0

* The $160 small entity status filing fee for a utility application is further reduced to $80 for a small entity status applicant who files the application via EFS-Web.

2. EXCESS CLAIM FEES

Fee Description	**Undiscounted Fee ($)**	**Small Entity Fee ($)**	**Micro Entity Fee ($)**
Each claim over 20 (including Reissues)	100	50	25
Each independent claim over 3 (including Reissues)	480	240	120
Multiple dependent claims	860	430	215

Total Claims		**Extra Claims**	**Fee ($)**		**Fee Paid ($)**
_____	-20 or HP =	_____ x	_____	=	$0

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims		**Extra Claims**	**Fee ($)**		**Fee Paid ($)**
_____	-3 or HP =	_____ x	_____	=	$0

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims	**Fee ($)**	**Fee Paid ($)**
	_____	$0

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $420 ($210 for small entity) ($105 for micro entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets		**Extra Sheets**		**Number of each additional 50 or fraction thereof**		**Fee ($)**		**Fee Paid ($)**
_____	- 100 =	_____	/ 50 =	_____ (round **up** to a whole number)	x	_____	=	$0

4. OTHER FEE(S)

	Fees Paid ($)
Non-English specification, $140 fee ($70 for small entity) ($35 for micro entity)	$0
Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, $400 fee ($200 small or micro entity)	$0
Other (e.g., late filing surcharge): Prioritized Examination Fee, Processing Fee	$4,340.00

SUBMITTED BY

Signature	/Heidi M. Berven/	Registration No. (Attorney/Agent) 48951	Telephone (269) 337-7710
Name (Print/Type)	Heidi M. Berven, Ph.D.		Date February 8, 2021

This collection of information is required by 37 CFR 1.136. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 15/348,716 filed on November 10, 2016.

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

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

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

WARNING:

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

LEGAL NAME OF INVENTOR

Inventor: Jo Ann Wilson Date (Optional) :

Signature:

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

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

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

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

Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 16/151,653

filed on October 4, 2018

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

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

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

WARNING:

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

LEGAL NAME OF INVENTOR

Inventor: Khalid Shah Date (Optional): 14 June 2019

Signature: [signature]

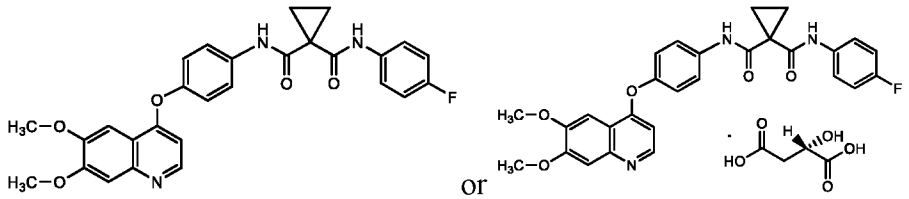
Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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

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

WHAT WE CLAIM IS:

1. A pharmaceutical composition comprising Compound IA or IB;



IA or IB

one or more fillers; one or more disintergrants; one or more glidants; and one or more lubricants, wherein the pharmaceutical composition is essentially free of process byproducts or contaminants.

2. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is a capsule.

3. The pharmaceutical composition according to any one of claims 1-2, wherein the pharmaceutical composition comprises Compound IA.

4. The pharmaceutical composition according to any one of claims 1-3, wherein the pharmaceutical composition comprises Compound IB.

5. The pharmaceutical composition according to claim 4, wherein Compound IB is the N-1 polymorph.

6. The pharmaceutical composition according to claim 4, wherein Compound IB is the N-2 polymorph.

7. The pharmaceutical composition according to claim 4, wherein Compound IB is a mixture of the N-1 form and the N-2 form.

8. The pharmaceutical composition according to any one of claims 1-7, wherein the filler comprises microcrystalline cellulose.

9. The pharmaceutical composition according to any one of claims 1-8, wherein the disintegrant comprises croscarmellose sodium.

10. The pharmaceutical composition according to any one of claims 1-9, wherein the disintegrant comprises croscarmellose sodium and sodium starch glycolate.

11. The pharmaceutical composition according to any one of claims 1-10, wherein the glidant comprises fumed silica.

12. The pharmaceutical composition according to any one of previous claims wherein the lubricant comprises stearic acid.

13. Pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; croscarmellose sodium; fumed silica; and stearic acid.

14. A pharmaceutical composition comprising Compound IA or IB and a pharmaceutically acceptable carrier, wherein the pharmaceutical composition is admixed with less than 100 ppm of 6,7-dimethoxy-quinoline-4-ol.

15. A pharmaceutical composition comprising Compound IA or IB; one or more fillers; one or more disintergrants; one or more glidants; and one or more lubricants, wherein the pharmaceutical composition is admixed with 100 ppm or less 6,7-dimethoxy-quinoline-4-ol.

16. The pharmaceutical composition according to claim 15, wherein the filler comprises microcrystalline cellulose.

17. The pharmaceutical composition according to any one of claims 15-16, wherein the disintegrant comprises croscarmellose sodium.

18. The pharmaceutical composition according to any one of claims 15-17, wherein the disintegrant comprises croscarmellose sodium and sodium starch glycolate.

19. The pharmaceutical composition according to any one of claims 15-18, wherein the glidant comprises fumed silica.

20. The pharmaceutical composition according to any one of claims 15-19, wherein the lubricant comprises stearic acid.

21. A pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; croscarmellose sodium; fumed silica; and stearic acid, wherein the pharmaceutical composition is admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

22. The pharmaceutical composition according to any one of claims 1-21, wherein the pharmaceutical composition is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

23. The pharmaceutical composition according to any one of claims 1-22, wherein the pharmaceutical composition is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

24. The pharmaceutical composition according to any one of claims 1-23, wherein the pharmaceutical composition is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

25. The pharmaceutical composition according to any one of claims 1-24, wherein the pharmaceutical composition is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

26. The pharmaceutical composition according to any one of claims 1-25, wherein the pharmaceutical composition is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

27. A pharmaceutical capsule composition according to Table 3.

Table 3

Ingredient	**mg/unit dose**
Compound IB (10 % drug load as Compound IA)	25
Silicified Microcrystalline Cellulose	196.75
Croscarmellose sodium	12.5
Sodium starch glycolate	12.5
Fumed Silica	0.75
Stearic acid	2.5
Total Fill Weight	250

28. A pharmaceutical capsule composition according to Table 4.

Table 4

Ingredient	**mg/unit dose**
Compound IB (50 % drug load as Compound IA)	100
Silicified Microcrystalline Cellulose	75.40
Croscarmellose sodium	10.00
Sodium Starch Glycolate	10.00
Fumed silica	0.6
Stearic Acid	4.0
Total Fill Weight	200

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

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

First Named Inventor:	Jo Ann Wilson	Nonprovisional Application Number (if known):	
Title of Invention:	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds		

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

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

3. The applicable box is checked below:

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

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

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

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

Signature /Heidi M. Berven/	Date 2021-02-08
Name (Print/Typed) Heidi M. Berven, Ph.D.	Practitioner Registration Number 48951

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☑ *Total of 1 forms are submitted.

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

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

Attorney Docket No.	224990/10-039C6-US/483214
First Named Inventor	Jo Ann Wilson
Title	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Con
Priority Mail Express® Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. [✔] **Fee Transmittal Form** (PTO/SB/17 or equivalent)
2. [ ] **Applicant asserts small entity status.** See 37 CFR 1.27
3. [ ] **Applicant certifies micro entity status.** See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. [✔] **Specification** [*Total Pages* 47] Both the claims and abstract must start on a new page. *(See MPEP § 608.01(a) for information on the preferred arrangement)*
5. [✔] **Drawing(s)** (35 U.S.C. 113) [*Total Sheets* 0]
6. **Inventor's Oath or Declaration** [*Total Pages* 2] *(including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))*
   a. [ ] Newly executed (original or copy)
   b. [✔] A copy from a prior application (37 CFR 1.63(d))
7. [✔] **Application Data Sheet** ** See note below.* See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
8. **CD-ROM or CD-R** in duplicate, large table, or Computer Program (*Appendix*)
   [ ] Landscape Table on CD
9. **Nucleotide and/or Amino Acid Sequence Submission** (*if applicable, items a. – c. are required*)
   a. [ ] Computer Readable Form (CRF)
   b. [ ] Specification Sequence Listing on:
      i. [ ] CD-ROM or CD-R (2 copies); or
      ii. [ ] Paper
   c. [ ] Statements verifying identity of above copies

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

ACCOMPANYING APPLICATION PAPERS

10. [ ] **Assignment Papers** (cover sheet & document(s))
    Name of Assignee _____
11. [ ] **37 CFR 3.73(c) Statement** (*when there is an assignee*) [✔] **Power of Attorney**
12. [ ] **English Translation Document** (*if applicable*)
13. [✔] **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    [ ] Copies of citations attached
14. [✔] **Preliminary Amendment**
15. [ ] **Return Receipt Postcard** (*MPEP § 503*) (*Should be specifically itemized*)
16. [ ] **Certified Copy of Priority Document(s)** (*if foreign priority is claimed*)
17. [ ] **Nonpublication Request** Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
18. [✔] **Other:** Cover Letter, Certificate of Transmission, Request for Prioritized Examination, Request for Participation in the Global/IP5 PPH Pilot Program

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

19. CORRESPONDENCE ADDRESS

[✔] The address associated with Customer Number: 91684 **OR** [ ] Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	/Heidi M. Berven/	Date	February 8, 2021
Name (Print/Type)	Heidi M. Berven, Ph.D.	Registration No. (Attorney/Agent)	48,951

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

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C6-US/483214
	Application Number	
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

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

Secrecy Order 37 CFR 5.2:

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

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Jo Ann		Wilson	

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

City	San Francisco	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	74 Seward Street		
Address 2			
City	San Francisco	State/Province	CA
Postal Code	94114	Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Khalid		Shah	

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

City	Half Moon Bay	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	281 Eagle Trace Drive		
Address 2			
City	Half Moon Bay	State/Province	CA
Postal Code	94019	Country	US

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

Correspondence Information:

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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C6-US/483214
	Application Number	
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

☐ **An Address is being provided for the correspondence Information of this application.**			
Customer Number	91684		
Email Address	patent@honigman.com	Add Email	Remove Email

Application Information:

Title of the Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds		
Attorney Docket Number	224990/10-039C6-US/483214	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		**Suggested Figure for Publication (if any)**	

Filing By Reference:

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

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

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

Publication Information:

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

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

Representative Information:

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

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	91684		

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C6-US/483214
	Application Number	
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

Domestic Benefit/National Stage Information:

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

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	17152394	2021-01-19
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
17152394	Continuation of	16706323	2019-12-06
Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16706323	Division of	16151653	2018-10-04	10543206	2020-01-28

Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16151653	Division of	15348716	2016-11-10	10123999	2018-11-13

Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15348716	Division of	13984559	2014-03-20	9717720	2017-08-01

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
13984559	a 371 of international	PCT/US2012/024591	2012-02-10
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2012/024591	Claims benefit of provisional	61441520	2011-02-10
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2012/024591	Claims benefit of provisional	61441527	2011-02-10

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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C6-US/483214
	Application Number	
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

Foreign Priority Information:

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

Remove

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

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

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

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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C6-US/483214
	Application Number	
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

Authorization or Opt-Out of Authorization to Permit Access:

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

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

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

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

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

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

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

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

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

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

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

PTO/AIA/14 (02-18)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C6-US/483214
	Application Number	
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

Applicant Information:

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

Applicant 1

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

Clear

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

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

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Exelixis, Inc.

Mailing Address Information For Applicant:

Address 1	1851 Harbor Bay Parkway		
Address 2			
City	Alameda	**State/Province**	CA
Country	US	Postal Code	94502
Phone Number		Fax Number	
Email Address			

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

Assignee Information including Non-Applicant Assignee Information:

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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C6-US/483214
	Application Number	
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

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

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
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Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Heidi M. Berven, Ph.D./			Date (YYYY-MM-DD)	2021-02-08
First Name	Heidi M.	Last Name	Berven	Registration Number	48,951

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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	224990/10-039C6-US/483214
	Application Number	
Title of Invention	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds	

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

PROCESSES FOR PREPARING QUINOLINE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 61/441,520, filed February 10, 2011, and 61/441,527, filed February 10, 2011, which are incorporated herein by reference

FIELD OF THE INVENTION

[0002] This disclosure relates to processes for preparing compounds useful for modulating protein kinase enzymatic activity. More specifically, this disclosure relates to processes for preparing quinolines that are useful for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration, and chemo-invasion and to pharmaceutical compositions containing such compounds.

BACKGROUND OF THE INVENTION

[0003] Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms. One mechanism that can be exploited in cancer treatment is the modulation of protein kinase activity because signal transduction through protein kinase activation is responsible for many of the characteristics of tumor cells. Protein kinase signal transduction is of particular relevance in, for example, renal, gastric, head and neck, lung, breast, prostate, and colorectal cancers; hepatocellular carcinoma; as well as in the growth and proliferation of brain tumor cells.

[0004] Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., DN&P 7(6): 334-339, 1994. Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases, including, for example, immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Therefore, protein kinases are attractive targets for small molecule drug discovery. Particularly attractive targets for small-molecule modulation with respect to antiangiogenic

and antiproliferative activity include receptor type tyrosine kinases c-Met, KDR, c-Kit, Axl, flt-3, and flt-4.

[0005] The kinase c-Met is the prototypic member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs) which include Met, Ron, and Sea. The endogenous ligand for c-Met is the hepatocyte growth factor (HGF), a potent inducer of angiogenesis. Binding of HGF to c-Met induces activation of the receptor via autophosphorylation, resulting in an increase of receptor dependent signaling, which promotes cell growth and invasion. Anti-HGF antibodies or HGF antagonists have been shown to inhibit tumor metastasis *in vivo* (See: Maulik et al Cytokine & Growth Factor Reviews 2002 13, 41-59). c-Met overexpression has been demonstrated on a wide variety of tumor types including breast, colon, renal, lung, squamous cell myeloid leukemia, hemangiomas, melanomas, astrocytomas, and glioblastomas. Additionally, activating mutations in the kinase domain of c-Met have been identified in hereditary and sporadic renal papilloma and squamous cell carcinoma. (See, e.g., Maulik et al., Cytokine & growth Factor reviews 2002 13, 41-59; Longati et al., Curr Drug Targets 2001, 2, 41-55; Funakoshi et al., Clinica Chimica Acta 2003 1-23).

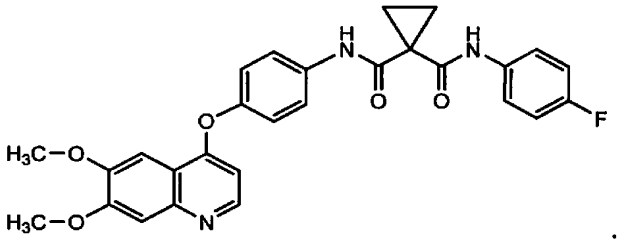
[0006] Inhibition of epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A., Drug Disc. Technol. 2001 6, 1005-1024). Kinase KDR (refers to kinase insert domain receptor tyrosine kinase) and flt-4 (fms-like tyrosine kinase-4) are both VEGF receptors. Inhibition of EGF, VEGF, and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc. Technol. 2001 6, 1005-1024). EGF and VEGF receptors are desirable targets for small molecule inhibition. All members of the VEGF family stimulate cellular responses by binding to tyrosine kinase receptors (the VEGFRs) on the cell surface, causing them to dimerize and become activated through transphosphorylation. The VEGF receptors have an extracellular portion with immunoglobulin-like domains, a single transmembrane spanning region, and an intracellular portion containing a split tyrosine-kinase domain. VEGF binds to VEGFR-1 and VEGFR-2. VEGFR-2 is known to mediate almost all of the known cellular responses to VEGF.

[0007] Kinase c-Kit (also called stem cell factor receptor or steel factor receptor) is a type 3 receptor tyrosine kinase (RTK) belonging to the platelet-derived growth factor receptor subfamily. Overexpression of c-Kit and c-Kit ligand has been described in variety of human

diseases, including human gastrointestinal stromal tumors, mastocytosis, germ cell tumors, acute myeloid leukemia (AML), NK lymphoma, small-cell lung cancer, neuroblastomas, gynecological tumors, and colon carcinoma. Moreover, elevated expression of c-Kit may also relate to the development of neoplasia associated with neurofibromatosis type 1 (NF-1), mesenchymal tumors GISTs, and mast cell disease, as well as other disorders associated with activated c-Kit.

[0008] Kinase Flt-3 (fms-like tyrosine kinase-3) is constitutively activated via mutation, either in the juxtamembrane region or in the activation loop of the kinase domain, in a large proportion of patients with AML (Reilly, Leuk. Lymphoma, 2003, 44: 1-7).

[0009] Small-molecule compounds that specifically inhibit, regulate, and/or modulate the signal transduction of kinases, such as c-Met, VEGFR2, KDR, c-Kit, Axl, flt-3, and flt-4 described above, are particularly desirable as a means to treat or prevent disease states associated with abnormal cell proliferation and angiogenesis. One such small-molecule is compound IA, which has the chemical structure:



IA

WO2005/030140 describes the synthesis of compound IA (Table 2, Compound 12, Example 48) and also discloses the therapeutic activity of this molecule to inhibit, regulate, and/or modulate the signal transduction of kinases (Assays, Table 4, entry 289), the entire contents of which is incorporated herein by reference.

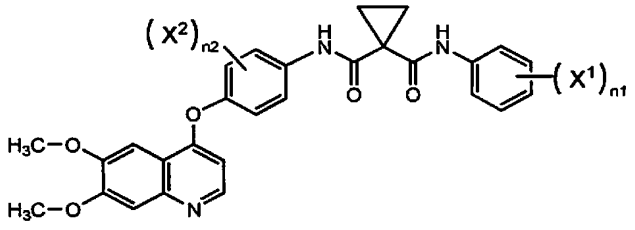
[0010] Although therapeutic efficacy is the primary concern for a therapeutic agent, the pharmaceutical composition can be equally important to its development. Generally, the drug developer endeavors to discover a pharmaceutical composition that possesses desirable properties, such as satisfactory water-solubility (including rate of dissolution), storage stability, hygroscopicity, and reproducibility, all of which can impact the processability, manufacture, and/or bioavailability of the drug.

[0011] Accordingly, there is a need for the discovery of new processes for making quinolines such as compound IA that minimize the formation of undesirable process contaminants or byproducts. There is also a need for new pharmaceutical compositions containing quinolines such as compound IA that are essentially free of process byproducts.

SUMMARY OF THE INVENTION

[0012] These and other needs are met by the present disclosure, which is directed to processes for making and compositions containing quinolines or pharmaceutically acceptable salts thereof.

[0013] In one aspect, the disclosure relates to processes for preparing a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is H, Br, Cl, or F;

X^2 is H, Br, Cl, or F;

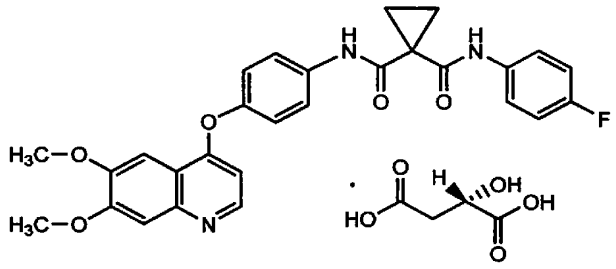
n1 is 1-2; and

n2 is 1-2.

[0014] Intermediates useful in preparing the above compounds are also disclosed.

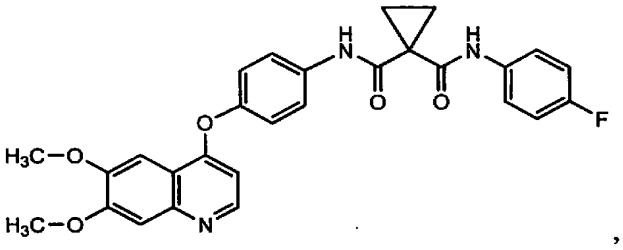
[0015] The compounds of formula I are useful as protein kinase modulators, and they inhibit various protein kinases including Ret and c-Met.

[0016] In another aspect, the disclosure provides a process for preparing compound IB:



IB

from compound IA:



IA,

comprising:

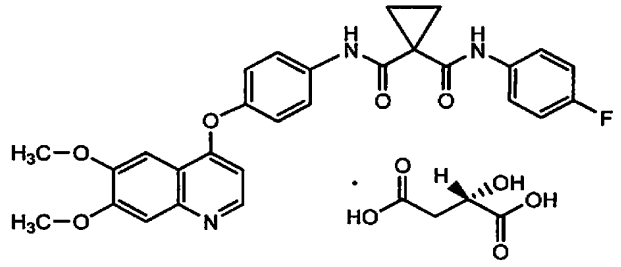
(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;

(b) cooling the mixture;

(c) vacuum distilling the mixture successively; and

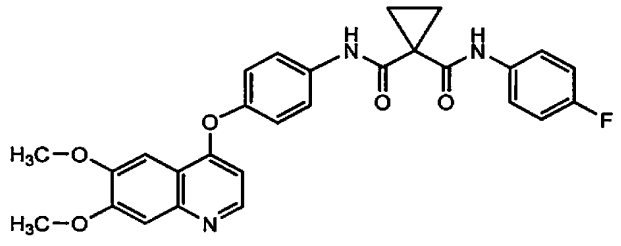
(d) isolating the compound of IB by filtration.

[0017] In another aspect, the disclosure provides a process for preparing compound IB:



IB

from compound IA:



IA,

comprising:

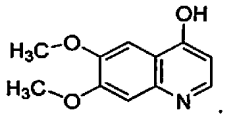
(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;

(b) cooling the mixture;

(c) seeding the mixture with compound IB;

(d) vacuum distilling the mixture; and

(e) isolating compound IB by filtration.

[0018] In another aspect, the disclosure provides compound I, IA, or IB admixed with less than 100 ppm 6,7-dimethoxy-quinoline-4-ol, the structure of which is 

.

[0019] In another aspect, the disclosure provides pharmaceutical compositions containing the compound of formula I, compound IA, or compound IB for oral administration.

[0020] In another aspect, the disclosure provides a pharmaceutical tablet composition according to Table 1.

Table 1

Ingredient	% w/w
Compound I	31.68
Microcrystalline Cellulose (MCC) (Avicel PH102)	38.85
Lactose anhydrous 60 M	19.42
Hydroxypropyl Cellulose, EXF	3.00
Croscarmellose Sodium	3.00
Total Intra-granular	**95.95**
Silicon dioxide, Colloidal PWD	0.30
Croscarmellose Sodium	3.00
Magnesium Stearate	0.75
Total	**100.00**

[0021] In another aspect, the disclosure provides a pharmaceutical tablet composition according to Table 2.

Table 2

Ingredient	(% w/w)
Compound I	25.0-33.3
Microcrystalline Cellulose, NF	q.s
Hydroxypropyl Cellulose, NF	3
Poloxamer, NF	0-3
Croscarmellose Sodium, NF	6.0
Colloidal Silicon Dioxide, NF	0.5
Magnesium Stearate, NF	0.5-1.0
Total	100

[0022] In another aspect, the disclosure provides a pharmaceutical tablet composition according to Table 2A.

Table 2A

Ingredient	**% w/w**
Compound IB (10 % drug load as Compound IA)	12.67
MCC	51.52
Lactose	25.76
Hydroxypropyl cellulose	3.0
Croscarmellose Sodium	6.0
Colloidal Silicon Dioxide	0.3
Magnesium Stearate	0.75
Total	**100**

[0023] In another aspect, the disclosure provides a pharmaceutical capsule composition according to Table 3.

Table 3

Ingredient	**mg/unit dose**
Compound IB (10 % drug load as Compound IA)	25
Silicified Microcrystalline Cellulose	196.75
Croscarmellose sodium	12.5
Sodium starch glycolate	12.5
Fumed Silica	0.75
Stearic acid	2.5
Total Fill Weight	250

[0024] In another aspect, the disclosure provides a pharmaceutical capsule composition according to Table 4.

Table 4

Ingredient	**mg/unit dose**
Compound IB (50 % drug load as Compound IA)	100
Silicified Microcrystalline Cellulose	75.40
Croscarmellose sodium	10.00
Sodium Starch Glycolate	10.00
Fumed silica	0.6
Stearic Acid	4.0
Total Fill Weight	200

[0025] In another aspect, the disclosure provides a pharmaceutical capsule composition according to Table 5, wherein the IB weight equivalents are provided.

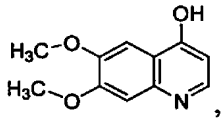
Table 5

	mg/unit dose
Ingredient	**50mg**
Compound IB	63.35
Microcrystalline Cellulose	95.39
Croscarmellose sodium	9.05
Sodium starch glycolate	9.05
Fumed Silica	0.54
Stearic acid	3.62
Total Fill Weight	181.00

[0026] In another aspect, the disclosure provides a pharmaceutical capsule composition according to Table 6, wherein the IB weight equivalents are provided.

Table 6

	mg/unit dose
Ingredient	**60mg**
Compound IB	73.95
Microcrystalline Cellulose	114.36
Croscarmellose sodium	10.85
Sodium starch glycolate	10.85
Fumed Silica	0.65
Stearic acid	4.34
Total Fill Weight	217.00

[0027] In another aspect, the invention is directed to a pharmaceutical composition comprising compound I, IA, or IB admixed with less than 100 ppm 6,7-dimethoxy-quinoline-4-ol, the structure of which is 

, and a pharmaceutically acceptable carrier.

[0028] There are many different aspects and embodiments of the disclosure described herein, and each aspect and each embodiment is non-limiting in regard to the scope of the disclosure. The terms "aspects" and "embodiments" are meant to be non-limiting regardless of where the terms "aspect" or "embodiment" appears in this specification. The transitional term "comprising," as used herein, which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0029] As used herein, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise or they are expressly defined to mean something different.

[0030] The word "can" is used in a non-limiting sense and in contradistinction to the word "must." Thus, for example, in many aspects of the invention a certain element is described as "can" having a specified identity, which is meant to convey that the subject element is permitted to have that identity according to the invention but is not required to have it.

[0031] If a group "R" is depicted as "floating" on a ring system, then unless otherwise defined, the substituent(s) "R" can reside on any atom of the ring system, assuming replacement of a depicted, implied, or expressly defined hydrogen from one of the ring atoms, so long as a stable structure is formed.

[0032] When there are more than one such depicted "floating" groups, such as where there are two groups; then, unless otherwise defined, the "floating" groups can reside on any atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

[0033] "Pharmaceutically acceptable salts" include acid addition salts.

[0034] "Pharmaceutically acceptable acid addition salt" refers to those salts that retain the biological effectiveness of the free bases and that are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or mixtures thereof, as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like, or mixtures thereof.

[0035] "Essentially free" as used in the phrase "essentially free of process byproducts or contaminants," means that a compound or composition as disclosed here in is admixed with 200 parts per million (ppm) or less of such byproducts or contaminants.

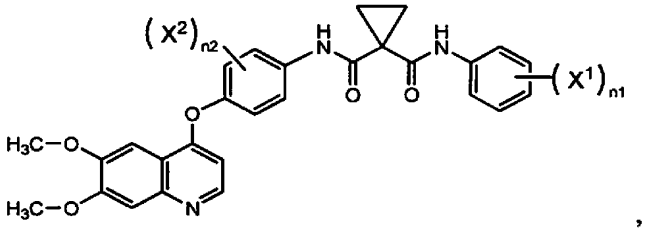
[0036] The disclosure is further illustrated by the following examples, which are not to be construed as limiting the disclosure in scope or spirit to the specific procedures described in them. Unless specified otherwise, the starting materials and various intermediates may be

obtained from commercial sources, prepared from commercially available organic compounds, or prepared using well-known synthetic processes.

Processes

Aspect 1: Processes for Making Compounds of Formula I

[0037] Aspect (1) of the invention relates to a process of preparing a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is H, Br, Cl, or F;

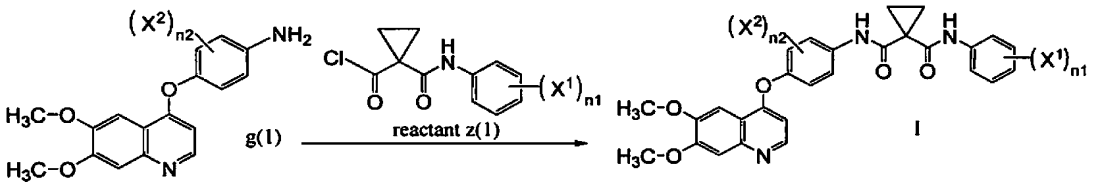
X^2 is H, Br, Cl, or F;

n1 is 1-2; and

n2 is 1-2;

the process comprising:

contacting the compound of formula g(1) with reactant z(1) to yield the compound of formula I:



[0038] The reaction is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions include using basic conditions. Non-limiting examples of basic conditions that can be used in Aspect (1) include the use of inorganic bases, such as aqueous KOH, NaOH, K_2CO_3, Na_2CO_3, K_3PO_4, Na_3PO_4, K_2HPO_4, Na_2HPO_4, and the like, or mixtures thereof. Other non-limiting examples of suitable reaction conditions include using suitable solvents. Non-limiting examples of suitable solvents that can be used include water miscible solvents, such as THF, acetone, ethanol, and the like, or mixtures thereof. Other non-limiting examples of suitable reaction conditions include using suitable temperatures. Suitable temperatures that may be used for the reaction include a

temperature at a range from about 10 °C to about 30 °C, or alternatively, at a range from about 15 °C to about 28 °C, or alternatively, at a range from about 20 °C to about 25 °C. The product formed by the reaction is in the free base form, and this free base form may be converted into a pharmaceutically acceptable salt thereof by processes known in the art. For example, the compound of formula I can be converted to the L-malate salt by the addition of L-malic acid and a suitable solvent.

[0039] Utilities of the compound of formula I are further described in WO 2005/030140 A2, which is incorporated herein by reference.

Embodiments of Aspect (1) Part A

[0040] In another embodiment of Aspect (1), X^1 is Cl or F.

[0041] In another embodiment of Aspect (1), X^2 is Cl or F.

[0042] In another embodiment of Aspect (1), X^1 is F.

[0043] In another embodiment of Aspect (1), X^2 is F.

[0044] In another embodiment of Aspect (1), X^1 is H.

[0045] In another embodiment of Aspect (1), X^2 is H.

[0046] In another embodiment of Aspect (1), n1 is 1.

[0047] In another embodiment of Aspect (1), n2 is 1.

[0048] In another embodiment of Aspect (1), n1 is 2.

[0049] In another embodiment of Aspect (1), n2 is 2.

[0050] All compounds of formula I for Aspect (1) disclosed above include any of the disclosed alternative embodiments in Part A for each of X^1, X^2, n1 or n2, in combination with any other of the disclosed alternative embodiments in Part A for each of X^1, X^2, n1, or n2, as well as a pharmaceutically acceptable salt of any such combination.

Embodiments of Aspect (1) Part B

[0051] In another embodiment of Aspect (1), n1 and n2 are each 1.

[0052] In another embodiment of Aspect (1), n1 and n2 are each 2.

[0053] In another embodiment of Aspect (1), n1 is 1; and n2 is 2.

[0054] In another embodiment of Aspect (1), n1 is 2 and n2 is 1.

[0055] In another embodiment of Aspect (1), X^1 is H; and X^2 is F.

[0056] In another embodiment of Aspect (1), X^1 is F; and X^2 is H.

[0057] In another embodiment of Aspect (1), X^1 and X^2 are each H.

[0058] In another embodiment of Aspect (1), X^1 and X^2 are each F.

[0059] In another embodiment of Aspect (1), X^1 is Cl; and X^2 is H.

[0060] In another embodiment of Aspect (1), X^1 is H; and X^2 is Cl.

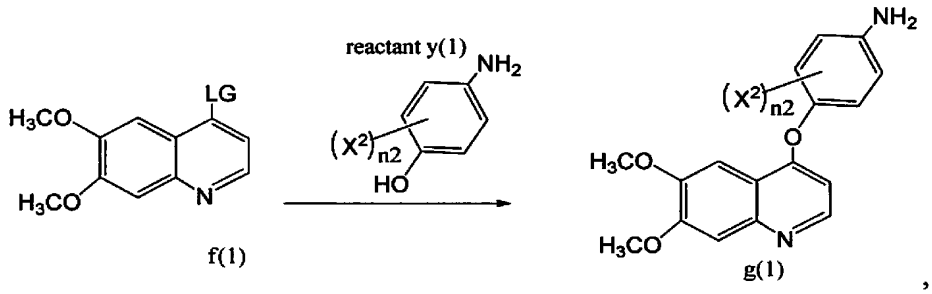
[0061] In another embodiment of Aspect (1), X^1 and X^2 are each Cl.

[0062] In another embodiment of Aspect (1), X^1 is Cl; and X^2 is F.

[0063] In another embodiment of Aspect (1), X^1 is F; and X^2 is Cl.

Embodiments of Aspect (1) Part C

[0064] In an embodiment of Aspect (1), the compound of formula g(1) can be made by reacting a compound of formula f(1) with reactant y(1) to yield the compound of g(1):



,

wherein LG represents a leaving group, and each of X^2, and n2 are as defined in Aspect (1), or as in any of the embodiments of Aspect (1) Part A. A non-limiting example of a leaving group includes a halo group such as Cl, Br, or F. Various compounds of reactant y(1) are commercially available, such as 2-fluoro-4-aminophenol and 4-aminophenol. Also, the skilled artisan would be able to make any variation of reactant y(1) using commercially available starting materials and by using known techniques to modify these commercially available starting materials to yield various compounds within the scope of reactant y(1).

[0065] The reaction in this embodiment is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions include using suitable solvents such as polar solvents. Non-limiting examples of polar solvents that can be used include tetrahydrofuran (THF), dimethylacetamide (DMA), dimethylsulfoxide (DMSO), dimethylformamide (DMF), ethyl acetate, N-methyl pyrrolidone (NMP), propylene carbonate, and the like, or mixtures thereof. In another embodiment, the polar solvent is dimethylacetamide (DMA). In another embodiment, the polar solvent is dimethylsulfoxide (DMSO). In another embodiment, the polar solvent is dimethylformamide (DMF). In another embodiment, the polar solvent is ethyl acetate. In another embodiment, the polar solvent is N-methyl pyrrolidone (NMP). In another embodiment, the polar solvent is propylene carbonate. In another embodiment, the solvent is a mixture of solvents, such as a mixture comprising THF and DMA.

[0066] The reactants f(1) and y(1) can be added together at a temperature ranging from about 10 °C to about 30 °C, or alternatively, from about 15 °C to about 28 °C, or alternatively, from about 20 °C to about 25 °C. The mixture is then heated to a temperature ranging from about 80 °C to about 125 °C, or alternatively, from about 95 °C to about 110 °C, or alternatively, from about 100 °C to about 105 °C, and the selected temperature is maintained until the reaction is complete.

[0067] Other non-limiting examples of suitable reaction conditions in this step of Aspect (1) include the use of a suitable base, such as a metal hydroxide or a non-nucleophilic base. Examples of metal hydroxides include sodium hydroxide or potassium hydroxide. Non-limiting examples of non-nucleophilic bases that can be used include lithium diisopropylamide, lithium tetramethylpiperidide, and alkali metal alkoxides such as sodium tert-butoxide, potassium tert-butoxide, sodium-pentoxide, and the like, or mixtures thereof. Preferably, the base is sodium tert-butoxide or sodium tert-pentoxide. In one embodiment, the base is sodium tert-pentoxide. Typically the sodium tert-pentoxide is commercially available as 35 weight percent solution of base in tetrahydrofuran, or as a 95 weight percent solid reagent. Preferably, the sodium tert-pentoxide is a 95 weight percent solid.

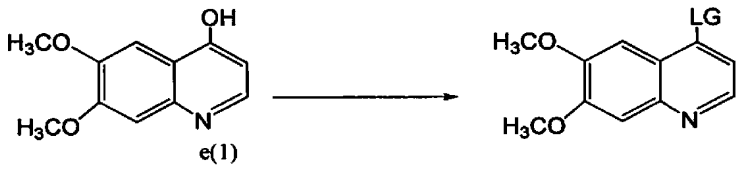
[0068] Typically, approximately 1.1 to 3.0 molar equivalents of base are used relative the moles of f(1) that are used. More preferably, 1.3 to 2.5 molar equivalents of base are used relative the moles of f(1) that are used. More preferably, 1.5 to 2.2 molar equivalents of base are used relative the moles of f(1) that are used. More preferably, 1.7 to 2.1 molar equivalents of base are used relative the moles of f(1) that are used.

[0069] Typically, the amount of molar equivalents of amino phenol that are used exceeds the molar equivalents of base that are used. In one embodiment, 1.1 to 2 molar equivalents of amino phenol are used relative to the molar equivalents of base that are used.

[0070] Once the reaction is substantially complete, the reaction mixture can be cooled to a temperature ranging from about 10 °C to about 25 °C. Precooled water can be charged at a rate to maintain a temperature that ranges from about 5 °C to about 35 °C. Alternatively, the precooled water can be charged at a rate to maintain a temperature that ranges from about 10 °C to about 25 °C. As a non-limiting example, the precooled water can be at a temperature ranging from about 0 °C to about 10 °C. As another non-limiting example, the precooled water can be at a temperature ranging from about 2 °C to about 7 °C. The precipitate can be collected by filtration under standard conditions and purified by standard purification techniques.

Embodiments of Aspect (1) Part D

[0071] In an embodiment of Aspect (1), the compound of formula f(1) can be made by converting a compound of formula e(1) to the compound of formula f(1):

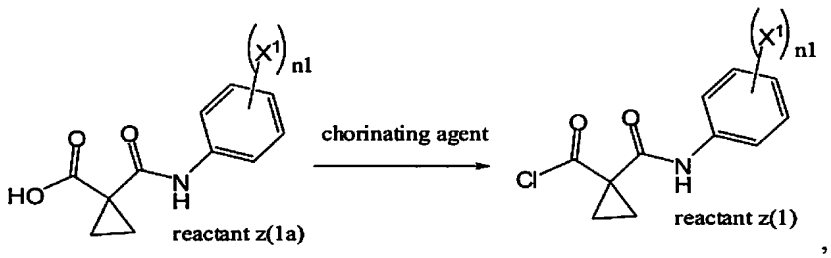


wherein LG represents a leaving group. Non-limiting examples of leaving groups that can be used include halo groups (e.g., Cl, Br, or F) that can be added by halogenating agents. Non-limiting examples of halogenating agents that can be used include chlorinating agents, such as $SOCl_2$, SO_2Cl_2, $COCl_2$, PCl_5, $POCl_3$, and the like.

[0072] The reaction is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions in Part D of Aspect (1) include the use of suitable solvents. Non-limiting example of suitable solvents that can be used during the halogenation of the compound of formula e(1) include a polar, aprotic solvent, such as CH_3CN, DMF, and the like, or mixtures thereof. In other embodiments, the chlorination can be carried out using $POCl_3$ in acetonitrile, $COCl_2$ in DMF, or $SOCl_2$ in DMF. The addition of the chlorination agent is advantageously carried out at a temperature ranging from about 60 °C to about 90 °C. In another embodiment, the addition of the chlorination agent can be carried out at a temperature ranging from about 70 °C to about 85 °C. In another embodiment, the addition of the chlorination agent can be carried out at a temperature ranging from about 74 °C to about 80 °C. The product can then be collected by filtration and purified using standard techniques.

Embodiments of Aspect (1) Part E

[0073] In an embodiment of Aspect (1), reactant z(1) can be made by reacting reactant z(1a) with a chlorinating agent to yield reactant z(1):

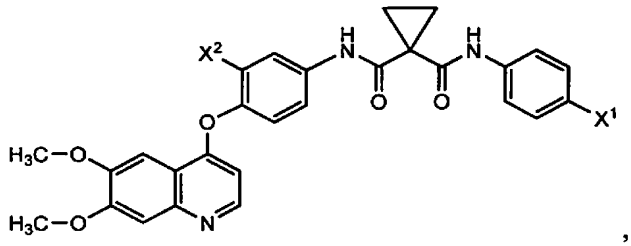


wherein X^1 is Br, Cl, or F; and n1 is 1-2. Compounds of reactant z(1a) can be made according to the process described in Example 25 of WO 2005/030140 A2, and the skilled artisan would be able to make any necessary substitutions using commercially available starting materials to come up with various compounds within the scope of reactant z(1a). Example 25 in WO 2005/030140 A2 is incorporated herein by reference.

[0074] The reaction is advantageously carried out under suitable reaction conditions. Non-limiting examples of suitable reaction conditions include using a chlorinating agent such as $POCl_3$, oxalyl chloride, and the like. In another embodiment, oxalyl chloride is used as a chlorinating agent. Non-limiting examples of suitable reaction conditions include carrying out the reaction at a temperature in the range from about 0 °C to about 25 °C, or alternatively at a temperature in the range from about 5 °C to about 20 °C. Other non-limiting examples of suitable reaction conditions include carrying out the reaction in a suitable solvent. Non-limiting examples of suitable solvents that can be used include polar aprotic solvents, such as halogenated hydrocarbons (e.g., dichloromethane and chloroform), ethers (e.g., Et_2O), dioxane, tetrahydrofuran (THF) containing catalytic DMF, and the like, or mixtures thereof. The resulting solution containing reactant z(1) can be used, without further processing, to make the compound of formula I.

Other Embodiments of Aspect (1)

[0075] In another embodiment of Aspect (1), the compound of formula I is a compound of formula IA-1:

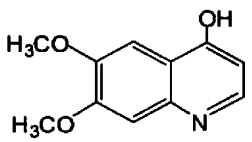


IA-1

or a pharmaceutically acceptable salt thereof, wherein:

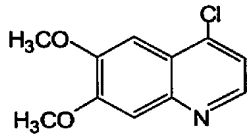
X^1 is H, Cl, Br, or F; and X^2 is H, Cl, Br, or F. Compound IA can be in the free base form or it can converted to a pharmaceutically acceptable salt thereof. Accordingly, compound IA can be converted to its L-malate salt by the addition of L-malic acid and a suitable solvent.

[0076] In another embodiment of Part D of Aspect (1), the compound of formula e(1) is compound e(2):



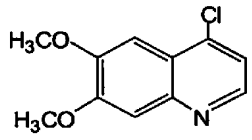
e(2) ;

and the compound of formula f(1) is compound f(2):



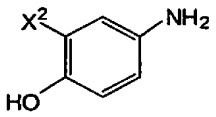
f(2) .

[0077] In another embodiment of Part C of Aspect (1), the compound of formula f(1) is compound f(2):



f(2) ;

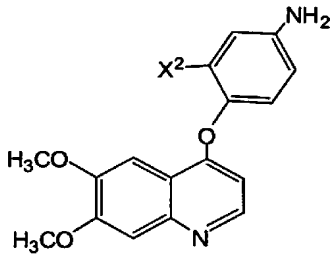
reactant y(1) is reactant (y)(2):



reactant (y)(2) ,

wherein X^2 is hydrogen or fluoro; and

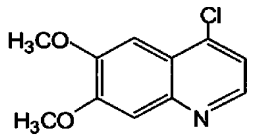
the compound of formula g(1) is of formula g(2):



g(2) .

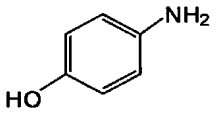
[0078] In a further embodiment, the reaction employs a non-nucleophilic base. In a further embodiment, the non-nucelophilic base is an alkali metal alkoxide; and the reaction is carried out in a polar solvent. In a further embodiment, the alkali metal alkoxide is sodium tert-butoxide, and the polar solvent is DMA.

[0079] In another embodiment of Part C of Aspect (1), the compound of formula f(1) is compound f(2):



f(2) ;

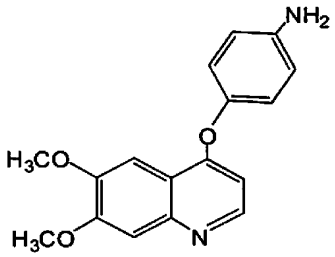
reactant y(1) is reactant (y)(3):



reactant (y)(3) ,

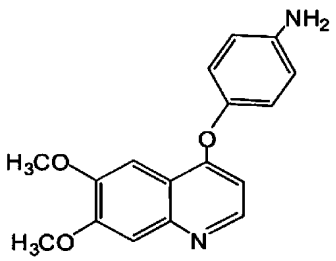
wherein X^2 is hydrogen or fluoro; and

the compound of formula g(1) is compound g(3):



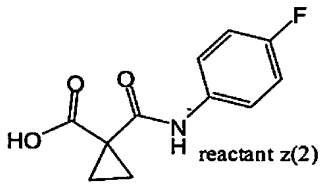
g(3) .

[0080] In another embodiment of Aspect (1) of this disclosure, the compound of formula g(1) is compound g(3):



g(3) ;

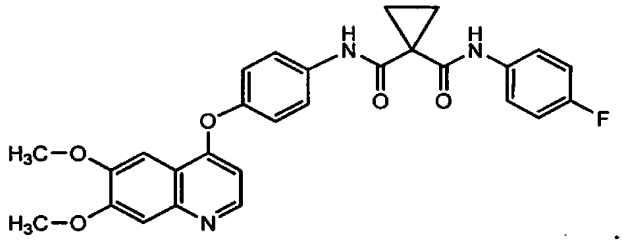
reactant z(1) is reactant (z)(2):



reactant z(2)

; and

the compound of formula I is compound IA:

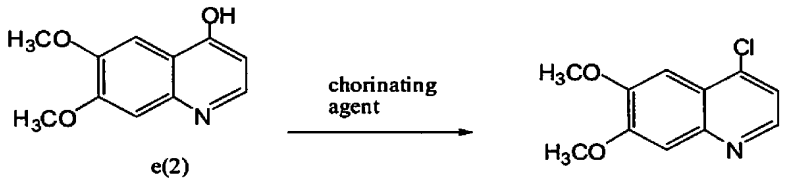


IA

[0081] In a further embodiment, the reaction is carried out in the presence of an inorganic base. In a further embodiment, the inorganic base is K_2CO_3, and the solvent employed in this reaction is a combination of THF and H_2O.

[0082] In another embodiment of Aspect (1) of this disclosure, X^1 and X^2 for each of formula g(1) and reactant z(1) are each selected from Cl or F. In another embodiment, X^1 and X^2 for each of formula g(2), and reactant z(1) are both F.

[0083] The compound of formula f(2),or a pharmaceutically acceptable salt thereof, can be made by converting the compound of formula e(2) to a compound of formula f(2) with a chlorinating agent in a suitable solvent:

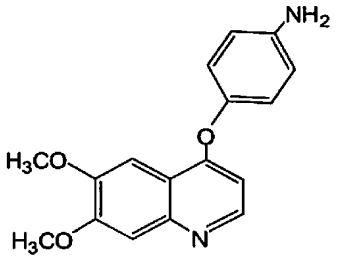


e(2) f(2)

The compound of formula f(2) can be in its free base form or converted to a pharmaceutically acceptable salt thereof. The reaction conditions that can be used in this aspect include any of the reaction conditions disclosed in Part E of Aspect (1).

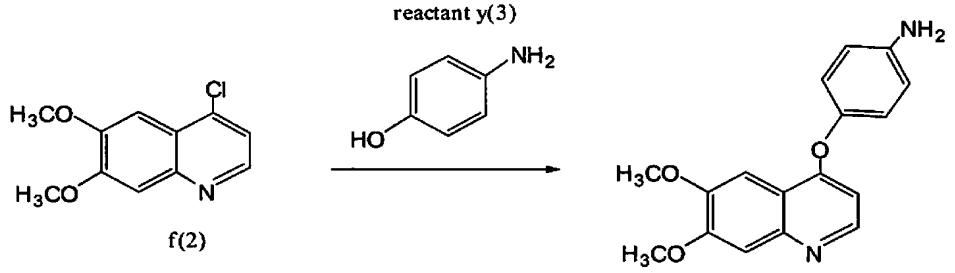
Aspect 2: Processes for Making Compounds of Formula g(2)

[0084] Aspect (2) of the disclosure relates to a process of preparing compound g(2):



g(2)

or a pharmaceutically acceptable salt thereof; the process comprising reacting compound f(2) with reactant y(3) under basic conditions (e.g., using 2,6-lutidine) in an appropriate solvent to yield compound g(3):



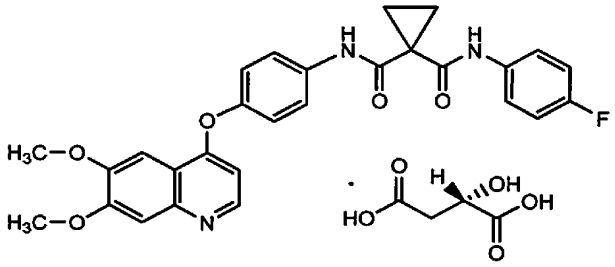
f(2) g(3)

The reaction conditions that can be used in this aspect include any of the reaction conditions disclosed in Part C of Aspect (1).

[0085] Alternative reaction conditions that can be used in this aspect include any of the reaction conditions disclosed in Parts C and D of Aspect (1).

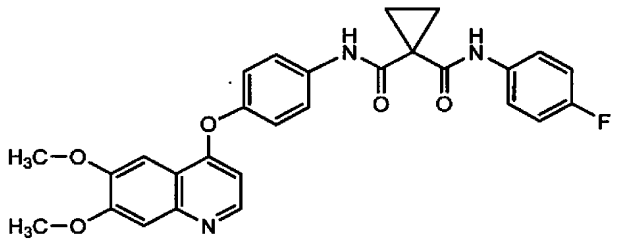
Aspect 3: Processes for Making Compounds of IB

[0086] As indicated above, in one aspect, the invention provides a process for preparing compound IB:



IB

from compound IA:



IA;

comprising:

(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;

(b) cooling the mixture;

(c) vacuum distilling the mixture successively; and

(d) isolating the compound of IB by filtration.

[0087] In one embodiment of this aspect, compound IA is admixed with a sufficient amount of L-malic acid in a methylethyl ketone (MEK)/water (1:1) mixture. Alternatively, L-malic acid is added as a solution in water to a mixture of compound IA in methyl ethyl ketone. Generally the amount of L-malic is greater than 1 molar equivalent relative to compound IA. The mixture of compound IA and L-malic acid in MEK/water is heated at about 40-70 °C, and preferably at about 50-60 °C, and more preferably at about 55-60 °C with agitation, such as by stirring or the like, for about 1 to about 5 hours. At the end of the heating, the mixture is optionally clarified by filtering to give a clear solution. The resulting clear solution is then vacuum distilled from 1 to about 5 times at 150 to 200 mm Hg and a maximum jacket temperature of 55 °C to provide the desired crystalline compound of IB.

[0088] In one embodiment, L-malic acid is charged as a solution in water to compound IA. Generally the amount of L-malic is greater than 1 molar equivalent relative to compound IA. The mixture of compound IA and L-malic acid in MEK/water is heated at about 40-70 °C, and preferably at about 50-60 °C, and more preferably at about 55-60 °C with agitation, such as by stirring or the like, for about 1 to about 5 hours. At the end of the heating, the mixture is optionally clarified by filtering to give a clear solution which is at a temperature of about 30-40 °C, and more preferably at a temperature of about 33-37 °C. This clear solution is optionally seeded to facilitate crystallization. After seeding, the resulting mixture is vacuum distilled as provided above.

[0089] In one embodiment, compound IB is in the N-1 form. In another embodiment, compound IB is in the N-2 form. In another embodiment, compound IB is a mixture of the N-1 form and the N-2 form. Processes for preparing the N-1 and N-2 forms of compound IB

are disclosed in WO 2010/083414 (PCT/US2010021194), the entire contents of which are incorporated herein by reference.

[0090] In another embodiment, the disclosure relates to compound IA or IB admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

[0091] In another embodiment, the disclosure relates to compound IA admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

[0092] In another embodiment, the disclosure relates to compound IB admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

[0093] In another embodiment, the disclosure relates to compound IB in the N-1 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

[0094] In another embodiment, the disclosure relates to compound IB in the N-2 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

[0095] In another embodiment, the disclosure relates to compound IB as a mixture of the N-1 form and the N-2 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment, the compound is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment, the compound is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

Pharmaceutical Compositions

[0096] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound I, IA, or IB. Various carriers used in formulating pharmaceutically acceptable compositions and known techniques for their bulk preparation and subsequent production into unit dosage forms are employed to make the pharmaceutical compositions disclosed herein and are described in Remington: The Science and Practice of Pharmacy, 21st edition, 2005, ed. D. B. Troy, Lippincott Williams & Wilkins, Philadelphia, and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York. The amount of carriers and excipients used in a composition can be varied proportionally according to the amount of active ingredient used (that is, Compound I, IA or IB).

[0097] In one embodiment, the pharmaceutical composition is a tablet.

[0098] In another embodiment, the pharmaceutical composition is a capsule.

[0099] In another embodiment, the pharmaceutical composition comprises Compound IA.

[00100] In another embodiment, the pharmaceutical composition comprises Compound IB.

[00101] In another embodiment, the pharmaceutical composition comprises Compound IB. as the N-1 polymorph.

[00102] In another embodiment, the pharmaceutical composition comprises Compound IB as the N-2 polymorph.

[00103] In another embodiment, the pharmaceutical composition comprises Compound IB as a mixture of the N-1 form and the N-2 form.

[00104] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; one or more fillers; one or more disintergrants; one or more glidants; and one or more lubricants.

[00105] In this embodiment, the filler comprises microcrystalline cellulose.

[00106] In this embodiment, the disintegrant comprises croscarmellose sodium.

[00107] In this embodiment, the disintegrant comprises croscarmellose sodium and sodium starch glycolate.

[00108] In this embodiment, the glidant comprises fumed silica.

[00109] In this embodiment, the lubricant comprises stearic acid.

[00110] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; lactose; hydroxypropyl cellulose; croscarmellose sodium; colloidal silicon dioxide; and magnesium stearate.

[00111] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; hydroxypropyl cellulose; a surfactant; croscarmellose sodium; colloidal silicon dioxide; and magnesium stearate.

[00112] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; croscarmellose sodium; fumed silica; and stearic acid.

[00113] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; anhydrous lactose; hydroxypropyl cellulose; croscarmellose sodium; silicon dioxide; and magnesium stearate.

[00114] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; anhydrous lactose; hydroxypropyl cellulose; a surfactant; croscarmellose sodium; silicon dioxide; and magnesium stearate.

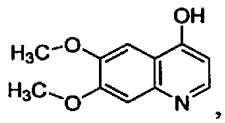
[00115] In another aspect, the disclosure provides a pharmaceutical composition according to Tables 1, 2, 2A, 3, 4, 5, and 6 as provided above. The compositions are prepared according to methods available to the skilled artisan. For example, the Tablet

formulations are prepared by combining, blending, and compacting the components of the tablet compositions. The capsule compositions are prepared by combining and blending the components and then placing the blend in a gelatin capsule.

[00116] For example, the 25 mg capsules (Table 3, 10 percent drug load formulation) are prepared as follows. The drug substance is delumped through a mill. The delumped drug substance is then co-screened with an equal volume Prosolv HD90. The excipients, except for stearic acid, are screened and charged to a blender along with the co-screened drug substance. The mixture is blended in a V-Blender. This process is repeated to manufacture a second sublot of unlubricated blend. The two sublots are then combined together in a V-blender and lubricated with stearic acid which has been co-screened with an equal volume of unlubricated blend. The final blend is then encapsulated into opaque, size 1 gelatin capsules using an automated capsule filling machine. The capsules are then weight sorted through an automatic weight sorter.

[00117] The 100-mg capsules (Table 4, 50% drug load formulation) are manufactured in two equal sublots of 5 kg of blend which are combined prior to lubricant blend The drug substance is delumped through a mill. The excipients, except for stearic acid, are screened and charged to the mixer along with the delumped drug substance. The mixture is blended with a high shear mixer. The process is repeated to manufacture a second sublot of unlubricated blend. The final blend is then encapsulated into Swedish oraopaque, size 1 gelatin capsules using an automated capsule filling machine. The capsuare then weight sorted through an automatic weight sorter.

[00118] The 50 and 60 mg capsules (Tables 5 and 6) are prepared in a similar fashion as the 25 and 100 mg capsules.

[00119] In another aspect, the disclosure relates to a pharmaceutical composition comprising a compound of Formula IA or IB and a pharmaceutically acceptable carrier admixed with less than 100 ppm of 6,7-dimethoxy-quinoline-4-ol. 6,7-dimethoxy-quinoline-4-ol, the structure of which is 

, can be used as reagent e(1) to make chloride f(1) and is a byproduct that may form during the synthesis of Compound IA or IB. Minimizing the concentration of contaminants or byproducts such as 6,7-dimethoxy-quinoline-4-ol in pharmaceutical compositions destined for human administration is desirable.

[00120] In one embodiment, the pharmaceutical composition as defined in any of the previous embodiments (for example, the pharmaceutical composition of Tables 1, 2, 2A, 3, 4, 5, and6) is admixed with 100 ppm 6,7-dimethoxy-quinoline-4-ol.

[00121] In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 50 ppm 6,7-dimethoxy-quinoline-4-ol.

[00122] In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 25 ppm 6,7-dimethoxy-quinoline-4-ol.

[00123] In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 15 ppm 6,7-dimethoxy-quinoline-4-ol.

[00124] In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 10 ppm 6,7-dimethoxy-quinoline-4-ol.

[00125] In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 5 ppm 6,7-dimethoxy-quinoline-4-ol.

[00126] In another embodiment, the pharmaceutical composition as defined in any of the previous embodiments is admixed with 2.5 ppm 6,7-dimethoxy-quinoline-4-ol.

[00127] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; one or more fillers; one or more disintergrants; one or more glidants; and one or more lubricants admixed with 100 ppm or less 6,7-dimethoxy-quinoline-4-ol.

[00128] In this embodiment, the filler comprises microcrystalline cellulose.

[00129] In this embodiment, the disintegrant comprises croscarmellose sodium.

[00130] In this embodiment, the disintegrant comprises croscarmellose sodium and sodium starch glycolate.

[00131] In this embodiment, the glidant comprises fumed silica.

[00132] In this embodiment, the lubricant comprises stearic acid.

[00133] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; croscarmellose sodium; fumed silica; and stearic acid; admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment of this embodiment, the composition is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with

5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

[00134] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; anhydrous lactose; hydroxypropyl cellulose; a surfactant; croscarmellose sodium; silicon dioxide; and magnesium stearate; admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment of this embodiment, the composition is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

[00135] In another embodiment, the disclosure relates to a pharmaceutical composition comprising Compound IA or IB; microcrystalline cellulose; croscarmellose sodium; fumed silica; and stearic acid; ; admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In one embodiment of this embodiment, the composition is admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol. In another embodiment of this embodiment, the composition is admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

EXAMPLES

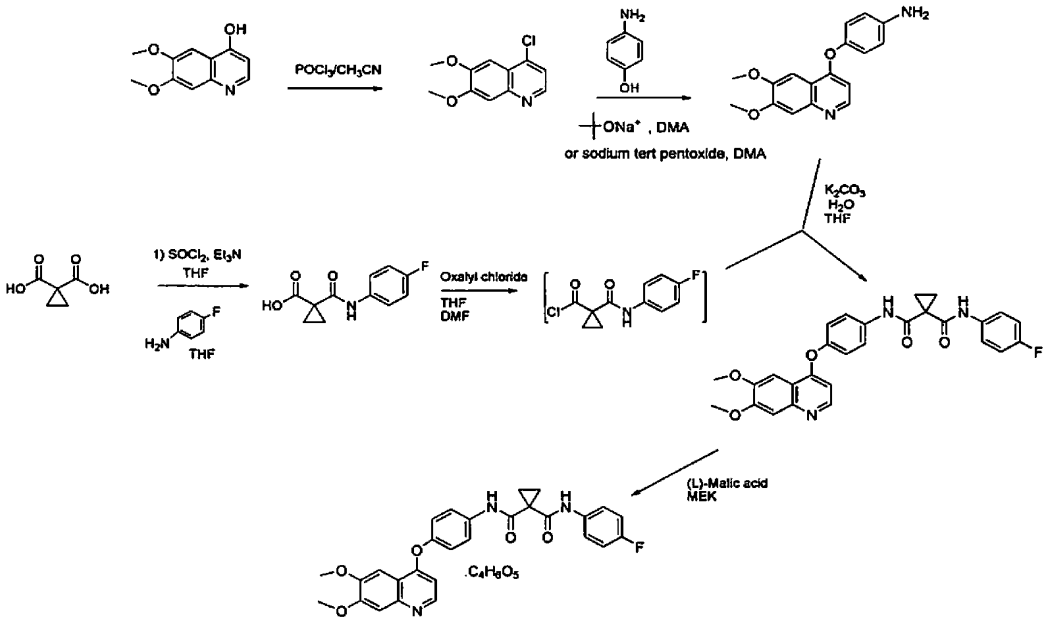
[00136] The invention is illustrated further by the following examples in Scheme 1 and the description thereof, which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the invention, as demonstrated by the following examples. Those skilled in the art will also recognize that it may be necessary to utilize different solvents or reagents to achieve some of the above transformations. Unless otherwise specified, all reagents and solvents are of standard commercial grade and are used without further purification. The

appropriate atmosphere to run the reaction under, for example, air, nitrogen, hydrogen, argon, and the like, will be apparent to those skilled in the art.

Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof.

[00137] A synthetic route that can be used for the preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof is depicted in Figure 1:

Figure 1



Preparation of 4-Chloro-6,7-dimethoxy-quinoline

[00138] A reactor was charged sequentially with 6,7-dimethoxy-quinoline-4-ol (47.0 kg) and acetonitrile (318.8 kg). The resulting mixture was heated to approximately 60 °C, and phosphorus oxychloride ($POCl_3$, 130.6 kg) was added. After the addition of $POCl_3$, the temperature of the reaction mixture was raised to approximately 77 °C. The reaction was deemed complete (approximately 13 hours) when less than 3% of the starting material remained (in-process high-performance liquid chromatography [HPLC] analysis). The reaction mixture was cooled to approximately 2 – 7 °C and then quenched into a chilled solution of dichloromethane (DCM, 482.8 kg), 26 % NH_4OH (251.3 kg), and water (900 L). The resulting mixture was warmed to approximately 20 – 25 °C, and phases were separated.

The organic phase was filtered through a bed of AW hyflo super-cel NF (Celite; 5.4 kg) and the filter bed was washed with DCM (118.9 kg). The combined organic phase was washed with brine (282.9 kg) and mixed with water (120 L). The phases were separated and the organic phase was concentrated by vacuum distillation with the removal of solvent (approximately 95 L residual volume). DCM (686.5 kg) was charged to the reactor containing organic phase and concentrated by vacuum distillation with the removal of solvent (approximately 90 L residual volume). Methyl t-butyl ether (MTBE, 226.0 kg) was then charged and the temperature of the mixture was adjusted to -20 to -25 °C and held for 2.5 hours resulting in solid precipitate which was then filtered and washed with n-heptane (92.0 kg), and dried on a filter at approximately 25 °C under nitrogen to afford the title compound. (35.6 kg).

Preparation of 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine

[00139] 4-Aminophenol (24.4 kg) dissolved in N,N-dimethylacetamide (DMA, 184.3 kg) was charged to a reactor containing 4-chloro-6,7-dimethoxyquinoline (35.3 kg), sodium t-butoxide (21.4 kg) and DMA (167.2 kg) at 20-25 °C. This mixture was then heated to 100-105 °C for approximately 13 hours. After the reaction was deemed complete as determined using in-process HPLC analysis (<2% starting material remaining), the reactor contents were cooled at 15 to 20 °C and water (pre-cooled, 2 to 7 °C, 587 L) charged at a rate to maintain 15 to 30 °C temperature . The resulting solid precipitate was filtered, washed with a mixture of water (47 L) and DMA (89.1 kg) and finally with water (214 L). The filter cake was then dried at approximately 25 °C on filter to yield crude 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (59.4 kg wet, 41.6 kg dry calculated based on LOD). Crude 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine was refluxed (approximately 75 °C) in a mixture of tetrahydrofuran (THF, 211.4 kg) and DMA (108.8 kg) for approximately 1hour and then cooled to 0-5 °C and aged for approximately 1 h after which time the solid was filtered, washed with THF (147.6 kg) and dried on a filter under vacuum at approximately 25 °C to yield 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (34.0 kg).

Alternative Preparation of 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine

[00140] 4-chloro-6,7-dimethoxyquinoline (34.8 kg) and 4-aminophenol (30.8 kg) and sodium tert pentoxide (1.8 equivalents) 88.7 kg, 35 wt percent in THF) were charged to a reactor, followed by N,N-dimethylacetamide (DMA, 293.3 kg). This mixture was then heated to 105-115 °C for approximately 9 hours. After the reaction was deemed complete as

determined using in-process HPLC analysis (<2% starting material remaining), the reactor contents were cooled at 15 to 25 °C and water (315 kg) was added over a two hour period while maintaining the temperature between 20 and 30 °C. The reaction mixture was then agitated for an additional hour at 20 to 5 °C. The crude product was collected by filtration and washed with a mixture of 88 kg water and 82.1 kg DMA, followed by 175 kg water. The product was dried on a filter drier for 53 hours. The LOD showed less than 1% w/w.

[00141] In an alternative procedure, 1.6 equivalents of sodium tert-pentoxide were used and the reaction temperature was increased from 110-120 °C. In addition , the cool down temperature was increased to 35-40 °C and the starting temperature of the water addition was adjusted to 35-40 °C, with an allowed exotherm to 45 °C.

Preparation of 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid

[00142] Triethylamine (19.5 kg) was added to a cooled (approximately 5 C) solution of cyclopropane-1,1-dicarboxylic acid (24.7 kg) in THF (89.6 kg) at a rate such that the batch temperature did not exceed 5 °C. The solution was stirred for approximately 1.3 hours, and then thionyl chloride (23.1 kg) was added, keeping the batch temperature below 10 °C. When the addition was complete, the solution was stirred for approximately 4 h keeping temperature below 10 °C. A solution of 4–fluoroaniline (18.0 kg) in THF (33.1 kg) was then added at a rate such that the batch temperature did not exceed 10 °C. The mixture was stirred for approximately 10 hours after which the reaction was deemed complete. The reaction mixture was then diluted with isopropyl acetate (218.1 kg). This solution was washed sequentially with aqueous sodium hydroxide (10.4 kg, 50 % dissolved in 119 L of water) further diluted with water (415 L), then with water (100 L) and finally with aqueous sodium chloride (20.0 kg dissolved in 100 L of water). The organic solution was concentrated by vacuum distillation (100 L residual volume) below 40 °C followed by the addition of n-heptane (171.4 kg), which resulted in the precipitation of solid. The solid was recovered by filtration and washed with n-Heptane (102.4 kg) resulting in wet crude, 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (29.0 kg). The crude, 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid was dissolved in methanol (139.7 kg) at approximately 25 °C followed by the addition of water (320 L) resulting in slurry which was recovered by filtration, washed sequentially with water (20 L) and n-heptane (103.1 kg) and then dried on the filter at approximately 25 °C under nitrogen to afford the title compound (25.4 kg).

Preparation of 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride

[00143] Oxalyl chloride (12.6 kg) was added to a solution of 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (22.8 kg) in a mixture of THF (96.1 kg) and N, N-dimethylformamide (DMF; 0.23 kg) at a rate such that the batch temperature did not exceed 25 °C. This solution was used in the next step without further processing.

Alternative Preparation of 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride

[00144] A reactor was charged with 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (35 kg), 344 g DMF, and 175kg THF. The reaction mixture was adjusted to 12-17 °C and then to the reaction mixture was charged 19.9 kg of oxalyl chloride over a period of 1 hour. The reaction mixture was left stirring at 12-17 °C for 3 to 8 hours. This solution was used in the next step without further processing.

Preparation of cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (Compound IA)

[00145] The solution from the previous step containing 1–(4–fluoro–phenylcarbamoyl)–cyclopropanecarbonyl chloride was added to a mixture of compound 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (23.5 kg) and potassium carbonate (31.9 kg) in THF (245.7 kg) and water (116 L) at a rate such that the batch temperature did not exceed 30 °C. When the reaction was complete (in approximately 20 minutes), water (653 L) was added. The mixture was stirred at 20-25 °C for approximately 10 hours, which resulted in the precipitation of the product. The product was recovered by filtration, washed with a pre-made solution of THF (68.6 kg) and water (256 L), and dried first on a filter under nitrogen at approximately 25 °C and then at approximately 45 °C under vacuum to afford the title compound (41.0 kg, 38.1 kg, calculated based on LOD).

Alternative Preparation of cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide

[00146] A reactor was charged with 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (35.7 kg, 1 equivalent), followed by 412.9 kg THF. To the reaction mixture was charged a solution of 48.3 K_2CO_3 in 169 kg water. The acid chloride solution of described in the Alternative Preparation of 1-(4–Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride above was transferred to the reactor containing 4-(6,7-dimethoxy-quinoline-4-yloxy)-

phenylamine while maintaining the temperature between 20-30 °C over a minimum of two hours. The reaction mixture was stirred at 20-25 °C for a minimum of three hours. The reaction temperature was then adjusted to 30-25 °C and the mixture was agitated. The agitation was stopped and the phases of the mixture were allowed to separate. The lower aqueous phase was removed and discarded. To the remaining upper organic phase was added 804 kg water. The reaction was left stirring at 15-25 °C for a minimum of 16 hours.

[00147] The product precipitated. The product was filtered and washed with a mixture of 179 kg water and 157.9 THF in two portions. The crude product was dried under a vacuum for at least two hours. The dried product was then taken up in 285.1 kg THF. The resulting suspension was transferred to reaction vessel and agitated until the suspension became a clear (dissolved) solution, which required heating to 30-35 °C for approximately 30 minutes. 456 kg water was then added to the solution, as well as 20 kg SDAG-1 ethanol (ethanol denatured with methanol over two hours. The mixture was agitated at 15-25 °C for at least 16 hours. The product was filtered and washed with a mixture of 143 kg water and 126.7 THF in two portions. The product was dried at a maximum temperature set point of 40 °C.

[00148] In an alternative procedure, the reaction temperature during acid chloride formation was adjusted to 10-15 °C. The recrystallization temperature was changed from 15-25 °C to 45-50 °C for 1 hour and then cooled to 15-25 °C over 2 hours.

Preparation of cyclopropane–1,1–dicarboxylic acid [4–(6,7–dimethoxy– quinoline–4–yloxy)–phenyl]–amide (4–fluoro–phenyl)–amide, (L) malate salt (Compound IB)

[00149] Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (1-5; 13.3 kg), L-malic acid (4.96 kg), methyl ethyl ketone (MEK; 188.6 kg) and water (37.3 kg) were charged to a reactor and the mixture was heated to reflux (approximately 74 °C) for approximately 2 hours. The reactor temperature was reduced to 50 to 55 °C and the reactor contents were filtered. These sequential steps described above were repeated two more times starting with similar amounts of 1-5 (13.3 kg), L-Malic acid (4.96 kg), MEK (198.6 kg) and water (37.2 kg). The combined filtrate was azeotropically dried at atmospheric pressure using MEK (1133.2 kg) (approximate residual volume 711 L; KF $\leq$ 0.5 % w/w) at approximately 74 °C. The temperature of the reactor contents was reduced to 20 to 25 °C and held for approximately 4 hours resulting in solid precipitate which was filtered, washed with MEK (448 kg) and dried under vacuum at 50°C to afford the title compound (45.5 kg).

Alternative Preparation of cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L) malate salt

[00150] Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (47.9 kg), L-malic acid (17.2), 658.2 kg methyl ethyl ketone, and 129.1 kg water (37.3 kg) were charged to a reactor and the mixture was heated 50-55 °C for approximately 1-3 hours, and then at 55-60 °C for an addition al 4-5 hours. The mixture was clarified by filtration through a 1 μm cartridge. The reactor temperature was adjusted to 20-25 °C and vacuum distilled with a vacuum at 150-200 mm Hg with a maximum jacket temperature of 55 °C to the volume range of 558-731 L.

[00151] The vacuum distillation was performed two more times with the charge of 380 kg and 380.2 kg methyl ethyl ketone, respectively. After the third distillation, the volume of the batch was adjusted to 18 v/w of Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide by charging 159.9 kg methyl ethyl ketone to give a total volume of 880L. An addition al vacuum distillation was carried out by adjusting 245.7 methyl ethyl ketone. The reaction mixture was left with moderate agitation at 20-25 °C for at least 24 hours. The product was filtered and washed with 415.1 kg methyl ethyl ketone in three portions. The product was dried under a vacuum with the jacket temperature set point at 45 °C.

[00152] In an alternative procedure, the order of addition was changed so that a solution of 17.7 kg L-malic acid dissolved in 129.9 kg water was added to Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (48.7 kg) in methyl ethyl ketone (673.3 kg).

Preparation of Compound IB, Form N-1

[00153] A solution was prepared by adding tetrahydrofuran (12 mL/g-bulk-LR (limiting reagent); 1.20 L) and N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (100 g; 1.00 equiv; 100.00 g) and (L)-malic acid (1.2 equiv (molar); 32.08 g) to a 1 L reactor. Water (0.5317 mL/g-bulk-LR; 53.17 mL) was added and the solution was heated to 60 °C and maintained at that temperature for one hour until the solids were fully dissolved. The solution was passed through a Polish Filter.

[00154] At 60 °C, acetonitrile (12 mL/g-bulk-LR; 1.20 L) was added over a period of 8 hours. The solution was held at 60 °C for 10 hours. The solution was then cooled to 20 °C and held for 1 hour. The solids were filtered and washed with acetonitrile (12 mL/g-bulk-LR;

1.20 L). The solids were dried at 60 °C (25 mm Hg) for 6 hours to afford compound (I), Form N-1 (108 g; 0.85 equivalent; 108.00 g; 85.22% yield) as a white crystalline solid.

Alternate Preparation of Compound IB, Form N-1

[00155] A solution was prepared with 190 mL tetrahydrofuran (110 mL), methyl isobutyl ketone, and 29 mL water. Next, 20 mL of this solution were transferred into an amber bottle, and then saturated by adding N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (L)-malate until a thick slurry formed, and aging for at least 2 hours with stirring at room temperature. The solids were removed by filtration through a Buchner funnel, rendering a clear saturated solution.

[00156] Separately, a powder blend was made with known amounts of two batches of compound IB: (1) 300 mg of batch 1, which contained approximately 41% compound IB, Form N-1 and 59% compound IB, Form N-2 by Raman spectroscopy analysis, and (2) 200 mg of batch 2, which had a XPRD pattern similar to compound IB, Form N-2.

[00157] The compound IB, Form N-1 and compound (I), Form N-2 powder blend was added into the saturated solution, and the slurry was aged under magnetic stirring at room temperature for 25 days. The slurry was then sampled and filtered through a Buchner funnel to obtain 162 mg of wet cake. The wet cake was dried in a vacuum oven at 45 °C to afford 128 mg of crystalline compound IB in the N-1 form.

Preparation of Crystalline Compound IB, Form N-2

Preparation of Crystalline Compound IB, Form N-2 Seed Crystals

[00158] A solution was prepared by combining 20 ml of acetone and 300 mg of compound IA (N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide) in a 25ml screw capped vial. Next, 0.758ml of a 0.79M (L)-malic acid stock solution was added to the vial with magnetic stirring. The solution was then left stirring for 24 hours at ambient temperature. The sample was then suction filtered with 0.45μm PTFE filter cartridge and dried *in vacuo* at ambient temperature overnight.

Preparation of Crystalline Compound IB, Form N-2.

[00159] To a reactor were added N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (48 g; 1.00 equiv; 48.00 g) and tetrahydrofuran (16.5 mL/g-bulk-LR; 792.00 mL). The water content was adjusted to 1 wt% water. The solution was heated to 60 °C. Once dissolved, the solution was passed through a polish filter to provide the first solution.

[00160] In a separate reactor, (L)-malic acid (1.2 equiv (molar); 15.40 g) was dissolved into methyl isobutyl ketone (10 mL/g-bulk-LR; 480.00 mL) and tetrahydrofuran (1 mL/g-bulk-LR; 48.00 mL). Next, 50 mL of the (L)-malic acid solution was added to the first solution at 50 °C. Seed crystals were added (1%, 480 mg) and the malic acid solution was added at 50 °C dropwise via an addition funnel (1.3 ml/min over 3 hours). The slurry was held at 50 °C for 18 hours and then was cooled to 25 °C over 30 minutes. The solids were filtered, and washed with 20% tetrahydrofuran/methyl isobutyl ketone (10V, 480 mL). The solids were dried under vacuum at 60 °C for 5 hours to afford compound IB (55.7 g; 0.92 equivalent; 55.70 g; 91.56% yield) as an off-white crystalline solid.

Stability Studies of Pharmaceutical Compositions

[00161] The pharmaceutical capsule compositions of Tables 3 and 4 were prepared by mixing the ingredients according to processes known in the art.

Table 3

Ingredient	mg/unit dose
Compound IB (10 % drug load as Compound IA)	25
Microcrystalline Cellulose	196.75
Croscarmellose sodium	12.5
Sodium starch glycolate	12.5
Fumed Silica	0.75
Stearic acid	2.5
Total Fill Weight	250

Table 4

Ingredient	mg/unit dose
Compound IB (50 % drug load as Compound IA)	100
Silicified Microcrystalline Cellulose	75.40
Croscarmellose sodium	10.00
Sodium Starch Glycolate	10.00
Fumed silica	0.6
Stearic Acid	4.0
Total Fill Weight	200

[00162] The capsule compositions were subjected to stability studies to monitor the formation of 6,7-dimethoxy-quinoline-4-ol at various temperatures and relative humidities over time. The results are summarized in Tables 7A and 7B and Tables 8A and 8B.

Table 7A: Stability of 25 Mg Capsules (Table 3)

	Conditions	Bottle A1	Bottle A2	Bottle A3	Bottle A4
		PPM of 6,7-dimethoxy-quinoline-4-ol			
Initial T=0	25 °C/60% RH	2	2	3	3
1 Month	25 °C/60% RH	3	4	5	NA
	30 °C/75% RH	4	4	NA	NA
	40 °C/75% RH	9	9	10	NA
3 Months	25 °C/60% RH	5	5	7	NA
	30 °C/75% RH	7	6	NA	NA
	40 °C/75% RH	22	23	24	NA
6 Months	25 °C/60% RH	6	6	7	7 (3M in blister)
	30 °C/75% RH	9	9	NA	NA
	40 °C/75% RH	40	44	43	27 (3M in blister)
9 Months	25 °C/60% RH	7	7	9	8 (6M in blister)
	30 °C/75% RH	13	12	NA	NA
	40 °C/75% RH	NA	NA	68	60 (6M in blister)

M=Months; NA=Not Applicable; RH= Relative Humidity; PPM= Parts per Million. A portion of Bottle A4 was repackaged in a blister pack after being stored in bottles for 3 months.

Table 7B: Stability of 25 Mg Capsules (Table 3)

	Conditions	Bottle B1	Bottle B	Bottle B3	Bottle B4
		PPM of 6,7-dimethoxy-quinoline-4-ol			
Initial T=0	25 °C/60% RH	3	1	2	2
1 Month	25 °C/60% RH	<2	<2	<2	NA
	30 °C/75% RH	<2	<2	NA	NA
	40 °C/75% RH	2	<2	<2	NA
3 Months	25 °C/60% RH	2	<2	<2	NA
	30 °C/75% RH	2	<2	NA	NA
	40 °C/75% RH	3	<2	<2	NA
6 Months	25 °C/60% RH	<2	<2	<2	<2 (3M in blister)
	30 °C/75% RH	2	<2	NA	NA
	40 °C/75% RH	4	<2	3	3 (3M in blister)
9 Months	25 °C/60% RH	<2	<2	<2	<2 (6M in blister)
	30 °C/75% RH	3	<2	NA	NA
	40 °C/75% RH	NA	NA	5	4 (6M in blister)

A portion of Bottle B4 was repackaged in a blister pack after being stored in bottles for 3 months.

Table 8A: Stability of 100 Mg Capsules (Table 4)

	Conditions	Bottle A1	Blister A2	Bottle A3
		PPM of 6,7-dimethoxy-quinoline-4-ol		
Initial T=0	25 °C/60% RH	4	4	6
1 Month	25 °C/60% RH	4	4	6
	30 °C/75% RH	4	NA	6
	40 °C/75% RH	6	6	9
3 Months	25 °C/60% RH	5	5	7
	30 °C/75% RH	6	NA	7
	40 °C/75% RH	10	10	12
6 Months	25 °C/60% RH	5	5	
	30 °C/75% RH	6	NA	
	40 °C/75% RH	11	17	

M=Months; NA=Not Applicable; RH= Relative Humidity; PPM= Parts per Million.

Table 8B: Stability of 100 Mg Capsules (Table 4)

	Conditions	Bottle B1	Blister B2	Bottle B3
		PPM of 6,7-dimethoxy-quinoline-4-ol		
Initial T=0	25 °C/60% RH	1	1	2
1 Month	25 °C/60% RH	<2	<2	<2
	30 °C/75% RH	<2	<2	2
	40 °C/75% RH	<2	<2	2
3 Months	25 °C/60% RH	<2	<2	<2
	30 °C/75% RH	<2	NA	<2
	40 °C/75% RH	<2	<2	2
6 Months	25 °C/60% RH	<2	<2	
	30 °C/75% RH	<2	NA	
	40 °C/75% RH	2	2	

M=Months; NA=Not Applicable; RH= Relative Humidity; PPM= Parts per Million.

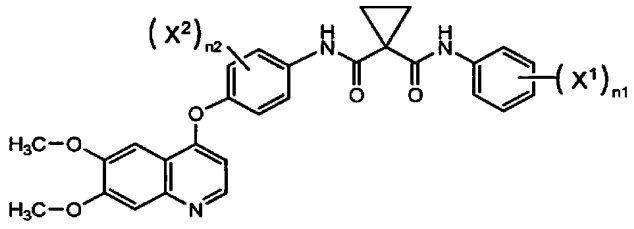
[00163] The results summarized in Tables 7A and 7B and 8A and 8B indicate that formation of 6,7-dimethoxy-quinoline-4-ol was minimized to 50 ppm or less over time in the capsule formulations.

[00164] The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that

changes and modifications can be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled. All references cited herein are incorporated by reference in their entirety.

CLAIMS

1. A process for preparing a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is H, Br, Cl, or F;

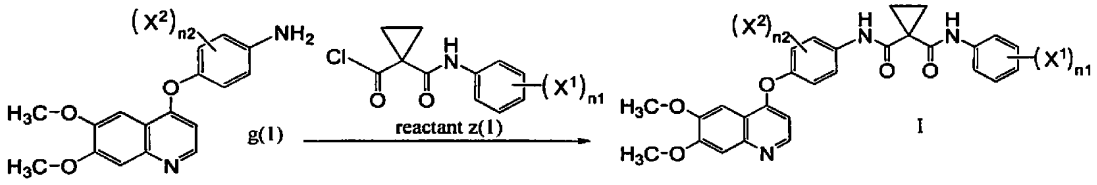
X^2 is H, Br, Cl, or F;

n1 is 1-2; and

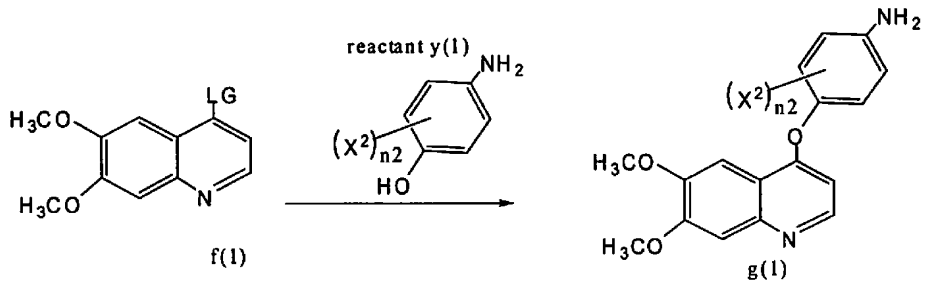
n2 is 1-2;

the process comprising:

contacting the compound of formula g(1) with reactant z(1) to yield the compound of formula I:

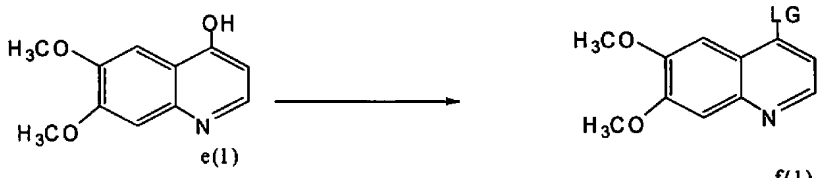


2. The process according to claim 1, wherein the compound of formula g(1) is made by reacting a compound of formula f(1) with reactant y(1) to yield the compound of formula g(1):



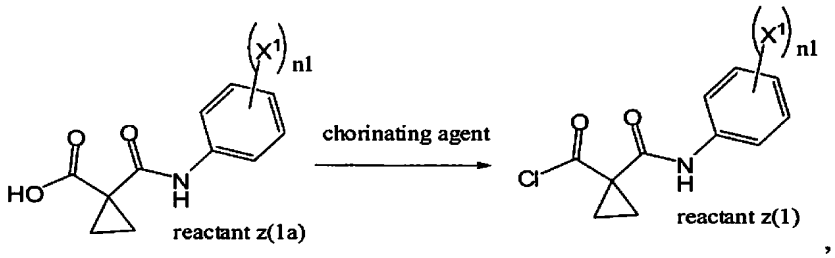
wherein LG represents a leaving group, and each X^2 and n2 are as defined in claim 1.

3. The process according to claim 2, wherein the compound of formula f(1) is made by converting compound e(1) to the compound of formula f(1):



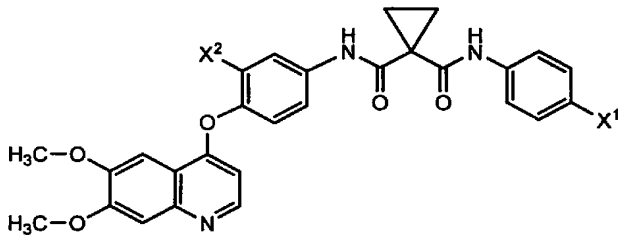
wherein LG represents a leaving group.

4. The process according to claim 1, wherein reactant z(1) is made by reacting reactant z(1a) with a chlorinating agent to yield reactant z(1):



wherein X^1 is Br, Cl, or F; and n1 is 1-2.

5. The process according to claim 1, wherein the compound of formula I is compound IA-1:



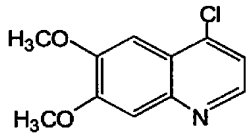
IA

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is H, Cl, Br, or F; and

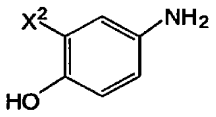
X^2 is H, Cl, Br, or F.

6. The process according to claim 5, wherein the compound of formula f(1) is compound f(2):



f(2) ;

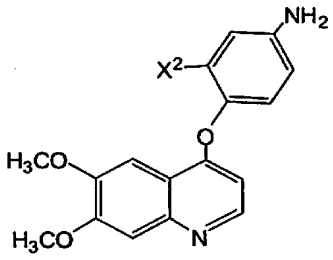
reactant y(1) is reactant (y)(2):



reactant (y)(2) ,

wherein X^2 is hydrogen or fluoro; and

the compound of formula g(1) is of formula g(2):



g(2) .

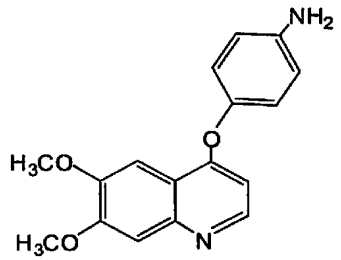
7. The process according to claim 6, wherein the reaction employs a non-nucleophilic base.

8. The process according to claim 7, wherein the non-nucleophilic base is an alkali metal alkoxide; and the reaction is carried out in a polar solvent.

9. The process according to claim 8, wherein the alkali metal alkoxide is sodium tert-butoxide, and the polar solvent is DMA.

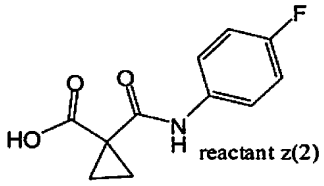
10. The process according to claim 8, wherein the alkali metal alkoxide is sodium tert-pentoxide, and the polar solvent is DMA.

11. The process according to claim 1, wherein the compound of formula g(1) is of compound g(3):



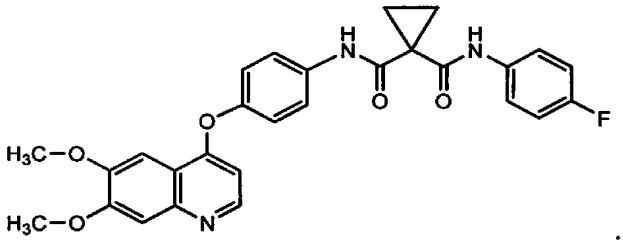
g(3) ;

reactant z(1) is reactant (z)(2):



reactant z(2) ; and

the compound of formula I is compound IA:

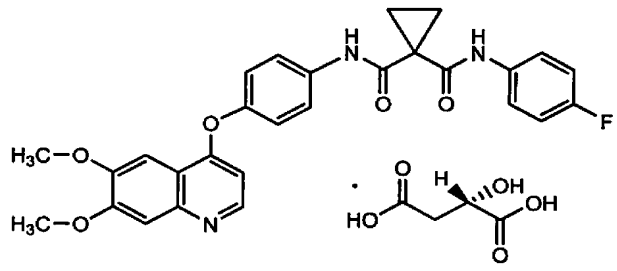


IA

12. The process according to claim 11, wherein the reaction is carried out in the presence of an inorganic base.

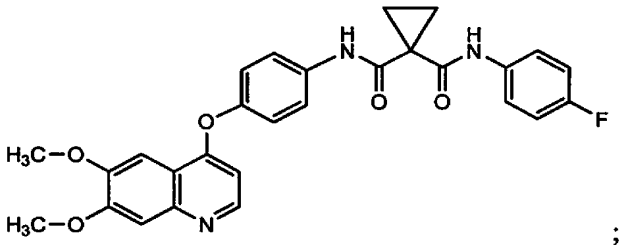
13. The process according to claim 12, wherein the inorganic base is K_2CO_3, and the solvent employed in this reaction is a combination of THF and H_2O.

14. A process for preparing compound IB:



IB

from compound IA:



;

IA

comprising:

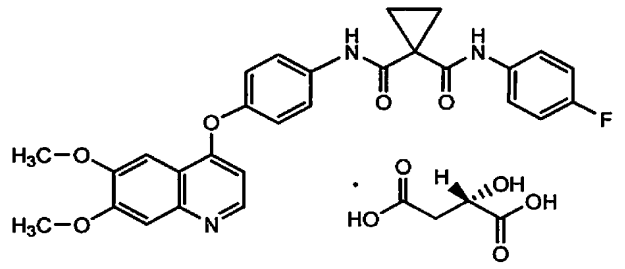
(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;

(b) cooling the mixture;

(c) vacuum distilling the mixture successively; and

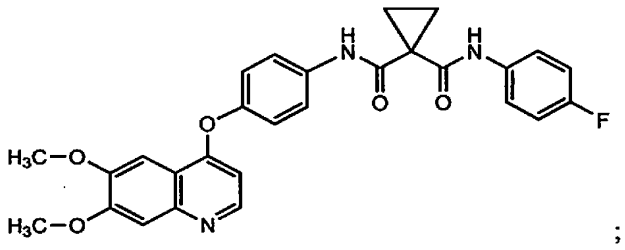
(d) isolating the compound of IB by filtration.

15. A process for preparing compound IB:



IB

from compound IA:



;

IA

comprising:

(a) heating and agitating a mixture comprising compound IA and L-malic acid, methylethyl ketone, and water;
(b) cooling the mixture;
(c) seeding the mixture with the compound of IB;
(d) vacuum distilling the mixture; and
(e) isolating the compound of IB by filtration.

16. Compound IA or IB admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

17. Compound IB admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

18. Compound IB in the N-1 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

19. Compound IB in the N-2 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

20. Compound IB as a mixture of the N-1 form and N-2 form admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

21. A pharmaceutical composition according to Table 1.

Table 1

Ingredient	% w/w
Compound I	31.68
Microcrystalline Cellulose (Avicel PH102)	38.85
Lactose anhydrous 60 M	19.42
Hydroxypropyl Cellulose, EXF	3.00
Croscarmellose Sodium	3.00
Total Intra-granular	**95.95**
Silicon dioxide, Colloidal PWD	0.30
Croscarmellose Sodium	3.00
Magnesium Stearate	0.75
Total	**100.00**

22. A pharmaceutical composition according to Table 2.

Table 2

Ingredient	(% w/w)
Compound I	25.0-33.3
Microcrystalline Cellulose, NF	q.s
Hydroxypropyl Cellulose, NF	3
Poloxamer, NF	0-3
Croscarmellose Sodium, NF	6.0
Colloidal Silicon Dioxide, NF	0.5
Magnesium Stearate, NF	0.5-1.0
Total	100

23. A pharmaceutical composition according to Table 2A.

Table 2A

Ingredient	**% w/w**
Compound IB (10 % drug load as Compound IA)	12.67
MCC	51.52
Lactose	25.76
Hydroxypropyl cellulose	3.0
Croscarmellose Sodium	6.0
Colloidal Silicon Dioxide	0.3
Magnesium Stearate	0.75
Total	**100**

24. A pharmaceutical composition according to Table 3.

Table 3

Ingredient	**mg/unit dose**
Compound IB (10 % drug load as Compound IA)	25
Silicified Microcrystalline Cellulose	196.75
Croscarmellose sodium	12.5
Sodium starch glycolate	12.5
Fumed Silica	0.75
Stearic acid	2.5
Total Fill Weight	250

25. A pharmaceutical composition according to Table 4.

Table 4

Ingredient	mg/unit dose
Compound IB (50 % drug load as Compound IA)	100
Silicified Microcrystalline Cellulose	75.40
Croscarmellose sodium	10.00
Sodium Starch Glycolate	10.00
Fumed silica	0.6
Stearic Acid	4.0
Total Fill Weight	200

26. A pharmaceutical composition according to Table 5.

Table 5

	mg/unit dose
Ingredient	**50mg**
Compound IB (10 % drug load as Compound IA)	63.35
Microcrystalline Cellulose	95.39
Croscarmellose sodium	9.05
Sodium starch glycolate	9.05
Fumed Silica	0.54
Stearic acid	3.62
Total Fill Weight	181.00

27. A pharmaceutical composition according to Table 6.

Table 6

	mg/unit dose
Ingredient	**60mg**
Compound IB	73.95
Microcrystalline Cellulose	114.36
Croscarmellose sodium	10.85
Sodium starch glycolate	10.85
Fumed Silica	0.65
Stearic acid	4.34
Total Fill Weight	217.00

28. The pharmaceutical composition of claims 20-27 admixed with 100 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

29. The pharmaceutical composition of claims 20-27 admixed with 50 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

30. The pharmaceutical composition of claims 20-27 admixed with 25 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

31. The pharmaceutical composition of claims 20-27 admixed with 15 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

32. The pharmaceutical composition of claims 20-27 admixed with 10 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

33. The pharmaceutical composition of claims 20-27 admixed with 5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

34. The pharmaceutical composition of claims 20-27 admixed with 2.5 ppm or less of 6,7-dimethoxy-quinoline-4-ol.

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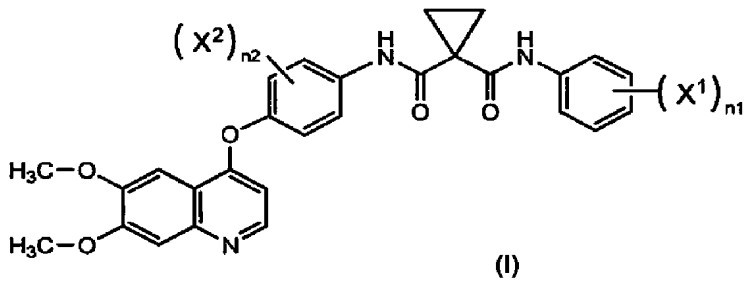
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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD,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

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

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

(54) Title: PROCESSES FOR PREPARING QUINOLINE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH COMPOUNDS



(I)

(57) Abstract: The present invention is directed to processes for making and compositions containing quinolines such as formula I or pharmaceutically acceptable salts thereof wherein: X1 is H, Br, CI, or X2 is H, Br, CI, or n1 is 1-2; and n2 is 1-2.

WO 2012/109510 A1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: Jo Ann Wilson, et al.
Application No.: To Be Determined
Filing Date: February 8, 2021

Art Unit: To Be Determined
Examiner: To Be Determined
Attorney Docket No.: 224990/10-039C6-US/483214

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313

PRELIMINARY AMENDMENT UNDER 37 C.F.R. § 1.115

Dear Sir or Madam:

Prior to examination of the present Application, the Applicant respectfully requests that the application be amended as follows.

Amendments to the claims begin on page 2.

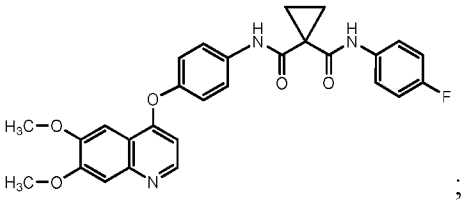
Amendments to the specification begin on page 3.

Remarks begin on page 4.

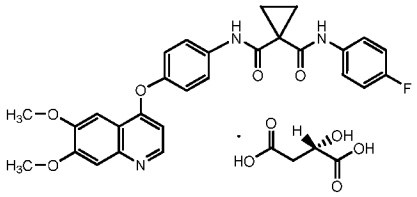
AMENDMENTS TO THE CLAIMS

1-34. Cancelled.

35. (New) A pharmaceutical composition comprising Compound IA or IB;



IA



IB

one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants, wherein the pharmaceutical composition is essentially free of process byproducts or contaminants.

36. (New) The pharmaceutical composition according to claim 35, wherein the pharmaceutical composition comprises Compound IA.

37. (New) The pharmaceutical composition according to claim 35, wherein the pharmaceutical composition comprises Compound IB.

AMENDMENTS TO THE SPECIFICATION

Please replace paragraph number [0001] under the heading "Cross-Reference to Related Applications" at page 1 with the replacement paragraph provided below:

[0001] This application is a continuation application of United States Serial Number 17/152,394 filed January 19, 2021, which is a continuation of United States Application Serial Number 16/706,323, filed December 6, 2019, which is a divisional of United States Application Serial Number 16/151,653, filed October 4, 2018, now United States Patent Number 10,543,206, which is a division of United States Application Serial Number 15/348,716, filed November 10, 2016, now United States Patent Number 10,123,999, which is a divisional of United States Application Serial Number 13/984,559, filed March 20, 2014, now united States Patent Number 9,717,720, which claims priority under 35 U.S.C. § 371 to Patent Cooperation Treaty Application Number PCT/US2012/024591, filed February 10, 2012, which claims the benefit of United States Provisional Application Number 61/441,520, filed February 10, 2011, and United States Provisional Application Number 61/441,527, filed February 10, 2011, the entire contents of which are incorporated herein by reference.

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REMARKS

Claim Status

Claims 1-34 are cancelled.

Claims 35-37 are new. The new claims are supported by the specification and claims as originally filed and do not introduce new matter.

Thus, claims 35-37 are currently pending.

The Applicant reserves the right to file divisional applications or take such other appropriate action as deemed necessary to protect the subject matter restricted, cancelled, or withdrawn from this application.

AMENDMENTS TO THE SPECIFICATION

Under the heading "Cross-Reference to Related Applications", paragraph [0001] of the specification has been amended to state that this application is a continuation application of United States Serial Number 17/152,394 filed January 19, 2021, which is a continuation of United States Application Serial Number 16/706,323, filed December 6, 2019, which is a divisional of United States Application Serial Number 16/151,653, filed October 4, 2018, now United States Patent Number 10,543,206, which is a division of United States Application Serial Number 15/348,716, filed November 10, 2016, now United States Patent Number 10,123,999, which is a divisional of United States Application Serial Number 13/984,559, filed March 20, 2014, now united States Patent Number 9,717,720, which claims priority under 35 U.S.C. § 371 to Patent Cooperation Treaty Application Number PCT/US2012/024591, filed February 10, 2012, which claims the benefit of United States Provisional Application Number 61/441,520, filed February 10, 2011, and United States Provisional Application Number 61/441,527, filed February 10, 2011, the entire contents of which are incorporated herein by reference.

USPTO TRACK ONE

The Applicant submits herewith as a large entity a Track One prosecution request and submits the processing fee set forth in 37 C.F.R. 1.17(i) in the amount of $140.00 as well as the prioritized examination fee set forth in 37 C.F.R. 1.17(c) in the amount of $4,200.00. Three new claims are presented by the Applicant for examination, none of which are multiply dependent. Thus, the claims are in compliance with Track One claim requirements, including: (i) no more

than thirty claims in total; (ii) no more than four independent claims; and (iii) no multiply depdendent claims. The Applicant therefore respectfully requests Track One status for the captioned application.

USPTO PATENT PROSECUTION HIGHWAY (PPH) PILOT PROGRAM

The Applicant submits herewith a Request for Participation in the Global/IP5 Patent Prosecution Highway (PPH) Pilot Program in the USPTO (PTO/SB/20GLBL). It is believed that no additional fees are required for this submission.

In support of the PPH application attached herewith, the Applicant submits the expanded Claims Correspondence Table depicted below. The table lists the new claims presented in the pending application and describes how they compare to claims granted in Australia. The table also lists a granted patent in Korea (KR), which also participates in the PPH program as an OEE country. Australia is the Office of Earlier Examination (OEE) for the purposes of this PPH request. The Australian patent, as well as Korean Patent and the present application, each share the priority date of February 10, 2011, and claim priority to PCT/US2012/024591, filed February 10, 2012.

Claims Correspondence Table

	Ser. No.	**Status**	**Claims**	**1-34**	**35**	**36**	**37**
US	TBD	Pending		Cancelled	New	New	New
PPH Country Patents					***Identical to PPH Country Claim***	***SI[a] to PPH Country Claim***	***SI to PPH Country Claim***
KR	10-2030447	Granted			1	3	4
AU OEE	2012214322	Granted			1	3	4

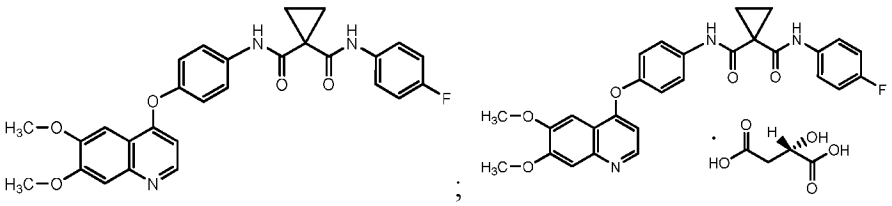
[a] SI means "Subtantially Identical"

The Applicant believes the Examiner has electronic access to the file wrapper for the AU granted patent listed in the table, and has therefore not included copies of the AU application as filed, the related office actions, or the issued patent with this submission. However, the Applicant is providing a copy of the AU granted claims with this filing for the conveince of the Office.

New claims 35-37 are substantially identical to the Australian Patent claims provided in the above Claims Correspondence Table, and as described in the following paragraphs.

- **AU Claim 1 is reproduced below.**

1. A pharmaceutical composition comprising Compound IA or IB;



IA ; IB

one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants, wherein the pharmaceutical composition is essentially free of process byproducts or contaminants.

AU claim 1 is a pharmaceutical composition claim. The Applicant's new claim 35 is identical to AU claim 1.

- **AU Claim 3 is reproduced below.**

3. The pharmaceutical composition according to any one of claims 1-2, wherein the pharmaceutical composition comprises Compound IA.

New claim 36 is a pharmaceutical composition claim. New claim 36 is substantially identical to AU claim 3 with the multiple dependancy removed. New claim 36 is dependent on new claim 35, which is identical to AU claim 1.

- **AU Claim 4 is reproduced below.**

4. The pharmaceutical composition according to any one of claims 1-3, wherein the pharmaceutical composition comprises Compound IB.

New claim 37 is a pharmaceutical composition claim. New claim 37 is substantially identical to AU claim 4 with the multiple dependancy removed. New claim 37 is dependent on new claim 35, which is identical to AU claim 1.

As a result, the Applicant requests acceptance of the application to the PPH Program.

INFORMATION DISCLOSURE STATEMENT

The Applicant notes that the filing of the enclosed Information Disclosure Statement shall not be construed to be an admission that the information cited in the statement qualifies as prior art under 35 U.S.C. § § 102 or 103, or is considered to be material to patentability as defined in 37 C.F.R. § 1.56(b). It is believed that no fee is due pursuant to 37 C.F.R. § 1.97(b)(3).

OTHER C-MET INHIBITOR CASES

The Applicant wishes to make the Examiner aware of the Applicant's other applications related to c-Met inhibitors and their use in the treatment of cancer. For the Examiner's convenience, the Applicant is providing a list of the Applicant's applications directed to the treatment of cancer using c-Met inhibitors. The Applicant understands the Examiner has electronic access to these applications and to the Office Actions that have issued in these applications, and has therefore not included copies with this Response. The Applicant will gladly provide the applications and Office Actions to the Examiner, however, upon request.

Application Number	Filing or 371 Date	Patent Number	Examiner	Status
10/573,336	09/18/2006		Koontz, Tammy J.	Abandoned
11/571,140	12/21/2006	7977345	Moore, Susanna	Expired
11/586,751	10/26/2006	9174947	Ward, Paul V.	Issued
11/753,462	05/24/2007	8178532	Ward, Paul V.	Issued
11/753,503	05/24/2007	8476298	Ward, Paul V.	Expired
11/753,514	05/24/2007	8067436	Bernhardt, Emily A.	Issued
12/393,806	02/26/2009	7579473	Seaman, D. Margaret M.	Issued
12/911,442	10/25/2010		Ward, Paul, V.	Abandoned
13/087,094	04/14/2011		Chickos, Sarah, J.	Abandoned
13/129,183	05/13/2011		Seaman, D. Margaret M.	Abandoned
13/132,650	06/03/2011		Seaman, D. Margaret M.	Abandoned
13/145,054	10/20/2011	8877776	Carter, Kendra D	Issued
13/249,815	09/30/2011	8497284	Bernhardt, Emily A.	Issued
13/384,451	07/12/2012	8673912	Anderson, Rebecca L.	Issued
13/389,266	07/12/2012		Perreira, Melissa Jean	Abandoned
13/427,093	03/22/2012		Ward, Paul V.	Abandoned
13/438,964	04/04/2012		Brown-Pettigrew, Angela C.	Abandoned
13/634,275	09/12/2012		Anderson, Rebecca L.	Abandoned
13/753,031	01/29/2013		Pagonakis, Anna	Abandoned
13/753,146	01/29/2013		Pagonakis, Anna	Abandoned
13/810,537	08/26/2013	9724342	Pallay, Michael B.	Issued

Application Number	Filing or 371 Date	Patent Number	Examiner	Status
13/810,546	08/27/2013		Branson, Daniel L.	Abandoned
13/876,290	11/05/2013		Stone, Christopher R.	Abandoned
13/876,306	11/08/2013		Lee, Andrew P.	Abandoned
13/876,318	10/25/2013		Karol, Jody Lynn	Abandoned
13/888,592	05/07/2013		Ward, Paul V.	Abandoned
13/928,977	06/27/2013		Bernhardt, Emily A.	Abandoned
13/984,559	03/20/2014	9717720	Rozof, Timothy R.	Issued
14/021,614	09/09/2013		Matos Negron, Taina Del Mar	Abandoned
14/115,236	02/28/2014		Anderson, James D.	Abandoned
14/166,545	01/28/2014		Not Yet Assigned	Abandoned
14/173,973	02/06/2014		Johannsen, Diana B.	Abandoned
14/340,871	07/25/2014	9809549	Carter, Kendra D.	Issued
14/346,570	03/21/2014	10166225	Wang, Shengjun	Issued
14/353,251	04/21/2014	9365516	Murray, Jeffrey H.	Issued
14/356,927	05/08/2014		Baek, Bong-Sook	Abandoned
14/356,938	05/08/2014		Cerioni, Daniel Lee	Abandoned
14/398,188	10/31/2014	9861624	Henley III, Raymond J.	Issued
14/426,580	03/06/2015		Jean-Louis, Samira J.M.	Abandoned
14/518,733	10/20/2014		Wright, Sarah C.	Abandoned
14/668,312	03/25/2015		Brown-Pettigrew, Angela C.	Abandoned
14/699,683	04/29/2015		Perreira, Melissa Jean	Abandoned
14/776,337	09/14/2015	10273211	Badio, Barbara P.	Issued
14/782,493	10/05/2015		Saeed, Kamal A.	Abandoned
14/782,537	10/05/2015		Alley, Genevieve S.	Pending
14/843,480	09/02/2015		Shen, Wu Cheng Winston	Abandoned
14/847,801	09/08/2015		Ward, Paul V.	Abandoned
14/933,801	11/05/2015		Brown-Pettigrew, Angela C.	Abandoned
15/066,872	03/10/2016		Ward, Paul V.	Abandoned
15/118,738	08/12/2016	10501418	Chandrakumar, Nizal S.	Issued
15/126,767	09/16/2016	10159666	Solola, Taofiq A.	Issued
15/133,708	04/20/2016	9969692	Murray, Jeffrey H.	Issued
15/305,854	10/21/2016		McMillian, Kara Renita	Pending
15/348,716	11/10/2016	10123999	Rozof, Timothy R.	Issued
15/500,312	01/30/2017		Seaman, D. Margaret M.	Pending
15/501,582	02/03/2017		Seaman, D. Margaret M.	Pending
15/426,804	02/07/2017	10039757	Pallay, Michael B.	Issued
15/612,703	06/02/2017	10034873	Pallay, Michael B.	Issued
15/617,725	06/08/2017		Neagu, Irina	Abandoned
15/618,593	06/09/2017		Carter, Kendra D.	Abandoned
15/621,527	06/13/2017		Carter, Kendra D.	Abandoned

Application Number	Filing or 371 Date	Patent Number	Examiner	Status
15/688,310	08/28/2017		Ward, Paul V.	Pending
15/955,246	04/17/2018		Not Yet Assigned	Abandoned
16/026,708	07/03/2018	10548888	Pallay, Michael B.	Issued
16/093,426	10/12/2018		Weddington, Kevin E.	Pending
16/095,221	10/19/2018		Saeed, Ali S.	Pending
16/142,691	09/26/2018		Howell, Theodore R.	Pending
16/151,653	10/04/2018	10543206	Rozof, Timothy R.	Issued
16/190,869	11/14/2018		Solola, Taofiq A.	Abandoned
16/230,267	12/21/2018		Kantamneni, Shobha	Pending
16/251,617	01/18/2019	10736886	Perreira, Melissa Jean	Issued
16/336,724	03/26/2019		Not Yet Assigned	Pending
16/362,863	03/25/2019		Reese, Heidi L.	Abandoned
16/479,143	07/18/2019		Lu, Cheng	Pending
16/671,834	11/01/2019	10851061	Chandrakumar, Nizal S.	Issued
16/617,352	11/26/2019		Not Yet Assigned	Pending
16/620,379	12/06/2019		Not Yet Assigned	Pending
16/706,323	12/06/2019		Rozof, Timothy R.	Pending
16/722,563	12/20/2019		Pallay, Michael B.	Pending
16/776,139	01/29/2020		Solola, Taofiq A.	Pending
16/787,212	02/11/2020		Anderson, James D.	Pending
16/796,250	02/20/2020		Not Yet Assigned	Pending
16/905,307	06/18/2020		Not Yet Assigned	Pending
16/919,562	07/02/2020		Not Yet Assigned	Pending
16/921,542	07/06/2020		Not Yet Assigned	Pending
17/031,196	09/24/2020		Not Yet Assigned	Pending
17/070,514	10/14/2020		Rozof, Timothy R.	Pending
17/070,790	10/14/2020		Seaman, D. Margaret M.	Abandoned
17/084,312	10/29/2020		Not Yet Assigned	Pending
17/149,365	01/14/2021		Not Yet Assigned	Pending
17/152,394	01/19/2021		Not Yet Assigned	Pending

CONCLUSION & FEES DUE

It is believed that due with this submission is the Basic Utility Application Fee of $320.00 set forth in 37 C.F.R. § 1.16(a), the Utility Search Fee of $700.00 set forth in § 1.16(k), the Utility Examination Fee of $800.00 set forth in § 1.16(o), the processing fee of $140.00 set forth in 37 C.F.R. 1.17(i), and the prioritized examination fee of $4,200.00 set forth in 37 C.F.R. 1.17(c). The Applicant hereby authorizes the Patent Office to charge this total of $6,160.00 to

Deposit Account No. 503145, referencing Attorney Docket Number 224990/10-039C6-US-US/483214. It is believed that no other fees are due at this time. However, if there are any additional charges for this submission, or any credits, please apply them to Deposit Account Number 503145, referencing Attorney Docket Number 224990/10-039C6-US/483214.

Respectfully submitted,

/Heidi M. Berven/

Date: February 8, 2021

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AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 **Director of the U.S. Patent and Trademark Office** **P.O. Box 1450** **Alexandria, VA 22313-1450**	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	3/16/2023	for the District of Delaware

PLAINTIFF	DEFENDANT
EXELIXIS, INC.	CIPLA LTD. & CIPLA USA, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,877,776 B2	11/4/2014	Exelixis, Inc.
2	11,091,439 B2	8/17/2021	Exelixis, Inc.
3	11,091,440 B2	8/17/2021	Exelixis, Inc.
4	11,098,015 B2	8/24/2021	Exelixis, Inc.
5	11,298,349 B2	4/12/2022	Exelixis, Inc.

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	7/18/2022	for the District of Delaware

PLAINTIFF	DEFENDANT
EXELIXIS, INC.	MSN LABORATORIES PRIVATE LIMITED and MSN PHARMACEUTICALS, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	11,298,349 B2	4/12/2022	EXELIXIS, INC.
2			
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/170,275	04/12/2022	11298349	224990/10-039C6-US/483214	8006

91684 7590 03/23/2022

JONATHAN P. O''BRIEN, PH.D.
HONIGMAN LLP
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PAIR WEB site http://pair.uspto.gov for additional inventors):

Jo Ann Wilson, San Francisco, CA;
Khalid Shah, Half Moon Bay, CA;

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Exelixis, Inc., Alameda, CA;

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

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	2021-02-08
First Named Inventor	Jo Ann Wilson
Art Unit	TBD
Examiner Name	TBD
Attorney Docket Number	224990/10-039C6-US/483214

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	9724342		2017-08-08	WILSON, et al.	
	2	9809549		2017-11-07	BROWN, et al.	
Change(s) applied to document, /S.D./ 3/10/2022	3	7579473		2009-08-25	~~EXELIXIS, INC.~~ Bannen , et al.	
	4	7977345		2011-07-12	~~EXELIXIS, INC.~~ Bannen , et al.	
	5	7999006		2011-08-16	~~EXELIXIS, INC.~~ Lamb	
	6	8067436		2011-11-29	~~EXELIXIS, INC.~~ Bannen , et al.	
	7	8178532		2012-05-15	~~EXELIXIS, INC.~~ Bannen , et al.	
	8	8314232		2012-11-20	~~EXELIXIS, INC.~~ Deschamps , et al.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.M.S/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	2021-02-08
	First Named Inventor	Jo Ann Wilson
	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

Change(s) applied to document. /S.D./ 3/10/2022	9	8476298		2013-07-02	~~EXELIXIS, INC.~~ Bannen , et al.	
	10	8497284		2013-07-30	~~EXELIXIS, INC.~~ Bannen , et al.	
	11	8673912		2014-03-18	~~EXELIXIS, INC.~~ Cannon , et al.	
	12	8877776		2014-11-04	~~EXELIXIS, INC.~~ Brown , et al.	
	13	9174947		2015-11-03	~~EXELIXIS, INC.~~ Bannen , et al.	
	14	9365516		2016-06-14	~~EXELIXIS, INC.~~ Wilson , et al.	
	15	7166722		2007-01-23	MATSUNAGA, et al.	
	16	7169789		2007-01-30	KUBO, et al.	
	17	5358941		1994-10-25	BECHARD, et al.	
	18	9717720		2017-08-01	WILSON, et al.	
	19	9969692		2018-05-15	WILSON, et al.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.M.S/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	2021-02-08
	First Named Inventor	Jo Ann Wilson
	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

	6	20150202196		2015-07-23	BANNEN, et al.	
	7	20160000772		2016-01-07	AFTAB, et al.	
	8	20160051532		2016-02-25	AFTAB, et al.	
	9	20160229805		2016-08-11	WILSON, et al.	
	10	20170143689		2017-05-25	WILSON, et al.	
	11	20170266178		2017-09-21	WILSON, et al.	
	12	20170275251		2017-09-28	BROWN, et al.	
	13	20180002289		2018-01-04	BROWN, et al.	
	14	20180037552		2018-02-08	BROWN, et al.	
Change(s) applied to document, /S.D./ 3/10/2022	15	20090274693		2009-11-05	~~EXELIXIS, INC.~~ Gilmer et al.	
	16	20110077233		2011-03-31	~~EXELIXIS, INC.~~ Bannen et al.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.M.S/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	2021-02-08
	First Named Inventor	Jo Ann Wilson
	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

Change(s) applied to document. /S.D./ 3/10/2022	17	20120070368		2012-03-22	~~EXELIXIS, INC.~~ Bannen et al.	
	18	20120184523		2012-07-19	~~EXELIXIS, INC.~~ Bannen et al.	
	19	20120252840		2012-10-04	~~EXELIXIS, INC.~~ Aftab et al.	
	20	20120282179		2012-11-08	~~EXELIXIS, INC.~~ Aftab et al.	
	21	20130030172		2013-01-31	~~EXELIXIS, INC.~~ Wilson et al.	
	22	20130142790		~~2013-01-31~~ 06/2013	~~EXELIXIS, INC.~~ Gilmer et al.	
	23	20130143881		~~2013-01-31~~ 06/2013	~~EXELIXIS, INC.~~ Cannon et al.	
	24	20130150363		2013-06-06	~~EXELIXIS, INC.~~ Gilmer et al.	
	25	20130197230		~~2013-06-06~~ 08/2013	~~EXELIXIS, INC.~~ Wilson et al.	
	26	20130252940		~~2013-06-13~~ 09/2013	~~EXELIXIS, INC.~~ Bannen et al.	
	27	20130252956		~~2013-08-01~~ 09/2013	~~EXELIXIS, INC.~~ Kallender et al.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.M.S/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	2021-02-08
	First Named Inventor	Jo Ann Wilson
	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

	28	20130330377		~~2013-09-26~~ 12/2013	~~EXELIXIS, INC.~~ Wilson	
	29	20130337015		~~2013-09-26~~ 12/2013	~~EXELIXIS, INC.~~ Wilson	
Change(s) applied to document. /S.D./ 3/10/2022	30	20140057943		~~2013-12-12~~ 02/2014	~~EXELIXIS, INC.~~ Smith et al.	
	31	20140057908		~~2013-12-19~~ 02/2014	~~EXELIXIS, INC.~~ Smith et al.	
	32	20140066444		~~2014-02-27~~ 03/2014	~~EXELIXIS, INC.~~ Smith et al.	
	33	20140155396		~~2014-02-27~~ 06/2014	~~EXELIXIS, INC.~~ Bannen et al.	
	34	20140179736		~~2014-03-06~~ 06/2014	~~EXELIXIS, INC.~~ Schwab et al.	
	35	20070054928		2007-03-08	BANNEN, et al.	
	36	20140200242		~~2014-06-05~~ 07/2014	~~EXELIXIS, INC.~~ Wilson	
	37	20140228401		~~2014-06-26~~ 08/2014	~~EXELIXIS, INC.~~ Aftab et al.	
	38	20140302012		~~2014-07-17~~ 10/2014	~~EXELIXIS, INC.~~ DeCillis et al.	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	2021-02-08
	First Named Inventor	Jo Ann Wilson
	Art Unit	TBD
	Examiner Name	TBD
	Attorney Docket Number	224990/10-039C6-US/483214

Change(s) applied to document, /S.D./ 3/10/2022	39	20140323522		~~2014-08-14~~ 10/2014	~~EXELIXIS, INC.~~ Aftab et al.	
	40	20150057310		~~2014-10-09~~ 02/2015	~~EXELIXIS, INC.~~ Brown et al.	
	41	20150196545		~~2014-10-30~~ 07/2015	~~EXELIXIS, INC.~~ Aftab et al.	
	42	20150202196		~~2015-02-26~~ 07/2015	~~EXELIXIS, INC.~~ Bannen et al.	
	43	20150376133		~~2015-07-16~~ 12/2015	~~EXELIXIS, INC.~~ Bannen et al.	
	44	20160000772		~~2015-07-23~~ 01/2016	~~EXELIXIS, INC.~~ Aftab et al.	
	45	20160051532		~~2015-12-31~~ 02/2016	~~EXELIXIS, INC.~~ Aftab et al.	
	46	20160185725		~~2016-01-07~~ 06/2016	~~EXELIXIS, INC.~~ Bannen et al.	
	47	20050209247		~~2005-09-22~~ 09/2005	~~CHIRON CORPORATION~~ Cai et al.	
	48	20070078159		2007-04-05	MATSUSHIMA, et al.	
	49	20110059081		2011-03-10	~~QUINTILES TRANSNATIONAL CORP.~~ Bacus	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.M.S/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/170,275	02/08/2021	Jo Ann Wilson	224990/10-039C6-US/483214	8006

91684 7590 03/10/2022

JONATHAN P. O''BRIEN, PH.D.
HONIGMAN LLP
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402

EXAMINER	
SEAMAN, D MARGARET M	

ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
03/10/2022	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

apeters@honigman.com
hberven@honigman.com
patent@honigman.com

Response to Rule 312 Communication	Application No.	Applicant(s)	
	17/170,275	Wilson et al.	
	Examiner	Art Unit	AIA (FITF) Status
	D MARGARET M SEAMAN	1625	No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

1. ☑ The amendment filed on 28 February 2022 under 37 CFR 1.312 has been considered, and has been:

a) ☑ entered.

b) ☐ entered as directed to matters of form not affecting the scope of the invention.

c) ☐ disapproved because the amendment was filed after the payment of the issue fee.

Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.

d) ☐ disapproved. See explanation below.

e) ☐ entered in part. See explanation below.

f) ☐ not entered because the supplemental or corrected Application Data sheet (ADS)

☐ was not accompanied by a petition to accept an unintentionally delayed claim under 37 CFR 1.55 or 27 CFR 1.78;

☐ did not identify the information being changed in accordance with 37 CFR 1.76(c)(2);

☐ was not properly signed in accordance with 37 CFR 1.76(e) (or 37 CFR 1.33(b) for applications filed prior to September 16, 2012).

/D MARGARET M SEAMAN/
Primary Examiner, Art Unit 1625

Please Enter
/DMS/
2 March 2022

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Jo Ann Wilson, et al.	Art Unit:	1625
Application No.:	17/170,275	Examiner:	Seaman, D. Margaret M.
Filing Date:	February 8, 2021	Conf. No.:	8006
Atty. Docket No.:	224990/10-039C6-US/483214		

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

MAIL STOP ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

via EFS-Web

RESPONSE TO THE NOTICE TO FILE CORRECTED APPLICATION PAPERS MAILED FEBRUARY 28, 2022

Dear Commissioner:

In response to the Notice to File Corrected Application Papers dated February 28, 2022, please amend the above-identified U.S. patent application as follows and consider the following remarks/arguments:

Amendments to the Specification begin on page 2 of this paper, and replacement specification page 27 of the specification is provided herewith.

Remarks begin on page 3 of this paper.

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/170,275	02/08/2021	Jo Ann Wilson	224990/10-039C6-US 483214	8006

91684 7590 02/28/2022

JONATHAN P. O"BRIEN, PH.D.
HONIGMAN LLP
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402

EXAMINER	
SEAMAN, D MARGARET M	

ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
02/28/2022	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patent@honigman.com
hberven@honigman.com
apeters@honigman.com

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Application No. : 17170275
Applicant : Wilson
Filing Date : 02/08/2021
Date Mailed : 02/28/2022

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Notice of Allowance Mailed

This application has been accorded an Allowance Date and is being prepared for issuance. The application, however, is incomplete for the reasons below.

Applicant is given two (2) months from the mail date of this Notice within which to respond. This time period for reply is extendable under 37 CFR 1.136(a) for only TWO additional MONTHS.

The informalities requiring correction are indicated in the attachment(s). If the informality pertains to the abstract, specification (including claims) or drawings, the informality must be corrected with an amendment in compliance with 37 CFR 1.121 (or, if the application is a reissue application, 37 CFR 1.173). Such an amendment may be filed after payment of the issue fee if limited to correction of informalities noted herein. See Waiver of 37 CFR 1.312 for Documents Required by the Office of Patent Publication, 1280 Off. Gaz. Patent Office 918 (March 23, 2004). In addition, if the informality is not corrected until after payment of the issue fee, for purposes of 35 U.S.C. 154(b)(1)(iv), "all outstanding requirements" will be considered to have been satisfied when the informality has been corrected. A failure to respond within the above-identified time period will result in the application being ABANDONED.

See attachment(s).

A copy of this notice MUST be returned with the reply. Please address response to "Mail Stop Issue Fee, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450".

/Naran Hem/
Publication Branch
Office of Data Management
(571) 272-4200

Application No. 17170275

IDENTIFICATION OF APPLICATION DEFICIENCIES IN APPLICATION FILED ON OR AFTER SEPTEMBER 16, 2012

[X] Applicant must provide legible text for the following item(s).

- [X] Specification filed 02/08/2021, page(s) 27.
- [ ] Claims filed , claim(s) .
- [ ] Other: .

[ ] Applicant must provide missing information on the following page(s) of the specification by amending the specification to add the missing text. No new matter may be added.
Page/line no(s).

[ ] The specification refers to one or more applications by attorney docket number and does not show the U.S. application number(s). Applicant must supply the U.S. application number in place of each attorney docket number.
Page/line no(s).

[ ] Applicant must provide an Abstract of the Disclosure.

[ ] The Application Data Sheet (ADS dated) does not supply the inventor's city and/or does not supply the inventor's U.S. state and/or does not supply the inventor's country. Applicant must submit a signed, in accordance with 37 CFR 1.76(e) and 1.33(b), application data sheet that corrects this deficiency. To be in compliance with 37 CFR 1.76, the corrected application data sheet must identify the information being changed by using underlining for additions and strikethroughs or brackets for deletions.

[ ] Other:

The response to this notice should contain only amended papers, as the waiver of 37 CFR 1.312 is limited to corrections of documents specifically requested in the notice.

HONIGMAN

Heidi M. Berven, Ph.D.
Office: 269.337.7710
Mobile: 269.365.8962
hberven@honigman.com

VIA EFS

February 18, 2022

Mail Stop: ISSUE FEE
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313

Re: US Patent Application No.: 17/170,275
Inventors: Jo Ann Wilson, et al.
Filing Date: February 8, 2021
Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
Conf. No.: 8006
Attorney Docket No.: 224990/10-039C6-US/483214

Dear Sir or Madam:

Enclosed for filing please find the following documents:

1. This Cover Letter to the Commissioner for Patents;
2. Response to the Notice to File Corrected Application Papers dated February 28, 2022;
3. Replacement Specification Page 27; and
4. Copy of Notice to File Corrected Application Papers dated February 28, 2022; and
5. Certificate of Transmission under 37 C.F.R. § 1.8(a).

It is believed that no fees are required for this submission. However, if there are any charges, or any credits, in direct relation to this response, please apply them to Deposit Account No. 503145, referencing Attorney Docket No. 224990/10-039C6-US/483214, from which the undersigned is authorized to draw.

Very truly yours,

HONIGMAN LLP

/Heidi M. Berven, Ph.D./

Heidi M. Berven, Ph.D.
Reg. No. 48,951

HMB/ayp
Enclosures

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Jo Ann Wilson, et al.	Art Unit:	1625
Application No.:	17/170,275	Examiner:	Seaman, D. Margaret M.
Filing Date:	February 8, 2021	Conf. No.:	8006
Atty. Docket No.:	224990/10-039C6-US/483214		

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

MAIL STOP ISSUE FEE
Commissioner for Patents
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Alexandria, VA 22313-1450

via EFS-Web

RESPONSE TO THE NOTICE TO FILE CORRECTED APPLICATION PAPERS MAILED FEBRUARY 28, 2022

Dear Commissioner:

In response to the Notice to File Corrected Application Papers dated February 28, 2022, please amend the above-identified U.S. patent application as follows and consider the following remarks/arguments:

Amendments to the Specification begin on page 2 of this paper, and replacement specification page 27 of the specification is provided herewith.

Remarks begin on page 3 of this paper.

AMENDMENTS TO THE SPECIFICATION

In response to the Notice to File Corrected Application Papers mailed February 28, 2022, the Applicant provides herewith replacement specification page 27 providing legible text and structures on the page as requested in the Notice.

REMARKS

AMENDMENTS TO THE SPECIFICATION

In response to the Notice to File Corrected Application Papers mailed February 28, 2022, the Applicant provides herewith replacement specification page 27 in accordance with 37 C.F.R. § 1.121, providing legible text on the page as requested in the Notice.

The Applicant previously paid the Issue Fee in this application on February 18, 2022.

CONCLUSION

The Applicant believes this submission is fully responsive to the Notice to File Corrected Application Papers dated February 28, 2022. It is believed that no fees are required for this submission. However, if there are any charges, or any credits, in direct relation to this response, please apply them to Deposit Account No. 503145, referencing Attorney Docket No. 224990/10-039C6-US/483214, from which the undersigned is authorized to draw.

Respectfully submitted,

/Heidi M. Berven, Ph.D./

Date: February 28, 2022

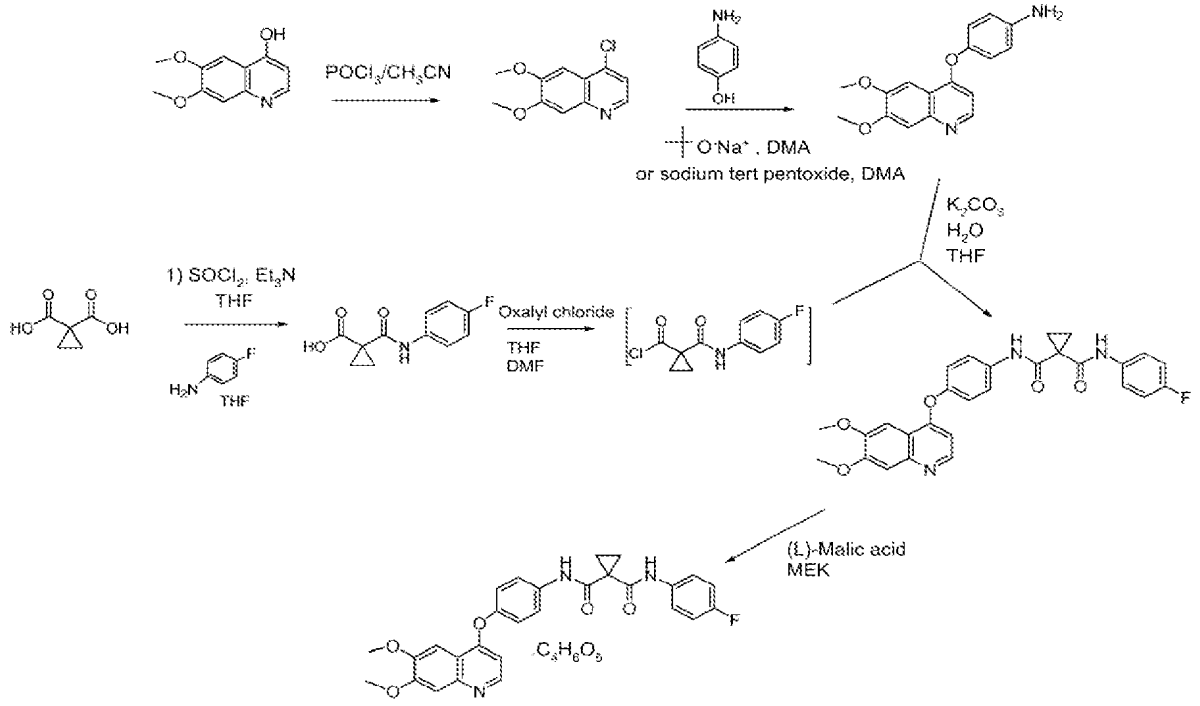
Heidi M. Berven, Ph.D.
Reg. No. 48,951
Honigman LLP
650 Trade Centre Way, Suite 200
Kalamazoo, MI 49002
Telephone: (269) 337-7710
Facsimile: (269) 337-7711

appropriate atmosphere to run the reaction under, for example, air, nitrogen, hydrogen, argon, and the like, will be apparent to those skilled in the art.

Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof.

[00137] A synthetic route that can be used for the preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof is depicted in Figure 1:

Figure 1



Preparation of 4-Chloro-6,7-dimethoxy-quinoline

[00138] A reactor was charged sequentially with 6,7-dimethoxy-quinoline-4-ol (47.0 kg) and acetonitrile (318.8 kg). The resulting mixture was heated to approximately 60 °C, and phosphorus oxychloride ($POCl_3$, 130.6 kg) was added. After the addition of $POCl_3$, the temperature of the reaction mixture was raised to approximately 77 °C. The reaction was deemed complete (approximately 13 hours) when less than 3% of the starting material remained (in-process high-performance liquid chromatography [HPLC] analysis). The reaction mixture was cooled to approximately 2 – 7 °C and then quenched into a chilled solution of dichloromethane (DCM, 482.8 kg), 26 % NH_4OH (251.3 kg), and water (900 L). The resulting mixture was warmed to approximately 20 – 25 °C, and phases were separated.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/170,275	02/08/2021	Jo Ann Wilson	224990/10-039C6-US 483214	8006

91684 7590 02/28/2022

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EXAMINER	
SEAMAN, D MARGARET M	

ART UNIT	PAPER NUMBER
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NOTIFICATION DATE	DELIVERY MODE
02/28/2022	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

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apeters@honigman.com

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Application No. : 17170275
Applicant : Wilson
Filing Date : 02/08/2021
Date Mailed : 02/28/2022

NOTICE TO FILE CORRECTED APPLICATION PAPERS

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See attachment(s).

A copy of this notice MUST be returned with the reply. Please address response to "Mail Stop Issue Fee, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450".

/Naran Hem/
Publication Branch
Office of Data Management
(571) 272-4200

Application No. 17170275

IDENTIFICATION OF APPLICATION DEFICIENCIES IN APPLICATION FILED ON OR AFTER SEPTEMBER 16, 2012

[X] Applicant must provide legible text for the following item(s).

- [X] Specification filed 02/08/2021, page(s) 27.
- [ ] Claims filed , claim(s) .
- [ ] Other: .

[ ] Applicant must provide missing information on the following page(s) of the specification by amending the specification to add the missing text. No new matter may be added.
Page/line no(s).

[ ] The specification refers to one or more applications by attorney docket number and does not show the U.S. application number(s). Applicant must supply the U.S. application number in place of each attorney docket number.
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[ ] Applicant must provide an Abstract of the Disclosure.

[ ] The Application Data Sheet (ADS dated) does not supply the inventor's city and/or does not supply the inventor's U.S. state and/or does not supply the inventor's country. Applicant must submit a signed, in accordance with 37 CFR 1.76(e) and 1.33(b), application data sheet that corrects this deficiency. To be in compliance with 37 CFR 1.76, the corrected application data sheet must identify the information being changed by using underlining for additions and strikethroughs or brackets for deletions.

[ ] Other:

The response to this notice should contain only amended papers, as the waiver of 37 CFR 1.312 is limited to corrections of documents specifically requested in the notice.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Jo Ann Wilson, et al.	Art Unit:	1625
Application No.:	17/170,275	Examiner:	Seaman, D. Margaret M.
Filing Date:	February 8, 2021	Conf. No.:	8006
Atty. Docket No.:	224990/10-039C6-US/483214		

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

CERTIFICATE OF TRANSMISSION UNDER 37 C.F.R. § 1.8(a)

The undersigned hereby certifies that the following documents are being submitted in accordance with 37 C.F.R. § 1.6(a)(4) on the 28th day of February 2022.

1. Cover Letter to the Commissioner for Patents;
2. Response to the Notice to File Corrected Application Papers dated February 28, 2022;
3. Replacement Specification Page 27; and
4. Copy of Notice to File Corrected Application Papers dated February 28, 2022; and
5. This Certificate of Transmission under 37 C.F.R. § 1.8(a).

/Amy L. Peters/

Amy L. Peters (for Heidi M. Berven, Reg. No. 48,951)

Electronic Acknowledgement Receipt

EFS ID:	45106757
Application Number:	17170275
International Application Number:	
Confirmation Number:	8006
Title of Invention:	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
First Named Inventor/Applicant Name:	Jo Ann Wilson
Customer Number:	91684
Filer:	Heid Marie Berven/Amy Peters
Filer Authorized By:	Heid Marie Berven
Attorney Docket Number:	224990/10-039C6-US/483214
Receipt Date:	28-FEB-2022
Filing Date:	08-FEB-2021
Time Stamp:	16:55:58
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2022-02-28_EX10-039C6-US_Response_to_NTFCAP_Docs.pdf	1252895 35ed2a13e2be2635930816f1c560d4165e37ed49	yes	9

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Miscellaneous Incoming Letter	1	1
	Post Allowance Communication - Incoming	2	2
	Specification	3	3
	Applicant Arguments/Remarks Made in an Amendment	4	4
	Specification	5	5
	Post Allowance Communication - Incoming	6	8
	Miscellaneous Incoming Letter	9	9
Warnings:			
Information:			
	Total Files Size (in bytes):	1252895	

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.

HONIGMAN

Heidi M. Berven, Ph.D.
Office: 269.337.7710
Mobile: 269.365.8962
hberven@honigman.com

VIA EFS

February 18, 2022

Mail Stop: ISSUE FEE
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313

Re: US Patent Application No.: 17/170,275
Inventors: Jo Ann Wilson, et al.
Filing Date: February 8, 2021
Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
Conf. No.: 8006
Attorney Docket No.: 224990/10-039C6-US/483214

Dear Sir or Madam:

Enclosed for filing please find the following documents:

1. This Cover Letter to the Commissioner for Patents;
2. Fee Transmittal (PTOL-85 Part B); and
3. Certificate of Transmission under 37 C.F.R. § 1.8(a).

It is believed that due with this submission is the $1,200.00 Issue Fee set forth in 37 C.F.R. § 1.18(a)(1). The Applicant hereby authorizes the Patent Office to charge this total of $1,200.00 to Deposit Account Number 503145 with reference to attorney docket number 224990/10-039C6-US/483214. It is believed that no other fees are due at this time. However, if there are any additional charges for this submission, or any credits, please apply them to Deposit Account Number 503145, referencing Attorney Docket Number 224990/10-039C6-US/483214.

Very truly yours,

HONIGMAN LLP

/Heidi M. Berven, Ph.D./

Heidi M. Berven, Ph.D.
Reg. No. 48,951

HMB/ayp
Enclosures

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

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

91684 7590 02/10/2022

JONATHAN P. O"BRIEN, PH.D.
HONIGMAN LLP
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/170,275	02/08/2021	Jo Ann Wilson	224990/10-039C6-US/483214	8006

TITLE OF INVENTION: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	05/10/2022

EXAMINER	ART UNIT	CLASS-SUBCLASS
SEAMAN, D MARGARET M	1625	514-312000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Honigman LLP
2 Heidi M. Berven, Ph.D.
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Exelixis, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Alameda, CA

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ☑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ☑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

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

☑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

☑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 503145

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Heidi M. Berven, Ph.D./ Date February 18, 2022

Typed or printed name Heidi M. Berven, Ph.D. Registration No. 48,951

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Jo Ann Wilson, et al.	Art Unit:	1625
Application No.:	17/170,275	Examiner:	Seaman, D. Margaret M.
Filing Date:	February 8, 2021	Conf. No.:	8006
Atty. Docket No.:	224990/10-039C6-US/483214		

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

CERTIFICATE OF TRANSMISSION UNDER 37 C.F.R. § 1.8(a)

The undersigned hereby certifies that the following documents are being submitted in accordance with 37 C.F.R. § 1.6(a)(4) on the 18th day of February 2022.

1. Cover Letter to the Commissioner for Patents;
2. Fee Transmittal (PTOL-85 Part B); and
3. This Certificate of Transmission under 37 C.F.R. § 1.8(a).

/Amy L. Peters/

Amy L. Peters (for Heidi M. Berven, Reg. No. 48,951)

Electronic Patent Application Fee Transmittal

Application Number:	17170275
Filing Date:	08-Feb-2021
Title of Invention:	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
First Named Inventor/Applicant Name:	Jo Ann Wilson
Filer:	Heid Marie Berven/Amy Peters
Attorney Docket Number:	224990/10-039C6-US/483214

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	1501	1	1200	1200

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1200**

Electronic Acknowledgement Receipt

EFS ID:	45036787
Application Number:	17170275
International Application Number:	
Confirmation Number:	8006
Title of Invention:	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
First Named Inventor/Applicant Name:	Jo Ann Wilson
Customer Number:	91684
Filer:	Heid Marie Berven/Amy Peters
Filer Authorized By:	Heid Marie Berven
Attorney Docket Number:	224990/10-039C6-US/483214
Receipt Date:	18-FEB-2022
Filing Date:	08-FEB-2021
Time Stamp:	15:52:49
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1200
RAM confirmation Number	E20222HF53064440
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		2022-02-18_EX10-039C6-US_Issue_Fee_Payment_Docs.pdf	379516 25240912d192d2de3df514b3f73a13f2e3797c5d	yes	3

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Miscellaneous Incoming Letter	1	1
	Issue Fee Payment (PTO-85B)	2	2
	Miscellaneous Incoming Letter	3	3

Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	38162 40b2d4da70b78ba525b5c14a3fe596f003511b92	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	417678	

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

91684 7590 02/10/2022

JONATHAN P. O"BRIEN, PH.D.
HONIGMAN LLP
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402

EXAMINER
SEAMAN, D MARGARET M

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 02/10/2022

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/170,275	02/08/2021	Jo Ann Wilson	224990/10-039C6-US/483214	8006

TITLE OF INVENTION: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	05/10/2022

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

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

91684 7590 02/10/2022

JONATHAN P. O"BRIEN, PH.D.
HONIGMAN LLP
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/170,275	02/08/2021	Jo Ann Wilson	224990/10-039C6-US/483214	8006

TITLE OF INVENTION: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	05/10/2022

EXAMINER	ART UNIT	CLASS-SUBCLASS
SEAMAN, D MARGARET M	1625	514-312000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required) ❑Advance Order - # of Copies _____

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

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/170,275	02/08/2021	Jo Ann Wilson	224990/10-039C6-US/483214	8006

91684 7590 02/10/2022

JONATHAN P. O"BRIEN, PH.D.
HONIGMAN LLP
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402

EXAMINER	
SEAMAN, D MARGARET M	
ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 02/10/2022

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

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

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

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 17/170,275	Applicant(s) Wilson et al.	
	Examiner D MARGARET M SEAMAN	Art Unit 1625	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to Response dated 1/20/2022.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 35 and 38-39 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information , please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/D MARGARET M SEAMAN/
Primary Examiner, Art Unit 1625

Reasons for Allowance

Notice of Pre-AIA or AIA Status

1. The present application is being examined under the pre-AIA first to invent provisions.

2. The following is an examiner's statement of reasons for allowance: The rejections of paper dated 7/20/2021 have been withdrawn in view of applicant's amendments, terminal disclaimer and arguments in paper dated 1/20/2022. .

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

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D MARGARET M SEAMAN whose telephone number is (571)272-0694. The examiner can normally be reached M-F 8am-4pm EST Telework Home.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/D MARGARET M SEAMAN/
Primary Examiner, Art Unit 1625

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/170,275	Wilson et al.
	Examiner	Art Unit
	D MARGARET M SEAMAN	1625

CPC - Searched*		
Symbol	**Date**	**Examiner**
A61K 31/47	03/26/2021	dms
C07D 215/233	03/26/2021	dms
above updated	07/15/2021	dms
above updated	01/31/2022	dms

CPC Combination Sets - Searched*		
Symbol	**Date**	**Examiner**

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	**Date**	**Examiner**
Inventor Name Search	03/26/2021	dms
STNext Structure search	03/26/2021	dms
google	07/15/2021	dms
Inventor Name UPdate Search	01/31/2022	dms

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/170,275	Wilson et al.
	Examiner	Art Unit
	D MARGARET M SEAMAN	1625

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
A61K	31/47	01/31/2022	dms
C07D	215/233	01/31/2022	dms

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/170,275	Wilson et al.
	Examiner	**Art Unit**
	D MARGARET M SEAMAN	1625

CPC						
Symbol					**Type**	**Version**
A61K	/	31	/	47	F	2013-01-01
C07D	/	215	/	233	I	2013-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	3	
/D MARGARET M SEAMAN/ Primary Examiner, Art Unit 1625	31 January 2022	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/170,275	Wilson et al.
	Examiner	**Art Unit**
	D MARGARET M SEAMAN	1625

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K	/	31	/	47

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

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

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	3	
/D MARGARET M SEAMAN/ Primary Examiner, Art Unit 1625	31 January 2022	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/170,275	Wilson et al.
	Examiner	**Art Unit**
	D MARGARET M SEAMAN	1625

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	3	
/D MARGARET M SEAMAN/ Primary Examiner, Art Unit 1625	31 January 2022	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

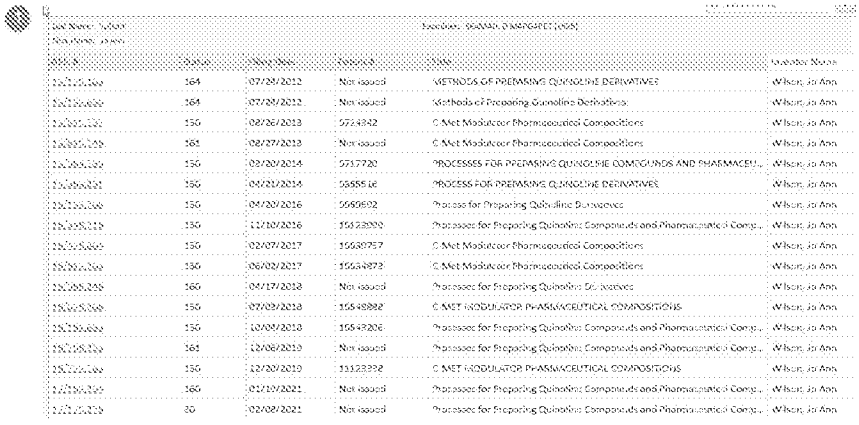
Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/170,275	Wilson et al.
	Examiner	Art Unit
	D MARGARET M SEAMAN	1625

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

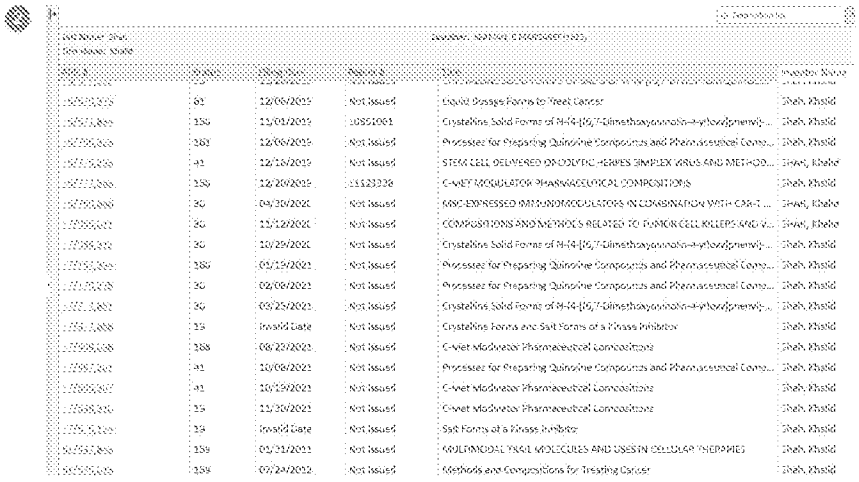
CLAIMS

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	03/26/2021	07/15/2021	01/31/2022						
	1	-								
	2	-								
	3	-								
	4	-								
	5	-								
	6	-								
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	27	-								
	28	-								
	29	-								
	30	-								
	31	-								
	32	-								
	33	-								
	34	-								
	35	✓	✓	=						
	36	✓	-							
	37	✓	-							
	38		✓	=						
	39		✓	=						



Application Number	Patent Term	Filing Date	Patent #	Title	Inventor Name
13/715,104	164	07/28/2012	Not Issued	METHODS OF PREPARING QUINOLINE DERIVATIVES	Wilson, Jo Ann
14/345,660	164	07/28/2012	Not Issued	Methods of Preparing Quinoline Derivatives	Wilson, Jo Ann
14/007,150	156	02/26/2013	9724342	C-Met Modulator Pharmaceutical Compositions	Wilson, Jo Ann
14/005,159	161	02/27/2013	Not Issued	C-Met Modulator Pharmaceutical Compositions	Wilson, Jo Ann
14/006,190	156	02/20/2014	9717720	PROCESSES FOR PREPARING QUINOLINE COMPOUNDS AND PHARMACEU...	Wilson, Jo Ann
14/460,231	156	04/21/2014	9855258	PROCESS FOR PREPARING QUINOLINE DERIVATIVES	Wilson, Jo Ann
15/130,568	156	04/20/2016	9669902	Process for Preparing Quinoline Derivatives	Wilson, Jo Ann
15/355,219	156	11/18/2016	10023599	Processes for Preparing Quinoline Compounds and Pharmaceutical Comp...	Wilson, Jo Ann
15/431,600	156	02/07/2017	10030757	C-Met Modulator Pharmaceutical Compositions	Wilson, Jo Ann
15/431,599	156	02/02/2017	10034873	C-Met Modulator Pharmaceutical Compositions	Wilson, Jo Ann
15/606,255	160	04/17/2018	Not Issued	Processes for Preparing Quinoline Derivatives	Wilson, Jo Ann
15/615,569	156	07/03/2018	10548882	C-MET MODULATOR PHARMACEUTICAL COMPOSITIONS	Wilson, Jo Ann
15/730,699	156	10/09/2018	10543206	Processes for Preparing Quinoline Compounds and Pharmaceutical Comp...	Wilson, Jo Ann
15/730,709	161	12/08/2018	Not Issued	Processes for Preparing Quinoline Compounds and Pharmaceutical Comp...	Wilson, Jo Ann
15/730,690	156	12/20/2018	11123338	C-MET MODULATOR PHARMACEUTICAL COMPOSITIONS	Wilson, Jo Ann
16/190,350	160	01/19/2021	Not Issued	Processes for Preparing Quinoline Compounds and Pharmaceutical Comp...	Wilson, Jo Ann
17/150,219	30	02/08/2021	Not Issued	Processes for Preparing Quinoline Compounds and Pharmaceutical Comp...	Wilson, Jo Ann



Application Number	Patent Term	Filing Date	Patent #	Title	Inventor Name
14/650,979	92	12/06/2013	Not Issued	Liquid Dosage Forms to Treat Cancer	Shah, Khalid
14/971,866	156	11/01/2013	10351661	Crystalline Solid Forms of N-(4-[(6,7-Dimethoxyquinolin-4-yl)oxy]phenyl)-...	Shah, Khalid
14/796,616	163	12/06/2013	Not Issued	Processes for Preparing Quinoline Compounds and Pharmaceutical Comp...	Shah, Khalid
14/374,616	42	12/16/2013	Not Issued	STEM CELL-DELIVERED ONCOLYTIC HERPES SIMPLEX VIRUS AND METHOD...	Shah, Khalid
14/777,866	156	12/20/2013	11123338	C-MET MODULATOR PHARMACEUTICAL COMPOSITIONS	Shah, Khalid
16/790,866	30	04/30/2020	Not Issued	GMC-EXPRESSED IMMUNOMODULATORS IN COMBINATION WITH CAR-T ...	Shah, Khalid
17/095,611	30	11/12/2020	Not Issued	COMPOSITIONS AND METHODS RELATED TO TUMOR CELL KILLERS AND V...	Shah, Khalid
17/085,111	30	10/29/2020	Not Issued	Crystalline Solid Forms of N-(4-[(6,7-Dimethoxyquinolin-4-yl)oxy]phenyl)-...	Shah, Khalid
17/151,300	180	01/19/2021	Not Issued	Processes for Preparing Quinoline Compounds and Pharmaceutical Comp...	Shah, Khalid
17/170,478	30	02/08/2021	Not Issued	Processes for Preparing Quinoline Compounds and Pharmaceutical Comp...	Shah, Khalid
17/211,601	30	03/25/2021	Not Issued	Crystalline Solid Forms of N-(4-[(6,7-Dimethoxyquinolin-4-yl)oxy]phenyl)-...	Shah, Khalid
17/211,606	15	Invalid Date	Not Issued	Crystalline Forms and Salt Forms of a Kinase Inhibitor	Shah, Khalid
17/308,108	188	05/05/2021	Not Issued	C-Met Modulator Pharmaceutical Compositions	Shah, Khalid
17/397,901	42	10/08/2021	Not Issued	Processes for Preparing Quinoline Compounds and Pharmaceutical Comp...	Shah, Khalid
17/500,907	42	10/19/2021	Not Issued	C-Met Modulator Pharmaceutical Compositions	Shah, Khalid
17/508,370	15	11/30/2021	Not Issued	C-Met Modulator Pharmaceutical Compositions	Shah, Khalid
17/511,120	15	Invalid Date	Not Issued	Salt Forms of a Kinase Inhibitor	Shah, Khalid
14/757,866	159	01/31/2011	Not Issued	MULTIMODAL RNAI MOLECULES AND USES IN CELLULAR THERAPIES	Shah, Khalid
14/650,979	159	09/24/2012	Not Issued	Methods and Compositions for Treating Cancer	Shah, Khalid

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	17170275
Filing Date	2021-02-08
First Named Inventor	Jo Ann Wilson
Art Unit	1625
Examiner Name	Seaman, D. Margaret M.
Attorney Docket Number	224990/10-039C6-US/483214

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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

FOREIGN PATENT DOCUMENTS

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

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NON-PATENT LITERATURE DOCUMENTS

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

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.M.S/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	17170275
	Filing Date	2021-02-08
	First Named Inventor	Jo Ann Wilson
	Art Unit	1625
	Examiner Name	Seaman, D. Margaret M.
	Attorney Docket Number	224990/10-039C6-US/483214

	1	United States Department of Health and Human Services, "Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products", Revision 2, November 2003, retrieved from the internet at https://www.fda.gov/media/71707/download on January 19, 2022.	☐
	2	United States Department of Health and Human Services, "Guidance for Industry Q3B(R2) Impurities in New Drug Products", Revision 2, August 2006, retrieved from the internet at https://www.fda.gov/media/71733/download on January 19, 2022.	☐

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

EXAMINER SIGNATURE

Examiner Signature	/D MARGARET M SEAMAN/	Date Considered	01/31/2022

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.M.S/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(**Not for submission under 37 CFR 1.99)**

Application Number	17170275
Filing Date	2021-02-08
First Named Inventor	Jo Ann Wilson
Art Unit	1625
Examiner Name	Seaman, D. Margaret M.
Attorney Docket Number	224990/10-039C6-US/483214

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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

OR

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

☐ See attached certification statement.

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

☒ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Heidi M. Berven, Ph.D./	Date (YYYY-MM-DD)	2022-01-20
Name/Print	Heidi M. Berven, Ph.D.	Registration Number	48951

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.M.S/


L1: (20,962) (a61k31/47).IPCR.
L2: (1,393) (c07d215/233).IPCR.

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United States Patent and Trademark Office
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BIB DATA SHEET

CONFIRMATION NO. 8006

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
17/170,275	02/08/2021	514	1625	224990/10-039C6-US/483214

APPLICANTS

Exelixis, Inc., Alameda, CA;

INVENTORS

Jo Ann Wilson, San Francisco, CA;
Khalid Shah, Half Moon Bay, CA;

**** CONTINUING DATA ***************************

This application is a CON of 17/152,394 01/19/2021 ABN
which is a CON of 16/706,323 12/06/2019 ABN
which is a DIV of 16/151,653 10/04/2018 PAT 10543206
which is a DIV of 15/348,716 11/10/2016 PAT 10123999
which is a DIV of 13/984,559 03/20/2014 PAT 9717720
which is a 371 of PCT/US2012/024591 02/10/2012
which claims benefit of 61/441,520 02/10/2011
and claims benefit of 61/441,527 02/10/2011

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

02/24/2021

Foreign Priority claimed ❑ Yes ☑ No 35 USC 119(a-d) conditions met ❑ Yes ❑ No Verified and Acknowledged /D M SEAMAN/ Examiner's Signature	❑ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		CA	0	3	1

ADDRESS

JONATHAN P. O"BRIEN, PH.D.
HONIGMAN LLP
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402
UNITED STATES

TITLE

Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

FILING FEE RECEIVED		
1820	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	❑ All Fees ❑ 1.16 Fees (Filing) ❑ 1.17 Fees (Processing Ext. of time) ❑ 1.18 Fees (Issue) ❑ Other _____ ❑ Credit

Application Number * 17/170,275 *	Application/Control No. 17/170,275	Applicant(s)/Patent under Reexamination Wilson et al.	
	Examiner SEAMAN, D MARGARET M	Art Unit 1625	

Document Code - DISQ	Internal Document - DO NOT MAIL

TERMINAL DISCLAIMER	☑ APPROVED	☐ DISAPPROVED
Date Filed: 20 January 2022	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:

/FELICIA D ROBERTS/

Technology Center: OPLC

Telephone: (571)272-0550

9,717,720

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	17170275
Filing Date	2021-02-08
First Named Inventor	Jo Ann Wilson
Art Unit	1625
Examiner Name	Seaman, D. Margaret M.
Attorney Docket Number	224990/10-039C6-US/483214

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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FOREIGN PATENT DOCUMENTS

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

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

NON-PATENT LITERATURE DOCUMENTS

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	17170275
	Filing Date	2021-02-08
	First Named Inventor	Jo Ann Wilson
	Art Unit	1625
	Examiner Name	Seaman, D. Margaret M.
	Attorney Docket Number	224990/10-039C6-US/483214

	1	United States Department of Health and Human Services, "Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products", Revision 2, November 2003, retrieved from the internet at https://www.fda.gov/media/71707/download on January 19, 2022.	☐
	2	United States Department of Health and Human Services, "Guidance for Industry Q3B(R2) Impurities in New Drug Products", Revision 2, August 2006, retrieved from the internet at https://www.fda.gov/media/71733/download on January 19, 2022.	☐

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

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	17170275
	Filing Date	2021-02-08
	First Named Inventor	Jo Ann Wilson
	Art Unit	1625
	Examiner Name	Seaman, D. Margaret M.
	Attorney Docket Number	224990/10-039C6-US/483214

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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

OR

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

☐ See attached certification statement.

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

☒ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Heidi M. Berven, Ph.D./	Date (YYYY-MM-DD)	2022-01-20
Name/Print	Heidi M. Berven, Ph.D.	Registration Number	48951

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

PTO/AIA/22 (10-20)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): 224990/10-039C6-US/483214

Application Number 17/170,275 | Filed February 8, 2021

For Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

Art Unit 1625 | Examiner Seaman, D. Margaret M.

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	Micro Entity Fee	
☐ One month (37 CFR 1.17(a)(1))	$220	$110	$55	$
☐ Two months (37 CFR 1.17(a)(2))	$640	$320	$160	$
☑ Three months (37 CFR 1.17(a)(3))	$1,480	$740	$370	$ 1,480.00
☐ Four months (37 CFR 1.17(a)(4))	$2,320	$1,160	$580	$
☐ Five months (37 CFR 1.17(a)(5))	$3,160	$1,580	$790	$

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 503145.

☑ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant.

☑ attorney or agent of record. Registration number 48951.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Heidi M. Berven, Ph.D./ — Signature

January 20, 2022 — Date

Heidi M. Berven, Ph.D. — Typed or printed name

269 377-7710 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☑ * Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public, which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Jo Ann Wilson, et al.	Art Unit:	1625
Application No.:	17/170,275	Examiner:	Seaman, D. Margaret M.
Filing Date:	February 8, 2021	Conf. No.:	8006
Atty. Docket No.:	224990/10-039C6-US/483214		

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

CERTIFICATE OF TRANSMISSION UNDER 37 C.F.R. § 1.8(a)

The undersigned hereby certifies that the following documents are being submitted in accordance with 37 C.F.R. § 1.6(a)(4) on the 20th day of January 2022.

1. Cover Letter to the Commissioner;
2. Response to Final Office Action dated July 20, 2021, and Request for Continued Examination;
3. Declaration of Khalid Shah under 37 C.F.R. § 1.132;
4. Other Reference Documents (3);
5. Request for Continued Examination Transmittal (PTO/SB/30);
6. Terminal Disclaimer (1);
7. Information Disclosure Statement (PTO/SB/08a);
8. Non-Patent Literature (2);
9. Petition for Extension of Time (PTO/AIA/22); and
10. This Certificate of Transmission under 37 C.F.R. § 1.8(a).

/Amy L. Peters/

Amy L. Peters (for Heidi M. Berven, Reg. No. 48,951)

Electronic Patent Application Fee Transmittal

Application Number:	17170275
Filing Date:	08-Feb-2021
Title of Invention:	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
First Named Inventor/Applicant Name:	Jo Ann Wilson
Filer:	Heid Marie Berven/Amy Peters
Attorney Docket Number:	224990/10-039C6-US/483214

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	1253	1	1480	1480
Miscellaneous:				
RCE- 1ST REQUEST	1801	1	1360	1360
STATUTORY OR TERMINAL DISCLAIMER	1814	1	170	170
		Total in USD ($)		**3010**

Electronic Acknowledgement Receipt

EFS ID:	44792869
Application Number:	17170275
International Application Number:	
Confirmation Number:	8006
Title of Invention:	Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
First Named Inventor/Applicant Name:	Jo Ann Wilson
Customer Number:	91684
Filer:	Heid Marie Berven/Amy Peters
Filer Authorized By:	Heid Marie Berven
Attorney Docket Number:	224990/10-039C6-US/483214
Receipt Date:	20-JAN-2022
Filing Date:	08-FEB-2021
Time Stamp:	15:34:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$3010
RAM confirmation Number	E20221JF35051758
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	Other Reference-Patent/App/Search documents	Q1A_R2.pdf	7685943 b1576a6a5a67447f879a00a6e7ed3d01faac7e55	no	25
Warnings:					
Information:					
2	Other Reference-Patent/App/Search documents	Q3B_R2.pdf	3672597 86c288c2d50a0d364eff78629f0454639c3b0d80	no	18
Warnings:					
Information:					
3	Other Reference-Patent/App/Search documents	MSDS_6-7-dimethoxy-quinoline-4-ol_Sigma-Aldrich2.pdf	167966 15afb3f6ec2472ff6ed820fc56ca3649e8d31e88	no	7
Warnings:					
Information:					
4	Non Patent Literature	NPL_Q1A_R2.pdf	7685943 b1576a6a5a67447f879a00a6e7ed3d01faac7e55	no	25
Warnings:					
Information:					
5	Non Patent Literature	NPL_Q3B_R2.pdf	3672597 86c288c2d50a0d364eff78629f0454639c3b0d80	no	18
Warnings:					
Information:					
6		2022-01-20_Response_to_Final_Office_Action_Filing_Docs.pdf	1518456 0745b42a3d965cad87bfd490ea8d9ffa52006d0f	yes	38
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	

	Miscellaneous Incoming Letter		1		2
	Response After Final Action		3		3
	Claims		4		5
	Applicant Arguments/Remarks Made in an Amendment		6		20
	Affidavit-traversing rejectns or objectns rule 132		21		30
	Request for Continued Examination (RCE)		31		32
	Terminal Disclaimer Filed		33		33
	Information Disclosure Statement (IDS) Form (SB08)		34		36
	Extension of Time		37		37
	Miscellaneous Incoming Letter		38		38
Warnings:					
Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	43084 51ae8d04730d1c59d9743db30a461a90cf090331	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	24446586		

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.

HONIGMAN

Heidi M. Berven, Ph.D.
Office: 269.337.7710
Mobile: 269.365.8962
hberven@honigman.com

VIA EFS

January 20, 2022

Commissioner for Patents
United States Patent and Trademark Office
P. O. Box 1450
Alexandria, VA 22313

Re: US Patent Application No.: 17/170,275
Inventors: Jo Ann Wilson, et al.
Filing Date: February 8, 2021
Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
Conf. No.: 8006
Attorney Docket No.: 224990/10-039C6-US/483214

Dear Sir or Madam:

Enclosed for filing please find the following documents:

1. This Cover Letter to the Commissioner;
2. Response to Final Office Action dated July 20, 2021, and Request for Continued Examination;
3. Declaration of Khalid Shah under 37 C.F.R. § 1.132;
4. Other Reference Documents (3);
5. Request for Continued Examination Transmittal (PTO/SB/30);
6. Terminal Disclaimer (1);
7. Information Disclosure Statement (PTO/SB/08a);
8. Non-Patent Literature (2);
9. Petition for Extension of Time (PTO/AIA/22); and
10. Certificate of Transmission under 37 C.F.R. § 1.8(a).

It is believed that the response with Information Disclosure Statement filed herewith satisfies the requirement under 37 C.F.R. § 1.114(c) for a submission accompanying a Request for Continued Examination. The fee set forth in 37 C.F.R. § 1.17(e)(1) is also submitted herewith.

The Applicant notes that the filing of the enclosed Information Disclosure Statement shall not be construed to be an admission that the information cited in the statement qualifies as prior art under 35 U.S.C. § § 102 or 103, or is considered to be material to patentability as defined in 37 C.F.R. § 1.56(b). It is believed that no fee is due pursuant to 37 C.F.R. § 1.97(b)(3).

The Applicant believes that due with this submission is the $1,360.00 fee set forth in § 1.17(e)(1) for the first Request for Continued Examination in this application, the $170.00 fee for a terminal disclaimer, and the $1,480.00 fee for a three month extension of time. The Applicant hereby authorizes the Patent Office to charge this total of $3,010.00 to Deposit Account Number 503145 with reference to attorney docket number 224990/10-039C6-US/483214. It is believed that no other fees are due at this time. However, if there are any additional charges for this submission, or any credits, please apply them to Deposit Account Number 503145, referencing Attorney Docket Number 224990/10-039C6-US/483214.

Very truly yours,

HONIGMAN LLP

/Heidi M. Berven, Ph.D./

Heidi M. Berven, Ph.D.
Reg. No. 48,951

HMB/ayp

Enclosures

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: Jo Ann Wilson, et al.
Application No.: 17/170,275
Filing Date: February 8, 2021

Art Unit: 1625
Conf. No.: 8006
Examiner: Seaman, D. Margaret M.
Attorney Docket No.: 224990/10-039C6-US/483214

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313

RESPONSE TO FINAL OFFICE ACTION DATED JULY 20, 2021, AND REQUEST FOR CONTINUED EXAMINATION UNDER 37 C.F.R. § 1.114

Dear Sir or Madam:

This submission is in response to the Final Office Action mailed in this application on July 20, 2021.

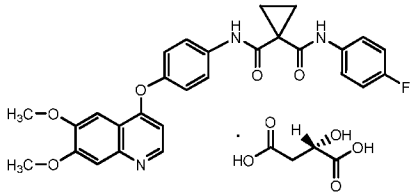
Amendments to the claims begin on page 2.

Remarks begin on page 4.

AMENDMENTS TO THE CLAIMS

1-34. Cancelled.

35. (Currently amended) A pharmaceutical composition for oral administration comprising Compound IB;



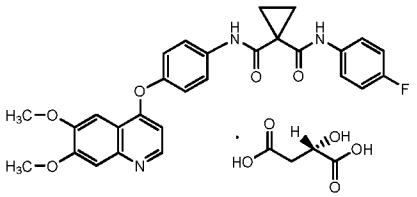
IB

one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants, wherein the pharmaceutical composition is a tablet or capsule pharmaceutical composition, and wherein the pharmaceutical composition is essentially free of process byproducts or contaminants.

36-37. Cancelled

38. (Previously presented) The pharmaceutical composition of claim 35, wherein the process byproduct or contaminant is 6,7-dimethoxy-quinoline-4-ol in the pharmaceutical composition.

39. (Currently amended) A pharmaceutical composition for oral administration comprising Compound IB;



IB

one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants, wherein the pharmaceutical composition is a tablet or capsule pharmaceutical composition; and wherein the pharmaceutical composition is essentially free of 6,7-dimethoxy-quinoline-4-ol.

REMARKS

Claim Status

Caims 1-34 and 36-37 are cancelled.

Claims 35 and 39 are currently amended. The currently amended claims are supported by thespecfication and claims as filed and do not present new matter.

Claim 38 is previously presented.

Thus, claims 35 and 38-39 are currently pending.

Rejections under 35 U.S.C. § 103

In the Office Action, the Examiner rejected claims 35 and 38-39 under pre-AIA 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Publication No. 20120035212 (US 8877776; hereinafter Brown) in view of Pingali (Int. J. Pharm. 2011 May 16; 409(0) 269-277), Li (Lubriancts 2014, 2, 21-43), and the "Overview of Pharmaceutical Excipients" (Drug Topics (October 24,2008)). The Examiner additionally rejected claims 35 and 38-39 under pre-AIA 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Publication No. 20070054928 (US 9,174,947; hereinafter Bannen) in view of Li, Pingali and the Drug Topics article. The Applicant respectfully disagrees.

The references cited by the Examiner fail to obviate the Applicant's claimed invention. They do not teach or suggest a pharmaceutical composition for oral administration as claimed by the Applicant, let alone a pharmaceutical composition containing Compound I, L-malate salt that is essentially free of process byproducts or contaminants as recited in claim 35, or that is essentially free of 6,7-dimethoxy-quinoline-4-ol, as recited in claim 39. As defined in paragraph [0035] of the application as originally filed, "essentially free" means that the composition is admixed with 200 ppm or less byproducts or contaminants. One of ordinary skill in the art reading the cited art would thus not envision the pharmaceutical compositions claimed by the Applicant.

The references are silent as to the development of pharmaceutical compositions as disclosed by the Applicant. The process of making Compound IB is described at page 26-28 of the above-captioned application as filed, and requires reacting cabozantinib with L-malic acid. The Applicant discovered that this process can give rise to 6,7-dimethoxy-quinoline-4-ol as a

decomposition product. Any 6,7-dimethoxy-quinoline-4-ol that is formed is carried through to the product. The Material Safety Data Sheet (MSDS) of 6,7-dimethoxy-quinoline-4-ol (attached herewith and cited in the Supplemental Information Disclosure Statement filed with this response) indicates that 6,7-dimethoxy-quinoline-4-ol has acute oral toxicity and is harmful if swallowed. Because 6,7-dimethoxy-quinoline-4-ol is toxic, it is necessary to minimize the amount of 6,7-dimethoxy-quinoline-4-ol in pharmaceutical compositions of the L-malate salt of cabozantinib.

Brown in view of Pingali, Li, and the Drug Topics Article

Brown does not teach or otherwise provide a suggestion or a motivation to the skilled person to develop a pharmaceutical composition for oral administration of Compounf IB that is essentially free of process byproducts or contaminants as recited in claim 35, or that is essentially free of 6,7-dimethoxy-quinoline-4-ol, as recited in claim 39. The Examiner asserts Brown teaches that Compound I, L-malate salt is substantially pure. This disclosure, however, does not suggest that a pharmaceutical composition of Compound I, L-malate salt is substantially pure.

Furthermore, "substantially pure" is defined in Brown as containing "at least about 90% wt.%" (See Col. 18, lines 18-20 in Brown). As stated above, the claimed composition contains 200 ppm or less byproducts, contaminants, or 6,7-dimethoxy-quinoline-4-ol, which is equivalent to 0.02 wt.% or less. Brown does not disclose or suggest this level of purity of a pharmaceutical composition of Compound I, L-malate salt.

The shortcomings of Brown are not cured by Pingali, Li, or the Drug Topics article. Li provides an overview of the fundamental principles on lubrication and the uses of lubricants in pharmaceutcical formulations (Page 22). Pingali discloses the effect of mixing order of Cabo-O-Sil (CS) and magnesium stearate and microlayers during mixing on blend and tsablet propoerties (Abstract). The Drug Topics article provides an overview of pharmaceutical excipients used in tablets and capsules (Title). Pingali, Li, and the Drug Topics article do not provide a suggestion or motivation to the skilled person for a need to provide pharmaceutical formulations of Compound IB that are essentially free of process byproducts or contaminants or essentially free of 6,7-dimethoxy-quinoline-4-ol, nor do they provide a road map to the skilled person for preparing such formulations.

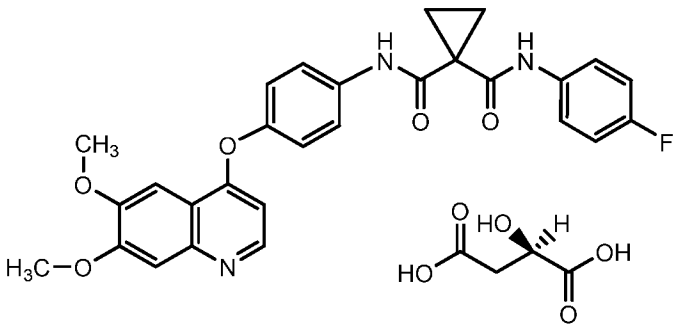
The Applicant asserts that"[a]n obviousness determination requires finding that a person of ordinary skill in the art would have been motivated to combine or modify the teachings in the prior art and would have had a reasonable expectation of success in doing so." *OSI Pharmaceuticals, LLC v. Apotex Inc.*, No. 18-1925 (Fed. Cir. 2019) *(Citing Regents of Univ. of Cal. v. Broad Inst., Inc.,* 903 F.3d 1286, 1291 (Fed. Cir. 2018)). The skilled person would not have a reasonable expectation of success in developing a formulation as recited in the Applicant's currently pending claims.

Bannen in view of Pingali, Li, and the Drug Topics Article

Bannen does not teach or otherwise motivate the skilled person to make the L-malate salt of cabozantinib, let alone developing a pharmaceutical composition for oral administration of Compounf IB that is essentially free of process byproducts or contaminants as recited in claim 35, or that is essentially free of 6,7-dimethoxy-quinoline-4-ol, as recited in claim 39. As with Brown, the shortcomings of Bannen are not cured by Pingali, Li, or the Drug Topics article. The Applicant submits that a skilled person would not have a reasonable expectation of success in developing a formulation as recited in the Applicant's currently pending claims.

Unexpected Results

The Applicant additionally asserts evidence of unexpected results. In the present application, the Applicant has not merely provided a pharmaceutical composition for oral administration. The Applicant has invented capsule and tablet pharmaceutical compositions that are stable upon storage and that do not give rise to process byproducts or contaminants. The pharmaceutical compositions disclosed and claimed by the Applicant relates to the compound of Formula IB.



Compound of Formula IB

The compound of Formula IB is also known by the generic name cabozantinib and by the tradenames Cometriq® (capsule formulation) and Cabometyx® (tablet formulation). Cometriq is approved for the treatment of medullary thyroid cancer and cabometyx is approved for the treatment of renal cell carcinoma and hepatocellular carcinoma.

The Applicant sought to develop a storage-stable pharmaceutical composition for oral oadministration that minimized formation of the toxic degradant 6,7-dimethoxy-quinoline-4-ol. As provided in the declaration of Kal Shah, Ph.D. that accomapanies this response, (hereinafter the Shah declaration), the development of a storage-stable pharmaceutical composition of Compound IB was made difficult because exposure to water, atmospheric moisture, or even residual moisture can cause degradation to form 6,7-dimethoxy-quinoline-4-ol

However, in the claimed pharmaceutical compositions, surprisingly no more than 44 ppm of 6,7-dimethoxy-quinoline-4-ol in capsules and no more than 18, 20, and 16 ppm of 6,7-dimethoxy-quinoline-4-ol in the 20- 60- or 100 mg tablets was present after six months of storage under accelerated conditions. These levels of impurities are much lower than the reporting threshold established by the FDA. As provided in the attached FDA's *Guidance for Industry Q3B(R2) Impurities in New Drug Products* on page 13, the reporting thresholds of an impurity for a $\leq$ 1g maximum daily dose and > 1g maximum daily dose are 0.1% and 0.05%, respectively, which are equivalent to 1000 ppm and 500 ppm, respectively.[1] Thus, the claimed pharmaceutical compositions have surprisingly high purity that would not have been expected based on the disclosure of the cited references.

The stability of the tablet and capsule pharmaceutical compositions was evaluated in accordance with FDA recommendations as provided in *Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances* (attached herewith).[2] The *Guidance* provides recommended stability testing conditions (long-term, intermediate, and accelerated storage conditions) in the Table at page 11, which is reproduced here.

[1] *See* https://www.fda.gov/media/71733/download
[2] *See* https://www.fda.gov/media/71707/download

Study	Storage condition	Minimum time period covered by data at submission
Long-term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

* It is up to the applicant to decide whether long-term stability studies are performed at 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.
** If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

Capsule Stability

In the Applicant's stability studies as described at pages 34-36 of the application, capsules were placed in bottles or blister packs. The capsules or tablets were then stored under long-term 25 ºC/60 percent relative humidity (RH), intermediate (30 ºC/75 percent RH), or accelerated storage conditions (40 ºC/75 percent RH). The bottles were monitored for 6,7-dimethoxy-quinoline-4-ol formation over time. The results of the stability studies are provided below showing the amount of 6,7-dimethoxy-quinoline-4-ol in parts per million.

The results of the capsule stability studies are given in Tables 7A-B and 8A-B of the application as filed, which are reproduced on the following pages for the Examiner's convenience. As provided by Tables 7A-B of the appolication as filed, the Applicant observed up to 44 ppm of 6,7-dimethoxy-quinoline-4-ol in capsules after six months of storage under accelerated conditions. Based on the accelerated conditions results, one of ordinary skill in the formulation art would have expected similar degradation of the long-term condition samples over time. Tables 7A-B indicate that capsules stored under long-term conditions surprisingly exhibited very little change from T=0 to T=6 Months or even T=9 Months.

Table 7A: Stability of 25 Mg Capsules (Table 3)

	Conditions	Bottle A1	Bottle A2	Bottle A3	Bottle A4
		PPM of 6,7-dimethoxy-quinoline-4-ol			
Initial T=0	25 °C/60% RH	2	2	3	3
1 Month	25 °C/60% RH	3	4	5	NA
	30 °C/75% RH	4	4	NA	NA
	40 °C/75% RH	9	9	10	NA
3 Months	25 °C/60% RH	5	5	7	NA
	30 °C/75% RH	7	6	NA	NA
	40 °C/75% RH	22	23	24	NA
6 Months	25 °C/60% RH	6	6	7	7 (3M in blister)
	30 °C/75% RH	9	9	NA	NA
	40 °C/75% RH	40	44	43	27 (3M in blister)
9 Months	25 °C/60% RH	7	7	9	8 (6M in blister)
	30 °C/75% RH	13	12	NA	NA
	40 °C/75% RH	NA	NA	68	60 (6M in blister)

M=Months; NA=Not Applicable; RH= Relative Humidity; PPM= Parts per Million. A portion of Bottle A4 was repackaged in a blister pack after being stored in bottles for 3 months.

Table 7B: Stability of 25 Mg Capsules (Table 3)

	Conditions	Bottle B1	Bottle B	Bottle B3	Bottle B4
		PPM of 6,7-dimethoxy-quinoline-4-ol			
Initial T=0	25 °C/60% RH	3	1	2	2
1 Month	25 °C/60% RH	<2	<2	<2	NA
	30 °C/75% RH	<2	<2	NA	NA
	40 °C/75% RH	2	<2	<2	NA
3 Months	25 °C/60% RH	2	<2	<2	NA
	30 °C/75% RH	2	<2	NA	NA
	40 °C/75% RH	3	<2	<2	NA
6 Months	25 °C/60% RH	<2	<2	<2	<2 (3M in blister)
	30 °C/75% RH	2	<2	NA	NA
	40 °C/75% RH	4	<2	3	3 (3M in blister)
9 Months	25 °C/60% RH	<2	<2	<2	<2 (6M in blister)
	30 °C/75% RH	3	<2	NA	NA
	40 °C/75% RH	NA	NA	5	4 (6M in blister)

A portion of Bottle B4 was repackaged in a blister pack after being stored in bottles for 3 months. The results in Tables 8A-B similarly indicate that capsules stored under long-term conditions exhibited very little change from T=0 to T=6 Months or even T=9 Months.

Table 8A: Stability of 100 Mg Capsules (Table 4)

	Conditions	Bottle A1	Blister A2	Bottle A3
		PPM of 6,7-dimethoxy-quinoline-4-ol		
Initial T=0	25 °C/60% RH	4	4	6
1 Month	25 °C/60% RH	4	4	6
	30 °C/75% RH	4	NA	6
	40 °C/75% RH	6	6	9
3 Months	25 °C/60% RH	5	5	7
	30 °C/75% RH	6	NA	7
	40 °C/75% RH	10	10	12
6 Months	25 °C/60% RH	5	5	
	30 °C/75% RH	6	NA	
	40 °C/75% RH	11	17	

Table 8B: Stability of 100 Mg Capsules (Table 4)

	Conditions	Bottle B1	Blister B2	Bottle B3
		PPM of 6,7-dimethoxy-quinoline-4-ol		
Initial T=0	25 °C/60% RH	1	1	2
1 Month	25 °C/60% RH	<2	<2	<2
	30 °C/75% RH	<2	<2	2
	40 °C/75% RH	<2	<2	2
3 Months	25 °C/60% RH	<2	<2	<2
	30 °C/75% RH	<2	NA	<2
	40 °C/75% RH	<2	<2	2
6 Months	25 °C/60% RH	<2	<2	
	30 °C/75% RH	<2	NA	
	40 °C/75% RH	2	2	

Moreover, the Applicant found that 25 mg and 100 mg capsules stored under long-term conditions for as long as 4 years gave less degradation than the capsules stored for six months under accelerated conditions, as evidenced from the results of additional stability studies that are presented in the Shah.

Stability of 25mg Capsules

	Conditions	Bottle A1	Bottle A2	Bottle A3	Blister A4
		PPM of 6,7-dimethoxy-quinoline-4-ol			
Initial T=0	25°C/60%RH	2	<2	3	3
1 month	25°C/60%RH	3	4	5	N/A
	30°C/75%RH	4	4	N/A	N/A
3 month	25°C/60%RH	5	5	7	N/A
	30°C/75%RH	7	6	N/A	N/A
6 month	25°C/60%RH	6	6	7	7 (3M in blister)
	30°C/75%RH	9	9	N/A	N/A
9 month	25°C/60%RH	7	7	9	8 (6M in blister)
	30°C/75%RH	13	12	N/A	N/A
12 month	25°C/60%RH	9	9	10	10 (9M in blister)
	30°C/75%RH	17	17	N/A	N/A
18 month	25°C/60%RH	11	11	13	12 (15M in blister)
	30°C/75%RH	24	22	N/A	N/A
24 month	25°C/60%RH	14	13	15	16 (21M in blister)
36 month	25°C/60%RH	19	18	20	22 (33M in blister)
48 month	25°C/60%RH	24	25	26	N/A

Stability of 100mg Capsules

	Conditions	Bottle B1	Blister B2	Bottle B3
		PPM of 6,7-dimethoxy-quinoline-4-ol		
Initial T=0	25°C/60%RH	4	4	6
1 month	25°C/60%RH	4	4	6
	30°C/75%RH	4	N/A	6
3 month	25°C/60%RH	5	5	7
	30°C/75%RH	6	N/A	7
6 month	25°C/60%RH	5	5	8
	30°C/75%RH	6	N/A	10
9 month	25°C/60%RH	5	6	8
	30°C/75%RH	7	N/A	10
12 month	25°C/60%RH	6	7	9
	30°C/75%RH	9	N/A	12
18 month	25°C/60%RH	7	8	10
	30°C/75%RH	11	N/A	14
24 month	25°C/60%RH	8	8	11
	30°C/75%RH	12	N/A	16
36 month	25°C/60%RH	10	8	13

	Conditions	Bottle B1	Blister B2	Bottle B3
		PPM of 6,7-dimethoxy-quinoline-4-ol		
	30°C/75%RH	17	N/A	23
48 month	25°C/60%RH	11	10	16

Tablet Stability

The results of the tablet stability studies are given in the following tables which appear in the Shah declaration. Tablet pharmaceutical compositions are disclosed in the application as filed at paragraphs [0020] and [0115] and elsewhere. The Applicant observed almost no change in the levels of 6,7-dimethoxy-quinoline-4-ol in the 20, 60, and 100 mg tablet pharmaceutical compositons after long term storage at 25 °C/60% RH or under accelerated storage conditions for 6 months at 40 °C/75% RH. Moreover, under accelerated conditions, surprisingly no more than 18, 20, and 16 ppm of 6,7-dimethoxy-quinoline-4-ol was present in the 20- 60- or 100 mg tablets after six months of storage under accelerated conditions. The stability of the tablet formulations is made even more surprising since the tablet formulation is manufactured using a wet process as provided in the Shah declaration. As a clarification, all moisture absorbed from processing was dried following completion of manufacturing/coating the tablets and the resultant tablet moisture was approximately 2% w/w prior to the commencement of the stability studies.

Summary of Stability Results (ppm) of 6,7-dimethoxy-quinoline-4-ol in Cabozantinib L-Malate 20-mg Tablets

Batch Number	Conditions	Time Point (Months, M)							
		T=0	T = 1	T = 3	T = 6	T = 9	T = 12	T = 18	T = 24
Batch #1 (bottle)	25 °C/60% RH 40 °C/75% RH	11	10 11	10 11	12 15	11	11	13	15
Batch #2 (bottle)	25 °C/60% RH 40 °C/75% RH	10	11 11	11 12	11 14	11	14	17	12
Batch #3 (bottle)	25 °C/60% RH 40 °C/75% RH	7	6 7	7 7	10 18	6	7	13	8
Batch #4 (bottle)	25 °C/60% RH 40 °C/75% RH	5	4 5	4 6	6 8	7	5	5	6

M, month; RH, relative humidity; T, time.

Summary of Stability Results (ppm) of 6,7-dimethoxy-quinoline-4-ol in Cabozantinib L-Malate 60-mg Tablets

Batch Number	Conditions	Time Point (Months, M)								
		T=0	T = 1	T = 3	T = 6	T = 9	T = 12	T = 18	T = 24	T = 36
Batch #1 (bottle)	25 °C/60% RH	11	11	10	12	11	12	13	15	13
	40 °C/75% RH		10	12	15					
Batch #2 (bottle)	25 °C/60% RH	12	11	11	12	12	14	17	13	
	40 °C/75% RH		12	12	14					
Batch #3 (bottle)	25 °C/60% RH	7	6	7	10	7	8	9	8	
	40 °C/75% RH		9	9	20					
Batch #4 (bottle)	25 °C/60% RH	4	5	5	6	6	6	5	7	
	40 °C/75% RH		5	6	9					

M, month; RH, relative humidity; T, time.

Summary of Stability Results (ppm) of 6,7-dimethoxy-quinoline-4-ol in Cabozantinib L-Malate 100-mg Tablets

Batch Number	Conditions	Time Point (Months, M)								
		T=0	T = 1	T = 3	T = 6	T = 9	T = 12	T = 18	T = 24	T = 36
Batch #1 (bottle)	25 °C/60% RH	11	11	12	10	8	11	11	10	11
	40 °C/75% RH		12	14	13					
Batch #2 (bottle)	25 °C/60% RH	11	12	11	12	12	12	13	16	11
	40 °C/75% RH		11	12	16					
(bottle)	40 °C/75% RH				9					

M, month; NS, not scheduled; RH, relative humidity; T, time; TBP, to be performed.

Thus, the surprising stability of the capsule and tablet formulations claimed by the Applicant was neither disclosed nor suggested by references cited by the Examiner.

As a result, the Applicant respectfully requests withdrawal of the obviousness rejection and allowance of the claims.

Double Patenting

The Examiner rejected claims 35 and 38-39 on the ground of nonstatutory double patenting as allegedly being unpatentable over claims of U.S. Patent No. 9,717,720. Without acceding to the Examiner's grounds for rejection and to expedite proseuciton, the Applicant files a terminal disclaimer with this response. The Applicant therefore respectfully requests removal of the rejection.

REQUEST FOR CONTINUED EXAMINATION

The Applicant's amendments to the claims, arguments, Declaration under 37 C.F.R. § 1.132, Information Disclosure Statement submitted herewith satisfy the requirement under § 1.114 for a submission accompanying a Request for Continued Examination. The fee set forth in 37 C.F.R. § 1.17(e)(1) is also submitted herewith.

INFORMATION DISCLOSURE STATEMENT

The Applicant notes that the filing of the enclosed Information Disclosure Statement shall not be construed to be an admission that the information cited in the statement qualifies as prior art under 35 U.S.C. § § 102 or 103, or is considered to be material to patentability as defined in 37 C.F.R. § 1.56(b). It is believed that no fee is due pursuant to 37 C.F.R. § 1.97(b)(3).

EXTENSION OF TIME

The Applicant hereby petitions for a three-month extension of time under 37 C.F.R. § 1.136(a) for responding to the Final Office Action in this application dated July 20, 2021. The fee set forth in 37 C.F.R. § 1.17(a)(3) is submitted herewith.

OTHER C-MET INHIBITOR CASES

The Applicant wishes to make the Examiner aware of the Applicant's other applications related to c-Met inhibitors and their use in the treatment of cancer. For the Examiner's convenience, the Applicant is providing a list of the Applicant's applications directed to the treatment of cancer using c-Met inhibitors. The Applicant understands the Examiner has electronic access to these applications and to the Office Actions that have issued in these applications, and has therefore not included copies with this Response. The Applicant will gladly provide the applications and Office Actions to the Examiner, however, upon request.

Application Number	Filing or 371 Date	Patent Number	Examiner	Status
10/573,336	09/18/2006		Koontz, Tammy J.	Abandoned
11/571,140	12/21/2006	7977345	Moore, Susanna	Expired
11/586,751	10/26/2006	9174947	Ward, Paul V.	Issued

Application Number	Filing or 371 Date	Patent Number	Examiner	Status
11/753,462	05/24/2007	8178532	Ward, Paul V.	Issued
11/753,503	05/24/2007	8476298	Ward, Paul V.	Expired
11/753,514	05/24/2007	8067436	Bernhardt, Emily A.	Issued
12/393,806	02/26/2009	7579473	Seaman, D. Margaret M.	Issued
12/911,442	10/25/2010		Ward, Paul, V.	Abandoned
13/087,094	04/14/2011		Chickos, Sarah, J.	Abandoned
13/129,183	05/13/2011		Seaman, D. Margaret M.	Abandoned
13/132,650	06/03/2011		Seaman, D. Margaret M.	Abandoned
13/145,054	10/20/2011	8877776	Carter, Kendra D	Issued
13/249,815	09/30/2011	8497284	Bernhardt, Emily A.	Issued
13/384,451	07/12/2012	8673912	Anderson, Rebecca L.	Issued
13/389,266	07/12/2012		Perreira, Melissa Jean	Abandoned
13/427,093	03/22/2012		Ward, Paul V.	Abandoned
13/438,964	04/04/2012		Brown-Pettigrew, Angela C.	Abandoned
13/634,275	09/12/2012		Anderson, Rebecca L.	Abandoned
13/753,031	01/29/2013		Pagonakis, Anna	Abandoned
13/753,146	01/29/2013		Pagonakis, Anna	Abandoned
13/810,537	08/26/2013	9724342	Pallay, Michael B.	Issued
13/810,546	08/27/2013		Branson, Daniel L.	Abandoned
13/876,290	11/05/2013		Stone, Christopher R.	Abandoned
13/876,306	11/08/2013		Lee, Andrew P.	Abandoned
13/876,318	10/25/2013		Karol, Jody Lynn	Abandoned
13/888,592	05/07/2013		Ward, Paul V.	Abandoned
13/928,977	06/27/2013		Bernhardt, Emily A.	Abandoned
13/984,559	03/20/2014	9717720	Rozof, Timothy R.	Issued
14/021,614	09/09/2013		Matos Negron, Taina Del Mar	Abandoned
14/115,236	02/28/2014		Anderson, James D.	Abandoned
14/166,545	01/28/2014		Not Yet Assigned	Abandoned
14/173,973	02/06/2014		Johannsen, Diana B.	Abandoned
14/340,871	07/25/2014	9809549	Carter, Kendra D.	Issued
14/346,570	03/21/2014	10166225	Wang, Shengjun	Issued
14/353,251	04/21/2014	9365516	Murray, Jeffrey H.	Issued
14/356,927	05/08/2014		Baek, Bong-Sook	Abandoned
14/356,938	05/08/2014		Cerioni, Daniel Lee	Abandoned
14/398,188	10/31/2014	9861624	Henley III, Raymond J.	Issued
14/426,580	03/06/2015		Jean-Louis, Samira J.M.	Abandoned
14/518,733	10/20/2014		Wright, Sarah C.	Abandoned
14/668,312	03/25/2015		Brown-Pettigrew, Angela C.	Abandoned
14/699,683	04/29/2015		Perreira, Melissa Jean	Abandoned
14/776,337	09/14/2015	10273211	Badio, Barbara P.	Issued

Application Number	Filing or 371 Date	Patent Number	Examiner	Status
14/782,493	10/05/2015		Saeed, Kamal A.	Abandoned
14/782,537	10/05/2015		Alley, Genevieve S.	Pending
14/843,480	09/02/2015		Shen, Wu Cheng Winston	Abandoned
14/847,801	09/08/2015		Ward, Paul V.	Abandoned
14/933,801	11/05/2015		Brown-Pettigrew, Angela C.	Abandoned
15/066,872	03/10/2016		Ward, Paul V.	Abandoned
15/118,738	08/12/2016	10501418	Chandrakumar, Nizal S.	Issued
15/126,767	09/16/2016	10159666	Solola, Taofiq A.	Issued
15/133,708	04/20/2016	9969692	Murray, Jeffrey H.	Issued
15/305,854	10/21/2016		McMillian, Kara Renita	Pending
15/348,716	11/10/2016	10123999	Rozof, Timothy R.	Issued
15/500,312	01/30/2017	11124481	Seaman, D. Margaret M.	Issued
15/501,582	02/03/2017	11065240	Seaman, D. Margaret M.	Issued
15/426,804	02/07/2017	10039757	Pallay, Michael B.	Issued
15/612,703	06/02/2017	10034873	Pallay, Michael B.	Issued
15/617,725	06/08/2017		Neagu, Irina	Abandoned
15/618,593	06/09/2017		Carter, Kendra D.	Abandoned
15/621,527	06/13/2017		Carter, Kendra D.	Abandoned
15/688,310	08/28/2017	11124482	Ward, Paul V.	Issued
15/955,246	04/17/2018		Not Yet Assigned	Abandoned
16/026,708	07/03/2018	10548888	Pallay, Michael B.	Issued
16/093,426	10/12/2018	11141413	Weddington, Kevin E.	Issued
16/095,221	10/19/2018		Saeed, Ali S.	Pending
16/142,691	09/26/2018	11116759	Howell, Theodore R.	Issued
16/151,653	10/04/2018	10543206	Rozof, Timothy R.	Issued
16/190,869	11/14/2018		Solola, Taofiq A.	Abandoned
16/230,267	12/21/2018		Kantamneni, Shobha	Pending
16/251,617	01/18/2019	10736886	Perreira, Melissa Jean	Issued
16/336,724	03/26/2019		Not Yet Assigned	Pending
16/362,863	03/25/2019		Reese, Heidi L.	Abandoned
16/479,143	07/18/2019	11198731	Lu, Cheng	Issued
16/671,834	11/01/2019	10851061	Chandrakumar, Nizal S.	Issued
16/617,352	11/26/2019		Seaman, D. Margaret M.	Pending
16/620,379	12/06/2019		Oh, Taylor V.	Pending
16/706,323	12/06/2019		Rozof, Timothy R.	Abandoned
16/722,563	12/20/2019	11123338	Pallay, Michael B.	Issued
16/776,139	01/29/2020		Solola, Taofiq A.	Pending
16/787,212	02/11/2020		Anderson, James D.	Pending
16/796,250	02/20/2020		Neagu, Irina	Abandoned
16/905,307	06/18/2020		Not Yet Assigned	Pending

Application Number	Filing or 371 Date	Patent Number	Examiner	Status
16/919,562	07/02/2020		Perreira, Melissa Jean	Pending
16/921,542	07/06/2020		Not Yet Assigned	Pending
17/031,196	09/24/2020		Not Yet Assigned	Pending
17/070,514	10/14/2020	11091439	Rozof, Timothy R.	Issued
17/070,790	10/14/2020		Seaman, D. Margaret M.	Abandoned
17/084,312	10/29/2020		Chandrakumar, Nizal S.	Pending
17/149,365	01/14/2021	11,091,440	Rozof, Timothy R.	Issued
17/152,394	01/19/2021		Not Yet Assigned	Abandoned
17/171,752	02/09/2021	11098015	Rozof, Timothy R.	Issued
17/212,851	03/25/2021		Not Yet Assigned	Pending
17/409,098	08/23/2021		Not Yet Assigned	Abandoned
17/466,328	09/03/2021		Not Yet Assigned	Pending
17/497,201	10/08/2021		Seaman, D. Margaret M.	Pending
17/505,275	10/19/2021		Rozof, Timothy R.	Pending
17/505,307	10/19/2021		Pallay, Michael B.	Pending
17/519,327	11/04/2021		Not Yet Assigned	Pending
17/538,310	11/30/2021		Not Yet Assigned	Pending

CONCLUSION & FEES DUE

The Applicant believes this submission is fully responsive to the Final Office Action in this application dated July 20, 2021. The Applicant reserves the right to file divisional applications or take such other appropriate action as deemed necessary to protect the subject matter restricted, cancelled, or withdrawn from this application.

The Applicant believes that due with this submission is the $1,360.00 fee set forth in § 1.17(e)(1) for the first Request for Continued Examination in this application, the $170.00 fee for a terminal disclaimer, and the $1,480.00 fee for a three month extension of time. The Applicant hereby authorizes the Patent Office to charge this total of $3,010.00 to Deposit Account Number 503145 with reference to attorney docket number 224990/10-039C6-US/483214. It is believed that no other fees are due at this time. However, if there are any additional charges for this submission, or any credits, please apply them to Deposit Account Number 503145, referencing Attorney Docket Number 224990/10-039C6-US/483214.

Respectfully submitted,

/Heidi M. Berven, Ph.D./

Date: January 20, 2022

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	Jo Ann Wilson, et al.	Art Unit:	1625
Application No.:	17/170,275	Examiner:	Margaret D. Seaman
Filing Date:	February 8, 2021	Conf. No.:	8006
Atty. Docket No.:	224990/10-039C6-US/483214		

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

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

DECLARATION OF KHALID SHAH UNDER 37 C.F.R. § 1.132

I, Khalid Shah, hereby state the following:

1. I am currently the Senior Vice President, Pharmaceutical Operations & Supply Chain at Exelixis ("Exelixis"), Inc. Prior to serving as Senior Vice President, I served in a number of capacities of increasing responsibility within Exelixis starting in July 2009, including:

- Vice President, CMC, Pharmaceutical Operations and Supply Chain;
- Executive Director;
- Senior Director, Formulations Development, Manufacturing, and Clinical Supplies
- Director, Formulations Development

2. Prior to joining Exelixis (January 2002-July 2009), I held positions at Array BioPharma, Abbott Laboratories (Kos Pharma), and Abbott. From April 2006, to September, 2007, I was also an Adjunct Professor at Nova Eastern University College of Pharmacy.

3. I have authored articles in the field of formulation development.

4. I have held a post-doctoral research fellowship at Aston University (United Kingdom) working in the field of drug formulation design and drug delivery.

5. I have a Ph.D. degree in Oral Drug Delivery Systems from Aston University (United Kingdom).

6. I have a B.Sc. degree in Pharmaceutical Chemistry from Coventry University (United Kingdom).

7. I am an inventor of United States Application Serial Number 17/170,275 (the '275 application).

8. The '275 application is directed to pharmaceutical compositions of the L-malate salt of cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide (Compound IB). Compound IB is also known by the generic name cabozantinib and by the tradenames Cometriq® (capsule formulation) and Cabometyx® (tablet formulation). Cometriq® is approved for the treatment of medullary thyroid cancer and Cabometyx® is approved for the treatment of renal cell carcinoma and hepatocellular carcinoma.

9. The process for making Compound IB can give rise to 6,7-dimethoxy-quinoline-4-ol as a decomposition product. The process is described at page 26-28 of the above-captioned application as filed, and requires reacting cabozantinib with L-malic acid. Any 6,7-dimethoxy-quinoline-4-ol that is formed during the process from Compound IA is carried through to Compound IB.

10. I have reviewed the Material Safety Data Sheet (MSDS) of 6,7-dimethoxy-quinoline-4-ol. 6,7-Dimethoxy-quinoline-4-ol has acute oral toxicity and is harmful if swallowed

11. Because of the toxicity of 6,7-dimethoxy-quinoline-4-ol, a storage-stable capsule pharmaceutical composition of Compound IB that minimized formation of the toxic degradant 6,7-dimethoxy-quinoline-4-ol was required.

12. The development of a storage-stable pharmaceutical composition of Compound IB was made difficult because exposure to water, atmospheric moisture, or even residual moisture can cause degradation to form 6,7-dimethoxy-quinoline-4-ol.

Capsule Pharmaceutical Composition Stability

13. To minimize degradation, no water was used in preparing the capsule pharmaceutical compositions. According to paragraphs 115-116, pages 23-24 of the '275 application, the pharmaceutical compositions were prepared by combining and blending the components and then placing the blend in a gelatin capsule. The capsule pharmaceutical compositions of Tables 3 and 4 (see pages 7 and 34-36) were prepared according to this method. The capsules were then stored in sealed containers.

14. The stability of the capsule pharmaceutical compositions of Tables 3 and 4 were evaluated as described at pages 34-36 of the '275 application, in accordance with FDA recommendations as provided in *Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances* (posted at www.fda.gov/downloads/drugs/guidancecomplianceregulatory information/guidances/ucm073369.pdf *last visited* September 9, 2015). The *Guidance* provides recommended stability testing conditions (long-term, intermediate, and accelerated storage conditions) in the Table at page 10, which is reproduced here.

Study	Storage condition	Minimum time period covered by data at submission
Long-term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

* It is up to the applicant to decide whether long-term stability studies are performed at 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.
** If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

15. In the stability studies described at pages 34-36 of the '275 application, capsules were placed in bottles or blister packs. The capsules were then stored under long-term 25 °C/60 percent relative humidity (RH), intermediate (30 °C/75 percent RH), or accelerated storage conditions (40 °C/75 percent RH). The bottles were monitored for 6,7-dimethoxy-quinoline-4-ol formation from Initial T=0 to 1 month, 3 months, 6, months, and 9 months. A portion of Bottle B4 was repackaged in a blister pack after being stored in bottles for 3 months. Results of

the capsule stability studies are given in Tables 7A-B and 8A-B of the '275 application, which are reproduced below.

Table 7A: Stability of 25 Mg Capsules (Table 3)

	Conditions	Bottle A1	Bottle A2	Bottle A3	Bottle A4
		PPM of 6,7-dimethoxy-quinoline-4-ol			
Initial T=0	25 °C/60% RH	2	2	3	3
1 Month	25 °C/60% RH	3	4	5	NA
	30 °C/75% RH	4	4	NA	NA
	40 °C/75% RH	9	9	10	NA
3 Months	25 °C/60% RH	5	5	7	NA
	30 °C/75% RH	7	6	NA	NA
	40 °C/75% RH	22	23	24	NA
6 Months	25 °C/60% RH	6	6	7	7 (3M in blister)
	30 °C/75% RH	9	9	NA	NA
	40 °C/75% RH	40	44	43	27 (3M in blister)
9 Months	25 °C/60% RH	7	7	9	8 (6M in blister)
	30 °C/75% RH	13	12	NA	NA
	40 °C/75% RH	NA	NA	68	60 (6M in blister)

M=Months; NA=Not Applicable; RH= Relative Humidity; PPM= Parts per Million. A portion of Bottle A4 was repackaged in a blister pack after being stored in bottles for 3 months.

Table 7B: Stability of 25 Mg Capsules (Table 3)

	Conditions	Bottle B1	Bottle B	Bottle B3	Bottle B4
		PPM of 6,7-dimethoxy-quinoline-4-ol			
Initial T=0	25 °C/60% RH	3	1	2	2
1 Month	25 °C/60% RH	<2	<2	<2	NA
	30 °C/75% RH	<2	<2	NA	NA
	40 °C/75% RH	2	<2	<2	NA
3 Months	25 °C/60% RH	2	<2	<2	NA
	30 °C/75% RH	2	<2	NA	NA
	40 °C/75% RH	3	<2	<2	NA
6 Months	25 °C/60% RH	<2	<2	<2	<2 (3M in blister)
	30 °C/75% RH	2	<2	NA	NA
	40 °C/75% RH	4	<2	3	3 (3M in blister)
9 Months	25 °C/60% RH	<2	<2	<2	<2 (6M in blister)
	30 °C/75% RH	3	<2	NA	NA
	40 °C/75% RH	NA	NA	5	4 (6M in blister)

A portion of Bottle B4 was repackaged in a blister pack after being stored in bottles for 3 months.

Table 8A: Stability of 100 Mg Capsules (Table 4)

	Conditions	Bottle A1	Blister A2	Bottle A3
		PPM of 6,7-dimethoxy-quinoline-4-ol		
Initial T=0	25 °C/60% RH	4	4	6
1 Month	25 °C/60% RH	4	4	6
	30 °C/75% RH	4	NA	6
	40 °C/75% RH	6	6	9
3 Months	25 °C/60% RH	5	5	7
	30 °C/75% RH	6	NA	7
	40 °C/75% RH	10	10	12
6 Months	25 °C/60% RH	5	5	
	30 °C/75% RH	6	NA	
	40 °C/75% RH	11	17	

Table 8B: Stability of 100 Mg Capsules (Table 4)

	Conditions	Bottle B1	Blister B2	Bottle B3
		PPM of 6,7-dimethoxy-quinoline-4-ol		
Initial T=0	25 °C/60% RH	1	1	2
1 Month	25 °C/60% RH	<2	<2	<2
	30 °C/75% RH	<2	<2	2
	40 °C/75% RH	<2	<2	2
3 Months	25 °C/60% RH	<2	<2	<2
	30 °C/75% RH	<2	NA	<2
	40 °C/75% RH	<2	<2	2
6 Months	25 °C/60% RH	<2	<2	
	30 °C/75% RH	<2	NA	
	40 °C/75% RH	2	2	

16. Tables 7A-B and 8A-B show that no more than 44 ppm of 6,7-dimethoxy-quinoline-4-ol in capsules was observed after six months of storage under accelerated conditions. No more than 68 ppm of 6,7-dimethoxy-quinoline-4-ol in capsules was observed after 9 months of storage under accelerated conditions.

17. Capsules (25 and 100 mg) stored under long-term conditions for as long as 4 years gave no more than 26 ppm of 6,7-dimethoxy-quinoline-4-ol, which is less than for the capsules stored for six months under accelerated conditions. The data is presented in the following tables.

Stability of 25mg Capsules

	Conditions	Bottle A1	Bottle A2	Bottle A3	Blister A4
		PPM of 6,7-dimethoxy-quinoline-4-ol			
Initial T=0	25°C/60%RH	2	<2	3	3
1 month	25°C/60%RH	3	4	5	N/A
	30°C/75%RH	4	4	N/A	N/A
3 month	25°C/60%RH	5	5	7	N/A
	30°C/75%RH	7	6	N/A	N/A
6 month	25°C/60%RH	6	6	7	7 (3M in blister)
	30°C/75%RH	9	9	N/A	N/A
9 month	25°C/60%RH	7	7	9	8 (6M in blister)
	30°C/75%RH	13	12	N/A	N/A
12 month	25°C/60%RH	9	9	10	10 (9M in blister)
	30°C/75%RH	17	17	N/A	N/A
18 month	25°C/60%RH	11	11	13	12 (15M in blister)
	30°C/75%RH	24	22	N/A	N/A
24 month	25°C/60%RH	14	13	15	16 (21M in blister)
36 month	25°C/60%RH	19	18	20	22 (33M in blister)
48 month	25°C/60%RH	24	25	26	N/A

Stability of 100mg Capsules

	Conditions	Bottle B1	Blister B2	Bottle B3
		PPM of 6,7-dimethoxy-quinoline-4-ol		
Initial T=0	25°C/60%RH	4	4	6
1 month	25°C/60%RH	4	4	6
	30°C/75%RH	4	N/A	6
3 month	25°C/60%RH	5	5	7
	30°C/75%RH	6	N/A	7
6 month	25°C/60%RH	5	5	8
	30°C/75%RH	6	N/A	10
9 month	25°C/60%RH	5	6	8
	30°C/75%RH	7	N/A	10
12 month	25°C/60%RH	6	7	9
	30°C/75%RH	9	N/A	12
18 month	25°C/60%RH	7	8	10
	30°C/75%RH	11	N/A	14
24 month	25°C/60%RH	8	8	11
	30°C/75%RH	12	N/A	16
36 month	25°C/60%RH	10	8	13

	Conditions	Bottle B1	Blister B2	Bottle B3
	30°C/75%RH	17	N/A	23
48 month	25°C/60%RH	11	10	16

Tablet Pharmaceutical Composition Stability

18. Tablet pharmaceutical compositions are disclosed in the application as filed at paragraphs [0020] and [0115] and elsewhere.

19. The stability of the tablet pharmaceutical compositions were evaluated as described in paragraph 14, above.

20. In the stability studies, 20, 60, or 100 mg tablets were placed in bottles. The tablets were then stored under long-term 25 °C/60 percent relative humidity (RH), or accelerated storage conditions (40 °C/75 percent RH). The long-term samples were monitored for 6,7-dimethoxy-quinoline-4-ol formation from Initial T=0 to 1 month, 3 months, 6, months, and 9 months, 12 months, 18 months, and 24 months. The accelerated storage condition samples were monitored for 6,7-dimethoxy-quinoline-4-ol formation from Initial T=0 to 1 month, 3 months, and 6, months. The results of the stability studies are given in the following tables.

Stability of 20-mg Tablets

Batch Number	Conditions	Time Point (Months, M)							
		T=0	T = 1	T = 3	T = 6	T = 9	T = 12	T = 18	T = 24
Batch #1 (bottle)	25 °C/60% RH	11	10	10	12	11	11	13	15
	40 °C/75% RH		11	11	15				
Batch #2 (bottle)	25 °C/60% RH	10	11	11	11	11	14	17	12
	40 °C/75% RH		11	12	14				
Batch #3 (bottle)	25 °C/60% RH	7	6	7	10	6	7	13	8
	40 °C/75% RH		7	7	18				
Batch #4 (bottle)	25 °C/60% RH	5	4	4	6	7	5	5	6
	40 °C/75% RH		5	6	8				

M, month; RH, relative humidity; T, time.

Stability of 60-mg Tablets

Batch Number	Conditions	Time Point (Months, M)								
		T=0	T = 1	T = 3	T = 6	T = 9	T = 12	T = 18	T = 24	T = 36
Batch #1 (bottle)	25 °C/60% RH 40 °C/75% RH	11	11 10	10 12	12 15	11	12	13	15	13
Batch #2 (bottle)	25 °C/60% RH 40 °C/75% RH	12	11 12	11 12	12 14	12	14	17	13	
Batch #3 (bottle)	25 °C/60% RH 40 °C/75% RH	7	6 9	7 9	10 20	7	8	9	8	
Batch #4 (bottle)	25 °C/60% RH 40 °C/75% RH	4	5 5	5 6	6 9	6	6	5	7	

M, month; RH, relative humidity; T, time.

Stability of 100-mg Tablets

Batch Number	Conditions	Time Point (Months, M)								
		T=00	T = 1	T = 3	T = 6	T = 9	T = 12	T = 18	T = 24	T = 36
Batch #1 (bottle)	25 °C/60% RH 40 °C/75% RH	11	11 12	12 14	10 13	8	11	11	10	11
Batch #2 (bottle)	25 °C/60% RH 40 °C/75% RH	11	12 11	11 12	12 16	12	12	13	16	11
(bottle)	40 °C/75% RH				9					

M, month; NS, not scheduled; RH, relative humidity; T, time; TBP, to be performed.

21. No more than 20 ppm of 6,7-dimethoxy-quinoline-4-ol was observed in the 20, 60, and 100 mg tablet pharmaceutical compositions after long term storage at 25 °C/60% RH.

22. Under accelerated conditions, no more than 20 ppm of 6,7-dimethoxy-quinoline-4-ol was present in the 20, 60, or 100 mg tablets after six months of storage under accelerated conditions.

23. The tablet formulations is manufactured using a wet process as provided below:

a) Delumping unmilled Compound I;

b) Premixing the delumped Compound I with Avicel PH102, lactose anhydrous 60M, and croscarmellose sodium to form a binder solution;

c) Wet high shear granulation of the binder solution to produce wet granules;

d) Wet screening of the wet granules to produce wet screened granules;

e) Fluid bed drying of the wet screened granules to produce dried granules;

f) Dry milling of the dried granules to produce dried milled granules;

g) Blending the dried milled granules with colloidal silicon and croscarmellose to produce an extragranular blend;

h) Lubricant blending of the extragranular blend and magnesium stearate to produce a final blend;

i) Tablet compression of the final blend to form an uncoated core tablet; and

j) Film coating of the uncoated core tablet.

24. Yet, according to the tablet stability data in the tables, no more than 12 ppm of dimethoxy-quinoline-4-ol was observed in tablets at T=0.

25. As a clarification, all moisture absorbed from processing was dried following completion of manufacturing/coating the tablets and the resultant tablet moisture was approximately 2% w/w prior to the commencement of the stability studies.

26. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Khalid Shah

13 JAN, 2022

Date

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	17/170,275	Filing Date	2021-02-08	Docket Number (if applicable)	224990/10-039C6-US/483214	Art Unit	1625
First Named Inventor	Jo Ann Wilson			Examiner Name	Seaman, D. Margaret M.		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☒ Affidavit(s)/ Declaration(s)
- ☒ Other Terminal Disclaimer

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 503145

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (01-22)
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Signature of Registered U.S. Patent Practitioner			
Signature	/Heidi M. Berven, Ph.D./	Date (YYYY-MM-DD)	2022-01-20
Name	Heidi M. Berven, Ph.D.	Registration Number	48951

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

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PTO/AIA/26 (04-14)
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TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) 224990/10-039C6-US/483214

In re Application of: Jo Ann Wilson, et al.

Application No.: 17/170,275

Filed: February 8, 2021

For: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

The applicant, Exelixis, Inc., owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. 9,717,720 as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

expires for failure to pay a maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

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

2. ☑ The undersigned is an attorney or agent of record. Reg. No. 48951

/Heidi M. Berven, Ph.D./ — Signature
January 20, 2022 — Date

Heidi M. Berven, Ph.D. — Typed or printed name

Attorney of Record — Title
269-337-7710 — Telephone Number

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

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

This collection of information is required by 37 CFR 1.321. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/170,275	02/08/2021	Jo Ann Wilson	224990/10-039C6-US/483214	8006

91684 7590 07/20/2021

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EXAMINER	
SEAMAN, D MARGARET M	

ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
07/20/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

apeters@honigman.com
hberven@honigman.com
patent@honigman.com

Office Action Summary	Application No. 17/170,275	Applicant(s) Wilson et al.	
	Examiner D MARGARET M SEAMAN	Art Unit 1625	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 6/30/2021.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 35 and 38-39 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 35 and 38-39 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application is being examined under the pre-AIA first to invent provisions.

Claim Rejections - 35 USC § 102

The rejections of claim under 35 USC 102 (as stated in paper dated 3/31/2021) have been reconsidered and rewritten to rejections of claim under 35 USC 103.

Claim Rejections - 35 USC § 103

2. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

3. The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 35 and new claims 38-39 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over USPGPub20120035212 (US8877776) in view of Li, Pingali and article

Overview of Pharmaceutical Excipients (2008). Brown teaches the instant compound (col 6 line 1) and its salt (col 5 line 30) and col 3 under SUMMARY teaches that the disclosure relates to malate salts of the compound described herein. Col 8 lines 60-65 teach that this compound is substantially pure. Col 11 line 40 teaches that this is in combination with pharmaceutically acceptable excipients. Col 14 lines 10-25 discuss the pharmaceutical compositions with excipients and adjuvants. Col 15 teaches starches, cellulose derivatives, disintegrating agents including carmellose sodium. Complex silicates (glidants) and stearate (lubricants) and lubricants such as talc, calcium stearate and magnesium stearate are also taught. Brown does not specifically teach one formulation that is the salt, pure without the specific unwanted byproduct with a specific filler, with a specific disintegrant with one specific glidant and one specific lubricant. However, Brown does teach that the compound is a salt, that is pure and can be mixed with other compounds to make the composition easy to handle, make, distribute and dose.

Li teaches that lubricants are part of the common knowledge that the ordinary skilled artisan would know of and how to use such. Along this same line, Pingali and the article both teach that the use of disintegrants, glidants, lubricants as well as fillers are common knowledge and their use is well known in the pharmaceutical art. As such, the ordinary skilled artisan would know of their presence and would use them as needed.

It would have been obvious to the ordinary skilled artisan to make the salt of the compound taught by Brown, pure, with fillers, disintegrants, glidants, libricants and other fillers in the pharmaceutical composition as taught by Brown. Rationale: All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as

claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

5. Claims 35 and new claims 38-39 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over US PGPub20070054928 in view of Li, Pingali and the article "Overview". '928 teaches the instant composition on page 316 #12 and claim 106. '928 teaches starch and carmellose sodium (disintegrating agents) as well as silicates (glidants") and magnesium sterate (lubricants) in paragraph 302. Further paragraph 297 teaches that the compounds are pure. The pharmaceutical composition with carriers and excipients are taught in paragraphs 298-304. '928 teaches the compound, as a salt, in pure form and in a pharmaceutical composition that can contain many different other filler/excipients as needed for their properties. These fillers/excipients include disintegrants, glidants and lubricants as are instantly claimed. '928 does not have a specific example of all of these together in one dose. However, '928 does teach that these all can be combined. To further this, Li teaches that lubricants are part of the common knowledge that the ordinary skilled artisan would know of and how to use such. Along this same line, Pingali and the article both teach that the use of disintegrants, glidants, lubricants as well as fillers are common knowledge and their use is well known in the pharmaceutical art. As such, the ordinary skilled artisan would know of their presence and would use them as needed.

It would have been obvious to the ordinary skilled artisan to make the salt of the compound taught by '928, pure, with fillers, disintegrants, glidants, libricants and other fillers in

the pharmaceutical composition as taught by '928. Rationale: All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to

examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

7. Claims 35 and 38-39 remain rejected on the ground of nonstatutory double patenting as being unpatentable over claims of U.S. Patent No. 9717720. The rejection over 10123999 and 10543206 are withdrawn. Applicant has stated in paper dated 6/30/2021, that a terminal disclaimer will be filed as necessary.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D MARGARET M SEAMAN whose telephone number is (571)272-0694. The examiner can normally be reached on M-F 8-4 Telework Home.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/D MARGARET M SEAMAN/
Primary Examiner, Art Unit 1625

Notice of References Cited	Application/Control No. 17/170,275	Applicant(s)/Patent Under Reexamination Wilson et al.	
	Examiner D MARGARET M SEAMAN	Art Unit 1625	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-8877776-B2	11-2014	Brown; Adrian St. Clair	A61P35/00	514/312
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Li, Lubricants, 2014, Vol 2, 21-43. (Year: 2014)
	V	Pingali, Int J Pharm, 2011, Vol 409(0), 269-277. (Year: 2011)
	W	"Overview of PHarmaceutical Excipients Used in Tablets and Capsules", 2008, Drug Topics, https://www.drugtopics.com/view/overview-pharmaceutical-excipients-used-tablets-and-capsules. (Year: 2008)
	X	

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

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/170,275	Wilson et al.
	Examiner	Art Unit
	D MARGARET M SEAMAN	1625

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	03/26/2021	07/15/2021							
	1	-								
	2	-								
	3	-								
	4	-								
	5	-								
	6	-								
	7	-								
	8	-								
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	28	-								
	29	-								
	30	-								
	31	-								
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	33	-								
	34	-								
	35	✓	✓							
	36	✓	-							
	37	✓	-							
	38		✓							
	39		✓							

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/170,275	Wilson et al.
	Examiner	Art Unit
	D MARGARET M SEAMAN	1625

CPC - Searched*		
Symbol	**Date**	**Examiner**
A61K 31/47	03/26/2021	dms
C07D 215/233	03/26/2021	dms
above updated	07/15/2021	dms

CPC Combination Sets - Searched*		
Symbol	**Date**	**Examiner**

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	**Date**	**Examiner**
Inventor Name Search	03/26/2021	dms
STNext Structure search	03/26/2021	dms
google	07/15/2021	dms

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**

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www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 8006

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
17/170,275	02/08/2021	514	1625	224990/10-039C6-US/483214

APPLICANTS

Exelixis, Inc., Alameda, CA;

INVENTORS

Jo Ann Wilson, San Francisco, CA;
Khalid Shah, Half Moon Bay, CA;

**** CONTINUING DATA ***************************

This application is a CON of 17/152,394 01/19/2021
which is a CON of 16/706,323 12/06/2019 ABN
which is a DIV of 16/151,653 10/04/2018 PAT 10543206
which is a DIV of 15/348,716 11/10/2016 PAT 10123999
which is a DIV of 13/984,559 03/20/2014 PAT 9717720
which is a 371 of PCT/US2012/024591 02/10/2012
which claims benefit of 61/441,520 02/10/2011
and claims benefit of 61/441,527 02/10/2011

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

02/24/2021

Foreign Priority claimed ❑ Yes ☑ No 35 USC 119(a-d) conditions met ❑ Yes ❑ No Verified and Acknowledged /D M SEAMAN/ Examiner's Signature	❑ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		CA	0	3	1

ADDRESS

JONATHAN P. O"BRIEN, PH.D.
HONIGMAN LLP
650 Trade Centre Way
Suite 200
Kalamazoo, MI 49002-0402
UNITED STATES

TITLE

Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

FILING FEE RECEIVED		
1820	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	❑ All Fees ❑ 1.16 Fees (Filing) ❑ 1.17 Fees (Processing Ext. of time) ❑ 1.18 Fees (Issue) ❑ Other _____ ❑ Credit

10:06 AM	G	montelukast structure - Google Search	www.google.com
10:05 AM	W	Montelukast - Wikipedia	en.wikipedia.org
10:04 AM	E	Gliding Agent - an overview | ScienceDirect Topics	www.sciencedirect.com
10:04 AM	G	pharmaceutical glidant - Google Search	www.google.com
9:48 AM		Lubricants in Pharmaceutical Solid Dosage Forms	file:
9:48 AM		Selecting Lubricants for Pharmaceutical Facilities	www.machinerylubrication.com
9:48 AM		Lubricant Excipients | American Pharmaceutical Review	www.americanpharmaceuticalreview.com
9:48 AM	G	pharmaceutical lubricant - Google Search	www.google.com
9:47 AM		Glidants and Lubricant Properties of Several Types of Talcs: Drug Development and Industrial Pha...	www.tandfonline.com

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	17170275
Filing Date	2021-02-08
First Named Inventor	Jo Ann Wilson
Art Unit	1625
Examiner Name	Seaman, D. Margaret M.
Attorney Docket Number	224990/10-039C6-US/483214

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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U.S.PATENT APPLICATION PUBLICATIONS

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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2009136663	WO		2009-11-12	TAKEDA PHARMACEUTICAL COMPANY LIMITED		☐
	2	2010113183	WO		2010-10-07	MSN LABORATORIES LIMITED		☐

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NON-PATENT LITERATURE DOCUMENTS

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /D.M.S/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
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	Art Unit	1625
	Examiner Name	Seaman, D. Margaret M.
	Attorney Docket Number	224990/10-039C6-US/483214

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		☐

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

EXAMINER SIGNATURE

Examiner Signature	/D MARGARET M SEAMAN/	Date Considered	07/15/2021

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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Attorney Docket Number	224990/10-039C6-US/483214

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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

OR

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

☐ See attached certification statement.

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

☒ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Heidi M. Berven/	Date (YYYY-MM-DD)	2021-06-30
Name/Print	Heidi M. Berven, Ph.D.	Registration Number	48951

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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PTO/SB/08a (02-18)
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	First Named Inventor	Jo Ann Wilson
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	Attorney Docket Number	224990/10-039C6-US/483214

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		☐

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

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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OR

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

☐ See attached certification statement.

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

☒ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Heidi M. Berven/	Date (YYYY-MM-DD)	2021-06-30
Name/Print	Heidi M. Berven, Ph.D.	Registration Number	48951

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

REMARKS

Claim Status

Claim 35 is currently amended. Currently amended claim 35 is supported by the specification and claims as originally filed and does not introduce new matter.

Claims 1-34, 36, and 37 are cancelled.

Claims 38 and 39 are new. The new claims are supported by the specification and claims as originally filed and do not present new matter.

Thus, claims 35, 38, and 39 are currently pending.

The Applicant reserves the right to file divisional applications or take such other appropriate action as deemed necessary to protect the subject matter restricted, cancelled, or withdrawn from this application.

Rejections Under 35 U.S.C. § 102

In the Office Action, the Examiner rejected claims 35-37 under pre-AIA 35 U.S.C. § 102(a)(1) as allegedly being anticipated by U.S. Application Publication No. 20120035212 (the '212 Application). The Applicant respectfully submits that the '212 Application does not technically qualify as prior art under pre-AIA 35 U.S.C. § 102(a). The '212 Application was published on February 9, 2012, which is after the priority date of February 10, 2011 for the captioned application. However, the '212 Application has a priority dated back to January 16, 2009, and further claims priority to WO2010083414 (the '414 PCT Publication) which published on July 22, 2010. The Applicant therefore suggests that another part of pre-AIA 35 U.S.C. 102 may be operative. Even so, the '212 Application and the '414 PCT Publication do not disclose a pharmaceutical composition having all the limitations claimed by the Applicant. Notably "one or more glidants" is not disclosed, nor that the "pharmaceutical composition is essentially free of process byproducts or contaminants." One of ordinary skill could not envisage these limitations from a reading of the '212 Application or the '414 PCT Publication. As a result, the Applicant respectfully requests removal of the rejection.

The Examiner additionally rejected claims 35-37 under pre-AIA 35 U.S.C. § 102(a)(1) as allegedly being anticipated by U.S. Application Publication No. 20090105299 (the '299 Application). According to the Examiner, the '299 Application discloses the claimed

compostion on claim 68, 69, and 71, and maleic acid on paragraph 278. The Applicant respectfully disagrees. The '299 Application does not teach a pharmaceutical compoisition of Compound IB and "one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants," nor that the "pharmaceutical composition is essentially free of process byproducts or contaminants." The '299 Application also does not disclose "malic acid." While "maleic acid" appears at paragraph 278, "malic acid" is absent from the list of organic acids, and malate salts of the compounds disclosed in the '299 Application *let alone* the malate salt of Compound IB are not disclosed. One of ordinary skill could not envisage these limitations from a reading of the '299 Application. As a result, the Applicant respectfully requests removal of the rejection.

The Examiner further rejected claims 35-37 under pre-AIA 35 U.S.C. § 102(a)(1) as allegedly being anticipated by U.S. Application Publication No. 20070054928 (the '928 Application). According to the Examiner, the '928 Application teaches the instant composition on page 316 #12 and claim 106. The Applicant respectfully disagrees for the same reason as provided for the '299 Application--namely, the '928 application does not teach a pharmaceutical compoisition of Compound IB and "one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants," nor that the "pharmaceutical composition is essentially free of process byproducts or contaminants." The '928 Applicatoin also does not disclose malic acid or malate salts of any compounds, let alone the malate salt of Compound IB. One of ordinary skill could not envisage these limitations from a reading of the '928 Application. As a result, the Applicant respectfully requests removal of the rejection.

Lastly, the Examiner rejected claims 35-37 under pre-AIA 35 U.S.C. § 102(a)(1) as allegedly being anticipated by US Patent No. 7,579,473 (the '473 Patent). According to the Examiner, the '473 Patent teaches the compound, salt, or its pharmaceutical composition on claim 3, and that paragraph 312 teaches the maleic acid salt. The Applicant respectfully disagrees for the same reason as provided for the '299 and '928 applications--namely, the '473 Patent does not teach a pharmaceutical compoisition of Compound IB and "one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants," nor that the "pharmaceutical composition is essentially free of process byproducts or contaminants." The '473 Patent also does not disclose malic acid or malate salts of any compounds, let alone

Compound IB. One of ordinary skill could not envisage these limitations from a reading of the '473 Patent. As a result, the Applicant respectfully requests removal of the rejection.

Double Patenting

The Examiner rejected claims 35-37 on the ground of nonstatutory double patenting as being unpatentable over claim 9 of U.S. Patent No. 10,123,999 (the '999 Patent). The Applicant respectfully disagrees, because the currently pending claims, which are directed to a pharmaceutical composition, are patentably distinct from claim 9 of the '999 Patent, which is directed to a process. Therefore, the Applicant respectfully requests removal of the rejection.

The Examiner further rejected claims 35-37 on the ground of nonstatutory double patenting as being unpatentable over the claims of US Patent No. 10,543,206 (the '206 Patent). The Applicant respectfully disagrees, because the currently pending claims, which are directed to a pharmaceutical composition, are patentably distinct from the claims of the '206 Patent, which are directed to a process. Therefore, the Applicant respectfully requests removal of the rejection.

The Examiner also rejected claims 35-37 on the ground of nonstatutory double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 9,717,720 (the '720 Patent). Once the Examiner has indicated that the claims are in condition for allowance but for the nonstatutory double patenting rejection, the Applicant will file a terminal disclaimer as necessary. The Applicant encourages the Examiner to contact the undersigned attorney regarding the same at (269) 337-7710 at the Examiner's convenience.

INFORMATION DISCLOSURE STATEMENT

The Applicant notes that the filing of the enclosed Information Disclosure Statement shall not be construed to be an admission that the information cited in the statement qualifies as prior art under 35 U.S.C. § § 102 or 103, or is considered to be material to patentability as defined in 37 C.F.R. § 1.56(b). The fee set forth in 37 C.F.R. § 1.17(p) is submitted in support.

OTHER C-MET INHIBITOR CASES

The Applicant wishes to make the Examiner aware of the Applicant's other applications related to c-Met inhibitors and their use in the treatment of cancer. For the Examiner's convenience, the Applicant is providing a list of the Applicant's applications directed to the

treatment of cancer using c-Met inhibitors. The Applicant understands the Examiner has electronic access to these applications and to the Office Actions that have issued in these applications, and has therefore not included copies with this Response. The Applicant will gladly provide the applications and Office Actions to the Examiner, however, upon request.

Application Number	Filing or 371 Date	Patent Number	Examiner	Status
10/573,336	09/18/2006		Koontz, Tammy J.	Abandoned
11/571,140	12/21/2006	7977345	Moore, Susanna	Expired
11/586,751	10/26/2006	9174947	Ward, Paul V.	Issued
11/753,462	05/24/2007	8178532	Ward, Paul V.	Issued
11/753,503	05/24/2007	8476298	Ward, Paul V.	Expired
11/753,514	05/24/2007	8067436	Bernhardt, Emily A.	Issued
12/393,806	02/26/2009	7579473	Seaman, D. Margaret M.	Issued
12/911,442	10/25/2010		Ward, Paul, V.	Abandoned
13/087,094	04/14/2011		Chickos, Sarah, J.	Abandoned
13/129,183	05/13/2011		Seaman, D. Margaret M.	Abandoned
13/132,650	06/03/2011		Seaman, D. Margaret M.	Abandoned
13/145,054	10/20/2011	8877776	Carter, Kendra D	Issued
13/249,815	09/30/2011	8497284	Bernhardt, Emily A.	Issued
13/384,451	07/12/2012	8673912	Anderson, Rebecca L.	Issued
13/389,266	07/12/2012		Perreira, Melissa Jean	Abandoned
13/427,093	03/22/2012		Ward, Paul V.	Abandoned
13/438,964	04/04/2012		Brown-Pettigrew, Angela C.	Abandoned
13/634,275	09/12/2012		Anderson, Rebecca L.	Abandoned
13/753,031	01/29/2013		Pagonakis, Anna	Abandoned
13/753,146	01/29/2013		Pagonakis, Anna	Abandoned
13/810,537	08/26/2013	9724342	Pallay, Michael B.	Issued
13/810,546	08/27/2013		Branson, Daniel L.	Abandoned
13/876,290	11/05/2013		Stone, Christopher R.	Abandoned
13/876,306	11/08/2013		Lee, Andrew P.	Abandoned
13/876,318	10/25/2013		Karol, Jody Lynn	Abandoned
13/888,592	05/07/2013		Ward, Paul V.	Abandoned
13/928,977	06/27/2013		Bernhardt, Emily A.	Abandoned
13/984,559	03/20/2014	9717720	Rozof, Timothy R.	Issued
14/021,614	09/09/2013		Matos Negron, Taina Del Mar	Abandoned
14/115,236	02/28/2014		Anderson, James D.	Abandoned
14/166,545	01/28/2014		Not Yet Assigned	Abandoned
14/173,973	02/06/2014		Johannsen, Diana B.	Abandoned
14/340,871	07/25/2014	9809549	Carter, Kendra D.	Issued
14/346,570	03/21/2014	10166225	Wang, Shengjun	Issued

Application Number	Filing or 371 Date	Patent Number	Examiner	Status
14/353,251	04/21/2014	9365516	Murray, Jeffrey H.	Issued
14/356,927	05/08/2014		Baek, Bong-Sook	Abandoned
14/356,938	05/08/2014		Cerioni, Daniel Lee	Abandoned
14/398,188	10/31/2014	9861624	Henley III, Raymond J.	Issued
14/426,580	03/06/2015		Jean-Louis, Samira J.M.	Abandoned
14/518,733	10/20/2014		Wright, Sarah C.	Abandoned
14/668,312	03/25/2015		Brown-Pettigrew, Angela C.	Abandoned
14/699,683	04/29/2015		Perreira, Melissa Jean	Abandoned
14/776,337	09/14/2015	10273211	Badio, Barbara P.	Issued
14/782,493	10/05/2015		Saeed, Kamal A.	Abandoned
14/782,537	10/05/2015		Alley, Genevieve S.	Pending
14/843,480	09/02/2015		Shen, Wu Cheng Winston	Abandoned
14/847,801	09/08/2015		Ward, Paul V.	Abandoned
14/933,801	11/05/2015		Brown-Pettigrew, Angela C.	Abandoned
15/066,872	03/10/2016		Ward, Paul V.	Abandoned
15/118,738	08/12/2016	10501418	Chandrakumar, Nizal S.	Issued
15/126,767	09/16/2016	10159666	Solola, Taofiq A.	Issued
15/133,708	04/20/2016	9969692	Murray, Jeffrey H.	Issued
15/305,854	10/21/2016		McMillian, Kara Renita	Pending
15/348,716	11/10/2016	10123999	Rozof, Timothy R.	Issued
15/500,312	01/30/2017		Seaman, D. Margaret M.	Pending
15/501,582	02/03/2017	TBD	Seaman, D. Margaret M.	Issued
15/426,804	02/07/2017	10039757	Pallay, Michael B.	Issued
15/612,703	06/02/2017	10034873	Pallay, Michael B.	Issued
15/617,725	06/08/2017		Neagu, Irina	Abandoned
15/618,593	06/09/2017		Carter, Kendra D.	Abandoned
15/621,527	06/13/2017		Carter, Kendra D.	Abandoned
15/688,310	08/28/2017		Ward, Paul V.	Pending
15/955,246	04/17/2018		Not Yet Assigned	Abandoned
16/026,708	07/03/2018	10548888	Pallay, Michael B.	Issued
16/093,426	10/12/2018		Weddington, Kevin E.	Pending
16/095,221	10/19/2018		Saeed, Ali S.	Pending
16/142,691	09/26/2018		Howell, Theodore R.	Pending
16/151,653	10/04/2018	10543206	Rozof, Timothy R.	Issued
16/190,869	11/14/2018		Solola, Taofiq A.	Abandoned
16/230,267	12/21/2018		Kantamneni, Shobha	Pending
16/251,617	01/18/2019	10736886	Perreira, Melissa Jean	Issued
16/336,724	03/26/2019		Not Yet Assigned	Pending
16/362,863	03/25/2019		Reese, Heidi L.	Abandoned
16/479,143	07/18/2019		Lu, Cheng	Pending

Application Number	Filing or 371 Date	Patent Number	Examiner	Status
16/671,834	11/01/2019	10851061	Chandrakumar, Nizal S.	Issued
16/617,352	11/26/2019		Seaman, D. Margaret M.	Pending
16/620,379	12/06/2019		Oh, Taylor V.	Pending
16/706,323	12/06/2019		Rozof, Timothy R.	Abandoned
16/722,563	12/20/2019		Pallay, Michael B.	Pending
16/776,139	01/29/2020		Solola, Taofiq A.	Pending
16/787,212	02/11/2020		Anderson, James D.	Pending
16/796,250	02/20/2020		Neagu, Irina	Abandoned
16/905,307	06/18/2020		Not Yet Assigned	Pending
16/919,562	07/02/2020		Not Yet Assigned	Pending
16/921,542	07/06/2020		Not Yet Assigned	Pending
17/031,196	09/24/2020		Not Yet Assigned	Pending
17/070,514	10/14/2020		Rozof, Timothy R.	Pending
17/070,790	10/14/2020		Seaman, D. Margaret M.	Abandoned
17/084,312	10/29/2020		Not Yet Assigned	Pending
17/149,365	01/14/2021		Rozof, Timothy R.	Pending
17/152,394	01/19/2021		Not Yet Assigned	Pending
17/171,752	02/09/2021		Rozof, Timothy R.	Pending
17/212,851	03/25/2021		Not Yet Assigned	Pending

CONCLUSION & FEES DUE

The Applicant believes this submission is fully responsive to the Non-Final Office Action in this application dated March 31, 2021. The Applicant reserves the right to file divisional applications or take such other appropriate action as deemed necessary to protect the subject matter restricted, canceled, or withdrawn from this application.

The Applicant believes that due with this submission is the $260.00 Information Disclosure Statement fee. The Applicant hereby authorizes the Patent Office to charge this total of $260.00 to Deposit Account Number 503145 with reference to attorney docket number 224990/10-039C6-US/483214. It is believed that no other fees are due at this time. However, if there are any additional charges for this submission, or any credits, please apply them to Deposit Account Number 503145, referencing Attorney Docket Number 224990/10-039C6-US/483214.

Respectfully submitted,

/Heidi M. Berven/

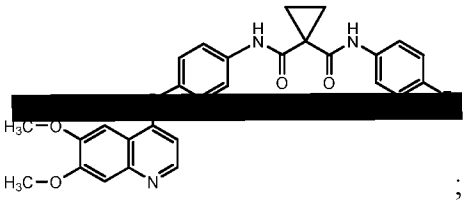
Date: June 30, 2021

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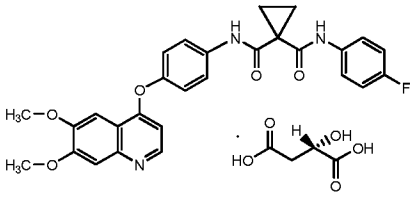
AMENDMENTS TO THE CLAIMS

1-34. Cancelled.

35. (Currently Amended) A pharmaceutical composition comprising Compound [[IA or]] IB;



[[IA]]



IB

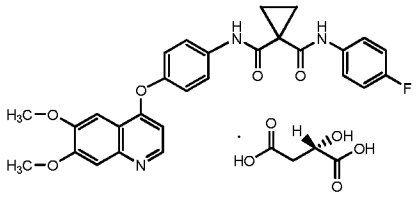
one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants, wherein the pharmaceutical composition is essentially free of process byproducts or contaminants.

36. (Cancelled) ~~The pharmaceutical composition according to claim 35, wherein the pharmaceutical composition comprises Compound IA.~~

37. (Cancelled) ~~The pharmaceutical composition according to claim 35, wherein the pharmaceutical composition comprises Compound IB.~~

38. (New) The pharmaceutical compositon of claim 35, wherein the process byproduct or contaminant is 6,7-dimethoxy-quinoline-4-ol in the pharmaceutical composition.

39. (New) A pharmaceutical composition comprising Compound IB;



IB

one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants, wherein the pharmaceutical composition is essentially free of 6,7-dimethoxy-quinoline-4-ol.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: Jo Ann Wilson, et al.
Application No.: 17/170,275
Filing Date: February 8, 2021

Art Unit: 1625
Examiner: Seaman, D. Margaret M.
Attorney Docket No.: 224990/10-039C6-US/483214

Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313

RESPONSE TO NON-FINAL OFFICE ACTION DATED MARCH 31, 2021

Dear Sir or Madam:

This submission is in response to the Non-Final Office Action mailed in this application on March 31, 2021.

Amendments to the claims begin on page 2.

Remarks begin on page 4.

HONIGMAN

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VIA EFS

June 30, 2021

Commissioner for Patents
United States Patent and Trademark Office
P. O. Box 1450
Alexandria, VA 22313

Re: US Patent Application No.: 17/170,275
Inventors: Jo Ann Wilson, et al.
Filing Date: February 8, 2021
Title: Processes for Preparing Quinoline Compounds and Pharmaceutical Compositions Containing Such Compounds
Conf. No.: 8006
Attorney Docket No.: 224990/10-039C6-US/483214

Dear Sir or Madam:

Enclosed for filing please find the following documents:

1. This Cover Letter to the Commissioner;
2. Response to Non-Final Office Action dated March 31, 2021;
3. Information Disclosure Statement (PTO/SB/08a);
4. Foreign Patent Documents (2);
5. Fee Transmittal (PTO/SB/17); and
6. Certificate of Transmission under 37 C.F.R. § 1.8(a).

The Applicant notes that the filing of the enclosed Information Disclosure Statement shall not be construed to be an admission that the information cited in the statement qualifies as prior art under 35 U.S.C. § § 102 or 103, or is considered to be material to patentability as defined in 37 C.F.R. § 1.56(b). The fee set forth in 37 C.F.R. § 1.17(p) is submitted in support.

The Applicant believes that due with this submission is the $260.00 Information Disclosure Statement fee. The Applicant hereby authorizes the Patent Office to charge this total of $260.00 to Deposit Account Number 503145 with reference to attorney docket number 224990/10-039C6-US/483214. It is believed that no other fees are due at this time. However, if there are any additional charges for this submission, or any credits, please apply them to Deposit Account Number 503145, referencing Attorney Docket Number 224990/10-039C6-US/483214.

Very truly yours,

HONIGMAN LLP

/Heidi M. Berven/

Heidi M. Berven, Ph.D.
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HMB/ayp

Enclosures

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

(19) World Intellectual Property Organization
International Bureau

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7 October 2010 (07.10.2010)

PCT

(10) International Publication Number
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(51) International Patent Classification:
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PCT/IN2010/000216

(22) International Filing Date:
1 April 2010 (01.04.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
774/CHE/2009 3 April 2009 (03.04.2009) IN
546/CHE/2010 3 March 2010 (03.03.2010) IN

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(75) Inventors/Applicants *(for US only)*: **SATYANARAYANA REDDY, Manne** [IN/IN]; MSN Laboratories Limited, Survey No: 317 & 323, Rudraram (V), Patancheru (M), Medak (Dist) Hyderabad 502 329 Andhra Pradesh (IN). **ESWARAIAH, Sajja** [IN/IN]; MSN Laboratories Limited, Survey No: 317 & 323, Rudraram (V), Patancheru (M), Medak (Dist) Hyderabad 502 329 Andhra Pradesh (IN). **SAHADEVA REDDY, Maramreddy** [IN/IN]; MSN Laboratories Limited, Survey No: 317 & 323, Rudraram (V), Patancheru (M), Medak (Dist) Hyderabad 502 329 Andhra Pradesh (IN). **SATYANARAYANA, Komati** [IN/IN]; MSN Laboratories Limited, Survey No: 317 & 323, Rudraram (V), Patancheru (M), Medak (Dist) Hyderabad 502 329 Andhra Pradesh (IN).

(74) Common Representative: **SATYANARAYANA REDDY, Manne**; MSN Laboratories Limited, Survey No: 317 & 323, Rudraram (V), Patancheru (M), Medak (Dist) Hyderabad 502 329 Andhra Pradesh (IN).

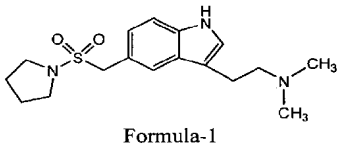
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG,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

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

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) **Title**: PROCESS FOR THE PREPARATION OF 1-[[[3-[2-(DIMETHYLAMINO)ETHYL]-1H-INDOL-5-YL]METHYL]SULFONYL] PYRROLIDINE AND ITS PHARMACEUTICALLY ACCEPTABLE SALTS



Formula-1

(57) **Abstract**: The present invention relates to an improved process for the preparation of 1-[[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl] methyl] sulfonyl]pyrrolidine compound of formula- 1 and its pharmaceutically acceptable salts.

WO 2010/113183 A2

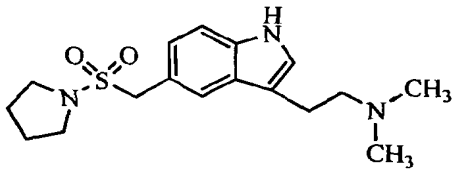
Process for the preparation of 1-[[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl] methyl]sulfonyl] pyrrolidine and its pharmaceutically acceptable salts

Related Application:

This application claims the benefit of priority of our Indian patent application numbers 774/CHE/2009 filed on 3/4/2009 and 546/CHE/2010 filed on 3/3/2010, which are incorporated herein by reference.

Field of the Invention:

The present invention relates to an improved process for the preparation of 1-[[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]sulfonyl]pyrrolidine and its pharmaceutically acceptable salts, which is commonly known as Almotriptan and is represented by the following structural formula-1



Formula-1

The present invention also relates to novel salts of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of general formula-2 and their use.

Almotriptan binds with high affinity to 5-HT_{1D}, 5-HT_{1B} and 5-HT_{1F} receptors. The malate salt of almotriptan is indicated for the acute treatment of migraine with or without aura in adults. Almotriptan malate is commercially available under the brand name of AXERT® and ALMOGRAN®.

Background of the Invention:

Almotriptan and its pharmaceutically acceptable salts as well as the process for their preparation are disclosed in US 5565447. The disclosed process involves the decarboxylation of 1-[2-carboxy-3-dimethylaminoethyl)-5-indolyl]methanesulfonyl] pyrrolidine using copper oxide and quinoline. The decarboxylation reaction requires very high temperature and hence is difficult to carry out in a commercial scale.

ES 2084560 describes a process for the preparation of almotriptan based on Fisher indole synthesis using a phenyl hydrazine and 4-chloro-butyraldehyde diethyl acetal to provide 1-[[3-(2-aminoethyl)-5-indolyl]methanesulfonyl]pyrrolidine, which is further treated with aqueous formaldehyde and then with sodium borohydride to provide almotriptan. Thus obtained almotriptan is converted into its DL-malate salt. This process provides almotriptan in poor yields. Moreover it was observed that the purity of the intermediates like 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine (herein after referred as "amino indole" intermediate) and final products are not of adequate quality and are having approximately 75-80% of purity by HPLC. Specifically the amino indole intermediate obtained as a residue and is not stable at ambient temperature.

WO 2006/129190 describes a process for the preparation almotriptan malate. The disclosed process comprises of treating 5-(1-pyrrolidinyl-sulfonylmethyl)-1H-indole-3-ethanol with methane sulfonyl chloride and then dimethylamine followed by column purification of almotriptan. The said application schematically represents the conversion of almotriptan into almotriptan succinate and subsequent conversion in to almotriptan malate. Other than the schematic representation, the applicant has not disclosed/exemplified the process for the preparation of almotriptan succinate and neither has disclosed any physical properties. Moreover the preparation of 5-(1-pyrrolidinyl-sulfonylmethyl)-1H-indole-3-ethanol involves the usage of n-butyl lithium. As this process involves the usage of reagents like n-butyl lithium and purification techniques like column chromatography, they are commercially not recommendable.

WO 2008/151584 describes a process for the preparation of almotriptan malate, which involves the conversion of 4-(pyrrolidinylsulfonylmethyl) phenyl hydrazine 4-chloro-1-hydroxybutane-1-sulfonate or 4-(pyrrodinylsulfonylmethyl) phenyl hydrazine toluene sulfonate into crude almotriptan and then converting the crude almotriptan into its fumarate salt. Thus formed almotriptan fumarate is converted into crystalline almotriptan free base. The crystalline free base was treated with malic acid to provide almotriptan malate. Even though this process avoids some of problems of above reported process, it involves the additional steps like isolation of intermediate complex and almotriptan free

base, which are time consuming and decrease the yields of the products. Moreover the fumarate salt of almotriptan is obtained in very poor purity of about 92%.

US 2007/112055 describes the process for the preparation of crystalline almotriptan free base, which involves treating the organic layer containing almotriptan with aqueous succinic acid then basifying the aqueous layer containing almotriptan succinate, followed by extraction of almotriptan into isopropyl acetate and then its conversion into crystalline almotriptan. Even though this process involves the formation of almotriptan succinate, which has been carried out in solution phase only and does not involve its isolation, further it does not disclose its physical properties.

In general, the reported processes for the preparation of almotriptan or its salts proceed through the amino indole intermediate in the form of crude with very less purity of about 75-80%. The said intermediate was not stable at ambient temperature and usage of same in further steps leads the final compound contaminated with high level of impurities. When the present inventors working to resolve these problems, the present inventors surprisingly found that the salts of amino indole intermediate make it highly stable at ambient condition and having the purity of greater than 97% by HPLC and does not require any specific equipment and temperature for storage.

It has been observed that the almotriptan malate prepared as per the reported processes containing amino indole and monomethyl compounds as a major impurities in the range of 0.5 to 1% by HPLC along with other known and unknown impurities in the limit of more than 0.1% by HPLC. Hence it is necessary to have a process for the purification of almotriptan malate to eliminate the above said impurities. Also there is a need in the art for an improved process for the preparation of almotriptan malate through a high pure intermediate salt compounds, which avoids the addition crystallization steps to make it economically affordable.

The required purity of almotriptan malate free of impurities is attained by the present inventor in three different ways one is by preparing the acid addition salts of amino indole compound and second way by proceeding through the almotriptan succinate and in third way, by specific purification of almotriptan malate from a suitable solvent.

Brief Description of the Invention:

The first aspect of the present invention is to provide novel salts of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of general formula-2, process for its preparation and its use in the preparation of highly pure almotriptan and its pharmaceutically acceptable salts.

The second aspect of the present invention is to provide a process for the preparation of highly pure almotriptan compound of formula-1 through the novel salt compound of formula-2, which comprises of the following steps;

a) treating the 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine or its salt compound of formula-3 with source of 4-chlorobutyraldehyde in presence of disodium hydrogen phosphate and acid in a suitable solvent, followed by treating the obtained compound with a suitable acid to provide the corresponding acid addition salt of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compounds of general formula-2,

b) reacting the salt compounds of general formula-2 with a suitable base in a suitable solvent to provide free base compound of formula-5, which on in-situ reaction with formalin in presence of sodiumborohydride in aqueous sodium hydroxide, in a suitable solvent to provide almotriptan, which on in-situ treatment with malic acid in a suitable solvent provides almotriptan malate compound of formula-1a,

c) optionally purifying the obtained almotriptan malate compound of formula-1a.

The third aspect of the present invention is to provide novel crystalline form of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine oxalate compound of formula-2a and process for its preparation. The novel crystalline form of the present invention is characterized by its powder X-ray diffractogram.

The fourth aspect of the present invention is to provide an improved process for the purification of almotriptan malate compound of formula-1a, which comprises of treating almotriptan malate with suitable base in a suitable solvent to provide almotriptan, which on in-situ treatment with malic acid in a suitable solvent provides almotriptan malate compound of formula-1a.

The fifth aspect of the present invention is to provide an improved process for the preparation of almotriptan malate compound of formula-1a, which comprises of the following steps,

a) treating the 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine or its salt compound of formula-3 with protected derivative of 4-chlorobutyraldehyde compound of formula-4 in presence of disodium hydrogen phosphate in a suitable solvent, to provide 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of formula-5,

b) reacting the 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine with formalin in presence of sodiumborohydride in aqueous sodium hydroxide, in a suitable solvent to provide almotriptan, which on in-situ treatment with suitable acid in a suitable solvent provides corresponding almotriptan acid addition salt compound of formula-1,

c) optionally purifying the obtained almotriptan acid addition salt compound of formula-1,

d) treating the above pure almotriptan acid addition salt compound of formula-1 with a suitable base in a suitable solvent to provide almotriptan, which on in-situ treatment with malic acid in a suitable solvent provides almotriptan malate compound of formula-1a.

The sixth aspect of the present invention is to provide an improved process for the preparation of almotriptan malate compound of formula-1a, which comprises of the following steps;

a) treating the alkali metal salt of 4-chloro-1-hydroxybutane-1-sulfonate compound of formula-6 with a suitable aqueous base, and then extracting the obtained 4-chlorobutyraldehyde into a suitable solvent, which on in-situ reaction with 1-(4-hydrazinylbenzyl sulfonyl)pyrrolidine compound of formula-3 or its salts thereof in presence of disodium phosphate in a suitable solvent provides 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound formula-5,

b) reacting the 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound formula-5 with formalin in presence of sodiumborohydride in aqueous sodium hydroxide, in a suitable solvent to provide almotriptan, which on in-situ

treatment with suitable acid in a suitable solvent provides corresponding almotriptan acid addition salt compound of formula-1,

c) optionally purifying the obtained almotriptan acid addition salt compound of formula-1,

d) treating the above pure almotriptan acid addition salt compound of formula-1 with suitable base in a suitable solvent to provide almotriptan, which on in-situ treatment with malic acid in a suitable solvent provides almotriptan malate compound of formula-1a.

The seventh aspect of the present invention is to provide novel crystalline forms of almotriptan succinate. The crystalline forms of the present invention are characterized by its PXRD, IR spectrum and DSC thermogram.

The eighth aspect of the present invention is to provide a novel crystalline form of almotriptan oxalate. The crystalline form of the present invention is characterized by its PXRD, IR spectrum and DSC thermogram.

Brief Description of the Drawings:

Figure-1: Illustrates the PXRD of crystalline compound of formula-2a

Figure-2: Illustrates the PXRD of crystalline form-1 of almotriptan succinate

Figure-3: Illustrates the PXRD of crystalline form-2 of almotriptan succinate

Figure-4: Illustrates the PXRD of crystalline form-M of almotriptan oxalate

Figure-5: Illustrates the PXRD of crystalline almotriptan malate prepared as per the present invention.

Detailed Description of the Invention:

Unless otherwise specified, as used herein the term "suitable solvent" refers to the solvents selected from "alcoholic solvent" such as methanol, ethanol, n-propanol, isopropnol, n-butanol and isobutanol; "chloro solvent" such as to methylene chloride, chloroform and ethylene dichloride; "ketone solvent" such as acetone, methyl ethyl ketone, methyl isobutyl ketone; "hydrocarbon solvent" such as to toluene, hexane, heptane and cyclohexane; "nitrile solvent" such as acetonitrile; "ester solvent" such as ethyl acetate, methyl acetate and isopropyl acetate; "ether solvent" such as tetrahydrofuran, diethyl ether and methyl tert-butyl ether; "polar solvent" such as water.

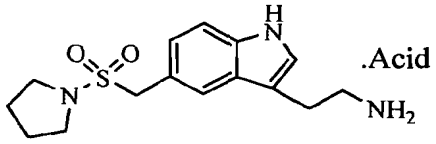
As used herein the term "suitable base" refers to the bases selected from alkali metal hydroxide like sodium hydroxide, potassium hydroxide; alkali metal carbonate like sodium carbonate, potassium carbonate and bicarbonates like sodium bicarbonate, potassium bicarbonate; ammonia or their aqueous solution.

The term "protected 4-chlrobutyraldehyde" refers to a derivative of 4-chlorobutyraldehyde in which the aldehyde group is protected by converting it into an acetal or an adduct.

As used herein the term "source of 4-chlorobutyraldehyde" refers to alkali metal adduct of 4-chlorobutyraldehyde, acetal protected 4-chlorobutyraldehyde or its free form.

The present invention relates to novel salts of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of general formula-2 and their use in the preparation of highly pure almotriptan compound of formula-1.

Accordingly the first aspect of the present invention provides novel salts of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compounds of general formula-2



Formula-2

wherein "Acid" is an acid group which is capable of forming acid addition salt with 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of formula-5 and is selected from group comprising of oxalic acid, succinic acid, fumaric acid, malonic acid, malic acid, maleic acid, d-tartaric acid, l-tartaric acid, dl-tartaric acid, citric acid, methanesulfonic acid, paratoluene sulfonic acid, acetic acid, sulfuric acid, phosphoric acid or hydrobromic acid and hydrochloric acid.

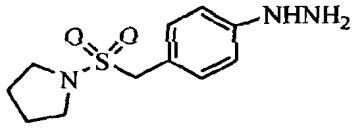
The novel salts of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of general formula-2 of the present invention is highly stable and having high purity when compared to the free base obtained as per the prior art. It also used to prepare pure 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-

yl)ethanamine free base, almotriptan and its pharmaceutically acceptable salts thereof. The 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound prepared from above novel salts having purity greater than 97 % by HPLC, preferably >98.5% and more preferably >99% by HPLC.

The present invention also provides a process for the preparation of novel salts compound of general formula-2, which comprises of treating the 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine with a suitable acid as defined above. in a suitable solvent selected from alcohol solvents, ester solvents, hydrocarbon solvent, ketone solvents, nitrile solvents, chloro solvents or mixtures thereof, to provide the corresponding salt compound of general formula-2.

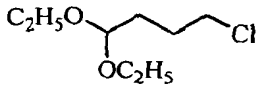
The second aspect of the present invention provides a process for the preparation of highly pure almotriptan malate compound of formula-1a through novel salts compound of general formula-2, which comprises of the following steps;

a) reacting the 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine compound of formula-3 or its salts thereof, preferably hydrochloride



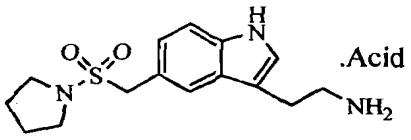
Formula-3

with 4-chloro butyraldehyde diethyl acetal compound of formula-4 or a source of 4-chlorobutyraldehyde,



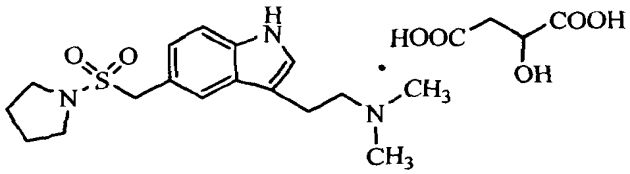
Formula-4

in presence of disodium hydrogenphosphate and a suitable acid in a suitable solvent followed by treating the obtained product with suitable acid in a suitable polar solvent to provide the corresponding acid addition salt of 2-(5-((pyrrolidin-1-yl-sulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of general formula-2



Formula-2

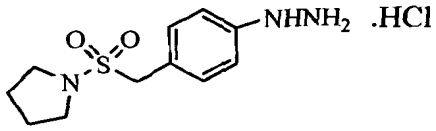
b) treating the salt compounds of general formula-2 with a suitable base in a suitable solvent to provide 2-(5-((pyrrolidin-1-yl-sulfonyl)methyl)-1H-indol-3-yl)ethanamine, which on in-situ reaction with formalin in presence of sodiumborohydride in aqueous sodium hydroxide, in a suitable solvent provides almotriptan, which is followed by in-situ treatment with malic acid in a suitable solvent to provide almotriptan malate compound of formula-1a,



Formula-1a

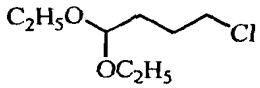
In a preferred embodiment, improved process for the preparation of highly pure almotriptan malate compound of formula-1a comprises of the following steps;

a) reacting the 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine hydrochloride compound of formula-3a



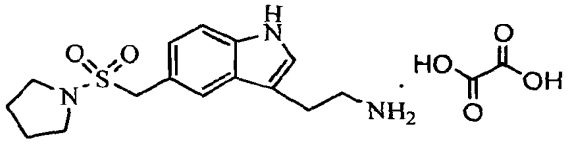
Formula-3a

with 4-chloro butyraldehyde diethyl acetal compound of formula-4



Formula-4

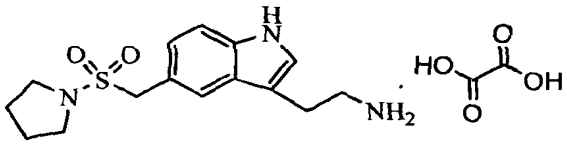
in presence of disodium hydrogen phosphate, aqueous hydrochloric acid in methanol provides 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine, which on-insitu treatment with oxalic acid in water provides the 2-(5-((pyrrolidin-1-yl-sulfonyl)methyl)-1H-indol-3-yl)ethanamine oxalate compound of formula-2a



Formula-2a

b) treating the oxalate salt compound of formula-2a with aqueous ammonia and extracting the obtained 2-(5-((pyrrolidin-1-yl-sulfonyl)methyl)-1H-indol-3-yl)ethanamine into methylene chloride, which on in-situ reaction with formalin in presence of sodium borohydride in aqueous sodium hydroxide, in methanol provides almotriptan, followed by treating it in-situ with malic acid in methanol provides almotriptan malate compound of formula-1a.

The third aspect of the present invention provides a novel crystalline form of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine oxalate salt represented by the following structural formula



The novel crystalline oxalate salt of the present invention is characterized by its powder X-ray diffractogram having peaks at about 7.97, 14.06, 16.52, 16.85, 17.28, 18.26, 19.45, 19.94, 21.16, 22.74, 24.52, 25.13, 26.29, 30.08, 33.41, 36.28 and 39.91 ± 0.2 degrees 2θ. The novel crystalline form of the present invention is used to prepare highly pure almotriptan or its pharmaceutically acceptable salts.

The fourth aspect of the present invention provides a process for the purification of almotriptan malate compound of formula-1a, which comprises of treating the almotritpan malate with a suitable base selected from alkali metal hydroxides like sodium hydroxide, potassium hydroxide; alkali metal carbonates like sodium carbonate, potassium carbonate and bicarbonates like sodium bicarbonate, potassium bicarbonate; ammonia or their aqueous solution, in a suitable solvent selected from ester solvents, hydrocarbon solvent, chloro solvents or mixtures thereof, to provide almotriptan, which on in-situ treatment with malic acid in a suitable solvent selected from alcohols, ketones,

nitrile or polar solvents or mixtures thereof, to provide highly pure almotriptan malate compound of formula-1a.

A process for the purification of almotriptan malate compound of formula-1a is provided to reduce the amount of impurities particularly amino indole impurity and monomethyl impurity present in it to the level of 0.5-1% by HPLC along with other impurities to the concentration of around 0.05% to levels of non detection. The said purification process comprises of the following steps;

a) Treating the almotritpan malate with a suitable base in a suitable solvent selected from ester solvents, hydrocarbon solvents and chloro solvents,
b) separating the organic and aqueous layers,
c) distilling off the solvent from organic layer under reduced pressure,
d) dissolving the obtained residue in suitable solvent or mixtures thereof at reflux temperature,
e) subjecting the reaction mixture to carbon treatment,
f) filtering the reaction mixture through hyflow,
g) adding malic acid or its solution in a suitable solvent to the filtrate at 35-80°C and stirring,
h) cooling the reaction mixture to 25-30°C and stirring
i) filtering the solid and washing with a suitable solvent,
j) drying the solid to get the highly pure almotriptan malate.

In a preferred embodiment, process for the purification of almotriptan malate compound of formula-1a comprises of the following steps,

a) treating the almotritpan malate in ethylacetate with aqueous ammonia,
b) separating the organic and aqueous layers,
c) distilling off the ethylacetate from organic layer under reduced pressure,
d) dissolving the obtained residue in a mixture of isopropylalochol and methanol at reflux temperature,
e) subjecting the reaction mixture to carbon treatement,
f) filtering the reaction mixture through hyflo,

g) adding malic acid solution in a mixture of isopropyl alcohol and methanol to the filtrate,

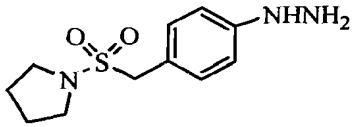
h) cooling the reaction mixture and stirring

i) filtering the solid and washing with a mixture of isopropyl alcohol and methanol,

j) drying the solid to get the highly pure almotriptan malate.

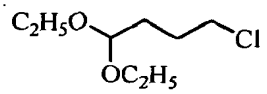
The almotriptan malate prepared as per the prior art processes containing residual solvents like methanol and ethanol in high levels than the required levels set by ICH. The same problem has been rectified by the present inventors by adding malic acid to the almotriptan free base in a mixture of isopropyl alcohol and methanol in the ratio of 1:6 to 9:4 at reflux temperature, which controls the residual solvent well below the limits of solvents set by ICH.

The fifth aspect of the present invention provides an improved process for the preparation of almotriptan malate compound of formula-1a, which comprises of treating the 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine compound of formula-3 or its salts thereof



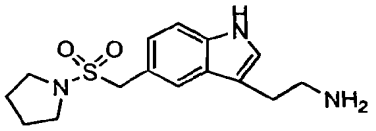
Formula-3

preferably hydrochloride salt of the compound of formula-3, with protected 4-chlrobutyralehyde derivative, 4-chloro-1,1-diethoxybutane compound of formula-4



Formula-4

in presence of a disodium hydrogen phosphate in a suitable solvent selected from alcoholic solvents, ether solvents, chloro solvents, water or mixtures thereof, preferably aqueous alcohols, to provide 2-(5-((pyrrolidin-1-yl-sulfonyl)methyl)-1H-indol-3-yl)ethanamine compound formula-5,



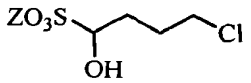
Formula-5

Reacting the 2-(5-((pyrrolidin-1-yl-sulfonyl)methyl)-1H-indol-3-yl)ethanamine compound formula-5 with formalin in presence of sodiumborohydride in aqueous sodium hydroxide, in a suitable alcoholic solvent to provide almotriptan, which on in-situ treatment with suitable acid like succinic acid or oxalic acid in a suitable solvent selected from alcohol solvents, ester solvents, hydrocarbon solvents, ketone solvents, nitrile solvents, chloro solvents or mixtures thereof, provides corresponding almotriptan acid addition salt compound of formula-1,

Optionally purifying the obtained almotriptan acid addition salt compound of formula-1 using a suitable solvent selected from alcoholic solvents, ester solvents, hydrocarbon solvents, ketone solvents, nitrile solvents, chloro solvents, water or mixtures thereof to provide high pure almotriptan acid addition salt compound of formula-1.

The pure almotriptan acid addition salt compound of formula-1 is treated with a suitable base selected from alkali metal hydroxides like sodium hydroxide, potassium hydroxide; alkali metal carbonate like sodium carbonates, potassium carbonate and bicarbonates like sodium bicarbonate, potassium bicarbonate; ammonia or their aqueous solution, in a suitable solvent selected from alcohol solvents, ester solvents, hydrocarbon solvents, ketone solvents, nitrile solvents or mixtures thereof, to provide almotriptan which on in-situ treatment with malic acid in a suitable solvent described above to provide almotriptan malate compound of formula-1a.

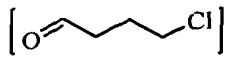
The sixth aspect of the present invention provides an improved process for the preparation of almotriptan malate compound of formula-1a, which comprises of treating the alkali metal salt compound of 4-chloro-1-hydroxybutane-1-sulfonate compound of formula-6, preferably sodium or potassium salt of 4-chloro-1-hydroxybutane sulfonate,



Formula-6

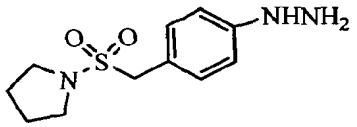
Wherein Z is Na or K ion,

with a suitable aqueous base selected from sodium carbonate or potassium carbonate, followed by extraction of the obtained 4-chlorobutaraladhyde compound of formula-7 into a suitable chloro solvent,



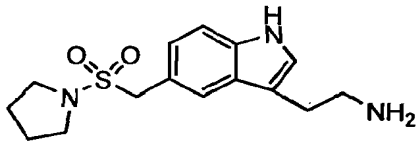
Formula-7

which on in-situ treatment with 1-(4-hydrazinyl benyzlsulfonyl)pyrrolidine compound of formula-3 or its salts thereof,



Formula-3

preferably hydrochloride salt of compound of formula-3, in presence of disodium hydrogen phosphate in a suitable solvent selected from alcoholic solvents, ether solvents, chloro solvents, water or mixtures thereof, preferably aqueous alcohol provides 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound formula-5



Formula-5

Reacting the 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound formula-5 with formalin in presence of sodiumborohydride in aqueous sodium hydroxide in a suitable alcoholic solvent to provide almotriptan, which on in-situ treatment with suitable acid like succinic acid or oxalic acid in a suitable solvent selected from alcohol solvents, ester solvents, hydrocarbon solvents, ketone solvents, nitrile solvents, chloro solvents or mixtures thereof, provides corresponding almotriptan acid addition salt compound of formula-1,

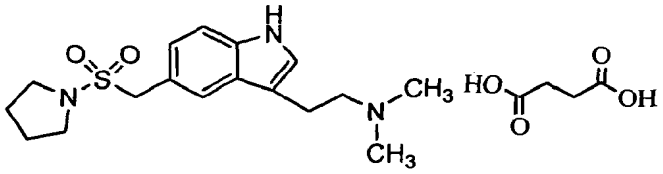
Optionally purifying the obtained almotriptan acid addition salt compound of formula-1 using a suitable solvent selected from alcoholic solvents, ester solvents, hydrocarbon solvent, ketone solvents, nitrile solvents, chloro solvents, water or mixtures thereof to provide high pure almotriptan acid addition salt compound of formula-1.

The pure almotriptan acid addition salt compound of formula-1 is treating with a suitable base selected from alkali metal hydroxide like sodium hydroxide, potassium hydroxide, alkali metal carbonate like sodium carbonate, potassium carbonate and bicarbonates like sodium bicarbonate, potassium bicarbonate; ammonia or their aqueous solution, in a suitable solvent selected from alcohol solvents, ester solvents, hydrocarbon

solvents, ketone solvents, nitrile solvents or mixtures thereof to provide almotriptan, which on in-situ treatment with malic acid in a suitable solvent described above provides almotriptan malate compound of formula-1a.

The almotriptan malate can be further purified by recrystallisation from a suitable solvent selected from alcoholic solvents, ketone solvents, ester solvents or mixtures thereof to get high pure almotriptan malate.

The seventh aspect of the present invention provides a novel crystalline form of almotriptan succinate compound of formula-1b having the following structure.



Formula-1b

The crystalline almotriptan succinate compound of formula-1b of the present invention is characterized by its powder X-ray diffractogram having 2θ peaks at about 9.2, 14.7, 16.1, 16.9, 18.0, 18.7, 20.3, 21.8, 22.9, 23.4, 24.7, 26.0, 29.8, 35.0 and 41.3 ± degrees 2θ. This novel crystalline form of the presence invention is herein designated as "form-1". The crystalline form-1 is also characterized by its IR spectrum having peaks at 3373.62, 2981.26, 2887.95, 2397.10, 1708.66, 1563.89, 1463.94, 1411.65, 1373.46, 1358.76, 1322.83, 1322.83, 1202.40, 1122.84, 1015.63, 829.03, 804.79 and 656.64 cm^{-1} and also characterized by its DSC thermogram showing endothermic peak at 178.14°C.

The present invention further provides a process for the preparation of crystalline form-1 of almotriptan succinate compound of formula-1b, which comprises of the following steps,

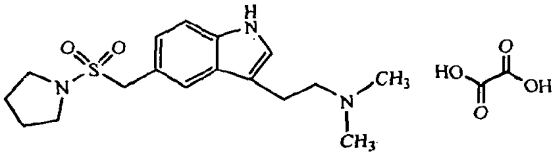
a) heating a mixture of almotriptan and succinic acid in a suitable solvent selected from alcoholic solvents, nitrile solvents, water or mixtures thereof to reflux,
b) stirring the reaction mixture for 45 minutes at reflux,
c) cooling the reaction mixture to 25-30°C and stirring the reaction further for 2 hours,
d) filtering the solid, washing with suitable solvent,
e) drying the solid to get the crystalline form-1 of almotriptan succinate.

Further the present invention provides another novel crystalline almotriptan succinate compound of formula-1b characterized by its Powder X-ray diffractogram having 2θ peaks at about 6.7, 10.2, 12.2, 13.7, 14.5, 15.2, 15.8, 16.9, 17.4, 19.0, 19.9, 20.3, 21.2, 23.4, 24.4, 25.0, 26.5, 27.0, 28.5 and 32.9 ± degrees 2θ. This novel crystalline form of the present invention is herein designated as "form-2". The crystalline form-2 of the present invention is also characterized by its IR spectrum having peaks at 3424.20, 3218.62, 3198.16, 2976.28, 2918.84, 2478.49, 1711.46, 1559.15, 1486.01, 1398.27, 1342.21, 1320.92, 1236.06, 1218.29, 1175.83, 1133.61, 986.79, 959.54, 818.70, 754.90, 667.41 and 610.17 cm^{-1} and also characterized by its DSC thermo gram showing endothermic peak at 169.96°C.

The present invention further provides a process for the preparation of crystalline form-2 of almotriptan succinate compound of formula-1b, which comprises of the following steps,

a) heating a mixture of almotriptan and succinic acid in a suitable solvent selected from ester solvents; ketone solvents, hydrocarbon solvents, alcoholic solvents, water or mixtures thereof to reflux,
b) stirring the reaction mixture for 45 minutes at reflux,
c) cooling the reaction mixture to 25-30°C and stirring the reaction mixture further for 2 hours,
d) filtering the solid, washing with suitable solvent,
e) drying the solid to get the crystalline form-2 of almotriptan succinate.

The eighth aspect of the present invention is to provide crystalline form of almotriptan oxalate compound of formula-1c having the following structure.



Formula-1c

The novel crystalline form almotriptan oxalate of the present invention is characterized by its powder X-ray diffractogram having 2θ peaks at about 6.5, 11.7, 12.9, 14.6, 15.9, 17.8, 18.4, 19.9, 20.3, 20.7, 21.9, 25.5, 26.6, 36.0 and 39.7 ± degrees 2θ. This

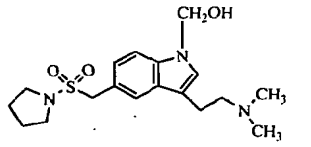
crystalline form of the presence invention is herein designated as crystalline "form-M". The crystalline form-M of the present invention is also characterized by its IR spectrum 3418.28, 3298.26, 2927.01, 2683.12, 2512.94, 1731.28, 1631.54, 1483.10, 1434.19, 1310.03, 1196.21, 1011.26, 963.96, 805.23, 710.27 and 643.84 cm^{-1} and by its DSC thermo gram showing endothermic peaks at 208.30°C and 227.33°C.

The novel crystalline form-M of almotriptan oxalate is prepared by heating a mixture of almotriptan and oxalic acid in a suitable alcoholic solvent to reflux temperature and then cooling the reaction mixture to 25-30°C followed by stirring the reaction mixture for 2 hours, then the obtained solid was filtered, washed with alcoholic solvent and dried to get the crystalline form-M of almotriptan oxalate.

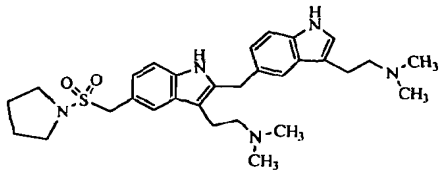
The novel crystalline form-1, form-2 of almotriptan succinate compound of formula-1b and novel crystalline form-M of almotriptan oxalate compound of formula-1c were used to prepare high pure almotriptan and its pharmaceutically acceptable salts especially malate salt.

As used herein the term "highly pure" refers to the compound with purity greater than 98 % by HPLC, preferably greater than 99 % by HPLC and more preferably greater than 99.50% by HPLC.

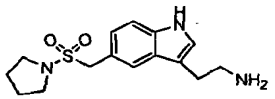
The following impurities are the possible impurities which are formed during the process for the preparation of almotriptan and its pharmaceutically acceptable salts.



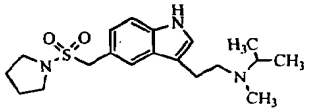
N-Hydroxymethyl impurity



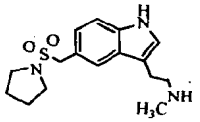
Dimer impurity



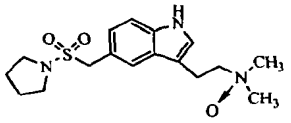
Aminoindole impurity



N-Isopropyl impurity



Monomethyl impurity



N-Oxide impurity

One of the major focus of the invention was to control the impurities formed in the process to as minimum levels as possible in the final pharma. This is ensure by purification process involving the conversion of almotriptan malate into free base by treating it with base followed by extracting it with a suitable solvent and then subsequently subjecting it to carbon treatment and treating it with malic acid to convert it into almotriptan malate with high purity. The major impurities formed in substantial quantities were the amino indole impurity and mono methyl impurity which were purified from the levels of 0.5 to 1% each to the level of non-detection and 0.02% respectively. All the above impurities are well controlled in the process to the levels of 2.0% which were reduced to the levels of 0.2% after purification. The each individual impurities are reduced to the levels of 0.1%, preferably to the level of 0.05% by the purification method.

Almotriptan or its pharmaceutically acceptable salts can be further micronized or milled to get the desired particle size. Almotriptan malate particles prepared as per the present invention having D_{90} particles in the range of 40 to 200 microns and mean particle size is in the range of 15 to 70 microns.

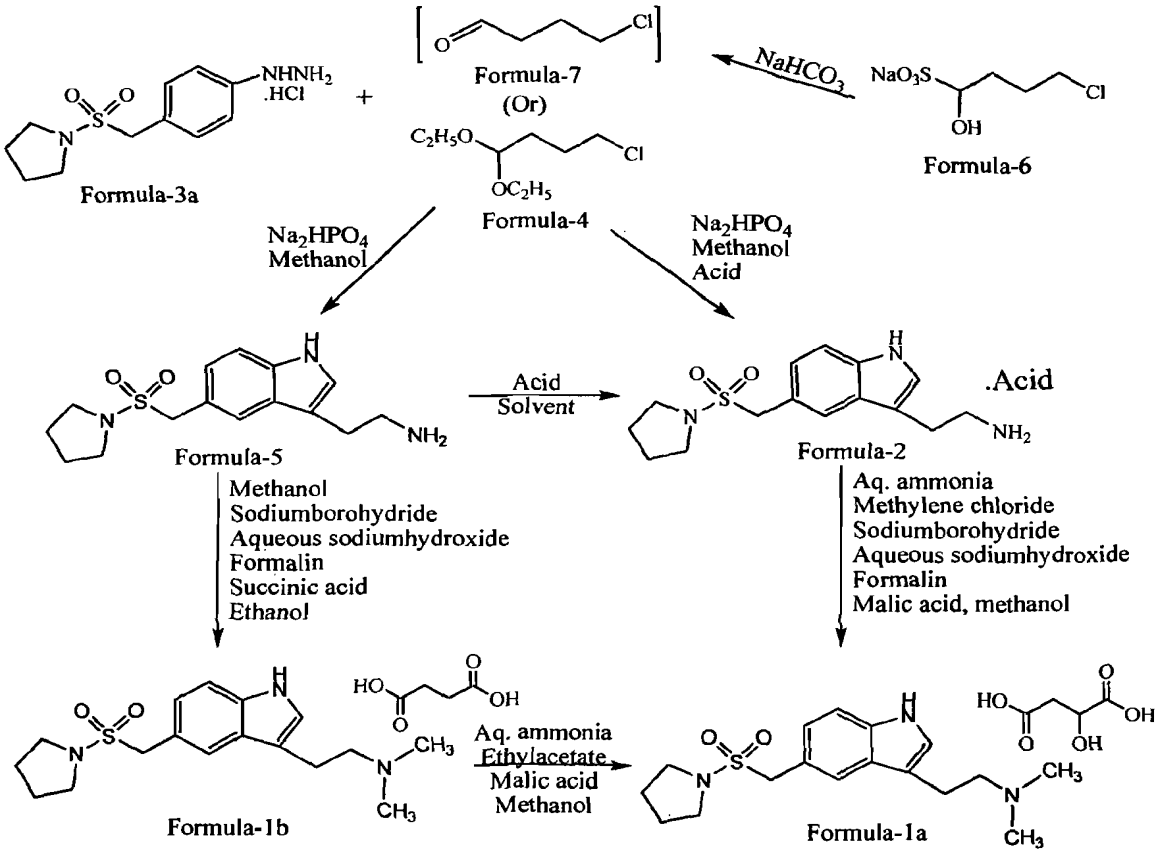
XRD analysis of pharmaceutically acceptable salts of almotriptan were carried out using SIEMENS/D-5000 X-Ray diffractometer using Cu, Ka radiation of wavelength 1.54 A° and continuous scan speed of 0.045°/min. FT-IR spectrum of pharmaceutically acceptable salts of almotriptan was recorded on Thermo model Nicolet-380 as KBr pellet. The thermal analysis of pharmaceutically acceptable salts of almotriptan was carried out on Waters DSC Q-10 model differential scanning calorimeter.

The related substance of pharmaceutically acceptable salts of almotriptan was analyzed by HPLC using the following conditions: Column: X-terra, 259 x 4.6 mm, 5.0 µm ; Flow rate: 1.0 ml/min; wavelength: 227 nm ; Temperature: 40°C; Load: 10 µl; Run time: 50 min; and using monobasic sodium phosphate in water and methanol as diluents.

The related substance of almotriptan malate and salts of 2(5-(pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine were were analyzed by HPLC using the following conditions: Column: Symmetry C18 250 x 4.6 mm, 5.0 µm ; Flow rate: 1.6

ml/min; wavelength: 228 nm ; Temperature: 35°C; Load: 20 µl; Run time:50 min; Elution: gradient; and using mixture of buffer and acetonitirle as a diluent and mobile phase. The buffer is prepared by a mixture of triethylamine and water.

The present invention is represented by the following schematic representation



The process described in the present invention was demonstrated in examples illustrated below. These examples are provided as illustration only and therefore should not be construed as limitation of the scope of the invention.

Examples:

Example-1: Preparation of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine oxalate compound of formula-2a:

A mixture of 4-chlorobutaraldehyde diethyl acetal (120 grams), hydrochloric acid (48 ml) and water (1050 ml) was stirred at 20-25°C. This mixture was added to a mixture of 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine hydrochloride (150 grams), water (450 ml) and methanol (1.2 l) at 10-15°C and stirred. The solid obtained was filtered and washed with water. Methanol followed by disodium hydrogen phosphate solution ((73 grams in 600 ml of water) was added to the solid and the acidified the reaction mixture with aqueous hydrochloric acid. The reaction mixture was heated to reflux and stirred at reflux. After completion of the reaction, methanol was distilled off completely under reduced pressure. The residue was cooled, water (1.5 L) and methylene chloride (450 ml) was added to it and basified with sodium carbonate solution. The aqueous layer was separated and expelled with nitrogen. Oxalic acid (51.8 grams) was added to it and stirred at 25-30°C. The reaction mixture was cooled to 5-10°C and stirred. The obtained solid was filtered, washed with water and dried to get the title compound. The PXRD of crystalline form of the obtained oxalate salt is represented in figure-1.

Yield: 95 grams

M.R: 128-133°C; Purity by HPLC: 98.95%

Example-2: Preparation of almotriptan malate of formula-1a:

A mixture of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine oxalate compound of formula-2a (50 grams), water (500 ml) and methylene chloride (250 ml) was stirred and basified with aqueous ammonia then stirred. The organic layer was separated and solvent from it distilled off completely under reduced pressure. The residue was dissolved in methanol (770 ml) and cooled to 5-15°C. Sodiumborohydride (24 grams) in aqueous sodium hydroxide (0.77 grams in 335 ml of water) and formalin solution (161.4 ml) in methanol (161.4 ml) was added to the reaction mixture lotwise at 5-15°C and stirred. After completion of the reaction, quenched it with aqueous

hydrochloric acid and stirred. The reaction mixture was basified with sodium bicarbonate solution and methanol was distilled off completely under reduced pressure. The reaction mixture washed with ethylacetate and then basified with potassium carbonate. The reaction mixture extracted into ethylacetate and then washed with sodium chloride solution and then ethylacetate was distilled off completely under pressure. Methanol was added to the obtained residue followed by malic acid (17.9 grams) and stirred for 45 minutes. The reaction mixture was heated to reflux and stirred. The reaction mixture was cooled to 0-5°C and stirred for an hour. The solid obtained was filtered and washed with methanol. The obtained wet solid was recrystallized from methanol to get the title compound.

Yield: 32 grams

Purity by HPLC: 99.02%; 0.06% (amino indole impurity); 0.13 % (monomethylimpurity)

Example-3: Purification of almotriptan malate of formula-1a:

Almotriptan malate (having purity of 98.57% and containing 0.59% of aminoindole impuriy & 0.40% of monomethylimpurity) (100 grams) was dissolved in water (1L), and then added ethyl acetate (600 ml) and basified the reaction mixture with aqueous ammonia. The reaction mixture was stirred for 30 minute at 25-30°C and the ethyl acetate layer was separated. Aqueous layer was extracted with ethyl acetate and then total ethyl acetate layer was distilled off completely under reduced pressure at a temperature below 60°C. The residue was dissolved in methanol (200 ml) and subjected to carbon treatment, then filtered through hyflow. Malic acid (37.2 grams) was added to the filtrate and heated to reflux temperature then stirred for 30 minutes at reflux. The reaction mixture was cooled to 25-30°C and stirred for 2 hours. Filtered the solid, washed with methanol and dried to get the pure title compound.

Yield: 77 grams

Purity by HPLC: 99.84%; 0.02% (amino indole impurity); 0.06% (monomethylimpurity)

Particle Size Distribution: D(0.1): 5.41 μm ; D(0.5): 4.59 μm ; D(0.9):128.61 μm ; D(1.00): 275.38 μm;

Example-4: Purification of almotriptan malate of formula-1a:

Almotriptan malate (having purity of 98.39% and containing 0.20% of aminoindole impurity & 0.60% of monomethyl impurity) (55 grams) was dissolved in water (550 ml), added ethyl acetate (330 ml) and basified the reaction mixture with aqueous ammonia. The reaction mixture was stirred for 30 minute at 25-30°C and the ethyl acetate layer was separated. Aqueous layer was extracted with ethyl acetate and then total ethyl acetate layer was distilled off under reduced pressure at below 60°C. The residue was dissolved in a mixture of isopropylalcohol and methanol in the ratio of 6:4 (55 ml) and subjected to carbon treatment, then filtered through hyflow. Malic acid (9 grams) in a mixture of IPA:MeOH (220 ml) was added and heated to reflux temperature then stirred for 30 minutes at reflux. The reaction mixture was cooled to 25-30°C and stirred for 2 hours. Filtered the solid, washed with a mixture of isopropylalcohol and methanol and dried to get the pure title compound.

Yield: 49 grams: RS/OVI: Methanol: 2865 ppm

Purity by HPLC: 99.87%; 0.01% (amino indole impurity); 0.04% (monomethylimpurity)

Particle Size Distribution: D(0.1):4.25 μm ; D(0.5): 34.85 μm ; D(0.9): 115.61 μm ; D(1.00): 235.14 μm.

Example-5: Preparation of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine crude:

A mixture of 4-chlorobutaraldehyde diethyl acetal (120 grams), hydrochloric acid (48 ml) and water (1050 ml) was stirred at 20-25°C. This mixture was added to a mixture of 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine hydrochloride (150 grams), water (450 ml) and methanol (1.2 l) at 10-15°C and stirred. The solid obtained was filtered and washed with water. Methanol followed by disodium hydrogen phosphate solution (73 grams in 600 ml of water) was added to the solid and the acidified the reaction mixture with aqueous hydrochloric acid. The reaction mixture was heated to reflux and stirred. After completion of the reaction, methanol was distilled off completely under reduced pressure. The residue was cooled, water (1.5 L) and methylene chloride (450 ml) was added to it and basified with sodium carbonate solution. The aqueous layer was separated, basified it with sodium carbonate and then product extracted into methylene chloride. The

methylene chloride layer was dried over sodium sulphate and distilled off completely under reduced pressure to get the title compound.
Yield: 90 grams

Example-6: Preparation of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine succinate:

A mixture of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine crude prepared as per example-5 (2 grams) and ethanol (10 ml) was heated to 50-55°C and stirred. Succinic acid (0.77 grams) was added to the reaction mixture and stirred for an hour at 50-55°C. The reaction mixture was cooled to 25-30°C and stirred. The obtained solid was filtered, washed with ethanol and then dried to get the title compound.
Yield: 2.2 grams
M.R: 163-167°C; Purity by HPLC: 99.10%

Example-7: Preparation of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine malate:

A mixture of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine crude prepared as per example-5 (2 grams) and ethanol (10 ml) was heated to 50-55°C and stirred. Malic acid (0.9 grams) was added to the reaction mixture and stirred for an hour at 50-55°C. The reaction mixture was cooled to 25-30°C and stirred. The obtained solid was filtered, washed with ethanol and then dried to get the title compound.
Yield: 1.9 grams
M.R: 167-171°C; Purity by HPLC: 98.87%

Example-8: Preparation of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine tartarate:

A mixture of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine crude prepared as per example-5 (2 grams) and ethanol (10 ml) was heated to 50-55°C and stirred. Tartaric acid (0.97 grams) was added to the reaction mixture and stirred for an hour at 50-55°C. The reaction mixture was cooled to 25-30°C and stirred. The obtained solid was filtered, washed with ethanol and then dried to get the title compound.
Yield: 2.3 grams;
M.R: 156-158°C; Purity by HPLC: 98.10%

Example-9: Preparation of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine fumarate:

A mixture of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine crude prepared as per example-5 (2 grams) and ethanol (10 ml) was heated to 50-55°C and stirred. Fumaric acid (0.76 grams) was added to the reaction mixture and stirred for an hour at 50-55°C. The reaction mixture was cooled to 25-30°C and stirred. The obtained solid was filtered, washed with ethanol and then dried to get the title compound.
Yield: 1.5 grams
M.R: 189-191°C; Purity by HPLC: 98.17%

Example-10: Preparation of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine compound of formula-4:

A mixture of 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine hydrochloride (35.0 grams), hydrochloric acid (6.6 ml) and water (330 ml) was stirred for an hour at 25-30°C. In another vessel a mixture of 4-chloro-1,1-diethoxybutane (27.2 grams), hydrochloric acid (12.5 ml), water (82 ml) and methanol (375 ml) was stirred for an hour at 25-30°C and then added this mixture to the mixture containing 1-(4-hydrazinylbenzylsulfonyl) pyrrolidine. The reaction mixture was cooled to 0-5°C and stirred for an hour. The solid obtained was filtered and washed with aqueous methanol. Water (90 ml), disodium hydrogen phosphate (15 grams), methanol (560 ml) and hydrochloric acid (30 grams) was added to the obtained wet solid, heated the reaction mixture to reflux and stirred at reflux for 12 hours. The methanol was distilled off from the reaction mixture and water (375ml) was added to it. The reaction mixture was neutralized with sodium carbonate, washed with methylene chloride, saturated with sodium carbonate and then extracted into methylene chloride. The methylene chloride from the reaction mixture was distilled off under reduced pressure. Thus obtained residue isolated using diisopropyl ether.
Yield: 30 grams

Example-11: Preparation of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine compound of formula-4:

A mixture of 4-chloro-1,1-diethoxybutane (4.6 grams), hydrochloric acid (0.95 ml) and water (47.5 ml) was stirred for an hour at 20-25°C. Methanol (52.5 ml) was

added to 1-(4-hydrazinylbenzylsulfonyl) pyrrolidine hydrochloride (5 grams) in water (15 ml) and the reaction mixture was acidified with hydrochloric acid at 10-15°C and to this 4-chlorobutyraldehyde layer was added and stirred for 3 hours at 10-15°C. The reaction mixture was cooled to 10-15°C and stirred for 2 hours. The obtained solid was filtered and washed with water. The solid was dissolved in methanol and aqueous disodium hydrogen phosphate (2.67 grams in 18 ml of water) at 10-15°C and reaction mixture was acidified with hydrochloric acid. The reaction mixture was heated to reflux and stirred at reflux for 10 hours. The methanol was distilled off completely under reduced pressure then water (15 ml) was added to it. The reaction mixture was washed with methylene chloride. The reaction mixture was basified with sodium carbonate and the reaction mixture was extracted into methylene chloride. The methylene chloride was distilled off under reduced pressure to give the title compound.

Yield: 2.5 grams

Example-12: Preparation of almotriptan succinate compound of formula-1b:

A solution of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine compound of formula-4 (15 grams) in methanol (300 ml) was cooled to 0-10°C. Sodium borohydride (9.28 grams) in aqueous sodium hydroxide (0.3 gram in 130 ml water) and formalin solution (63 ml in 64 ml of methanol) was added to the above reaction mixture slowly at 5-15°C and then stirred for an hour. The reaction mixture was quenched with aqueous hydrochloric acid and stirred for 20 minutes at 25-30°C. The pH of the reaction mixture was adjusted to 6.5 with aqueous acetic acid. The methanol from the reaction mixture was distilled off under reduced pressure and then reaction mixture washed with ethyl acetate. Potassium carbonate (75 grams) was added to the reaction mixture, stirred for 35 minutes at 25-35°C and then the reaction mixture extracted into ethyl acetate. Succinic acid (5.7 grams) was added to the ethyl acetate layer and stirred for 15 hours 25-35°C. The solid was filtered, washed with ethanol. Isopropyl alcohol (12 ml) was added to the wet solid and heated to reflux then stirred for an hour at reflux. The reaction mixture was cooled slowly to 25-30°C in 90 minutes. The solid obtained was filtered, washed with isopropyl alcohol and then dried to get the title compound.

Yield: 18 grams

Purity by HPLC: 97.81 %

Example-13: Preparation of almotriptan malate compound of formula-1a:

Ethyl acetate (15 ml) was added to a solution of almotriptan succinate (2.3 grams in 23 ml of water) and stirred for 15 minutes. The reaction mixture was basified with ammonia and stirred for 30 minutes at 25-30°C. The layers were separated, aqueous layer extracted with ethyl acetate and organic layer washed with water. The solvent from the organic layer was distilled off under reduced pressure. Methanol was added to the residue and then distilled off the methanol. The residue was dissolved in methanol and subjected to carbon treatment and then filtered through hyflow and the bed was washed with methanol. Malic acid solution (0.8 gram in 2 ml methanol) was added to the filtrate and then the reaction mixture was heated to reflux, stirred for an hour. The reaction mixture was cooled to 25-30°C and stirred for 2 hours. The solid obtained was filtered, washed with methanol and the dried to get the title compound.

Yield: 1.8 grams; Yield: 99.51 %

Example-14: Purification of almotriptan malate compound of formula-1a:

A mixture of almotriptan (1.7 grams) and methanol (10 ml) was heated to reflux and stirred for 1.5 hours. The reaction mixture was cooled to 25-30°C and stirred for 2 hours. The solid obtained was filtered, washed with methanol and dried to get the pure title compound.

Yield: 1.5 grams; Purity by HPLC: 99.95 %

Particle Size Distribution: D(0.1):3.51 μm ; D(0.5):17.01 μm ; D(0.9):91.60 μm ; D(1.00): 173.53 μm.

Example-15: Preparation of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine compound of formula-4:

Sodium carbonate (18 grams) was added to a solution of 4-chlorobutyraldehyde sodium bisulphate (54 grams in 750 ml of water), stirred for 30 minutes at 25-35°C and extracted the 4-chlorobutyraldehyde into methylene chloride (350 ml). 1-(4-hydrazinyl benzylsulfonyl) pyrrolidine hydrochloride (75 grams) was added to aqueous sodium bicarbonate (52 grams in 750 ml) and then the above extracted 4-chlorobutyraldehyde in methylene chloride was added to it. The reaction mixture was stirred for 1.5 hours at 25-30°C and then methylene chloride distilled off at 40-45°C. Hyflow was added to the

residue and stirred for 45 minutes at 25-30°C. The reaction mixture was filtered and extracted the filtrate with methylene chloride. The hyflow solid is slurried with methylene chloride. The extracted methylene chloride layer was dried with sodium sulphate and then distilled off methylene chloride under reduced pressure at below 40°C. The residue was dissolved in methanol then water (450 ml), disodium hydrogen phosphate (43 grams) and hydrochloric acid (20.3 ml) was added to it and heated to reflux temperature. The reaction mixture was stirred at reflux (65-70°C) for 12 hours and then distilled off the solvent under reduced pressure at below 60°C. Water (1200 ml) was added to the reaction mixture, washed with methylene chloride and sodium carbonate (450 grams) was added to it. The reaction mixture extracted into methylene chloride and distilled off the solvent from reaction mixture to get the title compound.
Yield: 23 grams.

Example-16: Preparation of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine compound of formula-4:

Hydrochloric acid (300 ml) was added to 4-((pyrrolidin-1-ylsulfonyl)methyl aniline (35 grams) was added and cooled to -10°C. Sodium nitrite solution (13.6 grams in 80 ml) was added to it and stirred for 1.5 hours at -10 to 0°C. The reaction mixture was added slowly to the cooled mixture of stannous chloride dihydrate (164.6 grams) and hydrochloric acid (120 ml) at -10 to 0°C and stirred for 1.5 hours. The obtained 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine hydrochloride was filtered off and washed with hydrochloric acid. 4-chloro-1,1-diethoxybutane (27.2 grams), hydrochloric acid (12.5 ml) and water (82 ml) was stirred for an hour at 25-30°C. In another vessel a previously obtained 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine hydrochloride (35 grams), hydrochloric acid (12.5 ml) and water (82 ml) was stirred for an hour at 25-30°C and to this mixture to the above 4-chlorobutyraldehyde layer was added and stirred for 2 hours. The reaction mixture was cooled to 0-5°C and stirred for an hour. The solid obtained was filtered, washed with aqueous methanol. Water (90 ml), disodium hydrogen phosphate (15 grams), methanol (560 ml) and hydrochloric acid (30 grams) was added to the obtained wet solid, heated the reaction mixture reflux and stirred at reflux for 12 hours. The methanol was distilled off from the reaction mixture and water was added to it. The reaction mixture was basified with sodium carbonate. The reaction mixture was washed

with methylene chloride, saturated with sodium carbonate and then extracted into methylene chloride. The methylene chloride from the reaction mixture was distilled off under reduced pressure to get the title compound.
Yield: 29 grams.

Example-17: Purification of almotriptan succinate compound of formula-1b:

Almotriptan succinate (3.2 grams) was dissolved in water (32 ml), added ethyl acetate (25 ml) and basified the reaction mixture with aqueous ammonia. The reaction mixture was stirred for 30 minute at 25-30°C and the ethyl acetate layer was separated. Aqueous layer was extracted with ethyl acetate and then total ethyl acetate layer was distilled off under reduced pressure at below 60°C. The residue was dissolved in ethanol (10 ml) and succinic acid (1.09 ml) was added and heated to reflux temperature then stirred for 60 minutes at reflux. The reaction mixture was cooled to 25-30°C and stirred for 2 hours. Filtered the solid, washed with ethanol and dried to get the pure title compound.
Yield: 2.1 grams; Purity by HPLC: 99.72 %

Example-18: Preparation of crystalline form-1 almotriptan succinate compound of formula-1b:

A mixture of almotriptan (3 grams) in ethanol (15 ml) and succinic acid (1.17 grams) was heated reflux and stirred for 45 minutes. The reaction mixture was cooled to 25-30°C and stirred for 2 hours at 25-35°C. Filter the solid, washed with ethanol and then dried to get the crystalline form-1 of almotriptan succinate:
Yield: 2.4 grams

Example-19: Preparation of crystalline form-1 almotriptan succinate compound of formula-1b:

A mixture of almotriptan (3 grams) and succinic acid (1.17 grams) in acetonitrile (15 ml) was heated to reflux and stirred for 45 minutes at reflux. The reaction mixture was cooled to 25-35°C and stirred for 2 hours at 25-35°C. Filter the solid, washed with acetonitrile and then dried to get the crystalline form-1 of almotriptan succinate:
Yield: 2.2 grams

Example-20: Preparation of crystalline form-2 almotriptan succinate compound of formula-1b:

A mixture of almotriptan (3 grams) and succinic acid (1.17 grams) in acetone (15 ml) was heated to reflux and stirred for 45 minutes at reflux. The reaction mixture was cooled to 25-35°C and stirred for 2 hours at 25-35°C. Filter the solid, washed with acetonitrile and then dried to get the crystalline form-2 of almotriptan succinate:
Yield: 2.6 grams

Example-21 & 22: Preparation of crystalline form-2 almotriptan succinate compound of formula-1b:

The crystalline form-2 of almotriptan succinate has been prepared analogues manner to example-11 using the appropriate solvent as shown in the following table in place of acetone.

Example No.	Solvent	Yield
21	IPA + Toluene	3.6 grams
22	Ethyl acetate	3.8 grams

Example-23: Preparation of crystalline form-M of almotriptan oxalate compound of formula-1c:

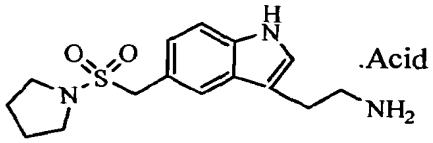
A mixture of almotriptan (5 grams) and oxalic acid (2 grams) in ethanol (25 ml) was heated to reflux and stirred for 45 minutes. The reaction mixture was cooled to 25-30°C and stirred for 2 hours at 25-35°C. Filter the solid, washed with ethanol and then dried to get the crystalline form-M of almotriptan oxalate.
Yield: 2.8 grams

Example-24: Preparation of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine of formula-5:

A mixture of 2(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl) ethanamine oxalate compound of formula-2a (25 grams), water (250 ml) and methylene chloride (125 ml) was stirred and basified with aqueous ammonia then stirred. The organic layer was separated and solvent from it distilled off completely under reduced pressure to get the title compound.
Yield: 17 grams; Purity by HPLC: 98.80%

We Claim:

1. Novel salts of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine represented by the following general formula-2

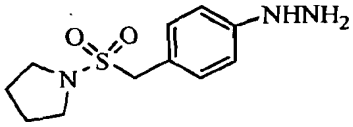


Formula-2

wherein "Acid" is an acid group which is capable of forming acid addition salt with 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine and is selected from oxalic acid, succinic acid, fumaric acid, malonic acid, malic acid, maleic acid, d-tartaric acid, l-tartaric acid, dl-tartaric acid, citric acid, methanesulfonic acid, paratoluene sulfonic acid, acetic acid, sulfuric acid, phosphoric acid, hydrobromic acid or hydrochloric acid.

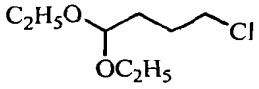
2. A process for the preparation of novel salts compound of general formula-2, which comprises of treating the 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine with a suitable acid as defined in claim 1 in a suitable solvent selected from alcohol solvents, ester solvents, hydrocarbon solvents, ketone solvents, nitrile solvents, chloro solvents or mixtures thereof.

3. A process for the preparation of novel salts compound of general formula-2, which comprises of reacting the 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine compound of formula-3 or its salts thereof, preferably hydrochloride salt,



Formula-3

with 4-chloro butyraldehyde diethyl acetal compound of formula-4 or a source of 4-chloro butyraldehyde

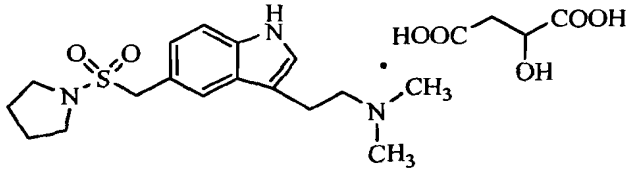


Formula-4

in presence of disodium hydrogen phosphate and acid in a suitable solvent followed by treating the obtained product with a suitable acid in a suitable solvent like alcohols or polar solvent or mixtures thereof, provides the corresponding acid addition salt of 2-(5-((pyrrolidin-1-yl-sulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of general formula-2

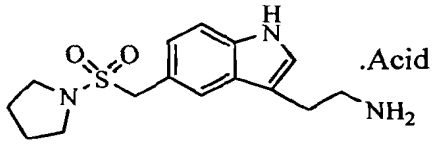
4. Use of novel salts of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compounds of general formula-2 as claimed in claim 1, in the preparation of highly pure 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine, almotriptan or its pharmaceutically acceptable salts.

5. A process for the preparation of highly pure almotriptan malate compound of formula-1a,



Formula-1a

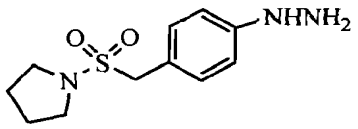
Which comprises of treating the acid addition salt of 2-(5-((pyrrolidin-1-yl-sulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of general formula-2



Formula-2

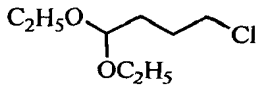
with a suitable base in a suitable solvent to provide 2-(5-((pyrrolidin-1-yl-sulfonyl)methyl)-1H-indol-3-yl)ethanamine, which on in-situ reaction with formalin in presence of sodiumborohydride in aqueous sodium hydroxide, in a suitable solvent provides almotriptan, which on in-situ treatment with malic acid in a suitable solvent provides almotriptan malate compound of formula-1a.

6. An improved process for the preparation of highly pure almotriptan malate compound of formula-1a, which comprises of the following steps;
   a) reacting the 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine compound of formula-3 or its salts thereof, preferably hydrochloride salt,



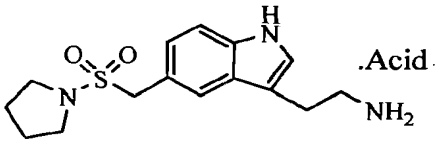
Formula-3

with 4-chloro butyraldehyde diethyl acetal compound of formula-4 or 4-chloro butyraldehyde



Formula-4

in presence of disodium hydrogen phosphate and acid in a suitable solvent followed by treating the obtained product with a suitable acid in a suitable solvent like alcohols or polar solvent or mixtures thereof, provides the corresponding acid addition salt of 2-(5-((pyrrolidin-1-yl-sulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of general formula-2



Formula-2

b) treating the salt compounds of general formula-2 with a suitable base in a suitable solvent to provide 2-(5-((pyrrolidin-1-yl-sulfonyl)methyl)-1H-indol-3-yl)ethanamine, which on in-situ reaction with formalin in presence of sodiumborohydride in aqueous sodium hydroxide, in a suitable solvent provides almotriptan, which on in-situ treatment with malic acid in a suitable solvent provides almotriptan malate compound of formula-1a.

7. A process according to claim 5& 6, wherein the acid addition salt compound of formula-2 selected from oxalic acid, succinic acid, fumaric acid, malonic acid, malic acid, maleic acid, d-tartaric acid, l-tartaric acid, dl-tartaric acid, citric acid, methanesulfonic acid, paratoluene sulfonic acid, acetic acid, sulfuric acid, phosphoric acid, hydrobromic acid or hydrochloric acid.

8. Crystalline form of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine oxalate salt characterized by its powder X-ray diffractogram having peaks at about

7.97, 14.06, 16.52, 16.85, 17.28, 18.26, 19.45, 19.94, 21.16, 22.74, 24.52, 25.13, 26.29, 30.08, 33.41, 36.28 and 39.91 ± 0.2 degrees 2θ.

9. Succinic acid, malic acid, fumaric acid and tartaric acid salts of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine as a crystalline solids.

10. Use of crystalline salts of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine as claimed in claim 8 & 9 in the preparation of highly pure 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine free base, almotriptan or its pharmaceutically acceptable salts.

11. A process for the purification of almotriptan malate compound of formula-1a, which comprises of
    a) treating the almotritpan malate with a suitable base in a suitable solvent selected from ester solvents, hydrocarbon solvents and chloro solvents,
    b) separating the organic and aqueous layer,
    c) distilling off the solvent from organic layer under reduced pressure,
    d) dissolving the obtained residue in suitable solvent or mixtures thereof at reflux temperature,
    e) subjecting the reaction mixture to carbon treatment,
    f) filtering the reaction mixture through hyflo,
    g) adding malic acid or its solution in a suitable solvent to the filtrate,
    h) cooling the reaction mixture,
    i) filtering the solid and washing with a suitable solvent,
    j) drying the solid to get the highly pure almotriptan malate.

12. A process for the purification of almotriptan malate compound of formula-1a, which comprises of
    a) treating the almotritpan malate in ethylacetate with aqueous ammonia,
    b) separating the organic and aqueous layer,
    c) distilling off the ethylacetate from organic layer under reduced pressure,
    d) dissolving the obtained residue in a mixture of isopropylalochol and methanol at reflux temperature,

e) subjecting the reaction mixture to carbon treatment,

f) filtering the reaction mixture through hyflo,

g) adding malic acid solution in a mixture of isopropyl alcohol and methanol to the filtrate,

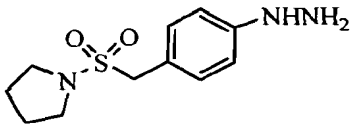
h) cooling the reaction mixture,

i) filtering the solid and washing with a mixture of isopropyl alcohol and methanol,

j) drying the solid to get the highly pure almotriptan malate.

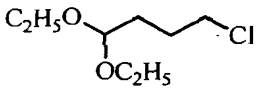
13. An improved process for the preparation of almotriptan malate compound of formula-1a, which comprises of the following steps,

a) treating the 1-(4-hydrazinylbenyzlsulfonyl)pyrrolidine compound of formula-3 or its salt thereof,



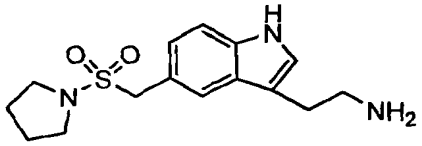
Formula-3

with 4-chloro-1,1-diethoxybutane compound of formula-4,



Formula-4

in presence of disodium hydrogen phosphate in a suitable solvent, to provide 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of formula-5,



Formula-5

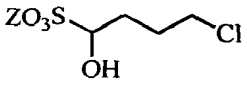
b) reacting the 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of formula-5 with formalin in presence of sodiumborohydride in aqueous sodium hydroxide, in a suitable solvent to provide almotriptan, which on in-situ treatment with suitable acid like succinic acid or oxalic acid in a suitable solvent provides corresponding almotriptan acid addition salt compound of formula-1,

c) optionally purifying the obtained almotriptan acid addition salt compound of formula-1,

d) treating the above pure almotriptan acid addition salt compound of formula-1 with a suitable base in suitable solvent provides almotriptan, which on in-situ treatment with malic acid in a suitable solvent provides almotriptan malate compound of formula-1a.

14. An improved process for the preparation of almotriptan malate compound of formula-1a, which comprises of the following steps,

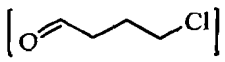
a) treating the alkali metal salt compound of 4-chloro-1-hydroxybutane-1-sulfonic acid compound of formula-6



Formula-6

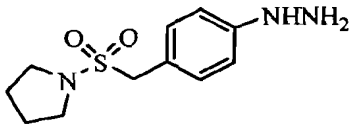
Wherein in Z is Na or K ion,

with a suitable aqueous base, and then extracting the obtained 4-chloro butyraldehyde compound of formula-7 into a suitable solvent,



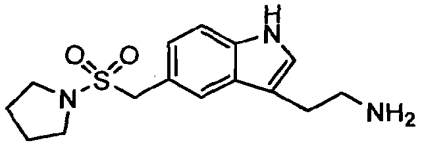
Formula-7

which on in-situ treatment with 1-(4-hydrazinylbenzylsulfonyl)pyrrolidine compound of formula-3 or its salts thereof



Formula-3

in presence of disodium hydrogen phosphate in a suitable solvent to provide 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound formula-5,



Formula-5

b) reacting the 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound formula-5 with formalin in presence of sodiumborohydride in aqueous sodium hydroxide, in a suitable solvent to provide almotriptan, which on in-situ treatment with suitable acid like oxalic acid or succinic acid in a suitable solvent provides corresponding almotriptan acid addition salt compound of formula-1,

c) optionally purifying the obtained almotriptan acid addition salt compound of formula-1,

d) treating the above pure almotriptan acid addition salt compound of formula-1 with suitable base in a suitable solvent to provide almotriptan, which on in-situ treatment with malic acid in a suitable solvent provides almotriptan malate compound of formula-1a.

15. The process of claim 13 or 14, comprising at least one of the following;

i) in step a) wherein the suitable solvent is selected from alcoholic solvents, ether solvents, chloro solvents, water or mixtures thereof; and base is selected from aqueous sodium carbonate and potassium carbonate;

ii) in step b) & c), wherein the suitable solvent is selected from alcohol solvents, ester solvents, hydrocarbon solvent, ketone solvents, nitrile solvents, chloro solvents and water or mixtures thereof;

iii) in step d) suitable solvent is selected from alcohol solvents, ester solvents, hydrocarbon solvent, ketone solvents, nitrile solvents, chloro solvents and water or mixtures thereof; and base is selected from sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate and ammonia or mixtures thereof.

16. A process for the preparation of almotriptan malate compound of formula-1a, which comprises of the following steps,

a) treating the hydrochloride salt of 1-(4-hydrazinylbenyzlsulfonyl)pyrrolidine hydrochloride compound of formula-3a with 4-chloro-1,1-diethoxybutane compound of formula-4 in presence of disodium hydrogen phosphate in aqueous methanol to provide 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of formula-5,

b) reacting the 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of formula-5 with formalin in presence of sodiumborohydride in aqueous sodium hydroxide, in methanol to provide almotriptan, which on in-situ treatment with succinic acid in ethanol or acetonitrile provides almotriptan succinate compound of formula-1b,

c) purifying the almotriptan succinate compound of formula-1b using ethanol, ethyl acetate, water or mixtures thereof,

d) treating the almotriptan succinate compound of formula-1b with aqueous ammonia and then extracting the almotriptan with ethyl acetate, and then treating it with malic acid in methanol to provide almotriptan malate compound of formula-1a.

17. An improved process for the preparation of almotriptan malate compound of formula-1a, which comprises of the following steps,

a) treating the sodium 4-chloro-1-hydroxybutane-1-sulfonate compound of formula-6a with aqueous sodium carbonate, and then extracting the obtained 4-chloro butyraldehyde compound of formula-7 into methylene chloride, which on in-situ reaction with 1-(4-hydrazinylbenzyl sulfonyl)pyrrolidine hydrochloride compound of formula-3a in the presence of disodium hydrogen phosphate in aqueous methanol, provides 2-(5-((pyrrolidin-1-ylsulfonyl) methyl)-1H-indol-3-yl)ethanamine compound of formula-5,

b) reacting the 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of formula-5 with formalin in presence of sodiumborohydride in aqueous sodium hydroxide in methanol to provide almotriptan, which on in-situ treatment with succinic acid in ethanol provides almotriptan succinate compound of formula-1b,

c) treating almotriptan succinate compound of formula-1b with aqueous ammonia and then extracting the almotriptan with ethyl acetate, and then treating it with malic acid in methanol to provide almotriptan malate compound of formula-1a.

18. A novel crystalline form-1 of almotriptan succinate characterized by any one of the following;

a) its power X-ray diffractogram having 2θ peaks at about 9.2, 14.7, 16.1, 16.9, 18.0, 18.7, 20.3, 21.8, 22.9, 23.4, 24.7, 26.0, 29.8, 35.0 and 41.3 ± degrees 2θ. This crystalline form is herein designated as "form-1";

b) its IR spectrum having peaks at 3373.62, 2981.26, 2887.95, 2397.10, 1708.66, 1563.89, 1463.94, 1411.65, 1373.46, 1358.76, 1322.83, 1322.83, 1202.40, 1122.84, 1015.63, 829.03, 804.79 and 656.64 cm^{-1};

c) its DSC thermo gram showing endothermic peak at 178.14°C.

19. A novel crystalline form-2 of almotriptan succinate characterized by any of the following;

a) its Powder X-ray diffractogram having 2θ peaks at about 6.7, 10.2, 12.2, 13.7, 14.5, 15.2, 15.8, 16.9, 17.4, 19.0, 19.9, 20.3, 21.2, 23.4, 24.4, 25.0, 26.5, 27.0, 28.5 and 32.9 ± degrees 2θ;

b) its IR spectrum having peaks at 3424.20, 3218.62, 3198.16, 2976.28, 2918.84, 2478.49, 1711.46, 1559.15, 1486.01, 1398.27, 1342.21, 1320.92, 1236.06, 1218.29, 1175.83, 1133.61, 986.79, 959.54, 818.70, 754.90, 667.41 and 610.17 cm^{-1};

c) its DSC thermo gram showing endothermic peak at 169.96°C.

20. A novel crystalline form-M of almotriptan oxalate is characterized by any one of the following;

i. its powder X-ray diffractogram having 2θ peaks at about 6.5, 11.7, 12.9, 14.6, 15.9, 17.8, 18.4, 19.9, 20.3, 20.7, 21.9, 25.5, 26.6, 36.0 and 39.7 ± degrees 2θ;

ii. its IR spectrum 3418.28, 3298.26, 2927.01, 2683.12, 2512.94, 1731.28, 1631.54, 1483.10, 1434.19, 1310.03, 1196.21, 1011.26, 963.96, 805.23, 710.27 and 643.84 cm^{-1};

iii. its DSC thermo gram showing peaks at 208.30°C and 227.33°C.

21. A process for the preparation of crystalline form-1 of almotriptan succinate compound of formula-1b, which comprises of the following steps,

a) heating a mixture of almotriptan and succinic acid in a suitable solvent selected from alcoholic solvents; nitrile solvents and water or mixtures thereof to reflux,

b) stirring the reaction mixture for 45 minutes at reflux,
c) cooling the reaction mixture to 25-30°C and stirring the reaction further for 2 hours,
d) filtering the solid, washing with suitable solvent,
e) drying the solid to get the crystalline form-1 of almotriptan succinate.

22. A process for the preparation of crystalline form-2 of almotriptan succinate compound of formula-1b, which comprises of the following steps,
a) heating a mixture of almotriptan and succinic acid in a suitable solvent selected from ester solvents; ketone solvents, hydrocarbon solvents, alcoholic solvents and water or mixtures thereof to reflux,
b) stirring the reaction mixture for 45 minutes at reflux,
c) cooling the reaction mixture to 25-30°C and stirring the reaction further for 2 hours,
d) filtering the solid, washing with suitable solvent,
e) drying the solid to get the crystalline form-2 of almotriptan succinate.

23. Almotriptan or its pharmaceutically acceptable salts having purity more than 99.80% by HPLC, preferably more than 99.90%.

24. Almotriptan malate having purity more than 99.90% by HPLC.

25. Almotriptan or its pharmaceutically acceptable salts containing less than 0.1% any individual impurity namely N-hydroxymethyl impurity, dimer impurity, amino indole impurity, N-isopropyl impurity, monomethyl impurity or n-oxide impurity, preferably 0.05% by HPLC and total impurities taken together less than 1.0 % by HPLC.

26. Crystalline oxalic acid, succinic acid, malic acid, fumaric acid and tartaric acid salts of 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethanamine having purity greater than 97% by HPLC, preferably greater than 98% by HPLC.

27. 2-(5-((pyrrolidin-1-yl-sulfonyl)methyl)-1H-indol-3-yl)ethanamine compound of formula-5 having purity greater than 97% by HPLC, preferably > 98% by HPLC.

28. A process for the preparation of almotriptan malate free from methanol, which comprises of the following steps,
    a) dissolving the almotriptan in a mixture of isopropylalochol and methanol at reflux temperature,
    b) subjecting the reaction mixture to carbon treatment,
    c) filtering the reaction mixture through hyflow,
    d) adding malic acid solution in a mixture of isopropyl alcohol and methanol to the filtrate,
    e) cooling the reaction mixture,
    f) filtering the solid and washing with a mixture of isopropyl alcohol and methanol,
    g) drying the solid to get the highly pure almotriptan malate.

29. A process according to claim 28, wherein isopropyl alcohol and methanol taken in the ratio of 6:4.

30. Usage of mixture of Isopropyl alcohol/MeOH in the ratio of 6:4 at reflux temperature in the preparation of almotriptan malate for the reduction of RS/OVI levels of solvents.

31. Almotriptan malate having purity greater than 99.90% and containing methanol at level of less than 3000 ppm.

32. Almotriptan malate particles having D_{90} particles in the range of 40 to 200 microns.

33. Almotriptan malate particle having mean particle size is in the range of 15 to 70 microns.

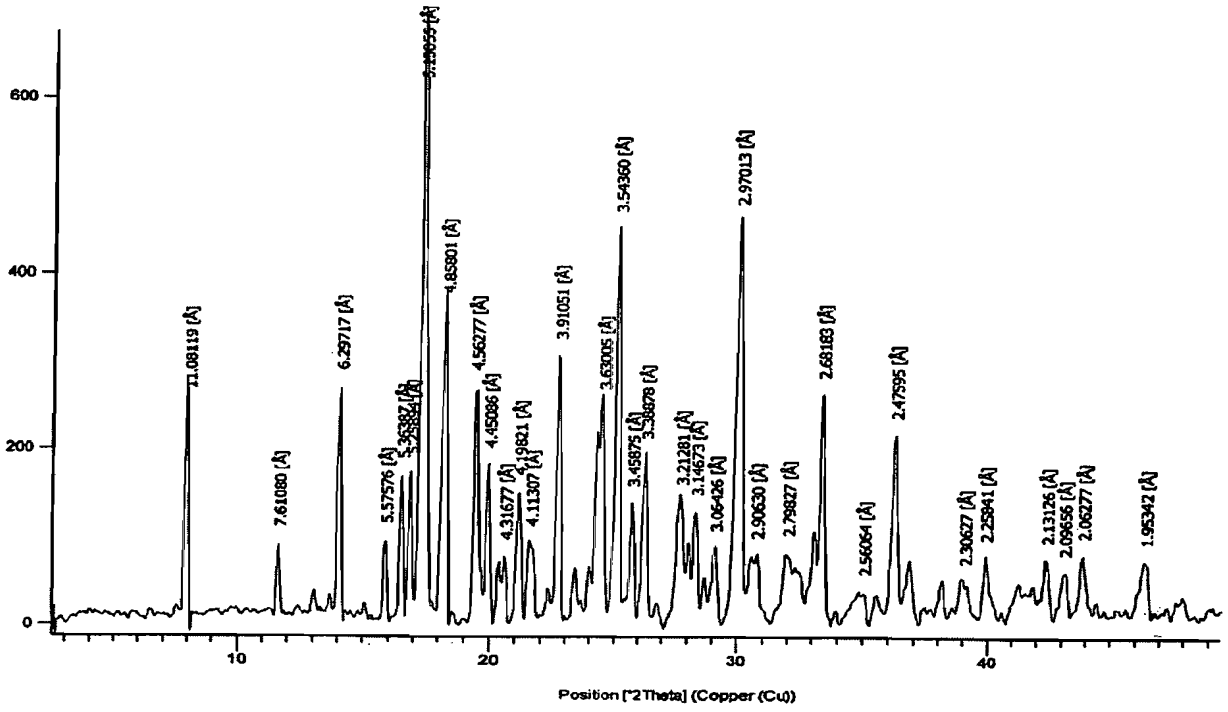


Figure-1

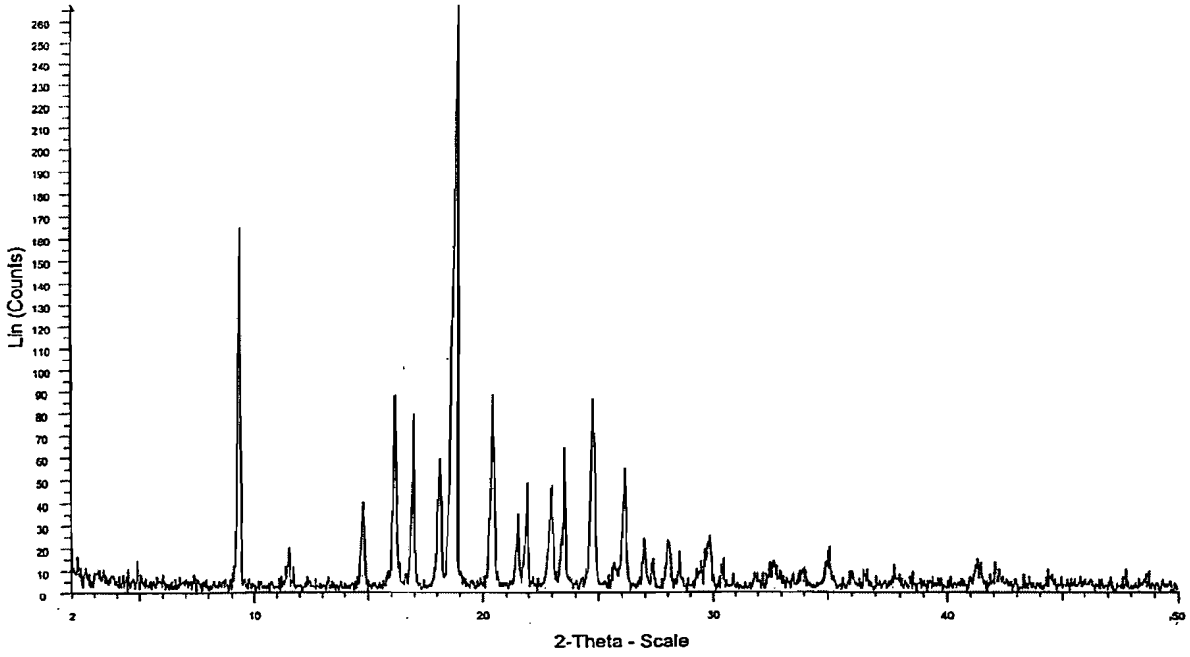


Figure-2

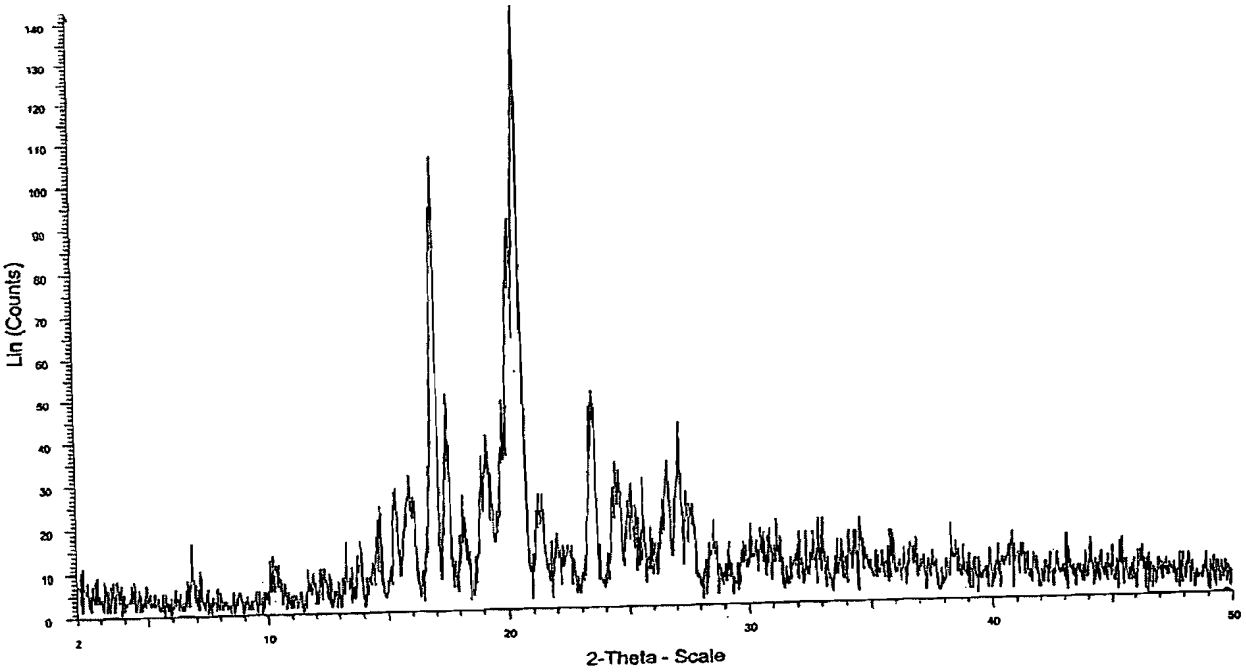


Figure-3

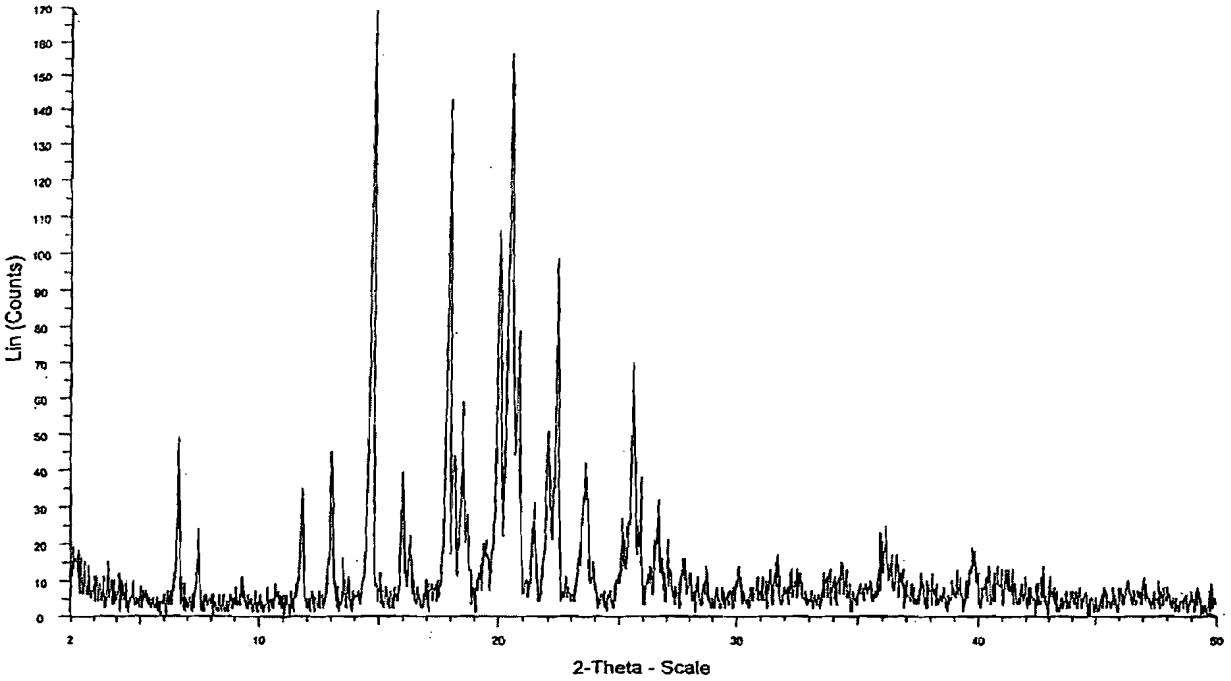


Figure-4

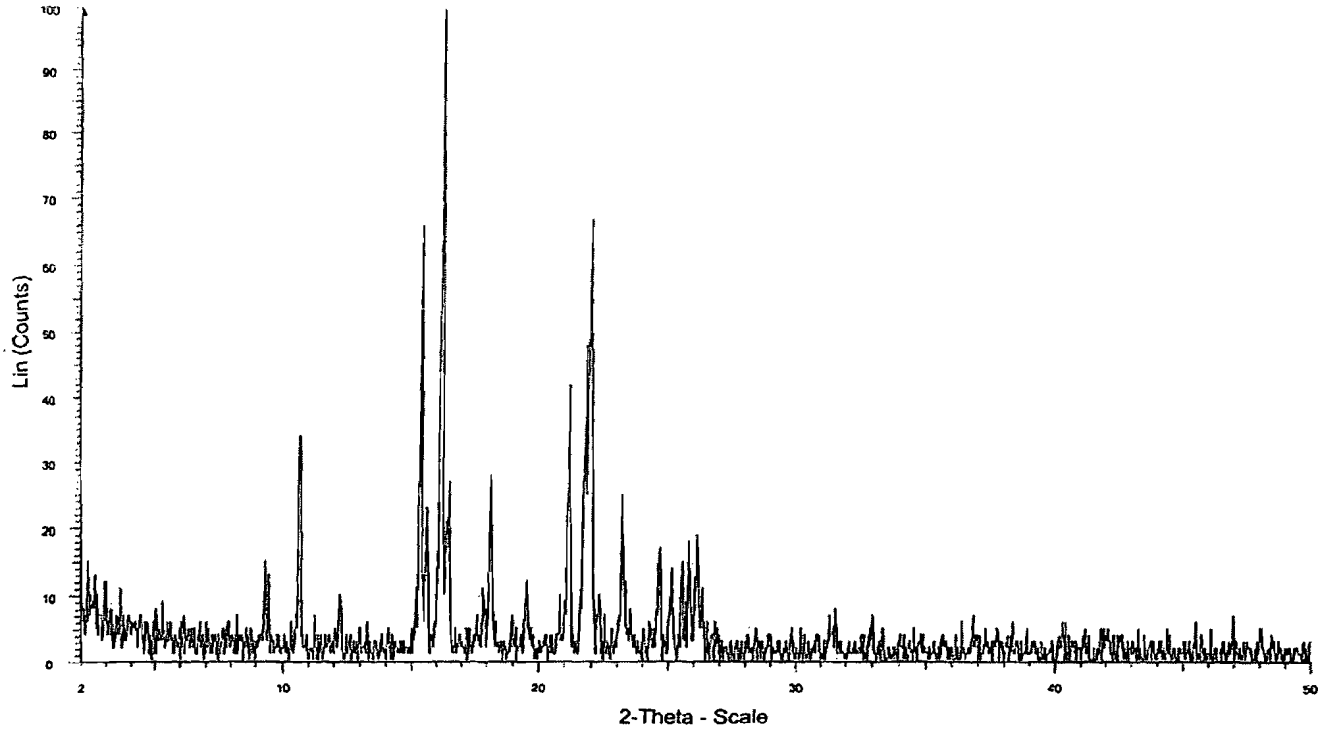

Lin (Counts)
0
10
20
30
40
50
60
70
80
90
100
2
10
20
30
40
50
2-Theta - Scale

Figure-5