

Electronic Acknowledgement Receipt	
EFS ID:	13444169
Application Number:	10378956
International Application Number:	
Confirmation Number:	4742
Title of Invention:	Multiple-component solid phases containing at least one active pharmaceutical ingredient
First Named Inventor/Applicant Name:	Michael J. Zaworotko
Customer Number:	23557
Filer:	Mark A. Buese/Paula Shultz
Filer Authorized By:	Mark A. Buese
Attorney Docket Number:	USF.106XC1
Receipt Date:	08-AUG-2012
Filing Date:	03-MAR-2003
Time Stamp:	11:21:50
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		SIDS12.pdf	302040	yes	4
			2effb0b6e2edf27c1393f650b8e33bb357be983f		

	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Transmittal Letter		1	2	
	Information Disclosure Statement (IDS) Form (SB08)		3	4	
Warnings:					
Information:					
2	Non Patent Literature	D14-Caira-1992.pdf	416848	no	8
			e4096e05244739b26feb42ff50957a286b5f6a27		
Warnings:					
Information:					
3	Non Patent Literature	D15-Caira-1994.pdf	342785	no	7
			f3e33559fd897a47d83771f572ee2df5d441d01		
Warnings:					
Information:					
4	Non Patent Literature	D11-Cox-2007.pdf	334742	no	4
			2f6c9efd2e233034df7c01f9b231185d6d67a2a		
Warnings:					
Information:					
5	Non Patent Literature	D12-Martins-2009.pdf	709267	no	9
			caacedf205c0c686ca84586e6527756dd32438de		
Warnings:					
Information:					
6	Non Patent Literature	D13-Wheatley-1964.pdf	816495	no	13
			818b16ae5e1ea5ff59a3f905be963c6fdb5d2291		
Warnings:					
Information:					
Total Files Size (in bytes):			2922177		

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.

I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on August 8, 2012.

Mark A. Buese
Mark A. Buese, Ph.D., Patent Agent

SUPPLEMENTAL INFORMATION
DISCLOSURE STATEMENT
Patent Application
Docket No. USF.106XC1
Serial No. 10/378,956

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner : Sahar Javanmard
Art Unit : 1627
Applicants : Michael J. Zaworotko, Brian Moulton, Nair Rodriguez-Hornedo
Serial No. : 10/378,956
Filed : March 3, 2003
Conf. No. : 4742
For : Multiple-Component Solid Phases Containing at Least One Active Pharmaceutical Ingredient

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

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT
UNDER 37 C.F.R. §§ 1.97 AND 1.98

Sir:

In accordance with 37 C.F.R. § 1.56, the references listed on the attached form PTO/SB/08 are being brought to the attention of the Examiner for consideration in connection with the examination of the above-identified patent application. A copy of each cited reference is attached. However, Applicants have not submitted copies of the U.S. Patents cited on attached form PTO/SB/08 pursuant to 37 CFR §1.98(a)(2)(ii).

This Supplemental Information Disclosure Statement is being submitted to the Patent Office before the mailing of a first Office Action after the filing of a Request for Continued Examination under 37 CFR §1.114.

J:\USF\106XC1\PTO\SIDS12.doc/ps

The undersigned hereby certifies that each item of information contained in this Supplemental Information Disclosure Statement was first cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Supplemental Information Disclosure Statement.

It is respectfully requested that the references cited on the attached form PTO/SB/08 be considered in the examination of the subject application and that their consideration be made of record.

Applicants respectfully assert that the substantive provisions of 37 C.F.R. §§ 1.97 and 1.98 are met by the foregoing statement.

Respectfully submitted,



Mark A. Buese, Ph.D.
Patent Agent
Registration No. 52,669
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

MAB/ps

Attachments: Form PTO/SB/08; copies of references cited therein.



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.
10/378,956	03/03/2003	Michael J. Zaworotko	USF.106XC1	4742
23557 7590 08/02/2013 SALIWANCHIK, LLOYD & EISENSCHENK A PROFESSIONAL ASSOCIATION PO Box 142950 GAINESVILLE, FL 32614			EXAMINER JAVANMARD, SAHAR	
			ART UNIT 1627	PAPER NUMBER
			NOTIFICATION DATE 08/02/2013	DELIVERY MODE 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):

euspto@slpatents.com

Office Action Summary	Application No. 10/378,956	Applicant(s) ZAWOROTKO ET AL.	
	Examiner SAHAR JAVANMARD	Art Unit 1627	AIA (First Inventor to File) 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 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 22 October 2010.
☐ 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) 25, 27 and 38-53 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) 25, 27, 38-43, and 46-53 is/are rejected.

8) ☒ Claim(s) 42-45 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/08)
Paper No(s)/Mail Date ____.

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

4) ☐ Other: ____.

DETAILED ACTION

Status of the Claims

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 22, 2010 has been entered.

Claim(s) 25, 27-28, 37-53 are pending and examined herein.

Response to Arguments

In view of Applicant's amendments/arguments, the rejections of the previous Office action are hereby withdrawn. The following rejections are made of record in the Non-Final Office action below.

Claim Rejections - 35 USC § 102

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.

Claims 25, 27, 28, 38-41, 43, 48, and 51-53 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Jackson (GB 2169601) of record.

Jackson teaches sucralose co-crystallized with an aliphatic or cyclic secondary or tertiary amine, specifically niacinamide (claims 1-11), meeting the limitations of claims 25, 27, 38, 43, 48, 51, 52, and 53.

Jackson teaches that the nitrogenous base should be a food additive (page 1, line 41), meeting the limitations of claims 39-41.

Jackson teaches that if a solution of sucralose in ethyl acetate is augmented with 1 to 10% by weight (based on the sucralose) of niacinamide, the sucralose can be crystallized from the solution, washed with further ethyl acetate and dried under vacuum to give a fine crystalline material containing) about 0.3 - 0.9% of niacinamide in the sucralose. Such a material has a much improved color stability compared with normal sucralose and, for example, under the test conditions described above, would be practically unchanged after 7 or more hours at 100°C (page 1, lines 46-51), meeting the limitations of claim 28.

Claims 25, 27, 28, 38-41, 43, 48, and 51-53 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Caira (*Journal of Chemical Crystallography*, 1994) of record.

Caira teaches that 1:1 complexation of 5-methoxysulfadiazine with acetylsalicylic acid (abstract; page 700, figure 4), meeting the limitations of claims 25, 37, 38, 48, 49, 51, 52, and 53.

Caira discloses that the crystal structures were determined by X-ray diffraction (page 696), meeting the limitations of claims 46 and 47.

Claims 25 and 42 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by over Freemont (*Proc. Natl. Acad. Sci.*, 1988).

Freemont discloses high-resolution crystal structures of editing complexes of both duplex and single-stranded DNA bound to Escherichia coli DNA polymerase I large fragment (Klenow fragment) show four nucleotides of single-stranded DNA bound to the 3'-5' exonuclease active site and extending toward the polymerase active site, meeting the limitations of claim 25.

Freemont teaches the sugar-phosphate backbone of a single-stranded DNA interacts with three amino acid side chains and presumably also with the two divalent metal ions (Fig. 2), meeting the limitations of claim 42.

Based on the foregoing arguments, the instant claims are deemed unpatentable over the cited art.

Conclusion

Claims 25, 27-28, 37-43, 46-53 are not allowed.

Claims 44-45 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

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 <http://pair-direct.uspto.gov>. 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.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sahar Javanmard whose telephone number is (571) 270-3280. The examiner can normally be reached on 8 AM-5 PM MON-FRI (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/S. J./

Examiner, Art Unit 1627

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627

Application/Control Number: 10/378,956
Art Unit: 1627

Page 6

Notice of References Cited	Application/Control No. 10/378,956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.	
	Examiner SAHAR JAVANMARD	Art Unit 1627	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

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

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Freemont, "Cocrystal structure of an editing complex of Klenow fragment with DNA", PNAS, December 1988, vol. 85, no. 23, pp. 8924-8928.
	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.

Substitute for form 1449A/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(use as many sheets as necessary)</i>			Complete if Known		
			Application Number	10/378,956	
			Filing Date	March 3, 2003	
			First Named Inventor	Michael J. Zaworotko	
			Art Unit	1627	
			Examiner Name	Sahar Javanmard	
Sheet	1	of	2	Attorney Docket Number	USF.106XC1

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number Number - Kind Code ² (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	U1				
	U2				
	U3				
	U4				
	U5				
	U6				
	U7				
	U8				
	U9				

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ⁶
		Country Code ³ - Number ⁴ - Kind Code ⁵ (if known)				
	F1	EP 0 731 795 B1	12-22-1999	G.D. Searle & Co.	All	
	F2	WO 2000/42021 A1	07-20-2000	Merck Frosst Canada & Co.	All	
	F3					
	F4					
	F5					
	F6					

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard T.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

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 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, 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 (1-800-786-9199) and select option 2.

JAUSF106XC1 PTO-81059-10-01-0001-0001 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J./

Substitute for form 1449A/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(use as many sheets as necessary)</i>				Complete if Known	
				Application Number	10/378,956
				Filing Date	March 3, 2003
				First Named Inventor	Michael J. Zaworotko
				Art Unit	1627
				Examiner Name	Sahar Javanmard
Sheet	1	of	11	Attorney Docket Number	USF.106XC1

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number - Kind Code* (if known)			
	U1	US-2002/0006951	01-17-2002	Hageman <i>et al.</i>	All
	U2	US-2002/0013357	01-31-2002	Nadkarni, Sreekant <i>et al.</i>	All
	U3	US-2002/0015735	02-07-2002	Hedden <i>et al.</i>	All
	U4	US-2002/0034542	03-21-2002	Thombre <i>et al.</i>	All
	U5	US-2002/0037925	03-28-2002	Dewey <i>et al.</i>	All
	U6	US-2002/0042446	04-11-2002	Dewey <i>et al.</i>	All
	U7	US-2002/0071857	06-13-2002	Tugrul T. Kararli <i>et al.</i>	All
	U8	US-2002/0107250	08-08-2002	Hariharan <i>et al.</i>	All
	U9	US-2002/0119193	08-29-2002	Trang T. Le <i>et al.</i>	All

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ⁶
		Country Code ³ - Number ⁴ - Kind Code ⁵ (if known)				
	F1	FR 2849029 A1	06-25-2004	Laboratoire L. Lafon <i>et al.</i>	All	
	F2	JP 46-33588	10-01-1971	Sanzu Inc.	All	
	F3	JP 54-095589	07-28-1979	Sumitomo Chemical Co.	All	
	F4	EP 1167355	10-01-2003	Fako Ilacilari A.S.	All	
	F5	GB 1297261 A	11-22-1972	E.R. Squibb & Sons, Inc.	All	
	F6	GB 2169601 A	07-16-1986	Tate & Lyle Public Limited Company	All	
	F7	WO 1995/23596 A1	09-08-1995	The Boots Company PLC	All	

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard T.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

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 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, 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 (1-800-786-9199) and select option 2.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J./

Substitute for form 1449A/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(use as many sheets as necessary)</i>				Complete if Known	
				Application Number	10/378,956
				Filing Date	March 3, 2003
				First Named Inventor	Michael J. Zaworotko
				Art Unit	1627
				Examiner Name	Sahar Javanmard
Sheet	2	of	11	Attorney Docket Number	USF.106XC1

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number - Kind Code* (if known)			
	U10	US-2003/0069190	04-10-2003	Abdel-Magid <i>et al.</i>	All
	U11	US-2004/0019211	01-29-2004	Remenar <i>et al.</i>	All
	U12	US-2004/0106055	06-03-2004	Molaire <i>et al.</i>	All
	U13	US-2004/0171062	09-02-2004	Hirth <i>et al.</i>	All
	U14	US-2005/0256127	11-17-2005	Ku <i>et al.</i>	All
	U15	US-2006/0223794	10-05-2006	Bourghol Hickey <i>et al.</i>	All
	U16	US-2007/0015841	01-18-2007	Tawa <i>et al.</i>	All
	U17	US-2007/0021510	01-25-2007	Hickey <i>et al.</i>	All
	U18	US-2007/0059356	03-15-2007	Almarsson <i>et al.</i>	All

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ⁶
		Country Code ³ - Number ⁴ - Kind Code ⁵ (if known)				
	F8	WO 1996/33193 A1	10-24-1996	Janssen Pharmaceutica N.V.	All	
	F9	WO 2000/07583 A3	02-17-2000	Brookhaven Science Associates	All	
	F10	WO 2000/32189 A1	06-08-2000	G.D. Searle & Co.	All	
	F11	WO 2000/50020 A2	08-21-2000	University of Cincinnati	All	
	F12	WO 2000/72841 A1	12-07-2000	Berlant, Jeffrey	All	
	F13	WO 2001/41536 A2	06-14-2001	Pharmacia Corporation	All	
	F14	WO 2001/41760 A3	06-14-2001	Pharmacia Corporation	All	

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard T.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. ⁶ Applicant is to place a check mark here if English language translation is attached.

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 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, 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 (1-800-786-9199) and select option 2.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J./

Substitute for form 1449A/PTO			Complete if Known		
INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(use as many sheets as necessary)</i>			Application Number	10/378,956	
			Filing Date	March 3, 2003	
			First Named Inventor	Michael J. Zaworotko	
			Art Unit	1627	
			Examiner Name	Sahar Javanmard	
Sheet	3	of	11	Attorney Docket Number	USF.106XC1

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number Number - Kind Code ² (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	U19	US-2007/0293674	12-20-2007	Scoppettuolo <i>et al.</i>	All
	U20	US-3,970,651	07-20-1976	Kaplan <i>et al.</i>	All
	U21	US-4,008,321	02-15-1977	Kamishita <i>et al.</i>	All
	U22	US-4,513,006	04-23-1995	Maryanoff <i>et al.</i>	All
	U23	US-4,853,379	08-01-1989	Shroot <i>et al.</i>	All
	U24	US-4,925,674	05-15-1990	Giannini <i>et al.</i>	All
	U25	US-4,927,855	05-22-1990	Lafon	All
	U26	US-4,994,604	02-19-1991	Tung <i>et al.</i>	All
	U27	US-5,242,942	09-07-1993	Costanzo <i>et al.</i>	All

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document		Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Country Code ³	- Number ⁴ - Kind Code ⁵ (if known)			
	F15	WO 2001/42222 A2		06-14-2001	Pharmacia Corporation	All
	F16	WO 2001/45706 A1		06-28-2001	Pharmacia Corporation	All
	F17	WO 2001/51919 A2		07-19-2001	Transform Pharmaceuticals, Inc.	All
	F18	WO 2001/78724 A1		10-25-2001	Pharmacia Corporation	All
	F19	WO 2001/91750 A1		12-06-2001	Pharmacia Corporation	All
	F20	WO 2002/000627 A1		01-03-2002	Fako Ilacilari A.S.	All
	F21	WO 2002/056878 A2		07-25-2002	Pharmacia Corporation	All

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard T.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

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 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, 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 (1-800-786-9199) and select option 2.

J:\USF106X\IPR\PTO\Sheet 1 of 11

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J./

Substitute for form 1449A/PTO			Complete if Known		
INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(use as many sheets as necessary)</i>			Application Number	10/378,956	
			Filing Date	March 3, 2003	
			First Named Inventor	Michael J. Zaworotko	
			Art Unit	1627	
			Examiner Name	Sahar Javanmard	
Sheet	4	of	11	Attorney Docket Number	USF.106XC1

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number Number - Kind Code ² (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	U28	US-5,273,760	12-28-1993	Oshlack <i>et al.</i>	All
	U29	US-5,286,493	02-15-1994	Oshlack <i>et al.</i>	All
	U30	US-5,324,351	06-28-1994	Oshlack <i>et al.</i>	All
	U31	US-5,356,467	10-18-1994	Oshlack <i>et al.</i>	All
	U32	US-5,366,738	11-22-1994	Rork <i>et al.</i>	All
	U33	US-5,384,327	01-24-1995	Costanzo <i>et al.</i>	All
	U34	US-5,466,823	11-14-1995	Talley <i>et al.</i>	All
	U35	US-5,472,712	12-05-1995	Oshlack <i>et al.</i>	All
	U36	US-5,510,496	04-23-1996	Talley <i>et al.</i>	All

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ³
		Country Code ³ - Number ⁴ - Kind Code ⁵ (if known)				
	F22	WO 2002/056915 A2	07-25-2002	Cephalon, Inc.	All	
	F23	WO 2002/10125 A1	02-07-2002	Teva Pharmaceutical Industries Ltd.	All	
	F24	WO 2002/102376 A1	12-27-2002	Pharmacia Corporation	All	
	F25	WO 2003/033462 A2	04-24-2003	The Regents of the University of Michigan	All	
	F26	WO 2005/053612 A2	06-16-2005	Shire Laboratories, Inc.	All	

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard T.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

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 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, 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 (1-800-786-9199) and select option 2.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J./

Sheet 5 of 11

Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number - Kind Code ² (if known)			
	U37	US-5,521,207	05-28-1996	Graneto	All
	U38	US-5,563,165	10-08-1996	Talley <i>et al.</i>	All
	U39	US-5,631,250	05-20-1997	Bunnell <i>et al.</i>	All
	U40	US-5,633,272	05-27-1997	Talley <i>et al.</i>	All
	U41	US-5,641,512	06-24-1997	Cimiluca	All
	U42	US-5,703,232	12-30-1997	Bunnell <i>et al.</i>	All
	U43	US-5,736,541	04-07-1998	Bunnell <i>et al.</i>	All
	U44	US-5,753,688	05-19-1998	Talley <i>et al.</i>	All
	U45	US-5,753,693	05-19-1998	Shank	All
	U46	US-5,760,007	06-02-1999	Shank <i>et al.</i>	All
	U47	US-5,760,068	06-02-1998	Talley <i>et al.</i>	All
	U48	US-5,932,598	08-03-1999	Talley <i>et al.</i>	All
	U49	US-5,935,933	08-10-1999	Shank <i>et al.</i>	All
	U50	US-5,952,187	09-14-1999	Stenglein <i>et al.</i>	All
	U51	US-5,972,986	10-26-1999	Seibert <i>et al.</i>	All
	U52	US-5,985,902	11-16-1999	Talley <i>et al.</i>	All
	U53	US-5,998,380	12-07-1999	Ehrenberg <i>et al.</i>	All
	U54	US-6,054,136	04-25-2000	Farah <i>et al.</i>	All
	U55	US-6,071,537	06-06-2000	Shank	All
	U56	US-6,132,420	10-17-2000	Dionne <i>et al.</i>	All
	U57	US-6,156,781	12-05-2000	Talley <i>et al.</i>	All
	U58	US-6,191,117	02-20-2001	Kozachuk	All

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

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 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, 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

Page 4033 of 4460

Sheet	6	of	11
-------	---	----	----

Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number - Kind Code ² (if known)			
	U59	US-6,201,010	03-13-2001	Cottrell	All
	U60	US-6,245,357	06-12-2001	Edgren <i>et al.</i>	All
	U61	US-6,270,787	08-07-2001	Ayer	All
	U62	US-6,283,953	09-04-2001	Ayer <i>et al.</i>	All
	U63	US-6,287,295	09-11-2001	Chen <i>et al.</i>	All
	U64	US-6,294,192	09-25-2001	Patel <i>et al.</i>	All
	U65	US-6,319,903	11-20-2001	Carrazana <i>et al.</i>	All
	U66	US-6,323,266	11-27-2001	Phillips	All
	U67	US-6,333,050	12-25-2001	Wong <i>et al.</i>	All
	U68	US-6,342,249	01-29-2002	Wong <i>et al.</i>	All
	U69	US-6,348,458	02-19-2002	Hamied <i>et al.</i>	All
	U70	US-6,365,185	04-02-2002	Ritschel <i>et al.</i>	All
	U71	US-6,368,626	04-09-2002	Bhatt <i>et al.</i>	All
	U72	US-6,375,978	04-23-2002	Kleiner <i>et al.</i>	All
	U73	US-6,384,034	05-07-2002	Simitchieva <i>et al.</i>	All
	U74	US-6,403,640	06-11-2002	Stoner <i>et al.</i>	All
	U75	US-6,413,965	07-02-2002	Banavara L. Mylari	All
	U76	US-6,420,394	07-16-2002	Supersaxo	All
	U77	US-6,488,962	12-03-2002	Berner <i>et al.</i>	All
	U78	US-6,503,884	01-07-2003	Ehrenberg <i>et al.</i>	All
	U79	US-6,579,895	06-17-2003	Karim <i>et al.</i>	All
	U80	US-6,613,790	09-02-2003	Jeffrey Carter	All

Examiner Signature		Date Considered	
-----------------------	--	--------------------	--

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 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, 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

REFERENCES

Page 4034 of 4460

Substitute for form 1449B/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)			Complete if Known		
			Application Number	10/378,956	
			Filing Date	March 3, 2003	
			First Named Inventor	Michael J. Zaworotko	
			Group Art Unit	1627	
			Examiner Name	Sahar Javanmard	
			Attorney Docket Number	USF.106XC1	
Sheet	8	of	11		

NON PATENT LITERATURE DOCUMENTS				
Examiner Initials*	Cite No. ¹	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, page(s), volume-issue number(s), publisher, city and/or country where published.		T ²
	R1	AAKERÖY, C.B. <i>et al.</i> "Do Polymorphic Compounds Make Good Cocrystalizing Agents? A Structural Case Study that Demonstrates the Importance of Synthon Flexibility" <i>Crystal Growth & Design</i> , 2003, 3(2):159-165.		
	R2	BASTIN, R.J. <i>et al.</i> "Salt Selection and Optimisation Procedures for Pharmaceutical New Chemical Entities" <i>Organic Process Research & Development</i> , 2000, 4:427-435.		
	R3	BRADER, M.L. <i>et al.</i> "Hybrid insulin cocrystals for controlled release delivery" <i>Nature Biotechnology</i> , August 2002, 20:800-804.		
	R4	BRITTAIN, H.G. <i>et al.</i> "Polymorphism in Pharmaceutical Solids" 1999, New York: Marcel Dekker, pp. 183, 202-208, 219.		
	R5	COWAN, J.A. <i>et al.</i> "Neutron diffractions studies of the 1:1 and 2:1 cocrystals of benzene-1,2,4,5-tetracarboxylic acid and 4,4'-bipyridine" <i>Acta Crystallographica Section C: Crystal Structure Communications</i> , 2006, C62:o157-o161.		
	R6	DATABASE WPI, Section Ch, Week 197936, Derwent Publishing Ltd., London, Great Britain, Class B02, AN 1979-65538B, XP002282989 and JP 54 095589A (Sumitomo) 1979 Abstract.		
	R7	DAVIDOVICH, M. <i>et al.</i> "Detection of Polymorphism by Powder X-Ray Diffraction Interference by Preferred Orientation" <i>American Pharmaceutical Review</i> , 2004, pp. 10, 12, 14, 16, 100, Vol. 7, No. 1.		
	R8	DAVIES, N.M. <i>et al.</i> "Clinical Pharmacokinetics and Pharmacodynamics of Celecoxib: A Selective Cyclo-Oxygenase-2 Inhibitor" <i>Clin Pharmacokinet</i> , March 2000, 38(3):225-242.		
	R9	DE JONG, E.M.G.J. <i>et al.</i> "Dystrophic Psoriatic Fingernails Treated with 1% 5-Fluorouracil in a Nail Penetration-Enhancing Vehicle: A Double-Blind Study" <i>Dermatology</i> , 1999, 199:313-318.		
	R10	DEAN, J.A. "Analytical Chemistry Handbook" 1995, New York: McGraw-Hill, Inc., pp. 10.24-10.26.		
	R11	Definition of solvate, The Free Dictionary, http://www.thefreedictionary.com/solvate , accessed online on 21 July 2009, pp. 1-3.		
	R12	DOELKER, E. "Crystalline Modifications and Polymorphism changes during drug manufacturing" <i>Annales Pharmaceutiques Francaises</i> , 2002, 60(3):161-176.		

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

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

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 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 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, 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 (1-800-786-9199) and select option 2.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J./

UM00017179

NOVARTIS EXHIBIT 1517

Novartis v. Regents, IPR2023-01347

Page 4036 of 4460

Substitute for form 1449B/PTO		Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)		Application Number	10/378,956
		Filing Date	March 3, 2003
		First Named Inventor	Michael J. Zaworotko
		Group Art Unit	1627
		Examiner Name	Sahar Javanmard
Sheet	9	of	11
		Attorney Docket Number	USF.106XC1

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	R13	DOELKER, E. "Physicochemical behavior of active substances. Consequences for the feasibility and stability of pharmaceutical forms" <i>S.T.P. Pharma Practiques</i> , 1999, 9(5):399-409.	
	R14	DUNITZ, J.D. "Are crystal structures predictable" <i>Chem Commun.</i> , 2003, pp. 545-548.	
	R15	DVORKIN et al. "Crystal and Molecular Structure of a Complex 18-crown-6 with 6-chloro-7-sulfamido-3,4-dihydro-1,2,4-benzothiadiazine-1, 1-dioxide (hypothiazide) of 1:1 Composition" <i>Kristallagafiya</i> , 1990, 35(3):682-686.	
	R16	EL-NAHHAS, S.A. " Physico-Chemical characteristics of Carbamazepine-beta-cyclodextrin inclusion compounds and carbamazepine-peg solid dispersions" <i>Pharmazie</i> , 1996, 51(12):960-963.	
	R17	FAUGHT, E. <i>et al.</i> "Topiramate Dose-Ranging Trial in Refractory Partial Epilepsy" <i>Amer. Epilepsy Soc. Proc.</i> , 1995, pg. 33, Vol. 36, Supp. 4.	
	R18	FITZGERALD, G.A. <i>et al.</i> "The Coxibs, Selective Inhibitors of Cyclooxygenase-2", <i>New England Journal of Medicine</i> , August 9, 2001, 345(6):433-442.	
	R19	FLEISCHMAN, S.G. <i>et al.</i> "Crystal Engineering of the Composition of Pharmaceutical Phases: Multiple-Component Crystalline Solids Involving Carbamazepine" <i>Crystal Growth & Design</i> , 2003, 3(6):909-919.	
	R20	FUNG, H.L. <i>et al.</i> "Solvent Effects on Comparative Dissolution of Pharmaceutical Solvates" <i>Chemical and Pharmaceutical Bulletin</i> , 1974, 22(2):454-458.	
	R21	JAIN, N.K. <i>et al.</i> "Polymorphism in Pharmacy" <i>Indian Drugs</i> , 1986, 23(6):315-329.	
	R22	Japanese Notice of Reasons for Rejection dated October 8, 2009, Japanese Application No. 2003-572946, 11 pages.	
	R23	KIRCHNER, M.T. <i>et al.</i> "Co-crystals with Acetylene: Small Is not Simple" <i>Chem. Eur J.</i> , 2010, 16:2131-2146.	
	R24	KLEIN, C.L. <i>et al.</i> "Molecular Structure of Two Conformationally Restrained Fentanyl Analogues: cis- and trans-Isomers of N-(3-Methyl-1-[2-(1,2,3,4-tetrahydro)naphthyl]-4-piperidinyl)-N-phenylpropanamide" <i>Journal of Pharmaceutical Sciences</i> , November 1985, 74(11):1147-1151.	

Examiner Signature	Date Considered
--------------------	-----------------

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

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 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 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, 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 (1-800-786-9199) and select option 2.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J./

UM00017180

NOVARTIS EXHIBIT 1517

Novartis v. Regents, IPR2023-01347

Page 4037 of 4460

Substitute for form 1449B/PTO			Complete if Known		
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)			Application Number	10/378,956	
			Filing Date	March 3, 2003	
			First Named Inventor	Michael J. Zaworotko	
			Group Art Unit	1627	
			Examiner Name	Sahar Javanmard	
Sheet	10	of	11	Attorney Docket Number	USF.106XC1

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	R25	MUZAFFAR, N.A. <i>et al.</i> "Polymorphism and Drug Availability" <i>Journal of Pharmacy (Lahore)</i> , 1997, 1(1):59-66.	
	R26	OSORIO-LOZADA, A. <i>et al.</i> "Synthesis and determination of the absolute stereochemistry of the enantiomers of adrafinil and modafinil" <i>Tetrahedron: Asymmetry</i> , 2004, 15:3811-3815.	
	R27	OSWALD, I.D.H. <i>et al.</i> "The formation of paracetamol (acetaminophen) adducts with hydrogen-bond acceptors" <i>Acta Crystallographica Section B</i> , 2002, B58:1057-1066.	
	R28	OTSUKA, M. <i>et al.</i> "Effect of Polymorphic Forms of Bulk Powders on Pharmaceutical Properties of Carbamazepine Granules" <i>Chem Pharm Bull</i> , 1999, 47(6):852-856.	
	R29	PEDIREDDI, V.R. <i>et al.</i> "Layered Structures Formed by Dinitrobenzoic Acids" <i>Tetrahedron Letters</i> , 1998, 39:9831-9834.	
	R30	Physician's Desk Reference, 56th Edition, 2002, pp. 2590-2595.	
	R31	Press Release. "Clinical Development of Topiramate for Obesity Extended to Simplify Dosing, Improve Tolerability". http://www.orthomcneil.com/news/article020402.html (February 4, 2002), New Jersey, 2 pages.	
	R32	PRIVITERA, M. <i>et al.</i> "Dose-Ranging Trial with Higher Doses of Topiramate in Patients with Resistant Partial Seizures", <i>Amer. Epilepsy Soc. Proc.</i> , 1995, pg. 33, Vol. 36, Supp. 4.	
	R33	REYNOLDS, J.E.F. (ed). "Martindale, The Extra Pharmacopoeia" 1993, London, England: The Pharmaceutical Press, 13 th Edition, pp. 1431 (e.g., Acetaminophen, Aspirin, and Caffeine Tablets), 1465 (e.g., Aspirin plus C), 1521 (Codafen Continus), 1610 (Gaboril Complex).	
	R34	ROSENFELD, W.E. "Topiramate: A Review of Preclinical, Pharmacokinetic, and Clinical Data" <i>Clinical Therapeutics</i> , 1997, 19(6):1294-1308.	
	R35	RUBINO, J.T. <i>et al.</i> "Influence of solvent composition on the solubilities and solid-state properties of the sodium salts of some drugs" <i>International Journal of Pharmaceutics</i> , 1990, 65:141-145.	
	R36	SACHDEO, S.K. <i>et al.</i> "Topiramate: Double-Blind Trial as Monotherapy", <i>Amer. Epilepsy Soc. Proc.</i> , 1995, pg. 33, Vol. 36, Supp. 4.	

Examiner Signature	Date Considered
-----------------------	--------------------

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

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 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 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, 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 (1-800-786-9199) and select option 2.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J./

UM00017181

NOVARTIS EXHIBIT 1517

Novartis v. Regents, IPR2023-01347

Page 4038 of 4460

Substitute for form 1449B/PTO		Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)		Application Number	10/378,956
		Filing Date	March 3, 2003
		First Named Inventor	Michael J. Zaworotko
		Group Art Unit	1627
		Examiner Name	Sahar Javanmard
Sheet	11	of	11
		Attorney Docket Number	USF.106XC1

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	R37	SALEM, M.S. <i>et al.</i> "Preparation, characterisation and transformation of terfenadine polymorphic forms" <i>International Journal of Pharmaceutics</i> , 1996, 141:257-259.	
	R38	THAYER, A.M. <i>et al.</i> "Form and Function" <i>Chemical & Engineering News</i> , June 18, 2007, 85(25):17-30 (8 pages).	
	R39	U.S. Pharmacopia #23, 1995, p. 1843.	
	R40	WALSH, R.D.B. <i>et al.</i> " Crystal Engineering of the composition of pharmaceutical phases". <i>Chem. Commun.</i> , 2003, pp. 186-187.	
	R41	WEISSBUCH, I. <i>et al.</i> "Understanding and Control of Nucleation, Growth, Habit, Dissolution and Structure of Two- and Three-Dimensional Crystals Using 'Tailor-Made' Auxiliaries" <i>Acta Cryst.</i> , 1995, B51:115-148.	
	R42	WUNDERLICH, H.F. <i>et al.</i> " The Derivatives of carbamazepine with ammonium halogenides and formamide" <i>Pharmazie</i> , 1991,46(7):507-509.	
	R43	ZAMAN, M.B. <i>et al.</i> "Crystal Engineering Using Anilic Acids and Dipyrldyl Compounds through a New Supramolecular Synthon" <i>J. Org. Chem.</i> , 2001, 66:5987-5995.	
	R44	ZERKOWSKI, J.A. <i>et al.</i> "Steric Control of Secondary, Solid-State Architecture in 1:1 Complexes of Melamines and Barbiturates That Crystallize as Crinkled Tapes" <i>J Am Chem Soc</i> , 1004, 116:4298-4304.	
	R45	DESIRAJU, G.R. "The C--H...O Hydrogen Bond in Crystals: What Is It?" <i>Acc. Chem. Res.</i> , 1991, pp. 24:290-296.	
	R46		
	R47		
	R48		

Examiner Signature	/Sahar Javanmard/	Date Considered	07/01/2013
--------------------	-------------------	-----------------	------------

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

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 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 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, 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 (1-800-786-9199) and select option 2.

J:\USFV106\CHPT\BRIEF\106-11000001\BRIEF

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J./

Substitute for form 1449B/PTO		Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)		Application Number	10/378,956
		Filing Date	March 3, 2003
		First Named Inventor	Michael J. Zaworotko
		Group Art Unit	1627
		Examiner Name	Sahar Javanmard
		Attorney Docket Number	USF.106XC1
Sheet	1	of	1

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	R1	STAHL, P.H. <i>The Practice of Medicinal Chemistry</i> ; "Chapter 35: Preparation of water-soluble compounds through salt formation" 1 January 2003, Elsevier, NL, pp. 601-615, XP002566271.	
	R2	RASENACK, N. <i>et al.</i> "Dissolution Rate Enhancement by <i>in Situ</i> Micronization of Poorly Water-Soluble Drugs" <i>Pharmaceutical Research</i> , December 2002, 19(12):1894-1900.	
	R3		
	R4		
	R5		
	R6		
	R7		
	R8		
	R9		
	R10		
	R11		
	R12		
	R13		

Examiner Signature	/Sahar Javanmard/	Date Considered	07/01/2013
--------------------	-------------------	-----------------	------------

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

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 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 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, 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 (1-800-786-9199) and select option 2.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J./

Substitute for form 1449A/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(use as many sheets as necessary)</i>				Complete if Known	
				Application Number	10/378,956
				Filing Date	March 3, 2003
				First Named Inventor	Michael J. Zaworotko
				Art Unit	1627
				Examiner Name	Sahar Javanmard
Sheet	1	of	2	Attorney Docket Number	USF.106XC1

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number - Kind Code* (if known)			
	U1	US-5,635,535	06-03-1997	Wagstaff	All
	U2	US-6,294,186	09-25-2001	Beerse <i>et al.</i>	All
	U3	US-			
	U4	US-			
	U5	US-			
	U6	US-			
	U7	US-			
	U8	US-			
	U9	US-			

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document		Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Country Code ³	Number ⁴ - Kind Code ⁵ (if known)			
	F1					
	F2					
	F3					
	F4					
	F5					
	F6					
	F7					

Examiner Signature	Date Considered
-----------------------	--------------------

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard T.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

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 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, 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 (1-800-786-9199) and select option 2.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J./

J:\USF106XC1\PTO\SH512-form.docx

Substitute for form 1449B/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)				Application Number	10/378,956
				Filing Date	March 3, 2003
				First Named Inventor	Michael J. Zaworotko
				Group Art Unit	1627
				Examiner Name	Sahar Javanmard
Sheet	2	of	2	Attorney Docket Number	USF.106XC1

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	R1	CAIRA, M.R., "Molecular complexes of sulfonamides. 2. 1:1 complexes between drug molecules: sulfadimidine-acetylsalicylic acid and sulfadimidine-4-aminosalicylic acid," <i>Journal of Crystallographic and Spectroscopic Research</i> , 1992, pp. 193-200, Vol. 22, No. 2.	
	R2	CAIRA, M.R., "Molecular complexes of sulfonamides. 3. Structure of 5-methoxysulfadiazine (Form II) and its 1:1 complex with acetylsalicylic acid," <i>Journal of Chemical Crystallography</i> , 1994, pp. 695-701, Vol. 24, No. 10.	
	R3	COX, J.R. <i>et al.</i> , "Selective Crystal Growth of the Anhydrous and Monohydrate Forms of Theophylline on Self-Assembled Monolayers," <i>Angew. Chem. Int. Ed.</i> , 2007, pp. 1988-1991, Vo. 46.	
	R4	MARTINS, F.T. <i>et al.</i> , "Intermolecular Contacts Influencing the Conformational and Geometric Features of the Pharmaceutically Preferred Mebendazole Polymorph C," <i>Journal of Pharmaceutical Sciences</i> , July 2009, pp. 2336-2344, Vol. 98, No. 7.	
	R5	WHEATLEY, P.J., "The Crystal and Molecular Structure of Aspirin," <i>J. Chem. Soc.</i> , 1964, pp. 6036-6048.	
	R6		
	R7		
	R8		
	R9		
	R10		
	R11		
	R12		
	R13		
	R14		

Examiner Signature	/Sahar Javanmard/	Date Considered	07/01/2013
--------------------	-------------------	-----------------	------------

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

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 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 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, 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 (1-800-786-9199) and select option 2.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J./

J:\USF\106XC1\PTO\USFDS12-form.doc.ps

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.

Substitute for form 1449B/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(use as many sheets as necessary)</i>				Complete if Known	
				Application Number	10/378,956
				Filing Date	March 3, 2003
				First Named Inventor	Michael J. Zaworotko
				Group Art Unit	1617
				Examiner Name	Sahar Javanmard
Sheet	1	of	1	Attorney Docket Number	USF.106XC1

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	R1	DESIRAJU, G.R., "Crystal engineering: A brief overview," <i>J. Chem. Sci.</i> , September 2010, pp. 667-675, Vol. 122, No. 5.	
	R2		
	R3		
	R4		
	R5		
	R6		
	R7		
	R8		
	R9		
	R10		

Examiner Signature	/Sahar Javanmard/	Date Considered	07/01/2013
--------------------	-------------------	-----------------	------------

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

¹ Applicant's unique citation designation number (optional). ² Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 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 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, 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 (1-800-786-9199) and select option 2.

JAUSF106XC1NDX00000501000006

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J./

UM00017186

NOVARTIS EXHIBIT 1517

Novartis v. Regents, IPR2023-01347

Page 4043 of 4460



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

BIB DATA SHEET

CONFIRMATION NO. 4742

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/378,956	03/03/2003	424	1627	USF.106XC1
APPLICANTS Michael J. Zaworotko, Tampa, FL; Brian Moulton, Temple Terrace, FL; Nair Rodriguez-Hornedo, Ann Arbor, MI;				
** CONTINUING DATA ***** This appln claims benefit of 60/360,768 03/01/2002				
** FOREIGN APPLICATIONS *****				
** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** ** SMALL ENTITY ** 04/23/2003				
Foreign Priority claimed 35 USC 119(a-d) conditions met Verified and Acknowledged	☐ Yes ☒ No ☐ Yes ☒ No /SAHAR JAVANMARD/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY FL	SHEETS DRAWINGS 22
			TOTAL CLAIMS 36	INDEPENDENT CLAIMS 9
ADDRESS SALIWANCHIK, LLOYD & EISENSCHENK A PROFESSIONAL ASSOCIATION PO Box 142950 GAINESVILLE, FL 32614 UNITED STATES				
TITLE Multiple-component solid phases containing at least one active pharmaceutical ingredient				
FILING FEE RECEIVED 836	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		

Substitute for form 1449A/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(use as many sheets as necessary)</i>				Application Number	10/378,956
				Filing Date	March 3, 2003
				First Named Inventor	Michael J. Zaworotko
				Art Unit	1627
				Examiner Name	Sahar Javanmard
Sheet	1	of	2	Attorney Docket Number	USF.106XC1

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number Number - Kind Code ² (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	U1				
	U2				
	U3				
	U4				
	U5				
	U6				
	U7				
	U8				
	U9				

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ⁶
		Country Code ³ - Number ⁴ - Kind Code ⁵ (if known)				
	F1	CA 1 101 840	05-26-1981	Sumitomo Chemical Company, Limited	All	
	F2					
	F3					
	F4					
	F5					
	F6					

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard T.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

JAUSF106A (11/15/02) **ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J./**

Substitute for form 1449B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet

2

of

2

Complete if Known

Application Number	10/378,956
Filing Date	March 3, 2003
First Named Inventor	Michael J. Zaworotko
Group Art Unit	1627
Examiner Name	Sahar Javanmard
Attorney Docket Number	USF 106XC1

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. ¹	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	R1	REMENAR, J.F. <i>et al.</i> "Celecoxib sodium salt: engineering crystal forms for performance" <i>CrystEngComm</i> , 2011, 13:1081-1089.	
	R2	YADAV, A.V. <i>et al.</i> "Co-crystals: A novel approach to modify physicochemical properties of active pharmaceutical ingredients" <i>Indian Journal of Pharmaceutical Sciences</i> " 2009, 71(4):359-370.	
	R3		
	R4		
	R5		
	R6		
	R7		
	R8		
	R9		
	R10		
	R11		
	R12		
	R13		

Examiner
Signature

/Sahar Javanmard/

Date	
Cons	

07/01/2013

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kind codes of USPTO Patent Documents at www.uspto.gov or MPEP901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard T.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached

JAUSEV106X.D\INDS\IDS4-feral.doc

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J./

UM00017189

NOVARTIS EXHIBIT 1517

Novartis v. Regents, IPR2023-01347

Page 4046 of 4460

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	9	((MICHAEL) near2 (ZAWOROTKO)).INV.	US-PGPUB; USPAT	OR	OFF	2008/09/30 13:51
L2	5	((BRIAN) near2 (MOULTON)).INV.	US-PGPUB; USPAT	OR	OFF	2008/09/30 13:51
L3	5	((NAIR) near2 (RODRIGUEZ-HORNEDO)).INV.	US-PGPUB; USPAT	OR	OFF	2008/09/30 13:51
L4	77	(40/424).CCLS.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2008/09/30 14:23
L5	8	(400/424).CCLS.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2008/09/30 14:23
S2	2	("6559293").PN.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2008/07/30 09:53
S3	1	aspirin cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/12 14:28
S4	1	almarrson	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/12 14:29
S5	246	almarsson	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/12 14:29
S6	280	cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/12 14:30
S7	5	S5 S6	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/12 14:30

S8	1303795	crystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/12 14:30
S9	102	S5 S8	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/12 14:30
S10	17	aspirin crystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/12 14:36
S11	1	wo "0151919"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/12 14:51
S12	1	wo "0142222"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/12 14:59
S13	4182	supramolecul\$2	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/12 15:00
S14	31445	aspirin	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/12 15:00
S15	157	S13 S14	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/12 15:00
S16	5	S13 S14	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	WITH	OFF	2008/09/12 15:00
S17	2200	active pharmaceutical ingredient	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/12 15:02

S18	19	S13 S17	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/12 15:02
S19	2	heterosynthon	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/12 15:04
S20	47880	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetaminophen	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2008/09/30 08:31
S21	1329	co crystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/30 08:31
S22	126	S20 S21	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 08:31
S23	18	S20 S21	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	SAME	OFF	2008/09/30 08:31
S24	2	S22 and @pd< "20020301"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 08:45
S25	283	cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/30 08:48
S26	18	S20 S25	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 08:48
S27	57	co crystal.ti.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/30 09:39

S28	14	S27 drug	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 09:39
S29	458	Pharmaceutical co adj crystal compositions drugs	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 09:55
S30	543	Pharmaceutical co adj crystal composition drug	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 09:55
S31	543	Pharmaceutical (co adj crystal) composition drug	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 09:56
S32	29	Pharmaceutical (co adj crystal) composition drug	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	SAME	OFF	2008/09/30 09:56
S33	47	S31 and @pd<"20030303"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 09:56
S34	119	crystal engineering	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/30 10:03
S35	32	S34 and @pd<"20030303"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:03
S36	29	S34 drug	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:04
S37	4	S36 and @pd<"20030303"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:04

S38	228231	crystallization	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:26
S39	7179	S20 S38	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:26
S40	200	S20 S38	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	SAME	OFF	2008/09/30 10:26
S41	132	S40 and @pd< "20030303"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:26
S42	106	S20 S38	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	WITH	OFF	2008/09/30 10:26
S43	64	S42 and @pd< "20030303"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:27
S44	472	cocrystallization	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:28
S45	41	S20 S44	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:28

9/ 30/ 2008 2:23:43 PM

C:\ Documents and Settings\ sjavanmard\ My Documents\ EAST\ Workspaces\ 10378956.wsp

Substitute for form 1449B/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(use as many sheets as necessary)</i>		Complete if Known			
		Application Number	10/378,956		
		Filing Date	March 3, 2003		
		First Named Inventor	Michael J. Zaworotko		
		Group Art Unit	1627		
		Examiner Name	Sahar Javanmard		
Sheet	1	of	1	Attorney Docket Number	USF.106XC1

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	R1	Zaworotko, Michael J., "Binary Crystals by Design," Abstracts of Papers, 23rd ACS National Meeting, Orlando, FL, United States, April 7-11, 2002, IEC-030.	
	R2	Fleischman, Scott et al., "Crystal engineering of binary crystals that contain pharmaceutical molecules, Abstracts of Papers, 23rd ACS National Meeting, Orlando, FL, United States, April 7-11, 2002, IEC-076.	
	R3		
	R4		
	R5		
	R6		
	R7		
	R8		
	R9		
	R10		
	R11		
	R12		
	R13		

Examiner Signature	/Sahar Javanmard/	Date Considered	07/01/2013
--------------------	-------------------	-----------------	------------

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard T.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J./

UM00017195

NOVARTIS EXHIBIT 1517
 Novartis v. Regents, IPR2023-01347
 Page 4052 of 4460

Cocrystal structure of an editing complex of Klenow fragment with DNA

(3'–5' exonuclease/DNA polymerase/protein–DNA interaction/x-ray crystallography/metal ion catalysis)

P. S. FREEMONT*, J. M. FRIEDMAN, L. S. BEESE, M. R. SANDERSON†, AND T. A. STEITZ

Department of Molecular Biophysics and Biochemistry and the Howard Hughes Medical Institute at Yale University, New Haven, CT 06511

Communicated by Julian M. Sturtevant, August 26, 1988 (received for review July 21, 1988)

ABSTRACT High-resolution crystal structures of editing complexes of both duplex and single-stranded DNA bound to *Escherichia coli* DNA polymerase I large fragment (Klenow fragment) show four nucleotides of single-stranded DNA bound to the 3'–5' exonuclease active site and extending toward the polymerase active site. Melting of the duplex DNA by the protein is stabilized by hydrophobic interactions between Phe-473, Leu-361, and His-666 and the last three bases at the 3' terminus. Two divalent metal ions interacting with the phosphodiester to be hydrolyzed are proposed to catalyze the exonuclease reaction by a mechanism that may be related to mechanisms of other enzymes that catalyze phospho-group transfer including RNA enzymes. We suggest that the editing active site competes with the polymerase active site some 30 Å away for the newly formed 3' terminus. Since a 3' terminal mismatched base pair favors the melting of duplex DNA, its binding and excision at the editing exonuclease site that binds single-stranded DNA is enhanced.

The large proteolytic fragment (Klenow fragment) of *Escherichia coli* DNA polymerase I utilizes an editing 3'–5' exonuclease activity (1) to reduce the misincorporation of erroneous nucleotides by about 10-fold (2) at an active site that is some 30 Å away from the polymerase site of misincorporation (3). How might this be accomplished? The crystal structure of the Klenow fragment shows that it is folded into two domains (3). Various experiments (reviewed in ref. 4) establish that the domain to which the dNMP binds in the crystal catalyzes the 3'–5' exonuclease activity, whereas the larger C-terminal domain contains the active site for the polymerase reaction. Mutant proteins that contain amino acid changes in the dNMP binding site have been made by directed mutagenesis; they are devoid of exonuclease activity but retain full polymerase activity (5). Furthermore, the DNA encoding the C-terminal domain has been cloned, and the product has been expressed, isolated, and shown to possess significant DNA polymerase activity with no measurable 3'–5' exonuclease activity (6). The observation (3) that these two active sites are ≈25–30 Å apart poses the interesting question of how they work together to achieve high-fidelity synthesis of DNA.

The C-terminal domain contains a cleft that is large enough to accommodate the double-stranded B-DNA product of DNA synthesis (3). The approximate position of the 3' terminus of the primer strand has been derived from the cross-linking of 8-azido-dATP to Tyr-776, footprinting of Klenow fragment on DNA (7), and the position of site-directed mutants that alter polymerase activity but not exonuclease activity (A. Polesky and C. Joyce, personal communication). This model of DNA at the polymerase active site places about 8 base pairs (bp) of duplex product DNA in the cleft.

A more detailed understanding of the structural basis of the polymerase and exonuclease activities requires the separate determination of the crystal structures of suitable DNAs complexed with each of these two active sites on the Klenow fragment. We report here the high-resolution crystal structure analyses of three different complexes between DNA and the 3'–5' exonuclease active site. The structures of these complexes suggest a possible mechanism for the exonuclease reaction and provide some insight into how these two separate active sites might work together to enhance the accuracy of DNA synthesis.

EXPERIMENTAL METHODS

Structural Analysis. The first crystals of polymerase–DNA complex examined were obtained by cocrystallizing the Klenow fragment in the presence of a 2-fold molar excess of an 8-bp duplex DNA containing a 3-base single-stranded 5' overhang

($5' \text{ AGACCGCCCGG}$
 GGCGGGCC). These crystals were grown

from solutions containing 38% (wt/vol) saturated ammonium sulfate and 1 mM EDTA, which inhibits the 3'–5' exonuclease activity. In spite of the crystallization at high ionic strength, HPLC analysis of the crystals suggested a one-to-one stoichiometry of duplex DNA to protein as well as the presence of equimolar amounts of each strand (data not shown). The cocrystals are tetragonal space group $P4_3$ ($a = b = 104.7$ Å, $c = 86.0$ Å) and are isomorphous with the crystals of a native Klenow fragment (3) except for a 1-Å increase in the length of the a/b axes.

Two other complexes of the Klenow fragment with DNA were prepared by diffusing single-stranded deoxytetranucleotides into crystals of two different mutant proteins (5) that are devoid of 3'–5' exonuclease activity. Crystals of D424A (Asp-424 to Ala) and crystals of D355A, E357A (Asp-355 to Ala; Glu-357 to Ala) were soaked in solutions containing 1 mM p(dT)₄ for a period of 1 week. X-ray diffraction data were measured from crystals of all three of these DNA complexes to high resolution by using a Mark II two-dimensional position-sensitive area detector (8) (Table 1).

RESULTS

Editing Complex with Duplex DNA. Although the duplex DNA substrate was expected to form a complex at the polymerase active site, it binds to the 3'–5' exonuclease active site under the high ionic strength conditions of the crystallization. The 3.5-Å resolution difference electron density map between the DNA complex and the metal-free

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

*Present address: Imperial Cancer Research Fund Laboratories, London, England.

†Present address: Cancer Research Campaign Biomolecular Structure Unit, The Institute of Cancer Research, Sutton, Surrey, England.

Table 1. Data collection and soaking

Crystals*	Maximum resolution, [†] Å	Unique reflections, no.	Rmerge, [‡] %	Isomorphous differences, [§] %
Klenow (citrate)	2.8	18,900	4.1	11.4
Klenow (SAS)	3.3	11,100	3.3	—
Klenow cocrystals	3.8	6,500	4.1	19.6 (19.4) [¶]
D424A/p(dT) ₄	2.9	16,200	5.1	15.1
D355A,E357A/p(dT) ₄	3.1	13,700	5.6	14.5

*Klenow DNA cocrystals and Klenow (citrate) crystals were soaked in 60% saturated ammonium sulfate/1 mM EDTA/200 mM citrate, pH 5.6. Klenow (SAS) crystals were soaked in 70% saturated ammonium sulfate/1 mM ZnSO₄/20 mM MgSO₄/66 mM Pipes, pH 7.0 (SAS buffer). The D424A and D355A,E357A mutant crystals were soaked for 1 week in SAS buffer containing 1 mM p(dT)₄.

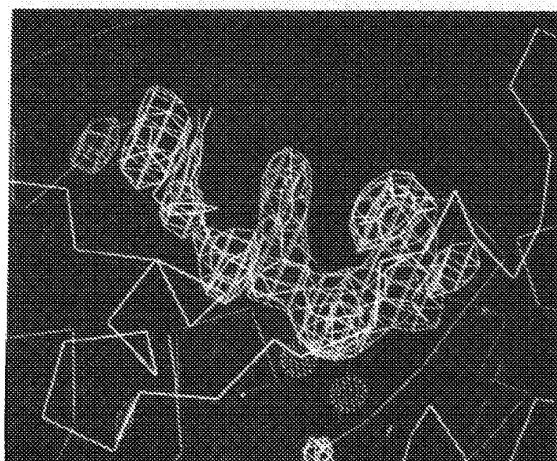
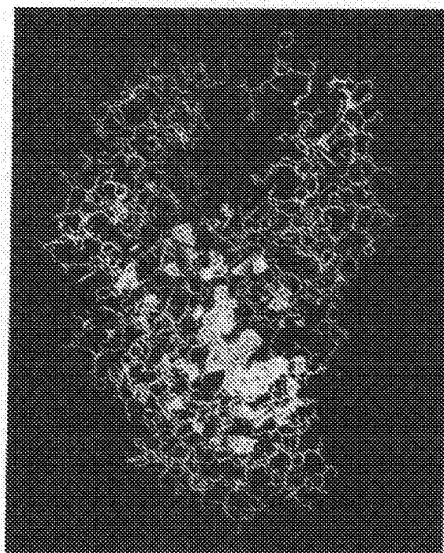
[†]Maximum resolution was chosen as the resolution where $\langle I \rangle_{\text{shell}} = 2 \langle (I \pm I^{-1})^2 \rangle_{\text{shell}}^{1/2}$.

[‡]Rmerge = $\sum_h (\sum_i |I_{ih} - \langle I_h \rangle|) / \sum_h \langle I_h \rangle$, where I_h = intensity of the i th observation of reflection h .

[§]The percent isomorphous differences were calculated against Klenow (SAS) between 20- and 3.8-Å resolution (20–3.8 Å for the Klenow cocrystal). $\sum_h |I_{hD} - I_{hN}| / \sum_h |I_{hD} + I_{hN}|$, where I_D and I_N are the observed diffraction intensities of the complexed and uncomplexed protein, respectively.

[¶]Calculated between Klenow cocrystal and Klenow (citrate), 20- to 3.8-Å resolution.

Klenow fragment shows electron density arising from three to four bases of ordered single-stranded DNA bound at the 3'–5' exonuclease active site and extending toward the cleft believed to bind duplex DNA (Fig. 1 *Upper*). The protein



appears to have at least partially denatured the DNA and bound to the 3' terminal sequence since the difference electron density can be fitted by the 3' terminal sequence but not the sequence of the 5' single-stranded overhang with its associated 5' phosphate. Numerous conformational changes are seen in the protein, prominent among these being a movement of two helices (helices I and H) (3) that make up one side of the DNA binding cleft.

It appears, therefore, that we have cocrystallized and determined the structure of an editing complex with DNA. It is not certain why the rest of the DNA does not appear in this difference electron density map. It may be partially disordered. Furthermore, the difference map has a high noise level due to the significant differences in structure between the complexed and uncomplexed enzyme.

Single-Stranded DNA Complex. Because it was clear from the complex with duplex DNA that the exonuclease active site contains a binding site for single-stranded DNA, p(dT)₄ was diffused into preformed crystals of two different mutant proteins deficient in 3'–5' exonuclease activity. High-resolution crystallographic analyses of these mutant proteins

Fig. 1. (*Upper*) Portion of the 3.8-Å resolution difference electron density map between the cocrystallized DNA complex and the metal-free native protein superimposed on the structure of the Klenow fragment. The structure factor amplitudes were measured from crystals soaked in 60% saturated ammonium sulfate/1 mM EDTA/200 mM citrate, pH 6.5. Electron density for 3 or 4 nucleotides is seen emanating from 3'–5' exonuclease active site and extending towards the large cleft in the protein. (*Lower*) Model of the single-strand DNA sequence (dT)₃ fitted into a 2.8-Å resolution difference electron density map between the (dT)₄ complex with D424A mutant protein and free native wild-type protein containing Zn²⁺ calculated by using $F_{\text{DNA complex}} - F_{\text{native}}$ as coefficients. The structure factor amplitudes $F_{\text{DNA complex}}$ were measured from crystals soaked in 1 mM p(dT)₄/70% saturated ammonium sulfate/1 mM ZnSO₄/20 mM MgSO₄/66 mM Pipes, pH 7.0. Wild-type Klenow crystals were soaked in 70% saturated ammonium sulfate/1 mM ZnSO₄/20 mM MgSO₄/66 mM Pipes, pH 7.0. The phases used in the calculation were experimentally derived isomorphous replacement phases between 20- and 8.0-Å resolution and calculated phases from 8.0- to 2.9-Å resolution. The positive electron density is contoured at a level of 4σ where σ is the root-mean-square density throughout the unit cell. The α -carbon backbone of the protein is superimposed. Only three nucleotides are shown. Although electron density for the fourth nucleotide is weak in this difference map, it is significantly stronger in a difference map in which data from the dTMP complex with the D424A mutant Klenow fragment are used as the parent. The two spheres are at the positions of the two divalent metal ions found in the dTMP complex. The high-resolution difference electron density maps of the Klenow–DNA cocrystal and the tetranucleotide complex with the D355A, E357A mutant Klenow fragment indicate a similar position for the tetranucleotide.

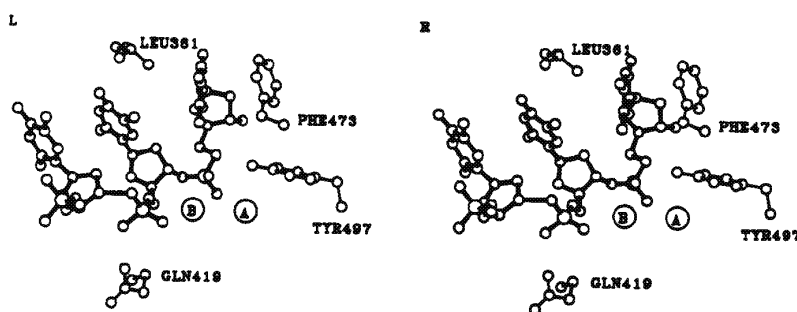


FIG. 2. Stereo drawing of some of the protein side chains (thin bonds) that interact with $p(dT)_3$ (thick bonds). The phenyl ring of Phe-473 interacts with the base of the 3' terminal nucleotide. The side chain of Leu-361 is wedged between the 3' terminal and penultimate bases. The two divalent metal ions are labeled A and B and have been placed in positions that had been previously determined in the dTMP complex. Only metal A is bound in the $(dT)_4$ complex with the mutant protein (1, 5). The penultimate phosphate is interacting with a main chain amide (not shown).

complexed with dNMP and divalent metals showed no major structural changes (5). The loss of exonuclease activity seems to be a direct consequence of the loss of the metal ion at site B in the D424A mutant and both metal ions in the D355A, E357A mutant protein. The high-resolution difference electron density maps (Fig. 1 *Lower*) show a substantially greater degree of structural isomorphism with the uncomplexed protein and essentially the same mode of binding single-stranded DNA as seen in the cocrystallized complex. Low-resolution studies (7 Å) of crystals soaked in longer single-stranded deoxyoligonucleotides did not show additional difference electron density suggesting that single-stranded DNA beyond four residues from the 3' terminus may be partially or totally disordered in these high ionic strength soaking conditions.

DNA-Protein Interactions. In all three complexes, the single-stranded DNA is bound to the 3'-5' exonuclease active site through several interactions with the protein (Fig. 2). Three protein side chains are making hydrophobic interactions with the 3' terminal three bases. Leu-361 is wedged between (and interacting with) both the 3' terminal and penultimate bases. Phe-474 interacts with the other side of the 3' terminal base. The third base from the 3' terminus is interacting with His-660, which moves from its position in the native Klenow structure. The 3' terminal residue binds nearly identically to dTMP although its 5' phosphate may be in a slightly different orientation. The 3'-OH of the sugar moiety is buried and hydrogen-bonded to the backbone amide of Thr-358, as previously observed in the binding of dTMP (3).

The sugar-phosphate backbone of the single-stranded DNA interacts with three amino acid side chains and presumably also with the two divalent metal ions (Fig. 2). Although refinement will be required to confirm the existence of hydrogen bonds, it appears that the third phosphate from the 3' terminus is hydrogen-bonded to the guanidinium group of Arg-455; the penultimate phosphate is hydrogen-bonded to Gln-419 and a main chain amide of Met-458. In the complex with D424A, the phosphate of the bond to be cleaved is hydrogen-bonded to Tyr-497 and bound to a zinc ion at site A. If we assume that metal ion B binds as observed in the complex with dNMP, then it would also interact with the same phosphate in the DNA complex.

The conformation of the single-stranded DNA is extended. The binding site will only accommodate single-stranded DNA; it appears impossible to build into the model a complementary single strand without creating numerous close contacts. This is consistent with the results of Brutlag and Kornberg (9) who concluded from the temperature dependence of 3'-5' exonuclease reaction that the 3' terminus must be single stranded in the exonuclease active site.

However, our observation that four 3' terminal nucleotides of a duplex become single stranded indicates a larger degree of melting of the duplex than previously anticipated. The bound single-stranded DNA in all three complexes has a very similar, but probably not identical, structure and orientation on the protein.

DISCUSSION

Mechanism of 3'-5' Exonuclease. The structural studies reported here as well as previous studies place constraints on the possible catalytic mechanisms of the 3'-5' exonuclease reaction. Assuming that the complex observed with the deoxytetranucleotide substrate approximates a Michaelis complex, it appears that only the two divalent metal ions assumed to be bound at sites A and B and the γ -OH of Tyr-497 are in close enough contact with the phosphate of the bond to be cleaved to directly affect hydrolysis. Other protein side chains appear too far away to be directly involved with catalysis. These metal ion sites in the crystalline complex with dTMP can be substituted by Mn^{2+} , Zn^{2+} , or Mg^{2+} although the metal ion *in vivo* is unknown. The fact that the divalent metal ion at site B is essential for 3'-5' exonuclease activity was demonstrated by the failure of the D424A mutant protein lacking this metal site B to catalyze this hydrolysis (5). Gupta and Benkovic (10) showed that the hydrolysis results in inversion of configuration at phosphorus. Assuming that the reaction is an associative in-line mechanism and proceeds through a transient pentacoordinate species, then the water molecule must attack from an apical position opposite the leaving 3'-OH.

Although we do not see a water molecule bound in the appropriate attacking position in this inactive complex, the observed position of the leaving group plus the requirement that the reaction proceed with inversion of configuration (10) necessitates that this water molecule attack from a position near the γ -OH of Tyr-497 and metal ion A (Figs. 2 and 3). There are no other protein side chains in the vicinity that could function as a general base.

It appears plausible that metal ion B may function to stabilize the transient pentacoordinate species and/or to facilitate the leaving of the 3' oxyanion from an axial position; the metal ion A may facilitate the formation of an attacking hydroxide ion. Herschlag and Jencks (11) have concluded from a series of nucleophilic displacement reactions at phosphorus that divalent metal ions can serve to stabilize an oxyanion leaving group. Thus for phosphomonoesters, divalent metal ions render phospho-group transfer less sensitive to the nucleophilicity of the attacking group while increasing the overall reaction rate. We suggest that the metal ion in site

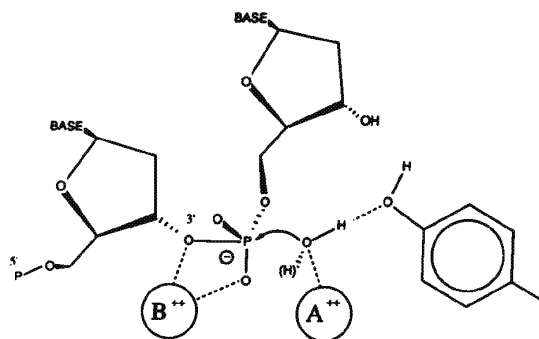


FIG. 3. Proposed enzymatic mechanism for the 3'-5' exonuclease reaction. Two divalent metal ions (Mg^{2+} , Mn^{2+} , or Zn^{2+} *in vitro*) are represented by A and B. Metal ion B is proposed to stabilize the transient pentacoordinate species and the leaving of a 3' oxyanion, whereas metal ion A may facilitate the formation of an attacking water or hydroxide ion. The metal ions are separated by 4.3 Å.

B could be playing an additional role in stabilizing the transient pentacoordinate species. The hydrolysis of methylethylene phosphate proceeds some 10^6 times faster than the trimethyl analog (12), presumably because the ethylene bridge strains the O—P—O bond angle to 99° , 10° less than the tetrahedral angle (13). Perhaps metal ion B performs a function analogous to that played by the ethylene group in methylethylene phosphate by reducing the energy required to form the 90° O—P—O bond angle between apical and equatorial oxygens in the transition state (Fig. 3). A similar hypothesis has been proposed to explain the enhancement of hydrolysis of methyl phosphate when bound to the cobalt(III) ion (14). The metal ion A might be stabilizing a hydroxide ion to facilitate the attack on phosphate by water. Both the structure of the catalytic site and the proposed mechanism are reminiscent of the active site and mechanism for one step of the two-step reaction proposed for alkaline phosphatase (15), which has two bound zinc atoms 4 Å apart that interact with phosphate.

Whether Tyr-497 serves primarily to orient the substrate and/or a water molecule or plays a more vital role in catalysis can be tested by site-directed mutagenesis.

The phospho-group transfer reaction catalyzed by the 3'-5' exonuclease of DNA polymerase I is similar to (or in some cases the same as) the phospho-group transfer reactions catalyzed by those enzymes in which the catalytic function is provided by an RNA molecule alone (21, 22). This raises the possibility that the catalytic mechanisms of these RNA enzymes may also be related to the catalytic mechanism of the DNA polymerase I 3'-5' exonuclease. What makes this type of mechanism a particularly attractive possibility for RNA enzymes is that it may require only the involvement of two appropriately positioned metal ions and perhaps a tyrosyl hydroxyl and does not appear to necessitate the involvement of any side chains with the specialized chemical properties found in protein-based enzymes. The RNA enzymes would be required to (i) bind two magnesium ions 4.3 Å apart and (ii) bind and orient the RNA substrate(s) in appropriate juxtaposition to these two metal ions.

Relationship Between the Exonuclease and Polymerase Active Sites. How then do the polymerase and 3'-5' exonuclease active sites work together to assure that mismatched base pairs incorporated at the polymerase active site are edited out at the 3'-5' exonuclease active site some 25 to 30 Å away? An earlier hypothesis proposed that the exonuclease activity was a manifestation of a different conformational state of the polymerase active site and that the two active sites were in the same position (1). It has now been established, however,

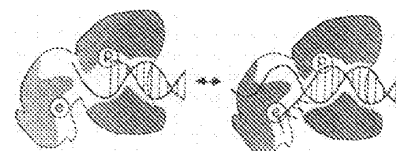
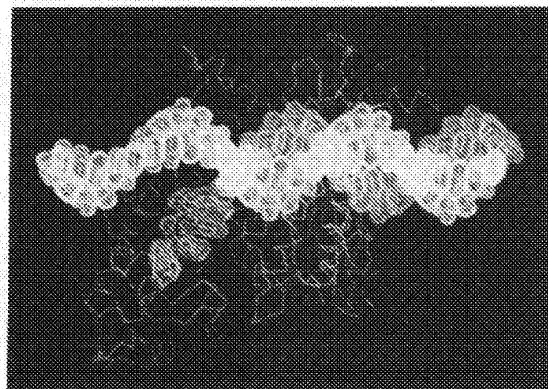


FIG. 4. (Upper) Model of the Klenow fragment and model-built DNA with the 3' terminus of the primer strand (blue and orange) placed in the exonuclease active site. The DNA is represented by a skeletal model superimposed on a Van der Waals dot surface. The structure of the four single-stranded nucleotides in the model are experimentally derived (orange), whereas the remaining DNA is model built. Note that the 3' terminus of the model-built duplex DNA is adjacent to the 5' terminus of the single-stranded DNA. (Lower) Schematic drawings of Klenow fragment with DNA in the polymerase active site (Left) and exonuclease active site (Right). To slide from the polymerase to exonuclease active sites, the path of the 3' terminus follows about four nucleotides of duplex DNA and four nucleotides of single-stranded DNA. A pathway involving dissociation is also possible.

that the polymerase and exonuclease activities reside on different subunits in the case of DNA polymerase III (16, 17) and on different domains of the same polypeptide chain in the case of DNA polymerase I (5, 6). We have demonstrated here that the exonuclease active site is extensive and contains a binding site for four single-stranded nucleotides spanning a distance of some 15 Å from the 3' terminus.

Comparison of the crystal structure of the Klenow fragment complexed with single-stranded DNA at the exonuclease active site and the previously proposed model (3) with duplex DNA model built at the polymerase active site suggests that these two active sites might be in "communication" by virtue of the DNA sliding between them (Fig. 4). The 5' end of experimentally observed single-stranded DNA comes close to the 3' end of model-built duplex DNA forming a continuous pathway between the observed exonuclease and putative polymerase active sites. The path that the 3' terminus must follow to proceed from the presumed polymerase active site to the exonuclease active site involves ≈ 4 bp of duplex DNA plus four bases of single-stranded frayed end.

Structural Basis of Editing. We suppose that after each polymerization step the 3' terminus of the DNA may dissociate from the polymerase active site but not necessarily from the protein; rather, the protein may diffuse along the DNA. DNA polymerase I, like other polymerases, is processive (18) in that it incorporates about 20–25 nucleotides between each dissociation from the DNA. Thus, access of both active sites to the 3' terminus after each nucleotide incorporation may require the 3' terminus to slide between the sites some

portion of the time. Since the 3'-5' exonuclease activity excises $\approx 10\%$ of all correctly incorporated nucleotides (19), it appears that the polymerase and exonuclease activities are in a delicately poised competition. In order for the two active sites to compete for the newly formed 3' terminus, the rate of sliding between these two active sites would have to be faster than either of the two enzymatic rates. This would require that the DNA must slide the distance of 25 Å in less than 100 msec, a rate that is not unreasonably large (18).

For the 3'-5' exonuclease to improve the fidelity of DNA synthesis, the enzyme must exert a significant bias in favor of excising mismatched base pairs over correctly matched base pairs (20). This requires the enzyme to exhibit an increased rate of exonuclease activity and/or a decreased rate of polymerase activity on 3' terminal mismatched base pairs. How is this achieved? Since the 8-bp duplex DNA used in the cocrystallization experiment is found to bind with at least four nucleotides becoming single stranded, the melting of 4 bp at the 3' terminus appears necessary for the 3' terminus to bind to the exonuclease active site. If formation of single-stranded DNA is rate limiting, an increased exonuclease activity on DNAs containing mismatched base pairs could result from an increased rate of melting reflected in its lower thermal stability. Since a mismatched base pair in any of the four 3' terminal nucleotides reduces free energy cost of forming a four nucleotide single-stranded DNA, binding of a mismatched 3' terminus to the exonuclease active site would be enhanced relative to its binding to the polymerase active site. In fact, this model predicts that any factor favoring the formation of single-stranded DNA at the 3' terminus and its binding to the exonuclease active site would enhance the efficiency of editing.

A reduced polymerase activity on DNAs containing mismatched base pairs would require their detection by the polymerase active site. Since many mismatched base pairs can assume the sugar-phosphate backbone structure of normal B-DNA, some other aspect of the mismatched base pair may be recognized by the enzyme. It has been suggested (23) that the enzyme may have a "reading head" in the minor groove that can detect mismatched base pairs and suppress either translocation or formation of a catalytically competent active site.

To provide a structural basis for understanding the role of the polymerase active site in the fidelity of this enzyme will require determination of the structure of a ternary complex of DNA and dNTP with the polymerase active site. Large crystals of D424A Klenow fragment have been grown at low ionic strength and neutral pH in the presence of DNA, α , β -methylene dTTP, and Mg^{2+} that may prove appropriate for these issues.

We thank Catherine Joyce, Nigel Grindley, Victoria Derbyshire, and Andrea Polesky for their continued help and suggestions; Harold Wyckoff and Olke Uhlenbeck for discussions; and Sherin Abdel-Meguid and colleagues at Monsanto for use of their Mark II area detector. This work was supported by American Cancer Society Grant NP-421 and National Institutes of Health Grant GM-22778 to T.A.S. and a Jane Coffin Childs Memorial Fund Fellowship to J.M.F.

1. Kornberg, A. (1980) *DNA Replication* (Freeman, San Francisco).
2. Loeb, L. A. & Kunkel, T. A. (1982) *Annu. Rev. Biochem.* **52**, 429-457.
3. Ollis, D. L., Brick, P., Hamlin, R., Xuong, N. G. & Steitz, T. A. (1985) *Nature (London)* **313**, 762-766.
4. Joyce, C. M. & Steitz, T. A. (1987) *Trends Biochem. Sci.* **12**, 288-292.
5. Derbyshire, V., Freemont, P. S., Sanderson, M. R., Beese, L. S., Friedman, J. M., Steitz, T. A. & Joyce, C. M. (1988) *Science* **240**, 199-201.
6. Freemont, P. S., Ollis, D. L., Steitz, T. A. & Joyce, C. M. (1986) *Proteins* **1**, 66-73.
7. Joyce, C. M., Ollis, D. L., Rush, J., Steitz, T. A., Konigsberg, W. H. & Grindley, N. D. F. (1986) in *Protein Structure, Folding and Design*, UCLA Symposia on Molecular and Cellular Biology, ed. Oxender, D. (Liss, New York), pp. 197-205.
8. Xuong, A. P., Freer, S. T., Hamlin, R., Neilsen, C. & Vernon, W. (1978) *Acta Crystallogr. Sect. A* **34**, 289-296.
9. Brutlag, D. & Kornberg, A. (1972) *J. Biol. Chem.* **247**, 241-248.
10. Gupta, A. P. & Benkovic, S. J. (1984) *Biochemistry* **23**, 5874-5881.
11. Herschlag, D. & Jencks, W. P. (1987) *J. Am. Chem. Soc.* **109**, 4665-4674.
12. Westheimer, F. H. (1968) *Acc. Chem. Res.* **1**, 70-79.
13. Steitz, T. A. & Lipscomb, W. N. (1965) *J. Am. Chem. Soc.* **87**, 2488-2489.
14. Farrell, F. J., Kjellstrom, W. A. & Spiro, T. G. (1969) *Science* **164**, 320-321.
15. Sowadski, J. M., Handschumacher, M. D., Murthy, H. M. K., Foster, B. A. & Wyckoff, H. W. (1985) *J. Mol. Biol.* **186**, 417-433.
16. Scheuermann, R. H. & Echols, H. (1984) *Proc. Natl. Acad. Sci. USA* **81**, 7747-7751.
17. Maki, H. & Kornberg, A. (1985) *J. Biol. Chem.* **260**, 12987-12992.
18. Berg, O. G., Winter, R. B. & von Hippel, P. H. (1982) *Trends Biochem. Sci.* **7**, 52-55.
19. Fersht, A. R., Knill-Jones, J. W. & Tsui, W.-C. (1982) *J. Mol. Biol.* **156**, 37-51.
20. Fersht, A. R. (1985) *Enzyme Structure and Mechanism* (Freeman, San Francisco), 2nd Ed.
21. Guerrier-Takeda, C., Gardiner, K., Marsh, T., Pace, N. & Altman, S. (1983) *Cell* **35**, 849-857.
22. Cech, T. R. (1987) *Science* **236**, 1532-1539.
23. Steitz, T. A. (1987) in *Biological Organization: Macromolecular Interactions at High Resolution*, eds. Burnett, R. & Vogel, H. J. (Academic, New York), pp. 45-55.

Substitute for form 1449A/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(use as many sheets as necessary)</i>				Complete if Known	
				Application Number	10/378,956
				Filing Date	March 3, 2003
				First Named Inventor	Michael J. Zaworotko
				Art Unit	1627
				Examiner Name	Sahar Javanmard
Sheet	1	of	2	Attorney Docket Number	USF.106XC1

U.S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number - Kind Code ² (if known)			
	U1	US- 2010/0331285 A1	12-30-2010	Almarsson <i>et al.</i>	All
	U2				
	U3				
	U4				
	U5				
	U6				
	U7				
	U8				
	U9				

FOREIGN PATENT DOCUMENTS							
Examiner Initials*	Cite No. ¹	Foreign Patent Document		Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T ⁶
		Country Code ³ - Number ⁴ - Kind Code ⁵ (if known)					
	F1						
	F2						
	F3						
	F4						
	F5						
	F6						

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard T.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

J:\USF\106XC1\PTO\S\SB\08A\106XC1.doc ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J./

UM00017201

NOVARTIS EXHIBIT 1517
Novartis v. Regents, IPR2023-01347
Page 4058 of 4460

Substitute for form 1449B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet

2

of

2

Complete if Known

Application Number	10/378,956
Filing Date	March 3, 2003
First Named Inventor	Michael J. Zaworotko
Group Art Unit	1627
Examiner Name	Sahar Javanmard
Attorney Docket Number	USF.106XC.1

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. ¹	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, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
	R1	BOND, A.D. <i>et al.</i> "On the Polymorphism of Aspirin" <i>Angew. Chem. Int. Ed.</i> , 2007, 46:615-617.	
	R2	BOND, A.D. <i>et al.</i> "On the Polymorphism of Aspirin: Crystalline Aspirin as Intergrowths of Two "Polymorphic" Domains" <i>Angew. Chem. Int. Ed.</i> , 2007, 46:618-622.	
	R3	SUMMERS, M.P. <i>et al.</i> "The polymorphism of aspirin" <i>J. Pharm. Pharmac.</i> , 1970, 22:615-616.	
	R4	WHEATLEY, P.J. "The Crystal and Molecular Structure of Aspirin" <i>J. Chem. Soc.</i> , 1964, 6036-6048.	
	R5	Office Action dated April 13, 2011 in U.S. Application Serial No. 12/861,203, filed August 23, 2010.	
	R6		
	R7		
	R8		
	R9		
	R10		
	R11		
	R12		
	R13		

Examiner Signature	/Sahar Javanmard/	Date Considered	07/01/2013
-----------------------	-------------------	--------------------	------------

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kind codes of USPTO Patent Documents at www.uspto.gov or MPEP901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard T.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J./

UM00017202

NOVARTIS EXHIBIT 1517

Novartis v. Regents, IPR2023-01347

Page 4059 of 4460

<i>Index of Claims</i> 	Application/Control No. 10378956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.
	Examiner SAHAR JAVANMARD	Art Unit 1627

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

☐ Claims renumbered in the same order as presented by applicant		☐ CPA		☐ T.D.		☐ R.1.47			
CLAIM		DATE							
Final	Original	09/30/2008	09/28/2009	06/18/2010	07/01/2013				
	1	-	-	-	-				
	2	-	-	-	-				
	3	-	-	-	-				
	4	-	-	-	-				
	5	-	-	-	-				
	6	-	-	-	-				
	7	-	-	-	-				
	8	-	-	-	-				
	9	-	-	-	-				
	10	-	-	-	-				
	11	-	-	-	-				
	12	-	-	-	-				
	13	-	-	-	-				
	14	-	-	-	-				
	15	-	-	-	-				
	16	-	-	-	-				
	17	-	-	-	-				
	18	-	-	-	-				
	19	-	-	-	-				
	20	-	-	-	-				
	21	-	-	-	-				
	22	-	-	-	-				
	23	-	-	-	-				
	24	-	-	-	-				
	25	✓	✓	✓	✓				
	26	-	-	-	-				
	27	✓	✓	✓	✓				
	28	✓	✓	✓	✓				
	29	-	-	-	-				
	30	-	-	-	-				
	31	-	-	-	-				
	32	-	-	-	-				
	33	-	-	-	-				
	34	-	-	-	-				
	35	-	-	-	-				
	36	-	-	-	-				

<i>Index of Claims</i> 	Application/Control No. 10378956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.
	Examiner SAHAR JAVANMARD	Art Unit 1627

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

☐ Claims renumbered in the same order as presented by applicant		☐ CPA		☐ T.D.		☐ R.1.47			
CLAIM		DATE							
Final	Original	09/30/2008	09/28/2009	06/18/2010	07/01/2013				
	37	✓	✓	✓	✓				
	38	✓	✓	✓	✓				
	39			✓	✓				
	40			✓	✓				
	41			✓	✓				
	42			✓	✓				
	43			○	✓				
	44			○	○				
	45			○	○				
	46			✓	✓				
	47			✓	✓				
	48			✓	✓				
	49			✓	✓				
	50				✓				
	51				✓				
	52				✓				
	53				✓				

Search Notes 	Application/Control No. 10378956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.
	Examiner SAHAR JAVANMARD	Art Unit 1627

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
424	400 (update 7/1/13)	9/30/2008	

SEARCH NOTES		
Search Notes	Date	Examiner
EAST (searched each inventor name)(update 6/17/10)	8/31/2009	SJ
EAST (keyword search)(update 6/17/10)	8/31/2009	SJ
Pubmed	8/31/2009	SJ
Google	8/31/2009	SJ
(update 7/1/13)		sj

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

/S. J./ Examiner, Art Unit 1627	
------------------------------------	--

To: euspto@slepatents.com,,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 23557

Aug 02, 2013 05:27:17 AM

Dear PAIR Customer:

SALIWANCHIK, LLOYD & EISENSCHENK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 23557 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

Disclaimer:

The list of documents shown below is provided as a courtesy and is not part of the official file wrapper. The content of the images shown in PAIR is the official record.

Application	Document	Mailroom Date	Attorney Docket No.
10378956	CTNF	08/02/2013	USF.106XC1
	892	08/02/2013	USF.106XC1
	1449	08/02/2013	USF.106XC1
	1449	08/02/2013	USF.106XC1
	1449	08/02/2013	USF.106XC1
	1449	08/02/2013	USF.106XC1
	1449	08/02/2013	USF.106XC1
	1449	08/02/2013	USF.106XC1
	1449	08/02/2013	USF.106XC1
	1449	08/02/2013	USF.106XC1

To view your correspondence online or update your email addresses, please visit us anytime at <https://sportal.uspto.gov/secure/myportal/privatepair>.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Michael J. Zaworotko
Application No.: 10/378,956
Confirmation No.: 4742
Filed: March 3, 2003
For: MULTIPLE-COMPONENT SOLID PHASES
CONTAINING AT LEAST ONE ACTIVE
PHARMACEUTICAL INGREDIENT
Examiner: Javanmard Sahar
Art Unit: 1627

Certificate of Electronic Filing Under 37 CFR 1.8

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

Dated: January 14, 2014

Electronic Signature for Nicole M. Forgrave: /Nicole M. Forgrave/

RESPONSE TO NON-FINAL OFFICE ACTION

Mail Stop Amendment

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

Dear Commissioner:

In response to the Office Action dated August 2, 2013, Applicant respectfully requests entrance of the following Amendment and consideration of the following Remarks. The deadline for responding to the Office Action is December 3, 2013.

Please amend the above-identified Application as follows:

Amendments to the Claims are reflected in the Listing of Claims, which begins on on page 2 of this paper.

Remarks/Arguments begin on page 8 of this paper.

AMENDMENTS TO THE CLAIMS

This Listing of Claims will replace all prior versions, and listings, of claims in the Application:

Listing of Claims

1-24 (canceled).

25. (currently amended). A method for ~~the designing and preparing preparation of~~ a co-crystal, said method comprising:

(a) providing an active pharmaceutical ingredient (API) comprising ~~at least one~~ a first chemical functionality, wherein ~~at least one of said first~~ chemical functionality ~~functionalities~~ forms ~~a synthon of a supramolecular~~ API homosynthons comprising a hydrogen bond;

(b) identifying and selecting ~~at least one~~ a co-crystal former from among a plurality of candidate co-crystal formers, ~~wherein by determining that~~ said selected co-crystal former(s) forms a ~~second~~ supramolecular synthon via non-covalent hydrogen bonding between the first chemical functionality and the second chemical functionality ~~a complementary second chemical functionality of said co-crystal former(s) that is identified to form a non-covalent bond with at least one of said chemical functionalities of said API~~, wherein ~~at least one of~~ said selected co-crystal formers in its pure form is a solid at room temperature and atmospheric pressure and wherein the co-crystal former is not an active pharmaceutical ingredient; and

(c) preparing a co-crystal comprising stoichiometric proportions of said API and said selected co-crystal former(s) upon formation of said ~~second~~ supramolecular synthon by said non-covalent bonding between said complementary chemical functionality of said co-crystal former(s) and said chemical functionality of said API.

26. (canceled).

27. (cancelled).

28. (previously presented). The method of claim 25, wherein said preparing comprises crystallization from solution, crystallization from a melt, sublimation, or grinding.

29-36. (canceled).

37. (previously presented). The method according to claim 25, wherein said API is selected from aspirin, ibuprofen, flurbiprofen, carbamazepine, phenytoin or acetaminophen.

38. (cancelled).

39. (currently amended). The method of claim 25, wherein the ~~at least one~~ co-crystal former is a GRAS compound.

40. (currently amended). The method of claim 25, wherein the ~~at least one~~ co-crystal former is a food additive.

41. (currently amended). The method of claim 25, wherein the ~~at least one~~ co-crystal former is a low toxicity organic.

42. (currently amended). The method of claim 25, wherein the ~~at least one~~ co-crystal former is a metal organic complex.

43. (currently amended). The method of claim 25, wherein the ~~at least one~~ co-crystal former comprises at least two heterocyclic groups.

44. (currently amended). The method of claim 25, wherein the ~~at least one~~ co-crystal former is bipyridine.

45. (currently amended). The method of claim 25, wherein the ~~at least one~~ co-crystal former is bis(pyridyl)ethene.

46. (currently amended). The method of claim 25, wherein said ~~first supramolecular~~ homosynthon is identified from the crystal structure of said API.

47. (currently amended). The method of claim 25, wherein said ~~first supramolecular~~ homosynthon is identified by determining the structure of at least one pure solid phase of said API.

48. (currently amended). The method of claim 25, wherein the ~~at least one identified~~ complementary second chemical functionality is an unsaturated N-heterocycle, saturated N-heterocycle, aldehyde, amide, carboxylic acid, nitro, ketone, or sulfoxide.

49. (currently amended). The method of claim 25, wherein the ~~at least one identified~~ complementary second chemical functionality is a carboxylic acid.

50. (currently amended). The method of claim 25, wherein said ~~identified complementary chemical functionality of said co-crystal former is complementary to said chemical functionality of said API that comprises said first supramolecular synthon and said second supramolecular synthon with the loss of said first supramolecular synthon to form said co-crystal~~ comprises heterosynthons of said co-crystal former and said API.

51. (currently amended). The method of claim 25, wherein said ~~identified complementary chemical functionality of said co-crystal former is complementary to said chemical functionality of said API other than said chemical functionality that forms said first supramolecular synthon, wherein said first supramolecular synthon is retained in addition to said second supramolecular synthon of said co-crystal~~ comprises homosynthons of said API.

52. (currently amended). The method of claim 25, wherein said first chemical functionality ~~that comprises said first supramolecular synthon~~ is an acid, amide, alcohol, phenol, thiol, or other hydrogen bond former, comprising a hydrogen bond donor, wherein no covalent bonds are formed upon said non-covalent bonding between said co-crystal former and complementary ~~chemical functionality that forms said second supramolecular synthon and said chemical functionality of said API.~~

53. (currently amended). The method of claim 25, wherein said complementary second chemical functionality ~~that comprises said second supramolecular synthon~~ is an amine, amide, unsaturated aromatic nitrogen bases, or other ~~supramolecular heterosynthon hydrogen bond former~~ chemical functionality that lacks a hydrogen bond donor, wherein no covalent bonds are formed upon said non-covalent bonding between said co-crystal former and complementary ~~second chemical functionality and said chemical functionality of said API to form said second supramolecular synthon.~~

54. (new). The method of claim 25, wherein the non-covalent bonding between said co-crystal former and complementary second chemical functionality and said chemical functionality of said API to form said supramolecular synthon comprises carbonyl:amine hydrogen bonding.

55. (new). The method of claim 25, wherein the non-covalent bonding between said co-crystal former and complementary second chemical functionality and said chemical functionality of said API to form said supramolecular synthon comprises carboxylic acid:pyridine hydrogen bonding.

56. (new). The method of claim 51, wherein the non-covalent bonding of said homodimers is carboxylic acid:carboxylic acid hydrogen bonding.

57. (new). The method of claim 51, wherein the non-covalent bonding of said homodimers is carboxamide hydrogen bonding.

58. (new). A method for the preparation of a pharmaceutical product containing a co-crystal, said method comprising:

(a) providing an active pharmaceutical ingredient (API) comprising a first chemical functionality, wherein said first chemical functionality forms a first crystal of API homosynthons that is non-covalent hydrogen bonding;

(b) selecting a co-crystal former having a second chemical functionality complementary to the first chemical functionality via non-covalent bonding, wherein said co-crystal former forms a supramolecular synthon by non-covalent hydrogen bonding between the first chemical functionality of the API and the complementary second chemical functionality of said co-crystal former, wherein said selected co-crystal former in its pure form is a solid at room temperature and atmospheric pressure;

(c) preparing a co-crystal of stoichiometric proportions of said API and said co-crystal former, said co-crystal consisting of said supramolecular synthon, and

(d) combining said co-crystal with a pharmaceutically acceptable carrier to form the pharmaceutical product.

59. (new). The method of claim 58, wherein said co-crystal comprises heterosynthons of said co-crystal former and said API.

60. (new). The method of claim 58, wherein said co-crystal comprises homosynthons of said API.

61. (new). The method of claim 58, wherein said first chemical functionality is an acid, amide, alcohol, phenol, or thiol.

62. (new). The method of claim 58, wherein said complementary second chemical functionality is an amine, amide, or unsaturated aromatic nitrogen base.

63. (new). The method of claim 58, wherein the non-covalent bonding between said co-crystal former and complementary second chemical functionality and said chemical functionality of said API to form said supramolecular synthon comprises carbonyl:amine hydrogen bonding.

64. (new). The method of claim 58, wherein the non-covalent bonding between said co-crystal former and complementary second chemical functionality and said chemical functionality of said API to form said supramolecular synthon comprises carboxylic acid:pyridine hydrogen bonding.

65. (new). The method of claim 58, wherein the non-covalent bonding of said homodimers is carboxylic acid:carboxylic acid hydrogen bonding.

66. (new). The method of claim 58, wherein the non-covalent bonding of said homodimers is carboxamide hydrogen bonding.

REMARKS

In response to the Office Action mailed August 8, 2013, Applicants respectfully request reconsideration. All of the issues raised in the Office Action have been carefully considered and are addressed herein.

Claims 25, 27-28, and 37-53 are pending in this application. By this Amendment, 25, 38, and 39-53 are amended, claim 27 is canceled, and new claims 54-66 are added. Accordingly, claims 25, 28, and 37-66 are under consideration by the Examiner at this time, with claims 25 and 58 being independent. No new matter has been added.

The foregoing amendments to and cancelations of the claims should not be construed as an acquiescence to the Examiner's comments in the Office Action and were done solely to expedite prosecution and allowance of the pending claims. Applicant reserves the right to pursue the subject matter of the claims as originally filed or previously pending prior to entry of this Amendment in this or one or more continuing applications claiming priority to the present Application.

The application as now presented is believed to be in allowable condition. Each of the rejections levied by the Office Action is addressed in turn below.

Interview

The Examiner and the Examiner's supervisor are thanked for the courtesy extended during the interview on December 18, 2013. The substance of the Applicants remarks at the interview are presented below.

I. The Invention

The invention is directed to the rational design of drug co-crystals. The present claims are directed to a method for screening, selecting and preparing such drug co-crystals. It was explained at the Interview that prior to the present invention, it was not understood even by leading scientists which chemical factors would predetermine the formation of a drug co-crystal. The aspects of different kinds of charges, functional groups, size and shape in molecules and the relationships between them were heretofore not understood in a manner that one could predictably- to almost a certainty- predesign a co-crystal. In short, prior to this invention, co-

crystals were like polymorphs, solvates and hydrates in that random trial-and-error was used to isolate them. Subsequent to this invention, co-crystals became readily available through a design strategy based upon supramolecular synthons. Co-crystals are in a sense now similar to salts, the existence of which is predictable according to the “delta pK rule”. The present inventor discovered the critical aspects which control the formation of drug co-crystals, and demonstrated the power of this discovery by making numerous such co-crystals without trial and error, something that heretofore was not remotely possible. This discovery has marked a sea-change in drug development as evidenced by patent applications, scientific publications, NDAs and ANDAs filed and commercial activity all focused upon drug co-crystals.

The claims are directed to the process for identifying, selecting and preparing a co-crystal. The process involves identifying which entities will form supramolecular synthons through non-covalent hydrogen bonding, all of which can be predicted in advance. These synthons form the smallest, basic repeating unit of the co-crystal. It was described how one starts with identifying whether and how a drug forms a homosynthon through non-covalent hydrogen bonding. For those drugs which form a homosynthon, it then can be determined what chemical moiety will form a supramolecular synthon with that drug, either by (i) non-covalent hydrogen bonding with the moieties forming the homosynthon of the drug and not disrupting the the homosynthon of the drug or by (ii) non-covalent hydrogen bonding with the moieties forming the homosynthon of the drug and disrupting the homosynthon of the drug to form a heterosynthon.

II. Rejections Under 35 U.S.C. §102(b)

Claims 25, 27-28, 37-43, and 46-53 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Jackson (GB 2169601) (hereinafter “Jackson”), Caira (Journal of Chemical Crystallography, 1994, 24(10) 695-701) (hereinafter “Caira”), and Freemont (Proc. Natl. Acad. Sci. USA, 1988, 85, 8924-8929) (hereinafter “Freemont”). Specifically, the Examiner asserts that “Jackson teaches sucralose co-crystallized with an aliphatic or cyclic secondary or tertiary amine, specifically niacinamide”, Caira teaches “1:1 complexation of 5-methoxysulfadiazine with acetylsalicylic acid”, Freemont “discloses high-resolution crystal structures of editing

complexes of both duplex and single-stranded DNA bound to *Escherichia coli* DNA polymerase I large fragment (Klenow fragment) show four nucleotides of single-stranded DNA bound to the 3'-5' exonuclease active site and extending toward the polymerase active site".

Regarding the Examiner's assertions that Jackson meets the limitations of claim 25, 27, 28, 38-41, 43, 48, and 51-53, Applicant respectfully disagrees. The limitations of claim 25, amended herein, comprise "(c) preparing a co-crystal comprising *stoichiometric* (emphasis added) proportions of said API and said selected co-crystal former". Jackson does not teach or suggest every element of the amended claim as the alleged "co-crystals" provided by Jackson are a.) formed over and b.) demonstrate the desired effect over a *broad range* of compound ratios. For example, Jackson states "better compounds provide a crystalline sucralose containing 0.2 to 3% of amino acid" (page 1, line 39-40) and "if a solution of sucralose in ethyl acetate is augmented with 1 to 10% by weight (based on the sucralose) of niacinamide, the sucralose can be crystallized from the solution... to give a fine crystalline material containing about 0.3 - 0.9% of niacinamide in the sucralose" (page 1, lines 47-50).

The co-crystals embodied within the limitations of claim 25 are formed and demonstrate their desired benefit in *discrete stoichiometric ratios* (e.g. 1:1:1 stoichiometry, ex. 1, 1:1 stoichiometry, ex. 2, 2:1 stoichiometry, ex. 3, 2:3 stoichiometry, ex. 10). Thus, claim 25, as amended, and claims 28, 38, 40, 41, 43, 48, and 51-53 depending therefrom, are novel over Jackson. Claims 27 and 39 are cancelled, rendering these objections moot. Applicant respectfully requests that this rejection be withdrawn.

Regarding the Examiner's assertions that Cairra meets the limitations of claim 25, 37, 38, 48, 49, and 51-53, Applicant submits that all the claims as amended are novel in view of Cairra. Claim 25 requires that the co-crystal former is not an active pharmaceutical ingredient. Cairra does not teach or suggest every element of the amended claim, because Cairra, if it does in fact teach a crystal structure, teaches such a structure formed of two pharmaceutical ingredients. The co-crystal former in Cairra is acetylsalicylic acid (aspirin). Thus, claim 25, as amended, and all claims depending therefrom, are novel over Cairra. Applicant respectfully requests that this rejection be withdrawn.

Regarding the Examiner's assertions that Freemont meets the limitations of claim 25, Applicant respectfully disagrees. The limitations of claim 25, amended herein, require that the API possess a chemical functionality that forms API homosynthons comprising a hydrogen bond. Freemont does not teach or suggest every element of the amended claim as the "duplex or single stranded DNA" (or "*Escherichia coli* DNA polymerase I large fragment [Klenow fragment])" as disclosed does not possess a chemical functionality that forms API homosynthons comprising a hydrogen bond. Freemont does not explicitly teach or address forming a homosynthon. Nor does Freemont inherently disclose such a capability. The size and complexity of Freemont's molecular entities, which individually possess numerous hydrogen bonding moieties, would result in an unpredictable range of molecular conformations. Thus, claim 25, as amended, and claim 42 depending therefrom, are novel over Freemont. Applicant respectfully requests that this rejection be withdrawn.

II. General Comments on Dependent Claims

Since each of the dependent claims depends from a base claim that is believed to be in condition for allowance, Applicants believe that it is unnecessary at this time to argue the allowability of each of the dependent claims individually. However, Applicants do not concur with the interpretation of the dependent claims as set forth in the Office Action, nor do the Applicants concur that the basis for the rejection of any of the dependent claims is proper. The Examiner has not made a *prima facie* case for rejecting the dependent claims, as the dependent claims include limitations not disclosed in the cited references, which limitations were not addressed by the Examiner. Therefore, Applicants reserves the right to specifically address the patentability of the dependent claims in the future should there be a need to do so.

CONCLUSION

It is respectfully believed that all of the rejections set forth in the Office Action have been addressed. However, the absence of a reply to a specific rejection, objection, or comment set forth in the Office Action does not signify agreement with or concession of that rejection, objection, or comment. In addition, there may be reasons for patentability of any or all pending claims (or other claims) that have not been expressed. Furthermore, nothing in this paper should be construed as an intent to concede any issue with regard to any claim.

In view of the foregoing remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this response, that the application is not in condition for allowance, the Examiner is requested to call the Applicants' representative at the telephone number indicated below to discuss any outstanding issues relating to the allowability of the application.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, please charge any deficiency to Deposit Account No. 23/2825, referencing Atty. Docket No. U0157.70023US01.

Respectfully submitted,

By: /Edward R. Gates/
Edward R. Gates, Reg. No. 31,616
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
Telephone: (617) 646-8000

Docket No.: U0157.70023US01
Date: 1/14/2014

Electronic Patent Application Fee Transmittal				
Application Number:		10378956		
Filing Date:		03-Mar-2003		
Title of Invention:		Multiple-component solid phases containing at least one active pharmaceutical ingredient		
First Named Inventor/Applicant Name:		Michael J. Zaworotko		
Filer:		Edward R. Gates/Nicole Forgrave		
Attorney Docket Number:		USF.106XC1		
Filed as Small Entity				
Utility under 35 USC 111(a) Filing Fees				
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:				
Extension - 3 months with \$0 paid	2253	1	700	700

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
Total in USD (\$)				700

Electronic Acknowledgement Receipt	
EFS ID:	17907390
Application Number:	10378956
International Application Number:	
Confirmation Number:	4742
Title of Invention:	Multiple-component solid phases containing at least one active pharmaceutical ingredient
First Named Inventor/Applicant Name:	Michael J. Zaworotko
Customer Number:	23557
Filer:	Edward R. Gates/Nicole Forgrave
Filer Authorized By:	Edward R. Gates
Attorney Docket Number:	USF.106XC1
Receipt Date:	14-JAN-2014
Filing Date:	03-MAR-2003
Time Stamp:	13:55:42
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	\$700
RAM confirmation Number	162
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
-----------------	----------------------	-----------	-------------------------------------	------------------	------------------

1	Transmittal Letter	U015770023US01-TRN-ERG.pdf	26232 4913196e81c569443a760906089ae7da7b651c47	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	U015770023US01-FEE-ERG.pdf	31986 28bfe84a1836dd9a11ad28f11d7e428084fb2b5	no	1
Warnings:					
Information:					
3	Extension of Time	U015770023US01-EXT-ERG.pdf	23420 90a6b71a3e53480df476f570aca6fb7ca4aa43ab	no	1
Warnings:					
Information:					
4		U015770023US01-AMN-ERG.pdf	58939 267e484b893213e0d4e875c7b6a35a3de9d3a6dd	yes	12
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	7	
	Applicant Arguments/Remarks Made in an Amendment		8	12	
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	30233 82d21069bfd965fe1f1c35b93f7e444764ee4752	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			170810		

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.

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 FORM <i>(to be used for all correspondence after initial filing)</i>	Application Number	10/378,956-Conf. #4742
	Filing Date	March 3, 2003
	First Named Inventor	Michael J. Zaworotko
	Art Unit	1627
	Examiner Name	S. Javanmard
Total Number of Pages in This Submission	Attorney Docket Number	U0157.70023US01

ENCLOSURES <i>(Check all that apply)</i>		
☒ Fee Transmittal Form ☐ Fee Attached ☒ Amendment/Reply ☐ After Final ☐ Affidavits/declaration(s) ☒ Extension of Time Request ☐ Express Abandonment Request ☐ Information Disclosure Statement ☐ Certified Copy of Priority Document(s) ☐ Reply to Missing Parts/Incomplete Application ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53	☐ Drawing(s) ☐ Licensing-related Papers ☐ Petition ☐ Petition to Convert to a Provisional Application ☐ Power of Attorney, Revocation Change of Correspondence Address ☐ Terminal Disclaimer ☐ Request for Refund ☐ CD, Number of CD(s) _____ ☐ Landscape Table on CD	☐ After Allowance Communication to TC ☐ Appeal Communication to Board of Appeals and Interferences ☐ Appeal Communication to TC (Appeal Notice, Brief, Reply Brief) ☐ Proprietary Information ☐ Status Letter ☐ Other Enclosure(s) (please identify below):
Remarks		

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT			
Firm Name	WOLF, GREENFIELD & SACKS, P.C.		
Signature	/Edward R. Gates/		
Printed name	Edward R. Gates		
Date	January 14, 2014	Reg. No.	31,616

Certificate of Electronic Filing Under 37 CFR 1.8	
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).	
Dated: January 14, 2014	Electronic Signature for Nicole M. Forgrave: /Nicole M. Forgrave/

3394283.1

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

FEE TRANSMITTAL				Complete if known							
				Application Number		10/378,956-Conf. #4742					
				Filing Date		March 3, 2003					
				First Named Inventor		Michael J. Zaworotko					
				Examiner Name		S. Javanmard					
☒ 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				Art Unit		1627					
TOTAL AMOUNT OF PAYMENT				(\$)		700.00					
METHOD OF PAYMENT (check all that apply) ☐ Check ☒ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____ ☐ Deposit Account Deposit Account Number: <u>23/2825</u> Deposit Account Name: <u>Wolff, Greenfield & Sacks, P.C.</u> 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	280	140*	70	600	300	150	720	360	180	_____	
Design	180	90	45	120	60	30	460	230	115	_____	
Plant	180	90	45	380	190	95	580	290	145	_____	
Reissue	280	140	70	600	300	150	2,160	1,080	540	_____	
Provisional	260	130	65	0	0	0	0	0	0	_____	
* The \$140 small entity status filing fee for a utility application is further reduced to \$70 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)				80		40		20			
Each independent claim over 3 (including Reissues)				420		210		105			
Multiple dependent claims				780		390		195			
Total Claims		Extra Claims		Fee (\$)		Fee Paid (\$)		Multiple Dependent Claims			
_____ - 20 or HP = _____		x _____		= _____		Fee (\$)		Fee Paid (\$)			
HP = highest number of total claims paid for, if greater than 20.											
Indep. Claims		Extra Claims		Fee (\$)		Fee Paid (\$)		Multiple Dependent Claims			
_____ - 3 or HP = _____		x _____		= _____		Fee (\$)		Fee Paid (\$)			
HP = highest number of independent claims paid for, if greater than 3.											
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 \$400 (\$200 for small entity) (\$100 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 _____		= _____		Fee Paid (\$)			
4. OTHER FEE(S) Non-English specification, \$130 fee (no small or micro entity discount) _____ Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, \$400 fee (\$200 small or micro entity) _____ Other (e.g., late filing surcharge): <u>2253</u> Extension for response within third month _____ 700.00											
SUBMITTED BY											
Signature		/Edward R. Gates/		Registration No.		31,616		Telephone		617.646.8000	
Name (Print/Type)		Edward R. Gates		Date		January 14, 2014					

Certificate of Electronic Filing Under 37 CFR 1.8

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

Dated: January 14, 2014

Electronic Signature for Nicole M. Forgrave: /Nicole M. Forgrave/

3394281.1

UM00017225

NOVARTIS EXHIBIT 1517

Novartis v. Regents, IPR2023-01347

Page 4082 of 4460

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)		Docket Number (Optional) U0157.70023US01	
Application Number 10/378,956-Conf. #4742		Filed March 3, 2003	
For MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT			
Art Unit 1627		Examiner S. Javanmard	

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))	\$200	\$100	\$50	\$ _____
☐ Two months (37 CFR 1.17(a)(2))	\$600	\$300	\$150	\$ _____
☒ Three months (37 CFR 1.17(a)(3))	\$1,400	\$700	\$350	\$ 700.00
☐ Four months (37 CFR 1.17(a)(4))	\$2,200	\$1,100	\$550	\$ _____
☐ Five months (37 CFR 1.17(a)(5))	\$3,000	\$1,500	\$750	\$ _____

☒ 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 23/2825.

☒ 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/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71. 37 CFR 3.73(b) statement is enclosed (Form PTO/SB/96).

☒ attorney or agent of record. Registration number 31,616.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

_____/Edward R. Gates/
Signature

Edward R. Gates
Typed or printed name

January 14, 2014
Date

617.646.8000
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.

Certificate of Electronic Filing Under 37 CFR 1.8	
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).	
Dated: January 14, 2014	Electronic Signature for Nicole M. Forgrave: /Nicole M. Forgrave/

3394284.1

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.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875				Application or Docket Number 10/378,956		Filing Date 03/03/2003		☐ To be Mailed	
ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO									
APPLICATION AS FILED – PART I									
(Column 1)		(Column 2)							
FOR		NUMBER FILED		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), (l), 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(j))		minus 20 =		*		X \$ =			
INDEPENDENT CLAIMS (37 CFR 1.16(h))		minus 3 =		*		X \$ =			
☐ 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))									
						TOTAL			
* If the difference in column 1 is less than zero, enter "0" in column 2.									
APPLICATION AS AMENDED – PART II									
(Column 1)		(Column 2)		(Column 3)					
AMENDMENT	01/14/2014	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	* 31	Minus	** 36	= 0	X \$40 =		0	
	Independent (37 CFR 1.16(h))	* 2	Minus	***9	= 0	X \$210 =		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	
(Column 1)		(Column 2)		(Column 3)					
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =			
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =			
	☐ 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.									
** 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 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.

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 OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS	Application Number		10/378,956-Conf. #4742	
	Filing Date		March 3, 2003	
	First Named Inventor		Michael J. Zaworotko	
	Title	MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE, etc.		
	Art Unit	1627		
	Examiner Name	S. Javanmard		
	Attorney Docket No.	U0157.70023US01		

I hereby revoke all previous powers of attorney given in the above-identified application.

☐ A Power of Attorney is submitted herewith.
OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

23628

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number	Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified application 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/Inventor.
OR

☒ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____

SIGNATURE of Applicant or Assignee of Record

Signature	Date	January 24, 2014
Name	Telephone	734-647-5234
Title and Company: Patent Administrator, The Regents of the University of Michigan		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of 1 forms are submitted.

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 TO PROSECUTE APPLICATIONS BEFORE THE USPTO

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

I hereby appoint:

☒ Practitioners associated with the Customer Number: 23628

OR

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

Name	Registration Number	Name	Registration Number

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

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

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name

Address

City

State

Zip

Country

Telephone

Email

Assignee Name and Address:

University of South Florida
3802 Spectrum Boulevard
Suite 100
Tampa, Florida 33612

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

SIGNATURE of Assignee of Record

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

Signature		Date	3/1/13
Name	Valerie Landrio McDevitt	Telephone	(813) 974-0994
Title	Assistant Vice President, Division of Patents & Licensing		

3014146.1

UM00017229

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: The Regents of the University of Michigan

Application No./Patent No.: 10/378,956 Filed/Issue Date: March 3, 2003

Titled: MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE
PHARMACEUTICAL INGREDIENT

The Regents of the University of Michigan, a corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. ☐ the assignee of the entire right, title, and interest in;
2. ☐ an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is _____ %); or
3. ☒ an assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)
the patent application/patent identified above by virtue of either:

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

OR

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

1. From: Nair Rodriguez-Hornedo To: The Regents of the University of Michigan
The document was recorded in the United States Patent and Trademark Office at
Reel 013743 , Frame 0500 , or for which a copy thereof is attached.
2. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.
3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

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

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

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

<u>/Edward R. Gates/</u>	<u>January 24, 2014</u>
Signature	Date
<u>Edward R. Gates</u>	<u>Attorney for Assignee</u>
Printed or Typed Name	Title

Certificate of Electronic Filing Under 37 CFR 1.8

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

Dated: January 24, 2014

Electronic Signature for Nicole M. Forgrave: /Nicole M. Forgrave/

3411678.1

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: University of South Florida

Application No./Patent No.: 10/378,956 Filed/Issue Date: March 3, 2003

Titled: MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE
PHARMACEUTICAL INGREDIENT

University of South Florida, a Non-profit corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. ☐ the assignee of the entire right, title, and interest in;
2. ☐ an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is _____ %); or
3. ☒ an assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)
the patent application/patent identified above by virtue of either:

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

OR

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

1. From: Michael J. Zaworotko To: University of South Florida
The document was recorded in the United States Patent and Trademark Office at
Reel 013743 , Frame 0500 , or for which a copy thereof is attached.
2. From: Brian Moulton To: University of South Florida
The document was recorded in the United States Patent and Trademark Office at
Reel 013743 , Frame 0500 , or for which a copy thereof is attached.
3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

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

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

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

/Edward R. Gates/
Signature
Edward R. Gates
Printed or Typed Name

January 24, 2014
Date
Attorney for Assignee
Title

Certificate of Electronic Filing Under 37 CFR 1.8

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

Dated: January 24, 2013

Electronic Signature for Nicole M. Forgrave: /Nicole M. Forgrave/

3370402.1

Electronic Acknowledgement Receipt	
EFS ID:	18020043
Application Number:	10378956
International Application Number:	
Confirmation Number:	4742
Title of Invention:	Multiple-component solid phases containing at least one active pharmaceutical ingredient
First Named Inventor/Applicant Name:	Michael J. Zaworotko
Customer Number:	23557
Filer:	Edward R. Gates/Nicole Forgrave
Filer Authorized By:	Edward R. Gates
Attorney Docket Number:	USF.106XC1
Receipt Date:	24-JAN-2014
Filing Date:	03-MAR-2003
Time Stamp:	16:06:40
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	Transmittal Letter	U015770023US01-TRN-ERG.pdf	26337 cacec4c57a5372d2aec10e515d13b125e10b60c9	no	1
Warnings:					
Information:					

2	Power of Attorney	U015770023US01-UM-POA-ERG.pdf	1300043 28bc9ccf3dfdac562d2bfe57a67c40fe3a6ccb8b	no	1
Warnings:					
Information:					
3	Power of Attorney	U015770023US01-USF-POA-ERG.pdf	151622 9e06effb19cfd8a9695996a394f1a9127b89b	no	1
Warnings:					
Information:					
4	Assignee showing of ownership per 37 CFR 3.73.	U015770023US01-UM-373-ERG.pdf	22158 b5df8c0b2ad831603966797ce7aae1174307766	no	1
Warnings:					
Information:					
5	Assignee showing of ownership per 37 CFR 3.73.	U011570023US01-USF-373-ERG.pdf	22214 7b2830a9e2fe879b9bce65952d0bbf63f448ae3	no	1
Warnings:					
Information:					
Total Files Size (in bytes):			1522374		
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.					

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 FORM <i>(to be used for all correspondence after initial filing)</i>	Application Number	10/378,956-Conf. #4742
	Filing Date	March 3, 2003
	First Named Inventor	Michael J. Zaworotko
	Art Unit	1627
	Examiner Name	S. Javanmard
Total Number of Pages in This Submission	Attorney Docket Number	U0157.70023US01

ENCLOSURES <i>(Check all that apply)</i>		
☐ Fee Transmittal Form ☐ Fee Attached ☐ Amendment/Reply ☐ After Final ☐ Affidavits/declaration(s) ☐ Extension of Time Request ☐ Express Abandonment Request ☐ Information Disclosure Statement ☐ Certified Copy of Priority Document(s) ☐ Reply to Missing Parts/Incomplete Application ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53	☐ Drawing(s) ☐ Licensing-related Papers ☐ Petition ☐ Petition to Convert to a Provisional Application ☒ Power of Attorney, Revocation Change of Correspondence Address ⁽²⁾ ☐ Terminal Disclaimer ☐ Request for Refund ☐ CD, Number of CD(s) _____ ☐ Landscape Table on CD	☐ After Allowance Communication to TC ☐ Appeal Communication to Board of Appeals and Interferences ☐ Appeal Communication to TC (Appeal Notice, Brief, Reply Brief) ☐ Proprietary Information ☐ Status Letter ☒ Other Enclosure(s) (please identify below): Statement Under 37 CFR 3.73(b) (2)
Remarks		

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT			
Firm Name	WOLF, GREENFIELD & SACKS, P.C.		
Signature	/Edward R. Gates/		
Printed name	Edward R. Gates		
Date	January 24, 2014	Reg. No.	31,616

Certificate of Electronic Filing Under 37 CFR 1.8	
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).	
Dated: January 24, 2014	Electronic Signature for Nicole M. Forgrave: /Nicole M. Forgrave/

3370404.1



UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/378,956	03/03/2003	Michael J. Zaworotko	U0157.70023US01

CONFIRMATION NO. 4742

POA ACCEPTANCE LETTER

23628
WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206



Date Mailed: 01/31/2014

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 01/24/2014.

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

/qtran/

Office of Data Management, 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 NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/378,956	03/03/2003	Michael J. Zaworotko	USF.106XC1

CONFIRMATION NO. 4742

POWER OF ATTORNEY NOTICE

23557
SALIWANCHIK, LLOYD & EISENSCHENK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614



Date Mailed: 01/31/2014

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 01/24/2014.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/qtran/

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

To: Patents_eOfficeAction@WolfGreenfield.com,WGS_eOfficeAction@WolfGreenfield.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 23628

Jan 31, 2014 05:19:59 AM

Dear PAIR Customer:

WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 23628 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

Disclaimer:

The list of documents shown below is provided as a courtesy and is not part of the official file wrapper. The content of the images shown in PAIR is the official record.

Application	Document	Mailroom Date	Attorney Docket No.
10378956	N570	01/31/2014	U0157.70023US01
	N570	01/31/2014	U0157.70023US01

To view your correspondence online or update your email addresses, please visit us anytime at <https://sportal.uspto.gov/secure/myportal/privatepair>.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

FORM PTO-1449/A and B (modified PTO/SB/08) INFORMATION DISCLOSURE STATEMENT BY APPLICANT				APPLICATION NO.: 10/378,956		ATTY. DOCKET NO.: U0157.70023US01	
				FILING DATE: March 3, 2003		CONFIRMATION NO.: 4742	
				FIRST NAMED INVENTOR: Michael J. Zaworotko			
				GROUP ART UNIT: 1627		EXAMINER: Sahar Javanmard	
Sheet	1	of	1				

U.S. PATENT DOCUMENTS

Examiner's Initials #	Cite No.	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication or Issue of Cited Document MM-DD-YYYY
		Number	Kind Code		

FOREIGN PATENT DOCUMENTS

Examiner's Initials #	Cite No.	Foreign Patent Document			Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Translation (Y/N)
		Office/Country	Number	Kind Code			

OTHER ART — NON PATENT LITERATURE DOCUMENTS

Examiner's 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, page(s), volume-issue number(s), publisher, city and/or country where published.	Translation (Y/N)
		European Search Report for Application No. EP 03711407.1 mailed November 22, 2006 (U0157.70023EP00).	
		International Search Report for Application No. PCT/US2003/06662 mailed October 24, 2003 (U0157.70023WO00).	
		The Merck Index, 12 th Ed. Merck & Co., Inc. Whitehouse Station, NJ. 1996. Entries 5683, 9094.	
		ITO et al., Compelled Orientational Control of the Solid-State Photodimerization of <i>trans</i> -Cinnamamides: Dicarboxylic Acid as a Non-covalent Linker. Tetrahedron. 2000;56:6833-44.	
		IWAMOTO et al., Structure of Cinnamamide. Acta Cryst. 1989;C45:1110-2.	
		JIANG et al., Cinnamamide, an antitumor agent with low cytotoxicity acting on matrix metalloproteinase. Anti-Cancer Drugs. 2000 Jan;11(1):49-54.	
		SMITH et al., The Determination of the Crystal Structure of Anhydrous Theophylline by X-ray Powder Diffraction with a Systematic Search Algorithm, Lattice Energy Calculations, and ¹³ C and ¹⁵ N Solid-State NMR: A Question of Polymorphism in a Given Unit Cell. J Phys Chem B. 2001;105(24):5818-26.	

[NOTE – No copies of U.S. patents, published U.S. patent applications, or pending, unpublished patent applications stored in the USPTO's Image File Wrapper (IFW) system, are included. See 37 CFR § 1.98 and 1287OG163. Copies of all other patent(s), publication(s), unpublished, pending U.S. patent applications, or other information listed are provided as required by 37 CFR § 1.98 unless 1) such copies were provided in an IDS in an earlier application that complies with 37 CFR § 1.98, and 2) the earlier application is relied upon for an earlier filing date under 35 U.S.C. § 120.]

EXAMINER:	DATE CONSIDERED:
-----------	------------------

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

INTERNATIONAL SEARCH REPORT

International Application No
PC17US 03/06662

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C233/25 C07C69/86 C07D233/74 C07C57/30 C07C57/58
C07D223/26 C07D213/22 C07D213/16 C07C47/544 C07D213/82
C07D275/06 C07D213/80 C07C53/08 C07C61/125 C07C50/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D

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

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

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
------------	--	-----------------------

P,X	BAILEY WALSH ET AL.: "Crystal engineering of the composition of pharmaceutical phases" CHEM. COMMUN., 2003, pages 186-187, XP002248827 the whole document	1-20,22
P,X	OSWALD, I.D.H. ET AL.: "The formation of paracetamol (acetaminophen) adducts with hydrogen-bond acceptors" ACTA CRYST., vol. B58, 2002, pages 1057-1066, XP009014505 the whole document	1-9, 11-19,21

-/--

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

24 July 2003

Date of mailing of the international search report

24. 10. 03

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Johnson, C.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/93/06662

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EL-NAHHAS S A: "PHYSICO-CHEMICAL CHARACTERISTICS OF CARBAMAZEPINE-BETA-CYCLODEXTRININ CLUSION COMPOUNDS AND CARBAMAZEPINE-PEG SOLID DISPERSIONS" PHARMAZIE, VEB VERLAG VOLK UND GESUNDHEIT. BERLIN, DD, vol. 51, no. 12, 1 December 1996 (1996-12-01), pages 960-963, XP000633833 ISSN: 0031-7144 paragraph [3.2.4.3] -----	1-9, 11-19,24
X	JAMES E. F. REYNOLDS, EDITOR: "Martindale. The extra pharmacopoeia" 1993, THE PHARMACEUTICAL PRESS, LONDON, XP002248828 page 1431 (e.g. acetaminophen, aspirin, and caffeine tablets), page 1465 (e.g. Aspirin plus C), page 1521 (Codafen Continus), page 1610 (Gaboril Complex) -----	1-9, 11-23
X	GB 1 297 261 A (E.R. SQUIBB & SONS INC.) 22 November 1972 (1972-11-22) the whole document -----	1-9, 11-19,21

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

page 2 of 2

INTERNATIONAL SEARCH REPORT

In international application No.
PCT/US 03/06662

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 25, 29, 33
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iii) PCT - Scheme, rules and method for performing mental acts
The methods of independent claims 25, 29 and 33 comprise 4 purely intellectual steps and therefore constitute methods for performing mental acts, for which no search is necessary.
2. ☒ Claims Nos.: 1-9, 11-24
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
10, 26-28, 30-32, 34-36 (all part)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 25,29,33

Rule 39.1(iii) PCT - Scheme, rules and method for performing mental acts

The methods of independent claims 25, 29 and 33 comprise 4 purely intellectual steps and therefore constitute methods for performing mental acts, for which no search is necessary.

Continuation of Box I.2

Claims Nos.: 1-9,11-24

The technical features of claim 1 are: i) a solid composition ii) having at least 2 components iii) at least one of which is a pharmaceutical molecule.

Pharmaceuticals which are administered in a solid form (e.g. as tablets) rarely contain 100% pharmaceutical - in the majority of cases other components such as fillers are present. All such pharmaceutical compositions fall within the scope of claim 1. None of the features of dependent claims 2-9 appear to add any characteristic that would distinguish the subject matter of these claims from the vast majority of solid pharmaceutical compositions currently on the market. An extract of "Martindale" has been cited to illustrate examples of compositions falling within the scope of claim 9 (see e.g. acetaminophen, aspirin and caffeine tablets, acetaminophen and codeine tablets, aspirin and ascorbic acid). Pharmazie 51 (1996) 12 960-963 is cited to illustrate an example of a carbamazepine composition falling within present claim 9. The dependent claims 11-24 also do not contain any feature that would distinguish their subject matter from well-known pharmaceutical preparations such as those cited in the documents mentioned above.

In view of the huge number of pharmaceutical compositions that fall within the scope of present claims 1-9 and 11-24, of which the compositions cited above form only an arbitrary selection, it is not possible to perform any meaningful search of these claims.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase

page 2 of 3

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

page 3 of 3

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are acetaminophen, 4,4'-bipyridine and water, and its method of preparation.

2. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are phenytoin and pyridine, and its method of preparation.

3. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are aspirin and 4,4'-bipyridine, and its method of preparation.

4. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are ibuprofen and 4,4'-bipyridine, and its method of preparation.

5. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are flurbiprofen and 4,4'-bipyridine, and its method of preparation.

6. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are flurbiprofen and trans-1,2-bis(4-pyridyl)ethylene, and its method of preparation.

7. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are carbamazepine and p-phthalaldehyde, and its method of preparation.

8. claims: 10, 26-28, 30-32, 34-36 (all part)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Composition according to claim 1 wherein the two or more components are carbamazepine and nicotinamide, and its method of preparation.

9. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are carbamazepine and saccharin, and its method of preparation.

10. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are carbamazepine and 2,6-pyridinedicarboxylic acid, and its method of preparation.

11. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are carbamazepine and 5-nitroisophthalic acid, and its method of preparation.

12. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are carbamazepine and acetic acid, and its method of preparation.

13. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are carbamazepine and 1,3,5,7-adamantanetetracarboxylic acid, and its method of preparation.

14. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are carbamazepine and benzoquinone, and its method of preparation.

15. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are carbamazepine and butyric acid, and its method of preparation.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

16. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are carbamazepine and dimethyl sulfoxide, and its method of preparation.

17. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are carbamazepine and formamide, and its method of preparation.

18. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are carbamazepine and formic acid, and its method of preparation.

19. claims: 10, 26-28, 30-32, 34-36 (all part)

Composition according to claim 1 wherein the two or more components are carbamazepine and trimesic acid, and its method of preparation.

INTERNATIONAL SEARCH REPORT

mation on patent family members

International Application No

PCT/JP 03/06662

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
GB 1297261	A	22-11-1972	CA 948642 A1	04-06-1974
			CH 507253 A	15-05-1971
			DE 2000210 A1	23-07-1970
			FR 2034467 A1	11-12-1970

Form PCT/ISA/210 (patent family annex) (July 1992)

UM00017247

NOVARTIS EXHIBIT 1517

Novartis v. Regents, IPR2023-01347

Page 4104 of 4460

THE MERCK INDEX

AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

TWELFTH EDITION

Susan Budavari, *Editor*
Maryadele J. O'Neil, *Senior Associate Editor*
Ann Smith, *Associate Editor*
Patricia E. Heckelman, *Assistant Editor*
Joanne F. Kinneary, *Assistant Editor*

Published by
Merck Research Laboratories
Division of

MERCK & CO., INC.

Whitehouse Station, NJ

1996

UM0001724

15°. Sol in 190

no)methyl]-3,4,
no)methyl]vera-
mino)methyl]-
methoxyphenyl
98%, H 8.50%,
Manna et al.,
Proc. Roy.
Soc. Lond.
1963, 273.
1-forms: La
cactus, Cory-
don and Rose.

147.01° (c =
200 g/ml abs

crystals from

8-179°. [α]_D²⁵

nol, mp 178-

gically active,
in animals

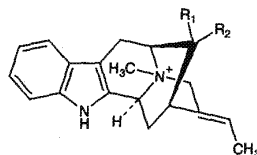
actor. Colo-
ecies specific
the develop-
ocytes (macro-
d monocyte-
glycosylated
ic activating
ocytes, fibro-
ral molecular
d via alterna-
gene. The
tein, which is
, and a fully
ner. Murine
Isoln from
oc. 34, 2272
inoma cells:
Purification
d, *ibid.* 252,
P: S. K. Das
al., *ibid.* 60,
lone pcCSF-
985); of long
g et al., *ibid.*
n: E. S. Ka-
76 (1990); of
n, N.-K. V.

r 1 (human
limer, Costi-

ne p3ACSF-
218 amino
inant DNA
ctive homo-
710 (1989).
J. Nemu-
modulatory

effects and pharmacokinetics: R. M. Bukowski et al., *J. Clin. Oncol.* **12**, 97 (1994).
THERAP CAT: Immunomodulator.

5679. Macusines. Isoln of A and B from *Strychnos toxifera* Schomb., *Loganiaceae*: A. R. Battersby et al., *J. Chem. Soc.* **1960**, 1848. Structure of A: A. T. McPhail et al., *Proc. Chem. Soc.* **1961**, 223; of B: A. R. Battersby, D. A. Yeowell, *ibid.* 17. Config of A: M.-M. Janot et al., *Bull. Soc. Chim. France* **1962**, 1079. Crystal and molecular structure of A: A. T. McPhail et al., *J. Chem. Soc.* **1963**, 1832. Sepn of C and abs config of A, B and C: A. R. Battersby, D. A. Yeowell, *ibid.* **1964**, 4419.



	R ₁	R ₂
Macusine A	CH ₂ OH	COOCH ₃
Macusine B	H	CH ₂ OH
Macusine C	COOCH ₃	CH ₂ OH

Macusine A, [C₂₂H₂₇N₂O₃]⁺, (16*R*)-17-hydroxy-16-(methoxycarbonyl)-4-methylsarpaganium. Chloride, prisms from ethanol + ether, mp 252°. [α]_D²⁵ -57.5° (c = 1.45).

Macusine B, [C₂₀H₂₅N₂O]⁺, (4*α*)-17-hydroxy-4-methylsarpaganium. Chloride, prisms from ethanol + ether, dec 248-249°. [α]_D²⁵ +15.6° (c = 1.21). uv max (water): 222, 273, 280, 291 nm (log ε 4.61, 3.84, 3.82, 3.74).

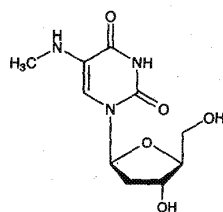
Macusine C, [C₂₂H₂₇N₂O₃]⁺, the C-16 epimer of A. Chloride, crystals from ethanol + ether, dec 264-265°. [α]_D²⁵ -60.8° (c = 2.13). uv max (water): 222, 272, 278, 289 nm (log ε 4.63, 3.88, 3.87, 3.76).

5680. Maddrell's Salt. Polymeric sodium metaphosphate. Upon heating NaH₂PO₄ or NaNH₄HPO₄ to 250° and then slowly to 350°, first Na₂H₂P₂O₇, and then the insol Maddrell's salt is obtained, which is stable to about 500°; at 505° it changes to sodium trimetaphosphate, and above 607° to sodium hexametaphosphate. According to Maddrell, *Ann.* **61**, 63 (1847) the salt may be prep'd by heating two parts NaNO₃ with one part H₃PO₄. An improved procedure is described by v. Knorre, *Z. Anorg. Chem.* **24**, 397 (1900). Structure: Jost, *Acta Cryst.* **16**, 428 (1963). Reviews: see Sodium Metaphosphate.

White powder. Practically insol in water and in aq solns of pyrophosphates and hexametaphosphates. Sol in mineral acids. Does not form complexes with Fe(II), Fe(III), U(IV) salts.

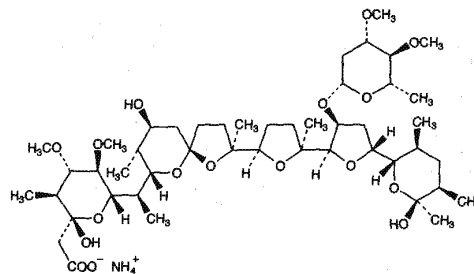
USE: In dentifrices, polishing agents, abrasive detergents.

5681. MADU. 2'-Deoxy-5-(methylamino)uridine; 5-(methylamino)-2'-deoxyuridine. C₁₀H₁₅N₃O₅; mol wt 257.25. C 46.69%, H 5.88%, N 16.33%, O 31.10%. Prepn: Visser et al., *Biochim. Biophys. Acta* **76**, 463 (1963). Active *in vitro* against herpes infections: Nemes, Hilleman, *Proc. Soc. Exp. Biol. Med.* **119**, 515 (1965); Shen, U.S. pat. 3,322,627 (1967 to Merck & Co.).



Crystals from ethanol + water, mp 180-182°. THERAP CAT: Antiviral.

5682. Maduramicin. (3*R*,4*S*,5*S*,6*R*,7*S*,22*S*)-23,27-Dide-methoxy-2,6,22-tridemethyl-11-*O*-demethyl-22-[(2,6-dideoxy-3,4-di-*O*-methyl-β-L-arabino-hexopyranosyl)oxy]-6-methoxy-lonomycin A monoammonium salt; antibiotic X-14868A ammonium salt; CL-273703; Cygro. C₄₇H₈₃NO₁₇; mol wt 934.17. C 60.43%, H 8.96%, N 1.50%, O 29.12%. Polyether antibiotic chemically related to the lonomycins, *q.v.* Isoln as sodium salt from *Nocardia* sp X-14868 and biological activity: C.-M. Liu et al., U.S. pat. 4,278,663 (1981 to Hoffmann-La Roche); as free acid hydrate from *Actinomadura yumaense* sp nov.: D. P. Labeda et al., U.S. pat. 4,407,946 (1983 to Am. Cyanamid). Fermentation and properties: C.-M. Liu et al., *J. Antibiot.* **36**, 343 (1983). ¹³C-NMR spectrum: S. Rajan, *ibid.* **37**, 1495 (1984). Biosynthetic studies: H.-R. Tsou et al., *ibid.* 1651; H.-R. Tsou et al., *ibid.* **40**, 94 (1987). Antimalarial activity: L. Oronsky, U.S. pat. 4,496,549 (1985 to Am. Cyanamid). Nematocidal activity: I. B. Wood, U.S. pat. 4,510,134 (1985 to Am. Cyanamid).

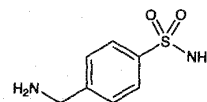


Sodium salt, C₄₇H₈₃NaO₁₇, crystals from ethyl acetate + n-hexane, mp 193-195°. [α]_D²⁵ +40.6° (chloroform). [α]_D²⁵ +23.8° (methanol).

Note: Not to be confused with *maduramicin* isolated from *Actinomadura rubra*, C₂₈H₄₂O₁₀; W. F. Fleck et al., 16th Interscience Conference on Antimicrob. Ag. Chemother., Chicago, 1976, Abstracts of Papers, no. 51.

THERAP CAT (VET): Coccidiostat.

5683. Mafenide. 4-(Aminomethyl)benzenesulfonamide; α-amino-*p*-toluenesulfonamide; *p*-(aminomethyl)benzenesulfonamide; 4-homosulfanilamide; maphenide; Marfanil; Mesudrin; Mesudin; Sulfamylon; Homosulfamine; Ambamide; Neofamid; Septicid; Emilene; Homonal; Paramenyl. C₇H₁₀N₂O₂S; mol wt 186.23. C 45.15%, H 5.41%, N 15.04%, O 17.18%, S 17.22%. Prepn: Miller et al., *J. Am. Chem. Soc.* **62**, 2099 (1940); Klarer, U.S. pat. 2,288,531 (1942 to Winthrop); Bergeim, Braker, *J. Am. Chem. Soc.* **66**, 1459 (1944); Kusami et al., *J. Pharm. Soc. Japan* **64**, no. 9a, 51 (1944); Komokina et al., *J. Appl. Chem. (USSR)* **21**, 681 (1948); Angyal, Jenkin, *Aust. J. Sci. Res.* **3A**, 461 (1950). Toxicity study: T. W. Skulan, J. O. Hoppe, *Life Sci.* **5**, 2279 (1966).



Crystals from alc, mp 151-152°. Sol in dil alkali, acid. Hydrochloride, C₇H₁₀N₂O₂S.HCl, crystals from 95% alc, mp 256°. Neutral in soln. LD₅₀ in rats, mice (mg/kg): 1170, 900 i.v. (Skulan, Hoppe).

Acetate, C₉H₁₂N₂O₄S. Mafatate, Mefamide. LD₅₀ in rats, mice (mg/kg): 2040, 1580 i.v. (Skulan, Hoppe).

Propionate, C₉H₁₀N₂O₄S.C₃H₆O₂, Sulfomyl. Crystals, mp 158°. Readily sol in water.

THERAP CAT: Antibacterial.

5684. Magainins. A class of potent antimicrobial peptides isolated from the glanular gland of clawed toad *Xenopus laevis*. Name coined by Zasloff from the Hebrew

Consult the Name Index before using this section.

Page 967

B. Z.
). Re-
mixture
59-518
Rev

ily in
Apo-
maz-
exim,
prim,
olim,
only
5513
mp

meth-
pyri-
dine;
like;
wt
S
Am.
15,
na-
226

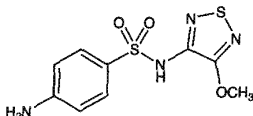
in
at
3)
/1
ly

i-
e-
>
T
S
L
v

in solns of alkali hydroxides and carbonates and in dil min-
eral acids.

Sodium salt, *Ultraseptyl*. Sol in water.
THERAP CAT: Antibacterial.

9089. Sulfametrole. 4-Amino-N-(4-methoxy-1,2,5-thia-
diazol-3-yl)benzenesulfonamide; N¹-(4-methoxy-1,2,5-thia-
diazol-3-yl)sulfanilamide; 3-methoxy-4-(4'-aminobenzenesul-
fonylamido)-1,2,5-thiadiazole. C₉H₁₀N₄O₃S₂; mol wt
286.34. C 37.75%, H 3.52%, N 19.57%, O 16.76%, S
22.40%. Anti-infective sulfanilamide, related structurally to
sulfadiazine, q.v. Prepn: Belg. pat. 629,551 corresp to K.
Menzl, U.S. pat. 3,247,193 (1963, 1966 both to OSSW).
Improved prepn: *idem*, U.S. pat. 4,151,164 (1979 to
Chemie Linz). Bacteriological study (of mixture with tri-
methoprim): G. Nabert-Bock, H. Grims, *Arzneimittel-
Forsch.* 27, 1109 (1977). Tolerance, therapeutic effect, phar-
macokinetics: S. Breyer *et al.*, *Wien Med. Wochenschr.* 130,
448 (1980). Renal excretion mechanism, pharmacokinetics:
T. B. Vree *et al.*, *Eur. J. Clin. Pharmacol.* 20, 283 (1981).
Pharmacokinetics of sulfametrole and its metabolite in man:
Y. A. Hester *et al.*, *J. Antimicrob. Chemother.* 8, 133 (1981).
Crystal and molecular structures: C. H. Koo *et al.*, *Bull.
Korean Chem. Soc.* 3, 9 (1982), *C.A.* 96, 208771 (1982).
Single-dose therapy of chancroid with trimethoprim-
sulfametrole: F. A. Plummer *et al.*, *N. Engl. J. Med.* 309, 67
(1983).



Cryst from dilute acetic acid, mp 149-150°.
Mixture with trimethoprim, *Lidaprim*, *Maderan*.
THERAP CAT: Antibacterial.

9090. Sulfamic Acid. Amidosulfonic acid. H₂NO₂S;
mol wt 97.09. H 3.11%, N 14.43%, O 49.43%, S 33.03%.
H₂NSO₃H. Obtained from chlorosulfonic acid and ammo-
nia, or by heating urea with H₂SO₄. Purification: Sisler *et al.*,
Inorg. Syn. 2, 178 (1946). Toxicity data: Ambrose, *J.
Ind. Hyg. Toxicol.* 25, 26 (1943). Reviews: Audrieth *et al.*,
Chem. Rev. 26, 49 (1940); Burton, Nickless, "Amido- and
Imido-Sulfonic Acids" in *Inorganic Sulphur Chemistry*, G.
Nickless, Ed. (Elsevier, New York, 1968) pp 607-627, 661-
667; E. B. Bell in *Kirk-Othmer Encyclopedia of Chemical
Technology* vol. 21 (Wiley-Interscience, New York, 3rd ed.,
1983) pp 949-960.

Orthorhombic crystals. d 2.15. mp ~205° (dec). Stable
when dry but in soln it slowly hydrolyzes forming am-
monium bisulfate. Sol in 6.5 parts water at 0°, in about 2
parts water at 80°. Sulfuric acid decreases its soly in water.
It is sparingly sol in alcohol, methanol; slightly sol in ace-
tone. Insol in ether. Freely sol in nitrogenous bases, e.g.,
liq ammonia, also in nitrogen contg organic solvents, e.g.,
pyridine, formamide, dimethylformamide. A strong acid;
pH of a 1% soln at 25° 1.18. Can be titrated with bases by
means of indicators showing color change between pH 4.5
to 9. MLD orally in rats: 1.6 g/kg (Ambrose).

Caution: Moderately irritating to skin, mucous mem-
branes.

USE: As standard in alkalimetry; in acid cleaning; in ni-
trite removal; in chlorine stabilization for use in swimming
pools, cooling towers, paper mills. The acid or its ammo-
nium salt has been recommended for flameproofing fabrics
and wood. Metal salts are used in electroplating. Ammo-
nium sulfamate, q.v., is also widely used as a weed killer.

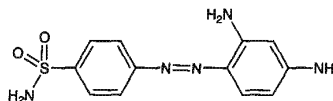
9091. Sulfamide. Sulfuryl amide. H₂N₂O₃S; mol wt
96.11. H 4.19%, N 29.15%, O 33.29%, S 33.36%. H₂N-
SO₂NH₂. Prepd from sulfuryl chloride and gaseous am-
monia: Traube, *Ber.* 25, 2427 (1892); 26, 610 (1893);
Hantzsch, *Holl. Ber.* 34, 3430 (1902); Schenk in *Handbook
of Preparative Inorganic Chemistry* vol. 1, G. Brauer, Ed.
(Academic Press, New York, 2nd ed., 1963) pp 482-483.
Orthorhombic, tasteless plates from abs alcohol, mp 93°;
dec 250°. Dipole moment: 3.9. Freely sol in water, hot

alcohol, acetone. Sparingly sol in cold alc. Solid and solns
are stable.

Note: Not to be confused with ammonium sulfamate or
with sulfanilamide.

USE: Similar to urea in many of its reactions, but is more
acidic, and can act as a dibasic acid.

9092. Sulfamidochrysoidine. 4-[(2,4-Diaminophenyl)-
azo]benzenesulfonamide; 2,4-diaminoazobenzene-4'-sulfon-
amide; 4'-sulfamyl-2,4-diaminoazobenzene. C₁₂H₁₃N₅O₂S;
mol wt 291.33. C 49.47%, H 4.50%, N 24.04%, O 10.98%, S
11.01%. Prototype compd leading to the development of
sulfonamide antibacterials. Prepn: F. Mietzsch, J. Klarer,
Ger. pat. 607,537 (1935 to I. G. Farbenind.); *idem*, U.S.
pat. 2,085,037 (1937 to Winthrop). Antibacterial activity *in
vivo*: G. Domagk, *Deut. Med. Wochenschr.* 61, 573 (1935);
(for English translation see *Rev. Inf. Dis.* 8, 163 (1986)).
Identification of sulfanilamide as active metabolite: J. Tré-
fouel *et al.*, *Compt. Rend. Soc. Biol.* 120, 756 (1935); L.
Colebrook *et al.*, *Lancet* 2, 1323 (1936). Polymorphic forms
in commercial preps: L. Kofler, A. Kofler, *Monatsh.* 81,
321 (1950). Use to visualize carbonic anhydrase during
isoelectric focusing in polyacrylamide gels: W. Siffert *et al.*,
J. Biochem. Biophys. Methods 8, 331 (1983). Historical re-
view: M. H. Bickel, *Gesnerus* 45, 67-86 (1988).

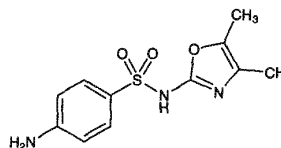


Hydrochloride, C₁₂H₁₃N₅O₂S.HCl, *Prontosil*, *Prontosil
flavum*, *Prontosil rubrum*, *Rubiazol I*, *Septosan*, *Streptocide*,
Streptozon. Orange-red crystals, mp 248-250°. One gram
dissolves in 400 ml water; much more sol in hot water. Sol
in alcohol, acetone, fats, oils.

USE: Specific stain for carbonic anhydrase in polyacryl-
amide gels.

THERAP CAT: Antibacterial.

9093. Sulfamoxole. 4-Amino-N-(4,5-dimethyl-2-oxazol-
yl)benzenesulfonamide; N¹-(4,5-dimethyl-2-oxazolyl)sulfanil-
amide; 2-(p-aminobenzenesulfonamido)-4,5-dimethyloxaz-
ole; 4,5-dimethyl-2-sulfanilamidooxazole; p-aminobenzenesul-
fonyl-2-amino-4,5-dimethyloxazole; sulfadimethyloxaz-
ole; Justamil; Sulfmidil; Sulfuno; Tardamide. C₁₁H₁₃N₃O₃S;
mol wt 267.31. C 49.43%, H 4.90%, N 15.72%, O
17.96%, S 12.00%. Prepn: Loop *et al.*, U.S. pat. 2,809,966
(1957 to Nordmark-Werke). Series of articles on anti-
microbial activity, pharmacology and clinical efficacy of
mixture with trimethoprim: *Arzneimittel-Forsch.* 26, 595-
684 (1976). Toxicity data: F. Lagler *et al.*, *ibid.* 634.



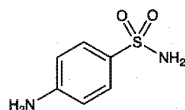
Crystals, mp 193-194°. Soly in mg/100 ml at 20°: Water
85; 0.01N HCl 163; 0.01N NaOH 196; methanol 2315;
chloroform 240. uv max (4.91 µg/ml methanol): 210, 250,
270 nm (ε 740, 546, 857). LD₅₀ in mice, rats (g/kg):
> 10.0, > 12.5 orally; 1.80, ~2.50 i.p. (Lagler).

Mixture with trimethoprim, *co-trifamole*, *CN-3123*, *Co-
Fram*, *Dibactil*, *Nevin*, *Supristol*. LD₅₀ in mice, rats (g/kg):
> 12.0, 14.0 orally; 1.87, 2.00 i.p. (Lagler).

THERAP CAT: Antibacterial.

9094. Sulfanilamide. 4-Aminobenzenesulfonamide; p-
anilinesulfonamide; p-sulfamidoaniline; 1162-F; Albexan;
Desepyl; Prontalbin; Prontosil album; Prontylin; Septopix;
Streptocid album; Streptocide. C₆H₇N₂O₂S; mol wt 172.21.
C 41.85%, H 4.68%, N 16.27%, O 18.58%, S 18.62%. Prepd
by the action of ammonia on acetylsulfanilyl chloride; the
resulting N'-acetylsulfanilamide is then hydrolyzed: Gelfmo,

J. Prakt. Chem. 77, 369 (1908). Lab procedures: L. F. Fieser, *Experiments in Organic Chemistry* (Boston, 3rd ed., 1955) p 147; Hurd, Yang, *J. Chem. Ed.* 46, 697 (1969). Large-scale production and purification: Mietzsch, Klarer, U.S. pats. 2,132,178 (1938); 2,276,664 (1942). Alternate prepn: Simons, U.S. pat. 2,237,372 (1941).

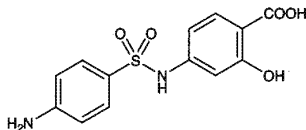


Crystals, mp 164.5-166.5°. pKa 10.43; pKb 11.63. Neutral to litmus. pH (0.5% aq soln): 5.8-6.1. uv max: 257, 313 nm. Soly in water (g/liter): 2.6 (10°); 7.5 (25°); 17.0 (40°); 40 (60°); 477 (100°). One gram dissolves in about 37 ml alcohol; in about 5 ml acetone. Also sol in glycerol, propylene glycol, HCl, solns of K and Na hydroxides. Practically insol in chloroform, ether, benzene, petr ether. LD₅₀ orally in dogs: 2.0 g/kg.

THERAP CAT: Antibacterial.

THERAP CAT (VET): Antimicrobial.

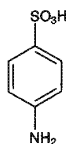
9095. 4-Sulfanilamidosalicylic Acid. *p*-Sulfanilamidosalicylic acid; 4-(*p*-aminobenzenesulfonamido)-2-hydroxybenzoic acid; Metrasil. C₁₃H₁₂N₂O₅S; mol wt 308.31. C 50.64%, H 3.92%, N 9.09%, O 25.95%, S 10.40%. Prepn: Benedikt, Eibl, *Monatsh.* 81, 419 (1950); Goldberg, Salame, *Brit. pat.* 648,467 (1951 to Ward, Blenkinsop).



Crystals from dil alcohol, dec 220°. The water soly is described as high between pH 5 and 8.

THERAP CAT: Antibacterial.

9096. Sulfanilic Acid. 4-Aminobenzenesulfonic acid; *p*-anilinesulfonic acid. C₆H₇NO₃S; mol wt 173.19. C 41.61%, H 4.07%, N 8.09%, O 27.71%, S 18.51%. Readily prepd from aniline and sulfuric acid: I. G. Farben, *FIAT Final Rept.* 1313 (I), 255 (1948); Fierz-David, Blangey, *Fundamental Processes of Dye Chemistry* (Interscience, New York, 1949) pp 126-128; A. I. Vogel, *Practical Organic Chemistry* (Longmans, London, 3rd ed., 1959) p 586; R. Q. Brewster et al., *Unutilized Experiments in Organic Chemistry* (Van Nostrand, Princeton, 2nd ed., 1964) pp 162-163. Improved procedure: Jacobs et al., *Ind. Eng. Chem.* 35, 321-323 (1943).



Monohydrate, orthorhombic plates from water (very slow crystn can yield the dihydrate), becomes anhydr at around 100°. Dec without melting at ~288° (also reported as > 360°). pK₂ (25°): 3.23. Slowly sol in water: ~1% at 20°, 1.45% at 30°, 1.94% at 40° (w/w anhydr). Almost insol in ethanol, benzene, ether. Slightly sol in hot methanol.

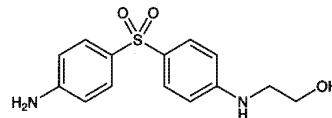
Sodium salt dihydrate, C₆H₆NNaO₃S.2H₂O, orthorhombic bipyramidal plates. Freely sol in water, sol in hot methanol.

Zinc salt tetrahydrate, C₁₂H₁₂N₂O₆S₂Zn.4H₂O, zinc sulfanilate tetrahydrate *Nirin*.

USE: Manuf various dyes and organic chemicals; as reagent in anal. chemistry (Ehrlich's reagent, detn of nitrites).

THERAP CAT: Antibacterial.

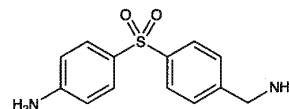
9097. 2-*p*-Sulfanilylanilinoethanol. 2-[[4-(4-Aminophenyl)sulfonylphenyl]amino]ethanol; 4-amino-4'-(β-hydroxyethylamino)diphenyl sulfone; *p*-aminophenyl *p*-(2-hydroxyethylamino)phenyl sulfone; Smith's sulfone. C₁₈H₁₆N₂O₃S; mol wt 292.36. C 57.52%, H 5.52%, N 9.58%, O 16.42%, S 10.97%. Preparation: Jackson, *J. Am. Chem. Soc.* 70, 680 (1948); Wejlard, Swanezy, *ibid.* 71, 4134 (1949); Jackson, *ibid.* 72, 395 (1950); Anand et al., *J. Sci. Ind. Res (India)* 13B, 260 (1954); Onishi, Fukagawa, *Japan. pat.* 2,975(56) (to Yoshitomi Drug).



Exists in diamorphic forms, crystals, mp 130.5-131.5° and crystals, mp 144°. The lower melting crystals' soly in water: 74 mg/100 ml at 37°. The higher melting form is readily sol in acetone; sol in ethanol, dioxane, cold 1% HCl; fairly sol in hot water; slightly sol in cold water.

THERAP CAT: Antibacterial (Mycobacterium).

9098. *p*-Sulfanilylbenzylamine. 4-[(4-Aminophenyl)sulfonyl]benzenemethanamine; *p*-sulfanilidobenzylamine; 4-aminomethyl-4'-aminodiphenyl sulfone; *p*-aminophenyl-*p*-aminomethylphenyl sulfone; Alphamide. C₁₃H₁₄N₂O₂S; mol wt 262.33. C 59.52%, H 5.38%, N 10.68%, O 12.20%, S 12.22%. Prepn: Dewing, *J. Chem. Soc.* 1946, 466; Wenner, *J. Org. Chem.* 22, 1508 (1957).



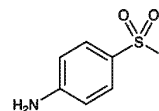
Needles from water, mp 159°.

Monohydrochloride monohydrate, C₁₃H₁₄N₂O₂S.HCl.H₂O, crystals, mp 195°. Very sol in water.

Dihydrochloride, C₁₃H₁₄N₂O₂S.2HCl, mp 285°.

THERAP CAT: Antibacterial.

9099. Sulfanilyl Fluoride. *p*-Aminobenzenesulfonyl fluoride. C₆H₆FN₂O₂S; mol wt 175.18. C 41.14%, H 3.45%, F 10.84%, N 8.00%, O 18.27%, S 18.30%. Prepd by heating potassium fluoride with 4-acetamidobenzenesulfonyl chloride: Parker, Hofmann, U.S. pat. 2,576,037 (1951 to Am. Cyanamid).



Crystals, mp 68-69°.

USE: In the prepn of dyes which pick up light readily.

9100. *N*'-Sulfanilylsulfanilamide. 4'-Sulfamoylsulfanililide; 4-aminobenzenesulfonono-*p*-sulfamoylanilide; 4-(4'-aminobenzenesulfonamido)benzenesulfonamide; DB-32; Diaminobenzenesulfonamide; Neosanamid II; Albasil C; septal C; Uliron C; Disulon; Neosanamid II; Albasil C; Disulfan. C₁₂H₁₃N₃O₄S₂; mol wt 327.39. C 44.03%, H 4.00%, N 12.84%, O 19.55%, S 19.59%. Prepn: Fr. pat. 817,034 (to I. G. Farben.), C.A. 32, 1714i (1938); Sakai, Yamamoto, *J. Pharm. Soc. Japan* 58, 683 (1938); Golovchinskaya, *J. Appl. Chem. USSR* 18, 647 (1945); Sasa, *J. Chem. Syn. Chem. Japan* 12, 211 (1954), C.A. 51, 2780h (1957); Grigorovskii, Dvkanov, *J. Appl. Chem. USSR* 30,

Ni
Mas
cold
meth
in pr
Nc
H₂N
ture.
TH
9
benz
sulf
C₆H
O 2
amic
with
alco
sligh
al, l
amic
Haa
wari
Win
proc

C
in w
a ve
M
Tr
?
ylsu
304.
Prep
benz
oyl
Mar

N
wat
ing
Ti
ylp
lde
not
sult
335
Pre
19



Pergamon

Tetrahedron 56 (2000) 6833–6844

TETRAHEDRON

Compelled Orientational Control of the Solid-State Photodimerization of *trans*-Cinnamamides: Dicarboxylic Acid as a Non-covalent Linker

Yoshikatsu Ito,^{a,*} Hiroyuki Hosomi^b and Shigeru Ohba^b^aDepartment of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 606-8501, Japan^bDepartment of Chemistry, Faculty of Science and Technology, Keio University, Yokohama 223-8522, Japan

Received 17 November 1999; accepted 17 February 2000

Abstract—The 2:1 hydrogen-bonded cocrystals **1a-ox**, **1a-su**, **1a-pht**, **1a-fu**, **1b-ox**, **1c-ox**, **1d-ox** between *trans*-cinnamamides (**1a–1d**) and dicarboxylic acids (**ox**, **su**, **gl**, **fu**, **pht**) were prepared and characterized by IR and powder X-ray techniques. The crystal structures of **1a-pht**, **1a-ox** and **1a-fu** were solved by single crystal X-ray diffraction. Phthalic acid (**pht**) caused β -type photodimerization of *trans*-cinnamamide (**1a**) in the cocrystal and functioned as a non-covalent linker like gauche 1,2-diamines in photodimerization of *trans*-cinnamic acids. Oxalic acid (**ox**) enforced **1a** to take a bilayer structure that is suitable for β -type photodimerization. In the case of fumaric acid (**fu**), cross photodimerization with **1a** occurred to give a cycloadduct **4**. For the cocrystals **1a-pht** and **1a-fu**, pedal-like motion was assumed to occur prior to the dimerization. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

Recently, we have explored compelled orientational control of the solid-state photodimerization of particular compounds like *trans*-cinnamic acids and anthracene-carboxylic acids.^{1–7} Our strategy is based on crystalline double salt formation with diamines, which are used as a supramolecular linker to connect two acid molecules in a sort of pre-designed orientation. A series of diamines were investigated. As a result of these studies, it was disclosed that *trans*- and *cis*-cyclohexane-1,2-diamines or gauche 1,2-diamines were useful linkers for preparing double salts of unusual photoreactivity. Evidently, photoreactive overlap configurations are more likely to happen to the gauche conformation of 1,2-diamine.

Upon photolysis in the solid state, *trans*-cinnamamide (**1a**) and its derivatives undergo photodimerization to afford exclusively the corresponding α -truxillamides,⁸ whereas in solution only the *trans*-*cis* photoisomerization was observed to occur as confirmed by us. In this paper, orientational control of the [2+2] photodimerization of *trans*-cinnamamides in the solid state by using a series of dicarboxylic acids as a non-covalent intermolecular linker will be described. The carboxamide group and the carboxyl group can interact in the crystal via hydrogen bonding as

was demonstrated by formation of, e.g. a 2:1 hydrogen-bonded cocrystal between benzamide and succinic acid.⁹

Results and Discussion

A 2:1 mixture of *trans*-cinnamamide (**1a**) and each of dicarboxylic acids, which are listed in Scheme 1, was recrystallized from suitable solvent. Cocrystals of **1a** with oxalic acid (**ox**), succinic acid (**su**), phthalic acid (**pht**) and fumaric acid (**fu**) (**1a-ox**, **1a-su**, **1a-pht**, **1a-fu**) were successfully obtained (Table 1). Their melting points were sharp and melted near mp of **1a**. The molar ratio of the constituents was estimated by NMR and was determined by elemental analysis to be 2:1 in all the cocrystals. The IR frequencies of CONH₂ and COOH groups for these cocrystal, along with those for the component amide and acid, are summarized in Table 2. The IR spectra of the cocrystals were different from the superposition of the spectra of their components throughout the whole region (4000–600 cm^{−1}).

The identity of the cocrystal between **1a** and glutaric acid (**gl**) (**1a-gl**) is ambiguous. Although its C, H, N analysis was correct as the 2:1 stoichiometry, its melting point was very broad (Table 1) and the carbonyl stretching bands nearly overlapped with the sum of those for **1a** and **gl** (Table 2). In the fingerprint region (1500–600 cm^{−1}), however, the absorption peaks corresponding to **gl** were not discernible, while those to **1a** were clearly visible.

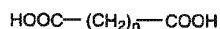
Keywords: cinnamamides; dicarboxylic acids; cocrystals; solid-state photodimerization; hydrogen bond; dynamic disorder.

* Corresponding author. Tel.: +81-75-753-5654; fax: +81-75-753-5668; e-mail: yito@sbchem.kyoto-u.ac.jp

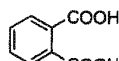
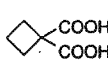
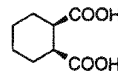
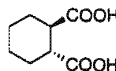
0040-4020/00/\$ - see front matter © 2000 Elsevier Science Ltd. All rights reserved.
PII: S0040-4020(00)00505-6

Linker Tested:

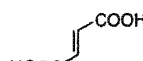
dicarboxylic acids


 $n = 0, 1, 2, 3, 4$

ox su gl



pht



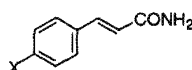
fu



gl

Substrate Tested:

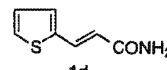
trans-cinnamamides


 $X = \text{H}, \text{Me}, \text{Cl}$

1a

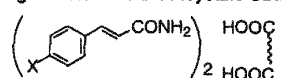
1b

1c



1d

Hydrogen-Bonded 1:2 Cocystals Obtained:



1a•ox, 1a•su, 1a•gl, 1a•pht, 1a•fu,

1b•ox, 1c•ox, 1d•ox

Scheme 1.

Table 1. Solvents for recrystallization, melting points and analytical data for the cocystals prepared from recrystallization of an amide (1a, 1b, 1c, or 1d) with a dicarboxylic acid (ox, su, gl, fu, or pht)

Cocystal	Recrystzn solvent	Crystal habit, mp, °C ^a	Calcd (%) ^b			Found (%) ^b		
			C	H	N	C	H	N
1a•ox	iPrOH	Colorless plates, 159–166.5	62.49	5.25	7.29	62.46	5.29	7.32
1a•su	iPrOH	White needles, 150.5–151.5	64.06	5.87	6.79	64.16	5.95	6.86
1a•gl	C ₆ H ₆	Colorless plates + a small amount of prisms, 88.5–124	64.78	6.14	6.57	64.59	6.08	6.47
1a•pht	iPrOH	Colorless needles, 142–143.5	67.82	5.25	6.08	67.90	5.23	6.11
1a•fu	iPrOH	Colorless needles, 164–166	64.38	5.40	6.83	64.44	5.28	6.69
1b•ox	iPrOH	Colorless prisms, 194–202	64.07	5.87	6.79	64.19	5.91	6.83
1c•ox	C ₆ H ₆ /i-PrOH	Colorless prisms, 207.5–211	53.00	4.00	6.18 ^c	53.10	4.02	6.19 ^d
1d•ox	iPrOH	Pale brown plates, 146–166	48.48	4.07	7.07 ^e	48.44	4.10	6.93 ^f

^a Melting points for the components: 1a, 148–150°C; 1b, 189–190°C; 1c, 209–210°C; 1d, 152–153°C; ox (anhyd), 190°C dec; su, 187–189°C; gl, 95–98°C; fu, 299–300°C subl; pht, 210°C dec.

^b The crystals were dried in vacuo at 35°C for a few days. All samples gave correct C, H, N analyses (within ±0.3%) as (amide)₂(dicarboxylic acid).

^c Cl, 15.64.

^d Cl, 15.66.

^e S, 16.17.

^f S, 16.31.
Table 2. FT IR frequencies in cm⁻¹ for CONH₂ and COOH groups in KBr

trans-Cinnamamide		Dicarboxylic acid		Cocystal	
CONH ₂		COOH		CONH ₂ and COOH	
1a	1664, 1608	ox (anhyd)	1686 ^a	1a•ox	1682, 1639
		su	1735, 1705	1a•su	1700, 1656, 1636
		gl	1701	1a•gl	1704, 1663, 1608
		pht	1701, 1682	1a•pht	1694, 1655, 1648
		fu	1684	1a•fu	1697, 1651, 1628, 1572
1b	1672, 1605			1b•ox	1674, 1638
1c	1676, 1613			1c•ox	1677, 1637
1d	1671, 1600			1d•ox	1671, 1600

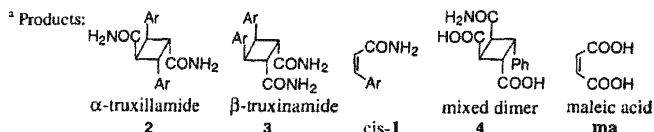
^a ox (dihydrate) 1683 cm⁻¹.

The above results on the melting point and the IR spectrum, combined with the following powder X-ray studies (Fig. 2) and photoreactivities (Table 3), indicate that cocystals 1a•ox, 1a•su, 1a•pht and 1a•fu are crystalline complexes,

whereas 1a•gl may possibly be a mixture containing the homocrystal of 1a and one polymorph of gl. The crystal structures of 1a•ox, 1a•pht and 1a•fu could be determined by single crystal X-ray diffraction.

Table 3. Products from solid-state photolyses of the cocrystals (except 1a-fu (50 h), irradiated for 20 h)

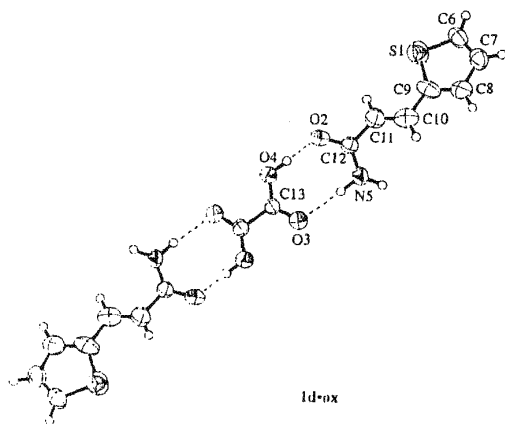
Cocrystals	Products (%) ^{a,b}				Recovery (%)	
	2	3	cis-1	Others	1	Acid
1a-ox	6	42	8		26	ne
1a-su			Photostable		100	100
1a-gl	44	4	2		44	100
1a-pht	3	37	5		51	100
1a-fu	1	5	5		39	45
1b-ox	0	43	0	4, 50; ma, 5	1	ne
1c-ox	2	86	0	Polymeric	5	ne
1d-ox	0	3	7		83	ne
1a, 1b, 1c, or 1d ^c	18, 100, 100, or 97	0	0		82, 0, 0, 3	–



^b Yields and recoveries were estimated by NMR and HPLC and calculated as follows: 100 (moles of dimer)/(moles of 2:1 cocrystal)% for α - and β -dimers and 4, 50 (moles of monomer)/(moles of 2:1 cocrystal)% for *trans*- and *cis*-cinnamides, and 100 (moles of acid)/(moles of 2:1 cocrystal)% for dicarboxylic acids; ne=not estimated.

^c Homococrystals.

Attempts to cocrystallize *trans*-4-methylcinnamamide (1b), *trans*-4-chlorocinnamamide (1c), and *trans*- β -(2-thienyl)-acrylamide (1d) with the above dicarboxylic acids were partly investigated. Cocrystallization with pht or with fu all failed. In contrast, 2:1 cocrystals with oxalic acid (1b-ox, 1c-ox, 1d-ox) were successfully obtained. Their data for the recrystallization solvent, mp, elemental analyses, and carbonyl frequencies are also summarized in Tables 1 and 2. Judging from the fairly sharp mp and also from the IR spectra that are distinct from those of the components, cocrystals 1b-ox and 1c-ox are undoubtedly a crystalline complex rather than a simple mechanical mixture. From the data given above, the identity of cocrystal 1d-ox is uncertain, because its mp is broad (Table 1) and its IR spectrum is close to that of 1d (Table 2). The powder as well as single crystal X-ray studies, however, have demonstrated that 1d-ox is also a crystalline complex (vide infra).



The diffuse reflectance UV–Vis spectra for cocrystals 1a-ox, 1a-su, 1a-gl, 1a-pht, 1a-fu and for the crystals of their constituents were measured (Fig. 1). It can be seen from this figure that the Pyrex-filtered light (>290 nm)

incident upon the sample is mainly or exclusively absorbed by the component 1a. In the spectrum of 1a-fu, an inflection is observed at ~343 nm, suggesting that the 1a molecule and the fu molecule are interacting not only via hydrogen bonds but also through a π – π interaction. In this case, as described later, cross photodimerization occurred to give 4 (Table 3).

The powder X-ray diffraction (PXRD) for cocrystals 1a-ox, 1a-pht, 1a-fu, 1a-su and 1d-ox were collected (Fig. 2). The diffraction intensities for these cocrystals were much weaker than those for the corresponding components (ox, pht, gl, fu, su, 1a and 1d). This may imply that the crystal structures of these cocrystals are loose. In fact, the X-ray molecular structure for 1a-ox has proved to be disordered and the photocycloaddition stereoselectivities for 1a-pht and 1a-fu could only be rationalized by assuming the dynamic torsional motions (vide infra).

Inspection of Fig. 2 shows that the PXD patterns for 1a-ox, 1a-pht, 1a-fu, 1a-su and 1d-ox cannot be represented as a sum of those for the components, indicating that these cocrystals are crystalline complexes. On the other hand, the PXD pattern for 1a-gl is peculiar like its IR spectrum. Note that the major peaks at 2θ =20.70, 22.28, 23.58, 24.78, 25.58, 26.38, 28.10, 29.42, 33.66 and 37.50° observed for 1a are still present for 1a-gl at 2θ =20.66, 22.22, 23.46, 24.78, 25.48, 26.32, 28.00, 29.36, 33.58 and 37.56°, respectively. However, the strong peaks for gl at 2θ =22.00, 24.04 and 27.32° are virtually missing for 1a-gl. It may be likely that the lattice structure of homocrystal 1a is largely retained after cocrystallization with gl, but the crystal packing for the gl component in 1a-gl is different from that of homocrystal gl.

Pulverized samples of cocrystals 1a-ox, 1a-su, 1a-gl, 1a-pht, 1a-fu, 1b-ox, 1c-ox and 1d-ox were spread between two Pyrex plates and irradiated with a 400 W high pressure mercury lamp under an argon stream. During the irradiation, the photolysis vessel was cooled from the outside with tap

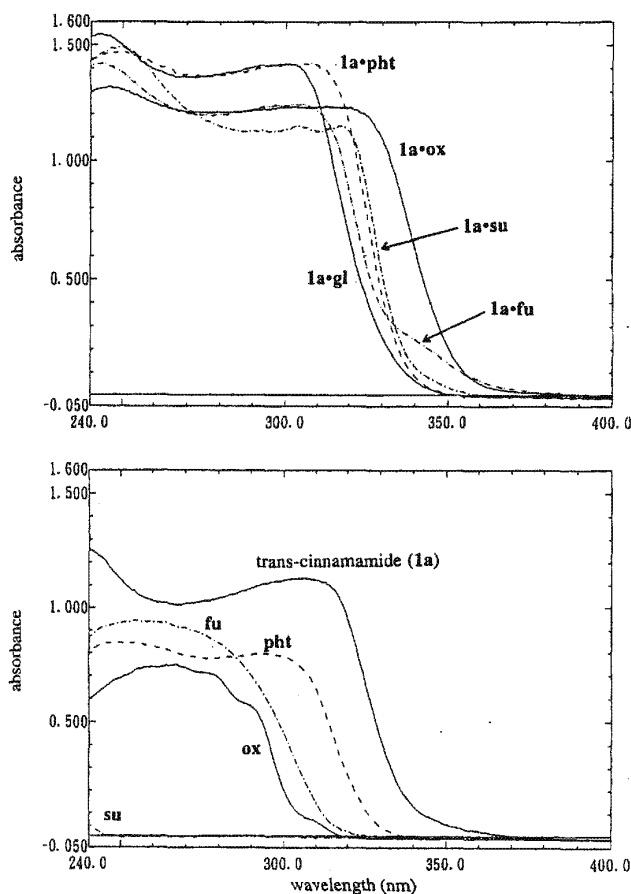


Figure 1. Diffuse reflectance spectra for cocrystals **1a·ox**, **1a·su**, **1a·gl**, **1a·pht**, **1a·fu** and for their constituent crystals **1a**, **ox** (anhyd), **su**, **pht**, and **fu**. The spectrum for **gl**, which is almost the same as that of **su**, is not shown.

water. The photoproducts and their yields are summarized in Table 3. As readily seen from the table, the unusual head-to-head dimer of amides (i.e. β -truxinamide **3** rather than α -truxillamide **2**) was mainly produced by photolyses of the hydrogen-bonded 2:1 complexes formed between the amide and oxalic or phthalic acid **1a·ox**, **1a·pht**, **1b·ox**, **1c·ox** and **1d·ox**, although the reaction was inefficient for **1d·ox**. Noticeably, the cocrystal of **1a** with fumaric acid **1a·fu** afforded a mixed dimer **4** as the predominant photoproduct (50% yield). The cocrystal with succinic acid **1a·su** was completely photostable. Finally, crystal **1a·gl**, like homocrystal **1a**, gave α -truxillamide **2a** as the main product. The formation of the usual photodimer **2a** from **1a·gl** is consistent with the above inference, where **1a·gl** was likened to a mixture comprised of the homocrystal of **1a** and a certain modification of **gl**, on the basis of both the IR spectrum and the PXD pattern.

The structure of **4** was determined after it was hydrolyzed to a tricarboxylic acid **5**, which is unsymmetrical in stereochemical configuration (Scheme 2). A possible symmetrical stereoisomer **5A** could be eliminated by ^1H NMR. The

compound **5** was subsequently converted to a trimethyl ester **6** and the structure of **6** was established by single crystal X-ray diffraction (see Experimental).

The crystal structures of cocrystals **1a·pht**, **1a·ox** and **1a·fu** and their packing diagrams are displayed in Figs. 3 and 4, respectively. Inspection of the crystal packing for **1a·pht** (Fig. 4a) has revealed that the nearest amide molecules are related in a head-to-head fashion via a supramolecular linker **pht** as shown in Fig. 3a. The ethylene bonds in this pair are anti and are not parallel with the C...C distances 3.82 and 4.85 Å. Although such a twisted arrangement is not ideal for photodimerization,¹⁰ the dimer, if formed from this crystal structure, will be δ -truxinamide, which was not observed (Table 3). In order to accommodate the observed product β -truxinamide **3a**, therefore, a pedal-like dynamic conformational change^{11,12} is thought to occur in the crystal prior to cycloaddition into **3a** (Scheme 3).¹³ This torsional motion will bring about a parallel orientation that is favorable for the photodimerization. Although molecules of **1a** related by translation along the *c*-direction possess a perfect arrangement for formation of **3a**, the olefine bond separation

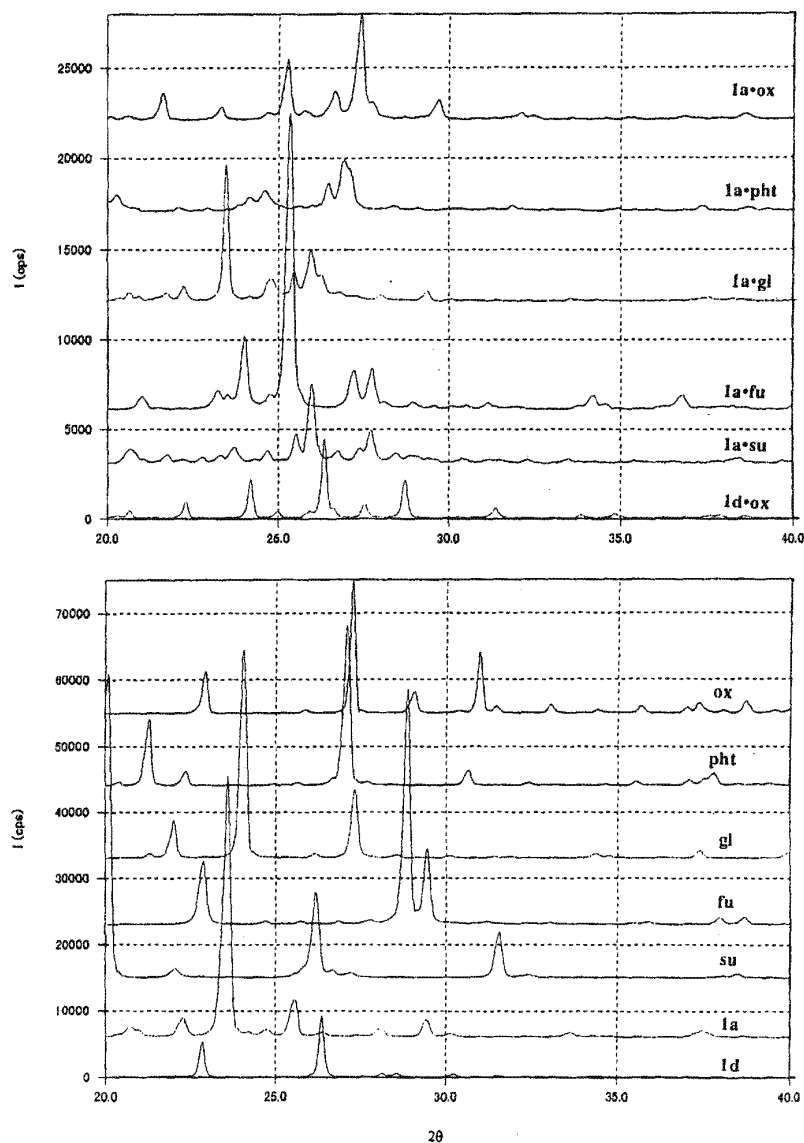


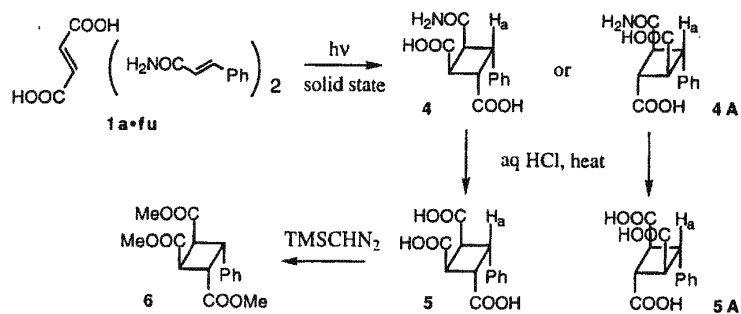
Figure 2. X-Ray powder patterns for cocrystals **1a•ox**, **1a•pht**, **1a•gl**, **1a•fu**, **1a•su** and **1d•ox** and for the constituents **ox** (anhyd), **pht**, **gl**, **fu**, **su**, **1a** and **1d**.

(7.52 Å which is the length of the *c*-axis) is far too long for the reaction to occur.

The X-ray structural features of **1a•ox** are: (a) the presence of disorder at the ethylene carbons (Fig. 3b); and (b) the layered crystal structure (Fig. 4b).¹⁵ The occupancy for C7, C8, C9 and C10 atoms was assumed 50%. The feature (b) is considered to be another mode that can be utilized for the compulsory reaction control. As pictured in Scheme 4, the **1a** molecules are bilayered in a syn head-to-head orientation and are thus in accord with the formation of β-truxinamide **3a**. The photodimerization was not very efficient, however,

because of a somewhat long distance between the nearest C=C bonds (C7...C7=C8...C8=C9...C9=C10...C10=4.96 Å).

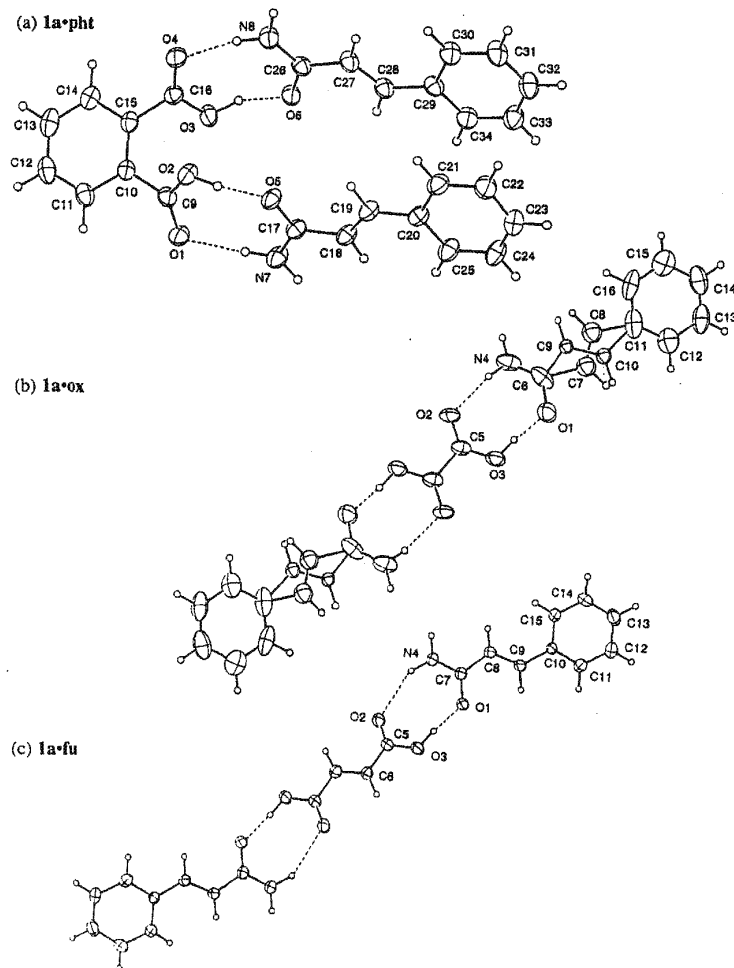
Fig. 3c shows an ORTEP diagram for **1a•fu**. Scheme 5 depicts the nearest neighbor of **1a** and **fu** in the crystal packing; for example, the pair A and B in the packing diagram Fig. 4c. The distances between the ethylene carbons are 3.82 and 4.22 Å. It is interesting that in order to accommodate the stereochemical configuration of the observed product **4**, a pedal-like conformational change in either **1a** or **fu** (see Scheme 5) is required like in the case of



Scheme 2.

1a•pht (see Scheme 3).¹³ There is an array of **1a** and **fu** molecules that are oriented properly to explain the stereochemistry of **4**: for example, A and C' in Fig. 4c, where C' is generated by -1 cell translation of C along the a axis.

However, the ethylene carbons in this array are by far apart, i.e. 7.39 and 7.51 Å. Hence, the nearest separated **1a** and **fu** molecules shown in Scheme 5 will be the reacting partner. Furthermore, there is a good π -overlap between the

Figure 3. ORTEP drawings of co-crystals: (a) **1a•pht**; (d) **1a•ox**; and (c) **1a•fu**.

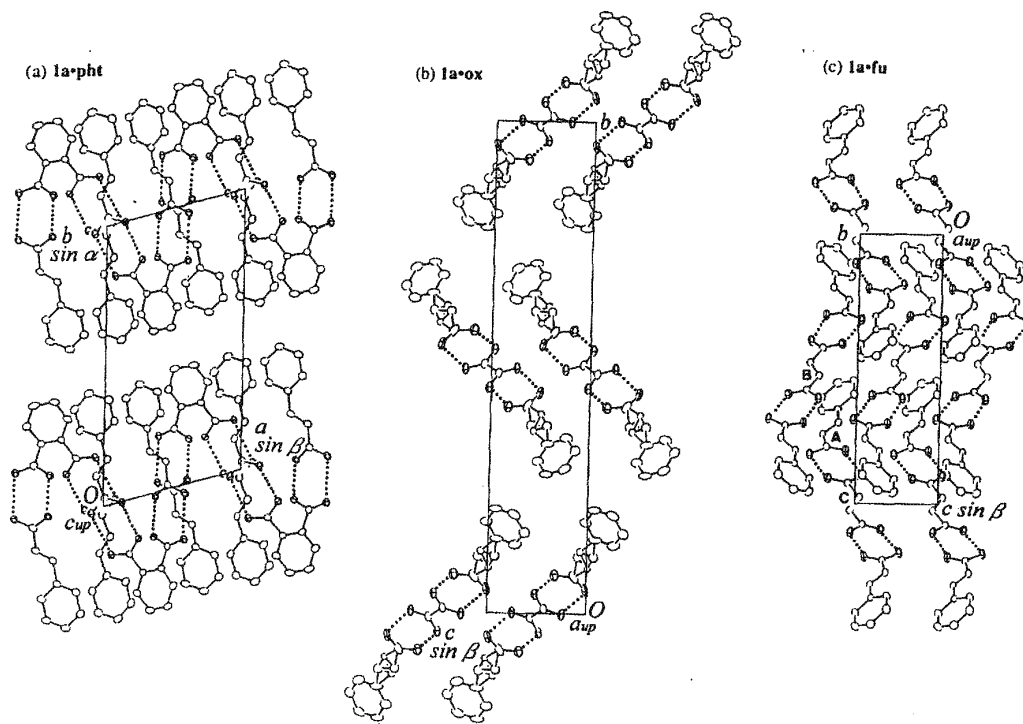
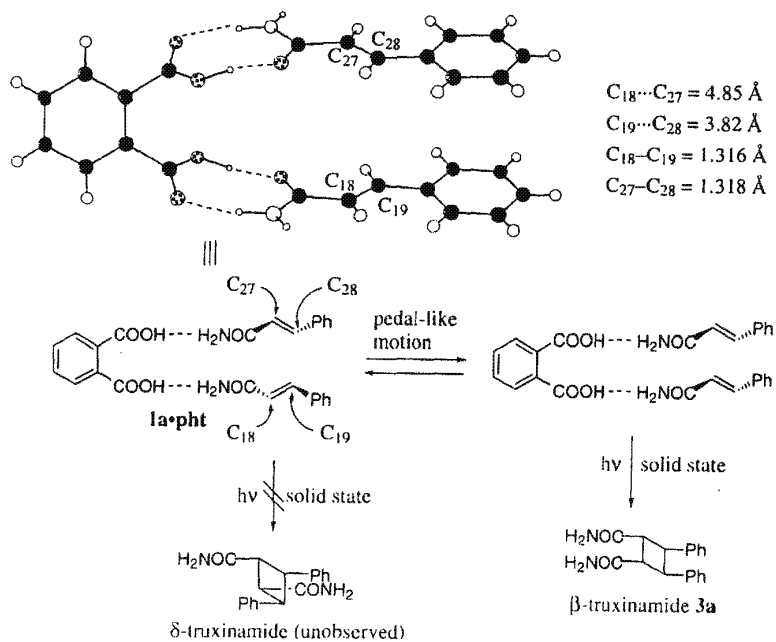
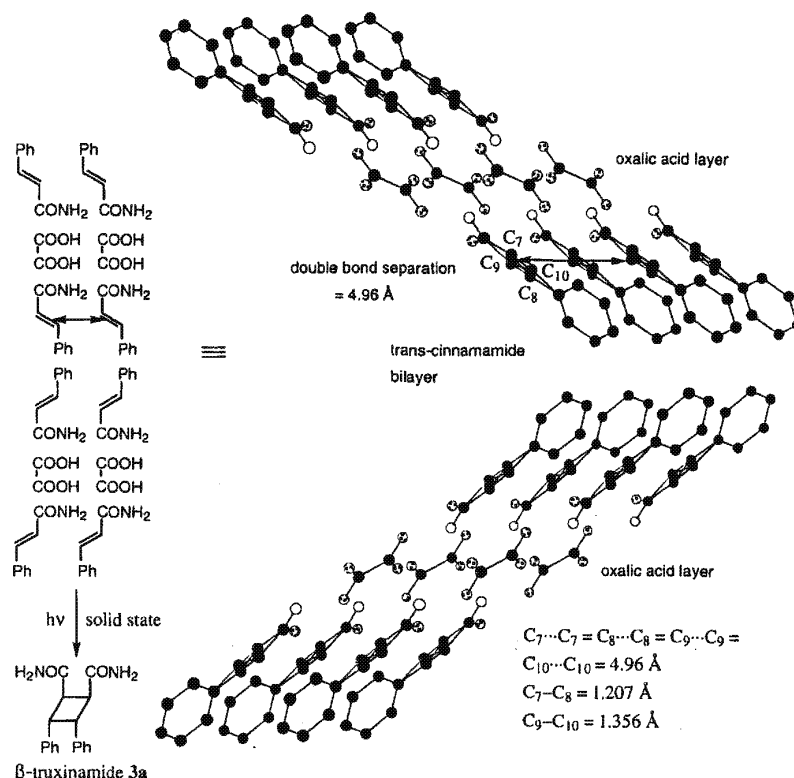


Figure 4. Packing diagrams of cocrystals: (a) **1a•pht**; (b) **1a•ox**; and (c) **1a•fu**, which are projected along the *c*-axis, the *a*-axis and the *a*-axis, respectively.



Scheme 3. A pedal-like dynamic conformational change in cocrystal **1a•pht** and the solid-state photodimerization.



Scheme 4. A layered crystal packing of **1a·ox** and the solid state photodimerization.

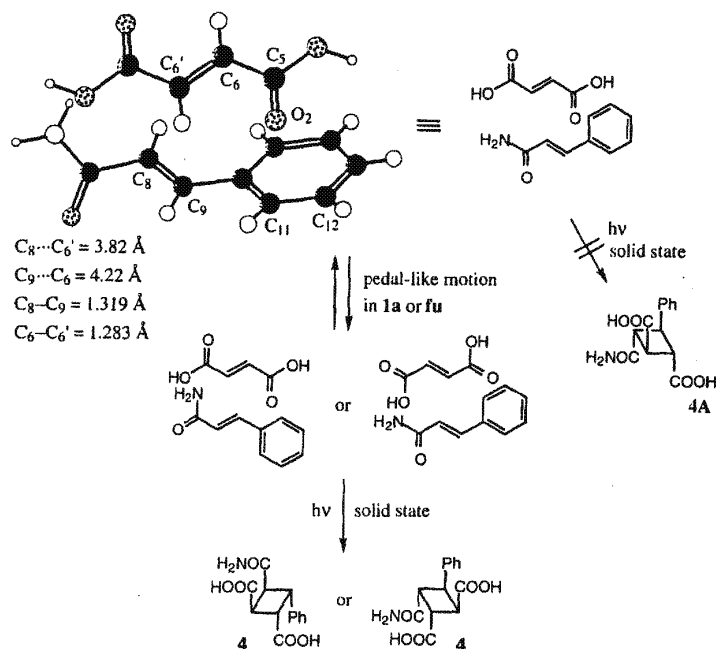
phenyl ring and the carbonyl group ($O2 \cdots C11 = 3.50$ Å, $O2 \cdots C12 = 3.43$ Å, $C11 \cdots O2-C5 = 89^\circ$, $C12 \cdots O2-C5 = 89^\circ$). This overlap should be responsible for the 343 nm inflection which appeared in the diffuse reflectance spectrum of **1a·fu** (Fig. 1). An attractive interaction between the carbonyl and phenyl groups, referred to as $C=O \cdots \pi$ interaction, was reported to exist and this interaction was utilized for asymmetric dimerization and polymerization.¹⁷ Such a $C=O \cdots \pi$ interaction could not be recognized in the X-ray structures of cocrystals **1a·ox** and **1a·pht**.

The crystallographically determined lengths of the ethylenic bond in **1a·ox**, **1a·pht**, and **1a·fu** are ~ 1.28 (disordered), 1.316(2) and 1.318(2) (two **1a** molecules in the asymmetric unit), and 1.319(2) (1.283(2) Å for the **fu** component) Å, respectively. For the **1a** homocrystal, the length was reported to be 1.331(4) Å.¹⁸ For the **fu** homocrystal, it was 1.348 (α form) or 1.315 (β form) Å.¹⁹ Consequently, the ethylenic bonds in **1a·pht** and **1a·fu** are considerably shorter than the corresponding ones in the homocrystals. This fact strongly suggests¹¹ that there is dynamic disorder at the ethylene bond in the hydrogen bonded cocrystals **1a·pht** and **1a·fu**, in line with the pedal-like motion deduced from the product stereochemistry (Schemes 3 and 5 and cf. Ref. 13). Maybe **1a·ox** is an extreme case, since here the static disorder is present at the ethylene bond (Fig. 3b). Facility of the dynamic or static disorder in these cocrystals

is not unexpected, because the crystal packing for two-component molecular crystals is often loose.^{1,2} The loose crystal packing for **1a·ox**, **1a·pht** and **1a·fu** was also indicated from their weak PXD intensities, as described above.

Although the *R* value was reduced to only 0.141 owing to the poor quality of crystals, the crystal structure for **1d·ox** was found to be very similar to that of **1a·ox**, as expected from identical space group and similar lattice constants.²⁰ For instance, there are double layers of **1d** and the nearest ethylene bonds are 4.97 Å apart (cf. 4.96 Å apart for **1a·ox**). However, the ethylene bond in **1d·ox** is not disordered. For **1a·ox** (Fig. 3b), disorder is present at the ethylene carbons, indicating that **1a·ox** possesses larger free space²¹ around the ethylene bond than **1d·ox**. This difference is apparently reflected on the smaller photodimerization reactivity of **1d·ox** (only 3% yield of **3d**) as compared with that of **1a·ox** (42% yield of **3a**) (Table 3).²²

In conclusion, a compulsory control of solid-state photodimerization like that by double salts of *gauche* 1,2-diamine¹⁻⁷ was also achieved by using **pht** as a hydrogen-bonding intermolecular linker. Furthermore, a new mode of control by **ox** was found. A key point of the latter control was ascribed to the layered crystal structure enforced by **ox**. The crystal structure–reactivity relationship is well investigated and it is believed that the reactivity and the product



Scheme 5. A pedal-like dynamic conformational change in cocrystal 1a-fu and the mixed photodimerization.

stereochemistry are precisely predictable from the crystal structure.²⁴ Our study suggests that this is not always the case when there is a dynamic disorder. It seems that this situation is particularly ubiquitous for mixed molecular crystals, because their crystal packings are often loose.^{1,2} Torsional vibrations may bring about orientations or configurations that are more favorable for the reaction.

Experimental

General procedures

¹H NMR spectra were measured on a Varian Gemini-200, JEOL EX-270J, or JEOL JNM-A400 spectrometer. The solvent employed is DMSO-d₆, unless otherwise specified. IR spectra were recorded in a JASCO FT/IR-5M or SHIMADZU FTIR-8100A spectrometer. Mass spectra were obtained in a JEOL JMS-DX 300 or JEOL JMS-SX 102A spectrometer. Diffuse reflectance spectra were gathered with a SHIMADZU UV-2400PC spectrometer equipped with a diffuse-reflectance attachment and a BaSO₄ powder was used as a standard of reflectivity. Powder X-ray diffraction (PXD) patterns were obtained with a MAC Science MX Labo diffractometer equipped with CuKα radiation (1.5406 Å). Data were collected between 20 and 70° in 2θ at a scan rate of 4°/min. HPLC analyses were performed with a SHIMADZU LC-5A chromatograph and a UV detector (fixed at 217 nm) by using a Cosmosil 5C₁₈-AR column (4.6 mm i.d.×150 mm) and were eluted with a mixture of methanol and water, a mixture of methanol and 20 mM acetate buffer (pH 3.6), or a mixture of methanol and 10 mM phosphate buffer (pH 2.6).

Materials

trans-Cinnamamide (1a), *trans*-4-chlorocinnamamide (1c), oxalic acid (ox) (anhydrous and dihydrate), malonic acid, succinic acid (su), glutaric acid (gl), adipic acid, fumaric acid (fu), maleic acid, phthalic acid (pht), (±)-*trans*-1,2-cyclohexanedicarboxylic acid, *cis*-1,2-cyclohexanedicarboxylic acid, and 1,1-cyclobutanedicarboxylic acid were commercially available. *trans*-4-Methylcinnamamide (1b) and *trans*-β-(2-thienyl)acrylamide (1d) were prepared according to the literature method.^{8,25} Prior to measuring the diffuse reflectance or PXD spectra, 1a, ox (dihydrate), su, gl, fu, and pht were recrystallized from EtOH, water, water, water, water, and EtOH, respectively, while ox (anhydrous) was used as received.

Cocrystallization

A hot solution containing 1.472 g (10.0 mmol) of 1a in *i*PrOH (15 mL) was mixed with a hot solution containing 0.831 g (5.0 mmol) of pht in *i*PrOH (15 mL) and the mixture was filtered immediately. Upon cooling to room temperature, colorless needles crystallized out of the filtrate and were collected by filtration to afford 1.59 g (69%) of 1a-pht. This was dried in vacuo at 35°C for a few days. Other cocrystals were similarly prepared from mixing 2 equiv. of amides 1a–1d with 1 equiv. of dicarboxylic acids ox (dihydrate), su, gl, and fu in appropriate solvent (Table 1).

Small-scale irradiation of cocrystals

Cocrystals of 1a-ox, 1a-su, 1a-gl, 1a-pht, 1a-fu, 1b-ox, 1c-ox

or **1d-ox** (15–20 mg) were crushed and spread between two Pyrex plates. This sandwiched sample was placed in our solid-state photolysis vessel.^{1,2} Irradiation was carried out with a 400 W high-pressure mercury lamp under an argon atmosphere for 20 h. During the irradiation, the vessel was cooled from outside by running water. After the irradiation, the reaction mixture was dissolved in MeOH or DMSO-*d*₆ for HPLC and ¹H NMR analyses, respectively. Yields thus estimated are summarized in Table 3.

Similar irradiation of homocrystals **1a–1d** gave cleanly the corresponding α -truxinamides **2a–2d**, as was previously reported.⁸

Isolation and characterization of β -truxinamides

(a) Cocrystal **1a-ox** (51 mg) was irradiated for 20 h as described above. The slightly colored photolysate, which contained **3a** with 29% yield (estimated by ¹H NMR and HPLC), was taken up in 2 mL of water and was stirred at 45°C for 1 h. After cooling in a refrigerator, an insoluble pale yellow solid was collected by filtration. This was stirred into 2 mL of acetonitrile and an insoluble solid was filtered off to afford 5 mg (13% yield) of **3a** as a white crystalline solid: mp 246–252°C (dec); ¹H NMR (200 MHz) δ 3.64 (2H, quasi-d, *J*=6.5 Hz, cyclobutyl), 4.20 (2H, quasi-d, *J*=6.5 Hz, cyclobutyl), 6.88–7.18 (10H, m, aromatic); MS (EI) *m/z* (rel intensity) 277 (42, M⁺–NH₃), 205 (63), 180 (31, [PhCH=CHPh]⁺), 147 (21, M⁺/2), 131 (100); IR (KBr) 3430, 3402, 1665, 1605, 1414, 698 cm^{–1}. The stereochemistry of the cyclobutane ring of **3a** was determined on the basis of the characteristic ¹H NMR chemical shift and coupling pattern of the cyclobutyl protons, which were similar to those of the corresponding cinnamic acid photodimer. In fact, upon heating 2 mg of **3a** in 0.4 mL of conc HCl at 95°C for 1 h, **3a** was hydrolyzed to β -truxinic acid^{3,26} in 81% yield (HPLC).

(b) Cocrystal **1a-pht** (53 mg) was irradiated for 50 h as described above. The resultant white powder, which contained **3a** with 37% yield (estimated by ¹H NMR and HPLC), was recrystallized from 5.5 mL of 10:1 acetonitrile–methanol to furnish 10 mg (31%) of **3a** as white needles.

The cyclobutane ring protons for **3b–3d** also exhibited the ¹H NMR pattern characteristic of the β -type photodimer. Attempts to purify β -truxinamides **3c** and **3d** were not carried out. Their ¹H NMR data were derived from the mixtures.

(c) The photolysate from **1b-ox** (50 mg, 40 h irradiation) was recrystallized twice with *i*-PrOH (first 3 mL, then 2 mL) to remove polymeric materials (11 mg). The residue was then recrystallized from MeCN (1 mL) to afford, although still a little contaminated with the polymer, 5 mg of **3b** as pale yellow crystals: mp 188–202°C; ¹H NMR (200 MHz) δ 2.11 (6H, s), 3.56 (2H, quasi-d, *J*=6 Hz, cyclobutyl), 4.11 (2H, quasi-d, *J*=6 Hz, cyclobutyl), 6.87 (10H, AB with almost vanishing end peaks, *J*=8 Hz, aromatic); MS (EI) *m/z* (rel intensity) 305 (3), 233 (12), 208 (7, [MePhCH=CHPhMe]⁺), 161 (100, M⁺/2), 145

(62); IR (KBr) 3394, 3358, 1664, 1516, 1421, 1406, 1245, 811, 722 cm^{–1}.

(d) From the ¹H NMR analysis of the photolysate from **1c-ox**, **3c**: ¹H NMR (200 MHz) δ 3.61 (2H, quasi-d, *J*=6 Hz, cyclobutyl), 4.19 (2H, quasi-d, *J*=6 Hz, cyclobutyl), 7.00 and 7.16 (8H, AB, *J*=8.4 Hz). This photolysate was directly hydrolyzed with conc HCl as described above. The dimer **3c** was led cleanly to the previously known *p,p'*-dichloro- β -truxinic acid.^{4,26}

(e) The pale brown photolysate from **1d-ox** (80 mg, 45 h irradiation) was recrystallized first with 10 mL of 1:1 chloroform–MeOH, then with 7 mL of 5:2 EtOH–MeOH. The mother liquor was evaporated and the residue was recrystallized from 11 mL of 10:1 benzene–EtOH. A pale brown solid (16 mg) containing **3d** in ca. 30% (¹H NMR) precipitated. **3d**: ¹H NMR (CD₃OD, 270 MHz) δ 3.80 (2H, quasi-d, *J*=6 Hz, cyclobutyl), 4.51 (2H, quasi-d, *J*=6 Hz, cyclobutyl), 6.81–6.89 (2H, m), 7.16 (1H, d with each peaks slightly split, *J*=5 Hz). This spectrum was very similar to that of the corresponding dicarboxylic acid previously prepared.^{4,27}

Isolation of heterodimer 4. Cocrystal **1a-fu** (101 mg) was irradiated for 90 h as described above. The resultant pale yellow powder, which contained the product **4** with 50% yield (¹H NMR and HPLC), was fractionally recrystallized from water (2 mL), then acetonitrile–water, and finally acetonitrile (5 mL). As a result of these recrystallization procedures, fumaric and maleic acids, β -truxinamide **3a**, α -truxinamide **2a**, and *cis*-**1a** could be entirely removed and finally 18 mg of a mixture of **4** and **1a** was isolated as a solid. This mixture was further recrystallized from 7 mL of 4:3 acetonitrile–ether and then 7 mL of 4:3 acetonitrile–benzene to afford 4 mg (6%) of *t*-3-carbamoyl-*c*-4-phenyl-*r*-1,2-cyclobutanedicarboxylic acid **4** as white small needles: mp 187–190°C; ¹H NMR (CD₃OD, 400 MHz) δ 3.74–3.78 (1H, dd, *J*=10.1 and 6.1 Hz, H₂N–COCH), 3.79–3.83 (1H, dd, *J*=10.1 and 6.1 Hz, H₂NCOCH–COOH), 3.89–3.93 (1H, dd, *J*=10.7 and 6.1 Hz, PhCHCHCOOH), 4.09–4.13 (1H, dd, *J*=10.7 and 6.1 Hz, PhCH), 7.19–7.32 (5H, m, aromatic); ¹³C NMR (CD₃OD, 100 MHz) δ 41.12 (CH), 43.97 (CH), 45.61 (CH), 46.14 (CH), 128.10 (CH), 128.71 (CH), 129.37 (CH), 140.45 (C), 174.84 (CO), 175.16 (CO), 176.69 (CO); IR (KBr) 3425 and >2500 (CONH₂ and COOH), 1706 (COOH), 1665 (CONH₂), 1648 (CONH₂), 1602, 1424, 1301, 1223, 1179, 741, 699 cm^{–1}.

Hydrolysis of 4. (a) Heterodimer **4** (2 mg) in conc. HCl (0.5 mL) was heated at 95°C for 1 h. The reaction mixture was evaporated in vacuo. The residue was essentially pure *c*-4-phenyl-*r*-1,2-*t*-3-cyclobutanetricarboxylic acid **5** (¹H NMR and HPLC).

(b) In order to obtain more **5**, 20 mg of a mixture of **4** and **1a** (molar ratio, ca. 1:1) in conc. HCl (3 mL) was heated at 90°C for 5 h. The reaction mixture was evaporated and the residue was recrystallized with 2 mL of 1:1 methanol–water and then with 5 mL of ether. Relatively insoluble cinnamic acid and other insoluble materials were removed. The resultant soluble part (16 mg) was again recrystallized

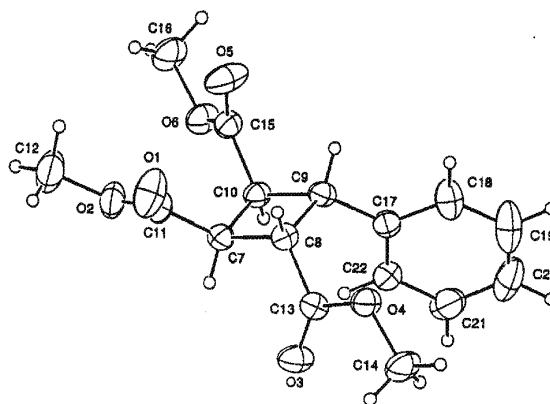


Figure 5. ORTEP drawing of compound 6.

from CHCl_3 (5 mL) to give 9 mg of **5** as white plates: mp 205–208°C; ^1H NMR (CD_3OD , 400 MHz) δ 3.72–3.79 (2H, m), 3.82–3.87 (1H, m), 4.22–4.27 (1H, m, PhCH), 7.19–7.32 (5H, m, aromatic); ^{13}C NMR (CD_3OD , 100 MHz) δ 41.55 (CH), 44.28 (CH), 44.87 (CH), 45.80 (CH), 128.11 (CH), 128.52 (CH), 129.34 (CH), 140.04 (C), 174.64 (CO), 175.36 (CO), 175.71 (CO); MS (EI) m/z (rel intensity) 219 (17, M^+-COOH), 200 (18), 174 (45, M^+-2COOH), 172 (56), 148 (97, $[\text{PhCH}=\text{CHCOOH}]^+$), 147 (80), 129 (100, M^+-3COOH), 128 (93), 103 (44), 77 (50, Ph^+); IR (KBr) 3500–2500 (COOH), 1724 (COOH), 1709 (COOH), 1409, 1272, 1204, 743, 698 cm^{-1} .

In a separate experiment, the photolysate from 539 mg of **1a-fu** (irradiated for 170 h, containing **4** with ca. 75% yield by ^1H NMR) was heated in 25 mL of conc. HCl at 95°C for 3 h. The resulting brown to yellow precipitate was filtered off, the filtrate was evaporated to dryness, and then the yellow residue (440 mg) was recrystallized from 18 mL of 5:1 water–methanol. After filtration, a yellow solid (390 mg) was obtained from evaporation of the mother liquor and this was refluxed in CHCl_3 (50 mL) for 1 h. Tricarboxylic acid **5** (175 mg, 51% yield on the basis of **1a-fu**) was obtained as an insoluble pale yellow solid.

Esterification of 5. Into a solution containing 10 mg (0.038 mmol) of **5** in 2 mL of 1:1 methanol–benzene was added a 10% hexane solution of (trimethylsilyl)diazomethane (1 mL, ca. 0.8 mmol). The mixture was kept at room temperature for 4 h under stirring. After evaporation, the residue was subjected to preparative TLC (Merck Kieselgel 60 F_{254} , 10:1 CHCl_3 –acetone) to afford 8 mg (69%) of trimethyl *c*-4-phenyl-*r*-1,*r*-2,*r*-3-cyclobutanetricarboxylate **6**. This was crystallized from 0.6 mL of 5:1 hexane–acetonitrile to afford 4 mg of colorless prisms: mp 88–94°C; ^1H NMR (CDCl_3 , 200 MHz) δ 3.29 (3H, s), 3.70 (3H, s), 3.75 (3H, s), 3.81–4.02 (3H, m), 4.28–4.40 (1H, m, PhCH), 7.16–7.37 (5H, m, aromatic); MS (EI) m/z (rel intensity) 306 (11, M^+), 275 (16), 246 (44), 214 (41), 187 (35), 162 (100, $[\text{PhCH}=\text{CHCOOMe}]^+$), 131 (96), 113 (42); IR (neat) 1742, 1728, 1436, 1314, 1301, 1274, 1216, 1204, 1172, 1018, 754, 701 cm^{-1} . This compound was

successfully analyzed by single crystal X-ray diffraction (Fig. 5).

X-Ray crystal structure determination

X-ray intensities were measured on Rigaku AFC-5 or AFC-7R diffractometer with graphite monochromatized $\text{MoK}\alpha$ radiation ($\lambda=0.71073\text{ \AA}$). The structures were solved by direct methods and were refined using CRYSTAN-GM or TEXSAN software.²⁸

Crystal data. **1a-ph**: triclinic, $P\bar{1}$, $a=9.562(1)$, $b=17.402(2)$, $c=7.522(1)\text{ \AA}$, $\alpha=90.82(1)$, $\beta=105.71(1)$, $\gamma=75.50(1)^\circ$, $V=1164.6(3)\text{ \AA}^3$, $Z=2$, $D_x=1.313\text{ g/cm}^3$, $R=0.043$. **1a-ox**: monoclinic, $P2_1/n$, $a=4.961(5)$, $b=30.536(9)$, $c=6.471(3)\text{ \AA}$, $\beta=101.62(5)$, $V=960.2(11)\text{ \AA}^3$, $Z=2$, $D_x=1.330\text{ g/cm}^3$, $R=0.052$. **1a-fu**: monoclinic, $P2_1/n$, $a=11.503(1)$, $b=5.297(1)$, $c=16.888(1)\text{ \AA}$, $\beta=94.09(1)$, $V=1026.4(2)\text{ \AA}^3$, $Z=2$, $D_x=1.328\text{ g/cm}^3$, $R=0.050$. **6**: monoclinic, $P2_1/c$, $a=5.789(2)$, $b=17.576(2)$, $c=15.667(2)\text{ \AA}$, $\beta=99.85(2)$, $V=1570.6(6)\text{ \AA}^3$, $Z=4$, $D_x=1.295\text{ g/cm}^3$, $R=0.061$.

Acknowledgements

This work was supported by the grant-in-aid for Scientific Research from the Japanese Government (Nos. 10440215, 10132229, 11119229). The authors also acknowledge Ms Ryoko Yoshihara for her assistance in X-ray work.

References

- Ito, Y. *Synthesis* **1998**, 1–32.
- Ito, Y. *Mol. Supramol. Photochem.* **1999**, 3, 1–70.
- Ito, Y.; Borecka, B.; Scheffer, J. R.; Trotter, J. *Tetrahedron Lett.* **1995**, 36, 6083–6086.
- Ito, Y.; Borecka, B.; Olovsson, G.; Trotter, J.; Scheffer, J. R. *Tetrahedron Lett.* **1995**, 36, 6087–6090.
- Ito, Y.; Olovsson, G. *J. Chem. Soc., Perkin Trans. I* **1997**, 127–133.
- Ito, Y. *Mol. Cryst. Liq. Cryst.* **1996**, 277, 247–253.

7. Ito, Y.; Fujita, H. *J. Org. Chem.* **1996**, *61*, 5677–5680.
8. Hung, J. D.; Lahav, M.; Luwisch, M.; Schmidt, G. M. J. *Isr. J. Chem.* **1972**, *10*, 585–599.
9. Huang, C.-M.; Leiserowitz, L.; Schmidt, G. M. J. *J. Chem. Soc., Perkin Trans. 2* **1973**, 503–508; Leiserowitz, L. *Acta Crystallogr. B* **1976**, *32*, 775–801.
10. Schmidt, G. M. J. *Pure Appl. Chem.* **1971**, *27*, 647–678.
11. (a) Ogawa, K.; Sano, T.; Yoshimura, S.; Takeuchi, Y.; Toriumi, K. *J. Am. Chem. Soc.* **1992**, *114*, 1041–1051. (b) Ogawa, K.; Harada, J.; Tomoda, S. *Acta Crystallogr. B* **1995**, *51*, 240–248. (c) Harada, J.; Ogawa, K.; Tomoda, S. *Acta Crystallogr. B* **1997**, *53*, 662–672.
12. Galli, S.; Mercandelli, P.; Sironi, A. *J. Am. Chem. Soc.* **1999**, *121*, 3767–3772.
13. We have recently proved unequivocally by crystallographic analysis of the crystal-to-crystal phototransformation of **1a**·pht and **1a**·fu that the pedal-like motion prior to cycloaddition is true.¹⁴ It is possible, however, that this motion preferentially occurs at defect sites, which may be regarded as the effect of dynamic defects on reactions.
14. Hosomi, H.; Ito, Y.; Ohba, S. In preparation.
15. Single crystals of benzamide form hydrogen-bonded bilayers¹⁶ but those of **1a** do not.¹⁸
16. Edgar, R.; Schultz, T. M.; Rasmussen, F. B.; Feidenhans'l, R.; Leiserowitz, L. *J. Am. Chem. Soc.* **1999**, *121*, 632–637.
17. Addadi, L.; Lahav, M. *Pure Appl. Chem.* **1979**, *51*, 1269–1284.
18. Iwamoto, T.; Kashino, S.; Haisa, M. *Acta Crystallogr. C* **1989**, *45*, 1110–1112.
19. (a) Brown, C. J. *Acta Crystallogr.* **1966**, *21*, 1–5. (b) Bednowitz, A. L.; Post, B. *Acta Crystallogr.* **1966**, *21*, 566–571.
20. Crystal data of **1d**·ox: monoclinic, *P*2₁/*n*, *a*=4.968(3), *b*=28.435(18), *c*=6.592(4) Å, β =104.80(5), *V*=900.3(9) Å³, *Z*=2, *D*_x=1.462 g/cm³.
21. (a) Cohen, M. D. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 386–393. (b) Gavezzotti, A. *J. Am. Chem. Soc.* **1983**, *105*, 5220–5225. (c) Marubayashi, N.; Ogawa, T.; Hirayama, N. *Bull. Chem. Soc. Jpn* **1998**, *71*, 321–327. (d) Ito, Y.; Matsuura, T. *Tetrahedron Lett.* **1988**, *29*, 3087–3090. Ito, Y.; Ito, H.; Ino, M.; Matsuura, T. *Tetrahedron Lett.* **1988**, *29*, 3091–3094.
22. The yields of α -truxillamide **2** from the solid-state photodimerization of homocrystals **1a**, **1c**, **1d** (18, 100, 97%, respectively) is consistent with the separation of the nearest neighbor C=C bonds (4.11, 3.63, 3.76 Å, respectively).²³ As a result, the intrinsic reactivity of **1d** appears normal.
23. Hosomi, H.; Ito, Y.; Ohba, S. *Acta Crystallogr. B* **2000**, (in press).
24. Ihmels, H.; Scheffer, J. R. *Tetrahedron* **1999**, *55*, 885–907.
25. Mason, C. D.; Nord, F. F. *J. Org. Chem.* **1951**, *16*, 1869–1872.
26. Cohen, M. D.; Schmidt, G. M. J.; Sonntag, F. I. *J. Chem. Soc.* **1964**, 2000–2013.
27. Lahav, M.; Schmidt, G. M. J. *J. Chem. Soc. (B)* **1967**, 239–243.
28. (a) Edwards, C.; Gilmore, C. J.; Mackay, S.; Stewart, N. 1996. CRYSTAN-GM Version 6.3.3; Computer Program for the Solution and Refinement of Crystal Structures, MAC Science, Japan. (b) Molecular Structure Corporation. TEXSAN, Single Crystal Structure Analysis Software, Version 1.9. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA; 1998.

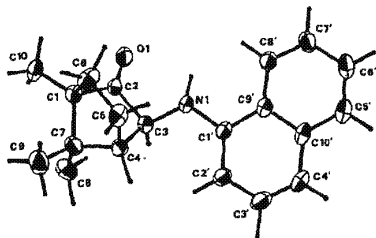


Fig. 1. ORTEP drawing (Johnson, 1965) of the title compound with atom numbering. The anisotropic ellipsoids for non-H atoms enclose 30% probability.

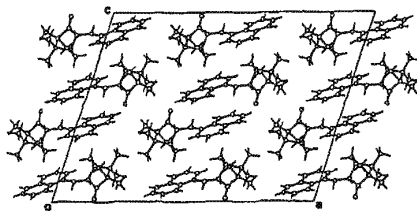


Fig. 2. A view of the unit cell.

2434 with $|F_o| > 3\sigma(|F_o|)$ used for structure determination, $2\theta_{\max} = 125^\circ$, hkl range: $h -29$ to 27 , $k -8$ to 8 , $l -22$, three standard reflections (02 $\bar{9}$, 134 and 13,1,0) remeasured every 50 reflections without showing any significant change in intensity; corrections for Lorentz and polarization effects, absorption ignored; structure solved by direct methods with *MULTAN78* (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978), refinement by full-matrix least squares on F

using *SHELX76* (Sheldrick, 1976), all H atoms are on the difference map; anisotropic temperature factors for all non-H atoms and isotropic temperature factors for H atoms using riding model with C-H 1.00 Å for the 9-methyl group; $R = 0.050$, $wR = 0.068$, $w^{-1} = \sigma^2(F) + 0.00625F^2$, $S = 1.06$, $(\Delta/\sigma)_{\max} = 0.03$, largest peak in final ΔF map $0.12 \text{ e } \text{\AA}^{-3}$; atomic scattering factors from *International Tables for X-ray Crystallography* (1974). Table 1 contains final atomic coordinates and equivalent isotropic thermal parameters for non-H atoms.* Table 2 lists bond distances and angles. Fig. 1 shows the molecule and the numbering scheme adopted. Fig. 2 shows a view of the unit cell.

* Lists of anisotropic thermal parameters for non-H atoms, positional and thermal parameters for H atoms, bond distances and angles, and structure factors have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51769 (16 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

References

- International Tables for X-ray Crystallography* (1974). Vol. IV. Birmingham: Kynoch Press. (Present distributor Kluwer Academic Publishers, Dordrecht.)
JOHNSON, C. K. (1965). ORTEP. Report ORNL-3794. Oak Ridge National Laboratory, Tennessee, USA.
MAIN, P., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J.-P. & WOOLFSON, M. M. (1978). *MULTAN78. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*. Univ. of York, England, and Louvain, Belgium.
SHELDRICK, G. M. (1976). *SHELX76*. Program for crystal structure determination. Univ. of Cambridge, England.
YAGI, E., ISHIGE, M., NAGASAWA, Y. & MAEDA, K. (1989). *J. Chem. Soc. Perkin Trans. 2*. Submitted.

Acta Cryst. (1989). **C45**, 1110–1112

Structure of Cinnamamide

BY TETSUYUKI IWAMOTO, SETSUO KASHINO* AND MASAO HAISA

Department of Chemistry, Faculty of Science, Okayama University, Tsushima, Okayama 700, Japan

(Received 23 January 1989; accepted 3 March 1989)

Abstract. $\text{C}_9\text{H}_9\text{NO}$, $M_r = 147.08$, m.p. = 416–418 K, monoclinic, $P2_1/a$, $a = 16.015$ (3), $b = 5.072$ (1), $c = 9.563$ (2) Å, $\beta = 93.99$ (2)°, $V = 775.0$ (3) Å³, $Z = 4$, $D_m = 1.26$ (2), $D_x = 1.261 \text{ Mg m}^{-3}$, $\text{Cu K}\alpha$, $\lambda = 1.5418$ Å, $\mu = 0.63 \text{ mm}^{-1}$, $F(000) = 312$, $T = 295 \text{ K}$, $R = 0.066$ for 1042 reflections with $|F_o| >$

$2\sigma(F_o)$. The C=C double bonds of the nearest neighbours are related by $\bar{1}$ with a C...C distance of 4.109 (4) Å, the interplanar spacing being 3.762 (4) Å for the planes through four C atoms involving the C=C bond. No topochemical reaction was observed.

Experimental. Crystals from a chloroform solution by slow evaporation. D_m by flotation in aqueous KI.

© 1989 International Union of Crystallography

* To whom correspondence should be addressed.

0108-2701/89/071110-03\$03.00

Colourless prism elongated along *b*; $0.08 \times 0.18 \times 0.10$ mm. Systematic absences $h0l$ for h odd, $0k0$ for k odd. Rigaku AFC-5 four-circle diffractometer equipped with rotating anode (40 kV, 200 mA), Ni-filtered Cu K α . 20 reflections within $14 < 2\theta < 38^\circ$ used to determine the lattice parameters. Intensity data collected within $2\theta_{\max} = 125^\circ$ ($-18 \leq h \leq 18$, $0 \leq k \leq 5$, $0 \leq l \leq 11$), ω - 2θ scan method [scan speed 4° min^{-1} in ω , scan range $(1.2 + 0.15 \tan \theta)^\circ$ in ω], background measured for 4 s on either side of the peak, three standard reflections recorded after every 57 reflections, fluctuations within 1%. Lorentz and polarization corrections, no absorption correction. 1235 unique reflections measured, $R_{\text{int}} = 0.022$ for 79 $hk0$ reflections. 1042 reflections with $|F_o| > 2\sigma(F_o)$ used in the structure analysis. Structure solved by Patterson method and refined by block-diagonal least squares (non-H atoms anisotropically). H atoms determined from a difference Fourier map and refined isotropically; $\sum w(|F_o| - |F_c|)^2$ minimized with $w = 1.0/[\sigma(F_o)^2 + 0.0269|F_o| + 0.0003|F_o|^2]$. Correction for secondary extinction applied for six strongest reflections [$U_{\text{corr}} = I_o(1 + 2.4 \times 10^{-5} I_o)$]. Final $R = 0.066$ for 1042 reflections, $wR = 0.089$, $S = 1.26$, $(\Delta/\sigma)_{\max} = 0.2$. The residual electron density in the final difference map was within $\pm 0.27 \text{ e } \text{\AA}^{-3}$. No change was observed for crystals exposed to sunlight for two months.

Atomic scattering factors from *International Tables for X-ray Crystallography* (1974). Programs: *RSSF-5* (Sakurai, 1967), *HBL5-V* and *DAPH* (Ashida, 1973), *MOLCON* (Fujii, 1979) and *ORTEPII* (Johnson, 1971). Computations carried out at the Crystallographic Research Center, Institute for Protein Research, Osaka University, and at the Okayama University Computer Center. The final atomic parameters are listed in Table 1.* The thermal ellipsoids of the molecule are shown in Fig. 1 with atomic numbering. Bond lengths and angles are listed in Table 2. A stereoscopic view of the crystal structure is shown in Fig. 2.

Related literature. The lattice parameters, space group and two-dimensional structure of the title compound have been described by Schmidt (1964). However, no three-dimensional structure has been published. We have determined the structure as part of studies of solid-state photoreactions (Kashino, Oka & Haisa, 1989; Iwamoto, Kashino & Haisa, 1989). In the crystals the molecules are held together by N—H...O hydrogen bonds between the amide groups as in

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters, and bond lengths and angles involving H atoms have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51797 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. Final atomic coordinates ($\times 10^4$) and equivalent isotropic thermal parameters ($\text{\AA}^2$) with e.s.d.'s in parentheses

$$B_{\text{eq}} = (4/3) \sum \beta_{11} / a_i^2$$

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> _{eq}
O(1)	4571 (2)	-2029 (4)	8475 (2)	5.1 (1)
N(1)	4377 (2)	2282 (5)	8871 (3)	4.3 (1)
C(1)	3633 (2)	-1222 (6)	4191 (3)	4.6 (1)
C(2)	3039 (2)	619 (7)	3719 (3)	4.4 (1)
C(3)	2709 (2)	602 (8)	2348 (4)	5.2 (2)
C(4)	2977 (2)	-1251 (8)	1424 (3)	5.7 (2)
C(5)	3554 (2)	-3078 (9)	1873 (4)	5.9 (2)
C(6)	3881 (2)	-3101 (8)	3255 (4)	5.1 (2)
C(7)	3992 (2)	-1300 (6)	5639 (3)	4.0 (1)
C(8)	3931 (2)	535 (6)	6621 (3)	4.1 (1)
C(9)	4323 (2)	163 (6)	8061 (3)	3.8 (1)

Table 2. Bond lengths ($\text{\AA}$) and angles ($^\circ$) with e.s.d.'s in parentheses

O(1)—C(9)	1.236 (4)	C(3)—C(4)	1.379 (6)
N(1)—C(9)	1.324 (4)	C(4)—C(5)	1.357 (6)
C(1)—C(2)	1.386 (5)	C(5)—C(6)	1.387 (6)
C(1)—C(6)	1.384 (5)	C(7)—C(8)	1.331 (4)
C(1)—C(7)	1.462 (4)	C(8)—C(9)	1.485 (4)
C(2)—C(3)	1.379 (6)		
O(1)—C(9)—N(1)	122.4 (3)	C(2)—C(1)—C(6)	118.3 (3)
O(1)—C(9)—C(8)	121.1 (3)	C(2)—C(1)—C(7)	122.8 (3)
N(1)—C(9)—C(8)	116.5 (3)	C(3)—C(4)—C(5)	119.9 (4)
C(1)—C(2)—C(3)	121.0 (4)	C(4)—C(5)—C(6)	120.7 (4)
C(1)—C(6)—C(5)	120.3 (4)	C(6)—C(1)—C(7)	118.8 (3)
C(1)—C(7)—C(8)	127.3 (3)	C(7)—C(8)—C(9)	121.2 (3)
C(2)—C(3)—C(4)	119.9 (4)		

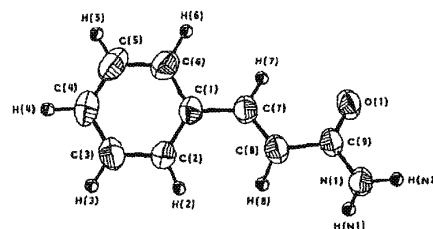


Fig. 1. The thermal ellipsoids of the molecule with atomic numbering. Ellipsoids of 50% probability are drawn for the non-H atoms; the H atoms are represented as spheres equivalent to $B = 1.0 \text{ \AA}^2$.

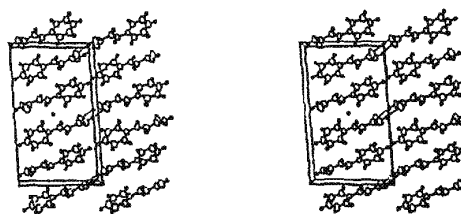


Fig. 2. Stereoscopic view of the crystal structure. The *a* axis points upwards, the *b* axis onto the plane of the paper and the *c* axis left to right.

benzamide (Blake & Small, 1972): (a) N(1)–H(N2)···O(1)(1–x, –y, 2–z) [N···O 2.950 (4), H···O 2.02 (3) Å, N–H···O 170 (3)°]; (b) N(1)–H(N1)···O(1)(x, 1+y, z) [N···O 2.930 (4), H···O 2.09 (3) Å, N–H···O 160 (1)°].

The authors thank the Crystallographic Research Center, Institute for Protein Research, Osaka University, for the use of the facility.

References

- ASHIDA, T. (1973). *HBLS-V and DAPH. The Universal Crystallographic Computing System*, Osaka. The Computation Center, Osaka Univ., Japan.
- BLAKE, C. C. F. & SMALL, R. W. H. (1972). *Acta Cryst.* B28, 2201–2206.
- FUJII, S. (1979). *MOLCON. The Universal Crystallographic Computing System*, Osaka. The Computation Center, Osaka Univ., Japan.
- International Tables for X-ray Crystallography* (1974). Vol. IV. Birmingham: Kynoch Press. (Present distributor Kluwer Academic Publishers, Dordrecht.)
- IWAMOTO, T., KASHINO, S. & HAISA, M. (1989). *Acta Cryst.* C45. In the press.
- JOHNSON, C. K. (1971). *ORTEP*. Report ORNL-3794, revised. Oak Ridge National Laboratory, Tennessee, USA.
- KASHINO, S., OKA, H. & HAISA, M. (1989). *Acta Cryst.* C45, 154–157.
- SAKURAI, T. (1967). *RSSFR-5. The Universal Crystallographic Computing System* (I). Tokyo: The Crystallographic Society of Japan.
- SCHMIDT, G. M. J. (1964). *J. Chem. Soc.* pp. 2014–2021.

Acta Cryst. (1989). C45, 1112–1113

Structure of 6-Amino-1,6-dideoxy-1-[3,4-dihydro-3-methyl-2,4-dioxo-1(2H)-pyrimidinyl]-4-thio-L-glycero- α -L-ido-heptofuranuronic Acid Monohydrate

BY Y. NAWATA,* Y. ISHITANI, I. MATSUURA, H. OISHI AND K. ANDO

Research Laboratories, Chugai Pharmaceutical Co. Ltd, Takada, Toshima, Tokyo 171, Japan

(Received 13 January 1989; accepted 19 April 1989)

Abstract. $C_{12}H_{17}N_3O_8S \cdot H_2O$, $M_r = 365.36$, monoclinic, $P2_1$, $a = 15.105$ (2), $b = 7.915$ (1), $c = 6.451$ (1) Å, $\beta = 91.29$ (1)°, $V = 771.1$ Å³, $Z = 2$, $D_x = 1.574$ g cm⁻³, $\lambda(\text{Cu K}\alpha) = 1.5418$ Å, $\mu = 22.806$ cm⁻¹, $F(000) = 384$, $T = 298$ K, final $R = 0.062$ for 1665 unique reflections [$F_o^2 > 2\sigma(F_o^2)$]. The thiofuranosyl ring adopts an envelope conformation (E_3). The pyrimidyl moiety of the title compound is in a +*anti* orientation ($\chi = -133.5^\circ$), in contrast to the methyl ester of the tetraacetylsulfoxide derivative which adopts a +*syn* orientation ($\chi = 67.7^\circ$).

Experimental. Colorless prisms of title compound were grown from an aqueous ethanol solution [$H_2O/$

$C_2H_5OH = 1:1$ (v/v)] at 277 K. Crystal size 0.38 × 0.20 × 0.18 mm, Enraf–Nonius CAD-4 diffractometer, Cu K α radiation, graphite monochromator, θ – 2θ

* To whom correspondence should be addressed.

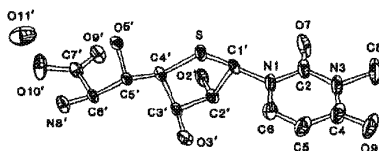


Fig. 1. Perspective view of the molecule with the numbering scheme. To show the absolute configuration correctly, the figure was drawn in the left-handed coordinate system.

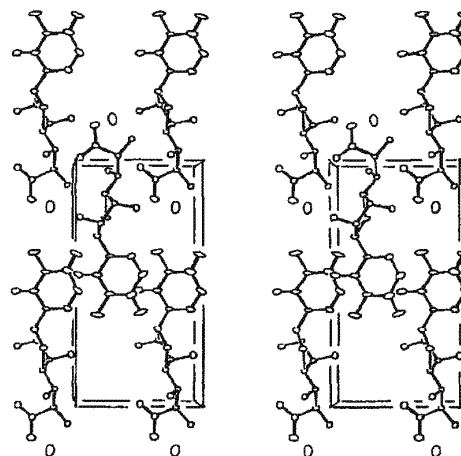


Fig. 2. Stereoscopic view of the crystal packing. The projection is down [001] and the b axis is horizontal.

0108-2701/89/071112-02\$03.00

© 1989 International Union of Crystallography

Preclinical report

Cinnamamide, an antitumor agent with low cytotoxicity acting on matrix metalloproteinase

Xiao-feng Jiang¹ and Yong-su Zhen¹

¹Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China.

The antitumor activity of cinnamamide (CNM), an agent acting on matrix metalloproteinase (MMP), was investigated in the present study. CNM displayed low cytotoxicity. By the MTT assay the IC₅₀ (50% inhibitory concentration) values of CNM on cell proliferation ranged from 1.29 to 1.94 mM in human oral epidermoid carcinoma KB cells, human hepatoma BEL-7402 cells and human fibrosarcoma HT-1080 cells. Moreover, the IC₅₀ for human fetal lung 2BS cells reached 4.33 mM. The administration of CNM in the range of 50–150 mg/kg (i.p. or p.o.) showed moderate antitumor effects in mice. When administered i.p. or p.o., CNM (150 mg/kg) inhibited the growth of transplanted hepatoma 22 by 48.8 or 40.5%, respectively. At the dose of 100 mg/kg, CNM inhibited the growth of colon 26 carcinoma by 39.0% and that of Lewis lung carcinoma by 53.9%. In the Lewis lung carcinoma model, CNM at the dose of 100 mg/kg (i.p.) also reduced the lung metastasis by 59.1%. Gelatine zymography revealed that CNM was able to decrease the level of MMP-2 in conditioned medium of HT-1080 tumor cells in a concentration-dependent manner. These results indicate that CNM is an antitumor agent with low cytotoxicity acting on MMP and may serve as a lead compound in the development of antitumor drugs. [© 2000 Lippincott Williams & Wilkins.]

Key words: Antitumor agent, cinnamamide, matrix metalloproteinase inhibitor.

Introduction

Matrix metalloproteinases (MMP) represent a family of at least 15 secreted and membrane-bound zinc

endopeptidases.^{1–3} The enzymes can degrade all of the components of the extracellular matrix and the basement membrane. This activity is necessary for local tissue remodeling during tumor growth, tumor-induced angiogenesis, tumor cell intravasation and tissue invasion during metastatic spread. Numerous studies have shown that there is a close association between expression of those endopeptidases such as the 72 kDa type collagenase (MMP-2), and the proliferative, invasive behavior and metastatic potential.^{4–7} Animal experiments with MMP inhibitors, such as Batimasta (BB-94) and Marimastat (BB-2516), have demonstrated their antitumor efficacy.^{8–11} Due to the unique mode of action, MMP inhibitors may provide a new modality in cancer therapy, particularly useful in preventing post-operative metastatic recurrence.

Natural products have been a good source of antitumor agents. In our laboratory, the nucleoside transport assay was established to direct the discovery of novel antitumor agents of natural origin.¹² Under the direction of the nucleoside transport assay, 6011W-A was isolated from the broth of an Actinomycete strain 6011W collected in Yunnan Province, China. Based on its physicochemical properties and spectral data, 6011W-A was identified to be cinnamamide (CNM; Figure 1). In this paper we report the antitumor activity of CNM and the inhibition of MMP.

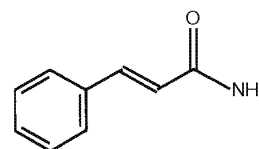


Figure 1. Chemical structure of cinnamamide (CNM).

This work was supported by the National Natural Sciences Foundation of China (grant no. 39670823).

Correspondence to Y-s Zhen, Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China.
Tel: (+86) 10 63010985; Fax: (+86) 10 63017302;
E-mail: zhenys@public.bta.net.cn

Materials and methods

Chemicals

CNM was purchased from Beijing Chemical Factory (Beijing, China) and its purity was over 98% as examined by high-performance liquid chromatography.

Cells and cell culture

Human oral epidermoid carcinoma KB cells, human hepatoma BEL-7402 cells, human fibrosarcoma HT-1080 cells and human fetal lung 2BS cells were cultured separately in RPMI 1640 medium supplemented with 10% newborn calf serum, penicillin (100 U/ml) and streptomycin (100 µg/ml) at 37°C in an incubator containing 5% CO₂.

MTT assay

The growth rate of cultured cells was determined by the MTT assay. Briefly, cells in the mid-log phase were harvested and seeded in 96-well plates (Costar, Cambridge, MA). After 24 h the drug was added and cells were incubated again for 72 h in the presence or absence of the drug. Then the cell population was determined using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT), according to the method described by Carmichael *et al.*¹³

Animals

For *in vivo* experiments, BALB/c mice, Kunming (KM) mice and C57BL/6 mice, weighing 18–22 g, were supplied by the Experimental Animal Institute of the Chinese Academy of Medical Sciences (Beijing, China), and kept in a room with controlled temperature and humidity.

In vivo antitumor effects

Antitumor effects *in vivo* (inhibition of primary tumor growth and metastasis) were assessed using colon carcinoma 26 (C26), hepatoma 22 (H22) and Lewis lung carcinoma (LLC) models, which were described previously.^{14,15}

In the C26 model, BALB/c mice, eight per group, were s.c. implanted with a tumor fragment approximately 2 mm in diameter. CNM was administrated daily, i.p., beginning 24 h after tumor implantation. Mice were killed 1 day after the last injection, and the tumors were dissected and weighed. In the H22 model, groups of 10 KM mice were s.c. implanted with 1×10^6 cells suspended in saline solution. Drug was administrated daily, i.p. or p.o., beginning 24 or

96 h after tumor implantation. The latter treatment schedule was applied to assess if the inhibition of primary tumor is depended on angiogenesis. Mice were killed 1 day after the last injection, and the tumors were dissected and weighed.

In the LLC model, groups of eight C57BL/6 male mice were s.c. implanted with 0.2 ml suspension of viable LLC tumor tissue and serum-free RPMI 1640 medium in a ratio of 1:4 (w/v). Drug was given i.p., daily or on alternate days, beginning 24 h after tumor implantation and continuing throughout the course of the experiment. Tumor sizes were measured with calipers and tumor volumes were calculated by the formula $a \times b^2/2$, where a is the long axis and b is the short axis perpendicular to a . Mice were killed on day 21. The metastasized nodules on the lung surface were scored using a dissecting microscope after fixation in Bouin's solution.

Zymograph

Identification of MMP secreted by human fibrosarcoma HT-1080 cells was performed by electrophoresis based on the method described by Ata *et al.*¹⁶ HT-1080 cells were seeded in 96-well plates and cultured for 24 h in RPMI 1640 medium containing CNM. The cells were extensively washed with 0.2 M PBS and then further cultured in serum-free RPMI 1640 medium for 24 h. The serum-free culture supernatants were withdrawn and centrifuged at 10 000 r.p.m. and the aliquots of the supernatant were mixed with SDS sample buffer without β-mercaptoethanols. Electrophoresis was carried out at 4°C in 7.5% polyacrylamide gels containing 0.1% gelatine. After being rinsed twice with 2.5% Triton X-100, the gels were incubated for 48 h in 50 mM Tris-HCl (pH 7.4), containing 0.2 M NaCl, 10 mM CaCl₂ and 1 µM ZnCl₂. Gels were stained overnight in 0.2% (v/v) Coomassie brilliant blue R250 and then destained with 30% methanol/10% acetic acid. The active enzyme bands that appeared as colorless bands on a blue background were quantitated by scanning of absorbance at 560 nm.

Statistical analysis

Significant difference between two values was determined with Student's *t*-test.

Results

Effect of CNM on the growth of cultured tumor cells

In the MTT assay, the IC₅₀ values of CNM for cultured human tumor cell lines including epidermoid carcino-

ma KB cells, hepatoma BEL-7402 cells and fibrosarcoma HT-1080 cells were between 1.29 and 1.94 mM, and that for human fetal lung 2BS cells was 4.33 mM (Table 1). These results indicate that CNM shows very low cytotoxicity to cultured cancer cells and even much lower cytotoxicity to fetal lung 2BS cells.

In vivo antitumor effects of CNM

In mice experiments, CNM inhibited the growth of colon carcinoma 26 (Table 2) and hepatoma 22 (Table

Table 1. Inhibitory effect of CNM on the growth of cultured human cell lines^a

Cell line	IC ₅₀ (mM, mean ± SD)
Human oral epidermoid carcinoma cell KB	1.62 ± 0.21
Human hepatoma cell BEL-7402	1.94 ± 0.33
Human fibrosarcoma cell HT-1080	1.29 ± 0.17
Human normal fetal lung cell 2BS	4.33 ± 1.34

^aCells were cultured with CNM for 3 days.

3). While the treatment started 96 h after tumor transplantation, CNM still displayed inhibition of tumor growth in the hepatoma 22 model (Table 4). It is suggested that CNM might exert its inhibitory effect at the step of tumor angiogenesis. In mice bearing Lewis lung carcinoma, CNM suppressed the growth of primary tumors as compared with the control (Figure 2). Furthermore, a decrease in the incidence of metastasis and in the number of lung metastases was also observed (Table 5). These results indicate that CNM could inhibit not only the growth of primary tumors but also metastasis.

Effect of CNM on the level of MMP-2

The above results demonstrate that CNM shows activity to inhibit tumor growth as well as tumor metastasis. The effect of CNM on the level of MMP was examined in zymography to study the mechanism of the antitumor actions of CNM. When the conditioned medium of HT-1080 cells was analyzed by gelatinase zymography, a proteolytic enzyme of apparent weight

Table 2. Inhibitory effect of CNM on the growth of colon carcinoma 26 in mice^a

	No. of mice (initial/end)	Body weight change (g)	Tumor weight (g, mean ± SD)	Inhibition (%)
Control	8/8	+2.64	2.41 ± 0.40	
CNM, 40 mg/kg	8/8	+0.94	1.67 ± 0.53	30.7 ^b
CNM, 100 mg/kg	8/8	+0.46	1.47 ± 0.26	39.0 ^b

^aColon carcinoma 26 was implanted s.c. on day 0. CNM was given 24 h after transplantation, i.p., daily for 10 days.

^b*p* < 0.01 versus control.

Table 3. Inhibitory effect of CNM on hepatoma 22 in mice^a

	No. of mice (initial/end)	Body weight change (g)	Tumor weight (g, mean ± SD)	Inhibition (%)
Control	10/10	+10.85	3.01 ± 1.01	
CNM, 75 mg/kg, i.p.	10/10	+8.08	1.76 ± 0.67	41.5 ^b
CNM, 75 mg/kg, p.o.	10/10	+8.19	2.29 ± 0.97	23.9 ^b
CNM, 150 mg/kg, i.p.	10/10	+3.38	1.54 ± 0.38	48.8 ^b
CNM, 150 mg/kg, p.o.	10/10	+6.69	1.79 ± 0.58	40.5 ^b

^aHepatoma 22 was implanted s.c. on day 0. CNM was given 24 h after transplantation, i.p. or p.o., daily for 10 days.

^b*p* < 0.01 versus control.

Table 4. Inhibitory effect of CNM on established hepatoma 22 in mice^a

	No. of mice (initial/end)	Body weight change (g)	Tumor weight (g, mean ± SD)	Inhibition (%)
Control	10/10	+14.31	2.92 ± 1.21	
CNM, 75 mg/kg	10/10	+8.66	1.63 ± 0.56	42.2 ^b
CNM, 150 mg/kg	10/10	+7.11	1.47 ± 1.26	50.3 ^b

^aHepatoma 22 was implanted s.c. on day 0. CNM was given 96 h after transplantation, i.p., daily for 7 days.

^b*p* < 0.01 versus control.

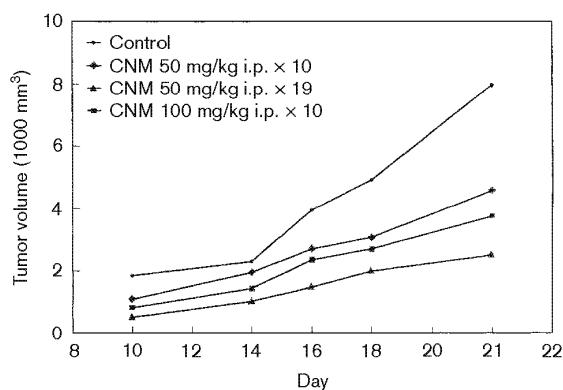


Figure 2. Effect of CNM on the growth of Lewis lung carcinoma in mice. Lewis lung carcinoma was implanted s.c. on day 0. CNM was given 24 h after transplantation, i.p., daily or on alternate days. There were eight mice in each group and no animal died during the experiment.

Table 5. Effect of CNM on the pulmonary metastases of Lewis lung carcinoma in mice^a

	No. of mice (initial/end)	Incidence of metastases	No. of metastases (mean $\pm$ SD)	Inhibition (%)
Control	8/8	8/8	11.0 $\pm$ 5.7	
CNM, 50 mg/kg, i.p. $\times$ 10	8/8	7/8	10.3 $\pm$ 5.7	
CNM, 50 mg/kg, i.p. $\times$ 19	8/8	5/8	4.8 $\pm$ 1.9	56.8 ^b
CNM, 100 mg/kg, i.p. $\times$ 10	8/8	5/8	4.5 $\pm$ 3.6	59.1 ^b

^aLewis lung carcinoma was implanted s.c. on day 0. CNM was given 24 h after transplantation, i.p., daily or on alternate days.

^b $p < 0.01$ versus control.

72 kDa (MMP-2) was detected as a clear band (Figure 3). Densitometric analysis revealed that degradation of gelatine substance by MMP-2 was inhibited by CNM in a concentration-dependent manner. It demonstrates that CNM reduced the level of MMP-2 in tumor cells.

Discussion

It has been reported that some cinnamoyl analogs may show antitumor activity *in vitro*.¹⁷ Pretreatment of tumor cells *in vitro* with U-77,863 (*O*-methyl cinnamamide) could inhibit their ability of invasion.¹⁸ To our knowledge, no report on the *in vivo* antitumor effect of CNM has yet been published. As shown in this report, CNM exhibited an inhibitory effect not only on the growth of solid primary tumor but also tumor metastasis in mice. Cell culture experiment results show that IC₅₀ values of CNM for cultured cancer cells ranged between 1.29 and 1.94 mM, a level approximately several thousand times higher than that of widely used anticancer drugs such as methotrexate, doxorubicin and vincristine. Apparently, CNM is an

active compound with low cytotoxicity. The anti-tumor effect of CNM *in vivo* does not seem to be related to a direct cytotoxic effect on tumor cells. Treatment of established tumor by CNM at a late dosing schedule still exerted inhibition on the growth of primary tumor. This suggests that the effect of CNM may be related to the inhibition of angiogenesis in tumor tissue.¹⁹ The antitumor action of CNM is similar to that obtained in other studies with synthetic MMP inhibitors. It is speculated that CNM exerts its antitumor effects, at least in part, on the level of MMP-2 of tumor cells. CNM may inhibit the breakdown of the extracellular matrix and the basement membrane by reducing the level of MMP, and thus the aggressive behavior of tumor cells is retarded. Further study on the mechanism of antitumor activity of CNM is underway.

The antitumor effect of CNM is moderate as compared with that of the antitumor drugs used in chemotherapy. However, the results described here are interesting. Neither weight loss nor any other obvious sign of toxicity was observed in the *in vivo* experiments. Moreover, CNM has a relatively unique

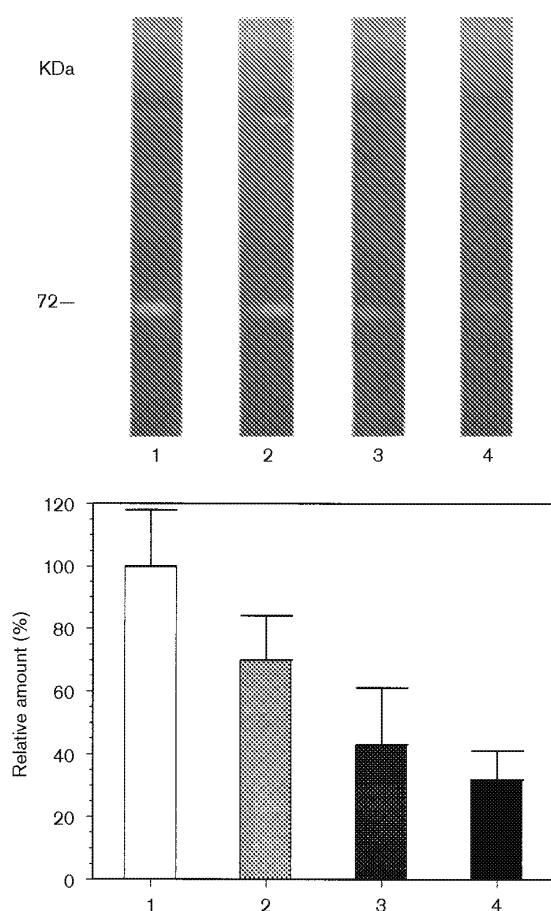


Figure 3. Effect of CNM on the level of MMP-2 in HT-1080 cells. HT-1080 cells were cultured for 24 h in serum-free RPMI 1640 medium with or without CNM: medium (lane 1); CNM, 200 μ M (lane 2); CNM, 800 μ M (lane 3) and CNM, 2 mM (lane 4). The conditioned media were subjected to electrophoresis in a gelatine-embedded SDS-polyacrylamide gel. After electrophoresis, strips of the gel were incubated and then stained with Coomassie brilliant blue. The locations of gelatinolytic enzymes were detected as clear bands (upper panel) and the gelatinolytic levels were densitometrically quantified (lower panel).

structure compared with that of other MMP inhibitors, which have a collagen-mimicking hydroxamate structure.³ CNM has a simple structure containing only one phenyl ring and an acrylamido side chain. It is feasible to modify the structure of CNM to design more effective compounds. Those features of CNM suggest that it might provide a lead compound for developing a novel class of antitumor and antimetastatic drugs.

References

1. Stetler-Stevenson WG, Liotta LA, Kleiner DE Jr. Extracellular matrix: role of matrix metalloproteinase in tumor invasion and metastasis. *FASEB J* 1993; 7: 1434-41.
2. Liotta LA, Steeg PS, Stetler-Stevenson WG. Cancer metastasis and angiogenesis: an imbalance of positive and negative regulation. *Cell* 1991; 64: 327-36.
3. Wojtowicz-Praga SM, Dickson RB, Hawkins MJ. Matrix metalloproteinase inhibitors. *Invest New Drugs* 1997; 15: 61-75.
4. Bernhard EJ, Muschel RJ, Hughes EN. Mr 92000 gelatinase release correlates with the metastatic phenotype in transformed rat embryo cells. *Cancer Res* 1990; 50: 3872-7.
5. Zucker S, Lysik RM, Zarrabi MH, Moll U. Mr 92,000 type IV collagenase is increased in plasma of patients with colon and breast cancer. *Cancer Res* 1993; 53: 140-6.
6. Levy TD, Cioce V, Sobel ME, et al. Increased expression of the Mr 72,000 type IV collagenase in human colonic adenocarcinoma. *Cancer Res* 1991; 51: 439-44.
7. Sawaya R, Yamamoto M, Gokaslan ZL, et al. Expression and localization of 72-kDa type IV collagenase (MMP-2) in human malignant gliomas *in vitro*. *Clin Exp Metastasis* 1996; 14: 35-42.
8. Taraboletti G, Garofalo A, Belotti D, et al. Inhibition of angiogenesis and murine hemangioma growth by batimastat, a synthetic inhibitor of matrix metalloproteinase. *J Natl Cancer Inst* 1995; 87: 293-8.
9. Davies B, Brown PD, East N, Crimmin MJ, Balkwill FR. A synthetic matrix metalloproteinase inhibitor decreases tumor burden and prolongs survival of mice bearing human ovarian carcinoma xenografts. *Cancer Res* 1993; 53: 2087-91.
10. Waston SA, Morris TM, Robinson G, Crimmin MJ, Brown PD, Hardcastle JD. Inhibition of organ invasion by matrix metalloproteinase inhibitor batimastat (BB-94) in two human colon carcinoma metastasis models. *Cancer Res* 1995; 55: 3629-33.
11. Drummond AH, Beckett P, Bone EA, et al. BB-2516: an orally bioavailable matrix metalloproteinase inhibitor with efficacy in animal cancer models. *Proc Am Ass Cancer Res* 1995; 36: 100.
12. Zhen YS, Su J, Xue YC, Qi CQ, Hu JL. Novel nucleoside transport inhibitors of natural origin. *Adv Exp Med Biol* 1994; 370: 779-82.
13. Carmichael J, DeGraff WG, Gazdar AF, Minna JD, Mitchell JB. Evaluation of a tetrazolium-based semiautomated colorimetric assay: assessment of chemosensitivity testing. *Cancer Res* 1987; 47: 936-42.
14. Cao SS, Zhen Y-s. Potentiation of antimetabolite antitumor activity *in vivo* by dipyridamole and amphotericin B. *Cancer Chemother Pharmacol* 1989; 24: 181-6.
15. Santos O, McDermott CD, Daniels RG, Appelt K. Rodent pharmacokinetic and antitumor efficacy studies with a series of synthetic inhibitors of matrix metalloproteinase. *Clin Exp Metastasis* 1997; 15: 499-508.
16. Ata N, Oku T, Hattori M, Fujii H, Nakajima M, Saiki I. Inhibition by galloylglucose (GG6-10) of tumor invasion through extracellular matrix and gelatinase-mediated degradation of type IV collagenase by metastasis tumor cells. *Oncol Res* 1996; 8: 503-11.

X-f Jiang and Y-s Zhen

17. Liu L, Hudgins WR, Shack S, Yin MQ, Samid D. Cinnamic acid: a natural product with potential use in cancer intervention. *Int J Cancer* 1995; **62**: 345-50.
18. Welch DR, Harper DE, Yohem KH. U-77863, a novel cinnamamide isolated from *Streptomyces griseolentus* that inhibits cancer invasion and metastasis. *Clin Exp Metastasis* 1993; **11**: 201-12.
19. Folkman J. What is the evidence that tumors are angiogenesis dependent? *J Natl Cancer Inst* 1990; **82**: 4-6.

(Received 13 July 1999; revised form accepted October 1999)

The Determination of the Crystal Structure of Anhydrous Theophylline by X-ray Powder Diffraction with a Systematic Search Algorithm, Lattice Energy Calculations, and ^{13}C and ^{15}N Solid-State NMR: A Question of Polymorphism in a Given Unit Cell

Elaine D. L. Smith[†]

Centre for Molecular and Interface Engineering, Department of Mechanical and Chemical Engineering, Heriot-Watt University, Riccarton, Edinburgh EH14 4AS, U.K.

Robert B. Hammond,* Matthew J. Jones, and Kevin J. Roberts

Centre for Particle and Colloid Engineering, Department of Chemical Engineering, University of Leeds, Leeds LS2 9JT, U.K.

John B. O. Mitchell[‡] and Sarah L. Price

Centre for Theoretical and Computational Chemistry, Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, U.K.

Robin K. Harris and David C. Apperley

Department of Chemistry, Durham University, South Road, Durham DH1 3LE, U.K.

Julian C. Cherryman and Robert Docherty[§]

Avecia Research Centre, Hexagon House, Blackley, Manchester, M9 8ZS, U.K.

Received: June 7, 2000; In Final Form: December 21, 2000

When determining crystal structures of organic molecular materials from high-resolution powder diffraction data, the key step is the generation of reliable trial structures for final refinement. The subject of the study reported here is the pharmaceutical material anhydrous theophylline (3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione), which contains both oxygen and nitrogen as possible hydrogen bond acceptor atoms. A systematic search of direct space was employed to assess *every* possible packing arrangement of the asymmetric unit within the experimentally determined unit cell. Trial structures were ranked in terms of calculated lattice energy and weighted residuals from a comparison of calculated and experimental X-ray diffraction profiles. The systematic search found two packing arrangements with different intermolecular hydrogen-bonding motifs within the same unit cell. In one, denoted $\text{NH}\cdots\text{N}$, the amino hydrogen is hydrogen bonded to the aldimine nitrogen, and in the other, denoted $\text{NH}\cdots\text{O}$, to the carbonyl oxygen neighboring the imidazole ring. These trial structures were “virtually indistinguishable” in terms of calculated lattice energy or X-ray profile fit. Solid-state NMR spectra of a commercial sample not only confirmed immediately that there was only one molecule in the crystallographic asymmetric unit but also produced distinctive ^{13}C and ^{15}N chemical shifts. The experimentally determined ^{15}N chemical shifts showed considerably better agreement with values from *ab initio* calculations for the trial crystal structure with $\text{N}-\text{H}\cdots\text{N}$ hydrogen bonding. In these calculations, representative chains of three hydrogen-bonded molecules were employed as models for the $\text{NH}\cdots\text{N}$ and $\text{NH}\cdots\text{O}$ trial crystal structures. In addition, a more sophisticated analysis of the lattice energy hypersurfaces, using a distributed multipole based intermolecular potential, indicated that the $\text{N}-\text{H}\cdots\text{N}$ trial structure is the more stable. It was noted that the $\text{NH}\cdots\text{N}$ packing motif identified by our studies is observed in a single-crystal determination for theophylline reported independently while our investigations were ongoing. Our study shows how the potential for polymorphism in a “given unit cell” may be assessed successfully by combining several complementary experimental and theoretical approaches.

1. Introduction

The development of a more complete understanding of polymorphism, the manifestation of two or more distinct, crystalline forms of a material, is, perhaps, one of the most

important touchstones for the solid-state chemist or process engineer at the present time. However, advances in our understanding of polymorphism can occur only if structural data are available to allow us to make a comparison of all the polymorphs of a given material. Frequently this is not the case, particularly when single-crystal methods of structure determination cannot be applied to one or more polymorphs due to inadequacies in the size or quality of the available crystals. When the present study was initiated, however, it was not as an investigation of the polymorphism of anhydrous theophylline *per se* but rather to address the fact that, at that time, there was

* To whom all correspondence should be addressed.

[†] Present address: DuPont Central Research & Development, Experimental Station, Wilmington, DE 19880-0304

[‡] Present address: Unilever Centre for Molecular Informatics, Department of Chemistry, Lensfield Road, Cambridge CB2 1EW, U.K.

[§] Present address: Pfizer Central Research, Sandwich, Kent, CT13 9NJ, U.K.

no reported crystal structure for this material. The realization that there was a potential for two polymorphs of anhydrous theophylline to exist within the context of a fixed unit cell emerged directly from that initial study. This prompted further investigations, described in this paper, in an effort to resolve the question through the application of several complementary experimental and theoretical techniques.

When single-crystal methods cannot be applied for structure determination, two main alternative approaches are available. First, *ab initio* structure prediction, which has been developed by Gavezzotti,¹ Holden,² Perlstein,³ and Karfunkel.⁴ A summary of their elegant work has been documented by Docherty and Jones.⁵ Second, the approach adopted here, structure solution using powder X-ray diffraction data. Compared to single-crystal data, there is considerable loss of information due to peak overlap in the diffraction pattern. The general methodology is to index the diffraction pattern, define the molecular structure using molecular modeling techniques, generate trial structures, and finally carry out Rietveld refinement.⁶ Good trial structures are necessary for successful determinations, and several methods for generating these initial models have been reported including the Metropolis Monte Carlo method,⁷ genetic algorithms,^{8–10} and a systematic search strategy.¹¹ The latter method has been applied successfully to various materials including 6,13-dichlorotriphenyldiazine,¹² the X-form of metal-free phthalocyanine,¹³ the metastable phase of benzophenone,¹⁴ and in a study of polymorphism in perylene and phenazine.¹⁵

Anhydrous theophylline (3,7-dihydro-1,3-dimethyl-1*H*-purine-2,6-dione) is a pharmaceutical material that is used as a vasodilator and a muscle relaxant. Our interest in this material stemmed from a search of the Cambridge Crystallographic Database (CCDC Database)¹⁶ to identify organic molecular materials for which cell parameters and space group, but no atomic positional coordinates had been reported. One such entry was for anhydrous theophylline¹⁷ (ref-code BAPLOT), and this molecule also appeared interesting in its potential to form intermolecular hydrogen bonds.

Initial results suggested that two distinct crystal structures with different hydrogen-bonding networks, in the same given unit cell, were consistent with the experimental powder diffraction data and it was not possible, at that stage, to identify which was the correct one or, indeed, whether both structures coexisted. While further investigations were underway, a full single-crystal structure determination for anhydrous theophylline was reported¹⁸ (ref-code BAPLOT01). The structural model from the single crystal determination was found to be similar to one of the two trial structures found in this work. Nevertheless, two important questions still remained to be answered: first, was it possible that there was a second polymorph with essentially the same cell parameters and space group, and, second, could other experimental and theoretical methods be used to allow discrimination between the two putative structures.

In the literature there is an issue of the existence of a second polymorph of anhydrous theophylline^{19–22} with a very similar X-ray diffraction pattern. This has led us to question whether the second trial structure found by the systematic search procedure could be the second polymorph. It is common practice to use powder X-ray diffraction profiles to characterize and authenticate different polymorphs of a given material. Because the unit cell dimensions and/or space group are generally different, there is a characteristic set of peak positions and peak intensities for every polymorph. However, if the second trial structure were indeed representative of a second polymorph, having essentially the same powder X-ray diffraction profile,

this would have serious implications for cases where powder diffraction data are used to verify a particular polymorph but are unsupported by other experimental data.

To determine whether the two trial crystal structures were indeed of similar stability, lattice energy minimization calculations were carried out using a theoretically rigorous model for the intermolecular forces. The electrostatic forces were calculated from sets of atomic multipoles instead of atomic monopole charges alone. This approach has been shown to give a better description of the directionality of hydrogen bonding interactions.²³ It has been demonstrated that the use of distributed multipole analysis, for calculating the electrostatic interactions, together with an empirical atom–atom repulsion–dispersion model yields energy minimized crystal structures that are close to those found experimentally for a wide range of polar organic materials.²⁴

Solid-state NMR spectroscopy has been applied successfully to distinguish subtle conformational and packing differences by comparison of experimental and calculated isotropic chemical shifts.^{25–29} Moreover, the sensitivity of the chemical shifts can be utilized to determine the nature of intermolecular interactions by fitting to *ab initio* MO calculations. For instance, this method has been applied to quantify the effect of the hydrogen bond on the ¹⁵N chemical shifts of substituted imidazoles.³⁰ The principal values (σ_{11} , σ_{22} , σ_{33}) of the shielding tensor may be provided by MO calculations. The average of these values is the isotropic chemical shift, $\delta \equiv (\sigma_{\text{ref}} - \sigma_{\text{sample}})$ where σ_{ref} is the isotropic shielding tensor for a reference compound and σ_{sample} is that of the sample. The individual principal components can be measured (e.g., by spinning sideband analysis) and give additional structural and electronic information. In this study, ¹³C and ¹⁵N solid-state NMR techniques were employed to establish the nature of the hydrogen bonding present in anhydrous theophylline.

2. Experimental Section

2.1. X-ray Diffraction Experiments and Molecular Structure Generation. Anhydrous theophylline was obtained from SIGMA and, apart from grinding, was used as supplied. Powder X-ray diffraction data (2θ , 5–70°) were collected at a wavelength of 1.301 Å at Station 2.3 of the Synchrotron Radiation Source of the CCLRC at Daresbury, U.K. and using a laboratory-based instrument, Bruker AXS D5000 diffractometer with primary beam monochromator, Cu K α_1 radiation, and position sensitive detector, (2θ , 5–60°). Indexing was performed using the program, ITO.³¹ The space group was determined using the program DRAGON³² in combination with the International Tables of Crystallography.³³

Molecular geometry optimizations were carried out for the three tautomeric forms of theophylline illustrated in Figure 1 (also indicating the numbering scheme used throughout this study),³⁴ using the semiempirical, MOPAC³⁵/AM1³⁶ method and *ab initio*, BPW91/TZVP (DFT) calculations. Only the most stable tautomer was progressed to the trial structure generation procedure.

Systematic searches were carried out with respect to powder X-ray profile fit and calculated lattice energy, employing both Dreiding³⁷ and Nemethy et al.³⁸ force fields. The AM1 calculated point charges were employed to assess the electrostatic contribution to lattice energy. At the start of the search procedure, the model molecular structure was centered on the origin of the unit cell in a random orientation. The step ranges and step sizes employed in the systematic search are given in Table 1. Because the space group had been determined as *Pna*2₁,

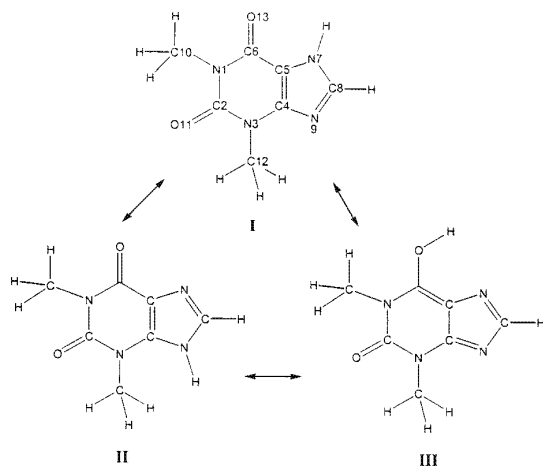


Figure 1. Theoretically possible tautomeric forms of the theophylline molecule. Numbering scheme after ref 34.

TABLE 1: Systematic Search Criteria for Anhydrous Theophylline

rotation/ $^{\circ}$		translation		total configurations tried
step size	range	step size/cell length	range	
5	0–175	0.025	0– $1/2a$	18,662,400
		0.025	0– $1/2b$	

no translation of the asymmetric unit along the *c*-axis was necessary in the search procedure. The minimum approach distance used throughout was 2.1 and 1.7 Å for two nonbonded and two hydrogen-bonded atoms, respectively.

2.2. Structure Refinement. Refinement of the best trial structures resulting from the systematic searches was undertaken using the Rietveld method,⁶ as implemented in the program GSAS.³⁹ A fixed background was introduced and a Le Bail fit⁴⁰ used to define a pseudo-Voigt function to model the profile peak shape prior to refinement of the atomic positional coordinates. The parameters included in the refinement model were the scale factor, two-theta zero point, lattice parameters, isotropic thermal parameters, and atomic positions. Soft constraints were defined in the refinement, excluding hydrogen atoms, using standard bond lengths and angles (angles were indirectly constrained over 1,3 atomic distances) in an attempt to maintain a “chemically sensible” molecular geometry during the refinements. A comparison of full profile refinements against, respectively, synchrotron and laboratory diffraction data showed that laboratory data were sufficient for satisfactory refinements to be achieved. It is these refinements, therefore, that are reported in more detail below.

2.3. Lattice Energy Minimizations Using a Distributed Multipole Analysis-Based Intermolecular Potential. CAD-PAC⁴¹ ab initio calculations (6-31G** SCF) on an isolated theophylline molecule provided the self-consistent field (SCF) energy of the molecule and the distributed multipoles⁴² for DMAREL.⁴³ This program calculates accurate lattice energies (the repulsion–dispersion parameters being taken from the set FIT)²⁴ and relaxes the initial structure (including the cell parameters and space group), using a Newton–Raphson procedure, to find a nearby minimum in the 6-31G** 0.9DMA + FIT potential. It is common practice to use an empirical scaling factor of 0.9 on 6-31G** multipoles to compensate for the overestimation of the polarity of the charge distribution by SCF methods.²⁴

Using the scaled electrostatics and the FIT repulsion–dispersion potential, single point lattice energy calculations and DMAREL minimizations were carried out for the best trial structures found in the systematic search procedure. The molecular geometry, originally from an AM1 optimization, was modified so as to use normalized bond lengths to hydrogen throughout the DMAREL analyses (C–H 1.08 Å; N–H 1.01 Å). The same procedure was also applied to the published, single-crystal structure for comparison.

2.4. Carbon-13 and Nitrogen-15 Solid-State NMR Experiments and ab initio MO Calculations. Nitrogen-15 and carbon-13 spectra were measured using a Varian UnityPlus 300 spectrometer at 30.40 and 75.43 MHz, respectively, at ambient probe temperature. Spectra were obtained under magic-angle spinning conditions, with rates in the range 4–5 kHz. A Doty Scientific probe was used, with 7 mm o.d. zirconia rotors and kel-F end caps. Cross-polarization from protons was employed, together with high-power proton decoupling during signal acquisition. Chemical shifts for ¹⁵N and ¹³C were measured with respect to the reference standards ammonium nitrate (NH₄¹⁵NO₃) and tetramethylsilane (TMS), respectively. The experimentally determined isotropic chemical shielding of NH₄¹⁵NO₃ and TMS used herein were –116 ppm⁴⁴ and 188 ppm,⁴⁵ respectively.

All ab initio calculations were performed with DGauss, version 4.1 within UniChem,⁴⁶ with the BPW91/TZVP level of theory and the LORG⁴⁷ method to calculate the nuclear magnetic shielding tensors. Initially a calculation was performed using the ab initio optimized geometry of an isolated theophylline molecule to provide a point of reference. In addition, calculations were performed on two ab initio optimized trimers taken as models of the structural motifs characterizing the competing crystal structures. The DFT method allows for electron correlation, though for NMR chemical shifts it tends to predict NMR values that are deshielded in comparison to experimental results. This is particularly noticeable for ¹⁵N calculated shifts. Hence, the calculated values were rebased by 30 ppm before comparison with the experimental data.

3. Results

3.1. Structure Determination Using the Systematic Search Strategy. Indexing of the X-ray diffraction data yielded unit cell parameters similar to those previously determined by Naqvi and Bhattacharyya.¹⁷ The cell parameters from the single-crystal determination published after the commencement of this work are included in Table 2 for comparison. The cell parameters and cell volume determined in the present study are slightly smaller than those previously published, although the diffraction data were measured at ambient temperature. This work concurred with the previously reported space group, *Pna2*₁. The unit cell volume and space group were consistent with there being one molecule in the asymmetric unit.

Table 3 gives the enthalpy of formation (ΔH_f) of tautomers I, II, and III in vacuo, calculated after MOPAC/AM1 geometry optimization, and corresponding total energy values from ab initio calculations. Comparing the energy differences between tautomers (with respect to tautomer I), ab initio calculations indicate a greater energy separation between tautomers I and II. However, both methods indicate that tautomer I is the most stable by a considerable margin of energy. FTIR measurements (KBr disk) confirmed that there was no OH functionality present in the solid.

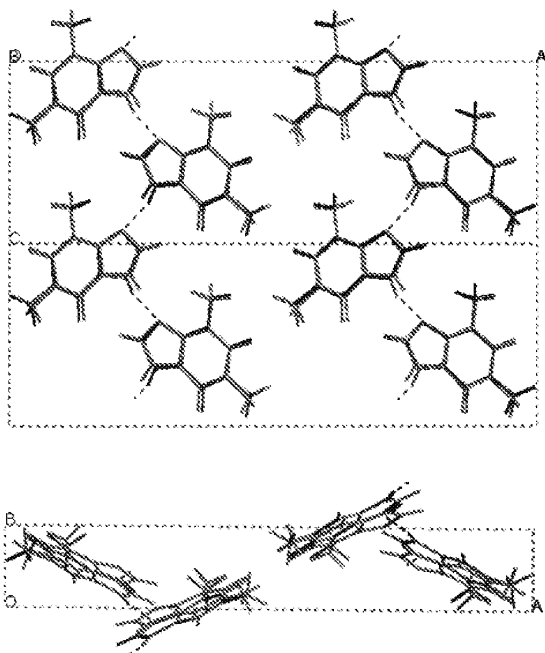
Systematic searches used both lattice energy and X-ray profile fit as criteria for ranking the trial structures. The results were intriguing: two distinct molecular arrangements, manifesting

TABLE 2: Comparison of Reported and Calculated Cell Parameters

structure (CSD ref-code)	<i>a</i> [Å]	<i>b</i> [Å]	<i>c</i> [Å]	space group	unit cell volume [Å ³]	molecules per unit cell (Z)	calculated density [g/cm ³]
BAPLOT ¹⁷	24.628	3.833	8.501	Pna2 ₁	802.49		
BAPLOT01 ¹⁸	24.612	3.8302	8.5010	Pna2 ₁	801.38	4	1.493
this study	24.580	3.828	8.487	Pna2 ₁	798.56	4	1.499

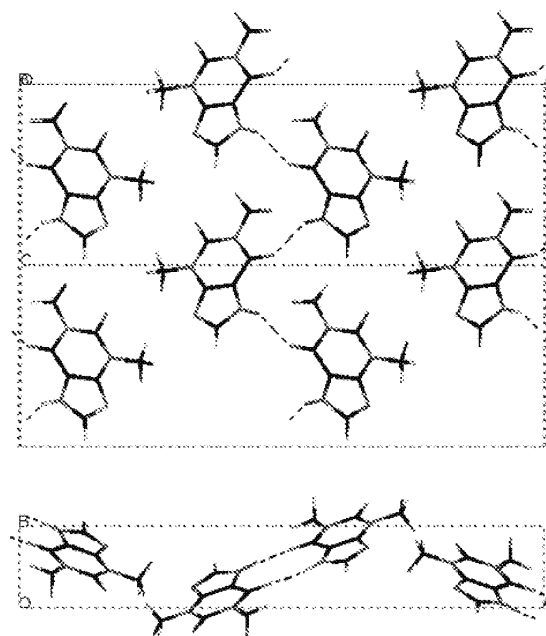
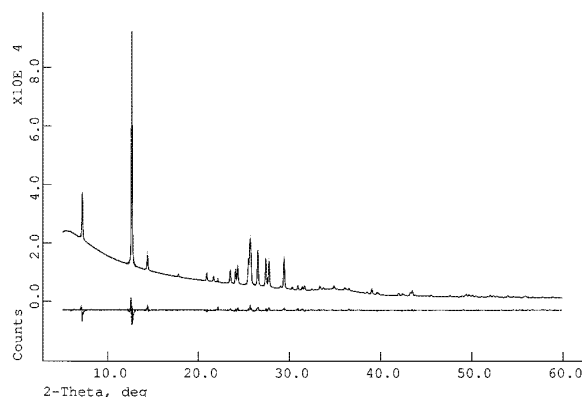
TABLE 3: Comparison of Calculated Enthalpies of Formation of Tautomers in Figure 1, Using MOPAC/AM1 and Ab Initio (DFT) Methods

calculation method	tautomer I	tautomer II	tautomer III
MOPAC (AM1)/kJ mol ⁻¹	18.60	34.52	96.88
difference to tautomer I/kJ mol ⁻¹	—	15.9	78.3
ab initio (DFT)/Hartree	-641.221	-641.207	-641.192
difference to tautomer I/kJ mol ⁻¹	—	37.4	75.5

**Figure 2.** Predicted packing arrangement involving N-H...N interactions found by lattice energy systematic search (green), overlaid with published single-crystal structure (red).

different hydrogen-bonding motifs, were found within the same, fixed unit cell. The first, Figure 2, is similar to the reported single-crystal structure,¹⁸ exhibiting N7-H7...N9 and bifurcated C8-H8...O13 hydrogen bonds, but the second, Figure 3, exhibits hydrogen bonding with the same N-H functionality and the carbonyl oxygen neighboring the imidazole ring (i.e., N7-H7...O13=C6). These trial structures have very similar calculated lattice energies irrespective of the force field used -82.25 and -82.21 kJ mol⁻¹, -97.62 and -98.08 kJ mol⁻¹ for Dreiding and Nemethy et al., respectively. The two best trial structures determined using X-ray profile fit as a ranking criterion manifested packing motifs that were almost identical to those found in the structures ranked first and second according to the lattice energy criterion.

An examination of the CCDC Database using the package ISOSTAR⁴⁸ yielded a similar number of occurrences for N-H...N and N-H...O=C hydrogen-bonding interactions. This suggested that N-H...N and N-H...O=C motifs are equally likely. In light of the available information, our working

**Figure 3.** Predicted packing arrangement involving N-H...O interactions found by lattice energy systematic search.**Figure 4.** Laboratory X-ray powder diffraction data, N-H...N simulated diffraction pattern, and final soft constraints GSAS refined difference plot.

hypothesis, at this stage, was that both of these trial structures represented plausible crystal structures.

3.2. Rietveld Refinement. Four trial crystal structures were progressed for Rietveld refinement. Two were representative of the N-H...N motif two of the N-H...O motif, i.e., the two highest ranked trial structures from the systematic searches in terms of lattice energy and powder X-ray profile fit, respectively. The profile difference plots resulting after refinement of the four structures appeared to be very similar. Two examples are illustrated in Figures 4 and 5 for the starting structures ranked highest on lattice energy (N-H...N and NH...O, respectively).

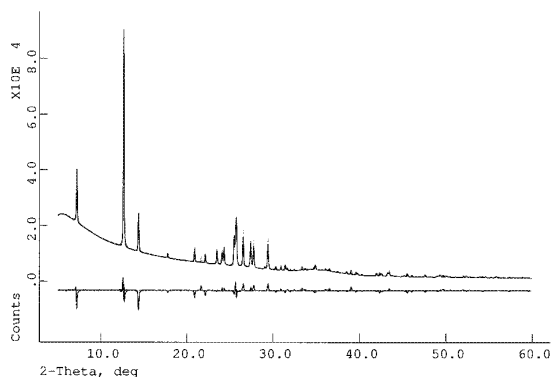


Figure 5. Laboratory X-ray powder diffraction data, N-H...O simulated diffraction pattern, and final soft constraints GSAS refined difference plot.

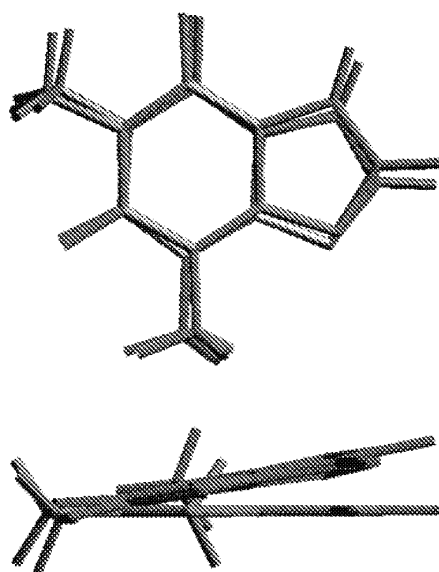


Figure 6. Overlay of the N-H...N lattice energy structure (green), GSAS refined (blue), and DMAREL minimized (red) structures.

However, as shown in Table 4, the N-H...N structures refine to lower R_{wp} values (3.37% and 3.38%) than do the N-H...O structures (7.80% and 8.04%). The inclusion of hydrogen atoms did not significantly improve the refinements. Although it is noted that the trial structures identified by lattice energy criteria refined to give slightly better R_{wp} factors than the XRD profile fit counterparts, the resulting structures are almost indistinguishable. The refined molecular structures are distorted out of plane (see Figures 6 and 7), but as can be seen, the imidazole ring in the N-H...N structure is better maintained. Selected geometric parameters for the NH...N refined structure are included in Table 5. The published crystal structure was also used as a starting point for refinement against the laboratory powder X-ray diffraction data. The resulting structural model ($R_{wp} = 3.35\%$) was found to be extremely similar to the one refined from the best N-H...N trial structure. Nevertheless, in our view, the results of the Rietveld refinements were not sufficiently convincing to justify disregarding the N-H...O motif as a plausible structural model purely on the basis of the powder diffraction data.

3.3. Lattice Energy Minimizations using a Distributed Multipole Analysis-Based Intermolecular Potential. Molec-

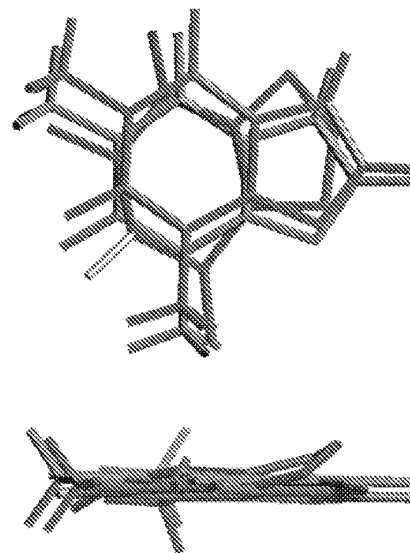


Figure 7. Overlay of the N-H...O lattice energy structure (green), GSAS refined (blue), and DMAREL minimized (red) structures.

TABLE 4: Summary of Results from GSAS Soft Constraints Refinement

refinement parameters	published structure	NH...N energy structure	NH...O energy structure	NH...N XRD structure	NH...O XRD structure
$R_{wp}\%$	3.35	3.37	7.80	3.38	8.04
χ^2	0.1608	0.1774	0.8808	0.1811	1.0870
U_{iso}	0.0353	0.0330	0.4377	0.0371	0.0400

ular structures for theophylline derived, respectively, using the MOPAC/AM1 method and from the single-crystal structure were used for ab initio single point SCF calculations using CADPAC. The calculated total energies are given in Table 6. The absolute energy values differ slightly from those derived using density functional theory (see Table 3).

Calculated lattice energies, evaluated using DMAREL, were found to be very similar for the two best trial structures elucidated by the systematic search on energy (-98.33 and -100.34 kJ mol $^{-1}$ for the N-H...N and N-H...O structures, respectively). When these structures were minimized with respect to lattice energy, however, there was a profound effect on the magnitude of the lattice energy difference evaluated at the minima (-119.84 kJ mol $^{-1}$ and -108.20 kJ mol $^{-1}$, respectively). The cell parameters and symmetry constraints, as well as the positions and orientations of the molecules, were allowed to relax in the minimization procedure. Despite the large change in the lattice energy difference between the crystal structures, the observed percentage changes in the cell lengths and angles were small. This indicates that the structural changes were within the margin usually allowed for the neglect of thermal effects and other approximations. The $Pna2_1$ symmetry was retained as judged by the program PLATON.⁴⁹ Thus, both structures found by the systematic search, using the simpler model potential, within the fixed unit cell were acceptably close, structurally, to unconstrained lattice energy minima obtained with a more accurate model potential.

Because the decrease in lattice energy of the N-H...N structure was large, it seemed probable that a bad contact was improved by minimization. Several significant intermolecular bond lengths and angles were measured in the unminimized and minimized structures in order to find evidence for this (see

TABLE 5: Selected Geometric Parameters of the Published Molecule, MOPAC/AM1 Optimized Molecule, and GSAS Soft Constraints Refined NH...N Molecule Found by Lattice Energy Criteria

molecule				molecule			
parameter	published	AM1	NH⋯N refined	parameter	published	AM1	NH⋯N refined
Bond Lengths/Å							
N1–C2	1.413(9)	1.420	1.437(4)	C4–N9	1.350(6)	1.405	1.401(4)
N1–C6	1.418(7)	1.411	1.426(4)	C5–C6	1.430(7)	1.451	1.450(4)
N1–C10	1.488(8)	1.444	1.450(4)	C5–N7	1.388(5)	1.395	1.425(5)
C2–N3	1.360(8)	1.417	1.408(4)	C6–O13	1.213(6)	1.244	1.255(4)
C2–O11	1.221(6)	1.251	1.254(4)	N7–C8	1.327(8)	1.390	1.385(4)
N3–C4	1.384(6)	1.386	1.412(4)	N7–H7	0.90(7)	0.987	-
N3–C12	1.469(8)	1.439	1.446(4)	C8–N9	1.316(7)	1.362	1.360(4)
C4–C5	1.349(8)	1.432	1.464(5)	C8–H8	1.02(6)	1.097	-
Bond Angles/°							
C2–N1–C6	126.6(4)	123.6	120.3(4)	C4–C5–N7	105.4(4)	106.3	105.1(4)
C2–N1–C10	117.1(5)	116.3	120.4(5)	C6–C5–N7	129.8(5)	130.7	133.6(5)
C6–N1–C10	116.3(5)	120.1	118.8(5)	N1–C6–C5	110.1(5)	113.8	117.6(4)
N1–C2–N3	117.4(4)	120.8	122.0(4)	N1–C6–O13	122.0(5)	121.7	117.8(5)
N1–C2–O11	120.2(6)	119.6	118.1(5)	C5–C6–O13	127.9(4)	124.5	124.5(5)
N3–C2–O11	122.4(6)	119.6	118.7(5)	C5–N7–C8	105.7(5)	106.3	106.5(4)
C2–N3–C4	119.7(5)	118.3	118.8(4)	C5–N7–H7	128(4)	125.1	-
C2–N3–C12	120.1(5)	120.9	120.8(5)	C8–N7–H7	126(4)	128.7	-
C4–N3–C12	120.2(5)	120.8	120.5(5)	N7–C8–N9	113.4(4)	113.3	112.8(4)
N3–C4–C5	-	120.5	120.2(4)	N7–C8–H8	-	122.7	-
N3–C4–N9	-	129.7	130.9(4)	N9–C8–H8	-	124.0	-
C5–C4–N9	-	109.8	108.1(4)	C4–N9–C8	-	104.4	106.1(4)
C4–C5–C6	-	123.0	120.3(4)				

TABLE 6: Summary of Results from SCF and DMAREL Calculations

	structure				
	published	NH...N energy	NH...O energy	NH...N XRD	NH...O XRD
Isolated Molecule					
SCF energy/Hartree	−637.318	−637.293	−637.293	−637.293	−637.293
SCF difference/kJ mol ^{−1}	0.00	64.64	64.72	64.64	64.72
Crystal Structure					
initial energy/kJ mol ^{−1}	−120.14	−98.33	−100.34	−101.17	−44.80
final energy/kJ mol ^{−1}	−122.18	−119.84	−108.20	−119.83	−84.49
initial cell volume/Å ³	801.38	798.56	798.56	798.56	798.56
final cell volume/Å ³	822.72	847.09	826.07	847.11	882.17
final a/Å	24.596	24.453	25.383	24.452	26.469
final b/Å	3.910	3.923	4.000	3.924	3.875
final c/Å	8.554	8.830	8.137	8.830	8.602
RMS % error in cell edges ^a	1.26	2.76	3.99	2.76	4.56

^a Relative to the experimental cell parameters determined in this study (Table 2).**TABLE 7: Comparison of Selected Intermolecular Bond Lengths and Angles for Published Structure and NH...N Structure before and after DMAREL Minimization**

parameter/Å, °	structure			
	unminimized published	minimized published	unminimized NH...N	minimized NH...N
N7...N9	2.827	2.780	3.049	2.771
H7...N9	1.818	1.775	2.124	1.763
N7–H7...N9	179	173	152	175

Table 7). In the N–H...N trial structure, the most striking change occurs in the length and orientation of the N–H...N hydrogen bond which was initially about 0.2 Å longer and 27° less linear than that found in the single-crystal structure. This alone could account for the large improvement in lattice energy. The extent of adjustment of the hydrogen bond in the alternative N–H...O structure was less (see Table 8). The N–H...N minimized structure also agrees very well with the structure refined through GSAS (see Figure 6). Thus, minimization with DMAREL was necessary to allow reliable comparisons of different structures.

The magnitude of the energy difference between the minimized structures (11.64 kJ mol^{−1}) allows us to make a confident

TABLE 8: Comparison of Selected Intermolecular Bond Lengths and Angles for N–H...O Structure before and after DMAREL Minimization

parameter/Å, °	structure	
	unminimized NH...O	minimized NH...O
N7...O13	3.007	2.995
H7...O13	2.130	2.091
N7–H7...O13	144	148

assignment that the N–H...N structure is the correct model. This is also in good agreement with the published crystal structure both in terms of the type of hydrogen bonding present and the calculated lattice energy (that of the published structure being −122.18 kJ mol^{−1} after minimization). In addition, the lattice energy calculated for the N–H...N structure was reassuringly similar in magnitude to the experimental sublimation energy⁵⁰ of 126 kJ mol^{−1}.

Is the N–H...O structure a plausible polymorph in the given unit cell? The lattice energy difference of 11.64 kJ mol^{−1} corresponds to around 10% of the lattice energy, with little difference found in the intramolecular energy (Table 6). This value is very much toward the top end of the differences

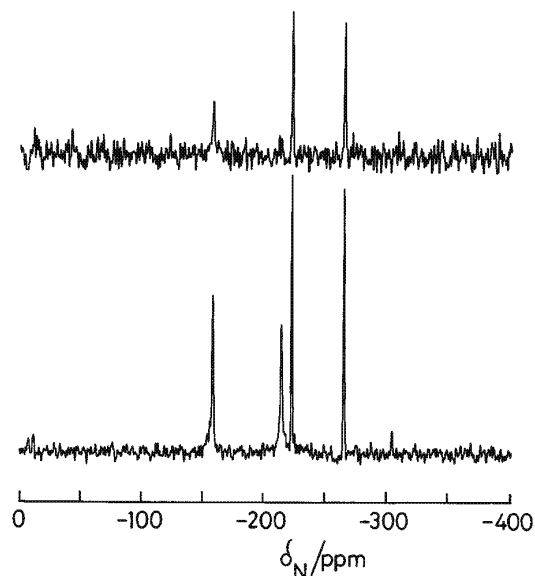


Figure 8. CPMAS ^{15}N solid-state NMR spectra of theophylline at 30.40 MHz and ambient probe temperature, with flip-back.⁵⁸ Bottom: full spectrum. Top: dipolar-dephased spectrum (dephasing time 200 μs). Spectrometer parameters: contact time 20 ms; recycle delay 4.0 s; number of transients 6000; spin rate 4.47 kHz.

expected for polymorphs, so the answer to the question as posed is “probably not.” The work done here does not, however, rule out the possibility of $\text{N}-\text{H}\cdots\text{O}$ polymorphs with different unit cells, symmetry, and packing.

3.4. Carbon-13 and Nitrogen-15 Solid-State NMR Analysis. The experimental solid-state NMR data are presented in Table 9, and the spectra are shown in Figures 8 and 9. Single signals are seen for each ^{13}C and ^{15}N (though the two methyl carbon resonances cannot be resolved). These observations indicate that there is a single molecule in the asymmetric unit, confirming the inference drawn from the powder diffraction data. Carbon-13 assignments were assumed to be analogous to those reported for solution-state spectra^{51,52} (for which D_2O and CDCl_3 were used as solvents and shifts were relative to TMS). Dipolar dephasing⁵³ experiments identified the ^{13}C signal at $\delta_{\text{C}} = 141$ ppm and the ^{15}N peak at $\delta_{\text{N}} = -214$ ppm as those from the CH and NH atoms 8 and 7, respectively. However, such measurements failed to distinguish between the remaining ^{13}C and ^{15}N signals and so could not be used to identify the sites of hydrogen bonding.

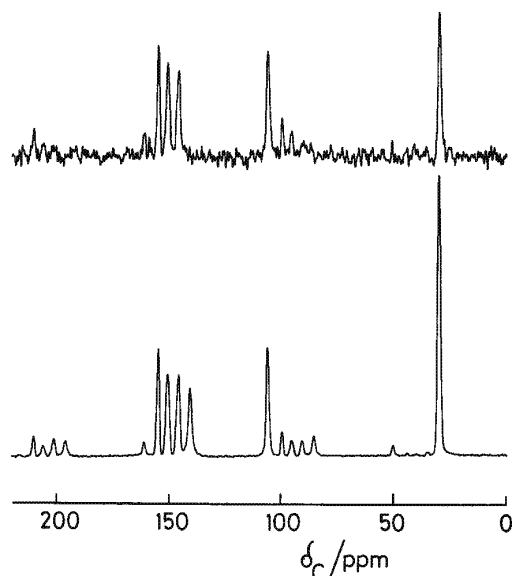


Figure 9. CPMAS ^{13}C solid-state NMR spectra of theophylline at 75.43 MHz and ambient probe temperature, with flip-back.⁵⁸ Bottom: full spectrum. Top: dipolar-dephased spectrum (dephasing time 40 μs). Small peaks are spinning sidebands. Spectrometer parameters: contact time 5.0 ms; recycle delay 4.0 s; number of transients 1000 (full spectrum) and 300 (dipolar-dephased spectrum); spin rate 4.25 kHz.

Chemical shifts were calculated using DGAUSS, in particular for the two nitrogen atoms in the imidazole ring of a molecule of theophylline optimized in vacuo. The calculated values showed equal and opposite discrepancies with those measured experimentally (22 ppm and -22 ppm, see Table 9). If a proposed crystal structure is to be deemed plausible when confronted with solid-state NMR data, then it should be possible to account for any changes in the pattern of chemical shifts, taking an isolated molecule as the point of reference, in terms of the intermolecular interactions present in the crystal structure. Hence, although it was not feasible to perform high-level DFT calculations on full crystal structures, chemical shifts were calculated for trimer arrangements, optimized in vacuo, representative of the $\text{N}-\text{H}\cdots\text{N}$ and $\text{N}-\text{H}\cdots\text{O}$ trial crystal structures. For the trimer consisting of a chain of three theophylline molecules $\text{N}-\text{H}\cdots\text{N}$ hydrogen bonded through the imidazole ring, chemical shifts calculated for the imidazole ring nitrogen atoms on the central molecule were found to be much closer to the values determined experimentally (1 ppm and -4 ppm). Interestingly, the difference between the calculated and experi-

TABLE 9: Summary of Results of the Ab Initio NMR Calculations/ppm

	reported solution-state ¹³ C NMR shifts		expt. shifts	optimized monomer			optimized trimer NH···N			optimized trimer NH···O		
	ref 50	ref 51		calc. shift	expt. – calc.	rebased (+30)	calc. shift	expt. – calc.	rebased (+30)	calc. shift	expt. – calc.	rebased (+30)
¹⁵ N												
1			–222	–188	–34		–190	–32		–188	–34	
3			–264	–228	–36		–229	–35		–225	–39	
7			–214	–206	–8	22	–185	–29	1	–194	–20	10
9			–158	–106	–52	–22	–124	–34	–4	–106	–52	–22
¹³ C												
2	158.7	151.4	151	156	–5		155	–4		155	–4	
4	150.7	148.0	145	155	–9		154	–9		157	–12	
5	110.1	106.5	106	117	–11		118	–12		118	–12	
6	155.2	154.6	155	159	–4		160	–5		159	–4	
8	144.0	140.3	141	131	10		143	–2		134	7	
10	30.8	27.4	30	32	–2		31	–1		33	–3	
12	32.8	27.4	30	32	–2		32	–2		32	–2	

mentally determined chemical shifts was also reduced for the apical C8 atom (10 ppm to -2 ppm). This carbon atom lies between the two nitrogen atoms involved in hydrogen bonds. Although this improvement could be due to the bifurcated hydrogen bonding apparent in the N-H...N structure, it is considered that the major reason is the account the model takes of the redistribution of charge on the central molecule.

The trimer representative of the N-H...O trial crystal structure was unable to account for the experimentally observed ^{15}N chemical shifts. Although the calculated chemical shift for the amino nitrogen N7 improved somewhat compared to an isolated molecule, no improvement in the predicted value was observed for the aldimine nitrogen of the imidazole ring. As expected, calculations on isolated dimers showed that only chemical shift values for the imidazole nitrogens involved in hydrogen bonding improved, and that calculations involving trimers were needed to describe sufficiently the intermolecular interactions.

4. Conclusions

Trial crystal structure generation for anhydrous theophylline, via a systematic search strategy, elucidated two different hydrogen-bonding motifs involving, respectively, N-H...N and N-H...O intermolecular interactions in a fixed unit cell. These were "indistinguishable" in terms of calculated lattice energy, employing the isotropic atom-atom approximation, and X-ray diffraction profile fitting to experimental data. Progression through Rietveld refinement, excluding H atoms and using soft constraints, resulted in a lower R_{wp} factor for the N-H...N structure and a more "sensible" molecular geometry than for the N-H...O motif, although the latter could not be ruled out as an alternative structural model. Unconstrained lattice energy minimization of these structures, using a distributed multipole-based intermolecular potential, was able to distinguish between the two structures in terms of their stability. Minimization of the proposed N-H...N crystal structure changed the cell parameters only slightly, giving better agreement with the hydrogen bond geometry observed in the published crystal structure, and a significantly better lattice energy. The initial N-H...O structure was also close to a local minimum in the lattice energy. Within the context of the experimentally determined unit cell and space group, the magnitude of lattice energy difference between the optimized structures implies that the N-H...O structure is unlikely to be an observable polymorph and that the N-H...N model is correct. Analysis of the solid-state NMR data shows that the N-H...N model accounts for the experimental chemical shifts far more adequately than does the N-H...O structural model.

The synthesis of advanced computational and experimental techniques, in conjunction with a systematic search strategy, presented in this paper, exemplifies the approach that is required to tackle issues of structure elucidation and polymorph prediction for complex materials with the potential to form many, varied hydrogen bonding networks.

Acknowledgment. E.D.L.S. gratefully acknowledges Avecia Ltd. (ex. Zeneca Specialties) for the financial support of a research studentship. J.B.O.M. is grateful for support from the AstraZeneca Strategic Research Fund project SRF 309. EPSRC is acknowledged for support of computing resources via research grants (GR/H40891, GR/J44711, and GR/J31834), software development (GR/L82373) and for access to the Solid-State NMR Service based at Durham. We also acknowledge a very useful discussion with Dr. M. Tremayne about the implications

of the use of soft constraints on the molecular geometry during refinement on the plausibility of polymorphs.

References and Notes

- (1) Gavezzotti, A. *J. Am. Chem. Soc.* **1991**, *113*, 4622.
- (2) Holden, J. R.; Du, Z.; Ammon, L. *J. Comput. Chem.* **1992**, *14*, 422.
- (3) Perlstein, J. *Chem. Mater.* **1994**, *6*, 319.
- (4) Karfunkel, R.; Gdanitz, R. J. *J. Comput. Chem.* **1993**, *13*, 1171.
- (5) Docherty, R.; Jones, W.; *Organic Molecular Solids*; Jones, W., Ed; CRC Press: Boca Raton, 1997; Chapter 5.
- (6) Rietveld, H. M. *J. Appl. Crystallogr.* **1969**, *2*, 65.
- (7) Harris, K. D. M.; Tremayne, M.; Lightfoot, P.; Bruce, P. G. *J. Am. Chem. Soc.* **1994**, *116*, 3543.
- (8) Kariuki, B. M.; Serrano-Gonzalez, H.; Johnston, R. L.; Harris, K. D. M. *Chem. Phys. Lett.* **1997**, *280*, 189.
- (9) Harris, K. D. M.; Johnston, R. L.; Kariuki, B.; M. *Acta Crystallogr. A* **1998**, *54*, 632.
- (10) David, W. I. F.; Shankland, K.; Shankland, N. *J. Chem. Soc., Chem. Commun.* **1998**, *8*, 931.
- (11) Hammond, R. B.; Roberts, K. J.; Docherty, R.; Edmondson, M. J. *Phys. Chem. B* **1997**, *101*, 6532.
- (12) Fagan, P. G.; Hammond, R. B.; Roberts, K. J.; Docherty, R.; Chorlton, A. P.; Jones, W.; Potts, G. D. *Chem. Mater.* **1995**, *7*, 2322.
- (13) Hammond, R. B.; Roberts, K. J.; Docherty, R.; Edmondson, M.; Gairns, R. J. *Chem. Soc., Perkin Trans. 2* **1996**, *8*, 1527.
- (14) Hammond, R. B.; Roberts, K. J.; Hutzke, H.; Klapper, H. *Acta Crystallogr. B* **2000**, *56*, 486.
- (15) Hammond, R. B.; Roberts, K. J.; Smith, E. D. L.; Docherty, R. J. *Phys. Chem. B* **1999**, *103*, 7762.
- (16) Allen, F. H.; Kennard, O. *Chem. Des. Automation News* **1993**, *8*, 31.
- (17) Naqvi, A. A.; Bhattacharyya, G. C. *J. Appl. Cryst.* **1991**, *14*, 464.
- (18) Ebisuzaki, Y.; Boyle, P. D.; Smith, J. A. *Acta Crystallogr. C* **1997**, *53*, 777.
- (19) Ketolainen, J.; Suihko, E.; Poso, A.; Ahlgren, M.; Gynther, J.; Paronen, P.; 14th Pharmaceutical Technology Conference, Barcelona, Spain, April 4-6, 1995, 109.
- (20) Otsuka, M.; Kaneniwa, N.; Kawakami, K.; Umezawa, O. *J. Pharm. Pharmacol.* **1990**, *42*, 606.
- (21) Burger, A.; Ramberger, R. *Mikrochim. Acta [Wien]* **1979**, *II*, 273.
- (22) Phadnis, N. V.; Suryanarayanan, R. J. *J. Pharm. Sci.* **1997**, *86*, 1258.
- (23) Price, S. L. *J. Chem. Soc., Faraday Trans.* **1996**, *92*, 2997.
- (24) Coombes, D. S.; Price, S. L.; Willock, D. J.; Leslie, M. J. *Phys. Chem.* **1996**, *100*, 7352.
- (25) Fletton, R. A.; Lancaster, R. W.; Harris, R. K.; Kenwright, A. M.; Packer, K. J.; Waters, D. N.; Yeadon, A. J. *Chem. Soc., Perkin Trans.* **1986**, 1705.
- (26) Harris, R. K.; Say, B. J.; Yeung, R. R.; Fletton, R. A.; Lancaster, R. W. *Spectrochim. Acta* **1989**, *45A*, 465.
- (27) Christopher, E. A.; Harris, R. K.; Fletton, R. A. *Solid State NMR*, **1992**, *1*, 93.
- (28) Harris, R. K.; Yeung, R. R.; Lamont, R. B.; Lancaster, R. W.; Lynn, S. M.; Stanniforth, S. E. *J. Chem. Soc., Perkin Trans. 2*, **1997**, 2653.
- (29) Apperley, D. C.; Fletton, R. A.; Harris, R. K.; Lancaster, R. A.; Tavener, S.; Threlfall, T. L. *J. Pharm. Sci.* **1999**, *88*, 1275.
- (30) Ueda, T.; Nagatomo, S.; Masui, H.; Nakamura, N.; Hayashi, S. Z. *Naturforsch.* **1999**, *54a*, 437.
- (31) Visser, J. W. *J. Appl. Crystallogr.* **1969**, *2*, 89.
- (32) Cockcroft, J. K. Institute Laue Langevin, 1968.
- (33) *International Tables of Crystallography. Volume A: Space Group Symmetry*; Hahn, T., Ed.; D Riedel: Dordrecht, 1983.
- (34) Sutor, D. J. *Acta Cryst.* **1958**, *11*, 83.
- (35) MOPAC (v. 6.0), Quantum Chemistry Program Exchange Program No. 455. Creative Arts Building 181, Indiana University, Bloomington, IN 47405.
- (36) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
- (37) Mayo, S. L.; Olafson, B. D.; Goddard, W. A., III *J. Phys. Chem.* **1990**, *94*, 8897.
- (38) Nemethy, G.; Pottle, M. S.; Scheraga, H. A. *J. Phys. Chem.* **1983**, *87*, 1883.
- (39) Larson, A. C.; Von Dreele, R. B. Technical Report LA-UR-86-748, Los Alamos National Laboratory, New Mexico 1987. Larson, A. C.; Von Dreele, R. B. GSAS Training and Technical Manual, Los Alamos National Laboratory, New Mexico, 1994.
- (40) Le Bail, A.; Duroy, H.; Fourquet, J. L. *Mater. Res. Bull.* **1988**, *23*, 447.
- (41) CADPAC6: The Cambridge Analytical Derivatives Package Issue 6, A suite of quantum chemistry programs developed by R.D. Amos with contributions from Alberts, I. L.; Andrews, J. S.; Colwell, S. M.; Handy, N. C.; Jayatilaka, D.; Knowles, P. J.; Kobayashi, R.; Koga, N.; Laidig, K.

E.; Laming, G.; Lee, A.; Maslen, P. E.; Murray, C. W.; Rice, J. E.; Snaz, J.; Simandiras, E. D.; Stone, A. J.; Su, M.-D.; Tozer, D. J. Cambridge University: Cambridge, U.K., 1995.

(42) Stone, A. J. *Chem. Phys. Lett.* **1981**, 83, 233.

(43) Willock, D. J.; Price, S. L.; Leslie, M.; Catlow, C. R. A. *J. Comput. Chem.* **1995**, 16, 628.

(44) Kukolich, S. G. *J. Am. Chem. Soc.* **1975**, 97, 5704. Jameson, C. J.; Jameson, A. K.; Oppunsunggu, D.; Wille, S.; Burrell, P. M.; Mason, J. *J. Chem. Phys.* **1981**, 74, 81.

(45) Jameson, A. K.; Jameson, C. J. *Chem. Phys. Lett.* **1987**, 134, 461.

(46) UniChem V4.1. Oxford Molecular, Medawar Centre, Oxford Science Park, Oxford, OX4 4GA, England.

(47) Hansen, A. E.; Bouman, T. D. *J. Chem. Phys.* **1985**, 82, 5035.

(48) Bruno, I. J.; Cole, J. C.; Lommerse, J. P. M.; Rowland, R. S.; Taylor, R.; Verdonk, M. L. *J. Comput.-Aided Mol. Des.* **1997**, 11, 525.

(49) Spek, A. L. 2000 PLATON, a Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands.

(50) Fokkens, J. G.; van Amelsfoort, J. G. M.; de Blaey, C. J.; de Kruif, C. G. Wilting, J. *Int. J. Pharm.* **1983**, 14, 79.

(51) Nicolau, C.; Hildenbrand, K. *Z. Naturforsch C* **1974**, 29, 475.

(52) Bennet, G. B.; Simpson, W. R. J.; Mason, R. B.; Strohschein, R. J. Manukhani, R. *J. Org. Chem.* **1977**, 42, 221.

(53) Opella, S. J.; Frey, M. H. *J. Am. Chem. Soc.* **1979**, 101, 5854.



P.B. 5818 - Patentlaan 2
2280 HV Rijswijk (ZH)
☎ +31 70 340 2040
TX 31651 epo nl
FAX +31 70 340 3016

Europäisches
Patentamt

Zweigstelle
in Den Haag
Recherchen-
abteilung

European
Patent Office

Branch at
The Hague
Search
division

Office européen
des brevets

Département à
La Haye
Division de la
recherche

Wau B, Jan B.
Zwicker, Jörk
Forrester & Boehmert
Pettenkoferstrasse 20-22
80336 München
DE

FORRESTER & BOEHMERT	
Eng./Rea:	24. NOV. 2006
Frist/Term:	
Ent./Daat w.:	mf

Datum/Date
22.11.06

Zeichen/Ref./Réf. FB14326	Anmeldung Nr./Application No./Demande n°/Patent Nr./Brevet n° 03711407.1
Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire UNIVERSITY OF SOUTH FLORIDA, et al	

COMMUNICATION

The European Patent Office herewith transmits

- ☐ the European search report
- ☐ the declaration under Rule 45 EPC
- ☐ the partial European search report under Rule 45 EPC
- ☒ the European search report under Rule 112 EPC
relating to the above-mentioned European patent application. Copies of the documents cited in the search report are enclosed.

The following specifications given by the applicant have been approved by the Search Division :

- ☐ Abstract ☐ Title ☐ Figure
- ☐ The abstract was modified by the Search Division and the definitive text is attached to this communication.
- ☐ The following figure will be published with the abstract, since the Search Division considers that it better characterises the invention than the one indicated by the applicant.
- Figure:
- ☐ Additional copy(copies) of the documents cited in the European search report.

REFUND OF THE SEARCH FEE

If applicable under Article 10 Rules relating to fees, a separate communication from the Receiving Section on the refund of the search fee will be sent later.



EPO Form 1507 02.93				



European Patent
Office

EUROPEAN SEARCH REPORT
under Rule 112 EPC

Application Number
EP 03 71 1407

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
	On request of the applicant the present search report has been drawn up for claims 1-9 relating to inventions		INV. C07C233/25 C07C69/86 C07D233/74 C07C57/30 C07C57/58 C07D223/26 C07D213/22 C07D213/16 C07C47/544 C07D213/82 C07D275/06 C07D213/80 C07C53/08 C07C61/125 C07C50/04 C07C53/124 C07C317/04
X ✓	CAIRA, M.R. ET AL.: "Structure of a 1:1 complex between the antihelmintic drug mebendazole and propionic acid." J. CHEM. CRYST., vol. 28, no. 1, 1998, page 11-15, XP002404063 * the whole document *	1-9	
X ✓	SHEFTER, E.: "Structural studies on complexes IV: Crystal structure of a 1:1 5-chlorosalicylic acid and theophylline complex." J. PHARM. SCI., vol. 58, no. 6, 1969, pages 710-714, XP009073431 * the whole document *	1-9	
X ✓	ZAITU, S. ET AL.: "1:1 molecular complex of theophylline and p-nitroaniline" ACTA CRYST., vol. C51, 1995, pages 2390-2392, XP009073408 * the whole document *	1-9	TECHNICAL FIELDS SEARCHED (IPC) C07C C07D
X ✓	GB 1 297 261 A (E.R. SQUIBB & SONS INC.) 22 November 1972 (1972-11-22) * the whole document *	1-9, 11-19,21	
X ✓	AOKI, K. ET AL.: "A 1:1 complex of theophylline and p-nitrophenol" ACTA CRYST., vol. B34, 1978, pages 2333-2336, XP009073410 * the whole document *	1-9	
	-/--		
3	Place of search Munich	Date of completion of the search 23 October 2006	Examiner Johnson, Claire
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

EPO FORM 1503 03/82 (P04C64)



European Patent
Office

EUROPEAN SEARCH REPORT
under Rule 112 EPC

Application Number
EP 03 71 1407

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X ✓	ZAITU, S. ET AL.: "A 2:1 molecular complex of theophylline and 5-fluorouracil as the monohydrate" ACTA CRYST., vol. C51, 1995, pages 1857-1859, XP009073409 * the whole document * -----	1-9	C07C233/03 C07C63/307 C07C205/57
X ✓	PATEL, U. ET AL.: "Structure of the 1:1 complex between 4-amino-N-(4,6-dimethyl-2-pyrimidinyl)-benzenesulfonamide (sulfadimidine) and 2-hydroxybenzoic acid (salicylic acid)." ACTA CRYST., vol. C44, 1988, pages 1264-1267, XP009073407 * the whole document * -----	1-9	
			TECHNICAL FIELDS SEARCHED (IPC)
Place of search		Date of completion of the search	Examiner
Munich		23 October 2006	Johnson, Claire
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons 8 : member of the same patent family, corresponding document	

3
EPO FORM 1503 03.82 (P04C64)

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 03 71 1407

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

23-10-2006

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 1297261 A	22-11-1972	CA 948642 A1	04-06-1974
		CH 507253 A	15-05-1971
		DE 2000210 A1	23-07-1970
		FR 2034467 A1	11-12-1970

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

Electronic Patent Application Fee Transmittal				
Application Number:		10378956		
Filing Date:		03-Mar-2003		
Title of Invention:		Multiple-component solid phases containing at least one active pharmaceutical ingredient		
First Named Inventor/Applicant Name:		Michael J. Zaworotko		
Filer:		Edward R. Gates/Joshua Goldkind		
Attorney Docket Number:		U0157.70023US01		
Filed as Small Entity				
Utility under 35 USC 111(a) Filing Fees				
Description		Fee Code	Quantity	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(\$)
Miscellaneous:				
Submission- Information Disclosure Stmt	2806	1	90	90
Total in USD (\$)				90

Electronic Acknowledgement Receipt	
EFS ID:	18182187
Application Number:	10378956
International Application Number:	
Confirmation Number:	4742
Title of Invention:	Multiple-component solid phases containing at least one active pharmaceutical ingredient
First Named Inventor/Applicant Name:	Michael J. Zaworotko
Customer Number:	23628
Filer:	Edward R. Gates/Joshua Goldkind
Filer Authorized By:	Edward R. Gates
Attorney Docket Number:	U0157.70023US01
Receipt Date:	12-FEB-2014
Filing Date:	03-MAR-2003
Time Stamp:	10:26:02
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	\$90
RAM confirmation Number	7275
Deposit Account	232825
Authorized User	GATES, EDWARD R.
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	U015770023US01-TRN-ERG.pdf	26387	no	1
			27b3452b10a99fdd743da085db8eb1563253e9d7		
Warnings:					
Information:					
2	Fee Worksheet (SB06)	U015770023US01-FEE-ERG.pdf	31911	no	1
			74f4e8d8e07e47052efd311a7bb9cc4cccba5b9		
Warnings:					
Information:					
3		U015770023US01-IDS-ERG.pdf	36288	yes	4
			fab765840fe38a794382a9a01d2d27d5d6a5fef6		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Transmittal Letter		1	3	
	Information Disclosure Statement (IDS) Form (SB08)		4	4	
Warnings:					
Information:					
4	Other Reference-Patent/App/Search documents	U015770023WO00_ISR_mailed_10-24-2003_QC.pdf	322961	no	9
			670b5740aa18e0f8aeca9e68a6db7a782bcbec326		
Warnings:					
Information:					
5	Non Patent Literature	The_Merck_Index_12th_ed_1996_Entries_5683_9094_QC.pdf	835931	no	4
			e1eadff9e41f657b41af609497c359a81ebfb6c7		
Warnings:					
Information:					
6	Non Patent Literature	Ito_et_al_Tetrahedron_2000_v56_p6833_QC.PDF	749913	no	12
			0849a9d3ede60fc6395e7d6725f72fa47ae4590f		
Warnings:					
Information:					
7	Non Patent Literature	Iwamoto_et_al_Acta_Cryst_1989_vC45_p1110_QC.PDF	226687	no	3
			aecce3be960afc2318ea5de13ba39a3772056dc6		
Warnings:					
Information:					

8	Non Patent Literature	Jiang_et_al_Anti_Cancer_Drugs_2000_v11_p49_QC.pdf	131612 40fc2a53ba8adc161936d35ab131d475309ba6b	no	6
Warnings:					
Information:					
9	Non Patent Literature	Smith_et_al_J_Phys_Chem_B_2001_v105_p5818_QC.pdf	357514 ae64037c687307745d3745db337f903ef99ef76	no	9
Warnings:					
Information:					
10	Other Reference-Patent/App/Search documents	U015770023EP00_ESR_mailed_11-22-2006_QC.pdf	515619 11d3b7b4589a544f7700f922f4dc6acfd0c55f1	no	4
Warnings:					
Information:					
11	Fee Worksheet (SB06)	fee-info.pdf	30156 3a24f1979515e1cad1b328d8a03958dc13eeb1f5	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			3264979		
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.					

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 FORM <i>(to be used for all correspondence after initial filing)</i>	Application Number	10/378,956-Conf. #4742
	Filing Date	March 3, 2003
	First Named Inventor	Michael J. Zaworotko
	Art Unit	1627
	Examiner Name	Sahar Javanmard
Total Number of Pages in This Submission	Attorney Docket Number	U0157.70023US01

ENCLOSURES <i>(Check all that apply)</i>		
☒ Fee Transmittal Form ☐ Fee Attached ☐ Amendment/Reply ☐ After Final ☐ Affidavits/declaration(s) ☐ Extension of Time Request ☐ Express Abandonment Request ☒ Information Disclosure Statement ☐ Certified Copy of Priority Document(s) ☐ Reply to Missing Parts/Incomplete Application ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53	☐ Drawing(s) ☐ Licensing-related Papers ☐ Petition ☐ Petition to Convert to a Provisional Application ☐ Power of Attorney, Revocation Change of Correspondence Address ☐ Terminal Disclaimer ☐ Request for Refund ☐ CD, Number of CD(s) _____ ☐ Landscape Table on CD	☐ After Allowance Communication to TC ☐ Appeal Communication to Board of Appeals and Interferences ☐ Appeal Communication to TC (Appeal Notice, Brief, Reply Brief) ☐ Proprietary Information ☐ Status Letter ☒ Other Enclosure(s) (please identify below): Form PTO-1449 Copies of cited references
Remarks		

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT			
Firm Name	WOLF, GREENFIELD & SACKS, P.C.		
Signature	/Edward R. Gates/		
Printed name	Edward R. Gates		
Date	2/12/2014	Reg. No.	31,616

Certificate of Electronic Filing Under 37 CFR 1.8	
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).	
Dated: February 12, 2014	Electronic Signature for Joshua E. Goldkind: /Joshua E. Goldkind/

3424673.1

FEE TRANSMITTAL		Complete if known								
☒ 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		Application Number	10/378,956-Conf. #4742							
		Filing Date	March 3, 2003							
		First Named Inventor	Michael J. Zaworotko							
		Examiner Name	Sahar Javanmard							
		Art Unit	1627							
TOTAL AMOUNT OF PAYMENT (\$)		90.00	Practitioner Docket No. U0157.70023US01							
METHOD OF PAYMENT (check all that apply)										
☐ Check ☒ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____										
☐ Deposit Account Deposit Account Number: 23/2825 Deposit Account Name: Wolf, Greenfield & Sacks, P.C.										
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	280	140*	70	600	300	150	720	360	180	_____
Design	180	90	45	120	60	30	460	230	115	_____
Plant	180	90	45	380	190	95	580	290	145	_____
Reissue	280	140	70	600	300	150	2,160	1,080	540	_____
Provisional	260	130	65	0	0	0	0	0	0	_____
* The \$140 small entity status filing fee for a utility application is further reduced to \$70 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)				80	40	20				
Each independent claim over 3 (including Reissues)				420	210	105				
Multiple dependent claims				780	390	195				
Total Claims				Fee Paid (\$)	Multiple Dependent Claims					
_____ - 20 or HP = _____ x _____ = _____				_____	_____	_____				
HP = highest number of total claims paid for, if greater than 20.				Fee Paid (\$)	Fee Paid (\$)					
Indep. Claims				Fee Paid (\$)	Fee Paid (\$)					
_____ - 3 or HP = _____ x _____ = _____				_____	_____	_____				
HP = highest number of independent claims paid for, if greater than 3.										
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 \$400 (\$200 for small entity) (\$100 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 _____	= _____						
4. OTHER FEE(S)										
Non-English specification, \$130 fee (no small or micro entity discount) _____										
Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, \$400 fee (\$200 small or micro entity) _____										
Other (e.g., late filing surcharge): 2806 Submission of an Information Disclosure Statement 90.00										
SUBMITTED BY										
Signature	/Edward R. Gates/			Registration No. (Attorney/Agent)	31,616	Telephone 617.646.8000				
Name (Print/Type)	Edward R. Gates			Date	2/12/2014					

Certificate of Electronic Filing Under 37 CFR 1.8	
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).	
Dated: February 12, 2014	Electronic Signature for Joshua E. Goldkind: /Joshua E. Goldkind/

3424672.1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor: Michael J. Zaworotko
Application No.: 10/378,956
Confirmation No.: 4742
Filed: March 3, 2003
For: Multiple-component solid phases containing at least one
active pharmaceutical ingredient
Examiner: Sahar Javanmard
Art Unit: 1627

CERTIFICATE OF ELECTRONIC FILING UNDER 37 C.F.R. § 1.8

The undersigned hereby certifies that this paper, along with any paper referred to as being attached or enclosed, is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4), on the 12th day of February, 2014.

/Joshua E. Goldkind/
Joshua E. Goldkind

MAIL STOP AMENDMENT

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

STATEMENT FILED PURSUANT TO THE DUTY OF
DISCLOSURE UNDER 37 C.F.R. §§ 1.56, 1.97 AND 1.98

Madam:

Pursuant to the duty of disclosure under 37 C.F.R. §§ 1.56, 1.97 and 1.98, the undersigned requests consideration of this Information Disclosure Statement.

PART I: Compliance with 37 C.F.R. § 1.97

This Information Disclosure Statement has been filed more than three months after the filing date of this application and after the mailing date of a first Office Action, but before the mailing date of any of a Final Action under 37 C.F.R. § 1.113, a Notice of Allowance under 37 C.F.R. § 1.311, or an action that otherwise closes prosecution in this application.

Please charge our Credit Card in the amount of \$90.00 covering the fee set forth in 37 C.F.R. § 1.17(p).

PART II: Information Cited

The undersigned hereby makes of record in the above-identified application the information listed on the attached form PTO-1449 (modified PTO/SB/08). The order of presentation of the references should not be construed as an indication of the importance of the references.

The undersigned hereby makes the following additional information of record in the above identified application.

The undersigned would like to bring to the Examiner's attention the enclosed search report or other communication from a corresponding or related International or Foreign National Application.

<u>Serial No.</u>	<u>Date of Mailing</u>	<u>Type(s) of Communication</u>	<u>Docket No.</u>
EP 03711407.1	November 22, 2006	European Search Report	U0157.70023EP00
PCT/US2003/06662	October 24, 2003	International Search Report	U0157.70023WO00

PART III: Remarks

Documents cited anywhere in the Information Disclosure Statement are enclosed unless otherwise indicated. It is respectfully requested that:

1. The Examiner consider completely the cited information, along with any other information, in reaching a determination concerning the patentability of the present claims;
2. The enclosed form PTO-1449 (modified PTO/SB/08) be signed by the Examiner to evidence that the cited information has been fully considered by the United States Patent and Trademark Office during the examination of this application;
3. The citations for the information be printed on any patent which issues from this application.

By submitting this Information Disclosure Statement, the undersigned makes no representation that a search has been performed, of the extent of any search performed, or that more relevant information does not exist.

By submitting this Information Disclosure Statement, the undersigned makes no representation that the information cited in the Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

By submitting this Information Disclosure Statement, the undersigned makes no representation that the information cited in the Statement is, or is considered to be, in fact, prior art as defined by 35 U.S.C. § 102.

Notwithstanding any statements by the undersigned, the Examiner is urged to form his or her own conclusion regarding the relevance of the cited information.

An early and favorable action is hereby requested.

The Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825 under Docket No. U0157.70023US01 from which the undersigned is authorized to draw.

Respectfully submitted,

By: /Edward R. Gates/
Edward R. Gates, Reg. No. 31,616
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
Telephone: (617) 646-8000

Docket No.: U0157.70023US01
Date: 2/12/2014
xNDDx



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.
10/378,956	03/03/2003	Michael J. Zaworotko	U0157.70023US01	4742
23628 7590 07/15/2014 WOLF GREENFIELD & SACKS, P.C. 600 ATLANTIC AVENUE BOSTON, MA 02210-2206			EXAMINER JAVANMARD, SAHAR	
			ART UNIT	PAPER NUMBER
			1627	
			NOTIFICATION DATE	DELIVERY MODE
			07/15/2014	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):

Patents_eOfficeAction@WolfGreenfield.com
WGS_eOfficeAction@WolfGreenfield.com

Office Action Summary	Application No. 10/378,956	Applicant(s) ZAWOROTKO ET AL.	
	Examiner SAHAR JAVANMARD	Art Unit 1627	AIA (First Inventor to File) 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 1/14/14.
☐ 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) 25, 28, 37 and 39-66 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) 25, 28, 39-43 and 46-66 is/are rejected.

8) ☒ Claim(s) 37, 44 and 45 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

Status of the Application

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

This Office Action is in response to Applicant's arguments filed on January 14, 2014. Claim(s) 25, 28, 37, 39-66 are pending and examined herein.

Response to Arguments

In view of Applicant's amendments/arguments, the rejections of the previous Office action are hereby withdrawn. The following rejections are made of record in the Final Office action below as necessitated by amendment.

Claim Rejections - 35 USC § 103

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 of this title, 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 negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 25, 28, 39-43, 46-48, 50-55, 57-64, and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jackson (GB 2169601) of record.

Jackson teaches sucralose co-crystallized with an aliphatic or cyclic secondary or tertiary amine, specifically niacinamide (claims 1-11).

Jackson teaches that the nitrogenous base should be a food additive (page 1, line 41).

Jackson teaches the metal salts are highly effective (page 1, lines 27-37). Jackson teaches that if a solution of sucralose in ethyl acetate is augmented with 1 to 10% by weight (based on the sucralose) of niacinamide, the sucralose can be crystallized from the solution, washed with further ethyl acetate and dried under vacuum to give a fine crystalline material containing) about 0.3 - 0.9% of niacinamide in the sucralose. Such a material has a much improved color stability compared with normal sucralose and, for example, under the test conditions described above, would be practically unchanged after 7 or more hours at 100 °C (page 1, lines 46-51).

Jackson does not specifically teach a working example of a co-crystal in stoichiometric ratios.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have envisioned the co-crystals of niacinamide with that of sucralose as taught by Jackson to be in stoichiometric amounts. It is common practice to the ordinary artisan to form specific ratios (i.e., 1:1, 1:2, etc.) between the two entities in order to get optimal results.

Thus, based on the foregoing reasons, the instant claims are deemed unpatentable over the cited art.

Conclusion

Claims 25, 27-28, 38-43, 46-66 are not allowed.

Claims 37, 44-45 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

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 mailing date of this final action.

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 <http://pair-direct.uspto.gov>. 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.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAHAR JAVANMARD whose telephone number is (571) 270-3280. The examiner can normally be reached on 8 AM-5 PM MON-FRI (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Application/Control Number: 10/378,956
Art Unit: 1627

Page 6

/S. J./

Examiner, Art Unit 1627

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627

<i>Index of Claims</i> 	Application/Control No. 10378956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.
	Examiner SAHAR JAVANMARD	Art Unit 1627

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

☐ Claims renumbered in the same order as presented by applicant		☐ CPA		☐ T.D.		☐ R.1.47	
CLAIM		DATE					
Final	Original	09/30/2008	09/28/2009	06/18/2010	07/01/2013	05/19/2014	
	1	-	-	-	-	-	
	2	-	-	-	-	-	
	3	-	-	-	-	-	
	4	-	-	-	-	-	
	5	-	-	-	-	-	
	6	-	-	-	-	-	
	7	-	-	-	-	-	
	8	-	-	-	-	-	
	9	-	-	-	-	-	
	10	-	-	-	-	-	
	11	-	-	-	-	-	
	12	-	-	-	-	-	
	13	-	-	-	-	-	
	14	-	-	-	-	-	
	15	-	-	-	-	-	
	16	-	-	-	-	-	
	17	-	-	-	-	-	
	18	-	-	-	-	-	
	19	-	-	-	-	-	
	20	-	-	-	-	-	
	21	-	-	-	-	-	
	22	-	-	-	-	-	
	23	-	-	-	-	-	
	24	-	-	-	-	-	
	25	✓	✓	✓	✓	✓	
	26	-	-	-	-	-	
	27	✓	✓	✓	✓	✓	
	28	✓	✓	✓	✓	✓	
	29	-	-	-	-	-	
	30	-	-	-	-	-	
	31	-	-	-	-	-	
	32	-	-	-	-	-	
	33	-	-	-	-	-	
	34	-	-	-	-	-	
	35	-	-	-	-	-	
	36	-	-	-	-	-	

<i>Index of Claims</i> 	Application/Control No. 10378956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.
	Examiner SAHAR JAVANMARD	Art Unit 1627

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

☐ Claims renumbered in the same order as presented by applicant		☐ CPA		☐ T.D.		☐ R.1.47			
CLAIM		DATE							
Final	Original	09/30/2008	09/28/2009	06/18/2010	07/01/2013	05/19/2014			
	37	✓	✓	✓	✓	✓			
	38	✓	✓	✓	✓	-			
	39			✓	✓	✓			
	40			✓	✓	✓			
	41			✓	✓	✓			
	42			✓	✓	✓			
	43			○	✓	✓			
	44			○	○	○			
	45			○	○	○			
	46			✓	✓	✓			
	47			✓	✓	✓			
	48			✓	✓	✓			
	49			✓	✓	✓			
	50				✓	✓			
	51				✓	✓			
	52				✓	✓			
	53				✓	✓			
	54					✓			
	55					✓			
	56					✓			
	57					✓			
	58					✓			
	59					✓			
	60					✓			
	61					✓			
	62					✓			
	63					✓			
	64					✓			
	65					✓			
	66					✓			

FORM PTO-1449/A and B (modified PTO/SB/08) INFORMATION DISCLOSURE STATEMENT BY APPLICANT				APPLICATION NO.: 10/378,956		ATTY. DOCKET NO.: U0157.70023US01	
				FILING DATE: March 3, 2003		CONFIRMATION NO.: 4742	
				FIRST NAMED INVENTOR: Michael J. Zaworotko			
				GROUP ART UNIT: 1627		EXAMINER: Sahar Javanmard	
Sheet	1	of	1				

U.S. PATENT DOCUMENTS

Examiner's Initials #	Cite No.	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication or Issue of Cited Document MM-DD-YYYY
		Number	Kind Code		

FOREIGN PATENT DOCUMENTS

Examiner's Initials #	Cite No.	Foreign Patent Document			Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Translation (Y/N)
		Office/Country	Number	Kind Code			

OTHER ART — NON PATENT LITERATURE DOCUMENTS

Examiner's 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, page(s), volume-issue number(s), publisher, city and/or country where published.	Translation (Y/N)
		European Search Report for Application No. EP 03711407.1 mailed November 22, 2006 (U0157.70023EP00).	
		International Search Report for Application No. PCT/US2003/06662 mailed October 24, 2003 (U0157.70023WO00).	
		The Merck Index, 12 th Ed. Merck & Co., Inc. Whitehouse Station, NJ. 1996. Entries 5683, 9094.	
		ITO et al., Compelled Orientational Control of the Solid-State Photodimerization of <i>trans</i> -Cinnamamides: Dicarboxylic Acid as a Non-covalent Linker. Tetrahedron. 2000;56:6833-44.	
		IWAMOTO et al., Structure of Cinnamamide. Acta Cryst. 1989;C45:1110-2.	
		JIANG et al., Cinnamamide, an antitumor agent with low cytotoxicity acting on matrix metalloproteinase. Anti-Cancer Drugs. 2000 Jan;11(1):49-54.	
		SMITH et al., The Determination of the Crystal Structure of Anhydrous Theophylline by X-ray Powder Diffraction with a Systematic Search Algorithm, Lattice Energy Calculations, and ¹³ C and ¹⁵ N Solid-State NMR: A Question of Polymorphism in a Given Unit Cell. J Phys Chem B. 2001;105(24):5818-26.	

[NOTE – No copies of U.S. patents, published U.S. patent applications, or pending, unpublished patent applications stored in the USPTO's Image File Wrapper (IFW) system, are included. See 37 CFR § 1.98 and 1287OG163. Copies of all other patent(s), publication(s), unpublished, pending U.S. patent applications, or other information listed are provided as required by 37 CFR § 1.98 unless 1) such copies were provided in an IDS in an earlier application that complies with 37 CFR § 1.98, and 2) the earlier application is relied upon for an earlier filing date under 35 U.S.C. § 120.]

EXAMINER: /Sahar Javanmard/	DATE CONSIDERED: 07/09/2014
--------------------------------	--------------------------------

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

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J./

Search Notes 	Application/Control No. 10378956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.
	Examiner SAHAR JAVANMARD	Art Unit 1627

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
424	400 (update 5/19/14)	9/30/2008	

SEARCH NOTES		
Search Notes	Date	Examiner
EAST (searched each inventor name)(update 6/17/10)	8/31/2009	SJ
EAST (keyword search)(update 6/17/10)	8/31/2009	SJ
Pubmed	8/31/2009	SJ
Google	8/31/2009	SJ
(update 5/19/14)		SJ

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

/S. J./ Examiner, Art Unit 1627	
------------------------------------	--

To: Patents_eOfficeAction@WolfGreenfield.com,WGS_eOfficeAction@WolfGreenfield.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 23628

Jul 15, 2014 05:33:50 AM

Dear PAIR Customer:

WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 23628 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

Disclaimer:

The list of documents shown below is provided as a courtesy and is not part of the official file wrapper. The content of the images shown in PAIR is the official record.

Application	Document	Mailroom Date	Attorney Docket No.
10378956	CTFR	07/15/2014	U0157.70023US01
	1449	07/15/2014	U0157.70023US01

To view your correspondence online or update your email addresses, please visit us anytime at <https://sportal.uspto.gov/secure/myportal/privatepair>.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

Request for Continued Examination (RCE) Transmittal Address to: Mail Stop RCE Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Application Number	10/378,956-Conf. #4742
	Filing Date	March 3, 2003
	First Named Inventor	Michael J. Zaworotko
	Art Unit	1627
	Examiner Name	S. Javanmard
	Attorney Docket Number	U0157.70023US01

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. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. **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).
- a. ☐ 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.
- i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ii. ☐ Other _____
- b. ☒ Enclosed
- i. ☒ Amendment/Reply
- iii. ☒ Information Disclosure Statement (IDS)
- ii. ☐ Affidavit(s)/Declaration(s)
- iv. ☒ Other Petition for Extension of Time; Fee Transmittal
2. **Miscellaneous**
- a. ☐ 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)
- b. ☐ Other _____
3. **Fees** The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
- a. ☐ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 23/2825.
- i. ☒ RCE fee required under 37 CFR 1.17(e)
- ii. ☒ Extension of time fee (37 CFR 1.136 and 1.17)
- iii. ☐ Other _____
- b. ☐ Check in the amount of \$ _____ enclosed
- c. ☒ Payment by credit card (~~Form PTO-2038 enclosed~~)

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.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Amy J. McMahon, Ph.D./	Date	January 15, 2015
Name (Print/Type)	Amy J. McMahon, Ph.D.	Registration No.	73,073

Certificate of Electronic Filing Under 37 CFR 1.8

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

Dated: January 15, 2015

Electronic Signature: /Trish McDonald/

3882983.1

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)		Docket Number (Optional) U0157.70023US01	
Application Number 10/378,956-Conf. #4742		Filed March 3, 2003	
For MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT			
Art Unit 1627		Examiner S. Javanmard	

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):

	<u>Fee</u>	<u>Small Entity Fee</u>	<u>Micro Entity Fee</u>	
☐ One month (37 CFR 1.17(a)(1))	\$200	\$100	\$50	\$ _____
☐ Two months (37 CFR 1.17(a)(2))	\$600	\$300	\$150	\$ _____
☒ Three months (37 CFR 1.17(a)(3))	\$1,400	\$700	\$350	\$ 700.00
☐ Four months (37 CFR 1.17(a)(4))	\$2,200	\$1,100	\$550	\$ _____
☐ Five months (37 CFR 1.17(a)(5))	\$3,000	\$1,500	\$750	\$ _____

☒ 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 23/2825.

☒ 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/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71. 37 CFR 3.73(b) statement is enclosed (Form PTO/SB/96).

☒ attorney or agent of record. Registration number 73,073.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

_____/Amy J. McMahon, Ph.D./_____
Signature

_____/January 15, 2015_____
Date

_____/Amy J. McMahon, Ph.D._____
Typed or printed name

_____/617.646.8000_____
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.

Certificate of Electronic Filing Under 37 CFR 1.8

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

Dated: January 15, 2015

Electronic Signature: /Trish McDonald/

3882984.1

UM00017309

NOVARTIS EXHIBIT 1517

Novartis v. Regents, IPR2023-01347

Page 4166 of 4460

FEE TRANSMITTAL

☒	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.

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

☐ Deposit Account
 Deposit Account Number: 23/2825
 Deposit Account Name: Wolf, Greenfield & Sacks, P.C.

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			
<u>Application Type</u>	<u>U (\$)</u>	<u>S (\$)</u>	<u>M (\$)</u>	<u>U (\$)</u>	<u>S (\$)</u>	<u>M (\$)</u>	<u>U (\$)</u>	<u>S (\$)</u>	<u>M (\$)</u>	<u>Fees Paid (\$)</u>
Utility	280	140*	70	600	300	150	720	360	180	
Design	180	90	45	120	60	30	460	230	115	
Plant	180	90	45	380	190	95	580	290	145	
Reissue	280	140	70	600	300	150	2,160	1,080	540	
Provisional	260	130	65	0	0	0	0	0	0	

* The \$140 small entity status filing fee for a utility application is further reduced to \$70 for a small entity status applicant who files the application via EFS-Web.

2. EXCESS CLAIM FEES

<u>Fee Description</u>	<u>Undiscounted Fee (\$)</u>	<u>Small Entity Fee (\$)</u>	<u>Micro Entity Fee (\$)</u>
Each claim over 20 (including Reissues)	80	40	20
Each independent claim over 3 (including Reissues)	420	210	105
Multiple dependent claims	780	390	195

<u>Total Claims</u>	<u>Extra Claims</u>	<u>Fee (\$)</u>	<u>Fee Paid (\$)</u>	<u>Multiple Dependent Claims</u>
- 20 or HP =	x	=		<u>Fee (\$)</u> <u>Fee Paid (\$)</u>

- 20 or HP = x =

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

<u>Indep. Claims</u>	<u>Extra Claims</u>	<u>Fee (\$)</u>	<u>Fee Paid (\$)</u>
----------------------	---------------------	-----------------	----------------------

_____ - 3 or HP = _____ x _____ = _____
 HP = highest number of independent claims paid for, if greater than 3

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 \$400 (\$200 for small entity) (\$100 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).

<u>Total Sheets</u>	<u>Extra Sheets</u>	<u>Number of each additional 50 or fraction thereof</u>	<u>Fee (\$)</u>	<u>Fee Paid (\$)</u>
- 100 =	/50 =	(round up to a whole number) x	=	

4. OTHER FEE(S)
 Non-English specification, \$130 fee (no small or micro entity discount)
 Non-electronic filing fee under 37 CFR 1.16(f) for a utility application, \$400 fee (\$200 small or micro entity)

Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, \$400 fee (\$200 small or micro entity)

Other (e.g., late filing surcharge):	2253 Extension for response within third month	700.00
	2820 Request for RCE - 2nd request (see 37 CFR 1.114)	850.00

SUBMITTED BY					
Signature	/Amy J. McMahon, Ph.D./	Registration No. (Attorney/Agent)	73,073	Telephone	617.646.8000
Name (Print/Type)	Amy J. McMahon, Ph.D.			Date	January 15, 2015

Certificate of Electronic Filing Under 37 CFR 1.8

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

Dated: January 15, 2015

Electronic Signature: /Trish McDonald/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor: Michael J. Zaworotko
Application No.: 10/378,956
Confirmation No.: 4742
Filed: March 3, 2003
For: MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT
LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT
Examiner: S. Javanmard
Art Unit: 1627

Certificate of Electronic Filing Under 37 CFR 1.8

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

Dated: January 15, 2015

Electronic Signature: /Trish McDonald/

AMENDMENT AFTER FINAL ACTION UNDER 37 C.F.R. 1.116

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

Dear Madam:

INTRODUCTORY COMMENTS

In response to the Office Action dated July 15, 2014, finally rejecting claims 25, 28, 39-43 and 46-66, please amend the above-identified U.S. patent application as follows. A Request for Continued Examination and a petition for a three-month extension of time is being filed concurrently herewith.

Amendments to the Claims are reflected in the listing of claims which begins on page 7 of this paper.

Remarks/Arguments begin on page 7 of this paper.

AMENDMENTS TO THE CLAIMS

Please replace all prior versions, and listings, of claims in the application with the following list of claims:

1-24 (Canceled)

25. (Currently amended) A method for designing and preparing a co-crystal, said method comprising:

(a) providing an active pharmaceutical ingredient (API) comprising a first chemical functionality, wherein said first chemical functionality forms API homosynthons comprising a hydrogen bond;

(b) identifying and selecting a co-crystal former from among a plurality of candidate co-crystal formers by determining that said selected co-crystal former forms a supramolecular synthon via non-covalent hydrogen bonding between the first chemical functionality and a[[the]] complementary second chemical functionality of the co-crystal former, wherein said selected co-crystal former in its pure form is a solid at room temperature and atmospheric pressure and wherein the co-crystal former is not an active pharmaceutical ingredient; and

(c) preparing a co-crystal comprising stoichiometric proportions of said API and said selected co-crystal former upon formation of said supramolecular synthon by said non-covalent bonding between said complementary second chemical functionality of said co-crystal ~~former~~former(s) and said chemical functionality of said API, and wherein the first chemical functionality is a carboxylic acid, a carboxamide, a carbonyl or an amine.

26-27. (Canceled)

28. (Previously Presented) The method of claim 25, wherein said preparing comprises crystallization from solution, crystallization from a melt, sublimation, or grinding.

29-36. (Canceled)

3720030.1

37. (Previously Presented) The method according to claim 25, wherein said API is selected from aspirin, ibuprofen, flurbiprofen, carbamazepine, phenytoin or acetaminophen.

38. (Canceled)

39. (Previously Presented) The method of claim 25, wherein the co-crystal former is a GRAS compound.

40. (Previously Presented) The method of claim 25, wherein the co-crystal former is a food additive.

41. (Previously Presented) The method of claim 25, wherein the co-crystal former is a low toxicity organic.

42. (Previously Presented) The method of claim 25, wherein the co-crystal former is a metal organic complex.

43. (Previously Presented) The method of claim 25, wherein the co-crystal former comprises at least two heterocyclic groups.

44. (Previously Presented) The method of claim 25, wherein the co-crystal former is bipyridine.

45. (Previously Presented) The method of claim 25, wherein the co-crystal former is bis(pyridyl)ethene.

46. (Previously Presented) The method of claim 25, wherein said homosynthon is identified from the crystal structure of said API.

47. (Previously Presented) The method of claim 25, wherein said homosynthon is identified by determining the structure of at least one pure solid phase of said API.

48. (Previously Presented) The method of claim 25, wherein the complementary second chemical functionality is an unsaturated N-heterocycle, saturated N-heterocycle, aldehyde, amide, carboxylic acid, nitro, ketone, or sulfoxide.

49. (Previously Presented) The method of claim 25, wherein the complementary second chemical functionality is a carboxylic acid.

50. (Previously Presented) The method of claim 25, wherein said co-crystal comprises heterosynthons of said co-crystal former and said API.

51. (Previously Presented) The method of claim 25, wherein said co-crystal comprises homosynthons of said API.

52. (Canceled)

53. (Previously Presented) The method of claim 25, wherein said complementary second chemical functionality is an amine, amide, unsaturated aromatic nitrogen bases, or other chemical functionality that lacks a hydrogen bond donor, wherein no covalent bonds are formed upon said non-covalent bonding between said co-crystal former and said API.

54. (Currently amended) The method of claim 25, wherein the non-covalent bonding between said co-crystal former and complementary second chemical functionality and said first chemical functionality of said API to form said supramolecular synthon comprises carbonyl:amine hydrogen bonding.

55. (Currently amended) The method of claim 25, wherein the non-covalent bonding between said co-crystal former and complementary second chemical functionality and said first chemical functionality of said API to form said supramolecular synthon comprises carboxylic acid:pyridine hydrogen bonding.

56. (Currently amended) The method of claim 51, wherein the non-covalent bonding of said ~~homodimers~~ homosynthons of said API is carboxylic acid:carboxylic acid hydrogen bonding.

57. (Currently amended) The method of claim 51, wherein the non-covalent bonding of said ~~homodimers~~ homosynthons of said API is carboxamide:carboxamide hydrogen bonding.

58. (Currently amended) A method for the preparation of a pharmaceutical product containing a co-crystal, said method comprising:

(a) providing an active pharmaceutical ingredient (API) comprising a first chemical functionality, wherein said first chemical functionality forms a first crystal of API homosynthons that is non-covalent hydrogen bonding;

(b) selecting a co-crystal former having a second chemical functionality complementary to the first chemical functionality via non-covalent bonding, wherein said co-crystal former forms a supramolecular synthon by non-covalent hydrogen bonding between the first chemical functionality of the API and the complementary second chemical functionality of said co-crystal former, wherein said selected co-crystal former in its pure form is a solid at room temperature and atmospheric pressure;

(c) preparing a co-crystal of stoichiometric proportions of said API and said co-crystal former, said co-crystal consisting of said supramolecular synthon, and

(d) combining said co-crystal with a pharmaceutically acceptable carrier to form the pharmaceutical product, and wherein the first chemical functionality is a carboxylic acid, a carboxamide, a carbonyl or an amine.

59. (Previously Presented) The method of claim 58, wherein said co-crystal comprises heterosynthons of said co-crystal former and said API.
60. (Previously Presented) The method of claim 58, wherein said co-crystal comprises homosynthons of said API.
61. (Canceled)
62. (Previously Presented) The method of claim 58, wherein said complementary second chemical functionality is an amine, amide, or unsaturated aromatic nitrogen base.
63. (Currently amended) The method of claim 58, wherein the non-covalent bonding between said co-crystal former and complementary second chemical functionality and said first chemical functionality of said API to form said supramolecular synthon comprises carbonyl:amine hydrogen bonding.
64. (Currently amended) The method of claim 58, wherein the non-covalent bonding between said co-crystal former and complementary second chemical functionality and said first chemical functionality of said API to form said supramolecular synthon comprises carboxylic acid:pyridine hydrogen bonding.
65. (Currently amended) The method of claim ~~[[58]]60~~, wherein the non-covalent bonding of said ~~homodimers~~ homosynthons of said API is carboxylic acid:carboxylic acid hydrogen bonding.
66. (Currently amended) The method of claim ~~[[58]]60~~, wherein the non-covalent bonding of said ~~homodimers~~ homosynthons of said API is carboxamide:carboxamide hydrogen bonding.

REMARKS

Applicant respectfully requests reconsideration. Claims 25, 28, 37 and 39-66 were previously pending in this application. By this amendment, Applicant is canceling claims 52 and 61 without prejudice or disclaimer. Claims 25, 54-58, and 63-66 have been amended. Support for the amended claims can be found throughout the application as filed, e.g., in original claims 1-6, 11, 12, and 13; in paragraphs [0009], [0014], [0042]-[0048], and [0050]; in Examples 1-19; and in Figs. 4, 7, 6, 10, 11, 12, 14, 15, 18, 20, 21, and 23. As a result, claims 25, 28, 37, 39-51, 53-60, and 62-66 are pending for examination with claims 25 and 58 being independent claims. No new matter has been added.

Rejections Under 35 U.S.C. §103

The Examiner rejected claims 25, 28, 39-43, 46-48, 50-55, 57-64 and 66 under 35 U.S.C. §103(a) as being unpatentable over Jackson (GB 2169601). Claims 52 and 61 are canceled herein without prejudice or disclaimer and thus are not discussed below. Reconsideration is respectfully requested in light of the amendment and arguments presented herein.

Jackson discloses sucralose crystalized with a nitrogenous base, such as niacinamide, for improving color under hot and dry conditions (see, e.g., Abstract and page 1, lines 5-6 and 19-45). Applicant respectfully asserts that the compound in Jackson is not a co-crystal and that the Examiner has not provided any evidence that the compound in Jackson is a co-crystal. However, even if the compound in Jackson were a co-crystal, the “co-crystal” would theoretically comprise a supramolecular heterosynthon with the first chemical functionality—the amide group on the niacinamide—and the second chemical functionality—the hydroxyl group on the sucralose—forming a hydroxyl:pyridine bond.

Without conceding the correctness of the Examiner’s allegations that Jackson discloses a co-crystal and solely for the purpose of advancing prosecution, independent claims 25 and 58 have been amended such that they do not encompass production or use of a co-crystal comprising a supramolecular heterosynthon formed by hydroxyl:pyridine hydrogen bonding. In particular, both claims 25 and 58 have been amended to recite that the first chemical functionality of the API is a

carboxylic acid, a carboxamide, a carbonyl or an amine. Jackson does not teach or suggest a method for designing and preparing a co-crystal or a method for the preparation of a pharmaceutical product containing a co-crystal utilizing an API comprising a first chemical functionality that is a carboxylic acid, a carboxamide, carbonyl or an amine. As a result, Jackson does not teach or suggest each and every limitation of amended claims 25 and 58 and therefore does not render obvious amended claims 25 and 58.

Accordingly, amended claims 25 and 58 are patentable over Jackson. Claims 28, 39-43, 46-48, 50, 51, 53-55, 57-60, 62-64 and 66 all depend directly or indirectly from amended claim 25 or 58. Thus, dependent claims 28, 39-43, 46-48, 50, 51, 53-55, 57-60, 62-64 and 66 are also patentable over Jackson.

Withdrawal of this rejection is respectfully requested.

CONCLUSION

In view of the foregoing, the present application is believed to be in condition for allowance. A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the application in condition for allowance.

Applicant believes no additional fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 23/2825 under Docket No. U0157.70023US01 from which the undersigned is authorized to draw.

Dated: January 15, 2015

Respectfully submitted,

By /Amy J. McMahon, Ph.D./
Amy J. McMahon, Ph.D.
Registration No.: 73,073
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor: Michael J. Zaworotko
Application No.: 10/378,956
Confirmation No.: 4742
Filed: March 3, 2003
For: MULTIPLE-COMPONENT SOLID PHASES
CONTAINING AT LEAST ONE ACTIVE
PHARMACEUTICAL INGREDIENT
Examiner: Sahar Javanmard
Art Unit: 1627

CERTIFICATE OF ELECTRONIC FILING UNDER 37 C.F.R. § 1.8

The undersigned hereby certifies that this paper, along with any paper referred to as being attached or enclosed, is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4), on the 15th day of January, 2015.

Electronic Signature: /Trish McDonald/

MAIL STOP RCE

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

STATEMENT FILED PURSUANT TO THE DUTY OF
DISCLOSURE UNDER 37 C.F.R. §§ 1.56, 1.97 AND 1.98

Madam:

Pursuant to the duty of disclosure under 37 C.F.R. §§ 1.56, 1.97 and 1.98, the undersigned requests consideration of this Information Disclosure Statement.

PART I: Compliance with 37 C.F.R. § 1.97

This Information Disclosure Statement has been filed before the mailing of a first Office Action after the filing of a Request for Continued Examination under 37 C.F.R. § 1.114.

No fee or certification is required.

PART II: Information Cited

The undersigned hereby makes of record in the above-identified application the information listed on the attached form PTO-1449 (modified PTO/SB/08). The order of

presentation of the references should not be construed as an indication of the importance of the references.

The undersigned hereby makes the following additional information of record in the above-identified application.

The undersigned would like to bring to the Examiner's attention the following co-pending applications that may contain subject matter related to this application:

<u>Serial No.</u>	<u>Filing Date</u>	<u>Inventor(s)</u>	<u>Docket No.</u>
*14/179,862	February 13, 2014	Zaworotko et al.	U0157.70023US02

*A copy of this reference is not provided as the Office has waived the requirement under 37 C.F.R. § 1.98(a)(2)(iii) for submitting a copy of a cited U.S. patent application if it is scanned to the Image File Wrapper system and is available on Private PAIR.

PART III: Remarks

Documents cited anywhere in the Information Disclosure Statement are enclosed unless otherwise indicated. It is respectfully requested that:

1. The Examiner consider completely the cited information, along with any other information, in reaching a determination concerning the patentability of the present claims;
2. The enclosed form PTO-1449 (modified PTO/SB/08) be signed by the Examiner to evidence that the cited information has been fully considered by the United States Patent and Trademark Office during the examination of this application;
3. The citations for the information be printed on any patent which issues from this application.

By submitting this Information Disclosure Statement, the undersigned makes no representation that a search has been performed, of the extent of any search performed, or that more relevant information does not exist.

By submitting this Information Disclosure Statement, the undersigned makes no representation that the information cited in the Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

By submitting this Information Disclosure Statement, the undersigned makes no representation that the information cited in the Statement is, or is considered to be, in fact, prior art as defined by 35 U.S.C. § 102.

Notwithstanding any statements by the undersigned, the Examiner is urged to form his or her own conclusion regarding the relevance of the cited information.

An early and favorable action is hereby requested.

The Director is hereby authorized to charge any deficiency or credit any overpayment in the fees occasioned by the filing of this Information Disclosure Statement to our Deposit Account No. 23/2825 under Docket No. U0157.70023US01 from which the undersigned is authorized to draw.

Respectfully submitted,

By: /Amy J. McMahon, Ph.D./
Amy J. McMahon, Ph.D., Reg. No. 73,073
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
Telephone: (617) 646-8000

Docket No.: U0157.70023US01
Date: January 15, 2015
xNDDx

FORM PTO-1449/A and B (modified PTO/SB/08) INFORMATION DISCLOSURE STATEMENT BY APPLICANT				APPLICATION NO.: 10/378,956		ATTY. DOCKET NO.: U0157.70023US01	
				FILING DATE: March 3, 2003		CONFIRMATION NO.: 4742	
				FIRST NAMED INVENTOR: Michael J. Zaworotko			
				GROUP ART UNIT: 1627		EXAMINER: Sahar Javanmard	
Sheet	1	of	1				

U.S. PATENT DOCUMENTS

Examiner's Initials #	Cite No.	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication or Issue of Cited Document MM-DD-YYYY
		Number	Kind Code		
		3,664,858		Huffman	05-23-1972
		2014-0162989	A1	Zaworotko et al.	06-12-2014

FOREIGN PATENT DOCUMENTS

Examiner's Initials #	Cite No.	Foreign Patent Document			Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Translation (Y/N)
		Office/Country	Number	Kind Code			

OTHER ART – NON PATENT LITERATURE DOCUMENTS

Examiner's 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, page(s), volume-issue number(s), publisher, city and/or country where published.	Translation (Y/N)

EXAMINER:	DATE CONSIDERED:
-----------	------------------

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

[NOTE – No copies of U.S. patents, published U.S. patent applications, or pending, unpublished patent applications stored in the USPTO's Image File Wrapper (IFW) system, are included. See 37 CFR § 1.98 and 1287OG163. Copies of all other patent(s), publication(s), unpublished, pending U.S. patent applications, or other information listed are provided as required by 37 CFR § 1.98 unless 1) such copies were provided in an IDS in an earlier application that complies with 37 CFR § 1.98, and 2) the earlier application is relied upon for an earlier filing date under 35 U.S.C. § 120.]

Electronic Patent Application Fee Transmittal				
Application Number:		10378956		
Filing Date:		03-Mar-2003		
Title of Invention:		Multiple-component solid phases containing at least one active pharmaceutical ingredient		
First Named Inventor/Applicant Name:		Michael J. Zaworotko		
Filer:		Amy Jeanette McMahon/Trish McDonald		
Attorney Docket Number:		U0157.70023US01		
Filed as Small Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description		Fee Code	Quantity	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	2253	1	700	700
Miscellaneous:				
RCE- 2nd and Subsequent Request	2820	1	850	850
Total in USD (\$)				1550

Electronic Acknowledgement Receipt	
EFS ID:	21225023
Application Number:	10378956
International Application Number:	
Confirmation Number:	4742
Title of Invention:	Multiple-component solid phases containing at least one active pharmaceutical ingredient
First Named Inventor/Applicant Name:	Michael J. Zaworotko
Customer Number:	23628
Filer:	Amy Jeanette McMahon/Trish McDonald
Filer Authorized By:	Amy Jeanette McMahon
Attorney Docket Number:	U0157.70023US01
Receipt Date:	15-JAN-2015
Filing Date:	03-MAR-2003
Time Stamp:	18:33:29
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	\$1550
RAM confirmation Number	5023
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	Request for Continued Examination (RCE)	U015770023US01-RCE-AM.pdf	25246 d374cb9fd23544ce643a79d3f70ffcd2f37645c	no	1
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					
2	Extension of Time	U015770023US01-EXT-AM.pdf	23359 2d63ce63772196dba7220b4f17f88006e09f5ca8	no	1
Warnings:					
Information:					
3	Fee Worksheet (SB06)	U015770023US01-FEE-AM.pdf	31738 264be89491eb48291df53f68d2238e14c5f79ce6	no	1
Warnings:					
Information:					
4		U015770023US01-116AMN-AM.pdf	43662 8f9a6563976c1a88a69fc6ea79bc5c95dad5bc43	yes	9
	Multipart Description/PDF files in .zip description				
	Document Description	Start		End	
	Response After Final Action	1		1	
	Claims	2		6	
	Applicant Arguments/Remarks Made in an Amendment	7		9	
Warnings:					
Information:					
5		U015770023US01-IDS-AM.pdf	30873 36ee52e9c7029d7cc9d88eef232ad23e560e9756	yes	4
	Multipart Description/PDF files in .zip description				
	Document Description	Start		End	

	Transmittal Letter	1	3				
	Information Disclosure Statement (IDS) Form (SB08)	4	4				
Warnings:							
Information:							
6	Fee Worksheet (SB06)	fee-info.pdf	<table border="1"> <tr> <td>32189</td><td rowspan="2">no</td><td rowspan="2">2</td></tr> <tr> <td>974c3387a13ecb9125159884e4079239da652b58</td></tr> </table>	32189	no	2	974c3387a13ecb9125159884e4079239da652b58
32189	no	2					
974c3387a13ecb9125159884e4079239da652b58							
Warnings:							
Information:							
Total Files Size (in bytes):			187067				
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.							

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.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875				Application or Docket Number 10/378,956		Filing Date 03/03/2003		☐ To be Mailed	
ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO									
APPLICATION AS FILED – PART I									
(Column 1)		(Column 2)							
FOR	NUMBER FILED	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), (l), 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(j))	minus 20 =	*			X \$	=			
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*			X \$	=			
☐ 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									
(Column 1)		(Column 2)		(Column 3)					
AMENDMENT	01/15/2015	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	* 29	Minus	** 36	= 0	X \$40 =		0	
	Independent (37 CFR 1.16(h))	* 2	Minus	***9	= 0	X \$210 =		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	
(Column 1)		(Column 2)		(Column 3)					
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$		=	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$		=	
	☐ 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. ** 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 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 NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/378,956	03/03/2003	Michael J. Zaworotko	U0157.70023US01	4742
23628 7590 06/16/2015 WOLF GREENFIELD & SACKS, P.C. 600 ATLANTIC AVENUE BOSTON, MA 02210-2206			EXAMINER JAVANMARD, SAHAR	
			ART UNIT 1627	PAPER NUMBER
			NOTIFICATION DATE 06/16/2015	DELIVERY MODE 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):

Patents_eOfficeAction@WolfGreenfield.com
WGS_eOfficeAction@WolfGreenfield.com

Office Action Summary	Application No. 10/378,956	Applicant(s) ZAWOROTKO ET AL.	
	Examiner SAHAR JAVANMARD	Art Unit 1627	AIA (First Inventor to File) 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 1/15/15.
☐ 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) 25,28,37,39-51,53-60 and 62-66 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) 25,28,37,39-51,53-60 and 62-66 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

Status of the Application

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

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 15, 2015 has been entered.

Claim(s) 25, 28, 37, 39-51, 53-60, and 62-66 are pending and examined herein.

Response to Arguments

In view of Applicant's amendments, any rejection not made of record in the Office action below is hereby withdrawn.

The rejections of record are set forth on record in the Non-Final Office action below as necessitated by amendment.

Double Patenting

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 claims at issue 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); and *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 a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit <http://www.uspto.gov/forms/>. The filing date of the application will determine what form 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 <http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp>.

Claims 25, 28, 37, 39-51, 53-60, and 62-66 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 37-50 and 52-58 of copending Application No. 14/179,862. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending claims are drawn to a pharmaceutical composition comprising a co-crystal comprising an API and a co-former (see claims for details), whereas the instant claims are drawn to the method of designing said co-crystals. The two inventions overlap greatly in scope and the utilities are the same.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 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.

Claims 25, 28, 39-42, 48-49, and 58 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by McCoy (CA 1148020A1).

McCoy teaches improved amino acid food additive comprising a uniform cocrystalline matrix of (1) an amino acid material, and (2) an "effective amount of a soluble edible cocrystallizer material, wherein said improved amino acid food additive is better-tasting, more stable and less hygroscopic than the amino acid material alone.

McCoy teaches the amino acid material is preferably selected from the group consisting of: lysine, tryptophan, methionine, threonine, phenylalanine, leucine, valine, isoleucine, histidine, cystine, cysteine, their derivatives, their salts and mixtures thereof. All nutritionally useful amino acids, their derivatives, particularly their salts and mixtures thereof are contemplated. The other essential component of the improved amino acid food additive is a soluble, edible, cocrystallizer material preferably selected from the group consisting of: alkali and alkaline earth metal salts of halides, phosphates and nitrates, polyhydric alcohols, crystalline cellulose, crystalline starches, crystalline organic acids and their salts, and mixtures thereof (page 6-7; page 15, Table II), meeting the limitations of claims 25, 39-42, 48-49, and 58.

McCoy teaches the method comprises dissolving at least one amino acid material in water along with an effective amount of at least one edible cocrystallizer material. The term "an effective amount" means "enough" to enable successful dehydration of the amino acid cocrystallizer solution. Then the solution is preferably neutralized to form a salt of the amino acid. Generally, an effective amount of cocrystallizer material will be such that the ratio by weight of the amount of cocrystallizer to the amount of edible amino acid salt is from about 0.9:1 to about 6:1. Preferably,

equal amounts of amino acid and cocrystallizer are used. The final pH range of the solution should be from about 2 to 7 and more preferably 4 to 7. The mixture is then dried using an appropriate technique. Freeze drying is preferred (page 6-7), meeting the limitations of claims 28.

Claim Rejections - 35 USC § 103

The following is a quotation of 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 of this title, 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 negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 46, 47, 50, 51, 53-57, 59, 60, and 62-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCoy (CA 1148020A1) as applied to claims 25, 28, 39-42, 48-49, and 58 in the 102(b) rejection above.

McCoy is discussed above.

McCoy identifies the amino acid food additive comprising a uniform cocrystalline matrix of (1) an amino acid material, and (2) an "effective amount of a soluble edible cocrystallizer material, however, specific examples wherein the homo- and heterosynthons as required by claims 50, 51, 53-57, 59, 60, and 62-66 are not explicitly exemplified.

Moreover, McCoy does not specifically teach the identification of the synthon from the crystal structure.

As discusses above, McCoy teaches specific amount of amino acid to co-crystallizer.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have envisioned the co-crystals as taught by McCoy to have also envisioned that the potential choices of amino acid material and cocrystallizer as taught could be formed in combinations with the same functionalities, giving rise to a homosynthon, or two different fuctionalities, giving rise to heterosynthons. Therefore, preparing and identifying the cocrystals, as required by the limitations of the instant claims, are well within the scope of the teachings of McCoy.

Claims 25, 28, 37, 39-43, 46-51, 53-60, and 62-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huffman (US Patent No. 3,664,858) of record.

Examiner respectfully notes at the outset that the instant invention is drawn to method of designing and preparing a co-crystal, wherein said method comprises a first chemical functionality and a co-crystal former. Applicant is labeling the first chemical functionality as an "API", however, it is respectfully pointed out that a recitation of an intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Thus in the instant case, if the first chemical functionality is capable of forming a co-crystal with a co-crystal former, then the limitations of the claims are met.

Thus the intended use recited in claim 25, namely that the first chemical functionality is an API, is not afforded patentable weight.

Huffman teaches co-crystal complexes or adducts of amines with aromatic hydroxy compounds.

Examples of organic acidic materials which have been found useful are carboxylic acid, sulfonic acid, phenolic, and fluorosulfone compounds. Typical examples

include the following, the name of the acid being followed by its pKa value where known: benzoic 4.17, o-chlorobenzoic 2.92, o-bromobenzoic 2.84, p-chlorobenzoic 3.98, o-hydroxybenzoic 2.97, 2,5-dihydroxybenzoic 2.94, 3,4-dihydroxybenzoic 4.48, o-nitrobenzoic 2.16, trihydroxybenzoic 1.68, o-iodobenzoic 2.85, 2,4-dinitrophenol 3.96, 3,6-dinitrophenol 5.15, gallic 4.41, trichlorophenol 6.00, trinitrophenol 0.80, o-chlorophenylacetic 4.07, o-chlorophenoxyacetic 3.05, o-bromophenoxyacetic 2.60, benzosulfonic 0.70, terephthalic 3.82, alpha naphthol 3.70, o-phthalic 2.89, naphthalenesulfonic 0.57, quinolinic 2.52, thiophencarboxylic 3.48, mandelic 3.85, maleic 1.83, furancarboxylic 3.15, dihydroxymalic 1.92, ascorbic 4.10, succinic 4.17, malonic 2.80, oxalic 1.46, glyoxylic 4.88, glycolic 3.83, trichloroacetic 4.08, fluoroacetic 2.66, citric, bis(trifluoromethylsulfanyl)methane, xanthanoic, thiophendicarboxylic, cyclohexanecarboxylic, norcamphoric, naphthalenedicarboxylic, naphthalenetetracarboxylic, mellitic, trimesic, biphenyldicarboxylic, resorcinol-o-acetic, anthracenecarboxylic, o-bromotoluic, p-bromomandelic, salicylacetic, dinitrophenylacetic, 2-furanacetate, 4-sulfobenzoic, 3-formylbenzoic, 5-formylsalicylic, lactic, phenanthrenecarboxylic, isophthalic, 2-cyclopentenecarboxylic, naphthylaminetrisulfonic, 5-chlorosalicylic, 3,5-dinitrotoluic, benzohydroxamic, indolecarboxylic, xanthenecarboxylic, 2,3 pyridinecarboxylic, pentanetricarboxylic, cyanoacetic (column 1-2, bridging paragraph).

Huffman teaches substantially stoichiometric proportions of amine and acid are normally preferred but other ratios are not precluded, provided that the adduct composition contains no free amine, since it is the liberation of the basic organic

nitrogen compound by heat-promoted dissociation of the adduct which initiates the color change.

Huffman teaches piperidine and morpholine are presently preferred examples of basic organic amino nitrogen compounds useful in the practice of the invention.

Primary, secondary and tertiary amines, and hydrazines, are useful. Typical examples include the following: triethanolamine, ethanolamine, cyclohexylamine, tributylamine, di-n-propylamine, isopropylamine, 2-amino-1-butanol, monoisopropanolamine, propylenediamine, isobutylamine, di-n-hexylamine, di-n-butylamine, hydrazine, di-isopropylamine, diamylamine, methylhydrazine, phenyl hydrazine, hexanediamine, methylaniline, aniline, guanidine, propylenediamine, polyglycolamine, ethylenediamine, diethylamine, diethanolamine, hydroxyethyl diethylenetriamine, isooctylamine, n-decylamine, methylethanolamine, tetramethylguanidine, methyl diethanolamine, 2-amino--propanediol, diethylaminopropylamine, amino-bispropylamine, benzylamine, morpholine, piperidine, dimethylformamide (column 2, lines 44-68).

In a typical preparation, salicylic acid (1.39 gm., 0.1 mol) and piperidine (0.85 gm., 0.1 mol) are mixed together in 20 grams of benzene, the mixture is evaporated to dryness, and the cocrystal adduct is washed with hexane and dried (column 2, lines 30-35).

Huffman does not teach the first chemical functionality as an API.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have envisioned that the adducts taught by Huffman, while not employed in the pharmaceutical art, can be formed regardless of the utility of the adduct. See *In re*

Dillon 16 U.S.Q.P.2d 1897, 1900 (CAFC 1990) (en banc) ("it is not necessary in order to establish a prima facie case of obviousness that both a structural similarity between a claimed and prior art compound (or a key component of a composition) be shown and that there be a suggestion in or expectation from the prior art that the claimed compound or composition will have the same or a similar utility as one newly discovered by applicant. To the extent that Wright suggests or holds to the contrary, it is hereby overruled. In particular, the statement that a prima facie obviousness rejection is not supported if no reference shows or suggests the newly-discovered properties and results of a claimed structure is not the law. ").

Therefore, it would have been obvious to one skilled in the art to envision the adducts disclosed by Huffman for pharmaceutical compositions.

Based on the foregoing arguments, the instant claims are deemed unpatentable over the cited art.

Conclusion

Claims 25, 28, 37, 39-51, 53-60, and 62-66 are not allowed.

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 <http://pair-direct.uspto.gov>. 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.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAHAR JAVANMARD whose telephone number is (571) 270-3280. The examiner can normally be reached on 8 AM-5 PM MON-FRI (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/SAHAR JAVANMARD/
Examiner, Art Unit 1627

Notice of References Cited	Application/Control No. 10/378,956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.	
	Examiner SAHAR JAVANMARD	Art Unit 1627	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N	CA 1148020A1	06-1983	CANADA	McCoy	---
	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.

Search Notes 	Application/Control No. 10378956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.
	Examiner SAHAR JAVANMARD	Art Unit 1627

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
424	400 (update 5/19/14)	9/30/2008	

SEARCH NOTES		
Search Notes	Date	Examiner
EAST (searched each inventor name)(update 6/17/10)	8/31/2009	SJ
EAST (keyword search)(update 6/17/10)	8/31/2009	SJ
Pubmed	8/31/2009	SJ
Google	8/31/2009	SJ
(update 6/11/15)		SJ
Google Patents (search amine acid cocrystal; aspirin cocrystal; bipyridine cocrystal)	6/11/2015	SJ

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

/S. J./ Examiner.Art Unit 1627	
-----------------------------------	--

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S2	2	("6559293").PN.	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2008/07/30 09:53
S3	1	aspirin cocrystal	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/12 14:28
S4	1	almarsson	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/12 14:29
S5	246	almarsson	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/12 14:29
S6	280	cocrystal	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/12 14:30
S7	5	S5 S6	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/12 14:30
S8	1303795	crystal	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/12 14:30
S9	102	S5 S8	US-	AND	OFF	2008/09/12

			PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT			14:30
S10	17	aspirin crystal	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/12 14:36
S11	1	wo "0151919"	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/12 14:51
S12	1	wo "0142222"	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/12 14:59
S13	4182	supramolecul\$2	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/12 15:00
S14	31445	aspirin	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/12 15:00
S15	157	S13 S14	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/12 15:00
S16	5	S13 S14	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	WITH	OFF	2008/09/12 15:00
S17	2200	active pharmaceutical ingredient	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO;	ADJ	OFF	2008/09/12 15:02

			DERWENT			
S18	19	S13 S17	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/12 15:02
S19	2	heterosynthon	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/12 15:04
S20	47880	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetaminophen	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2008/09/30 08:31
S21	1329	co crystal	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/30 08:31
S22	126	S20 S21	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 08:31
S23	18	S20 S21	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	SAME	OFF	2008/09/30 08:31
S24	2	S22 and @pd<"20020301"	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 08:45
S25	283	cocrystal	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2008/09/30 08:48
S26	18	S20 S25	US- PGPUB; USPAT; USOCR;	AND	OFF	2008/09/30 08:48

			FPRS; EPO; JPO; DERWENT			
S27	57	co crystal.ti.	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/30 09:39
S28	14	S27 drug	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 09:39
S29	458	Pharmaceutical co adj crystal compositions drugs	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 09:55
S30	543	Pharmaceutical co adj crystal composition drug	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 09:55
S31	543	Pharmaceutical (co adj crystal) composition drug	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 09:56
S32	29	Pharmaceutical (co adj crystal) composition drug	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	SAME	OFF	2008/09/30 09:56
S33	47	S31 and @pd< "20030303"	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 09:56
S34	119	crystal engineering	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2008/09/30 10:03
S35	32	S34 and @pd< "20030303"	US- PGPUB;	AND	OFF	2008/09/30 10:03

			USPAT; USOCR; FPRS; EPO; JPO; DERWENT			
S36	29	S34 drug	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:04
S37	4	S36 and @pd< "20030303"	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:04
S38	228231	crystallization	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:26
S39	7179	S20 S38	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:26
S40	200	S20 S38	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	SAME	OFF	2008/09/30 10:26
S41	132	S40 and @pd< "20030303"	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:26
S42	106	S20 S38	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	WITH	OFF	2008/09/30 10:26
S43	64	S42 and @pd< "20030303"	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:27

S44	472	cocrystallization	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:28
S45	41	S20 S44	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2008/09/30 10:28
S46	9	((MICHAEL) near2 (ZAWOROTKO)).INV.	US- PGPUB; USPAT	OR	OFF	2008/09/30 13:51
S47	5	((BRIAN) near2 (MOULTON)).INV.	US- PGPUB; USPAT	OR	OFF	2008/09/30 13:51
S48	5	((NAIR) near2 (RODRIGUEZ- HORNEDO)).INV.	US- PGPUB; USPAT	OR	OFF	2008/09/30 13:51
S49	77	(40/424).CCLS.	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2008/09/30 14:23
S50	8	(400/424).CCLS.	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2008/09/30 14:23
S51	9	((("7452555") or ("7446107") or ("7205413") or ("7078526"))).PN.	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2009/08/31 06:23
S52	4	("2003/0224006").URPN.	USPAT	OR	OFF	2009/08/31 06:38
S53	3	("2665277").PN.	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2009/08/31 07:13
S54	2904	active pharmaceutical ingredient	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/08/31 07:18

S55	53594	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetaminophen	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2009/08/31 07:18
S56	607	S54 S55	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 07:18
S57	335	cocrystal	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	NEAR	OFF	2009/08/31 07:19
S58	13	S56 S57	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 07:19
S59	27058	hydrogen bond	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/08/31 07:20
S60	28	S56 S59	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 07:20
S61	58	co-crystal former	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/08/31 07:21
S62	14	S55 S61	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 07:22
S63	2904	active pharmaceutical ingredient	US- PGPUB; USPAT; USOCR; FPRS;	ADJ	OFF	2009/08/31 08:44

			EPO; JPO; DERWENT			
S64	791	S63 crystal	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 08:44
S65	20	S63 cocrystal	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 08:44
S66	2904	active pharmaceutical ingredient	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/08/31 08:58
S67	53594	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetaminophen	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2009/08/31 08:58
S68	607	S67 S66	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 08:58
S69	210	S68 CRYSTAL	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/08/31 08:58
S70	4	((("7452555") or ("7446106") or ("7205413") or ("7078526")).PN.	USPAT	OR	OFF	2009/09/28 10:26
S71	95	phosphate hemihydrate	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/09/28 14:42
S72	54110	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetaminophen	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2009/09/28 14:42

S73	5	S72 S71	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/09/28 14:42
S74	2	((("3028420") or ("5521207"))).PN.	USPAT	OR	OFF	2009/09/28 14:52
S75	19	API cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2009/09/28 15:02
S76	0	ep "0548028"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/09/28 15:46
S77	6	supramolecular synthon	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2009/09/28 22:18
S78	20	US-2711411-\$.DID. OR US-4198507-\$.DID. OR US-4368197-\$.DID. OR US-4994604-\$.DID. OR US-5177262-\$.DID. OR US-5332834-\$.DID. OR US-5338644-\$.DID. OR US-5380867-\$.DID. OR US-5412094-\$.DID. OR US-5523090-\$.DID. OR US-5614342-\$.DID. OR US-5998413-\$.DID. OR US-6001996-\$.DID. OR US-6268385-\$.DID. OR US-6570036-\$.DID. OR US-20030162226-\$.DID. OR US-20030166581-\$.DID. OR US-20030224006-\$.DID. OR US-20040019211-\$.DID.	US-PGPUB; USPAT; USOCR; EPO; JPO	OR	OFF	2009/09/28 23:04
S79	20	US-20040106053-\$.DID. OR US-20040106055-\$.DID. OR US-20040171062-\$.DID. OR US-20040176335-\$.DID. OR US-20050070551-\$.DID. OR US-20050181041-\$.DID. OR US-20050169982-\$.DID. OR US-20050252649-\$.DID. OR US-20050256127-\$.DID. OR US-6559293-\$.DID. OR US-6699840-\$.DID. OR US-20040053853-\$.DID. OR US-3536809-\$.DID. OR US-3598123-\$.DID. OR US-3845770-\$.DID. OR US-3916899-\$.DID. OR US-4008719-\$.DID. OR US-4267179-\$.DID. OR US-4764604-\$.DID.	US-PGPUB; USPAT; USOCR; EPO; JPO	OR	OFF	2009/09/28 23:07
S80	15	US-4916134-\$.DID. OR US-5006513-\$.DID. OR US-5059595-\$.DID. OR US-	US-PGPUB;	OR	OFF	2009/09/28 23:08

		5073543-\$.DID. OR US-5120548-\$.DID. OR US-5354556-\$.DID. OR US-5414997-\$.DID. OR US-5474997-\$.DID. OR US-5591767-\$.DID. OR US-5633015-\$.DID. OR US-5639476-\$.DID. OR US-5661151-\$.DID. OR US-5674533-\$.DID. OR US-5707975-\$.DID. OR US-5733566-\$.DID.	USPAT; USOCR; EPO; JPO;			
S81	35195	bipyridine phthalaldehyde nicotinamide saccharin pyridinecarboxylic adj acid nitroisophthalic adj acid adamantanetetracarboxylic adj acid	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2010/06/17 10:11
S82	59011	aspirin ibuprofen flurbiprofen carbamazepine phenytoin acetaminophen	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2010/06/17 10:12
S84	2951	S81 S82	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2010/06/17 10:12
S85	1424	co-crystal	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2010/06/17 10:12
S86	39	S84 S85	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2010/06/17 10:12
S87	147955	(active pharmaceutical ingredient) or API	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2010/06/17 10:29
S88	725	S87 S81	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2010/06/17 10:29
S89	35	S88 S85	US- PGPUB; USPAT; USOCR;	AND	OFF	2010/06/17 10:29

			FPRS; EPO; JPO; DERWENT			
S90	3689	(active pharmaceutical ingredient)	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	OFF	2010/06/17 10:31
S91	143	S81 S90	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2010/06/17 10:31
S92	23	S91 S85	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2010/06/17 10:31
S93	11	((MICHAEL) near2 (ZAWOROTKO)).INV.	US- PGPUB; USPAT	OR	OFF	2010/06/17 10:36
S94	6	((BRIAN) near2 (MOULTON)).INV.	US- PGPUB; USPAT	OR	OFF	2010/06/17 10:36
S95	5	((NAIR) near2 (RODRIGUEZ- HORNEDO)).INV.	US- PGPUB; USPAT	OR	OFF	2010/06/17 10:36
S96	14	S93 S94 S95	US- PGPUB; USPAT	OR	OFF	2010/06/17 10:36
S97	103	S85 S81	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	OFF	2010/06/17 11:41
S98	14	((MICHAEL) near2 (ZAWOROTKO)).INV.	US- PGPUB; USPAT	OR	OFF	2010/10/13 10:14
S99	6	((BRIAN) near2 (MOULTON)).INV.	US- PGPUB; USPAT	OR	OFF	2010/10/13 10:14
S100	5	((NAIR) near2 (RODRIGUEZ- HORNEDO)).INV.	US- PGPUB; USPAT	OR	OFF	2010/10/13 10:14
S101	17	S98 S99 S100	US- PGPUB; USPAT	OR	OFF	2010/10/13 10:14
S102	160	ferrocene co-crystal	US- PGPUB; USPAT; USOCR;	AND	ON	2013/07/26 12:46

EAST Search History

			FPRS; EPO; JPO; DERWENT			
S103	0	S102 and @pd<"20020301"	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2013/07/26 12:46
S104	2	S102 and @pd<"20030301"	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2013/07/26 12:47
S105	8	((("3664858") or ("20140162989")).PN.	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/06/09 23:49
S106	1	CA "1148020" A1	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	ON	2015/06/11 09:10
S109	2	("6570036").PN.	US- PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2015/06/11 10:04

EAST Search History (Interference)

< This search history is empty >

6/ 11/ 2015 2:25:52 PM**C:\ Users\ sjavanmard\ Documents\ EAST\ Workspaces\ 10\ 10378956.wsp**

FORM PTO-1449/A and B (modified PTO/SB/08) INFORMATION DISCLOSURE STATEMENT BY APPLICANT				APPLICATION NO.: 10/378,956		ATTY. DOCKET NO.: U0157.70023US01	
				FILING DATE: March 3, 2003		CONFIRMATION NO.: 4742	
				FIRST NAMED INVENTOR: Michael J. Zaworotko			
				GROUP ART UNIT: 1627		EXAMINER: Sahar Javanmard	
Sheet	1	of	1				

U.S. PATENT DOCUMENTS

Examiner's Initials #	Cite No.	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication or Issue of Cited Document MM-DD-YYYY
		Number	Kind Code		
		3,664,858		Huffman	05-23-1972
		2014-0162989	A1	Zaworotko et al.	06-12-2014

FOREIGN PATENT DOCUMENTS

Examiner's Initials #	Cite No.	Foreign Patent Document			Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Translation (Y/N)
		Office/ Country	Number	Kind Code			

OTHER ART – NON PATENT LITERATURE DOCUMENTS

Examiner's 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, page(s), volume-issue number(s), publisher, city and/or country where published.	Translation (Y/N)

EXAMINER: /Sahar Javanmard/	DATE CONSIDERED: 06/11/2015
------------------------------------	------------------------------------

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

[NOTE – No copies of U.S. patents, published U.S. patent applications, or pending, unpublished patent applications stored in the USPTO's Image File Wrapper (IFW) system, are included. See 37 CFR § 1.98 and 1287OG163. Copies of all other patent(s), publication(s), unpublished, pending U.S. patent applications, or other information listed are provided as required by 37 CFR § 1.98 unless 1) such copies were provided in an IDS in an earlier application that complies with 37 CFR § 1.98, and 2) the earlier application is relied upon for an earlier filing date under 35 U.S.C. § 120.]

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.J./

<i>Index of Claims</i> 	Application/Control No. 10378956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.
	Examiner SAHAR JAVANMARD	Art Unit 1627

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

☐ Claims renumbered in the same order as presented by applicant		☐ CPA		☐ T.D.		☐ R.1.47			
CLAIM		DATE							
Final	Original	09/30/2008	09/28/2009	06/18/2010	07/01/2013	05/19/2014	06/11/2015		
	1	-	-	-	-	-	-		
	2	-	-	-	-	-	-		
	3	-	-	-	-	-	-		
	4	-	-	-	-	-	-		
	5	-	-	-	-	-	-		
	6	-	-	-	-	-	-		
	7	-	-	-	-	-	-		
	8	-	-	-	-	-	-		
	9	-	-	-	-	-	-		
	10	-	-	-	-	-	-		
	11	-	-	-	-	-	-		
	12	-	-	-	-	-	-		
	13	-	-	-	-	-	-		
	14	-	-	-	-	-	-		
	15	-	-	-	-	-	-		
	16	-	-	-	-	-	-		
	17	-	-	-	-	-	-		
	18	-	-	-	-	-	-		
	19	-	-	-	-	-	-		
	20	-	-	-	-	-	-		
	21	-	-	-	-	-	-		
	22	-	-	-	-	-	-		
	23	-	-	-	-	-	-		
	24	-	-	-	-	-	-		
	25	✓	✓	✓	✓	✓	✓		
	26	-	-	-	-	-	-		
	27	✓	✓	✓	✓	-	-		
	28	✓	✓	✓	✓	✓	✓		
	29	-	-	-	-	-	-		
	30	-	-	-	-	-	-		
	31	-	-	-	-	-	-		
	32	-	-	-	-	-	-		
	33	-	-	-	-	-	-		
	34	-	-	-	-	-	-		
	35	-	-	-	-	-	-		
	36	-	-	-	-	-	-		

Index of Claims 	Application/Control No. 10378956	Applicant(s)/Patent Under Reexamination ZAWOROTKO ET AL.
	Examiner SAHAR JAVANMARD	Art Unit 1627

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

☐ Claims renumbered in the same order as presented by applicant		☐ CPA		☐ T.D.		☐ R.1.47			
CLAIM		DATE							
Final	Original	09/30/2008	09/28/2009	06/18/2010	07/01/2013	05/19/2014	06/11/2015		
	37	✓	✓	✓	✓	✓	✓		
	38	✓	✓	✓	✓	-	-		
	39			✓	✓	✓	✓		
	40			✓	✓	✓	✓		
	41			✓	✓	✓	✓		
	42			✓	✓	✓	✓		
	43			○	✓	✓	✓		
	44			○	○	○	✓		
	45			○	○	○	✓		
	46			✓	✓	✓	✓		
	47			✓	✓	✓	✓		
	48			✓	✓	✓	✓		
	49			✓	✓	✓	✓		
	50				✓	✓	✓		
	51				✓	✓	✓		
	52				✓	✓	-		
	53				✓	✓	✓		
	54					✓	✓		
	55					✓	✓		
	56					✓	✓		
	57					✓	✓		
	58					✓	✓		
	59					✓	✓		
	60					✓	✓		
	61					✓	-		
	62					✓	✓		
	63					✓	✓		
	64					✓	✓		
	65					✓	✓		
	66					✓	✓		

To: Patents_eOfficeAction@WolfGreenfield.com,WGS_eOfficeAction@WolfGreenfield.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 23628

Jun 16, 2015 05:26:58 AM

Dear PAIR Customer:

WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 23628 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

Disclaimer:

The list of documents shown below is provided as a courtesy and is not part of the official file wrapper. The content of the images shown in PAIR is the official record.

Application	Document	Mailroom Date	Attorney Docket No.
10378956	CTNF	06/16/2015	U0157.70023US01
	892	06/16/2015	U0157.70023US01
	1449	06/16/2015	U0157.70023US01

To view your correspondence online or update your email addresses, please visit us anytime at <https://sportal.uspto.gov/secure/myportal/privatepair>.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

Docket No.: U0157.70023US01
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor: Michael J. Zaworotko
Application No.: 10/378,956
Confirmation No.: 4742
Filed: March 3, 2003
For: MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT
LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT
Examiner: S. Javanmard
Art Unit: 1627

Certificate of Electronic Filing Under 37 CFR 1.8

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

Dated: October 20, 2015

Signature: /Nancy J. Arsenault/ (Nancy J. Arsenault)

RESPONSE TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.111

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

Dear Sir:

INTRODUCTORY COMMENTS

This paper is filed in response to the Office Action dated June 16, 2015. The response includes the following:

Pending Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 7 of this paper.

4261077.1

PENDING CLAIMS

Listing of the Claims:

1-24. (Canceled)

25. (Previously Presented) A method for designing and preparing a co-crystal, said method comprising:

(a) providing an active pharmaceutical ingredient (API) comprising a first chemical functionality, wherein said first chemical functionality forms API homosynthons comprising a hydrogen bond;

(b) identifying and selecting a co-crystal former from among a plurality of candidate co-crystal formers by determining that said selected co-crystal former forms a supramolecular synthon via non-covalent hydrogen bonding between the first chemical functionality and a complementary second chemical functionality of the co-crystal former, wherein said selected co-crystal former in its pure form is a solid at room temperature and atmospheric pressure and wherein the co-crystal former is not an active pharmaceutical ingredient; and

(c) preparing a co-crystal comprising stoichiometric proportions of said API and said selected co-crystal former upon formation of said supramolecular synthon by said non-covalent bonding between said complementary second chemical functionality of said co-crystal former and said chemical functionality of said API, and wherein the first chemical functionality is a carboxylic acid, a carboxamide, a carbonyl or an amine.

26-27. (Canceled)

28. (Previously Presented) The method of claim 25, wherein said preparing comprises crystallization from solution, crystallization from a melt, sublimation, or grinding.

29-36. (Canceled)

37. (Previously Presented) The method according to claim 25, wherein said API is selected from aspirin, ibuprofen, flurbiprofen, carbamazepine, phenytoin or acetaminophen.
38. (Canceled)
39. (Previously Presented) The method of claim 25, wherein the co-crystal former is a GRAS compound.
40. (Previously Presented) The method of claim 25, wherein the co-crystal former is a food additive.
41. (Previously Presented) The method of claim 25, wherein the co-crystal former is a low toxicity organic.
42. (Previously Presented) The method of claim 25, wherein the co-crystal former is a metal organic complex.
43. (Previously Presented) The method of claim 25, wherein the co-crystal former comprises at least two heterocyclic groups.
44. (Previously Presented) The method of claim 25, wherein the co-crystal former is bipyridine.
45. (Previously Presented) The method of claim 25, wherein the co-crystal former is bis(pyridyl)ethene.
46. (Previously Presented) The method of claim 25, wherein said homosynthon is identified from the crystal structure of said API.

47. (Previously Presented) The method of claim 25, wherein said homosynthon is identified by determining the structure of at least one pure solid phase of said API.

48. (Previously Presented) The method of claim 25, wherein the complementary second chemical functionality is an unsaturated N-heterocycle, saturated N-heterocycle, aldehyde, amide, carboxylic acid, nitro, ketone, or sulfoxide.

49. (Previously Presented) The method of claim 25, wherein the complementary second chemical functionality is a carboxylic acid.

50. (Previously Presented) The method of claim 25, wherein said co-crystal comprises heterosynthons of said co-crystal former and said API.

51. (Previously Presented) The method of claim 25, wherein said co-crystal comprises homosynthons of said API.

52. (Canceled)

53. (Previously Presented) The method of claim 25, wherein said complementary second chemical functionality is an amine, amide, unsaturated aromatic nitrogen bases, or other chemical functionality that lacks a hydrogen bond donor, wherein no covalent bonds are formed upon said non-covalent bonding between said co-crystal former and said API.

54. (Previously Presented) The method of claim 25, wherein the non-covalent bonding between said co-crystal former and complementary second chemical functionality and said first chemical functionality of said API to form said supramolecular synthon comprises carbonyl:amine hydrogen bonding.

55. (Previously Presented) The method of claim 25, wherein the non-covalent bonding between said co-crystal former and complementary second chemical functionality and said first chemical functionality of said API to form said supramolecular synthon comprises carboxylic acid:pyridine hydrogen bonding.

56. (Previously Presented) The method of claim 51, wherein the non-covalent bonding of said homosynthons of said API is carboxylic acid:carboxylic acid hydrogen bonding.

57. (Previously Presented) The method of claim 51, wherein the non-covalent bonding of said homosynthons of said API is carboxamide:carboxamide hydrogen bonding.

58. (Previously Presented) A method for the preparation of a pharmaceutical product containing a co-crystal, said method comprising:

- (a) providing an active pharmaceutical ingredient (API) comprising a first chemical functionality, wherein said first chemical functionality forms a first crystal of API homosynthons that is non-covalent hydrogen bonding;
- (b) selecting a co-crystal former having a second chemical functionality complementary to the first chemical functionality via non-covalent bonding, wherein said co-crystal former forms a supramolecular synthon by non-covalent hydrogen bonding between the first chemical functionality of the API and the complementary second chemical functionality of said co-crystal former, wherein said selected co-crystal former in its pure form is a solid at room temperature and atmospheric pressure;
- (c) preparing a co-crystal of stoichiometric proportions of said API and said co-crystal former, said co-crystal consisting of said supramolecular synthon, and
- (d) combining said co-crystal with a pharmaceutically acceptable carrier to form the pharmaceutical product, and wherein the first chemical functionality is a carboxylic acid, a carboxamide, a carbonyl or an amine.

59. (Previously Presented) The method of claim 58, wherein said co-crystal comprises heterosynthons of said co-crystal former and said API.
60. (Previously Presented) The method of claim 58, wherein said co-crystal comprises homosynthons of said API.
61. (Canceled)
62. (Previously Presented) The method of claim 58, wherein said complementary second chemical functionality is an amine, amide, or unsaturated aromatic nitrogen base.
63. (Previously Presented) The method of claim 58, wherein the non-covalent bonding between said co-crystal former and complementary second chemical functionality and said first chemical functionality of said API to form said supramolecular synthon comprises carbonyl:amine hydrogen bonding.
64. (Previously Presented) The method of claim 58, wherein the non-covalent bonding between said co-crystal former and complementary second chemical functionality and said first chemical functionality of said API to form said supramolecular synthon comprises carboxylic acid:pyridine hydrogen bonding.
65. (Previously Presented) The method of claim 60, wherein the non-covalent bonding of said homosynthons of said API is carboxylic acid:carboxylic acid hydrogen bonding.
66. (Previously Presented) The method of claim 60, wherein the non-covalent bonding of said homosynthons of said API is carboxamide:carboxamide hydrogen bonding.

REMARKS

Applicant respectfully requests reconsideration. Claims 25, 28, 37, 39-51, 53-60, and 62-66 are pending in this application. No amendments to the claims are made herein. For consistency, a listing of the claims (claims 25, 28, 37, 39-51, 53-60, and 62-66) is reproduced above. No new matter has been added.

Double Patenting Rejection

The Examiner provisionally rejected claims 25, 28, 37, 39-51, 53-60 and 62-66 as allegedly being unpatentable over claims 37-50 and 52-58 of co-pending application 14/179,182.

Respectfully, Applicant does not concede to the rejection. Applicant also respectfully requests that this rejection be held in abeyance until the Examiner has agreed to otherwise allowable subject matter in the instant case. Only then can Applicant fashion an appropriate strategy and response.

Rejections Under 35 U.S.C. §102.

The Examiner rejected claims 25, 28, 39-42, 48-49, and 58 under 35 U.S.C. §102(b) as allegedly being anticipated by McCoy (CA 1148020A1). Reconsideration is respectfully requested in light of the arguments presented herein.

McCoy discloses improved amino acid food additives which comprises a uniform dehydrated cocrystalline matrix of (1) an amino acid material, and (2) an effective amount of a soluble edible cocrystallizer material. (McCoy, Abstract). McCoy discloses physical mixtures of multiple components in *non-stoichiometric* ratios. Indeed, McCoy discloses that “[g]enerally, an effective amount of cocrystallizer material will be such that the *ratio by weight* of the amount of cocrystallizer to the amount of edible amino acid salt is from about 0.9:1 to about 6:1. Preferably, equal amounts of cocrystallizer are used.” (McCoy, page 7, lines 10-15, emphasis added). The equal amounts of cocrystallizer disclosed by McCoy are equal amount by *weight*, not equal amount by *moles*. In contrast to the McCoy, the present claims require preparation of a co-crystal having

stoichiometric proportions of the active pharmaceutical ingredient (API) and the selected co-crystal former.

For at least these reasons, McCoy does not disclose each and every element of the claimed invention, and therefore cannot anticipate the claims. Applicant respectfully requests reconsideration and withdrawal of the rejection.

Rejections Under 35 U.S.C. §103

The Examiner rejected claims 46, 47, 50, 51, 53-57, 59, 60, and 62-66 under 35 U.S.C. §103(a) as being unpatentable over McCoy (CA 1148020A1) as applied to claims 25, 28, 39-42, 48-49, and 58 in the 35 U.S.C. §102(b) rejection above.

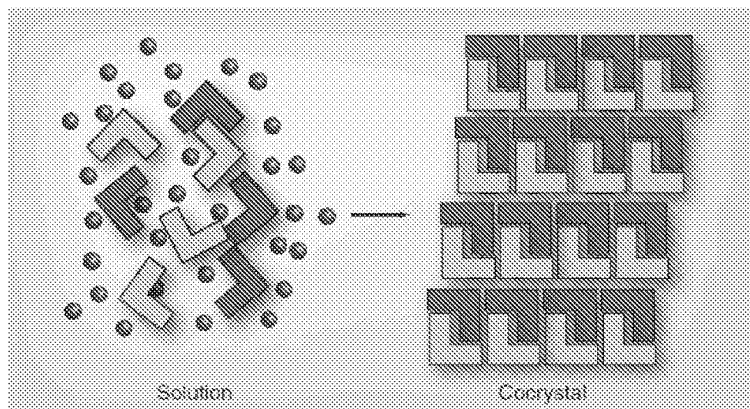
McCoy

In particular, the Examiner appreciates that McCoy does not disclose the specific examples of homo- and heterosynthons required by the claims. The Examiner also appreciates that McCoy does not disclose the identification of the synthon from the crystal structure. However, the Examiner alleged that it would have been obvious to one of skill in the art in view of McCoy to prepare and identify the co-crystals as claimed. Applicant traverses the rejection and requests reconsideration in light of the arguments presented herein.

As discussed above, McCoy discloses physical mixtures of multiple components in *non-stoichiometric* ratios. Indeed, the equal amounts of cocrystallizer disclosed by McCoy are equal amount by *weight*, not equal amount by *moles*. In contrast to the McCoy, the present claims require preparation of a co-crystal having *stoichiometric proportions* of the active pharmaceutical ingredient (API) and the selected co-crystal former. Such stoichiometric proportions are important for intermolecular interactions between two or more independent molecular entities in a co-crystal. Indeed, as provided in the review article by Almarsson, a copy of which is submitted herewith in connection with an Information Disclosure Statement, “[c]ocrystals are a class of crystalline solids that occur when complementary molecules of different structures are crystallized to form single

crystalline phases that contain stoichiometric ratios of the components” (Almarsson et al.; Pharm. Pat. Analyst 1(3):313-327 (2012)).

Co-crystal formers encompassed by the presently claimed methods also contribute to the co-crystal structure in that they are complementary in supramolecular chemistry, i.e., they form supramolecular synthons with the API molecules” (see, e.g., paragraph [0009] of the instant application). As discussed further below, these multiple-component solids “exhibit physical properties different from the parent pharmaceutical ingredient as a direct result of hydrogen bonding interaction”, which “can afford improved drug solubility, dissolution rate, stability and bioavailability, for example” (see, e.g., paragraph [0039] of the instant application). Figure 1 of Almarsson et al., reproduced below for the Examiner’s convenience, provides a prototypical example of a 1:1 composition co-crystal, and demonstrates that stoichiometric ratios of the complementary components permit formation of the co-crystal structure, e.g., a repeating array of molecules or ions in three dimensions.



Almarsson et al.; Pharm. Pat. Analyst 1(3):313-327 (2012) (page 314)

There is no evidence in McCoy that the mixture of the amino acid material and soluble edible cocrystallizer material in non-stoichiometric amounts leads to the formation of a crystalline structure, e.g., a repeating array of molecules or ions in three dimensions, for example, as opposed to an amorphous solid or some other structure. McCoy discloses freeze drying of the mixture of amino acid material and soluble edible cocrystallizer material. (McCoy, page 7, lines 17-19). One

of ordinary skill in the art would understand freeze drying to produce an amorphous solid or a mix of crystalline and amorphous phase (e.g., Bedu-Addo, Pharmaceutical Technology Lyophilization 10-18 2004; a copy of which is provided herewith in connection with an Information Disclosure Statement). However, one skilled in the art would also understand you would not use freeze drying in order to get an ordered supramolecular synthon as presently claimed.

For at least these reasons, McCoy does not teach or suggest the co-crystals of the present claims.

Huffman

The Examiner rejected claims 25, 28, 37, 39-43, 46-51, 53-60 and 62-66 under 35 U.S.C. §103(a) as allegedly being unpatentable over Huffman (US 3,664,858). Reconsideration is respectfully requested in light of the arguments presented herein.

Applicant respectfully disagrees with the Examiner's rejection. The Examiner has not established a prima facie case for rejecting the claims as being unpatentable over Huffman because (a) Huffman is not a proper reference for use in an obviousness rejection, (b) the Examiner has not met their burden of articulating the reasons for rejecting each and every limitation of the claims as pending, and (c) one of ordinary skill in the art would not have a reasonable expectation of success in forming a co-crystal of an API and have maintained activity and/or improved properties.

Huffman discloses heat-sensitive copy-sheet coatings (see, e.g. Abstract). Huffman discloses that such coatings and copy-sheets are useful in the preparation of projection transparencies (see, e.g., Column 1, lines 1-11).

As stated in MPEP §2141.01(a), "In order for a reference to be proper for use in an obviousness rejection under 35 U.S.C. 103, the reference must be analogous art to the claimed invention. In re Bigio, 381 F.3d 1320, 1325, 72 USPQ2d 1209, 1212 (Fed. Cir. 2004)." Also as stated in MPEP §2141.01(a), "a reference is analogous art to the claimed invention if: (1) the reference is from the same field of endeavor as the claimed invention (even if it addresses a different problem); or (2) the reference is reasonably pertinent to the problem faced by the inventor (even if it is not in the same field of endeavor as the claimed invention). See Bigio, 381 F.3d at

1325, 72 USPQ2d at 1212.” Huffman is not analogous art as required by MPEP §2141.01(a) as described above because it is not from the same field of endeavor as the claimed subject matter and the reference is not reasonably pertinent to the problem faced by the inventors.

With respect to the field of endeavor, the present claims are directed to methods relating to co-crystal formation with an active pharmaceutical ingredient (API) and therefore relate to the field of pharmaceutical arts. Huffman is related to improved projection transparencies, which is not the same field of endeavor as the pharmaceutical arts.

With respect to the problem faced and whether the reference is reasonably pertinent to that problem, as described in the application, “[u]ndesirable physicochemical properties, physiological barriers, or issues of toxicity often limit the therapeutic benefit of drugs” and crystalline self-assemblies may improve such characteristics, but “many drug molecules are prone to form multiple phases, and crystal size and morphology can vary for a given phase” and “physical properties of crystalline solids are critically dependent on the internal arrangement of molecules or ions, making prediction of composition, crystal structure and morphology from knowledge of molecular structure a scientific challenge of the highest order” (see, e.g., paragraphs [0003] and [0004]). The present application provides, as a solution to this problem, the “design of new pharmaceutical solid phases, such as multiple-component phases, using co-crystal formers that are complementary in the sense of supramolecular chemistry, i.e. they form supramolecular synthons with pharmaceutical molecules or ions” (see, e.g., paragraph [0009]). These multiple-component solids “exhibit physical properties different from the parent pharmaceutical ingredient as a direct result of hydrogen bonding interaction”, which “can afford improved drug solubility, dissolution rate, stability and bioavailability, for example” (see, e.g., paragraph [0039]).

In contrast, the problem faced in Huffman is that when heating prior art copy-sheets, “the sheet causes dissociation of the adduct with liberation of amine and formation of color-bodies” (see, e.g., column 1, lines 28-33). The solution provided by Huffman is “to produce clear transparent films and coatings containing heat-dissociable amine adducts in non-particulate form” as this coating “does not obscure desired colors or markings on the underlying carrier” and produces “excellent projection transparencies” (see, e.g., column 1, lines 34-40). Producing excellent

projection transparencies that do not obscure desired colors or markings is not reasonably pertinent to problem described in the instant application. As described in MPEP §2141.01(a), “[i]n order for a reference to be “reasonably pertinent” to the problem, it must “logically [] have commended itself to an inventor’s attention in considering his problem. ” In re Icon Health and Fitness, Inc., 496 F.3d 1374, 1379-80 (Fed. Cir. 2007) (quoting In re Clay, 966 F.2d 656,658, 23 USPQ2 1058, 1061 (Fed. Cir. 1992)).” The inventors would not have considered producing excellent projection transparencies that do not obscure desired colors or markings in solving the problem described in the instant application, which relates to the lack of rational design of crystalline pharmaceuticals, which was hampered by the multiple phases formed by most drugs. As a result, Huffman is not analogous art under MPEP §2141.01(a) and is not a proper reference for use in an obviousness rejection. For this reason alone, this rejection should be withdrawn.

Even if, *arguendo*, Huffman was a proper reference for use in an obviousness rejection, which Applicant asserts is not the case, the Examiner has not met his burden in articulating the reason for rejecting the claims based on Huffman alone, as Huffman provides no teaching or suggestion to make co-crystals, as recited in the present claims. Huffman makes salts rather than co-crystals. Huffman discloses mixtures of amines and acids, e.g., carboxylic acids. Indeed, one of ordinary skill in the art will readily appreciate that the amines disclosed in Huffman will deprotonate the carboxylic acids disclosed in Huffman to make salts. The present claims recite co-crystals.

Furthermore, Huffman provides no teaching or suggestion to use the adducts described therein in a pharmaceutical composition. The Examiner’s reason for arriving at the claimed subject matter, which relates to methods of preparing co-crystals (claim 25) and methods of preparing pharmaceutical compositions (claim 58), is that “it would have been obvious to one skilled in the art to envision the adducts disclosed by Huffman, while not employed in the pharmaceutical art, can be formed regardless of the utility of the adduct.” (Office Action, page 10). The Examiner provides no evidence or rationale to support this conclusory statement. As outlined in MPEP §2141, subsection III, “[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the

legal conclusion of obviousness.” KSR, 550 U.S. at 418, 82 USPQ2d at 1396.” Huffman provides no teaching or suggestion to use the adducts described therein in a method of designing and preparing a *co-crystal* comprising an *active pharmaceutical ingredient*. As a result, Huffman does not teach or suggest each and every limitation of claims 25 and 58 and therefore does not render obvious claims 25 and 58.

In addition, the Examiner states that “if the first chemical functionality is capable of forming a co-crystal with a co-crystal former, then the limitations of the claim are met.” (Office Action, page 8). The Examiner states that “the intended use recited in claim 25, namely that the first chemical functionality is an API, is not afforded patentable weight.” (Office Action, page 8). Applicant respectfully disagrees, and submits that the recitation of an API comprising a first chemical functionality should be given patentable weight.

It is well established that a claim term is to be accorded “the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention” (see *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005)). Phillips also indicated that evidence for the meaning of a term may be derived from “the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art” (see *Id.* at 1314). Applicant respectfully submits that the present specification supports an interpretation where the claim term “said selected co-crystal former forms a supramolecular synthon via non-covalent hydrogen bonding between the first chemical functionality and a complementary second chemical functionality of the co-crystal former” denotes an actual state that fundamentally ties the formation of the supramolecular synthon to the physical characteristics of the API. As a result, the disputed claim language reaches well beyond merely describing an intended use since the claims actively recite an actual configuration, e.g., non-covalent hydrogen bonding between an API and a complementary co-crystal former. The Examiner provides no reasoning why one of ordinary skill in the art would interpret the claim as merely reciting an intended use, as opposed to a state which ties the formation of the supramolecular synthon to the physical characteristics of the API.

In further support of the patentable weight of an API, Applicant submits that one of ordinary skill in the art would not have had a reasonable expectation of success in forming a co-crystal with an API. Moreover, one of ordinary skill in the art would not have had a reasonable expectation that a co-crystal of an API would be useful, e.g., maintain activity and/or have improved properties. Indeed, combining an API with a co-crystal co-former could have had a negative impact on the activity of the API, including decreased solubility, dissolution rate, stability, and/or bioavailability. However, the teachings of the instant application demonstrate the unpredictable finding that APIs could not only be used in co-crystals, but that the co-crystals exhibit *improved* characteristics as compared to the API alone. For example, the instant application provides, *inter alia*, methods relating to formation of multiple-component solids which “exhibit physical properties different from the parent pharmaceutical ingredient as a direct result of hydrogen bonding interaction”, and which “can afford improved drug solubility, dissolution rate, stability and bioavailability, for example” (see, e.g., paragraph [0039]).

Accordingly, claims 25 and 58 are patentable over Huffman. Claims 28, 39-43, 46-48, 50, 51, 53-55, 57-60, 62-64 and 66 all depend directly or indirectly from claim 25 or 58. Thus, dependent claims 28, 39-43, 46-48, 50, 51, 53-55, 57-60, 62-64 and 66 are also patentable over Huffman.

In view of the foregoing, the claims are non-obvious and withdrawal of the rejections is respectfully requested.

CONCLUSION

In view of the foregoing, the present application is believed to be in condition for allowance. A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the application in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825 under Docket No. U0157.70023US01 from which the undersigned is authorized to draw.

Dated: October 20, 2015

Respectfully submitted,

By____/Jessica R. Colantonio/_____
Edward R. Gates
Registration No.: 31,616
Jessica R. Colantonio, Ph.D.
Registration No.: 66,132
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)		Docket Number (Optional) U0157.70023US01																																			
Application Number 10/378,956-Conf. #4742		Filed March 3, 2003																																			
For MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT																																					
Art Unit 1627		Examiner S. Javanmard																																			
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): <table style="width: 100%; border-collapse: collapse;"><thead><tr><th></th><th style="text-align: center;"><u>Fee</u></th><th style="text-align: center;"><u>Small Entity Fee</u></th><th style="text-align: center;"><u>Micro Entity Fee</u></th><th></th></tr></thead><tbody><tr><td>☐ One month (37 CFR 1.17(a)(1))</td><td style="text-align: center;">\$200</td><td style="text-align: center;">\$100</td><td style="text-align: center;">\$50</td><td>\$ _____</td></tr><tr><td>☒ Two months (37 CFR 1.17(a)(2))</td><td style="text-align: center;">\$600</td><td style="text-align: center;">\$300</td><td style="text-align: center;">\$150</td><td>\$ 300.00</td></tr><tr><td>☐ Three months (37 CFR 1.17(a)(3))</td><td style="text-align: center;">\$1,400</td><td style="text-align: center;">\$700</td><td style="text-align: center;">\$350</td><td>\$ _____</td></tr><tr><td>☐ Four months (37 CFR 1.17(a)(4))</td><td style="text-align: center;">\$2,200</td><td style="text-align: center;">\$1,100</td><td style="text-align: center;">\$550</td><td>\$ _____</td></tr><tr><td>☐ Five months (37 CFR 1.17(a)(5))</td><td style="text-align: center;">\$3,000</td><td style="text-align: center;">\$1,500</td><td style="text-align: center;">\$750</td><td>\$ _____</td></tr></tbody></table> ☒ 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 <u>23/2825</u>. ☒ 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/inventor. ☐ assignee of record of the entire interest. See 37 CFR 3.71. 37 CFR 3.73(b) statement is enclosed (Form PTO/SB/96). ☒ attorney or agent of record. Registration number <u>66,132</u>. ☐ attorney or agent acting under 37 CFR 1.34. Registration number _____. <table style="width: 100%; border-collapse: collapse;"><tr><td style="width: 60%; text-align: center;">_____ /Jessica R. Colantonio/ Signature</td><td style="width: 40%; text-align: center;">_____ October 20, 2015 Date</td></tr><tr><td style="text-align: center;">_____ Jessica R. Colantonio, Ph.D. Typed or printed name</td><td style="text-align: center;">_____ 617.646.8000 Telephone Number</td></tr></table> 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 <u>1</u> forms are submitted.					<u>Fee</u>	<u>Small Entity Fee</u>	<u>Micro Entity Fee</u>		☐ One month (37 CFR 1.17(a)(1))	\$200	\$100	\$50	\$ _____	☒ Two months (37 CFR 1.17(a)(2))	\$600	\$300	\$150	\$ 300.00	☐ Three months (37 CFR 1.17(a)(3))	\$1,400	\$700	\$350	\$ _____	☐ Four months (37 CFR 1.17(a)(4))	\$2,200	\$1,100	\$550	\$ _____	☐ Five months (37 CFR 1.17(a)(5))	\$3,000	\$1,500	\$750	\$ _____	_____ /Jessica R. Colantonio/ Signature	_____ October 20, 2015 Date	_____ Jessica R. Colantonio, Ph.D. Typed or printed name	_____ 617.646.8000 Telephone Number
	<u>Fee</u>	<u>Small Entity Fee</u>	<u>Micro Entity Fee</u>																																		
☐ One month (37 CFR 1.17(a)(1))	\$200	\$100	\$50	\$ _____																																	
☒ Two months (37 CFR 1.17(a)(2))	\$600	\$300	\$150	\$ 300.00																																	
☐ Three months (37 CFR 1.17(a)(3))	\$1,400	\$700	\$350	\$ _____																																	
☐ Four months (37 CFR 1.17(a)(4))	\$2,200	\$1,100	\$550	\$ _____																																	
☐ Five months (37 CFR 1.17(a)(5))	\$3,000	\$1,500	\$750	\$ _____																																	
_____ /Jessica R. Colantonio/ Signature	_____ October 20, 2015 Date																																				
_____ Jessica R. Colantonio, Ph.D. Typed or printed name	_____ 617.646.8000 Telephone Number																																				

Certificate of Electronic Filing Under 37 CFR 1.8	
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).	
Dated: October 20, 2015	Electronic Signature for Nancy J. Arsenault: /Nancy J. Arsenault/

4339029.1

Electronic Patent Application Fee Transmittal				
Application Number:		10378956		
Filing Date:		03-Mar-2003		
Title of Invention:		Multiple-component solid phases containing at least one active pharmaceutical ingredient		
First Named Inventor/Applicant Name:		Michael J. Zaworotko		
Filer:		Jessica Russell Colantonio/Nancy Arsenault		
Attorney Docket Number:		U0157.70023US01		
Filed as Small Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension - 2 months with \$0 paid	2252	1	300	300
Miscellaneous:				
Total in USD (\$)				300

Electronic Acknowledgement Receipt	
EFS ID:	23837689
Application Number:	10378956
International Application Number:	
Confirmation Number:	4742
Title of Invention:	Multiple-component solid phases containing at least one active pharmaceutical ingredient
First Named Inventor/Applicant Name:	Michael J. Zaworotko
Customer Number:	23628
Filer:	Jessica Russell Colantonio/Nancy Arsenault
Filer Authorized By:	Jessica Russell Colantonio
Attorney Docket Number:	U0157.70023US01
Receipt Date:	20-OCT-2015
Filing Date:	03-MAR-2003
Time Stamp:	15:32:27
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	\$ 300
RAM confirmation Number	2005
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	Miscellaneous Incoming Letter	U015770023US01-TRN-JRC.pdf	24620 29da21e46d28417771c6cc7bba6fbcab829d0a30	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	U015770023US01-FEE-JRC.pdf	31585 c16c7541dc0a56ce07bc1f20e170f934604a7856	no	1
Warnings:					
Information:					
3		U015770023US01-RESP-JRC.pdf	165073 ebaec862246940b0b816ddb15f679aa71cd652	yes	15
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	6	
	Applicant Arguments/Remarks Made in an Amendment		7	15	
Warnings:					
Information:					
4	Extension of Time	U015770023US01-EXT-JRC.pdf	23423 3f633fe884c391bf0502a39efde8db3025d19882	no	1
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	30420 33ac33dfa0e9c2c75efc345820a69c0432e3bd00	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			275121		

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.

TRANSMITTAL FORM <i>(to be used for all correspondence after initial filing)</i>	Application Number	10/378,956-Conf. #4742
	Filing Date	March 3, 2003
	First Named Inventor	Michael J. Zaworotko
	Art Unit	1627
	Examiner Name	S. Javanmard
Total Number of Pages in This Submission	Attorney Docket Number	U0157.70023US01

ENCLOSURES (Check all that apply)		
☒ Fee Transmittal Form ☐ Fee Attached ☒ Amendment/Reply ☐ After Final ☐ Affidavits/declaration(s) ☒ Extension of Time Request ☐ Express Abandonment Request ☐ Information Disclosure Statement ☐ Certified Copy of Priority Document(s) ☐ Reply to Missing Parts/ Incomplete Application ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53	☐ Drawing(s) ☐ Licensing-related Papers ☐ Petition ☐ Petition to Convert to a Provisional Application ☐ Power of Attorney, Revocation Change of Correspondence Address ☐ Terminal Disclaimer ☐ Request for Refund ☐ CD, Number of CD(s) _____ ☐ Landscape Table on CD	☐ After Allowance Communication to TC ☐ Appeal Communication to Board of Appeals and Interferences ☐ Appeal Communication to TC (Appeal Notice, Brief, Reply Brief) ☐ Proprietary Information ☐ Status Letter ☐ Other Enclosure(s) (please Identify below):
Remarks		

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT			
Firm Name	WOLF, GREENFIELD & SACKS, P.C.		
Signature	/Jessica R. Colantonio/		
Printed name	Jessica R. Colantonio, Ph.D.		
Date	October 20, 2015	Reg. No.	66,132

Certificate of Electronic Filing Under 37 CFR 1.8	
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).	
Dated: October 20, 2015	Electronic Signature for Nancy J. Arsenaault: /Nancy J. Arsenaault/

4339028.1

FEE TRANSMITTAL		Complete if known	
☒ 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.		Application Number	10/378,956-Conf. #4742
		Filing Date	March 3, 2003
		First Named Inventor	Michael J. Zaworotko
		Examiner Name	S. Javanmard
		Art Unit	1627
TOTAL AMOUNT OF PAYMENT		(\$)	300.00
		Practitioner Docket No.	U0157.70023US01

METHOD OF PAYMENT (check all that apply)
☐ Check ☒ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____
☐ Deposit Account Deposit Account Number: 23/2825 Deposit Account Name: Wolf, Greenfield & Sacks, P.C.
 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)

Application Type	FILING FEES			SEARCH FEES			EXAMINATION FEES			Fees Paid (\$)
	U (\$)	S (\$)	M (\$)	U (\$)	S (\$)	M (\$)	U (\$)	S (\$)	M (\$)	
Utility	280	140*	70	600	300	150	720	360	180	
Design	180	90	45	120	60	30	460	230	115	
Plant	180	90	45	380	190	95	580	290	145	
Reissue	280	140	70	600	300	150	2,160	1,080	540	
Provisional	260	130	65	0	0	0	0	0	0	

* The \$140 small entity status filing fee for a utility application is further reduced to \$70 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)	80	40	20
Each independent claim over 3 (including Reissues)	420	210	105
Multiple dependent claims	780	390	195

Total Claims	Extra Claims	Fee (\$)	Fee Paid (\$)	Multiple Dependent Claims	Fee (\$)	Fee Paid (\$)
- or HP = _____ x _____ = _____ HP = highest number of total claims paid for, if greater than 20.						
Indep. Claims Extra Claims Fee (\$) Fee Paid (\$) - or HP = _____ x _____ = _____ HP = highest number of independent claims paid for, if greater than 3.						

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 \$400 (\$200 for small entity) (\$100 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 _____ = _____				

4. OTHER FEE(S)

	Fees Paid (\$)
Non-English specification, \$130 fee (no small or micro entity discount)	
Non-electronic filing fee under 37 CFR 1.16(t) for a utility application, \$400 fee (\$200 small or micro entity)	
Other (e.g., late filing surcharge): <u>2252</u> Extension for response within second month	300.00

SUBMITTED BY			
Signature	/Jessica R. Colantonio/	Registration No. (Attorney/Agent)	66,132
Telephone	617.646.8000		
Name (Print/Type)	Jessica R. Colantonio, Ph.D.	Date	October 20, 2015

Certificate of Electronic Filing Under 37 CFR 1.8	
I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).	
Dated: October 20, 2015	Electronic Signature for Nancy J. Arsenaault: /Nancy J. Arsenaault/

4339027.1

FORM PTO-1449/A and B (modified PTO/SB/08) INFORMATION DISCLOSURE STATEMENT BY APPLICANT				APPLICATION NO.: 10/378,956		ATTY. DOCKET NO.: U0157.70023US01			
				FILING DATE: March 3, 2003		CONFIRMATION NO.: 4742			
				FIRST NAMED INVENTOR: Michael J. Zaworotko					
				GROUP ART UNIT: 1627		EXAMINER: Sahar Javanmard			
Sheet	1	of	1						

U.S. PATENT DOCUMENTS

Examiner's Initials #	Cite No.	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication or Issue of Cited Document MM-DD-YYYY
		Number	Kind Code		

FOREIGN PATENT DOCUMENTS

Examiner's Initials #	Cite No.	Foreign Patent Document			Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Translation (Y/N)
		Office/ Country	Number	Kind Code			

OTHER ART – NON PATENT LITERATURE DOCUMENTS

Examiner's 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, page(s), volume-issue number(s), publisher, city and/or country where published.	Translation (Y/N)
		[NO AUTHOR LISTED], Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances Q6A. ICH Harmonised Tripartite Guideline. 1999 Oct 6; 4:46.	
		[NO AUTHOR LISTED], X-ray Diffraction. In: The United States Pharmacopeia – The National Formulary (USP #24 NF19). 2000 Jan. Chapter 941: 2005-7	
		ABOURAHMA et al., Network Hydrogen Bonding in Two New Cocrystals Sustained by [Mn(CO)3(OH)]4, a tetrahedral hydrogen bond donor. J Chem Crystallogr. 1995 Nov; 25:731-736.	
		ALMARSSON et al., The A to Z of pharmaceutical cocrystals: a decade of fast-moving new science and patents. Pharm Pat Anal. 2012 Jul;1(3):313-27. doi: 10.4155/ppa.12.29.	
		BEDU-ADDO, Understanding Lyophilization Formulation Development. Pharmaceutical Technology. 2004 Mar: 10-18.	
		BERGE et al., Pharmaceutical salts. J Pharm Sci. 1977 Jan;66(1):1-19.	
		BYRN et al., Pharmaceutical solids: a strategic approach to regulatory considerations. Pharm Res. 1995 Jul;12(7):945-54.	

EXAMINER:	DATE CONSIDERED:
-----------	------------------

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

[NOTE – No copies of U.S. patents, published U.S. patent applications, or pending, unpublished patent applications stored in the USPTO's Image File Wrapper (IFW) system, are included. See 37 CFR § 1.98 and 1287OG163. Copies of all other patent(s), publication(s), unpublished, pending U.S. patent applications, or other information listed are provided as required by 37 CFR § 1.98 unless 1) such copies were provided in an IDS in an earlier application that complies with 37 CFR § 1.98, and 2) the earlier application is relied upon for an earlier filing date under 35 U.S.C. § 120.]