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APPLICATION NUMBER: *14/179,862*
FILING DATE: *February 13, 2014*

By Authority of the
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and Director of the United States Patent and Trademark Office

Rodney Glover
Certifying Officer


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Disc 1 of 1

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Application Number: 14179862 Document Date: 02/13/2014

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NOVARTIS EXHIBIT 1516
Novartis v. Regents, IPR2023-01347

PTO/AIA/15 (03-13)
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UTILITY PATENT APPLICATION TRANSMITTAL

(ONLY FOR NEW NONPROVISIONAL APPLICATIONS UNDER 37 CFR 1.53(B))

Attorney Docket No.	U0157.70023US02
First Named Inventor	Michael J. Zaworotko
Title	MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT
Express Mail Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. [X] **Fee Transmittal Form** (PTO/SB/17 or equivalent)
2. [X] **Applicant asserts small entity status.** See 37 CFR 1.27
3. [ ] **Applicant certifies micro entity status.** See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. [X] **Specification** [*Total Pages* 42]
   Both the claims and abstract must start on a new page.
   (See MPEP § 608.01(a) for information on the preferred arrangement)
5. [X] **Drawing(s)** *(35 U.S.C. 113)* [*Total Sheets* 25]
6. **Inventor's Oath or Declaration** [*Total Pages* 3]
   (including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))
   a. [X] Newly executed (original or copy)
   b. [ ] A copy from a prior application (37 CFR 1.63(d))
7. [X] **Application Data Sheet** **See note below.*
   See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
8. [ ] **CD-ROM or CD-R**
   In duplicate, large table, or Computer Program *(Appendix)*
   [ ] Landscape Table on CD
9. **Nucleotide and/or Amino Acid Sequence Submission** *(if applicable, items a. – c. are required)*
   a. [ ] Computer Readable Form (CRF)
   b. Specification Sequence Listing on:
      i. [ ] CD-ROM or CD-R (2 copies); or ii. [ ] Paper
   c. [ ] Statements verifying identity of above copies

ADDRESS TO: **Commissioner for Patents**
P.O. Box 1450
Alexandria, VA 22313-1450

ACCOMPANYING APPLICATION PARTS

10. [ ] **Assignment Papers**
    (cover sheet & document(s))
    Name of Assignee
11. [ ] **37 CFR 3.73(c) Statement** *(when there is an assignee)* [ ] **Power of Attorney**
12. [ ] **English Translation Document** *(if applicable)*
13. [X] **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    [X] Copies of citations attached
14. [X] **Preliminary Amendment**
15. [ ] **Return Receipt Postcard** *(MPEP § 503) (Should be specifically itemized)*
16. [ ] **Certified Copy of Priority Document(s)** *(if foreign priority is claimed)*
17. [ ] **Nonpublication Request** Under 35 U.S.C.122 (b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
18. [x] Other: Request for Prioritized Examination
    Petition Under 37 CFR 1.84(a)(2)

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

18. CORRESPONDENCE ADDRESS

[X] The address associated with Customer Number: 23628 *OR* [ ] Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	/Edward R. Gates/	Date	February 13, 2014
Name (Print/Type)	Edward R. Gates	Registration No. (Attorney/Agent)	31,616

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FEE TRANSMITTAL

Complete if known	
Application Number	Not Yet Assigned
Filing Date	Concurrently Herewith
First Named Inventor	Michael J. Zaworotko
Examiner Name	Not Yet Assigned
Art Unit	Not Yet Assigned
Practitioner Docket No.	U0157.70023US02

[X] Applicant asserts small entity status. See 37 CFR 1.27

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

TOTAL AMOUNT OF PAYMENT ($) 2,870.00

METHOD OF PAYMENT (check all that apply)

[ ] Check [X] 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**
[X] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17
[X] 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	730.00
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 ($)	Fee Paid ($)
_____ - 20 or HP =	_____ x	_____ =	_____

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

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

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
_____ - 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)

		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):	2817 Request for prioritized examination	2,000.00
	2830 Processing fee, except in provisional applications	70.00
	2464 Petitions requiring the petition fee set forth in...	70.00
	1504 Publication fee for early, voluntary, or normal...	0.00

SUBMITTED BY

Signature	/Edward R. Gates/	Registration No. (Attorney/Agent)	31,616	Telephone	617.646.8000
Name (Print/Type)	Edward R. Gates			Date	February 13, 2014

3436578.1

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (03-13)

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

First Named Inventor:	Michael J. Zaworotko	Nonprovisional Application Number (if known):	Not Yet Assigned
Title of Invention:	MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT		

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

1. The processing fee set forth in 37 CFR 1.17(i)(1), the prioritized examination fee set forth in 37 CFR 1.17(c), and if not already paid, the publication fee set forth in 37 CFR 1.18(d) have been filed with the request. The basic filing fee, search fee, examination fee, and any required excess claims and application size fees are filed with the request or have been already been paid.
2. The application contains or is amended to contain no more than four independent claims and no more than thirty total claims, and no multiple dependent claims.
3. The applicable box is checked below:

I. [x] **Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)**

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

---OR---

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

ii The executed inventor's oath or declaration is filed with the application. (37 CFR 1.63 and 1.64)

II. [ ] **Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)**

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

Signature	/Edward R. Gates/	Date	February 13, 2014
Name (Print/Typed)	Edward R. Gates	Practitioner Registration Number	31,616

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

[ ] *Total of 1 forms are submitted.

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Application Data Sheet

Inventor Information

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Correspondence Information

Correspondence Customer Number::	23628

Application Information

Application Type::	Regular
Subject Matter::	Utility
CD-ROM or CD-R?::	None
Sequence submission?::	None
Computer Readable Form (CRF)?::	No

Title::	MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT
Attorney Docket Number::	U0157.70023US02
Request for Early Publication?::	No
Request for Non-Publication?::	No
Total Drawing Sheets::	25
Small Entity?::	Yes
Petition included?::	Yes
Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2::	No
Authorization to Permit Access to the Instant Application by the Participating Offices::	No

Representative Information

Representative Customer Number::	23628

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Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This Application	Continuation of	10/378956	03/03/03
10/378956	An application claiming the benefit under 35 USC 119(e)	60/360768	03/01/02

Applicant Information

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Applicant Type::	Assignee
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City of mailing address::	Ann Arbor
State or Province of mailing address::	MI
Postal or Zip Code of mailing address::	48109-1280

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.			
Signature	/Edward R. Gates/	Date	February 13, 2014
Name (Print/Type)	Edward R. Gates	Registration No. (Attorney/Agent)	31,616

DESCRIPTION

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

CROSS-REFERENCE TO RELATED APPLICATION

The present application is a continuation of U.S. Application Serial No. 10/378,956, filed March 2, 2003, which is hereby incorporated by reference herein in its entirety, including any figures, tables, or drawings. U.S. Application Serial No. 10/378,956 claims the benefit of priority of U.S. Provisional Application Serial No. 60/360,768, filed March 1, 2002, which is hereby incorporated by reference herein in its entirety, including any figures, tables, or drawings.

BACKGROUND OF THE INVENTION

[0001] The last decade has witnessed tremendous advances in the understanding of, and the ability to manipulate, molecular and supramolecular assemblies (Moulton, B. *et al.*, *Chem. Rev.*, 2001, 101:1629-1658). There are new paradigms concerning the design and synthesis of a new generation of functional materials and molecules. Such advances are a consequence of the fundamental importance of intermolecular interactions, structure and cooperativity in many aspects of molecular science, from environmental science to molecular biology, to pharmacology, to materials science. Thus, the prospects for control and manipulation of materials at the molecular level, particularly in areas related to non-covalent bonding and nanotechnology, are now truly exceptional. However, whereas crystal structure determination has been a tool used by scientists since the 1920's, crystal structure prediction remains a largely unmet goal (Ball, P. *Nature*, 1996, 381:648-650; Gavezzotti, A. *Acc. Chem. Res.*, 1994, 27:309-314). Furthermore, the existence of more than one crystalline form of a given molecular compound, typically in the form of polymorphs or solvates, represents both a problem and an opportunity (Desiraju, G.R. *Science*, 1997, 278:404-405; Bernstein, J. *et al.*, *Angew. Chem., Int. Ed. Engl.*, 1999, 38:3441-3461). This is particularly true for the pharmaceutical industry.

[0002] Crystal engineering (Schmidt, G.M.J. *Pure Appl. Chem.*, 1971, 27:647-678; Desiraju, G.R. *Crystal Engineering: the Design of Organic Solids*, 1989, Elsevier: Amsterdam) is predicated on the assumption that crystals are *de facto* examples of self-assembly, *i.e.* crystals

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are comprised from a series of molecular recognition events or *supramolecular synthons* (Desiraju, G.R. *Angew. Chem., Int. Ed. Engl.*, 1995, 34:2311-2327). It also offers a more realizable goal than crystal structure prediction since it relies on design and allows for careful selection of substrates, *i.e.* substrates that are predisposed to form predictable self-assembled superstructures can be targeted for study. Furthermore, the prototypal molecules used in crystal engineering contain exofunctional molecular recognition sites and they can be complementary with themselves (self-assembly) (Boucher, E. *et al.*, *J. Org. Chem.*, 1995, 60:1408-1412) or with other molecules (modular self-assembly) (Zaworotko, M.J. *Chem. Soc. Rev.*, 1994, 23:283-288; Sharma, C.V.K. and M.J. Zaworotko *Chem. Commun.*, 1996, 2655-2656). Coincidentally, most pharmaceutical molecules also contain exterior molecular recognition sites and, although this makes them susceptible to polymorphism and solvate formation, it also makes them attractive candidates for crystal engineering studies.

[0003] The ability of crystalline self-assemblies to be built from a bottom-up approach (Feynman, R. *Engineering and Science*, 1960, 22-36) could provide an exceptional control of the design of new phases at a molecular level. This contrasts with the current state-of-the-art: "The number of forms known for a given compound is proportional to the time and money spent in research on that compound" (McCrone, W.C. *Polymorphism in Physics and Chemistry of the Organic Solid-State*, pp. 726, Fox *et al.* Eds., Interscience: New York, 1965). This statement summarizes the predicaments and opportunities that one faces when dealing with a need to assert control over the composition and structure of pharmaceutical compounds in the solid state. Specifically, 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. However, crystal structure prediction and even prediction of composition remains a largely unmet goal. Nonetheless, crystal engineering offers the intriguing possibility of using molecular components for their ability to impart functional characteristics (such as solubility, dissolution rate and stability) for the development of new delivery systems.

[0004] Undesirable physicochemical properties, physiological barriers, or issues of toxicity often limit the therapeutic benefit of drugs. This has motivated research in drug delivery systems for poorly soluble, poorly absorbed and labile substances. Crystalline self-assemblies represent a promising delivery modality for improving drug solubility, dissolution rate, stability

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and bioavailability. In addition, enhancement of drug activity can be achieved by means of inclusion complexation or molecular encapsulation. These systems offer various advantages over amorphous polymeric delivery systems both from design and stability perspectives. In this context, the existence of more than one crystalline form of a given compound, typically in the form of polymorphs or solvates, represents both a problem and an opportunity. Several factors further complicate the situation. For example, the Food and Drug Administration's (FDA's) strict purity requirements effectively mean that a particular crystalline phase of a drug must be selected and that its composition must be established. This has typically meant that a consistent X-ray powder diffraction (XPD) pattern is required (Federal Drug Administration *Fed. Regist.*, 1997, 62:62893-62894). The need to ensure that processing produces both purity and ease of processing is problematic because many drug molecules are prone to form multiple phases, and crystal size and morphology can vary for a given phase. The commercial and public image costs of not ensuring that processing is reliable and reproducible is at best very high, as demonstrated by the recent pull back and reformulation of NORVIR by ABBOTT LABORATORIES).

[0005] That XPD patterns have been relied on for quality control is convenient but is in many ways unfortunate since XPD is not as foolproof as single crystal X-ray crystallography (*e.g.* similar patterns can be obtained for different phases, composition is not unambiguously determined), and XPD does not determine crystal packing. Knowledge of crystal packing is important because it helps explain the solubility and composition of a particular phase and provides other valuable information. However, the materials properties of pharmaceuticals and the existence of polymorphs are generally investigated at the tail end of the drug development process.

[0006] Accordingly, it would be advantageous to provide novel crystalline phases having properties, such as melting point, solubility, dissolution rate, chemical stability, thermodynamic stability, and/or bioavailability, which are different from existing solid forms of the pharmaceutical compound upon which they are based.

BRIEF SUMMARY OF THE INVENTION

[0007] The subject invention relates to the application of the concepts of crystal engineering towards the design of new pharmaceutical phases that contain more than one molecular component.

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[0008] The subject invention concerns multiple-component solids having at least one active pharmaceutical ingredient. Examples of pharmaceutical molecules that may be utilized as active pharmaceutical ingredients in the multiple-component solids of the subject invention include, but are not limited to, aspirin, one or more members of the profen series (*e.g.*, ibuprofen and flurbiprofen), carbamazepine, phenytoin, and acetaminophen. Multiple-component solids, such as multiple-component crystals, containing these pharmaceutical ingredients and complementary molecules (hereafter referred to as "co-crystal formers") have been characterized by various techniques and can exhibit physical and/or chemical properties that are the same or different from the parent pharmaceutical ingredient as a direct result of alternative molecular recognition patterns. These novel crystalline assemblies can afford improved drug solubility, dissolution rate, stability and bioavailability.

[0009] The subject invention relates to the application of the concepts of crystal engineering towards the design of new pharmaceutical solid phases, such as multiple-component phases, using cocrystal formers that are complementary in the sense of supramolecular chemistry, *i.e.* they form supramolecular synthons with pharmaceutical molecules or ions. The cocrystal formers can be, but are not limited to, solvent molecules, other drug molecules, GRAS compounds, or approved food additives. Pharmaceutical molecules or ions are inherently predisposed for such crystal engineering studies since they already contain molecular recognition sites that bind selectively to biomolecules, and they are prone to supramolecular self-assembly. Examples of the groups commonly found in active pharmaceutical ingredients, and which are capable of forming supramolecular synthons include, but are not limited to, acids, amides, aliphatic nitrogen bases, unsaturated aromatic nitrogen bases (*e.g.* pyridines, imidazoles), amines, alcohols, halogens, sulfones, nitro groups, S-heterocyles, N-heterocycles (saturated or unsaturated), and O-heterocycles. Other examples include ethers, thioethers, thiols, esters, thioesters, thioketones, epoxides, acetonates, nitrils, oximes, and organohalides. Some of these groups can form supramolecular synthons with identical groups in similar or different molecules and are termed homosynthons, *e.g.* acids and amides. Other groups can form supramolecular synthons with different groups and are termed heterosynthons, *e.g.* acide/amide, pyridine/amide; alcohol/amine. Heterosynthons are particularly suitable for formation of multiple-component crystals whereas homosynthons can sometimes form multiple-component crystals.

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[0010] In one aspect, the subject invention concerns methods for identifying complementary chemical functionalities to form a desired supramolecular synthon, wherein the method comprises the steps of evaluating the structure of an active pharmaceutical ingredient (API), which can include determining its crystal structure; determining whether the API contains chemical functionalities capable of forming supramolecular synthons with itself; identifying from a plurality of chemical functionalities that are known to form a supramolecular synthon at least one chemical functionality that will form a further supramolecular synthon to the supramolecular synthon formed by the API, wherein the identified chemical functionality is not capable of disrupting non-covalent bonding within the supramolecular synthon formed by the supramolecular synthon formed by the API, and wherein the selected chemical functionality is capable of forming a noncovalent bond to the supramolecular synthon formed by the API; and identifying co-crystal formers having chemical functionalities that are complementary with the API.

[0011] In another aspect, the subject invention concerns methods for identifying complementary chemical functionalities to form a desired supramolecular synthon, wherein the method comprises the steps of evaluating the structure of an API, which can include determining its crystal structure; determining whether the API contains chemical functionalities capable of forming supramolecular synthons with itself; identifying from a plurality of chemical functionalities that are known to form supramolecular synthons at least one functionality that will from a supramolecular synthon with the API, wherein the identified chemical functionality is capable of disrupting non-covalent bonding within the supramolecular synthon formed by the API, and wherein the selected chemical functionality is capable of forming a noncovalent bond to a complementary chemical functionality on the API; and identifying co-crystal formers having chemical functionalities that are complementary with the API. Thus, according to this method, the formation of homosynthons for the purpose of disrupting the intermolecular interactions between pharmaceutical moieties can be carried out.

[0012] In still another aspect, the subject invention concerns methods for identifying complementary chemical functionalities to form a desired supramolecular synthon, wherein the method comprises the steps of evaluating the structure of an API, which can include determining its crystal structure; determining whether the API contains chemical functionalities capable of forming supramolecular synthons with different molecules; identifying from a plurality of

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chemical functionalities that are known to form supramolecular synthons at least one functionality that will form a supramolecular synthons with the API; and wherein the selected chemical functionality is capable of forming a noncovalent bond to a complementary chemical functionality on the API, and identifying co-crystal formers having chemical functionalities that are complementary with the active pharmaceutical ingredient.

[0013] As indicated above, certain aspects of the subject invention can involve selecting a chemical functionality that is capable of disrupting the non-covalent bonding between identical functionalities (homosynthon) and form a non-covalent bond between different, yet complementary, functionalities (heterosynthon); selecting a plurality of molecular entities that comprise the complementary functionality (preferably GRAS compounds or approved food additives); identifying additional chemical features on the molecular entities that will not interfere with the formation of the desired supramolecular synthon and that will impart the desired physical properties to the target phase; and, optionally, preparing a new solid phase that is composed of the pharmaceutical moiety and the complementary molecular entity (such as a multiple-component phase or two component phase) by crystallization techniques comprising reactions in solvent, and/or solventless reactions, that afford crystalline materials. Optionally, the methods can further include at least one of the subsequent steps of determining the structure of the new solid phase formed; and analyzing the physical properties of the new solid phase.

[0014] The subject invention further concerns new solid phases identified or produced using the methods identified herein. The subject invention further pertains to a multiple-component phase composition comprising a solid material (phase) that is sustained by intermolecular interactions between two or more independent molecular entities, in any stoichiometric ratio, wherein at least one of the independent molecular entities is a pharmaceutical entity. The multiple-component phase composition can be, for example, a discrete supramolecular entity or a polymeric structure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] Figure 1 shows the chemical structure of ibuprofen. The external functionalities are an isopropyl group (encircled on the left, in cyan) and a carboxylic acid (encircled on the right, in magenta).

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[0016] Figure 2 shows a scheme with the synthon of pure ibuprofen on the left and the supramolecular entity containing the synthon on the right, demonstrating that pure phases of ibuprofen are sustained by carboxylic acid-carboxylic acid interactions. The standard chemical color correlation appears in all the figures where color is utilized (*e.g.* red = oxygen; white = oxygen; dark blue = nitrogen; light blue = fluorene; yellow = sulfur).

[0017] Figure 3 shows a scheme wherein the carboxylic acid-carboxylic acid interactions of ibuprofen are disrupted by co-crystallization with an aromatic amine. Specifically, by using diamines, 2:1 multiple-component phases are produced.

[0018] Figures 4A–4B show an acetaminophen 1-D polymeric chain and an acetaminophen/4,4'-bipyridine/water crystal, respectively. Reported forms are monoclinic ($P2_1/n$) (Haisa, M. *et al.*, *Acta Crystallogr., Sect B*, 1974, 30:2510) and orthorhombic (*Pbca*) (Haisa, M. *et al.*, *Acta Crystallogr., Sect B*, 1976, 32:1283) polymorphs. The monoclinic polymorph forms pleated sheets with all hydrogen bonding donors and acceptors interacting. The orthorhombic polymorph forms form 1-D polymeric chains with all donors and acceptors interacting.

[0019] Figures 5A-5B show pure phenytoin and a phenytoin/pyridone co-crystal, respectively. Phenytoin has one known pure form (Carmerman, A. *et al.*, *Acta Crystallogr., Sect B*, 1971, 27:2207). The crystal structure reveals a two dimensional network formed by hydrogen bonds between both the carbonyl and 2° amine.

[0020] Figures 6A-6D show supramolecular entities containing synthons and corresponding crystal structures of pure aspirin and aspirin/4,4'-bipyridine. Figures 3A and 3B show the supramolecular entity containing the synthon of pure aspirin and corresponding crystal structure, respectively. Figures 6C and 6D show the supramolecular entity containing the synthon and corresponding co-crystal of aspirin/4,4'-bipyridine, respectively. The pure phase (Chiari, G. *et al.*, *Acta Crystallogr., Sect B*, 1981, 37:1623) of acetylsalicylic acid, has centrosymmetric carboxylic acid homodimers and crystallizes in the space group $P2_1/c$, packing in 2D polymeric sheets with hydrophobic planes.

[0021] Figures 7A-7D show supramolecular entities containing synthons and corresponding crystal structures of pure ibuprofen [2-(4-isobutylphenyl) propionic acid] and ibuprofen/4,4'-bipyridine. Figures 7A and 7B show the supramolecular entity containing the synthon of pure ibuprofen and corresponding crystal structure, respectively. Figures 7C and 7D

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show the supramolecular entity containing the synthon of ibuprofen/4,4'-bipyridine and corresponding co-crystal, respectively. The reported crystal structures of ibuprofen are racemic (McConnell, J.F. *Cryst. Strucut. Commun.*, 1974, 3:73) and S (+) forms (Freer, A.A. *et al.*, *Acta Crystallogr., Sect C (Cr. Str. Comm)*, 1993, 49:1378). Both contain hydrogen bonded carboxylic acid homodimers. Racemic dimers have centers of inversion across the dimer, which crystallize in the space group $P2_1/c$. The S (+) form contains asymmetric dimers, which crystallize in the space group $P2_1$. Both crystals pack in 2-D polymeric sheets sustained by π-π stacking and hydrophobic in-layer interactions.

[0022] Figures 8A-8D show supramolecular entities containing synthons and corresponding crystal structures of pure flurbiprofen [2-(2-fluror-4-biphenyl) propionic acid] and flurbiprofen/4,4'-bipyridine. Figures 8A and 8B show the supramolecular entity containing the synthon of pure flurbiprofen and corresponding crystal structure, respectively. Figures 5C and 5D show the supramolecular synthon of flurbiprofen/4,4'-bipyridine and corresponding co-crystal, respectively. Flurbiprofen has one reported pure form (Flippen, J.L. *et al.*, *Acta Crystallogr., Sect. B*, 1975, 31:926) and contain hydrogen bonded carboxylic acid homodimers with a center of inversion and crystallizes in the *P-1* space group. 2-D polymeric sheets are formed through π-π and hydrophobic interactions from the phenyl rings.

[0023] Figures 9A and 9B show the supramolecular entity containing the synthon of flurbiprofen/trans-1,2-bis(4-pyridyl)ethylene and the corresponding crystal structure, respectively.

[0024] Figures 10A and 10B show the crystal structures of pure carbamazepine and carbamazepine/*p*-phthalaldehyde, respectively. Carbamazepine [5H-Dibenz(b, f) azepine-5-carboxamide] (CBZ) has been shown to exist in at least three anhydrous forms and two solvated forms (a dihydrate and an acetonate) (Himes, V.L. *et al.*, *Acta Crystallogr.*, 1981, 37:2242-2245; Lowes, M.M.J. *et al.*, *J. Pharm. Sci.*, 1987, 76:744-752; Reck, G. *et al.*, *Cryst. Res. Technol.*, 1986, 21:1463-1468). The primary intermolecular interaction in these crystal forms is the dimer formed between the carboxamide moieties of each CBZ molecule forming centrosymmetric dimers. The anhydrous polymorphs are monoclinic, trigonal, and triclinic. The polymorphs are enantiotropically related with the monoclinic form being the most thermodynamically stable at room temperature.

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[0025] Figure 11 shows the crystal structure of carbamazepine/nicotinamide (vitamin B3).

[0026] Figure 12 shows the crystal structure of carbamazepine/saccharin, engineered using the carbamazepine/nicotinamide co-crystal as a model.

[0027] Figures 13A-13C show the chemical structures of ibuprofen, flurbiprofen, and aspirin, respectively.

[0028] Figures 14A and **14B** show the crystal structures of carbamazepine and carbamazepine/2,6-pyridinedicarboxylic acid, respectively.

[0029] Figures 15A and 15B show the crystal structures of carbamazepine and carbamazepine/5-nitroisophthalic acid, respectively.

[0030] Figures 16A and **16B** show the crystal structures of carbamazepine and carbamazepine/acetic acid.

[0031] Figures 17A and **17**B show the crystal structure of carbamazepine and carbamazepine/adamantanetetracarboxylic acid.

[0032] Figures 18A and **18B** show the crystal structure of carbamazepine and carbamazepine/benzoquinone.

[0033] Figures 19A and **19B** show the crystal structure of carbamazepine and carbamazepine/butyric acid.

[0034] Figures 20A and **20B** show the crystal structure of carbamazepine and carbamazepine/DMSO.

[0035] Figures 21A and **21B** show the crystal structure of carbamazepine and carbamazepine/formamide.

[0036] Figures 22A and **22B** show the crystal structure of carbamazepine and carbamazepine/formic acid.

[0037] Figures 23A and **23B** show the crystal structure of carbamazepine and carbamazepine/trimesic acid.

[0038] Figure 24 shows an exemplified scheme for preparing multiple-component phase compositions of the subject invention.

DETAILED DISCLOSURE OF THE INVENTION

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[0039] The subject invention relates to the application of the concepts of crystal engineering towards the design of new multiple-component solid phases, such as multiple-component crystals, having at least one active pharmaceutical component. Examples of multiple-component crystals of the subject invention include, but are not limited to, acetominophen/4,4'-bipyridine/water, phenytoin/pyridone, aspirin/4,4'-bipyridine, ibuprofen/4,4'-dipyridyl, flurbiprofen/4,4'-dipyridine, flurbiprofen/trans-1,2-bis(4-pyridyl)ethylene, carbamazepine/*p*-phthalaldehyde, carbamazepine/nicotinamide (GRAs), carbamazepine/saccharin (GRAs), carbamazepine/2,6-pyridinedicarboxylic acid, carbamazepine/5-nitroisophthalic acid, carbamazepine/acetic acid, carbamazepine/1,3,5,7-adamantanetetracarboxylic acid, carbamazepine/benzoquinone, carbamazepine/butyric acid, carbamazepine/dimethyl sulfoxide (DMSO), carbamazepine/formamide, carbamazepine/formic acid, and carbamazepine/tremesic acid, which have been characterized by various techniques and exhibit physical properties different from the parent pharmaceutical ingredient as a direct result of hydrogen bonding interaction. These crystalline assemblies can afford improved drug solubility, dissolution rate, stability and bioavailability, for example.

[0040] In one aspect, the subject invention concerns a method for identifying complementary chemical functionalities to form a desired supramolecular synthon, wherein the method comprises the steps of evaluating the structure of an active pharmaceutical ingredient (API), which can include determining its crystal structure; determining whether the API contains chemical functionalities capable of forming supramolecular synthons with itself; identifying from a plurality of chemical functionalities that are known to form a supramolecular synthon at least one chemical functionality that will form a further supramolecular synthon to the supramolecular synthon formed by the API, wherein the identified chemical functionality is not capable of disrupting non-covalent bonding within the supramolecular synthon formed by the supramolecular synthon formed by the API, and wherein the selected chemical functionality is capable of forming a noncovalent bond to the supramolecular synthon formed by the API; and identifying co-crystal formers having chemical functionalities that are complementary with the API.

[0041] In another aspect, the subject invention concerns methods for identifying complementary chemical functionalities to form a desired supramolecular synthon, wherein the method comprise the steps of evaluating the structure of an API, which can include determining

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its crystal structure; determining whether the API contains chemical functionalities capable of forming supramolecular synthons with itself; identifying from a plurality of chemical functionalities that are known to form supramolecular synthons at least one functionality that will form a supramolecular synthon with the API, wherein the identified chemical functionality is capable of disrupting non-covalent bonding within the supramolecular synthon formed by the API, and wherein the selected chemical functionality is capable of forming a noncovalent bond to a complementary chemical functionality on the API; and identifying co-crystal formers having chemical functionalities that are complementary with the API. Thus, according to this method, the formation of homosynthons for the purpose of disrupting the intermolecular interactions between pharmaceutical moieties can be carried out.

[0042] In still another aspect, the subject invention concerns methods for identifying complementary chemical functionalities to form a desired supramolecular synthon, wherein the method comprises the steps of evaluating the structure of an API, which can include determining its crystal structure; determining whether the API contains chemical functionalities capable of forming supramolecular synthons with different molecules; identifying from a plurality of chemical functionalities that are known to form supramolecular synthons at least one functionality that will form a supramolecular synthons with the API, and wherein the selected chemical functionality is capable of forming a noncovalent bond to a complementary chemical functionality on the API; and identifying co-crystal formers having chemical functionalities that are complementary with the active pharmaceutical ingredient.

[0043] In each of the three aspects of the methods described above, the methods can further comprise preparing a multiple-component solid phase composition composed of the API and at least one of the identified co-crystal formers. The identified co-crystal formers can be, for example, a different API, a GRAS compound, a food additive, a low toxicity organic, or a metal-organic complex. Various methods can be utilized for preparing the multiple-component solid phase composition, such as crystallization from solution, cooling the melt, sublimation and grinding. In addition, the methods of the subject invention can further comprise either or both of the following steps: determining the structure of the new multiple-component solid phase composition, and analyzing the physical and/or chemical properties of the new multiple-component solid phase composition.

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[0044] The subject invention further concerns new solid phase identified or produced using the methods identified herein. The subject invention further pertains to a multiple-component phase composition comprising a solid material (phase) that is sustained by intermolecular interactions between two or more independent molecular entities, in any stoichiometric ratio, wherein at least one of the independent molecular entities is a pharmaceutical entity. The multiple-component phase composition of the subject invention can be, for example, a discrete supramolecular entity or a polymeric structure. The multiple-component phase compositions of the subject invention can have properties, such as melting point, solubility, dissolution rate, stability, and/or bioavailability, which are different from the pharmaceutical compound, or compounds, upon which they are based.

[0045] By way of example, the external functionalities of ibuprofen are an isopropyl group and a carboxylic acid, as shown in Figure 1.

[0046] Using the methods of the subject invention, it has been determined that this interaction can be disrupted by co-crystallization with an aromatic amine, as shown in Figure 2. Specifically, by using diamines, 2:1 binary phases of ibuprofen have been prepared, as shown in Figure 3, as well as other phases exemplified herein. Therefore, the methods of the subject invention can be used to identify complementary chemical functionalities and produce multiple-component phase compositions for a variety of pharmaceuticals, including those pharmaceutical compounds with structures very different those of ibuprofen, flurbiprofen, and aspirin, which are shown in Figures 13A-13C, respectively.

[0047] As used herein, the term "multiple-component phase" refers to any solid material (phase) that is sustained by intermolecular interactions between at least two independent molecular entities, in any stoichiometric ratio, wherein at least one of the independent molecular entities is a pharmaceutical entity. Examples of intermolecular interactions include, but are not limited to one or more of the following: hydrogen bonding (weak and/or strong), dipole interactions (induced and/or non-induced), stacking interactions, hydrophobic interactions, and other inter-static interactions. Each independent molecular entity can be a discrete supramolecular entity or polymeric structure, for example. Preferably, one or more of the independent molecular entities comprises a molecule of a "GRAS" compound, that is, a compound "Generally Regarded as Safe by the Food and Drug Administration (FDA)". More preferably, the GRAS compound is a non-pharmaceutical entity.

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[0048] The terms "pharmaceutical entity," pharmaceutical moiety", "pharmaceutical component", "pharmaceutical molecule", and "active pharmaceutical ingredient (API)", and grammatical variations thereof, are used interchangeably herein to refer to any biologically active moiety having a therapeutic effect on a human or animal suffering from a given pathological condition, when administered in a given concentration. Therefore, pharmaceutical entities useful as the active pharmaceutical ingredients in the multiple phase solids of the subject invention can be administered to a human or animal, which may or may not be suffering from a pathological condition, and the pharmaceutical entity can have a prophylactive effect, a palliative effect, and/or be a curative intervention. As used herein, these pharmaceutical entities are intended to include pharmaceutically acceptable salts of a given pharmaceutical entity that retain all or a portion of their pharmaceutical activity. Pharmaceutical molecules or ions are inherently predisposed for such crystal engineering studies since they already contain molecular recognition sites that bind selectively to biomolecules, and they are prone to supramolecular self-assembly. Examples of the groups commonly found in active pharmaceutical ingredients, and which are capable of forming supramolecular synthons include, but are not limited to, acids, amides, aliphatic nitrogen bases, unsaturated aromatic nitrogen bases (*e.g.* pyridines, imidazoles), amines, alcohols, halogens, sulfones, nitro groups, S-heterocyles, N-heterocycles (saturated or unsaturated), and O-heterocycles. Other examples include ethers, thioethers, thiols, esters, thioesters, thioketones, epoxides, acetonates, nitrils, oximes, and organohalides. Some of these groups can form supramolecular synthons with identical groups in similar or different molecules and are termed homosynthons, *e.g.* acids and amides. Other groups can form supramolecular synthons with different groups and are termed heterosynthons, *e.g.*, acid/amide; pyridine/amide; alcohol/amine. Heterosynthons are particularly suitable for formation of multiple-component crystals whereas homosynthons can sometimes form multiple-component crystals.

[0049] As used herein, the term "supramolecular synthon" refers to the sum of the components of a multi-component non-covalent interaction, wherein the non-covalent interaction contributes to the formation of a discrete supramolecular entity or polymeric structure, wherein each component is a chemical functionality. A supramolecular synthon can be a dimer, trimer, or *n*-mer, for example.

[0050] The multiple-component phase compositions can be formulated according to known methods for preparing pharmaceutically useful compositions. Such pharmaceutical

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compositions can be adapted for various forms of administration, such as oral, parenteral, nasal, topical, transdermal, *etc*. The multiple-component phase solids of the subject invention can be made into solutions or amorphous compounds, as injections, pills, or inhalants, for example. Optionally, the pharmaceutical compositions can include a pharmaceutically acceptable carrier or diluent. Formulations are described in a number of sources which are well known and readily available to those skilled in the art. For example, *Remington's Pharmaceutical Science* (Martin EW [1995] Eastone Pennsylvania, Mack Publishing Company, 19th ed.) describes formulations that can be used in connection with the subject invention. Formulations suitable for administration include, for example, aqueous sterile injection solutions, which may contain antioxidants, buffers, bacteriostats, and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and nonaqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the condition of the sterile liquid carrier, for example, water for injections, prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powder, granules, or tablets of the multiple-component phase compositions of the subject invention, for example. It should be understood that in addition to the ingredients particularly mentioned above, the formulations of the subject invention can include other agents conventional in the art having regard to the type of formulation in question.

[0051] In terms of superstructure, three general types of compounds generated by interaction of a drug molecule with another molecule include: (1) multiple-component compounds, in which superstructure is generated by two or more molecules, both of which are integral components of the network and complementary; (2) clathrate inclusion compounds, in which the compounds' superstructure is generated by self-assembly of one or more molecules and a guest molecules is enclosed within the superstructure; and (3) porous inclusion compounds, in which the superstructure is open framework in nature.

[0052] The subject invention concerns multiple-component compositions, and it is demonstrated herein that the concepts of crystal engineering and supramolecular synthons can be applied to prepare a wide range of novel pharmaceutical materials that are based on rational design. Therefore, the binary compounds of the subject invention can be generated in such a fashion that they have desirable composition, structure and properties. More specifically, an

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issue that is particularly relevant to pharmaceutical compositions of matter and processing is addressed by the subject invention: the diversity of compositions, superstructures and solubilities that can be generated when drug molecules form binary phases with complementary molecules. Binary phases involving the following drugs are exemplified herein: aspirin, acetaminophen, ibuprofen (and related compounds), phenytoin and carbamazepine and appropriate molecular additives. These novel phases include both "multiple-component phases" that illustrate the concept of crystal engineering and multiple-component phases that incorporate pharmaceuticals with "GRAS" compounds, that is, compounds "Generally Regarded as Safe by the FDA", and/or food additives.

[0053] In the context of organic and pharmaceutical solids, the subject invention addresses these issues by demonstrating that crystal engineering offers a paradigm for the supramolecular synthesis (Chang, Y.L. *et al.*, *J. Am. Chem. Soc.*, 1993, 115:5991-6000) of a wide range of new multiple component phases that have predetermined compositions and, in some instances, predetermined topology. Such an ability to build hierarchical structures from molecular or supramolecular modules facilitates precise control of structure and function of solid phases. These multiple-component phases have the following advantages over single component phases and traditional multiple-component phases (solid dispersions): high thermodynamic stability (thereby reducing problems associated with solid phase transformations), modified bioavailability (finely tunable solubility and delivery), and enhanced processability (crystal morphology, mechanical properties, hygroscopicity).

[0054] The subject invention has the following implications from a scientific perspective: (a) protocols are now available for the rational design of a new generation of pharmaceutical phases that contain at least two components that are sustained by supramolecular synthons; (b) correlation of structure and function of the new pharmaceutical phases via characterization of structure, crystal energy, solubility, dissolution rate, and stability is now possible; and (c) a new range of novel phases for the treatment of pathological conditions in humans and animals are available.

[0055] The subject invention extends the state-of-the-art in at least three ways: (1) by generating a rational, supramolecular strategy for the design of novel, multiple component crystalline phases; (2) by extending this strategy to pharmaceutical phases; and (3) by using this strategy to control the delivery properties and stability of pharmaceutical compounds.

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[0056] The following pages describe examples of multiple component crystalline phases that have been characterized using single crystal X-ray crystallography and structure-sensitive analytical techniques: FT-IR, XRPD, DSC, TGA. They represent prototypal examples of the invention as they are all based upon pharmaceutical molecules that are inherently predisposed to form supramolecular synthons with other complementary functional groups. They were chosen for study because of well-known limitations in their solubility/bioavailibility. In each example, the nature of the pure phase is discussed and it is sustained by a supramolecular homosynthon (self-complementary functionalities). The multiple-component phases prepared confirm the ability to persistently and rationally disrupt the homosynthon by judicious choice of a second molecular component that is predisposed to form a supramolecular heterosynthon. That these new solid phases will have different solubility profiles than their pure phases is to be expected. Examples designated as GRAS are those in which second a component that is "Generally Regarded as Safe by the FDA" was used.

Example 1—Multi-Component Crystal of Acetaminophen: Acetominophen/4,4'-bipyridine/water (1:1:1 stoichiometry)

[0057] 50 mg (0.3307 mmol) acetaminophen and 52 mg (0.3329 mmol) 4,4'-bipyridine were dissolved in hot water and allowed to stand. Slow evaporation yielded colorless needles of a 1:1:1 acetaminophen/4,4'-bipyridine/water co-crystal, as shown in Figure 4B.

[0058] Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{36}H_{44}N_2O_4$, M=339.84, triclinic, space group $P\bar{1}$; a = 7.0534(8), b = 9.5955(12), c = 19.3649(2) Å, α = 86.326(2), β = 80.291(2), γ = 88.880(2)°, U = 1308.1(3) Å^3, T = 200(2) K, Z = 2, μ(Mo-Kα) = 0.090 mm^{-1}, D_c = 1.294 Mg/m^3, λ = 0.71073 Å^3, F(000) = 537, $2\theta_{max}$ = 25.02°; 6289 reflections measured, 4481 unique (R_{int} = 0.0261). Final residuals for 344 parameters were R_1 = 0.0751, wR_2 = 0.2082 for I>2σ(I), and R_1 = 0.1119, wR_2 = 0.2377 for all 4481data.

[0059] Crystal packing: The co-crystals contain bilayered sheets in which water molecules act as a hydrogen bonded bridge between the network bipyridine moieties and the acetaminophen. Bipyridine guests are sustained by π-π stacking interactions between two network bipyridines. The layers stack via π-π interactions between the phenyl groups of the acetaminophen moieties.

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[0060] Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 57.77° C (endotherm); m.p. = 58-60° C (MEL-TEMP); (acetaminophen m.p. = 169° C, 4,4'-bipyridine m.p. = 111-114° C).

Example 2—Multi-Component Crystal of Phenytoin: Phenytoin/Pyridine (1:1 stoichiometry)

[0061] 28 mg (0.1109 mmol) phenytoin and 11 mg (0.1156 mmol) 4-hydroxypyridone were dissolved in 2 mL acetone and 1 mL ethanol with heating and stirring. Slow evaporation yielded colorless needles of a 1:1 phenytoin/pyridone co-crystal, as shown in Figure 5B.

[0062] Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{20}H_{17}N_3O_3$, M = 347.37, monoclinic $P2_1/c$; a = 16.6583(19), b = 8.8478(10), c = 11.9546(14) Å, $\beta = 96.618(2)°$, $U = 1750.2(3)$ Å^3, T = 200(2) K, Z = 4, μ(Mo-Kα) = 0.091 mm^{-1}, $D_c = 1.318$ Mg/m^3, $\lambda = 0.71073$ Å^3, F(000) = 728, $2\theta_{max} = 56.60°$; 10605 reflections measured, 4154 unique ($R_{int} = 0.0313$). Final residuals for 247 parameters were $R_1 = 0.0560$, $wR_2 = 0.1356$ for $I>2\sigma(I)$, and $R_1 = 0.0816$, $wR_2 = 0.1559$ for all 4154 data.

[0063] Crystal packing: The co-crystal is sustained by hydrogen bonding of adjacent phentoin molecules between the carbonyl and the amine closest to the tetrahedral carbon, and by hydrogen bonding between pyridone carbonyl functionalities and the amine not involved in phenytoin-phenytoin interactions. The pyridone carbonyl also hydrogen bonds with adjacent pyridone molecules forming a one-dimensional network.

[0064] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), characteristic peaks for the co-crystal were identified as: 2°amine found at 3311cm^{-1}, carbonyl (ketone) found at 1711cm^{-1}, olephin peak found at 1390cm^{-1}.

[0065] Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 233.39° C (endotherm) and 271.33° C (endotherm); m.p. = 231-233° C (MEL-TEMP); (phenytoin m.p. = 295° C, pyridone m.p. = 148° C).

[0066] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), a 29.09% weight loss starting at 192.80° C, 48.72% weight loss starting at 238.27° C, and 18.38% loss starting at 260.17° C followed by complete decomposition.

[0067] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα ($\lambda = 1.540562$), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute.

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XRPD: Showed analogous peaks to the simulated XRPD derived from the single crystal data. In all cases of recrystallization and solid state reaction, experimental (calculated): 5.2 (5.3); 11.1 (11.3); 15.1 (15.2); 16.2 (16.4); 16.7 (17.0); 17.8 (17.9); 19.4 (19.4); 19.8 (19.7); 20.3 (20.1); 21.2 (21.4); 23.3 (23.7); 26.1 (26.4); 26.4 (26.6); 27.3 (27.6); 29.5 (29.9).

Example 3—Multi-Component Crystal of Aspirin (acetylsalicylic acid): Aspirin/4,4'-bipyridine (2:1 stoichiometry)

[0068] 50 mg (0.2775 mmol) aspirin and 22 mg (0.1388 mmol) 4,4'-bipyridine were dissolved in 4 mL hexane. 8 mL ether was added to the solution and allowed to stand for one hour, yielding colorless needles of a 2:1 aspirin/4,4'-bipyridine co-crystal, as shown in Figure 6D. Alternatively, aspirin/4,4'-bipyridine (2:1 stoichiometry) can be made by grinding the solid ingredients in a pestle and mortar.

[0069] Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{28}H_{24}N_2O_8$, M = 516.49, orthorhombic *Pbcn*; a = 28.831(3), b = 11.3861(12), c = 8.4144(9) Å, U = 2762.2(5) Å^3, T = 173(2) K, Z = 4, μ(Mo-Kα) = 0.092 mm^{-1}, D_c = 1.242 Mg/m^3, λ = 0.71073 Å^3, F(000) = 1080, $2\theta_{max}$ = 25.02°; 12431 reflections measured, 2433 unique (R_{int} = 0.0419). Final residuals for 202 parameters were R_1 = 0.0419, wR_2 = 0.1358 for I>2σ(I), and R_1 = 0.0541, wR_2 = 0.1482 for all 2433 data.

[0070] Crystal packing: The co-crystal contains the carboxylic acid-pyridine heterodimer that crystallizes in the *Pbcn* space group. The structure is an inclusion compound containing disordered solvent in the channels. In addition to the dominant hydrogen bonding interaction of the heterodimer, π-π stacking of the bipyridine and phenyl groups of the aspirin and hydrophobic interactions contribute to the overall packing interactions.

[0071] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), characteristic (-COOH) peak at 1679 cm^{-1} was shifted up and less intense at 1694cm^{-1}, where as the lactone peak is shifted down slightly from 1750cm^{-1} to 1744cm^{-1}.

[0072] Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 95.14° C (endotherm); m.p. = 91-96° C (MEL-TEMP); (aspirin m.p. = 1345° C, 4,4'-bipyridine m.p. = 111-114° C).

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[0073] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), weight loss of 9% starting at 22.62° C, 49.06% weight loss starting at 102.97° C followed by complete decomposition starting at 209.37° C.

Example 4—Multi-Component Crystal of Ibuprofen: Ibuprofen/4,4'-Bipyridine (2:1 stoichiometry)

[0074] 50 mg (0.242 mmol) racemic ibuprofen and 18mg (0.0960 mmol) 4,4'-bipyridine were dissolved in 5 mL acetone. Slow evaporation of the solvent yielded colorless needles of a 2:1 ibuprofen/4,4'-bipyridine co-crystal, as shown in Figure 7D.

[0075] Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{36}H_{44}N_2O_4$, M = 568.73, triclinic, space group *P-1*; a = 5.759(3), b = 11.683(6), c = 24.705(11) Å, α = 93.674(11), β = 90.880(10), γ = 104.045(7)°, *U* = 1608.3(13) Å^3, T= 200(2) K, Z = 2, μ(Mo-Kα) = 0.076 mm^{-1}, D_c = 1.174 Mg/m^3, λ = 0.71073 Å^3, F(000) = 612, $2\theta_{max}$ = 23.29°; 5208 reflections measured, 3362 unique (R_{int} = 0.0826). Final residuals for 399 parameters were R_1 = 0.0964, wR_2 = 0.2510 for I>2σ(I), and R_1 = 0.1775, wR_2 = 0.2987 for all 3362 data.

[0076] Crystal packing: The co-crystal contains ibuprofen/bipyridine heterodimers, sustained by two hydrogen bonded carboxylic acidpyridine supramolecular synthons, arranged in a herringbone motif that packs in the space group *P-1*. The heterodimer is an extended version of the homodimer and packs to form a two-dimensional network sustained by π-π stacking of the bipyridine and phenyl groups of the ibuprofen and hydrophobic interactions from the ibuprofen tails.

[0077] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). Analysis observed stretching of aromatic C-H at 2899 cm^{-1}; N--H bending and scissoring at 1886 cm$_{-1}$; C=O stretching at 1679 cm^{-1}; C-H out-of-plane bending for both 4,4'-bipyridine and ibuprofen at 808 cm^{-1} and 628 cm^{-1}.

[0078] Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 64.85° C (endotherm) and 118.79° C (endotherm); m.p. = 113-120° C (MEL-TEMP); (ibuprofen m.p. = 75-77° C, 4,4'-bipyridine m.p. = 111-114° C).

[0079] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 13.28% weight loss between room temperature and 100.02° C immediately followed by complete decomposition.

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[0080] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. XRPD derived from the single crystal data, experimental (calculated): 3.4 (3.6); 6.9 (7.2); 10.4 (10.8); 17.3 (17.5); 19.1 (19.7).

Example 5—Multi-Component Crystal of Flurbiprofen: Flurbiprofen/4,4'-bipyridine (2:1 stoichiometry)

[0081] 50 mg (0.2046 mmol) flurbiprofen and 15 mg (0.0960 mmol) 4,4'-bipyridine were dissolved in 3 mL acetone. Slow evaporation of the solvent yielded colorless needles of a 2:1 flurbiprofen/4,4'-bipyridine co-crystal, as shown in Figure 8D.

[0082] Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{40}H_{34}F_2N_2O_4$, M = 644.69, monoclinic $P2_1/n$; a = 5.860(4), b = 47.49(3), c = 5.928(4) Å, β = 107.382 (8)°, U = 1574.3(19) Å^3, T = 200(2) K, Z = 2, μ(Mo-Kα) = 0.096 mm^{-1}, D_c = 1.360 Mg/m^3, λ = 0.71073 Å^3, F(000) = 676, $2\theta_{max}$ = 21.69°; 4246 reflections measured, 1634 unique (R_{int} = 0.0677). Final residuals for 226 parameters were R_1 = 0.0908, wR_2 = 0.2065 for I>2σ(I), and R_1 = 0.1084, wR_2 = 0.2209 for all 1634 data.

[0083] Crystal packing: The co-crystal contains flurbiprofen/bipyridine heterodimers, sustained by two hydrogen bonded carboxylic acidpyridine supramolecular synthon, arranged in a herringbone motif that packs in the space group $P2_1/n$. The heterodimer is an extended version of the homodimer and packs to form a two-dimensional network sustained by π-π stacking and hydrophobic interactions of the bipyridine and phenyl groups of the flurbiprofen.

[0084] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), aromatic C-H stretching at 3057 cm^{-1} and 2981 cm^{-1}; N--H bending and scissoring at 1886 cm^{-1}; C=O stretching at 1690 cm^{-1}; C=C and C=N ring stretching at 1418 cm^{-1}.

[0085] Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 162.47° C (endotherm); m.p. = 155-160° C (MEL-TEMP); (flurbiprofen m.p. = 110-111° C, 4,4'-bipyridine m.p. = 111-114° C).

[0086] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 30.93% weight loss starting at 31.13° C and a 46.26% weight loss starting at 168.74° C followed by complete decomposition.

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[0087] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα ($\lambda = 1.540562$), 30kV, 15mA), the powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. XRPD derived from the single crystal data: experimental (calculated): 16.8 (16.8); 17.1 (17.5); 18.1 (18.4); 19.0 (19.0); 20.0 (20.4); 21.3 (21.7); 22.7 (23.0); 25.0 (25.6); 26.0 (26.1); 26.0 (26.6); 26.1 (27.5); 28.2 (28.7); 29.1 (29.7).

Example 6—Multi-Component Crystal of Flurbiprofen: Flurbiprofen/trans-1,2-bis (4-pyridyl) ethylene (2:1 stoichiometry)

[0088] 25 mg (0.1023 mmol) flurbiprofen and 10 mg (0.0548 mmol) trans-1, 2-bis (4-pyridyl) ethylene were dissolved in 3 mL acetone. Slow evaporation of the solvent yielded colorless needles of a 2:1 flurbiprofen/1,2-bis (4-pyridyl) ethylene co-crystal, as shown in Figure 9B.

[0089] Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{42}H_{36}F_2N_2O_4$, M = 670.73, monoclinic $P2_1/n$; a = 5.8697(9), b = 47.357(7), c = 6.3587(10) Å, β = 109.492(3)°, U = 1666.2(4) Å^3, T = 200(2) K, Z = 2, μ(Mo-Kα) = 0.093 mm^{-1}, D_c = 1.337 Mg/m^3, λ = 0.71073 Å^3, F(000) = 704, $2\theta_{max}$ = 21.69°, 6977 reflections measured, 2383 unique (R_{int} = 0.0383). Final residuals for 238 parameters were R_1 = 0.0686, wR_2 = 0.1395 for I>2σ(I), and R_1 = 0.1403, wR_2 = 0.1709 for all 2383 data.

[0090] Crystal packing: The co-crystal contains flurbiprofen/1,2-bis (4-pyridyl) ethylene heterodimers, sustained by two hydrogen bonded carboxylic acid-pyridine supramolecular synthons, arranged in a herringbone motif that packs in the space group $P2_1/n$. The heterodimer from 1,2-bis (4-pyridyl) ethylene further extends the homodimer relative to example 5 and packs to form a two-dimensional network sustained by π-π stacking and hydrophobic interactions of the bipyridine and phenyl groups of the flurbiprofen.

[0091] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), aromatic C-H stretching at 2927 cm^{-1} and 2850 cm^{-1}; N--H bending and scissoring at 1875 cm^{-1}; C=O stretching at 1707 cm^{-1}; C=C and C=N ring stretching at 1483 cm^{-1}.

[0092] Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 100.01° C, 125.59° C and 163.54°C (endotherms); m.p. = 153-158° C (MEL-TEMP); (flurbiprofen m.p. = 110-111° C, trans-1, 2-bis (4-pyridyl) ethylene m.p. = 150-153° C).

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[0093] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 91.79% weight loss starting at 133.18° C followed by complete decomposition.

[0094] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA), the powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. XRPD derived from the single crystal data, experimental (calculated): 3.6 (3.7); 17.3 (17.7); 18.1 (18.6); 18.4 (18.6); 19.1 (19.3); 22.3 (22.5); 23.8 (23.9); 25.9 (26.4); 28.1 (28.5).

Example 7—Multi-Component Crystal of Carbamazepine: Carbamazepine/*p*-Phthalaldehyde (1:1 stoichiometry)

[0095] 25 mg (0.1058 mmol) carbamazepine and 7 mg (0.0521 mmol) *p*-phthalaldehyde were dissolved in approximately 3 mL methanol. Slow evaporation of the solvent yielded colorless needles of a 1:1 carbamazepine/*p*-phthalaldehyde co-crystal, as shown in Figure 10B.

[0096] Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{38}H_{30}N_4O_4$, M = 606.66, monoclinic *C2/c*; a = 29.191(16), b = 4.962(3), c = 20.316(11) Å, β = 92.105(8)°, *U* = 2941(3) Å^3, T= 200(2) K, Z = 4, μ(Mo-Kα) = 0.090 mm^{-1}, D_c = 1.370 Mg/m^3, λ = 0.71073 Å^3, F(000) = 1272, $2\theta_{max}$ = 43.66°, 3831 reflections measured, 1559 unique (R_{int} = 0.0510). Final residuals for 268 parameters were R_1 = 0.0332, wR_2 = 0.0801 for I>2σ(I), and R_1 = 0.0403, wR_2 = 0.0831 for all 1559 data.

[0097] Crystal packing**:** The co-crystals contain hydrogen bonded carboxamide homodimers that crystallize in the space group *C2/c*. The 1° amines of the homodimer are bifurcated to the carbonyl of the *p*-phthalaldehyde forming a chain with an adjacent homodimer. The chains pack in a crinkled tape motif sustained by π-π interactions between phenyl rings of the CBZ.

[0098] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). The 1° amine unsymmetrical and symmetrical stretching was shifted down to 3418 cm^{-1}; aliphatic aldehyde and 1° amide C=O stretching was shifted up to 1690 cm^{-1}; N-H in-plane bending at 1669 cm^{-1}; C-H aldehyde stretching at 2861 cm^{-1} and H-C=O bending at 1391 cm^{-1}.

[0099] Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 128.46° C (endotherm), m.p. = 121-124° C (MEL-TEMP), (carbamazepine m.p. = 190.2° C, *p*-phthalaldehyde m.p. = 116° C).

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[00100] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 17.66% weight loss starting at 30.33° C then a 17.57% weight loss starting at 100.14° C followed by complete decomposition.

[00101] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. XRPD derived from the single crystal data, experimental (calculated): 8.5 (8.7); 10.6 (10.8); 11.9 (12.1); 14.4 (14.7) 15.1 (15.2); 18.0 (18.1); 18.5 (18.2); 19.8 (18.7); 23.7 (24.0); 24.2 (24.2); 26.4 (26.7); 27.6 (27.9); 27.8 (28.2); 28.7 (29.1); 29.3 (29.6); 29.4 (29.8).

Example 8—Multi-Component Crystal of Carbamazepine: Carbamazepine/nicotinamide (GRAs) (1:1 stoichiometry)

[00102] 25 mg (0.1058 mmol) carbamazepine and 12 mg (0.0982 mmol) nicotinamide were dissolved in 4 mL of DMSO, methanol or ethanol. Slow evaporation of the solvent yielded colorless needles of a 1:1 carbamazepine/nicotinamide co-crystal, as shown in Figure 11.

[00103] Using a separate method, 25 mg (0.1058 mmol) carbamazepine and 12 mg (0.0982mmol) nicotinamide were ground together with mortar and pestle. The solid was determined to be 1:1 carbamazepine/nicotinamide microcrystals (XPD).

[00104] Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{21}H_{18}N_4O_2$, M = 358.39, monoclinic $P2_1/n$; a = 5.0961(8), b = 17.595(3), c = 19.647(3) Å, β = 90.917(3)°, U = 1761.5(5) $Å^3$, T = 200(2) K, Z = 4, μ(Mo-Kα) = 0.090 mm^{-1}, D_c = 1.351 Mg/m^3, λ = 0.71073 $Å^3$, F(000) = 752, $2\theta_{max}$ = 56.60°, 10919 reflections measured, 4041 unique (R_{int} = 0.0514). Final residuals for 248 parameters were R_1 = 0.0732, wR_2 = 0.1268 for I>2σ(I), and R_1 = 0.1161, wR_2 = 0.1430 for all 4041 data.

[00105] Crystal packing: The co-crystals contain hydrogen bonded carboxamide homodimers. The 1° amines are bifurcated to the carbonyl of the nicotinamide on each side of the dimer. The 1° amines of each nicotinamide are hydrogen bonded to the carbonyl of the adjoining dimer. The dimers form chains with π-π interactions from the phenyl groups of the CBZ.

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[00106] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), unsymmetrical and symmetrical stretching shifts down to 3443 cm^{-1} and 3388 cm^{-1} accounting for 1° amines; 1° amide C=O stretching at 1690 cm^{-1}; N-H in-plane bending at 1614 cm^{-1}; C=C stretching shifted down to 1579 cm^{-1}; aromatic H's from 800 cm^{-1} to 500 cm^{-1} are present.

[00107] Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 74.49° C (endotherm) and 59.05° C (endotherm), m.p. = 153-158° C (MEL-TEMP), (carbamazepine m.p. = 190.2° C, nicotinamide m.p. = 150-160° C).

[00108] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 57.94% weight loss starting at 205.43° C followed by complete decomposition.

[00109] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. XRPD: Showed analogous peaks to the simulated XRPD derived from the single crystal data. XRPD analysis experimental (calculated): 6.5 (6.7); 8.8 (9.0); 10.1 (10.3); 13.2 (13.5); 15.6 (15.8); 17.7 (17.9); 17.8 (18.1); 18.3 (18.6); 19.8 (20.1); 20.4 (20.7); 21.6 (22.); 22.6 (22.8); 22.9 (23.2); 26.4 (26.7); 26.7 (27.0); 28.0 (28.4).

Example 9—Multi-Component Crystal of Carbamazepine: Carbamazepine/saccharin (GRAs) (1:1 stoichiometry)

[00110] 25 mg (0.1058mmol) carbamazepine and 19 mg (0.1037 mmol) saccharin were dissolved in approximately 4 mL ethanol. Slow evaporation of the solvent yielded colorless needles of a 1:1 carbamazepine/saccharin cocrystal, as shown in Figure 12. Solubility measurements indicate that this multiple-component crystal of carbamazepine has improved solubility over previously known forms of carbamezepine (*e.g.*, increased molar solubility and longer solubility in aqueous solutions).

[00111] Crystal data: (Bruker SMART-APEX CCD Diffractometer), $C_{22}H_{17}N_3O_4S_1$, M = 419.45, triclinic *P-1*; a = 7.5140(11), b = 10.4538(15), c = 12.6826(18) Å, α = 83.642(2)°, β = 85.697(2) °, γ = 75.411(2) °, *U* = 957.0(2) $Å^3$, T = 200(2) K, Z = 2, μ(Mo-Kα) = 0.206 mm^{-1}, D_c = 1.456 Mg/m^3, λ = 0.71073 $Å^3$, F(000) = 436, $2\theta_{max}$ = 56.20°; 8426 reflections measured, 4372 unique (R_{int} = 0.0305). Final residuals for 283 parameters were R_1 = 0.0458, wR_2 = 0.1142 for I>2σ(I), and R_1 = 0.0562, wR_2 = 0.1204 for all 4372 data.

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[00112] Crystal packing: The co-crystals contain hydrogen bonded carboxamide homodimers. The 2° amines of the saccharin are hydrogen bonded to the carbonyl of the CBZ on each side forming a tetramer. The crystal has a space group of *P-1* with π-π interactions between the phenyl groups of the CBZ and the saccharin phenyl groups.

[00113] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), unsymmetrical and symmetrical stretching shifts up to 3495 cm^{-1} accounting for 1° amines; C=O aliphatic stretching was shifted up to 1726 cm^{-1}; N-H in-plane bending at 1649 cm^{-1}; C=C stretching shifted down to 1561 cm^{-1}; (O=S=O) sulfonyl peak at 1330 cm^{-1} C-N aliphatic stretching 1175 cm^{-1}.

[00114] Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 75.31° C (endotherm) and 177.32° C (endotherm), m.p. = 148-155°C (MEL-TEMP); (carbamazepine m.p. = 190.2° C, saccharin m.p. = 228.8° C).

[00115] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 3.342% weight loss starting at 67.03° C and a 55.09% weight loss starting at 118.71° C followed by complete decomposition.

[00116] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2θ in continuous scan mode using a step size of 0.02° 2θ and a scan speed of 2.0°/minute. XRPD derived from the single crystal data, experimental (calculated): 6.9 (7.0); 12.2 (12.2); 13.6 (13.8); 14.0 (14.1); 14.1 (14.4); 15.3 (15.6); 15.9 (15.9); 18.1 (18.2); 18.7 (18.8); 20.2 (20.3); 21.3 (21.5); 23.7 (23.9); 26.3 (26.4); 28.3 (28.3).

Example 10—Multi-Component Crystal of Carbamazepine: Carbamazepine/2,6-pyridinedicarboxylic acid (2:3 stoichiometry)

[00117] 36 mg (0.1524 mmol) carbamazepine and 26 mg (0.1556 mmol) 2,6-pyridinedicarboxylic acid were dissolved in approximately 2 mL ethanol. Slow evaporation of the solvent yielded clear needles of a 1:1 carbamazepine/2,6-pyridinedicarboxylic acid co-crystal, as shown in Figure 14B.

[00118] Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{22}H_{17}N_3O_5$, M=403.39, orthorhombic P2(1)2(1)2(1); a=7.2122, b=14.6491, c=17.5864 Å,α=90°, β=90°, γ=90°, V=1858.0(2) $Å^3$, T=100 K, Z=4, μ(MO-Kα)=0.104 mm^{-1}, D_c=1.442 Mg/m^3,

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λ=0.71073Å^3 , F(000)840, $2\theta_{max}$=28.3. 16641 reflections measured, 4466 unique (R_{int}=0.093). Final residuals for 271 parameters were R_1=0.0425 and wR_2=0.0944 for I>2σ(I).

[00119] Crystal packing: Each hydrogen on the CBZ 1° amine is hydrogen bonded to a carbonyl group of a different 2,6-pyridinedicarboxylic acid moiety. The carbonyl of the CBZ carboxamide is hydrogen bonded to two hydroxide groups of one 2,6-pyridinedicarboxylic acid moiety.

[00120] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3439 cm^{-1}, (N-H stretch, 1° amine, CBZ); 1734 cm^{-1}, (C=O); 1649 cm^{-1} , (C=C).

[00121] Melting Point: 214-216°C (MEL-TEMP). (carbamazepine m.p. = 191-192°C, 2,6-pyridinedicarboxylic acid m.p. = 248-250°C).

[00122] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 69% weight loss starting at 215° C and a 17% weight loss starting at 392° followed by complete decomposition.

Example 11—Multi-Component Crystal of Carbamazepine: Carbamazepine/5-nitroisophthalic acid (1:1 stoichiometry)

[00123] 40 mg (0.1693 mmol) carbamazepine and 30 mg (0.1421 mmol) 5-nitroisophthalic acid were dissolved in approximately 3 mL methanol or ethanol. Slow evaporation of the solvent yielded yellow needles of a 1:1 carbamazepine/5-nitroisophthalic acid co-crystal, as shown in Figure 15B.

[00124] Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{47}H_{40}N_6O_{16}$, M=944.85, monoclinic C2/c; a=34.355(8), b=5.3795(13), c=23.654(6) Å,α=90°, β=93.952(6)°, γ=90°, V=4361.2(18)Å^3, T=200(2) K, Z=4, μ(MO-Kα)=0.110 mm^{-1}, D_c=1.439 Mg/m^3, λ=0.71073Å^3 , F(000)1968, $2\theta_{max}$=26.43°. 11581 reflections measured, 4459 unique (R_{int}=0.0611). Final residuals for 311 parameters were R_1=0.0725, wR_2=0.1801 for I>2σ(I), and R_1=0.1441, wR_2=0.1204 for all 4459 data.

[00125] Crystal packing: The co-crystals are sustained by hydrogen bonded carboxylic acid homodimers between the two 5-nitroisophthalic acid moieties and hydrogen bonded carboxy-amide heterodimers between the carbamazepine and 5-nitroisophthalic acid moiety. There is solvent hydrogen bonded to an additional N-H donor from the carbamazepine moiety.

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[00126] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3470 cm^{-1}, (N-H stretch, 1° amine, CBZ); 3178 cm^{-1}, (C-H stretch, alkene); 1688 cm^{-1}, (C=O); 1602 cm^{-1}, (C=C).

[00127] Differential Scanning Calorimetry: (TA Instruments 2920 DSC). 190.51°C (endotherm). m.p. = NA (decomposes at 197-200°C) (MEL-TEMP). (carbamazepine m.p. = 191-192°C, 5-nitroisophthalic acid m.p. = 260-261°C).

[00128] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 32.02% weight loss starting at 202°, a 12.12% weight loss starting at 224° and a 17.94% weight loss starting at 285° followed by complete decomposition.

[00129] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using CuKα (λ=1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3 to 40 2 in continuous scan mode using a step size of 0.02 2 and a scan speed of 2.0 /min. XRPD: Showed analogous peaks to the simulated XRPD derived from the single crystal data. XRPD analysis experimental (calculated): 10.138 (10.283), 15.291 (15.607), 17.438 (17.791), 21.166 (21.685), 31.407 (31.738), 32.650 (32.729).

Example 12—Multi-Component Crystal of Carbamazepine: Carbamazepine/acetic acid (1:1 stoichiometry)

[00130] 25 mg (0.1058 mmol) carbamazepine was dissolved in approximately 2 mL acetic acid. Slow evaporation of the solvent yielded yellow needles of a 1:1 carbamazepine/acetic acid co-crystal, as shown in Figure 16B.

[00131] Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{17}H_{16}N_2O_3$, M=296.32, monoclinic P2(1)/c; a=5.1206(4), b=15.7136(13), c=18.4986(15) Å,α=90°, β=96.5460(10)°, γ=90°, V=1478.8(2)$Å^3$, T=100(2) K, Z=4, μ(MO-Kα)=0.093 mm^{-1}, D_c=1.331 Mg/m^3, λ=0.71073$Å^3$, F(000)624, $2\theta_{max}$=28.4°. 12951 reflections measured, 3529 unique (R_{int}=0.076). Final residuals for 203 parameters were R_1=0.0492, wR_2=0.1335 for I>2σ(I).

[00132] Crystal packing: The co-crystal is sustained by hydrogen bonded carboxamide-carboxylic heterodimers. The second 1° amine hydrogen from each CBZ joins 2 heterodimers side by side forming a tetramer.

[00133] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3462 cm^{-1}, (N-H stretch, 1° amine, CBZ); 1699 cm^{-1}, (C=O); 1629 cm^{-1}, (C=C, CBZ); 1419 cm^{-1}, (COOH, acetic acid).

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[00134] Melting Point: 187°C (MEL-TEMP). (carbamazepine m.p. = 191-192°C, acetic acid m.p. = 16.6°C).

[00135] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 20.62% weight loss starting at 104° and a 77.05% weight loss starting at 200° followed by complete decomposition.

Example 13—Multi-Component Crystal of Carbamazepine: Carbamazepine/1,3,5,7-adamantanetetracarboxylic acid (1:1 stoichiometry)

[00136] 15 mg (0.1524 mmol) carbamazepine and 20 mg (0.1556 mmol) 1,3,5,7-adamantanetetracarboxylic acid were dissolved in approximately 1 mL methanol or 1 mL ethanol. Slow evaporation of the solvent yields clear plates of a 2:1 carbamazepine/1,3,5,7-adamantanetetracarboxylic acid co-crystal, as shown in Figure 17B.

[00137] Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{44}H_{40}N_2O_{10}$, M=784.80, monoclinicC2/c; a=18.388(4), b=12.682(3), c=16.429(3) Å, β=100.491(6)°, V=3767.1(14) $Å^3$, T=100(2) K, Z=4, μ(MO-Kα)=0.099 mm^{-1}, D_c=1.384 Mg/m^3, λ=0.71073$Å^3$, F(000)1648, $2\theta_{max}$=28.20°. 16499 reflections measured, 4481 unique (R_{int}=0.052). Final residuals for 263 parameters were R_1=0.0433 and wR_2=0.0913 for I>2σ(I).

[00138] Crystal packing: The co-crystals form a single 3D network of four tetrahedron, linked by square planes similar to the *PtS* topology. The crystals are sustained by hydrogen bonding.

[00139] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3431 cm^{-1}, (N-H stretch, 1° amine, CBZ); 3123 cm^{-1}, (C-H stretch, alkene); 1723 cm^{-1}, (C=O); 1649 cm^{-1}, (C=C).

[00140] Melting Point: (MEL-TEMP). 258-260°C (carbamazepine m.p. = 191-192°C, adamantanetetracarboxylic acid m.p. = >390°C).

[00141] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 9% weight loss starting at 189°C, a 52% weight loss starting at 251°C and a 31% weight loss starting at 374°C followed by complete decomposition.

Example 14—Multi-Component Crystal of Carbamazepine: Carbamazepine/benzoquinone (1:1 stoichiometry)

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[00142] 25 mg (0.1058 mmol) carbamazepine and 11 mg (0.1018 mmol) benzoquinone was dissolved in 2 mL methanol or THF. Slow evaporation of the solvent produced an average yield of yellow crystals of a 1:1 carbamazepine/benzoquinone co-crystal, as shown in Figure 18B.

[00143] Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{21}H_{16}N_2O_3$, M=344.36, monoclinic P2(1)/c; a=10.3335(18), b=27.611(5), c=4.9960(9) Å, β=102.275(3)°, V=1392.9(4) $Å^3$, T=100(2) K, Z=3, D_c=1.232 Mg/m^3, μ(MO-Kα)=0.084 mm^{-1}, λ=0.71073$Å^3$, F(000)540, $2\theta_{max}$=28.24°. 8392 reflections measured, 3223 unique (R_{int}=0.1136). Final residuals for 199 parameters were R_1=0.0545 and wR_2=0.1358 for I>2σ(I), and R_1=0.0659 and wR_2=0.1427 for all 3223 data.

[00144] Crystal packing: The co-crystals contain hydrogen bonded carboxamide homodimers. Each 1° amine on the CBZ is bifurcated to a carbonyl group of a benzoquinone moiety. The dimers form infinite chains.

[00145] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3420 cm^{-1}, (N-H stretch, 1° amine, CBZ); 2750 cm^{-1}, (aldehyde stretch); 1672 cm^{-1}, (C=O); 1637 cm^{-1}, (C=C, CBZ).

[00146] Melting Point: 170°C (MEL-TEMP). (carbamazepine m.p. = 191-192°C, benzoquinone m.p. = 115.7°C).

[00147] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 20.62% weight loss starting at 168° and a 78% weight loss starting at 223° followed by complete decomposition.

Example 15—Multi-Component Crystal of Carbamazepine: Carbamazepine/butyric acid (1:1 stoichiometry)

[00148] 10 mg (0.0423 mmol) carbamazepine was dissolved in approximately 1 mL butyric acid. Slow evaporation of the solvent mixture produced an average yield of yellow/brown crystals of a 1:1 carbamazepine/butyric acid co-crystal, as shown in Figure 19B.

[00149] Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{19}H_{20}N_2O_3$, M=324.37, triclinic P-1; a=9.1567, b=10.1745, c=10.5116 Å,α=72.850°, β=70.288°, γ=67.269°, V=832.17 $Å^3$, T=100° K, Z=2, μ(MO-Kα)=0.088 mm^{-1}, D_c=1.290 Mg/m^3, λ=0.71073$Å^3$, F(000)344, $2\theta_{max}$=28.28°. 5315 reflections measured, 3686 unique (R_{int}=0.0552). Final residuals

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for 217 parameters were R_1=0.0499, wR_2=0.1137 for I>2σ(I), and R_1=0.0678, wR_2=0.1213 for all 3686 data.

[00150] Crystal packing: The co-crystals are sustained by hydrogen bonded carboxamide-carboxylic heterodimers between the carbamazepine moieties and the butyric acid moieties. The second 1° amine hydrogen from each CBZ joins 2 heterodimers side by side forming a tetramer.

[00151] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3486 cm^{-1}, (N-H stretch, 1° amine, CBZ); 3307 cm^{-1}, (C-H stretch, alkene); 1684 cm^{-1}, (C=O); 1540 cm^{-1}, (C=C).

[00152] Melting Point: 63-64°C (MEL-TEMP). (carbamazepine m.p. = 191-192°C, butyric acid m.p. = -94°C).

[00153] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA).16 % weight loss starting at 54°, a 16% weight loss starting at 134° and a 49% weight loss starting at 174° followed by complete decomposition.

Example 16—Multi-Component Crystal of Carbamazepine: Carbamazepine/DMSO (1:1 stoichiometry)

[00154] 25 mg (0.1058 mmol) carbamazepine was dissolved in approximately 1.5 mL DMSO. Slow evaporation of the solvent yielded colorless plates of a 1:1 carbamazepine/ DMSO co-crystal, as shown in Figure 20B.

[00155] Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{34}H_{36}N_4O_4S_2$, M=628.79, triclinic P-1; a=7.3254(19), b=8.889(2), c=12.208(3) Å,α=94.840(5)°, β=94.926(5)°, γ=100.048(5)°, V=775.8(3)$Å^3$, T=200(2) K, Z=2, μ(MO-Kα)=0.216 mm^{-1}, D_c=1.320 Mg/m^3, λ=0.71073$Å^3$, F(000)320, $2\theta_{max}$=28.3°. 4648 reflections measured, 3390 unique (R_{int}=0.0459). Final residuals for 209 parameters were R_1=0.0929, wR_2=0.3043 for I>2σ(I).

[00156] Crystal packing: The co-crystals are sustained by the hydrogen bonded carboxamide homosynthon. The 1° amines are hydrogen bonded to the sulfoxide of the DMSO on each side of the homosynthon. The crystal is stabilized by π-π interactions from the tricyclic azepine ring system groups of the CBZ.

[00157] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3369 cm^{-1} (N-H stretch, 1° amine, CBZ); 1665 cm^{-1} (C=O stretching); 1481cm^{-1} (C=C).

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[00158] Differential Scanning Calorimetry: (TA Instruments 2920 DSC). 100°C, 193°C (endotherms). m.p. = 189°C (MEL-TEMP). (carbamazepine m.p. = 191-192°C, DMSO m.p. = 18.45°C)

[00159] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 26% weight loss starting at 102°, a 64% weight loss starting at 212° followed by complete decomposition.

Example 17—Multi-Component Crystal of Carbamazepine: Carbamazepine/formamide (1:1 stoichiometry)

[00160] 10 mg (0.0423 mmol) carbamazepine was dissolved in a mixture of approximately 1 mL formamide/1 mL THF or 1 mL formamide/1 mL methanol. Slow evaporation of the solvent mixture produced an average yield of clear needles of a 1:1 carbamazepine/formamide co-crystal, as shown in Figure 21B.

[00161] Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{16}H_{15}N_3O_2$, M=281.31, triclinic P-1; a=5.1077(11), b=16.057(3), c=17.752(4) Å,α=73.711(3)°, β=89.350(3)°, γ=88.636(3)°, V=1397.1(5) $Å^3$, T=100° K, Z=4, μ(MO-Kα)=0.091 mm^{-1}, D_c=1.337 Mg/m^3, λ=0.71073$Å^3$, F(000)592, $2\theta_{max}$=28.33°. 11132 reflections measured, 6272 unique (R_{int}=0.1916). Final residuals for 379 parameters were R_1=0.0766 and wR_2=0.1633 for I>2σ(I).

[00162] Crystal packing: The co-crystals are sustained by hydrogen bonded carboxamide homodimers between two carbamazepine moieties and carboxylic acid homodimers between two formamide moieties. Infinite chains are formed by the homodimers linked side by side, with every other set of CBZ molecules attached on the sides of the chain but not bonded to form a dimer.

[00163] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3392 cm^{-1}, (N-H stretch, 1° amine, CBZ); 2875 cm^{-1}, (C-H stretch, alkene); 1653 cm^{-1}, (C=O); 1590 cm^{-1} , (C=C).

[00164] Melting Point: 142-144°C (MEL-TEMP). (carbamazepine m.p. = 191-192°C, formamide m.p. = -94°C).

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[00165] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 27% weight loss starting at 138°, a 67% weight loss starting at 195° followed by complete decomposition.

Example 18—Multi-Component Crystal of Carbamazepine: Carbamazepine/formic acid (1:1 stoichiometry)

[00166] 40 mg (0.1693 mmol) carbamazepine was dissolved in approximately 2 mL formic acid. Slow evaporation of the solvent yielded off-white starbursts of a 1:1 carbamazepine/formic acid co-crystal, as shown in Figure 22B.

[00167] Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{16}H_{14}N_2O_3$, M=282.29, monoclinic P21/c; a=5.2031(9), b=14.741(2), c=17.882(3) Å,α=90°, β=98.132(3)°, γ=90°, V=1357.7(4)Å^3, T= 100 K, Z=4, μ(MO-Kα)=0.097 mm^{-1}, D_c=1.381 Mg/m^3, λ=0.71073Å^3 , F(000)592, $2\theta_{max}$=28.3. 9402 reflections measured, 3191 unique (R_{int}=0.111). Final residuals for 190 parameters were R_1=0.0533 and wR_2=0.1268 for I>2σ(I).

[00168] Crystal packing: The co-crystals are sustained by hydrogen bonded carboxylic acid-amine heterodimers arranged in centrosymmetric tetramers.

[00169] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3439 cm^{-1}, (1° amine stretch, CBZ); 3026 cm^{-1} (C-H stretch, CBZ); 1692 cm^{-1}, (1° amide, C=O stretch).

[00170] Melting Point: 187°C (MEL-TEMP). (carbamazepine m.p. = 191-192°C, formic acid m.p. = 8.4°C).

[00171] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 14.60% weight loss starting at 123° and a 68.91% weight loss starting at 196° followed by complete decomposition.

Example 19—Multi-Component Crystal of Carbamazepine: Carbamazepine/trimesic acid (1:1 stoichiometry)

[00172] 36 mg (0.1524 mmol) carbamazepine and 31 mg (0.1475 mmol) trimesic acid were dissolved in a solvent mixture of approximately 2 mL methanol and 2mL dichloromethane. Slow evaporation of the solvent mixture yielded white starbursts of a 1:1 carbamazepine/trimesic acid co-crystal, as shown in Figure 23B.

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[00173] Crystal data: (Bruker SMART-APEX CCD Diffractometer). $C_{24}H_{18}N_2O_7$, M=446.26, monoclinic C2/c; a=32.5312(50), b=5.2697(8), c=24.1594(37) Å,α=90°, β=98.191(3)°, γ=90°, V=4099.39(37) $Å^3$, T=-173 K, Z=8, μ(MO-Kα)=0.110 mm^{-1}, D_c=1.439 Mg/m^3, λ=0.71073$Å^3$, F(000)1968, $2\theta_{max}$=26.43°. 11581 reflections measured, 4459 unique (R_{int}=0.0611). Final residuals for 2777 parameters were R_1=0.1563, wR_2=0.1887 for I>2σ(I), and R_1=0.1441, wR_2=0.1204 for all 3601 data.

[00174] Crystal packing: The co-crystals are sustained by hydrogen bonded carboxylic acid homodimers between carbamazepine and trimesic acid moieties and hydrogen bonded carboxylic acid-amine heterodimers between two trimesic acid moieties arranged in a stacked ladder formation.

[00175] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3486 cm^{-1}(N-H stretch, 1° amine, CBZ); 1688 cm^{-1} (C=O, 1° amide stretch, CBZ); 1602 cm^{-1} (C=C, CBZ).

[00176] Differential Scanning Calorimetry: (TA Instruments 2920 DSC). 273°C (endotherm). m.p. = NA, decomposes at 278°C (MEL-TEMP). (carbamazepine m.p. = 191-192°C, trimesic acid m.p. = 380°C)

[00177] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA). 62.83% weight loss starting at 253° and a 30.20% weight loss starting at 278° followed by complete decomposition.

[00178] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using CuKα (λ=1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3 to 40 2 in continuous scan mode using a step size of 0.02 2 and a scan speed of 2.0 /min. XRPD analysis experimental: 10.736, 12.087, 16.857, 24.857, 27.857.

[00179] All patents, patent applications, provisional applications, and publications referred to or cited herein are incorporated by reference in their entirety, including all figures and tables, to the extent they are not inconsistent with the explicit teachings of this specification.

[00180] It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application.

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Claims

1. A multiple-component phase composition comprising a solid phase that is sustained by intermolecular interactions between two or more independent molecular entities, wherein at least one of said two or more independent molecular entities is a pharmaceutical molecule.

2. The multiple-component phase composition of claim 1, wherein said multiple-component phase composition is a discrete supramolecular entity.

3. The multiple-component phase composition of claim 1, wherein said multiple-component phase composition is a polymeric structure.

4. The multiple-component phase composition of claim 1, wherein said pharmaceutical molecule is sustained by a supramolecular homosynthon when said pharmaceutical molecule is in its pure phase.

5. The multiple-component phase composition of claim 1, wherein said multiple-component phase composition has at least one physical property or chemical property that is different from that of said pharmaceutical when said pharmaceutical molecule is in its pure phase.

6. The multiple-component phase composition of claim 1, wherein said multiple-component phase composition has at least one physical or chemical property that is the same as that of said pharmaceutical molecule when said pharmaceutical molecule is in its pure phase.

7. The multiple-component phase composition of claim 5, wherein said at least one physical or chemical property is selected from the group consisting of chemical stability, thermodynamic stability, solubility, dissolution, bioavailability, crystal morphology, and hygroscopicity.

8. The multiple-component phase composition of claim 6, wherein said at least one physical or chemical property is selected from the group consisting of chemical stability, thermodynamic stability, solubility, dissolution, bioavailability, crystal morphology, and hygroscopicity.

9. The multiple-component phase composition of claim 1, wherein said pharmaceutical molecule is selected from the group consisting of aspirin, acetaminophen, profen, phenytoin, and carbamazepine.

10. The multiple-component phase composition of claim 1, wherein said two or more independent molecular entities are selected from the group consisting of: acetaminophen, 4,4'-bipyridine, and water; phenytoin and pyridine; aspirin and 4,4'-bipyridine; ibuprofen and 4,4'- . bipyridine; flurbiprofen and 4,4'-bipyridine; flurbiprofen, trans-1,2-bis (4-pyridyl) ethylene; carbamazepine, *p*-phthalaldehyde; carbamazepine and nicotinamide; carbamazepine and saccharin; carbamazepine and 2,6-pyridinedicarboxylic acid; carbamazepine and 5-nitroisophthalic acid; carbamazepine and acetic acid; carbamazepine and 1,3,5,7,-adamantanetetracarboxylic acid; carbamazepine and benzoquinone; carbamazepine and butyric acid; carbamazepine and dimethyl stilfoxide; carbamazepine and formamide; carbamazepine and formic acid; and carbamazepine and trimesic acid.

11. The multiple-component phase composition of claim 1, wherein said intermolecular interactions are selected from the group consisting of hydrogen bonding (weak and/or strong), dipole interactions (induced and/or non-induced), stacking interactions, hydrophobic interactions, and other inter-static interactions.

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12. The multiple-component phase composition of claim 1, wherein said intermolecular interactions are between complementary chemical functionalities on said two or more independent molecular entities.

13. The multiple-component phase composition of claim 15, wherein said complementary chemical functionalities include at least one chemical functionality selected from the group consisting of acids, amides, aliphatic nitrogen bases, unsaturated aromatic nitrogen bases, amines, alcohols, halogens, sulfones, nitro groups, S-heterocycles, N-heterocycles, O-heterocycles, ethers thioethers, thiols, esters, thioesters, thioketones, epoxides, acetonates, nitrils, oximes, and organohalides.

14. The multiple-component phase composition of claim 12, wherein said complementary chemical functionalities on said two or more independent molecular entities are the same.

15. The multiple-component phase composition of claim 14, wherein said complementary chemical functionalities are acids.

16. The multiple-component phase composition of -.claim 14, wherein said complementary chemical functionalities are amides.

17. The multiple-component phase composition of claim 12, wherein said complementary chemical functionalities on said two or more independent molecular entities are not the same.

18. The multiple-component phase composition of claim 17, wherein said complementary chemical functionalities on said two or more independent molecular entities are selected from the group consisting of acids and amides; pyridines and amides; and alcohols and amines.

19. The multiple-component phase composition of claim 1, wherein two or more of said independent molecular entities is a pharmaceutical molecule.

20. A multiple-component phase composition comprising a solid phase that is sustained by intermolecular interactions between aspirin and at least one independent molecular entity.

21. A multiple-component phase composition comprising a solid phase that is sustained by intermolecular interactions between acetaminophen and at least one independent molecular entity.

22. A multiple-component phase composition comprising a solid phase that is sustained by intermolecular interactions between a profen and at least one independent molecular entity.

23. A multiple-component phase composition comprising a solid phase that is sustained by intermolecular interactions between phenytoin and at least one independent molecular entity.

24. A multiple-component phase composition comprising a solid phase that is sustained by intermolecular interactions between carbamazepine and at least one independent molecular entity.

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25. A method for identifying complementary chemical functionalities in order to form a desired supramolecular synthon, said method comprising:

(a) evaluating the structure of an active pharmaceutical ingredient;

(b) determining whether the active pharmaceutical ingredient contains chemical functionalities capable of forming supramolecular synthons with itself;

(c) identifying from a plurality of chemical functionalities that are known to form a supramolecular synthon at least one functionality that will form a further supramolecular synthon to the supramolecular synthon formed by the active pharmaceutical ingredient, wherein the identified chemical functionality is not capable of disrupting non-covalent bonding within the supramolecular synthon formed by the supramolecular synthon formed by the active pharmaceutical ingredient, and wherein the selected chemical functionality is capable of forming a noncovalent bond to the supramolecular synthon formed by the active pharmaceutical ingredient; and

(d) identifying co-crystal formers having chemical functionalities that are complementary with the active pharmaceutical ingredient.

26. The method of claim 25, wherein said method further comprises preparing a multiple-component solid phase composition, wherein the multiple-component solid phase composition comprises the active pharmaceutical ingredient and at least one of the identified co-crystal formers.

27. The method of claim 26, wherein the at least one co-crystal former is selected from the group consisting of a different active pharmaceutical ingredient, a GRAS compound, a food additive, a low toxicity organic, and a metal-organic complex.

28. The method of claim 26, wherein the multiple-component solid phase composition is formed by one or more methods selected from the group consisting of crystallization from solution, cooling the melt, sublimation, and grinding.

29. A method for identifying complementary chemical functionalities in order to form a desired supramolecular synthon, said method comprising:

(a) evaluating the structure of an active pharmaceutical ingredient;

(b) determining whether the active pharmaceutical ingredient contains chemical functionalities capable of forming supramolecular synthons with itself;

(c) identifying from a plurality of chemical functionalities that are known to form supramolecular synthons at least one functionality that will form a supramolecular synthon with the active pharmaceutical ingredient, wherein the identified chemical functionality is capable of disrupting non-covalent bonding within the supramolecular synthon formed by the active pharmaceutical ingredient, and wherein the selected chemical functionality is capable of forming a noncovalent bond to a complementary chemical functionality on the active pharmaceutical ingredient; and

(d) identifying co-crystal formers having chemical functionalities that are complementary with the active pharmaceutical ingredient.

30. The method of claim 29, wherein said method further comprises preparing a multiple-component solid phase composition, wherein the multiple-component solid phase composition comprises the active pharmaceutical ingredient and at least one of the identified co-crystal formers.

31. The method of claim 30, wherein the at least one co-crystal former is selected from the group consisting of a different active pharmaceutical ingredient, a GRAS compound, a food additive, a low toxicity organic, and a metal-organic complex.

32. The method of claim 30, wherein the multiple-component solid phase composition is formed by one or more methods selected from the group consisting of crystallization from solution, cooling the melt, sublimation, and grinding.

33. A method for identifying complementary chemical functionalities in order to form a desired supramolecular synthon, said method comprising:

(a) evaluating the structure of an active pharmaceutical ingredient;

(b) determining whether the active pharmaceutical ingredient contains chemical functionalities capable of forming supramolecular synthons with different molecules;

(c) identifying from a plurality of chemical functionalities that are known to form supramolecular synthons at least one functionality that will form a supramolecular synthon with the active pharmaceutical ingredient, and wherein the selected chemical functionality is capable of forming a noncovalent bond to a complementary chemical functionality on the active pharmaceutical ingredient; and

(d) identifying co-crystal formers having chemical functionalities that are complementary with the active pharmaceutical ingredient.

34. The method of claim 33, wherein said method further comprises preparing a multiple-component solid phase composition, wherein the multiple-component solid phase composition comprises the active pharmaceutical ingredient and at least one of the identified co-crystal formers.

35. The method of claim 34, wherein the at least one co-crystal former is selected from the group consisting of a different active pharmaceutical ingredient, a GRAS compound, a food additive, a low toxicity organic, and a metal-organic complex.

36. The method of claim 34, wherein the multiple-component solid phase composition is formed by one or more methods selected from the group consisting of crystallization from solution, cooling the melt, sublimation, and grinding.

Abstract

The subject invention concerns a method for identifying complementary chemical functionalities to form a desired supramolecular synthon. The subject invention also pertains to binary phase compositions comprising one or more pharmaceutical entities and methods for producing such compositions.

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Docket No.: U0157.70023US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Michael J. Zaworotko
Application No.:	Not Yet Assigned
Confirmation No.:	Not Yet Assigned
Filed:	Concurrently Herewith
For:	MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT
Examiner:	Not Yet Assigned
Art Unit:	Not Yet Assigned

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

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

Dear Madam:

INTRODUCTORY COMMENTS

Prior to examination on the merits, please amend the above-identified U.S. patent application as follows:

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

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this paper.

Remarks/Arguments begin on page 8 of this paper.

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AMENDMENTS TO THE SPECIFICATION

Please add the following paragraph under the BRIEF DESCRIPTION OF THE DRAWINGS on page 6 before paragraph [0015]:

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

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AMENDMENTS TO THE CLAIMS

Please replace all prior versions, and listings, of claims in the application with the following list of claims:

1-36. (Canceled)

37. (New) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former,

wherein the API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form,

wherein the co-former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding,

wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form,

wherein said co-former is not an API, and

wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former.

38. (New) The pharmaceutical composition of claim 37, wherein the supramolecular synthon comprises a supramolecular heterosynthon dimer formed by non-covalent hydrogen bonding of the API to the co-former.

39. (New) The pharmaceutical composition of claim 37, wherein the supramolecular synthon comprises a plurality of the API and a plurality of the co-former, wherein the supramolecular synthon is a chain of supramolecular heterosynthons, each supramolecular heterosynthon formed by

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non-covalent hydrogen bonding of one API to one co-former, and wherein the supramolecular heterosynthons are bonded to one another by non-covalent hydrogen bonding.

40. (New) The pharmaceutical composition of claim 37, wherein the cocrystal is a hydrated cocrystal, wherein the supramolecular synthon comprises a plurality of the API and a plurality of the co-former, wherein the supramolecular synthon affords a sheet of the API, each of the APIs in the sheet bonded to one another and to a co-former by non-covalent hydrogen bonding to a water molecule.

41. (New) The pharmaceutical composition of claim 37, wherein the at least one pharmaceutical entity participating in each supramolecular synthon is two APIs and the at least one co-former is one co-former, and wherein each of the two APIs is bonded by non-covalent bonding to the one co-former.

42. (New) The pharmaceutical composition of claim 37, wherein the at least one co-former participating in each supramolecular synthon is two co-formers forming a homosynthon, the at least one API in each supramolecular synthon is APIs, and wherein each of the two APIs is bonded by non-covalent bonding to one of the two co-formers.

43. (New) The pharmaceutical composition of claim 37, wherein the at least one API participating in each supramolecular synthon is two APIs and the at least one co-former participating in each supramolecular synthon is two co-formers forming a homosynthon, and wherein one of the two APIs is non-covalently bonded to one of the co-formers and the other of the two APIs is non-covalently bonded to the other of the two co-formers.

44. (New) The pharmaceutical composition of claim 37, wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule. [15B]

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45. (New) The pharmaceutical composition of claim 37, wherein the at least one API participating in each supramolecular synthon is two APIs of the at least one API that are bonded to one another through hydrogen bonding to form at least one homosynthon dimer.

46. (New) The pharmaceutical composition of claim 45, wherein the at least one co-former is two of the co-former and the at least one API is two of the API, wherein the at least one homosynthon dimer is one homosynthon dimer, and wherein the supramolecular synthon forms a tetramer, the tetramer being comprised of the two co-formers and two APIs, and each co-former being attached to the homodimer by hydrogen bonds.

47. (New) The pharmaceutical composition of claim 45, wherein the at least one co-former is two co-formers, wherein the at least one homosynthon dimer is two homosynthon dimers, and wherein the supramolecular synthon results in a hexamer.

48. (New) The pharmaceutical composition of claim 37, wherein the supramolecular synthon comprises a plurality of the API and a plurality of the co-former, wherein the supramolecular synthon comprises a chain of homosynthon dimers, each homosynthon dimer formed by hydrogen bonding of one of the plurality of the API to another of the plurality of the API, and wherein the homosynthon dimers are bonded to the co-former by hydrogen bonding.

49. (New) The pharmaceutical composition of claim 45, wherein the at least one co-former participating in each supramolecular synthon is two co-formers forming a homosynthon.

50. (New) The pharmaceutical composition of claim 37, wherein the second chemical functionality complimentary to the first chemical functionality is (i) two identical second chemical functionalities on the co-former, (ii) three identical second chemical functionalities on the co-former, or (iii) four identical second chemical functionalities on the co-former.

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51. (New) The pharmaceutical composition of claim 37, wherein the first chemical functionality is selected from the group consisting of acids, amides, aliphatic nitrogen bases, pyridines, imidazoles, amines, alcohols, halogens, sulfones, nitro groups, S-heterocycles, N-heterocycles (saturated or unsaturated), O-heterocycles, ethers, thioethers, thiols, esters, thioesters, thioketones, epoxides, acetonates, nitrils, oximes, and organohalides.

52. (New) The pharmaceutical composition of claim 37, wherein the first chemical functionality is (i) a carboxylic acid, (ii) a carbonyl, or (iii) an amine.

53. (New) The pharmaceutical composition of claim 37, wherein the first chemical functionality and the second chemical functionality form (i) a carbonyl-amide hydrogen bond, (ii) a carbonyl:amine hydrogen bond, or (iii) a carboxylic acid:pyridine hydrogen bond (iv) .

54. (New) The pharmaceutical composition of claim 37, wherein the non-covalent bonding of said API homosynthons is carboxylic acid:carboxylic acid hydrogen bonding.

55. (New) The pharmaceutical composition of claim 37, wherein the non-covalent bonding of said API homosynthons is carboxamide:carboxamide hydrogen bonding.

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REMARKS

The specification is amended to include the paragraph required for the petition of color drawings into an application under 37 C.F.R. § 1.84(a)(2).

Claims 1-36 are canceled without prejudice or disclaimer. New claims 37-55 are added. Support for the new 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, 14, 15, 18, 20, 21, and 23.

No new matter is added.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

If there is a fee occasioned by this response, 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. U0157.70023US02 from which the undersigned is authorized to draw.

Dated: February 13, 2014

Respectfully submitted,

By: /Edward R. Gates/

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617.646.8000

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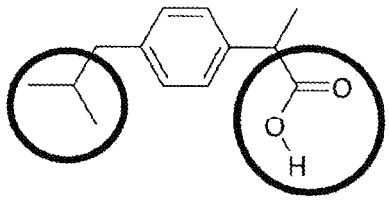


FIG. 1

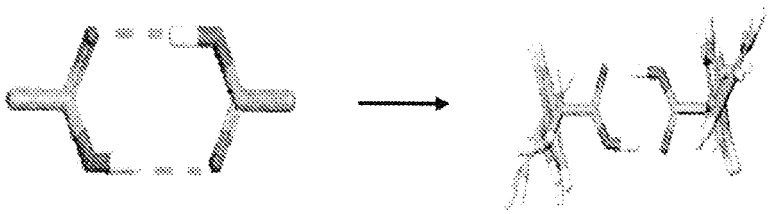


FIG. 2

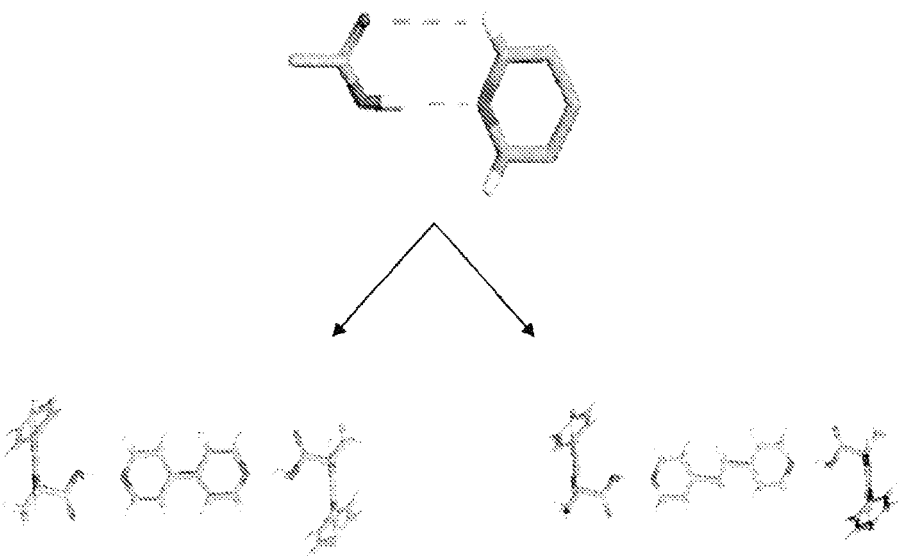


FIG. 3

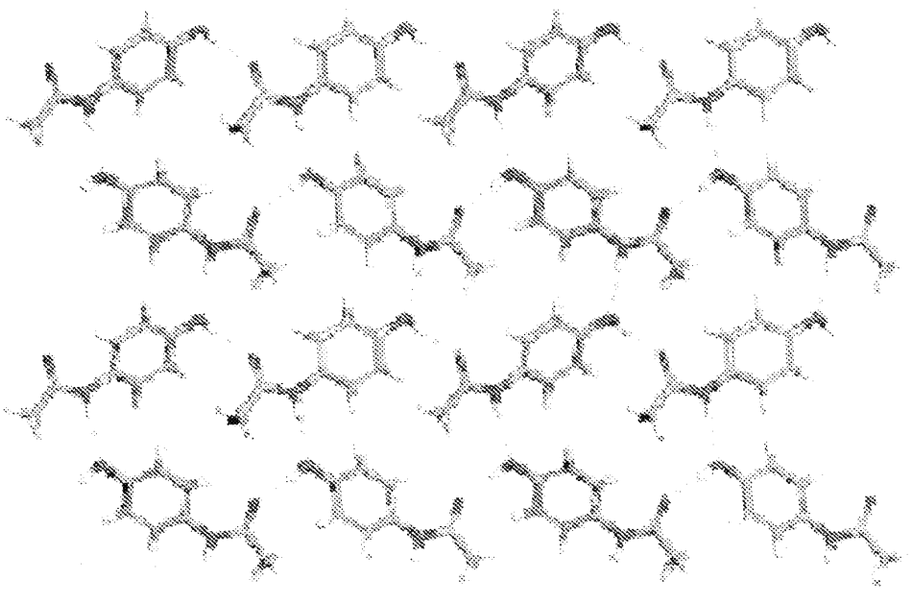


FIG. 4A

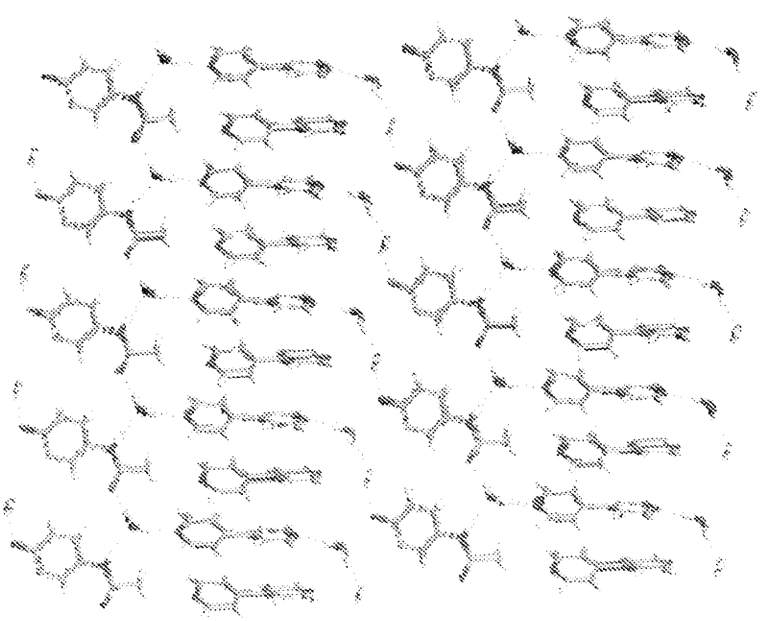


FIG. 4B

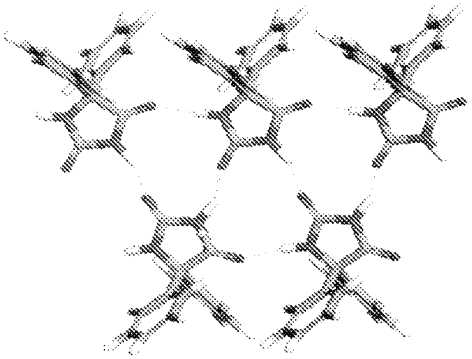


FIG. 5A

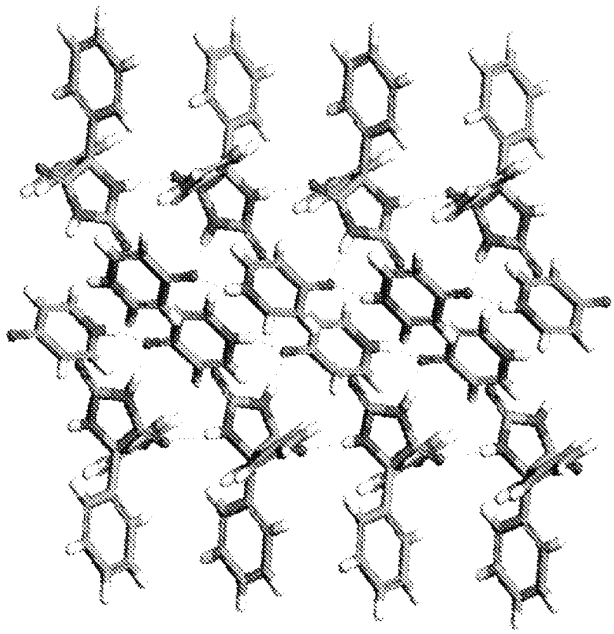


FIG. 5B

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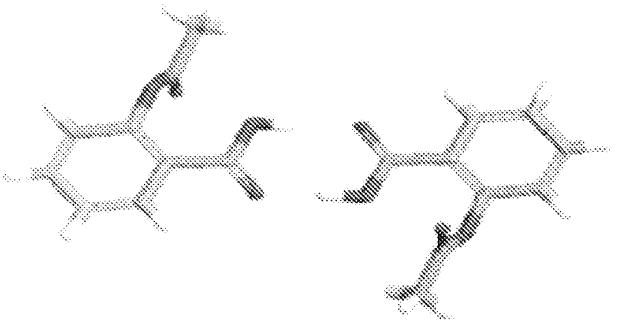


FIG. 6A

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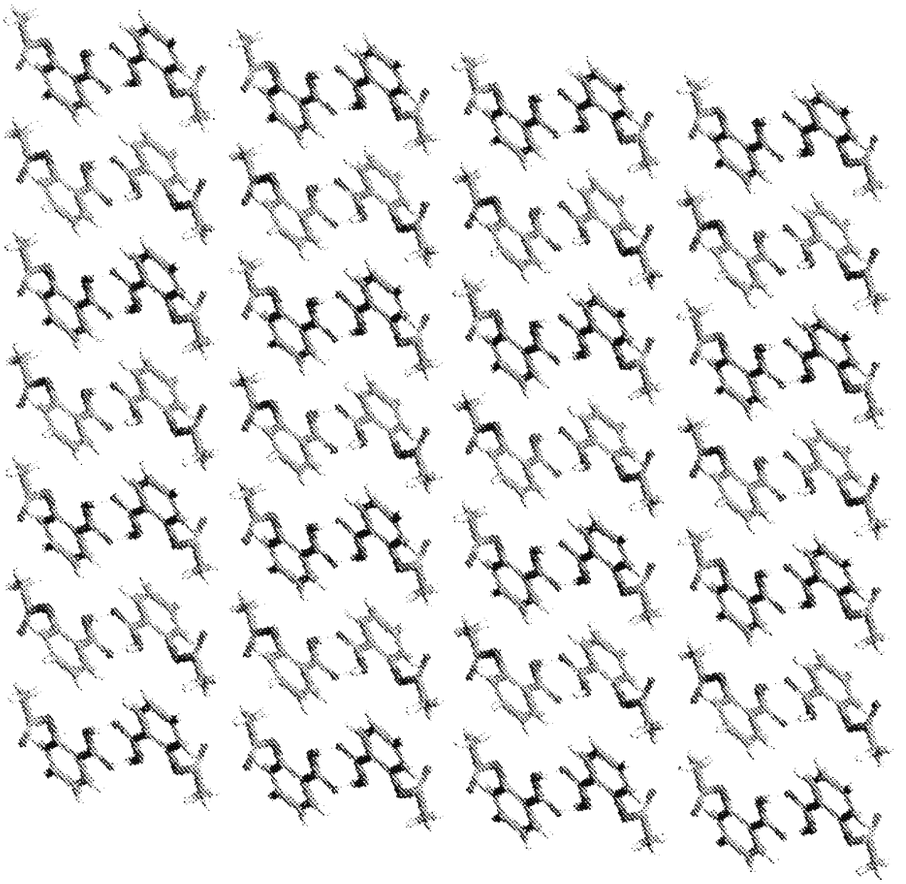


FIG. 6B

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FIG. 6C

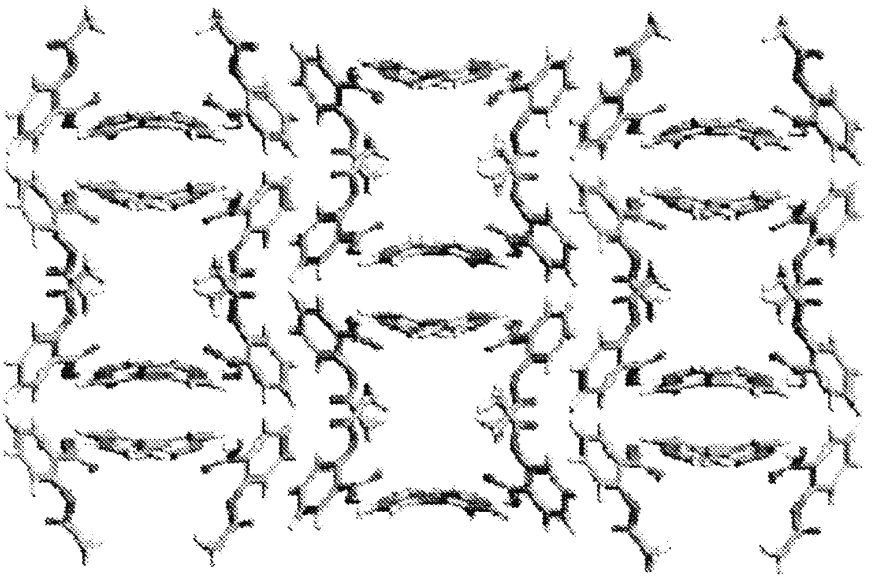
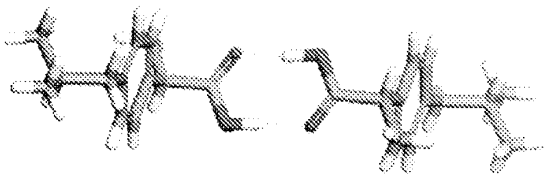


FIG. 6D

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FIG. 7A



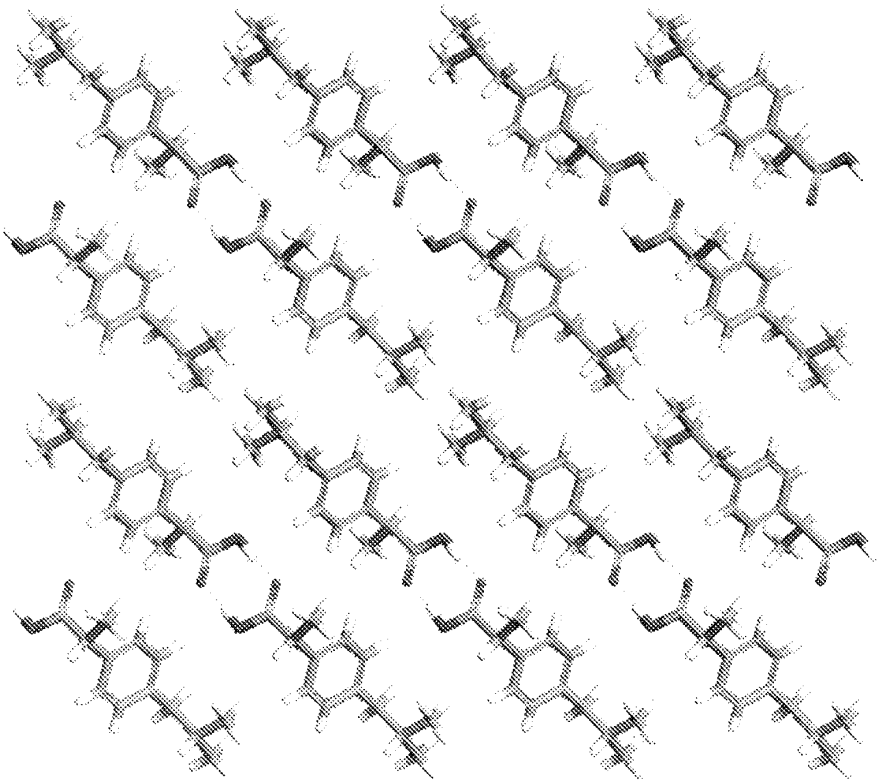
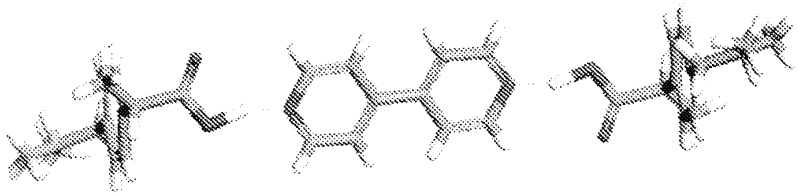


FIG. 7B

FIG. 7C



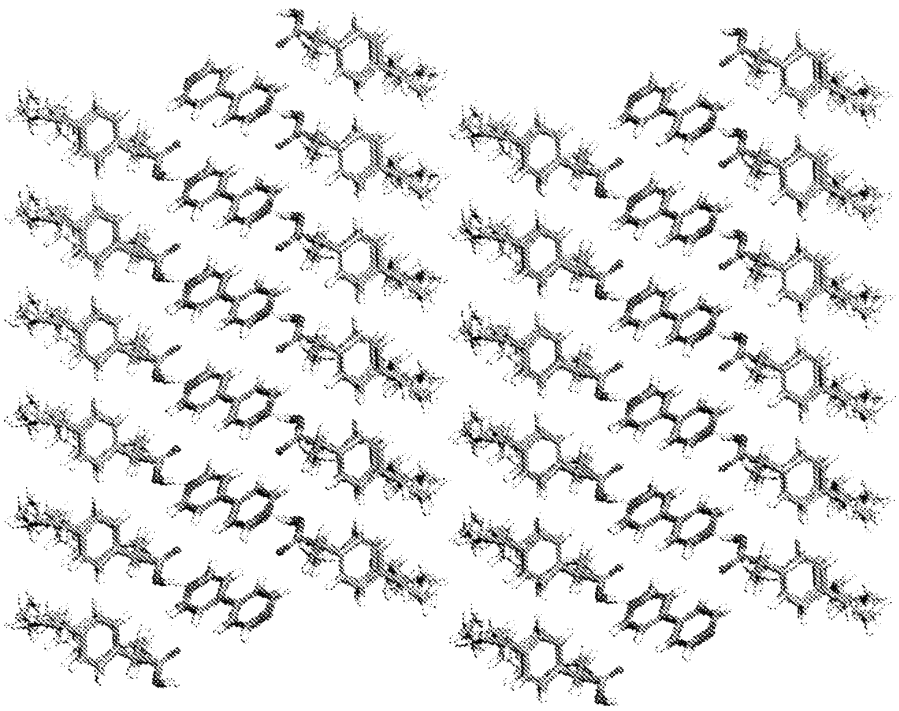
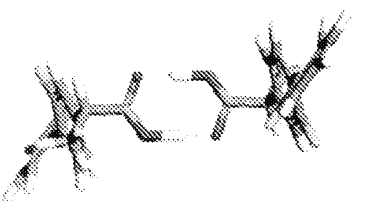


FIG. 7D

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FIG. 8A



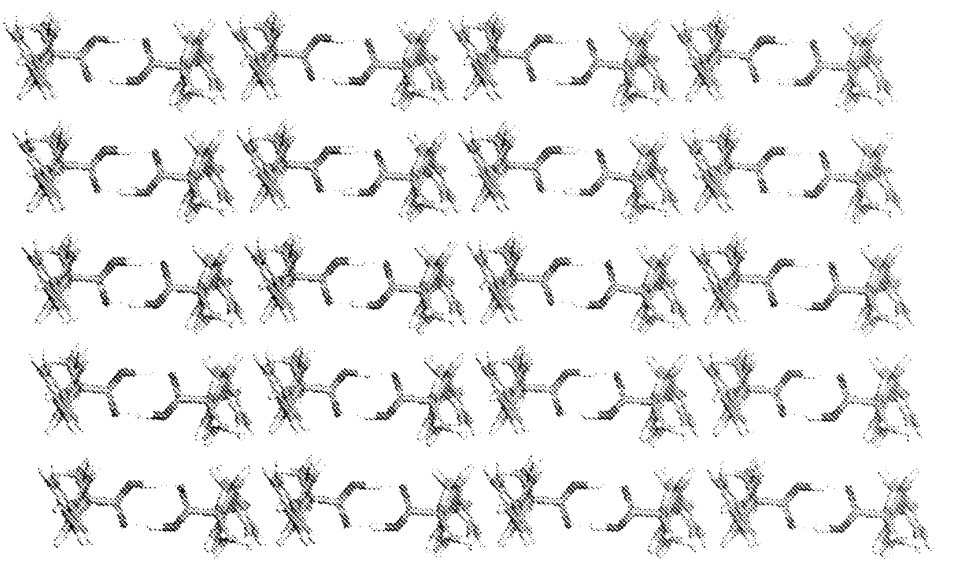
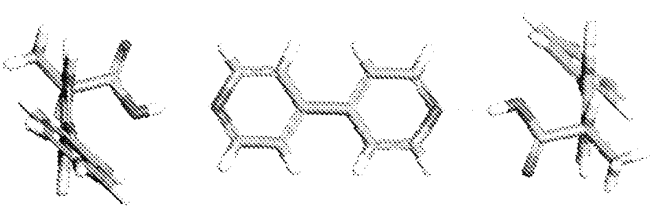


FIG. 8B

FIG. 8C



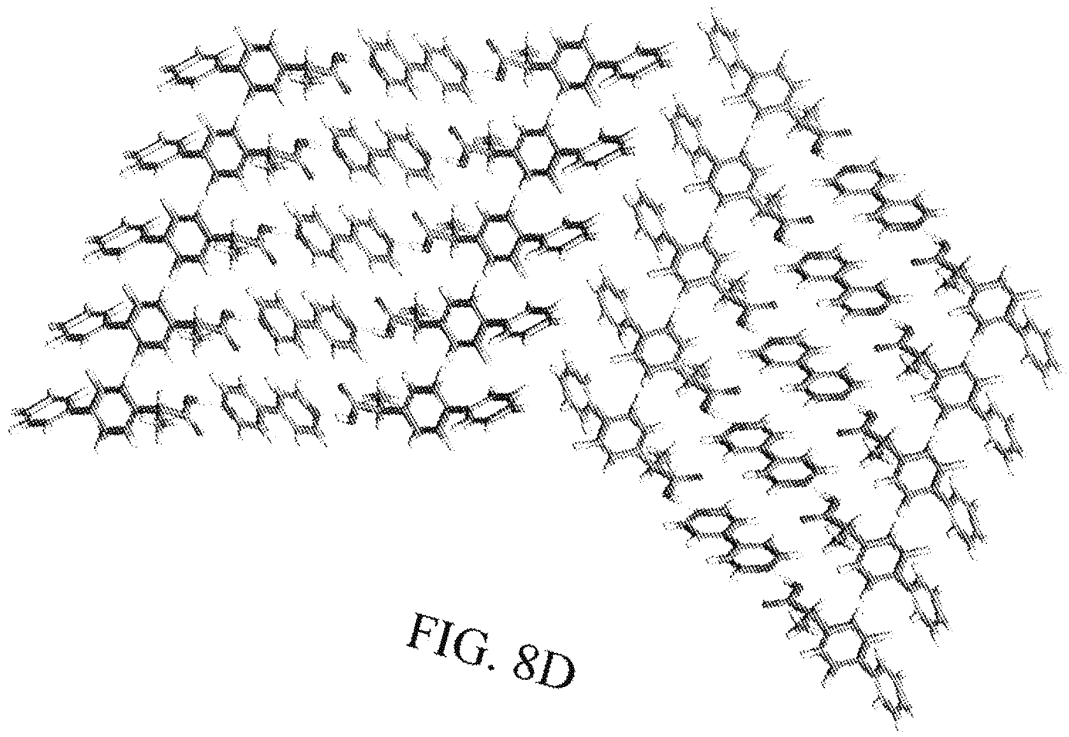


FIG. 8D

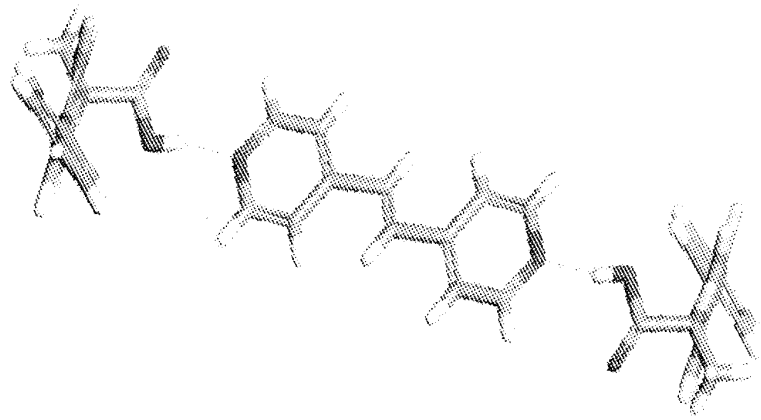


FIG. 9A

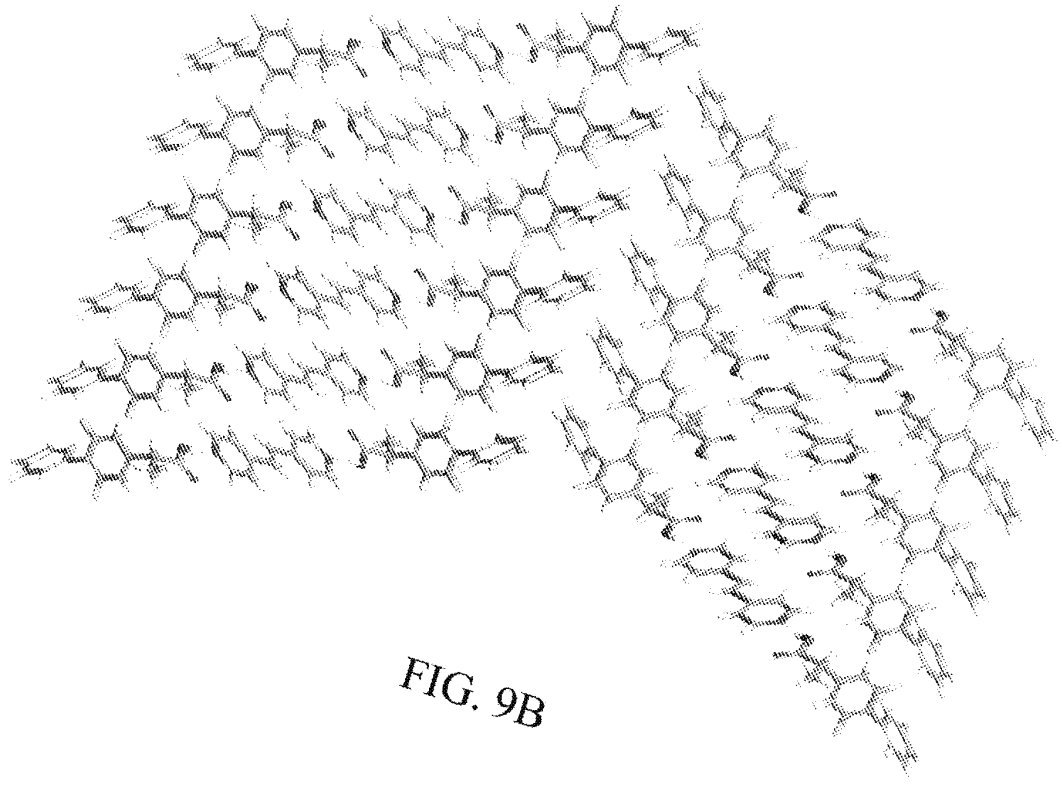


FIG. 9B

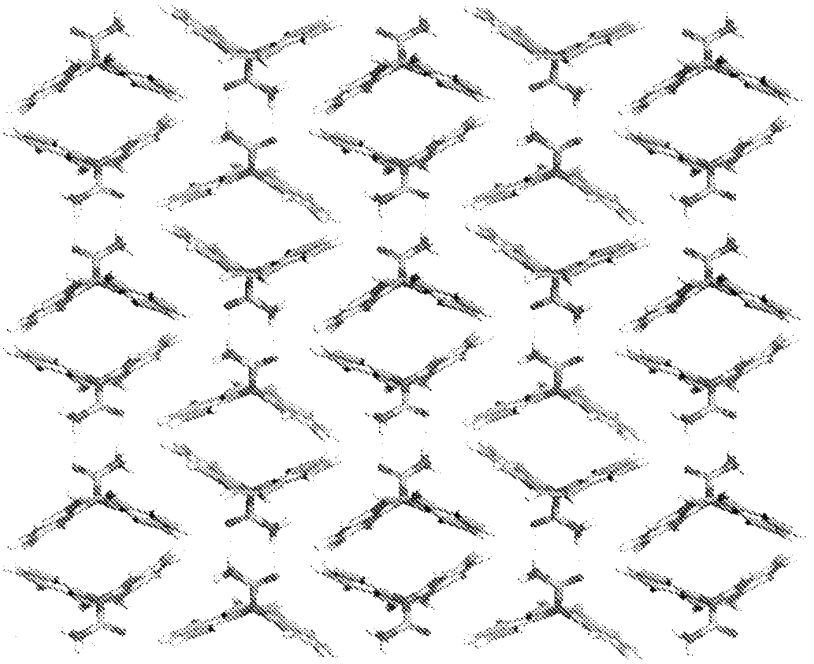


FIG. 10A

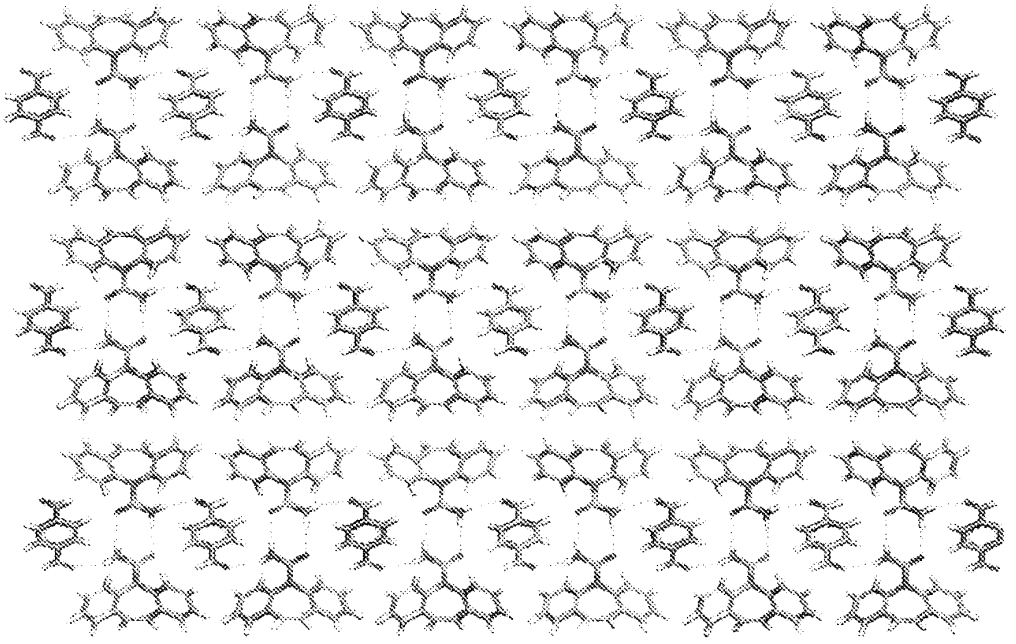


FIG. 10B

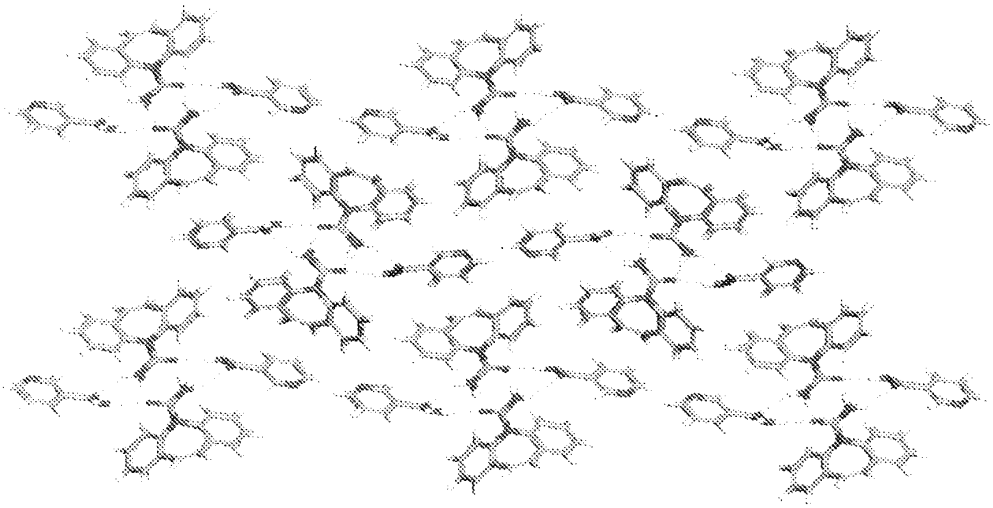


FIG. 11

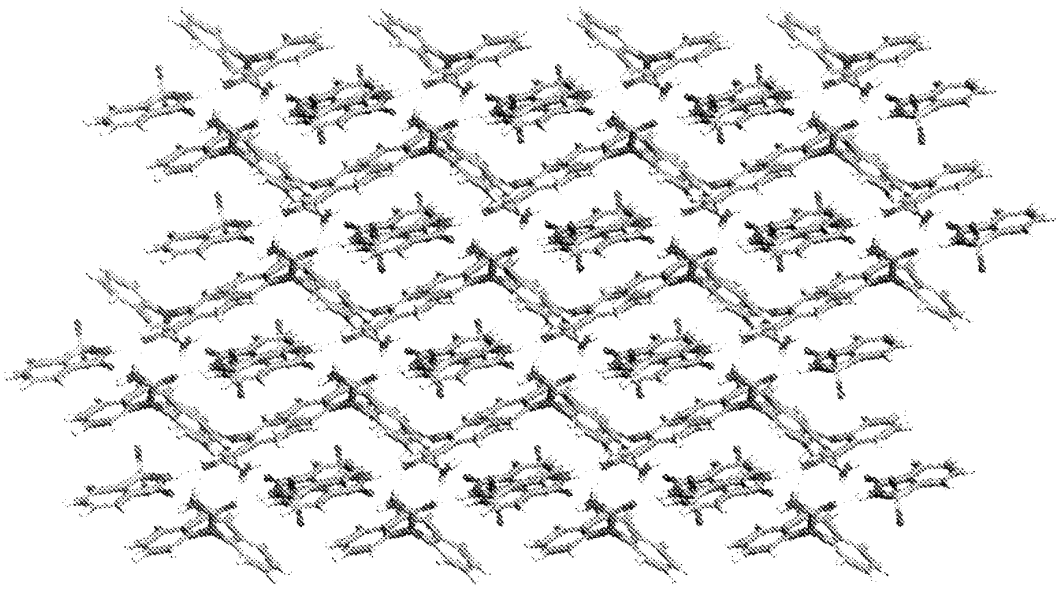


FIG. 12

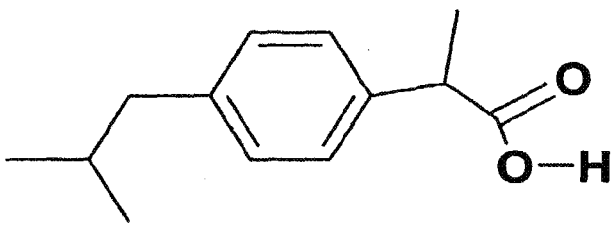


FIG. 13A

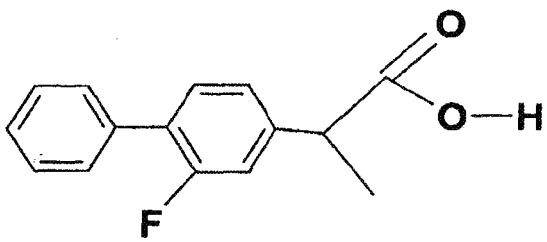


FIG. 13B

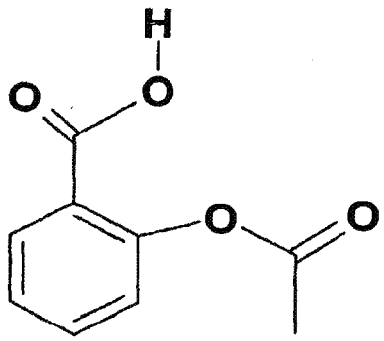


FIG. 13C

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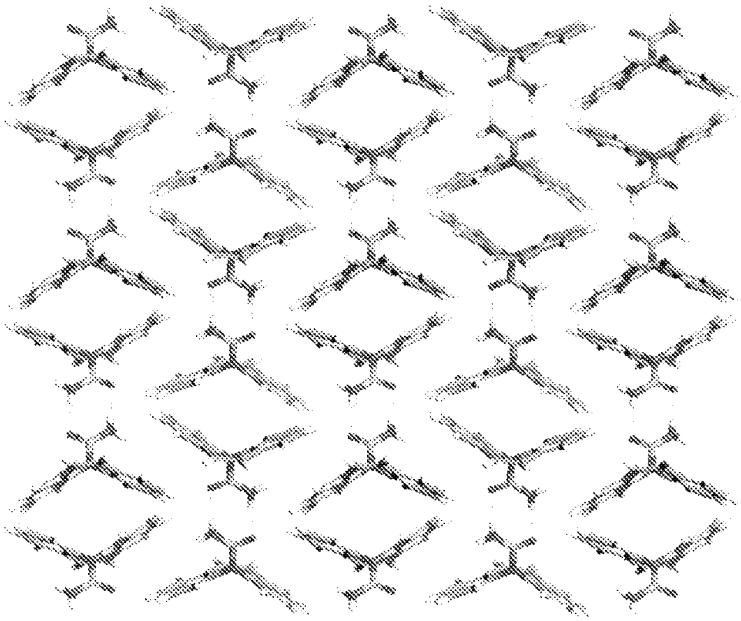


FIG. 14A

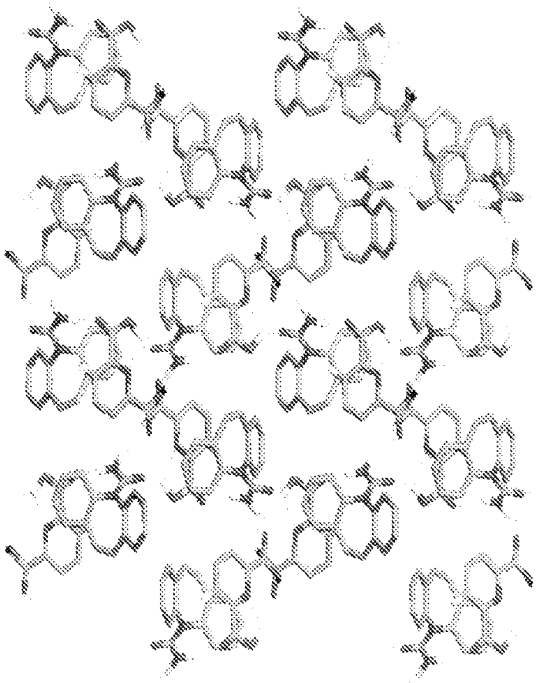


FIG. 14B

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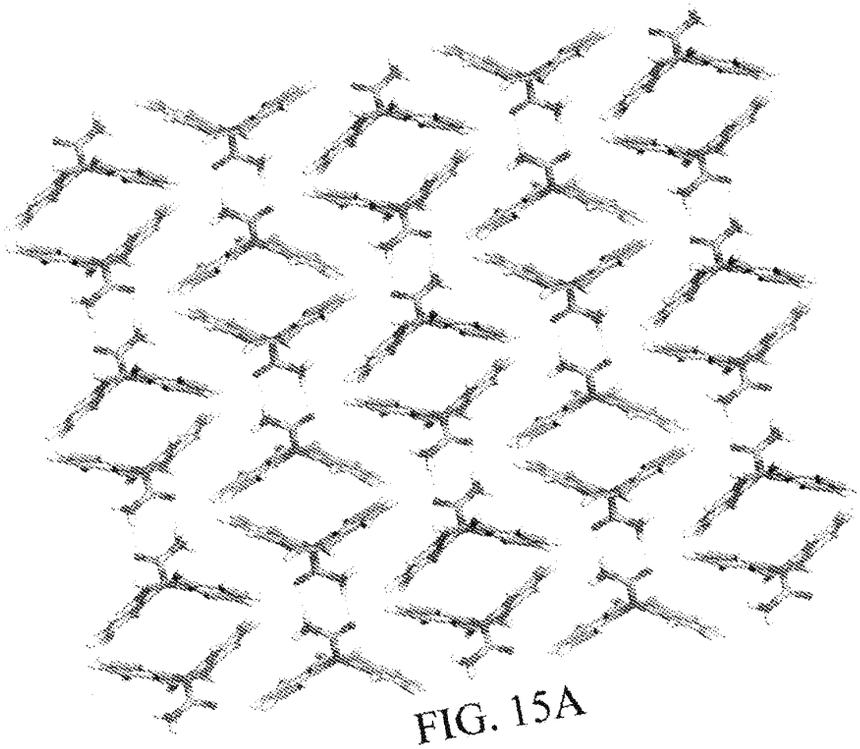


FIG. 15A

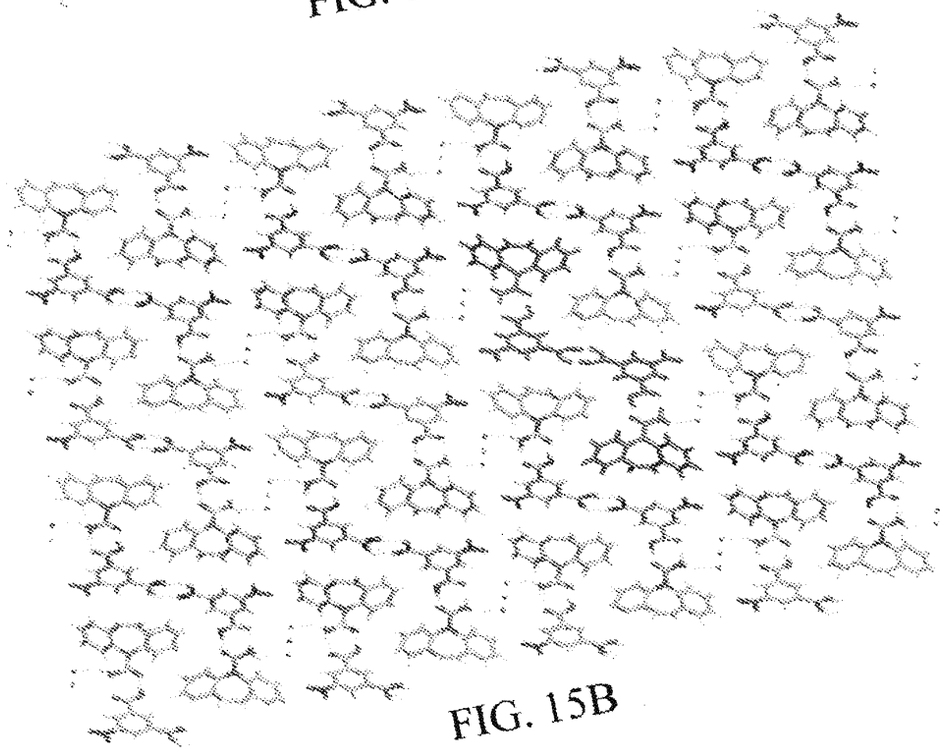


FIG. 15B

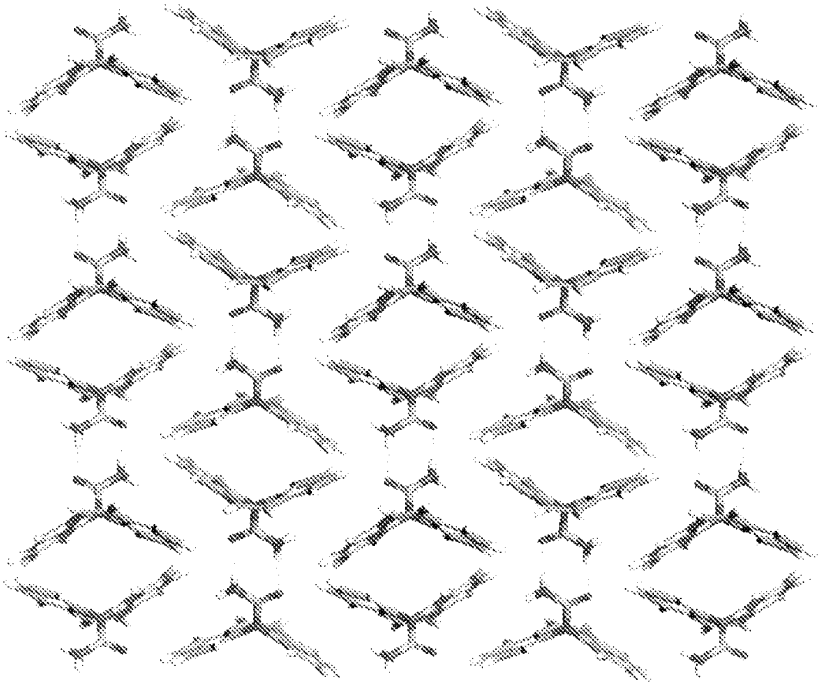


FIG. 16A

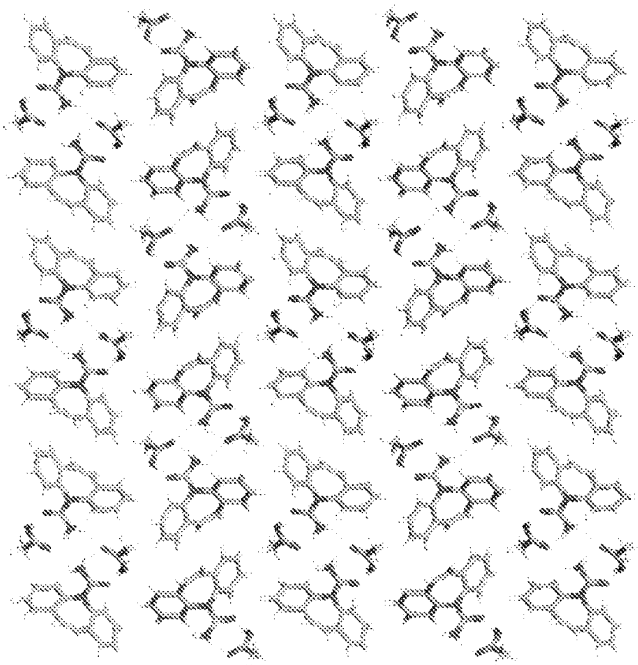


FIG. 16B

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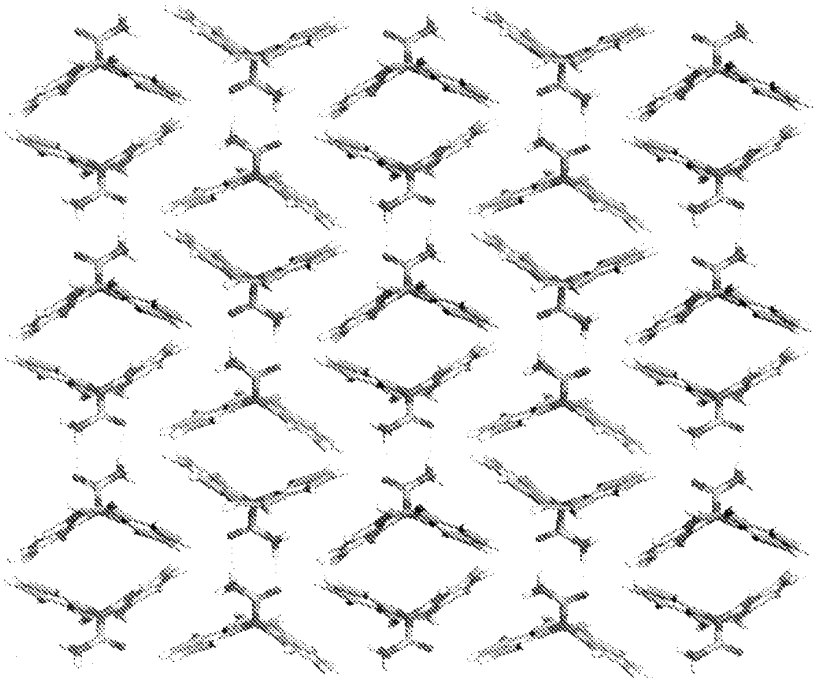


FIG. 17A

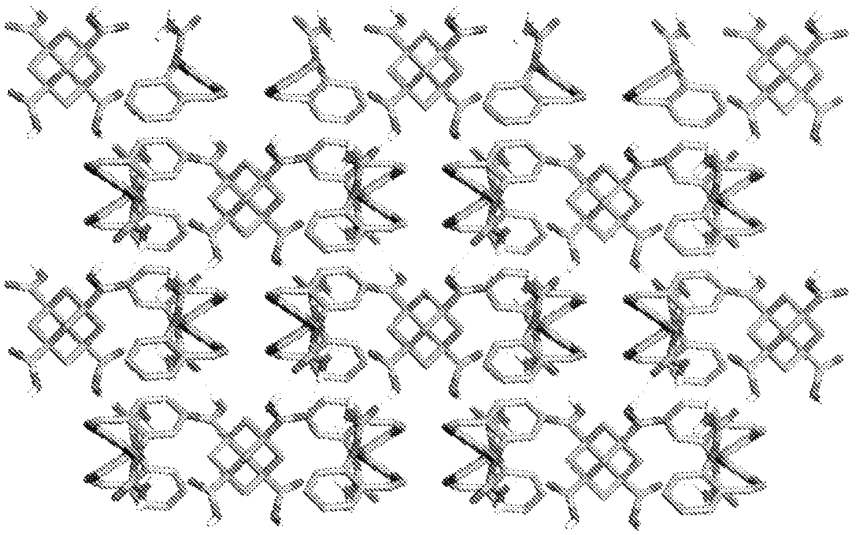


FIG. 17B

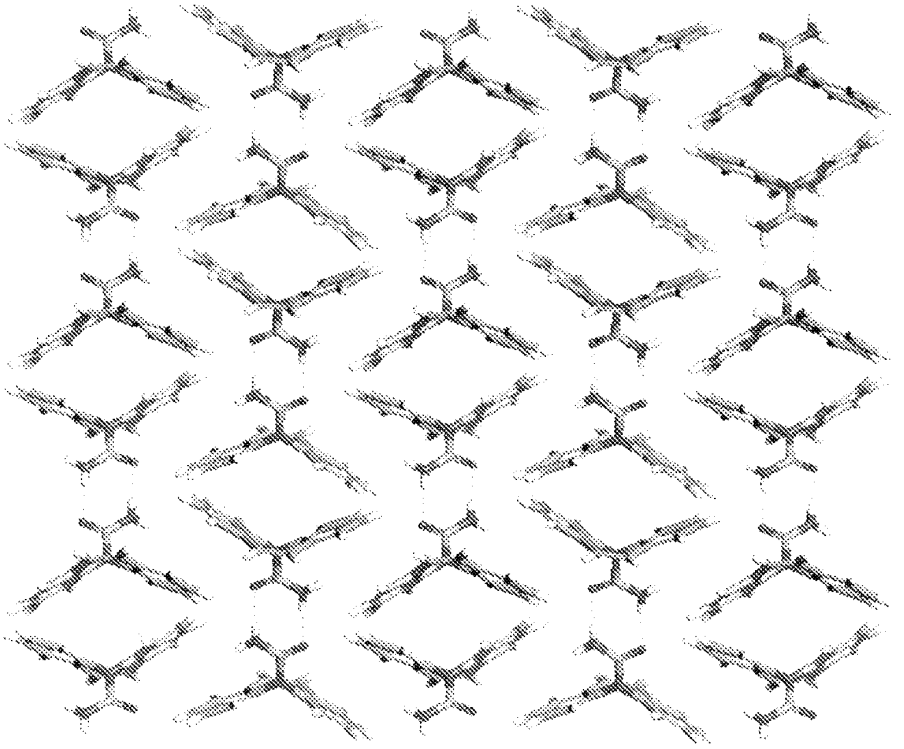


FIG. 18A

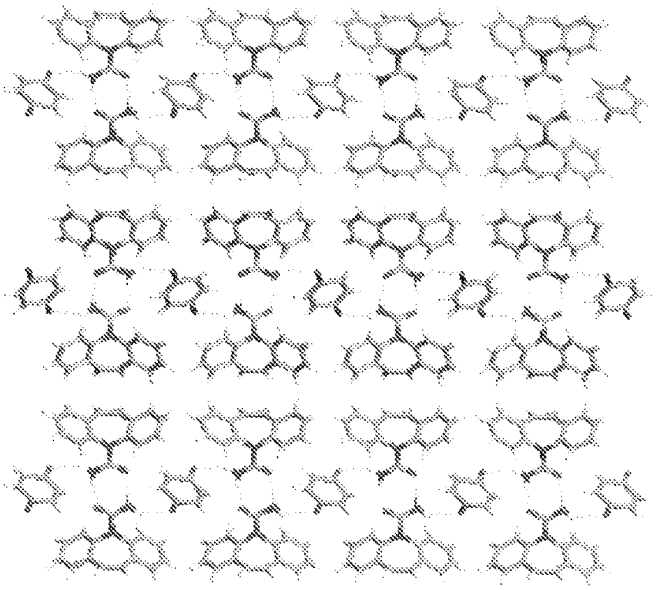


FIG. 18B

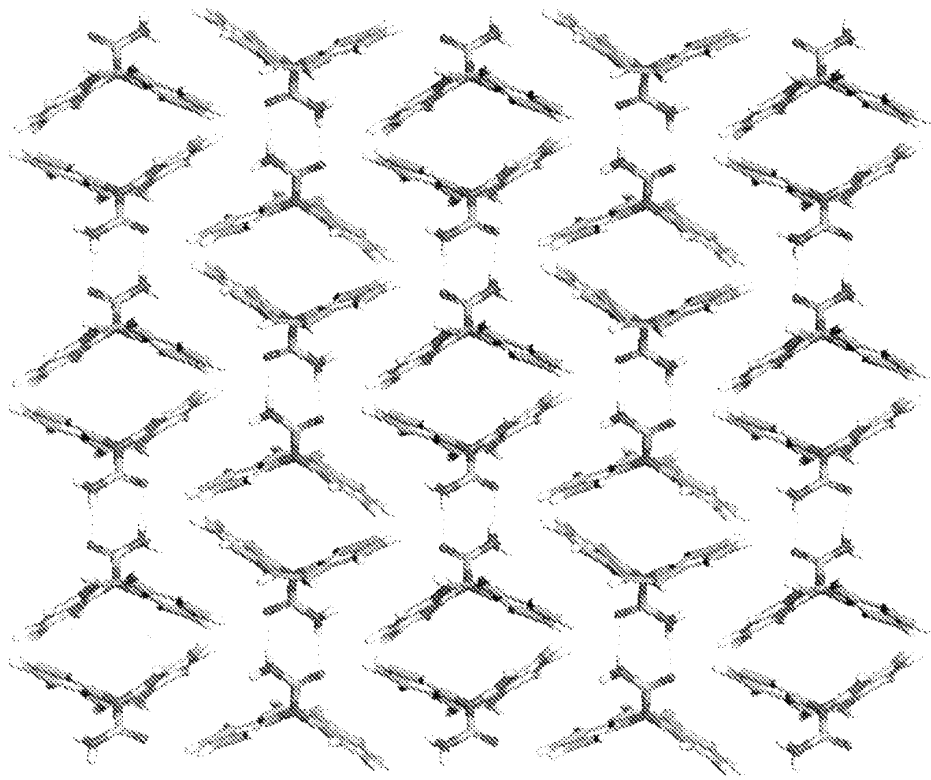


FIG. 19A

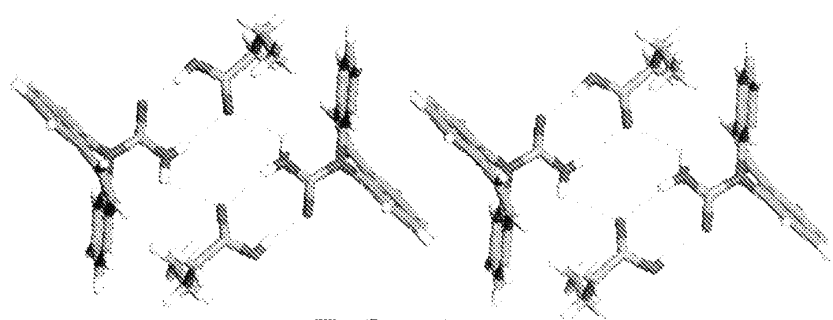


FIG. 19B

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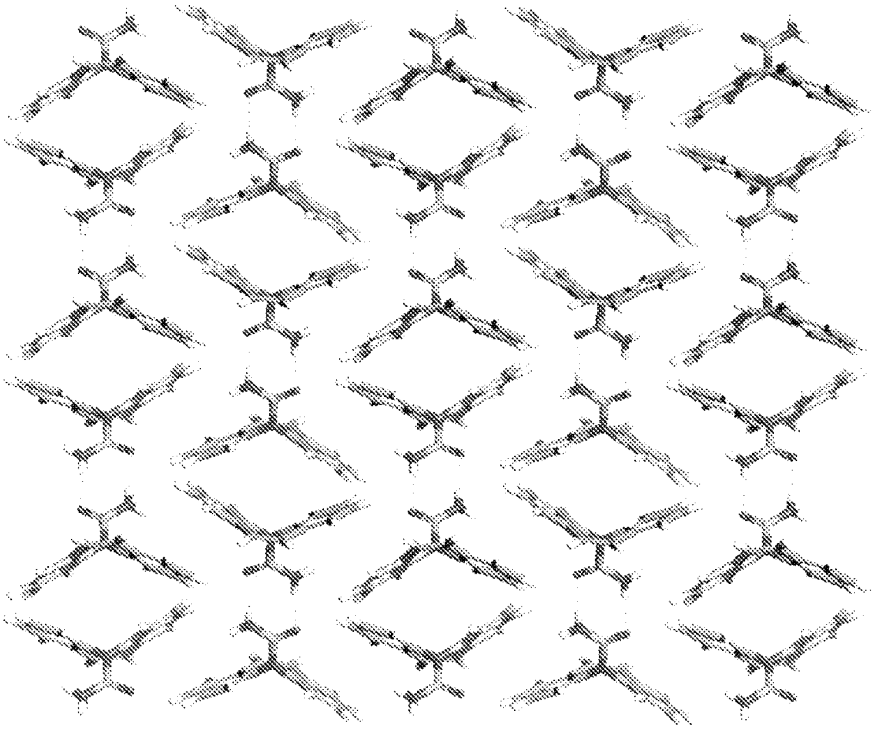


FIG. 20A

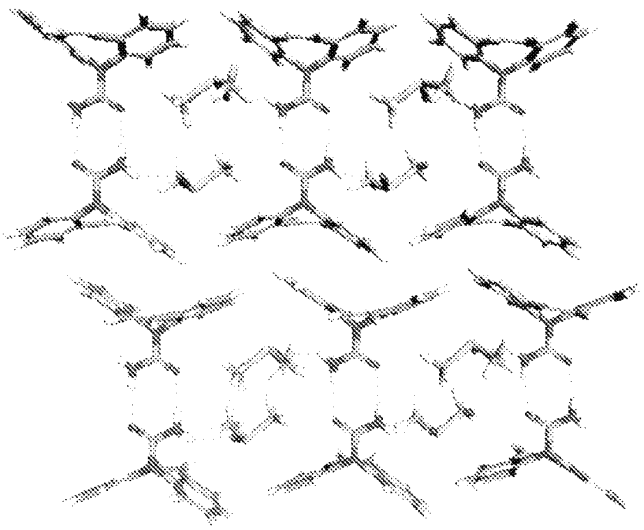


FIG. 20B

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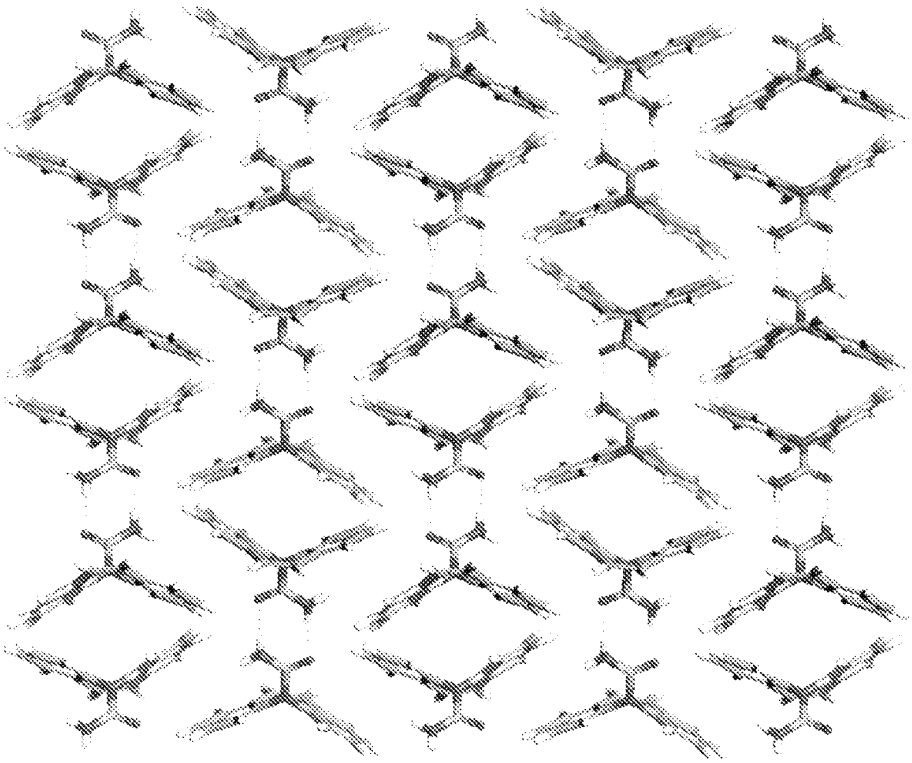


FIG. 21A

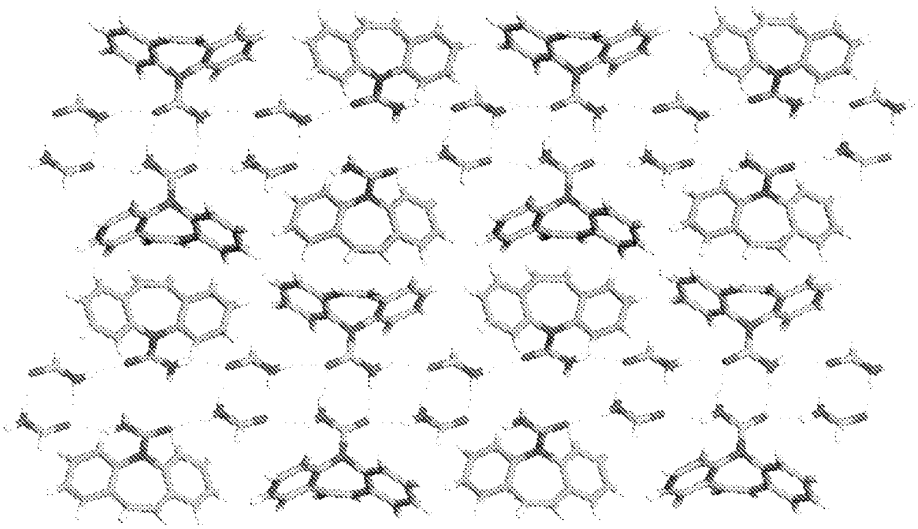


FIG. 21B

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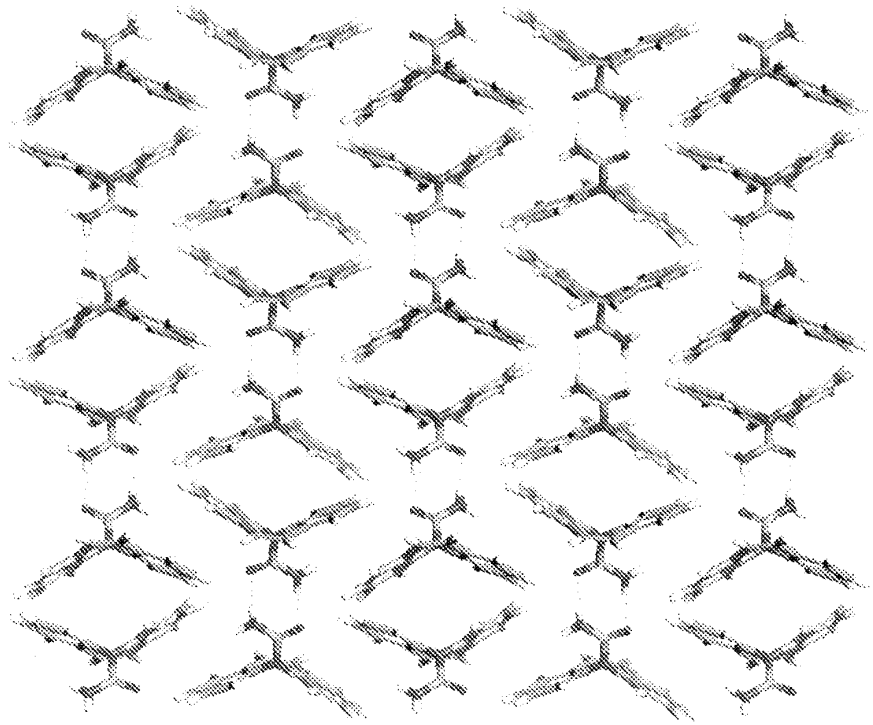


FIG. 22A

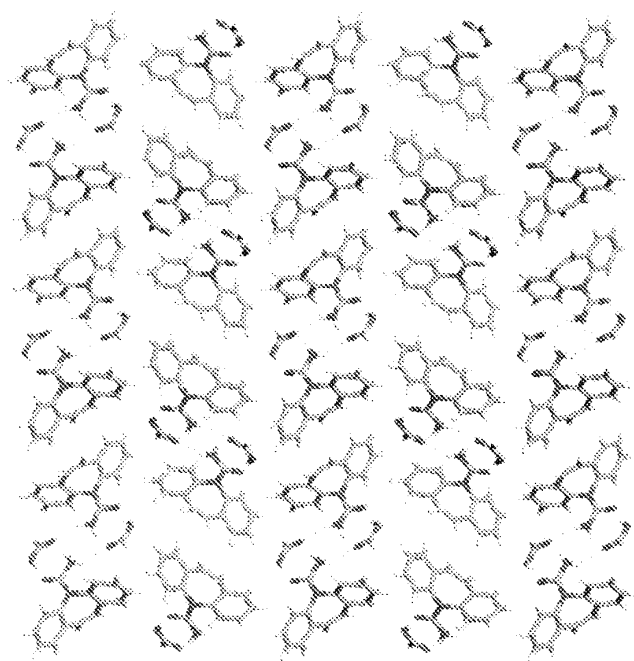


FIG. 22B

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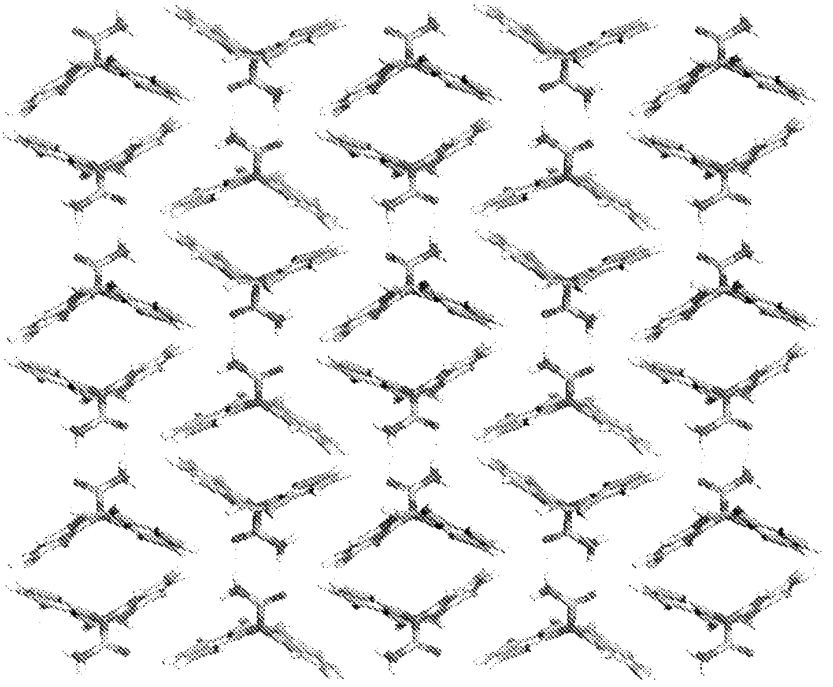


FIG. 23A

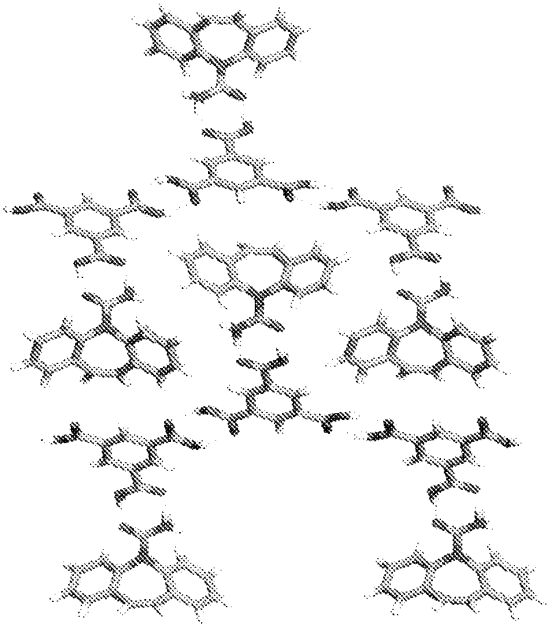


FIG. 23B

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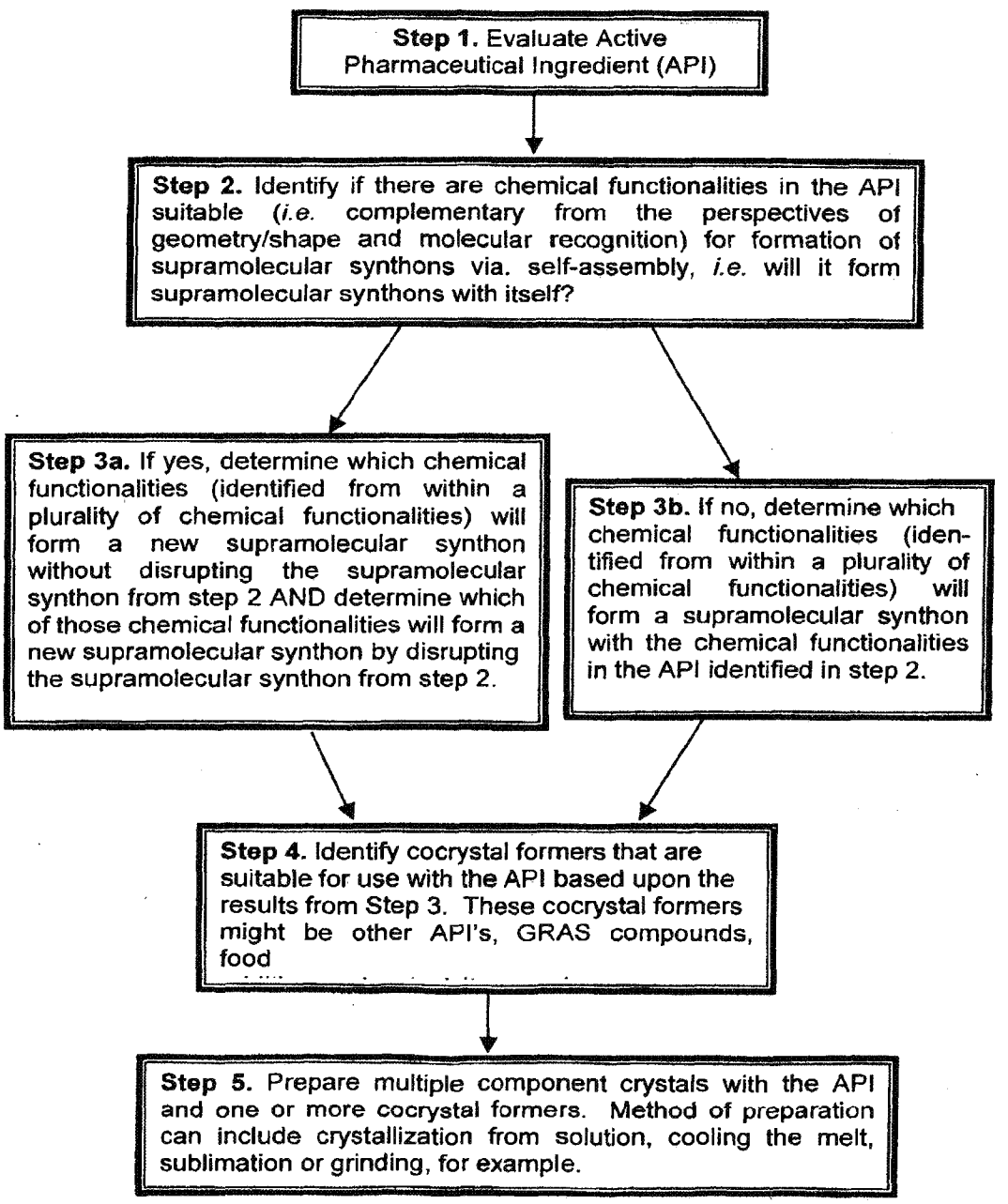

Step 1. Evaluate Active Pharmaceutical Ingredient (API)
Step 2. Identify if there are chemical functionalities in the API suitable (i.e. complementary from the perspectives of geometry/shape and molecular recognition) for formation of supramolecular synthons via. self-assembly, i.e. will it form supramolecular synthons with itself?
Step 3a. If yes, determine which chemical functionalities (identified from within a plurality of chemical functionalities) will form a new supramolecular synthon without disrupting the supramolecular synthon from step 2 AND determine which of those chemical functionalities will form a new supramolecular synthon by disrupting the supramolecular synthon from step 2.
Step 3b. If no, determine which chemical functionalities (identified from within a plurality of chemical functionalities) will form a supramolecular synthon with the chemical functionalities in the API identified in step 2.
Step 4. Identify cocrystal formers that are suitable for use with the API based upon the results from Step 3. These cocrystal formers might be other API's, GRAS compounds, food
Step 5. Prepare multiple component crystals with the API and one or more cocrystal formers. Method of preparation can include crystallization from solution, cooling the melt, sublimation or grinding, for example.

FIG. 24

Docket No.: U0157.70023US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Michael J. Zaworotko
Application No.:	Not Yet Assigned
Confirmation No.:	Not Yet Assigned
Filed:	Concurrently Herewith
For:	MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT
Examiner:	Not Yet Assigned
Art Unit:	Not Yet Assigned

PETITION UNDER 37 CFR 184(A)(2)

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

Dear Madam:

Submitted herewith are color drawings for Figures 1-24 (25 pages total). Color drawings are necessary to represent contents of the Figures accurately and are the only practical medium by which aspects of the claimed subject matter may be accurately conveyed. The color drawings portray the synthons of the invention, formed from interactions between different chemical entities. Similar chemical entities are indicated by the same color and each different chemical entity is indicated by a different color. These colors allow for visualization of the structure of each synthon and visualization of crystal supra-structures formed from the synthons.

Pursuant to 37 C.F.R. § 1.84(a)(2), Applicant hereby petitions for permission to include color drawings in the application and for publication in the patent upon allowance and payment of the issue fee. An amendment to the specification is being filed concurrently herewith to insert the required language under 37 CFR § 1.84(a)(2)(iii) as the first paragraph of the brief description of the drawings. As color drawings are being filed electronically via EFS-Web, only one set of drawings is submitted because the requirement for three sets of color drawings under 37 C.F.R. §

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1.84(a)(2)(ii) is not applicable (see Legal Framework for EFS-Web, Section H, 74 FR 55200, October 27, 2009).

The fee of $70.00 for this Petition under to 37 C.F.R. § 1.84(a)(2)(i), as set forth in 37 C.F.R. § 1.17(h), is being paid by credit card.

Dated: February 13, 2014

Respectfully submitted,

By: /Edward R. Gates/

Edward R. Gates
Registration No.: 31,616
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

DECLARATION (37 C.F.R. § 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 C.F.R. § 1.76)

Title of Invention	MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT

As the below named inventor, I declare that:

This declaration is directed to:

[x] The attached application, or

[ ] United States application or PCT international application number _____ filed on _____

[ ] As amended on _____ (if applicable);

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

I believe the inventor(s) named below to be the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought.

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

I have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above.

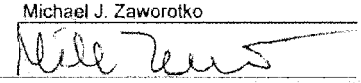
I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in 37 C.F.R. § 1.56.

All statements made herein of my own knowledge are true, and all statements made herein on information and belief are believed to be true.

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

LEGAL NAME OF SOLE OR FIRST INVENTOR

Inventor one: Michael J. Zaworotko Date: Feb 4th 2014

Signature:  Citizen of: United Kingdom and Canada

LEGAL NAME OF ADDITIONAL JOINT INVENTOR, if any

Inventor two: Nair Rodriguez-Hornedo Date: _____

Signature: _____ Citizen of: United States

LEGAL NAME OF ADDITIONAL JOINT INVENTOR, if any

Inventor three: Brian Moulton Date: _____

Signature: _____ Citizen of: Canada

LEGAL NAME OF ADDITIONAL JOINT INVENTOR, if any

Inventor four: _____ Date: _____

Signature: _____ Citizen of _____

[ ] Additional inventors are being named on _____ additional form(s) attached hereto.

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NOVARTIS EXHIBIT 1516
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Page 88 of 725

DECLARATION (37 C.F.R. § 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 C.F.R. § 1.76)

Title of Invention	MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT

As the below named inventor, I declare that:

This declaration is directed to:

[x] The attached application, or

[ ] United States application or PCT international application number _____ filed on _____

[ ] As amended on _____ (if applicable);

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

I believe the inventor(s) named below to be the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought.

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

I have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in 37 C.F.R. § 1.56.

All statements made herein of my own knowledge are true, and all statements made herein on information and belief are believed to be true.

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

LEGAL NAME OF SOLE OR FIRST INVENTOR

Inventor one: Michael J. Zaworotko Date: _____

Signature: _____ Citizen of: United Kingdom and Canada

LEGAL NAME OF ADDITIONAL JOINT INVENTOR, if any

Inventor two: Nair Rodriguez-Hornedo Date: Jan. 27, 2014

Signature: Nair Rodriguez-Hornedo Citizen of: United States

LEGAL NAME OF ADDITIONAL JOINT INVENTOR, if any

Inventor three: Brian Moulton Date: _____

Signature: _____ Citizen of: Canada

LEGAL NAME OF ADDITIONAL JOINT INVENTOR, if any

Inventor four: _____ Date: _____

Signature: _____ Citizen of: _____

[ ] Additional inventors are being named on _____ additional form(s) attached hereto.

UM00000107
NOVARTIS EXHIBIT 1516
Novartis v. Regents, IPR2023-01347
Page 89 of 725

DECLARATION (37 C.F.R. § 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 C.F.R. § 1.76)

Title of Invention	MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT

As the below named inventor, I declare that:

This declaration is directed to:

[x] The attached application, or

[ ] United States application or PCT international application number _____ filed on _____

[ ] As amended on _____ (if applicable);

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

I believe the inventor(s) named below to be the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought.

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

I have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in 37 C.F.R. § 1.56.

All statements made herein of my own knowledge are true, and all statements made herein on information and belief are believed to be true.

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

LEGAL NAME OF SOLE OR FIRST INVENTOR

Inventor one: Michael J. Zaworotko Date: _____

Signature: _____ Citizen of: United Kingdom and Canada

LEGAL NAME OF ADDITIONAL JOINT INVENTOR, if any

Inventor two: Nair Rodriguez-Hornedo Date: _____

Signature: _____ Citizen of: United States

LEGAL NAME OF ADDITIONAL JOINT INVENTOR, if any

Inventor three: Brian Moulton Date: 01.28.14

Signature: _____ Citizen of: Canada

LEGAL NAME OF ADDITIONAL JOINT INVENTOR, if any

Inventor four: _____ Date: _____

Signature: _____ Citizen of: _____

[ ] Additional inventors are being named on _____ additional form(s) attached hereto.

UM00000108
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Novartis v. Regents, IPR2023-01347
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DOCKET NO.: U0157.70023US02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Michael J. Zaworotko
Application No.:	Not Yet Assigned
Confirmation No.:	Not Yet Assigned
Filed:	Herewith
For:	MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT
Examiner:	Not Yet Assigned
Art Unit:	Not Yet Assigned

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 within three months of the filing date of a national application other than a continued prosecution application under 37 C.F.R. § 1.53(d).

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.

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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:

Serial No.	Filing Date	Inventor(s)	Docket No.
†10/378,956	March 3, 2003	Michael J. Zaworotko et al.	U0157.70023US01

†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.

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.

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)
***Office Action dated 04/13/2011 in U.S. Application No. 12/861,203**
***Notice of Reasons for Rejection dated 10/08/2009 for Japanese Application No. 2003-572946**

*a copy of this reference is not provided as it was previously cited by or submitted to the office in a prior application, Serial No. 10/378,956, filed March 3, 2003, and relied upon for an earlier filing date under 35 U.S.C. 120 (continuation, continuation-in-part, and divisional applications).

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.

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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. U0157.70023US02 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.: U0157.70023US02
Date: February 13, 2014
xNDDx

UM00000111
NOVARTIS EXHIBIT 1516
Novartis v. Regents, IPR2023-01347
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FORM PTO-1449/A and B (modified PTO/SB/08)				APPLICATION NO.: Not Yet Assigned	ATTY. DOCKET NO.: U0157.70023US02
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				FILING DATE: Herewith	CONFIRMATION NO.: Not Yet Assigned
				FIRST NAMED INVENTOR: Michael J. Zaworotko	
Sheet	1	of	27	GROUP ART UNIT: Not Yet Assigned	EXAMINER: Not Yet Assigned

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		
		2,554,816		Clapp et al.	05-29-1951
		2,665,277		Homeyer et al.	01-05-1954
		2,711,411		Holbert et al.	06-21-1955
		2,980,679		Gianfranco	04-18-1961
		3,028,420		Petrow et al.	04-03-1962
		3,536,809		Schaller et al.	04-09-1991
		3,598,123		Zaffaroni	08-10-1971
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		3,970,651		Kaplan et al.	07-20-1976
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		4,267,179		Heeres et al.	05-12-1981
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		4,764,604		Muller	08-16-1988
		4,792,569		Maryanoff et al.	12-20-1988
		4,853,379		Shroot et al.	08-01-1989
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		4,925,674		Giannini et al.	05-15-1990
		4,927,855		Lafon	05-22-1990
		4,994,604		Tung et al.	02-19-1991
		5,006,513		Hector et al.	04-09-1991
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		5,059,595		Le Grazie	10-22-1991
		5,073,543		Marshall et al.	12-17-1991
		5,120,548		McClelland et al.	06-09-1992
		5,177,262		Taylor et al.	01-15-1993
		5,242,942		Costanzo et al.	09-07-1993
		5,258,402		Maryanoff	11-02-1993
		5,273,760		Oshlack et al.	12-28-1993
		5,286,493		Oshlack et al.	02-15-1994

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.

*a copy of this reference is not provided as it was previously cited by or submitted to the office in a prior application, Serial No. 10/378,956, filed March 3, 2003, and relied upon for an earlier filing date under 35 U.S.C. 120 (continuation, continuation-in-part, and divisional applications).

FORM PTO-1449/A and B (modified PTO/SB/08)	APPLICATION NO.: Not Yet Assigned	ATTY. DOCKET NO.: U0157.70023US02
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	FILING DATE: Herewith	CONFIRMATION NO.: Not Yet Assigned
	FIRST NAMED INVENTOR: Michael J. Zaworotko	
Sheet 2 of 27	GROUP ART UNIT: Not Yet Assigned	EXAMINER: Not Yet Assigned

		5,324,351		Oshlack et al.	06-28-1994
		5,332,834		Bhattacharya et al.	07-26-1994
		5,338,644		Taylor et al.	08-16-1994
		5,354,556		Sparks et al.	10-11-1994
		5,356,467		Oshlack et al.	10-18-1994
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		5,380,867		Bhattacharya et al.	01-10-1995
		5,384,327		Costanzo et al.	01-24-1995
		5,387,700		Maryanoff et al.	02-07-1995
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		5,466,823		Talley et al.	11-14-1995
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		5,614,342		Molaire et al.	03-25-1997
		5,631,250		Bunnell et al.	05-20-1997
		5,633,015		Gilis et al.	05-27-1997
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		5,639,476		Oshlack et al.	06-17-1997
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		5,703,232		Bunnell et al.	12-30-1997
		5,707,975		Francois et al.	01-13-1998
		5,733,566		Lewis	03-31-1998
		5,736,541		Bunnell et al.	04-07-1998
		5,753,688		Talley et al.	05-19-1998
		5,753,693		Shank	05-19-1998
		5,760,007		Shank et al.	06-02-1999
		5,760,068		Talley et al.	06-02-1998

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.

*a copy of this reference is not provided as it was previously cited by or submitted to the office in a prior application, Serial No. 10/378,956, filed March 3, 2003, and relied upon for an earlier filing date under 35 U.S.C. 120 (continuation, continuation-in-part, and divisional applications).

FORM PTO-1449/A and B (modified PTO/SB/08)	APPLICATION NO.: Not Yet Assigned	ATTY. DOCKET NO.: U0157.70023US02
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	FILING DATE: Herewith	CONFIRMATION NO.: Not Yet Assigned
	FIRST NAMED INVENTOR: Michael J. Zaworotko	
Sheet 3 of 27	GROUP ART UNIT: Not Yet Assigned	EXAMINER: Not Yet Assigned

		5,932,598		Talley et al.	08-03-1999
		5,935,933		Shank et al.	08-10-1999
		5,952,187		Stenglein et al.	09-14-1999
		5,972,986		Seibert et al.	10-26-1999
		5,985,902		Talley et al.	11-16-1999
		5,994,365		Zaworotko et al.	11-30-1999
		5,998,380		Ehrenberg et al.	12-07-1999
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		6,001,996		Amos et al.	12-14-1999
		6,054,136		Farah et al.	04-25-2000
		6,071,537		Shank	06-06-2000
		6,132,420		Dionne et al.	10-17-2000
		6,156,781		Talley et al.	12-05-2000
		6,191,117	B1	Kozachuk	02-20-2001
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		6,245,357	B1	Edgren et al.	06-12-2001
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		6,319,903	B1	Carrazana et al.	11-20-2001
		6,323,266	B2	Phillips	11-27-2001
		6,333,050	B2	Wong et al.	12-25-2001
		6,342,249	B1	Wong et al.	01-29-2002
		6,348,458	B1	Hamied et al.	02-19-2002
		6,365,185	B1	Ritschel et al.	04-02-2002
		6,368,626	B1	Bhatt et al.	04-09-2002
		6,375,978	B1	Kleiner et al.	04-23-2002
		6,384,034	B2	Simitchieva et al.	05-07-2002
		6,403,640	B1	Stoner et al.	06-11-2002
		6,413,965	B1	Mylari	07-02-2002
		6,420,394	B1	Supersaxo	07-16-2002
		6,488,962	B1	Berner et al.	12-03-2002
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EXAMINER:	DATE CONSIDERED:

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				FILING DATE: Herewith	CONFIRMATION NO.: Not Yet Assigned
				FIRST NAMED INVENTOR: Michael J. Zaworotko	
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				FIRST NAMED INVENTOR: Michael J. Zaworotko	
Sheet	27	of	27	GROUP ART UNIT: Not Yet Assigned	EXAMINER: Not Yet Assigned

	*	ZHU, H. et al. "Influence of water activity in organic solvent + water mixtures on the nature of the crystallizing drug phase. 1. theophylline" *International Journal of Pharmaceutics*, 1996, pp. 151-160, Vol. 135.	

[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.

*a copy of this reference is not provided as it was previously cited by or submitted to the office in a prior application, Serial No. 10/378,956, filed March 3, 2003, and relied upon for an earlier filing date under 35 U.S.C. 120 (continuation, continuation-in-part, and divisional applications).

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Zwicker, Jörk
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FORRESTER & BOEHMERT
Eing./Rec.: 24. NOV. 2006
Frist / Term:
Erl. / Dealt w.: wf

Datum/Date
22.11.06

Zeichen/Ref./Réf.	Anmeldung Nr./Application No./Demande n°./Patent Nr./Patent No./Brevet n°.
FB14326	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.

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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
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	C07C57/30 C07C57/58 C07D223/26 C07D213/22 C07D213/16 C07C47/544 C07D213/82 C07D275/06
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	C07D213/80 C07C53/08 C07C61/125 C07C50/04 C07C53/124 C07C317/04
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	
	-/--		

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

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EPO FORM 1503 03.82 (P04C64)

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Novartis v. Regents, IPR2023-01347
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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
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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

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INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/US 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

-/--

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

[X] 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	Date of mailing of the international search report
24 July 2003	24. 10. 03

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Johnson, C.

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

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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

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Novartis v. Regents, IPR2023-01347
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INTERNATIONAL SEARCH REPORT

In ional 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. [X] 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. [X] 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. [X] 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.

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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

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.

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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)

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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.

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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.

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Novartis v. Regents, IPR2023-01347
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INTERNATIONAL SEARCH REPORT

mation on patent family members

International Application No
PCT/US 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)

THE MERCK INDEX

AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

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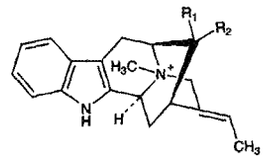
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1996

UM00000152
NOVARTIS EXHIBIT 1516
Novartis v. Regents, IPR2023-01347
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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 waxifera* 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_2OH	$COOCH_3$
Macusine B	H	CH_2OH
Macusine C	$COOCH_3$	CH_2OH

Macusine A, $[C_{22}H_{27}N_2O_3]^+$, *(16R)-17-hydroxy-16-(methoxycarbonyl)-4-methylsarpaganium.* Chloride, prisms from ethanol + ether, mp 252°. $[\alpha]_D^{25}$ −57.5° (c = 1.45).

Macusine B, $[C_{20}H_{25}N_2O]^+$, *(4α)-17-hydroxy-4-methylsarpaganium.* Chloride, prisms from ethanol + ether, dec 248-249°. $[\alpha]_D^{22}$ +15.6° (c = 1.21). uv max (water): 222, 273, 280, 291 nm (log ε 4.61, 3.84, 3.82, 3.74).

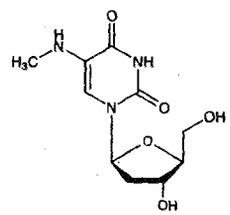
Macusine C, $[C_{22}H_{27}N_2O_3]^+$, the C-16 epimer of A. Chloride, crystals from ethanol + ether, dec 264-265°. $[\alpha]_D^{24}$ −60.8° (c = 2.13). uv max (water): 222, 272, 278, 289 nm (log ε 4.63, 3.88, 3.87, 3.76).

5680. Maddrell's Salt. Polymeric sodium metaphosphate. Upon heating NaH_2PO_4 or $NaNH_4HPO_4$ to 250° and then slowly to 350°, first $Na_2H_2P_2O_7$ 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 prepd by heating two parts $NaNO_3$ with one part H_3PO_4. 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.

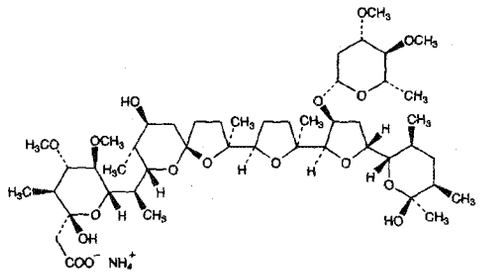
USE: In dentifrices, polishing agents, abrasive detergents.

5681. MADU. *2'-Deoxy-5-(methylamino)uridine;* 5-(methylamino)-2'-deoxyuridine. $C_{10}H_{15}N_3O_5$; 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.

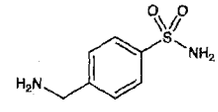
5682. Maduramicin. *(3R,4S,5S,6R,7S,22S)-23,27-Didemethoxy-2,6,22-tridemethyl-11-O-demethyl-22-[(2,6-dideoxy-3,4-di-O-methyl-β-L-arabino-hexopyranosyl)oxy]-6-methoxylonomycin A monoammonium salt;* antibiotic X-14868A ammonium salt; CL-273703; Cygro. $C_{47}H_{83}NO_{17}$; mol wt 934.17. C 60.43%, H 8.96%, 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). ^{13}C-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, $C_{47}H_{79}NaO_{17}$, crystals from ethyl acetate + n-hexane, mp 193-195°. $[\alpha]_D$ +40.6° (chloroform). $[\alpha]_D$ +23.8° (methanol).

Note: Not to be confused with ***maduramycin*** isolated from *Actinomadura rubra,* $C_{28}H_{22}O_{10}$: 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. $C_7H_{10}N_2O_2S$; 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, $C_7H_{10}N_2O_2S.HCl$, crystals from 95% alc, mp 256°. Neutral in soln. LD_{50} in rats, mice (mg/kg): 1170, 900 i.v. (Skulan, Hoppe).

Acetate, $C_9H_{14}N_2O_4S$, *Mafatate, Mefamide.* LD_{50} in rats, mice (mg/kg): 2040, 1580 i.v. (Skulan, Hoppe).

Propionate, $C_7H_{10}N_2O_2S.C_3H_6O_2$, *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

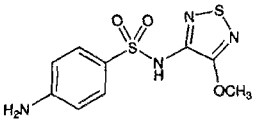
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in solns of alkali hydroxides and carbonates and in dil mineral acids.

Sodium salt, *Ultraseptyl.* Sol in water.

THERAP CAT: Antibacterial.

9089. Sulfametrole. ***4-Amino-N-(4-methoxy-1,2,5-thiadiazol-3-yl)benzenesulfonamide;*** *N^1*-(4-methoxy-1,2,5-thiadiazol-3-yl)sulfanilamide; 3-methoxy-4-(4′-aminobenzenesulfonamido)-1,2,5-thiadiazole. $C_9H_{10}N_4O_3S_2$; 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 trimethoprim): G. Nabert-Bock, H. Grims, *Arzneimittel-Forsch.* **27,** 1109 (1977). Tolerance, therapeutic effect, pharmacokinetics: 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. H_3NO_3S; mol wt 97.09. H 3.11%, N 14.43%, O 49.43%, S 33.03%. H_2NSO_3H. Obtained from chlorosulfonic acid and ammonia, or by heating urea with H_2SO_4. 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 ammonium 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 acetone. 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 membranes.

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

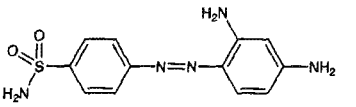
9091. Sulfamide. ***Sulfuryl amide.*** $H_4N_2O_2S$; mol wt 96.11. H 4.19%, N 29.15%, O 33.29%, S 33.36%. $H_2NSO_2NH_2$. Prepd from sulfuryl chloride and gaseous ammonia: Traube, *Ber.* **25,** 2427 (1892); **26,** 610 (1893); Hantzsch, Holl, *Ber.* **34,** 3430 (1902); Schenk in *Handbook of Preparative 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′-sulfonamide; 4′-sulfamyl-2,4-diaminoazobenzene. $C_{12}H_{13}N_5O_2S$; 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.); *eidem,* **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. Tréfouel *et al., Compt. Rend. Soc. Biol.* **120,** 756 (1935); L. Colebrook *et al., Lancet* **2,** 1323 (1936). Polymorphic forms in commercial prepns: 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 review: M. H. Bickel, *Gesnerus* **45,** 67-86 (1988).

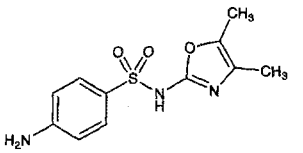


Hydrochloride, $C_{12}H_{13}N_5O_2S.HCl$, ***Prontosil, Prontosil flavum, Prontosil rubrum, Rubiazol I, Septosan, Streptocide, Streptozon.*** Orange-red crystals, mp 248-250°. One gram dissolves in 400 ml water; much more sol in hot water. Sol in alcohol, acetone, fats, oils.

USE: Specific stain for carbonic anhydrase in polyacrylamide gels.

THERAP CAT: Antibacterial.

9093. Sulfamoxole. ***4-Amino-N-(4,5-dimethyl-2-oxazolyl)benzenesulfonamide;*** *N^1*-***(4,5-dimethyl-2-oxazolyl)sulfanilamide;*** 2-(*p*-aminobenzenesulfonamido)-4,5-dimethyloxazole; 4,5-dimethyl-2-sulfanilamidooxazole; *p*-aminobenzenesulfonyl-2-amino-4,5-dimethyloxazole; sulfadimethyloxazole; Justamil; Sulfmidil; Sulfuno; Tardamide. $C_{11}H_{13}N_3O_3S$; 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 antimicrobial 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; 0.01*N* HCl 163; 0.01*N* NaOH 196; methanol 2315; chloroform 240. uv max (4.91 μg/ml methanol): 210, 250, 270 nm (ε 740, 546, 857). LD_{50} in mice, rats (g/kg): > 10.0, > 12.5 orally; 1.80, ~2.50 i.p. (Lagler).

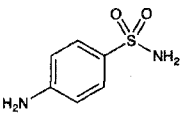
Mixture with trimethoprim, ***co-trifamole, CN-3123, Co-Fram, Dibactil, Nevin, Supristol.*** LD_{50} in mice, rats (g/kg): > 12.0, 14.0 orally; 1.87, 2.00 i.p. (Lagler).

THERAP CAT: Antibacterial.

9094. Sulfanilamide. ***4-Aminobenzenesulfonamide;*** *p*-anilinesulfonamide; *p*-sulfamidoaniline; 1162-F; Albexan; Deseptyl; Prontalbin; Prontosil album; Prontylin; Septoplix; Streptocid album; Streptocide. $C_6H_8N_2O_2S$; 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^4*-acetylsulfanilamide is then hydrolyzed: Gelmo,

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J. Prakt. Chem. **77,** 369 (1908). Lab procedures: L. F. Fieser, *Experiments in Organic Chemistry* (Boston, 3rd ed., 1955) p 147; Hurdis, 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).

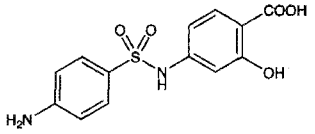


Crystals, mp 164.5-166.5°. pKa 10.43; pKb 11.63. Neutral to litmus. pH (0.5% aq soln): 5.8-6.1. uv max: 257, 313 nm. Soly in water (g/liter): 2.6 (10°); 7.5 (25°); 17.0 (40°); 40 (60°); 477 (100°). One gram dissolves in about 37 ml alcohol; in about 5 ml acetone. Also sol in glycerol, propylene glycol, HCl, solns of K and Na hydroxides. Practically insol in chloroform, ether, benzene, petr ether. LD_{50} orally in dogs: 2.0 g/kg.

THERAP CAT: Antibacterial.

THERAP CAT (VET): Antimicrobial.

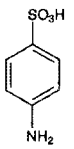
9095. 4-Sulfanilamidosalicylic Acid. *p*-Sulfanilamidosalicylic acid; 4-(*p*-aminobenzenesulfonamido)-2-hydroxybenzoic acid; Metrasil. $C_{13}H_{12}N_2O_5S$; mol wt 308.31. C 50.64%, H 3.92%, N 9.09%, O 25.95%, S 10.40%. Prepn: Benedikt, Eibl, *Monatsh.* **81,** 419 (1950); Goldberg, Salame, **Brit.** pat. **648,467** (1951 to Ward, Blenkiusop).



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. $C_6H_7NO_3S$; 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., Unitized 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°). pK_2 (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.

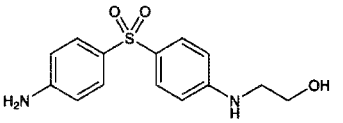
Sodium salt dihydrate, $C_6H_6NNaO_3S.2H_2O$, orthorhombic bipyramidal plates. Freely sol in water, sol in hot methanol.

Zinc salt tetrahydrate, $C_{12}H_{12}N_2O_6S_2Zn.4H_2O$, *zinc sulfanilate tetrahydrate.* Nivin

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

THERAP CAT: Antibacterial.

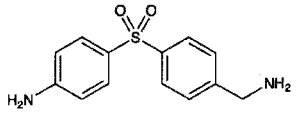
9097. 2-*p*-Sulfanilylanilinoethanol. *2-[[4-[(4-Aminophenyl)sulfonyl]phenyl]amino]ethanol;* 4-amino-4′-(β-hydroxyethylamino)diphenyl sulfone; *p*-aminophenyl *p*-(2-hydroxyethylamino)phenyl sulfone; Smith's sulfone. $C_{14}H_{16}N_2O_3S$; mol wt 292.36. C 57.52%, H 5.52%, N 9.58%, O 16.42%, S 10.97%. Preparation: Jackson, *J. Am. Chem. Soc.* **70,** 680 (1948); Weijlard, 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. $C_{13}H_{14}N_2O_2S$; 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).



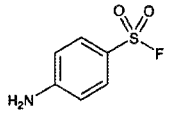
Needles from water, mp 159°.

Monohydrochloride monohydrate, $C_{13}H_{14}N_2O_2S.HCl.H_2O$, crystals, mp 195°. Very sol in water.

Dihydrochloride, $C_{13}H_{14}N_2O_2S.2HCl$, mp 285°.

THERAP CAT: Antibacterial.

9099. Sulfanilyl Fluoride. *p-Aminobenzenesulfonyl fluoride.* $C_6H_6FNO_2S$; 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^4-Sulfanilylsulfanilamide. *4′-Sulfamoylsulfanilanilide;* 4-aminobenzenesulfono-*p*-sulfamoylanilide; 4-(4′-diaminobenzenesulfonamido)benzenesulfonamide; DB-32; Disulfan C; septal C; Uliron C; Disulon; Neosanamid II; Albasil C; Disulfan. $C_{12}H_{13}N_3O_4S_2$; 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. Soc. Org. Syn. Chem. Japan* **12,** 211 (1954), *C.A.* **51,** 2780h (1957); Grigorovskii, Dykhanov, *J. Appl. Chem. USSR* **30,**

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Pergamon

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TETRAHEDRON

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

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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

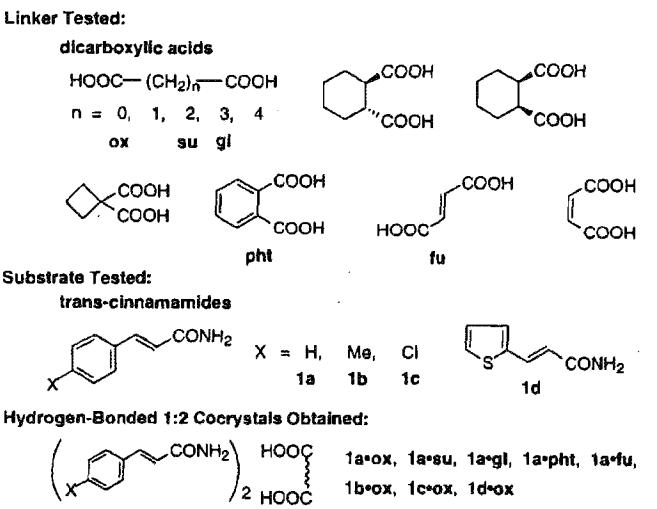
A 2:1 mixture of *trans*-cinnamamide (**1a**) and each of dicarboxylic acids, which are listed in Scheme 1, was recrystallized from suitable solvent. Cocrystals of **1a** with oxalic acid (**ox**), succinic acid (**su**), phthalic acid (**pht**) and fumaric acid (**fu**) (**1a·ox, 1a·su, 1a·pht, 1a·fu**) 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 $CONH_2$ 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.
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Scheme 1.

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

Cocrystal	Recrystzn solvent	Crystal habit, mp, °C[a]	Calcd (%)[b]			Found (%)[b]		
			C	H	N	C	H	N
1a•ox	*i*PrOH	Colorless plates, 159–166.5	62.49	5.25	7.29	62.46	5.29	7.32
1a•su	*i*PrOH	White needles, 150.5–151.5	64.06	5.87	6.79	64.16	5.95	6.86
1a•gl	C_6H_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	*i*PrOH	Colorless needles, 142–143.5	67.82	5.25	6.08	67.90	5.23	6.11
1a•fu	*i*PrOH	Colorless needles, 164–166	64.38	5.40	6.83	64.44	5.28	6.69
1b•ox	*i*PrOH	Colorless prisms, 194–202	64.07	5.87	6.79	64.19	5.91	6.83
1c•ox	C_6H_6/*i*-PrOH	Colorless prisms, 207.5–211	53.00	4.00	6.18[c]	53.10	4.02	6.19[d]
1d•ox	*i*PrOH	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* $CONH_2$ *and COOH groups in KBr*

trans-Cinnamamide		Dicarboxylic acid		Cocrystal	
$CONH_2$		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}.

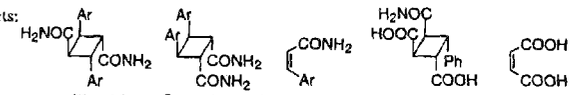
The above results on the melting point and the IR spectrum, combined with the following powder X-ray studies (Fig. 2) and photoreactivities (Table 3), indicate that cocrystals **1a•ox**, **1a•su**, **1a•pht** and **1a•fu** are crystalline complexes, whereas **1a•gl** may possibly be a mixture containing 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.

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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	4, 50; **ma**, 5	39	45
1b·ox	0	43	0	Polymeric	1	ne
1c·ox	2	86	0		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	–

[a] Products:

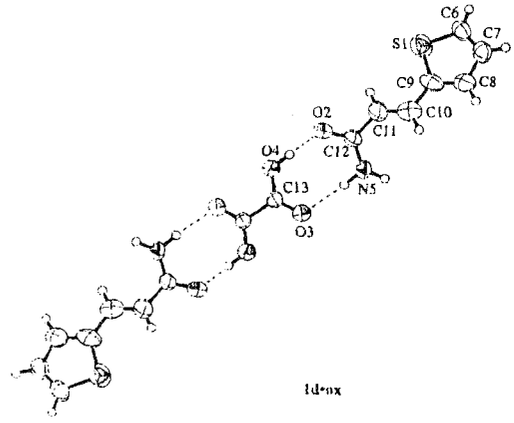


2 **3** cis-**1** **4** **ma**

[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*-cinnamamides, and 100(moles of acid)/(moles of 2;1 cocrystal)% for dicarboxylic acids; ne=not estimated.

[c] Homocrystals.

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).



1d·ox

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 (PXD) for cocrystals **1a·ox**, **1a·pht**, **1a·gl**, **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

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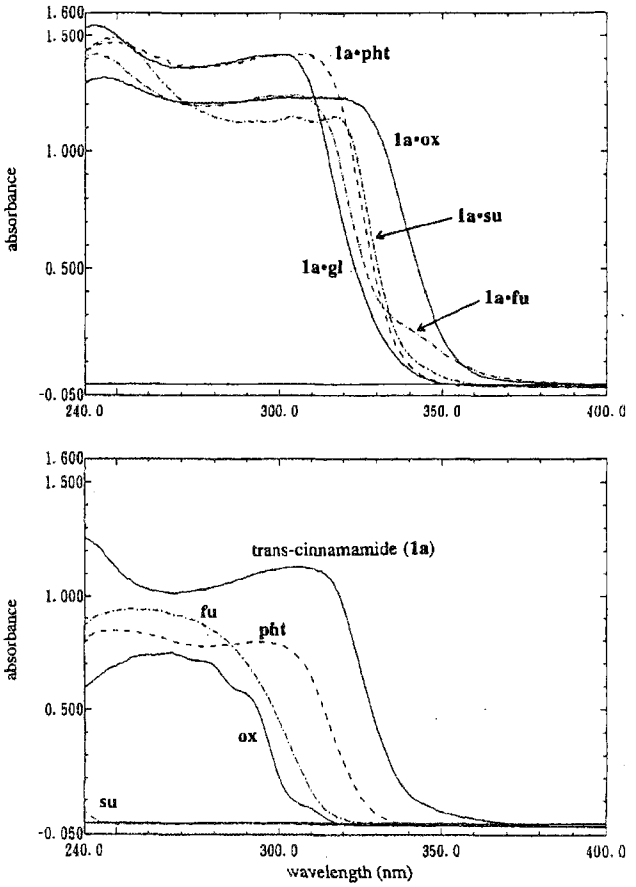


Figure 1. Diffuse reflectance spectra for cocrystals **1a·ox**, **1a·su**, **1a·gl**, **1a·pht**, **1a·fu** and for their constituent crystals **1a**, **ox** (anhyd), **su**, **pht**, and **fu**. The spectrum for **gl**, which is almost the same as that of **su**, is not shown.

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 ^{1}H 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

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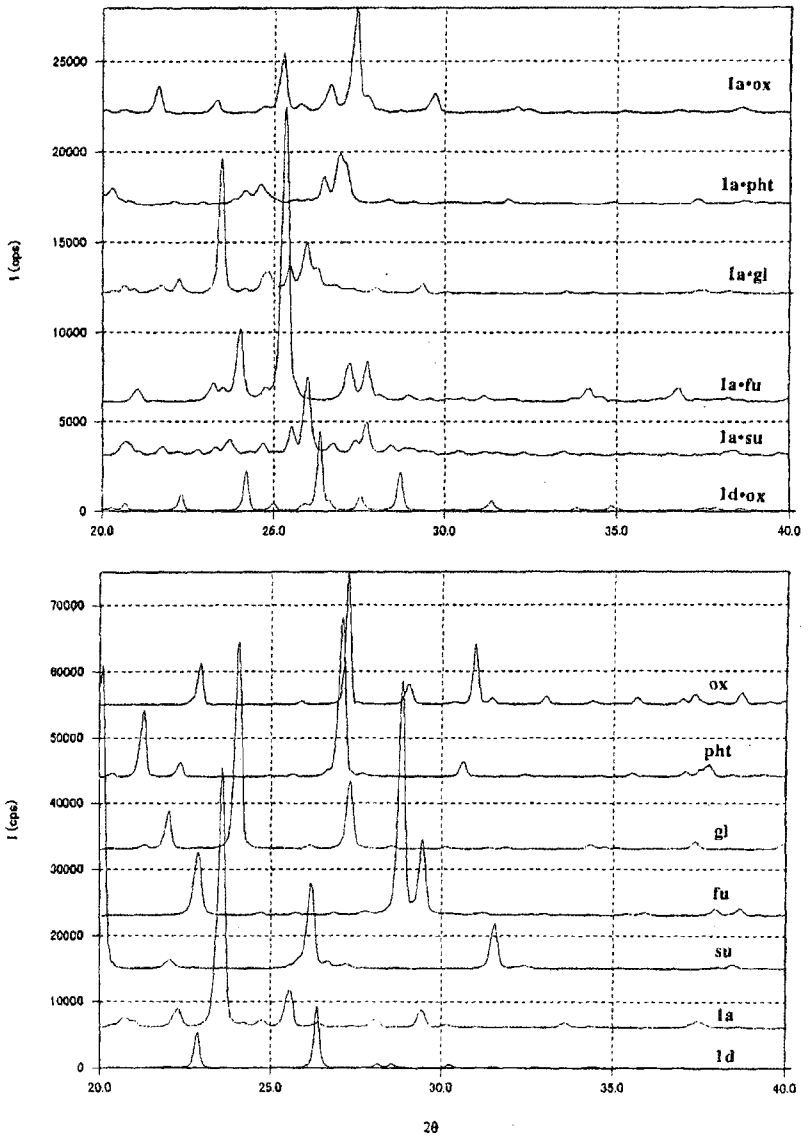


Figure 2. X-Ray powder patterns for cocrystals **1a·ox**, **1a·pht**, **1a·gl**, **1a·fu**, **1a·su** and **1d·ox** and for the constituents ox (anhyd), **pht**, **gl**, **fu**, **su**, **1a** and **1d**.

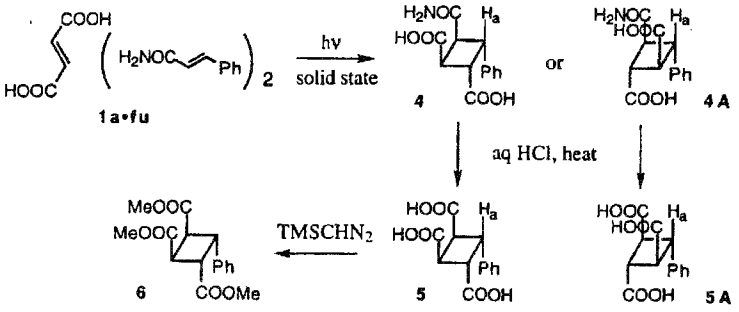
(7.52 Å which is the length of the *c*-axis) is far too long for the reaction to occur.

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

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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

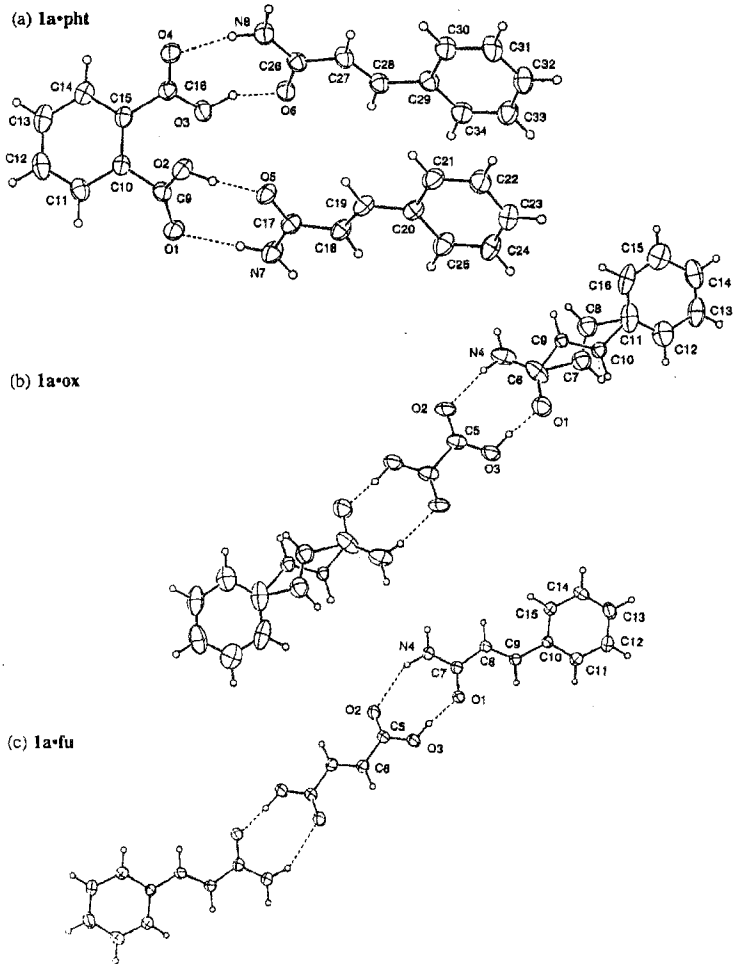


Figure 3. ORTEP drawings of cocrystals: (a) **1a•pht**; (b) **1a•ox**; and (c) **1a•fu**.

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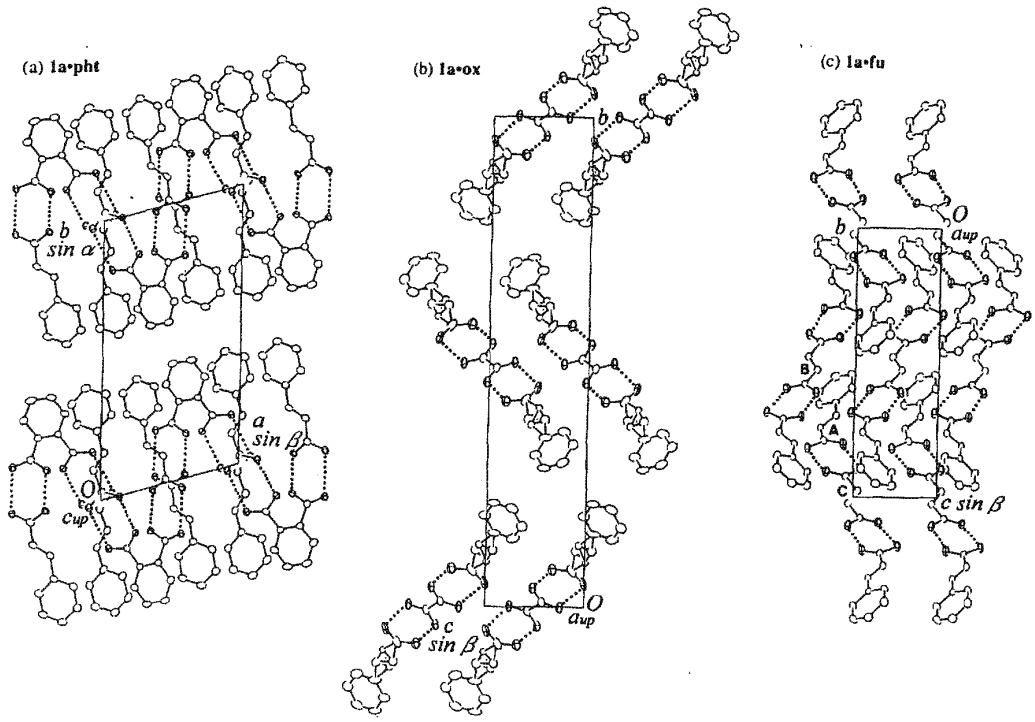
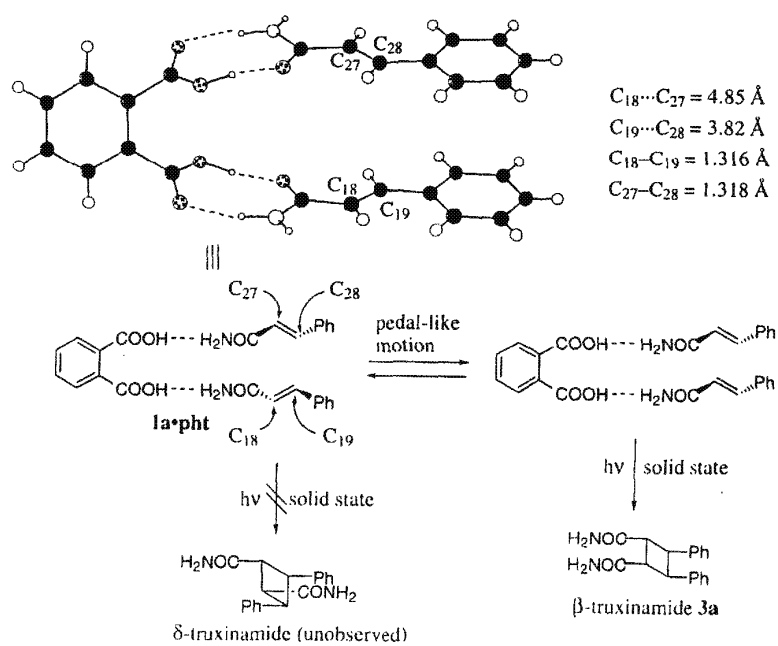
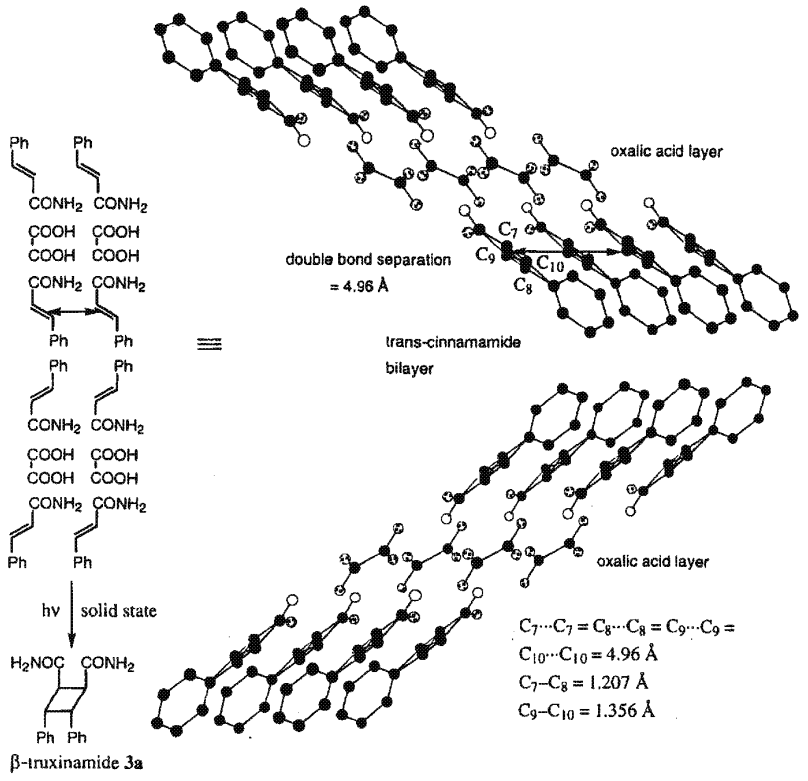


Figure 4. Packing diagrams of cocrystals: (a) **1a•pht**; (b) **1a•ox**; and (*c*) **1a•fu**, which are projected along the *c*-axis, the *a*-axis and the *a*-axis, respectively.



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

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

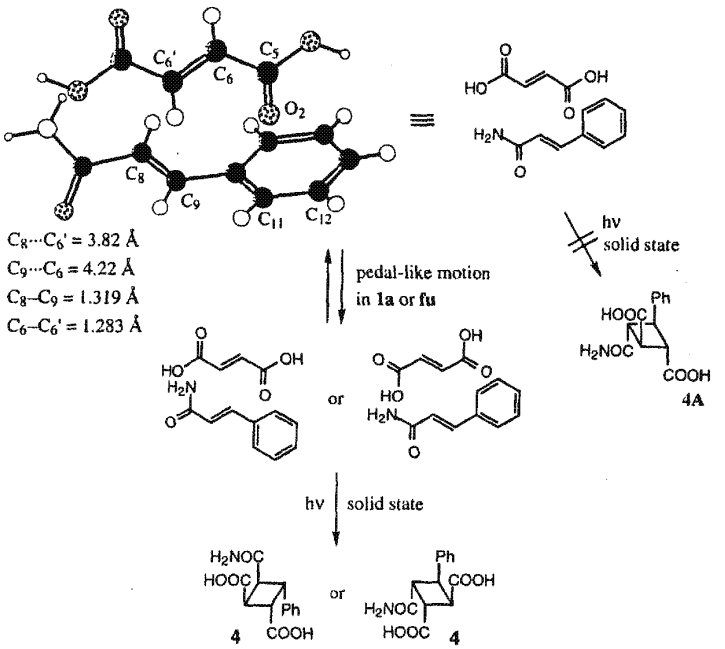
phenyl ring and the carbonyl group (O2···C11=3.50 Å, O2···C12=3.43 Å, C11···O2–C5=89°, C12···O2–C5=89°). This overlap should be responsible for the 343 nm inflection which appeared in the diffuse reflectance spectrum of **1a·fu** (Fig. 1). An attractive interaction between the carbonyl and phenyl groups, referred to as C=O···π interaction, was reported to exist and this interaction was utilized for asymmetric dimerization and polymerization.[17] Such a C=O···π 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 ethylene bonds in **1a·pht** and **1a·fu** are considerably shorter than the corresponding ones in the homocrystals. This fact strongly suggests[11] 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 space[21] 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-diamine[1–7] 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

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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

^{1}H NMR spectra were measured on a Varian Gemini-200, JEOL EX-270J, or JEOL JNM-A400 spectrometer. The solvent employed is DMSO-d_6, 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 $BaSO_4$ 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 5C_{18}-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 recrystalized 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**

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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 ^{1}H NMR analyses, respectively. Yields thus estimated are summarized in Table 3.

Similar irradiation of homocrystals **1a–1d** gave cleanly the corresponding α-truxillamides **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 ^{1}H 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); ^{1}H 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, $M^{+\cdot}-NH_3$), 205 (63), 180 (31, $[PhCH{=}CHPh]^{+}$), 147 (21, $M^{+\cdot}/2$), 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 ^{1}H 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 ^{1}H 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 ^{1}H NMR pattern characteristic of the β-type photodimer. Attempts to purify β-truxinamides **3c** and **3d** were not carried out. Their ^{1}H 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; ^{1}H 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, $M^{+\cdot}/2$), 145 (62); IR (KBr) 3394, 3358, 1664, 1516, 1421, 1406, 1245, 811, 722 cm^{-1}.

(d) From the ^{1}H NMR analysis of the photolysate from **1c·ox**, **3c**: ^{1}H 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% (^{1}H NMR) precipitated. **3d**: ^{1}H NMR (CD_3OD, 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 (^{1}H 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-truxillamide **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,*t*-2-cyclobutanedicarboxylic acid **4** as white small needles: mp 187–190°C; ^{1}H NMR (CD_3OD, 400 MHz) δ 3.74–3.78 (1H, dd, J=10.1 and 6.1 Hz, H_2N–COC*H*), 3.79–3.83 (1H, dd, J=10.1 and 6.1 Hz, $H_2NCOCHCH$-COOH), 3.89–3.93 (1H, dd, J=10.7 and 6.1 Hz, PhCHC*H*COOH), 4.09–4.13 (1H, dd, J=10.7 and 6.1 Hz, PhC*H*), 7.19–7.32 (5H, m, aromatic); ^{13}C NMR (CD_3OD, 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 ($CONH_2$ and COOH), 1706 (COOH), 1665 ($CONH_2$), 1648 ($CONH_2$), 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,*t*-2,*t*-3-cyclobutanetricarboxylic acid **5** (^{1}H 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

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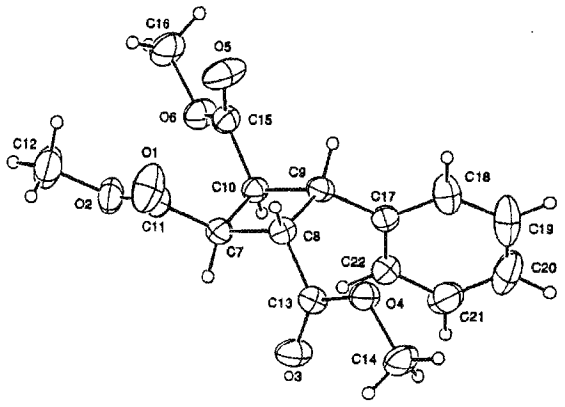


Figure 5. ORTEP drawing of compound **6**.

from $CHCl_3$ (5 mL) to give 9 mg of **5** as white plates: mp 205–208°C; ^{1}H NMR (CD_3OD, 400 MHz) δ 3.72–3.79 (2H, m), 3.82–3.87 (1H, m), 4.22–4.27 (1H, m, PhC*H*), 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, $M^{+\cdot}$−COOH), 200 (18), 174 (45, $M^{+\cdot}$−2COOH), 172 (56), 148 (97, [PhCH=CHCOOH]$^{+\cdot}$), 147 (80), 129 (100, $M^{+\cdot}$−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 ^{1}H 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,*t*-2,*t*-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; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.29 (3H, s), 3.70 (3H, s), 3.75 (3H, s), 3.8 1–4.02 (3H, m), 4.28–4.40 (1H, m, PhC*H*), 7.16–7.37 (5H, m, aromatic); MS (EI) *m/z* (rel intensity) 306 (11, $M^{+\cdot}$), 275 (16), 246 (44), 214 (41), 187 (35), 162 (100, [PhCH=CHCOOMe]$^{+\cdot}$), 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 MoKα radiation (λ=0.71073 Å). The structures were solved by direct methods and were refined using CRYSTAN-GM or TEXSAN software.[28]

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

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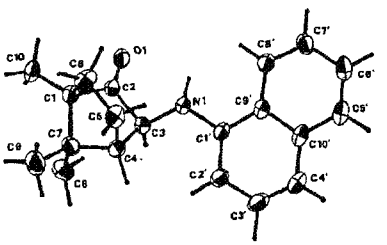


Fig. 1. *ORTEP* drawing (Johnson, 1965) of the title compound with atom numbering. The anisotropic ellipsoids for non-H atoms enclose 30% probability.

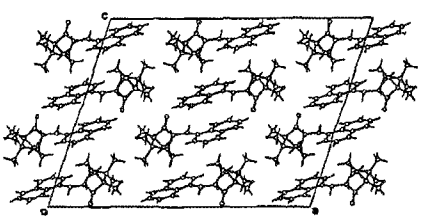


Fig. 2. A view of the unit cell.

2434 with $|F_o| > 3\sigma(|F_o|)$ used for structure determination, $2\theta_{max} = 125°$, *hkl* range: h −29 to 27, k 0–8, l 0–22, 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 *MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978), refinement by full-matrix least squares on F using *SHELX*76 (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; $R = 0{\cdot}050$, $wR = 0{\cdot}068$, $w^{-1} = \sigma^2(F) + 0{\cdot}00625F^2$, $S = 1{\cdot}06$, $(\Delta/\sigma)_{max} = 0{\cdot}03$, largest peak in final ΔF map 0·12 e Å^{-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.

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Structure of Cinnamamide

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Abstract. C_9H_9NO, $M_r = 147{\cdot}08$, m.p. = 416–418 K, monoclinic, $P2_1/a$, $a = 16{\cdot}015$ (3), $b = 5{\cdot}072$ (1), $c = 9{\cdot}563$ (2) Å, $\beta = 93{\cdot}99$ (2)°, $V = 775{\cdot}0$ (3) Å^3, $Z = 4$, $D_m = 1{\cdot}26$ (2), $D_x = 1{\cdot}261$ Mg m^{-3}, Cu $K\alpha$, $\lambda = 1{\cdot}5418$ Å, $\mu = 0{\cdot}63$ mm^{-1}, $F(000) = 312$, $T = 295$ K, $R = 0{\cdot}066$ 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.

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Colourless prism elongated along **b**; 0·08 × 0·18 × 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 $K\alpha$. 20 reflections within $14 < 2\theta < 38°$ used to determine the lattice parameters. Intensity data collected within $2\theta_{max} = 125°$ ($-18 \le h \le 18$, $0 \le k \le 5$, $0 \le l \le 11$), ω–2θ scan method [scan speed 4° min^{-1} in ω, scan range $(1{\cdot}2 + 0{\cdot}15\tan\theta)°$ 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, $R_{int} = 0{\cdot}022$ 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 $w = 1{\cdot}0/[\sigma(F_o)^2 + 0{\cdot}0269|F_o| + 0{\cdot}0003|F_o|^2]$. Correction for secondary extinction applied for six strongest reflections [$I_{corr} = I_o(1 + 2{\cdot}4 \times 10^{-5} I_c)$]. Final $R = 0{\cdot}066$ for 1042 reflections, $wR = 0{\cdot}089$, $S = 1{\cdot}26$, $(\Delta/\sigma)_{max} = 0{\cdot}2$. The residual electron density in the final difference map was within $\pm 0{\cdot}27$ e Å^{-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: *RSSFR*-5 (Sakurai, 1967), *HBLS*-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* (× 10^4) *and equivalent isotropic thermal parameters* (Å^2) *with e.s.d.'s in parentheses*

$B_{eq} = (4/3)\sum_i \beta_{ii}/a_{ii}^{*2}$.

	x	y	z	B_{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* (Å) *and angles* (°) *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)		

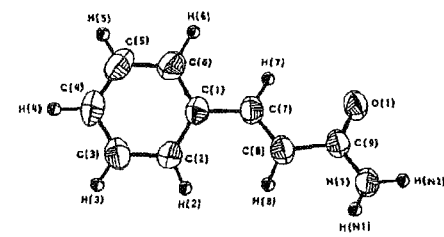


Fig. 1. The thermal ellipsoids of the molecule with atomic numbering. Ellipsoids of 50% probability are drawn for the non-H atoms; the H atoms are represented as spheres equivalent to $B = 1{\cdot}0$ Å^2.

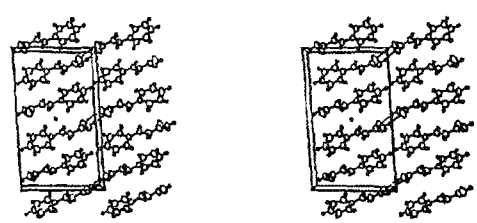


Fig. 2. Stereoscopic view of the crystal structure. The a axis points upwards, the b axis onto the plane of the paper and the c axis left to right.

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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)°].

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

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

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(*Received* 13 *January* 1989; *accepted* 19 *April* 1989)

Abstract. $C_{12}H_{17}N_3O_7S.H_2O$, $M_r = 365{\cdot}36$, monoclinic, $P2_1$, $a = 15{\cdot}105\ (2)$, $b = 7{\cdot}915\ (1)$, $c = 6{\cdot}451\ (1)$ Å, $\beta = 91{\cdot}29\ (1)°$, $V = 771{\cdot}1$ Å^3, $Z = 2$, $D_x = 1{\cdot}574$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 22{\cdot}806$ cm^{-1}, $F(000) = 384$, $T = 298$ K, final $R = 0{\cdot}062$ for 1665 unique reflections [$F_o^2 > 2\sigma(F_o^2)$]. The thiofuranosyl ring adopts an envelope conformation (E_1). The pyrimidyl moiety of the title compound is in a +*anti* orientation ($\chi = -133{\cdot}5°$), in contrast to the methyl ester of the tetraacetylsulfoxide derivative which adopts a +*syn* orientation ($\chi = 67{\cdot}7°$).

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 $K\alpha$ radiation, graphite monochromator, θ–2θ

* To whom correspondence should be addressed.

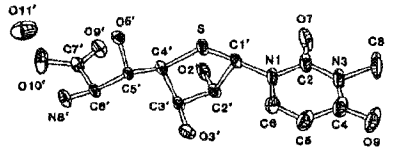


Fig. 1. Perspective view of the molecule with the numbering scheme. To show the absolute configuration correctly, the figure was drawn in the left-handed coordinate system.

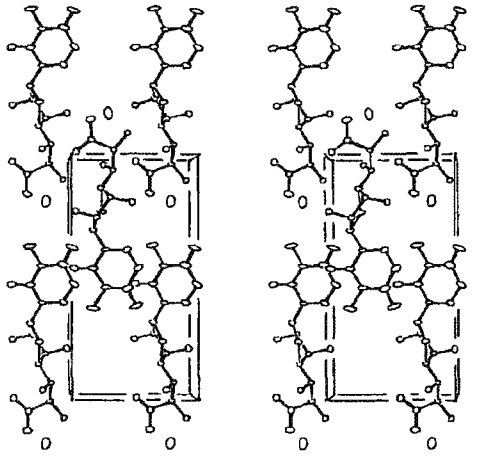


Fig. 2. Stereoscopic view of the crystal packing. The projection is down [001] and the *b* axis is horizontal.

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Anti-Cancer Drugs 2000, **11**, pp. 49–54

Preclinical report

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

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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 IC_{50} (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 IC_{50} 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.

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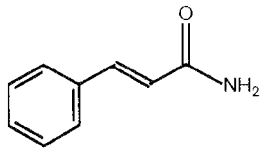


Figure 1. Chemical structure of cinnamamide (CNM).

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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% CO_2.

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 $CaCl_2$ and 1 μM $ZnCl_2$. 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 IC_{50} values of CNM for cultured human tumor cell lines including epidermoid carcino-

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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 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.

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

[a]Cells were cultured with CNM for 3 days.

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 gelatine 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]

[a]Colon 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]

[a]Hepatoma 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]

[a]Hepatoma 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.

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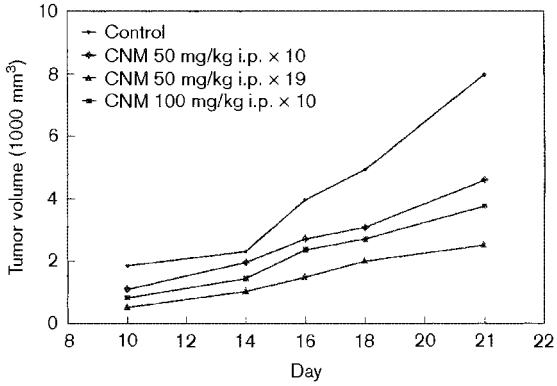


Figure 2. Effect of CNM on the growth of Lewis lung carcinoma in mice. Lewis lung carcinoma was implanted s.c. on day 0. CNM was given 24 h after transplantation, i.p., daily or on alternate days. There were eight mice in each group and no animal died during the experiment.

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 ± SD)	Inhibition (%)
Control	8/8	8/8	11.0 ± 5.7	
CNM, 50 mg/kg, i.p. × 10	8/8	7/8	10.3 ± 5.7	
CNM, 50 mg/kg, i.p. × 19	8/8	5/8	4.8 ± 1.9	56.8[b]
CNM, 100 mg/kg, i.p. × 10	8/8	5/8	4.5 ± 3.6	59.1[b]

[a]Lews 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 IC_{50} values of CNM for cultured cancer cells ranged between 1.29 and 1.94 mM, a level approximately several thousand times higher that of widely used anticancer drugs such as methotrexate, doxorubicin and vincristine. Apparently, CNM is an active compound with low cytotoxicity. The antitumor 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 or nor any other obvious sign of toxicity was observed in the *in vivo* experiments. Moreover, CNM has a relatively unique

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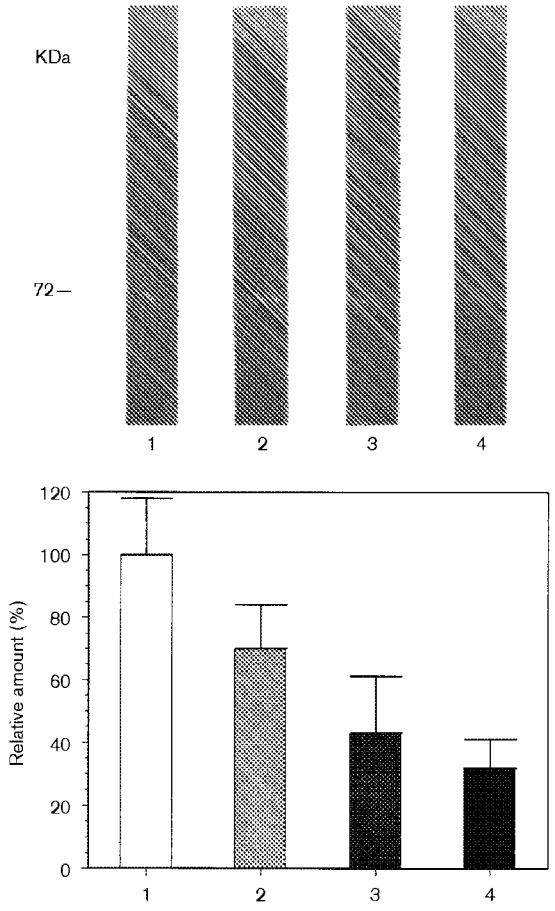


Figure 3. Effect of CNM on the level of MMP-2 in HT-1080 cells. HT-1080 cells were cultured for 24 h in serum-free RPMI 1640 medium with or without CNM: medium (lane 1); CNM, 200 μM (lane 2); CNM, 800 μM (lane 3) and CNM, 2 mM (lane 4). The conditioned media were subjected to electrophoresis in a gelatine-embedded 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.

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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

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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-1*H*-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 NH···N, the amino hydrogen is hydrogen bonded to the aldimine nitrogen, and in the other, denoted NH···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 N−H···N hydrogen bonding. In these calculations, representative chains of three hydrogen-bonded molecules were employed as models for the NH···N and NH···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 N−H···N trial structure is the more stable. It was noted that the NH···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

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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-dichlorotriphendioxazine,[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 theophylline[17] (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 reported[18] (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 ^{15}N 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, $\delta \equiv (\sigma_{ref} - \sigma_{sample})$ 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, ^{13}C and ^{15}N 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 $K\alpha_1$ radiation, and position sensitive detector, (2θ, 5−60°). Indexing was performed using the program, ITO.[31] The space group was determined using the program DRAGON[32] 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, MOPAC[35]/AM1[36] 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 Dreiding[37] 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 $Pna2_1$,

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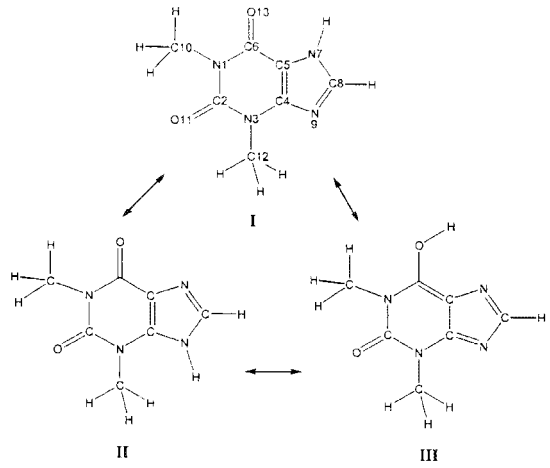


Figure 1. Theoretically possible tautomeric forms of the theophylline molecule. Numbering scheme after ref 34.

TABLE 1: Systematic Search Criteria for Anhydrous Theophylline

rotation/°		translation		total configurations tried
step size	range	step size/cell length	range	
5	0−175	0.025	0-1/2*a*	18,662,400
		0.025	0-1/2*b*	

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 fit[40] 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. CADPAC[41] ab initio calculations (6-31G** SCF) on an isolated theophylline molecule provided the self-consistent field (SCF) energy of the molecule and the distributed multipoles[42] 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 ^{15}N and ^{13}C were measured with respect to the reference standards ammonium nitrate ($NH_4{}^{15}NO_3$) and tetramethylsilane (TMS), respectively. The experimentally determined isotropic chemical shielding of $NH_4{}^{15}NO_3$ and TMS used herein were −116 ppm[44] 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 LORG[47] 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 ^{15}N 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

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TABLE 2: Comparison of Reported and Calculated Cell Parameters

structure (CSD ref-code)	a [Å]	b [Å]	c [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

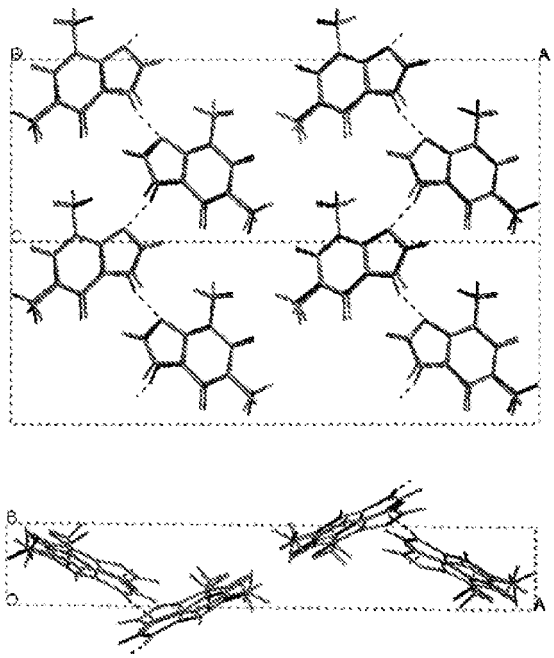


Figure 2. Predicted packing arrangement involving N−H···N interactions found by lattice energy systematic search (green), overlaid with published single-crystal structure (red).

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 ISOSTAR[48] 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

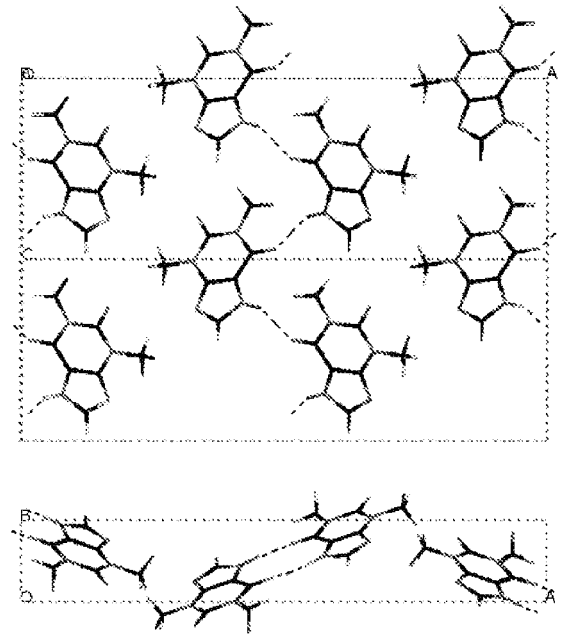


Figure 3. Predicted packing arrangement involving N−H···O interactions found by lattice energy systematic search.

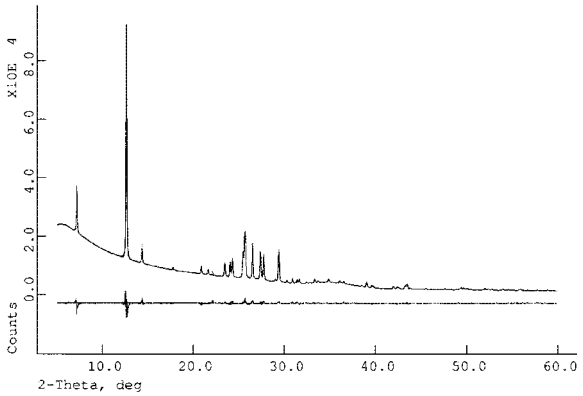


Figure 4. Laboratory X-ray powder diffraction data, N−H···N simulated diffraction pattern, and final soft constraints GSAS refined difference plot.

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).

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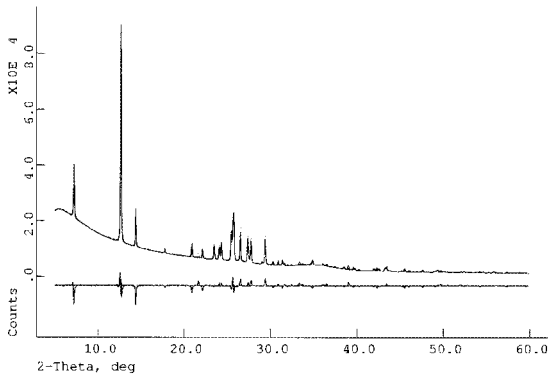


Figure 5. Laboratory X-ray powder diffraction data, N−H···O simulated diffraction pattern, and final soft constraints GSAS refined difference plot.

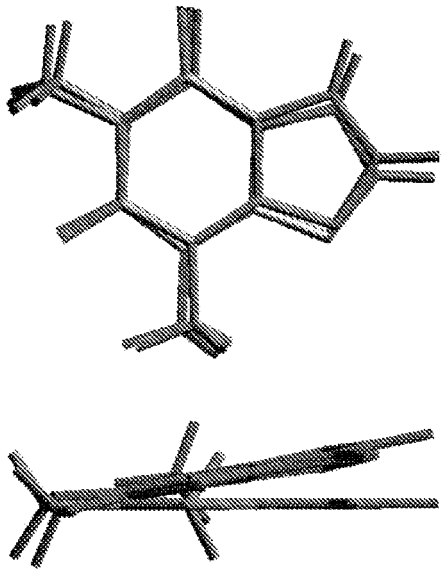


Figure 6. Overlay of the N−H···N lattice energy structure (green), GSAS refined (blue), and DMAREL minimized (red) structures.

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. Molecular 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).

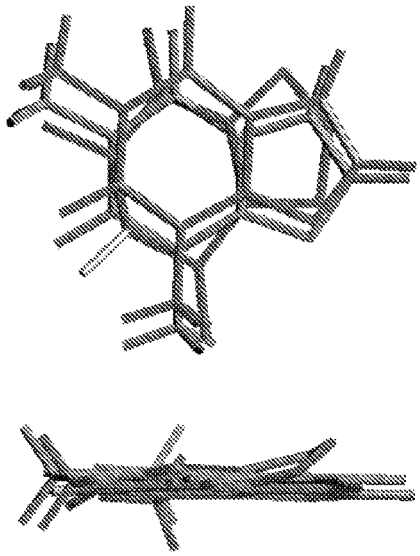


Figure 7. Overlay of the N−H···O lattice energy structure (green), GSAS refined (blue), and DMAREL minimized (red) structures.

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

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

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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 paramters 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

	structure			
parameter/Å, °	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 8: Comparison of Selected Intermolecular Bond Lengths and Angles for N−H···O Structure before and after DMAREL Minimization

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

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 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 energy[50] 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

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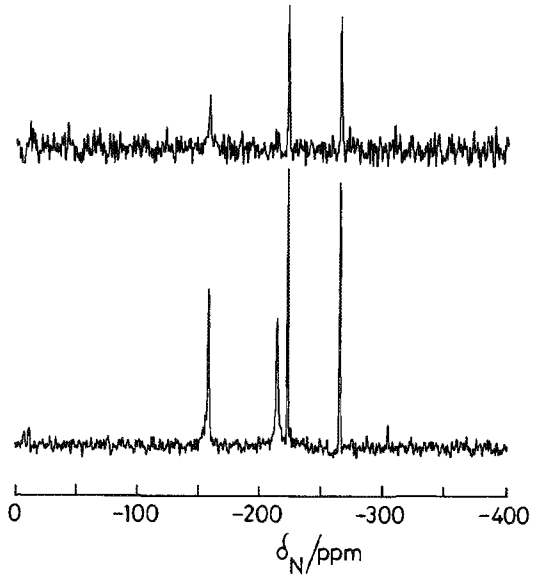


Figure 8. CPMAS ^{15}N solid-state NMR spectra of theophylline at 30.40 MHz and ambient probe temperature, with flip-back.[58] Bottom: full spectrum. Top: dipolar-dephased spectrum (dephasing time 200 μs). Spectrometer parameters: contact time 20 ms; recycle delay 4.0 s; number of transients 6000; spin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

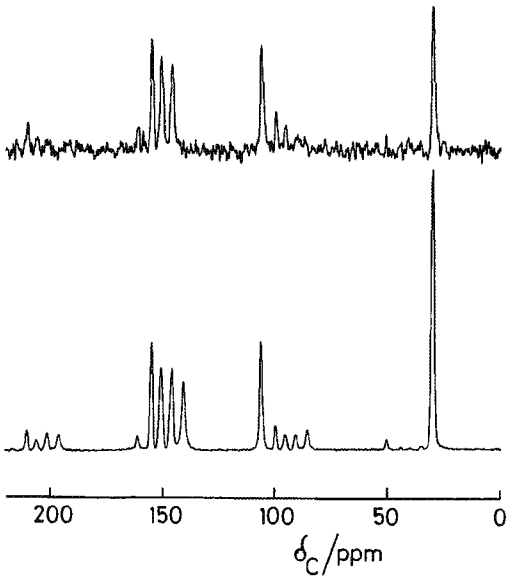


Figure 9. CPMAS ^{13}C solid-state NMR spectra of theophylline at 75.43 MHz and ambient probe temperature, with flip-back.[58] Bottom: full spectrum. Top: diploar-dephased spectrum (dephasing time 40 μs). Small peaks are spinning sidebands. Spectrometer parameters: contact time 5.0 ms; recycle delay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

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 N−H···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 dephasing[53] experiments identified the ^{13}C signal at $\delta_C = 141$ ppm and the ^{15}N peak at $\delta_N = -214$ 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.

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 N−H···N and N−H···O trial crystal structures. For the trimer consisting of a chain of three theophylline molecules N−H···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			optimized monomer			optimized trimer NH···N			optimized trimer NH···O		
	ref 50	ref 51	expt. shifts	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	

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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.

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Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
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:	U0157.70023US02

Filed as Small Entity

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	70	70
Utility Search Fee	2111	1	300	300
Utility Examination Fee	2311	1	360	360
Request for Prioritized Examination	2817	1	2000	2000
Pages:				
Claims:				
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Publ. Fee- Early, Voluntary, or Normal	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	2830	1	70	70
Petition:				
Petition Fee-37CFR 1.17(h) (Group II)	2464	1	70	70
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**2870**

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EFS ID:	18198225
Application Number:	14179862
International Application Number:	
Confirmation Number:	7725
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/Nicole Forgrave
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Attorney Docket Number:	U0157.70023US02
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Deposit Account	
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1	Transmittal of New Application	U015770023US02-TRN-ERG.pdf	33863 b9336ff471016ae2797f5003561e64417669d969	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	U015770023US02-FEE-ERG.pdf	31178 2294125451909fc6b157fd829dceefc78b7ffd03	no	1
Warnings:					
Information:					
3	TrackOne Request	U015770023US02-CERT-ERG.pdf	30869 cf6754e71cc7a108f69df46f04c64757fef74aee	no	1
Warnings:					
Information:					
4	Application Data Sheet	U015770023US02-ADS-ERG.pdf	18825 9f9aedc5d599912562f164e7309ab653e9dfbf1d	no	5
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
5		U015770023US02-UTLAPL-ERG.pdf	179210 e22980fdf3ee790badd972d4e438d6ef9fcb62a3	yes	42

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	33
	Claims	34	41
	Abstract	42	42

Warnings:					
Information:					
6		U015770023US02-PAMN-ERG.pdf	32071 0106ddd749339e98af20500a6deb1fc6a2ebe537	yes	7

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Preliminary Amendment	1	1
	Specification	2	2

	Claims		3		6
	Applicant Arguments/Remarks Made in an Amendment		7		7
Warnings:					
Information:					
7	Drawings-other than black and white line drawings	U015770023US02-DRW-ERG.pdf	21970615 16b400aaccc56ec0d0014e731ca3e5c1d71ee030	no	25
Warnings:					
Information:					
8	Miscellaneous Incoming Letter	U015770023US02-PET-ERG.pdf	18999 2582e479e369782c713089a2ea344a816182063a	no	2
Warnings:					
Information:					
9	Oath or Declaration filed	U015770023US02-DEC-ERG.pdf	418849 08ea55fc970cdcc08934eff227f9002ab611bcecb	no	3
Warnings:					
Information:					
10	Information Disclosure Statement (IDS) Form (SB08)	U015770023US02-IDS-ERG.pdf	296168 e1f62644c71e93946a31d397a7ef16e519f366f3	no	30
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
11	Non Patent Literature	U015770023US02-NPL1-ERG.pdf	519396 caf32725fab6f604e982b6eb664035b1e22284ed	no	4
Warnings:					
Information:					
12	Non Patent Literature	U015770023US02-NPL2-ERG.pdf	1072558 b8cdbe2c5cd5504b27fafdf2966e07376c27134d	no	9
Warnings:					
Information:					
13	Non Patent Literature	U015770023US02-NPL3-ERG.pdf	836425 8cf05baadb067a6b30f5758715 3f231a41bb2979	no	4
Warnings:					
Information:					

14	Non Patent Literature	U015770023US02-NPL4-ERG.pdf	2061677 9662bbd2a5e1efd04828e46322bb8097ee4341ac	no	12
Warnings:					
Information:					
15	Non Patent Literature	U015770023US02-NPL5-ERG.pdf	624745 3330e68a738c19ab121cf7a81a056278f44d7779	no	3
Warnings:					
Information:					
16	Non Patent Literature	U015770023US02-NPL6-ERG.pdf	140908 c5aa875edcba5f57eb6f8cbe1de6c429c2c6664b	no	6
Warnings:					
Information:					
17	Non Patent Literature	U015770023US02-NPL7-ERG.pdf	433413 f4131d3d4c2e8420305d75ea432330c291fe5810	no	9
Warnings:					
Information:					
18	Fee Worksheet (SB06)	fee-info.pdf	42106 8dd7f82f04a878fae7fd38260c9b8cd300f29bba	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	28761875		

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<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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

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

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/179,862

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	70		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	300		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	360		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	19 minus 20 =	*	x 40 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*	x 210 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	730		TOTAL	

APPLICATION AS AMENDED - PART II

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

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

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

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/179,862	02/13/2014	1765	730	U0157.70023US02	19	1

CONFIRMATION NO. 7725

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

FILING RECEIPT

OC000000066867840

Date Mailed: 03/05/2014

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Michael J. Zaworotko, Tampa, FL;
Nair Rodriguez-Hornedo, Ann Arbor, MI;
Brian Moulton, Temple Terrace, FL;

Applicant(s)

The Regents of the University of Michigan, Ann Arbor, MI
University of South Florida, Tampa, FL

Assignment For Published Patent Application

University of South Florida, Tampa, FL
The Regents of the University of Michigan, Ann Arbor, MI

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 10/378,956 03/03/2003
which claims benefit of 60/360,768 03/01/2002

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

If Required, Foreign Filing License Granted: 02/27/2014
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/179,862**
Projected Publication Date: 06/12/2014

Non-Publication Request: No

Early Publication Request: No
** **SMALL ENTITY** **
Title

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

Preliminary Class

525

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

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

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

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

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

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

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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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

Mar 05, 2014 05:32:44 AM

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Application	Document	Mailroom Date	Attorney Docket No.
14179862	APP.FILE.REC	03/05/2014	U0157.70023US02

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600 ATLANTIC AVENUE
BOSTON MA 02210-2206

MAILED
MAR 07 2014
OFFICE OF PETITIONS

Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 14/179,862

1. THE REQUEST FILED February 13, 2014 IS **GRANTED**.

The above-identified application has met the requirements for prioritized examination

A. ☒ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to JoAnne Burke at 571-272-4584. In his/her absence, calls may be directed to Brian Brown, 571-272-5338.

/JoAnne Burke/
[Signature]

Paralegal Specialist, Office of Petitions
(Title)

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

Mar 12, 2014 05:30:11 AM

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BOSTON, MA 02210-2206
UNITED STATES

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14179862	TRACK1.GRANT	03/07/2014	U0157.70023US02

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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.: U0157.70023US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Michael J. Zaworotko
Application No.:	14/179,862
Confirmation No.:	7725
Filed:	February 13, 2014
For:	MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT
Examiner:	Not Yet Assigned
Art Unit:	N/A

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: April 1, 2014 Electronic Signature for Nicole M. Forgrave: /Nicole M. Forgrave/

REQUEST FOR CORRECTED FILING RECEIPT

Office of Initial Patent Examination's Filing Receipt Corrections
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Madam:

Applicant hereby requests that a corrected Filing Receipt be issued in the above-identified patent application. The Applicant Information on the official Filing Receipt is listed incorrectly. We are attaching a copy of the Filing Receipt showing the marked-up changes, along with a copy of the ADS showing the Applicant Information as filed on January 13, 2014. Under the section entitled "**Applicant(s)**, the Filing Receipt should be corrected as follows:

Applicant(s)
University of South Florida, Tampa, FL
The Regents of the University of Michigan, Ann Harbor, MI

3498557.13498557.1

NOVARTIS EXHIBIT 1516
Novartis v. Regents, IPR2023-01347

Applicant additionally requests that all pertinent U.S. Patent and Trademark Office records relating to the subject application be changed to reflect this correction.

Applicant believes no fee is due with this request. However, if a fee is due, please charge our Deposit Account No. 23/2825 under Docket No. U0157.70023US02 from which the undersigned is authorized to draw.

Dated: March 31, 2014

Respectfully submitted,

By: /Edward R. Gates/

Edward R. Gates
Registration No.: 31,616
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

Attachments

3498557.1

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United States Patent and Trademark Office
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/179,862	02/13/2014	1765	730	U0157.70023US02	19	1

CONFIRMATION NO. 7725

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

FILING RECEIPT



Date Mailed: 03/05/2014

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Inventor(s)

Michael J. Zaworotko, Tampa, FL;
Nair Rodriguez-Hornedo, Ann Arbor, MI;
Brian Moulton, Temple Terrace, FL;

Applicant(s)

~~The Regents of the University of Michigan, Ann Arbor, MI~~
~~University of South Florida, Tampa, FL~~ **University of South Florida, Tampa, FL**
The Regents of the University of Michigan, Ann Harbor, MI

Assignment For Published Patent Application

University of South Florida, Tampa, FL
The Regents of the University of Michigan, Ann Arbor, MI

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 10/378,956 03/03/2003
which claims benefit of 60/360,768 03/01/2002

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

If Required, Foreign Filing License Granted: 02/27/2014
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/179,862**
Projected Publication Date: 06/12/2014

UM00000201
NOVARTIS EXHIBIT 1516
Novartis v. Regents, IPR2023-01347
Page 183 of 725

Non-Publication Request: No

Early Publication Request: No
** **SMALL ENTITY** **
Title

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

Preliminary Class

525

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

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

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

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

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

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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

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

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NOT GRANTED

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

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Application Data Sheet

Inventor Information

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Postal or Zip Code of mailing address::	33637

Correspondence Information

Correspondence Customer Number::	23628

Application Information

Application Type::	Regular
Subject Matter::	Utility
CD-ROM or CD-R?::	None
Sequence submission?::	None
Computer Readable Form (CRF)?::	No

Title::	MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT
Attorney Docket Number::	U0157.70023US02
Request for Early Publication?::	No
Request for Non-Publication?::	No
Total Drawing Sheets::	25
Small Entity?::	Yes
Petition included?::	Yes
Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2::	No
Authorization to Permit Access to the Instant Application by the Participating Offices::	No

Representative Information

Representative Customer Number::	23628

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This Application	Continuation of	10/378956	03/03/03
10/378956	An application claiming the benefit under 35 USC 119(e)	60/360768	03/01/02

Applicant Information

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Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.			
Signature	/Edward R. Gates/	Date	February 13, 2014
Name (Print/Type)	Edward R. Gates	Registration No. (Attorney/Agent)	31,616

Electronic Acknowledgement Receipt

EFS ID:	18641076
Application Number:	14179862
International Application Number:	
Confirmation Number:	7725
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/Nicole Forgrave
Filer Authorized By:	Edward R. Gates
Attorney Docket Number:	U0157.70023US02
Receipt Date:	01-APR-2014
Filing Date:	13-FEB-2014
Time Stamp:	15:12:05
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	U015770023US02-TRN-ERG.pdf	26717 756a054b0547118d916291d2dcc236453f49ac67	no	1
Warnings:					
Information:					

2	Request for Corrected Filing Receipt	U015770023US02-RCFR-ERG.pdf	27144 e076c2956add87d51bc800dc252f8af4588d7e17	no	2
Warnings:					
Information:					
3	Request for Corrected Filing Receipt	U015770023US02-CFR-ERG.pdf	523693 d3420653fecc5f7ce9e665527907e74d56a22fbf	no	3
Warnings:					
Information:					
4	Application Data Sheet	U015770023US02-ADS-ERG.pdf	24154 7a268a80758d2044532577 4ea6244e69969088a6	no	5
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
		Total Files Size (in bytes):	601708		

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.

PTO/SB/21 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	

Application Number	14/179,862-Conf. #7725
Filing Date	February 13, 2014
First Named Inventor	Michael J. Zaworotko
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	U0157.70023US02

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
- [x] Other Enclosure(s) (please identify below):

1. Request for Corrected Filing Receipt
2. COPY of Filing Receipt showing marked-up changes with a COPY of the ADS showing Applicant Information as filed 01-13-14

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	WOLF, GREENFIELD & SACKS, P.C.		
Signature	/Edward R. Gates/		
Printed name	Edward R. Gates		
Date	March 31, 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: April 1, 2014 Electronic Signature for Nicole M. Forgrave: /Nicole M. Forgrave/

3498556.1 3498556.1

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/179,862	02/13/2014	Michael J. Zaworotko	U0157.70023US02	7725

23628 7590 04/11/2014

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

EXAMINER	
JAVANMARD, SAHAR	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
04/11/2014	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

UM00000212
NOVARTIS EXHIBIT 1516
Novartis v. Regents, IPR2023-01347
Page 194 of 725

Office Action Summary	Application No. 14/179,862	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 *2/13/14*.

☐ 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) *37-55* 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) *37-55* 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

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

The Office Action is in response to the continuation filed February 13, 2014. Claims 37-55 are being examined on the merits herein.

Objections

Claim 44 has extraneous text at the end of line 2 "[15B]". Appropriate action is required.

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 37-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25, 28, 37, 39-66 of copending Application No. 10/378,956. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to a pharmaceutical composition comprising a co-crystal comprising an API and a co-former (see claims for details), whereas the copending 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 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 37-39 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 the instant claims.

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 37-39 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). Caira discloses that the crystal structures were determined by X-ray diffraction (page 696), meeting the limitations of the instant claims.

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

Conclusion

Claims 37-55 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.

/S. J./

Examiner, Art Unit 1627

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627

FORM PTO-1449/A and B (modified PTO/SB/08)	APPLICATION NO.: Not Yet Assigned	ATTY. DOCKET NO.: U0157.70023US02
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	FILING DATE: Herewith	CONFIRMATION NO.: Not Yet Assigned
	FIRST NAMED INVENTOR: Michael J. Zaworotko	
Sheet 1 of 27	GROUP ART UNIT: Not Yet Assigned	EXAMINER: Not Yet Assigned

U.S. PATENT DOCUMENTS

Examiner's Initials #	Cite No.	U.S. Patent Document Number	U.S. Patent Document Kind Code	Name of Patentee or Applicant of Cited Document	Date of Publication or Issue of Cited Document MM-DD-YYYY
		2,554,816		Clapp et al.	05-29-1951
		2,665,277		Homeyer et al.	01-05-1954
		2,711,411		Holbert et al.	06-21-1955
		2,980,679		Gianfranco	04-18-1961
		3,028,420		Petrow et al.	04-03-1962
		3,536,809		Schaller et al.	04-09-1991
		3,598,123		Zaffaroni	08-10-1971
		3,845,770		Theeuwes et al.	11-05-1974
		3,916,899		Theeuwes et al.	11-04-1975
		3,970,651		Kaplan et al.	07-20-1976
		4,008,321		Kamishita et al.	02-15-1977
		4,008,719		Theeuwes et al.	02-22-1977
		4,198,507		Barry et al.	04-15-1980
		4,267,179		Heeres et al.	05-12-1981
		4,368,197		Shefter et al.	01-11-1983
		4,513,006		Maryanoff et al.	04-23-1995
		4,764,604		Muller	08-16-1988
		4,792,569		Maryanoff et al.	12-20-1988
		4,853,379		Shroot et al.	08-01-1989
		4,916,134		Heeres et al.	04-10-1990
		4,925,674		Giannini et al.	05-15-1990
		4,927,855		Lafon	05-22-1990
		4,994,604		Tung et al.	02-19-1991
		5,006,513		Hector et al.	04-09-1991
		5,023,092		DuRoss	07-11-1991
		5,059,595		Le Grazie	10-22-1991
		5,073,543		Marshall et al.	12-17-1991
		5,120,548		McClelland et al.	06-09-1992
		5,177,262		Taylor et al.	01-15-1993
		5,242,942		Costanzo et al.	09-07-1993
		5,258,402		Maryanoff	11-02-1993
		5,273,760		Oshlack et al.	12-28-1993
		5,286,493		Oshlack et al.	02-15-1994

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.

*a copy of this reference is not provided as it was previously cited by or submitted to the office in a prior application, Serial No. 10/378,956, filed March 3, 2003, and relied upon for an earlier filing date under 35 U.S.C. 120 (continuation, continuation-in-part, and divisional applications).

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

FORM PTO-1449/A and B (modified PTO/SB/08)				APPLICATION NO.: Not Yet Assigned	ATTY. DOCKET NO.: U0157.70023US02
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				FILING DATE: Herewith	CONFIRMATION NO.: Not Yet Assigned
				FIRST NAMED INVENTOR: Michael J. Zaworotko	
Sheet	2	of	27	GROUP ART UNIT: Not Yet Assigned	EXAMINER: Not Yet Assigned

		5,324,351		Oshlack et al.	06-28-1994
		5,332,834		Bhattacharya et al.	07-26-1994
		5,338,644		Taylor et al.	08-16-1994
		5,354,556		Sparks et al.	10-11-1994
		5,356,467		Oshlack et al.	10-18-1994
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				FIRST NAMED INVENTOR: Michael J. Zaworotko	
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NOVARTIS EXHIBIT 1516
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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.

*a copy of this reference is not provided as it was previously cited by or submitted to the office in a prior application, Serial No. 10/378,956, filed March 3, 2003, and relied upon for an earlier filing date under 35 U.S.C. 120 (continuation, continuation-in-part, and divisional applications).

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

FORM PTO-1449/A and B (modified PTO/SB/08)				APPLICATION NO.: Not Yet Assigned	ATTY. DOCKET NO.: U0157.70023US02
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				FILING DATE: Herewith	CONFIRMATION NO.: Not Yet Assigned
				FIRST NAMED INVENTOR: Michael J. Zaworotko	
Sheet	26	of	27	GROUP ART UNIT: Not Yet Assigned	EXAMINER: Not Yet Assigned

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

FORM PTO-1449/A and B (modified PTO/SB/08)				APPLICATION NO.: Not Yet Assigned	ATTY. DOCKET NO.: U0157.70023US02
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				FILING DATE: Herewith	CONFIRMATION NO.: Not Yet Assigned
				FIRST NAMED INVENTOR: Michael J. Zaworotko	
Sheet	27	of	27	GROUP ART UNIT: Not Yet Assigned	EXAMINER: Not Yet Assigned

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CONFIRMATION NO. 7725

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/179,862	02/13/2014 **RULE**	424	1627	U0157.70023US02

APPLICANTS

The Regents of the University of Michigan, Ann Arbor, MI, Assignee (with 37 CFR 1.172 Interest);
University of South Florida, Tampa, FL, Assignee (with 37 CFR 1.172 Interest);

INVENTORS

Michael J. Zaworotko, Tampa, FL;
Nair Rodriguez-Hornedo, Ann Arbor, MI;
Brian Moulton, Temple Terrace, FL;

**** CONTINUING DATA ************************

This application is a CON of 10/378,956 03/03/2003
which claims benefit of 60/360,768 03/01/2002

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

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
02/27/2014

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /SAHAR JAVANMARD/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		FL	25	19	1

ADDRESS

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

TITLE

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

FILING FEE RECEIVED		
730	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

EAST Search History

EAST Search History (Prior Art)

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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 acetominophen	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

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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;	SAME	OFF	2008/09/30 09:56

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			EPO; JPO; DERWENT			
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;	AND	OFF	2008/09/30 10:26

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			USOCR; FPRS; EPO; JPO; DERWENT			
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;	OR	OFF	2009/08/31 06:23

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			EPO; JPO; DERWENT			
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 acetominophen	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

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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; EPO; JPO; DERWENT	ADJ	OFF	2009/08/31 08:44
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 acetominophen	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;	AND	OFF	2009/08/31 08:58

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			EPO; JPO; DERWENT			
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 acetominophen	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-	US-PGPUB; USPAT; USOCR; EPO; JPO	OR	OFF	2009/09/28 23:04

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		20040019211-$.DID.				
S79	20	US-20040106053-$.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-$.DID. OR US-5073543-$.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.	US-PGPUB; USPAT; USOCR; EPO; JPO	OR	OFF	2009/09/28 23:08
S81	35195	bipyridine phthalaldehyde nicotinamide saccharrin 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 acetominophen	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

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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; FPRS; EPO; JPO; DERWENT	AND	OFF	2010/06/17 10:29
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;	AND	OFF	2010/06/17 11:41

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			DERWENT			
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; FPRS; EPO; JPO; DERWENT	AND	ON	2013/07/26 12:46
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	24	((MICHAEL) near2 (ZAWOROTKO)).INV.	US-PGPUB; USPAT	OR	OFF	2014/04/04 13:43
S106	8	((BRIAN) near2 (MOULTON)).INV.	US-PGPUB; USPAT	OR	OFF	2014/04/04 13:43
S107	7	((NAIR) near2 (RODRIGUEZ-HORNEDO)).INV.	US-PGPUB; USPAT	OR	OFF	2014/04/04 13:43
S108	27	S105 S106 S107	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/04/04 13:43
S109	8	(400/424).CCLS.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2014/04/04 13:44
S110	0	S108 S109	US-PGPUB;	AND	ON	2014/04/04 13:44

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			USPAT; USOCR; FPRS; EPO; JPO; DERWENT			
S111	10	S108 and cocrystal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2014/04/04 13:44
S112	12	gb "2169601"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	ADJ	ON	2014/04/04 14:46

EAST Search History (Interference)

<This search history is empty>

4/7/2014 11:14:34 AM
C:\Users\sjavanmard\Documents\EAST\Workspaces\14\14179862.wsp

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14179862	ZAWOROTKO ET AL.
	Examiner	Art Unit
	SAHAR JAVANMARD	1627

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
424	400	4/4/2014	SJ

SEARCH NOTES		
Search Notes	Date	Examiner
EAST (searched inventor names)	4/4/2014	SJ
EAST (keyword search)	4/4/2014	SJ

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

/S.J./ Examiner.Art Unit 1627	

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14179862	ZAWOROTKO ET AL.
	Examiner	Art Unit
	SAHAR JAVANMARD	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	03/21/2014								
	1	-								
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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14179862	ZAWOROTKO ET AL.
	Examiner	Art Unit
	SAHAR JAVANMARD	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	03/21/2014								
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	38	✓								
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	53	✓								
	54	✓								
	55	✓								

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To: Patents_eOfficeAction@WolfGreenfield.com,WGS_eOfficeAction@WolfGreenfield.com,
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Application	Document	Mailroom Date	Attorney Docket No.
14179862	CTNF	04/11/2014	U0157.70023US02
	1449	04/11/2014	U0157.70023US02

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/179,862	02/13/2014	Michael J. Zaworotko	U0157.70023US02

CONFIRMATION NO. 7725

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

PUBLICATION NOTICE

OC000000068981841

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

Publication No.US-2014-0162989-A1
Publication Date:06/12/2014

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

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To: Patents_eOfficeAction@WolfGreenfield.com,WGS_eOfficeAction@WolfGreenfield.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
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Jun 13, 2014 05:31:20 AM

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Application	Document	Mailroom Date	Attorney Docket No.
14179862	NTC.PUB	06/12/2014	U0157.70023US02

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UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

Docket No.: U0157.70023US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Michael J. Zaworotko
Application No.:	14/179,862
Confirmation No.:	7725
Filed:	February 13, 2014
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: July 10, 2014 Electronic Signature for Nancy J. Arsenault: /Nancy J. Arsenault/

AMENDMENT IN 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 Madam:

INTRODUCTORY COMMENTS

In response to the Office Action dated April 11, 2014, please amend the above-identified U.S. patent application as follows:

Amendments to the Specification begin on page 3 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this paper.

Remarks/Arguments begin on page 9 of this paper.

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AMENDMENTS TO THE SPECIFICATION

Please replace the first paragraph on page 1 with the following replacement paragraph:

CROSS-REFERENCE TO RELATED APPLICATION

The present application is a continuation of U.S. Application Serial No. 10/378,956, filed March [[2]]3, 2003, which is hereby incorporated by reference herein in its entirety, including any figures, tables, or drawings. U.S. Application Serial No. 10/378,956 claims the benefit of priority of U.S. Provisional Application Serial No. 60/360,768, filed March 1, 2002, which is hereby incorporated by reference herein in its entirety, including any figures, tables, or drawings.

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AMENDMENTS TO THE CLAIMS

Please replace all prior versions, and listings, of claims in the application with the following list of claims:

1-36. (Canceled)

37. (Currently amended) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former and each supramolecular synthon comprising an API homosynthon formed via non-covalent hydrogen bonding,

wherein the API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form,

wherein the co-former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding,

wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form,

~~wherein said co-former is not an API~~, and

wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former.

38. (Currently amended) The pharmaceutical composition of claim [[37]]52, wherein the supramolecular synthon comprises a ~~supramolecular~~ heterosynthon dimer formed by non-covalent hydrogen bonding of the API to the co-former.

39. (Currently amended) The pharmaceutical composition of claim [[37]]52, wherein the supramolecular synthon comprises a plurality of the API and a plurality of the co-former, wherein the supramolecular synthon is a chain of supramolecular heterosynthons, each supramolecular

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heterosynthon formed by non-covalent hydrogen bonding of one API to one co-former, and wherein the supramolecular heterosynthons are bonded to one another by non-covalent hydrogen bonding.

40. (Currently amended) The pharmaceutical composition of claim [[37]]52, wherein the co-crystal is a hydrated co-crystal, wherein the supramolecular synthon comprises a plurality of the API and a plurality of the co-former, wherein the supramolecular synthon affords a sheet of the API, each of the APIs in the sheet bonded to one another and to a co-former by non-covalent hydrogen bonding to a water molecule.

41. (Currently amended) ~~The pharmaceutical composition of claim 37,~~ A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former,

wherein the API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form,

wherein the co-former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding,

wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form,

wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former, and wherein the at least one API~~pharmaceutical entity~~ participating in each supramolecular synthon is two APIs and the at least one co-former is one co-former, and wherein each of the two APIs is bonded by non-covalent bonding to the one co-former.

42. (Currently amended) The pharmaceutical composition of claim [37]52, wherein the at least one co-former participating in each supramolecular synthon is two co-formers forming a

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homosynthon, the at least one API in each supramolecular synthon is two APIs, and wherein each of the two APIs is bonded by non-covalent bonding to one of the two co-formers.

43. (Currently amended) The pharmaceutical composition of claim [[37]]52, wherein the at least one API participating in each supramolecular synthon is two APIs and the at least one co-former participating in each supramolecular synthon is two co-formers forming a homosynthon, and wherein one of the two APIs is non-covalently bonded to one of the co-formers and the other of the two APIs is non-covalently bonded to the other of the two co-formers.

44. (Currently amended) The pharmaceutical composition of claim [[37]]52, wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule. ~~[15B]~~

45. (Previously Presented) The pharmaceutical composition of claim 37, wherein the at least one API participating in each supramolecular synthon is two APIs of the at least one API that are bonded to one another through hydrogen bonding to form at least one homosynthon dimer.

46. (Previously Presented) The pharmaceutical composition of claim 45, wherein the at least one co-former is two of the co-former and the at least one API is two of the API, wherein the at least one homosynthon dimer is one homosynthon dimer, and wherein the supramolecular synthon forms a tetramer, the tetramer being comprised of the two co-formers and two APIs, and each co-former being attached to the homodimer by hydrogen bonds.

47. (Previously Presented) The pharmaceutical composition of claim 45, wherein the at least one co-former is two co-formers, wherein the at least one homosynthon dimer is two homosynthon dimers, and wherein the supramolecular synthon results in a hexamer.

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48. (Previously Presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthon comprises a plurality of the API and a plurality of the co-former, wherein the supramolecular synthon comprises a chain of homosynthon dimers, each homosynthon dimer formed by hydrogen bonding of one of the plurality of the API to another of the plurality of the API, and wherein the homosynthon dimers are bonded to the co-former by hydrogen bonding.

49. (Previously Presented) The pharmaceutical composition of claim 45, wherein the at least one co-former participating in each supramolecular synthon is two co-formers forming a homosynthon.

50. (Currently amended) The pharmaceutical composition of claim [[37]]52, wherein the second chemical functionality complimentary to the first chemical functionality is (i) two identical second chemical functionalities on the co-former, (ii) three identical second chemical functionalities on the co-former, or (iii) four identical second chemical functionalities on the co-former.

51. (Canceled)

52. (Currently amended) ~~The pharmaceutical composition of claim 37,~~ A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former,

wherein the API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form,

wherein the co-former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding,

wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form,

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wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former, and

wherein the first chemical functionality is (i) a carboxamide ~~a carboxylic acid~~, (ii) a carbonyl, or (iii) an amine.

53. (Currently amended) ~~The pharmaceutical composition of claim 37,~~ A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former,

wherein the API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form,

wherein the co-former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding,

wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form,

wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former, and

wherein the first chemical functionality and the second chemical functionality form (i) a carbonyl[[-]]:amide hydrogen bond, (ii) a carbonyl:amine hydrogen bond, [[or]] (iii) a carboxylic acid:pyridine hydrogen bond, (iv) a carboxylic acid:aromatic amine hydrogen bond, (v) a carboxylic acid:carboxylic acid hydrogen bond, (vi) a carboxylic acid:carboxamide hydrogen bond, (vii) a carboxylic acid:amine hydrogen bond, (viii) a carboxylic acid:carbonyl hydrogen bond, (ix) an amine:sulfonamide hydrogen bond, or (x) a carbonyl:sulfonamide hydrogen bond.

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54. (Previously Presented) The pharmaceutical composition of claim 37, wherein the non-covalent bonding of said API homosynthons is carboxylic acid:carboxylic acid hydrogen bonding.

55. (Previously Presented) The pharmaceutical composition of claim 37, wherein the non-covalent bonding of said API homosynthons is carboxamide:carboxamide hydrogen bonding.

56. (New) The pharmaceutical composition of claim 52, wherein the first chemical functionality is a carboxamide.

57. (New) The pharmaceutical composition of claim 52, wherein the first chemical functionality is a carbonyl.

58. (New) The pharmaceutical composition of claim 52, wherien the first chemical functionality is an amine.

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REMARKS

Applicant respectfully requests reconsideration. Claims 37-55 were previously pending in this application. By this amendment, claim 43 has been canceled without prejudice or disclaimer. Claims 37-44, and 50-53 have been amended. Claims 56-58 have been added. Support for the new and 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 37-42 and 44-58 are pending for examination with claims 37, 41, 52, and 53 being independent claims. No new matter has been added.

Allowable Subject Matter

It is Applicant's understanding that claim 41 was not rejected under 35 U.S.C. §102(b) in the Office Action. Claim 41 has been re-written into independent form. Thus, Applicant asserts that amended claim 41 is in condition for allowance.

Claim Objections

The Examiner objected to claim 44 for the recitation of extraneous text. Claim 44 has been amended to remove the extraneous text. Withdrawal of this objection is respectfully requested.

Double Patenting Rejection

The Examiner provisionally rejected claims 37-55 as being unpatentable over claims 25, 28, 37 and 39-66 of copending Application No. 10/378,956.

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.

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Rejections Under 35 U.S.C. §102

I

The Examiner rejected claims 37-39 and 51-53 under 35 U.S.C. §102(b) as being anticipated by Jackson (GB 2169601). 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. Thus, without conceding the correctness of the Examiner's allegations that Jackson discloses a co-crystal and solely for the purpose of advancing prosecution, claims 37-39 and 51-53 have been amended such that they do not recite a co-crystal comprising a supramolecular heterosynthon formed by hydroxyl:pyridine hydrogen bonding. In particular, claims 37, 52, and 53, which are now all independent claims, have been amended such that they do not recite or encompass a co-crystal comprising a supramolecular heterosynthon formed by hydroxyl:pyridine hydrogen bonding.

Claim 37 has been amended to recite, in part, a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former ***and each supramolecular synthon comprising an API homosynthon formed via non-covalent hydrogen bonding***. Jackson does not disclose a co-crystal comprising supramolecular synthons comprising an API homosynthon.

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Claim 52 has been re-written in independent form and has been amended to recite a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former, wherein the API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form, wherein the co-former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding, wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form,wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former, and ***wherein the first chemical functionality is a carboxamide, a carbonyl or an amine.*** Jackson does not disclose an API comprising a first chemical functionality that is a carboxamide, carbonyl or an amine.

Claim 53 has been re-written in independent form and now recites a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former, wherein the API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form, wherein the co-former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding, wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form, wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former, and ***wherein the first chemical functionality and the second chemical functionality form (i) a carbonyl:amide hydrogen bond, (ii) a carbonyl:amine hydrogen bond, (iii) a carboxylic acid:pyridine hydrogen bond, (iv) a carboxylic acid:aromatic amine hydrogen bond, (v) a carboxylic acid:carboxylic acid hydrogen bond, (vi) a carboxylic acid:carboxamide hydrogen bond, (vii) a carboxylic acid:amine hydrogen bond, (viii)***

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a carboxylic acid:carbonyl hydrogen bond, (ix) an amine:sulfonamide hydrogen bond, or (x) a carbonyl:sulfonamide hydrogen bond. Jackson does not disclose a co-crystal comprising a first chemical functionality and a second chemical functionality that form (i) a carbonyl:amide hydrogen bond, (ii) a carbonyl:amine hydrogen bond, (iii) a carboxylic acid:pyridine hydrogen bond, (iv) a carboxylic acid:aromatic amine hydrogen bond, (v) a carboxylic acid:carboxylic acid hydrogen bond, (vi) a carboxylic acid:carboxamide hydrogen bond, (vii) a carboxylic acid:amine hydrogen bond, (viii) a carboxylic acid:carbonyl hydrogen bond, (ix) an amine:sulfonamide hydrogen bond, or (x) a carbonyl:sulfonamide hydrogen bond.

As a result, amended claims 37, 52 and 53 are not anticipated by Jackson. Claims 38 and 39 have been amended to depend from amended claim 52. Claim 51 depends from amended claim 37. Thus, dependent claims 38, 39, and 51 are also not anticipated by Jackson.

Applicant also respectfully notes that the Office Action refers to claims 39-41 (see page 4) and claim 28 (see page 5) within the body of the rejection over Jackson. It is believed that these references to these claims are typographical errors, as there is no reference to a food additive in claims 39-41 and there is no pending claim 28 in the instant application. Accordingly, Applicant has not addressed the statements related to these typographical errors.

Accordingly, withdrawal of this rejection is respectfully requested.

II

The Examiner rejected claims 37-39 and 51-53 under 35 U.S.C. §102(b) as being anticipated by Caira (Journal of Chemical Crystallography, 1994). Reconsideration is respectfully requested in light of the amendment and arguments presented herein.

Caira discloses a co-crystal comprising 5-methoxysulfadiazine (SMD) and acetylsalicylic acid that forms a supramolecular synthon comprising heterosynthons formed by hydrogen bonds between the sulfonamide group of the SMD and the carboxylic acid group of the acetylsalicylic acid (see, e.g., Fig. 4). Solely for the purpose of advancing prosecution, claims 37-39 and 51-53 have been amended to exclude supramolecular heterosynthons formed by sulfonamide:carboxylic acid bonding and to exclude supramolecular heterosynthons formed by hydrogen bonding involving a

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first chemical functionality comprising a carboxylic acid. In particular, claims 37, 52, and 53, which are now all independent claims, have been amended such that they do not recite or encompass supramolecular synthons comprising heterosynthons formed by hydrogen bonding involving a first chemical functionality comprising a carboxylic acid and a second chemical functionality comprising a sulfonamide.

The amendments to claims 37, 52, and 53 are described above. Caira does not disclose a co-crystal comprising supramolecular synthons comprising an API homosynthon, as recited in amended claim 37. Caira also does not disclose an API comprising a first chemical functionality that is a carboxamide, carbonyl or an amine, as recited in amended claim 52. Lastly, Caira also does not disclose a co-crystal comprising a first chemical functionality and a second chemical functionality that form (i) a carbonyl:amide hydrogen bond, (ii) a carbonyl:amine hydrogen bond, (iii) a carboxylic acid:pyridine hydrogen bond, (iv) a carboxylic acid:aromatic amine hydrogen bond, (v) a carboxylic acid:carboxylic acid hydrogen bond, (vi) a carboxylic acid:carboxamide hydrogen bond, (vii) a carboxylic acid:amine hydrogen bond, (viii) a carboxylic acid:carbonyl hydrogen bond, (ix) an amine:sulfonamide hydrogen bond, or (x) a carbonyl:sulfonamide hydrogen bond., as recited in amended claim 53.

As a result, amended claims 37, 52, and 53 are not anticipated by Caira. Claims 38 and 39 have been amended to depend from amended claim 52. Claim 51 depends from amended claim 37. Thus, dependent claims 38, 39, and 51 are also not anticipated by Caira.

Withdrawal of this rejection is respectfully requested.

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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 fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 23/2825 under Docket No. U0157.70023US02 from which the undersigned is authorized to draw.

Dated: July 10, 2014

Respectfully submitted,

By /Edward R. Gates/
Edward R. Gates
Registration No.: 31,616
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

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Electronic Patent Application Fee Transmittal

Application Number:	14179862
Filing Date:	13-Feb-2014
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/Nancy Arsenault
Attorney Docket Number:	U0157.70023US02

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:				
Claims in excess of 20	2202	1	40	40
Independent Claims in Excess of 3	2201	1	210	210
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**250**

Electronic Acknowledgement Receipt

EFS ID:	19538244
Application Number:	14179862
International Application Number:	
Confirmation Number:	7725
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/Nancy Arsenault
Filer Authorized By:	Edward R. Gates
Attorney Docket Number:	U0157.70023US02
Receipt Date:	10-JUL-2014
Filing Date:	13-FEB-2014
Time Stamp:	07:16:30
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$250
RAM confirmation Number	6417
Deposit Account	
Authorized User	

File Listing:

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

1	Miscellaneous Incoming Letter	U015770023US02-TRN-ERG.pdf	24961 0d3f11e20a6ef3136e3ec5fdb427f42303a4ee2a	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	U015770023US02-FEE-ERG.pdf	31814 4dadce94358f46b4dacf988942521c7f36f0cb90	no	1
Warnings:					
Information:					
3		U015770023US02-AMN-ERG.pdf	63783 da765bb98fd9398886ed1c9c3467603e85951fbd	yes	14

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Specification	2	2
	Claims	3	8
	Applicant Arguments/Remarks Made in an Amendment	9	14

Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	32067 66d90e6b80bf9ed13baa7fa10fbe719db35a1827	no	2
Warnings:					
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		Total Files Size (in bytes):	152625		

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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.

PTO/SB/21 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	14/179,862-Conf. #7725
Filing Date	February 13, 2014
First Named Inventor	Michael J. Zaworotko
Art Unit	1627
Examiner Name	S. Javanmard
Total Number of Pages in This Submission	
Attorney Docket Number	U0157.70023US02

ENCLOSURES (*Check all that apply*)

- [x] Fee Transmittal Form
- [ ] Fee Attached
- [x] 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	July 10, 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: July 10, 2014 Electronic Signature for Nancy J. Arsenault: /Nancy J. Arsenault/

3636981.1

PTO/SB/17 (03-13)
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FEE TRANSMITTAL

Complete if known	
Application Number	14/179,862-Conf. #7725
Filing Date	February 13, 2014
First Named Inventor	Michael J. Zaworotko
Examiner Name	S. Javanmard
Art Unit	1627
Practitioner Docket No.	U0157.70023US02

[X] Applicant asserts small entity status. See 37 CFR 1.27

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

TOTAL AMOUNT OF PAYMENT ($) 250.00

METHOD OF PAYMENT (check all that apply)

[ ] Check [X] 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**

[X] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17 [X] 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 ($)	Fee Paid ($)
21 - 20 or HP =	1 x	40.00 =	40.00

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

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
4 - 3 or HP =	1 x	210.00 =	210.00

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

Multiple Dependent Claims	Fee ($)	Fee Paid ($)

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): _____ _____

SUBMITTED BY					
Signature	/Edward R. Gates/	Registration No. (Attorney/Agent)	31,616	Telephone	617.646.8000
Name (Print/Type)	Edward R. Gates			Date	July 10, 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: July 10, 2014 Electronic Signature for Nancy J. Arsenault: /Nancy J. Arsenault/

3636980.1

PTO/SB/06 (09-11)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/179,862	Filing Date 02/13/2014	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
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

AMENDMENT	07/10/2014	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 21	Minus	** 20	= 1	X $40 =	40
	Independent (37 CFR 1.16(h))	* 4	Minus	***3	= 1	X $210 =	210
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**250**

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	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.

LIE
/NICOLLE L. SCRIVNER/

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.

PTO/SB/21 (07-09)
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	

Application Number	14/179,862-Conf. #7725
Filing Date	February 13, 2014
First Named Inventor	Michael J. Zaworotko
Art Unit	1627
Examiner Name	S. Javanmard
Attorney Docket Number	U0157.70023US02

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
- [x] 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
- [x] Other Enclosure(s) (*please* Identify below):

Statement Under 37 CFR 3.73(c) (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	October 16 2014	Reg. No.	31,616

Certificate of Electronic Filing Under 37 CFR 1.8

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Dated: October 16 2014 Electronic Signature for Nicole M. Forgrave: /Nicole M. Forgrave/

3769422.1

PTO/AIA/96 (08-12)
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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: University of South Florida

Application No./Patent No.: 14/179,862 Filed/Issue Date: February 13, 2014

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

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

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☐ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ (The extent (by percentage) of its ownership interest is _____ %). Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☒ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Regents of the University of Michigan

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2, or 3 above (not option 4) is evidence by either (choose **one** of options A or B below):

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.

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 033184, Frame 0069, 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 033184, Frame 0069, or for which a copy thereof is attached.

3769348.1

PTO/AIA/96 (08-12)
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STATEMENT UNDER 37 CFR 3.73(c)

3. From: Nair Rodriguez-Hornedo To: Regents of the University of Michigan
The document was recorded in the United States Patent and Trademark Office at
Reel 033183 , Frame 0079 , or for which a copy thereof is attached.

4. 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.

5. 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.

6. 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(c)(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	October 16 2014
Signature	Date
Edward R. Gates	Attorney for Assignee
Printed or Typed Name	Title or Registration 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 16 2014 Electronic Signature for Nicole M. Forgrave: /Nicole M. Forgrave/

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Regents of the University of Michigan

Application No./Patent No.: 14/179,862 Filed/Issue Date: February 13, 2014

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

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

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☐ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ (The extent (by percentage) of its ownership interest is _____ %). Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☒ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   University of South Florida

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2, or 3 above (not option 4) is evidence by either (choose **one** of options A or B below):

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.

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 033184, Frame 0069, 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 033184, Frame 0069, or for which a copy thereof is attached.

3769352.1

PTO/AIA/96 (08-12)
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STATEMENT UNDER 37 CFR 3.73(c)

3. From: Nair Rodriguez-Hornedo To: Regents of the University of Michigan
The document was recorded in the United States Patent and Trademark Office at
Reel 033183 , Frame 0079 , or for which a copy thereof is attached.

4. 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.

5. 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.

6. 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(c)(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	October 16, 2014
Signature	Date
Edward R. Gates	Attorney for Assignee
Printed or Typed Name	Title or Registration 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 16, 2014 Electronic Signature for Nicole M. Forgrave: /Nicole M. Forgrave/

PTO/AIA/80 (07-12)
Approved for use through 11/30/2014. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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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:

[X] 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

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

PTO/AIA/82B (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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POWER OF ATTORNEY BY APPLICANT

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

Application Number	Filing Date
14/179,862	February 13, 2014

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

[X] I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 23628

OR

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

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

[ ] The address associated with the above-mentioned Customer Number

OR

[ ] The address associated with Customer Number:

OR

Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

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

The Regents of the University of Michigan

[ ] Inventor or Joint Inventor (title not required below)

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

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

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

SIGNATURE of Applicant for Patent

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

Signature	Maryann Kostiuk	Date (Optional)	9/12/14
Name	Maryann Kostiuk		
Title	Patent Administrator, The Regents of the University of Michigan		

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

[ ] Total of 1 forms are submitted.

3622780.1

Electronic Acknowledgement Receipt

EFS ID:	20436210
Application Number:	14179862
International Application Number:	
Confirmation Number:	7725
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/Nicole Forgrave
Filer Authorized By:	Edward R. Gates
Attorney Docket Number:	U0157.70023US02
Receipt Date:	16-OCT-2014
Filing Date:	13-FEB-2014
Time Stamp:	15:37:10
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	U015770023US02-TRN-ERG.pdf	368326 a967e7ff4fec38c8df7ef6fcbda7b61c28210f34	no	1
Warnings:					
Information:					

2	Assignee showing of ownership per 37 CFR 3.73.	U015770023US02-USF-373-ERG.pdf	776139 4c2e9443c1bbedbb4dfd3d5bd214ab3853 1042cf	no	2
Warnings:					
Information:					
3	Assignee showing of ownership per 37 CFR 3.73.	U015770023US02-UM-373-ERG.pdf	775444 8fd813f1c660d2d2af54b466e0a155c1bac1 f982	no	2
Warnings:					
Information:					
4	Oath or Declaration filed	U015770023US02-USF-POA-ERG.pdf	151665 bbcffefdc33e0e88fd086d93220a38fbaa5be 4e9	no	1
Warnings:					
Information:					
5	Oath or Declaration filed	U015770023US02-UM-POA-ERG.pdf	503189 ede35725be6a359d29d62f0018bdff1e3af3 bbdc	no	1
Warnings:					
Information:					
		Total Files Size (in bytes):	2574763		

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

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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

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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/179,862	02/13/2014	Michael J. Zaworotko	U0157.70023US02	7725

23628 7590 12/19/2014

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

EXAMINER	
JAVANMARD, SAHAR	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
12/19/2014	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

UM00000300
NOVARTIS EXHIBIT 1516
Novartis v. Regents, IPR2023-01347
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Office Action Summary	Application No. 14/179,862	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 *7/10/14*.

☐ 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) *37-50 and 52-58* 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) *37-50 and 52-58* 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: _____.

UM00000301
NOVARTIS EXHIBIT 1516
Novartis v. Regents, IPR2023-01347
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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 July 10, 2014. Claim(s) 37-50 and 52-58 and examined herein.

Response to Arguments

The double patenting rejection of claims 37-55 is hereby maintained due to Applicant's decision to hold said rejection in abeyance.

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 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 37-50 and 52-58 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25, 28, 37, 39-66

of copending Application No. 10/378,956. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to a pharmaceutical composition comprising a co-crystal comprising an API and a co-former (see claims for details), whereas the copending 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 § 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 negatived 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 37-50 and 52-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huffman (US Patent No. 3,664,858).

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-bromophenox yacetic 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(trifluoromethyisulfanyl)methane, xanthanoic, thiophendicarboxylic, cyclohexanecarboxylic, norcamphoric, naphthalenedicarboxylic,

naphthalenetricarboxylic, mellitic, trimesic, biphenyldicarboxylic, resorcinol-o-acetic, anthracenecarboxylic, o-bromotoluic, p-bromomandelic, salicylacetic, dinitrophenylacetic, 2-furanace-tic, 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 incorporating said cocrystals into pharmaceutical formulations.

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. 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 37-50 and 52-58 are not allowed.

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.

/S. J./

Examiner, Art Unit 1627

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627

Notice of References Cited	Application/Control No. 14/179,862	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-3,664,858	05-1972	Huffman, William A.	503/216
	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	
	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.

UM00000310
NOVARTIS EXHIBIT 1516
Novartis v. Regents, IPR2023-01347
Page 292 of 725

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14179862	ZAWOROTKO ET AL.
	Examiner	Art Unit
	SAHAR JAVANMARD	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	03/21/2014	10/20/2014							
	1	-	-							
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	3	-	-							
	4	-	-							
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UM00000311
NOVARTIS EXHIBIT 1516
Novartis v. Regents, IPR2023-01347
Page 293 of 725

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14179862	ZAWOROTKO ET AL.
	Examiner	Art Unit
	SAHAR JAVANMARD	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	03/21/2014	10/20/2014							
	37	✓	✓							
	38	✓	✓							
	39	✓	✓							
	40	✓	✓							
	41	✓	✓							
	42	✓	✓							
	43	✓	✓							
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	45	✓	✓							
	46	✓	✓							
	47	✓	✓							
	48	✓	✓							
	49	✓	✓							
	50	✓	✓							
	51	✓	-							
	52	✓	✓							
	53	✓	✓							
	54	✓	✓							
	55	✓	✓							
	56		✓							
	57		✓							
	58		✓							

UM00000312
NOVARTIS EXHIBIT 1516
Novartis v. Regents, IPR2023-01347
Page 294 of 725

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14179862	ZAWOROTKO ET AL.
	Examiner	Art Unit
	SAHAR JAVANMARD	1627

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
424	400	4/4/2014	SJ
	updated 10/2014		SJ

SEARCH NOTES		
Search Notes	Date	Examiner
EAST (searched inventor names)	4/4/2014	SJ
EAST (keyword search)	4/4/2014	SJ
updated 10/2014		SJ
Google Patents (searched:organic acids amines adducts crystals)	12/12/2014	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

Dec 19, 2014 05:39:35 AM

Dear PAIR Customer:

WOLF GREENFIELD & SACKS, P.C.
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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.

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Application	Document	Mailroom Date	Attorney Docket No.
14179862	CTFR	12/19/2014	U0157.70023US02
	892	12/19/2014	U0157.70023US02

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

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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

PTO/SB/30 (07-09)
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Request for Continued Examination (RCE) Transmittal

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

Application Number	14/179,862-Conf. #7725
Filing Date	February 13, 2014
First Named Inventor	Michael J. Zaworotko
Art Unit	1627
Examiner Name	S. Javanmard
Attorney Docket Number	U0157.70023US02

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. [X] Enclosed
     - i. [X] Amendment/Reply
     - ii. [ ] Affidavit(s)/Declaration(s)
     - iii. [ ] Information Disclosure Statement (IDS)
     - iv. [X] 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. [X] RCE fee required under 37 CFR 1.17(e)
     - ii. [X] Extension of time fee (37 CFR 1.136 and 1.17)
     - iii. [ ] Other _____
   - b. [ ] Check in the amount of $ _____ enclosed
   - c. [X] 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	May 18, 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: May 18, 2015 Electronic Signature for Nancy J. Arsenault: /Nancy J. Arsenault/

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Docket No.: U0157.70023US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Michael J. Zaworotko
Application No.:	14/179,862
Confirmation No.:	7725
Filed:	February 13, 2014
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: May 18, 2015 Signature: /Nancy J. Arsenault/ (Nancy J. Arsenault)

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 December 19, 2014, finally rejecting claims 37-50 and 52-58, please amend the above-identified U.S. patent application as follows. A Request for Continued Examination and a petition for a two-month extension of time is being filed concurrently herewith.

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

Remarks/Arguments begin on page 8 of this paper.

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AMENDMENTS TO THE CLAIMS

Please replace all prior versions, and listings, of claims in the application with the following list of claims:

1-36. (Canceled)

37. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former and each supramolecular synthon comprising an API homosynthon formed via non-covalent hydrogen bonding,

wherein the API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form,

wherein the co-former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding,

wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form, and

wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former.

38. (Previously Presented) The pharmaceutical composition of claim 52, wherein the supramolecular synthon comprises a heterosynthon dimer formed by non-covalent hydrogen bonding of the API to the co-former.

39. (Previously Presented) The pharmaceutical composition of claim 52, wherein the supramolecular synthon comprises a plurality of the API and a plurality of the co-former, wherein the supramolecular synthon is a chain of supramolecular heterosynthons, each supramolecular heterosynthon formed by non-covalent hydrogen bonding of one API to one co-former, and wherein the supramolecular heterosynthons are bonded to one another by non-covalent hydrogen bonding.

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40. (Previously Presented) The pharmaceutical composition of claim 52, wherein the co-crystal is a hydrated co-crystal, wherein the supramolecular synthon comprises a plurality of the API and a plurality of the co-former, wherein the supramolecular synthon affords a sheet of the API, each of the APIs in the sheet bonded to one another and to a co-former by non-covalent hydrogen bonding to a water molecule.

41. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former,

wherein the API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form,

wherein the co-former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding,

wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form,

wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former, and wherein the at least one API participating in each supramolecular synthon is two APIs and the at least one co-former is one co-former, and wherein each of the two APIs is bonded by non-covalent bonding to the one co-former.

42. (Previously Presented) The pharmaceutical composition of claim 52, wherein the at least one co-former participating in each supramolecular synthon is two co-formers forming a homosynthon, the at least one API in each supramolecular synthon is two APIs, and wherein each of the two APIs is bonded by non-covalent bonding to one of the two co-formers.

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43. (Previously Presented) The pharmaceutical composition of claim 52, wherein the at least one API participating in each supramolecular synthon is two APIs and the at least one co-former participating in each supramolecular synthon is two co-formers forming a homosynthon, and wherein one of the two APIs is non-covalently bonded to one of the co-formers and the other of the two APIs is non-covalently bonded to the other of the two co-formers.

44. (Previously Presented) The pharmaceutical composition of claim 52, wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule.

45. (Previously Presented) The pharmaceutical composition of claim 37, wherein the at least one API participating in each supramolecular synthon is two APIs of the at least one API that are bonded to one another through hydrogen bonding to form at least one homosynthon dimer.

46. (Previously Presented) The pharmaceutical composition of claim 45, wherein the at least one co-former is two of the co-former and the at least one API is two of the API, wherein the at least one homosynthon dimer is one homosynthon dimer, and wherein the supramolecular synthon forms a tetramer, the tetramer being comprised of the two co-formers and two APIs, and each co-former being attached to the homodimer by hydrogen bonds.

47. (Previously Presented) The pharmaceutical composition of claim 45, wherein the at least one co-former is two co-formers, wherein the at least one homosynthon dimer is two homosynthon dimers, and wherein the supramolecular synthon results in a hexamer.

48. (Previously Presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthon comprises a plurality of the API and a plurality of the co-former, wherein the supramolecular synthon comprises a chain of homosynthon dimers, each homosynthon dimer

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formed by hydrogen bonding of one of the plurality of the API to another of the plurality of the API, and wherein the homosynthon dimers are bonded to the co-former by hydrogen bonding.

49. (Previously Presented) The pharmaceutical composition of claim 45, wherein the at least one co-former participating in each supramolecular synthon is two co-formers forming a homosynthon.

50. (Previously Presented) The pharmaceutical composition of claim 52, wherein the second chemical functionality complimentary to the first chemical functionality is (i) two identical second chemical functionalities on the co-former, (ii) three identical second chemical functionalities on the co-former, or (iii) four identical second chemical functionalities on the co-former.

51. (Canceled)

52. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former,

wherein the API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form,

wherein the co-former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding,

wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form,

wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former, and

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wherein the first chemical functionality is (i) a carboxamide, (ii) a carbonyl, or (iii) an amine.

53. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former,

wherein the API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form,

wherein the co-former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding,

wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form,

wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former, and

wherein the first chemical functionality and the second chemical functionality form (i) a carbonyl:amide hydrogen bond, (ii) a carbonyl:amine hydrogen bond, (iii) a carboxylic acid:pyridine hydrogen bond, (iv) a carboxylic acid:aromatic amine hydrogen bond, (v) a carboxylic acid:carboxylic acid hydrogen bond, (vi) a carboxylic acid:carboxamide hydrogen bond, (vii) a carboxylic acid:amine hydrogen bond, (viii) a carboxylic acid:carbonyl hydrogen bond, (ix) an amine:sulfonamide hydrogen bond, or (x) a carbonyl:sulfonamide hydrogen bond.

54. (Previously Presented) The pharmaceutical composition of claim 37, wherein the non-covalent bonding of said API homosynthons is carboxylic acid:carboxylic acid hydrogen bonding.

55. (Previously Presented) The pharmaceutical composition of claim 37, wherein the non-covalent bonding of said API homosynthons is carboxamide:carboxamide hydrogen bonding.

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56. (Previously Presented) The pharmaceutical composition of claim 52, wherein the first chemical functionality is a carboxamide.

57. (Previously Presented) The pharmaceutical composition of claim 52, wherein the first chemical functionality is a carbonyl.

58. (Currently amended) The pharmaceutical composition of claim 52, ~~wherien~~wherein the first chemical functionality is an amine.

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REMARKS

Applicant respectfully requests reconsideration. Claims 37-50 and 52-58 were previously pending in this application. Claim 58 has been amended to fix a typographical error. As a result, claims 37-50 and 52-58 are pending for examination with claims 37, 41, 52, and 53 being independent claims. No new matter has been added.

Double Patenting Rejection

The Examiner provisionally rejected claims 37-50 and 52-58 as being allegedly unpatentable over claims 25, 28, 37, and 39-66 of copending Application No. 10/378,956.

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. §103

The Examiner rejected claims 37-50 and 52-58 under 35 U.S.C. §103(a) as being allegedly unpatentable over Huffman (US Patent No. 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 (a) because Huffman is not a proper reference for use in an obviousness rejection and (b) because the Examiner has not met their burden of articulating the reasons for rejecting each and every limitation of the claims as pending.

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

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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 pharmaceutical compositions 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 cocrystal 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 Hoffman 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,

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e.g., column 1, lines 28-33). The solution provided by Hoffman 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.

Further, the Examiner is using impermissible hindsight based on the teachings of the present application in order to choose the Huffman reference and to conclude that Huffman would lead the subject matter of the present claims. The Examiner's reason for arriving at the claimed subject matter, which relates to pharmaceutical compositions, is that "it would have been obvious to one skilled in the art to envision the adducts disclosed by Huffman for pharmaceutical compositions." 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." As a result, 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 their burden in articulating the reason for rejecting the claims based on Huffman alone, as Huffman provides no teaching or suggestion to use the adducts described therein in a pharmaceutical composition.

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For at least the above reasons, claims 37-50 and 52-58 are patentable over Huffman. Accordingly, withdrawal of this rejection is respectfully requested.

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CONCLUSION

In view of the above amendment, applicant believes the pending application is 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, including a fee for an extension of time, please charge our Deposit Account No. 23/2825 under Docket No. U0157.70023US02 from which the undersigned is authorized to draw.

Dated: May 18, 2015

Respectfully submitted,

By /Amy J. McMahon, Ph.D./
Amy J. McMahon, Ph.D.
Registration No.: 73,073
Edward R. Gates
Registration No.: 31,616
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000

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PTO/AIA/22 (03-13)
Approved for use through 7/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) U0157.70023US02
Application Number 14/179,862-Conf. #7725	Filed February 13, 2014
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	$
[X] 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	$

[X] 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.

[X] 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.

[X] The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 23/2825 .

[X] Payment made via EFS-Web.

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

I am the

[ ] applicant.

[ ] attorney or agent of record. Registration number _____ .

[X] attorney or agent acting under 37 CFR 1.34. Registration number 73,073 .

/Amy J. McMahon, Ph.D./ — Signature
May 18, 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: May 18, 2015 — Electronic Signature for Nancy J. Arsenault: /Nancy J. Arsenault/

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PTO/SB/17 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995 no persons are required to respond to a collection of information unless it displays a valid OMB control number

FEE TRANSMITTAL

	Complete if known
Application Number	14/179,862-Conf. #7725
Filing Date	February 13, 2014
First Named Inventor	Michael J. Zaworotko
Examiner Name	S. Javanmard
Art Unit	1627
Practitioner Docket No.	U0157.70023US02

[X] Applicant asserts small entity status. See 37 CFR 1.27.

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

TOTAL AMOUNT OF PAYMENT ($) 900.00

METHOD OF PAYMENT (check all that apply)

[ ] Check [X] 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**

[X] Charge any additional fee(s) or underpayment of fee(s) under 37 CFR 1.16 and 1.17 [X] 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 ($)	Fee Paid ($)
_____ - 41 or HP =	_____ x	_____ =	_____

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

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

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

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

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): 2252 Extension for response within second month	300.00
2801 Request for RCE - 1st request (see 37 CFR 1.114)	600.00

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	May 18, 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: May 18, 2015 Electronic Signature for Nancy J. Arsenault: /Nancy J. Arsenault/

4052139.1

Electronic Patent Application Fee Transmittal

Application Number:	14179862
Filing Date:	13-Feb-2014
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/Nancy Arsenault
Attorney Docket Number:	U0157.70023US02

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 $0 paid	2252	1	300	300
Miscellaneous:				
Request for Continued Examination	2801	1	600	600
		Total in USD ($)		**900**

Electronic Acknowledgement Receipt	
EFS ID:	22374817
Application Number:	14179862
International Application Number:	
Confirmation Number:	7725
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/Nancy Arsenault
Filer Authorized By:	Amy Jeanette McMahon
Attorney Docket Number:	U0157.70023US02
Receipt Date:	18-MAY-2015
Filing Date:	13-FEB-2014
Time Stamp:	15:15:58
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$900
RAM confirmation Number	1888
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)	U015770023US02-RCE-AM.pdf	25934 6e333c3858193a82ba4366e7d3a04cc27aa5185a	no	1
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					
2		U015770023US02-116AMN-AM.pdf	62410 1fda27b79aa176152ff5706de96429635b5e4eea	yes	12

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment Submitted/Entered with Filing of CPA/RCE	1	1
Claims	2	7
Applicant Arguments/Remarks Made in an Amendment	8	12

Warnings:					
Information:					
3	Extension of Time	U015770023US02-EXT-AM.pdf	23142 15e3ba88fbbb9c8be1f3193b4948fb3912eff650	no	1
Warnings:					
Information:					
4	Fee Worksheet (SB06)	U015770023US02-FEE-AM.pdf	31762 35a744d40b38400b61756b89053bade220e006eb	no	1
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	32759 725c5dfd7bc1cff57f75261b62b3a6b5ef3cc559	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	176007		

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.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/179,862	Filing Date 02/13/2014	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 = *		X $ =	
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

AMENDMENT	05/18/2015	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 21	Minus	** 21	= 0	X $40 =	0
	Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 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

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	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.

LIE
/VANESSA HODGES/

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.

FORM PTO-1449/A and B (modified PTO/SB/08)	APPLICATION NO.: 14/179,862	ATTY. DOCKET NO.: U0157.70023US02
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	FILING DATE: February 13, 2014	CONFIRMATION NO.: 7725
	FIRST NAMED INVENTOR: Michael J. Zaworotko	
Sheet 1 of 1	GROUP ART UNIT: 1627	EXAMINER: Sahar Javanmard

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			
		CA	1 148 020	A1	McCoy	06-14-1983	

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 notcitation 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 Acknowledgement Receipt

EFS ID:	23070432
Application Number:	14179862
International Application Number:	
Confirmation Number:	7725
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/Yehoshua Zehavi
Filer Authorized By:	Edward R. Gates
Attorney Docket Number:	U0157.70023US02
Receipt Date:	30-JUL-2015
Filing Date:	13-FEB-2014
Time Stamp:	14:16:09
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	Miscellaneous Incoming Letter	U015770023US02-TRN-ERG.PDF	58603 66172db61f9d87c77a16626fbacd842414d61228	no	1
Warnings:					
Information:					

2		U015770023US02-IDS-ERG.PDF	171317 ec8cd16f7579a7396ad353b0b8cae1da494fef41	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:					
3	Foreign Reference	CA1148020A1.pdf	1069724 63d21f07e46a9e6b5155f030b13a1e9212b5a14f	no	29
Warnings:					
Information:					
		Total Files Size (in bytes):	1299644		

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
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New International Application Filed with the USPTO as a Receiving Office
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Doc Code: TRAN.LET
Document Description: Transmittal Letter

USED IN LIEU OF PTO/SB/21 (07-09)

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	

Application Number	14/179,862-Conf. #7725
Filing Date	February 13, 2014
First Named Inventor	Michael J. Zaworotko
Art Unit	1627
Examiner Name	Sahar Javanmard
Attorney Docket Number	U0157.70023US02

ENCLOSURES (*Check all that apply*)

- [ ] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [x] 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
- [x] Other Enclosure(s) (please Identify below):

  Form PTO-1449
  Copy of cited reference

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	WOLF, GREENFIELD & SACKS, P.C.		
Signature	Edward R Gates		
Printed name	Edward R. Gates		
Date	July 30, 2015	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: July 30, 2015 Electronic Signature for Yehoshua E. Zehavi: //

4179855.1

DOCKET NO.: U0157.70023US02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Michael J. Zaworotko
Application No.:	14/179,862
Confirmation No.:	7725
Filed:	February 13, 2014
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 30th day of July, 2015.

Yehoshua E. Zehavi

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 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

UM00000369
NOVARTIS EXHIBIT 1516
Novartis v. Regents, IPR2023-01347
Page 322 of 725

presentation of the references should not be construed as an indication of the importance of the references.

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.

UM00000370
NOVARTIS EXHIBIT 1516
Novartis v. Regents, IPR2023-01347
Page 323 of 725

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. U0157.70023US02 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.: U0157.70023US02
Date: 7/30/2015
xNDDx

UM00000371
NOVARTIS EXHIBIT 1516
Novartis v. Regents, IPR2023-01347
Page 324 of 725

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.
14/179,862	02/13/2014	Michael J. Zaworotko	U0157.70023US02	7725

23628 7590 10/05/2015

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

EXAMINER	
JAVANMARD, SAHAR	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
10/05/2015	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

UM00000372
NOVARTIS EXHIBIT 1516
Novartis v. Regents, IPR2023-01347
Page 325 of 725

Office Action Summary	Application No. 14/179,862	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 5/18/15.

☐ 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) 37-50 and 52-58 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) 37-50 and 52-58 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 May 18, 2015 has been entered.

Claim(s) 37-50 and 52-58 are pending and examined herein.

Response to Arguments

The double patenting rejection of claims 37-50 and 52-58 is hereby maintained due to Applicant's decision to hold said rejection in abeyance.

Applicant's arguments with respect to the 103(a) rejection of claims 37-50 and 52-58 as being unpatentable over Huffman (US Patent No. 3,664,858) of record have been fully considered but are not persuasive.

Applicant argues:

> "With respect to the field of endeavor, the present claims are directed to pharmaceutical compositions 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 this argument, Examiner respectfully notes that, while the Huffman reference does not teach the pharmaceutical arts, the adducts can be formed regardless of the utility. 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. ").

Moreover, Applicant argues:

> "Further, the Examiner is using impermissible hindsight based on the teachings of the present application in order to choose the Huffman reference and to conclude that Huffman would lead the subject matter of the present claims."

In response to Applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a

reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Based on the foregoing reasons, the rejections of record are hereby maintained.

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 37-50 and 52-58 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25, 28, 37, 39-66 of copending Application No. 10/378,956. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to a pharmaceutical composition comprising a co-crystal comprising an API and a co-former (see claims for details), whereas the copending 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 § 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 negatived 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 37-50 and 52-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCoy (CA 1148020A1) of record.

Examiner respectfully notes at the outset that the instant invention is drawn to pharmaceutical composition, wherein said composition 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.

Therefore, the intended use recited in the instant claims, namely that the first chemical functionality is an API, is not afforded patentable weight.

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).

McCoy teaches the method comprises dissolving at least one amino acid material in water along with an effective amount of at last 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).

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 the instant claims are not explicitly exemplified.

Moreover, McCoy does not specifically teach the identification of the synthon from the crystal structure.

As discussed 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 37-50 and 52-58 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 pharmaceutical composition, wherein said composition 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.

Therefore, the intended use recited in the instant claims, 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-bromophenox yacetic 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(trifluoromethyisulfanyl)methane, xanthanoic, thiophendicarboxylic, cyclohexanecarboxylic, norcamphoric, naphthalenedicarboxylic, naphthalenetricarboxylic, mellitic, trimesic, biphenyldicarboxylic, resorcinol-o-acetic, anthracenecarboxylic, o-bromotoluic, p-bromomandelic, salicylacetic, dinitrophenylacetic, 2-furanace-tic, 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 co-crystal complexes in pharmaceutical compositions.

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 37-50 and 52-58 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

FORM PTO-1449/A and B (modified PTO/SB/08)	APPLICATION NO.: 14/179,862	ATTY. DOCKET NO.: U0157.70023US02
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	FILING DATE: February 13, 2014	CONFIRMATION NO.: 7725
	FIRST NAMED INVENTOR: Michael J. Zaworotko	
Sheet 1 of 1	GROUP ART UNIT: 1627	EXAMINER: Sahar Javanmard

U.S. PATENT DOCUMENTS

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

FOREIGN PATENT DOCUMENTS

Examiner's Initials #	Cite No.	Foreign Patent Document Office/ Country	Foreign Patent Document Number	Foreign Patent Document Kind Code	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Translation (Y/N)
		CA	1 148 020	A1	McCoy	06-14-1983	

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:
/SAHAR JAVANMARD/	09/29/2015

EXAMINER: Initial if reference considered, whether or notcitation 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. /SJ/

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14179862	ZAWOROTKO ET AL.
	Examiner	Art Unit
	SAHAR JAVANMARD	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	03/21/2014	10/20/2014	09/29/2015						
	1	-	-	-						
	2	-	-	-						
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	32	-	-	-						
	33	-	-	-						
	34	-	-	-						
	35	-	-	-						
	36	-	-	-						

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14179862	ZAWOROTKO ET AL.
	Examiner	Art Unit
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☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	03/21/2014	10/20/2014	09/29/2015						
	37	✓	✓	✓						
	38	✓	✓	✓						
	39	✓	✓	✓						
	40	✓	✓	✓						
	41	✓	✓	✓						
	42	✓	✓	✓						
	43	✓	✓	✓						
	44	✓	✓	✓						
	45	✓	✓	✓						
	46	✓	✓	✓						
	47	✓	✓	✓						
	48	✓	✓	✓						
	49	✓	✓	✓						
	50	✓	✓	✓						
	51	✓	-	-						
	52	✓	✓	✓						
	53	✓	✓	✓						
	54	✓	✓	✓						
	55	✓	✓	✓						
	56		✓	✓						
	57		✓	✓						
	58		✓	✓						

UM00000388
NOVARTIS EXHIBIT 1516
Novartis v. Regents, IPR2023-01347
Page 341 of 725

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14179862	ZAWOROTKO ET AL.
	Examiner	Art Unit
	SAHAR JAVANMARD	1627

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
424	400	4/4/2014	SJ
	updated 10/2014		SJ

SEARCH NOTES		
Search Notes	Date	Examiner
EAST (searched inventor names)	4/4/2014	SJ
EAST (keyword search)	4/4/2014	SJ
updated 10/2014		SJ
Google Patents (searched:organic acids amines adducts crystals)	12/12/2014	SJ
updated 9/29/15		SJ

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

/SAHAR JAVANMARD/ Examiner.Art Unit 1627	

To: Patents_eOfficeAction@WolfGreenfield.com,WGS_eOfficeAction@WolfGreenfield.com,
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14179862	CTNF	10/05/2015	U0157.70023US02
	1449	10/05/2015	U0157.70023US02

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/179,862	02/13/2014	Michael J. Zaworotko	U0157.70023US02

CONFIRMATION NO. 7725

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

POA ACCEPTANCE LETTER

OC000000079956162

Date Mailed: 01/19/2016

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 10/16/2014.

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.

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

/ytdemisse/

UM00000391
NOVARTIS EXHIBIT 1516
Novartis v. Regents, IPR2023-01347
Page 344 of 725

To: Patents_eOfficeAction@WolfGreenfield.com,WGS_eOfficeAction@WolfGreenfield.com,
From: PAIR_eOfficeAction@uspto.gov
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Application	Document	Mailroom Date	Attorney Docket No.
14179862	N570	01/19/2016	U0157.70023US02

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

Docket No.: U0157.70023US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Michael J. Zaworotko
Application No.:	14/179,862
Confirmation No.:	7725
Filed:	February 13, 2014
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: April 1, 2016 Electronic Signature for Allison E. Parker: /Allison E. Parker/

AMENDMENT IN 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

In response to the Office Action dated October 5, 2015, please amend the above-identified U.S. patent application as follows:

Listing of the Claims begins on page 2 of this paper.

Remarks/Arguments begin on page 8 of this paper.

LISTING OF THE CLAIMS

The pending claims are reproduced below:

1-36. (Canceled)

37. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former and each supramolecular synthon comprising an API homosynthon formed via non-covalent hydrogen bonding,

wherein the API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form,

wherein the co-former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding,

wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form, and

wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former.

38. (Previously Presented) The pharmaceutical composition of claim 52, wherein the supramolecular synthon comprises a heterosynthon dimer formed by non-covalent hydrogen bonding of the API to the co-former.

39. (Previously Presented) The pharmaceutical composition of claim 52, wherein the supramolecular synthon comprises a plurality of the API and a plurality of the co-former, wherein the supramolecular synthon is a chain of supramolecular heterosynthons, each supramolecular heterosynthon formed by non-covalent hydrogen bonding of one API to one co-former, and wherein the supramolecular heterosynthons are bonded to one another by non-covalent hydrogen bonding.

40. (Previously Presented) The pharmaceutical composition of claim 52, wherein the co-crystal is a hydrated co-crystal, wherein the supramolecular synthon comprises a plurality of the API and a plurality of the co-former, wherein the supramolecular synthon affords a sheet of the API, each of the APIs in the sheet bonded to one another and to a co-former by non-covalent hydrogen bonding to a water molecule.

41. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former,
wherein the API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form,

wherein the co-former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding,

wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form,

wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former, and wherein the at least one API participating in each supramolecular synthon is two APIs and the at least one co-former is one co-former, and wherein each of the two APIs is bonded by non-covalent bonding to the one co-former.

42. (Previously Presented) The pharmaceutical composition of claim 52, wherein the at least one co-former participating in each supramolecular synthon is two co-formers forming a homosynthon, the at least one API in each supramolecular synthon is two APIs, and wherein each of the two APIs is bonded by non-covalent bonding to one of the two co-formers.

43. (Previously Presented) The pharmaceutical composition of claim 52, wherein the at least one API participating in each supramolecular synthon is two APIs and the at least one co-former participating in each supramolecular synthon is two co-formers forming a homosynthon, and wherein one of the two APIs is non-covalently bonded to one of the co-formers and the other of the two APIs is non-covalently bonded to the other of the two co-formers.

44. (Previously Presented) The pharmaceutical composition of claim 52, wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule.

45. (Previously Presented) The pharmaceutical composition of claim 37, wherein the at least one API participating in each supramolecular synthon is two APIs of the at least one API that are bonded to one another through hydrogen bonding to form at least one homosynthon dimer.

46. (Previously Presented) The pharmaceutical composition of claim 45, wherein the at least one co-former is two of the co-former and the at least one API is two of the API, wherein the at least one homosynthon dimer is one homosynthon dimer, and wherein the supramolecular synthon forms a tetramer, the tetramer being comprised of the two co-formers and two APIs, and each co-former being attached to the homodimer by hydrogen bonds.

47. (Previously Presented) The pharmaceutical composition of claim 45, wherein the at least one co-former is two co-formers, wherein the at least one homosynthon dimer is two homosynthon dimers, and wherein the supramolecular synthon results in a hexamer.

48. (Previously Presented) The pharmaceutical composition of claim 37, wherein the supramolecular synthon comprises a plurality of the API and a plurality of the co-former, wherein the supramolecular synthon comprises a chain of homosynthon dimers, each homosynthon dimer formed by hydrogen bonding of one of the plurality of the API to another of the plurality of the API, and wherein the homosynthon dimers are bonded to the co-former by hydrogen bonding.

49. (Previously Presented) The pharmaceutical composition of claim 45, wherein the at least one co-former participating in each supramolecular synthon is two co-formers forming a homosynthon.

50. (Previously Presented) The pharmaceutical composition of claim 52, wherein the second chemical functionality complimentary to the first chemical functionality is (i) two identical second chemical functionalities on the co-former, (ii) three identical second chemical functionalities on the co-former, or (iii) four identical second chemical functionalities on the co-former.

51. (Canceled)

52. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former,

wherein the API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form,

wherein the co-former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding,

wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form,

wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former, and

wherein the first chemical functionality is (i) a carboxamide, (ii) a carbonyl, or (iii) an amine.

53. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a co-crystal comprising supramolecular synthons, each supramolecular synthon formed from stoichiometric amounts of at least one active pharmaceutical ingredient (API) and at least one co-former,

wherein the API has a first chemical functionality that permits formation of API homosynthons through non-covalent hydrogen bonding when the API is in its pure form,

wherein the co-former has a second chemical functionality complimentary to the first chemical functionality via non-covalent hydrogen bonding,

wherein said co-former is a solid at room temperature and atmospheric pressure when the co-former is in its pure form,

wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-former, and

wherein the first chemical functionality and the second chemical functionality form (i) a carbonyl:amide hydrogen bond, (ii) a carbonyl:amine hydrogen bond, (iii) a carboxylic acid:pyridine hydrogen bond, (iv) a carboxylic acid:aromatic amine hydrogen bond, (v) a carboxylic acid:carboxylic acid hydrogen bond, (vi) a carboxylic acid:carboxamide hydrogen bond, (vii) a carboxylic acid:amine hydrogen bond, (viii) a carboxylic acid:carbonyl hydrogen bond, (ix) an amine:sulfonamide hydrogen bond, or (x) a carbonyl:sulfonamide hydrogen bond.

54. (Previously Presented) The pharmaceutical composition of claim 37, wherein the non-covalent bonding of said API homosynthons is carboxylic acid:carboxylic acid hydrogen bonding.

55. (Previously Presented) The pharmaceutical composition of claim 37, wherein the non-covalent bonding of said API homosynthons is carboxamide:carboxamide hydrogen bonding.

56. (Previously Presented) The pharmaceutical composition of claim 52, wherein the first chemical functionality is a carboxamide.

57. (Previously Presented) The pharmaceutical composition of claim 52, wherein the first chemical functionality is a carbonyl.

58. (Previously Presented) The pharmaceutical composition of claim 52, wherein the first chemical functionality is an amine.

REMARKS

Applicant respectfully requests reconsideration. Claims 37-50 and 52-58 were previously pending in this application. No amendments to the claims are made herein. Therefore, claims 37-50 and 52-58 remain pending for examination with claims 37, 41, 52, and 53 being independent claims.

Double Patenting Rejection

The Examiner provisionally rejected claims 37-50 and 52-58 as being unpatentable over claims 25, 28, 37 and 39-66 of copending Application No. 10/378,956.

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. §103

McCoy

The Examiner rejected claims 37-50 and 52-58 under 35 U.S.C. §103(a) as being unpatentable over McCoy (CA 1148020A1).

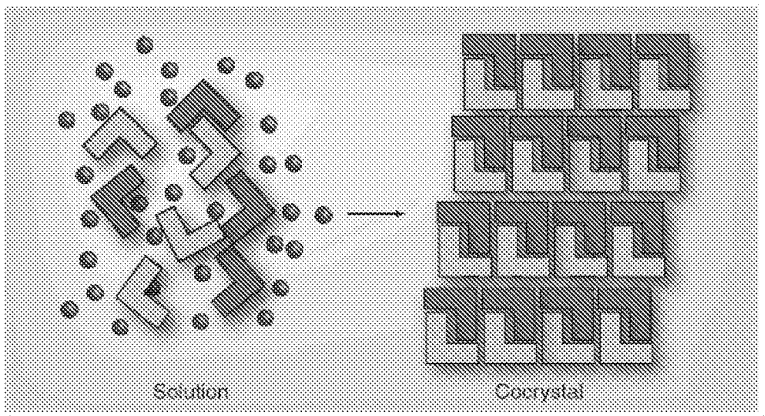
In particular, the Examiner appreciates that McCoy does not disclose the specific examples of homo- and heterosynthons required by the claims. The Examiner also appreciates that McCoy does not disclose the identification of the synthon from the crystal structure. However, the Examiner alleged that it 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.

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 McCoy, the present claims require pharmaceutical compositions comprising a co-crystal having supramolecular synthons, each formed from *stoichiometric amounts* of the active pharmaceutical ingredient (API) and the selected co-crystal former. Such stoichiometric amounts 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 compositions 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). 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 37-50 and 52-58 under 35 U.S.C. §103(a) as 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 pharmaceutical compositions comprising co-crystals including 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 pharmaceutical compositions including an active pharmaceutical ingredient (API), 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 12). 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 the claimed co-crystal comprising an active pharmaceutical ingredient. As a result, Huffman does not teach or suggest each and every limitation of the claims and therefore does not render the claims obvious.

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 7). The Examiner states that "the intended use recited in the instant claims, namely that the first chemical functionality is an API, is not afforded patentable weight." (Office Action, page 7). 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

"wherein supramolecular synthons are formed via non-covalent hydrogen bonding between the first chemical functionality of the API and the second chemical functionality of the co-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-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*, 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]).

For at least these reasons, Huffman does not teach or suggest the co-crystals of the present claims.

In view of the foregoing, the claims are non-obvious and withdrawal of the rejections of the claims under 35 U.S.C. §103 is respectfully requested.

CONCLUSION

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 case 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. U0157.70023US02.

Dated: April 1, 2016

Respectfully submitted,

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