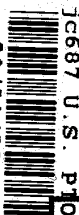


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03/01/02

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☒ Additional inventors are being named on the <u>1</u> separately numbered sheets attached hereto.					
TITLE OF THE INVENTION (280 characters max)					
Multiple Component Crystalline Phases Containing a Pharmaceutical Component					
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ENCLOSED APPLICATION PARTS (check all that apply)					
☒ Specification		Number of Pages	21	☐ CD(s), Number	
☒ Drawing(s)		Number of Sheets	11	☐ Other (specify)	
☐ Application Data Sheet. See 37 CFR 1.76					
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT					
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Respectfully submitted,

SIGNATURE

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Date March 1, 2002

REGISTRATION NO.

46,853

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USF-106P

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Provisional Patent Application
Docket No. USF-106P

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Docket No. : USF-106P
Applicants : Michael J. Zaworotko, Naír Rodríguez-Hornedo, Brian Moulton,
Rosa D. Bailey Walsh, Leslie Ann Morales, Scott Gerald Fleischman
For : Multiple Component Crystalline Phases Containing A Pharmaceutical
Component

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Assistant Commissioner for Patents
Washington, D.C. 20231

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DESCRIPTION

MULTIPLE COMPONENT CRYSTALLINE PHASES CONTAINING A PHARMACEUTICAL COMPONENT

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 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 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, stability, and/or bioavailability, which are different from 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.

[0008] The subject invention concerns co-crystals of pharmaceutical molecules, such as ibuprofen and flurbiprofen. The co-crystals of ibuprofen/4,4'-dipyridyl, flurbiprofen/4,4'-dipyridyl and flurbiprofen/trans-1,2-bis(4-pyridyl)ethylene have been characterized by various techniques and exhibit physical properties different from the parent compound as a direct result of alternative hydrogen bonding interaction. These 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 phases, such as binary phases, using

complementary molecules. Pharmaceutical molecules 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.

[0010] The subject invention concerns a method for identifying complementary chemical functionalities to form a desired supramolecular synthon, wherein the method comprises the steps of determining the structure of a pharmaceutical moiety; identifying external chemical functionalities that are amenable to formation of supramolecular synthons; comparing those external chemical functionalities amenable to formation of supramolecular synthons to a plurality of known supramolecular synthons; and identifying complementary chemical functionalities.

[0011] Optionally, the method of the subject invention can further comprise one or more of the following steps: 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); identifying additional external 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; preparing a new solid phase that consists of the pharmaceutical moiety and the complementary molecular entity (such as a binary phase or two component phase) by crystallization techniques comprising reactions in solvent, and/or solventless reactions, that afford crystalline materials; determining the structure of the new solid phase; and analyzing the physical properties of the new solid phase.

[0012] Alternatively, the formation of homosynthons for the purpose of disrupting the intermolecular interactions between pharmaceutical moieties can be carried out.

[0013] The subject invention further concerns new solid phases identified or produced using the methods identified herein. The subject invention further pertains to a binary 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 binary phase composition can be, for example, a discrete supramolecular entity or a polymeric structure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] **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).

[0015] **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.

[0016] **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 binary phases are produced.

[0017] **Figures 4A–4B** show an acetaminophen 1-D sheet 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 sheets with all donors and acceptors interacting.

[0018] **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.

[0019] **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 sheets with hydrophobic planes.

[0020] **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 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. Struct. 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 sheets sustained by π - π stacking and hydrophobic in-layer interactions.

[0021] Figures 8A-8D show supramolecular entities containing synthons and corresponding crystal structures of pure flurbiprofen [2-(2-fluor-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 sheets are formed through π - π and hydrophobic interactions from the phenyl rings.

[0022] 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.

[0023] 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 acetate) (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.

[0024] Figure 11 shows the crystal structure of carbamazepine/nicotinamide (vitamin B3).

[0025] Figure 12 shows the crystal structure of carbamazepine/saccharin, engineered using the carbamazepine/nicotinamide co-crystal as a model.

[0026] Figures 13A-13C show the chemical structure of ibuprofen, flurbiprofen, and aspirin, respectively.

DETAILED DISCLOSURE OF THE INVENTION

[0027] The subject invention relates to the application of the concepts of crystal engineering towards the design of new pharmaceutical phases, such as ibuprofen/4,4'-dipyridyl, flurbiprofen/4,4'-dipyridyl and flurbiprofen/trans-1,2-bis(4-pyridyl)ethylene have been characterized by various techniques and exhibit physical properties different from the parent compound as a direct result of hydrogen bonding interaction. These crystalline assemblies can afford improved drug solubility, dissolution rate, stability and bioavailability.

[0028] The subject invention concerns a method for identifying complementary chemical functionalities comprising the steps of determining the structure of a pharmaceutical moiety; identifying external chemical functionalities that are amenable to formation of supramolecular synthons; comparing those external chemical functionalities amenable to formation of supramolecular synthons to a plurality of known supramolecular synthons; and identifying complementary chemical functionalities.

[0029] Optionally, the method of the subject invention can further comprise one or more of the following steps: 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); identifying additional external 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; preparing a new solid phase that consists of the pharmaceutical moiety and the complementary molecular entity (such as a binary phase or two component phase) by crystallization techniques comprising reactions in solvent, and/or

solventless reactions, that afford crystalline materials; determining the structure of the new solid phase; and analyzing the physical properties of the new solid phase.

[0030] Alternatively, the formation of homosynthons for the purpose of disrupting the intermolecular interactions between pharmaceutical moieties can be carried out.

[0031] The subject invention further concerns new solid phases identified or produced using the methods identified herein. The subject invention further pertains to a binary 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 binary phase composition of the subject invention can be, for example, a discrete supramolecular entity or a polymeric structure. The binary 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.

[0032] By way of example, the external functionalities of ibuprofen are an isopropyl group and a carboxylic acid, as shown in Figure 1.

[0033] 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 binary 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.

[0034] As used herein, the term “binary 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. 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 FDA”. More preferably, the GRAS compound is a non-pharmaceutical entity.

[0035] As used herein, the term “pharmaceutical entity” refers to any biologically active moiety having a therapeutic effect on a human or animal suffering from a pathological condition, when administered in a given concentration.

[0036] 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.

[0037] In terms of superstructure, three general types of compounds generated by interaction of a drug molecule with another molecule include: (1) binary 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.

[0038] The subject invention concerns binary compounds, 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 issue that is particularly relevant to pharmaceutical composition 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 “model binary phases” that illustrate the concept of crystal engineering and binary phases that incorporate pharmaceuticals with “GRAS” compounds, that is, compounds “Generally Regarded as Safe by the FDA”.

[0039] 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 composition 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 binary 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).

[0040] 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.

[0041] 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.

[0042] 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/bioavailability. 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—Co-Crystal of Acetaminophen: Acetaminophen/4,4'-bipyridine/water (1:1:1 stoichiometry)

[0043] 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.

[0044] 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, $\alpha=86.326(2)^\circ$, $\beta=80.291(2)^\circ$, $\gamma=88.880(2)^\circ$, $U=1308.1(3)$ Å³, $T=200(2)$ K, $Z=2$, $\mu(\text{Mo-K}\alpha)=0.090$ mm⁻¹, $D_c=1.294$ Mg/m³, $\lambda=0.71073$ Å, $F(000)=537$, $2\theta_{\text{max}}=25.02^\circ$; 6289 reflections measured, 4481 unique ($R_{\text{int}}=0.0261$). Final residuals for 344 parameters were $R_1=0.0751$, $wR_2=0.2082$ for $I>2\sigma(I)$, and $R_1=0.1119$, $wR_2=0.2377$ for all 4481 data.

[0045] 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.

[0046] Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 57.77° C (endotherm); m.p. = $58-60^\circ$ C (MEL-TEMP); (acetaminophen m.p. = 169° C, 4,4'-bipyridine m.p. = $111-114^\circ$ C).

Example 2—Co-crystal of Phenytoin: Phenytoin/Pyridine (1:1 stoichiometry)

[0047] Method 1: In a typical reaction, 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.

[0048] 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, $\beta=96.618(2)^\circ$, $U=1750.2(3)$ Å³, $T=200(2)$ K, $Z=4$, $\mu(\text{Mo-K}\alpha)=0.091$ mm⁻¹, $D_c=1.318$

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Mg/m^3 , $\lambda = 0.71073 \text{ \AA}$, $F(000) = 728$, $2\theta_{\text{max}} = 56.60^\circ$; 10605 reflections measured, 4154 unique ($R_{\text{int}} = 0.0313$). 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.

[0049] Crystal packing: The co-crystal is sustained by hydrogen bonding of adjacent phenytoin 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.

[0050] 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} , olefin peak found at 1390cm^{-1} .

[0051] Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 233.39°C (endotherm) and 271.33°C (endotherm); m.p. = $231\text{--}233^\circ \text{C}$ (MEL-TEMP); (phenytoin m.p. = 295°C , pyridone m.p. = 148°C).

[0052] 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.

[0053] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using $\text{Cu K}\alpha$ ($\lambda = 1.540562$), 30kV, 15mA). The powder data were collected over an angular range of 3° to $40^\circ 2\theta$ in continuous scan mode using a step size of $0.02^\circ 2\theta$ and a scan speed of $2.0^\circ/\text{minute}$. 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—Co-crystal of Aspirin (acetylsalicylic acid): Aspirin/4,4'-bipyridine (2:1 stoichiometry)

[0054] 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.

[0055] 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, $U = 2762.2(5)$ Å³, $T = 173(2)$ K, $Z = 4$, $\mu(\text{Mo-K}\alpha) = 0.092$ mm⁻¹, $D_c = 1.242$ Mg/m³, $\lambda = 0.71073$ Å³, $F(000) = 1080$, $2\theta_{\text{max}} = 25.02^\circ$; 12431 reflections measured, 2433 unique ($R_{\text{int}} = 0.0419$). Final residuals for 202 parameters were $R_1 = 0.0419$, $wR_2 = 0.1358$ for $I > 2\sigma(I)$, and $R_1 = 0.0541$, $wR_2 = 0.1482$ for all 2433 data.

[0056] 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.

[0057] Infrared Spectroscopy: (Nicolet Avatar 320 FTIR), characteristic (-COOH) peak at 1679 cm⁻¹ was shifted up and less intense at 1694 cm⁻¹, where as the lactone peak is shifted down slightly from 1750 cm⁻¹ to 1744 cm⁻¹.

[0058] 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).

[0059] 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—Co-crystal of Ibuprofen: Ibuprofen/4,4'-Bipyridine (2:1 stoichiometry)

[0060] 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.

[0061] 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, $\alpha = 93.674(11)$, $\beta = 90.880(10)$, $\gamma = 104.045(7)^\circ$, $U = 1608.3(13)$ Å³, $T = 200(2)$ K, $Z = 2$, $\mu(\text{Mo-K}\alpha) = 0.076$ mm⁻¹, $D_c = 1.174$ Mg/m³, $\lambda = 0.71073$ Å³, $F(000) = 612$, $2\theta_{\text{max}} = 23.29^\circ$; 5208 reflections measured, 3362 unique ($R_{\text{int}} = 0.0826$). Final residuals for 399 parameters were $R_1 = 0.0964$, $wR_2 = 0.2510$ for $I > 2\sigma(I)$, and $R_1 = 0.1775$, $wR_2 = 0.2987$ for all 3362 data.

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[0062] 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.

[0063] 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} .

[0064] 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).

[0065] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 13.28% weight loss between room temperature and 100.02° C immediately followed by complete decomposition.

[0066] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu K α (λ = 1.540562), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2 θ in continuous scan mode using a step size of 0.02° 2 θ 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—Co-crystal of Flurbiprofen: Flurbiprofen/4,4'-bipyridine (2:1 stoichiometry)

[0067] 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.

[0068] Crystal data: (Bruker SMART-APEX CCD Diffractometer), C₄₀H₃₄F₂N₂O₄, M = 644.69, monoclinic *P*2₁/*n*; a = 5.860(4), b = 47.49(3), c = 5.928(4) Å, β = 107.382 (8)°, U = 1574.3(19) Å³, T = 200(2) K, Z = 2, μ (Mo-K α) = 0.096 mm⁻¹, D_c = 1.360 Mg/m³, λ = 0.71073 Å, F(000) = 676, 2 θ_{max} = 21.69°; 4246 reflections measured, 1634 unique

($R_{\text{int}} = 0.0677$). Final residuals for 226 parameters were $R_1 = 0.0908$, $wR_2 = 0.2065$ for $I > 2\sigma(I)$, and $R_1 = 0.1084$, $wR_2 = 0.2209$ for all 1634 data.

[0069] 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.

[0070] 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} .

[0071] Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 162.47° C (endotherm); m.p. = $155\text{--}160^\circ\text{ C}$ (MEL-TEMP); (flurbiprofen m.p. = $110\text{--}111^\circ\text{ C}$, 4,4'-bipyridine m.p. = $111\text{--}114^\circ\text{ C}$).

[0072] 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.

[0073] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu $K\alpha$ ($\lambda = 1.540562$), 30kV, 15mA), the powder data were collected over an angular range of 3° to $40^\circ 2\theta$ in continuous scan mode using a step size of $0.02^\circ 2\theta$ and a scan speed of $2.0^\circ/\text{minute}$. 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—Co-crystal of Flurbiprofen: Flurbiprofen/trans-1,2-bis (4-pyridyl) ethylene (2:1 stoichiometry)

[0074] 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.

[0075] Crystal data: (Bruker SMART-APEX CCD Diffractometer), $\text{C}_{42}\text{H}_{36}\text{F}_2\text{N}_2\text{O}_4$, $M = 670.73$, monoclinic $P2_1/n$; $a = 5.8697(9)$, $b = 47.357(7)$, $c = 6.3587(10)\text{ \AA}$, $\beta = 109.492(3)^\circ$,

$U = 1666.2(4) \text{ \AA}^3$, $T = 200(2) \text{ K}$, $Z = 2$, $\mu(\text{Mo-K}\alpha) = 0.093 \text{ mm}^{-1}$, $D_c = 1.337 \text{ Mg/m}^3$, $\lambda = 0.71073 \text{ \AA}$, $F(000) = 704$, $2\theta_{\text{max}} = 21.69^\circ$, 6977 reflections measured, 2383 unique ($R_{\text{int}} = 0.0383$). Final residuals for 238 parameters were $R_1 = 0.0686$, $wR_2 = 0.1395$ for $I > 2\sigma(I)$, and $R_1 = 0.1403$, $wR_2 = 0.1709$ for all 2383 data.

[0076] 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.

[0077] 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} .

[0078] Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 100.01° C , 125.59° C and 163.54° C (endotherms); m.p. = $153\text{--}158^\circ \text{ C}$ (MEL-TEMP); (flurbiprofen m.p. = $110\text{--}111^\circ \text{ C}$, trans-1, 2-bis (4-pyridyl) ethylene m.p. = $150\text{--}153^\circ \text{ C}$).

[0079] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 91.79% weight loss starting at 133.18° C followed by complete decomposition.

[0080] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu $K\alpha$ ($\lambda = 1.540562$), 30kV, 15mA), the powder data were collected over an angular range of 3° to $40^\circ 2\theta$ in continuous scan mode using a step size of $0.02^\circ 2\theta$ and a scan speed of $2.0^\circ/\text{minute}$. 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—Co-crystal of Carbamazepine: Carbamazepine/*p*-Phthalaldehyde (1:1 stoichiometry)

[0081] 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.

[0082] Crystal data: (Bruker SMART-APEX CCD Diffractometer), $\text{C}_{38}\text{H}_{30}\text{N}_4\text{O}_4$, $M = 606.66$, monoclinic $C2/c$; $a = 29.191(16)$, $b = 4.962(3)$, $c = 20.316(11) \text{ \AA}$, $\beta = 92.105(8)^\circ$,

$U = 2941(3) \text{ \AA}^3$, $T = 200(2) \text{ K}$, $Z = 4$, $\mu(\text{Mo-K}\alpha) = 0.090 \text{ mm}^{-1}$, $D_c = 1.370 \text{ Mg/m}^3$, $\lambda = 0.71073 \text{ \AA}$, $F(000) = 1272$, $2\theta_{\text{max}} = 43.66^\circ$, 3831 reflections measured, 1559 unique ($R_{\text{int}} = 0.0510$). Final residuals for 268 parameters were $R_1 = 0.0332$, $wR_2 = 0.0801$ for $I > 2\sigma(I)$, and $R_1 = 0.0403$, $wR_2 = 0.0831$ for all 1559 data.

[0083] 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.

[0084] 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} .

[0085] Differential Scanning Calorimetry: (TA Instruments 2920 DSC), 128.46° C (endotherm), m.p. = $121\text{--}124^\circ \text{ C}$ (MEL-TEMP), (carbamazepine m.p. = 190.2° C , *p*-phthalaldehyde m.p. = 116° C).

[0086] 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.

[0087] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using $\text{Cu K}\alpha$ ($\lambda = 1.540562$), 30kV, 15mA). The powder data were collected over an angular range of 3° to $40^\circ 2\theta$ in continuous scan mode using a step size of $0.02^\circ 2\theta$ and a scan speed of $2.0^\circ/\text{minute}$. 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—Co-crystal of Carbamazepine: Carbamazepine/nicotinamide (GRAs) (1:1 stoichiometry)

[0088] 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.

[0089] 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).

[0090] 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, $\beta = 90.917(3)^\circ$, $U = 1761.5(5)$ Å³, $T = 200(2)$ K, $Z = 4$, $\mu(\text{Mo-K}\alpha) = 0.090$ mm⁻¹, $D_c = 1.351$ Mg/m³, $\lambda = 0.71073$ Å, $F(000) = 752$, $2\theta_{\text{max}} = 56.60^\circ$, 10919 reflections measured, 4041 unique ($R_{\text{int}} = 0.0514$). Final residuals for 248 parameters were $R_1 = 0.0732$, $wR_2 = 0.1268$ for $I > 2\sigma(I)$, and $R_1 = 0.1161$, $wR_2 = 0.1430$ for all 4041 data.

[0091] 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.

[0092] 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.

[0093] 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).

[0094] Thermogravimetric Analysis: (TA Instruments 2950 Hi-Resolution TGA), 57.94% weight loss starting at 205.43° C followed by complete decomposition.

[0095] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu K α ($\lambda = 1.540562$), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2 θ in continuous scan mode using a step size of 0.02° 2 θ 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—Co-crystal of Carbamazepine: Carbamazepine/saccharin (GRAs) (1:1 stoichiometry)

[0096] 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.

[0097] 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, $\alpha = 83.642(2)^\circ$, $\beta = 85.697(2)^\circ$, $\gamma = 75.411(2)^\circ$, $U = 957.0(2)$ Å³, $T = 200(2)$ K, $Z = 2$, $\mu(\text{Mo-K}\alpha) = 0.206$ mm⁻¹, $D_c = 1.456$ Mg/m³, $\lambda = 0.71073$ Å, $F(000) = 436$, $2\theta_{\text{max}} = 56.20^\circ$; 8426 reflections measured, 4372 unique ($R_{\text{int}} = 0.0305$). Final residuals for 283 parameters were $R_1 = 0.0458$, $wR_2 = 0.1142$ for $I > 2\sigma(I)$, and $R_1 = 0.0562$, $wR_2 = 0.1204$ for all 4372 data.

[0098] 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.

[0099] 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.

[00100] 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).

[00101] 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.

[00102] X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu K α ($\lambda = 1.540562$), 30kV, 15mA). The powder data were collected over an angular range of 3° to 40° 2 θ in continuous scan mode using a step size of 0.02° 2 θ 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).

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ABSTRACT

[00105] 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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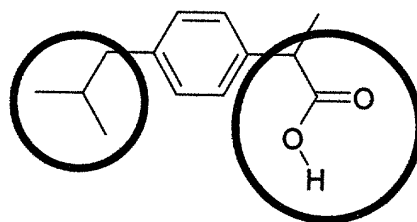


FIG. 1

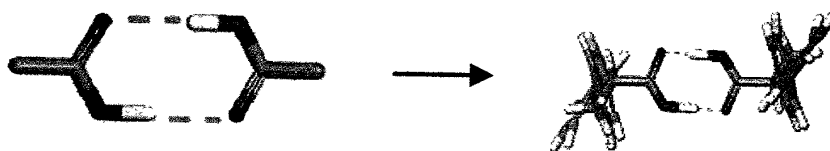


FIG. 2

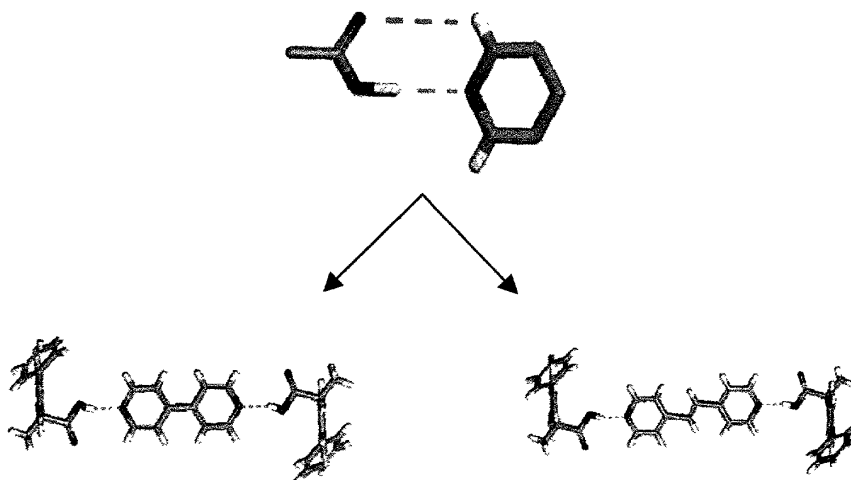


FIG. 3

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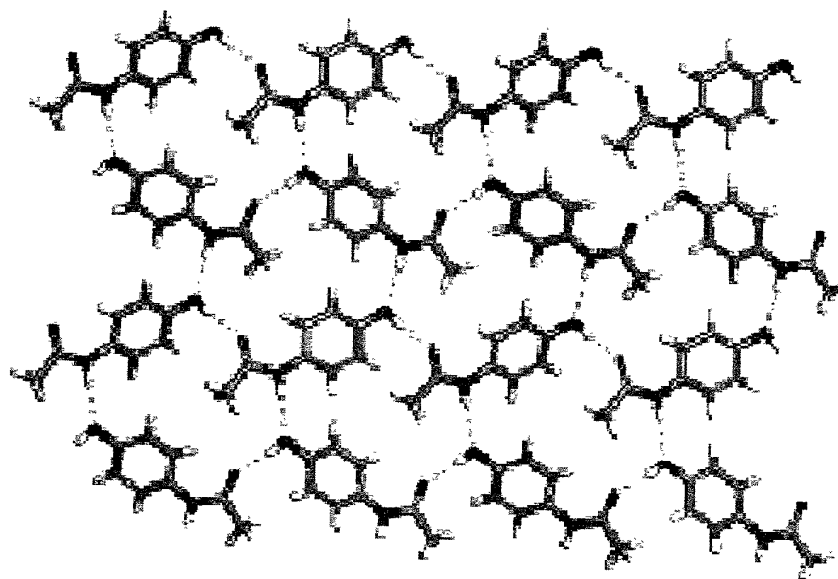


FIG. 4A

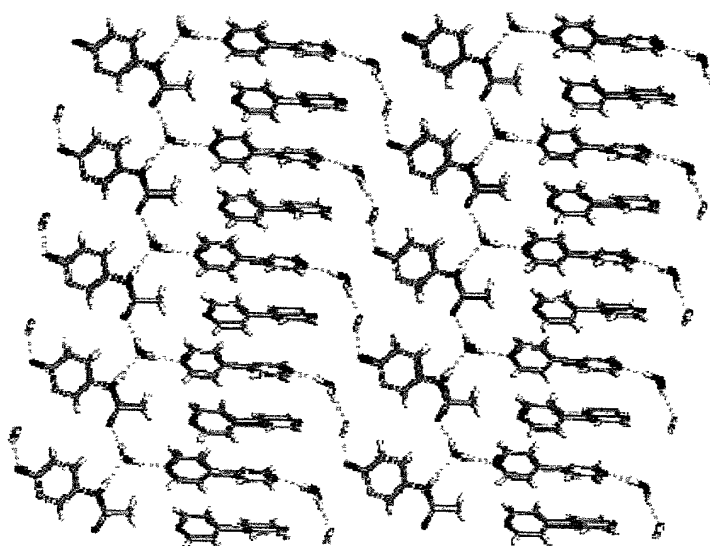


FIG. 4B

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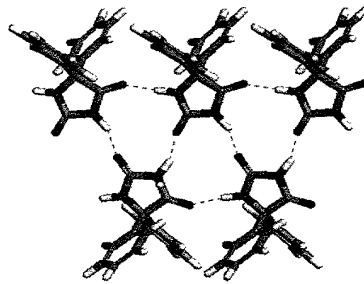


FIG. 5A

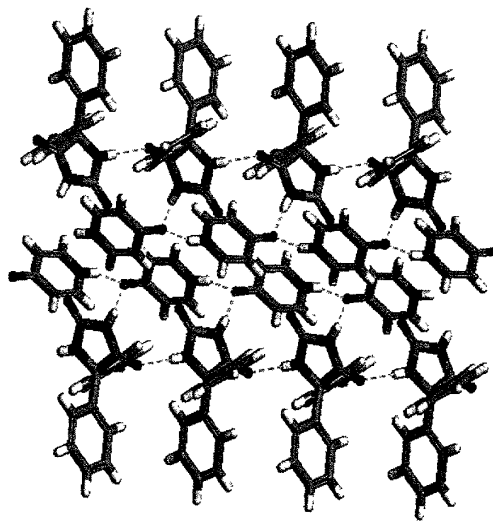


FIG. 5B

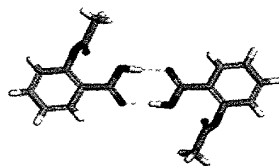


FIG. 6A

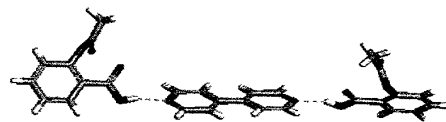


FIG. 6C

NOVARTIS EXHIBIT 1014

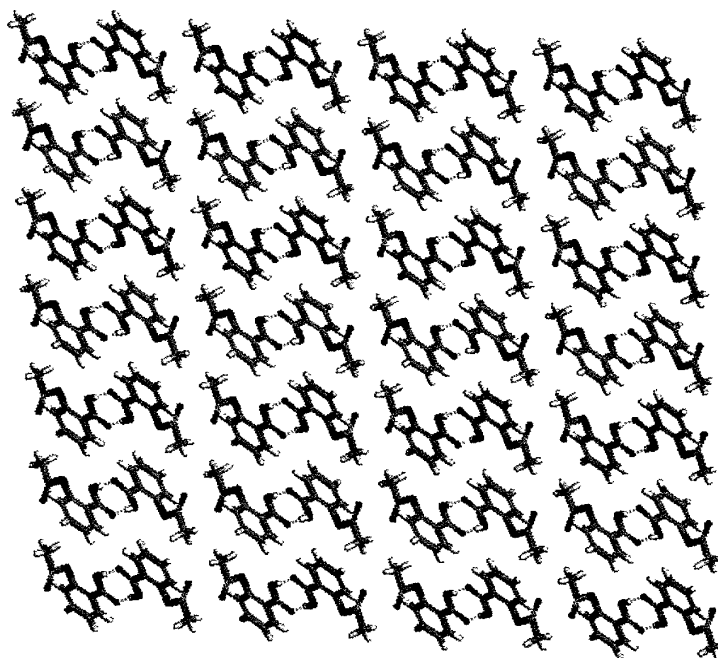


FIG. 6B

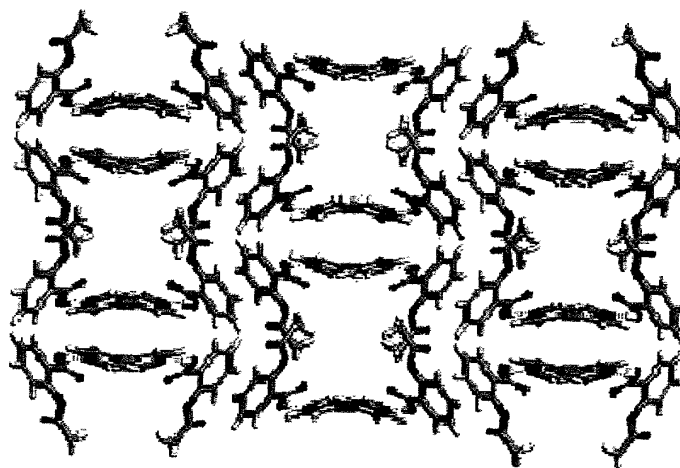


FIG. 6D

50360755.030102

FIG. 7A

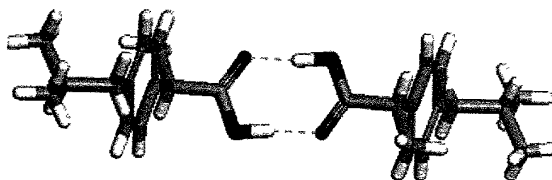


FIG. 7C

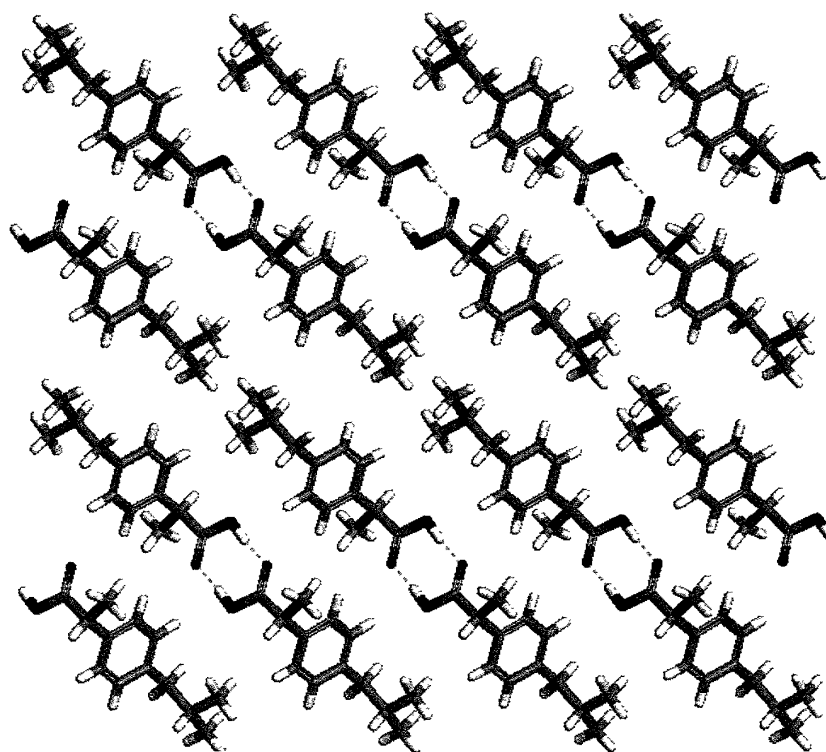
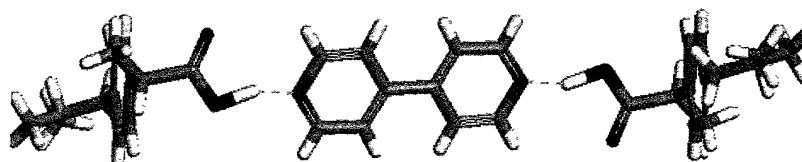


FIG. 7B

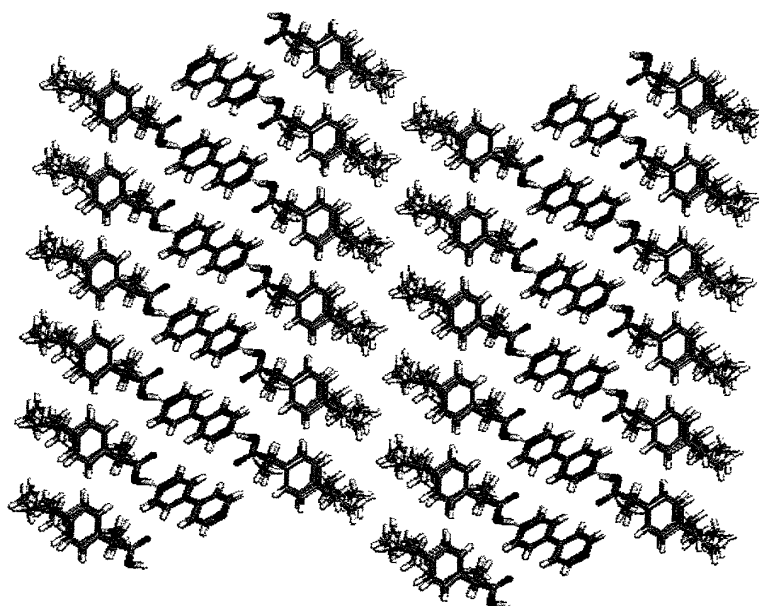


FIG. 7D

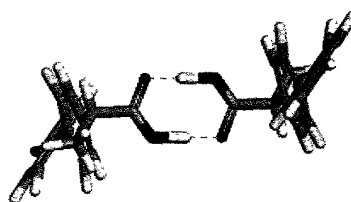


FIG. 8A

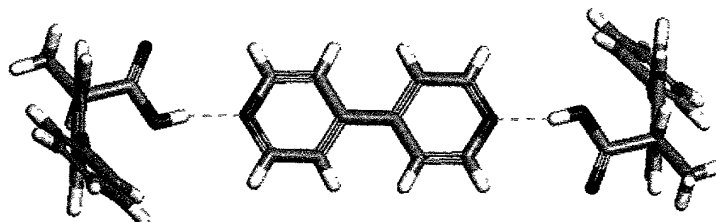


FIG. 8C

NOVARTIS EXHIBIT 1014

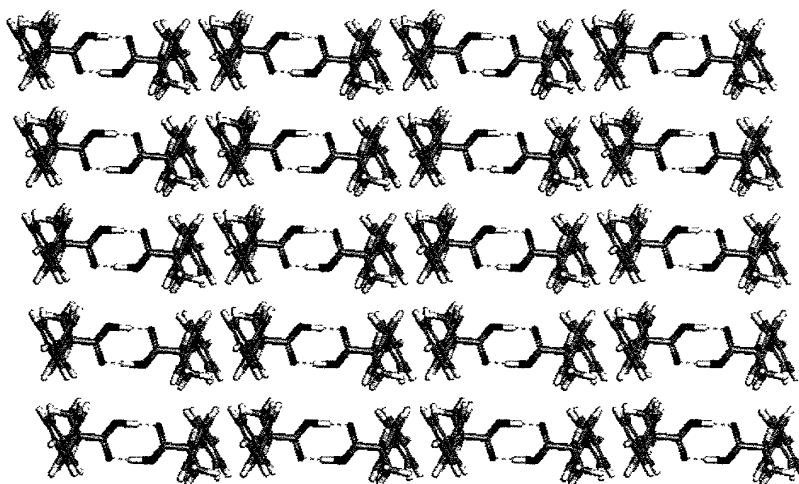


FIG. 8B

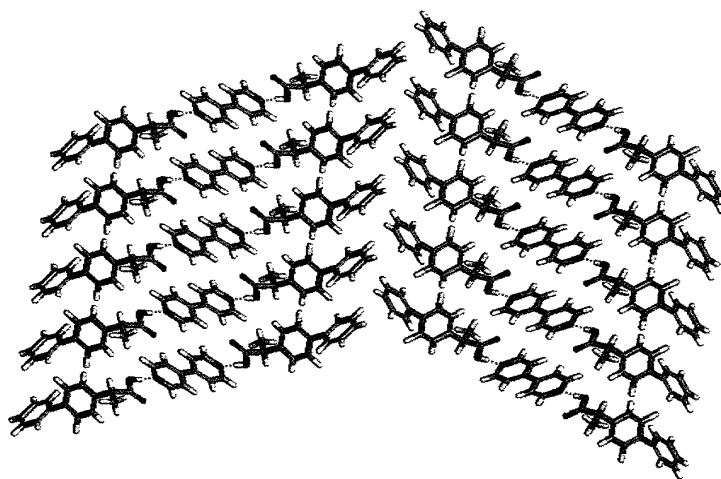


FIG. 8D

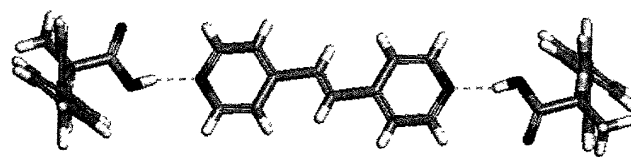


FIG. 9A

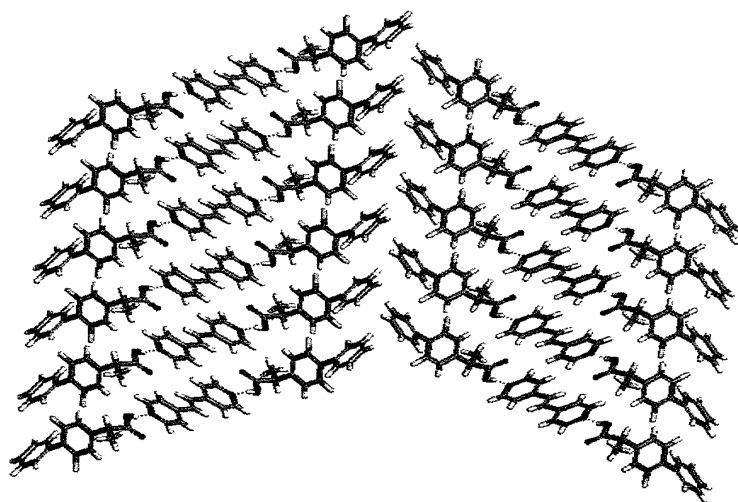


FIG. 9B

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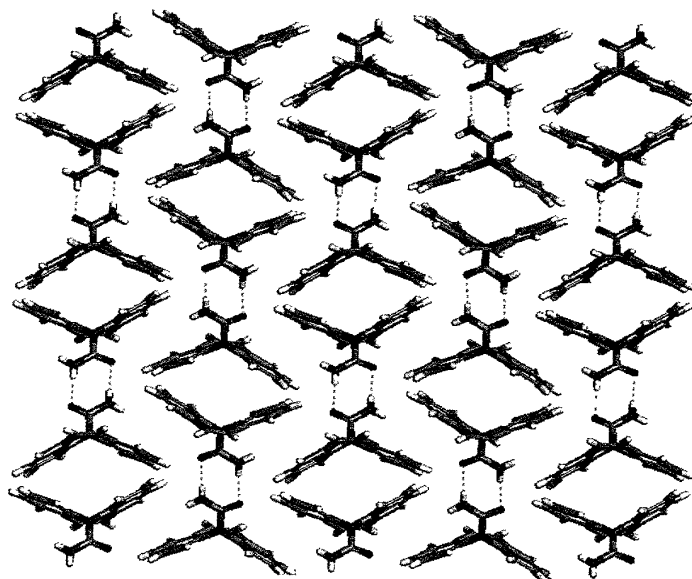


FIG. 10A

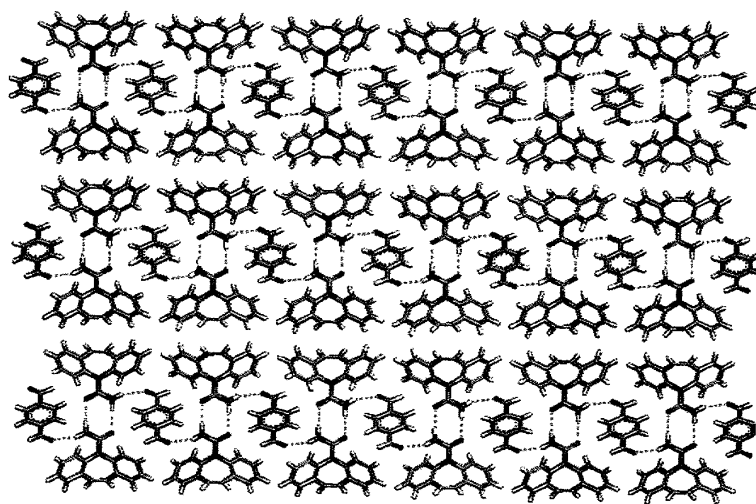


FIG. 10B

NOVARTIS EXHIBIT 1014

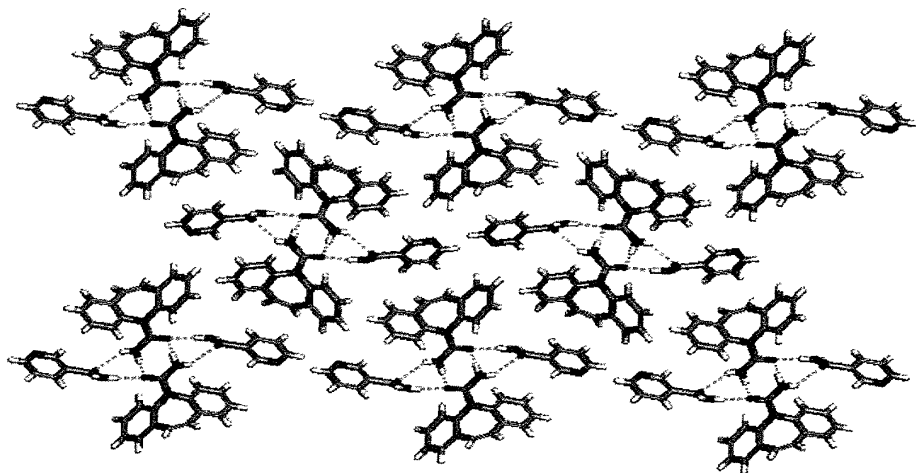


FIG. 11

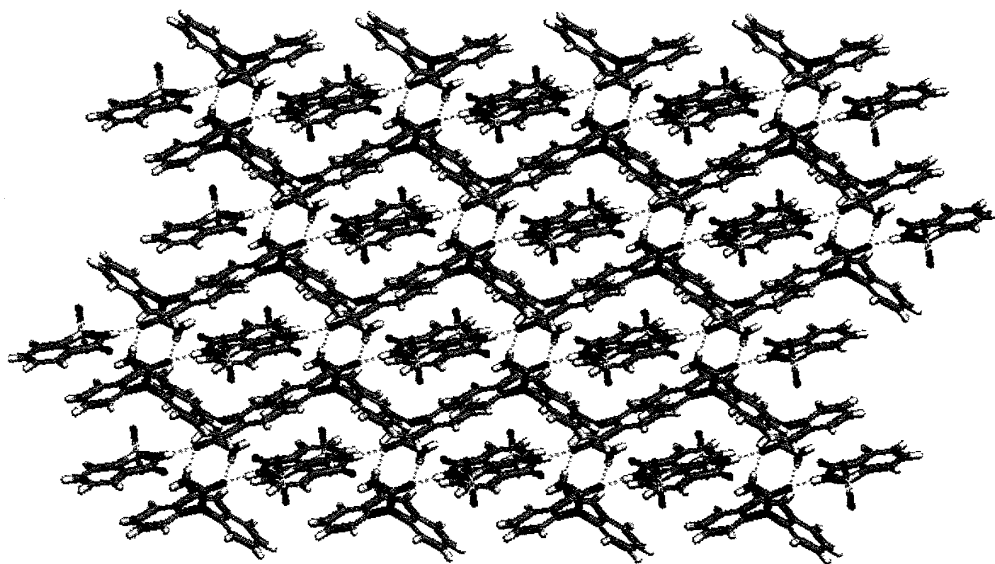


FIG. 12

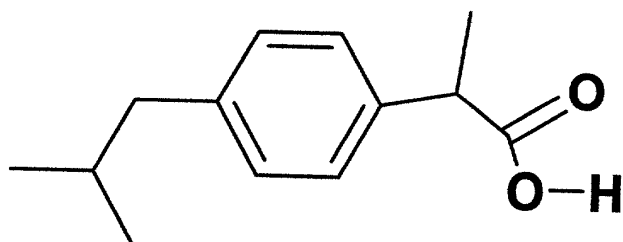


FIG. 13A

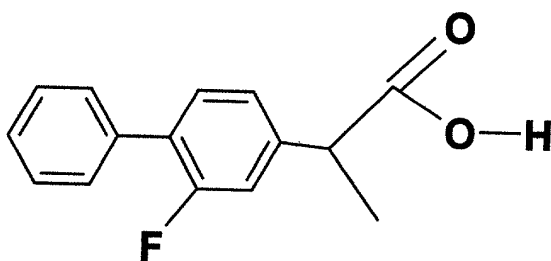


FIG. 13B

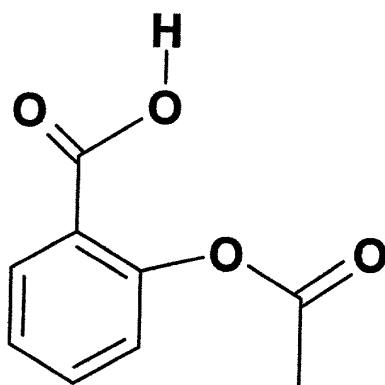


FIG. 13C