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(54) **MULTIPLE-COMPONENT SOLID PHASES CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL INGREDIENT**

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See application file for complete search history.

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(57) **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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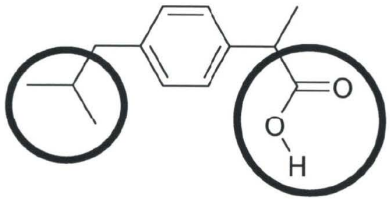


FIG. 1

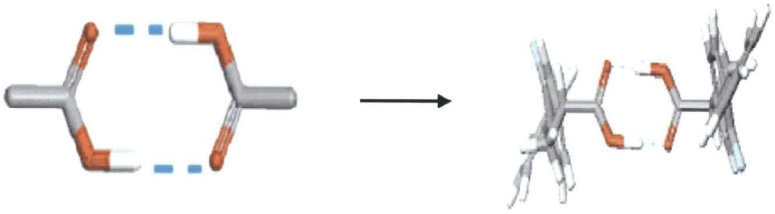


FIG. 2

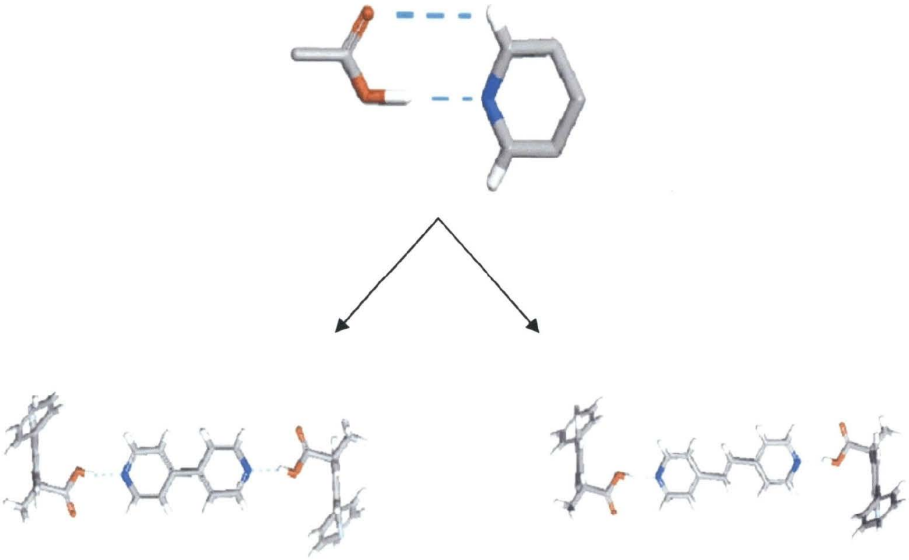


FIG. 3

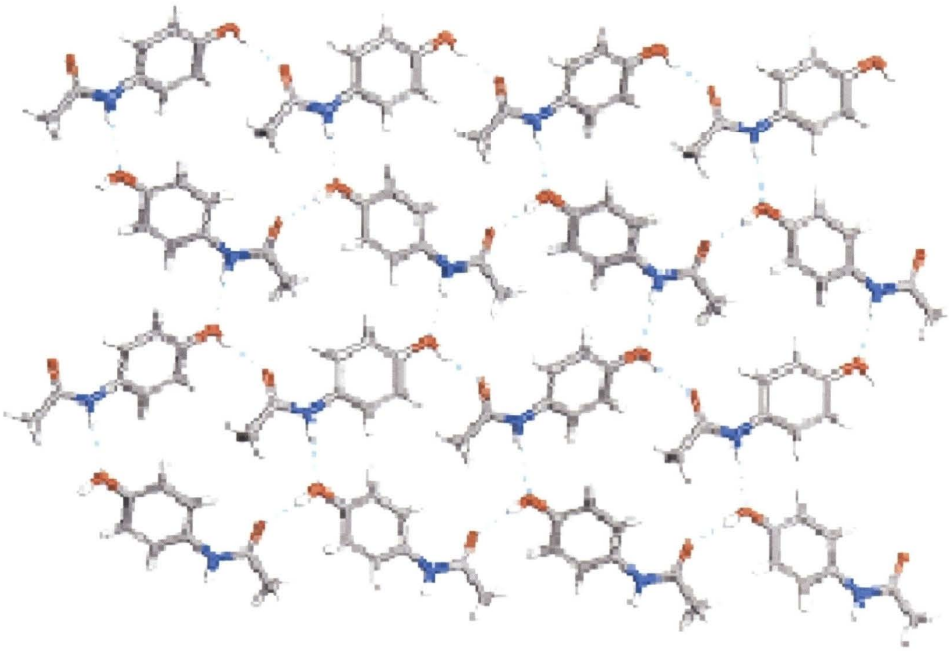


FIG. 4A

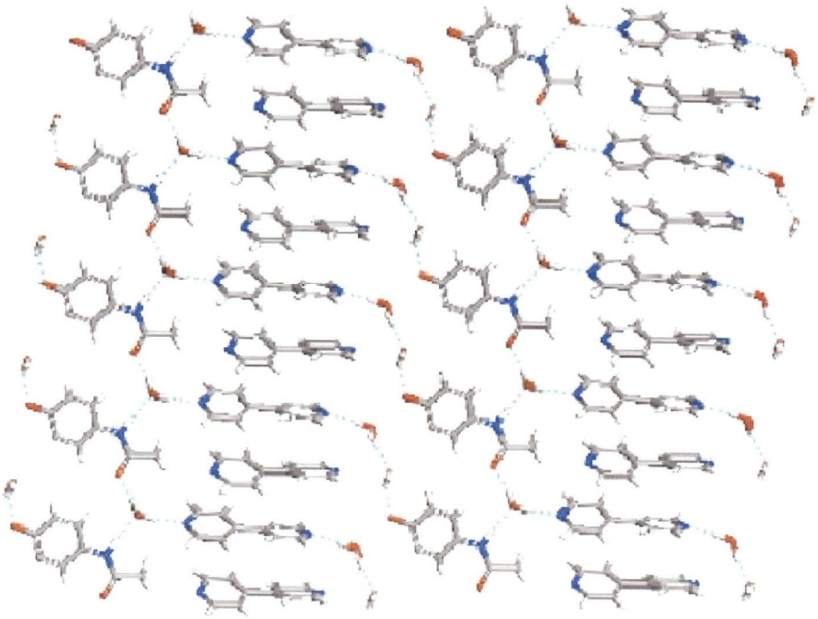


FIG. 4B

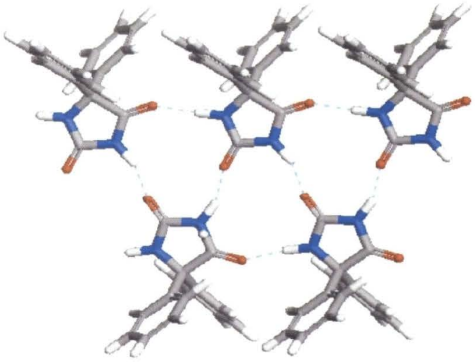


FIG. 5A

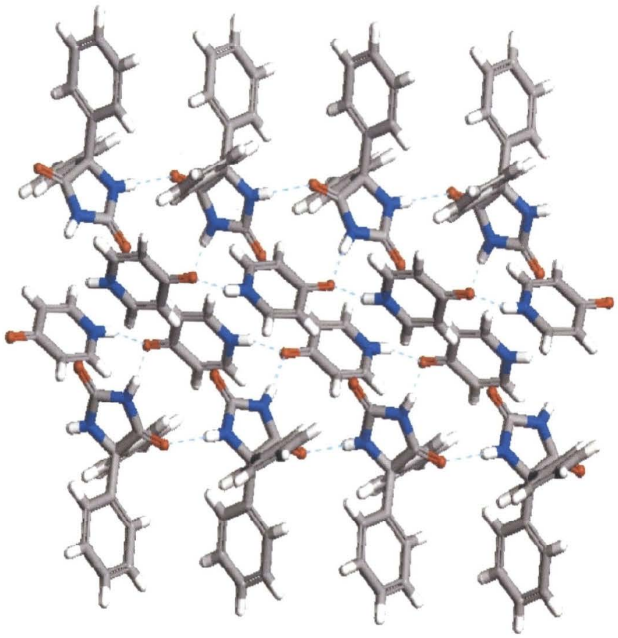


FIG. 5B

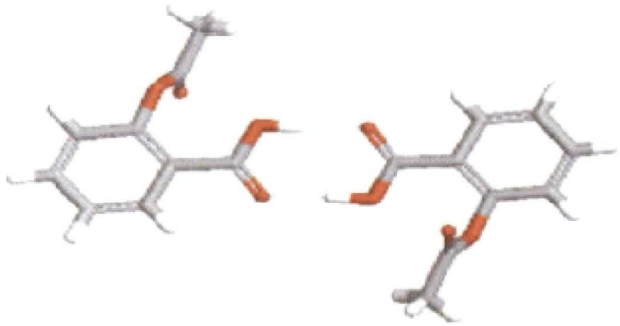


FIG. 6A

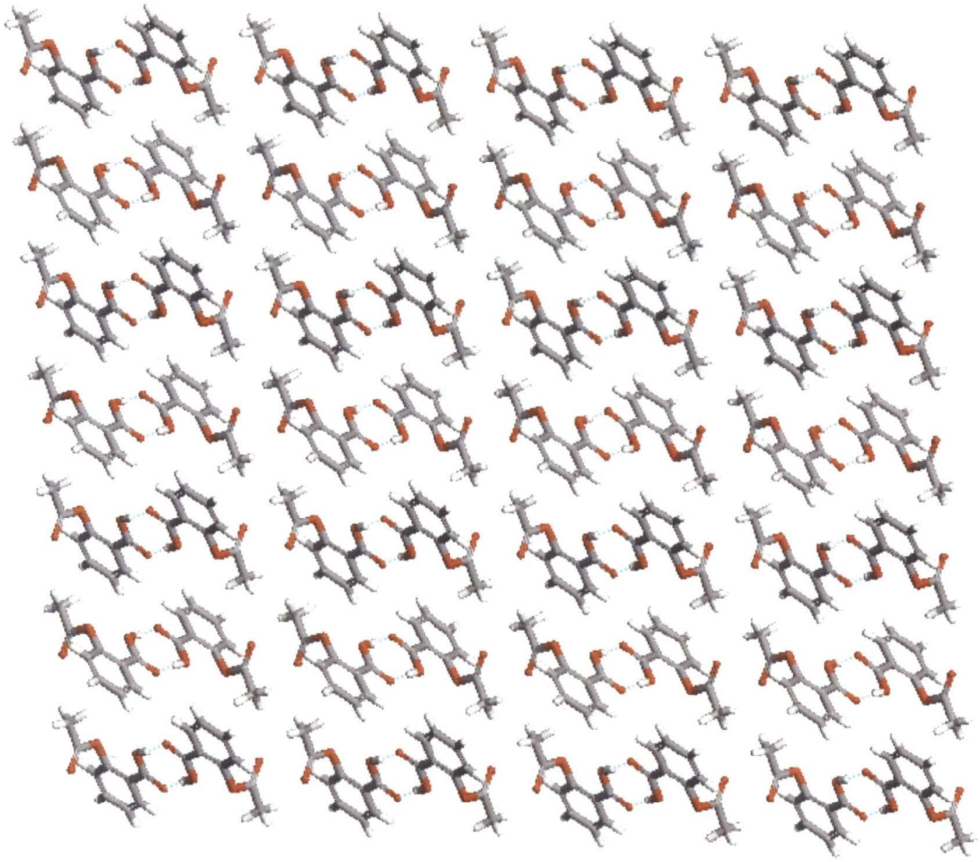


FIG. 6B

FIG. 6C

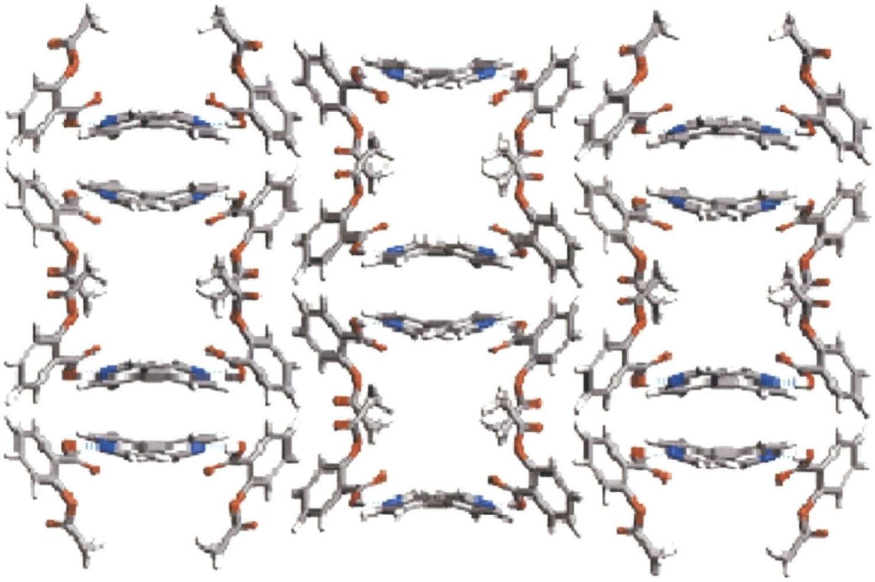


FIG. 6D

FIG. 7A

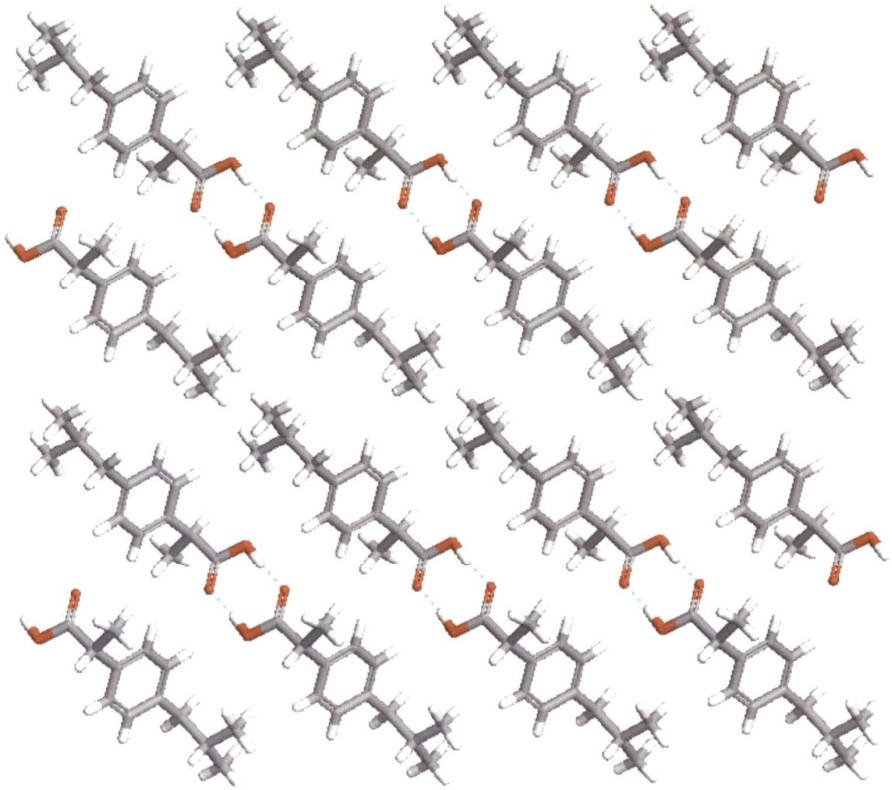


FIG. 7B

FIG. 7C

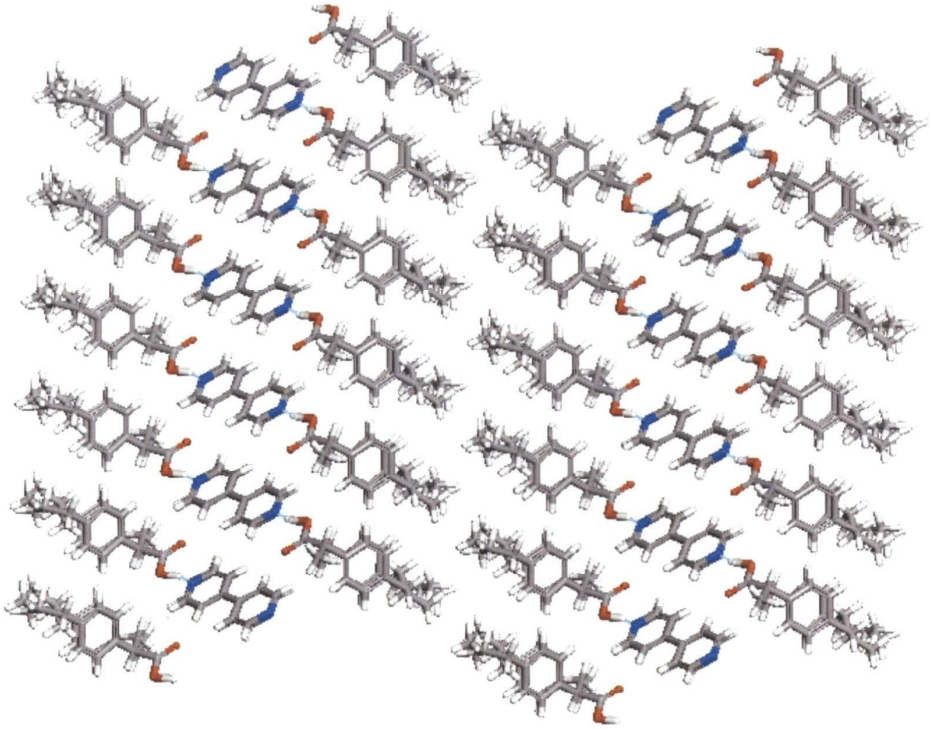


FIG. 7D

FIG. 8A

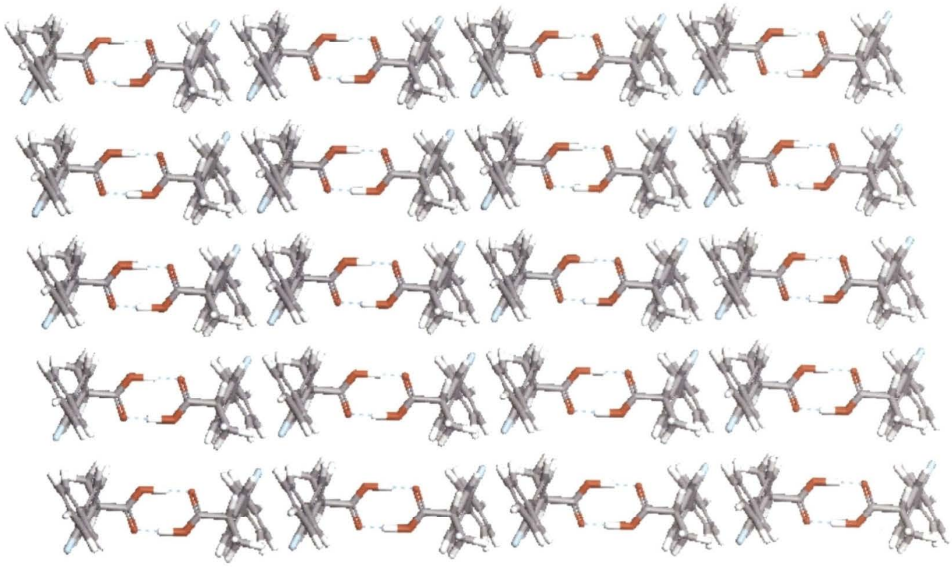
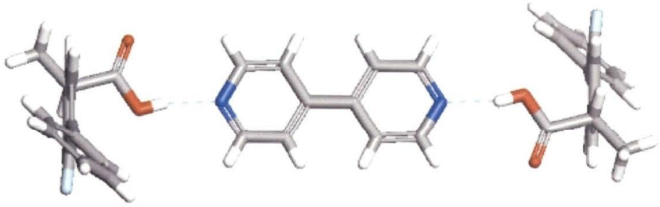


FIG. 8B

FIG. 8C



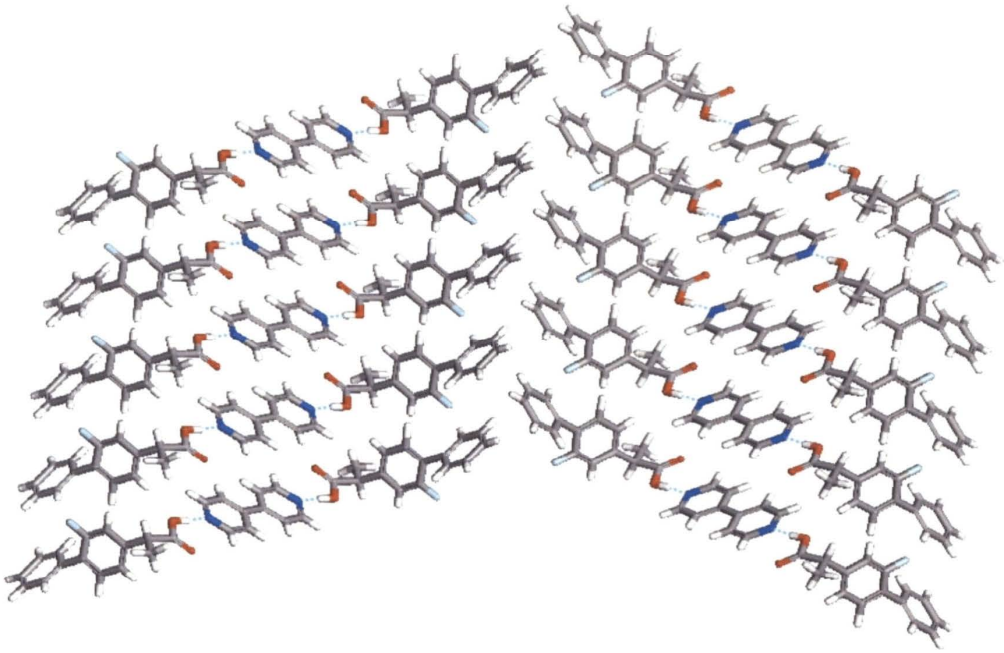


FIG. 8D

FIG. 9A

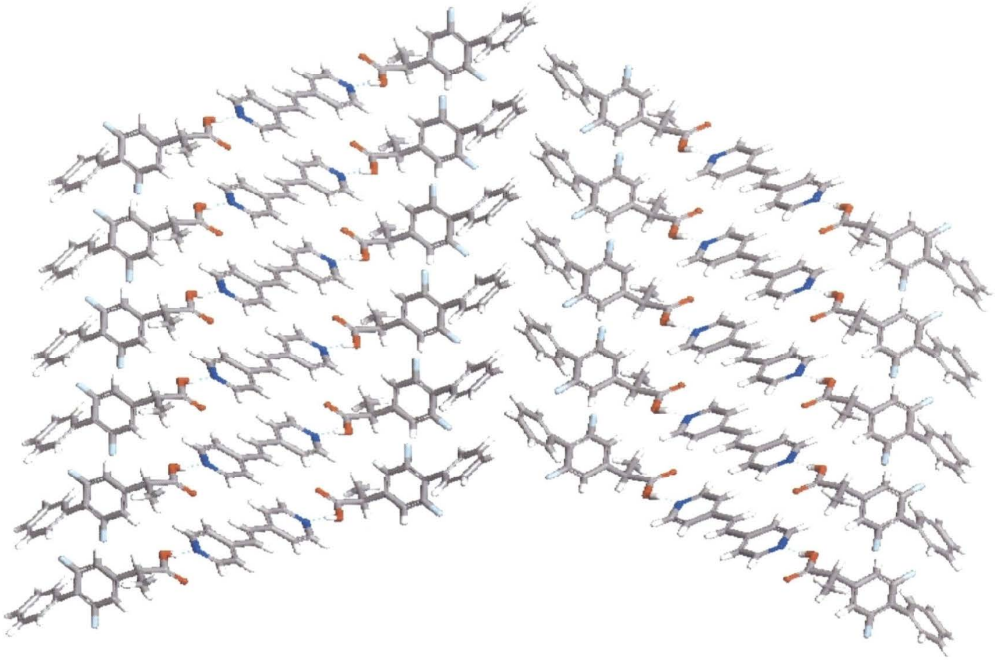


FIG. 9B

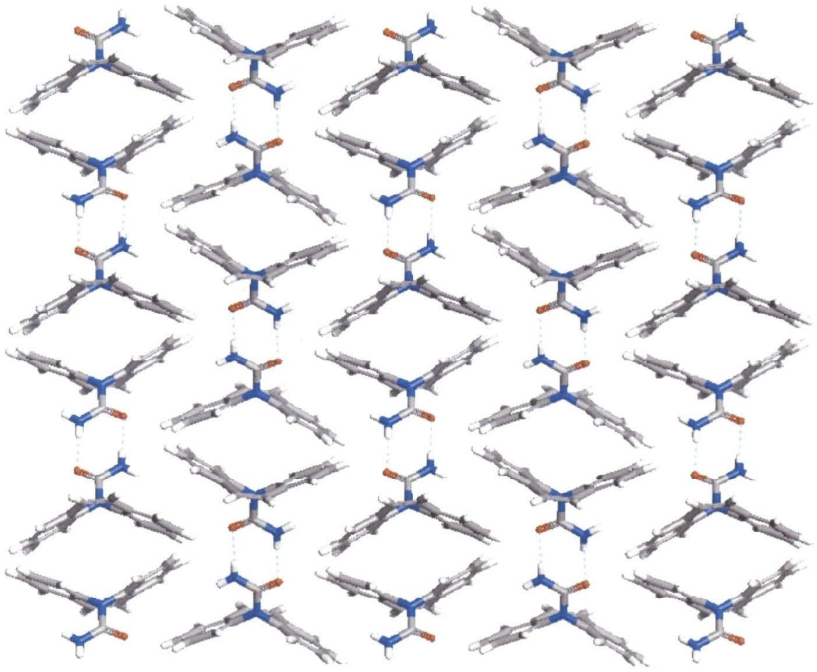


FIG. 10A

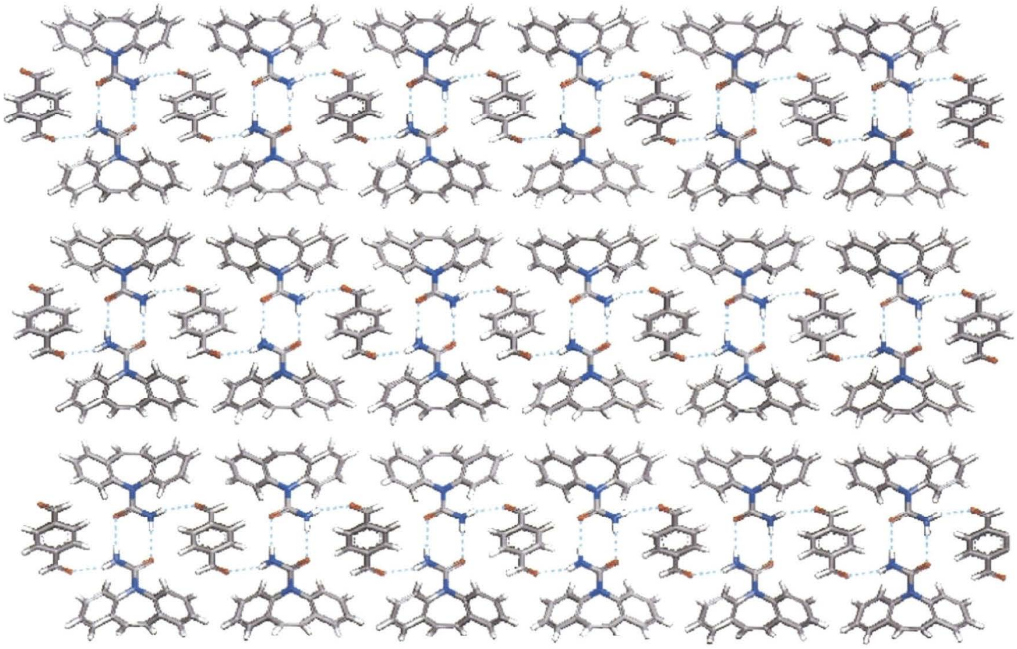


FIG. 10B

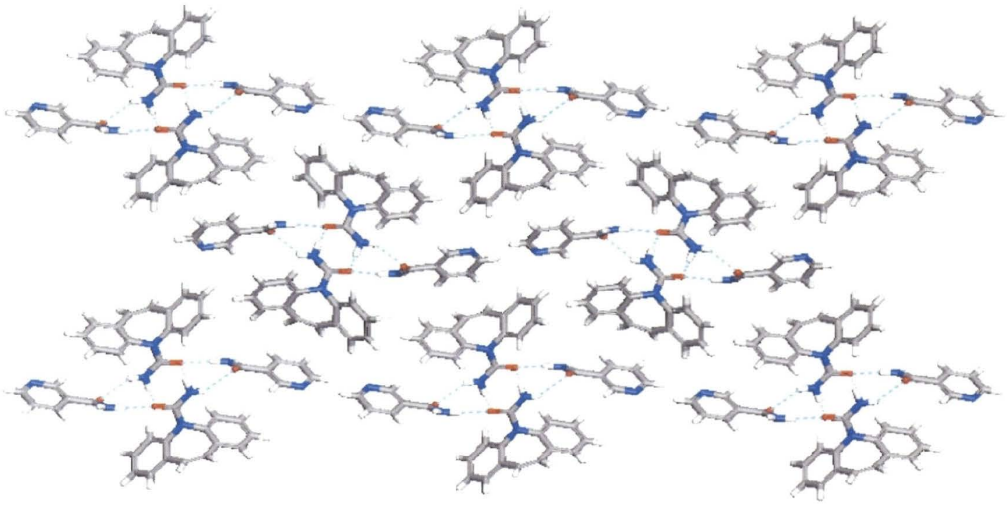


FIG. 11

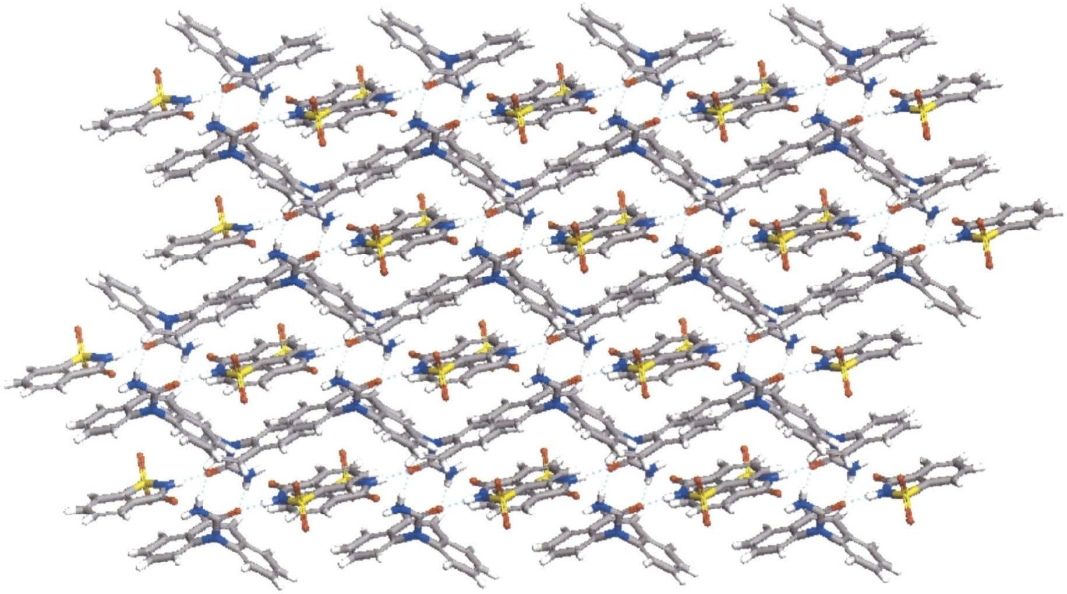


FIG. 12

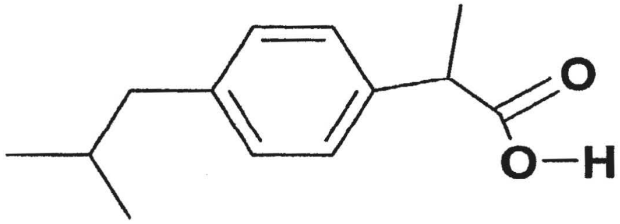


FIG. 13A

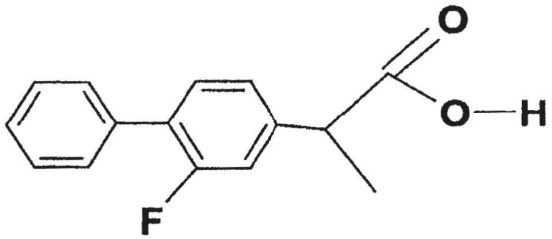


FIG. 13B

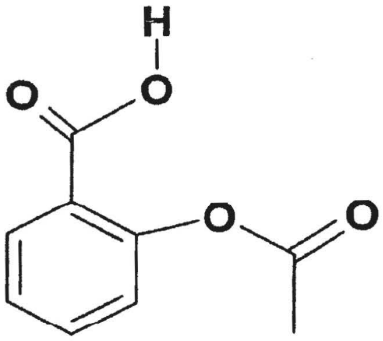


FIG. 13C

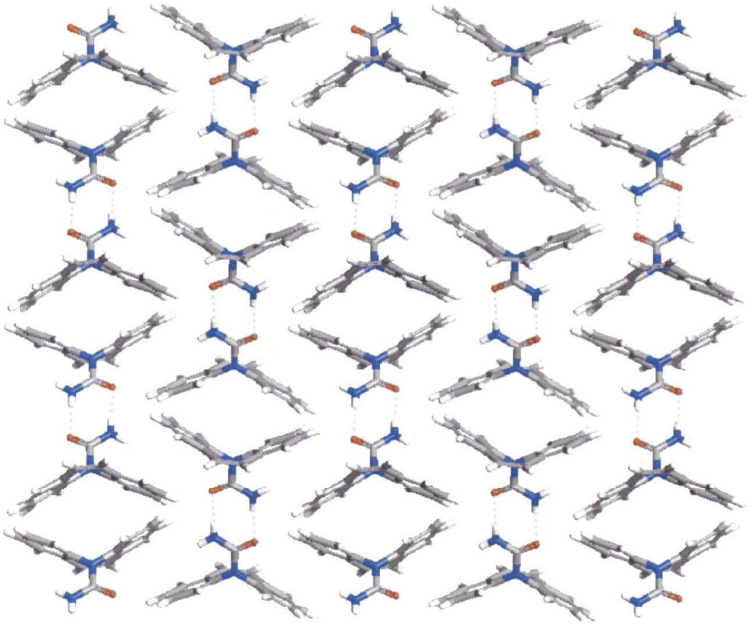


FIG. 14A

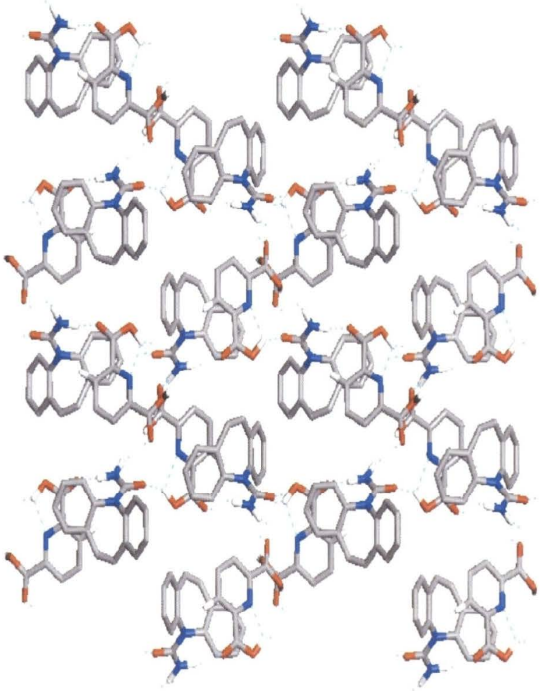


FIG. 14B

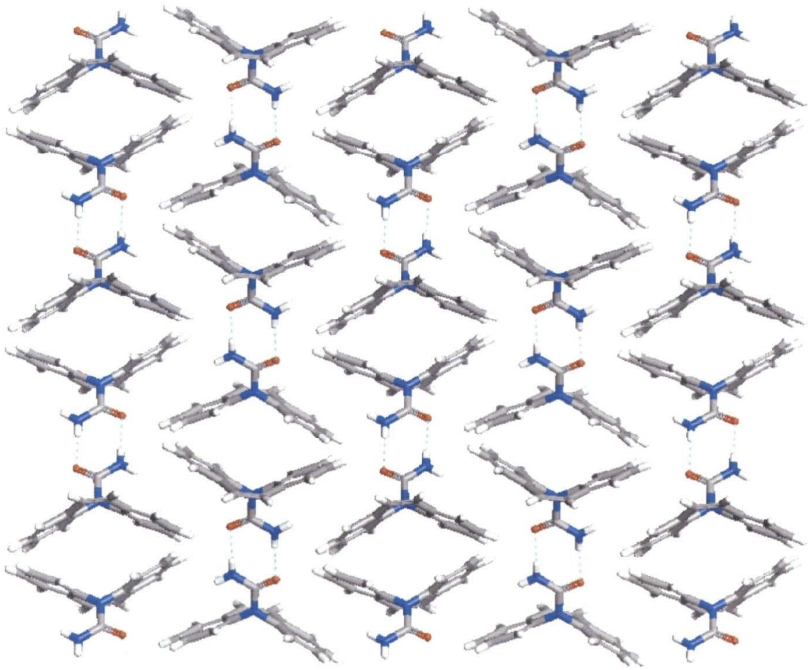


FIG. 15A

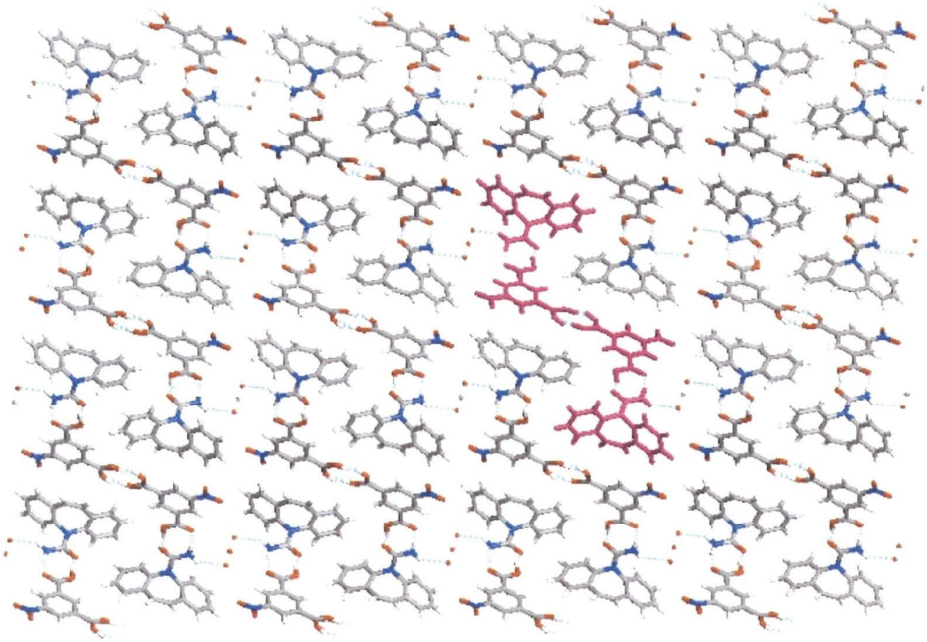
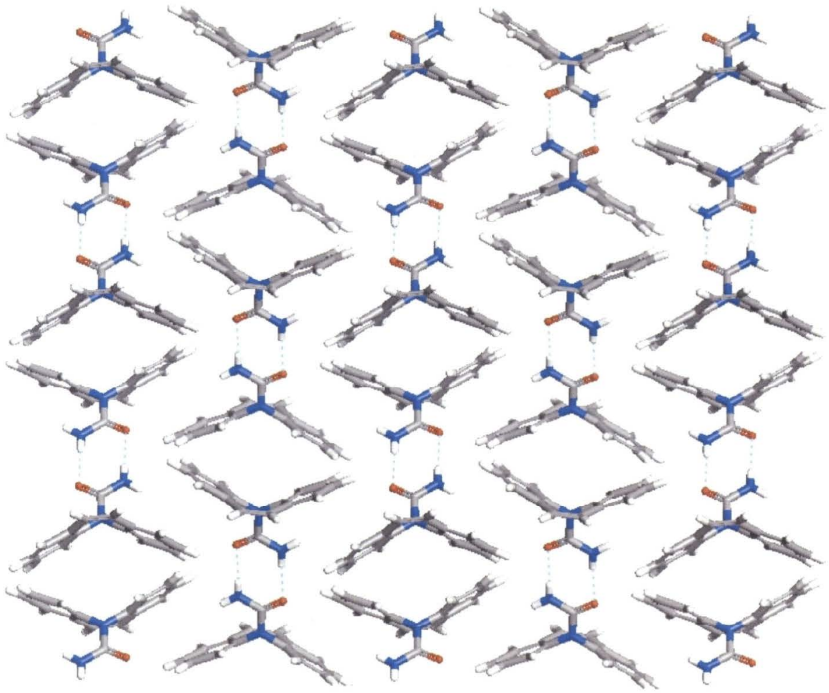


FIG. 15B



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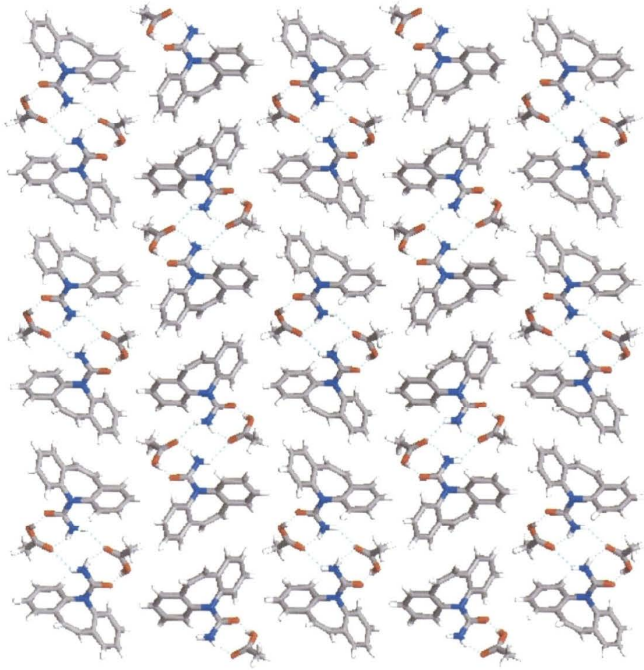

FIG. 16B

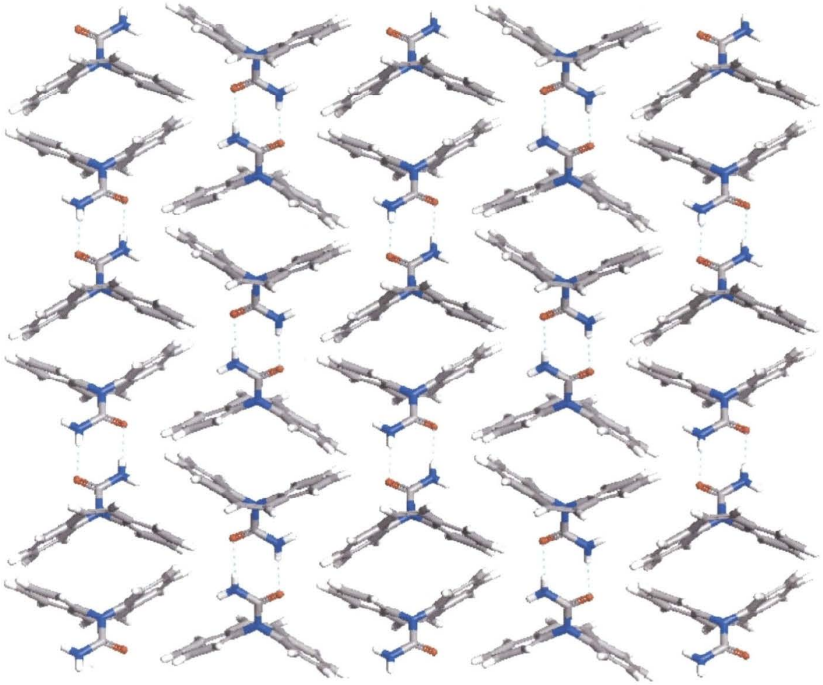

FIG. 17A

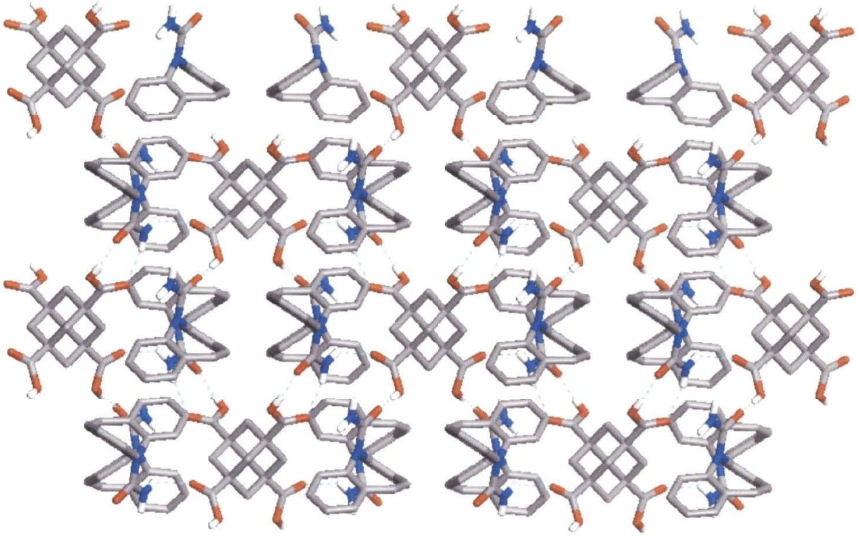

FIG. 17B

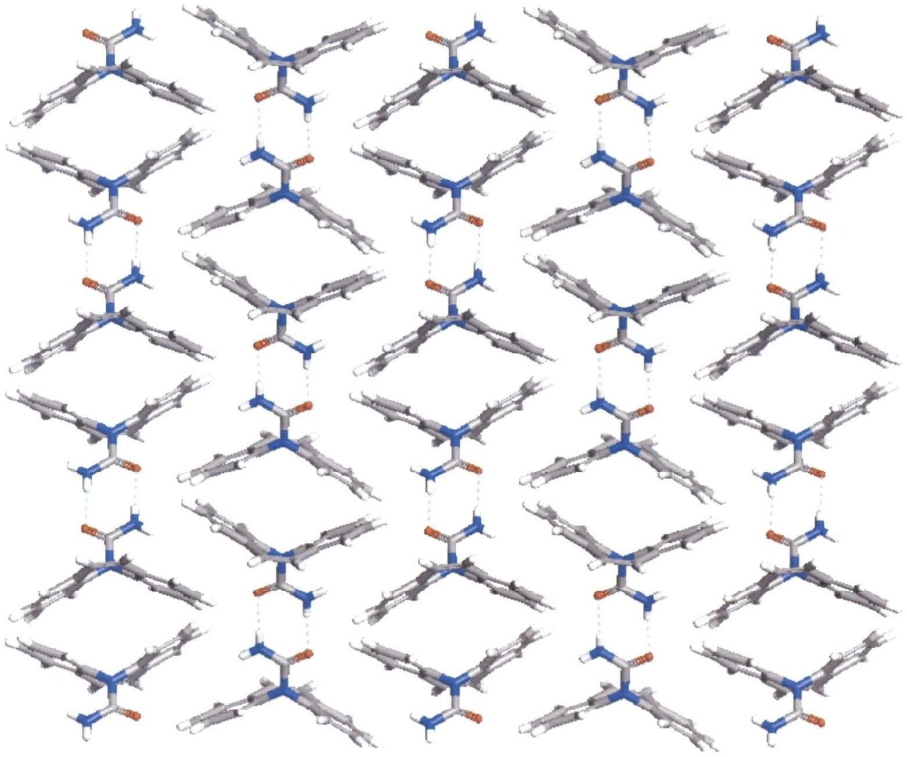

FIG. 18A

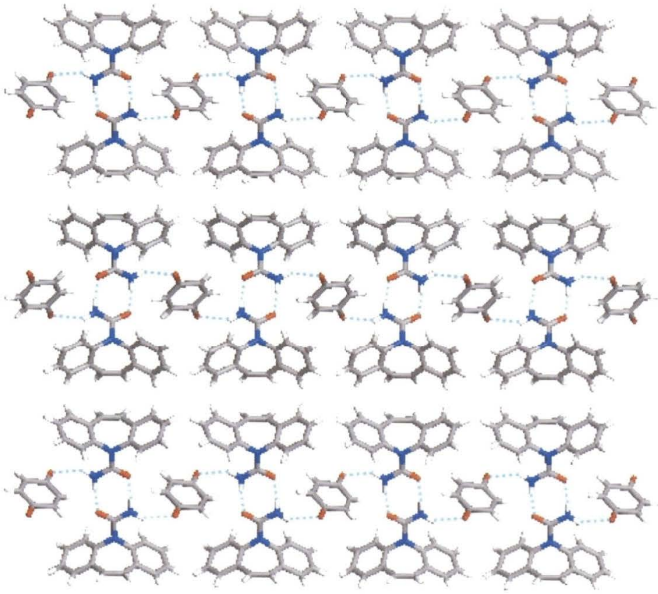

FIG. 18B

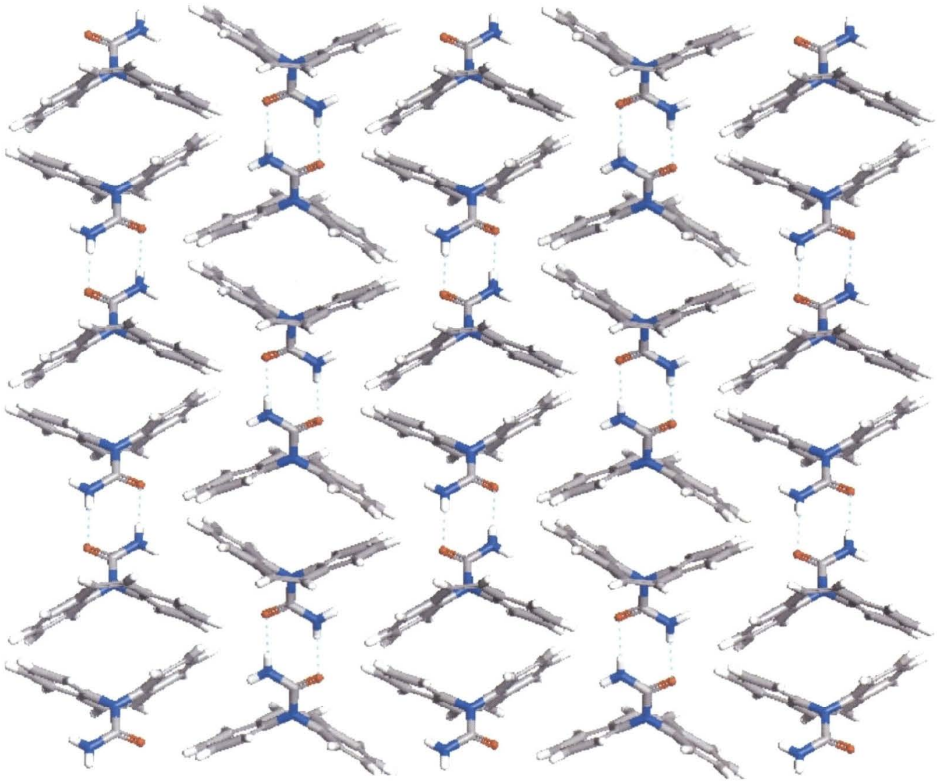

FIG. 19A

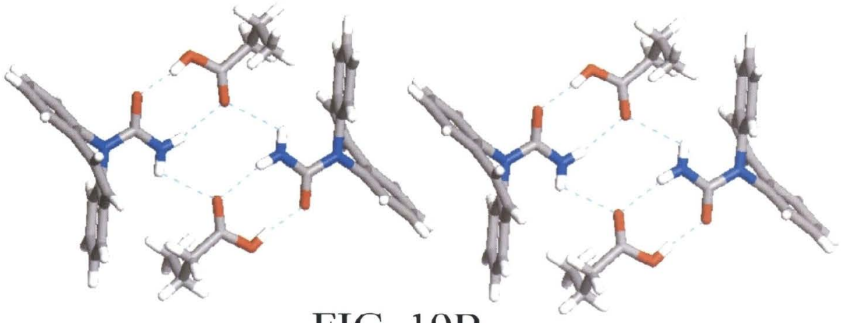

FIG. 19B

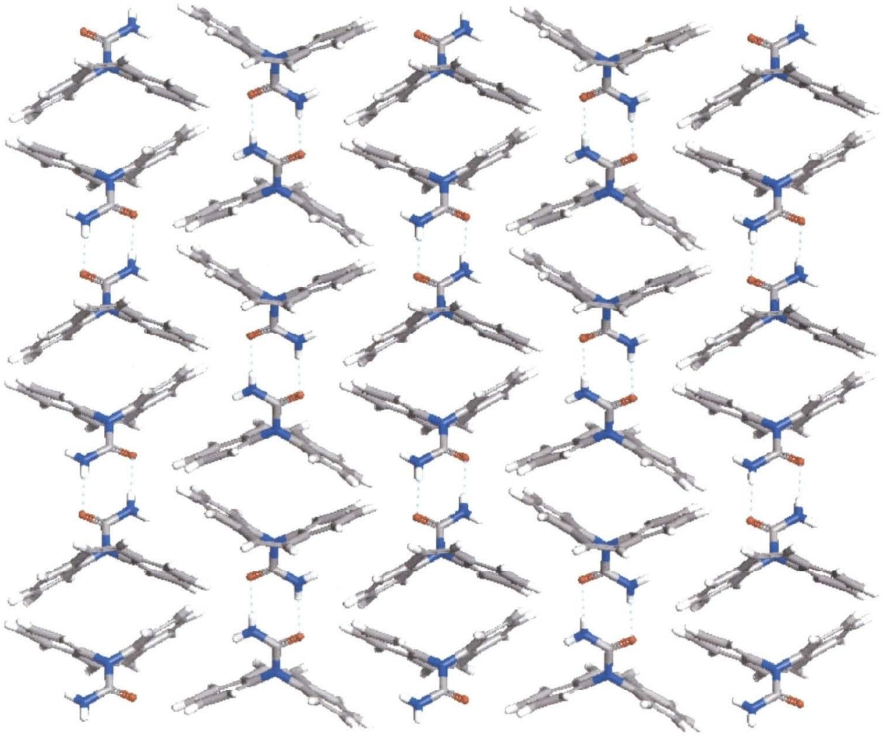

FIG. 20A

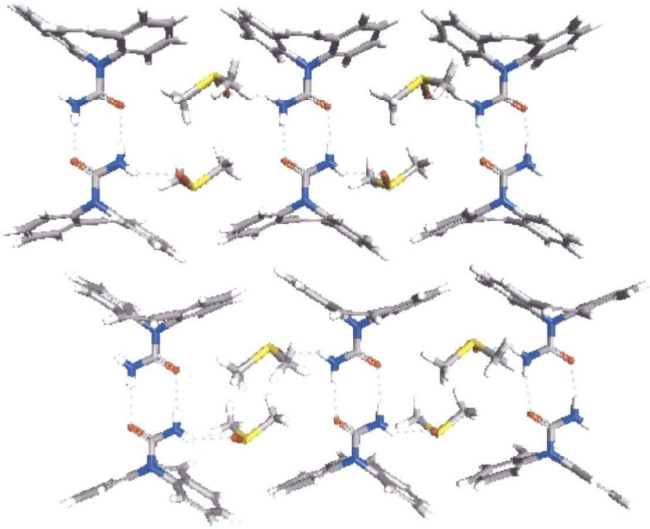

FIG. 20B

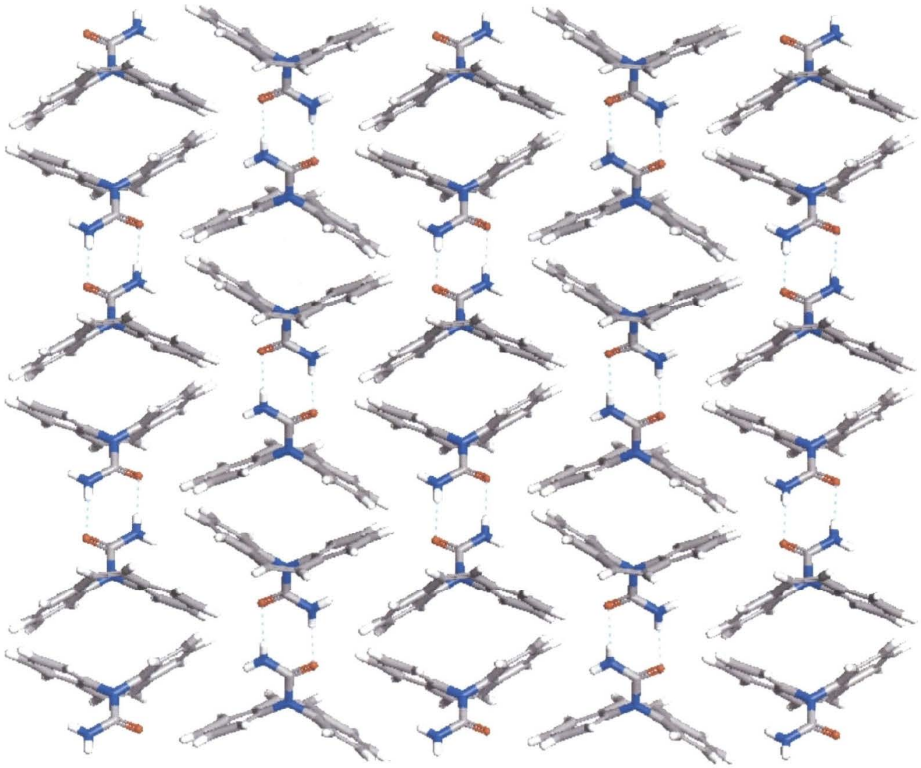

FIG. 21A

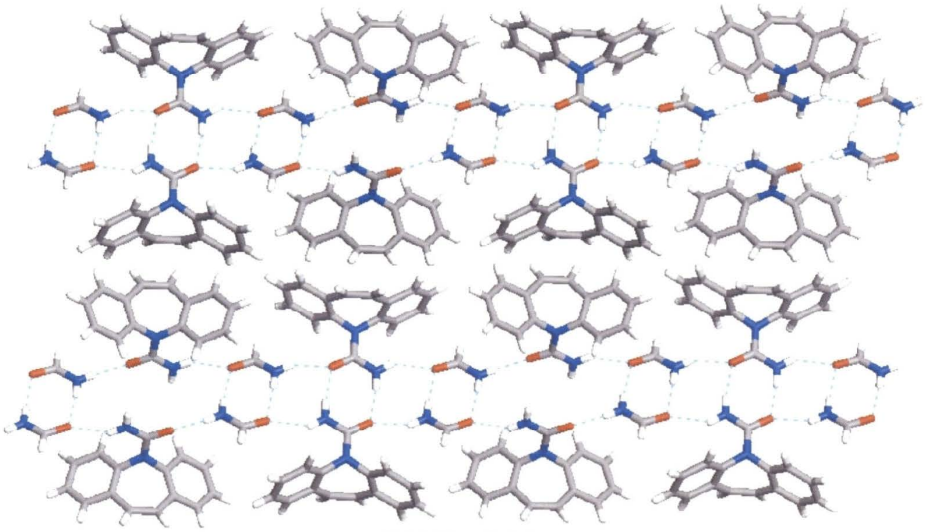

FIG. 21B

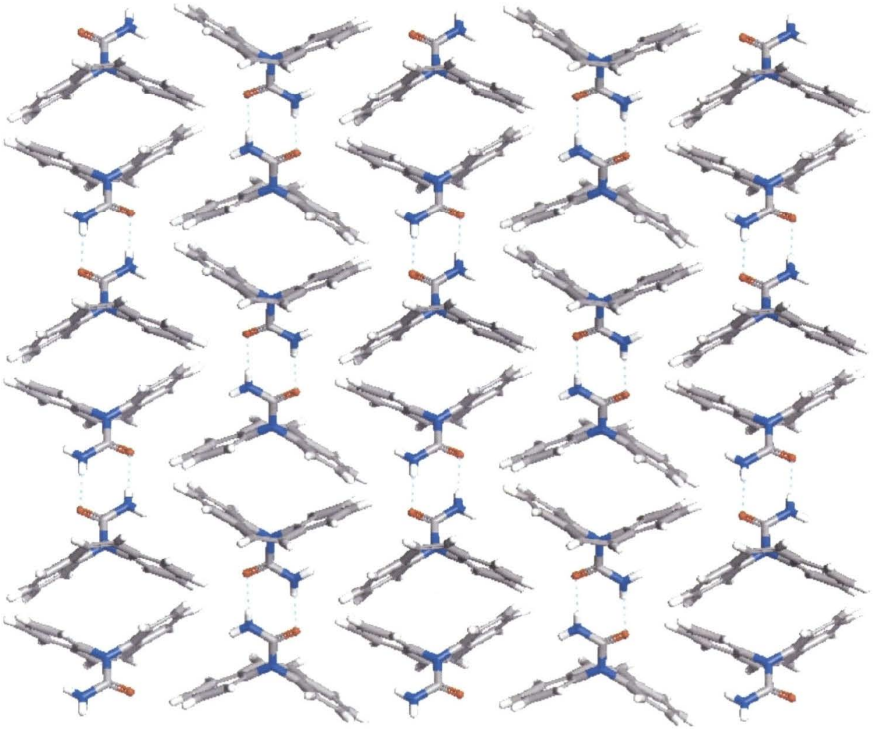

FIG. 22A

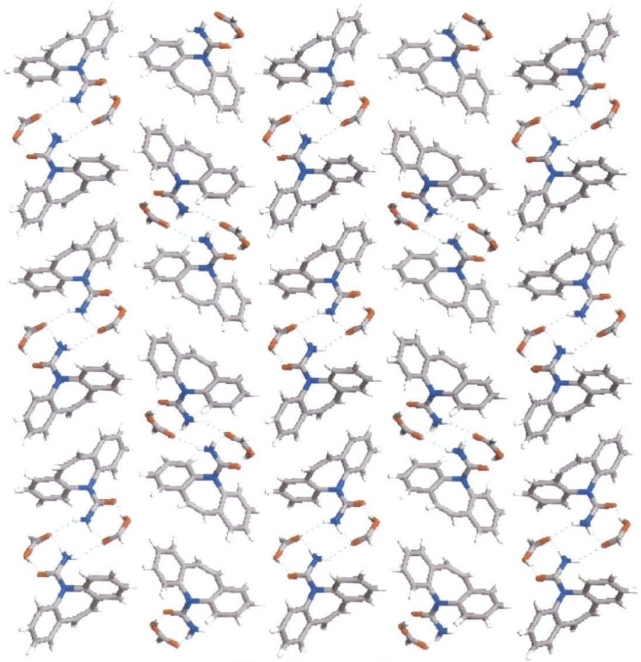

FIG. 22B

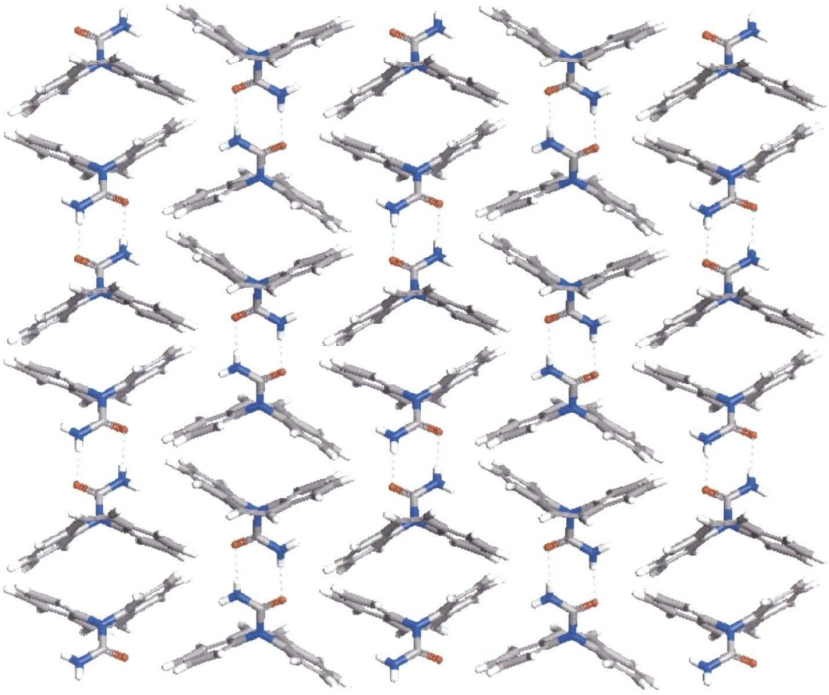

FIG. 23A

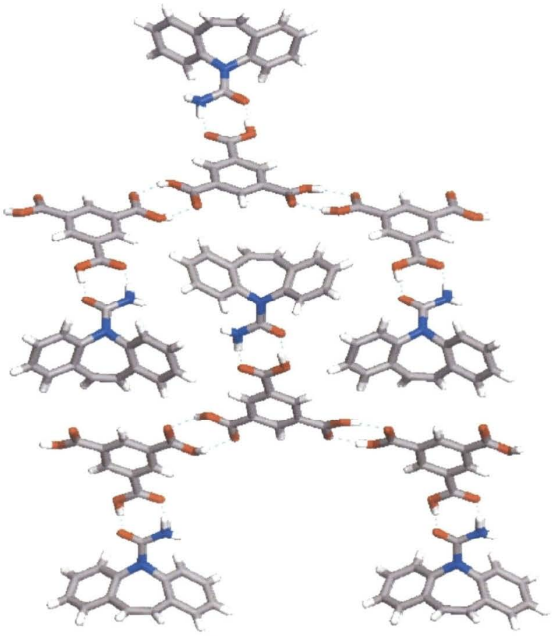

FIG. 23B

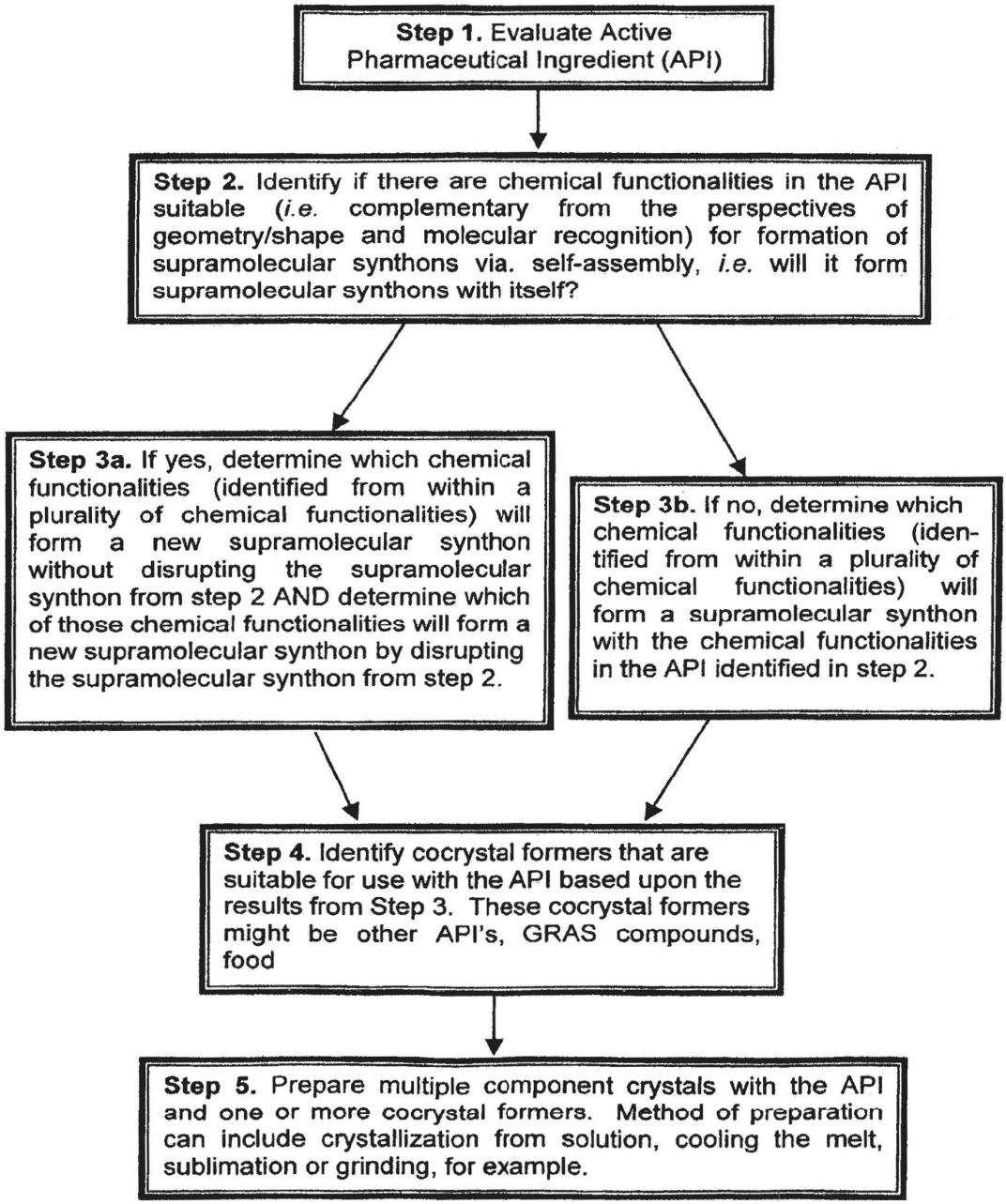
Step 1. Evaluate Active Pharmaceutical Ingredient (API)
Step 2. Identify if there are chemical functionalities in the API suitable (*i.e.* complementary from the perspectives of geometry/shape and molecular recognition) for formation of supramolecular synthons via. self-assembly, *i.e.* will it form 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

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 Ser. No. 10/378,956, filed Mar. 3, 2003, which is hereby incorporated by reference herein in its entirety, including any figures, tables, or drawings. U.S. application Ser. No. 10/378,956 claims the benefit of priority of U.S. Provisional Application Ser. No. 60/360,768, filed Mar. 1, 2002, which is hereby incorporated by reference herein in its entirety, including any figures, tables, or drawings.

BACKGROUND OF THE INVENTION

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.

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 exo-functional 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.

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.

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).

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.

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

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.

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, phenyloin, 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.

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.

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.

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.

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.

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.

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

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.

FIG. **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).

FIG. **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).

FIG. **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.

FIGS. **4**A-**4**B 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.

FIGS. **5**A-**5**B show pure phenyloin and a phenyloin/pyridone co-crystal, respectively. Phenyloin 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.

FIGS. **6**A-**6**D show supramolecular entities containing synthons and corresponding crystal structures of pure aspirin and aspirin/4,4'-bipyridine. FIGS. **3**A and **3**B show the supramolecular entity containing the synthon of pure aspirin and corresponding crystal structure, respectively. FIGS. **6**C and **6**D 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.

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

FIGS. **8**A-**8**D show supramolecular entities containing synthons and corresponding crystal structures of pure flurbiprofen [2-(2-fluoror-4-biphenyl) propionic acid] and flurbiprofen/4,4'-bipyridine. FIGS. **8**A and **8**B show the supramolecular entity containing the synthon of pure flurbiprofen and corresponding crystal structure, respectively. FIGS. **5**C and **5**D 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.

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

FIGS. **10**A and **10**B 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.

FIG. **11** shows the crystal structure of carbamazepine/nicotinamide (vitamin B3).

FIG. **12** shows the crystal structure of carbamazepine/saccharin, engineered using the carbamazepine/nicotinamide co-crystal as a model.

FIGS. **13**A-**13**C show the chemical structures of ibuprofen, flurbiprofen, and aspirin, respectively.

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

FIGS. **15**A and **15**B show the crystal structures of carbamazepine and carbamazepine/5-nitroisophthalic acid, respectively.

FIGS. **16**A and **16**B show the crystal structures of carbamazepine and carbamazepine/acetic acid.

FIGS. **17**A and **17**B show the crystal structure of carbamazepine and carbamazepine/adamantanetetracarboxylic acid.

FIGS. **18**A and **18**B show the crystal structure of carbamazepine and carbamazepine/benzoquinone.

FIGS. **19**A and **19**B show the crystal structure of carbamazepine and carbamazepine/butyric acid.

FIGS. **20**A and **20**B show the crystal structure of carbamazepine and carbamazepine/DMSO.

FIGS. **21**A and **21**B show the crystal structure of carbamazepine and carbamazepine/formamide.

FIGS. **22**A and **22**B show the crystal structure of carbamazepine and carbamazepine/formic acid.

FIGS. **23**A and **23**B show the crystal structure of carbamazepine and carbamazepine/trimesic acid.

FIG. **24** shows an exemplified scheme for preparing multiple-component phase compositions of the subject invention.

DETAILED DISCLOSURE OF THE INVENTION

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, phenyloin/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.

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.

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 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.

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.

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.

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.

By way of example, the external functionalities of ibuprofen are an isopropyl group and a carboxylic acid, as shown in FIG. **1**.

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 FIG. **2**.

Specifically, by using diamines, 2:1 binary phases of ibuprofen have been prepared, as shown in FIG. **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 FIGS. **13**A-**13**C, respectively.

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.

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.

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.

The multiple-component phase compositions can be formulated according to known methods for preparing pharmaceutically useful compositions. Such pharmaceutical 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 E W [1995] Eastone Pa., Mack Publishing Company, 19th ed.) a) 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.

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.

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 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), phenyloin and carbamazepine and appropriate molecular additives. These novel phases include both "multiple-com-

ponent 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.

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).

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.

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.

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)

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 FIG. **4**B.

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 4481 data.

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-πstacking interactions between two network bipyridines. The layers stack via π-πinteractions between the phenyl groups of the acetaminophen moieties.

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 Phenyloin: Phenyloin/Pyridine (1:1 Stoichiometry)

28 mg (0.1109 mmol) phenyloin 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 phenyloin/pyridone co-crystal, as shown in FIG. **5**B.

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, β=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, λ=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>2σ(I), and R_1=0.0816, wR_2=0.1559 for all 4154 data.

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 phenyloin-phenyloin interactions. The pyridone carbonyl also hydrogen bonds with adjacent pyridone molecules forming a one-dimensional network.

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

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

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.

X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ=1.540562), 30 kV, 15 mA). 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. 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)

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 FIG. **6**D. Alternatively, aspirin/4,4'-bipyridine (2:1 stoichiometry) can be made by grinding the solid ingredients in a pestle and mortar.

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.

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.

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}.

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.).

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)

50 mg (0.242 mmol) racemic ibuprofen and 18 mg (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 FIG. **7**D.

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.

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.

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}.

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.).

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

X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ=1.540562), 30 kV, 15 mA). 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)

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 FIG. **8**D.

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.

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.

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}.

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.).

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.

X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ=1.540562), 30 kV, 15 mA), 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)

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 FIG. **9**B.

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.

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.

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}.

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.).

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

X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ=1.540562), 30 kV, 15 mA), 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)

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 FIG. **10**B.

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.

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.

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}.

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.).

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.

X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ=1.540562), 30 kV, 15 mA). 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)

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 FIG. **11**.

Using a separate method, 25 mg (0.1058 mmol) carbamazepine and 12 mg (0.0982 mmol) nicotinamide were

ground together with mortar and pestle. The solid was determined to be 1:1 carbamazepine/nicotinamide microcrystals (XPD).

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.

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.

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.

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.).

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

X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ=1.540562), 30 kV, 15 mA). 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)

25 mg (0.1058 mmol) 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 FIG. **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).

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.

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-l with π-π interactions between the phenyl groups of the CBZ and the saccharin phenyl groups.

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}.

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.).

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.

X-ray powder diffraction: (Rigaku Miniflex Diffractometer using Cu Kα (λ=1.540562), 30 kV, 15 mA). 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)

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 FIG. **14**B.

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, λ=0.71073 Å^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).

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.

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).

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

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)

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 FIG. **15**B.

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=0.71073 Å^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.

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.

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).

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.).

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.

X-ray powder diffraction: (Rigaku Miniflex Diffractometer using CuKα (λ=1.540562), 30 kV, 15 mA). 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)

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 FIG. **16**B.

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).

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.

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).

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

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)

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 FIG. **17**B.

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=0.71073Å^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).

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.

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).

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

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)

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 FIG. **18**B.

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.

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.

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).

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

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)

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 FIG. **19**B.

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 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.

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.

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).

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

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)

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 FIG. **20**B.

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).

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.

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

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.)

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)

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 FIG. **21**B.

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).

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.

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).

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

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)

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 FIG. **22**B.

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°, 13=98.132(3)°, γ90°, 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=0.71073 Å^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).

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

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).

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

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)

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 2 mL dichloromethane. Slow evaporation of the solvent mixture yielded white starbursts of a 1:1 carbamazepine/trimesic acid co-crystal, as shown in FIG. **23**B.

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)°, 7=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.

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.

Infrared Spectroscopy: (Nicolet Avatar 320 FTIR). 3486 cm^{-1}(N—H stretch, 1° amine, CBZ); 1688 cm^{-1} (C=0, 1° amide stretch, CBZ); 1602 cm^{-1} (C=C, CBZ).

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.)

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.

X-ray powder diffraction: (Rigaku Miniflex Diffractometer using CuKα (λ=1.540562), 30 kV, 15 mA). 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.

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.

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.

The invention claimed is:

1. 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.

2. The pharmaceutical composition of claim **1**, 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.

3. The pharmaceutical composition of claim **2**, 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.

4. The pharmaceutical composition of claim **2**, 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.

5. The pharmaceutical composition of claim **1**, 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.

6. The pharmaceutical composition of claim **2**, wherein the at least one co-former participating in each supramolecular synthon is two co-formers forming a homosynthon.

7. The pharmaceutical composition of claim **1**, wherein the non-covalent bonding of said API homosynthons is carboxylic acid:carboxylic acid hydrogen bonding.

8. The pharmaceutical composition of claim **1**, wherein the non-covalent bonding of said API homosynthons is carboxamide:carboxamide hydrogen bonding.

9. 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.

10. 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.

11. The pharmaceutical composition of claim **10**, wherein the supramolecular synthon comprises a heterosynthon dimer formed by non-covalent hydrogen bonding of the API to the co-former.

12. The pharmaceutical composition of claim **10**, 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.

13. The pharmaceutical composition of claim **10**, 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.

14. The pharmaceutical composition of claim **10**, 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.

15. The pharmaceutical composition of claim **10**, 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.

16. The pharmaceutical composition of claim **10**, wherein the supramolecular synthons are non-covalently bonded to one another by non-covalent bonding to a solvent molecule.

17. The pharmaceutical composition of claim **10**, 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.

18. The pharmaceutical composition of claim **10**, wherein the first chemical functionality is a carboxamide.

19. The pharmaceutical composition of claim **10**, wherein the first chemical functionality is a carbonyl.

20. The pharmaceutical composition of claim **10**, wherein the first chemical functionality is an amine.

21. 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.

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