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(72) Inventeur/Inventor:
CHILDS, SCOTT L., US

(73) Propriétaire/Owner:
APTUIT (WEST LAFAYETTE), LLC, IN

(74) Agent: MBM INTELLECTUAL PROPERTY LAW LLP

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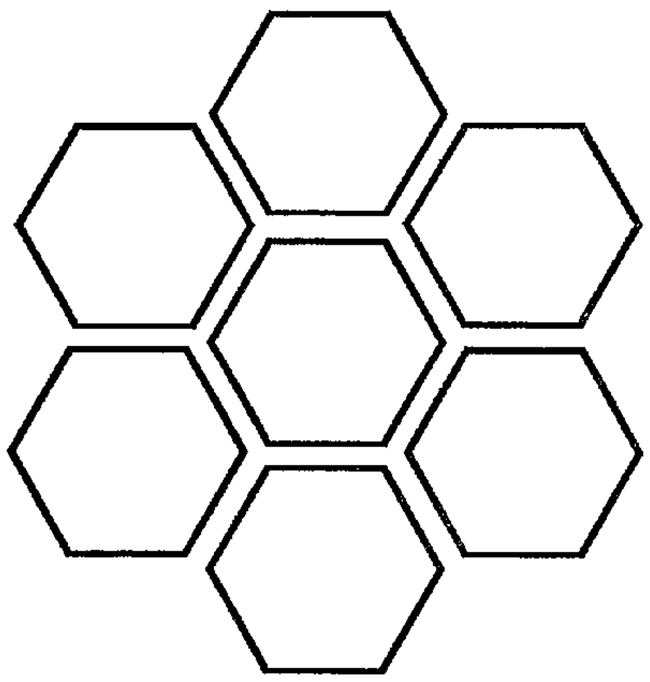
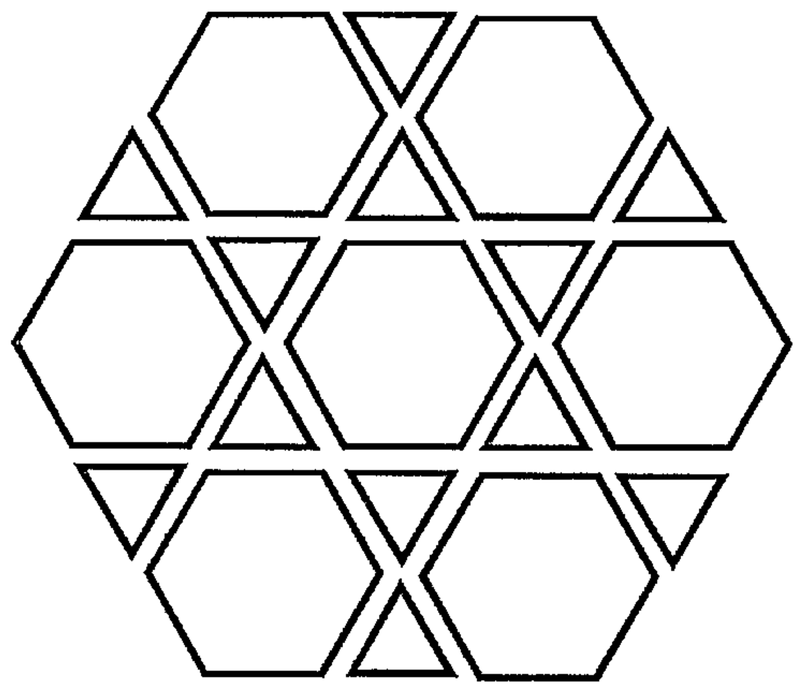
(54) Title: NOVEL COCRYSTALLIZATION OF HYDROCHLORIC ACID SALT OF AN ACTIVE AGENT



API structure

(a)



1:2 API:guest co-crystal

(b)

(57) Abrégé/Abstract:
The present disclosure relates to novel cocrystals and novel methods for cocrystallization. In particular, the disclosure includes cocrystals comprising a salt of an active agent, such as a chloride salt of an active pharmaceutical ingredient. The present disclosure also relates to methods of preparing cocrystals and methods for screening for solid state phases.

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(71) Applicant *(for all designated States except US)*: **S.S.C.I. INC.** [US/US]; 3065 Kent Avenue, West Lafayette, IN 47906 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **CHILDS, Scott, L.,** [US/US]; EmTechBio, 1256 Briarcliff Rd., Atlanta, GA 30307 (US).

(74) Agent: **HARLIN, Michael B.**; McAndrews, Held & Malloy, Ltd, 500 West Madison Street, 34th Floor, Chicago, IL 60606 (US).

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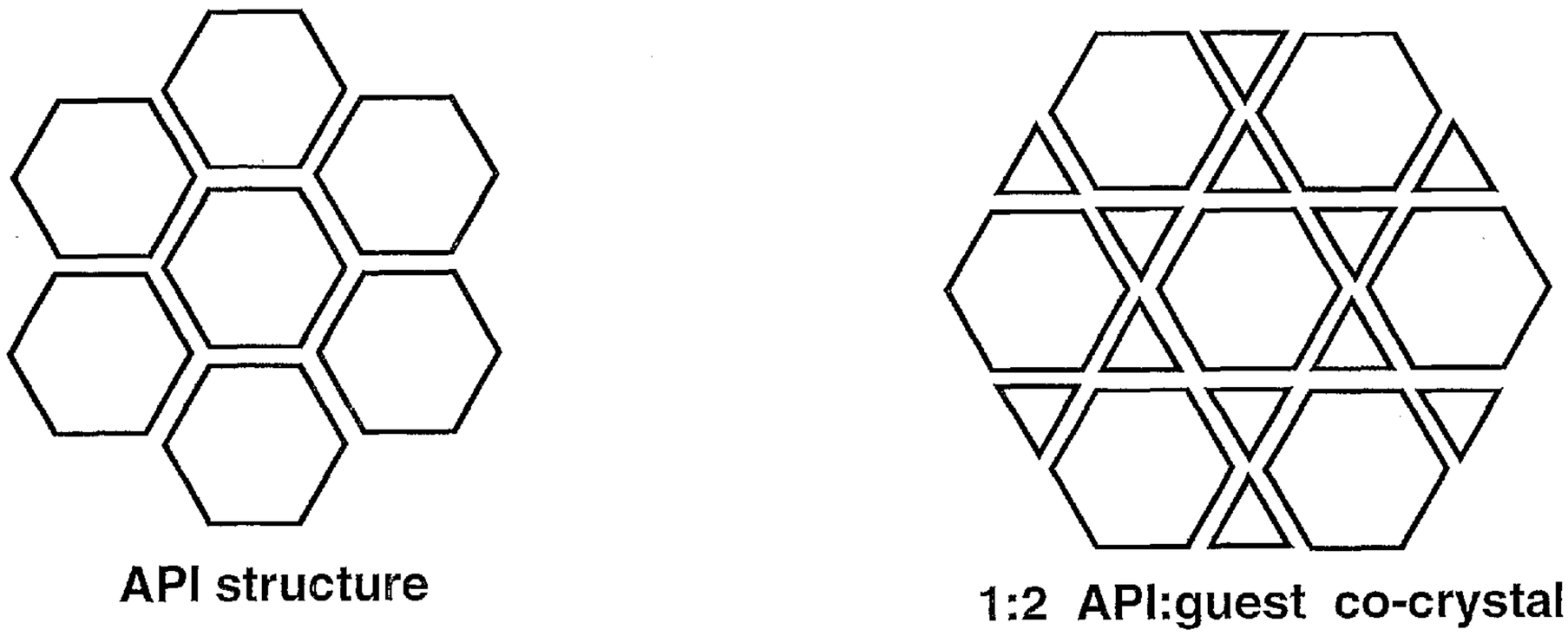

(a) (b)

(57) Abstract: The present disclosure relates to novel cocrystals and novel methods for cocrystallization. In particular, the disclosure includes cocrystals comprising a salt of an active agent, such as a chloride salt of an active pharmaceutical ingredient. The present disclosure also relates to methods of preparing cocrystals and methods for screening for solid state phases.

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NOVEL COCRYSTALLIZATION OF HYDROCHLORIC ACID SALT OF AN ACTIVE AGENT

FIELD OF THE INVENTION

The present disclosure describes cocrystals comprising active agents, especially active pharmaceutical ingredients (APIs), and methods relating to cocrystals. In particular, novel cocrystals are provided of a salt of an active pharmaceutical ingredient (such as a salt having chloride as the counterion) and a guest that forms a relatively strong interaction with the counterion. Methods are provided for searching for possible solid state phases of a sample and include solidifying the sample as a cocrystal. Methods are also provided for screening a sample for solid state phases and include solidifying the sample as a cocrystal.

BACKGROUND OF THE INVENTION

Cocrystals are crystals that contain two or more non-identical molecules. Examples of cocrystals may be found in the Cambridge Structural Database. Examples of cocrystals may also be found at Etter, Margaret C., and Daniel A. Adsmond (1990) "The use of cocrystallization as a

method of studying hydrogen bond preferences of 2-aminopyridine" *J. Chem. Soc., Chem. Commun.* **1990** 589-591, Etter, Margaret C., John C. MacDonald, and Joel Bernstein (1990a) "Graph-set analysis of hydrogen-bond patterns in organic crystals" *Acta Crystallogr., Sect. B, Struct. Sci.* **B46** 256-262, Etter, Margaret C., Zofia Urbańczyk-Lipkowska, Mohammad Zia-Ebrahimi, and Thomas W. Panunto (1990b) "Hydrogen bond directed cocrystallization and molecular recognition properties of diarylureas" *J. Am. Chem. Soc.* **112** 8415-8426.

The following articles are also referenced: Carl Henrik Görbotz and Hans-Petter Hersleth, 2000, "On the inclusion of solvent molecules in the crystal structures of organic compounds" Acta Cryst. (2000), B56, 625-534; and V.S. Senthil Kumar, Ashwini Nangia, Amy K. Katz and H.L. Carrell, 2002, "Molecular Complexes of Some Mono- and Dicarboxylic Acids with *trans*-1,4,-Dithiane-1,4-dioxide" American Chemical Society, Crystal Growth & Design, Vol. 2, No. 4, 2002.

The identification of an optimal composition, formulation, and/or solid state phase is important in the pharmaceutical field, as well as in other fields including nutraceuticals, agricultural chemicals, dyes, explosives, polymer additives, lubricant additives, photographic chemicals, and structural and electronic materials. The new methods described herein may be useful in any of these fields as well as others where solid materials are used.

SUMMARY OF THE INVENTION

As one aspect, novel cocrystals are provided. The novel cocrystals comprise one or more active agents, particularly of the salts of such active agents.

As another aspect, novel cocrystallization methods are provided which have increased probability of successful cocrystallization. A suitable method of cocrystallization may include identifying a crystal comprising a salt of an active agent, wherein the salt comprises the active agent and a negative counterion. One may identify coordination of the negative counterion (for example, its hydrogen bond interactions within that crystal). One may then select a guest to coordinate more strongly with the negative counterion than the coordination within the crystal. Based upon the evaluation of the nonbonded interactions involving one component of an active agent and/or guest, one selects another molecule or molecules or a salt that will coordinate well, or interact strongly with a hydrogen bond acceptor site that has been identified as being involved in a weak hydrogen bond. If the acceptor site has the ability to interact with stronger hydrogen bond donors, and thus form a more energetically favorable interaction, yet it is presently involved in a weak interaction, then the opportunity exists to replace the weak donor with a stronger one. For example, if a strong hydrogen bond acceptor is interacting with a weak hydrogen bond donor in a crystal, a cocrystal could be created by adding a strong hydrogen bond donor molecule to the system which would replace the weak donor and bond to the strong acceptor site in the resulting cocrystal. After the selection of a suitable guest, a solution, melt, or physical mixture comprising the active agent, the counterion, and the guest

may be prepared. The solution or melt is subjected to a crystallization process, such as evaporation, cooling, or any of the many well-known processes for forming a crystal from a solution or melt. The physical mixture can be ground to form the cocrystal. A cocrystal is formed comprising the salt of the active agent and the guest.

As another aspect, the present disclosure provides a cocrystallization method that produces a novel type of chloride salt cocrystal structure.. The method can be useful for generating beneficial solid chloride salts of APIs in cases where the chloride salt was previously disfavored.

As yet another aspect, novel forms of salts of active pharmaceutical ingredients are provided. For example, the present disclosure provides novel cocrystals of fluoxetine HCl and benzoic acid; fluoxetine HCl and succinic acid; and fluoxetine HCl and fumaric acid. Novel forms or solid state phases of active pharmaceutical ingredients may be prepared for which there are no known polymorphs, solvates or hydrates, or where such polymorphs, solvates or hydrates were disfavored.

As a further aspect, a method of modifying one or more physical properties of a drug formulation or drug composition which comprises an API, the method comprising forming a series of cocrystals of the API with a plurality of guests. The method may further comprise measuring a physical property of the cocrystal and/or adjusting the drug formulation or drug composition.

As yet another aspect, an improved method for screening or selecting the optimal solid state phase for active agents, particularly active pharmaceutical ingredients, and salts thereof, is provided. The screening

method comprises crystallizing or attempting to crystallize the free base of the active agent, a chloride salt of the active agent, and optionally other salts of the active agent, and cocrystallizing or attempting to cocrystallize the free base of the active agent, a chloride salt of the active agent, and optionally other salts of the active agent. The method may further comprise evaluating one or more properties of the solid forms, such as one or more physical properties.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1(a) and (b) illustrate a crystal structure of an active pharmaceutical ingredient and a cocrystal structure containing the same API with a guest molecule.

FIGS. 2(a) and (b) are drawings of two-dimensional and three-dimensional models of a cocrystal of fluoxetine HCl and benzoic acid (1:1).

FIGS. 3(a) and (b) are drawings of two-dimensional and three-dimensional models of a cocrystal of fluoxetine HCl and succinic acid (2:1).

FIGS. 4(a) and (b) show a two-dimensional drawing of nabumetone and 2,3-naphthalenediol and a three-dimensional model of a cocrystal of nabumetone and 2,3-naphthalenediol (1:1).

FIG. 5 shows examples of general classes of guests.

DETAILED DESCRIPTION OF THE INVENTION

The present disclosure provides a way of investigating cocrystals and a way of creating new solid state phases in which one or more active agents are cocrystallized with a guest. By cocrystallizing an active agent with a guest such as a pharmaceutically acceptable compound, one can

create new solid state phases which may have improved properties over existing solid state phases of that active agent. For example, new drug formulations comprising cocrystals of active pharmaceutical ingredients may have superior properties over existing drug formulations. The active agent and guest will vary depending on the industry. For example, in the pharmaceutical field, the active agent or guest may be an API, and the other component of the cocrystal must be a pharmaceutically acceptable compound. The present techniques are also applicable to active agents from other fields including nutraceuticals, agricultural chemicals, pigments, dyes, explosives, polymer additives, lubricant additives, photographic chemicals, and structural and electronic materials.

Broadly speaking, one aspect relates to the use of undercoordinated counterions to facilitate cocrystallization. While the inventor does not wish to be bound to theory, the inventor believes excellent cocrystals may be formed using hydrochloride salts and similar salts which are strong hydrogen bond acceptors yet contain relatively undercoordinated ions. "Undercoordinated" in this case refers to ions, for example a chloride ion, that are able to form a number of strong hydrogen bonds. An undercoordinated counterion may have hydrogen bonds within a crystal of that salt, but it could form additional hydrogen bonds in a cocrystal and/or form relatively stronger hydrogen bonds in a cocrystal with a guest. An ion is "undercoordinated" when the system is limited in the number of hydrogen bond donors that are available and bonded to the ion. In these cases, the extra hydrogen bond acceptor sites are typically filled by weakly interacting donors such as C-H groups. Chloride ions are strong

hydrogen bond acceptors in a crystal structure. In a crystal structure such as fluoxetine hydrochloride, the chloride ion coordinates to the two strong hydrogen bond donors available in the system, and the chloride ion also has three weaker CH-Cl interactions resulting in a pseudo-octahedral coordination environment. There is an opportunity for bonding with these coordination sites, by displacing the weak CH donors that the chloride has recruited to fill its coordination sphere with somewhat stronger hydrogen bond donors from a guest such as benzoic acid, succinic acid, fumaric acid, or another carboxylic acid.

It is useful in forming cocrystals to recognize that relatively weak interactions may be replaced by stronger interactions, even though those stronger interactions may be relatively weak themselves, compared to other interactions. For example, an undercoordinated chloride may have one strong hydrogen bond donor and several weak hydrogen bond donors or two strong hydrogen bond donors and several weak hydrogen bond donors. In a cocrystal, weaker interactions may be replaced by stronger interactions, although those stronger interactions may still be weaker than the strong interactions (charge-assisted hydrogen bonds) present in fluoxetine HCl crystals. The strongest interactions involving chloride ions in crystal structures of organic salts are the charge assisted hydrogen bonds that invariably form between the protonated nitrogen base and the chloride ion. The strongest interactions between neutral molecular groups and the chloride ion involve acids and the chloride ion. Carboxylic acids, for instance, have strong interactions with chloride ions. It can be seen that a combination of carboxylic acids and hydrochloride

salts of nitrogen containing bases are especially well suited to cocrystal formation (as demonstrated by the examples included). Furthermore, it can be anticipated that different combinations of these elements could lead to other cocrystals. For example, the active molecule of interest may contain either the neutral carboxylic acid moiety or the protonated nitrogen. The potential exists to cocrystallize an API having a neutral carboxylic acid moiety with a guest that is a hydrochloride salt of a nitrogen-containing organic base.

It is further contemplated that the nature of the protonated nitrogen base will affect the potential for cocrystallization. Numerous strong hydrogen bond donor groups will compete with the carboxylic acid guest for the open acceptor sites on the chloride ion. In order to favor cocrystal formation, the nitrogen base is preferably a tertiary amine because this presents a situation where only one strong charged hydrogen bond donor exists and thus will only occupy one site on the chloride acceptor. Additionally, systems that have only this one tertiary amine and no other strong donors present an especially favorable system for potential cocrystallization. Protonated secondary amines with two N-H donor groups are also favored, although protonated primary amines may also be used. Special consideration must be taken for systems with additional strong hydrogen bond donor and acceptor sites in order to determine the potential for cocrystallization and the optimal guest molecule type for cocrystallization. The potential for cocrystallization involving a carboxylic acid and a hydrochloride salt may be reduced as the number of available strong donors in the system is increased. Additional guidance as to evaluating

undercoordination may be found in the inventor's prior work,

particularly in its discussion of nonbonded motifs: Scott L. Childs, "Nonbonded Interactions In Molecular Crystal Structures", Emory Univ., USA, available from UMI, Order No. DA3009424 (288 pp.), Dissertation Abstract Int. Ref. B2001, 62(3), 1394. In some circumstances, the undercoordination can be determined by measuring distances, comparing profiles in the Cambridge Structural Database, measuring the pKa of the donors and acceptors, or evaluating the ratio of strong hydrogen bond donors to available acceptors. Other crystal engineering theories may also be used.

The formation of cocrystals is very unpredictable. It is difficult to foresee structural changes as a function of changes in molecular substitution patterns or in molecular geometry. However, the present disclosure provides greater predictability and better probability of success in designing and forming cocrystals.

The present techniques may be employed to generate a wide variety of cocrystals of active agents and guests. For example, the present techniques may be used to generate cocrystals of a salt of an active agent, such as a salt of an active pharmaceutical ingredient, with a neutral guest. Alternatively, a cocrystal of a neutral or zwitterionic active agent (or a salt of an active agent) may be generated with a guest salt, which includes a positive ion and a negative ion of its own. Where the active agent is provided in a salt, it may be positively or negatively charged and have a negative or positive counterion. As an example, for fluoxetine HCl, the active agent fluoxetine is positively charged by virtue of accepting a proton from HCl

to form a protonated amine, and chloride is present as a negative counterion. Furthermore, some of the present methods may be employed with a neutral or zwitterionic active agent to form a cocrystal with a neutral guest or ionic guest.

The present techniques provide an opportunity to create a stable solid state phase of a hydrochloride salt of an API that was previously found to have properties that were unsuitable for development. Opportunities for continued development in such a situation have often relied on the fortuitous formation of a stable hydrate or solvate, but the present techniques present the ability to systematically examine alternative formulations of the hydrochloride salt by cocrystallizing the hydrochloride salt of the API with appropriate guest molecules.

Cocrystallization may be an attractive technique for salts of APIs that have been rejected due to problems relating to physical properties. Since cocrystals may have different physical properties than the individual components, APIs with unfavorable physical properties can be cocrystallized with suitable guest molecules and the physical properties of the resulting crystalline solids can be evaluated.

The cocrystals of fluoxetine HCl provide examples of the modification of a physical property (solubility) of an API salt. Cocrystals of fluoxetine HCl:benzoic acid are less soluble and have a lower dissolution rate than crystals of fluoxetine HCl, while cocrystals of fluoxetine HCl:succinic acid are more soluble and have a faster dissolution rate than crystals of fluoxetine HCl.

Other physical properties of APIs or their salts that may be modified by forming a cocrystal include: melting

point, density, hygroscopicity, crystal morphology, loading volume, compressibility, and shelf life. Furthermore, other properties such as bioavailability, toxicity, taste, physical stability, chemical stability, production costs, and manufacturing method may be modified by the use of the present cocrystallization techniques.

An active agent can be screened for possible cocrystals where polymorphic forms, hydrates or solvates are especially problematic. A neutral compound that can only be isolated as amorphous material could be cocrystallized. Forming a cocrystal may up-grade the performance of a drug formulation of an active pharmaceutical ingredient by changing physical properties. Some APIs are problematic during wet granulation and compression stages. A bioequivalent cocrystal could rectify this problem.

A cocrystal can be used to isolate or purify a compound during manufacturing. If it is desirable to identify all of the solid state phases of an active pharmaceutical ingredient, then cocrystallization may be particularly desirable.

The present techniques provide new methods of developing and screening active pharmaceutical ingredients. Non-toxic cocrystalline forms of neutral active pharmaceutical ingredients may be prepared, screened, tested, and commercialized. Screening based on cocrystal formation is equivalent in many respects to a salt-screen for neutral APIs. Furthermore, new types of HCl salt structures may be prepared. The properties of hydrochloride salts can be tuned and perfected. New, unique, stable, and marketable phase of hydrochloride salts

may be prepared. One can choose whether to make the formulation more soluble or less soluble.

As another aspect, the present techniques may also be used to remove or reduce the water of hydration, and/or to prepare a cocrystal substantially free of water of hydration. A hydrate may be viewed as a cocrystal having water as the guest. Water and guest acids perform a similar role in the stabilization of the crystal structure. In fact, about 28% of the hydrochloride salts of API in the Cambridge Structure Database are hydrates, compared to about 8% of all other organic structures. This indicates an affinity for hydration. The present techniques both capitalize and rectify this affinity, in that an affinity for cocrystallization (as evidence by hydration) is likely indicated, and this affinity for cocrystallization may be employed for the formation of cocrystals with a suitable guest, such as an acid, for example a carboxylic acid. Indeed, in many cocrystals, an acid may have stronger interactions than water molecules and may displace the water of hydration during the formation of the cocrystal. Accordingly, the present techniques provide a method of preparing a cocrystal from a hydrate. A hydrate of a salt is provided, and the hydrate comprises water of hydration. A guest is selected to coordinate with the counterion. Preferably, the guest coordinates more strongly with the counterion than the solvent does. A solution, melt or physical mixture is prepared which comprises the hydrate and the guest. The solution or melt is subjected to a crystallization process, or the physical mixture is subjected to grinding, and a cocrystal comprising the salt of the active agent and the guest is formed, and the salt comprises the active agent and a counterion. Similarly,

the present techniques provide a method of preparing a cocrystal from a solvate. A solvate of a salt is provided, and the solvate comprises solvent molecules coordinated with the salt. A guest is selected to coordinate with the counterion. Preferably, the guest coordinates more strongly with the counterion than the solvent does. A solution, melt or physical mixture is prepared comprising the solvate and the guest. The solution or melt is subjected to a crystallization process, or the physical mixture is subjected to grinding, and a cocrystal comprising the salt of the active agent and the guest is formed. The salt comprises the active agent and a counterion.

FIGS. 2(a) and (b) are drawings of two-dimensional and three-dimensional models of a cocrystal of fluoxetine HCl and benzoic acid (1:1). FIG. 2(a) shows a two-dimensional model in which the chloride ion interacts with the hydrogens of the amine group of fluoxetine and of the hydroxyl group of benzoic acid. Through these interactions, which may be characterized as hydrogen bonding, fluoxetine hydrochloride and benzoic acid form a supramolecular structure that may be the basis of a cocrystal. FIG. 2(b) shows a three-dimensional model of the supramolecular organization of fluoxetine hydrochloride and benzoic acid.

FIG. 3(a) and (b) are drawings of two-dimensional and three-dimensional models of a cocrystal of fluoxetine HCl and succinic acid (2:1). FIG. 3(a) shows a two-dimensional model in which the chloride ion interacts with the hydrogens of the ammonium group of fluoxetine and of the hydroxyl group of succinic acid. Through these interactions, which may be characterized as hydrogen

bonding, two molecules of fluoxetine hydrochloride and one molecule of succinic acid form a supramolecular structure that may be the basis of a cocrystal. FIG. 3(b) shows a three-dimensional model of the supramolecular organization of the molecules of fluoxetine hydrochloride and succinic acid.

FIGS. 4(a) and (b) show a two-dimensional drawing of nabumetone and 2,3-naphthalenediol and a three-dimensional model of a cocrystal of nabumetone and 2,3-naphthalenediol (1:1).

Active agent

The active agent is the molecule whose activity is desirable or the object of interest. It is contemplated that one or more active agents may be employed in a cocrystal, according to any of the present techniques. For example, where the active agent is an active pharmaceutical ingredient, the pharmaceutical activity of the active agent is desirable. Other active agents may be nutraceuticals, agricultural chemicals, pigments, dyes, explosives, polymer additives, lubricant additives, photographic chemicals, or structural and electronic materials.

The active agent may be provided as a salt. It is contemplated that one or more salts may be employed in a cocrystal, according to any of the present techniques. The salt may be prepared from the active agent or obtained from a commercial source. Hydrochloride salts of active pharmaceutical ingredients, especially of amine APIs, are especially preferred in the pharmaceutical industry.

In general, it is contemplated that the present techniques will have particularly good results as applied to amine HCl salts as well as other ammonium salts as

described in more detail herein. In ammonium acid salts, the active agent has at least one amine moiety which is relatively basic (at least one relatively basic nitrogen), and a salt is formed with an acid that reacts with the amine moiety. Cocrystals may be then formed between the ammonium salts and guests which act as hydrogen-bond donors to the salts. Cocrystals may be formed of chloride salts of APIs, for example buspirone hydrochloride, fluoxetine hydrochloride, and metformin hydrochloride.

The present cocrystals may comprise salts other than chloride salts -- the hydrochloride API salts that are listed above are only a sampling of the relevant compounds because the starting material need not be a known hydrochloride. Indeed, many relevant APIs are salts that are not HCl salts because the HCl salt was not believed to be an appropriate material and a different salt was commercialized instead. The present techniques may enable one to employ an HCl salt of an API that is marketed as another type of salt. Alternatively, it may be desirable to employ a salt other than an HCl salt, by replacing the HCl or by forming a salt comprising an active agent that acts as a base with an acid other than HCl. The following acids provide anionic counterions that would be used to replace chlorine. These are relatively strong acids, and include but are not limited to mineral acids, and the carboxylic acid guest is expected to form one or more hydrogen bonds with a hydrogen bond acceptor on the anionic counterion. The list is the conjugate acid that would react with a basic active agent to form a salt:

sulfuric acid

phosphoric acid

hydrobromic acid

nitric acid

pyrophosphoric acid

methanesulfonic acid

thiocyanic acid

naphthalene-2-sulfonic acid

1,5-naphthalenedisulfonic acid

cyclamic acid

p-toluenesulfonic acid

maleic acid

L-aspartic acid

2-hydroxy-ethanesulfonic acid

glycerophosphoric acid

ethanesulfonic acid

hydroiodic acid

The present techniques also extend beyond salts as starting materials and also include many weak bases that may have been marketed as neutral forms because the known salts did not have appropriate properties. These salts could be revisited and attempts could be made to cocrystallize the HCl salt. For example, a drug formulation marketed as a tartrate salt of an API could be reformulated by cocrystallizing the HCl salt of the active molecule with an appropriate guest molecule. Thus, cocrystallization could make a useful HCl cocrystal out of the API that is currently marketed as a tartrate, sulfate, or other salt formulation. For this reason the present disclosure includes APIs that are not HCl salts as starting materials.

Furthermore, the present techniques relate to salts other than chloride salts. It is contemplated that hydrobromide salts and sodium salts of APIs may especially benefit from the present techniques, since they form

relatively strong nonbonded interactions. For example, the hydrobromide salts citalopram hydrobromide and galantamine hydrobromide are contemplated for cocrystallization with benzoic acid, succinic acid, and other guests compatible with hydrochloride salts.

The present techniques may be employed to form cocrystals of sodium salts of APIs such as, for example, naproxen sodium, tolmetin sodium, and warfarin sodium. When a sodium salt (or other salt of an API having a positive counterion) is employed, different guests are expected to be suitable for cocrystallization than when a hydrochloride salt (or other anionic salt) of an API is employed.

Anions and Cations

As one aspect, the active agent is provided as a salt. A salt of the active agent is formed. Alternatively or additionally, the guest is provided as a salt or a salt of the guest is formed. The salt may comprise the active agent and a counterion that is either a cation or an anion. Among the preferred cations (including cations as well as compounds that can form cations) are aluminum, ammonium, benzathine, calcium, diethanolamine, diethylamine, dimeglumine, disodium, lithium, lysine, magnesium, meglumine, potassium, sodium, and zinc. Among the preferred anions are acetate, L-aspartate, besylate, bicarbonate, carbonate, D-camsylate, L-camsylate, citrate, edisylate, fumarate, gluconate, hydrobromide/bromide, hydrochloride/chloride, D-lactate, L-lactate, DL-lactate, D,L-malate, L-malate, mesylate, pamoate, phosphate, succinate, sulfate, D-tartrate, L-tartrate, D,L-tartrate, meso-tartrate, benzoate, gluceptate, D-glucuronate,

hybenzate, isethionate, malonate, methylsufate, 2-napsylate, nicotinate, nitrate, orotate, stearate, tosylate, acefyllinate, aceturate, aminosalicylate, ascorbate, ascorbate, borate, butyrate, camphorate, camphocarbonate, decanoate, hexanoate, cholate, cypionate, dichloroacetate, edentate, ethyl sulfate, furate, fusidate, galactarate (mucate), galacturonate, gallate, gentisate, glutamate, glutamate, glutarate, glycerophosphate, heptanoate (enanthate), hydroxybenzoate, hippurate, phenylpropionate, iodide, xinafoate, lactobionate, laurate, maleate, mandelate, methanesufonate, myristate, napadisilate, oleate, oxalate, palmitate, picrate, pivalate, propionate, pyrophosphate, salicylate, salicylsulfate, sulfosalicylate, sulfosalicylate, tannate, terephthalate, thiosalicylate, tribrophenate, valerate, valproate, adipate, 4-acetamidobenzoate, camsylate, octanoate, estolate, esylate, glycolate, thiocyanate, and undecylenate.

When a metal cation is employed as a counterion of the active agent, the interaction between guest and cation is not a hydrogen bond but rather is an intermolecular interaction between an electron rich group such as a carbonyl and the metal cation. This interaction is often not as strong as a hydrogen bond, but is still a favorable interaction and thus can contribute to the stabilization of a cocrystal.

The HCl salt of an active pharmaceutical ingredient is especially preferred to create a new type of cocrystal. In this type of solid state phase, one can cocrystallize the HCl salt with a neutral guest molecule. By doing this one can create solid state phases with specific properties. For instance one can make a solid comprising an active

pharmaceutical ingredient having greater or lesser intrinsic solubility and/or a faster or slower dissolution rate, depending on the guest compound that is chosen.

Guests

The guest is present in order to form the cocrystal with the active agent. It is contemplated that one or more guests may be employed in a cocrystal, according to any of the present techniques. Accordingly, the guest is not required to have an activity of its own, although it may have some activity that does not overly derogate from the desired activity of the active agent. In some situations, the guest may have the same activity as or an activity complementary to that of the active agent. The guest may be another API. For example, some guests may facilitate the therapeutic effect of an active pharmaceutical ingredient. For pharmaceutical formulations, the guest may be any pharmaceutically acceptable molecule(s) that forms a cocrystal with the API or its salt. The RTECS database is a useful source for toxicology information, and the GRAS list contains about 2500 relevant compounds.

The guest may be neutral (such as benzoic acid and succinic acid in the examples below) or ionic (such as sodium benzoate or sodium succinate). Neutral guests are nonionic guests. Ionic guests are compounds or complexes having ionic bonds. FIG. 5 shows several general classes of guests (organic bases, organic salts, alcohols & aldehydes, amino acids, sugars, ionic inorganics, aliphatic esters & ketones, organic acids, and aromatic esters & ketones).

The guest may be an acid that forms hydrogen bonds with the chloride (or other anion). For example, suitable

guests which are acids include (but not are not limited to):

ascorbic acid
glucoheptonic acid
sebacic acid
alginic acid
cyclamic acid
ethane-1,2-disulfonic acid
2-hydroxyethanesulfonic acid
2-oxo-glutaric acid
naphthalene-1,5-disulfonic acid
nicotinic acid
pyroglutamic acid
4-acetamidobenzoic acid

Table 1 sets forth a group of presently preferred guests. It is contemplated that the guests set forth in the Table may be arranged in subgroups based upon molecular structure and/or physiological effect. Furthermore, the foregoing list is intended to provide a written description of any sublist that omits one or more guests.

Table 2 sets forth another group of preferred guests. It is contemplated that the guests set forth in the Table may be arranged in subgroups based upon molecular structure and/or physiological effect. Furthermore, the foregoing list is intended to provide a written description of any sublist that omits one or more guests.

Table 3 sets forth the group comprising molecules believed at present to be suitable guests. It is contemplated that the guests set forth in the Table may be arranged in subgroups based upon molecular structure and/or physiological effect. Furthermore, the foregoing list is

intended to provide a written description of any sublist that omits one or more guests.

Ionic guests are salts themselves, and may be formed from bases and acids prior to being used to form cocrystals. For example, the following bases and acids may be reacted to form ionic guests:

Bases

Ammonia

L-Arginine

Benethamine

Benzathine

Betaine

Calcium Hydroxide

Choline

Deanol

Diethanolamine

Diethylamine

2-(Diethylamino)ethanol

2-Aminoethanol

Ethylenediamine

N-Methylglucamine

Hydrabamine

1H-Imidazole

Lysine

Magnesium Hydroxide

Morpholine

4-(2-Hydroxyethyl)Morpholine

Piperazine

Potassium Hydroxide

Pyrrolidine

1-(2-Hydroxyethyl)Pyrrolidine

Sodium Hydroxide

Triethanolamine

Tromethamine

Zinc Hydroxide

Acids

(+)-L-Tartaric Acid

1,2,2-Trimethyl-1,3-cyclopentanedicarboxylic Acid

10-Undecylenic Acid

1-Hydroxy-2-naphthoic Acid

(+)-Camphor-10-sulfonic Acid

2,5-Dihydroxybenzoic Acid

2-Furancarboxylic Acid

2-Mercaptobenzoic Acid

3-Cyclopentylpropionic Acid

3-Phenylpropionic Acid

4-Aminosalicylic Acid

4-Hydroxybenzoic Acid

Acetic Acid

Adipic Acid

alpha-Hydroxypropionic Acid

Benzenesulfonic Acid

Benzoic Acid

Carbonic Acid

Cholic Acid

Citric Acid

(-)-D-Tartaric Acid

(+)-D-Camphoric Acid

(+)-D-Malic Acid

(+)-L-Malic Acid

2,2-Dichloroacetic Acid

DL-10-Camphorsulfonic Acid

DL-Glutamic Acid

DL-Malic Acid

DL-Tartaric Acid

Dodecylsulfuric Acid

Ethanesulfonic Acid

Ethylenediaminetetraacetic Acid

Ethylsulfuric Acid

Fumaric Acid

Galactaric Acid

Gallic Acid

Gluconic Acid

Glutaric Acid

Glycolic Acid

Hippuric Acid

Hydriodic Acid

Hydrobromic Acid

Hydrochloric Acid

(-)-L-Apple Acid

(+)-L-Lactic Acid

(+)-L-Tartaric Acid

D,L-Lactic Acid

Lactobionic Acid

L-Aspartic Acid

Lauric Acid

L-Glutamic Acid

Maleic Acid

(-)-L-Malic Acid

Malonic Acid

D,L-Mandelic Acid

Methanesulfonic Acid

Naphthalene-2-sulfonic acid

n-Butyric Acid

n-Decanoic Acid

n-Hexanoic Acid

Nitric acid

n-Tetradecanoic Acid

Octanoic Acid

Oleic Acid

Orotic Acid

Orthoboric Acid

Oxalic Acid

4-Acetamidobenzoic Acid

Palmitic Acid

Pamoic Acid

Phosphoric Acid

Picric Acid

Pivalic Acid

Propionic Acid

p-Toluenesulfonic Acid

Pyrophosphoric Acid

Salicylic Acid

Stearic Acid

Succinic Acid

Sulfosalicylic Acid

Sulfuric Acid

Terephthalic Acid

Thiocyanic Acid

Valeric Acid

Valproic Acid

Typically, suitable guests will have complementary ability to noncovalently bond to the active agent or its salt, for example the ability to form hydrogen bonds with the active agent or its salt. Suitable guests for active agents having negative counterions include, but are not limited to, compounds having alcohol, ketone, ester, and/or

carboxylic acid functionalities. Suitable guests may include organic acids, organic bases, organic salts, alcohols, aldehydes, amino acids, sugars, ionic inorganic compounds, aliphatic esters and ketones, and aromatic esters and ketones.

Among the presently preferred neutral guests are those which are not liquids at room temperature. Also among the presently preferred neutral guests are carboxylic acids having at least three carbon atoms, alternatively at least four carbon atoms, and which do not form solvates. For example, if the following acids were combined with active agents, the combination would more properly be considered a solvate than a cocrystal: acetic acid, propionic acid, and butyric acid. However, in certain embodiments of the present invention (for example, in certain cocrystals, cocrystallization methods, and screening methods), the use of solvents and solvates may still be desirable, and the use of solvents and solvates is not excluded from the scope of any cocrystal or method except where explicitly stated.

Detection of Cocrystals

Cocrystals may be detected by x-ray diffraction analysis or other suitable techniques. The observation of physical properties of a solid (particularly its melting point) which differ from the physical properties of the starting materials and the polymorphs and/or solvates and/or hydrates of the starting materials, is an indicator that a cocrystal has been formed.

A method of crystal engineering is described. An active pharmaceutical ingredient such as fluoxetine

hydrochloride is recognized as possessing a strong hydrogen bond acceptor. The API is screened against a library of strong hydrogen bond donors or other possible guest compounds. Such a library is selected and ordered based upon nontoxicity, physical property, and the availability and geometric arrangement of hydrogen bond donors that are complementary to the API.

The results from a cocrystal screen of fluoxetine hydrochloride demonstrate a new class of cocrystal that is broadly applicable to a wide variety of hydrochloride salts of APIs. This new approach is a general method that allows creation of cocrystals starting with the hydrochloride salt of the API. Starting with the hydrochloride retains the advantages of the salt, yet one is still able to use the cocrystal method to alter the physical properties of the resulting solid by adding guest molecules.

Example 1: Cocrystallization of fluoxetine HCl and benzoic acid

Cocrystals of fluoxetine HCl:benzoic acid were formed using the following procedures. In one preparation, a 505 mg sample of fluoxetine HCl and 178 mg of benzoic acid were dissolved with heating in 5 mL of acetonitrile. The solution was allowed to crystallize in a small crystallization dish. Well-formed crystalline material formed within 7 minutes. This material was isolated on filter paper and dried in the air to yield 546 (80%) of fluoxetine HCl:benzoic acid (1:1) cocrystal.

In another preparation, a 5.00g sample of fluoxetine HCl and 1.76 g of benzoic acid were dissolved in 50 mL of acetonitrile with heating. The solution was allowed to crystallize in a large evaporating dish. The resulting

solid was isolated on filter paper and dried in the air to yield 5.40 g (92%) of fluoxetine HCl:benzoic acid (1:1) cocrystal.

The cocrystal had a relatively slow dissolution rate and lower water solubility. The measured melting point was 134ºC +/- 2ºC for the cocrystal. The cocrystal is expected to have a good toxicology profile, since benzoic acid is known to be safe and appears on the GRAS list from the U.S. Food and Drug Administration.

The resulting cocrystal is a ternary system comprising the protonated API base, the chloride ion, and the neutral guest molecule.

The present inventor believes there are no known solvates or hydrates of fluoxetine hydrochloride. Thus, the formation of a cocrystal of fluoxetine hydrochloride constitutes a surprising achievement and provides a unique composition.

Example 2: Cocrystallization of fluoxetine HCl and succinic acid

Cocrystals of fluoxetine HCl and succinic acid were prepared as follows. In one preparation, a 458 mg sample of fluoxetine HCl was dissolved in 8 mL of acetonitrile by heating the solution gently. A 78 mg sample of succinic acid was added to the warm solution and dissolved. The solution was allowed to evaporate rapidly in a crystallization dish. Well-formed crystals as blocks formed as the solvent evaporated over 8 minutes. The product was collected on filter paper and dried to yield 401 mg of fluoxetine HCl:succinic acid (2:1) cocrystal (75% yield).

In another preparation, a 5.00 g sample of fluoxetine HCl and 0.85 g of succinic acid were dissolved in acetonitrile with heating. The solution was allowed to crystallize in an open evaporating dish over a 15 minute period. The solid material was isolated on filter paper and dried to yield 5.40 g (92% yield) of fluoxetine HCl:succinic acid (2:1) cocrystal.

The measured melting points were 158ºC for fluoxetine HCl, 184ºC for succinic acid, and 137ºC for the cocrystal. The cocrystal is expected to have a good toxicology profile, since succinic acid is known to be safe and appears on the Generally Recognized As Safe ("GRAS") list from the U.S. Food and Drug Administration.

Example 3: Cocrystallization of nabumetone and 2,3-naphthalenediol

As a demonstrative example, a cocrystal comprising a neutral API is described in this example. Cocrystals of nabumetone (a neutral API) and 2,3-naphthalenediol were prepared as follows. A 4.01 g sample of 2,3-naphthalenediol and 5.7 g of nabumetone were dissolved in 50 mL of nitromethane with heating. A solid was formed as the solution cooled and was allowed to stand overnight. The solid was filtered from the remaining solvent and dried in the air to yield 6.61 g (68%) of nabumetone:2,3-naphthalenediol (1:1) cocrystal.

The resulting cocrystal had a 1:1 molar ratio of nabumetone to 2,3-naphthalienediol. The measured melting points were 80ºC for nabumetone, 162ºC for 2,3-naphthalienediol, and 98ºC for the cocrystal. The cocrystal is expected to have a relatively poor toxicology profile. However, this example demonstrates one basis for

the selection of guest molecules: molecular structural similarities. In this case the molecular recognition of the naphthalene moieties of the API and the guest contribute to the stability of the cocrystal. In addition, the stronger alcohol to ketone hydrogen bonds formed by the cocrystal contribute to the stability of the cocrystal. The only hydrogen bond donors available in the API crystal structure are weak C-H groups. The stronger hydrogen bond donors on the guest molecule are able to form stronger intermolecular interaction between the API and guest, compared to the interactions between molecules of the API.

Example 4: Crystal Structure Analysis of fluoxetine HCl:benzoic acid cocrystal (1:1)

A suitable cocrystal of fluoxetine HCl:benzoic acid (1:1) was coated with Paratone N oil, suspended in a small fiber loop and placed in a cooled nitrogen gas stream at 100 K on a Bruker D8 SMART APEX CCD sealed tube diffractometer with graphite monochromated MoK_α (0.71073Å) radiation. Data were measured using a series of combinations of phi and omega scans with 10 second frame exposures and 0.3° frame widths. Data collection, indexing and initial cell refinements were all carried out using SMART software (SMART Version 5.624, **2000**, Bruker AXS, Inc., Analytical X-ray Systems, 5465 East Cheryl Parkway, Madison WI 53711-5373). Frame integration and final cell refinements were done using SAINT software (SAINT Version 6.02, **2000**, Bruker AXS, Inc., Analytical X-ray Systems, 5465 East Cheryl Parkway, Madison WI 53711-5373). The final cell parameters were determined from least-squares refinement on 5435 reflections. The SADABS program was used

to carry out absorption corrections (SADABS Version 2.03, **2001**, George Sheldrick, University of Göttingen).

The structure was solved using Direct methods and difference Fourier techniques (SHELXTL V5.10, **2000**, Bruker AXS, Inc., Analytical X-ray Systems, 5465 East Cheryl Parkway, Madison WI 53711-5373). Hydrogen atoms were placed their expected chemical positions using the HFIX command and were included in the final cycles of least squares with isotropic U_{ij} 's related to the atom's ridden upon. The C-H distances were fixed at 0.93 Å(aromatic and amide), 0.98 Å (methine), 0.97 Å (methylene), or 0.96 Å (methyl). All non-hydrogen atoms were refined anisotropically. Scattering factors and anomalous dispersion corrections are taken from A. J. C. Wilson (ed), *International Tables for X-ray Crystallography, Volume C.* Kynoch, Academic Publishers, Dordrecht, **1992**, Tables 6.1.1.4 (pp. 500-502) and 4.2.6.8 (pp. 219-222). the *International Tables for X-ray Crystallography*. Structure solution, refinement, graphics and generation of publication materials were performed by using SHELXTL, V5.10 software. Additional details of data collection and structure refinement are given in Table 4 which follows.

Example 5: Crystal Structure Analysis of fluoxetine HCl:succinic acid cocrystal (2:1)

A suitable cocrystal of fluoxetine HCl-succinic acid (2:1) was coated with Paratone N oil, suspended in a small fiber loop and placed in a cooled nitrogen gas stream at 100 K on a Bruker D8 SMART APEX CCD sealed tube diffractometer with graphite monochromated MoK_α (0.71073Å) radiation. Data were measured using a series of

combinations of phi and omega scans with 10 second frame exposures and 0.3° frame widths. Data collection, indexing and initial cell refinements were all carried out using SMART software (SMART Version 5.624, **2000**, Bruker AXS, Inc., Analytical X-ray Systems, 5465 East Cheryl Parkway, Madison WI 53711-5373). Frame integration and final cell refinements were done using SAINT software (SAINT Version 6.02, **2000**, Bruker AXS, Inc., Analytical X-ray Systems, 5465 East Cheryl Parkway, Madison WI 53711-5373). The final cell parameters were determined from least-squares refinement on 5435 reflections. The SADABS program was used to carry out absorption corrections (SADABS Version 2.03, **2001**, George Sheldrick, University of Göttingen).

The structure was solved using Direct methods and difference Fourier techniques (SHELXTL V5.10, **2000**, Bruker AXS, Inc., Analytical X-ray Systems, 5465 East Cheryl Parkway, Madison WI 53711-5373). Hydrogen atoms were placed their expected chemical positions using the HFIX command and were included in the final cycles of least squares with isotropic U_{ij} 's related to the atom's ridden upon. The C-H distances were fixed at 0.93 Å(aromatic and amide), 0.98 Å (methine), 0.97 Å (methylene), or 0.96 Å (methyl). All non-hydrogen atoms were refined anisotropically. Scattering factors and anomalous dispersion corrections are taken from A. J. C. Wilson (ed), *International Tables for X-ray Crystallography, Volume C.* Kynoch, Academic Publishers, Dordrecht, **1992**, Tables 6.1.1.4 (pp. 500-502) and 4.2.6.8 (pp. 219-222). Structure solution, refinement, graphics and generation of publication materials were performed by using SHELXTL, V5.10 software. Additional details of data collection and structure refinement are given in Table 5 which follows.

Example 6: Crystal Structure Analysis of nabumetone: 2,3-naphthalenediol cocrystal (1:1)

A suitable cocrystal of nabumetone:2,3-naphthalenediol (1:1) was coated with Paratone N oil, suspended in a small fiber loop and placed in a cooled nitrogen gas stream at 100 K on a Bruker D8 SMART 1000 CCD sealed tube diffractometer with graphite monochromated CuK_α (1.54178 Å) radiation. Data were measured using a series of combinations of phi and omega scans with 10 second frame exposures and 0.3° frame widths. Data collection, indexing and initial cell refinements were all carried out using SMART software (SMART Version 5.55, **2000**, Bruker AXS, Inc., Analytical X-ray Systems, 5465 East Cheryl Parkway, Madison WI 53711-5373). Frame integration and final cell refinements were done using SAINT software (SAINT Version 6.02, **1999**, Bruker AXS, Inc., Analytical X-ray Systems, 5465 East Cheryl Parkway, Madison WI 53711-5373). The final cell parameters were determined from least-squares refinement on 2869 reflections.

The structure was solved using Direct methods and difference Fourier techniques (SHELXTL V5.10, **1997**, Bruker AXS, Inc., Analytical X-ray Systems, 5465 East Cheryl Parkway, Madison WI 53711-5373). Hydrogen atoms were placed their expected chemical positions using the HFIX command and were included in the final cycles of least squares with isotropic U_{ij} 's related to the atom's ridden upon. The C-H distances were fixed at 0.93 Å(aromatic and amide), 0.98 Å (methine), 0.97 Å (methylene), or 0.96 Å (methyl). All non-hydrogen atoms were refined anisotropically. Scattering factors and anomalous

dispersion corrections are taken from A. J. C. Wilson (ed), *International Tables for X-ray Crystallography, Volume C.* Kynoch, Academic Publishers, Dordrecht, **1992**, Tables 6.1.1.4 (pp. 500-502) and 4.2.6.8 (pp. 219-222). Structure solution, refinement, graphics and generation of publication materials were performed by using SHELXTL, V5.10 software. Additional details of data collection and structure refinement are given in Table 6 which follows.

Example 7: Cocrystals of Active Agent salts and guests

The experiments of Examples 1 and 2 are repeated, using conditions similar to those of those previous Examples, with each possible combination of the salts of active agents and guests identified earlier in this disclosure. Cocrystals are formed which have utility according to the known activity of the active agent.

Example 8: Cocrystals of Active Agents and guest salts

The experiments of Example 3 are repeated, using conditions similar to those of those previous Examples, with each possible combination of the neutral or zwitterionic active agents and guest salts identified earlier in this disclosure. Cocrystals are formed which have utility according to the known activity of the active agent.

Example 9: Cocrystallization of fluoxetine HCl and fumaric acid

Cocrystals of fluoxetine HCl and succinic acid were prepared as follows. A 6.00 g sample of fluoxetine HCl and 1.01 g of fumaric acid were dissolved in 20 mL of ethanol with heating. The solution was filtered through a 0.2 µm nylon filter, concentrated to a volume of 8 mL, and cooled

in an ice bath for 6 hours. The solid material was isolated on filter paper and allowed to dry in the air to give 5.74 g (82% yield) of fluoxetine HCl:fumaric acid (2:1) cocrystal. The measured melting points were 158ºC for fluoxetine HCl, >300ºC (decomposes) for fumaric acid, and 164ºC for the cocrystal. The cocrystal is expected to have a good toxicology profile, since fumaric acid is known to be safe and appears on the Generally Recognized As Safe ("GRAS") list from the U.S. Food and Drug Administration.

Example 10: Crystal Structure Analysis of fluoxetine HCl:fumaric acid cocrystal (2:1)

A suitable cocrystal of fluoxetine HCl and fumaric acid was coated with Paratone N oil, suspended in a small fiber loop and placed in a cooled nitrogen gas stream at 100 K on a Bruker D8 SMART 1000 CCD sealed tube diffractometer with graphite monochromated CuKa (1.54178 Å) radiation. Data were measured using a series of combinations of phi and omega scans with 10 second frame exposures and 0.3° frame widths. Data collection, indexing and initial cell refinements were all carried out using SMART software (SMART Version 5.55, 2000, Bruker AXS, Inc., Analytical X-ray Systems, 5465 East Cheryl Parkway, Madison WI 53711-5373). Frame integration and final cell refinements were done using SAINT software (SAINT Version 6.02, 1999, Bruker AXS, Inc., Analytical X-ray Systems, 5465 East Cheryl Parkway, Madison WI 53711-5373). The final cell parameters were determined from least-squares refinement on 5625 reflections.

The structure was solved using Direct methods and difference Fourier techniques (SHELXTL V5.10, 1997, Bruker AXS, Inc., Analytical X-ray Systems, 5465 East Cheryl

Parkway, Madison WI 53711-5373). All the hydrogen atoms were located from difference Fouriers and included in the final cycles of least squares with isotropic Uij 's. All non-hydrogen atoms were refined anisotropically. Scattering factors and anomalous dispersion corrections are taken from A. J. C. Wilson (ed), International Tables for X-ray Crystallography, Volume C. Kynoch, Academic Publishers, Dordrecht, 1992, Tables 6.1.1.4 (pp. 500-502) and 4.2.6.8 (pp. 219-222). Structure solution, refinement, graphics and generation of publication materials were performed by using SHELXTL, V5.10 software. Additional details of data collection and structure refinement are given in Table G which follows.

While the present invention has been described and illustrated by reference to particular embodiments, it will be appreciated by those of ordinary skill in the art that the invention lends itself to many different variations not illustrated herein. For these reasons, then, reference should be made solely to the appended claims for purposes of determining the true scope of the present invention.

THE EMBODIMENTS OF THE INVENTION FOR WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A method of screening for a cocrystal of a hydrochloric acid salt of an active agent, comprising the steps of:

selecting a carboxylic acid having at least 4 carbons to coordinate via hydrogen bonding with the chloride anion of the hydrochloric acid salt of the active agent,

preparing a solution, melt, or physical mixture of the hydrochloric acid salt of the active agent and the carboxylic acid,

subjecting the solution or melt to a crystallization process, or the physical mixture to grinding, and

determining whether a cocrystal of the hydrochloric acid salt of the active agent and the carboxylic acid has formed.

2. The method of claim 1, wherein the carboxylic acid having at least 4 carbons is selected from benzoic acid, succinic acid, and fumaric acid.

3. The method of claim 1, wherein the active agent is an active pharmaceutical ingredient.

4. The method of claim 1, wherein the active agent is a nitrogen containing base.

5. The method of claim 4, wherein the nitrogen containing base is a tertiary amine.

6. The method of claim 4, wherein the nitrogen containing base is a secondary amine.

7. The method of claim 4, wherein the nitrogen containing base is a primary amine.

8. The method of claim 1, wherein x-ray diffraction is used to determine whether a cocrystal of the hydrochloric acid salt of the active agent and the carboxylic acid has formed.

9. The method of claim 1, wherein the preparing step comprises preparing a solution of the hydrochloric acid salt of the active agent and the carboxylic acid.

10. The method of claim 1, wherein the preparing step comprises preparing a melt of the hydrochloric acid salt of the active agent and the carboxylic acid.

11. The method of claim 1, wherein the preparing step comprises preparing a physical mixture of the hydrochloric acid salt of the active agent and the carboxylic acid.

Figure 1

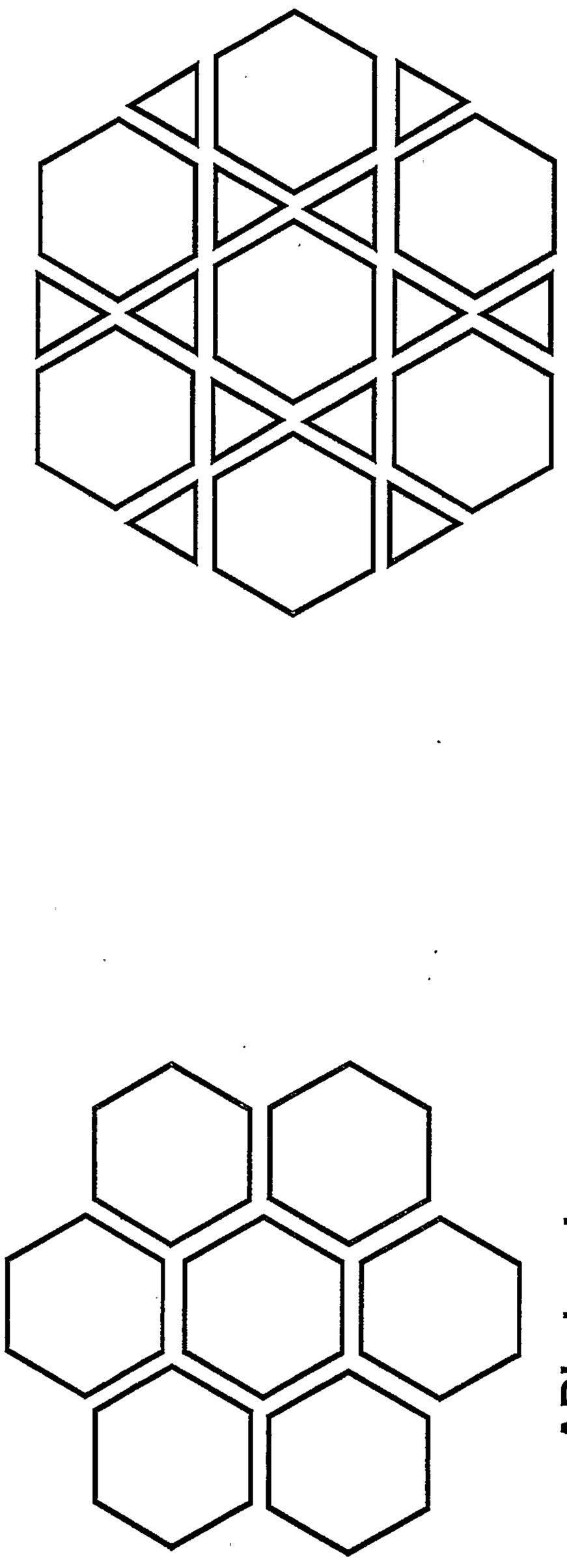
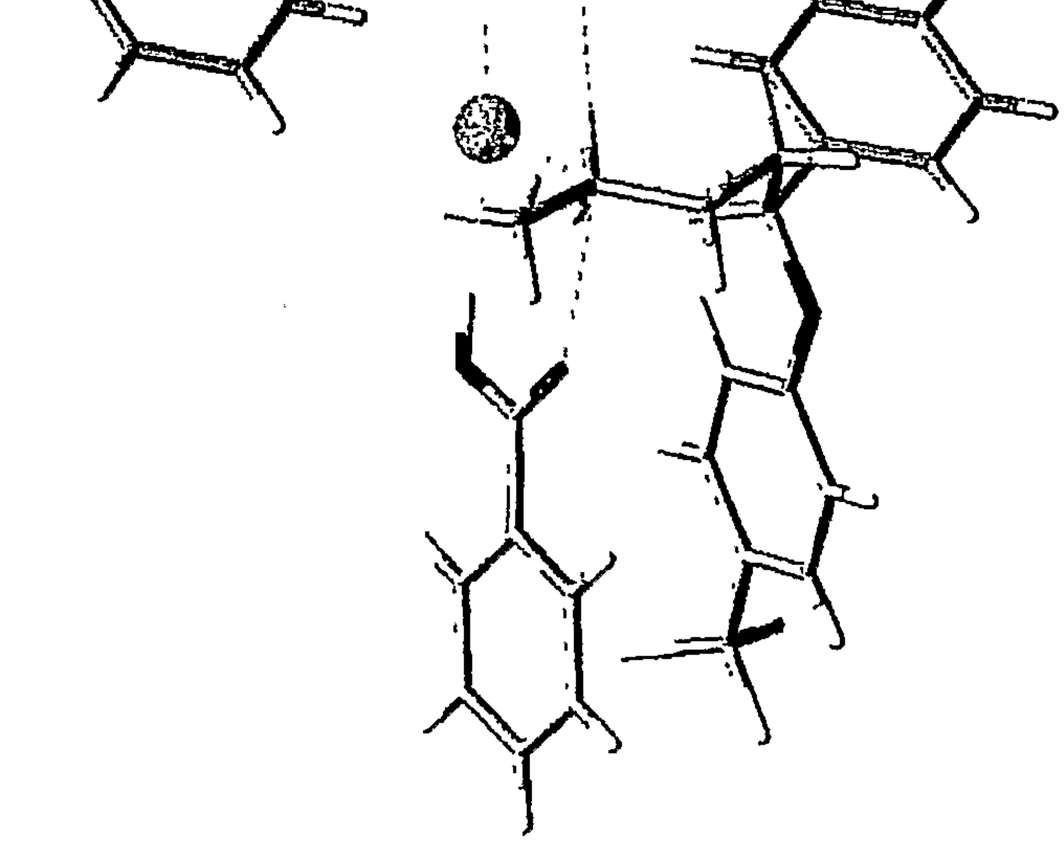
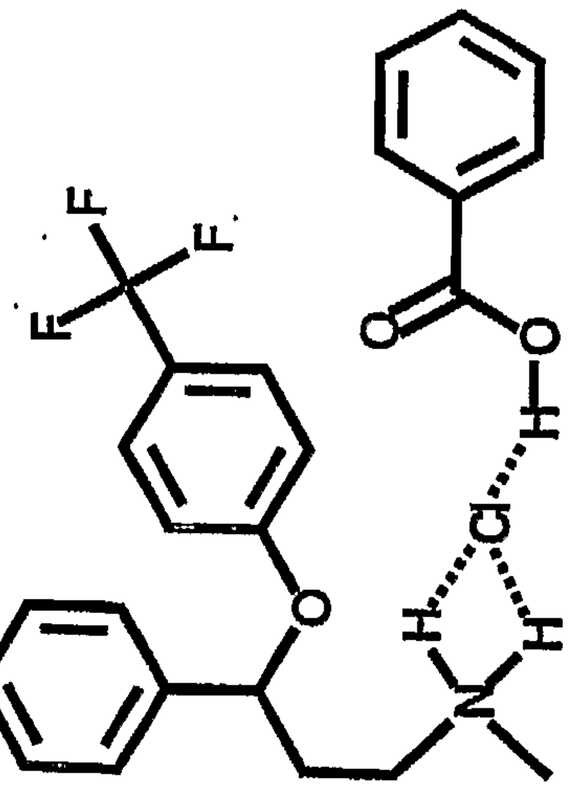


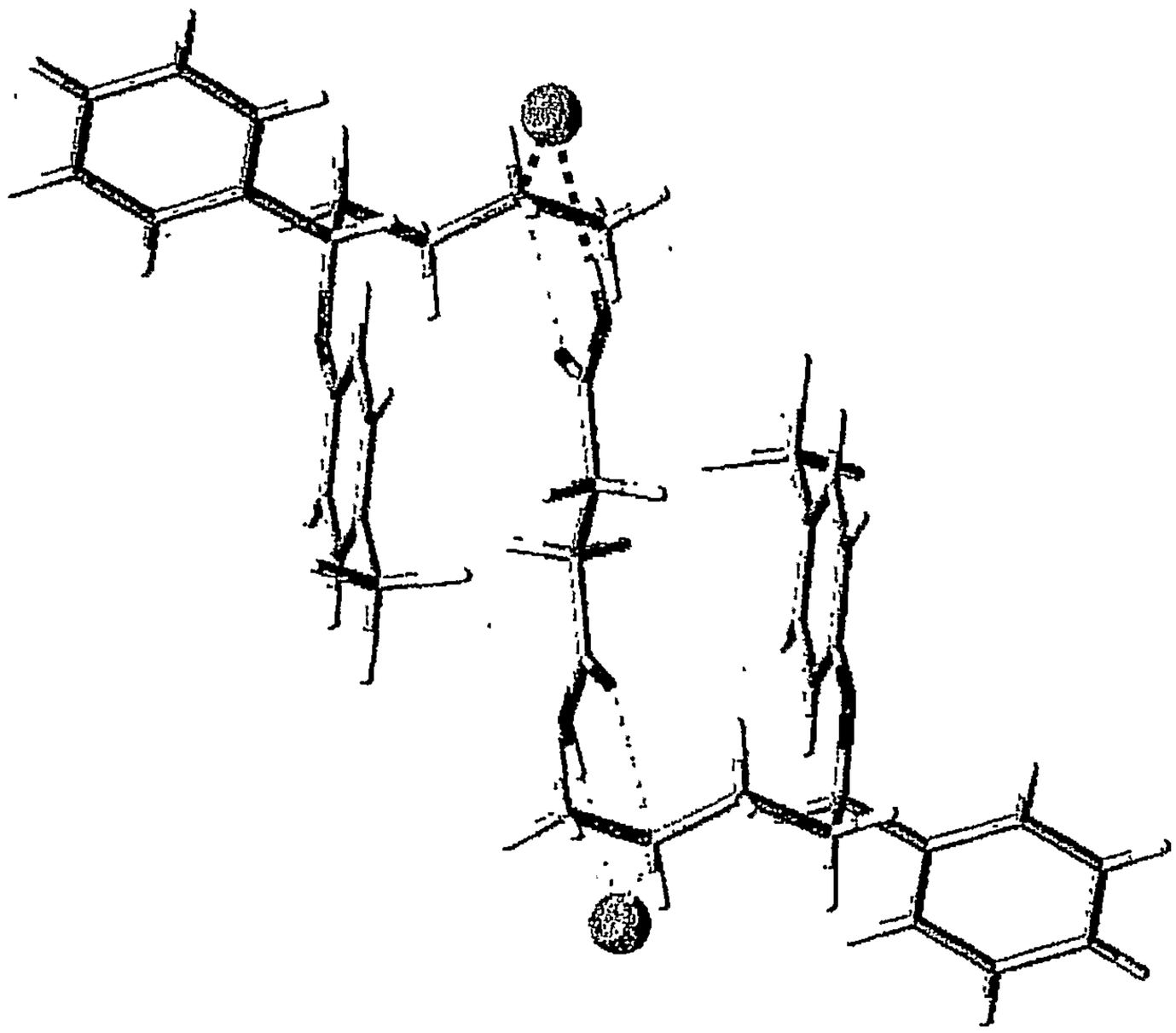
Figure 2



(b)

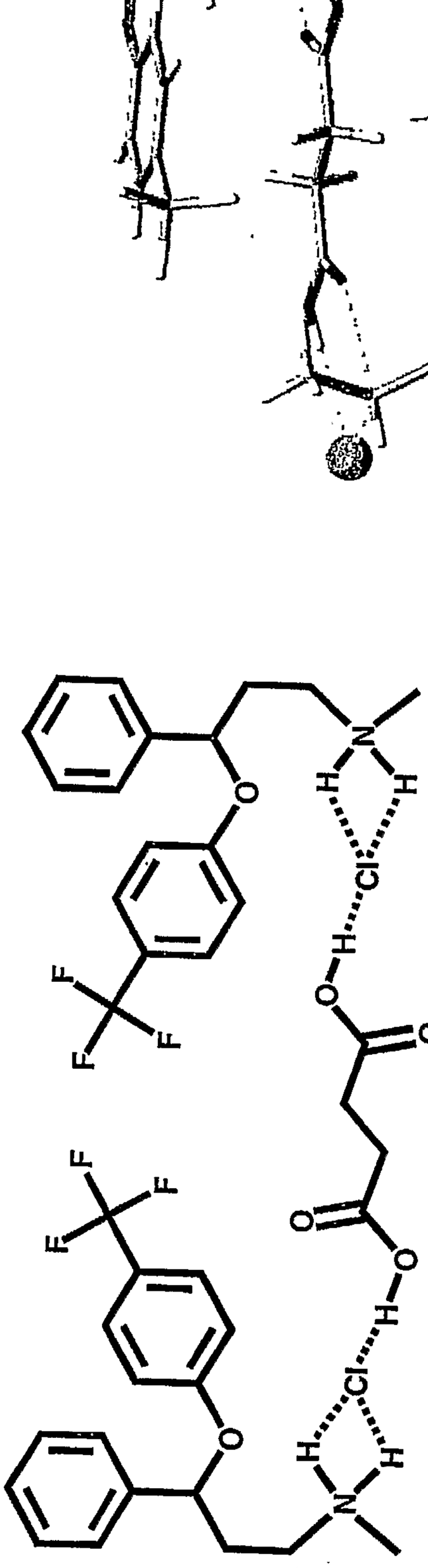


(a)



(b)

Figure 3



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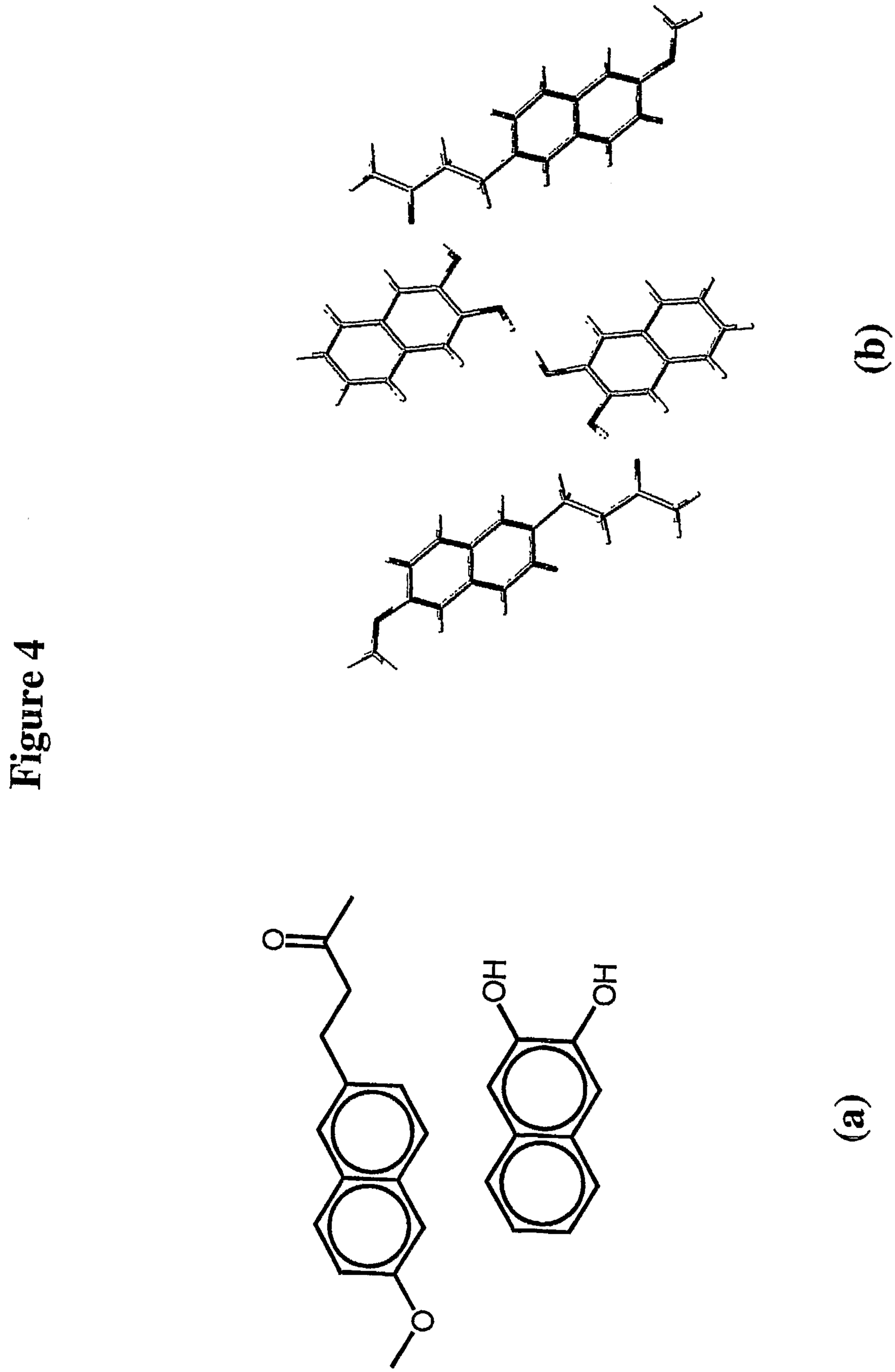
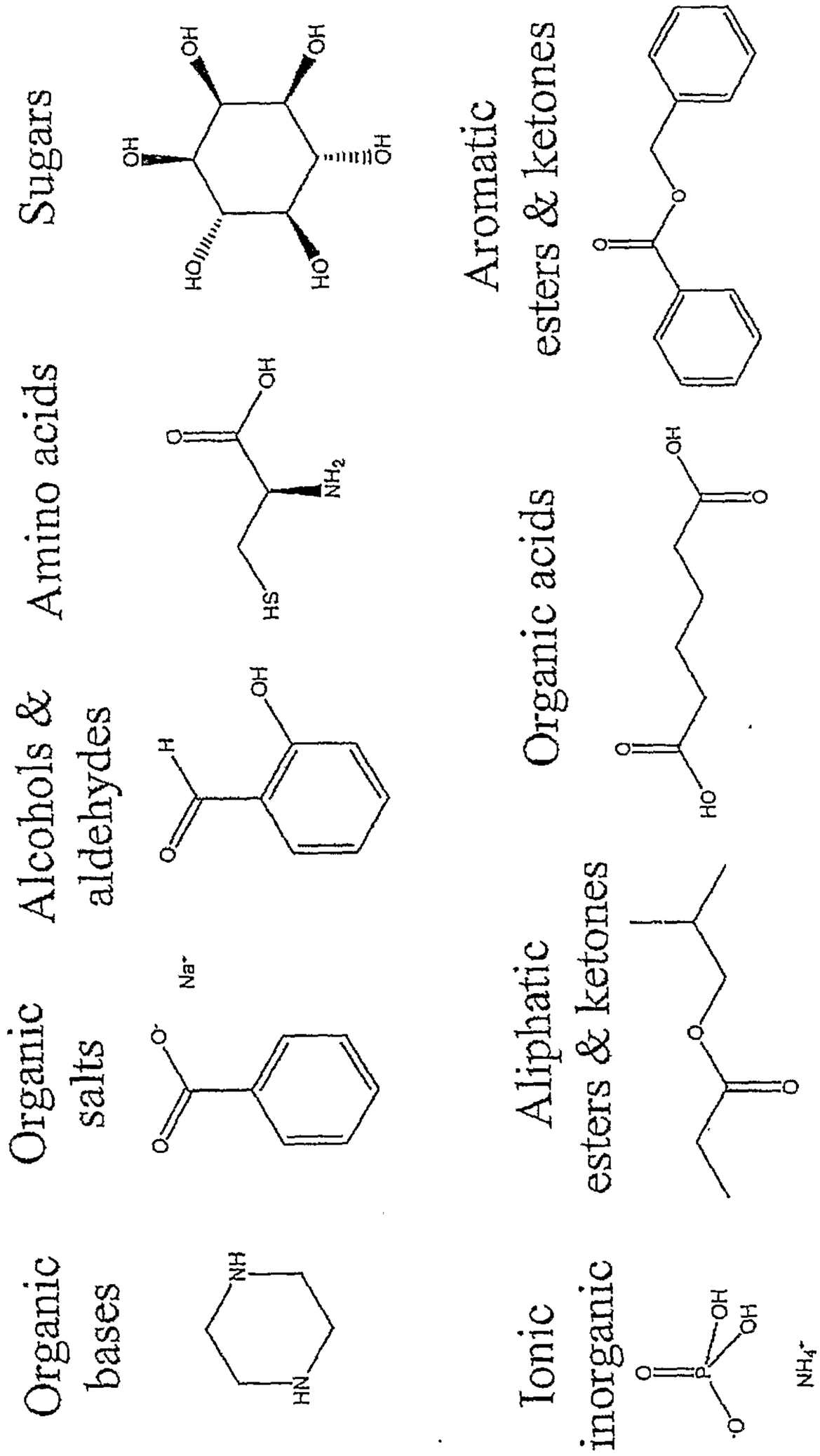
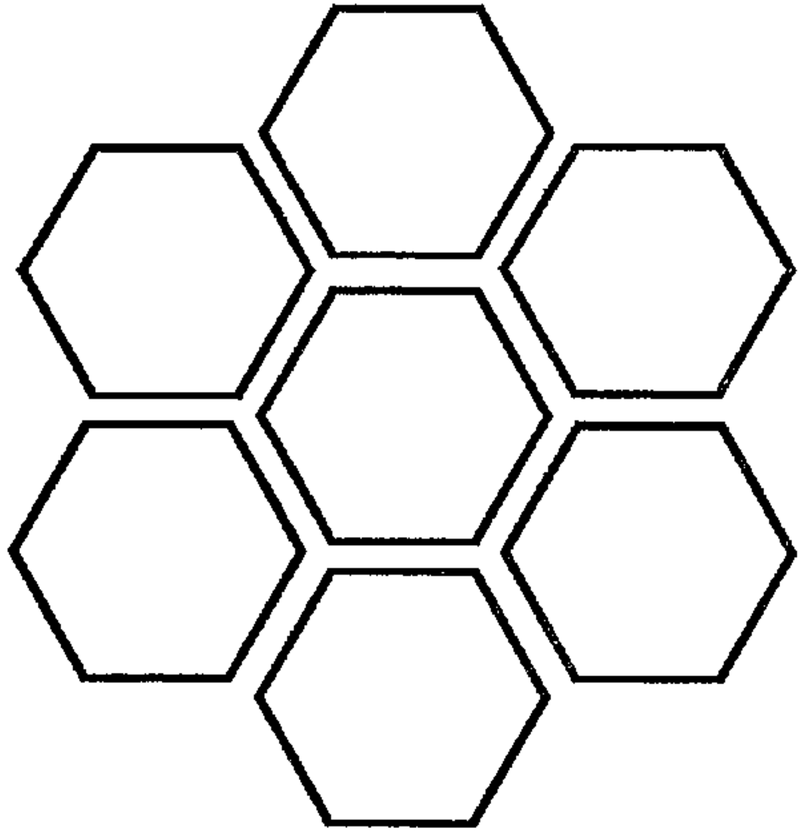


Figure 4

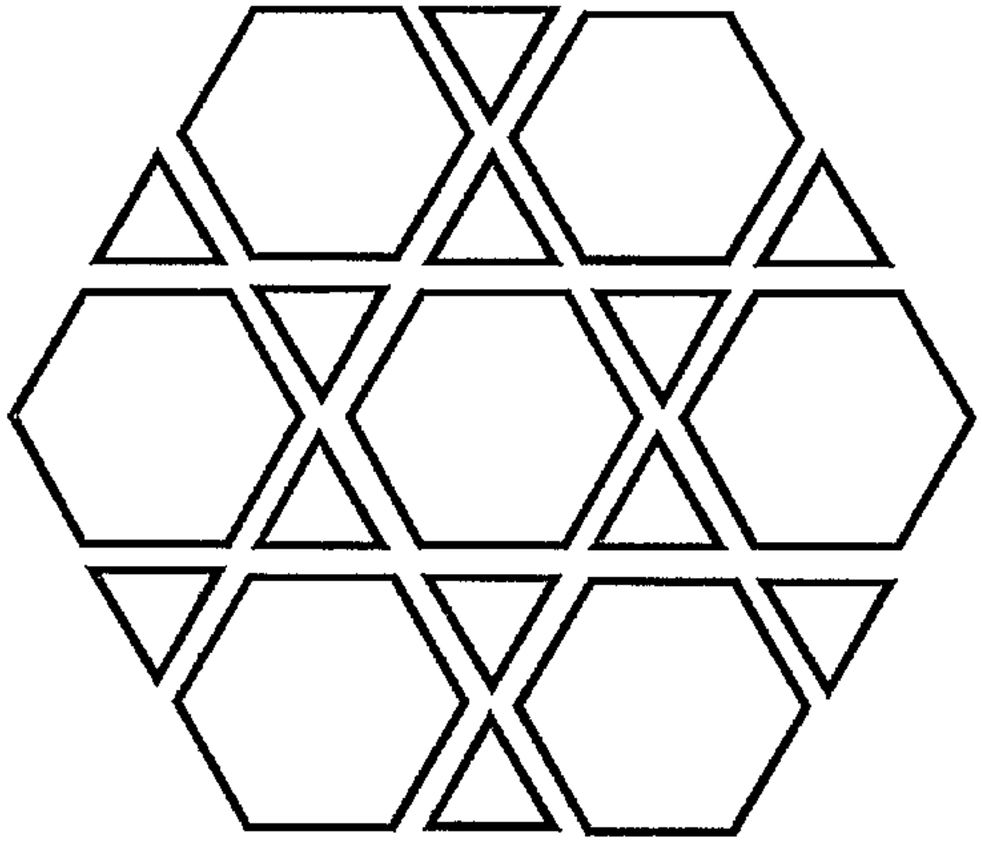
Figure 5


Sugars
Amino acids
Aromatic esters & ketones
Alcohols & aldehydes
Organic acids
Organic salts
Aliphatic esters & ketones
Organic bases
Ionic inorganic



API structure

(a)



1:2 API:guest co-crystal

(b)