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Homo- or Heterosynthon? A Crystallographic Study on a Series of New Cocrystals Derived from Pyrazinecarboxamide and Various Carboxylic Acids Equipped with Additional Hydrogen Bonding Sites

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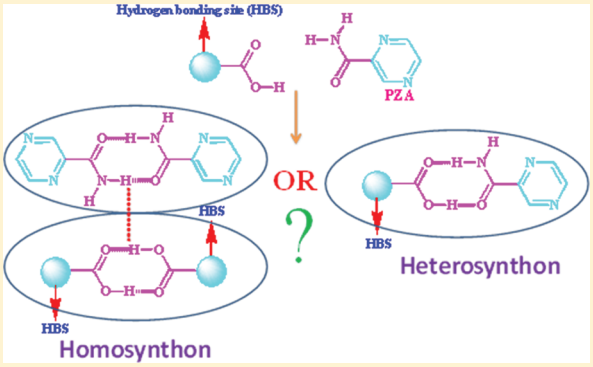
Supporting Information

ABSTRACT: Four new cocrystals of a well studied active pharmaceutical ingredient (API), namely, pyrazinecarboxamide (**PZA**), with various monocarboxylic acids equipped with additional hydrogen bonding sites such as vanillic acid (**VA**), gallic acid (**GA**), 1-hydroxy-2-naphthoic acid (**1HNA**), and indole-2-carboxylic acid (**I2CA**) have been successfully prepared and characterized by FT-IR, ^{1}H NMR, differential scanning calorimetry (DSC), and single crystal and powder X-ray diffraction (SXRD and PXRD, respectively) techniques. In the majority of the cases, preferential occurrence amide−amide and acid−acid homosynthons has been observed. Since the heterosynthon is energetically preferred to homosynthon, such unusual occurrence of homosynthon in these cocrystals is intriguing.



INTRODUCTION

Active pharmaceutical ingredients (APIs) have to go through a series of biological tests and clinical trials before they can be accepted as drug candidates. In many cases, particularly in their solid form, they do not perform well due to their poor solubility and consequently inefficient bioavailability[1] resulting in their withdrawal from the market.[2] Some of the commonly used techniques exploited to address the solubility and bioavailability issues of APIs are salt formation,[3] suitable solvate[4] (particularly hydrates[5]) formation, and polymorph[6] selections. Cocrystals of APIs popularly known as pharmaceutical cocrystals[1,7] have also become popular in improving the physical properties of APIs. Cocrytallization of APIs with other bioacceptable molecules, such as aminoacids and nutrients,[8] even with other drug molecules,[9] have been reported wherein the stability of the parent APIs with respect to relative humidity,[10] solubility,[11] dissolution rate, and bioavailability[12] have been shown to have improved. Since no covalent bond formation is required in making the cocrystals, the bioactivity of the APIs of interests is not expected to alter. Supramolecular synthon, a concept originally developed by Desiraju,[13] can be used to generate desired cocrystals of APIs.[14] With the advancement of supramolecular chemistry[15] and crystal engineering,[16] the concept of supramolecular synthon has become a matured and accepted tool in crystal engineering. Supramolecular synthon plays the same fundamental role in supramolecular synthesis that a synthon[17] does in covalent synthesis; spatial arrangements of intermolecular noncovalent interactions that frequently occur in supramolecular structures (for example, crystals) are supramolecular synthons that can be relied upon to generate supramolecular functional materials. The concept has already been demonstrated in molecular templating,[18] NLO materials,[19] photoreactions,[20] organo gels,[21] etc. While designing cocrystals of APIs, it is important to pay attention to the various noncovalent functionalities (for example, hydrogen bonding) present in both the target API and the cocrystal formar; the noncovalent functionality of the cocrystal formar should be able to form complementary noncovalent interactions with the target API without getting involved in chemical reaction. In other words, the supramolecular synthon considered should be robust enough to ensure cocrystal formation.

Pyrazinecarboxamide (**PZA**) is a bacteriostatic drug and administered along with Isoniazid and Rifampicin in the treatment of tuberculosis to reduce the duration of treatment.[22] A CSD (version 5.33, November 2011) search on **PZA** reveals that four different polymorphic forms (α, β, γ, and δ)[23] and three cocrystals of it have so far been reported in the structural database. The first binary cocrystal (ref code ASAYIC) with 4-nitrobenzamide was reported by Aakeröy et al.,[24] and the amide−amide homodimer is preserved in the structure. The second one with 2,5-dihydroxybenzoic acid (ref code

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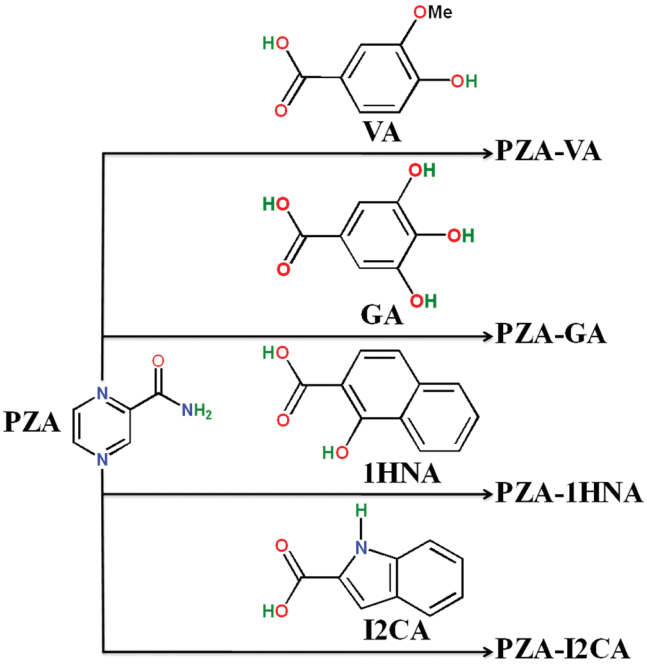
XAQQOW) was reported by Zaworotko et al.,[25] and the formation of an acid−amide heterosynthon is noteworthy in that structure. The third one was a hydrated cocrystal with 4-aminosalicylic acid (ref code URUGIY) reported by Desiraju et al.,[26] and the amide−amide homosynthon was maintained in the crystal srtucture. Recently, another cocrystal with 2-amino benzoic acid was reported by Abourahma et al.[27], and the amide−amide homeric homosynthon was manifested in the crystal structure. In a most recent example, two other cocrystals of **PZA** with succinic and fumaric acid were reported by Nangia et al.[28] wherein amide−amide homosynthon was observed along with the acid-py heterosynthon.

In the present study, we focus our attention to **PZA** as a target API to form cocrystals with various cocrystal formars in order to study the synthon perference in the corresponding crystal structures of the cocrystals and their impact on the solubility. Out of 40 odd various cocrystal formars scanned in the present study (Supporting Information), only four carboxylic acid based cocrystal formars gave **PZA** cocrystals (Scheme 1). **PZA** has a primary amide group and an N-containing electron rich aromatic heterocyclic nucleus. As a result, the most plausible supramolecular synthons expected in the crystal structures of the binary cocrystals of **PZA** with various functionalized aromatic acids as enlisted in Scheme 1 are shown in Scheme 2.

Scheme 1. Chemical Structure of Pyrazinecarboxamide (PZA) and Various Cocrystal Formars; Vanilic Acid (VA), Gallic Acid (GA), 1-Hydroxy-2-naphthoic Acid, (1HNA), and Indole-2-carboxylic Acid (I2CA); PZA-VA, PZA-GA, PZA-1HNA, and PZA-I2CA Are the Corresponding Cocrystals



RESULTS AND DISCUSSION

Cocrystal Screening. All the cocrystals were grown by slow evaporation technique. The equivalent amount of **PZA** and cocrystal formar were taken in a 20 mL beaker and dissolved in methanol by sonication or by applying mild warming wherever necessary. The homogeneous solution was kept undisturbed for slow evaporation. The crystalline material was then subjected to various physicochemical analyses. The formation of cocrystals were confirmed by FT-IR, powder X-ray diffraction (**PXRD**), thermogravimetric analysis (**TGA**), differential scanning calorimetry (**DSC**), and, finally, by single crystal X-ray diffraction (**SXRD**).

FT-IR. Table 1 enlists the FT-IR bands of amide-I and >C═O stretching of COOH of the resultant cocrystals as well as the parent API and cocrystal formars. The FT-IR spectra of the cocrystals and the individual components are depicted in Figure 1; the absence of any new band within the range of 1550−1650 cm^{-1} (νC−O of COO^-) indicates that no proton transfer has taken place; the amide-I band of **PZA** (1712 cm^{-1}) underwent significant red-shift in the corresponding cocrystals.

The same is true for the ν >C═O of COOH moiety as compared to the corresponding cocrystal formars except in the case of **PZA-1HNA**; the single crystal structure of the parent cocrystal formar **1HNA** reveals that the COOH moiety is involved in both intramolecular (with *o*-hydroxyl group) and intermolecular (self-complementary) hydrogen bonding.[29] As a result, the COOH band appears significantly red-shifted (1633 cm^{-1}) as compared to the other carboxylic acid cocrystal formars studied herein. Even if an acid−amide heterosynthon is formed in **PZA-1HNA**, it is not expected to influence the COOH band further because of its hydrogen bond saturation (both intra- and intermolecular hydrogen bonding), and therefore, the COOH band in **PZA-1HNA** appears at 1631 cm^{-1}. In **PZA-1HNA**, both amide−amide homosynthon and amide−COOH heterosynthon are possible. Therefore, the amide-I band is not expected to appear significantly red-shifted. However, it is interesting to note that the amide-I band of **PZA** (1712 cm^{-1}) is significantly red-shifted to 1685 cm^{-1} in **PZA-1HNA** indicating further participation of hydrogen bonding in the cocrystals.

Differential Scanning Calorimetry (DSC) and Thermogravimetric Analyses (TGA). The cocrystals were further characterized by DSC and TGA. In DSC experiments, the sample was heated at a rate of 10 °C per minute. The data were recorded from 30 °C and continued until the decomposition was commenced as indicated by the corresponding TGA thermogram (Supporting Information).

The endotherm peaks at 150.09 °C (heat of fusion, 119. 98 J g^{-1}) for **PZA-VA**, 116.86 °C, 153.05, and 206.26 °C (heat of fusion, 28.23, 27.71, and 169.25 J g^{-1}, respectively) for **PZA-GA**, 144.06 °C (heat of fusion, 153.02 J g^{-1}) for **PZA-1HNA**, and 214.70 °C (247.89 J g^{-1}) for **PZA-I2CA** were noted in DSC analysis (Figure 2). Except **PZA-GA**, all the other cocrystals displayed a sharp endotherm indicating the binary nature of these cocrystals. However, in the case of **PZA-GA**, the appearance of three endothermic peaks at 116.86 °C, 153.05 °C, and 206.26 °C indicates the presence of another component (solvates) in the cocrystals. It is interesting to note tha, except in **PZA-I2CA**, the melting points of the other cocrystals lies in between the melting points of the individual components (Table 2).

Single Crystal X-ray Diffraction. To study the synthon preferences in the resultant cocrystals reported herein, serious attempts were made to grow the corresponding X-ray quality single crystals. Fortunately, it was possible to grow the suitable single crystals of all the cocrystals studied herein (Table 3).

Cocrystal of Pyrazinecarboxamide and Vanilic Acid (PZA-VA). A single crystal of **PZA-VA** was grown from a 1:1

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Scheme 2. Plausible Supramolecular Synthons in the Cocrystals Studied Herein

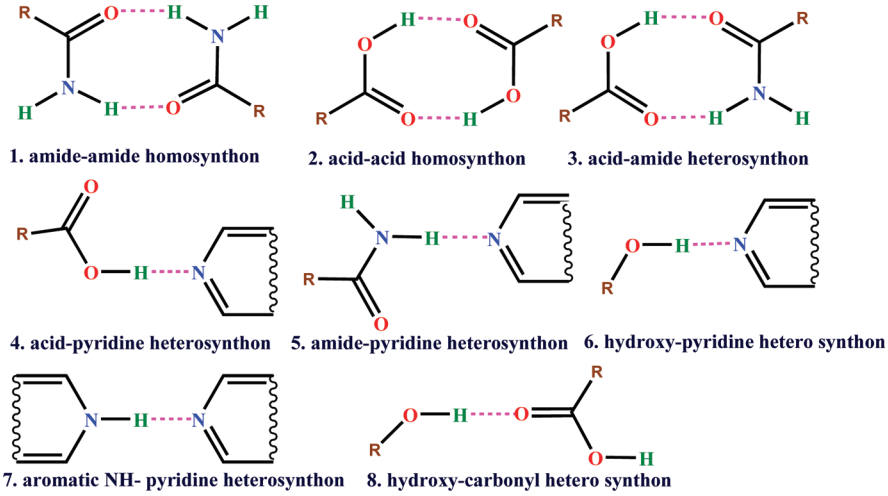

Table 1. Selected FT-IR Bands

name of the compound	ν-amide-I (cm^{-1})	ν-COOH (cm^{-1})
PZA	1712	
VA		1681
GA		1701
1HNA		1633
I2CA		1685
PZA-VA	1701	1668
PZA-GA	1693	1674
PZA-1HNA	1685	1631
PZA-I2CA	1693	1656

mixture of acetonitrile and methanol. It was crystallized in the centrosymmetric triclinic space group $P\bar{1}$. The asymmetric unit contains two molecules of **PZA** and **VA** each. The C−O bond distances of 1.253(2) Å and 1.281(2) Å clearly indicate the cocrystal (no salt formation) nature of **PZA-VA**. In the crystal structure, the classical acid−acid [O···O = 2.621(2) Å; ∠O−H···O = 170.6°] as well as amide−amide [N···O = 2.956(3) Å; ∠N−H···O = 176.3°] supramolecular homosynthons are preserved even in the presence of a pyridine moiety, which frequently gets involved in acid−pyridine heterosynthon.[14f] The crystal structure can be best described as a 2-D sheet wherein the hydrogen bonded dimer of *VA* participates in hydrogen bonding via O−H···N interactions [O···N = 2.799(3) Å; ∠O−H···N = 149.9°] with the **PZA** dimer that in turn displayed intermolecular hydrogen bonding involving the amide N−H and pyridyl N atoms [N···N = 3.061(3) Å; ∠N−H···N = 140.4°] (Figure 3). The 2-D sheets are further packed in parallel fashion along the *b* axis sustained by weak $\pi-\pi$ stacking interactions (3.880 Å) involving the **PZA** and **VA**

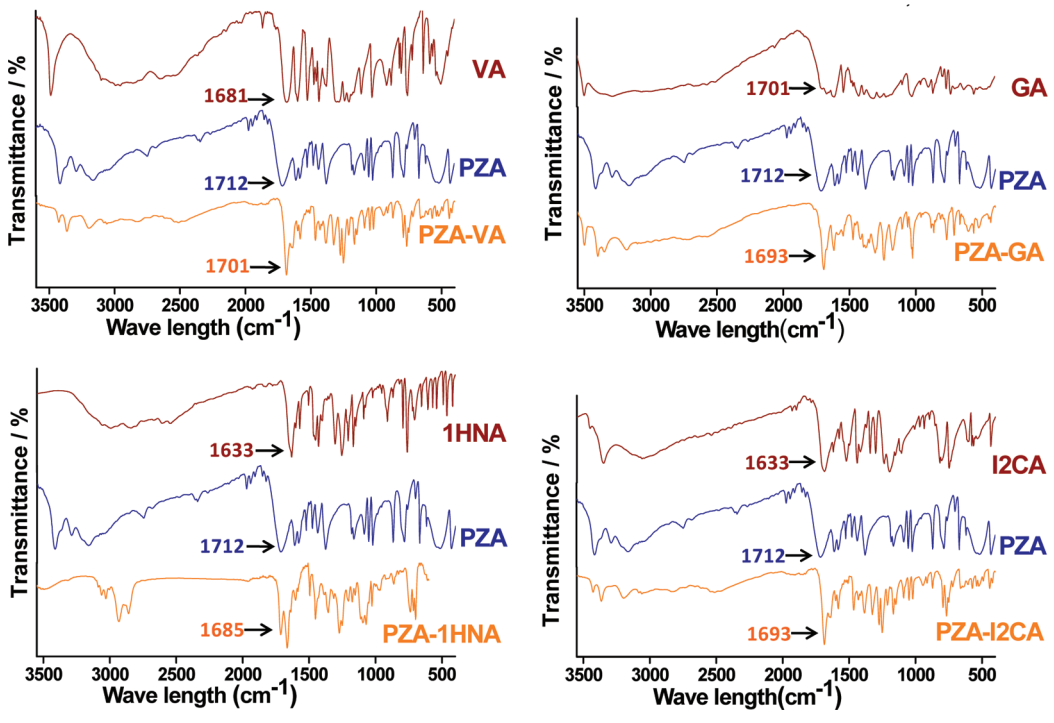

Figure 1. FT-IR comparison plot of cocrystals, **PZA**, and cocrystal formers.

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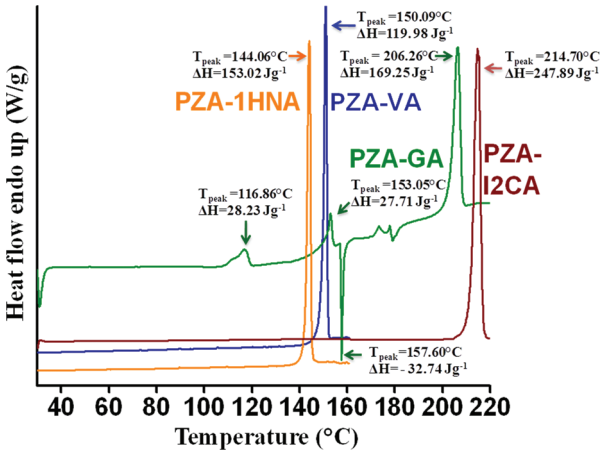

Figure 2. DSC traces of all the cocrystals studied herein.

Table 2. Melting Points of the Cocrystals and Their Individual Components

name of the compounds	reported melting points of the individual components (°C)	name of the cocrystal	melting point of the cocrystals (°C) as obtained in DSC trace
PZA	189		
VA	208−210	**PZA-VA**	150.09
GA	250	**PZA-GA**	206.26
1HNA	195	**PZA-1HNA**	144.06
I2CA	202 - 206	**PZA-I2CA**	214.70

aromatic nucleus of the adjacent 2-D sheet (Supporting Information).

Cocrystal of Pyrazinecarboxamide and Gallic Acid (PZA-GA). The single crystals of **PZA-GA** crystallized in the centrosymmetric monoclinic space group $P2_1/c$ were harvested from acetonitrile solution. The asymmetric unit contains one molecule of **PZA**, **GA**, and H_2O each. It is clear from the C−O distances (1.2326−1.3131 Å) of the COOH moiety that no proton transfer (salt formation) has taken place in **PZA-GA**. Crystal structure of this hydrated cocrystal showed that the well-known acid−acid [O···O = 2.6612(15) Å; ∠O−H···O = 179.9°] and amide−amide [N···O = 2.877(2) Å; ∠N−H···O = 171.9°] homosynthons were maintained. The hydrogen bonded dimer of **GA** makes further contact with the **PZA** dimer via O−H···N interactions [N···O = 2.768(2) Å; ∠N−H···O = 152.3°] involving one of the *m*-OH groups of **GA** and pyridyl N of **PZA.** The solvate water molecule participates in hydrogen bonding interactions with one of the *m*-OH and two *p*-OH groups of **GA** [O···O = 2.7732 and 2.5878 Å] (Figure 4). The overall crystal structure may be best described as a 3-D hydrogen bonded network wherein there is a weak $\pi-\pi$ stacking interaction (4.004 Å) involving **PZA** and **GA** aromatic rings (Supporting Information).

Cocrystal of Pyrazinecarboxamide and 1-Hydroxy-2-naphthoic Acid (PZA-1HNA). The single crystals of **PZA-1HNA** were grown from ethanol; it belonged to the centrosymmetric monoclinic space group $P2_1/c$. The asymmetric unit contains one molecule of **PZA** and **1HNA** each. The C−O distances of 1.228(2)−1.3139(18) Å clearly supports the formation of a binary cocrystal (no salt formation). Strong intramolecular hydrogen bonding [O···O = 2.5889(15) Å;

Table 3. Crystallographic Parameters for the Cocrystals

crystal parameters	PZA-VA	PZA-GA	PZA-1HNA	PZA-I2CA
CCDC no	864871	864872	864873	864874
empirical formula	$C_{13}H_{13}N_3O_5$	$C_{12}H_{13}N_3O_7$	$C_{16}H_{13}N_3O_4$	$C_{14}H_{12}N_4O_3$
formula weight	291.26	311.25	311.29	284.28
crystal size (mm)	0.32 × 0.26 × 0.12	0.28 × 0.22 × 0.16	0.40 × 0.36 × 0.35	0.24 × 0.18 × 0.08
crystal system	triclinic	monoclinic	monoclinic	monoclinic
space group	$P\bar{1}$	$P2_1/c$	$P2_1/c$	$P2_1/n$
a (Å)	7.424(7)	7.2384(3)	14.389(2)	5.5331(3)
b (Å)	7.628(7)	27.1544(7)	6.5565(9)	29.5175(10)
c (Å)	25.70(2)	7.5412(3)	15.523(2)	8.3142(4)
α (deg)	88.959(7)	90.00	90.00	90.00
β (deg)	87.126(8)	115.909(5)	94.289(4)	108.789(5)
γ (deg)	66.359(8)	90.00	90.00	90.00
volume/Å^3	1332(2)	1333.27(8)	1460.4(4)	1285.54(10)
Z	4	4	4	4
F(000)	608	648	648	592
μ MoKα (mm^{-1})	0.114	0.130	0.104	0.107
temp (K)	100(2)	100(2)	100(2)	100(2)
R_{int}	0.0256	0.0415	0.0365	0.0350
range of h, k, l	−8/8, −9/9, −30/30	−8/8, −32/32, −8/8	−18/18, −8/8, −19/19	−6/6, −34/35, −9/9
θ min/max (deg)	7.67/25.00	3.00/25.00	1.42/27.10	2.68/25.00
reflections collected/unique/observed [$I > 2\sigma(I)$]	11 494/4519/3332	12 63/2350/1544	15 296/3204/2153	6659/2224/1418
data/restraints/parameters	4519/0/385	2350/1/191	3204/0/198	2224/0/174
goodness of fit on F^2	0.971	0.935	1.044	0.982
final R indices [$I > 2\sigma(I)$]	R_1 = 0.0395	R_1 = 0.0432	R_1 = 0.0460	R_1 = 0.0474
	wR_2 = 0.1121	wR_2 = 0.1066	wR_2 = 0.1212	wR_2 = 0.1171
R indices (all data)	R_1 = 0.0580	R_1 = 0.0727	R_1 = 0.0690	R_1 = 0.0782
	wR_2 = 0.1283	wR_2 = 0.1167	wR_2 = 0.1353	wR_2 = 0.1265

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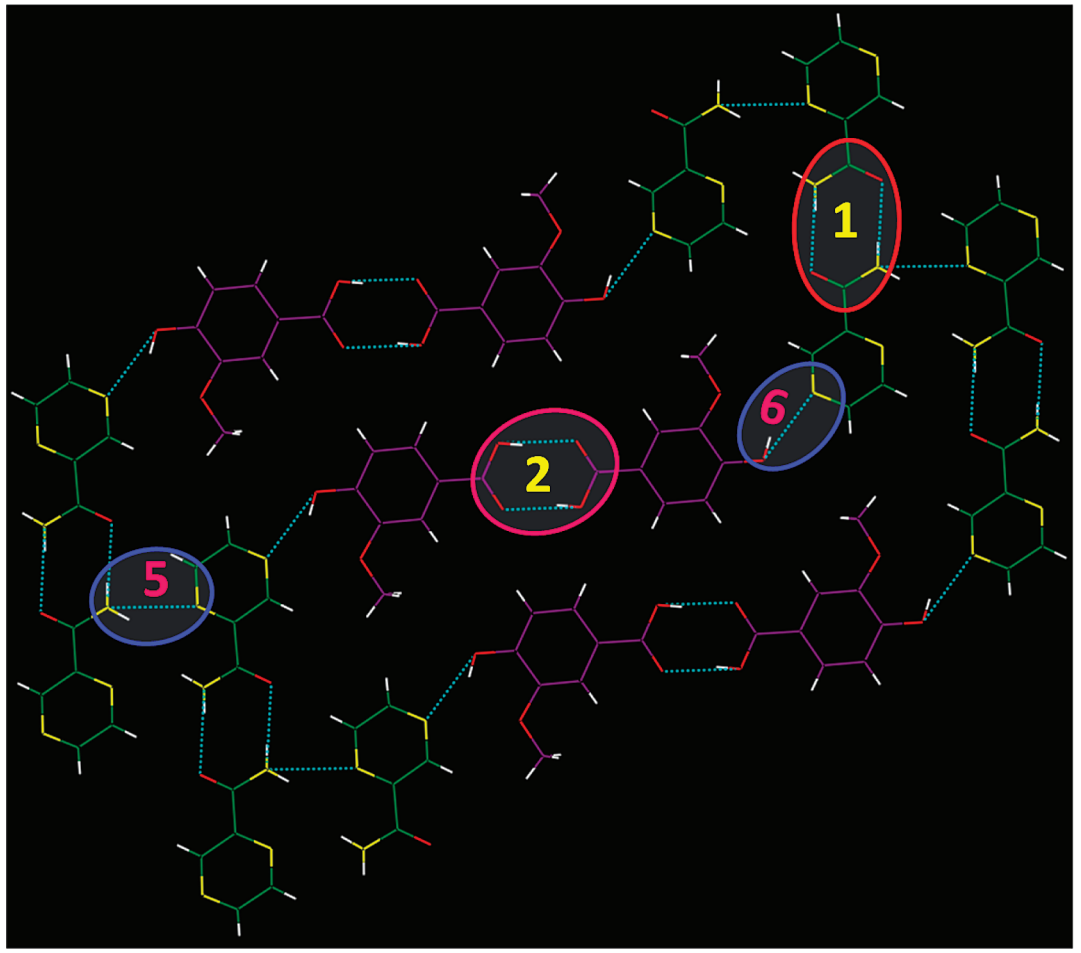

Figure 3. Supramolecular synthons (marked in accordance with Scheme 2) present in the crystal structure of **PZA-VA**.

∠O−H···O = 145.0°] involving the COOH and OH moieties of the **1HNA** could be observed in the crystal structure. The API **PZA** is found to display amide−amide homosynthon [N···O = 2.9126(17) Å and ∠N−H···O = 171.8°], which in turn participates in intermolecular hydrogen bonding via O−H···N interactions [O···N = 2.6894(18) Å; ∠O−H···N = 170.0°] involving the pyridyl moiety of **PZA** and COOH of **1HNA**. Thus, the crystal structure may be best described as a discrete hydrogen bonded complex of **PZA** and **1HNA** (Figure 5). The crystal structure was further stabilized by reasonably strong $\pi-\pi$ stacking interactions (3.666 Å) involving the aromatic moieties of the API and cocrystal formar (Supporting Information).

Cocrystal of Pyrazinecarboxamide and Indole-2-carboxylic Acid (PZA-I2CA). The single crystals of **PZA-I2CA** were grown from ethanol; SXRD experiments revealed that they crystallized in the centrosymmetric monoclinic space group $P2_1/n$. The asymmetric unit contains one molecule of **PZA** and **I2CA** each. The C−O bond distances [1.208(2)−1.324(2) Å] of the COOH moiety supports the formation of cocrystal (no salt formation). In the crystal structure, the acid−amide heterosynthon [O···O = 2.5779(15) Å; ∠O−H···O = 169.3° and N···O = 2.945(3) Å; ∠N−H···O = 160.9°] was found to be responsible for the cocrystal formation. The hydrogen bonded **PZA** and **I2CA** were further involved in hydrogen bonding interactions with the neighboring molecules via N−H···O [N···O = 2.972(3)Å; ∠N−H···O = 128.4°] and N−H···N [N···N = 3.079(3) Å; ∠N−H···O = 165.7°] interactions involving amide NH and O atom of COOH, and indole NH and pyridyl N, respectively, resulting a 1-D hydrogen bonded tape, which is further packed in parallel fashion sustained by weak $\pi-\pi$ stacking interactions (3.739 Å) involving the **PZA** and **I2CA** aromatic ring (Figure 6 and Supporting Information)

Powder X-ray Diffraction. The fact that the crystallized bulk samples actually represent the cocrystals as revealed by SXRD is further supported by PXRD experiments. It is clear from Figure 7 that the PXRD pattern of the bulk sample in each case is superimposable with that of the simulated pattern obtained from SXRD data and that it does not have any resemblance to the PXRD patterns of the parent components.

Thus, the majority of the structures displayed the presence of homosynthons (acid−acid and amide−amide). Since the acid−amide heterosynthon is energetically more favored than the corresponding homosynthons,[14f] this observation is quite intriguing. To gain more insight into the synthon preference, we decided to look at the related cocrystal structures reported in the literature. A CSD (version 5.33, November 2011) search with **PZA** as the search molecule resulted in 18 hits of which only two examples were relevant to our present study. Further literature search gave another three such examples. The details are enlisted in Table 4. It is interesting to note that amide−amide homosynthon is present in the majority of the reported cases as well. However, acid−acid homosynthon as observed in **PZA-VA** and **PZA-GA** was observed only once in the reported cases. Thus, it appears that homosynthon is preferred to

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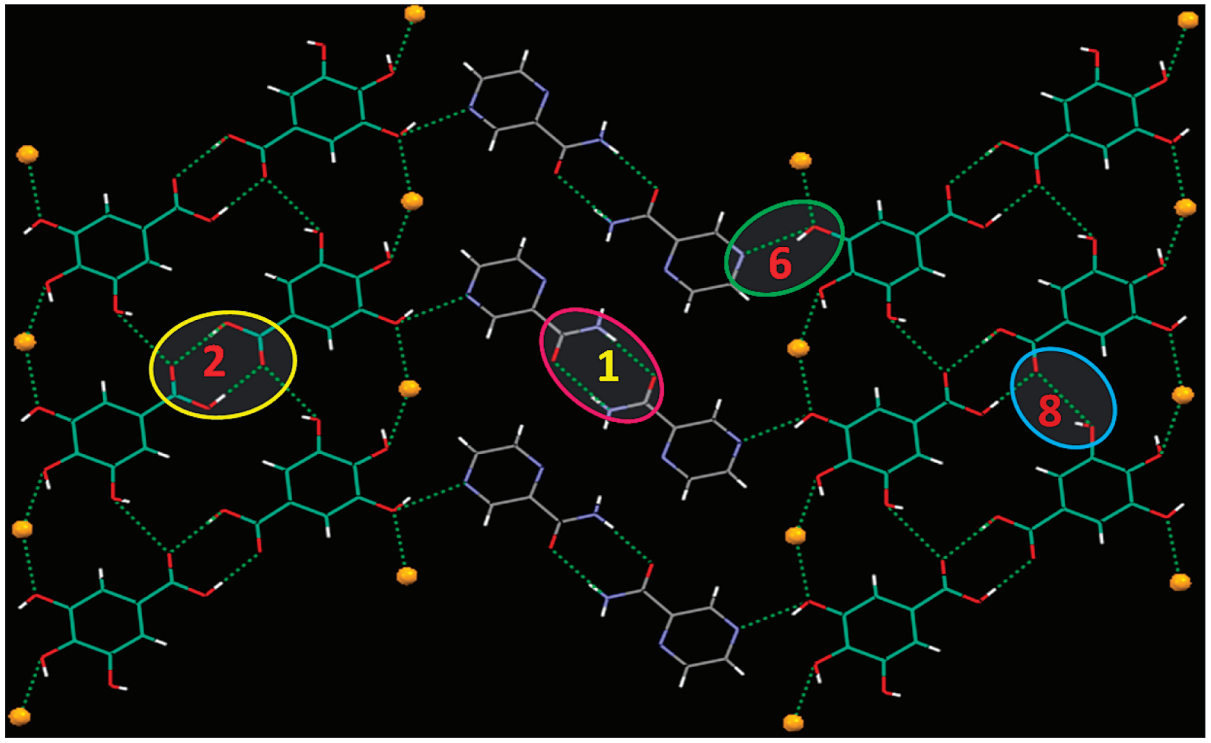

Figure 4. Supramolecular synthons (marked in accordance with Scheme 2) present in the crystal structure of **PZA-GA** displaying the lattice occluded water molecules (orange ball).

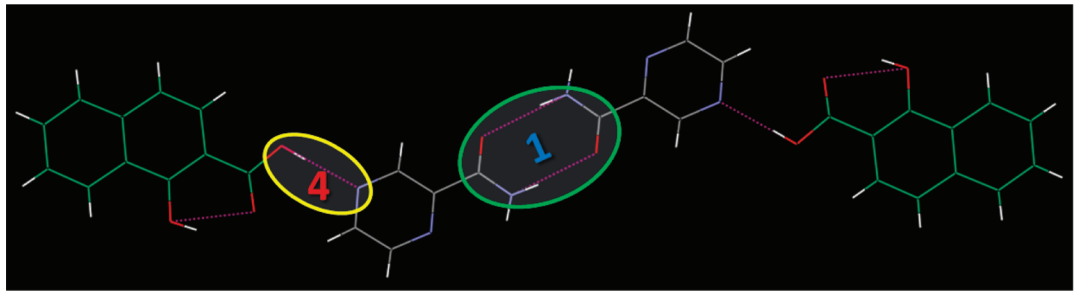

Figure 5. Supramolecular synthons (marked in accordance with Scheme 2) present in the crystal structure of **PZA-1HNA**.

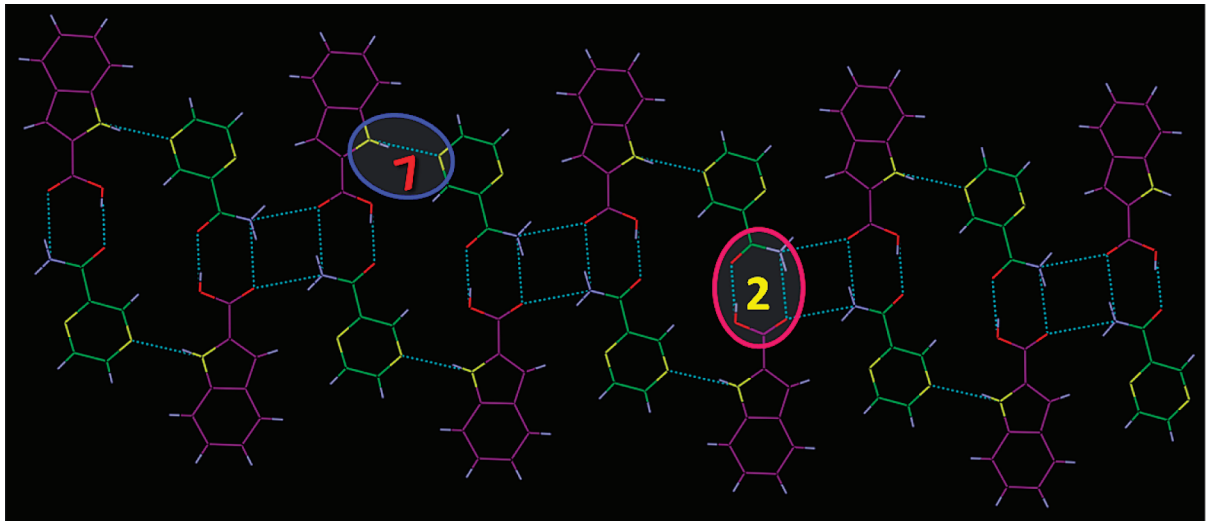

Figure 6. Supramolecular synthons (marked in accordance with Scheme 2) present in the crystal structure of **PZA-I2CA**.

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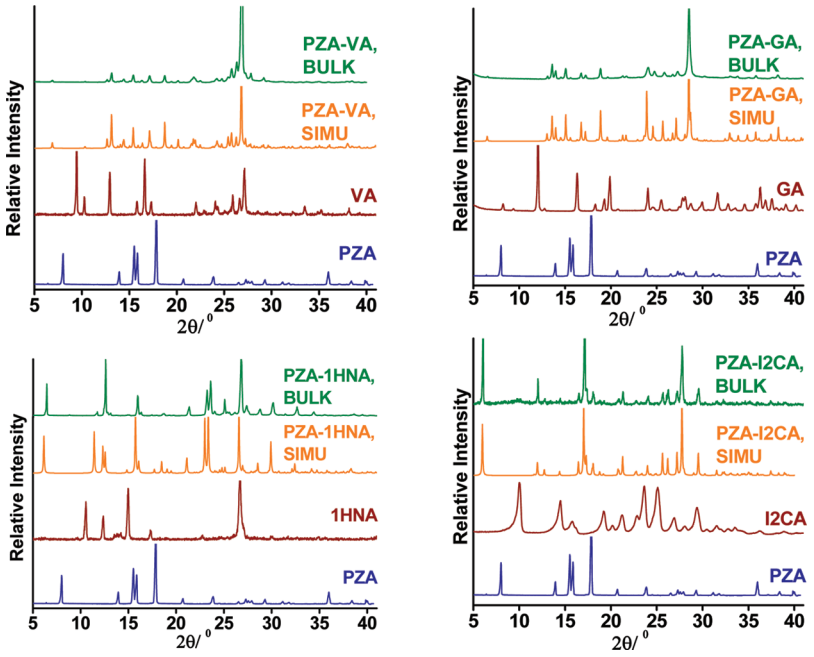

Figure 7. PXRD patterns of the cocrystals and the individual components under various conditions.

heterosynthon in the cocrystals of **PZA** with carboxylic acid cocrystal formars. Understandbly, further investigation would be required to address this unusual behavior of **PZA** cocrystals.

Solubility. To assess the effect of cocrystal formation on the solubility of the API, a stock solution of **PZA** (1.96 mg in 100 mL double distilled water (dd-water)) has been used to generate a calibration plot by serial dilution using the absorbance of λ_{max} 268 nm. For solubility measurement, a slurry containing 300 mg of each sample (**PZA**, **PZA-VA**, **PZA-GA**, **PZA-1HNA**, and **PZA-I2CA**) in 1 mL of double-distilled water was kept undisturbed for 72 h and then filtered through a Whatman 40 filter paper. The filtrate was then diluted to 100 mL from which an aliquot of 0.5 mL was further diluted to 10 mL. The solubility of **PZA** was then measured in each case using the absorbance data of this final stock solution with the help of the calibration plot. The solubility of **PZA**, **PZA-VA**, **PZA-GA**, **PZA-1HNA**, and **PZA-I2CA** thus obtained were 17.33, 37.18, 21.87, 13.51, and 1.34 μg L^{-1}, respectively. While the solubility of **PZA-VA** was remarkably improved, those of **PZA-1HNA** and **PZA-I2CA** were considerably decreased, whereas that of **PZA-GA** marginally increased.

■ CONCLUSIONS

Thus, four cocrystals of **PZA** with various carboxylic acid cocrystal formars having additional hydrogen bond functionality have been successfully prepared and characterized. The single crystal structures of the cocrystals revealed the presence of both acid−acid and amide−amide homonsynthon in **PZA-VA** and **PZA-GA**, whereas in the case of **PZA-1HNA**, amide−amide homosynthon along with acid−pyridine heterosynthon were observed. In the case of **PZA-I2CA**, acid−amide heterosynthon was observed. Since acid−amide heterosynthon is energetically more favored as compared to the corresponding homosynthon,[14f] the presence of both acid−acid and amide−amide homonsynthons in **PZA-VA** and **PZA-GA**, and also amide−amide homonsynthon in **PZA-1HNA**, is noteworthy. Comparing the present observation with the reported **PZA** cocrystal structures (with carboxylic acid cocrystal formars) revealed that in the majority of the cases, homosynthon (amide−amide) is preferred to heterosynthon (acid−amide) although acid−acid homosynthon is not observed in the reported structures. The reason for preferring homosynthon in **PZA**−carboxylic acid cocrystals is difficult to explain as the conformation of **PZA** in the cocrystals reported herein is found to be almost identical (Supporting Information) with each other meaning that there must be some other factors responsible for such unusual behavior. The fact that **PZA-I2CA** has the highest melting point (216 °C) and lowest solubility among the samples studied herein could be due to the presence of a much stronger acid−amide heterosynthon in the crystal structure of **PZA-I2CA**.

■ EXPERIMENTAL SECTION

Materials and Physical Measurements. **PZA**, **VA**, **GA**, **1HNA**, and **I2CA** were acquired from Sigma Aldrich and used as such without further purification. Solvents were of L.R. grade (Ranchem, Spectrochem, India etc.) and were used without further distillation. Melting point was determined by a Veego programmable melting point apparatus, India. IR spectra were recorded on an FT-IR instrument (FTIR-8300, Shimadzu). ^{1}H NMR spectra were recorded on a Brukar AVANCE DPX 300 (for 300 MHz) and III 500 (for 500 MHz). The elemental compositions of the purified compounds were confirmed by elemental analysis (Perkin-Elmer Precisely, Series-II, CHNO/S Analyzer-2400). TGA analyses were performed on a SDT Q Series 600 Universal VA.2E TA Instruments. DSC was recorded in a Perkin-Elmer, Pyris Diamond DSC. Powder X-ray patterns were recorded on a Bruker AXS D8 Advance Powder (Cu $K_{\alpha 1}$ radiation, λ = 1.5406 Å) diffractometer.

Single Crystal X-ray Diffraction. Data were collected using Mo$K\alpha$ (λ = 0.7107 Å) radiation on a BRUKER APEX II diffractometer equipped with CCD area detector. Data collection, data reduction, and structure solution/refinement were carried out using the software package of SMART APEX II. All structures were solved by the direct method and refined in a routine manner. In all the cases, nonhydrogen atoms were treated anisotropically. All the hydrogen atoms were geometrically fixed. CCDC (CCDC No. 864871−864874) contains the supplementary crystallographic data

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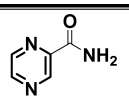
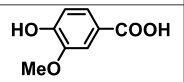
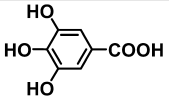
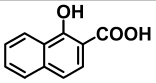
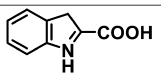
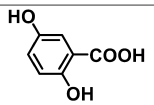
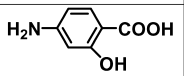
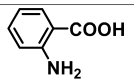
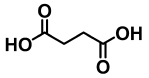
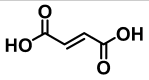
Table 4. List of Cocrystal Formars Reported in the Present Study (Entries 1−4), in the Literature (Entries 5−9) of PZA and the Synthon Observed in the Crystal Structure; Synthon Numbering with Third Bracket in Accordance with Scheme 2; # Names Synthons Not Shown in Scheme 2



PZA

Sl. no	Cocrystal formar	Synthons present	Ref./REFCODE
1		A) amide-amide [1]. B) acid-acid [2]. C) amide-py [5]. D) hydroxyl-py [6]. 50% homosynthon	Present study
2		A) amide-amide [1]. B) acid-acid [2]. C) hydroxyl-py [6]. D) hydroxyl-carbonyl [8]. 50% homosynthon	Present study
3		A) amide-amide [1]. B) acid-py [4]. 50% homosynthon	Present study
4		A) acid-amide [3]. B) aromatic NH-py [7]. 100% heterosynthon	Present study
5		**A)** acid-amide [3]. B) acid-py [4]. C) hydroxyl-amide N 100% heterosynthon	25/XAQQOW
6		A) amide-amide [1]. B) acid-py [4]. C) amino NH- carbonyl# 100% heterosynthon	26/URUGIY
7		A) amide-amide [1]. B) acid-acid [2]. C) amino NH- carbonyl# 50% homosynthon	27
8		A) amide-amide [1]. B) acid-py [4]. 50% homosynthon	28
9		A) amide-amide [1]. B) acid-py [4]. C) carboxylic OH- amide N# 33% homosynthon	28

for this article. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html.

■ ASSOCIATED CONTENT

Supporting Information

List of other cocrystal formars that did not react with **PZA** in the present study; FT-IR, ^{1}H NMR, elemental analyses data, molecular plot with hydrogen bonding parameters, molecular packing diagram, molecular overlay of PZA observed in the reported cocrystals, and DSC-TGA overlay; crystallographic data (CIF files) of the cocrystals **PZA-VA**, **PZA-GA**, **PZA-1HNA**, and **PZA-I2CA**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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