Journal of Molecular Structure 1034 (2013) 302–309

Contents lists available at SciVerse ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstruc

Cocrystals of caffeine with formylphenoxyaliphatic acids: Syntheses, structural characterization, and biological activity

G.S. Suresh Kumar [a], P.G. Seethalakshmi [b], N. Bhuvanesh [c], S. Kumaresan [a,*]

[a] Department of Chemistry, Manonmaniam Sundaranar University, Tirunelveli 627 012, Tamilnadu, India
[b] Department of Chemistry, A.P.C. Mahalaxmi College for Women, Thoothukudi 628 002, Tamilnadu, India
[c] Department of Chemistry, Texas A&M University, College Station, TX 77842, USA

HIGHLIGHTS

- Imidazole–carboxylic acid synthon is present in all the three (**1**–**3**) cocrystals.
- Cocrystals (**1**–**3**) are stabilized by intermolecular H-bonding and π–π interactions.
- Caffeine and the corresponding acid are directly connected in **1** and **3**.
- Cocrystal **2** contains a polymeric motif.
- Cocrystals **1**–**3** have slightly higher DPPH radical scavenging activity than caffeine.

ARTICLE INFO

Article history:
Received 13 September 2012
Received in revised form 15 October 2012
Accepted 15 October 2012
Available online 8 November 2012

Keywords:
Caffeine
Cocrystal
Formylphenoxyaliphatic acids
Synthon
X-ray diffraction
Hydrogen bonding

ABSTRACT

Three organic cocrystals namely, caffeine:*p*-formylphenoxyacetic acid [(caf)(*p*-fpaa)] (**1**) caffeine:*o*-formylphenoxyacetic acid monohydrate [(caf)(*o*-fpaa)]H_2O (**2**) and caffeine:*p*-formylphenoxypropionic acid [(caf)(*p*-fppa)] (**3**) were synthesized and studied by FT-IR, NMR, and single crystal XRD studies. The crystal system of cocrystal [(caf)(*p*-fpaa)] (**1**) is monoclinic with space group $P2_1/n$ and $Z = 16$, that of cocrystal [(caf)(*o*-fpaa)]H_2O (**2**) is triclinic with space group $P-1$ and $Z = 2$, and that of cocrystal [(caf)(*p*-fppa)] (**3**) is monoclinic with space group $P2_1/c$ and $Z = 4$. The imidazole–carboxylic acid synthon is observed in all the three cocrystals. The intermolecular hydrogen bonds, O—H···N and π–π interactions together play a major role in stabilizing the crystal structure of all the three cocrystals. The biological activities of crystals **1**–**3** were studied.

1. Introduction

The term cocrystal was first coined in the perspective of complexes between nucleic bases [1] and later it was subsequently popularized by Etter [2]. The definition of cocrystal is often a topic of debate [3,4]. Cocrystals have gained a lot of recent attention owing to their amenability to design and their ability to tailor physiochemical properties. Cocrystals were recognized as valuable materials [5,2,6,7] during the late 1990s. The great potential of cocrystals resides in the improvement of physical properties of cocrystals like solubility, dissolution rate, melting point, color, etc. with respect to those of the co-formers [8–10]. The reported uses of cocrystals include pharmaceutical materials [11], electronic, and optical materials [12], as well as media for conducting controlled solid-state organic syntheses [13].

Caffeine (methylxanthine) is a natural alkaloid found in various plants, commonly used as a formulation or food additive and as a pharmaceutical model compound [14]. It is a metabolic stimulant [15] of the central nervous system. Caffeine is present in medications for asthma, apnea in newborns [11], and Alzheimer's disease (AD) [16–20]. Aryloxyacetic acid derivatives possess a wide array of diverse bioactivities such as antimicrobacterial-, anti-inflammatory-, antioxidant-, antibacterial-, analgesic-, antisickling-, antipaemic-, antiplatelet-, non-prostanoid prostacyclin mimetic-, diuretic-, and growth regulators [21].

Earlier we have synthesized some cocrystals/molecular salts [22–24] of organic acidic and basic components. In continuation of our work in organic cocrystals, herein we report the synthesis and the crystal structures of three cocrystals namely, caffeine:*p*-formylphenoxyacetic acid [(caf)(*p*-fpaa)] (**1**), caffeine:*o*-formyl-

* Corresponding author. Tel.: +91 9443182502; fax: +91 462 2334363.
E-mail address: skumarmsu@yahoo.com (S. Kumaresan).

0022-2860/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.molstruc.2012.10.033

phenoxyacetic acid monohydrate [(caf)(*o*-fpaa)]H_2O (**2**), and caffeine:*p*-formylphenoxypropionic acid [(caf)(*p*-fppa)] (**3**).

2. Experimental

2.1. General

The FT-IR spectra were recorded in pellet form with spectral grade KBr on a JASCO FT-IR 410 spectrometer in the range 4000–400 cm^{-1}. The ^1H NMR spectra were recorded on a BRUKER spectrometer operating at 300 MHz using TMS as internal standard and DMSO-d_6 as solvent. The crystal structures of cocrystals caffeine:*p*-formylphenoxyacetic acid [(caf)(*p*-fpaa)] (**1**), caffeine:*o*-formylphenoxyacetic acid monohydrate [(caf)(*o*-fpaa)]H_2O (**2**), and caffeine:*p*-formylphenoxypropionic acid [(caf)(*p*-fppa)] **(3)** were determined using a BRUKER APEX 2 X-ray (three-circle) diffractometer. The data reduction was done with the program APEX2 [25]. The absorption correction was employed using the program SADABS [26]. The structure solution was obtained using SHELXTL (XS) [27] and refined on F^2 to convergence [27,28]. Absence of additional symmetry was verified using PLATON (ADDSYM) [29]. Caffeine was purchased from commercial source. Formylphenoxy-aliphatic acids were synthesized by literature method [30].

2.2. Synthesis of [(caf)(p-fpaa)] (1), [(caf)(o-fpaa)]H_2O (2), and [(caf)(p-fppa)] (3)

Caffeine (0.097 g, 0.5 mmol) and 0.5 mmol of formylphenoxy-aliphatic acids (*p*-fpaa and *o*-fpaa 0.090 g, and *p*-fppa 0.097 g) were dissolved separately in 1:1 v/v aqueous methanol. One solution is gradually added into the other with stirring and allowed to stand at room temperature. Slow evaporation of the mixture under ambient conditions yielded colorless crystals of the compounds in 3 days (Yield: **1**, 85%, **2**, 83% and **3**, 80%). Anal. Calcd. for [(caf)(*p*-fpaa)] (**1**) $C_{17}H_{18}N_4O_6$: C, 54.54; H, 4.81; N, 14.97%. Found: C, 54.44; H, 4.61; N, 14.77%, for [(caf)(*o*-fpaa)]H_2O (**2**) $C_{17}H_{20}N_4O_7$: C, 52.04; H, 5.102; N, 14.28%. Found: C, 52.00; H, 5.08; N, 14.22%, and for [(caf)(*p*-fppa)] **(3)** $C_{18}H_{20}N_4O_6$: C, 55.67; H, 5.15; N, 14.43%. Found: C, 55.60; H, 5.08; N, 14.32%.

2.3. Antimicrobial activity

The *in vitro* biological screening effects of all the three synthesized cocrystals were tested against the bacteria: *Staphylococcus aureus*, *Streptococcus* sps., *Enterobacter* sps., *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus* sps., and *Klebsiella* sps., by well diffusion method [31] using Muller Hinton agar nutrient as the medium. The antifungal activities of the compounds were also evaluated by the well-diffusion method against the fungi viz., *Candida* sps., *Aspergillus* sps., cultured on antimitotic medium. The compounds were tested at a concentration of 50 μg/0.01 mL in aqueous solution. In the typical procedure [32], a well was made on the agar medium inoculated with microorganisms. The well was filled with the test solution using a micropipette and the plate was incubated 24 h for bacteria and 72 h for fungi at 35 °C. During this period, the test solution diffused and the growth of the inoculated microorganisms was affected. The concentration was noted at which the inhibition zone was developed. The percentage of inhibition was calculated as $100(C - T)/C$, where C is the average diameter of bacteria/fungal growth on the control plate and T is the average diameter of bacteria/fungal growth on the test plate. The susceptibility zones were measured in diameter (mm). The susceptibility zones measured were the clear zones around the disks killing the bacteria.

2.4. DPPH radical scavenging assay

Scavenging effect of 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical was measured according to the procedure described by Blois with a slight modification [33]. 0.1 mL of 1 mM methanol solution

Table 1
Crystal data and structure refinement parameters for caffeine:*p*-formylphenoxyacetic acid [(caf)(*p*-fpaa)] (**1**), caffeine:*o*-formylphenoxyacetic acid monohydrate [(caf)(*o*-fpaa)]H_2O (**2**) and caffeine:*p*-formylphenoxypropionic acid [(caf)(*p*-fppa)] (**3**).

Empirical formula	$C_{17}H_{18}N_4O_6$	$C_{17}H_{20}N_4O_7$	$C_{18}H_{20}N_4O_6$
Formula weight	374.35	392.37	388.38
Temperature	110(2) K	110(2) K	110(2) K
Wavelength	0.71073 Å	0.71073 Å	1.54178 Å
Crystal system	Monoclinic	Triclinic	Monoclinic
Space group	$P21/n$	$P-1$	$P21/c$
Unit cell dimensions	a = 16.047(8) Å	a = 16.430(2) Å	a = 16.430(2) Å
	b = 26.395(13) Å	b = 6.6440(11) Å	b = 6.6440(11) Å
	c = 17.137(9) Å	c = 17.785(2) Å	c = 17.785(2) Å
	$\alpha = \gamma = 90°$	α = 78.979(2)°	$\alpha = \gamma = 90°$
	β = 113.803(5)°	β = 71.473(2)°	β = 113.871(7)°
		γ = 65.741(2)°	
Volume	6641(6) $Å^3$	884.8(3) $Å^3$	1775.3(4) $Å^3$
Z	16	2	4
Density (calculated)	1.498 Mg/m^3	1.473 Mg/m^3	1.453 Mg/m^3
Absorption coefficient	0.116 mm^{-1}	0.116 mm^{-1}	0.934 mm^{-1}
$F(000)$	3136	412	816
Crystal size	0.57 × 0.52 × 0.38 mm^3	0.57 × 0.54 × 0.32 mm^3	0.15 × 0.08 × 0.02 mm^3
θ Range for data collection	1.47–27.50°	1.97–27.46°	2.94–61.01°
Index ranges	$-20 \leqslant h \leqslant 20$, $-34 \leqslant k \leqslant 34$, $-22 \leqslant l \leqslant 22$	$-12 \leqslant h \leqslant 12$, $-12 \leqslant k \leqslant 12$, $-14 \leqslant l \leqslant 14$	$-17 \leqslant h \leqslant 18$, $-7 \leqslant k \leqslant 7$, $-20 \leqslant l \leqslant 19$
Reflections collected	73,511	10,191	22,301
Independent reflections	15138 [R(int) = 0.0619]	3960 [R(int) = 0.0312]	2603 [R(int) = 0.0759]
Completeness to θ = 27.50°	99.1%	97.9%	95.8%
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	0.9574 and 0.9370	0.9638 and 0.9367	0.9816 and 0.8725
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	15138/0/990	3960/0/258	2603/0/258
Goodness-of-fit on F^2	1.031	1.035	1.043
Final R indices [I > 2sigma(I)]	R_1 = 0.0639, wR_2 = 0.1605	R_1 = 0.0437, wR_2 = 0.1163	R_1 = 0.0377, wR_2 = 0.0885
R indices (all data)	R_1 = 0.0962, wR_2 = 0.1768	R_1 = 0.0486, wR_2 = 0.1212	R_1 = 0.0534, wR_2 = 0.0921
Extinction coefficient	0.00056(11)	0.019(4)	0.0026(4)
Largest diff. peak and hole	0.643 and −0.452 e $Å^{-3}$	0.557 and −0.531 e $Å^{-3}$	0.326 and −0.199 e $Å^{-3}$

Table 2
Selected bond lengths (Å) and bond angles (°) for caffeine:*p*-formylphenoxyacetic acid [(caf)(*p*-fpaa)] (**1**), caffeine:*o*-formylphenoxyacetic acid monohydrate [(caf)(*o*-fpaa)]H_2O (**2**), and caffeine:*p*-formylphenoxypropionic acid [(caf)(*p*-fppa)] (**3**).

Cocrystal **1**						Cocrystal **2**			Cocrystal **3**		
Bond lengths (Å)											
C(16)—N(3)	1.343(3)	C(16A)—N(3A)	1.343(3)	C(16B)—N(3B)	1.341(3)	C(16C)—N(3C)	1.343(3)	C(15)—N(3)	1.349(3)	C(16)—N(3)	1.3353(19)
C(16)—N(4)	1.336(3)	C(16)—N(4A)	1.339(3)	C(16B)—N(4B)	1.337(3)	C(16C)—N(4C)	1.327(3)	C(15)—N(4)	1.345(3)	C(16)—N(4)	1.3386(18)
C(9)—O(2)	1.202(3)	C(9A)—O(2A)	1.207(3)	C(9B)—O(2B)	1.194(3)	C(9C)—O(2C)	1.208(2)	C(9)—O(2)	1.201(2)	C(9)—O(2)	1.2149(18)
C(9)—O(3)	1.318(3)	C(9A)—O(3A)	1.323(2)	C(9B)—O(3B)	1.317(3)	C(9C)—O(3C)	1.320(2)	C(9)—O(3)	1.337(2)	C(9)—O(3)	1.3190(17)
C(1)—O(1)	1.363(3)	C(1A)—O(1A)	1.367(3)	C(1B)—O(1B)	1.362(3)	C(1C)—O(1C)	1.359(3)	C(1)—O(1)	1.365(2)	C(1)—O(1)	1.3714(16)
C(7)—O(4)	1.221(3)	C(7A)—O(4A)	1.225(3)	C(7B)—O(4B)	1.216(3)	C(7C)—O(4C)	1.218(3)	N(3)—C(13)	1.357(2)	C(7)—O(4)	1.2163(18)
Bond angles (°)											
C(11)—N(1)—C(10)	119.00(18)	C(11A)—N(1A)—C(10A)	118.94(18)	C(11B)—N(1B)—C(10B)	119.13(18)	C(11C)—N(1C)—C(10C)	119.27(18)	C(15)—N(4)—C(14)	105.50(16)	C(11)—N(1)—C(14)	122.25(12)
N(3)—C(11)—N(1)	125.8(2)	N(3A)—C(11A)—N(1A)	126.3(2)	N(3B)—C(11B)—N(1B)	126.03(19)	N(3C)—C(11C)—N(1C)	126.42(19)	C(4)—C(10)— O (4)	124.9(2)	N(3)—C(11)—N(1)	126.81(12)
N(3)—C(11)—C(12)	111.59(19)	N(3A)—C(11A)—C(12A)	111.63(19)	N(3B)—C(11B)—C(12B)	111.76(18)	N(3C)—C(11C)—C(12C)	111.56(18)	C(13)—N (2)—C(12)	119.40(16)	N(3)—C(11)—C(12)	111.07(12)
O(2)—C(9)—O(3)	124.0(2)	O(2A)—C(9A)—O(3A)	124.4(2)	O(2B)—C(9B)—O(3B)	124.2(2)	O(2C)—C(9C)—O(3C)	124.87(19)	O(2)—C(9)—O(3)	123.59(17)	O(2)—C(9)—O(3)	124.88(13)
C(1)—O(1)—C(8)	116.55(16)	C(1A)—O(1A)—C(8A)	116.77(16)	C(1B)—O(1B)—C(8B)	116.95(16)	C(1C)—O(1C)—C(8C)	117.27(16)	C(1)—O(1)—C(7)	117.22(14)	C(1)—O(1)—C(8)	116.15(10)
O(4)—C(7)—C(4)	124.1(2)	O(4A)—C(7A)—C(4A)	124.3(2)	O(4B)—C(7B)—C(4B)	124.5(2)	O(4C)—C(7C)—C(4C)	124.5(2)	C(15)—N(3)—C(13)	103.72(15)	C(16)—N(3)—C(11)	104.35(11)

of DPPH was incubated with various concentrations of each cocrystal (100 and 200 μg/mL). After 30 min incubation period at room temperature, absorbance of the resulting solution was recorded at 517 nm. DPPH radical scavenging activity was expressed as the inhibition percentage was calculated as absorbance of control minus absorbance of sample/absorbance of control × 100. Standard butylatedhydroxyanisole (BHA) and caffeine were used for comparison. The principle involved in this method is that the antioxidants react with the stable DPPH free radical (deep violet color) and convert it to 2,2-diphenyl-1-picrylhydrazine with discoloration. The degree of discoloration indicates the scavenging potential of the antioxidant sample [34].

3. Results and discussion

3.1. Crystal structure

Crystallographic data and structural refinement details for the cocrystals [(caf)(*p*-fpaa)] (**1**), [(caf)(*o*-fpaa)]H_2O (**2**), and [(caf)(*p*-fppa)] (**3**) are presented in Table 1. Their geometrical parameters are listed in Table 2. Some of the weak intermolecular interactions are listed in Table 3. The complete sets of structural parameters for the three cocrystals **1**–**3** are deposited in CCDC with deposition numbers 889465, 889466, and 889464 respectively.

3.1.1. Crystal structure of caffeine:p-formylphenoxyacetic acid [(caf)(p-fpaa)] (1)

The asymmetric unit of **1** contains four molecules of caffeine and four molecules of *p*-formylphenoxyacetic acid. The crystal structure shows that there is no proton transfer from the carboxyl group of *p*-fpaa to the caffeine in the asymmetric unit [35]. A predicted intermolecular hydrogen bonding motif O3—H3A···N3 is observed between the carboxyl group of *p*-fpaa and the imidazole nitrogen of caffeine as in many cocrystals of caffeine [36]. Excepting this strong O—H···N hydrogen bonding, there is no weak C—H···O hydrogen bonding between the carbonyl oxygen of —COOH group of *p*-fpaa and the acidic proton (C16H) in the imidazole moiety of caffeine as in many cases [37,21]. The C—O bond lengths [C9—O2: 1.202(3) Å, C9—O3: 1.318(3) Å; C9A—O2A: 1.207(3) Å, C9A—O3A: 1.323(2) Å; C9B—O2B: 1.194(3) Å, C9B—O3B: 1.317(3) Å; C9C—O2C: 1.208(2) Å, C9C—O3C: 1.320(2) Å; Table 2] confirm the asymmetric structure of the —COOH moiety.

Each *p*-fpaa combines with one unit of caffeine through O3—H3···N3 hydrogen bonding with Etter's [38,39,2] graph set designator D forming discrete molecules. Table 3 shows the hydrogen bonding geometry of cocrystal 1. This hydrogen bond is essentially linear, with an angle about hydrogen atom 176.03° for O(3)—H(3A)···N(3), 177.75° for O(3A)—H(3AB)···N(3A), 177.28° for O(3B)—H(3BA)···N(3B), and 176.11°

Table 3
Hydrogen bond geometry (Å and °).

D—H···A	D(D—H)	d(H···A)	D(D···A)	∠D—H···A
Cocrystal **1**				
O(3)—H(3A)···N(3)	0.840	1.818	2.657	176.03°
O(3A)—H(3AB)···N(3A)	0.841	1.829	2.669	177.75°
O(3B)—H(3BA)···N(3B)	0.840	1.827	2.667	177.28°
O(3C)—H(3CA)···N(3C)	0.839	1.830	2.668	176.11°
Cocrystal **2**				
O(3)—H(3A)···N(3)	0.840	1.795	2.633	172.58°
Cocrystal **3**				
O(3)—H(3)···N(3)	0.839	1.852	2.690	176.43

for O(3C)—H(3CA)···N(3C) (Table 3) (Fig. s1, vide Supporting information for the packing diagram of [(caf)(p-fpaa)]).

The carboxyl group O3—C9—O2 of *p*-fpaa lies almost on the same plane of the phenyl ring (C1—C6), since it makes a dihedral angle of 9.27° with the phenyl ring of *p*-fpaa. The caffeine molecule and the *p*-fpaa molecule are nearly coplanar as their mean plane angle is only 2.97°.

The crystal structure is stabilized by the face-to-face π–π stacking force (3.639 Å) which is found between the parallel imidazole moiety of caffeine and the phenyl ring of *p*-fpaa (Fig. s2, vide Supporting information).

3.1.2. Crystal structure of caffeine:*o*-formylphenoxyacetic acid monohydrate [(caf)(*o*-fpaa)]H_2O (**2**)

Fig. 1c shows the ORTEP diagram of [(caf)(*o*-fpaa)]H_2O (**2**) along with the adopted atomic numbering scheme. The asymmetric unit of [(caf)(*o*-fpaa)]H_2O (**2**) contains one molecule of caffeine, one molecule of *o*-formylphenoxyacetic acid, and a molecule of water. Cocrystal hydrates are formed with inclusion of water molecules in their crystal structures. These materials receive high stability from high humidity conditions [40]. The crystal structure of **2** shows that there is no proton transfer from the carboxyl group of *o*-fpaa to the caffeine in the asymmetric unit. The C—O bond lengths [C9—O2: 1.2149(18) Å, C9—O3: 1.3190(17) Å, Table 2] indicate that the acid moiety is present as —COOH. An intermolecular hydrogen bonding motif O3—H3···N3 [O3—H3A = 0.84 Å, O3···N3 = 2.633 Å, O3—H3A···N3 = 172.58°] is observed between the carboxyl group of *o*-fpaa and the imidazole nitrogen of caffeine [35,36]. In addition to this strong O—H···N hydrogen bonding, there is no weak C—H···O hydrogen bonding between the carbonyl oxygen of —COOH group of *o*-fpaa and the acidic proton in the imidazole moiety of caffeine as in other cases [37,21]. But the carbonyl

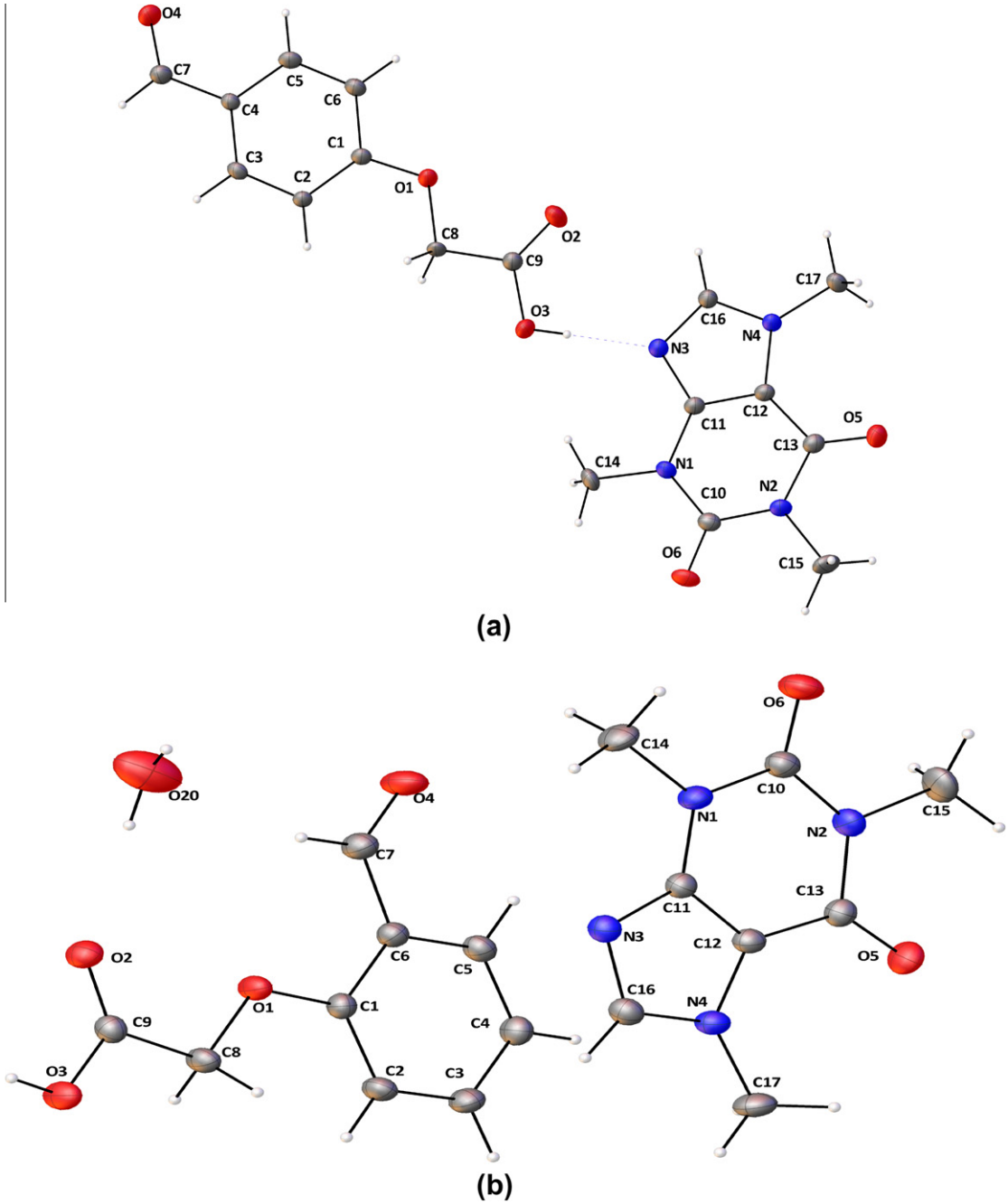

Fig. 1. ORTEP view for (a) [(caf)(*p*-fpaa)] (**1**), (b) [(caf)(*o*-fpaa)]H_2O (**2**), and (c) [(caf)(*p*-fppa)] (**3**).

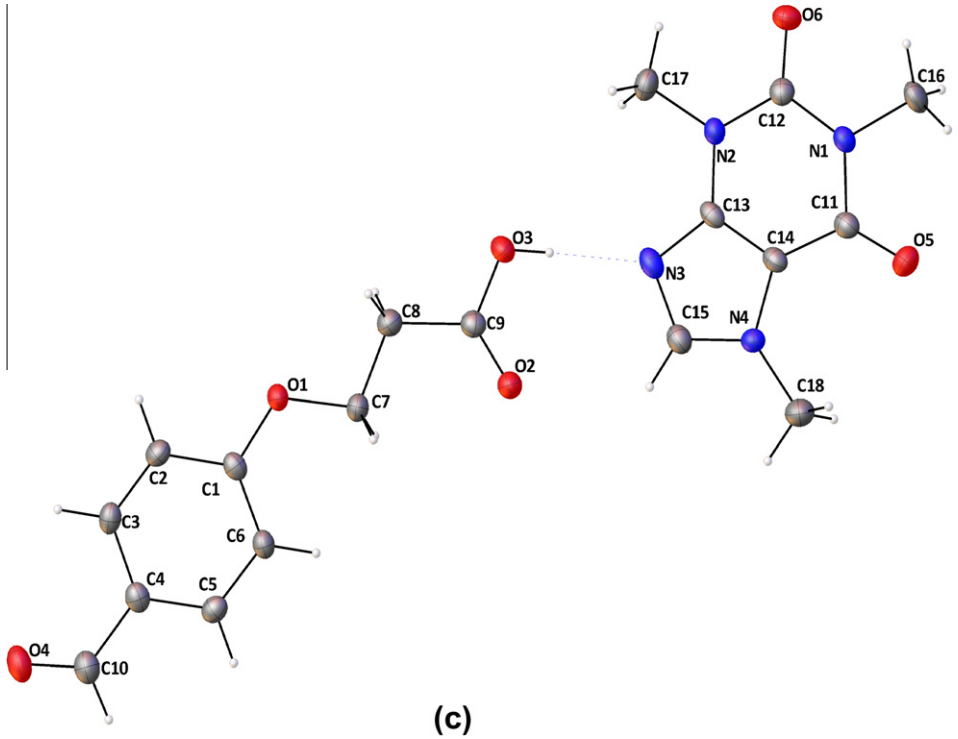

Fig. 1. (*continued*)

oxygen of —COOH group forms H-bonding with the water molecule Ow—H1w···O2 [Ow—H1w = 0.87 Å, Ow···O2 = 2.968 Å, Ow—H1w···O2 = 179.86°, Table 3].

Each *o*-fpaa molecule is connected with two molecules of caffeine. With one caffeine it is directly connected by hydrogen bonding with the imidazole nitrogen [O3—H3A···N3, H-bond donor],

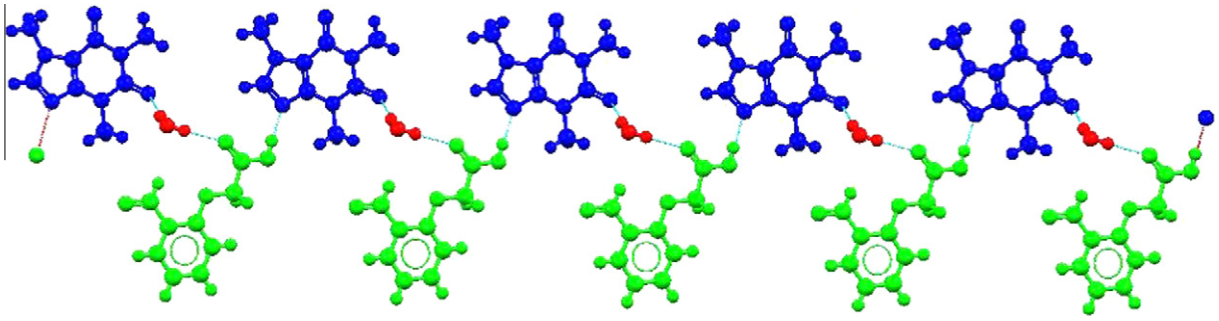

Fig. 2. 1D chain of [(caf)(*o*-fpaa)]H_2O (**2**).

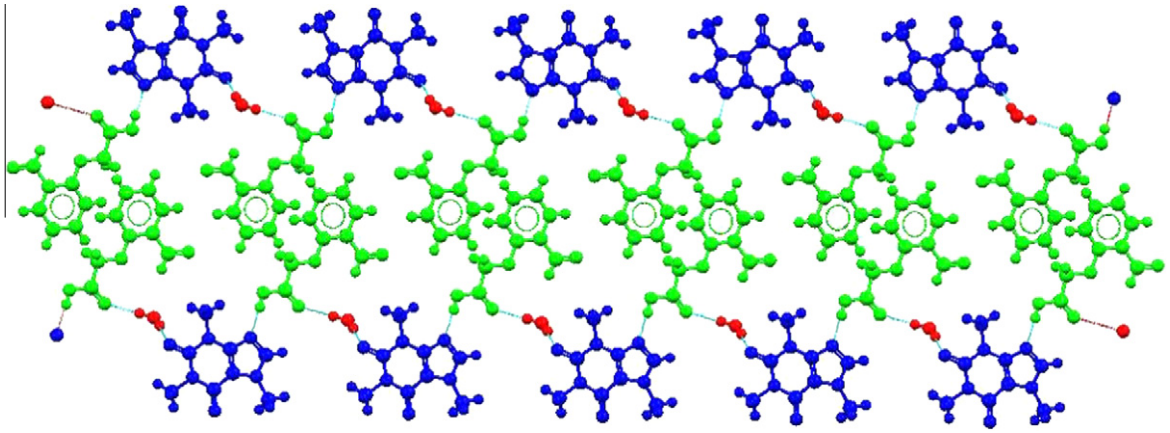

Fig. 3. Tube-like structure of [(caf)(*o*-fpaa)]H_2O (**2**).

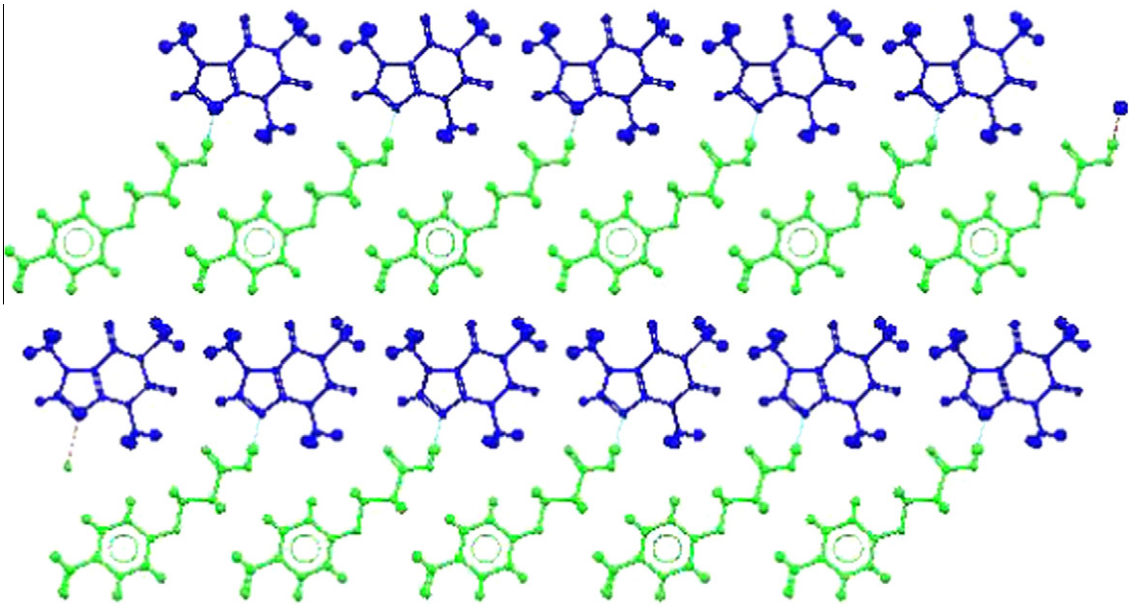

Fig. 4. Packing along *b*-axis in [(caf)(*p*-fppa)] **(3)**.

whereas with the second caffeine it is connected by hydrogen bonding through water molecule [Ow—H1w···O2, H-bond acceptor]. The second hydrogen atom of water forms H-bonding with the carbonyl oxygen of caffeine Ow—H2w···O6. So, each caffeine is also connected with two molecules of *o*-fpaa, one directly and another through water molecule.

This mode of connection gives rise to 1D chain with Etter's [38,39,2] graph set designator $C_3^3(12)$. In the formation of the chain, all the caffeine molecules are lying on one side and all the *o*-fpaa molecules are lying on the other side (Fig. 2).

In the crystal packing of [(caf)(*o*-fpaa)]H_2O (**2**), the 1D chains are arranged antiparallel to each other so as to form a tube-like chain (Fig. 3) in which the caffeine molecules are present outside the tube and *o*-fpaa molecules are present inside the tube.

The caffeine molecule and the *o*-fpaa molecule are almost parallel to each other, since the dihedral angle between them is 8.33°. The carboxyl group of *o*-fpaa lies in the same plane of the phenyl ring of *o*-fpaa as revealed by the dihedral angle of 1.07°. The crystal structure is stabilized by a π–π stacking interaction (3.582 Å) which is present between the phenyl ring of *o*-fpaa and the imidazole ring of caffeine (Fig. s3, vide Supporting information).

3.1.3. Crystal structure of caffeine:p-formylphenoxypropionic acid [(caf)(p-fppa)] (3)

The ORTEP diagram of the cocrystal **3** is shown in Fig. 1b. The asymmetric unit of **3** contains one molecule of caffeine and a molecule of *p*-formylphenoxypropionic acid. The crystal structure shows that there is no proton transfer from the carboxyl group of *p*-fppa to the caffeine in the asymmetric unit. The C—O bond lengths [C9—O2: 1.201(2) Å, C9—O3: 1.337(2) Å, indicate that the acid moiety is not deprotonated.

As in the cocrystals **1** and **2** an intermolecular hydrogen bonding motif O3—H3---N3 [O3—H3 = 0.839 Å, O3···N3 = 2.690 Å, O3—H3···N3 = 176.43°] is observed between the carboxyl group of *p*-fppa and the imidazole nitrogen of caffeine. The weak C—H···O hydrogen bonding between the carbonyl oxygen of —COOH group of *p*-fppa and the acidic proton (C15—H15) in the imidazole moiety of caffeine is not found in this cocrystal **3** as in the cocrystals **1** and **2**. Each *p*-fppa combines with one unit of caffeine through O3—H3···N3 hydrogen bonding with Etter's [38,39,2] graph set designator D forming discrete molecules. The O3···N3 distance is 2.690 Å. The ∠D—H···A 176.43° shows that this bond is linear. When the discrete molecules are packed in the crystal, they form zigzag chains when viewed along *b* axis (Fig. 4).

The carboxyl group O3—C9—O2 of *p*-fppa lies almost on the same plane of the phenyl ring (C1—C6), since it makes a dihedral

Table 4
^{1}H NMR (DMSO-d_6) data of cocrystals **1**–**3**.

No. of protons, splitting, type of proton	Proton numbering as mentioned in ORTEP	Chemical shift (δ ppm)
Cocrystal (**1**)		
3H, s, N—CH_3	14	3.19
3H, s, N—CH_3	15	3.38
3H, s, N—CH_3	17	3.85
2H, s, OCH_2	8	4.83
2H, d, Ar—H	2, 6	7.10
2H, d, Ar—H	3, 5	7.85
1H, s, Ar—H (caf)	16	7.98
1H, s, CHO	7	9.86
Cocrystal (**2**)		
3H, s, N—CH_3	14	3.21
3H, s, N—CH_3	15	3.40
3H, s, N—CH_3	17	3.87
2H, s, OCH_2	8	4.90
1H, t, Ar—H	3	7.10
1H, d, Ar—H	2	7.15
1H, t, Ar—H	4	7.64
1H, d, Ar—H	5	7.71
1H, s, Ar—H (caf)	16	8.00
1H, s, CHO	7	10.44
1H, s, COOH	O3	13.21
Cocrystal (**3**)		
2H, t, CH_2—CO	8	2.74
3H, s, N—CH_3	17	3.21
3H, s, N—CH_3	16	3.40
3H, s, N—CH_3	18	3.87
2H, s, O—CH_2	7	4.28
2H, d, Ar—H	2, 6	7.13
2H, d, Ar—H	3, 5	7.86
1H, s, Ar—H (caf)	15	8.00
1H, s, CHO	10	9.87
1H, s, COOH	O4	12.46

Table 5
Antibacterial activity of cocrystals **1**–**3**.

Cocrystals	Bacterial species						
	a	b	c	d	e	f	g
[(caf)(*p*-fpaa)] (**1**)	++ +	++ +	++ +	–	–	++ +	++ +
[(caf)(*o*-fpaa)]H_2O (**2**)	++	++	–	++	++	++	–
[(caf)(*p*-fppa)] (**3**)	++	++	++ +	++	++	–	++

a. *Staphylococcus aureus*, b. *Streptococcus* sps., c. *Enterobacter* sps. d. *E. coli*, e. *Pseudomonas aeroginosa*, f. *Proteus* sps., g. *Klebsiella* sps.

Table 6
Antifungal activity of cocrystals **1**–**3**.

Cocrystals	Fungal species	
	a	b
[(caf)(*p*-fpaa)] (**1**)	–	–
[(caf)(*o*-fpaa)]H_2O (**2**)	–	–
[(caf)(*p*-fppa)] (**3**)	++	++

a. *Candida* sps., b. *Aspergillus* sps. Inhibition zone diameter mm (% inhibition): +, 6–10 (27–45%); ++, 10–14 (45–64%); ++ +, 14–18 (64–82%); ++ ++, 18–22 (82–100%). (–) = No inhibition zone. Percent inhibition values are relative to inhibition zone of standard antibacterial (chloramphenicol) and standard antifungal (Nystatin), considered as 100% inhibition, tested under the same conditions as the new compounds reported here.

Table 7
DPPH radical-scavenging activity of cocrystals **1**–**3**.

Samples	DPPH radical scavenging (%)	
	100 μg/mL	200 μg/mL
[(caf)(*p*-fpaa)] (**1**)	56.32	54.12
[(caf)(*o*-fpaa)]H_2O (**2**)	50.32	50.28
[(caf)(*p*-fppa)] (**3**)	57.36	55.34
Standard (caffeine)	47.70	52.78
BHA	95.74	94.02

angle of 7.03° with the phenyl ring of *p*-fppa. The caffeine molecule and the *p*-fppa molecule are lying nearly parallel because their mean plane angle is 14.88°. The crystal structure is stabilized by a π–π stacking interaction (3.482 Å) which is present between the phenyl ring of *o*-fppa and the imidazole ring of caffeine (Fig. s4, vide Supporting information).

*3.2. IR spectrum of caffeine:p-formylphenoxyacetic acid [(caf)(p-fpaa)] (**1**), caffeine:o-formylphenoxyacetic acid monohydrate [(caf)(o-fpaa)]H_2O (**2**) and caffeine:p-formylphenoxypropionic acid [(caf)(p-fppa)] (**3**)*

Compounds (**1**–**3**) exhibit broad bands between 3442 and 3563 cm^{-1} indicating the intermolecularly H-bonded OH group [41–43] (Fig. s5a–f, vide Supporting information). In the IR spectra of cocrystals [(caf)(*p*-fpaa)] (**1**) and [(caf)(*o*-fpaa)]H_2O (**2**), three intense bands were displayed at 1745 cm^{-1}, 1700 cm^{-1} and 1656 cm^{-1} for [(caf)(*p*-fpaa)] (**1**) and at 1706 cm^{-1}, 1681 cm^{-1}, and 1660 cm^{-1} for [(caf)(*o*-fpaa)]H_2O (**2**). Cocrystal [(caf)(*p*-fppa)] (**3**) displayed two intense bands at 1706 cm^{-1} and 1655 cm^{-1}. It is presumed that the stretching frequencies of the carbonyl group of caffeine (N(CH_3)—C═O, 1700 cm^{-1}), and that of the carbonyl (—C═O, 1717 cm^{-1}) and the carboxylic carbonyl (—COOH, 1754 cm^{-1}) of the free formylphenoxyaliphatic acids merge together and appear as these new bands in the cocrystals. The formation of the new compounds could be confirmed by the changes in the carbonyl frequencies in the crystals. The change in carbonyl frequency in cocrystals is due to the involvement of carboxyl group in hydrogen bond formation [41–43].

*3.3. ^{1}H NMR of caffeine:p-formylphenoxyacetic acid [(caf)(p-fpaa)] (**1**), caffeine:o-formylphenoxyacetic acid monohydrate [(caf)(o-fpaa)]H_2O (**2**), and caffeine:p-formylphenoxypropionic acid [(caf)(p-fppa)] (**3**)*

^{1}H NMR spectra of cocrystals **1**–**3** (Fig. s6a–c, vide Supporting information) confirms the 1:1 stoichiometric ratio of caffeine with formylphenoxyaliphatic acids. The details of the ^{1}H NMR spectra are given in Table 4.

*3.4. Thermogravimetric studies of [(caf)(p-fpaa)] (**1**), [(caf)(o-fpaa)]H_2O (**2**), and [(caf)(p-fppa)] (**3**)*

TGA measurement (Fig. s7a–c, vide Supporting information) shows that the cocrystals **1** and **3** undergo gradual decomposition after 175 °C and the cocrystal **2** remains intact until 125 °C. The first weight loss of 6.15% (calculated 4.587%) for the cocrystal **2** may be due to the removal of a molecule of water. There is a gradual decomposition after 240 °C. The weight loss process in all the three cocrystals is an endothermic process which has been identified from their DTA curves.

3.5. Biological activity

3.5.1. Antimicrobial activity

The *in vitro* biological screening effects of all the three cocrystals were tested against the bacteria: *S. aureus*, *Streptococcus* species, *Enterobacter* species, *E. coli*, *P. aeruginosa*, *Proteus* species, and Klebsiella species by the well-diffusion method [31] using Muller Hinton agar nutrient as the medium. The antifungal activities of the compounds were also evaluated by the well-diffusion method against the fungi viz., *Candida* species, *Aspergillus* species cultured on anti mytotic medium. The compounds were tested at a concentration of 50 μg/0.01 mL in methanol solution. The results are tabulated in Tables 5 and 6 respectively.

From the antibacterial activity result (Table 5) it is clear that [(caf)(*p*-fpaa)] (**1**) has good activity against five tested bacteria and has no activity against *E. coli* and *Pseudomonas aeroginosa*. [(caf)(*o*-fpaa)]H_2O (**2**) has moderate activity against five tested bacteria and has no activity against *Enterobacter* sps. and *Klebsiella* sps. Whereas [(caf)(*p*-fppa)] (**3**) has good activity against *Enterobacter* sps., moderate activity against five tested bacteria but no activity against *Proteus* sps.

From the antifungal activity result (Table 6) it is evident that [(caf)(*p*-fpaa)](**1**) and [(caf)(*o*-fpaa)]H_2O (**2**) are not active against the tested two fungi whereas [(caf)(*p*-fppa)] (**3**) has moderate activity towards the tested two fungi.

3.5.2. Free radical-scavenging activity

The free radical-scavenging activity for the cocrystals [(caf)(*p*-fpaa)] (**1**), [(caf)(*o*-fpaa)]H_2O (**2**), and [(caf)(*p*-fppa)] (**3**) was evaluated using DPPH model system [33,34] and the results are presented in Table 7. From the result it is clear that the free radical-scavenging activities of cocrystals are slight greater than that of caffeine.

4. Conclusions

Three organic cocrystals [(caf)(*p*-fpaa)] (**1**), [(caf)(*o*-fpaa)]H_2O (**2**), and [(caf)(*p*-fppa)] (**3**) were synthesized and their structures were determined from FT-IR, NMR, TGA/DTA, and single crystal XRD studies. All the three cocrystals form two-component

assemblies based on the well-established caffeine (imidazole)–carboxylic acid synthon. Intermolecular hydrogen bonds O—H···N with graph set designator D and π–π interactions play a vital role in the formation of the cocrystals [(caf)(*p*-fpaa)] (**1**) and [(caf)(*p*-fppa)] (**3**). In cocrystal [(caf)(*o*-fpaa)]H_2O (**2**), the intermolecular hydrogen bond, O—H···N with graph set designator $C_3^3(12)$, and the π–π interactions are important in stabilizing the structure. Cocrystal,[(caf)(*p*-fpaa)] (**1**) has good activity against five tested bacteria, [(caf)(*o*-fpaa)]H_2O (**2**) has moderate activity against five tested bacteria, and [(caf)(*p*-fppa)] (**3**) has good activiy against *Enterobacter* sps., and moderate activity against five tested bacteria. Cocrystal, [(caf)(*p*-fppa)] (**3**) has moderate activity towards the two fungi, *Candida* sps., and *Aspergillus* sps. Cocrystals **1**–**3** have slightly more DPPH radical scavenging activity than caffeine.

Acknowledgments

Authors thank Ms. K. Ramalakshmi, Plantation Products Spices and Flavour Technology Department, Central Food Technological Research Institute, Council of Scientific and Industrial Research (CSIR), Mysore, India and SAIF, CDRI, Lucknow, India for spectral studies.

Appendix A. Supplementary material

CCDC 889465, 889466 and 889464 contain the supplementary crystallographic data for [(caf)(*p*-fpaa)] (**1**), [(caf)(*o*-fpaa)]H_2O (**2**), and [(caf)(*p*-fppa)] (**3**) respectively. This can be obtained free of charge from the Director, CCDC, 12, Union Road, Cambridge CBZ 1E2, UK. E-mail: deposit@ccdc.cam.ac.uk. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molstruc.2012.10.033.

References

[1] J. Schmidt, W. Snipes, Int. J. Radiat. Biol. 13 (1967) 101.
[2] M.C. Etter, J. Phys. Chem. 95 (1991) 4601.
[3] G.R. Desiraju, Cryst. Eng. Commun. 5 (2003) 466.
[4] J.D. Dunitz, Cryst. Eng. Commun. 5 (2003) 506.
[5] T.W. Panunto, Z.U. Lipkowska, R. Johnson, M.C. Etter, J. Am. Chem. Soc. 109 (1987) 7786.
[6] M.C. Etter, Z.U. Lipkowska, S. Mohammad Zia-Ebrahimi, T.W. Panunto, J. Am. Chem. Soc. 112 (1990) 8415.
[7] M.C. Etter, S.M. Reutzel, C.G. Choo, J. Am. Chem. Soc. 115 (1993) 4411.
[8] M. Zaworotko, Acta Cryst. A64 (2008) c11.
[9] C.C. Sun, H. Hou, Cryst. Growth Des. 8 (2008) 1575.
[10] N.R. Horendo, S.J. Nehm, A. Jayasankar, Cocrystals: design, properties and formation mechanisms, in: Encyclopedia of Pharmaceutical Technology, third ed. Taylor & Francis, London, 2007, p. 815.
[11] (a) A.V. Trask, W.D.S. Motherwell, W. Jones, Cryst. Growth Des. 5 (2005) 1013;
(b) P. Vishweshwar, J.A. McMahon, J.A. Bis, M.J. Zaworotko, J. Pharm. Sci. 95 (2006) 499;
(c) D.P. McNamara, S.L. Childs, J. Giordano, A. Iarriccio, J. Cassidy, M.S. Shet, R. Mannion, E. O'Donnell, A. Park, Pharm. Res. 23 (2006) 1888;
(d) A. Jayasankar, A. Somwangthanaroj, Z.J. Shao, N.R. Hornedo, Pharm. Res. 23 (2006) 2381;
(e) S.J. Nehm, B.R. Spong, N.R. Hornedo, Cryst. Growth Des. 6 (2006) 592.
[12] (a) A.N. Sokolov, T. Friščić, L.R. MacGillivray, J. Am. Chem. Soc. 128 (2006) 2806;
(b) G.S. Papaefstathiou, Z. Zhong, L. Geng, L.R. MacGillivray, J. Am. Chem. Soc. 126 (2004) 9158.
[13] (a) M.L. Cheney, G.J. McManus, J.A. Perman, Z. Wang, M.J. Zaworotko, Cryst. Growth Des. 7 (2007) 616;
(b) T. Friščić, L.R. MacGillivray, Chem. Commun. (2006) 5748;
(c) X. Gao, T. Friščić, L.R. MacGillivray, Angew. Chem. Int. Ed. 43 (2004) 232;
(d) J.H. Kim, S.V. Lindeman, J.K. Kochi, J. Am. Chem. Soc. 123 (2001) 4951.
[14] D.K. Bucar, R.F. Henry, X. Lou, R.W. Duerst, L.R. MacGillivray, G.G.Z. Zhang, Cryst. Growth Des. 9 (4) (2009) 1932.
[15] A. Nehlig, J.L. Daval, G. Debry, Brain Res. Rev. 17 (1992) 139.
[16] R. Brookmeyer, S. Gray, C. Kawas, Am. J. Public Health 88 (1998) 1337.
[17] (a) G. Arendash, W. Schleif, K.R. Zadeh, E. Jackson, L. Zacharia, J. Cracchiolo, D. Shippy, J. Tan, Neuroscience 142 (2006) 941;
(b) G. Arendash, T. Mori, M. Mamcarz, M. Runfeldt, A. Dickson, K.R. Zadeh, J. Tan, B. Citron, X. Lin, C. Cao, V.E. Moran, H. Potter, J. Alzheimer's Disease 17 (2009) 661.
[18] G. Arendash, C. Chuanhai, J. Alzheimer's Disease 20 (2010) S117.
[19] J. Hardy, D. Selkoe, Science 297 (2002) 353.
[20] T. Tomita, Expert Rev. Neurother. 9 (2009) 661.
[21] V. Bala, Y.S. Chhonker, S.R. Hashim, Asian J. Chem. 22 (5) (2010) 3447.
[22] T.A.H. William, P. Ramadevi, P.G. Seethalakshmi, S. Kumaresan, Acta Cryst. E63 (2007) o3911.
[23] P.G. Seethalakshmi, P. Ramadevi, S. Kumaresan, T.A.H. William, Acta Cryst. E63 (2007) o4837.
[24] S. Kumaresan, P.G. Seethalakshmi, P. Kumaradhas, B. Devipriya, J. Mol. Struct. 1032 (2013) 169.
[25] APEX2 "Program for Data Collection on Area Detectors" BRUKER AXS Inc., 5465 East Cheryl Parkway, Madison, WI 53711-5373, USA.
[26] SADABS, G.M. Sheldrick, "Program for Absorption Correction of Areadetector Frames", BRUKER AXS Inc., 5465 East Cheryl Parkway, Madison, WI 53711-5373, USA.
[27] G.M. Sheldrick, Acta Cryst. A64 (2008) 112; X.S. BRUKER AXS Inc., 5465 East Cheryl Parkway, Madison, WI 53711-5373, USA.
[28] O.V. Dolomanov, L.J. Bourhis, R.J. Gildea, J.A.K. Howard, H. Puschmann, J. Appl. Cryst. 42 (2009) 339.
[29] A.L. Spek, Appl. Cryst. 36 (2003) 7.
[30] (a) B.S. Furniss, A.J. Hannaford, P.W.G. Smith, R. Austin, Vogel's Textbook of Practical Organic Chemistry, Longman Scientific & Technical, V edition, 1989, p. 1160.;
(b) G.S. Suresh Kumar, S. Kumaresan, J. Chem. Sci. 124 (4) (2012) 857;
(c) G.S. Suresh Kumar, S. Kumaresan, A. Antony Muthu Prabu, P.G. Seethalakshmi, Spectrochim. Acta A. doi: http://dx.doi.org/10.1016/j.saa.2012.09.046.
[31] O.N. Irobi, M.M. Young, W.A. Anderson, Int. J. Pharm. 34 (1996) 87.
[32] M.J. Pelczar, E.C.S. Chan, N.R. Krieg, Microbiology, fifth ed., Blackwell Science, New York, 1998.
[33] K. Ramalakshmi, L. Jagan Mohan Rao, Y.T. Ishikawa, M. Goto, Food Chem. 115 (2009) 79.
[34] M.H. Abdille, R.P. Singh, G.K. Jayaprakasha, B.S. Jena, Food Chem. 90 (2005) 891.
[35] L.H. Thomas, A.J. Florence, C.C. Wilson, New J. Chem. 33 (2009) 2486.
[36] (a) A.V. Trask, W.D.S. Motherwell, W. Jones, Cryst. Growth Des. 5 (3) (2005) 1013;
(b) D.K. Bucar, R.F. Henry, X. Lau, R.W. Duerst, T.B. Borchardt, L.R. Mac Gillivray, G.G. Zhang, Mol. Pharm. 4 (3) (2007) 339.
[37] S. Kumaresan, M. Indrani, R. Ramasubramanian, R. Suba, P.E. Karthik, S. Athaven, F.R. Fronzcek, Int. J. Curr. Chem. 1 (3) (2010) 163.
[38] M.C. Etter, J.C. MacDonald, J. Bernstein, Acta Cryst. B46 (1990) 256.
[39] (a) M.C. Etter, Acc. Chem. Res. 23 (1990) 120;
(b) J. Bernstein, R.E. Davis, L. Shimoni, N.L. Chang, Angew. Chem. Int. Ed. Engl. 34 (1995) 1555.
[40] (a) S. Karki, T. Friscic, W. Jones, W.D.S. Motherwell, Mol. Pharm. 4 (3) (2007) 347;
(b) S.P. Velaga, S. Basavoju, D. Bostrom, J. Mol. Struct. 889 (2008) 150.
[41] J.B. Lambert, H.F. Shurvell, D.A. Lightner, R.G. Cooks, Organic Structural Spectroscopy, Prentice Hall, New Jersey, 1998.
[42] R.M. Silverstein, G.C. Bassler, T.C. Morrill, Spectrometric Identification of Organic Compounds, fifth ed., John Wiley & Sons, New York, 1991.
[43] P. Pretsch, P. Buhlman, C. Affolter, Structure Determination of Organic Compounds Tables of Spectral Data, Springer, Berlin, 2000.