Supporting Information

Ciprofloxacin salts with benzoic acid derivatives: structural aspects, solid-state properties and solubility performance

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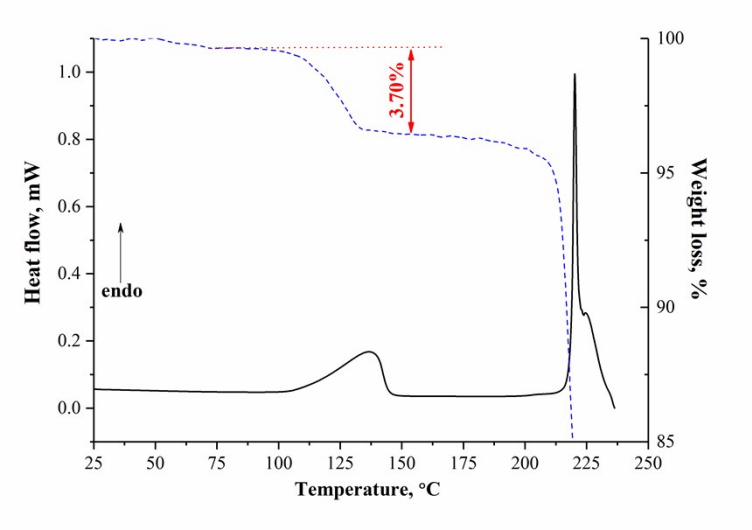
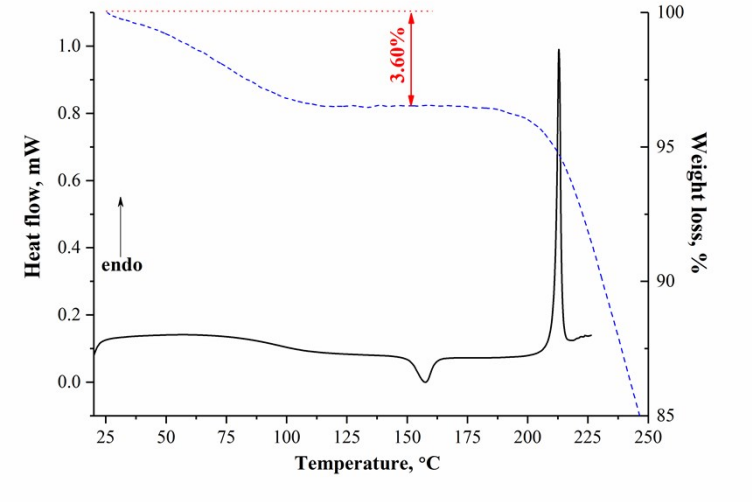


(**a**)



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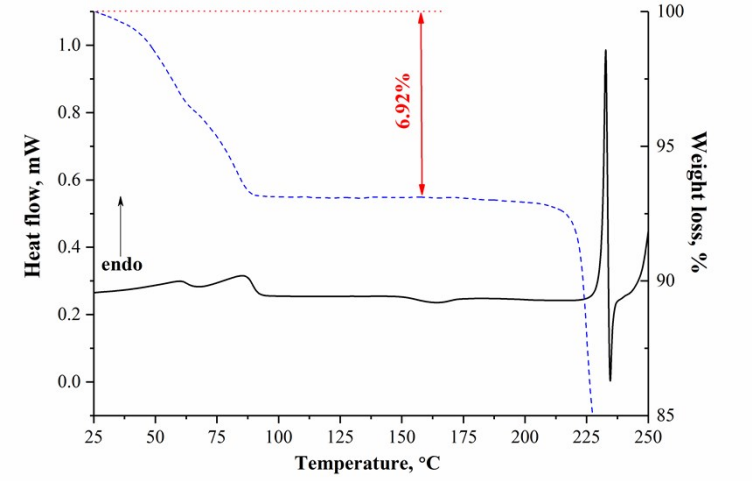


(**c**)

Figure S1. Results of DSC and TGA analyses of (a) [**CIP**+**4OHBA**+**H_2O**] (1:1:1), (b) [**CIP**+**4AmBA**+**H_2O**] (1:1:1), and (c) [**CIP**+**GA**+**H_2O**] (1:1:2).

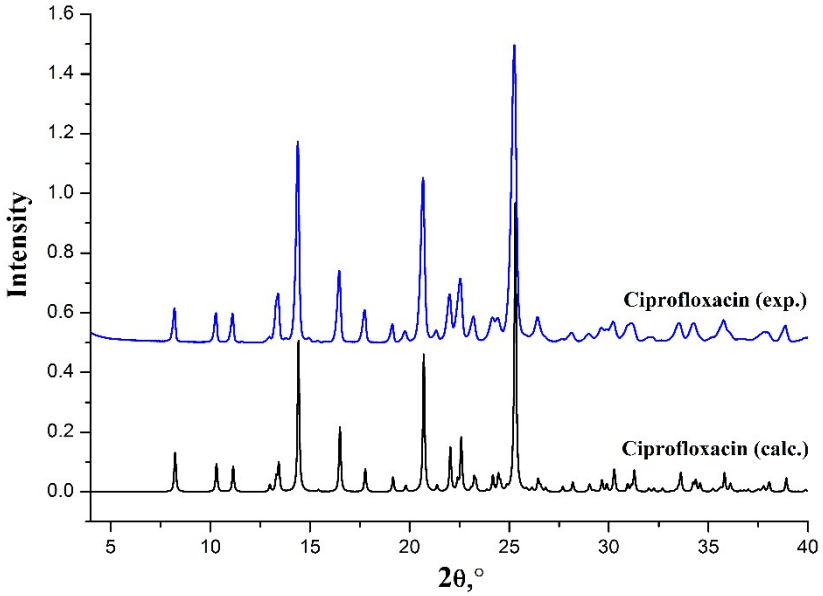


Figure S2. Experimental and calculated PXRD patterns of zwitterionic ciprofloxacin.

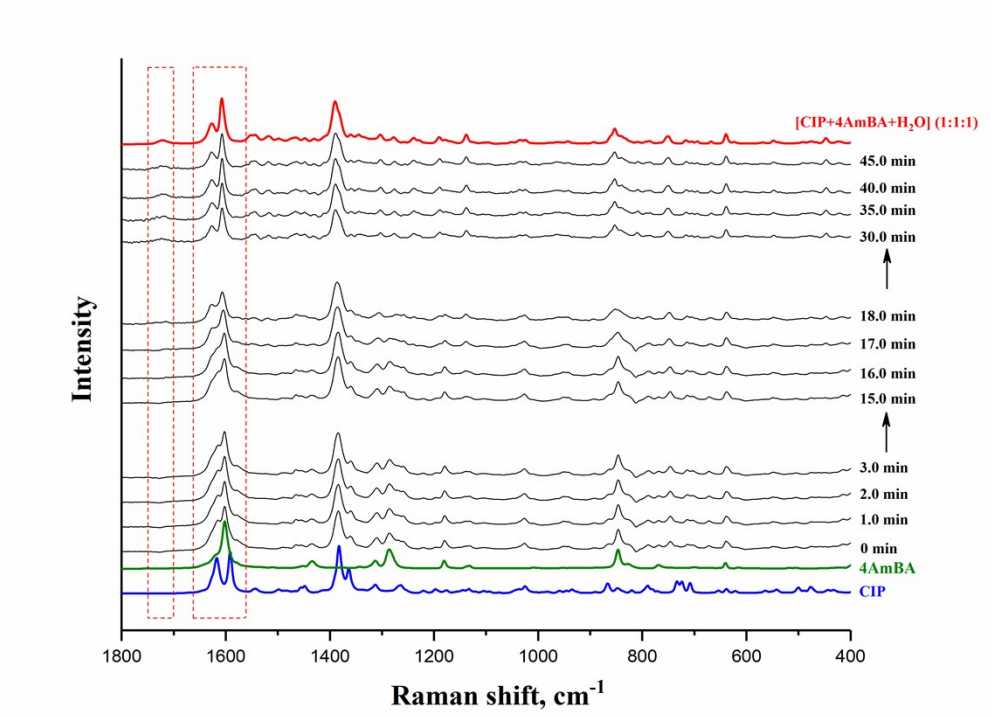


Figure S3. Time resolved *in situ* Raman spectra collected during the mechanochemical reaction of the anhydrous ciprofloxacin and 4-aminobenzoic acid in the presence of water.

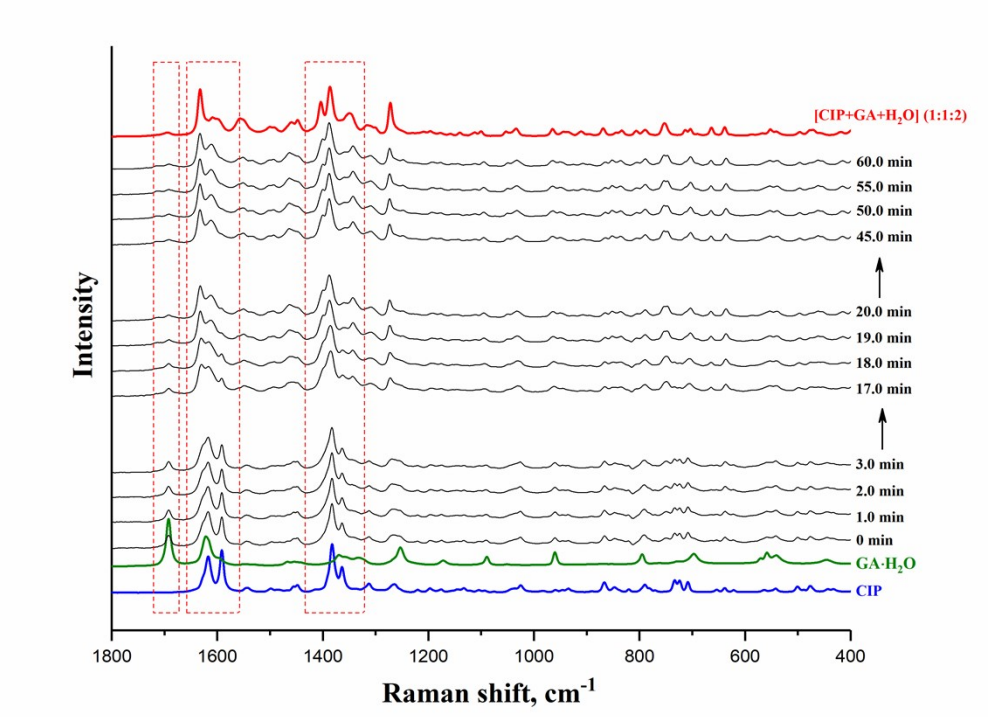


Figure S4. Time resolved *in situ* Raman spectra collected during the mechanochemical reaction of the anhydrous ciprofloxacin and gallic acid monohydrate in the presence of water.

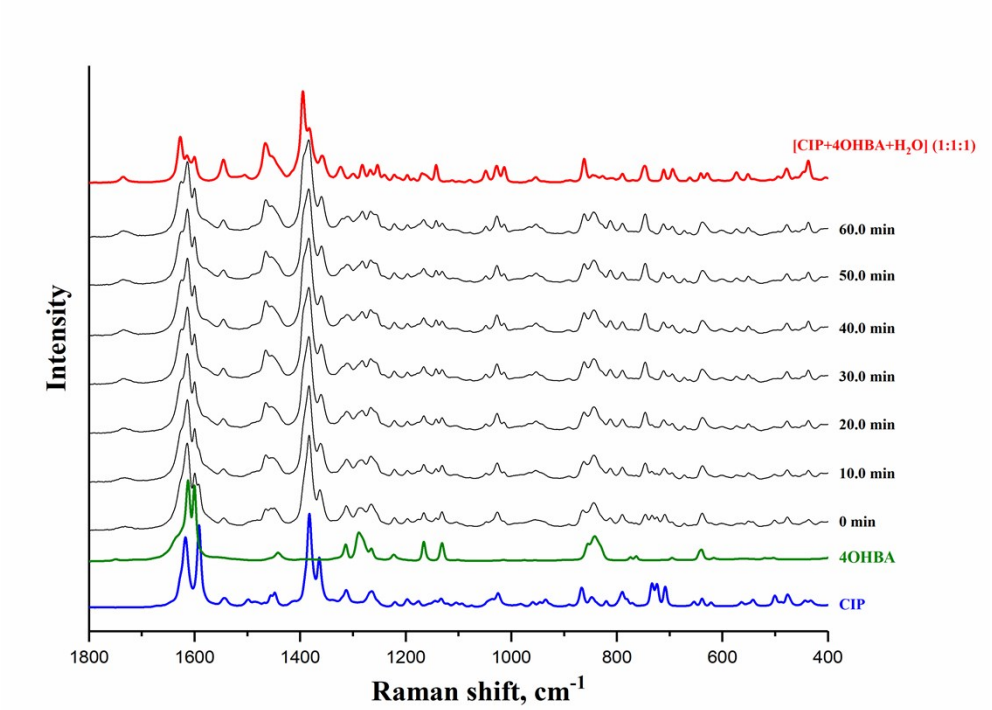
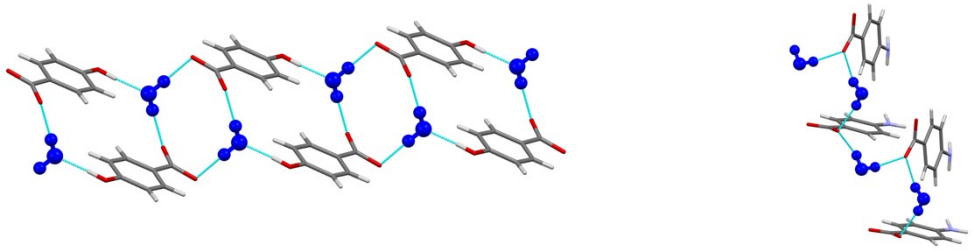


Figure S5. Time resolved *in situ* Raman spectra collected during the mechanochemical reaction of the anhydrous ciprofloxacin and 4-hydroxybenzoic acid in the presence of water.



(**a**) (**b**)

Figure S6. Hydrogen bonded motives between counterions and water molecules in the crystals of (a) **[CIP+4OHBA+H_2O]** (1:1:1) and (b) **[CIP+4AmBA+H_2O]** (1:1:1).

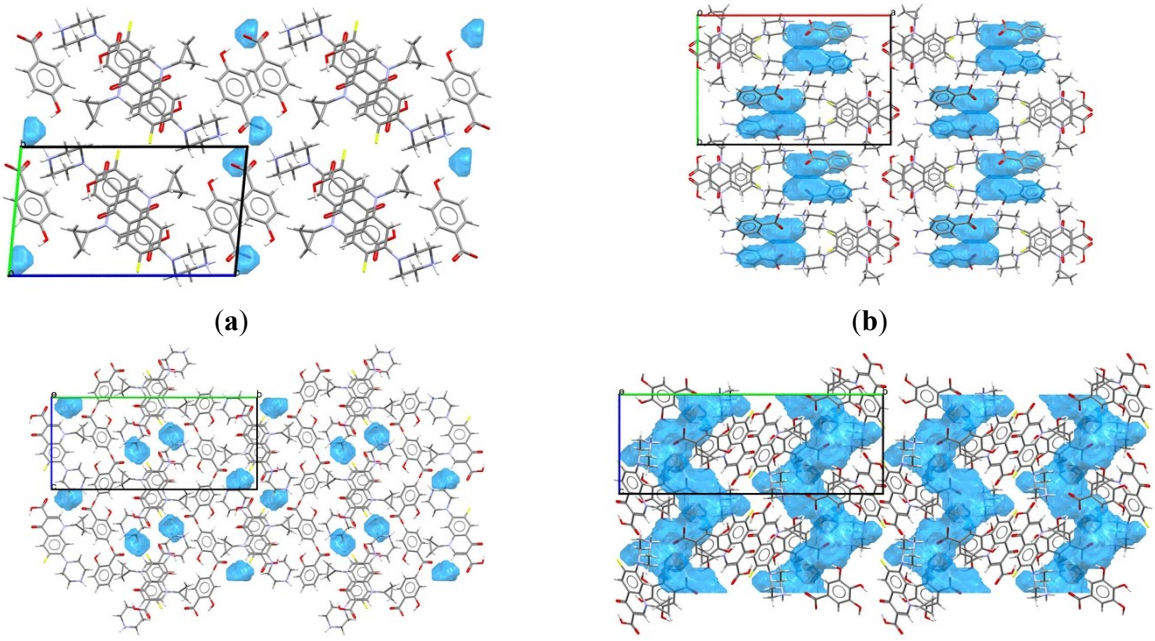


Figure S7. Void maps in the crystal structures of (a) **[CIP+4OHBA+H_2O]** (1:1:1), (b) **[CIP+4AmBA+H_2O]** (1:1:1), (c) **[CIP+SA+H_2O]** (1:1:1) and (d) **[CIP+GA+H_2O]** (1:1:2).

(**a**) (**b**)

Figure S8. Geometry of CIP dimer (a) taken from the **[CIP+4AmBA+H_2O]** (1:1:1) crystal structure and (b) after geometry optimization at the B3LYP-D3/aug-cc-pVTZ level of theory

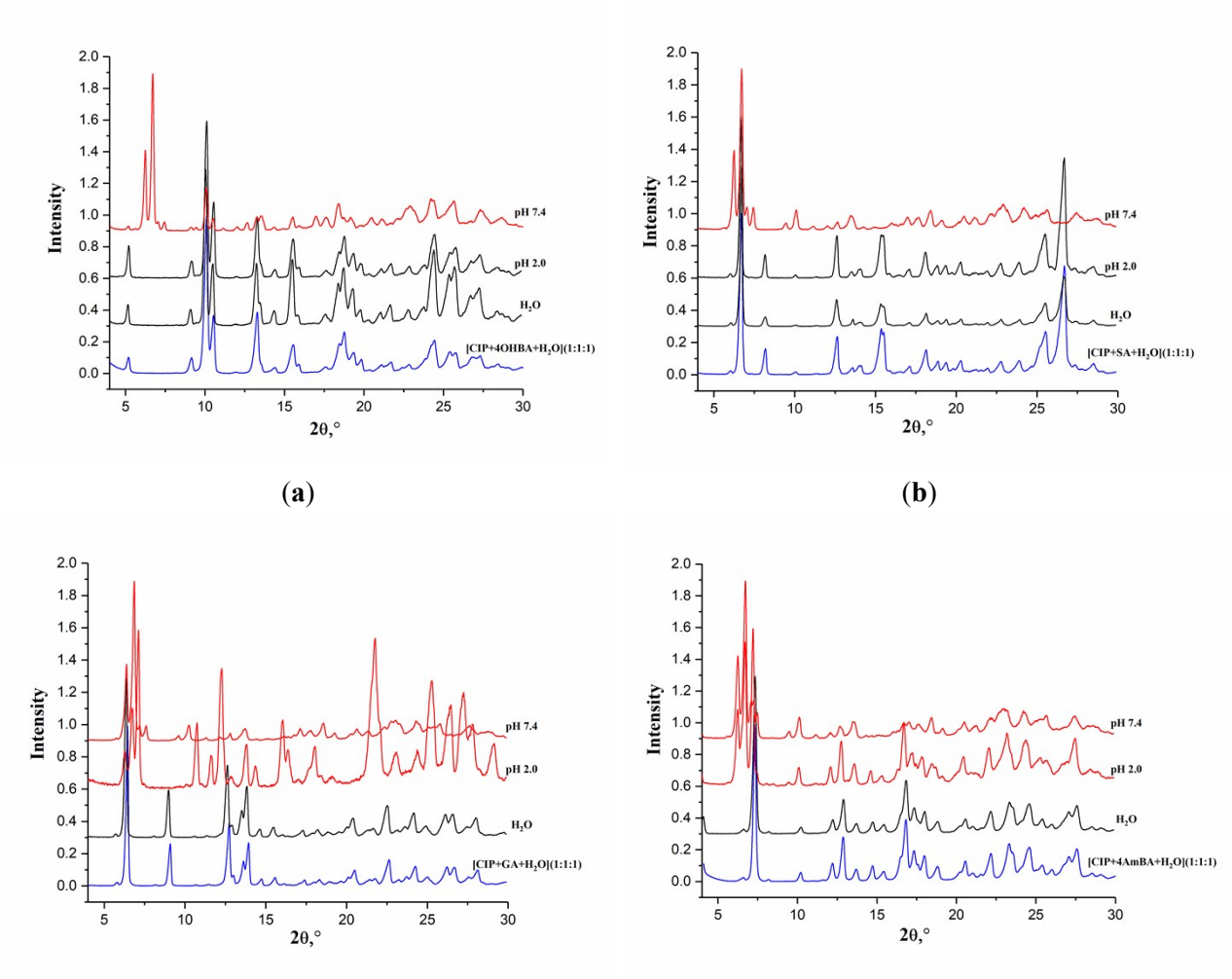


Figure S9. Experimental PXRD patterns of residual materials after dissolution of (a) **[CIP+4OHBA+H_2O]** (1:1:1), (b) **[CIP+SA+H_2O]** (1:1:1) form II, (c) **[CIP+GA+H_2O]** (1:1:2) and (d) **[CIP+4AmBA+H_2O]** (1:1:1) in water and buffer solutions with pH 2.0 and pH 7.4.

Table S1. Crystallographic data for hydrated salts of ciprofloxacin

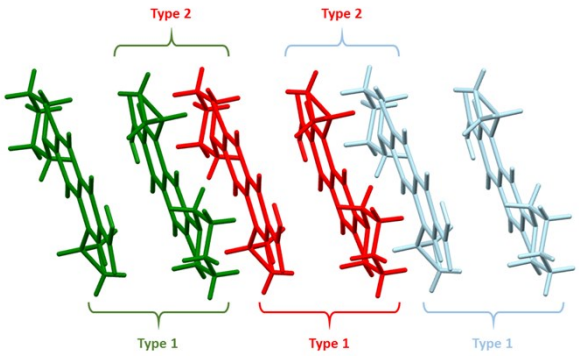
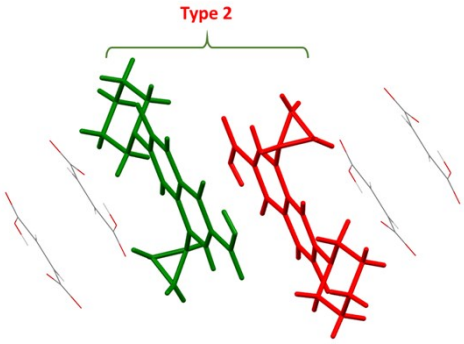
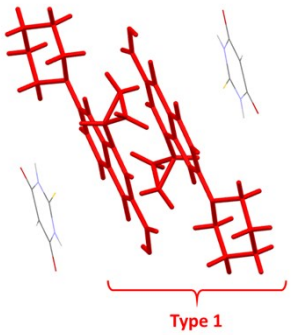
Compound reference	**[CIP+4OHBA+H_2O]** (1:1:1)	**[CIP+4AmBA+H_2O]** (1:1:1)	**[CIP+ GA+H_2O]** (1:1:2)
Chemical formula	$C_{17}H_{19}FN_3O_3 \cdot C_7H_5O_3 \cdot H_2O$	$C_{17}H_{19}FN_3O_3 \cdot C_7H_6NO_2 \cdot H_2O$	$C_{17}H_{19}FN_3O_3 \cdot C_7H_5O_5 \cdot 2.167(H_2O)$
*F*w	487.48	486.50	540.47
Crystal system	Triclinic	Monoclinic	Monoclinic
a, Å	7.1977 (13)	21.457 (2)	9.1210 (7)
b, Å	9.9766 (18)	14.4489 (15)	27.264 (2)
c, Å	16.836 (3)	7.3700 (8)	10.3393 (8)
α, °	81.999 (3)	90.00	90.00
β, °	80.626 (3)	90.013 (2)	93.365 (1)
γ, °	72.472 (3)	90.00	90.00
Unit cell volume, Å^3	1132.2 (4)	2284.9 (4)	2566.7 (3)
Temperature, K	150(2)	150(2)	150(2)
Space group	*P-1*	$P2_1/c$	$P2_1/n$
No. of formula units per unit cell, *Z*	2	4	4
Absorption coefficient, μ·mm^{-1}	0.110	0.110	0.110
No. of reflections measured	12642	23168	28802
No. of independent reflections	5996	5512	6829
R_{int}	0.020	0.039	0.035
Final R_1 values ($I > 2\sigma(I)$)	0.043	0.049	0.043
Final $wR(F^2)$ values (all data)	0.114	0.134	0.106
Goodness of fit on F^2	1.05	1.05	1.03
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.37, −0.26	0.36, −0.23	0.39, −0.24

Table S2. Metric parameters of intermolecular hydrogen bonds and notable C-H···O(N) bonds in CIP salt hydrates with aromatic acid salt formers (SF)

Fragment	H-bond type	D(X···O), Å[a)]	D(H···O), Å	∠(X-H···O), °[a)]
		[CIP+4OHBA+H_2O] (1:1:1)		
O23-H25···O10	SF-H_2O	2.611	1.722	176.6
N3-H31···O21	CIP-SF	2.709	1.791	166.1
N3-H32···O22	CIP-SF	2.730	1.768	175.3
O10-H10···O21	H_2O-SF	2.696	1.789	177.6
O10-H11···O22	H_2O-SF	2.720	1.869	171.0
C26-H26···O10	SF-H_2O	3.257	2.580	127.5
C15-H15B···O23	CIP-SF	3.266	2.338	158.3
C15-H15A···O3	CIP-CIP	3.377	2.423	171.1
C7-H71···O1	CIP-CIP	3.463	2.554	158.0
C16-H16A···O3	CIP-CIP	3.439	2.677	136.0
C24-H24···O1	SF-CIP	3.609	2.676	161.4
		[CIP+4AmBA+H_2O] (1:1:1)		
O10-H10···O21	H_2O-SF	2.844	1.978	161.3
O10-H11···O21	H_2O-SF	2.842	2.010	169.9
N3-H31···O22	CIP-SF	2.706	1.768	168.8
N3-H32···O22	CIP-SF	2.885	2.101	123.1
N3-H31···O21	CIP-SF	3.092	2.469	148.0
N21-H21···O2	SF-CIP	3.071	2.324	139.3
N21-H22···O2	SF-CIP	3.063	2.373	137.0
C17-H172···O21	CIP-SF	3.444	2.518	161.7
C17-H172···O10	CIP-H_2O	3.157	2.475	127.2
C15-H152···O10	CIP-H_2O	3.361	2.464	156.4
C7-H71···O1	CIP-CIP	3.442	2.472	164.5
C6-H61···O3	CIP-CIP	3.580	2.698	148.0
C5-H5···O1	CIP-CIP	3.342	2.711	125.8
C6-H62···O2	CIP-CIP	3.488	2.658	143.3
C6-H62···N21	CIP-CIP	3.344	2.709	122.9
		[CIP+GA+H_2O] (1:1:2)		
O24-H24···O22	SF-SF	2.614	1.707	173.5
N3-H31···O21	CIP-SF	2.714	1.770	173.1
O26-H26···O10	SF-H_2O	2.721	1.854	174.6
O10-H1···O2	H_2O-CIP	2.848	1.997	173.0
O13-H13···O2	H_2O-CIP	3.213	2.362	179.8
O25-H25···O1	SF-CIP	2.689	1.847	159.5
O13-H14···O11	H_2O-H_2O	3.02	2.17	180
N3-H32···O2	CIP-CIP	2.861	2.193	131.9
O11-H11···O22	H_2O-SF	2.96	2.04	153-167
O11-H12···O21	H_2O-SF	2.96	2.08	157-161
C9-H9···O25	CIP-SF	3.505	2.578	159.3
C17-H172···O3	CIP-CIP	3.526	2.654	151.1
C16-H161···O26	CIP-SF	3.317	2.598	128.9

[a)] X = O,N,C.

Table S3. Different types of packing arrangements observed in the ciprofloxacin multi-component crystals with organic anions according to Cambridge Structural Database analysis

Refcodes	Illustration of dimers	Description
VELREM JIRYAL DOFXOO ORUYIK ORUYOQ OXAYUJ UHITOV01 DOFXII DOFWUT QABTOF DOFWUT01 PEFZIL QUKHOV QUKHIP02 ORUZAD KOFFAO GUYWII QUKHUB [Cip+4OHBA+H_2O] (1:1:1)		Infinite columnar π-stack consisting of type 1 and type 2 dimers of **CIP**
QUKHIP KOFFES KEWSOX ENODOB [Cip+GA+H2O] (1:1:2)		Discrete **CIP** dimers of type 2 separated by counterions
KEWSEN KEWSIR		Discrete **CIP** dimers of type 1 separated by counterions

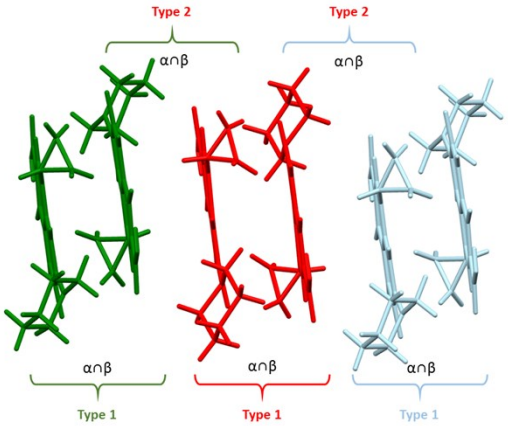
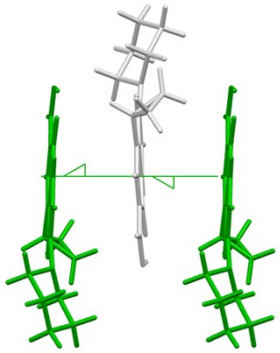
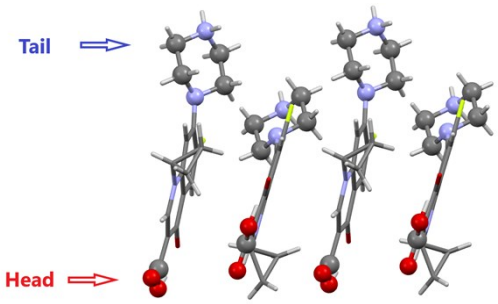
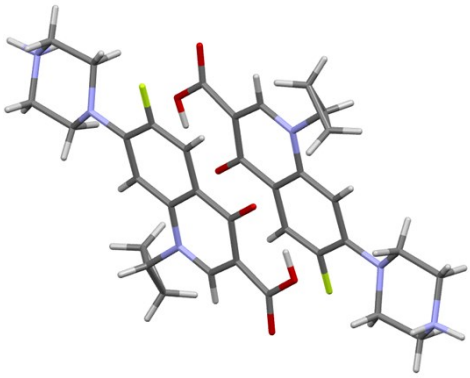
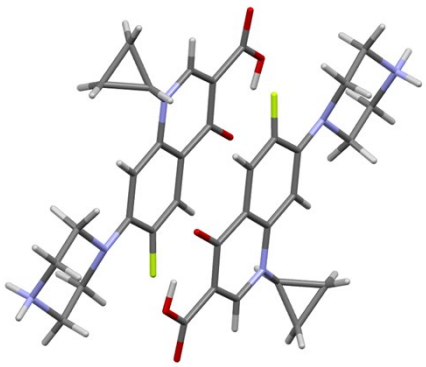
IDARUA QABTUL GUYWUU		Infinite columnar stack consisting of type 1 and type 2 dimers of **CIP** with anti-parallel organization
WEFLEA QUKHIP03		Columnar stack of CIP molecules related by 2-fold screw axis symmetry
[CIP+4AmBA+H_2O] (1:1:1)		"Head-to-head" packing arrangements of CIP molecules

Table S4. Stabilization energies of CIP dimers calculated at the B3LYP-D3/aug-cc-pVTZ level of theory

.	Dimer type	E_{int}, kJ·mol^{-1}	$E_{int,1}$ - $E_{int,2}$, kJ·mol^{-1}
	Type 1	-156.3	
			-41.4
	Type 2	-114.9	

Equilibrium reactions and solubility of **CIP** salts

K_{sp} is the constant associated with the equilibrium between salt (or cocrystal) and a solution phase. It involves dissociation of a salt into its constituents according to the following equilibrium reaction

$$(CIPH^{+}SF^{-})_{\text{solid}} \rightleftarrows a_{[CIPH^{+}]_{\text{sol}}} + a_{[SF^{-}]_{\text{sol}}}$$

where $a_{[\mathbf{CIPH}+]\text{sol}}$ and $a_{[\mathbf{SF}-]\text{sol}}$ represent activities of $CIPH^{+}$ and SF^{-} species in a solution. Assuming the activity of solid phase equals to 1 and approximating the activities of dissolved components by their concentration, K_{sp} can be written as:

$$K_{sp} = [CIPH^{+}]_{sol}[SF^{-}]_{sol} \tag{S1}$$

Since protonated ciprofloxacin cation ($CIPH^{+}$) can be considered as a diprotic acid, its total concentration in a solution can be written as:

$$[CIPH^{+}]_{T} = [CIPH^{+}] + [CIP] + [CIP^{-}]$$

or

$$[\mathrm{CIPH}^{+}]_{T} = [\mathrm{CIPH}^{+}] \cdot (1 + 10^{pH - pK_{a1,CIP}} + 10^{2pH - pK_{a1,CIP} - pK_{a2,CIP}})$$

where, $K_{a1,CIP}$ and $K_{a2,CIP}$ are ionization constants of ciprofloxacin (pK_{a1} = 6.16, pK_{a2} = 8.62).

In the case of deprotonated monoprotic acids (4-hydroxybenzoic, gallic and salicylic acids), their total concentration in a solution can be described as:

$$[SF^{-}]_{T} = [SF^{-}] + [SF]$$

or

$$[SF^{-}]_{T} = [SF^{-}] \cdot (1 + 10^{pK_{a,SF} - pH})$$

where, $K_{a,SF}$ is ionization constant of the corresponding acid (pK_a = 4.50 for 4-hydroxybenzoic acid; pK_a = 4.50 for gallic acid; pK_a = 2.97 for salicylic acid)

Combining equations above and substituting in general expression for Ksp, the salt solubility can be written as:

$$S_{salt} = \sqrt{K_{sp}(1+10^{pH-pK_{a1,CIP}}+10^{2pH-pK_{a1,CIP}-pK_{a2,CIP}})(1+10^{pK_{a,SF}-pH})} \quad \text{(S2)}$$

Since, 4-aminobenzoic acid has two ionizable functional group, the deprotonated form of the compound can be treated as a dibasic component and its total concentration in a solution can be written as:

$[SF^-]_T = [SF^-] + [SF] + [SFH^+]$

Therefore, the equation that describes the **[CIP+4AmBA+H$_2$O]** (1:1:1) salt solubility dependence on pH is given by

$$S_{salt} = \sqrt{K_{sp}(1+10^{pH-pK_{a1,CIP}}+10^{2pH-pK_{a1,CIP}-pK_{a2,CIP}})(1+10^{pK_{a2,SF}-pH}+10^{pK_{a1,SF}+pK_{a2,SF}-2pH})} \quad \text{(S3)}$$

where, $K_{a1,SF}$ and $K_{a2,SF}$ are ionization constants of 4-aminobenzoic acid (pK_{a1} = 4.80, pK_{a2} = 2.40)

Table S5. Experimental concentrations of CIP, counterions and pH values at equilibrium with the corresponding solid phases at 37.0°C.

	[**CIP**]$_{eq}$, mol·l^{-1}	[**SF**]$_{eq}$, mol·l^{-1}	pH at equilibrium	Solid phase(s) at equilibrium
		Water		
[CIP+4OHBA+H$_2$O] (1:1:1)	(8.0±0.1)·10^{-4}	(8.1±0.1)·10^{-4}	5.4	**[CIP+4OHBA+H$_2$O]** (1:1:1)
[CIP+SA+H$_2$O] (1:1:1)	(4.8±0.1)·10^{-3}	(4.8±0.1)·10^{-3}	3.9	**[CIP+SA+H$_2$O]** (1:1:1)
[CIP+GA+H$_2$O] (1:1:2)	(3.8±0.1)·10^{-3}	(3.9±0.1)·10^{-3}	5.1	**[CIP+GA+H$_2$O]** (1:1:2)
[CIP+4AmBA+H$_2$O] (1:1:1)	(2.95±0.05)·10^{-2}	(3.10±0.05)·10^{-2}	4.3	**[CIP+4AmBA+H$_2$O]** (1:1:1)
		pH = 2.0		
[CIP+4OHBA+H$_2$O] (1:1:1)	(8.6±0.1)·10^{-3}	(8.7±0.1)·10^{-3}	2.4	**[CIP+4OHBA+H$_2$O]** (1:1:1)
[CIP+SA+H$_2$O] (1:1:1)	(1.1±0.1)·10^{-2}	(1.2±0.1)·10^{-2}	2.3	**[CIP+SA+H$_2$O]** (1:1:1)
[CIP+GA+H$_2$O] (1:1:2)	(1.4±0.1)·10^{-2}	(2.1±0.2)·10^{-3}	4.5	**CIP hydrate** + **[CIP+GA+H$_2$O]** (1:1:2)
[CIP+4AmBA+H$_2$O] (1:1:1)	(5.9±0.1)·10^{-2}	(6.8±0.1)·10^{-2}	3.9	**CIP hydrate** + **[CIP+4AmBA+H$_2$O]** (1:1:1)
		pH = 7.4		
[CIP+4OHBA+H$_2$O] (1:1:1)	(4.1±0.1)·10^{-4}	(8.4±0.1)·10^{-3}	6.9	**CIP hydrate**
[CIP+SA+H$_2$O] (1:1:1)	(3.8±0.1)·10^{-4}	(1.4±0.1)·10^{-2}	7.0	**CIP hydrate**
[CIP+GA+H$_2$O] (1:1:2)	(3.9±0.1)·10^{-4}	(9.6±0.1)·10^{-3}	6.9	**CIP hydrate**
[CIP+4AmBA+H$_2$O] (1:1:1)	(3.7±0.1)·10^{-4}	(8.8±0.2)·10^{-3}	7.1	**CIP hydrate**