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Avoiding the Irreversible 5-Fluorocytosine Hydration via Supramolecular Synthesis of Pharmaceutical Cocrystals

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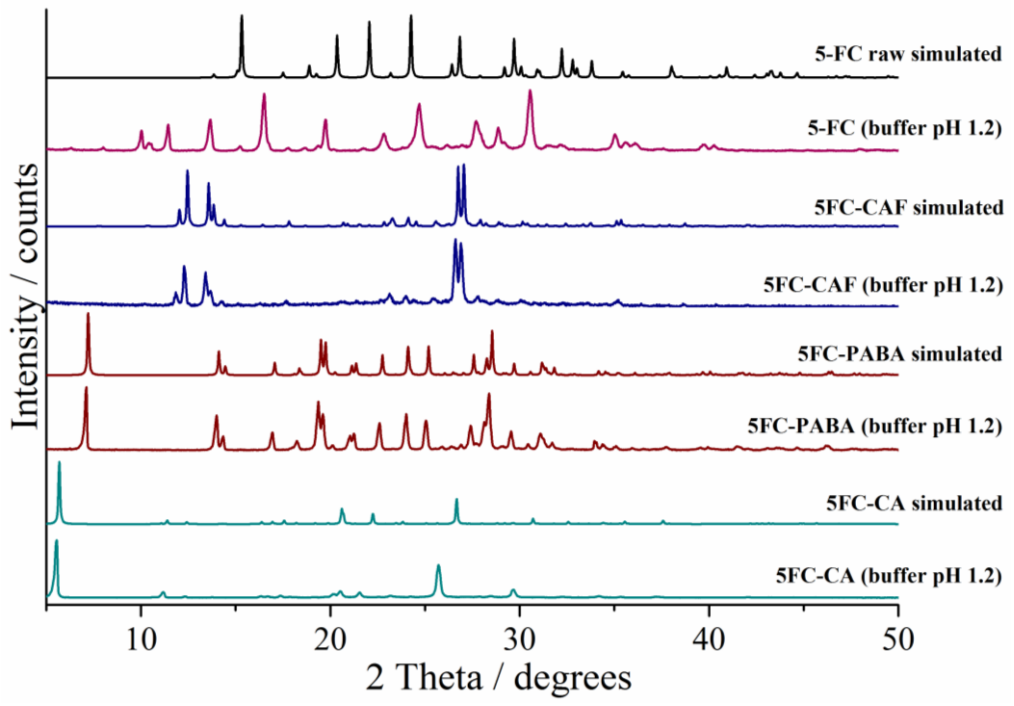

Figure S1. Experimental powder X-ray diffraction patterns of 5-FC and its cocrystals that remain non-solubilized after the solubility test.

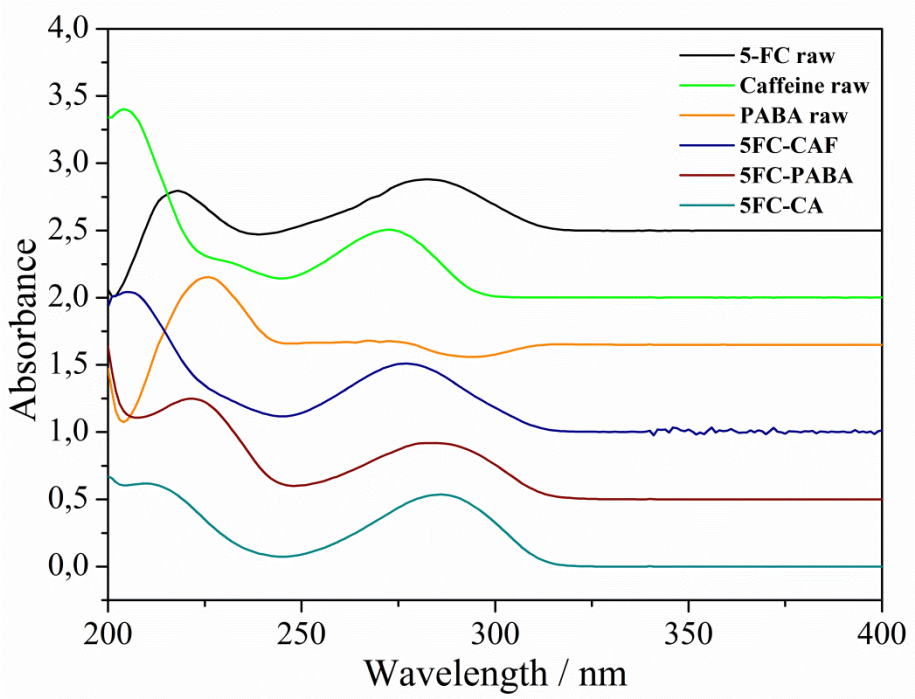

Figure S2. Absorption spectra of 5-FC 0.0055 mg mL^{-1}, caffeine 0.0086 mg mL^{-1}, *p*-aminobenzoic acid 0.0065 mg mL^{-1}; and the cocrystals 5FC-CAF 0.016 mg mL^{-1}, 5FC-PABA 0.013 mg mL^{-1} and 5FC-CA 0.016 mg mL^{-1} in buffer pH = 1.2.

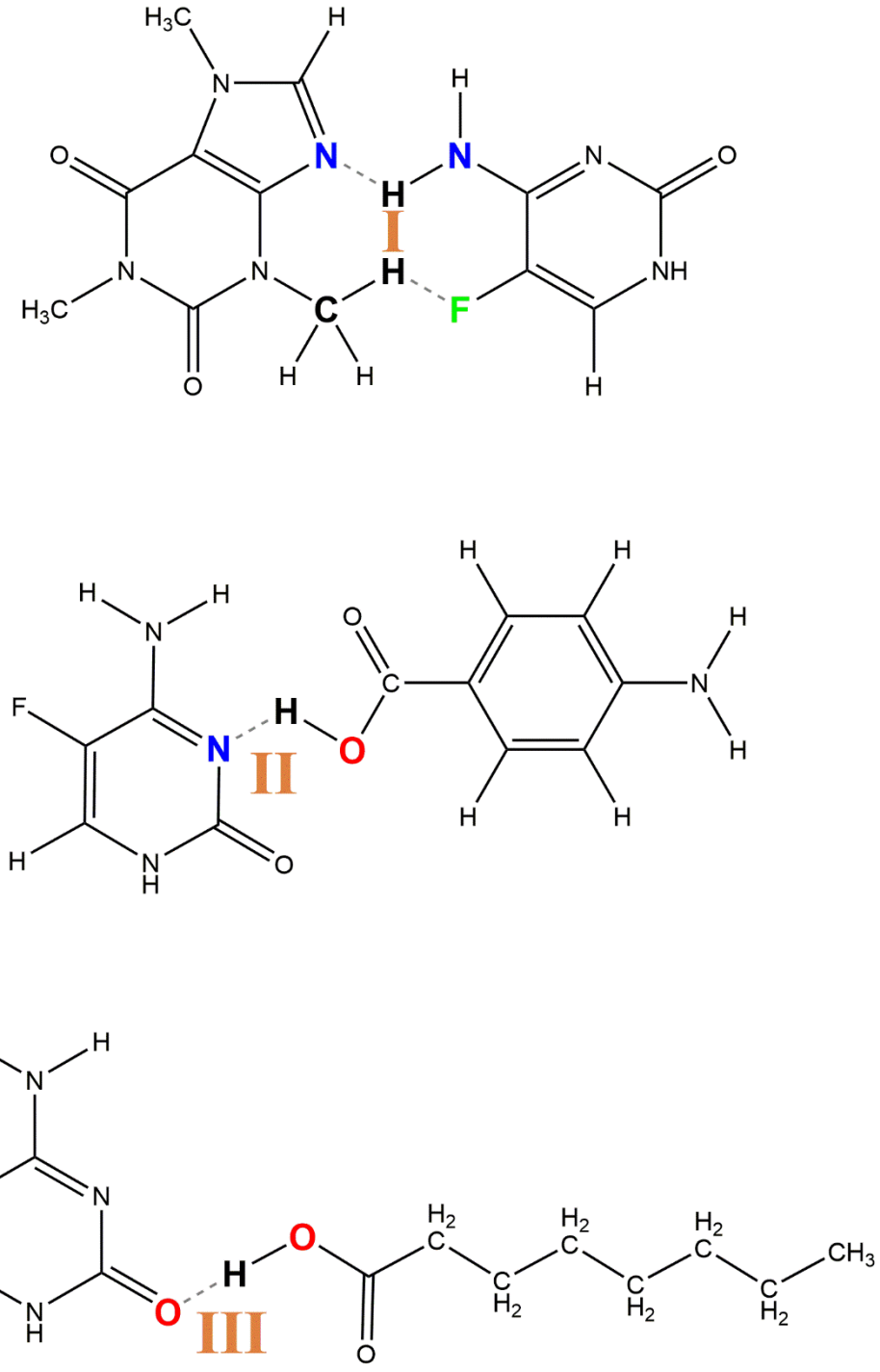

Figure S3. Heterosynthons observed in the 5-FC cocrystals.

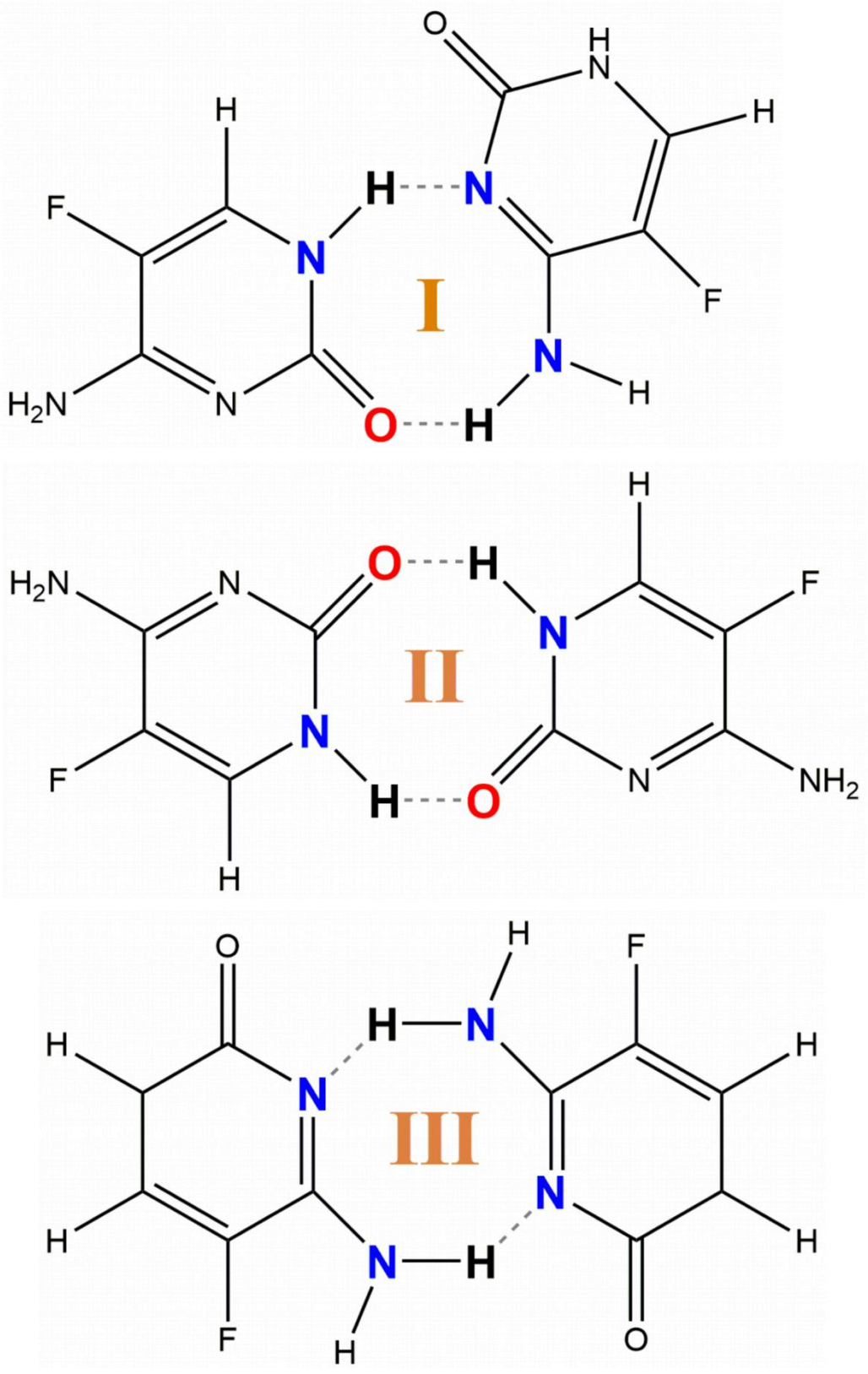

Figure S4. Homosynthons observed in the 5-FC cocrystals.

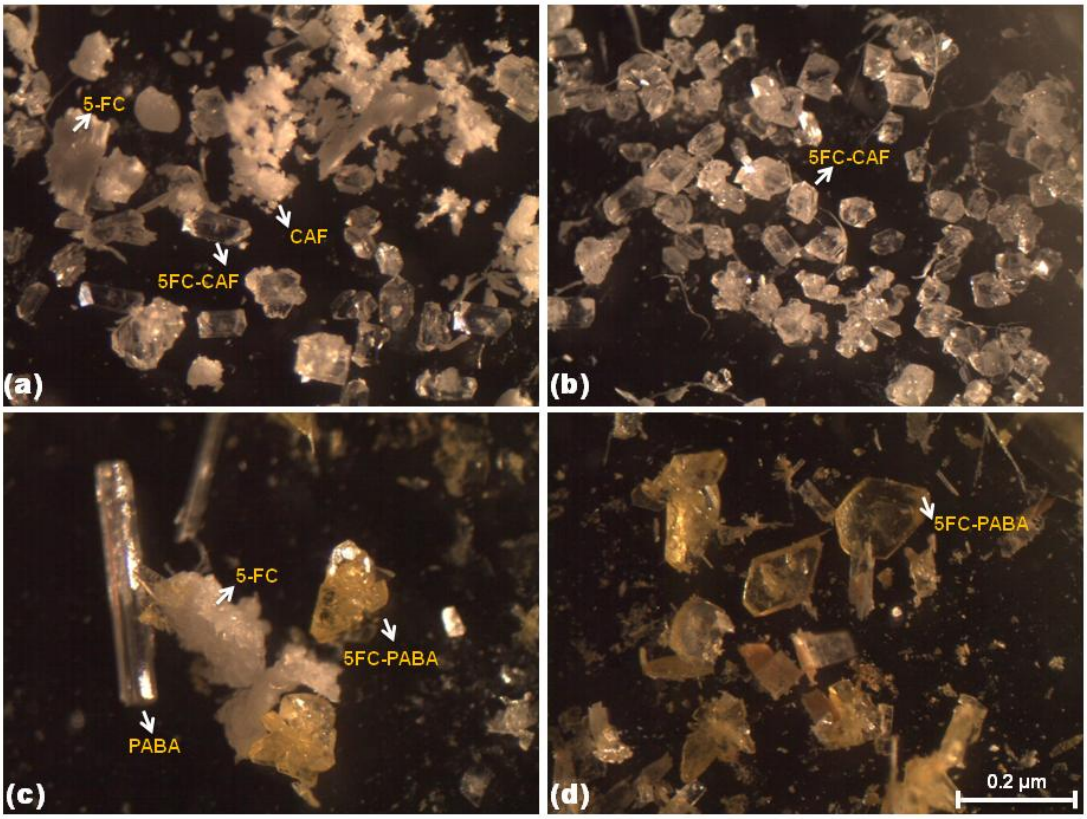

Figure S5. (a) and **(c)**: Microscope images of crystalline phases with single-crystals of different habits obtained directly from SES method for 5FC-CAF and 5FC-PABA cocrystals, respectively. **(b)** and **(d)**: Grinding products recrystallized through SES as a unique crystalline phase.

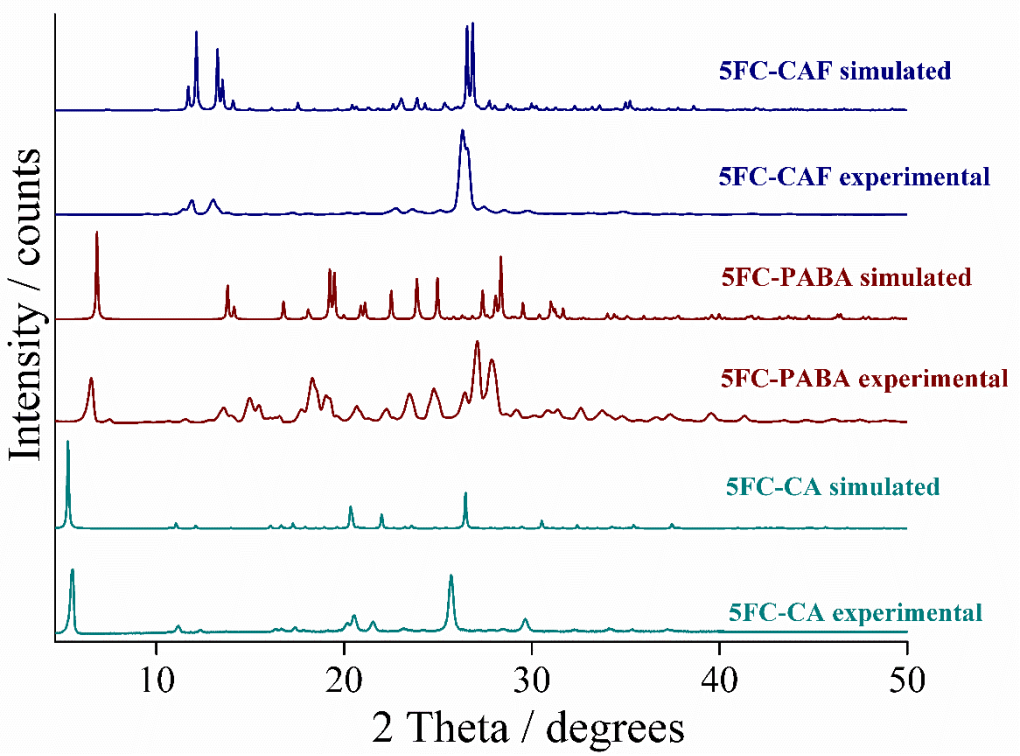

Figure S6. Simulated and experimental powder X-ray diffraction patterns of 5-FC cocrystals. All diffractograms are in a good agreement indicating that the samples present high purity and representativeness.

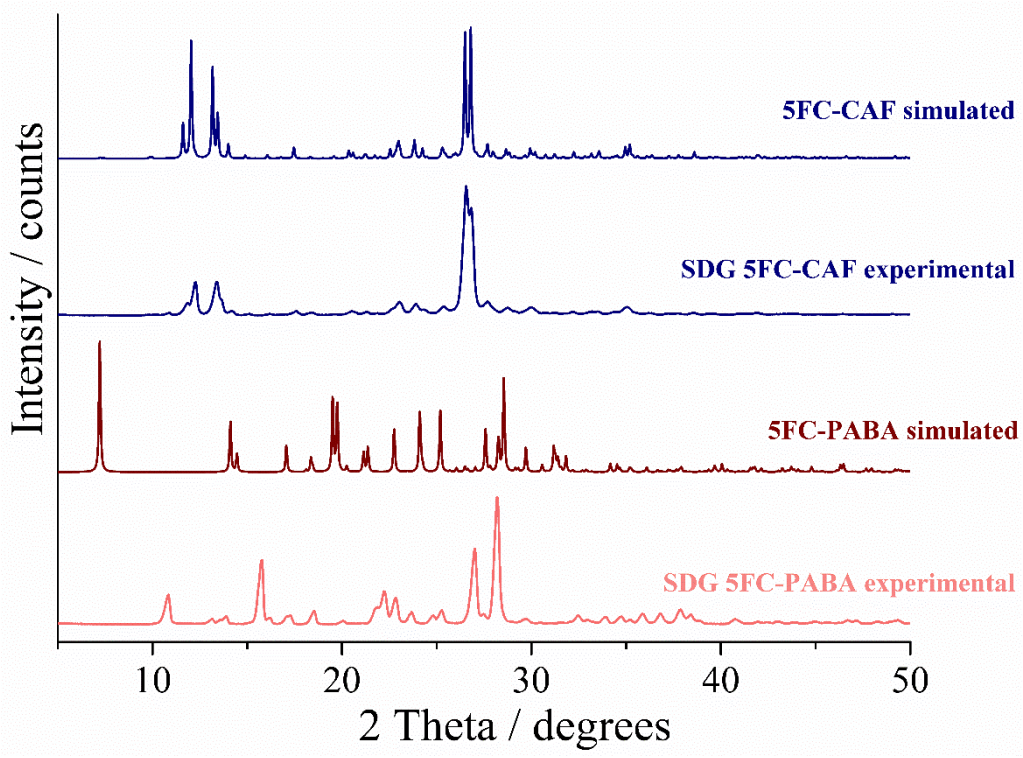

Figure S7. Experimental powder X-ray diffraction patterns of 5-FC cocrystals obtained from solvent-drop grinding (SDG) compared to simulated ones. Only the diffractograms of 5FC-PABA are not in a good agreement which suggest a possible physical mixture between the starting materials.

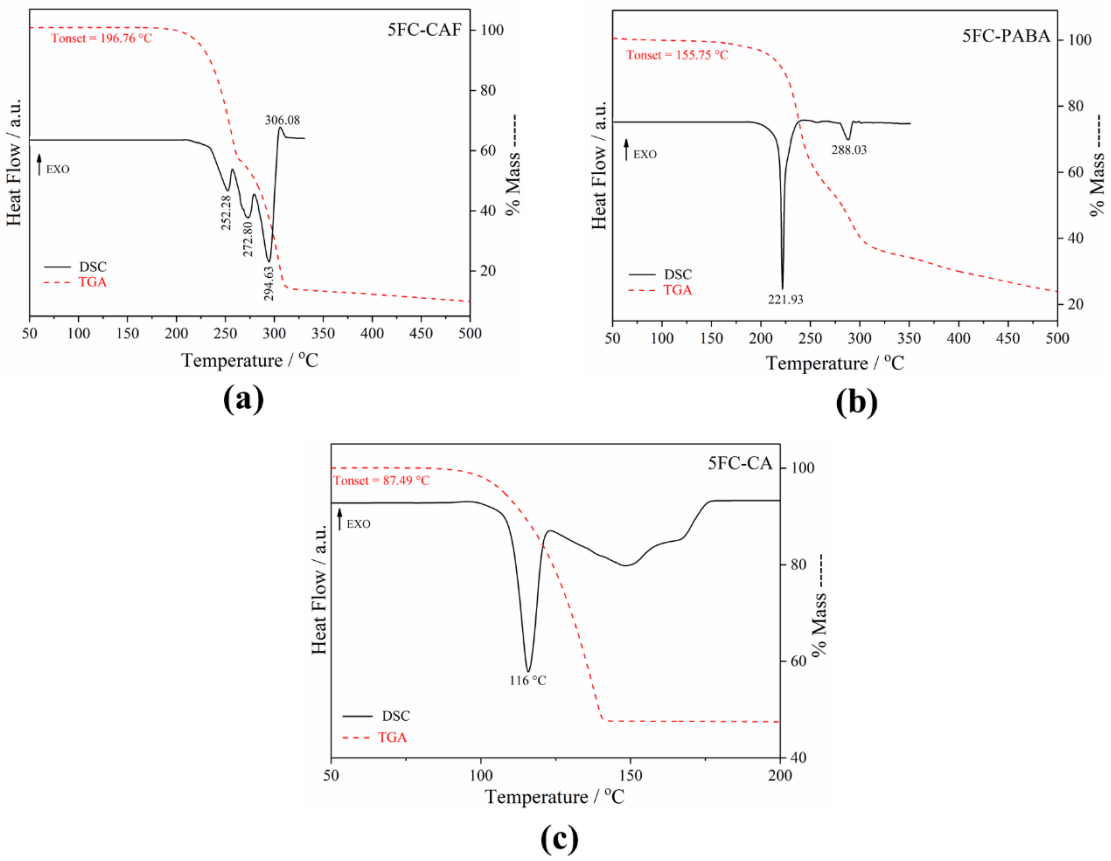

Figure S8. TGA and DSC curves of the 5-FC's cocrystals.

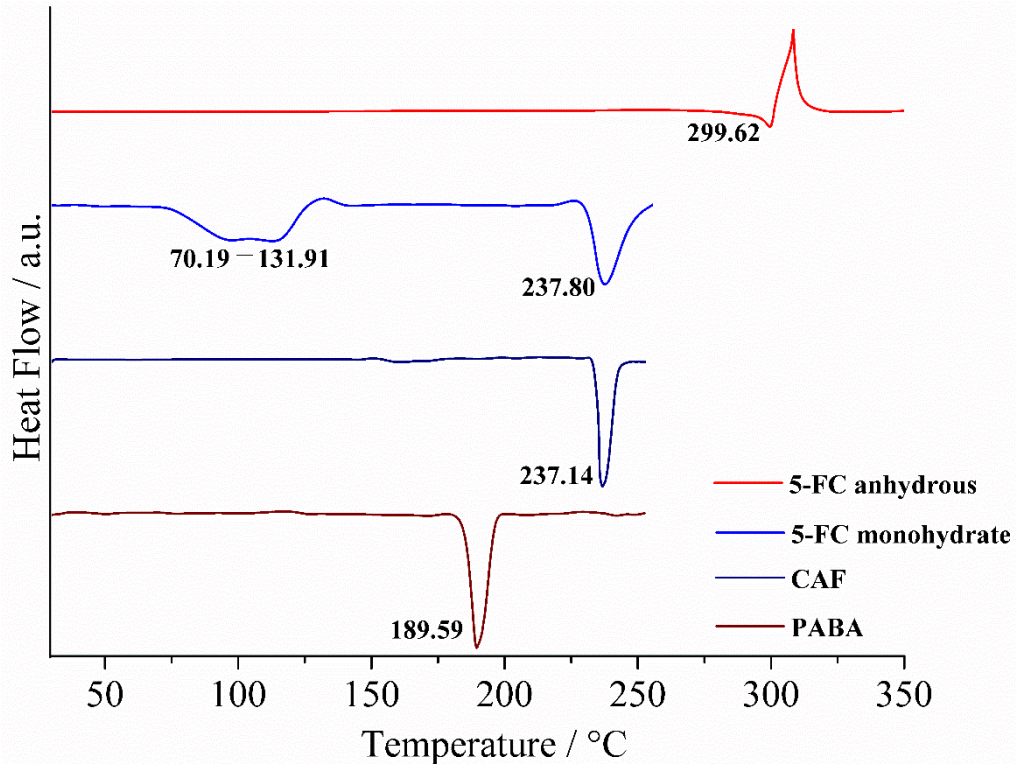

Figure S9. DSC curves of: **(i)** the raw material 5-Fluorocytosine (5-FC anhydrous); **(ii)** the 5-FC after one week in environment with high relative humidity (5-FC monohydrate) and **(iii)** the two solid coformers, namely: CAF (caffeine) and PABA (*p*-aminobenzoic acid).

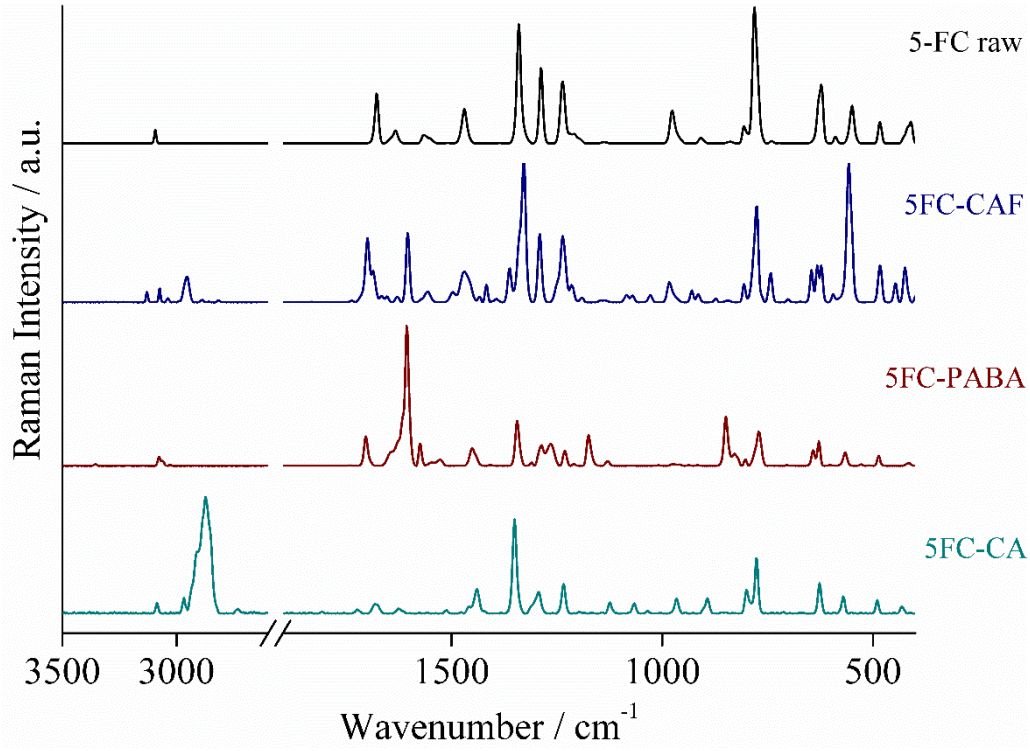

Figure S10. FT-Raman spectra of 5-FC and its cocrystals.

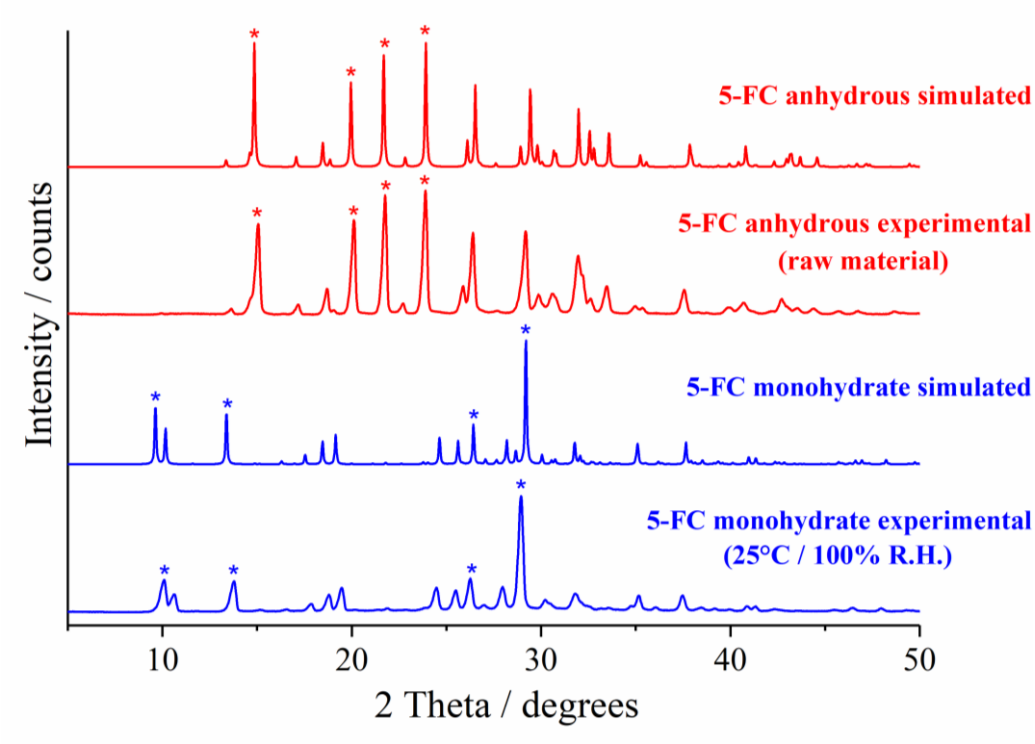

Figure S11. Powder X-ray diffraction patterns of 5-FC confirming that this API undergoes a phase transition from the anhydrous to the monohydrate form when exposed to humid environments.

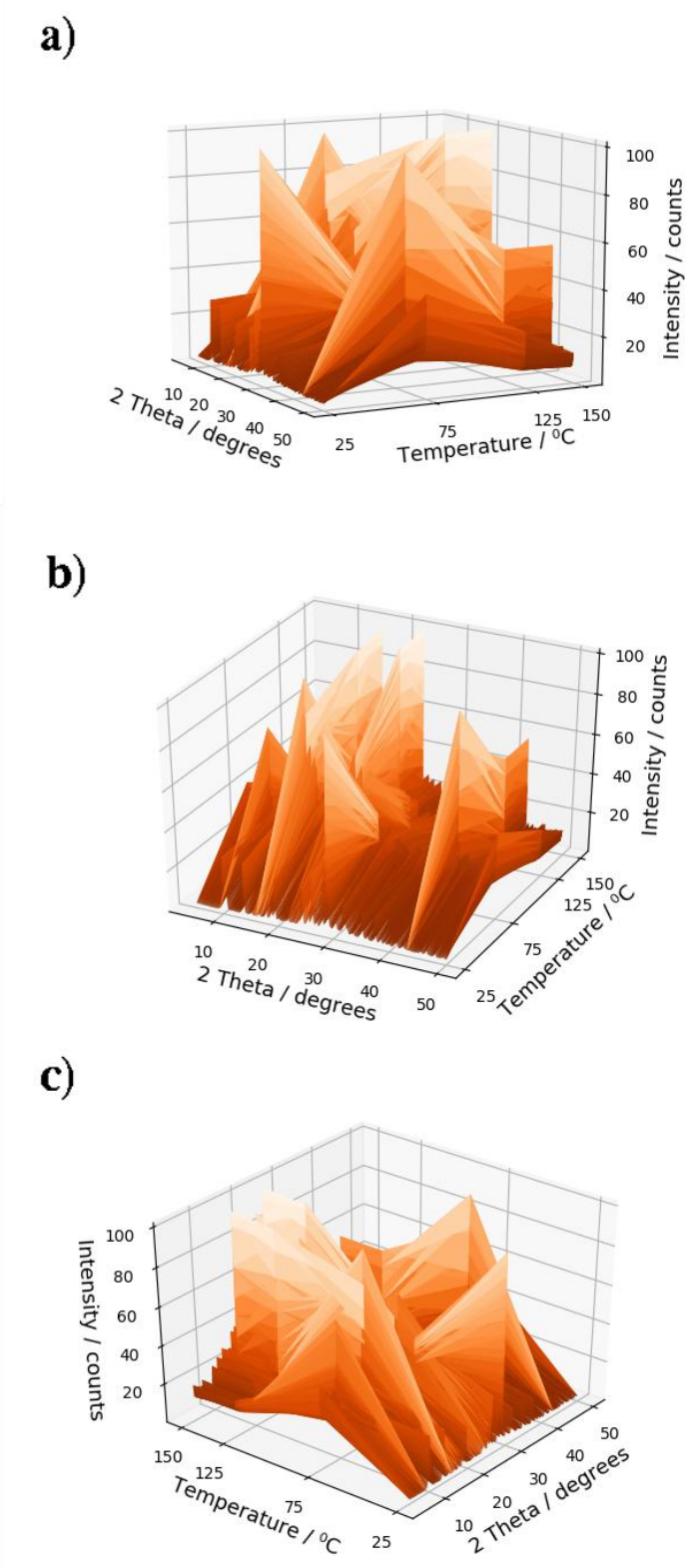

Figure S12. 3D surfaces generated through a script in Python from the 5-FC monohydrate patterns overlap collected during a VT-PXRD experiment.

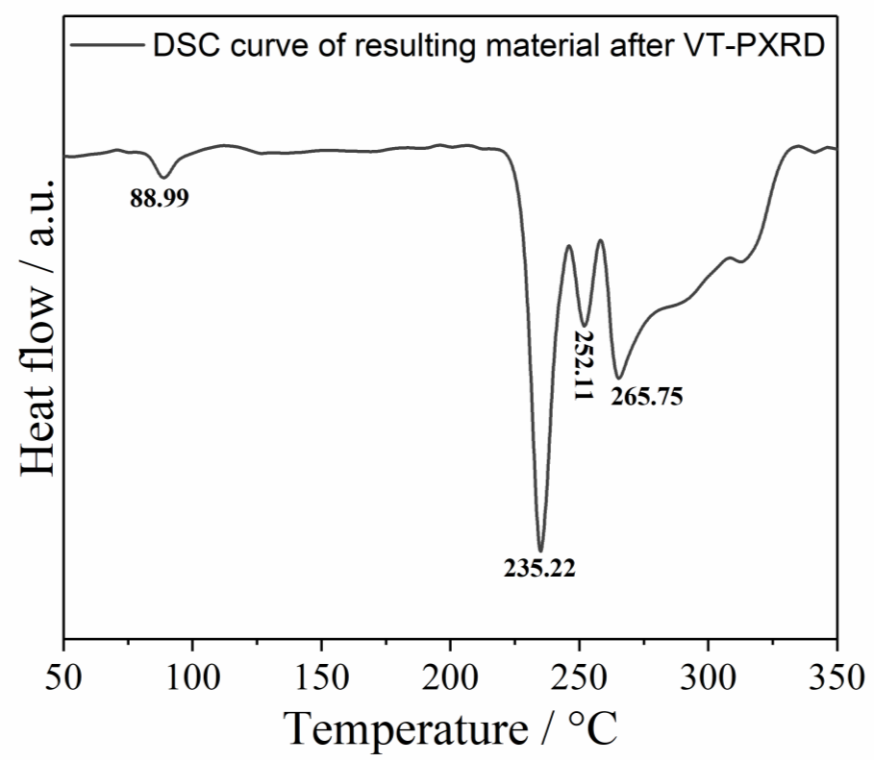

Figure S13. DSC curve of resulting material after VT-PXRD.

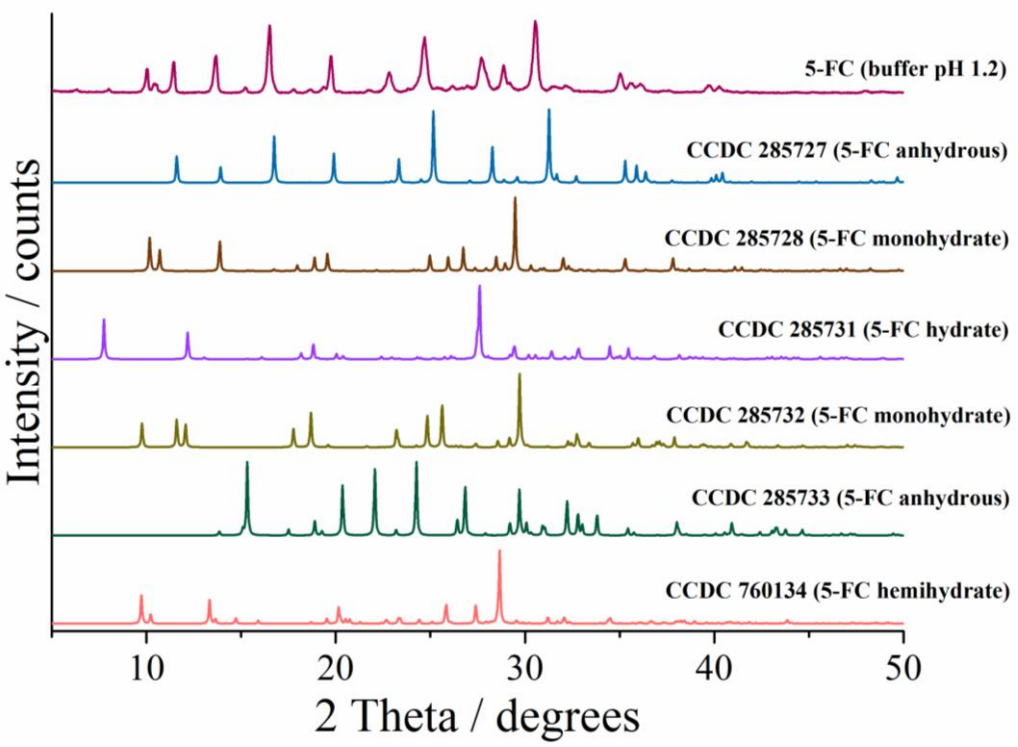

Figure S14. Powder X-ray diffraction patterns of 5-FC after solubility study (upper) and different solid forms of 5-FC anhydrous and hydrated reported in literature.

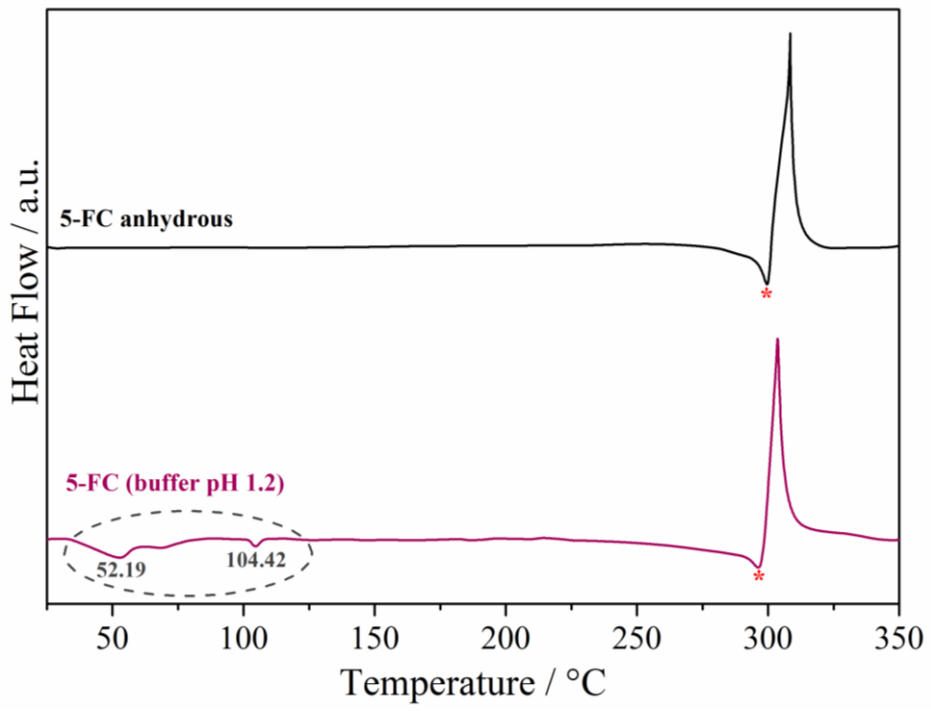

Figure S15. DSC profiles of 5-FC before (black) and after (purple) the solubility study.

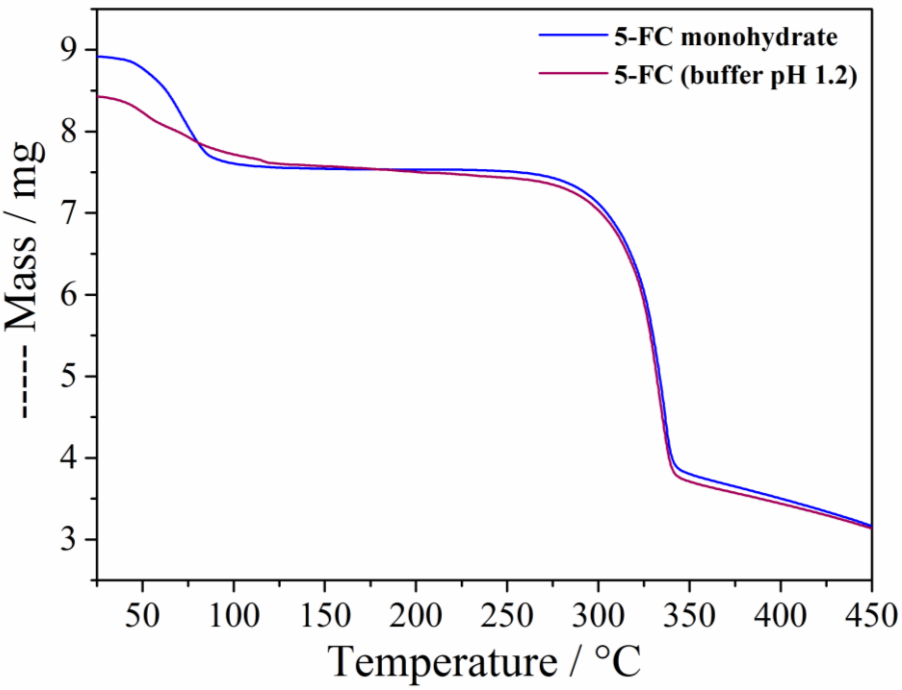

Figure S16. TGA profiles of 5-FC monohydrate (blue) and 5-FC anhydrous (purple) after the solubility study.

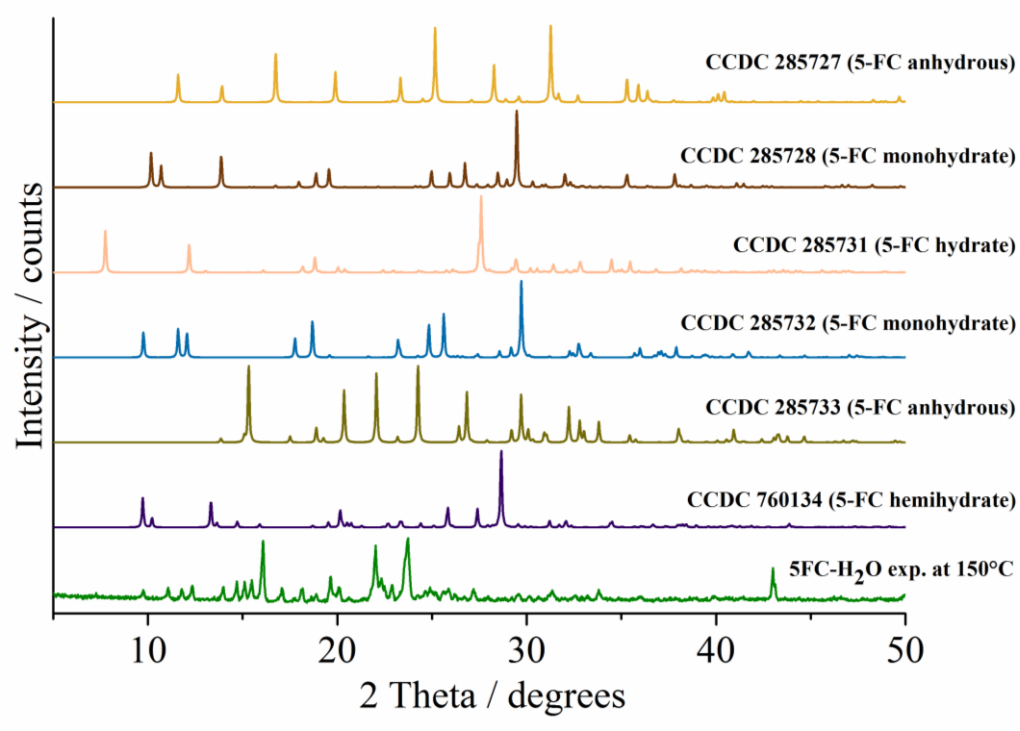

Figure S17. PXRD patterns of 5-FC (anhydrous, monohydrate, hydrate and hemihydrate) structures confirming that the 5-FC monohydrate sample gives rise under heating to a totally different crystalline phase that do not corresponds to any other similar crystal structure deposited in the Cambridge Structure Database.

Table S1. Composition of the solution used for the preparing of the calibration curves and solubility determinations.

Hydrochloric Buffer (1000 mL)	
pH	1.2
0.2 M HCl	322.5 mL
0.2 M KCl (mL)	250 mL
Deionized water to complete the 1000 mL volumetric flask	

Table S2. Standard solutions of 5-FC, caffeine and *p*-aminobenzoic acid used to construct the calibration curves.

Concentration 5-FC (mg mL^{-1})	Absorbance (281 nm)	Concentration caffeine (mg mL^{-1})	Absorbance (272.5 nm)	Concentration PABA (mg mL^{-1})	Absorbance (225.5 nm)
0.0096	0.714	0.01716	1.008	0.01086	0.922
0.0085	0.637	0.01373	0.774	0.00814	0.712
0.0077	0.568	0.01144	0.681	0.00652	0.503
0.0064	0.455	0.00981	0.568	0.00543	0.39
0.0055	0.381	0.00858	0.505	0.00465	0.333
0.0038	0.243	0.00763	0.446	0.00407	0.281

Table S3. Regression coefficients for the calibration curves of 5-FC and the cocrystal formers at buffer media, pH = 1.2.

Compound and Wavenumber	Linear Coefficient	Angular Coefficient	R^2
5-FC (281 nm)	-0.068	10598 M^{-1}	0.9988
5-FC (272.5 nm)	-0.033	7941.7 M^{-1}	0.9976
5-FC (225.5 nm)	-0.201	7999.5 M^{-1}	0.9901
caffeine (281 nm)	0.005	871.8 M^{-1}	0.9941
caffeine (272.5 nm)	0.005	11228 M^{-1}	0.9943
PABA (281 nm)	0.090	1637.9 M^{-1}	0.9903
PABA (225.5 nm)	-0.122	13383 M^{-1}	0.9909

Table S4. pH values measured after solubility.

Solution	pH
pH (dissolution media)	1.20
pH (5-FC solution)	2.00
pH (5FC-CAF solution)	1.50
pH (5FC-PABA solution)	2.20
pH (5FC-CA solution)	1.40

Table S5. Geometric parameters of the intermolecular interactions for 5-FC organic cocrystals.

Interaction	*d*(D•••A) (Å)	*d*(H•••A) (Å)	∠D-H•••A (º)	Symmetry codes
		5FC-CAF		
N1'-H1'···O21	3.382(2)	2.772(2)	129(2)	x,y,z
N1'-H1'···N3	2.761(2)	1.902(2)	176(2)	x,y,z
N41-H41A···O21'	2.983(2)	2.134(3)	169(2)	x,y,z
N41-H41B···N7	3.022(2)	2.174(2)	168(2)	x,y,z
N41'-H41D···N7'	3.047(2)	2.197(2)	169(2)	x,y,z
C6'-H6'···O21	3.404(2)	2.803(2)	123(2)	x,y,z
C7'-H7'···F51'	3.062(2)	2.388(2)	129(1)	x,y,z
C7-H7···F51	3.067(2)	2.399(2)	128(1)	x,y,z
C14-H14E···F51	3.743(2)	2.796(2)	168(1)	x+1,+y,+z
N41'-H41C···O21	2.956(2)	2.102(3)	171(1)	x+1,+y,+z
C14'-H41B···F51'	3.701(2)	2.788(2)	159(1)	x+1,+y,+z
N1-H1···O21'	3.390(2)	2.786(2)	128(1)	x-1,+y,+z
C12'-H12B···O3'	3.582(2)	2.661(2)	161(1)	x-1,+y,+z
C7-H7···O3	3.618(2)	2.797(2)	147(1)	x-1,+y,+z
C6-H6···O21'	3.404(2)	2.794(2)	124(1)	x-1,+y,+z
N1-H1···N3'	2.752(2)	1.896(2)	173(1)	x-1,+y,+z
C7'-H7'···O3'	3.617(2)	2.804(2)	146(1)	x-1,+y,+z
C12-H12E···O3	3.659(2)	2.746(2)	159(1)	x-1,+y,+z
C13-H13F···O21	3.740(2)	2.783(2)	175(2)	-x+1,+y-1/2,-z+1/2
C12'-H12A···N3	3.618(2)	2.902(2)	132(2)	-x+1,-y+1,-z+1
C12'-H12A···N41	3.817(2)	2.866(2)	171(2)	-x+1,-y+1,-z+1
C12'-H12C···N41	3.569(2)	2.982(2)	120(2)	-x+1,+y+1/2,-z+1/2
C14-H14D···O3'	3.423(2)	2.672(2)	135(2)	-x+2,+y-1/2,-z+1/2
C14-H14F···O4	3.498(2)	2.657(2)	146(2)	-x+1,-y,-z+1
C14'-H14C···O3	3.514(2)	2.626(2)	154(2)	-x+2,+y+1/2,-z+1/2
C13'-H13C···O21'	3.689(2)	2.732(2)	175(2)	-x+2,-y+1,-z+1
		5FC-PABA		
O2-H2···O21	3.278(3)	2.777(2)	121(1)	x,y,z
O2-H2···N3	2.745(2)	1.934(1)	169(1)	x,y,z
N1-H1···O21	2.771(2)	1.912(2)	177(2)	-x+1,-y+1,-z+2
N41-H41A···O3	2.892(2)	2.081(2)	157(2)	x+1,+y,+z
C9-H9'···F51	3.840(5)	2.824(1)	129(2)	-x+2,-y+1,-z+1
N41-H41B···O3	2.941(2)	2.107(2)	163(1)	-x+2,-y+1,-z+1
N4-H4A···O2	3.133(3)	2.325(2)	154(2)	x-1,-y+1/2+1,+z-1/2
N4-H4B···O21	2.965(3)	2.104(1)	154(2)	x,-y+1/2+1,+z-1/2
C6-H6···N4	3.453(3)	2.713(2)	137(2)	-x+1,+y-1/2,-z+1/2+1
C12'-H12'···F51	3.553(6)	2.634(1)	170(2)	-x+2,+y+1/2,-z+1/2+1
C12-H12'···F51	3.834(6)	2.634(1)	155(2)	-x+2,+y+1/2,-z+1/2+1
C9-H9A···F51	3.421(4)	2.565(1)	153(2)	-x+1,-y+1,-z+1

C9’-H9’···F51	3.544(5)	2.822(2)	135(1)	-x+1,-y+1,-z+1
C9’-H9A···F51	3.544(5)	2.565(1)	126(2)	-x+1,-y+1,-z+1
		5FC-CA		
O2-H2···O21	2.618(2)	1.804(2)	171(2)	x,y,z
N1-H1···O21	2.792(2)	1.936(2)	173(2)	x,y,z
C7-H7···O3	3.150(2)	2.312(1)	150(2)	x,y,z
N41-H41B···O2	2.810(2)	2.217(1)	126(2)	-x+1,-y,-z+1
N41-H41A···N3	2.981(2)	2.129(1)	172(2)	-x+1,-y,-z+1
N41-H41A···N41	3.631(2)	2.970(1)	136(2)	-x+1,-y,-z+1
C9-H9B···O3	3.682(2)	2.804(1)	151(2)	x-1,+y,+z
C11-H11B···O3	3.674(2)	2.802(1)	150(2)	x-1,+y,+z
C14-H14B···F51	3.631(3)	2.846(1)	138(2)	x-1,+y+1,+z-1

Table S6. Main FT-IR and FT-Raman bands (cm^{-1}) for 5-FC and 5-FC cocrystals

5-FC		5FC-CAF		5FC-PABA		5FC-CA		
IR	**Raman**	**IR**	**Raman**	**IR**	**Raman**	**IR**	**Raman**	**Assignment**
-	-	-	-	3476	-	3458	-	$\nu(OH)_{carboxyl}$
-	-	-	-	3442	-	-	-	$\nu(NH)_{PABA}$
-	-	-	-	3397	-	-	-	$\nu(NH)_{INH}$
3375	-	3280	-	3386	-	3326	-	$\nu(NH)_{cytosine}$
3094	3093	3072	3073	3073	3076	3080	3085	$\nu(CH)_{aromatic}$
-	-	2960	2956	-	-	2922	2877	$\nu(CH)_{aliphatic}$
-	-	-	-	1675	1703	1720	1722	$\nu(CO)_{carboxyl}$
1682	1677	1675	1683	1661	1643	1687	1679	$\nu(CO)_{cytosine}$
-	-	1650	1630	-	-	-	-	$\nu(CO)_{amide}$
1644	1630	1648	1604	1616	1606	1629	1620	$\delta(NH)$
1337	1340	1332	1328	1341	1344	1352	1349	$\nu(CN)_{cytosine}$
1227	1236	1223	1236	1222	1232	1227	1234	$\nu(CF)$

ν = stretching, as = antisymmetric, s = symmetric, δ = angular deformation.

Table S7. Solubility values of the four compounds.

Compound	Solubility (mmol mL^{-1})
5-FC raw	0.153 ± 0.007
5FC-CAF	0.097 ± 0.002
5FC-PABA	0.096 ± 0.009
5FC-CA	0.087 ± 0.005