Electronic Supplementary Information

The curious case of (caffeine)·(benzoic acid): how heteronuclear seeding allowed the formation of an elusive cocrystal

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1. Cocrystal screening experiments performed at the University of Cambridge

1.1. Materials

Caffeine (*ReagentPlus*®, *Sigma Aldrich*), benzoic acid (99%, *Aldrich*) and nitromethane (*ReagentPlus*®, ≥99.0%, *Sigma Aldrich*) were used as received.

1.2. Cocrystal screening

Cocrystal screens were performed using liquid-assisted grinding (LAG) and solution-mediated phase transformation (SMPT) as methods. Equimolar amounts of caffeine (**caf**) and benzoic acid (**BA**) ($n = 0.63$ mmol) were ground together in a *Retsch MM 200* mixer mill using a stainless steel grinding jar (V=15 mL) and two stainless steel balls ($2r = 7$ mm). Nitromethane ($V = 50$ µL) was utilised to facilitate cocrystal formation during the milling experiment (30 Hz, 30 min).

The SMPT experiments were conducted using equimolar amounts of **caf** and **BA** ($n = 1.26$ mmol) and nitromethane as solvent (V = 1.6 mL). The physical mixture of **caf** and **BA** was suspended in the solvent, mixed with a magnetic stir bar and left to equilibrate at ambient conditions overnight.

The solids obtained from the cocrystal screens were analysed using a laboratory *Panalytical X'Pert PRO* powder diffractometer operating at 40 kV and 40 mA using Ni-filtered CuK_α radiation ($\lambda = 1.5418$ Å). The utilized diffractometer exhibited the Bragg-Brentano geometry and was equipped with an *X'Celerator RTMS* detector. The sample was placed into a flat glass sample holder. The scans were performed in the continuous mode (gonio scan axis) in the 2θ range of 3.0-60.0° with counting times of 40 s. The data was analysed using the *X'Pert HighScore Plus* software.[1] The results of the cocrystal screens are shown in Fig. S1.

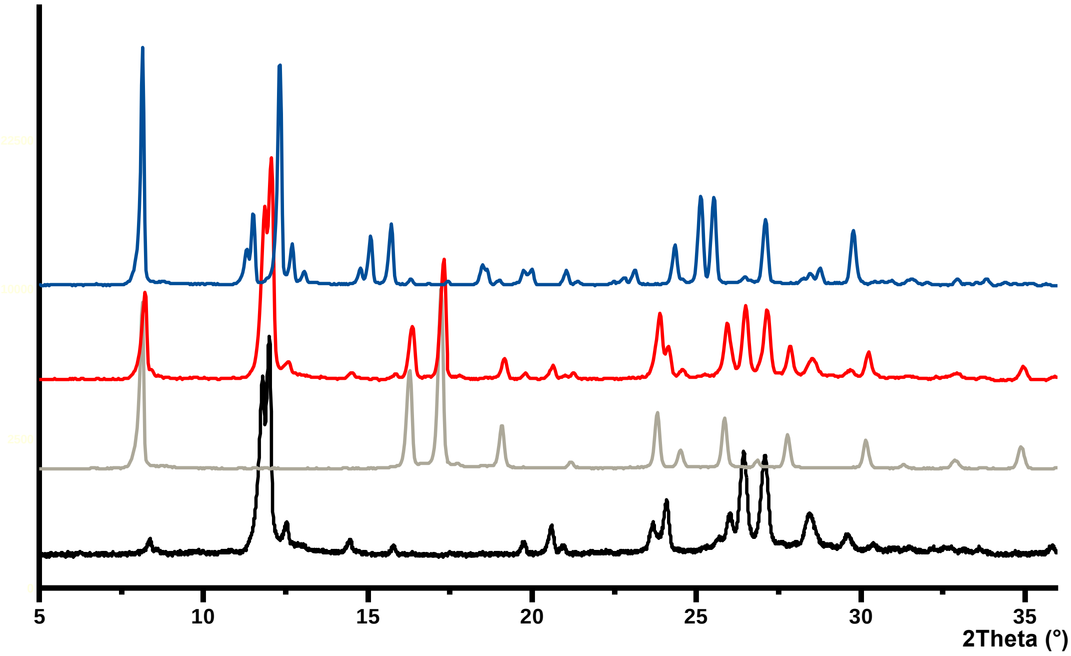

Figure S1. PXRD traces of solids obtained in cocrystal screens without seeds at the University of Cambridge. *Black*: *β*-**caf**, *grey*: **BA**, *red*: physical mixture of **caf** and **BA** obtained in the initial cocrystallisation attempt *via* LAG (using nitromethane as solvent), *blue*: (**caf**)·(**BA**) cocrystal obtained *via* SMPT (using nitromethane as solvent) after the heteronuclear seeds were introduced to the laboratory.

2. Screening experiments performed at AbbVie Inc.

2.1. Materials

Caffeine (*ReagentPlus*®, *Sigma Aldrich*), benzoic acid (*puriss. p.a.*, ACS reagent, reag. Ph. Eur., ≥99.9%, *Sigma Aldrich*), 2-fluorobenzoic acid (97%, *Aldrich*), 3-fluorobenzoic acid (97%, *Aldrich*), 2,3-difluorobenzoic acid (98%, *Aldrich*), 2,5-difluorobenzoic acid (98%, *Aldrich*), 2,6-difluorobenzoic acid (98%, *Aldrich*), 2,3,4,5-tetrafluorobenzoic acid (99%, *Aldrich*), nitromethane, ethanol and acetonitrile were used as received by the vendor. The purity grades of all solvents were reagent grade or higher.

2.2. Cocrystal screening

The cocrystal screens were performed using neat grinding (NG), LAG and SMPT as methods. The NG and LAG experiments were accomplished in a *Retsch MM 200* mixer mill using a stainless steel cell ($V = 1.5$ mL) and two stainless steel balls ($2r = 5$ mm). Physical mixtures of equimolar amounts of **caf** and **BA** ($n = 0.63$ mmol) were ground at 30 Hz for a total of 30 min. The 30 min grinding period was divided into three grinding periods of 10 min and two 5 min breaks that were introduced to minimize sample heating. Nitromethane ($V = 50$ µL) was used to facilitate cocrystal formation in the LAG experiments.

The SMPT experiments were conducted using equimolar amounts of **caf** and **BA** ($n = 1.26$ mmol) and nitromethane, acetonitrile and ethanol as solvent ($V = 300$ µL). The physical mixture of **caf** and **BA** was suspended in the solvent, sonicated in an ultrasonic bath (*Branson 2510R-DTM*, frequency: 42 kHz ± 6% at 100W) at room temperature for 5 min to facilitate the phase transformation, and then left to equilibrate overnight at room temperature, *i.e.* up to 19 h.

The seeding experiments were performed under the same LAG conditions as described in section 1.2. Specifically, physical mixtures of **caf** and **BA** were added to the grinding cell, followed by the addition of nitromethane and two stainless steel balls. The heteronuclear seeds, *i.e.* cocrystals composed of **caf** and fluorobenzoic acids (**FBA**s) ($m = 10.0 \pm 0.2$ mg), were added last to the grinding cell. The heteronuclear seeds were synthesised by SMPT using equimolar amounts ($n = 2$ mmol) of **caf** and the **FBA**s (*i.e.* 2-fluorobenzoic, 3-fluorobenzoic, 2,3-difluorobenzoic, 2,6-difluorobenzoic and 2,3,4,5-tetrafluorobenzoic acid), as well as a minimal amount of acetonitrile used as solvent. The formation of the cocrystal seeds was verified *via* powder X-ray diffraction (PXRD) using simulated powder traces obtained from the experimentally determined (**caf**)·(**FBA**) cocrystal structures (see section 5.3).

All obtained solids were analyzed with an *Inel G3000* powder diffractometer (*Inel Corp.*, Artenay, France) being equipped with a curved position sensitive detector and parallel beam optics. The instrument was operated with a Cu-anode tube (1.5 kW fine focus) at 40 kV and 30 mA producing monochromatic Cu$K_{\alpha1}$ radiation (germanium filtered). The sample was loaded onto an Al sample holder and leveled with a glass slide. The data was analysed using the *Jade* software.[2] The results of the cocrystal screens are shown in Fig. S2 and S4.

A *Kaiser RamanRXN2* Raman spectrometer equipped with a 785 nm laser was utilised to probe the content of sealed vials for cocrystal formation. The obtained Raman spectra are shown in Fig. S3, S5 and S6.

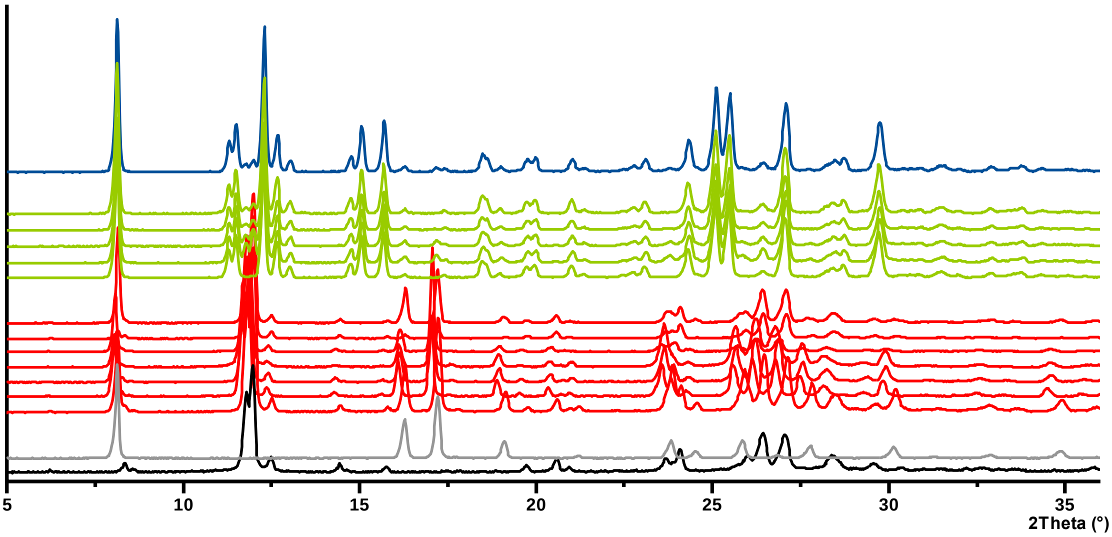

Figure S2. PXRD traces of solids obtained in cocrystal screens without seeds at AbbVie Inc. From bottom to top: β-**caf** (black), **BA** (grey), physical mixtures of **caf** and **BA** obtained in cocrystallisation attempt *via* LAG using nitromethane as solvent (red), LAG using ethanol as solvent (red), LAG using acetonitrile as solvent (red); NG; SMPT using nitromethane as solvent (red), SMPT using ethanol as solvent (red), SMPT using acetonitrile as solvent (red), (**caf**)·(**BA**) cocrystal obtained *via* LAG using nitromethane as solvent and (**caf**)·(**2FBA**) as seed (green), LAG using nitromethane as solvent and (**caf**)·(**23diFBA**) as seed (green), LAG using nitromethane as solvent and (**caf**)·(**26diFBA**) as seed (green), LAG using nitromethane as solvent and (**caf**)·(**3FBA**) as seed (green), LAG using nitromethane as solvent and (**caf**)·(**2345tetraFBA**) as seed (green), (**caf**)·(**BA**) cocrystal obtained *via* LAG using nitromethane as solvent after the heteronuclear seeds were introduced to the laboratory (blue). Abbreviations: **2FBA** = 2-fluorobenzoic acid, **3FBA** = 2-fluorobenzoic acid, **23diFBA** = 2,3-difluorobenzoic acid, **26diFBA** = 2,6-difluorobenzoic acid, **2345tetraFBA** = 2,3,4,5-tetrafluorobenzoic acid.

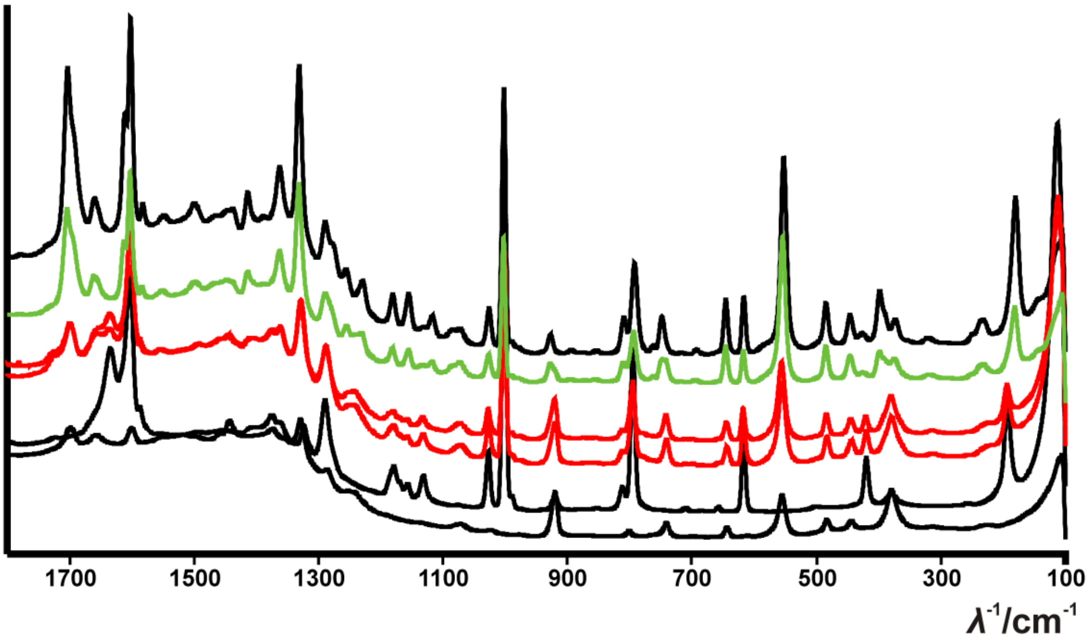

Figure S3. Raman spectra of a **caf**:**BA** physical mixture before and after being exposed to a seed-contaminated atmosphere in the AbbVie Inc. From bottom to top: β-**caf** (black), **BA** (black), physical mixtures of **caf** and **BA** sonicated for 5 min (red), physical mixtures of **caf** and **BA** sonicated for 5 min and subsequently slurried for 19 hours (red), **caf**:**BA** physical mixture from a sealed screening vial that converted to **1** upon exposure to the seed-contaminated atmosphere (green), **1** (black). The PXRD trace of the *transformed* **caf**:**BA** physical mixture (shown in green) is presented in blue in Figure S4.

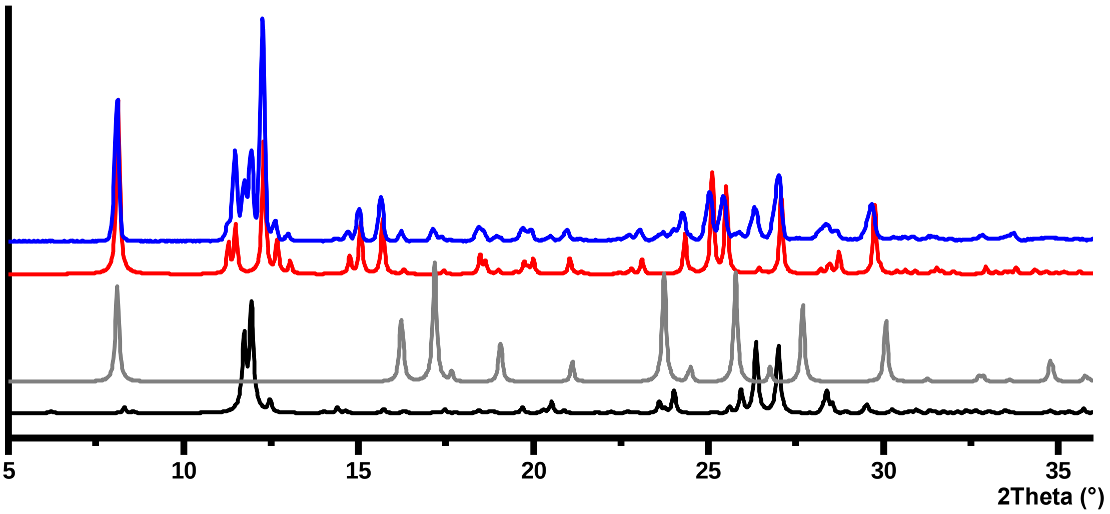

Figure S4. PXRD trace of a **caf**:**BA** physical mixture that converted to **1** after being exposed to a seed-contaminated atmosphere in the AbbVie laboratory (blue), as compared to the simulated powder traces of *β*-**caf** (black), **BA** (grey) and **1** (red).

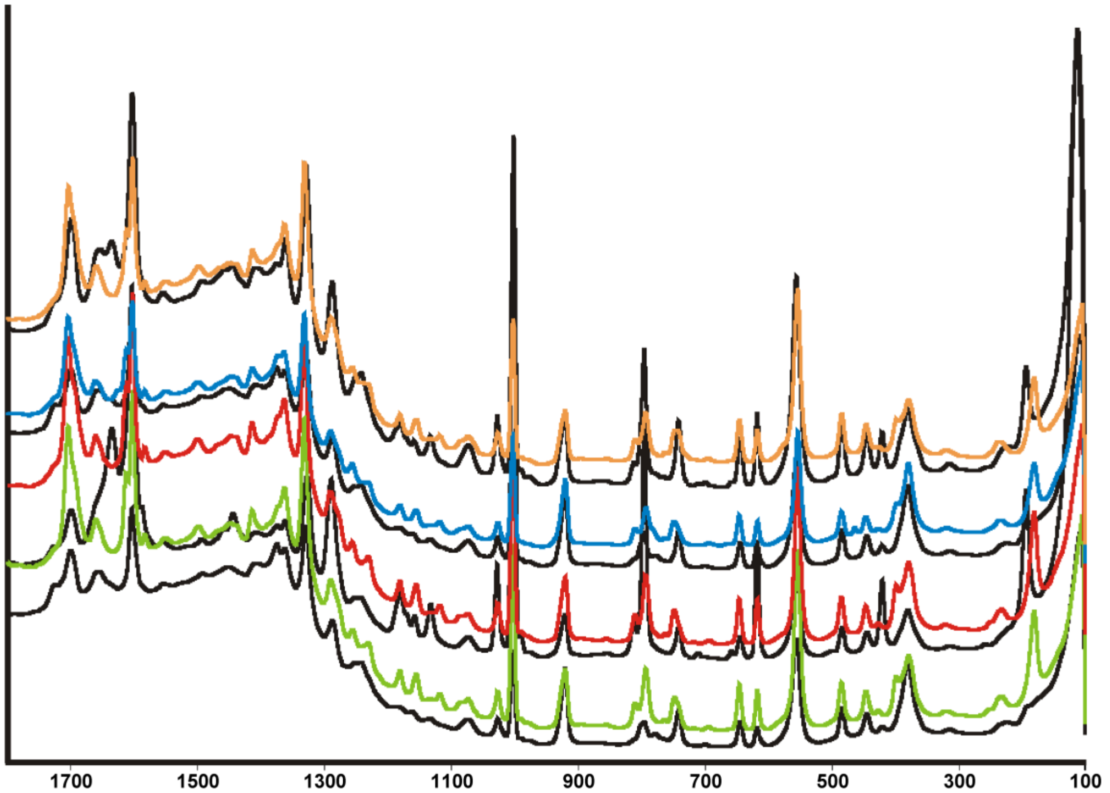

Figure S5. Raman spectra of **caf**:**BA** physical mixtures (stored in rubber-septa-sealed vials) before being exposed to suspensions of a cocrystal seeds at AbbVie are shown in in black. The addition of a (**caf**)·(**FBA**) cocrystal suspension resulted in the conversion of the physical mixture into **1**. Raman spectra of cocrystal **1**, which formed upon adding a suspension of (**caf**)·(**2FBA**), (**caf**)·(**23diFBA**), (**caf**)·(**25diFBA**) or (**caf**)·(**26diFBA**) are shown in green, red, blue and orange (respectively). Abbreviation: **25diFBA** = 2,5-difluorobenzoic acid

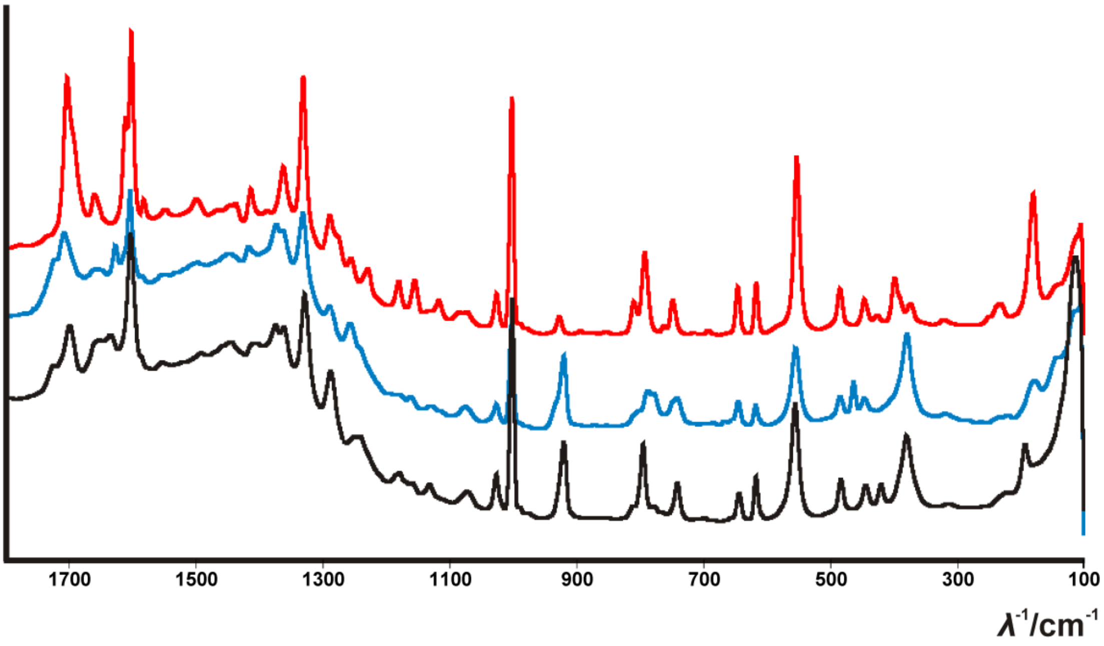

Figure S6. Raman spectra of a **caf**:**BA** physical mixtures before being exposed to a suspension of the **25diFBA** cocrystal former at AbbVie (shown in black). Raman spectra of cocrystal **1** (shown in blue), which formed upon adding the **25diFBA** suspension to the **caf**:**BA** physical mixture, as compared to the Raman spectrum of a pre-prepared batch of **1** (shown in red).

3. Screening experiments performed at the University of Zagreb

3.1. Materials

Caffeine, benzoic acid and nitromethane were received from an in-house source.

3.2. Cocrystal screening

All cocrystal screens were conducted using NG, LAG, SMPT and sonic slurry (SS) as methods. The NG and LAG experiments were accomplished in a *Retsch MM 200* mixer mill using a stainless steal cell ($V = 15$ mL) and two stainless steal balls ($2r = 7$ mm). Physical mixtures of equimolar amounts of **caf** and **BA** ($n = 0.63$ mmol) were ground at 25 Hz for 30 min in the presence of nitromethane and ethanol ($V = 50$ μL).

The SMPT experiments were performed using equimolar amounts ($n = 0.63$ mmol) of **caf** and **BA**, as well as nitromethane and ethanol as solvents ($V = 1.0$-1.5 mL). The physical mixture of **caf** and **BA** was suspended in the solvent, mixed with a magnetic stir bar and left to equilibrate overnight at room temperature.

The sonic slurry experiment was performed using an *Elma Transsonic 460/H* sonicator operating at a frequency of 35 kHz. A total of 0.63 mmol of both **caf** and **BA** were places in a capped vial that was immersed into the sonicator for 1 min while sonicated.

The seeding experiments were conducted *via* LAG (as described in section 1.2) with the addition of about 10 mg of selected heteronuclear seeds, namely **2FBA**, **3FBA**, **23diFBA**, **25diFBA**, **26diFBA**, **2345tetraFBA** and the corresponding cocrystal seeds provided by the Cambridge group (see sections 5.2. and 5.3), to the reaction mixtures.

All diffractograms used for qualitative analyses of the prepared samples were collected on a *Philips PW 3710* diffractometer (Bragg-Brentano geometry) using CuK_α radiation. The samples were placed on a on a flat zero-background holder. The instrument was operated at a tension of 40 kV and a current of 40 mA. The powder traces were collected in a 5-40° 2θ range with a step size of 0.01° and a 1.0 s counting time per step. The data was analysed using the *Topas* software.[3] The results of the cocrystal screens are shown in Fig. S7.

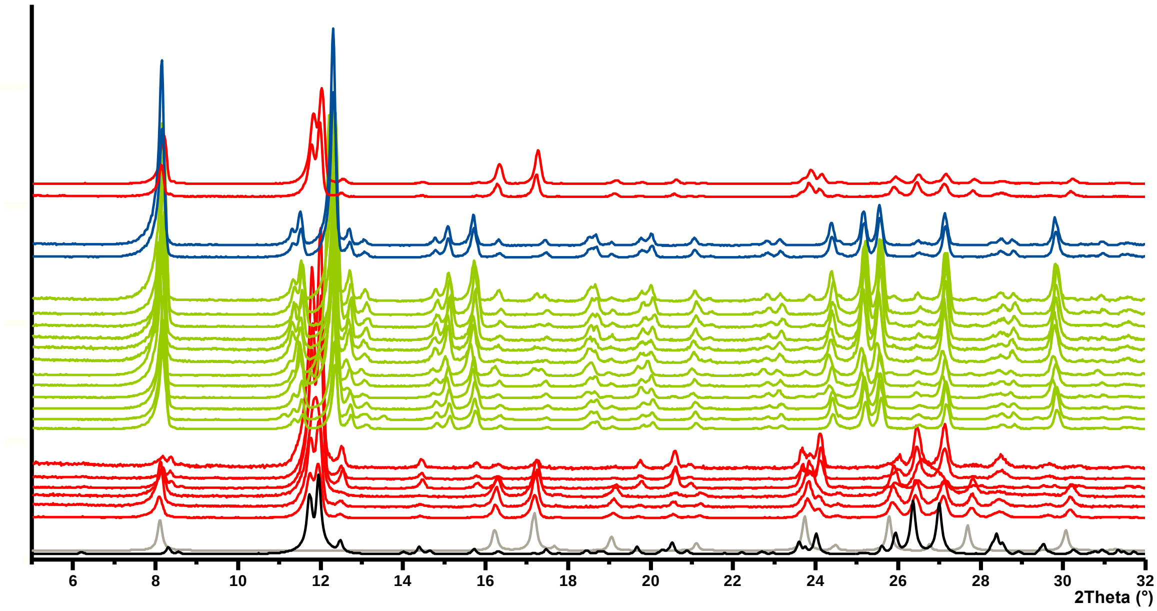

Figure S7. PXRD traces of solids obtained in cocrystal screens at the University of Zagreb. *Black*: *β*-**caf** (simulated); *grey*: **BA** (simulated); *red – from bottom to top*: physical mixtures of **caf** and **BA** obtained in cocrystallisation attempts *via* LAG using nitromethane and ethanol as solvent, NG, SMPT using nitromethane and ethanol as solvents and SS using nitromethane as solvent; *green – from bottom to top*: (**caf**)·(**BA**) cocrystal obtained *via* LAG using nitromethane as solvent and (**caf**)·(**2345tetraFBA**), **2345tetraFBA**, (**caf**)·(**3FBA**), **3FBA**, (**caf**)·(**2FBA**), **2FBA**, (**caf**)·(**23diFBA**), **23diFBA**, (**caf**)·(**25diFBA**), **25diFBA,** (**caf**)·(**26diFBA**) and **26diFBA** as heteronuclear seeds; *blue – from bottom to top*: (**caf**)·(**BA**) cocrystals obtained *via* LAG (using nitromethane and ethanol as solvent, respectively) without the use of heteronuclear seeds in the seed-contaminated laboratory; *red – from bottom to top*: physical mixtures of **caf** and **BA** obtained in cocrystallisation attempts *via* LAG (using nitromethane and ethanol as solvent, respectively) performed in a freshly uncontaminated, seed-free laboratory six weeks after the initial seeding experiments were accomplished.

4. Screening experiments performed at the University of Iowa

4.1. Materials

Caffeine (≥95%, *Sigma-Aldrich*), benzoic acid (≥99.5%, *Sigma-Aldrich*), 2-fluorobenzoic acid (97 %, *Sigma-Aldrich*), 2,3-difluorobenzoic acid (98%, *Aldrich*), 2,5-difluorobenzoic acid (98%, *Aldrich*), 2,6-difluorobenzoic acid (98%, *Aldrich*) and acetonitrile (99.9%, *Fisher Scientific*) were used as received.

4.2. Cocrystal screening

Cocrystal screens at the University of Iowa were conducted using NG, LAG, SMPT and SS as methods, and involved the use equimolar amounts of **caf** and **BA**. The NG and LAG experiments were performed manually with a mortar and pestle whereby the samples were ground for 15 min (3×5 min). The LAG experiments involved the use of acetonitrile (V = 50 μL) to facilitate cocrystal formation.

The SS screens were accomplished by sonicating a suspension of equimolar amounts (n = 0.63 mmol) of **caf** and **BA** in acetonitrile (V = 700 μL) for 15 or 60 min in a *Branson 1510* ultrasonic cleaner (40 kHz).

The seeding experiments were accomplished by using 5-15 mg of **2FBA**, **25diFBA**, **25diFBA**, **26diFBA** and (**caf**)·(**2FBA**) as heteronuclei. The (**caf**)·(**2FBA**) seed was prepared *via* SMPT of a physical mixture of **caf** (n = 1 mmol) and **2FBA** (n = 1 mmol) in acetonitrile (V = 0.5 mL). The **caf**:**BA** reaction mixtures were in all seeding experiments sonicated for a short period of time, and then equilibrated for 72 hours at room temperature.

All samples were characterized using a *Bruker D-5000* powder diffractometer equipped with a *Bruker SOL-X* energy-sensitive detector using Cu$K_{\alpha1}$ radiation (λ =1.54056 Å). The data was analysed using the *DIFFRAC^{plus} Eva* software.[4] The results of the cocrystal screens are shown in Fig. S8.

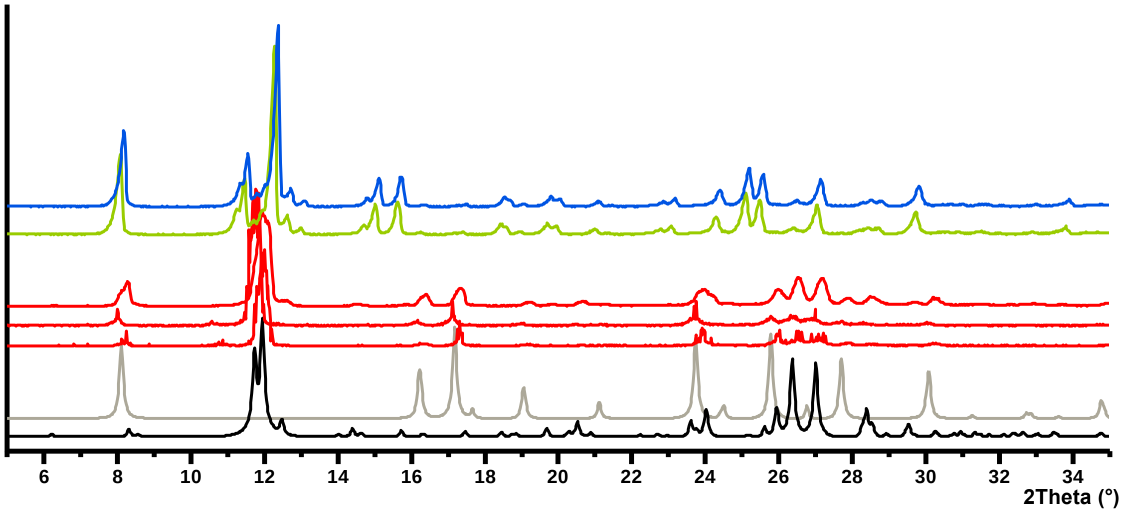

Figure S8. PXRD traces of solids obtained in cocrystal screens without seeds at the University of Iowa. *Black*: β-**caf** (simulated); *grey*: **BA** (simulated); *red – from bottom to top*: physical mixtures of **caf** and **BA** obtained in cocrystallisation attempt *via* LAG using acetonitrile as solvent, NG and SS using acetonitrile as solvent; *green*: (**caf**)·(**BA**) cocrystal obtained *via* LAG using acetonitrile as solvent and (**caf**)·(**2FBA**) as seed; *blue*: (**caf**)·(**BA**) cocrystal obtained *via* LAG (without the use of the (**caf**)·(**FBA**) seeds) in a seed-contaminated laboratory utilising acetonitrile as solvent.

5. Synthesis of the heteronuclear seeds and their structural analysis

5.1. Materials

Caffeine (*ReagentPlus*®, *Sigma Aldrich*), 2-fluorobenzoic acid (97%, *Aldrich*), 3-fluorobenzoic acid (97%, *Aldrich*), 2,3-difluorobenzoic acid (98%, *Aldrich*), 2,5-difluorobenzoic acid (98%, *Aldrich*), 2,6-difluorobenzoic acid (98%, *Aldrich*), 2,3,4,5-tetrafluorobenzoic acid (98+%, *Alfa Aesar*) and nitromethane (99%, *Acros*) were used as received by the vendor.

5.2. Cocrystal synthesis

The synthesis of the heteronuclear cocrystal seeds was accomplished *via* LAG. In a typical cocrystallisation experiment, equimolar amounts of **caf** and the fluorobenzoic acid ($n = 0.63$ mmol) were ground together using two stainless steel balls ($2r = 7$ mm) in a stainless steel grinding jar ($V = 15$ mL), which was mounted on a *Retsch MM 200* mixer mill. Nitromethane ($V = 50$ μL) was utilised to facilitate cocrystal formation during the milling experiment (30 Hz, 30 min). The samples were left to dry at ambient conditions for 30 min upon removal from the grinding jars. The products were then characterized *via* PXRD (for experimental details regarding the PXRD data collection, see section 1.2).

5.3. Structure solution *via* X-ray powder diffraction

All crystal structures were determined using *ab-initio* crystal structure solution from powder X-ray diffraction data that was acquired with a laboratory *Panalytical X'Pert PRO* powder diffractometer. The diffractometer specifications are described in section 1.2. Data collections were performed in the continuous mode (gonio scan axis) in the 2θ range of 3.0-60.0° with counting times of 260 s.

The unit cell content for each cocrystal was estimated based on expected volume increments per atom. Structure solutions were achieved in direct-space taking advantage of assumed molecular geometries of **caf** and **FBA** in question. The positions of structural fragments in the unit cell were then found by the simulated annealing procedure wherefrom atomic coordinates were calculated. ^{15}N CP-MAS NMR and ATR-IR studies indicated the presence of neutral **caf** and (fluoro)benzoic acid molecules in the analysed solids (see sections 5.4. and 5.5). The simulated annealing procedures were, therefore, conducted using neutral structure fragments. Thermogravimetric analyses indicated that the solids contain of two components only, namely **caf** and a (fluoro)benzoic acid.

Indexing, structure solution by simulated annealing and Rietveld refinement were performed using the program *Topas*.[3] The crystal data for (**caf**)·(**BA**), (**caf**)·(**2FBA**), (**caf**)·(**3FBA**), (**caf**)·(**23diFBA**), (**caf**)·(**25diFBA**), (**caf**)·(**26diFBA**) and (**caf**)·(**2345tetraFBA**) are listed in Table S1. The Rietveld plots for each cocrystal structure are shown in Fig. S9-S15. Crystallographic data for the structures reported herein have been deposited with the Cambridge Crystallographic Data Centre as CCDC 898406-898412. The data can be obtained free of charge at http://www.ccdc.cam.ac.uk/products/csd/request/.

Table S1. Crystallographic and refinement parameters for crystal structures solved from powder X-ray diffraction data.

Compound	**(caf)·(BA)**	**(caf)·(2FBA)**	**(caf)·(3FBA)**	**(caf)·(23diFBA)**
Chemical formula	$(C_8H_{10}N_4O_2)\cdot(C_7H_6O_2)$	$(C_8H_{10}N_4O_2)\cdot(C_7H_5F_1O_2)$	$(C_8H_{10}N_4O_2)\cdot(C_7H_5F_1O_2)$	$(C_8H_{10}N_4O_2)\cdot(C_7H_4F_2O_2)$
M_r	316.32	334.31	334.31	352.30
Crystal system	Monoclinic	Monoclinic	Triclinic	Monoclinic
a (Å)	11.236(1)	11.3070(7)	8.7811(9)	11.3960(9)
b (Å)	9.106(1)	9.0659(4)	10.0661(6)	9.1597(5)
c (Å)	15.913(2)	15.9446(9)	10.561(1)	15.870(1)
α (°)	90	90	105.871(6)	90
β (°)	104.579(4)	105.280(3)	72.717(6)	104.025(4)
γ (°)	90	90	71.152(6)	90
V (Å^3)	1575.6(3)	1576.7(2)	769.8(2)	1607.2(2)
T (K)	293	293	293	293
Space group	$P2_1/c$	$P2_1/c$	$P\bar{1}$	$P2_1/c$
Z	4	4	2	4
R_{wp}	0.081	0.056	0.078	0.072
R_p	0.062	0.042	0.059	0.052
R_{Bragg}	0.016	0.017	0.021	0.022
χ^2	3.11	5.01	7.53	6.67
No. of parameters	165	173	167	157
CCDC deposition number	898406	898407	898408	898409

Compound	**(caf)·(25diFBA)**	**(caf)·(26diFBA)**	**(caf)·(2345tetraFBA)**
Chemical formula	$(C_8H_{10}N_4O_2)\cdot(C_7H_4F_2O_2)$	$(C_8H_{10}N_4O_2)\cdot(C_7H_4F_2O_2)$	$(C_8H_{10}N_4O_2)\cdot(C_7H_2F_4O_2)$
M_r	352.30	352.30	388.29
Crystal system	Monoclinic	Monoclinic	Monoclinic
a (Å)	11.3610(8)	11.3356(7)	14.263(1)
b (Å)	9.1152(5)	9.1236(4)	8.1372(5)
c (Å)	15.883(1)	15.944(1)	16.013(2)
α (°)	90	90	90
β (°)	101.777(4)	104.260(4)	121.214(4)
γ (°)	90	90	90
V (Å^3)	1610.2(2)	1598.2(2)	1589.4(2)
T (K)	293	293	293
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$
Z	4	4	4
R_{wp}	0.062	0.058	0.056
R_p	0.047	0.045	0.042
R_{Bragg}	0.021	0.019	0.017
χ^2	5.28	5.12	5.01
No. of parameters	156	156	173
CCDC deposition number	898410	898411	898412

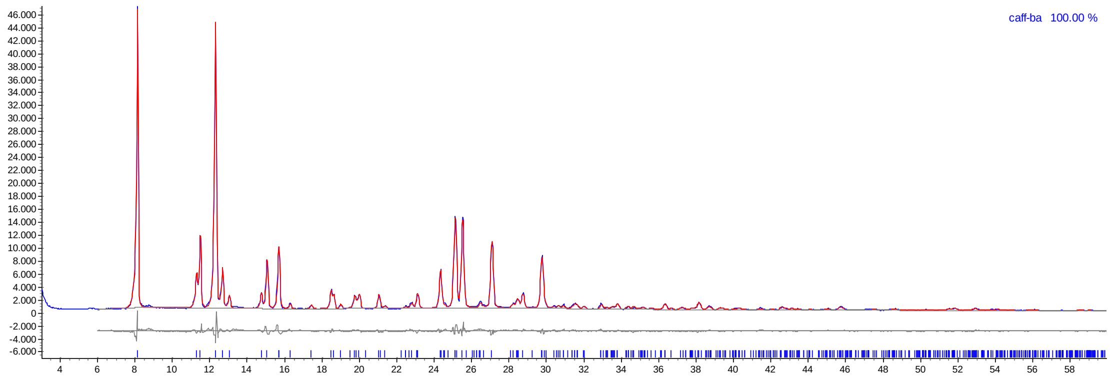

Figure S9. Rietveld fit of the (**caf**)·(**BA**) cocrystal (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

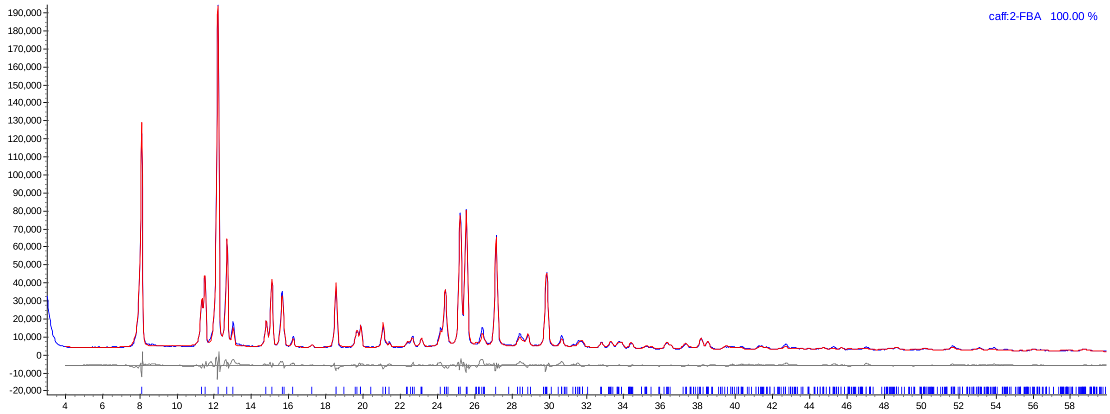

Figure S10. Rietveld fit of the (**caf**)·(**2FBA**) cocrystal (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

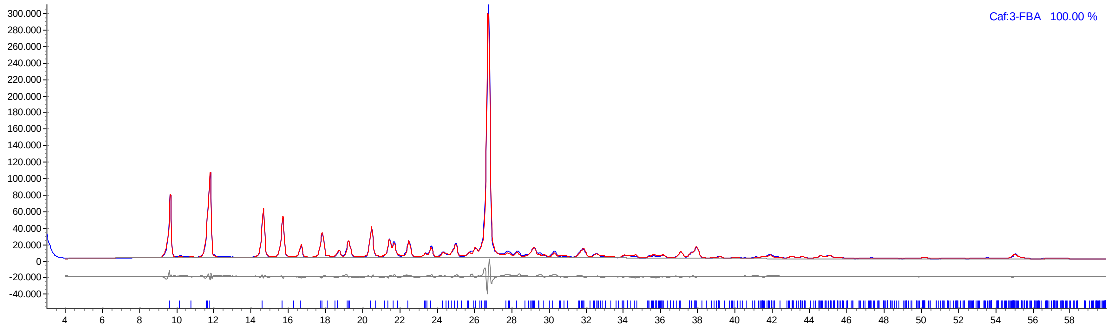

Figure S11. Rietveld fit of the (**caf**)·(**3FBA**) cocrystal (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

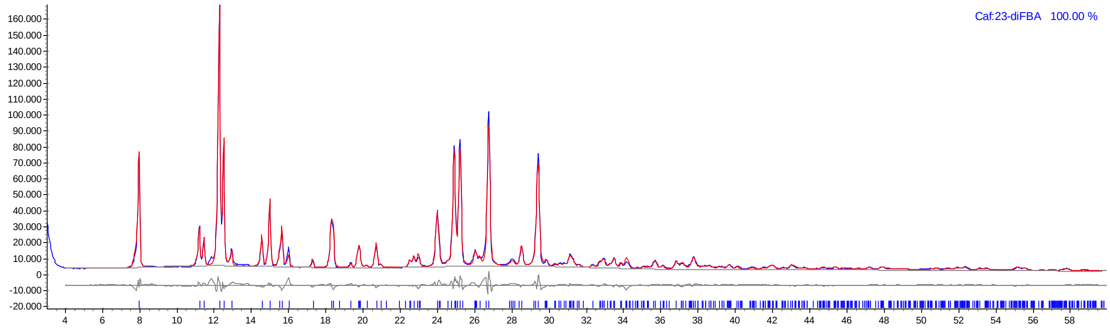

Figure S12. Rietveld fit of the (**caf**)·(**23diFBA**) cocrystal (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

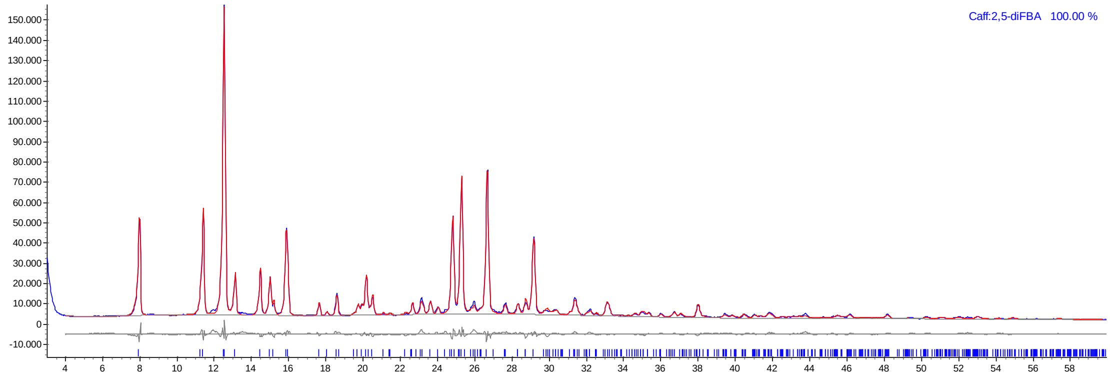

Figure S13. Rietveld fit of the (**caf**)·(**25diFBA**) cocrystal (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

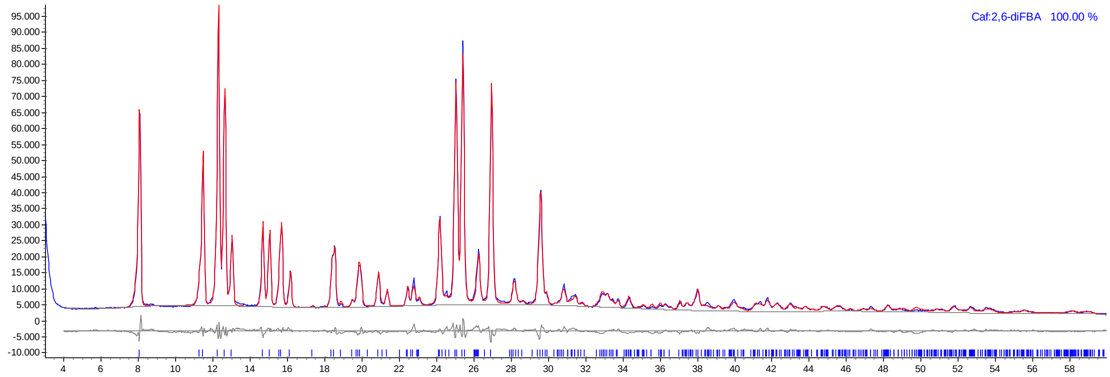

Figure S14. Rietveld fit of the (**caf**)·(**26diFBA**) cocrystal (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

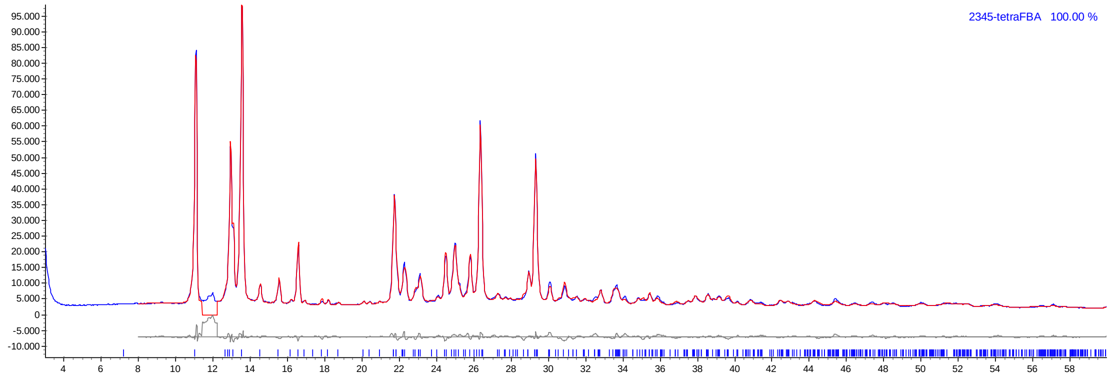

Figure S15. Rietveld fit of the (**caf**)·(**2345tetraFBA**) cocrystal (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

5.4. ^{15}N cross-polarization magic-angle spinning (CP-MAS) NMR analyses

^{15}N CP-MAS NMR experiments were performed at 9.4 T on a *Bruker Avance-400* spectrometer operating at 400.4 MHz (^{1}H) and 40.6 MHz (^{15}N) using: a *Bruker* double resonance probe, 4 mm zirconia rotors, a magic angle spinning frequency of 6 kHz, ^{1}H 90° pulse of 2.5 μs, ramped cross polarization (5 ms, field 70 kHz), ^{1}H decoupling (spinal-64 composite pulse decoupling, 100 kHz field), 1 min recycle time, and external chemical shift referencing to glycine at 10 ppm relative to the ammonium ion at 0 ppm. ^{15}N CP-MAS NMR spectra were collected for **caf** cocrystals involving the weakest and two of the strongest fluorobenzoic acids used in the study (*i.e.* **BA**, **2345tetraFBA** and **26diFBA**, respectively). The spectra of the (**caf**)·(**BA**), (**caf**)·(**2345tetraFBA**) and (**caf**)·(**26diFBA**) cocrystals are shown on Fig. S16.

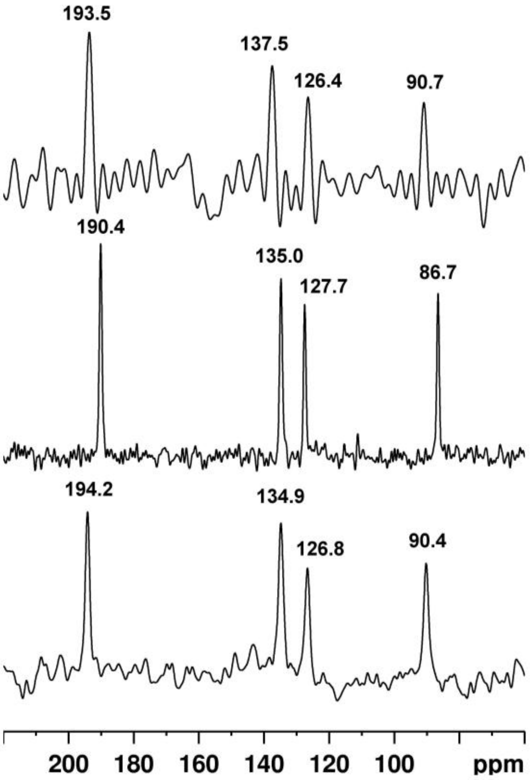

Figure S16. ^{15}N CP-MAS NMR spectrum of (**caf**)·(**BA**)(bottom), (**caf**)·(**2345tetraFBA**) (middle) and (**caf**)·(**26diFBA**) (top).

5.5. ATR-IR spectroscopic analyses

ATR-IR spectroscopy was used to identify a possible proton transfer from the carboxylic group of a **FBA** to the **caf** imidazole moiety in the studied cocrystals. Considering that the lack of a proton transfer in (**caf**)·(**BA**), (**caf**)·(**26diFBA**) and (**caf**)·(**2345tetraFBA**) was undoubtedly established using ^{15}N CP-MAS NMR, and that all prepared (**caf**)·(**FBA**) solids exhibit IR bands very similar to those observed in (**caf**)·(**BA**), (**caf**)·(**26diFBA**) and (**caf**)·(**2345tetraFBA**), it was concluded that **caf** forms cocrystals (rather than salts) with **BA**, **2FBA**, **3FBA**, **23diFBA**, **25diFBA**, **26diFBA** and **2345tetraFBA**. All ATR-IR spectra of the (**caf**)·(**FBA**) solids display carbonyl-stretching bands above 1600 cm^{-1} (Fig. S17), which are consistent with the presence of unionized carboxylic acid groups in each solid. Notably, these observations are in agreement with the ΔpK_a rule of thumb that suggests that acid-base pairs exhibiting a ΔpK_a < -1 almost exclusively crystallize as cocrystals.[5] All ΔpK_a values of the acid-base pairs in question exhibit ΔpK_a < -1.8 (see Table S2).

The ATR-IR spectroscopic measurements were accomplished using a *Thermo Nicolet Nexus FTIR* spectrometer equipped with a *Smart Golden Gate ZnSe* accessory. The spectra were collected in 256 scans (resolution: 4 cm^{-1}) in the range of 700-4000 cm^{-1}. The data was analysed using the *OMNIC* software.[6]

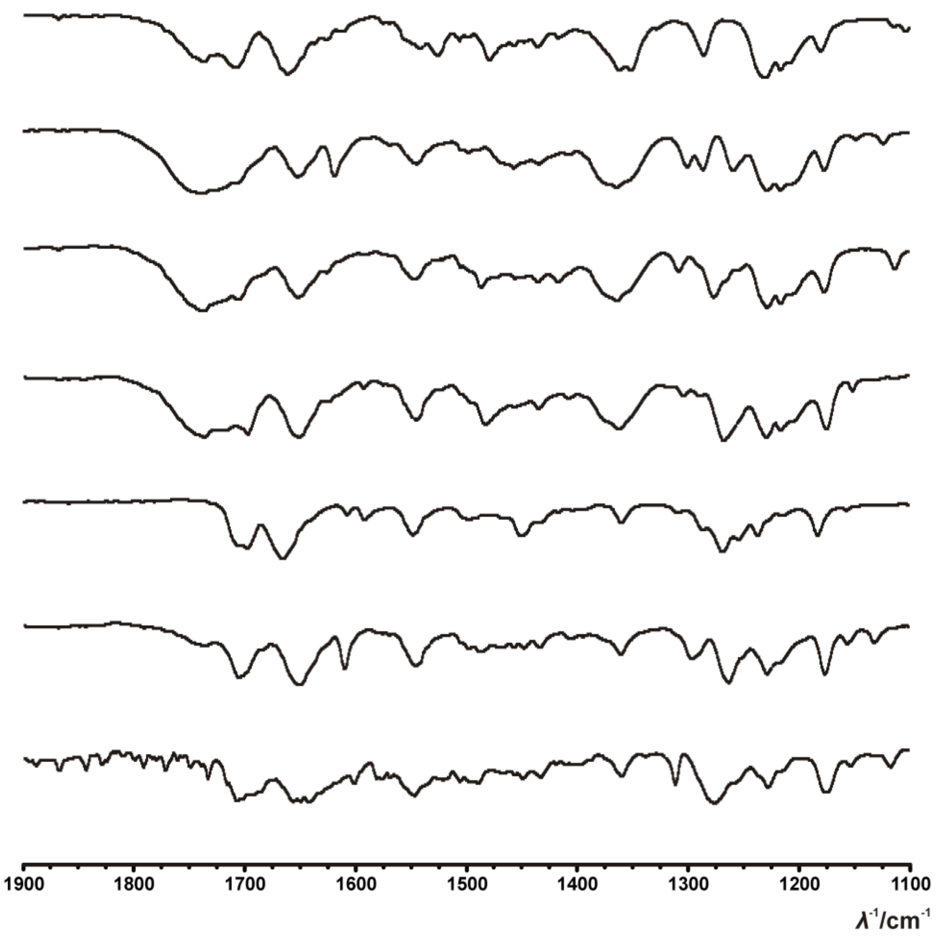

Figure S17. ATR-IR spectra of (from bottom to top): (**caf**)·(**BA**), (**caf**)·(**2FBA**), (**caf**)·(**3FBA**), (**caf**)·(**23diFBA**), (**caf**)·(**25diFBA**), (**caf**)·(**26diFBA**) and (**caf**)·(**2345tetraFBA**).

Table S2. Calculated pK_a values of **caf**, **BA**, **2FBA**, **3FBA**, **23diFBA**, **25diFBA**, **26diFBA** and **2345tetraFBA**. The values are calculated using the *Advanced Chemistry Development* software.[7]

	pK_a	**ΔpK_a***
caf	0.52 ± 0.70	N/A
BA	4.20±0.10	-3.68 ± 0.70
2FBA	3.27±0.10	-2.75 ± 0.70
3FBA	3.86±0.10	-3.34 ± 0.70
23diFBA	2.93±0.10	-2.41 ± 0.70
25diFBA	2.93±0.10	-2.41 ± 0.70
26diFBA	2.34±0.10	-1.82 ± 0.70
2345tetFBA	2.53±0.10	-2.01 ± 0.70

* ΔpK_a = pK_a(base)-pK_a(acid)

5.6. Thermogravimetric and differential-scanning calorimetric analyses

Thermal analyses were employed to verify that the prepared cocrystals have no solvent molecules included in their crystal lattices. The analyses were conducted using a *Mettler Toledo TGA/SDTA 851^e* thermal balance and a *DSC 822^e* calorimeter. The measurements were performed at a heating rate of 10 K min^{-1} in a dynamic atmosphere of nitrogen. The thermograms for all cocrystals are shown on Fig. S18-S24.

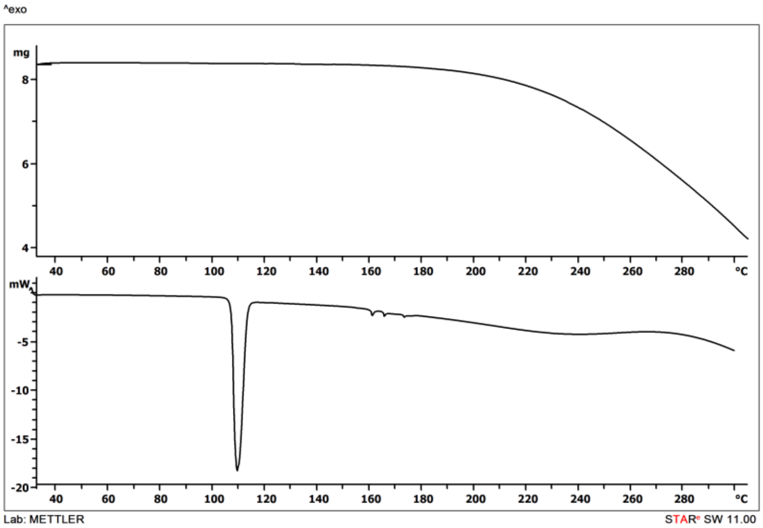

Figure S18. TGA (top) and DSC (bottom) thermograms of the (**caf**)·(**BA**) cocrystal (melting point: 107.3 °C).

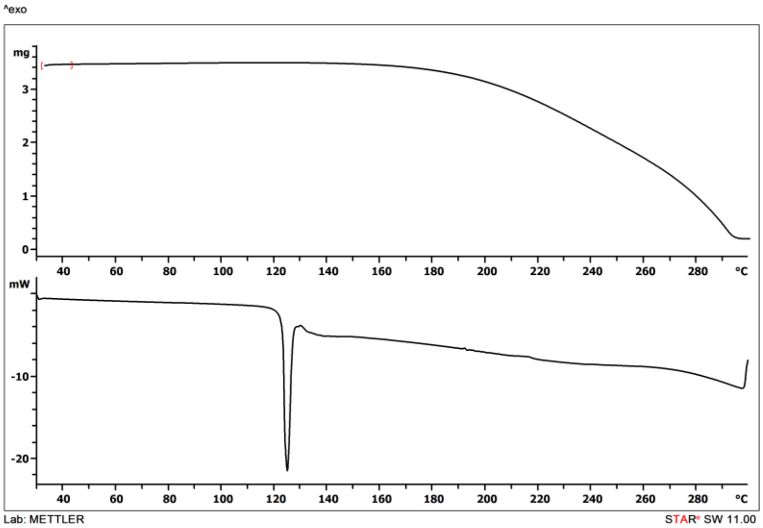

Figure S19. TGA (top) and DSC (bottom) thermograms of the (**caf**)·(**2FBA**) cocrystal (melting point, 123.2 °C).

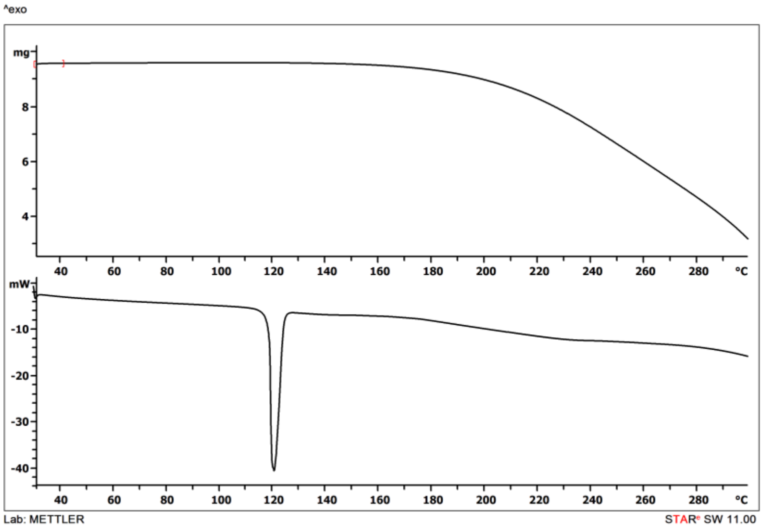

Figure S20. TGA (top) and DSC (bottom) thermograms of the (**caf**)·(**3FBA**) cocrystal (melting point: 118.8 °C).

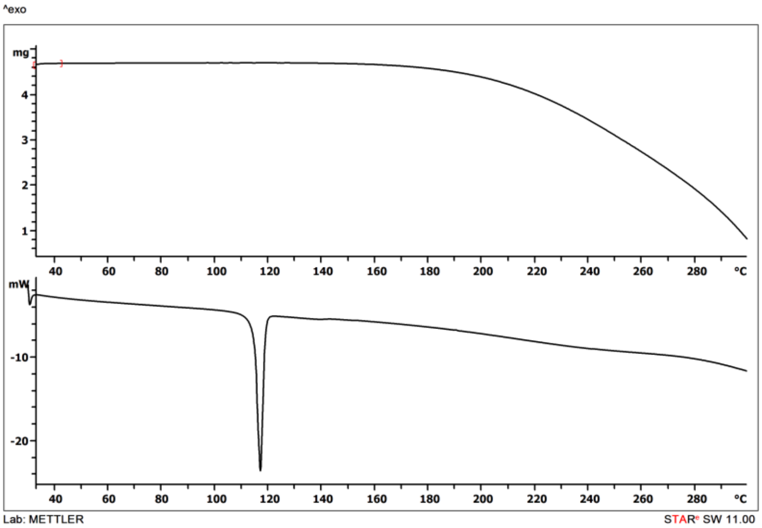

Figure S21. TGA (top) and DSC (bottom) thermograms of the (**caf**)·(**23diFBA**) cocrystal (melting point: 114.8 °C).

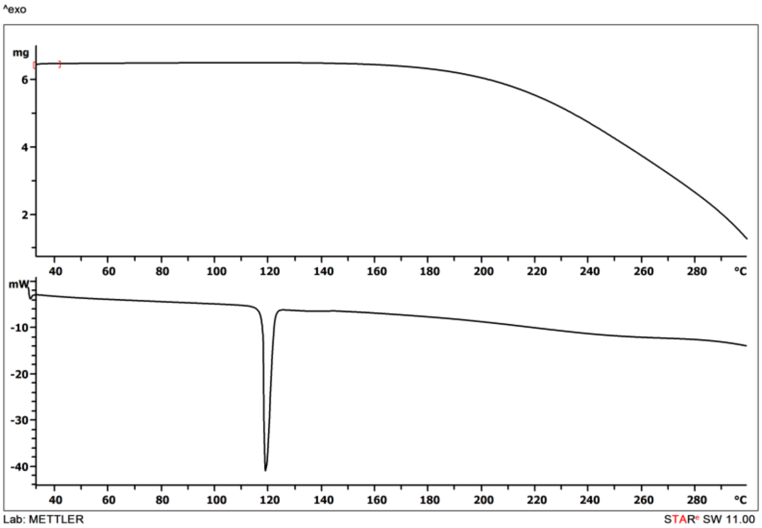

Figure S22. TGA (top) and DSC (bottom) thermograms of the (**caf**)·(**25diFBA**) cocrystal (melting point: 117.9 °C).

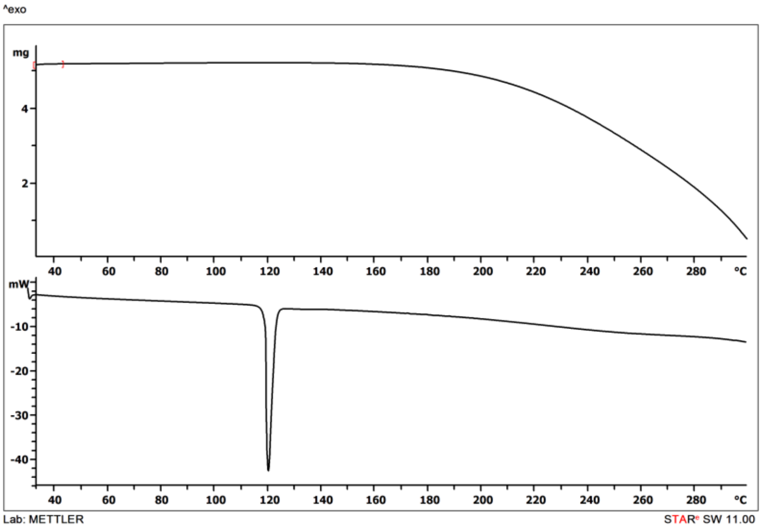

Figure S23. TGA (top) and DSC (bottom) thermograms of the (**caf**)·(**26diFBA**) cocrystal (melting point: 119.1 °C).

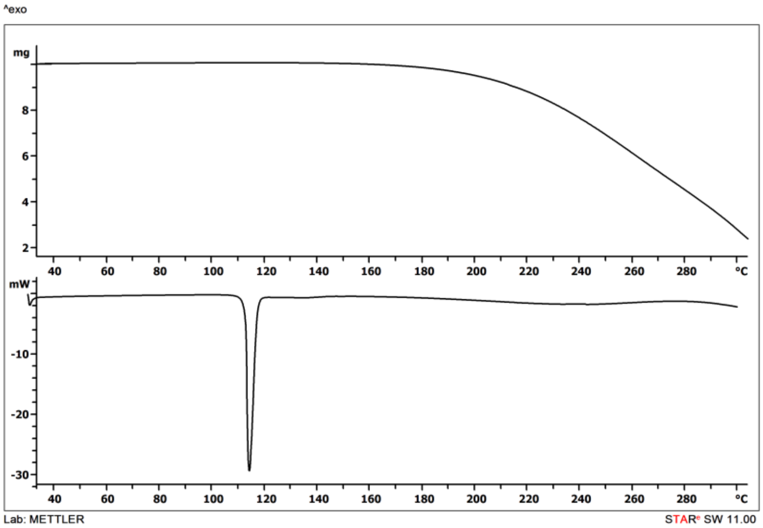

Figure S24. TGA (top) and DSC (bottom) thermograms of the (**caf**)·(**2345tetraFBA**) cocrystal (melting point: 112.9 °C).

6. References

1. X'Pert HighScore Plus v. 2.2 (PANalytical B. V., Almelo, The Netherlands, 2006).
2. Jade v. 6.5 (Materials Data, Inc., Livermore, CA, USA, 2002).
3. Topas v. 4.2 (Bruker-AXS, Karlsruhe, Germany, 2009).
4. DIFFRACplus Eva v. 6.0 (Bruker AXS, Inc., Madison, WI, 2000).
5. A. J. Cruz-Cabeza, *CrystEngComm* 2012, **14**, 6362-6365.
6. OMNIC v. 6.1a (Thermo Nicolet Corporation, Madison, WI, USA, 2001).
7. I-Lab v. 11.02 (Advanced Chemistry Development, Inc. (ACD/Labs), 1994-2011).