Electronic Supplementary Material (ESI) for CrystEngComm.

Solution cocrystallization, an effective tool to explore the variety of cocrystal systems: caffeine/dicarboxylic acid cocrystals

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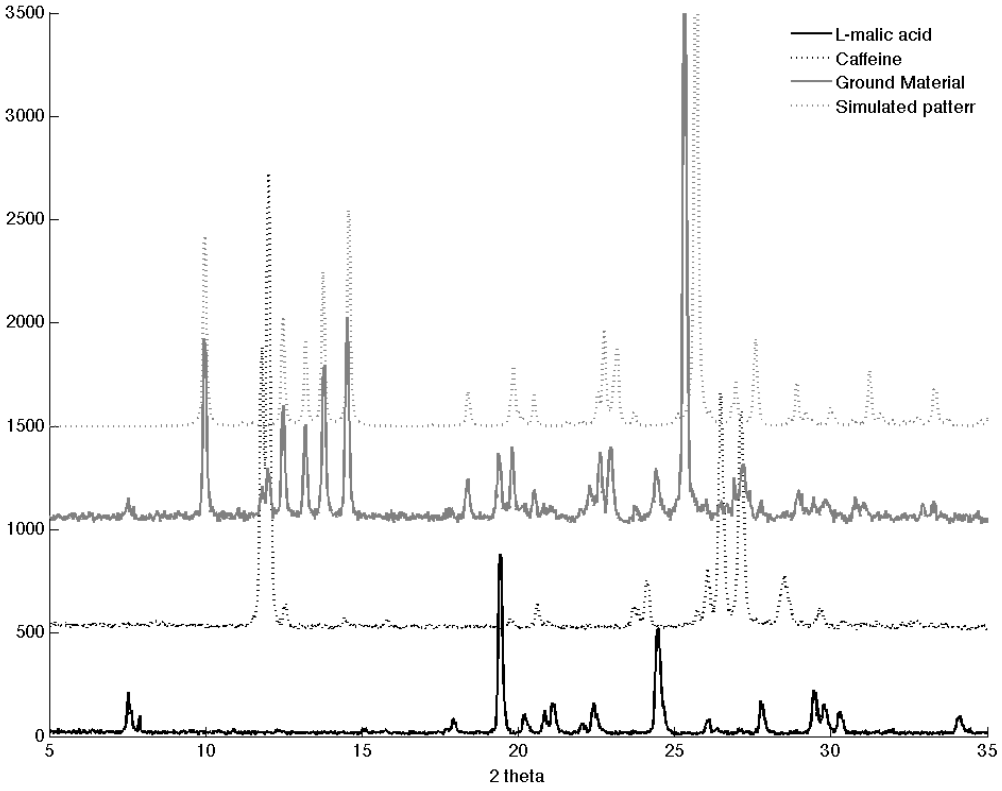


Figure S.1: X-ray powder diffraction patterns (Cu$K\alpha$, λ=1.5418Å) of L-malic acid, caffeine, 1:1 ground material (MeOH-assited grinding) and simulated XRPD pattern from single crystal (single-crystals grown from ethyl acetate).

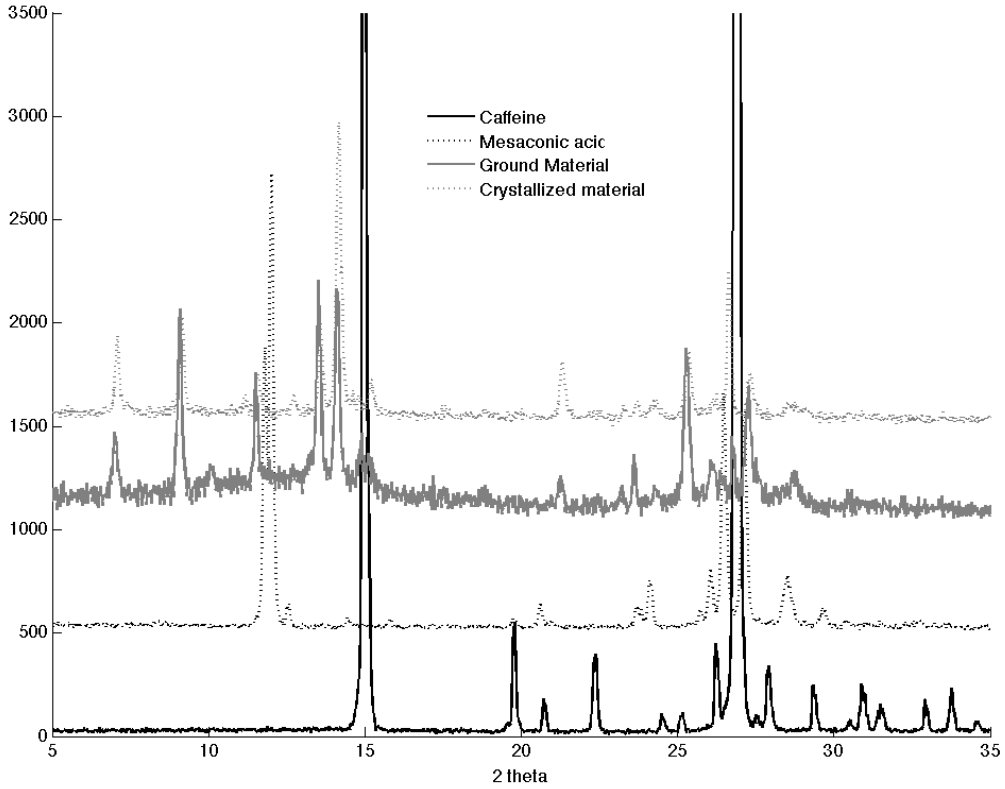


Figure S.2: XRPD of mesaconic acid, caffeine, 1:1 ground material (MeOH-assited grinding) and material obtained by spontaneous crystallization in ethyl acetate solution for the likely 1:1 cocrystal.

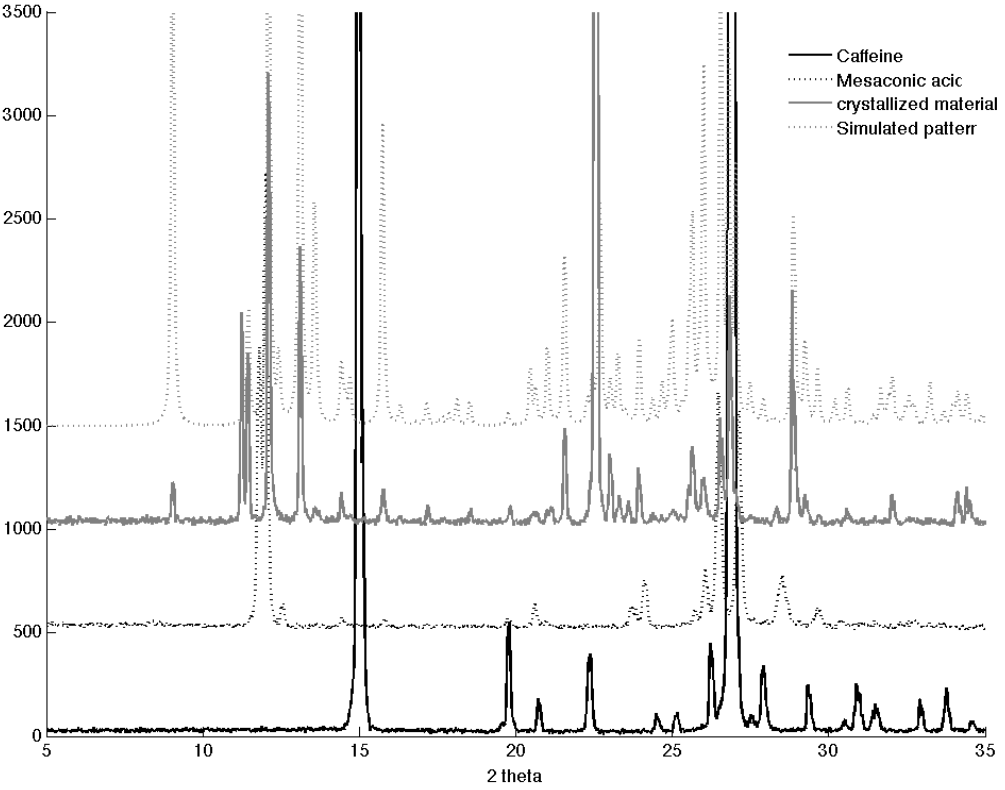


Figure S.3: XRPD of mesaconic acid, caffeine, 2:1_FI obtained through spontaneous crystallization (ethyl acetate) and simulated XRPD pattern.

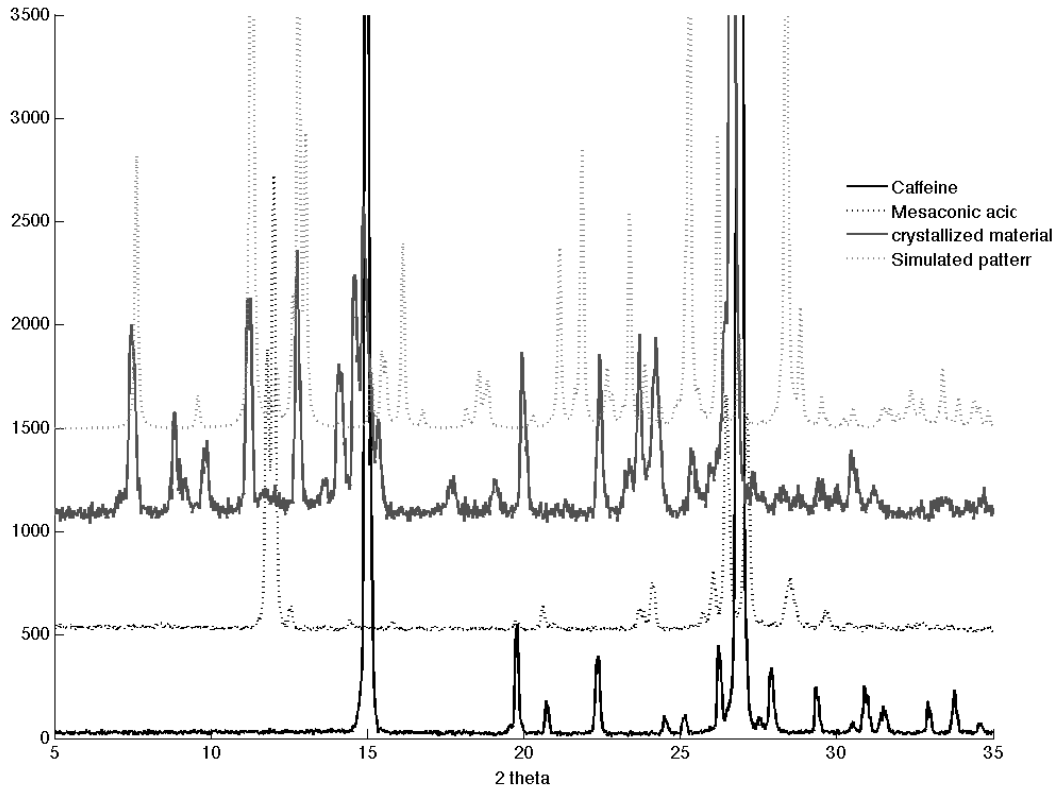


Figure S.4: XRPD of mesaconic acid, caffeine, 2:1_FII obtained through spontaneous crystallization in ethyl acetate and simulated XRPD pattern. The spontaneously crystallized material is contaminated with the other forms.

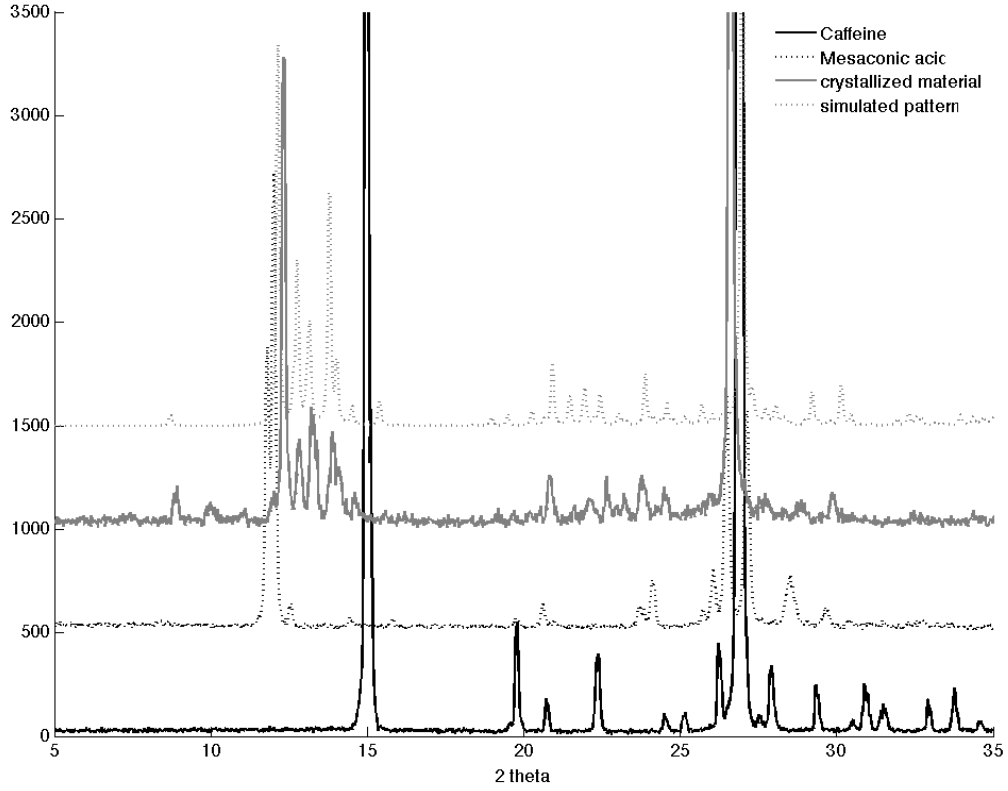


Figure S.5: XRPD of mesaconic acid, caffeine, 2:1_FIII obtained through spontaneous crystallization (ethyl acetate) and simulated XRPD pattern. The spontaneously crystallized material contains some contamination of the other forms.

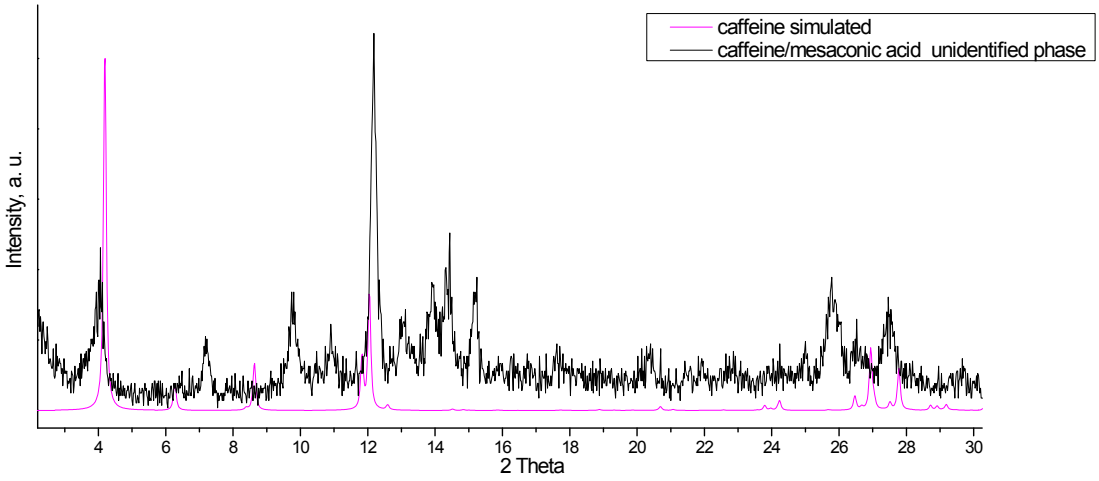


Figure S.6: XRPD of mesaconic acid (26.9 mg)/caffeine (11.6 mg), obtained through spontaneous crystallization (acetonitrile) and simulated XRPD pattern of caffeine NIWFEE05.

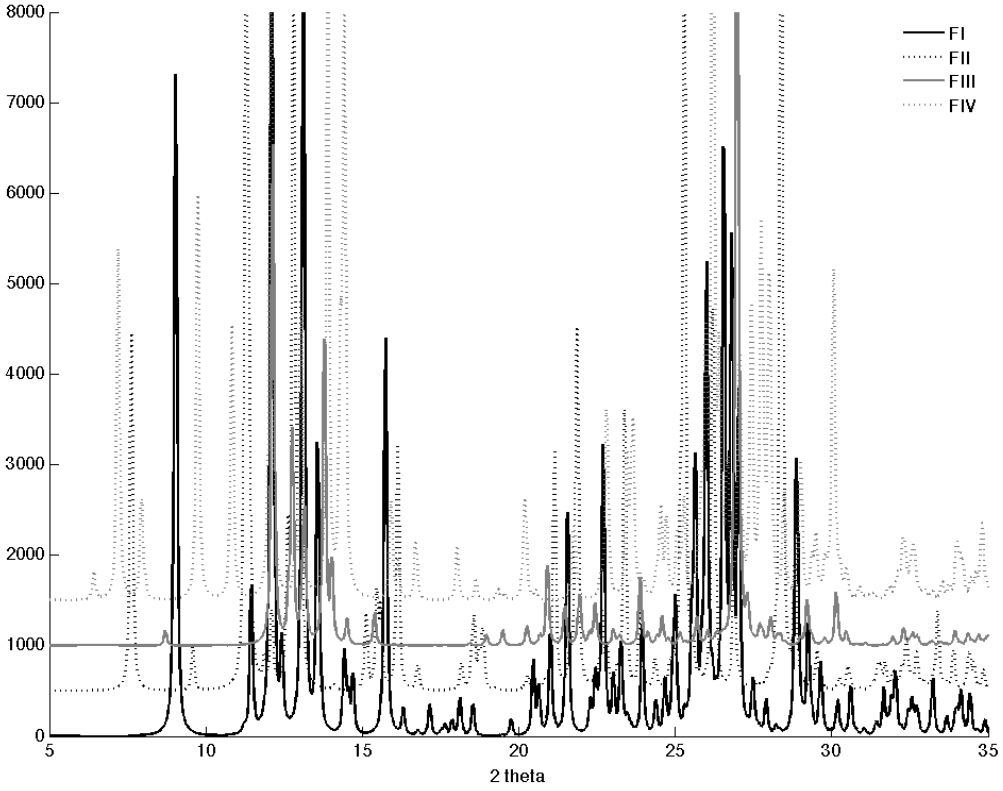


Figure S.7: 2:1_FI, 2:1_FII, 2:1_FIII, 2:1_FIV simulated XRPD patterns.

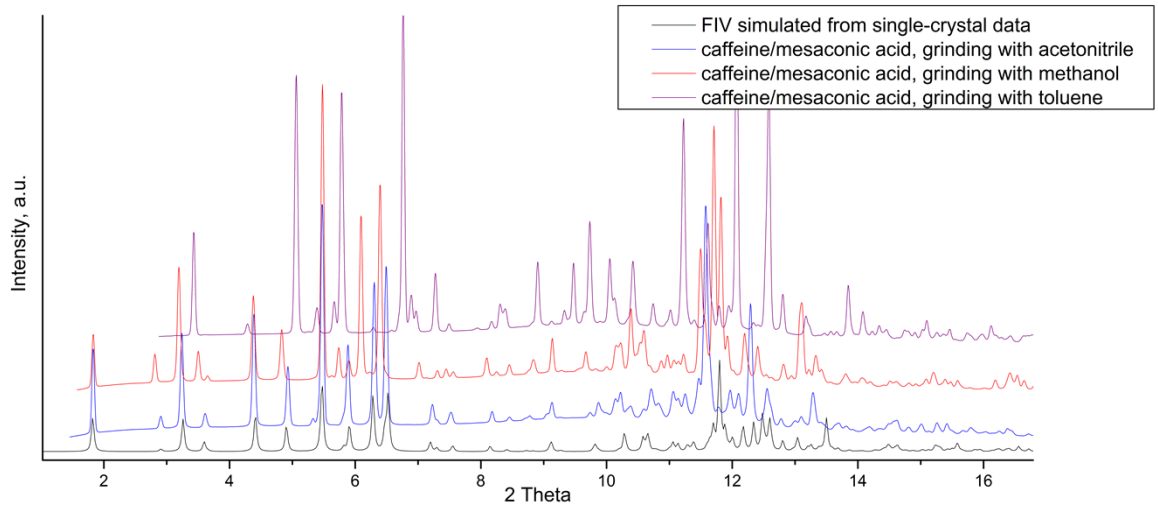
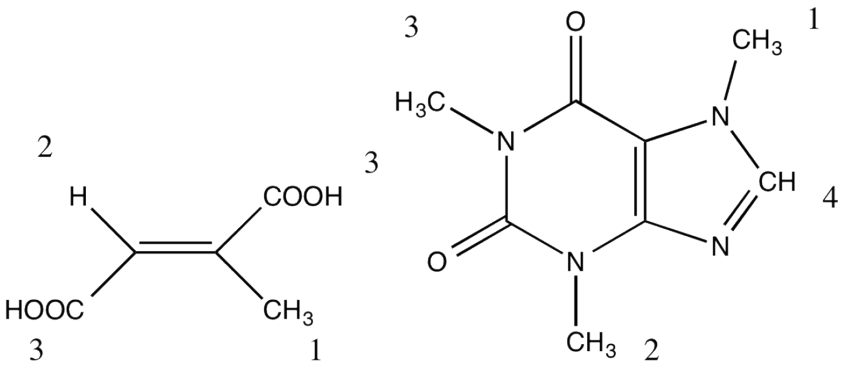


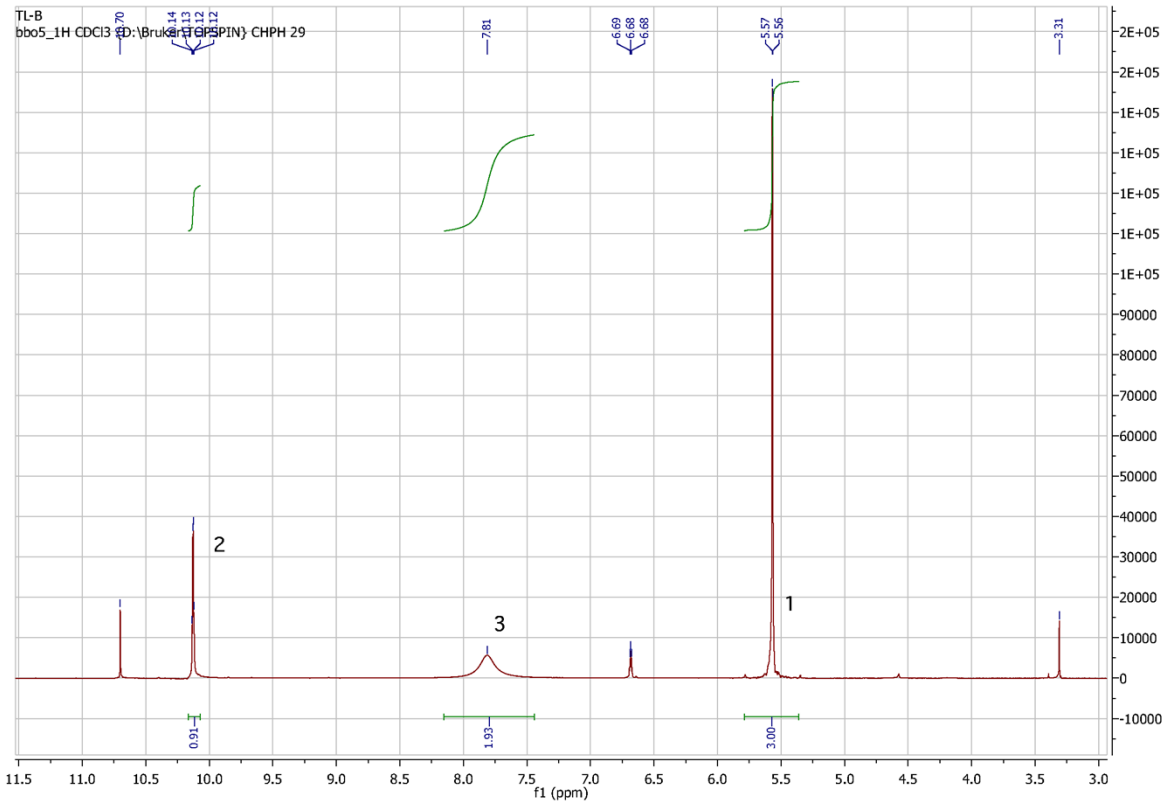
Figure S.8: 2:1_FIV simulated XRPD pattern, and patterns obtained from grinding experiments. Synchrotron data were measured on the Swiss Norwegian beamline SNBL at the ESRF synchrotron facility (Grenoble) on a Pilatus2M detector using a wavelength of 0.698520 Å

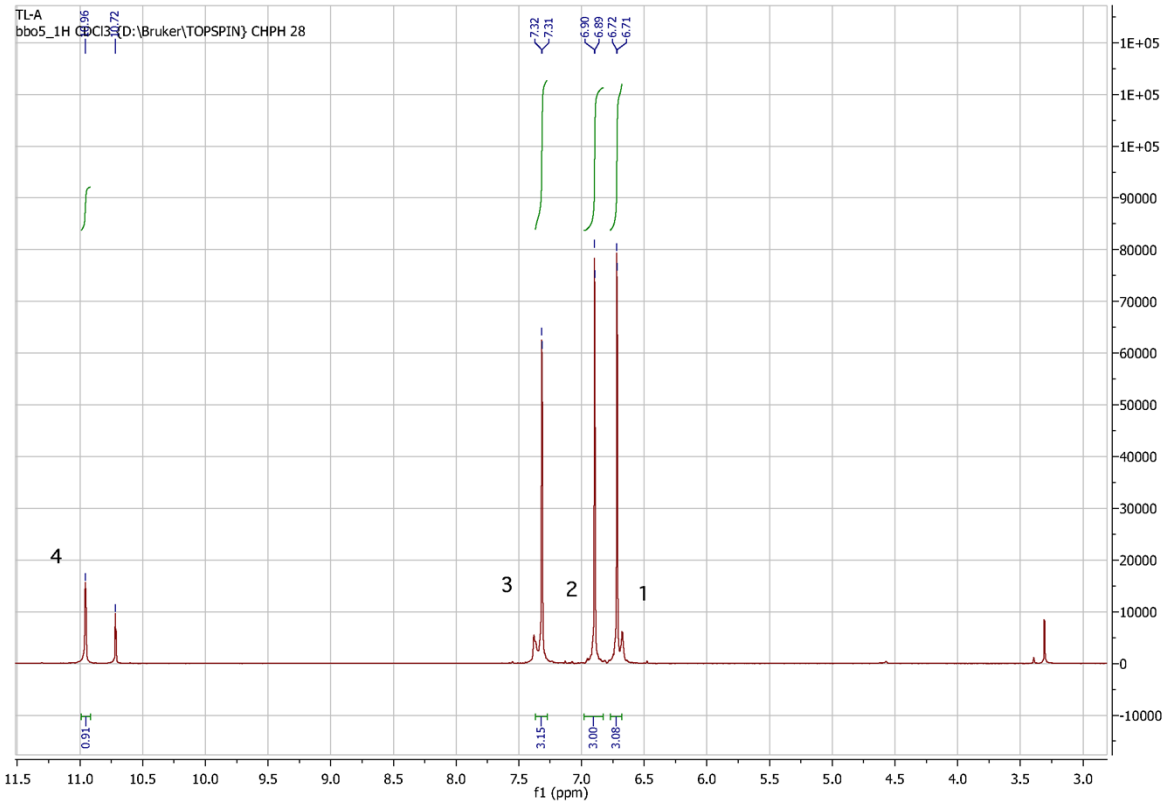
NMR DATA

1H NMR spectra were recorded on Bruker-300 spectrometers. 1H NMR chemical shifts are reported relative to CDCl3 (7.26, 77.0 ppm) and.

Figure S.9: 1H NMR spectra of Mesaconic acid, Caffeine, and the material that spontaneously crystallized and gave a XRPD pattern similar to that of the ground equimolar mixture; This phase is assumed to be the 1:1 cocrystal phase, as integration shows similar amounts of caffeine and mesaconic acid.




TL-B
bbo5_1H CDCl3 (D:\Bruker\TOPSPIN} CHPH 29
10.70
7.14
7.13
7.12
7.12
7.81
6.69
6.68
6.68
5.57
5.56
3.31
2
3
1
0.91
1.93
3.00
f1 (ppm)


TL-A
bbo5_1H CDCl3 (D:\Bruker\TOPSPIN} CHPH 28
10.96
10.72
7.32
7.31
6.90
6.89
6.72
6.71
4
3
2
1
0.91
3.15
3.00
3.08
f1 (ppm)

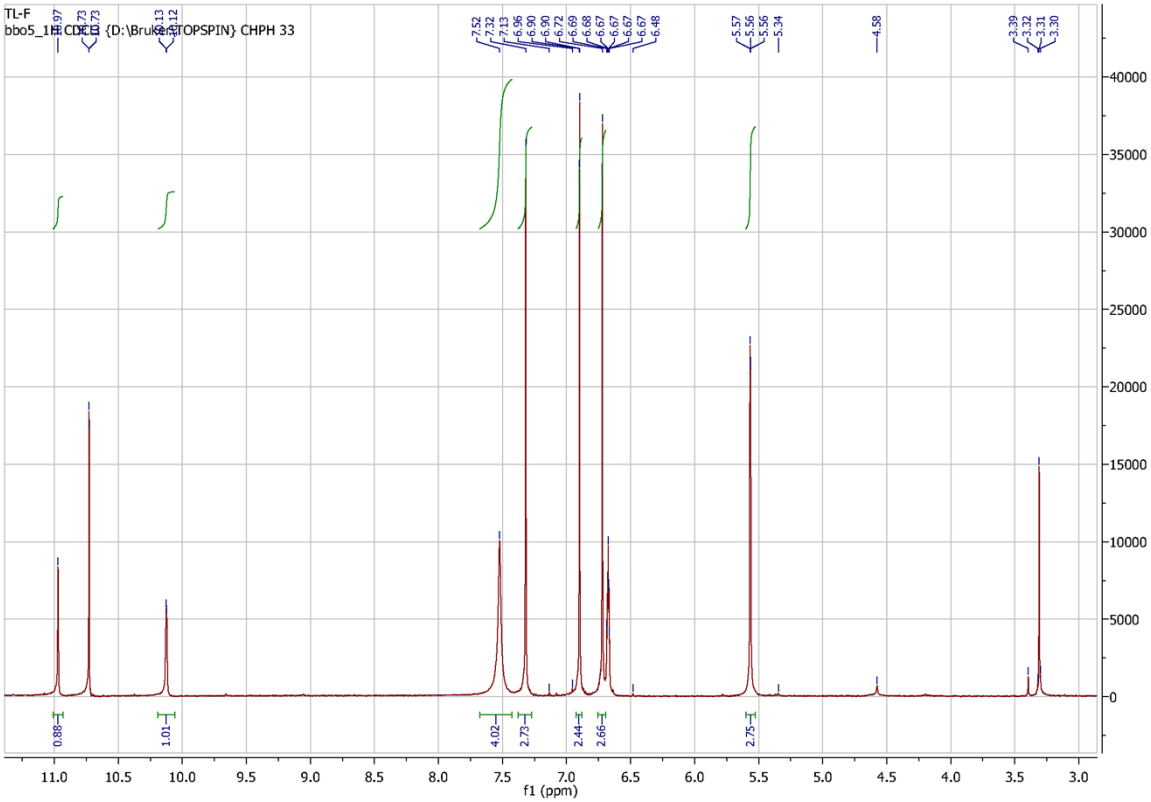
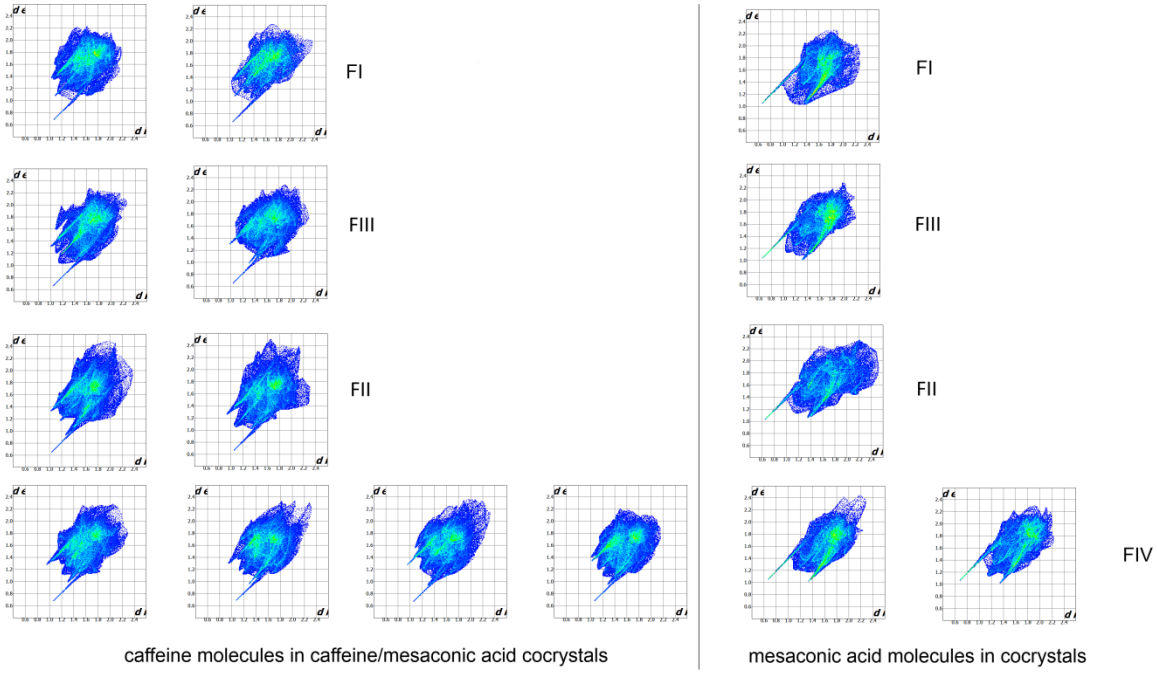


Figure S10: Two dimensional fingerprint plots for mesaconic acid and caffeine in caffeine/mesaconic cocrystals FI-FIV. All the fingerplots show similar patterns, except for mesaconic acid in form FII (see the main manuscript)



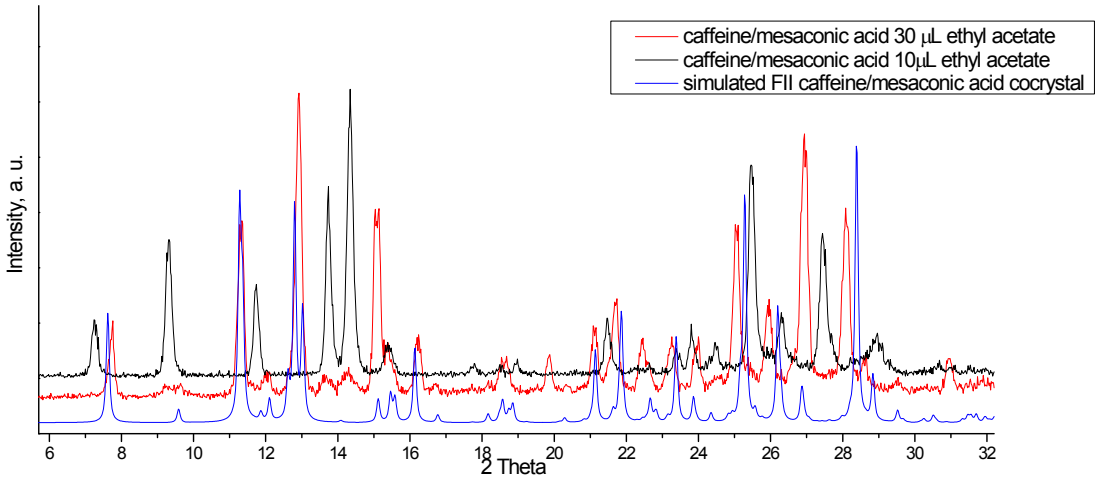


Fig. 11S: Diffraction patterns (CuKα) from the samples obtained by liquid-assisted grinding with ethyl acetate; the initial components were taken in 1 : 1 ratio; the black curve represents an assumed 1:1 cocrystal

Table S1 :Crystallographic and refinement details for all reported structures

Cocrystals	1:1 Caffeine:L-Malic acid	2:1 Caffeine:Dimethylsuccinic acid	2:1 Caffeine:Mesaconic acid_FI	2:1 Caffeine:Mesaconic acid_FII	2:1 Caffeine:Mesaconic acid_FIII	2:1 Caffeine:Mesaconic acid_solvate
Structural formula	$(C_8H_{10}N_4O_2)$ $(C_4H_6O_5)$	$(C_8H_{10}N_4O_2)_2$ $(C_6H_{10}O_4)$	$(C_8H_{10}N_4O_2)_2$ $(C_5H_6O_4)$	$(C_8H_{10}N_4O_2)_2$ $(C_5H_6O_4)$	$(C_8H_{10}N_4O_2)_2$ $(C_5H_6O_4)$	$(C_8H_{10}N_4O_2)_2$ $(C_5H_6O_4)$ (CH_3CN)
Formula weight (g/mol)	328.29	534.54	518.5	518.5	518.5	539.0
Crystal system	triclinic	monoclinic	orthorhombic	monoclinic	triclinic	monoclinic
Space group	*P*1	*P* 2_1/c	*P* bca	*P*2_1/n	*P*-1	*C*c
a(Å)	9.1390(1)	21.3368(9)	7.6414(6)	8.5926(3)	7.9317(6)	44.1572(13)
b(Å)	9.3060(1)	17.0520(5)	15.7487(9)	18.4382(7)	8.2797(2)	3.94520(10)
c (Å)	9.7714(1)	6.7877(3)	39.130(3)	14.9164(5)	20.4795(15)	27.6887(14)
α (°)	85.131	90	90	90	89.975(6)	90
β (°)	65.297	93.674(4)	90	92.437(3)	83.335(6)	96.230(3)
γ(°)	71.185	90	90	90	61.808(6)	90
V (Å^3)	713.43(14)	2464.52(17)	4709.0(6)	2361.10(15)	1175.10(13)	4759.13
Z	2	4	8	4	2	4
ρ_{calc} (g/cm^3)	1.528	1.441	1.463	1.459	1.465	1.494
T (K)	150	100	296	150	150	100
λ (Å)	Mo Kα	0.82103	Mo Kα	Mo Kα	Mo Kα	0.82103
R_1 (all) %	5.8 (6.09)	7.21 (9.06)	5.03 (8.57)	6.46 (8.12)	6.51 (7.04)	9.51 (10.03)
ωR2 (all) %	15.58 (15.95)	14.44 (15.04)	12.64 (14.69)	16.74 (17.98)	16.26 (16.62)	24.74 (25.44)
GooF	1.059	1.019	1.034	1.050	1.126	1.037
2θ (°)	50.706	59.288	50.614	50.517	50.712	59.026
refl. collected	5903	16281	26793	18835	17407	12341
Unique/ >2s(I)	4640/4347	16281/12903	4263/2821	4215/3338	4159/3756	12341/11132
Parameters/ restraints	505/57	407/110	341/0	343/0	341/0	712/2

Table S2 :Further experimental details for the L-malic acid/caffeine system. 1.5 ml HPLC vials were loaded with amount of material according to table below and 1 ml of EtOAc.

Acid mg	Caff mg	Outcome
49.0	12.5	Cocrystal
43.8	11.4	No crystallization
54.0	14.0	Caffeine
47.5	13.9	Cocrystal
54.0	11.4	No crystallization
52.8	15.3	Cocrystal
48.0	10.2	No crystallization
60.7	12.3	cocrystal
38.2	12.7	no crystallization

Table S3 :Further experimental details for the dimethylsuccinic acid/caffeine system. 1.5 ml HPLC vials were loaded with amount of material according to table below and 1 ml of EtOAc.

Acid mg	Caff mg	Outcome
92.3	12.4	Acid
82.6	14.2	Acid
98.6	10.9	Acid
108.1	12.4	cocrystal + acid
93.1	14.9	cocrystal + acid
108.4	14.2	cocrystal + acid
79.4	12.6	cocrystal + acid
83.6	11.5	cocrystal + acid
109.6	15.3	cocrystal + acid
52.0	13.1	cocrystal
53.0	15.5	cocrystal
52.0	11.3	cocrystal
64.2	13.4	cocrystal
34.2	13.5	cocrystal
29.4	13.3	cocrystal
20.5	15.3	caffeine

14.3	13.4	caffeine
19.9	13.8	caffeine

Table S4 :Further experimental details for the mesaconic acid/caffeine system. 1.5 ml HPLC vials were loaded with amount of material according to table below and 1 ml of EtOAc.

Acid mg	Caff mg	Outcome	Acid mg	Caff mg	Outcome
25.3	11.5	Assumed 1:1 cocrystal	23.9	12.4	2:1_FI cocrystal
40.4	13.3	Assumed 1:1 cocrystal	26.4	16.3	2:1_FI cocrystal
39.9	10.7	Assumed 1:1 cocrystal	12.3	13.2	2:1_FI cocrystal
32.8	13.5	Assumed 1:1 cocrystal	13.2	12.9	2:1_FI cocrystal
46.0	11.4	Assumed 1:1 cocrystal	23.7	12.7	2:1_FI cocrystal
42.2	16.2	Assumed 1:1 cocrystal	25.5	12.8	2:1_FI cocrystal
33.6	13.7	Assumed 1:1 cocrystal	23.5	12.4	2:1_FI cocrystal
34.5	11.5	Assumed 1:1 cocrystal	24.0	13.3	2:1_FII cocrystal
41.7	10.6	Assumed 1:1 cocrystal	38.0	30.3	2:1_FII cocrystal
38.0	11.3	Assumed 1:1 cocrystal	43.2	16.4	2:1_FII cocrystal
38.0	10.9	Assumed 1:1 cocrystal	39.5	27.4	2:1_FII cocrystal
40.7	11.6	Assumed 1:1 cocrystal	38.1	29.8	2:1_FII cocrystal
24.5	11.4	Assumed 1:1 cocrystal	37.9	30.2	2:1_FII cocrystal
25.0	12.5	Assumed 1:1 cocrystal	37.7	10.7	2:1_FII cocrystal
24.0	13.8	Unidentified phase	39.5	15.6	2:1_FIII cocrystal
24.3	15.3	Unidentified phase	33.4	13.3	2:1_FIII cocrystal
24.5	15.6	Unidentified phase			
26.9	11.6	Unidentified phase			

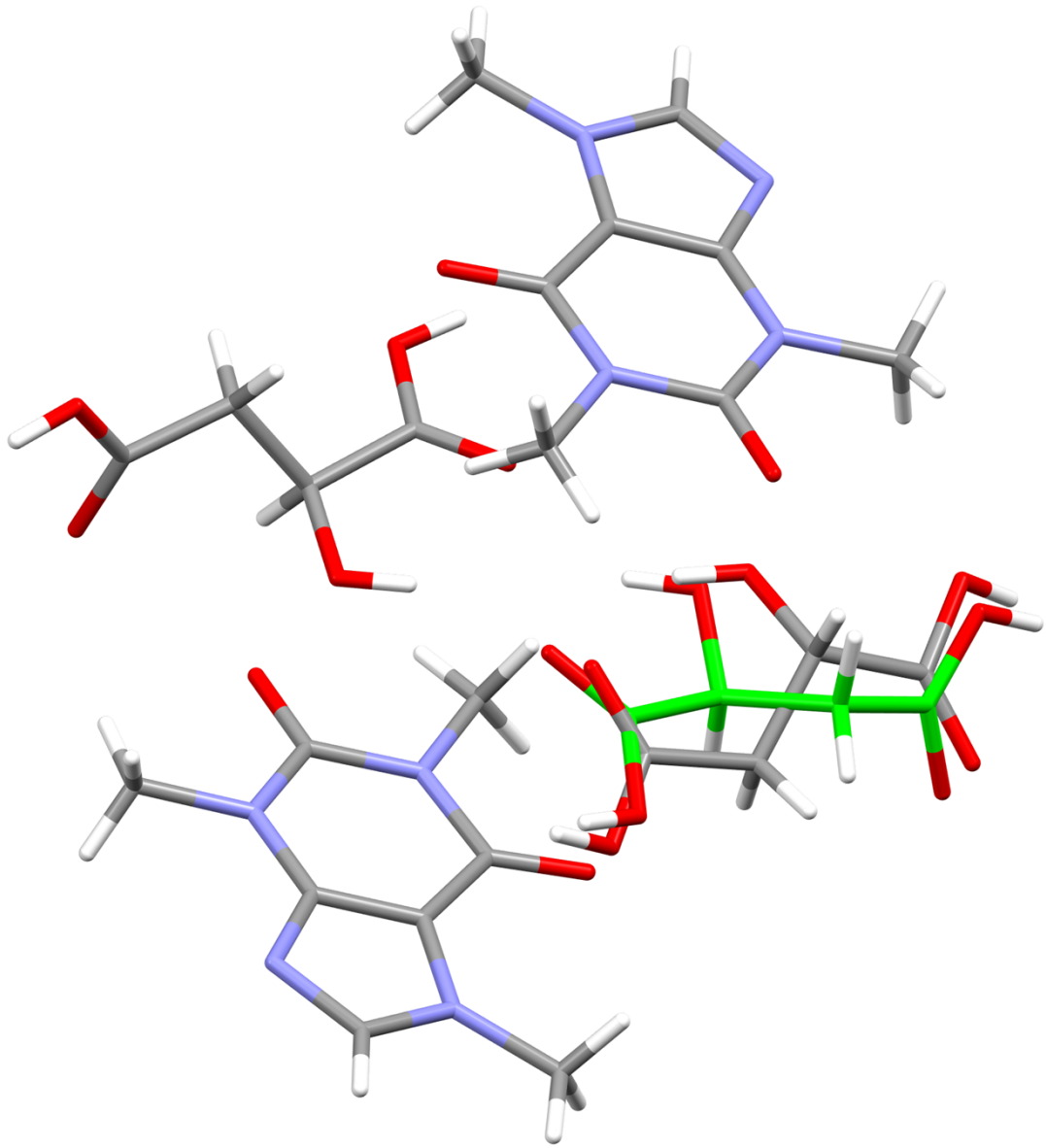
24.2	15.1	Unidentified phase
13.9	13.2	Unidentified phase

Further refinement details

Inhouse data were collected on a MAR345 image plate using Mo Kα radiation focused by a Xenocs Fox3D mirror (for the 2:1 Caffeine:Mesaconic acid_FI a Zr-filter was used to monochromate the beam) Synchrotron data were measured on the Swiss Norwegian beamline SNBL at the ESRF synchrotron facility (Grenoble) on a Pilatus2M detector using a wavelength of 0.82103Å.

Datasets measured at the synchrotron were low on completeness due to geometrical considerations (limited to phi scans and unable to move the detector closer towards the sample). For this reason datasets measured on different crystals were combined. As all synchrotron data was non-merohedrally twinned, data were integrated, passed through platon (twinrotmat) to obtain a hklf5 formatted reflection file. Individual hklf5 files were then recombined with different batch numbers and relative scale factors were refined during integration.

For 1:1 Caffeine:L-Malic acid, one maleic acid shows rotational disorder as can be seen in the figure below, one part has its carbon atoms shown in gray the other part has its carbon atoms coloured in green. The disorder can be seen as a rotation of about 180°, as can be seen the position of the carboxylic acid groups is conserved as well as the orientation of the individual C=O and C-O functions. This results in similar hydrogen bond patterns for either orientation (0° of 180° rotation).



For 2:1 Caffeine:Dimethylsuccinic acid, one caffeine moiety is completely disordered where the COOH hydrogen atom is on either of the two oxygen atoms depending on the orientation of the caffeine moiety. Consequently the difference in bond length between the C=O and C-OH, is averaged giving observed values of 1.250(5) and 1.266(4)Å.