Electronic Supplementary Information

The novel purine alkaloid cocrystals with trimesic and hemimellitic acid as coformers. Synthetic approach and supramolecular analysis.

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S1. Solution-based cocrystallization conditions.

Tab. S1. Solution-based cocrystallization conditions.

Alkaloid-acid	Solution-based cocrystallization conditions
TBR·TMSA	TBR (16.7 mg, 0.093 mmol), TMSA (19.4 mg, 0.092 mmol), MeOH-H$_2$O solution (10 ml, v/v 1:1)
TPH·TMSA	TPH (19.9 mg, 0.110 mmol), TMSA (23.2 mg, 0.111 mmol), MeOH-CHCl$_3$ solution (6 ml, v/v 1:1)
TPH·TMSA·2H$_2$O	TPH (21.8 mg, 0.121 mmol), TMSA (25.4 mg, 0.121 mmol), MeOH-H$_2$O solution (6 ml, v/v 1:1)
CAF·TMSA	CAF (24.4 mg, 0.126 mmol), TMSA (26.2 mg, 0.125 mmol), EtOH-H$_2$O solution (8 ml, v/v 1:1) *Good quality single crystals:* CAF (21.0 mg, 0.108 mmol), TMSA (43 mg, 0.205 mmol), 1:2 stoichiometric ratio, EtOH-H$_2$O solution (10 ml, v/v 1:1)
TBR·HMLA	TBR (11.9 mg, 0.066 mmol), HMLA (13.6 mg, 0.065 mmol), tBuOH-H$_2$O solution (8 ml, v/v 1:1)
TPH·HMLA	TPH (15.6 mg, 0.087 mmol), HMLA (18.1 mg, 0.086 mmol), MeCN-H$_2$O solution (8 ml, v/v 1:1)
(TPH)$^+$·(HMLA)$^-$·2H$_2$O[a)]	TPH (24.0 mg, 0.133 mmol), HMLA (28.1 mg, 0.134 mmol), MeOH-H$_2$O solution (6 ml, v/v 1:1) - the clear solution was transferred to four separate vials for slow evaporation. In one of them, crystals of (TPH)$^+$·(HMLA)$^-$·2H$_2$O were formed. These crystals were used for crystallization by nucleation. TPH (36.6 mg, 0.203 mmol), HMLA (42.5 mg, 0.202 mmol), MeOH-H$_2$O solution (6 ml, v/v 1:1) – the clear solution was transferred to two separate vials for slow evaporation and a few crystals, obtained as above, were added as seeds.
CAF·HMLA·H$_2$O	CAF (10.9 mg, 0.056 mmol), HMLA (12.7 mg, 0.060 mmol), MeOH-H$_2$O solution (6 ml, v/v 1:1) *Good quality single crystals:* CAF (95.2 mg, 0.490 mmol), HMLA (10.3 mg, 0.049 mmol), 10:1 stoichiometric ratio, MeOH-H$_2$O solution (6 ml, v/v 1:1)

a) It was complicated to selectively obtain this compound. The use of the different solvent systems, i.e. tBuOH-H$_2$O, iPrOH-H$_2$O, MeOH-H$_2$O most often resulted in obtaining the mixture of anhydrous TPH·HMLA and (TPH)$^+$·(HMLA)$^-$·2H$_2$O with a predominance of the anhydrous form, which was confirmed by PXRD and a few single crystals of dihydrate were visible under the microscope. Several times, it was possible to obtain selectively a dihydrate from the MeOH-H$_2$O mixture, but it was not possible to determine the exact conditions favouring the formation of this compound.

S2. Grinding cocrystallization conditions.

Tab. S2. Grinding cocrystallization conditions.

Alkaloid-acid	Grinding cocrystallization conditions
TBR·TMSA	TBR (21.1 mg, 0.117 mmol), TMSA (24.6 mg, 0.117 mmol), neat grinding
TPH·TMSA	TPH (15.4 mg, 0.085 mmol), TMSA (18.0 mg, 0.086 mmol), liquid-assisted grinding (20 µl MeOH)
TPH·TMSA·2H$_2$O	TPH (14.7 mg, 0.082 mmol), TMSA (17.2 mg, 0.082 mmol), liquid-assisted grinding (20 µl H$_2$O)
CAF·TMSA	CAF (16.1 mg, 0.083 mmol), TMSA (17.4 mg, 0.083 mmol), neat grinding
TBR·HMLA	TBR (8.7 mg, 0.048 mmol), HMLA (10.0 mg, 0.048 mmol), neat grinding
TPH·HMLA	TPH (10.9 mg, 0.061 mmol), HMLA (12.8 mg, 0.061 mmol), neat grinding
(TPH)$^+$·(HMLA)$^-$·2H$_2$O	no obtained by grinding
CAF·HMLA·H$_2$O	CAF (10.7 mg, 0.055 mmol), HMLA (11.5 mg, 0.055 mmol), neat grinding

S3. Additional details of crystal structure solution and refinement.

Tab. S3. Details of crystal structures solution and refinement.

TBR·TMSA	All of the H atoms were refined isotropically.
TPH·TMSA	The disordered H atoms in two methyl groups of TPH were positioned geometrically using HFIX 127 command and refined using the riding-model with $U_{iso}(H) = 1.2U_{eq}(C)$. The remaining H atoms were freely refined.
TPH·TMSA·2H$_2$O	All of the H atoms were derived from a difference Fourier map, but the disordered methyl group (C16) in TPH was refined as a rotating group using a riding-model with $U_{iso}(H) = 1.2U_{eq}(C)$, in which H atoms were positioned geometrically using HFIX 127 command. One of two hydrogen atoms in both water molecules is disordered over two positions with occupancies fixed at 0.5 and U_{iso} parameters fixed at 0.5. The geometry of these molecules was modelled used DFIX restraints. The hydrogen atom in one of the carboxyl groups in the TMSA molecule is disordered over two sites with occupancies 0.55:0.45 and with U_{iso} parameters fixed at 0.5. The O-H bond lengths in the above carboxyl group were restrained using the DFIX command. The rest of the H atoms were freely refined.
CAF·TMSA	The CAF and a half of the TMSA molecule are disordered over two positions with occupancies 0.89 and 0.11. Hydrogen atom in the carboxyl group of TMSA with greater occupancy involved in COOH···N$_{imidazole}$ hydrogen bond formation was visible on the difference Fourier map, but in the final refinement, all of the hydrogen atoms were placed in geometrically idealized positions and refined using the riding-model.
TBR·HMLA	The hydrogen atoms in both methyl groups of TBR were positioned geometrically using the AFIX 127 command. They were refined as rotating groups using the riding model with $U_{iso}(H) = 1.2U_{eq}(C)$. H atom near carbon atom in imidazole ring and H atom near nitrogen atom in pyrimidine ring were freely refined. Hydrogen atoms belonging to the aromatic ring of HMLA (C-H bonds) and hydrogen atoms in carboxylic groups within C7 and C8 atoms were derived from the difference Fourier map and they were freely refined. The carboxyl group within C9 atom is disordered over two positions with anisotropic thermal parameters for oxygen atoms (O5 and O5A, O6 and O6A) with occupancies fixed at 0.5 and disordered hydrogen atom over two positions with fixed occupancies 0.5 positioned in their calculated positions. Additionally, some geometrically restrains (DFIX and FLAT instructions) in the HMLA molecule were used in the refinement.
TPH·HMLA	One of the carbonyl oxygen atom in HMLA is disordered over two positions with occupancies 0.58(6) (O1) and 0.42(6) (O1A). All hydrogen atoms were freely refined. The final electron density difference map contains a relatively large residual peak (0.47 eÅ^{-3}). When this peak was treated as a water molecule, it would create several short contacts. Ultimately, the water molecule was not considered in the final model due to the very low occupancy, which would be refined to less than 0.05.
(TPH)$^+$·(HMLA)$^-$·2H$_2$O	The crystal used for the measurement was identified as a non-merohedral twin. The twin law 1 0 0 0 -1 0 -0.816 0 -1, corresponding to 180° rotation about [100] direct lattice direction, was determined with the program ROTAX. The reflection data were prepared in HKLF 5 format using the "Make HKLF5" function in the WinGX program and they were used in structure refinement. The reflections belonging to the larger domain that were not overlapping with the reflections originating from the smaller component were included in the refinement process. The BASF parameter was refined at 0.251(3). The oxygen atom in one water molecule is disordered on two positions with occupancies constrained at 0.8 and 0.2 for O9 and O9A atoms, respectively. The disordered hydrogen atoms near methyl groups in TPH were placed at a calculated positions using HFIX 127 and refined as riding on their parent atoms. The remaining H atoms were found on the electron density Fourier map and freely refined.
CAF·HMLA·H$_2$O	ROTAX was used to the twin matrix -1 0 0 0 -1 0 0.113 0 1 identification. It corresponds to a 2-fold rotation axis around [001] reciprocal lattice direction. Therefore, the crystal was recognized as a non-merohedral twin. The diffraction intensity data used to the structure refinement were converted into HKLF 5 format with "Make HKLF 5" function in WinGX. The reflections originating from the smaller domain that are not overlapping with the reflections from the larger component were excluded in the refinement process. The BASF parameter (smaller domain participation) was refined at 0.126(2). The difference Fourier map indicated the location of all hydrogen atoms, but in the final refinement the C16-methyl group in CAF was treated as a rotating group and these atoms were placed at calculated positions (C-H = 0.96 Å) using HFIX 127 command.

S4. UV-vis measurements - detection wavelengths (λ_{det})

Tab. S4. Detection wavelengths (λ_{det}) of theobromine, theophylline, and caffeine cocrystals.

		Detection wavelength - λ_{det}, nm
Theobromine cocrystals	*TBR·HMLA*	290
	TBR·TMSA	273
Theophylline cocrystals	*TPH·TMSA*	295
	TPH·TMSA·2H$_2$O	290
	TPH·HMLA	295
	(TPH)$^+$·(HMLA)$^-$·2H$_2$O	290
Caffeine cocrystals	*CAF·TMSA*	273
	CAF·HMLA·H$_2$O	290

S5. Crystallographic data for alkaloid cocrystals with trimesic acid (TMSA) as coformer.

Tab. S5 Crystallographic data and refinement details for compounds with trimesic acid.

	TBR·TMSA	TPH·TMSA	TPH·TMSA·2H$_2$O	CAF·TMSA
molecular formula	C$_7$H$_8$N$_4$O$_2$·C$_9$H$_6$O$_6$	C$_7$H$_8$N$_4$O$_2$·C$_9$H$_6$O$_6$	C$_7$H$_8$N$_4$O$_2$·C$_9$H$_6$O$_6$·2H$_2$O	C$_8$H$_{10}$N$_4$O$_2$·C$_9$H$_6$O$_6$
M_r	390.31	390.31	426.34	404.34
crystal system	monoclinic	monoclinic	triclinic	orthorhombic
space group	$P2_1/c$	$P2_1/c$	$P\overline{1}$	Pbca
a, Å	7.0932(1)	8.6220(2)	7.8522(2)	6.6261(2)
b, Å	28.5018(5)	13.4344(2)	8.9113(2)	16.9741(3)
c, Å	16.0248(3)	14.4816(3)	14.3420(3)	30.5619(7)
α, º	90	90	78.340(2)	90
β, º	93.447(2)	101.052(2)	82.760(2)	90
γ, º	90	90	66.474(2)	90
V, Å^3	3233.86(9)	1646.31(6)	900.00(4)	3437.36(14)
Z	8	4	2	8
D_c, gcm^{-1}	1.603	1.575	1.573	1.563
$F(000)$	1616	808	444	1680
μ(Cu K$_\alpha$), cm^{-1}	1.13	1.11	1.15	1.09
T, K	132(2)	129.9(2)	130.1(2)	130.0(1)
crystal size, mm	0.19 × 0.13 × 0.09	0.07 × 0.20 × 0.57	0.06 × 0.10 × 0.25	0.02 × 0.05 × 0.28
2Θ range, °	3.1 – 76.2	4.5 – 76.2	3.2 – 76.5	2.9 – 70.2
range of indices (h, k, l)	-8→7, -33→35, -18→20	-10→10, -11→16, -16→18	-9→9, -11→11, -18→17	-8→8, -20→11, -37→36
collected reflections	14433	8349	28755	8669
unique reflections	6573	3407	3748	3253
reflections with $I > 2\sigma(I)$	5641	2964	3566	3046
R_{int}	0.026	0.028	0.030	0.017
no. of parameters	617	290	341	448
$R(F)$, $wR(F^2)$, $F^2 > 2\sigma(F^2)$	0.0570, 0.1573	0.0417, 0.1117	0.0375, 0.1073	0.0523, 0.1412
$R(F)$, $wR(F^2)$, all data	0.0645, 0.1627	0.0477, 0.1185	0.0391, 0.1091	0.0548, 0.1427
GOF	1.128	1.016	1.076	1.220
Extinction coefficient	none	0.0019(3)	0.0043(10)	none
Δ_{min}, Δ_{max}, eÅ^{-3}	-0.25, 0.41	-0.29, 0.35	-0.35, 0.47	-0.26, 0.24
CCDC deposit no.	2019779	2019776	2019782	2019780

S6. Crystallographic data for alkaloid cocrystals with hemimellitic acid (HMLA) as coformer.

Tab. S6 Crystallographic data and refinement details for compounds with hemimellitic acid.

	TBR·HMLA	TPH·HMLA	(TPH)$^+$·(HMLA)$^-$·2H$_2$O	CAF·HMLA·H$_2$O
molecular formula	C$_7$H$_8$N$_4$O$_2$·C$_9$H$_6$O$_6$	C$_7$H$_8$N$_4$O$_2$·C$_9$H$_6$O$_6$	C$_7$H$_9$N$_4$O$_2$·C$_9$H$_5$O$_6$·2H$_2$O	C$_8$H$_{10}$N$_4$O$_2$·C$_9$H$_6$O$_6$·H$_2$O
M_r	390.31	390.31	426.34	422.35
crystal system	monoclinic	triclinic	monoclinic	monoclinic
space group	$C2/c$	$P\overline{1}$	$I2/a$	$P2_1/c$
a, Å	15.4925(10)	7.5176(5)	6.5563(1)	6.7565(2)
b, Å	28.544(2)	7.9224(5)	20.3491(4)	9.5374(3)
c, Å	7.5608(8)	13.7593(6)	26.8545(5)	28.0941(7)
α, º	90	85.132(4)	90	90
β, º	95.999(8)	85.720(4)	95.728(2)	90.787(3)
γ, º	90	88.029(5)	90	90
V, Å^3	3325.2(5)	813.91(8)	3564.90(11)	1810.20(9)
Z	8	2	8	4
D_c, gcm^{-1}	1.559	1.593	1.589	1.550
$F(000)$	1616	404	1776	880
μ(Cu K$_\alpha$), cm^{-1}	1.10	1.12	1.16	1.10
T, K	294(7)	130.1(1)	100.0(1)	133(1)
crystal size, mm	0.03 × 0.03 × 0.12	0.10 × 0.16 × 0.23	0.03 × 0.05 × 0.28	0.11 × 0.12 × 0.19
2Θ range, °	3.1 – 73.3	3.2 – 76.1	2.7 – 75.4	3.2 – 76.5
range of indices (h, k, l)	-18→12, -34→29, -9→9	-9→9, -9→9, -13→17	-8→8,-25→24, -33→33	-8→8, -11→11, 0→35
collected reflections	6478	5860	11503	3743
unique reflections	3220	3285	11503	3743
reflections with $I > 2\sigma(I)$	2255	2858	10411	3619
R_{int}	0.028	0.024	*0.021*	*merged*
no. of parameters	305	319	333	334
$R(F)$, $wR(F^2)$, $F^2 > 2\sigma(F^2)$	0.0495, 0.1197	0.0413, 0.1130	0.0343, 0.0915	0.0586, 0.1620
$R(F)$, $wR(F^2)$, all data	0.0765, 0.1354	0.0474, 0.1196	0.0384, 0.0937	0.0600, 0.1631
GOF	1.070	1.058	1.047	1.137
Δ_{min}, Δ_{max}, eÅ^{-3}	-0.22, 0.16	-0.20, 0.47	-0.24, 0.24	-0.24, 0.36
CCDC deposit no.	2019778	2019777	2019781	2019783

S7. Stacking interactions geometry in the described cocrystals with trimesic (TMSA) and hemimellitic acid (HMLA).

Tab. S7 Geometrical parameters for π···π interactions.

Cocrystal	ArM	ArN	ArM···ArN [Å][a)	Dihedral angle [°][b)	Interplanar distance [Å][c)	Offset [Å][d)
TBR·TMSA	Ar1B	Ar3B[iv]	3.579(1)	5.539(1)	3.233(1)	1.535(1)
	Ar3B	Ar1A[v]	3.679(1)	0.180(1)	3.265(1)	1.695(1)
Symmetry codes: (iv) *x*, ½-*y*, -½+*z*; (v) -1+*x*, ½-*y*, ½+*z*						
TPH·TMSA	Ar1	Ar3[iv]	3.554(1)	6.872(1)	3.312(1)	1.290(1)
	Ar1	Ar3[v]	3.791(1)	5.662(1)	3.281(1)	1.899(1)
	Ar2	Ar3[v]	3.475(1)	4.535(1)	3.470(1)	0.197(1)
Symmetry codes: (iv) 1-*x*, 1-*y*, 1-*z*; (v) 1-*x*, -½ +*y*, ½-*z*						
TPH·TMSA·2H₂O	Ar1	Ar3[iv]	3.543(1)	3.078(1)	3.258(1)	1.394(1)
	Ar2	Ar3[v]	3.516(1)	2.228(1)	3.235(1)	1.377(1)
Symmetry codes: (iv) 2-*x*, 1-*y*, 1-*z*; (v) 1-*x*, 1-*y*, 1-*z*						
CAF·TMSA	Ar2	Ar2[iv (e)]	3.824(1)	0	3.156(1)	2.160(1)
	Ar2	Ar2[iv (f)]	3.802(1)	0	3.200(1)	2.053(1)
Symmetry code: (iv) 1-*x*, 1-*y*, 1-*z*						
TBR·HMLA	Ar1	Ar1[i]	3.383(1)	0.058(1)	3.346(1)	0.497(1)
	Ar1	Ar2[i]	3.718(1)	0.533(1)	3.346(1)	1.621(1)
	Ar2	Ar2[iv]	3.574(1)	0	3.343(1)	1.263(1)
	Ar3	Ar3[v]	3.795(1)	4.128(1)	3.631(1)	1.104(1)
	Ar3	Ar3[vi]	3.795(1)	4.128(1)	3.607(1)	1.180(1)
Symmetry codes: (i) -*x*, *y*, -*z*+½; (iv) ½-*x*, ½-*y*, ½-*z*; (v) *x*, 1-*y*, ½+*z*; (vi) *x*, 1-*y*, *z*-½						
TPH·HMLA	Ar1	Ar3[iv]	3.862(1)	6.103(1)	3.652(1)	1.254(1)
	Ar1	Ar3[v]	4.016(1)	6.103(1)	3.555(1)	1.869(1)
	Ar2	Ar3[v]	3.763(1)	6.793(1)	3.339(1)	1.737(1)
Symmetry codes: (iv) 1-*x*, 1-*y*, 1-*z*; (v) -*x*, 1-*y*, 1-*z*.						
(TPH)⁺·(HMLA)⁻·2H₂O	Ar2	Ar2[iv]	3.692(1)	3.795(1)	3.220(1)	1.807(1)
	Ar2	Ar2[ii]	3.692(1)	3.795(1)	3.332(1)	1.590(1)
Symmetry codes: (ii) *x*+½, -*y*+1, *z*; (iv) *x*-½, -*y*+1, *z*.						
CAF·HMLA·H₂O	*No aromatic interactions*					

Ar1 – pyrimidine ring in purine alkaloid molecule; Ar2 – imidazole ring in purine alkaloid molecule; Ar3 – benzene ring in particular acid molecule; a) The distance between the ring centroids; b) The angle between aromatic ring planes; c) The distance between ArN plane to ArM centroid; d) The distance between ArM and ArN projected onto the ring plane M; (e) and (f) – Ar2 imidazole rings in caffeine molecules with greater (0.89) and smaller occupancy (0.11), respectively.

S8. Hydrogen bond parameters in the described cocrystals.

Tab. S8 Geometrical parameters for hydrogen bonds.

Cocrystal	D—H···A	D—H [Å]	H···A [Å]	D···A [Å]	D—H···A [°]
TBR·TMSA	O2A—H2A···N4A[i]	1.03(3)	1.64(3)	2.655(2)	171(3)
	O4A—H4A···O7A	0.92(4)	1.74(4)	2.649(2)	170(4)
	O6A—H6A···O3B	0.89(4)	1.79(4)	2.639(2)	160(3)
	O2B—H2B···N4B	0.91(3)	1.73(3)	2.641(2)	173(3)
	O4B—H4B···O7B[ii]	0.92(4)	1.78(4)	2.689(2)	172(3)
	O6B—H6B···O3A[iii]	0.90(4)	1.76(4)	2.641(2)	167(3)
	N1A—H1A···O8B	0.97(3)	1.83(3)	2.792(2)	171(3)
	N1B—H1B···O8A	0.95(3)	1.82(3)	2.774(2)	175(3)
Symmetry codes: (i) -x+2, y+½, -z+½; (ii) -x+1, y+½, −z+3/2; (iii) x-1, y, z+1.					
TPH·TMSA	O2—H2···N4	0.90(3)	1.72(3)	2.6164(16)	176(2)
	O4—H4···O1[i]	0.90(3)	1.83(3)	2.6777(16)	156(2)
	O6—H6···O7[ii]	0.88(3)	1.75(3)	2.6249(15)	172(2)
	N3—H3···O5[iii]	0.89(2)	1.85(2)	2.7415(17)	175(2)
Symmetry codes: (i) -x+2, y+½, -z+½; (ii) x, y+1, z; (iii) x, y-1, z.					
TPH·TMSA·2H₂O	O2—H2···O9	0.85(2)	1.78(2)	2.6203(14)	170(2)
	O4—H4···O3[i]	0.82(2)	1.81(2)	2.6291(13)	176(3)
	O6—H6···O7[ii]	0.96(3)	1.64(3)	2.5733(13)	164(2)
	N3—H3···O5[ii]	0.90(2)	1.90(2)	2.7901(15)	171.4(19)
	O9—H9A···N4	0.88(1)	1.94(1)	2.7930(15)	162(2)
	O9—H9B···O9[iii]	0.87(1)	1.96(1)	2.830(2)	176(5)
	O9—H9C···O10[iv]	0.87(1)	2.21(2)	2.8861(18)	135(2)
	O10—H10A···O9[iv]	0.88(1)	2.05(2)	2.8861(18)	160(3)
	O10—H10B···O1	0.89(1)	2.01(1)	2.8830(17)	168(2)
	O10—H10C···O10[ii]	0.90(1)	1.87(1)	2.757(3)	167(3)
	O3—H3A···O4[i]	0.81(2)	1.82(2)	2.6291(13)	171(9)
Symmetry codes: (i) −x-1, -y+1, -z+2; (ii) -x+1, -y, -z+1; (iii) -x, -y+2, -z+1; (iv) -x+1, -y+1, -z+1. The H9B, H9C, H10A, H10C atoms occupancy: 0.5. The H3A and H4 atoms occupancies are equal to 0.45 and 0.55, respectively.					
CAF·TMSA	O6—H6···O3[i]	0.82	1.88	2.696(2)	171
	O2A—H2A···N4A	0.82	1.84	2.66(3)	177
	O4—H4···O5[ii]	0.82	1.80	2.613(2)	169
	O2—H2···N4	0.82	1.82	2.633(3)	169
Symmetry codes: (i) -x+2, y+½, -z+3/2; (ii) -x+2, y-½, -z+3/2. The O2, N4 atoms occupancy: 0.89. The O2A, N4A atoms occupancy: 0.11.					
TBR·HMLA	O6—H6B···O6[i]	0.82	1.72	2.53(3)	170
	O6A—H6A···O6A[i]	0.91	1.86	2.76(3)	170
	N1—H1···O1[ii]	0.89(3)	2.05(3)	2.929(3)	171(3)
	O2—H2···O7[iii]	0.89(4)	1.74(4)	2.606(3)	163(4)
	O4—H4···N4	0.93(1)	1.81(1)	2.730(3)	168(4)
Symmetry codes: (i) -x, y, -z+½; (ii) x-½, -y+½, z+½; (iii) x+½, -y+½, z-½. The O6, O6A, H6A, H6B atoms occupancy: 0.50.					
TPH·HMLA	O4—H4···O8[i]	0.86(3)	1.86(3)	2.6851(17)	160(2)
	N3—H3···O5[ii]	0.91(3)	1.91(3)	2.8141(18)	171(2)
	O6—H6···O7[iii]	0.90(3)	1.73(3)	2.6225(16)	169(3)
	O2—H2···N4	0.91(3)	1.72(3)	2.6330(17)	177(3)
Symmetry codes: (i) -x+1, -y+2, -z+1; (ii) x, y, z-1; (iii) x, y, z+1.					
(TPH)⁺·(HMLA)⁻·2H₂O	O2—H2···O7[i]	0.83(2)	1.91(3)	2.7211(15)	164(2)
	O6—H6···O10	0.89(3)	1.70(3)	2.5864(15)	177(2)
	O10—H10A···O4[ii]	0.90(3)	1.85(3)	2.7416(17)	174(2)
	O10—H10B···O3[iii]	0.88(3)	1.92(3)	2.7895(16)	175(2)
	O9—H9A···O3[iii]	0.96(3)	1.76(3)	2.692(5)	163(2)
	O9A—H9A···O3[iii]	0.97(3)	1.76(3)	2.67(2)	156(3)
	N3—H3···O9	0.95(3)	1.68(3)	2.619(5)	168(2)
	N3—H3···O9A	0.95(3)	1.66(3)	2.60(2)	166(3)
	N4—H4···O4	1.07(3)	1.48(3)	2.5482(15)	173(2)
	O9—H9B···O1[iv]	0.89(3)	1.84(3)	2.703(5)	161(2)
	O9A—H9B···O1[iv]	0.95(3)	1.84(3)	2.67(2)	145(3)
Symmetry codes: (i) -x+1, y-½, -z+½; (ii) x-½, -y+1, z; (iii) x+½, -y+1, z; (iv) -x+1, y+½, -z+½. The O9 and O9A atoms with occupancies constrained at 0.8 and 0.2, respectively.					
CAF·HMLA·H₂O	O9—H9A···O1[i]	0.93(5)	1.83(5)	2.742(3)	167(5)
	O9—H9B···O3[ii]	0.87(5)	1.84(5)	2.679(3)	160(4)
	O2—H2···O5[iii]	1.00(4)	1.64(4)	2.610(3)	162(4)
	O4—H4···N4	0.95(4)	1.71(4)	2.661(3)	176(3)
	O6—H6···O9	1.01(5)	1.53(5)	2.516(3)	165(4)
Symmetry codes: (i) x, y+1, z; (ii) -x+1, y+½, -z+½; (iii) x, y-1, z.					

S9. Hirshfeld surface analysis.

The tables below (Tab. S9.1-8) represent the percentage contact contribution of each cocrystal component (excluding water molecule) on the Hirshfeld surface area. The figures (Fig. S1-S18) represent a two-dimensional fingerprint for cocrystal components.

Tab. S9.1 Data for TBR·TMSA.

Contact	TBR-A	TBR-B	TMSA-A	TMSA-B
C···C	4.6	4.8	3.1	6.0
C···H	7.1	10.2	14.0	7.8
C···N	3.0	4.1	3.5	3.4
C···O	6.5	5.4	8.2	9.6
H···H	30.3	28.5	19.7	18.8
O···H	36.7	37.4	43.5	42.6
O···O	2.5	1.7	3.2	4.3
O···N	2.4	2.7	1.2	2.9
N···H	6.8	5.2	3.7	4.6
N···N	-	-	-	-
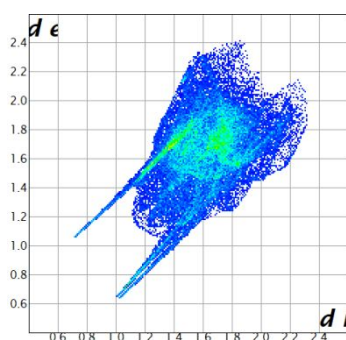
Fig. S1. 2D fingerprint of TBR-A molecule in TBR·TMSA.
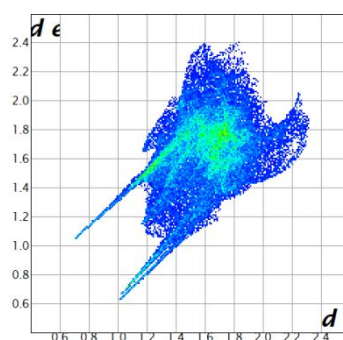
Fig. S2. 2D fingerprint of TBR-B molecule in TBR·TMSA.
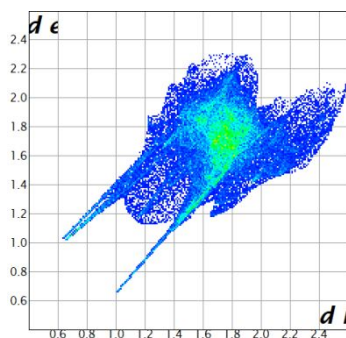
Fig. S3. 2D fingerprint of TMSA-A molecule in TBR·TMSA.
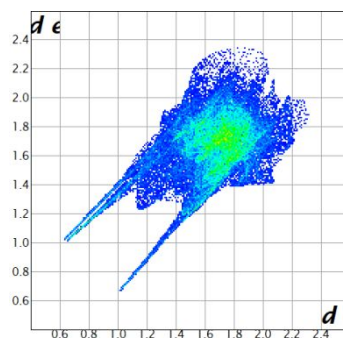
Fig. S4. 2D fingerprint of TMSA-B molecule in TBR·TMSA.

Tab. S9.2 Data for TPH·TMSA.

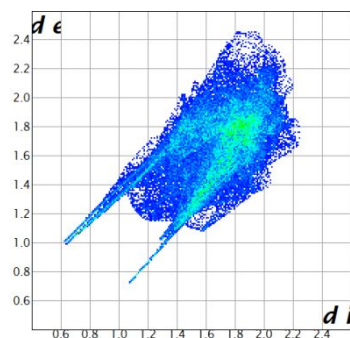| Contact	TPH	TMSA
C···C	7.2	6.7
C···H	8.7	8.6
C···N	4.2	4.2
C···O	2.7	5.1
H···H	33.6	21.2
O···H	34.6	44.2
O···O	1.7	5.0
O···N	1.5	1.3
N···H	5.9	3.6
N···N	-	-
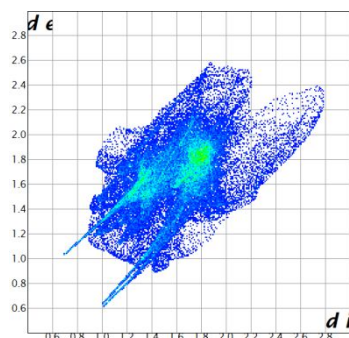
Fig. S5. 2D fingerprint of TPH molecule in TPH·TMSA.
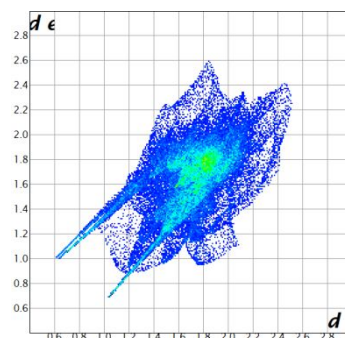
Fig. S6. 2D fingerprint of TMSA molecule in TPH·TMSA.

Tab. S9.3 Data for TPH·TMSA·2H$_2$O.

Contact	TPH	TMSA
C···C	6.8	6.3
C···H	7.9	9.2
C···N	3.5	3.5
C···O	4.7	5.8
H···H	34.8	33.4
O···H	32.3	34.6
O···O	2.2	4.2
O···N	1.5	1.2
N···H	6.2	1.7
N···N	-	-
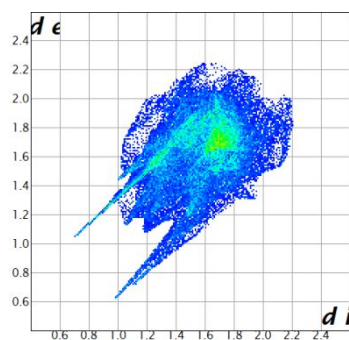
Fig. S7. 2D fingerprint of TPH molecule in TPH·TMSA·2H$_2$O.
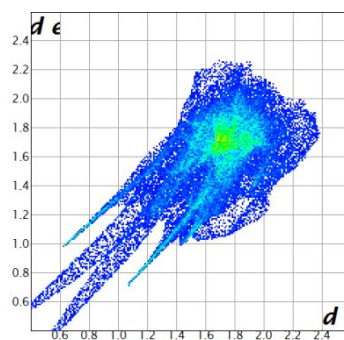
Fig. S8. 2D fingerprint of TMSA molecule in TPH·TMSA·2H$_2$O. Short H···H contacts come from a disordered carboxyl group of acid involved in the cyclic acid-acid dimer formation.

Tab. S9.4 Data for CAF·TMSA.

Contact*	CAF	TMSA
C···C	3.9	3.7
C···H	6.4	12.0
C···N	1.5	0.5
C···O	6.7	15.8
H···H	41.8	21.6
O···H	28.4	36.1
O···O	1.0	3.6
O···N	2.2	2.2
N···H	7.4	4.4
N···N	0.7	-
* contact data was generated for a refined structure with no designed disorder		
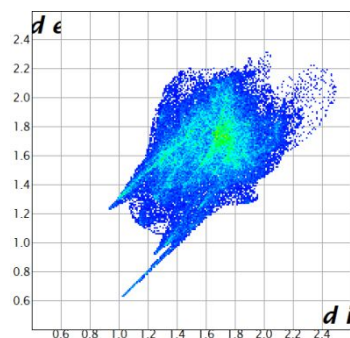
Fig. S9. 2D fingerprint of CAF molecule in CAF·TMSA.
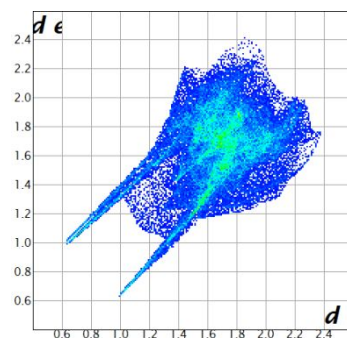
Fig. S10. 2D fingerprint of TMSA molecule in CAF·TMSA.

Tab. S9.5 Data for TBR·HMLA.

Contact	TBR	HMLA
C···C	3.6	9.8
C···H	5.0	6.0
C···N	5.0	-
C···O	4.0	4.6
H···H	37.1	28.5
O···H	30.8	41.5
O···O	2.5	7.5
O···N	2.5	-
N···H	8.3	2.1
N···N	1.1	-
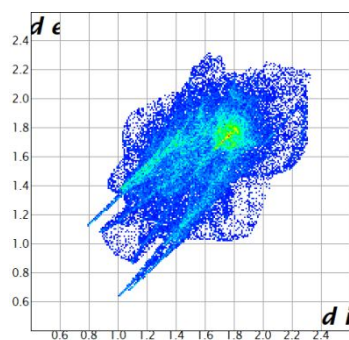
Fig. S11. 2D fingerprint of TBR molecule in TBR·HMLA.
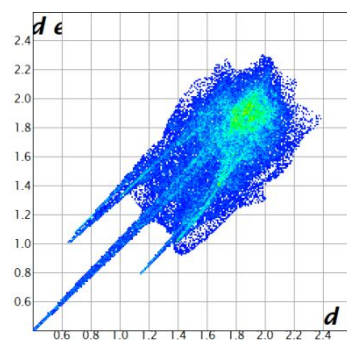
Fig. S12. 2D fingerprint of HMLA molecule in TBR·HMLA.
Short H···H contacts come from a disordered carboxyl group
of acid involved in the hydroxyl dimer formation.

Tab. S9.6 Data for TPH·HMLA.

Contact	TPH	HMLA
C···C	5.8	6.0
C···H	6.2	5.6
C···N	3.5	3.6
C···O	7.6	4.9
H···H	25.0	31.1
O···H	43.4	40.3
O···O	1.9	0.2
O···N	2.4	2.5
N···H	4.4	5.8
N···N	-	-

Fig. S13. 2D fingerprint of TPH molecule in TPH·HMLA.
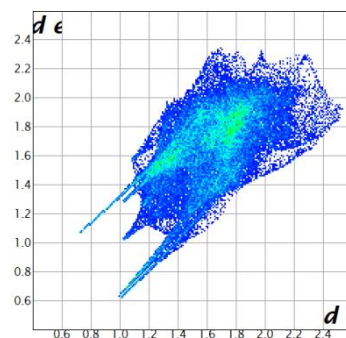
Fig. S14. 2D fingerprint of HMLA molecule in TPH·HMLA.

Tab. S9.7 Data for $(TPH)^+\cdot(HMLA)^-\cdot2H_2O$.

Contact	TPH	HMLA
C···C	3.2	3.9
C···H	6.5	17.6
C···N	2.1	-
C···O	7.4	5.0
H···H	35.8	16.2
O···H	36.6	54.3
O···O	1.1	2.9
O···N	3.1	0.1
N···H	3.2	0.1
N···N	1.1	-
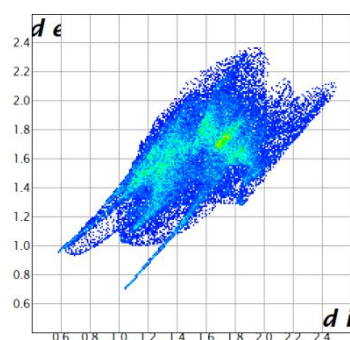
Fig. S15. 2D fingerprint of theophyllinium cation in $(TPH)^+\cdot(HMLA)^-\cdot2H_2O$.
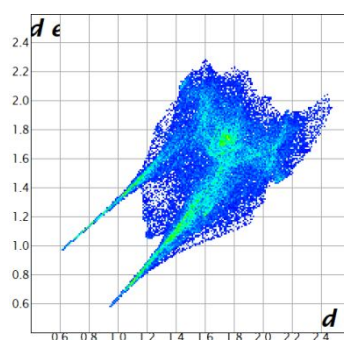
Fig. S16. 2D fingerprint of 2,6-dicarboxybenzoate anion in $(TPH)^+\cdot(HMLA)^-\cdot2H_2O$.

Tab. S9.8 Data for CAF·HMLA·H_2O.

Contact	CAF	HMLA
C···C	1.1	1.2
C···H	11.4	16.2
C···N	1.1	1.2
C···O	8.5	8.6
H···H	37.7	23.8
O···H	30.9	43.4
O···O	0.3	0.4
O···N	1.2	1.0
N···H	7.8	4.2
N···N	-	-
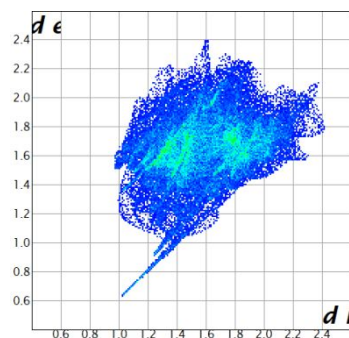
Fig. S17. 2D fingerprint of CAF molecule in CAF·HMLA·H$_2$O.
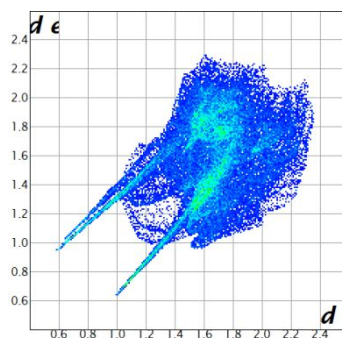
Fig. S18. 2D fingerprint of HMLA molecule in CAF·HMLA·H$_2$O.

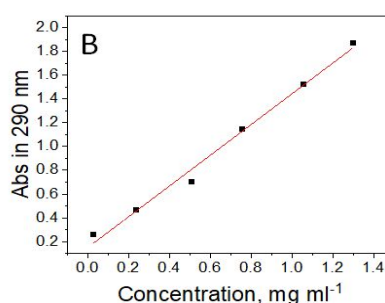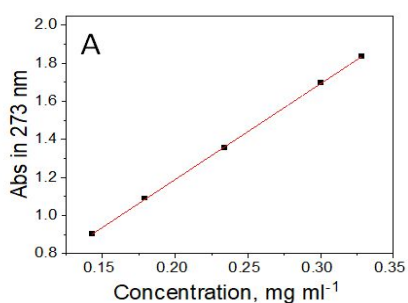**S10. Steady-state absorption standard curves**

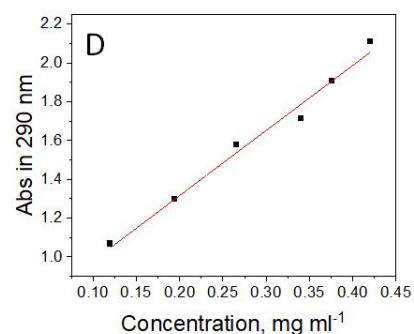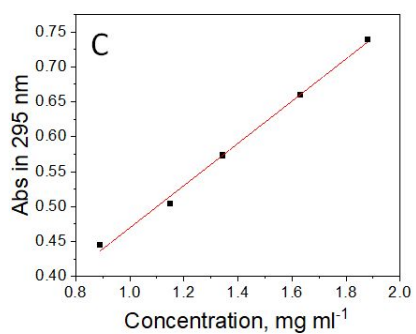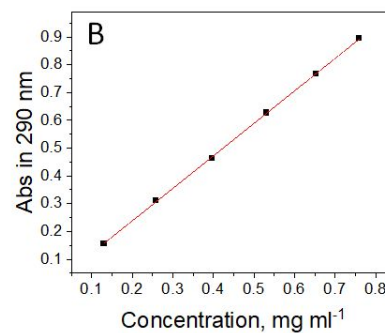Figure S19. Steady-state absorption standard curves of theobromine cocrystals: (A) TBR·TMSA and (B) TBR·HMLA.
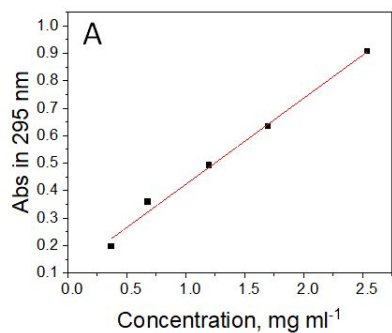

Figure S20. Steady-state absorption standard curves of theophylline cocrystals: (A) TPH·TMSA, (B) TPH·TMSA·2H$_2$O, (C) TPH·HMLA and (D) (TPH)$^+$·(HMLA)$^-$·2H$_2$O.
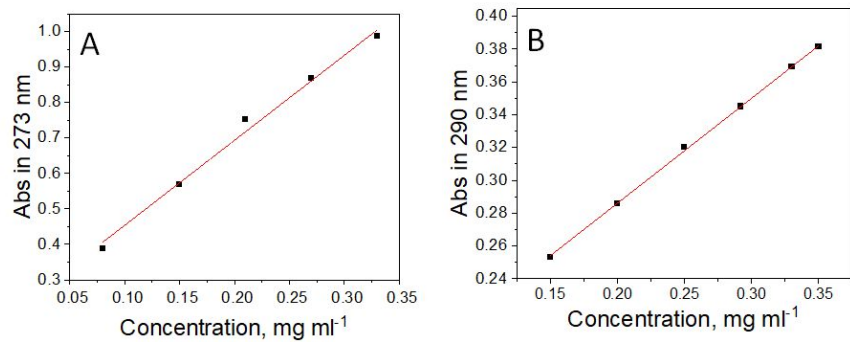
Figure S21. Steady-state absorption standard curves of caffeine cocrystals: (A) CAF·TMSA and (B) CAF·HMLA·H$_2$O.