Electronic Supplementary Information

On the predictability of supramolecular interactions in molecular cocrystals – the view from the bench

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1. Materials

Benzoic acid (**BA**) (99%, *Sigma Aldrich*), 2-fluorobenzoic acid (**2FBA**) (99%, *Acros Organics*), 3-fluorobenzoic acid (**3FBA**) (99%, *Acros Organics*), 4-fluorobenzoic acid (**4FBA**) (98%, *Aldrich*), 2,3-difluorobenzoic acid (**23diFBA**) (98%, *Sigma Aldrich*), 2,4-difluorobenzoic acid (**24diFBA**) (99%, *Acros Organics*), 2,5-difluorobenzoic acid (**25diFBA**) (98%, *Aldrich*), 2,6-difluorobenzoic acid (**26diFBA**) (97%, Maybridge), 3,4-difluorobenzoic acid (**34diFBA**) (98%, *Alfa Aesar*), 3,5-difluorobenzoic acid (**35diFBA**) (97%, *Aldrich*), 2,3,4-trifluorobenzoic acid (**234triFBA**) (98%, *Alfa Aesar*), 2,3,5-trifluorobenzoic acid (**235triFBA**) (97%, *Alfa Aesar*), 2,3,6-trifluorobenzoic acid (**236triFBA**) (99%, *Alfa Aesar*), 2,4,5-trifluorobenzoic acid (**245triFBA**) (98%, *Alfa Aesar*), 2,4,6-trifluorobenzoic acid (**246triFBA**) (99%, *Alfa Aesar*), 3,4,5-trifluorobenzoic acid (**345triFBA**) (98%, *Aldrich*), 2,3,4,5-tetrafluorobenzoic acid (**2345tetFBA**) (98+%, *Alfa Aesar*), 2,3,4,6-tetrafluorobenzoic acid (**2346tetFBA**) (98%, *Apollo Scientific Ltd.*), 2,3,5,6-tetrafluorobenzoic acid (**2356tetFBA**) (98%, *Acros Organics*), 2,3,4,5,6-pentafluorobenzoic acid (**23456pFBA**) (97+%, *Fluka*) and theophylline (**thp**) (99%, *Sigma Aldrich*) were purchased and used as received. Methanol (≥99.0%, *Emplura® Merck*), nitromethane (98+%, *Alfa Aesar*), acetonitrile (≥99 %, *Sigma Aldrich*) and ethanol (≥99.5%, *Emplura® Merck*) were also used without further purification.

2. Mechanochemical cocrystallisation

The mechanochemical cocrystal syntheses were performed by liquid-assisted grinding (LAG) using a *Retsch MM200* mixer mill. In a typical milling experiment, 200 mg of a physical mixture of equimolar amounts of **thp** and a **FBA** were added to a 15 mL stainless steel grinding jar, along with 50 µL of nitromethane and two 7 mm stainless steel milling balls. The mixer mill was operated at 30 Hz for 30 min. The obtained solids were subsequently analysed by powder X-ray diffraction.

3. Solution-based cocrystallisation

3.1. Single crystal growth by slow solvent evaporation

In a typical cocrystallisation experiment, about 10 mg of a (mechanochemically prepared) cocrystal were fully dissolved in 7-15 mL of a hot solvent (either methanol, ethanol or nitromethane). The obtained solution was then filtered through a cotton plug and left to evaporate slowly in a partially covered crystallisation vial at ambient conditions. Crystals suitable for single crystal X-ray diffraction experiments were observed within four days to four weeks.

3.2. Solution-mediated phase transformation (SMPT)

In a typical screening experiment, equimolar amounts of **thp** and a **FBA** (> 200 mg) were added to a low volume of nitromethane or acetonitrile (1-4 mL). The resulting suspension was sonicated for several minutes to facilitate the SMPT process and subsequently slurried overnight at ambient conditions to ensure complete conversion. Each suspension was then filtered and the residual solid was examined by powder X-ray diffraction (PXRD).

4. Crystallographic studies

4.1. Powder X-ray diffraction (PXRD)

Results of initial cocrystal screens were analysed using a *Philips X'Pert PRO MPD* powder X-ray diffractometer (equipped with an *X'Celerator* detector) using Ni-filtered CuK_α radiation (λ = 1.54056 Å), and operating at 40 kV and 40 mA. The mechanochemically prepared samples (20-50 mg) were mounted on a flat glass bracket (specimen size 10×14×0.5 mm^3) and followed by data collection 298 K (aided by the *X'Pert Data Collector* program[1]). 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 (for cocrystal screening purposes) and 260 s (for structure solution purposes). The data was analysed using the *X'Pert Highscore Plus*[2] and *TOPAS Academic*.[3]

Data for qualitative and structural analyses were collected using a *Stoe StadiP* diffractometer in transmission geometry using monochromated Cu$K_{\alpha1}$ radiation (λ = 1.54056 Å) generated at 40 kV and 30 mA. Each sample was prepared by placing few milligrams of compound into a 0.5 mm borosilicate capillary that was subsequently sealed. The sample was aligned with a wide collimator using the *Faceit (video) X.view* v2.14 software. Data were collected at room temperature using a 2-60° 2θ range (continuous mode, 0.5° step, 20 s/step).

Qualitative phase analyses of all solids obtained by LAG were performed with the program *TOPAS Academic*[3] using the Rietveld method.[4] The Rietveld plots in Figures S2-S21 indicate the composition of each analysed batch, as well as the crystallographic data used for the analysis.

For crystal structure determination from powder X-ray diffraction data, indexing was performed using the *DICVOL06* program.[5] The most probable space group was determined by analysing the individual diffracted intensities extracted using the Pawley refinement[6] procedure implemented in the program *DASH 3.3*.[7] Structure solution and Rietveld refinement[4] were performed in the software *TOPAS Academic*.[3] Molecular geometries were defined by rigid bodies and constraints were used to specify bond lengths, bond angles and most of the torsion angles.

The resulting crystal structures of selected cocrystal systems were optimised using the plane-wave DFT code *CASTEP 8.0*.[8] The calculations were performed using the PBE exchange-correlation functional,[9] G06 dispersion correction[10] and norm-conserving pseudopotentials[11] with the plane wave cut-off set to 700 eV. The *k*-point spacing was set to 0.03 Å^{-1}. The correctness of structure determination was verified by the close similarity of the experimental and DFT-optimised structures. The final Rietveld refinements were performed using the molecular geometries extracted from the DFT-optimised structures.

Standard uncertainties on atom coordinates were calculated using the bootstrap method. Crystallographic and refinement parameters for crystal structures (**thp**)·(**2FBA**), (**thp**)·(**2FBA**)·(CH_3NO_2), (**thp**)·(**3FBA**), (**thp**)·(**34diFBA**) (Form **I**), (**thp**)·(**35diFBA**), (**thp**)·(**235triFBA**), (**thp**)·(**236triFBA**), (**thp**)·(**2346tetFBA**), (**thp**)·(**2356tetFBA**) and (**thp**)·(**23456pFBA**) (Form **I**) are given in Table S1, while their Rietveld plots are shown in Figures S2-S4, S10, S11, S13, S14 and S19-S21, respectively. Figures of **thp**:**FBA** assemblies in (**thp**)·(**235triFBA**), (**thp**)·(**236triFBA**) and (**thp**)·(**2356tetFBA**) are shown in Figure S1, rather than in the main text.

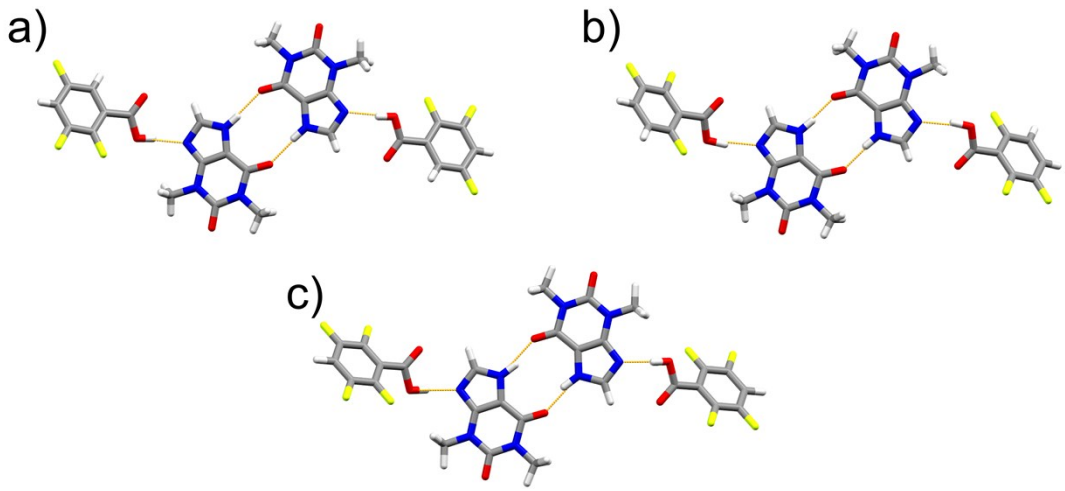


Figure S1. Perspective views of **thp**:**FBA** assemblies in the crystal structures of: a) (**thp**)·(**235triFBA**), b) (**thp**)·(**236triFBA**) and c) (**thp**)·(**2356tetFBA**).

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

Compound	(thp)·(2FBA)	(thp)·(2FBA)·(CH_3NO_2)	(thp)·(3FBA)
chemical formula	$(C_7H_8N_4O_2)\cdot(C_7H_5FO_2)$	$(C_7H_8N_4O_2)\cdot(C_7H_5FO_2)\cdot(CH_3NO_2)$	$(C_7H_8N_4O_2)\cdot(C_7H_5FO_2)$
M_r/g mol^{-1}	320.28	381.32	320.28
Crystal system	monoclinic	monoclinic	monoclinic
a/Å	6.99605(15)	8.00003(28)	6.95661(26)
b/Å	25.41715(87)	25.55132(99)	25.0530(13)
c/Å	8.60318(40)	8.73449(28)	8.67305(65)
α/°	90	90	90
β/°	109.6613(22)	105.0710(21)	107.5894(35)
γ/°	90	90	90
V/Å^3	1440.62(9)	1724.02(11)	1440.90(20)
T/K	293(2)	293(2)	293(2)
Space group	$P2_1/n$	$P2_1/c$	$P2_1/n$
Z	4	4	4
Radiation type	Cu$K_{\alpha1}$	Cu$K_{\alpha1}$	CuK_{α}
R_{wp}	0.062	0.065	0.055
R_p	0.046	0.051	0.044
R_{Bragg}	0.034	0.049	0.021
χ^2	3.903	1.329	2.698
No. of parameters	41	48	35
CCDC deposition number	1451260	1476652	1451261

Table S1 (continued). Crystallographic and refinement parameters for crystal structures solved using powder X-ray diffraction data.

Compound	(thp)·(34diFBA) Form I	(thp)·(35diFBA)	(thp)·(235triFBA)
chemical formula	$(C_7H_8N_4O_2)\cdot(C_7H_4F_2O_2)$	$(C_7H_8N_4O_2)\cdot(C_7H_4F_2O_2)$	$(C_7H_8N_4O_2)\cdot(C_7H_3F_3O_2)$
M_r/g mol^{-1}	338.28	338.28	356.26
Crystal system	triclinic	monoclinic	monoclinic
a/Å	9.17878(43)	3.86433(17)	3.91876(24)
b/Å	10.55176(55)	13.61115(66)	13.1931(12)
c/Å	11.09567(51)	27.6863(13)	28.9207(30)
α/°	125.2204(16)	90	90
β/°	58.5444(30)	94.8744(58)	91.1151(67)
γ/°	109.9620(28)	90	90
V/Å^3	747.641(68)	1450.98(12)	1494.93(29)
T/K	293(2)	293(2)	293(2)
Space group	*P*-1	$P2_1/c$	$P2_1/c$
Z	2	4	4
Radiation type	Cu$K_{\alpha1}$	CuK_{α}	CuK_{α}
R_{wp}	0.066	0.071	0.057
R_p	0.046	0.056	0.045
R_{Bragg}	0.044	0.021	0.011
χ^2	1.517	3.290	4.995
No. of parameters	63	46	41
CCDC deposition number	1476648	1451263	1451265

Table S1 (continued). Crystallographic and refinement parameters for crystal structures solved using powder X-ray diffraction data.

Compound	(thp)·(236triFBA)	(thp)·(2346tetFBA)	(thp)·(2356tetFBA)
Chemical formula	$(C_7H_8N_4O_2)\cdot(C_7H_3F_3O_2)$	$(C_7H_8N_4O_2)\cdot(C_7H_2F_4O_2)$	$(C_7H_8N_4O_2)\cdot(C_7H_2F_4O_2)$
M_r/g mol^{-1}	356.26	374.25	374.25
Crystal system	monoclinic	triclinic	monoclinic
a/Å	3.96986(28)	7.43730(14)	3.94083(11)
b/Å	13.0525(13)	7.32762(21)	13.00822(50)
c/Å	29.1541(34)	14.64086(43)	29.9781(13)
α/°	90	85.7805(17)	90
β/°	90.7519(70)	101.0840(18)	92.2242(30)
γ/°	90	101.4890(14)	90
V/Å^3	1510.54(36)	766.804(35)	1535.614(99)
T/K	293(2)	293(2)	293(2)
Space group	$P2_1/c$	*P*-1	$P2_1/c$
Z	4	2	4
Radiation type	CuK_α	Cu$K_{\alpha1}$	Cu$K_{\alpha1}$
R_{wp}	0.065	0.0423	0.0534
R_p	0.052	0.0323	0.0415
R_{Bragg}	0.011	0.018	0.0459
χ^2	5.969	1.252	1.160
No. of parameters	39	71	56
CCDC deposition number	1451266	1476649	1476650

Table S1 (continued). Crystallographic and refinement parameters for crystal structures solved using powder X-ray diffraction data.

Compound	(thp)·(23456pFBA) Form I
Chemical formula	$(C_7H_8N_4O_2)\cdot(C_7HF_5O_2)$
M_r/g mol^{-1}	392.25
Crystal system	triclinic
a/Å	7.93042(96)
b/Å	9.52612(99)
c/Å	10.9594(10)
α/°	92.8738(48)
β/°	105.7547(66)
γ/°	105.7529(70)
V/Å^3	760.02(18)
T/K	293(2)
Space group	*P-1*
Z	2
Radiation type	CuK_α
R_{wp}	0.082
R_p	0.063
R_{Bragg}	0.012
χ^2	6.944
No. of parameters	47
CCDC deposition number	1451273

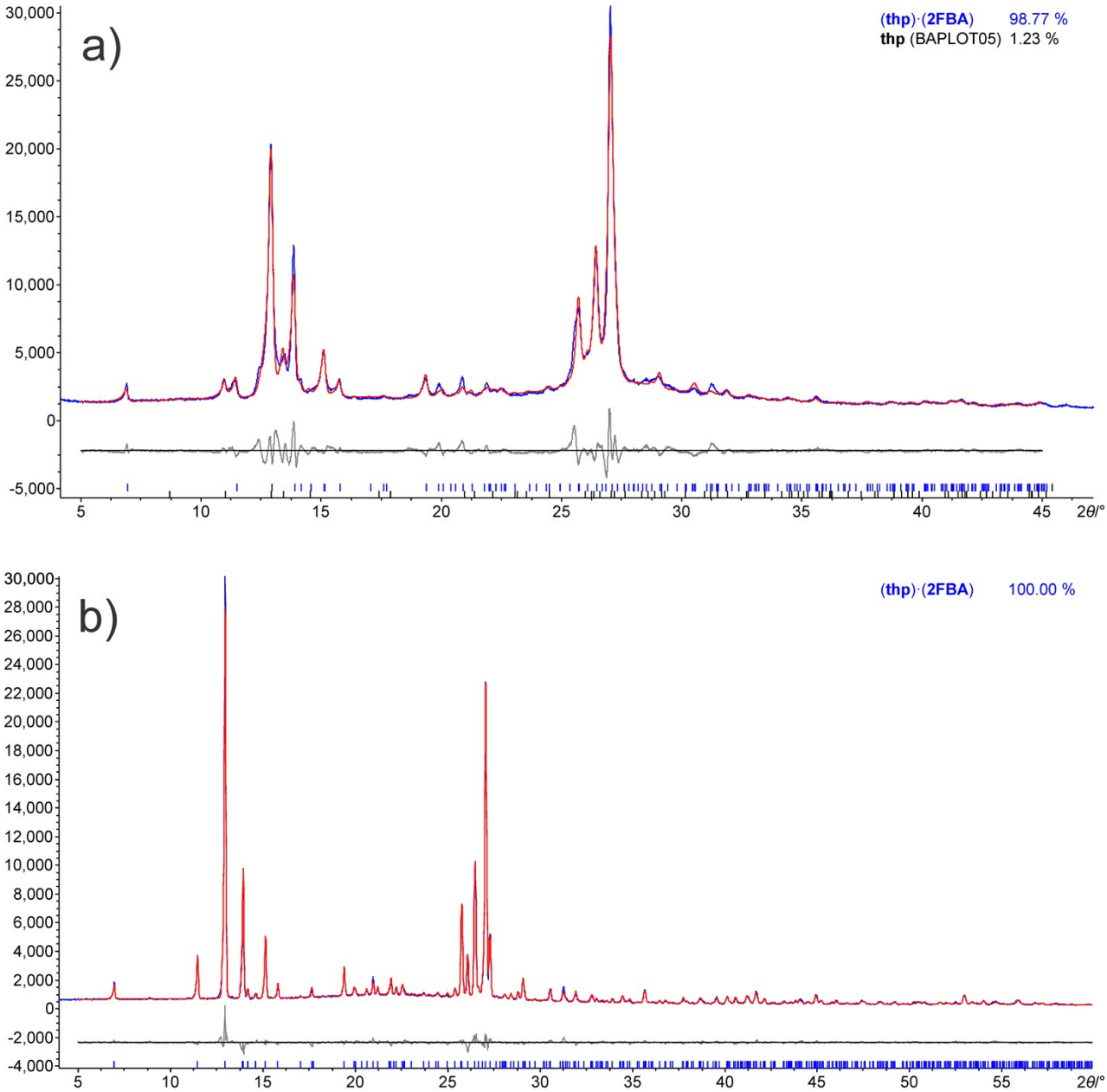


Figure S2. Rietveld plots for (**thp**)·(**2FBA**) relating to analyses of: a) the initially obtained sample that was prepared by LAG (at the University of Cambridge) and is likely to entail unidentified impurities, b) a phase-pure sample that was obtained (at UCL) by SMPT using acetonitrile as solvent (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks. The data obtained from the phase-pure batch shown in b) was used for structure solution and refinement.

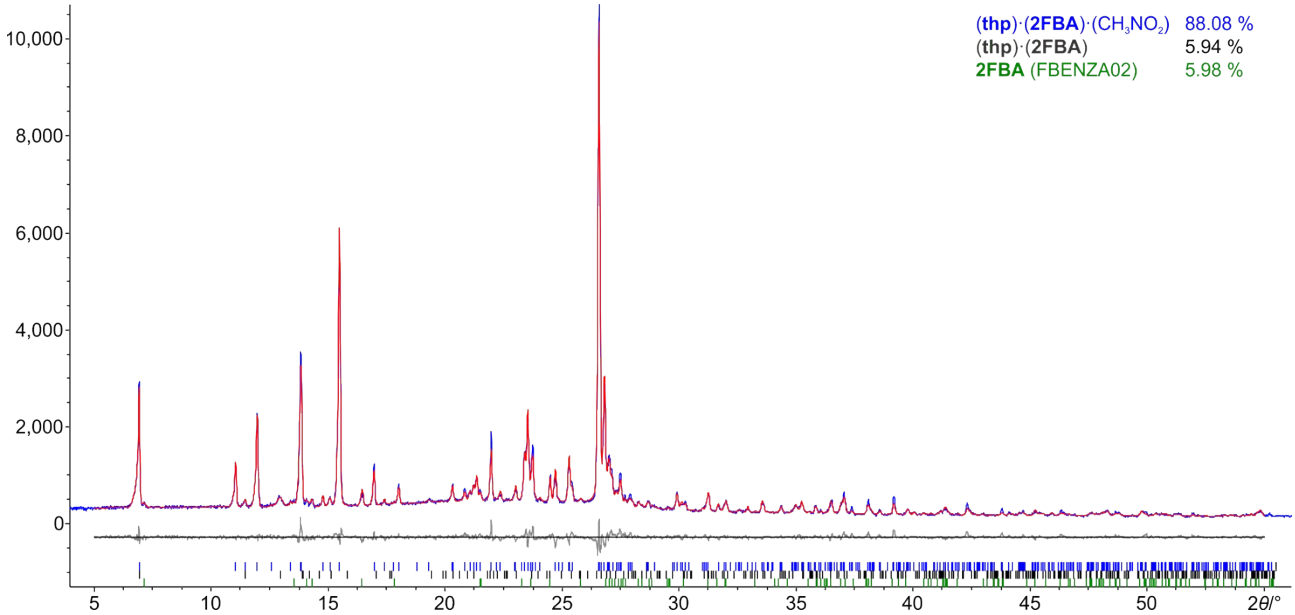


Figure S3. Rietveld plot for (**thp**)·(**2FBA**)·(CH_3NO_2) (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

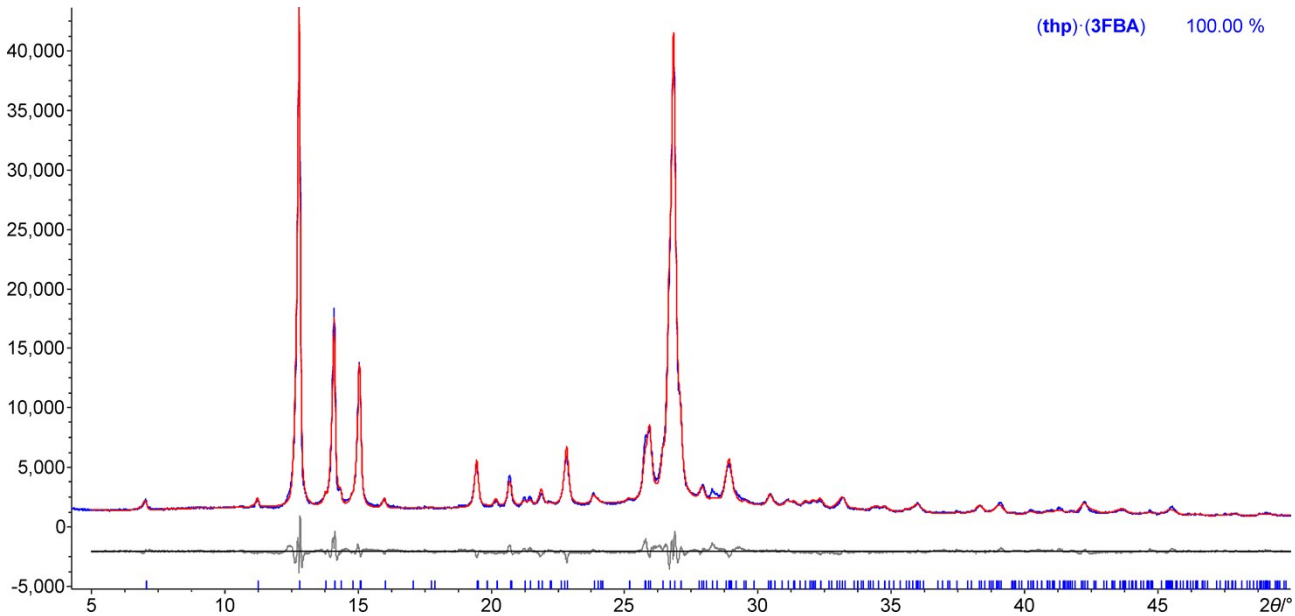


Figure S4. Rietveld plot for (**thp**)·(**3FBA**) (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

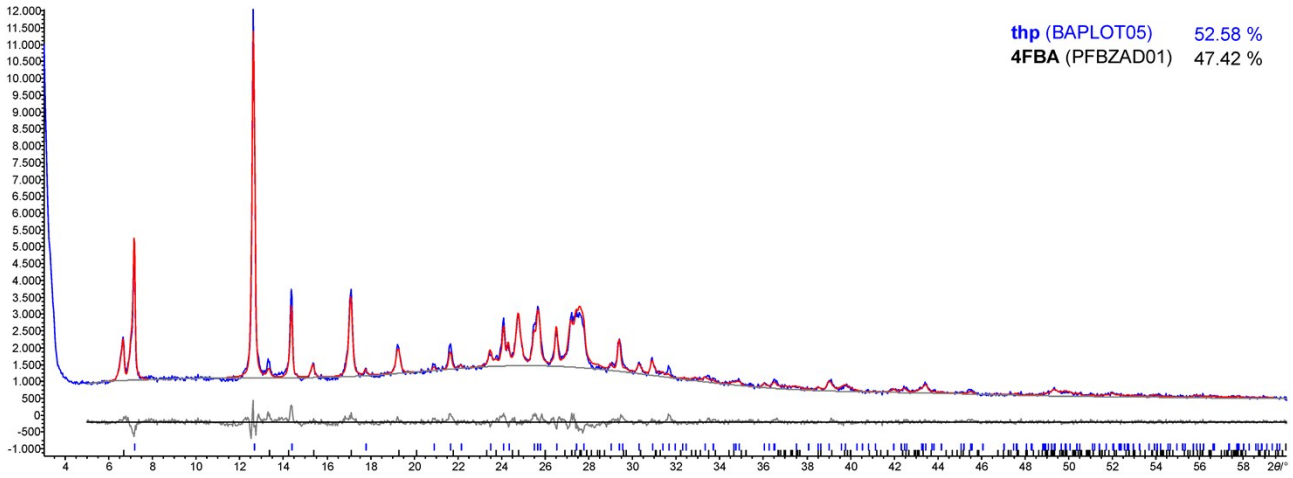


Figure S5. Rietveld plot for a physical mixture of **thp** and **4FBA** that was obtained in an unsuccessful attempt to prepare a cocrystal (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

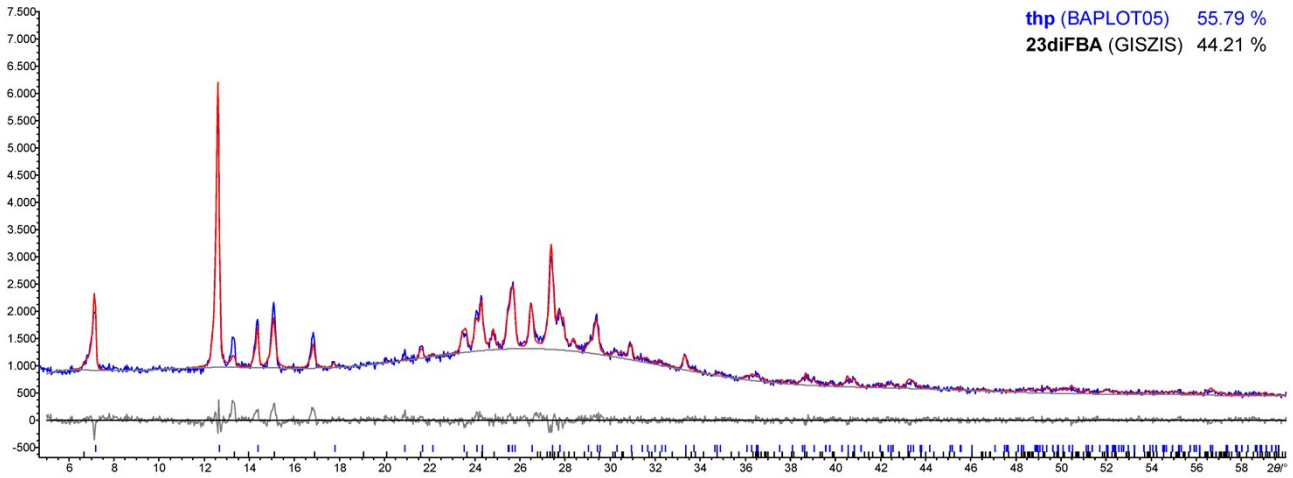


Figure S6. Rietveld plot for a physical mixture of **thp** and **23diFBA** that was obtained in an unsuccessful attempt to prepare a cocrystal (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

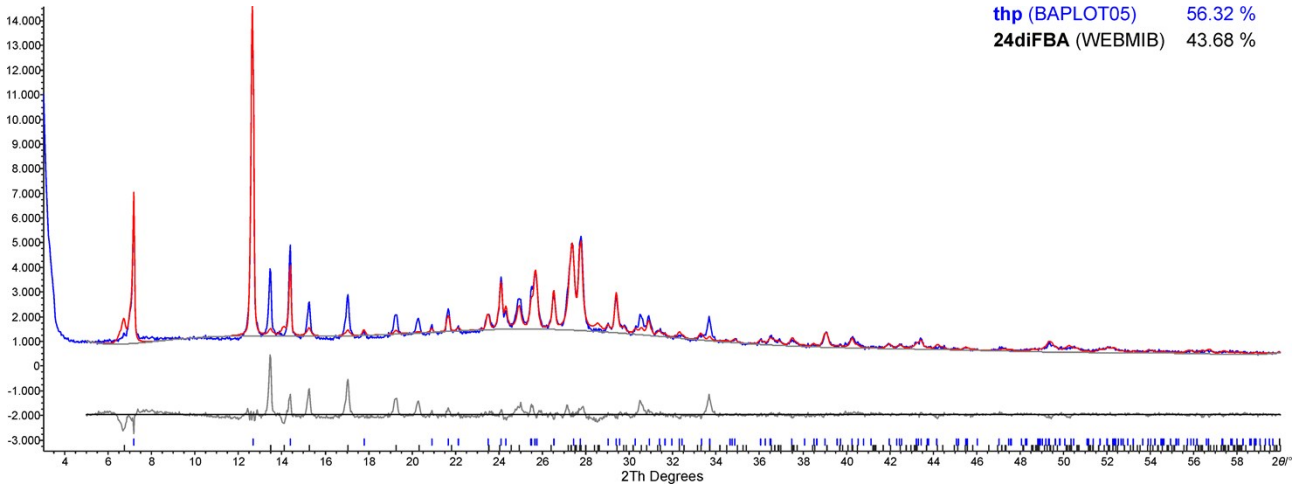


Figure S7. Rietveld plot for a physical mixture of **thp** and **24diFBA** that was obtained in an unsuccessful attempt to prepare a cocrystal (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

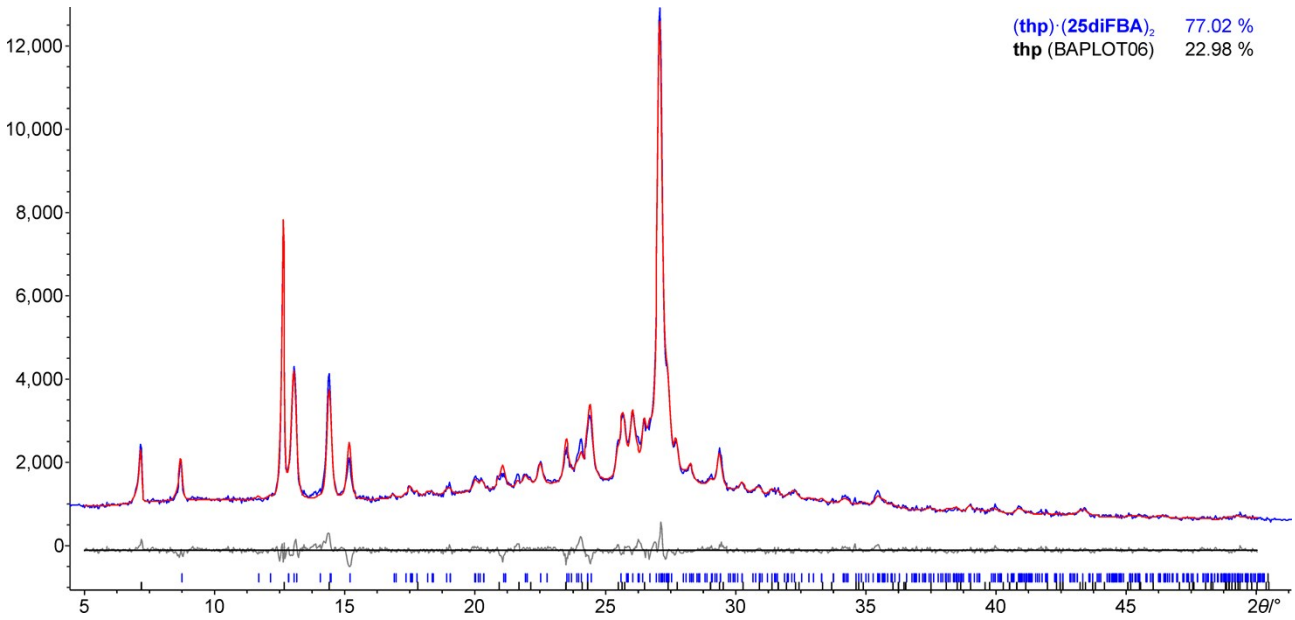


Figure S8. Rietveld plot for (**thp**)·(**25diFBA**)$_2$ obtained from a 1:1 **thp**:**25diFBA** physical mixture (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

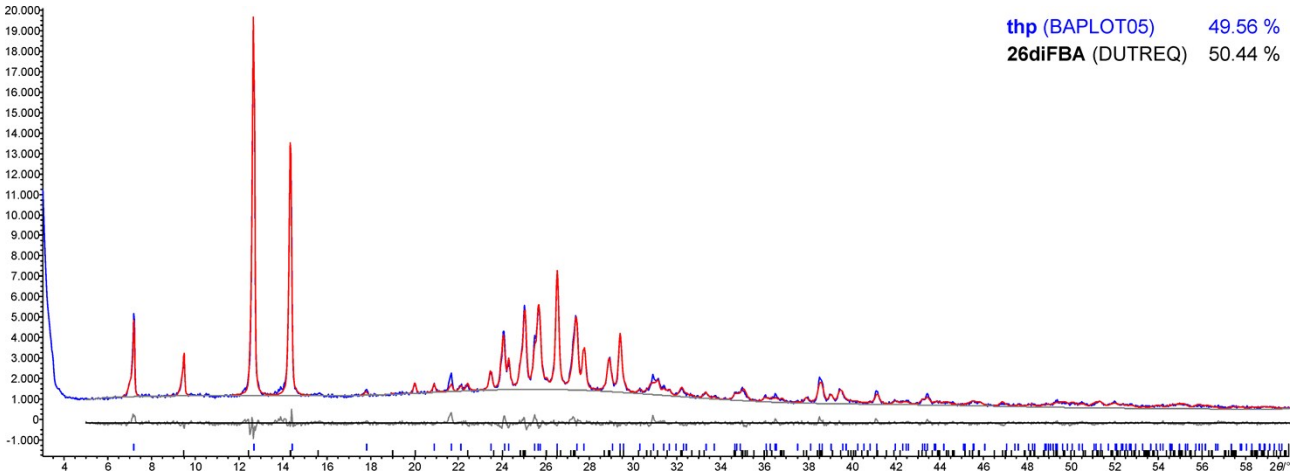


Figure S9. Rietveld plot for a physical mixture of **thp** and **26diFBA** that was obtained in an unsuccessful attempt to prepare a cocrystal (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

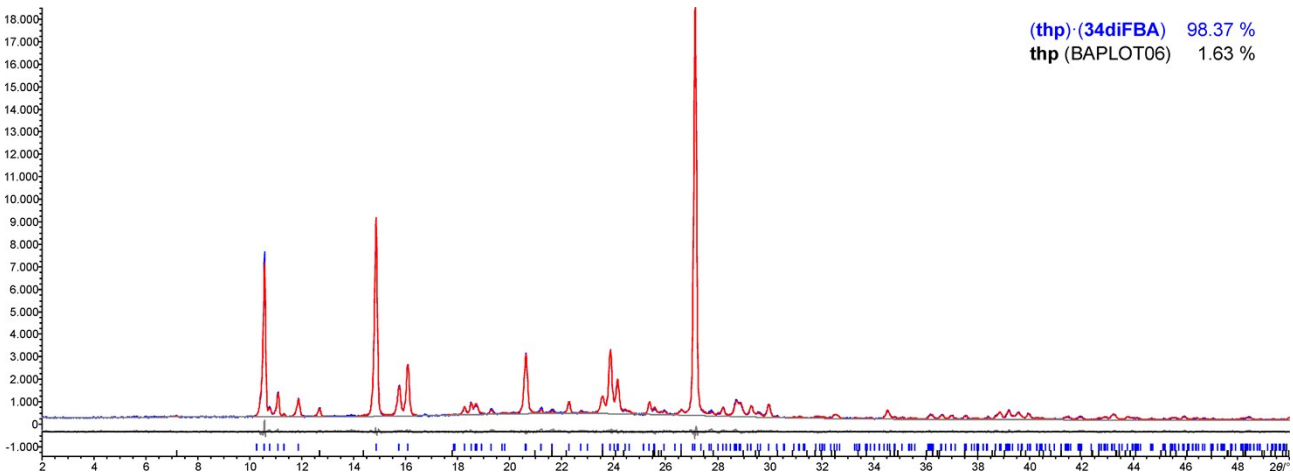


Figure S10. Rietveld plot for (**thp**)·(**34diFBA**) (Form **I**) (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

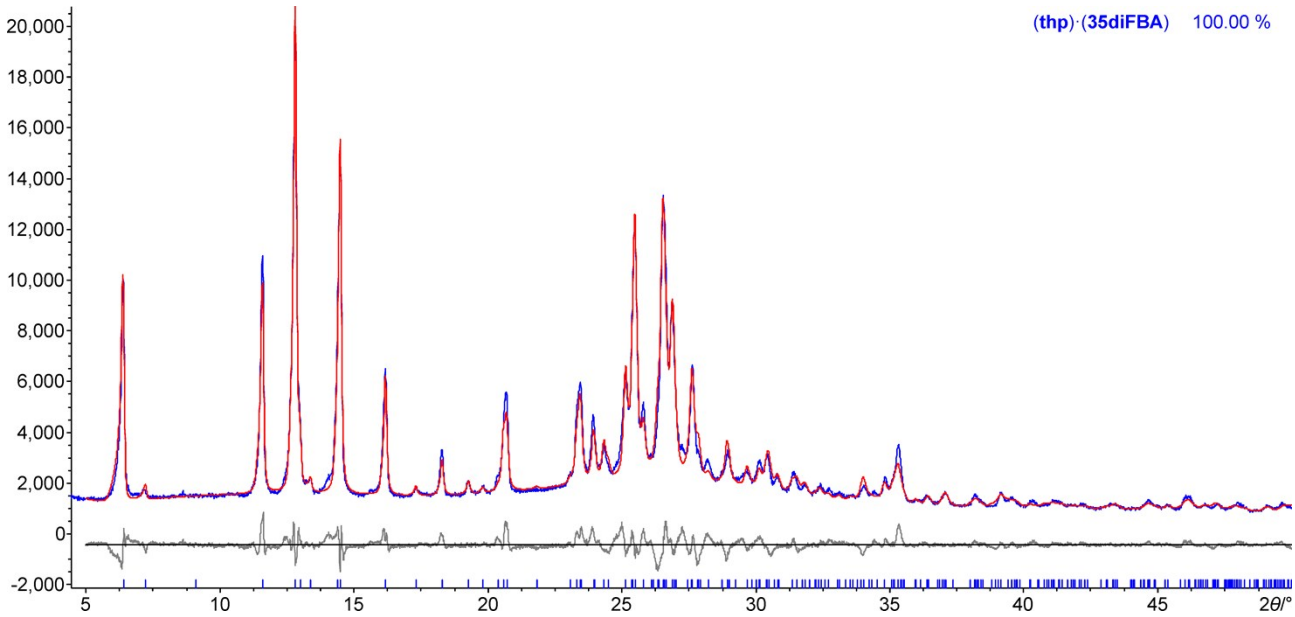


Figure S11. Rietveld plot for (**thp**)·(**35diFBA**) (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

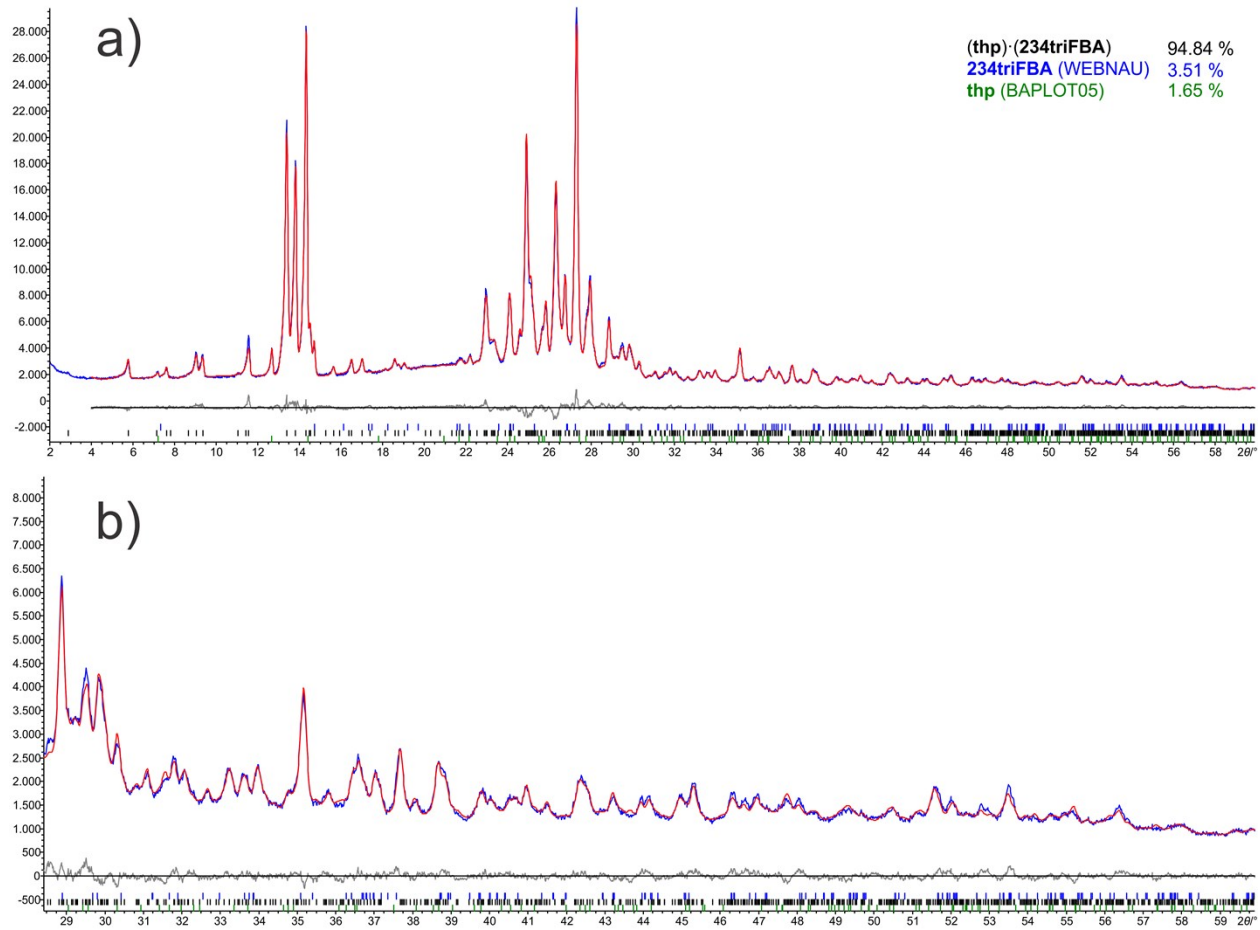


Figure S12. Rietveld refinement plot for (**thp**)·(**234triFBA**) using the crystal structure model as obtained from single crystal data: a) full pattern and b) high-angle portion of the pattern. Blue: measured, red: calculated, grey: difference. Tick marks represent calculated peak positions.

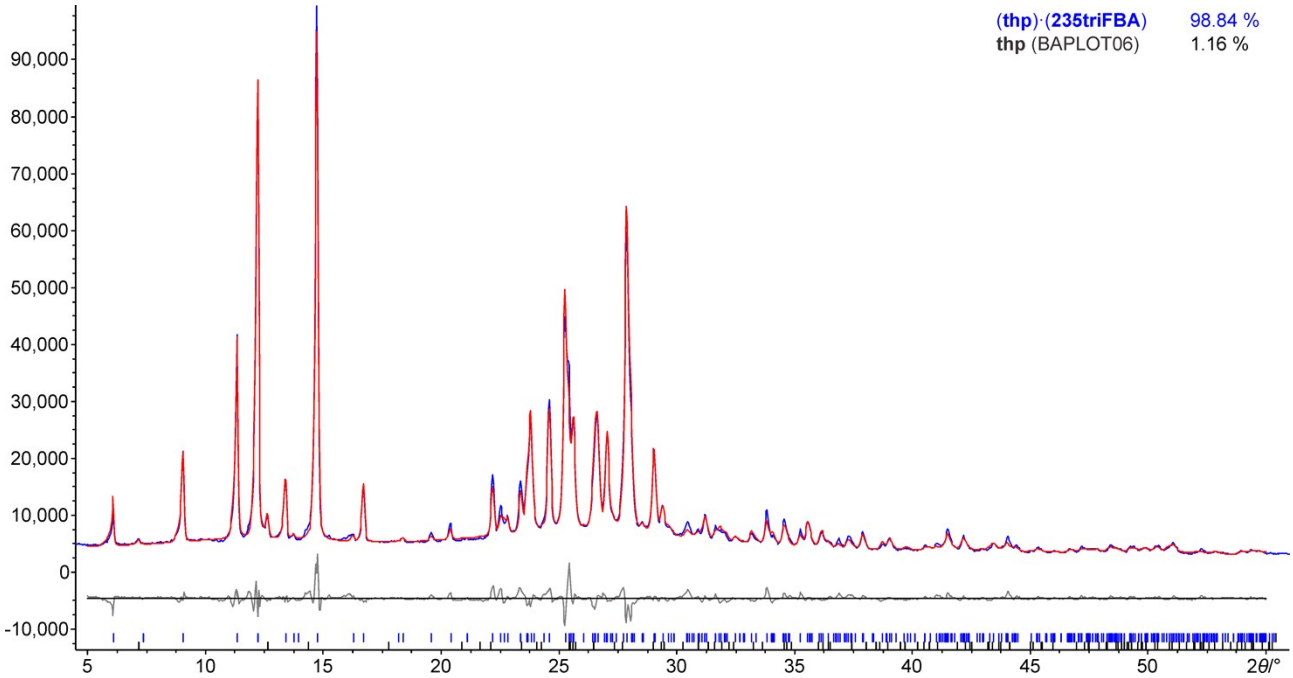


Figure S13. Rietveld plot for (**thp**)·(**235triFBA**) (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

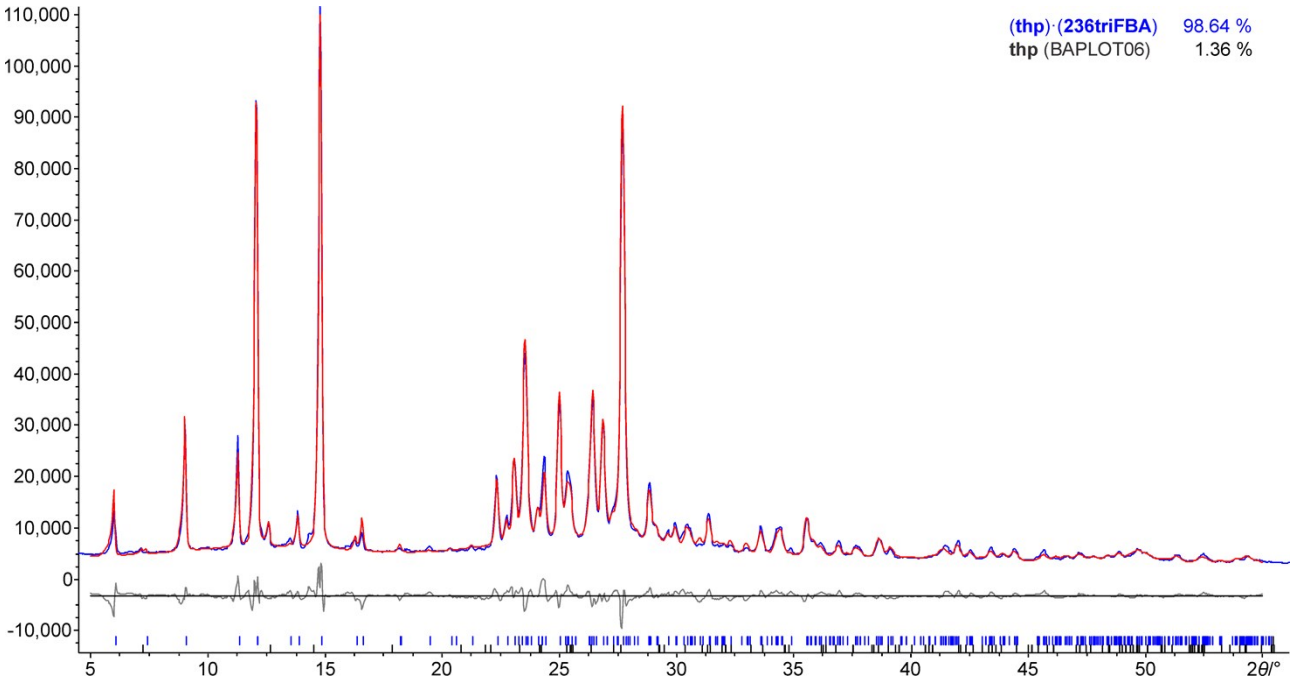


Figure S14. Rietveld plot for (**thp**)·(**236triFBA**) (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

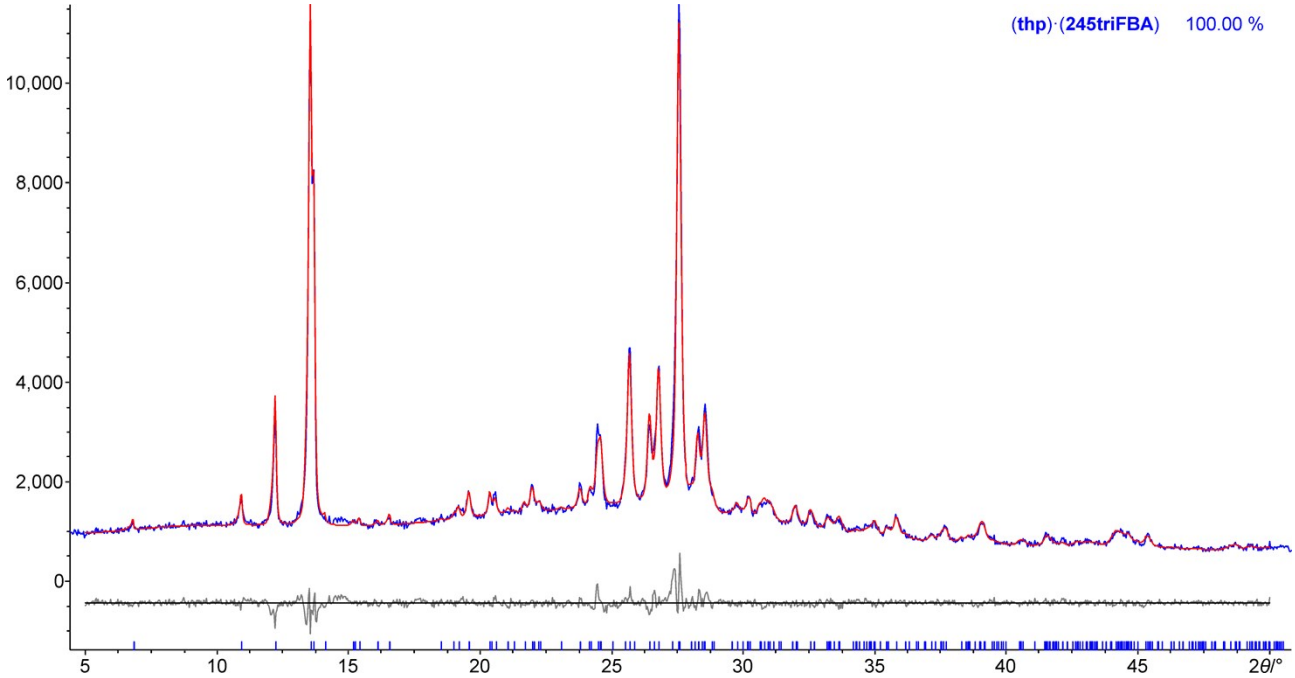


Figure S15. Rietveld plot for (**thp**)·(**245triFBA**) (Form **I**) (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

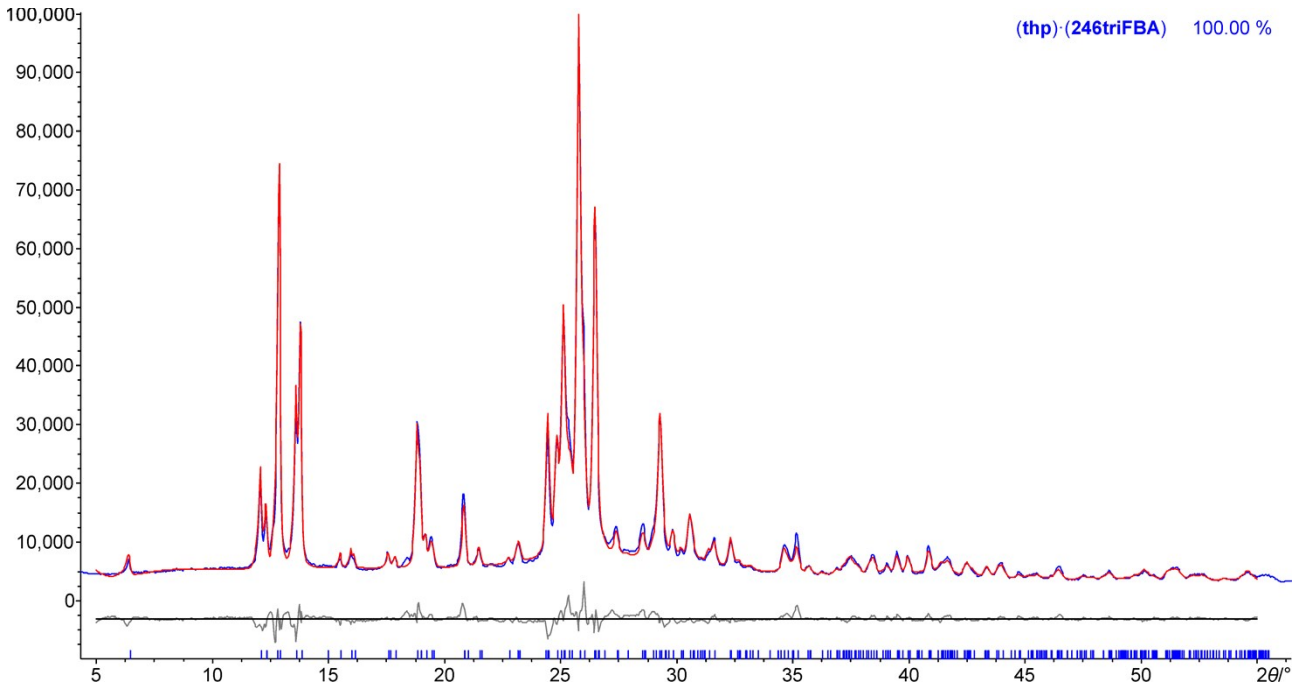


Figure S16. Rietveld plot for (**thp**)·(**246triFBA**) (Form **I**) (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

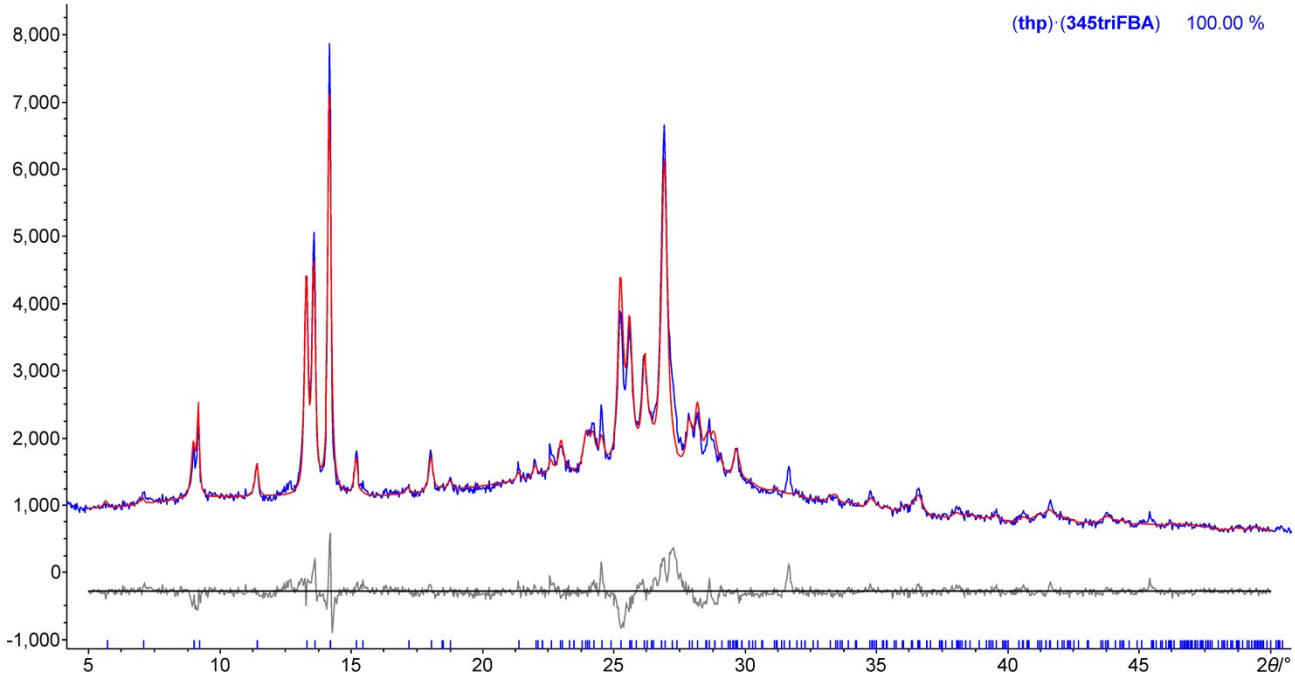


Figure S17. Rietveld plot for (**thp**)·(**345triFBA**) (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

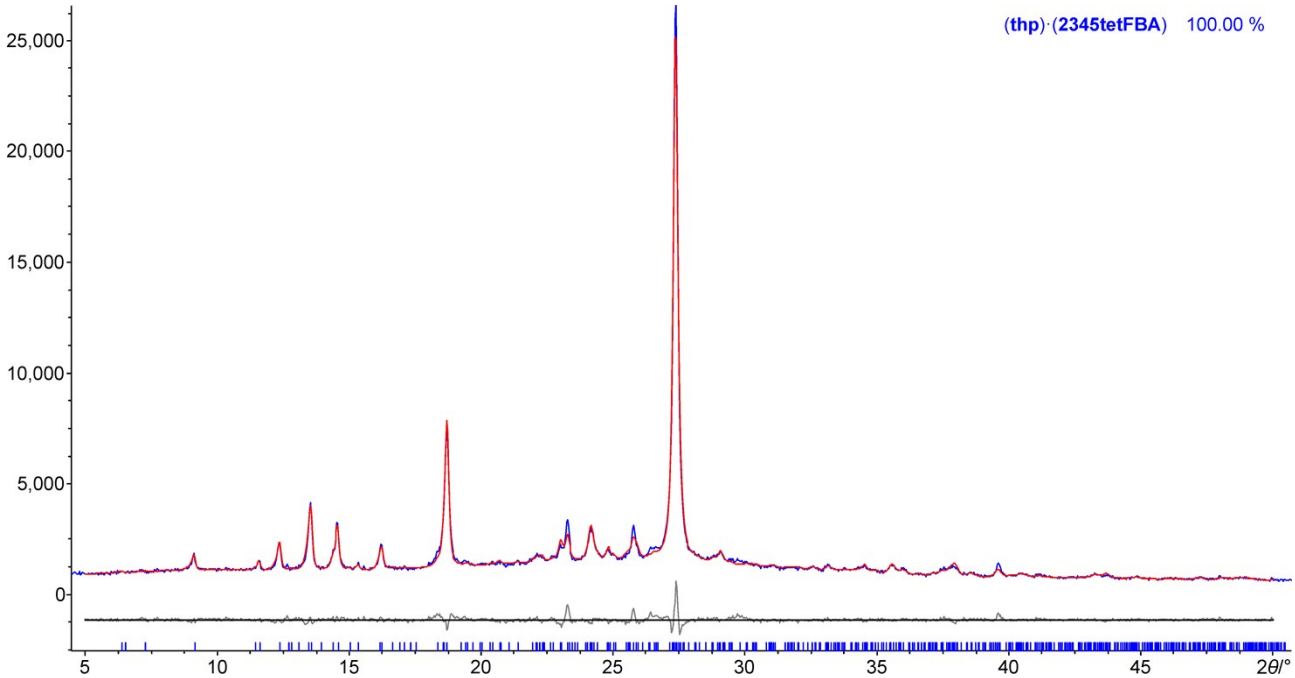


Figure S18. Rietveld plot for (**thp**)·(**2345tetFBA**) (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

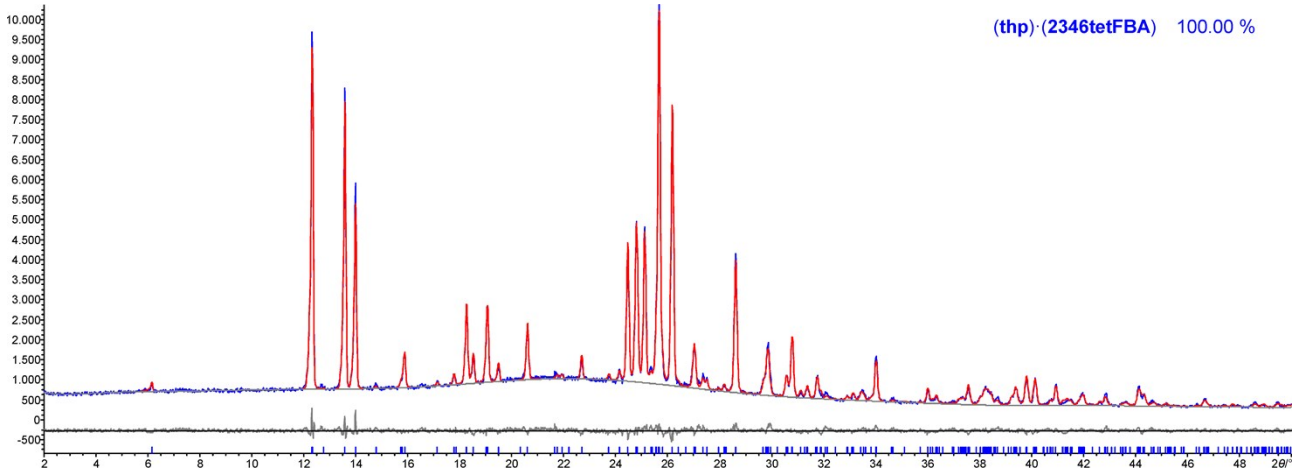


Figure S19. Rietveld plot for (**thp**)·(**2346tetFBA**) (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

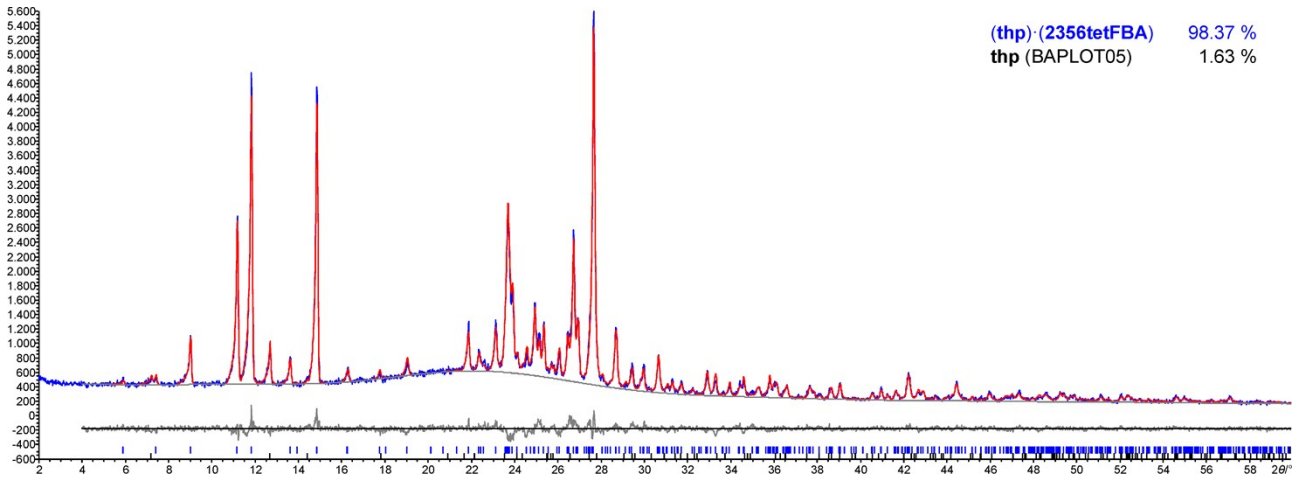


Figure S20. Rietveld plot for (**thp**)·(**2356tetFBA**) (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

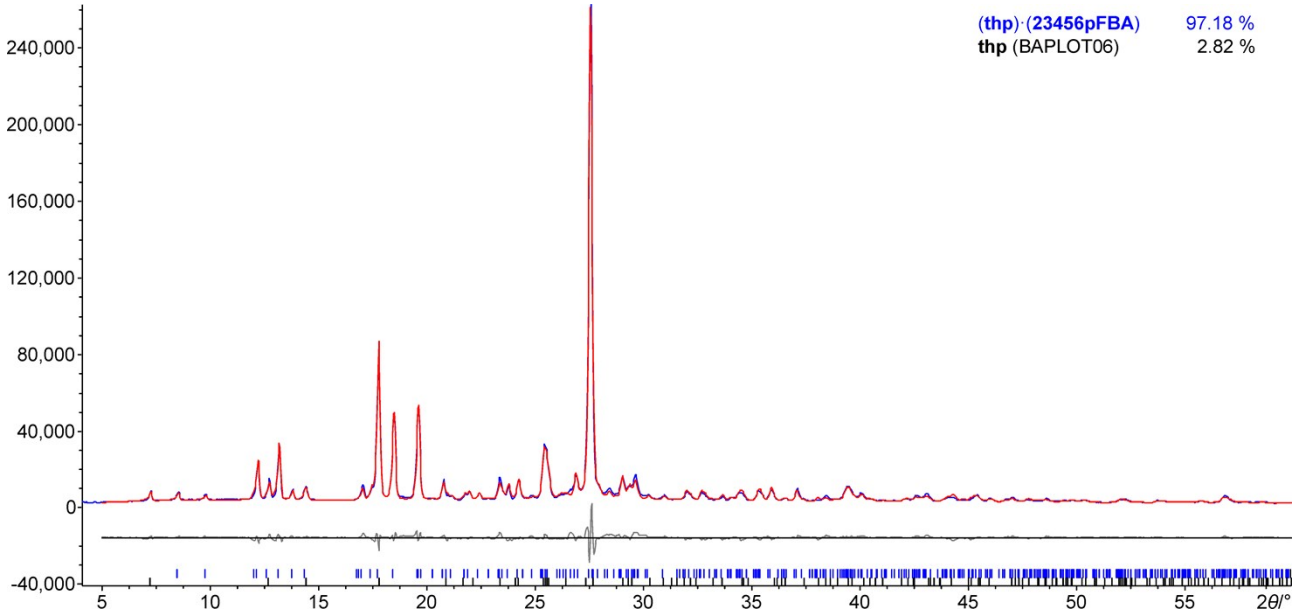


Figure S21. Rietveld plot for (**thp**)·(**23456pFBA**) (**Form I**) (*red*: calculated, *blue*: measured, *grey*: difference). The peak positions are represented with tick marks.

4.2. Single crystal X-ray diffraction (SCXRD)

Single X-ray diffraction data was collected using an *Agilent SuperNova (Dual Source)* single crystal X-ray diffractometer equipped with an *Atlas* CCD detector. All data sets were collected at 150 K using CuK_α radiation (λ = 1.54184 Å). The data was acquired and processed using the *CrysAlis^{Pro}* program,[12] while all datasets were corrected for Lorentz and polarization effects. Structure solution and refinement were accomplished using SHELXS-97 and SHELXL-97, respectively.[13] The crystal structures were solved using direct methods. All non-hydrogen atoms were refined anisotropically, while hydrogen atoms associated with carbon and oxygen atoms were refined isotropically in geometrically constrained positions. Hydrogen atoms affiliated with nitrogen atoms were refined isotropically in positions identified in the difference Fourier map. The crystal structure of (**thp**)·(**234triFBA**) was solved and refined using an incomplete dataset and its validity was, therefore, further evaluated using PXRD data and Rietveld refinements (see Figure S12). Crystallographic and refinement parameters for crystal structures (**thp**)·(**BA**), (**thp**)·(**25diFBA**)$_2$, (**thp**)·(**34diFBA**) (Form **II**), (**thp**)·(**234triFBA**)**,** (**thp**)·(**245triFBA**) (Form **I**), (**thp**)·(**245triFBA**) (Form **II**), (**thp**)·(**246triFBA**) (Form **I**), (**thp**)·(**246triFBA**) (Form **II**), (**thp**)·(**345triFBA**), (**thp**)·(**2345tetFBA**) and (**thp**)·(**23456pFBA**) (Form **II**) are given in Table S2. Figures of **thp**:**FBA** assemblies in (**thp**)·(**34diFBA**) (Form **II**), (**thp**)·(**246triFBA**) (Form **I**), (**thp**)·(**246triFBA**) (Form **II**), (**thp**)·(**345triFBA**) and (**thp**)·(**2345tetFBA**) are shown in Figure S22, rather than in the main text.

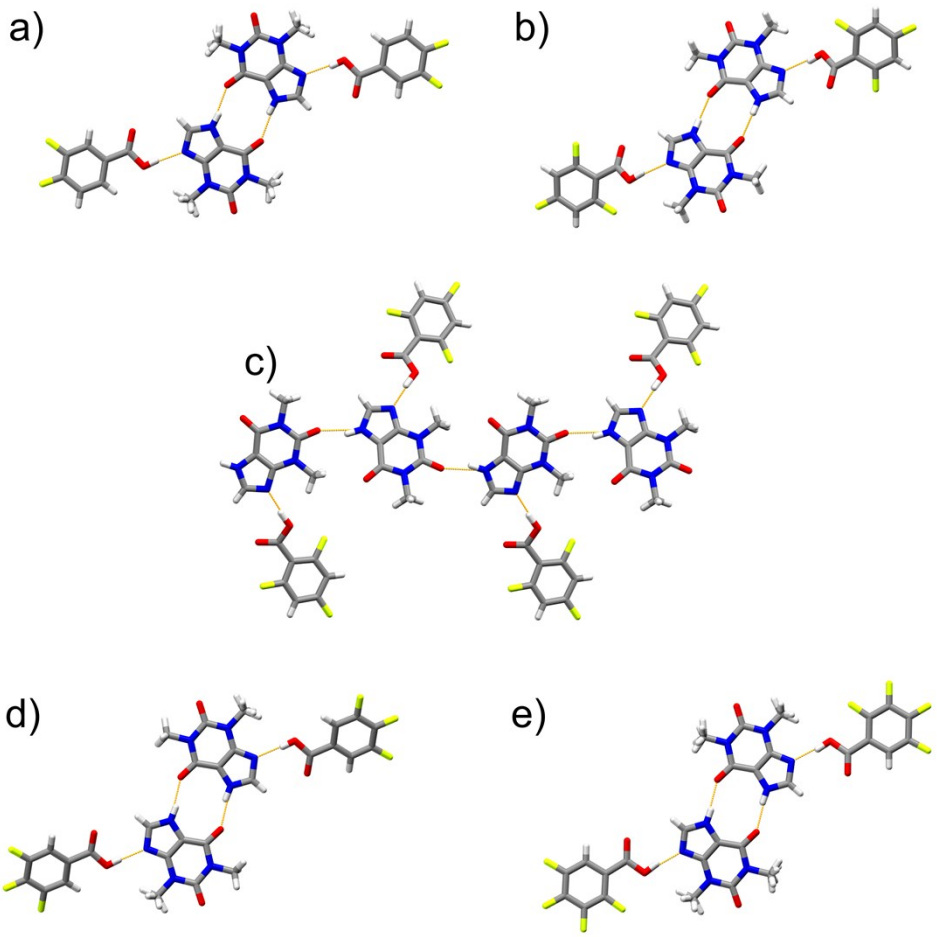


Figure S22. Perspective views of **thp**:**FBA** assemblies in the crystal structures of: a) (**thp**)·(**34diFBA**) (Form **II**), b) (**thp**)·(**246triFBA**) (Form **I**), c) (**thp**)·(**246triFBA**) (Form **II**), d) (**thp**)·(**345triFBA**) and e) (**thp**)·(**2345tetFBA**).

Table S2. Crystallographic and refinement parameters for crystal structures solved using single crystal X-ray diffraction data.

compound	**(thp)·(BA)**	**(thp)·(25diFBA)$_2$**	**(thp)·(34diFBA) Form II**
chemical formula	$(C_7H_8N_4O_2)\cdot(C_7H_6O_2)$	$(C_7H_8N_4O_2)\cdot(C_7H_4F_2O_2)_2$	$(C_7H_8N_4O_2)\cdot(C_7H_4F_2O_2)$
M_r/g mol^{-1}	302.29	496.38	338.28
crystal system	monoclinic	triclinic	triclinic
space group	$P2_1/n$	$P\bar{1}$	$P\bar{1}$
a/Å	6.9150(2)	6.8052(5)	9.1293(3)
b/Å	25.1050(6)	7.4527(3)	9.7717(4)
c/Å	8.6000(3)	20.4399(17)	10.0297(4)
α/°	90	93.757(5)	110.888(3)
β/°	109.190(1)	99.392(7)	109.827(3)
γ/°	90	90.405(4)	102.048(3)
V/Å^3	1410.01(7)	1020.39(12)	728.97(5)
Z	4	2	2
D_c/g cm^{-3}	1.424	1.616	1.541
F(000)	632	508	348
μ(Cu K$_\alpha$)/mm^{-1}	0.107	1.256	1.144
T/K	180(2)	150.00(10)	150(3)
crystal size/mm	0.46 x 0.10 x 0.05	0.10 x 0.05 x 0.05	0.41 x 0.19 x 0.09
index range	$-8 \rightarrow 8$ $-29 \rightarrow 28$ $-7 \rightarrow 10$	$-7 \rightarrow 8$ $-6 \rightarrow 8$ $-24 \rightarrow 20$	$-10 \rightarrow 10$ $-11 \rightarrow 11$ $-11 \rightarrow 11$
collected reflections	7041	6589	10103
unique reflections	2452	3576	2577
R_{int}	0.0398	0.0395	0.0199
reflections with $I > 2\sigma(I)$	2093	3218	2371
no. parameters	208	321	218
$R(F)$, $F > 2\sigma(F)$	0.0379	0.0427	0.0364
$wR(F^2)$, $F > 2\sigma(F)$	0.0888	0.1183	0.0391
$R(F)$, all data	0.0467	0.0475	0.0982
$wR(F^2)$, all data	0.0925	0.1226	0.1017
Δ_r (min., max.) e Å^{-3}	−0.202, 0.227	−0.306, 0.349	−0.323, 0.373
CCDC deposition number	1451259	1451262	1476651

Table S2 (continued). Crystallographic and refinement parameters for crystal structures solved using single crystal X-ray diffraction data.

compound	(thp)·(234triFBA)	(thp)·(245triFBA) Form I	(thp)·(245triFBA) Form II
chemical formula	$(C_7H_8N_4O_2)\cdot(C_7H_5F_3O_2)$	$(C_7H_8N_4O_2)\cdot(C_7H_5F_3O_2)$	$(C_7H_8N_4O_2)\cdot(C_7H_5F_3O_2)$
M_r/g mol^{-1}	356.27	356.27	356.27
crystal system	triclinic	triclinic	triclinic
space group	*P*–1	*P*–1	*P*–1
a/Å	3.8518(1)	6.8186(5)	4.7579(4)
b/Å	12.4949(4)	8.6806(5)	12.5624(11)
c/Å	30.534(2)	12.9733(7)	13.4092(11)
α/°	91.623(2)	83.266(4)	76.403(7)
β/°	93.593(1)	88.380(5)	80.880(7)
γ/°	97.772(1)	68.110(6)	82.885(7)
V/Å^3	1452.17(11)	707.51(8)	766.03(11)
Z	4	2	2
D_c/g cm^{-3}	1.630	1.672	1.545
F(000)	728	364	364
μ(CuK_α)/mm^{-1}	0.146	1.32	1.22
T/K	180(2)	150.00(10)	298
crystal size/mm	0.46 x 0.07 x 0.05	0.60 × 0.14 × 0.07	0.38 × 0.28 × 0.20
index range	−4 → 4 −14 → 14 −25 → 35	−7 → 8 −10 → 7 −15 → 15	−5 → 5 −14 → 14 −15 → 10
collected reflections	8542	4211	4098
unique reflections	4582	2479	2659
R_{int}	0.1129	0.0318	0.0326
reflections with $I > 2\sigma(I)$	2937	2290	1970
no. parameters	455	236	234
$R(F)$, $F > 2\sigma(F)$	0.0632	0.0456	0.0475
$wR(F^2)$, $F > 2\sigma(F)$	0.1589	0.1284	0.0638
$R(F)$, all data	0.0905	0.0483	0.1256
$wR(F^2)$, all data	0.1675	0.1314	0.1409
Δ_r (min., max.) e Å^{-3}	−0.281, 0.282	−0.273, 0.279	−0.180, 0.041
CCDC deposition number	1451264	1451268	1451267

Table S2 (continued). Crystallographic and refinement parameters for crystal structures solved using single crystal X-ray diffraction data.

compound	(thp)·(246triFBA) Form I	(thp)·(246triFBA) Form II	(thp)·(345triFBA)
chemical formula	$(C_7H_8N_4O_2)_2{\cdot}(C_7H_3F_3O_2)_2$	$(C_7H_8N_4O_2){\cdot}(C_7H_3F_3O_2)$	$(C_7H_8N_4O_2){\cdot}(C_7H_3F_3O_2)$
M_r/g mol^{-1}	738.91(14)	356.27	356.27
crystal system	triclinic	orthorhombic	triclinic
space group	*P*−1	*Pbca*	*P*−1
a/Å	7.4182(8)	14.9998(3)	3.8138(5)
b/Å	7.4269(9))	6.90710(10)	12.5214(12)
c/Å	13.9216(14)	28.5122(6)	15.3432(8)
α/°	79.224(9)	90	90.873(6)
β/°	88.766(8)	90	91.670(7)
γ/°	78.749(9)	90	96.870(9)
V/Å^3	738.91(14)	2954.01(10)	727.00(12)
Z	2	8	2
D_c/g cm^{-3}	1.672	1.602	1.627
F(000)	364	1456	364
μ(Cu K$_\alpha$)/mm^{-1}	1.32	0.144	1.219
T/K	298	180(2)	150.00(10)
crystal size/mm	0.13 x 0.09 x 0.05	0.10 x 0.07 x 0.05	0.70 × 0.15 × 0.11
index range	−7 → 8 −8 → 8 −15 → 16	−16 → 17 −7 → 8 −33 → 33	−3 → 4 −14 → 14 −14 → 10
collected reflections	4018	19572	4269
unique reflections	2562	2577	2565
R_{int}	0.0369	0.0588	0.0481
reflections with $I > 2\sigma(I)$	1965	1286	2056
no. parameters	236	234	228
$R(F)$, $F > 2\sigma(F)$	0.0449	0.0358	0.0523
$wR(F^2)$, $F > 2\sigma(F)$	0.1133	0.073	0.1405
$R(F)$, all data	0.059	0.0783	0.0626
$wR(F^2)$, all data	0.1313	0.076	0.1531
Δ_r (min., max.) e Å^{-3}	−0.246, 0.200	−0.219, 0.141	−0.313, 0.243
CCDC deposition number	1451269	1451270	1451271

Table S2 (continued). Crystallographic and refinement parameters for crystal structures solved using single crystal X-ray diffraction data.

compound	(thp)·(2345tetFBA)	(thp)·(23456pFBA) Form II
chemical formula	$(C_7H_8N_4O_2)\cdot(C_7H_2F_4O_2)$	$(C_7H_8N_4O_2)\cdot(C_7HF_5O_2)$
M_r/gmol^{-1}	374.26	392.25
crystal system	monoclinic	triclinic
space group	$P2_1/c$	$P-1$
a/Å	13.5149(2)	8.9430(3)
b/Å	27.5566(3)	11.5102(4)
c/Å	8.01140(10)	15.6500(5)
α/°	90	104.915(3)
β/°	99.5320(10)	99.944(3)
γ/°	90	93.655(3)
V/Å^3	2942.45(7)	1523.34(9)
Z	8	4
D_c/gcm^{-3}	1.69	1.710
F(000)	1520	792
μ(Cu K$_\alpha$)/mm^{-1}	1.404	1.487
T/K	150.00(10)	150
crystal size/mm	0.34× 0.30 × 0.18	0.14 x 0.11 x 0.07
index range	−16 → 16 −20 → 32 −9 → 9	−10 → 10 −13 → 13 −18 → 18
collected reflections	10721	25942
unique reflections	5169	9838
R_{int}	0.0337	0.0871
reflections with $I > 2\sigma(I)$	4642	8733
no. parameters	485	499
$R(F)$, $F > 2\sigma$(F)	0.0433	0.1016
$wR(F^2)$, $F > 2\sigma$(F)	0.1195	0.2655
$R(F)$, all data	0.0473	0.1072
$wR(F^2)$, all data	0.1245	0.2778
Δ_r (min., max.) eÅ^{-3}	−0.209, 0.336	−0.478, 0.586
CCDC deposition number	1451272	1451274

5. Hydrogen bond propensity calculations

Predictive models were prepared using Mercury 3.7.[14] The models used functional groups as displayed in Figure S23. For each model roughly 1300 structural entries were used as the data source for model fitting (the lowest value was 1155 and the highest was 1306 for the two polymorphs of (**thp**)·(**pFBA**) respectively. The preferred acceptance criterion for the propensity models was that each functional group is represented when possible by more than 400 structures. The minimum predictivity observed was 0.69.

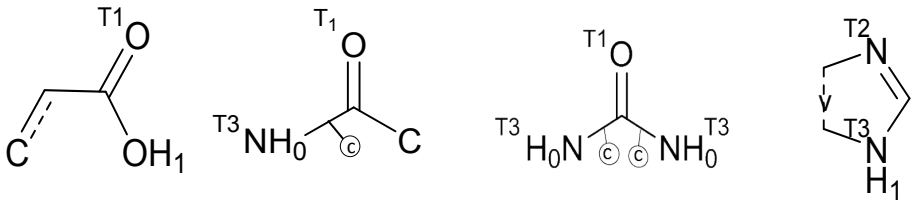
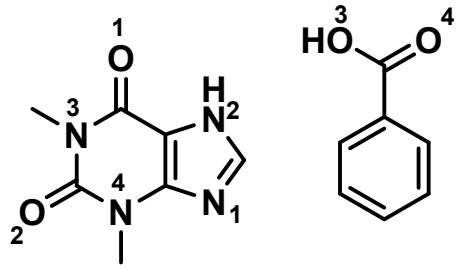


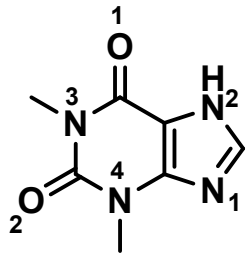
Figure S23. Functional groups used in all hydrogen bond propensity calculations.

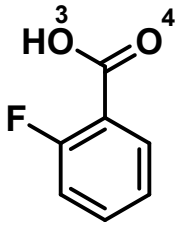
theophylline:benzoic acid



Donor	Acceptor	Competition	Donor steric density	Acceptor steric density	Donor aromaticity	Acceptor aromaticity	**Propensity**	Lower bound	Upper bound	Frequency	Observed Inter-?
N2	O1	3.33	49.07	44.52	0.29	0.29	**0.51**	0.43	0.58	39.4	
N2	O2	3.33	49.07	49.28	0.29	0.29	**0.47**	0.39	0.55	7.3	
O3	O1	3.33	28.95	44.52	0.29	0.78	**0.44**	0.37	0.51	24.5	yes
N2	N1	5.00	49.07	51.61	0.29	0.29	**0.43**	0.35	0.51	30.2	
N2	O4	3.33	49.07	30.04	0.78	0.29	**0.42**	0.34	0.51	26.9	yes
N2	O3	5.00	49.07	28.95	0.78	0.29	**0.41**	0.33	0.49	3.8	
O3	O2	3.33	28.95	49.28	0.29	0.78	**0.40**	0.33	0.48	3.5	
O3	N1	5.00	28.95	51.61	0.29	0.78	**0.36**	0.29	0.44	57.7	
O3	O4	3.33	28.95	30.04	0.78	0.78	**0.36**	0.29	0.43	29.8	
O3	O3	5.00	28.95	28.95	0.78	0.78	**0.35**	0.28	0.42	5.7	

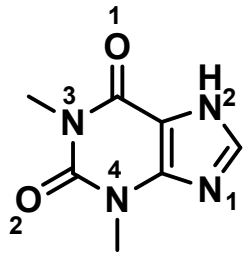
theophylline:2-fluorobenzoic acid

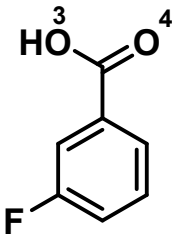




Donor	Acceptor	Competition	Donor steric density	Acceptor steric density	Donor aromaticity	Acceptor aromaticity	**Propensity**	Lower bound	Upper bound	Frequency	Observed Inter-?
N2	O1	3.33	45.14	42.96	0.29	0.29	**0.52**	0.44	0.59	39.4	
N2	O2	3.33	45.14	43.45	0.29	0.29	**0.51**	0.44	0.59	7.3	
N2	O4	3.33	45.14	30.19	0.70	0.29	**0.51**	0.43	0.59	26.9	yes
N2	O3	5.00	45.14	29.10	0.70	0.29	**0.50**	0.42	0.58	3.8	
N2	N1	5.00	45.14	45.78	0.29	0.29	**0.47**	0.40	0.55	30.7	
O3	O1	3.33	29.10	42.96	0.29	0.70	**0.44**	0.37	0.50	24.5	yes
O3	O2	3.33	29.10	43.45	0.29	0.70	**0.43**	0.37	0.50	3.5	
O3	O4	3.33	29.10	30.19	0.70	0.70	**0.43**	0.36	0.49	27.8	
O3	O3	5.00	29.10	29.10	0.70	0.70	**0.42**	0.36	0.49	6.5	
O3	N1	5.00	29.10	45.78	0.29	0.70	**0.39**	0.33	0.46	57.7	

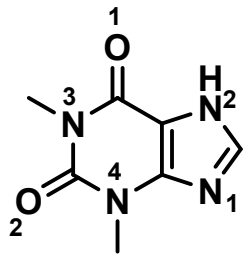
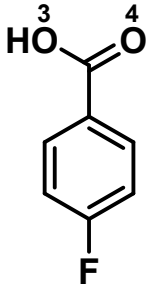
theophylline:3-fluorobenzoic acid





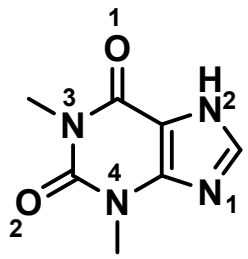
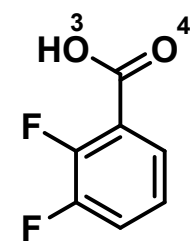
Donor	Acceptor	Competition	Donor steric density	Acceptor steric density	Donor aromaticity	Acceptor aromaticity	**Propensity**	Lower bound	Upper bound	Frequency	Observed Inter-?
N2	O1	3.33	45.14	42.96	0.29	0.29	**0.54**	0.47	0.61	39.4	
N2	O2	3.33	45.14	43.45	0.29	0.29	**0.54**	0.47	0.61	7.3	
N2	N1	5.00	45.14	45.78	0.29	0.29	**0.50**	0.42	0.57	30.2	
N2	O4	3.33	45.14	30.12	0.70	0.29	**0.47**	0.39	0.55	26.9	yes
N2	O3	5.00	45.14	29.03	0.70	0.29	**0.46**	0.38	0.54	3.8	
O3	O1	3.33	29.03	42.96	0.29	0.70	**0.45**	0.39	0.52	24.5	yes
O3	O2	3.33	29.03	43.45	0.29	0.70	**0.45**	0.38	0.52	3.5	
O3	N1	5.00	29.03	45.78	0.29	0.70	**0.41**	0.34	0.48	57.7	
O3	O4	3.33	29.03	30.12	0.70	0.70	**0.38**	0.32	0.45	26.7	
O3	O3	5.00	29.03	29.03	0.70	0.70	**0.37**	0.31	0.43	4.6	

theophylline:4-fluorobenzoic acid

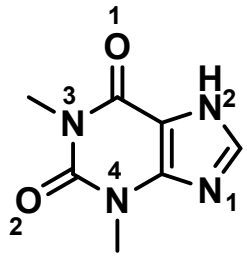
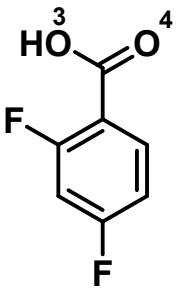
Donor	Acceptor	Competition	Donor steric density	Acceptor steric density	Donor aromaticity	Acceptor aromaticity	**Propensity**	Lower bound	Upper bound	Frequency	Observed Inter-?
N2	O1	3.33	45.14	42.96	0.29	0.29	**0.54**	0.47	0.61	37.8	
N2	O2	3.33	45.14	43.45	0.29	0.29	**0.53**	0.46	0.60	5.1	
N2	N1	5.00	45.14	45.78	0.29	0.29	**0.49**	0.42	0.57	30.7	
N2	O4	3.33	45.14	30.04	0.70	0.29	**0.46**	0.38	0.54	25.8	
O4	O1	3.33	28.95	42.96	0.29	0.70	**0.46**	0.39	0.52	24.7	
O3	O2	3.33	28.95	43.45	0.29	0.70	**0.45**	0.39	0.52	3.1	
N2	O3	5.00	45.14	28.95	0.70	0.29	**0.44**	0.37	0.52	3.2	
O3	N1	5.00	28.95	45.78	0.29	0.70	**0.41**	0.35	0.48	51.6	
O3	O4	3.33	28.95	30.04	0.70	0.70	**0.38**	0.32	0.44	25.5	
O3	O3	5.00	28.95	28.95	0.70	0.70	**0.36**	0.30	0.43	4.2	

theophylline:2,3-difluorobenzoic acid

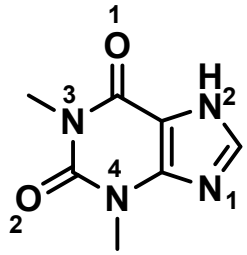
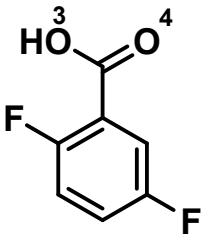
Donor	Acceptor	Competition	Donor steric density	Acceptor steric density	Donor aromaticity	Acceptor aromaticity	**Propensity**	Lower bound	Upper bound	Frequency	Observed Inter-?
N2	O1	3.33	45.14	42.96	0.29	0.29	**0.52**	0.45	0.59	36.8	
N2	O2	3.33	45.14	43.45	0.29	0.29	**0.52**	0.45	0.59	4.9	
N2	O4	3.33	45.14	30.27	0.64	0.29	**0.50**	0.43	0.58	24.2	
N2	O3	5.00	45.14	29.18	0.64	0.29	**0.49**	0.41	0.56	3.0	
N2	N1	5.00	45.14	45.78	0.29	0.29	**0.47**	0.40	0.55	30.5	
O3	O1	3.33	29.18	42.96	0.29	0.64	**0.45**	0.39	0.52	24.4	
O3	O2	3.33	29.18	43.45	0.29	0.64	**0.45**	0.39	0.51	3.0	
O3	O4	3.33	29.18	30.27	0.64	0.64	**0.43**	0.37	0.49	27.8	
O3	O3	5.00	29.18	29.18	0.64	0.64	**0.42**	0.36	0.48	5.8	
O3	N1	5.00	29.18	45.78	0.29	0.64	**0.41**	0.34	0.47	48.5	

theophylline:2,4-difluorobenzoic acid

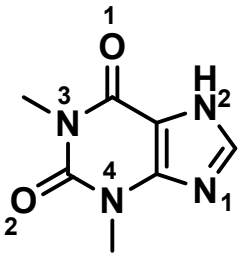
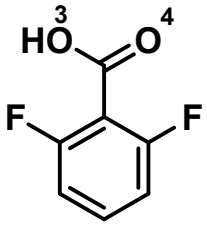
Donor	Acceptor	Competition	Donor steric density	Acceptor steric density	Donor aromaticity	Acceptor aromaticity	**Propensity**	Lower bound	Upper bound	Frequency	Observed Inter-?
N2	O1	3.33	45.14	42.96	0.29	0.29	**0.52**	0.45	0.59	35.4	
N2	O2	3.33	45.14	43.45	0.29	0.29	**0.51**	0.44	0.58	4.7	
N2	O4	3.33	45.14	30.19	0.64	0.29	**0.49**	0.42	0.57	22.2	
N2	O3	5.00	45.14	29.10	0.64	0.29	**0.48**	0.40	0.55	2.8	
N2	N1	5.00	45.14	45.78	0.29	0.29	**0.47**	0.40	0.54	30.3	
O3	O1	3.33	29.10	42.96	0.29	0.64	**0.45**	0.39	0.52	23.9	
O3	O2	3.33	29.10	43.45	0.29	0.64	**0.45**	0.38	0.51	2.9	
O3	O4	3.33	29.10	30.19	0.64	0.64	**0.43**	0.37	0.49	27.1	
O3	O3	5.00	29.10	29.10	0.64	0.64	**0.41**	0.35	0.48	5.8	
O3	N1	5.00	29.10	45.78	0.29	0.64	**0.40**	0.34	0.47	44.4	

theophylline:2,5-difluorobenzoic acid

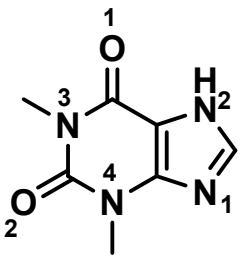
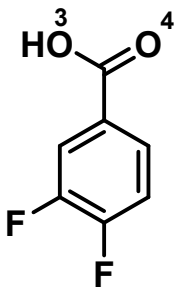
Donor	Acceptor	Competition	Donor steric density	Acceptor steric density	Donor aromaticity	Acceptor aromaticity	**Propensity**	Lower bound	Upper bound	Frequency	Observed Inter-?
N2	O4	3.33	45.14	30.27	0.64	0.29	**0.52**	0.44	0.60	28.6	yes
N2	O3	5.00	45.14	29.18	0.64	0.29	**0.51**	0.44	0.59	3.6	
N2	O1	3.33	45.14	42.96	0.29	0.29	**0.51**	0.44	0.58	39.4	
N2	O2	3.33	45.14	43.45	0.29	0.29	**0.51**	0.43	0.58	5.3	
N2	N1	5.00	45.14	45.78	0.29	0.29	**0.47**	0.39	0.54	30.8	
O3	O4	3.33	29.18	30.27	0.64	0.64	**0.45**	0.39	0.51	27.6	
O3	O3	5.00	29.18	29.18	0.64	0.64	**0.44**	0.38	0.50	6.7	
O3	O1	3.33	29.18	42.96	0.29	0.64	**0.44**	0.38	0.50	25.2	yes
O3	O2	3.33	29.18	43.45	0.29	0.64	**0.43**	0.37	0.50	3.2	
O3	N1	5.00	29.18	45.78	0.29	0.64	**0.40**	0.33	0.46	57.1	yes

theophylline:2,6-difluorobenzoic acid

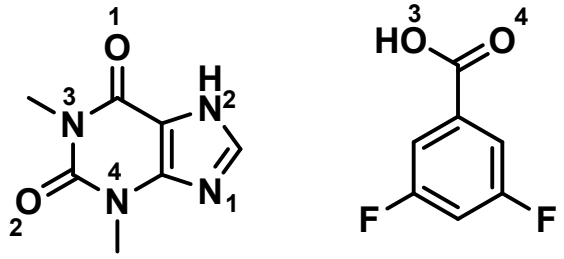
Donor	Acceptor	Competition	Donor steric density	Acceptor steric density	Donor aromaticity	Acceptor aromaticity	**Propensity**	Lower bound	Upper bound	Frequency	Observed Inter-?
N2	O4	3.33	45.14	30.34	0.64	0.29	**0.52**	0.45	0.60	27.6	
N2	O4	5.00	45.14	29.25	0.64	0.29	**0.52**	0.44	0.59	3.4	
N2	O1	3.33	45.14	42.96	0.29	0.29	**0.51**	0.44	0.58	38.9	
N2	O2	3.33	45.14	43.45	0.29	0.29	**0.51**	0.43	0.58	5.2	
N2	N12	5.00	45.14	45.78	0.29	0.29	**0.47**	0.39	0.54	30.8	
O3	O4	3.33	29.25	30.34	0.64	0.64	**0.45**	0.39	0.51	27.6	
O3	O3	5.00	29.25	29.25	0.64	0.64	**0.44**	0.38	0.50	6.7	
O3	O1	3.33	29.25	42.96	0.29	0.64	**0.43**	0.37	0.50	25.0	
O3	O2	3.33	29.25	43.45	0.29	0.64	**0.43**	0.37	0.49	3.2	
O3	N1	5.00	29.25	45.78	0.29	0.64	**0.39**	0.33	0.46	55.2	

theophylline:3,4-difluorobenzoic acid

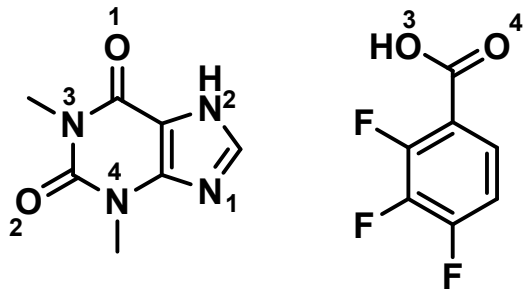
Donor	Acceptor	Competition	Donor steric density	Acceptor steric density	Donor aromaticity	Acceptor aromaticity	**Propensity**	Lower bound	Upper bound	Frequency	Observed Inter-?
N2	O1	3.33	45.14	42.96	0.29	0.29	**0.52**	0.45	0.59	35.9	yes
N2	O2	3.33	45.14	43.45	0.29	0.29	**0.52**	0.44	0.59	4.7	
N2	O4	3.33	45.14	30.12	0.64	0.29	**0.50**	0.42	0.57	22.9	
N2	O3	5.00	45.14	29.03	0.64	0.29	**0.48**	0.41	0.56	2.9	
N2	N1	5.00	45.14	45.78	0.29	0.29	**0.47**	0.40	0.55	30.3	
O3	O1	3.33	29.03	42.96	0.29	0.64	**0.46**	0.40	0.52	24.1	
O3	O2	3.33	29.03	43.45	0.29	0.64	**0.45**	0.39	0.52	2.9	
O3	O4	3.33	29.03	30.12	0.64	0.64	**0.44**	0.37	0.50	27.8	
O3	O3	5.00	29.03	29.03	0.64	0.64	**0.42**	0.36	0.48	6.5	
O3	N1	5.00	29.03	45.78	0.29	0.64	**0.41**	0.35	0.48	45.7	yes

theophylline:3,5-difluorobenzoic acid



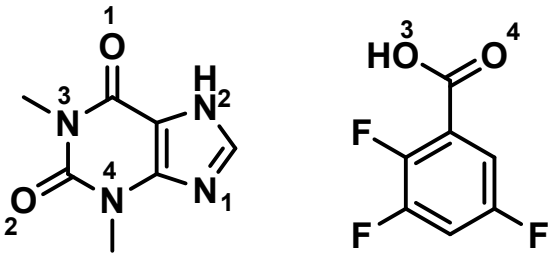
Donor	Acceptor	Competition	Donor steric density	Acceptor steric density	Donor aromaticity	Acceptor aromaticity	**Propensity**	Lower bound	Upper bound	Frequency	Observed Inter-?
N2	O1	3.33	45.14	42.96	0.29	0.29	**0.54**	0.47	0.61		yes
N2	O2	3.33	45.14	43.45	0.29	0.29	**0.54**	0.46	0.61		
N2	O4	3.33	45.14	30.20	0.64	0.29	**0.52**	0.44	0.59		
N2	O3	5.00	45.14	29.12	0.64	0.29	**0.50**	0.42	0.58		
N2	N1	5.00	45.14	45.78	0.29	0.29	**0.49**	0.42	0.57		
O3	O1	3.33	29.12	42.96	0.29	0.64	**0.48**	0.42	0.55		
O3	O2	3.33	29.12	43.45	0.29	0.64	**0.48**	0.41	0.54		yes
O3	O4	3.33	29.12	30.20	0.64	0.64	**0.46**	0.40	0.52		
O3	O3	5.00	29.12	29.12	0.64	0.64	**0.44**	0.38	0.51		
O3	N1	5.00	29.12	45.78	0.29	0.64	**0.43**	0.37	0.50		

theophylline:2,3,4-trifluorobenzoic acid



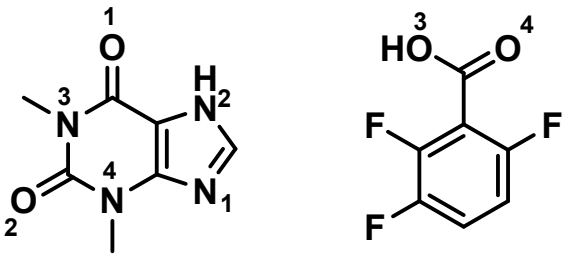
Donor	Acceptor	Competition	Donor steric density	Acceptor steric density	Donor aromaticity	Acceptor aromaticity	**Propensity**	Lower bound	Upper bound	Frequency	Observed Inter-?
N2	O1	3.33	45.14	30.27	0.58	0.29	**0.55**	0.47	0.62	28.6	yes
N2	O2	5.00	45.14	29.18	0.58	0.29	**0.54**	0.47	0.62	3.6	
N2	O4	3.33	45.14	42.96	0.29	0.29	**0.52**	0.44	0.59	39.4	
N2	O3	3.33	45.14	43.45	0.29	0.29	**0.51**	0.44	0.59	5.3	
O3	O1	3.33	29.18	30.27	0.58	0.58	**0.48**	0.42	0.54	27.6	
N2	N1	5.00	45.14	45.78	0.29	0.29	**0.47**	0.40	0.55	30.8	
O2	O2	5.00	29.18	29.18	0.58	0.58	**0.47**	0.41	0.53	6.7	
O3	O4	3.33	29.18	42.96	0.29	0.58	**0.45**	0.38	0.51	25.2	
O3	O3	3.33	29.18	43.45	0.29	0.58	**0.44**	0.38	0.50	3.2	
O3	N1	5.00	29.18	45.78	0.29	0.58	**0.40**	0.34	0.47	57.1	yes

theophylline:2,3,5-trifluorobenzoic acid



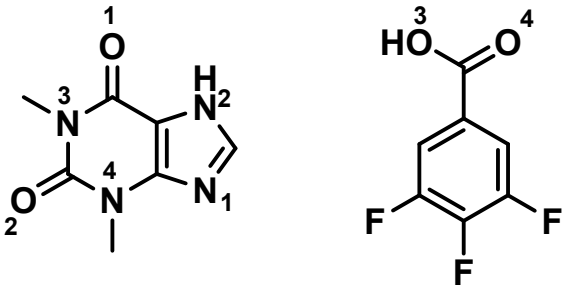
Donor	Acceptor	Competition	Donor steric density	Acceptor steric density	Donor aromaticity	Acceptor aromaticity	**Propensity**	Lower bound	Upper bound	Frequency	Observed Inter-?
N2	O4	3.33	45.14	30.35	0.58	0.29	**0.54**	0.47	0.62	26.9	
N2	O3	5.00	45.14	29.27	0.58	0.29	**0.54**	0.46	0.61	3.8	
N2	O1	3.33	45.14	42.96	0.29	0.29	**0.52**	0.44	0.59	39.4	yes
N2	O2	3.33	45.14	43.45	0.29	0.29	**0.51**	0.44	0.59	7.3	
O3	O4	3.33	29.27	30.35	0.58	0.58	**0.47**	0.41	0.53	27.8	
N2	N1	5.00	45.14	45.78	0.29	0.29	**0.47**	0.40	0.55	30.7	
O3	O3	5.00	29.27	29.27	0.58	0.58	**0.47**	0.41	0.53	6.5	
O3	O1	3.33	29.27	42.96	0.29	0.58	**0.45**	0.38	0.51	24.5	
O3	O2	3.33	29.27	43.45	0.29	0.58	**0.44**	0.38	0.51	3.5	
O3	N1	5.00	29.27	45.78	0.29	0.58	**0.40**	0.34	0.47	57.7	yes

theophylline:2,3,6-trifluorobenzoic acid



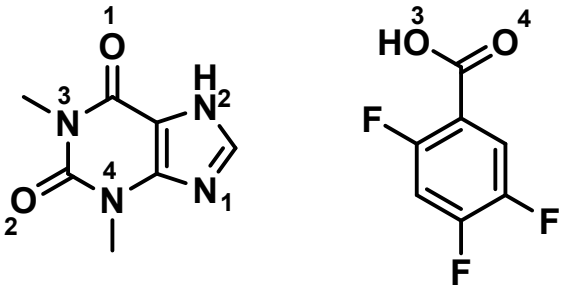
Donor	Acceptor	Competition	Donor steric density	Acceptor steric density	Donor aromaticity	Acceptor aromaticity	**Propensity**	Lower bound	Upper bound	Frequency	Observed Inter-?
N2	O4	3.33	45.14	30.42	0.58	0.29	**0.54**	0.46	0.62		
N2	O3	5.00	45.14	29.33	0.58	0.29	**0.54**	0.46	0.61		
N2	O1	3.33	45.14	42.96	0.29	0.29	**0.52**	0.44	0.59		yes
N2	O2	3.33	45.14	43.45	0.29	0.29	**0.51**	0.44	0.59		
N2	N1	5.00	45.14	45.78	0.29	0.29	**0.47**	0.40	0.55		
O3	O4	3.33	29.33	30.42	0.58	0.58	**0.47**	0.41	0.53		
O3	O3	5.00	29.33	29.33	0.58	0.58	**0.47**	0.41	0.53		
O3	O1	3.33	29.33	42.96	0.29	0.58	**0.45**	0.39	0.51		
O3	O2	3.33	29.33	43.45	0.29	0.58	**0.44**	0.38	0.51		
O3	N1	5.00	29.33	45.78	0.29	0.58	**0.40**	0.34	0.47		yes

theophylline:3,4,5-trifluorobenzoic acid



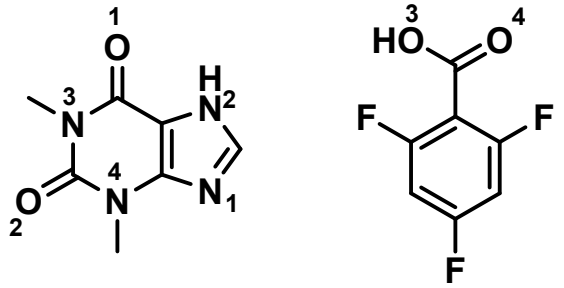
Donor	Acceptor	competition	Donor steric density	Acceptor steric density	Donor aromaticity	Acceptor aromaticity	**Propensity**	Lower bound	Upper bound	Frequency	Observed Inter-?
N2	O4	3.33	45.14	30.42	0.58	0.29	**0.54**	0.47	0.62		
N2	O1	3.33	45.14	42.96	0.29	0.29	**0.54**	0.47	0.61		yes
N2	O2	3.33	45.14	43.45	0.29	0.29	**0.53**	0.46	0.60		
N2	O3	5.00	45.14	29.33	0.58	0.29	**0.53**	0.45	0.60		
N2	N1	5.00	45.14	45.78	0.29	0.29	**0.49**	0.42	0.56		
O3	O4	3.33	29.33	30.42	0.58	0.58	**0.47**	0.41	0.53		
O3	O1	3.33	29.33	42.96	0.29	0.58	**0.46**	0.40	0.52		
O3	O2	3.33	29.33	43.45	0.29	0.58	**0.46**	0.40	0.52		
O3	O3	5.00	29.33	29.33	0.58	0.58	**0.45**	0.39	0.51		
O3	N1	5.00	29.33	45.78	0.29	0.58	**0.41**	0.35	0.48		yes

theophylline:2,4,5-trifluorobenzoic acid



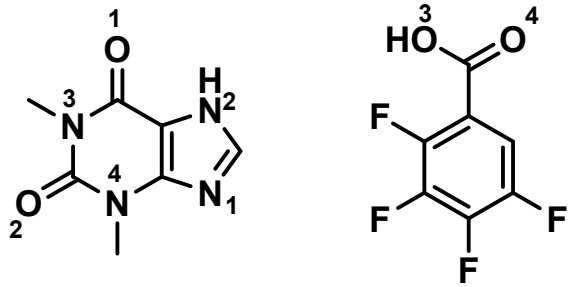
Donor	Acceptor	Competition	Donor steric density	Acceptor steric density	Donor aromaticity	Acceptor aromaticity	**Propensity**	Lower bound	Upper bound	Frequency	Observed Inter-?
N2	O4	3.33	45.14	30.27	0.58	0.29	**0.55**	0.47	0.62	26.9	yes
N2	O1	3.33	45.14	42.96	0.29	0.29	**0.54**	0.47	0.61	39.4	yes
N2	O2	3.33	45.14	43.45	0.29	0.29	**0.54**	0.47	0.61	7.3	
N2	O3	5.00	45.14	29.18	0.58	0.29	**0.53**	0.46	0.60	3.8	
N2	N1	5.00	45.14	45.78	0.29	0.29	**0.49**	0.42	0.57	30.2	
O3	O4	3.33	29.18	30.27	0.58	0.58	**0.47**	0.41	0.53	24.1	
O3	O1	3.33	29.18	42.96	0.29	0.58	**0.47**	0.41	0.53	24.5	yes
O3	O2	3.33	29.18	43.45	0.29	0.58	**0.46**	0.40	0.53	3.5	
O3	O3	5.00	29.18	29.18	0.58	0.58	**0.45**	0.40	0.51	5.4	
O3	N1	5.00	29.18	45.78	0.29	0.58	**0.42**	0.36	0.48	57.7	yes

theophylline:2,4,6-trifluorobenzoic acid



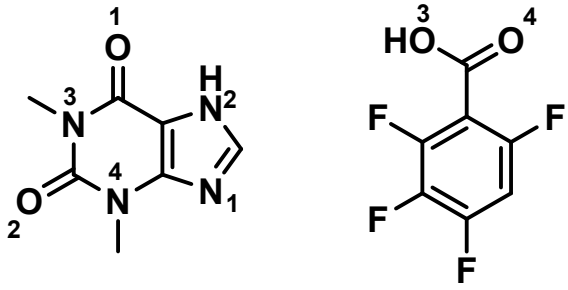
Donor	Acceptor	Competition	Donor steric density	Acceptor steric density	Donor aromaticity	Acceptor aromaticity	**Propensity**	Lower bound	Upper bound	Frequency	Observed Inter-?
N2	O1	3.33	45.14	42.96	0.29	0.29	**0.54**	0.47	0.61	39.4	yes
N2	O4	3.33	45.14	30.34	0.58	0.29	**0.54**	0.47	0.61	26.9	
N2	O2	3.33	45.14	43.45	0.29	0.29	**0.54**	0.47	0.61	7.3	yes
N2	O3	5.00	45.14	29.25	0.58	0.29	**0.53**	0.45	0.60	3.8	
N2	N1	5.00	45.14	45.78	0.29	0.29	**0.49**	0.42	0.57	30.2	
O3	O1	3.33	29.25	42.96	0.29	0.58	**0.46**	0.40	0.53	24.5	
O3	O4	3.33	29.25	30.34	0.58	0.58	**0.46**	0.40	0.52	25.0	
O3	O2	3.33	29.25	43.45	0.29	0.58	**0.46**	0.40	0.52	3.5	
O3	O3	5.00	29.25	29.25	0.58	0.58	**0.44**	0.39	0.50	5.2	
O3	N1	5.00	29.25	45.78	0.29	0.58	**0.41**	0.35	0.48	57.7	yes

theophylline:2,3,4,5-tetrafluorobenzoic acid



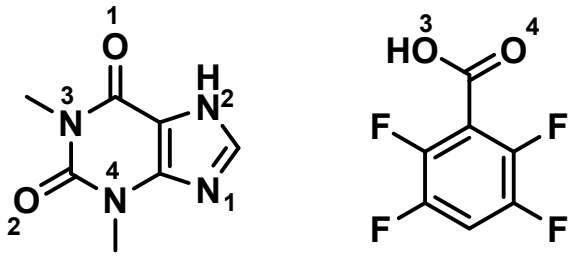
Donor	Acceptor	Competition	Donor steric density	Acceptor steric density	Donor aromaticity	Acceptor aromaticity	**Propensity**	Lower bound	Upper bound	Frequency	Observed Inter-?
N2	O4	3.33	45.14	30.35	0.54	0.29	**0.55**	0.48	0.62	28.6	yes
N2	O3	5.00	45.14	29.27	0.54	0.29	**0.54**	0.47	0.62	3.6	
N2	O1	3.33	45.14	42.96	0.29	0.29	**0.51**	0.44	0.59	39.4	
N2	O2	3.33	45.14	43.45	0.29	0.29	**0.51**	0.44	0.58	5.3	
O3	O4	3.33	29.27	30.35	0.54	0.54	**0.49**	0.43	0.54	27.6	
O3	O3	5.00	29.27	29.27	0.54	0.54	**0.48**	0.43	0.54	6.7	
N2	N1	5.00	45.14	45.78	0.29	0.29	**0.47**	0.40	0.54	30.8	
O3	O1	3.33	29.27	42.96	0.29	0.54	**0.45**	0.39	0.51	25.2	
O3	O2	3.33	29.27	43.45	0.29	0.54	**0.45**	0.39	0.51	3.2	
O3	N1	5.00	29.27	45.78	0.29	0.54	**0.41**	0.35	0.47	57.1	yes

theophylline-2,3,4,6-tetrafluorobenzoic acid



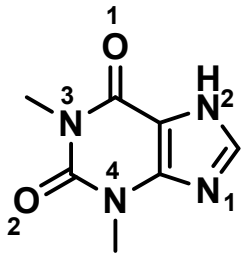
Donor	Acceptor	Competition	Donor steric density	Acceptor steric density	Donor aromaticity	Acceptor aromaticity	**Propensity**	Lower bound	Upper bound	Frequency	Observed Inter-?
N2	O4	3.33	45.14	30.42	0.54	0.29	**0.55**	0.48	0.62	28.6	
N2	O3	5.00	45.14	29.33	0.54	0.29	**0.55**	0.47	0.62	3.6	
N2	O1	3.33	45.14	42.96	0.29	0.29	**0.51**	0.44	0.58	39.4	yes
N2	O2	3.33	45.14	43.45	0.29	0.29	**0.51**	0.44	0.58	5.3	
O4	O4	3.33	29.33	30.42	0.54	0.54	**0.49**	0.43	0.54	27.6	
O3	O3	5.00	29.33	29.33	0.54	0.54	**0.48**	0.42	0.54	6.7	
N2	N1	5.00	45.14	45.78	0.29	0.29	**0.47**	0.40	0.54	30.8	
O3	O1	3.33	29.33	42.96	0.29	0.54	**0.45**	0.39	0.51	25.2	
O3	O2	3.33	29.33	43.45	0.29	0.54	**0.44**	0.38	0.50	3.2	
O3	N1	5.00	29.33	45.78	0.29	0.54	**0.40**	0.35	0.47	57.1	yes

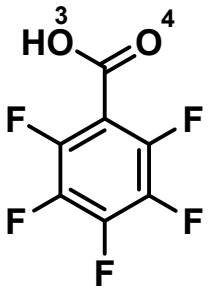
theophylline-2,3,5,6-tetrafluorobenzoic acid



Donor	Acceptor	Competition	Donor steric density	Acceptor steric density	Donor aromaticity	Acceptor aromaticity	**Propensity**	Lower bound	Upper bound	Frequency	Observed Inter-?
N2	O4	3.33	45.14	30.50	0.54	0.29	**0.55**	0.48	0.62	28.6	
N2	O3	5.00	45.14	29.42	0.54	0.29	**0.54**	0.47	0.62	3.6	
N2	O1	3.33	45.14	42.96	0.29	0.29	**0.51**	0.44	0.58	39.4	yes
N2	O2	3.33	45.14	43.45	0.29	0.29	**0.51**	0.44	0.58	5.3	
O3	O4	3.33	29.42	30.50	0.54	0.54	**0.49**	0.43	0.54	27.6	
O3	O3	5.00	29.42	29.42	0.54	0.54	**0.48**	0.42	0.54	6.7	
N2	N1	5.00	45.14	45.78	0.29	0.29	**0.47**	0.39	0.54	30.8	
O3	O1	3.33	29.42	42.96	0.29	0.54	**0.45**	0.39	0.51	25.2	
O3	O2	3.33	29.42	43.45	0.29	0.54	**0.44**	0.39	0.51	3.2	
O3	N1	5.00	29.42	45.78	0.29	0.54	**0.41**	0.35	0.47	57.1	yes

theophylline:2,3,4,5,6-pentafluorobenzoic acid





Donor	Acceptor	Competition	Donor steric density	Acceptor steric density	Donor aromaticity	Acceptor aromaticity	**Propensity**	Lower bound	Upper bound	Frequency	Observed Inter-?
O3	N1	5.00	29.42	45.78	0.29	0.50	**0.52**	0.43	0.60	57.1	yes
O3	O4	3.33	29.42	30.50	0.50	0.50	**0.48**	0.41	0.54	27.6	
O3	O1	3.33	29.42	42.96	0.29	0.50	**0.47**	0.39	0.56	25.2	
N2	N1	5.00	45.14	45.78	0.29	0.29	**0.40**	0.32	0.50	30.8	
N2	O4	3.33	45.14	30.50	0.50	0.29	**0.37**	0.29	0.45	28.6	
N2	O1	3.33	45.14	42.96	0.29	0.29	**0.36**	0.27	0.45	39.4	yes
O3	O2	3.33	29.42	43.45	0.29	0.50	**0.26**	0.20	0.34	3.2	
N2	O2	3.33	45.14	43.45	0.29	0.29	**0.18**	0.13	0.26	5.3	yes
O3	O3	5.00	29.42	29.42	0.50	0.50	**0.09**	0.06	0.12	6.7	
N2	O3	5.00	45.14	29.42	0.50	0.29	**0.06**	0.04	0.09	3.6	

6. Molecular electrostatic potential calculations

Electrostatic potential surfaces (0.002 e/au isosurface) of benzoic acid and all fluorobenzoic acids were calculated with the *Spartan'14* program[15] using the hybrid density functional B3LYP level of theory and the 6-31G* basis set in vacuum. Table S3 features the calculated electrostatic potential, the ΔpK_a values of the cocrystal formers[16] and the observed synthons in the cocrystals composed of the respective **FBA**s. No correlation could be found between the electrostatic potential values and the observed supramolecular synthon motifs.

Table S3. Calculated electrostatic potentials (expressed in kJ mol^{-1}) of acceptor and donor atoms of **thp** and **FBA**s.

Compound	O atom	H atom	(C=)O1	(C=)O2	(N-)H	pK_a*	ΔpK_a	Observed synthon in cocrystal
thp	n/a	n/a	−173.76	−159.7	262.45	1.64 ± 0.70	n/a	n/a
BA	−161.76	243.62	n/a	n/a	n/a	4.20±0.10	−2.56± 0.70	**B**
2FBA	−159.31	235.73	n/a	n/a	n/a	3.27±0.10	−1.63 ± 0.70	**B**
3FBA	−153.80	252.58	n/a	n/a	n/a	3.86±0.10	−2.22 ± 0.70	**B**
4FBA	−154.40	263.4	n/a	n/a	n/a	4.14±0.10	−2.5 ± 0.70	n/a
23diFBA	−149.71	242.34	n/a	n/a	n/a	2.93±0.10	−1.29 ± 0.70	n/a
24diFBA	−195.06	244.3	n/a	n/a	n/a	3.21±0.10	−1.57 ± 0.70	n/a
25diFBA	−184.79	262.74	n/a	n/a	n/a	2.93±0.10	−1.29 ± 0.70	**A, B**
26diFBA	−173.50	244.02	n/a	n/a	n/a	2.34±0.10	−0.7 ± 0.70	n/a
34diFBA	−146.23	253.42	n/a	n/a	n/a	3.80±0.10	−2.16 ± 0.70	**A, A**
35diFBA	−143.70	255.74	n/a	n/a	n/a	3.52±0.10	−1.88 ± 0.70	**C**
234triFBA	−174.87	265.09	n/a	n/a	n/a	2.87±0.10	−1.23 ± 0.70	**A**
235triFBA	−176.32	247.38	n/a	n/a	n/a	2.59±0.10	−0.95 ± 0.70	**A**
236triFBA	−162.95	264.33	n/a	n/a	n/a	2.00±0.10	−0.36 ± 0.70	**A**
245triFBA	−136.64	282.86	n/a	n/a	n/a	2.87±0.10	−1.23 ± 0.70	**A, B**
246triFBA	−177.42	262.02	n/a	n/a	n/a	2.28±0.10	−0.64 ± 0.70	**A, A**
345triFBA	−165.53	245.96	n/a	n/a	n/a	3.46±0.10	−1.79 ± 0.70	**A**
2345tetFBA	−166.57	260.41	n/a	n/a	n/a	1.60±0.10	0.04 ± 0.70	**A**
2356tetFBA	−152.78	262.55	n/a	n/a	n/a	1.60±0.10	0.04 ± 0.70	**A**
2456tetFBA	−150.43	257.57	n/a	n/a	n/a	1.60±0.10	0.04 ± 0.70	**A**
23456pFBA	−143.97	266.14	n/a	n/a	n/a	1.60±0.10	0.04 ± 0.70	**A, A**

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