Supporting Information

Cocrystals, Salts and Supramolecular Gels of Non-Steroidal Anti-Inflammatory Drug Niflumic Acid

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FT-IR Spectroscopy

IR spectroscopy is a simple and reliable technique for identifying functional groups, type of bond and also it gives preliminary information about the structure of the compound. Changes in the wave numbers of the products from the starting materials are indicative for the formation of new solids. Generally C=O (carboxylic acid) stretch absorbs strongly at 1700 cm^{-1} and a weaker stretch at 1200 cm^{-1} for C–O Stretch and carboxylate group absorbs strongly at 1600 cm^{-1} (asym). In NFA–PIP, NFA-BZA, and NFA-TYA salts, the stretching frequencies observed at 1592, 1604, 1611 cm^{-1} (asym) clearly indicate formation of salts. In NFA–BSA salt the proton transfer from the sulfonic acid to NFA leads to salt formation and its stretching frequency at 1701.2 cm^{-1} confirms the presence of carboxylic acid group. In NFA–CPR and NFA–2HP carbonyl (C=O) stretching frequencies were observed in 1650–1655 cm^{-1} range indicates no proton transfer from NFA, consistent with a cocrystal. FT-IR spectra are displayed in Figure S1, and the frequencies are listed in Table S1.

Table S1 Stretching and bending frequency in novel NFA crystalline forms.

Solid forms	N–H (Stretch) cm^{-1}	Carbonyl C=O (Stretch) cm^{-1}	Carboxylate (asym)	C–O (Stretch) (asym) cm^{-1}	C–O (Stretch) (sym) cm^{-1}
NFA	3317	1667.9	--	1448.5	1286.8
NFA–CPR	3415.7	1650.3	--	1445.5	1245.5
NFA–2HP	3434.3	1652.5	--	1446.2	1257.6
NFA–PIP	3449.4	----	1592.2	1453.7	1274.2
NFA–BSA	3417.7	1701.2	---	1447.2	1286.9
NFA–BZA II	3429.1	-----	1604.6	1455.7	1282.6
NFA–TYA	3452.7	-----	1611.6	1459.4	1282.8

Powder XRD Analysis

Powder XRD is a nondestructive analytical tool for identifying phase purity and identification of new solid forms. Change in the powder pattern of resulting ground material from the starting material indicates the formation of new solid phase. In this work, we prepared the seven novel solid forms of NFA such as two cocrystals with CPR, 2HP and five salts with PIP, BSA, BZA (NFA−BZA I and II) and TYA. New crystalline forms of the bulk materials matched with the X-ray crystal structures except for NFA−BZA I (Figure S2).

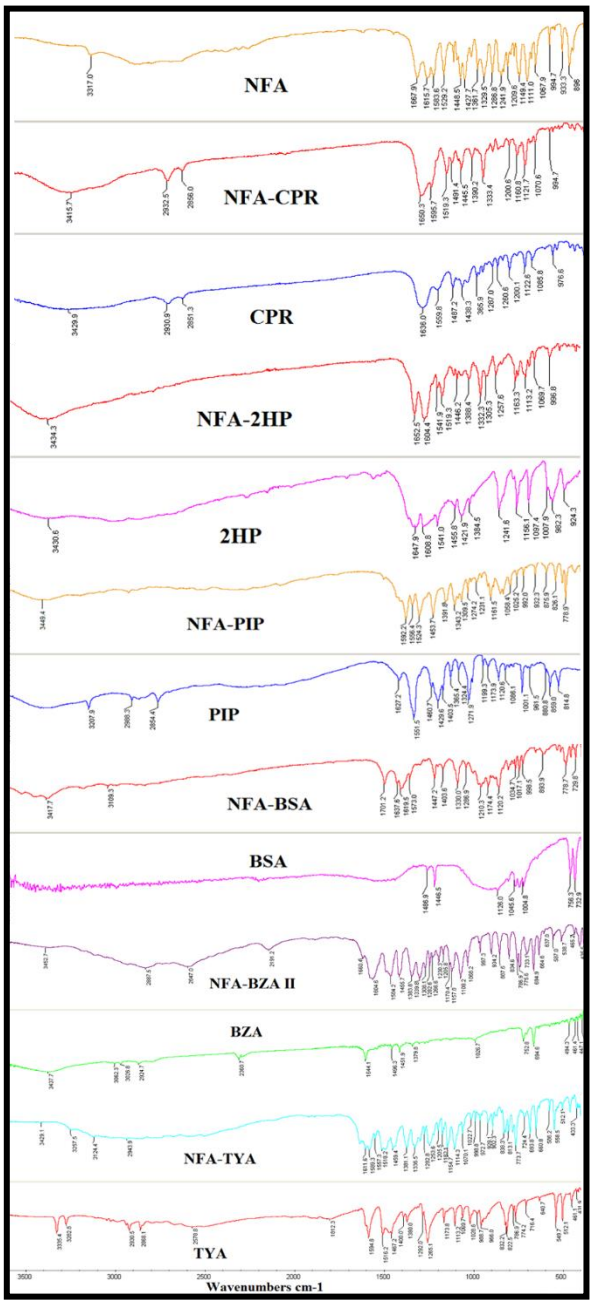


Figure S1 Vibrational IR bands for functional groups in NFA solids.

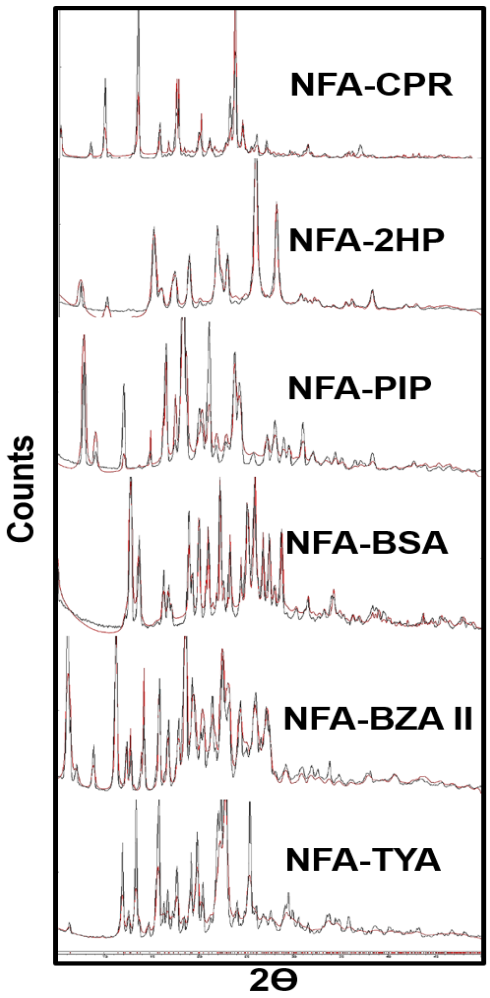
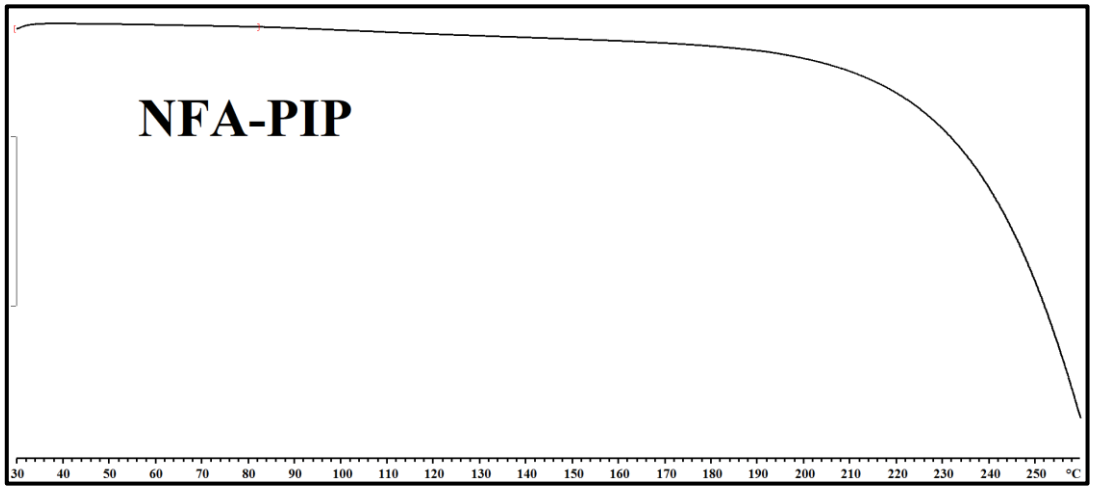
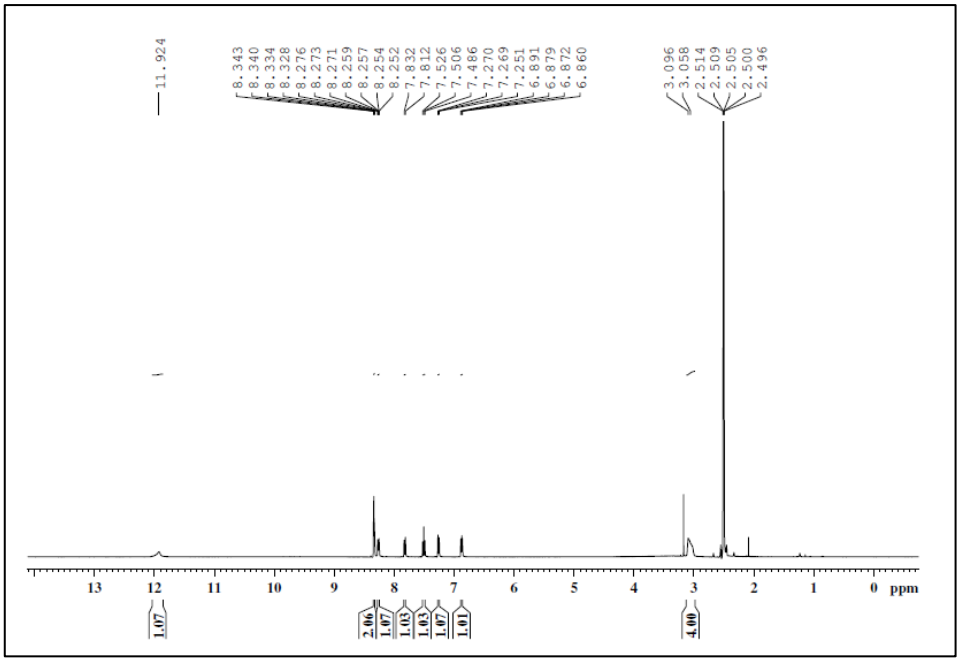


Figure S2 Overlay of experimental powder XRD pattern (black) with the calculated powder pattern from the X-ray crystal structure (red).



(a)



(b)

Figure S3 (a) TGA for NFA-PIP showing no weight loss during heating. (b) ^{1}H NMR spectrum of a single crystal of NFA-PIP does not show any solvent peaks. This confirms the absence of disordered solvent molecules in the voids and hints toward self-inclusion of the cocrystal molecules in random orientations.

Overlay:

From the chemical structure of NFA (Scheme 1), the molecule has two freely rotatable phenyl rings connected to a secondary amine nitrogen (N2) atom. In the reported guest free form, the acid group and the CF_3 groups are arranged opposite to each other, the dihedral angle between two phenyl rings is 8.66°. In the cocrystals of NFA (NFA–CPR and NFA–2HP) both the acid and CF_3 groups are on the same side due to the rotation about the C–N bond (Figure S4), and the angle between phenyl rings is 6.56° and 3.40°. In NFA-BSA, and NFA-BZA II salt structures there is significant variation in dihedral angles at 51.77, 23.43 and 21.71°. In NFA-PIP, NFA-BZA I and NFA-TYA the corresponding dihedral angles are 11.54, 6.49 and 6.88° (Table S2).

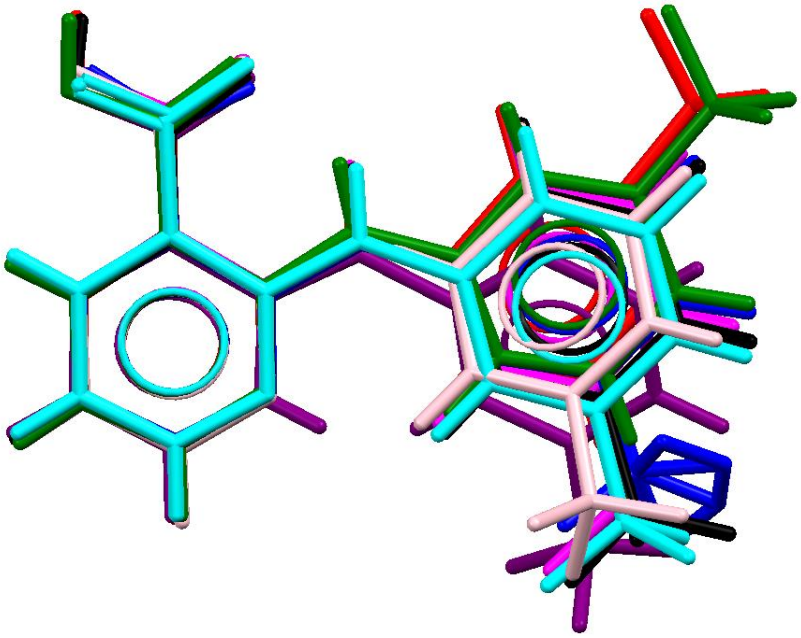
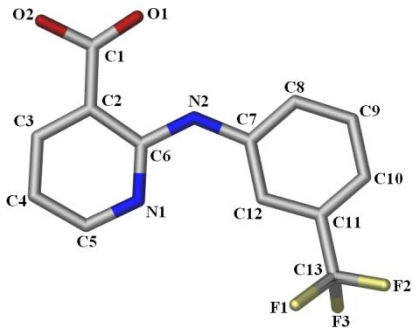


Figure S4 Overlay diagram of NFA in cocrystals and salts (NFA = black, NFA-CPR = red, NFA-2HP = green, NFA-PIP = blue, NFA-BSA = purple, NFA-BZA I = magenta, NFA-BZA II = pink, NFA-TYA = cyan.

Table S2 Torsion angles in NFA salts and cocrystals (as defined in Figure S3 and S4).

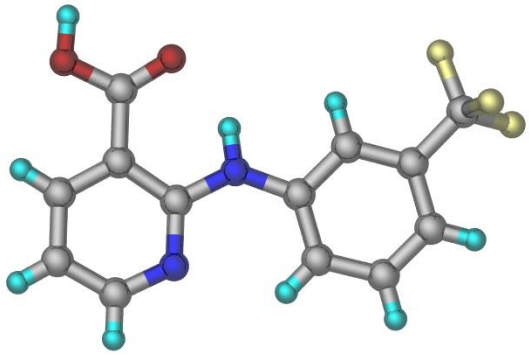
S. No.	Compound	τ_1	τ_2	τ_3	τ_4
1	NFA	176.99	–4.62	174.17	–6.29
2	NFA–CPR	4.45	–175.56	172.10	–8.0
3	NFA–2HP	4.51	–175.09	176.58	–3.51
4	NFA–PIP	179.09	–1.95	168.87	–10.41
5	NFA–BSA	–133.49	50.5	–174.44	7.45
6	NFA–BZA I	–174.09	5.48	174.70	–5.3
7	NFA–BZA II	–173.62	9.25	-165.37	14.41
8	NFA-TYA	173.23	-6.86	-179.56	–0.55



τ_1= C6–N2–C7–C8, τ_2= C6–N2–C7–C12

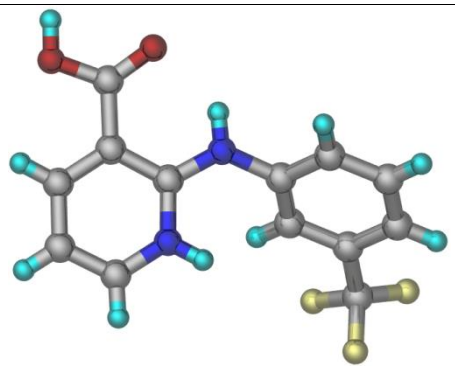
τ_3= C7–N2–C6–C2 τ_4= C7–N2–C6–N1

(a)



Conformation of NFA in CPR and 2HP cocrystals

(b)



Conformation of NFA in PIP, BSA and BZA salts

(c)

Figure S5 Definition of dihedral angles and NFA and conformation in cocrystals (b) and salts (c).

Table S3 Crystallographic Information.

	NFA−CPR Cocrystal (1:1)	**NFA−2HP Cocrystal (1:1)**	**NFA−PIP Salt (2:1)**	**NFA−BSA Salt (1:1)**	**NFA−BZA I Salt (1:1)**
Empirical Formula	$C_{13}H_9F_3N_2O_2$. $C_6H_{11}NO$	$C_{13}H_9F_3N_2O_2$. C_5H_5NO	$C_{13}H_8F_3N_2O_2$. 0.5 ($C_4H_{12}N_2$)	$C_{13}H_{10}F_3N_2O_2$. $C_6H_5O_3S$	C_{13} H_8 F_3 N_2 O_2, C_7 H_{10} N
Formula weight	395.38	377.32	325.59	440.39	389.37
Crystal system	Triclinic	Triclinic	Trigonal	Triclinic	Triclinic
Space group	*P*-1	*P*-1	*R*-3	*P*-1	*P*-1
T (K)	298	298	298	298	298
***a* (Å)**	5.4509(4)	7.207(3)	38.266(12)	7.8886(18)	4.7308(8)
***b* (Å)**	10.4784(10)	10.314(4)	38.266(12)	8.0739(18)	10.9132(18)
***c* (Å)**	16.8900(18)	11.889(5)	5.9992(2)	16.868(4)	18.450(3)
***α* (deg)**	89.604(8)	100.341(6)	90.00	84.051(4)	75.255(13)

***B* (deg)**	85.508(7)	101.773(6)	90.00	87.491(4)	85.065(13)
***γ* (deg)**	86.697(7)	90.484(7)	120.00	61.696(3)	82.971(14)
***V* (Å^3)**	960.14(15)	850.2(6)	7607.6(5)	940.8(4)	912.8(3)
***D*$_{calcd}$ (g cm^{-3})**	1.354	1.474	1.278	1.555	1.417
***μ* (mm^{-1})**	0.967	0.124	0.941	0.237	0.971
***θ* range**	2.62 to 66.60	1.78 to 26.59	4 to 66.59	1.21 to 26.43	4.33 to 66.55
Z/Z^1	2/1	2/1	18/1	2/1	2/1
Range *h*	-4 to 6	−9 to 8	−34 to 45	−9 to 9	-4 to 5
Range *k*	-12 to 12	−12 to 12	−26 to 45	−10 to 10	−12 to 12
Range *l*	-20 to 20	−14 to 14	−7 to 1	−21 to 20	−21 to 21
Reflections collected	6049	9151	5444	10073	6294
Total reflections	3399	3485	2993	3822	3217
Observed reflections	2220	2738	2359	3117	1174
***R*$_1$ [*I* > 2 σ (*I*)]**	0.0747	0.0496	0.785	0.0546	0.0736
***w*R$_2$ (all)**	0.2577	0.1444	0.2597	0.1617	0.2137
Goodness-of-fit	1.045	1.064	1.08	1.055	0.975
X-ray Diffracto meter	OXFORD Agilent	Bruker Smart CCD	OXFORD Agilent	Bruker Smart CCD	OXFORD Agilent

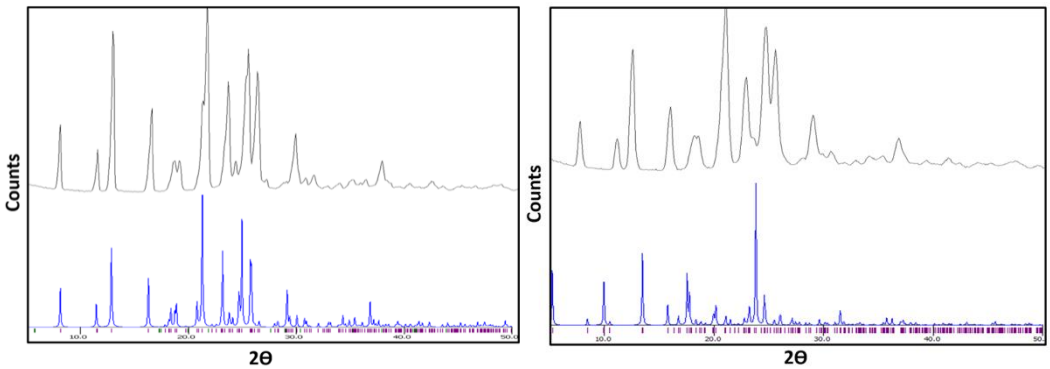
	NFA−BZA II Salt (1:1)	**NFA−TYA (1:1)**
Empirical Formula	C_{13} H_8 F_3 N_2 O_2, C_7 H_{10} N	$C_{13}H_9F_3N_2O_2$. $C_8H_{12}NO$
Formula weight	389.37	419.40
Crystal system	orthorhombic	monoclinic
Space group	*Pca*2$_1$	*P*2$_1$/*c*
T (K)	298	298
***a* (Å)**	27.525(3)	13.806(3)
***b* (Å)**	4.7904(5)	8.090(2)
***c* (Å)**	28.447(4)	17.873(4)
***α* (deg)**	90	90.00
***B* (deg)**	90	93.66(3)

γ (deg)	90	90.00
V (Å^3)	3751.0(7)	1992.3(8)
D_{calcd} (g cm^{-3})	1.379	1.398
μ (mm^{-1})	0.111	1.398
θ range	2.059 to 25.017	2.284 to 25.028
Z/Z^1	8/1	4/1
Range *h*	−32 to 30	−16 to 16
Range *k	−5 to 5	−9 to 9
Range *l*	−33 to 29	−21 to 21
Reflections collected	19949	25076
Total reflections	6435	3519
Observed reflections	4700	2674
R_1 [$I > 2\sigma(I)$]	0.0534	0.0579
wR_2 (all)	0.1481	0.1718
Goodness-of-fit	1.078	1.064
X-ray Diffractometer	Bruker D8 Quest	Bruker D8 Quest

Table S4 Hydrogen bond metrics table (X–H distance is neutron normalized).

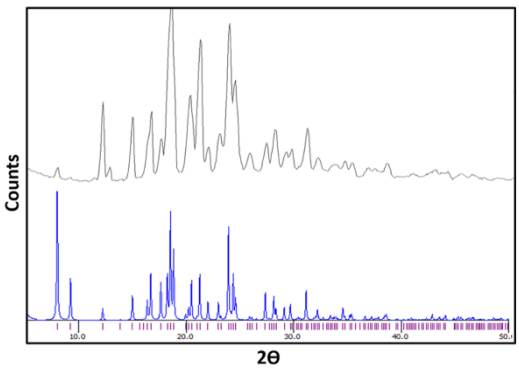
Cocrystal/Salt	Interaction	D–H/Å	H···A/Å	D···A/Å	∠D–H···A/Å	Symmetry code
NFA–CPR	O2–H2A···O3	0.87	1.75	2.597	165	2–x,1-y,–z
	N2–H2B···O1	0.86	1.94	2.6640	140	intramolecular
	N3–H3A···O3	0.84	2.23	3.0670	168	2–x,1–y, –z
	C10–H10···F3	0.93	2.59	3.512	171	x,y,z
NFA–2HP	O2–H2A···O3	0.93	1.64	2.5691(11)	176	1+x,1+y,z
	N2–H2B···O1	0.89	1.86	2.6578(2)	148	intramolecular
	N3–H3A···O3	0.95	1.90	2.8485(2)	176	–x, –y,1–z
	C14–H14···O1	0.93	2.39	3.1756(2)	142	1–x,1–y,1–z
NFA–PIP	N2–H2B···O1	0.86	1.93	2.656(4)	141	intramolecular
	N3–H3A···O1	0.89	1.80	2.6565(3)	162	-x+y,-x,z
	N3–H3B···O2	0.89	1.82	2.7014(3)	172	-x+y,-x,-1+z
	C14–H14A···N1	0.97	2.45	3.3753(1)	159	2/3-y,1/3+x-y,-2/3+z

NFA–BSA	N1–H1A···O5	0.86	1.98	2.7306(6)	145	x, y, z
	O2–H2A···O4	0.87	1.72	2.581(3)	171	–x,1-y, –z
	N2–H2B···O1	0.83	2.00	2.6886(3)	140	intramolecular
	C4–H4···O4	0.93	2.36	3.2636(8)	163	1–x, –y, –z
	C8–H8···O3	0.93	2.46	3.270(8)	145	–1+x,1+y,z
NFA–BZA I	N2–H2B···O1	0.86	1.94	2.6584(4)	140	intramolecular
	N3–H3A···O2	1.15	1.66	2.7917(5)	168	1–x,1–y,–z
	N3–H3B···O1	1.07	1.73	2.7896(5)	170	1+y, y, z
	N3–H3C···O2	1.05	1.75	2.7814(5)	168	2–x,1–y,–z
NFA–BZA II	N2–H2B···O1	0.96	1.92	2.6465(4)	130	intramolecular
	N4–H4B···O3	0.75	1.99	2.6548(4)	148	intramolecular
	N5–H5A···O1	1.07	1.70	2.7669(4)	177	1/2+x, 1-y, z
	N5–H5B···O4	0.96	1.84	2.7931(4)	173	1/2-x,1+y,-1/2+z
	N5–H5C···O4	0.92	1.90	2.8165(4)	174	1/2-x, y, -1/2+z
	N6–H6A···O2	1.04	1.82	2.8006(4)	155	-x, 1-y, 1/2+z
	N6–H6B···O2	0.96	1.81	2.7484(4)	164	x,1+y,z
	N6–H6C···O2	1.07	1.72	2.7854(4)	175	-x, 1-y, 1/2+z
NFA–TYA	N2–H2A···O1	0.92	1.93	2.6733(7)	137	intramolecular
	N3–H3A···O2	0.89	1.94	2.7714(7)	155	-x, 1-y, -z
	N3–H3B···O3	0.89	2.06	2.9416(7)	169	x,3/2-y,-1/2+z
	N3–H3C···O2	0.89	1.91	2.7825(7)	168	x,1+y,z
	O3–H3D···O1	0.96	1.65	2.6096(6)	172	x,3/2-y,1/2+z



(a)

(b)



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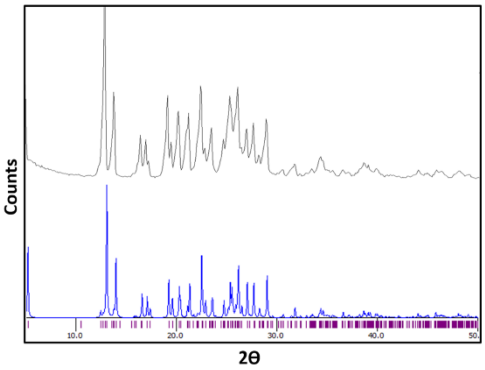

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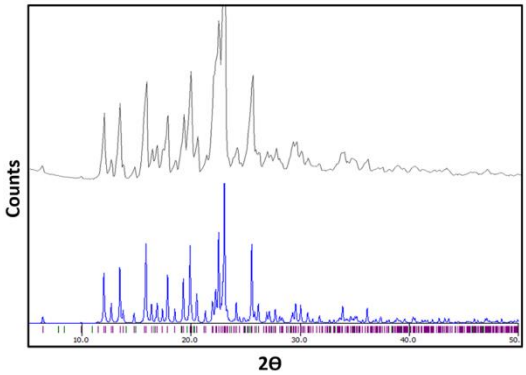

(e)

Figure S6 Comparison of powder patterns before and after equilibrium solubility (after 24 h slurry in 20% EtOH-water). NFA (a), NFA–CPR (b), NFA–PIP (c), NFA–BSA (d) and NFA–TYA (e).