Electronic Supplementary Material (ESI) for CrystEngComm.

Microwave assisted slurry conversion crystallization for manufacturing of new co-crystals of sulfamethazine and sulfamerazine

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PXRD patterns for various samples:

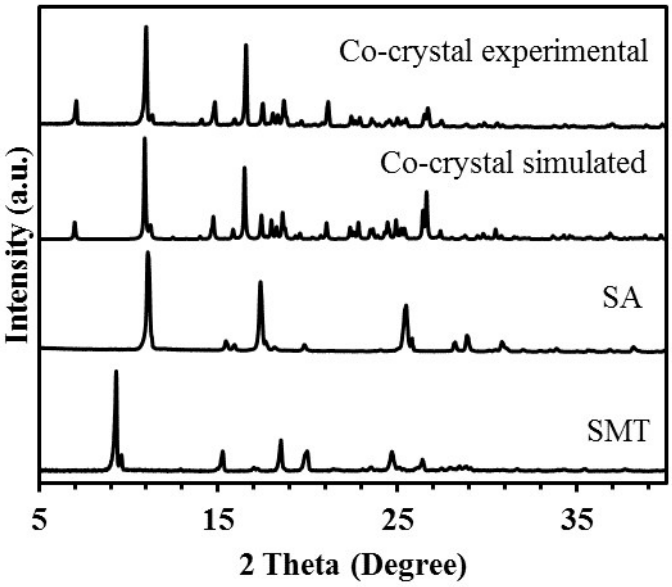

Figure S1. PXRD patterns of sulfamethazine (SMT), salicylic acid (SA), co-crystal obtained from CSD (simulated) and co-crystal from microwave assisted slurry crystallization (experimental).

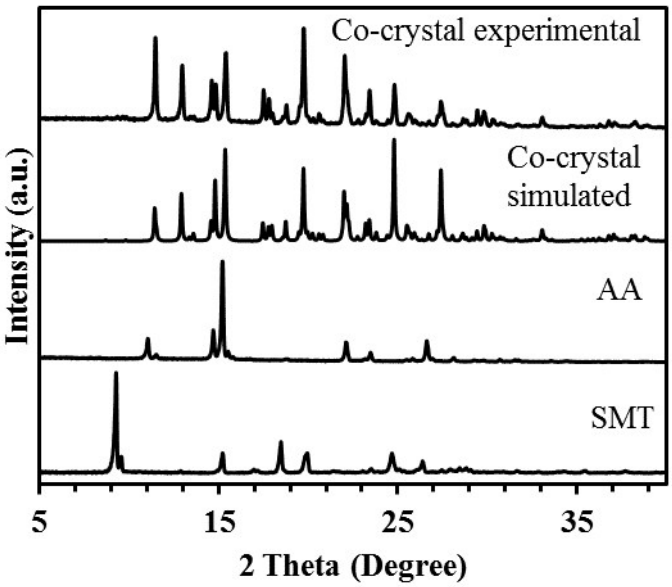

Figure S2. PXRD patterns of sulfamethazine (SMT), anthranilic acid (AA), co-crystal obtained from CSD (simulated) and co-crystal from microwave assisted slurry crystallization (experimental).

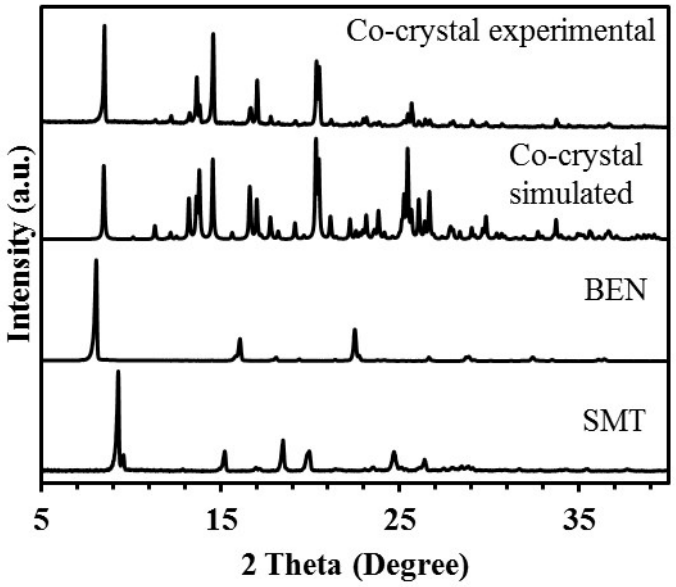

Figure S3. PXRD patterns of sulfamethazine (SMT), benzamide (BEN), co-crystal obtained from CSD (simulated) and co-crystal from microwave assisted slurry crystallization (experimental).

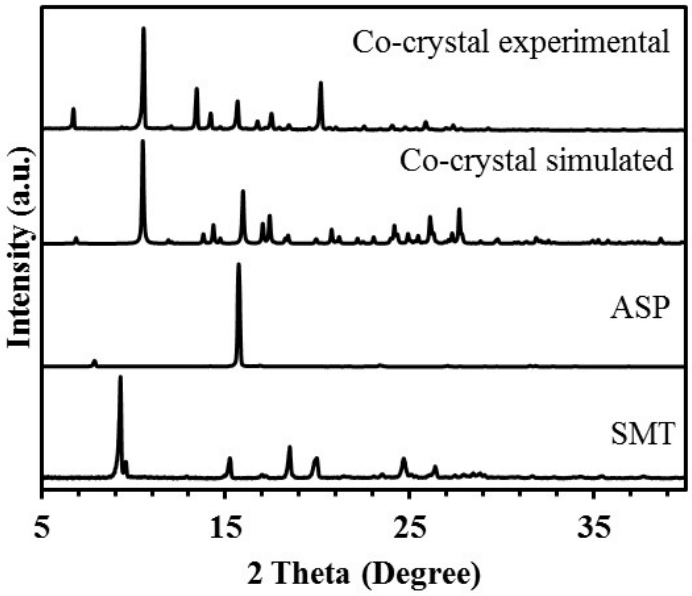

Figure S4. PXRD patterns of sulfamethazine (SMT), aspirin (ASP), co-crystal obtained from CSD (simulated) and co-crystal from microwave assisted slurry crystallization (experimental).

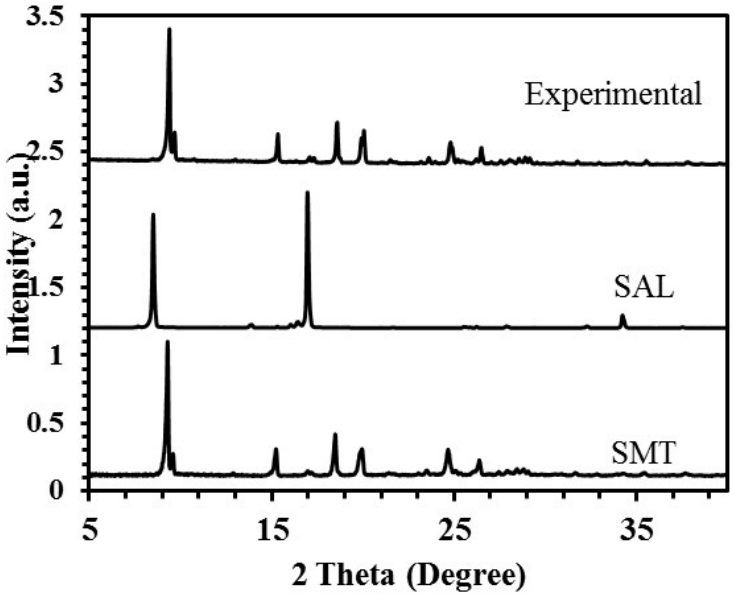

Figure S5. PXRD patterns of sulfamethazine (SMT), salicylamide (SAL) and solid from microwave assisted slurry crystallization.

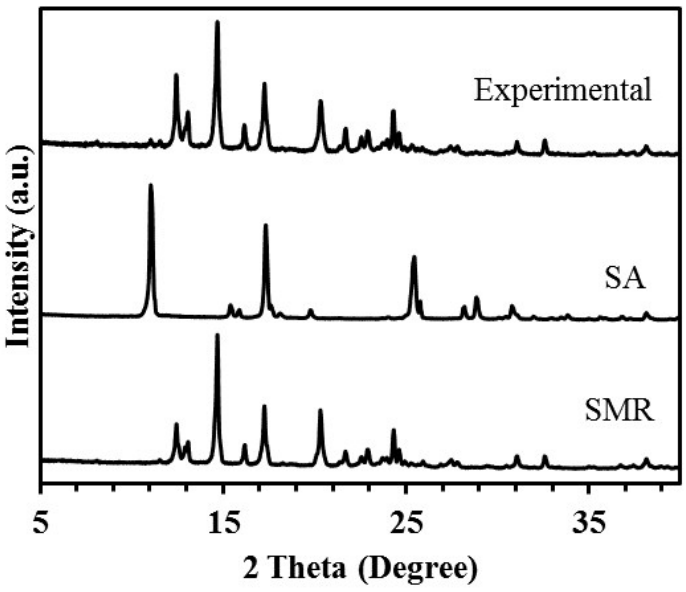

Figure S6. PXRD patterns of sulfamerazine (SMR), salicylic acid (SA) and solid from microwave assisted slurry crystallization.

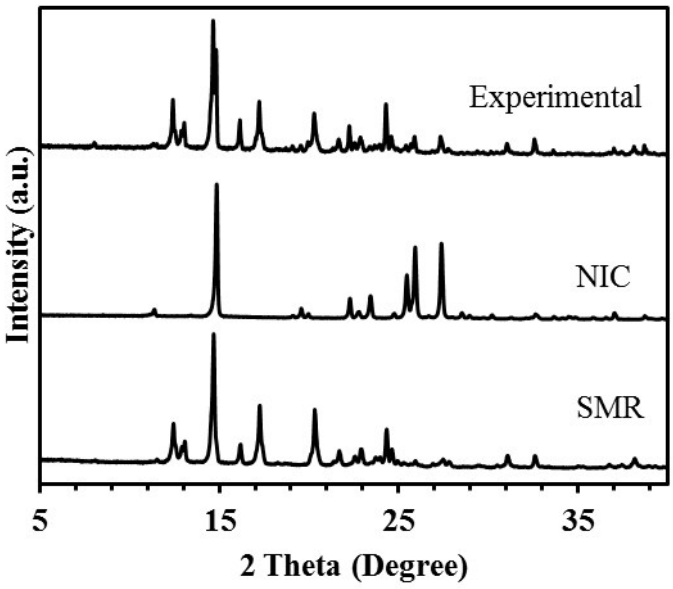

Figure S7. PXRD patterns of sulfamerazine (SMR), nicotinamide (NIC) and solid from microwave assisted slurry crystallization.

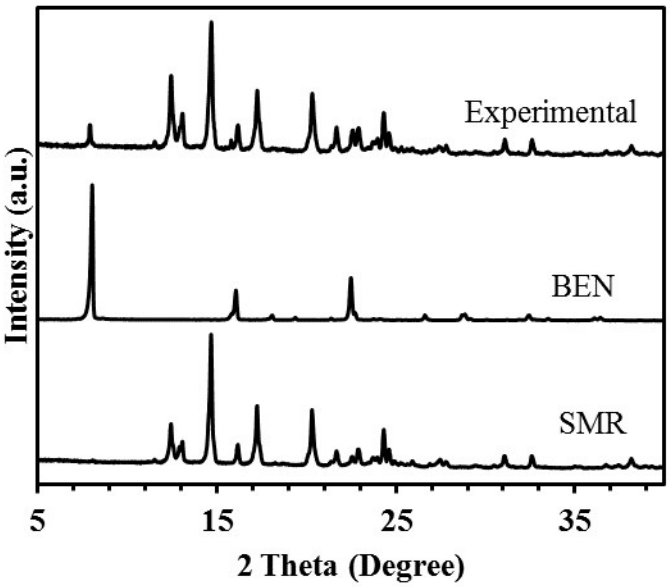

Figure S8. PXRD patterns of sulfamerazine (SMR), benzamide (BEN) and solid from microwave assisted slurry crystallization.

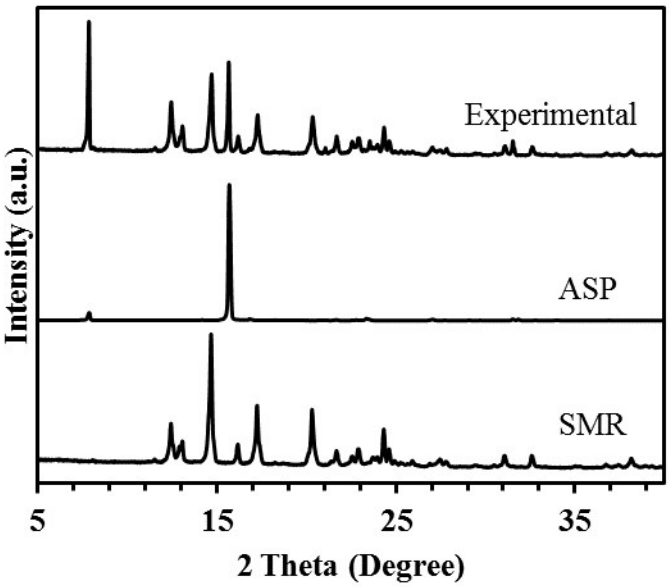

Figure S9. PXRD patterns of sulfamerazine (SMR), aspirin (ASP) and solid from microwave assisted slurry crystallization.

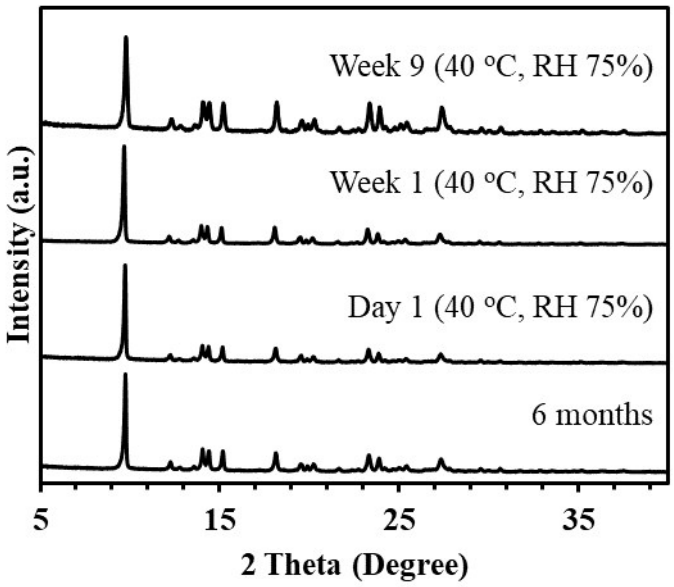

Figure S10. PXRD patterns of SMR-AA co-crystal after 6 months (bench), after 1 day, and after 1 and 9 weeks under accelerated conditions of 40 °C and RH 75 % (stability study).

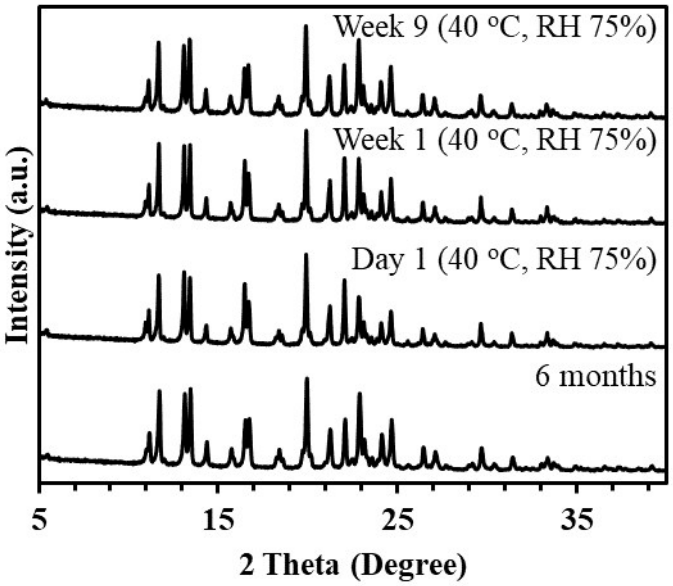

Figure S11. PXRD patterns of SMR-SAL co-crystal after 6 months (bench), after 1 day, and after 1 and 9 weeks under accelerated conditions of 40 °C and RH 75 % (stability study).

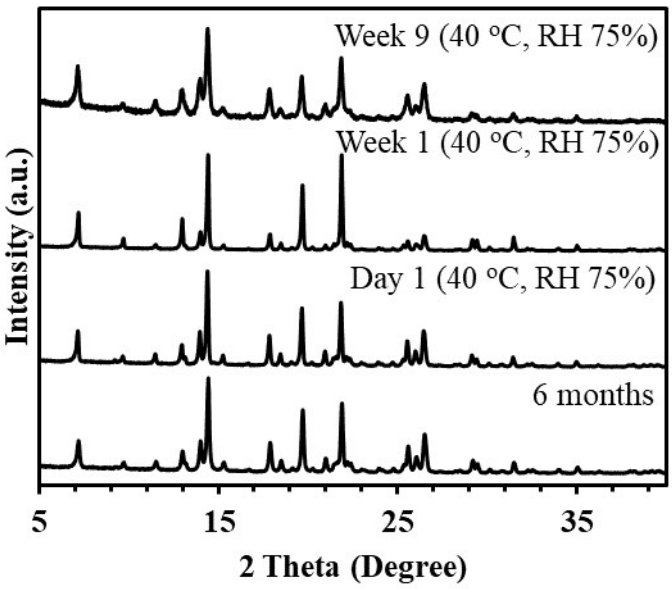

Figure S12. PXRD patterns of SMT-NIC co-crystal after 6 months (bench), after 1 day, and after 1 and 9 weeks under accelerated conditions of 40 °C and RH 75 % (stability study).

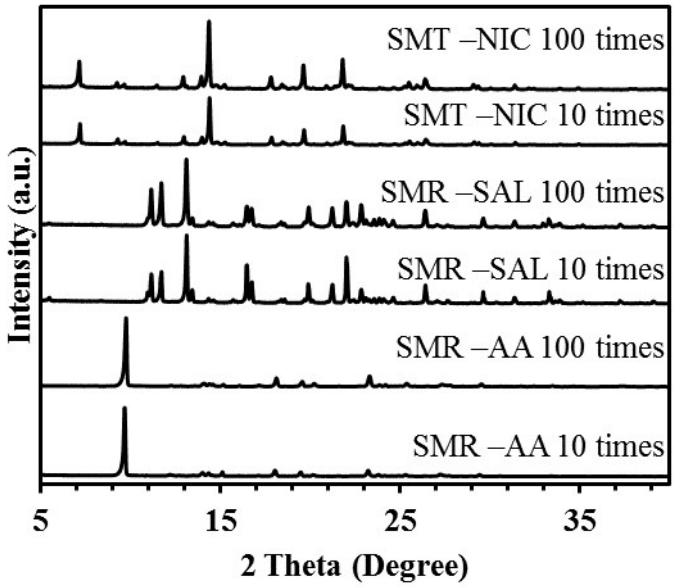

Figure S13. PXRD patterns of the three co-crystals after 10 times and 100 times scale-up.

Table S1. Hydrogen bond parameters for SMT-NIC co-crystal in (Å, °).

D-H--A	D-H	H--A	D--A	Å
N2B-H2B1--N7A	0.88	2.22	3.058(4)	159
N2B-H2B2--O17A	0.88	2.24	3.073(4)	157
N3A-H3A--O1B	0.88	1.83	2.699(4)	168
N15A-H15A--O16A	0.88	2.12	2.950(4)	157
N15A-H15B--N6B	0.88	2.43	3.105(4)	133
C14A-H14A--O16A	0.95	2.46	2.865(4)	105

.

Table S2. Hydrogen bond parameters for SMR-SAL co-crystal in (Å, °).

D-H--A	D-H	H--A	D--A	Å
N8B-H8B1--O10B	0.88	2.10	2.9153(19)	154
N8B-H8B2--O16A	0.88	2.25	3.0506(16)	151
N7A-H7A--N3A	0.88	2.10	2.8989(18)	151
O7B-H7B--O10B	0.84	1.77	2.5139(17)	147
N15A-H15A--O7B	0.88	2.17	3.0214(19)	162
N15A-H15B--O16A	0.88	2.28	3.0308(18)	143
N15A-H15B--N1A	0.88	2.52	3.2183(19)	137
C4A-H4A--O17A	0.95	2.52	3.2444(19	133
C10A-H10A--O16A	0.95	2.58	2.9397(19)	102

Table S3. Hydrogen bond parameters for SMR-AA co-crystal in (Å, °).

D-H--A	D-H	H--A	D--A	Å
O1B-H1B--N1A	0.82	2.00	2.813(2)	174
N7A-H7A--O2B	0.86	1.98	2.723(2)	144
N10B-H10B--O17A	0.86	2.29	3.030(2)	144
N10B-H10C--O2B	0.86	2.04	2.664(3)	129
N15A-H15A-- N3A	0.86	2.45	3.286(2)	163
C8B-H8B-- O16A	0.93	2.56	3.340(3)	142
C9B-H9B--O1B	0.93	2.42	2.742(3)	100

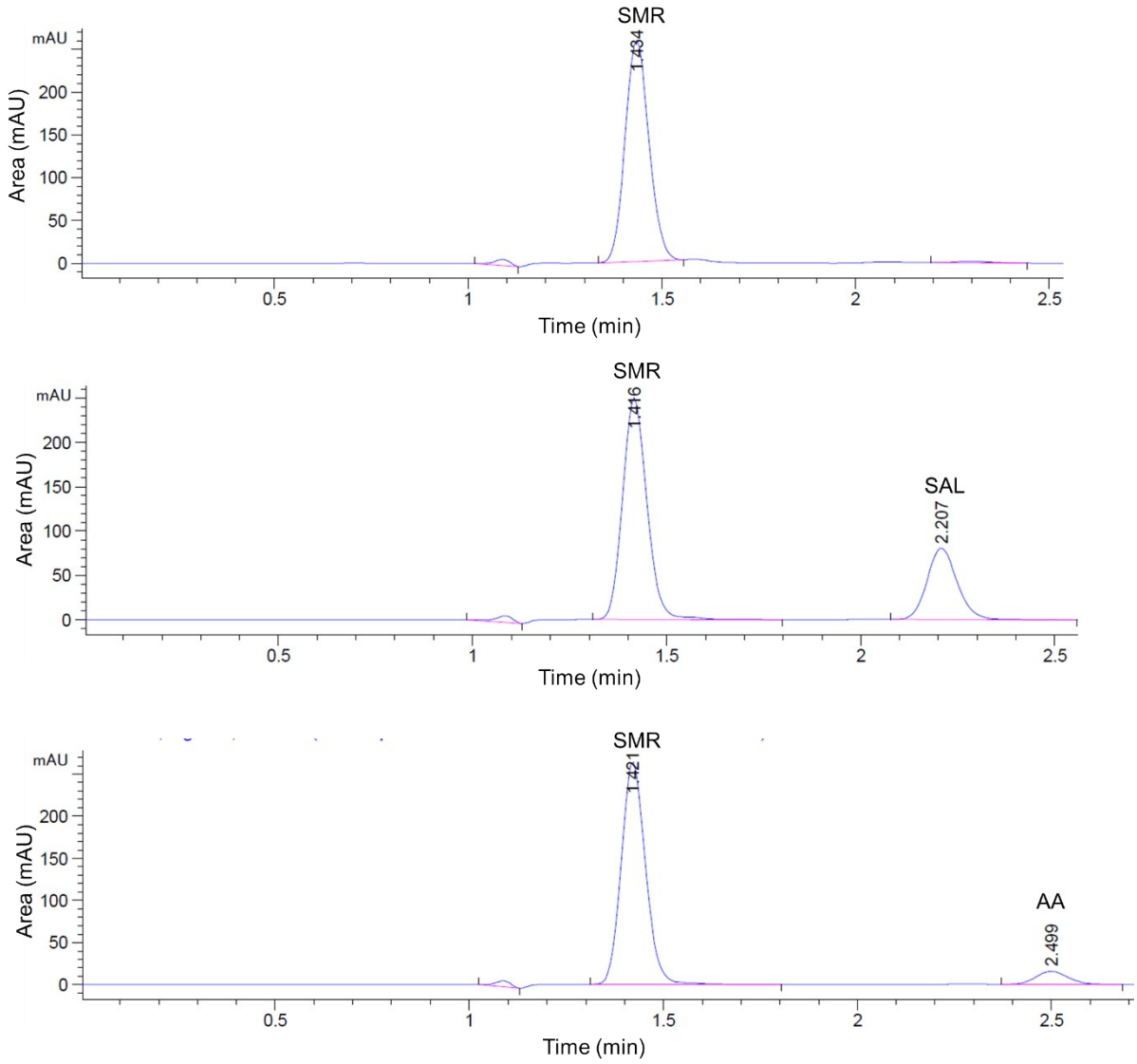

Figure S14. HPLC chromatograms of pure SMR, SMR-SAL and SMR-AA co-crystals.

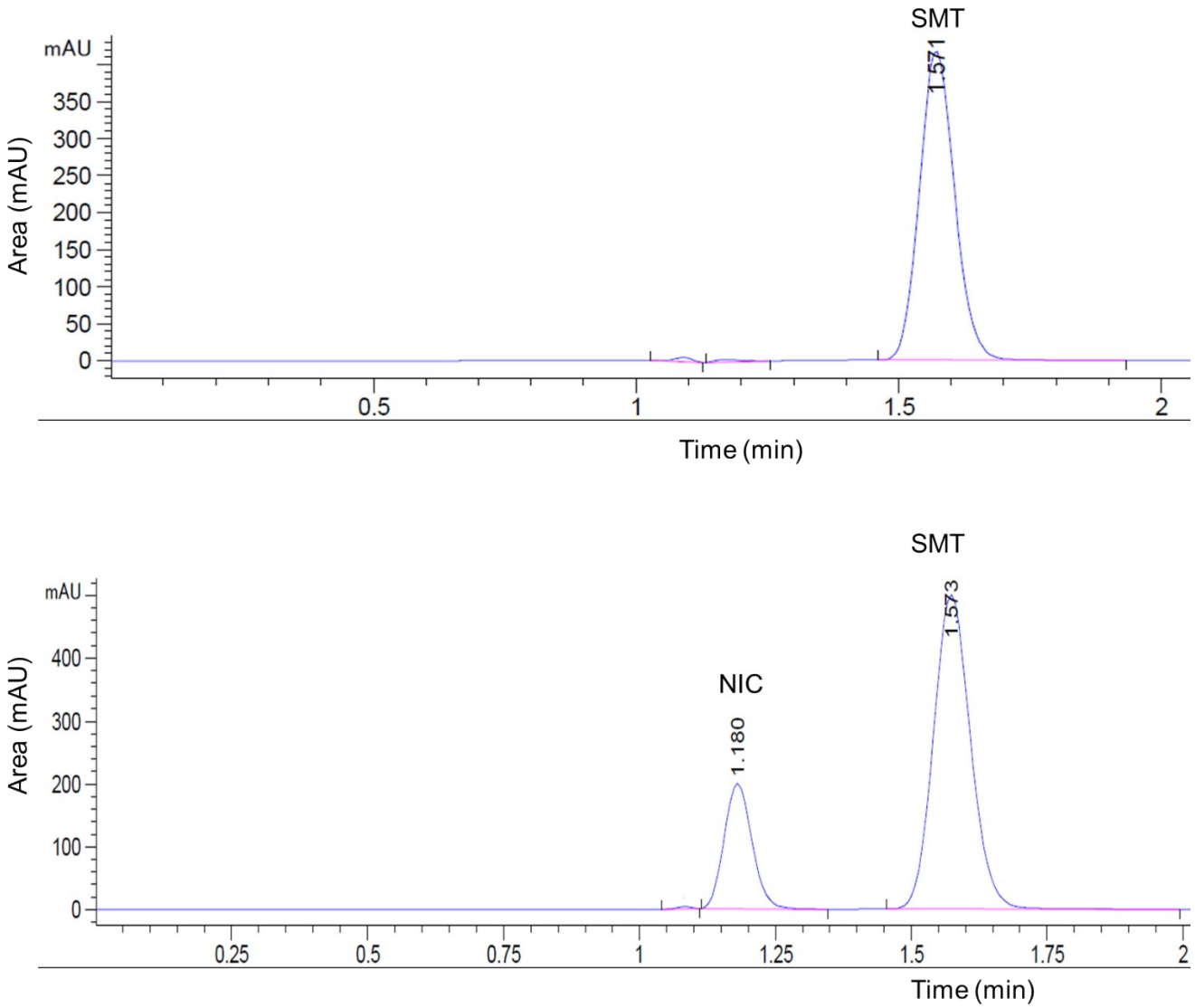

Figure S15. HPLC chromatograms of pure SMT, and SMT-NIC co-crystal.

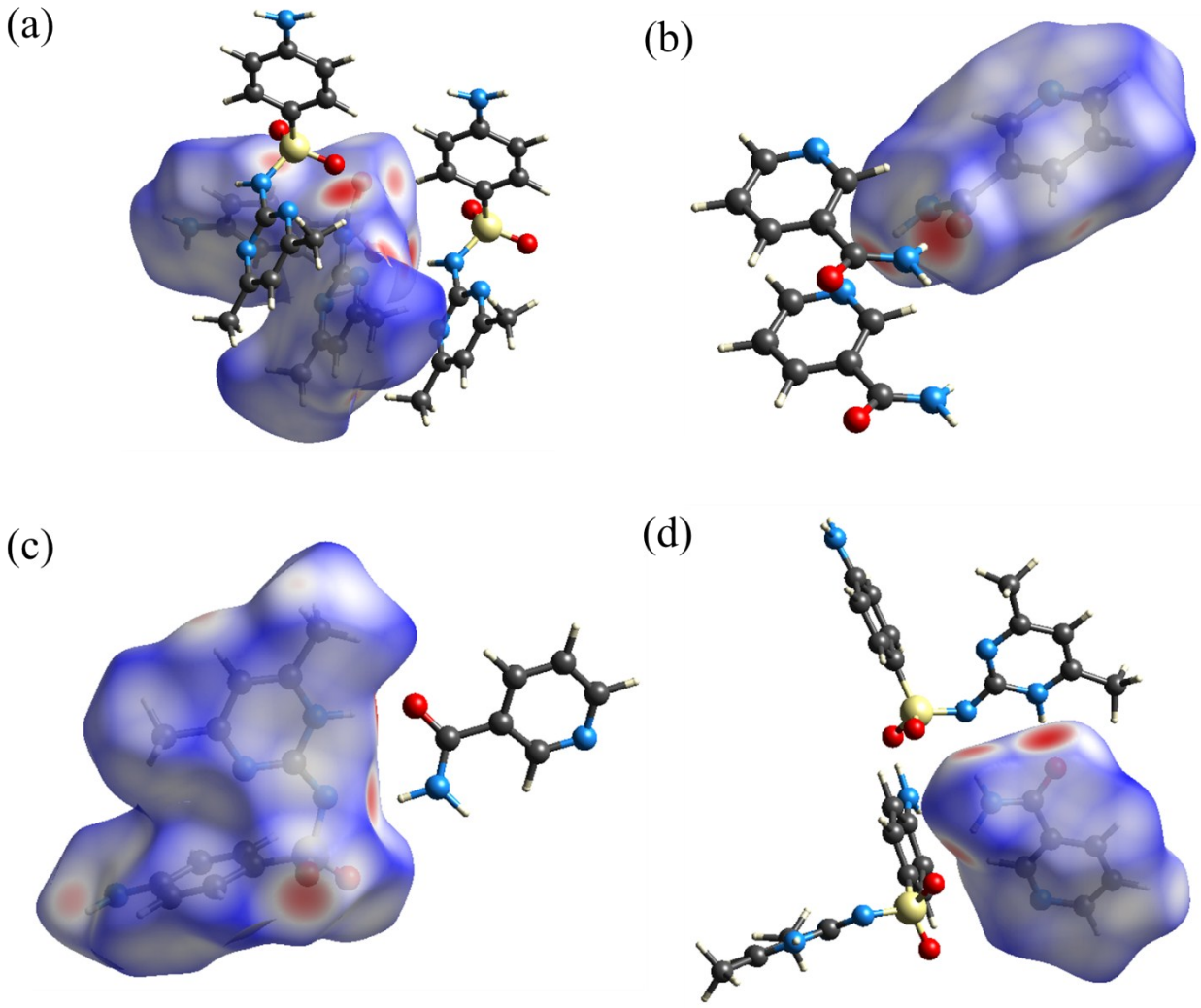

Figure S16. Hirshfeld surface plots of SMT form I (a), NIC (b), SMT molecule in SMT-NIC co-crystal (c) NIC molecule in SMT-NIC co-crystal (d).

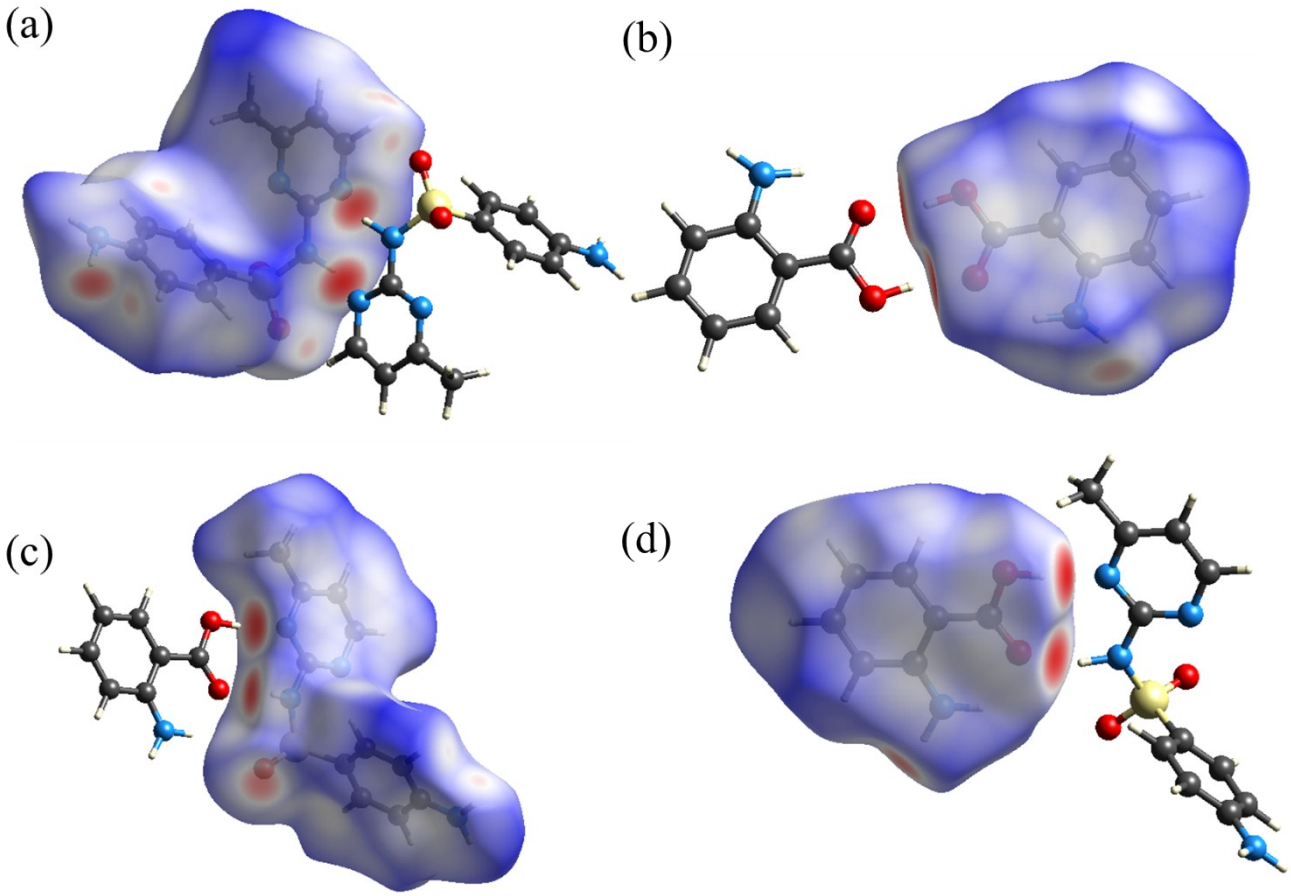

Figure S17. Hirshfeld surface plots of SMR form I (a), AA (b), SMR molecule in SMR-AA co-crystal (c) AA molecule in SMT-AA co-crystal (d).

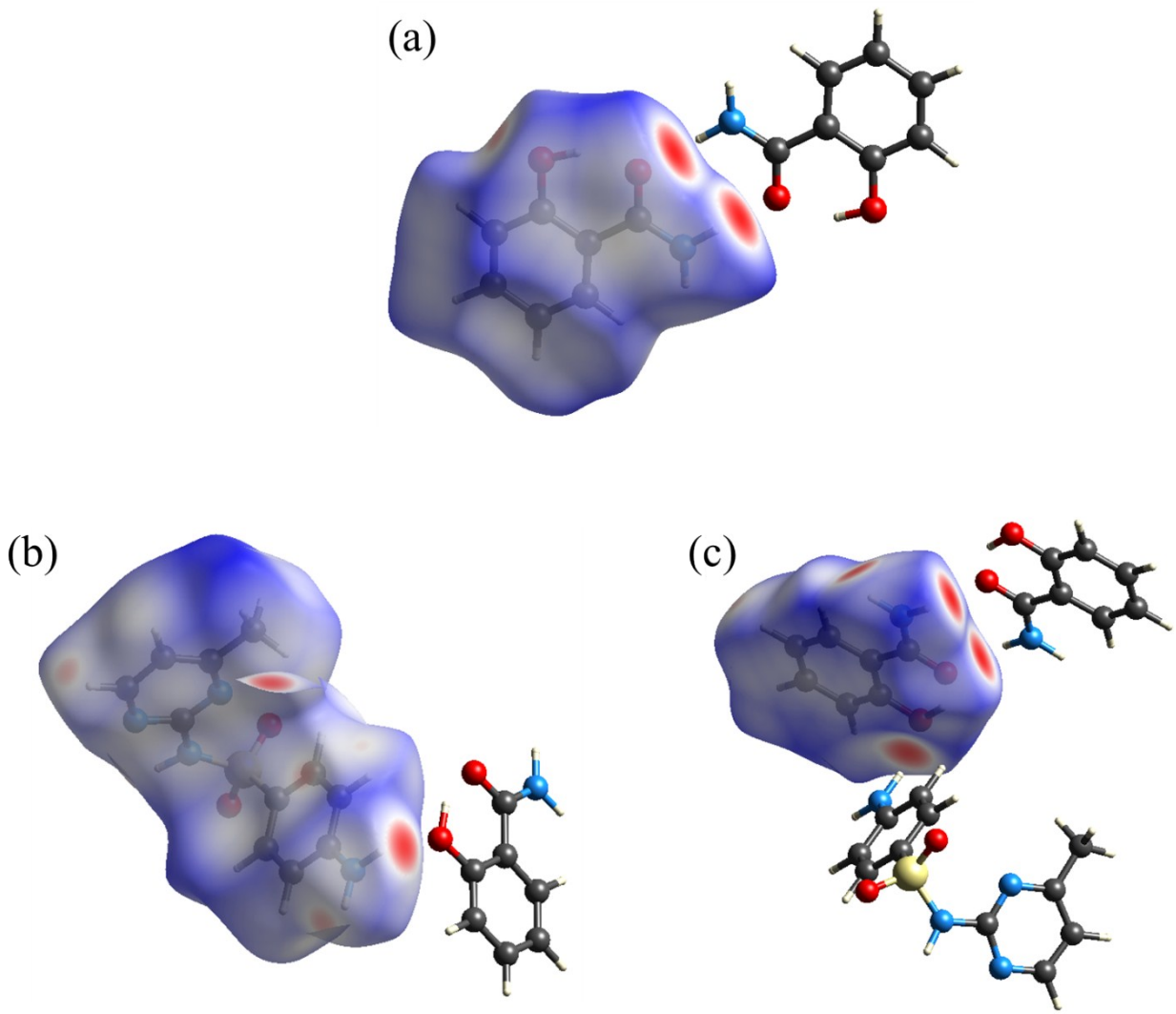

Figure S18. Hirshfeld surface plots of SAL (a), SMR molecule in SMR-SAL co-crystal (b) AA molecule in SMT-SAL co-crystal (c).

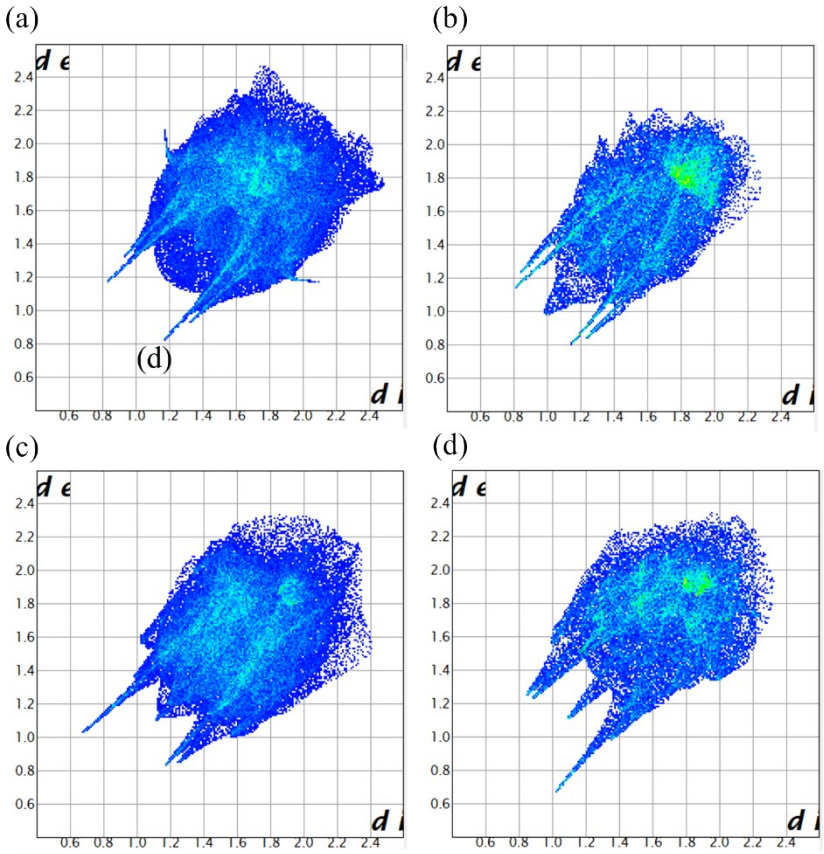

Figure S19. 2-D finger plots of SMT form I (a), NIC (b), SMT molecule in SMT-NIC co-crystal (c) NIC molecule in SMT-NIC co-crystal (d).

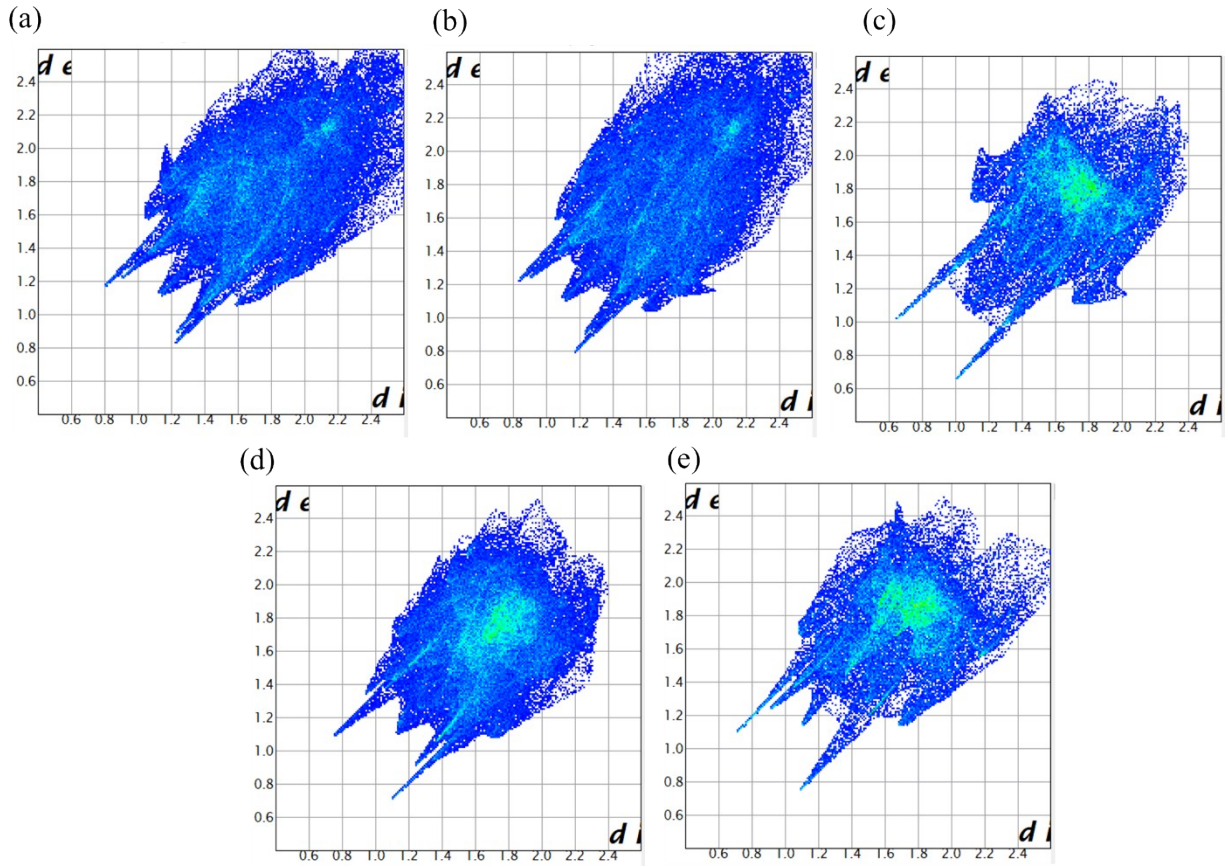

Figure S20. Hirshfeld surface plots of SMR molecule 1 (a), SMR molecule 2 (b) AA (c), SMR molecule in SMR-AA co-crystal (d) AA molecule in SMT-AA co-crystal (e).

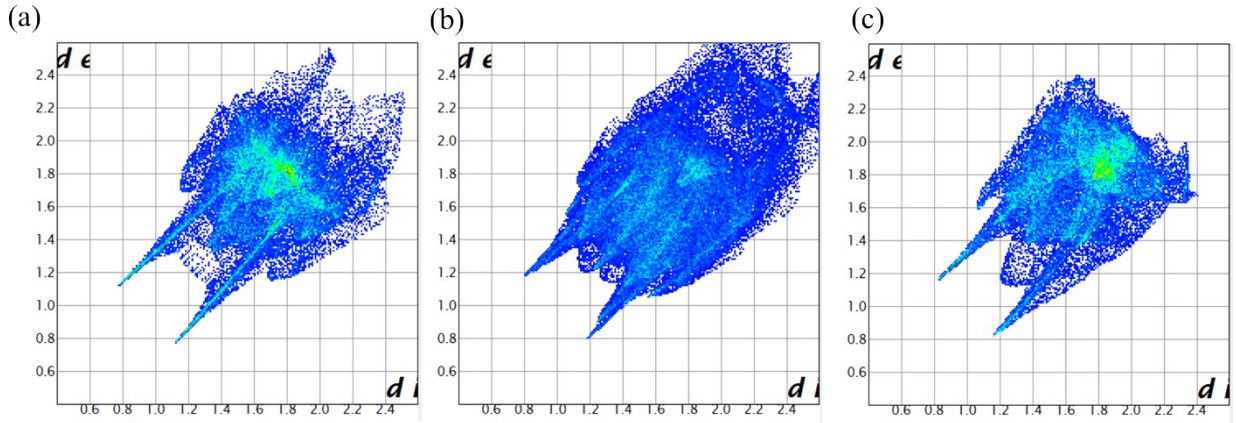

Figure S21. 2-D fingerprint plots of SAL (a), SMR molecule in SMR-SAL co-crystal (b) AA molecule in SMT-SAL co-crystal (c).

Information for Tables S4- S11:

The interaction energies are in kJ/mol. 'R' is the distance between molecular centroids in Å. Total energies are the sum of four energy components, scaled appropriately as per the scale factors:

Energy Model	k_ele	k_pol	k_disp	k_rep
CE-B3LYP ... B3LYP/6-31G(d,p) electron densities	1.057	0.740	0.871	0.618

$$E_{tot} = k_{ele}E_{ele} + k_{pol}E_{pol} + k_{dis}E_{dis} + k_{rep}E_{rep} \quad (1)$$

Table S4. Interaction energy profile for SMT.

Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
x, y, z	7.43	B3LYP/6-31G(d,p)	0.8	-2.5	-7.6	1.8	-6.6
-x+1/2, y+1/2, -z	12.41	B3LYP/6-31G(d,p)	0.2	-0.1	-2.1	0.1	-1.7
x, y, z	9.32	B3LYP/6-31G(d,p)	-9.2	-4.3	-21.7	18.1	-20.7
x+1/2, -y+1/2, z	10.29	B3LYP/6-31G(d,p)	-7.6	-2.9	-8.3	4.0	-14.9
x+1/2, -y+1/2, z	11.31	B3LYP/6-31G(d,p)	2.3	-0.4	-3.7	0.4	-0.9
x+1/2, -y+1/2, z	5.47	B3LYP/6-31G(d,p)	-19.1	-9.2	-47.9	49.7	-38.1
-x, -y, -z	10.24	B3LYP/6-31G(d,p)	1.7	-0.1	-2.0	0.0	0.1
-x, -y, -z	6.19	B3LYP/6-31G(d,p)	-33.6	-8.3	-45.6	44.3	-54.0
-x, -y, -z	7.38	B3LYP/6-31G(d,p)	-33.2	-9.1	-58.0	53.7	-59.1
-x+1/2, y+1/2, -z	9.63	B3LYP/6-31G(d,p)	-24.7	-4.6	-14.7	21.2	-29.3
-x, -y, -z	10.52	B3LYP/6-31G(d,p)	-1.2	-0.2	-4.6	1.8	-4.3

Table S5. Interaction energy profile for NIC.

Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
x, y, z	3.88	B3LYP/6-31G(d,p)	5.6	-1.3	-29.6	15.8	-11.0
-x, -y, -z	7.15	B3LYP/6-31G(d,p)	-3.9	-0.6	-12.0	11.2	-8.1
-x, -y, -z	8.20	B3LYP/6-31G(d,p)	-9.8	-1.6	-10.2	12.7	-12.6
x, -y+1/2, z+1/2	6.71	B3LYP/6-31G(d,p)	-37.7	-9.0	-12.5	35.4	-35.5
x, -y+1/2, z+1/2	5.95	B3LYP/6-31G(d,p)	-36.1	-8.2	-12.7	31.9	-35.6
-x, -y, -z	5.59	B3LYP/6-31G(d,p)	-12.0	-2.5	-17.7	16.3	-19.8
-x, y+1/2, -z+1/2	7.93	B3LYP/6-31G(d,p)	2.7	-1.0	-6.2	2.8	-1.5

-x, -y, -z	5.88	B3LYP/6-31G(d,p)	-7.5	-1.7	-12.4	13.9	-11.3
-x, y+1/2, -z+1/2	8.46	B3LYP/6-31G(d,p)	1.5	-0.5	-2.2	0.1	-0.6

Table S6. Interaction energy profile for SMT-NIC co-crystal

Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
-	4.31	B3LYP/6-31G(d,p)	0.1	-4.4	-41.6	19.0	-27.6
-	7.20	B3LYP/6-31G(d,p)	-112.1	-27.6	-20.2	105.4	-91.4
-	6.23	B3LYP/6-31G(d,p)	-33.2	-11.6	-25.1	34.1	-44.5
-	6.93	B3LYP/6-31G(d,p)	-0.1	-0.5	-3.6	0.1	-3.6
-	11.94	B3LYP/6-31G(d,p)	5.2	-0.5	-1.1	0.0	4.2
-x, -y, -z	5.23	B3LYP/6-31G(d,p)	-1.9	-1.8	-16.2	7.1	-13.1
-	5.96	B3LYP/6-31G(d,p)	-7.7	-7.4	-31.5	15.1	-31.7
-	7.78	B3LYP/6-31G(d,p)	-18.7	-4.4	-21.7	31.5	-22.4
-x, y+1/2, -z+1/2	9.96	B3LYP/6-31G(d,p)	-4.4	-2.5	-10.7	6.7	-11.7
-x, -y, -z	9.71	B3LYP/6-31G(d,p)	5.3	-0.7	-7.9	2.8	-0.0
-	7.78	B3LYP/6-31G(d,p)	-18.7	-4.4	-21.7	31.5	-22.4
-x, -y, -z	6.73	B3LYP/6-31G(d,p)	-14.4	-5.3	-28.6	14.1	-35.4
x, -y+1/2, z+1/2	9.55	B3LYP/6-31G(d,p)	-8.4	-4.1	-21.0	18.3	-18.9
x, y, z	8.35	B3LYP/6-31G(d,p)	-20.9	-10.6	-10.7	26.2	-23.1
-	6.93	B3LYP/6-31G(d,p)	-0.1	-0.5	-3.6	0.1	-3.6
-	4.31	B3LYP/6-31G(d,p)	0.1	-4.4	-41.6	19.0	-27.6
-x, -y, -z	7.56	B3LYP/6-31G(d,p)	-42.3	-15.5	-30.9	22.6	-69.1
x, -y+1/2, z+1/2	10.58	B3LYP/6-31G(d,p)	-28.3	-7.2	-8.8	9.8	-36.9
-x, y+1/2, -z+1/2	8.76	B3LYP/6-31G(d,p)	8.2	-5.0	-4.4	0.8	1.6
-	7.20	B3LYP/6-31G(d,p)	-112.1	-27.6	-20.2	105.4	-91.4
-	6.23	B3LYP/6-31G(d,p)	-33.2	-11.6	-25.1	34.1	-44.5
-	11.94	B3LYP/6-31G(d,p)	5.2	-0.5	-1.1	0.0	4.2
-	5.96	B3LYP/6-31G(d,p)	-7.7	-7.4	-31.5	15.1	-31.7

Table S7. Interaction energy profile for SMR.

-	6.72	B3LYP/6-31G(d,p)	12.4	-5.6	-29.8	17.2	-6.3
x+1/2, y, -z+1/2	7.72	B3LYP/6-31G(d,p)	-15.1	-4.3	-16.6	12.1	-26.0
x+1/2, y, -z+1/2	9.10	B3LYP/6-31G(d,p)	-0.6	-1.4	-9.8	5.2	-7.1
-	6.71	B3LYP/6-31G(d,p)	-74.9	-13.3	-31.4	91.8	-59.6
-	7.24	B3LYP/6-31G(d,p)	-8.2	-1.7	-30.1	14.1	-27.4
-	10.57	B3LYP/6-31G(d,p)	-14.0	-2.5	-4.2	1.4	-19.4
-	7.57	B3LYP/6-31G(d,p)	-14.7	-5.4	-23.5	16.7	-29.6
x, y, z	8.20	B3LYP/6-31G(d,p)	-25.8	-9.5	-21.6	27.5	-36.1
-	7.29	B3LYP/6-31G(d,p)	-10.1	-1.9	-33.3	19.8	-28.7
-	12.96	B3LYP/6-31G(d,p)	3.8	-0.7	-1.6	0.0	2.1
x, y, z	8.20	B3LYP/6-31G(d,p)	-26.1	-8.2	-18.2	25.6	-33.6
x+1/2, y, -z+1/2	7.69	B3LYP/6-31G(d,p)	-12.2	-3.9	-15.8	11.0	-22.8
x+1/2, y, -z+1/2	9.15	B3LYP/6-31G(d,p)	-0.7	-1.3	-9.1	4.0	-7.2

Table S8. Interaction energy profile for AA.

N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
1	-x, -y, -z	3.56	B3LYP/6-31G(d,p)	-1.4	-1.0	-38.7	19.9	-23.6
1	-x, -y, -z	7.18	B3LYP/6-31G(d,p)	-117.6	-26.6	-13.4	148.7	-63.8
2	-x, y+1/2, -z+1/2	7.29	B3LYP/6-31G(d,p)	2.7	-0.6	-5.4	1.4	-1.4
1	x, y, z	7.16	B3LYP/6-31G(d,p)	-3.2	-0.4	-6.3	1.0	-8.5
1	x, -y+1/2, z+1/2	6.78	B3LYP/6-31G(d,p)	-13.1	-2.9	-11.6	13.6	-17.7
0	-x+1/2, -y, z+1/2	5.78	B3LYP/6-31G(d,p)	-3.5	-0.6	-17.6	10.9	-12.7
0	-x+1/2, y+1/2, z	7.37	B3LYP/6-31G(d,p)	0.2	-0.3	-4.7	1.2	-3.3
1	x, -y+1/2, z+1/2	6.87	B3LYP/6-31G(d,p)	-2.1	-0.2	-10.4	8.6	-6.2

Table S9. Interaction energy profile for SMR-AA.

Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
-	7.02	B3LYP/6-31G(d,p)	-16.7	-5.6	-19.0	24.0	-23.6
-	10.91	B3LYP/6-31G(d,p)	0.4	-0.3	-3.5	0.7	-2.5
-x, -y, -z	7.83	B3LYP/6-31G(d,p)	-3.0	-0.5	-4.1	0.4	-6.9

-	5.97	B3LYP/6-31G(d,p)	-8.5	-3.9	-35.0	24.9	-26.9
-	6.91	B3LYP/6-31G(d,p)	-2.0	-0.2	-3.1	0.0	-5.0
-	12.16	B3LYP/6-31G(d,p)	0.2	-0.3	-1.4	0.0	-1.1
-x, -y, -z	5.31	B3LYP/6-31G(d,p)	-4.9	-0.7	-16.1	5.8	-16.2
-	9.56	B3LYP/6-31G(d,p)	0.4	-0.1	-1.3	0.0	-0.8
-x, -y, -z	8.71	B3LYP/6-31G(d,p)	-1.2	-0.1	-5.1	2.1	-4.5
-	6.61	B3LYP/6-31G(d,p)	-86.7	-19.7	-21.1	111.6	-55.7
-	4.58	B3LYP/6-31G(d,p)	-6.5	-1.5	-40.3	20.6	-30.4
-	8.65	B3LYP/6-31G(d,p)	-3.5	-0.7	-9.8	7.0	-8.4
-	9.53	B3LYP/6-31G(d,p)	1.4	-0.5	-2.9	0.1	-1.4
-x, -y, -z	8.51	B3LYP/6-31G(d,p)	-1.4	-0.1	-1.4	0.0	-2.8
x, y, z	7.94	B3LYP/6-31G(d,p)	-13.7	-5.5	-14.0	13.0	-22.7
-x, -y, -z	7.12	B3LYP/6-31G(d,p)	-1.2	-6.1	-11.1	10.5	-8.9
-	8.65	B3LYP/6-31G(d,p)	-3.5	-0.7	-9.8	7.0	-8.4
x, y, z	10.71	B3LYP/6-31G(d,p)	-4.7	-1.0	-1.9	0.1	-7.2
-	7.02	B3LYP/6-31G(d,p)	-16.7	-5.6	-19.0	24.0	-23.6
-	5.97	B3LYP/6-31G(d,p)	-8.5	-3.9	-35.0	24.9	-26.9
-x, -y, -z	6.79	B3LYP/6-31G(d,p)	-42.4	-14.0	-57.2	56.0	-70.4
x, y, z	10.38	B3LYP/6-31G(d,p)	0.7	-1.5	-14.8	9.9	-7.2
-x, -y, -z	9.16	B3LYP/6-31G(d,p)	-4.2	-0.5	-3.3	0.3	-7.5
-	9.56	B3LYP/6-31G(d,p)	0.4	-0.1	-1.3	0.0	-0.8
-x, -y, -z	7.55	B3LYP/6-31G(d,p)	-2.7	-2.3	-20.9	8.5	-17.5
-	6.61	B3LYP/6-31G(d,p)	-86.7	-19.7	-21.1	111.6	-55.7
-	4.58	B3LYP/6-31G(d,p)	-6.5	-1.5	-40.3	20.6	-30.4
-x, -y, -z	14.91	B3LYP/6-31G(d,p)	-0.0	-0.1	-2.9	0.6	-2.3
-	10.91	B3LYP/6-31G(d,p)	0.4	-0.3	-3.5	0.7	-2.5
-	12.16	B3LYP/6-31G(d,p)	0.2	-0.3	-1.4	0.0	-1.1
-	9.53	B3LYP/6-31G(d,p)	1.4	-0.5	-2.9	0.1	-1.4
-	6.91	B3LYP/6-31G(d,p)	-2.0	-0.2	-3.1	0.0	-5.0

Table S10. Interaction energy profile for SAL.

Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
x+1/2, -y+1/2, z	7.95	B3LYP/6-31G(d,p)	0.1	-0.3	-3.5	0.7	-2.7
-x, -y, -z	10.10	B3LYP/6-31G(d,p)	-0.1	-0.1	-1.4	0.1	-1.3
x+1/2, -y+1/2, z	6.46	B3LYP/6-31G(d,p)	-33.8	-7.9	-13.1	33.8	-32.2
-x, -y, -z	7.47	B3LYP/6-31G(d,p)	-3.5	-0.3	-8.4	3.7	-9.0
-x, y, -z+1/2	6.20	B3LYP/6-31G(d,p)	4.4	-0.9	-5.9	0.7	-0.7
x, y, z	4.98	B3LYP/6-31G(d,p)	3.5	-1.6	-24.5	12.9	-10.8
x+1/2, -y+1/2, z	8.36	B3LYP/6-31G(d,p)	-3.0	-0.4	-1.6	0.0	-4.8
-x+1/2, y+1/2, -z	6.63	B3LYP/6-31G(d,p)	-3.1	-0.5	-11.4	6.9	-9.4
-x+1/2, -y+1/2, -z+1/2	5.36	B3LYP/6-31G(d,p)	-17.0	-2.4	-22.0	13.8	-30.4
-x+1/2, -y+1/2, -z+1/2	7.54	B3LYP/6-31G(d,p)	-72.2	-15.2	-12.2	66.4	-57.3

Table S11. Interaction energy profile for SMR-SAL.

Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
-	6.95	B3LYP/6-31G(d,p)	-27.0	-7.4	-13.2	19.9	-33.3
-x, -y, -z	3.52	B3LYP/6-31G(d,p)	-7.9	-2.1	-40.4	23.7	-30.4
-x, -y, -z	7.43	B3LYP/6-31G(d,p)	-60.6	-12.4	-11.9	54.7	-49.9
-	7.21	B3LYP/6-31G(d,p)	3.6	-1.9	-11.6	6.3	-3.8
-	7.65	B3LYP/6-31G(d,p)	2.2	-2.6	-6.1	3.5	-2.8
-	8.09	B3LYP/6-31G(d,p)	0.7	-1.4	-15.4	12.3	-6.1
x, y, z	8.15	B3LYP/6-31G(d,p)	0.1	-0.9	-5.4	1.4	-4.4
-x, -y, -z	4.64	B3LYP/6-31G(d,p)	-6.1	-1.5	-21.5	7.2	-21.8
-	7.86	B3LYP/6-31G(d,p)	-23.0	-5.2	-13.9	23.3	-25.8
-x, -y, -z	9.24	B3LYP/6-31G(d,p)	0.2	-0.2	-4.4	1.2	-3.0
-	6.48	B3LYP/6-31G(d,p)	-0.7	-1.9	-15.6	8.3	-10.7
x, y, z	9.81	B3LYP/6-31G(d,p)	4.2	-0.5	-6.7	2.7	-0.2
x, y, z	7.48	B3LYP/6-31G(d,p)	-6.2	-4.1	-17.6	12.4	-17.2
-x, -y, -z	5.95	B3LYP/6-31G(d,p)	-19.3	-3.3	-65.1	48.2	-49.7
-x, -y, -z	10.08	B3LYP/6-31G(d,p)	-4.4	-0.5	-7.1	0.3	-11.1
x, y, z	8.15	B3LYP/6-31G(d,p)	-28.5	-10.8	-25.0	34.8	-38.3

-	6.95	B3LYP/6-31G(d,p)	-27.0	-7.4	-13.2	19.9	-33.3
-	6.48	B3LYP/6-31G(d,p)	-0.7	-1.9	-15.6	8.3	-10.7
-x, -y, -z	6.70	B3LYP/6-31G(d,p)	-83.4	-15.0	-32.1	103.9	-63.1
-	7.86	B3LYP/6-31G(d,p)	-23.0	-5.2	-13.9	23.3	-25.8
-	8.09	B3LYP/6-31G(d,p)	0.7	-1.4	-15.4	12.3	-6.1
-	7.65	B3LYP/6-31G(d,p)	2.2	-2.6	-6.1	3.5	-2.8
-	7.21	B3LYP/6-31G(d,p)	3.6	-1.9	-11.6	6.3	-3.8