Electronic Supplementary Material (ESI) for CrystEngComm.

Supporting Information

Lack of dependence of mechanical properties of baicalein cocrystals on those of the constituent components

Lili Liu[1,3], Chenguang Wang[2,3], Jiangnan Dun [2,3], Albert H. L. Chow[1] and Changquan Calvin Sun[2,*]*

[1.] *School of Pharmacy, the Chinese University of Hong Kong, Hong Kong, SAR, China*

[2.] *Pharmaceutical Materials Science and Engineering Laboratory, Department of Pharmaceutics, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 55455, USA*

[3.] *These authors contributed equally to this work*

1. Materials

Baicalein (BAI) was purchased from Nanjing Zelang Medical Technology Company, Ltd. (purity ≥ 98.0% by HPLC, Nanjing, China). Nicotinamide (NCT), caffeine (CAF), and isoniazid (ISN) were purchased from Sigma Aldrich (St. Louis, MO, USA).

2. Methods

Cocrystallization

Phase-pure bulk cocrystals, BAI-NCT (1:1), BAI-CAF (2:1) and BAI-ISN (1:1) were synthesized by dissolving stoichiometric amounts of each components in an appropriate solvent (ethyl acetate for BAI-NCT and BAI-ISN; ethanol for BAI-CAF), followed by quick solvent removal by rotary evaporation.

Tabletability

Before compaction, similar particle size and shape were showed in Figure S1. Phase purity of each triturated sample was verified with PXRD (Figure S2), and DSC (Figure S3).

After relaxation for at least one week at 32% RH and room temperature, a suitable amount of powder (140 – 300 mg depending on material) was manually filled into a die and compressed at predetermined pressures (50 – 300 MPa) using a universal material testing machine (model 1485, Zwick, Ulm, Germany). The speed for both compression and decompression was 2 mm/min without holding at the peak pressure. Both punch tips and die wall were lubricated by coating with a thin layer of 5% (w/v) magnesium stearate suspended in ethanol followed by thorough air drying. Cylindrical tablets (8 mm diameter) were allowed to relax overnight in a 32% RH chamber before their weights, diameters, and thickness were measured. Tablet diametral breaking force was determined using a Texture Analyzer (TA-XT2i, Texture Technologies Corp., NY, USA) at a testing speed of 0.01 mm/s. Tensile strength, σ (MPa), was calculated from the breaking force F (N), tablet diameter, d (mm), and tablet thickness, l (mm) according to Equation (1).

$$\sigma = \frac{2F}{\pi \cdot d \cdot l} \qquad (1)$$

Energy framework

The calculation for intermolecular interaction energy employed B3LYP-D2/6-31G(d,p) model based on dispersion-corrected density functional theory (CrystalExplorer, Version 17, University of Western Australia).[1] The total intermolecular interaction energy, including electrostatic, polarization, dispersion and exchange-repulsion energy with scale factor of 1.057, 0.740, 0.871 and 0.618, respectively, was calculated. The constructed “energy framework” was based on the total intermolecular interaction energy.

3. Results

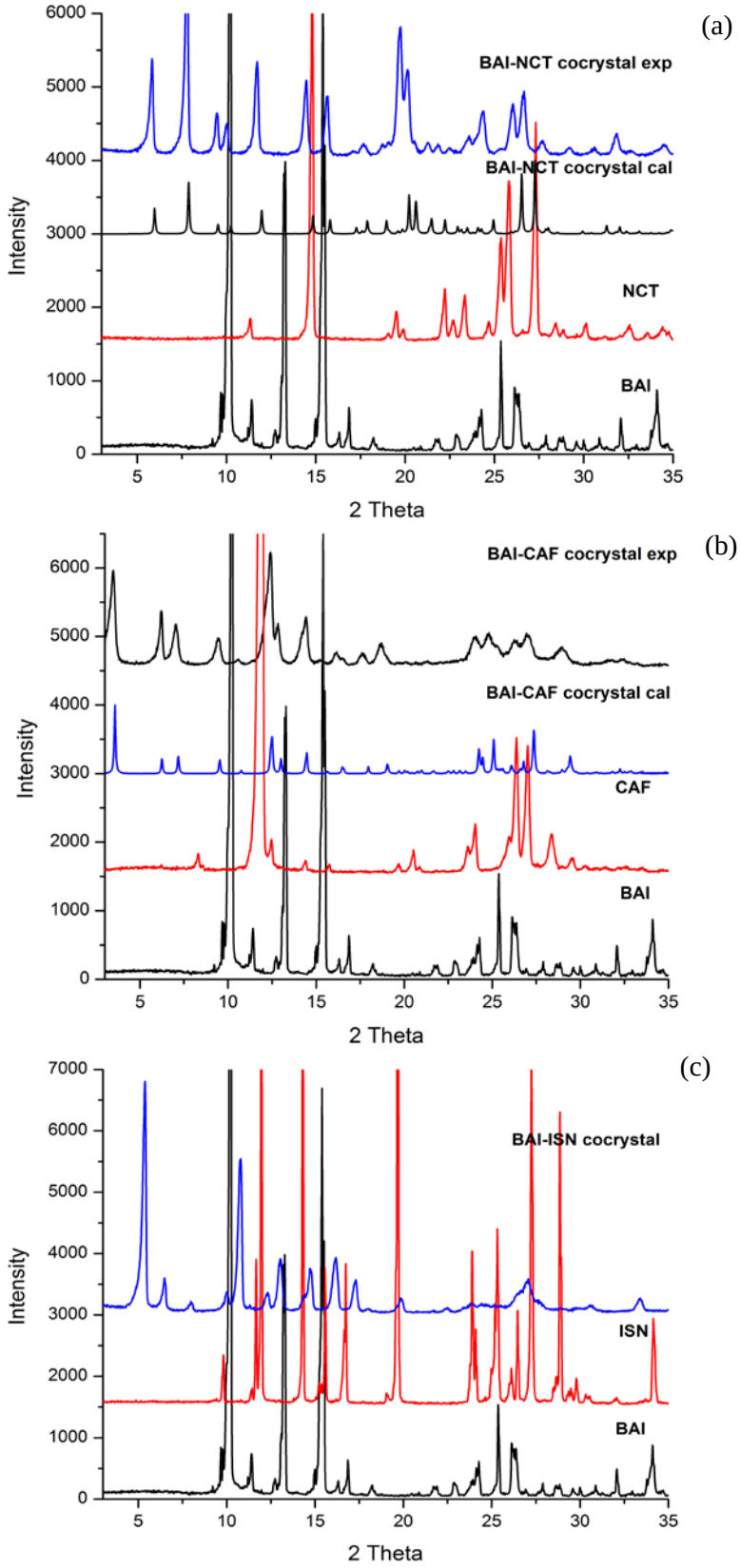

Figure S1. PXRD patterns of a) BAI-NCT, b) BAI-CAF and c) BAI-ISN cocrystal systems.

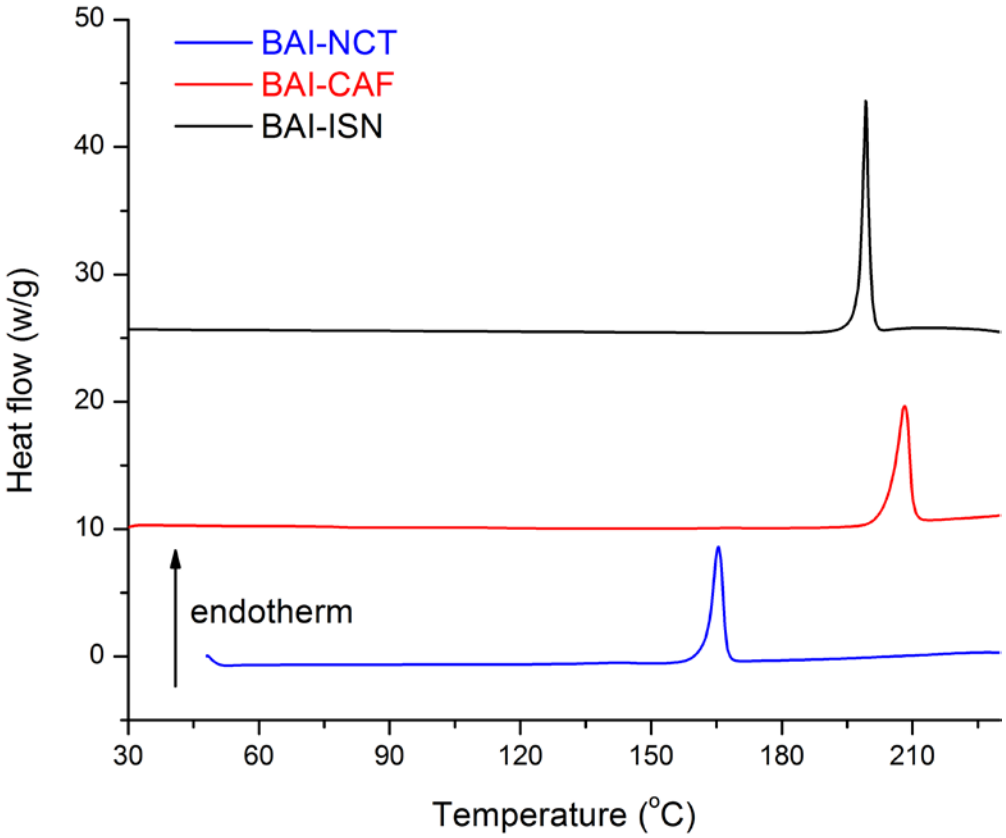

Figure S2. DSC thermograms of a) BAI-NCT, b) BAI-CAF, and c) BAI-ISN cocrystal.

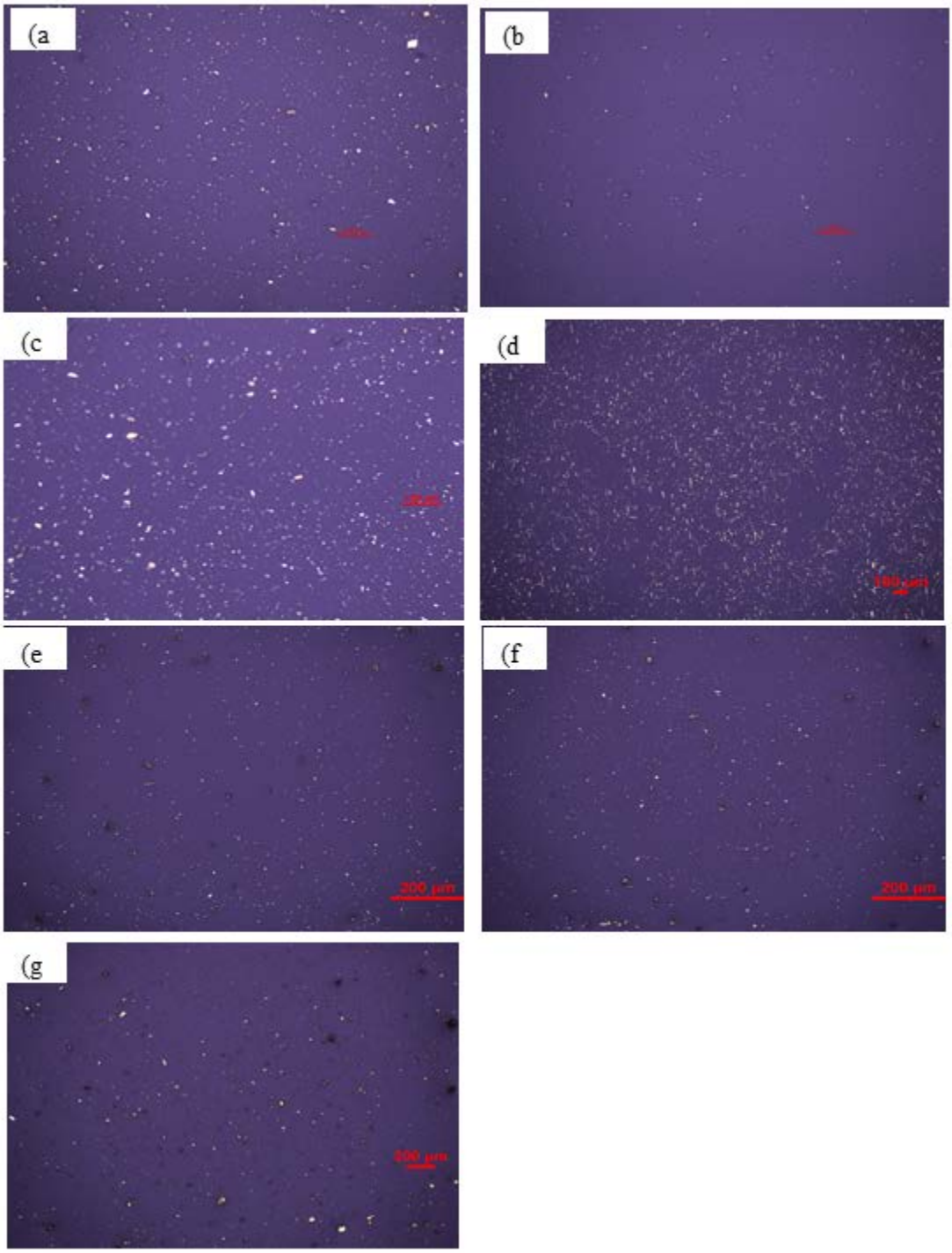

Figure S3. Polarized light microscope image of a) BAI, b) BAI-NCT cocrystal, c) BAI-CAF cocrystals, d) BAI-ISN cocrystals, e) NCT, f) CAF, and g) ISN.

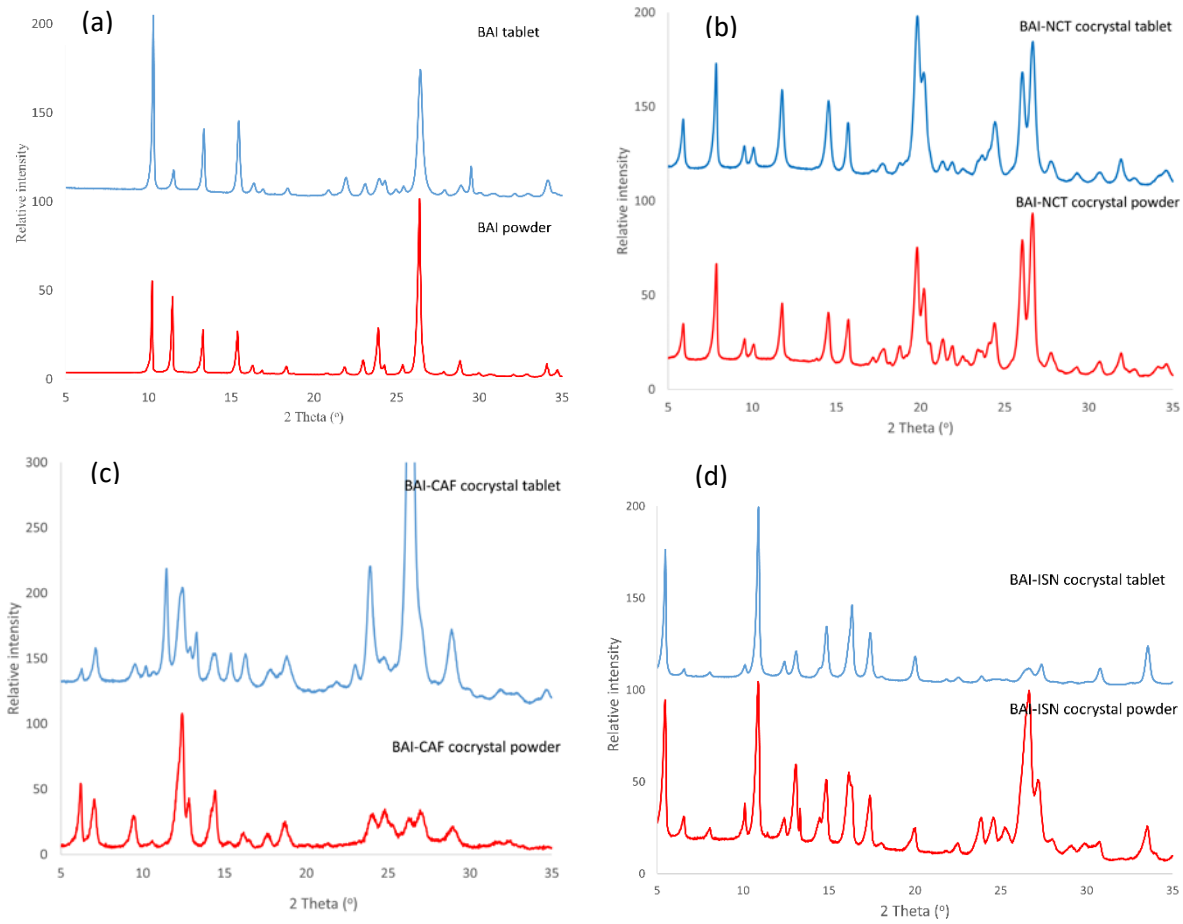

Figure S4. PXRD patterns of α-BAI and three BAI cocrystals powders and tablets compressed at 300 MPa.

Table S1. Crystallographic parameters of available crystal structures used in this work.

Compound	**BAI**	**BAI-NCT**	**BAI-CAF**
Chemical formula	$C_{15}H_{10}O_5$	$C_{21}H_{16}N_2O_6$	$C_{38}H_{30}O_{12}N_4$
Formula weight	270.23	392.36	734.66
Crystal system	Monoclinic	Triclinic	Monoclinic
Space group	$P2_1/c$	P-1	$P2_1/c$
a/Å	7.7707	5.2480	24.6690
b/Å	13.2573	11.4220	4.5593
c/Å	11.5427	14.9520	28.2670
α/°	90.00	90.00	90.00
β/°	101.03	82.29	90.32
γ/°	90.00	90.00	90.00
Z	4	2	4
Volume ($Å^3$)	1167.2	871.7	3179.2
Density (Mg/m^3)	1.538	1.495	1.535
Packing coefficient	0.743	0.721	0.733
CCDC	207266	893495	1522878

Table S2. Hydrogen bonding table for the BAI, BAI-NCT and BAI-CAF.

	D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)
BAI	O_4-H_3···O_2	0.97	1.713	2.616	153.4
	O_5-H_4···O_4	0.97	1.953	2.787	142.7
	O_3-H_2···O_2	0.97	1.736	2.611	148.2
BAI-NCT	O_4-H_2···N_1	0.84	1.908	2.694	155.3
	O_5-H_3···O_6	0.84	1.940	2.720	153.9
	N_2-H_{11}···O_4	0.88	2.328	2.885	121.2
	N_2-H_{11}···O_5	0.88	2.507	3.093	124.6
	N_2-H_{12}···O_6	0.88	2.232	2.996	145.1
	O_3-H_1···O_2	0.84	1.815	2.563	147.5
BAI-CAF	O_9-H_9···O_2	0.90	1.802	2.644	154.7
	O_{10}-H_{10}···N_2	0.82	2.021	2.786	154.9
	O_4-H_4···O_{11}	0.89	1.977	2.823	157.9
	O_5-H_5···O_{12}	0.95	1.844	2.709	150.0
	O_8-H_8···O7	0.92	1.724	2.593	157.0
	O_3-H_3···O_2	0.90	1.771	2.600	152.0

Table S3. Intermolecular interactions energies of BAI α form, BAI-NCT and BAI-CAF calculated at the B3LYP/6-31G(d,p) level of theory.

Solid form	Symop	R	E_{ele}	E_{pol}	E_{dis}	E_{rep}	E_{tot}
BAI	x, y, z	11.54	-1.5	-2.0	-10.9	5.3	-9.3
	-x, -y, -z	14.11	0.4	-0.3	-6.1	5.4	-1.8
	-x, -y, -z	3.48	-8.3	-9.8	-83.6	53.0	-56.1
	x, -y+1/2, z+1/2	8.60	-58.3	-2.4	-15.5	67.1	-35.5
	-x, y+1/2, -z+1/2	9.18	-7.5	-1.7	-11.5	10.0	-13.0
	-x, -y, -z	4.61	-11.8	-1.0	-82.3	52.8	-52.3
	-x, y+1/2, -z+1/2	10.99	-0.6	-6.6	-8.7	3.0	-11.2
	-x, -y, -z	11.63	-43.5	-1.3	-13.2	49.4	-27.9
	x, -y+1/2, z+1/2	8.98	-3.0	-0.4	-15.6	13.1	-9.0
BAI-NCT	-x, -y, -z	15.13	2.1	-0.5	-5.0	2.0	-1.3
	-x, -y, -z	8.65	-4.9	-0.5	-26.9	21.1	-15.9
	-	9.30	-51.1	-10.8	-12.8	57.5	-37.7
	-	7.07	-7.0	-1.0	-26.1	23.5	-16.4
	-	7.45	-7.3	-2.4	-10.9	17.3	-8.3
	x, y, z	5.25	-28.4	-7.1	-17.6	24.8	-35.4
	-x, -y, -z	9.49	1.0	-0.1	-1.2	0.1	0.1
	-	9.30	-51.1	-10.8	-12.8	57.5	-37.7
	-x, -y, -z	5.21	-4.2	-1.6	-16.4	9.6	-14.1
	-	8.88	-64.7	-14.2	-13.9	81.4	-40.7
	-	4.74	-14.1	-3.6	-31.6	22.5	-31.2
	-x, -y, -z	7.64	-3.0	-0.5	-11.9	12.1	-6.4
	-	9.35	-3.2	-1.8	-6.9	6.5	-6.8
	-	6.67	2.1	-0.5	-5.7	0.6	-2.7
	x, y, z	5.25	-4.5	-2.1	-53.1	30.3	-33.8
	-	6.67	2.1	-0.5	-5.7	0.6	-2.7
	-	9.35	-3.2	-1.8	-6.9	6.5	-6.8
	-x, -y, -z	12.88	-0.9	-0.2	-5.7	1.2	-5.4
	x, y, z	11.42	-1.5	-0.6	-5.2	1.6	-5.6
	-x, -y, -z	5.74	-6.5	-1.1	-48.1	31.0	-30.5
	-	4.74	-14.1	-3.6	-31.6	22.5	-31.2
	-	7.07	-7.0	-1.0	-26.1	23.5	-16.4
	-	8.88	-64.7	-14.2	-13.9	81.4	-40.7
	-	7.45	-7.3	-2.4	-10.9	17.3	-8.3
BAI-CAF	-	9.76	-2.2	0.0	-14.5	8.1	-10.0
	-	8.74	-0.2	-1.3	-8.3	3.3	-6.4
	-	7.11	-3.2	-2.4	-18.8	16.9	-11.1
	-	9.30	-48.2	0.0	-17.5	63.2	-27.2
	-	9.88	-24.0	-6.1	-10.4	26.1	-22.8
	x, y, z	4.56	-2.9	-1.3	-47.9	24.6	-30.5
	-x, y+1/2, -z+1/2	9.20	-2.3	-1.3	-8.8	6.0	-7.3
	-	8.13	-45.7	-12.3	-10.7	41.1	-41.4
	-x, -y, -z	7.82	-3.6	-1.7	-10.1	5.9	-10.3
	-	7.48	-2.3	-0.9	-18.3	10.3	-12.6
	-	8.04	-35.6	-6.1	-18.7	35.9	-36.3
	-	8.29	-9.3	-3.6	-16.6	9.9	-20.9
	-	7.52	-2.3	-0.8	-11.9	8.7	-8.0

-x, -y, -z	9.46	-0.8	-0.4	-9.4	7.9	-4.5
-	12.37	0.5	-0.4	-5.7	3.2	-2.8
x, y, z	4.56	1.4	-3.0	-75.8	47.0	-37.6
-	8.74	-0.2	-0.3	-8.3	3.3	-5.6
-	10.39	-0.1	-0.5	-7.9	5.1	-4.2
-	8.89	-3.7	-0.6	-8.2	3.5	-9.3
-	7.11	-3.2	-2.4	-18.8	16.9	-11.1
-	9.05	-55.6	-12.3	-13.1	56.9	-44.1
-	10.31	-0.2	-0.6	-12.2	8.5	-6.0
-	7.52	-2.3	-1.3	-11.9	8.7	-8.4
-	8.29	-9.3	-3.6	-16.6	9.9	-20.9
-	8.13	-45.7	-12.3	-10.7	41.1	-41.4
-	7.71	-2.2	-2.3	-14.8	7.2	-12.4
-	8.04	-35.6	-6.6	-18.7	35.9	-36.7
-	9.88	-24.0	-6.1	-10.4	26.1	-22.8
-x, y+1/2, -z+1/2	7.88	-18.2	-5.3	-11.8	22.2	-19.7
-x, -y, -z	12.41	-2.2	-0.4	-10.9	8.3	-7.0
x, y, z	4.56	-8.1	-1.1	-75.5	41.2	-49.7
-	7.48	-2.3	-1.0	-18.3	10.3	-12.7
-x, y+1/2, -z+1/2	10.18	-1.5	-0.4	-2.7	0.1	-4.2
-	9.30	-48.2	-9.8	-17.5	63.2	-34.5

REFERENCE

1. Turner, M. J.; Grabowsky, S.; Jayatilaka, D.; Spackman, M. A., Accurate and efficient model energies for exploring intermolecular interactions in molecular crystals. *J. Phys. Chem. Lett.* 2014, 5, (24), 4249-4255.