SUPPORTING INFORMATION

Two-component molecular crystals: Relationship between the entropy term and the molecular volume of co-crystal formation

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CONTENT:

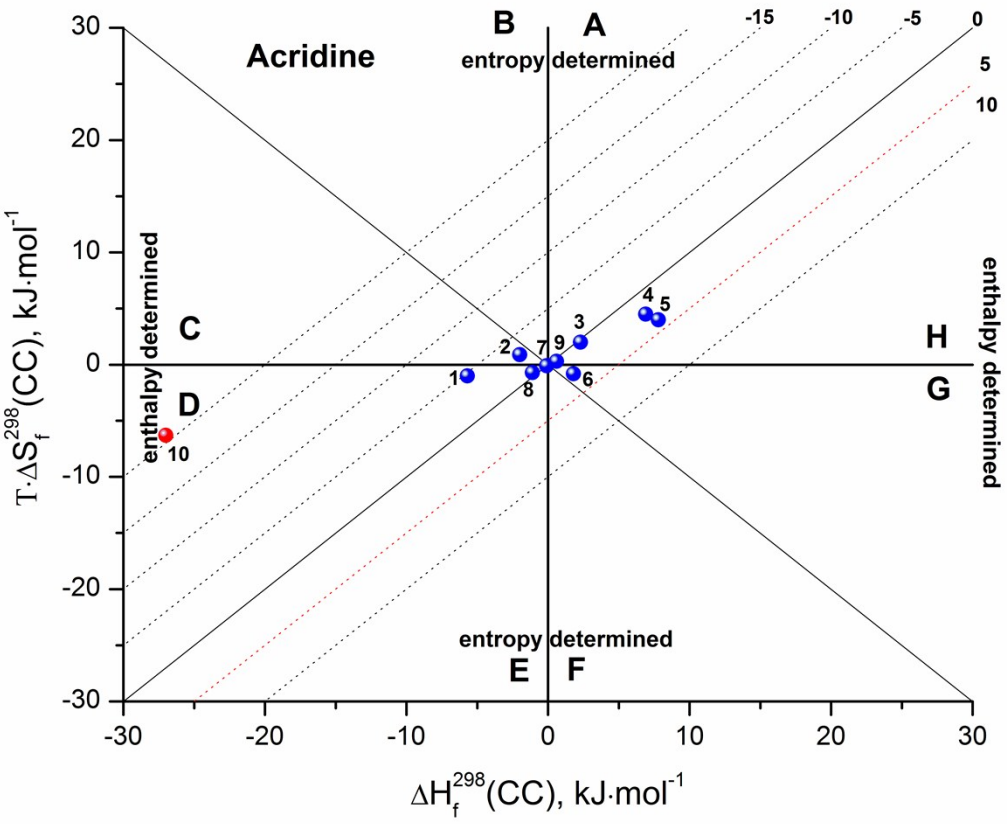

Fig. 1S Thermodynamic functions of Acridine two-component crystals formation in the entropy vs. enthalpy co-ordinates. The isoenergetic curves of the $\Delta G_f^{298}(CC)$ function are marked by dotted lines. The blue points correspond to the co-crystals with a stoichiometry of (1:1), whereas the red point corresponds to the co-crystal with a stoichiometry of (2:1). The numbering corresponds to the following CF: 1 – Benzoic Acid (BA); 2 – 2-F-BA; 3 – 2-Cl-BA; 4 – 2-Br-BA; 5 – 2-I-BA; 6 – 3-F-BA; 7 – 3-Cl-BA; 8 – 3-Br-BA; 9 – 3-I-BA; 10 – Phloroglucinol.

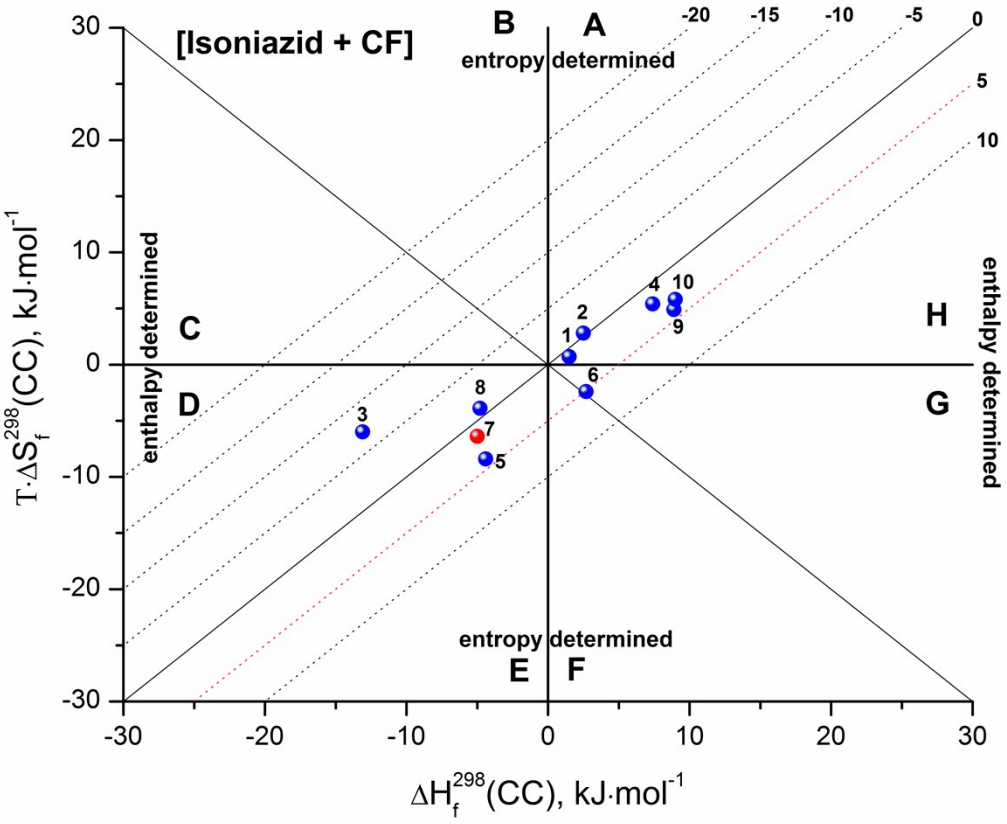

Fig. 2S Thermodynamic functions of Isoniazid two-component crystals formation in the entropy vs. enthalpy co-ordinates. The isoenergetic curves of the $\Delta G_f^{298}(CC)$ function are marked by dotted lines. The blue points correspond to the co-crystals with a stoichiometry of (1:1), whereas the red point corresponds to the co-crystal with a stoichiometry of (2:1). The numbering corresponds to the following CF: 1 – Gallic acid; 2 – 2,3-OH-Benzoic Acid (2,3-OH-BA); 3 – 3,5-OH-BA; 4 – 3-OH-BA; 5 – Cinnamic acid; 6 – Resorcinol; 7 – Malonic Acid; 8 – Pimelic Acid; 9 – 4-OH-BA; 10 – 2,4-OH-BA.

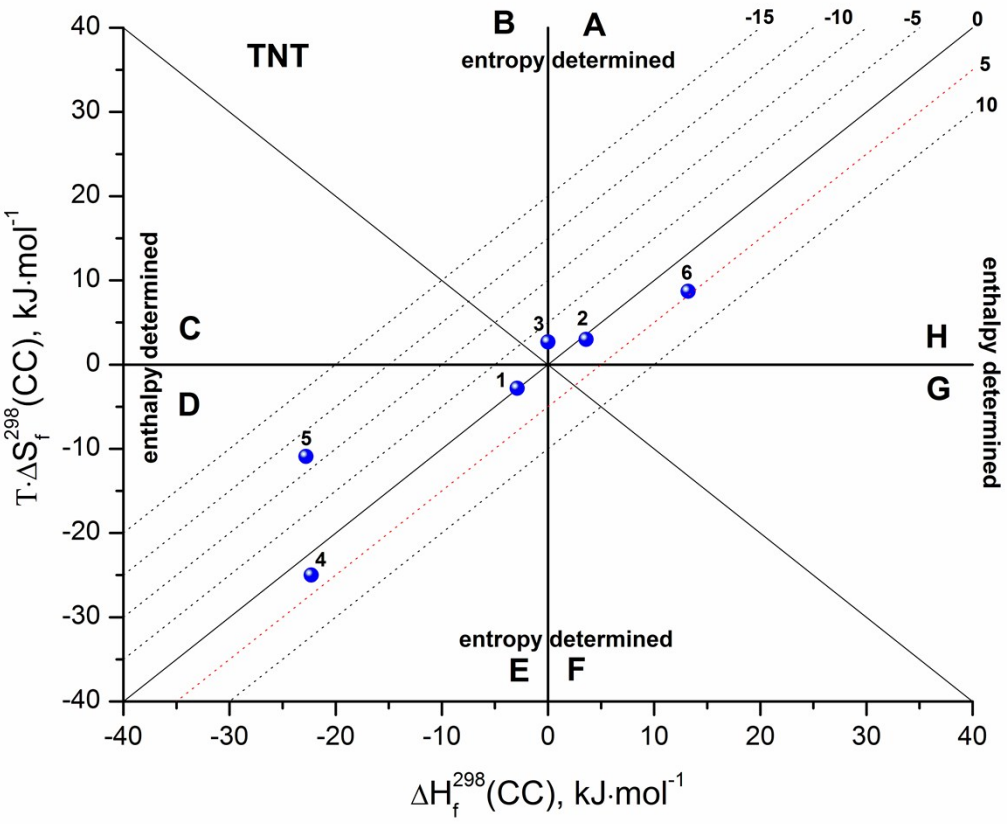

Fig. 3S Thermodynamic functions of TNT two-component crystals formation in the entropy vs. enthalpy co-ordinates. The isoenergetic curves of the $\Delta G_f^{298}(CC)$ function are marked by dotted lines. The blue points correspond to the co-crystals with a stoichiometry of (1:1). The numbering corresponds to the following CF: 1 – Anthracene; 2 – Tetrathiafulvalene; 3 – 4-NH_2-BA; 4 – Phenothiazine; 5 – 1,2-phenylenediamine; 6 – Phenanthrene.

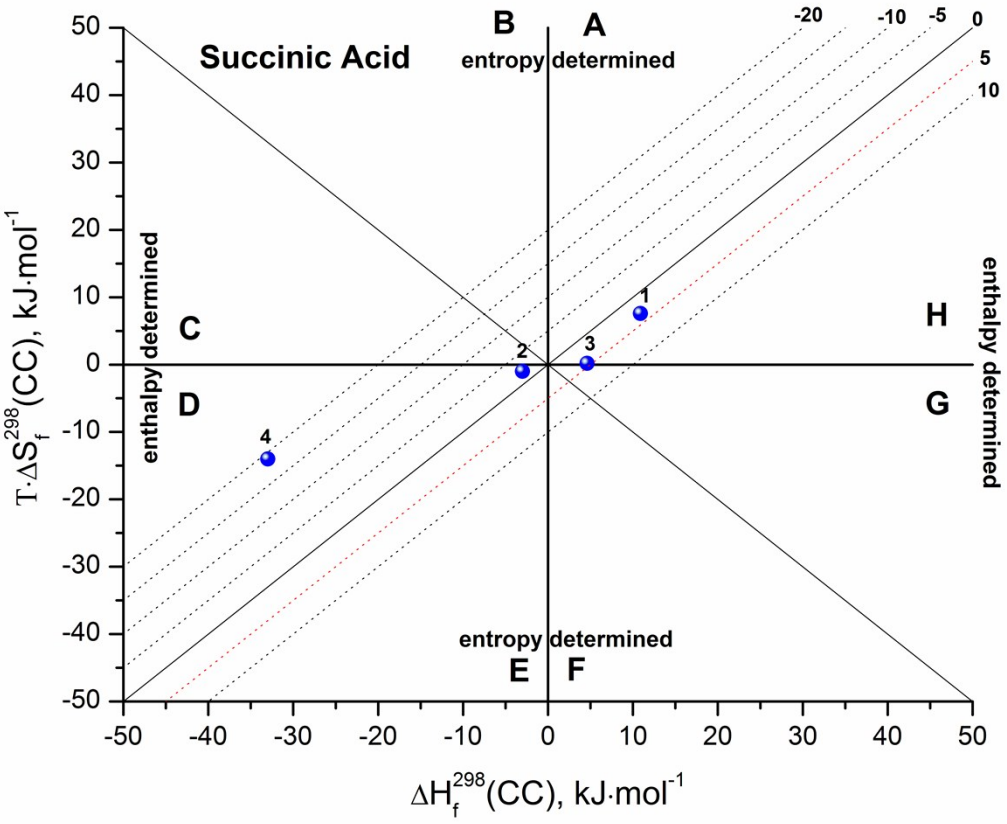

Fig. 4S Thermodynamic functions of Succinic Acid two-component crystals formation in the entropy vs. enthalpy co-ordinates. The isoenergetic curves of the $\Delta G_f^{298}(CC)$ function are marked by dotted lines. The blue points correspond to the co-crystals with a stoichiometry of (1:1). The numbering corresponds to the following CF: 1 – Urea; 2 – Pyrazine; 3 – Adenine; 4 – 1,2-NH_2–Ph.

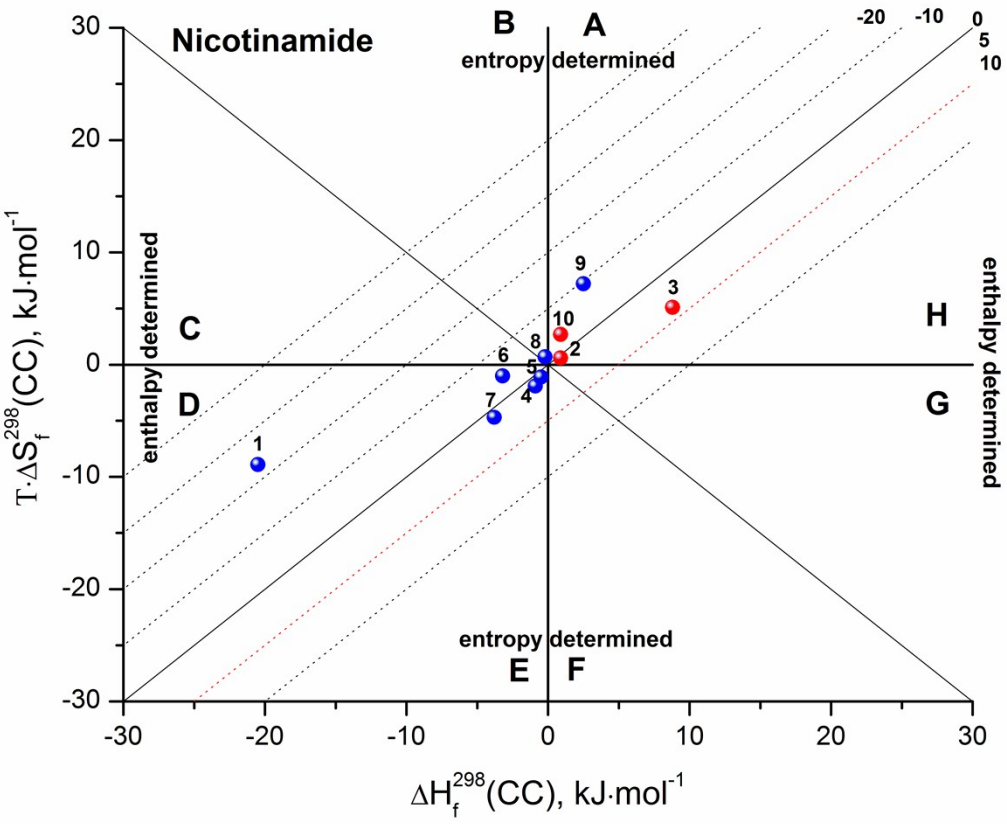

Fig. 5S Thermodynamic functions of Nicotinamide two-component crystals formation in the entropy vs. enthalpy co-ordinates. The isoenergetic curves of the $\Delta G_f^{298}(CC)$ function are marked by dotted lines. The blue points correspond to the co-crystals with a stoichiometry of (1:1), whereas the red point corresponds to (2:1). The numbering corresponds to the following CF: 1 – Flufenamic Acid; 2 – Tolfenamic Acid (2:1); 3 – Mefenamic Acid (2:1); 4 – (RS)-Ibuprofen; 5 – (S)-Ibuprofen; 6 – Salicylic Acid; 7 – 3-OH-Benzoic Acid; 8 – 4-OH-Benzoic Acid; 9 – Fumaric Acid (1:1); 10 – Fumaric Acid (2:1).

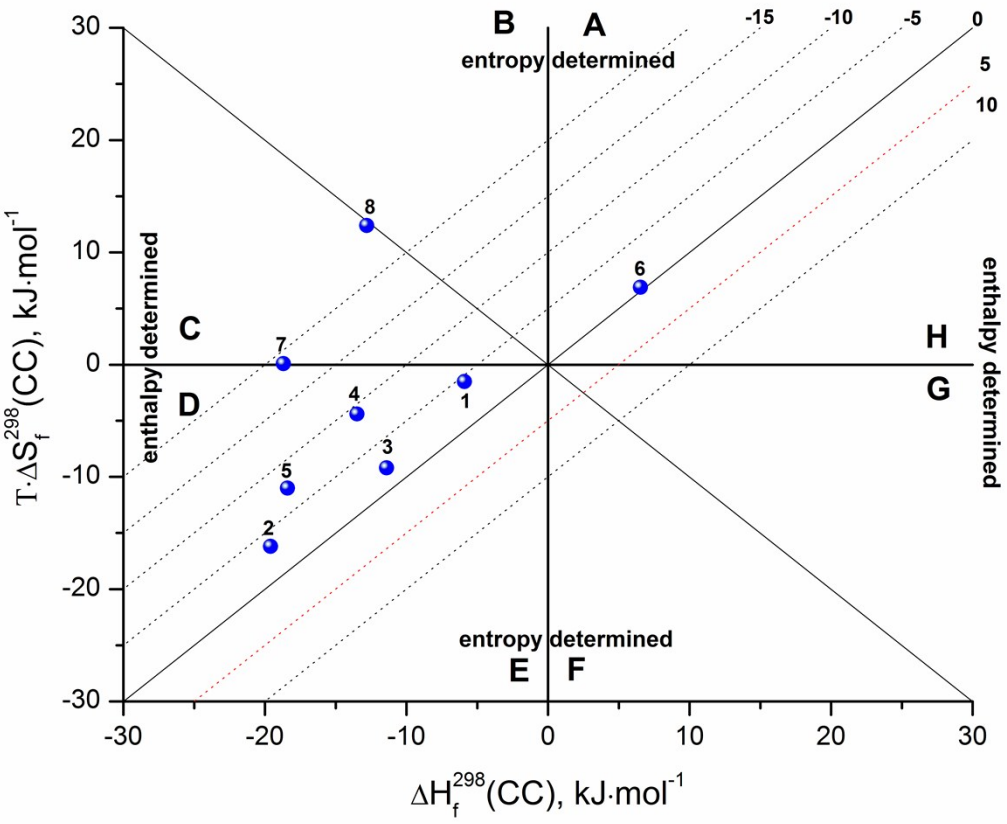

Fig. 6S Thermodynamic functions of the experimental obtained data of two-component crystals formation in the entropy vs. enthalpy co-ordinates. The isoenergetic curves of the $\Delta G_f^{298}(CC)$ function are marked by dotted lines. The blue points correspond to the co-crystals with a stoichiometry of (1:1). The numbering corresponds to the following CF: 1 – [CBZ + Saccharin] (1:1); 2 – [Bicalutamide + Benzamide] (1:1); 3 – [Bicalutamide + 2-OH-Benzamide] (1:1); 4 – [Vanillin isoniazid + Saccharin] (1:1); 5 – [Salinazid + Saccharin] (1:1); 6 – [Celecoxib + Nicotinamide] (1:1); 7 – [Arbidol + Benzoic Acid] (1:1); 8 – [Arbidol + Salicylic Acid] (1:1). For details see Table 2S.

Table 1S. Experimental and calculated values of thermodynamic functions (in kJ·mol^{-1}) of co-crystals formation

API	CF	Solvent	Stoich	$\Delta G_f^{298}(CC)_{\text{exp}}$	$\Delta H_f^{298}(CC)_{\text{exp}}$	$\Delta G_f^{298}(CC)_{\text{cal}}$	$\Delta H_f^{298}(CC)_{\text{cal}}$	Ref
Felodipine	4-4'-bipyridine	Methanol (25 °C)	1:1	-	-5.2	-	-7.1	1
CBZ[a]	Nicotinamide	Ethanol (25 °C)	1:1	-4.8	–			2
CBZ	Nicotinamide	Buffer pH 6.0 (25 °C)	1:1	0.87	–			2
CBZ	Nicotinamide	Ethanol (25 °C)	1:1	-4.82	–			2
CBZ	Nicotinamide	EtOAc (25 °C)	1:1	-5.17	–			2
		Average		-3.48	–	0	–	
Theophylline	Glutaric acid	Chloroform (30 °C)	1:1	-0.40	–	-2.8	–	3
Benzoic acid	Isonicotinamide	Ethanol (20 °C)	1:1	-10.80	–	-9.8	–	4
CBZ	Glutaric acid	Buffer pH 2.0 (25 °C)	1:1	-1.14	–			5
CBZ	Glutaric Acid	EtOAc (25 °C)	1:1	-4.23	–			5
CBZ	Glutaric Acid	Ethanol (25 °C)	1:1	-3.54	–			5
CBZ	Glutaric Acid	Isopropyl alcohol (25 °C)	1:1	-3.23	–			5
		Average		-3.04	–	1.8	–	
Theophylline	Nicotinamide	Buffer pH 5.8 (25 °C)	1:1	-0.37	–			5
Theophylline	Nicotinamide	Isopropyl alcohol (25 °C)	1:1	0.49	–			5
Theophylline	Nicotinamide	Ethanol (25 °C)	1:1	-3.04	–			5
Theophylline	Nicotinamide	EtOAc (25 °C)	1:1	-3.04	–			5
		Average		-1.5	–	-1.5	–	

[a]CBZ – Carbamazepine;

[1] Surov A.O., Solanko K.A., Bond A.D., Bauer-Brandl A., Perlovich G.L. CrystEngComm 2014, 16, 6603-6611.
[2] Schartman R.R. et al. Int. J. Pharm., 2009, 365, 77–80.
[3] Zhang S. and Rasmuson A.C., Crystal Growth & Design, 2013, 13, 1153–1161.
[4] Boyd S., Back K., Chadwick K., Davey R.J. and Seaton C.C., J. Pharm. Sci., 2010, 99, 3779–3786.
[5] Good D.J. et al. Crystal Growth & Design, 2009, 9(5), 2252-2264.

Table 2S. Results of correlation analysis using equation $T\Delta S_f^{298}(CC) = A + B \cdot \Delta V_f$

№	API	A	B	R	SD	n
1	Acridin	-5.21 ± 0.71	0.46 ± 0.05	0.9504	1.00	10
2	Isoniazid	-1.58 ± 0.44	0.50 ± 0.05	0.9703	1.33	9[a]
3	TNT	36.6 ± 1.1	2.96 ± 0.08	0.9988	0.73	5[b]
4	Succinic Acid	2.64 ± 0.80	1.91 ± 0.16	0.9919	1.40	4
5	Nicotinamide	-4.34 ± 0.84	0.69 ± 0.11	0.9400	1.84	7[c]
	Experimental Data	-0.14 ± 0.91	0.41 ± 0.04	0.9725	1.97	7[d]

[a] Co-crystal [Isoniazid + 2,4-OH-Benzoic Acid] has been rejected from the consideration;
[b] Co-crystal [TNT + 1,2-phenylenediamine] has been rejected from the consideration;
[c] Co-crystals [Nicotinamide + Tolfenamic Acid] (2:1), [Nicotinamide + Mefenamic Acid] (2:1) and [Nicotinamide + Fumaric Acid] (2:1) have been rejected from the consideration;
[d] Co-crystal [Arbidol + Salicylic Acid] (1:1) has been rejected from the consideration;

Table 3S. Experimental data of thermodynamic characteristics of co-crystals formation taken from literature

№	API	CF	Stoich	Solvent	T [°C]	$\Delta G_f^{298}(CC)$ [kJ·mol^{-1}]	$\Delta H_f^{298}(CC)$ [kJ·mol^{-1}]	$T\Delta S_f^{298}(CC)$ [kJ·mol^{-1}]	$\Delta V_f(CC)$ [Å^3]	Ref
1	CBZ	Saccharin	1:1	Methanol	33	-4.6	-5.9	-1.5	-2.52	1
2	Bicalutamide	Benzamide	1:1	Chloroform	25	-3.4	-19.6	-16.2	-34.9	2
3	Bicalutamide	2-OH-Benzamide	1:1	Chloroform	25	-2.2	-11.4	-9.2	-27.97	2
4	Vanillin isoniazid	Saccharin	1:1	Water	25	-9.1	-13.5	-4.4	-15.24	3
5	Salinazid	Saccharin	1:1	Water	25	-7.3	-18.4	-11	-20.4	3
6	Celecoxib	Nicotinamide	1:1	Chloroform	25	-0.35	6.54	6.9	18.2	4
7	Arbidol	Benzoic Acid	1:1	Ethyl Acetate	25	-18.6	-18.7	0.1	-0.37	5
8	Arbidol	Salicylic Acid	1:1	Ethyl Acetate	25	-25.2	-12.8	12.4	-1.24	5

[1] M.A. Oliveira, M.L. Peterson, R.J. Davey, *Crystal Growth & Design,* 2011, **11**, 449.
[2] A.O. Surov, K.A. Solanko, A.D. Bond, A. Bauer-Brandl, G.L. Perlovich, *CrystEngComm*, 2016, **18**, 4818.
[3] A.O. Surov, A.P. Voronin, A.A. Simagina, A.V. Churakov, S.Y. Skachilova, G.L. Perlovich, *New J. Chem.*, 2015, **39**, 8614.
[4] S.-W. Zhang, A.P.J. Brunskill, E. Schwartz, S. Sun, *Crystal Growth & Design,* 2017, **17**(5), 2836.
[5] A.O. Surov, A.N. Manin, A.V. Churakov, G.L. Perlovich, *Molecular Pharmaceutics*, 2015, **12** (11), 4154.