Electronic Supplementary Information (ESI)

for

Identification of previously unreported co-crystal form of acetazolamide: a combination of multiple experimental and virtual screening methods

Alex N. Manin [a], Ksenia V. Drozd [a], Artem O. Surov [a], Andrei V. Churakov [b], Tatyana V. Volkova [a], German L. Perlovich [a,]*

[a]G.A. Krestov Institute of Solution Chemistry RAS, 153045, Ivanovo, Russia
[b]Institute of General and Inorganic Chemistry RAS, Leninsky Prosp. 31, 119991, Moscow, Russia
[*]Corresponding author: glp@isc-ras.ru

Contents

S1. Hansen solubility parameter

To predict the substance physicochemical properties, such as solubility, melting point, etc., it is possible to use solubility parameters.[1] Cohesion energy represents the sum of the forces (van der Waals interactions, covalent, hydrogen and ionic bonds) which hold the substance in its original state. Cohesion energy can also be defined as the energy that must be overcome in order to move a substance molecule from the liquid or solid phase to the gaseous one.[1] Cohesion energy per unit volume is called cohesion energy density (CED). CED can be used to calculate the solubility parameter (δ) as follows:[2]

$$\delta = (CED)^{0.5} = \left(\frac{\Delta E_V}{V_m} \right)^{0.5} \quad \text{S1}$$

where ΔE_V is the evaporation energy, V_m is the molar volume. Parameter δ is measured in the following units: $(J/cm^3)^{0.5}$, $MPa^{0.5}$ or $(cal/cm^3)^{0.5}$, where $1(cal/cm^3)^{0.5}$ is equivalent to 2.0421 $MPa^{0.5}$ or $(J/cm^3)^{0.5}$.

Recently, Hansen's solubility parameters (HSPs) have been increasingly used to assess the solubility of drugs. In the Hansen approximation, the parameters of any organic substance consist of three components: solubility parameters characterized by the dispersion forces δ_d, polarization interactions δ_p and interactions resulting from the formation of hydrogen bonds δ_h. The total solubility parameter δ_t, or the three-dimensional solubility parameter, is determined as follows:

$$\delta_t = (\delta_d^2 + \delta_p^2 + \delta_h^2)^{0.5} \quad \text{S2}$$

Various theoretical and experimental methods based on solubility, calorimetry, sublimation, evaporation, reverse gas chromatography, and group contribution were used to estimate the HSPs of the substances.[3] Each component of the solubility parameter (δ_d , δ_p , δ_h) was calculated in the following way:[4,5]

$$\delta_d = \frac{\sum_i F_{d_i}}{\sum_i V_i} \quad \text{S3}$$

$$\delta_p = \frac{\left(\sum_i F_{p_i}^2 \right)^{0.5}}{\sum_i V_i} \quad \text{S4}$$

$$\delta_h = \left(\frac{\sum_i F_{h_i}}{\sum_i V_i} \right)^{0.5} \quad \text{S5}$$

where i is the structural group within the molecule, F_{d_i} is the group contribution to the dispersion forces, F_{p_i} is the group contribution to the polarization forces, F_{h_i} is the group contribution to the hydrogen bonding energy, and V_i is the group contribution to the molar volume.

The miscibility of compounds can be evaluated by various approaches, all of which are based on the general principle of "like dissolves like". In other words, compounds with similar δ values are more likely dissolve each other. Van Krevelen and Hoftyzer determined the miscibility of two compounds using $\Delta\overline{\delta}$, which is calculated as follows:

$$\Delta\overline{\delta} = \left[(\delta_{d2} - \delta_{d1})^2 + (\delta_{p2} - \delta_{p1})^2 + (\delta_{h2} - \delta_{h1})^2 \right]^{.5} \quad \text{S6}$$

Later, Krevlen et al. suggested that good solubility could be achieved if $\Delta\overline{\delta} < 5$ MPa$^{0.5}$.[5] Besides this, Bagley et al. noticed that the effects of δ_d and δ_p are thermodynamically similar, while the effect of δ_h differs in its nature from the others. In this regard, they introduced a volume dependent solubility parameter - δ_v:[6]

$$\delta_v = (\delta_d^2 + \delta_p^2)^{0.5} \quad \text{S7}$$

Subsequently, the coefficient $R_{a(v)}$ was used to determine the solubility of two compounds:

$$R_{a(v)} = \left[4(\delta_{v2} - \delta_{v1})^2 + (\delta_{h2} - \delta_{h1})^2 \right]^{.5} \quad \text{S8}$$

A two-dimensional plot of the δ_v dependence on δ_h is called the Bagley diagram. This diagram has been used for various purposes, including the study of the solubility (miscibility) of components and predicting the duration of the intestinal absorption of different drugs.[7,8] In the study of the drug/polymer miscibility, it was found that these two components are well miscible if $R_{a(v)} \leq 5.6$ MPa$^{0.5}$.[7]

Greenhalgh et al. used the difference in the total solubility parameter between the drug and the carrier ($\Delta\delta_t$) as a tool for predicting miscibility:[9]

$$\Delta\delta_t = \left| \delta_{t2} - \delta_{t1} \right| \quad \text{S9}$$

where *t1* and *t2* are the carrier and the drug, respectively. In their work, studying many API/carrier systems as an example, the authors showed the general trend, indicating that systems with $\Delta\delta_t < 7$ MPa$^{0.5}$ are miscible, while systems with $\Delta\delta_t > 10$ MPa$^{0.5}$ are immiscible.[9]

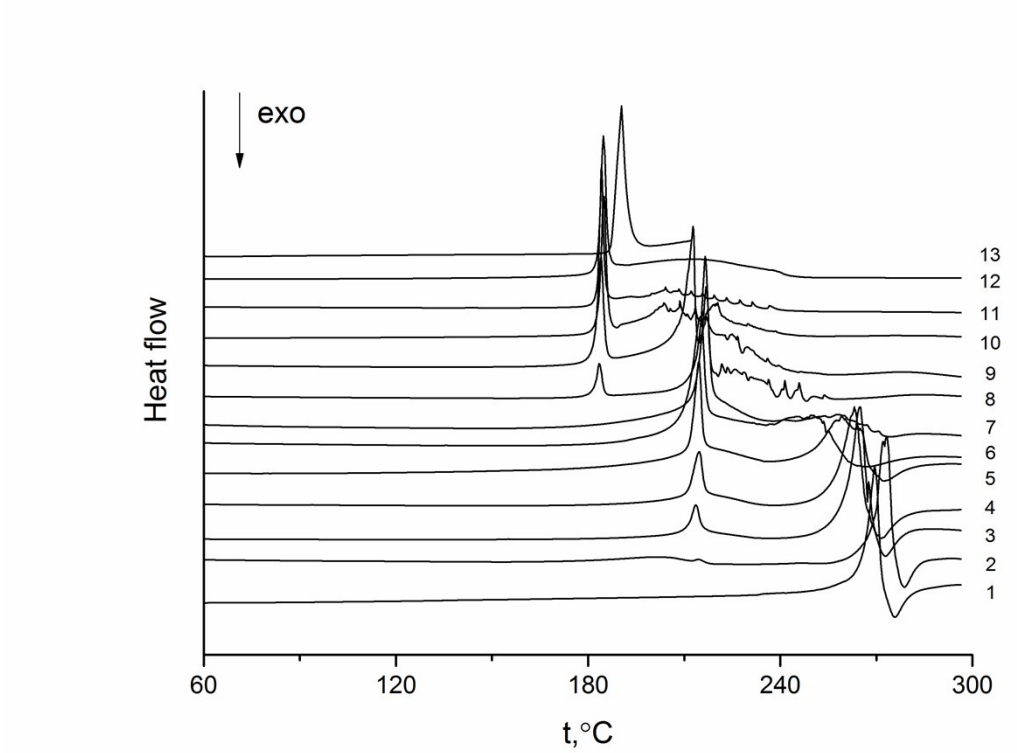
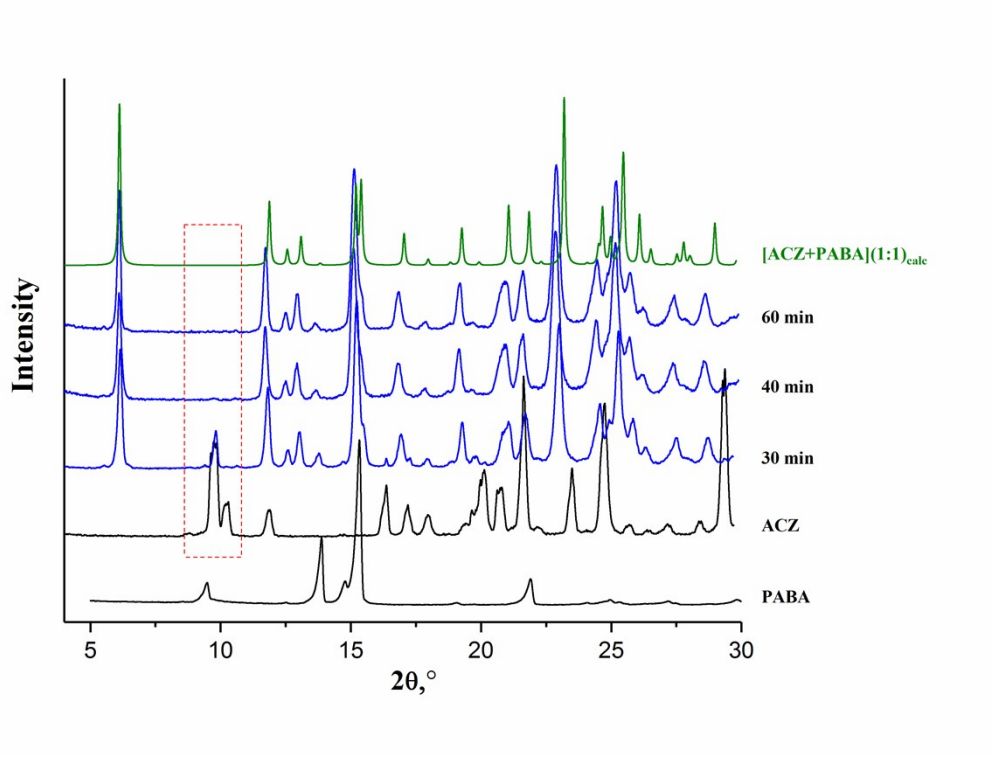
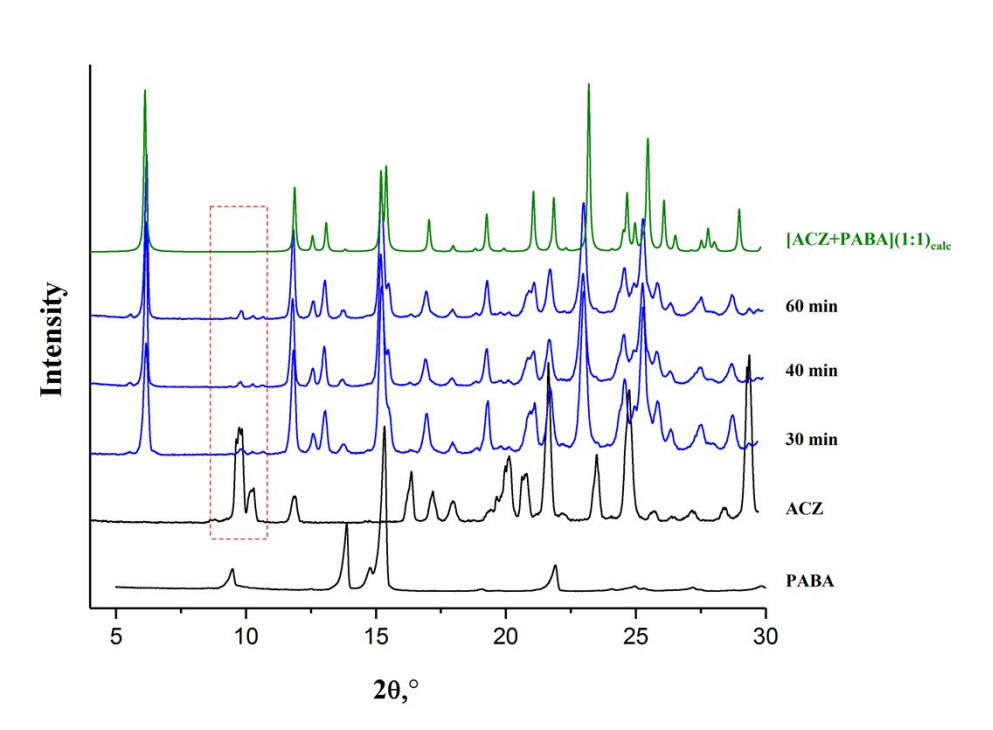


Figure S1. DSC heating for the selected (ACZ+PABA) mixtures at a heating rate of 10°C·min^{-1}. **1**. X_{PABA}=0; **2**. X_{PABA}=0.09; **3**. X_{FBP}=0.11; **4**. X_{PABA}=0.2; **5**. X_{PABA}=0.33; **6**. X_{PABA}=0.4; **7**. X_{PABA}=0.5; **8**. X_{PABA}=0.6; **9**. X_{PABA}=0.67; **10**. X_{PABA}=0.8; **11**. X_{PABA}=0.89; **12**. X_{PABA}=0.91; **13**. X_{PABA}=1



(**a**)



(**b**)

Figure S2. Time resolved XRPD patterns for the LAG reaction of ACZ and PABA (1:1) in the presence of (a) ACN and (b) H_2O

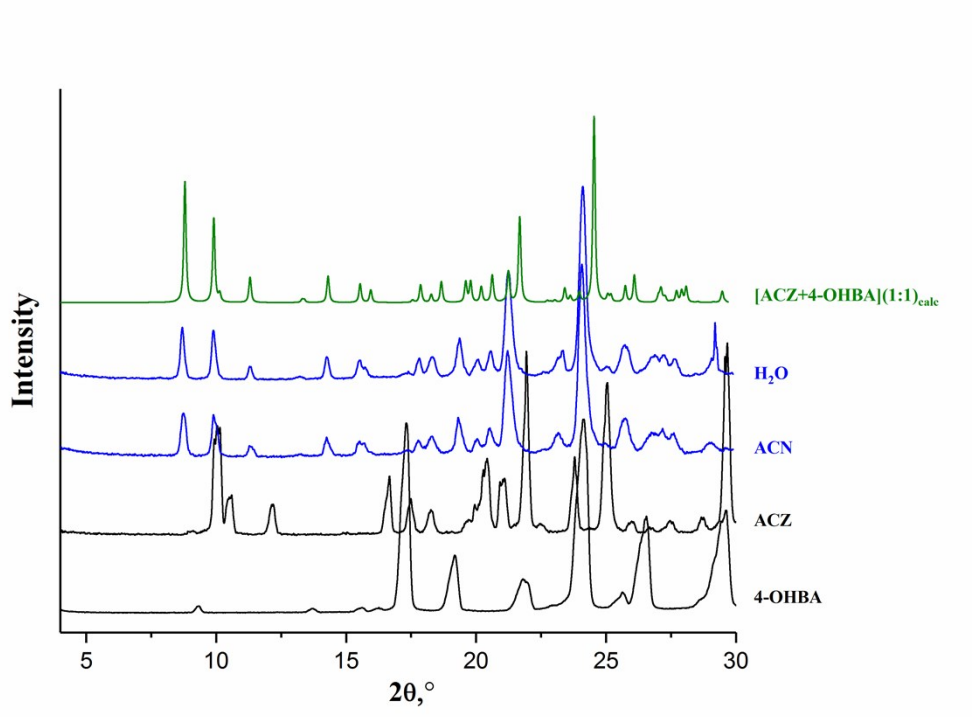
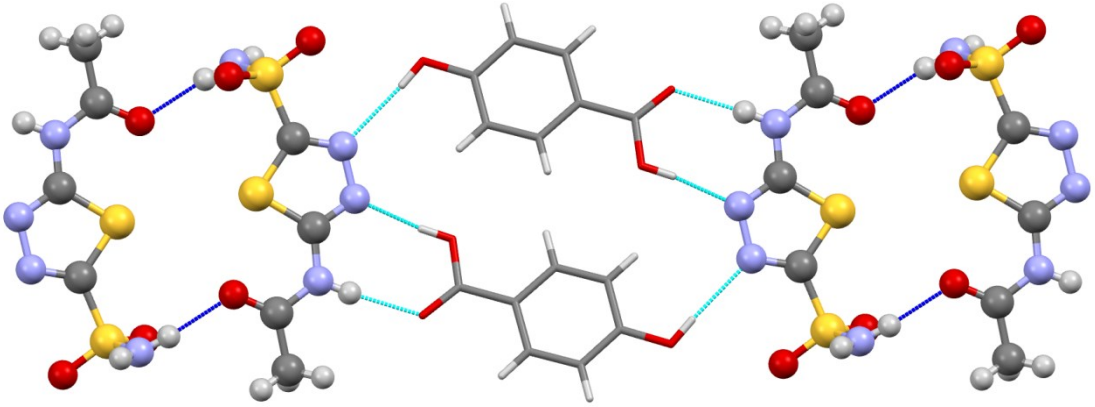
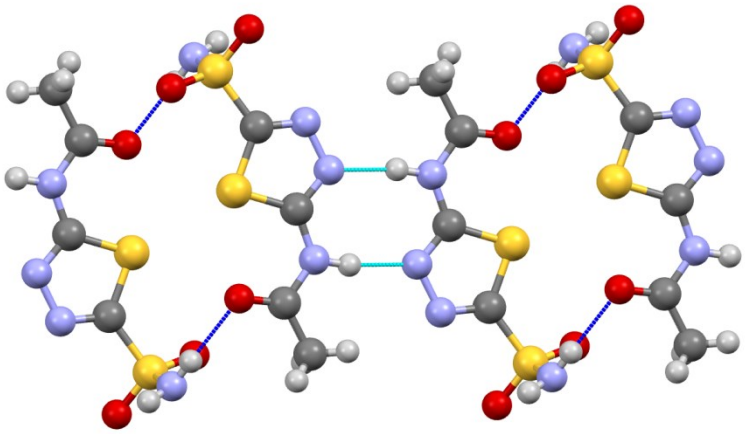


Figure S3. Experimental XRPD patterns of the [ACZ+4-OHBA] co-crystal obtained by LAG with ACN and H_2O after 30 min

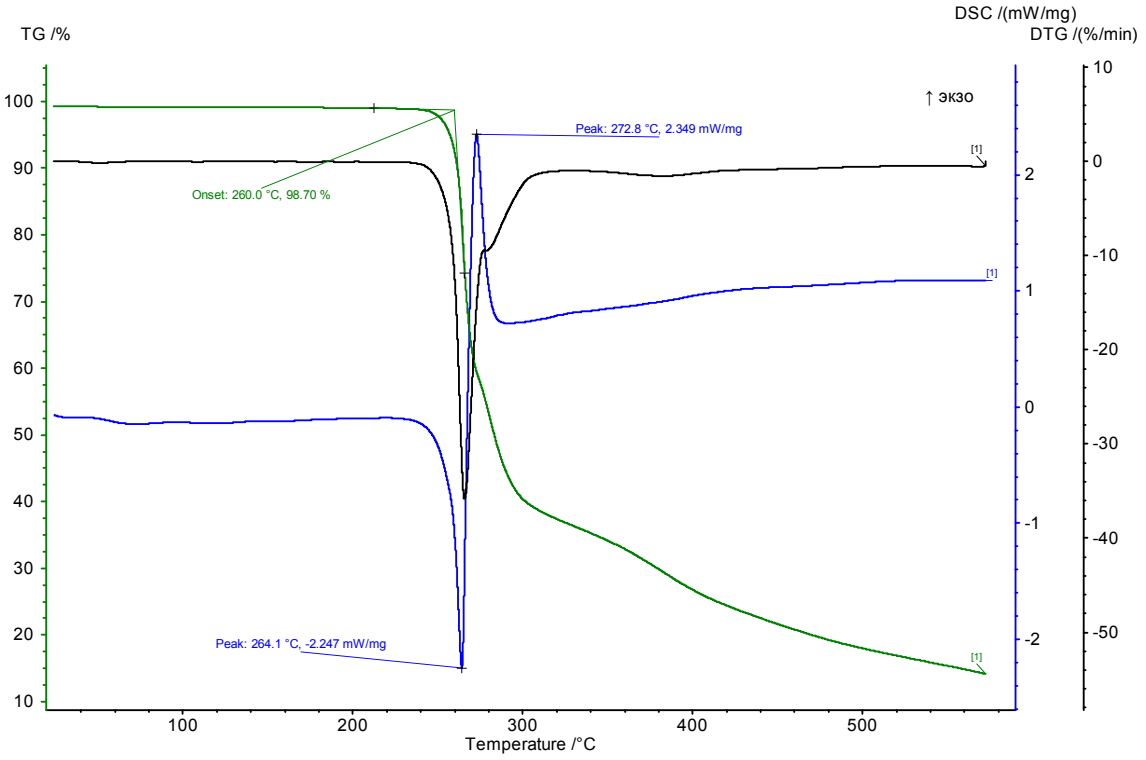


(a)

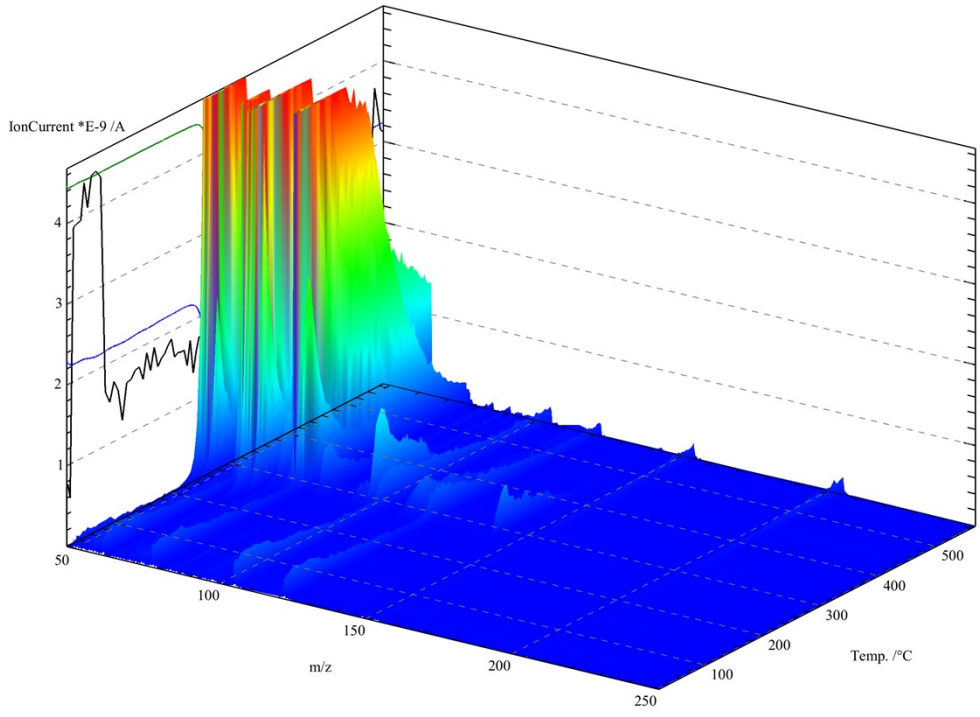


(b)

Figure S4. Illustration of ACZ dimers connected by $N_{sulfonamide}$-H···$O_{acetamide}$ hydrogen bonds (colored in blue) in the crystal structures of (a) [ACZ+PABA] (1:1) and (b) pure ACZ



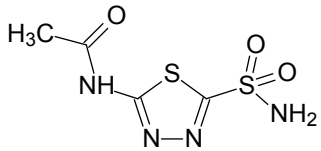
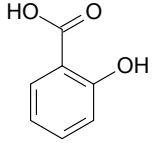
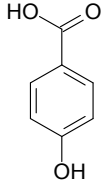
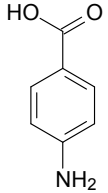
a

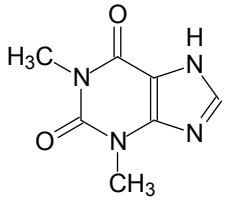
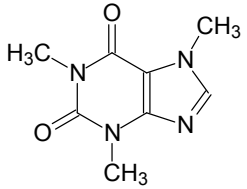
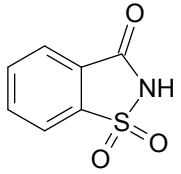


b

Figure S5. (a) DSC/TG/DTG curves of ACZ; (b) mass-spectrum of ACZ

Table S1. Group contribution parameters and associated molar volumes of the compounds according to the Hoftyzer–Van Krevelen method

Compound	Structural group	Quantity	F_{d_i}, $(J \cdot m^3)^{0.5} \cdot mol^{-1}$	$F_{p_i}^{\ 2}$, $(J \cdot m^3)^{0.5} \cdot mol^{-1}$	F_{h_i}, $J \cdot mol^{-1}$	$^{a}V_i$, $cm^3 \cdot mol^{-1}$
Acetazolamide (ACZ) 	$-CH_3$	1	420	0	0	33.5
	=C<	2	140	0	0	-11.0
	–CO–	1	290	592900	2000	10.8
	–NH–	1	160	44100	3100	4.5
	$-NH_2$	1	300	193600	8600	19.2
	–N=	2	40	2560000	10000	10.0
	–S–	1	440	-	-	12.0
	$-SO_2-$	1	1129	1844164	11670	51.0
	Σ		**2919**	**5234764**	**35370**	**130.0**
Salicylic acid (SA) 	Phenylene (o, m, p)	1	1270	12100	0	52.4
	–COOH	1	530	176400	10000	28.5
	–OH	1	210	250000	20000	13.0
	Σ		**2010**	**438500**	**30000**	**93.9**
4-Hydroxybenzoic acid (4-OHBA) 	Phenylene (o, m, p)	1	1270	12100	0	52.4
	–COOH	1	530	176400	10000	28.5
	–OH	1	210	250000	20000	13.0
	Σ		**2010**	**438500**	**30000**	**93.9**
4-Aminobenzoic acid (PABA) 	Phenylene (o, m, p)	1	1270	12100	0	52.4
	–COOH	1	530	176400	10000	28.5
	$-NH_2$	1	300	193600	8600	19.2
	Σ		**2100**	**382100**	**18600**	**100.1**
Theophylline (Tph)	$-CH_3$	2	840	0	0	67.0

	=CH–	1	200	0	0	13.5
	=C<	2	140	0	0	-11.0
	–CO	2	580	2371600	4000	21.6
	–NH–	1	160	44100	3100	4.5
	–N<	2	40	2560000	10000	-18.0
	–N=	1	20	640000	5000	5.0
	Σ		**1980**	**5615700**	**22100**	**82.6**
Caffeine (Caf)	$–CH_3$	3	1260	0	0	100.5
	=CH–	1	200	0	0	13.5
	=C<	2	140	0	0	-11.0
	–CO	2	580	2371600	4000	21.6
	–N<	3	60	5760000	15000	-27.0
	–N=	1	20	640000	5000	5.0
	Σ		**1972**	**8771600**	**24000**	**102.6**
Saccharin (Sacch)	=CH–	4	800	0	0	54.0
	=C<	2	140	0	0	-11.0
	–CO	1	290	595900	2000	10.8
	–NH–	1	160	44100	3100	4.5
	$–SO_2–$	1	1129	1844164	11670	51.0
	Σ		**2519**	**2481164**	**16770**	**109.3**

[a] The molar volume is calculated according to [4]

Table S2. Molar volumes and HSPs for the selected compounds and solvents

	V_m, $cm^3 \cdot mol^{-1}$	[a] δ_d, $MPa^{0.5}$	[b] δ_p, $MPa^{0.5}$	[c] δ_h, $MPa^{0.5}$	[d] δ_t, $MPa^{0.5}$	[e] δ_v, $MPa^{0.5}$	[f] $\Delta\overline{\delta}$, $MPa^{0.5}$	[g] $\Delta\delta_t$, $MPa^{0.5}$	[h] $R_{a(v)}$, $MPa^{0.5}$
ACZ	130.0	22.5	17.6	16.5	33.0	28.5	-	-	-
SA	93.9	21.4	7.1	17.9	28.8	22.5	10.7	4.2	12.3
4-OHBA	93.9	21.4	7.1	17.9	28.8	22.5	10.7	4.2	12.3
PABA	100.1	21.0	6.2	13.6	25.8	21.9	11.9	7.2	14.5
Tph	82.6	24.0	28.7	16.4	40.8	37.4	11.2	7.9	17.7
Caf	102.6	19.2	28.9	15.3	37.9	34.7	11.8	4.9	12.5
Sacch	109.3	23.0	14.4	12.4	29.9	27.2	5.2	3.1	8.6
ACN	52.9	15.3	18.0	6.1	24.4	23.6			
EtOAc	98.6	15.8	5.3	7.2	18.2	16.7			
THF	81.9	16.8	5.7	8.0	19.5	17.7			
AO	73.8	15.5	10.4	7.0	19.9	18.7			
EtOH	58.6	15.8	8.8	19.4	26.5	18.1			
MeOH	40.6	14.7	12.3	22.3	29.4	19.2			
H_2O	18.0	15.5	16.0	42.3	47.8	22.3			

[a] $\delta_d = \sum F_d / \sum V_i$

[b] $\delta_p = (\sum F_p^2)^{0.5} / \sum V_i$

[c] $\delta_h = (\sum F_h / \sum V_i)^{0.5}$

[d] $\delta_t = (\delta_d^2 + \delta_p^2 + \delta_h^2)^{0.5}$

[e] $\delta_v = (\delta_d^2 + \delta_p^2)^{0.5}$

[f] $\Delta\overline{\delta} = \left[(\delta_{d2} - \delta_{d1})^2 + (\delta_{p2} - \delta_{p1})^2 + (\delta_{h2} - \delta_{h1})^2\right]^{0.5}$

[g] $\Delta\delta_t = \left|\delta_{t2} - \delta_{t1}\right|$

[h] $R_{a(v)} = \left[4(\delta_{v2} - \delta_{v1})^2 + (\delta_{h2} - \delta_{h1})^2\right]^{0.5}$

Table S3. Sums of the intermolecular interaction energies ($kJ \cdot mol^{-1}$) of the different types of molecules in [ACZ+4-OHBA] (1:1) and [ACZ+PABA] (1:1) calculated by the CrystalExplorer method

	ACZ-ACZ	**ACZ-CF**	**CF-CF**	**E_{latt}**
[ACZ+4-OHBA] (1:1)	-99.7 (**30.5%**)	-210.7 (**64.5%**)	-16.3 (**5.0%**)	-326.6
[ACZ+PABA] (1:1)	-64.1 (**20.3%**)	-244.5 (**77.5%**)	-7.1 (**2.2%**)	-315.7

Table S4. Solution pH, eutectic concentrations of the ACZ and coformers, calculated solubility of the co-crystals at 25.0°C

	Final pH	$[ACZ]_{eu}$, mol·L^{-1}	$[CF]_{eu}$, mol·L^{-1}	S_{CC}, mol·L^{-1}
Initial pH 2.0				
[ACZ+PABA] (1:1)	2.9	$(3.9\pm0.2)\cdot10^{-3}$	$(2.1\pm0.2)\cdot10^{-2}$	$(9.0\pm0.1)\cdot10^{-3}$
[ACZ+4-OHBA] (1:1)	2.3	$(3.8\pm0.4)\cdot10^{-3}$	$(1.6\pm0.4)\cdot10^{-2}$	$(7.7\pm0.6)\cdot10^{-3}$
Initial pH 7.4				
[ACZ+PABA] (1:1)	5.1	$(4.0\pm0.1)\cdot10^{-3}$	$(5.4\pm0.1)\cdot10^{-2}$	$(1.5\pm0.2)\cdot10^{-2}$
[ACZ+4-OHBA] (1:1)	5.0	$(4.2\pm0.06)\cdot10^{-3}$	$(5.4\pm0.1)\cdot10^{-2}$	$(1.5\pm0.2)\cdot10^{-2}$

Table S5. Coefficients of correlation equation (S10) for the clusters including the considered compound as one from the components of the two-component crystal

$$T_{fus}(CC)/°C = A + B \cdot T_{fus}(API/CF)/°C \qquad \text{S10}$$

№	API	(API:CF)	A	B	R[a]	σ[b]	n[c]	$T_{fus}([API + ACZ)$ /°C
1	Salicylic Acid	1:1	51.9 ± 8.9	0.549 ± 0.045	0.9079	14.7	34	198.2
2	4-hydroxybenzoic acid	1:1	42.1 ± 10.6	0.74 ± 0.05	0.938	15.1	27	238.7
3	4-aminobenzoic acid	1:1	52.7 ± 10.5	0.62 ± 0.05	0.935	14.4	21	218.7
4	Theophylline	1:1	79.4 ± 13.0	0.571 ± 0.075	0.8079	18.5	33	231.6
5	Caffeine	1:1	42.7 ± 9.0	0.673 ± 0.045	0.9512	16.0	26	222.1
6	Saccharine	1:1	94.1 ± 8.7	0.459 ± 0.047	0.8504	13.5	39	216.4

[a] Pair correlation coefficient;
[b] Standard deviation;
[c] The number of points in the cluster

Table S6. Experimental temperature dependences of acetazolamide (ACZ)[a] and saccharin (Sacch)[b] saturation vapor pressure

ACZ		Sacch	
t, °C	P, Pa	t, °C	P, Pa
179.7	$3.24 \cdot 10^{-2}$	122	0.807
180.9	$3.62 \cdot 10^{-2}$	124	0.997
182.2	$4.04 \cdot 10^{-2}$	125	1.046
183.3	$4.64 \cdot 10^{-2}$	126	1.215
184.1	$5.03 \cdot 10^{-2}$	127	1.284
185.0	$5.45 \cdot 10^{-2}$	128	1.408
185.8	$5.84 \cdot 10^{-2}$	130	1.766
186.7	$6.46 \cdot 10^{-2}$	131	1.935
187.8	$7.07 \cdot 10^{-2}$	134	2.504
189.1	$7.89 \cdot 10^{-2}$	136	3.005
190.2	$8.63 \cdot 10^{-2}$	138	3.750
191.1	$9.73 \cdot 10^{-2}$	140	4.484
192.0	$1.04 \cdot 10^{-1}$	141	4.717
193.1	$1.20 \cdot 10^{-1}$	143	5.662
194.3	$1.39 \cdot 10^{-1}$	-	-

[a] $\ln(P[Pa]) = (42.1 \pm 0.6) - (20599 \pm 285)/T$; $\sigma = 6.8 \cdot 10^{-3}$; r = 0.99733; F = 5221; n = 15

[a] $\ln(P[Pa]) = (38.7 \pm 0.3) - (15382 \pm 133)/T$; $\sigma = 4.9 \cdot 10^{-3}$; r = 0.9996; n = 14

Table S7. Thermodynamic parameters of sublimation of the compounds studied

Compound	ΔH_{sub}^{T}, kJ·mol^{-1}	$C_{p,cr}^{298}$, J·mol^{-1}·K^{-1} [a]	ΔG_{sub}^{298}, kJ·mol^{-1}	ΔH_{sub}^{298}, kJ·mol^{-1}	ΔS_{sub}^{298}, J·mol^{-1}·K^{-1}	$T \cdot \Delta S_{sub}^{298}$, kJ·mol^{-1}
Acetazolamide	171.3±2.5	250.1	95.5	177.5±2.6	275±12	82.0
Saccharin	127.9±1.1	136.8	60.5	130.2±1.6	233±7	69.7

[a] $C_{p,cr}^{298}$ is calculated by Chickos' additive scheme [10], the calculation procedure error corresponds to a significant digit

Table S8. Results of estimating the formation thermodynamics of two-component acetazolamide crystals

N	Coformer (CF)	Molar ratio (ACZ:CF)	$T_{fus}(API)$ / °C	$T_{fus}(CF)$ / °C	$T_{fus}(CC)$ [a] / °C	$\Delta G_{sub}^{0,298}(CF)$ / kJ·mol^{-1}	$\Delta H_{sub}^{0,298}(CF)$ / kJ·mol^{-1}	$\Delta G_{f}^{0,298}(CC)$ / kJ·mol^{-1}	$\Delta H_{f}^{0,298}(CC)$ / kJ·mol^{-1}
1	SA	1:1	266.5	158.1	198.2	38.5[b]	96.6[b]	7.4	10.5
2	4-OHBA	1:1	266.5	214.9	238.7	55.0[b]	113.3[b]	0.0	-9.2
3	PABA	1:1	266.5	187.3	218.7	52.5[c]	118.0[c]	3.2	-3.8
4	Theophylline	1:1	266.5	271.5	231.6	69.1[d]	132.5[d]	-197.5[f]	-336.6
5	Caffeine	1:1	266.5	236.1	222.1	53.0[e]	108.1[e]	40.8	66.7
6	Saccharine	1:1	266.5	227.6	216.4	60.5	130.2	27.6	37.3

[a] calculated by correlation equation (S10);
[b] from [11].
[c] from [12].
[d] from [13].
[e] from [14].
[f] The high value is obtained due to the close melting points of API and CF. In this case, the algorithm does not predict adequate values of the thermodynamic functions, however, it unambiguously indicates the direction of the reaction.

Table S9. Results of molecular complementarity (MC) methods, multi-component score and ΔE values derived from the Hydrogen Bond Propensity and Molecular Electrostatic Potential calculations

	MC	Multi-component score	ΔE
ACZ+SA	PASS	-0.16	-2.6
ACZ+4OHBA	PASS	-0.13	12.4
ACZ+PABA	PASS	0.01	6.1
ACZ+Tph	FAIL	-0.11	17.1
ACZ+Caf	FAIL	0.01	4.7
ACZ+Sacch	FAIL	-0.10	-8.3

S2. References

1. B.C. Hancock, P. York and R.C. Rowe, *Int. J. Pharm.*, 1997, **148**, 1.
2. J.H. Hildebrand and R.L. Scott, The solubility of nonelectrolytes, 1964, Dover Publications.
3. C.M. Hansen, Hansen solubility parameters: a user's handbook, second edition, 2007, CRC Press.
4. R.F. Fedors, *Polym. Eng. Sci.*, 1974, **14**, 147.
5. D.W. van Krevelen and K. te Nijenhuis, Properties of polymers: their correlation with chemical structure; their numerical estimation and prediction from additive group contributions, 2009, Elsevier Science.
6. E.B. Bagley, T.P. Nelson and J.M. Scigliano, *J. Paint. Technol.*, 1971, **43**, 35.
7. J. Albers, Hot-melt extrusion with poorly soluble drugs, 2008, Cuvillier.
8. J. Breitkreutz, *Pharm. Res.*, 1998, **15**, 1370.
9. D.J. Greenhalgh, A.C. Williams, P. Timmins and P.York, *J. Pharm. Sci.*, 1999, **88**, 1182.
10. J.S. Chickos and W. Acree Jr., *J. Phys. Chem. Ref. Data*, 2003, **32**, 519.
11. G.L. Perlovich, T.V. Volkova and A. Bauer-Brandl, *J. Pharm. Sci.*, 2006, **95**, 2158.
12. T.V. Volkova, S.V. Blokhina, A.M. Ryzhakov, A.V. Sharapova, M.V. Ol'khovich and G.L. Perlovich, *J. of Therm. Anal. Calorim.*, 2016, **123**, 841.
13. A. Abdelaziz, D.H. Zaitsau, A. Buzyurove, A.A. Minakovf, S.P.Verevkin and C.Schick, *Thermochim. Acta*, 2019, **676**, 249.
14. V.N. Emel'yanenko and S.P. Verevkin, *J. Chem. Thermodyn.*, 2008, **40**, 1661.