Electronic Supplementary Information (ESI)

A combined experimental and theoretical study of miconazole salts and cocrystals: crystal structures, DFT computations, formation thermodynamics and solubility improvement.

Drozd K.V.,[a] Manin A.N.,[a] Voronin A.P.,[a] Boycov D.E.,[a] Churakov A.V.,[b] Perlovich G.L.[a*]

[a] G.A. Krestov Institute of Solution Chemistry of the Russian Academy of Sciences, 1 Akademicheskaya St., Ivanovo, 153045, Russian Federation

[b] Institute of General and Inorganic Chemistry, Russian Academy of Sciences, 31 Leninsky Prosp., Moscow, 119991, Russian Federation

*Corresponding author: e-mail: glp@isc-ras.ru

Table of contents

S1. Details of the Gibbs energy of cocrystal formation calculation

In order to calculate the Gibbs energy of cocrystal formation with the stoichiometric ratio $(API)_n(CF)_m$ $\Delta G_f^{0,298}(CC)$, we can use the following equations:

$$\Delta G_{sub}^{0,298}(PM) = X_1 \cdot \Delta G_{sub}^{0,298}(API) + X_2 \cdot \Delta G_{sub}^{0,298}(CF) \quad (1)$$

where $(API)_n(CF)_m$: X_1 = n/(n + m); X_2 = m/(n + m). $\Delta G_{sub}^{0,298}(PM)$, $\Delta G_{sub}^{0,298}(API)$, and $\Delta G_{sub}^{0,298}(CF)$ are the sublimation Gibbs energies of the physical mixture, API and CF, respectively. The API and CF abbreviations are used for convenience. In our case, API corresponds to the first cocrystal component and CF corresponds to the second one.

$$\Delta G_f^{0,298}(CC) = \Delta G_{sub}^{0,298}(PM) - \Delta G_{sub}^{0,298}(CC) \quad (2)$$

The cocrystal formation enthalpy value, $\Delta H_f^{0,298}(CC)$, was obtained by the following algorithm. It is well known that there is a linear dependence between $\Delta G_{sub}^{0,298}$ and $\Delta H_{sub}^{0,298}$ (the so-called compensation effect). Thus, knowing the experimental $\Delta G_{sub}^{0,298}$ and $\Delta H_{sub}^{0,298}$ values, it is possible to calculate the coefficients of eq. (3):

$$\Delta G_{sub}^{0,298} = C + D \cdot \Delta H_{sub}^{0,298} \quad (3)$$

and then calculate the necessary value:

$$\Delta H_f^{0,298}(CC) = \Delta H_{sub}^{0,298}(PM) - \Delta H_{sub}^{0,298}(CC) \quad (4)$$

$$\Delta H_{sub}^{0,298}(CC) = (\Delta G_{sub}^{0,298}(CC) - C)/D \quad (5)$$

$$\Delta H_{sub}^{0,298}(PM) = X_1 \cdot \Delta H_{sub}^{0,298}(API) + X_2 \cdot \Delta H_{sub}^{0,298}(CF) \quad (6)$$

$$T\Delta S_f^{0,298}(CC) = \Delta G_f^{0,298}(CC) - \Delta H_f^{0,298}(CC) \quad (7)$$

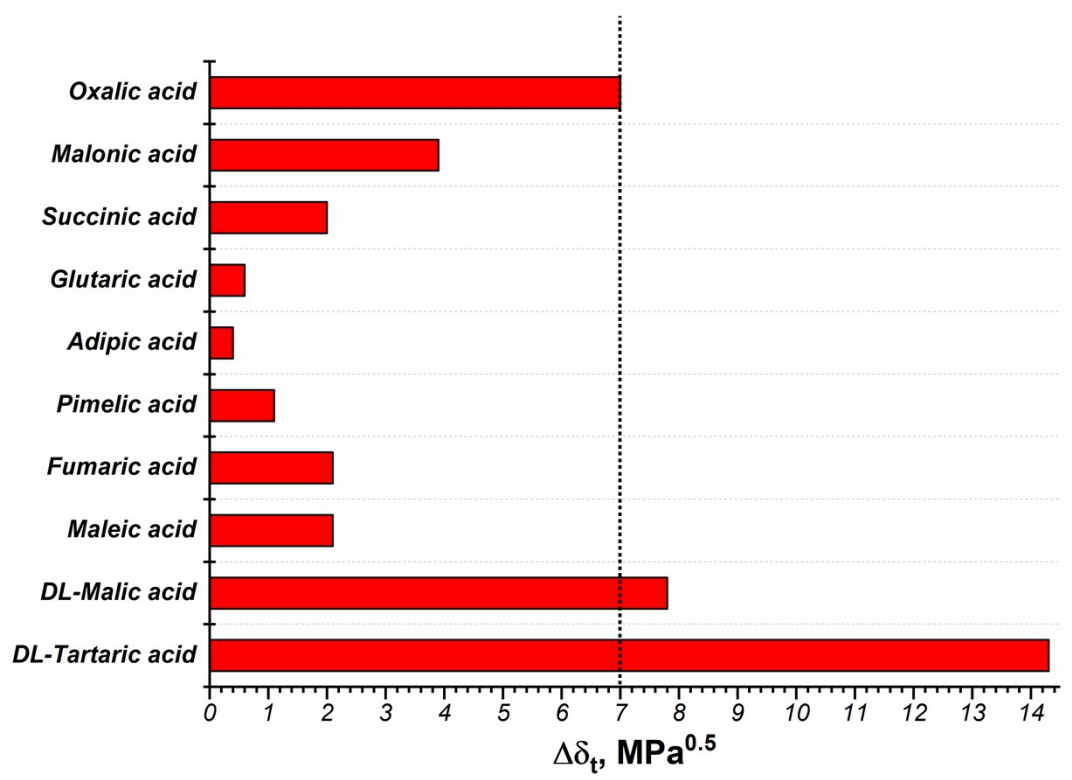


Figure S1. Differences in the total HSPs of the MCL with coformers. The range of ±7 $MPa^{0.5}$ is marked as an indicator of miscibility according to Greenhalgh et al.[1]

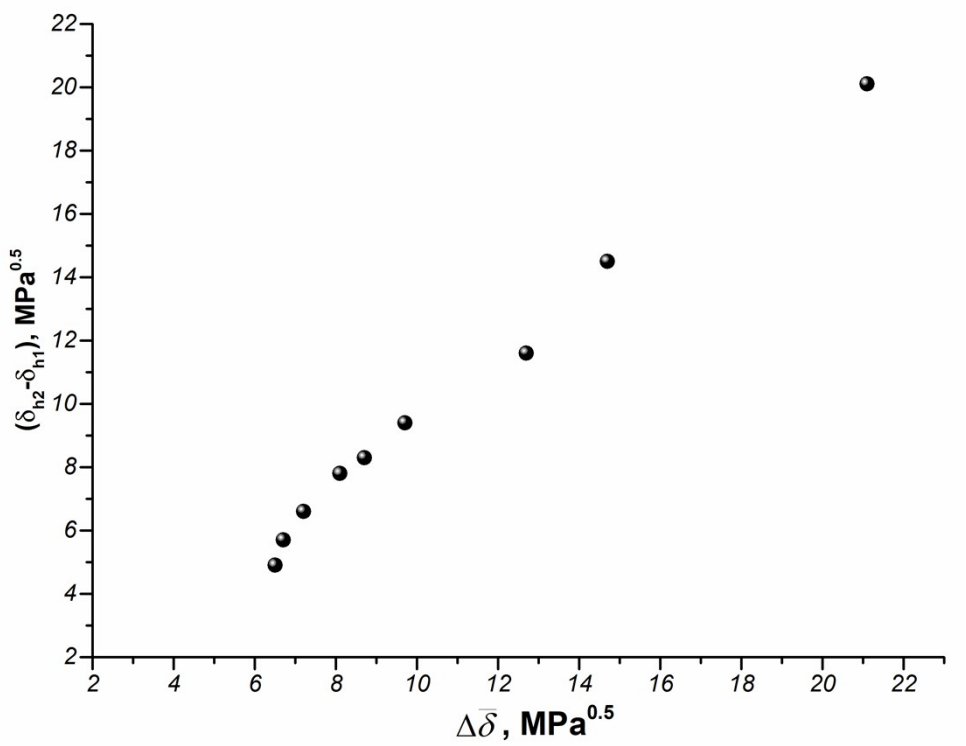


Figure S2. Correlation plots for $\Delta\bar{\delta}$ and differences in hydrogen bonding between MCL and coformers.

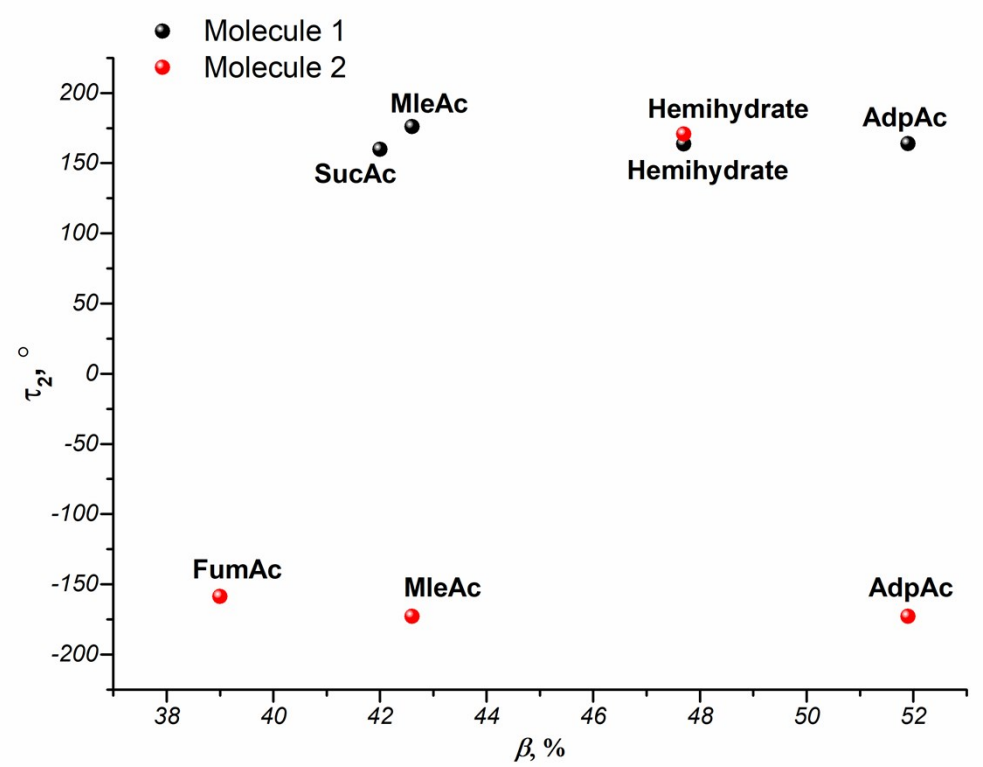


Figure S3. Dependence of the τ_2 torsion angle on the molecule packing density in a MCL crystal (β-parameter).

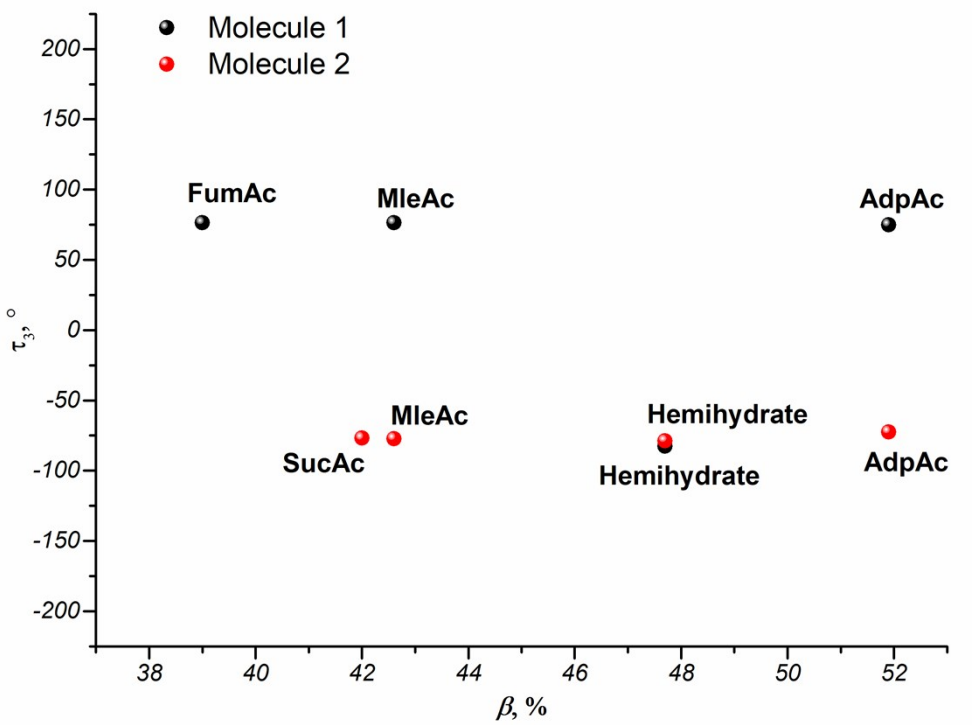
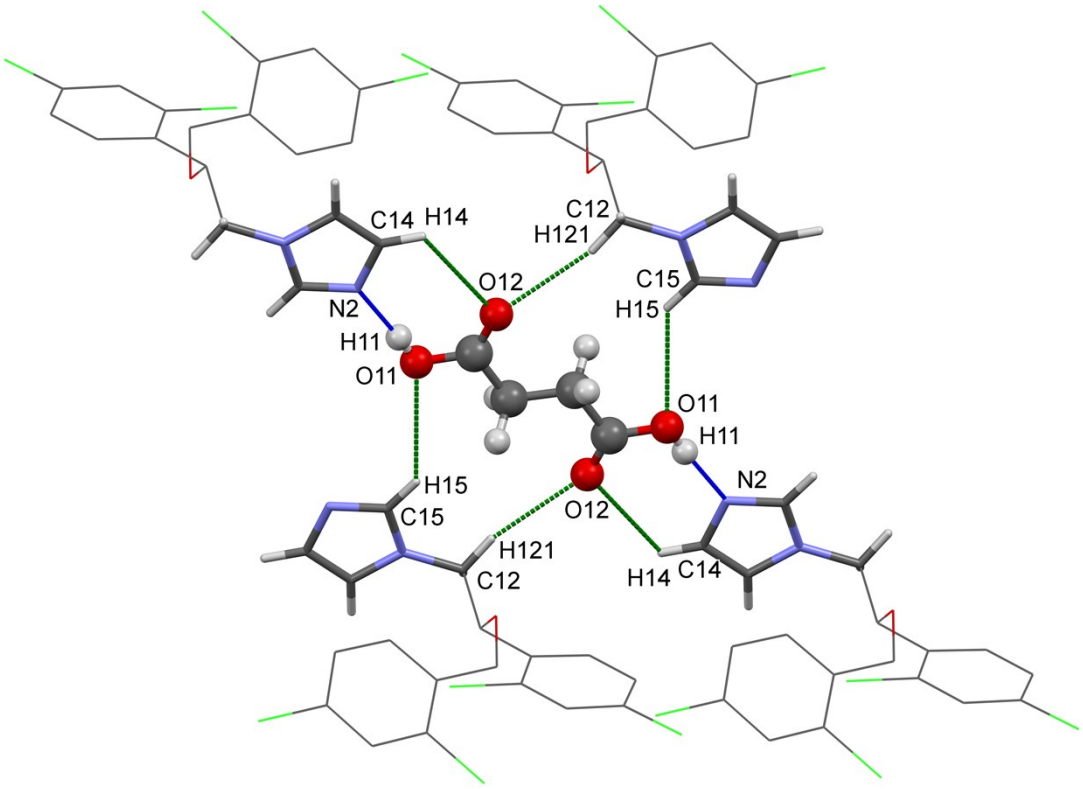
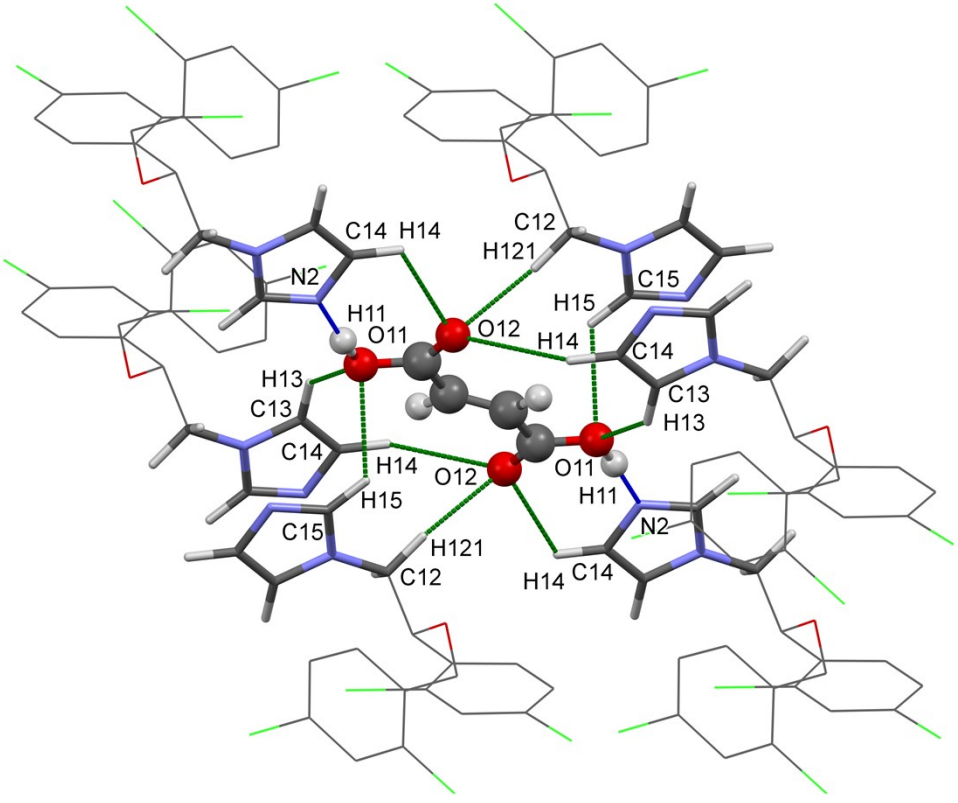


Figure S4. Dependence of the τ_3 torsion angle on the molecule packing density in a MCL crystal (β-parameter).



(a)



(b)

Figure S5. A fragment of the packing of the [MCL+SucAc] and [MCL+FumAc] cocrystals demonstrating the hydrogen bonds of the CF molecule with the surrounding MCL molecules.

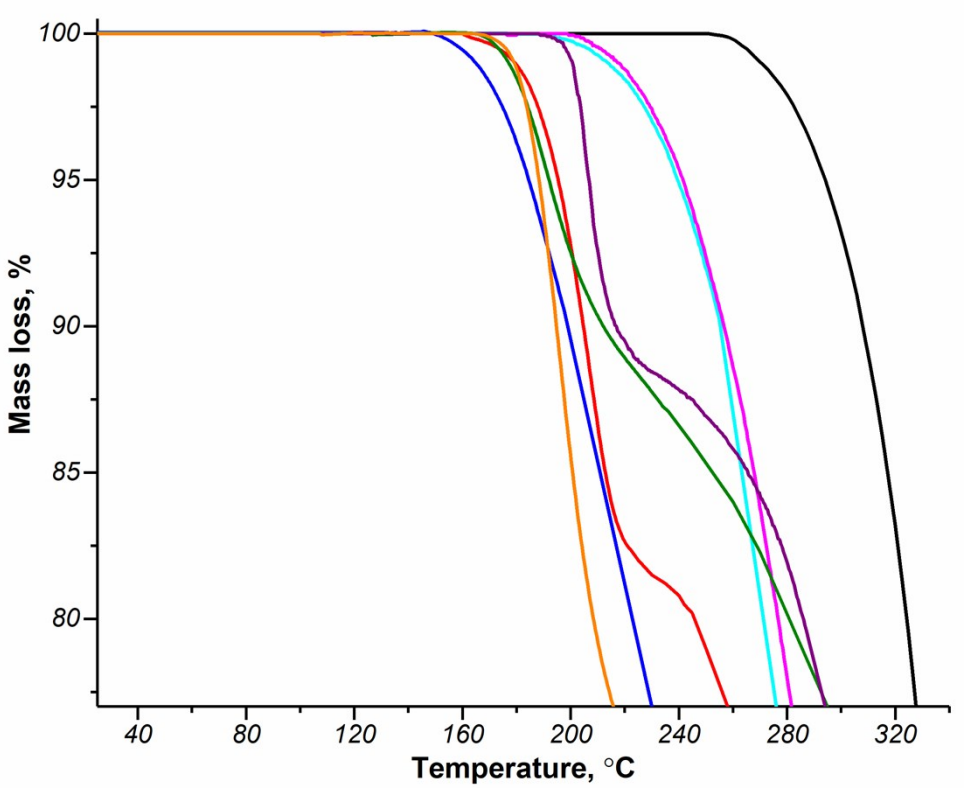


Figure S6. TGA thermograms of the MCL crystal forms (─ - MCL, ─ - [MCL+OxlAc] (1:1), ─ - [MCL+SucAc] (2:1), ─ - [MCL+AdpAc] (2:1), ─ - [MCL+PimAc] (2:1), ─ - [MCL+FumAc] (2:1), ─ - [MCL+MleAc] (1:1), ─ - [MCL+TartAc] (1:1)).

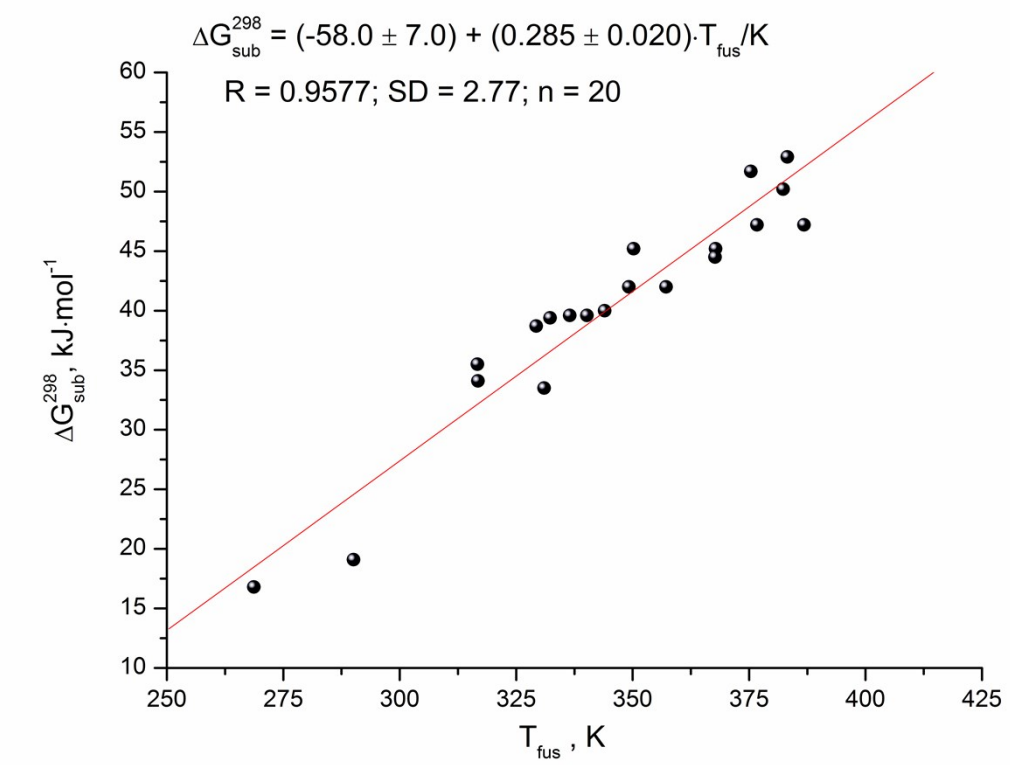


Figure S7. Dependence between ΔG_{sub}^{298} and T_{fus} for the compounds structurally related to miconazole.

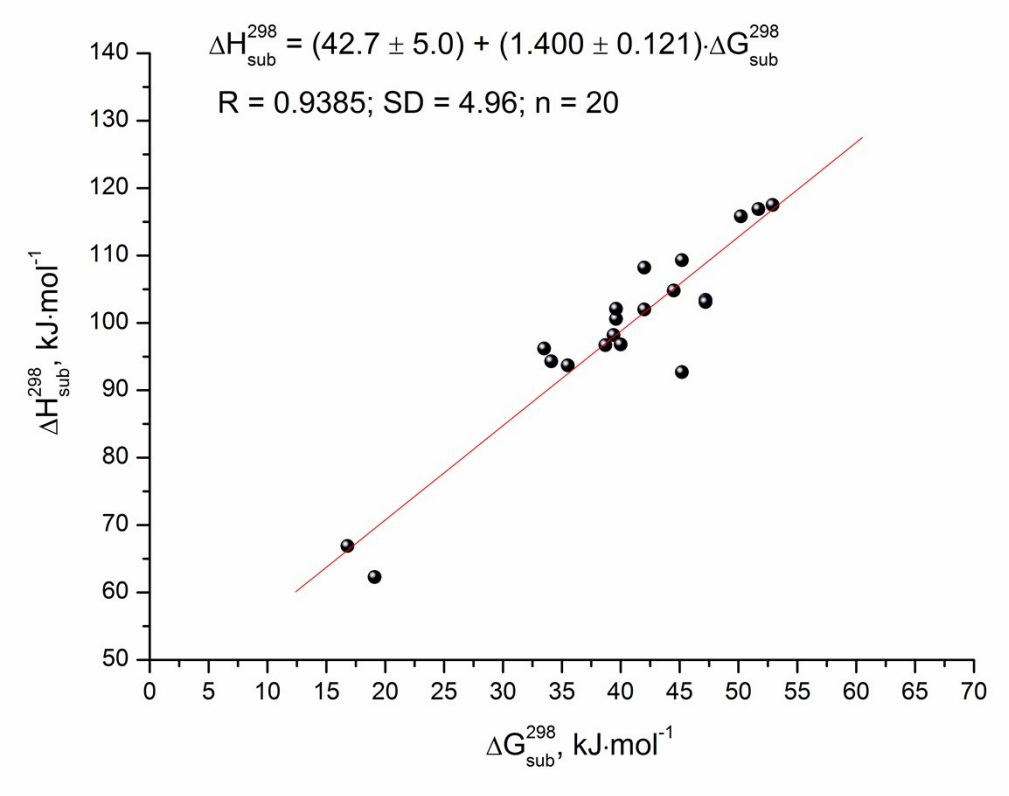


Figure S8. Dependence between ΔH^{298}_{sub} and ΔG^{298}_{sub} for the compounds structurally related to miconazole.

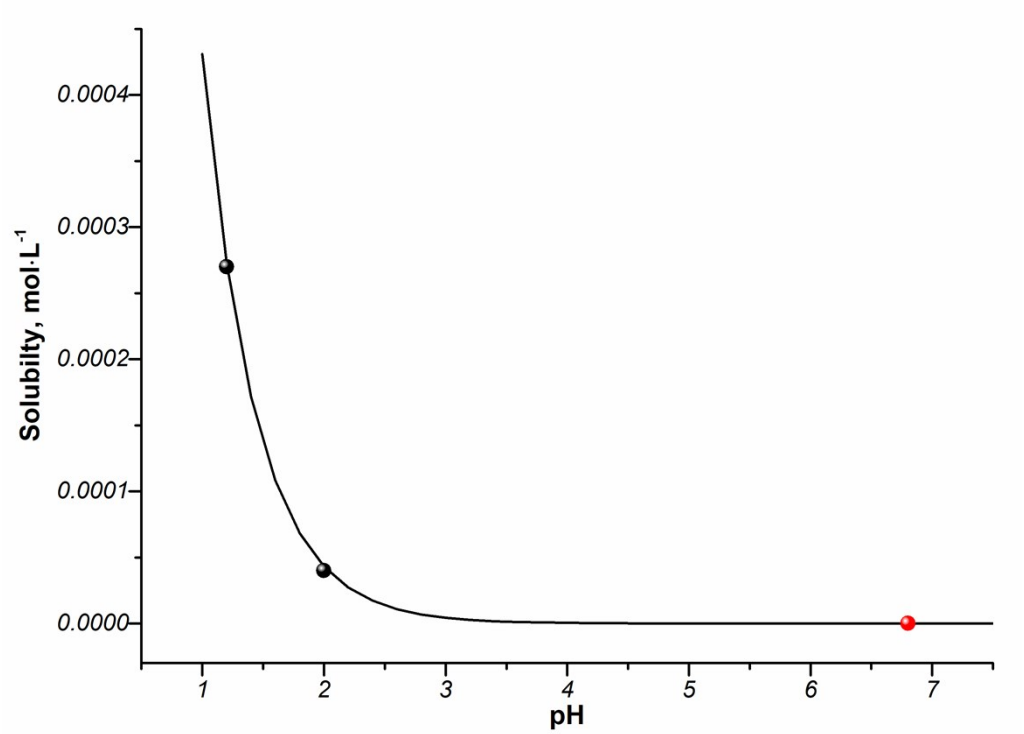


Figure S9. Solubility-pH profile of the MCL base (─ is the dependence of the MCL solubility on the pH calculated by the Henderson-Hasselbalch equation, ● is the MCL experimental solubility values in the pH 1.2 and 2.0 buffer solutions, ● is the MCL theoretical solubility)

Table S1. ΔpK_a values of miconazole and coformer combinations and cocrystal screening results

	pK_a[a]	ΔpK_a	Nature of the molecular complex	Experimental methods		Theoretical methods		
				DSC	PXRD[c]	MC[d]	HBP[e]	HSP[f]
MCL	6.77 (base)							
OxlAc	1.36; 4.11	5.41; 2.66	salt	-	+	-	-	+/-
MlnAc	2.43; 5.92	4.34; 0.85	salt	amorph	amorph	-	-	+
SucAc	3.55; 5.69	3.22; 1.08	cocrystal[b]	+	+	-	-	+
GluAc	3.76; 4.56	3.01; 2.21	cocrystal	amorph	amorph	-	-	+
AdpAc	3.92; 4.70	2.85; 2.07	cocrystal	+	+	-	-	+
PimAc	4.05; 4.81	2.72; 1.96	cocrystal	-	+	-	-	+
FumAc	3.35; 4.22	3.42; 2.55	cocrystal[b]	+	+	-	-	+
MleAc	2.85; 5.72	3.92; 1.05	salt[b]	-	+	-	-	+
MalAc	3.20; 5.13	3.57; 1.64	cocrystal	amorph	amorph	-	-	+/-
TartAc	2.72; 4.79	4.05; 1.98	salt	+	+	-	-	-

[a] The pK_a value were calculated in ChemAxon
[b] from ref. 2
[c] The samples for the PXRD analysis were obtained by liquid-assisted grinding
[d]MC stands for molecular complementarity
[e]HBP stands for hydrogen bond propensity
[f]HSP stands for Hansen solubility parameters

Table S2. Calculation of the Hansen solubility parameters of miconazole by the Hoftyzer-Van Krevelen group contribution method

Structural group	Frequency	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}, $J \cdot mol^{-1}$	V_m, $cm^3 \cdot mol^{-1}$
Phenylene (o, m, p)	2	2540	48400	0	104.8
–Cl	4	1800	4840000	1600	96.0
$–CH_2$	2	540	0	0	32.2
–O–	1	100	160000	3000	3.8
–CH–	1	80	0	0	-1.0
–N=	2	40	2560000	10000	10.0
=CH–	3	600	0	0	40.5
Σ	**-**	***5700***	***7608400***	***14600***	***286.3***
Calculations and results		$\delta_d = \sum F_d / \sum V_i$		δ_d = 19.9 $MPa^{0.5}$	
		$\delta_p = (\sum F_p^2)^{0.5} / \sum V_i$		δ_p = 9.6 $MPa^{0.5}$	
		$\delta_h = (\sum F_h / \sum V_i)^{0.5}$		δ_h = 7.1 $MPa^{0.5}$	
		$\delta_t = (d_d^2 + \delta_p^2 + \delta_h^2)^{0.5}$		δ_t = 23.2 $MPa^{0.5}$	

F_{d_i} is the group contribution to the dispersion forces

F_{p_i} is the group contribution to the polar forces

F_{h_i} is the group contribution to the hydrogen bonding energy

V_m is the group contribution to the molar volume calculated according to Fedors[3]

Table S3. Hansen solubility parameters of the coformers used in this study according to the Hoftyzer-Van Krevelen method

Compound	V_m, $cm^3 \cdot mol^{-1}$	δ_d, $MPa^{0.5}$	δ_p, $MPa^{0.5}$	δ_h, $MPa^{0.5}$	δ_v,[a] $MPa^{0.5}$	δ_t, $MPa^{0.5}$
Oxalic acid	57.0	18.6	14.7	18.7	23.7	30.2
Malonic acid	73.1	18.2	11.5	16.5	21.5	27.1
Succinic acid	89.2	17.9	9.4	15.0	20.3	25.2
Glutaric acid	105.3	17.8	8.0	13.8	19.5	23.9
Adipic acid	121.4	17.6	6.9	12.8	18.9	22.9
Pimelic acid	137.5	17.5	6.1	12.1	18.6	22.1
Fumaric acid	84.0	17.4	10.0	15.4	20.1	25.3
Maleic acid	84.0	17.4	10.0	15.4	20.1	25.3
DL-Malic acid	85.1	19.0	11.5	21.7	22.2	31.1
DL-Tartaric acid	81.0	20.2	16.1	27.2	25.9	37.6

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

Table S4. Crystallographic data and structural refinement summary of the MCL multi-component crystals

	MCL hemihydrate	[MCL+SucAc] (2:1)	[MCL+FumAc] (2:1)	[MCL+MleAc] (1:1)	[MCL+AdpAc] (2:1)
Chemical formula	$2(C_{18}H_{14}Cl_4N_2O)\cdot H_2O$	$2(C_{18}H_{14}Cl_4N_2O)\cdot C_4H_6O_4$	$2(C_{18}H_{14}Cl_4N_2O)\cdot C_4H_4O_4$	$C_{18}H_{15}Cl_4N_2O)\cdot C_4H_3O_4$	$2(C_{18}H_{14}Cl_4N_2O)\cdot C_6H_{10}O_4$
Formula weight	850.24	950.31	948.29	532.18	978.36
Crystal system	monoclinic	triclinic	triclinic	triclinic	triclinic
Space group	$P2_1/n$	P-1	P-1	P-1	P-1
Temperature, K	150(2)	120(2)	120(2)	100(2)	150(2)
a, Å	7.9812(4)	8.0830(3)	8.1544(2)	8.8026(3)	12.6233(9)
b, Å	32.6965(16)	9.0956(3)	8.9059(2)	8.8626(3)	13.3497(9)
c, Å	14.5964(7)	15.0054(6)	14.8899(4)	29.7363(10)	16.0081(11)
α, º	90	82.8035(14)	81.5113(8)	83.6323(10)	103.462(3)
β, º	91.2751(16)	80.0928(13)	81.5921(8)	85.5987(13)	100.435(3)
γ, º	90	71.2636(12)	70.0821(7)	89.6660(12)	113.091(2)
Volume, Å^3	3808.1(3)	1026.25(7)	1000.15(4)	2298.73(13)	2298.7(3)
Calc. density, g·cm^{-3}	1.483	1.538	1.574	1.538	1.413
Z	4	1	1	4	2
Total reflections	8309	4921	4814	12011	11091
Independent reflections	7843	4366	4526	10567	7257
R_{int}	0.0354	0.0278	0.0198	0.0260	0.0489
R_1 (all data)	0.0700	0.0382	0.0282	0.0606	0.0784
wR_2 (all data)	0.1209	0.0899	0.0639	0.1222	0.1110
$R_1[I > 2\sigma(I)]$	0.0657	0.0335	0.0262	0.0525	0.0427
w$R_2[I > 2\sigma(I)]$	0.1193	0.0869	0.0629	0.1188	0.0993
GOF	1.316	1.062	1.065	1.106	1.057

[a] Adsorption corrections based on measurements of equivalent reflections were applied (SADABS, ver. 2016/2, Bruker AXS area detector scaling and absorption correction program, Bruker AXS Inc., Madison, Wisconsin, USA., 2016).

Table S5. Compounds selected for estimating the thermodynamic sublimation characteristics of MCL

N	CAS registry number	T_{fus}, K	ΔH^{298}_{sub}, kJ·mol^{-1}	ΔG^{298}_{sub}, kJ·mol^{-1}	Ref
1	13029-08-8	331.0	96.2	33.5	[4]
2	120-82-1	290.1	62.3	19.1	[5]
3	33979-03-2	386.8	103.4	47.2	[6]
4	37680-73-2	350.2	92.7	45.2	[7]
5	50-29-3	383.2	117.5	52.9	[5]
6	37680-65-2	316.7	93.7	35.5	[8]
7	35693-99-3	357.2	102	42.0	[8]
8	34883-43-7	316.8	94.3	34.1	[8]
9	7012-37-5	329.3	96.7	38.7	[8]
10	16606-02-3	340.2	100.6	39.6	[8]
11	38444-86-9	332.3	98.2	39.4	[8]
12	38444-85-8	344.0	96.8	40.0	[8]
13	35065-27-1	375.4	116.9	51.7	[9]
14	55712-37-3	336.5	102.1	39.6	[9]
15	32598-11-1	376.7	103.1	47.2	[9]
16	38379-99-6	367.8	109.3	45.2	[9]
17	60233-25-2	367.7	104.8	44.5	[9]
18	31508-00-6	382.3	115.8	50.2	[9]
19	616-47-7	268.7	66.9	16.8	[10]
20	134-85-0	349.2	108.2	42.0	[11]

References

1 D. J. Greenhalgh, A. C. Williams, P. Timmins and P. York, *J. Pharm. Sci.*, 1999, **88**, 1182–1190.

2 S. Tsutsumi, M. Iida, N. Tada, T. Kojima, Y. Ikeda, T. Moriwaki, K. Higashi, K. Moribe and K. Yamamoto, *Int. J. Pharm.*, 2011, **421**, 230–236.

3 R. F. Fedors, *Polym. Eng. Sci.*, 1974, **14**, 147–154.

4 N. K. Smith, G. Gorin, W. D. Good and J. P. McCullough, *J. Phys. Chem.*, 1964, **68**, 940–946.

5 A. H. Jones, *J. Chem. Eng. Data*, 1960, **5**, 196–200.

6 F. Wania, W.-Y. Shiu and D. Mackay, *J. Chem. Eng. Data*, 1994, **39**, 572–577.

7 J. W. Westcott and T. F. Bidleman, *J. Chromatogr. A*, 1981, **210**, 331–336.

8 K. Nakajoh, E. Shibata, T. Todoroki, A. Ohara, K. Nishizawa and T. Nakamura, *Environ. Toxicol. Chem.*, 2005, **24**, 1602–1608.

9 K. Nakajoh, E. Shibata, T. Todoroki, A. Ohara, K. Nishizawa and T. Nakamura, *Environ. Toxicol. Chem.*, 2006, **25**, 327–336.

10 A. R. R. P. Almeida and M. J. S. Monte, *J. Chem. Thermodyn.*, 2012, **44**, 163–168.

11 M. A. V Ribeiro da Silva, L. M. P. F. Amaral and J. R. B. Gomes, *J. Phys. Chem. B*, 2007, **111**, 13033–13040.