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Supporting information for article:

Electrostatic properties of the pyrimethamine–2,4-dihydroxybenzoic acid cocrystal in methanol studied using transferred electron-density parameters

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Table S1: Refinement details

Refinement IAM_SHELX	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.042, 0.125, 1.06
No. of reflections	5182
No. of parameters	282
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{\max}$, $\Delta\rho_{\min}$ (e Å ⁻³)	0.35, -0.44
Refinement IAM_MoPro	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.043, 0.085, 1.38
No. of reflections	5182
No. of parameters	281
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{\max}$, $\Delta\rho_{\min}$ (e Å ⁻³)	0.26, -0.25
Refinement ELMAM2_MoPro	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.032, 0.061, 1.02
No. of reflections	5182
No. of parameters	271
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{\max}$, $\Delta\rho_{\min}$ (e Å ⁻³)	0.18, -0.33

Table S2:

Topological properties at the critical points of **O**···**H**, **C**···**H** and **H**···**H** intermolecular interactions in the crystal packing of compound 2 for the ELMAM2 model. Where d_{12} , $d_{1\text{CP}}$ and $d_{2\text{CP}}$ are the distances (\AA) between the two atoms, between the first atom and the CP, and between the CP and the second atom. ρ_{CP} is the total electron density (e\AA^{-3}) at the CP and $\nabla^2\rho_{\text{cp}}$, its Laplacian (e\AA^{-5}). λ_1 , λ_2 , λ_3 are the eigenvalues (e\AA^{-5}) of the Hessian matrix $\partial^2\rho/\partial x_i \partial x_j \cdot \epsilon = \lambda_1/\lambda_2 \cdot \mathbf{1}$ is the ellipticity. $G_{\text{cp}} = \text{Bond Kinetic energy}$ $V_{\text{cp}} = \text{Bond Potential Energy}$ (KJ /mol/Bohr 3)

Interacting atoms	d_{12} (\AA)	$d_{1\text{cp}}$ (\AA)	$d_{2\text{cp}}$ (\AA)	$\rho_{(\text{rb})}$ ($\text{e}/\text{\AA}^3$)	$\nabla^2\rho_{(\text{cp})}$ ($\text{e}/\text{\AA}^5$)	λ_1 ($\text{e}/\text{\AA}^5$)	λ_2 ($\text{e}/\text{\AA}^5$)	λ_3 ($\text{e}/\text{\AA}^5$)	ϵ	G_{cp}	V_{cp}
Cl1···H3B ⁽ⁱ⁾	2.6225	1.6966	0.9345	0.0665	0.7	-0.23	-0.18	1.11	0.2941	16.07	-13.16
Cl1···H12C ⁽ⁱⁱ⁾	2.9231	1.8176	1.1065	0.0467	0.43	-0.15	-0.15	0.73	0.0243	9.66	-7.67
N1···H16 ⁽ⁱⁱⁱ⁾	2.1967	1.3735	0.8233	0.1276	1.36	-0.62	-0.59	2.57	0.0576	34.76	-32.56
H2A···O1 ^(iv)	1.6329	0.5324	1.1006	0.3732	2.47	-2.66	-2.65	7.78	0.0025	105.39	-143.45
H3A···O3 ⁽ⁱⁱⁱ⁾	2.2044	0.84	1.365	0.0983	0.88	-0.49	-0.47	1.85	0.0413	22.54	-21.09
H3···O4 ⁽ⁱ⁾	2.6735	1.1499	1.543	0.0363	0.63	-0.11	-0.07	0.81	0.4732	12.63	-8.18
H12B···O1 ^(iv)	2.6039	1.0954	1.5088	0.0414	0.66	-0.12	-0.1	0.89	0.2247	13.58	-9.11
H4A···O2 ^(iv)	1.7652	0.5941	1.171	0.256	2.22	-1.62	-1.61	5.44	0.006	72.53	-84.68
H4B···O4 ⁽ⁱⁱⁱ⁾	2.215	0.848	1.3678	0.0968	0.9	-0.47	-0.46	1.83	0.018	22.65	-20.91
O2···H5A ^(v)	1.7032	1.1286	0.5758	0.327	1.23	-2.3	-2.27	5.81	0.0166	70.96	-108.31
H3C···O1	1.6421	0.5356	1.1102	0.3642	2.25	-2.63	-2.32	7.2	0.1337	98.96	-136.64

(i) -x+1 ; -y+1 ; -z+1 (ii) -x ; -y+2 ; -z+1 (iii) -x+1 ; -y+1 ; -z (iv) -x ; -y+2 ; -z (v) -x ; -y+1 ; -z+1.

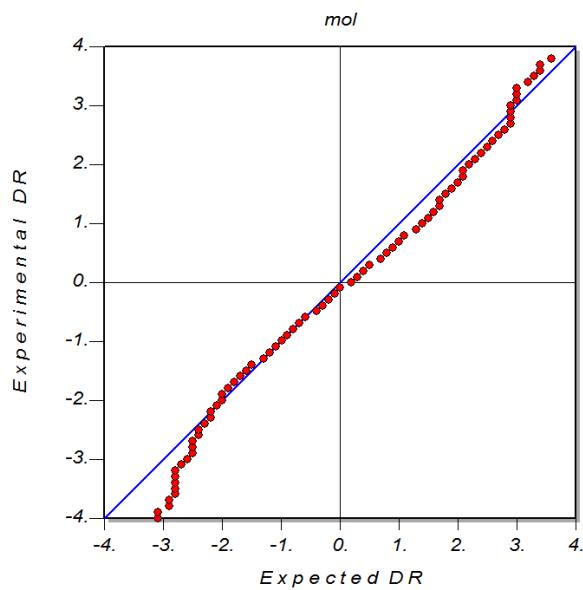


Fig. S1. The normal probability plots (Zhurov *et al.*, 2008)

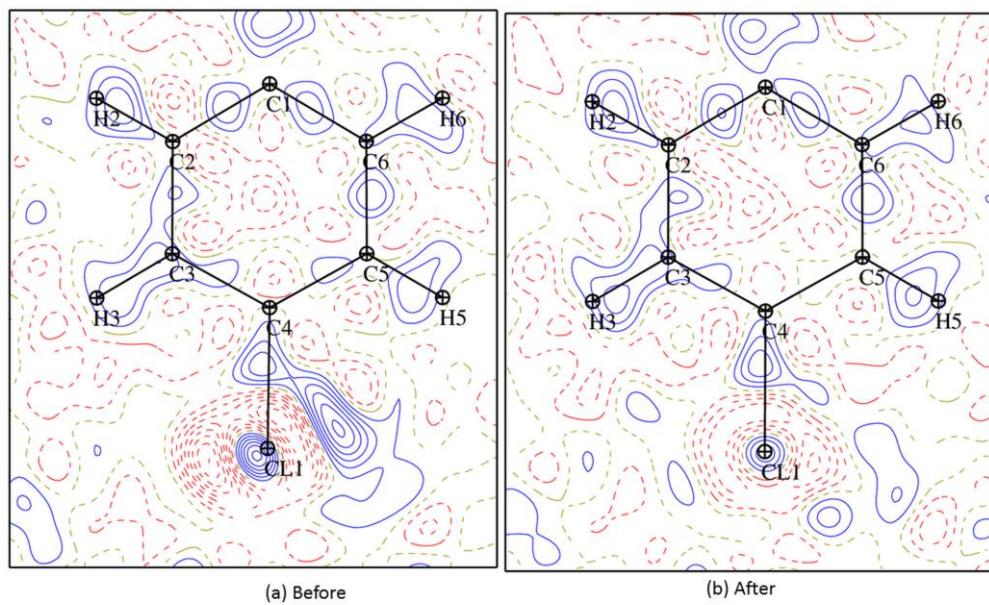


Fig. S2: Improvement in residual maps after 3rd order anharmonic refinement.

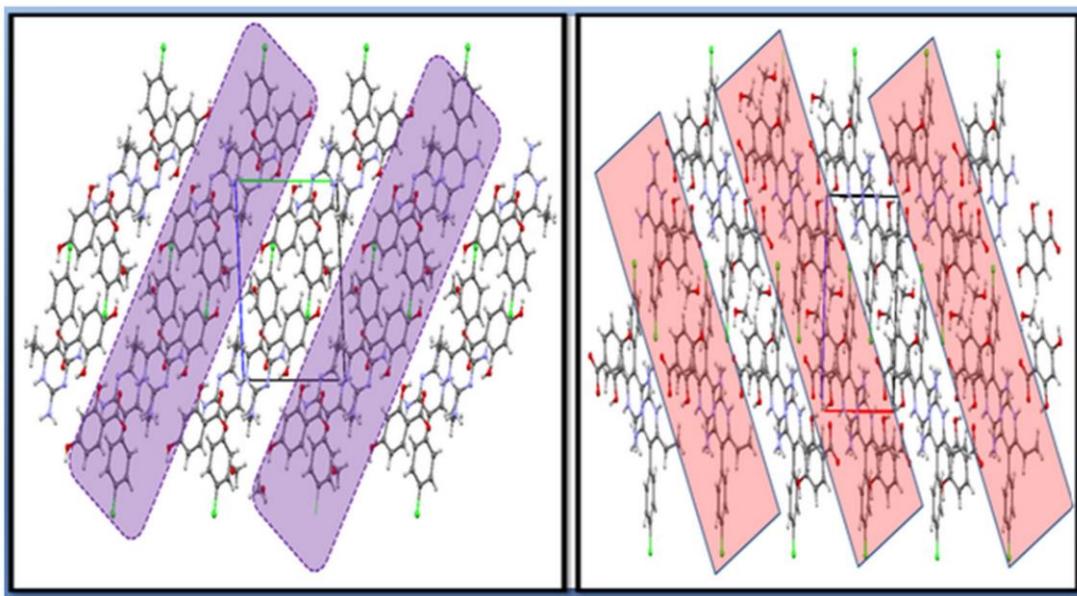


Fig. S3. Along the c axis, a three-dimensional supramolecular network shows alternative arrangements of pyrimethamine and dihydroxybenzoic acid molecules, with one step forward from each other.

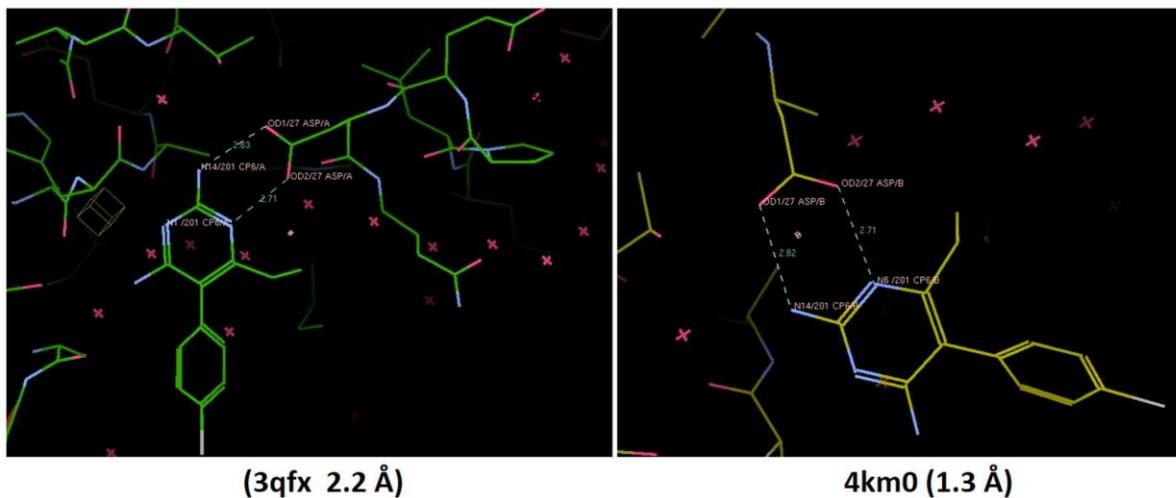


Fig. S4. The Protein Data Bank (PDB) lists 11 protein structures bound with pyrimethamine. A careful analysis has revealed that the same supramolecular synthon based on an N-H...O interaction constitutes the main binding mode of the pyrimethamine molecule with the carboxylic group of the aspartic acid of proteins. The highest resolution structure (4KMO, 1.3 Angstrom) shows that the contact distances between donor and acceptor atoms are 2.71 Angstrom for pyrimidine N atoms and 2.82 Angstrom for amino N atoms. The same trend is observed in other structures, for example, 3QFX (2.3 Angstrom).