DFT–assisted Structure Determination from Powder X-Ray Diffraction Data of a new Zonisamide/ϵ-caprolactam Cocrystal

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Electronic Supplementary Information

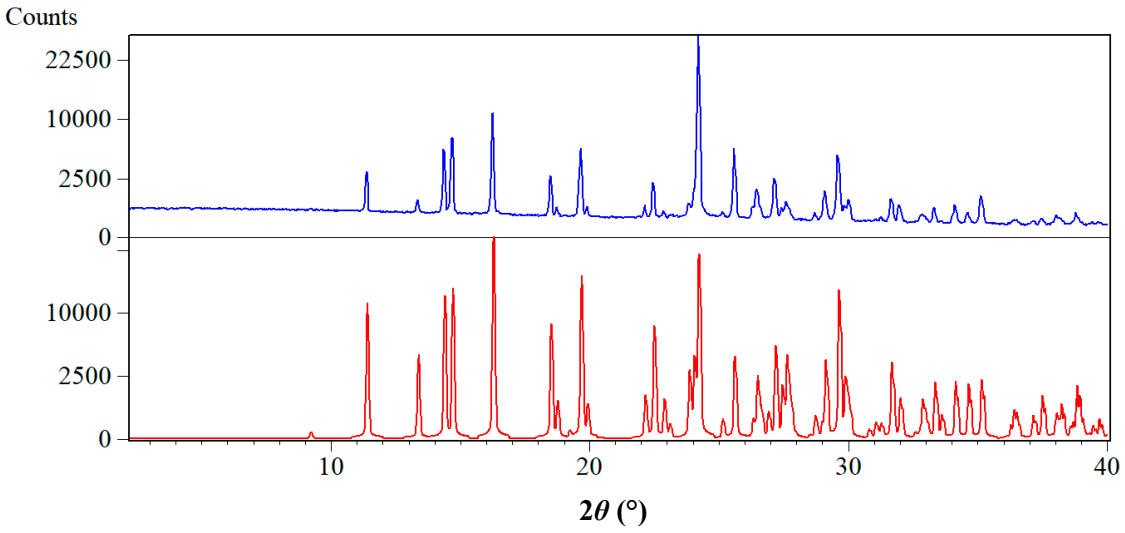
1. Materials and experimental methods

1.1 Materials

1.1.1. Zonisamide

Zonisamide used in this study corresponds to its anhydrous crystal form, Figure S1.

Figure S1: Comparative XRPD diffractograms of zonisamide powder used as starting material (blue) and simulated from the cif: zonisamide (CCDC refcode: VUXPUZ) (red)



1.1.2 Experimental methods

The formation of a new cocrystal was determined by comparing XRPD patterns of starting materials and product from cocrystal screening LAG experiment (Figure S2).

Figure S2: Comparative XRPD diffractograms of zonisamide bulk powder (blue), ϵ-caprolactam bulk powder polymorph I (according to the simulated from cif file: CCDC refcode: CAPLAC16) (green), ϵ-caprolactam polymorph II (simulated from cif file: CCDC refcode: CAPLAC18) (red) and zonisamide/ ϵ-caprolactam cocrystal (black).

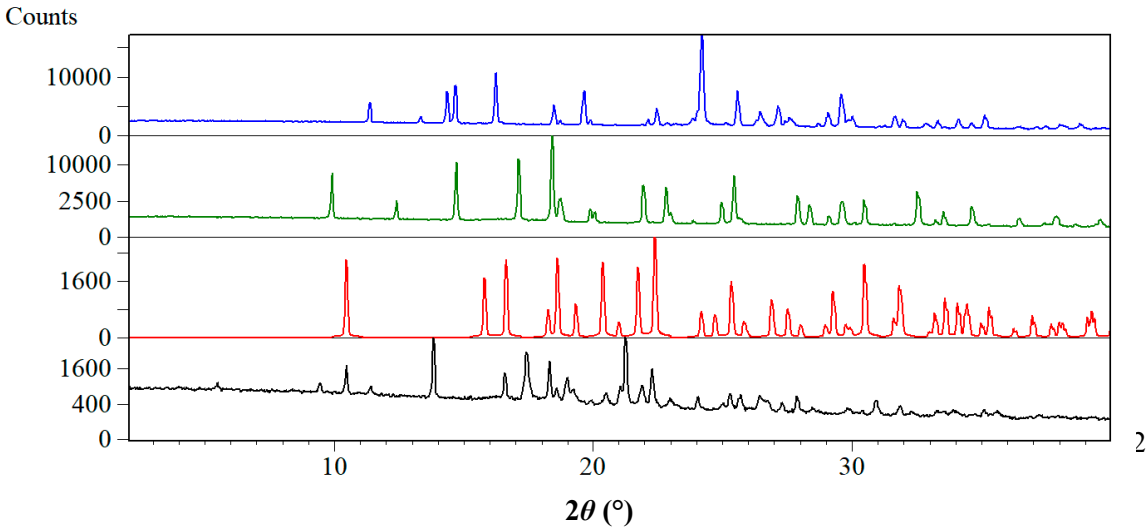
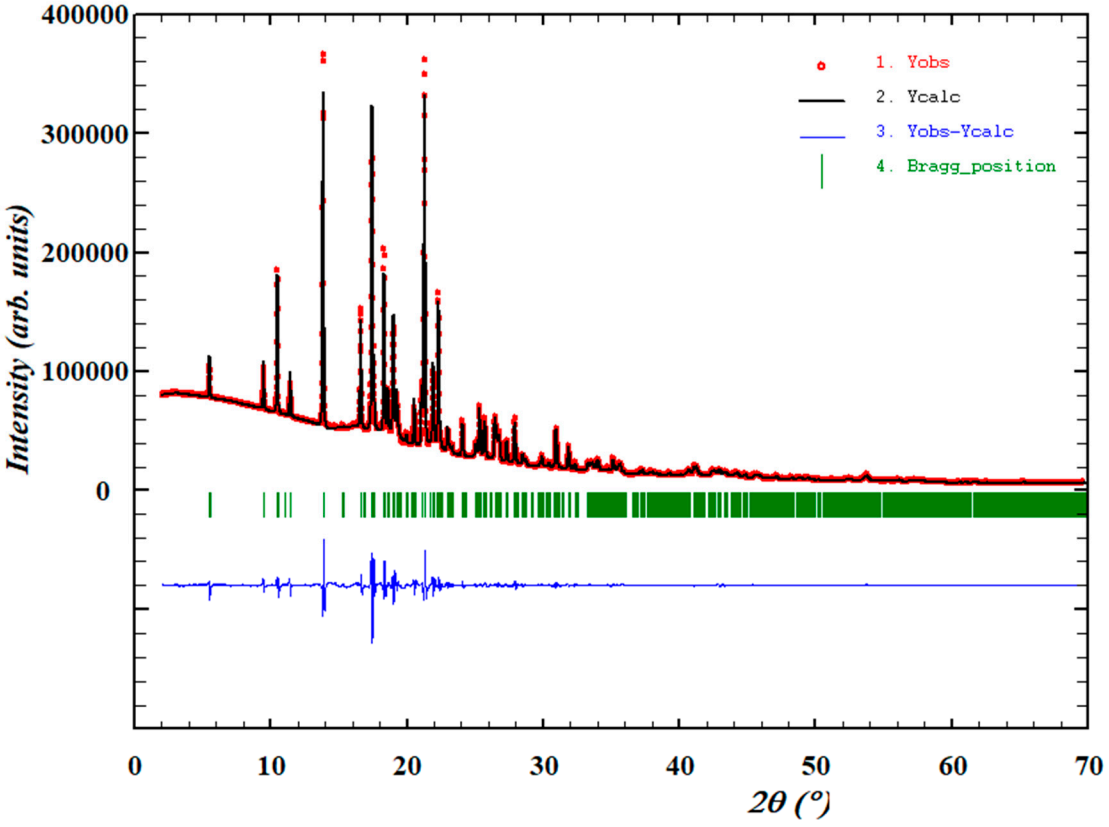


Figure S3: The XRPD of zonisamide/ϵ-caprolactam cocrystal has been indexed with the following proposed monoclinic cell values: a= 32.150(4) Å, b= 5.3272(5) Å, c= 18.730(2) Å, β= 95.623(6) °, V= 3192.5(6) Å^3, (Figures of Merit: M_{20} = 11.9, F_{20} = 33.3 (0.0078, 77), with number of impurities equal to zero. A *C* 2/*c* space group is compatible with the cell and the cell volume is compatible with 8 molecules of zonisamide and 8 molecules of ϵ-caprolactam. (R_{wp} = 4.18%, R_p = 2.46% and), Z=8, Z′=1.



2. Mogul analysis

Figure S4: Label atom representation corresponding to the asymmetric unit of zonisamide/ ϵ-caprolactam cocrystal.

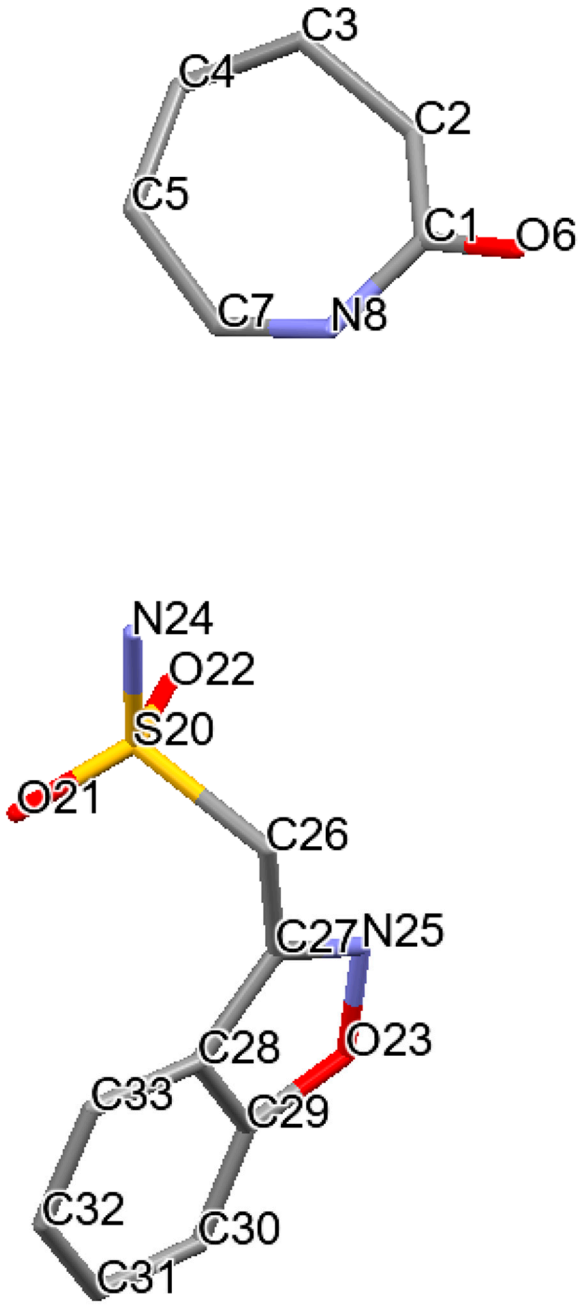


Table S1. The bond distances of the structural models of zonisamide/ϵ-caprolactam cocrystal were restrained based on the values reported in the CSD, analyzed with Mogul. In blue median values according to Mogul analysis, in red unusual values, in purple worsening values and in green improving values respect to median Mogul values, respectively. Only significant bonds distances are included (| z-score | >2.0).

Mogul: 500 hits							best FOX		initial optimized structure		optimization step 9		optimization step 10		optimization step 11		optimization step 20	
Fragment	**Number**	**Minimum**	**Maximum**	**Mean**	**Median**	**Std. dev.**	**| z-score |**	**Query value**	**| z-score |**	**Query value**	**| z-score |**	**Query value**	**| z-score |**	**Query value**	**| z-score |**	**Query value**	**| z-score |**	**Query value**
O6 C1	10000	0.978	1.572	1.228	**1.228**	0.020	0.004	1.228	0.002	1.228	**1.823**	**1.265**	**1.789**	**1.265**	**2.033**	**1.269**	**2.098**	**1.271**
C33 C28	10000	1.160	1.672	1.394	1.394	0.016	0.853	1.408	0.856	1.408	0.308	1.399	0.643	1.405	0.368	1.389	0.126	1.396
C30 C29	10000	1.108	1.605	1.391	1.389	0.021	0.188	1.395	0.193	1.395	0.537	1.403	0.186	1.395	0.452	1.401	0.038	1.392
C31 C30	10000	0.755	1.691	1.385	1.385	0.021	0.716	1.400	0.719	1.400	0.233	1.390	0.623	1.398	0.164	1.388	0.153	1.388
C32 C31	10000	0.588	1.729	1.376	1.378	0.027	0.949	1.401	0.952	1.401	1.316	1.410	1.078	1.404	1.318	1.410	1.225	1.408
C32 C33	10000	0.755	1.691	1.385	1.385	0.021	0.937	1.404	0.942	1.405	0.107	1.387	0.078	1.383	0.022	1.384	0.111	1.387
C4 C3	6543	1.070	2.054	1.513	1.520	0.042	0.320	1.526	0.321	1.526	0.091	1.517	0.410	1.530	0.297	1.525	0.362	1.528
C5 C4	6543	1.070	2.054	1.513	1.520	0.042	0.405	1.530	0.407	1.530	0.291	1.525	0.036	1.515	0.271	1.524	0.387	1.529
C3 C2	1726	1.058	1.680	1.522	1.528	0.032	0.023	1.523	0.025	1.523	0.660	1.543	0.655	1.543	0.764	1.547	0.734	1.546
C28 C29	1318	1.325	1.548	1.391	1.391	0.013	0.428	1.386	0.423	1.386	0.367	1.396	0.865	1.402	1.327	1.408	0.628	1.399
C7 N8	526	1.334	1.591	1.462	1.463	0.020	0.878	1.444	0.876	1.444	0.663	1.475	0.055	1.463	0.349	1.469	0.310	1.468
C5 C7	433	1.300	1.661	1.510	1.515	0.030	0.474	1.524	0.476	1.524	0.617	1.528	0.855	1.535	0.718	1.531	0.644	1.529
C27 N25	228	1.238	1.605	1.281	**1.280**	0.025	**2.503**	**1.344**	**1.372**	**1.316**	**1.703**	**1.324**	**1.946**	**1.330**	**1.590**	**1.321**	**1.649**	**1.322**
C2 C1	146	1.440	1.601	1.503	1.505	0.018	0.402	1.510	0.407	1.510	0.443	1.511	0.129	1.505	0.404	1.495	0.198	1.506
O23 N25	100	1.410	1.469	1.431	**1.431**	0.010	**4.102**	**1.389**	**2.414**	**1.406**	**0.421**	**1.426**	**2.311**	**1.407**	**1.315**	**1.417**	**1.180**	**1.419**
C1 N8	93	1.298	1.417	1.333	1.330	0.019	1.582	1.362	1.585	1.362	1.607	1.363	0.340	1.339	1.422	1.359	0.536	1.343
O23 C29	75	1.341	1.398	1.358	**1.358**	0.009	0.562	1.363	1.043	1.367	0.593	1.363	**3.016**	**1.384**	**2.240**	**1.378**	1.284	1.369
C28 C27	38	1.411	1.485	1.448	1.442	0.022	1.201	1.421	1.122	1.423	0.785	1.430	1.131	1.423	0.569	1.435	0.960	1.426
S20 N24	23	1.550	1.643	1.594	**1.599**	0.023	**4.536**	**1.489**	**4.532**	**1.489**	**1.838**	**1.636**	**2.345**	**1.648**	**1.837**	**1.636**	**1.317**	**1.624**
O21 S20	18	1.426	1.441	1.434	**1.434**	0.005	0.962	1.429	0.949	1.429	**3.470**	**1.452**	**4.546**	**1.458**	**2.081**	**1.445**	**3.377**	**1.451**
O22 S20	18	1.426	1.441	1.434	**1.434**	0.005	**3.739**	**1.453**	**3.753**	**1.453**	**2.666**	**1.448**	**3.775**	**1.454**	**2.990**	**1.449**	**3.591**	**1.453**
C26 S20	15	1.768	1.807	1.785	**1.783**	0.009	**7.790**	**1.715**	**7.783**	**1.715**	**4.885**	**1.829**	**3.063**	**1.812**	**3.695**	**1.818**	**4.298**	**1.823**
C26 C27	10	1.482	1.513	1.498	**1.496**	0.010	**5.378**	**1.443**	**3.377**	**1.463**	**1.412**	**1.483**	**1.316**	**1.484**	**0.050**	**1.497**	**2.370**	**1.474**

Table S2. The angles of the structural models of zonisamide/ϵ-caprolactam cocrystal were restrained based on the values reported in the CSD, analyzed with Mogul. In blue median values according to Mogul analysis, in red unusual values, in purple worsening values and in green improving values respect to median Mogul values, respectively. Only significant angles are included (| z-score | >2.0).

Mogul: 500 hits							best FOX		initial optimized structure		optimization step 9		optimization step 10		optimization step 11		optimization step 20	
Fragment	Number	Minimum	Maximum	Mean	Median	Std. dev.	| z-score |	Query value	| z-score |	Query value	| z-score |	Query value	| z-score |	Query value	| z-score |	Query value	| z-score |	Query value
C31 C30 C29	10000	93.781	134.994	119.712	119.877	1.839	1.980	116.072	1.979	116.073	2.709	114.732	1.905	116.210	1.774	116.450	2.321	115.444
C32 C31 C30	10000	62.866	142.195	120.190	120.180	1.523	0.702	121.259	0.701	121.258	1.253	122.098	0.703	121.260	1.007	121.725	1.556	122.561
C31 C32 C33	10000	62.866	142.195	120.190	120.180	1.523	0.615	121.127	0.616	121.128	1.167	121.968	1.344	122.237	0.761	121.349	0.598	121.101
C32 C33 C28	10000	78.949	132.751	119.815	120.039	1.891	0.773	118.354	0.772	118.354	1.541	116.901	1.464	117.047	1.198	117.548	1.426	117.118
C5 C4 C3	2669	94.080	156.910	116.338	115.538	4.216	0.448	114.450	0.448	114.450	0.861	112.709	1.061	111.866	1.171	111.403	0.779	113.056
C4 C3 C2	1397	94.129	135.037	114.740	114.482	2.575	0.478	113.509	0.479	113.507	0.844	112.567	0.928	112.349	0.984	112.207	0.837	112.585
C30 C29 C28	1044	109.818	129.897	123.596	123.747	1.163	0.765	124.487	0.766	124.487	0.354	124.008	0.764	122.708	1.591	121.745	0.533	122.976
C33 C28 C29	774	111.857	126.590	118.883	118.843	1.176	0.154	118.701	0.156	118.699	0.978	120.033	1.243	120.345	1.782	120.978	1.611	120.777
C5 C7 N8	410	98.297	129.771	114.017	113.906	2.600	0.424	112.914	0.425	112.913	0.783	116.053	0.765	116.007	0.879	116.304	0.570	115.500
C4 C5 C7	395	100.370	129.333	114.117	114.125	2.181	0.235	113.604	0.234	113.606	1.056	116.420	1.306	116.965	1.585	117.574	1.115	116.549
O22 S20 O21	164	114.187	129.658	119.323	119.207	1.415	8.659	107.070	8.658	107.071	1.742	121.788	1.248	121.089	0.433	119.935	0.086	119.201
O6 C1 C2	146	109.096	125.387	121.005	121.286	2.077	0.334	121.698	0.334	121.698	0.793	119.359	0.210	120.569	0.355	121.743	0.368	121.769
C3 C2 C1	109	103.507	132.025	114.099	113.592	3.149	0.561	112.333	0.561	112.334	0.489	115.640	0.475	115.594	0.581	115.928	0.284	114.994
O6 C1 N8	93	110.765	126.455	120.576	120.746	1.744	0.159	120.299	0.160	120.297	1.435	123.079	0.431	121.328	0.139	120.334	0.304	120.047
C2 C1 N8	84	114.313	130.543	118.704	118.292	2.570	0.274	118.000	0.273	118.001	0.448	117.553	0.242	118.083	0.304	117.923	0.206	118.174
C7 N8 C1	84	105.267	135.230	126.269	126.052	3.190	0.221	126.973	0.220	126.972	0.326	125.229	0.189	125.667	0.493	124.694	0.043	126.132
C29 O23 N25	74	105.900	109.115	107.479	107.465	0.478	4.599	109.678	0.224	107.372	2.794	108.815	2.216	108.539	1.318	108.109	1.655	108.270
O23 C29 C28	65	106.666	111.476	110.296	110.302	0.655	1.518	109.301	1.131	111.036	1.638	109.223	3.270	108.154	2.531	108.638	1.296	109.446
C29 C28 C27	45	102.812	106.176	103.897	103.811	0.585	0.255	103.747	3.081	102.095	0.188	104.007	1.911	105.014	1.296	104.654	0.204	103.777
C28 C27 N25	43	110.078	112.349	111.471	111.556	0.517	0.506	111.732	3.169	113.108	1.134	112.057	0.869	111.022	1.466	110.713	1.088	112.033
C33 C28 C27	38	126.982	137.692	132.630	131.235	3.628	1.356	137.552	1.785	139.106	0.908	135.924	0.545	134.606	0.468	134.328	0.774	135.437
O23 C29 C30	34	124.044	128.206	125.890	126.193	0.925	0.349	126.212	1.529	124.476	0.935	126.754	3.511	129.136	4.030	129.616	1.812	127.565
O21 S20 C26	30	105.512	110.813	107.921	107.987	1.559	2.363	104.238	2.364	104.236	0.227	108.275	0.902	109.327	1.060	109.574	0.372	108.501
O22 S20 C26	30	105.512	110.813	107.921	107.987	1.559	3.969	114.107	3.969	114.108	1.704	105.265	2.133	104.596	2.237	104.434	1.591	105.441
O23 N25 C27	26	104.161	108.479	106.110	106.108	1.121	0.508	105.541	0.175	106.306	0.298	105.776	0.968	107.195	1.519	107.814	0.312	106.460
O21 S20 N24	18	106.264	111.574	107.817	107.688	1.146	2.128	105.378	2.127	105.380	1.523	106.072	1.478	106.124	0.972	106.703	0.240	108.092
O22 S20 N24	18	106.264	111.574	107.817	107.688	1.146	4.029	112.434	4.029	112.433	0.668	107.051	0.449	107.302	0.161	108.001	0.584	108.486
C27 C26 S20	18	109.631	116.333	113.138	113.296	2.110	2.261	108.368	0.790	111.471	1.728	109.492	1.375	110.236	0.898	111.243	0.794	111.463
C26 C27 N25	17	116.991	121.794	120.026	120.188	1.274	2.015	117.457	0.761	119.056	0.054	119.956	0.224	119.741	0.413	120.552	0.236	120.326
C26 S20 N24	16	102.276	109.966	107.129	107.929	2.060	2.701	112.692	2.701	112.692	0.302	107.750	0.338	107.825	0.265	107.675	0.333	106.442
C26 C27 C28	15	123.927	130.477	127.730	128.205	1.842	0.919	129.423	0.062	127.615	0.137	127.982	0.811	129.223	0.504	128.658	0.053	127.632

3.- Rietveld refinements plots

Figure S5: Rietveld plot for the best solution of zonisamide/ϵ-caprolactam cocrystal obtained by FOX. Agreement factors: R_{wp} = 8.32%, Chi-square = 210. The plot shows the experimental powder XRD profile (red marks), the calculated powder XRD profile (black solid line), and the difference profile (blue, lower line). Tick marks indicate peak positions (green). Only enlargement from 4 to 40 ° in 2θ is represented to clarify.

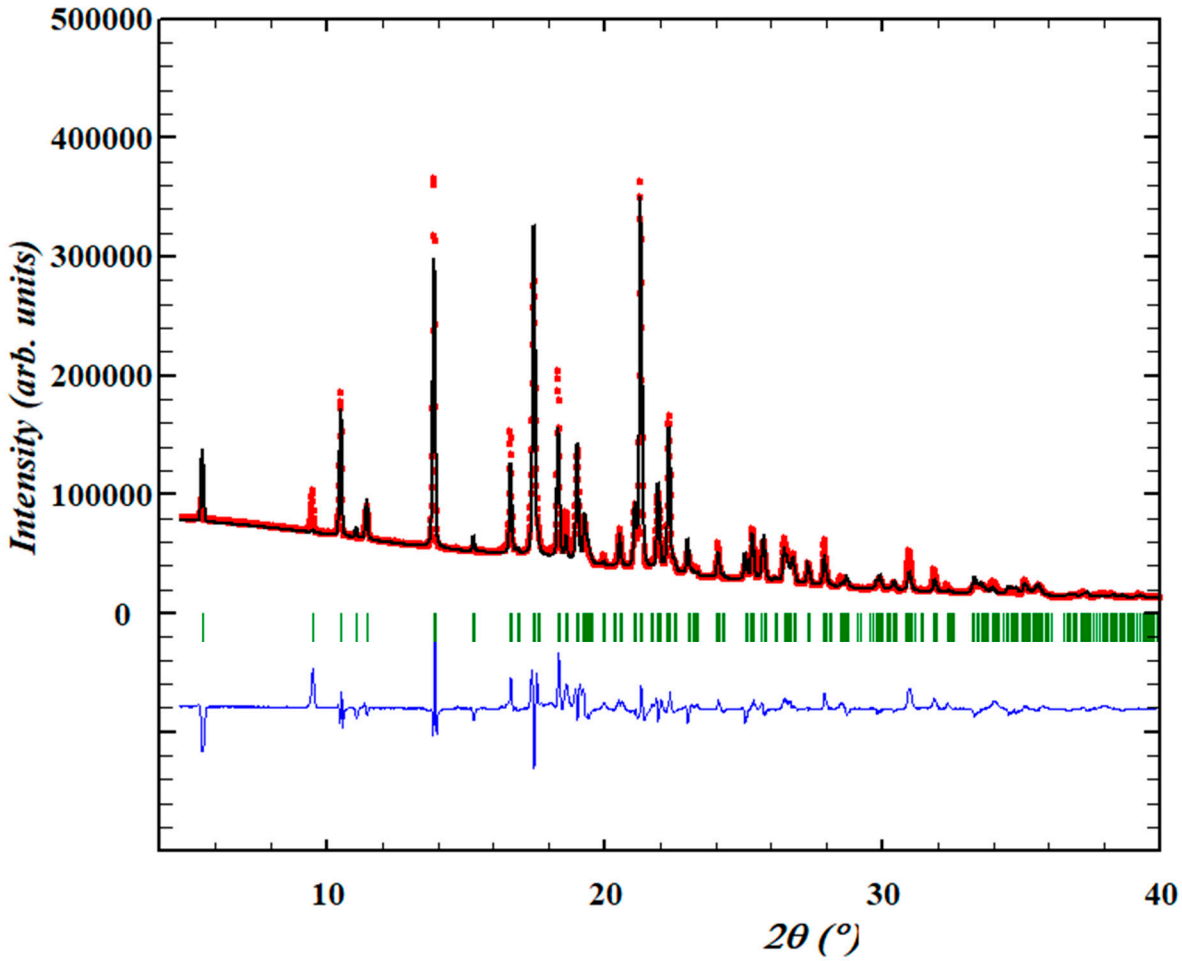


Figure S6: Rietveld plot for the initial structure model after some structural arrangements of the FOX best solution. Agreement factors: R_{wp} = 8.20%, Chi-square = 204. The plot shows the experimental powder XRD profile (red marks), the calculated powder XRD profile (black solid line), and the difference profile (blue, lower line). Tick marks indicate peak positions (green). Only enlargement from 4 to 40 ° in 2θ is represented to clarify.

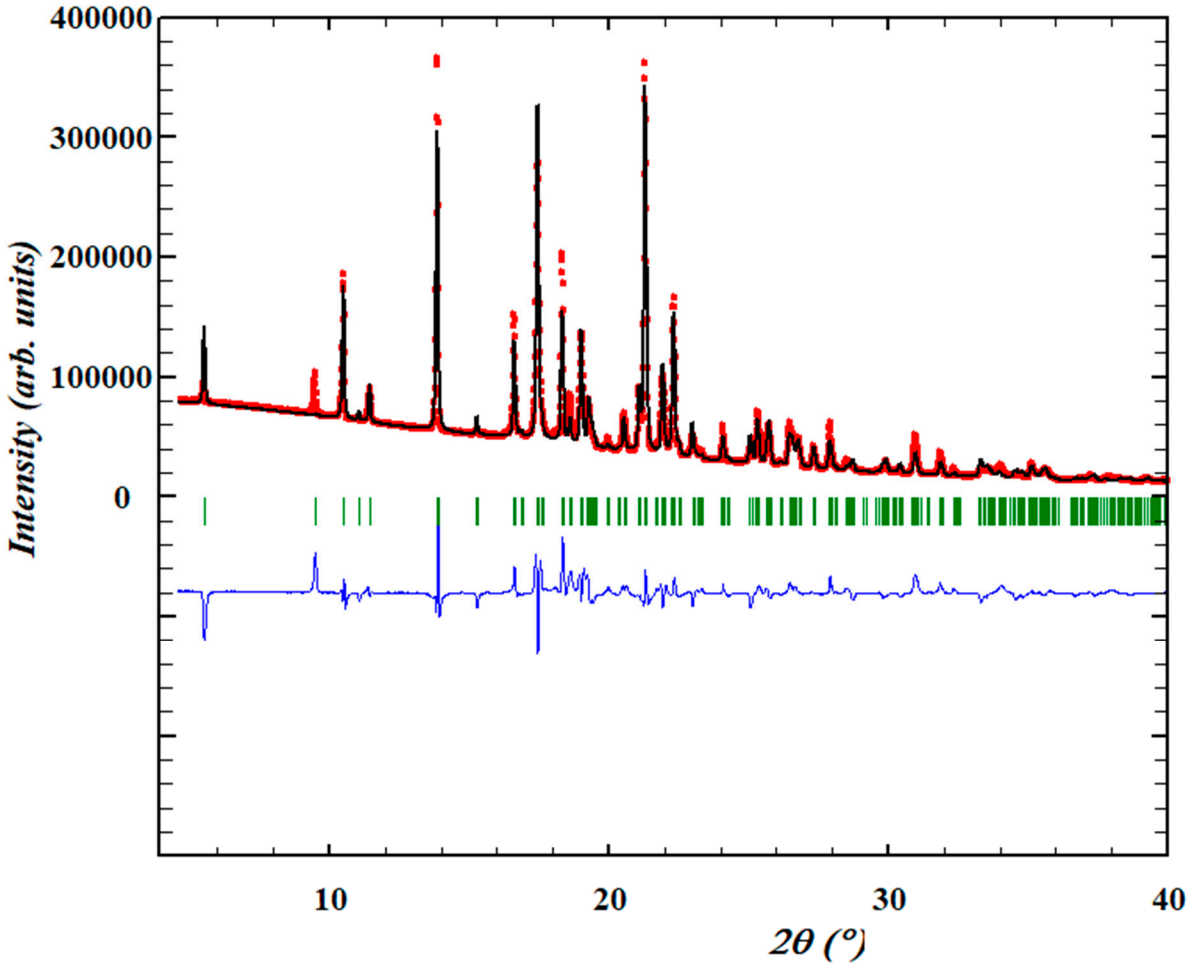


Figure S7: Rietveld plot for the structure model computed in the optimization step number 9. Agreement factors: R_{wp} = 9.06%, Chi-square = 249. The plot shows the experimental powder XRD profile (red marks), the calculated powder XRD profile (black solid line), and the difference profile (blue, lower line). Tick marks indicate peak positions (green). Only enlargement from 4 to 40 ° in 2θ is represented to clarify.

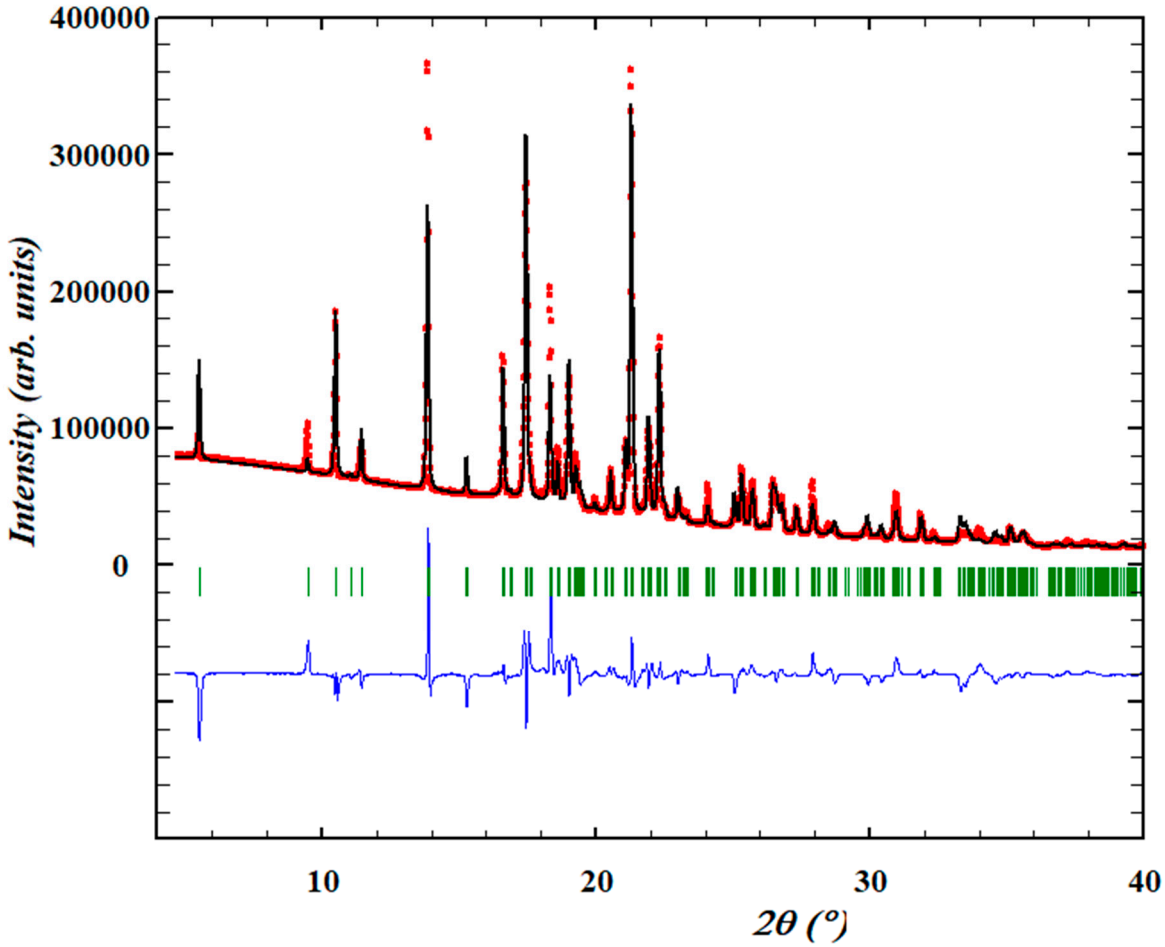


Figure S8: Rietveld plot for the structure model computed in the optimization step number 10. Agreement factors: R_{wp} = 9.26%, Chi-square = 260. The plot shows the experimental powder XRD profile (red marks), the calculated powder XRD profile (black solid line), and the difference profile (blue, lower line). Tick marks indicate peak positions (green). Only enlargement from 4 to 40 ° in 2θ is represented to clarify.

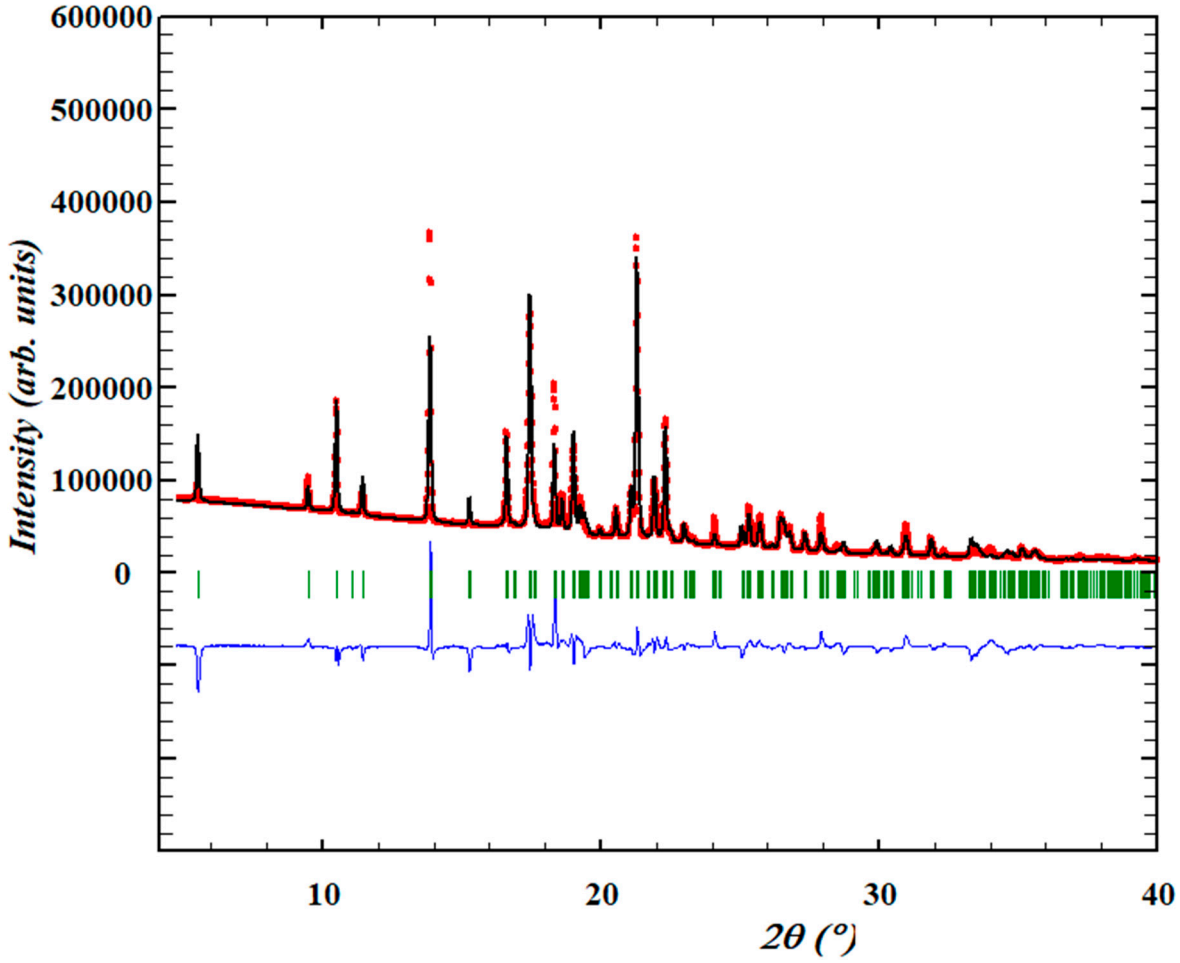


Figure S9: Rietveld plot for the structure model computed in the optimization step number 11. Agreement factors: R_{wp} = 9.66%, Chi-square = 283. The plot shows the experimental powder XRD profile (red marks), the calculated powder XRD profile (black solid line), and the difference profile (blue, lower line). Tick marks indicate peak positions (green). Only enlargement from 4 to 40 ° in 2θ is represented to clarify.

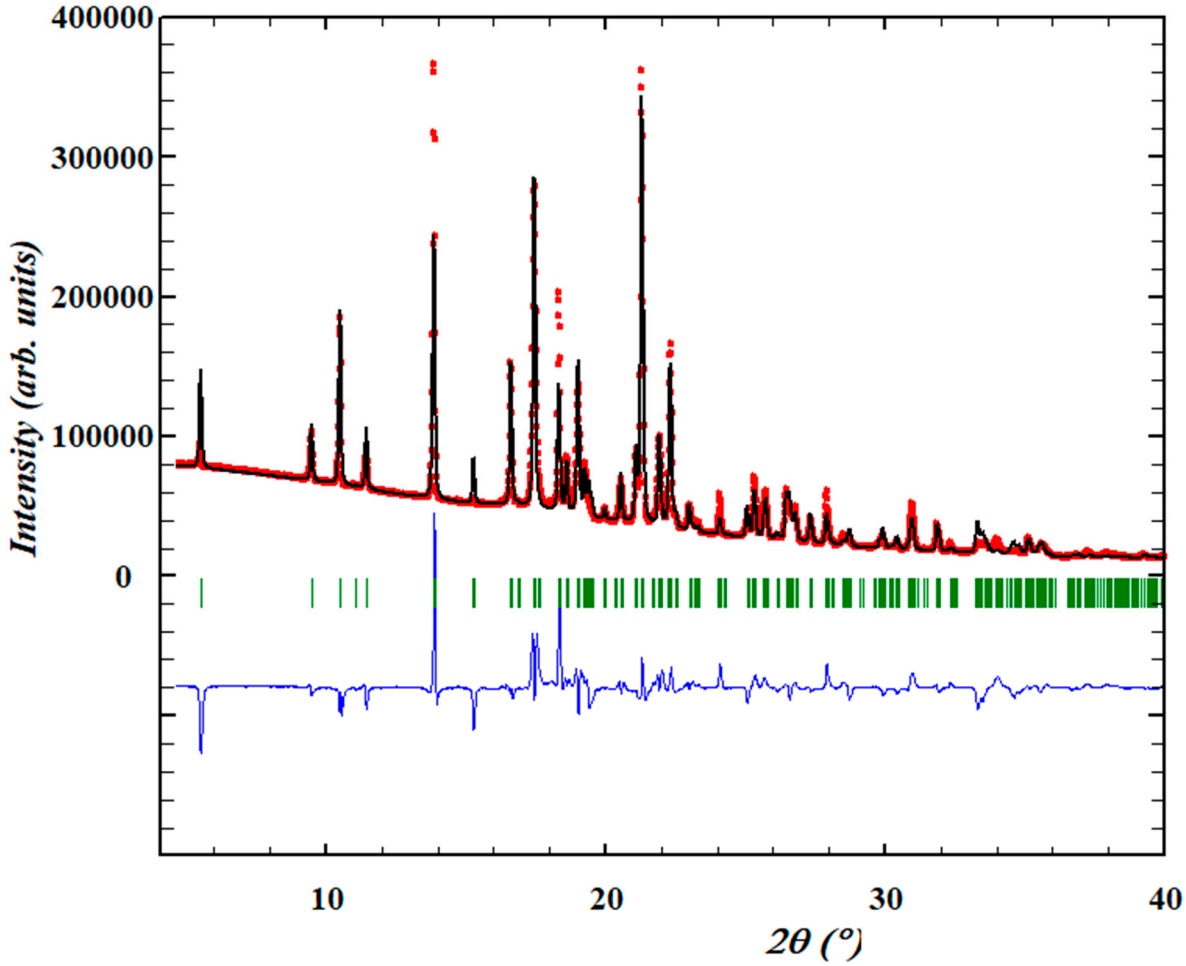


Figure S10: Rietveld plot for the structure model computed in the optimization step number 20. Agreement factors: R_{wp} = 11.5%, Chi-square = 398. The plot shows the experimental powder XRD profile (red marks), the calculated powder XRD profile (black solid line), and the difference profile (blue, lower line). Tick marks indicate peak positions (green). Only enlargement from 4 to 40 ° in 2θ is represented to clarify.

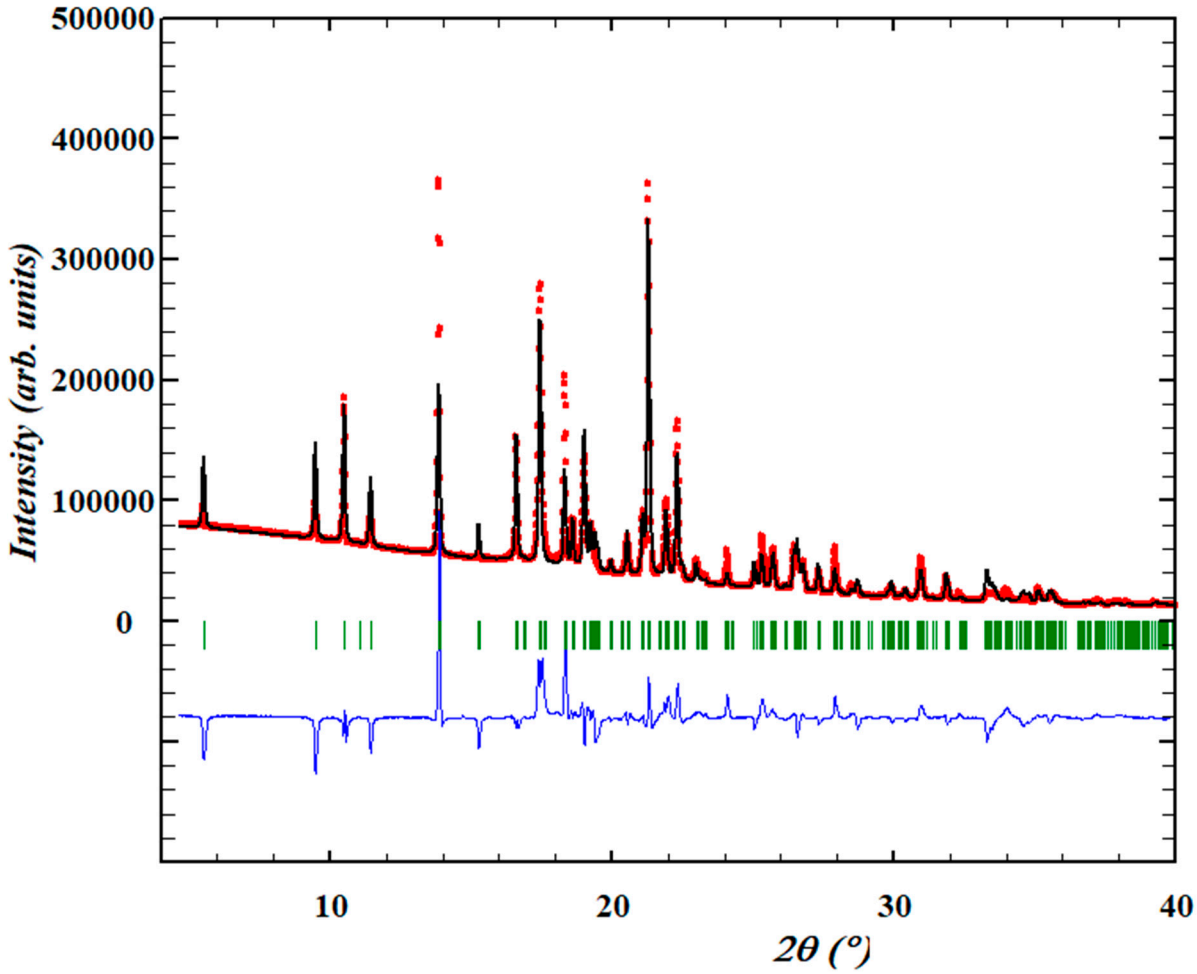


Figure S11: Rietveld plot for the structure model computed in the optimization step number 30. Agreement factors: R_{wp} = 12.7%, Chi-square = 490. The plot shows the experimental powder XRD profile (red marks), the calculated powder XRD profile (black solid line), and the difference profile (blue, lower line). Tick marks indicate peak positions (green). Only enlargement from 4 to 40 ° in 2θ is represented to clarify.

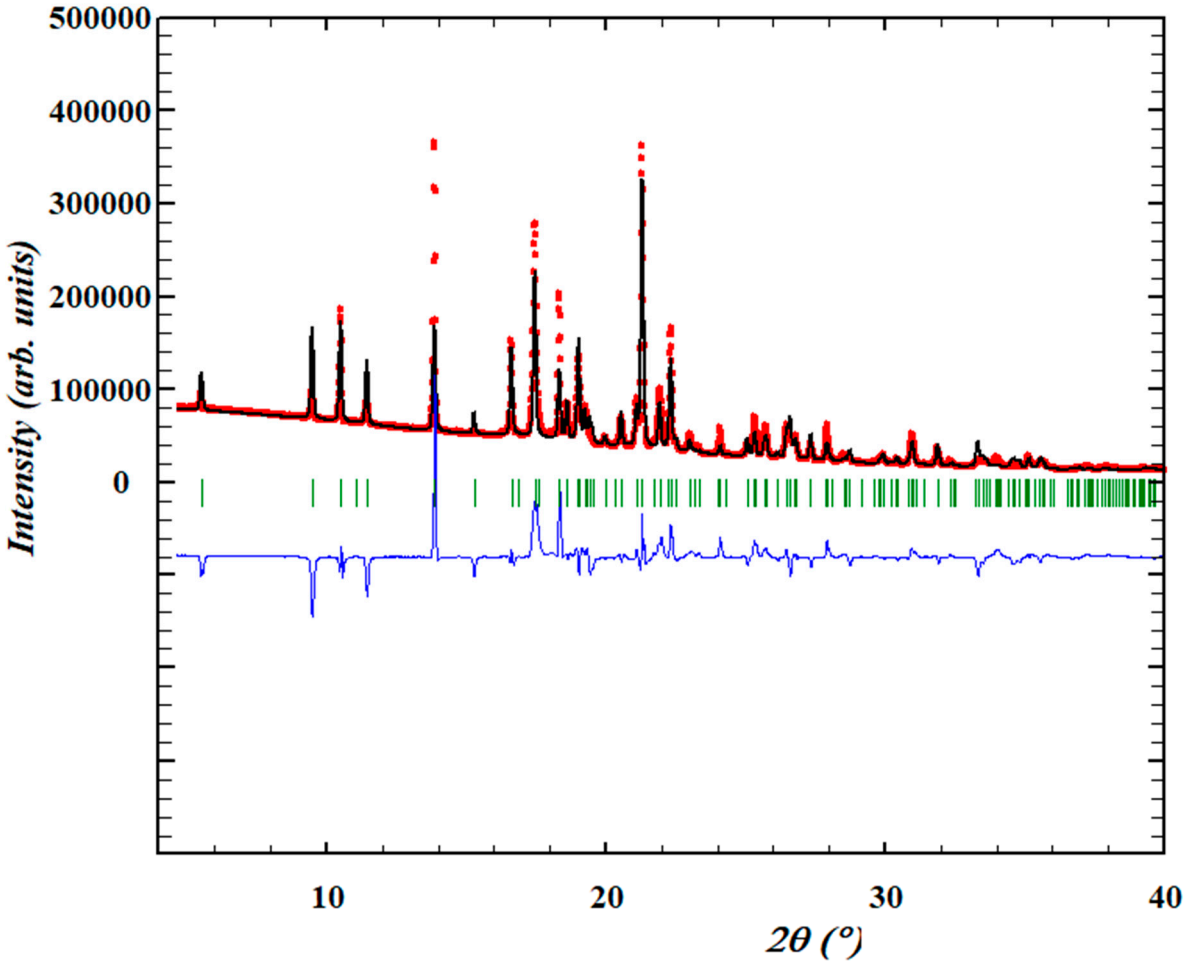
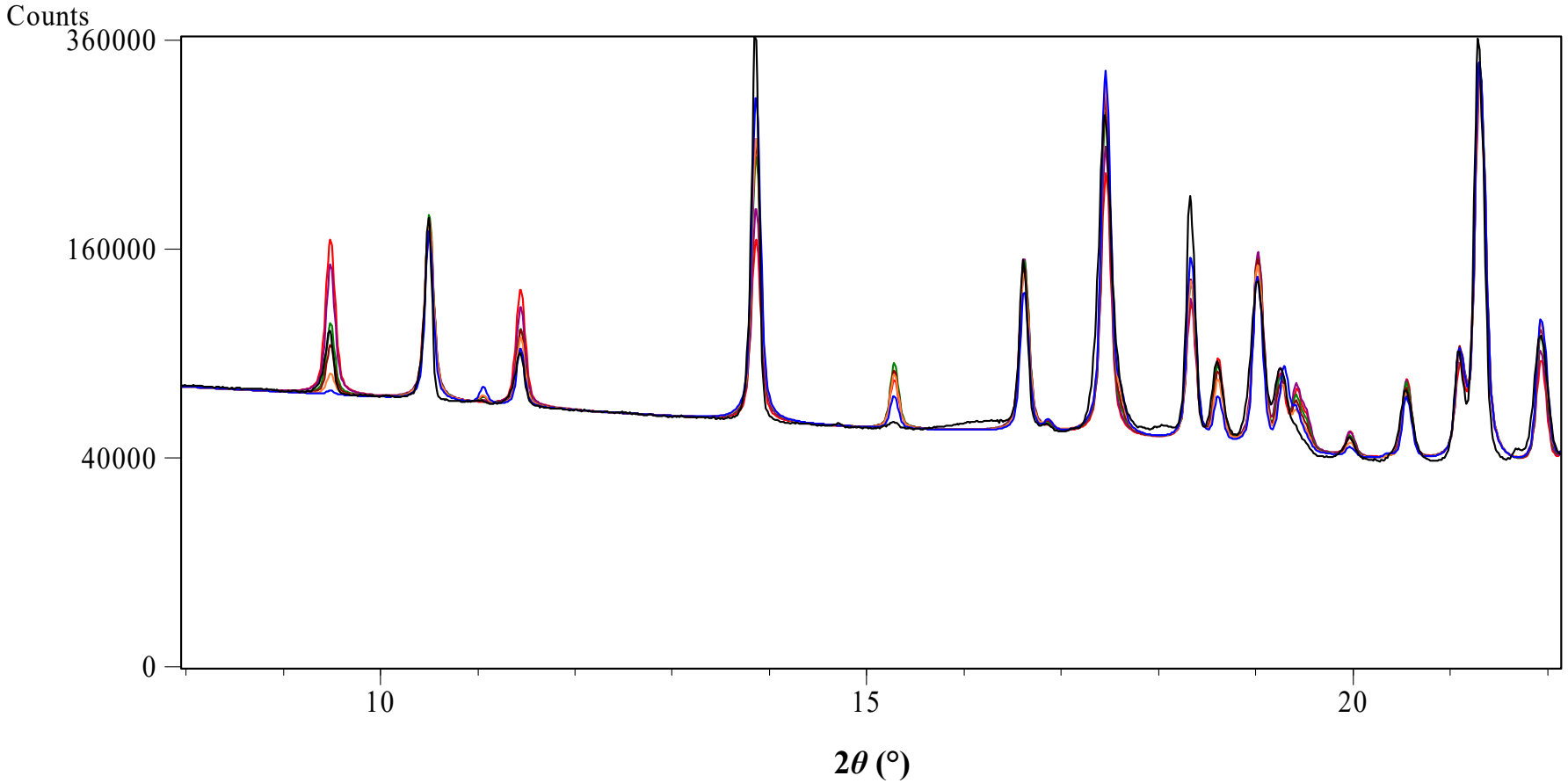
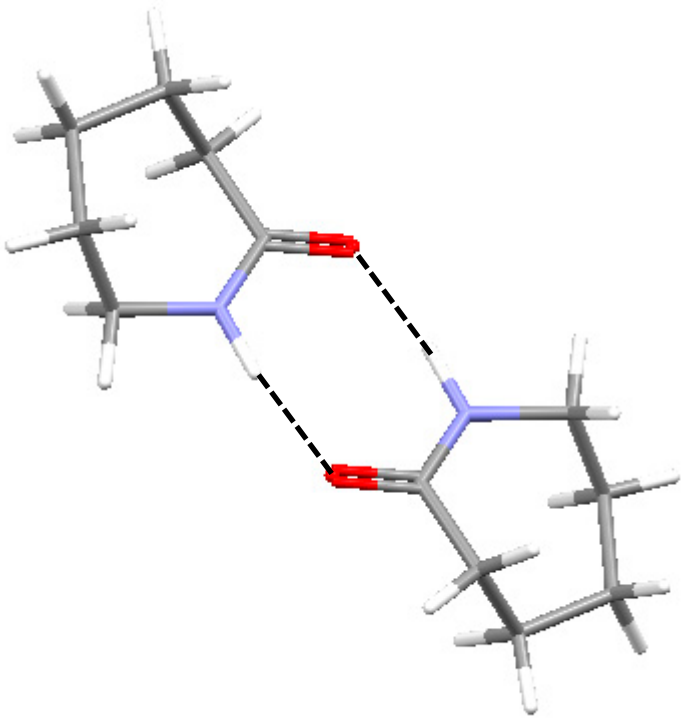


Figure S12: Comparison between XRPD diffractograms of bulk powder zonisamide/ϵ-caprolactam cocrystal (black) and the calculated powder XRD profile from Rietveld refinements (structure models before (blue) and after DFT-D geometry optimization: optimization step 9 (orange), optimization step 10 (brown), optimization step 11 (green), optimization step 20 (purple) and optimization step 30 (red). Only enlargement from 8 to 22 ° in 2θ is represented to clarify.



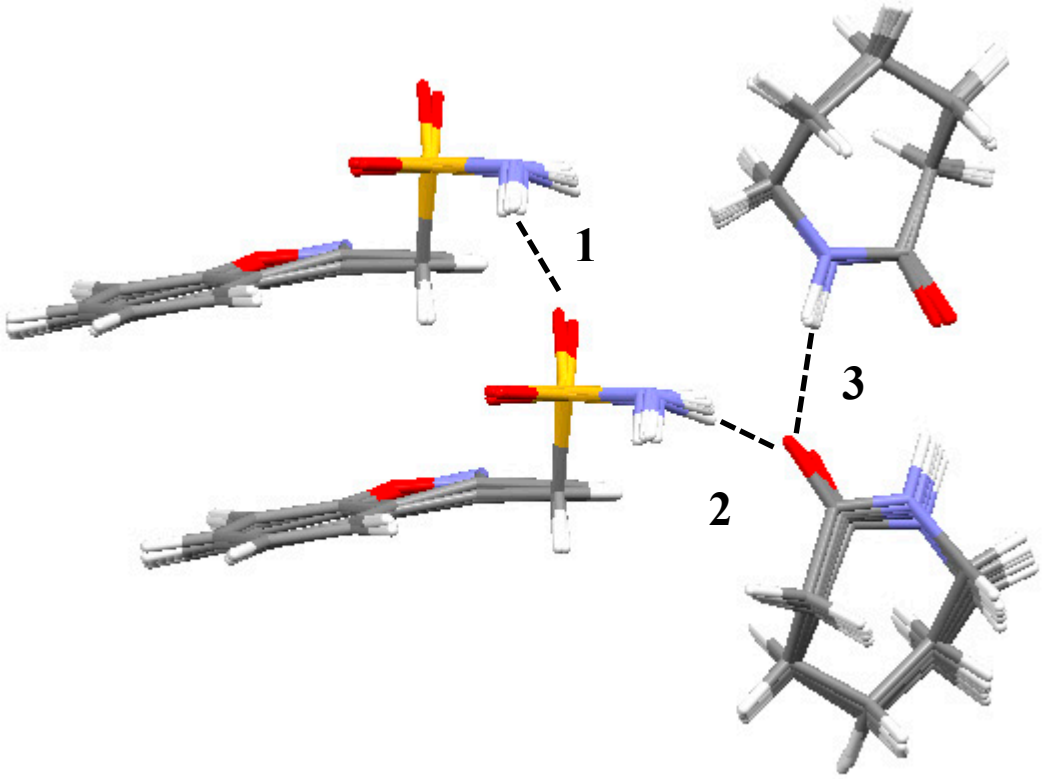
4.- Relevant H-bond distances

Figure S13: N-H···O distances of the self-assembling of ϵ-caprolactam dimer reported in the CCDC at 298-303 K



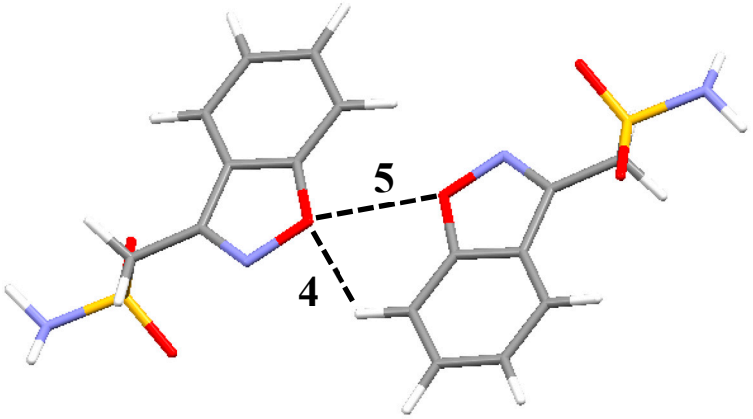
Distances (Å) at 298-303 K	
CCDC refCode	**N-H···O**
CAPLAC	1.841
CAPLAC16	2.025
CAPLAC17	1.988
JAQVOP	2.108
KEWZUI	1.980
MADSIW	2.133
NUMGUZ	2.131
NUMJAI	2.041
QQQGHM01	1.969
WIXDIS	2.115
Average	**2.022**

Figure S14: Overlay of the crystal structures of the different structures before and after optimization steps. N-H···O distances measured are represented.



Distances (Å) N-H···O			
structures	**1**	**2**	**3**
best FOX	2.057	2.634	2.185
initial optimized structure	2.057	2.634	2.185
optimized step 9	2.185	2.248	2.040
optimized step 10	2.183	2.134	2.000
optimized step 11	**2.189**	**2.084**	**1.971**
optimized step 20	2.124	1.722	1.908
CCDC average			2.022

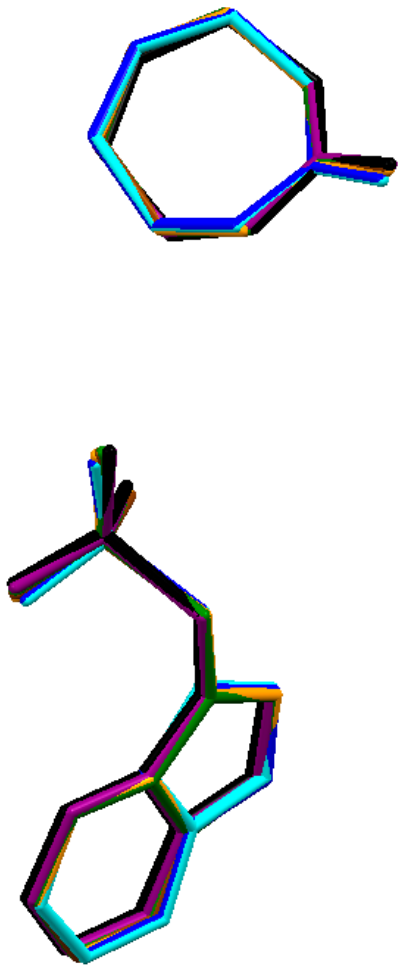
Figure S15: C-H···O_{23} and O_{23} ···· O_{23} distances measured for the different structures before and after optimization steps are represented. More relevant Alerts reported from each checkcif are also included.



structures	Distances (Å)		Checkcif
	CH···O_{23} (4)	O_{23}···O_{23} (5)	
best FOX	2.564	3.057	Alert level C Bond Without Acceptor N_{24} -H_{35}
initial optimized structure	2.548	2.975	-
optimized step 9	2.553	2.880	Alert level C Short contact O_{23}···O_{23}
optimized step 10	2.548	2.867	Alert level C Short contact O_{23}···O_{23}
optimized step 11	**2.551**	**2.835**	**Alert level B** **Short contact O_{23}···O_{23}**
optimized step 20	2.519	2.855	Alert level C Short contact O_{23}···O_{23}

5.- RMSD values

Figure S16: The RMS Cartesian displacement of the non-hydrogen atoms for zonisamide and ϵ-caprolactam molecules in the asymmetric unit between the DFT-optimized free cell parameters (black) and different structures



	RMSD (Å)	
structures	**Zonisamide molecule**	**ϵ-Caprolactam molecule**
best FOX	0.1271	0.0282
initial optimized structure	0.1229	0.0282
optimized step 9	0.0515	0.0336
optimized step 10	0.0431	0.0289
optimized step 11	**0.0415**	**0.0350**
optimized step 20	0.0333	0.0305

6. QTAIM parameters

Table S3. Density (ρ), λ_1, λ_2, λ_3 and Laplacian $\nabla^2\rho$ of electron density at the bond CPs of the noncovalent contacts of the cocrystal (see Figure 10, main text) in atomic units.

CP	**ρ**	**λ_1**	**λ_2**	**λ_3**	**$\nabla^2\rho$**
Figure 10a					
CH···O	0.0053	-0.0045	-0.0044	0.0274	0.0186
NH···O	0.0314	-0.0487	-0.0472	0.1984	0.1022
NH2···O	0.0463	-0.0808	-0.0788	0.2887	0.1291
Figure 10b					
CH···O	0.0075	-0.0068	-0.0065	0.0459	0.0326
O···O	0.0080	-0.0076	-0.0069	0.0556	0.0410
NH2···O	0.0171	-0.0212	-0.0204	0.1161	0.0745
C···O	0.0049	-0.0027	-0.0018	0.0237	0.0193
C···N	0.0062	-0.0029	-0.0020	0.0258	0.0209