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Supporting information for article:

Pharmaceutical salts of emoxypine with dicarboxylic acids

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S1. Neutralization of Emoxypine hydrochloride (EMX·HCl).

Emoxypine hydrochloride was obtained from BION Ltd, Obninsk, Russia, at a stated purity of 99% and no attempt was made at further purification. [EMX·HCl] (1 g) was dissolved in water (10 mL) and neutralized with NaOH until a highly alkaline solution of ~ pH =9 was achieved. The solution was filtered from the bottom phase by washing it with water, the obtained precipitate was dried and washed with water until the pH of the sample became neutral. As a result, a white solid emoxypine base was obtained. Mp: 169-171 °C.

Table S1 Results of CBZ and PASA crystallization from different solvents.

	MeOH	ACN	AO	EtOCH ₃	THF	EtOH	MeOH/AO
[EMX+Mln] (1:1)	poly	mix	poly	mix	mix	poly	+
[EMX+Mlt] (1:1)	poly	mix	poly	poly	mix	poly	+
[EMX+Adp] (1:1)	poly	mix	poly	mix	poly	poly	+

poly – polycrystalline form of salt

mix – mixture of individual components

– + single crystal of salt

S2. Details of the periodic DFT-D2 computations

The space groups and unit cell parameters of the considered two-component crystals obtained in the single-crystal X-ray studies were fixed and structural relaxations were limited to the positional parameters of atoms. As the starting point in the solid-state DFT computations, we took the coordinates of non-hydrogen atoms directly from the experiment with hydrogen atoms positions normalized to the standard X-H distances from the neutron diffraction data. The CRYSTAL14 options were set as default values for the level of accuracy in evaluating the Coulomb and Hartree-Fock exchange series and for the grid size used in evaluating the DFT exchange-correlation contribution. The tolerance on the energy controlling the self-consistent field convergence for geometry optimizations and frequency computations was set to 10^{-10} hartree. The mixing coefficient of Hartree-Fock/Kohn-Sham matrices is set to 25%. The number of points in the numerical first derivative calculation of the analytic nuclear gradients equals 2. The shrinking factor of the reciprocal space net was set to 4. The frequencies of the normal modes were calculated within the harmonic approximation by numerical differentiation of the analytical gradient of the potential energy with respect to the atomic position.

Table S2 Metric parameters and electron-density features at the (3;-1) bond critical points corresponding to noncovalent interactions* in the [EMX+Mlt] (1:1) cocrystal.

Interaction	D(D···A)/ Å D(H···A)/ Å	∠(D-H-A)/ °	ρ_b / a.u.	$\nabla^2\rho_b$ / a.u.	G_b / a.u.	E_{int} / kJ·mol ⁻¹
O11-H11···O14 ^a	2.436 1.364	174.22	0.112	0.066	0.078	88.2**
O1-H2···O13 ^a	2.566 1.555	171.26	0.065	0.160	0.048	54.1
N1-H1···O12 ^b	2.729 1.710	163.48	0.044	0.130	0.033	36.8
C3-H3···O13 ^a	3.109 2.360	124.93	0.011	0.044	0.010	10.8
C7-H71···O12 ^b	3.121 2.447	118.61	0.010	0.039	0.008	9.5
C8-H82···O13 ^c	3.554 2.460	177.87	0.011	0.032	0.008	8.5
C8-H83···O14 ^d	3.442 2.460	148.61	0.010	0.032	0.007	8.4
C6-H63···O11 ^b	3.570 2.547	154.87	0.008	0.027	0.006	6.8
H3···H82 ^e	2.112	-	0.008	0.030	0.006	6.7
C6-H61···O14 ^e	3.589 2.523	164.45	0.008	0.026	0.006	6.7
C8-H81···O1 ^d	3.557 2.625	142.58	0.007	0.024	0.005	6.0
O12···O14 ^f	3.149	-	0.006	0.023	0.005	5.7
O1···C1 ^g	3.171	-	0.007	0.023	0.005	5.5
H13···H82 ^e	2.256	-	0.006	0.024	0.005	5.2
N1···O13 ^g	3.210	-	0.006	0.020	0.005	5.1
C8-H83···O12 ^b	3.372 2.779	113.73	0.005	0.022	0.005	5.1
C7-H71···C6 ^h	3.695 2.808	138.17	0.006	0.023	0.004	5.0
H81···H4 ⁱ	2.290	-	0.006	0.024	0.004	4.9
C4-H4···O1 ^e	3.764 2.687	171.72	0.006	0.020	0.004	4.8
C2···C2 ^h	3.264	-	0.006	0.020	0.004	4.3
C6-H62···C13 ^g	3.742 2.833	140.13	0.005	0.019	0.004	4.0
H12···H12 ^j	2.499	-	0.005	0.019	0.003	3.8
C6-H62···O13 ^g	3.666 2.984	120.53	0.004	0.016	0.003	3.5
H72···H72 ^g	2.392	-	0.004	0.016	0.003	3.3

C12···O11 ^f	3.394	-	0.004	0.014	0.003	3.2
H4···H72 ^e	2.559	-	0.004	0.015	0.003	3.1
C3···C3 ^g	3.492	-	0.004	0.012	0.002	2.8
H4···H72 ^k	2.602	-	0.003	0.013	0.002	2.6
<i>E</i> _{latt} / kJ·mol ⁻¹						226.3

*Distance between the donor and acceptor atoms D(D···A) and between the hydrogen and acceptor atom D(H···A), where D= O, N, C and A= O, N, C, angle \angle (D-H-A), electron density in bond CP ρ_b , Laplacian of electron density in bond CP $\nabla^2\rho_b$, local kinetic energy in bond CP G_b , energy of intermolecular interaction E_{int} obtained using eq. (1). All the solid-state calculations are performed at the B3LYP-D2/6-31G(d,p) level of theory.

** Intramolecular contacts are not taken into account in E_{latt} evaluation.

Symmetry codes: a) x,y,z; b) 1/2+x,1-y,1/2-z; c) 1/2-x,y,-1/2+z; d) 1/2-x,1/2-y,z; e) 1/2-x,y,1/2+z; f) -x,-1/2+y,1/2-z; g) 1/2-x,1.5-y,z; h) x,1.5-y,-1/2+z; i) x,1/2-y,-1/2+z; j) -x,1-y,1-z; k) x,1.5-y,1/2+z.

Table S3 Metric parameters and electron-density features at the (3;-1) bond critical points corresponding to noncovalent interactions* in the [EMX+Mln] (1:1) cocrystal.

Interaction	D(D···A)/ Å D(H···A)/ Å	∠(D-H-A)/ °	ρ_b / a.u.	$\nabla^2\rho_b$ / a.u.	G_b / a.u.	E_{int} / kJ·mol ⁻¹
O31-H31···O34 ^a	2.477 1.474	158.21	0,086	0,145	0,061	68.9**
O41-H41···O44 ^a	2.488 1.499	157.30	0.080	0.154	0.058	65.1**
O1-H12···O33 ^a	2.569 1.557	170.90	0.065	0.159	0.048	53.6
O2-H22···O43 ^b	2.567 1.570	166.48	0.061	0.161	0.046	51.5
N2-H21···O32 ^a	2.756 1.728	167.00	0.042	0.124	0.031	34.8
N1-H11···O42 ^a	2.807 1.774	172.49	0.037	0.111	0.027	30.9
C23-H23···O44 ^b	3.351 2.288	165.35	0.014	0.039	0.010	11.3
C16-H163···O41 ^a	3.392 3.237	164.69	0.013	0.038	0.009	10.5
C32-H322···O42 ^c	3.379 2.338	158.30	0.013	0.039	0.009	10.5
C13-H13···O33 ^a	3.112 2.381	123.38	0.011	0.042	0.009	10.4
C14-H14···O43 ^d	3.366 2.355	154.49	0.013	0.037	0.009	10.2
C28-H282···O2 ^a	3.145 2.524	114.97	0.010	0.037	0.008	9.1**
C16-H161···O2 ^e	3.101 2.491	113.98	0.009	0.036	0.008	8.6
C16-H161···O2 ^f	3.425 2.531	141.23	0.009	0.031	0.007	7.8
C27-H272···O31 ^a	3.577 2.484	176.54	0.009	0.029	0.007	7.6
C26-H261···O43 ^c	3.450 2.530	140.94	0.009	0.030	0.007	7.5
C28-H283···O44 ^c	3.515 2.502	153.22	0.008	0.030	0.007	7.4
C26-H263···O1 ^d	3.162 2.611	110.40	0.007	0.029	0.006	6.8
C26-H262···O32 ^a	3.233 2.645	112.97	0.007	0.028	0.006	6.5
C32-H321···C33 ^f	3.453 2.657	129.06	0.007	0.029	0.006	6.2
C26-H263···O34 ^d	3.645 2.598	160.57	0.008	0.025	0.005	6.2
C42-H422···O44 ^g	3.315 2.673	116.63	0.007	0.026	0.005	6.0
O32···O41 ^c	3.148	-	0.006	0.024	0.005	5.8
C17-H172···O42 ^a	3.505 2.644	134.98	0.006	0.024	0.005	5.8

C27-H271…O43 ^h	3.650 2.626	154.98	0.007	0.023	0.005	5.7
C13-H13…O31 ^f	3.370 2.721	118.07	0.006	0.024	0.005	5.5
O44…O44 ^g	3.263	-	0.005	0.022	0.005	5.3
C17-H171…C26 ^f	3.453 2.839	115.37	0.006	0.024	0.005	5.1
H282…H24 ⁱ	2.309	-	0.006	0.024	0.004	5.0
C24-H24…O34 ^d	3.670 2.696	149.37	0.005	0.020	0.004	4.6
C11…C25 ^f	3.283	-	0.006	0.020	0.004	4.6
H281…H281 ^j	2.471	-	0.006	0.021	0.004	4.5
C26-H262…O1 ^f	3.810 2.817	150.93	0.005	0.019	0.004	4.3
C15…C21 ^f	3.314	-	0.006	0.019	0.004	4.2
O41…O44 ^g	3.359	-	0.004	0.018	0.004	4.1
C18-H182…O32 ^k	3.705 2.835	136.41	0.005	0.018	0.004	4.1
C23…O42 ^f	3.364	-	0.005	0.017	0.003	3.9
C24…O2 ⁱ	3.379	-	0.005	0.017	0.003	3.9
C18-H183…O33 ^c	3.780 2.855	142.12	0.005	0.017	0.003	3.8
C18-H181…C13 ^c	3.658 2.932	123.92	0.005	0.017	0.003	3.7
N1…O33 ^c	3.398	-	0.004	0.015	0.003	3.7
C23…C22 ⁱ	3.376	-	0.006	0.016	0.003	3.6
C17-H171…O1 ^h	3.904 2.837	164.93	0.004	0.016	0.003	3.5
H261…H14 ⁱ	2.409	-	0.005	0.017	0.003	3.5
N2…O44 ^c	3.410	-	0.004	0.015	0.003	3.5
H182…H322 ^k	2.495	-	0.004	0.016	0.003	3.3
H181…H261 ^k	2.496	-	0.004	0.016	0.003	3.3
H283…H23 ⁱ	2.501	-	0.004	0.016	0.003	3.2
C13…O32 ^f	3.530	-	0.003	0.013	0.003	2.9
C16-H162…O34 ^c	3.688 3.035	118.78	0.003	0.013	0.003	2.9
H283…H422 ^m	2.448	-	0.004	0.013	0.002	2.7

H271···H161 ^f	2.592	-	0.003	0.013	0.002	2.7
C18-H182···O42 ^l	3.857 3.023	133.30	0.003	0.013	0.002	2.7
C16-H162···C26 ⁿ	4.036 3.065	148.08	0.004	0.012	0.002	2.6
C42-H421···C18	3.957 3.044	141.49	0.004	0.012	0.002	2.6
H162···H282 ^e	2.589	-	0.003	0.013	0.002	2.6
<i>E</i> _{latt} / kJ·mol ⁻¹						213.7

*Distance between the donor and acceptor atoms D(D···A) and between the hydrogen and acceptor atom D(H···A), where D= O, N, C and A= O, N, C, angle \angle (D-H-A), electron density in bond CP ρ_b , Laplacian of electron density in bond CP $\nabla^2\rho_b$, local kinetic energy in bond CP G_b , energy of intermolecular interaction E_{int} obtained using eq. (1). All the solid-state calculations are performed at the B3LYP-D2/6-31G(d,p) level of theory.

** Intramolecular contacts are not taken into account in E_{latt} evaluation.

Symmetry codes: a) x,y,z; b) 1+x,-2+y,-1+z; c) 1-x,2-y,1-z; d) 1+x,-1+y,z; e) x,1+y,1+z; f) 1-x,1-y,1-z; g) -x,3-y,2-z; h) -x,2-y,1-z; i) 2-x,-y,-z; j) 1-x,1-y,-z; k) -1+x,1+y,z; l) 2-x,1-y,1-z; m) 1+x,-1+y,-1+z; n) -x,3-y,1-z.

Table S4 Metric parameters and electron-density features at the (3;-1) bond critical points corresponding to noncovalent interactions* in the [EMX+Adp] (1:1) cocrystal.

Interaction	D(D···A)/ Å D(H···A)/ Å	∠(D-H-A)/ °	ρ_b / a.u.	$\nabla^2\rho_b$ / a.u.	G_b / a.u.	E_{int} / kJ·mol ⁻¹
O11-H11···O ⁻ 13 ^a	2.495 1.437	177.32	0.091	0.126	0.064	72.5
O1-H2···O14 ^b	2.521 1.515	164.64	0.072	0.161	0.053	59.9
N ⁺ 1-H1···O12 ^c	2.729 1.713	165.47	0.044	0.128	0.032	36.3
C3-H3···O ⁻ 13 ^b	3.246 2.212	158.01	0.017	0.045	0.012	13.3
C7-H71···O11 ^c	3.285 2.519	126.16	0.009	0.033	0.007	8.1
C8-H81···O11 ^c	3.240 2.681	111.12	0.007	0.028	0.006	6.6
C14-H141···O14 ^d	3.524 2.603	141.13	0.008	0.026	0.006	6.4
C6-H61···O12 ^c	3.268 2.682	112.90	0.006	0.026	0.005	6.0
C7-H71···O ⁻ 13 ^e	3.492 2.658	132.54	0.007	0.024	0.005	5.8
C15-H151···O12 ^e	3.322 2.740	112.79	0.007	0.025	0.005	5.7
C8-H82···O12 ^f	3.472 2.682	128.65	0.006	0.024	0.005	5.6
C6-H62···O14 ^e	3.539 2.674	135.26	0.006	0.023	0.005	5.6
C6-H63···O1 ^g	3.441 2.629	130.63	0.006	0.024	0.005	5.6
H131···H131 ^e	2.286	-	0.007	0.023	0.005	5.1
O11···O11 ^h	3.240	-	0.005	0.020	0.004	4.9
C8-H81···N ⁺ 1 ^f	3.601 2.760	133.49	0.006	0.020	0.004	4.8
H71···H121 ^h	2.359	-	0.006	0.022	0.004	4.7
H63···H62 ⁱ	2.406	-	0.006	0.022	0.004	4.7
C13-H132···O1 ^f	3.608 2.774	132.64	0.005	0.020	0.004	4.6
C6-H63···O14 ^j	3.826 2.742	172.04	0.005	0.019	0.004	4.2
N ⁺ 1···O14 ^e	3.334	-	0.005	0.017	0.004	4.1
C6-H61···C8 ^f	3.674 2.888	128.74	0.005	0.018	0.003	3.8
C8-H83···C15 ^a	3.844 2.974	136.62	0.005	0.018	0.003	3.8
C15-H152···C4 ^k	3.839 2.859	148.55	0.005	0.017	0.003	3.7

C2···C2 ^l	3.382	-	0.006	0.016	0.003	3.6
H4···H141 ^j	2.422	-	0.005	0.017	0.003	3.6
C14-H142···O12 ^e	3.599 2.960	117.29	0.004	0.016	0.003	3.5
C4···O1 ^l	3.530	-	0.004	0.014	0.003	3.2
H142···H62 ^e	2.450	-	0.004	0.014	0.003	3.0
C12-H122···O1 ^f	3.669 3.083	114.02	0.003	0.013	0.003	2.9
C7-H72···C3 ^l	3.660 3.090	113.02	0.004	0.013	0.002	2.8
H83···H132 ^a	2.635	-	0.004	0.012	0.002	2.6
H4···H62 ⁱ	2.577	-	0.004	0.013	0.002	2.6
C12-H122···C3 ^f	4.071 3.140	143.13	0.003	0.010	0.002	2.2
<i>E</i> _{latt} / kJ·mol ⁻¹	315.8					

*Distance between the donor and acceptor atoms D(D···A) and between the hydrogen and acceptor atom D(H···A), where D= O, N, C and A= O, N, C, angle \angle (D-H-A), electron density in bond CP ρ_b , Laplacian of electron density in bond CP $\nabla^2\rho_b$, local kinetic energy in bond CP G_b , energy of intermolecular interaction E_{int} obtained using eq. (1). All the solid-state calculations are performed at the B3LYP-D2/6-31G(d,p) level of theory.

Symmetry codes: a) 1+x,y,z; b) 1+x,-1+y,1+z; c) x,y,z; d) 1-x,2-y,-z; e) 1-x,2-y,1-z; f) 2-x,1-y,1-z; g) -1+x,y,z; h) 2-x,2-y,1-z; i) 1-x,1-y,2-z; j) x,-1+y,1+z; k) 1-x,1-y,1-z; l) 2-x,1-y,2-z.

Table S5 Contributions into the lattice energy of the [EMX+Mln] (1:1) cocrystal from the interactions between the molecules of different conformation*.

Sums of pair interaction energies					Fragment contributions	
Mol. 1 \ Mol. 2	EMX-A	EMX-B	Mln-A	Mln-B	Molecule	ΣE_{int}
EMX-A	5.2	28.1	45.0	31.3	EMX-A	57.5 (26.9%)
EMX-B	-	8.4	29.9	46.8	EMX-B	60.8 (28.5%)
Mln-A	-	-	3.1	8.1	Mln-A	44.6 (20.9%)
Mln-B	-	-	-	7.7	Mln-B	50.8 (23.8%)

*The values are given in $\text{kJ}\cdot\text{mol}^{-1}$ and percents of the lattice energy value.

S3. Details of the gas-phase calculations of Mln anions with different conformation

A single point calculation was performed in the Gaussian09 program [S1] using the long range-corrected wB97XD functional and the aug-cc-pVTZ basis set. The choice of this level of theory is based on the negative charge and the effect that the intramolecular hydrogen bond has on the conformation of the anion. Total electronic energies of Mln-A and Mln-B were found to be equal to -417.13489954 and -417.13955107 a.u., respectively. The difference between a more stable bent Mln-B conformation and a planar Mln-A equals 12.2 $\text{kJ}\cdot\text{mol}^{-1}$.

References:

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Figure S1 A part of the crystal lattice showing the non-covalent interactions accepted by oxygen atoms of the planar Mln-A (a) and bent Mln-B (b) anions in the [EMX+Mln] (1:1) salt. N-H \cdots O and C-H \cdots O hydrogen bonds are shown as blue dotted lines, while C-H \cdots O contacts are presented as green lines. The numbers indicate the energy of the particular non-covalent interactions in kJ \cdot mol $^{-1}$ obtained by solid-state DFT/QTAIMC using the equation (1). The energy values of intramolecular interactions in malonate ions are colored red.

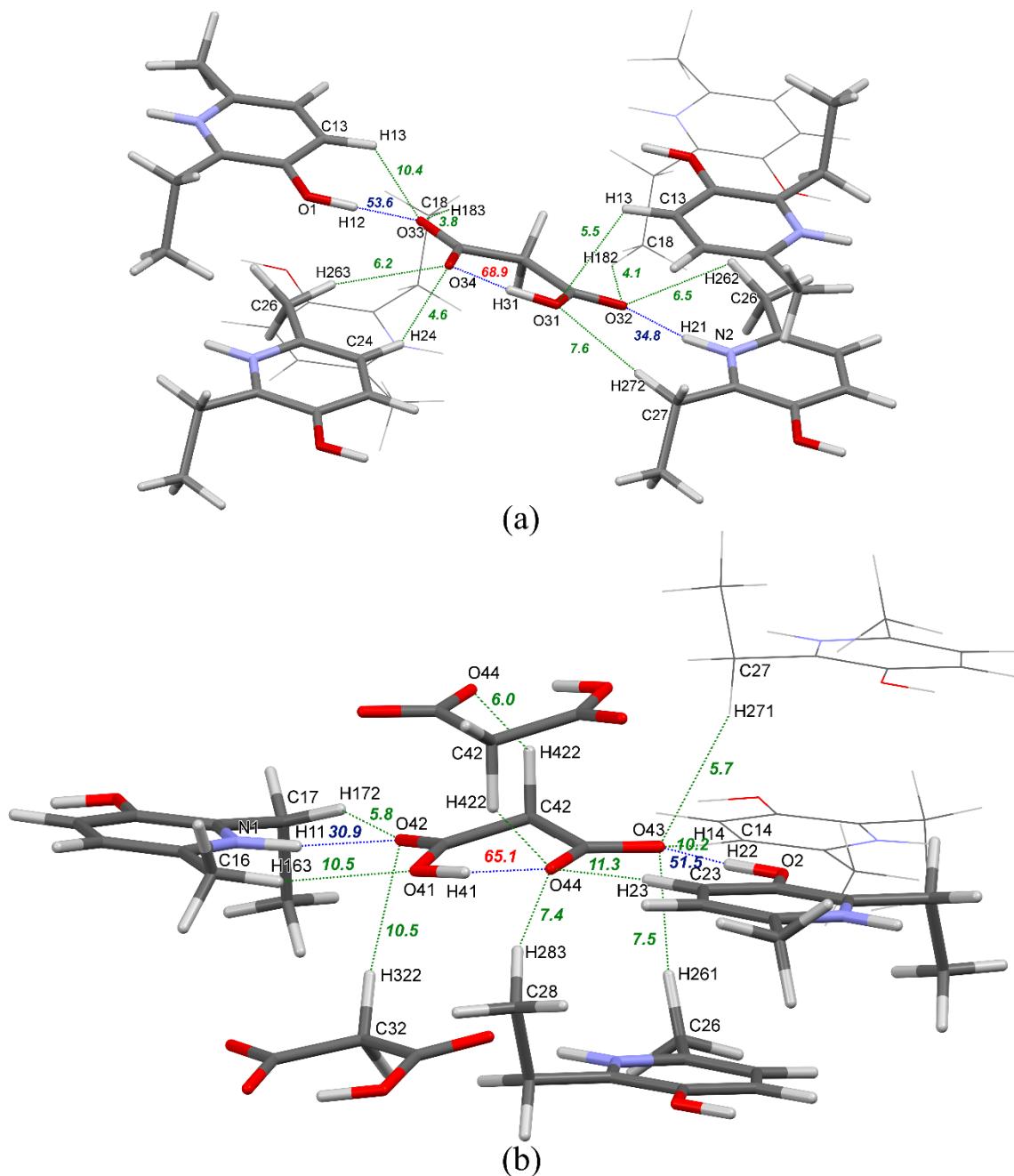


Figure S2 Comparison of the XRPD pattern of the product obtained from the dissolution experiment in buffer pH 7.4 using EMX (red line) with XRPD patterns of EMX (black line).

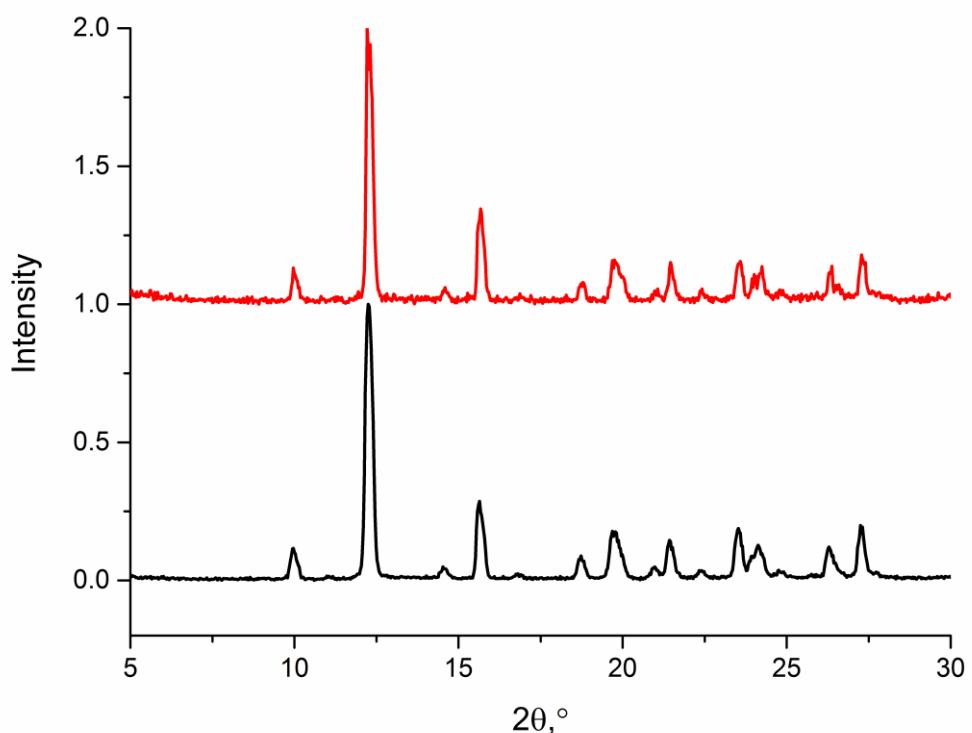


Figure S3 Comparison of the XRPD pattern of the product obtained from the dissolution experiment in buffer pH 7.4 using [EMX+Mlt] salt (red line) with XRPD patterns of EMX (black line), Mlc (green line), and simulated XRPD pattern of [EMX+Mlt] salt (blue line).

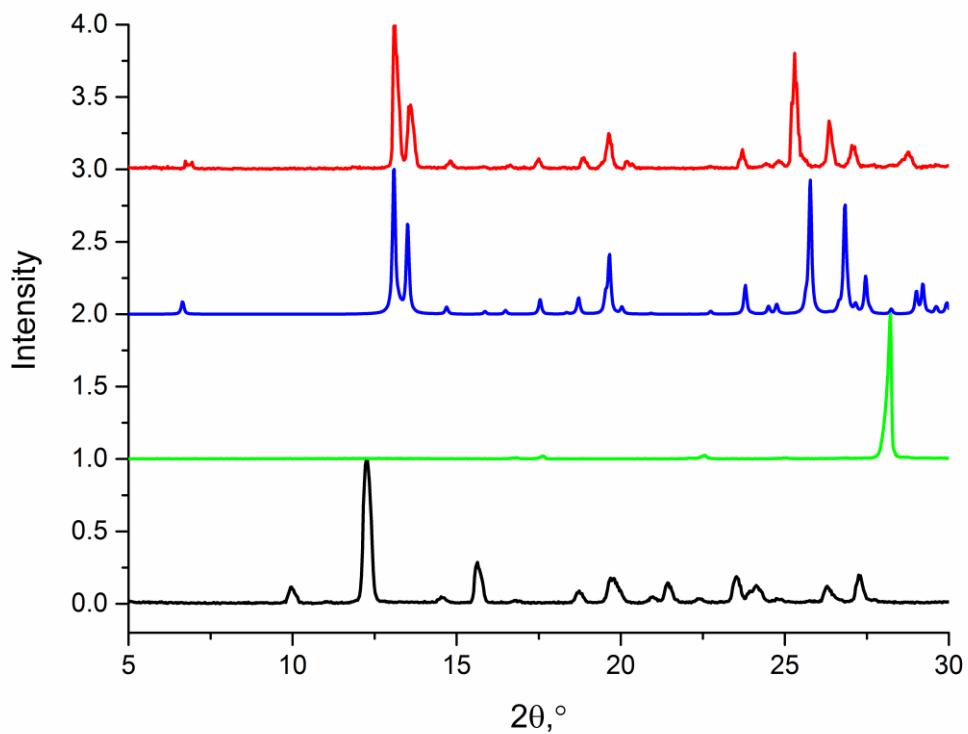


Figure S4 Comparison of the XRPD pattern of the product obtained from the dissolution experiment in buffer pH 7.4 using [EMX+Mln] salt (red line) with XRPD patterns of EMX (black line), Mln (green line), and simulated XRPD pattern of [EMX+Mln] salt (blue line).

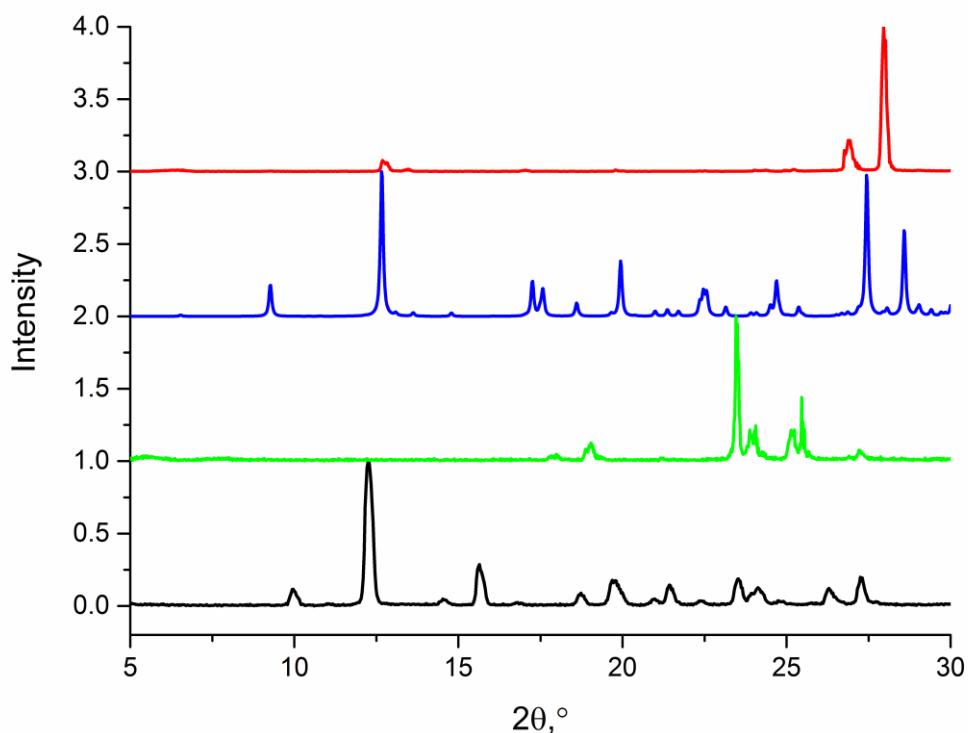


Figure S5 Comparison of the XRPD pattern of the product obtained from the dissolution experiment in buffer pH 7.4 using [EMX+Adp] salt (red line) with XRPD patterns of EMX (black line), Adp (green line), and simulated XRPD pattern of [EMX+Adp] salt (blue line).

