Electronic Supplementary Material (ESI) for CrystEngComm.

Molecular salts of propranolol with dicarboxylic acids: Diversity of stoichiometry, supramolecular structures and physicochemical properties

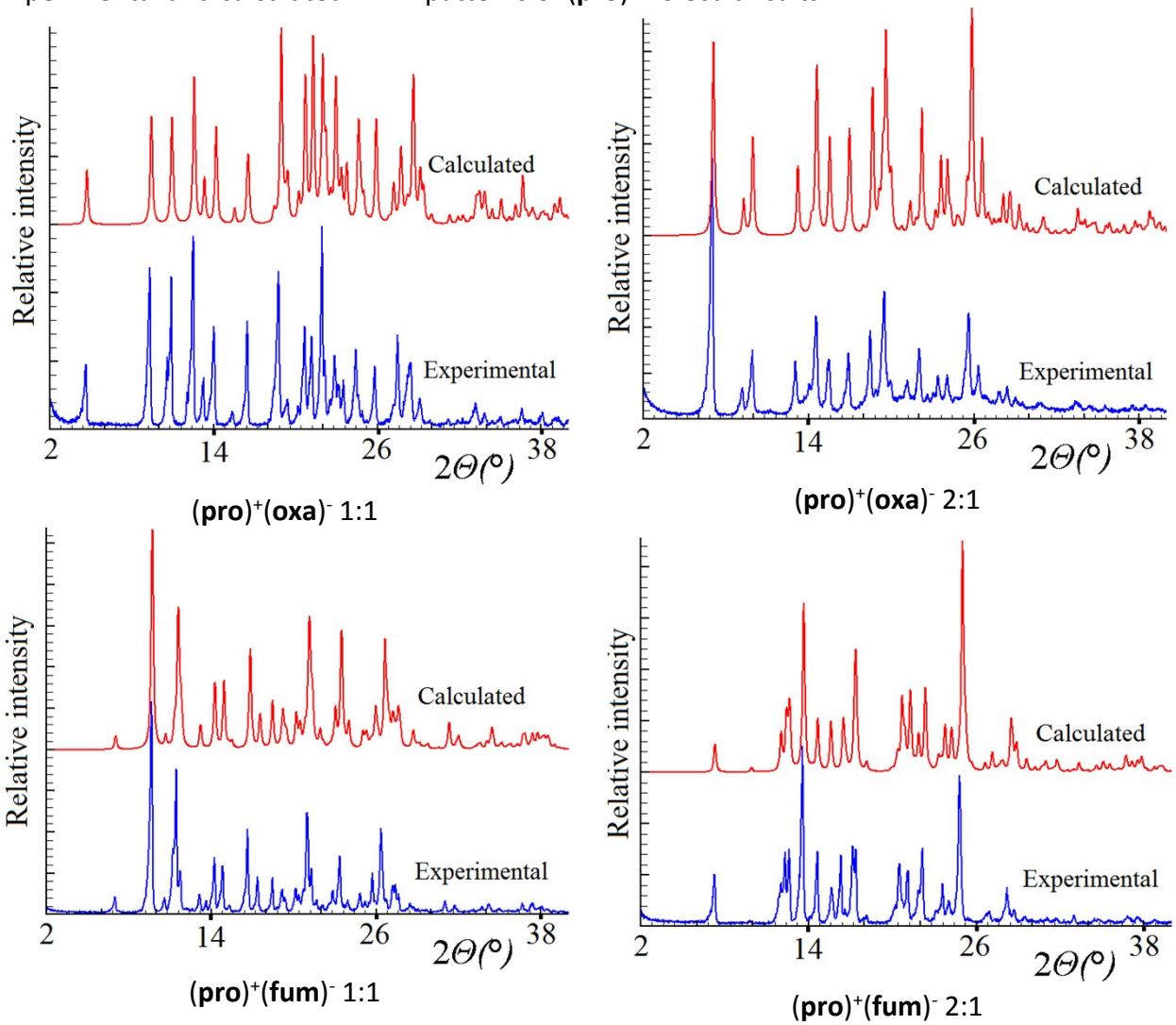
D. Stepanovs, M. Jure, A. Yanichev, S. Belyakov, and A. Mishnev

S1

Powder X-ray diffraction (PXRD)

Powder diffraction was used to observe the results of molecular salt synthesis. Powder X-ray data were collected at room temperature with 0.02° step and scan speed of 0.5 s/step on *Rigaku ULTIMA IV* powder diffractometer (CuKα radiation, λ = 1.5418 Å) equipped with parallel beam geometry.

Experimental and calculated PXRD patterns of (**pro**) molecular salts:

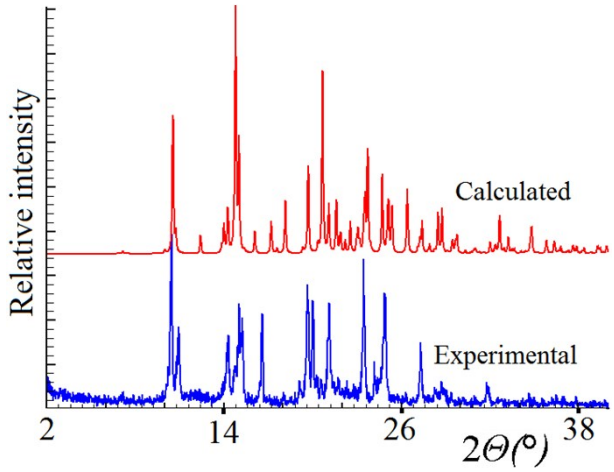


(**pro**)$^+$(**oxa**)$^-$ 1:1

(**pro**)$^+$(**oxa**)$^-$ 2:1

(**pro**)$^+$(**fum**)$^-$ 1:1

(**pro**)$^+$(**fum**)$^-$ 2:1



(**pro**)$^+$(**mal**)$^-$

S2

Single crystal synthesis by slow solvent evaporation (SSE)

Molecular salts formed when (**pro**) base (50 mg, 0.19 mmol) and dicarboxylic acid in 1:1 and 2:1 molar ratios were dissolved in corresponding solvent (**Table 1**) and left for solvent evaporation for several days. Single crystals suitable for X-ray analysis were collected during these experiments.

Experiments attempted to synthesize molecular salts of propranolol:

Molecular salt	Solvent		Stoichiometry 1:1	Stoichiometry 2:1
	1:1	2:1		
	Stoichiometry			
(**pro**)$^+$(**oxa**)$^-$	MeOH	DMFA	***PXRD***, Single Crystal	***PXRD***, Single Crystal
(**pro**)$^+$(**fum**)$^-$	MeOH/MeCN (50/50)	MeOH	***PXRD***, Single Crystal	***PXRD***, Single Crystal
(**pro**)$^+$(**mal**)$^-$	MeOH	-	***PXRD***, Single Crystal	N.C.P.D.

N.C.P.D. – No crystalline phase detected

S3

Single crystal X-ray diffraction

X-Ray diffraction data were collected using a *Nonius Kappa CCD* diffractometer (CuKα radiation, λ = 0.71073 Å), equipped with low temperature *Oxford Cryosystems Cryostream Plus* device. Data were collected using *KappaCCD* Server Software, cell refined by *SCALEPACK*,[1] data reduction performed by *DENZO*[1] and *SCALEPACK*,[1] structures solved by direct method using *SIR2004*[2] and refined by *SHELXL97*[3] as implemented in the program package Win*GX*.[4] All non-

hydrogen atoms were refined anisotropically. The hydrogen atoms bound to carbon atoms and the carboxyl groups were positioned geometrically, with C–H = 0.93–0.97 Å and O–H = 0.82 Å, and refined as riding, with U_{iso}(H) = 1.2 or 1.5U_{eq}(C,O). Software used to prepare *CIF*[5] files was *SHELXL97*.[3]

Selected crystal data, experimental and refinement parameters for (**pro**) structures

	(**pro**)$^+$(**oxa**)$^-$ 1:1	(**pro**)$^+$(**oxa**)$^-$ 2:1	(**pro**)$^+$(**oxa**)$^-$ MeOH
molecular formula	$(C_{16}H_{22}NO_2)^+ \cdot (C_2HO_4)^-$	$(C_{16}H_{22}NO_2)^+ \cdot 0.5(C_2O_4)^{2-}$	$2(C_{16}H_{22}NO_2)^+ \cdot (C_2O_4)^{2-} \cdot 0.9(CH_4O)$
M_r	349.37	304.36	637.55
crystal system	monoclinic	monoclinic	orthorhombic
space group	$P2_1$	$P2_1/c$	$Pbn2_1$
a, Å	8.1696(3)	12.9928(6)	10.7741(2)
b, Å	5.6053(2)	6.4517(3)	11.3507(2)
c, Å	18.9321(9)	19.8420(13)	28.2413(6)
α, °	90	90	90
β, °	98.820(2)	106.600(2)	90
γ, °	90	90	90
V, Å^3	856.71(6)	1593.95(15)	3453.73(11)
Z	2	4	4
D_c/gcm^{-1}	1.354	1.267	1.226
F(000)	372	652	1368.8
μ(Mo K$_\alpha$)/mm^{-1}	0.102	0.090	0.088
T/K	173(2)	173(2)	173(2)
crystal size/mm	0.32 × 0.08 × 0.05	0.33 × 0.09 × 0.07	0.40 × 0.13 × 0.05
range of indices	h = –11→12 k = –8→7 l = –28→28	h = –16→17 k = –8→7 l = –25→26	h = –16→16 k = –16→16 l = –41→42
collected reflections	4766	6582	12030
unique reflections	3202	3782	12030
R_{int}	–	0.134	–
reflections with $I > 2\sigma(I)$	2562	1647	4389
no. parameters	244	200	423
$R(F)$, $F > 2\sigma(F)$	0.067	0.162	0.079
$wR(F^2)$, $F > 2\sigma(F)$	0.108	0.399	0.121
$R(F)$, all data	0.115	0.277	0.236
$wR(F^2)$, all data	0.124	0.453	0.160
S	1.01	1.05	0.99
Δ_r (max., min), eÅ^{-3}	0.27 and –0.24	0.57 and -0.45	0.38 and -0.27
CCDC deposition No	1407010	1407382	1407011

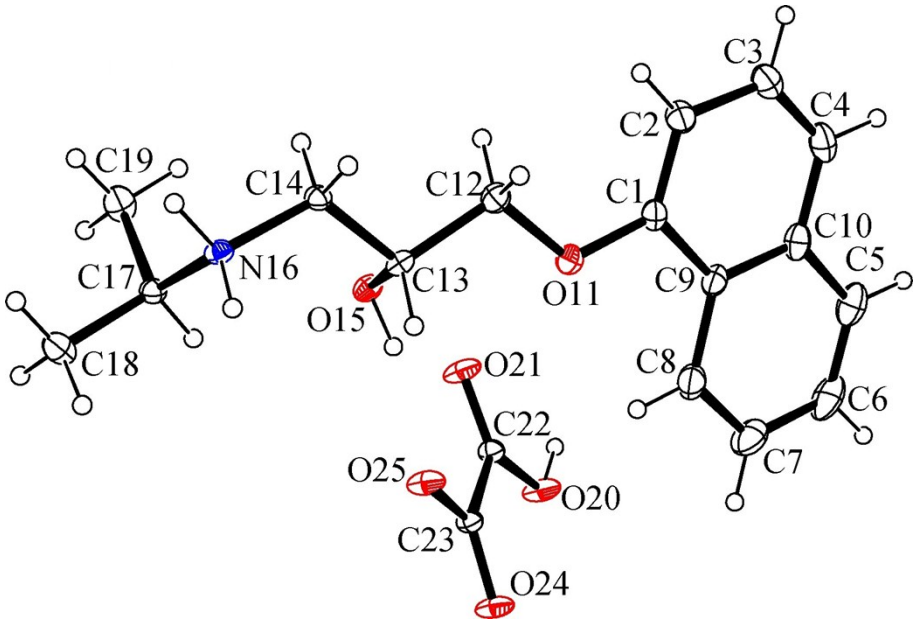
Selected crystal data, experimental and refinement parameters for (**pro**) structures (continued)

	(**pro**)$^+$(**fum**)$^-$ 1:1	(**pro**)$^+$(**fum**)$^-$ 2:1	(**pro**)$^+$(**mal**)$^-$
molecular formula	$(C_{16}H_{22}NO_2)^+$ $\cdot 0.5(C_4H_4O_4)$ $\cdot 0.5(C_4H_2O_4)^{2-}$	$(C_{16}H_{22}NO_2)^+ \cdot$ $0.5(C_4H_2O_4)^{2-}$	$(C_{16}H_{22}NO_2)^+ \cdot$ $(C_4H_3O_4)^-$
M_r	375.41	317.37	375.41
crystal system	triclinic	triclinic	monoclinic
space group	$P\bar{1}$	$P\bar{1}$	$P2_1/n$
a, Å	8.6157(2)	7.7989 (3)	9.2010(3)
b, Å	9.9155(2)	9.1669 (4)	8.7153(3)
c, Å	13.1345(4)	12.4724 (6)	24.7710(11)
α, °	97.391(1)	89.470 (2)	90
β, °	102.240(1)	75.754 (2)	94.618(1)
γ, °	109.899(1)	76.412 (3)	90
V, Å^3	1006.17(4)	838.95(6)	1979.93(13)
Z	2	2	4
D_c/gcm^{-1}	1.239	1.256	1.259
F(000)	400	340	800
μ(Mo K_α)/mm^{-1}	0.091	0.088	0.093
T/K	173(2)	173(2)	173 (2)
crystal size/mm	0.44 × 0.18 × 0.15	0.41 × 0.22 × 0.20	0.33 × 0.11 × 0.09
range of indices	h = –10→11 k = –12→12 l = –17→17	h = –10→10 k = –11→11 l = –15→16	h = –11→11 k = –9→11 l = –32→30
collected reflections	6668	5428	11927
unique reflections	4597	3805	4491
R_{int}	0.018	0.021	0.148
reflections with $I > 2\sigma(I)$	3915	3006	1813
no. parameters	260	225	260
$R(F)$, $F > 2\sigma(F)$	0.048	0.052	0.083
$wR(F^2)$, $F > 2\sigma(F)$	0.121	0.115	0.118
$R(F)$, all data	0.056	0.071	0.238
$wR(F^2)$, all data	0.127	0.126	0.153
S	1.04	1.04	0.98
Δ_r (max., min), eÅ^{-3}	0.46 and –0.22	0.18 and -0.19	0.44 and -0.22
CCDC deposition No	1407007	1407008	1407009

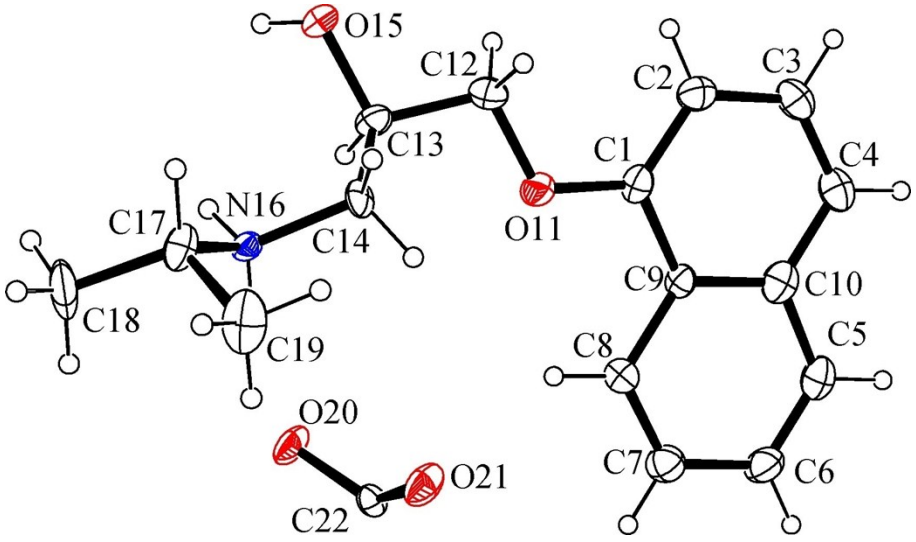
S4

ORTEP-3[4] drawings of the asymmetric unit of the:

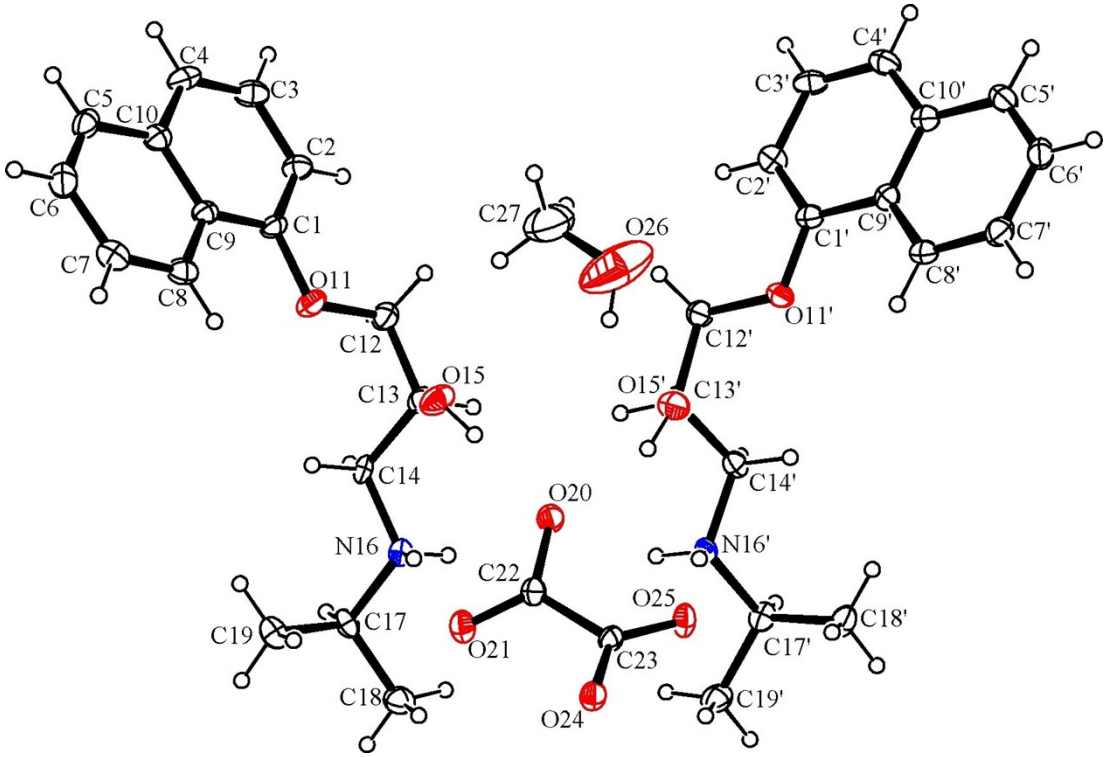
1) (**pro**)$^+$(**oxa**)$^-$ 1:1



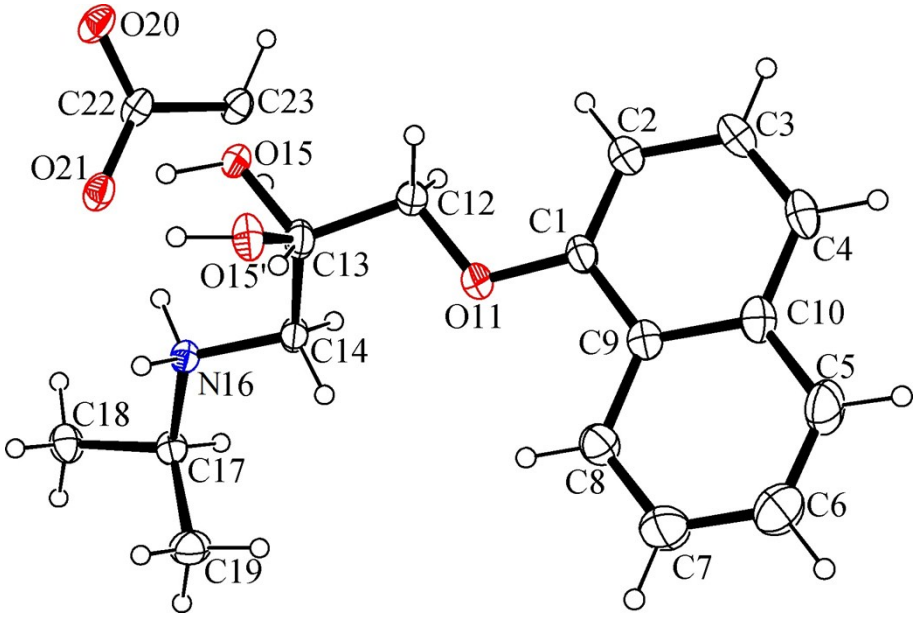
2) (**pro**)$^+$(**oxa**)$^-$ 2:1



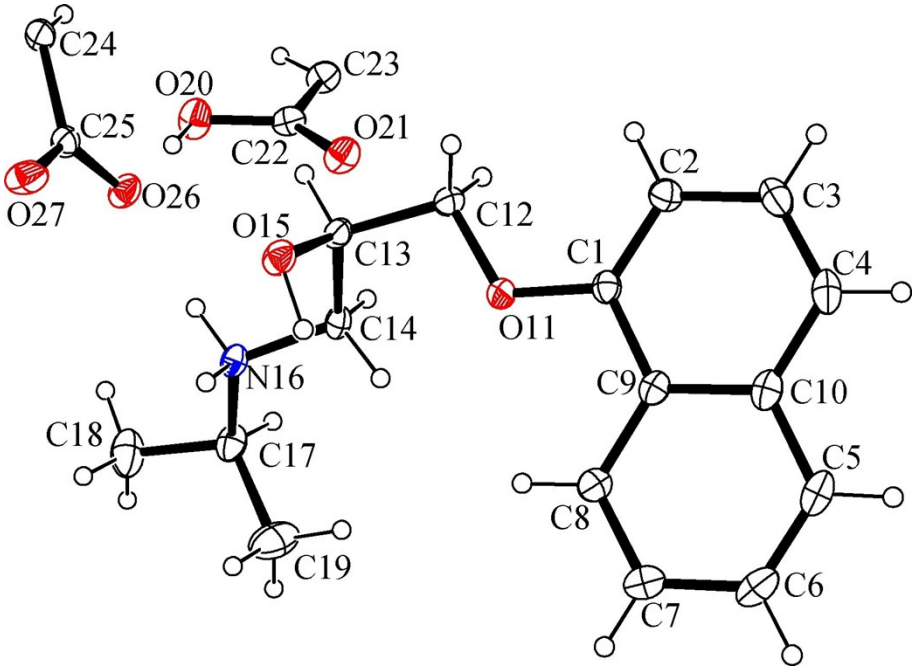
3) (**pro**)$^{+}$(**oxa**)$^{-}$ MeOH



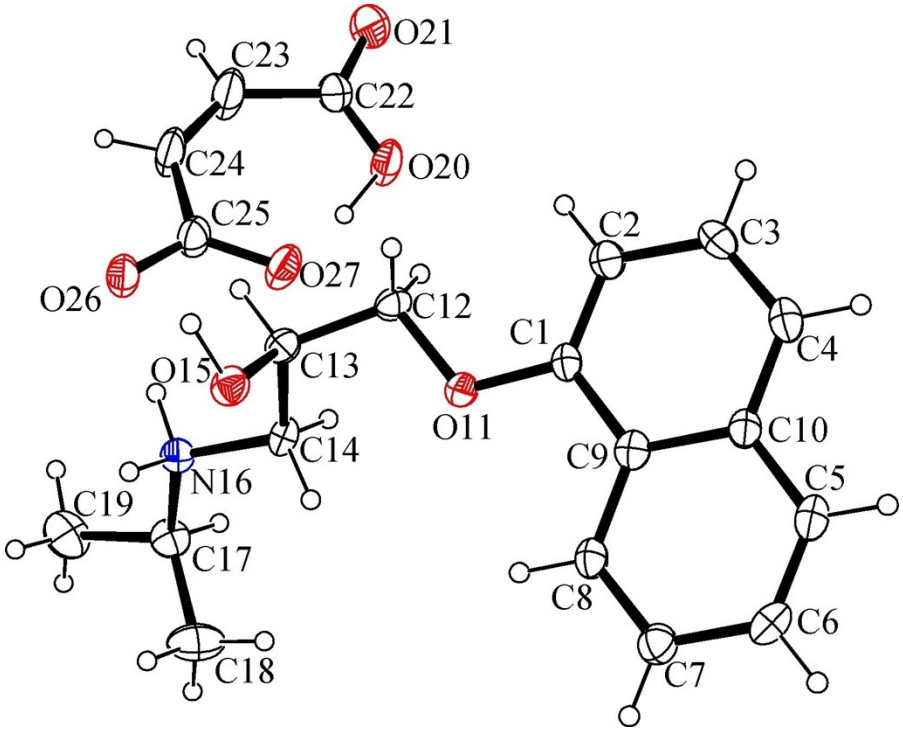
4) (**pro**)$^{+}$(**fum**)$^{-}$ 2:1



5) (**pro**)$^{+}$(**fum**)$^{-}$ 1:1



6) (**pro**)$^{+}$(**mal**)$^{-}$



S5

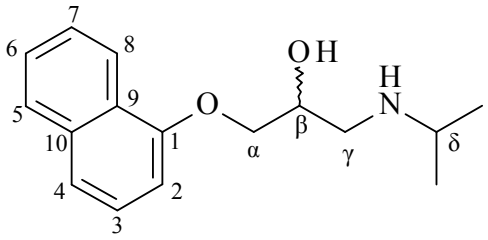
Parameters of the strong hydrogen bonds in the studied crystal structures

D–H···A	$d_{D–H}$ (Å)	$d_{H···A}$ (Å)	$d_{D···A}$ (Å)	∠ D–H···A (°)	Symmetry code
(**pro**)$^+$(**oxa**)$^-$ 1:1					
O15–H15···O25	0.90(4)	1.90(4)	2.767(3)	162(3)	*intra*
O20–H20···O25	0.94(4)	1.56(4)	2.504(3)	174(3)	*x*; *y*–1; *z*
N16–H16B···O24	0.99(4)	1.88(3)	2.847(3)	165(3)	*x* +1; *y*+1; *z*
N16–H16A···O15	0.91(4)	2.31(3)	3.062(3)	140(3)	*x*; *y*+1; *z*
N16–H16A···O21	0.91(4)	1.90(4)	2.767(3)	130(3)	*x*; *y*+1; *z*
(**pro**)$^+$(**oxa**)$^-$ 2:1					
O15–H15···O21	0.82	2.01	2.737(9)	147	*x*; *y*–1; *z*
N16–H16B···O20	0.90	1.84	2.731(9)	168	*intra*
N16–H16A···O20	0.90	2.26	2.890(9)	127	*x*; *y*–1; *z*
N16–H16A···O21	0.90	2.07	2.923(9)	157	*x*; *y*–1; *z*
(**pro**)$^+$(**oxa**)$^-$ MeOH					
O15–H15···O20	0.82	1.82	2.638(3)	175	*intra*
O15'–H15'···O20	0.82	1.89	2.633(4)	150	*intra*
O26–H26··· O15'	0.82	2.24	2.832(6)	129	*intra*
N16–H16A···O24	0.90	1.88	2.765(4)	167	1.5 – *x*; -0.5 + *y*; *z*
N16–H16B···O21	0.90	2.13	2.959(3)	154	*intra*
N16'–H16A'···O24	0.90	1.89	2.785(4)	172	1.5 – *x*; -0.5 + *y*; *z*
N16'–H16B'···O25	0.90	1.96	2.817(3)	159	*intra*
(**pro**)$^+$(**fum**)$^-$ 1:1					
O15–H15···O27	0.99(3)	1.71(3)	2.658(1)	159(1)	1 – *x*; – *y*; 1 – *x*
N16–H16A···O15	0.86(2)	2.15(2)	2.834(2)	136(2)	*intra*
N16–H16B···O26	0.90(2)	1.88(2)	2.787(2)	175(2)	*intra*
O20–H20···O26	0.95(3)	1.60(3)	2.546(2)	175(3)	*intra*
(**pro**)$^+$(**fum**)$^-$ 2:1					
O15–H15···O21	0.96	1.78	2.737(2)	176	2 – *x*; 1 – *y*; 1 – *z*
O15'–H15'···O21	0.90	1.76	2.643(2)	168	2 – *x*; 1 – *y*; 1 – *z*
N16–H16A···O21	0.94(2)	1.87(2)	2.809(2)	174(2)	*intra*
N16–H16B···O20	0.98(2)	1.76(2)	2.726(2)	169(2)	2 – *x*; 1 – *y*; 1 – *z*
(**pro**)$^+$(**mal**)$^-$					
O15–H15···O26	0.98(4)	1.75(4)	2.725(4)	168(4)	0.5 – *x*; –0.5 + *y*; 0.5 – *z*
N16–H16A···O26	0.96(3)	1.81(3)	2.770(4)	177(3)	*intra*
N16–H16B···O21	0.91(3)	2.18(3)	2.899(4)	135(4)	–1 + *x*; *y*; *z*
O20–H20···O27	1.07(5)	1.37(5)	2.423(4)	169(4)	*intra*

S6

Nuclear magnetic resonanse (NMR)

NMR spectra (^{1}H, ^{13}C) were recorded on Varian 400MR spectrometers. Samples were dissolved in [d_6]-DMSO. Chemical shifts are measured relative to TMS (δ = 0) for ^{1}H and ^{13}C shifts were referenced to the residual carbon signal of the solvent. ^{1}H and ^{13}C chemical shifts assignments were supported by 2D ^{1}H–^{13}C correlations performed on (**pro**) and (**pro**)-HCl.



Proton designation, used in following tables:

(pro)-HCl	**(pro)**-HCl		**(pro)**	HSQC (**pro**)	(**pro**)$^+$(**oxa**)$^-$ 1:1	(**pro**)$^+$(**oxa**)$^-$ 1:1	(**pro**)$^+$(**oxa**)$^-$ 2:1	(**pro**)$^+$(**oxa**)$^-$ 2:1
^{13}C	^{1}H		^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
124.87	-	C-1	-	125.01	-	124.89	-	124.93
120.20	7.49	H-2	7.45	119.79	7.49	120.23	7.47	120.03
126.16	7.42	H-3	7.40	126.21	7.42	-	7.41	126.19
105.27	6.98	H-4	6.95	105.13	6.97	105.26	6.96	105.20
121.76	8.27	H-5	8.24	121.73	8.26	121.79	8.24	121.74
125.25	7.51	H-6	7.49	125.10	7.51, 7.53	-	7.50	125.20
126.49	7.53	H-7	7.51	126.38	7.49	-	7.52	126.45
127.41	7.87	H-8	7.85	127.36	7.87	127.43	7.86	127.40
153.75	-	C-9	-	154.17	-	153.77	-	153.94
134.00	-	C-10	-	134.00	-	134.02	-	134.01
69.97	4.18	H-α	4.06, 4.13	70.98	4.15, 4.17	70.02	4.12, 4.13	70.44
65.29	4.42	H-ß	4.01	68.49	4.34	65.35	4.19	66.68
46.9	3.11 3.24	H-γ	2.68, 2.78	50.06	3.11, 3.26	46.90	2.92, 3.05	48.31
49.83	3.38	H-δ	2.73	48.18	3.39	48.77	3.09	49.05
18.20, 18.63	1.29 1.30	δ-CH3	0.98, 0.99	22.95	1.26, 1.27	18.22 18.76	1.14, 1.15	20.22 20.56
-	6.0	O-H	5.10	-	4.80	-	4.20	-
-	8.8, 9.2	N-H	1.50	-	4.80	-	4.20	-
			(**oxa**)		-	164.94	-	165.82

	(**pro**)$^+$ (**fum**)$^-$ 1:1	(**pro**)$^+$ (**fum**)$^-$ 2:1	(**pro**)$^+$ (**fum**)$^-$ 2:1	(**pro**)$^+$ (**fum**)$^-$ 2:1	(**pro**)$^+$(**mal**)$^-$	(**pro**)$^+$(**mal**)$^-$
	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
C-1	-	124.91	-	124.95	-	124.86
H-2	7.48	120.17	7.47	119.99	7.50	120.31
H-3	7.41	126.18	7.41	126.20	7.43	126.16
H-4	6.96	105.24	6.96	105.19	6.98	105.26
H-5	8.26	121.79	8.24	121.76	8.26	121.73
H-6	7.51	125.25	7.50	125.19	7.52	125.28
H-7	7.53	126.49	7.52	126.44	7.54	126.54
H-8	7.86	127.42	7.86	127.39	7.88	127.46
C-9	-	153.83	-	153.98	-	153.69
C-10	-	134.02	-	134.00	-	134.03
H-α	4.14, 4.16	70.15	4.11, 4.13	70.52	4.16, 4.17	69.97
H-ß	4.34	65.39	4.18	66.76	4.30	65.35
H-γ	3.09, 3.23	47.23	2.90, 3.02	48.49	3.16, 3.27	46.72
H-δ	3.33	49.50	3.06	48.90	3.40	49.92
δ-CH3	1.24, 1.26	18.43, 18.99	1.13, 1.14	20.44 20.75	1.26, 1.27	18.16, 18.82
O-H	5.10	-	3.60	-	6.00	-
N-H	5.10	-	3.60	-	8.40	-
(**fum**)	6.52	135.13, 168.12				
				(**mal**)	6.026, 6.027, 6.028	136.12, 167.21

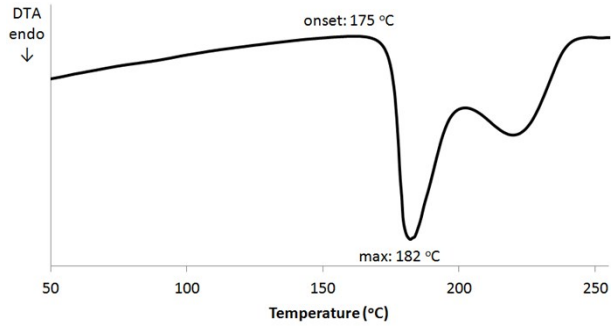
S7

Differential thermal analysis (DTA)

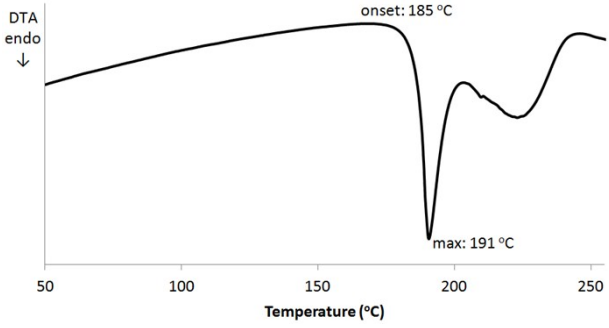
DTA was performed using Seiko Exstar6000 TG/DTA6300 (Seiko Instruments INC., Japan) equipment. The samples (4–10 mg) were heated in open aluminum pans at a rate of 10 °C/ min in nitrogen (flow of 20.0 mL/min).

DTA curves:

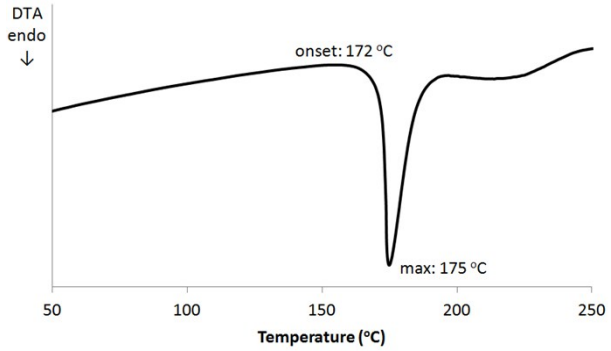
(**pro**)$^+$(**oxa**)$^-$ 1:1



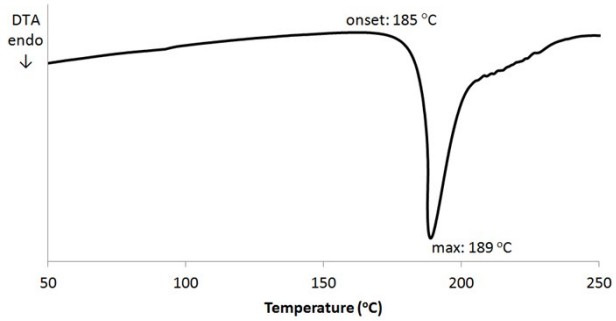
(**pro**)$^+$(**oxa**)$^-$ 2:1



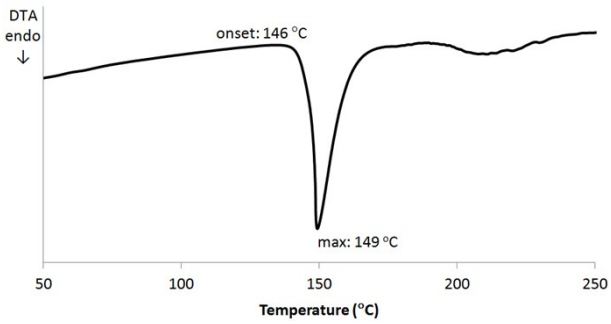
(**pro**)$^{+}$(**fum**)$^{-}$ 1:1



(**pro**)$^{+}$(**fum**)$^{-}$ 1:1



(**pro**)$^{+}$(**mal**)$^{-}$



S8

Elemental analysis (EA)

EA was performed on *Carlo ERBA Instruments EA1108* elemental analyzer.

Results of *EA:*

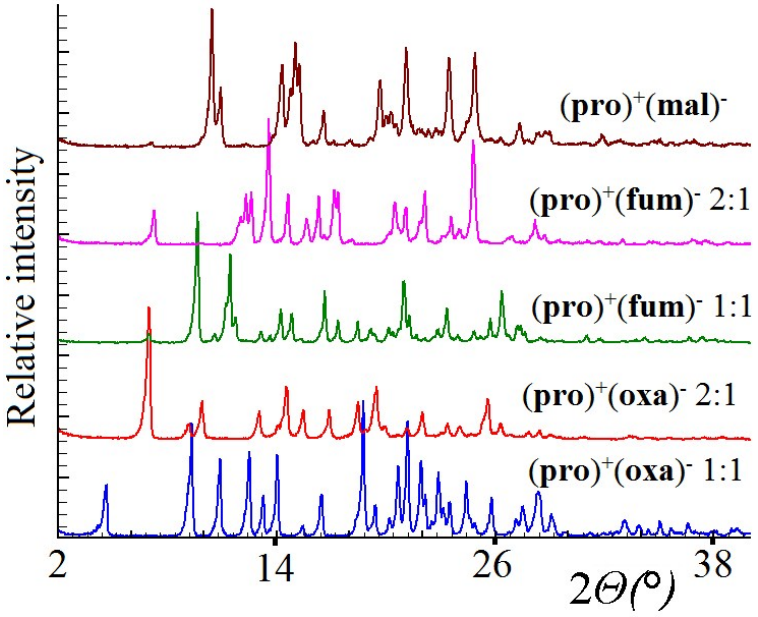
	Found, %			**Calculated, %**		
Element	C	H	N	C	H	N
(**pro**)$^{+}$(**oxa**)$^{-}$ 1:1	61.6823	6.5916	3.9342	61.8792	6.6354	4.0090
(**pro**)$^{+}$(**oxa**)$^{-}$ 2:1	66.9080	7.2682	4.5596	67.0855	7.2857	4.6020
(**pro**)$^{+}$(**fum**)$^{-}$ 1:1	63.9083	6.6853	3.6526	63.9862	6.7122	3.7310
(**pro**)$^{+}$(**fum**)$^{-}$2:1	68.1166	7.3006	4.3376	68.1180	7.3044	4.4132
(**pro**)$^{+}$(**mal**)$^{-}$	63.7951	6.6718	3.6856	63.9862	6.7122	3.7310

S9

*Solubility experiments and **UV/vis** spectrometry*

The concentration of salt aqueous solutions was determined by ***UV/vis*** using *Camspec M501* ***UV/vis*** Spectrophotometer. ***UV/vis*** absorbtion spectra in the 200-400 nm range were recorded for all samples. Separate linear calibration curve were plotted for each (**pro**) molecular salt. The absorption maxima with wavelength 237 nm have been used to calculate the concentrations for all samples.

The salt solubility was determined by dissolving of excess of cocrystal in 5 mL of deionized water at room temperature (23 ± 1 °C). Suspensions were mixed for 24 h. The concentration of the molecular salt in the solution was determined by ***UV/vis*** spectrometry, and composition of the solid phase was analyzed by ***PXRD***. ***UV/vis*** measurements were performed in triplicate.



Experimental *PXRD* patterns for precipitates obtained after solubility experiments

References

(1) Otwinowski, Z.; Minor, W. Processing of X-ray diffraction data collected in oscillation mode. *Methods in Enzymology*, 1997, *276*, 307–326.
(2) Burla, M. C.; Caliandro, R.; Camalli, M.; Carrozzini, B.; Cascarano, G. L.; De Caro, L.; Giacovazzo, C.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **2005**, *38*, 381–388.
(3) Sheldrick, G. M. *Acta Crystallogr. A.* **2008**, *64*, 112–122.
(4) Farrugia, L. J. *J. Appl. Crystallogr.* **2012**, *45*, 849–854.
(5) Brown, I. D.; McMahon, B. *Acta Crystallogr. Sect. B Struct. Sci.* **2002**, *58*, 317–324.