Supporting information

Exploring the polymorphic landscape of molecular complexes between naproxen drug and acridines

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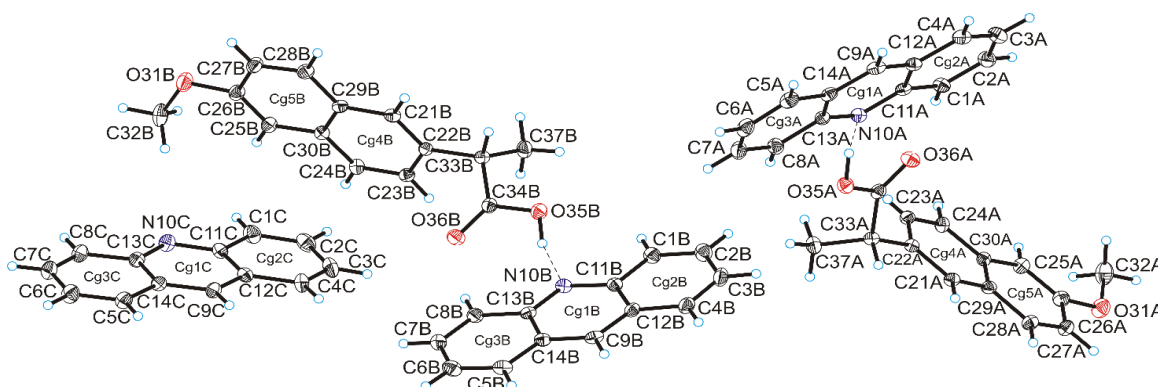
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Crystallographic data

Figure 1S. Molecular structure of molecular crystals 1α showing the atom-labelling scheme (Cg1, Cg2, Cg3, Cg4 and Cg5 denote the ring centroids; hydrogen bonds are represented by dashed lines).

Figure 2S. Molecular structure of molecular crystals 2α showing the atom-labelling scheme (Cg1, Cg2, Cg3, Cg4 and Cg5 denote the ring centroids; hydrogen bonds are represented by dashed lines).

Table 1S. Crystal data and structure refinement for molecular crystals 1α and 2α.

Compound	1α	2α
Chemical formula	$C_{67}H_{55}N_3O_6$	$C_{41}H_{40}N_2O_7$
Formula weight/g·mol^{-1}	998.14	672.75
Crystal system	monoclinic	monoclinic
Space group	$P2_1$	$P2_1$
a/Å	17.3435(14)	10.0768(11)
b/Å	5.9437(6)	6.2918(5)
c/Å	25.672(2)	27.347(3)
α/°	90	90
β/°	101.975(9)	98.004(11)
γ/°	90	90
V/Å^3	2588.8(4)	1717.0(3)
Z	2	2
T/K	295(2)	295(2)
λ_{Mo}/Å	0.71073	0.71073
ρ_{calc}/g·cm^{-3}	1.280	1.301
F(000)	1052	712
μ/mm^{-1}	0.082	0.089
θ range/°	3.25-25.00	3.32-25.00
Completeness θ/%	99.7	99.7
Reflections collected	18978	11483
Reflections unique	7896 [R_{int} = 0.0837]	5516 [R_{int} = 0.0978]
Data/restraints/parameters	7896/4/695	5516/7/473
Goodness of fit on F^2	0.955	0.939
Final R_1 value (I>2σ(I))	0.0585	0.0677
Final wR_2 value (I>2σ(I))	0.0927	0.0843
Final R_1 value (all data)	0.1578	0.1928
Final wR_2 value (all data)	0.1231	0.1174
CCDC number	2168756	2168757

Table 2S. Hydrogen-bond geometry for molecular crystals 1α, 1β and 2α.

Compound	D–H···A	d(D–H)[Å]	d(H···A)[Å]	d(D···A)[Å]	∠D–H···A [°]
1α	O35A–H35A···N10A	1.00(5)	1.80(6)	2.743(8)	157(5)
	O35B–H35B···N10B	0.98(6)	1.89(6)	2.810(7)	156(6)
	C8B–H8B···O36B	0.93	2.40	3.303(9)	164
	C33A–H33A···N10A^i	0.98	2.61	3.573(9)	166
	C37A–H37B···O36A^i	0.96	2.45	3.317(9)	150

Symmetry code : (i) x, -1+y, z.

Compound	D–H···A	d(D–H)[Å]	d(H···A)[Å]	d(D···A)[Å]	∠D–H···A [°]
1ß	OH···N	0.822	1.847	3.385	131
	C9AH9···O30	0.932	2.633	3.525	160

Compound	D–H···A	d(D–H)[Å]	d(H···A)[Å]	d(D···A)[Å]	∠D–H···A [°]
2α	N10–H10···O1W	0.97(5)	1.48(6)	2.427(9)	165(9)
	N15–H15B···O36A^i	0.89(9)	1.97(9)	2.857(9)	178(9)
	O1W–H1W···O36B^{ii}	0.91(3)	1.83(5)	2.717(9)	164(7)
	O1W–H2W···O35B	1.00(8)	1.75(8)	2.742(9)	169(5)
	O35A–H35A···O35B	0.90(9)	1.87(9)	2.511(9)	127(9)
	C23B–H23B···O36B	0.93	2.53	3.418(9)	160

Symmetry code: (i) -1+x, y, z; (ii) x, -1+y, z.

Table 3S. C–H···π interactions geometry for molecular crystals 1α, 1β and 2α.

Compound	D–H···A	d(H···A) [Å]	d(C···Cg) [Å]	∠D–H···A [°]
1α	C2A–H2A···Cg3C^{ii}	2.96	3.723(9)	140
	C2C–H2C···Cg4B	2.93	3.706(9)	141
	C5C–H5C···Cg1C^{iii}	2.90	3.529(8)	126
	C9B–H9B···Cg5A^{iv}	2.92	3.678(8)	140
	C28A–H28A···Cg1B^{v}	2.94	3.545(6)	124
	C32A–H32C···Cg4A^{v}	2.89	3.693(8)	142
	C33A–H33A···Cg1A^{i}	2.97	3.818(8)	145
	C33B–H33B···Cg3A^{vi}	2.94	3.810(6)	149
1β	C7AH···C4 (T-like)	2.683	3.515	149

Symmetry code: (i) x, -1+y, z; (ii) x, y, -1+z; (iii) 2-x, 1/2+y, 2-z; (iv) 2-x, 3/2+y, 1-z; (v) 2-x, -1/2+y, 1-z; (vi) 1-x, -1/2+y, 1-z.

2α	C2–H2···Cg4B[iii]	2.56	3.335(9)	141
	C6–H6···Cg4A	2.60	3.388(9)	142
	C28B–H28B···Cg5B[iv]	2.74	3.491(8)	138

Symmetry code: (iii) -1+x, -1+y, z ; (iv) 2-x, 1/2+y, -z.

Cg represents the centre of gravity of the rings as follows: Cg1A ring N(10A)-C(12A)/C(9A)/C(14A)/C(13A), Cg1B ring N(10B)-C(12B)/C(9B)/C(14B)/C(13B), Cg1C ring N(10C)-C(12C)/C(9C)/C(14C)/C(13C), Cg3A ring C(5A)-C(8A)/C(13A)/C(14A), Cg3C ring C(5C)-C(8C)/C(13C)/C(14C), Cg4A ring C(21A)-C(24A)/C(30A)/C(29A), Cg4B ring C(21B)-C(24B)/C(30B)/C(29B), Cg5A ring C(25A)-C(30A) for compound 1α, and Cg4A ring C(21A)-C(24A)/C(30A)/C(29A), Cg4B ring C(21B)-C(24B)/C(30B)/C(29B), Cg5B ring C(25B)-C(30B) for compound 2α.

Table 4S. π–π interactions geometry for molecular crystals 2α.

Compound	CgI [a]	CgJ [a]	CgI···CgJ [b] [Å]	Dihedral angle [c] [°]	Interplanar distance [d] [Å]	Offset [e] [Å]
2α	Cg1	Cg3[ii]	3.499(6)	1.8(5)	3.445(4)	0.713

Symmetry code: (ii) x, -1+y, z.

[a] Cg represents the centre of gravity of the rings as follows: Cg1 ring C(1)-C(4)/C(12)/C(11), Cg3 ring C(5)-C(8)/C(13)/C(14). [b] Cg···Cg is the distance between ring centroids. [c] The dihedral angle is that between the mean planes of CgI and CgJ. [d] The interplanar distance is the perpendicular distance from CgI to ring J. [e] The offset is the perpendicular distance from ring I to ring J.

Thermogravimetric data
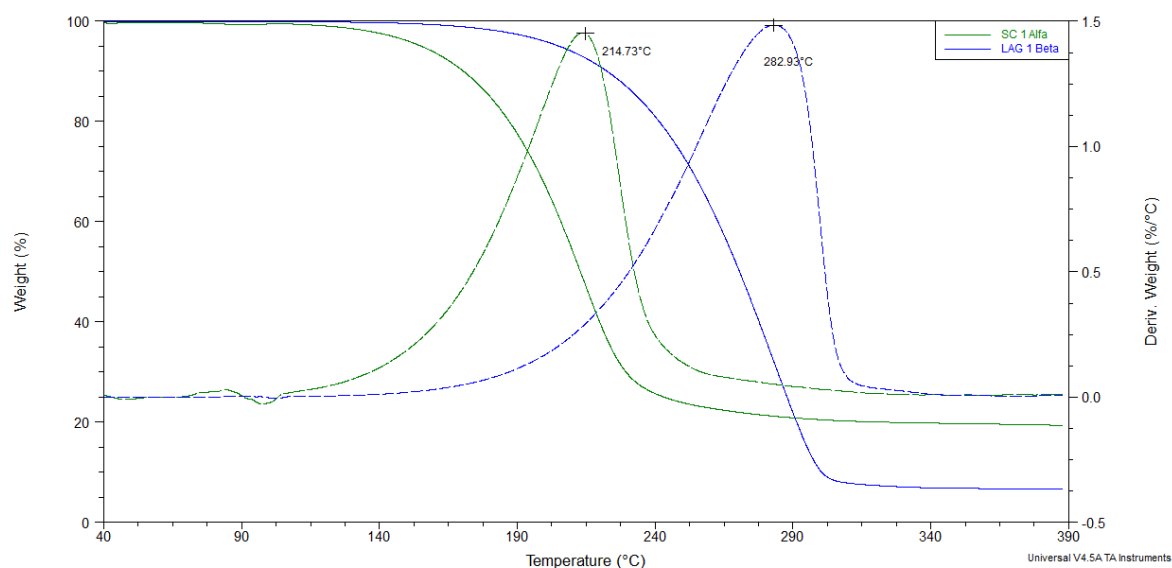
Figure 3S. TGA data of 1α and 1β phases.
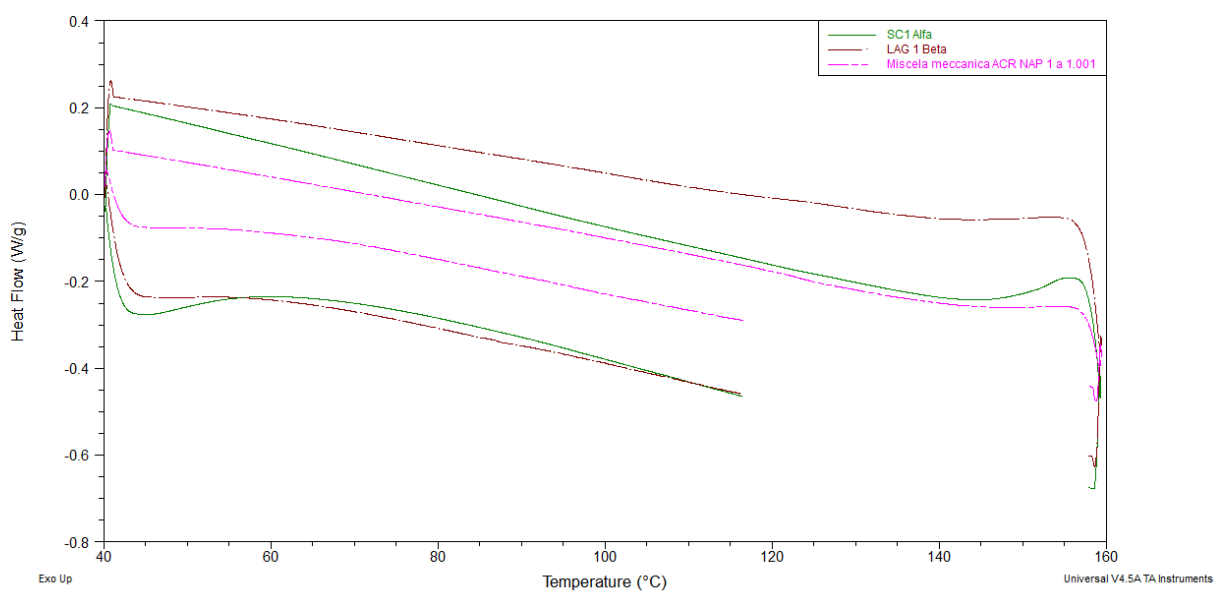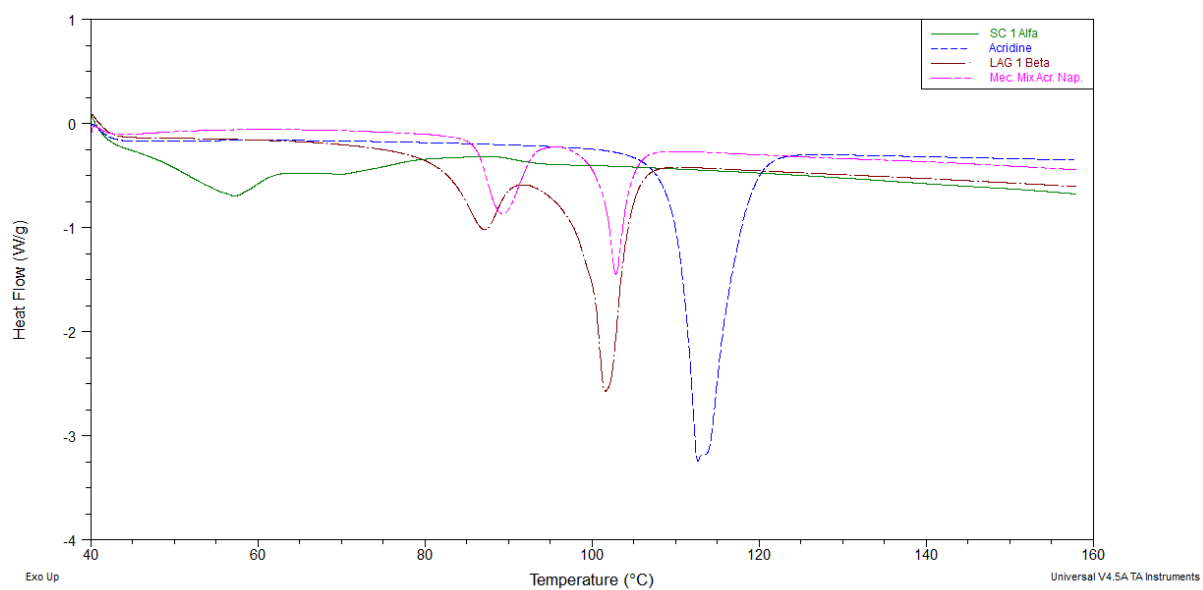
Figure 4S. DSC data of the stoichiometric 1:1 mechanical mixture of naproxen with acridine compared to 1α and 1β melting (top) and cooling and second heating (bottom) and with 9-aminoacridine (bottom); Acridine alone heating profile is also reported to highlight that all the signals are below its melting point (naproxen melt at 165°C).
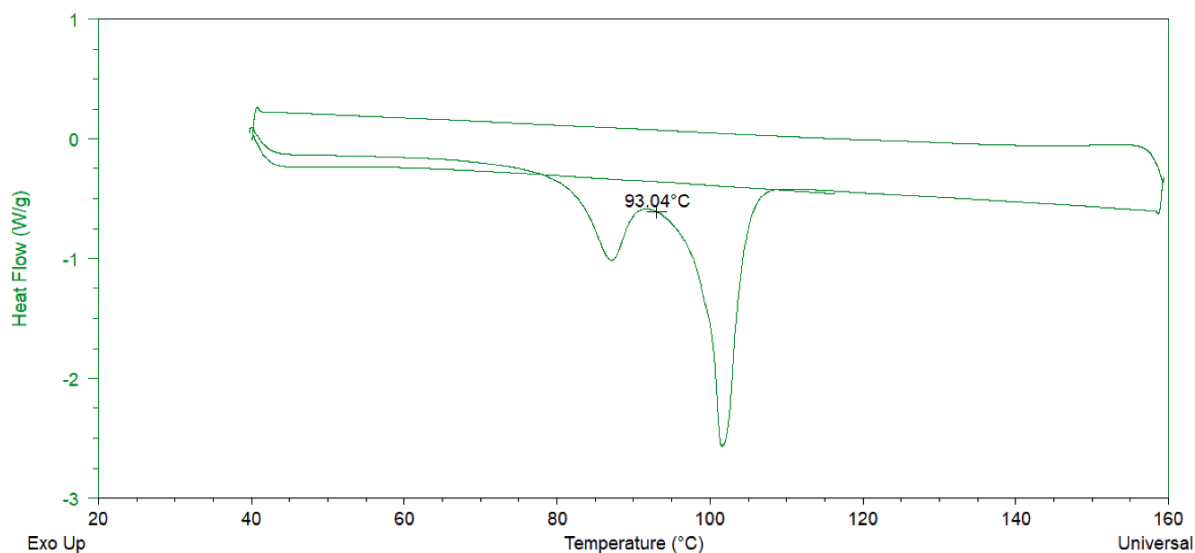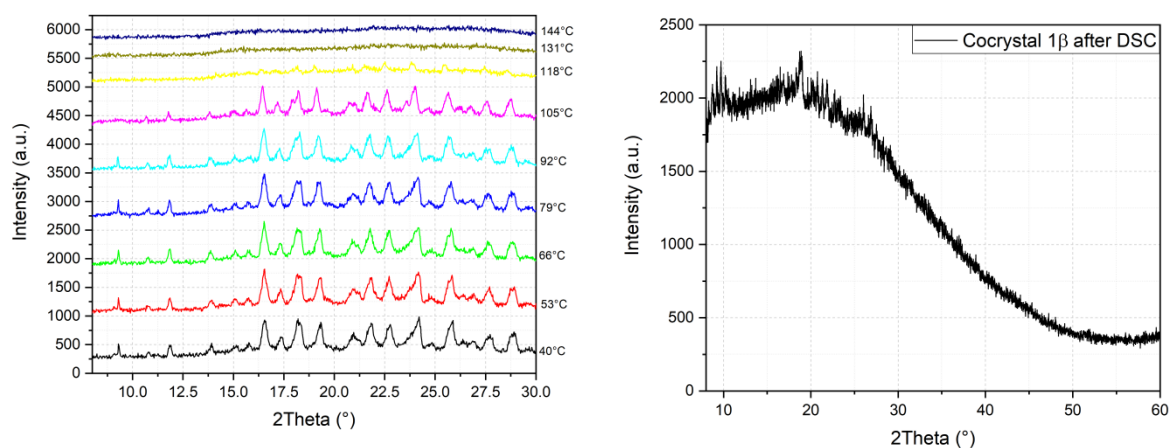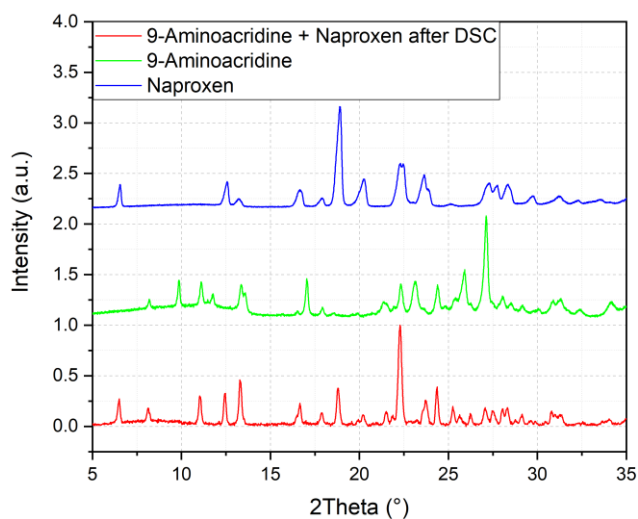
Figure 5S. DSC data of 1β molecular complex.
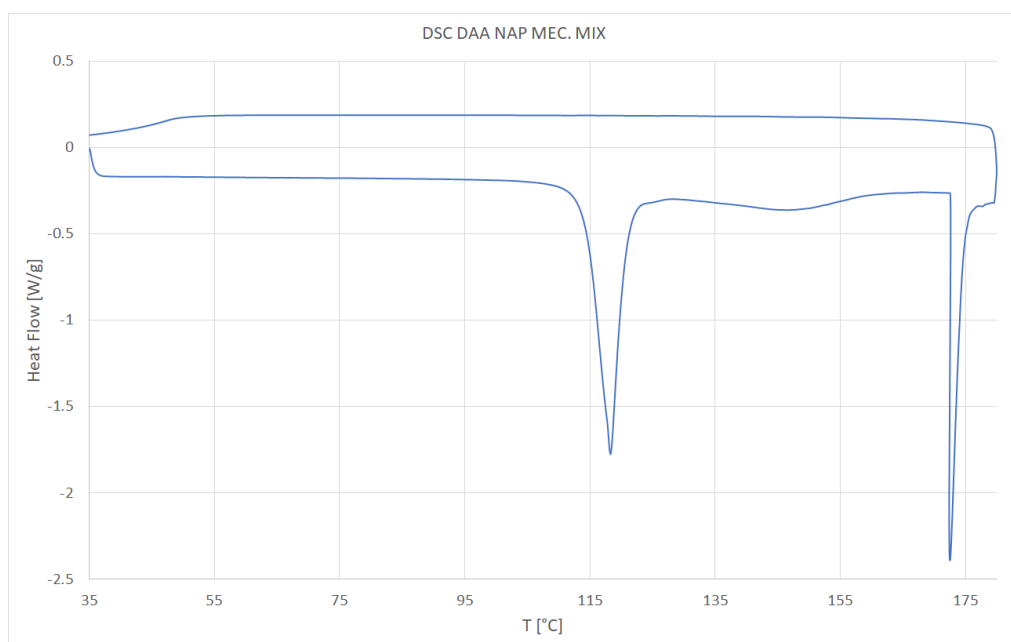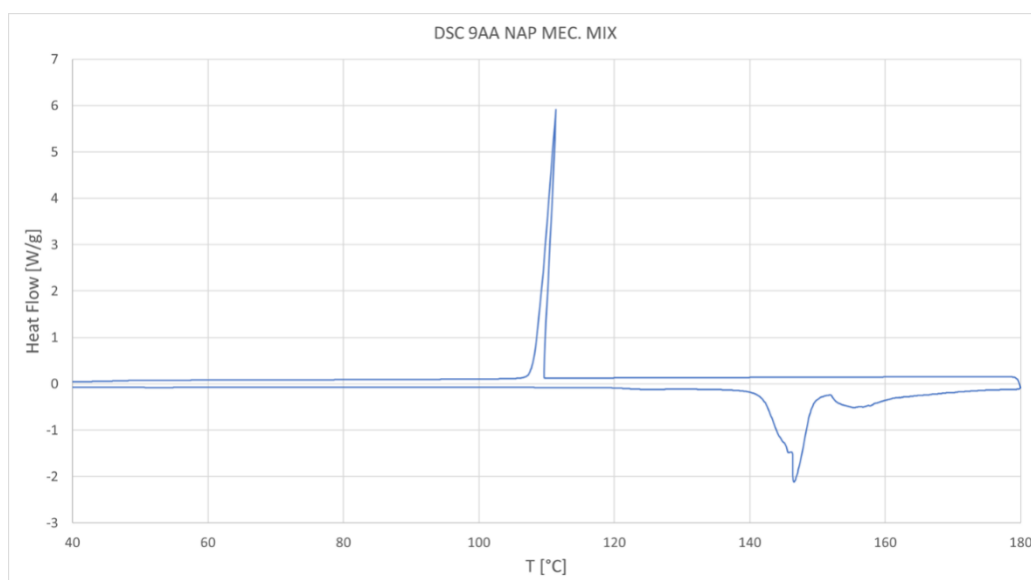
Figure 6S. DSC data of the stoichiometric 1:1 mechanical mixture of naproxen with 9-aminoacridine (top) and with 6,9-diamino-2-ethoxyacridine (bottom).

Figure 7S. In situ XRPD data from RT to 160°C of phase 1β (left) and XRPD pattern measured on 1β sample after cooling, showing its amorphous behaviour (right).
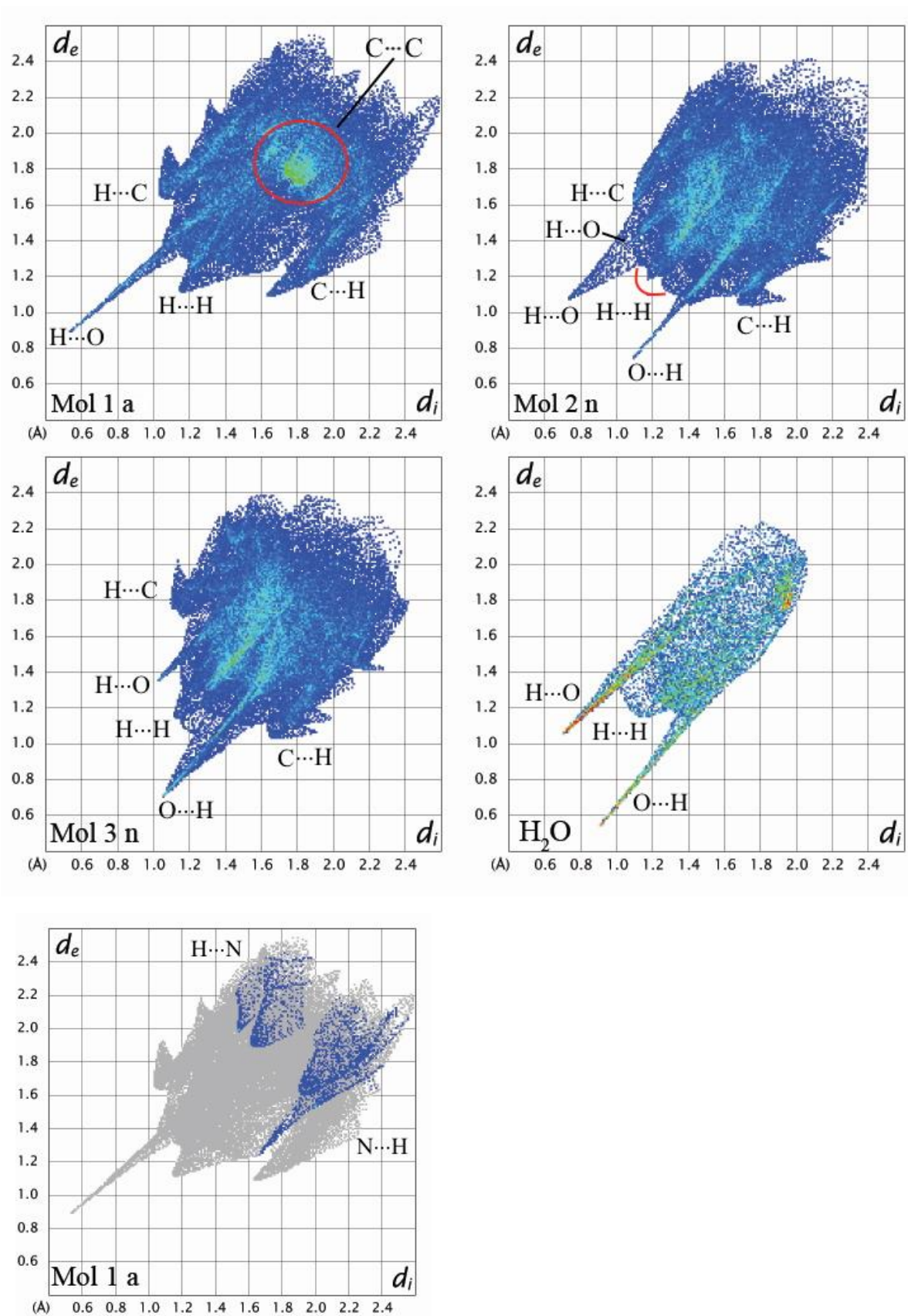

Figure 8S. XRPD pattern of mechanical mixture of 9-aminoacridine (green) and naproxen (blue) after DSC. The resulting curve is compared to the XRPD patterns of the pure reactants (red).
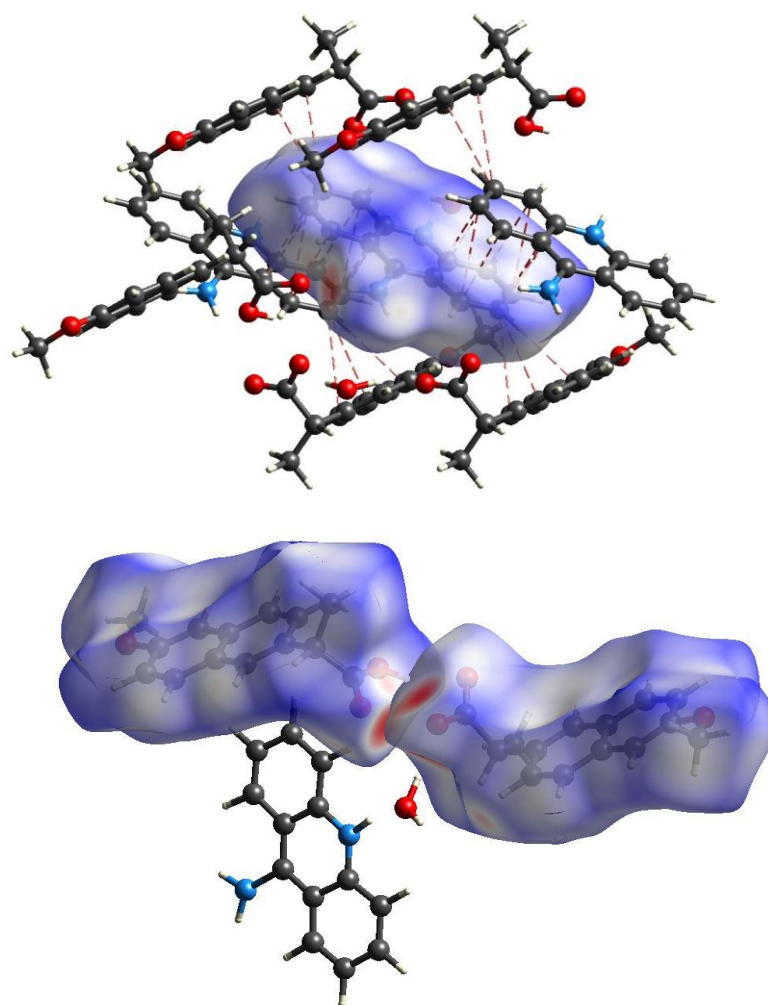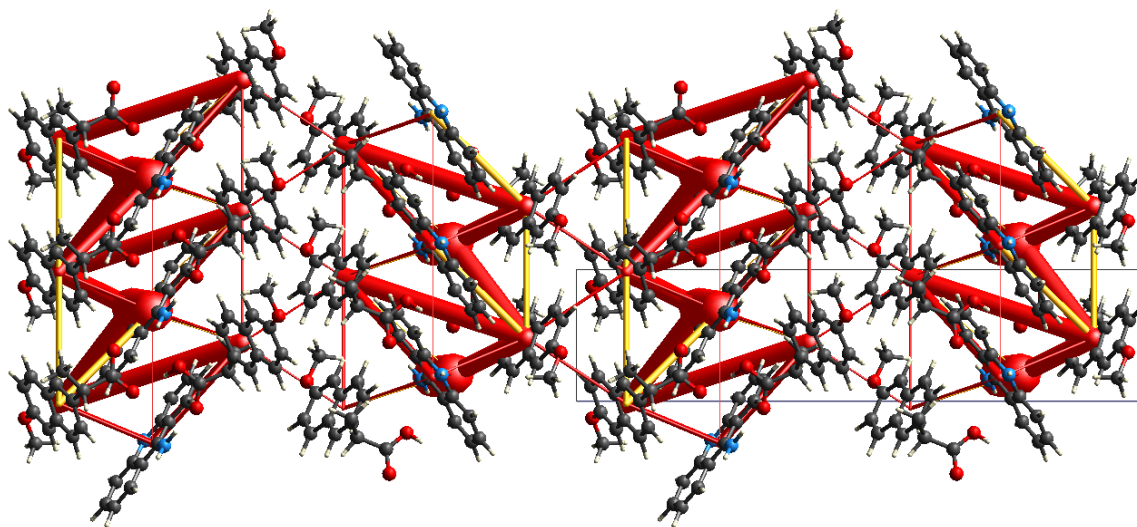
Figure 9S. Views of Hirshfeld surfaces for 2α with d-norm plotted evidencing the relevant interactions. Some molecules were omitted for clarity.
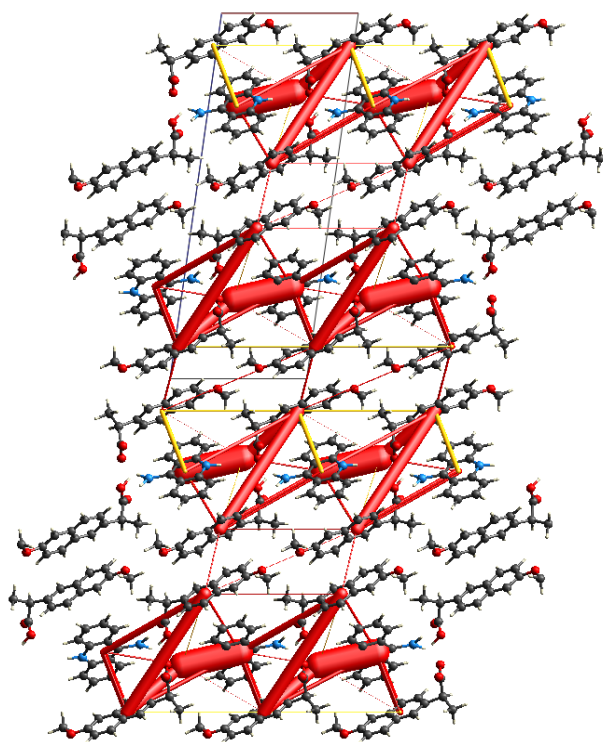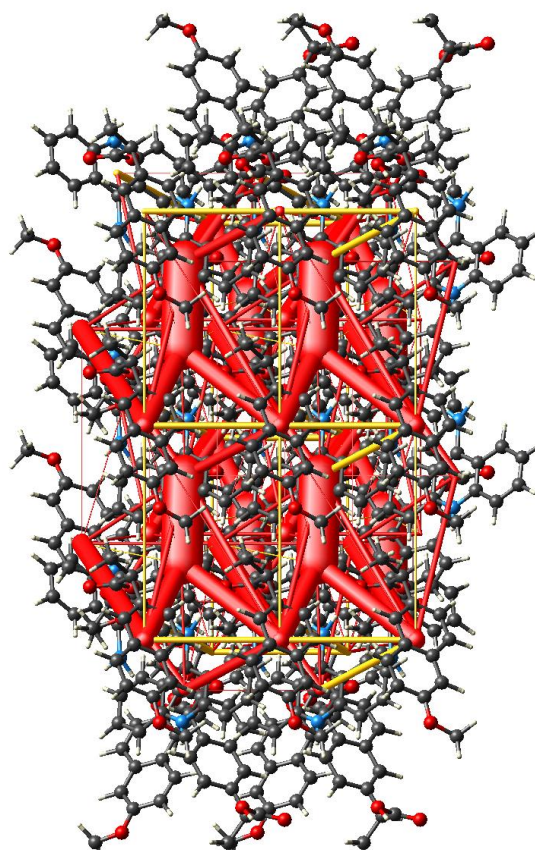
Figure 10S. Fingerprint plots for 9-aminoacridine (Mol_1_a), naproxen (Mol_2_n), deprotonated naproxen (Mol_3_n) and water in 2α. At the bottom, again the fingerprint plot of Mol_1_a filtered by element to show N···H interactions.
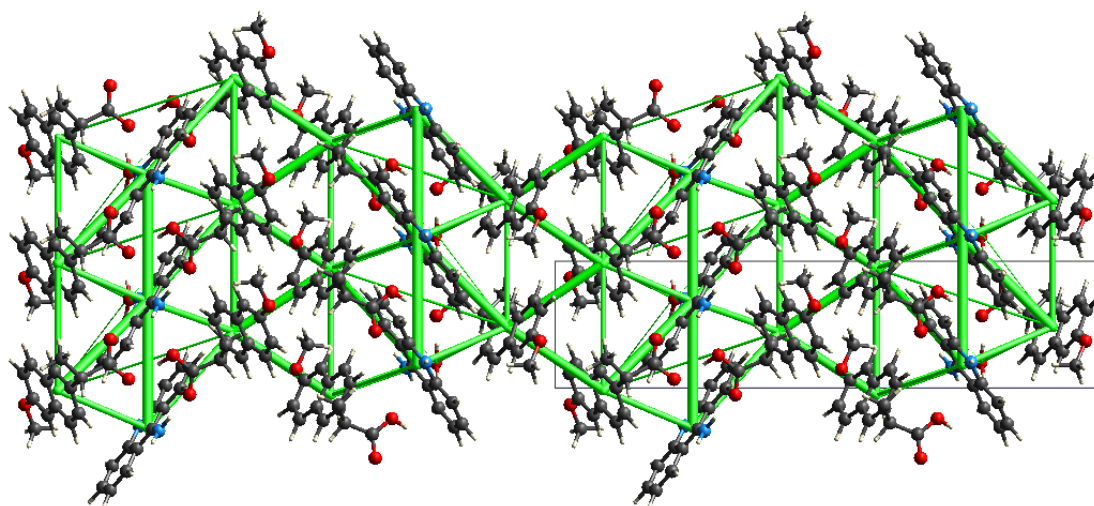
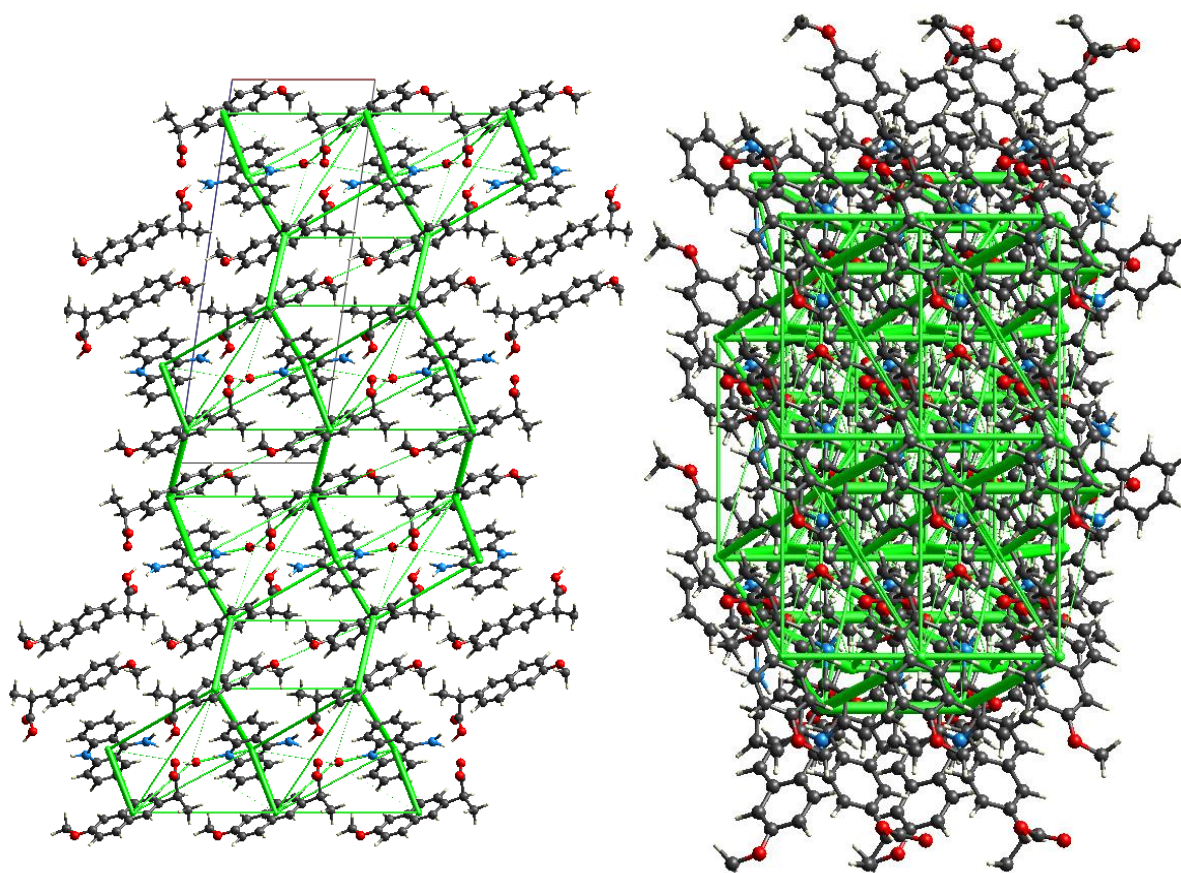Coulomb energy; view along a

Coulomb energy; view along b

Coulomb energy; view along c

Figure 11S. Energy frameworks for 2α viewed along a, b and c. Attractive coulomb forces in red, repulsive coulomb forces in yellow. The unit cell is drawn in black. Tube size was set to 80 and cutoff energy to 0.00 kJ/mol.

Dispersion energy; view along a

Dispersion energy; view along b

Dispersion energy; view along c

Figure 12S. Energy frameworks for 2α viewed along a, b and c. Dispersive forces are drawn in green. The unit cell is drawn in black. Tube size was set to 80 and cutoff energy to 0.00 kJ/mol.