Electronic Supplementary Information (ESI)

Why does niclosamide drug form solvates or hydrates?

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Table of Contents

Table S1. Crystal data of niclosamide solvate forms

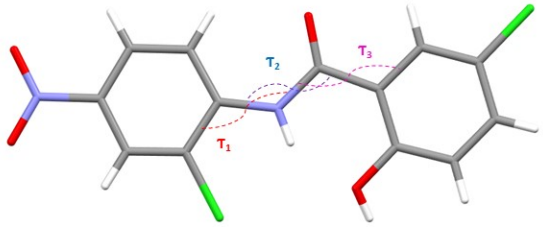
Compound code	NIC-DMF (1:1)	NIC-DMSO (1:1)	NIC-NN DMA (1:1)	NIC-N,N DMA (2:2)	NIC-DOX (1:0.5)	NIC-DOX (2:1.5)
Chemical formula	C13 H8 Cl2 N2 O4, C3 H7 N O	C13 H8 Cl2 N2 O4, C2 H6 O S	C13 H8 Cl2 N2 O4, C4 H9 N O	C13 H8 Cl2 N2 O4, C4 H9 N O	C13 H8 Cl2 N2 O4, 0.5(C4 H8 O2)	2(C13 H8 Cl2 N2 O4), 1.5(C4 H8 O2)
Formula Mass	400.21	405.24	414.23	414.23	371.17	786.38
Crystal system	Monoclinic	Monoclinic	Monoclinic	Triclinic	Triclinic	Triclinic
a/Å	3.9865(6)	16.821(16)	10.3963(4)	7.4340(8)	7.5264(10)	11.4503(5)
b/Å	37.612(5)	11.538(10)	20.4099(7)	14.1832(16)	9.7054(12)	12.5985(5)
c/Å	11.9718(15)	9.082(8)	9.9364(4)	18.431(2)	11.9792(14)	14.5875(7)
α/°	90	90	90	100.902(3)	69.028(4)	66.0849(14)
β/°	95.365(10)	95.92(2)	117.1041(18)	100.288(4)	85.313(4)	87.5929(15)
γ/°	90	90	90	91.378(4)	77.701(4)	64.4525(12)
Unit cell volume/Å^3	1787.2(4)	1753(3)	1876.84(13)	1874.2(4)	798.31(17)	1712.94(13)
Temperature /K	293(2)	293(2)	293(2)	293(2)	293(2)	293(2)
Space group	*P* 21/*n*	*P* 21/*c*	*P* 21/*c*	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
Formula units per unit cell, *Z*	4	4	4	4	2	2
Radiation type	MoKα	MoKα	MoKα	MoKα	MoKα	MoKα
Crystal size /mm^3	0.40×0.18×0.12	0.32×0.15×0.11	0.40×0.18×0.12	0.39×0.11×0.15	0.42×0.11×0.12	0.33×0.19×0.11
Absorption coefficient, *μ*/mm^{-1}	0.396	0.518	0.380	0.381	0.435	0.413
No. of reflections measured	12098	19293	23012	50878	14740	31623
No. of independent reflections	3156	4002	4308	8604	3664	7828
No. of independent reflections ($I>2\sigma(I)$)	1870	2255	3010	3526	1987	4583
R_{int}	0.0691	0.0472	0.0555	0.0970	0.0440	0.0476
Final *R1* values ($I > 2\sigma(I)$)	0.0685	0.0413	0.0470	0.0519	0.0438	0.0527
Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.1421	0.0916	0.1119	0.1146	0.0985	0.1295
Final *R1* values (all data)	0.1259	0.0972	0.0741	0.1641	0.1041	0.1031
Final $wR(F^2)$ values (all data)	0.1648	0.1112	0.1317	0.1614	0.1258	0.1671
Goodness of fit on F^2	1.041	1.025	1.052	1.005	1.014	1.038
Difference density max and min, e/Å^3	0.299 and -0.202	0.215 and -0.242	0.305 and -0.226	0.246 and -0.217	0.187 and -0.240	0.325 and -0.205
CCDC number	**2352670**	**2352671**	**2352672**	**2352673**	**2352674**	**2352675**

Table S2. Significant hydrogen bond interactions in niclosamide solvate forms.

D–H···A	D–H /Å	H···A /Å	D···A /Å	<D–H···A /°	Symmetry code
NIC-DMF (1:1)					
O2-H2O···O5	0.81(5)	1.76(5)	2.569(5)	174(6)	
C4-H4···O5	0.93	2.59	3.241(6)	127	
C10-H10···O3	0.93	2.59	3.430(50	150	1-x,1-y,2-z
C16-H16C···O1	0.96	2.59	3.548(6)	174	x,y,-1+z
NIC-DMSO (1:1)					
O2-H2O···S1	0.92(2)	2.80(2)	3.691(4)	163(2)	
O2-H2O···O5	0.92(2)	1.64(2)	2.546(5)	168(3)	
O2-H2O···O5D	0.92(2)	1.79(5)	2.70(4)	173(3)	
C15-H15B···O5	0.96	2.62	3.448(6)	145	x, 3/2-y, ½+z
NIC-N,N DMA(1:1)					
O2-H2O···O5	0.81(3)	1.76(3)	2.571(2)	178(3)	
C4-H4···O5	0.93	2.54	3.205(3)	129	
C16-H16···O3	0.96	2.51	3.325(3)	143	1+x,3/2-y,3/2+z
NIC-N,N DMA (2:2)					
O2A-H2AO···O5A	0.83(3)	1.75(3)	2.577(3)	179(4)	
O2B-H2BO···O5B	0.83(3)	1.72(3)	2.545(6)	175(2)	
O2B-H2BO···O5D	0.83(3)	1.93(4)	2.75(3)	167(3)	
C4A-H4A···O5A	0.93	2.52	3.187(4)	129	
C4B-H4B···O5B	0.93	2.53	3.174(7)	127	
C4B-H4B···O5D	0.93	2.43	3.12(2)	131	
C10A-H10A···O1A	0.93	2.56	3.361(4)	144	2-x,-y,1-z
C15A-H15A···O4A	0.96	2.36	3.181(4)	143	2-x,1-y,1-z
C15A-H15B···Cl2A	0.96	2.74	3.531(3)	141	
C15B-H15D···Cl2B	0.96	2.78	3.504(8)	133	
C15B-H15F···O4B	0.96	2.57	3.315(9)	134	1-x,2-y,1-z
C16B-H16F···O5D	0.96	2.00	2.48(3)	108	
C17A-H17C···O3B	0.96	2.57	3.363(5)	140	
NIC-DOX (1:0.5)					
O2-H2O···O5	0.84(3)	1.77(3)	2.589(3)	166(2)	
C15-H15A···O4	0.97	2.51	3.167(6)	125	1-x,1-y,-z
NIC-DOX (2:1.5)					
O2A-H2AO···O5A	0.79(3)	1.90(3)	2.675(6)	172(3)	
O2A-H2AO···O5D	0.79(3)	1.86(4)	2.63(3)	166(4)	
O2B-H2BO···O6A	0.80(4)	1.88(4)	2.668(5)	169(4)	
O2B-H2BO···O6D	0.80(4)	1.76(4)	2.49(2)	150(4)	
C7A-H7A···Cl1B	0.93	2.80	3.720(3)	171	-1+x,y,-1+z
C17A-H17A···O4B	0.97	2.58	3.243(6)	125	-x,1-y,1-z

C9B-H9B···O5B	0.93	2.62	3.312(4)	132	x,y,-1+z

Table S3. Torsion angles in the planar conformation of NIC.



S. No.	Crystal forms	τ_1 /°	τ_2 /°	τ_3 /°
1.	NIC-I	-175.0(2	176.3(1)	177.5(1)
2.	NIC-II	177.7(2)	-176.4(2)	177.8(2)
		177.5(2)	-179.8(2)	179.8(2)
		-179.9(2)	176.9(2)	-177.0(2)
		179.7(2)	178.3(2)	177.8(2)
3.	NIC-H_A	177.9(4)	-177.3(4)	-174.0(4)
4.	NIC-H_B	173.9(2)	177.6(2)	178.6(2)
5.	NIC-THF (1:1)	178.8(7)	177.7(7)	-177.7(7)
6.	NIC-MeCN (1:1)	177.2(4)	-179.4(4)	-171.3(4)
7.	NIC-ACETONE(2:2)	172.2(6)	-178.5(6)	178.9(6)
		174.6(6)	-179.3(6)	177.4(6)
8.	NIC-MeOH(1:1)	-179.9(6)	177.4(5)	178.7(5)
9.	NIC-TEG (2:1)	174.2(3)	-178.3(3)	-176.4(3)
		179.5(3)	178.8(3)	179.7(3)
10.	NIC-DMF (1:1)	177.9(4)	-179.9(4)	-174.0(4)
11.	NIC-DMSO (2:2)	-178.3 (2)	179.2(2)	178.8(2)
12.	NIC-N,N DMA (1:1)	179.1(2)	-177.8(2)	177.5(2)
13.	NIC-N, N DMA (2:2)	175.6(3)	-177.0(3)	176.2(2)
		178.5(3)	-179.8(2)	177.7(2)
14.	NIC-DOX (1:0.5)	-176.8(2)	174.4(2)	176.8(2)
15.	NIC-DOX (2:1.5)	179.9(2)	-179.5(2)	176.2(2)
		177.6(2)	-179.3(2)	-180.0(2)

Table S4. Desolvation and melting onset temperatures from DSC analysis.

Forms	Desolvation onset T (°C)	Melting onset T (°C)
NIC-H_A	83	229
NIC-DMF	129	229
NIC-DMSO	168	229
NIC-NNDMA (1:1)	148	229
NIC-NNDMA (2:2)	146	229
NIC-DOX (1:0.5)	83 and 127	229

Table S5. Comparison of the theoretical and experimental weight loss of solvates in TGA.

Forms	Theoretical weight loss (%)	Experimental weight loss (%)	Desolvation temperature range (°C)
NIC-Monohydrate H_A	5.14	5.1	73-102
NIC-NN DMA (1:1)	21.0	20.76	86-160
NIC-NNDMA (2:2)	21.0	20.37	76-144
NIC-DOX (1:0.5)	11.86	10.54	76-148

Table S6. Desolvation and melting ranges as captured by HSM experiments recorded with 10 °C/min heating rate.

Forms	Desolvation range / °C	Melting range /°C
NIC monohydrate - H_A	113-160	201-214
NIC-DMF (1:1)	106-130	225-234
NIC-DMSO (1:1)	120-170	208-224
NIC-NNDMA (1:1)	102-153	227-239
NIC-NNDMA (2:2)	106-146	198-227
NIC-DOX (1:0.5)	80-116	223-239
NIC-DOX (2:1.5)	46-121	206-238

Table S7. Comparison of crystal packing coefficients and crystal densities of niclosamide crystal forms.

Forms	**Packing Coefficient (%)**	**Density (g cm^{-3})**
Anhydrous structures		
NIC-Anhydrous polymorph I	73.9	1.700
NIC-Anhydrous polymorph II	71.1	1.646
Hydrates and solvates		
NIC-Monohydrate H_A	72.3	1.616
NIC-Monohydrate H_B	73.4	1.640
NIC-THF (1:1)	71.0	1.498
NIC-ACETONE (1:1)	72.1	1.554
NIC-MeCN (1:1)	74.3	1.621
NIC-MeOH (1:1)	73.9	1.651
NIC-TEG (2:1)	70.7	1.506
NIC-DMF	68.5	1.487
NIC-DMSO	68.9	1.536
NIC-NNDMA (1:1)	68.5	1.466
NIC-NNDMA (2:2)	68.5	1.468
NIC-DOX (1:0.5)	68.8	1.544
NIC-DOX (2:1.5)	68.8	1.524

Table S8. O-H···O/N interaction energies and it corresponding energy decomposition.

Forms	Dimer	D···A (Å)	D - H···A (°)	E_{ele} kJ.mol^{-1}	E_{pol} kJ.mol^{-1}	E_{dis} kJ.mol^{-1}	E_{rep} kJ.mol^{-1}	E_{total} kJ.mol^{-1}
NIC-I	O4-H2···O3	2.693(2)	173(2)	-52.6	-13.8	-24.7	69.9	-44.2
NIC-II	O4A-H4A···O3C	2.609(2)	168(3)	-60.3	-16.2	-20.4	76.5	-46.3
	O4B-H4B···O3D	2.646(2)	161(2)	-52.5	-13.9	-17	58	-44.9
	O4C-H4C···O3A	2.683(2)	178(3)	-57.5	-16.1	-19.6	67.2	-48.2
	O4D-H4D···O3B	2.659(2)	177(2)	-60.6	-17.1	-20.8	73.4	-49.5
NIC-H_A	O4-H4···O1W	2.658(9)	167	-67.9	-17.4	-6.3	59.2	-53.5
NIC-H_B	O4-H10···O5	2.606(3)	164	-70.2	-17.6	-7.0	71.2	-49.4
NIC-THF	O4-H18···O5	2.595(7)	162	-68.4	-21.4	-19.8	84.1	-53.4
NIC-MeCN	O4-H4···N3	2.782(6)	163	-57.7	-13.1	-6.6	52.5	-44.0
NIC-ACETONE (2:2)	O4-H1···O5	2.652(7)	149(6)	-63.1	-16.2	-17.3	74	-48.1
	O9-H15···O10	2.687(6)	169(5)	-65.7	-17	-15	71	-51.3
NIC-MEOH	O14-H41···O22	2.521(8)	168(6)	-87.5	-24.5	-12.5	113.1	-51.7
NIC-TEG (2:1)	O8-H38···O10	2.655(4)	160	-54.6	-17.9	-22.8	68.7	-48.3
	O4-H41···O13	2.586(5)	158	-84.8	-25.1	-18.6	83	-73.2
NIC-DMF (1:1)	O2-H2O···O5	2.569(5)	174(6)	-89.6	-23.8	-10.4	98.1	-60.8
NIC-DMSO (1:1)	O2-H2O···O5	2.546(5)	168(3)	-93.7	-25.1	-11.0	100.5	-65.1
NIC-N N DMA (1:1)	O2-H2O···O5	2.571(2)	178(3)	-98.2	-27.4	-16.4	107.5	-72.0
NIC-N N DMA (2:2)	O2A-H2AO···O5A	2.577(3)	179(4)	-103.6	-29.4	-18.6	117.1	-75.2
	O2B-H2BO···O5B	2.545(6)	175(2)	-106.1	-30.7	-19.7	130	-71.7
NIC-DOX (1:0.5)	O2-H2O···O5	2.589(3)	166(2)	-68.3	-19.7	-18.6	88.9	-48.0
NIC-DOX (2:1.5)	O2A-H2AO···O5A	2.675(6)	172(3)	-58.5	-17.1	-16.1	64.7	-48.5
	O2B-H2BO···O6A	2.668(5)	169(4)	-55.8	-16.9	-17.9	65.4	-46.8

$$E_{tot} = k_{ele}.E_{ele} + k_{pol}.E_{pol} + k_{dis}.E_{dis} + k_{rep}.E_{rep}$$

Energy Model	k_ele	k_pol	k_disp	k_rep
CE-B3LYP ... B3LYP/6-31G(d,p) electron densities	1.057	0.740	0.871	0.618

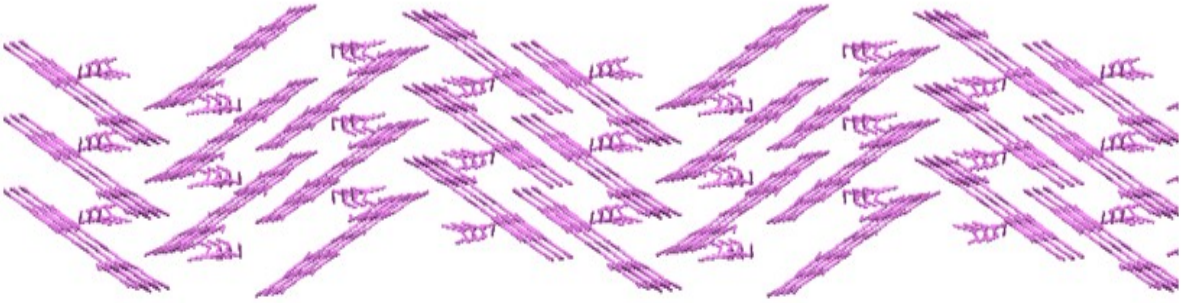
Table S9. Intermolecular energies of six NIC solvates and their energy decomposition.

Dimer	E_{ele} (kJ.mol^{-1})	E_{pol} (kJ.mol^{-1})	E_{dis} (kJ.mol^{-1})	E_{rep} (kJ.mol^{-1})	E_{tot} (kJ.mol^{-1})
NIC-DMF(1:1)					
O2-H2O···O5	-89.6	-23.8	-10.4	98.1	-60.8
C10-H10···O3	-8.1	-2	-6.1	6.1	-13.2
C16-H16A···O1	-4.1	-1.3	-10.4	8	-9.5
C12-H12···Cl2	-16.4	-1.2	-13.8	15.2	-20.8
NIC-NIC, π···π	2	-2.8	-84.2	42.2	-47.2
NIC-DMSO(1:1)					
O2-H2O···O5	-93.7	-25.1	-11.0	100.5	-65.1
C15-H15B···O5	-16	-5.3	-10.2	10.2	-23.5
C4-H4···Cl1	-11.5	-0.6	-6.1	0	-17.9
C15-H15A··· Cl1	-8.8	-1.4	-9	6.5	-14.2
NIC-NIC, π···π	-11.4	-2.9	-78.7	38.7	-58.8
NIC-NNDMA (1:1)					
O2-H2O···O5	-98.2	-27.4	-16.4	107.5	-72.0
C4-H4···O3 and C5-H5···O4	-11.9	-2.9	-7.6	0	-21.5
C17-H17A···O4	-4.7	-1.5	-10.3	9	-9.5
NIC-NIC, π···π	0	-3	-57.9	29.4	-34.4
Carbonyl (dipole-dipole)	-12.9	-3.2	-33.7	21.4	-32.2
NIC-NNDMA (2:2)					
O2A-H2AO···O5A	-103.6	-29.4	-18.6	117.1	-75.2
O2B-H2BO···O5B	-106.1	-30.7	-19.7	130	-71.7
C10A-H10A···O1A	-11.8	-3.4	-21.5	16.6	-23.5
C15B-H15F···O4B	-8.1	-1.9	-6.1	8.1	-10.3
C17A-H17C···O3B	-8.1	-1.7	-10.6	11.9	-11.8
NIC-NIC, π···π	1.9	-3.3	-59.2	27.1	-35.3
	0.8	-3.5	-64	29.1	-39.5
	-9.1	-1.9	-22	10.9	-23.4
	-9.3	-2.7	-27.4	13.3	-27.5
Carbonyl (dipole-dipole)	-11.2	-2.9	-30.8	15.5	-31.2
NIC-DOX (1:0.5)					
O2-H2O···O5	-68.3	-19.7	-18.6	88.9	-48.0
C15-H15A···O4	-8.6	-2.3	-8.8	13.5	-10.1
C4-H4···O3	-13.7	-1.7	-5	0	-20.2
C14-H14B···O1	-3.3	-0.9	-15.4	9.1	-11.9
C12-H8···Cl2	-9.8	-0.7	-8	3.2	-15.8
NIC-NIC, π···π	-3.8	-1.5	-34.8	15.5	-25.9
	-5.1	-4.1	-42.3	18.8	-33.6
	-12.4	-3.4	-72.9	37.3	-56.1

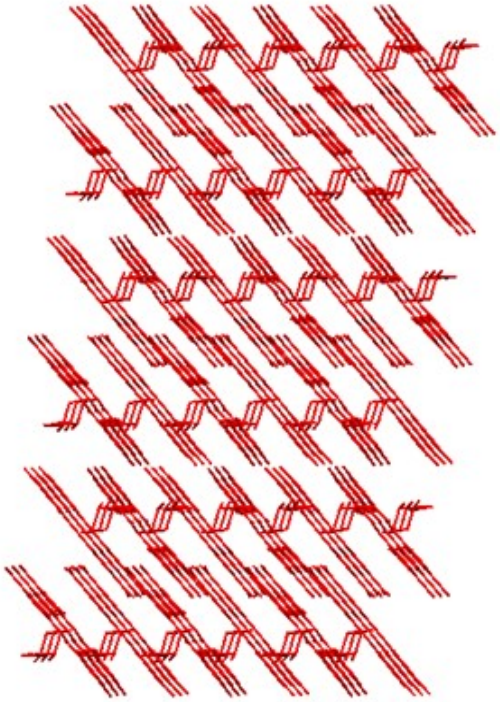
NIC-DOX (2:1.5)					
Dimer	E_{ele} (kJ.mol^{-1})	E_{pol} (kJ.mol^{-1})	E_{dis} (kJ.mol^{-1})	E_{rep} (kJ.mol^{-1})	E_{tot} (kJ.mol^{-1})
O2A-H2AO···O5A	-58.5	-17.1	-16.1	64.7	-48.5
O2B-H2BO···O6A	-55.8	-16.9	-17.9	65.4	-46.8
C9B-H9B···O5B	-10.3	-2.2	-15.2	11.7	-18.5
C4B-H4B···O3A	-9.9	-1.8	-5.6	0	-16.6
C14A-H14A···O5B	-3.6	-1.3	-15.8	11.5	-11.4
C7B-H7B···Cl1A and C7A-H7A···Cl1B	-7.5	-0.3	-12	16.8	-8.3
NIC-NIC, π···π	-13.6	-3.8	-86.2	45.9	-63.9
	-13	-2.1	-87.8	50.6	-60.5
	-10.7	-2.7	-85	45.1	-59.5

Table S10. Energy contribution of the drug and solvent in the NIC anhydrous and solvate crystal structures.

S.No	Compound Name	Energy contribution of Niclosamide (kJ/mol)	Energy contribution of Solvent (kJ/mol)
1	NIC anhydrous polymorph I	-180.5	-
2	NIC anhydrous polymorph II	-161.03	-
3	NIC monohydrate (H_A)	-196.4	-47.05
4	NIC monohydrate (H_B)	-168.5	-45.3
5	NIC acetonitrile (1:1)	-169	-59.25
6	NIC: THF (1:1)	-164.4	-61.3
7	NIC: MeOH (1:1)	-186.45	-49.5
8	NIC Acetone (2:2)	-154.75	-63.975
9	NIC: TEG (2:1)	-162.55	-73.4
10	NIC: DMF (1:1)	-168.05	-73.55
11	NIC: DMSO (1:1)	-169.4	-85.6
12	NIC:DOX (1:0.5)	-152.5	-44.25
13	NIC: DOX (2:1.5)	-153.47	-57.125
14	NIC:NNMDA (1:1)	-167.45	-82.6
15	NIC: NNMDA (2:2)	-162.6	-85.125



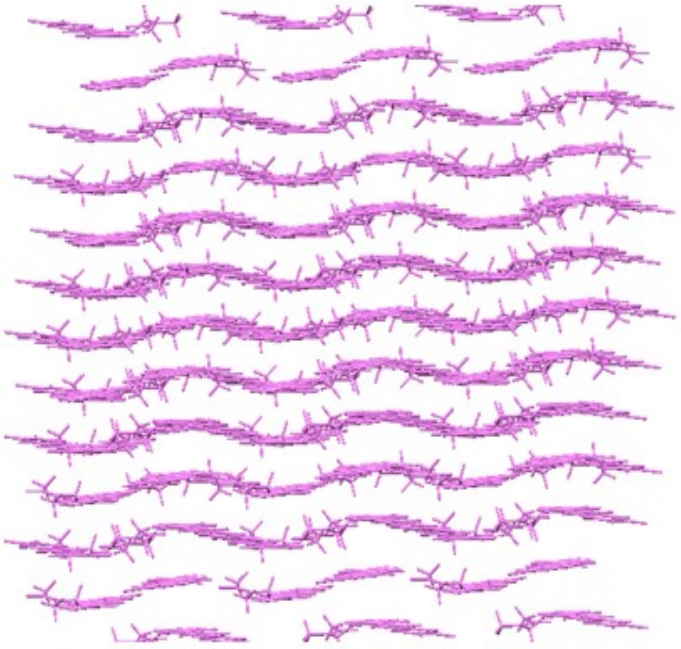
(a)



(b)

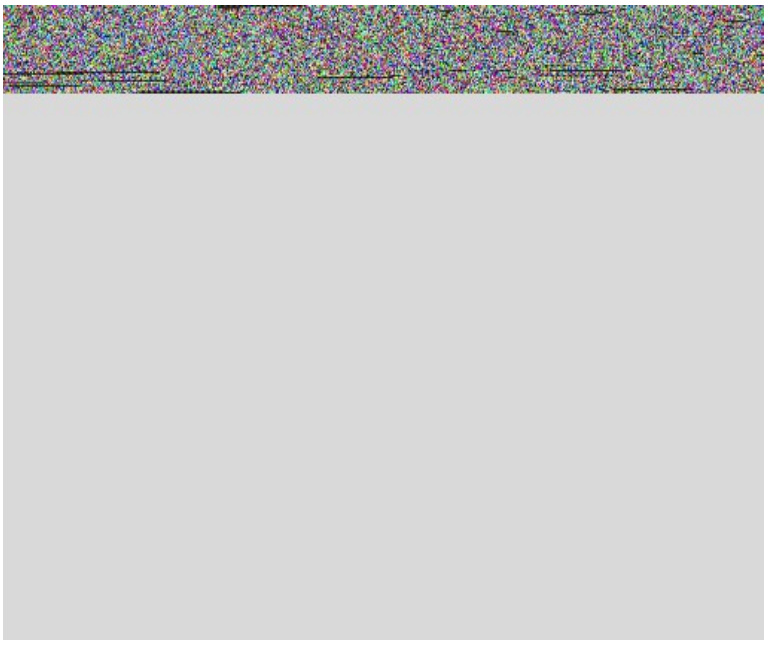
Figure S1. (a) crystal packing diagram of NIC-DMF (1:1) showing the zig-zag arrangement of molecules, **(b)** crystal packing diagram of NIC-DMSO (1:1) showing an interleaved type of arrangement.

(a)



(b)

Figure S2. (a) crystal packing of NIC-NNDMA (1:1) form I showing the stacking of layers one above the other, **(b)** crystal packing of NIC-NNDMA (2:2) form II system showing the formation of a corrugated sheet type layers stacked one upon the other.



(a)

(b)

Figure S3. (a) crystal packing diagram of NIC-DOX (1:0.5) showing layers which are stacked one upon the other, **(b)** crystal packing diagram of NIC-DOX (2:1.5) showing cavities occupied by 1,4-dioxan molecules.

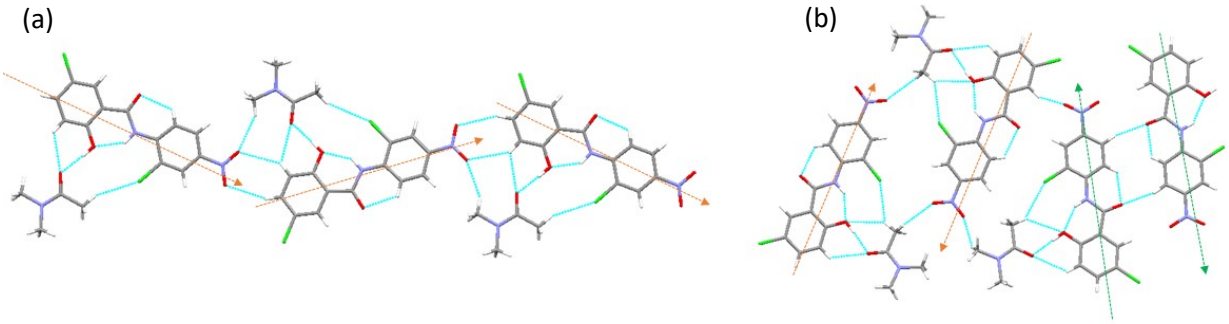


Figure S4. (a) showing the longitudinal allignment of NIC molecules in form I, (b) showing the antiparallel arrangement of NIC molecules in form II

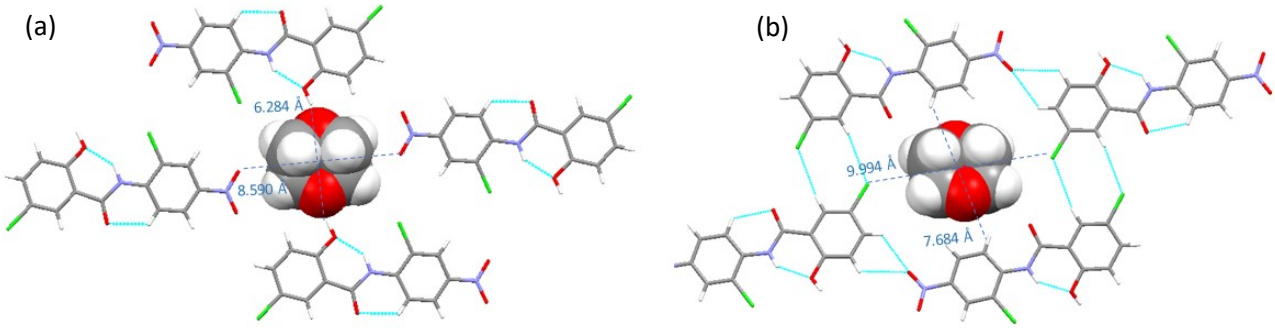


Figure S5. (a) shows that the void formed in NIC-DOX (1:0.5) is smaller in size (6.284 x 8.590 Å) as compared to the void in (b) NIC-DOX (2:1.5) (7.648 x 9.994Å) and hence the later hosts 1,4-dioxan solvate in the framework.

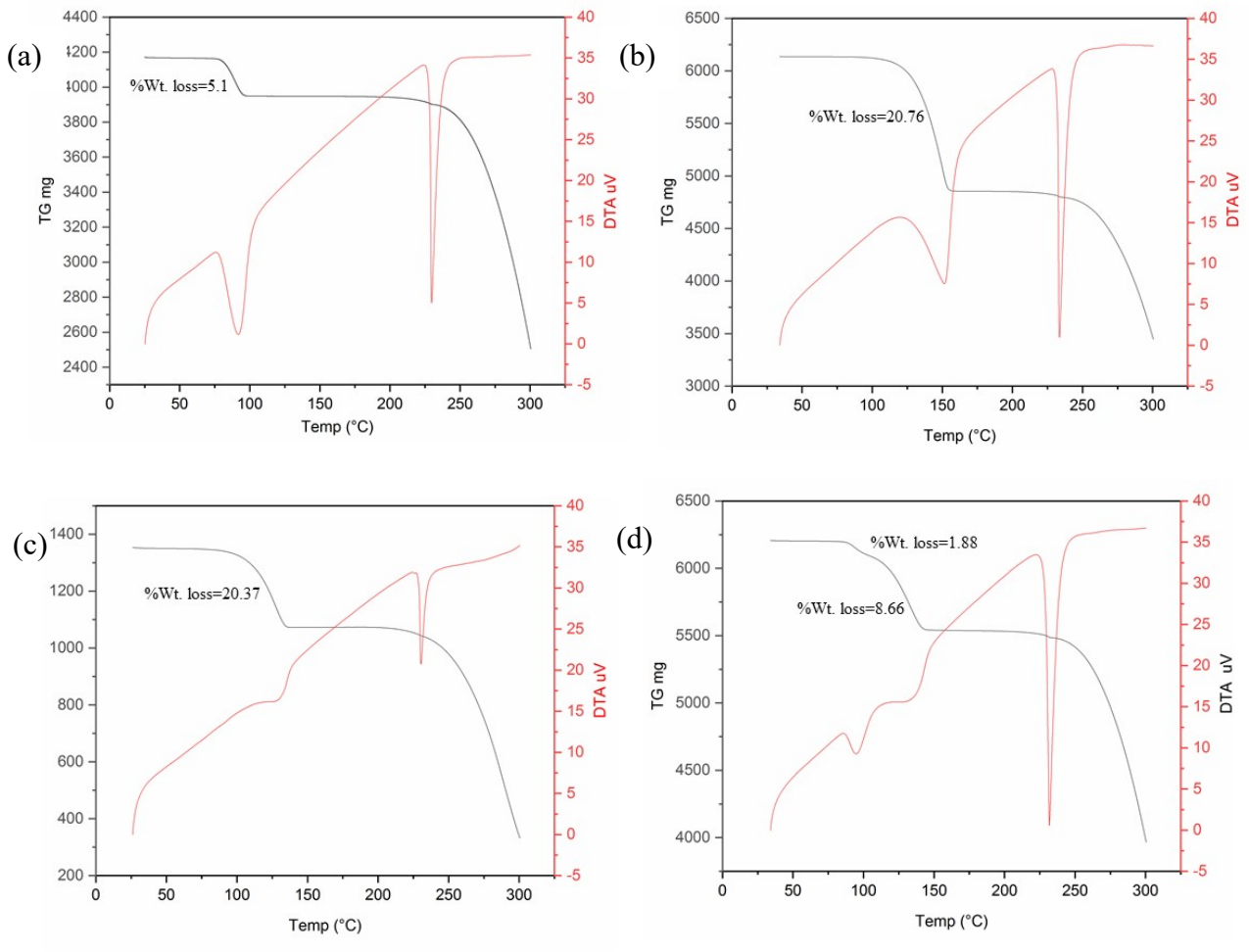


Figure S6. TG thermograms of (a) NIC-monohydrate, (b) NIC-NNDMA (1:1), (C) NIC-NNDMA (2:2) and (d) NIC-DOX (1:0.5)

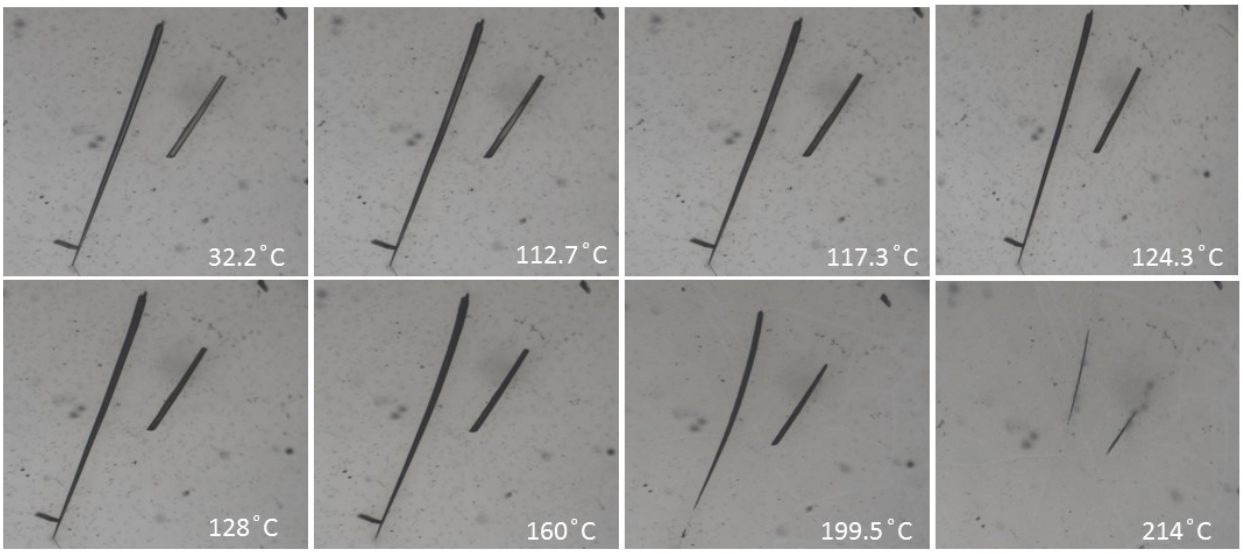


Figure S7. HSM images of NIC monohydrate crystals.

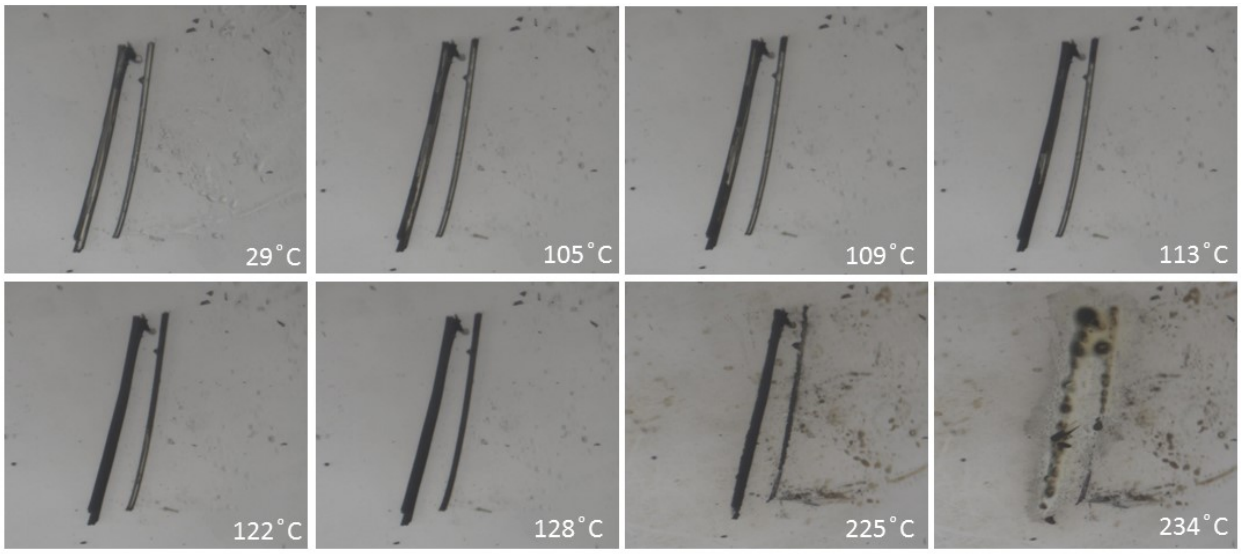


Figure S8. HSM images of NIC-DMF crystals.

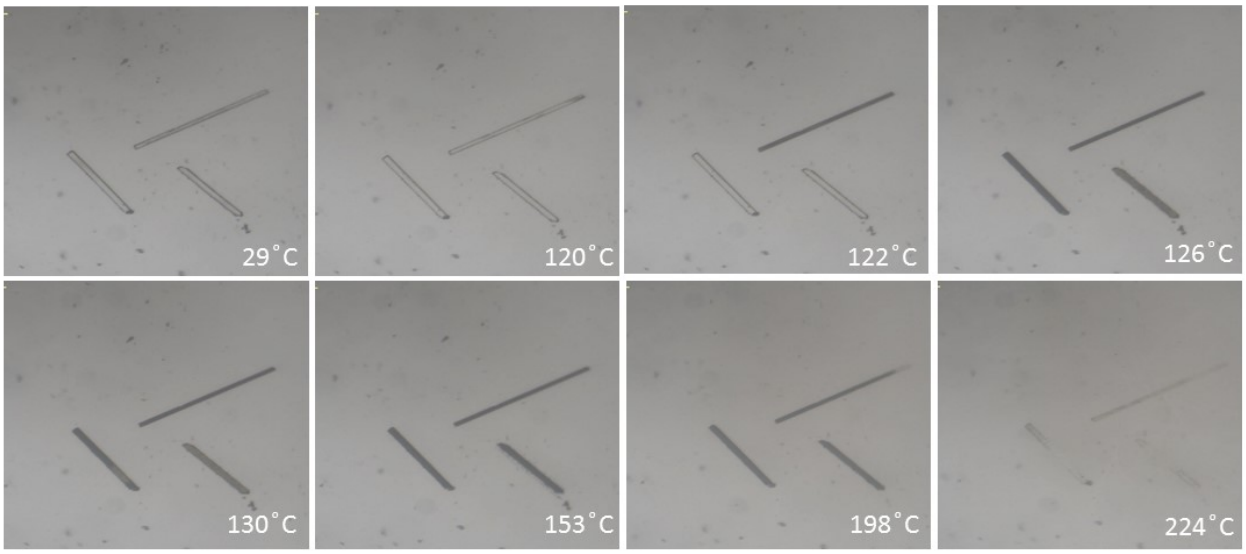
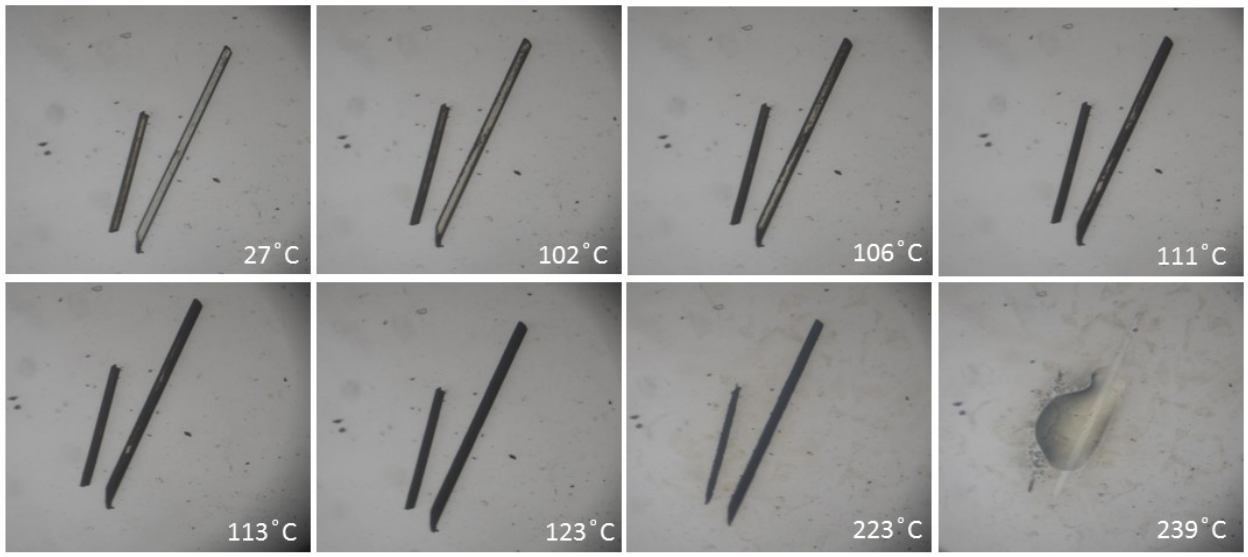
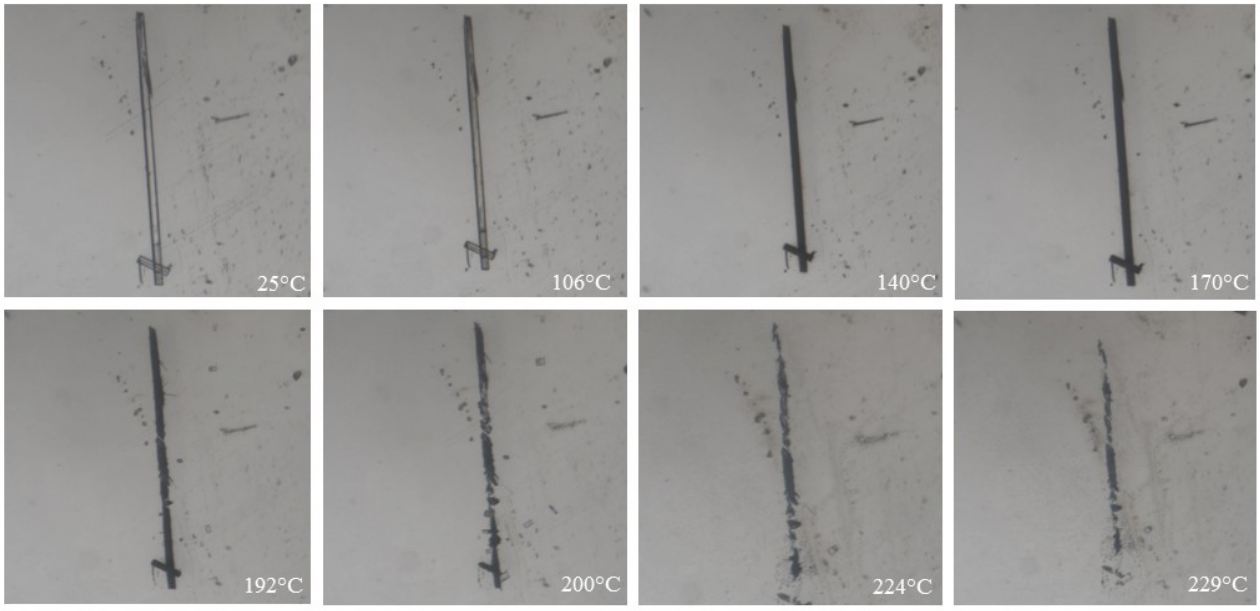


Figure S9. HSM images of NIC-DMSO.



(a)



(b)

Figure S10. (a) HSM images of NIC-NNDMA (1:1) form I, **(b)** HSM images of NIC-NNDMA (2:2) form I.

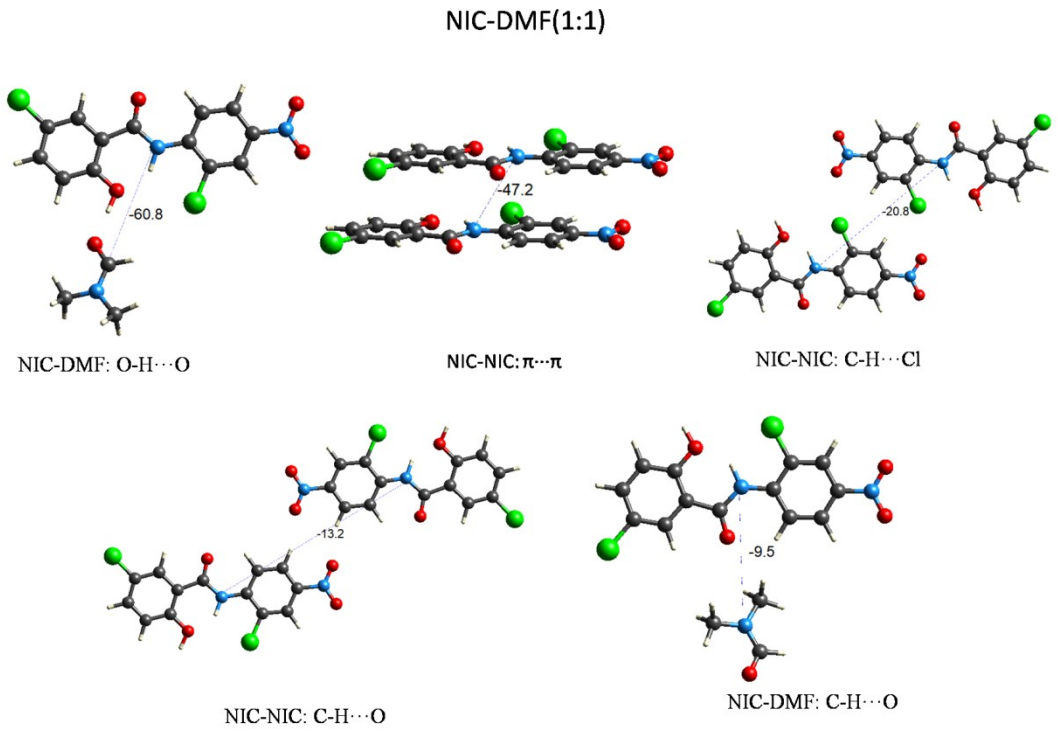


Figure S11. Prominent interactions in the different dimers of NIC-DMF (1:1) crystal and their associated energies (kJ.mol^{-1}).

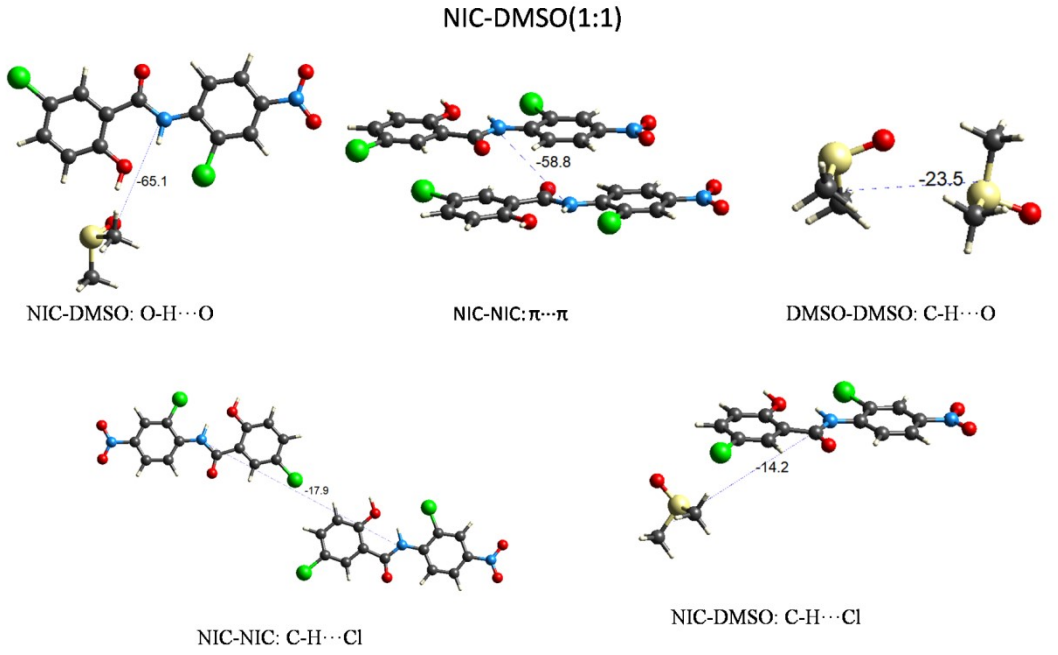
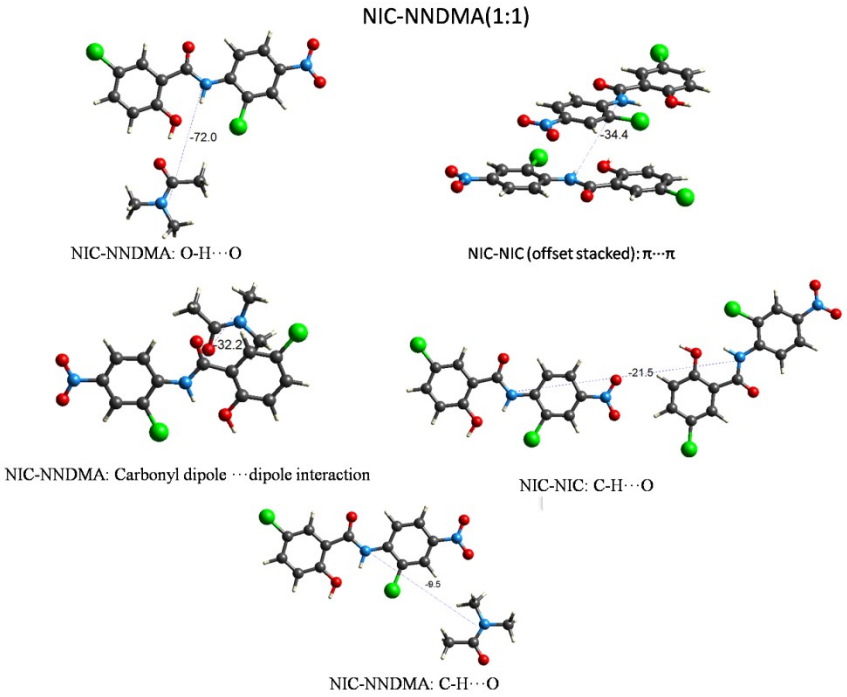
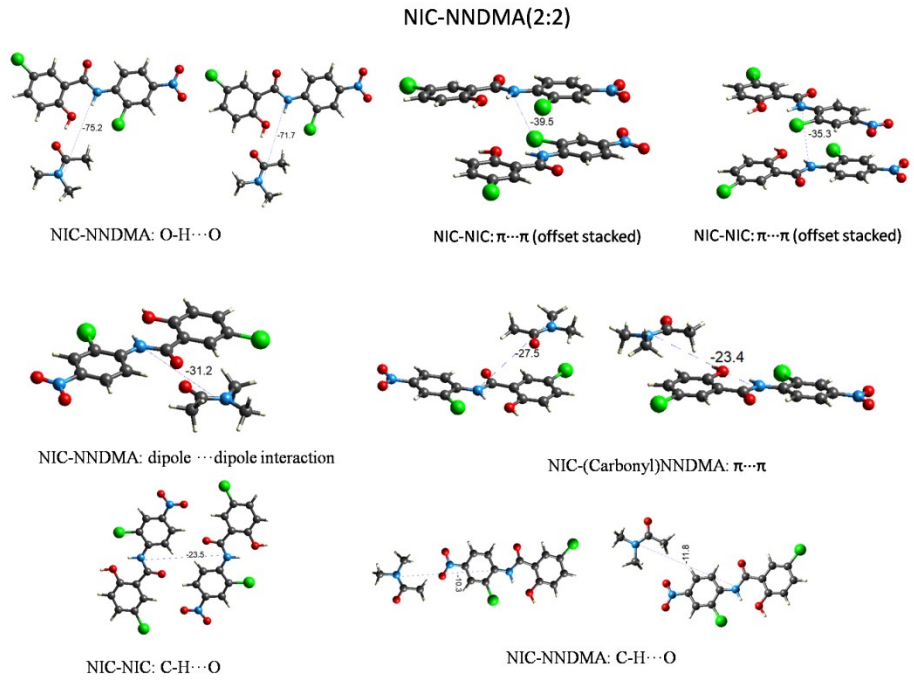


Figure S12. Prominent interactions in the different dimers of NIC-DMSO (1:1) crystal and their associated energies (kJ.mol^{-1}).

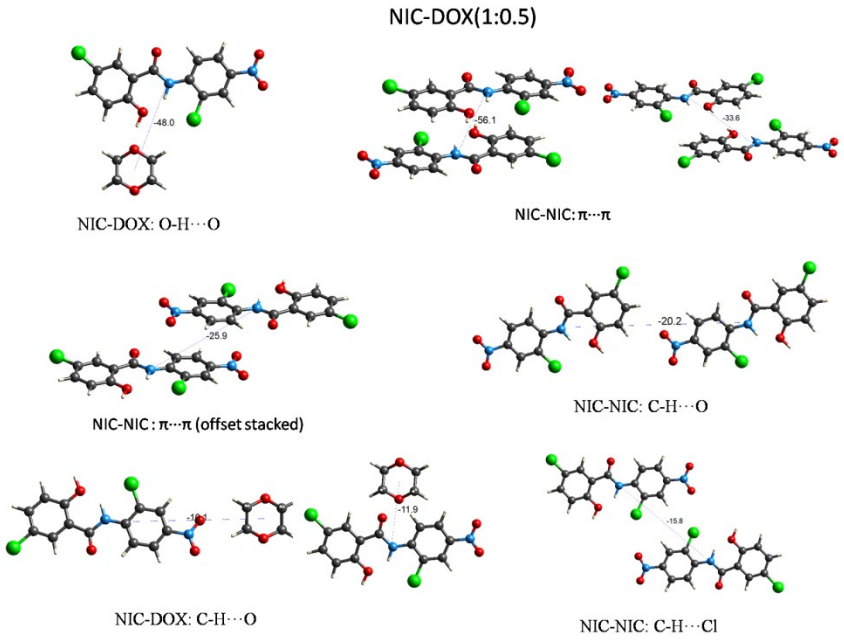


(a)

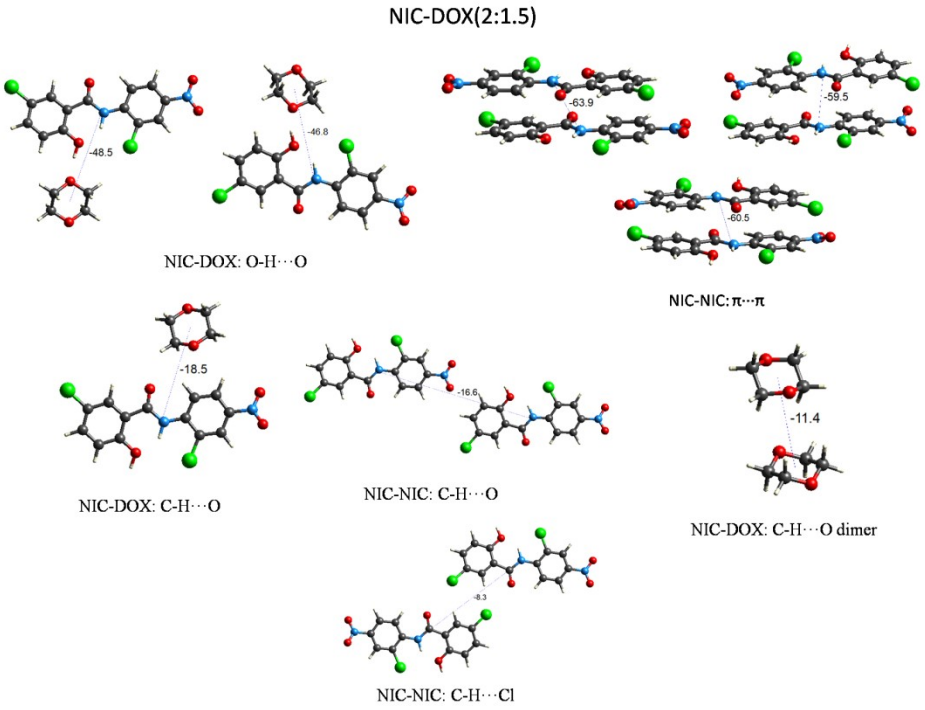


(b)

Figure S13. Prominent interactions in the different dimers of (a) NIC-NNDMA (1:1) and (b) NIC-NNDMA (2:2) crystal structures and their associated energies.



(a)



(b)

Figure S14. Prominent interactions in the different dimers of (a) NIC-DOX (1:0.5) and (b) NIC-DOX (2:1.5) crystal structures and their associated energies.

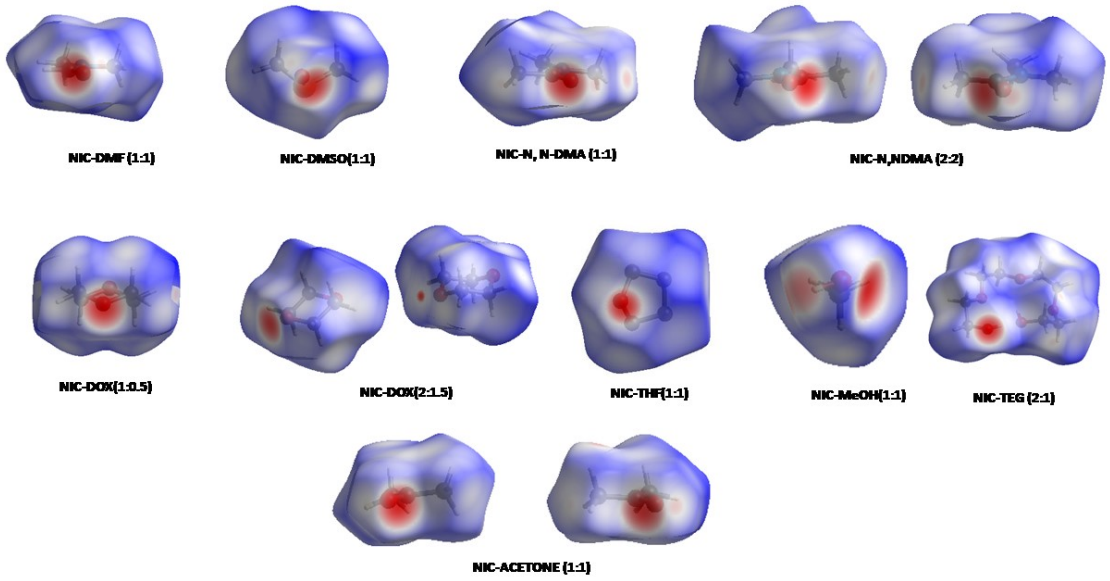


Figure S15. Hirshfeld surface maps with d_{norm} property mapped in NIC-DMF, NIC-DMSO, NIC-NNDMA (1:1), NIC-NNDMA (2:2) and NIC-DOX (2:1.5). Bright and large red spots indicate strong intermolecular O-H···O and small and faint red spots indicate C-H···O or other weak interactions like C-H···π and π···π interactions.