Electronic Supplementary Information

Biological activities tuning of antibacterial urotorpine *via* co-crystallization: Synthesis, biological activity evaluation and computational insight

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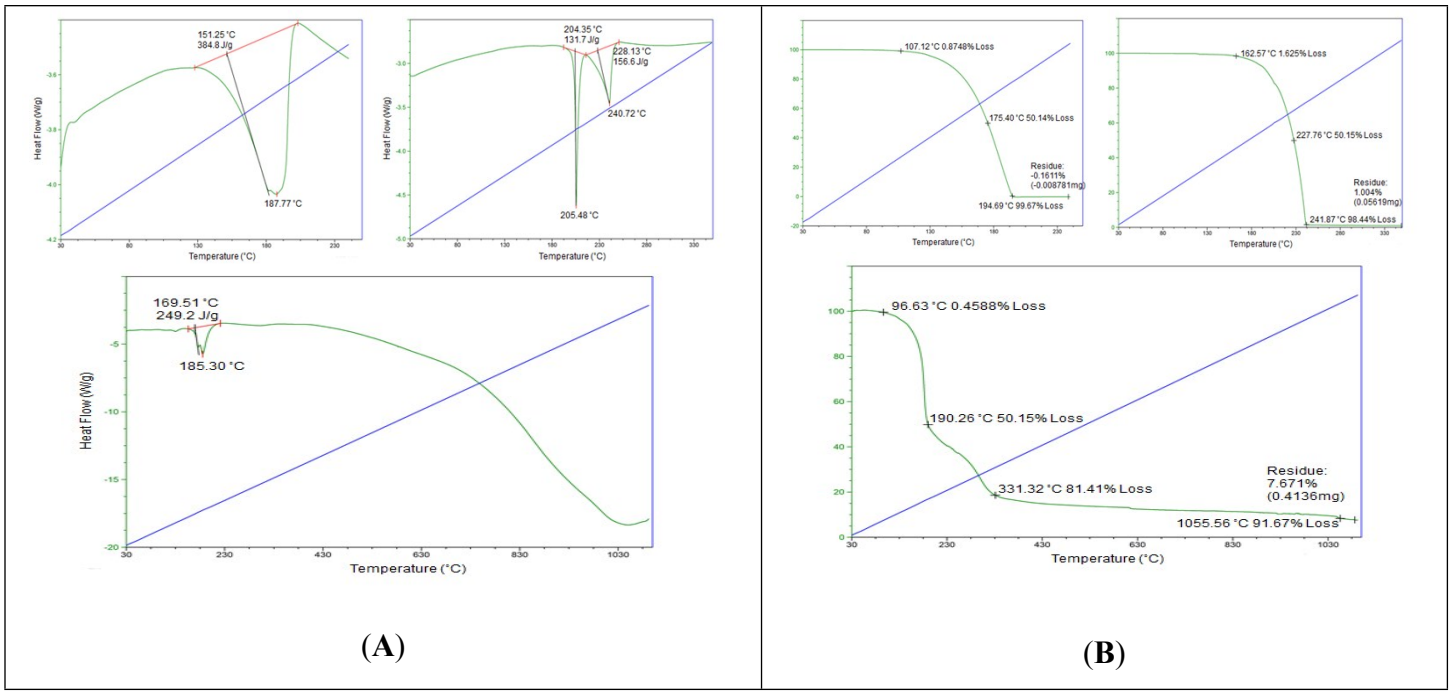


Fig. S1 (**A**) DSC Spectra of urotropine (**1**) (API), syringic acid (coformer) and urotropine: syringic acid (1:1) co-crystal **2**. (**B**) TGA spectra of urotropine (**1**) (API), syringic acid (coformer), and urotropine: syringic acid (1:1) co-crystal **2**.

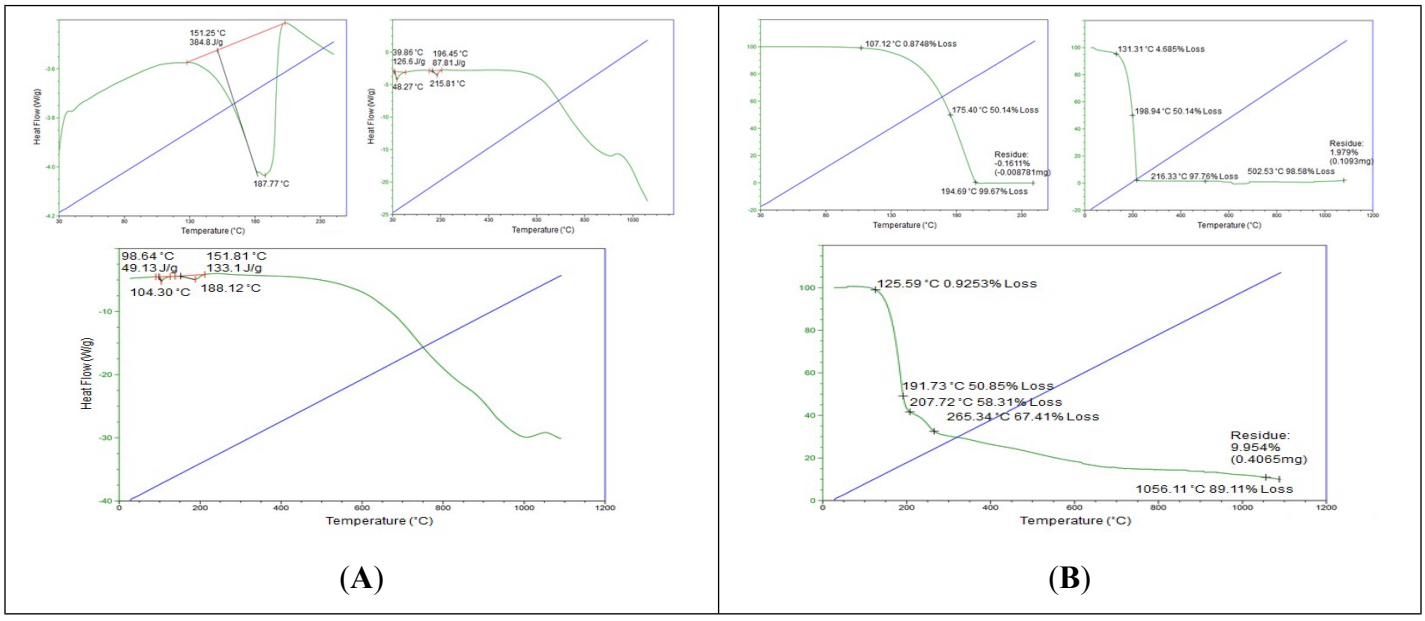


Fig. S2 (**A**) DSC Spectra of urotropine (**1**) (API), 4-[4-(trifluoromethyl) phenoxy] phenol (coformer) and urotropine: 4-[4-(trifluoromethyl) phenoxy] phenol (1:1) co-crystal **3**. (**B**) TGA Spectra of urotropine (**1**) (API), 4-[4-(trifluoromethyl) phenoxy] phenol (coformer), and urotropine: 4-[4-(trifluoromethyl) phenoxy] phenol (1:1) co-crystal **3**.

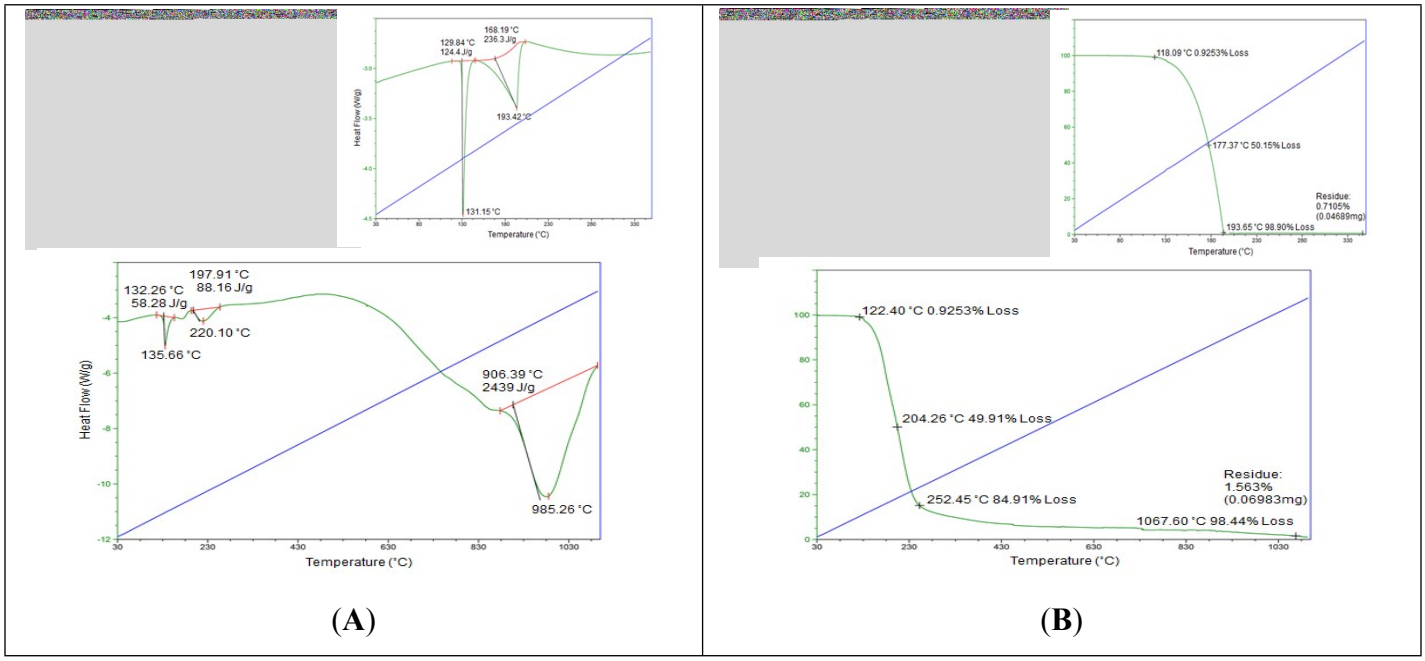
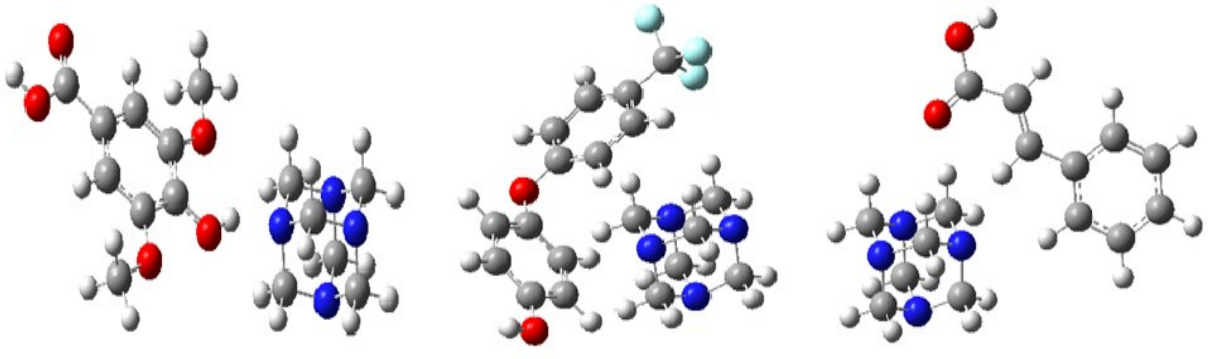
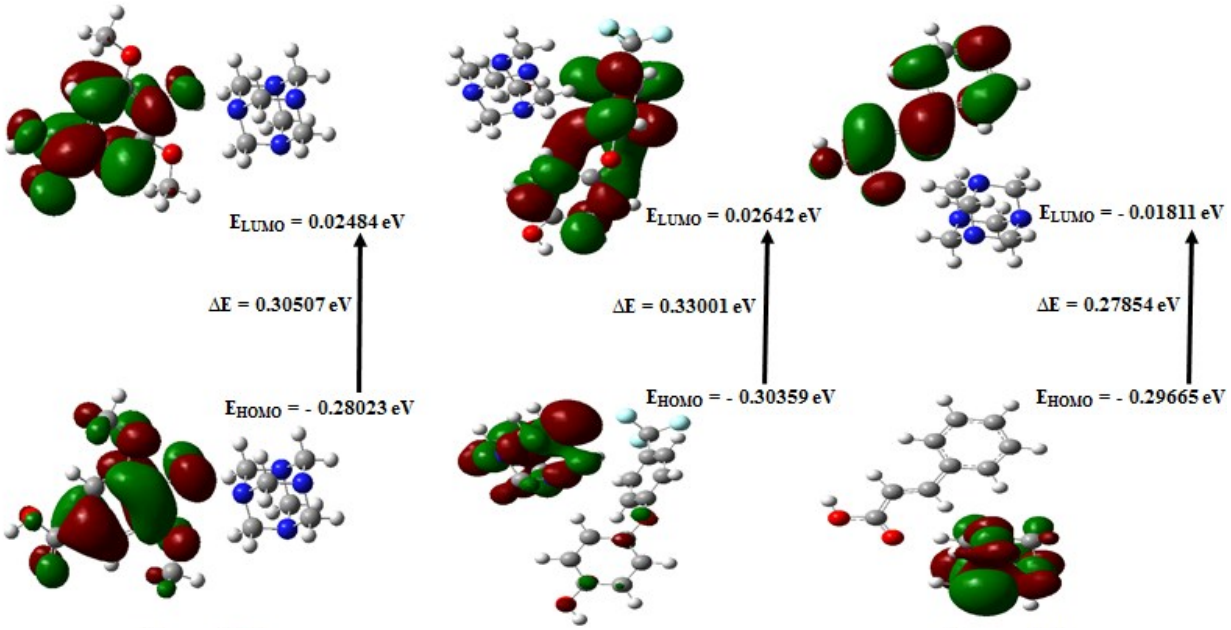


Fig. S3 (**A**) DSC Spectra of urotropine (**1**) (API), *trans*-cinnamic acid (coformer) and urotropine: *trans*-cinnamic acid (1:1) co-crystal **4**. (**B**) TGA Spectra of urotropine (**1**) (API), *trans*-cinnamic acid (coformer), and urotropine: *trans*-cinnamic acid (1:1) co-crystal **4**.



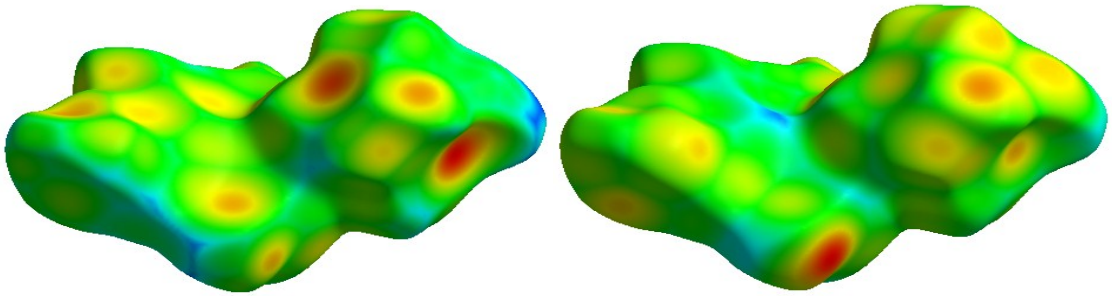
Co-crystal **2** Co-crystal **3** Co-crystal **4**

Fig. S4 Molecular structures of synthesized co-crystals obtained at ωB97XD/6311++G(d,p) level of theory.



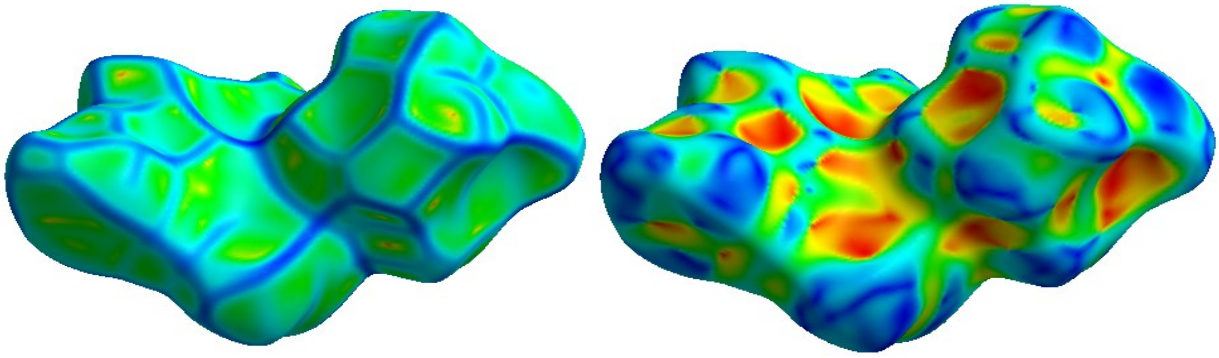
Co-crystal **2** Co-crystal **3** Co-crystal **4**

Fig. S5 The HOMO-LUMO energy gap of synthesized co-crystals, calculated at ωB97XD/6311++G(d,p) level of theory.



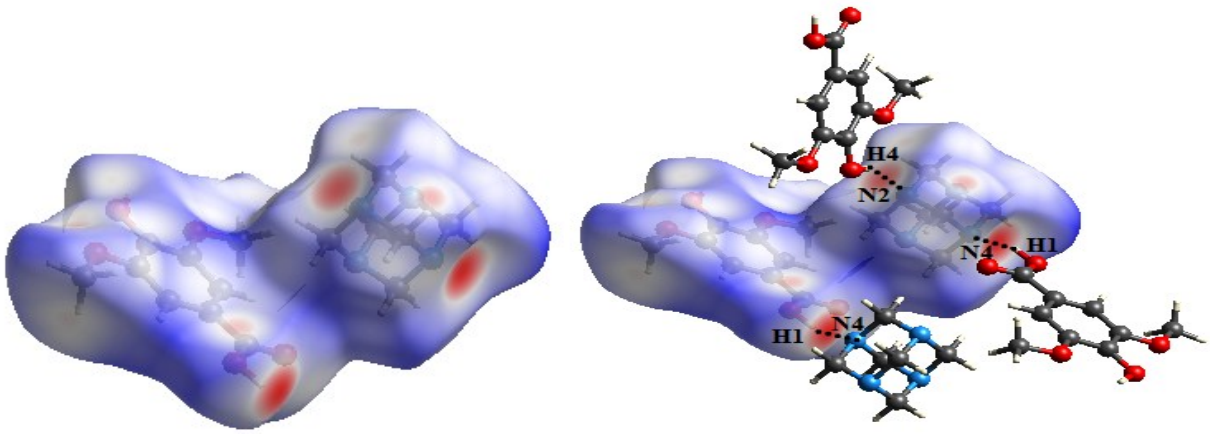
de **di**

Fig. S6 Generated 2D Hirshfeld surface for urotropine: syringic acid 1:1 co-crystal **2** on de and di parameters.



curvedness **Shape-index**

Fig. S7 Shape-index and curvedness mapped over Hirshfeld surface for urotropine: syringic acid 1:1 co-crystal **2**.



(A) **(B)**

Fig. S8 (A) Generated 2D Hirshfeld surface for urotropine: syringic acid 1:1 co-crystal **2** on dnorm parameters. (B) Urotropine: syringic acid 1:1 co-crystal interactions with generated Hirshfeld surface.

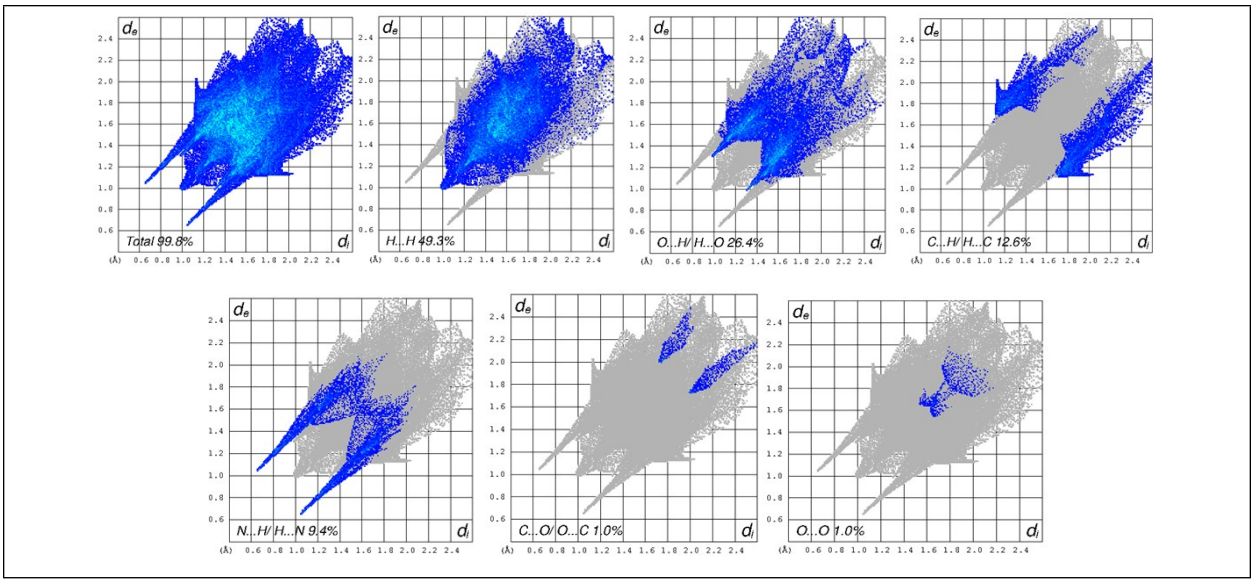
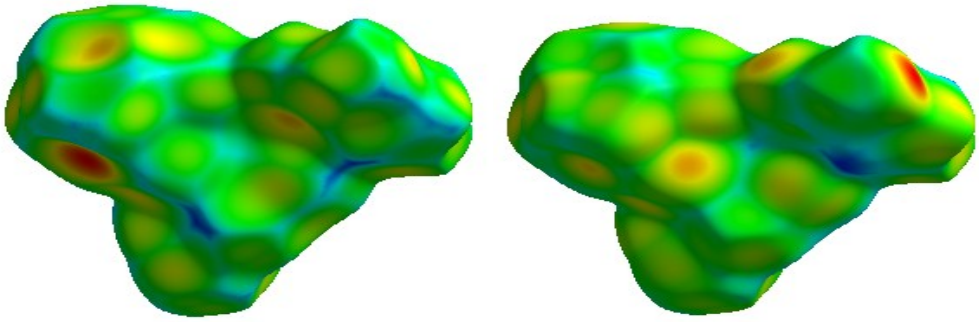
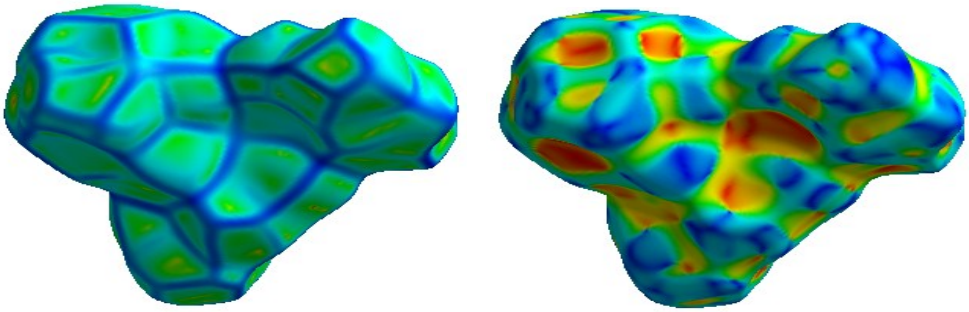


Fig. S9 2D Fingerprint plots representation of urotropine: syringic acid 1:1 co-crystal **2**.



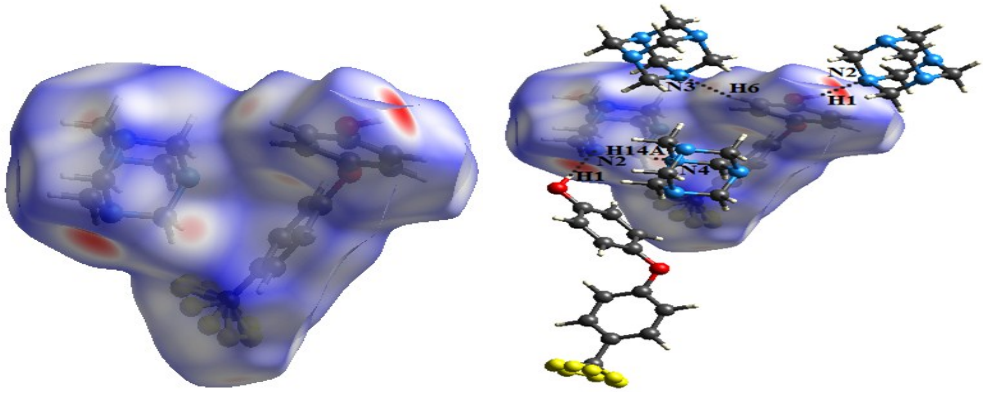
de **di**

Fig. S10 Generated 2D Hirshfeld surface for urotropine: 4-[4-(trifluoromethyl)phenoxy] phenol 1:1 co-crystal **3** on de and di parameters.



curvedness **Shape-index**

Fig. S11 Shape-index and curvedness mapped over Hirshfeld surface for urotropine: 4-[4-(trifluoromethyl)phenoxy] phenol 1:1 co-crystal **3.**



(A) **(B)**

Fig. S12 (A) Generated 2D Hirshfeld surface for urotropine: 4-[4-(trifluoromethyl)phenoxy] phenol 1:1 co-crystal **3** on dnorm parameters. (B) Urotropine: 4-[4-(trifluoromethyl)phenoxy] phenol 1:1 co-crystal **3** interactions with generated Hirshfeld surface.

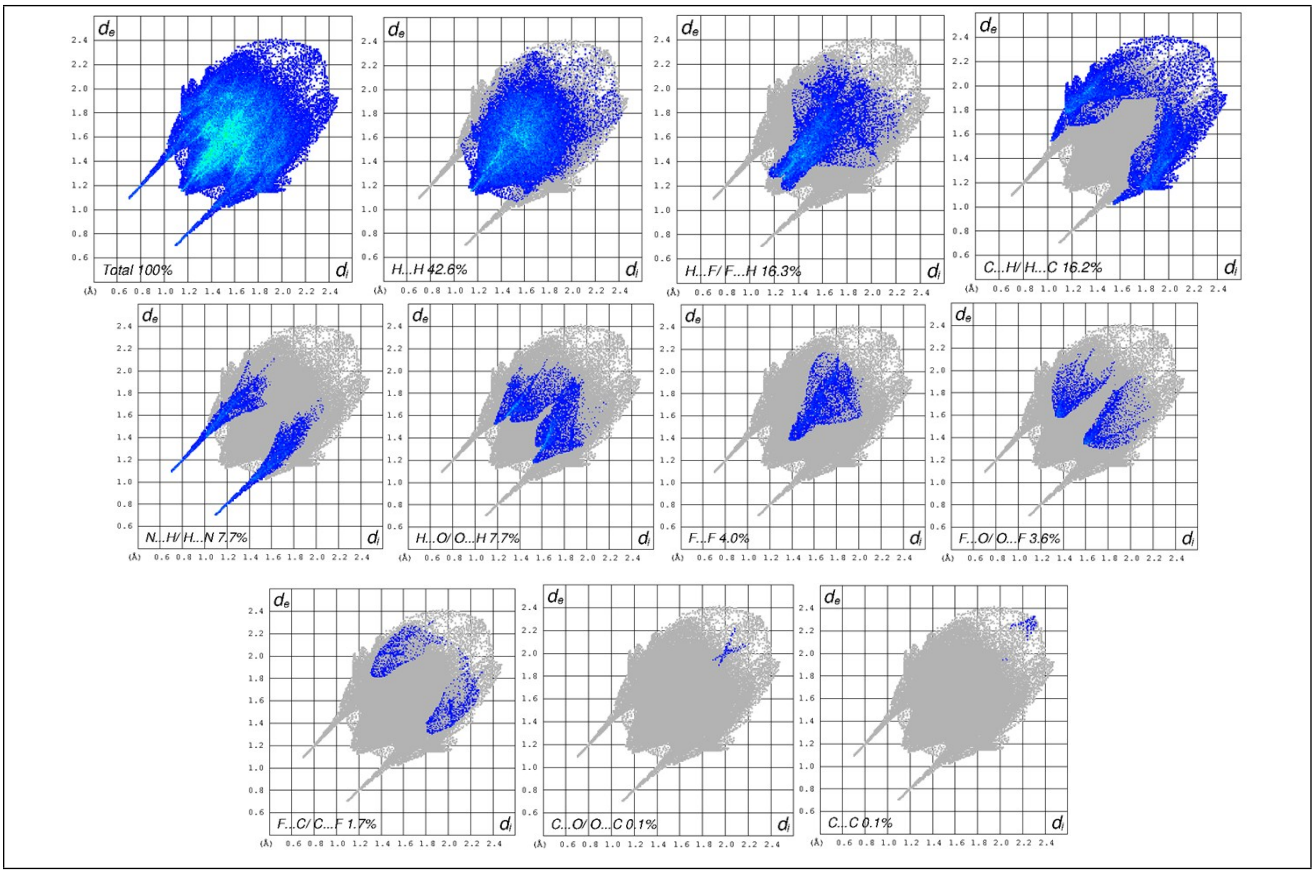
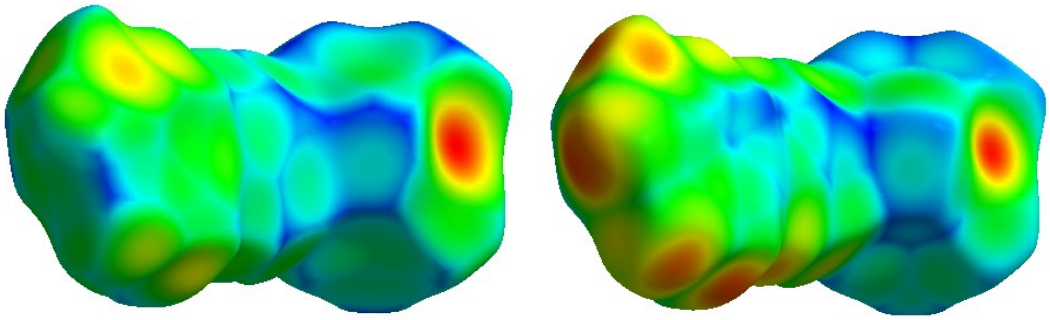
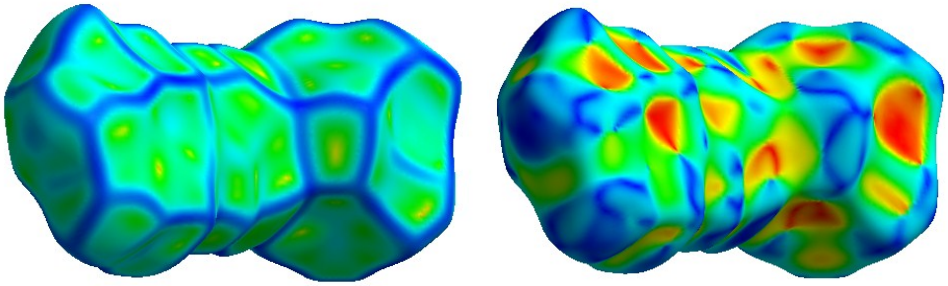


Fig. S13 2D Fingerprint plots representation of urotropine: 4-[4-(trifluoromethyl)phenoxy] phenol 1:1 co-crystal **3**.



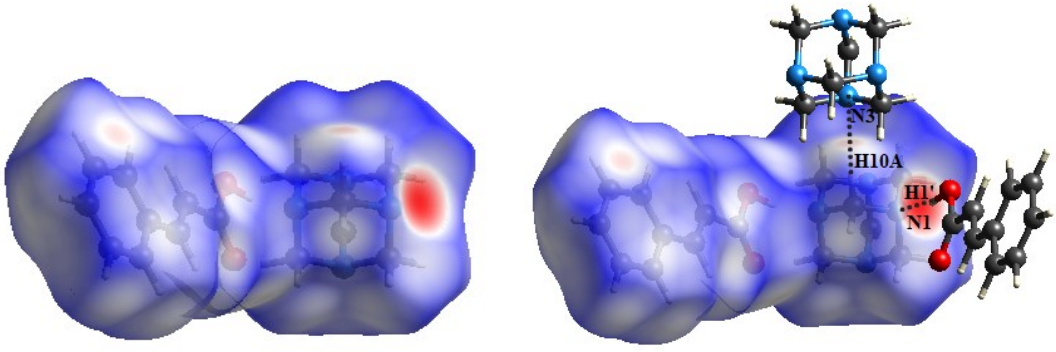
de **di**

Fig. S14 Generated 2D Hirshfeld surface for urotropine: *trans*-cinnamic acid 1:1 co-crystal **4** on de and di parameters.



curvedness **Shape-index**

Fig. S15 Shape-index and curvedness mapped over Hirshfeld surface for urotropine: *trans*-cinnamic acid 1:1 co-crystal **4**.



(A) **(B)**

Fig. S16 (A) Generated 2D Hirshfeld surface for urotropine: *trans*-cinnamic acid 1:1 co-crystal **4** on dnorm parameters. (B) Urotropine: *trans*-cinnamic acid 1:1 co-crystal **4** interactions with generated Hirshfeld surface.

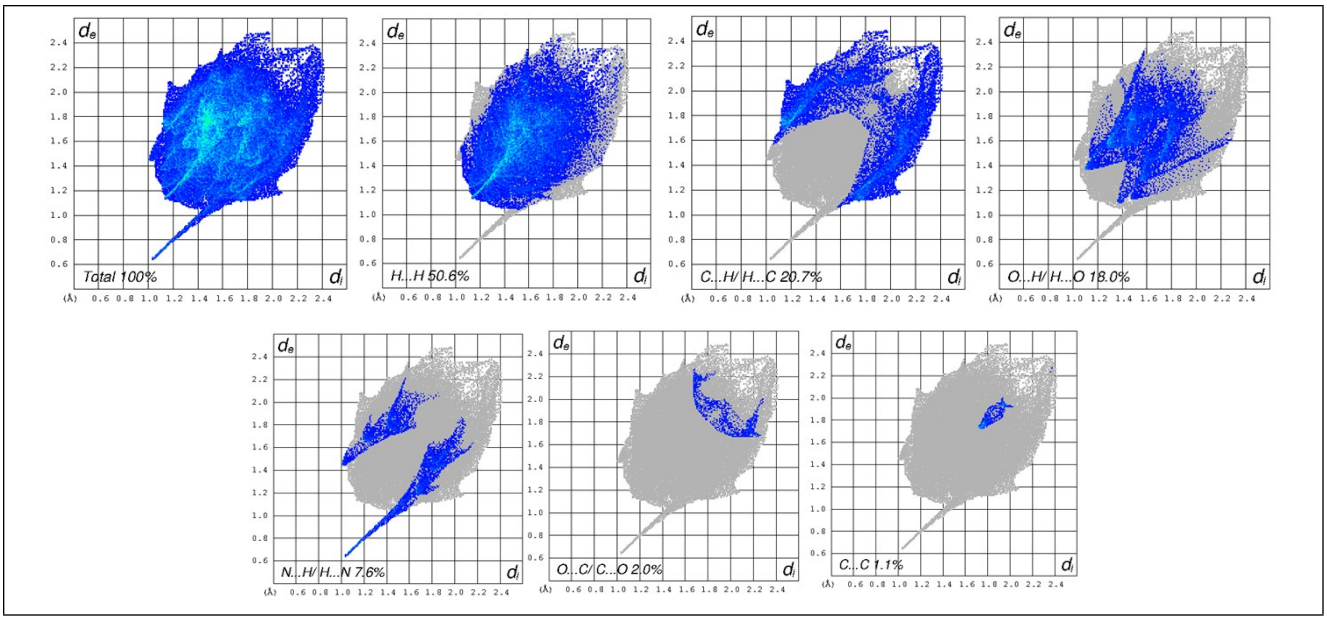


Fig. S17 2D Fingerprint plots representation of urotropine: *trans*-cinnamic acid 1:1 co-crystal **4**.

Table S1 The list of selected hydrogen bonds geometry (Å) in co-crystal **2**.

D	H	A	D-H	H…A	D…A	D-H…A
O1	H1	$N4^{\#1}$	0.84	1.83	2.638(1)	160
O4	H4	$N2^{\#2}$	0.84	2.10	2.828(1)	144
C8	H8C	$O1^{\#3}$	0.98	2.50	3.421(1)	157
C14	H14B	$O2^{\#4}$	0.99	2.38	3.334(1)	162

Symmetric codes #1: -x+1,-y,-z+1 #2: x-1/2,-y+1/2,z+1/2 #3: x-1,y,z #4: -x,-y,-z+1

Table S2 The list of selected hydrogen bonds geometry (Å) in co-crystal **3**.

D	H	A	D-H	H…A	D…A	D-H…A
O1	H1	$N2^{\#1}$	0.84	1.93	2.754	167
C6	H6	$N3^{\#2}$	0.95	2.60	3.530	168
C14	H14A	$N4^{\#3}$	0.99	2.50	3.465	163

Symmetric codes #1: x,-y-1/2,z+1/2 #2: -x,y-1/2,-z+3/2 #3: x,y-1,z

Table S3 The list of selected hydrogen bonds geometry (Å) in co-crystal **4**.

D	**H**	**A**	**D-H**	**H…A**	**D…A**	**D-H…A**
O2	H1'	N1$^{\#1}$	1.02	1.64	2.646(1)	168
C10	H10A	N3$^{\#2}$	0.99	2.54	3.514(1)	170

Symmetric code#1: x,y,z-1 #2: -x+1,-y+2,z+1/2

Table S4 The comparison of FT-IR spectra stretching frequency values in cm^{-1} for urotropine (**1**) (API), syringic acid (coformer of co-crystal **2**), 4-[4-(trifluoromethyl) phenoxy] phenol (coformer of co-crystal **3**), *trans*-cinnamic acid (conformer of co-crystal **4**), and co-crystals **2**, **3**, and **4**.

Functional Groups	C=O	C=C	C-O	C=C (Aromatic)	O-H (COOH)	O-H (Phenol)	C-N
Urotropine (**1**) **(API)**	-	-	-	-	-	-	1237
Syringic acid (coformer of co-crystal **2**)	1699	-	1246-1112	1461-1618	3247	3374	-
4-[4-(trifluoromethyl) phenoxy] phenol (coformer of co-crystal **3**)	-	-	1225	1446-1614	-	3294	-
Trans-cinnamic acid (coformer of co-crystal **4**)	1667	1626	1312	1419-1493	2522-2833	-	-
Co-crystal **2**	1572	-	1250-1120	1420-1518	3090-3895	3403	1286
Co-crystal **3**	-	-	1194	1465-1613	-	3960	1238
Co-crystal **4**	1689	1620	1374	1394-1493	3326-3587	-	1238