Supporting Information
Multicomponent Crystals of Clotrimazole: A Combined Theoretical and Experimental Study

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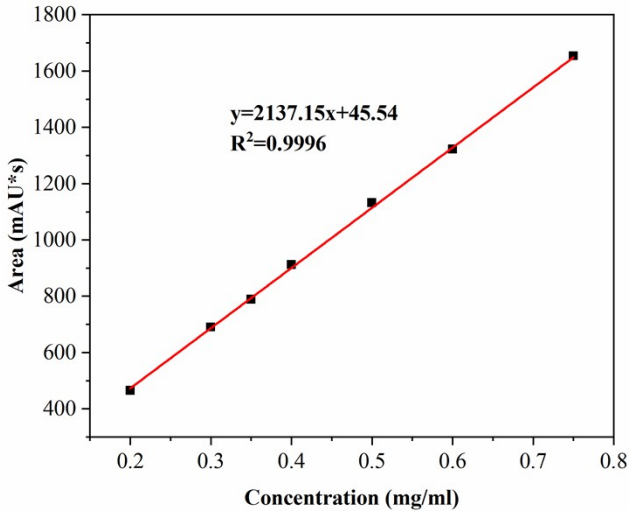


Fig. S1 HPLC standard curve of CLT.

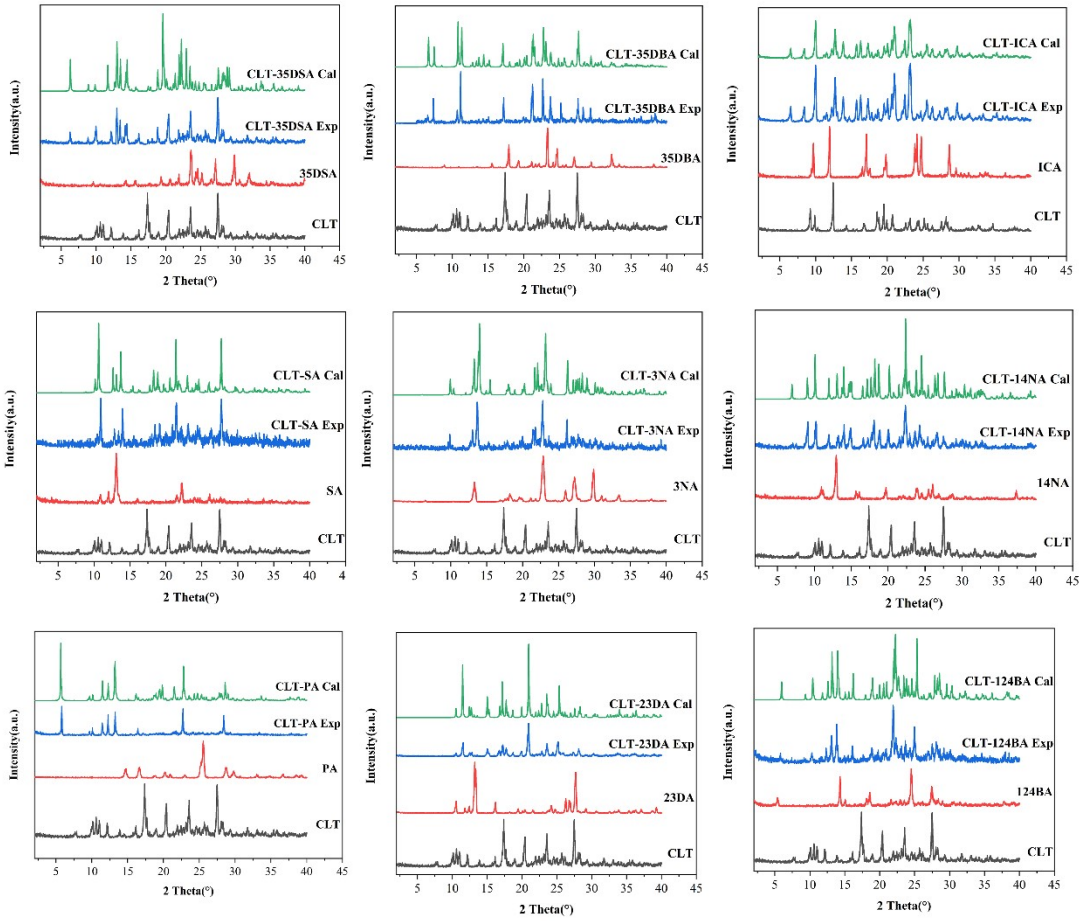
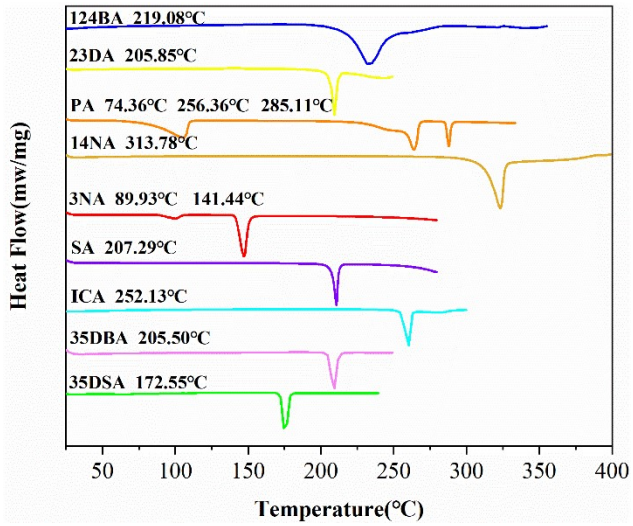


Fig. S2 PXRD patterns of raw materials and multicomponent crystals. (Exp: The experiment of synthetic，Cal: Calculated from the crystal structure).



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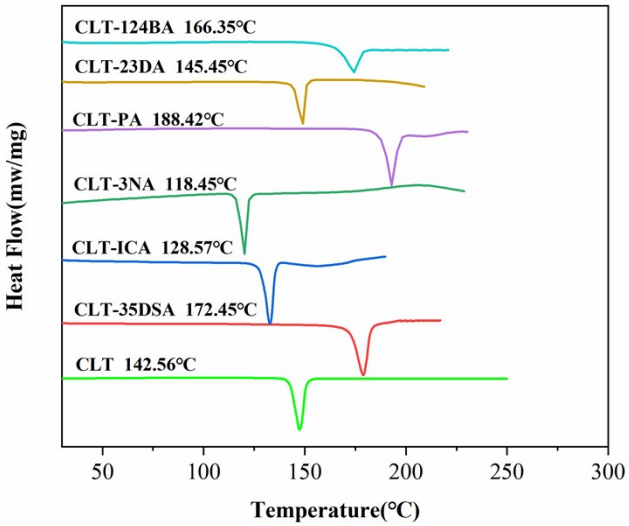

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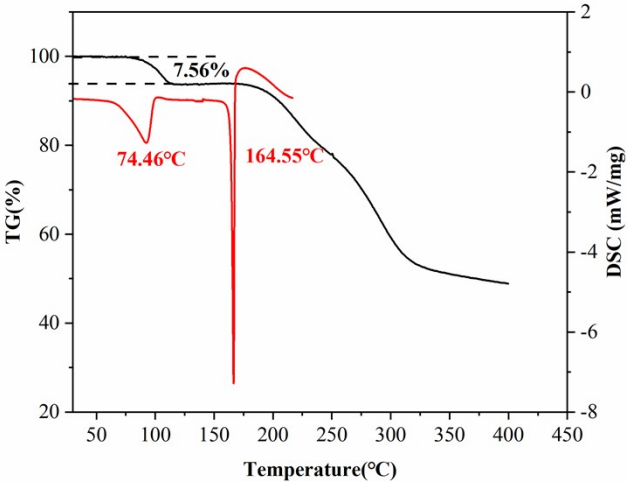

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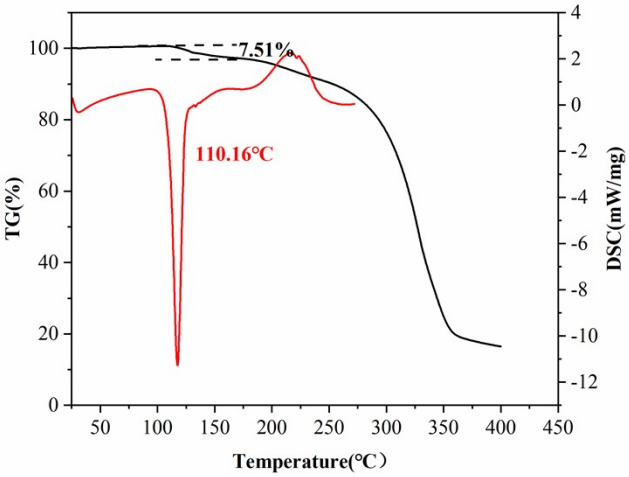

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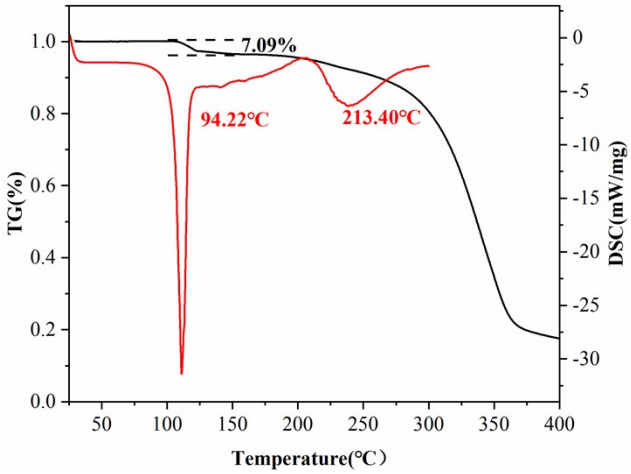

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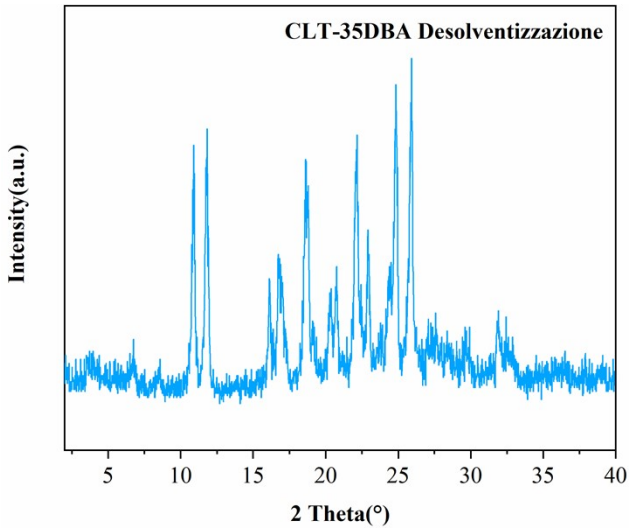

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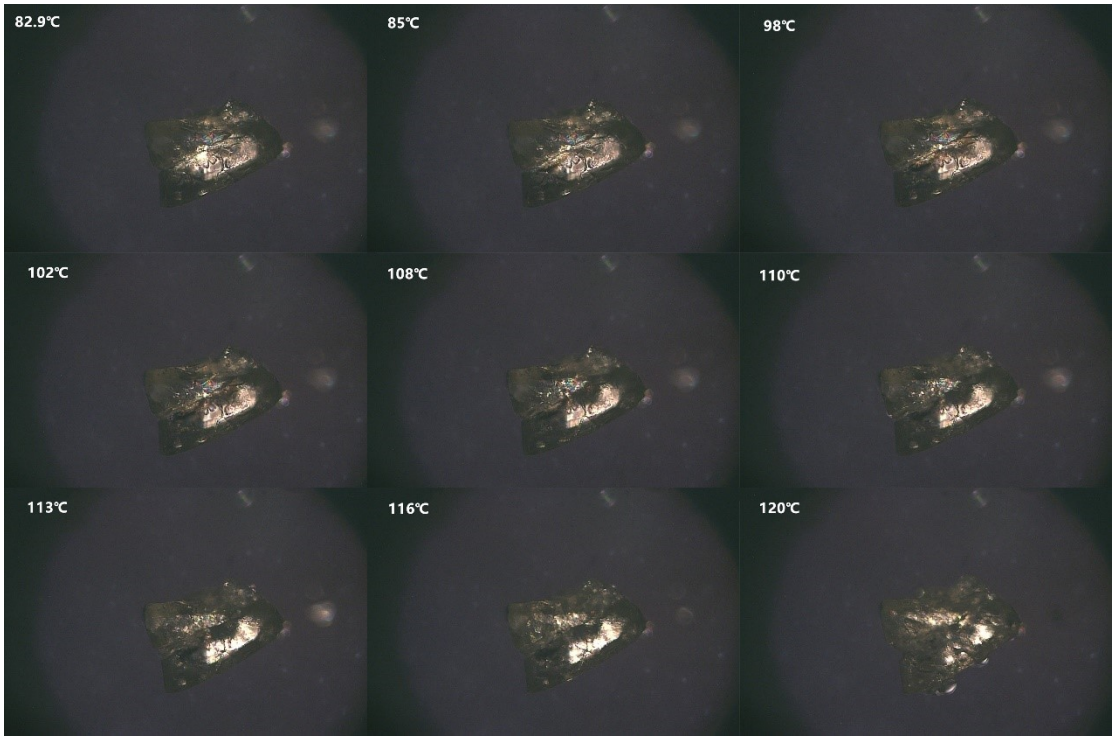

Fig. S9 The melting process of CLT-14NA salt was observed with a HSM. The HSM photograph showed that the ethanol could desolation until the melting point (108℃-113℃).

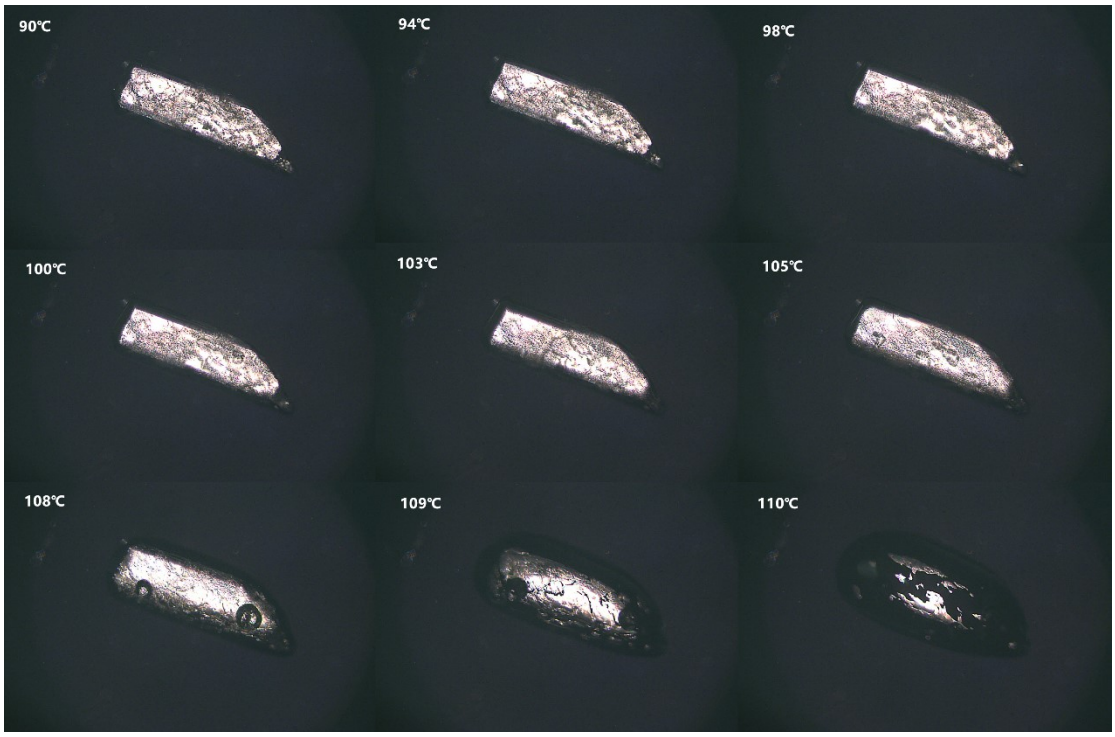

Fig. S10 The melting process of CLT-SA cocrystal was observed with a HSM. The HSM photograph showed that the acetonitrile could desolation until the melting point (90℃-98℃).

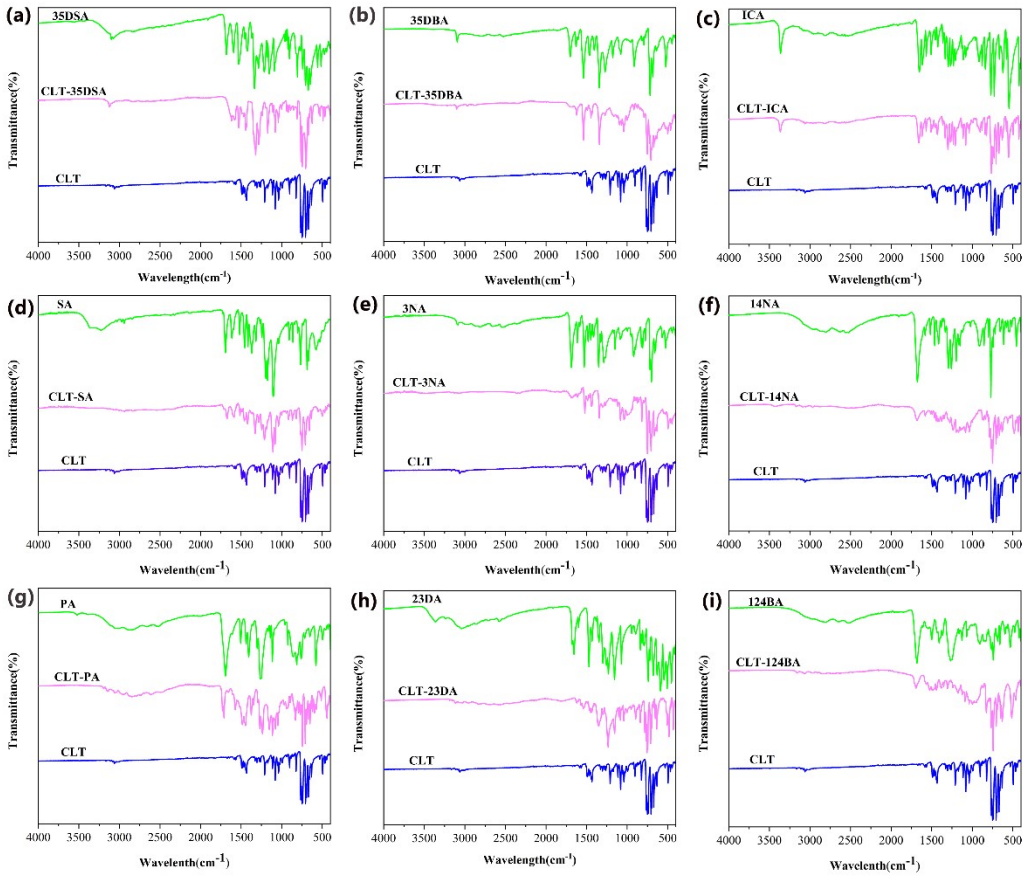

Fig. S11 FTIR spectrogram of the starting materials and multicomponent crystals.(a)CLT-35DSA, (b) CLT-35DBA, (c) CLT-ICA, (d) CLT-SA, (e) CLT-3NA,(f) CLT-14NA, (g) CLT-PA,(h) CLT-23DA,(i) CLT-124BA.

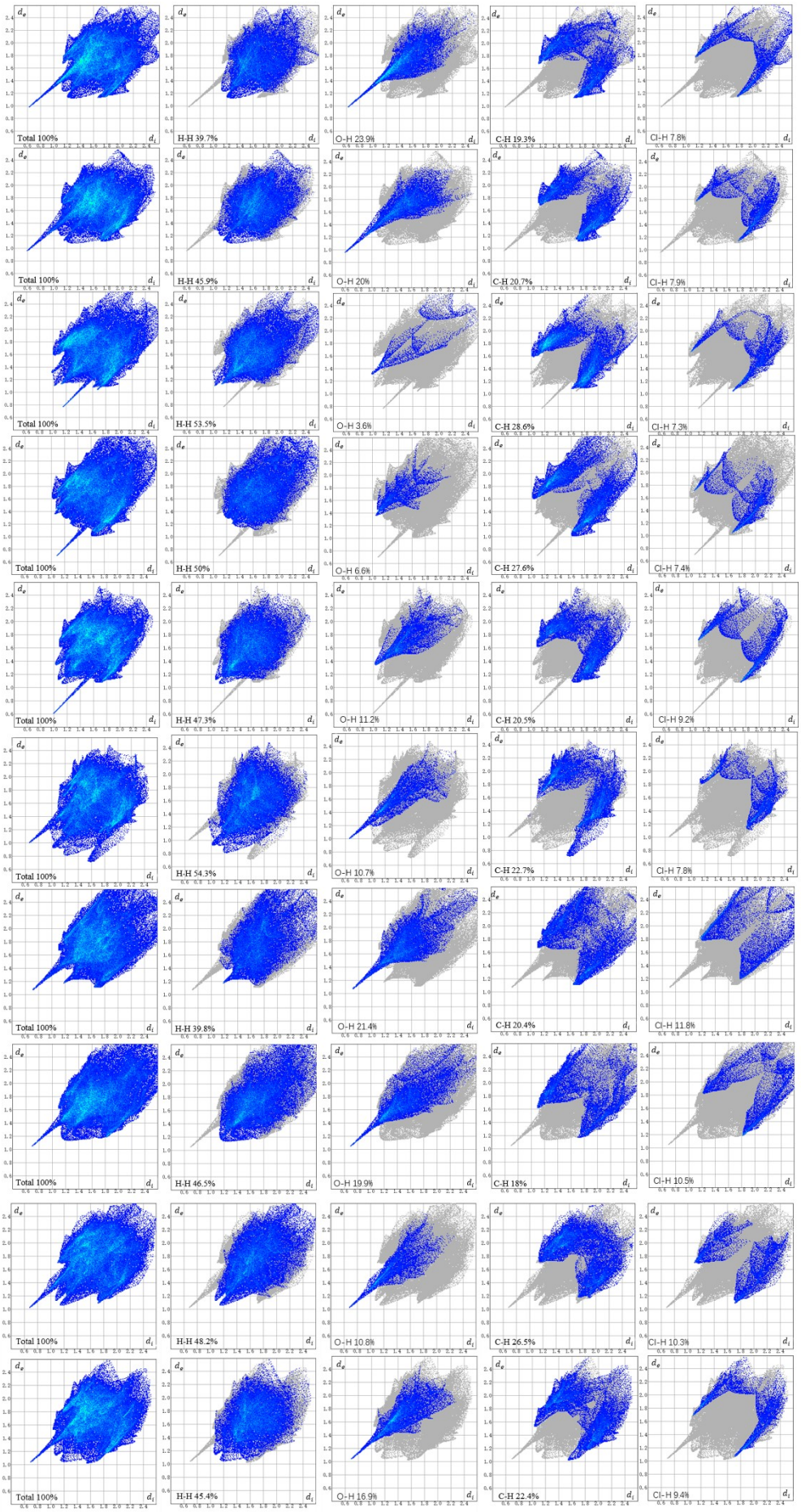
Total 100%
H-H 39.7%
O-H 23.9%
C-H 19.3%
Cl-H 7.8%
Total 100%
H-H 45.9%
O-H 20%
C-H 20.7%
Cl-H 7.9%
Total 100%
H-H 53.5%
O-H 3.6%
C-H 28.6%
Cl-H 7.3%
Total 100%
H-H 50%
O-H 6.6%
C-H 27.6%
Cl-H 7.4%
Total 100%
H-H 47.3%
O-H 11.2%
C-H 20.5%
Cl-H 9.2%
Total 100%
H-H 54.3%
O-H 10.7%
C-H 22.7%
Cl-H 7.8%
Total 100%
H-H 39.8%
O-H 21.4%
C-H 20.4%
Cl-H 11.8%
Total 100%
H-H 46.5%
O-H 19.9%
C-H 18%
Cl-H 10.5%
Total 100%
H-H 48.2%
O-H 10.8%
C-H 26.5%
Cl-H 10.3%
Total 100%
H-H 45.4%
O-H 16.9%
C-H 22.4%
Cl-H 9.4%

Fig. S12 2D fingerprint plots according to the dnorm value about different interactions. (a) CLT-35DSA, (b) CLT-35DBA, (c) CLT-ICA, (d) CLT-SA, (e) CLT-3NA, (f) CLT-14NA, (g) CLT-PA-A, (h)CLT-PA-B，(i) CLT-23DA, (j) CLT-124BA.

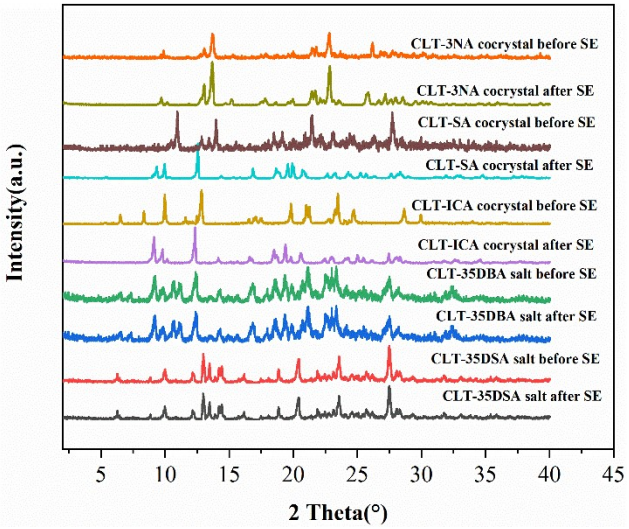

Fig. S13 PXRD patterns of multicomponent crystals before and after equilibrium solubility experiments (SE).

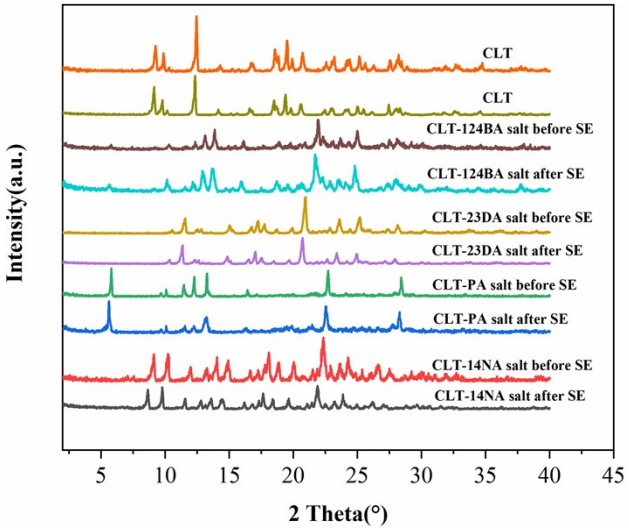

Fig. S14 PXRD patterns of CLT and its multicomponent crystals before and after equilibrium solubility experiments (SE).

Supporting Tables:

Table S1. Preparation of CLT Multicomponent Crystals

complex	detail
	liquid-assisted grinding method
CLT-35DSA	CLT: 0.1mmol; 35DSA: 0.1mmol; Ethanol: 10μL

CLT-35DBA	CLT: 0.1mmol; 35DBA: 0.1mmol; Ethanol: 10μL
CLT-ICA	CLT0.1mmol; 35DSA: 0.1mmol; Ethanol: 10μL
CLT-SA	CLT: 0.1mmol; SA: 0.1mmol; Ethanol: 10μL
CLT-3NA	CLT: 0.1mmol; 3NA: 0.1mmol; Ethanol: 10μL
CLT-14NA	CLT: 0.1mmol; 14NA: 0.1mmol; Ethanol: 10μL
CLT-PA	CLT: 0.1mmol; PA: 0.1mmol; Ethanol: 10μL
CLT-23DA	CLT: 0.1mmol; 23DA: 0.1mmol; Ethanol: 10μL
CLT-124BA	CLT: 0.1mmol; 124BA: 0.1mmol; Ethanol: 10μL
	Slurry suspension method
CLT-35DSA	CLT:0.01mol; 35DSA: 0.01mol; Ethanol:10mL
CLT-35DBA	CLT:0.01mol; 35DBA: 0.01mol; Ethanol:10mL
CLT-ICA	CLT:0.01mol; 35DSA: 0.01mol; Acetonitrile:10mL
CLT-SA	CLT:0.01mol; SA: 0.01mol; Acetonitrile:10mL
CLT-3NA	CLT:0.01mol; 3NA: 0.01mol; Ethanol:10mL
CLT-14NA	CLT:0.01mol; 14NA: 0.01mol; Ethanol:10mL
CLT-PA	CLT:0.01mol; PA: 0.01mol; Methanol:10mL
CLT-23DA	CLT:0.01mol; 23DA: 0.01mol; Ethanol:10mL
CLT-124BA	CLT:0.01mol; 124BA: 0.01mol; Ethanol:10mL
	Slowly solvent evaporation method
CLT-35DSA	CLT:0.004mol; 35DSA: 0.04mol; Ethanol:4mL
CLT-35DBA	CLT:0.004mol; 35DBA: 0.04mol; Ethanol:4mL
CLT-ICA	CLT:0.004mol; ICA: 0.04mol; Acetonitrile:4mL
CLT-SA	CLT:0.004mol; SA: 0.04mol; Acetonitrile:4mL
CLT-3NA	CLT:0.004mol; 3NA: 0.04mol; Ethanol:4mL
CLT-14NA	CLT:0.004mol; 14NA: 0.04mol; Ethanol:4mL
CLT-PA	CLT:0.004mol; 35DBA: 0.04mol; Methanol:4mL
CLT-23DA	CLT:0.004mol; 23DA: 0.04mol; Ethanol:4mL
CLT-124BA	CLT:0.004mol; 124BA: 0.04mol; Ethanol:4mL

Table S2. Calculation Results of Excess Enthalpy for 1:1 at 25℃

	coformer	ΔH_{ex}(kcal/mol)	new form	
1	3,5-dinitrosalicylic acid	-5.973	√	★
2	pyromellitic acid	-5.691	√	★
3	oxalic acid	-5.631	√	
4	2,3,4-trihydroxybenzoic acid	-5.411	√	
5	3,5-dinitrobenzoic acid	-4.857	√	★
6	2,4,6-trihydroxybenzoic acid	-4.728	√	☆
7	1,2,4-benzenetricarboxylic acid	-4.670	√	★
8	dimethylglyoxime	-4.415	√	
9	2,5-dihydroxybenzoic acid	-4.406	√	☆
10	2,3-dihydroxybenzoic acid	-4.375	√	★
11	citrazinic acid	-4.342		
12	fumaric acid	-4.325		
13	2,5-furandicarboxylic acid	-4.191	√	
14	4-nitrosalicylic acid	-4.100		
15	barbituric acid	-3.980	√	

16	terephthalic acid	-3.958		
17	3-nitrobenzoic acid	-3.788	√	★
18	1,4-naphthalenedicarboxylic acid	-3.720	√	★
19	thymol	-3.666		
20	hydroquinone	-3.649		
21	2,2-diphenylacetic acid	-3.260		
22	sasapyrine	-3.123		
23	vanillic acid	-3.093		
24	maleic acid	-3.084	√	☆
25	2,6-pyridinedicarboxylic acid	-2.956	√	
26	syringic acid	-2.951	√	★
27	acetylsalicylic acid	-2.946	√	
28	glutaric acid	-2.933		
29	1,4-cyclohexanedicarboxylic acid	-2.897		
30	pimelic acid	-2.813	√	☆
31	suberic acid	-2.800	√	☆
32	1-hydroxy-2-naphthoic acid	-2.421		
33	glycolic acid	-2.286		
34	acipimox	-2.222		
35	indole-6-carboxylic acid	-2.176	√	★
36	4-aminobenzoic acid	-2.143		
37	1H-pyrazole-4-carboxylic acid	-1.838		
38	p-acetylamino benzoic acid	-1.721		
39	2-hydroxypyridine	-1.671		
40	acetaminophen	-1.605		
41	2-pyrazinecarboxylic acid	-1.564		
42	prothioconazole	-1.545		
43	4-hydroxy-3-methoxy-benzaldehyde	-1.528		
44	3-aminopyrazine-2-carboxylic acid	-1.495		
45	quinaldic acid	-1.457		
46	kojic acid	-1.394		
47	4-hydroxybenzamide	-1.313		
48	n-acetylglycine	-1.292		
49	isonipecotic acid	-1.187		
50	riluzole	-1.111		
51	diflubenzuron	-1.110		
52	ticagrelor	-1.103		
53	rhodanine	-1.077		
54	saccharin	-1.028		
55	L-tyrosine	-0.964		
55	phenoxazine	-0.905		

56	celecoxib	-0.823
57	8-hydroxyquinoline	-0.820
58	fenbendazole	-0.811
59	D-mannitol	-0.738
60	L(+)-2-aminobutyric acid	-0.712
61	salicylamide	-0.703
62	daminozide	-0.695
63	hydrochlorothiazide	-0.668
64	tris base	-0.624
65	2,4-dihydroxy-6-methylpyridine	-0.594
66	L-threonine	-0.568

√ Form multicomponent crystals proved by PXRD.

★ Single crystal synthesized in this work.

☆ Single crystals that has been reported.[1]

Table S3. Melting points and Fusion enthalpy of CLT, Coformers, and the Salts/Cocrystals

	T_m (℃)	uncertainty (℃) [a]	$\Delta_{fus}H$ (J/g)	Uncertainty (J/g) [a]
CLT	142.42	0.02	114.73	1.45
35DSA	172.34	0.03	150.88	1.29
35DBA	205.01	0.38	142.32	0.81
ICA	253.06	0.53	225.37	0.90
SA	207.27	0.81	190.04	1.47
3NA	141.28	0.12	135.11	1.66
14NA	314.46	0.35	287.81	1.52
PA	256.48	0.57	535.12	1.48
23DA	206.10	0.04	221.23	0.76
124BA	218.73	0.50	428.03	1.42
CLT-35DSA	171.44	0.83	86.23	1.18
CLT-35DBA	164.56	0.43	86.98	0.95
CLT-ICA	127.95	0.61	101.51	1.19
CLT-SA	94.69	0.21	114.24	1.04
CLT-3NA	118.53	0.57	88.14	1.67
CLT-14NA	109.49	0.28	85.33	0.91
CLT-PA	188.12	0.43	89.32	0.18
CLT-23DA	144.56	0.47	117.41	1.74
CLT-124BA	166.31	0.50	74.49	1.04

[a] The uncertainty is calculated at a confidence level of 0.95.

Table S4. Hydrogen Bond Geometrical Parameters of Cocrystals and Salts

D–H···A	d(H···D)/Å	d(H···A)/Å	d(D···A)/Å	θ(D–H···A)/°	symmetry code
CLT-35DSA					

N1-H1···O1	0.81(3)	1.82(3)	2.610(3)	167(3)	
C8-H8···O2	0.93	2.46	3.316(4)	154	1-x,-y,1-z
C9-H9···O6	0.93	2.55	3.354(3)	146	2-x,1-y,1-z
C15-H15···O5	0.93	2.59	3.264(4)	130	2-x,1-y,1-z
C23-H23···N2	0.93	2.58	2.897(3)	101	
C27-H27···O4	0.93	2.55	3.351(4)	145	-1+x,y,1+z
CLT-35DBA					
N1-H1···O2	0.91(2)	1.67(2)	2.576(2)	169(2)	x,1+y,z
O7-H7A···O1	0.86(3)	1.85(3)	2.700(3)	174(2)	
C8-H8···O7	0.93	2.29	3.130(3)	149	
C9-H9···O6	0.93	2.32	3.093(3)	140	x,1+y,z
C17-H17···O2	0.93	2.57	3.495(2)	170	1-x,2-y,1-z
CLT-ICA					
O1-H1···O2	0.82	1.82	2.6424(17)	175	-x,-y,2-z
N3-H3···N1	0.92(2)	2.04(2)	2.9280(18)	164.1(17)	
C21-H21···N2	0.93	2.50	2.8371(19)	101	
C28-H28···O2	0.93	2.45	3.288(2)	150	-x,-y,2-z
CLT-SA					
O1-H1···O3	0.82	2.25	2.686(2)	114	
O1-H1···N1	0.82	1.95	2.724(2)	157	
O5-H5···O4	0.83(4)	1.77(4)	2.590(2)	170(6)	2-x,1-y,2-z
C7-H7B···Cl1	0.95(2)	2.83(3)	3.658(3)	146.4(19)	x,1+y,z
C15-H15···N2	0.93	2.53	2.860(3)	101	
C28-H28···O1	0.93	2.55	3.289(3)	137	x,-1+y,z
CLT-3NA					
O1-H1···N1	0.86(2)	1.74(2)	2.579(2)	164(3)	
C17-H17···O2	0.93	2.53	3.369(2)	151	1-x,1-y,1-z
C23-H23···N2	0.93	2.54	2.857(2)	101	
C27-H27···O3	0.93	2.51	3.274(3)	140	1+x,y,1+z
CLT-14NA					
N1-H1···O2	0.86	1.81	2.605(4)	153	1-x,-y,1-z
O4-H4···O1	0.82	1.67	2.492(3)	175	1+x,y,z
O5-H5···O2	0.82	2.06	2.838(8)	159	x,1+y,z
C8-H8···O1	0.93	2.48	3.019(3)	117	
C11-H11···O3	0.93	2.39	2.988(4)	122	
C13-H13···O4	0.93	2.59	3.266(3)	130	-1+x,y,z
C15-H15···O5	0.93	2.36	3.24(2)	157	
C18-H18···O1	0.93	2.56	3.424(3)	155	
C24-H24···N2	0.93	2.52	2.863(4)	102	
C31-H31···O3	0.93	2.59	3.158(4)	120	-1+x,1+y,z
C32-H32···O3	0.93	2.48	3.106(4)	124	-1+x,1+y,z
C37-H37A···O5	0.97	2.54	3.290(13)	134	2-x,1-y,1-z
C37-H37A···O6	0.97	2.11	2.92(2)	139	2-x,1-y,1-z
CLT-PA					
N1-H1···O8	0.86	1.88	2.708(3)	161	
O1-H1A ···O13	0.82	1.82	2.621(3)	166	
O1-H1A···O14	0.82	2.50	2.989(3)	120	
N3-H3···O16	0.86	1.92	2.738(3)	158	
O4-H4A···O15	0.82	1.80	2.609(3)	170	1+x,y,z
O9-H9···O5	0.82	1.81	2.626(3)	176	-1+x,1+y,z

O9-H9···O6	0.82	2.60	3.100(2)	121	-1+x,1+y,z
O12-H12A···O7	0.82	1.81	2.624(3)	170	x,1+y,z
C4-H4···O13	0.93	2.29	2.673(3)	104	
C7-H7···O9	0.93	2.40	2.739(3)	101	
C7-H7···O16	0.93	2.31	2.686(3)	104	
C13-H13···O10	0.93	2.28	3.051(3)	140	1-x,2-y,1-z
C31-H31···O3	0.93	2.58	3.267(4)	131	2-x,1-y,1-z
C31-H31···O3	0.93	2.58	3.267(4)	131	2-x,1-y,1-z
C32-H32···N4	0.93	2.40	2.787(3)	105	
C35-H35···O1	0.93	2.43	2.749(3)	100	
C35-H35···O8	0.93	2.30	2.682(3)	104	
C38-H38···O5	0.93	2.29	2.670(3)	104	
C45-H45···O2	0.93	2.45	3.142(3)	131	2-x,1-y,1-z
C64-H64···N2	0.93	2.41	2.792(3)	105	
CLT-23DA					
N1-H1···O1	0.86	1.85	2.649(3)	153	
N1-H1···O2	0.86	2.47	3.006(3)	121	
O1-H1A···O4	0.82	1.71	2.522(3)	171	3/2-x,1/2+y,1/2+z
O2-H2···O3	0.82	1.81	2.531(3)	146	
C8-H8···O3	0.93	2.40	3.200(3)	144	3/2-x,1/2+y,1/2+z
C13-H13···Cl1	0.93	2.76	3.215(3)	111	
C22-H22···O4	0.93	2.40	3.214(4)	146	3/2-x,3/2+y,1/2+z
C25-H25···O4	0.93	2.55	3.312(3)	140	1-x,-y,1/2+z
C28-H28···N2	0.93	2.36	2.750(3)	105	
CLT-124BA					
N1-H1···O2	0.86	1.89	2.7208(16)	163	
O1-H1A···O6	1.16(3)	1.29(3)	2.4465(15)	176(3)	x,-1+y,z
O1-H1A···O5	1.16(3)	2.45(3)	3.0851(16)	112.1(18)	
O3-H3···O5	0.82	1.62	2.4372(17)	177	
C3-H3A···O1	0.93	2.36	2.7073(17)	102	
C3-H3A···O4	0.93	2.28	2.6634(18)	104	
C6-H6···O6	0.93	2.29	2.6635(18)	104	
C11-H11···O4	0.93	2.39	3.1372(18)	137	-x,1-y,1-z
C25-H25···N2	0.93	2.60	2.9074(19)	100	
C25-H25···O4	0.93	2.58	3.328(2)	137'	-x,1-y,1-z
C29-H29···O4	0.93	2.49	3.2111(18)	134	

Table S5. Summary of the Various Contact Contributions to the Hirshfeld Surface Area in all Cocrystals and Salts

compound	H-H %	O-H %	C-H %	Cl-H %	C-C %	O-C %	Cl-O %	N-H %	N-O %	Cl-C %	N-C %
CLT											
CLT-35DSA	39.7	23.9	19.3	7.8	2.7	1.7	1.5	1.1	0.8	0.7	0.5
CLT-35DBA	45.9	20	20.7	7.9	0.3	1.4	0.4	1.5	0	0.8	1.1
CLT-ICA	53.5	3.6	28.6	7.3	0	0.1	0.1	5.1	0	1.4	0.3
CLT-SA	50	6.6	27.6	7.4	0.5	0	0	6.6	0.5	1.2	0.1
CLT-3NA	47.3	11.2	20.5	9.2	3.9	0.6	0.7	4.9	0.3	1.5	0
CLT-14NA	54.3	10.7	22.7	7.8	2.1	0.4	0.4	0.7	0.2	0.6	0
CLT-PA-A	39.8	21.4	20.4	11.8	2.1	1.8	0	0.4	0.6	1.7	0
CLT-PA-B	46.5	19.9	18	10.5	1.9	1.7	0	0.6	0.5	0.4	0

CLT-23DA	48.2	10.8	26.5	10.3	2.2	0.6	0	1.0	0	0.2	0
CLT-124BA	45.4	16.9	22.4	9.4	0.3	0.3	0.8	0.8	0.2	0.4	0

Table S6. Solubility of CLT and Multicomponent Crystals in Ethanol -Water (4:6 v/v) at 37 °C

	Solubility(mg/ml)
CLT	1.01 ± 0.03
CLT-35DSA salt	0.12 ± 0.03
CLT-35DBA salt	0.51 ± 0.04
CLT-ICA cocrystal	1.55 ± 0.03
CLT-SA cocrystal	1.95 ± 0.02
CLT-3NA cocrystal	2.25 ± 0.03
CLT-14NA salt	2.4 ± 0.03
CLT-PA salt	0.38 ± 0.02
CLT-23DA salt	3.16 ± 0.04
CLT-124BA salt	2.89 ± 0.02

[1]. S. Mittapalli, M. K. C. Mannava, U. B. R. Khandayilli, S. Allu and A. Nangia, Cryst. Growth Des., 2015, 15, 2493-2504.