Cocrystal/Salt Synthesis of Flucytosine Drug: Structural and Stability Aspects

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Table S1. Geometrical parameters of intermolecular interactions in the molecular salt/cocrystals of FLC.

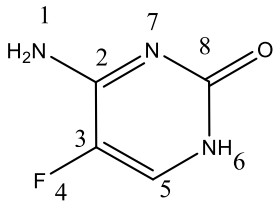
Cocrystal/Salt	D-H···A[a]	D-H···A/ Å	D···A/ Å	∠D-H···A/ °	Symmetry Code
FLC-2,3HBA	O3-H10···O2	1.714	2.448	147.96	x, y, z
	N6-H3···O6	1.919	2.772	170.72	x, y, z
	C8-H7···O5	2.398	3.292	161.25	-x+1, -y, -z
	C1-H1···F2	2.435	3.391	167.14	x+1, y+1, z
	N3-H9···O2	1.923	2.725	158.63	x, y, z+1
	N4-H4···N2	2.122	3.008	175.65	x, y, z
	N3-H8···O4	2.324	3.041	144.17	-x+1, -y+1, -z+1
	N4-H5···O1	1.758	2.751	179.83	x, y, z+1
	N4-H5···O2	2.602	3.247	122.58	x, y, z+1
	N5-H2···O5	1.958	2.804	175.83	-x+2, -y+1, -z
	N1-H6···O6	1.853	2.760	179.36	-x+1, -y, -z
	O4-H11···O3	2.303	2.728	116.71	x, y, z
	O4-H11···O3	2.117	2.783	147.02	-x+1, -y+1, -z
FLC-2,5HBA	O4-H11···O2	1.718	2.506	160.43	x-1, y, z
	O8-H5···O1	1.711	2.510	164.21	x, y-1, z
	O5-H16···O3	1.877	2.592	145.06	x, y, z
	O9-H6···O7	1.878	2.595	145.40	x, y, z
	O6-H13···O1	2.030	2.768	149.58	x-1, y, z
	O10-H9···O2	2.030	2.764	148.66	x, y, z
	C10-H12···N5	2.616	3.479	154.66	x-1, y, z
	C7-H10···N2	2.606	3.470	154.73	x, y, z
	C17-H17···O5	2.333	3.211	157.36	x, -y+3/2, z-1/2
	C22-H1···O9	2.338	3.217	157.55	x+1, -y+1/2, z+1/2
	N4-H19···O4	2.186	3.044	161.93	x+1, y, z
	N1-H3···O8	2.070	3.040	169.41	x, y, z
	N4-H20···O10	2.063	2.866	156.59	x, y, z
	N1-H4···O6	1.981	2.855	149.89	x+1, y-1, z
	N6-H18···O7	1.958	2.827	166.02	x, y+1, z
	N3-H2···O3	1.959	2 2.829	167.87	x+1, y, z
FLC-3,5HBA	O8-H8···O15	1.966	2.738	162.24	x, y, z-1

	O4-H4···O15	1.916	2.732	173.14	x, y, z
	O7-H7···O20	1.914	2.695	158.78	x, y, z
	O2-H2···O16	1.811	2.605	162.44	x, y, z
	N9-H9A···O5	1.886	2.721	163.22	-x, -y, -z+1
	N9-H9B···O4	2.053	2.900	168.01	-x+1, -y+1, -z+2
	N8-H8A···O9	1.841	2.700	177.52	-x, -y, -z+1
	N5-H5···O13	2.023	2.873	169.59	x, y, z
	N10-H10A···O11	1.910	2.765	172.64	-x+2, -y+1, -z+1
	N10-H10B ···O8	2.024	2.870	167.68	-x+1, -y, -z
	N7-H7A···O12	2.037	2.884	168.36	x, y, z
	C46-H46 ···F1	2.507	3.414	165.07	-x+1, -y+1, -z+1
	C30-H30···F2	2.502	3.393	160.34	-x+1, -y, -z+1
	C42-H42···O7	2.396	3.303	164.83	-x+1, -y+1, -z+1
	C28-H28···O2	2.397	3.290	160.81	-x+1, -y, -z+1
	N6-H6···O10	1.915	2.767	170.16	-x+2, -y+1, -z+1
FLC-2,6HBA	O5-H10···O4	1.857	2.583	146.92	x, y, z
	N1-H5···O4	1.946	2.804	174.29	x, y, z
	N1-H4···O2	1.968	2.824	172.95	x, y+1, z
	N3-H1···O6	1.905	2.746	165.48	x, y, z+1
	C2-H2···O6	2.615	3.401	142.54	-x+1, -y+2, -z+1
	N2-H3···O3	1.823	2.736	171.73	x, y, z
	O6-H11···O4	2.061	2.872	174.83	x-1/2, -y+3/2, z-1/2
	O6-H12···O1	2.027	2.800	166.40	-x+1, -y+1, -z+1]
	O2-H6···O3	1.593	2.505	155.33	x, y, z
FLC-GAA	O2-H4···N2	2.012	2.804	162.24	-x, -y+1, -z+1
	O6-H6···O1	1.762	2.579	174.40	x, y, z
	N1-H2···O4	2.194	3.054	177.01	-x+3/2, y+1/2, -z+1/2
	N3-H8···O5	2.069	2.875	155.76	x, y, z
	C11-H5···O1	2.318	3.226	165.28	-x, -y+1, -z+1
	O4-H1···O3	2.213	2.684	114.31	x, y, z
	O4-H1 ···O5	2.232	3.005	149.77	x+1/2, -y+1/2, z+1/2
	O3-H3 ··· O5	1.891	2.658	146.73	x-1/2, -y+1/2, z+1/2

FLC-GLA	C7-H9···O1	2.188	3.035	150.10	-x, y+1/2, -z+1/2
	O2-H4···O3	1.790	2.624	163.91	x, y, z
	N6-H6 ···O3	1.925	2.820	178.80	-x, y+1/2, -z+1/2
	N4-H7···N1	2.184	2.961	171.04	-x+1, y+1/2, -z+3/2
	O5-H5···O6	1.789	2.599	171.52	x, y, z
	C2-H13···O4	2.621	3.170	118.57	x, y, z
	N2-H3 ···O6	2.024	2.872	174.04	-x, y-1/2, -z+1/2
	N3-H1···O5	2.290	2.855	123.66	-x+1, y-1/2, -z+3/2
	N4-H8 ···O2	2.239	2.893	126.69	-x+1, y+1/2, -z+3/2
	C11-H2···O4	2.177	3.016	146.68	-x, y-1/2, -z+1/2
	N3-H16···N5	2.019	2.924	172.62	-x+1, y-1/2, -z+3/2

*D-donor, A-acceptor

Table S2: Torsion angles of FLC in synthesized FLC salt/cocrystal.



$\tau_{1:}$ N1-C2-C3-F4, $\tau_{2:}$ N6-C5-C3-F4, $\tau_{3:}$ C8N7C2N1

Molecular adducts	τ_1	τ_2	τ_3
FLC-2,3HBA	-0.55	-179.58	178.18
FLC-3,5HBA	0.19	-179.77	179.99
FLC-2,6HBA	-0.85	-179.46	180.00
FLC-GAA	0.54	-179.30	178.85
FLC-GLA	-2.00	-179.18	-178.84

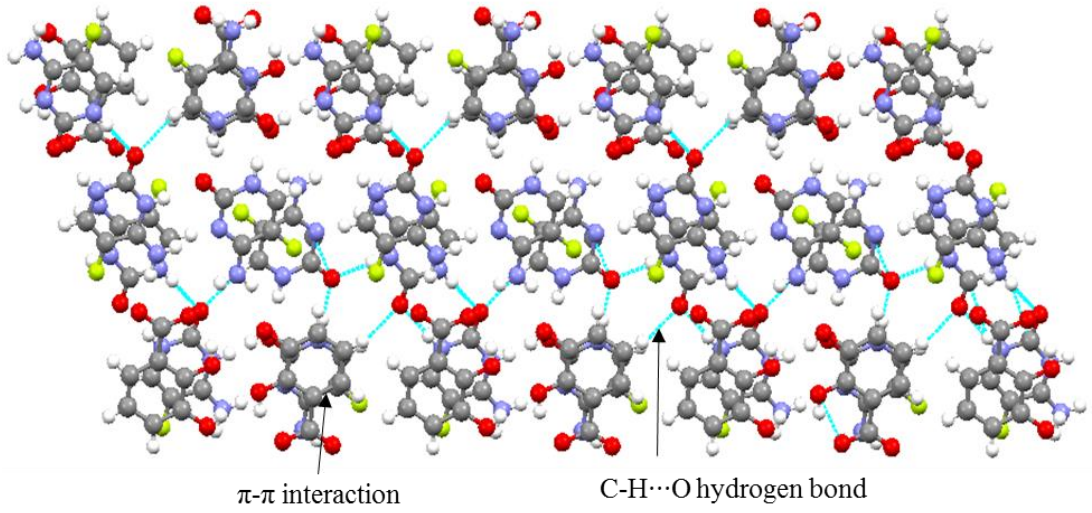


Figure S1: 3D representation of FLC-2,3HBA salt.

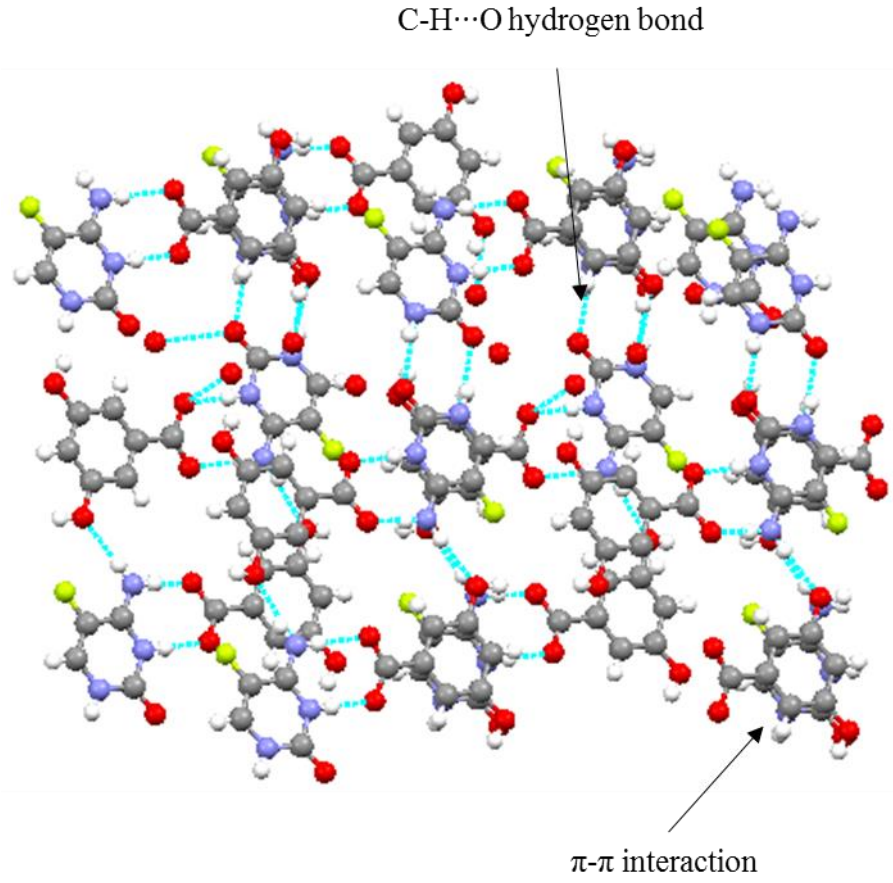


Figure S2: 3D representation of FLC-3,5HBA salt.

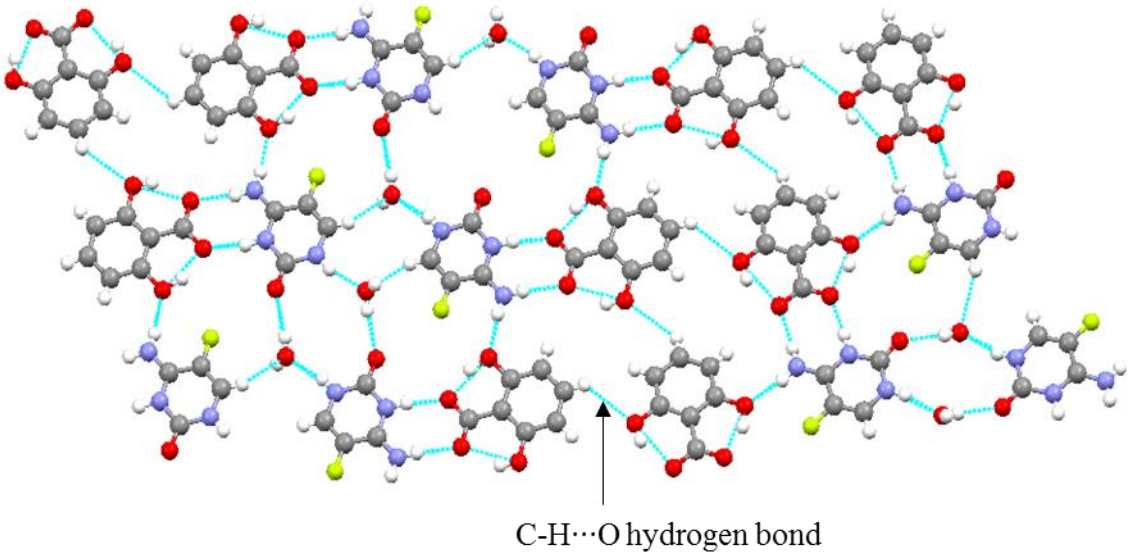


Figure S3: Weak C-H···O hydrogen bond in FLC-2,6HBA salt.

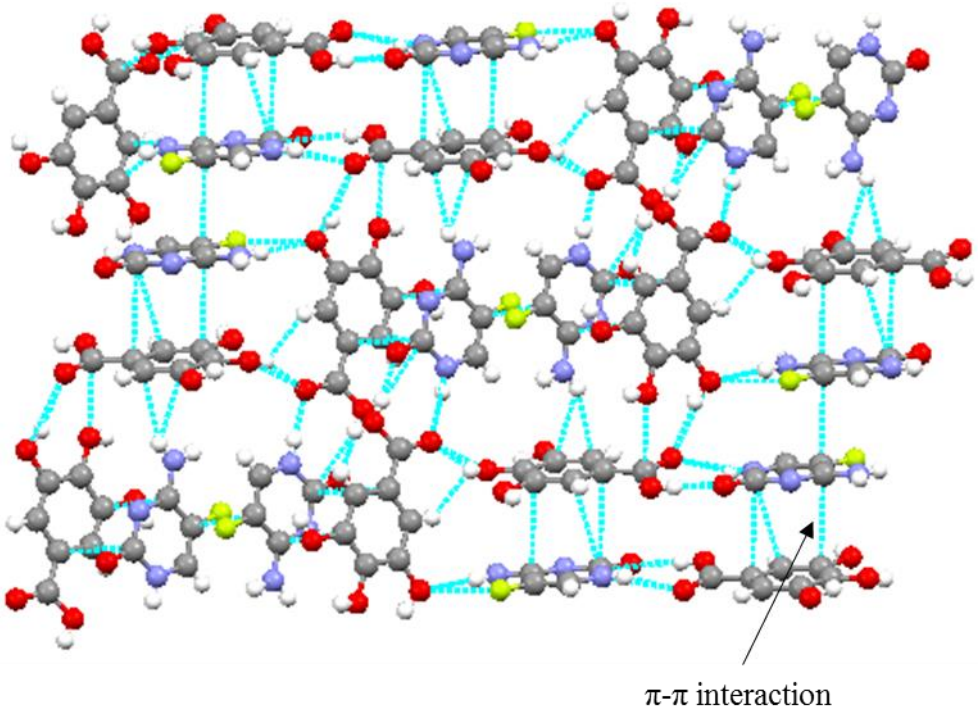
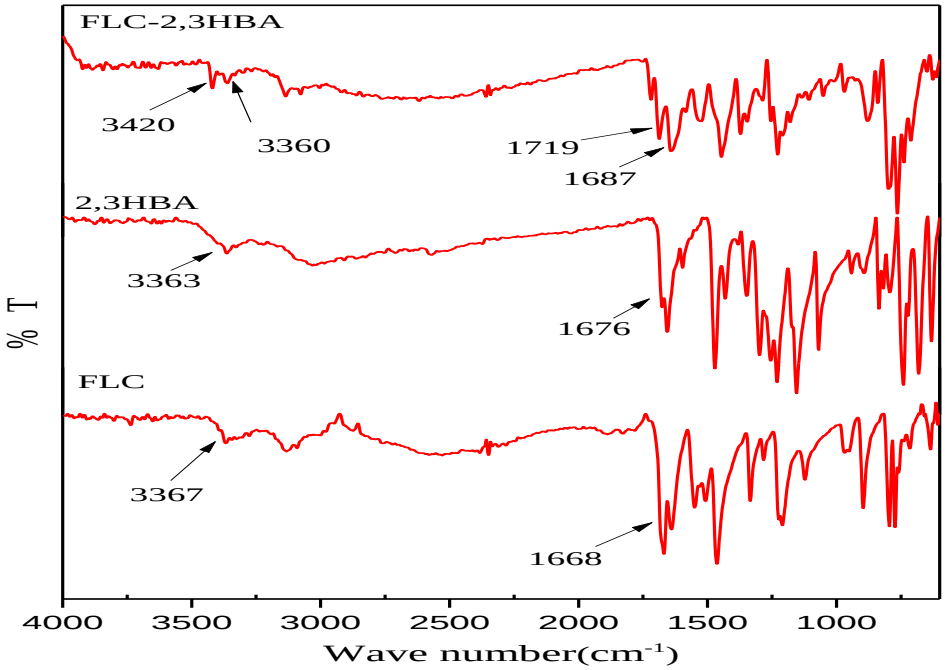
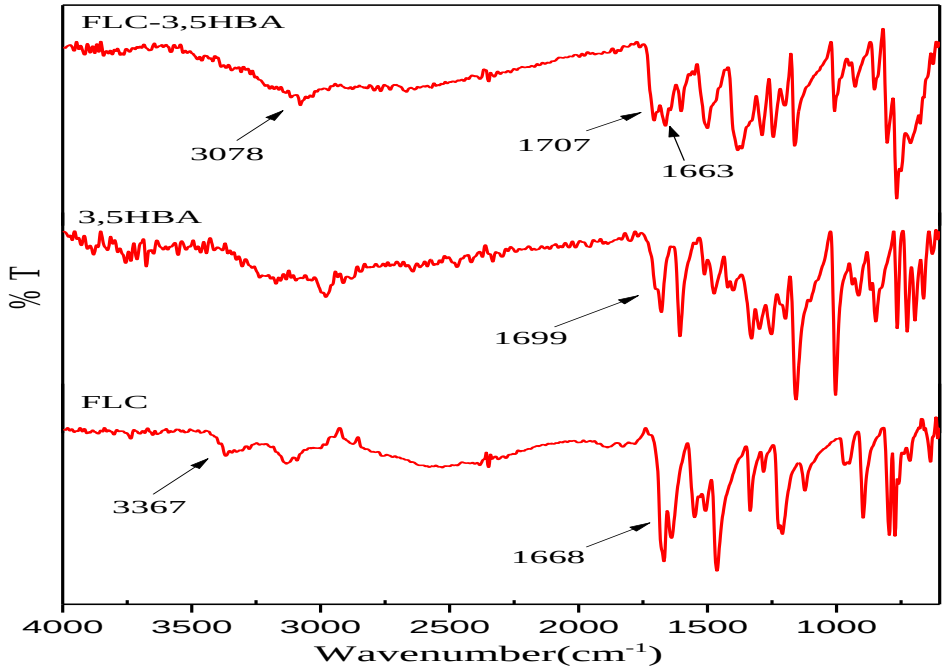


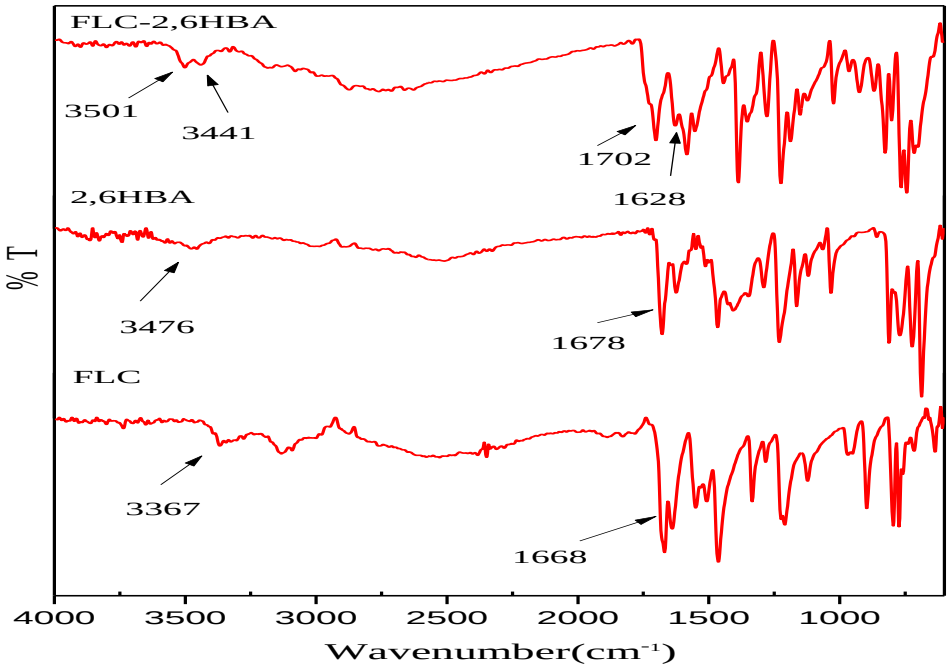
Figure S4: 3D representation of FLC-GAA cocrystal.


FLC-2,3HBA
3420
3360
1719
1687
2,3HBA
3363
1676
FLC
3367
1668
% T
4000
3500
3000
2500
2000
1500
1000
Wave number(cm⁻¹)

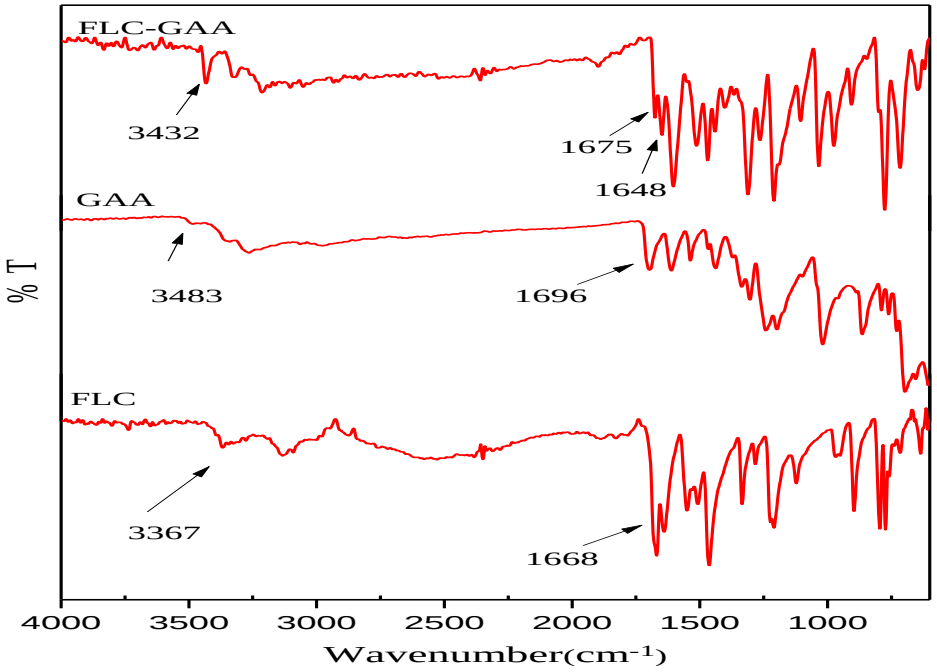
(a)


FLC-3,5HBA
3078
1707
1663
3,5HBA
1699
FLC
3367
1668
% T
4000
3500
3000
2500
2000
1500
1000
Wavenumber(cm⁻¹)

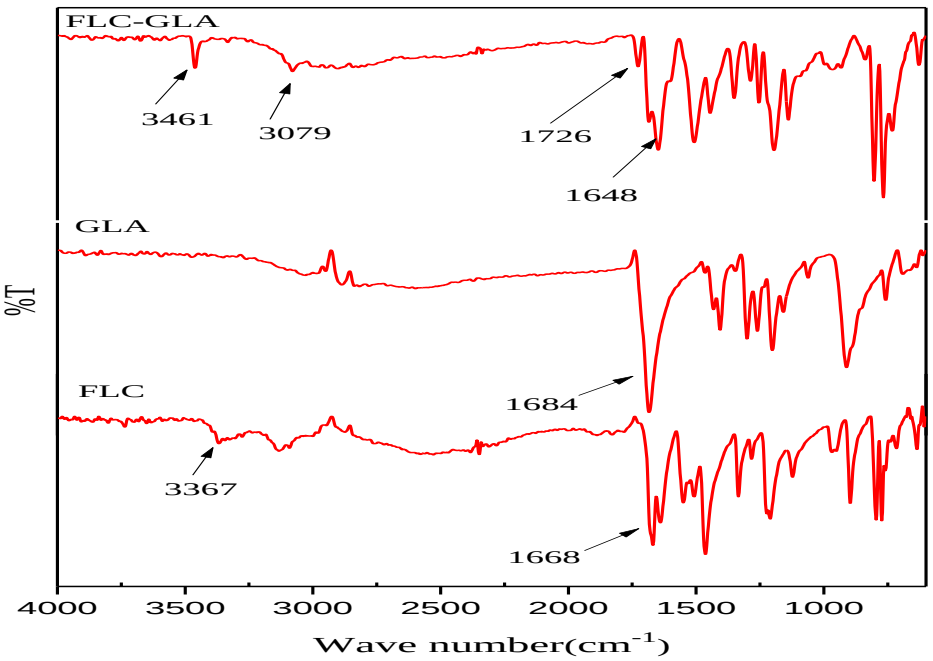
(b)


FLC-2,6HBA
3501
3441
1702
1628
2,6HBA
3476
1678
FLC
3367
1668
% T
4000
3500
3000
2500
2000
1500
1000
Wavenumber(cm⁻¹)

(c)

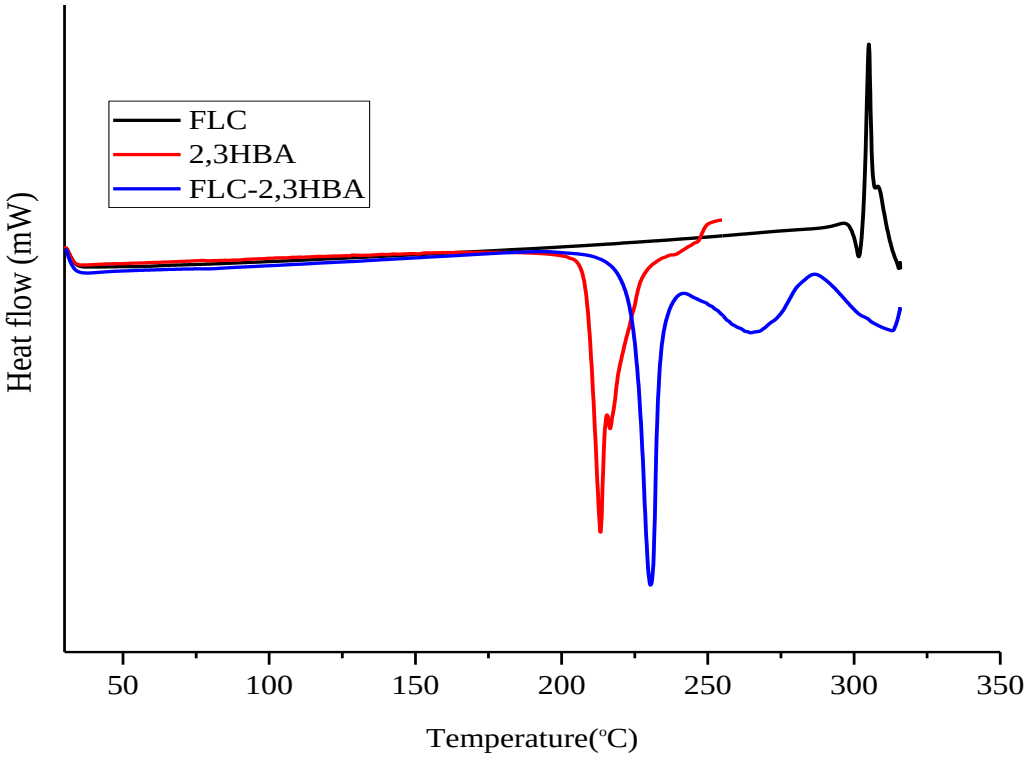

FLC-GAA
3432
1675
1648
GAA
3483
1696
FLC
3367
1668
% T
4000
3500
3000
2500
2000
1500
1000
Wavenumber(cm⁻¹)

(d)

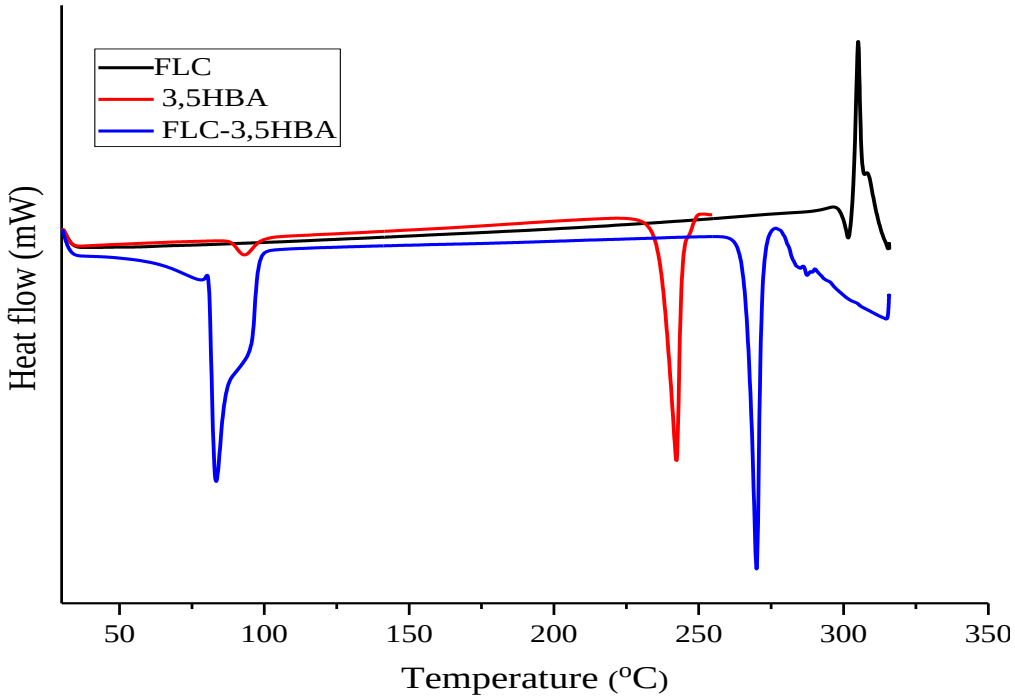


(e)

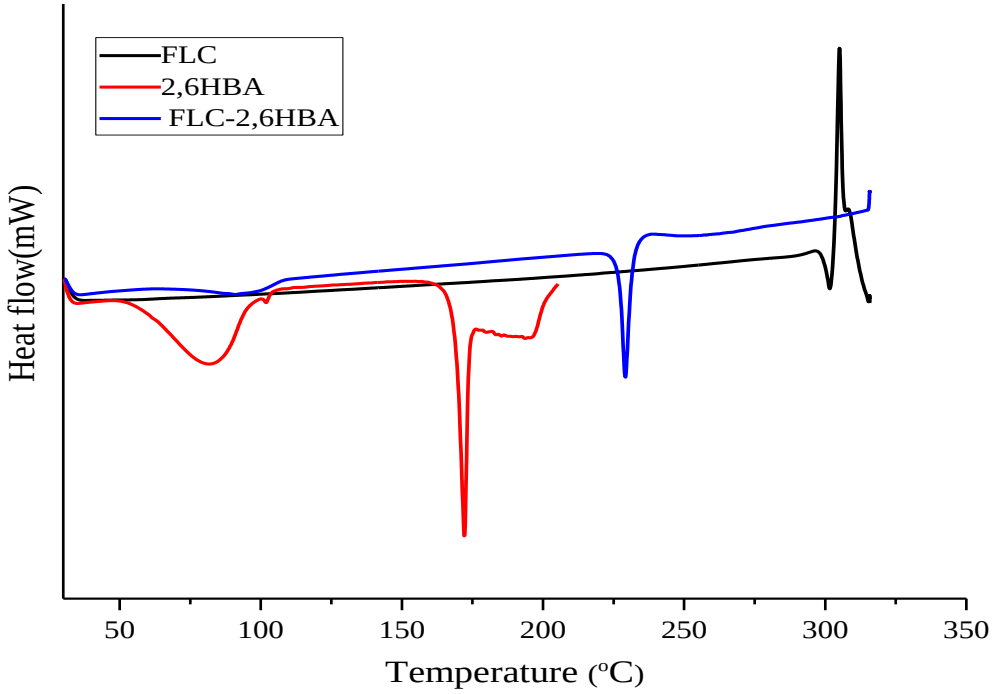
Figure S5. FT-IR comparison spectra of (a) FLC-2,3HBA, (b) FLC-3,5HBA, (c) FLC-2,6HBA, (d) FLC-GAA, and (e) FLC-GLA with respect to their respective starting materials.



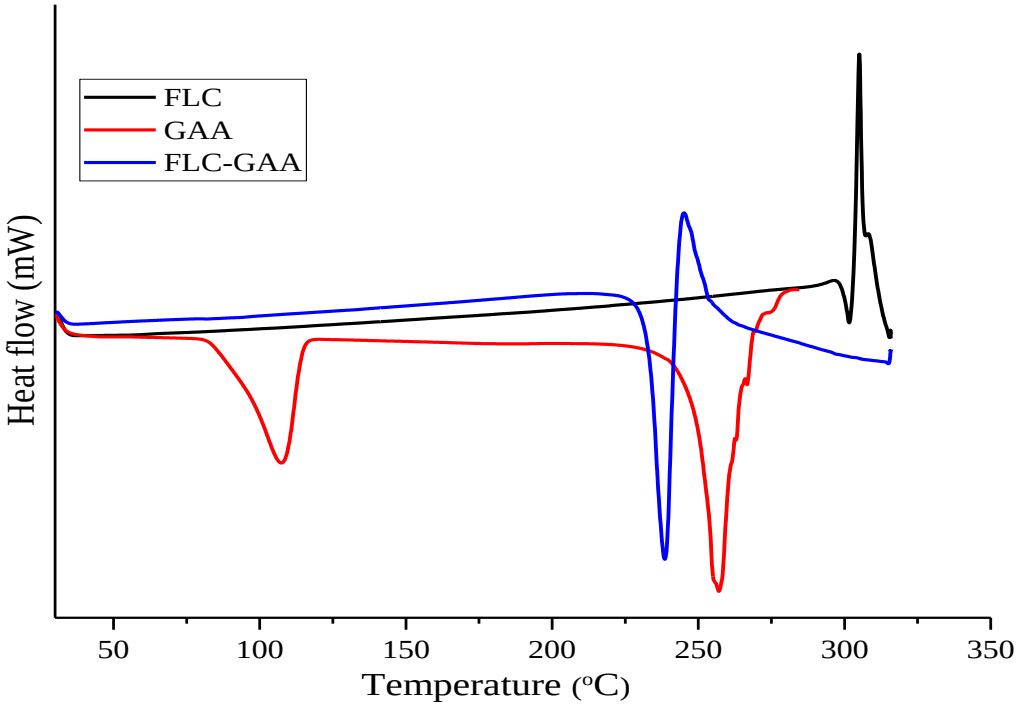
(a)


FLC
3,5HBA
FLC-3,5HBA
Heat flow (mW)
50
100
150
200
250
300
350
Temperature (°C)

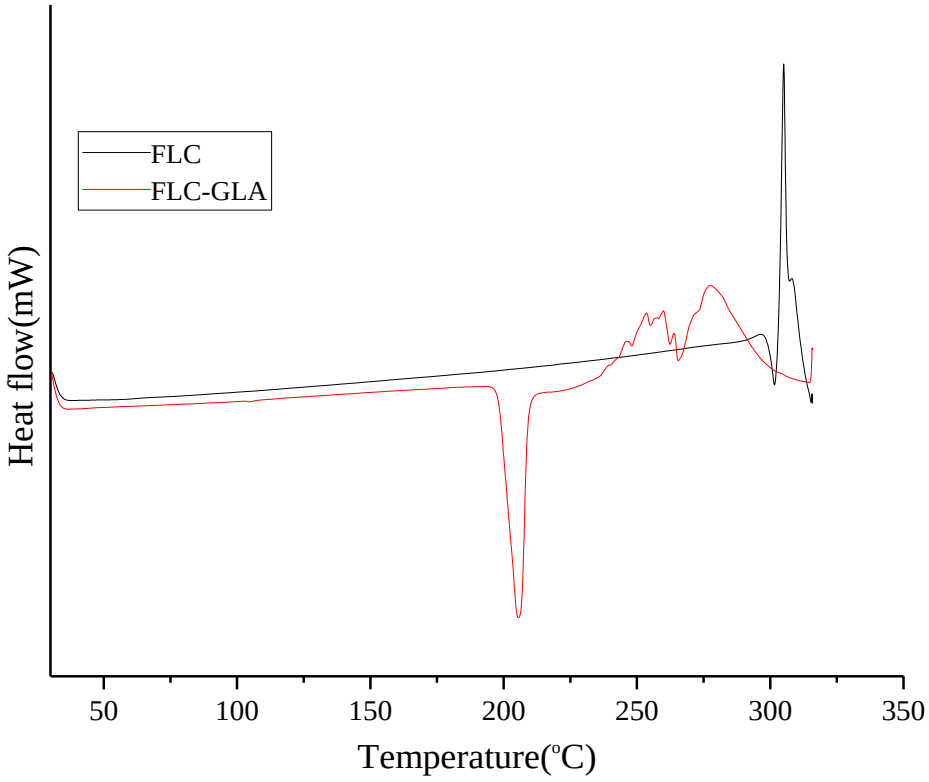
(b)


FLC
2,6HBA
FLC-2,6HBA
Heat flow(mW)
50
100
150
200
250
300
350
Temperature (°C)

(c)



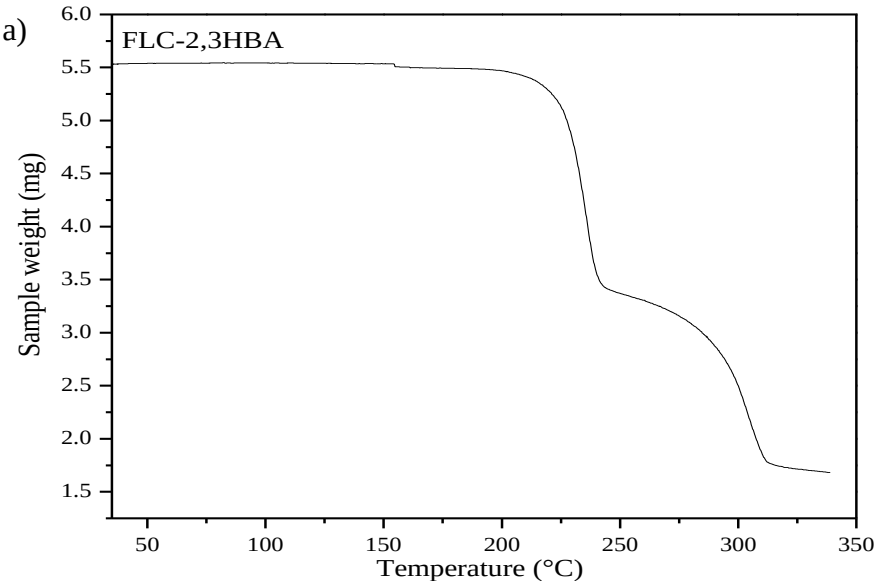
(d)



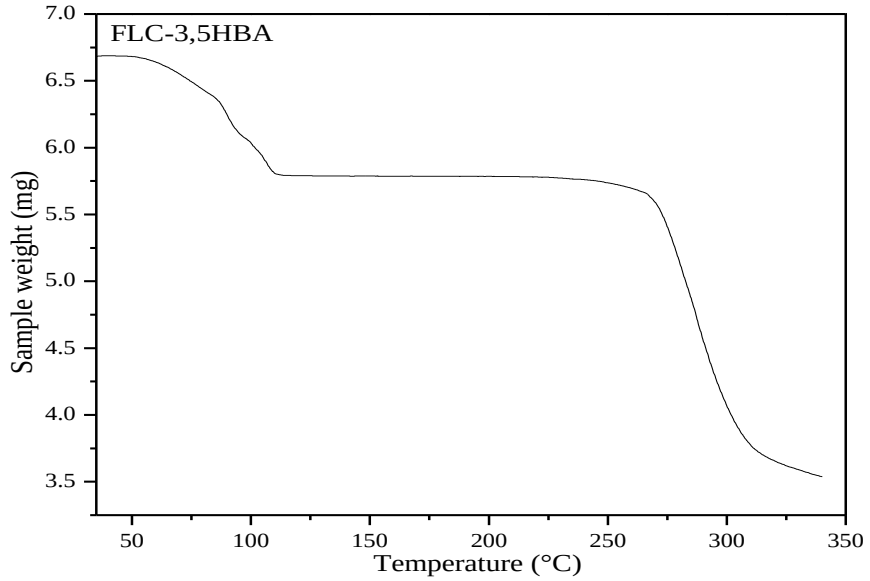
(e)

Figure S6. DSC plot of (a) FLC-2,3HBA, (b) FLC-3,5HBA (c) FLC-2,6HBA (d) FLC-GAA (e) FLC-GLA.

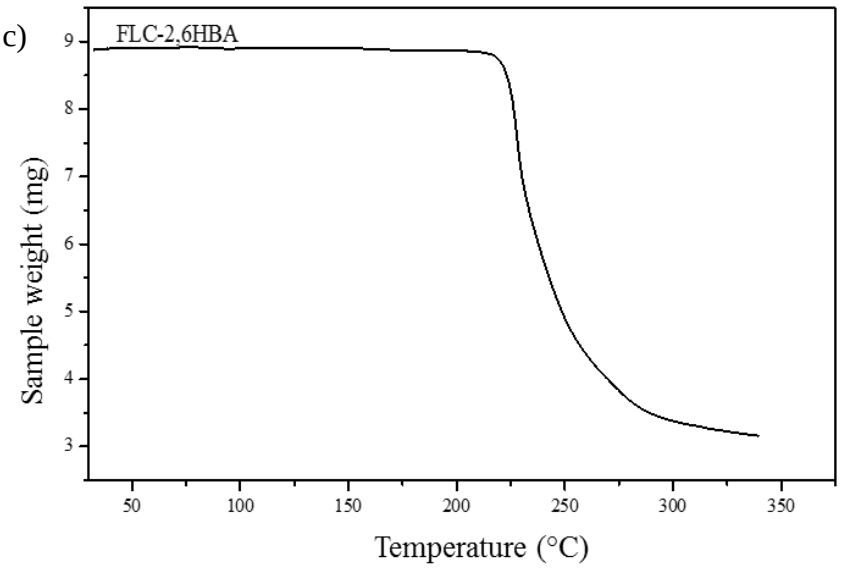
a)


FLC-2,3HBA
Sample weight (mg)
Temperature (°C)

b)


FLC-3,5HBA
Sample weight (mg)
Temperature (°C)

c)


FLC-2,6HBA
Sample weight (mg)
Temperature (°C)

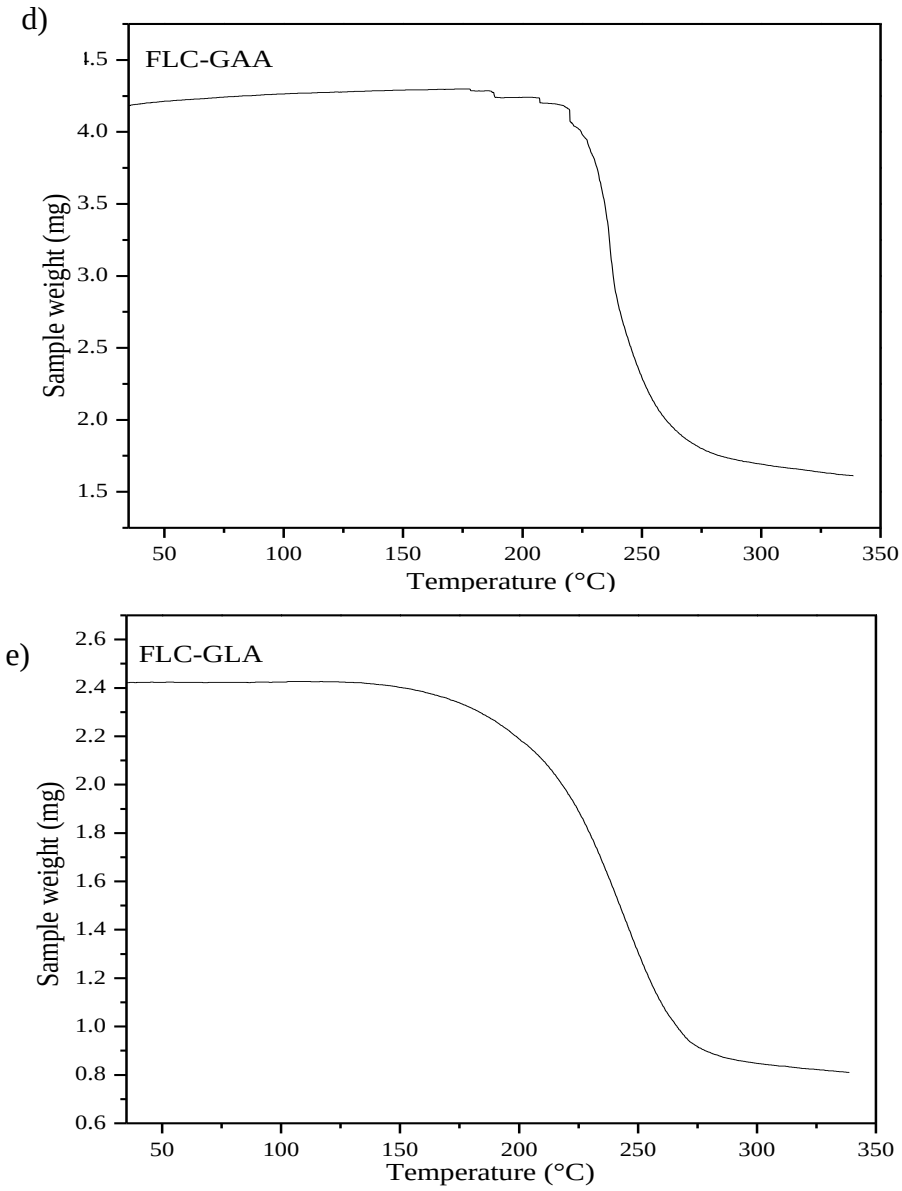
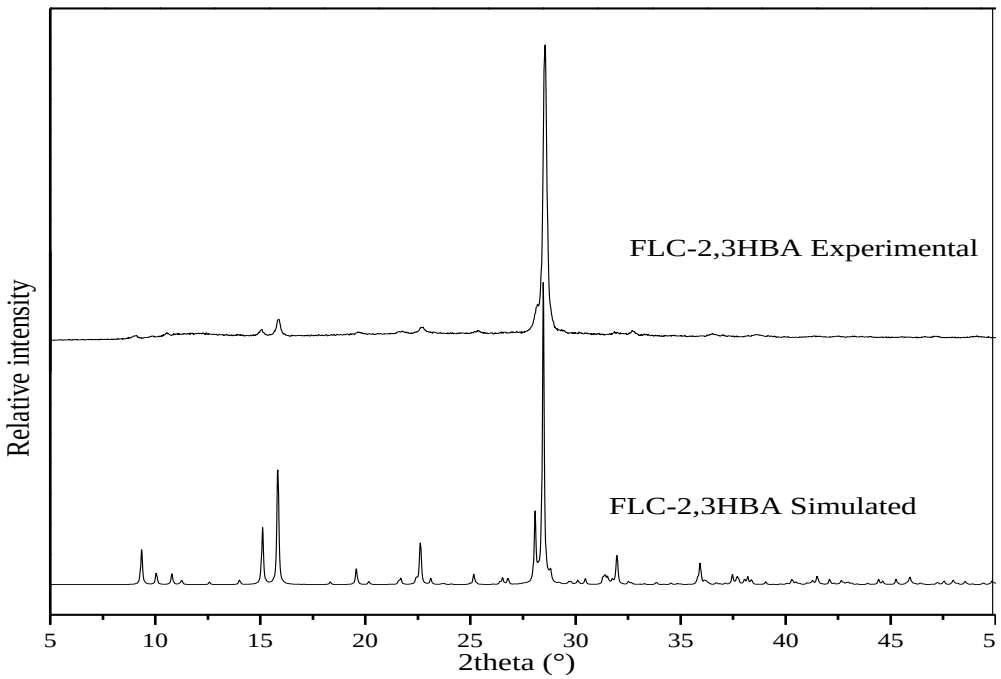
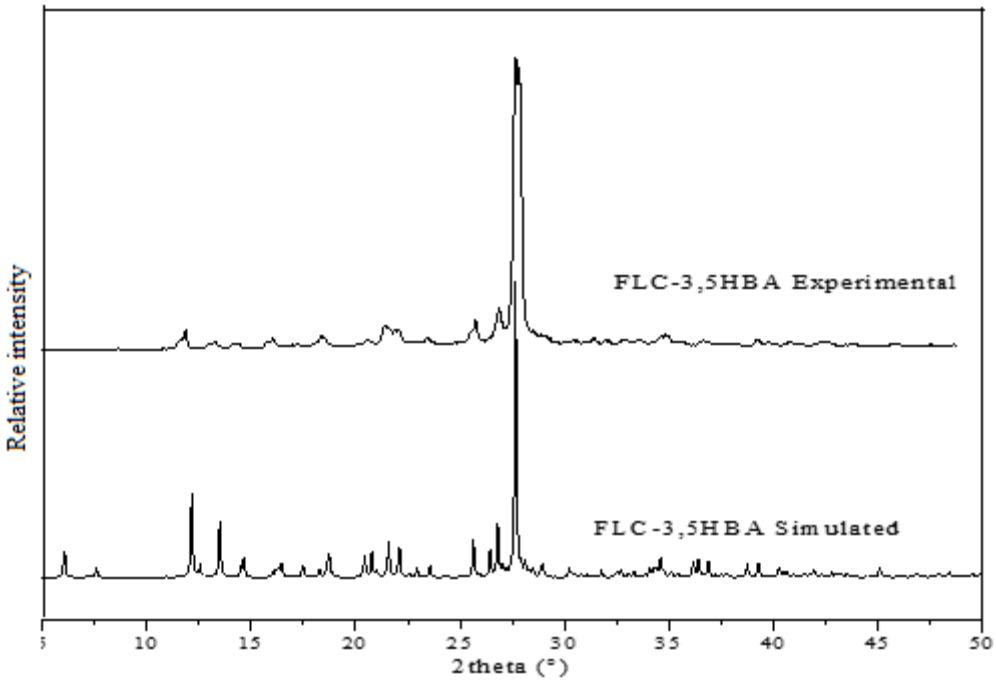


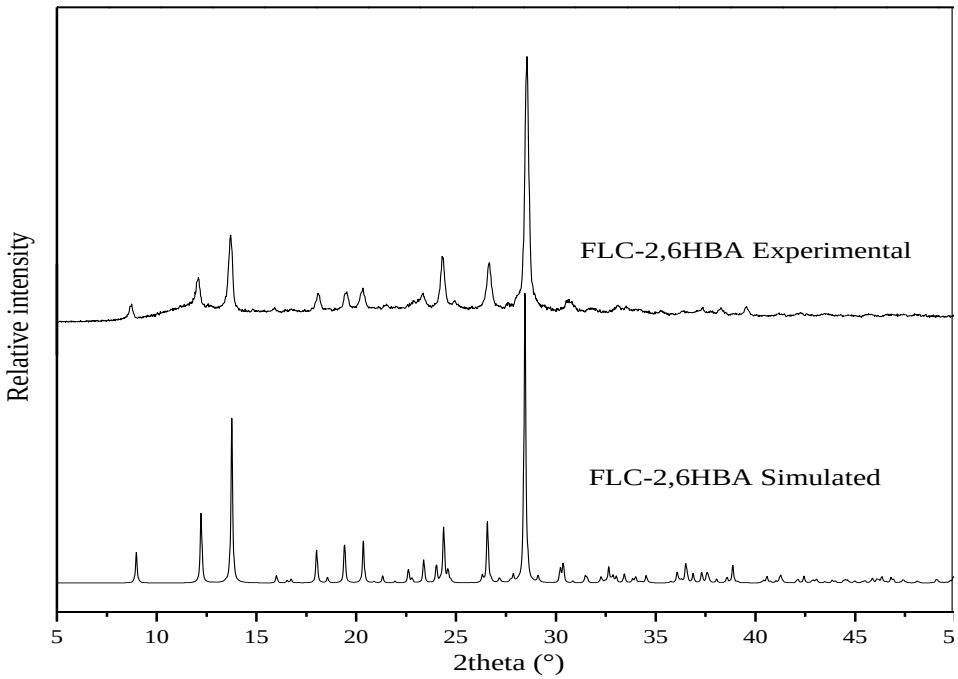
Figure S7: TGA plots of FLC salt/cocrystal; a) FLC-2,3HBA, b) FLC-3,5HBA, c) FLC-2,6HBA, d) FLC-GAA, and e) FLC-GLA.


FLC-2,3HBA Experimental
FLC-2,3HBA Simulated
Relative intensity
5
10
15
20
25
30
35
40
45
5
2theta (°)

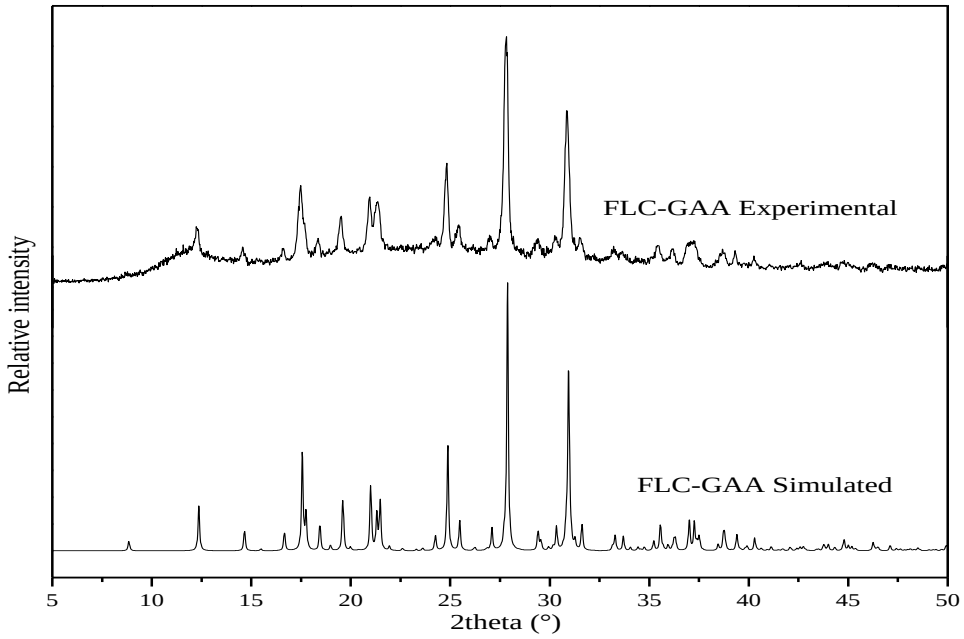
(a)


FLC-3,5HBA Experimental
FLC-3,5HBA Simulated
Relative intensity
10
15
20
25
30
35
40
45
50
2theta (°)

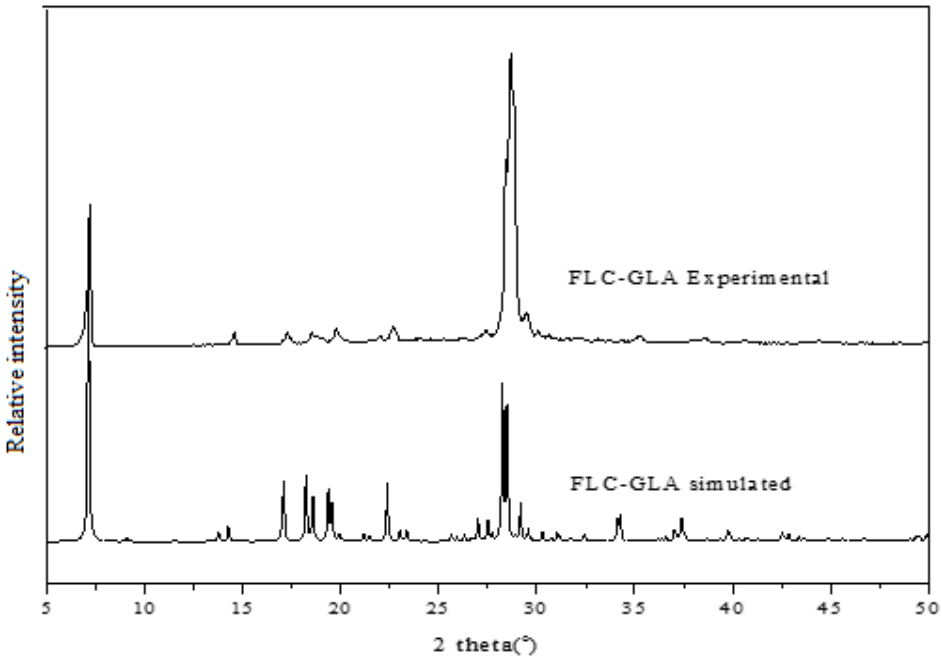
(b)


Relative intensity
FLC-2,6HBA Experimental
FLC-2,6HBA Simulated
5
10
15
20
25
30
35
40
45
5
2theta (°)

(c)

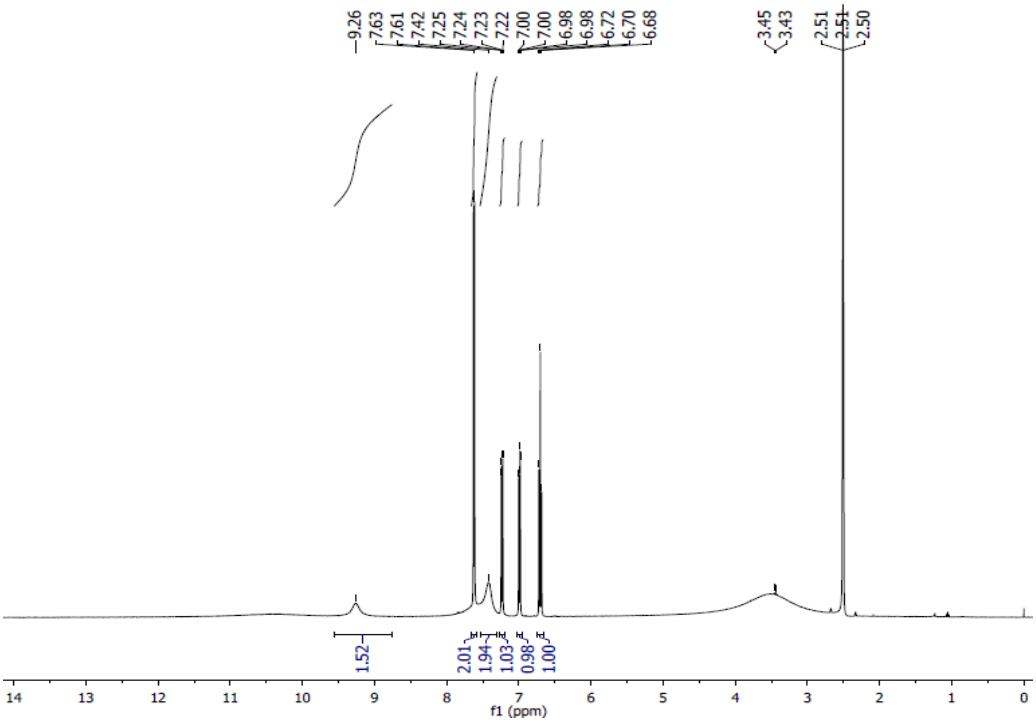

Relative intensity
FLC-GAA Experimental
FLC-GAA Simulated
5
10
15
20
25
30
35
40
45
50
2theta (°)

(d)

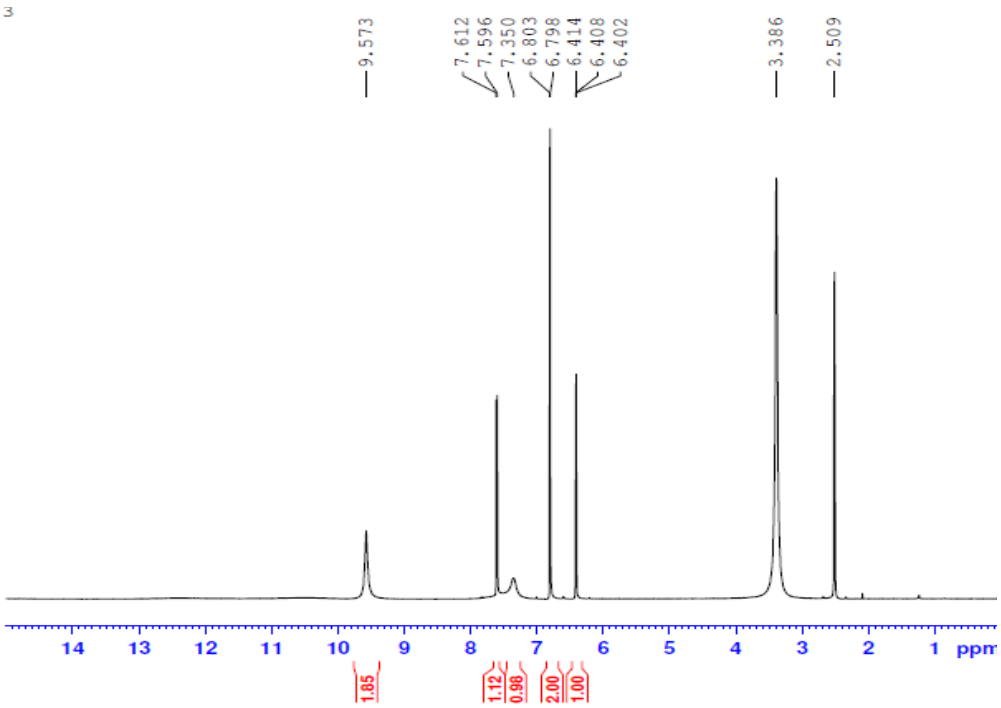


(e)

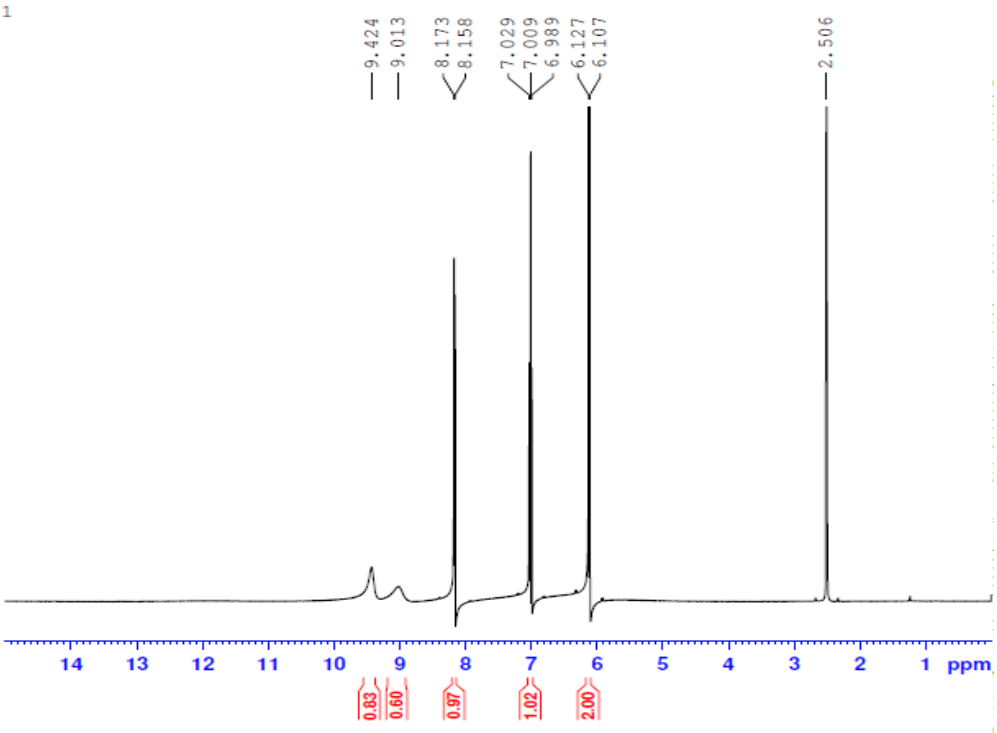
Figure S8. PXRD of calculated and experimental patterns of (a) FLC-2,3HBA (b) FLC-3,5HBA (c) FLC-2,6HBA (d) FLC-GAA (e) FLC-GLA.



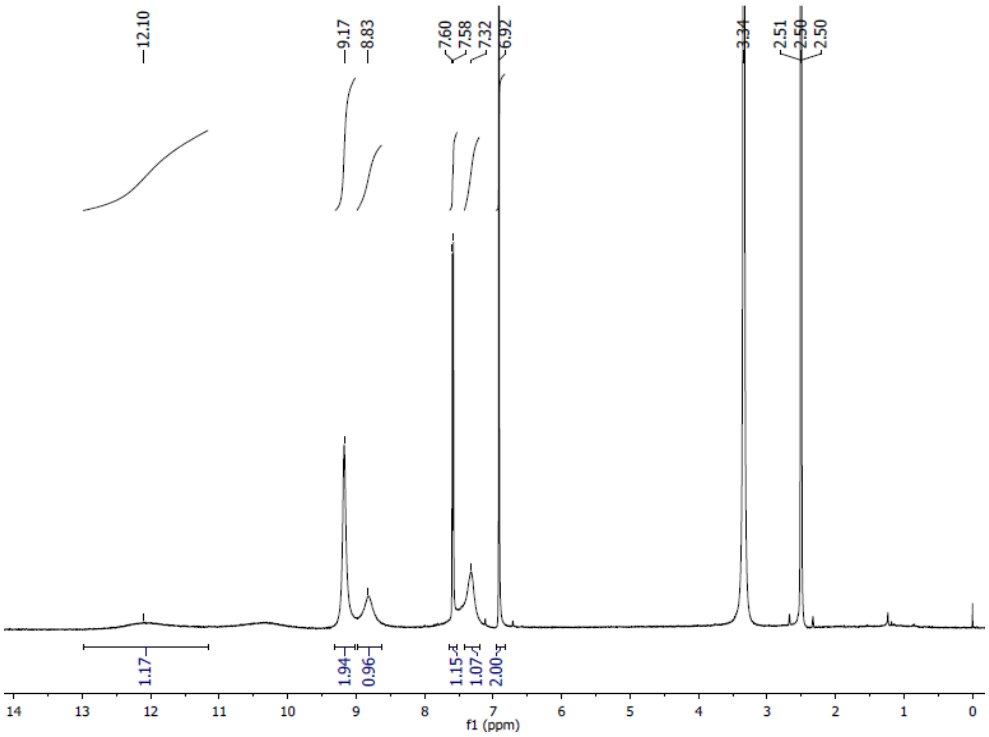
(a)


9.573
7.612
7.596
7.350
6.803
6.798
6.414
6.408
6.402
3.386
2.509
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
1.85
1.12
0.98
2.00
1.00

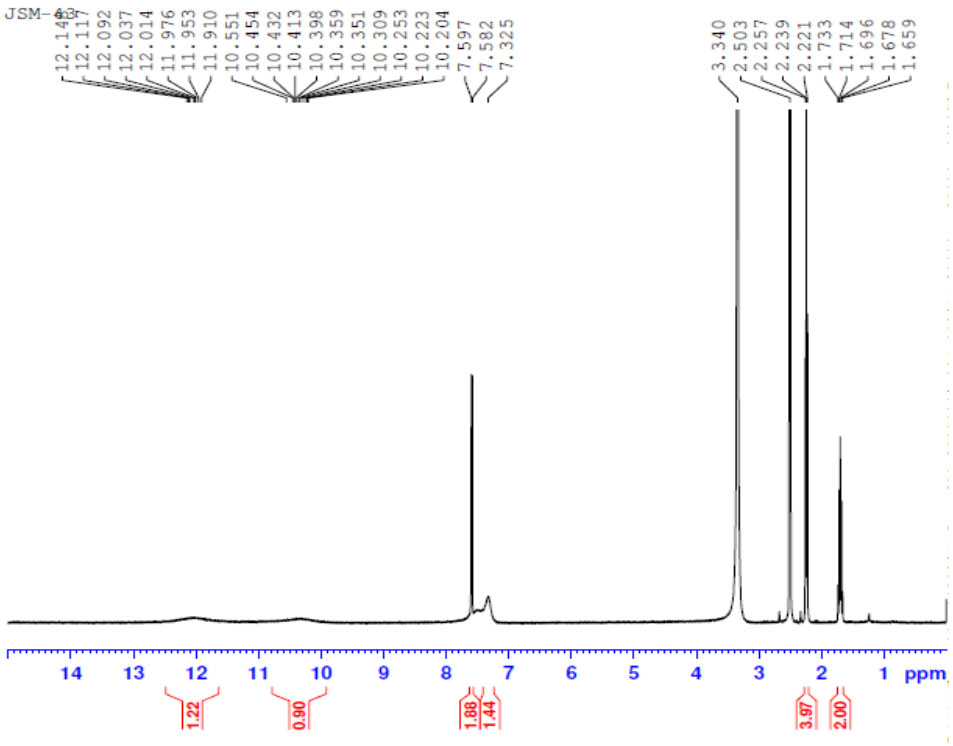
(b)


9.424
9.013
8.173
8.158
7.029
7.009
6.989
6.127
6.107
2.506
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
0.83
0.60
0.97
1.02
2.00

(c)

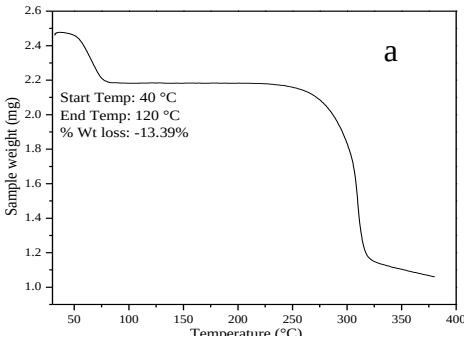


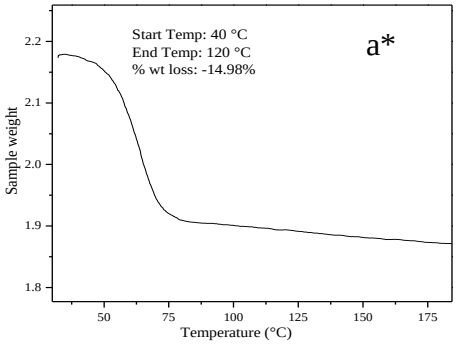
(d)

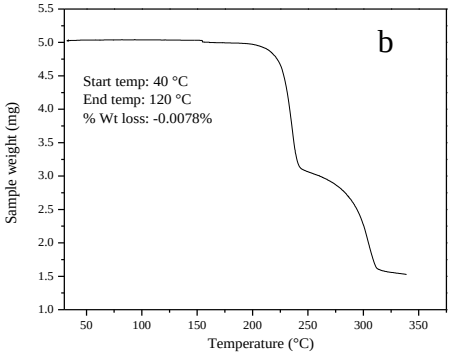


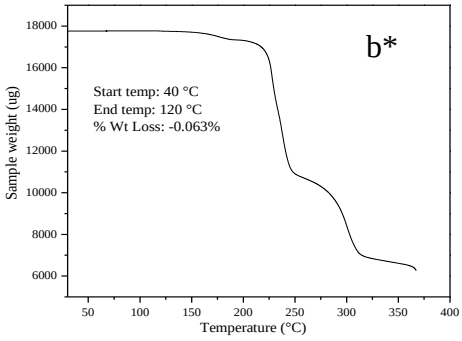
(e)

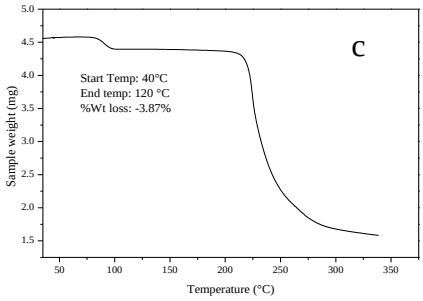
Figure S9. [1]HNMR spectra of (a) FLC-2,3HBA, (b) FLC-3,5HBA, (c) FLC-2,6HBA, (d) FLC-GAA, and (e) FLC-GLA.

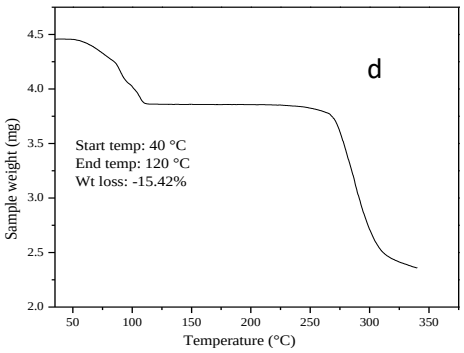

a
Start Temp: 40 °C
End Temp: 120 °C
% Wt loss: -13.39%
Sample weight (mg)
Temperature (°C)

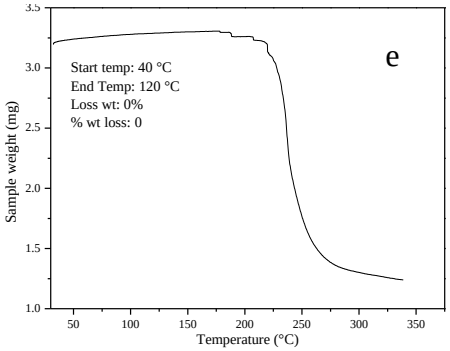

a*
Start Temp: 40 °C
End Temp: 120 °C
% wt loss: -14.98%
Sample weight
Temperature (°C)

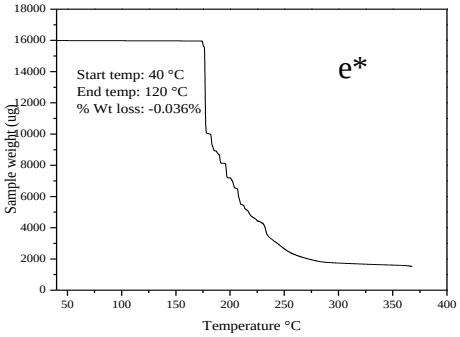

b
Start temp: 40 °C
End temp: 120 °C
% Wt loss: -0.0078%
Sample weight (mg)
Temperature (°C)


b*
Start temp: 40 °C
End temp: 120 °C
% Wt Loss: -0.063%
Sample weight (ug)
Temperature (°C)


c
Start Temp: 40°C
End temp: 120 °C
%Wt loss: -3.87%
Sample weight (mg)
Temperature (°C)


d
Start temp: 40 °C
End temp: 120 °C
Wt loss: -15.42%
Sample weight (mg)
Temperature (°C)


e
Start temp: 40 °C
End Temp: 120 °C
Loss wt: 0%
% wt loss: 0
Sample weight (mg)
Temperature (°C)


e*
Start temp: 40 °C
End temp: 120 °C
% Wt loss: -0.036%
Sample weight (ug)
Temperature °C

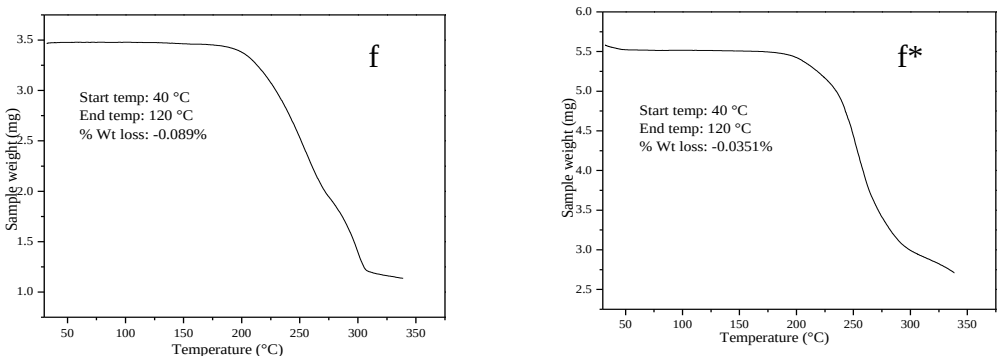
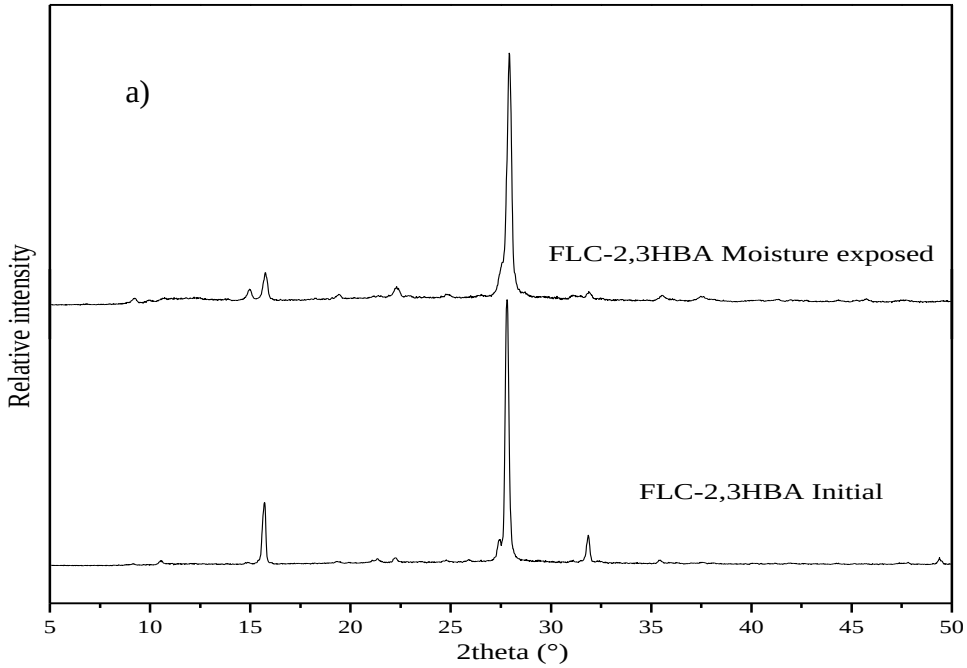
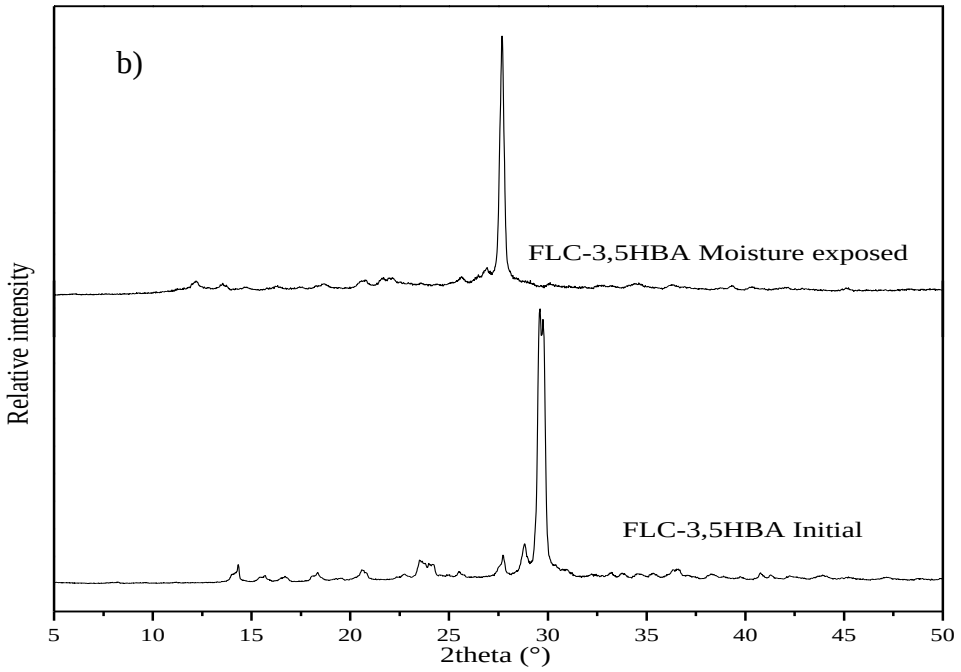
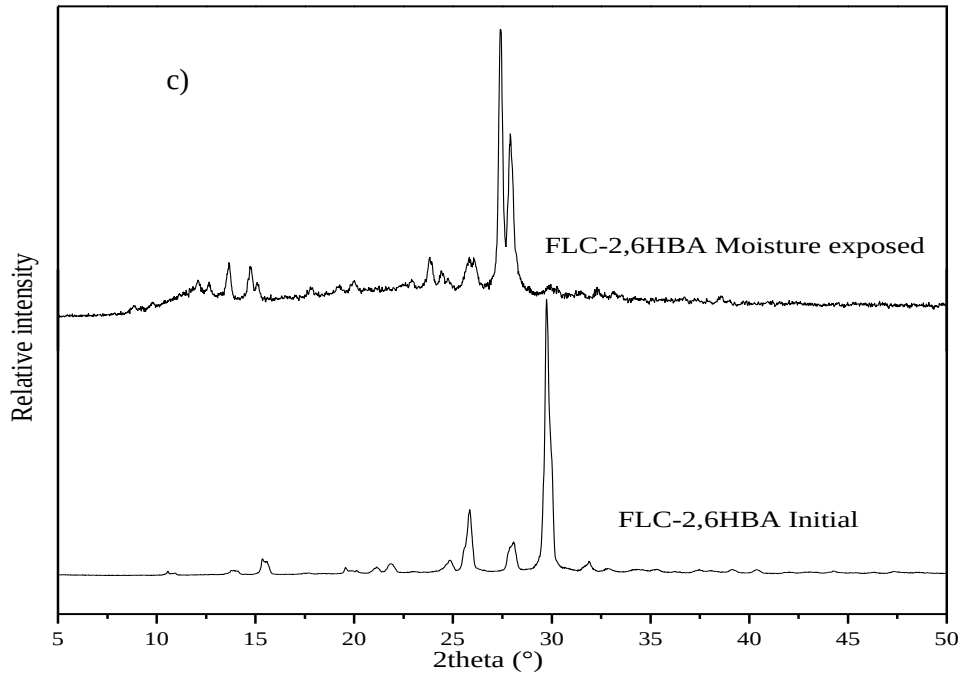


Figure S10: TGA plot of FLC salt/cocrystal at 70-75% RH and at 90-95% RH conditions. a, a*- FLC at 70-75 % RH and 90-95 % RH; b, b*-FLC-2,3HBA at 70-75% RH and 90-95% RH; c-FLC-2,6HBA at 70-75% RH; d- FLC-3,5HBA at 70-75% RH; e,e*-FLC-GAA at 70-75% RH and 90-95% RH; f,f*-FLC-GLA at 70-75% RH and 90-95% RH respectively.




b)
FLC-3,5HBA Moisture exposed
FLC-3,5HBA Initial
Relative intensity
5
10
15
20
25
30
35
40
45
50
2theta (°)


c)
FLC-2,6HBA Moisture exposed
FLC-2,6HBA Initial
Relative intensity
5
10
15
20
25
30
35
40
45
50
2theta (°)

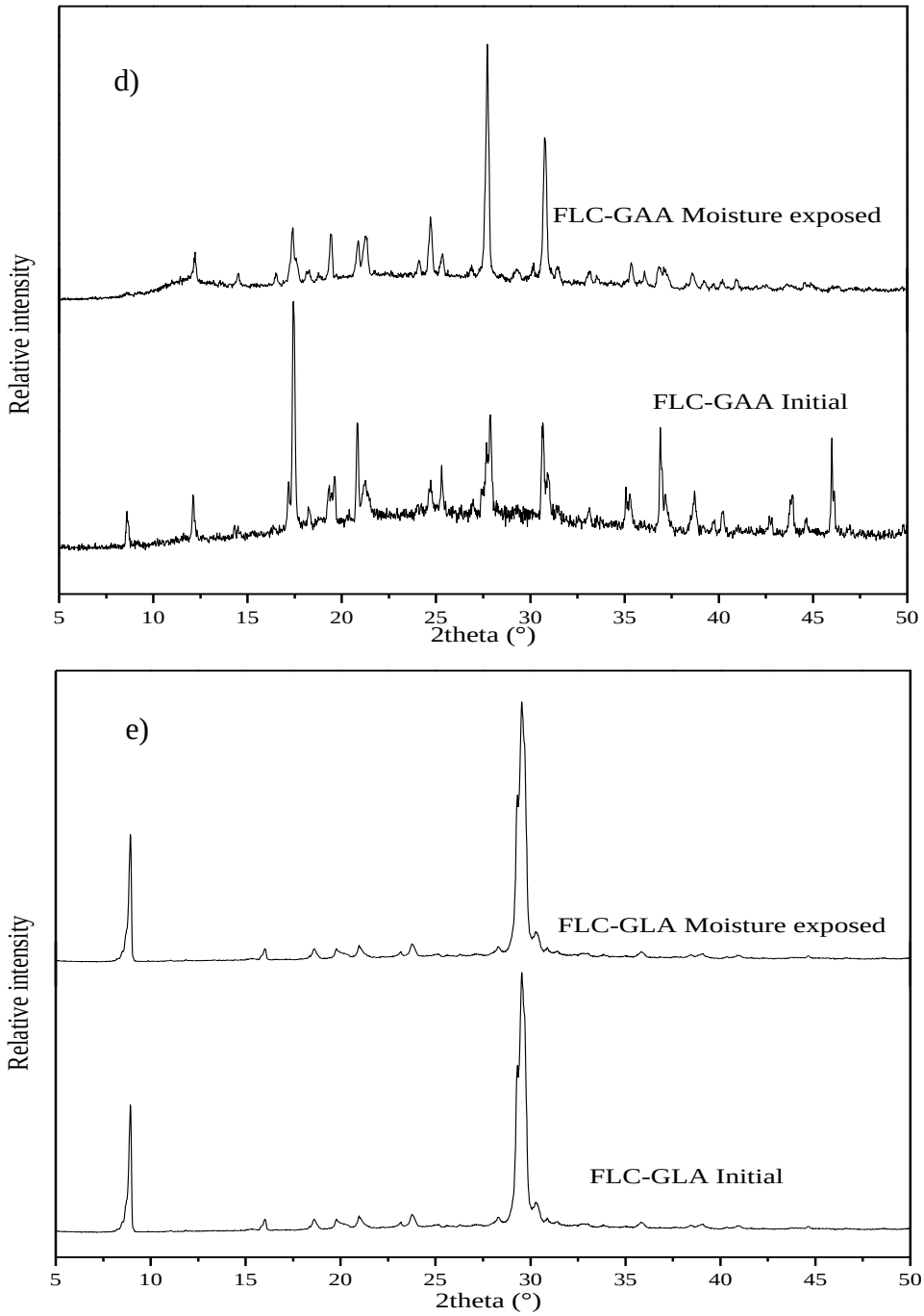


Figure S11: PXRD comparison spectra of moisture exposed samples with initial spectra: a) FLC-2,3HBA at 90-95% RH, b) FLC-3,5HBA at 70-75% RH, c) FLC-2,6HBA at 70-75% RH, d) FLC-GAA at 90-95% RH, and e) FLC-GLA at 90-95 % RH.