Electronic Supplementary Material (ESI) for CrystEngComm.

Molecular salts of quinine. A crystal engineering route to enhance the aqueous solubility

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Supporting Information

EXPERIMENTAL SECTION

Preparation method: Good quality crystals suitable for single-crystal XRD were obtained by slow evaporation of neat ground samples from various solvents. QUN-OXA was obtained from EtOH, that of QUN-ADI from 2:1 EtOH-H_2O solution, QUN-HBA from 2:1 MeOH-H_2O solution, QUN-SLA from EtOH, QUN-26DHB from 1:1 THF-Hexane solution, and QUN-TFA from 1:1 EtOH-H_2O solution. The crystals of QUN-FMA was obtained by vapor diffusion from MeOH-DEE.

The neat ground powder showed a partial melting at 124 ℃ which solidified and completely melted at 196-203 ℃. QN-SAC crystal obtained from 2:1 THF/Hexane solution on HSM experiment showed a melting at a temperature range of 198-206 ℃. The powder sample from slurry experiment conducted on 1:1 $CHCl_3$/MeOH solution (to obtain salt based on literature) also showed a melting at 198-204 ℃. The plate like crystal obtained by slow evaporation from 1:1 $CHCl_3$/MeOH using the above mentioned powder as seed on heating showed a desolvation like episode at 90 ℃. Some block like crystals grew from it which finally melted at 185 ℃ (MP of QN-SAC salt is 185.9 ℃).

Single crystal X-ray Diffraction: The diffraction data of single crystals were collected on a Rigaku Saturn 724+ diffractometer using graphite monochromated Mo-Kα radiation. In these cases, data were processed with the Rigaku CrystalClear software. The structure solution was carried out by direct methods, and the refinements were performed by full-matrix least-squares on *F*2 using the SHELXTL suite of programs. All calculations of intermolecular interactions were done with the HBOND NORM option of PLATON. A misassigned or additional symmetry check by the PLATON program confirms that each of the dimorphs is unique, and more convincingly, the packing and the conformational preferences of the molecules in the two structures are different.

Powder X-ray Diffraction (PXRD): PXRD patterns of the complexes were recorded at room temperature (25.0 ± 2.0 °C) on Philips X'pert Pro with Cu Kα radiation (1.54A °), at 30 mA, 45 kV. The analysis was performed in a continuous mode with a step size of 0.03 ° and a step time of 10 s over an angular range of 5-35 ° 2θ.

Optical and Hot-Stage Microscope (HSM). Phase transition studies were performed on a Leica DM 2500 P optical transmission microscope. The apparatus was equipped with a wide zoom camera and Mettler Toledo hot-stage. The powdered samples were placed on a micro slide, inserted in the hot stage, and observed under the microscope. Images were recorded on heating and cooling in the same temperature regions where phase transitions were observed in DSC. The heating-cooling rate was 5^{o}c/min.

Thermogravimetric analysis: The stability and desolvation behavior of the samples were analyzed using thermogravimetry (HITACHI STA7300). About 5 mg of each sample was accurately weighed in ceramic pans and subjected to the thermal scan from room temperature to 300°C at a rate of 5°C/min in an argon atmosphere.

Dissolution studies: QUN and its complexes showed punch sticking property i.e. powder adhesion during pellet preparation. To overcome this, we used Microcrystalline cellulose (MCC) (20% w/W) along with a standard weight of 300mg of each powder sample. Individual tablets were suspended in 10ml of distilled water and stirred for 24hrs in a shaker at 100 rpm to ensure complete drug release. 1ml of the sample was withdrawn periodically and an equal amount of pure distilled water was added to it. The solution was suitably diluted and measured the absorbance value using the Shimadzu UV-1800 spectophotometer. The spectra were recorded at a range of 200 to 800nm in a 1ml cuvette. Initially, a standard solution of QUN was prepared in the dissolution media. By appropriate dissolution of the stock solution, the calibration curve of QUN was plotted to obtain the molar absorptivity. Then the solubility of QUN and complexes were determined using the BEER-LAMBERT LAW $A=\varepsilon CL$ where A = Absorbance ε = Molar attenuation coefficient C = Concentration L= Optical Path length.

Table S1. Crystallographic Information

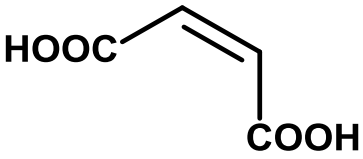
	QUN:OXA	**QUN:FUM**	**QUN:MAL**	**QUN:GLT**	**QUN:ADA**
Formula	$(C_{20}H_{24}N_2O_2)$: $(C_2H_2O_4)$	$(C_{20}H_{24}N_2O_2)$: $(C_4H_4O_4)$:(H_2O)	$(C_{20}H_{24}N_2O_2)$: $(C_3H_4O_4)$	$(C_{20}H_{24}N_2O_2)$: $(C_5H_8O_4)$	$(C_{20}H_{24}N_2O_2)$: $(C_6H_{10}O_4)$
CCDC Nos.	2036856	2036857	2036853	2036851	2036854
Formula Wt.	417.43	935.01	428.47	472.52	445.48
Crystal habit	Block	Block	Block	Needle	Needle
Crystal colour	colourless	colourless	colourless	colourless	colourless
Crystal system	Monoclinic	Triclinic	Orthorhombic	Monoclinic	Monoclinic
Space group	*C*2	*P*1	$P2_12_1 1$	*I* 2	*C*2
a (Å)	21.387(10)	6.5187(3)	6.6594(3)	20.206(7)	19.945(10)
b(Å)	6.419(3)	10.9299(6)	11.8450(5)	6.6378(19)	6.698(4)
c (Å)	18.467(8)	17.6311(9)	26.3450(13)	20.461(5)	18.303(10)
α (º)	90	99.531(2)	90	90	90
β (º)	121.541(7)	97.444(2)	90	116.74(2)	94.980(9)
γ (º)	90	106.711(2)	90	90	90
V (Å^3)	2160.8(17)	1165.47(10)	2078.11(16)	2450.8(13)	2436(2)
Z	4	1	4	4	4
D_{calc}(g cm^{-3})	1.283	1.332	1.370	1.281	1.215
T(K)	298	100(2)	150(2)	298	298
(λ)Mo K$_\alpha$	0.71073	0.71073	0.71073	0.71073	0.71073
μ(mm^{-1})	0.097	0.099	0.099	0.094	0.090
2θ range (º)	54.8	50.4	51.0	55	54.8
Total Reflns.	8062	24732	17111	11284	9227
Unique Reflns.	3738	8372	3641	5419	4214
Reflns. Used	2277	7393	3468	3726	2566
No. Parameters	260	667	301	304	292
GOF on F^2	0.950	1.050	1.095	1.003	0.945
Final R_1, wR_2	0.0728, 0.1904	0.0444,0.1041	0.0461,0.1224	0.0708, 0.1952	0.0832, 0.2455

Table S1. Crystallographic Information (Cont.)

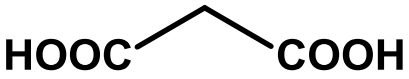
	QUN:SAL	**QUN:DHB**	**QUN:HBAm**	**QUN:TFA**	**QUN:SACh**
Formula	$(C_{20}H_{24}N_2O_2)$: $(C_7H_6O_3)$:(H_2O)	$(C_{20}H_{24}N_2O_2)$: $(C_7H_6O_4)$	$(C_{20}H_{24}N_2O_2)$: $(C_7H_6O_3)$:(CH_4O)	$(C_{20}H_{24}N_2O_2)$: $(C_2HF_3O_2)$: (H_2O)	$(C_{20}H_{24}N_2O_2)$: $(C_7H_{5N}O_3S)$: (H_2O):(C_4H_8O)
CCDC Nos.	2036859	2036852	2036855	2036858	2036860
Formula Wt.	480.54	478.53	494.57	570.48	1151.28
Crystal habit	Block	Block	Block	Block	Block
Crystal colour	colourless	colourless	colourless	colourless	colourless
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
a (Å)	6.943(3)	8.978(4)	6.5291(19)	6.722(2)	15.5984(5)
b(Å)	17.066(6)	9.713(5)	19.368(6)	19.671(6)	15.7897(5)
c (Å)	20.466(8)	28.903(14)	20.431(6)	20.290(6)	23.5416(7)
α (º)	90	90	90	90	90
β (º)	90	90	90	90	90
γ (º)	90	90	90	90	90
V (Å^3)	2424.9(16)	2520(2)	2583.6(13)	2683.1(14)	5798.2(3)
Z	4	4	4	4	4
D_{calc}(g cm^{-3})	1.316	1.261	1.271	1.412	1.319
T(K)	298(2)	298(2)	150(2)	298(2)	150(2)
(λ)Mo K$_\alpha$	0.71073	0.71073	0.71073	0.71073	0.71073
μ(mm^{-1})	0.093	0.089	0.089	0.130	0.164
2θ range (º)	55	55	55	55	55
Total Reflns.	21414	18342	18359	23898	69164
Unique Reflns.	5525	4541	4623	6082	17621
Reflns. Used	3253	1891	2582	3343	16878
No. Parameters	336	329	350	373	737
GOF on F^2	0.831	0.766	0.825	0.907	1.035
Final R_1, wR_2	0.0438, 0.0942	0.0495, 0.1102	0.0510, 0.0982	0.0591, 0.1813	0.0447, 0.1203

Scheme S1. Molecules of Interest

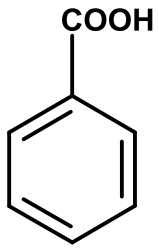
Oxalic acid (OXA)



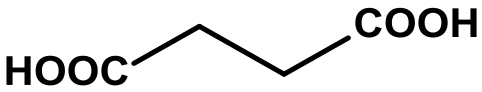
Maleic acid (MA)



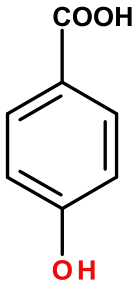
Malonic acid (MAL)



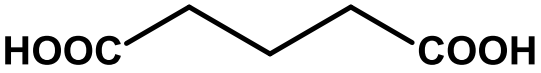
Benzoic acid (BZA)



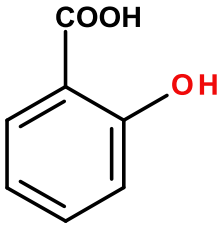
Succinic acid (SUC)



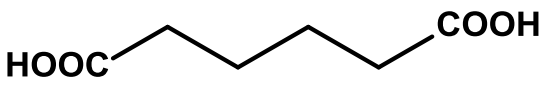
4-Hydroxybenzoic acid (HBA)



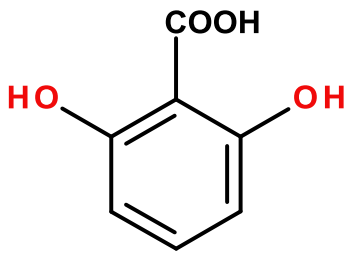
Glutaric acid (GLT)



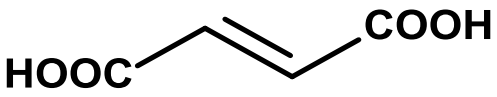
Salicylic acid (SAL)



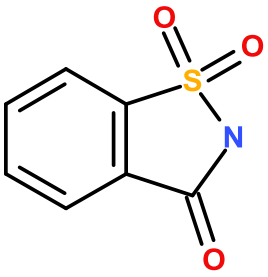
Adipic acid (ADA)



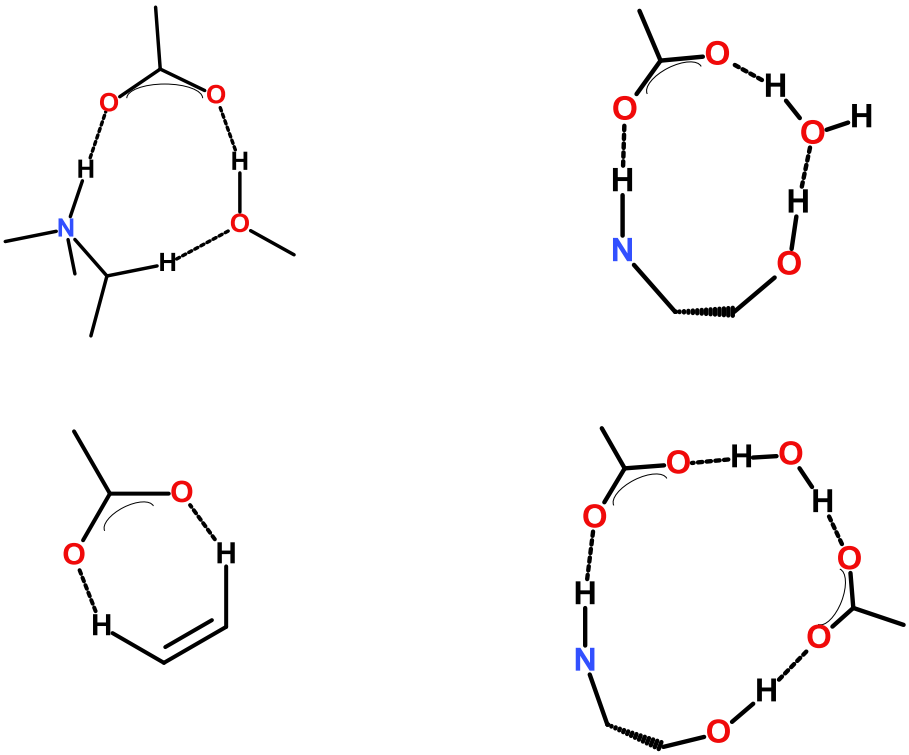
2,6-Dihydroxybenzoic acid (DHB)



Fumaric acid (FUM)



Saccharin (SAC)



Scheme S2. Types of major synthons observed in the complexes of QUN

Table S2. Computed ΔpKa values

Complex	ΔpK_a
QUN	—
QUN:OXA	7.38
QUN:MAL	6.32
QUN:SUC	5.19
QUN:GLT	4.99
QUN:ADA	4.83
QUN:FUM	5.40
QUN:MAE	5.90
QUN:BZA	4.97
QUN:HBA	4.67
QUN:SAL	6.26
QUN:DHB	7.41
QUN:SAC	6.21
	1.66
QUN:TFA	8.10
	3.55

Table S3. Measured melting points of the complexes

SL NO	DRUG/COFORMERS	TEMP (∘ C)	COMPLEXES	TEMP (∘C)
1	QN	177		
2	OXA	189	QUN:OXA	168-176
3	FUM	299	QUN:FUM	206-210
4	MAL	135	QUN:MAL	181-186
5	SUC	184	QUN:SUC	163-170
6	GLT	97	QUN:GLT	113-120
7	ADA	152	QUN:ADA	130-138
8	MAE	130	QUN:MAE	191-199
9	BZA	122	QUN:BZA	173-179
10	HBA	214	QUN:HBA	190-196
11	SAL	158	QUN:SAL	118-196
12	DHB	343	QUN:DHB	215-220
13	SAC	228	QUN:SAC	198-204

PXRD Results

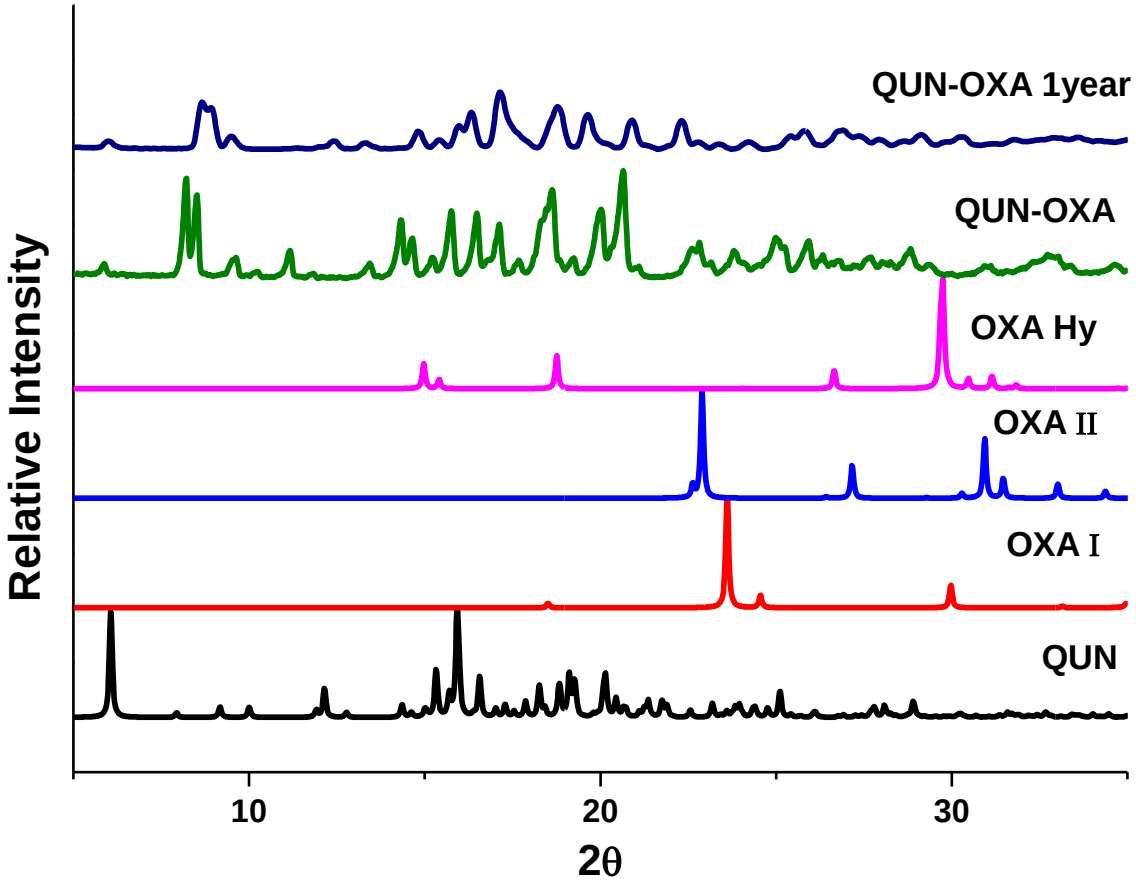


Fig. S1. PXRD pattern of the QUN:OXA complex

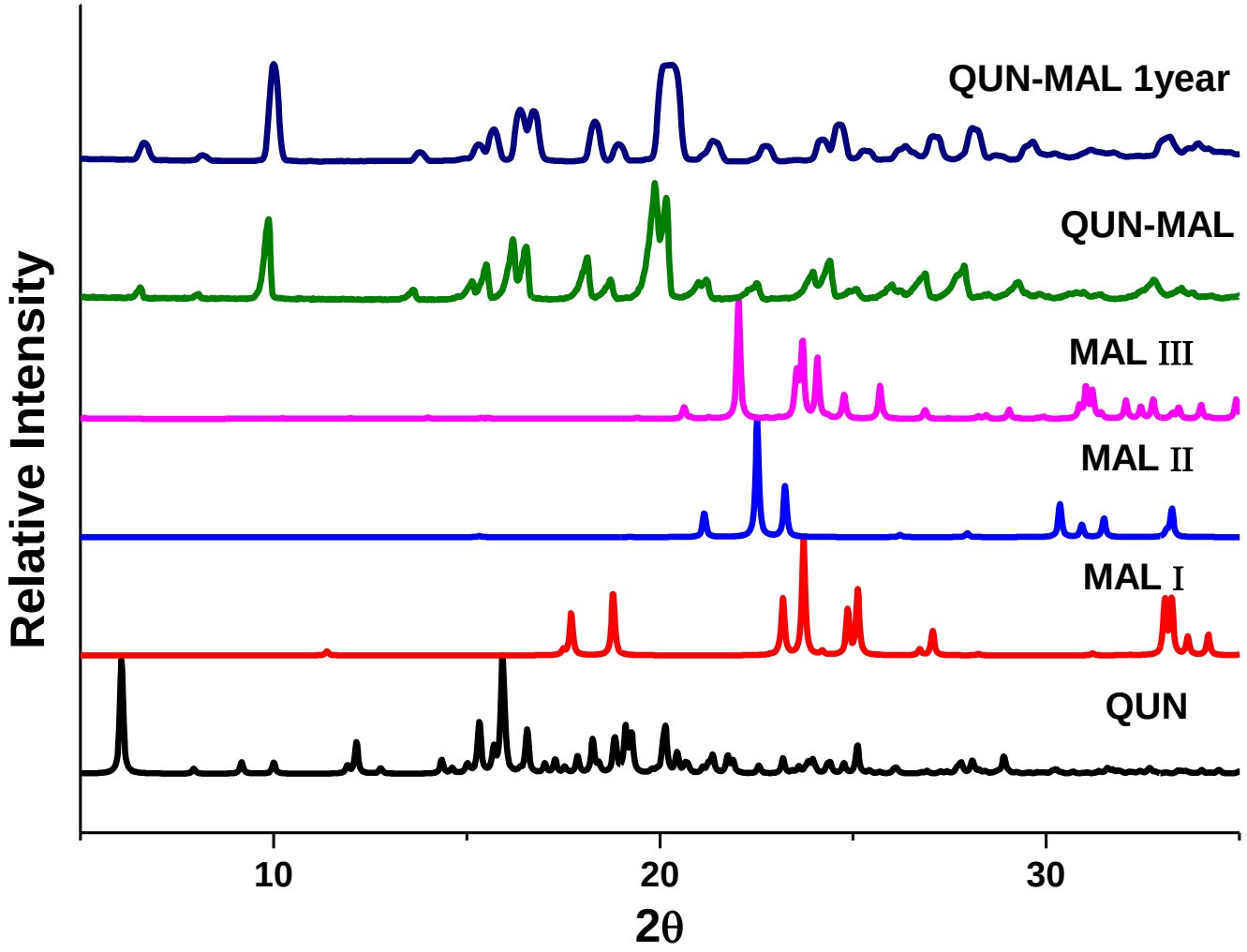


Fig. S2. PXRD pattern of the QUN:MAL complex

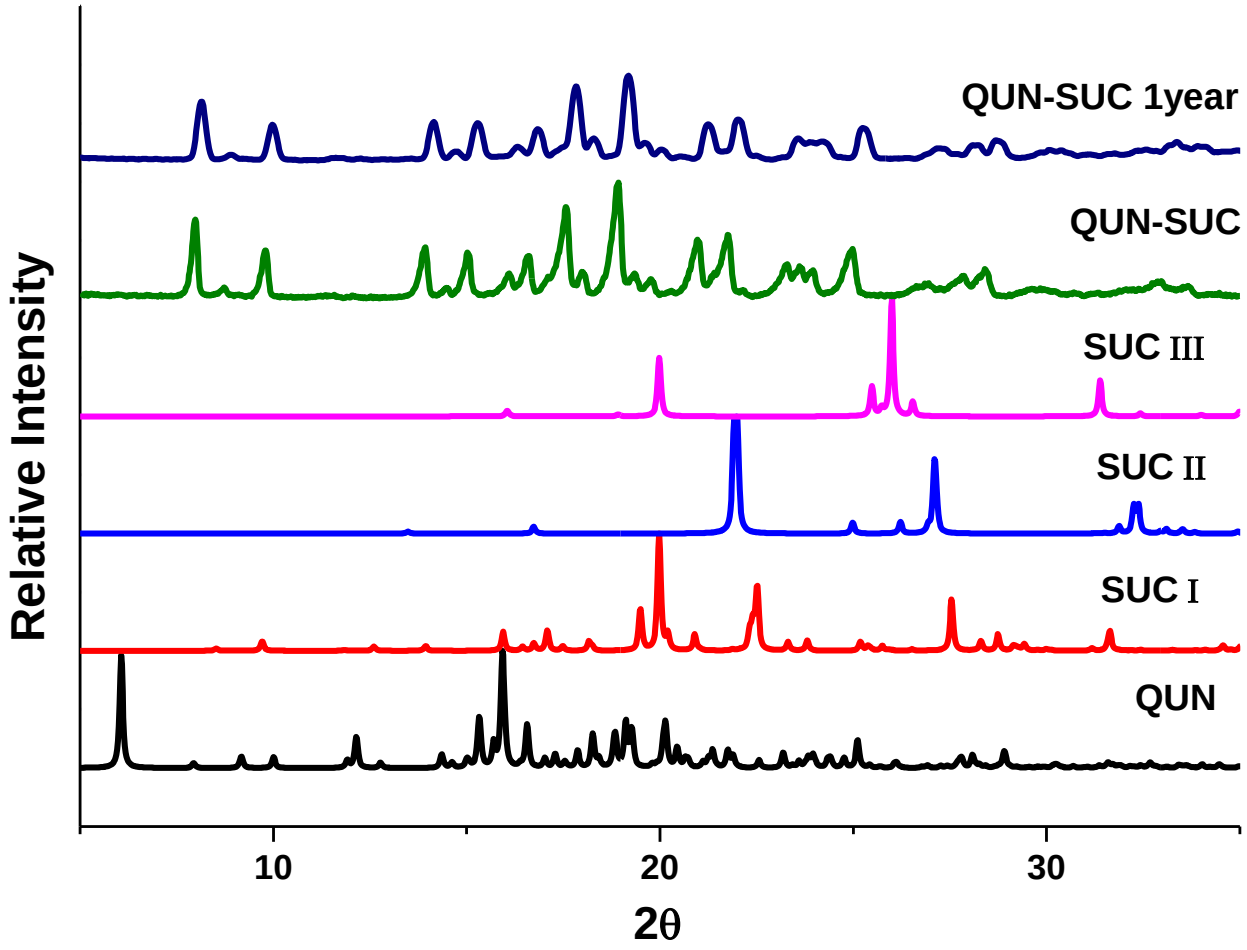


Fig. S3. PXRD pattern of the QUN:SUC complex

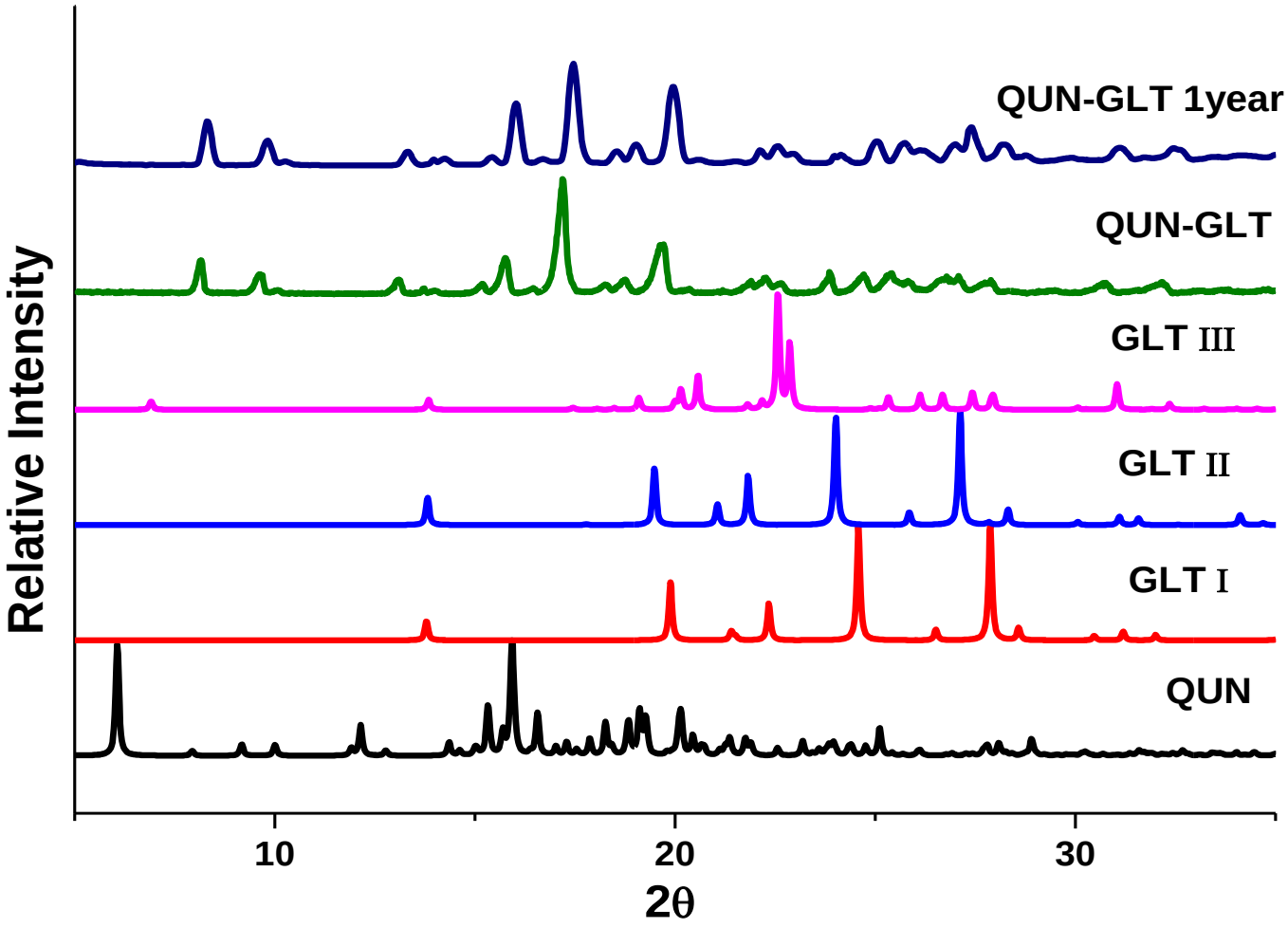


Fig. S4. PXRD pattern of the QUN:GLT complex

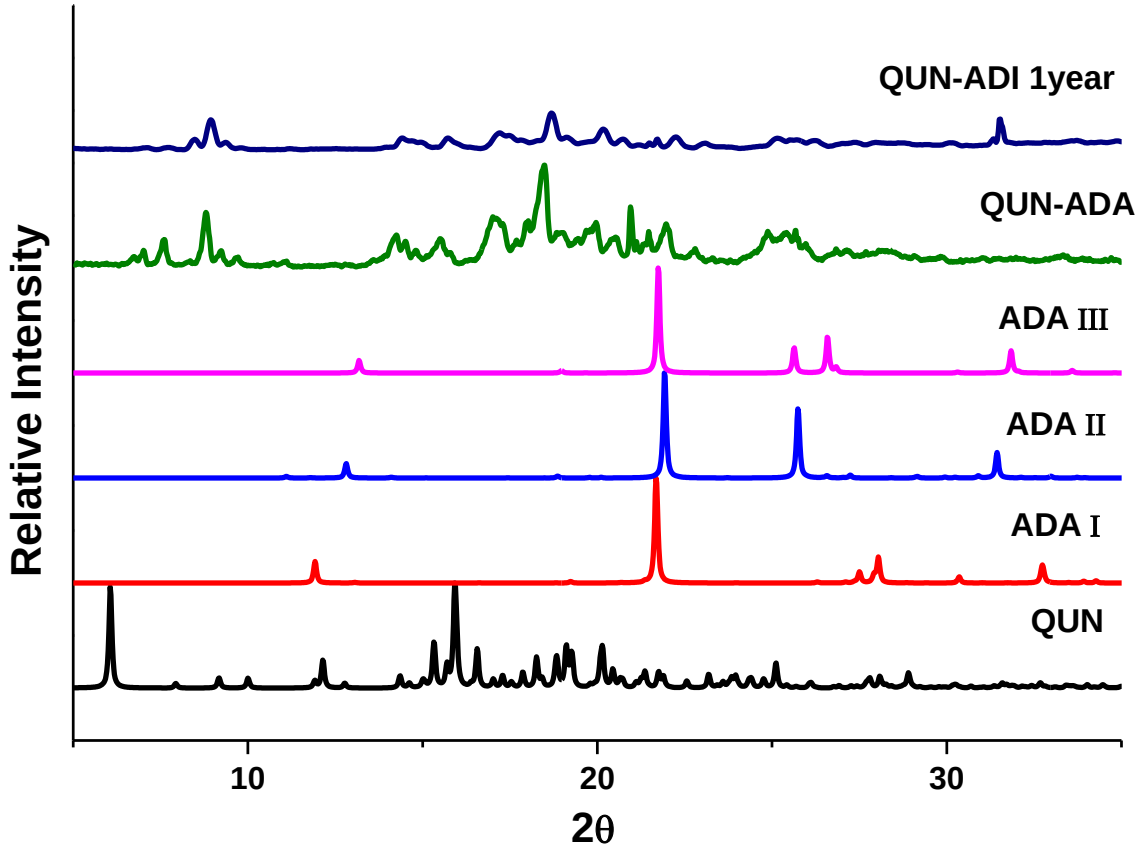


Fig. S5. PXRD pattern of the QUN:ADA complex

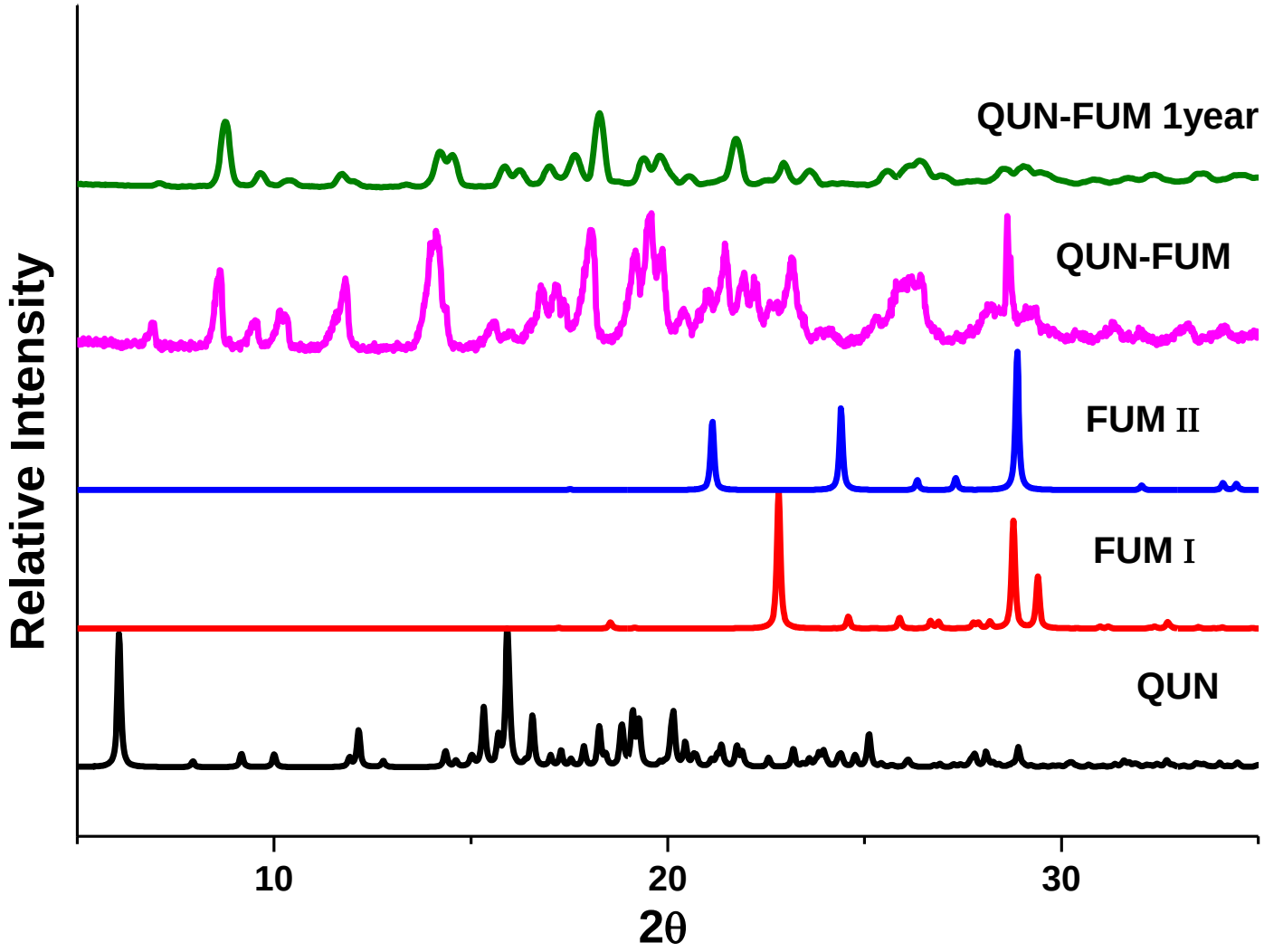


Fig. S6. PXRD pattern of the QUN:FUM complex

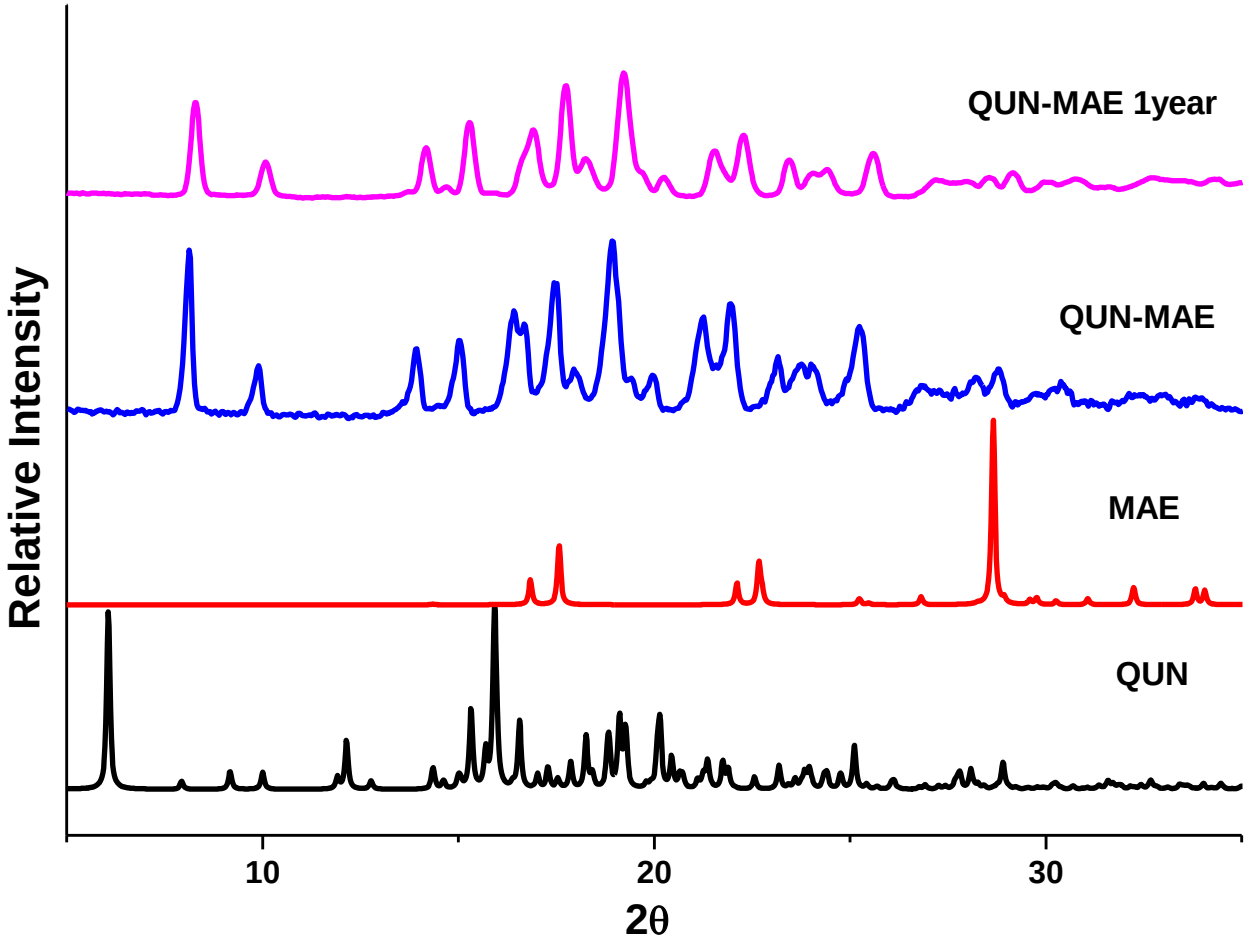


Fig. S7. PXRD pattern of the QUN:MAE complex

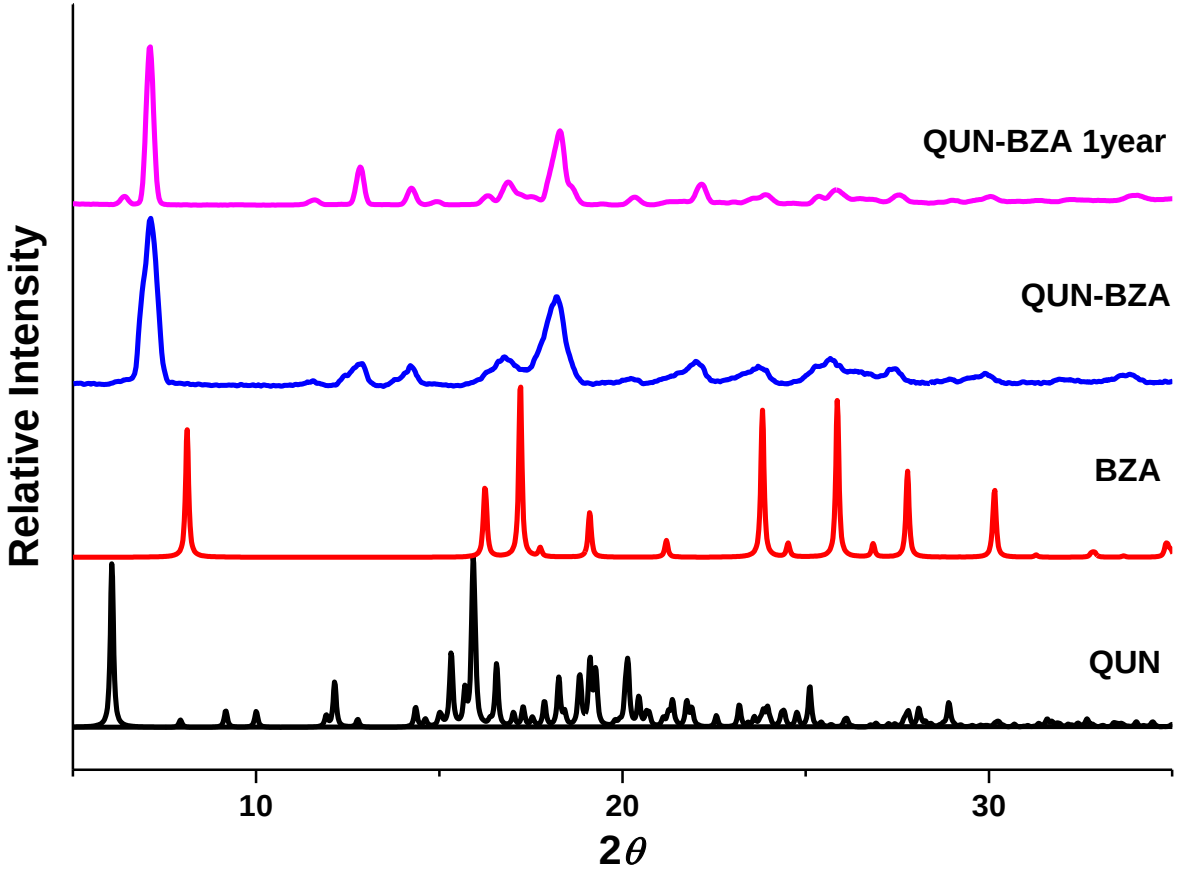


Fig. S8. PXRD pattern of the QUN:BZA complex

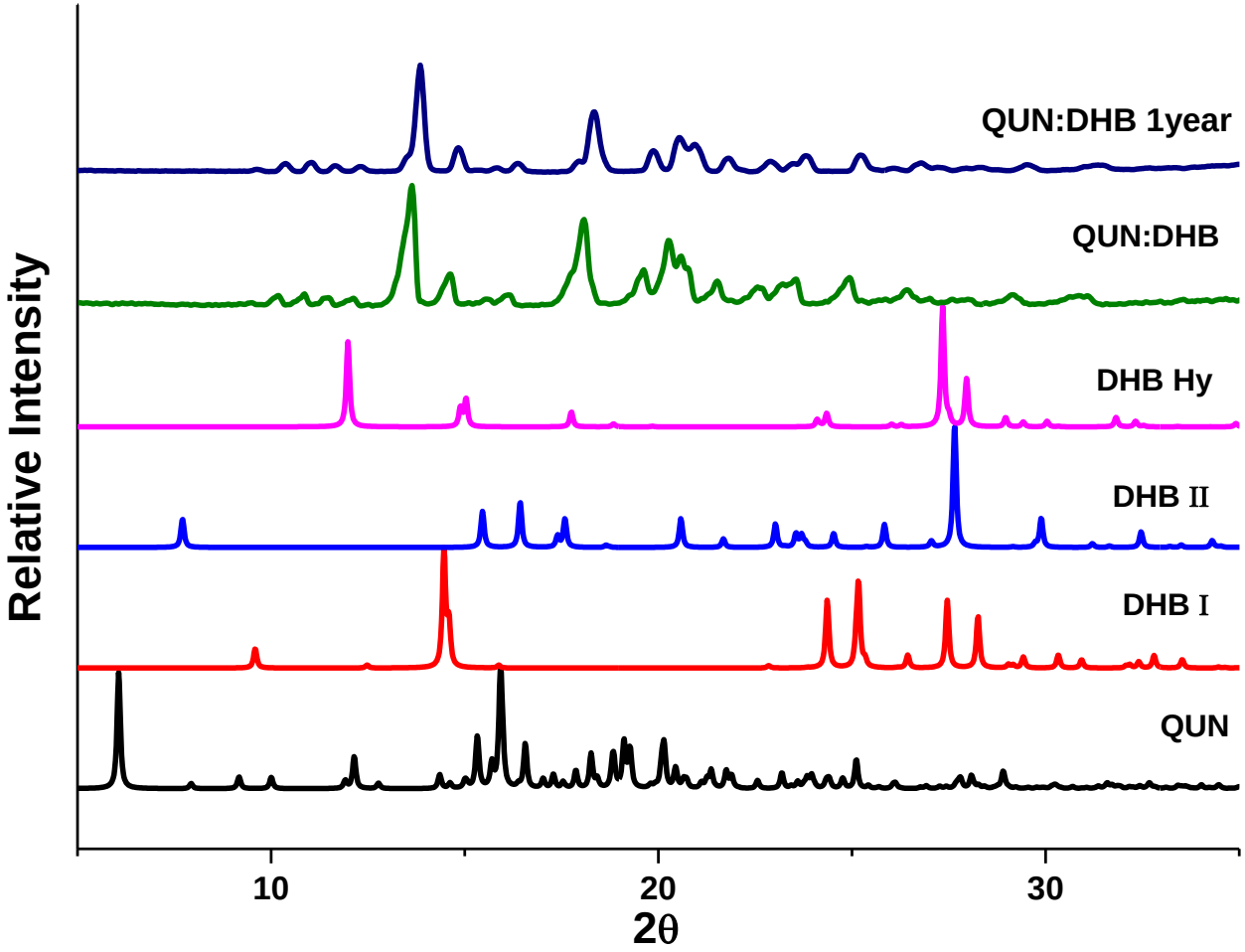


Fig. S9. PXRD pattern of the QUN:DHB complex

Hot-Stage Microscopy

QN-SAC Crystal

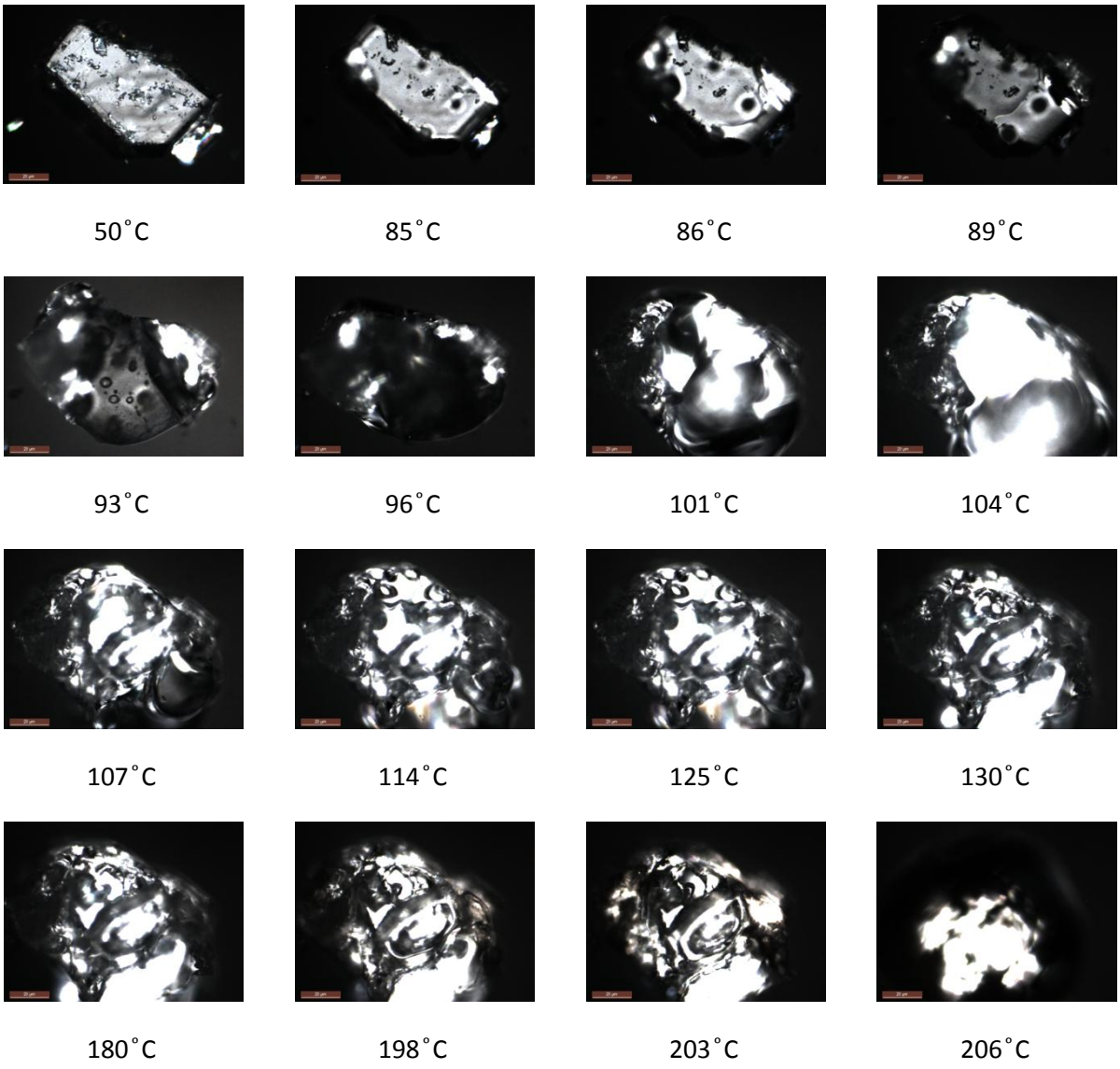
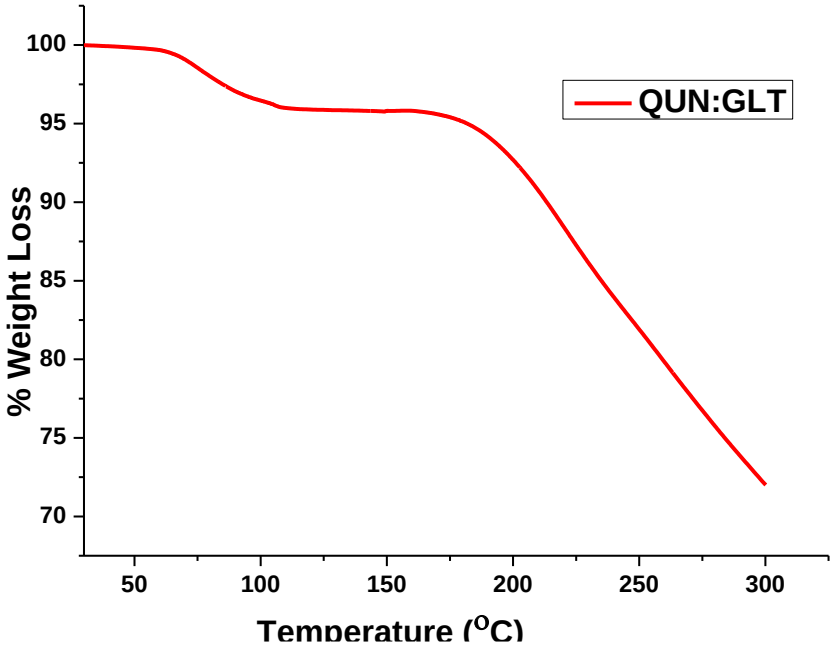


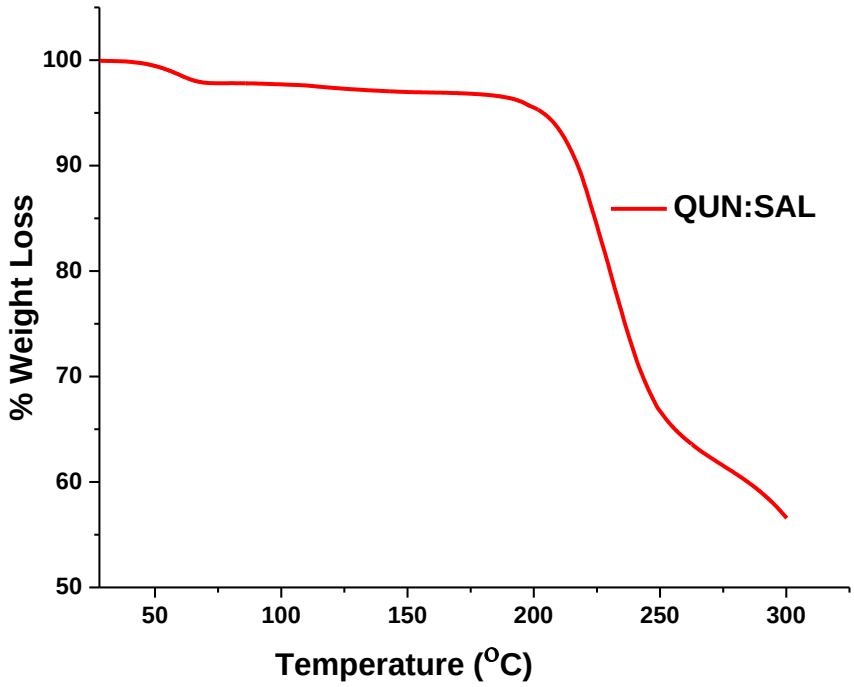
Fig. S10. The QN-SAC crystal obtained by slow evaporation from 2:1 THF-Hexane solution using melted sample as seed shows a melting at a temperature range of 85-104 °C.It then solidifies at 125 °C which finally melts at 198-206 °C.

Thermal Analysis

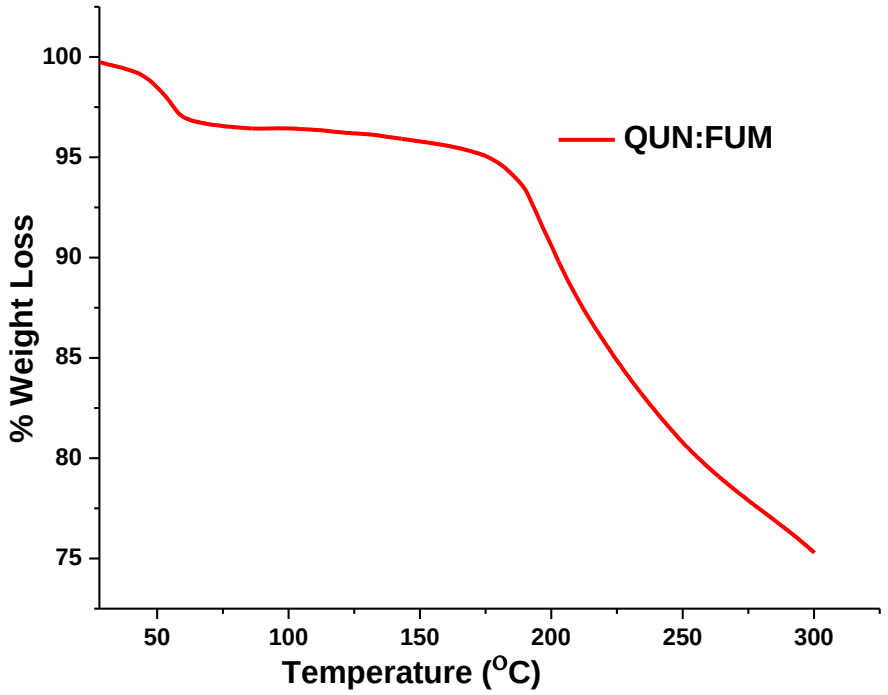
(a)



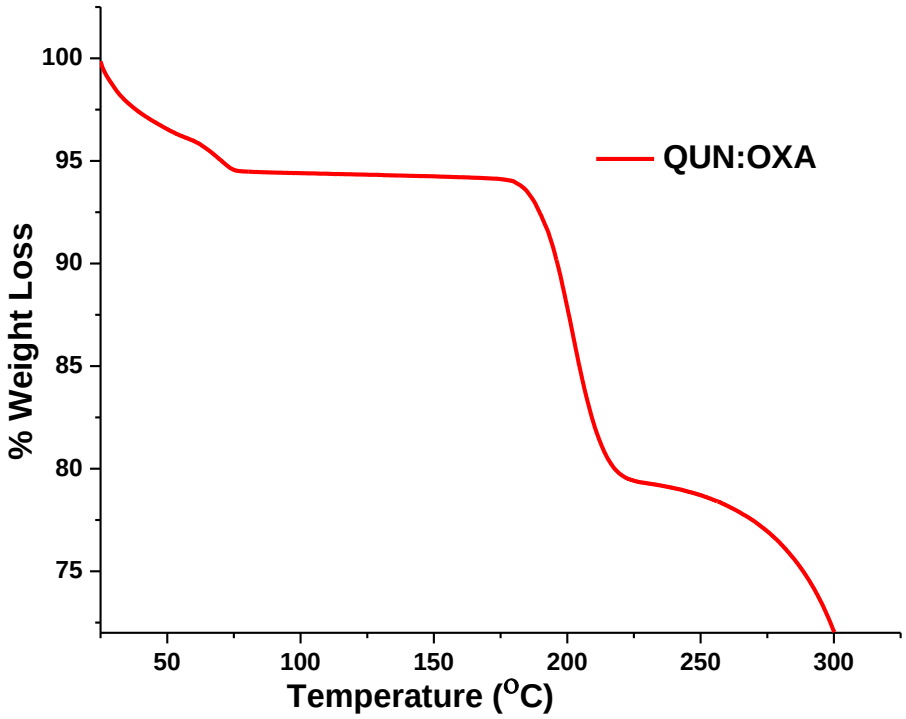
(b)



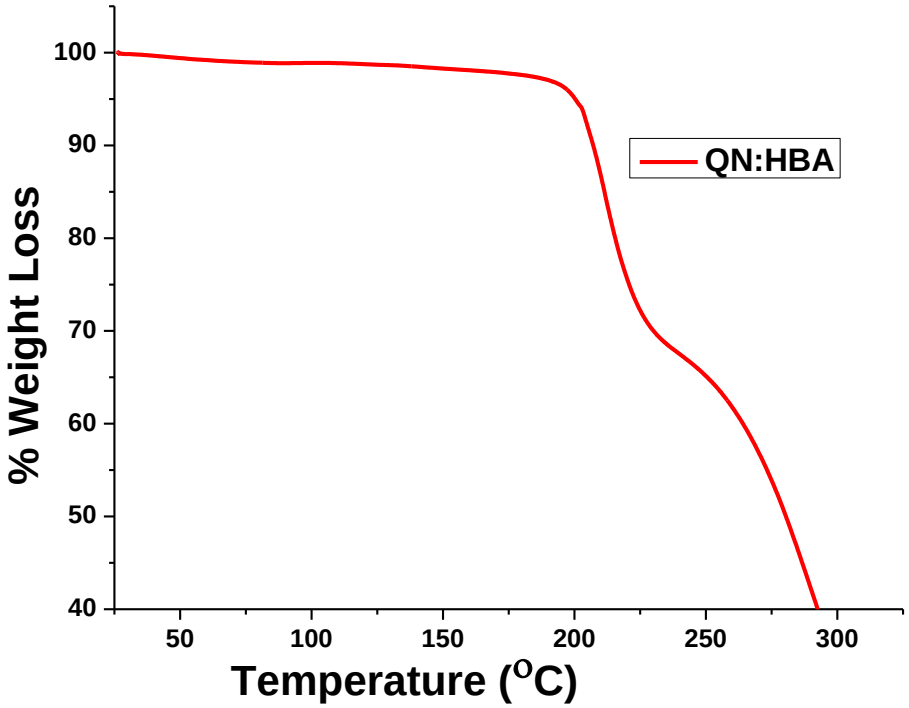
(c)


QUN:FUM
% Weight Loss
100
95
90
85
80
75
50
100
150
200
250
300
Temperature (°C)

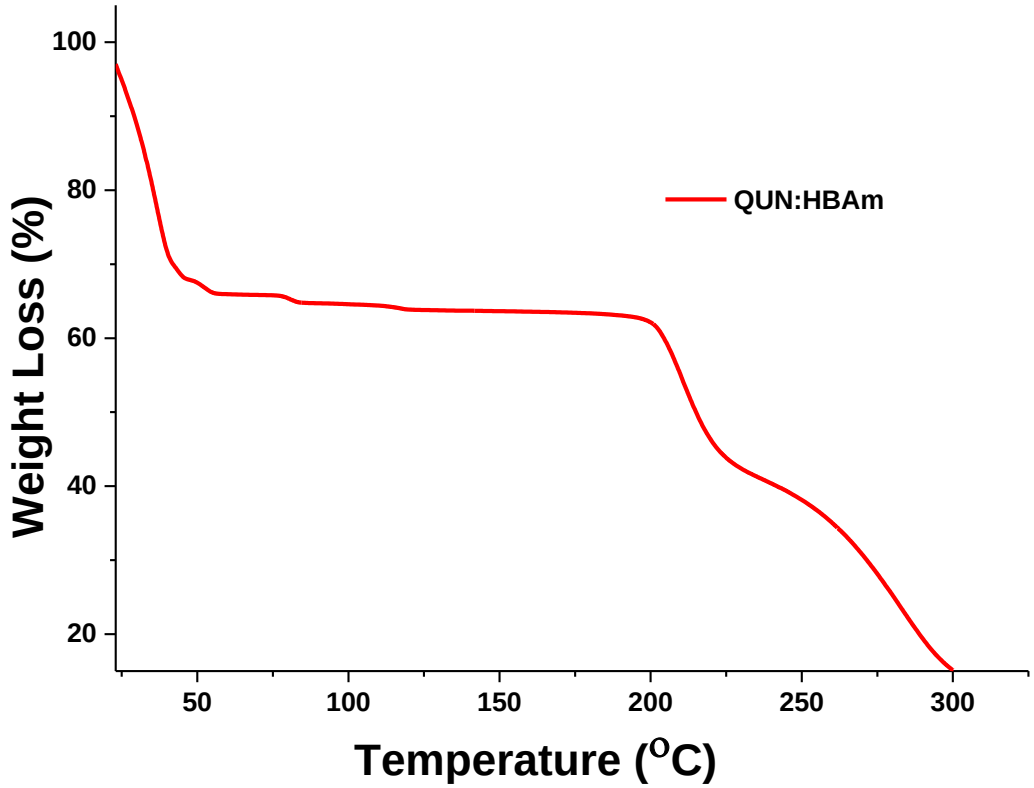
(d)


QUN:OXA
% Weight Loss
100
95
90
85
80
75
50
100
150
200
250
300
Temperature (°C)

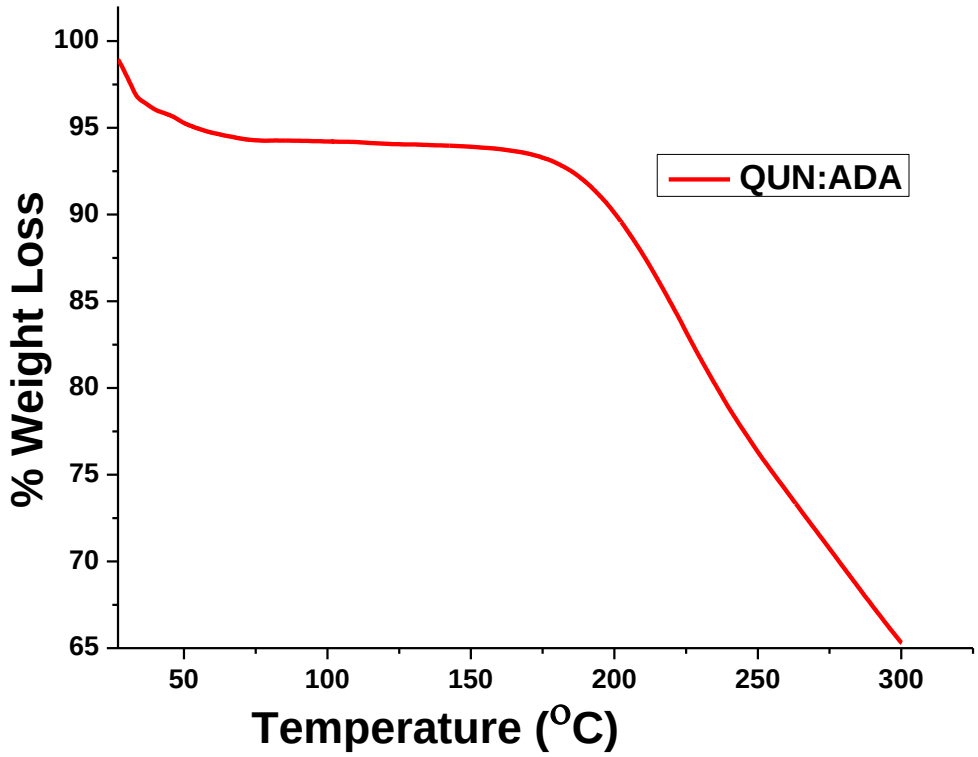
(e)


100
90
80
70
60
50
40
% Weight Loss
QN:HBA
50
100
150
200
250
300
Temperature (OC)

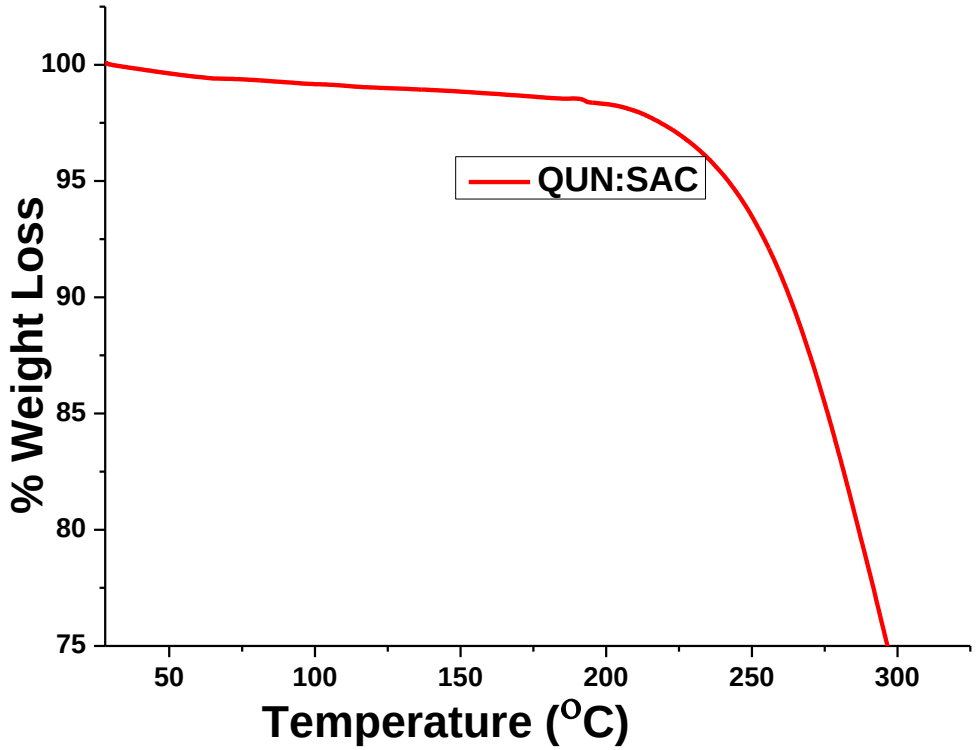
(f)


100
80
60
40
20
Weight Loss (%)
QUN:HBAm
50
100
150
200
250
300
Temperature (OC)

(g)


100
95
90
85
80
75
70
65
% Weight Loss
50
100
150
200
250
300
Temperature (°C)
QUN:ADA

(h)



(i)

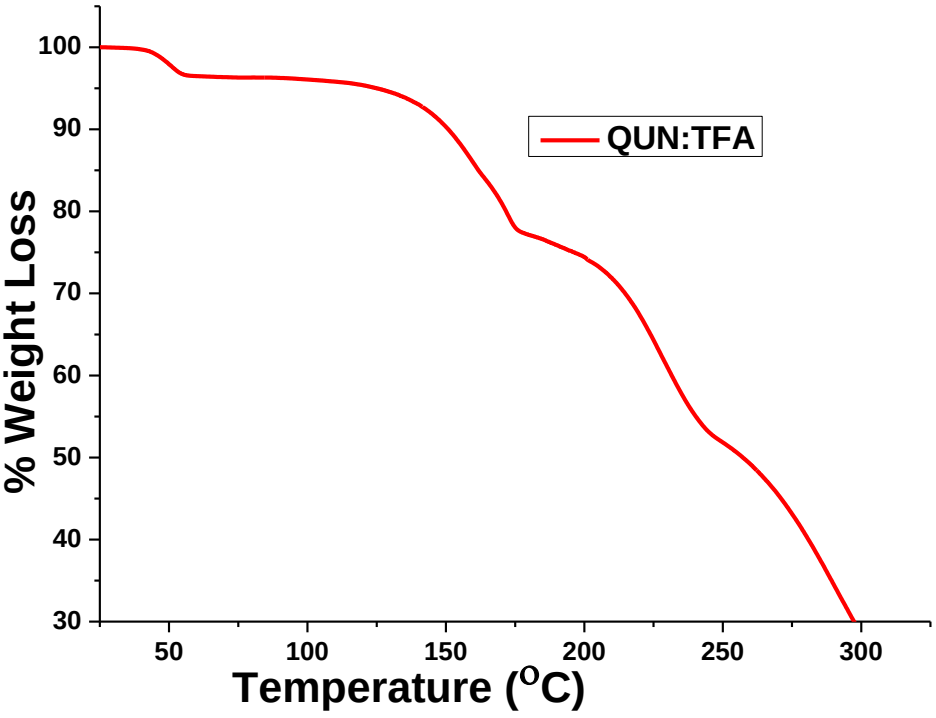


Fig. S11. The thermogram of the molecular complexes of QUN.

Table S4. Thermal induced % weight loss incurred in the complexes

Complex	Onset (°C)	Weight loss (%)	Inference
QUN:GLT	60	4.1	1 water
QUN:SAL	39	2.2	0.5 water
QUN:ADA	RT	5.9	1.5 water
QUN:FUM	38	4	2 water
QUN:OXA	RT	6	1.5 water
QUN:TFA	35	3.5	1 water
	117	20	1 TFA
QUN: HBAm	RT		
QUN:SAC			
QUN:MAL			

Table S5. REFCODE corresponding to QUN and its hydrates/solvates

No.	REFCODE	Hydrate	Solvate
1	BOMDUC	A	
2	BOMDUC01	A	
3	ELIPAQ	H	
4	JEYZIX	H	
5	MUHZUM		MeOH
6	QUINDE		EtOH
7	QUINDE01		EtOH
8	SOYXUA		MeOH

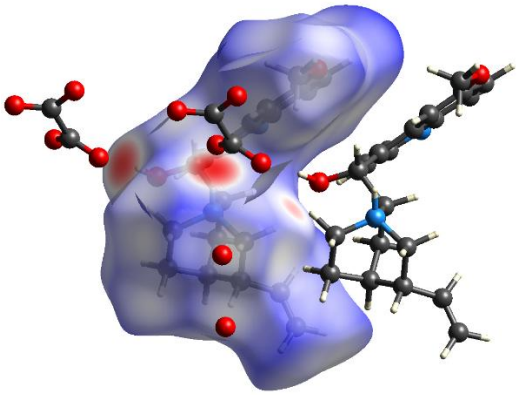
H = Hydrate; A = Anhydrous

Table S6. REFCODE corresponding to the complexes of QUN

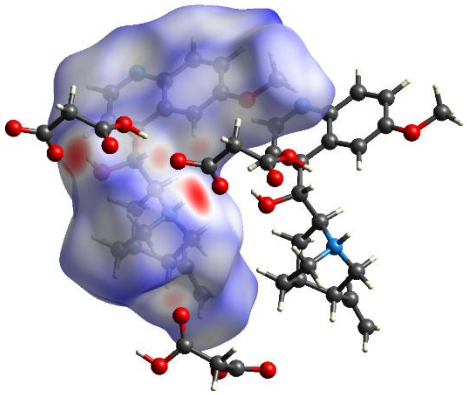
Index	REFCODE	Hydrate	Solvate	Moiety
1	TAKJUO	H		Carboxylate
2	APAKIM	A		Carboxylate
3	BEYTIJ	A		Carboxylate
4	DOZLUC	A		Hydroxylate
5	DOZMAJ	A		Hydroxylate
6	ECAQAD	A		Acesulfame
7	ECAQAD01	A		Acesulfame
8	EJUKAV		Acetone	Carboxylate
9	FABDAQ		Acetone	Other
10	FEQZEG	A		Carboxylate
11	FIJSUM	H		Carboxylate
12	IGATOC	A		Carboxylate
13	IROQEL	H		Carboxylate
14	JIFYOM	H		Carboxylate
15	KAMDAD	H		Toluene
16	LIVWOC	H		Carboxylate
17	MEKGUE		EtOAc	Carboxylate
18	PUVTUV	H		Carboxylate
19	ROHJAZ	A		Carboxylate
20	ROHJAZ01	A		Carboxylate
21	TIKBEX	H		Carboxylate
22	TIKBIB	H		Carboxylate
23	TIKBOH	H		Carboxylate
24	TIKBUN	H		Carboxylate
25	TUZCOI	H		Carboxylate
26	TUZCUO	H		Carboxylate
27	TUZDID	H		Carboxylate
28	TUZDOJ	A		Carboxylate
29	URIYAW	H		Carboxylate
30	UYEZII	A		Carboxylate
31	UYEZOO	A		Carboxylate
32	UYEZOO01	A		Carboxylate
33	UYIBAG	A		Carboxylate
34	VAPLUV	A		Carboxylate
35	VAZCUV	A		Carboxylate
36	VIYROM	H		Carboxylate
37	VUGSUL		MeCN	Carboxylate
38	VUKROL	H		Carboxylate
39	WANTOU	H		Carboxylate

40	WEGTAF	H	Dioxane	Carboxyl
41	XEGTAF	H		Cyclodextrin
42	YAFHUL	H		Acesulfame
43	YAFJAT	A		Acesulfame
44	YAJHAV	A		Saccharin
45	YANNIL	A		Saccharin
46	YUYFUU	A		Methyl paraben
47	ZZZFHU	A		Benzene
48	ZZZSQC	A		Benzene

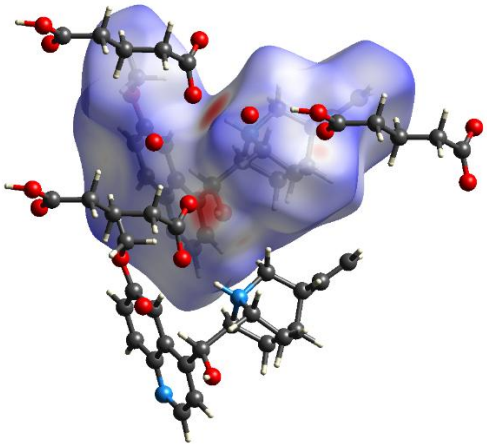
H = Hydrate; A = Anhydrous



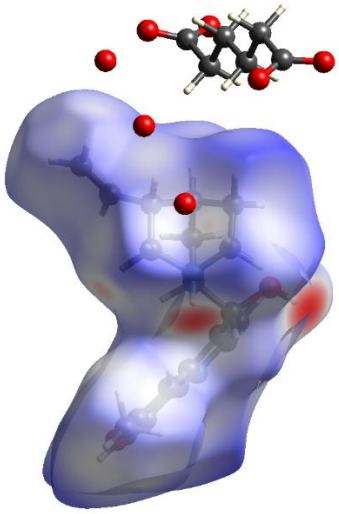
QUN:OXA



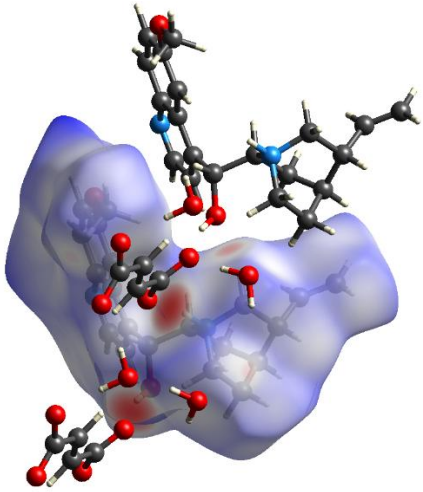
QUN:MAL



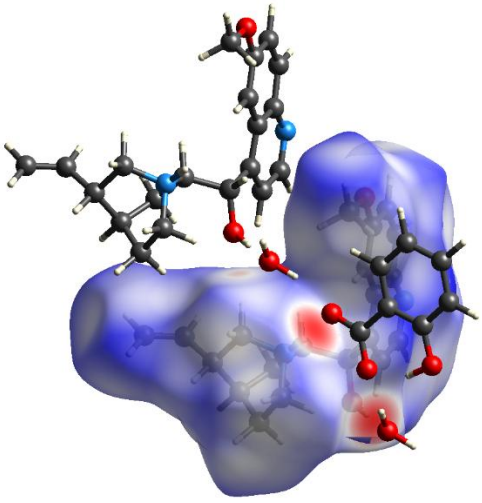
QUN:GLT



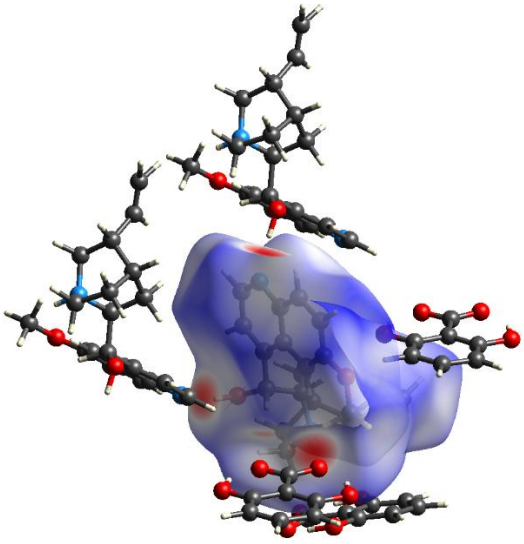
QUN:ADA



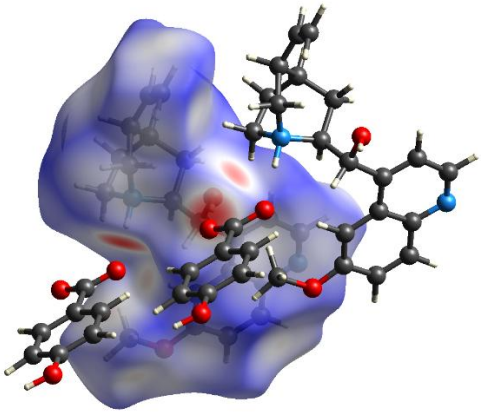
QUN:FUM



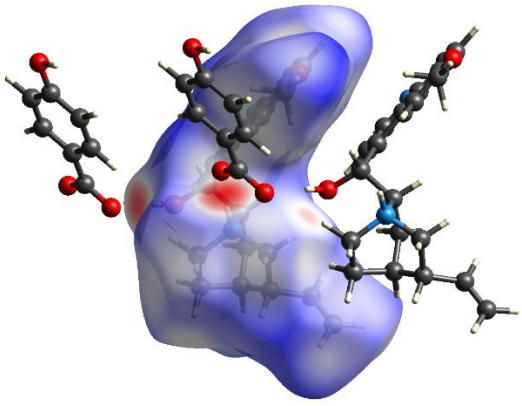
QUN:SAL



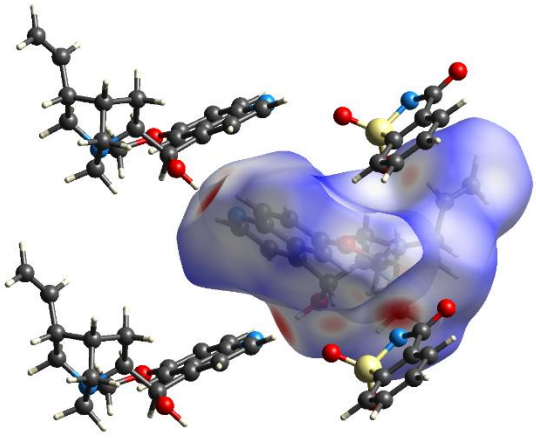
QUN:DHB



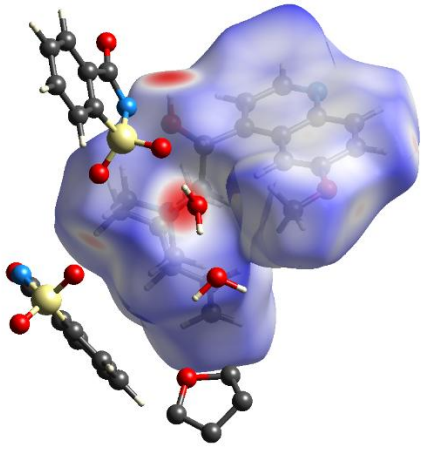
QUN:HBAa



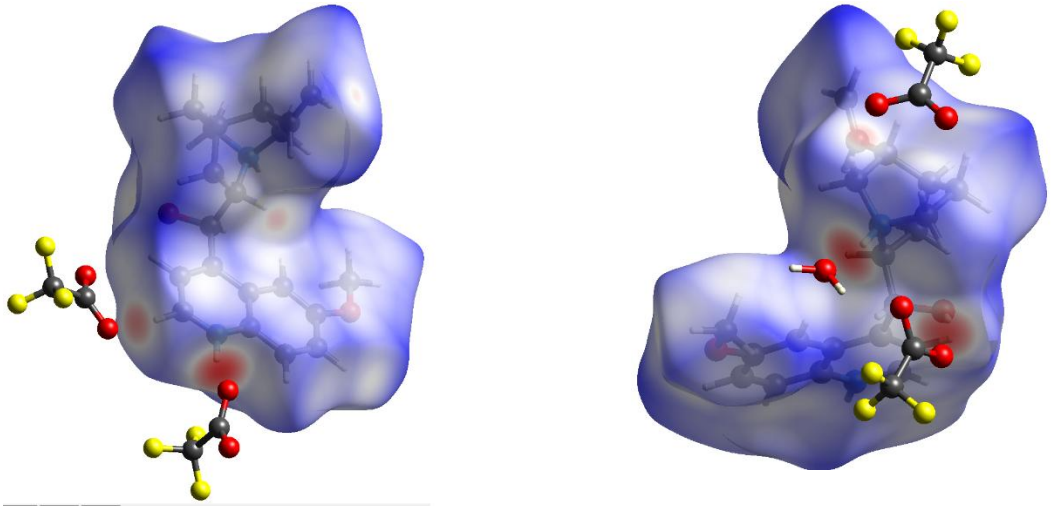
QUN:HBAm



QUN:SACa



QUN:SACh



QUN:TFA_a **QUN:TFA_b**

Fig. S12. The d_{norm} surface map of QUN from the Hirshfeld surface (HS) analysis depicts short contacts in blue, van der Waals interactions in white, and hydrogen bonding in red surfaces.

Solubility and dissolution studies

Table S7. The aqueous solubility calculated from the measured absorbance

QUN

Solubility calculated from measured absorbance

Time	Absorbance	Con. (mg/ml)
5	0.072	0.03258683
10	0.108	0.048880246
15	0.12	0.054311384
20	0.147	0.066531445
30	0.183	0.08282486
45	0.192	0.086898214
60	0.225	0.101833845
120	0.297	0.134420675
180	0.375	0.169723075
360	0.444	0.200952121
600	0.522	0.23625452
1440	0.675	**0.305501535**

Determined solubility and standard deviation

Time (min)	Exp 1	Exp 2	Exp 3	STDEV
5	0.038697	0.044807	0.032587	0.00611
10	0.055669	0.062458	0.04888	0.006789
15	0.062458	0.070605	0.054311	0.008147
20	0.077394	0.088256	0.066531	0.010862
30	0.089614	0.096403	0.082825	0.006789
45	0.105228	0.123558	0.086898	0.01833
60	0.116769	0.131705	0.101834	0.014936
120	0.154787	0.175154	0.134421	0.020367
180	0.189411	0.209099	0.169723	0.019688
360	0.217246	0.233539	0.200952	0.016293
600	0.243722	0.25119	0.236255	0.007468
1440	**0.300749**	**0.295997**	**0.305502**	0.004752

QUN:OXA

Solubility calculated from measured absorbance

Time	Absorbance	Con. (mg/ml)
5	0.675	0.305501535
10	0.831	0.376106334
15	0.954	0.431775502
20	1.137	0.514600363
30	1.293	0.585205162
45	1.602	0.725056975
60	2.001	0.905642327
120	2.157	0.976247126
180	2.589	1.171768108
360	3.081	1.394444782
600	3.885	1.758331055
1440	4.533	**2.051612528**

Determined solubility and standard deviation

Time (min)	Exp 1	Exp 2	Exp 3	STDEV
5	0.443996	0.58249	0.305502	0.138494
10	0.539719	0.703332	0.376106	0.163613
15	0.586563	0.74135	0.431776	0.154787
20	0.647663	0.780726	0.5146	0.133063
30	0.709442	0.83368	0.585205	0.124237
45	0.818065	0.911073	0.725057	0.093008
60	0.93144	0.957238	0.905642	0.025798
120	1.071292	1.166337	0.976247	0.095045
180	1.28107	1.390371	1.171768	0.109302
360	1.596755	1.799065	1.394445	0.20231
600	1.809927	1.861523	1.758331	0.051596
1440	**2.002732**	**1.953852**	**2.051613**	0.04888

QUN:FUM

Solubility calculated from measured absorbance

Time	Absorbance	Con. (mg/ml)
5	0.456	0.206383259
10	0.783	0.35438178
15	0.957	0.433133287
20	1.35	0.611003069
30	1.59	0.719625837
45	1.68	0.760359375
60	1.854	0.839110882
120	2.748	1.243730692
180	3.318	1.501709766
360	4.302	1.947063114
600	5.109	2.312307171
1440	5.241	**2.372049693**

Determined solubility and standard deviation

	Exp 1	Exp 2	Exp 3	STDEV
5	0.215888	0.206383	0.225392	0.009504
10	0.34963	0.354382	0.344877	0.004752
15	0.437886	0.433133	0.442638	0.004752
20	0.556692	0.611003	0.50238	0.054311
30	0.685002	0.719626	0.650379	0.034624
45	0.730488	0.760359	0.700617	0.029871
60	0.811955	0.839111	0.784799	0.027156
120	1.056356	1.243731	0.868982	0.187374
180	1.283785	1.50171	1.065861	0.217924
360	1.600828	1.947063	1.254593	0.346235
600	2.069943	2.312307	1.827578	0.242365
1440	**2.406673**	**2.37205**	**2.441297**	0.034624

QUN:SUC

Solubility calculated from measured absorbance

Time	Absorbance	Con. (mg/ml)
5	0.831	0.376106334
10	1.23	0.556691685
15	1.602	0.725056975
20	1.818	0.822817467
30	1.878	0.849973158
45	2.157	0.976247126
60	2.718	1.230152846
120	2.898	1.311619922
180	3.822	1.729817578
360	4.779	2.162950865
600	4.995	2.260711356
1440	5.181	**2.344894001**

Determined solubility and standard deviation

	Exp 1	Exp 2	Exp 3	STDEV
5	0.405299	0.434491	0.376106	0.029192
10	0.633407	0.710121	0.556692	0.076715
15	0.813313	0.901569	0.725057	0.088256
20	0.898175	0.973532	0.822817	0.075357
30	1.07265	1.295327	0.849973	0.222677
45	1.273602	1.570957	0.976247	0.297355
60	1.508499	1.786845	1.230153	0.278346
120	1.662607	2.013595	1.31162	0.350987
180	1.925339	2.12086	1.729818	0.195521
360	2.2675	2.37205	2.162951	0.104549
600	2.338105	2.415499	2.260711	0.077394
1440	**2.416857**	**2.488819**	**2.344894**	0.071963

QUN:ADA

Solubility calculated from measured absorbance

Time	Absorbance	Con. (mg/ml)
5	0.366	0.165649721
10	0.675	0.305501535
15	0.831	0.376106334
20	1.014	0.458931194
30	1.293	0.585205162
45	1.446	0.654452176
60	1.539	0.696543499
120	1.941	0.878486635
180	2.712	1.227437277
360	3.699	1.67414841
600	4.068	1.841155915
1440	4.131	**1.869669392**

Determined solubility and standard deviation

	Exp 1	Exp 2	Exp 3	STDEV
5	0.196879	0.228108	0.16565	0.031229
10	0.314327	0.323153	0.305502	0.008826
15	0.397152	0.418198	0.376106	0.021046
20	0.460289	0.461647	0.458931	0.001358
30	0.575701	0.566196	0.585205	0.009504
45	0.689755	0.725057	0.654452	0.035302
60	0.752892	0.80924	0.696543	0.056348
120	0.991862	1.105237	0.878487	0.113375
180	1.255951	1.284464	1.227437	0.028513
360	1.680258	1.686368	1.674148	0.00611
600	1.801101	1.761047	1.841156	0.040055
1440	**1.873743**	**1.877816**	**1.869669**	0.004073

QUN:MAL

Solubility calculated from measured absorbance

Time	Absorbance	Con. (mg/ml)
5	0.738	0.334015011
10	1.047	0.473866825
15	1.416	0.64087433
20	1.755	0.79430399
30	2.157	0.976247126
45	2.682	1.213859431
60	3.051	1.380866936
120	4.533	2.051612528
180	5.889	2.665331166
360	7.371	3.336076758
600	7.554	3.418901618
1440	7.77	**3.516662109**

Determined solubility and standard deviation

	Exp 1	Exp 2	Exp 3	STDEV
5	0.347593	0.361171	0.334015	0.013578
10	0.499665	0.525463	0.473867	0.025798
15	0.671424	0.701975	0.640874	0.03055
20	0.85812	0.921936	0.794304	0.063816
30	1.091659	1.207071	0.976247	0.115412
45	1.364574	1.515288	1.213859	0.150714
60	1.536333	1.6918	1.380867	0.155466
120	2.173813	2.296014	2.051613	0.122201
180	2.666689	2.668047	2.665331	0.001358
360	3.207766	3.079455	3.336077	0.128311
600	3.428406	3.437911	3.418902	0.009504
1440	**3.531598**	**3.546533**	**3.516662**	0.014936

QUN:GLT

Solubility calculated from measured absorbance

Time	Absorbance	Con. (mg/ml)
5	0.564	0.255263504
10	0.87	0.393757533
15	1.002	0.453500056
20	1.242	0.562122824
30	1.284	0.581131808
45	2.049	0.927366881
60	2.442	1.105236663
120	3.426	1.550590011
180	3.951	1.788202316
360	4.017	1.818073577
600	4.236	1.917191853
1440	4.344	**1.966072098**

Determined solubility and standard deviation

	Exp 1	Exp 2	Exp 3	STDEV
5	0.286493	0.317722	0.255264	0.031229
10	0.429739	0.46572	0.393758	0.035981
15	0.513243	0.572985	0.4535	0.059743
20	0.621186	0.68025	0.562123	0.059064
30	0.711479	0.841826	0.581132	0.130347
45	1.019017	1.110668	0.927367	0.09165
60	1.162264	1.219291	1.105237	0.057027
120	1.633415	1.71624	1.55059	0.082825
180	1.879853	1.971503	1.788202	0.09165
360	1.913797	2.009521	1.818074	0.095724
600	1.966751	2.01631	1.917192	0.049559
1440	**2.009521**	**2.05297**	**1.966072**	0.043449

QUN:MAE

Solubility calculated from measured absorbance

Time	Absorbance	Con. (mg/ml)
5	0.543	0.245759012
10	0.696	0.315006027
15	0.849	0.384253041
20	1.023	0.463004548
30	1.284	0.581131808
45	1.635	0.739992606
60	1.854	0.839110882
120	3.318	1.501709766
180	3.951	1.788202316
360	4.149	1.877816099
600	4.389	1.986438867
1440	4.848	**2.194179911**

Determined solubility and standard deviation

	Exp 1	Exp 2	Exp 3	STDEV
5	0.247796	0.249832	0.245759	0.002037
10	0.329942	0.344877	0.315006	0.014936
15	0.431776	0.479298	0.384253	0.047522
20	0.524784	0.586563	0.463005	0.061779
30	0.671424	0.761717	0.581132	0.090293
45	0.797698	0.855404	0.739993	0.057706
60	1.080118	1.321124	0.839111	0.241007
120	1.50782	1.51393	1.50171	0.00611
180	1.812642	1.837083	1.788202	0.02444
360	1.998659	2.119502	1.877816	0.120843
600	2.067227	2.148015	1.986439	0.080788
1440	**2.211152**	**2.228125**	**2.19418**	0.016972

QUN:BZA

Solubility calculated from measured absorbance

Time	Absorbance	Con. (mg/ml)
5	0.783	0.35438178
10	0.957	0.433133287
15	1.002	0.453500056
20	1.11	0.502380301
30	1.242	0.562122824
45	1.35	0.611003069
60	1.656	0.749497098
120	2.007	0.908357896
180	2.136	0.966742634
360	2.532	1.145970201
600	2.727	1.2342262
1440	3.252	**1.471838504**

Determined solubility and standard deviation

	Exp 1	Exp 2	Exp 3	STDEV
5	0.372033	0.389684	0.354382	0.017651
10	0.44128	0.449427	0.433133	0.008147
15	0.479977	0.506454	0.4535	0.026477
20	0.53293	0.563481	0.50238	0.03055
30	0.591315	0.620508	0.562123	0.029192
45	0.644948	0.678892	0.611003	0.033945
60	0.799735	0.849973	0.749497	0.050238
120	0.986431	1.064503	0.908358	0.078073
180	1.02988	1.093017	0.966743	0.063137
360	1.226758	1.307547	1.14597	0.080788
600	1.321124	1.408023	1.234226	0.086898
1440	**1.482701**	**1.493563**	**1.471839**	0.010862

QUN-SO_4

Solubility calculated from measured absorbance

Time	Absorbance	Con. (mg/ml)
5	0.831	0.462274157
10	1.24	0.689795373
15	1.648	0.916760302
20	1.625	0.903965711
30	1.912	1.063619962
45	2.144	1.192678452
60	2.282	1.269446001
120	2.346	1.305048343
180	2.706	1.505311516
360	2.812	1.564277895
600	2.832	1.575403626
1440	2.964	**1.648833456**

Determined solubility and standard deviation

	Exp 1	Exp 2	Exp 3	STDEV
5	0.468671	0.475069	0.462274	0.006397
10	0.692855	0.695915	0.689795	0.00306
15	0.895065	0.87337	0.91676	0.021695
20	0.907303	0.910641	0.903966	0.003338
30	1.045263	1.026905	1.06362	0.018357
45	1.171261	1.149844	1.192678	0.021417
60	1.299485	1.329525	1.269446	0.030039
120	1.397948	1.490848	1.305048	0.0929
180	1.5131	1.520888	1.505312	0.007788
360	1.579298	1.594317	1.564278	0.01502
600	1.59988	1.624357	1.575404	0.024477
1440	**1.67331**	**1.697787**	**1.648833**	0.024477

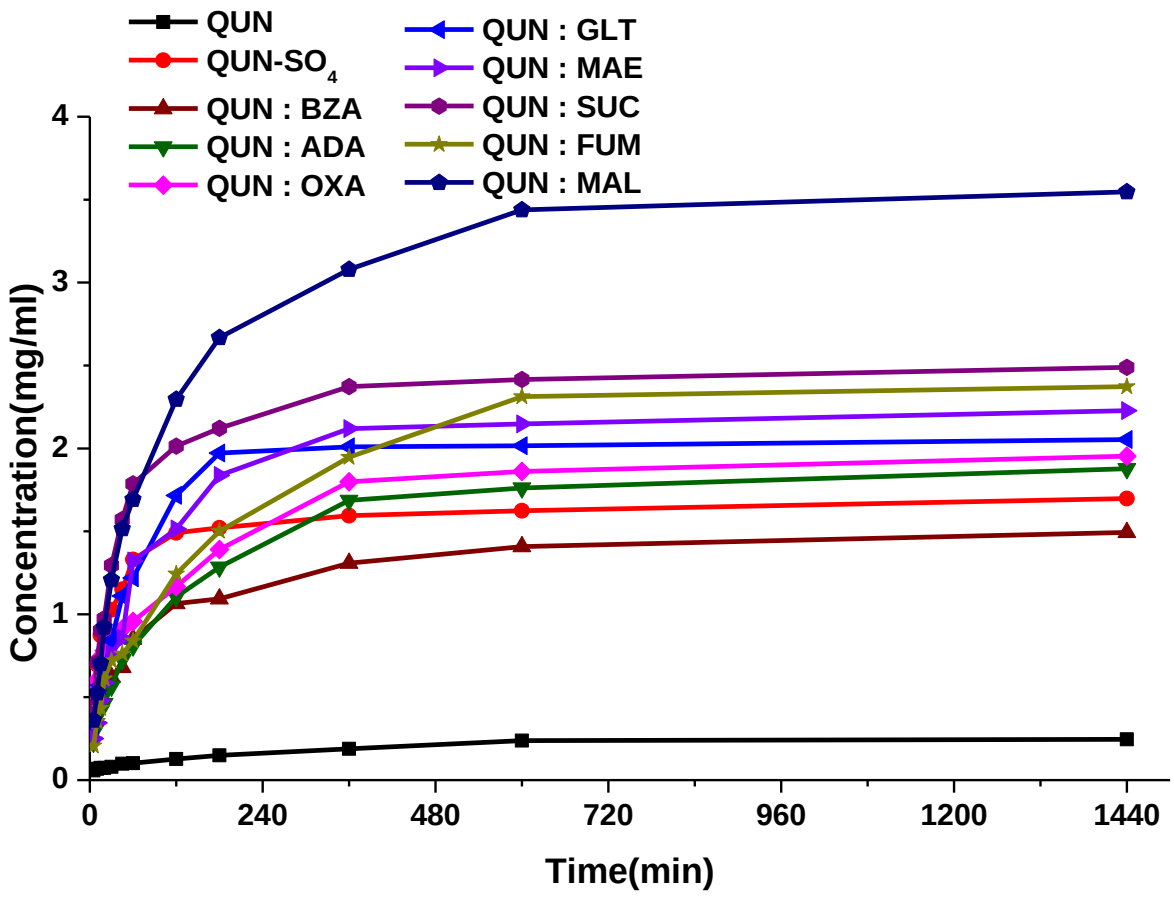
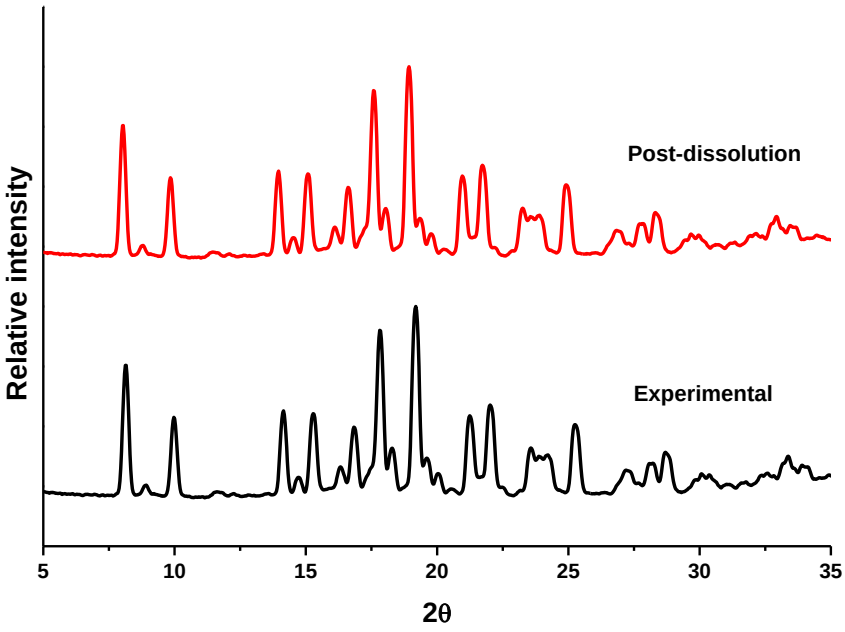
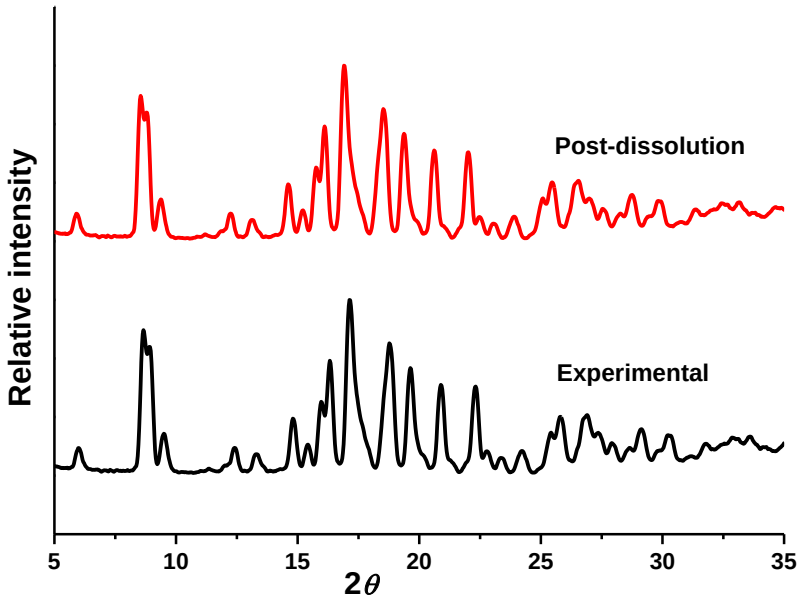


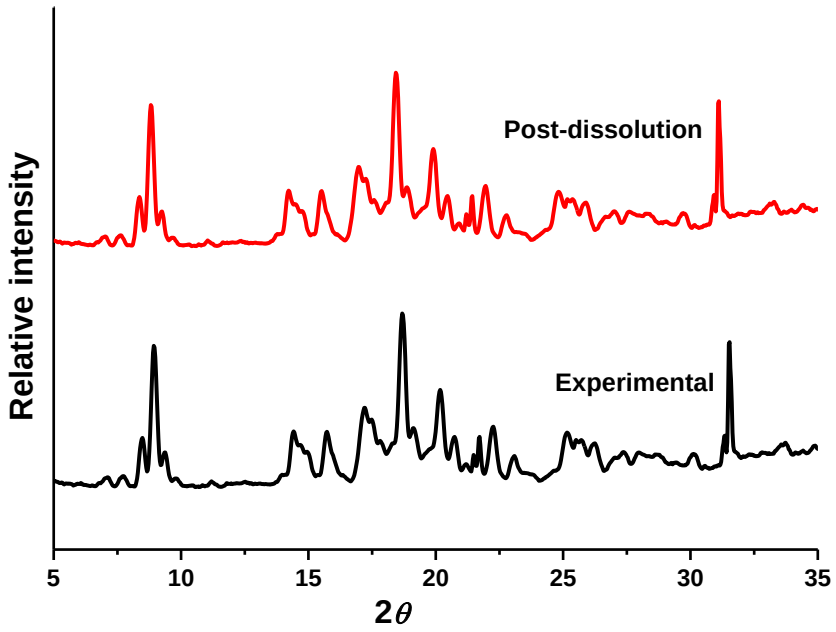
Fig. S13 The experimentally determined solubility curve till 24 hours (1440 minutes)



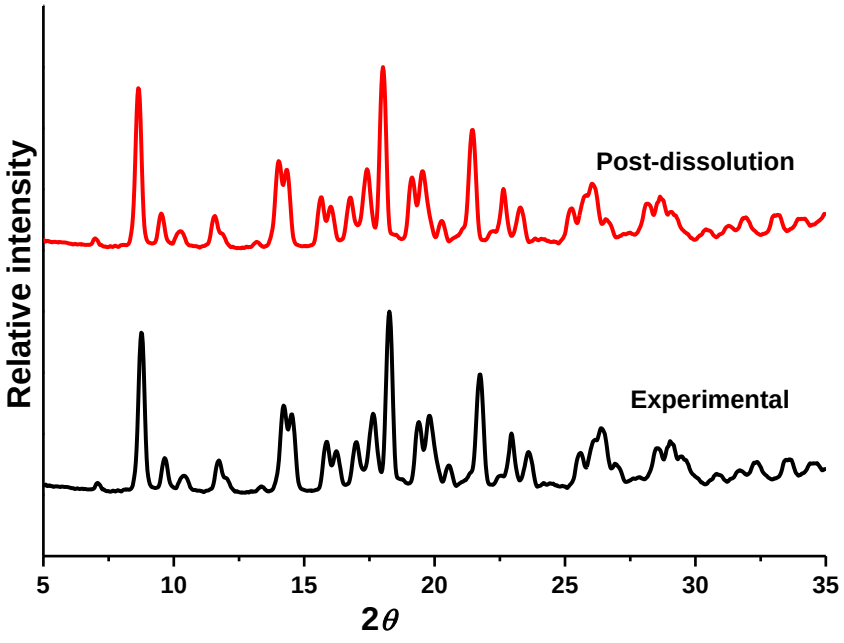
QUN:SUC



QUN:OXA



QUN:ADA



QUN:FUM

Fig. S14 PXRD patterns of the solid materials after the dissolution experiment to confirm the phase stability