9-Ethyladenine: Mechanochemical Synthesis, Characterization and DFT Calculations of Novel Cocrystals and Salts

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TABLE OF CONTENTS

Experimental details for the synthesis of the new salts and cocrystals

Synthesis of 9-ethyladenine- malonic acid (2:1) hydrated salt ***(1)***. A mixture of 9-ethyladenine (50.20 mg, 0.308 mmol) and malonic acid (31.79 mg, 0.306 mmol) was placed in the grinding jar with two drops of water. The mixture was milled for 30 min.

Suitable crystals were obtained by dissolving 26 mg of product obtained by grinding in a mixture of ethyl acetate (10 mL) and absolute ethanol (5 mL), filtered and left to evaporate at room temperature. After three weeks, plate-shaped crystals were collected.

Synthesis of 9-ethyladenine- succinic acid salt (1:1) ***(2)***. A mixture of 9-ethyladenine (101.07 mg, 0.617 mmol) and succinic acid (72.56 mg, 0.614 mmol) was placed in the grinding jar with two drops of water. The mixture was milled for 30 min.

Synthesis of 9-ethyladenine- succinic acid (1:1) salt ***(2)***. A mixture of 9-ethyladenine (101.36 mg, 0.621 mmol) and succinic acid (72.52 mg, 0.614 mmol) was placed in the grinding jar with two drops of methanol. The mixture was milled for 30 min.

Suitable crystals were afforded by dissolving 25 mg of product obtained by grinding in a mixture of acetonitrile (3 mL) and methanol (3 mL), filtered and left to evaporate at room temperature. After five days, needle-shaped crystals were collected.

Synthesis of 9-ethyladenine- succinic acid (2:1) cocrystal ***(3)***. A mixture of 9-ethyladenine (100.16 mg, 0.614 mmol) and succinic acid (36.23 mg, 0.307 mmol) was placed in the grinding jar with two drops of water. The mixture was milled for 30 min.

Synthesis of 9-ethyladenine- succinic acid (2:1) cocrystal ***(3)***. A mixture of 9-ethyladenine (100.76 mg, 0.617 mmol) and succinic acid (36.36 mg, 0.308 mmol) was placed in the grinding jar with two drops of methanol. The mixture was milled for 30 min.

Suitable crystals were obtained by dissolving 25 mg of product obtained by grinding in dimethyl sulfoxide (0.5 mL), filtered and left to evaporate at 60 °C. After six days, plate-shaped crystals were collected.

Synthesis of 9-ethyladenine- glutaric acid (1:1) cocrystal ***(4)***. A mixture of 9-ethyladenine (100.42 mg, 0.615 mmol) and glutaric acid (81.04 mg, 0.613 mmol) was placed in the grinding jar with two drops of water. The mixture was milled for 30 min.

Suitable crystals were afforded by dissolving 6 mg of product obtained by grinding in dimethyl sulfoxide (0.5 mL), filtered and left to evaporate at 60 °C. After five days, prismatic crystals were collected.

Synthesis of 9-ethyladenine- fumaric acid hydrated (1:1:1) salt ***(5)***. A mixture of 9-ethyladenine (100.31 mg, 0.615 mmol) and fumaric acid (71.17 mg, 0.613 mmol) was placed in the grinding jar with two drops of water. The mixture was milled for 30 min.

Suitable crystals were afforded by dissolving 28 mg of product obtained by grinding in methanol (13.5 mL), filtered and left to evaporate at room temperature. After two weeks, prismatic crystals were collected.

Synthesis of 9-ethyladenine-fumaric acid (2:1) cocrystal ***(6)***. A mixture of 9-ethyladenine (100.40 mg, 0.615 mmol) and fumaric acid (35.58 mg, 0.307 mmol) was placed in the grinding jar with two drops of water. The mixture was milled for 30 min.

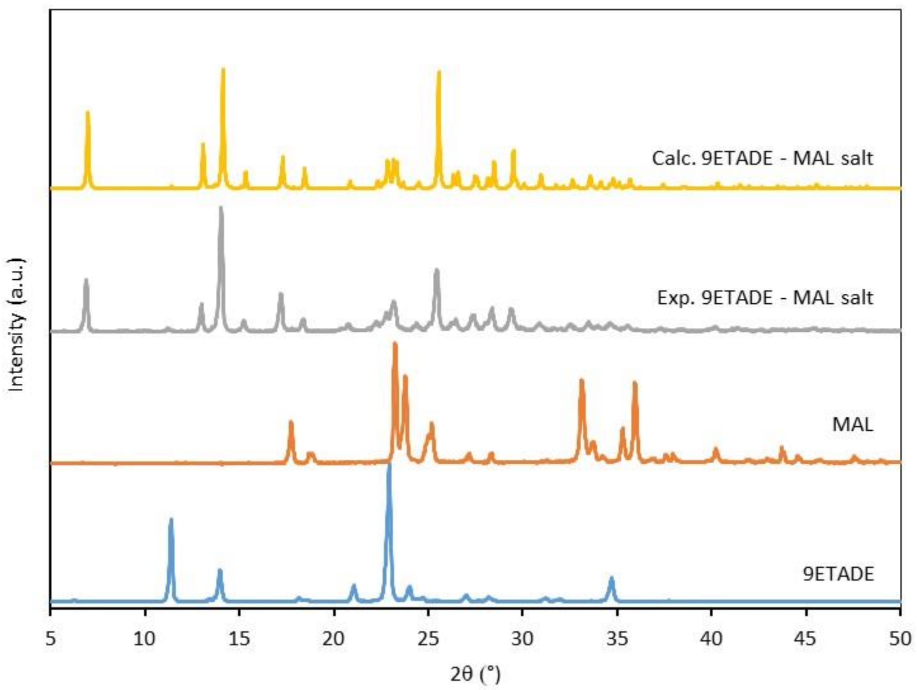
Suitable crystals were afforded by dissolving 6 mg of product obtained by grinding in dimethyl sulfoxide (0.5 mL), filtered and left to evaporate at 60 °C. After six days, prismatic crystals were collected.

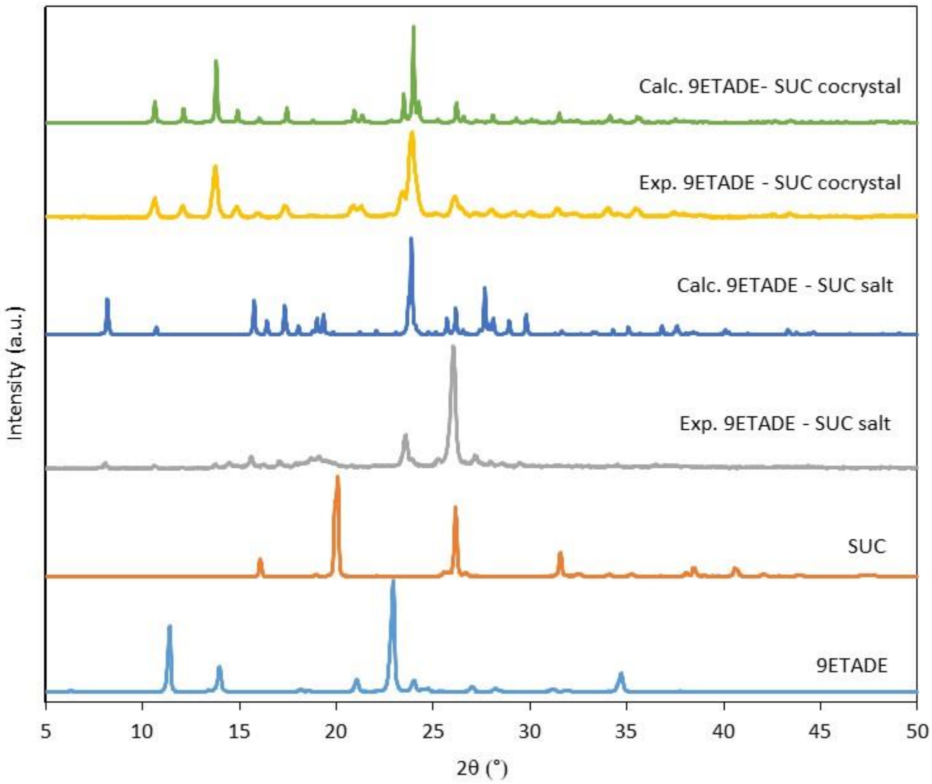
Synthesis of 9-ethyladenine- fumaric acid (2:1) cocrystal ***(6)***. A mixture of 9-ethyladenine (100.09 mg, 0.613 mmol) and fumaric acid (36.38 mg, 0.313 mmol) was placed in the grinding jar with two drops of methanol. The mixture was milled for 30 min.

Synthesis of 9-ethyladenine- adipic acid (2:1) cocrystal ***(7)***. A mixture of 9-ethyladenine (49.97 mg, 0.306 mmol) and adipic acid (44.83 mg, 0.307 mmol) was placed in the grinding jar with two drops of water. The mixture was milled for 30 min.

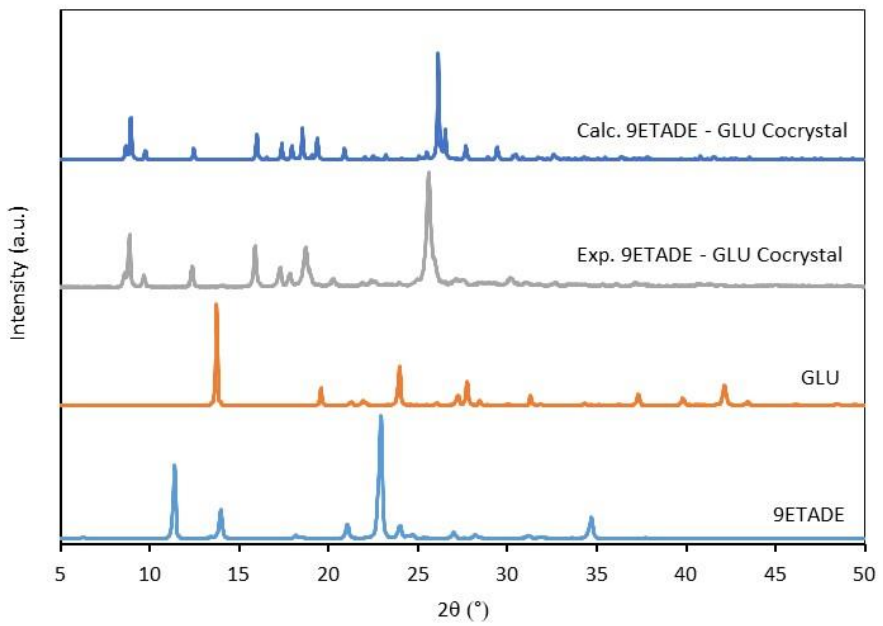
Crystals of this compound were obtained by dissolving 25.37 mg of 9-ethyladenine and 22.24 mg of adipic acid in a mixture of ethanol and deionized water (in a ratio 20:1) by slow evaporation.

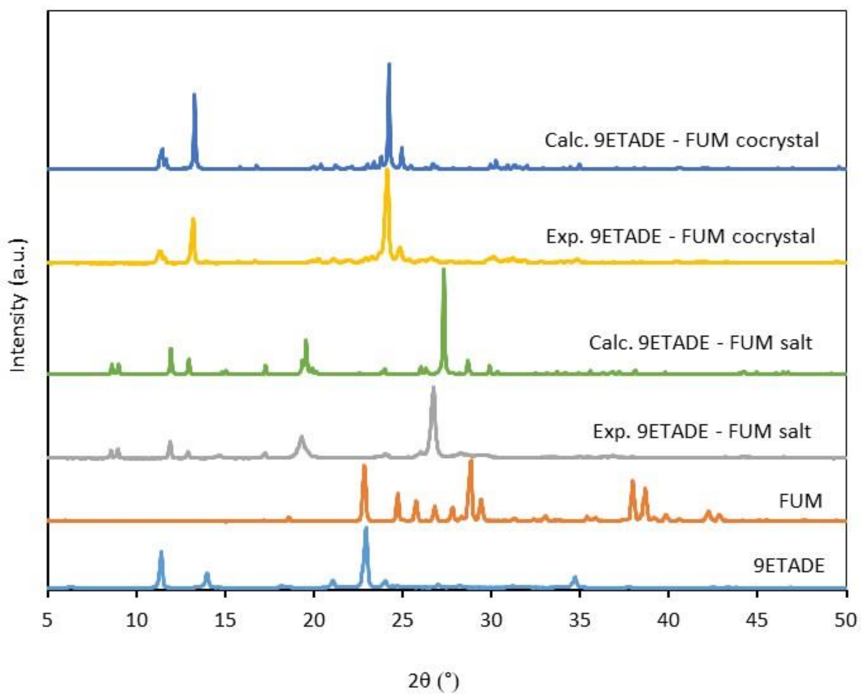
Figure S1. PXRD comparison of experimental and calculated patterns.





Calc. 9ETADE- SUC cocrystal
Exp. 9ETADE - SUC cocrystal
Calc. 9ETADE - SUC salt
Exp. 9ETADE - SUC salt
SUC
9ETADE
Intensity (a.u.)
5
10
15
20
25
30
35
40
45
50
2θ (°)


Calc. 9ETADE - GLU Cocrystal
Exp. 9ETADE - GLU Cocrystal
GLU
9ETADE
Intensity (a.u.)
5
10
15
20
25
30
35
40
45
50
2θ (°)


Calc. 9ETADE - FUM cocrystal
Exp. 9ETADE - FUM cocrystal
Calc. 9ETADE - FUM salt
Exp. 9ETADE - FUM salt
FUM
9ETADE
Intensity (a.u.)
5
10
15
20
25
30
35
40
45
50
2θ (°)

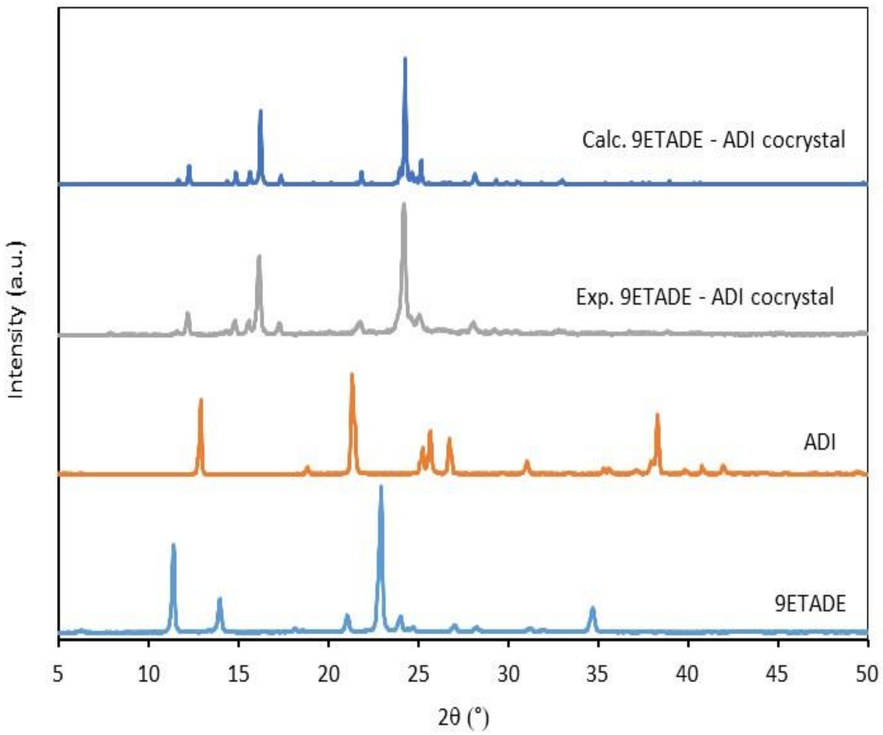
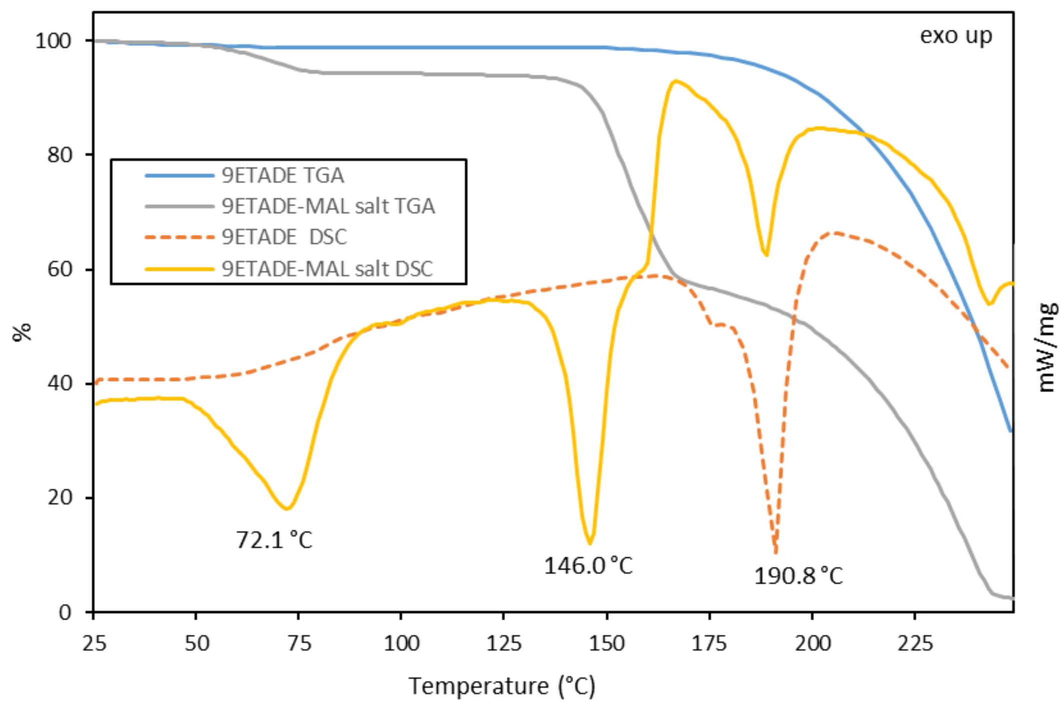
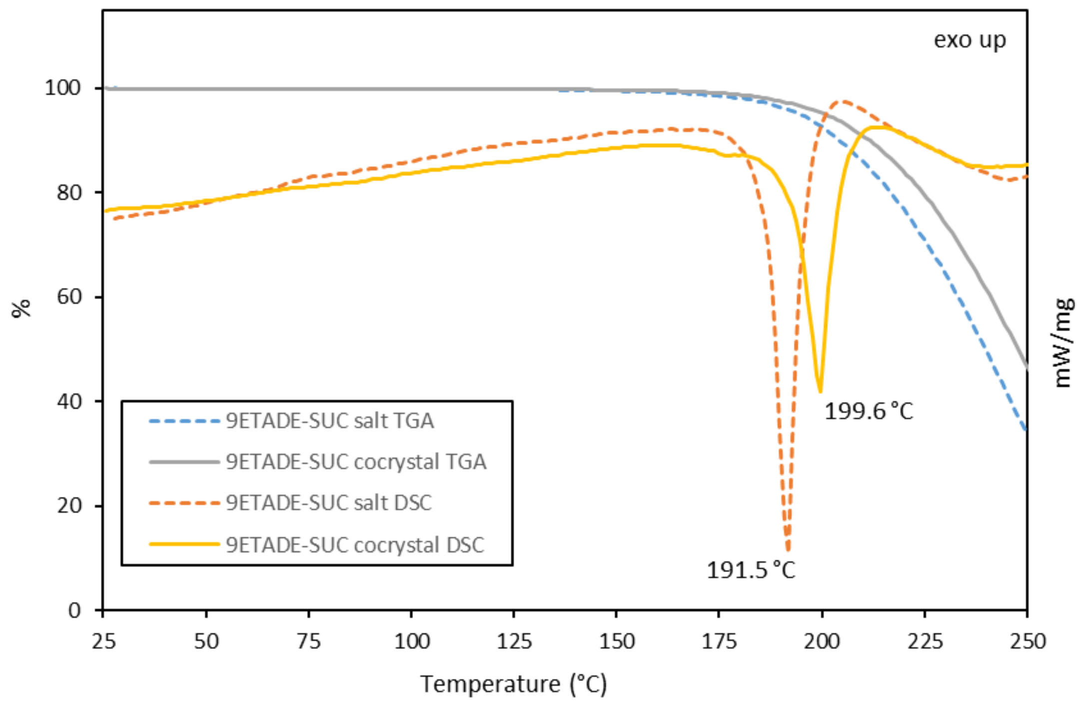
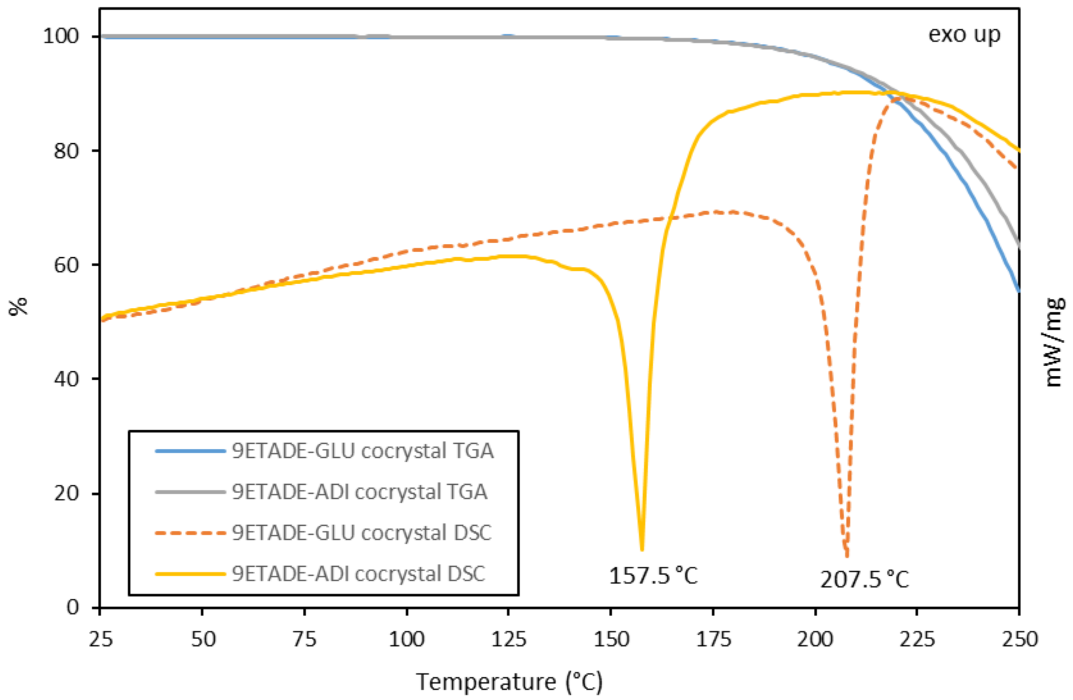

Calc. 9ETADE - ADI cocrystal
Exp. 9ETADE - ADI cocrystal
ADI
9ETADE
Intensity (a.u.)
5
10
15
20
25
30
35
40
45
50
2θ (°)

Figure S2. TGA and DSC comparison.






exo up
%
mW/mg
9ETADE-GLU cocrystal TGA
9ETADE-ADI cocrystal TGA
9ETADE-GLU cocrystal DSC
9ETADE-ADI cocrystal DSC
157.5 °C
207.5 °C
Temperature (°C)

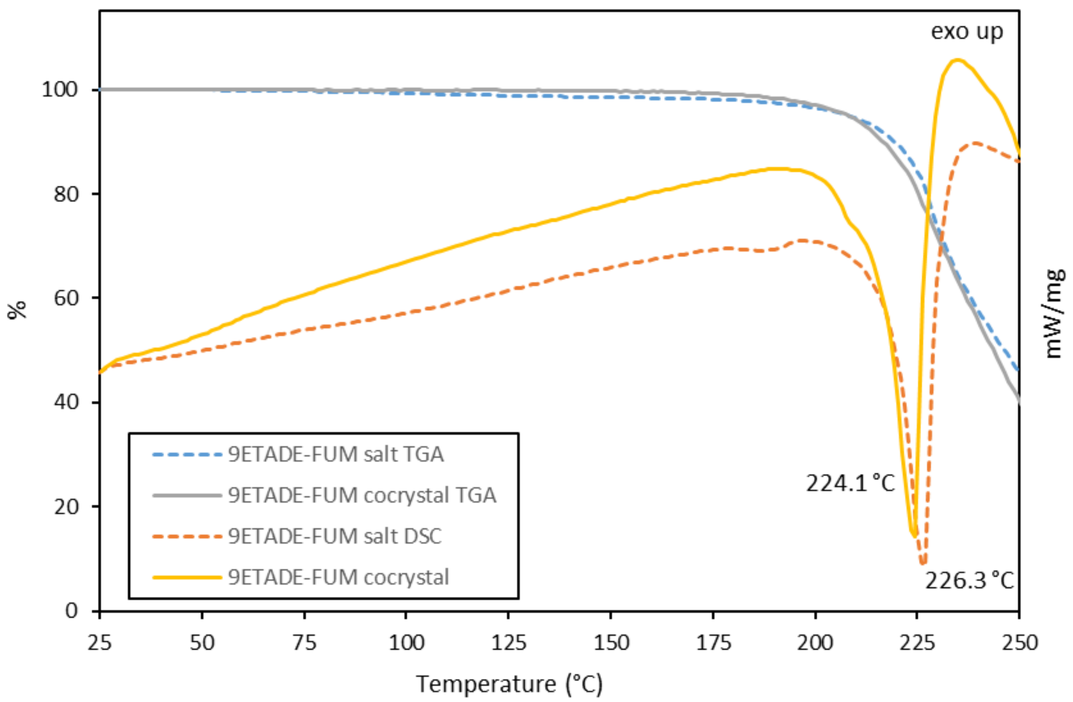
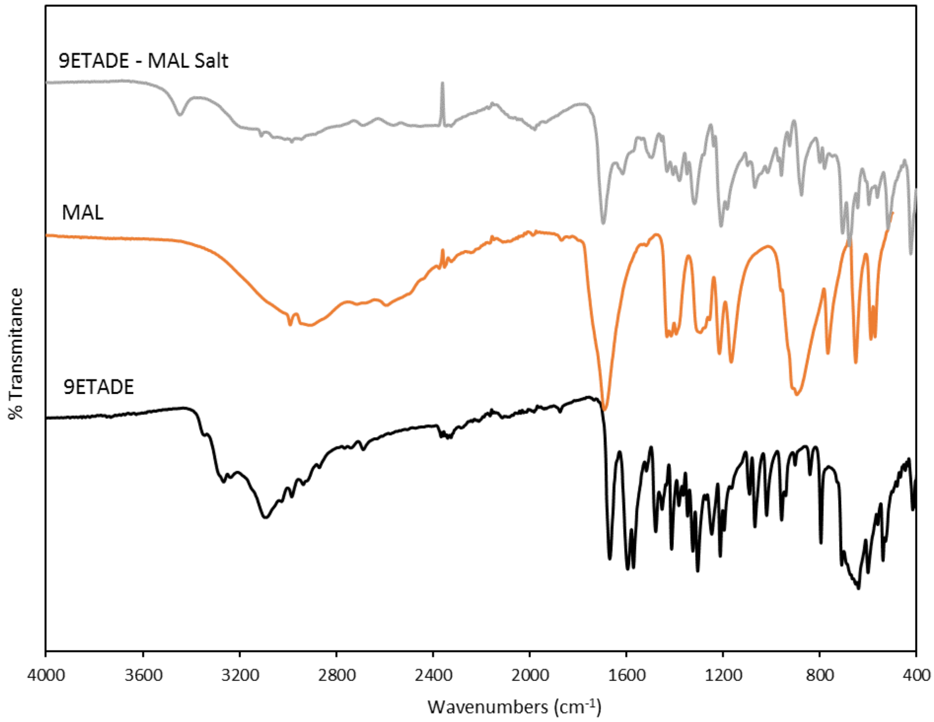
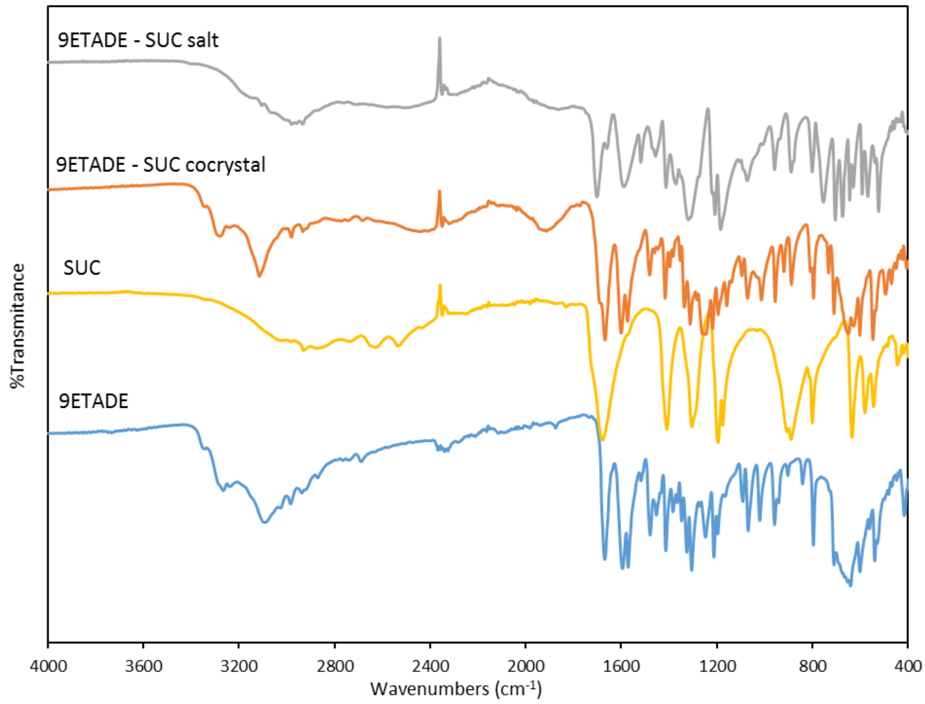
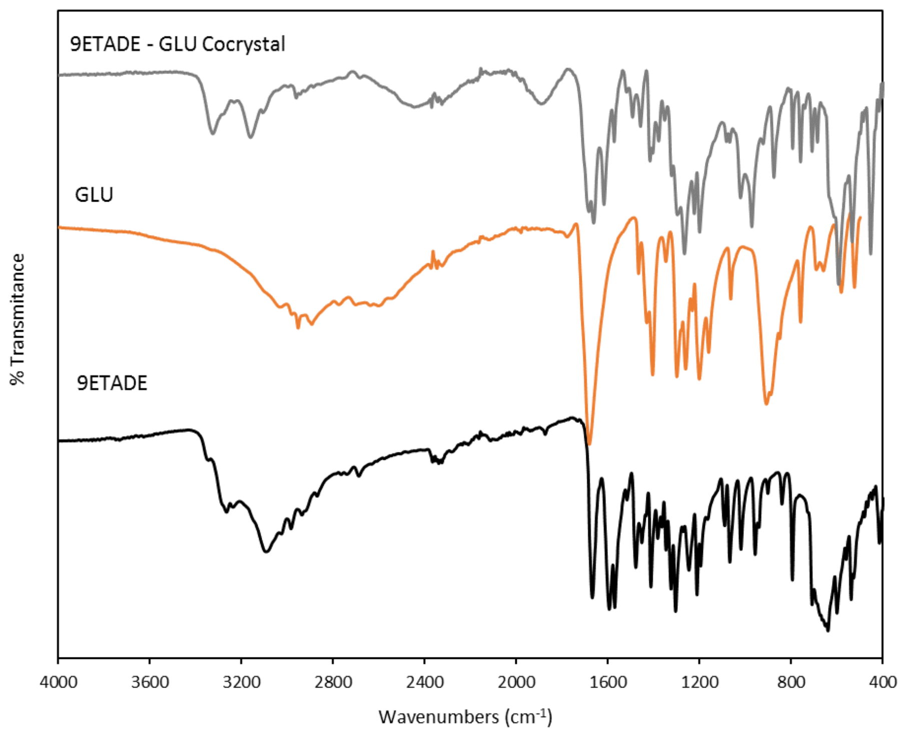
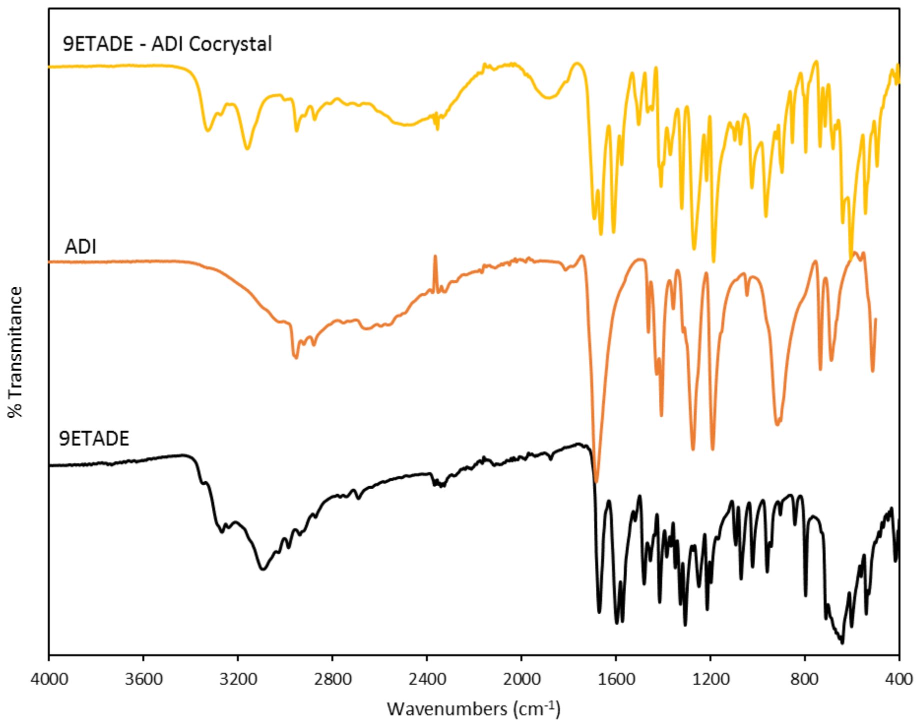

exo up
%
mW/mg
9ETADE-FUM salt TGA
9ETADE-FUM cocrystal TGA
9ETADE-FUM salt DSC
9ETADE-FUM cocrystal
224.1 °C
226.3 °C
Temperature (°C)

Figure S3. Comparison of FT-IR spectra.






9ETADE - GLU Cocrystal
GLU
9ETADE
% Transmitance
4000
3600
3200
2800
2400
2000
1600
1200
800
400
Wavenumbers (cm-1)


9ETADE - ADI Cocrystal
ADI
9ETADE
% Transmitance
4000
3600
3200
2800
2400
2000
1600
1200
800
400
Wavenumbers (cm-1)

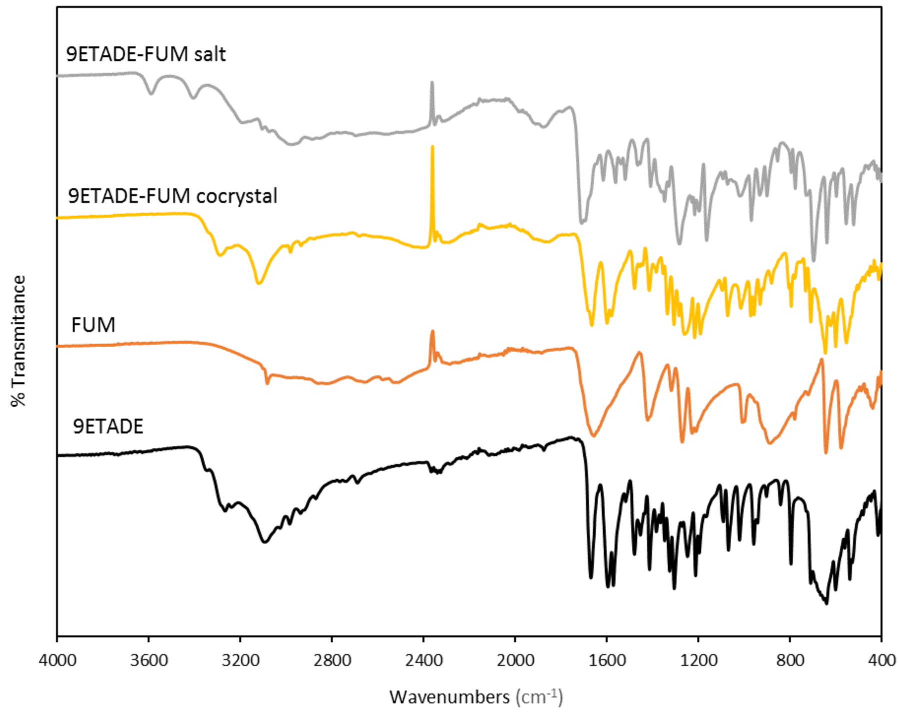

9ETADE-FUM salt
9ETADE-FUM cocrystal
FUM
9ETADE
% Transmitance
4000
3600
3200
2800
2400
2000
1600
1200
800
400
Wavenumbers (cm-1)

Table S1. Hydrogen bond parameters for the obtained structures.

Compound	D–H···A	D-H (Å)	H···A (Å)	D···A (Å)	<(DHA)	Symmetry code
(**1**)	N(1)-H1···O(1)	0.86	1.75	2.606(3)	171.3	2-x,-1-y,2-z
	N(6)-H(6A)···O(2)	0.86	1.97	2.821(3)	171.8	2-x,-1-y,2-z
	N(6)-H···N(7)	0.86	2.15	2.982(3)	161.8	-x+1, -y, -z+2
	C(2)-H(2)···O(1)	0.93	2.26	3.170(4)	164.2	1+x,y,z
	O(4)-H(4)···O(5)	0.82	1.76	2.556(3)	164.3	2-x,-1-y,1-z
	O(5)-H(51)···O(3)	0.951(18)	1.85(2)	2.798(3)	170(4)	x+1, y, z
	O(5)-H(52)···O(2)	0.954(18)	1.717(19)	2.662(3)	170(3)	
(**2**)	N(1)-H(1)···O(20)	0.976(19)	1.730(19)	2.6852(19)	165.1(17)	x-1,y,z
	N(6)-H(6A)···O(21)	0.91(2)	1.88(2)	2.760(2)	162.9(18)	-x+1,-y+1,-z+1
	N(6)-H(6B)···N(7)	0.899(19)	2.05(2)	2.914(2)	159.9(18)	-x+1,-y+1,-z+2
	O(30)-H(30)···O(20)	0.94(2)	1.60(2)	2.5466(16)	179.3(19)	x-1,y,z
(**3**)	C(8)-H(8)···O(1)	0.93	2.36	3.183(4)	147.6	-x+3/2, y-1/2, -z+1/2
	N(6)-H(6A)···N(7)	0.86	2.19	3.044(4)	174.5	-x+1/2, y+1/2, -z+1/2
	N(6)-H(6B)···N(1)	0.86	2.21	3.055(4)	165.6	-x+1/2, y-1/2, -z+1/2
	O(2)-H(2A)···N(3)	0.82	1.86	2.664(3)	167.2	-x+3/2, y-1/2, -z+1/2
(**4**)	C(2)-H(2)···N(3)	0.95	2.52	3.361(3)	147.2	-x+1,-y+2,-z+1
	N(6)-H(6A)···O(22)	0.88	2.05	2.925(2)	169.9	
	N(6)-H(6B)···O(26)	0.88	1.99	2.868(2)	171.8	x+1,-y+3/2,z+1/2
	C(10)-H(10B)···O(26)	0.99	2.53	3.331(4)	137.9	-x+1,y+1/2,-z+1/2
	C(11)-H(11A)···O(26)	0.98	2.51	3.398(4)	151.4	-x+1,y+1/2,-z+3/2
	C(11)-H(11B)···O(26)	0.98	2.56	3.459(3)	152.9	-x+1,-y+2,-z+1
	C(11)-H(11C)···O(22)	0.98	2.60	3.579(4)	173.3	-x+2,y+1/2,-z+3/2
	O(21)-H(21)···N(1)	0.97(2)	1.72(2)	2.673(2)	167(2)	
	O(27)-H(27)···N(7)	0.98(3)	1.69(3)	2.658(2)	169(2)	x-1,-y+3/2,z-1/2
(**5**)	N(1)-H(1)···O(21)	0.89(2)	1.82(2)	2.711(4)	179(5)	
	N(6)-H(6A)···O(22)	0.88	1.92	2.793(5)	175.4	
	N(6)-H(6B)···N(7)	0.88	2.13	2.966(5)	158.6	-x,-y,-z+1
	O(31)-H(31)···O(21)	0.91(2)	1.64(2)	2.550(4)	179(5)	
	O(1W)-H(1W1)···O(22)	0.94(2)	1.86(3)	2.790(6)	167(9)	
	O(1W)-H(1W2)···O(31)	0.94(2)	2.05(3)	2.974(7)	166(9)	-x-1,-y,-z
(**6**)	C(2B)-H(2B)···O(4)	0.966(18)	2.63(3)	3.316(5)	128(2)	-x-1/2, y-1/2, -z+1/2
	C(8A)-H(8A)···O(1)	0.936(18)	2.23(2)	3.109(5)	156(3)	-x, -y+1, -z+1
	C(8B)-H(8B)···O(4)	0.947(18)	2.32(2)	3.131(5)	143(3)	-x-1/2, y+1/2, -z+1/2
	N(6A)-H(6A1)···N(7A)	0.875(18)	2.187(19)	3.058(4)	174(3)	-x-1/2, y-1/2, -z+1/2
	N(6A)-H(6A2)···N(1A)	0.865(18)	2.25(2)	3.091(4)	163(3)	-x-1/2, y+1/2, -z+1/2
	N(6B)-H(6B1)···N(7B)	0.896(18)	2.154(19)	3.047(4)	175(3)	-x+1/2, y-1/2, -z+1/2
	N(6B)-H(6B2)···N(1B)	0.874(18)	2.26(2)	3.113(4)	165(3)	-x+1/2, y+1/2, -z+1/2
	O(2)-H(2C)···N(3A)	0.854(19)	1.82(2)	2.658(4)	168(5)	-x, -y, -z+1
	O(3)-H(3A)···N(3B)	0.860(19)	1.80(2)	2.647(4)	169(4)	-x-1/2, y+1/2, -z+1/2
(**7**)	C(2A)-H(2A)...O(1D)	0.93	2.56	3.475(5)	168.3	-x+1,y+1/2,-z+3/2
	N(6A)-H(6A1)...O(2C)	0.86	2.12	2.976(4)	170.6	
	N(6A)-H(6A2)...O(7D)	0.86	1.99	2.846(4)	171.4	
	N(7A)-H(7A)...O(8D)	1.027(19)	1.71(2)	2.714(4)	166(4)	

C(10A)-H(10B)...O(2C)	0.97	2.63	3.431(6)	139.7	-x+1,y+1/2,-z+3/2
C(11A)-H(11B)...O(7D)	0.96	2.64	3.494(8)	148.5	-x+1,y+1/2,-z+3/2
C(2B)-H(2B)...O(1C)	0.93	2.50	3.414(5)	169.2	-x+1,y-1/2,-z+3/2
N(6B)-H(6B1)...O(2D)	0.86	2.10	2.947(5)	169.7	
N(6B)-H(6B2)...O(7C)	0.86	1.99	2.843(5)	168.7	x+1,y,z-1
C(10B)-H(10D)...O(2D)	0.97	2.61	3.406(7)	139.1	-x+2,y-1/2,-z+1/2
C(11B)-H(11F)...N(3B)	0.96	2.68	3.306(9)	123.3	
O(1C)-H(1C)...N(1A)	0.89(2)	1.80(2)	2.669(4)	167(6)	
O(8C)-H(8C)...N(7B)	0.92(2)	1.83(3)	2.719(4)	163(5)	x-1,y,z+1
O(1D)-H(1D)...N(1B)	0.91(2)	1.78(3)	2.642(4)	156(6)	