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Understanding the thermal stability of apalutamide crystalline solvates through crystal structure analyses and computational studies

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Table S1. Experimental details

	(APA)	(APA-DMF-2-1)	(KA1087_0m_APA-DMF-2:1)	(APA-DMF_1-1)
CCDC	2121550	2151552	2152151	2151553
Crystal data				
Chemical formula	$C_{21}H_{15}F_4N_5O_2S$	$2(C_{21}H_{15}F_4N_5O_2S)\cdot C_3H_7NO$	$2(C_{21}H_{15}F_4N_5O_2S)\cdot C_3H_7NO$	$C_{21}H_{16}F_4N_5O_2S\cdot C_3H_7NO$
M_r	477.44	1027.97	1027.97	550.53
Crystal system, space group	Monoclinic, $P2_1/c$	Triclinic, $P\overline{1}$	Triclinic, $P\overline{1}$	Orthorhombic, $Pca2_1$
Temperature (K)	100	150	100	100
a, b, c (Å)	17.7813 (6), 13.0140 (4), 18.4676 (6)	12.3974 (9), 17.3988 (15), 23.2772 (17)	12.3588 (11), 17.3486 (15), 23.177 (2)	17.3059 (19), 12.2220 (13), 47.409 (5)
α, β, γ (°)	90, 100.8839 (11), 90	68.343 (3), 81.611 (3), 89.765 (3)	68.252 (5), 81.670 (5), 89.735 (5)	90, 90, 90
V (Å^3)	4196.6 (2)	4609.8 (6)	4560.4 (7)	10027.6 (19)
Z	8	4	4	16
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
μ (mm^{-1})	0.22	0.21	0.21	0.20
Crystal size (mm)	0.25 × 0.20 × 0.10	0.40 × 0.20 × 0.01	0.22 × 0.11 × 0.09	0.32 × 0.28 × 0.16
Data collection				
Diffractometer	Bruker *SMART APEX* II	Bruker *SMART APEX* II	Bruker D8 QUEST PHOTON-100	Bruker D8 Venture
Absorption correction	Multi-scan *SADABS* (Bruker, 2016)	Multi-scan *SADABS* (Bruker, 2016)	Multi-scan *SADABS* 2016/2: Krause, L., Herbst-Irmer, R.,	Multi-scan *SADABS* (Bruker, 2016)

			Sheldrick G.M. & Stalke D., J. Appl. Cryst. 48 (2015) 3-10	
T_{min}, T_{max}	0.621, 0.746	0.652, 0.783	0.652, 0.783	0.494, 0.746
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	42501, 9154, 7500	39826, 15816, 9831	45004, 45004, 32486	64602, 20533, 14775
R_{int}	0.039	0.070	?	0.073
$(\sin\theta/\lambda)_{max}$ ($Å^{-1}$)	0.639	0.596	0.595	0.626
Refinement				
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.043, 0.108, 1.03	0.104, 0.275, 1.06	0.082, 0.193, 1.12	0.070, 0.169, 1.08
No. of reflections	9154	15816	45004	20533
No. of parameters	616	1332	1352	1365
No. of restraints	0	3	0	1
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement	H atoms treated by a mixture of independent and constrained refinement	H atoms treated by a mixture of independent and constrained refinement	H atoms treated by a mixture of independent and constrained refinement
	$w = 1/[\sigma^2(F_o^2) + (0.0461P)^2 + 3.5281P]$ where $P = (F_o^2$	$w = 1/[\sigma^2(F_o^2) + (0.097P)^2 + 28.542P]$ where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + 25.5581P]$ where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0569P)^2 + 14.5178P]$ where $P = (F_o^2 + 2F_c^2)/3$

	$+ 2F_c^2)/3$			
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	1.01, −0.79	0.67, −0.36	0.68, −0.76	0.47, −0.53
Absolute structure	?	?	?	Refined as an inversion twin.
Absolute structure parameter	?	?	?	0.73 (13)

	(KA1156_0m_APA-DOX-2:1)	(KA1165_0m_APA-DMA-1:1)	(KB02_0m_a_APA-CHY-1:1)	(KB22_0m_APA-ACN-1:1)
CCDC	2152152	2152153	2152154	2152156
Crystal data				
Chemical formula	$2(C_{21}H_{15}F_4N_5O_2S)\cdot C_4H_8O_2$	$C_{21}H_{15}F_4N_5O_2S\cdot C_4H_9NO$	$C_{21}H_{15}F_4N_5O_2S\cdot C_6H_{10}O$	$C_{21}H_{15}F_4N_5O_2S\cdot C_2H_3N$
M_r	1042.98	564.56	575.58	518.49
Crystal system, space group	Monoclinic, *C*2/*c*	Monoclinic, $P2_1/c$	Monoclinic, $P2_1/c$	Orthorhombic, $Pna2_1$
Temperature (K)	294	294	100	100
a, *b*, *c* (Å)	41.7833 (6), 13.6224 (2), 17.4061 (3)	22.5794 (15), 13.3362 (7), 18.2192 (11)	25.2912 (7), 12.4809 (4), 17.6369 (5)	8.9856 (4), 15.2222 (6), 16.9653 (7)
α, β, γ (°)	90, 110.9090 (7), 90	90, 90.944 (2), 90	90, 108.109 (1), 90	90, 90, 90
V (Å^3)	9254.9 (3)	5485.5 (6)	5291.4 (3)	2320.52 (17)
Z	8	8	8	4
Radiation type	Mo *K*α	Mo *K*α	Mo *K*α	Mo *K*α
μ (mm^{-1})	0.21	0.18	0.19	0.21
Crystal size (mm)	0.26 × 0.22 × 0.12	0.28 × 0.26 × 0.11	0.26 × 0.24 × 0.18	0.26 × 0.22 × 0.16
Data collection				

Diffractometer	Bruker D8 QUEST PHOTON-100	Bruker D8 QUEST PHOTON-100	Bruker D8 QUEST PHOTON-100	Bruker D8 QUEST PHOTON-100
Absorption correction	Multi-scan *SADABS* 2014/5	Multi-scan *SADABS* 2014/5	Multi-scan *SADABS* 2016/2: Krause, L., Herbst-Irmer, R., Sheldrick G.M. & Stalke D., J. Appl. Cryst. 48 (2015) 3-10	Multi-scan *SADABS* 2016/2: Krause, L., Herbst-Irmer, R., Sheldrick G.M. & Stalke D., J. Appl. Cryst. 48 (2015) 3-10
T_{min}, T_{max}	0.579, 0.745	0.628, 0.746	0.630, 0.745	0.670, 0.746
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	36635, 9440, 6534	50692, 11078, 7054	46140, 9019, 5179	36626, 6979, 6697
R_{int}	0.062	0.073	0.104	0.054
$(\sin \theta/\lambda)_{max}$ ($Å^{-1}$)	0.625	0.622	0.588	0.713
Refinement				
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.083, 0.201, 1.06	0.062, 0.167, 1.04	0.077, 0.157, 1.04	0.027, 0.071, 1.05
No. of reflections	9440	11078	9019	6979
No. of parameters	669	894	815	330
No. of restraints	2	423	210	1
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement	H atoms treated by a mixture of independent and constrained refinement	H atoms treated by a mixture of independent and constrained refinement	H atoms treated by a mixture of independent and constrained

				refinement
	$w = 1/[\sigma^2(F_o^2) + (0.0679P)^2 + 56.7028P]$ where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0598P)^2 + 2.9625P]$ where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0473P)^2 + 9.1283P]$ where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0371P)^2 + 0.3003P]$ where $P = (F_o^2 + 2F_c^2)/3$
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.83, −0.88	0.32, −0.35	0.65, −0.33	0.32, −0.22
Absolute structure	?	?	?	Flack x determined using 3043 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259).
Absolute structure parameter	?	?	?	0.03 (2)

	(APA-ACE-2:1)	(KB06_0m_APA-BUT-1:0.5)	(KB101_0m_APA-EtOH-2:1)
CCDC	2151551	2152155	2152157
Crystal data			
Chemical formula	$2(C_{21}H_{15}F_4N_5O_2S)\cdot C_3H_6O$	$2(C_{21}H_{15}F_4N_5O_2S)\cdot C_4H_{10}O$	$2(C_{21}H_{15}F_4N_5O_2S)\cdot C_2H_6O$
M_r	1012.96	1029.00	1000.95
Crystal system, space group	Monoclinic, *C*2/*c*	Monoclinic, $P2_1/c$	Orthorhombic, $P2_12_12$
Temperature (K)	100	100	294
a, *b*, *c* (Å)	43.7534 (14), 12.7915 (5), 17.9103 (6)	19.3859 (8), 16.1915 (3), 7.3833 (1)	16.568 (10), 37.54 (2), 7.364 (5)
α, β, γ (°)	90, 113.481 (1), 90	90, 90.171 (5), 90	90, 90, 90
V (Å^3)	9193.8 (6)	2317.51 (11)	4580 (5)
Z	8	2	4

Radiation type	Mo *K*α	Mo *K*α	Mo *K*α
μ (mm^{-1})	0.21	0.21	0.21
Crystal size (mm)	0.25 × 0.20 × 0.02	0.28 × 0.22 × 0.16	0.26 × 0.24 × 0.18
Data collection			
Diffractometer	Bruker D8 QUEST PHOTON-100	Bruker D8 QUEST PHOTON-100	Bruker D8 QUEST PHOTON-100
Absorption correction	Multi-scan *SADABS* 2016/2: Krause, L., Herbst-Irmer, R., Sheldrick G.M. & Stalke D., J. Appl. Cryst. 48 (2015) 3-10	Multi-scan *SADABS* 2016/2: Krause, L., Herbst-Irmer, R., Sheldrick G.M. & Stalke D., J. Appl. Cryst. 48 (2015) 3-10	Multi-scan *SADABS* 2016/2: Krause, L., Herbst-Irmer, R., Sheldrick G.M. & Stalke D., J. Appl. Cryst. 48 (2015) 3-10
T_{min}, T_{max}	0.623, 0.765	0.556, 0.722	0.473, 0.746
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	43641, 8143, 5609	40466, 7083, 6096	27853, 8064, 5112
R_{int}	0.064	0.044	0.085
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.596	0.715	0.595
Refinement			
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.063, 0.137, 1.05	0.059, 0.136, 1.16	0.070, 0.214, 1.03
No. of reflections	8143	7083	8064
No. of parameters	794	411	776
No. of restraints	22	3	562
H-atom treatment	H atoms treated by a mixture of independent and constrained	H-atom parameters constrained	H-atom parameters constrained

	refinement		
	$w = 1/[\sigma^2(F_o^2) + (0.0339P)^2 + 30.2507P]$ where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0338P)^2 + 2.710P]$ where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.1186P)^2 + 0.5342P]$ where $P = (F_o^2 + 2F_c^2)/3$
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.43, −0.35	0.54, −0.59	0.56, −0.32
Absolute structure	?	?	Refined as an inversion twin.
Absolute structure parameter	?	?	0.45 (19)

Computer programs: *APEX2* (Bruker, 2008), *APEX3* (Bruker, 2018), *APEX3* (Bruker, 2016), *SAINT* (Bruker, 2008), *SAINT* (Bruker, 2018), *SAINT* (Bruker, 2016), Bruker *SAINT*, *SHELXTL* (Sheldrick, 2008), SHELXT (Sheldrick, 2016), SHELXT 2014/5 (Sheldrick, 2014), *SHELXT* (Sheldrick, 2015), *SHELXL2018*/3 (Sheldrick, 2018), *SHELXL2016*/6 (Sheldrick, 2016), *SHELXL2014* (Sheldrick, 2015), Bruker *SHELXTL*.

Single-crystal X-ray diffraction

In all structures (except APA-ACN-1:1 & APA-EtOH-2:1) and aromatic fluorine atoms were positionally disordered over two sites with occupancy ratios 0.795(4)/0.205(4) for molecule B of APA, 0.547(8)/0.453(8), 0.556(10)/0.444(10), 0.508(7) /0.492(7), 0.587(8)/0.413(7) for APA-DMF-2:1 and 0.54(1)/0.46(1), 0.60(1)/0.40(1), 0.56(1)/0.44(1), 0.51(1)/0.49(1) for APA-DMF-1:1, 0.542(7)/0.458(7) for APA-DOX-2:1, 0.879(3)/0.121(3), 0.755(5)/0.245(5) for APA-DMA-1:1, 0.620(7)/0.480(7), 0.667(6)/0.333(6) for APA-CYH-1:1, 0.726(6)/0.274(6) for APA-ACE-2:1, 0.545(4)/0.456(4) for APA-BUT-1:0.5. In APA-ACE-2:1 pyridine ring was positionally disordered with occupancies equal to 0.523(2) and 0.477(2). As for APA-DMF-2:1, cyclobutane ring was conformationally disordered with occupancy ratio 0.63(3)/0.37(3). In APA-DMF-1:1, atoms F1B/F2B of $–CF_3$ groups was rotationally disordered over two sites with occupancies equal to 0.556(10)/0.444(10). The studied crystal of APA-DMF-2:1 was pseudomerohedrally twinned with domain ratio 0.922(1)/0.078(1). The crystal APA-DMF-1:1 exhibited racemic twinning with domain ratio 0.75(13)/0.25(13). In APA-DMA-1:1, the fluorine atoms F1-F3 of molecule A and F1- F2 of molecule B of APA were disordered over two positions with occupancies equal to 0.879(3)/0.121(3), for molecule A, 0.755(5)/0.245(5), for molecule B, respectively. All atoms (C22-C25/O3/N6A) of DMA solvate molecules A & B were disordered, and their site occupational factors were refined to 0.654(10)/0.346(10) for molecule A and 0.560(13)/0.440(10) for molecule B, respectively. In APA-CYH-1:1, all the atoms (C22-C27/O3) of the CYH solvate molecule B were disordered over two positions (C23B-C27B/O3B and C23D-C27D/O3D), and their site occupational factors were refined to 0.538(6) and 0.462(6), respectively. In the APA-BUT-1:0.5 structure, the atoms C20/N5/C21 of APA molecule were disordered over two sites (C20/N5/C21 & C20D/N5D/C21D), and their site occupational factors were refined to equal occupancies of 0.5 for both the disordered components. The atoms F2/F3 of APA were disordered over two positions (F2/F3/F4/H15 & F2D/F3D/F4D/H13D), and their occupational factors were refined to 0.879(3)/0.121(3), respectively. In APA-EtOH-2:1**,** the atoms N5A/C21A and atoms F1-F3 of APA molecule A were disordered over two positions, and their site occupancies (C21A/N5A & C211/N51 and F1A/F2A/F3A & F11/F21/F31) were refined to 0.57(3)/0.43(3) and 0.68(4)/0.32(4), respectively. In APA molecule B, the atoms C20B/N5B/C21B/O2B and F1B/F2B/F3B were disordered, and their site (C20B/N5B/C21B/O2B & C202/N52/C212/O22 and F1B/F2B/F3B & F12/F22/F32)

occupational factors were refined to 0.658(13)/0.342(13) and 0.67(4)/0.33(4), respectively. The EtOH solvate A was disordered over the two-fold symmetry with the site occupancies of 0.5, while the atoms (C22B/C23B/O3B) were disordered over four-fold symmetry, and their disordered components (C22B/C23B/O3B & C222/C232/O32) were refined with 0.25 occupancies.

Table S2: Hydrogen-bond geometry (Å, º) for APA

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N5*A*—H5*NA*···O2*B*	0.85 (3)	2.02 (3)	2.854 (2)	165 (3)
N5*B*—H5*NB*···O2*A*^{i}	0.87 (2)	2.14 (3)	2.998 (2)	169 (2)
C18*A*—H18*A*···N4*B*^{ii}	0.99	2.57	3.429 (3)	145
C19*A*—H19*B*···O1*A*^{iii}	0.99	2.43	3.215 (3)	135
C2*B*—H2*B*···N4*B*^{ii}	0.95	2.38	3.234 (3)	149
C5*B*—H5*B*···S1*A*^{iv}	0.95	2.80	3.723 (2)	165
C15*B*—H15*B*···S1*A*^{v}	0.95	2.85	3.710 (2)	152

Symmetry codes: (i) *x*, −*y*+1/2, *z*−1/2; (ii) −*x*, *y*−1/2, −*z*+1/2; (iii) −*x*, −*y*+1, −*z*+1; (iv) *x*, −*y*+3/2, *z*−1/2; (v) −*x*+1, −*y*+1, −*z*+1.

Table S3: Hydrogen-bond geometry (Å, º) for APA-DMF-2:1

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N5*A*—H5*NA*···O2*B*	0.80 (6)	2.10 (6)	2.870 (6)	162 (6)
N5*B*—H5*NB*···O2*D*	0.94 (6)	1.85 (6)	2.761 (7)	163 (5)
N5*C*—H5*NC*···O2*A*	0.82 (6)	2.00 (6)	2.811 (7)	172 (6)
N5*D*—H5*ND*···O2*C*^{i}	0.92 (6)	2.03 (6)	2.939 (7)	170 (5)
C2*A*—H2*A*···O3*A*	0.95	2.43	3.226 (8)	141
C16*B*—H16*B*···S1*D*	0.95	2.83	3.680 (6)	149
C17*B*—H17*D*···F3*A*^{ii}	0.99	2.55	3.348 (7)	137
C18*B*—H18*D*···O3*B*	0.99	2.45	3.405 (7)	162
C21*C*—H21*I*···S1*B*^{iii}	0.98	2.84	3.746 (7)	154
C2*D*—H2*D*···O3*B*	0.95	2.55	3.334 (8)	140

C24*A*—H24*B*···N4*A*^{iv}	0.98	2.61	3.592 (11)	180

Symmetry codes: (i) *x*, *y*+1, *z*; (ii) −*x*+1, −*y*+1, −*z*; (iii) −*x*, −*y*, −*z*+1; (iv) *x*−1, *y*, *z*.

Table S4: Hydrogen-bond geometry (Å, º) for APA-DMF-1:1

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N5*A*—H5*NA*···O2*B*	0.88	1.93	2.789 (6)	163
N5*B*—H5*NB*···O2*A*^{i}	0.88	2.15	2.929 (6)	147
N5*C*—H5*NC*···O2*D*	0.88	1.94	2.792 (6)	162
N5*D*—H5*ND*···O2*C*^{ii}	0.88	2.15	2.932 (6)	148
C5*A*—H5*A*···O3*A*	0.95	2.29	3.233 (7)	171
C2*B*—H2*B*···O3*D*	0.95	2.48	3.243 (8)	137
C5*C*—H5*C*···O3*B*	0.95	2.33	3.275 (7)	173
C2*D*—H2*D*···O3*C*	0.95	2.59	3.296 (7)	132
C19*D*—H19*H*···F2*C*^{iii}	0.99	2.50	3.477 (7)	168
C23*A*—H23*A*···N4*B*^{ii}	0.98	2.56	3.509 (10)	162
C24*B*—H24*F*···O1*C*	0.98	2.54	3.295 (8)	133
C24*C*—H24*H*···O1*D*	0.98	2.51	3.457 (8)	163
C23*D*—H23*J*···O1*B*	0.98	2.38	3.322 (9)	162
C24*D*—H24*J*···N4*A*^{iv}	0.98	2.56	3.437 (8)	149

Symmetry codes: (i) *x*−1/2, −*y*+2, *z*; (ii) *x*+1/2, −*y*+1, *z*; (iii) *x*+1/2, −*y*+2, *z*; (iv) *x*, *y*+1, *z*.

Table S5: Hydrogen-bond geometry (Å, º) for APA-DOX-2:1

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N5*A*—H5*NA*···O2*B*^{i}	0.83 (2)	2.08 (2)	2.904 (4)	173 (4)
N5*B*—H5*NB*···O2*A*	0.84 (2)	2.02 (2)	2.849 (4)	173 (5)
C2*A*—H2*A*···O3^{ii}	0.93	2.47	3.179 (5)	133
C5*A*—H5*A*···S1*B*^{iii}	0.93	2.82	3.681 (4)	155
C15*A*—H15*A*···S1*B*^{iv}	0.93	2.79	3.611 (4)	148
C5*B*—H5*B*···S1*A*	0.93	2.67	3.412 (5)	138

C22—H22*A*···N4*B*	0.97	2.61	3.305 (7)	129

Symmetry codes: (i) *x*, −*y*+2, *z*−1/2; (ii) *x*, *y*+1, *z*; (iii) *x*, −*y*+1, *z*−1/2; (iv) −*x*+3/2, −*y*+3/2, −*z*+1.

Table S6: Hydrogen-bond geometry (Å, º) for APA-DMA-1:1

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N5*A*—H5*NA*···O2*B*^{i}	0.85 (3)	2.12 (3)	2.974 (3)	177 (3)
N5*B*—H5*NB*···O2*A*	0.79 (3)	2.06 (3)	2.847 (4)	171 (3)
C2*A*—H2*A*···O3*A*	0.93	2.46	3.158 (17)	132
C5*A*—H5*A*···S1*B*^{ii}	0.93	2.81	3.697 (3)	159
C5*B*—H5*B*···O3*B*	0.93	2.32	3.197 (19)	157
C23*B*—H23*H*···N4*A*^{iii}	0.96	2.52	3.448 (15)	162

Symmetry codes: (i) *x*, −*y*+3/2, *z*−1/2; (ii) *x*, −*y*+5/2, *z*−1/2; (iii) *x*, −*y*+5/2, *z*+1/2.

Table S7: Hydrogen-bond geometry (Å, º) for APA-CYH-1:1

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N5*A*—H5*N*···O2*B*	0.77 (4)	2.15 (4)	2.904 (5)	165 (4)
N5*B*—H2*N*···O2*A*^{i}	0.78 (5)	2.03 (5)	2.796 (6)	167 (5)
C2*A*—H2*A*···O3*B*	0.95	2.59	3.37 (3)	140
C19*A*—H19*A*···F4*A*^{i}	0.99	2.32	3.179 (7)	144
C5*B*—H5*B*···O3*A*	0.95	2.34	3.285 (6)	175
C17*B*—H17*C*···O3*B*^{i}	0.99	2.56	3.54 (2)	168
C21*B*—H21*E*···S1*B*^{ii}	0.98	2.85	3.753 (5)	154
C23*B*—H23*C*···O1*A*	0.99	2.54	3.415 (12)	147

Symmetry codes: (i) *x*, −*y*+3/2, *z*+1/2; (ii) −*x*+1, *y*+1/2, −*z*+3/2.

Table S8: Hydrogen-bond geometry (Å, º) for APA-ACN-1:1

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N5—H5*N*···N6	0.86 (3)	2.30 (3)	3.155 (3)	171 (2)
C2—H2···O2^{i}	0.95	2.39	3.1022 (19)	132
C12—H12···S1^{ii}	0.95	2.80	3.6131 (16)	144

C15—H15···O1^{iii}	0.95	2.47	3.4059 (19)	168
C18—H18*A*···N4^{iv}	0.99	2.54	3.475 (2)	158

Symmetry codes: (i) −*x*+1, −*y*+1, *z*+1/2; (ii) *x*−1/2, −*y*+1/2, *z*; (iii) −*x*+1, −*y*+1, *z*−1/2; (iv) −*x*+1/2, *y*+1/2, *z*−1/2.

Table S9: Hydrogen-bond geometry (Å, º) for APA-ACE-2:1

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N5*A*—H5*NA*···O2*B*^{i}	0.84 (4)	2.10 (4)	2.941 (4)	177 (4)
N5*B*—H5*NB*···O2*A*	0.87 (4)	1.96 (4)	2.794 (4)	160 (4)
C2*A*—H2*A*···O3	0.95	2.43	3.194 (5)	137
C5*A*—H5*A*···S1*B*^{ii}	0.95	2.79	3.683 (4)	156
C21*A*—H21*C*···S1*B*^{iii}	0.98	2.82	3.479 (4)	125
C23—H23*B*···N4*B*^{iv}	0.98	2.49	3.308 (12)	141

Symmetry codes: (i) *x*, −*y*+3, *z*−1/2; (ii) *x*, −*y*+2, *z*−1/2; (iii) −*x*+1/2, −*y*+5/2, −*z*+1; (iv) *x*, *y*+1, *z*.

Table S10: Hydrogen-bond geometry (Å, º) for APA-BUT-1:0.5

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N5—H5*N*···O2^{i}	0.88	2.24	2.936 (5)	136
O3—H3*O*···O2	0.84	2.10	2.699 (5)	128
C24—H24*A*···O2^{ii}	0.99	1.59	2.491 (7)	148
C24—H24*B*···F4^{iii}	0.99	2.32	3.218 (7)	150

Symmetry codes: (i) *x*, −*y*+5/2, *z*+1/2; (ii) −*x*, −*y*+2, −*z*; (iii) *x*, *y*, *z*−1.

Table S11: Hydrogen-bond geometry (Å, º) for APA-EtOH-2:1

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N5*A*—H5*NA*···O2*B*	0.86	2.10	2.93 (4)	162
C15*A*—H15*A*···O2*A*^{i}	0.93	2.56	3.454 (13)	160
C19*B*—H19*C*···F2*A*^{ii}	0.97	2.54	3.49 (2)	163
C22*A*—H22*B*···O2*A*^{i}	0.96	2.56	3.43 (5)	149

Symmetry codes: (i) −*x*+1, −*y*+1, *z*; (ii) *x*+1/2, −*y*+1/2, −*z*+2.

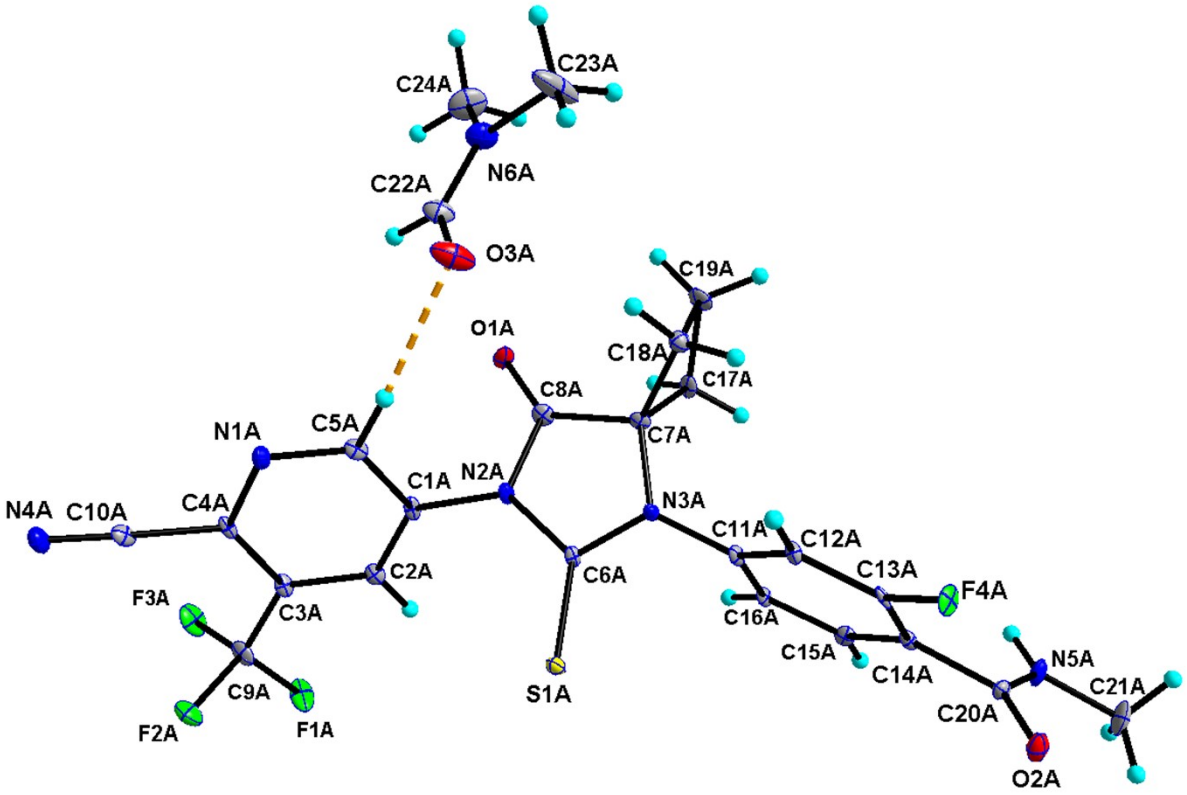
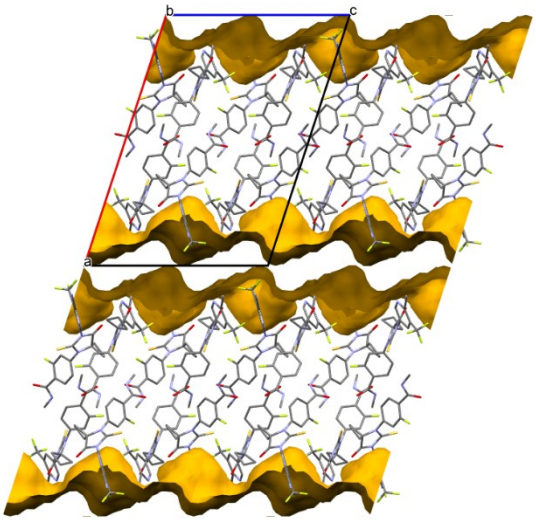
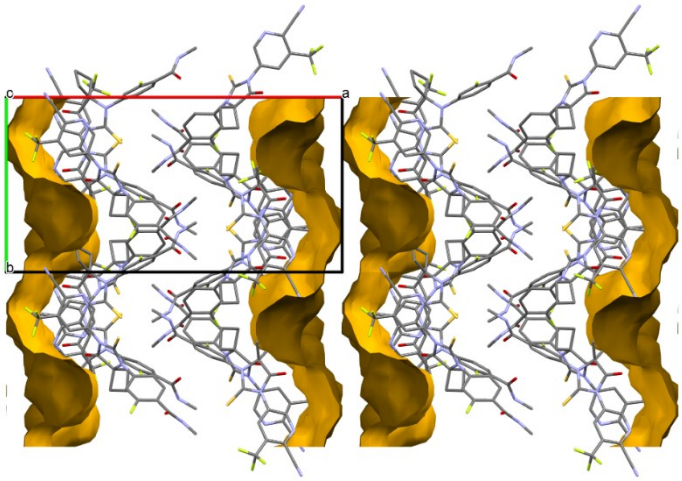


Figure S1. Displacement ellipsoids of APA-DMF-1:1 are drawn at the 30% probability level. Hydrogen bonds are shown as dashed lines. For representative purposes and clarity, only APA molecule A and DMF solvate A are shown. Similar atom numbering is followed for APA molecules B-D and DMF solvates A-D.

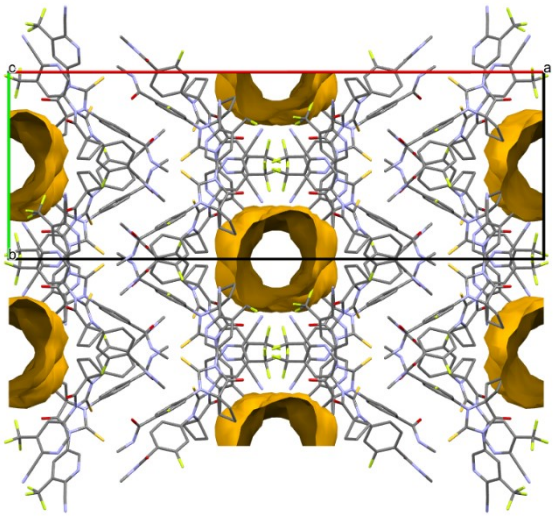


(a)

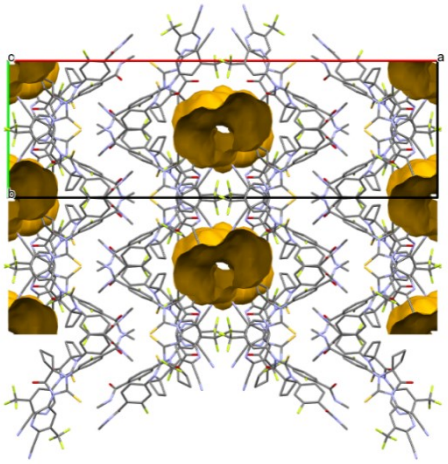


(b)

Figure S2. Packing arrangements and void maps for APA-CYH-1:1 along (a) b-axis and (b) c-axis

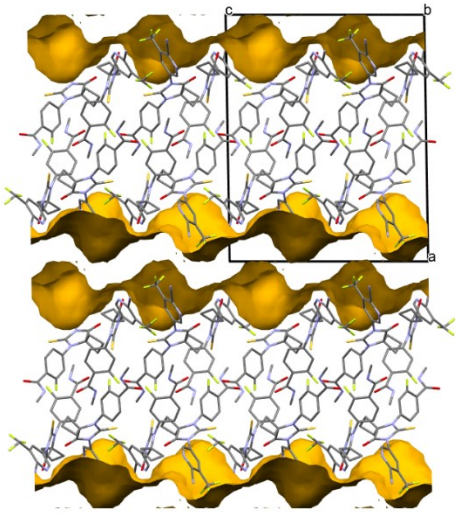


(a)

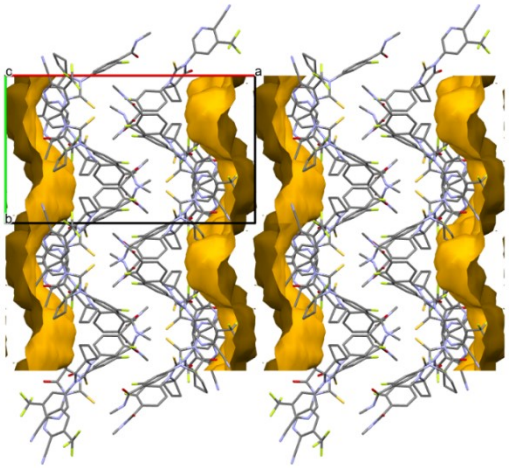


(b)

Figure S3. Packing arrangements and void maps for (a) APA-DOX-2:1 and (b) APA-ACE-2:1 along c-axis

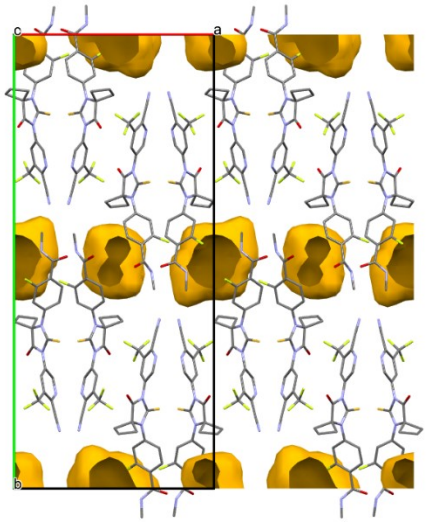


(a)

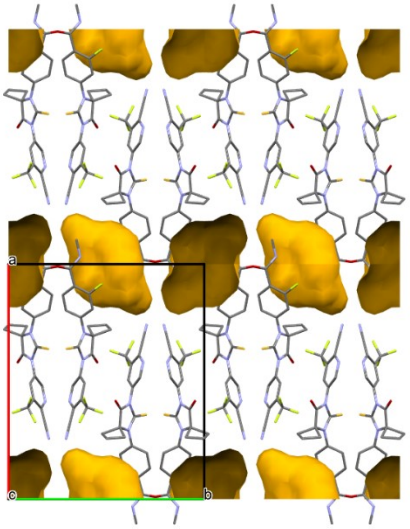


(b)

Figure S4. Packing arrangements and void maps for APA-DMA-1:1 along (a) b-axis and (b) c-axis



(a)



(b)

Figure S5. Packing arrangements and void maps for (a) APA-EtOH-2:1 and (b) APA-BUT-1:0.5 along c-axis

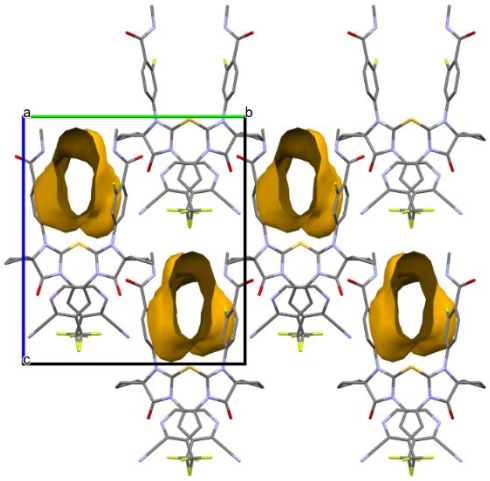


Figure S6. Packing arrangement and void map for APA-ACN-1:1 along a-axis

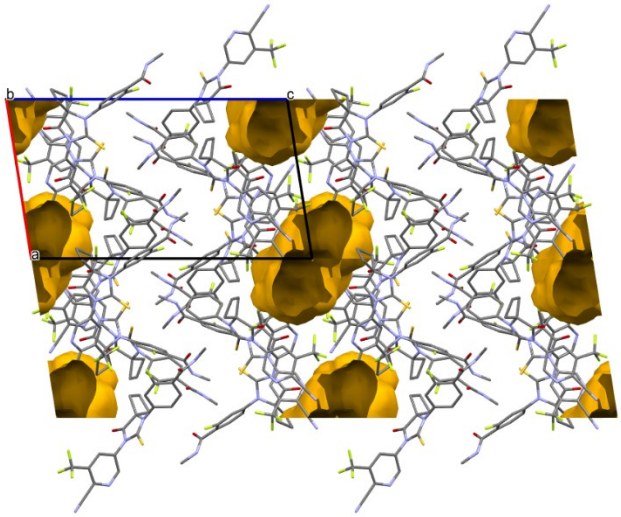
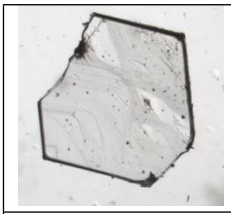
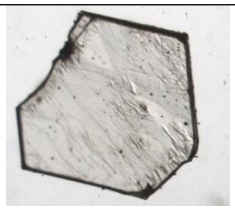
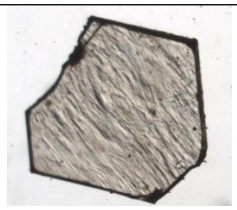
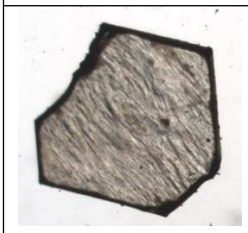
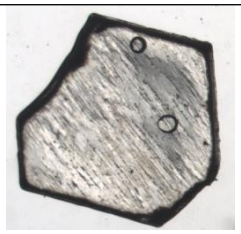
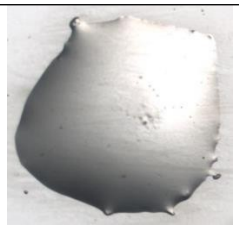


Figure S7. Packing arrangement and void map for APA-DMF-2:1 along b-axis

HSM studies

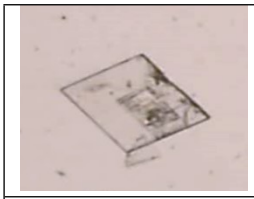
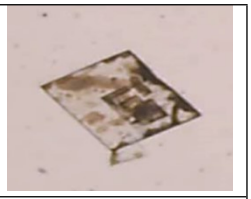
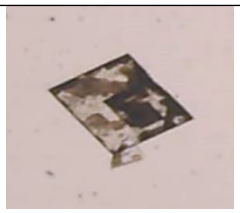
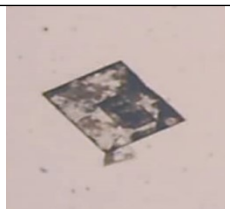
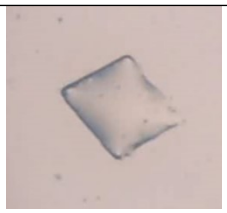
Apalutamide DMF 1:1 solvate (APA-DMF-1:1)

ne plate crystal was selected for HSM studies, the crystal shows two desolvation events, followed by complete melting. The first desolvation was observed from 108°C to 128°C, while the second desolvation was observed from 140°C to 148°C. Finally, the crystal melted at 199°C. Another two HSM experiments were performed in the following temperature ranges 25°C - 130°C and 25°C - 160°C. After that, the crystals were subjected to unit cell determinations. The first crystal unit cell matched with APA-DMF-2:1, while the crystal collected at 150°C unit cell corresponded the APA parent form.

		
25.7**°C**	110.8**°C**	124**°C**
		
140.6**°C**	173.1**°C**	199.8**°C**
Figure S8. Hot stage images of the APA-DMF-1:1 crystal		

Apalutamide DMF 2:1 solvate (APA-DMF-2:1)

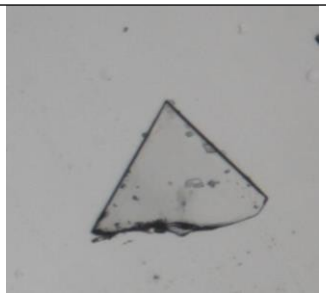
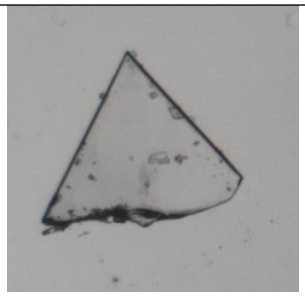
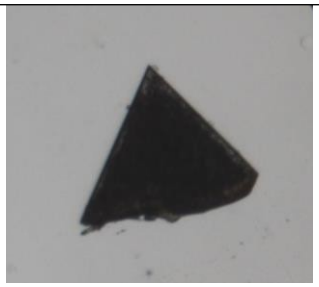
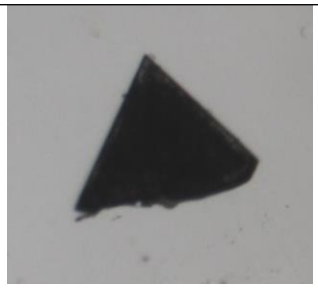
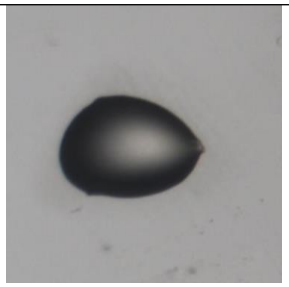
APA DMF 2:1 plate type crystal was opted for HSM studies where it desolvated from 136°C to 150°C followed by melting at 200°C.

		
32°C	100°C	136°C
		

160°C	191°C	205°C
Figure S.9 Hot stage images of the APA-DMF-2:1 crystal		

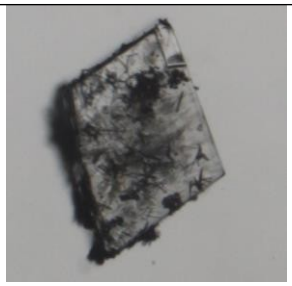
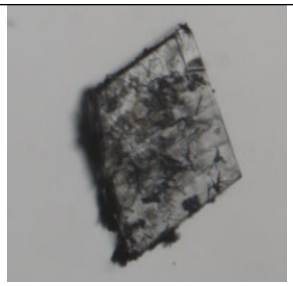
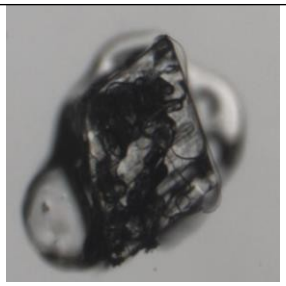
Apalutamide acetone 2:1 solvate (APA-ACE-2:1)

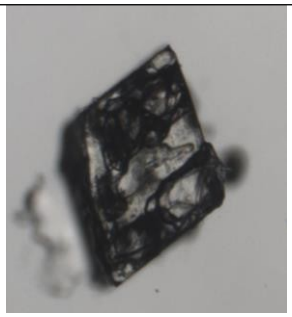
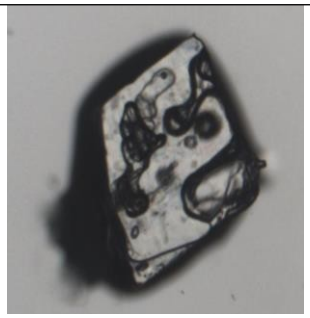
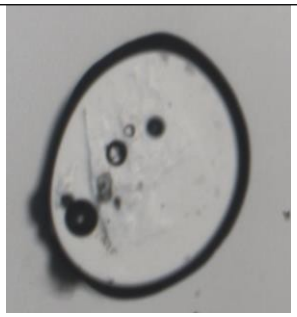
HSM studies were performed for APA Acetone plate type crystal where desolvation started from 97°C-123°C. The crystal lost its transparency after solvent removal, but the original crystal integrity was maintained during the desolvation process.

		
28°C	61.2°C	97.2°C
		
122.2°C	174.4C	200.1°C
Figure S10. Hot stage images of the APA-ACE-2:1 crystal		

Apalutamide 1,4-dioxane 2:1 solvate (APA-DOX-2:1)

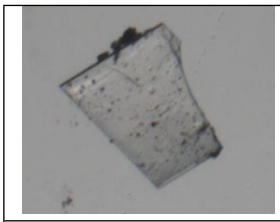
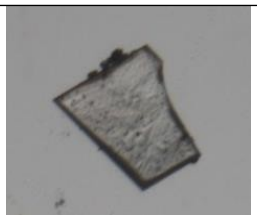
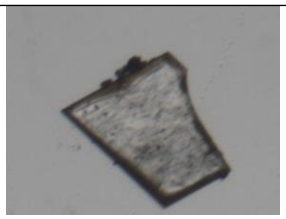
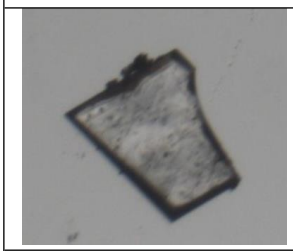
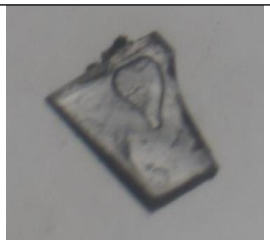
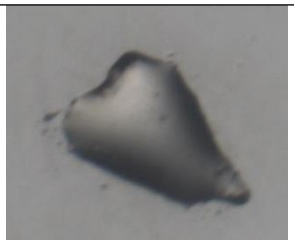
The HSM studies were performed for APA-DOX block shaped crystal in which desolvation started from 110°C-162°C, followed by completely melting at 192°C.

		
26.1**°C**	118.3**°C**	133.2**°C**

		
167.9°C	192.4°C	196.2°C
Figure S11. Hot stage images of the APA-DOX-2:1 crystal		

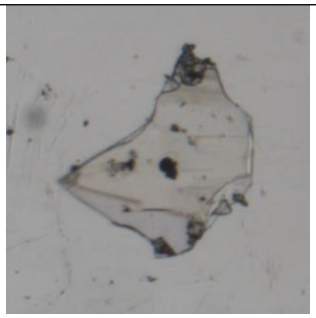
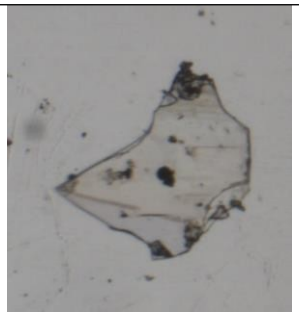
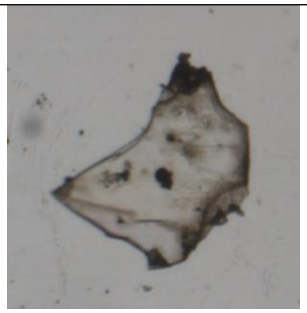
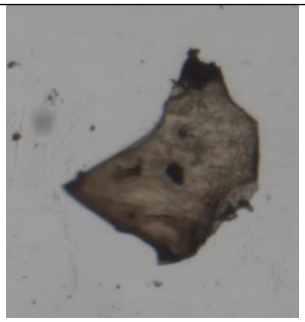
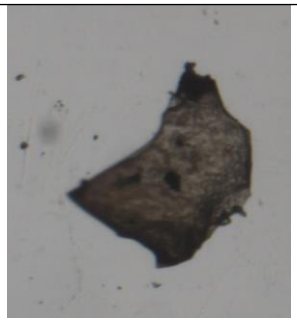
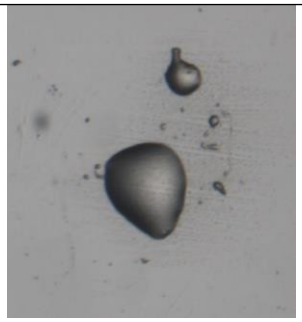
Apalutamide N, N-dimethylacetamide 1:1 solvate (APA-DMA-1:1)

The APA-DMA solvate plate was opted for HSM studies in which it started desolvating from 100°C - 117°C, followed by the melting around 196°C -200.6°C.

		
26.7°C	105.5°C	116.4°C
		
165.8°C	196.8°C	200.6°C
Figure S12. Hot stage images of the APA-DMA-1:1 crystal		

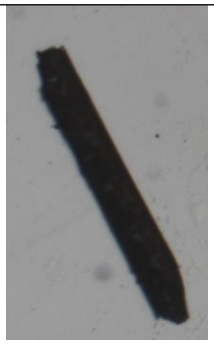
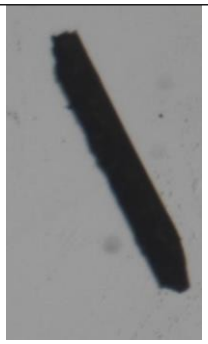
Apalutamide cyclohexanone 1:1 solvate (APA-CYH-1:1)

The APA-CYH plate crystal was subjected to the HSM analysis, which desolvated from 100°C to125°C, followed by complete melting around 198°C.

		
27°C	70.9°C	101.2°C
		
122.9°C	165.7°C	198.7°C
Figure S13. Hot stage images of the APA-CYH-1:1 crystal		

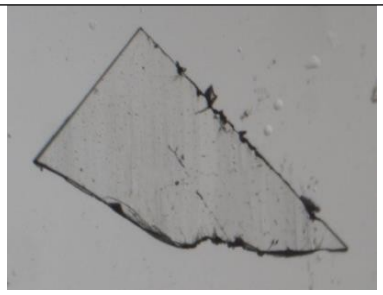
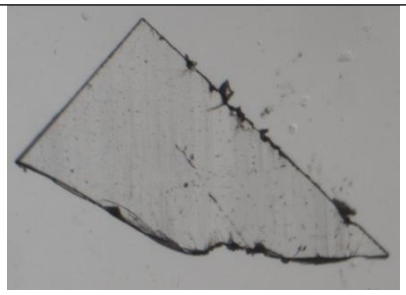
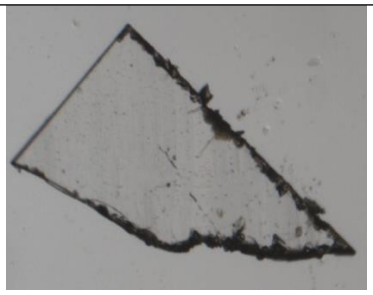
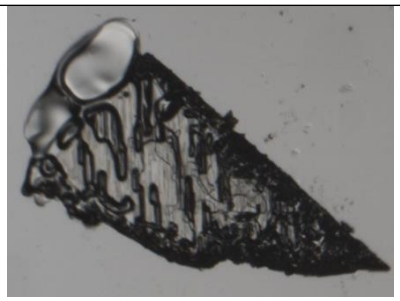
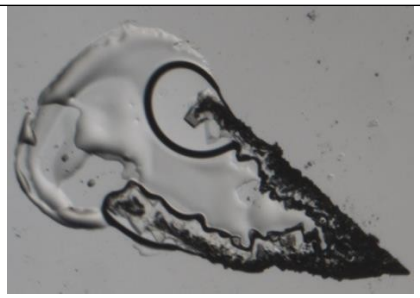
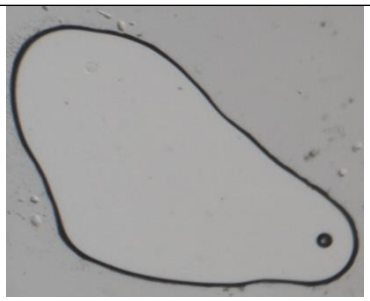
Apalutamide ethanol 2:1 solvate (APA-EtOH-2:1)

The HSM studies were performed for APA-EtOH needle type crystals, where desolvation started from 115°C-134°C, followed by complete melting at 201°C.

		
25°C	66°C	125.3°C
		
134.1°C	166.3°C	201.6°C
Figure S14. Hot stage images of the APA-EtOH-2:1 crystal		

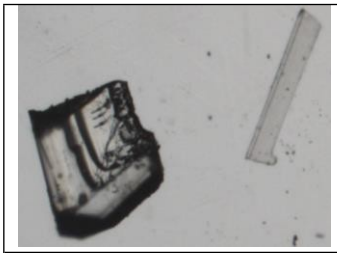
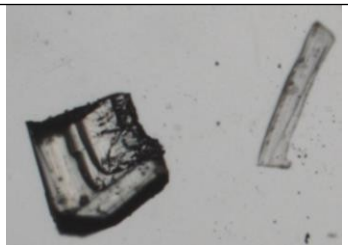
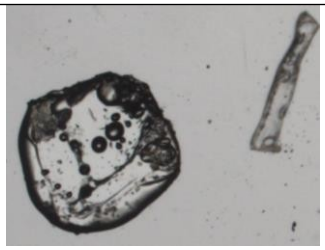
Apalutamide 2-butanol 1:0.5 solvate (APA-BUT-1:0.5)

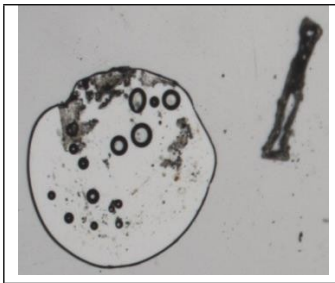
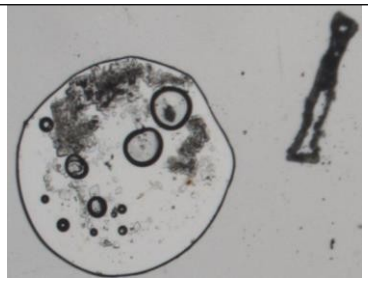
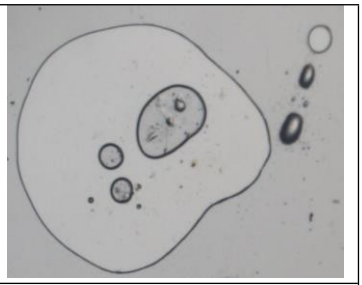
The APA-BUT plate type crystal was selected for HSM studies. Desolvation started from 111°C-130°C. At round 150°C, crystallization events occurred following by complete melting around 200°C.

		
26.1°C	70.9°C	117.8°C
		
133.9°C	152.6°C	200.7°C
Figure S15. Hot stage images of the APA-BUT-1:0.5 crystal		

Apalutamide acetonitrile 1:1 solvate (APA-ACN-1:1)

The APA-ACN crystals have selected for HSM studies whose desolvation started from 110°C - 118°C, followed by crystallization around 150- 170°C, after that it is completely melted at 200°C.

		
30°C	112°C	123°C

		
150°C	170°C	200.4°C
Figure S16. Hot stage images of the APA-ACN-1:1 crystals		

DSC and TG analysis

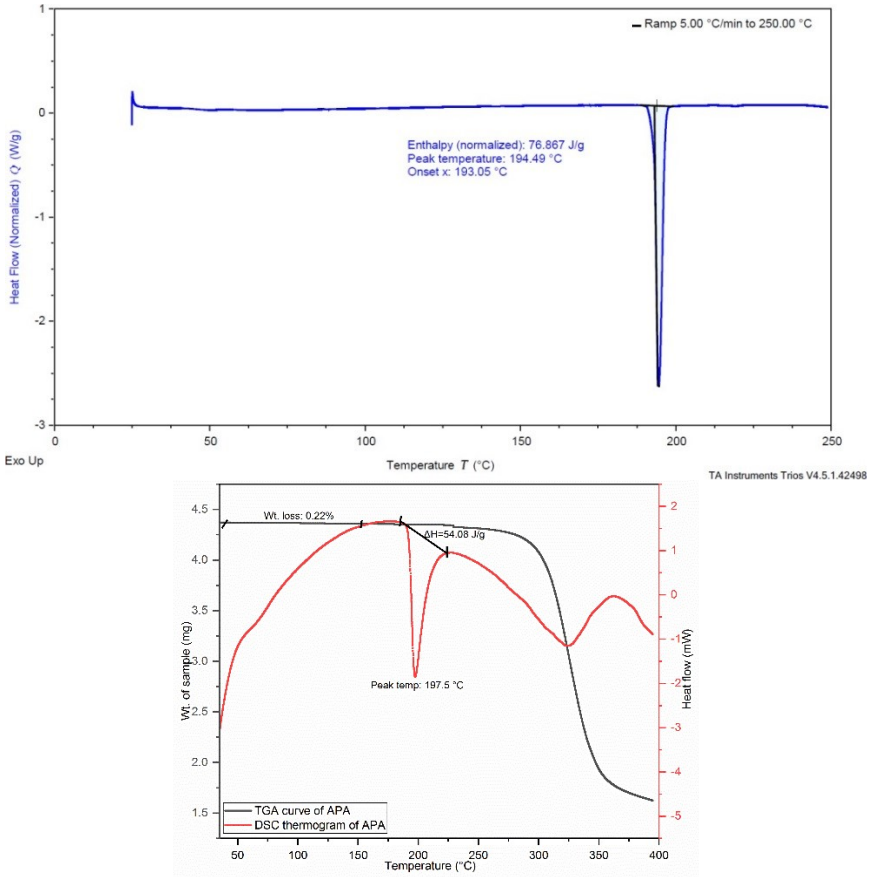


Figure S17. Results of DSC/TG analyses for APA

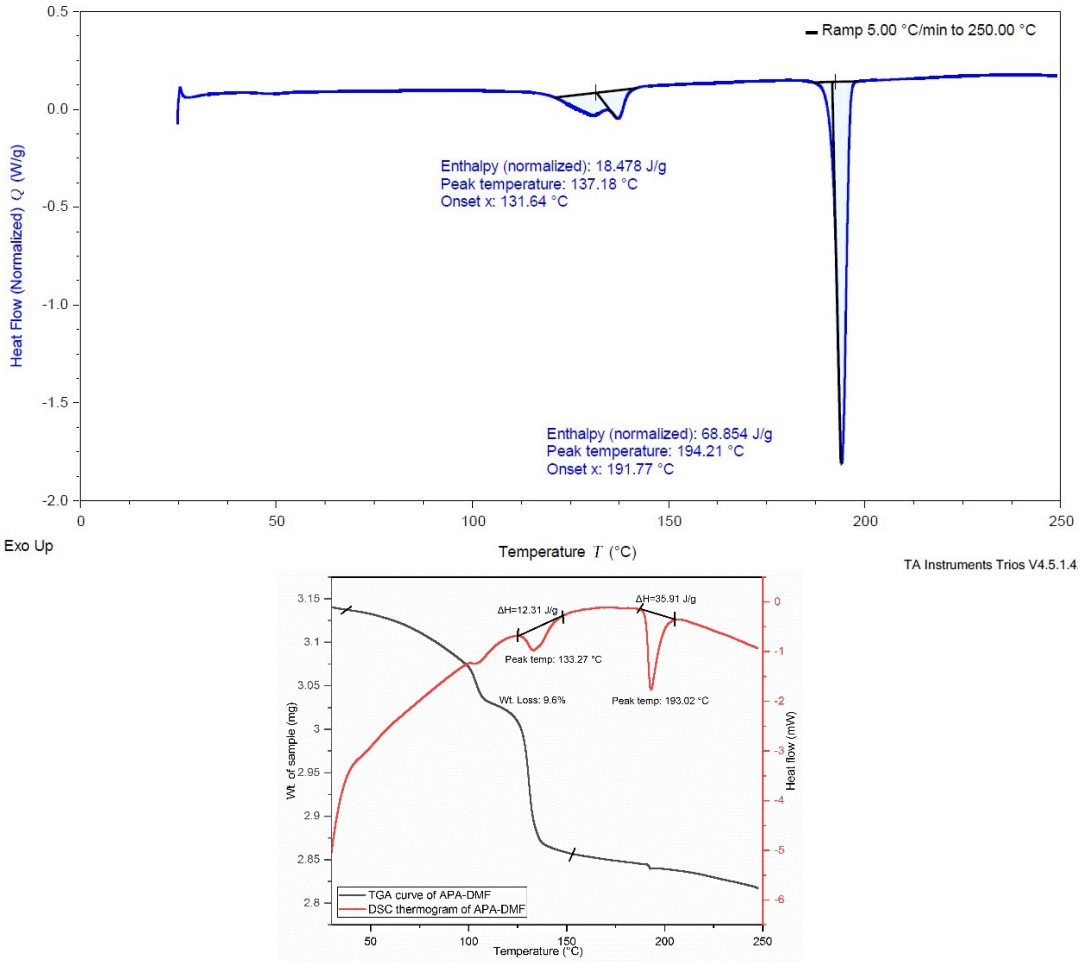


Figure S18. Results of DSC/TG analyses for the APA-DMF-2:1 solvate

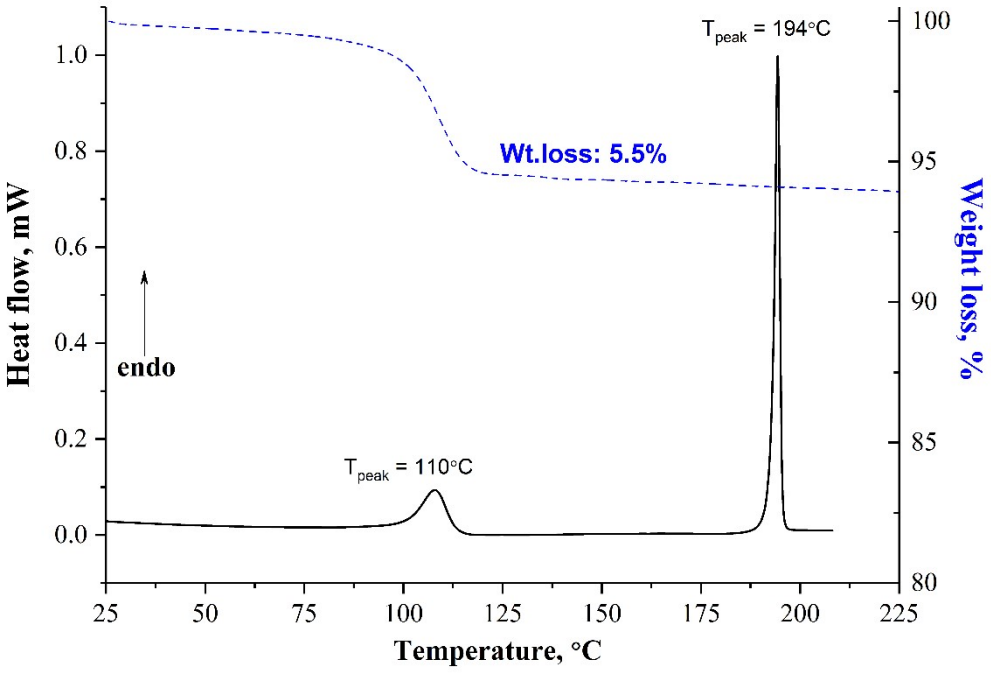


Figure S19. Results of DSC/TG analyses for the APA-ACE-2:1 solvate

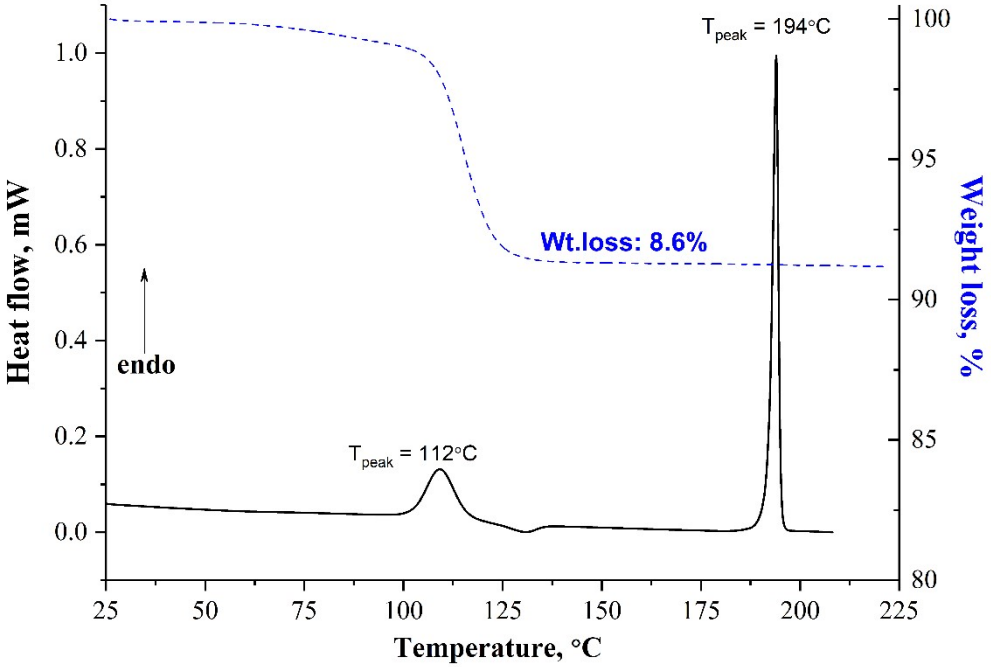
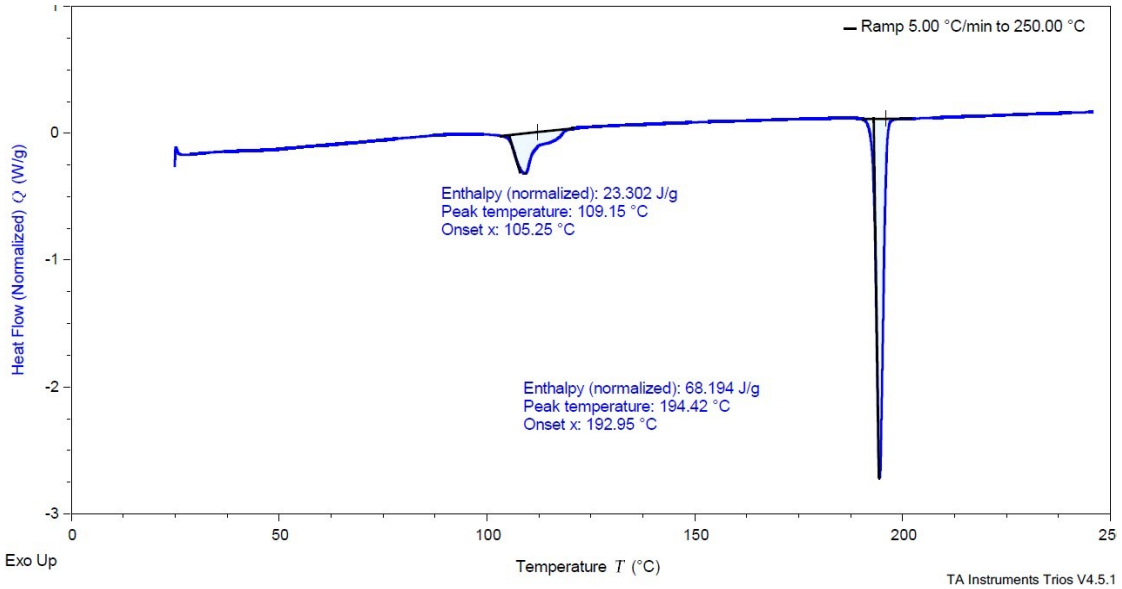


Figure S20. Results of DSC/TG analyses for the APA-DOX-2:1 solvate



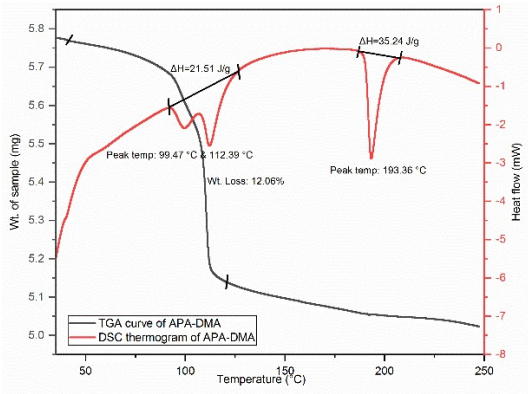


Figure S21. Results of DSC/TG analyses for the APA-DMA-1:1 solvate

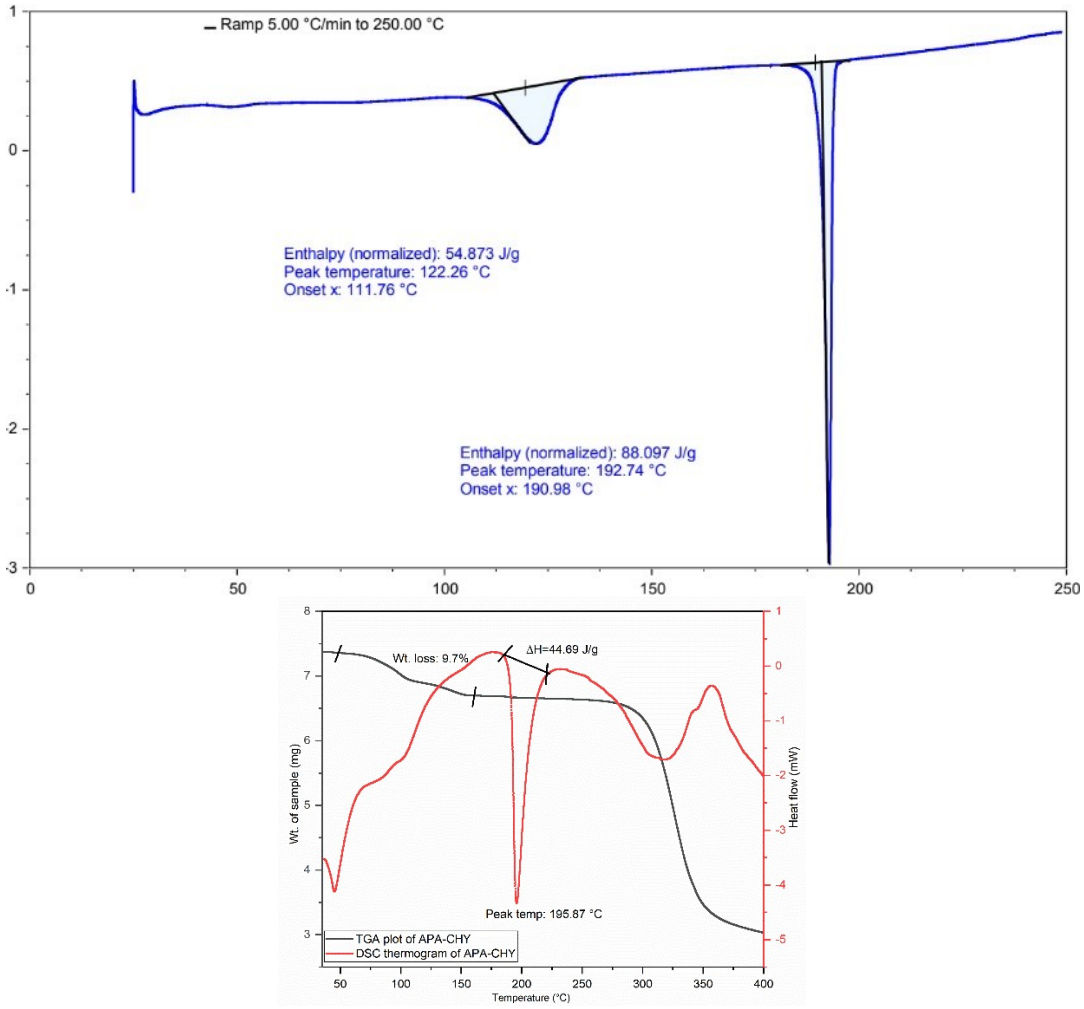


Figure S22. Results of DSC/TG analyses for the APA-CYH-1:1 solvate

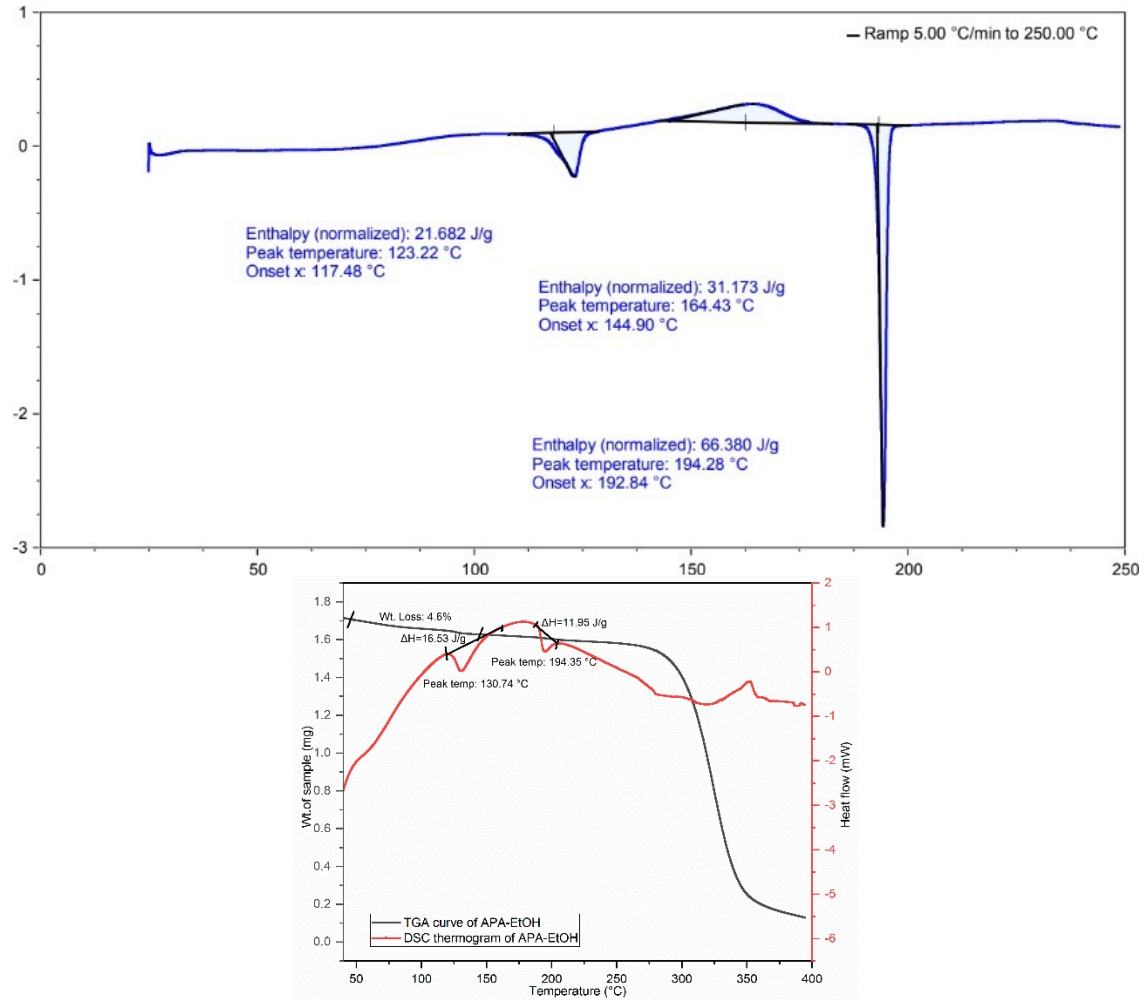
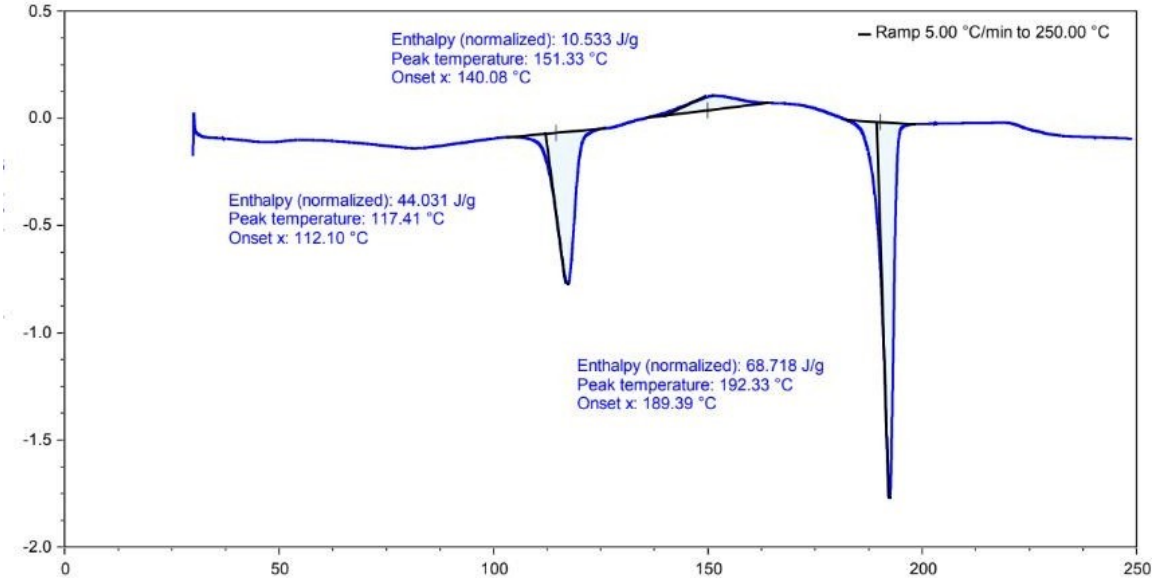


Figure S23. Results of DSC/TG analyses for the APA-EtOH-2:1 solvate



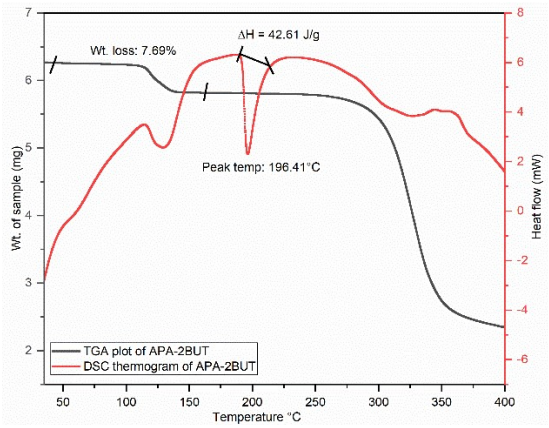


Figure S24. Results of DSC/TG analyses for the APA-BUT-1:0.5 solvate

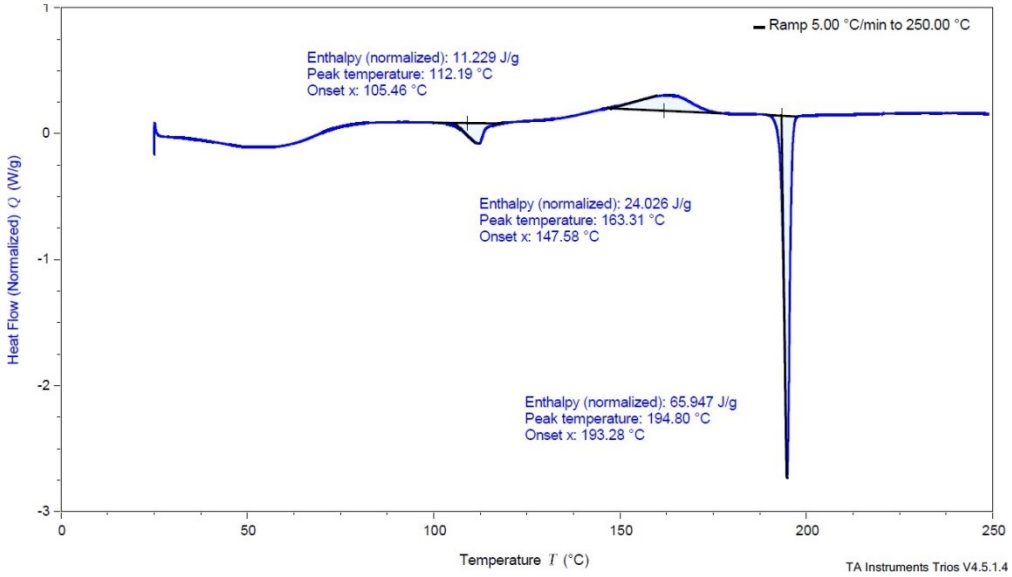


Figure S25. Results of DSC analyses for the APA-ACN-1:1 solvate

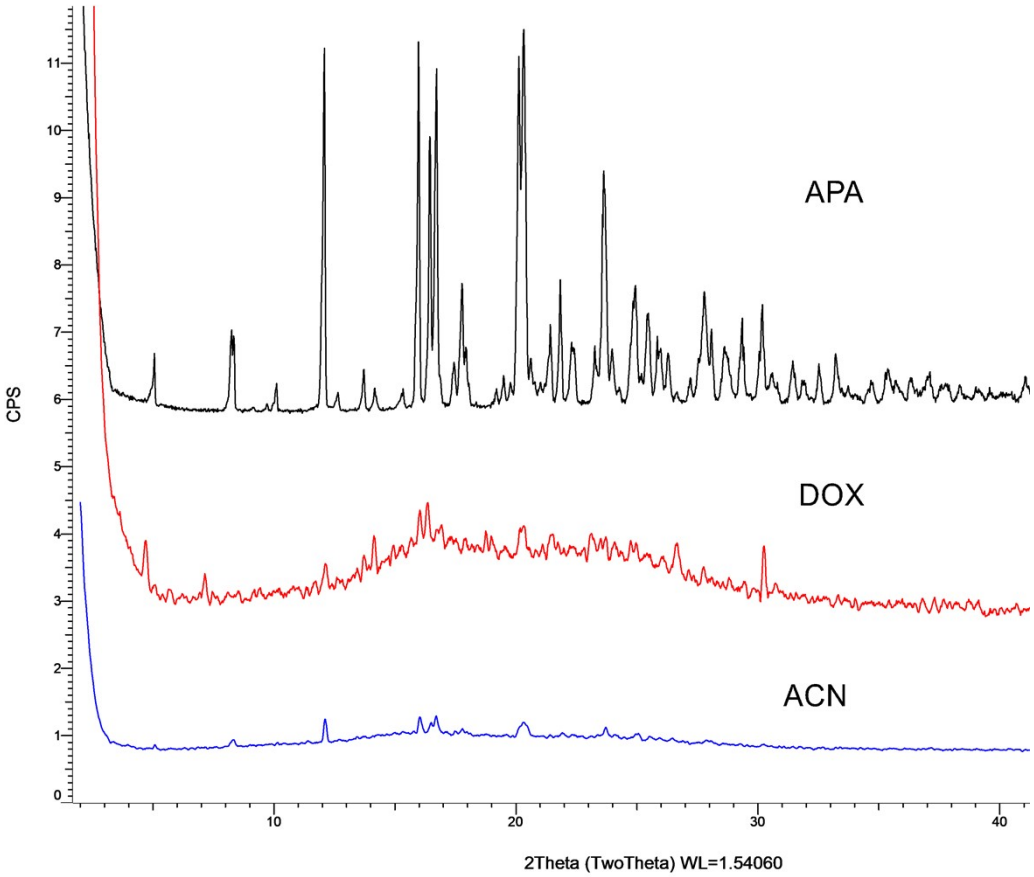


Figure S26. PXRD patterns of residual materials obtained via desolvation of APA-ACN-1:1 and APA-DOX-2:1 solid forms.

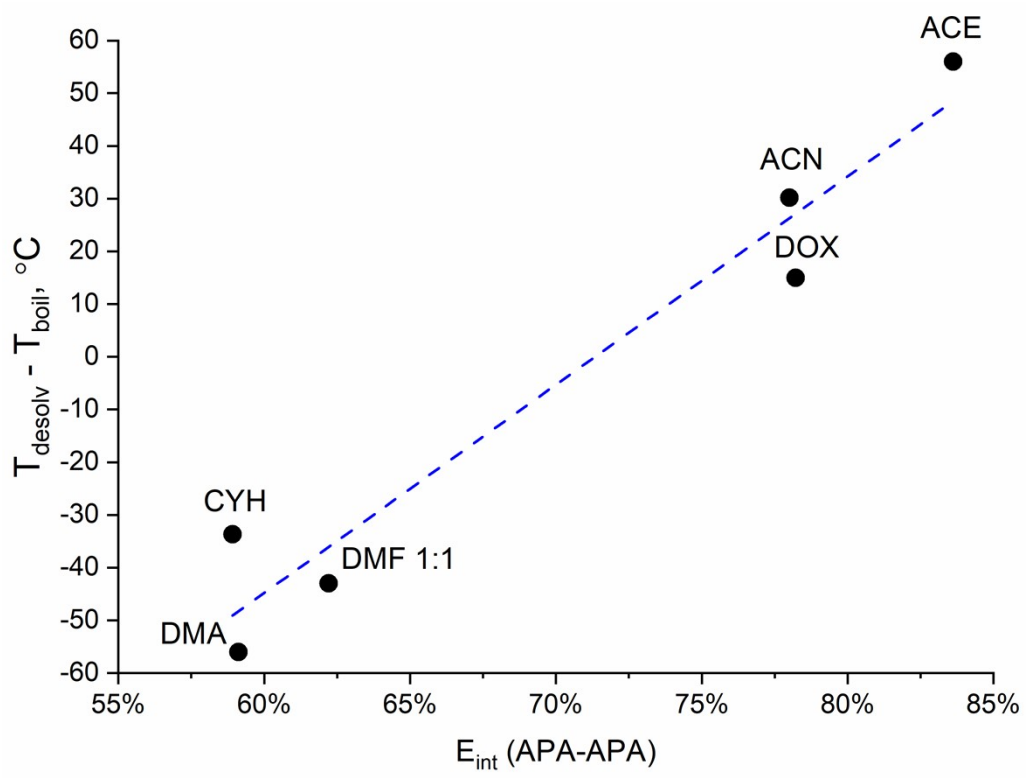


Figure S27. Difference between desolvation temperature of the APA solvate and boiling temperature of pure solvent plotted against the total energy of non-covalent interactions between APA molecules estimated using QTAIMC for open channel solvates

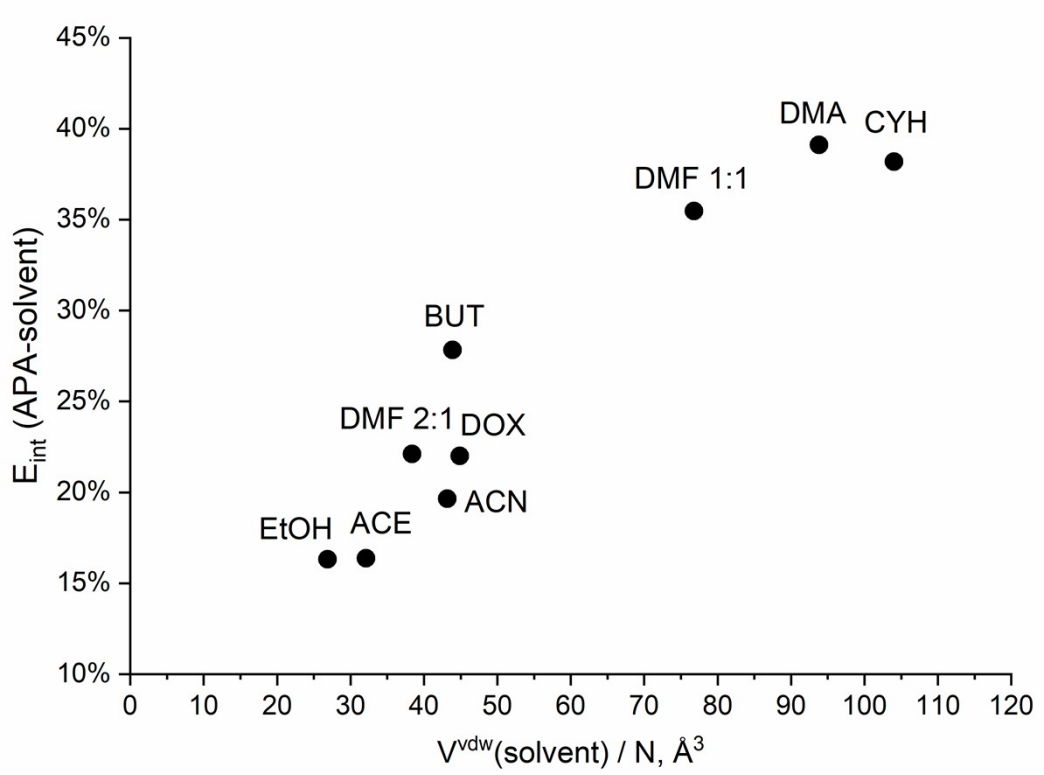


Figure S28. Total energy of non-covalent interactions between APA molecules estimated using QTAIMC plotted against the van-der-Waals volume of solvent molecules with respect to solvate stoichiometry