Derisking development by cocrystallisation screen of a novel selective inhaled JAK-STAT inhibitor

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Electronic Supplementary Information

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1.- Characterization of the solid forms

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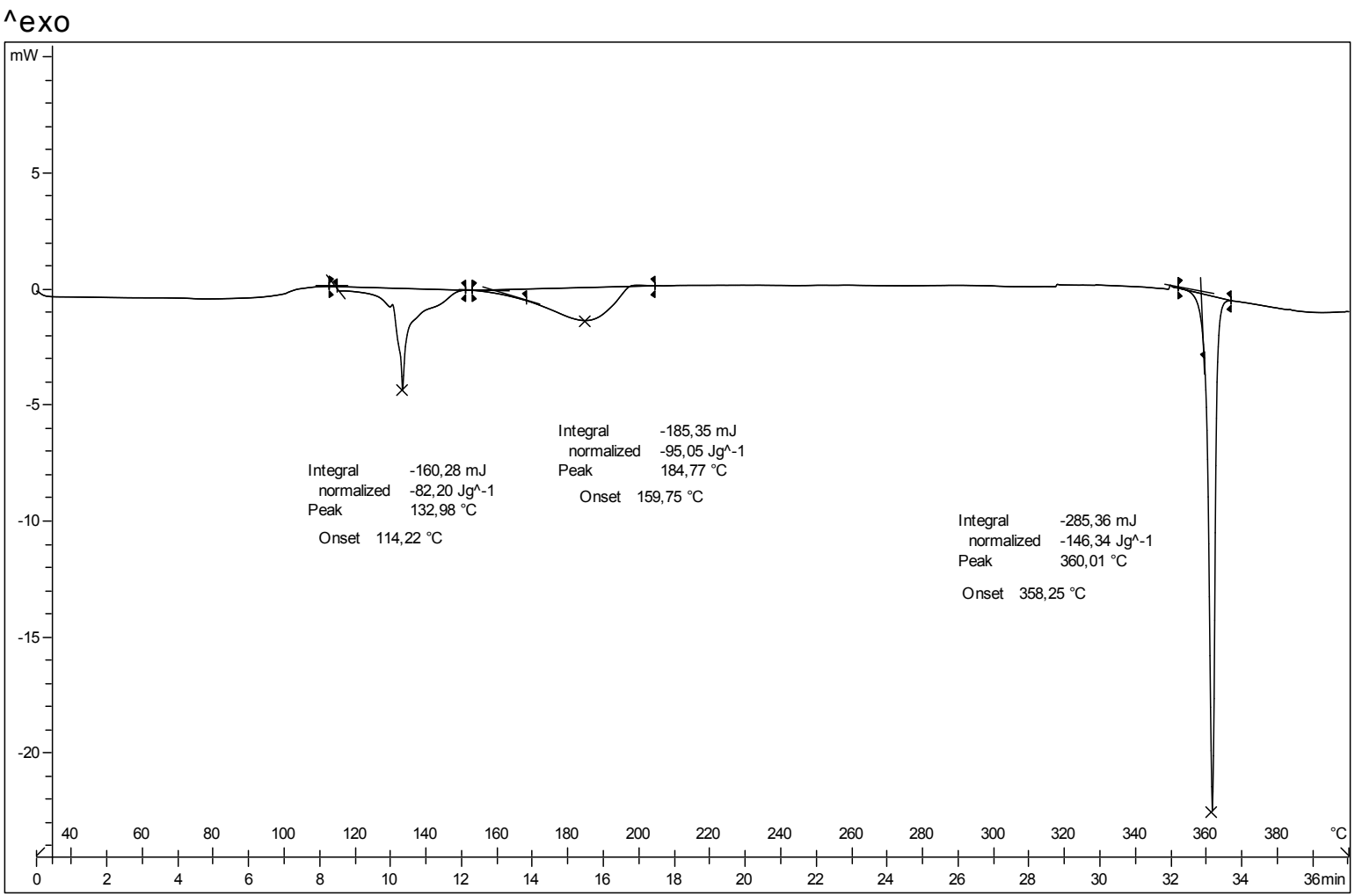


Figure S2: TGA of Form A

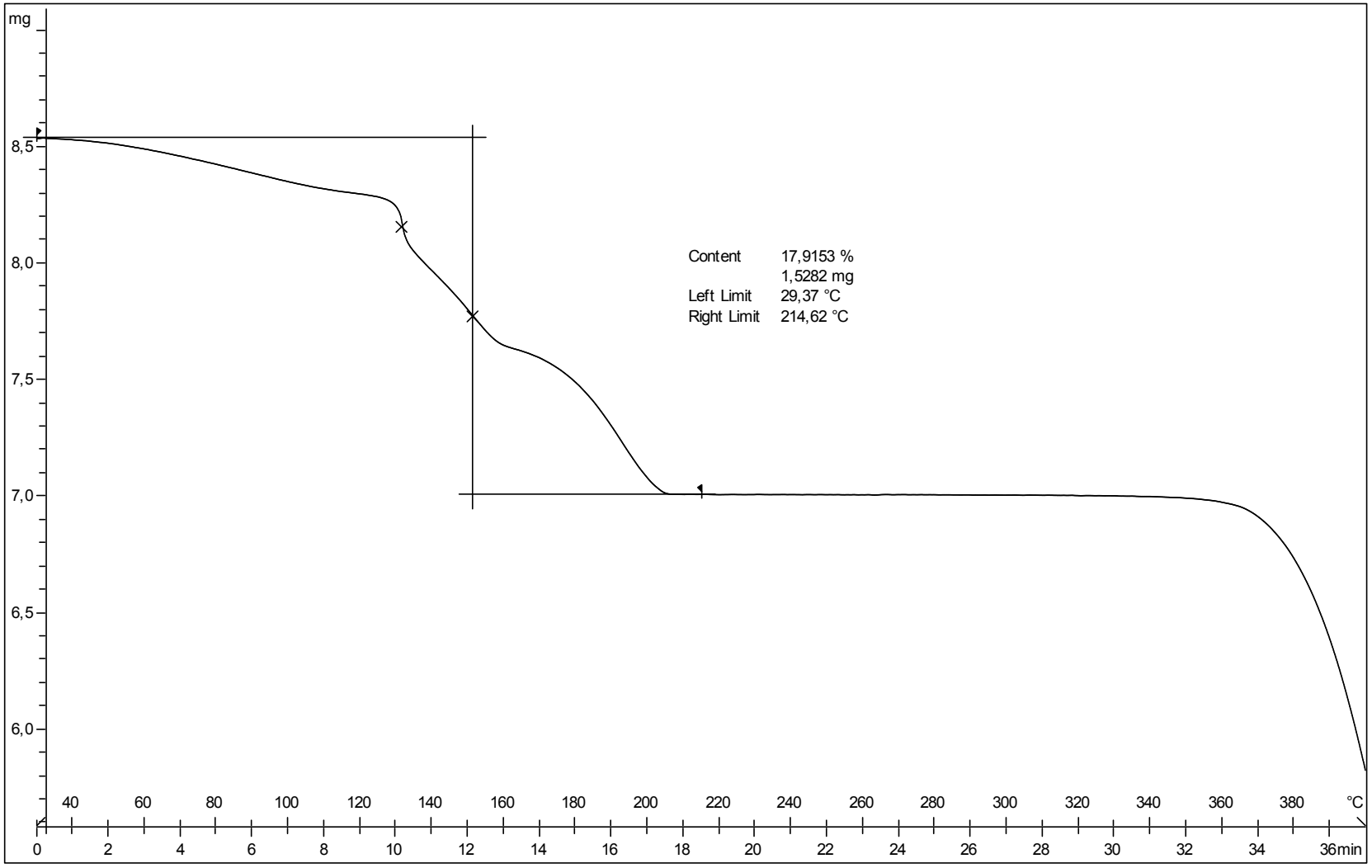


Figure S3: ^{1}H-NMR (dmso-d_6/delay: 1/pulse: 45°/scans: 32) of Form A

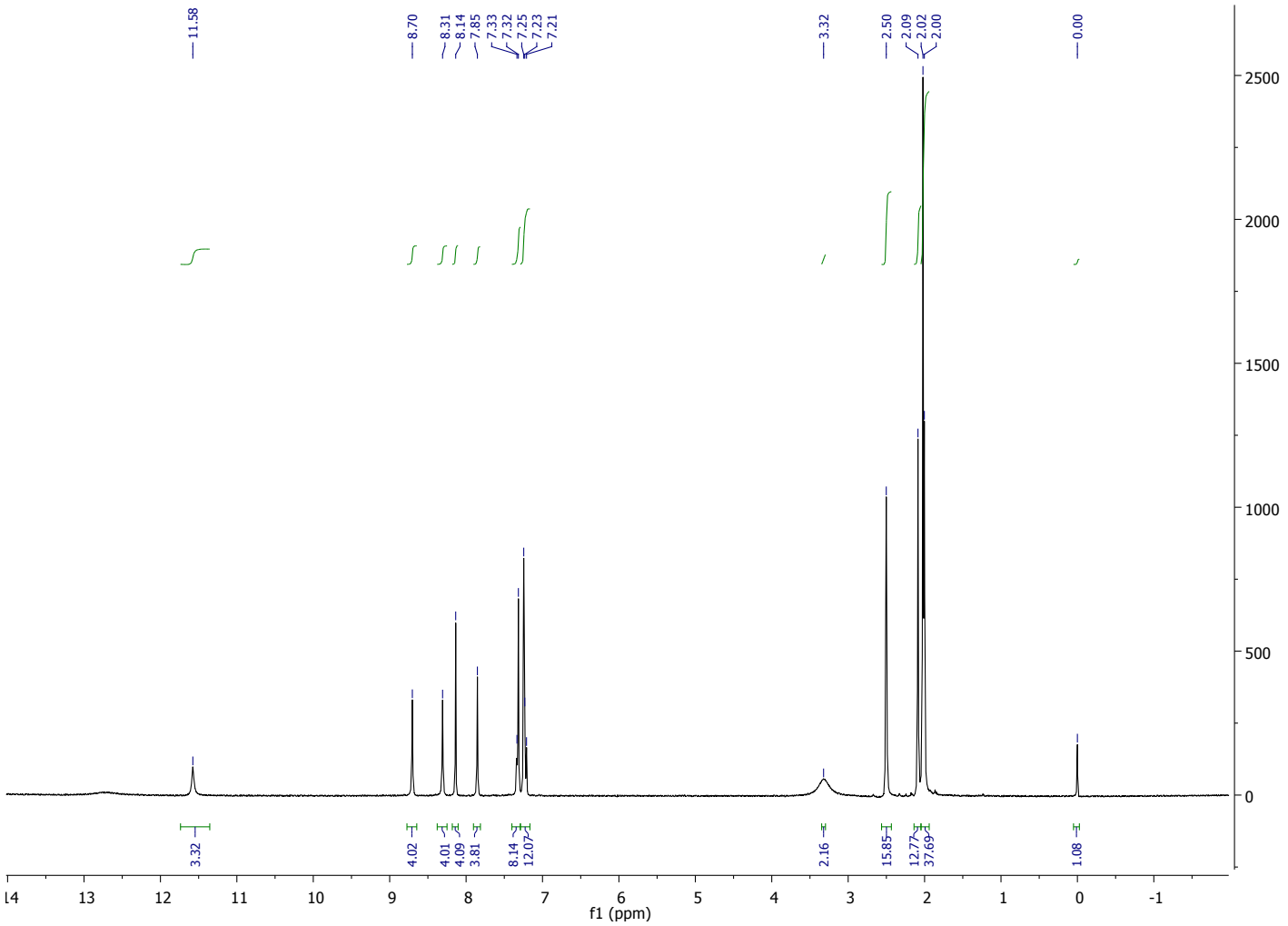


Figure S4: XRPD of Form A

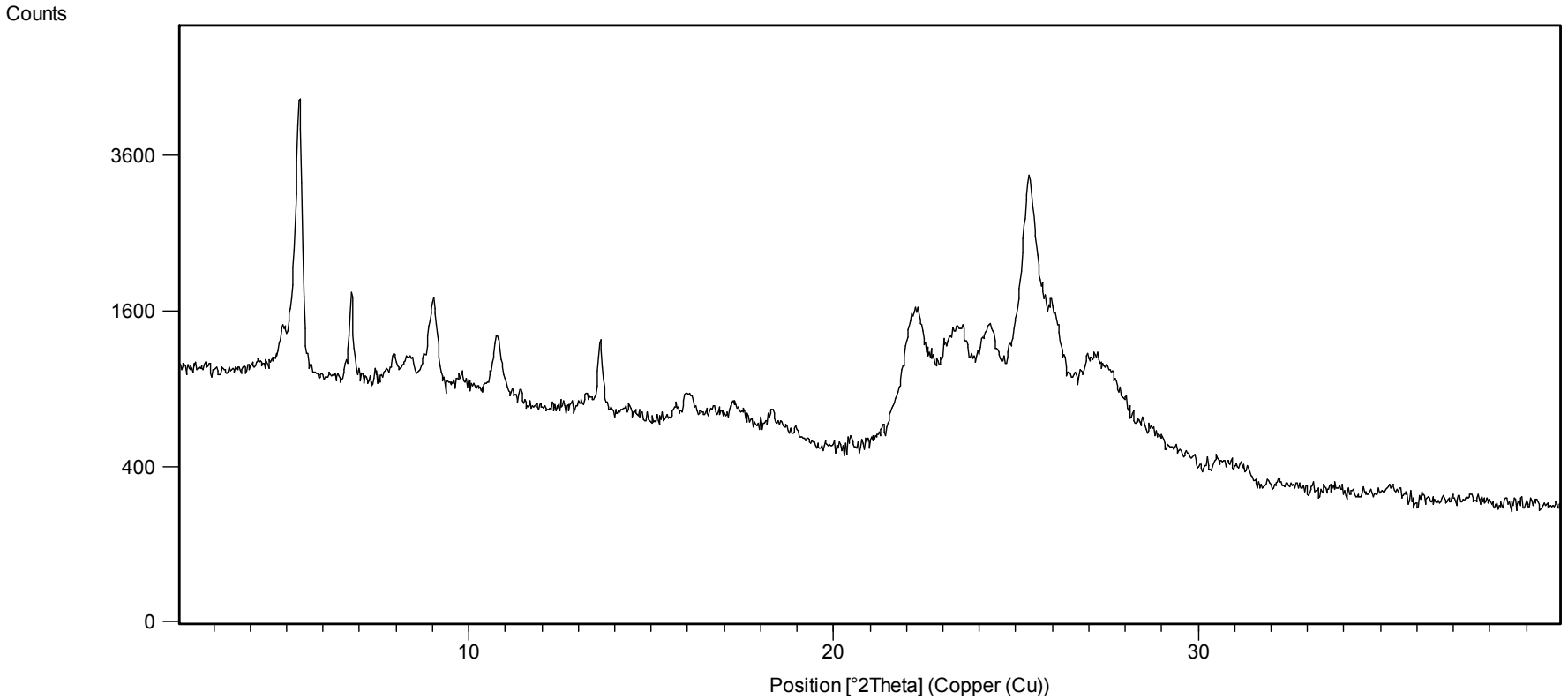


Figure S5: DSC of Form B

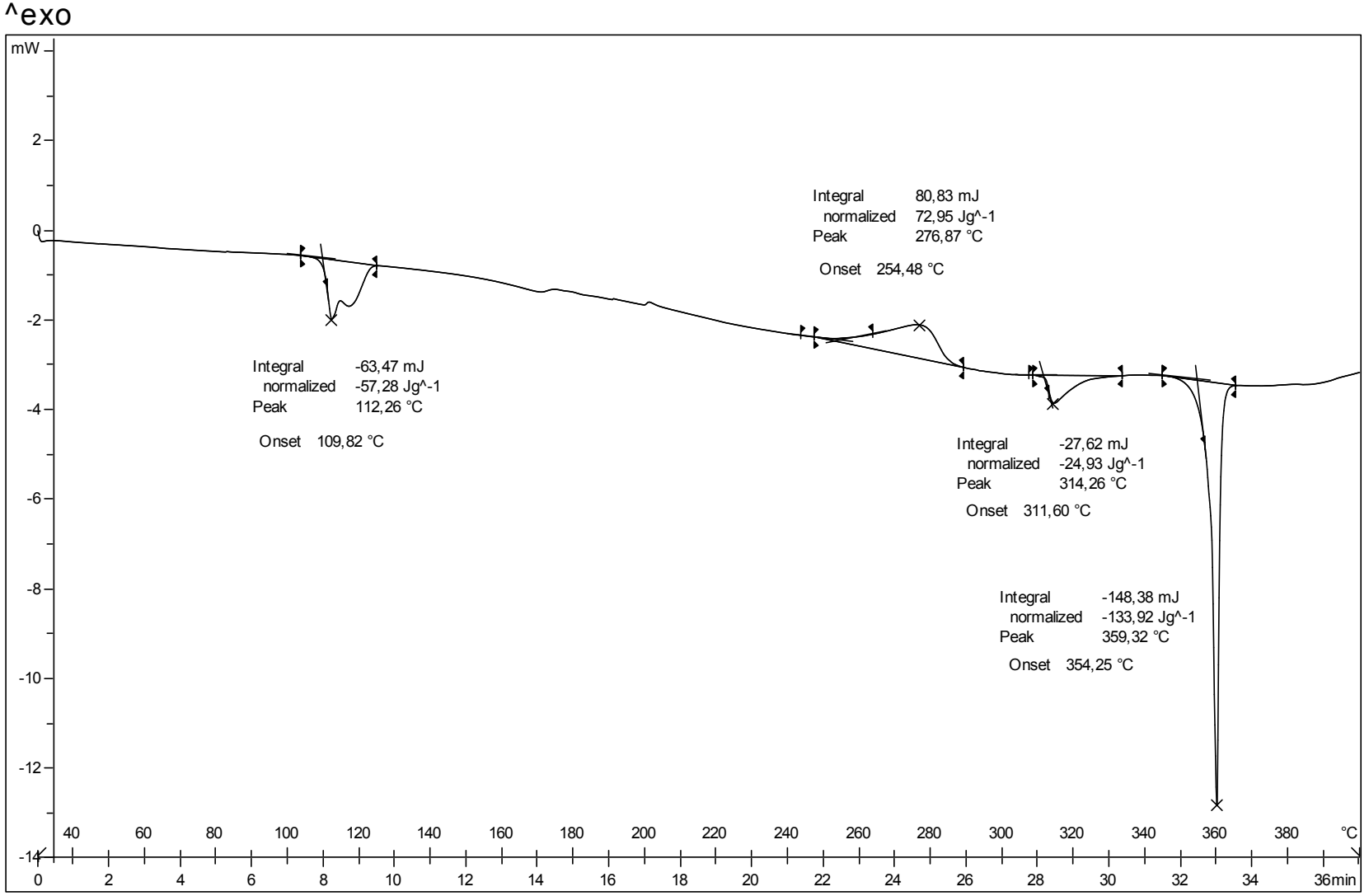


Figure S6: TGA of Form B

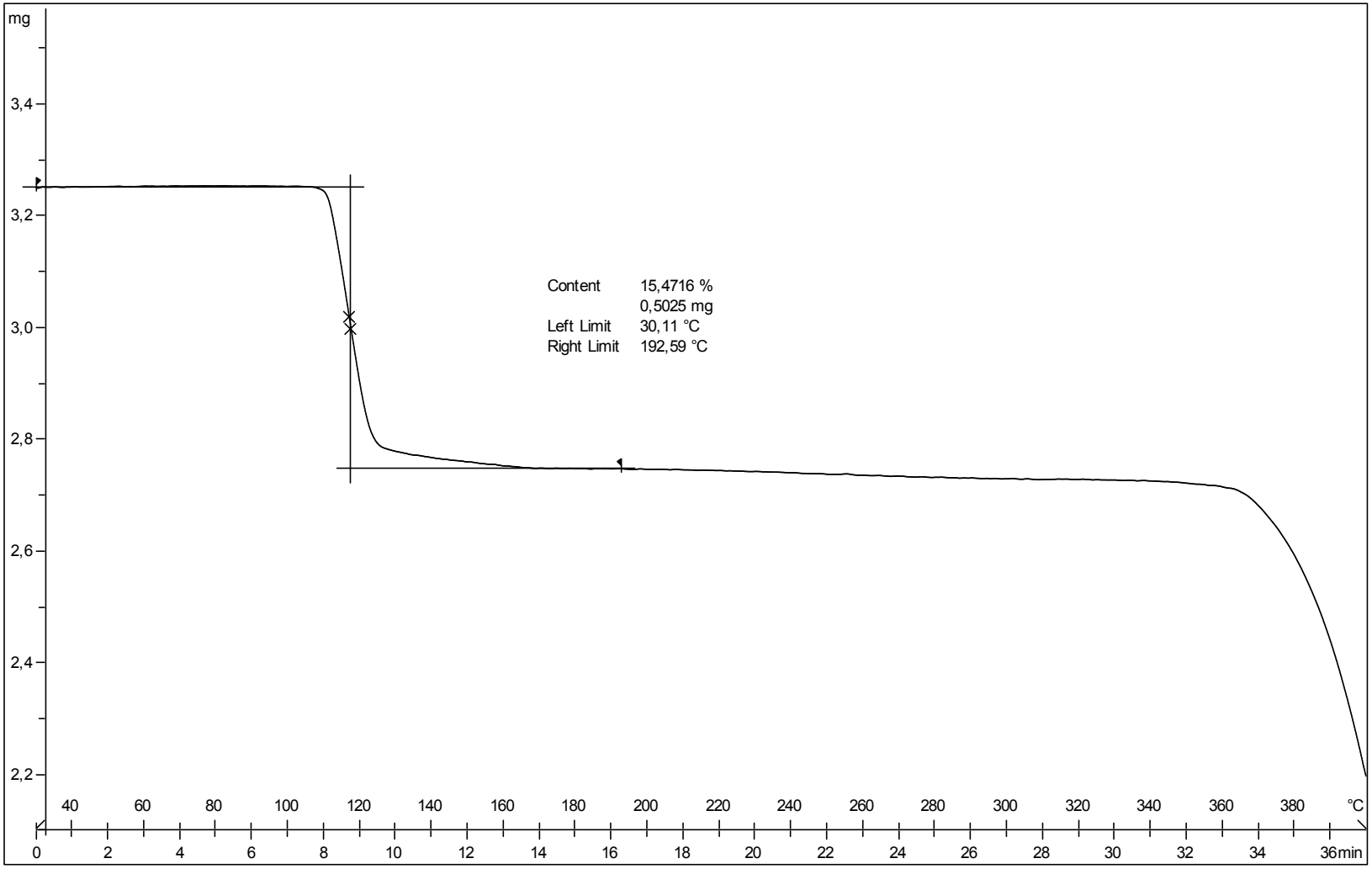


Figure S7: Simulated XRPD of Form B (from SCXRD)

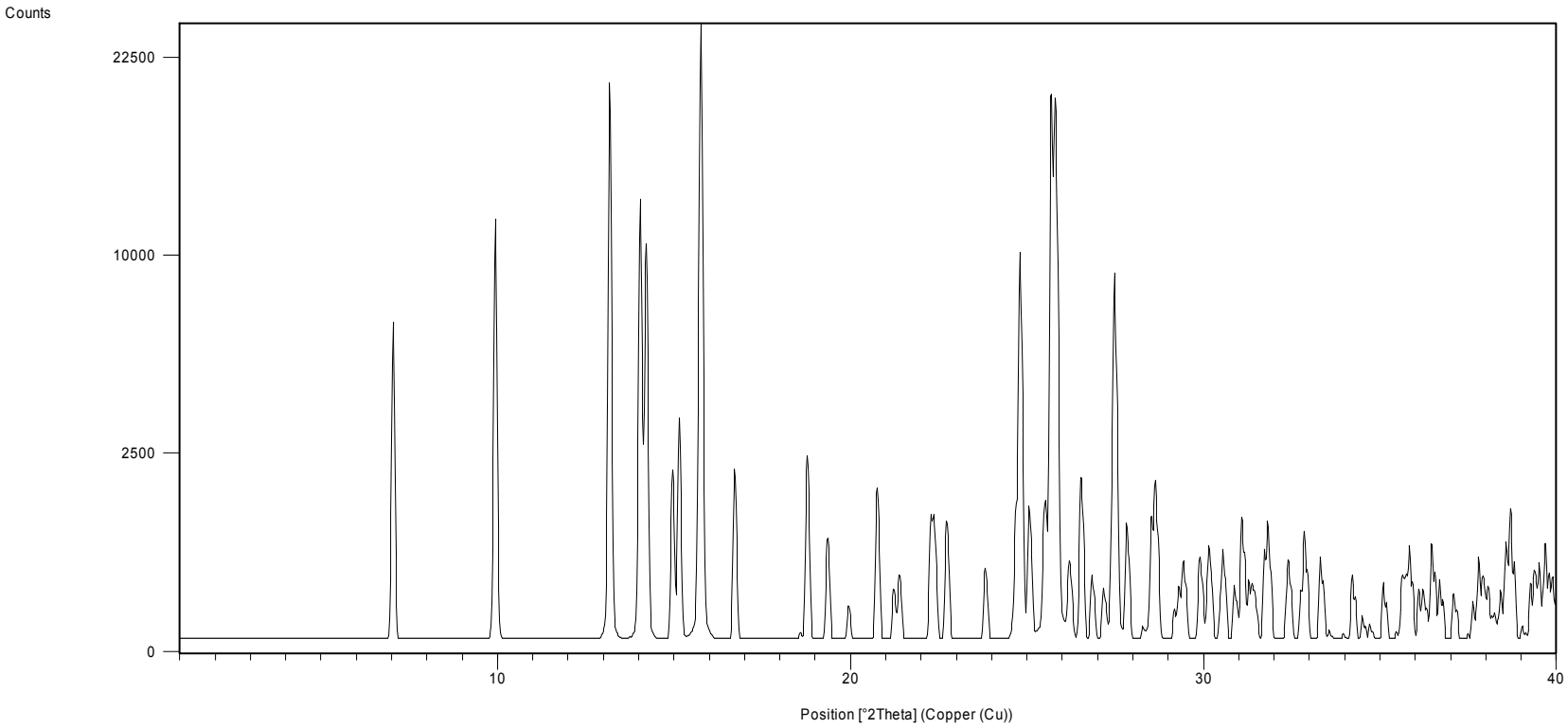


Figure S8: DSC of Form C

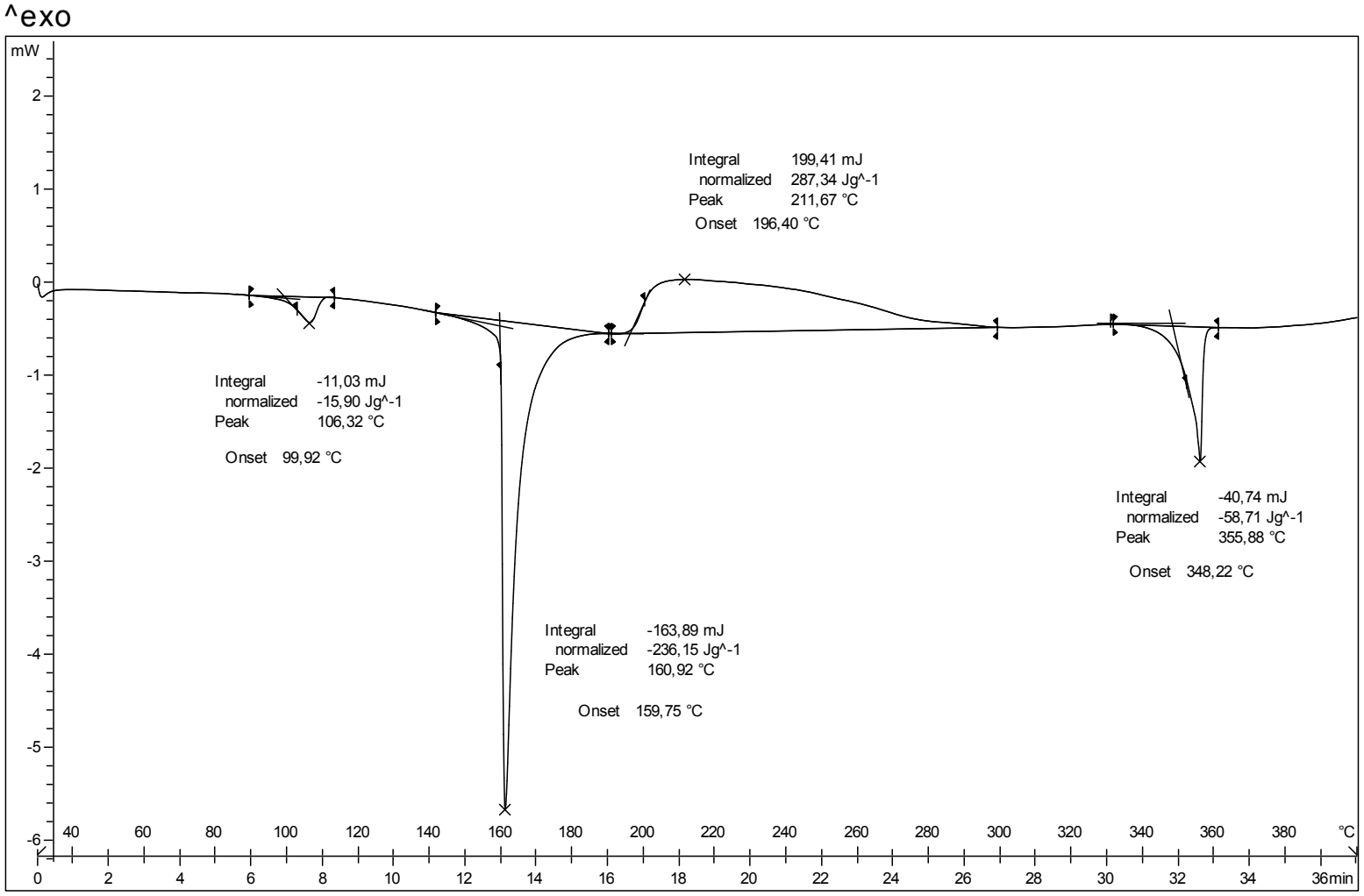


Figure S9: TGA of Form C

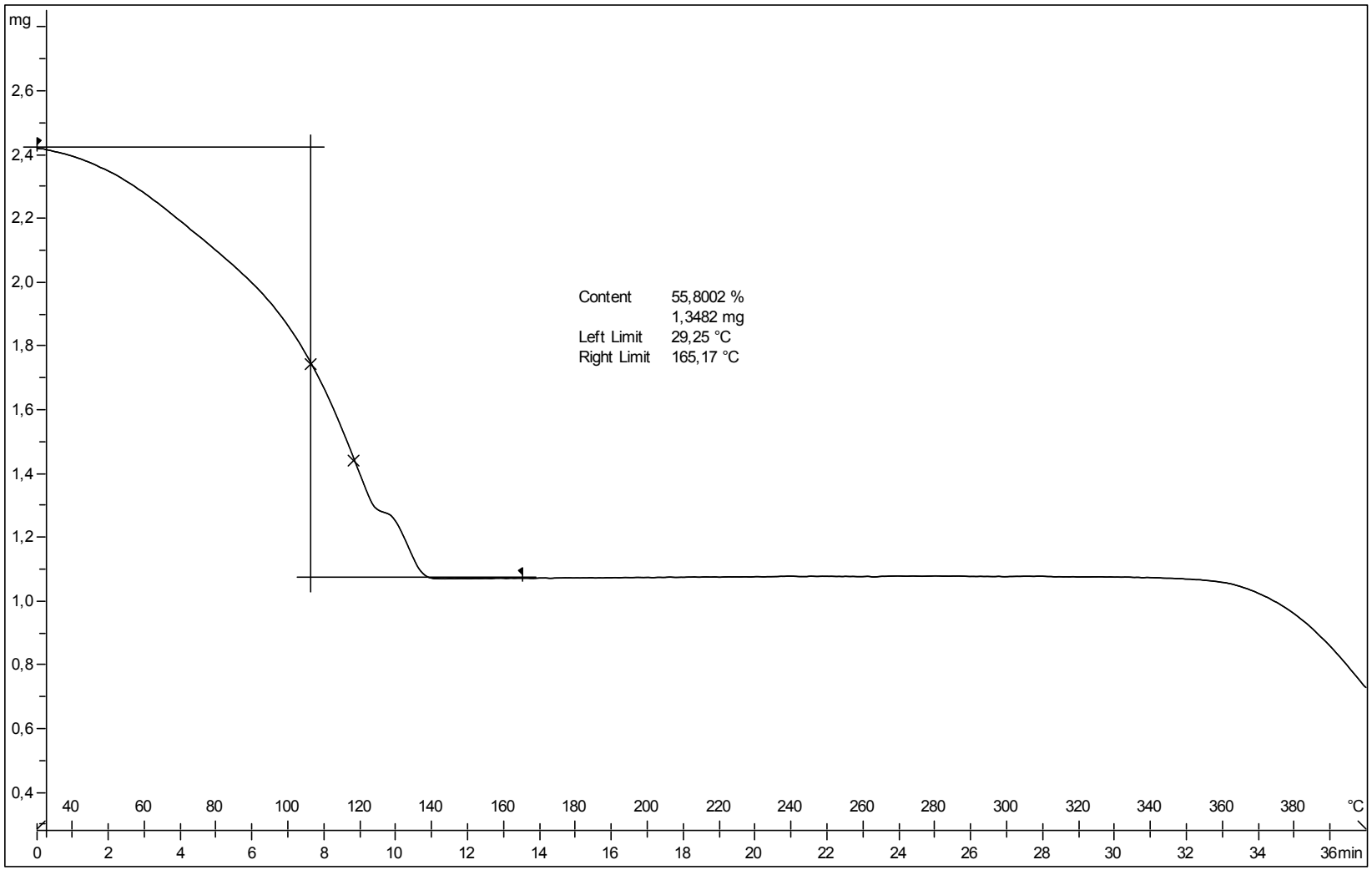


Figure S10: ^{1}H-NMR (dmso-d_6/delay: 1/pulse: 45°/scans: 32) of Form C

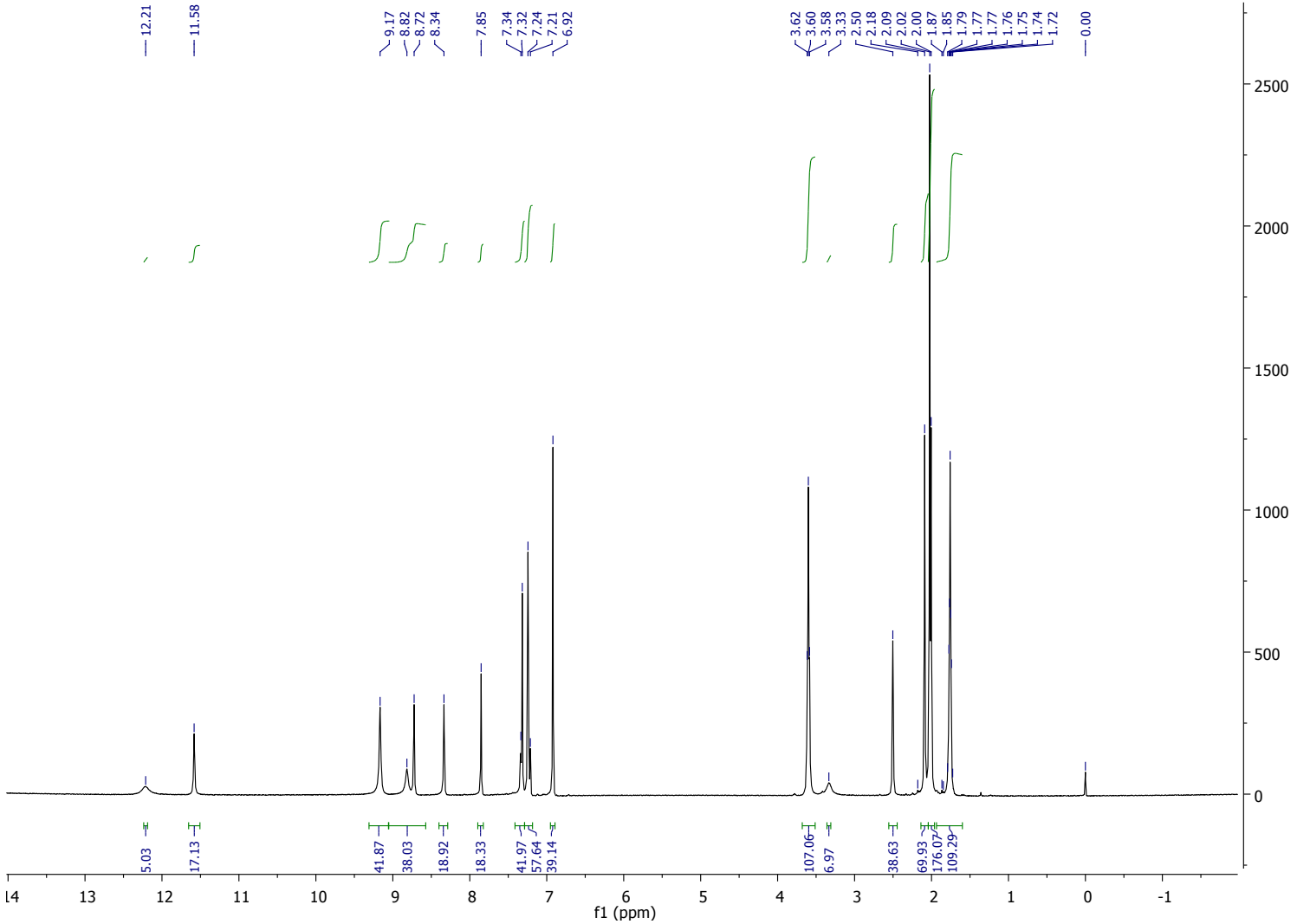


Figure S11: XRPD of Form C

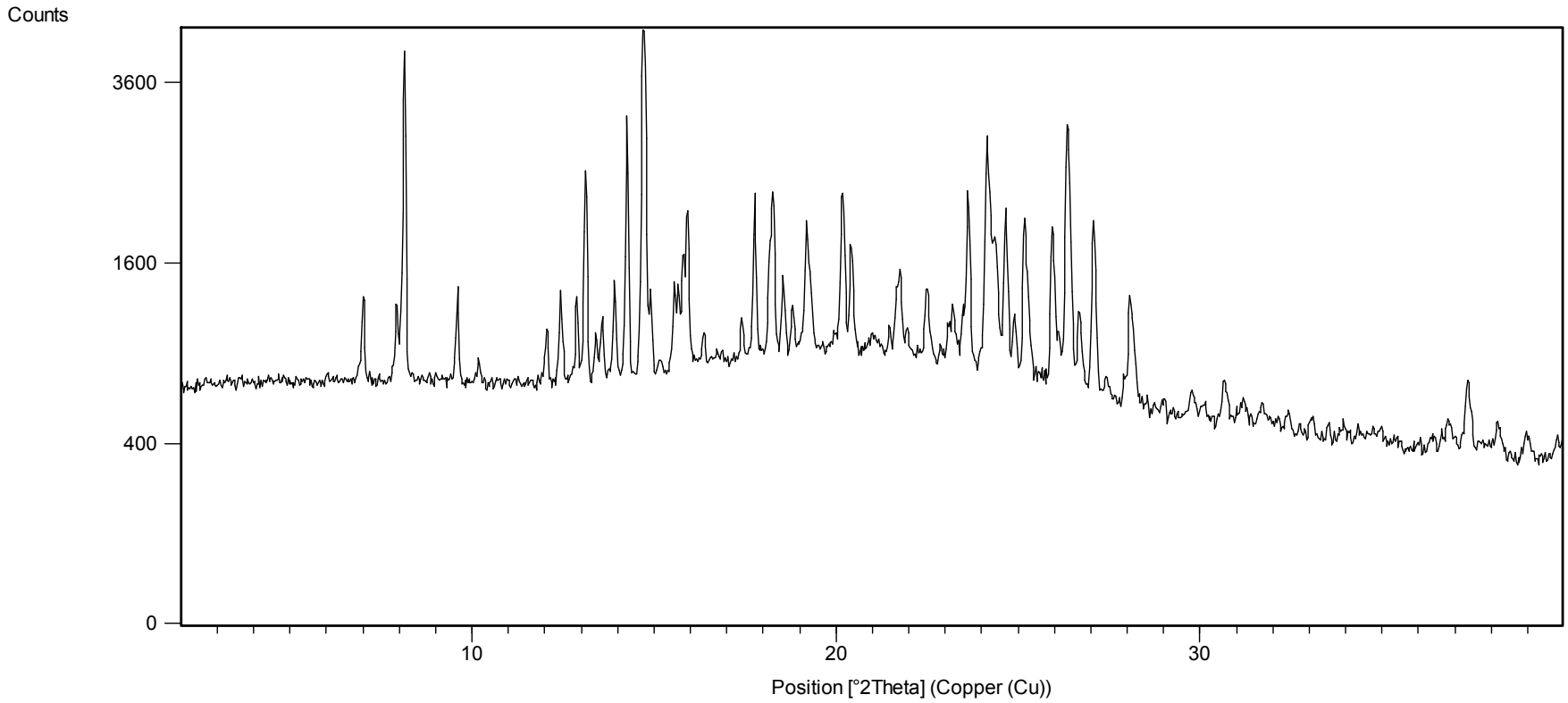


Figure S12: DSC of Form D-1

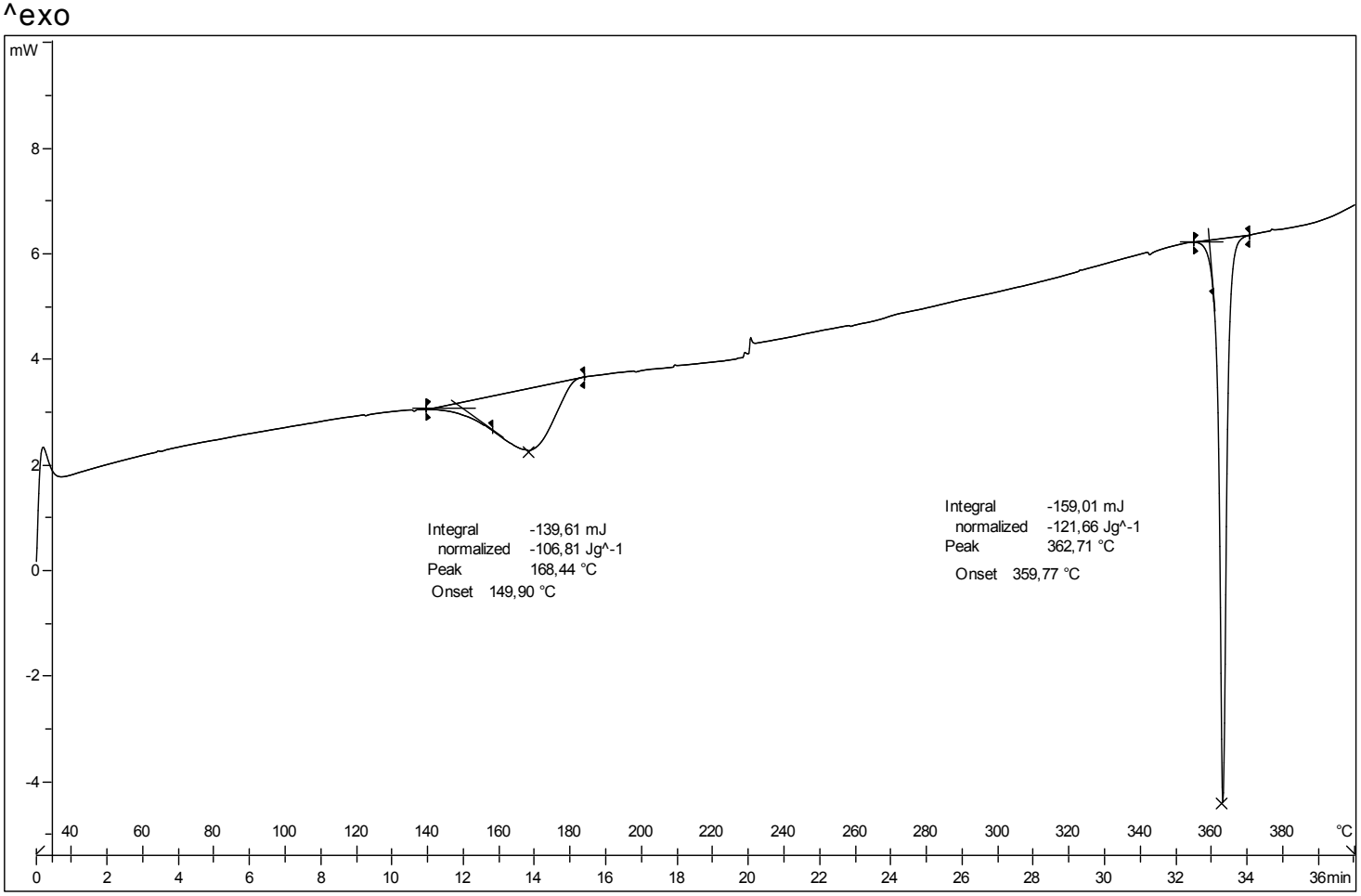


Figure S13: TGA of Form D-1

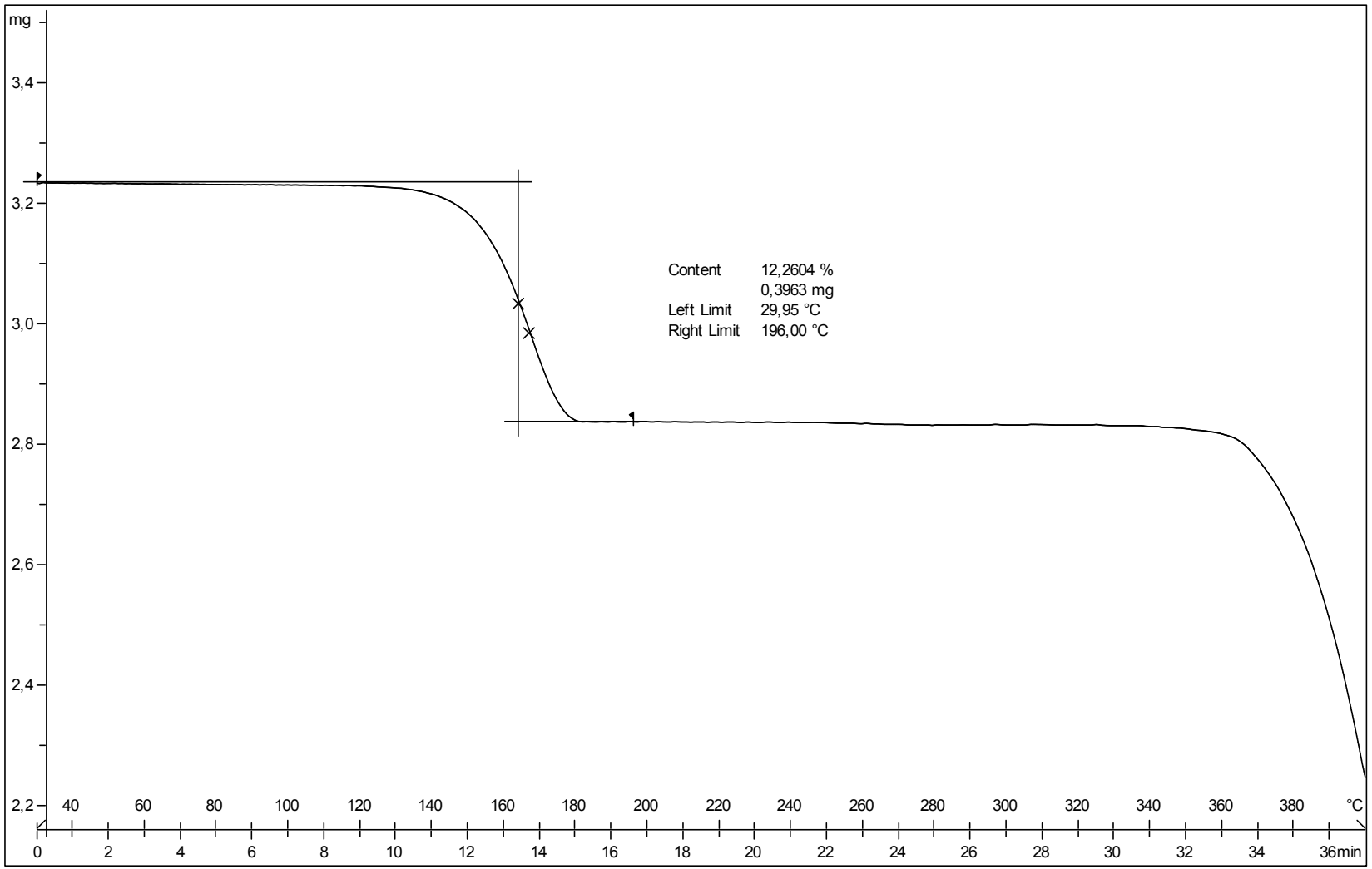


Figure S14: ^{1}H-NMR (dmso-d_6/delay: 1/pulse: 45°/scans: 32) of Form D-1

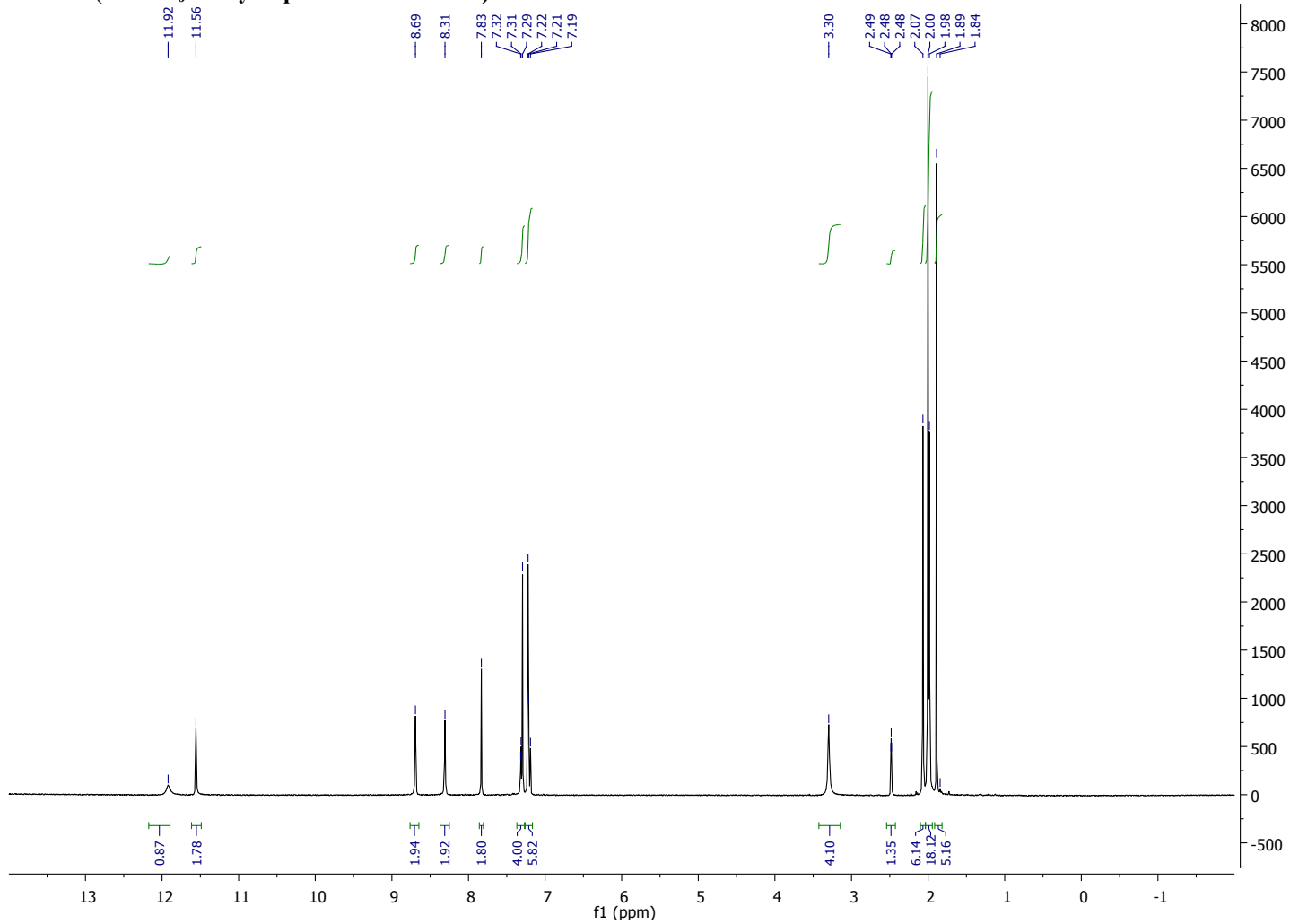


Figure S15: XRPD of Form D-1

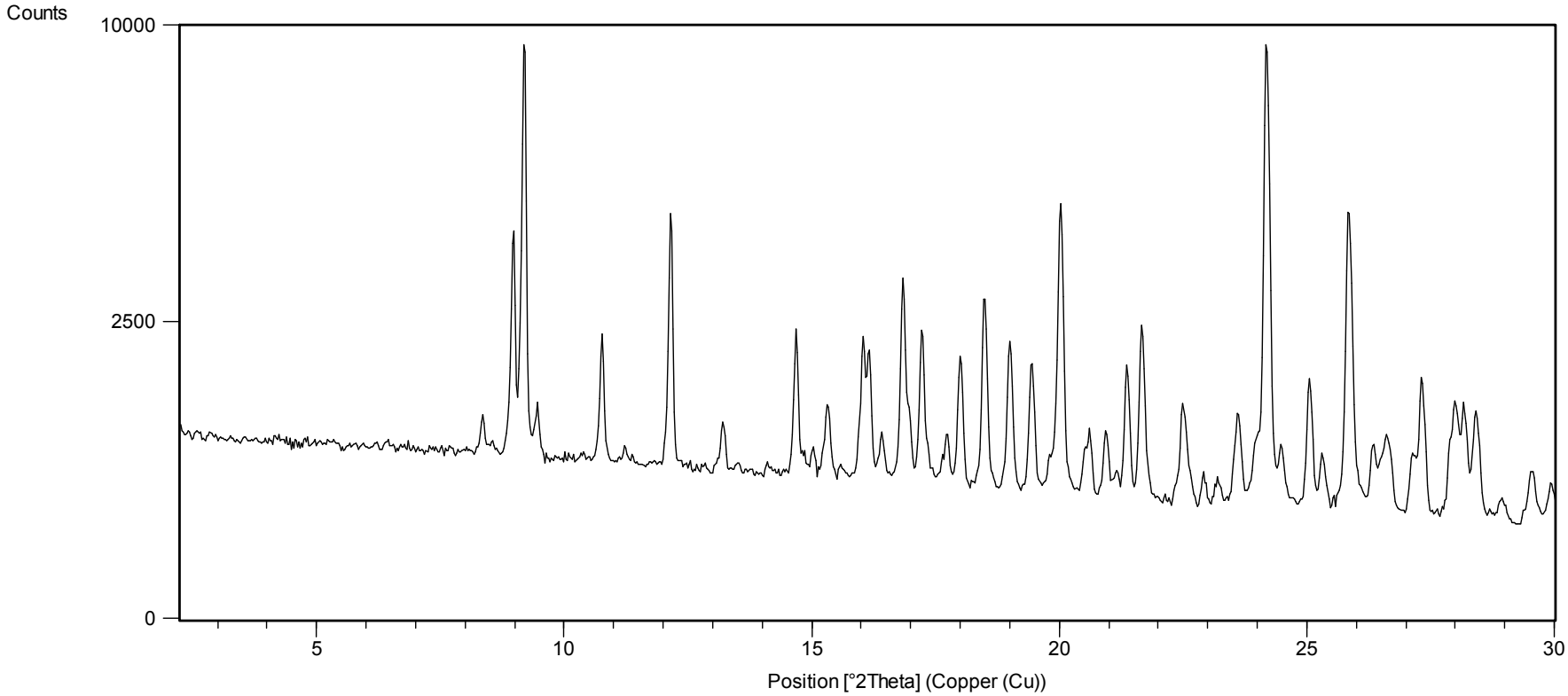


Figure S16: DSC of Form D-2

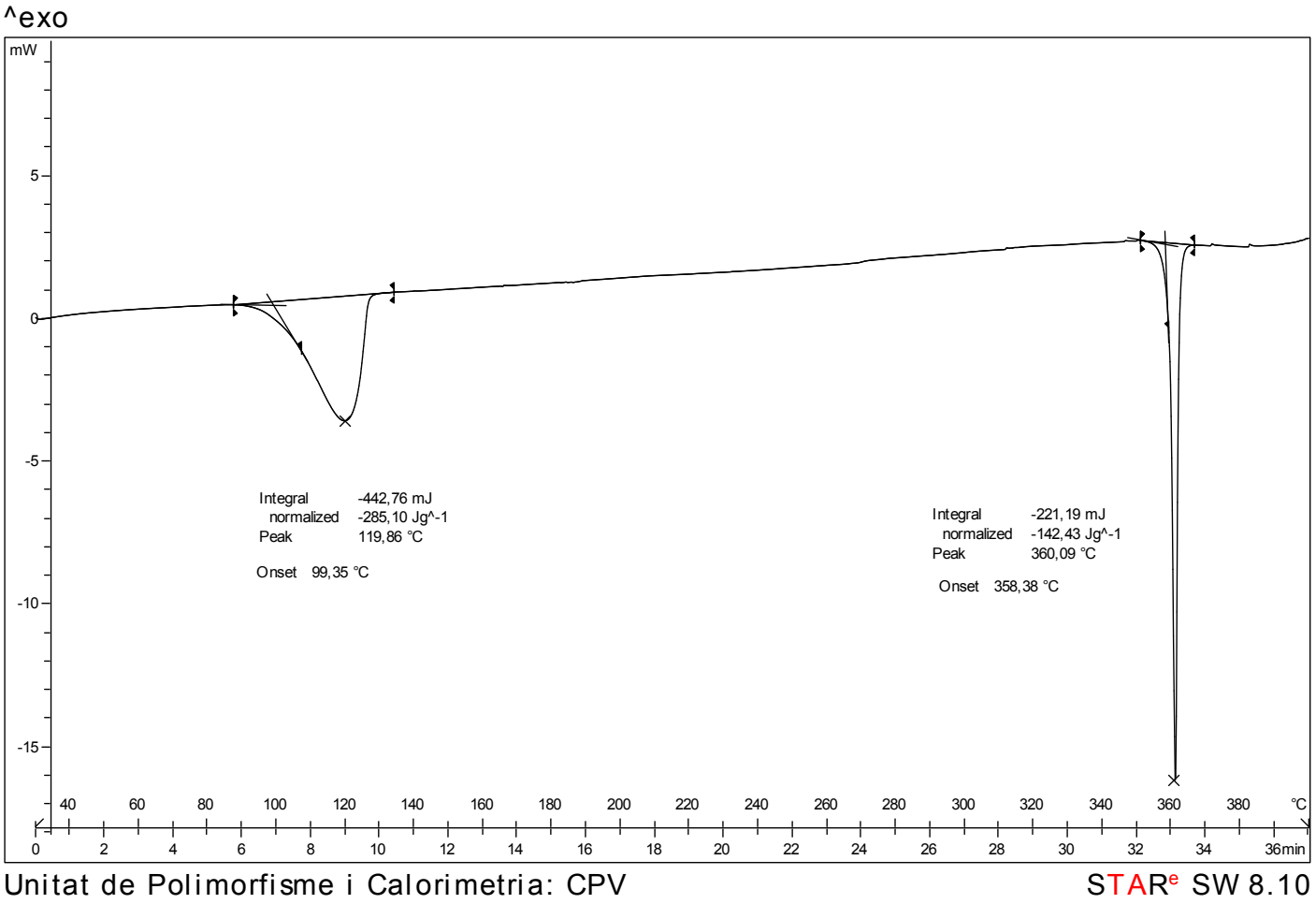


Figure S17: TGA of Form D-2

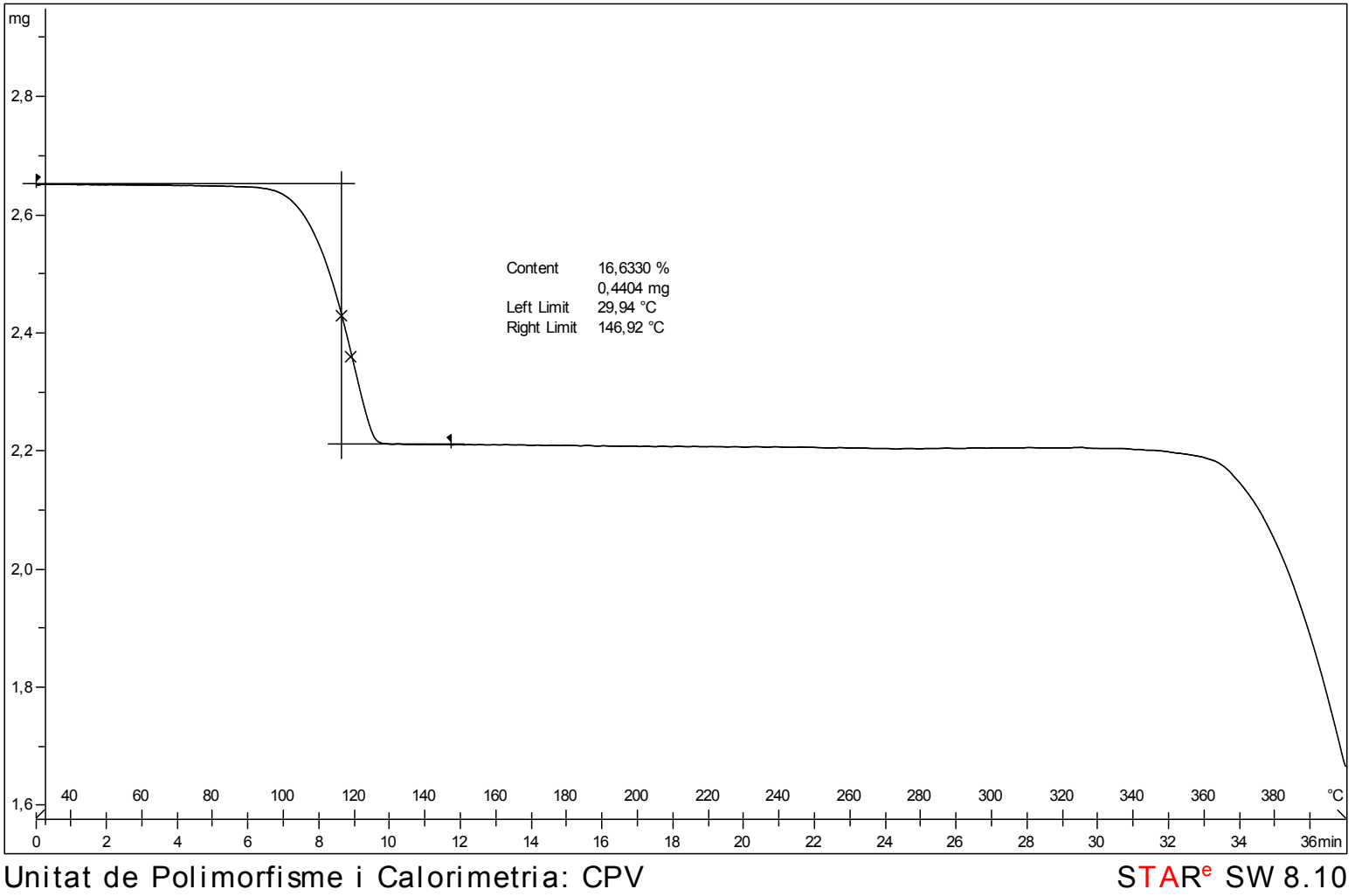


Figure S18: ^{1}H-NMR (dmso-d_6/delay: 1/pulse: 45°/scans: 32) of Form D-2

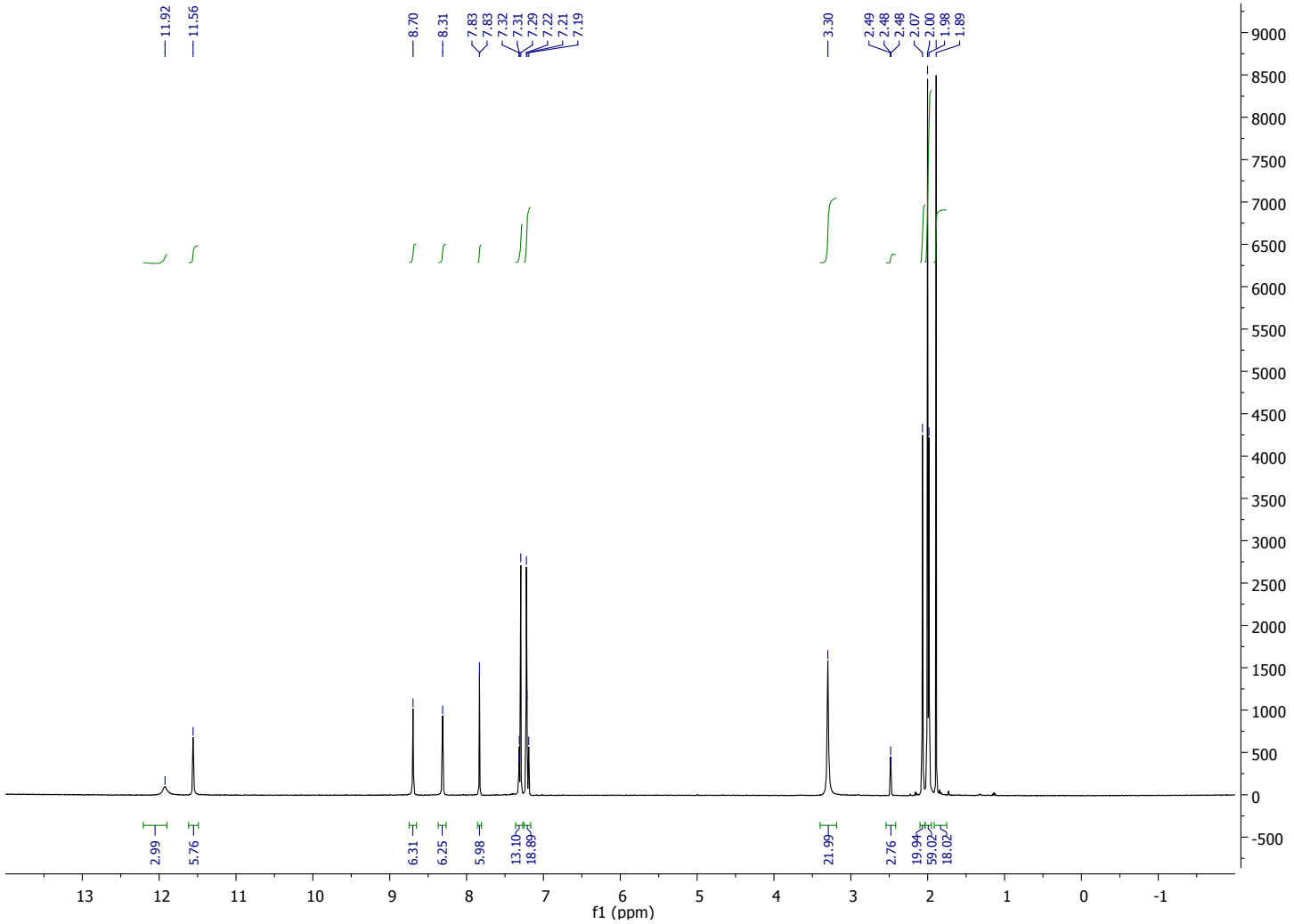


Figure S19: XRPD of Form D-2

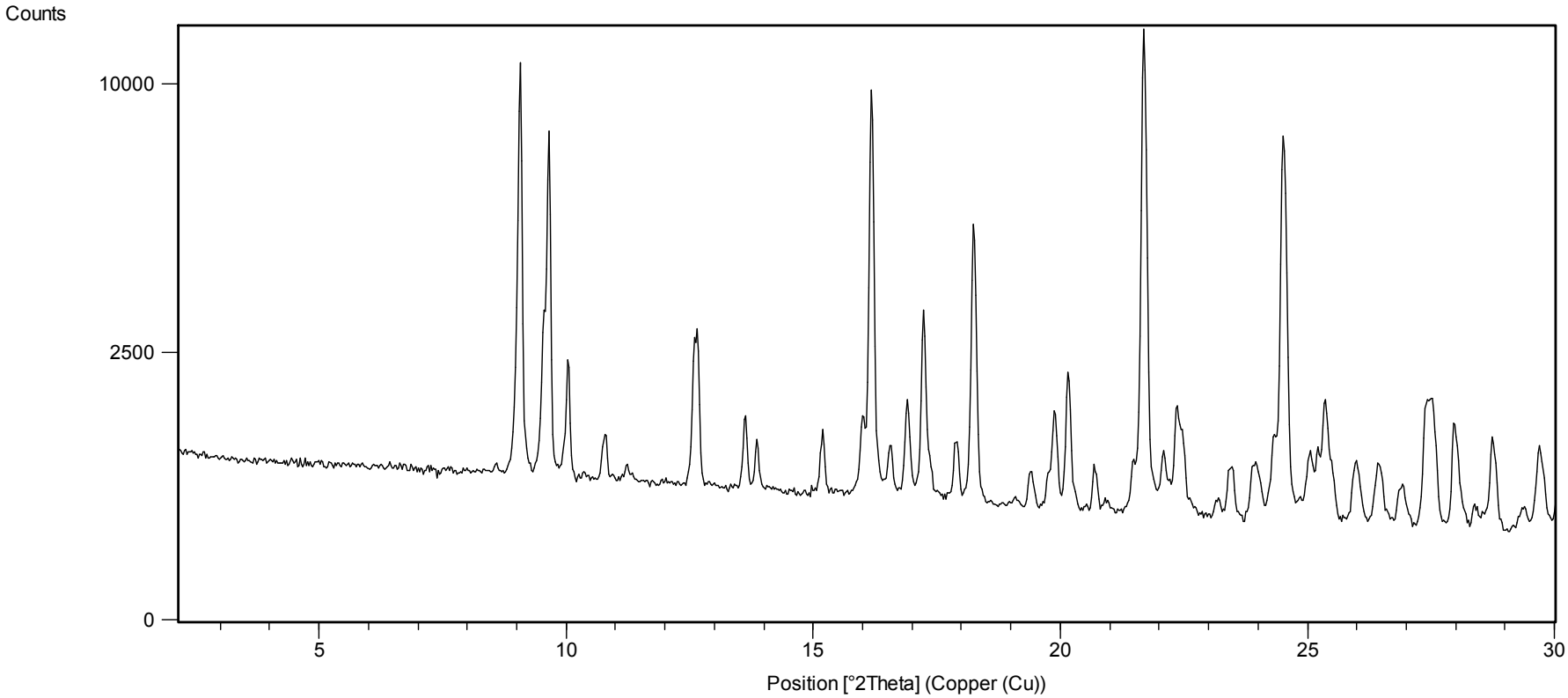


Figure S20: The XRPD of Form D-2 has been indexed with the following proposed monoclinic cell: a=12.123(2) Å, b=17.606(3) Å, c=11.136(2) Å, β=105.95º, V=2285.3(8) Å^3 (Figures of Merit: M= 46, F= 139), a *P2$_1$/n* space group is compatible with the cell.

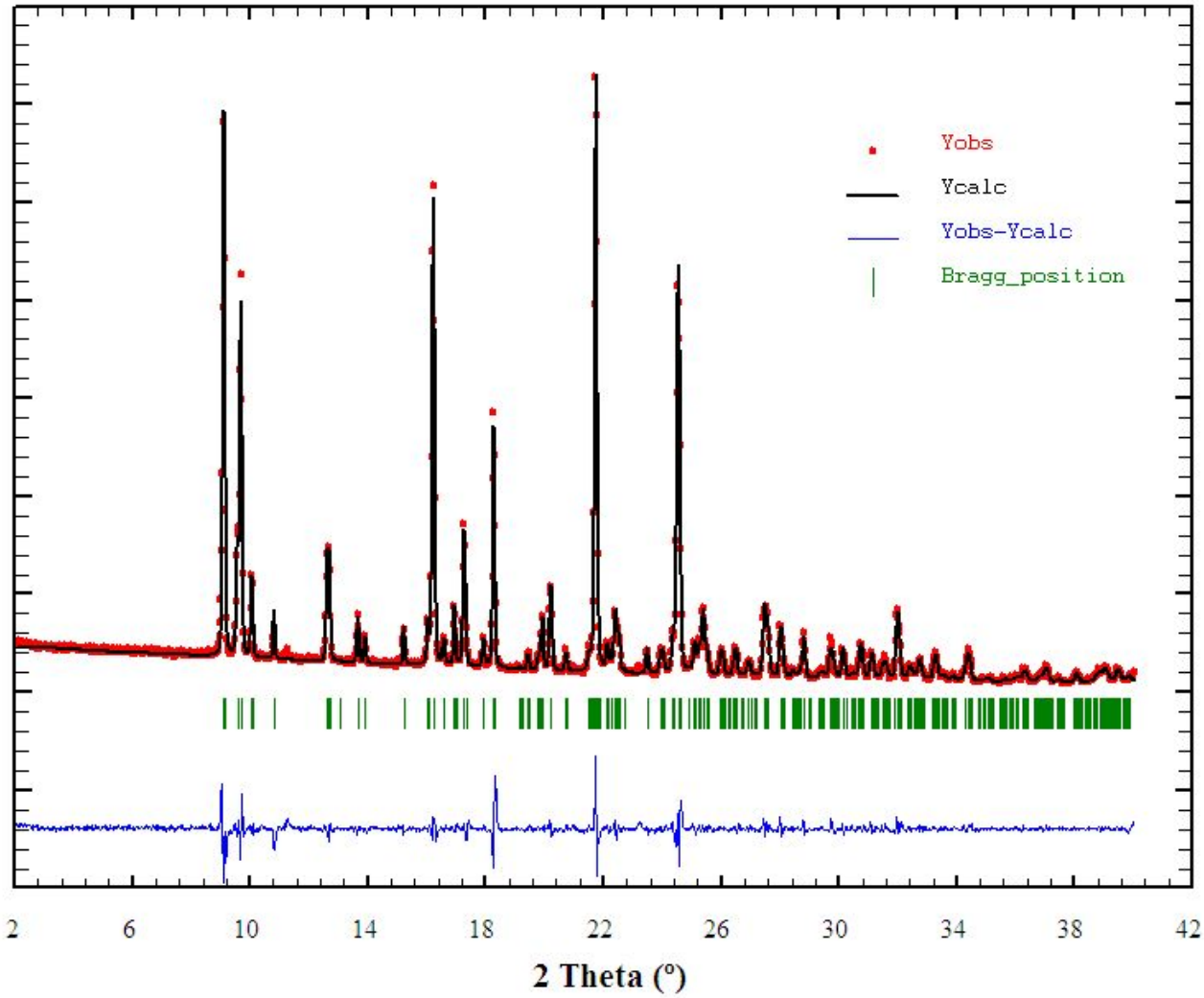


Figure S21: DSC of Form D-3

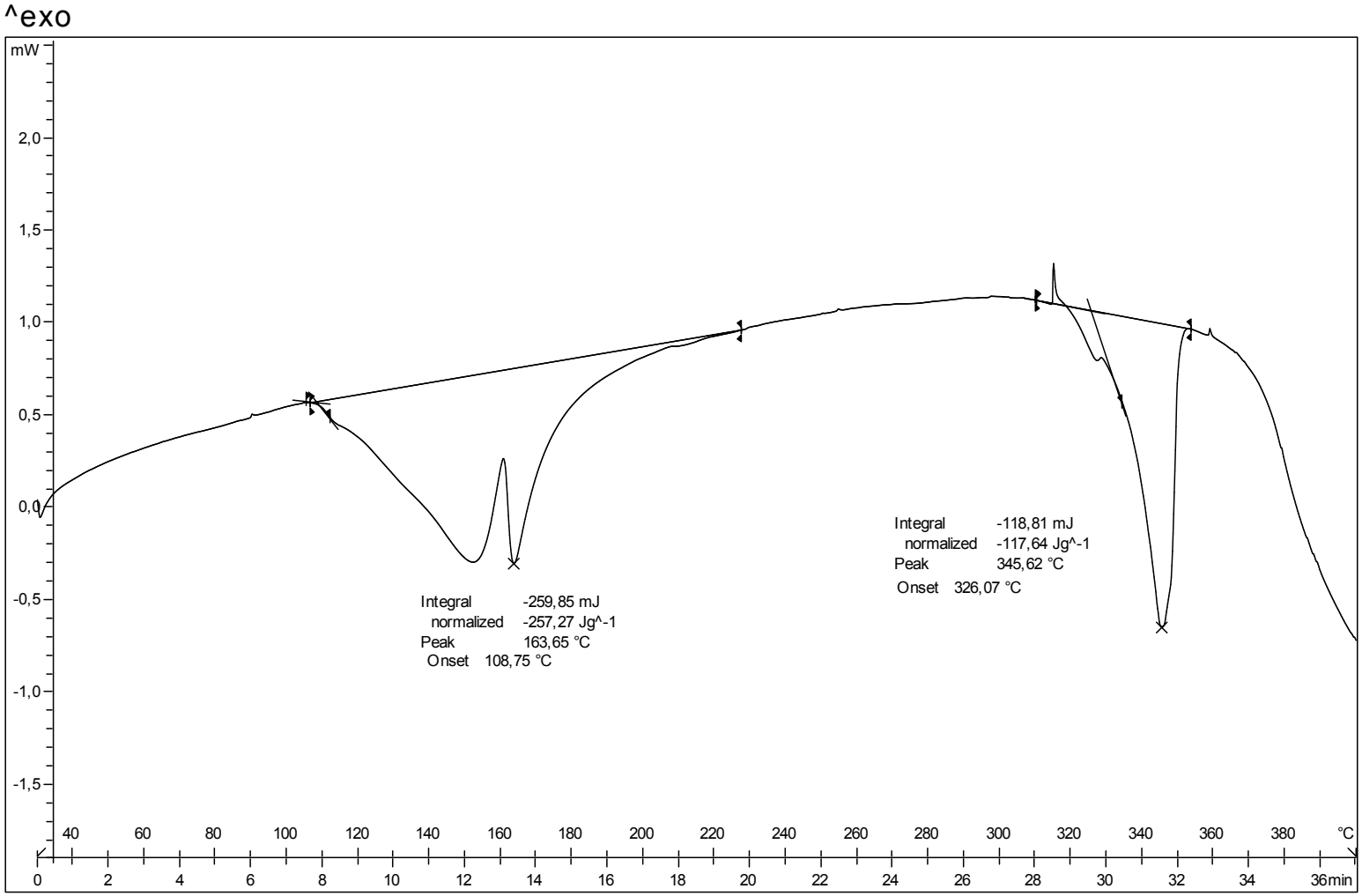


Figure S22: TGA of Form D-3

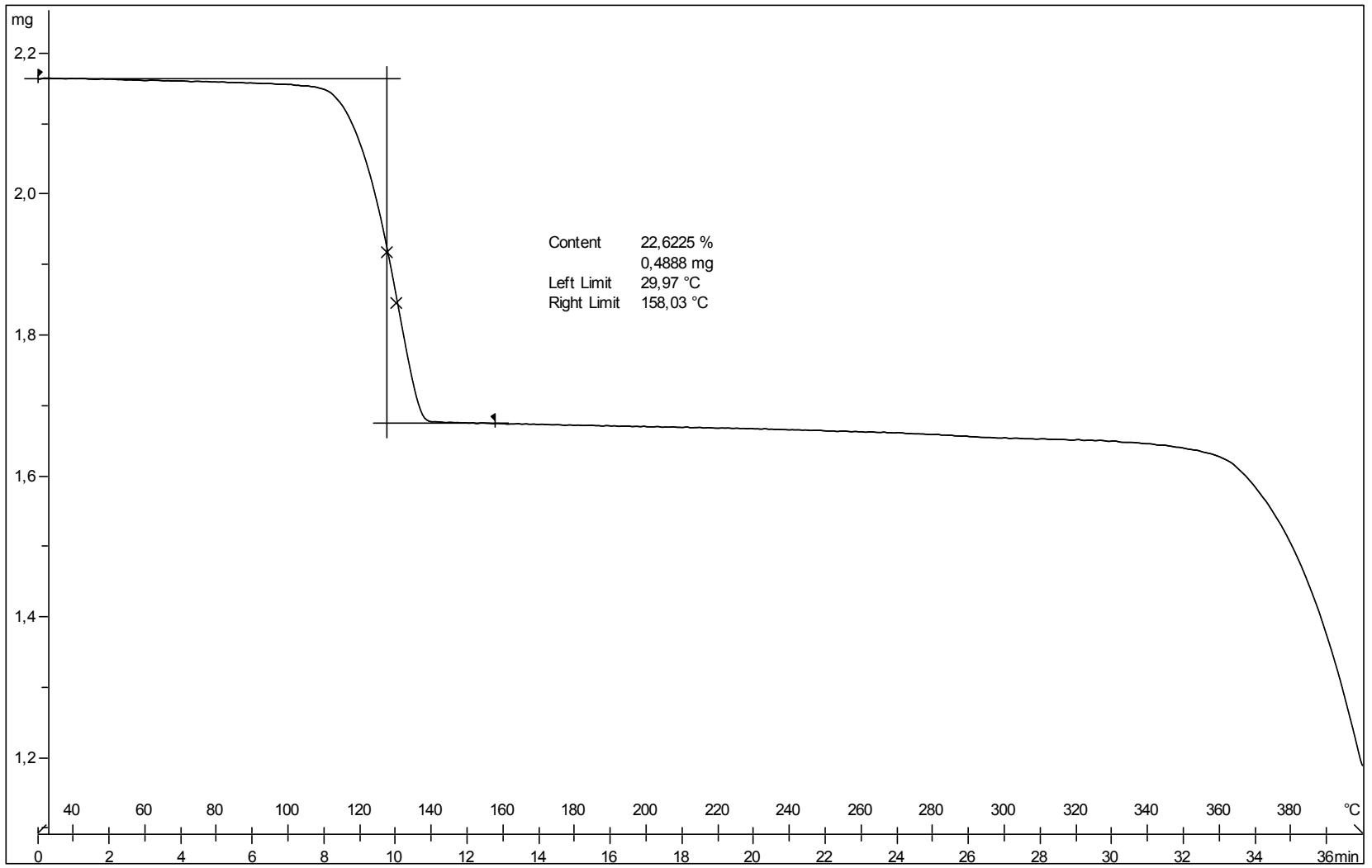


Figure S23: ^{1}H-NMR (dmso-d_6/delay: 1/pulse: 45°/scans: 32) of Form D-3

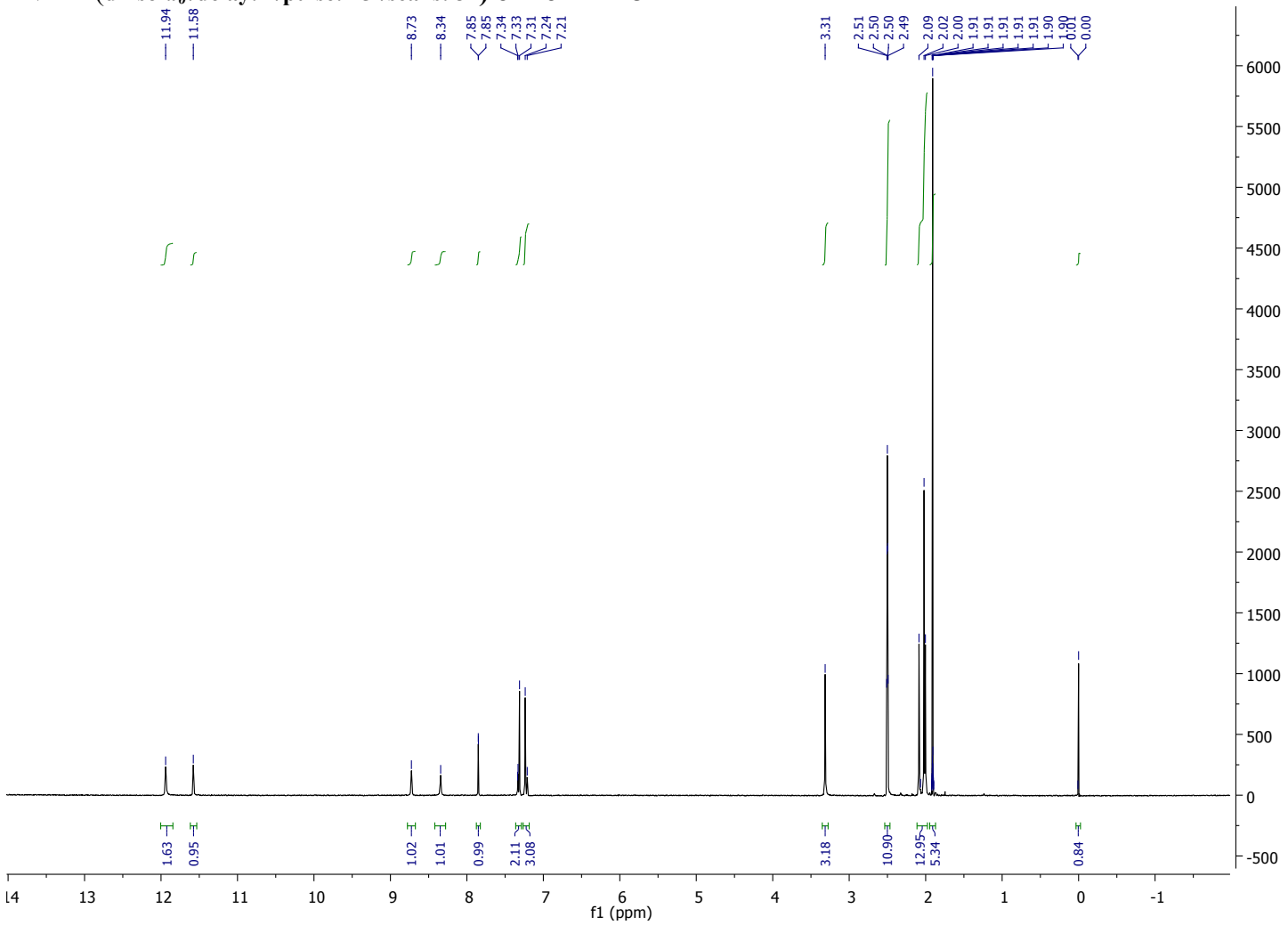


Figure S24: XRPD of Form D-3

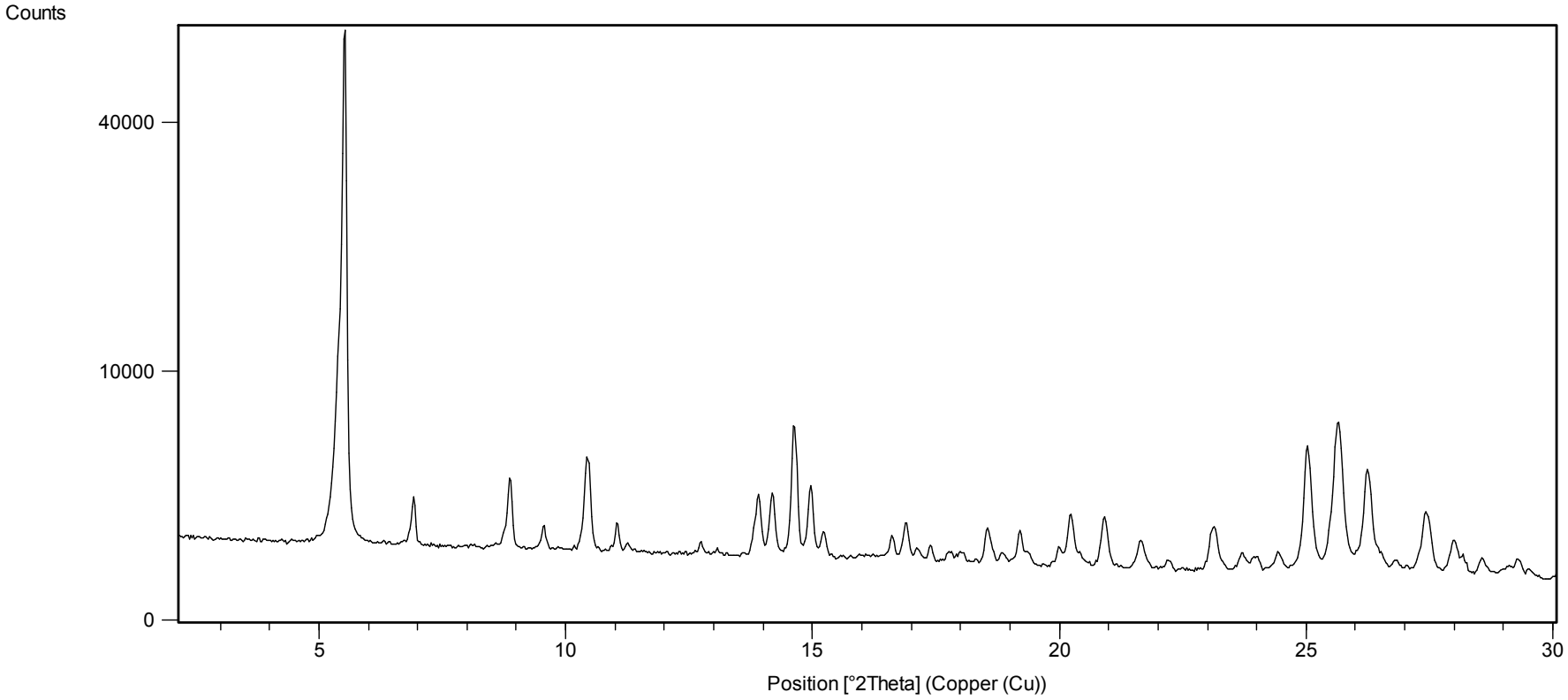


Figure S25: Simulated XRPD of Form D-4 (from SCXRD)

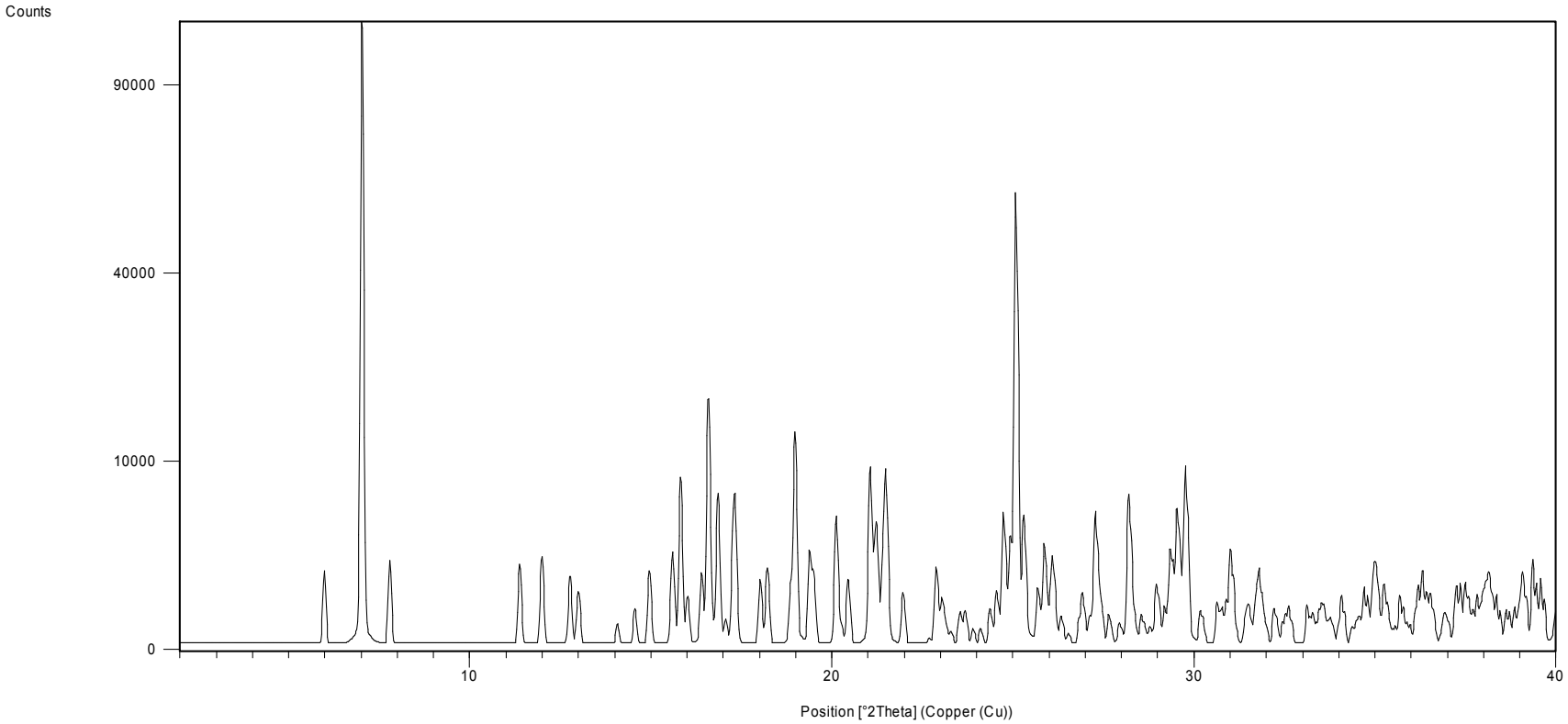


Figure S26: DSC of Form I

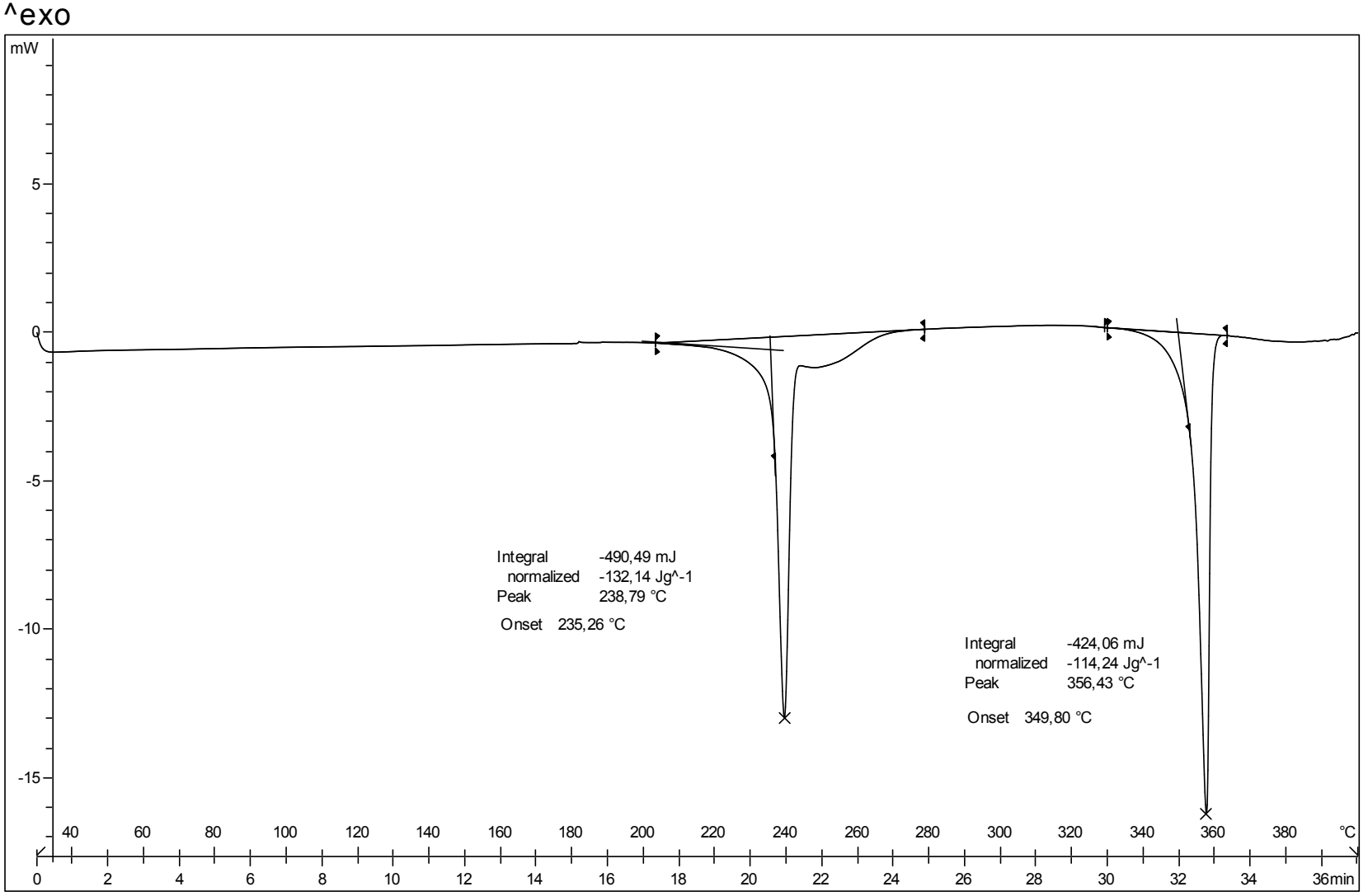


Figure S27: TGA of Form I

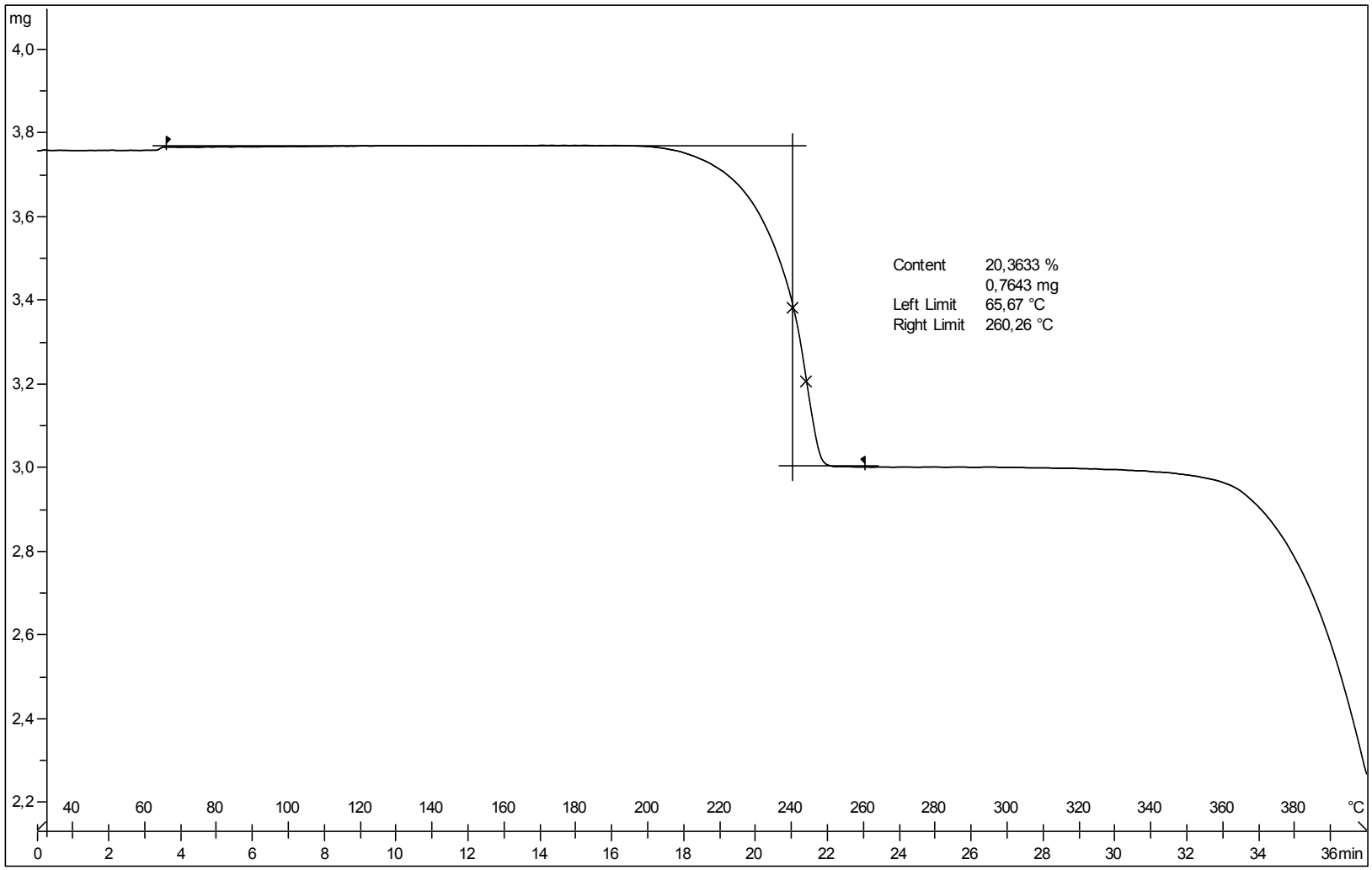


Figure S28: ^{1}H-NMR (dmso-d_6/delay: 1/pulse: 45°/scans: 32) of Form I

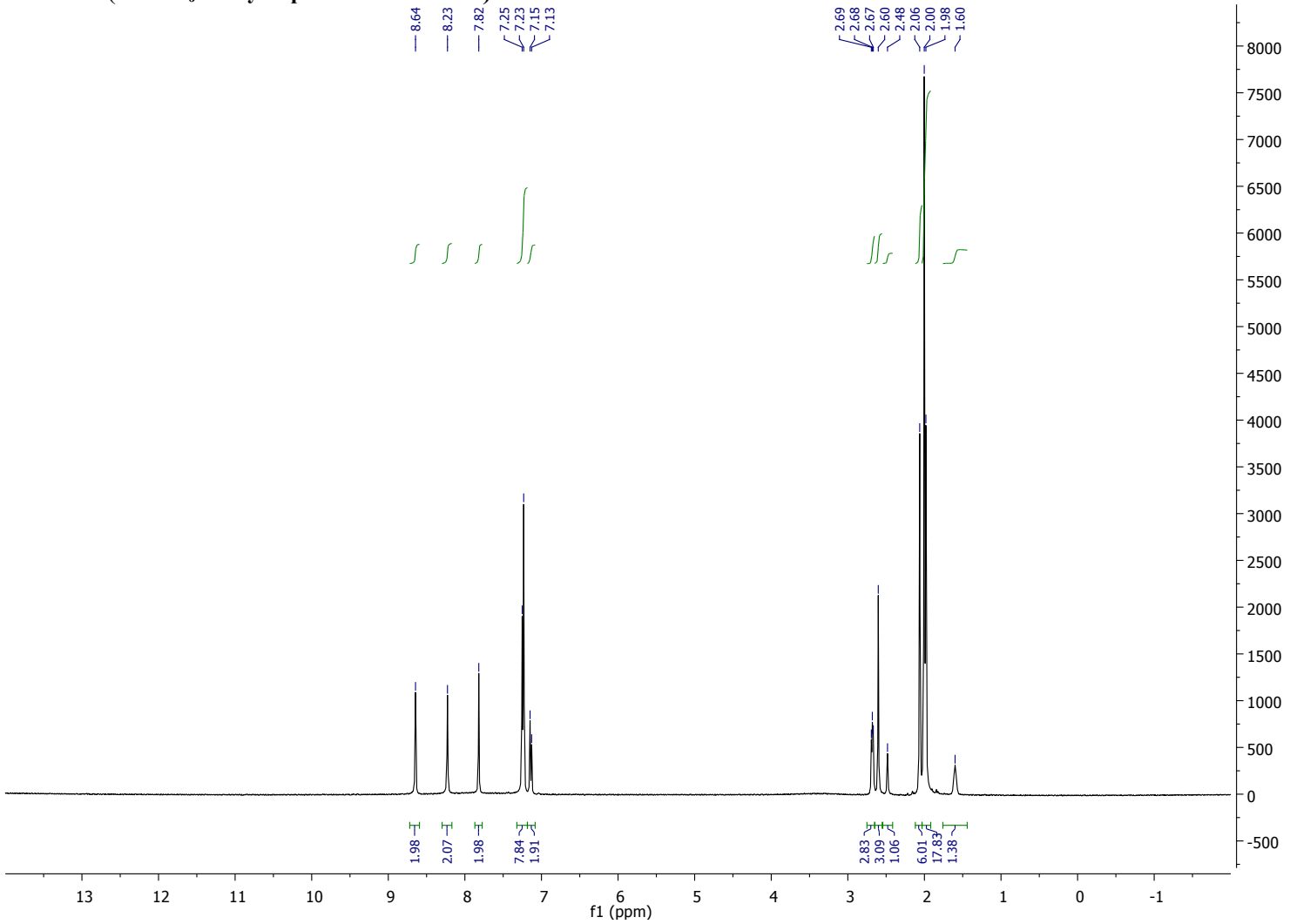


Figure S29: XRPD of Form I

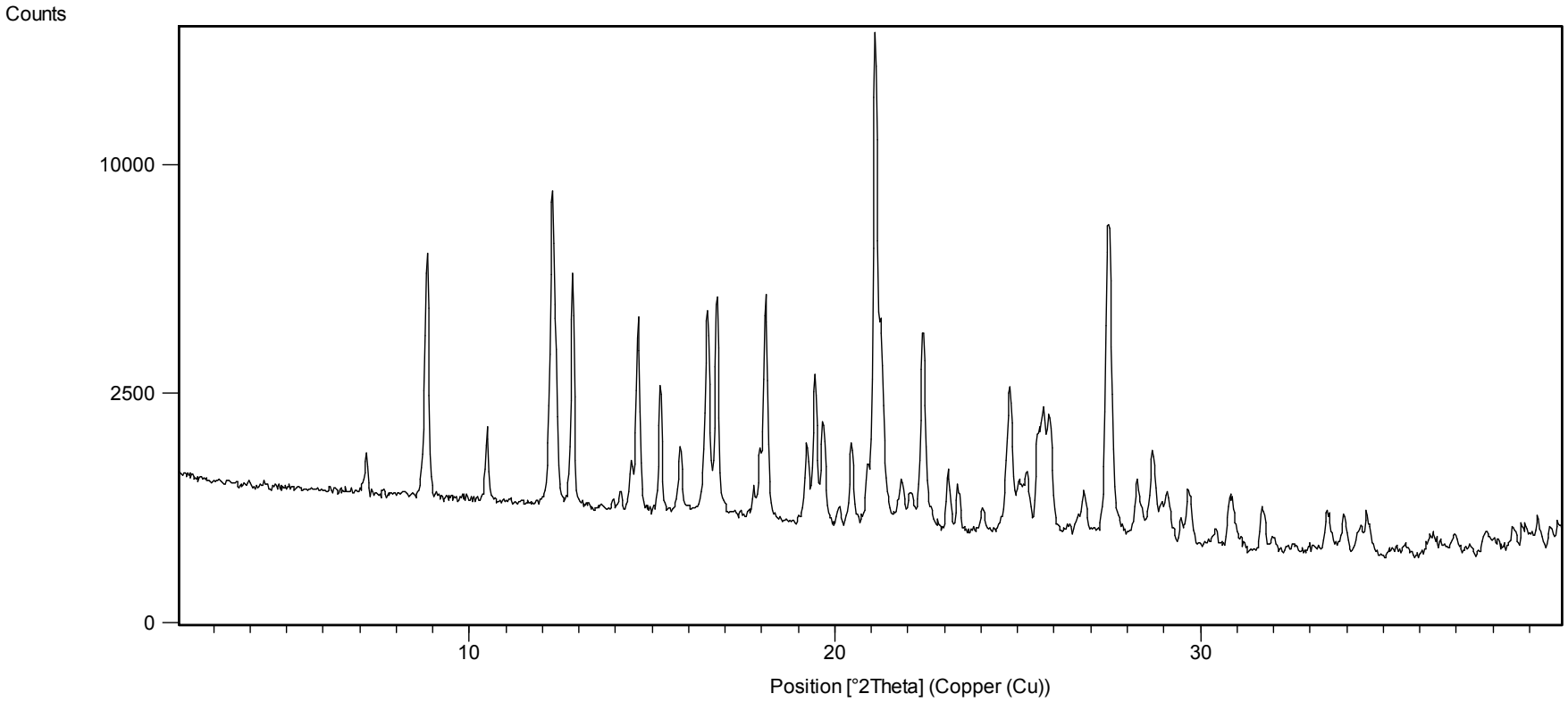


Figure S30: DSC of Form II-A

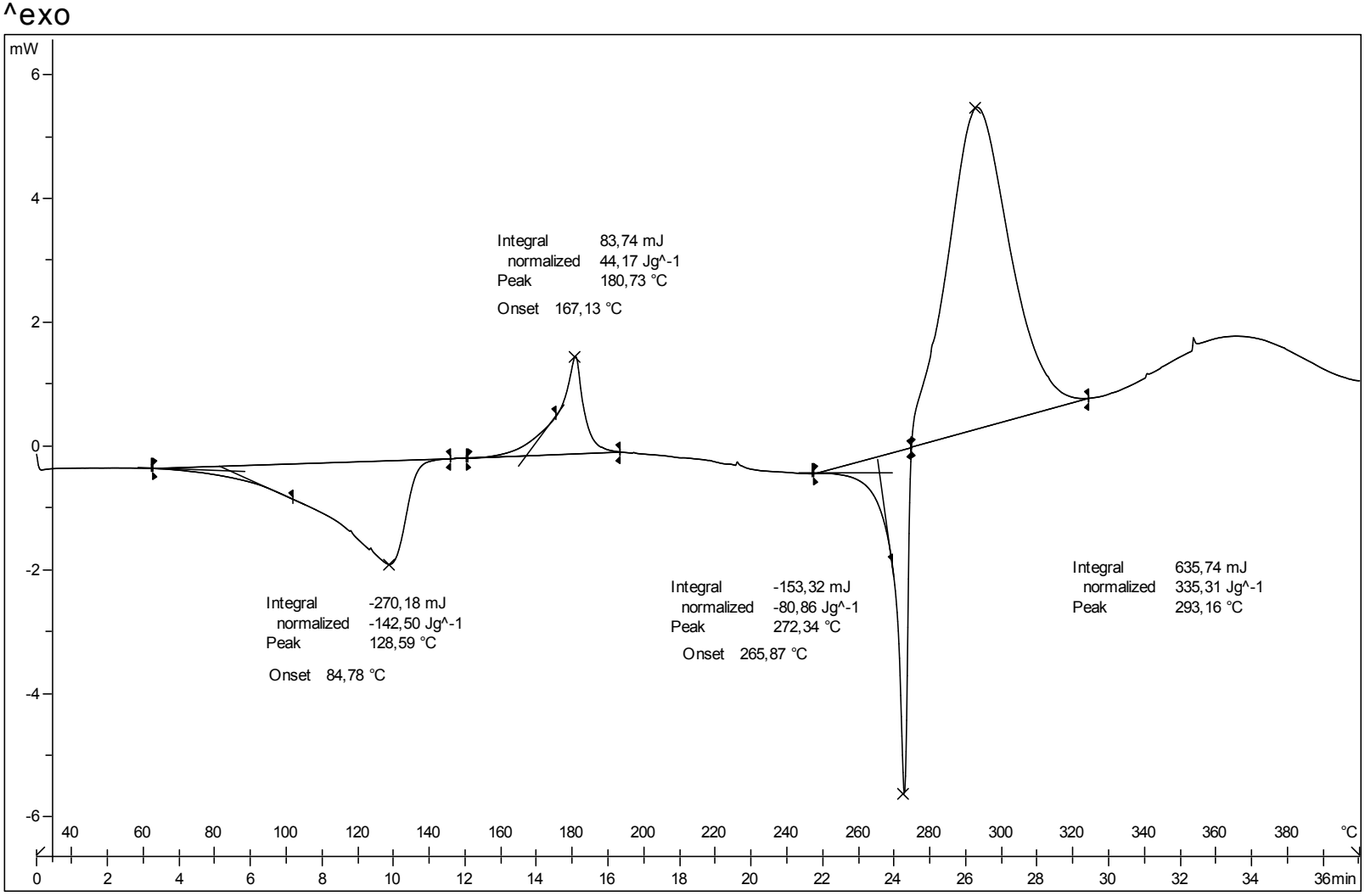


Figure S31: TGA of Form II-A

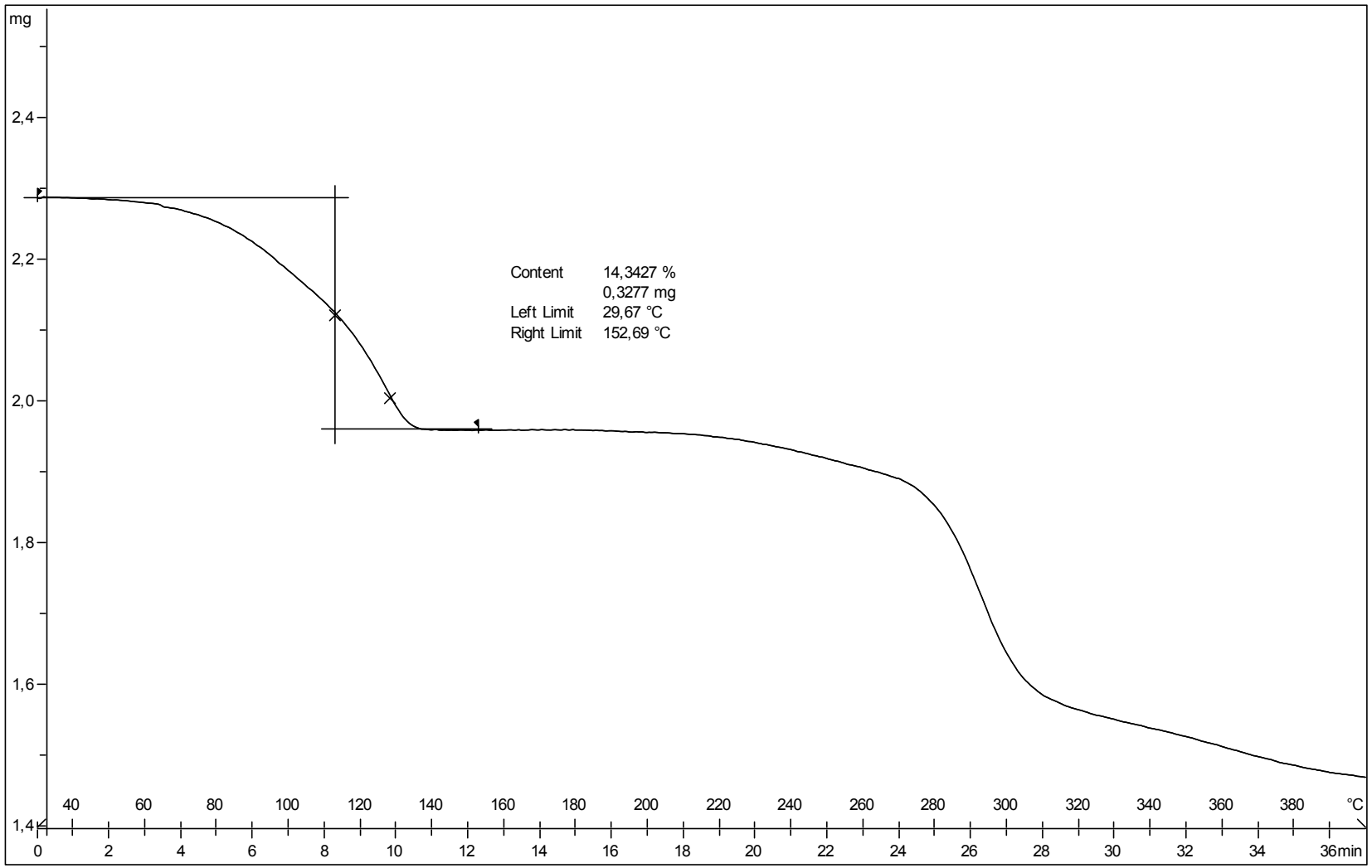


Figure S32: ^{1}H-NMR (dmso-d_6/delay: 1/pulse: 45°/scans: 32) of Form II-A

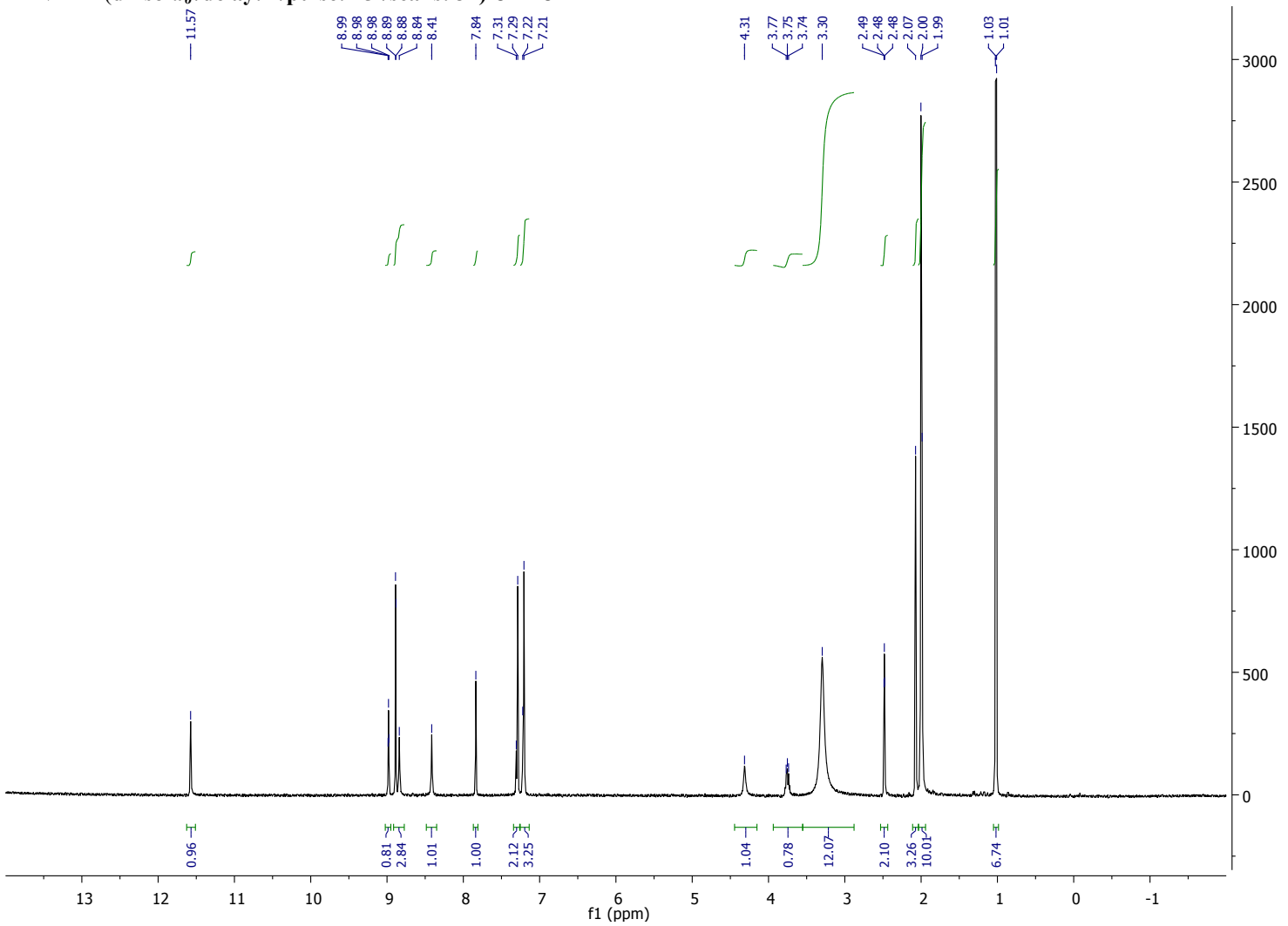


Figure S33: XRPD of Form II-A

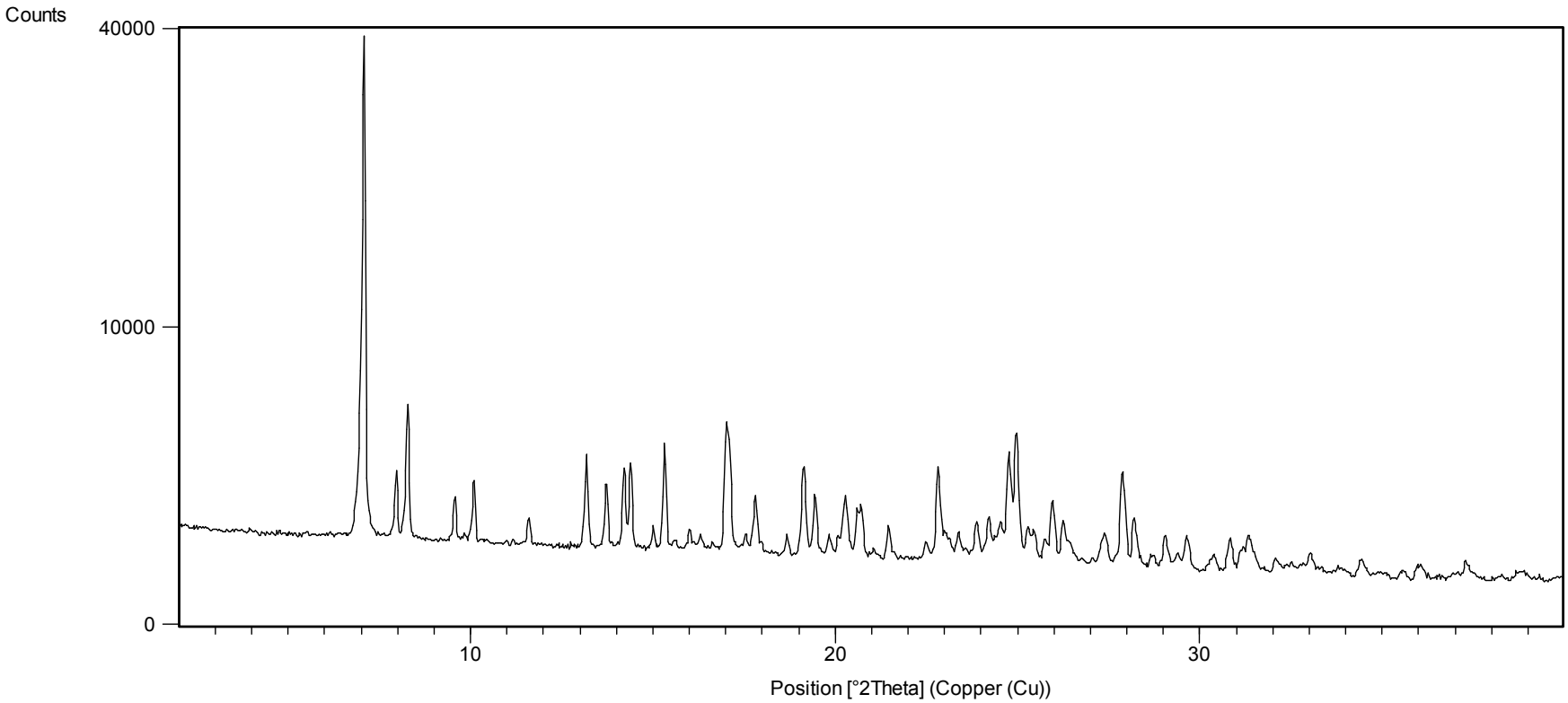


Figure S34: DSC of Form II-B

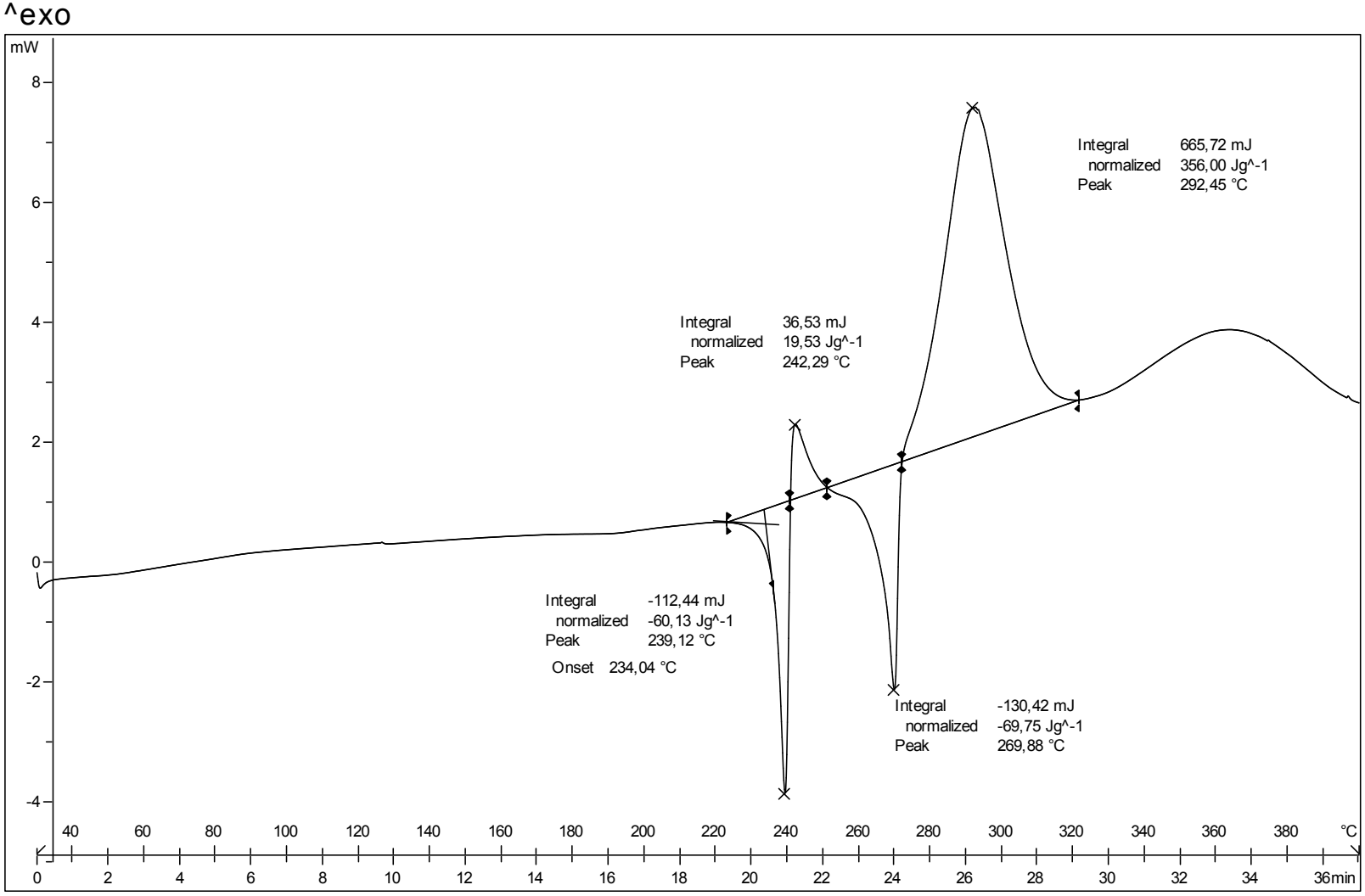


Figure S35: TGA of Form II-B

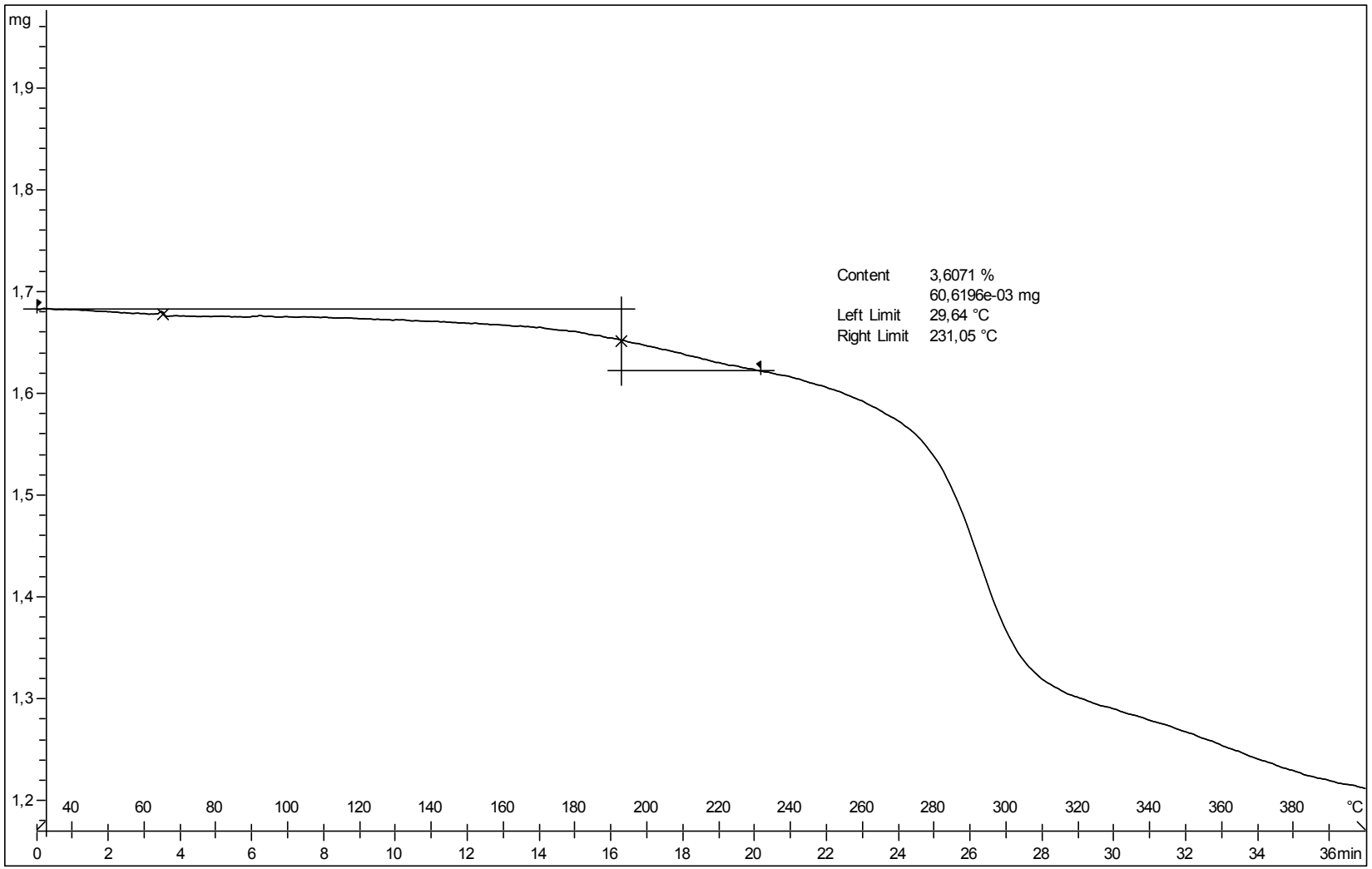


Figure S36: ^{1}H-NMR (dmso-d_6/delay: 1/pulse: 45°/scans: 32) of Form II-B

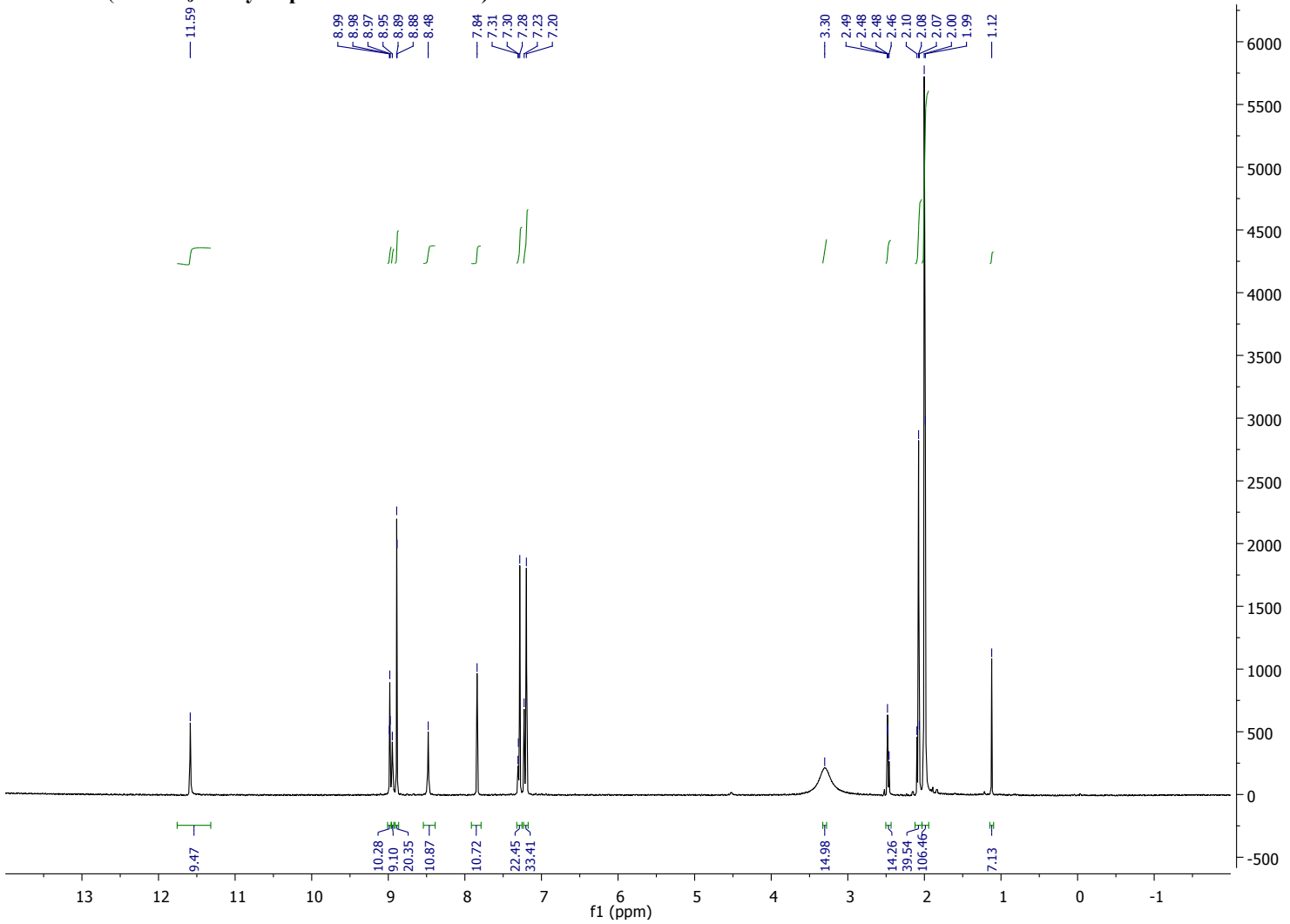


Figure S37: XRPD of Form II-B

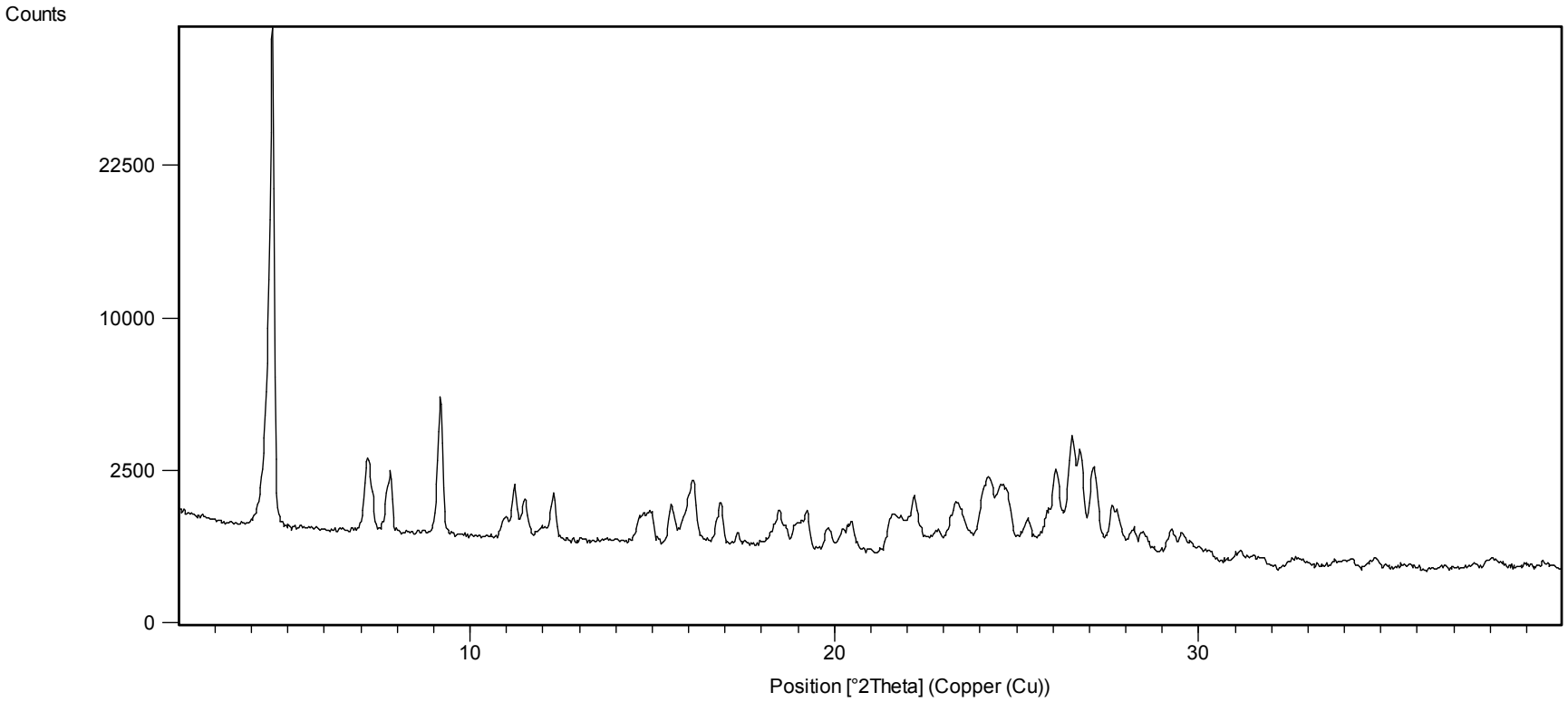


Figure S38: DSC of Form II-C

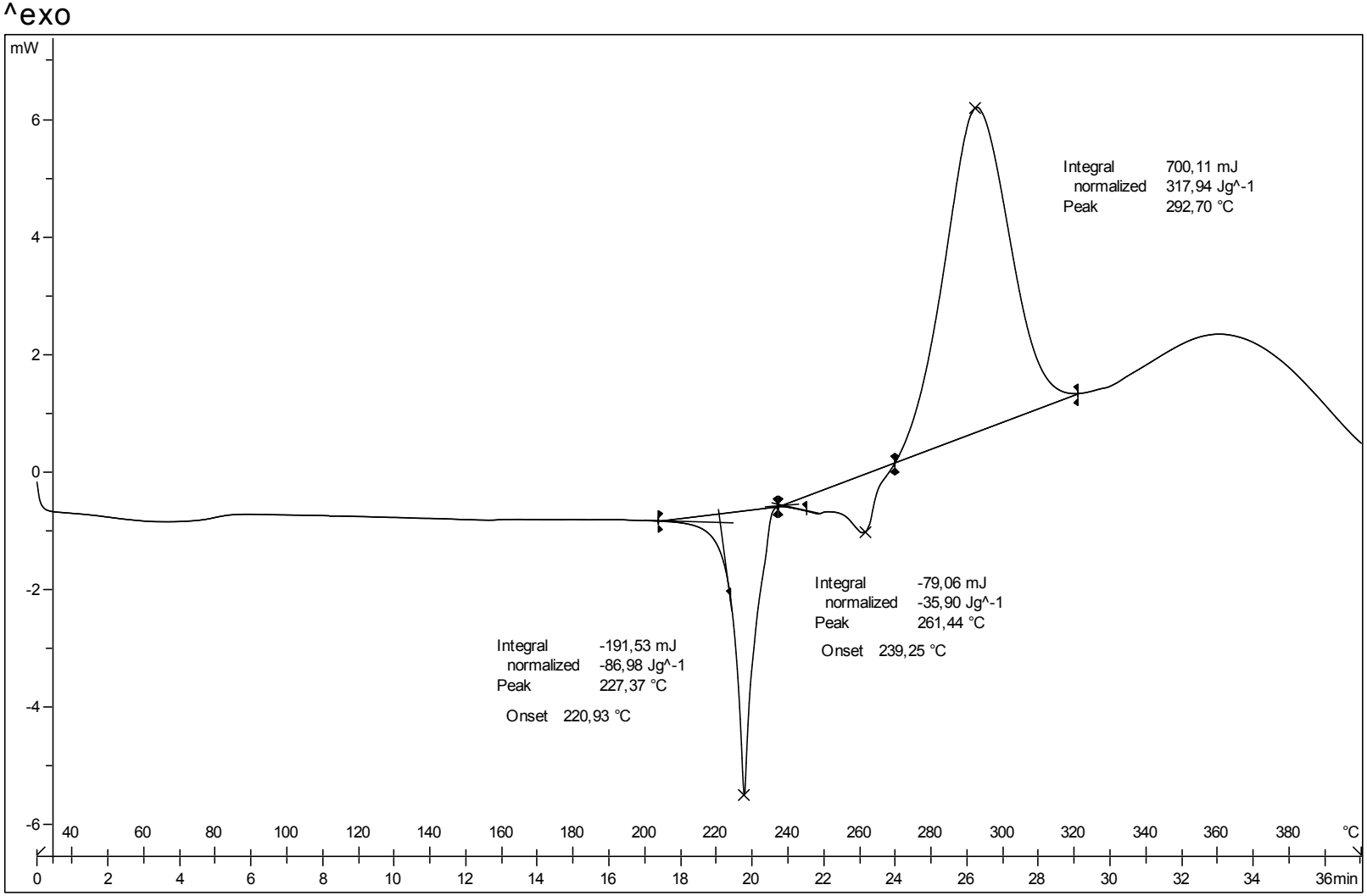


Figure S39: TGA of Form II-C

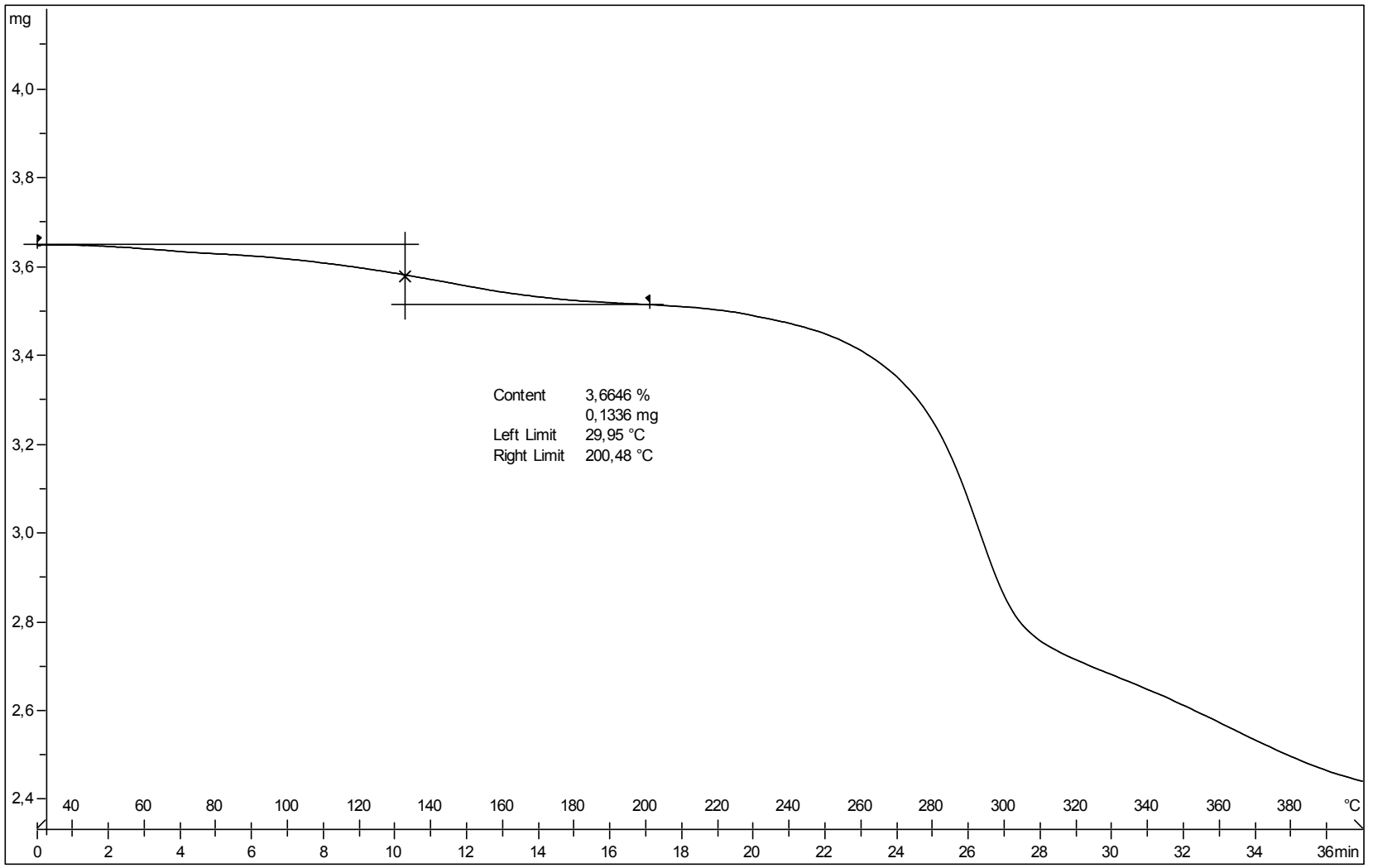


Figure S40: ^{1}H-NMR (dmso-d_6/delay: 1/pulse: 45°/scans: 32) of Form II-C

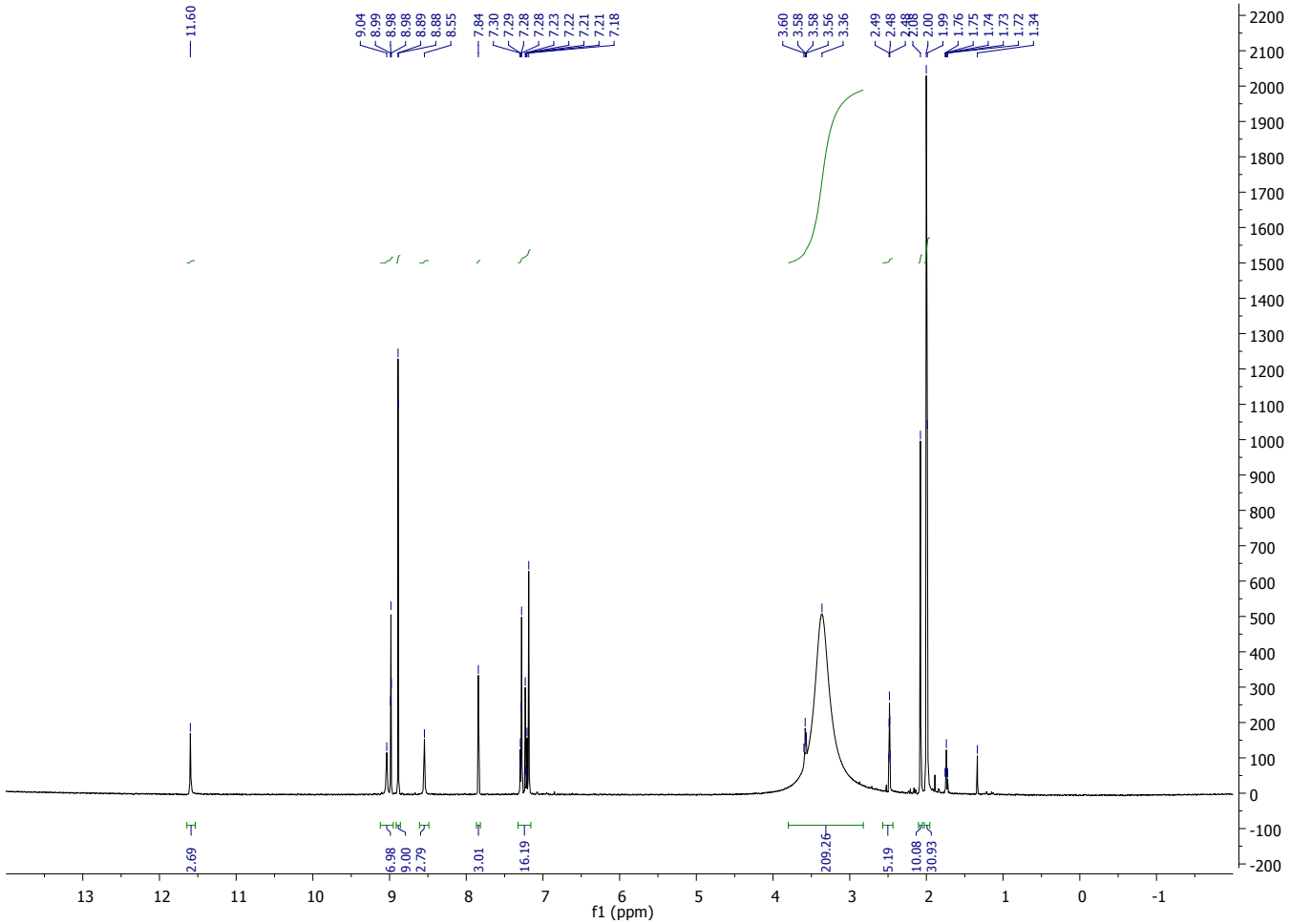


Figure S41: XRPD of Form II-C

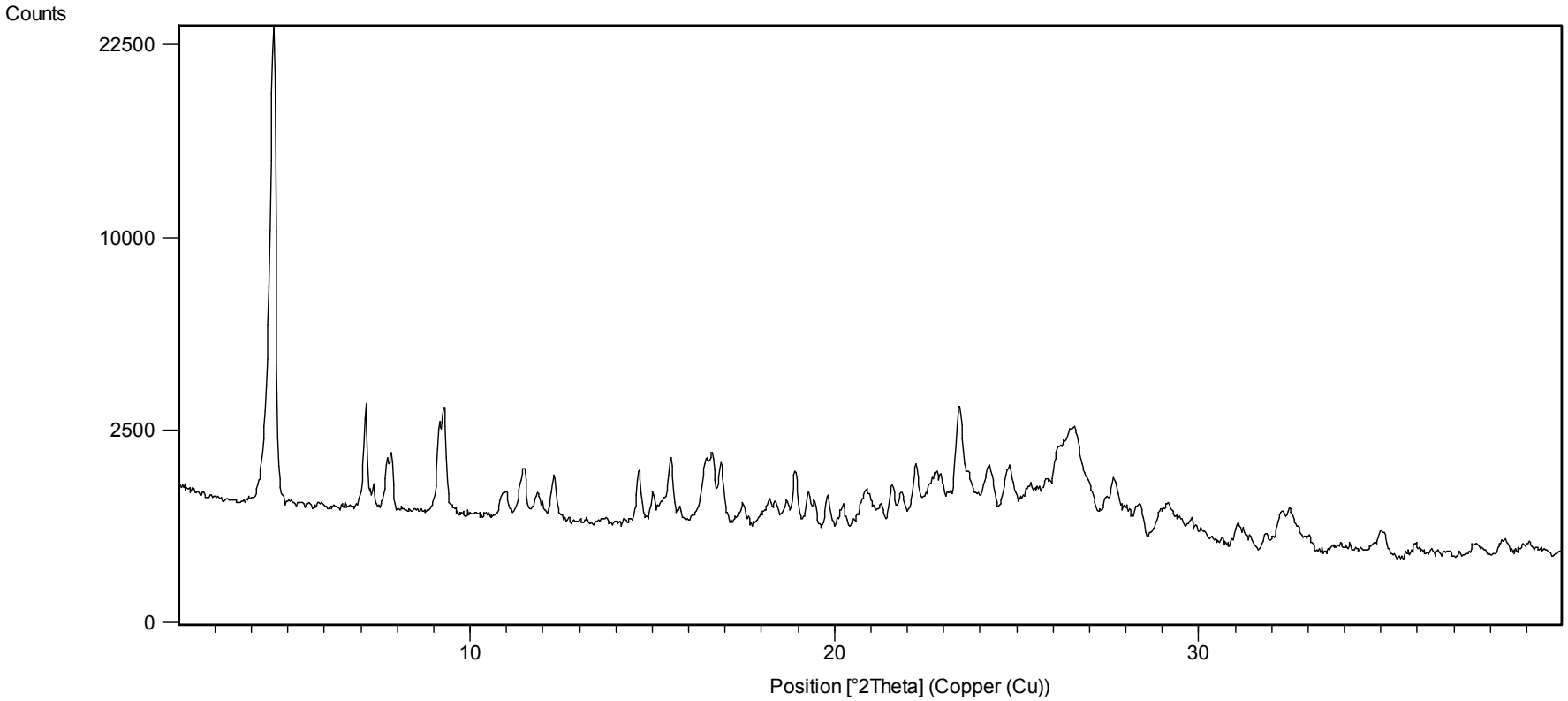


Figure S42: DSC of Form II-D

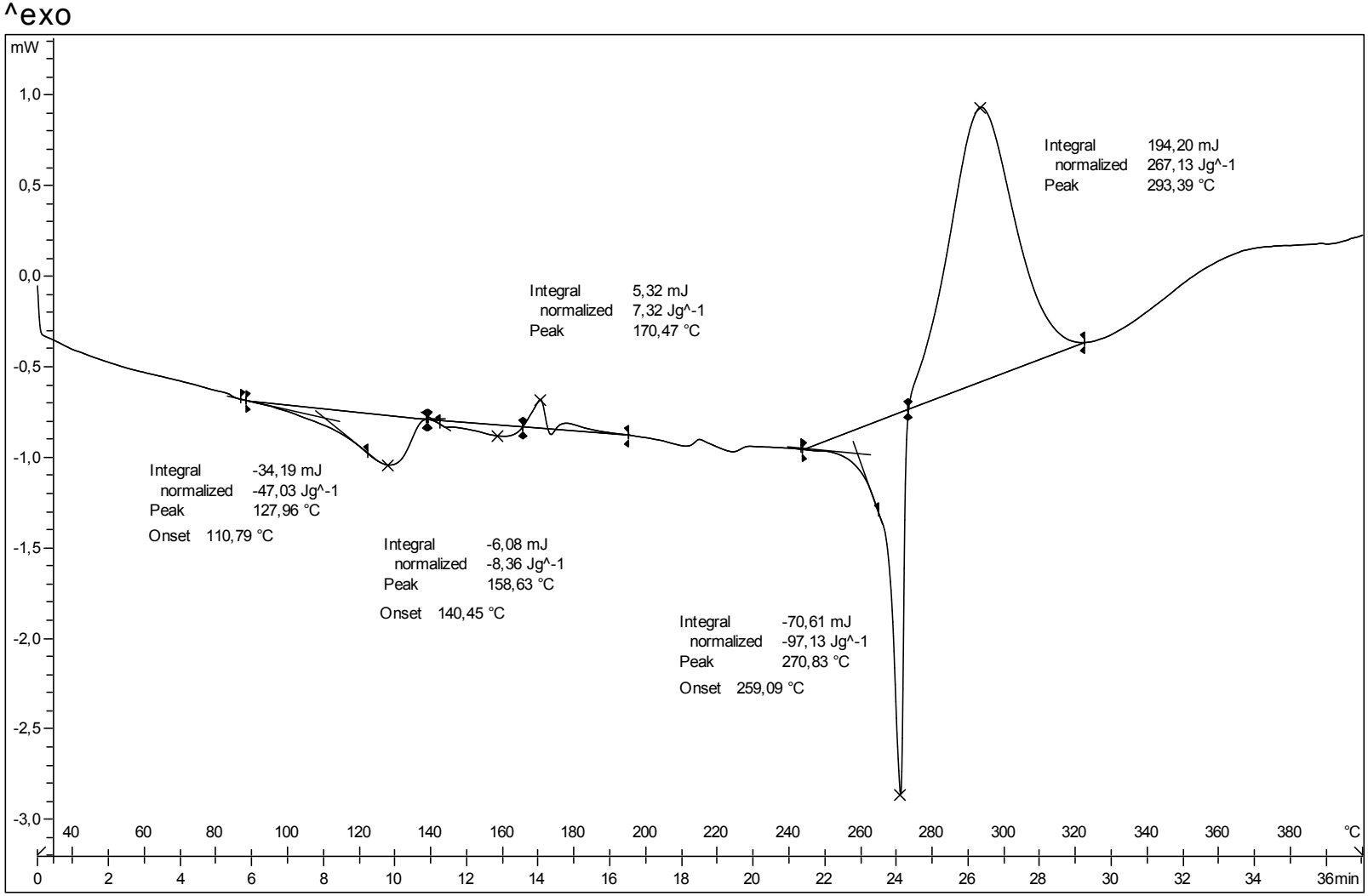


Figure S43: TGA of Form II-D

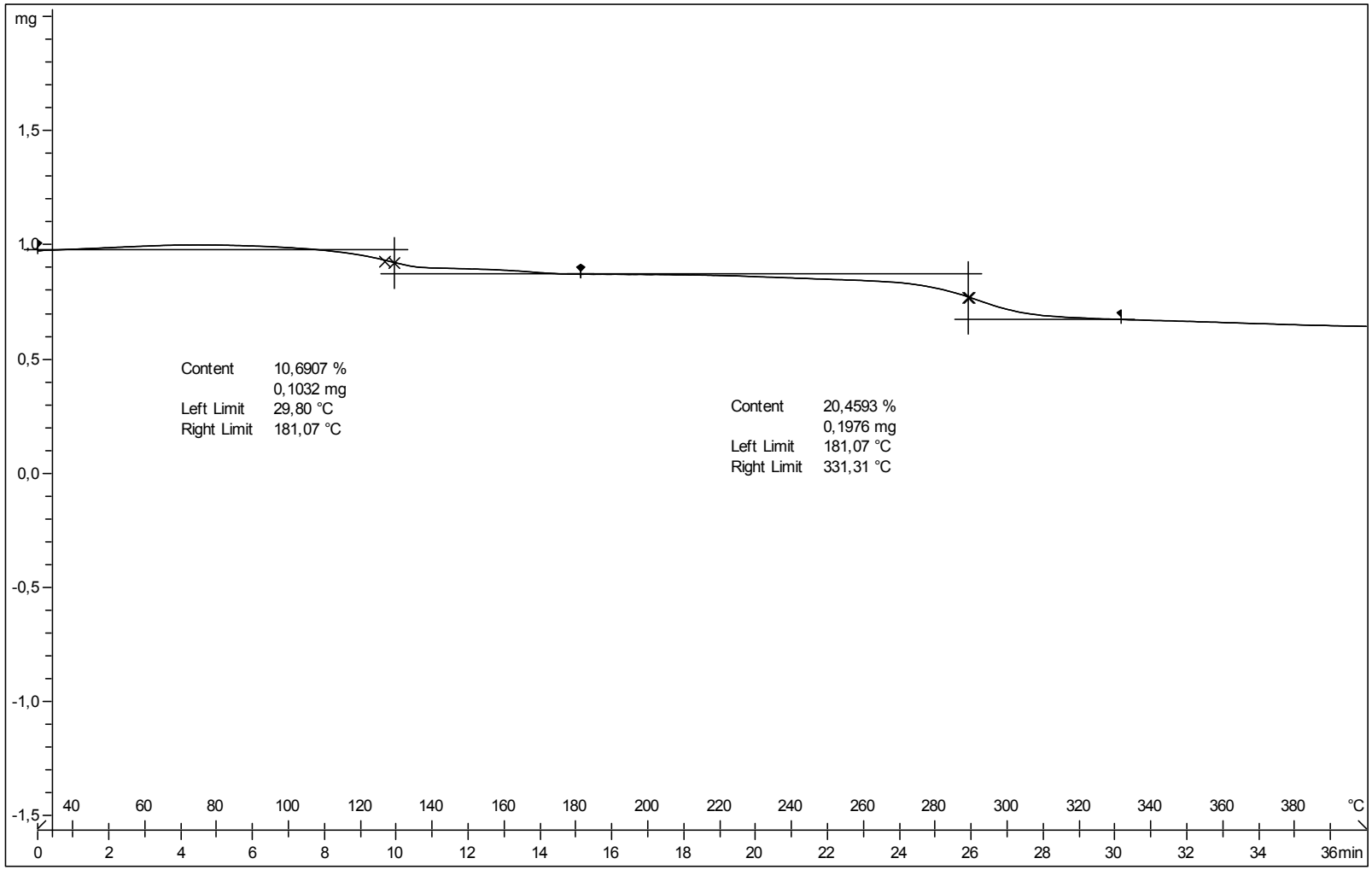


Figure S44: ^{1}H-NMR (dmso-d_6/delay: 1/pulse: 45°/scans: 32) of Form II-D

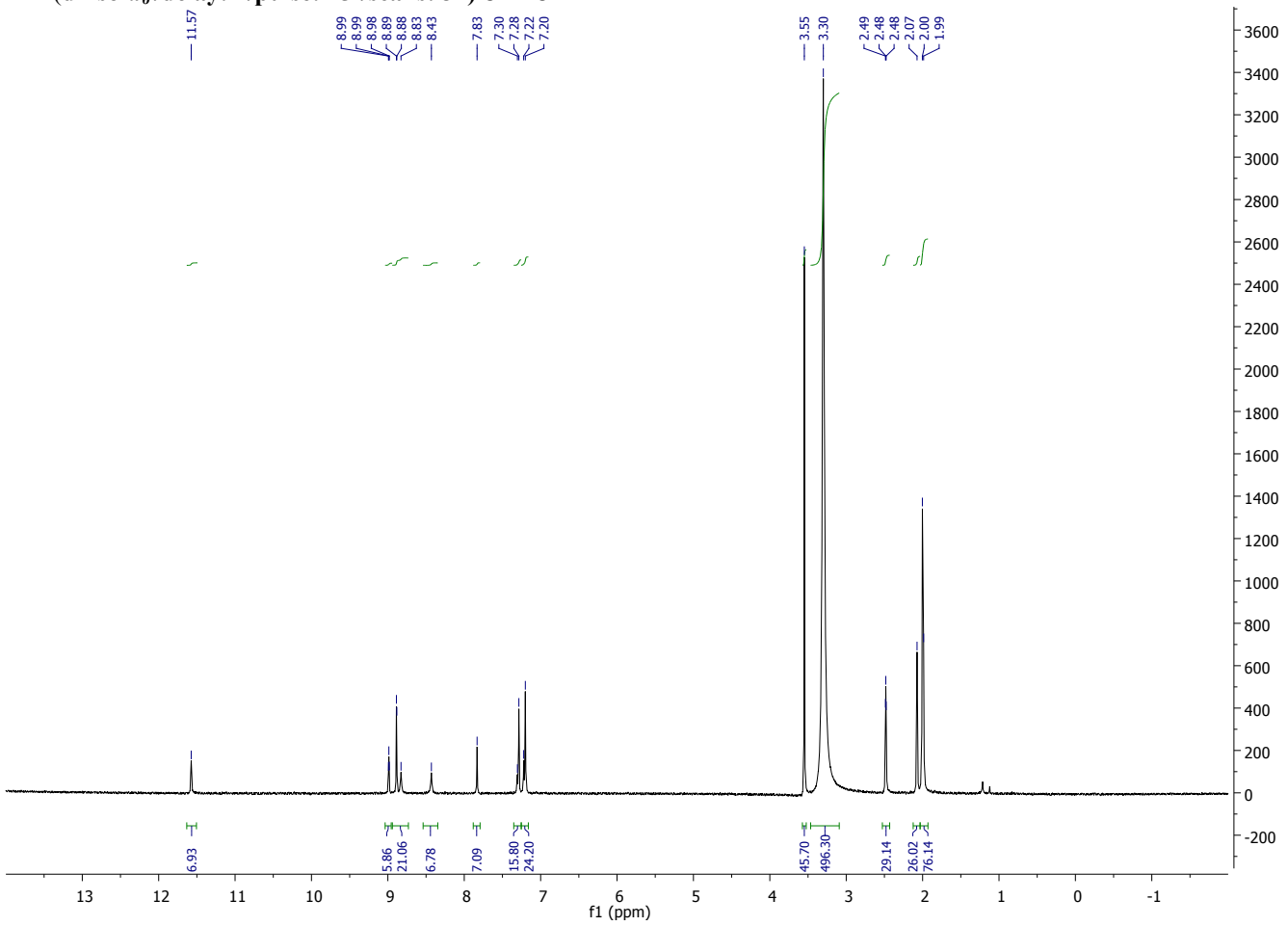


Figure S45: XRPD of Form II-D

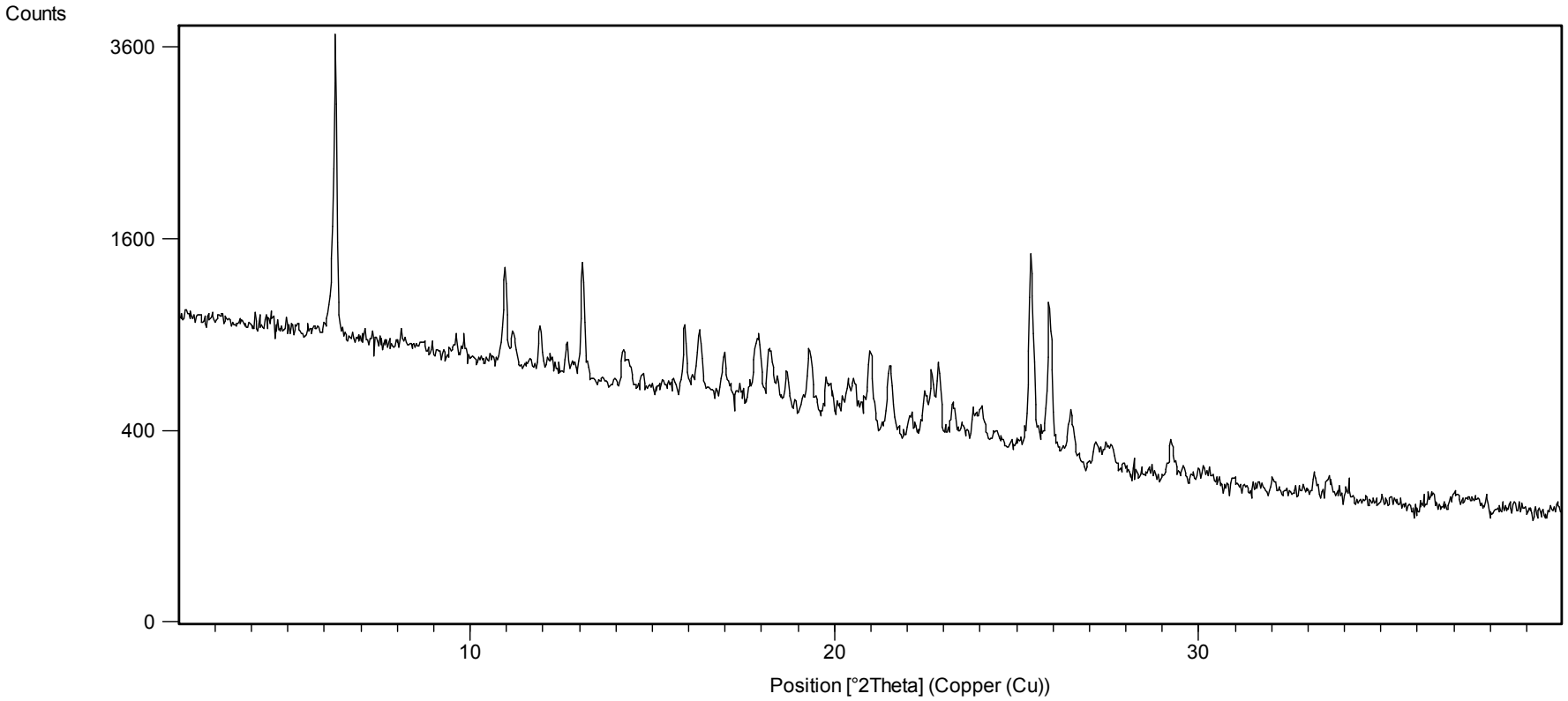


Figure S46: DSC of Form II-E

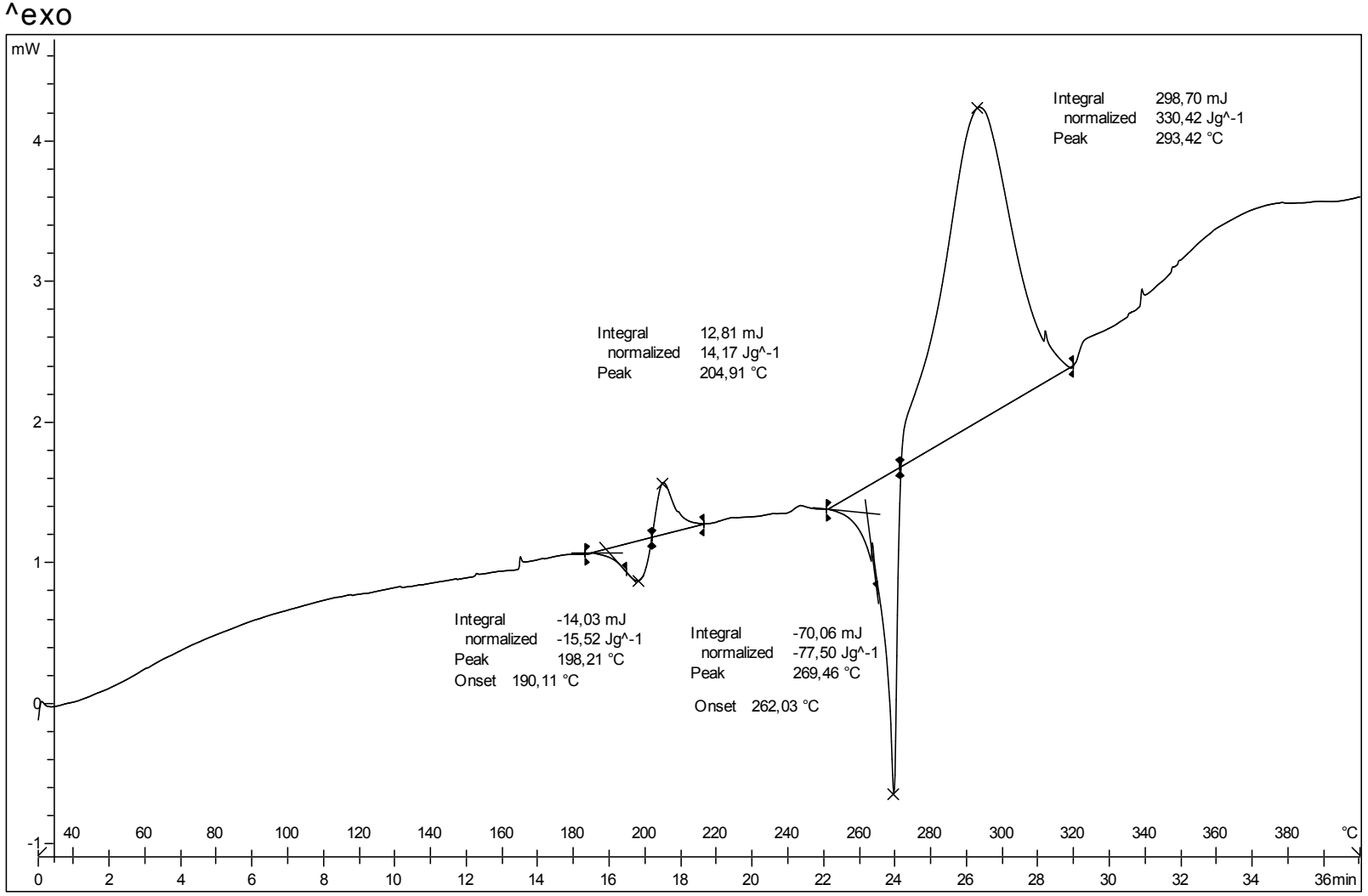


Figure S47: TGA of Form II-E

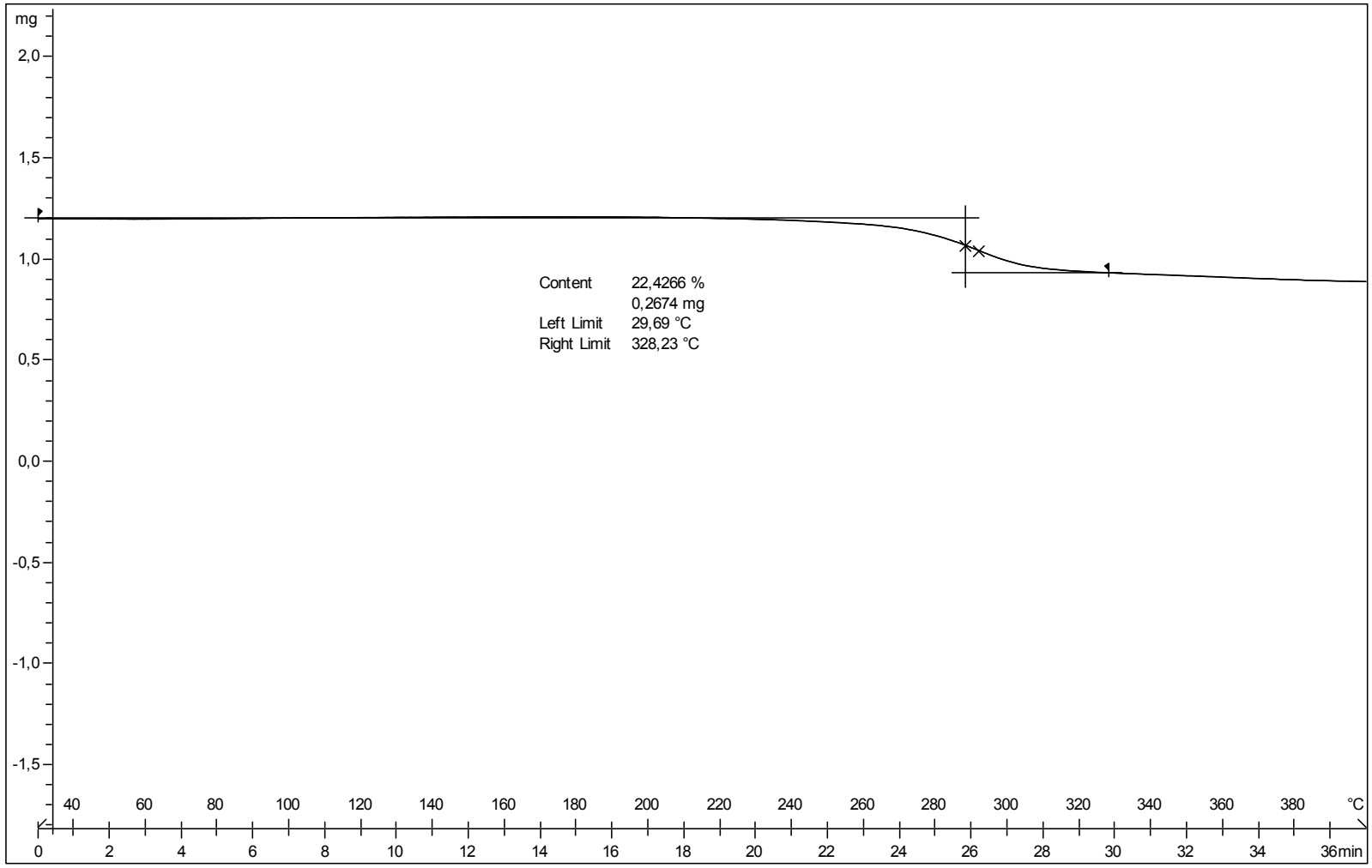


Figure S48: ^{1}H-NMR (dmso-d_6) of Form II-E

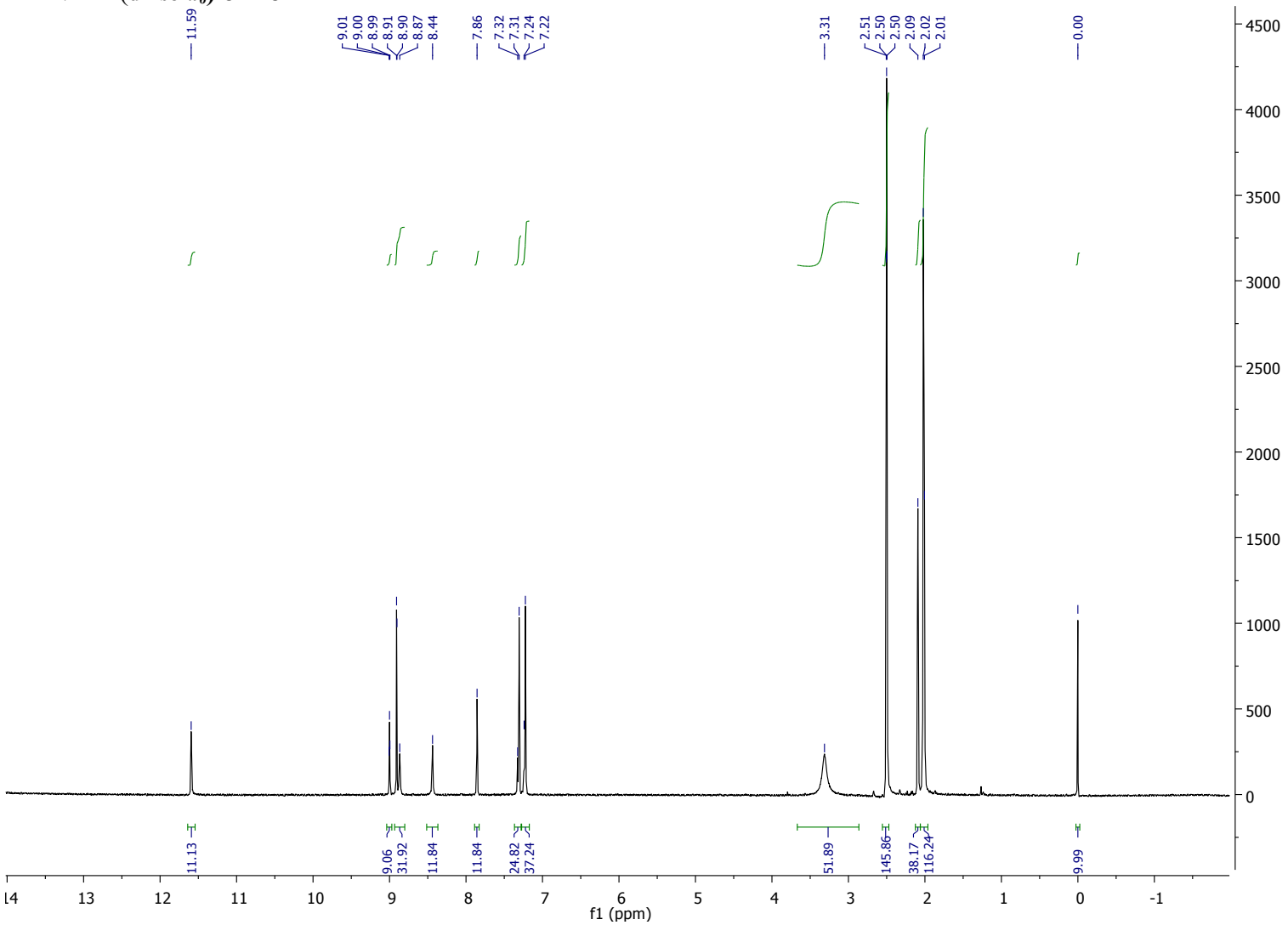


Figure S49: XRPD of Form II-E

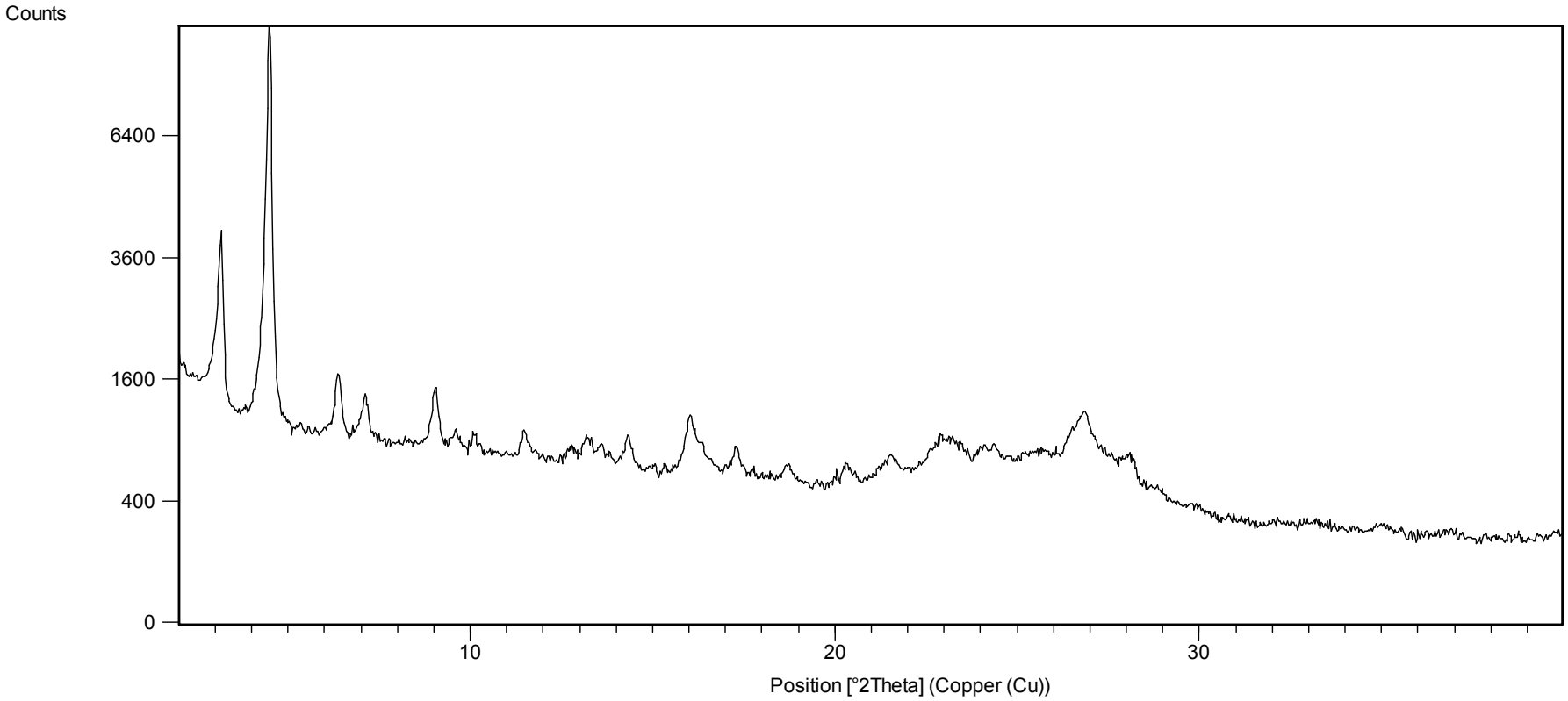


Figure S50: DSC of Form III

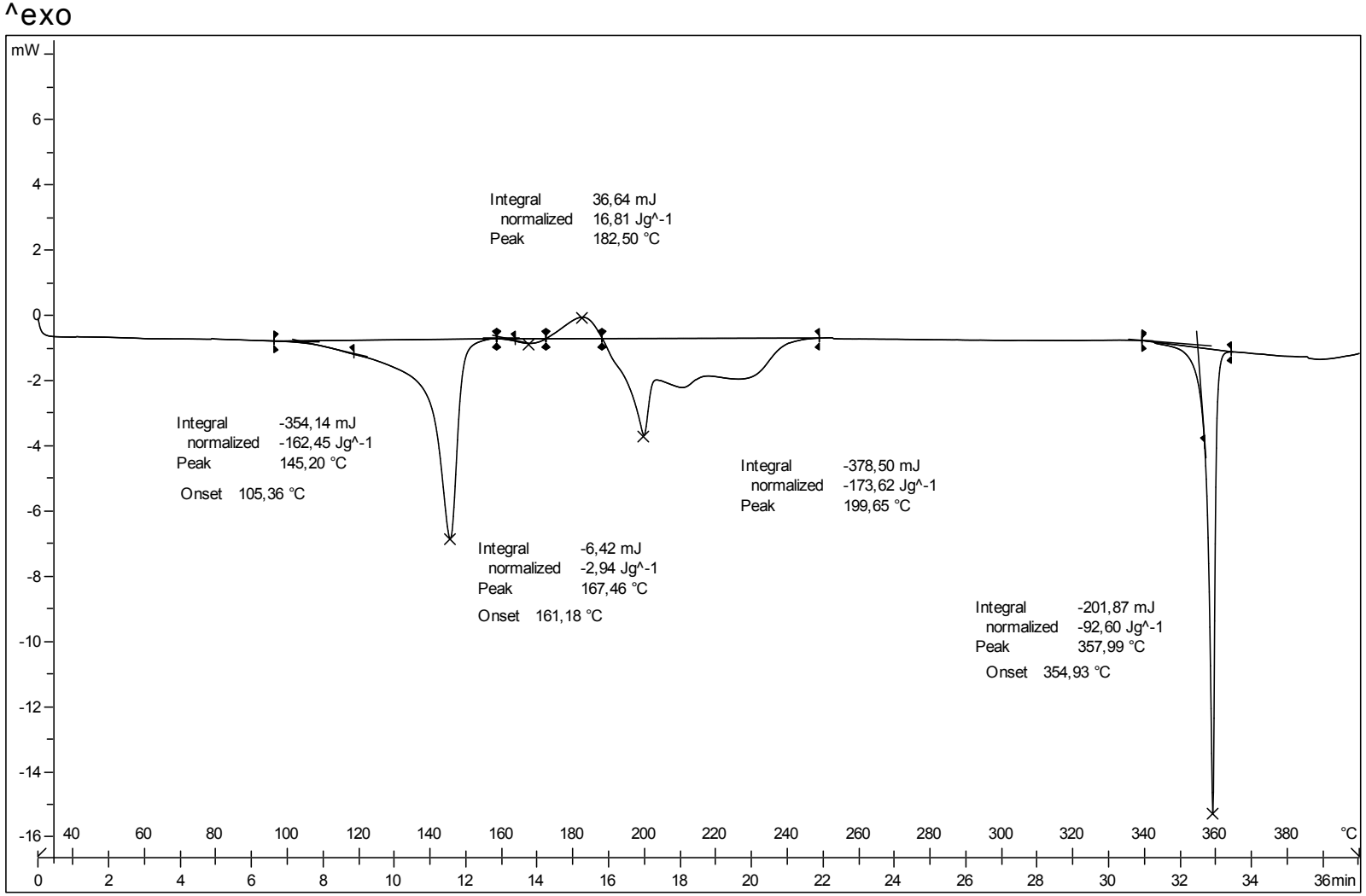


Figure S51: TGA of Form III

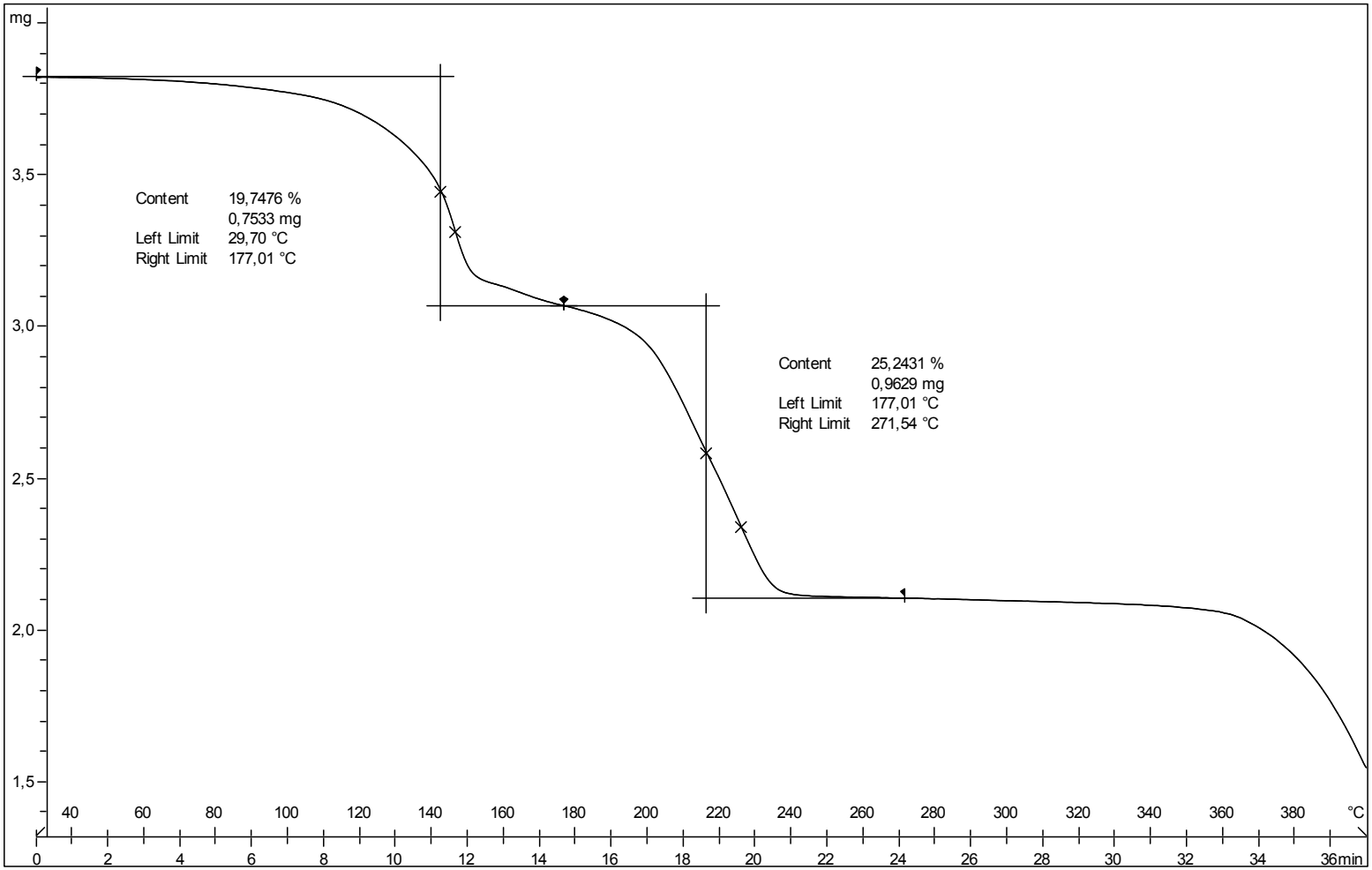


Figure S52: ^{1}H-NMR (dmso-d_6/delay: 1/pulse: 45°/scans: 32) of Form III

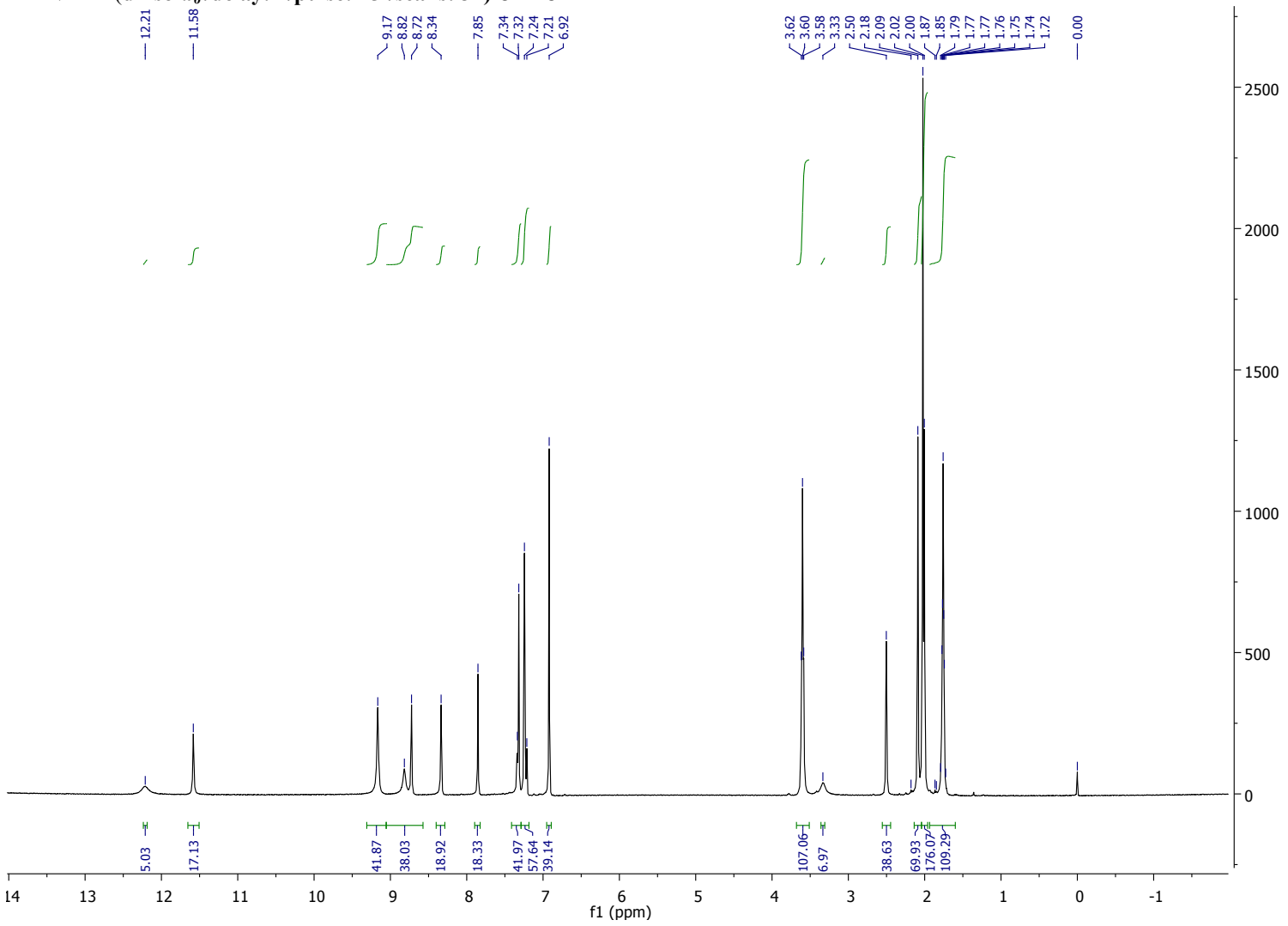


Figure S53: XRPD of Form III

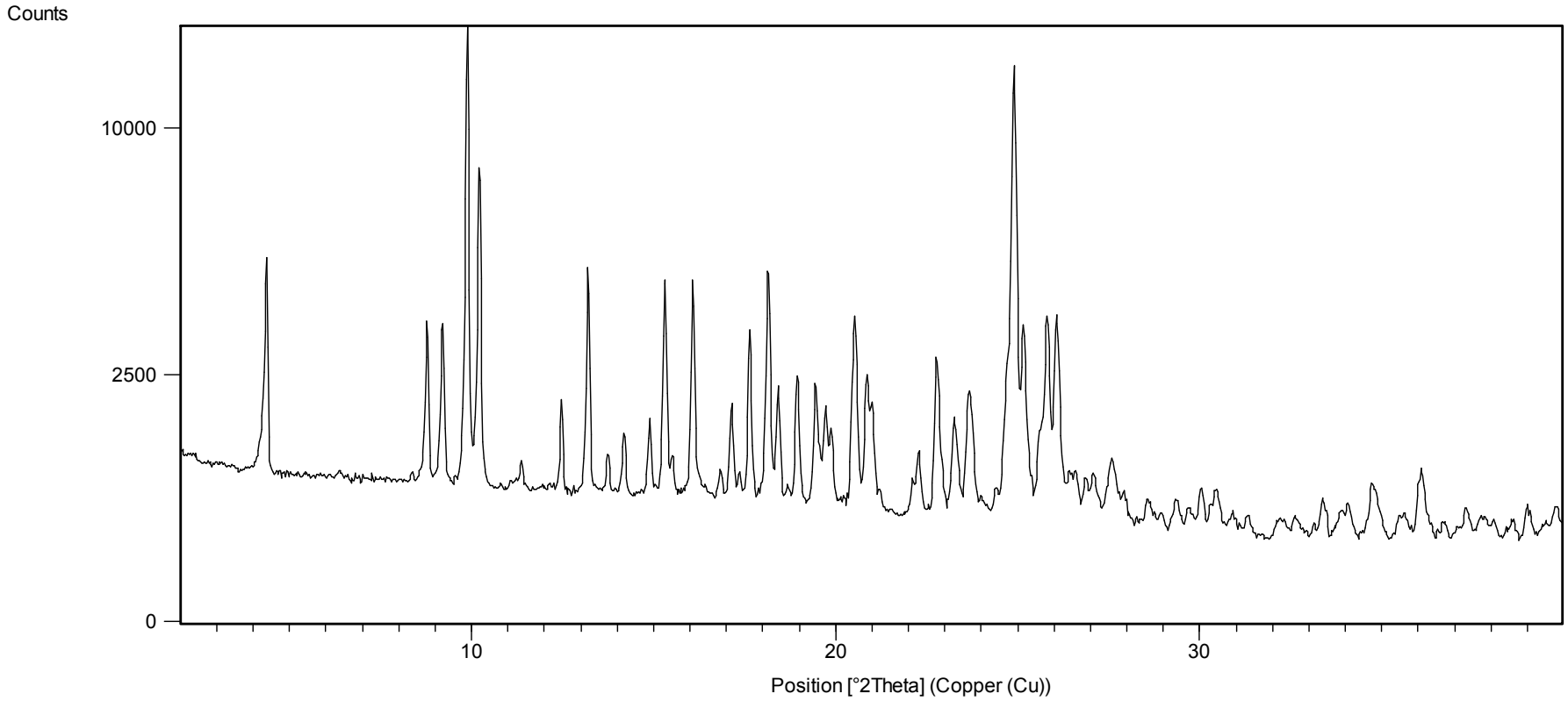


Figure S54: The XRPD of Form III has been indexed with the following proposed monoclinic cell: a=20.793(4) Å, b=10.906(1) Å, c=16.091(3) Å, β=104.80(1)º, V=3527(1) Å^3 (Figures of Merit: M= 63, F= 195), a *P2$_1$/c* space group is compatible with the cell.

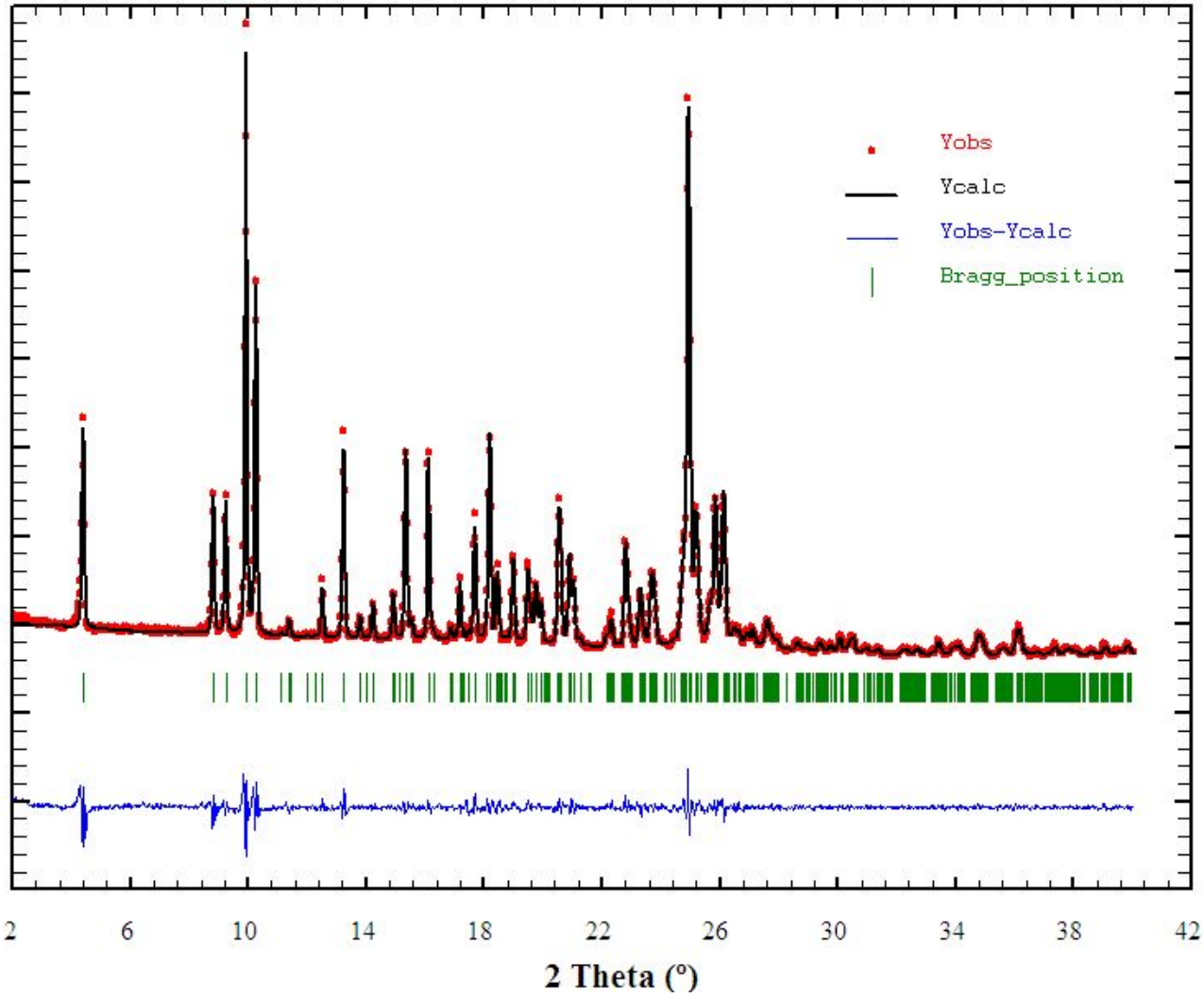


Figure S55: DSC of Form IV-A

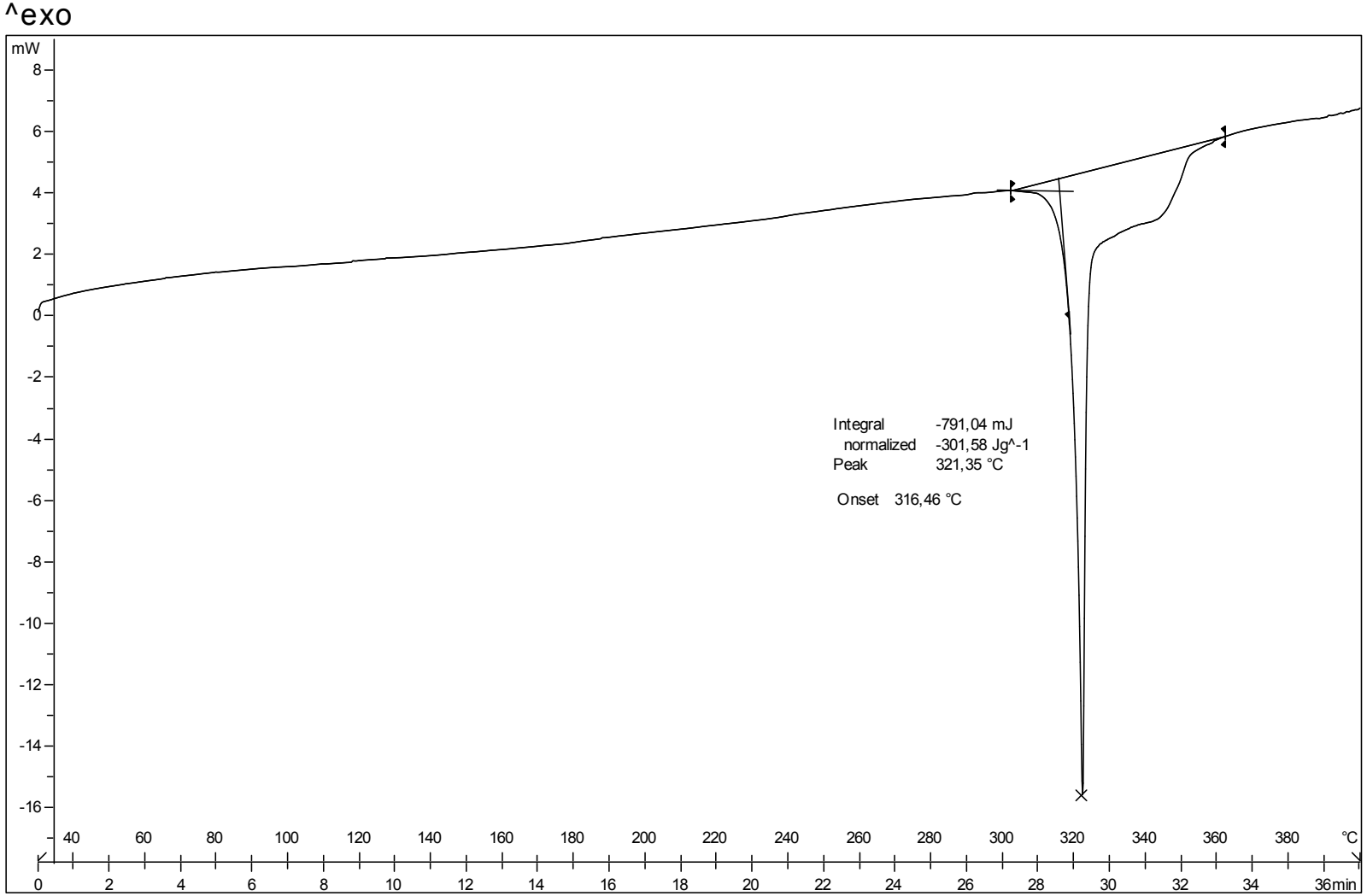


Figure S56: TGA of Form IV-A

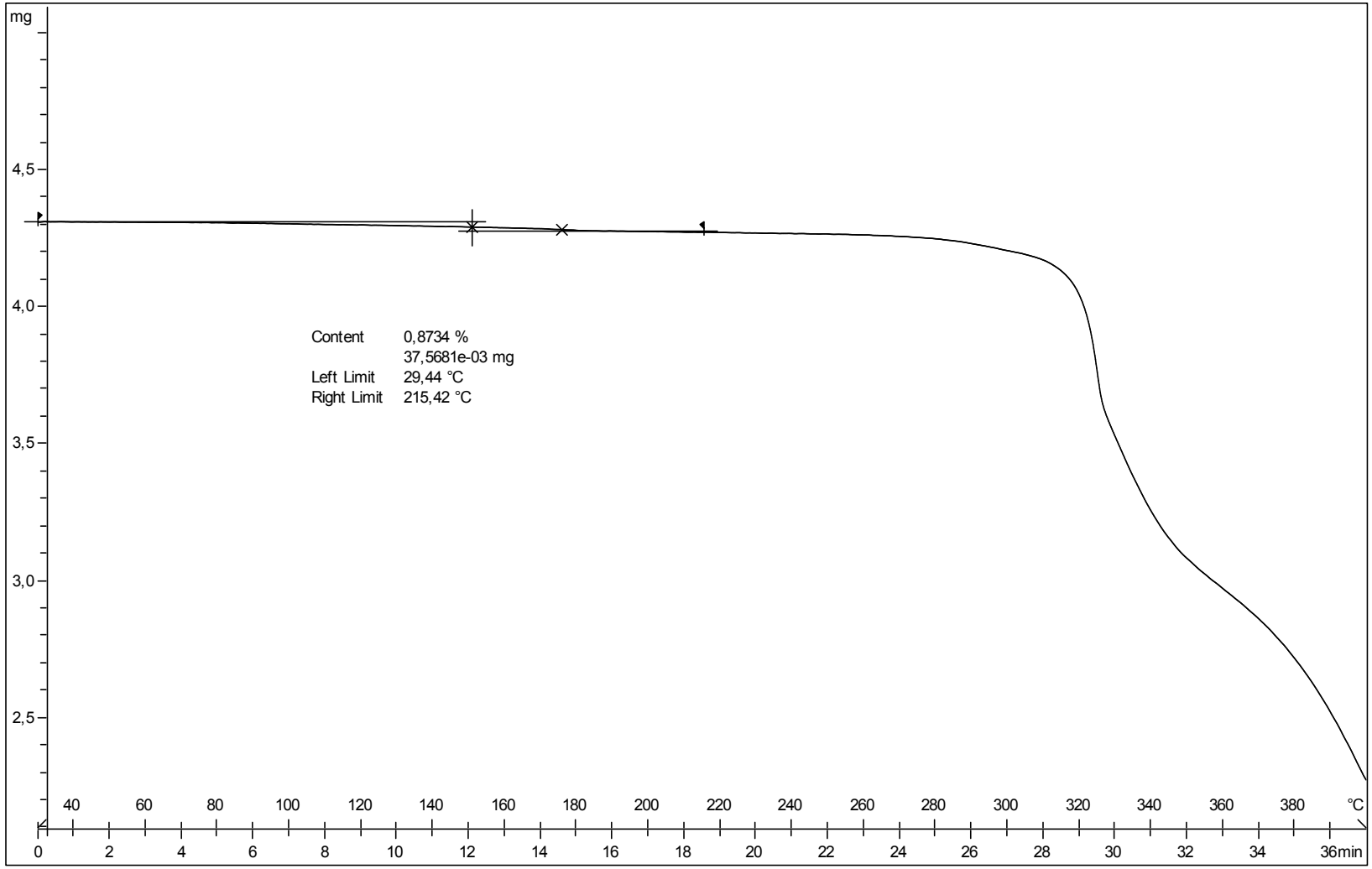


Figure S57: ^{1}H-NMR (dmso-d_6/delay: 1/pulse: 45°/scans: 32) of Form IV-A

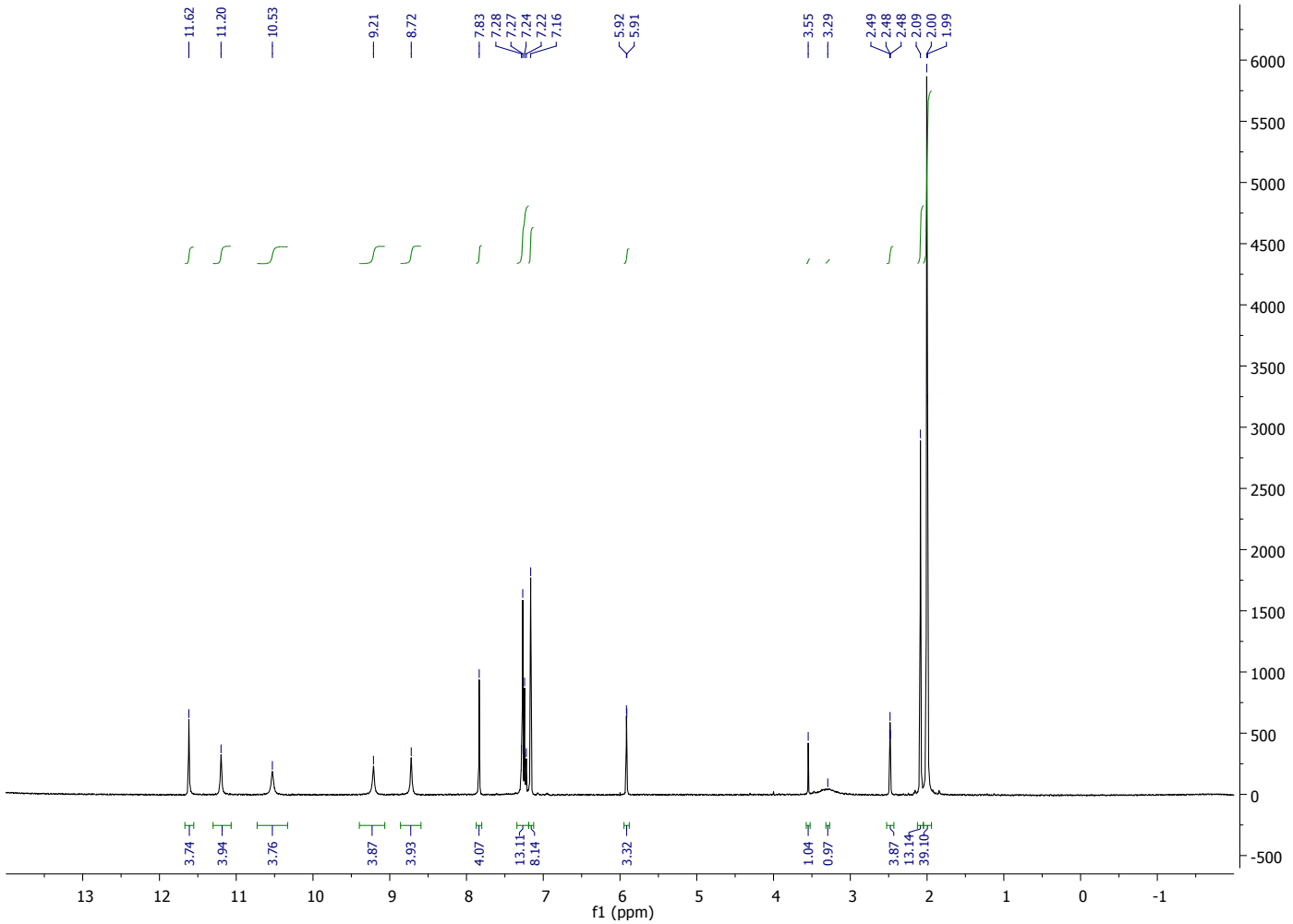


Figure S58: XRPD of Form IV-A

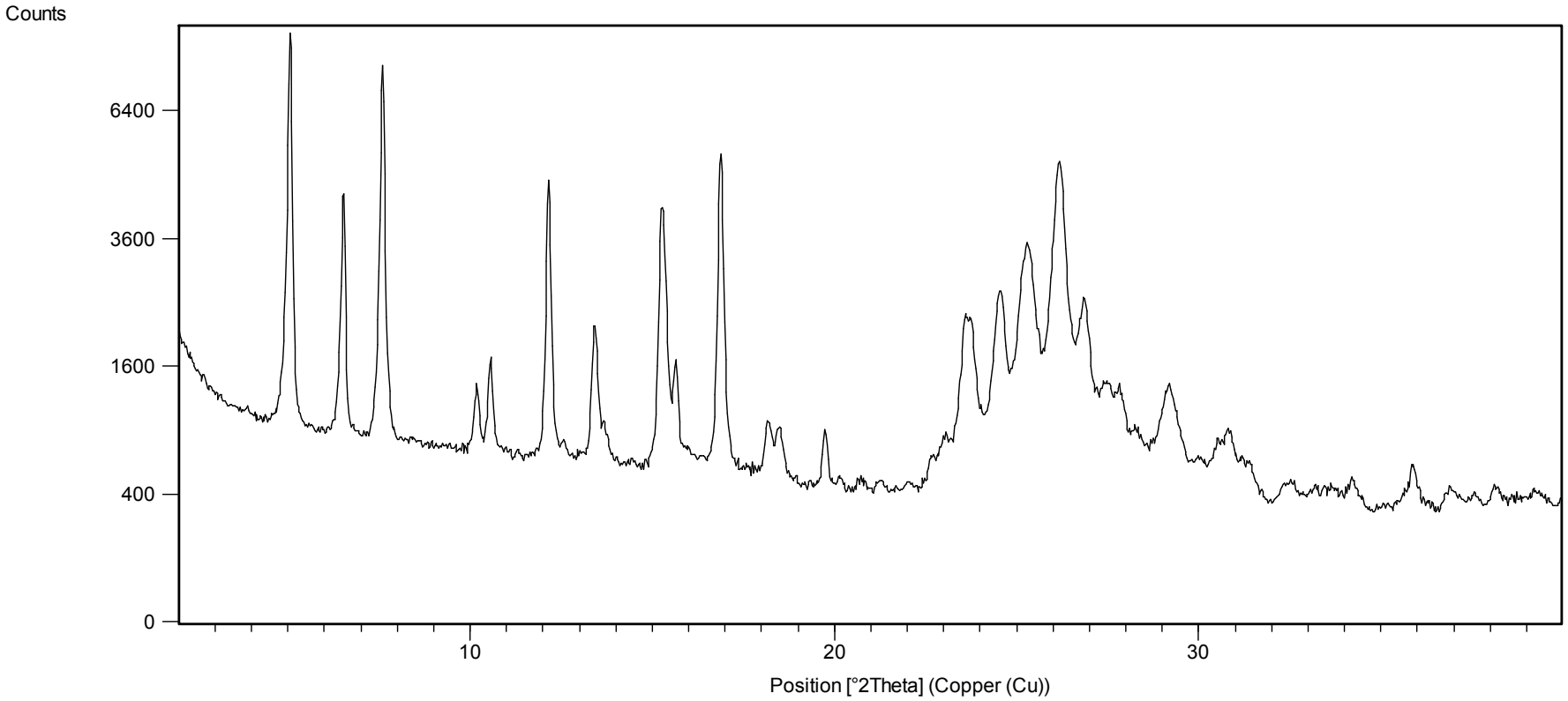


Figure S59: The XRPD of Form IV-A has been indexed with the following proposed monoclinic cell: a=30.07(1) Å, b=22.592(9) Å, c=4.308(2) Å, β=116.47(4)º, V=2619(2) Å^3 (Figures of Merit: M= 27, F= 61), a *P2$_1$/a* space group is compatible with the cell.

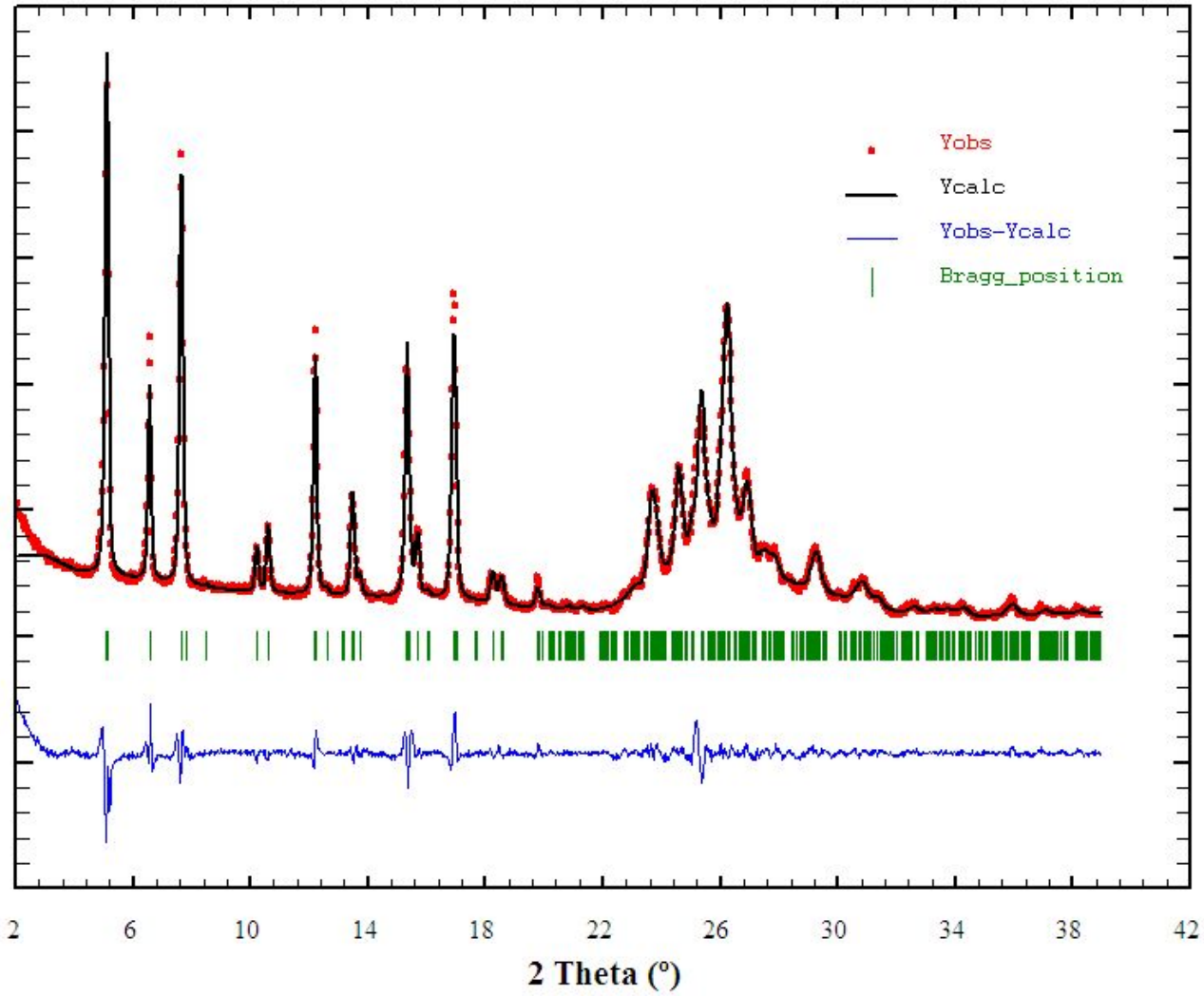


Figure S60: XRPD of Form IV-A (blue) and Form IV-B (red)

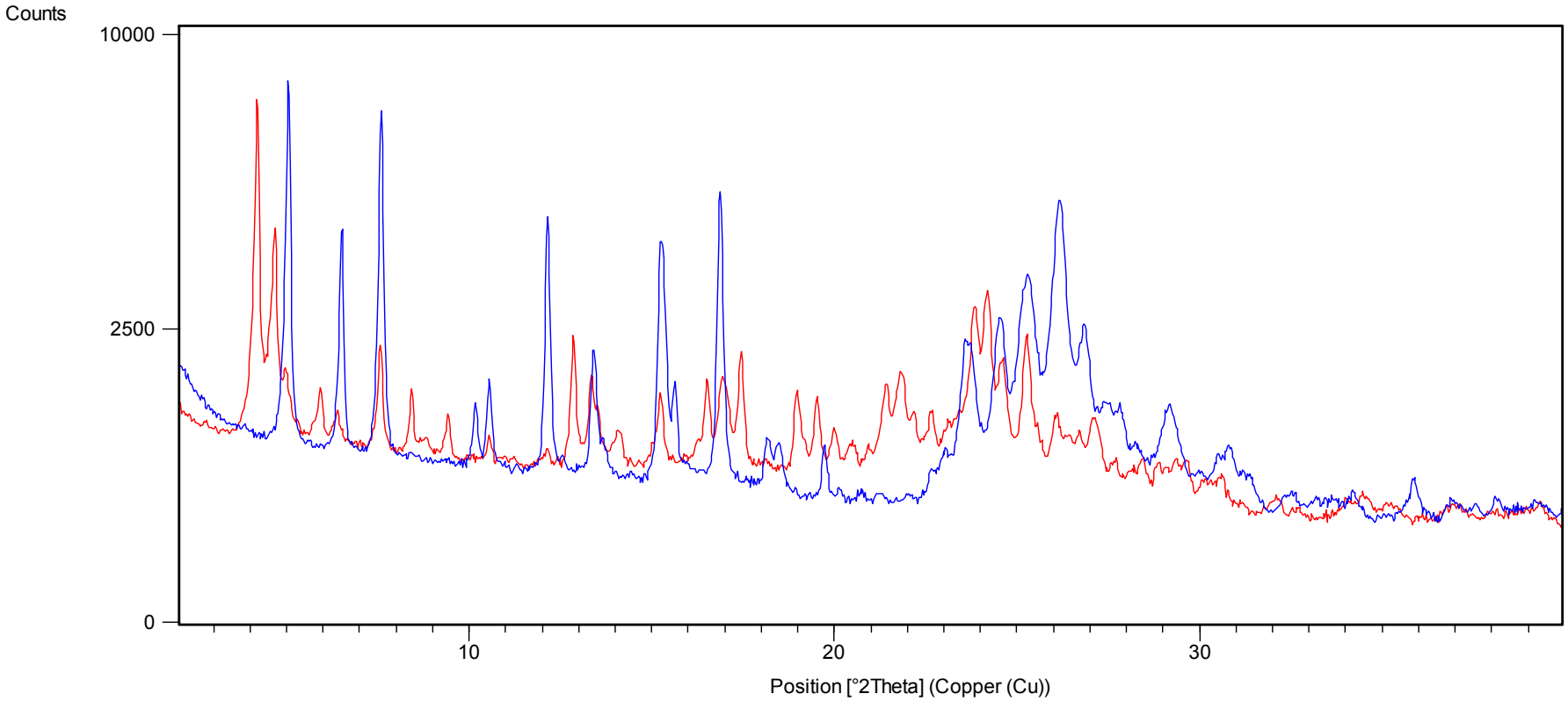


Figure S61: XRPD of Form IV-A (blue) and Form IV-C (green)

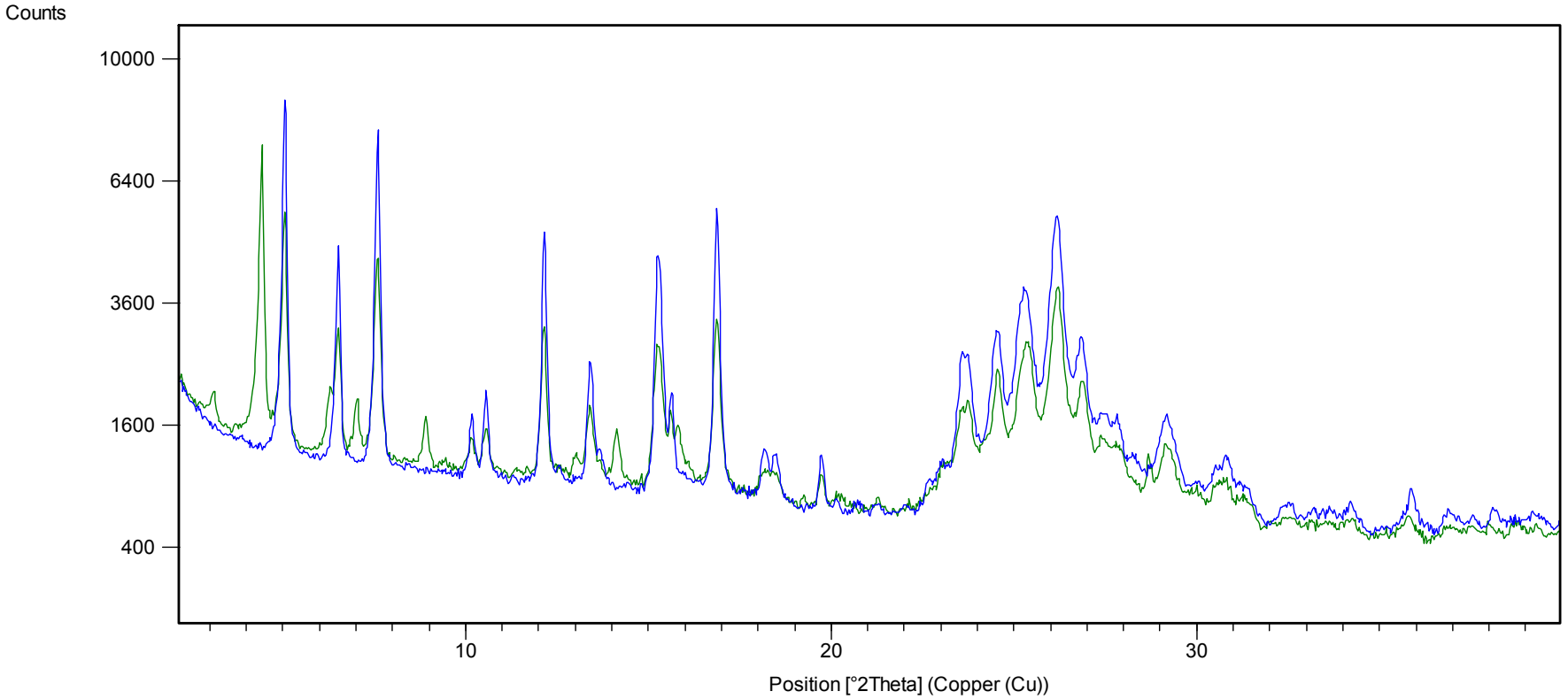


Figure S62: DSC of Form V-A

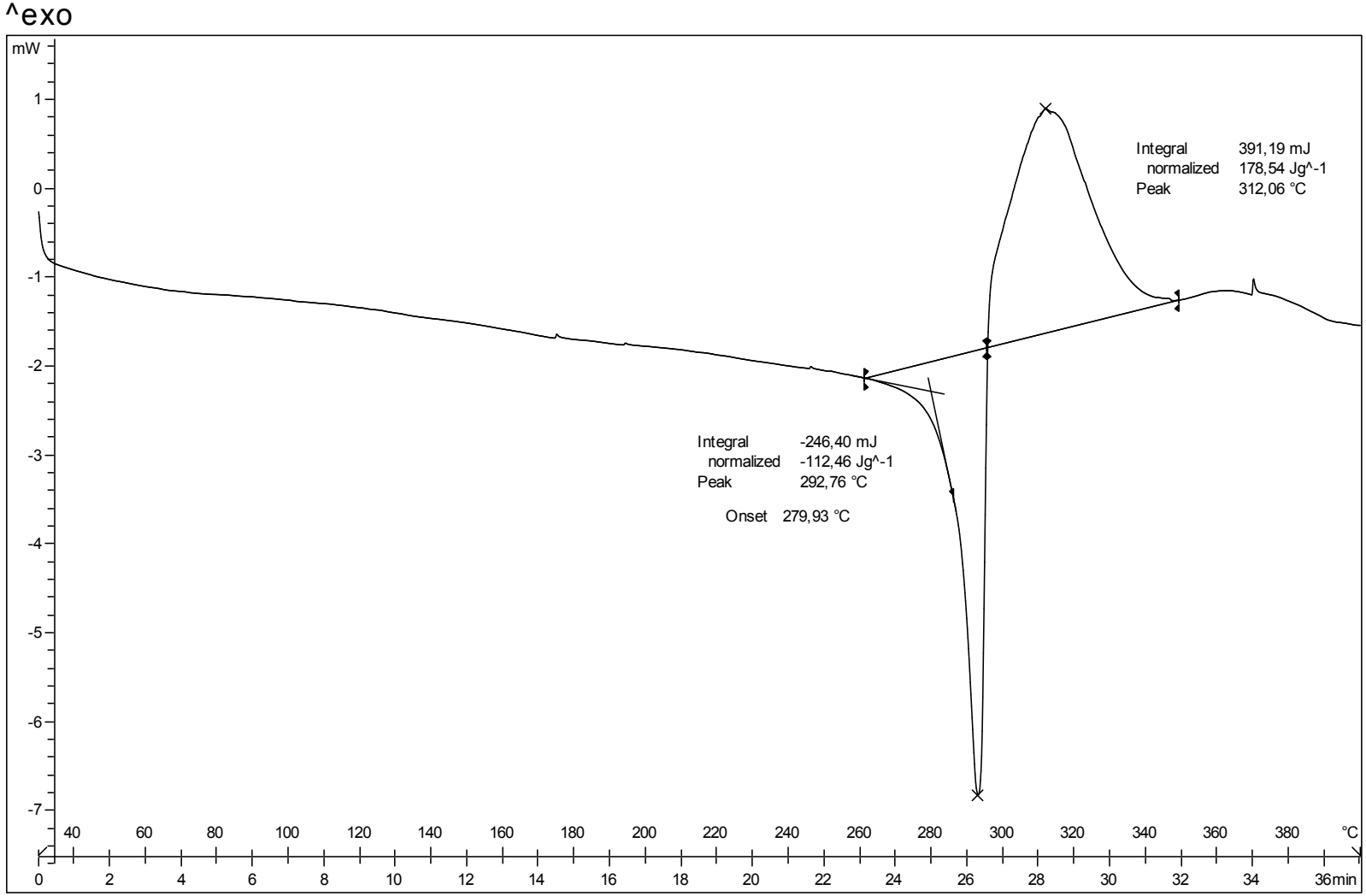


Figure S63: TGA of Form V-A

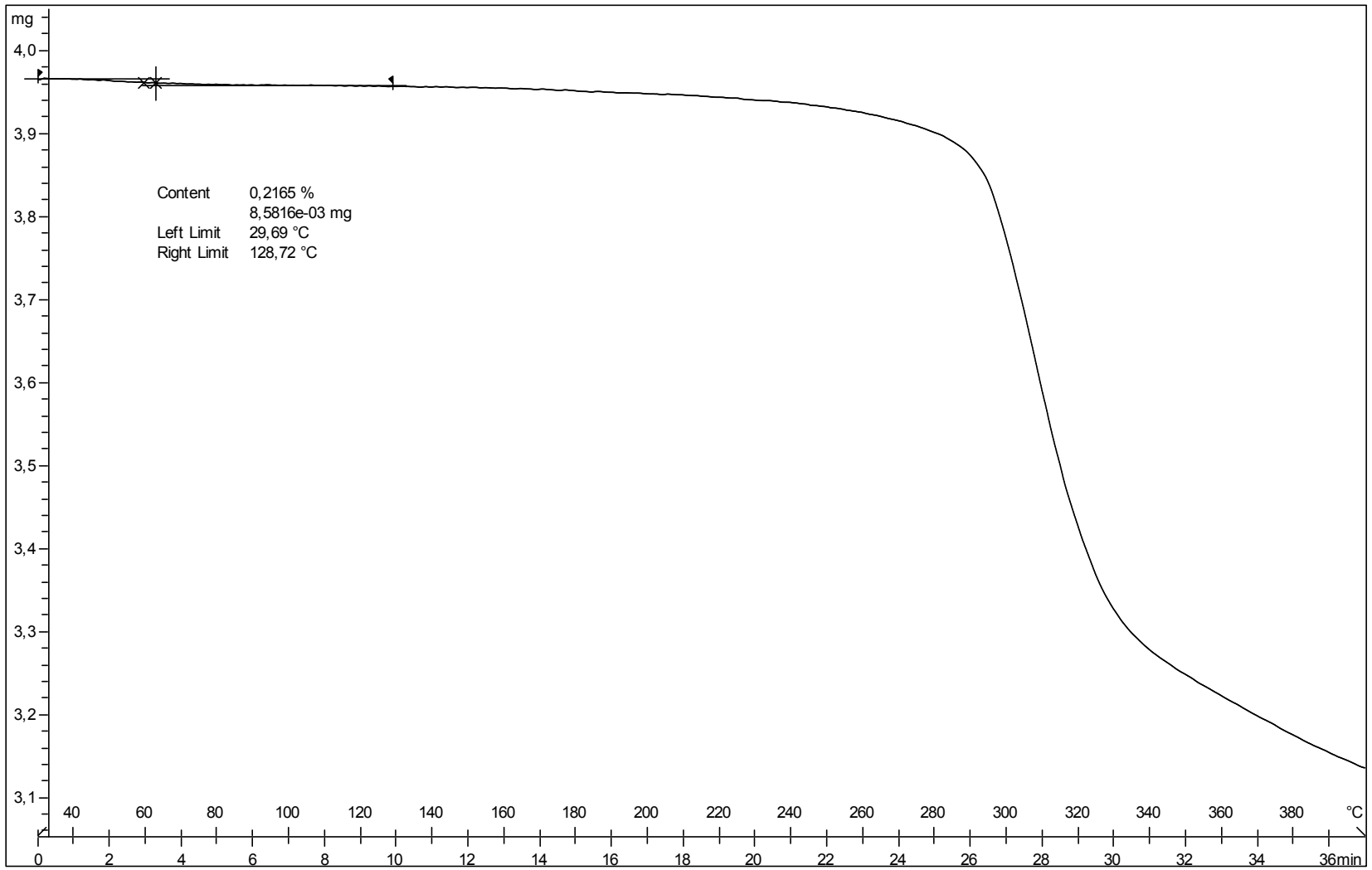


Figure S64: ^{1}H-NMR (dmso-d_6/delay: 1/pulse: 45°/scans: 32) of Form V-A

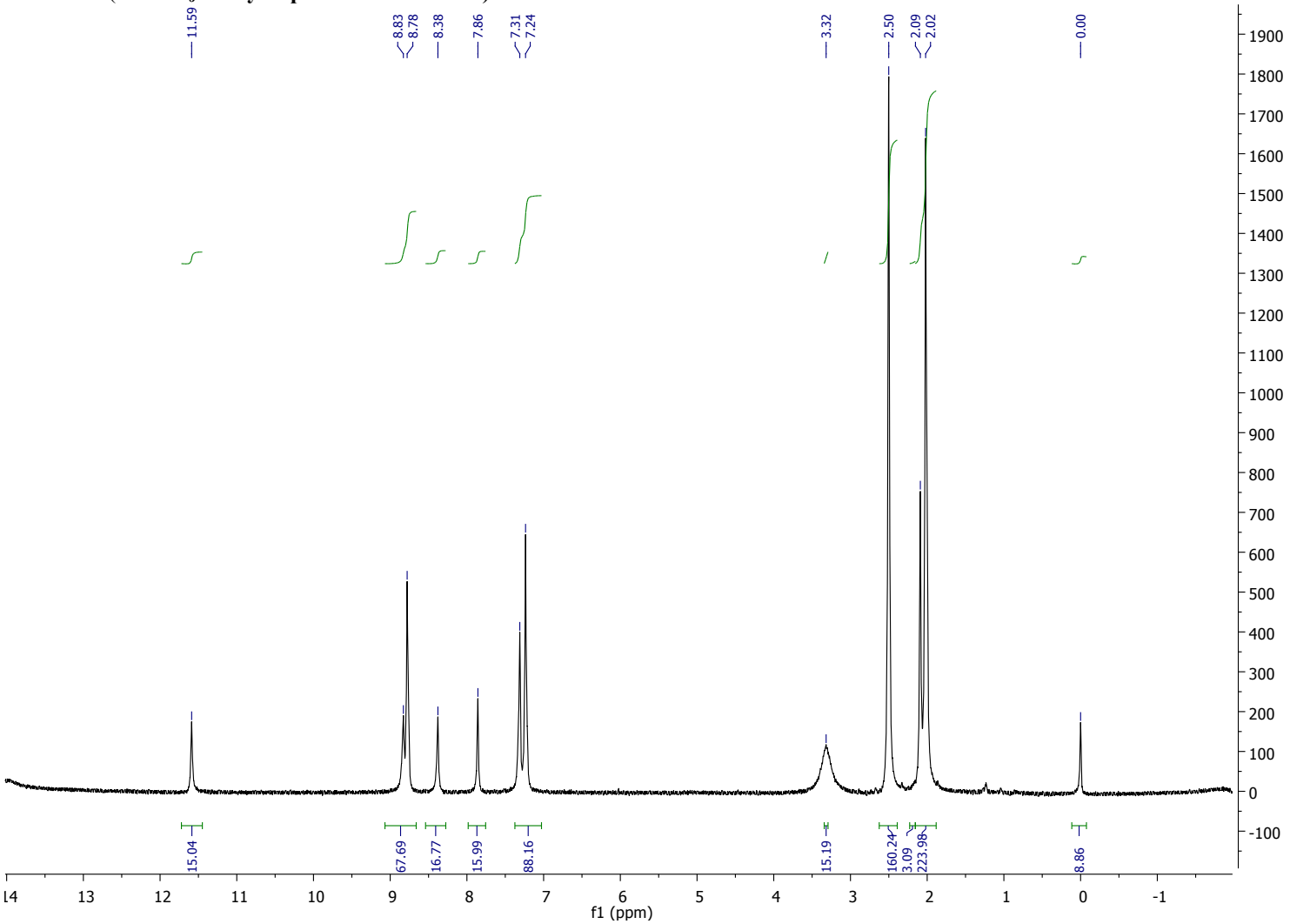


Figure S65: XRPD of Form V-A

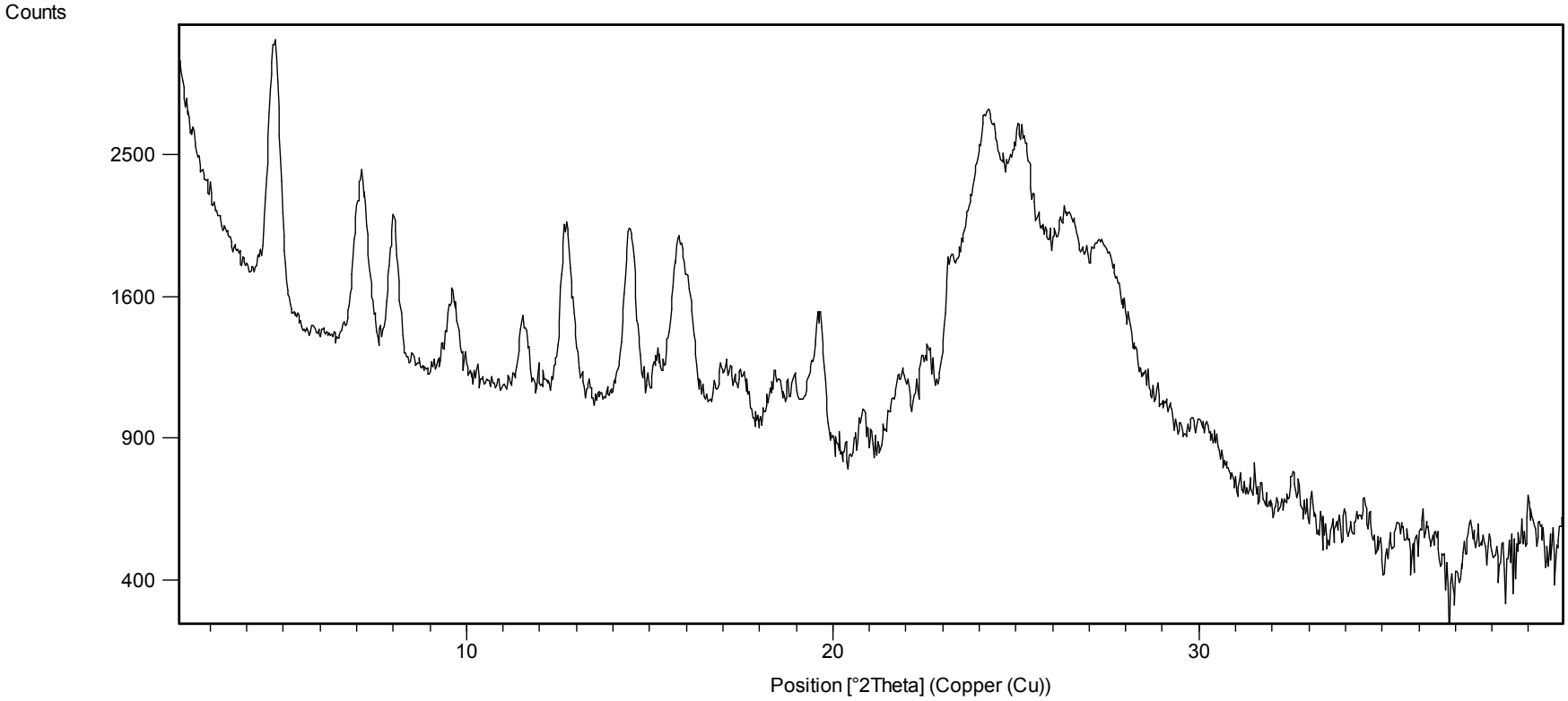


Figure S66: DSC of Form V-B

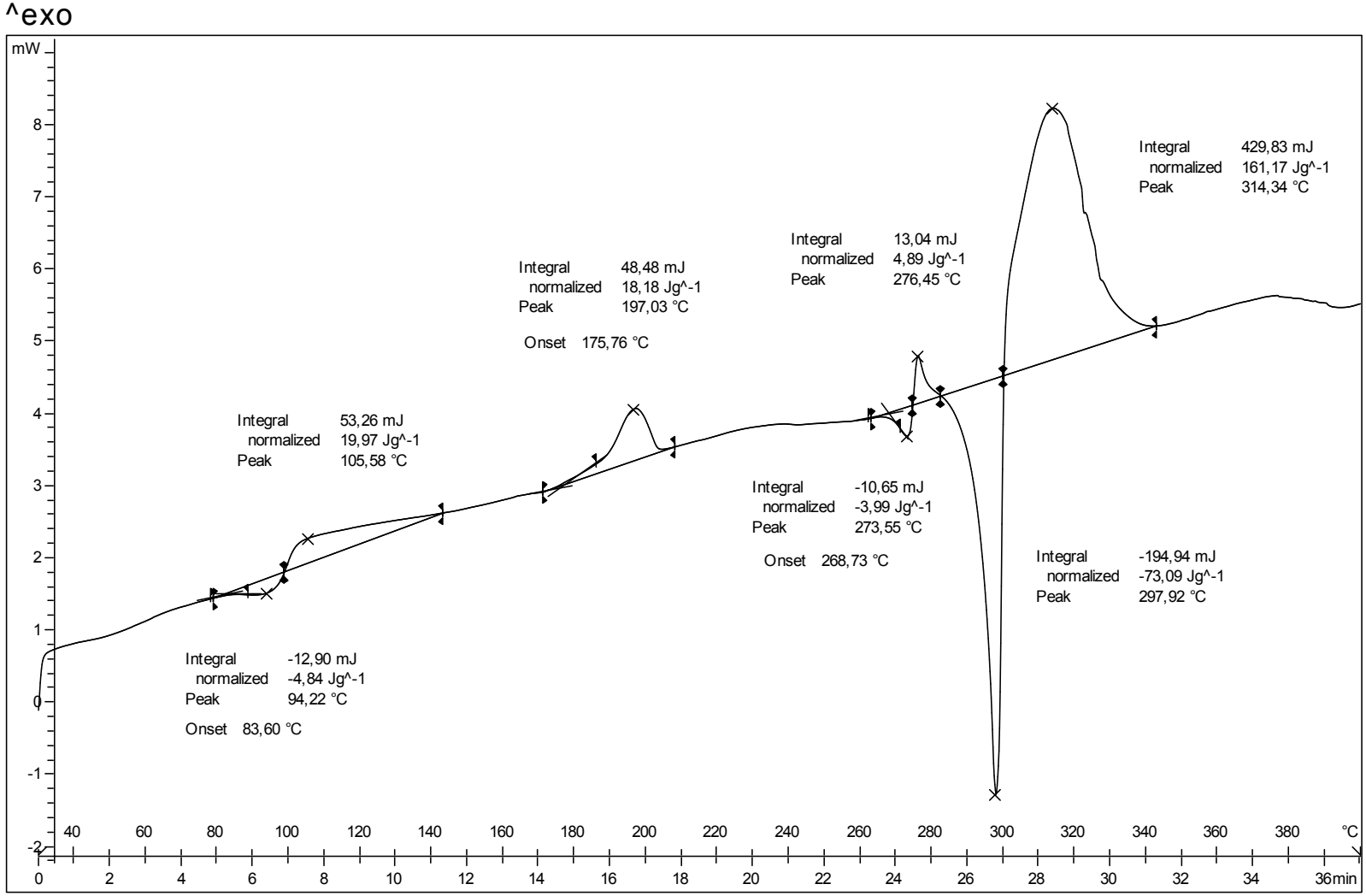


Figure S67: TGA of Form V-B

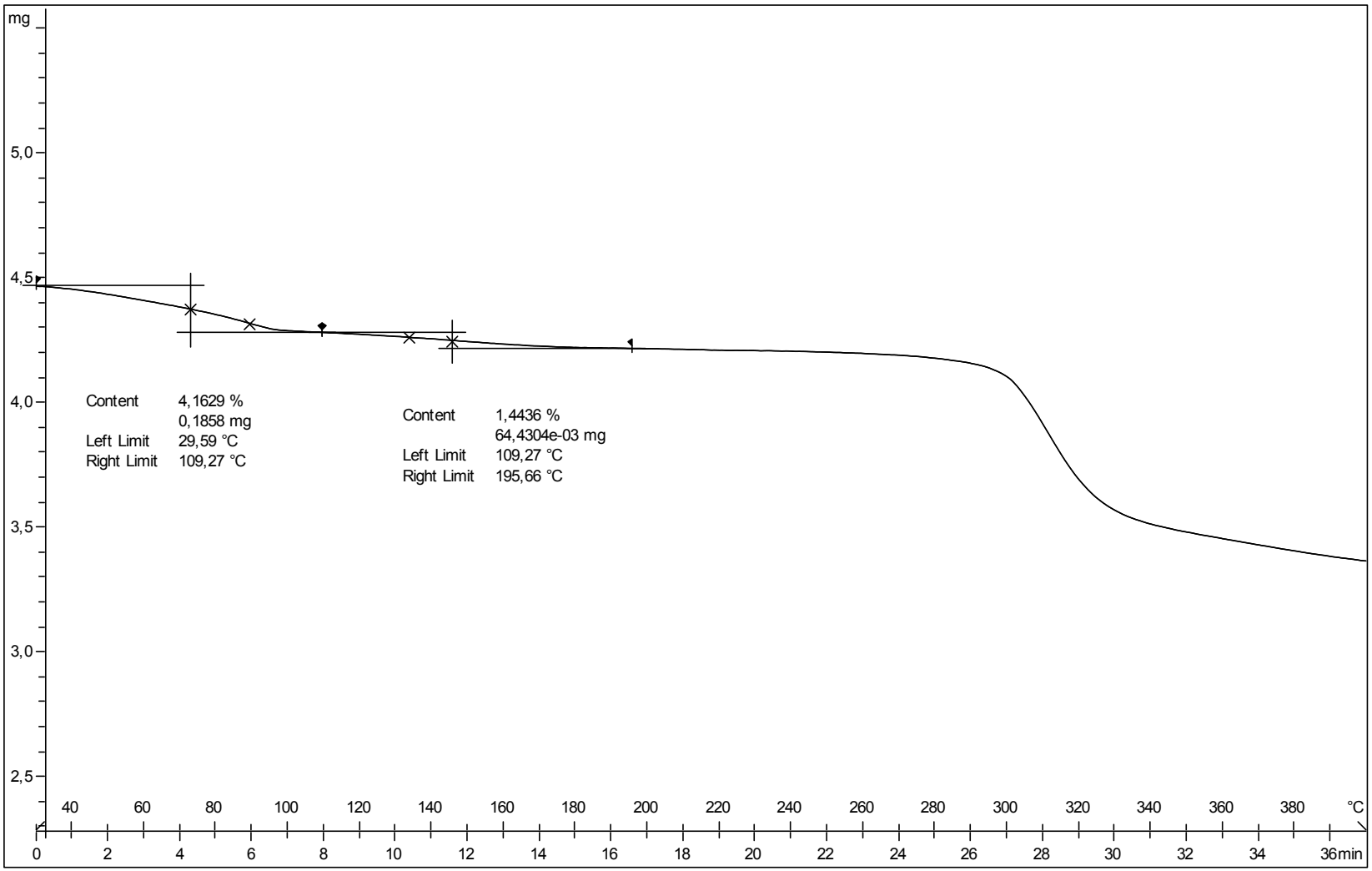


Figure S68: ^{1}H-NMR (dmso-d_6/delay: 1/pulse: 45°/scans: 32) of Form V-B

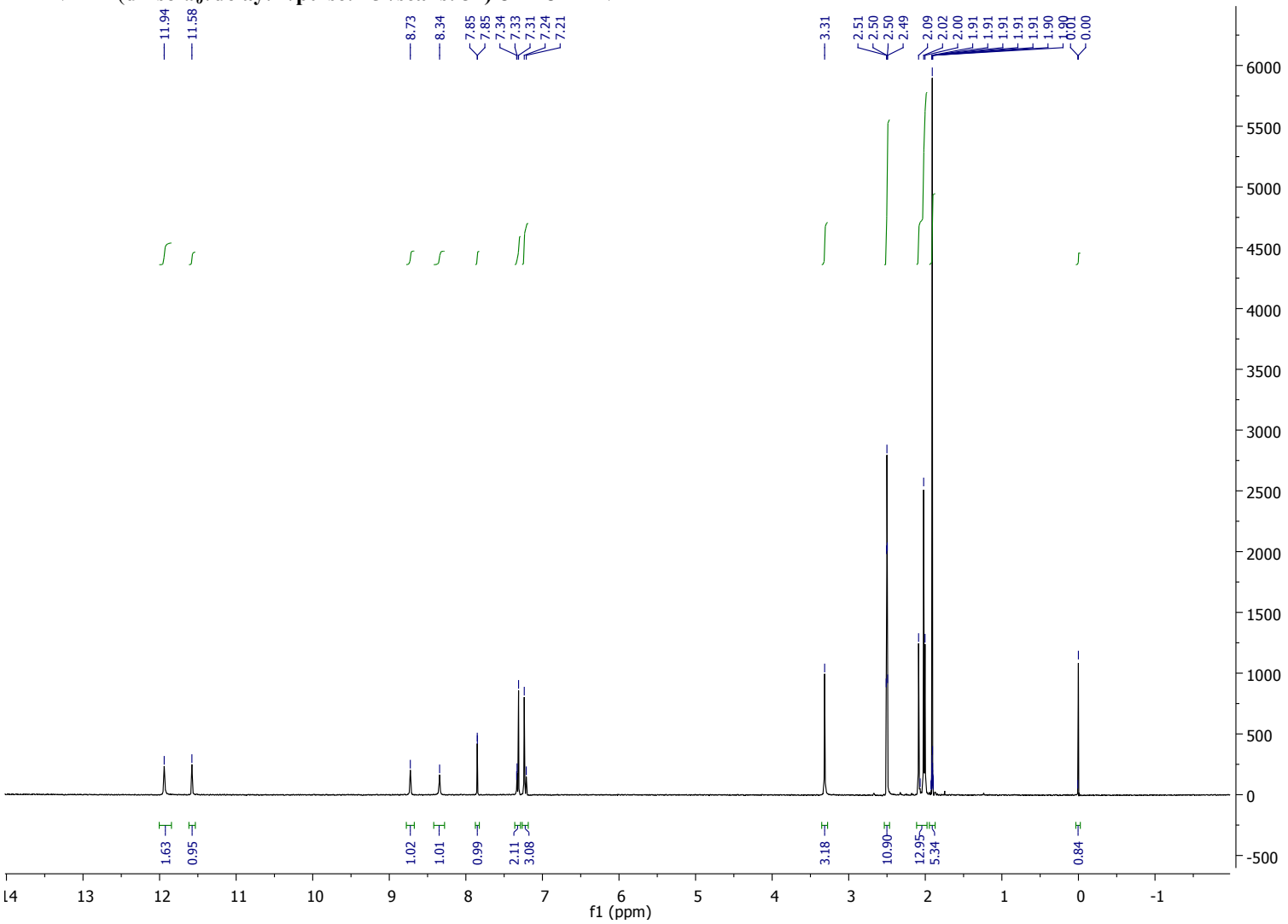


Figure S69: XRPD of Form V-B

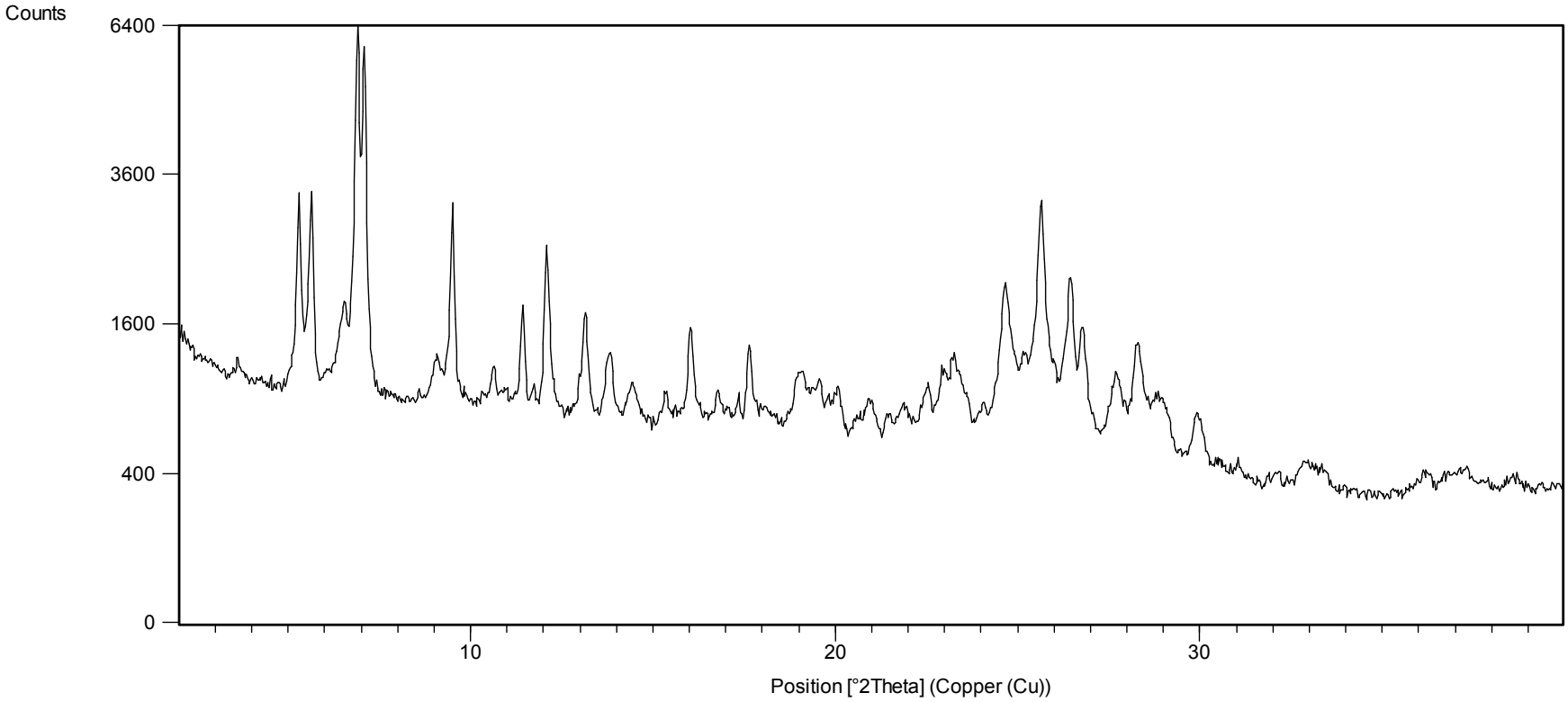


Figure S70: ^{1}H-NMR (dmso-d_6/delay: 1/pulse: 45°/scans: 32) of Form V-C

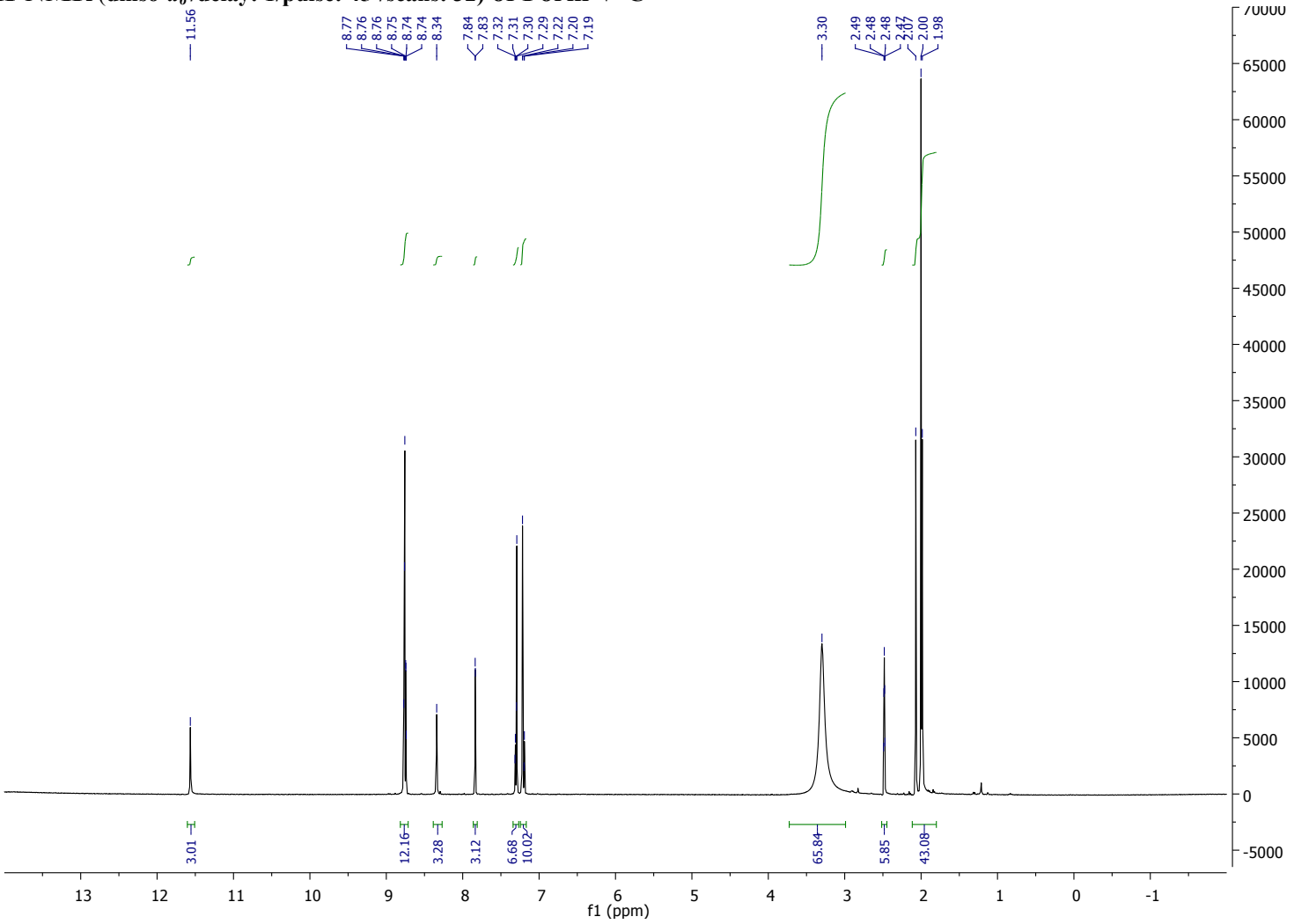


Figure S71: XRPD of Form V-C

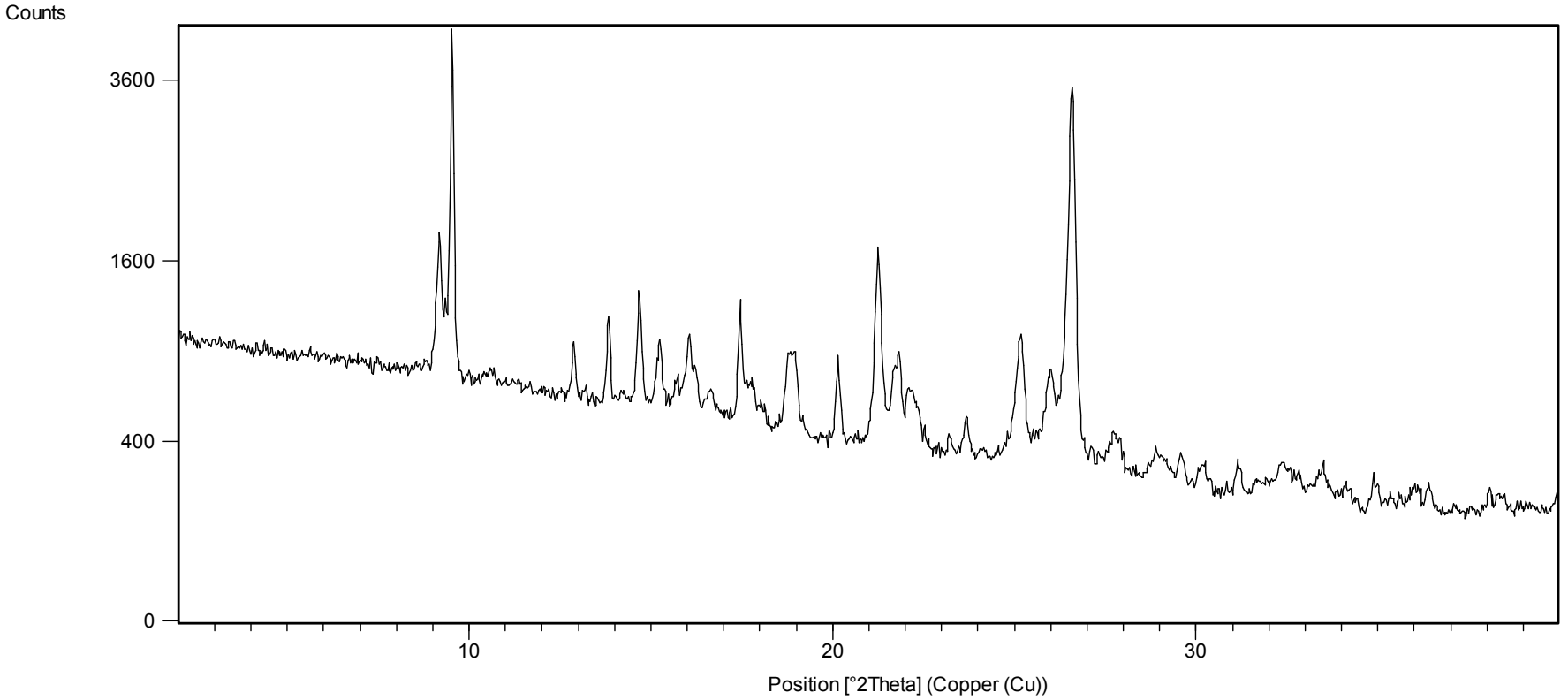


Figure S72: DSC of Form V-D

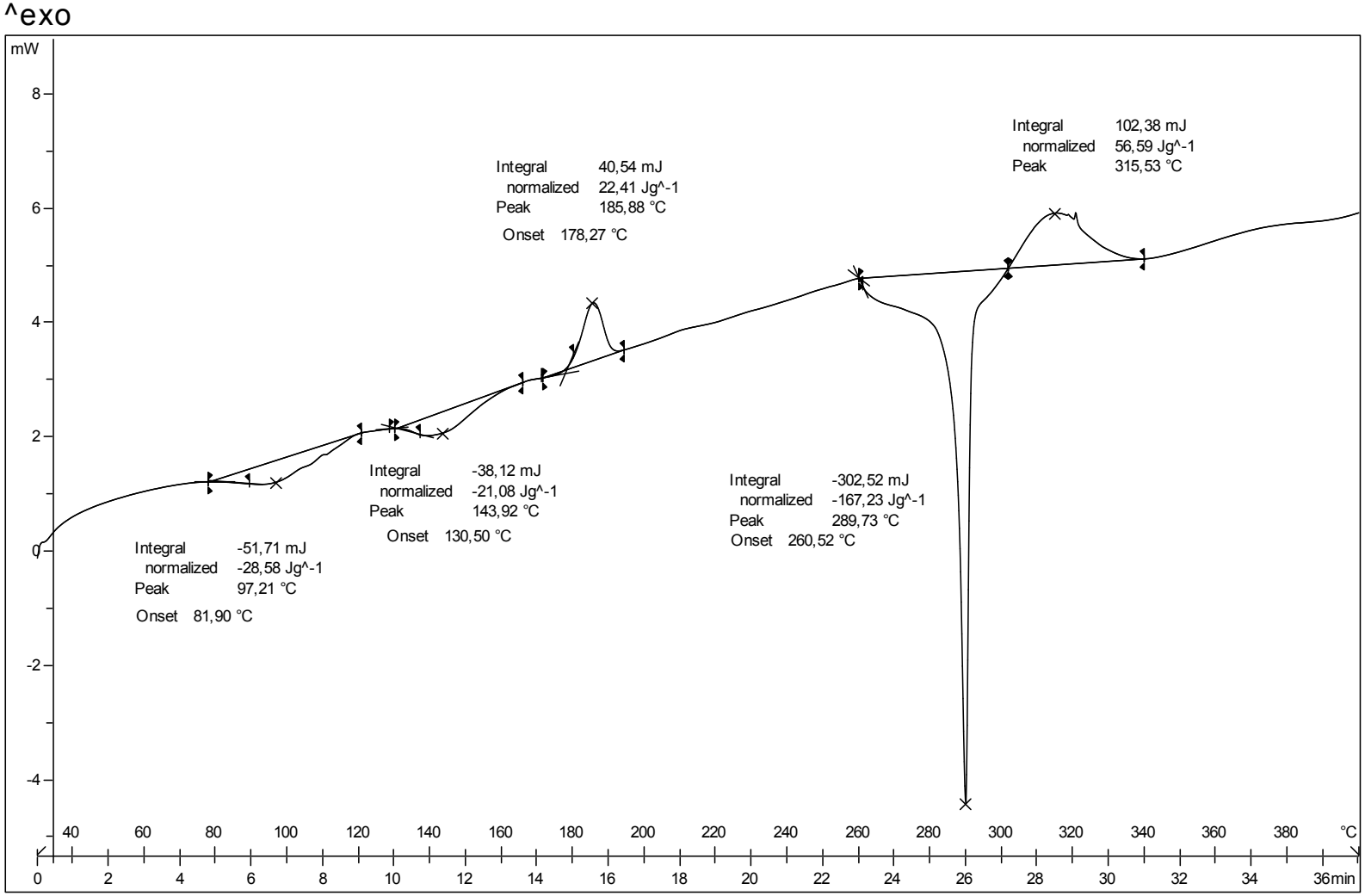


Figure S73: TGA of Form V-D

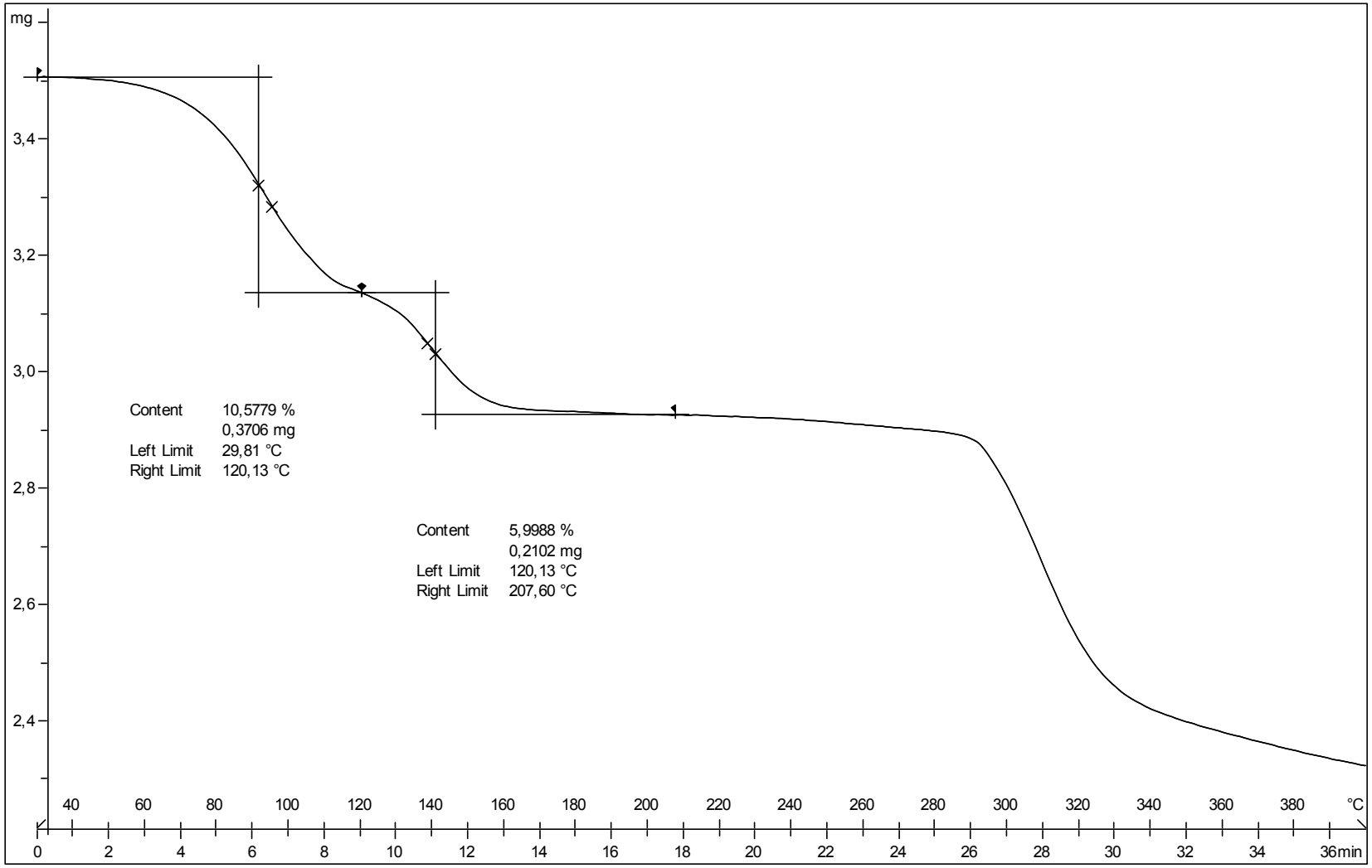


Figure S74: ^{1}H-NMR (dmso-d_6/delay: 1/pulse: 45°/scans: 32) of Form V-D

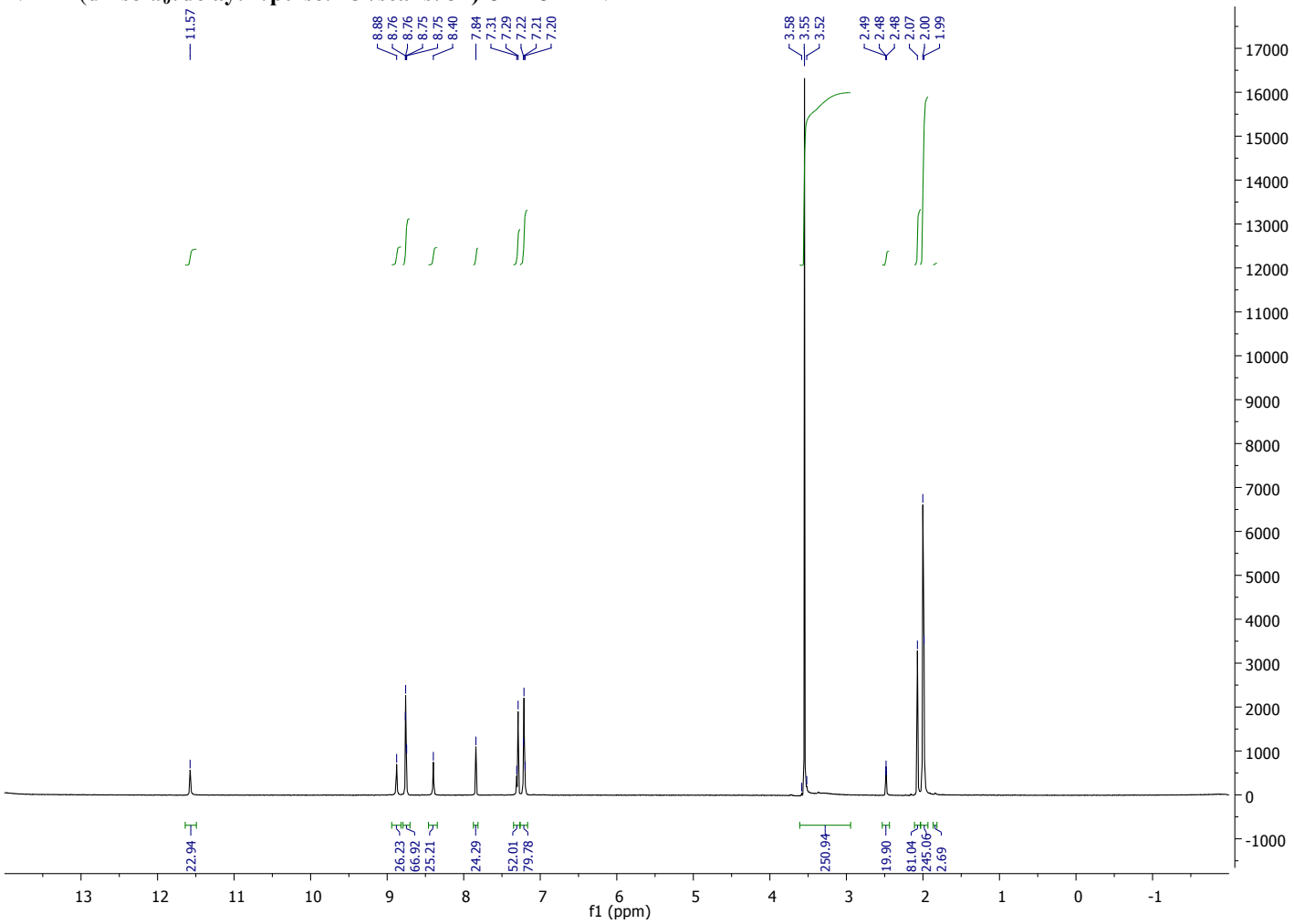


Figure S75: XRPD of Form V-D

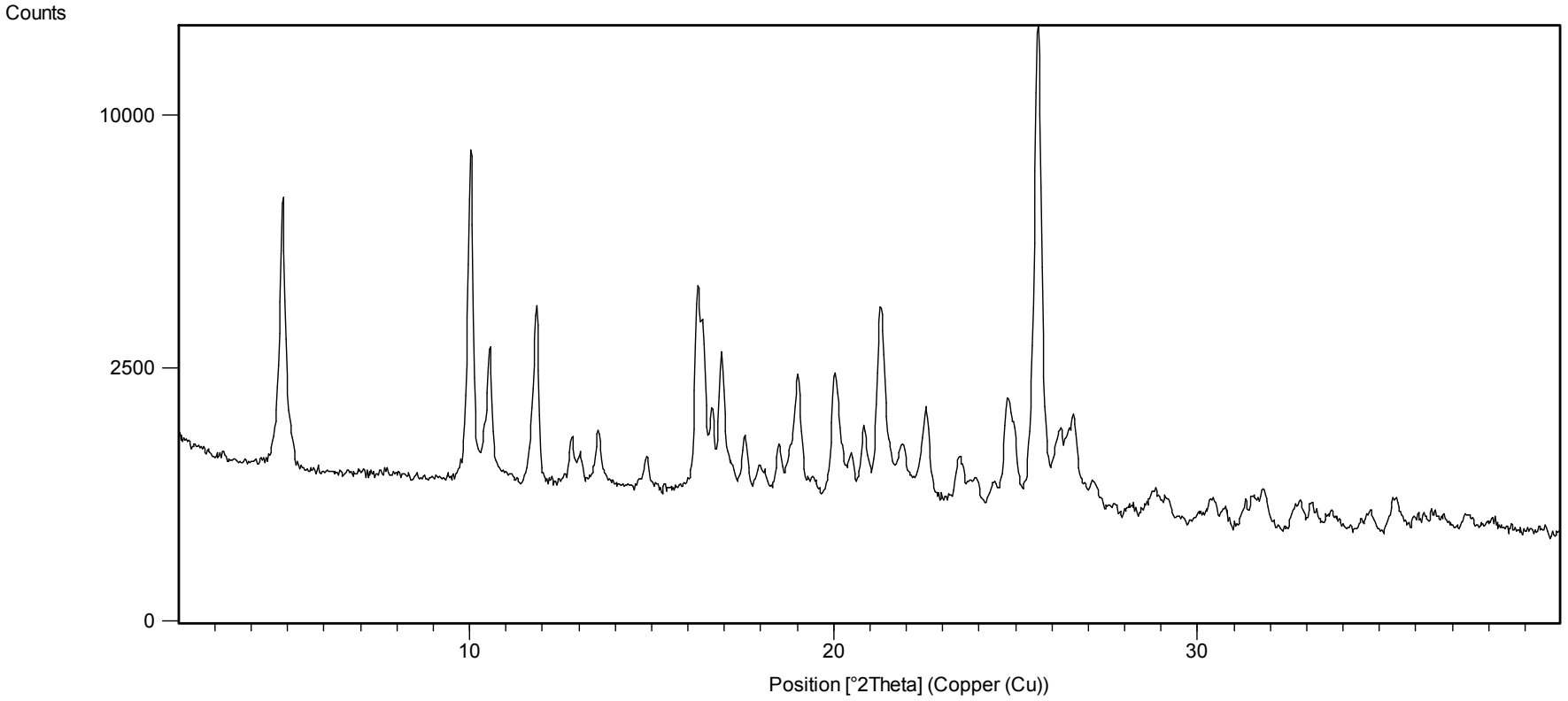


Figure S76: The XRPD of Form V-D has been indexed with the following proposed triclinic cell: a=18.422(8) Å, b=10.011(5) Å, c=10.972(3) Å, α=116.80(2)° β=87.75(2)°, γ=99.29(3)° V=1781(1) Å^3 (Figures of Merit: M= 14, F= 38), a *P-1* space group is compatible with the cell.

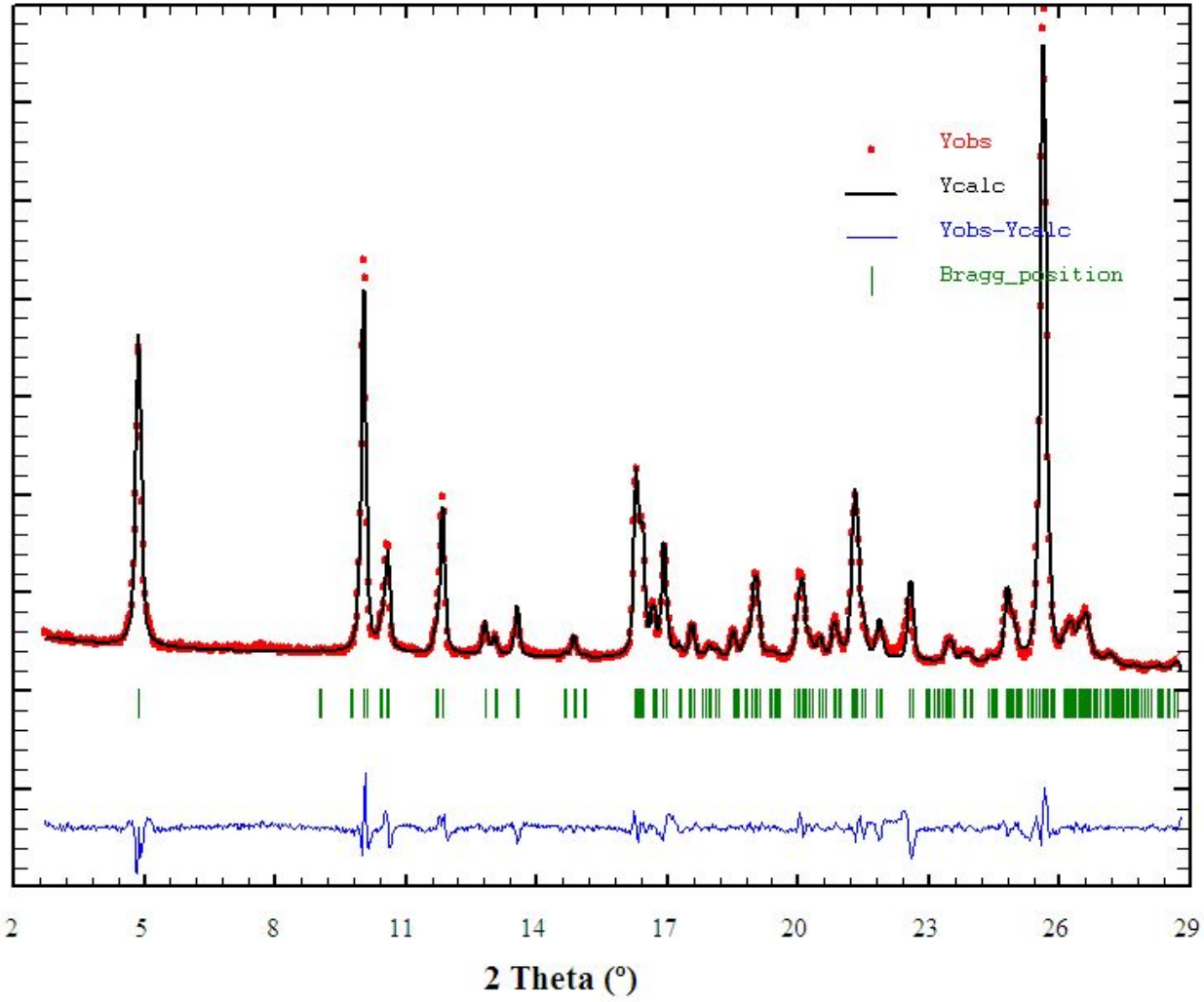


Figure S77: ^{1}H-NMR (dmso-d_6/delay: 1/pulse: 45°/scans: 32) of Form V-E

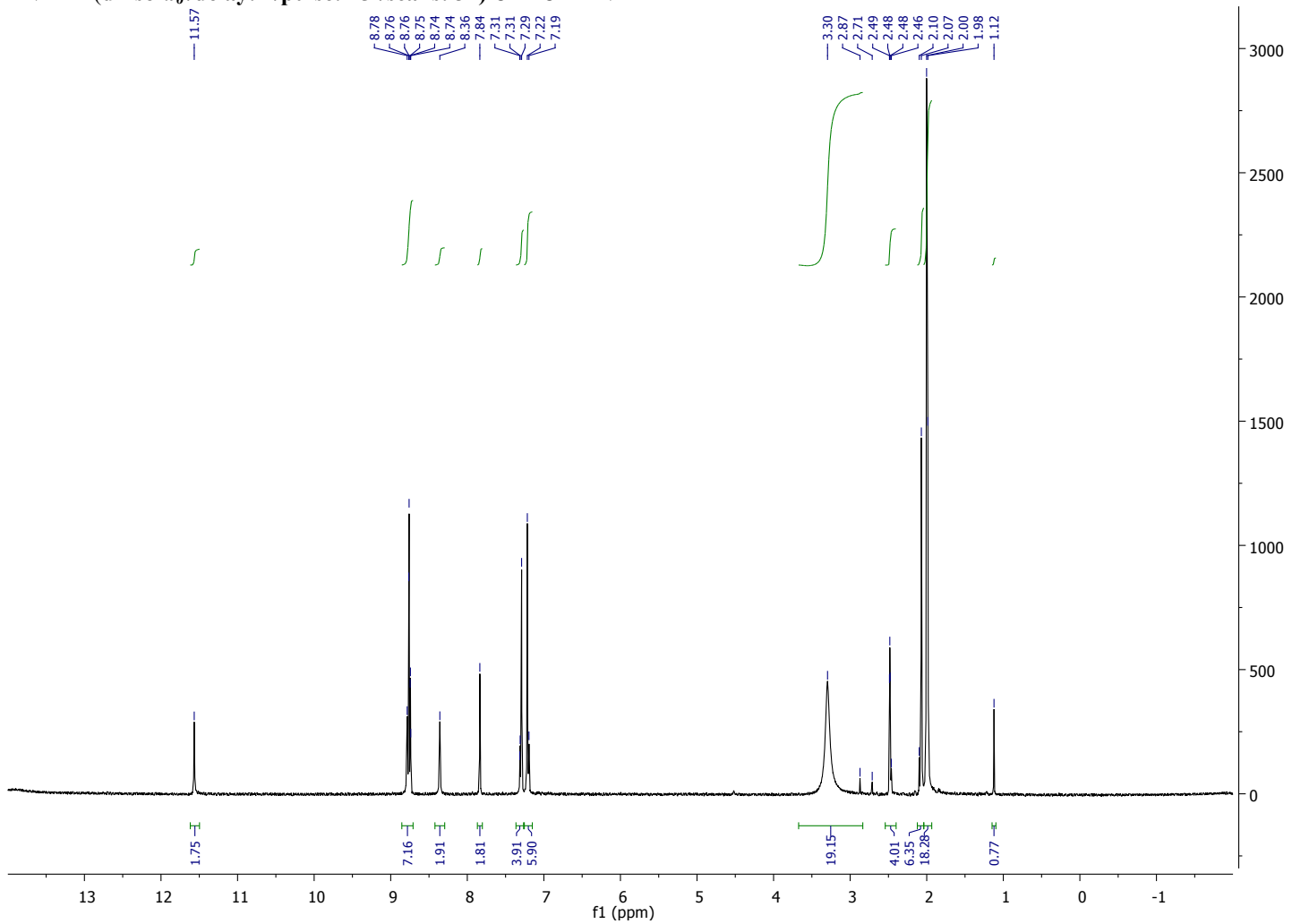


Figure S78: XRPD of Form V-E

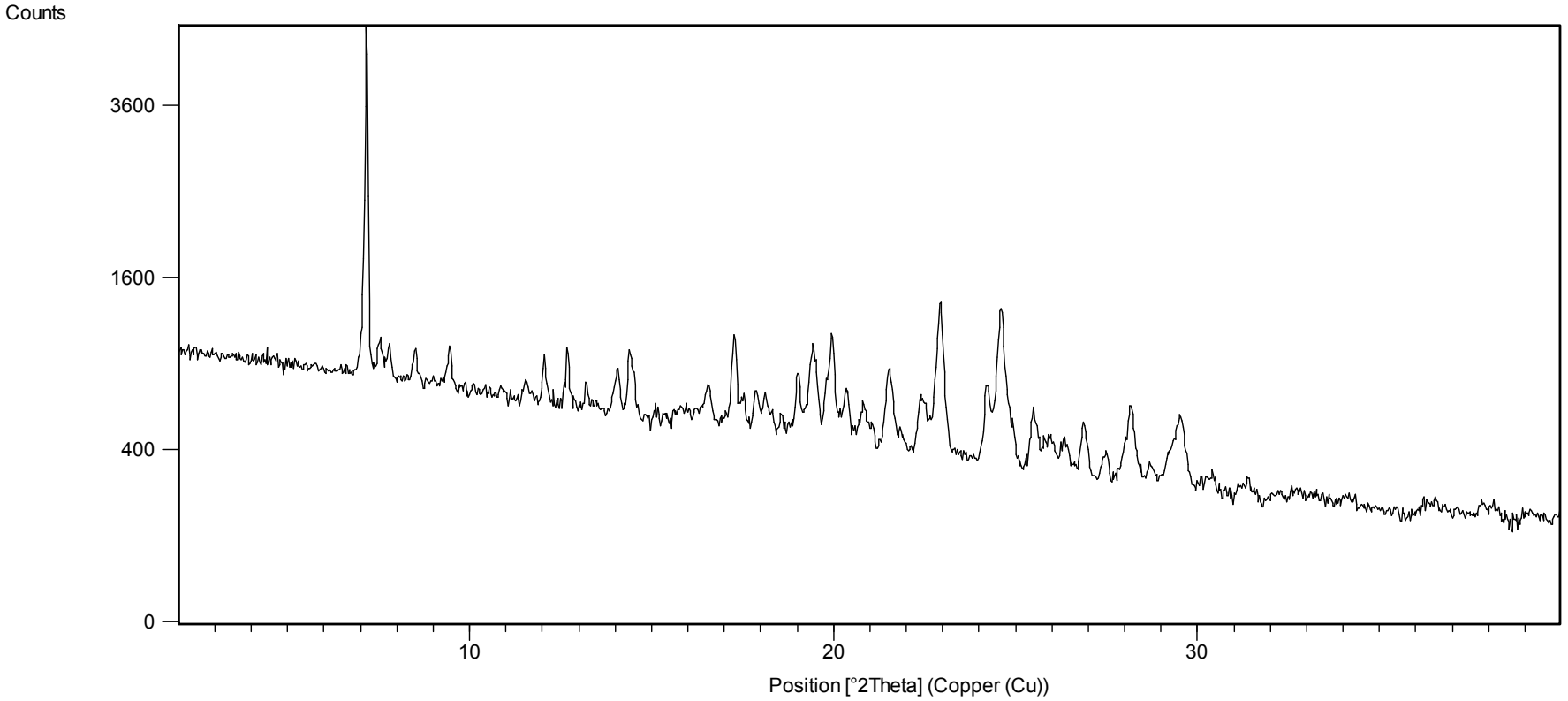


Figure S79: DSC of Form VI

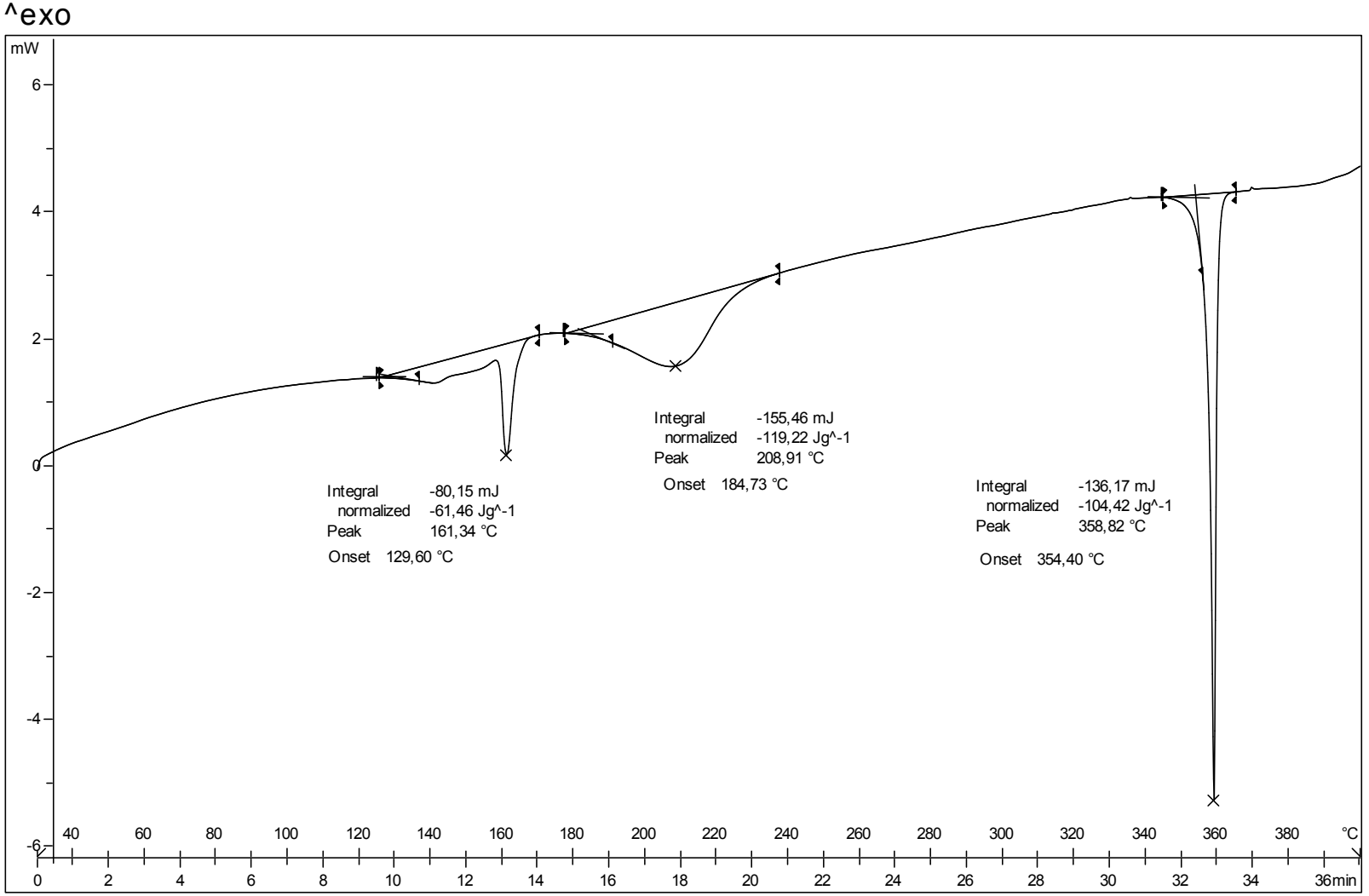


Figure S80: TGA of Form VI

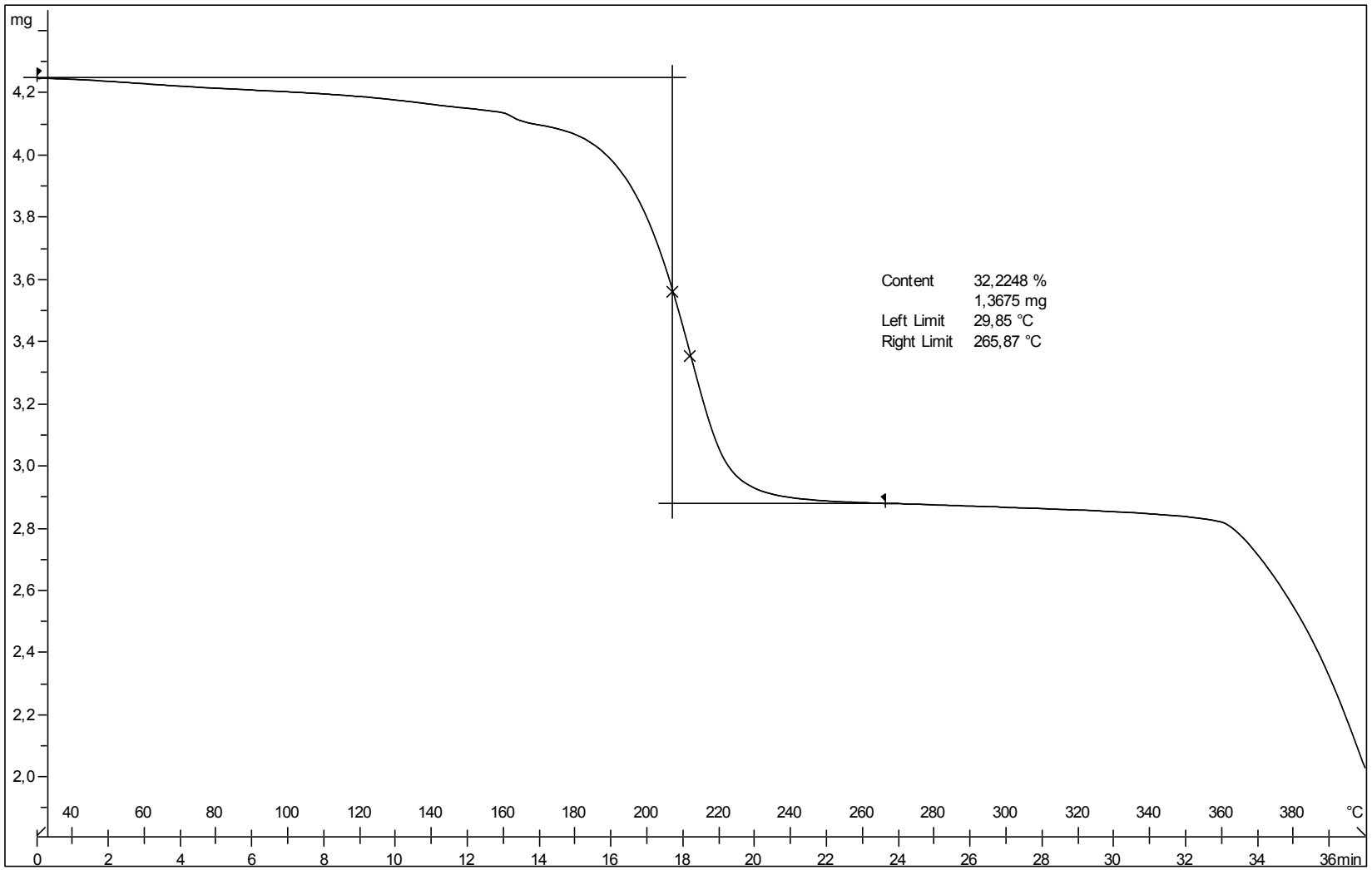


Figure S81: ^{1}H-NMR (dmso-d_6/delay: 1/pulse: 45°/scans: 32) of Form VI

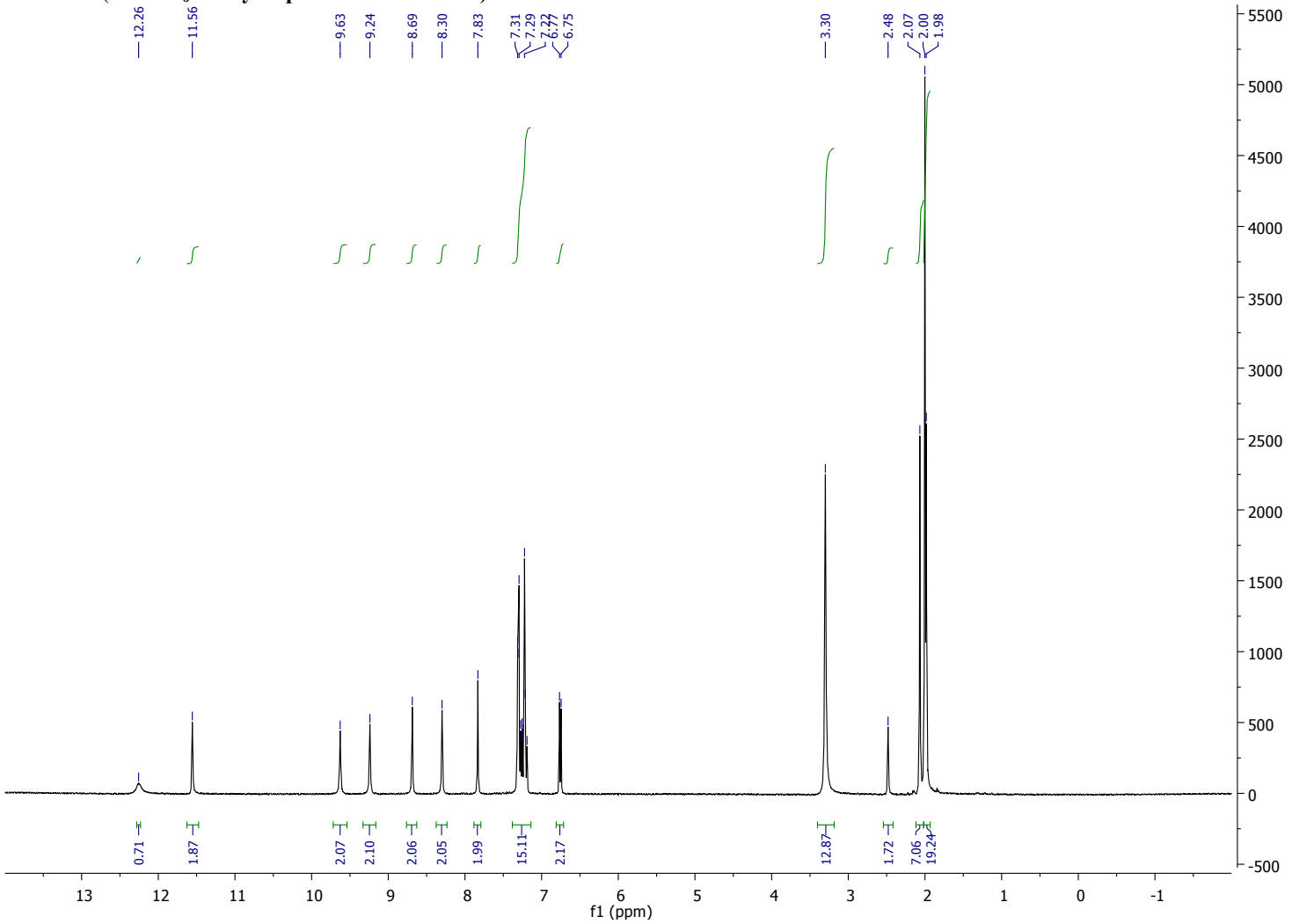


Figure S82: XRPD of Form VI

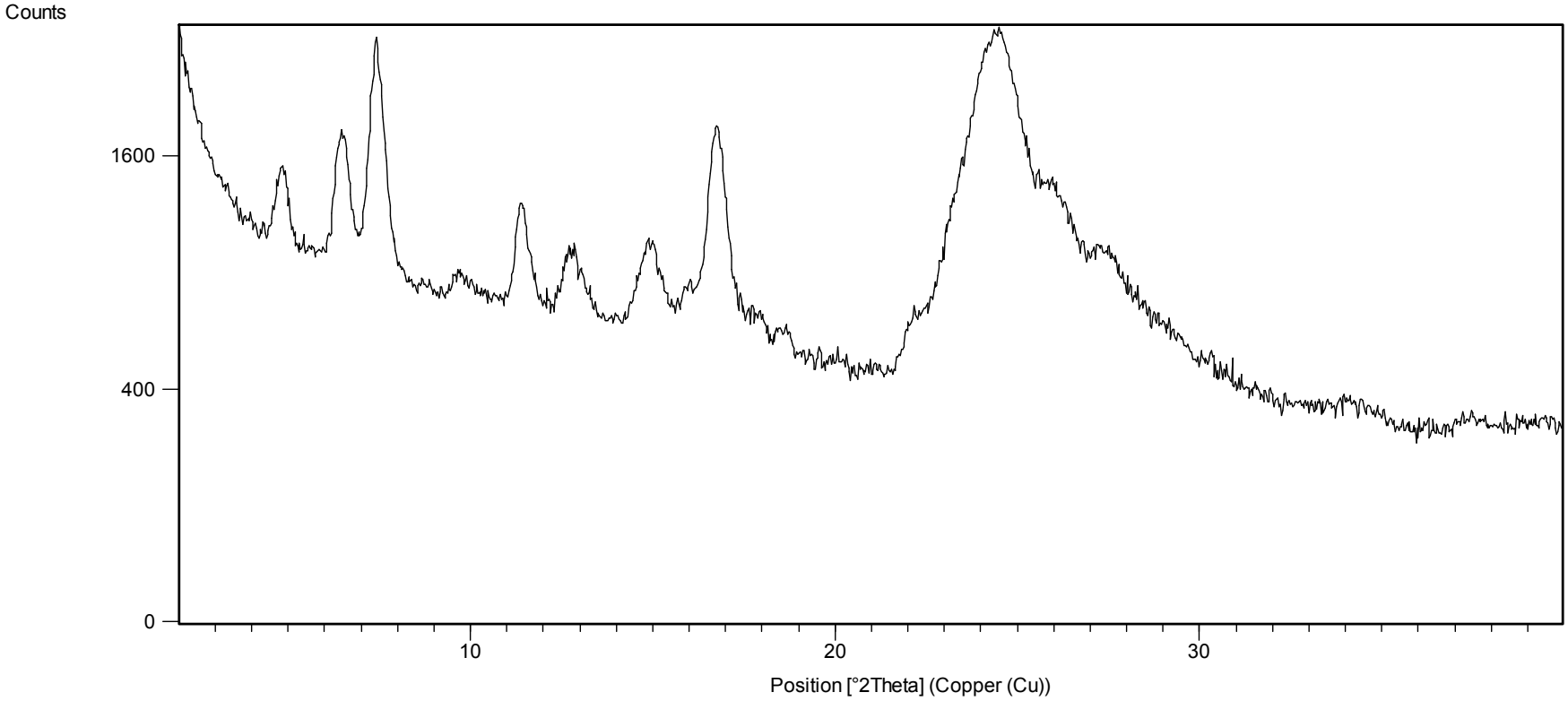


Figure S83: DSC of Form VII

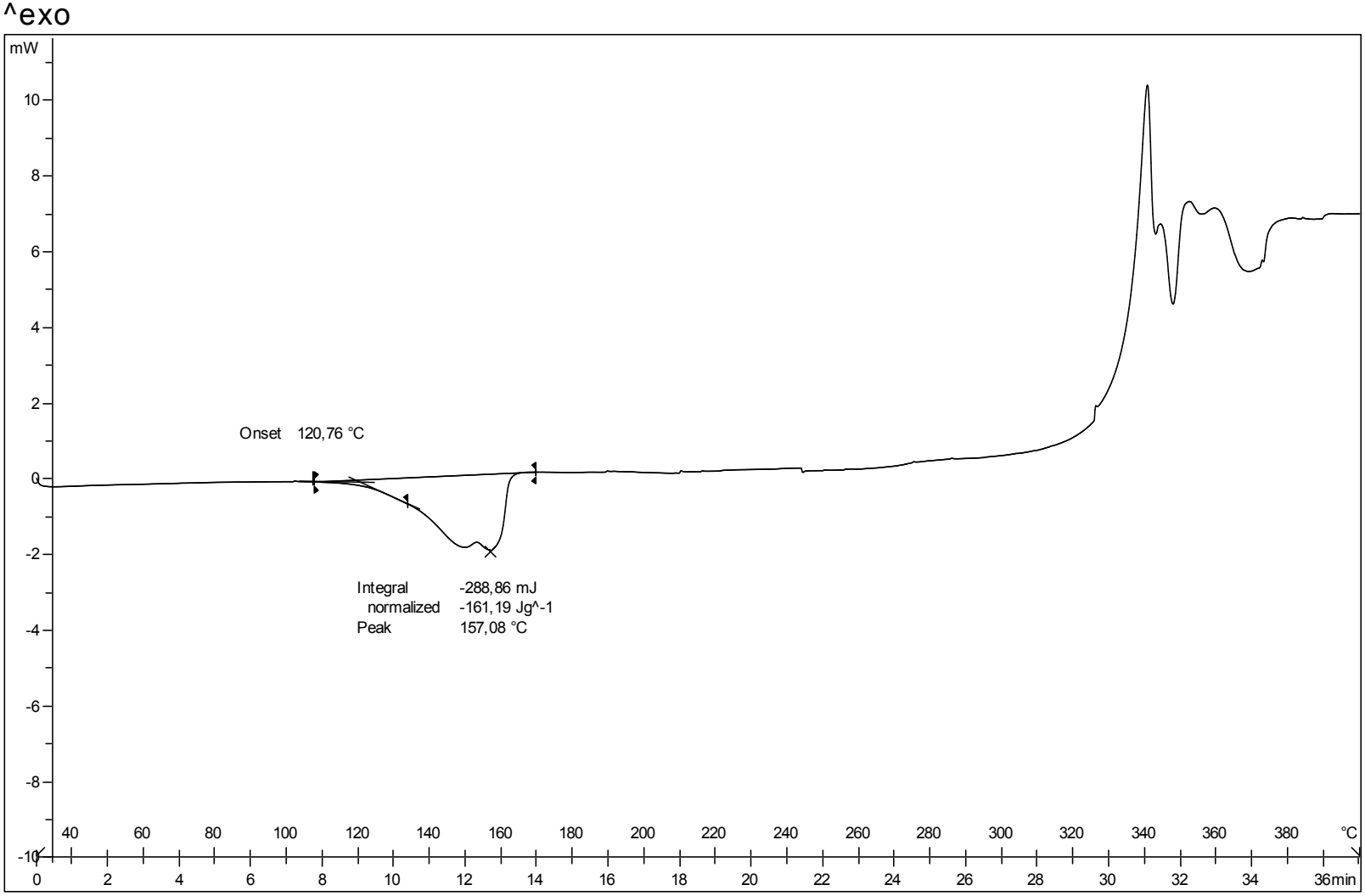


Figure S84: TGA of Form VII

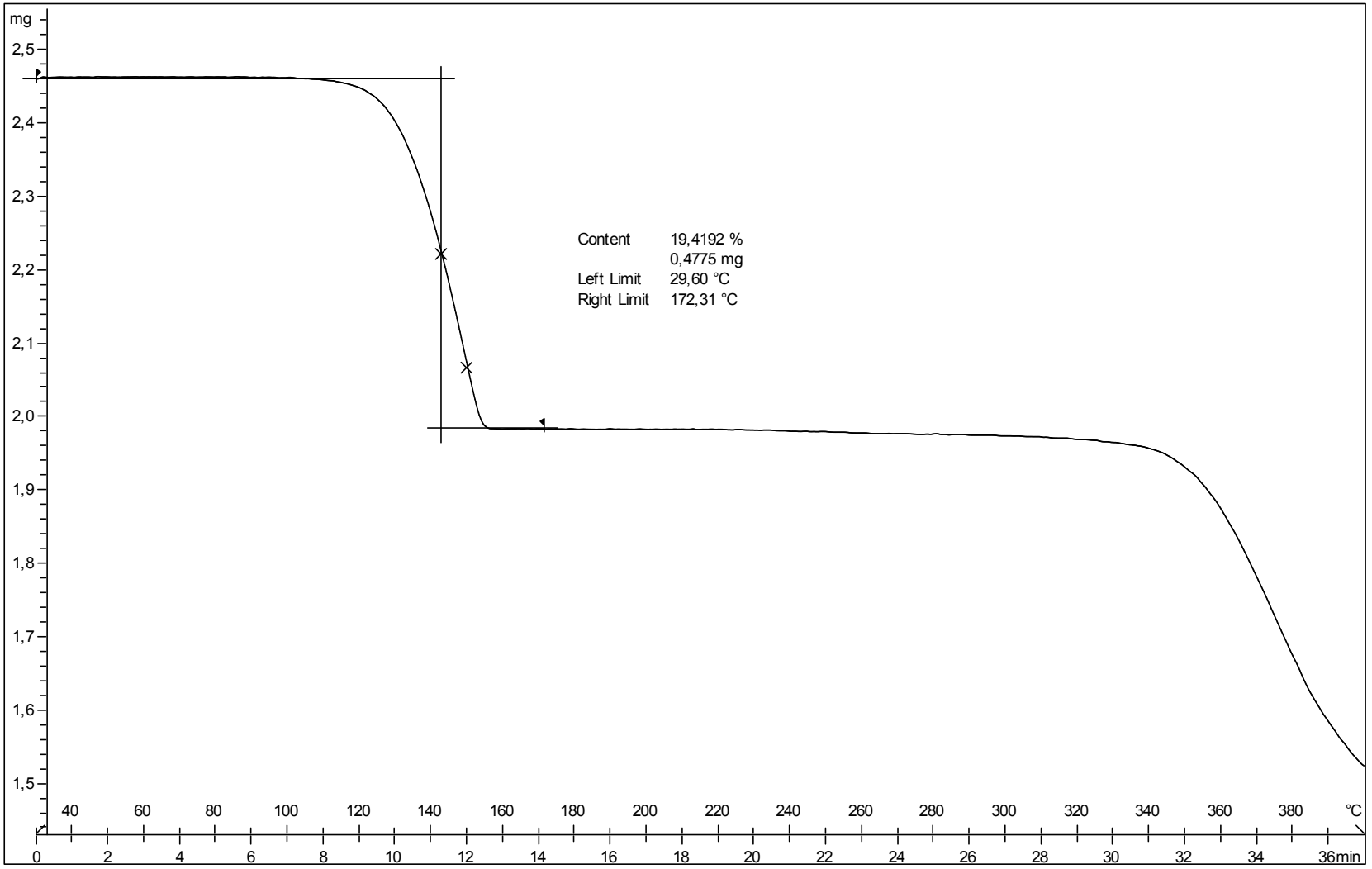


Figure S85: ^{1}H-NMR (dmso-d_6/delay: 1/pulse: 45°/scans: 32) of Form VII

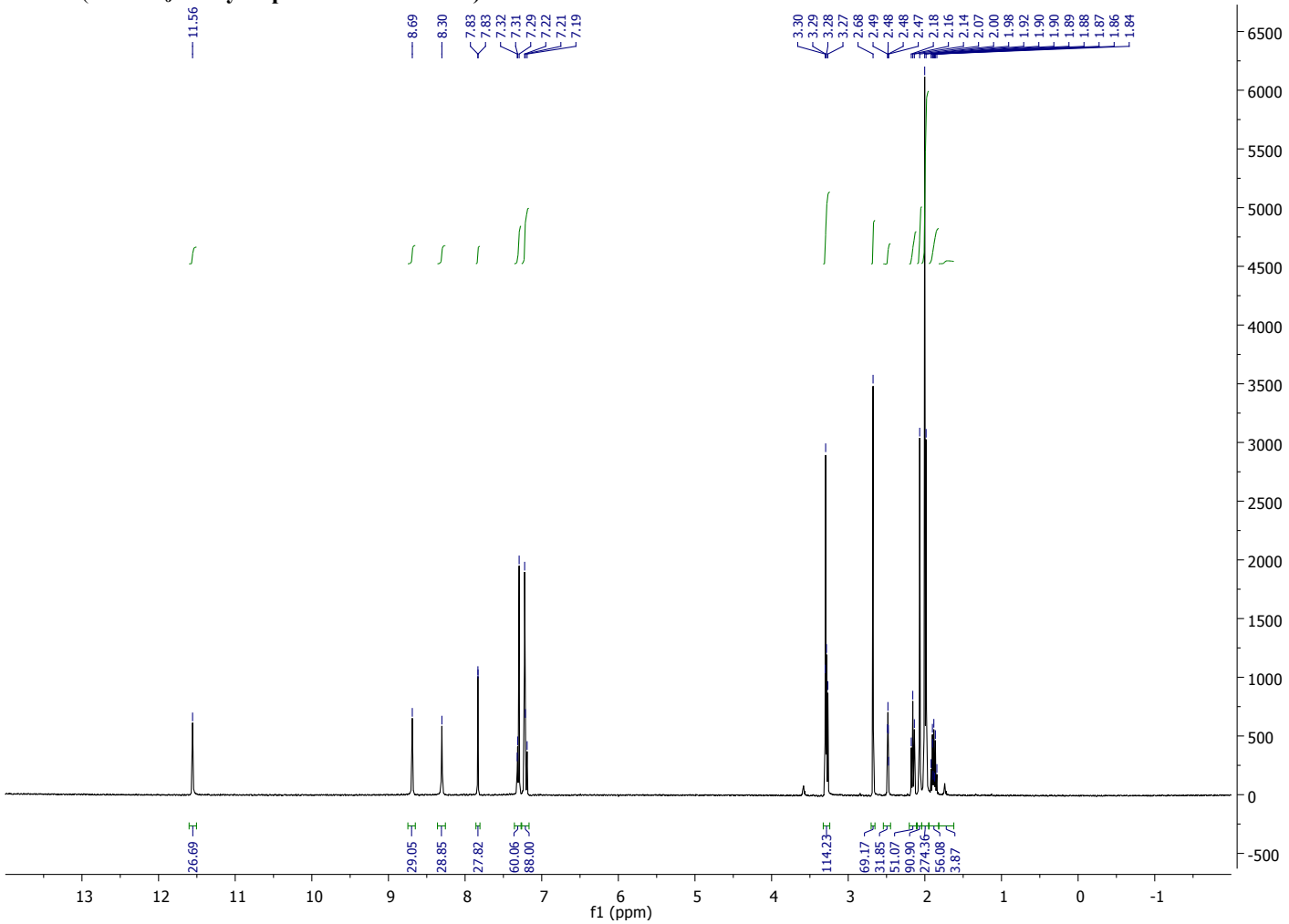


Figure S86: XRPD of Form VII

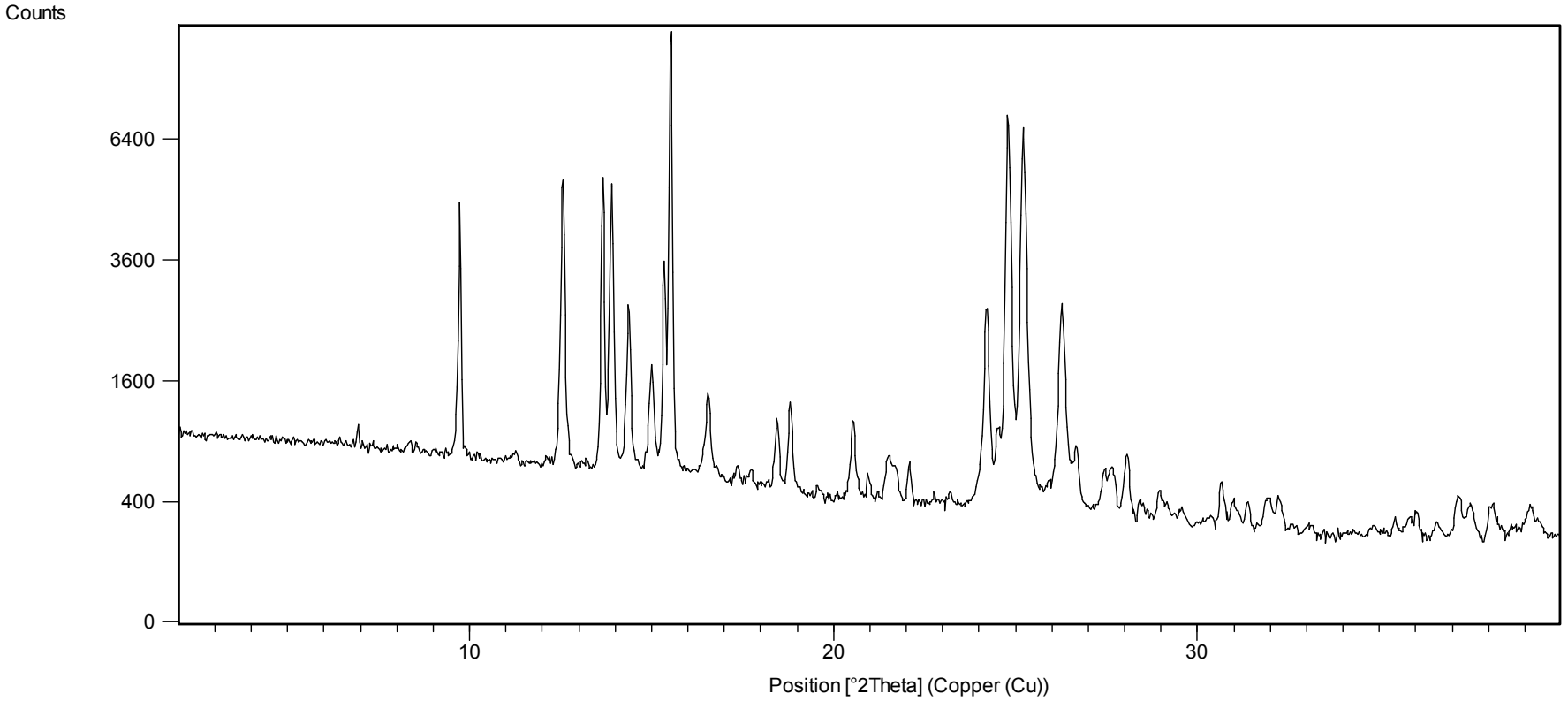


Figure S87: The XRPD of Form VII has been indexed with the following proposed monoclinic cell: a=13.201(5) Å, b=12.683(4) Å, c=7.498(2) Å, β=101.73(2)º, V=1229.2(7) Å^3 (Figures of Merit: M= 80, F= 172), a *P2/n* space group is compatible with the cell.

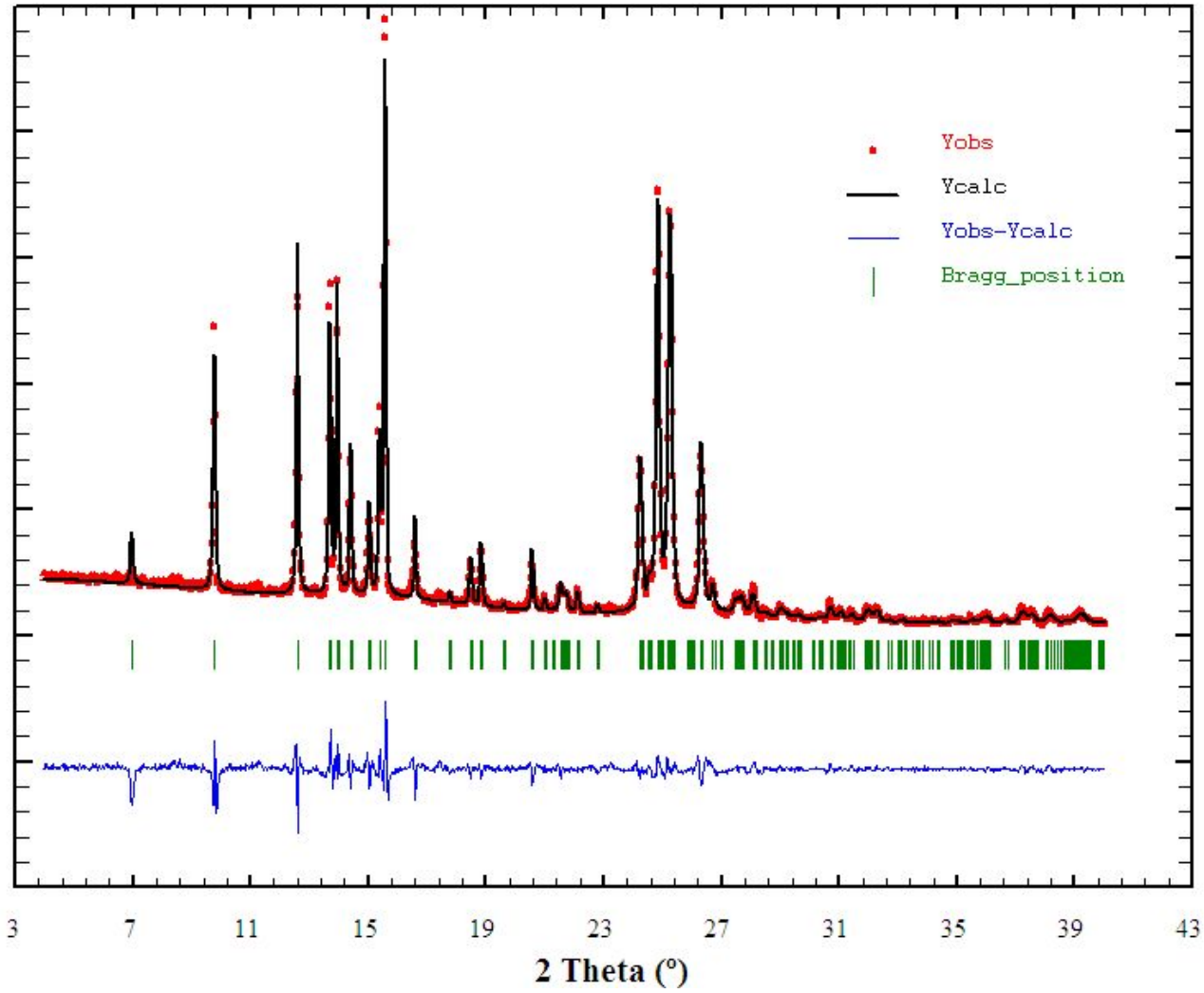


Figure S88: DSC of Form VIII

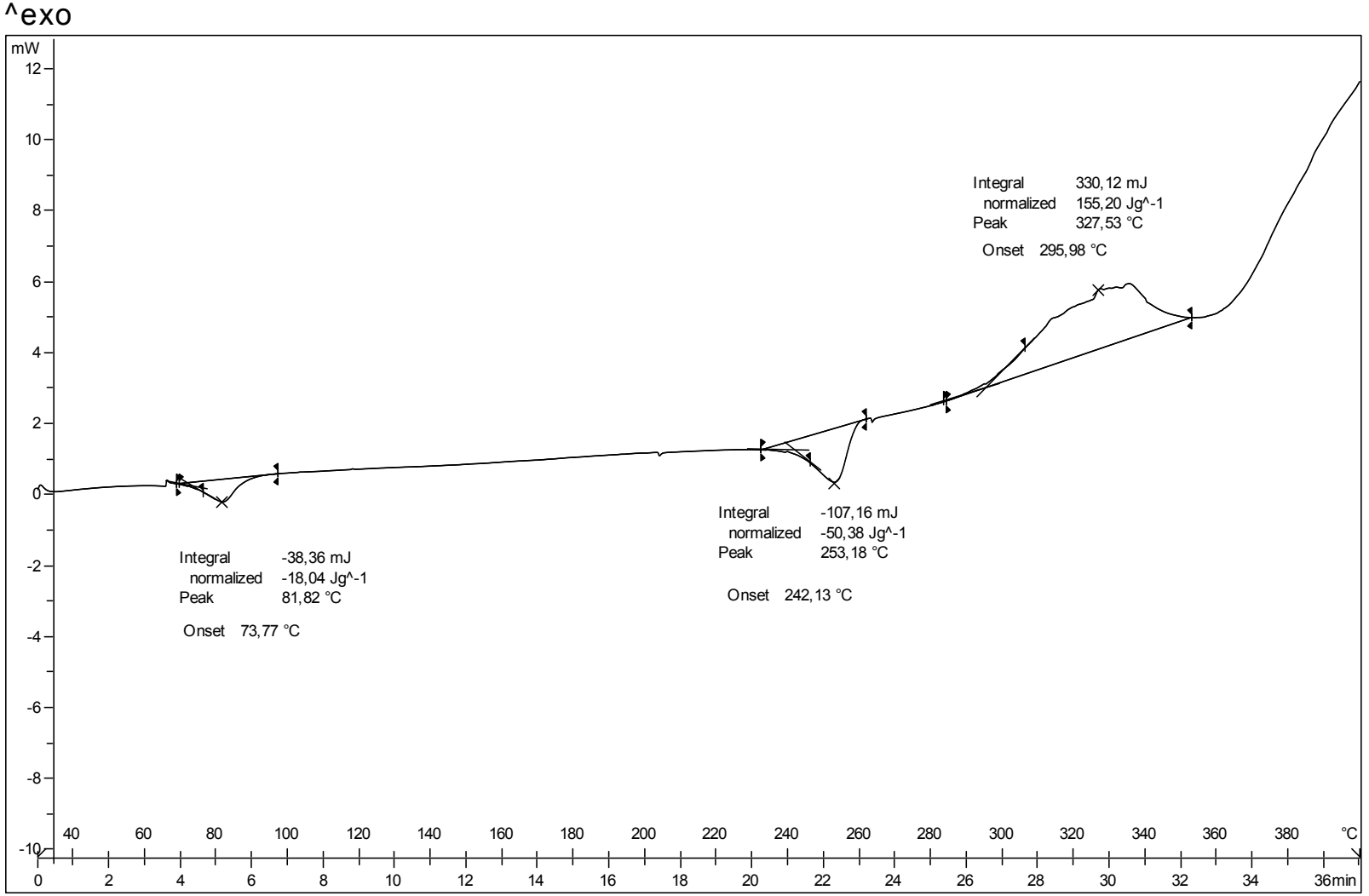


Figure S89: TGA of Form VIII

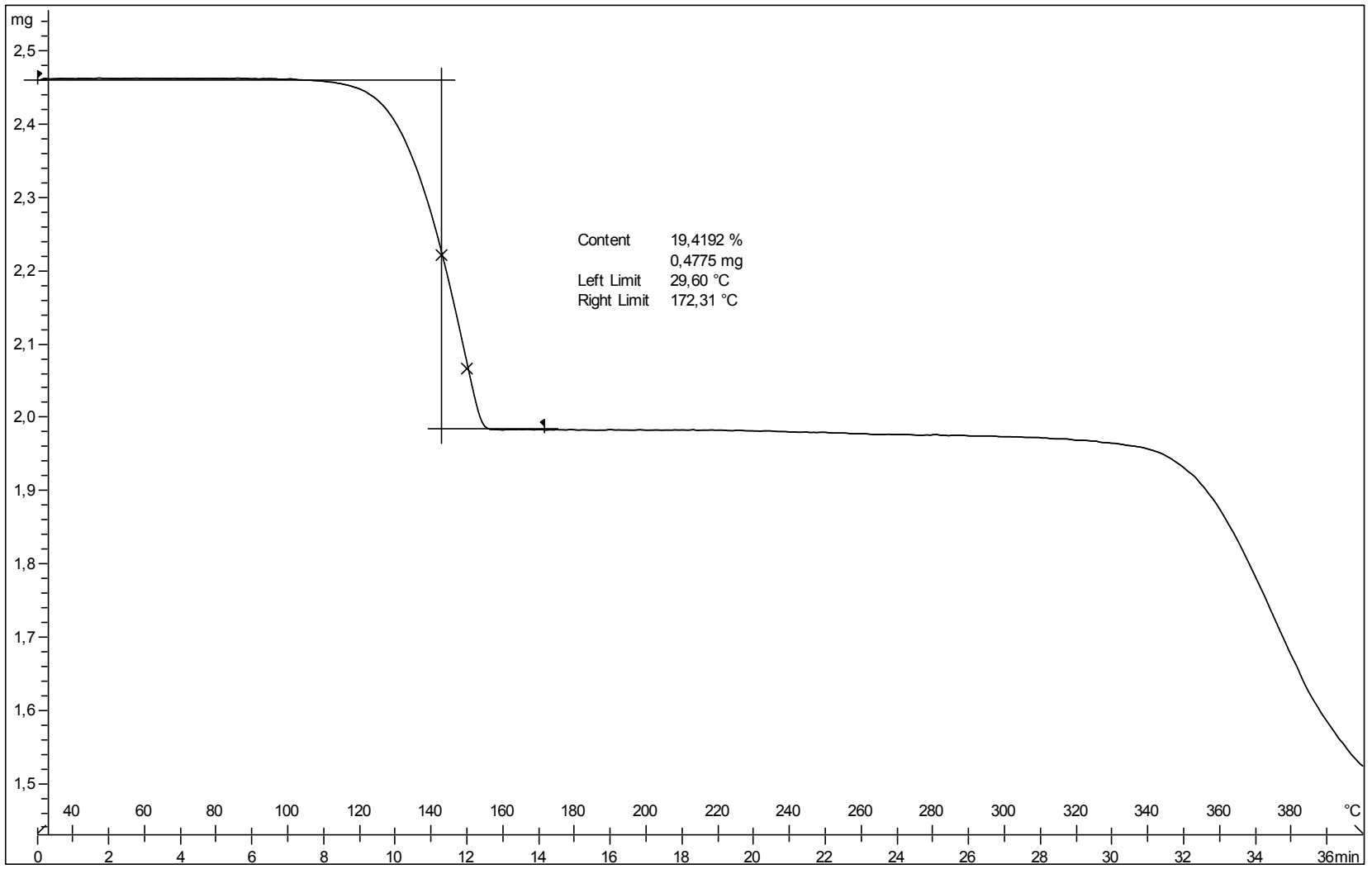


Figure S90: ^{1}H-NMR (dmso-d_6/delay: 1/pulse: 45°/scans: 32) of Form VIII

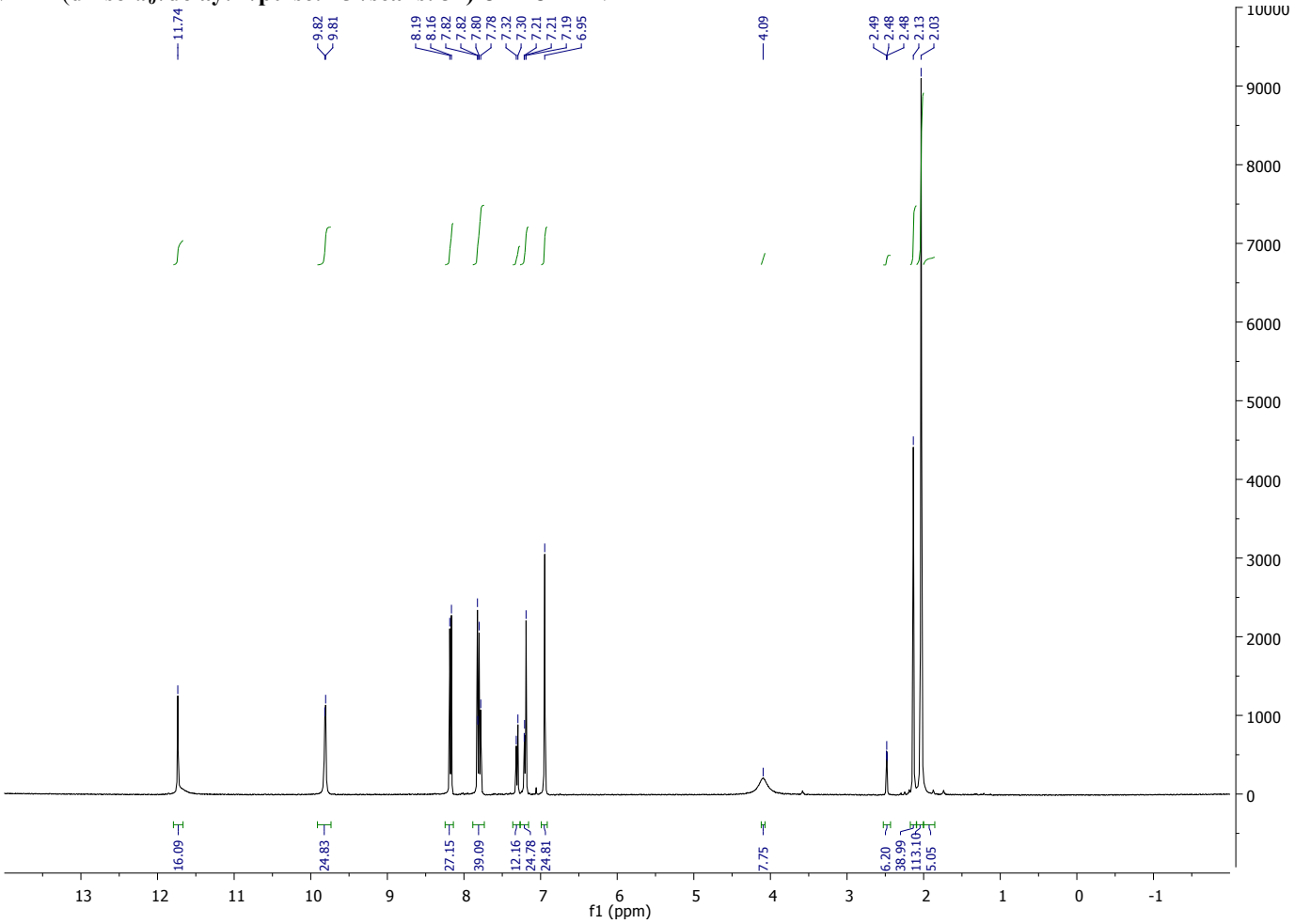
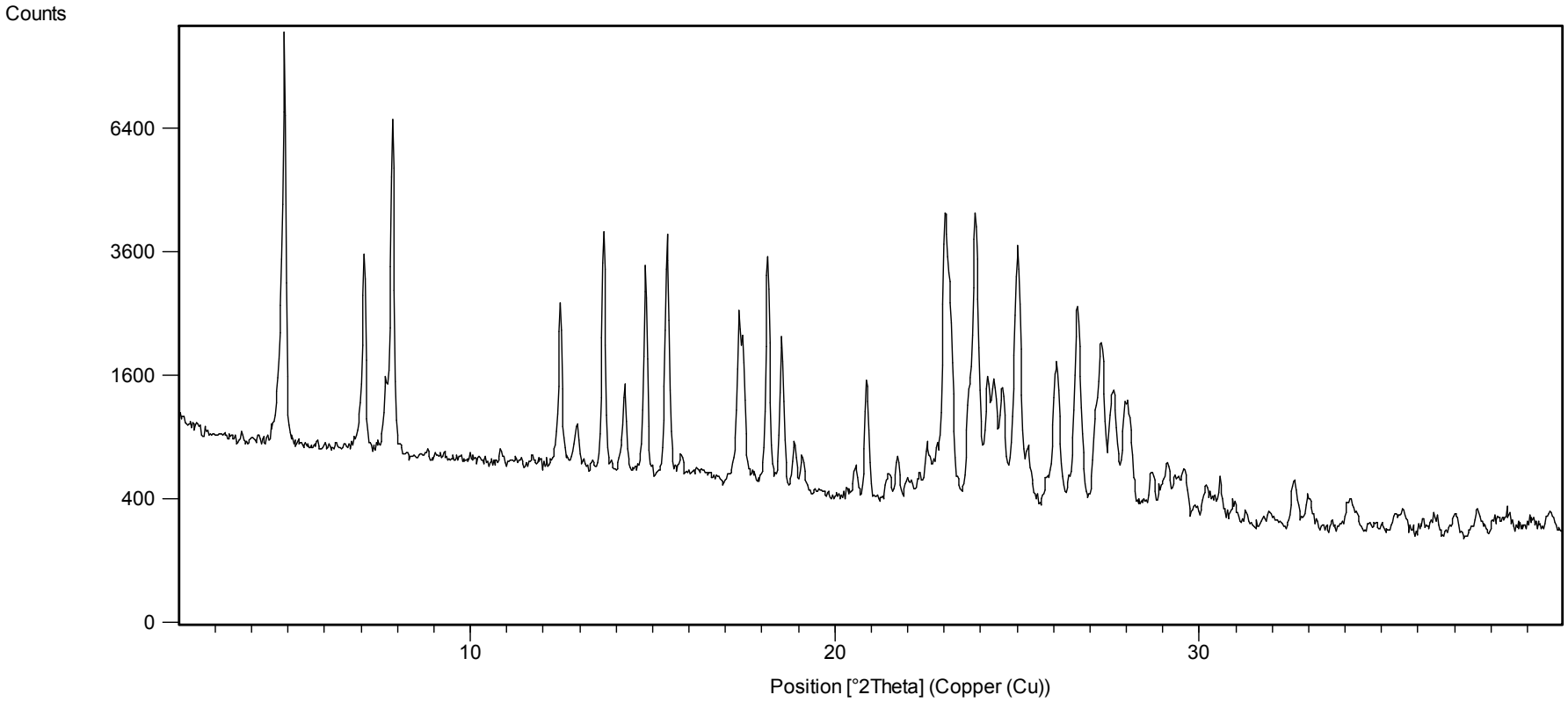


Figure S91: XRPD of Form VIII



2.- Crystal data and structure refinement

2.1 Form I: 1: 1,4,8,11-Tetrazacyclotetradecane (mo_023SB19_0m)

Table S1. Crystal data and structure refinement for mo_023SB19_0m.

Identification code	mo_023SB19_0m	
Empirical formula	C26 H33 N7 O2	
Formula weight	475.59	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 12.4888(17) Å	α= 90°.
	b = 13.8659(18) Å	β= 103.322(5)°.
	c = 14.4933(19) Å	γ = 90°.
Volume	2442.2(6) $Å^3$	
Z	4	
Density (calculated)	1.293 Mg/m^3	
Absorption coefficient	0.085 mm^{-1}	
F(000)	1016	
Crystal size	0.501 x 0.312 x 0.261 mm^3	
Theta range for data collection	2.228 to 33.181°.	
Index ranges	-19<=h<=19, -21<=k<=21, -18<=l<=22	
Reflections collected	77204	
Independent reflections	9331 [R(int) = 0.0448]	
Completeness to theta = 25.242°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7465 and 0.6968	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9331 / 0 / 335	
Goodness-of-fit on F^2	1.046	
Final R indices [I>2sigma(I)]	R1 = 0.0479, wR2 = 0.1409	
R indices (all data)	R1 = 0.0563, wR2 = 0.1485	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.758 and -0.709 $e.Å^{-3}$	

Table S2. Hydrogen bonds for mo_023SB19_0m [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N7 --H7NA ..N1 [x,3/2-y,-1/2+z]	1.063(15)	1.582(16)	2.6437(13)	177.0(12)
N7 --H7NB ..N6 [ ]	0.891(15)	2.140(15)	2.8589(14)	137.3(13)
N7 --H7NB ..N6 [1-x,2-y,-z]	0.891(15)	2.554(15)	2.9288(13)	106.1(11)
N2 --H2N ..O1 [1-x,1/2+y,1/2-z]	0.870(15)	2.121(15)	2.8995(13)	148.7(13)
N5 --H5N ..N3 [-x,1-y,1-z]	0.868(15)	2.554(16)	3.3869(13)	161.2(14)

2.2 Form II-A: 1:3,5-Dinitrobenzoic acid salt isopropanol solvate (mo_023SB22_0m_a)

Table S3. Crystal data and structure refinement for mo_023SB22_0m_a.

Identification code	mo_023SB22_0m_a	
Empirical formula	C34 H41 N7 O10	
Formula weight	707.74	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 11.4419(8) Å	α= 90°.
	b = 15.2684(12) Å	β= 103.182(3)°.
	c = 21.4335(17) Å	γ = 90°.
Volume	3645.8(5) $Å^3$	
Z	4	
Density (calculated)	1.289 Mg/m^3	
Absorption coefficient	0.096 mm^{-1}	
F(000)	1496	
Crystal size	0.522 x 0.091 x 0.040 mm^3	
Theta range for data collection	2.263 to 28.344°.	
Index ranges	-14<=h<=15, -20<=k<=20, -28<=l<=28	
Reflections collected	123319	
Independent reflections	9088 [R(int) = 0.1079]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7457 and 0.7046	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9088 / 397 / 522	
Goodness-of-fit on F^2	1.031	
Final R indices [I>2sigma(I)]	R1 = 0.0601, wR2 = 0.1510	
R indices (all data)	R1 = 0.0985, wR2 = 0.1753	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.730 and -0.817 $e.Å^{-3}$	

Table S4. Hydrogen bonds for mo_023SB22_0m_a.

Donor --- H....Acceptor	[ARU]	D - H	H...A	D...A	D - H...A
N(2) --H(2N) ..O(1)	[-1/2-x,-1/2+y,3/2-z]	0.89(2)	2.24(2)	3.049(2)	151(2)
N(4) --H(4N) ..O(3)	[ ]	1.03(3)	1.70(3)	2.726(2)	175(3)
N(5) --H(5) ..O(4)	[ ]	0.88	1.83	2.705(2)	176
O(9) --H(9O) ..O(2)	[-x,1-y,1-z]	0.90(3)	1.89(3)	2.759(3)	165(3)
O(10) --H(10O) ..O(3)	[ ]	0.82(8)	2.05(8)	2.861(4)	172(5)

2.3 Form B: DMF solvate (cu_023rb153_0m)

Table S5. Crystal data and structure refinement for cu_023RB153_0m.

Identification code	cu_023rb153_0m	
Empirical formula	C24 H28 N6 O3	
Formula weight	448.52	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P n	
Unit cell dimensions	a = 7.2802(5) Å	α= 90°.
	b = 12.5393(9) Å	β= 99.226(4)°.
	c = 12.7893(10) Å	γ = 90°.
Volume	1152.41(15) $Å^3$	
Z	2	
Density (calculated)	1.293 Mg/m^3	
Absorption coefficient	0.716 mm^{-1}	
F(000)	476	
Crystal size	0.862 x 0.488 x 0.305 mm^3	
Theta range for data collection	3.525 to 72.548°.	
Index ranges	-8<=h<=9, -15<=k<=15, -15<=l<=15	
Reflections collected	20741	
Independent reflections	4169 [R(int) = 0.0681]	
Completeness to theta = 67.679°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7536 and 0.5615	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4169 / 3 / 322	
Goodness-of-fit on F^2	1.023	
Final R indices [I>2sigma(I)]	R1 = 0.0465, wR2 = 0.1026	
R indices (all data)	R1 = 0.0671, wR2 = 0.1128	
Absolute structure parameter	0.2(4)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.297 and -0.292 $e.Å^{-3}$	

Table S6. Hydrogen bonds for cu_023RB153_0m [Å and °].

D-H...A			d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1) --H(1N)	..N(3)	[-1/2+x,1-y,-1/2+z]	0.88	1.84	2.723(4)	179
N(2) --H(2N)	..O(3)	[1/2+x,2-y,1/2+z]	0.88	2.02	2.857(5)	159
N(5) --H(5N)	..O(1)	[1/2+x,1-y,1/2+z]	0.88	2.43	3.300(4)	172

2.4 Form D-4: acetic acid hybrid salt-cocrystal (mo_023SB5_0m)

Table S7. Crystal data and structure refinement for mo_023SB5_0m.

Identification code	mo_023SB5_0m	
Empirical formula	C29 H37 N5 O10	
Formula weight	615.63	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 7.8386(12) Å	α= 72.782(6)°.
	b = 13.257(2) Å	β= 86.818(6)°.
	c = 15.457(3) Å	γ = 82.655(7)°.
Volume	1521.4(4) $Å^3$	
Z	2	
Density (calculated)	1.344 Mg/m^3	
Absorption coefficient	0.102 mm^{-1}	
F(000)	652	
Crystal size	0.460 x 0.072 x 0.070 mm^3	
Theta range for data collection	2.415 to 27.589°.	
Index ranges	-10<=h<=10, -17<=k<=17, -20<=l<=20	
Reflections collected	53225	
Independent reflections	7000 [R(int) = 0.1322]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7455 and 0.6771	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7000 / 0 / 409	
Goodness-of-fit on F^2	1.032	
Final R indices [I>2sigma(I)]	R1 = 0.0571, wR2 = 0.1067	
R indices (all data)	R1 = 0.1057, wR2 = 0.1225	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.277 and -0.292 $e.Å^{-3}$	

Table S8. Hydrogen bonds for mo_023SB5_0m [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1) --H(1N) ..O(7) [x,-1+y,1+z]	0.88	1.88	2.762(2)	175
N(2) --H(2N) ..O(3) [1-x,-y,1-z]	0.88	2.16	2.985(2)	156
N(4) --H(4N) ..O(10) [-x,-y,1-z]	0.91(3)	1.76(3)	2.665(2)	171(3)
O(4) --H(4O) ..O(1) [x,y,-1+z]	0.84	1.83	2.630(3)	159
N(5) --H(5N) ..O(9) [-x,-y,1-z]	0.88	2.06	2.900(2)	159
O(6) --H(6O) ..O(10) [x,1-y,1-z]	0.84	1.82	2.652(2)	170
O(8) --H(8O) ..O(9) [1+x,1+y,-1+z]	0.84	1.73	2.558(2)	167