Combined crystallographic and computational investigation of the Solvent Disorder present in a new Tipiracil hydrochloride methanol solvate - hydrate

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Electronic Supplementary Information

1. Crystal data and structure refinement

1.1 Tipiracil hydrochloride methanol solvate – hydrate (4:1:3, molar ratio)

Table S1. Crystal data and structure refinement for mo_023XB102A_0m_a.

Identification code	mo_023XB102A_0m_a	
Empirical formula	C37 H58 Cl8 N16 O12	
Formula weight	1202.59	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 7.1291(2) Å	α= 90°.
	b = 13.5358(5) Å	β= 90°.
	c = 27.2056(11) Å	γ = 90°.
Volume	2625.29(16) $Å^3$	
Z	2	
Density (calculated)	1.521 Mg/m^3	
Absorption coefficient	0.502 mm^{-1}	
F(000)	1248	
Crystal size	0.290 x 0.073 x 0.062 mm^3	
Theta range for data collection	2.704 to 33.782°.	
Index ranges	-7<=h<=11, -19<=k<=21, -42<=l<=30	
Reflections collected	29776	
Independent reflections	10351 [R(int) = 0.0317]	
Completeness to theta = 25.242°	99.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7467 and 0.6558	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10351 / 6 / 374	
Goodness-of-fit on F^2	1.048	
Final R indices [I>2sigma(I)]	R1 = 0.0498, wR2 = 0.1175	
R indices (all data)	R1 = 0.0593, wR2 = 0.1255	
Extinction coefficient	n/a	
Largest diff. peak and hole	1.507 and -0.872 $e.Å^{-3}$	

Table S2. Hydrogen bonds for Tipiracil hydrochloride methanol solvate - hydrate [Å and °]

Donor --- H....Acceptor	[ARU]	d(D – H)	d(H...A)	d(D...A)	<(D - H...A)
N1 --H1N ..Cl3	[1/2+x,1/2-y,1-z]	0.88	2.36	3.240(3)	175
N1 --H1N ..Cl3'	[1/2+x,1/2-y,1-z]	0.88	2.31	3.175(3)	167
N2 --H2N ..O3	[ ]	0.88	1.86	2.743(3)	176
O2W --H2W ..Cl3	[1+x,y,z]	0.84	1.81	2.578(7)	151
O2W --H2W ..Cl3'	[1+x,y,z]	0.84	2.49	3.236(7)	148
N4 --H4A ..O1	[1/2+x,1/2-y,1-z]	0.88	1.98	2.817(4)	159
N4 --H4B ..O2W	[ ]	0.88	1.86	2.722(6)	165
N9 --H9NA ..Cl3	[1+x,1+y,z]	0.88	2.22	3.017(5)	151

N9	--H9NA ..Cl3'	[1+x,1+y,z]	0.88	2.52	3.370(5)	162
N5	--H5N ..O1W	[ ]	0.88	1.90	2.766(3)	168
N9	--H9NB ..Cl4	[x,1+y,z]	0.88	2.30	3.155(3)	165
N6	--H6N ..Cl4	[2-x,1/2+y,3/2-z]	0.88	2.21	3.089(2)	174
O2W'	--H2A' ..Cl4	[ ]	0.79(4)	2.81(9)	3.089(6)	103(6)
O2W'	--H2A' ..N9	[x,-1+y,z]	0.79(4)	2.59(9)	3.047(8)	119(10)
O2W'	--H2B' ..Cl4	[ ]	0.80(6)	2.63(7)	3.089(6)	118(7)
O1W	--H1OA ..Cl4	[3/2-x,1-y,-1/2+z]	0.80(3)	2.44(3)	3.221(2)	165(3)
O1W	--H1OB ..O2	[ ]	0.796(17)	2.071(17)	2.855(3)	168(4)

1.2 Comparative of crystal data parameters of Tipiracil hydrochloride crystal forms

Table S3. Crystal data of Tipiracil hydrochloride crystal forms

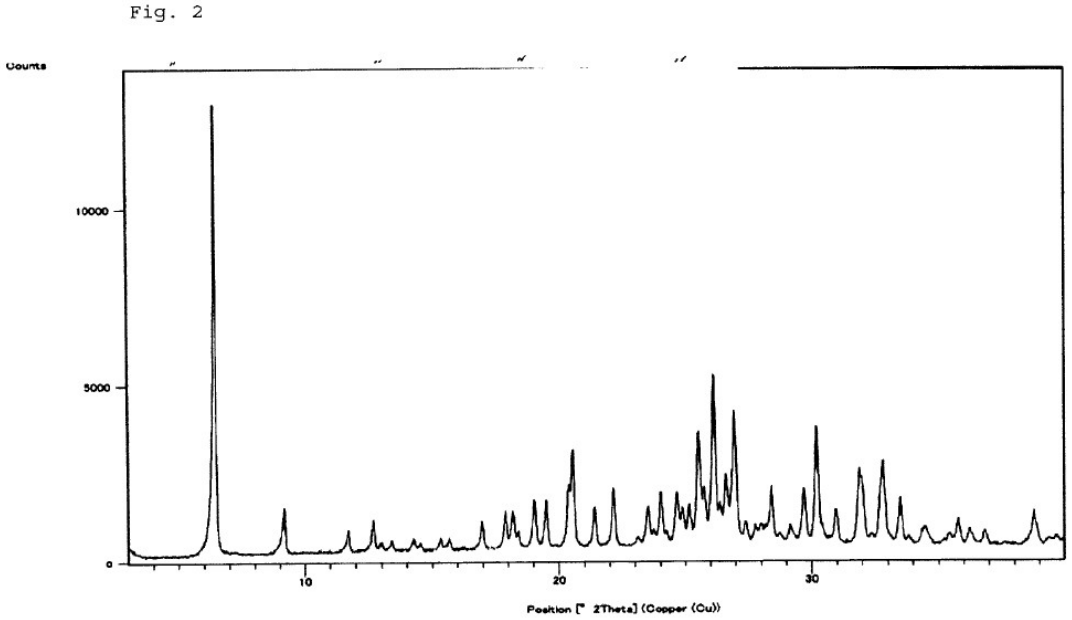
Crystal data		US 9.527.833 B2		methanol solvate – hydrate
		Crystal I	Crystal III	[4:1:3]
Temperature (K)		291	-[1]	100
Crystal system		Monoclinic	Monoclinic	Orthorhombic
Space group		$P\,2_1/n$	$P\,2_1$	$P\,2_1\,2_1\,2_1$
Unit cell dimensions	a (Å)	11.6006(9)	10.3221(14)	7.1291(2)
	b (Å)	10.3106(11)	9.8634(13)	13.5358(5)
	b (Å)	10.3036(10)	11.6643(16)	27.2056(11)
	α (°)	90	90	90
	β (°)	101.951(7)	100.317	90
	γ (°)	90	90	90
Volume (Å^3)		1205.7(2)	1169.5(3)	2625.29(16)

[1] "room temperature" is reported

1.3 Comparative XRPD of Tipiracil hydrochloride crystal II and methanol solvate – hydrate

Figure S1: (a) XRPD diffractogram of crystal II reported in patent US 9.527.833 B2 and (b) bulk powder of Tipiracil hydrochloride methanol solvate - hydrate

(a)



(b)

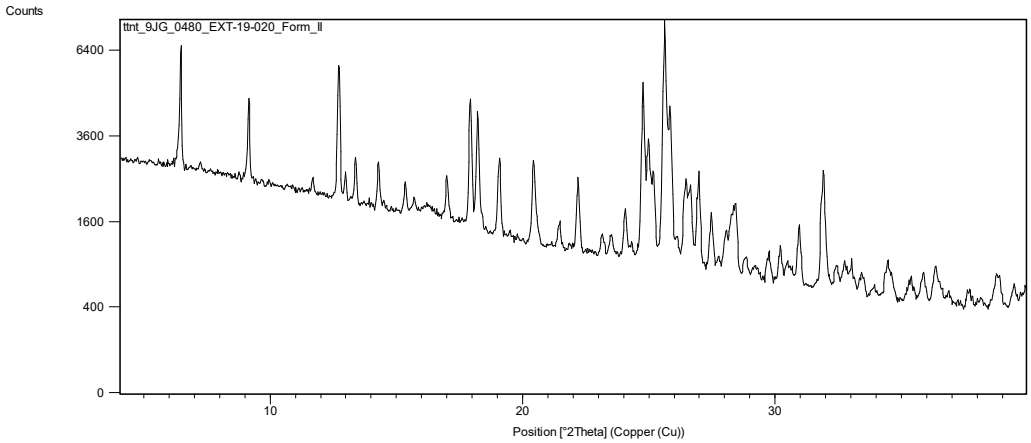


Table S4. 2θ peaks of Tipiracil hydrochloride crystal II and methanol solvate – hydrate at 298K

Tipiracil hydrochloride	**2θ peaks**					
Crystal II	6.5	20.6	25.5	26.1	27.0	30.2
methanol solvate – hydrate	6.5	20.6	25.6	26.1	27.0	30.2

2.- Characterization of the Tipiracil hydrochloride methanol solvate – hydrate crystal form

Powder X-ray Diffraction Analysis: the powder diffractogram was indexed and the lattice parameters were refined by means of LeBail fits by means of Dicvol04,[1] and the space groups was determined from the systematic absences.

Figure S2: The XRPD of Tipiracil hydrochloride methanol solvate - hydrate has been indexed with the following proposed orthorhombic cell: a=27.27(7) Å, b=13.613(2) Å, c=7.1818(8) Å, V=2666.5(9) Å ^{3} (Figures of Merit: M= 35, F= 84), with number of impurities equal to zero. A *P* $2_12_12_1$ space group is compatible with the cell and the cell volume is compatible with 4 molecules of Tipiracil hydrochloride, 1 molecule of methanol and 3 molecules of water. (R_{wp}: 3.17; R_{exp}: 2.40), Z=2

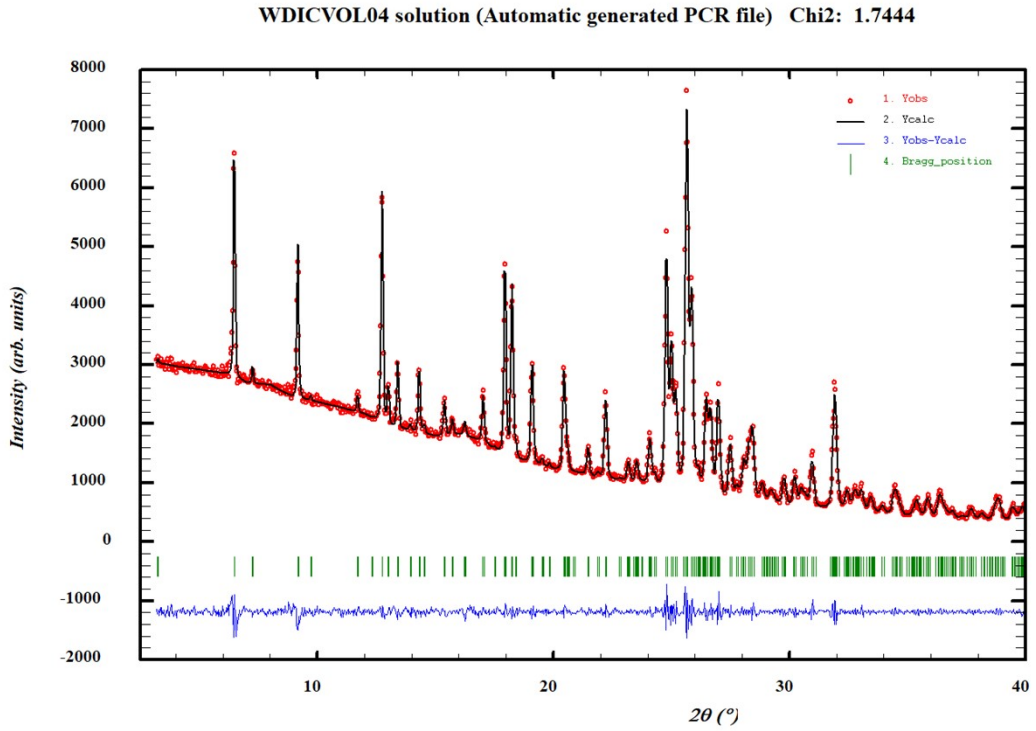


Figure S3: The structure was determined by single crystal X-ray diffraction at 100K showing a 4:1:3 (Tipiracil hydrochloride: methanol: water) molar ratio with the following orthorhombic cell: a=7.1291(2) Å, b=13.5358(5) Å, c=27.2056(11) Å, V=2625.29(12) Å^3, Z=2 and *P* 2_1 2_1 2_1 space group. (R_{int} (%)= 3.17; R-Factor (%) = 5.10). Comparative XRPD diffractograms between bulk Tipiracil hydrochloride methanol solvate - hydrate and simulated from the cif is shown

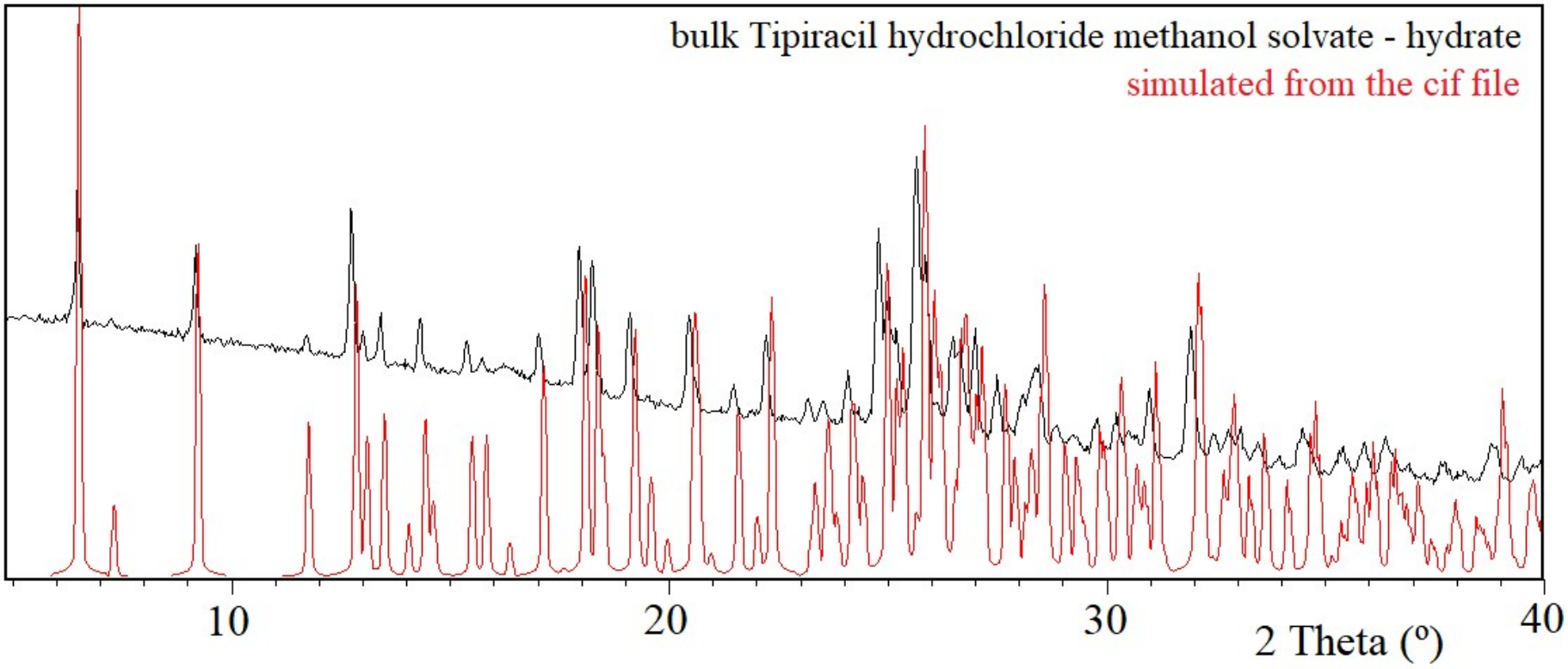


Figure S4: DSC of Tipiracil hydrochloride methanol solvate – hydrate. Differential scanning calorimetry analysis was carried out by means of a Mettler-Toledo DSC-822e calorimeter. Experimental conditions: aluminium crucibles of 40 µL volume, atmosphere of dry nitrogen with 50 mL/min flow rate, heating rate of 10 ºC/min. The calorimeter was calibrated with indium of 99.99% purity (mp: 156.6 °C; ΔH: 28.31 J/g).

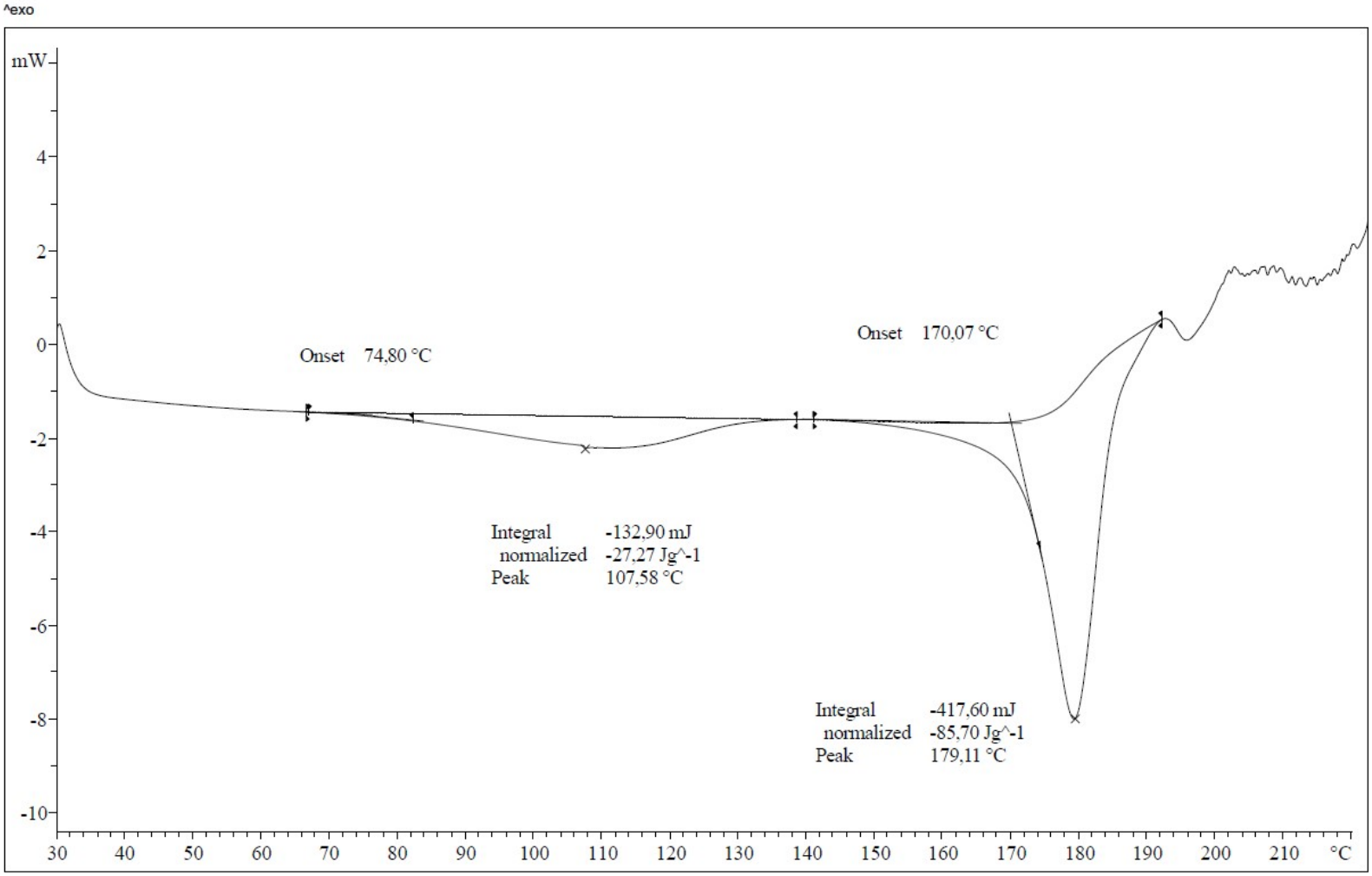


Figure S5: TGA of Tipiracil hydrochloride methanol solvate - hydrate

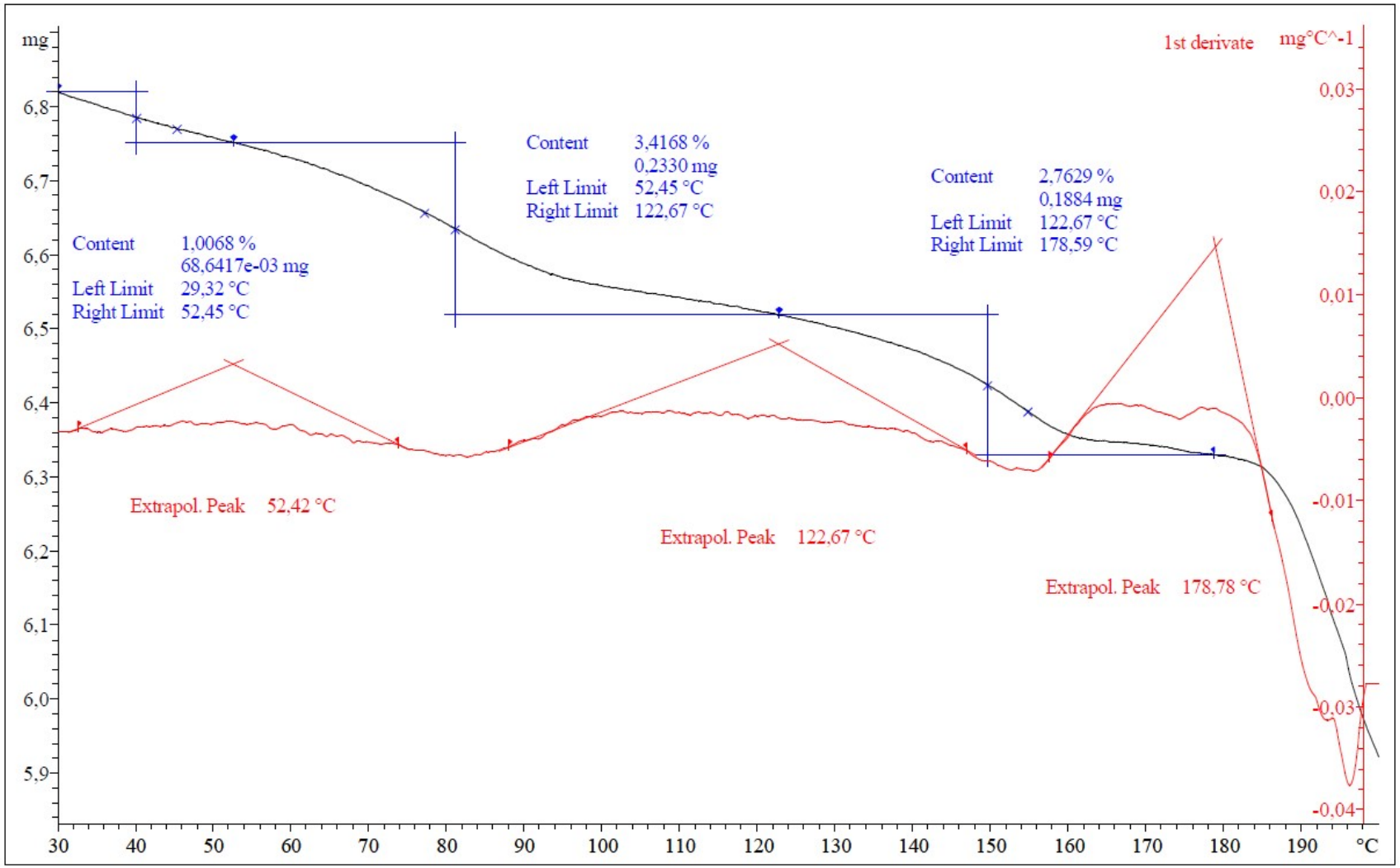
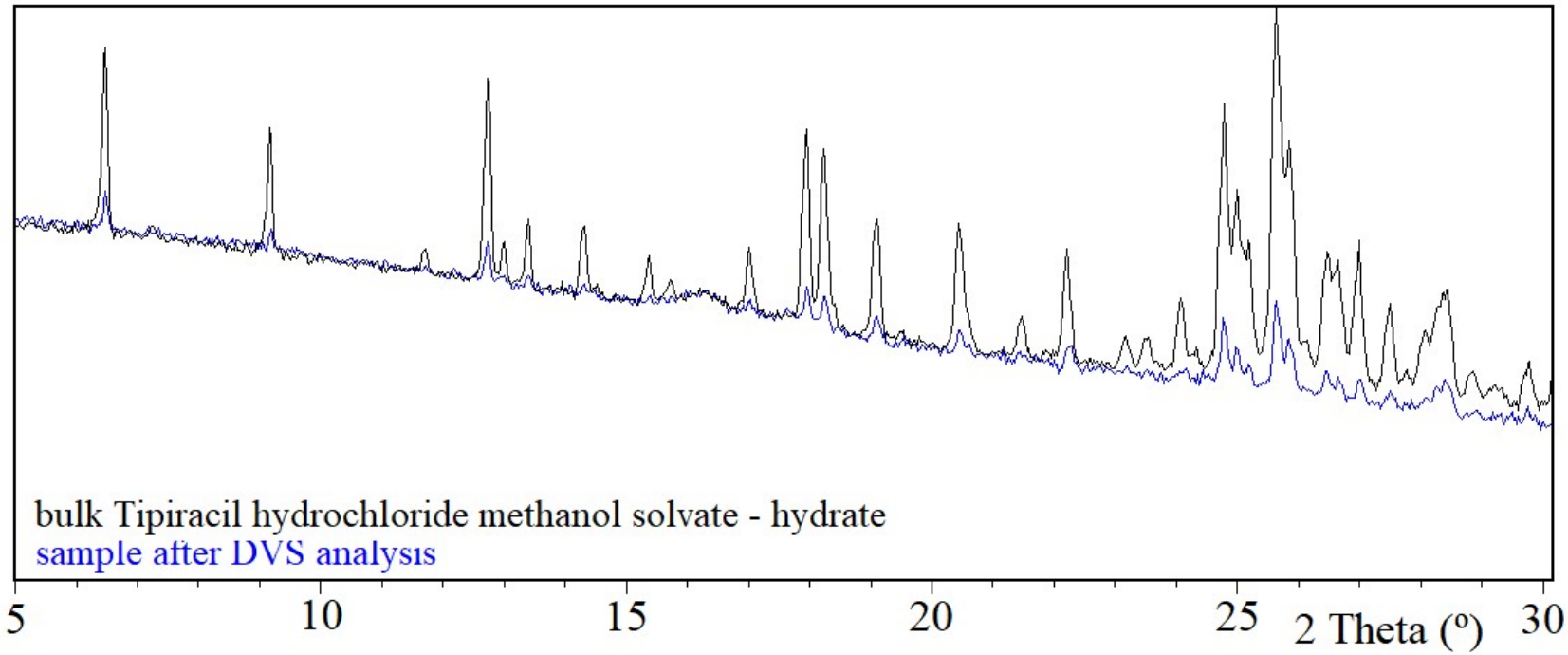


Figure S6: XRPD diffractograms of bulk Tipiracil hydrochloride methanol solvate - hydrate and the resulting solid after DVS analysis. Enlargement from 5 to 30º 2θ.



3. References

[1] Boultif, A.; Louër, D. Indexing of powder diffraction patterns for low-symmetry lattices by the successive dichotomy method *J. Appl. Crystallogr*. 1991, **24**, 987-993.