New Salt-solvates of Mirabegron: a combined experimental and computational study

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Electronic Supplementary Information

Table of contents:

1. Experimental: materials and methods

1.1 Materials

Mirabegron forms α was used as received by Interquim, S. A. (CCDC refcode: HOCHAM).

The following 8 coformers have been used: orotic acid, L-arginine, camphoric acid, sorbic acid, glycine, isobutyric acid, L-lysine, and L-leucine. The coformers where purchased from Sigma-Aldrich.

1.2. Solubility qualitative determination of mirabegron form α

The solvents selected to be used in the solid form screening are highlighted in black.
Mirabegron (form α) was dissolved in 28 solvents in a temperature range of 25-90 ºC. Mirabegron is soluble at 25 ºC in the following solvents: methanol (0,2 mL), **ethanol** (1,0 mL), ethylene glycol (0,4 mL), DMF (0,2 mL), DMSO (0,2 mL), **THF** (0,6 mL), **dimethyl ethylene glycol** (2,0 mL), **dioxane** (2,0 mL), **benzyl alcohol** (0,2 mL), and diethylamine (1,5 mL). At 50 ºC it is soluble in **IPA** (2,0 mL), butanol (2,0 mL), MEK (2,0 mL), and **acetone** (2,0 mL). At 70 ºC it is soluble in **ACN** (2,0 mL), **AcOEt** (2,0 mL), and **chloroform** (2,0 mL). At 90 ºC it is soluble in MiBK (2,0 mL). It is insoluble in **water**, pentane, heptane, cyclohexane, toluene, xylene and diethyl ether, diisopropyl ether, dichloromethane (0.05 mL), and NH_3 (32 %) in water.

Table S1. Solid form screening of Mirabegron

Methodology	Coformers	Nº Experiments	Nº Solids	Positive results[a]	Coformers	Form obtained (according to PXRD)
Solubility Study	-	28	20	2	-	-
Liquid assisted grinding at 25 ºC	8	53	46	1	1	1 new evidence
Reaction Crystallization at 25 ºC	1	4	4	2	1	Mirabegron orotic acid isopropanol solvate salt Mirabegron orotic acid acetonitrile solvate salt Mirabegron orotic acid dioxane solvate salt Mirabegron orotic acid hydrate salt
Solvent mediated transformation at 25 ºC	1	8	3	2	1	Mirabegron isobutyric acid salt Mirabegron isobutyric acid THF solvate salt
Solution crystallization at different temperatures	2	17	8	3	2	Mirabegron orotic acid isopropanol solvate salt Mirabegron orotic acid acetone solvate salt Mirabegron isobutyric acid acetonitrile solvate salt

[a] (1) positive: Mirabegron + coformer + new peaks observed in PXRD, (2) positive: new solid form, (3) positive: single crystal

2. Synthesis of Mirabegron salts

Synthesis of the new multicomponent forms of Mirabegron were conducted by solvent mediated transformation (SMT), reaction crystallization (RC) or solution crystallization methodologies. Stoichiometry has been assessed based on NMR and TGA measurements when the crystal structure was not available. Details of synthesis of the bulk powder and single crystal are as follows:

2.1 Mirabegron orotic acid isopropanol solvate salt (1:1:0.5) (polymorph I). It was obtained by reaction crystallization in IPA. Its stoichiometry has been deduced according to according to ^{1}H-NMR and TGA.

2.2 Mirabegron orotic acid isopropanol solvate salt (1:1:0.5) (polymorph II). It was obtained by solution crystallization in IPA/H_2O. Its stoichiometry has been deduced according to single crystal X-ray diffraction.

2.3 Mirabegron orotic acid acetonitrile solvate salt (1:1:0.25). It was obtained by reaction crystallization in acetonitrile. Its stoichiometry has been deduced according to ^{1}H-NMR and TGA.

2.4 Mirabegron orotic acid dioxane solvate salt (1:1:1). It was obtained by reaction crystallization in dioxane. Its stoichiometry has been deduced according to ^{1}H-NMR and TGA.

2.5 Mirabegron orotic acid hydrate salt (1:1.5:1.5). It was obtained by solvent mediated transformation in water. Its stoichiometry has been deduced according to ^{1}H-NMR and TGA.

2.6 Mirabegron orotic acid acetone solvate salt (1:1:1). It was obtained by solution crystallization in acetone. Its stoichiometry has been deduced according to single crystal X-ray diffraction.

2.7 Mirabegron isobutyric acid salt (1:1). It was obtained by solvent mediated transformation in acetonitrile. Its stoichiometry has been deduced according to ^{1}H-NMR.

2.8 Mirabegron isobutyric acid THF solvate salt (1:1:0.5). It was obtained by solvent mediated transformation in THF. Its stoichiometry has been deduced according to ^{1}H-NMR.

2.9 Mirabegron isobutyric acid acetonitrile solvate salt (1:1:1). It was obtained by solution crystallization in acetonitrilie. Its stoichiometry has been deduced according to single crystal X-ray diffraction.

PXRD patterns of the new mirabegron multicomponent forms are shown in Figure S1 and S2.

Figure S1: PXRD diagrams of mirabegron orotic acid isopropanol solvate salt (1:1:0.5) (polymorph I, black), mirabegron orotic acid isopropanol solvate salt (1:1:0.5) simulated from cif file (polymorph II, red), mirabegron orotic acid acetonitrile solvate salt (1:1:0.25) (blue), mirabegron orotic acid dioxane solvate salt (1:1:1) (green), mirabegron orotic acid hydrate salt (1:1.5:1.5) (brown), and mirabegron orotic acid acetone solvate salt (1:1:1) simulated from cif file (purple).

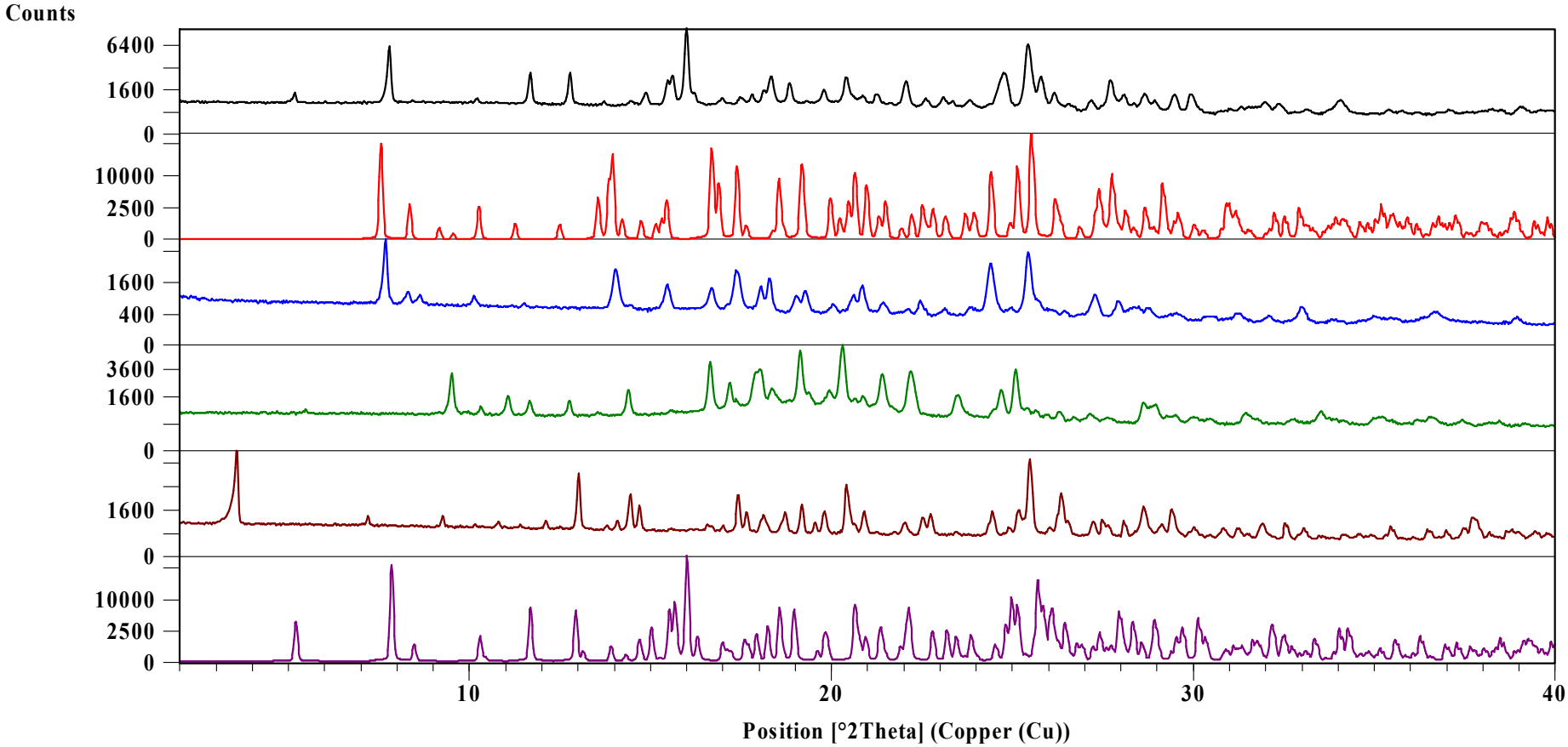
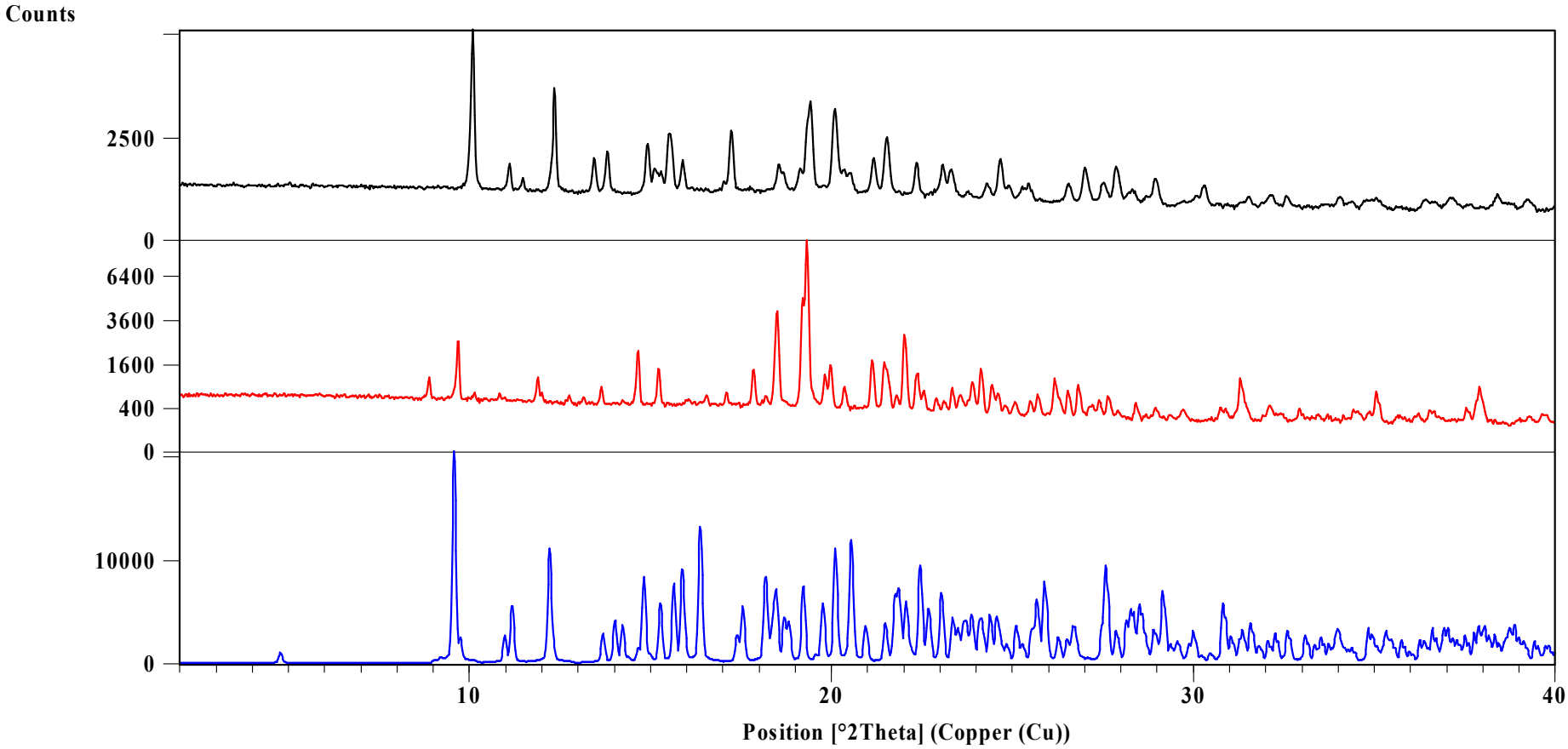


Figure S2: PXRD diagrams of mirabegron isobutyric acid salt (1:1) (black), mirabegron isobutyric acid THF solvate salt (1:1:0.5) (red), and mirabegron isobutyric acid acetonitrile solvate salt (1:1:1) simulated from cif file (blue).



3. Crystal data and structure refinement

3.1 Mirabegron orotic acid isopropanol solvate salt (1:1:0.5) (mo_023SB77_0m)

Table S2. Crystal data and structure refinement for mo_023SB77_0m.

Identification code	mo_023SB77_0m
Empirical formula	$C_{55}H_{64}N_{12}O_{13}S_2$
Formula weight	1165.30
Temperature/K	100.00
Crystal system	triclinic
Space group	P-1
a/Å	7.0067(9)
b/Å	11.6243(15)
c/Å	17.481(2)
α/°	100.627(5)
β/°	97.557(5)
γ/°	98.458(5)
Volume/Å^3	1365.6(3)
Z	1
ρ_{calc}g/cm^3	1.417
μ/mm^{-1}	0.175
F(000)	614.0
Crystal size/mm^3	? × ? × ?
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.744 to 56.746
Index ranges	-9 ≤ h ≤ 9, -15 ≤ k ≤ 15, -23 ≤ l ≤ 23
Reflections collected	56404
Independent reflections	6797 [R_{int} = 0.0545, R_{sigma} = 0.0265]
Data/restraints/parameters	6797/190/451
Goodness-of-fit on F^2	1.326
Final R indexes [I>=2σ (I)]	R_1 = 0.0938, wR_2 = 0.2138
Final R indexes [all data]	R_1 = 0.0980, wR_2 = 0.2155
Largest diff. peak/hole / e Å^{-3}	0.62/-0.54

Figure S3: Ellipsoid representation (50 % probability) for mo_023SB77_0m

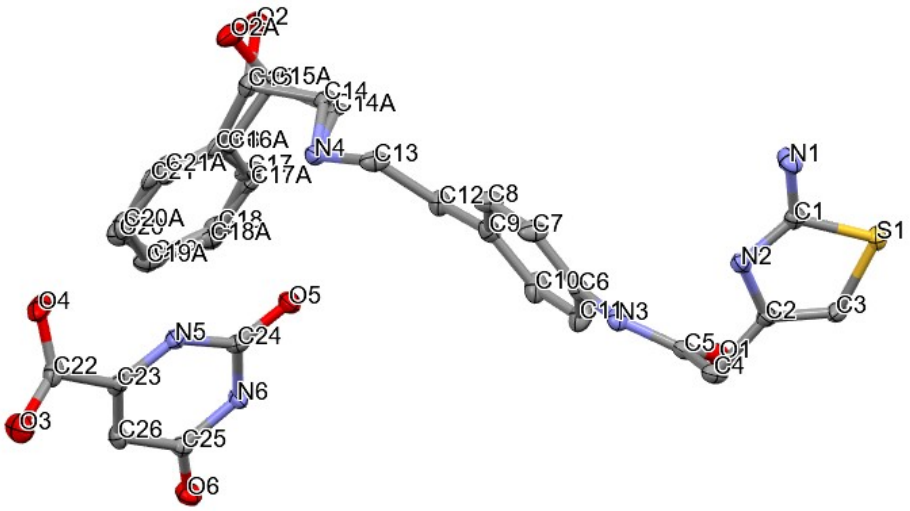


Table S4. Hydrogen Bonds for mo_023SB77_0m.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
N1	H1A	O5[1]	0.88	2.08	2.934(5)	162.1
N1	H1B	O1[2]	0.88	2.20	2.942(5)	141.4
N3	H3	O6[1]	0.88	1.93	2.803(4)	173.0
N4	H4A	O5	0.91	2.02	2.926(4)	175.6
N4	H4B	O3[3]	0.91	1.82	2.693(4)	160.3
N5	H5	O4[3]	0.88	1.95	2.805(4)	163.9
N6	H6	N2[4]	0.89(5)	2.15(5)	3.034(5)	173(4)
O2	H2	O4[5]	0.82	2.02	2.815(7)	162.9
C13	H13A	O2[6]	0.99	2.27	2.996(7)	128.8
C26	H26	O7[7]	0.95	2.52	3.16(2)	125.0
O7	H7A	O3[8]	0.84	2.23	2.85(2)	130.6

[1]-1+X,-1+Y,+Z; [2]-1-X,-1-Y,-Z; [3]1-X,1-Y,1-Z; [4]1+X,1+Y,+Z; [5]2-X,1-Y,1-Z; [6]1+X,+Y,+Z; [7]+X,1+Y,+Z; [8]+X,-1+Y,+Z

3.2 Mirabegron orotic acid acetone solvate salt (1:1:1) (mo_023SB90_0ma_ba)

Table S5. Crystal data and structure refinement for mo_023SB90_0ma_ba.

Identification code	mo_023SB90_0ma_ba
Empirical formula	$C_{29}H_{34}N_6O_7S$
Formula weight	610.68
Temperature/K	100
Crystal system	triclinic
Space group	P-1
a/Å	10.6139(6)
b/Å	13.0164(11)
c/Å	13.2023(8)
α/°	111.948(3)
β/°	95.785(2)
γ/°	114.007(2)
Volume/Å^3	1474.99(18)
Z	2
ρ_{calc}g/cm^3	1.375
μ/mm^{-1}	0.167
F(000)	644.0
Crystal size/mm^3	0.610 × 0.420 × 0.300
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.402 to 56.738
Index ranges	-14 ≤ h ≤ 14, -17 ≤ k ≤ 17, -17 ≤ l ≤ 17
Reflections collected	7375
Independent reflections	7375 [R_{int} = 0.0364, R_{sigma} = 0.0193]
Data/restraints/parameters	7375/1/409
Goodness-of-fit on F^2	1.272
Final R indexes [I>=2σ (I)]	R_1 = 0.0680, wR_2 = 0.1561
Final R indexes [all data]	R_1 = 0.0722, wR_2 = 0.1579
Largest diff. peak/hole / e Å^{-3}	0.51/-0.45

Figure S4: Ellipsoid representation (50 % probability) for mo_023SB90_0ma_ba

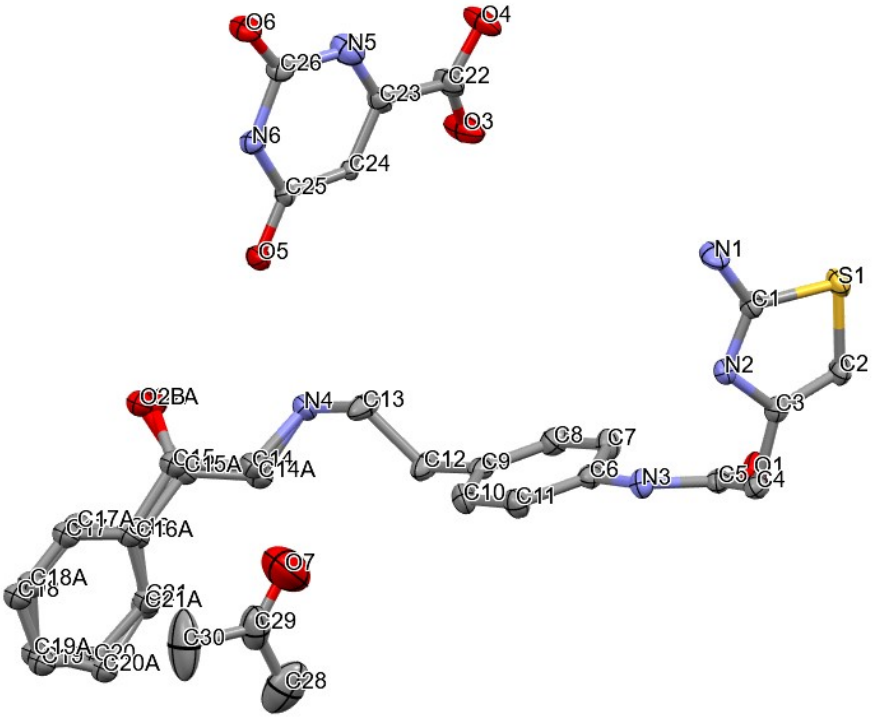


Table S6 Hydrogen Bonds for mo_023SB90_0ma_ba.ins.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
N1	H1A	O5[1]	0.88	1.99	2.865(3)	173.0
N3	H3	O6[1]	0.88	2.00	2.865(3)	168.5
N4	H4A	O5[2]	0.99	1.97	2.875(3)	151.3
N4	H4B	O4[3]	0.97	1.85	2.817(3)	172.4
O2A	H2A	O4[4]	0.93	1.83	2.753(3)	168.2
N6	H6	N2[1]	0.88	2.11	2.979(3)	167.2
C24	H24	O3[5]	0.95	1.95	2.874(3)	163.5

[1]1-X,1-Y,1-Z; [2]-1+X,-1+Y,+Z; [3]1-X,1-Y,-Z; [4]+X,-1+Y,+Z; [5]2-X,2-Y,-Z

3.3 Mirabegron isobutyric acid acetonitrile solvate salt (1:1:1) (mo_023sb84_0m_ba)

Table S7. Crystal data and structure refinement for mo_023sb84_0m_ba.

Identification code	mo_023sb84_0m_ba
Empirical formula	$C_{27}H_{35}N_5O_4S$
Formula weight	525.66
Temperature/K	100
Crystal system	triclinic
Space group	P-1
a/Å	7.9585(6)
b/Å	9.7595(8)
c/Å	18.6559(16)
α/°	81.610(4)
β/°	88.461(4)
γ/°	83.493(3)
Volume/Å^3	1424.2(2)
Z	2
ρ_{calc}g/cm^3	1.226
μ/mm^{-1}	0.153
F(000)	560.0
Crystal size/mm^3	0.313 × 0.187 × 0.101
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.244 to 56.642
Index ranges	-10 ≤ h ≤ 10, -13 ≤ k ≤ 13, -24 ≤ l ≤ 24
Reflections collected	7062
Independent reflections	7062 [R_{int} = 0.0616, R_{sigma} = 0.0326]
Data/restraints/parameters	7062/3/394
Goodness-of-fit on F^2	1.249
Final R indexes [I>=2σ (I)]	R_1 = 0.0773, wR_2 = 0.1697
Final R indexes [all data]	R_1 = 0.0909, wR_2 = 0.1741
Largest diff. peak/hole / e Å^{-3}	0.30/-0.32

Figure S5: Ellipsoid representation (50 % probability) for mo_023sb84_0m_ba

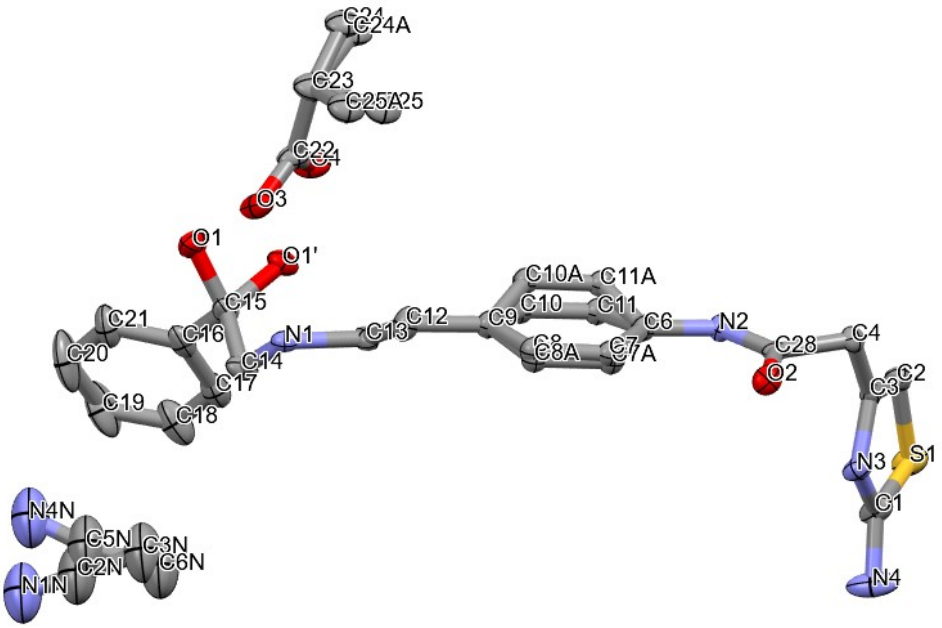


Table S8 Hydrogen Bonds for mo_023sb84_0m_ba.ins.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
O1	H1	O4	0.907(9)	1.908(9)	2.807(5)	171(6)
O1'	H1'	O4	1.03(8)	1.61(8)	2.617(5)	167(7)
N1	H1A	O3	0.91	1.86	2.740(3)	162.0
N1	H1B	N3[1]	0.91	1.95	2.841(3)	166.6
N2	H2	O4[2]	0.88	1.94	2.810(3)	170.0
N4	H4A	O3[1]	0.88	2.07	2.932(4)	167.7
N4	H4B	O2[3]	0.88	1.97	2.805(4)	156.9
C13	H13B	O2[1]	0.99	2.43	3.104(4)	125.1

[1]1-X,1-Y,-Z; [2]1-X,2-Y,-Z; [3]-1+X,+Y,+Z

Table S9. π···π interactions

Structure	$d_{centroid-centroid}$ (Å)
mo_023SB77 (mirabegron:orotic acid ipOH solvate)	3.481 / 3.579
mo_023SB90 (mirabegron:orotic acid acetone solvate)	3.659
mo_023sb84 (mirabegron: isobutyric acid acetonitrile solvate)	4.482

4.- Characterization of the solid forms

4.1.- Differential Scanning Calorimetry (DSC).

Differential scanning calorimetry analysis was carried out by means of a Mettler-Toledo DSC-822e calorimeter. Experimental conditions: aluminum crucibles of 40 µL volume, atmosphere of dry nitrogen with 50 mL/min flow rate, heating rate of 10 °C/min. The calorimeter was calibrated with indium of 99.99% purity (mp 156.6°C, ΔH = 28.47 J/g).

4.2- Thermogravimetric Analysis (TGA).

Thermogravimetric analysis was performed on a Mettler-Toledo TGA-851e thermobalance. Experimental conditions: alumina crucibles of 70 µL volume, atmosphere of dry nitrogen with 50 mL/min flow rate, heating rate of 10 °C/min.

4.3.- Nuclear Magnetic Resonance (NMR).

Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian Mercury 400 instrument (400 MHz). Chemical shifts for protons are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to residual protons in the NMR solvents (dmso-d_6, δ 2.50; acetone-d6, δ 2.05; chloroform-d, δ 7.26). Experimental conditions, delay, 1 s; pulse, 45°; scans, 32.

Figure S6: DSC of Mirabegron orotic acid isopropanol solvate salt (1:1:0.5)

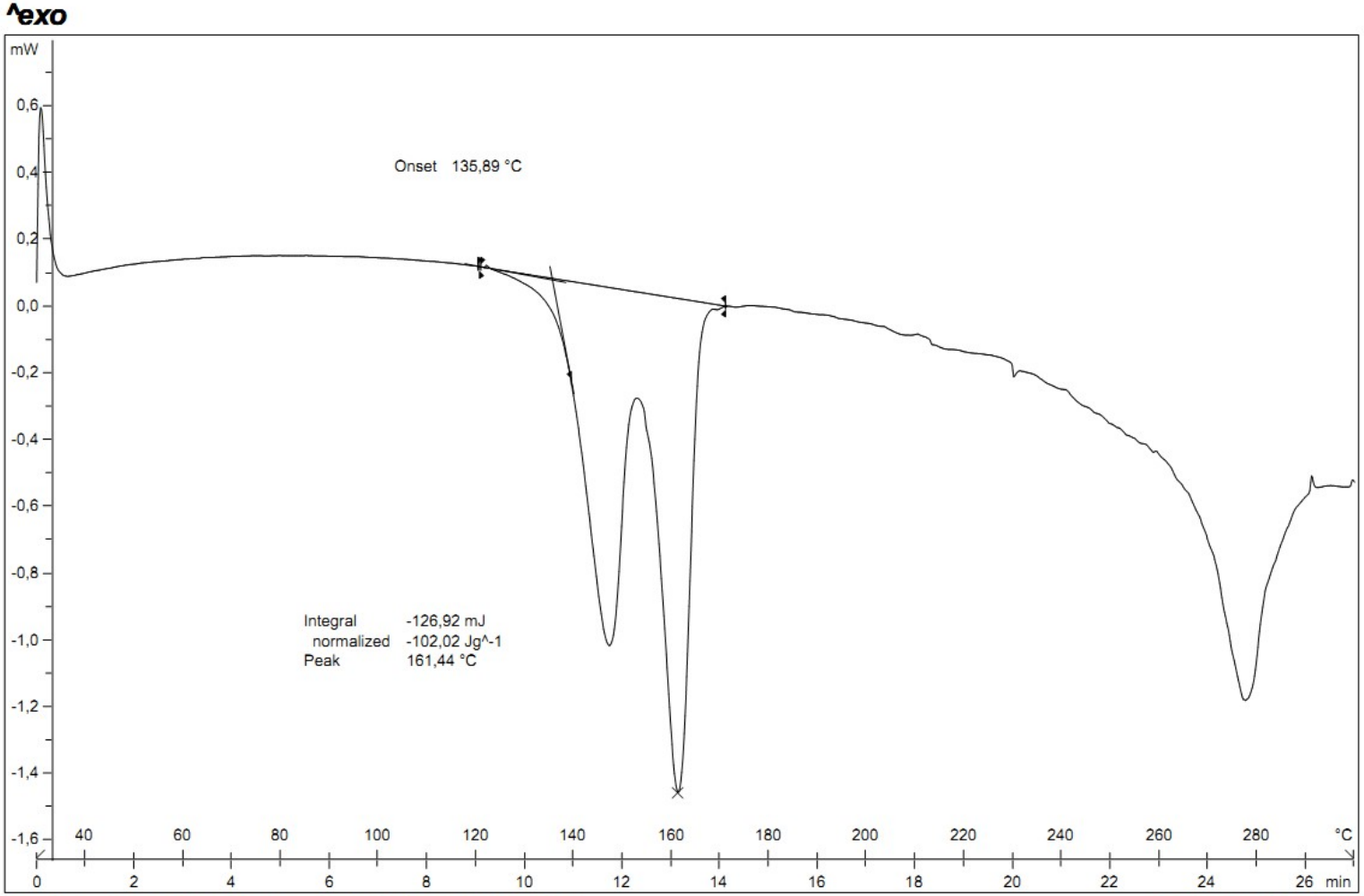


Figure S7: TGA of Mirabegron orotic acid isopropanol solvate salt (1:1:0.5)

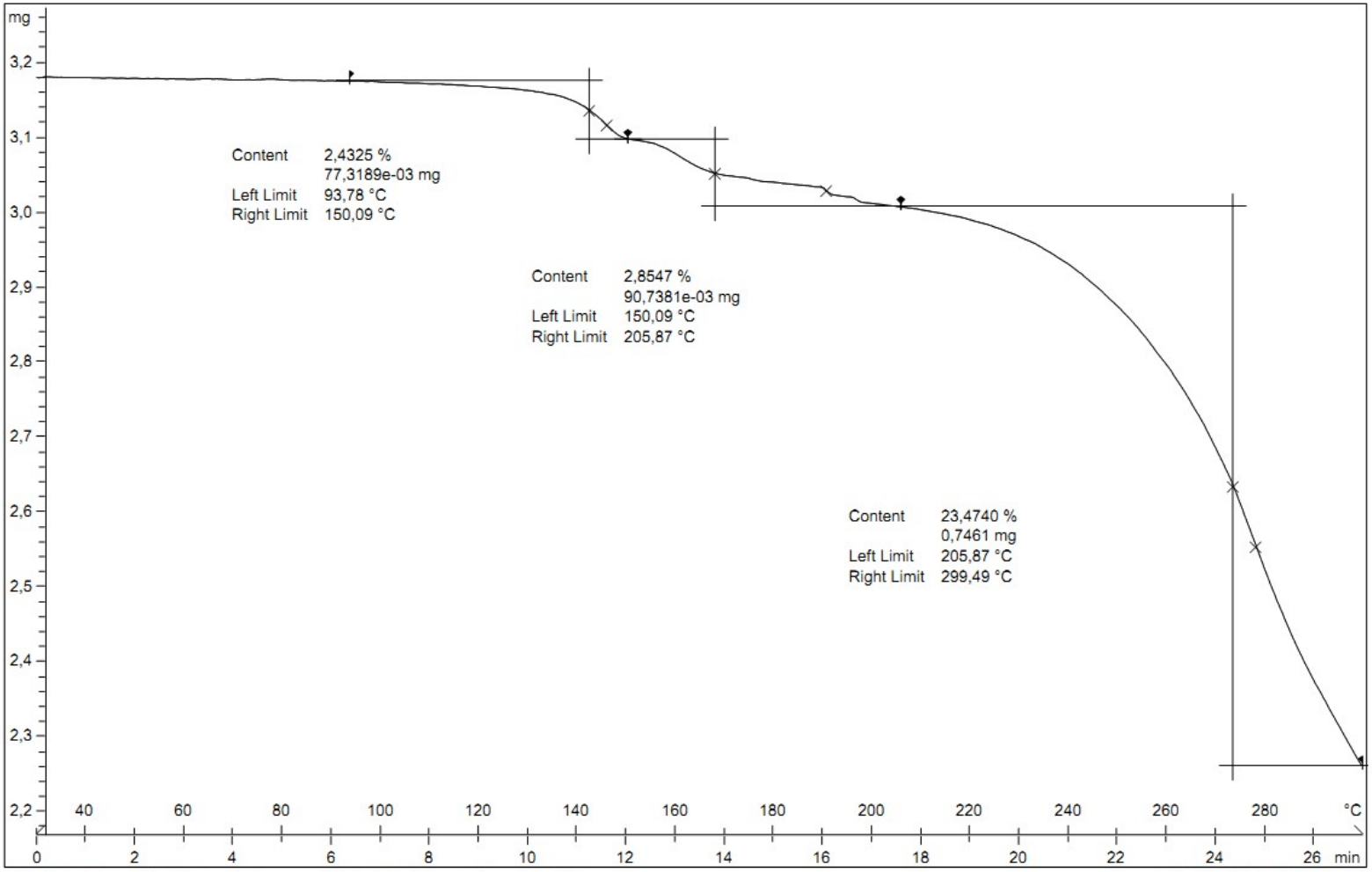


Figure S8: ^{1}H-NMR (dmso-d_6: delay: 1s/ pulse: 45°/ scans: 32) of Mirabegron orotic acid isopropanol solvate salt (1:1:0.5)

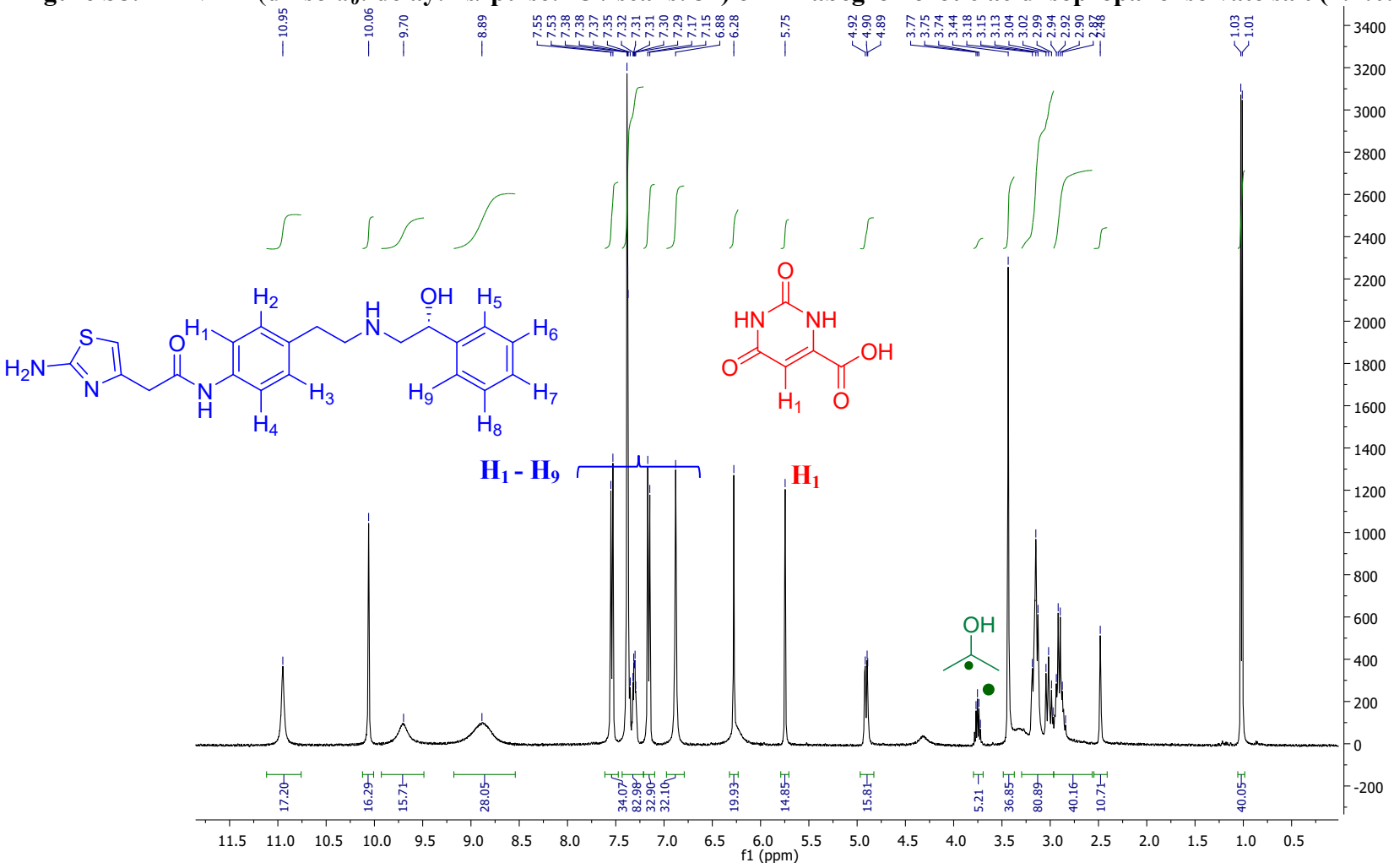


Figure S9: DSC of Mirabegron orotic acid acetonitrile solvate salt (1:1:0.25)

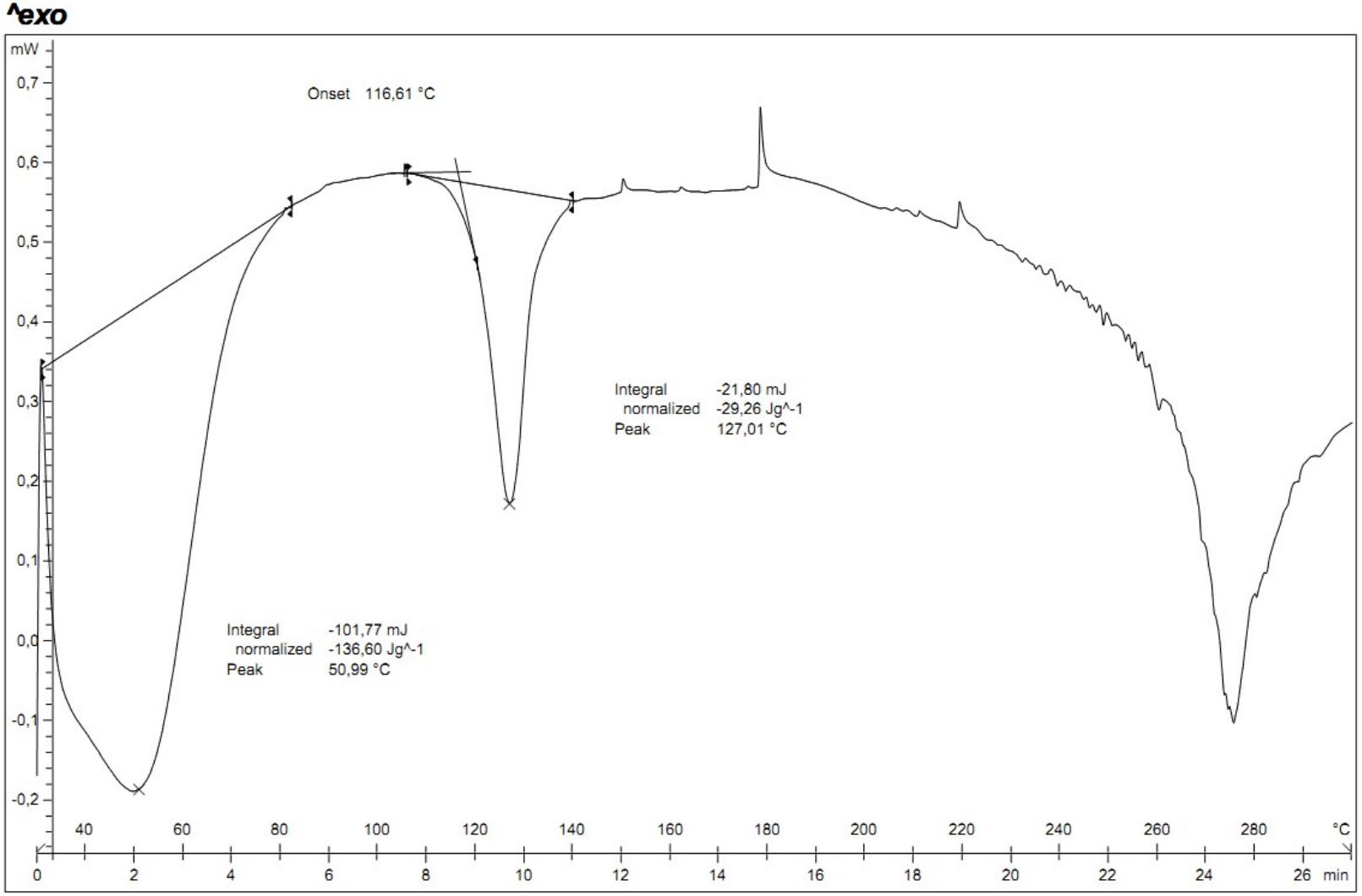


Figure S10: TGA of Mirabegron orotic acid acetonitrile solvate salt (1:1:0.25).

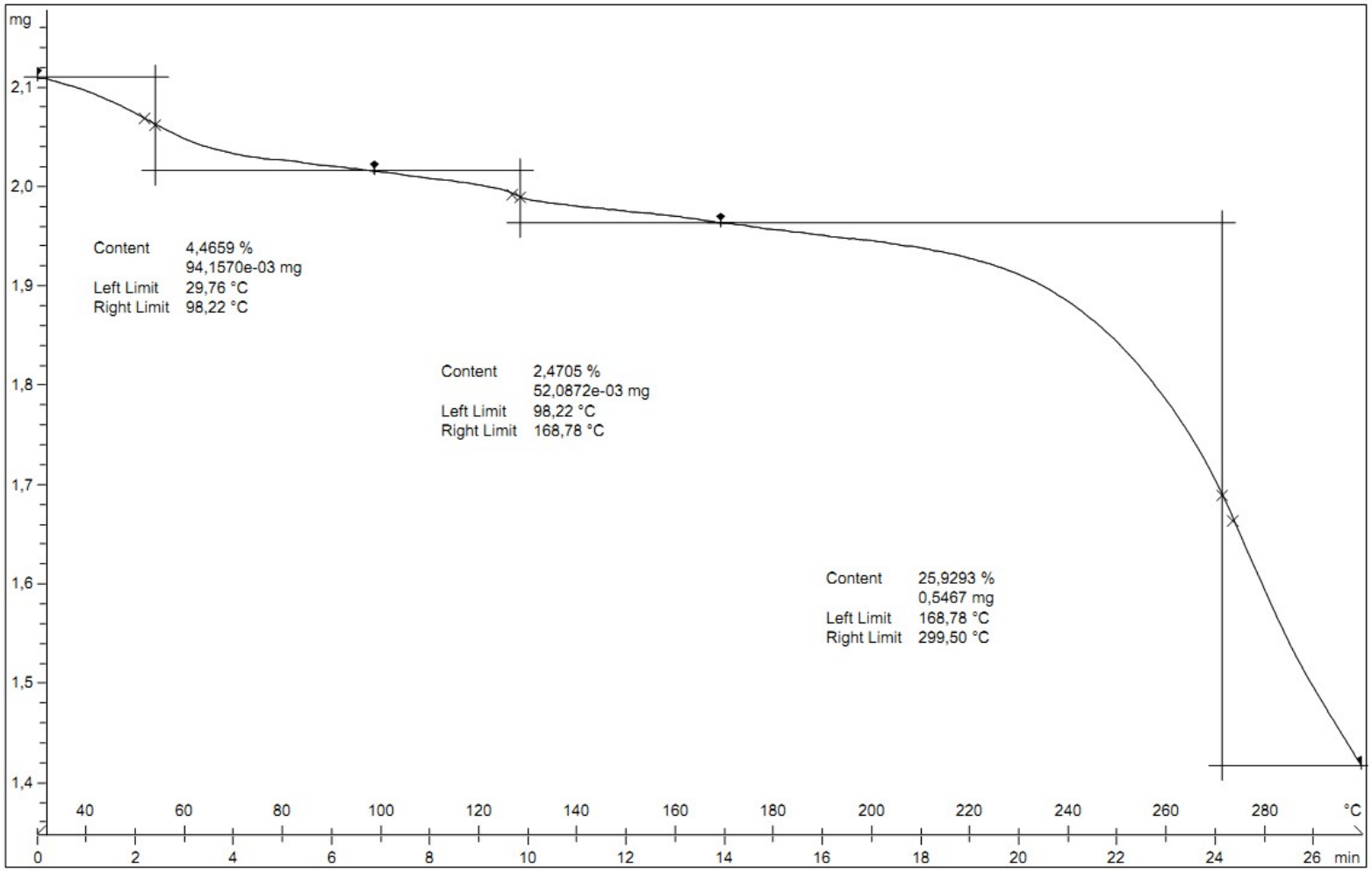


Figure S11: ^{1}H-NMR (dmso-d_6: delay: 1s/ pulse: 45°/ scans: 32) of Mirabegron orotic acid acetonitrile solvate salt (1:1:0.25).

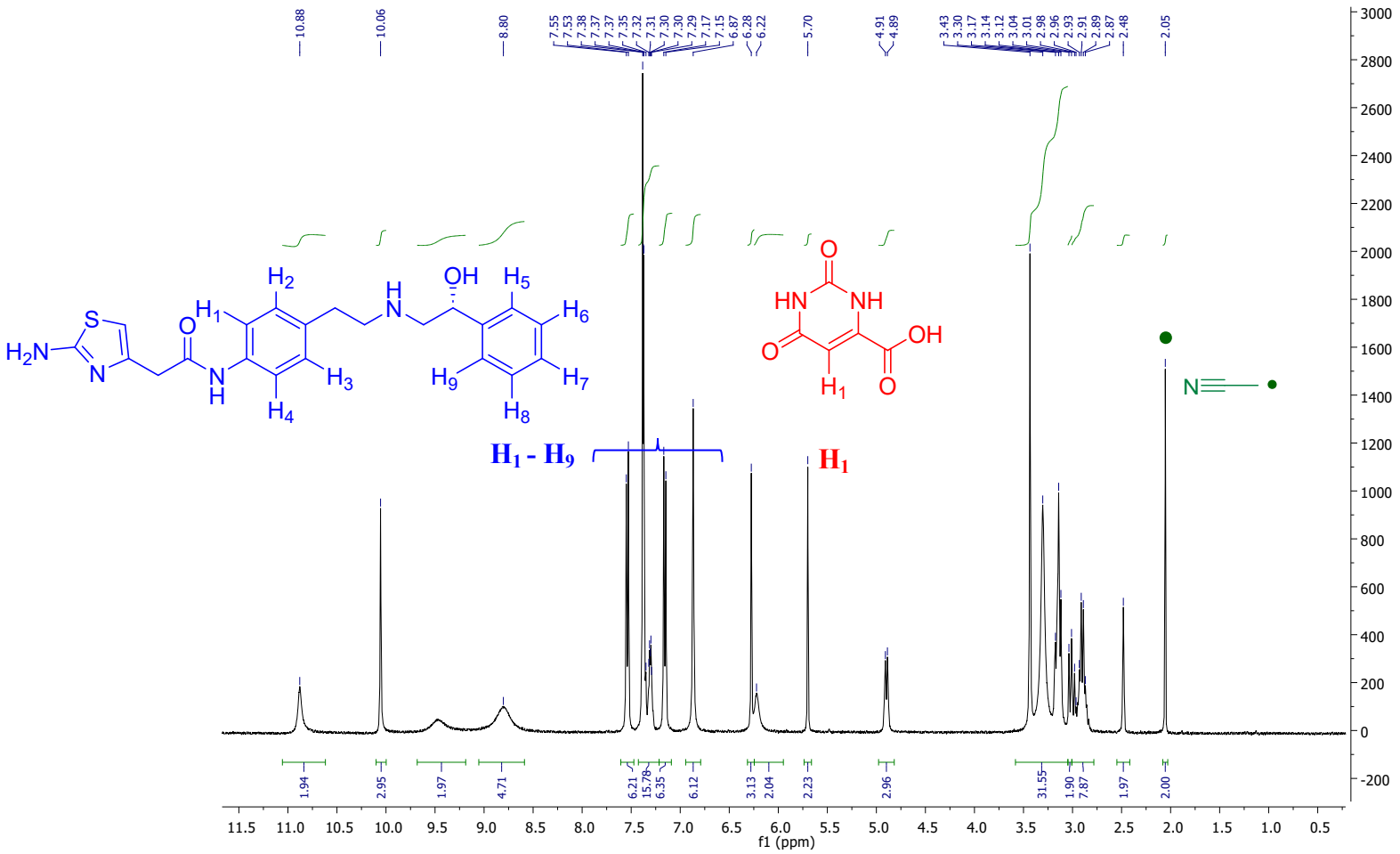


Figure S12: DSC of Mirabegron orotic acid dioxane solvate salt (1:1:1)

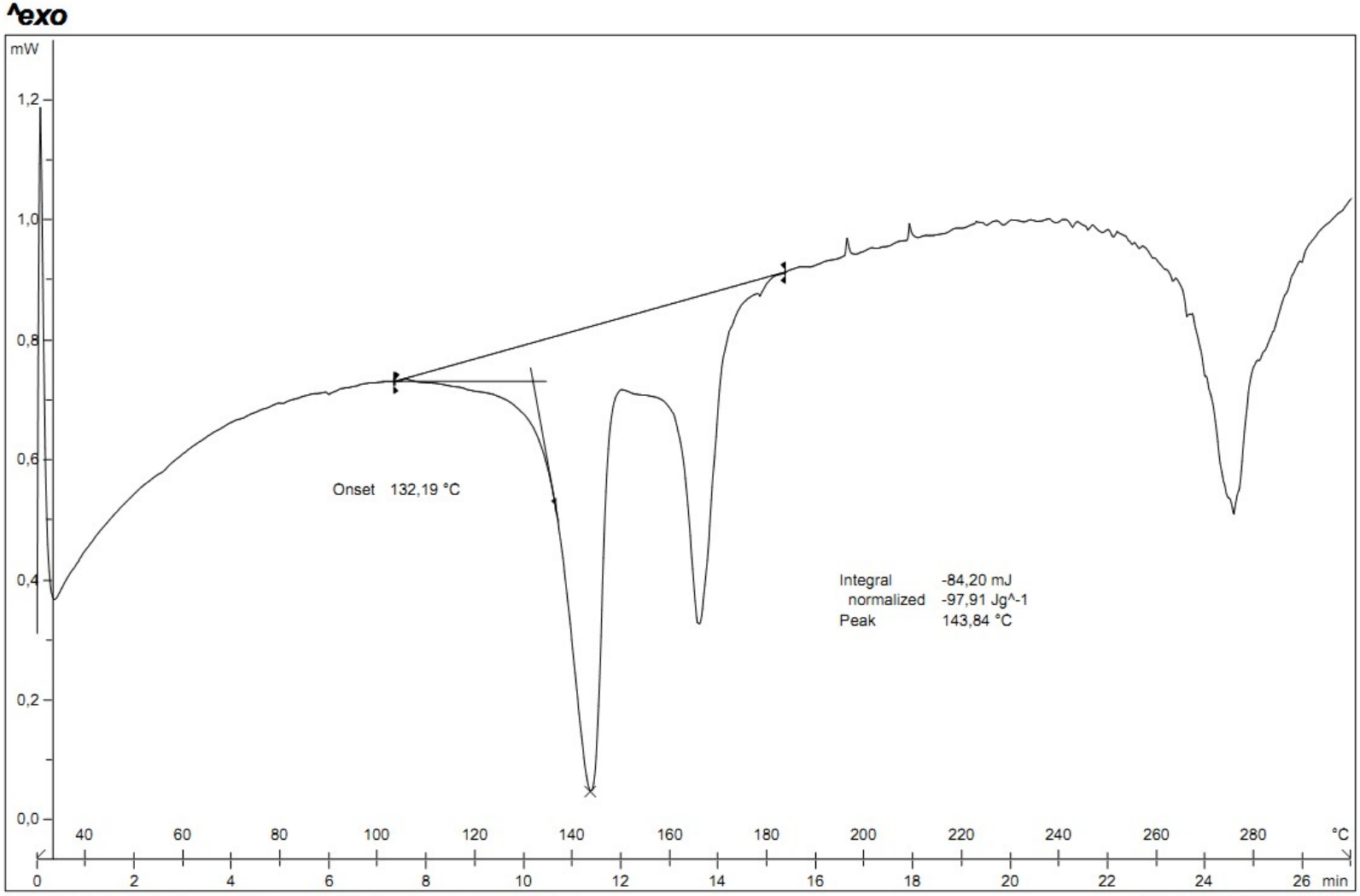


Figure S13: TGA of Mirabegron orotic acid dioxane solvate salt (1:1:1)

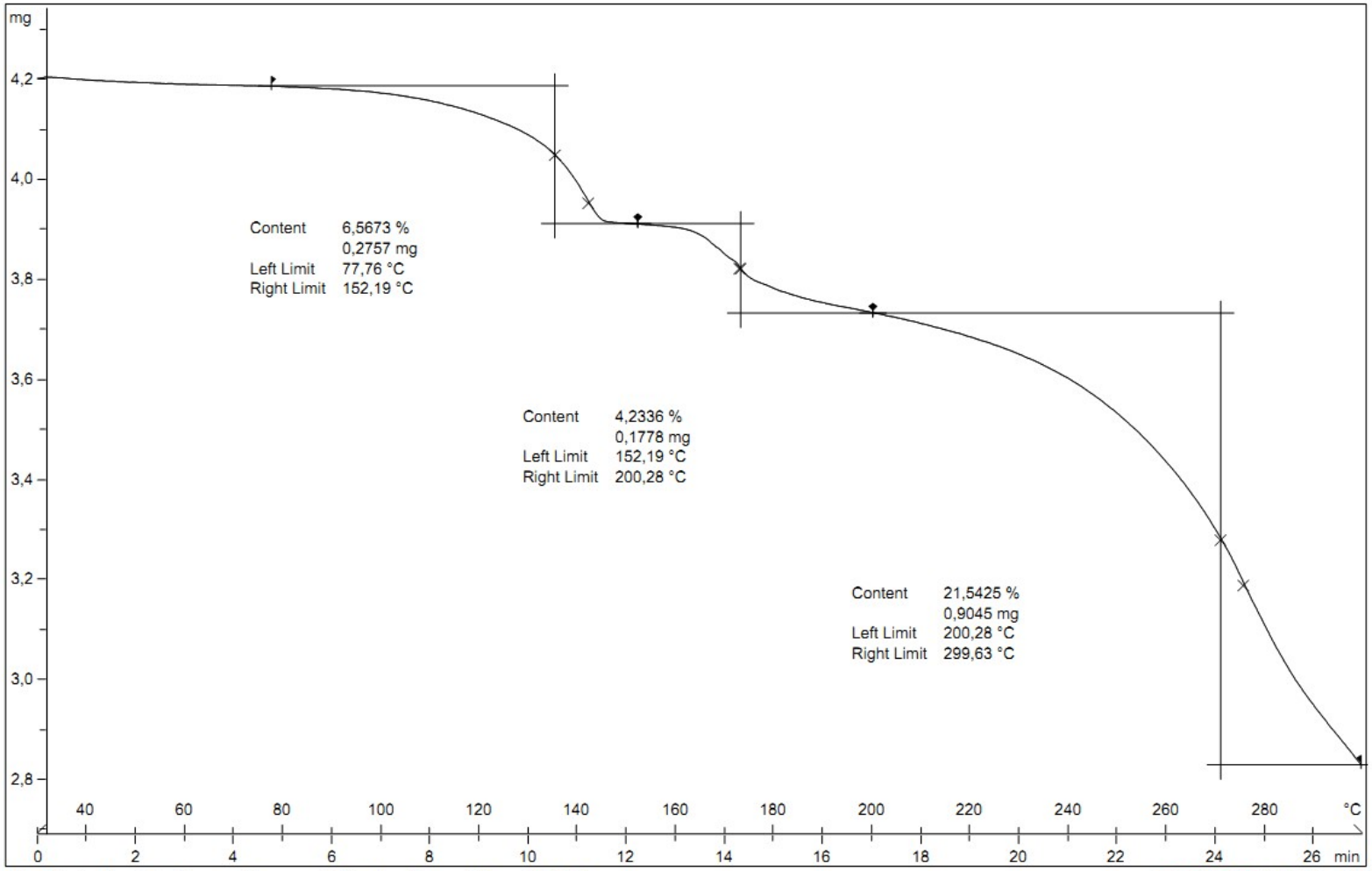


Figure S14: ^{1}H-NMR (dmso-d_6: delay: 1s /pulse: 45°/scans: 32) of Mirabegron orotic acid dioxane solvate salt (1:1:1)

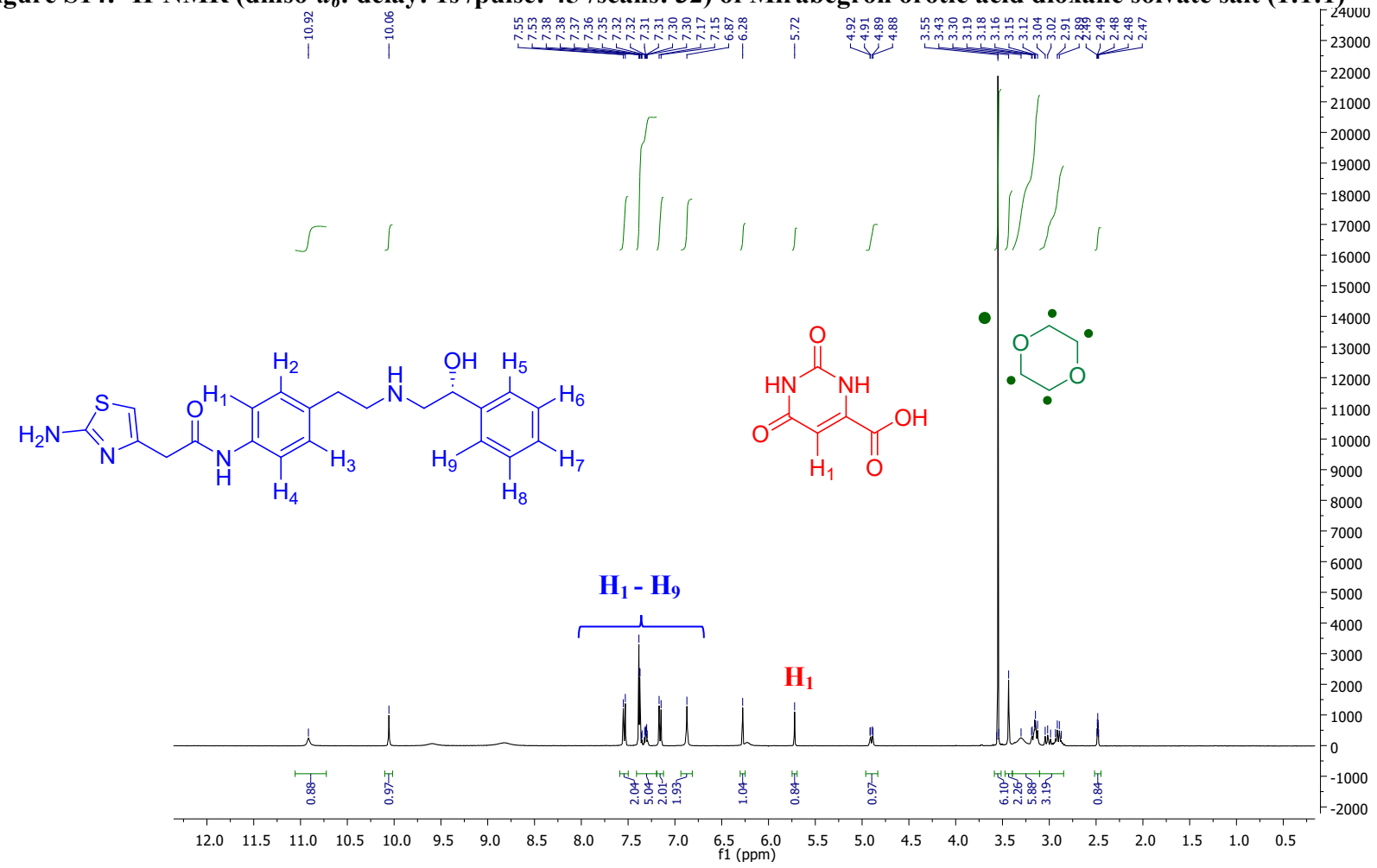


Figure S15: DSC of Mirabegron orotic acid hydrate salt (1:1.5:1.5)

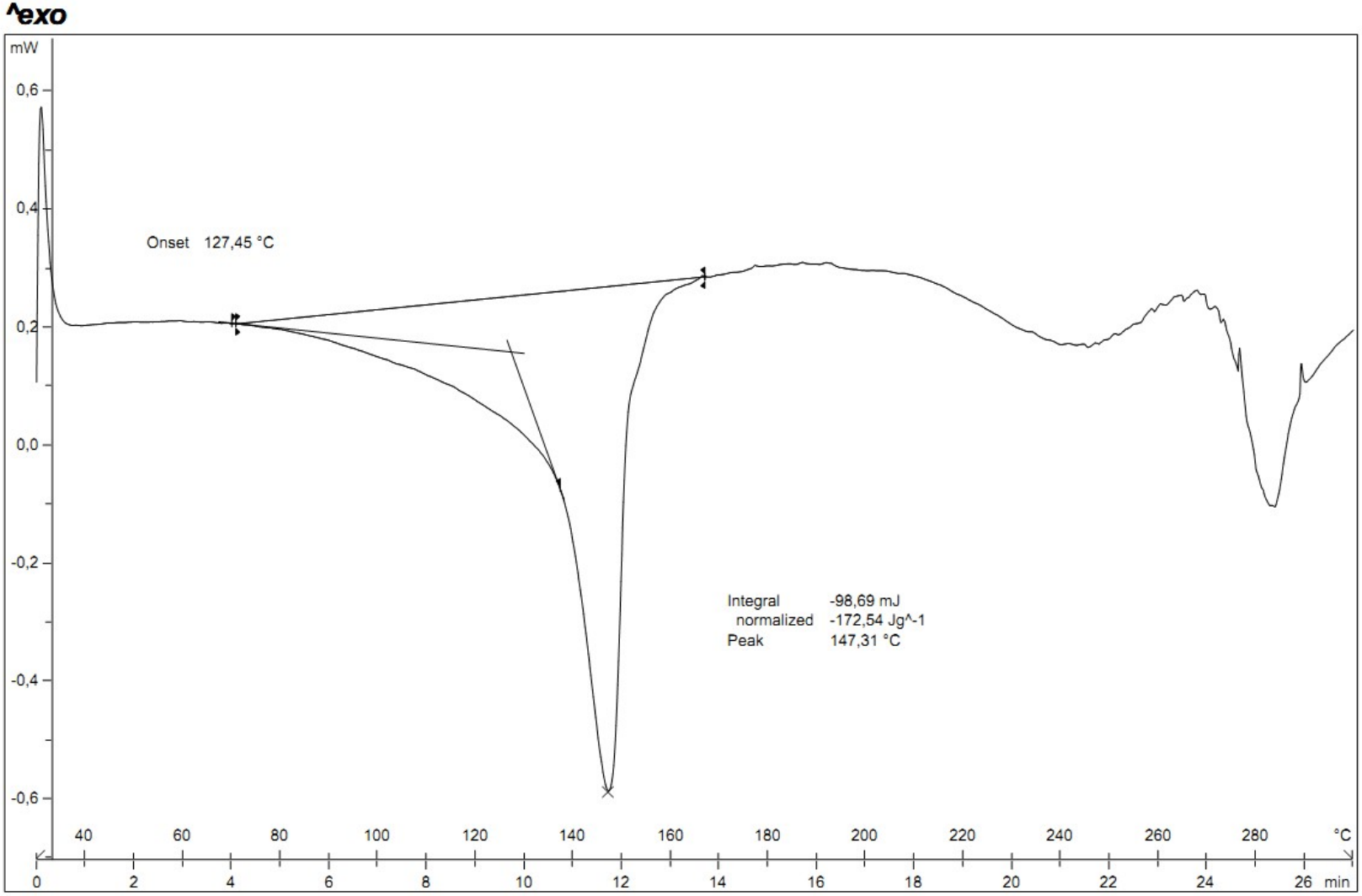


Figure S16: TGA of Mirabegron orotic acid hydrate salt (1:1.5:1.5)

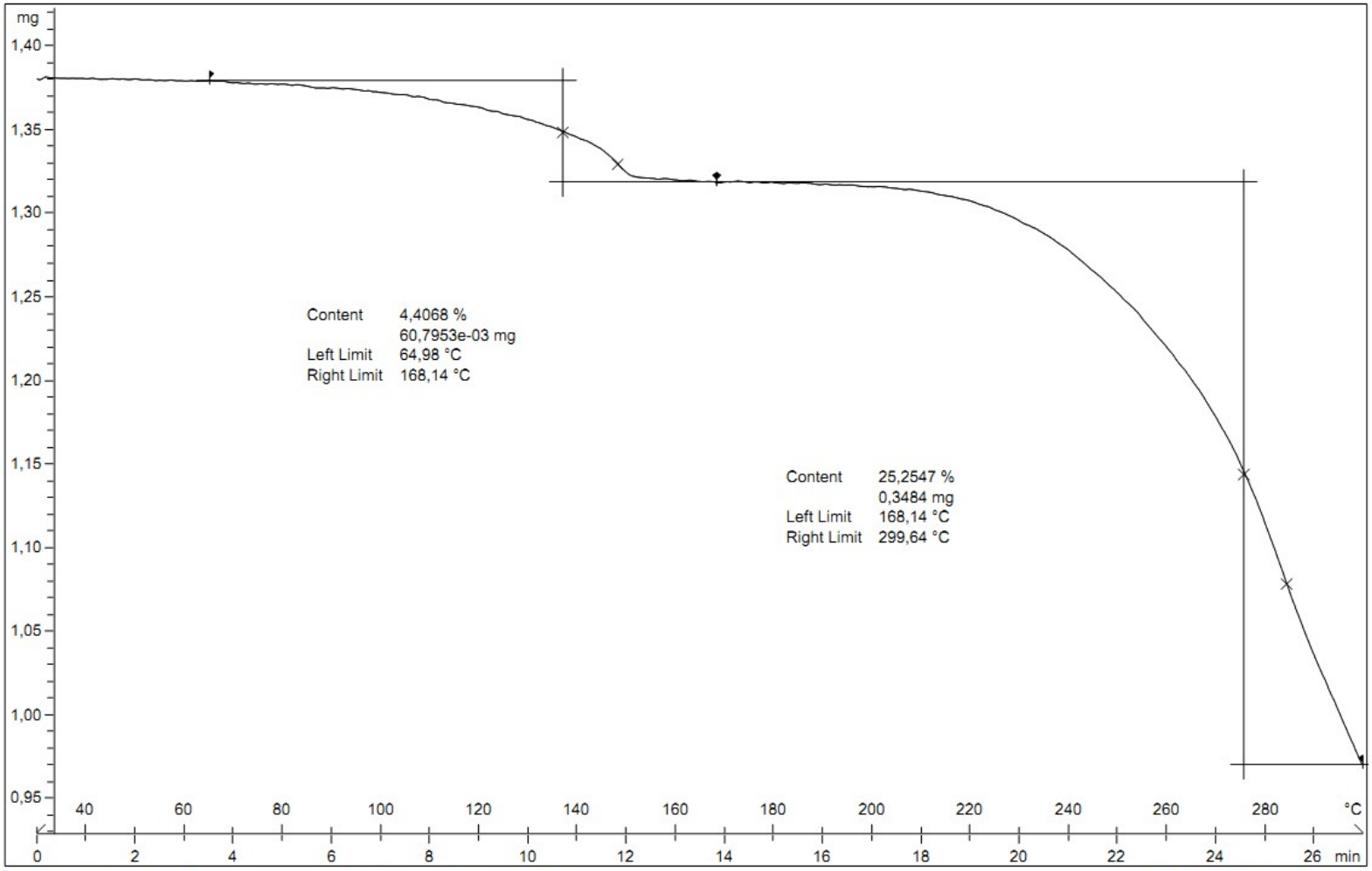


Figure S17: ^{1}H-NMR (dmso-d_6: delay: 1s /pulse: 45°/scans: 32) of Mirabegron orotic acid hydrate salt (1:1.5:1.5)

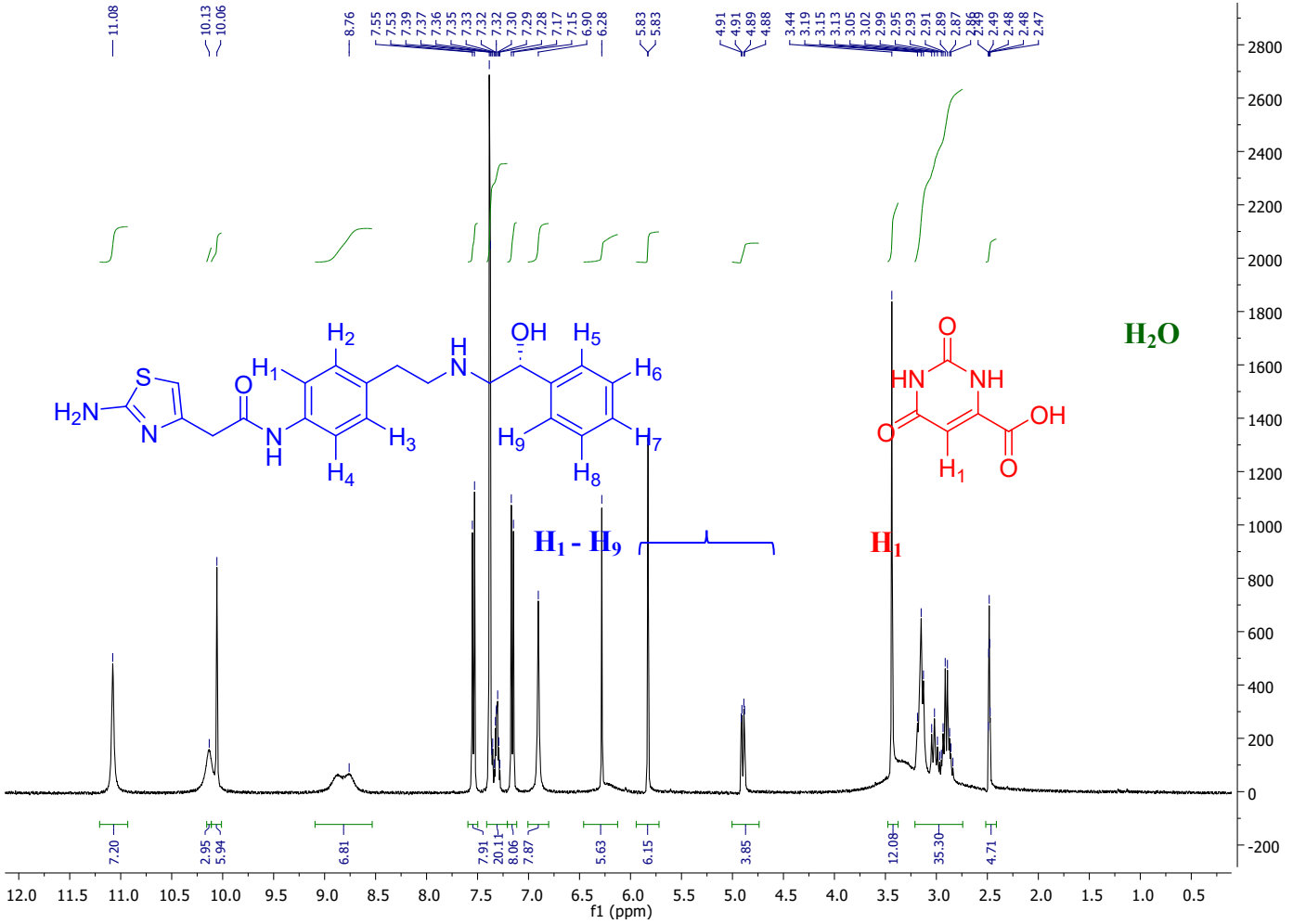


Figure S18: DSC of Mirabegron isobutyric acid salt (1:1)

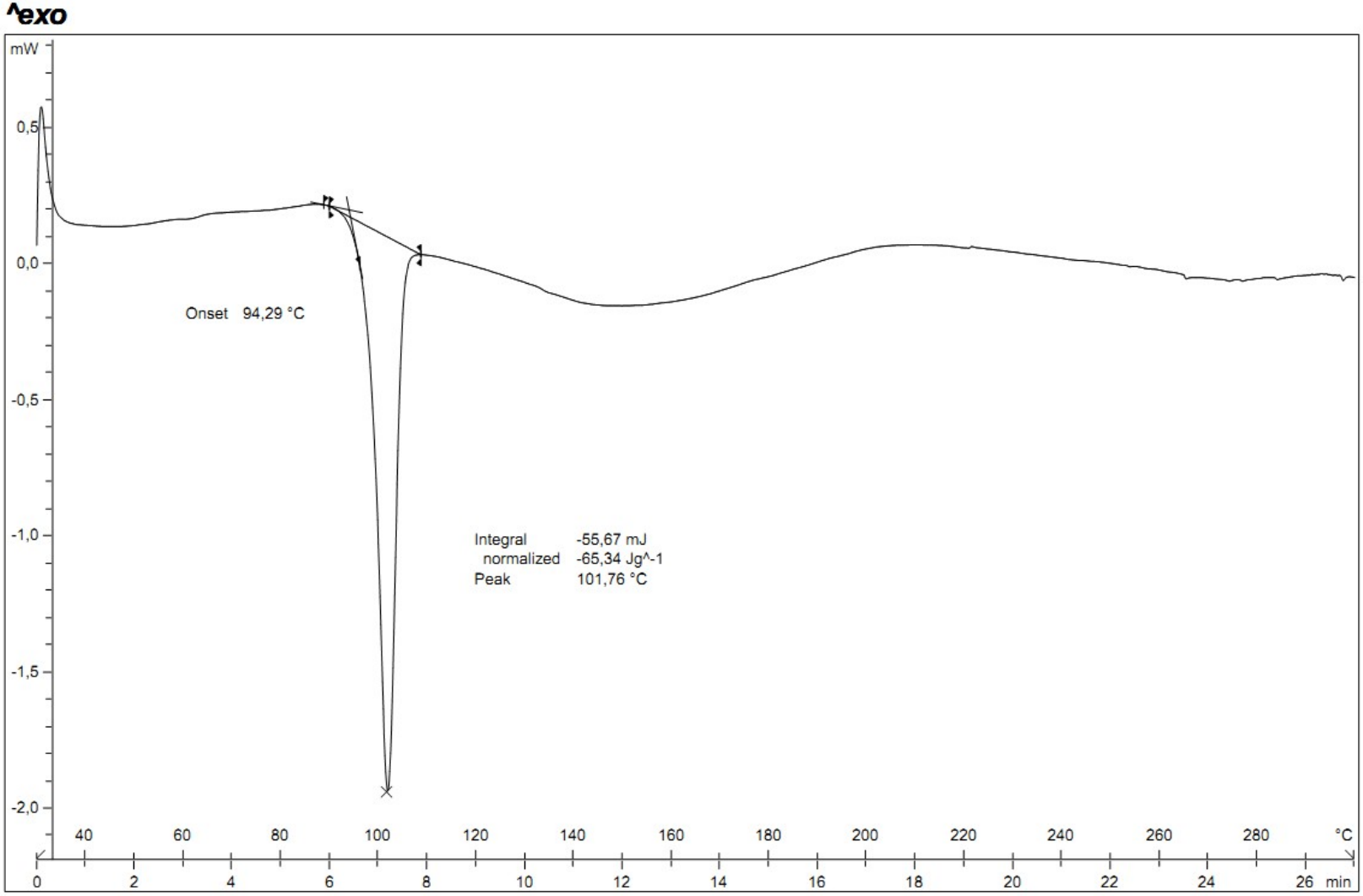


Figure S19: TGA of Mirabegron isobutyric acid salt (1:1)

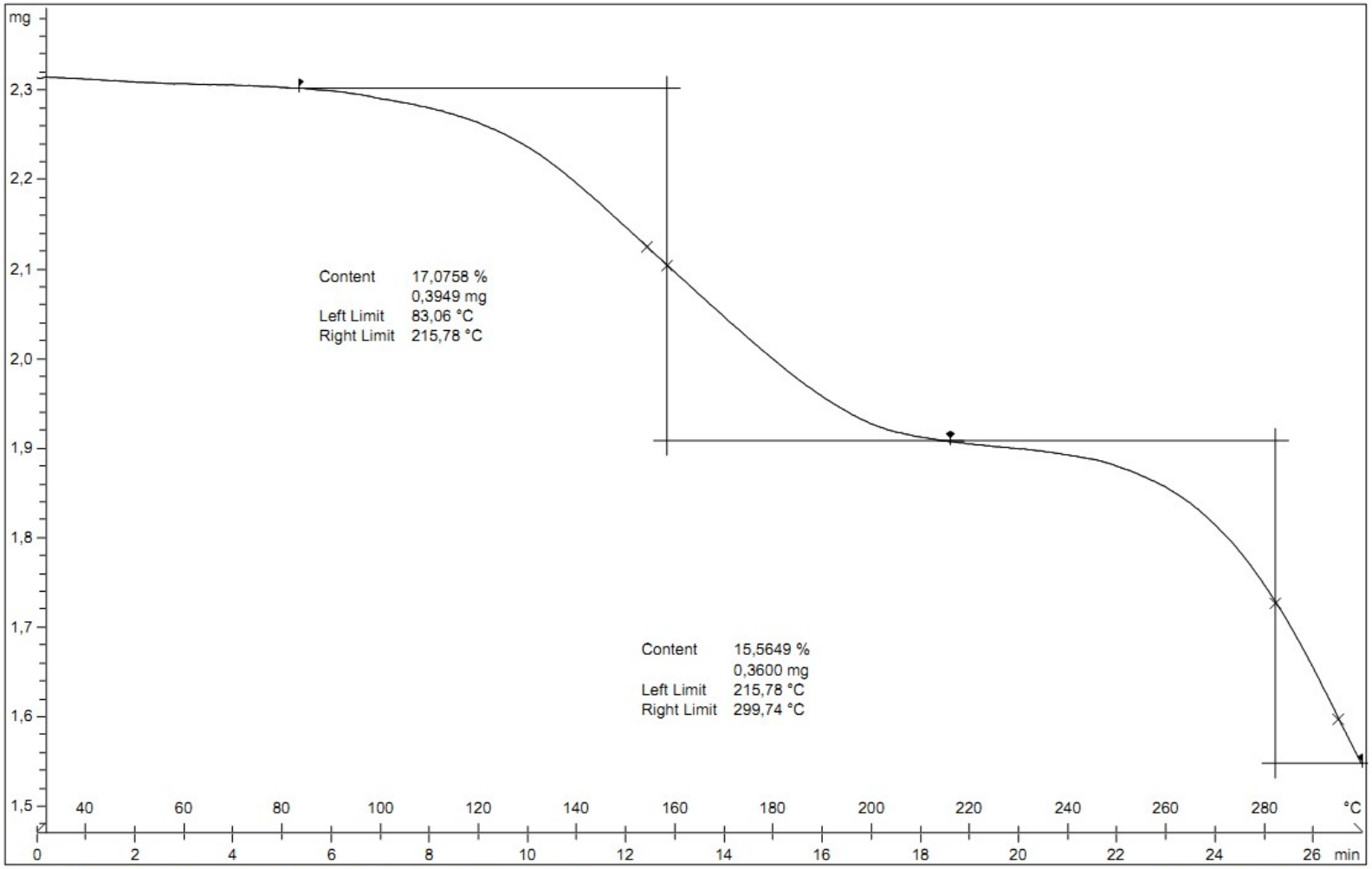


Figure S20: ^{1}H-NMR (dmso-d_6: delay: 1s /pulse: 45°/scans: 32) of Mirabegron isobutyric acid salt (1:1)

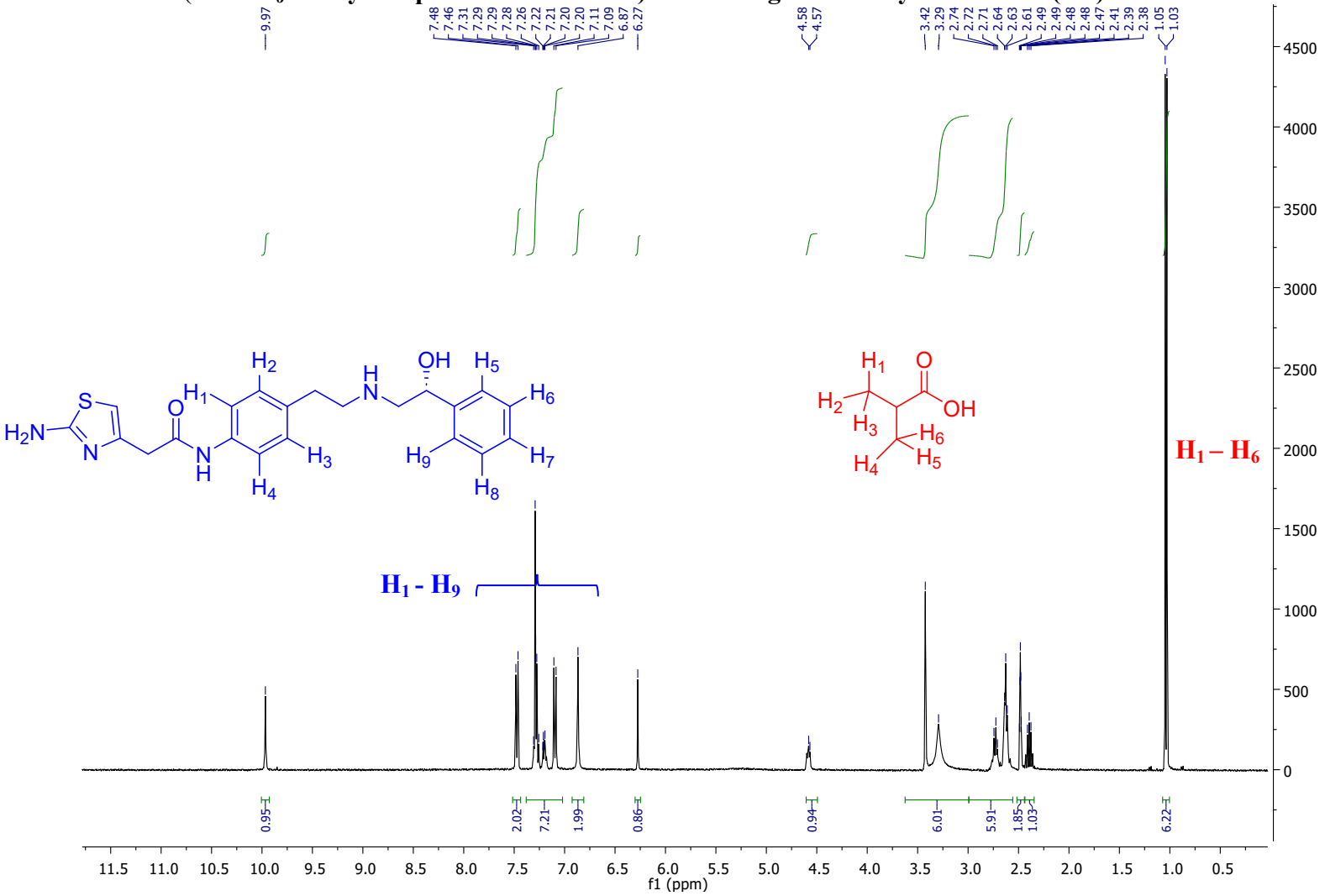


Figure S21: DSC of Mirabegron isobutyric acid THF solvate salt (1:1:0.5)

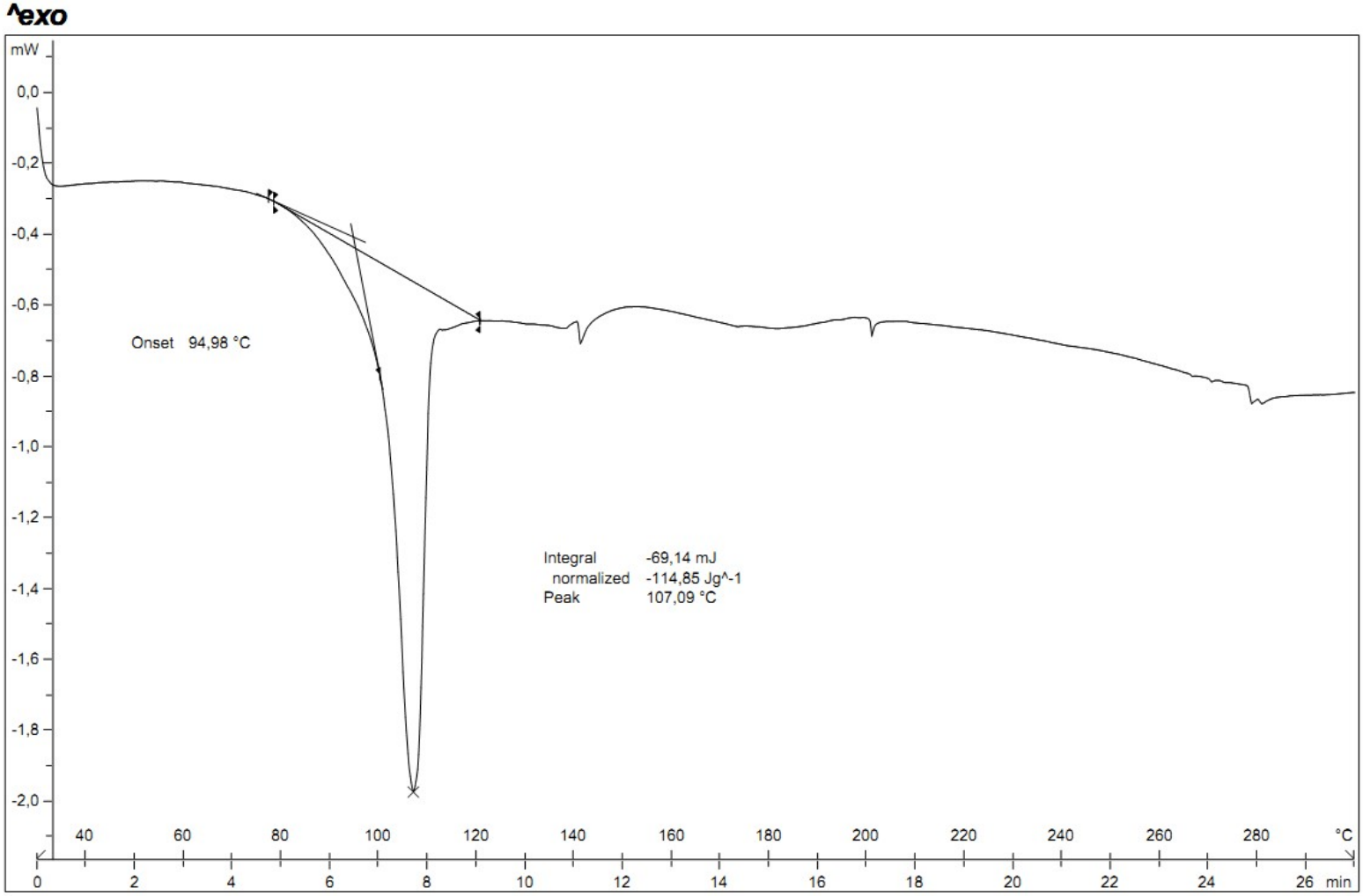


Figure S22: TGA of Mirabegron isobutyric acid THF solvate salt (1:1:0.5)

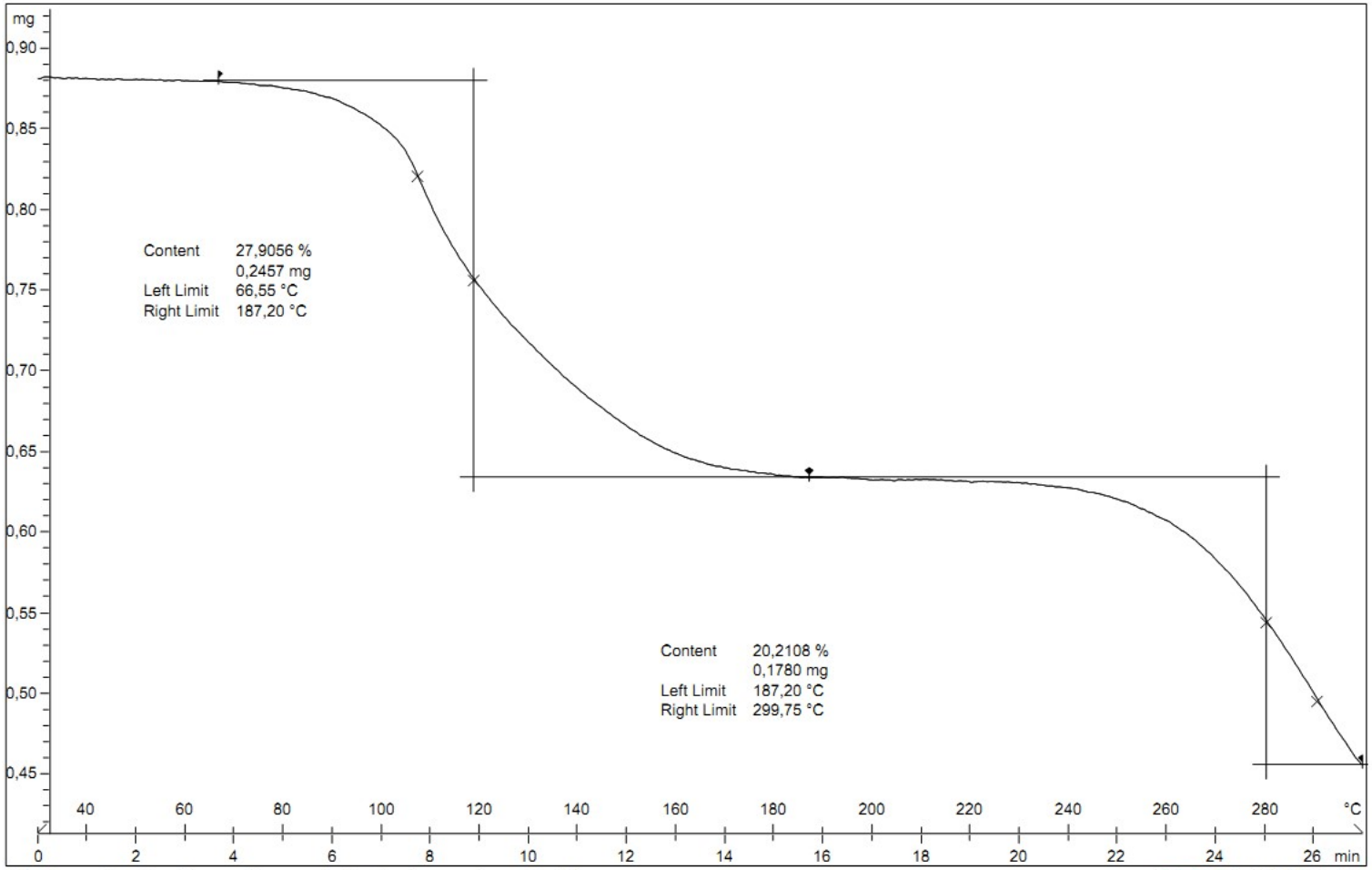


Figure S23: ^{1}H-NMR (dmso-d_6: delay: 1s /pulse: 45°/scans: 32) of Mirabegron isobutyric acid THF solvate salt (1:1:0.5)