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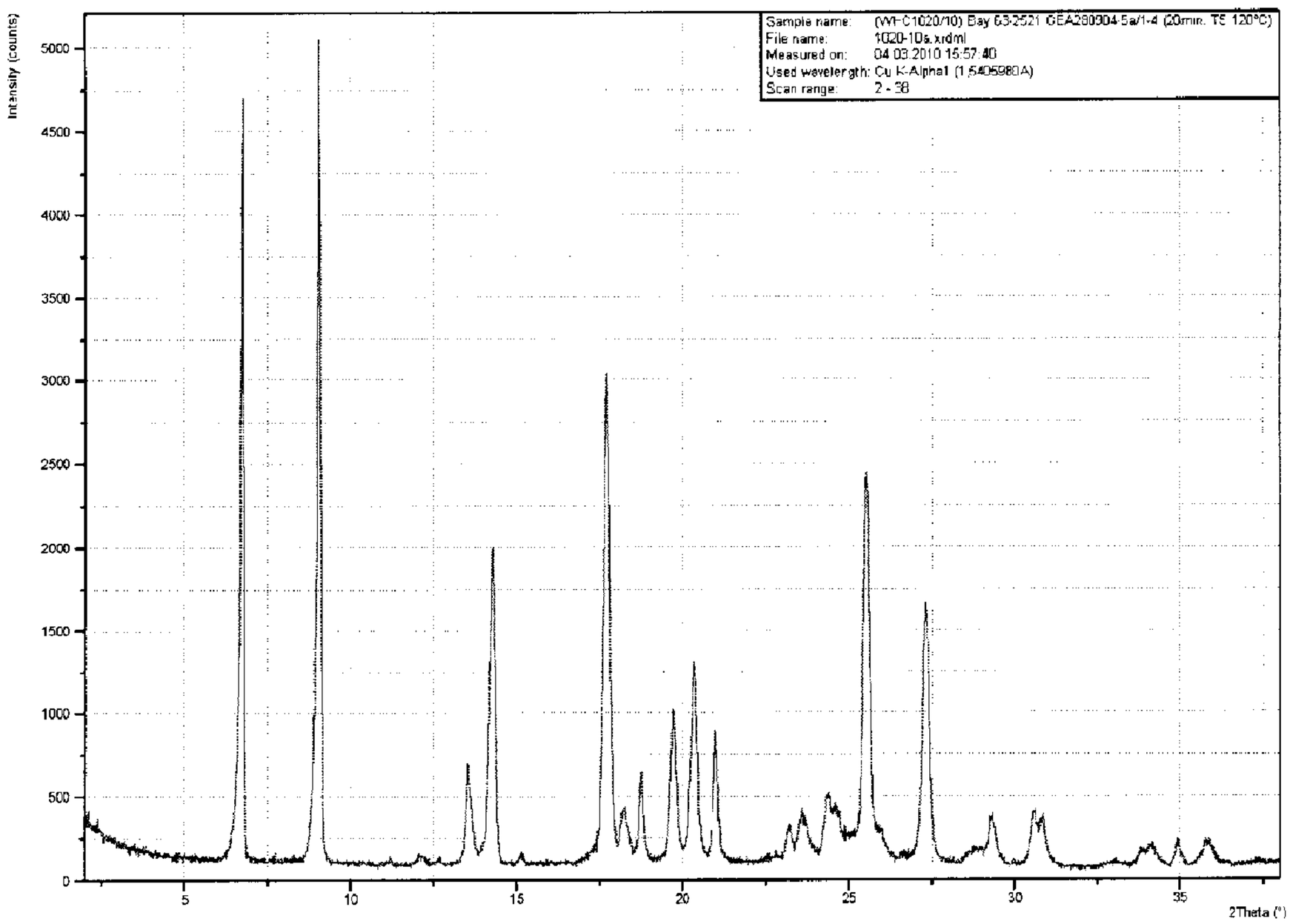
(54) Titre : FORMES DE METHYLE {4,6-DIAMINO-2-[1-(2-FLUOROBENZYLE)-1H-PYRAZOLO[3,4-B]PYRIDINO-3-YL]PYRI MIDINO-5-YL}METHYLE CARBAMATE

(54) Title: FORMS OF METHYL {4,6-DIAMINO-2-[1-(2-FLUOROBENZYL)-1H-PYRAZOLO[3,4-B]PYRIDINO-3-YL]PYRIMIDINO-5-YL}METHYL CARBAMATE

X-Ray powder diffractogram of the modification I



(57) Abrégé/Abstract:
This present invention relates to forms of methyl {4.6-diamino-2-[1-(2- fluorobenzyl)-1H- pyrazolo[3.4-b]pyridino-3-yl]pyrimidino-5-yl}methylcarbamate comprising its Modification I. Modification II. mono-DMSO solvate. sesqui-DMSO solvate and 1/4-ethyl acetate solvate.

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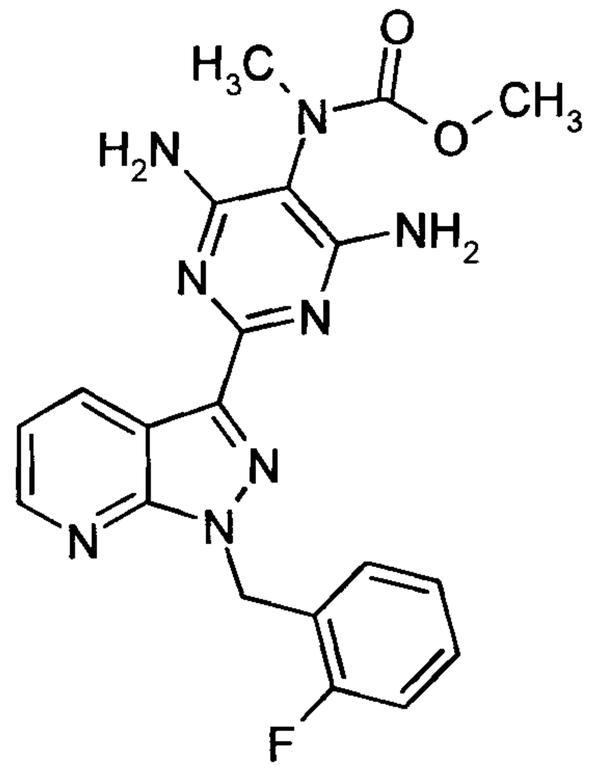
FORMS OF METHYL {4.6-DIAMINO-2-[1-(2-FLUOROBENZYL)-1H-PYRAZOLO[3.4-B]PYRIDINO-3-YL]PYRIMIDINO-5-YL}METHYL CARBAMATE

Abstract

This present invention relates to forms of methyl {4.6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3.4-b]pyridino-3-yl]pyrimidino-5-yl}methylcarbamate comprising its Modification I. Modification II. mono-DMSO solvate. sesqui-DMSO solvate and 1/4-ethyl acetate solvate.

FORMS OF METHYL {4,6-DIAMINO-2-[1-(2-FLUOROBENZYL)-1H-PYRAZOLO[3,4-B]PYRIDINO-3-YL]PYRIMIDINO-5-YL}METHYL CARBAMATE

This present invention relates to forms of methyl {4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridino-3-yl]pyrimidino-5-yl}methylcarbamate of formula (I):

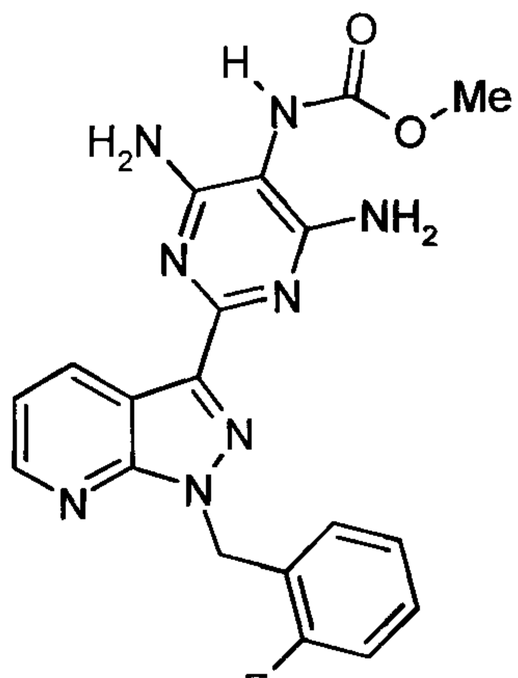


(I).

WO 03/095451 discloses the compound of formula (I), and further describes that this and other compounds disclosed therein are stimulators of soluble guanylate cyclase, and may therefore be used as agents for the prophylaxis and/or treatment of cardiovascular disorders.

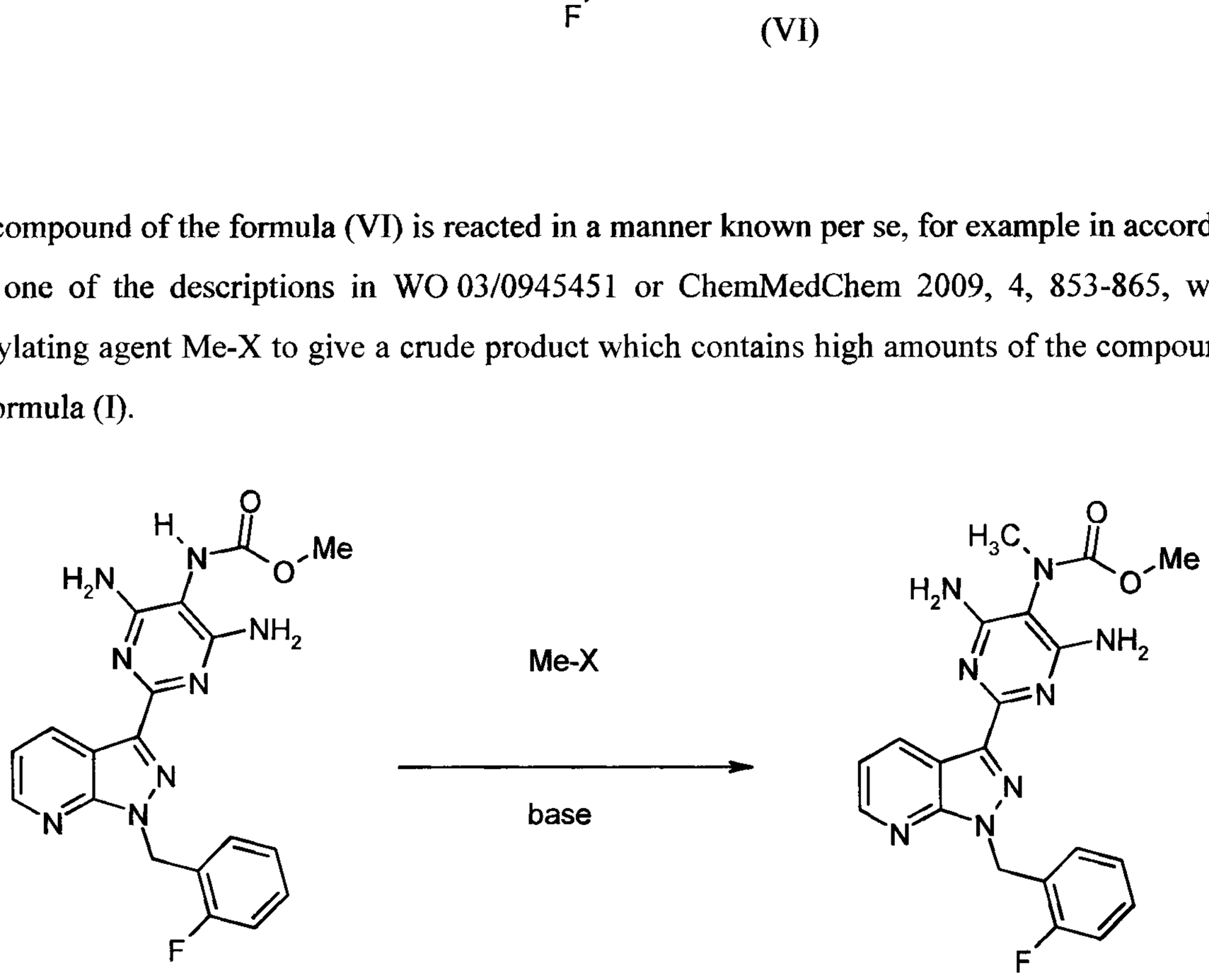
WO 03/095451 describes the preparation of the compound of the formula (I). However, there are a number of disadvantages associated with the process disclosed in WO 03/095451, as discussed in WO 2011/064171. WO 2011/064171 thus discloses an alternative process for preparing a compound of the formula (I).

In the process of WO 2011/064171, a compound of the formula (VI) is provided:



(VI)

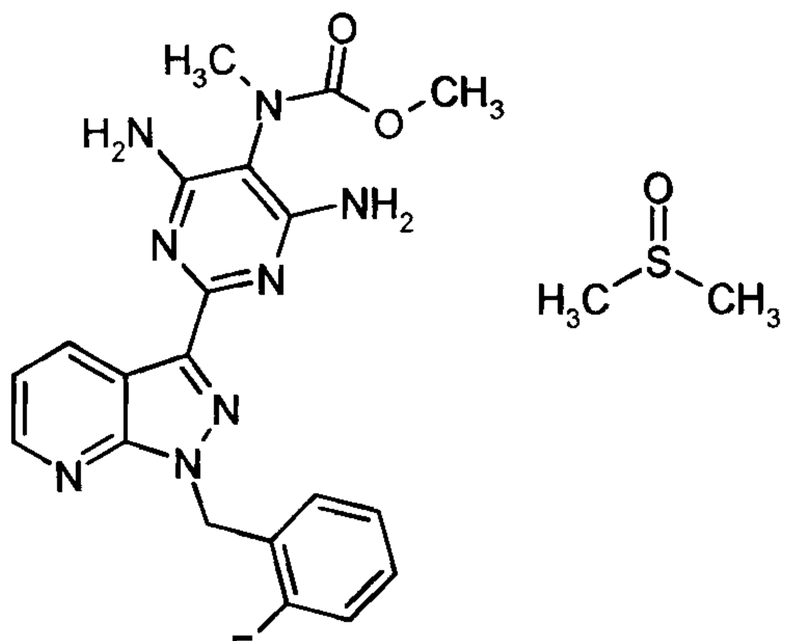
The compound of the formula (VI) is reacted in a manner known per se, for example in accordance with one of the descriptions in WO 03/0945451 or ChemMedChem 2009, 4, 853-865, with a methylating agent Me-X to give a crude product which contains high amounts of the compound of the formula (I).



(VI) (I) (crude product)

The methylating agent Me-X used is methyl iodide, dimethyl sulphate, methyl toluenesulphonate, etc., and methyl iodide or dimethyl sulphate is preferred.

The purification of the crude product of the formula (I) for use as pharmaceutically active compound is carried out via the compound methyl {4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl}methylcarbamate sulphinyldimethane (1:1), i.e. a compound of the formula (II) as isolated intermediate or generated in a mixture.



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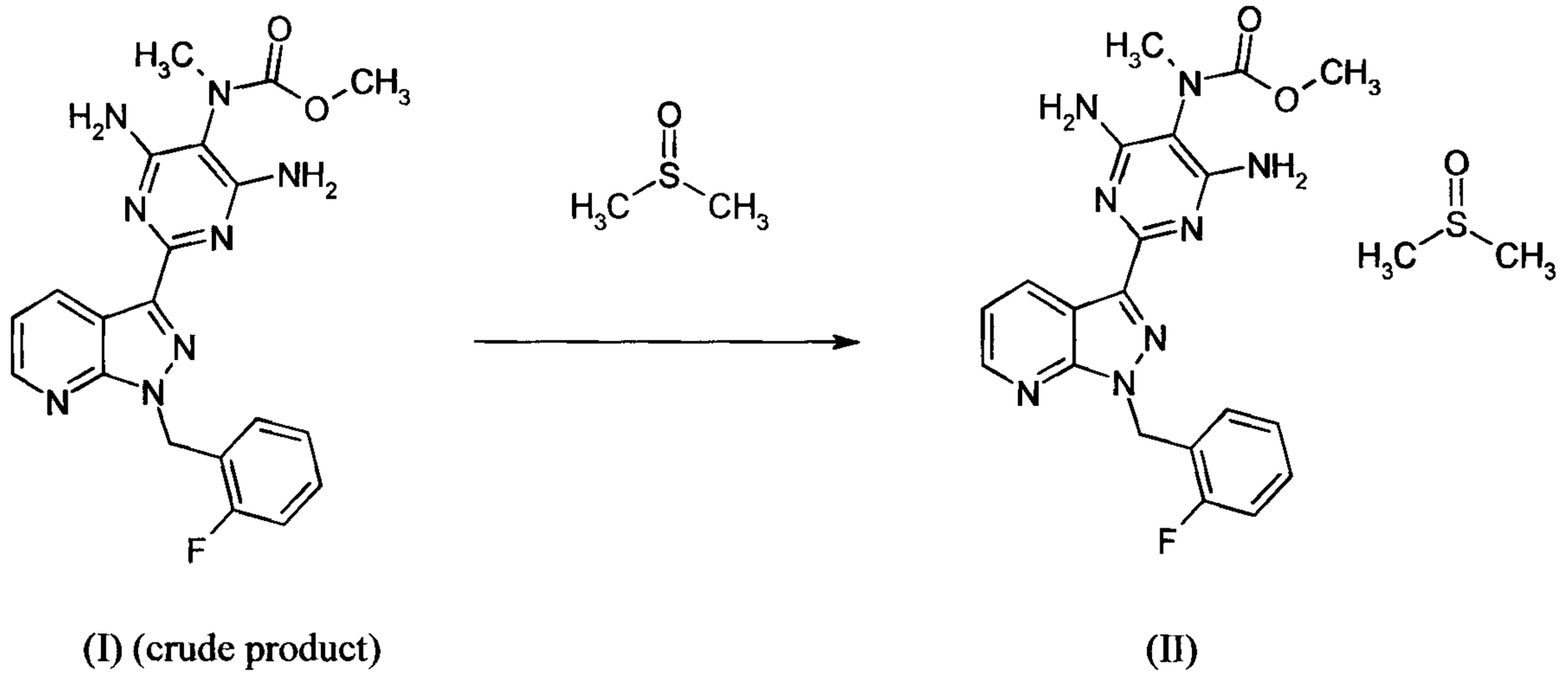
(II).

For the purification, initially, a mixture is formed which contains high amounts of the compound of the formula (II) as intermediate.



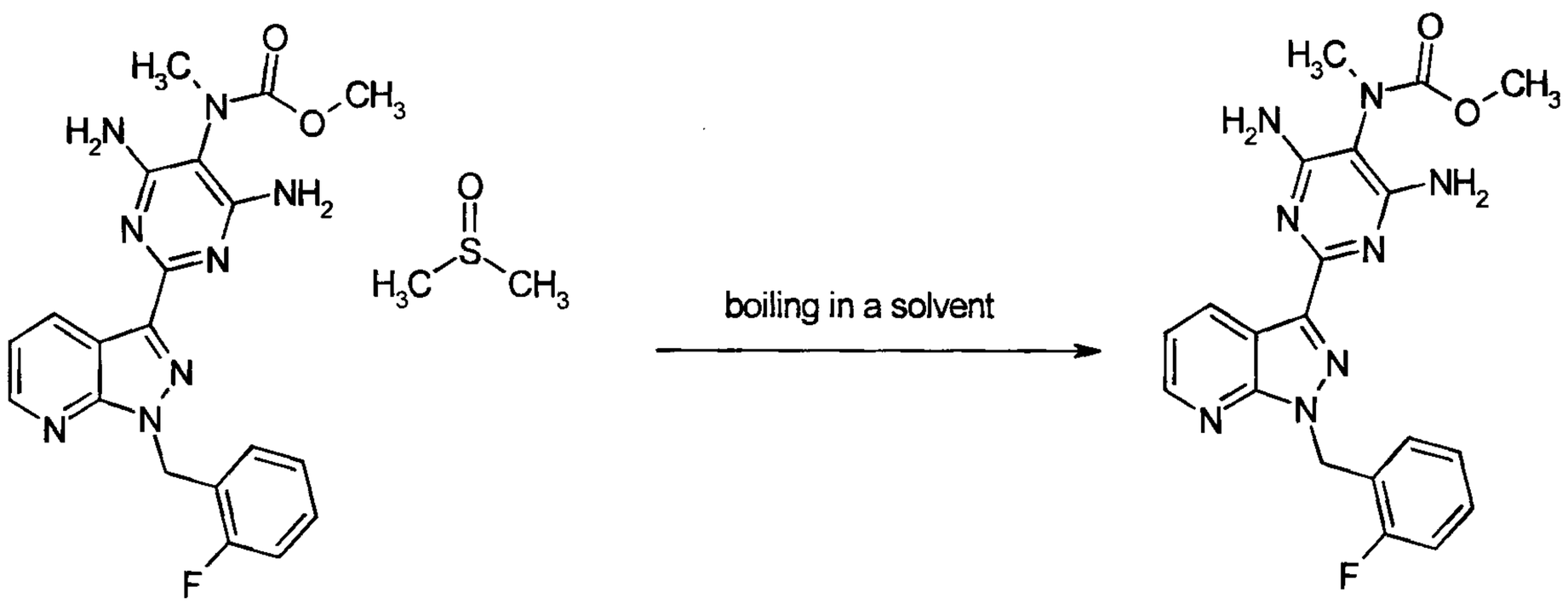
(I) (crude product) (II)

To this end, the crude product of the formula (I) is dissolved in DMSO (dimethylsulfoxide, sulphinyldimethane or (methylsulfinyl)methane which are different names for the same compound). To form a solution, the mixture is heated to 40-120°C, preferably 50-100°C. To form a pharmaceutically acceptable product of the formula (I), the solution has to be filtered, and the filtration is carried out hot, the temperatures are 40-120°C, preferably 50-100°C.

After the filtration, a pharmaceutically acceptable solvent, preferably the same solvent as above, is added to the hot filtrate. This results in a crystallization of the product of the formula (II).

Prior to the isolation of the solid which contains high amounts of the compound of the formula (II), to bring the precipitation to completion, the mixture is cooled to a temperature range of 0-35°C, preferably to an ambient temperature of, for example, 20-30°C.

For pharmaceutical use, the DMSO has to be removed from the product of the formula (II) or the mixture comprising high amounts of the compound of the formula (II).



(II) (I) (pure product)

To this end, the product of the formula (II) or the isolated mixture comprising high amounts of the product of the formula (II) is boiled in a pharmaceutically acceptable solvent from the class of the ketones, ethers, esters or alcohols. Examples of such solvents which may be mentioned are: methanol, ethanol, isopropanol, 1-butanol, 2-butanol, ethyl acetate, isopropyl acetate or propyl acetate, butyl acetate, tert-butyl methyl ether, diisopropyl ether, acetone, methyl ethyl ketone, methyl isobutyl ketone, etc. Preference is given to ethanol, isopropanol, ethyl acetate, isopropyl acetate, butyl acetate, methyl ethyl ketone, methyl isobutyl ketone. It is also possible to use mixtures of these solvents. Particular preference is given to ethyl acetate or a mixture of ethyl acetate with ethanol.

Boiling takes place at reflux of the solvent in question or, if appropriate, at slightly elevated pressure. The temperature is 50-150°C, preferably 80-120°C. The solid obtained is then filtered.

The present invention relates to new forms of methyl {4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridino-3-yl]pyrimidino-5-yl}methylcarbamate of formula (I).

Surprisingly it has been found that the compound of formula (I) crystallizes in two modifications with melting points at 268 °C (Modification I) and 250 °C (Modification II). In this context modifications and polymorphs have the same meaning. In addition, three pseudo-polymorphs, a mono-DMSO solvate, a sesqui-DMSO solvate, a 1/4-ethyl acetate solvate and the amorphous form have been found. The amorphous form can exist at room temperature, but crystallizes very quickly. All together – modifications or polymorphs, pseudo-polymorphs and amorphous forms – are different forms of the compound of formula (I) according to the present invention.

Aspects of some embodiments of the present invention which may be beneficial in the present pharmaceutical field may include stability (e.g. pressure stability, chemical stability, storage stability), compatibility over other ingredients, purity, solubility (thermodynamically, kinetically), crystallization properties, properties regarding isolation during the chemical synthesis and bioavailability of the forms of the compound of formula (I).

The compound of the formula (I) in the Modification I is the thermodynamically stable form between 0 °C and 80 °C.

Two of the solvates occur during synthesis, the mono-DMSO solvate and the 1/4-ethyl acetate solvate of the compound of the formula (I). The compound of the formula (I) in the Modification II can form from the solvates after solvent release, e.g. during drying at 80 °C.

Embodiments of the present invention are not only each single form the compound of the formula (I) which are Modification I, Modification II, mono-DMSO solvate, sesqui-DMSO solvate and 1/4-ethyl acetate solvate of the compound of the formula (I) but also mixtures comprising two, three, four or five forms of the aforementioned.

A pharmaceutical composition according to the present invention comprises preferably only one of the forms selected from the group comprising Modification I, Modification II, mono-DMSO solvate, sesqui-DMSO solvate and 1/4-ethyl acetate solvate of the compound of the formula (I) mainly and no significant fractions of another form of the compound of the formula (I), for example of another modification or pseudopolymorph of the compound of the formula (I). More preferably the pharmaceutical composition contains more than 90 percent by weight, most preferably more than 95 percent by weight, and up to 100 percent, of the compound of the formula (I) in one of the aforementioned forms related to the total amount of all forms of the compound of the formula (I) present in the composition.

Preference is given to a pharmaceutical composition comprising the compound of the formula (I) in the Modification I mainly and no significant fractions of another form of the compound of the formula (I), for example of another modification or pseudopolymorph of the compound of the formula (I). The pharmaceutical composition preferably contains more than 90 percent by weight, more preferably more than 95 percent by weight, and up to 100 percent of the compound of the formula (I) in the Modification I related to the total amount of all forms of the compound of the formula (I) present in the composition.

Further preference is given to a pharmaceutical composition comprising the compound of the formula (I) in the Modification II mainly and no significant fractions of another form of the compound of the

formula (I), for example of another modification or pseudopolymorph of the compound of the formula (I). The pharmaceutical composition preferably contains more than 90 percent by weight, more preferably more than 95 percent by weight, and up to 100 percent of the compound of the formula (I) in the Modification II related to the total amount of all forms of the compound of the formula (I) present in the composition.

Further preference is given to a pharmaceutical composition comprising the mono-DMSO solvate of the compound of the formula (I) mainly and no significant fractions of another form of the compound of the formula (I), for example of another modification or pseudopolymorph of the compound of the formula (I). The pharmaceutical composition preferably contains more than 90 percent by weight, more preferably more than 95 percent by weight, and up to 100 percent of the mono-DMSO solvate of the compound of the formula (I) related to the total amount of all forms of the compound of the formula (I) present in the composition.

Further preference is given to a pharmaceutical composition comprising the sesqui-DMSO solvate of the compound of the formula (I) mainly and no significant fractions of another form of the compound of the formula (I), for example of another modification or pseudopolymorph of the compound of the formula (I). The pharmaceutical composition preferably contains more than 90 percent by weight, more preferably more than 95 percent by weight, and up to 100 percent of the sesqui-DMSO solvate of the compound of the formula (I) related to the total amount of all forms of the compound of the formula (I) present in the composition.

Further preference is given to a pharmaceutical composition comprising the 1/4-ethyl acetate solvate of the compound of the formula (I) mainly and no significant fractions of another form of the compound of the formula (I), for example of another modification or pseudopolymorph of the compound of the formula (I). The pharmaceutical composition preferably contains more than 90 percent by weight, more preferably more than 95 percent by weight, and up to 100 percent of the 1/4-ethyl acetate solvate of the compound of the formula (I) related to the total amount of all forms of the compound of the formula (I) present in the composition.

The forms of the compound of the formula (I) of the present invention are used alone or together as a mixture in high purity in pharmaceutical formulations. As mixtures a combination of the compound of formula (I) in the Modification I and the compound of formula (I) in the Modification II, a combination of the compound of formula (I) in the Modification I and the mono-DMSO solvate of the compound of formula (I), a combination of the compound of formula (I) in the Modification I and the sesqui-DMSO solvate of the compound of formula (I), a combination of the compound of formula (I) in the Modification I and the 1/4-ethyl acetate solvate of the compound of formula (I), a combination of the compound of formula (I) in the Modification I and the mono-DMSO solvate of

the compound of formula (I) and the 1/4-ethyl acetate solvate of the compound of formula (I), or a combination of the compound of formula (I) in the Modification I and the sesqui-DMSO solvate of the compound of formula (I) and the 1/4-ethyl acetate solvate of the compound of formula (I) optionally with no other form of the compound of the formula (I) are preferred.

The different forms of the compound of formula (I) can be distinguished by X-ray powder diffraction, differential scanning calorimetry (DSC), IR-, Raman-, NIR-, FIR- and 13C-solid-state-NMR-spectroscopy:

Figure 1: X-Ray powder diffractogram of the modification I

Figure 2: DSC- and TGA-Thermogram of modification I

Figure 3: IR-Spectrum (ATR) of modification I

Figure 4: X-Ray powder diffractogram of the 1/4-ethyl acetate solvate

Figure 5: DSC- and TGA-Thermogram of the 1/4-ethyl acetate solvate

Figure 6: IR-Spectrum (ATR) of the 1/4-ethyl acetate solvate

Figure 7: X-Ray powder diffractogram of the mono-DMSO solvate

Figure 8: DSC- and TGA-Thermogram of the mono-DMSO solvate

Figure 9: IR-Spectrum (ATR) of the mono-DMSO solvate

Figure 10: X-Ray powder diffractogram of the sesqui-DMSO solvate

Figure 11: DSC- and TGA-Thermogram of the sesqui-DMSO solvate

Figure 12: IR-Spectrum (ATR) of the sesqui-DMSO solvate

Figure 13: X-Ray powder diffractogram of modification II

Figure 14: DSC- and TGA-Thermogram of modification II

Figure 15: IR-Spectrum (ATR) of modification II

Figure 16: X-Ray powder diffractogram of the amorphous form

Figure 17: DSC- and TGA-Thermogram of the amorphous form

Figure 18: IR-Spectrum of the amorphous form

The compound of formula (I) in the Modification I can be characterized unambiguously by a X-Ray powder diffractogram comprising peak maxima of the 2 Theta angle of 6.7, 9.1, 14.3, 14.4, 17.8, 19.8, 20.2, 24.8, 25.6, 27.3.

The compound of formula (I) in the Modification II can be characterized unambiguously by a X-Ray powder diffractogram comprising peak maxima of the 2 Theta angle of 11.2, 12.6, 12.7, 13.9, 15.2, 17.3, 22.5, 22.8, 25.0, 25.5.

The mono-DMSO solvate of the compound of formula (I) can be characterized unambiguously by a X-Ray powder diffractogram comprising peak maxima of the 2 Theta angle of 9.0, 10.8, 11.1, 11.2, 13.0, 15.5, 15.9, 16.0, 20.7, 25.6.

The sesqui-DMSO solvate of the compound of formula (I) can be characterized unambiguously by a X-Ray powder diffractogram comprising peak maxima of the 2 Theta angle of 8.3, 8.4, 13.7, 13.9, 15.7, 17.2, 18.4, 19.6, 21.4, 24.9.

The ¼-Ethylacetate solvate of the compound of formula (I) can be characterized unambiguously by a X-Ray powder diffractogram comprising peak maxima of the 2 Theta angle of 6.7, 8.3, 8.7, 12.9, 14.2, 17.8, 19.3, 24.0, 25.1, 26.7.

The compound of formula (I) in the Modification I can be characterized unambiguously by an IR-spectrogram comprising peak maxima of the 2 Theta angle of 3454, 3360, 3273, 3103, 1688, 1622, 1559, 1284, 1193, 989, 777.

The compound of formula (I) in the Modification II can be characterized unambiguously by an IR-spectrogram comprising peak maxima of the 2 Theta angle of 3498, 3382, 3269, 3104, 1704, 1622, 1586, 1563, 1326, 1288, 1106.

The mono-DMSO solvate of the compound of formula (I) can be characterized unambiguously by an IR-spectrogram fractogram comprising peak maxima of the 2 Theta angle of 3401, 3361, 3295, 3168, 1702, 1626, 1560, 1333, 1286, 1042, 751.

The sesqui-DMSO solvate of the compound of formula (I) can be characterized unambiguously by an IR-spectrogram comprising peak maxima of the 2 Theta angle of 3407, 3361, 3300, 3190, 1698, 1629, 1558, 1293, 1043, 770, 757.

The ¼-Ethylacetate solvate of the compound of formula (I) can be characterized unambiguously by an IR-spectrogram comprising peak maxima of the 2 Theta angle of 3363, 3275, 1732, 1702, 1619, 1560, 1457, 1246, 899, 810, 771.

The compounds according to the invention may bring about vessel relaxation and inhibition of thrombocyte aggregation and lead to a lowering of blood pressure and to an increase in coronary blood flow. These effects are due to direct stimulation of soluble guanylate cyclase and an increase in intracellular cGMP. Moreover, the compounds according to the invention may intensify the action of substances that raise the cGMP level, for example EDRF (endothelium-derived relaxing factor), NO donors, protoporphyrin IX, arachidonic acid or phenylhydrazine derivatives.

The weight data in the tests and examples which follow are, unless stated otherwise, percentages by weight; parts are parts by weight. Solvent ratios, dilution ratios and concentration data of liquid/liquid solutions are based on each case on the volume.

Working examples

DSC thermograms were recorded using Differential Scanning Calorimeters (model DSC7, Pyris-1 or Diamond) from Perkin-Elmer. The measurements were performed with a heating rate of 20 $Kmin^{-1}$ using non-gastight aluminium pans. Flow gas was nitrogen. There was no sample preparation.

TGA thermograms were recorded using thermobalances (model TGA7 and Pyris 1) from Perkin-Elmer.. The measurements were performed with a heating rate of 10 $Kmin^{-1}$ using open platinum pans. Flow gas was nitrogen. There was no sample preparation.

X-Ray diffraction patterns were recorded at room temperature using XRD –diffractometers X`Pert PRO (PANalytical) and STOE STADI-P (radiation Cu K alpha 1, wavelength 1.5406 Å). There was no sample preparation.

Raman spectra were recorded at room temperature using FT-Raman-spectrophotometers (model RFS 100 and MultiRam) from Bruker. Resolution was 2 cm^{-1}. Measurements were perfomed in glass vials or aluminium discs. There was no sample preparation.

IR-ATR-spectra were recorded at room temperature using a FT-IR-spectrophotometer one with universal diamond ATR device from Perkin-Elmer. Resolution was 4 cm^{-1}. There was no sample preparation.

Example 1

Preparation of purified methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-pyrimidinyl(methyl)carbamate (I) in its modification I

The entire amount of the product of the formula (II) prepared in the Example 6 of WO 2011/064171 was stirred in 135 ml of ethyl acetate at reflux (about 78°C) for 1 h and cooled to about 25°C. The solid was filtered off with suction, washed with a total of 36 ml of ethyl acetate and dried under reduced pressure. The weight was 7.6 g or 93.8% of theory. The content of the product was markedly above 98% by weight (HPLC). As solvent, ethyl acetate was present in an amount of about 0.2%. The DMSO content was below 0.1%.

Example 2

Preparation and analytical characterization of methyl {4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl}methylcarbamate sulphinyldimethane (compound according to formula (I) as mono-DMSO solvate)

14.8 g of a crude product of the formula (I) were dissolved in 28.9 g of DMSO and 11.85 g of ethyl acetate at about 94°C. 1.5 g of activated carbon Norit A-Supra and a further 11.85 g of ethyl acetate were then added, the mixture was stirred at reflux (88-90°C) for 1 h and the hot mixture was then filtered to remove the activated carbon. The solid, some of which had already precipitated, was re-dissolved by warming to about 78°C, and the solution was then allowed to cool slowly. The precipitated solid was filtered off with suction at RT, washed three times with in each case 50 ml of ethyl acetate and dried in a drying cabinet at 30°C for 18 h. This gave 9.2 g or 52.5% of theory of a slightly yellowish crystal powder of the compound of the formula (II).

HPLC: 99.90 area% (without taking the DMSO into account)

DMSO (GC): 14.7% by weight

^{1}H-NMR (400 MHz in DMF-d_7):

d = 2.59 (s, about 6H, 2 CH_3 at DMSO), 3.13 (s, 3H, N-CH_3), 3.58 + 3.67 (two s, 3H, hindered rotation at O-CH_3), 5.91 (s ,2H, -CH_2-), 6.53 (s, 4H, 2 -NH_2), 7.05-7.40 (m, 5H, 4 aromatic H at the o-fluorobenzyl substituent and 1H at the pyrido ring meta to the pyrido nitrogen), 8.60 (dd, 1H, at the pyrido ring ortho to the pyrido nitrogen), 9.12 (dd, 1H, at the pyrido ring para to the pyrido nitrogen).

Elemental analysis:

found	C: 52.2%	calculated	C: 52.79%
	H: 4.9%		H: 5.03%
	N: 22.7%		N: 22.39%

Example 3

Preparation of methyl {4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl}methylcarbamate of formula (I) in its Modification II

0.5 g of the compound according to formula (I) as mono DMSO sovlate was tempered for 2 days at 80°C.

Example 4

Preparation of methyl {4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl}methylcarbamate of formula (I) as sesqui-DMSO solvate

160 mg of the compound according to formula (I) in its amorphous form were suspended in 2 ml Ethylacetat:DMSO (1:1). The suspension was stirred in a sealed container for three weeks at room temperature. The residue was filtered and dried at room temperature.

Example 5

Preparation of methyl {4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl}methylcarbamate of formula (I) in its amorphous form.

0.5 g of the compound according to formula (I) in its Modification (I) were ground in a swing mill for 30 min with a vibration of 30 swings per second.

Example 6

Preparation of methyl {4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl}methylcarbamate of formula (I) as ¼ ethyl acetate solvate

9.6 g of compound according to formula (I) was stirred in 135 ml of ethyl acetate at reflux (about 78°C) for 1 h and cooled to about 25°C. The solid was filtered off with suction, washed with a total of 36 ml of ethyl acetate and dried under reduced pressure. The weight was 7.6 g or 93.8% of theory. The content of the product was markedly above 98% by weight (HPLC). As solvent, ethyl acetate was present in an amount of about 0.2%. The DMSO content was below 0.1%.

In this reaction, an ethyl acetate containing solid polymorph (¼-ethyl acetate-solvate) may be formed and isolated.

Tab. 1: IR bands of the different crystalline forms

IR Bands [cm^{-1}]				
Mod. I	Mod. II	Mono-DMSO-Solvate	Sesqui-DMSO-Solvate	¼-Ethylacetate-Solvate
3508	3498	3401	3508	3506
3454	3382	3361	3407	3459
3360	3269	3295	3361	3363
3273	3104	3168	3300	3275
3103	2951	2950	3190	3116
2956	1704	1702	2956	2954
1688	1622	1645	1698	1732
1622	1586	1626	1629	1702
1559	1563	1578	1558	1619
1489	1491	1560	1485	1560
1483	1482	1490	1456	1484
1457	1457	1456	1447	1457
1437	1436	1446	1425	1438
1425	1419	1426	1416	1417
1417	1390	1415	1370	1366
1366	1362	1370	1333	1333
1333	1327	1335	1293	1282
1326	1288	1286	1227	1246
1284	1231	1276	1192	1229
1227	1189	1228	1169	1191
1193	1176	1193	1142	1167
1167	1164	1171	1111	1140
1140	1140	1142	1094	1094
1094	1106	1112	1063	1032
1034	1035	1092	1043	1008
1008	1007	1042	992	991
989	990	1015	950	935
935	943	993	901	899
899	896	947	840	840
840	861	901	811	810
810	842	845	784	771

IR Bands [cm^{-1}] [cont.]				
Mod. I	Mod. II	Mono-DMSO-Solvate	Sesqui-DMSO-Solvate	¼-Ethylacetate-Solvate
799	809	810	770	753
777	796	784	757	700
771	769	775	698	637
756	631	751	667	592
700	590	692	572	572
594	573	622	512	512
512	559	593		
	512			

Tab. 2: 10 Major Peaks of IR bands of the different crystalline forms

IR Major Bands [cm^{-1}]				
Mod. I	Mod. II	Mono-DMSO-Solvate	Sesqui-DMSO-Solvate	¼-Ethylacetate-Solvate
3454	3498	3401	3407	3363
3360	3382	3361	3361	3275
3273	3269	3295	3300	1732
3103	3104	3168	3190	1702
1688	1704	1702	1698	1619
1622	1622	1626	1629	1560
1559	1586	1560	1558	1457
1284	1563	1333	1293	1246
1193	1326	1286	1043	899
989	1288	1042	770	810
777	1106	751	757	771

Tab. 3: X-Ray powder diffractogram of the different crystalline forms

Reflexes [Position °2Th.]				
Mod. I	Mod. II	Mono-DMSO-Solvate	Sesqui-DMSO-Solvate	¼-Ethylacetate-Solvate
6.7	7.6	5.5	6.2	6.7
9.1	8.3	6.2	6.7	7.2
13.7	10.3	6.7	7.3	8.3
13.8	11.2	7.5	8.3	8.7
14.3	12.6	8.4	8.4	9.1
14.4	12.7	9.0	9.0	10.9
17.8	13.9	10.3	10.1	12.9
18.4	14.3	10.8	11.1	13.3
18.7	15.2	11.1	12.4	13.7
18.9	16.6	11.2	12.8	13.8
19.8	17.3	12.4	13.7	14.2
20.2	17.6	12.8	13.9	14.5
21.0	18.2	13.0	14.3	15.4
21.2	20.0	13.4	15.1	16.4
23.3	20.3	13.7	15.7	17.5
23.7	21.8	13.9	16.1	17.8
24.3	22.5	14.2	16.8	18.6
24.8	22.8	14.3	17.2	18.8
25.6	24.9	15.1	17.2	19.3
26.1	25.0	15.5	17.7	19.8
27.3	25.5	15.7	18.4	20.2
27.9	26.2	15.9	18.8	20.3
29.1	26.8	16.0	19.1	20.5
29.4	27.5	16.5	19.1	21.0
30.5	28.1	16.8	19.6	22.8
31.0	28.8	17.2	20.7	23.2
31.3	29.4	17.7	21.1	23.6
33.2	30.0	18.4	21.4	24.0
34.0	30.5	18.7	21.9	24.4
34.2	32.3	19.1	22.3	24.7
34.9	34.0	19.6	22.6	25.1

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Reflexes [Position °2Th.] [cont.]				
Mod. I	Mod. II	Mono-DMSO-Solvate	Sesqui-DMSO-Solvate	¼-Ethylacetate-Solvate
36.1	34.4	20.2	22.8	25.6
37.5	35.0	20.7	23.4	26.3
	35.7	21.1	23.8	26.7
	36.5	21.4	24.6	27.1
		21.8	24.9	27.4
		22.2	25.4	27.6
		22.4	25.6	28.2
		22.6	25.9	28.6
		23.0	26.7	29.1
		23.5	26.8	29.7
		23.9	27.3	30.0
		24.3	27.9	30.7
		24.6	28.4	31.3
		24.8	28.8	31.8
		25.6	29.4	32.7
		26.0	29.6	33.1
		26.3	30.5	33.5
		26.7	31.5	35.2
		27.2	31.7	35.9
		28.8	32.1	37.6
		29.3	32.5	
		29.8	33.1	
		30.5	34.0	
		30.8	35.0	
		31.4	35.9	
		32.0	37.2	
		32.3		
		34.0		
		34.9		
		35.7		
		36.4		

Tab. 4: 10 Major Reflexes of X-Ray powder diffractogram of the different crystalline forms

10 Major Reflexes [Position °2Th.]				
Mod. I	Mod. II	Mono-DMSO-Solvate	Sesqui-DMSO-Solvate	¼-Ethylacetate-Solvate
6.7	11.2	9.0	8.3	6.7
9.1	12.6	10.8	8.4	8.3
14.3	12.7	11.1	13.7	8.7
14.4	13.9	11.2	13.9	12.9
17.8	15.2	13.0	15.7	14.2
19.8	17.3	15.5	17.2	17.8
20.2	22.5	15.9	18.4	19.3
24.8	22.8	16.0	19.6	24.0
25.6	25.0	20.7	21.4	25.1
27.3	25.5	25.6	24.9	26.7

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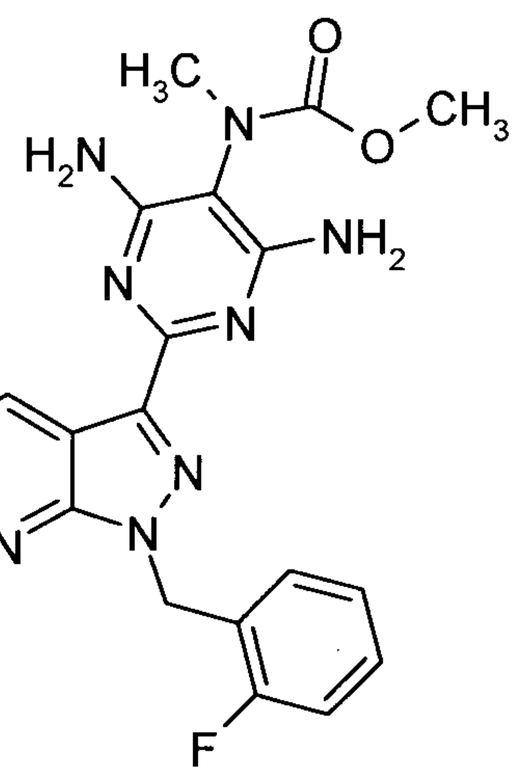
What is claimed is:

1. A the compound of the formula (I)



(I)

in the form of Modification I, Modification II, as mono-DMSO solvate, as sesqui-DMSO solvate, as 1/4-ethyl acetate solvate, in the amorphous form or a mixture thereof.

2. The compound of claim 1 characterized by one or more of the following: X-Ray powder diffractogram substantially as shown in Figures 1, 4, 7, 10, 13, 16; DSC- and TGA-Thermogram substantially as shown in Figures 2, 5, 8, 11, 14, 17; IR-Spectrum (ATR) substantially as shown in Figures 3, 6, 9, 12, 15, 18.

3. The compound of claim 1 which is methyl {4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridino-3-yl]pyrimidino-5-yl}methylcarbamate in the Modification I.

4. The compound of claim 3 characterized by a X-Ray powder diffractogram comprising peak maxima of the 2 Theta angle of 6.7, 9.1, 14.3, 14.4, 17.8, 19.8, 20.2, 24.8, 25.6, 27.3.

5. The compound of claim 1 which is methyl {4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridino-3-yl]pyrimidino-5-yl}methylcarbamate in the Modification II.

6. The compound of claim 5 characterized by a X-Ray powder diffractogram comprising peak maxima of the 2 Theta angle of 11.2, 12.6, 12.7, 13.9, 15.2, 17.3, 22.5, 22.8, 25.0, 25.5.

7. The compound of claim 1 which is the mono-DMSO solvate of methyl {4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridino-3-yl]pyrimidino-5-yl}methylcarbamate.

8. The compound of claim 7 characterized by a X-Ray powder diffractogram comprising peak maxima of the 2 Theta angle of 9.0, 10.8, 11.1, 11.2, 13.0, 15.5, 15.9, 16.0, 20.7, 25.6.

9. The compound of claim 1 which is the sesqui-DMSO solvate of methyl {4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridino-3-yl]pyrimidino-5-yl}methylcarbamate.

10. The compound of claim 9 characterized by a X-Ray powder diffractogram comprising peak maxima of the 2 Theta angle of 8.3, 8.4, 13.7, 13.9, 15.7, 17.2, 18.4, 19.6, 21.4, 24.9.

11. The compound of claim 1 which is the 1/4-ethyl acetate solvate of methyl {4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridino-3-yl]pyrimidino-5-yl}methylcarbamate.

12. The compound of claim 10 characterized by a X-Ray powder diffractogram comprising peak maxima of the 2 Theta angle of 6.7, 8.3, 8.7, 12.9, 14.2, 17.8, 19.3, 24.0, 25.1, 26.7.

13. The compound of claim 1 which is methyl {4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridino-3-yl]pyrimidino-5-yl}methylcarbamate in the amorphous form.

Figure 1: X-Ray powder diffractogram of the modification I

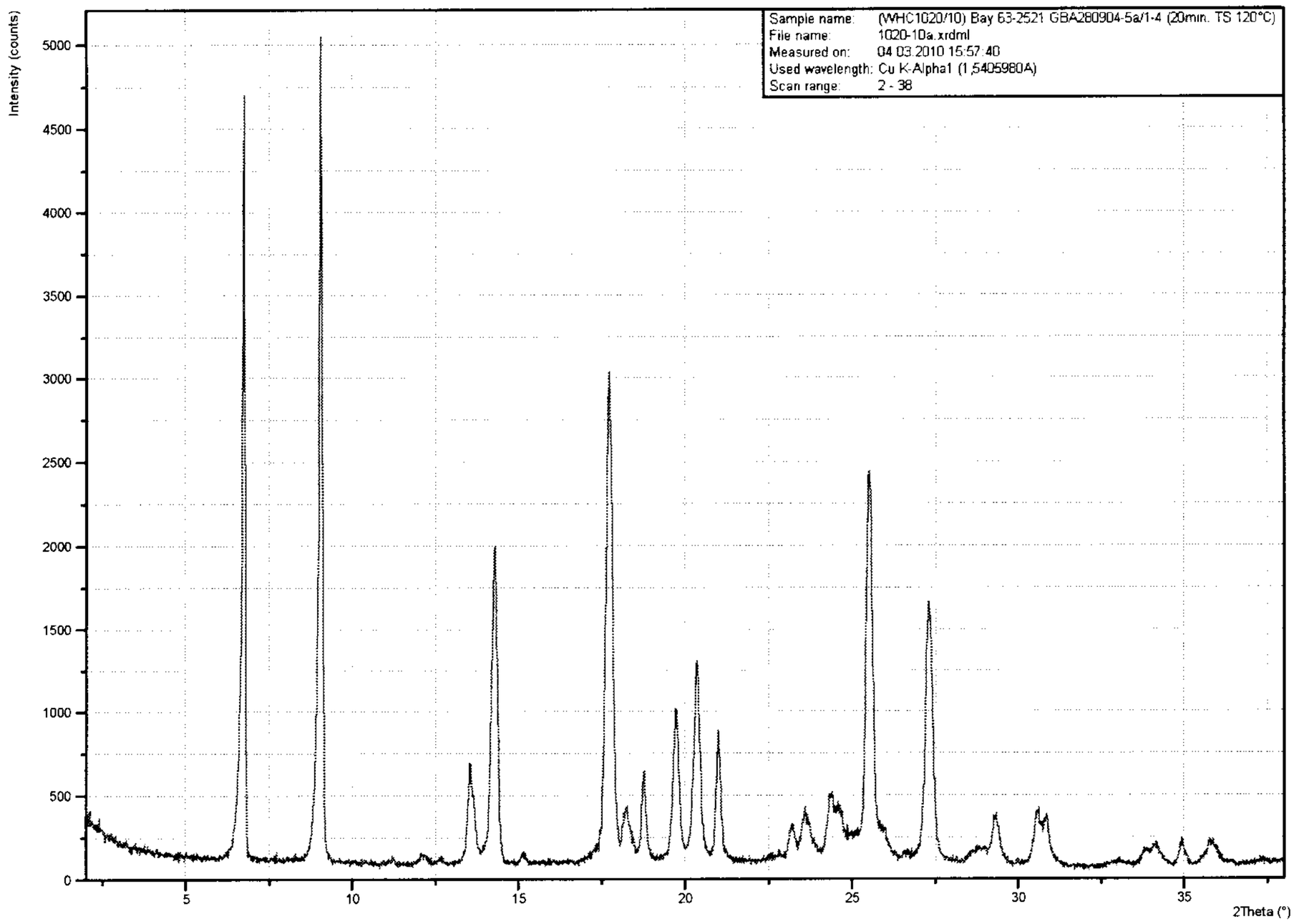


Figure 2: DSC- and TGA-Thermogram of modification I

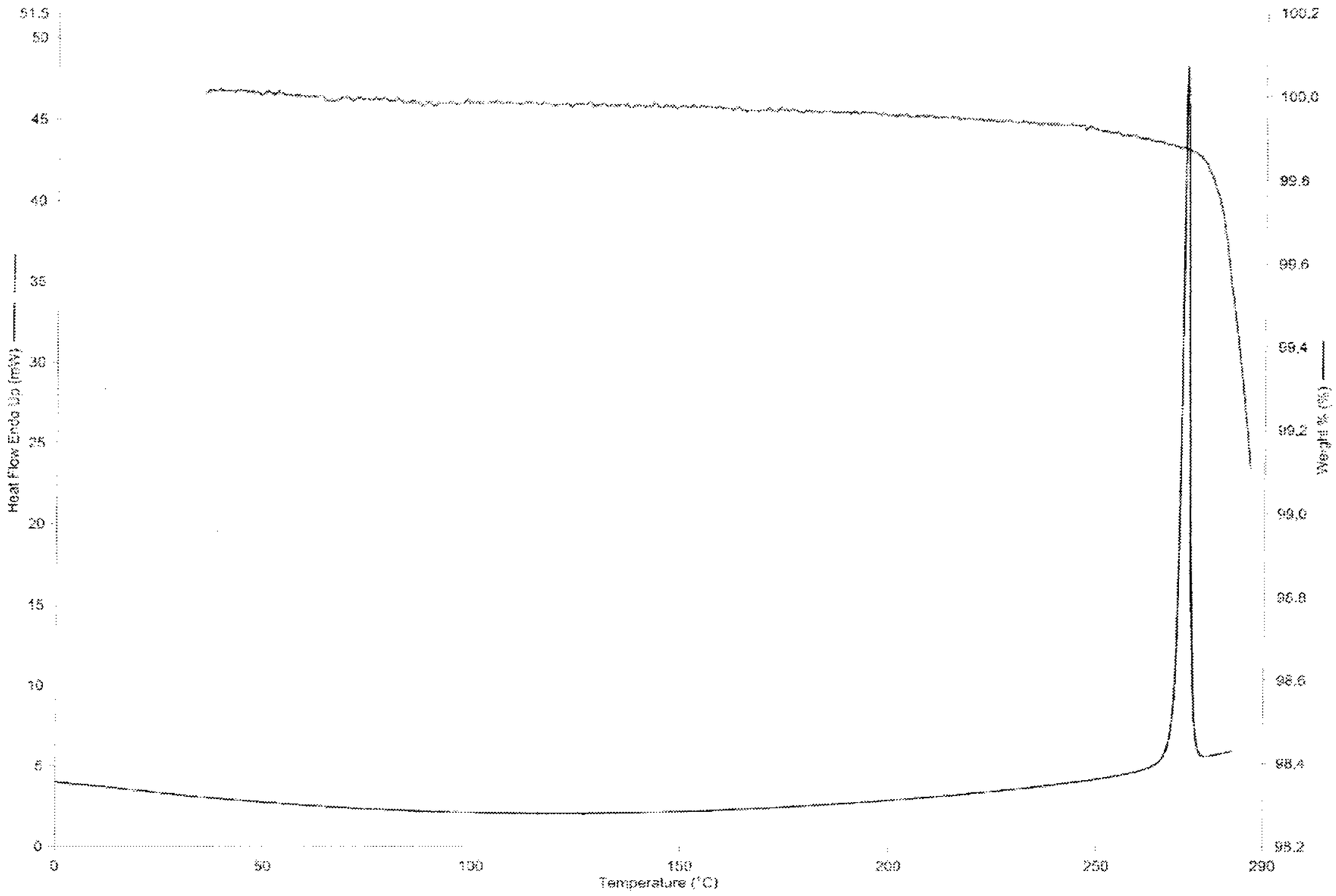


Figure 3: IR-Spectrum (ATR) of modification I

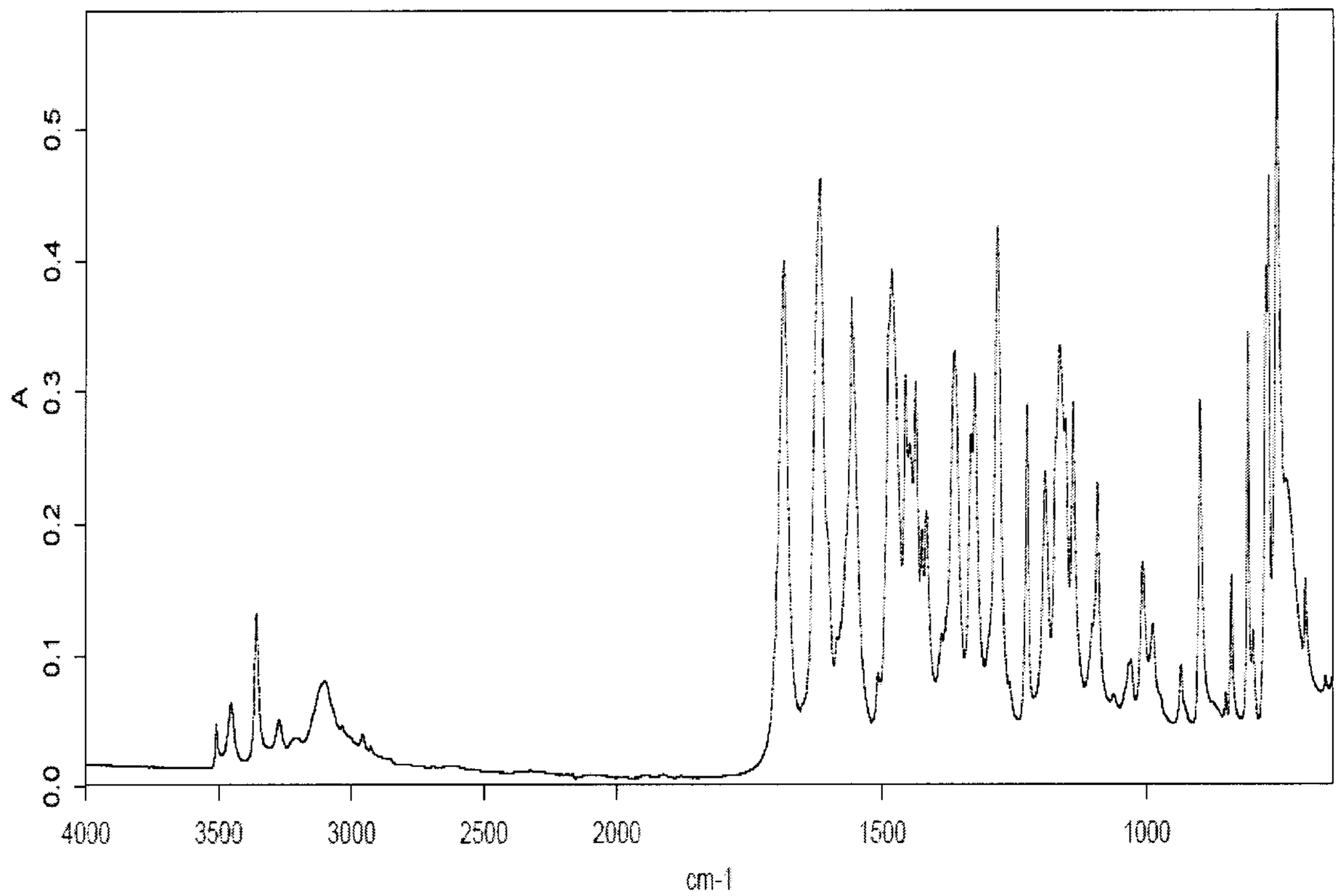


Figure 4: X-Ray powder diffractogram of the 1/4-ethyl acetate solvate

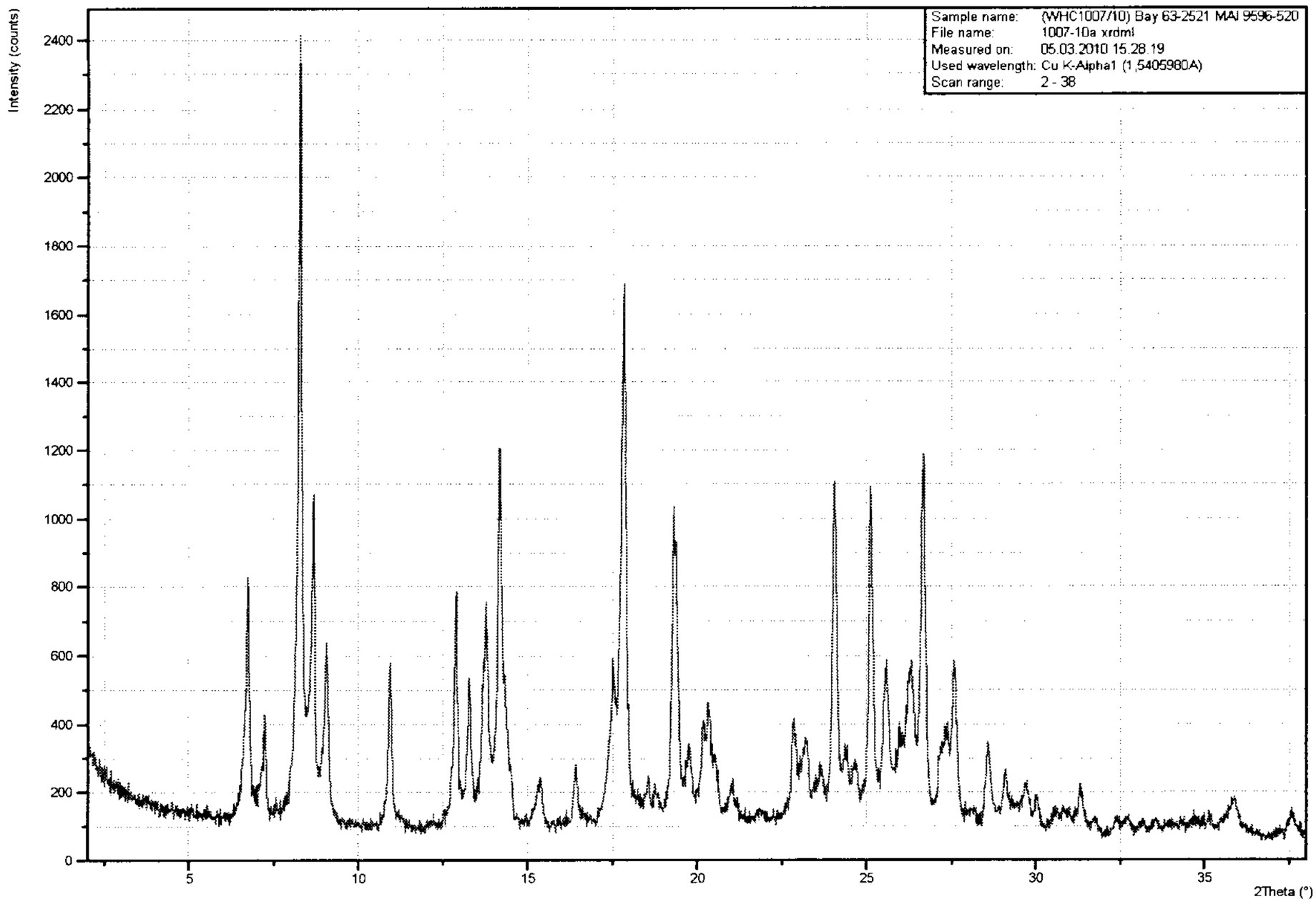


Figure 5: DSC- and TGA-Thermogram of the 1/4-ethyl acetate solvate

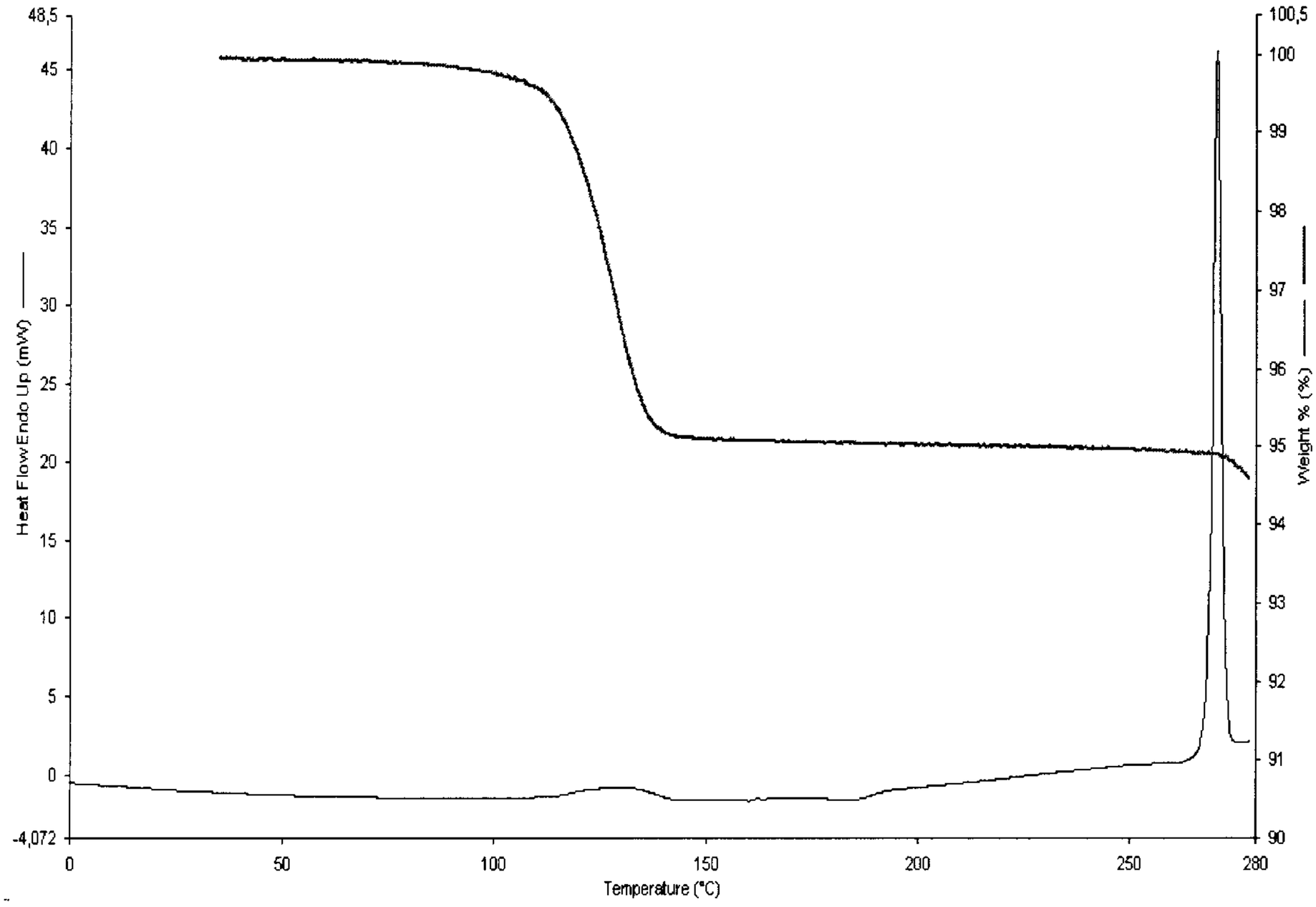


Figure 6: IR-Spectrum (ATR) of the 1/4-ethyl acetate solvate

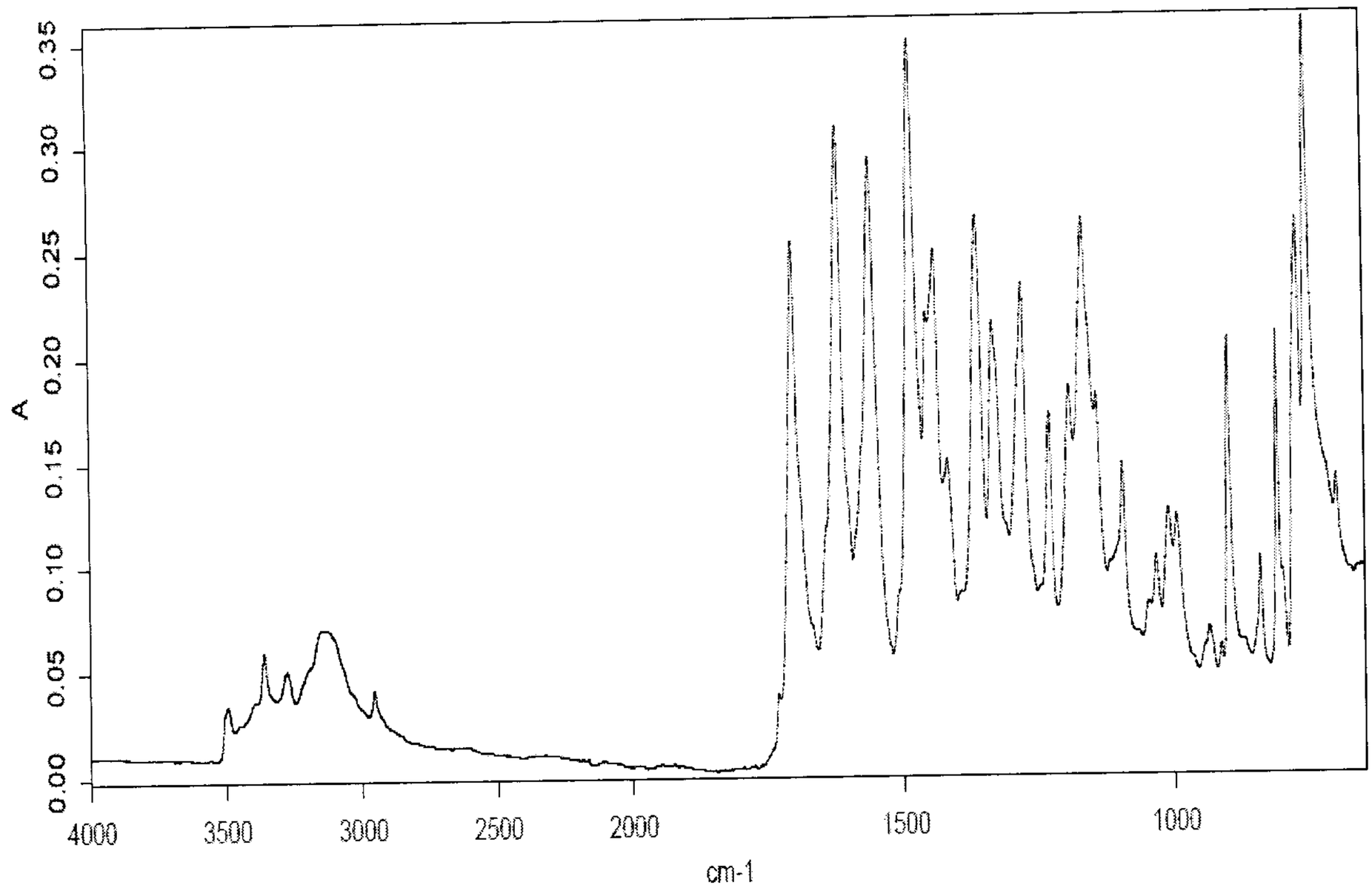


Figure 7: X-Ray powder diffractogram of the mono-DMSO solvate

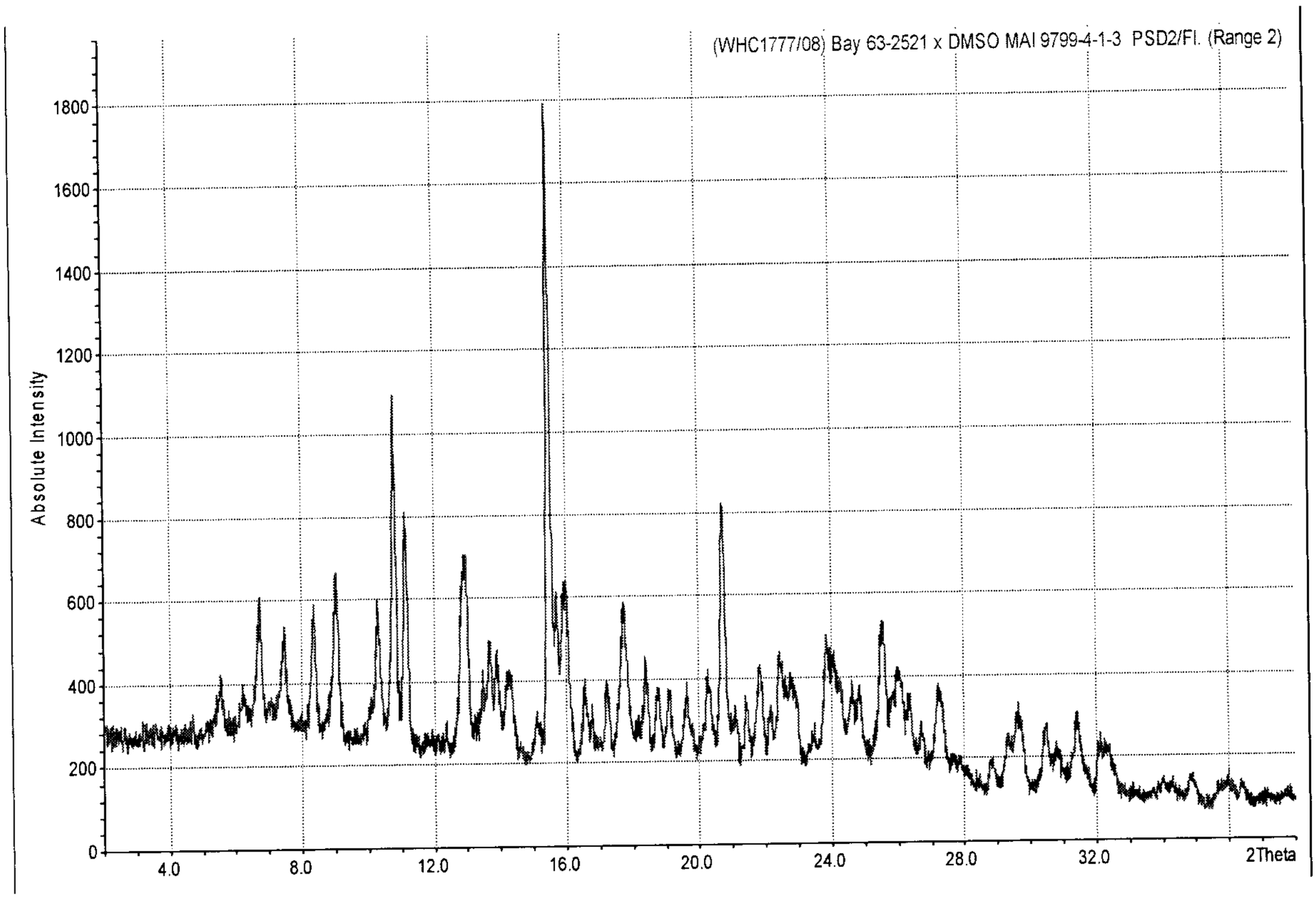


Figure 8: DSC- and TGA-Thermogram of the mono-DMSO solvate

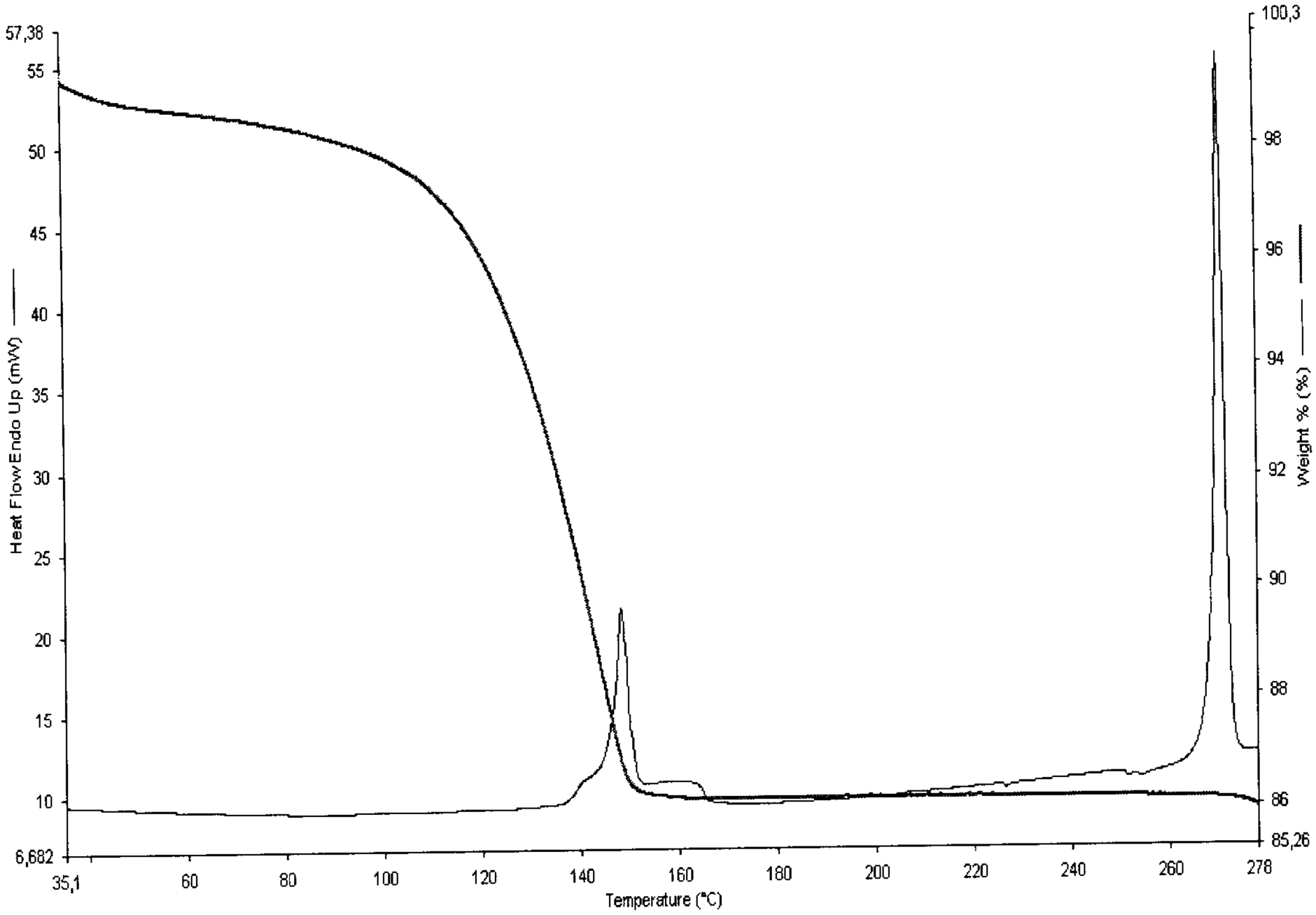


Figure 9: IR-Spectrum (ATR) of the mono-DMSO solvate

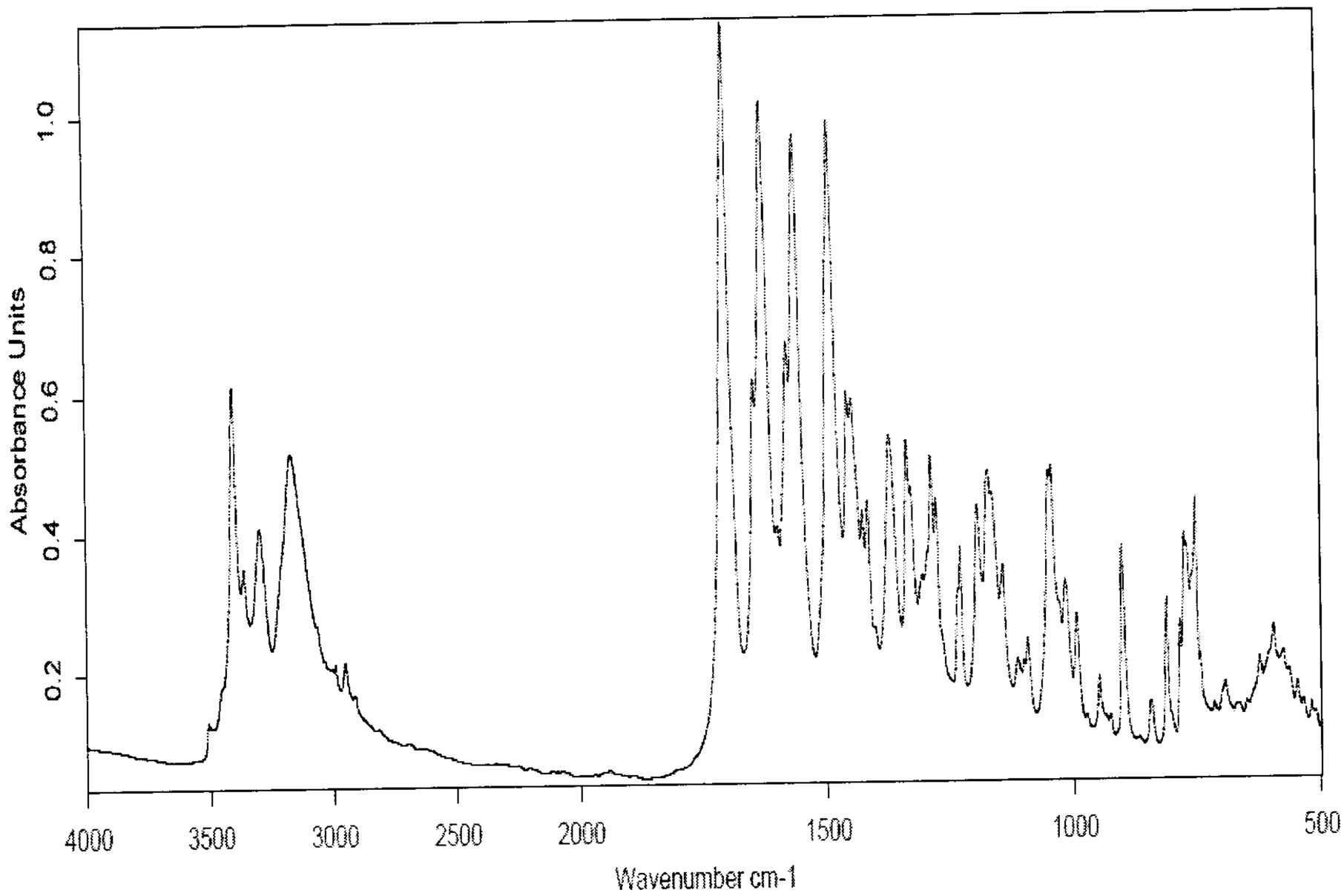


Figure 10: X-Ray powder diffractogram of the sesqui-DMSO solvate

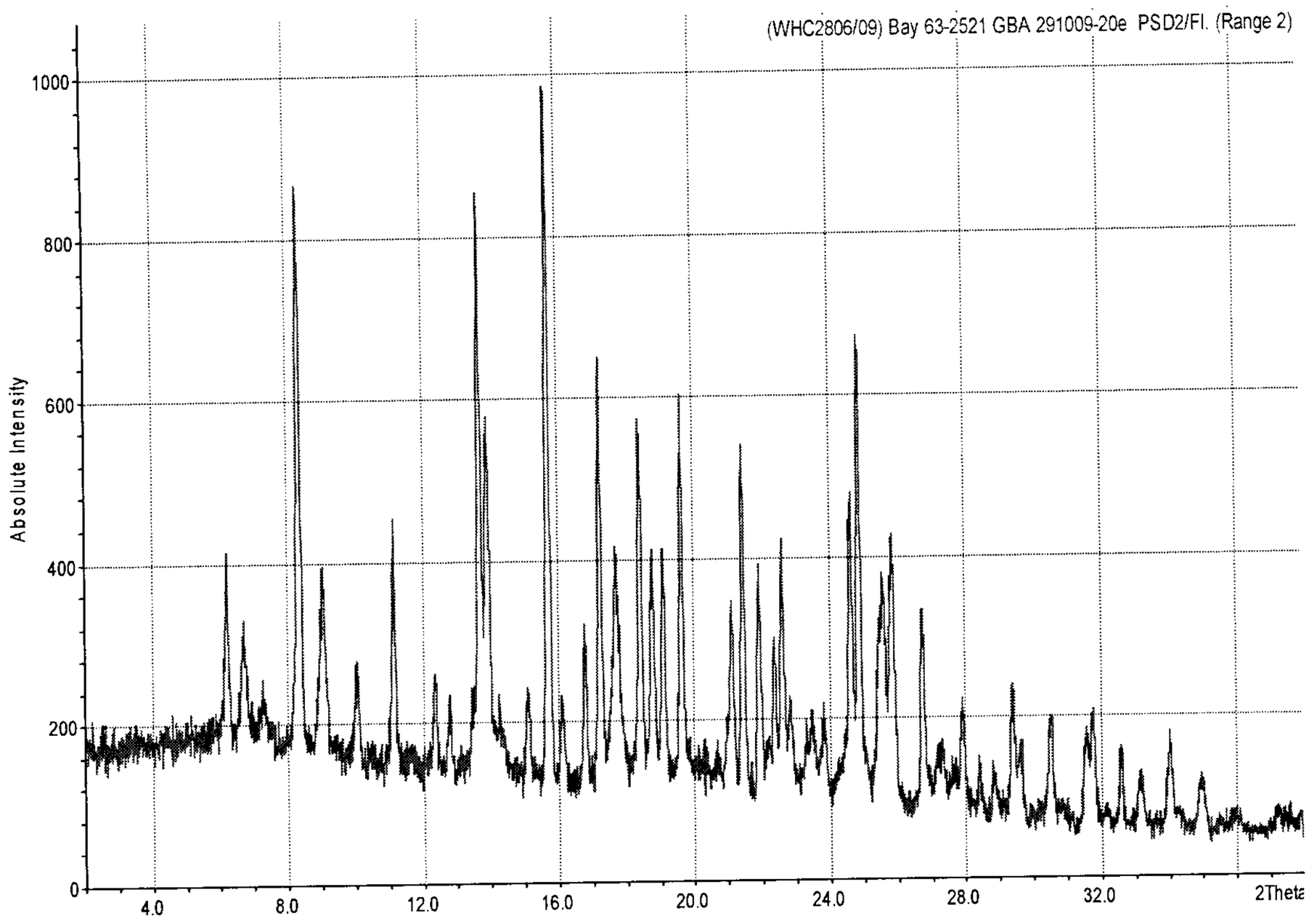


Figure 11: DSC- and TGA-Thermogram of the sesqui-DMSO solvate

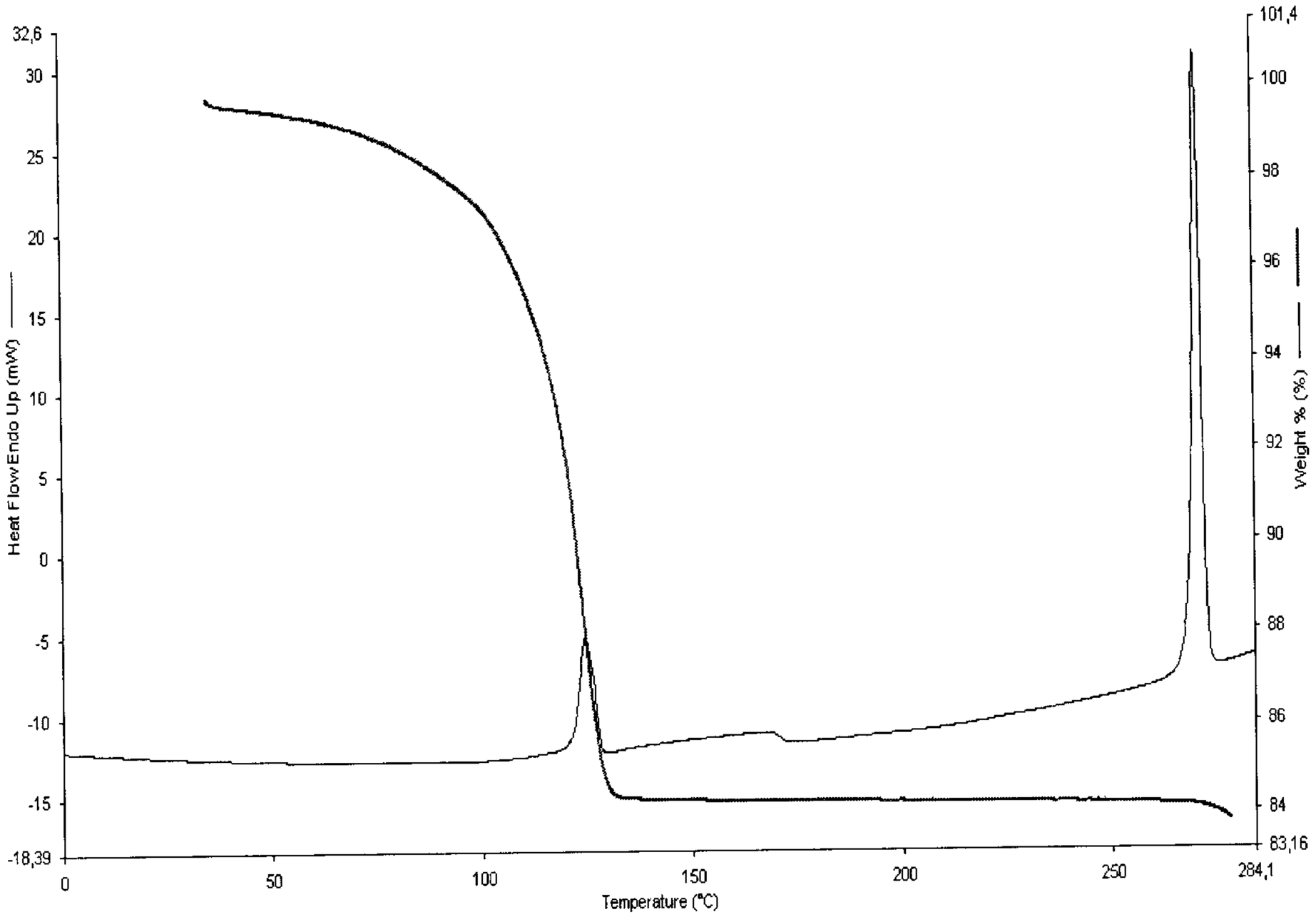


Figure 12: IR-Spectrum (ATR) of the sesqui-DMSO solvate

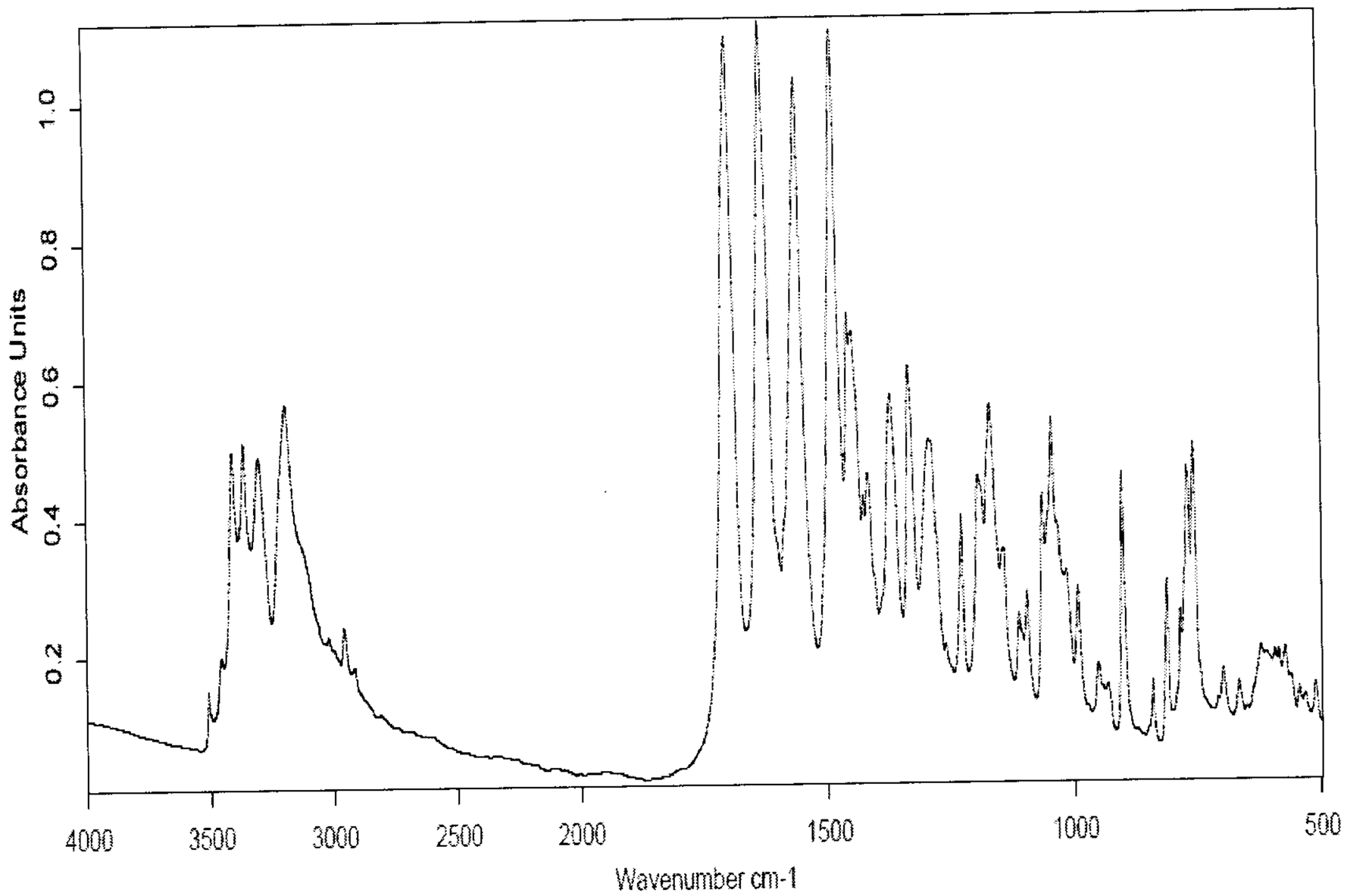


Figure 13: X-Ray powder diffractogram of modification II

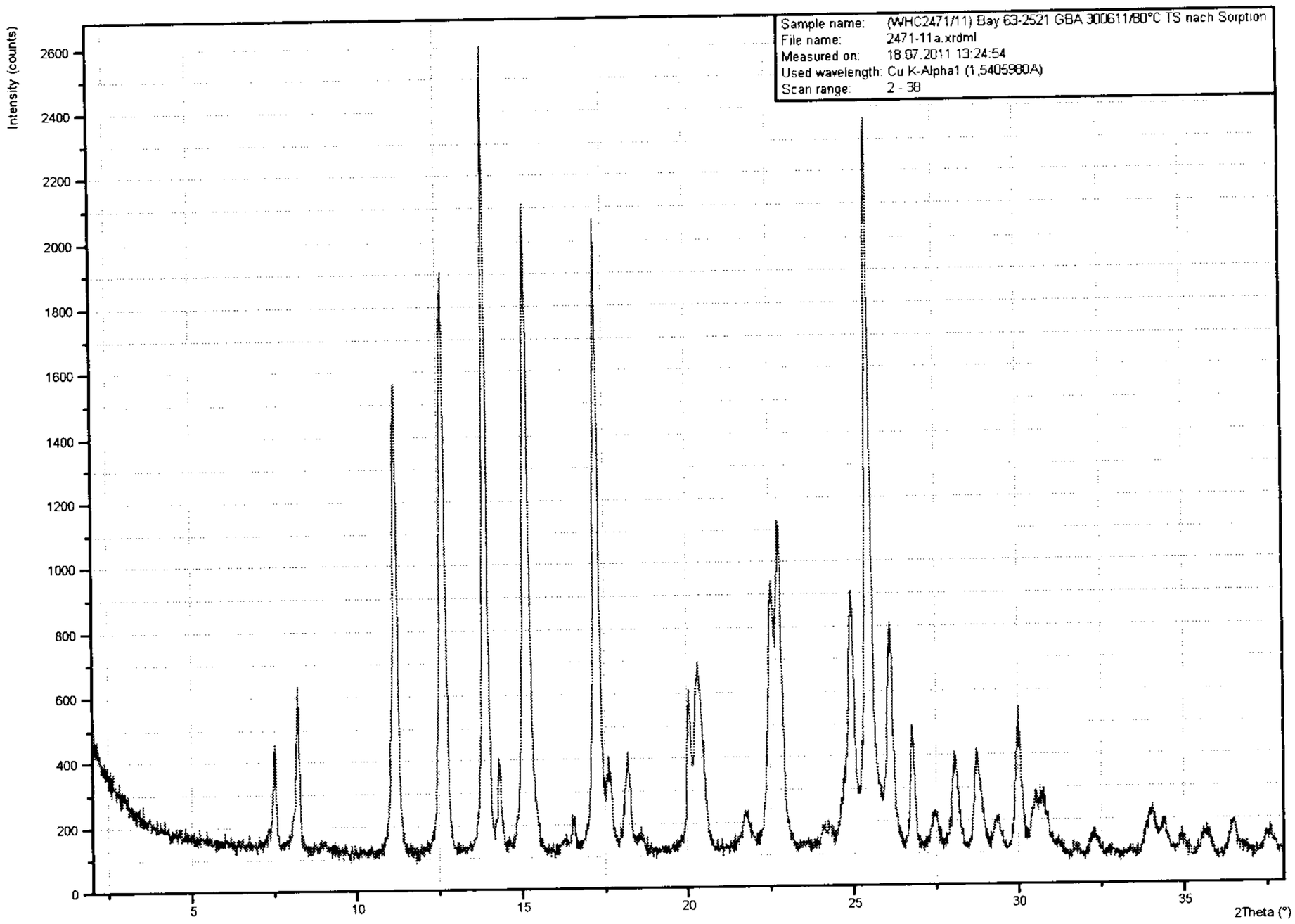


Figure 14: DSC- and TGA-Thermogram of modification II

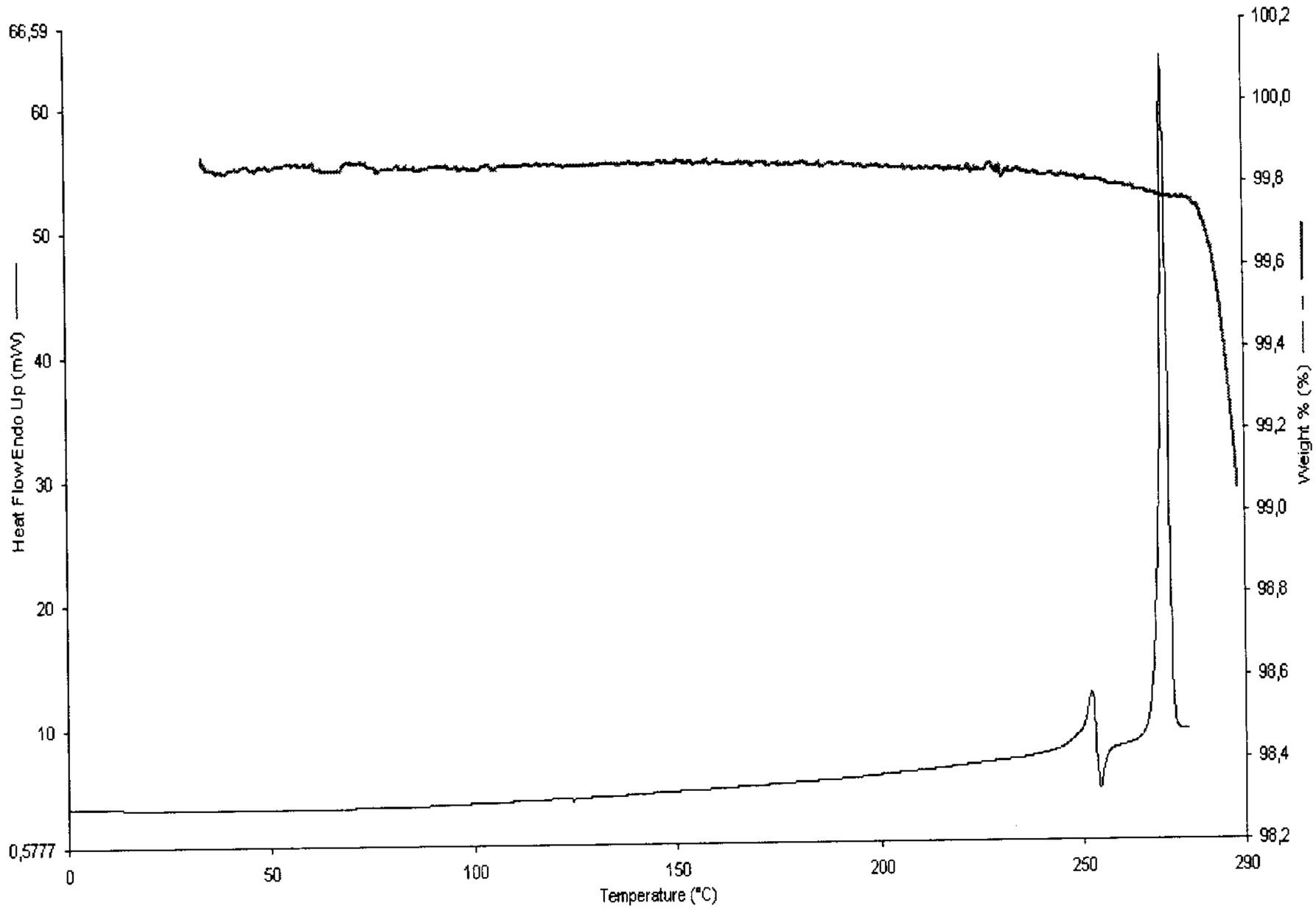


Figure 15: IR-Spectrum (ATR) of modification II

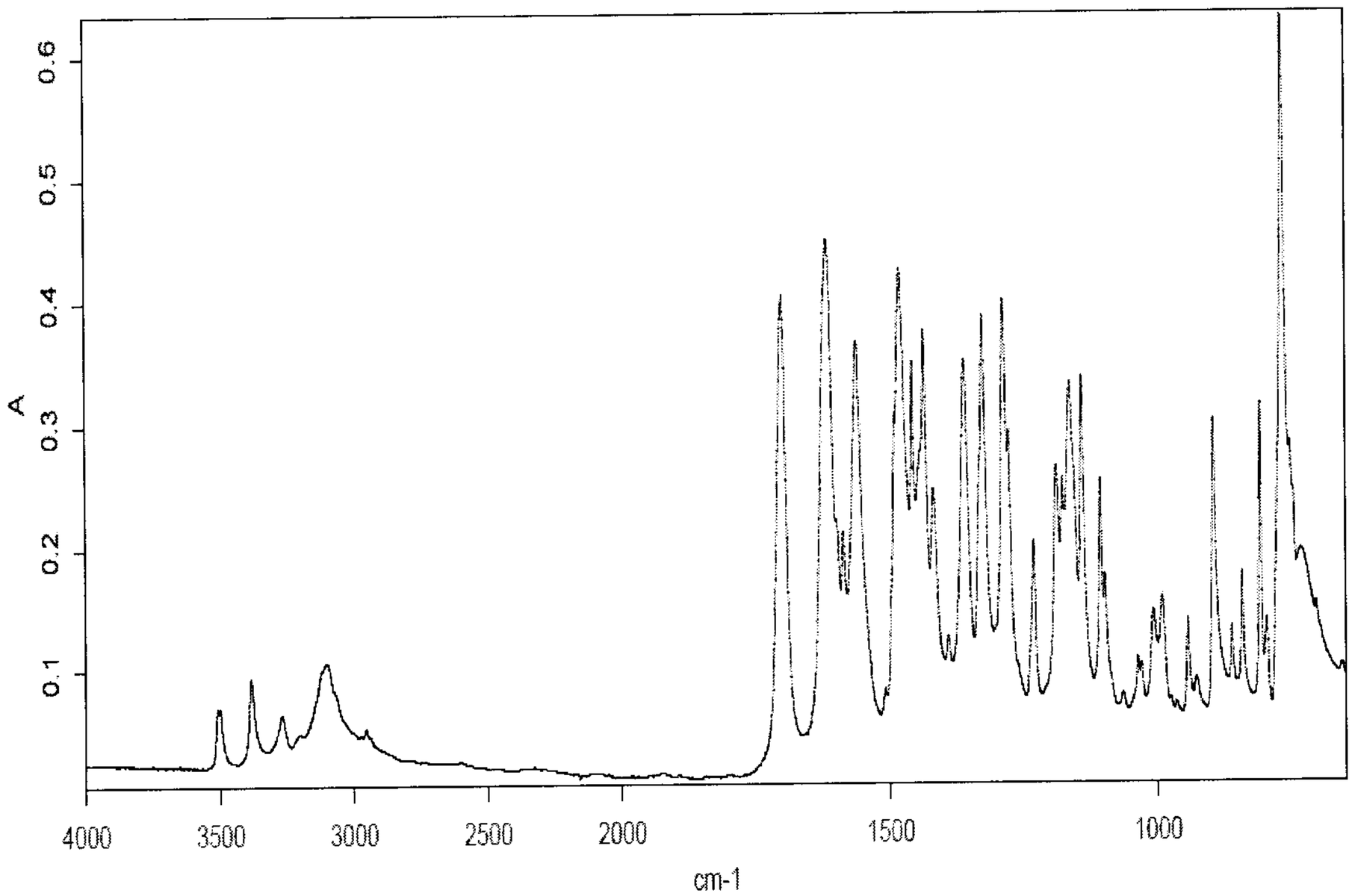


Figure 16: X-Ray powder diffractogram of the amorphous form

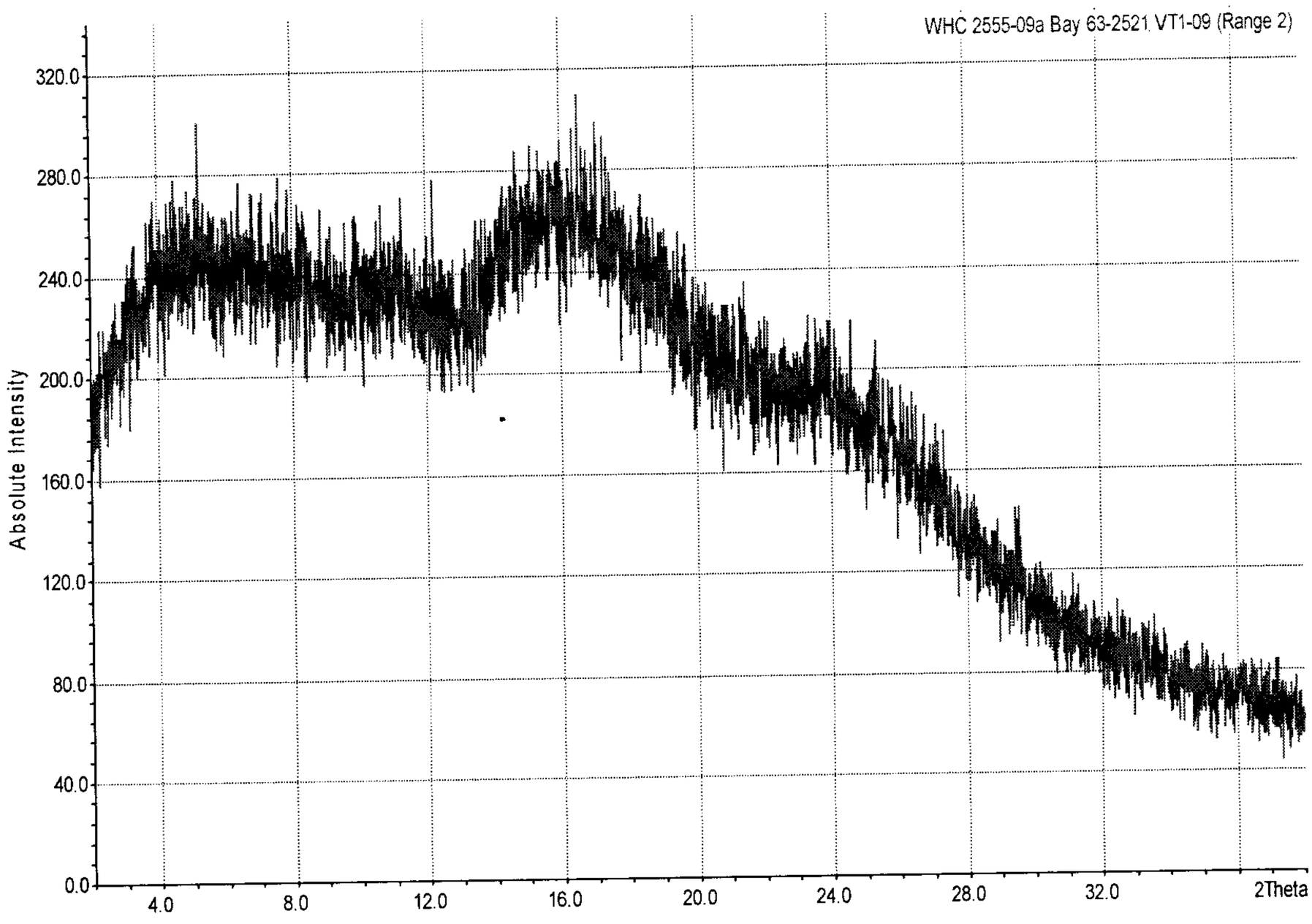


Figure 17: DSC- and TGA-Thermogram of the amorphous form

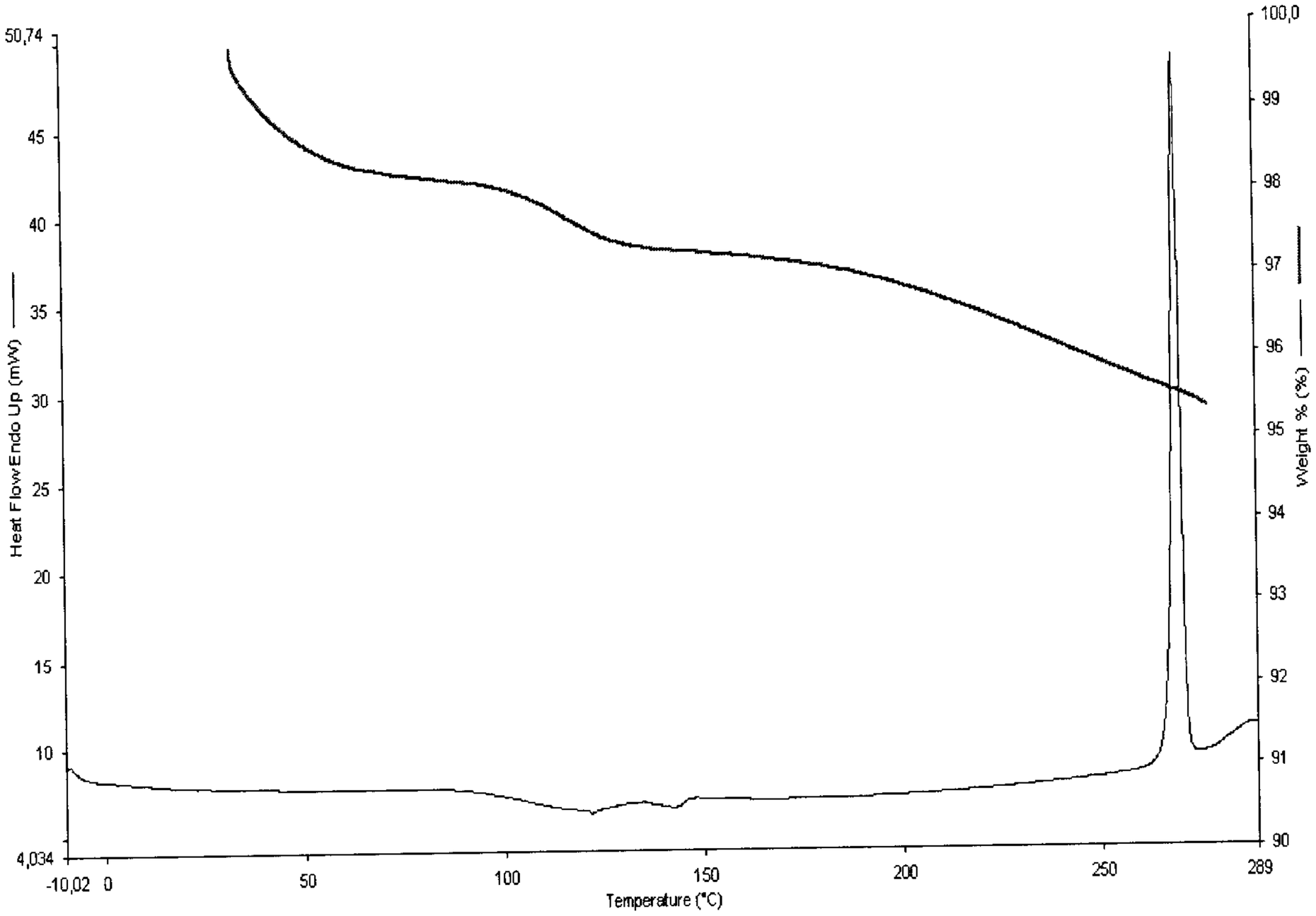
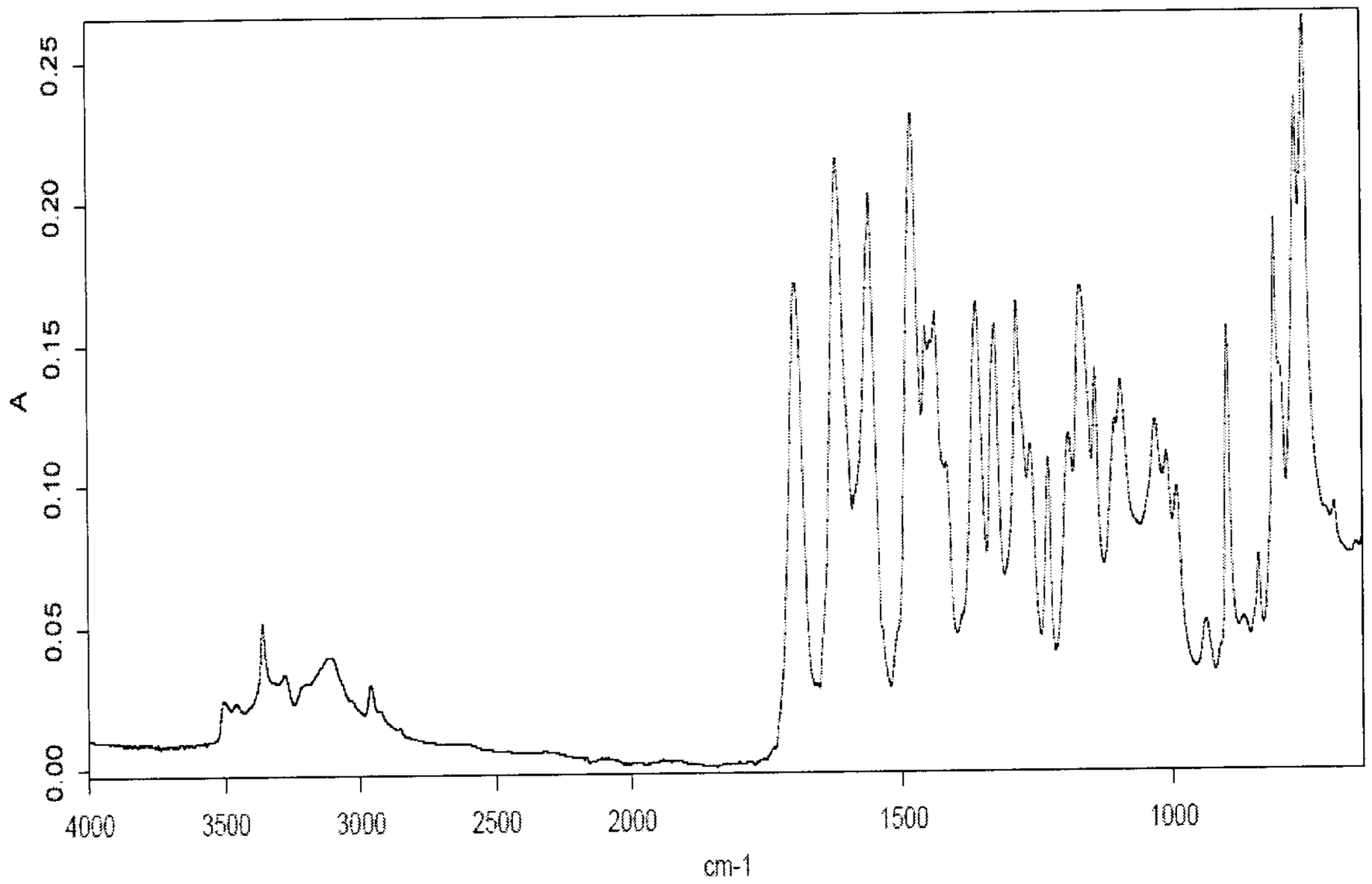


Figure 18: IR-Spectrum of the amorphous form



X-Ray powder diffractogram of the modification I