REPORT OF PHYSIOCHEMICAL ANALYSIS OF PRODUCT SOLUBAG®.

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1. Aims and scope.

The present report describes the results of the analysis of the characterisation physical chemistry for the sample of product Solubag®, requested by company SoluBag SpA (number of analysis CEQUC 90017). The physiochemical characterisation includes: infrared spectroscopy, spectroscopy by proton and carbon NMR, pH, loss of drying, acid value, analysis by ICP-MS, residue of ignition, insoluble substances in water and residual solvents.

2. Definitions and abbreviations.

2.1. NMR: Nuclear Magnetic Resonance.

2.2. ICP-OES: Inductively Coupled Plasma Optical Spectrometry.

2.3. DAD: Diode Array Detector.

2.4. IR: Infrared.

3. References and documents related. Not applied.

4. Equipment and labware.

4.1. Analytical balance.

4.2. Micropipetas.

4.3. Volumetric flasks.

4.4. ICP-OES analyzer.

4.5. Gas Cromatograph and HPLC coupled to DAD.

4.6. pHmeter.

4.7. Muffle Furnace.

4.8. Oven for loss of drying.

4.9. Infrared spectroscopy analyzer.

4.10. NMR spectrometer.

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5. Reference materials.

5.1. Polyvinyl Alcohol USP batch F1H039 (code CEQUC 9228), potency 100%, expiry date 07/2023.

6. Reagents and dissolutions.

6.1. Deuterated Water.

6.2. Nitric Acid.

6.3. Sulfuric Acid.

6.4. Purified Water.

6.5. Ethanol.

6.6. Standard solutions 1000 ppm of metals for analysis by ICP-OES.

6.7. Reagents for analysis of residual solvents by gas chromatography.

6.8. Sodium Hydroxide 0,05 N.

7. Description of activities.

7.1. Description. The sample is constituted by fragments with shape rectangular of white colour, rough to the touch and partially translucent. In his surface appreciate filaments of white colour had in shape random, conforming a characteristic appearance.

7.2. Solubility. A portion of sample (5 mg) was dissolved with 50 mL of Purified Water and Ethanol in room temperature. The sample is insoluble in Purified Water and Ethanol.
Then, taking 30 mg of sample to dissolve in 50 mL of Purified Water and elevating the temperature to 75°C, we observe that the sample was disaggregated in very thin pieces of fiber. The fibers begin to dissappear at higher temperature (above 90°C).

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7.3. Infrared spectroscopy. In the infrared spectrometer with Fourier transform Bruker model Vector 22, 500 mg of the sample was dissolved in 50 mL of Water to 80°C. Afterwards, it evaporates the solution and elaborates a tablet with KBr with the dried residue for reading in the infrared spectrum from 200 cm^{-1} to 4000 cm^{-1}. The results of the identification of functional groups are the following:

Frequency (cm^{-1})	Functional groups
3500-3200	Stretching O-H (wide signal)
~2800	Deformation C-H bond groups
1087,85	Stretching C-O-C
1458,18	Deformation CH_2

The sample analyzed does not show coherent signals with the stretching of the C=O bond, which shows that the polymer in the sample processed has not suffer tautomerization neither another similar reaction (group hydroxyl acetilation). Besides, they do not appear corresponding signals to aromatic compounds neither the presence of amines and other similar compounds.

To confirm the identification of the sample, IR spectrum was performed for the standard USP Polyvinyl Alcohol for the reading in the spectrophotometer. The result of the spectrum of reference is similar to the spectrum obtained for the sample, confirming that the identification is positive for Polyvinyl Alcohol.

7.4. Spectroscopy of RMN-1H. The analysis performed in Bruker Advance III HD-400, dissolving around 5 mg of sample in 50 mL of Water until dissolving entirely. Afterwards, it takes 0,3 mL and adds 0,3 mL of Deuterated Water and perform the analysis to 400 MHz to room temperature. The spectrums show in the Annex of this document.

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The signals (multiplets) in 4,0 ppm and 1,6 ppm are consistent with the chemical shifts of Polyvinyl Alcohol shown in bibliographic references (*Thermoresponsive, Well-defined, Poly (Vinyl Alcohol) co-polymers; Congdon et al, 2015*). There is not presence of characteristic signals of aromatic neither similar impurities (see Annexes).

7.5. Spectroscopy of RMN-13C. The analysis performed in Bruker Advance III HD-400, dissolving around 5 mg of sample in 50 mL of Water until dissolving entirely. Afterwards, it takes 0,3 mL and adds 0,3 mL of Deuterated Water and perform the analysis to 400 MHz to room temperature. The spectrums show in the Annex of this document.

The spectrum shows weak signals around 66 ppm and 44 ppm, but compatible with the informed in bibliography for Polyvinyl Alcohol (*Assignment of finely resolve 13C NMR spectra of poly (vinyl alcohol); Katsuraya et al, 2001*).

7.6. Residual solvents. The analysis was performed in the gas chromatograph with flame ionization detector (internal code GC-4), based in the USP chapter "Residual Solvents".

They dissolve 150 mg of sample in 50 mL of Purified Water, agitates with magnetic stir bar and increases the temperature of the solution until obtain a translucent liquid (above 90°C). Then, since this transparent solution takes 5 mL and places in a 10 mL volumetric flask. Cool to room temperature and this solution was diluted to volume with Purified Water.

Afterwards, of this solution takes 5 mL and diluted again to 10 mL with Purified Water in vial for headspace.

In this analysis we used the following reference solvents: Acetonitrile, Chloroform, Dichloromethane, 1,4-Dioxane, Trichloroethylene, Methanol, Acetone, Ethanol, Isopropanol, Cyclohexane, Xilenes, Ethyl Acetate and Tetrahydrofuran.

Two samples was analized, one of which shows a peak of area very small corresponding to Acetone and for the second sample detects a small peak, probably corresponding to Ethyl Acetate (see Annex).

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7.7. Analysis by ICP-OES. The analysis of metals requested was performed in ICP-OES analyzer code ICP-1, weighting 0,5 g of sample and dissolving with 10 mL of Nitric Acid and 2 mL of Sulfuric Acid to volume with 10 mL of Purified Water in volumetric flask. The results are the following:

Element	Result (mg/kg)
Arsenic	< 1,0
Cadmium	< 1,0
Mercurio	< 1,0
Lead	< 1,0

7.8. Physiochemical analysis. In the following table, it shows the summary of the results obtained:

Parameter	Result
Loss of drying *	3,3%
pH *	6,78
Residue of incineration *	0,5%
Acid value *	0,11
Insoluble substances in Water	< 0,5%

Note (*): Results complies the reference limits expressed in the monograph USP of Polyvinyl Alcohol (raw material).

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8. Conclusions.

8.1. In the analysis of residual solvents, we detected two residual solvents in the sample analyzed. This fact requires a confirmation through of quantification of these solvents in the product. Even so, the quantities detected are lower than 0,1%, which would not constitute important risk in the moment of use of the product.

8.2. The positive identity of Polyvinyl Alcohol in the sample with the physiochemical analysis performed complies with the limits indicated in the USP monograph of Polyvinyl Alcohol, therefore this product used in Solubag® complies with the quality requierements for a pharmaceutical raw material.

9. Annexes.

9.1. Infrared spectra.

9.2. RMN-1H spectra (characterisation).

9.3. RMN-13C spectra (characterisation).

9.4. GC chromatograms.

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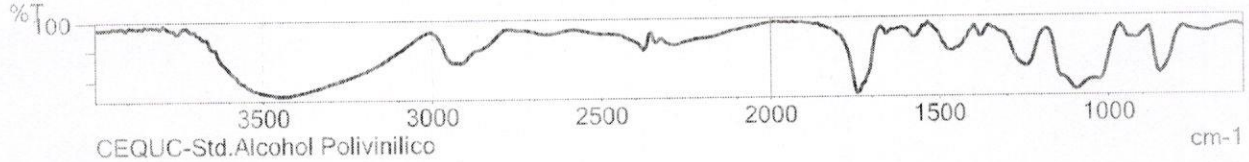
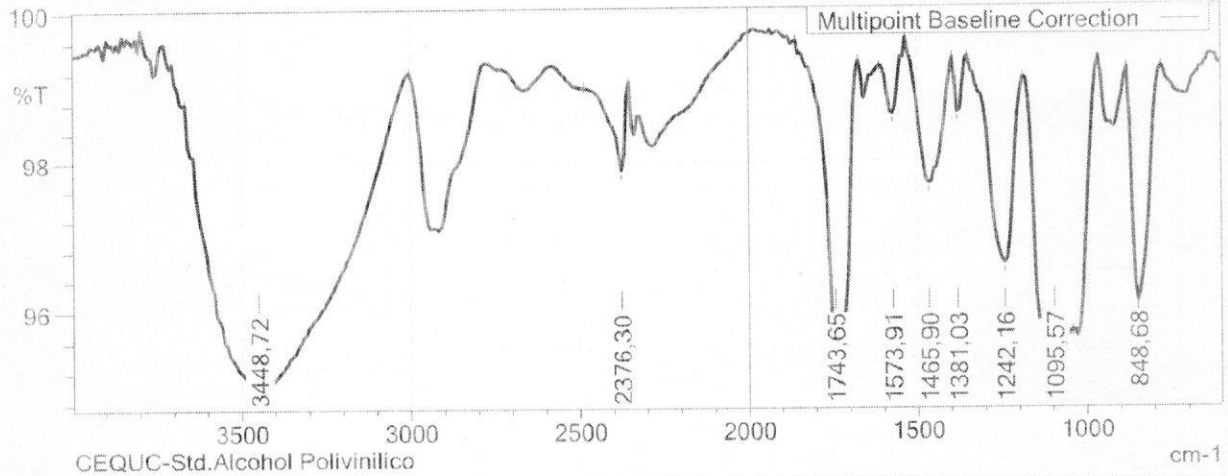
UCIPUC





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2	1095,57	95,08	0,75	1134,14	1041,56	419,624	32,038	
3	1242,16	96,61	2,59	1350,17	1188,15	322,629	201,182	
4	1381,03	98,65	0,72	1396,46	1350,17	44,761	15,921	
5	1465,90	97,69	1,81	1535,34	1396,46	209,880	140,334	
6	1573,91	98,63	0,82	1612,49	1535,34	72,463	30,165	
7	1743,65	94,97	4,47	1859,38	1674,21	408,861	310,708	
8	2376,30	97,87	1,19	2484,32	2353,16	177,778	52,162	
9	3448,72	95,02	3,92	3664,75	3001,24	2335,309	1679,578	

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INFORME FT-IR
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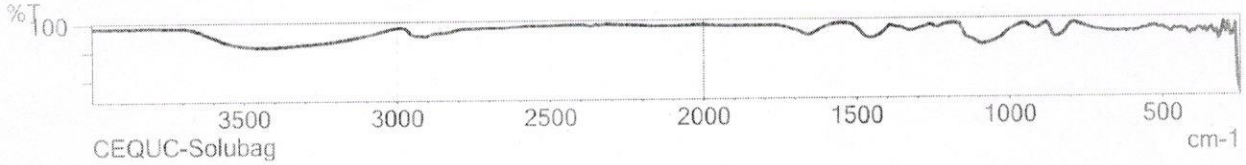

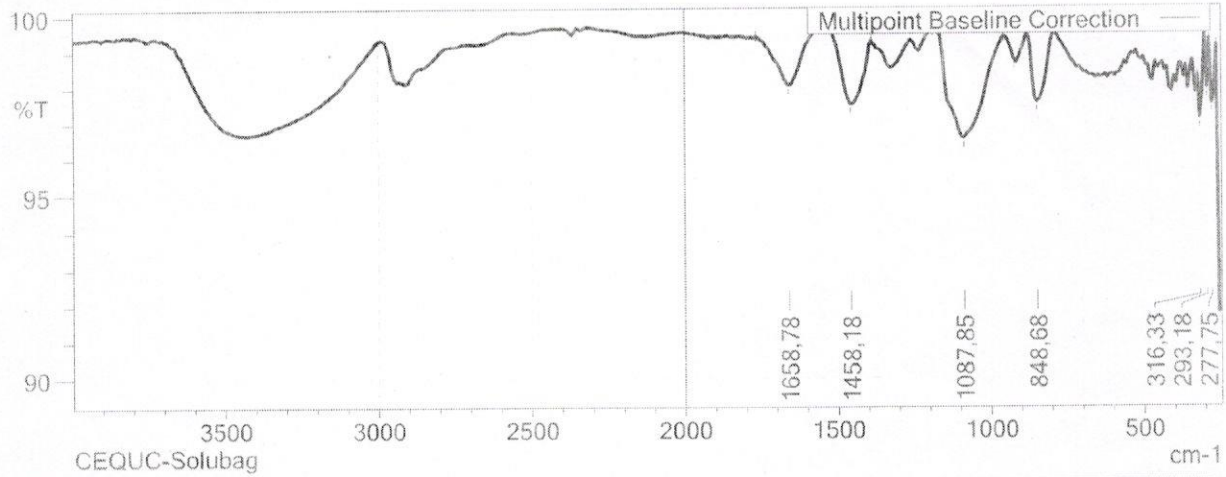

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2	293,18	97,91	1,42	300,90	285,46	21,221	10,957	
3	316,33	97,05	1,60	324,04	300,90	48,800	21,950	
4	848,68	97,52	1,95	879,54	786,96	145,473	96,829	
5	1087,85	96,52	2,91	1188,15	956,69	492,304	359,155	
6	1458,18	97,48	1,94	1535,34	1388,75	229,508	146,565	
7	1658,78	98,02	1,49	1766,80	1550,77	242,727	135,354	

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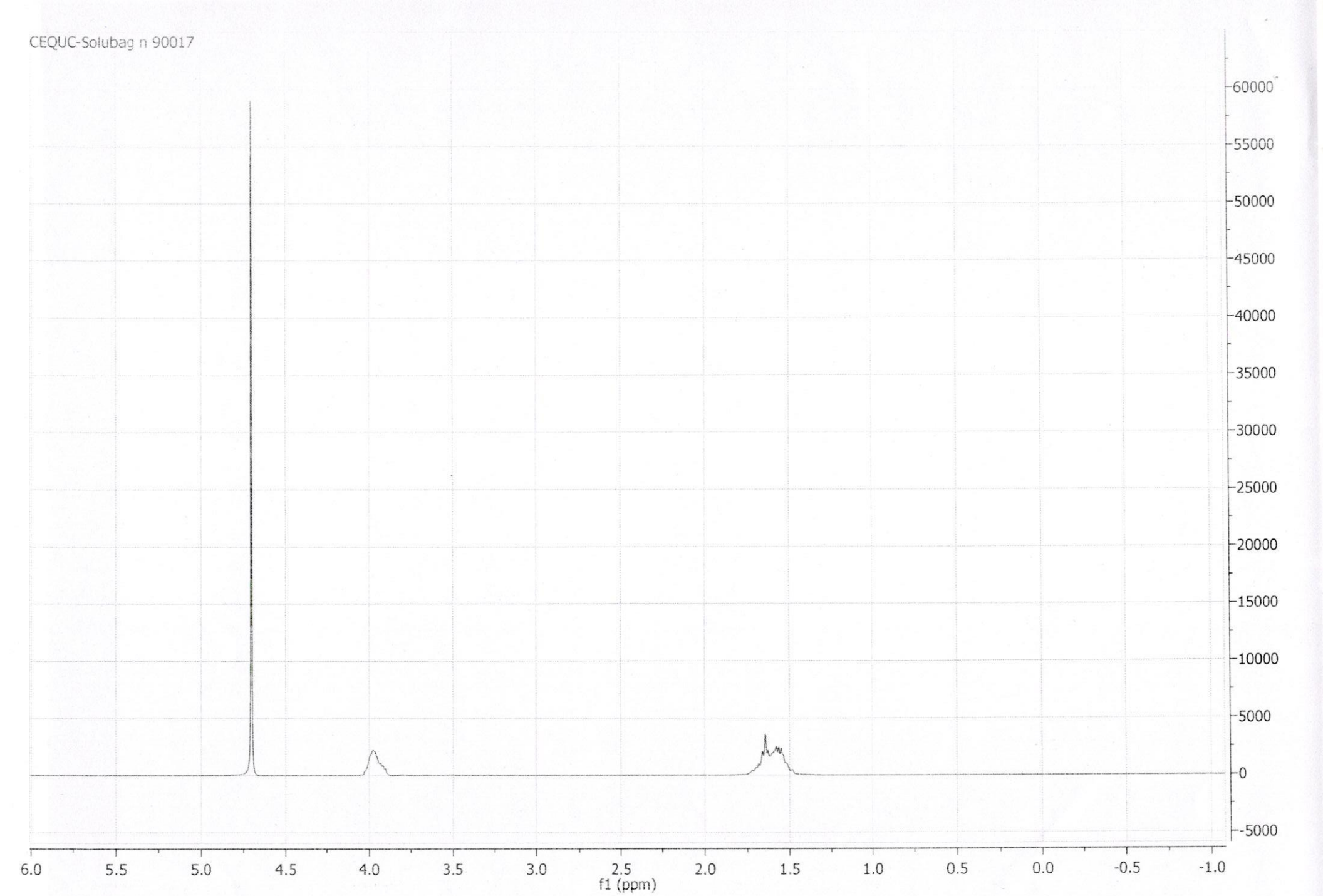
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40000
35000
30000
25000
20000
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10000
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0
-5000
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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0.0
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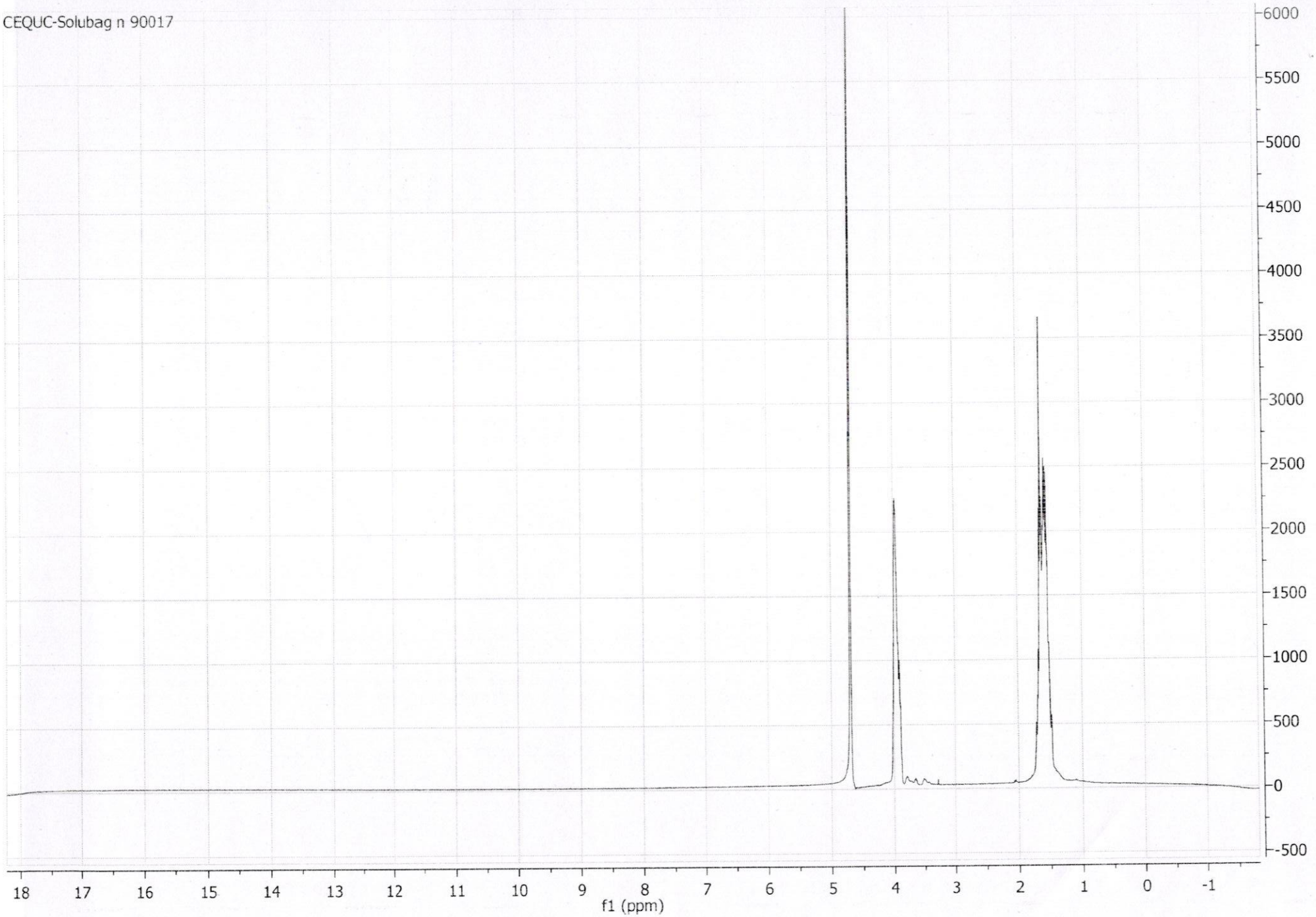
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3
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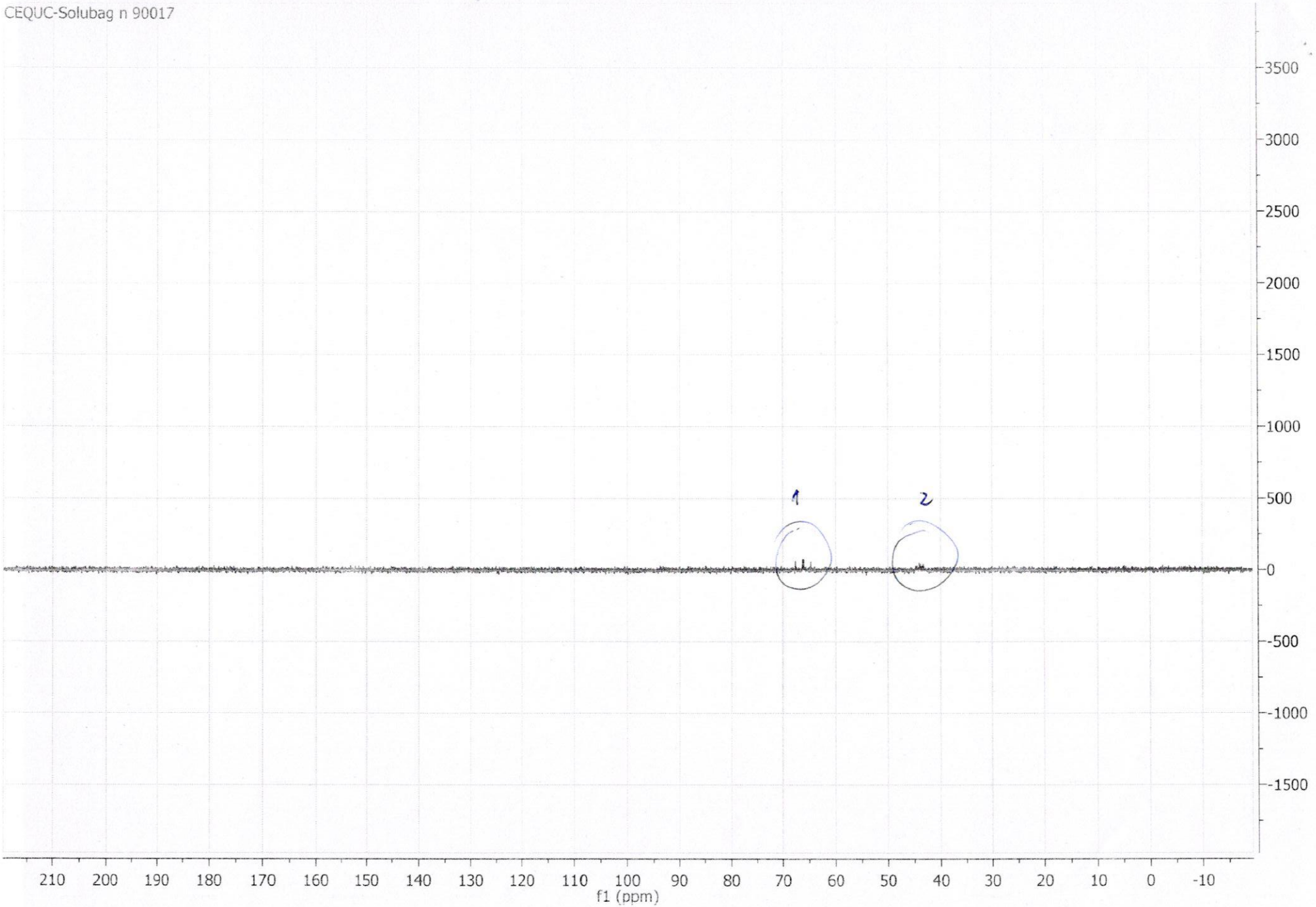
f1 (ppm)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3000
2500
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1500
1000
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0
-500
-1000
-1500
1
2
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200
190
180
170
160
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120
110
100
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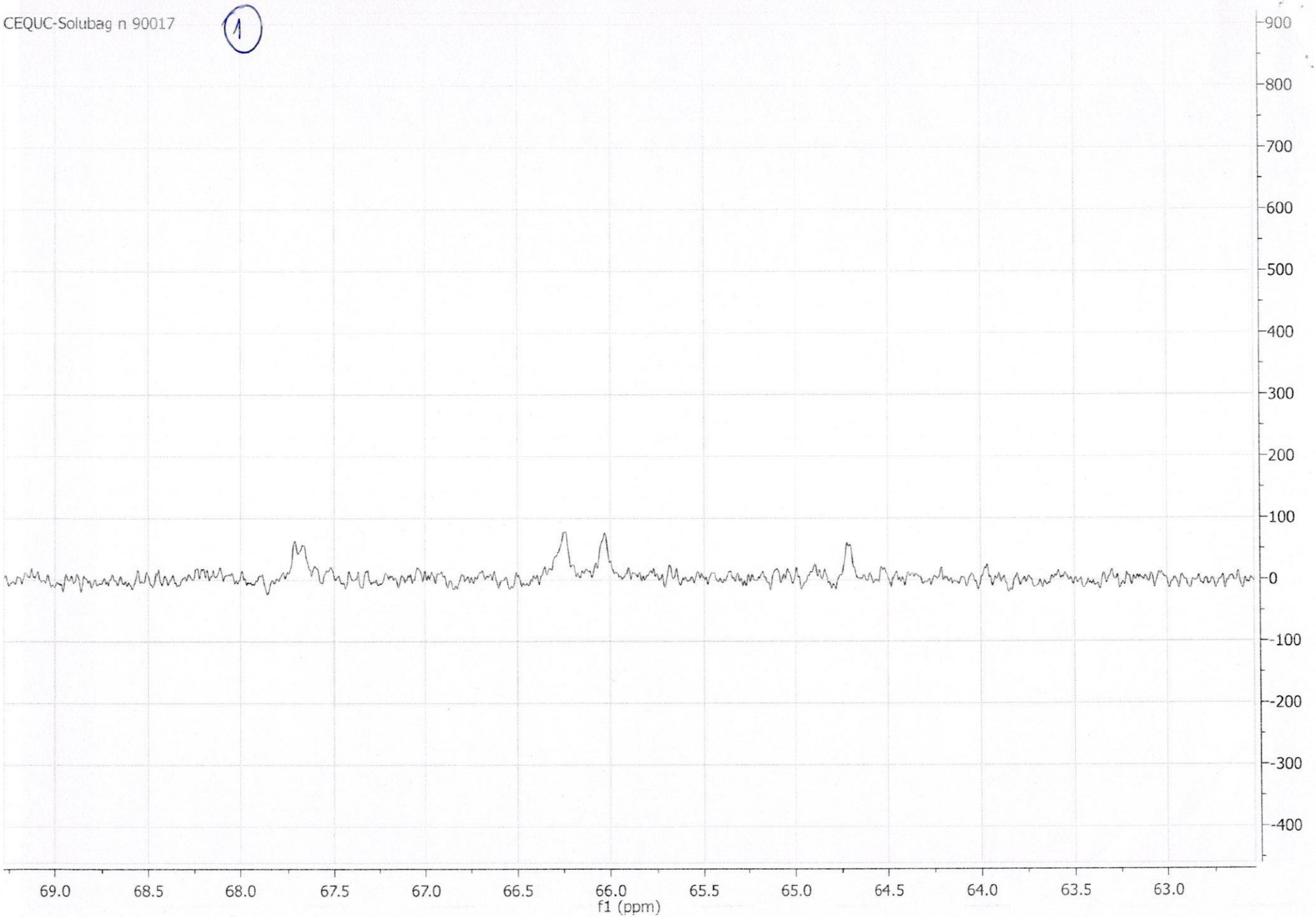
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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800
700
600
500
400
300
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-400
69.0
68.5
68.0
67.5
67.0
66.5
66.0
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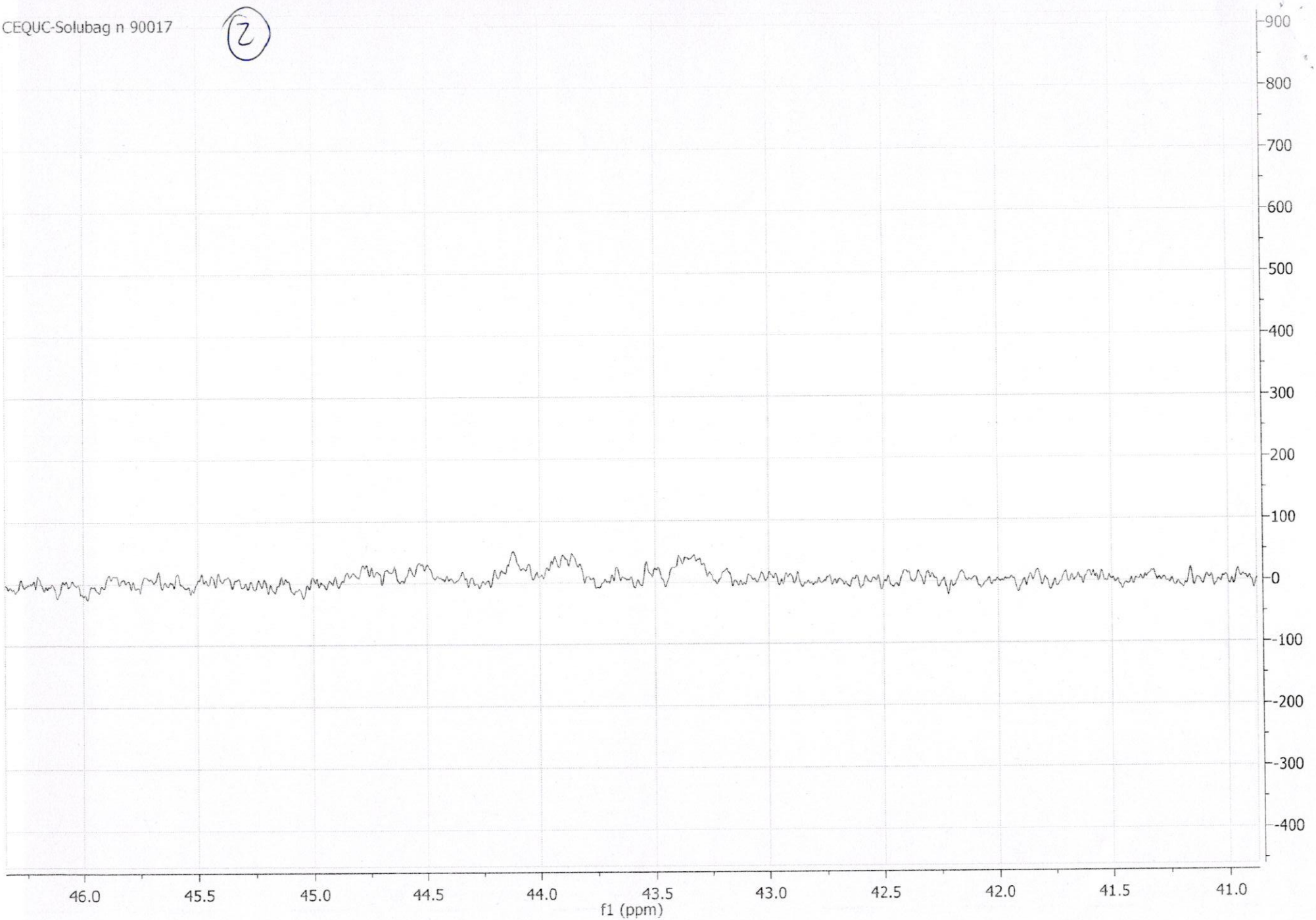
65.0
64.5
64.0
63.5
63.0
f1 (ppm)

CEQUC-Solubag n 90017

(2)



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Agilent Technologies

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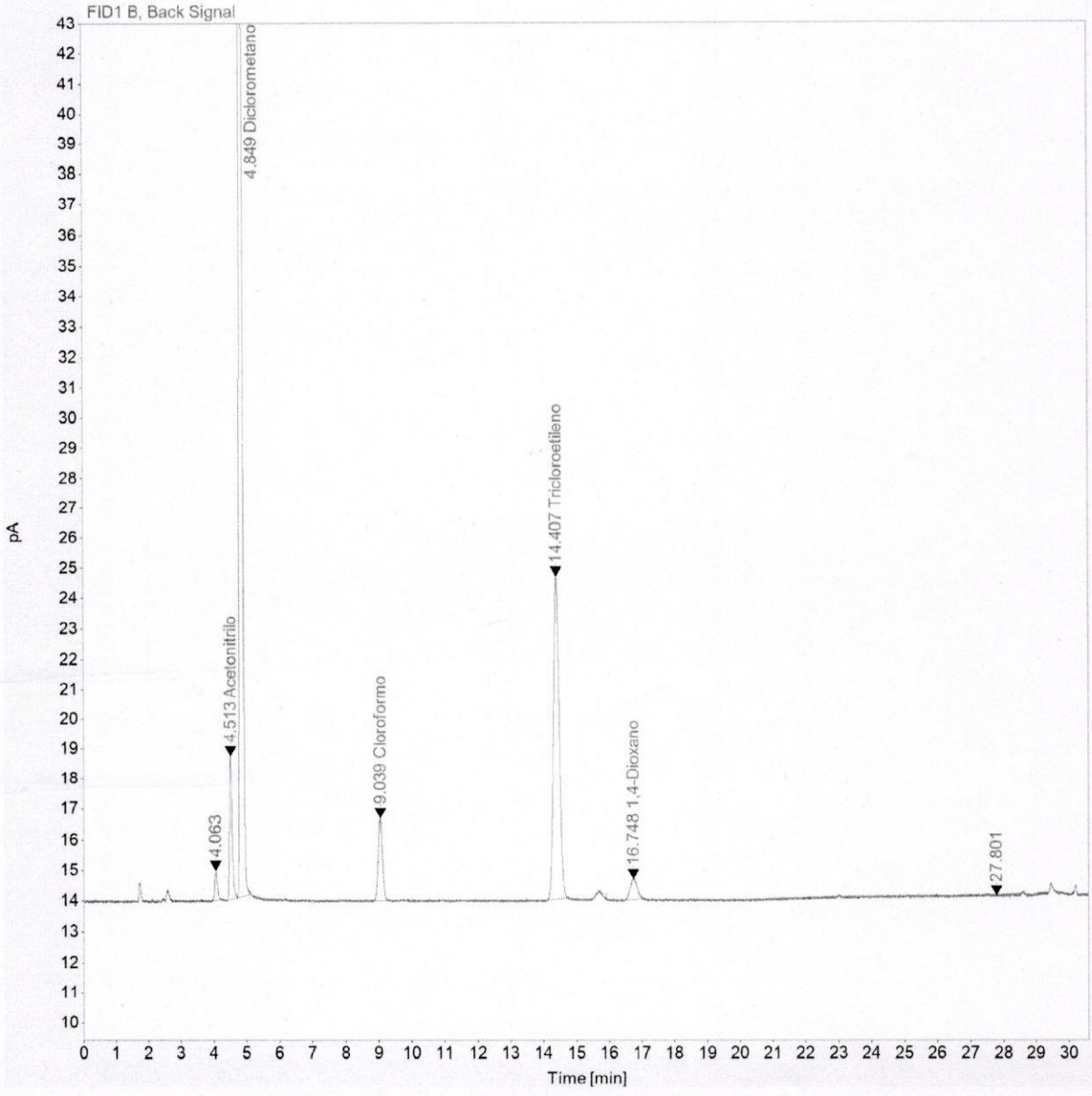

Area Percent Report

Agilent Technologies

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4.849	BB	0.0844	378.2088	70.2128	65.9889	Diclorometano
9.039	BB	0.1343	23.6256	2.6729	4.1221	Cloroformo
14.407	BB	0.1876	129.6617	10.6502	22.6231	Tricloroetileno
16.748	BB	0.1833	10.3757	0.6721	1.8103	1,4-Dioxano
27.801	VV +	0.0543	0.2391	0.0734	0.0417	
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Area Percent Report

Agilent Technologies

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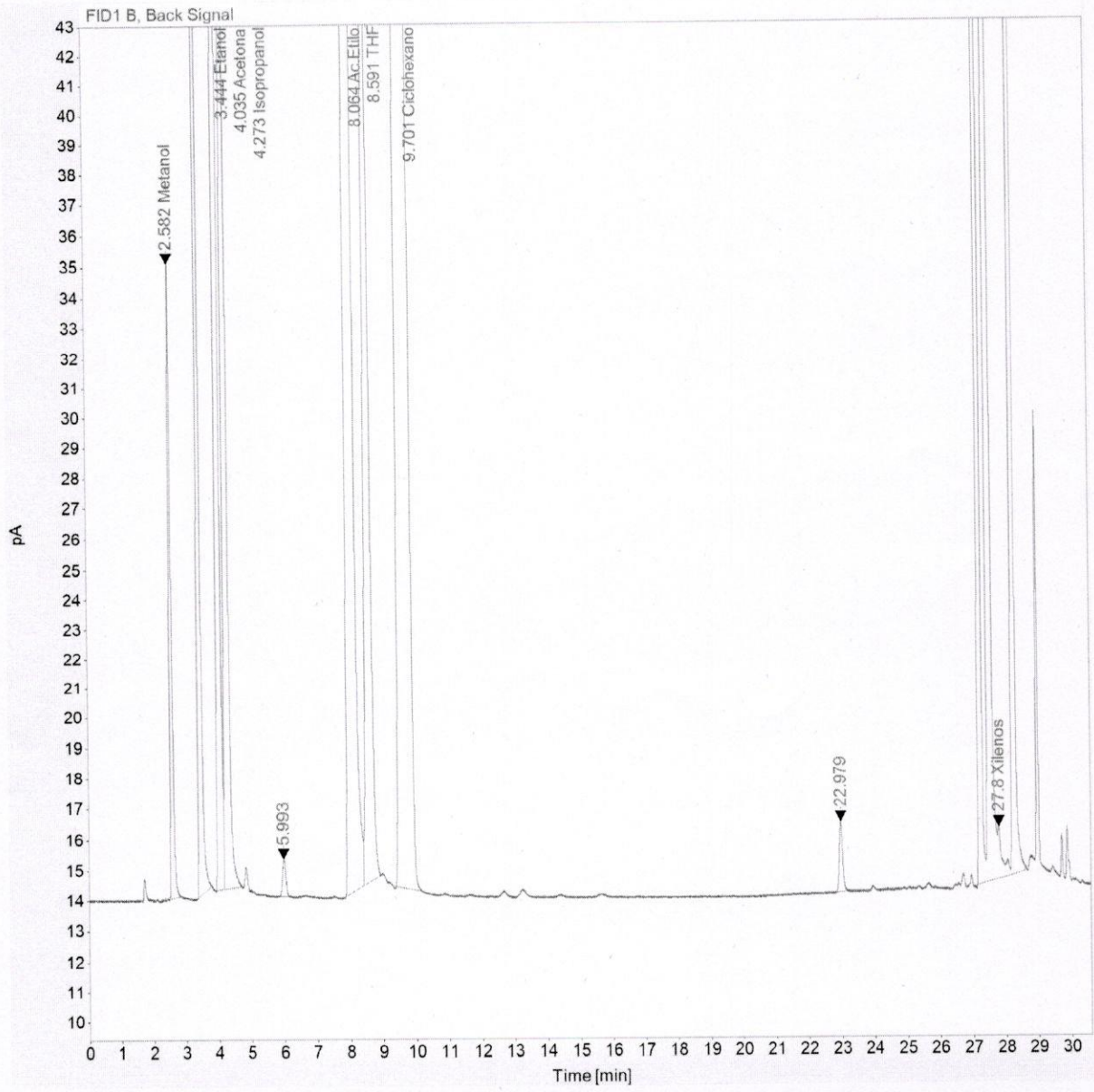

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4.273	VB	0.0868	752.0769	134.5894	2.5043	Isopropanol
5.993	BB	0.1051	8.8715	1.2639	0.0295	
8.064	BV	0.1288	3350.0278	410.4456	11.1550	Ac.Etilo
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Agilent Technologies

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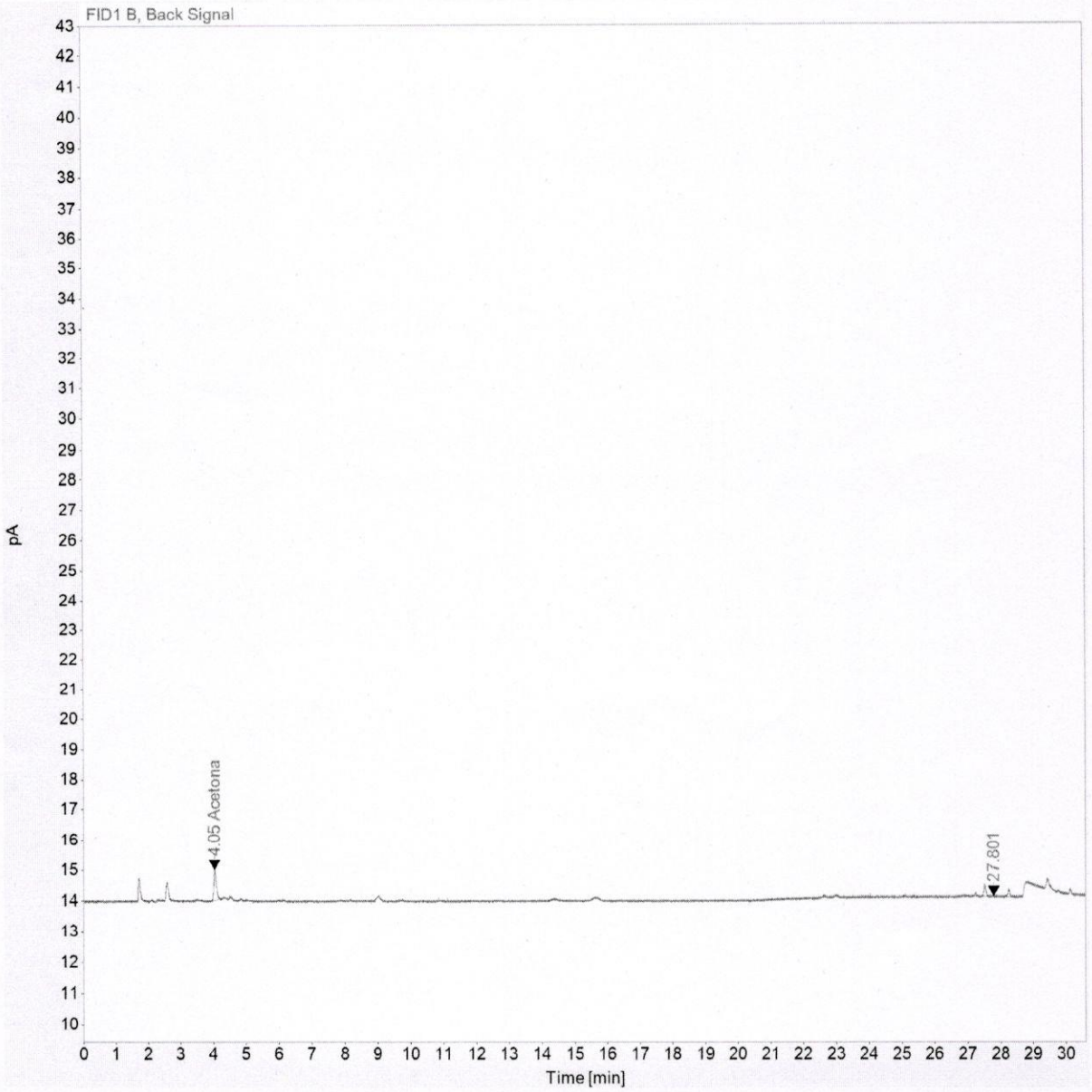

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Area Percent Report

Agilent Technologies

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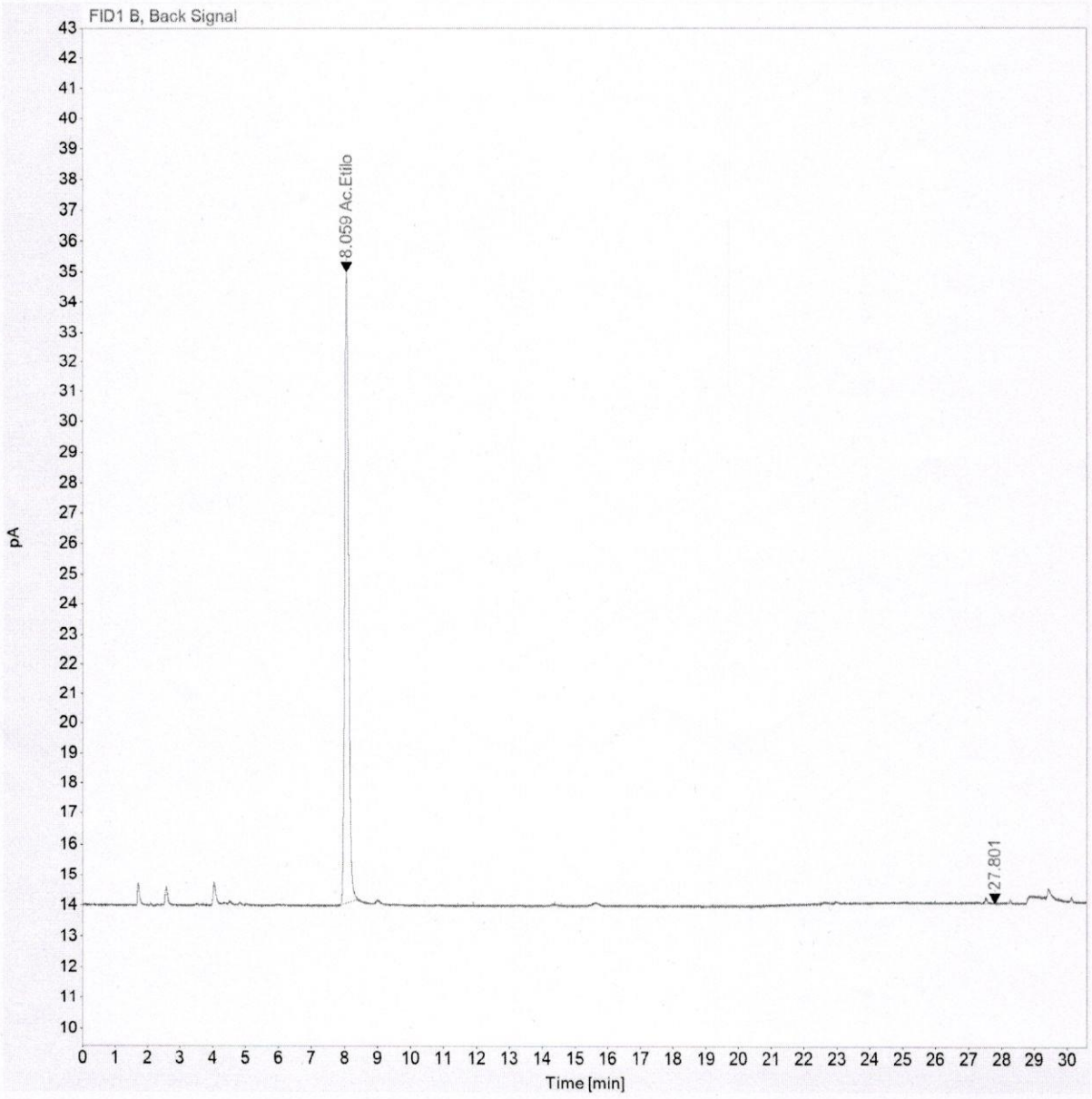

Area Percent Report

Agilent Technologies

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