Reductive deaminative conversion of nitriles to alcohols using paraformaldehyde in aqueous solution

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General Remarks

Paraformaldehyde was purchased from Alfa Aesar. D_2-pFA and $[RuCl_2(p\text{-cymene})]_2$ were purchased from Sigma Aldrich. All other chemicals were purchased from Sigma Aldrich and Across Organics and used without further purification. If not mentioned separately, deionized water was used for all experiments. All deaminative hydrogenation reactions were carried out without precautions against moisture or oxygen unless otherwise stated. NMR spectra were recorded with *Bruker Avance II 300* (^{1}H NMR 300 MHz, ^{13}C NMR 75 MHz) using TMS as reference. Hexamethyldisilane was employed as the internal standard for calculating the NMR conversions and yields. High resolution ESI-MS was performed on a *Thermo Scientific LTQ Orbitrap XL*. GC-MS measurements were performed on *Agilent Hewlett Packard 6890 Series Plus* chromatograph. A *HP 5973 Series* was used as mass detector and helium employed as the carrier gas. The structure of all the products was confirmed with regard to the data found in the literature.[1-2]

Experimental Section

General procedure for reductive deamination of nitriles under optimized conditions

Nitrile (1 eq., 1 mmol), paraformaldehyde (9 eq., 9 mmol, 270 mg) and $[Ru(p\text{-cymene})Cl_2]_2$ (1 mol%, 6.12 mg) were added to a 20 mL headspace screw cap vial sealed with rubber/teflon septa equipped with a magnetic stir bar in air followed by the addition of H_2O (2 mL) and toluene (2 mL). The vial was closed tightly to avoid any leakage and placed in a pre-heated (90 ^oC) aluminum block. The mixture was stirred at the rate of 750 rpm at this temperature. After 16 hours, the aluminium block was removed and the mixture was cooled to room temperature. Then, the cap was opened slowly to guarantee a slow gas release. The crude mixture was neutralized using sodium bicarbonate saturated aq. solution and extracted with ethyl acetate or dichloromethane (4x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum. If required, the purification of the product was done by flash column chromatography using a short silica column.

Synthesis of α,α-dideuterated benzyl alcohol ***A***

Benzonitrile (1 eq., 1 mmol, 103 μL), D_2-pFA (9 eq., 9 mmol, 285 mg) and $[Ru(p\text{-cymene})Cl_2]_2$ (1 mol%, 6.12 mg) were added to a 20 mL headspace screw cap vial sealed with rubber/teflon septa equipped with a magnetic stir bar under argon followed by the addition of D_2O (2 mL) and toluene (2 mL). The vial was closed tightly to avoid any leakage and placed in a pre-heated (90 ^oC) aluminum block. The mixture was stirred at the rate of 750 rpm at this temperature. After 24 hours, aluminum block was removed and the mixture was cooled to room temperature. Then, the cap was opened slowly to guarantee a slow gas release. The completion of the reaction was determined by analyzing a sample of the crude using GC-MS. The crude reaction mixture was neutralized using sodium bicarbonate saturated aq. solution and extracted with ethyl acetate (4x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum.

Procedure for the reaction in the two-connected flasks

Benzonitrile (1 mmol, 103 μL), pFA (18 mmol, 540 mg), ($[Ru(p\text{-cymene})Cl_2]_2$ (1 mol%, 6,12 mg), H_2O (2 mL) and toluene (2 mL) were added to one of the 5 mL round bottom flask (***A***) equipped with a magnetic stir bar. The second flask (***B***) contained the same reaction mixture excluding pFA. The two flasks were connected via a glass connection and were sealed carefully with Glindemann© teflon sealing rings to avoid any leakage (figure S1 shows the corresponding set-up). The whole system was placed in an oil bath and stirred overnight at 90 ^oC.

Caution: The system was protected with an extra shield in the fumehood owing to the gas evolution during the reaction.

Extraction of the contents of the second flask (***B***) was performed following the general procedure for deaminative hydrogenation of nitriles.

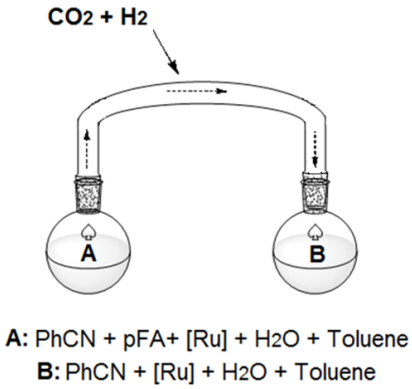


Figure S1. Set-up for the reaction in the two connected flask

Preparation of ESI-MS samples

Two samples have been prepared from each reaction mixture as follows:

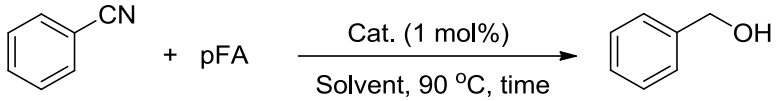
Sample 1: Benzonitrile (1 mmol, 103 µL), paraformaldehyde (9 mmol, 270 mg) and [Ru(*p*-cymene)Cl_2]$_2$ (1 mol%, 6.12 mg) were added to a 20 mL headspace screw cap vial sealed with rubber/teflon septa equipped with a magnetic stir bar in air followed by the addition of H_2O (2 mL) and toluene (2 mL). The vial was closed tightly to avoid any leakage and placed in a pre-heated (90 ^{o}C) aluminum block. The mixture was stirred at the rate of 750 rpm at this temperature. After 4 hours, the aluminium block was removed and the reaction was stopped. Samples of the crude reaction mixture were submitted to analysis without any extraction.

Sample 2: The same procedure was followed as the sample 1 except that in this case, paraformaldehyde was not added to the flask to see the effect of its absence on the reaction pathway.

Procedure for direct hydrogenation of benzonitrile using pressurized H_2

Benzonitrile (1 mmol, 103 µL), paraformaldehyde (9 mmol, 270 mg) and [Ru(*p*-cymene)Cl_2]$_2$ (1 mol%, 6.12 mg) were added to a 20 mL headspace screw cap vial sealed with rubber/teflon septa equipped with a magnetic stir bar followed by H_2O (2 mL) and toluene (2 mL). The vial was places in a steel autoclave and the pressure of hydrogen inside the vial was raised to 5 bar by purging H_2 through the septa with a canula. The autoclave was then placed in a pre-heated (90 ^{o}C) aluminum block. The mixture was stirred at the rate of 750 rpm at this temperature for 16 hours. After that, the aluminium block was removed and the mixture was cooled to room temperature. The crude mixture was neutralized using sodium bicarbonate saturated solution and extracted with ethyl acetate (4* 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under vacuum.

Table S1. Metal precursor screening



Entry	Solvent (ratio)	Cat. Loading (1 mol%)	Time (h)	pFA: PhCN ratio	Benzyl alcohol
1	H_2O	$[Ru(p\text{-cymene})Cl_2]_2$	10	9:1	ND[a]
2	H_2O: Toluene (1: 1)	$[Ru(p\text{-cymene})I_2]_2$	10	9:1	43
3	H_2O: Toluene (1: 1)	$[Ru(benzene)Cl_2]_2$	10	9:1	77
4	H_2O: Toluene (1: 1)	Pd_2dba_3	10	9:1	ND
5	H_2O: Toluene (1: 1)	CuI	10	9:1	ND
6	H_2O: Toluene (1:1)	$Cu(OAc)_2$	10	9:1	ND
7[b]	H_2O: Toluene (1:1)	Ru@Fe NPs	10	9:1	ND
8[c]	H_2O: Toluene (1:1)	Ru@silica coated Fe_3O_4 NPs	10	9:1	ND
9	H_2O: Toluene (1:1)	$[Ru(p\text{-cymene})Cl_2]_2$	4	9:1	41
10	H_2O: Toluene (1:1)	$[Ru(p\text{-cymene})Cl_2]_2$	8	9:1	70
11	H_2O: Toluene (1:1)	$[Ru(p\text{-cymene})Cl_2]_2$	12	9:1	89
12	H_2O: Toluene (1:1)	$[Ru(p\text{-cymene})Cl_2]_2$	16	9:1	100

Reaction conditions: Benzonitrile (1 eq., 103 μL), pFA (9 eq., 270 mg), Cat. (1 mol%), Solvent, 90 °C.

[a] Not detected (In most cases, benzamide was formed as the main product).

[b] The catalyst was synthesized according to literature[3-4]

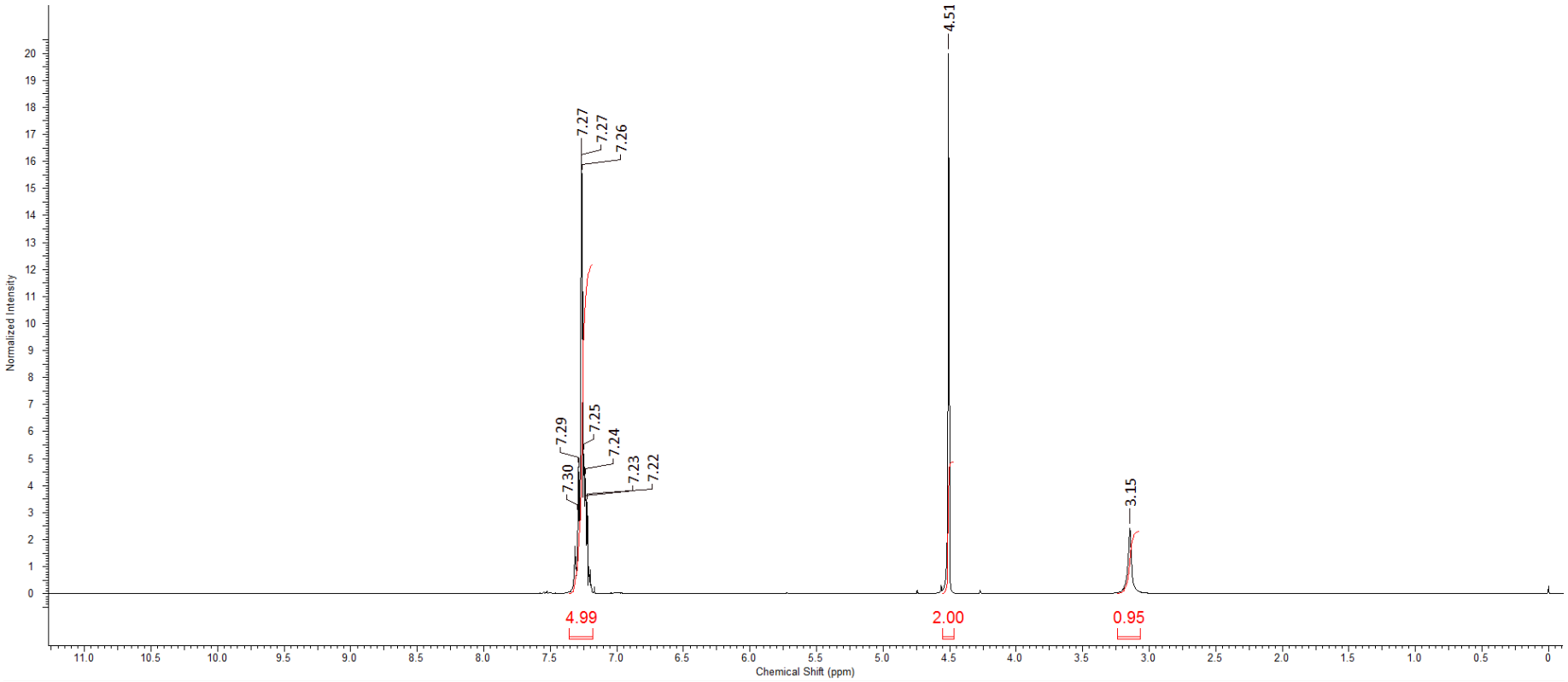
[c] The catalyst was synthesized according to the literature[5-6]

References

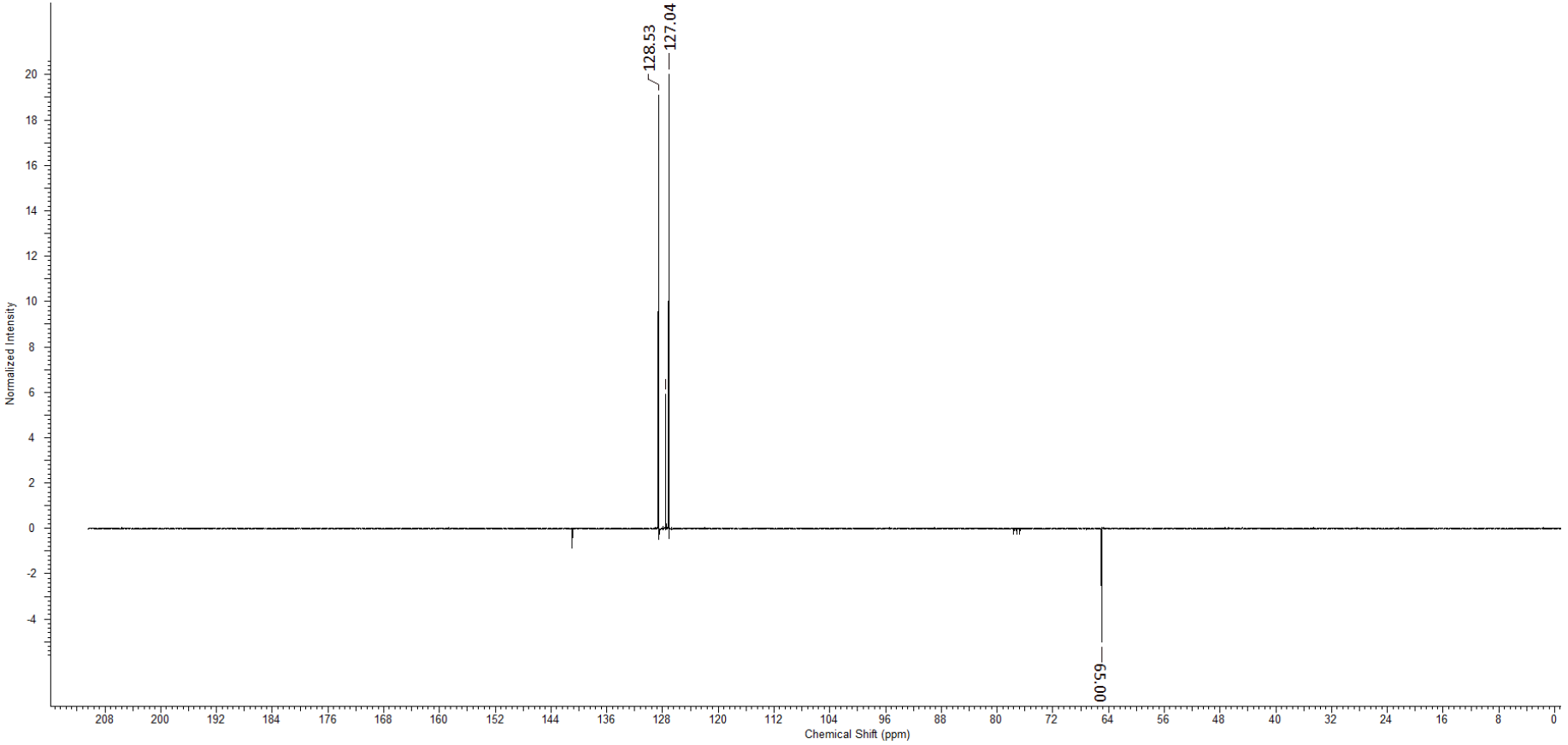
1. Molnár, I. G.; Calleja, P.; Ernst, M.; Hashmi, A. S. K.; Schaub, T., *ChemCatChem* 2017, **9** (22), 4175-4178.
2. Rezayee, N. M.; Samblanet, D. C.; Sanford, M. S., *ACS Catalysis* 2016, **6** (10), 6377-6383.
3. Hudson, R.; Li, C.-J.; Moores, A., *Green Chem.* 2012, **14** (3), 622-624.
4. Hudson, R.; Rivière, A.; Cirtiu, C. M.; Luska, K. L.; Moores, A., *Chem. Commun.* 2012, **48** (27), 3360-3362.
5. Shylesh, S.; Wang, L.; Thiel, W. R., *Adv. Synth. Catal.* 2010, **352** (2-3), 425-432.
6. Wang, D.; Salmon, L.; Ruiz, J.; Astruc, D., *Chem. Commun.* 2013, **49** (62), 6956-6958.

NMR spectra of the selected samples

^{1}H NMR of benzyl alcohol



^{13}C NMR of benzyl alcohol



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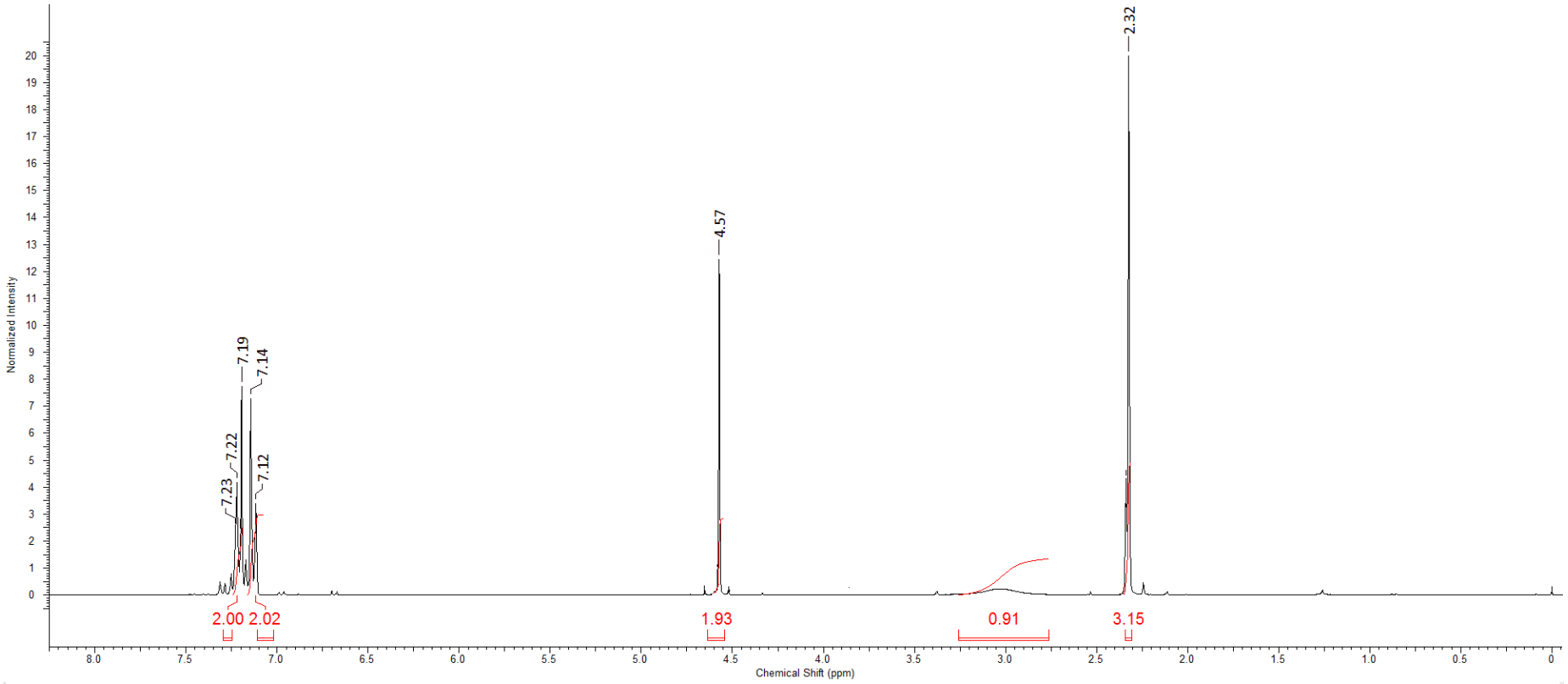

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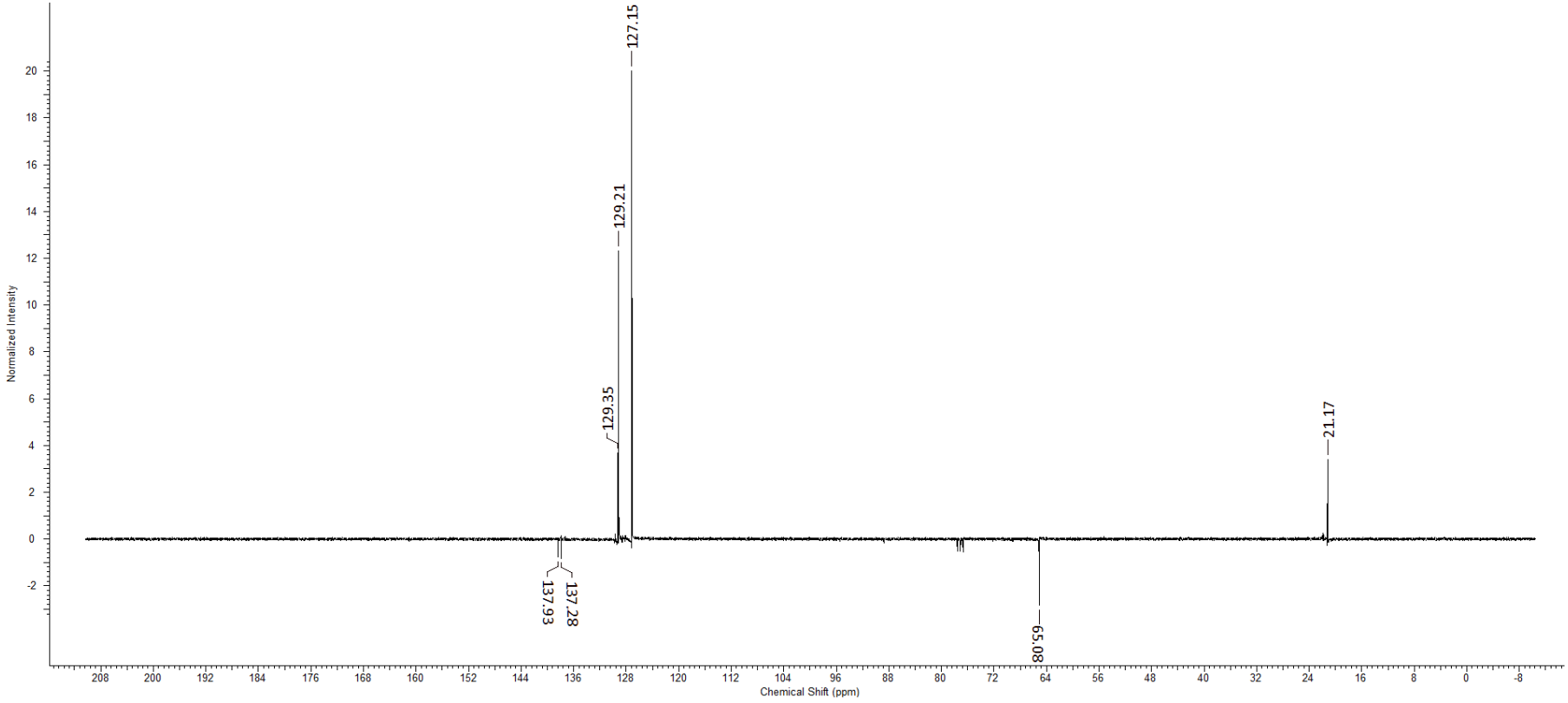

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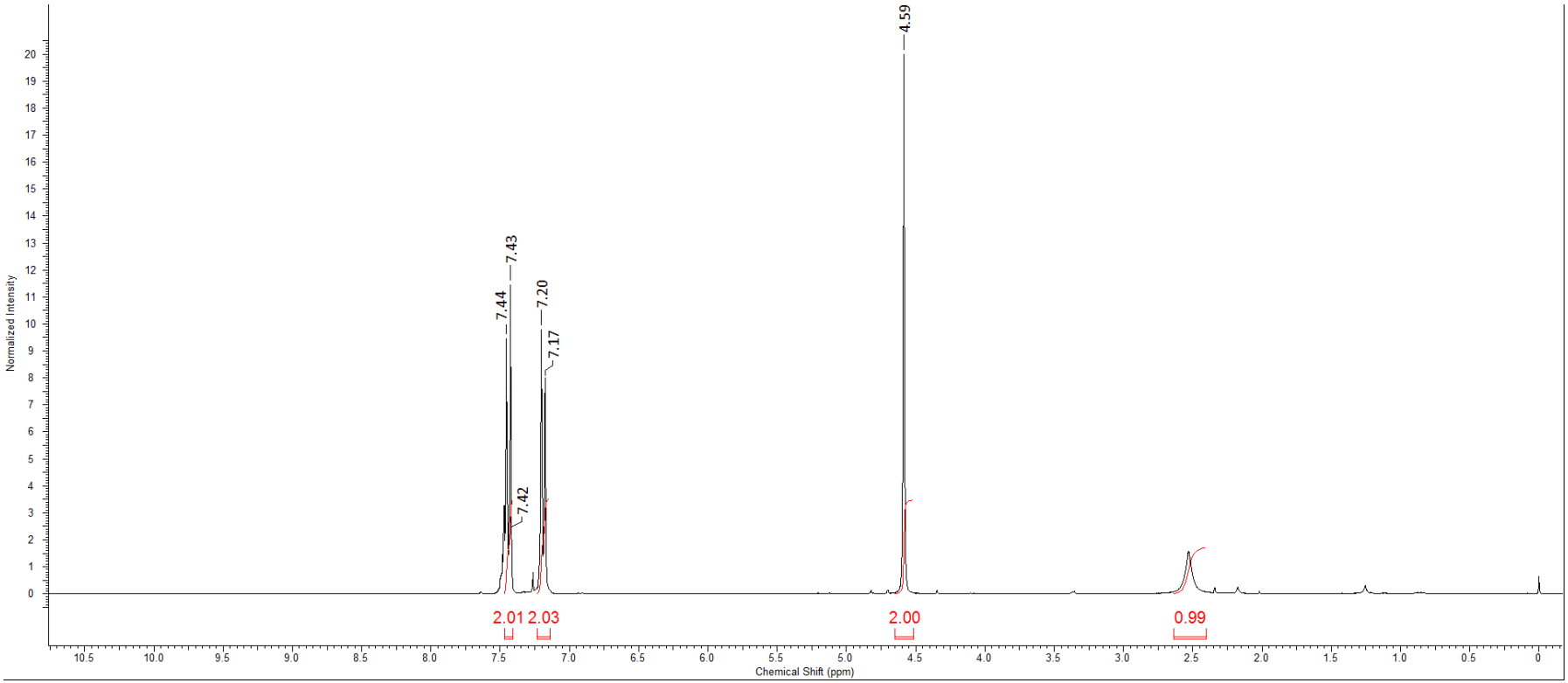

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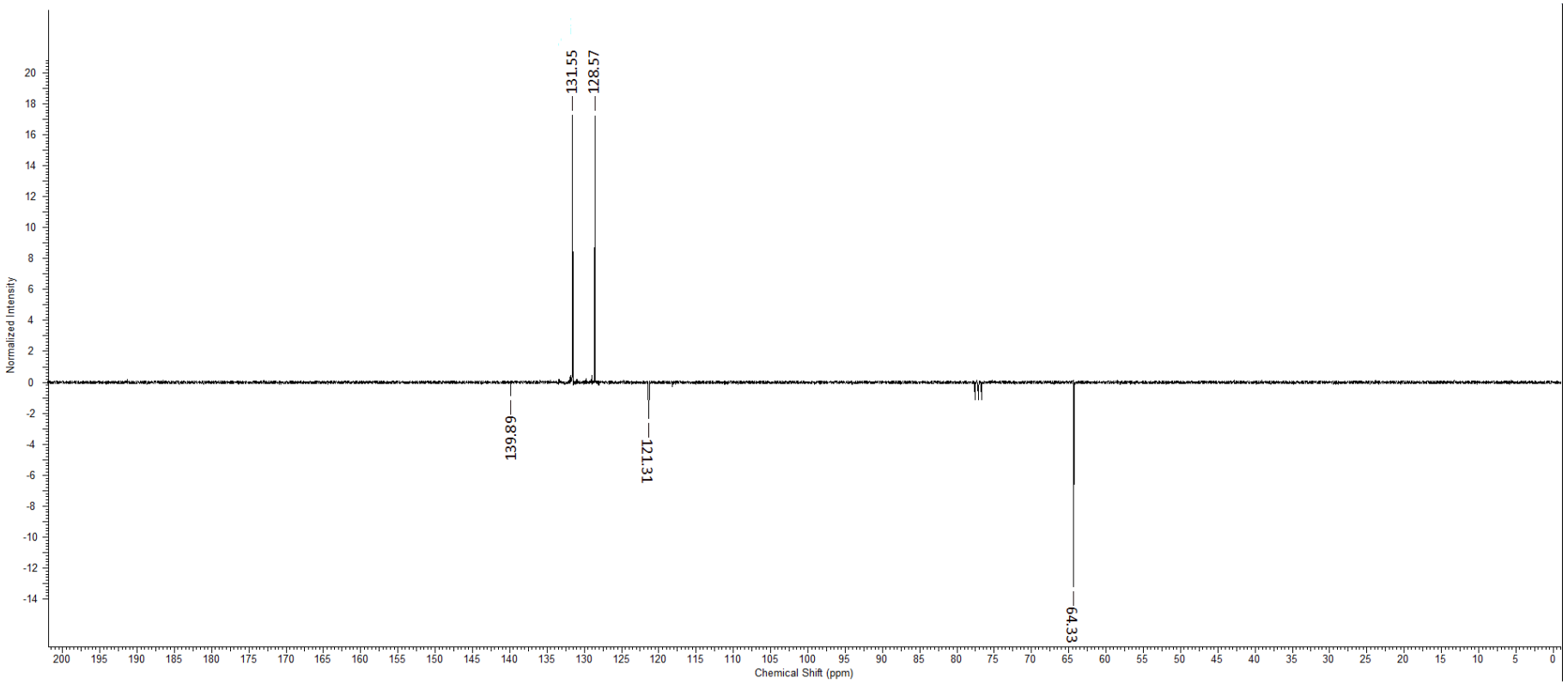

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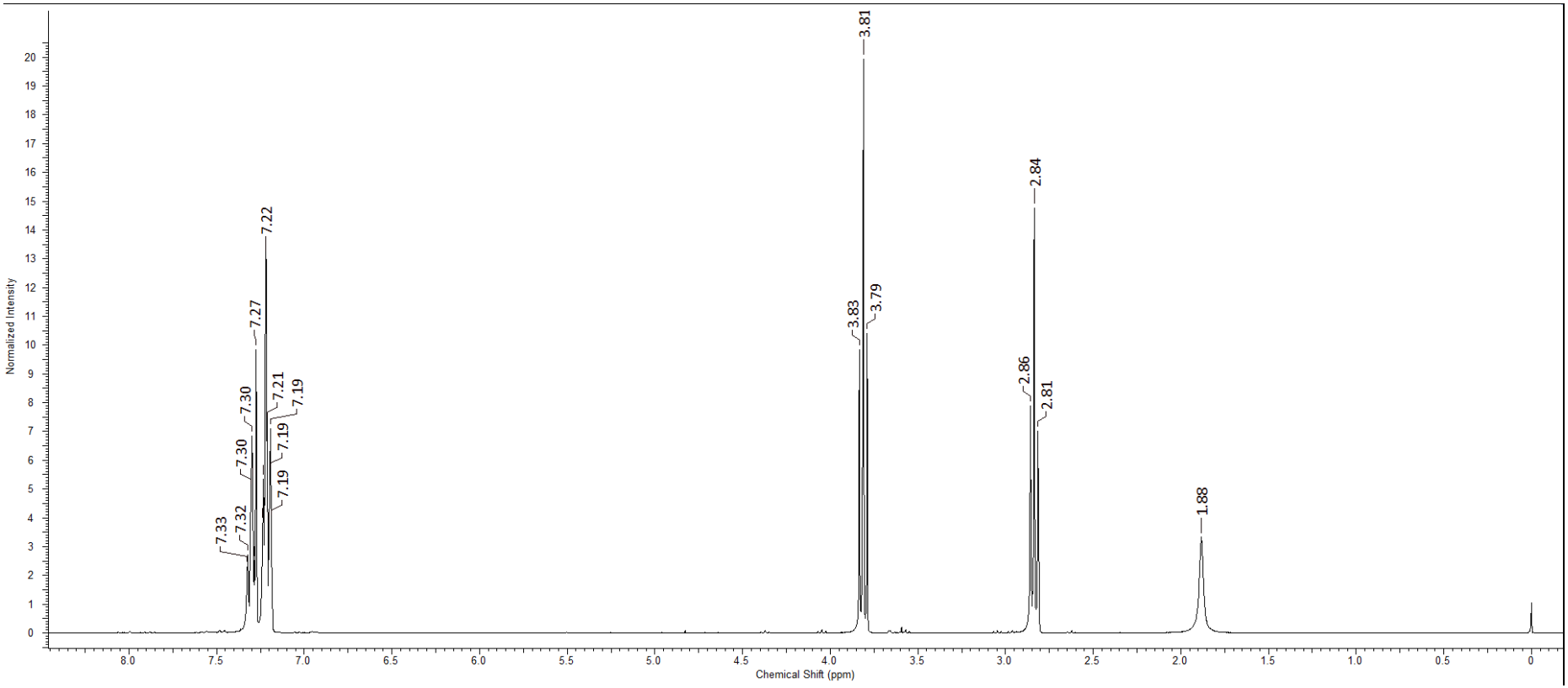

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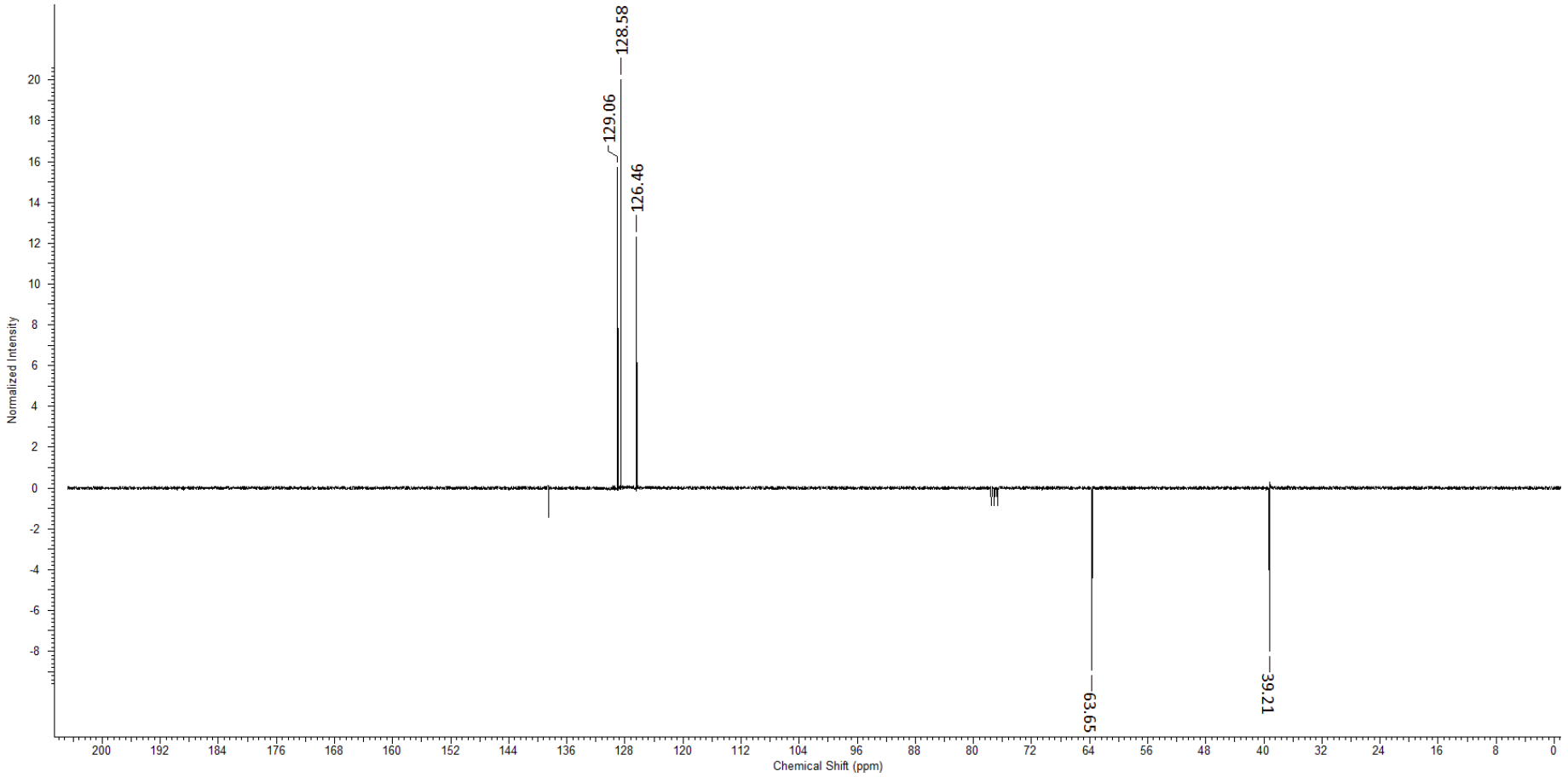

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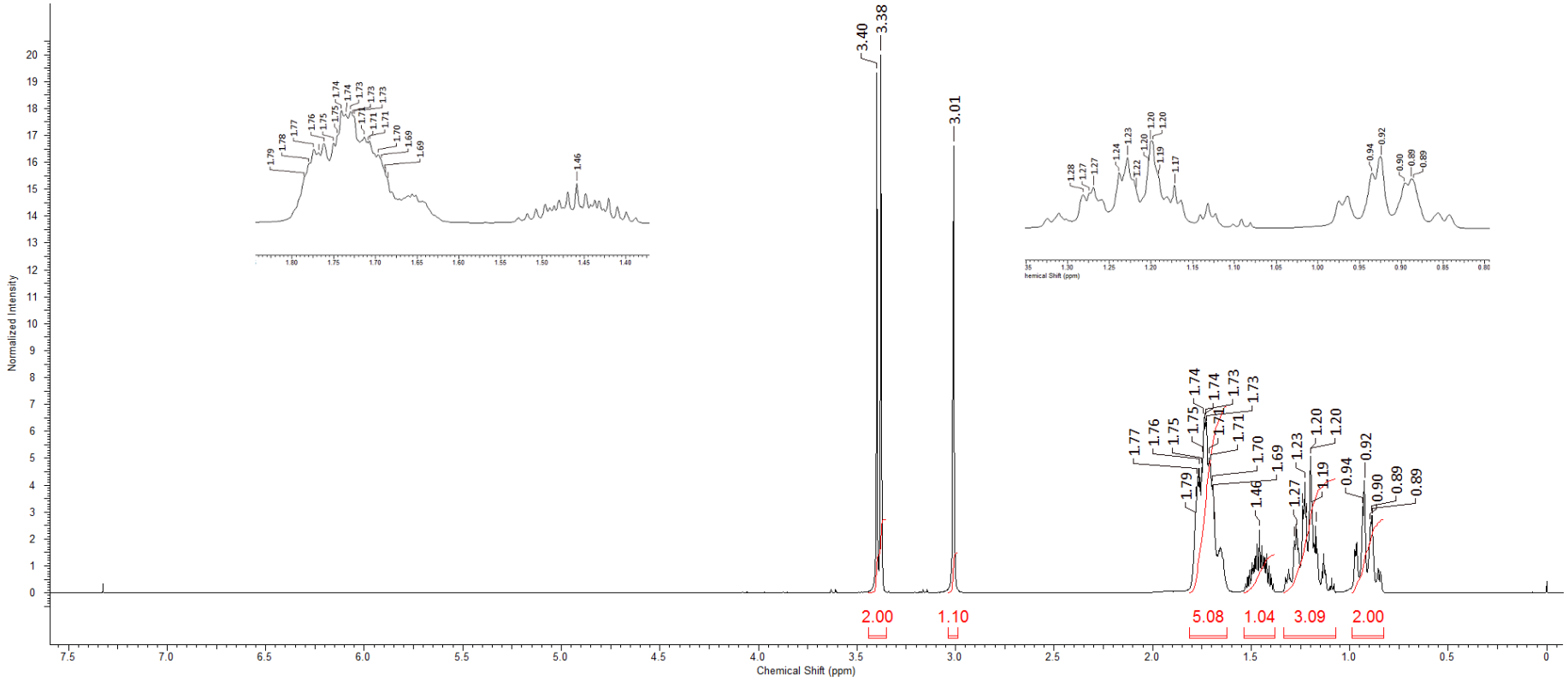

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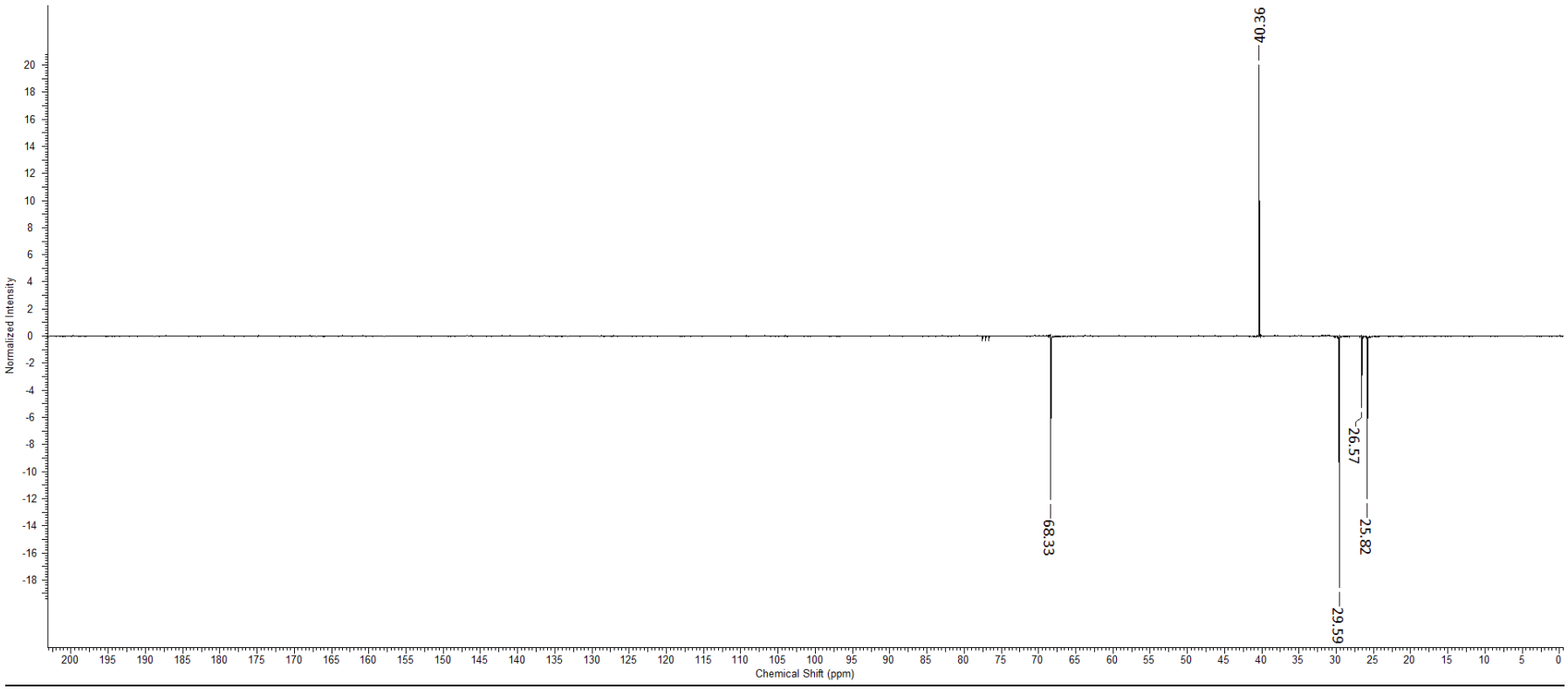

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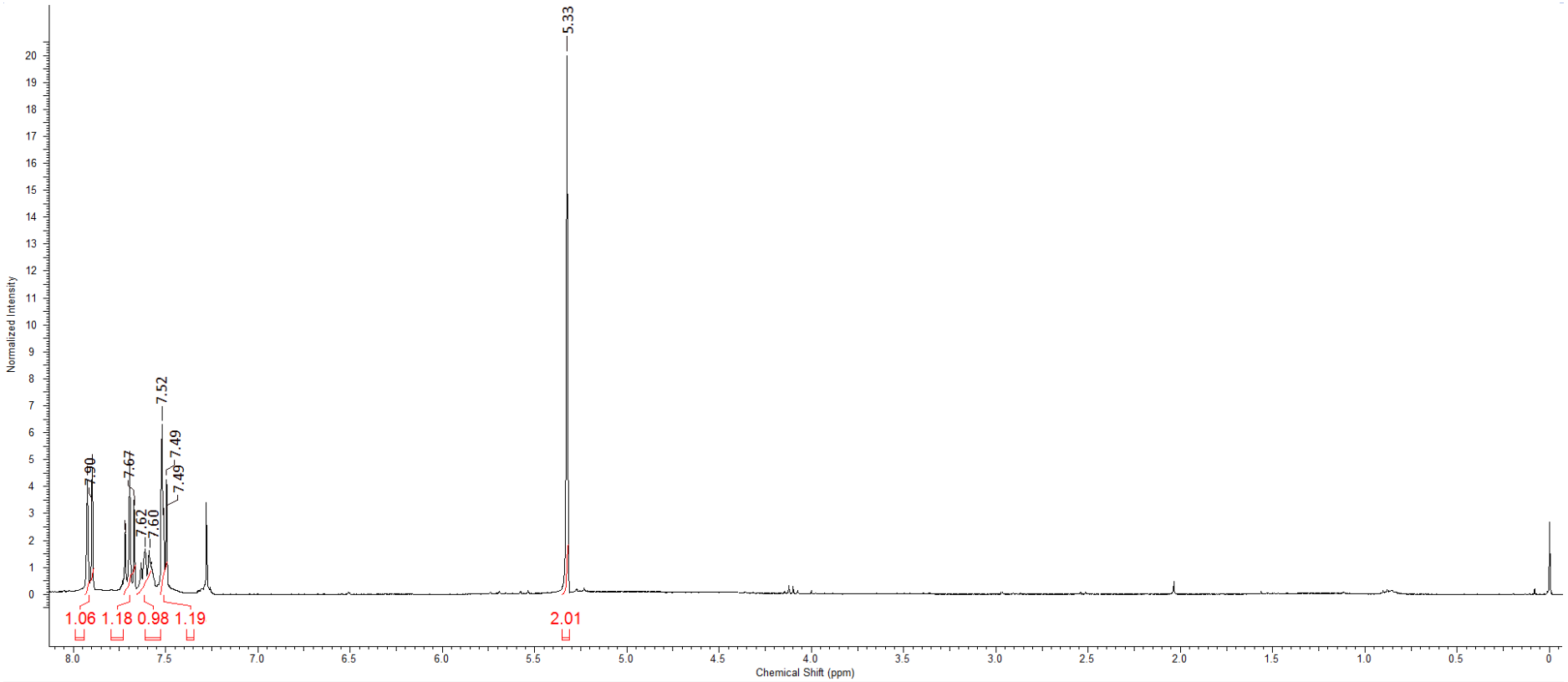
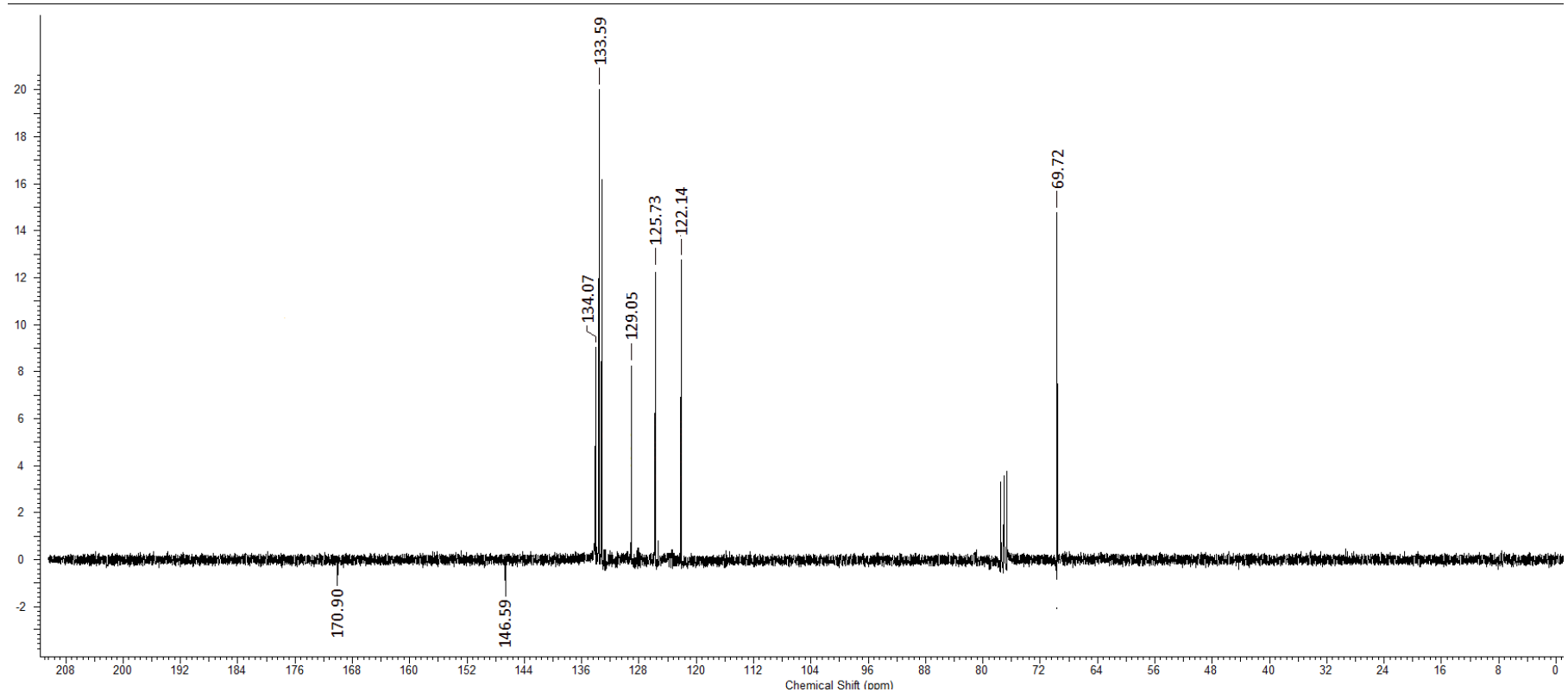


^{13}C NMR of phthalide



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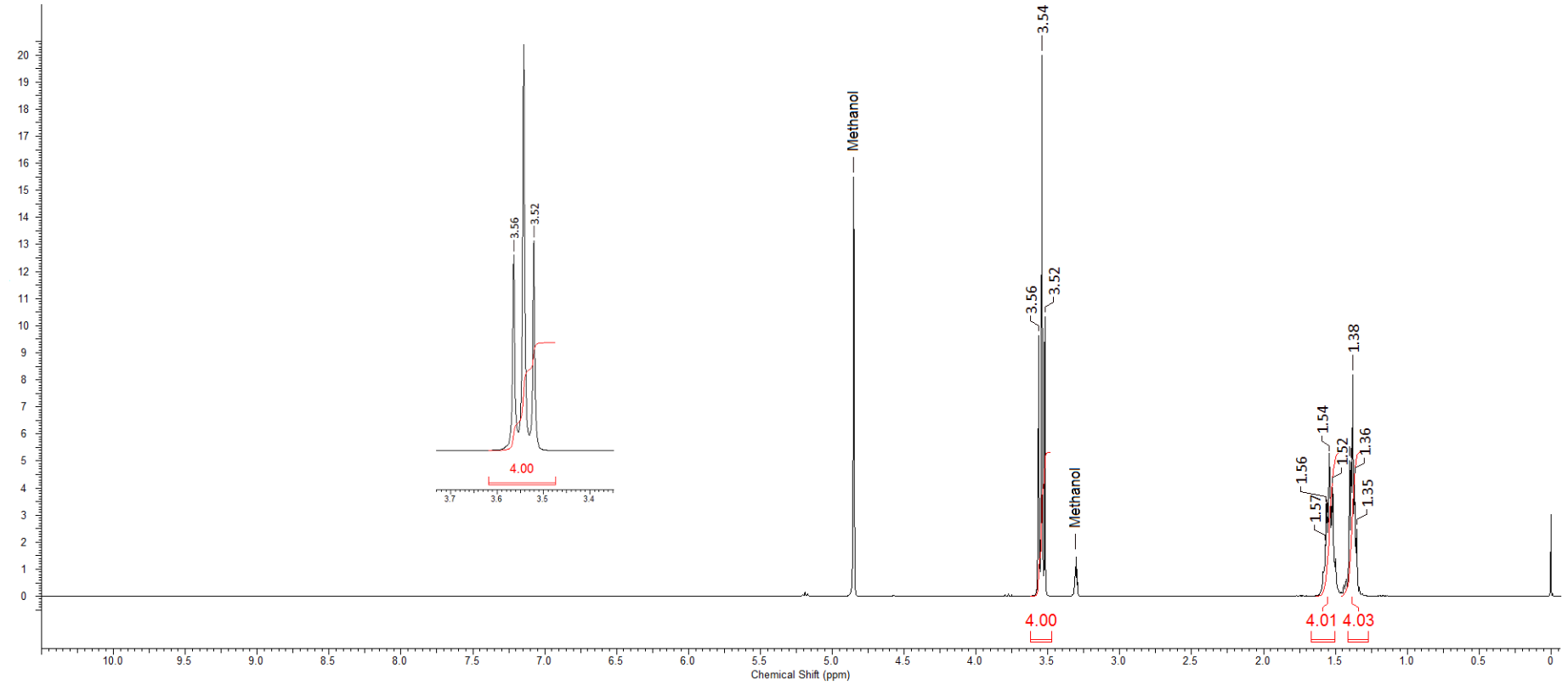

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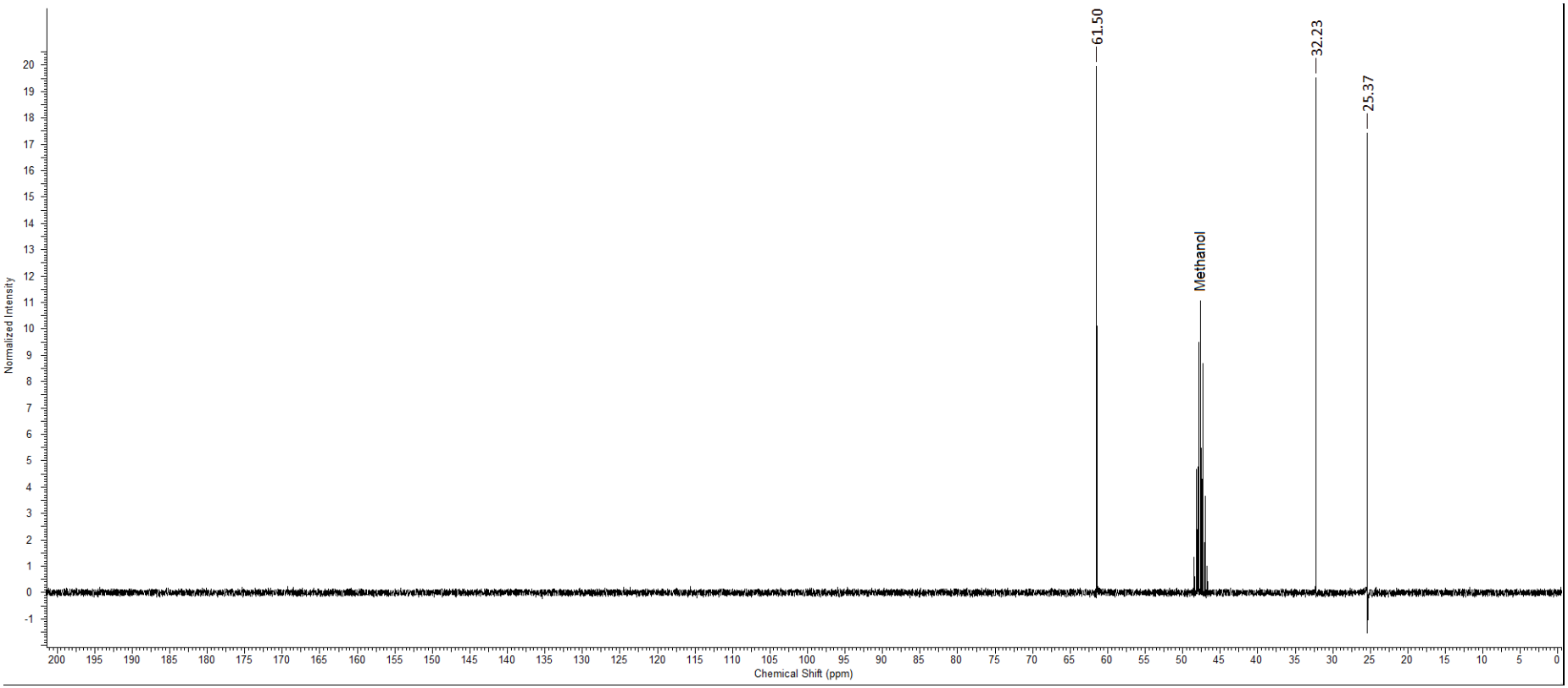

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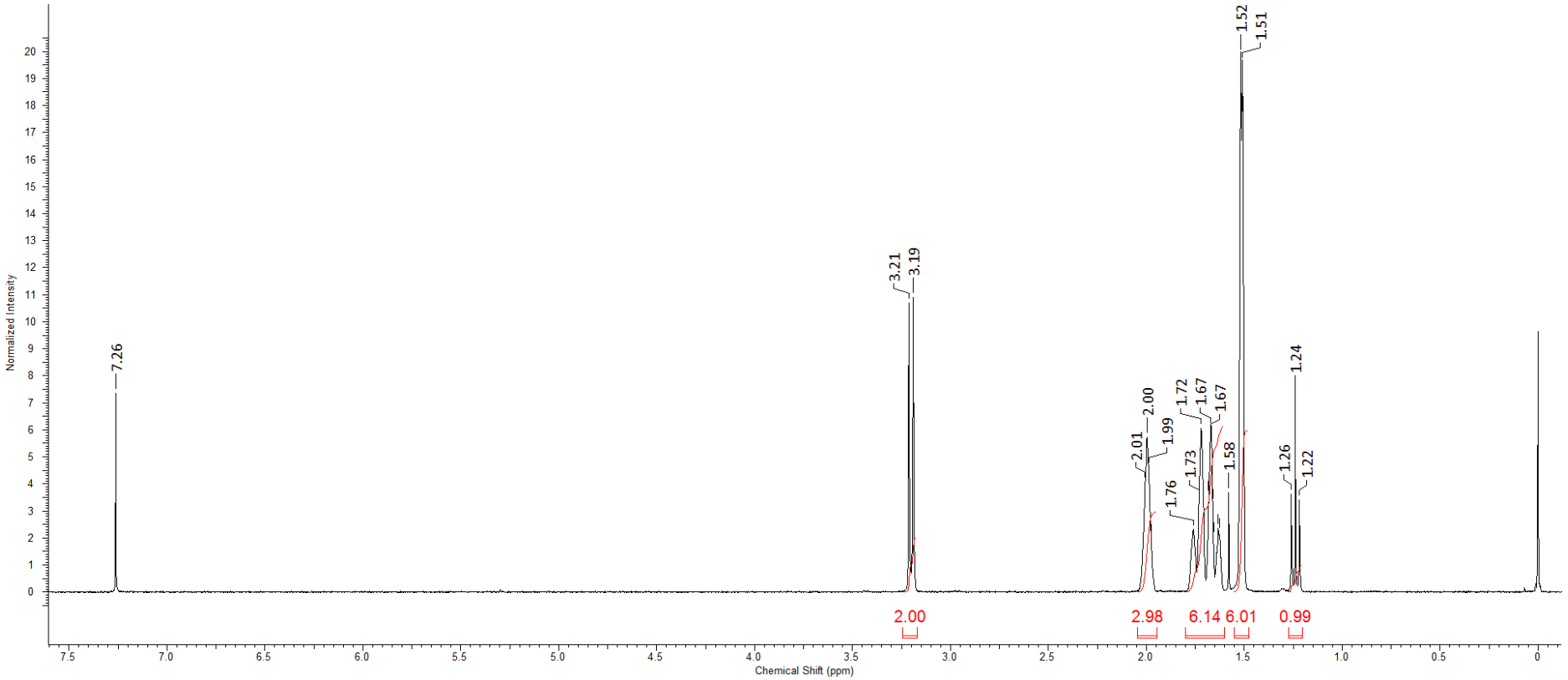

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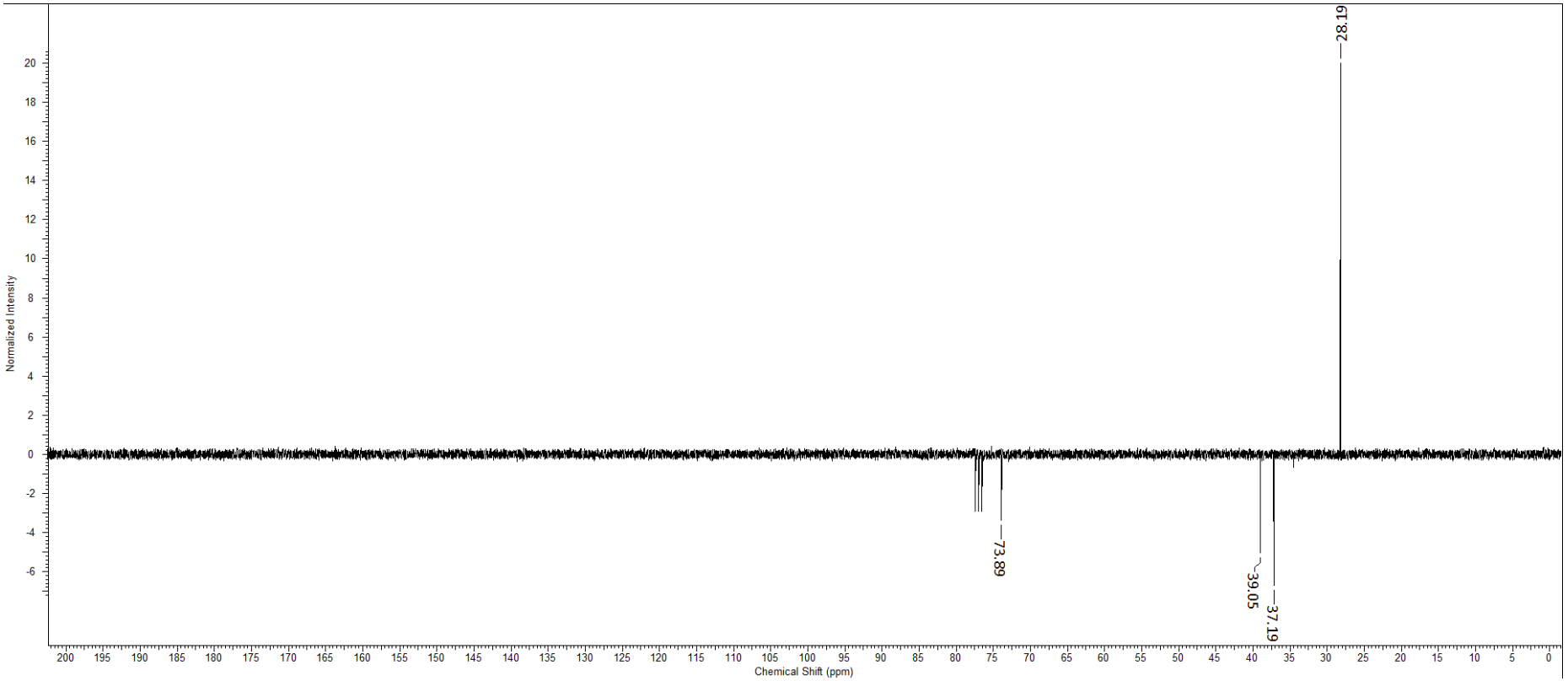

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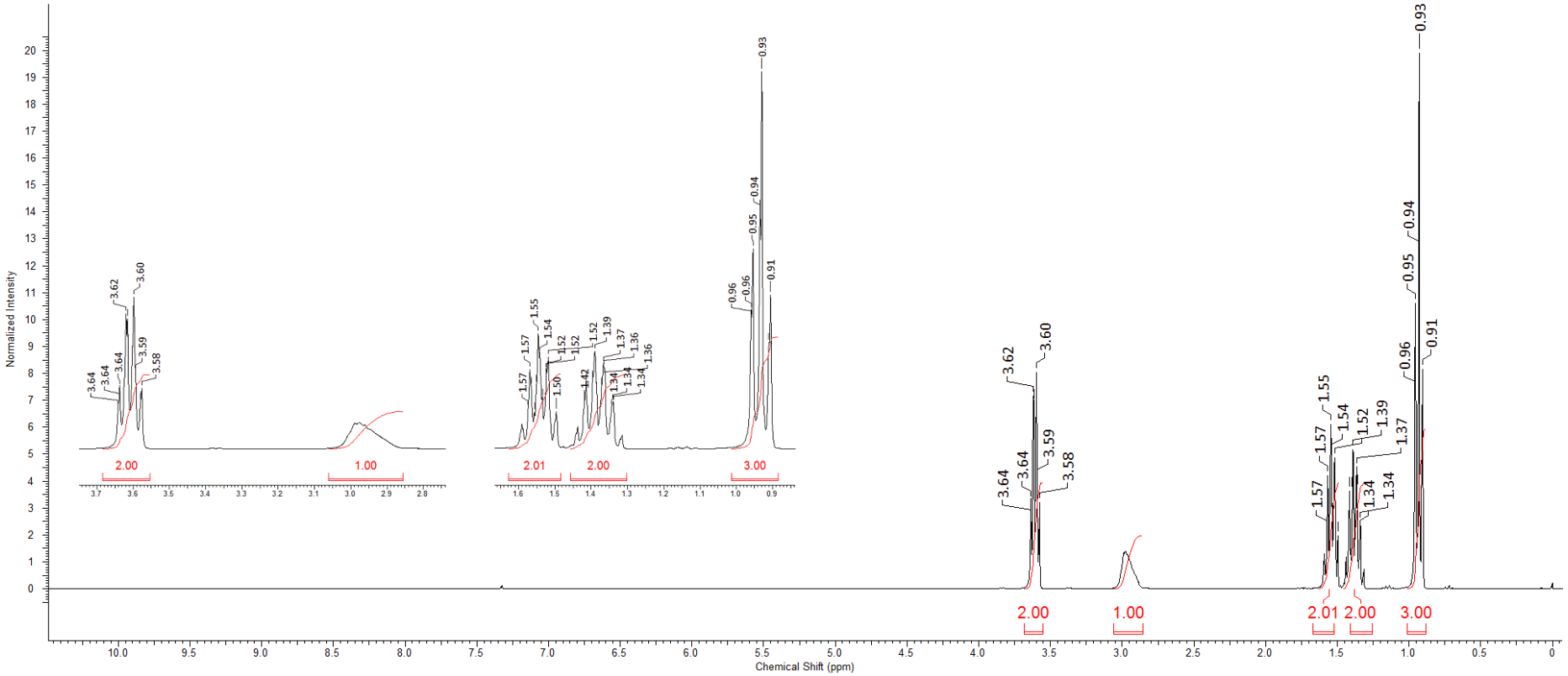

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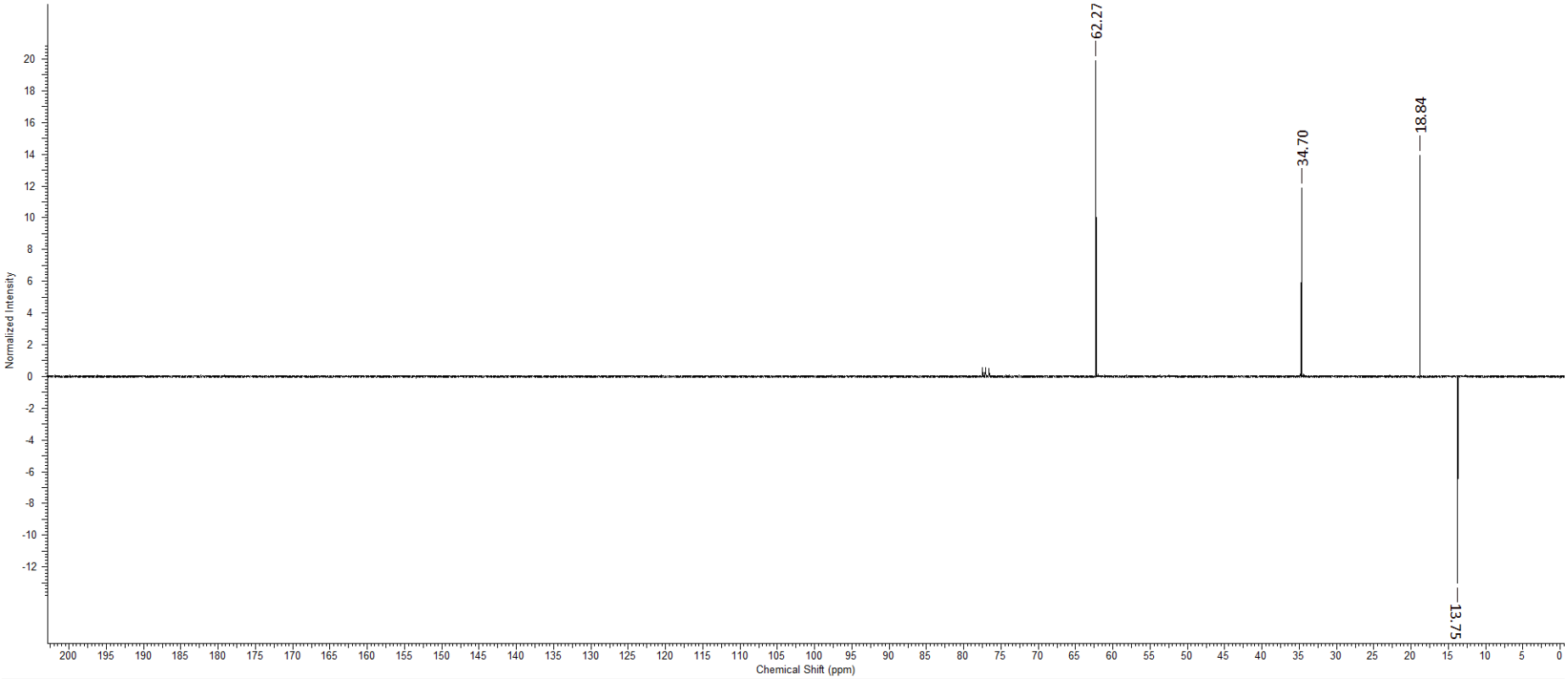

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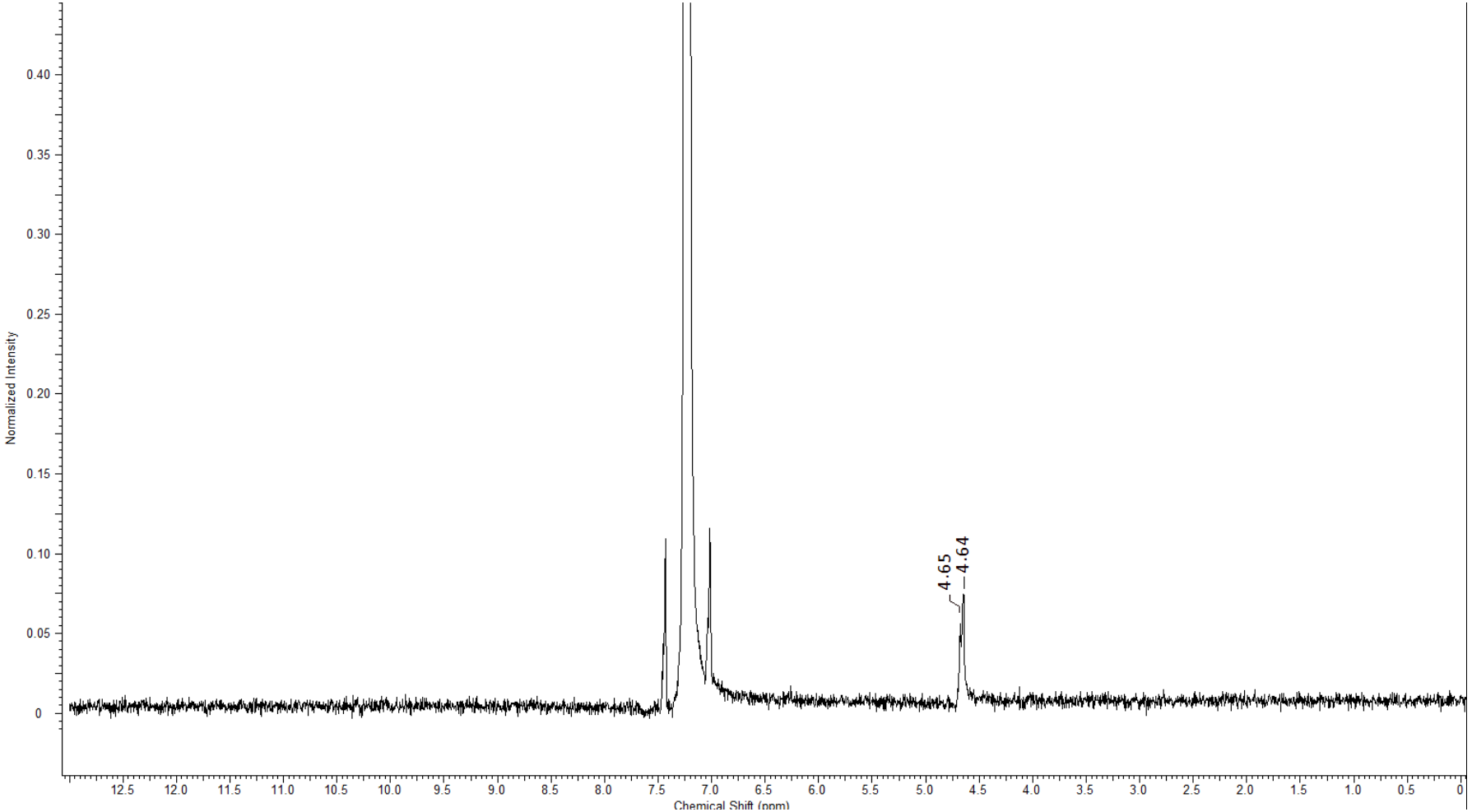

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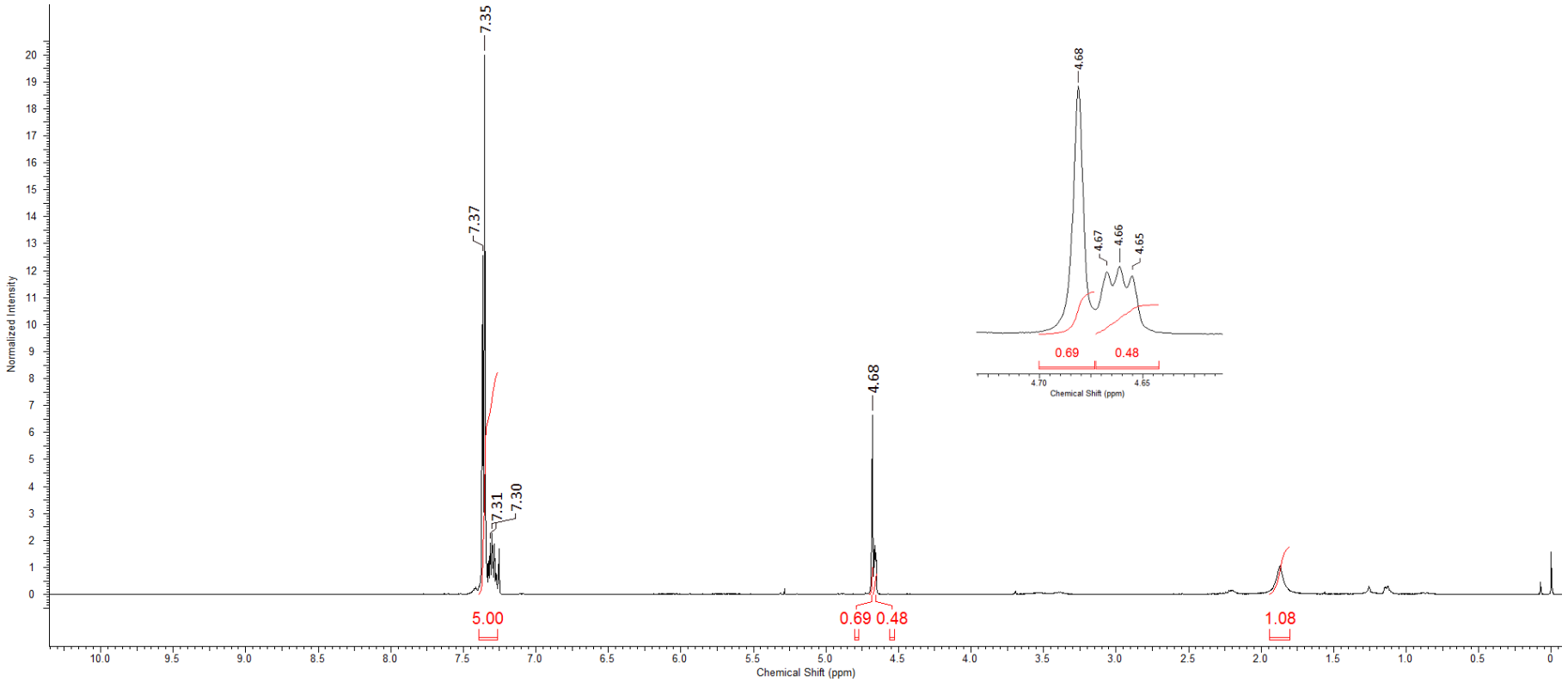
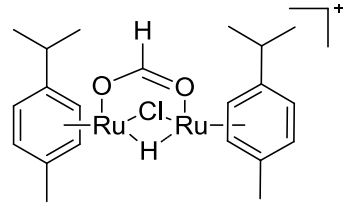


ESI MS Spectra

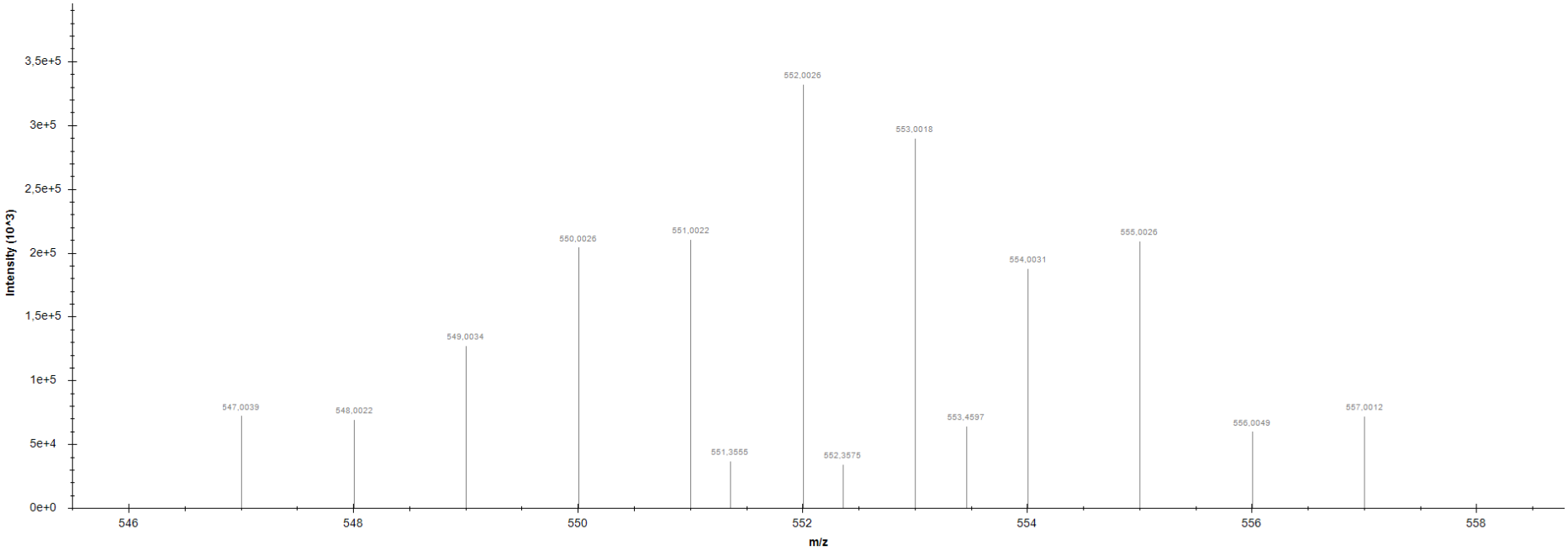
ESI MS spectrum of 3



3

$Ru_2C_{21}H_{30}ClO_2^+$

553.002



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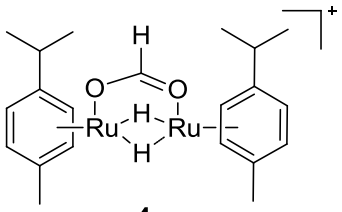

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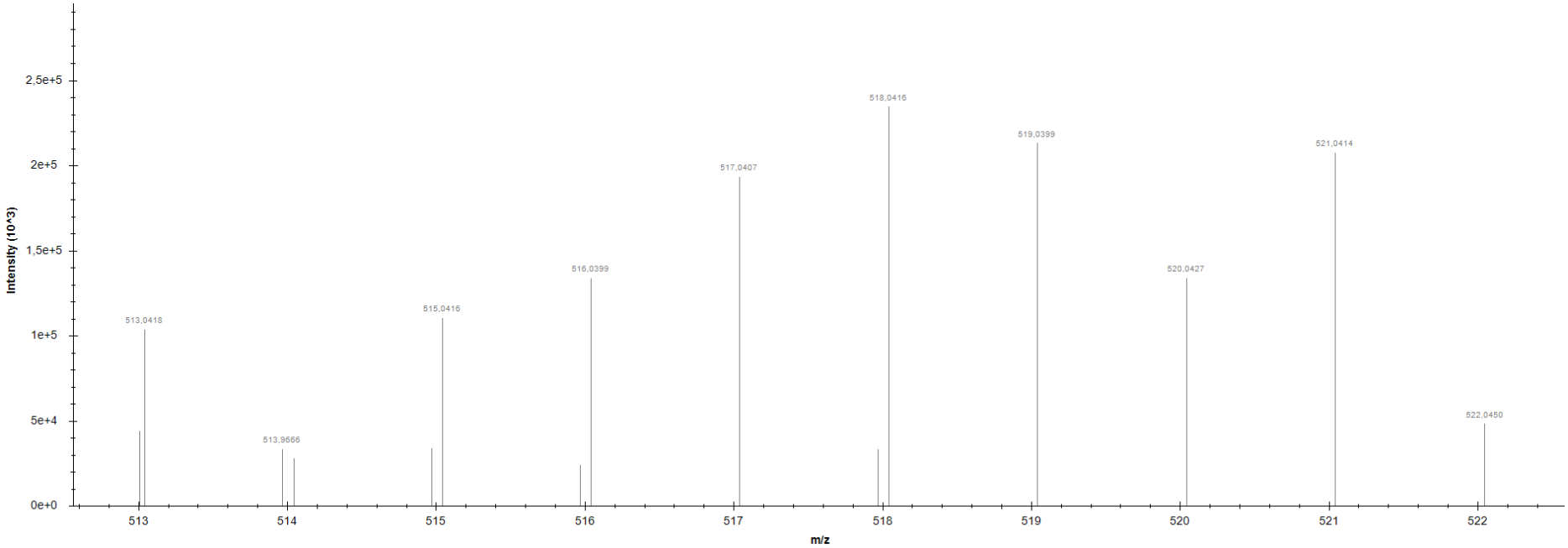
$Ru_2C_{21}H_{31}O_2^+$

518.042



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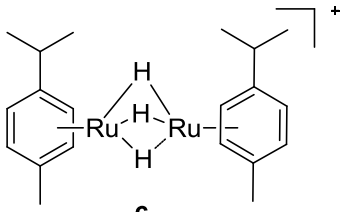

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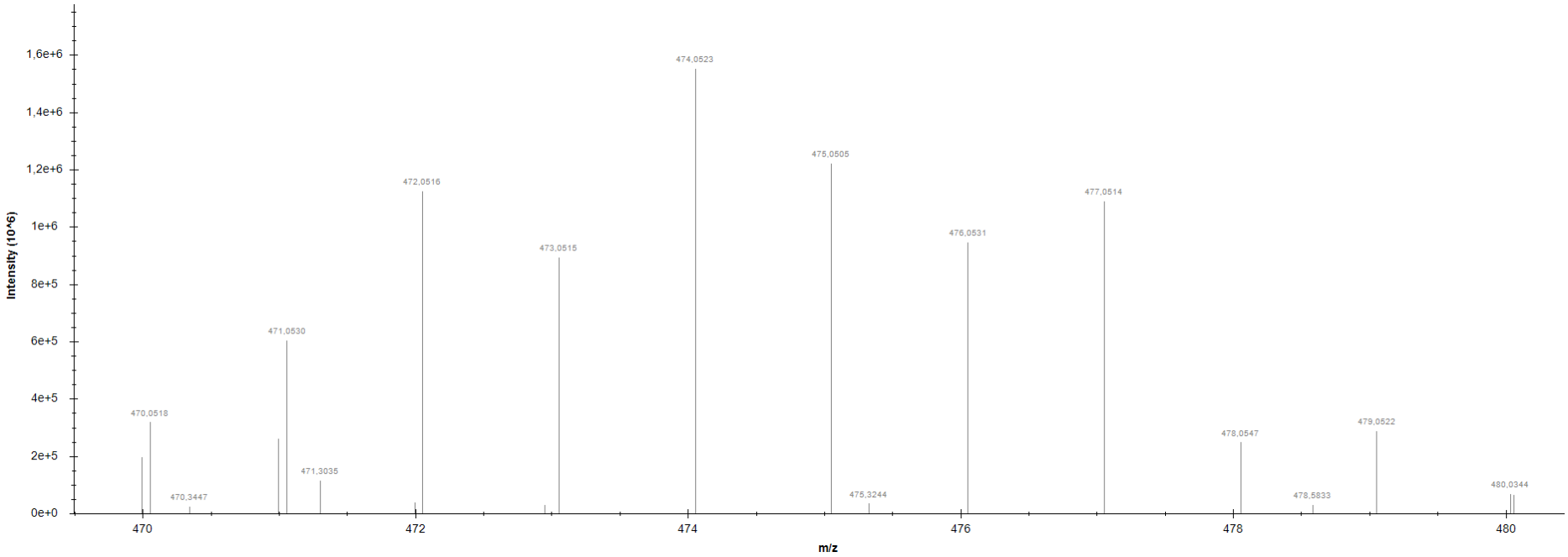
$Ru_2C_{20}H_{31}^+$

475.051



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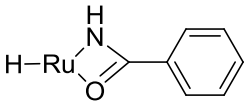

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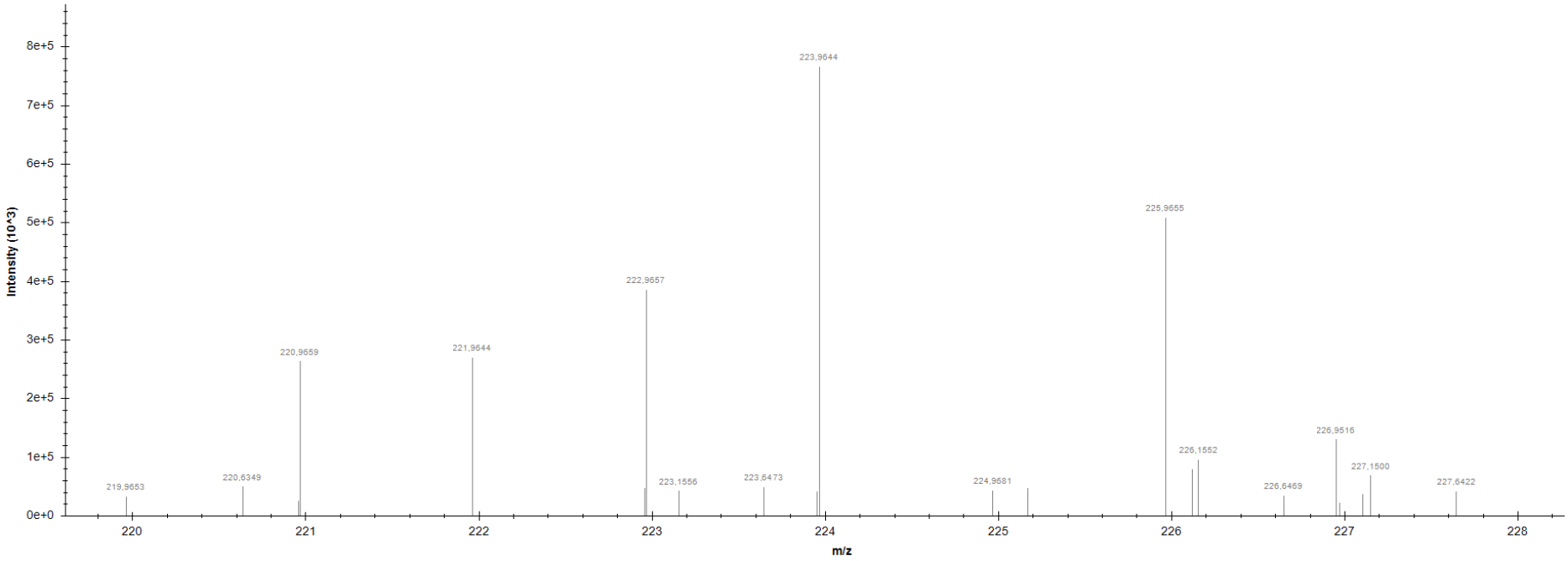
$RuC_7H_8NO^+$

223.9642



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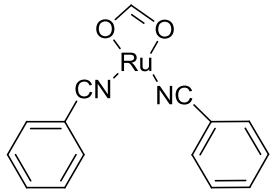

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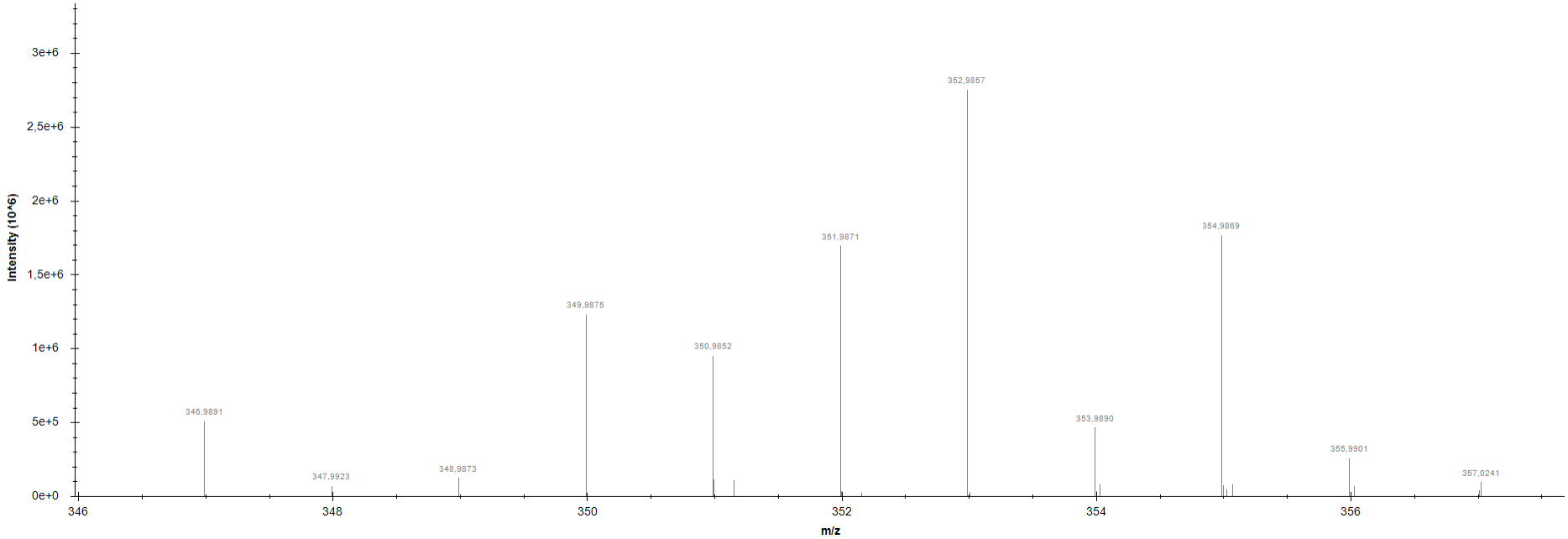
$RuC_{15}H_{11}O_2N_2^+$

352.9857



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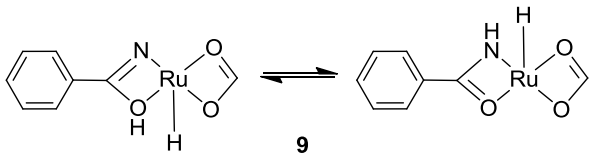

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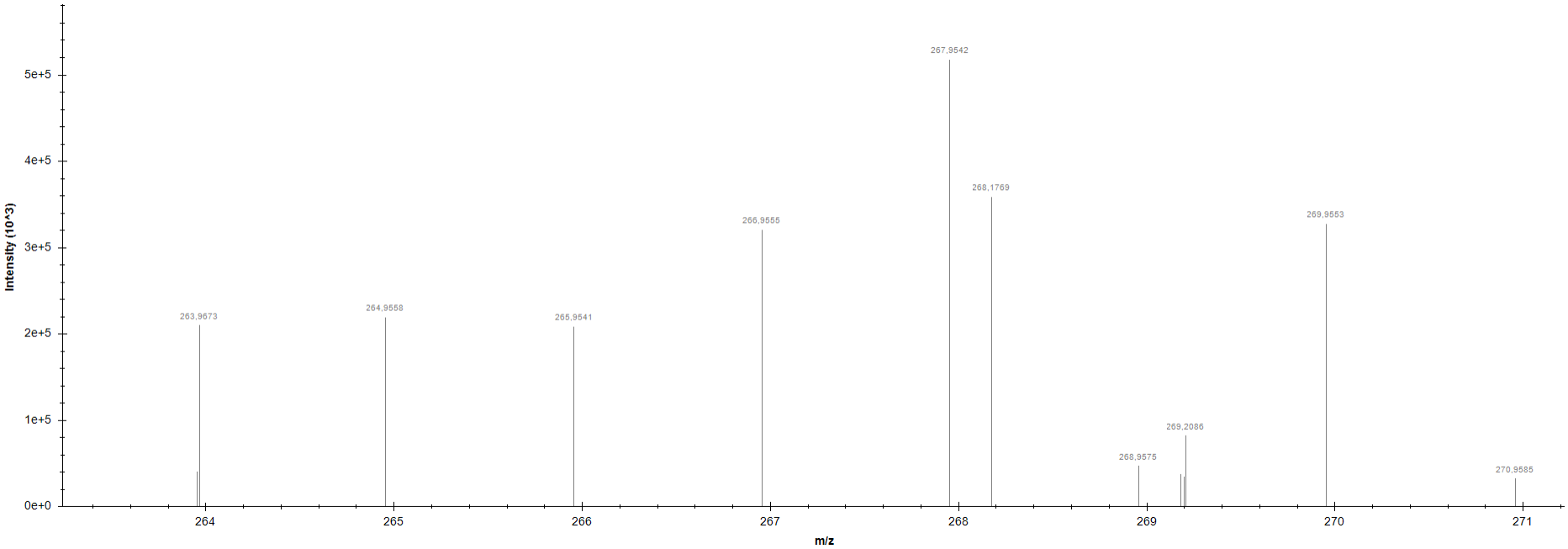
$RuC_8H_8O_3N^+$

267.9547



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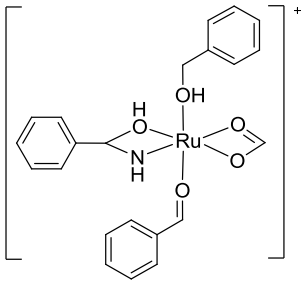
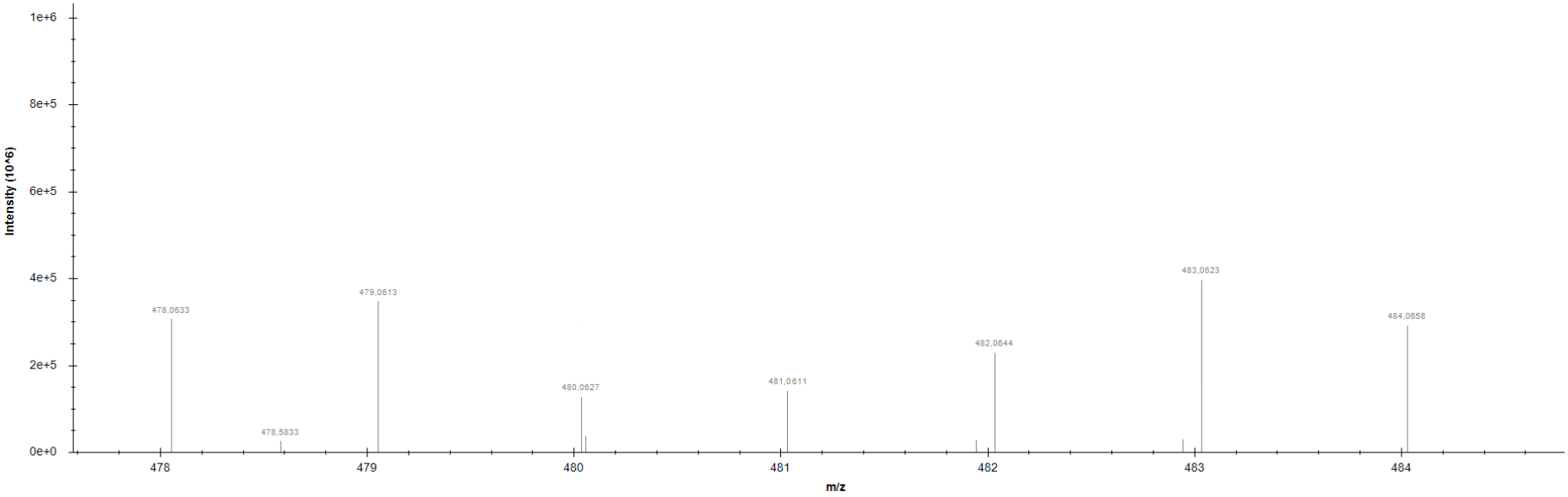


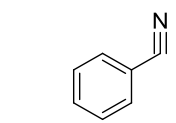
10

$RuC_{22}H_{23}O_5N^+$

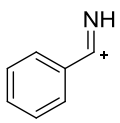
483,0619



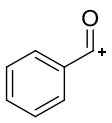
ESI MS spectrum of the organic intermediates. The spectrum verifies the formation of benzimine, benzaldehyde and benzyl alcohol in the course of the reaction



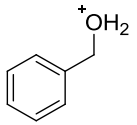
C_7H_5N
Exact Mass: 103.042



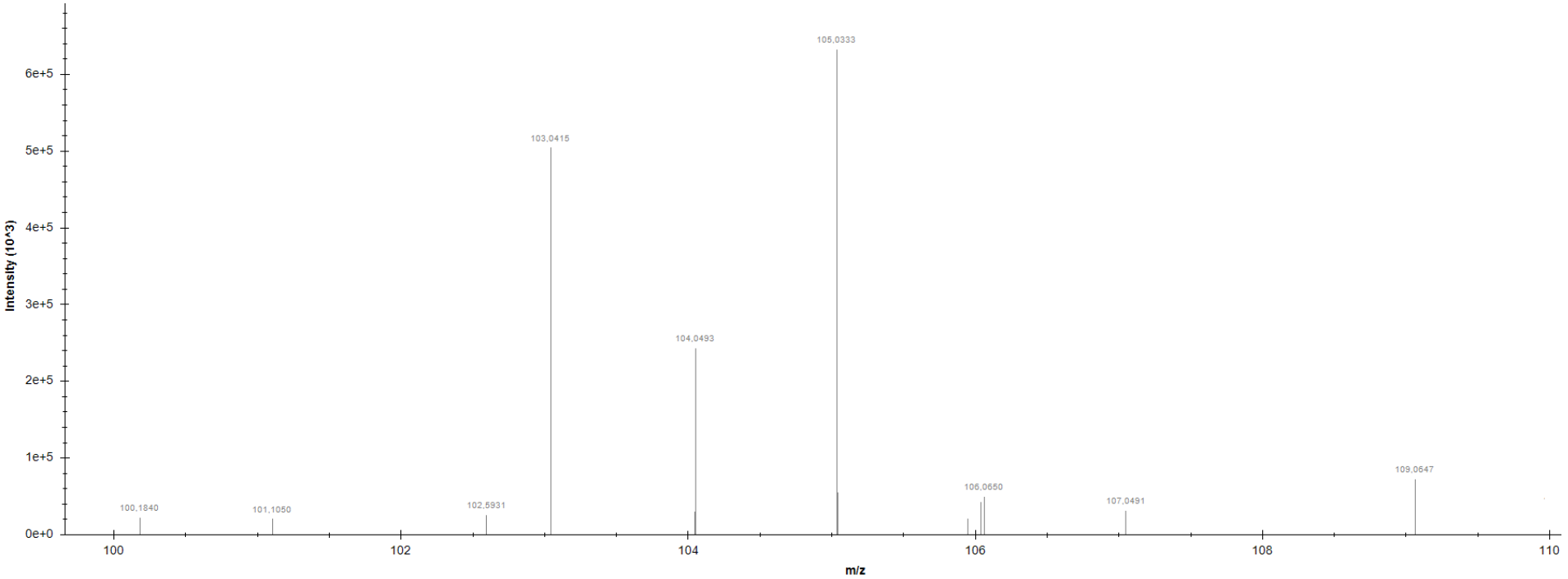
$C_7H_6N^+$
Exact Mass: 104.050



$C_7H_5O^+$
Exact Mass: 105.033



$C_7H_9O^+$
Exact Mass: 109.065



Comparison of the blank sample and the main reaction mixture. The spectra confirm the presence of benzimine, benzaldehyde and benzylalcohol cations in the reaction mixture.