SUPPORTING INFORMATION

Continuous Flow Ozonolysis in a Laboratory Scale Reactor

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General Experimental Details: ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a 300 or 360 MHz instrument at 300 or 360 and at 75 or 90 MHz, respectively. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q and m are used to indicate singlet, doublet, triplet, quadruplet and multiplet. Analytical HPLC analysis was carried out on a C18 reversed-phase (RP) analytical column (119 × 3 mm, particle size 5 mm) or a reversed-phase column (150 × 4.6 mm, particle size 5 mm) at 25 °C using a mobile phase A (water/acetonitrile 90:10 (v/v) + 0.1 % TFA) and B (MeCN + 0.1 % TFA) at a flow rate of 1 mL/min. The following gradient was applied: linear increase from solution 30% B to 100 % B in 6 min, hold at 100% solution B for 2.2 min. GC–MS conditions were as follows: splitless injection, injection temperature 250 °C, HP-5 MS column (30m×0.25mm ID, 0.25 μm film); carrier gas helium 5.0, flow 1 mL/min, temperature gradient programmed from 60 to 300 °C at 20 °C/min after an initial time of 6 min. The MS conditions were as follows: positive EI ionization, ionization energy 70 eV, ionization source temperature 280 °C, emission current 100 μA. Melting points were obtained on a standard melting point apparatus in open capillary tubes. 4-Fluorobenzoic acid methyl ester, 4-methoxybenzaldehyde and Nopinone (**4**) were additionally purified via flash chromatography on silica gel on automated flash chromatography system using cartridges packed with KP-SIL, 60 Å (32-63 μm particle size). TLC analyses were performed on pre-coated (silica gel 60 HF254) plates.

All chemicals and solvents were obtained from standard commercial vendors and were used without any further purification except where stated otherwise.

Flow Ozonolysis Apparatus (O-Cube):[S1]

Ozonolysis reactions were performed in O-Cube^{TM} reactor, a compact continuous flow (mesofluidic) device which operates at atmospheric pressure with temperature range from -25°C to room temperature. The liquid flow rate range of the system is 0.2-2 mL/min. The flow instrument is equipped with number of safety features including ozone leak detection and temperature and pressure limit shutdown. Syringe pumps are used to deliver substrate and quenching reagent to avoid any of the issues caused by HPLC pump check valve failures. Ozonolysis and quenching steps are carried out in sequence during the experimental run.

The instrument is connected with an O_2 gas cylinder (MESSER Austria, technical quality, >99.5% purity, CAS 7782-44-7) to supply an inbuilt O_3 generator with a continuous flow of O_2 at a maximum flow rate of 20 mL/min. The maximum generated O_3 concentration is 15 wt.% and is quantified in an internal analyzer before being mixed with a continuous stream of dissolved substrate. The stream of substrate is continuously cooled before and after being mixed with the O_3. The gas mixer where O_3 is mixed with substrate and mixer that combines the outlet of the reactor with the quench solution are standard T-mixers without frit.

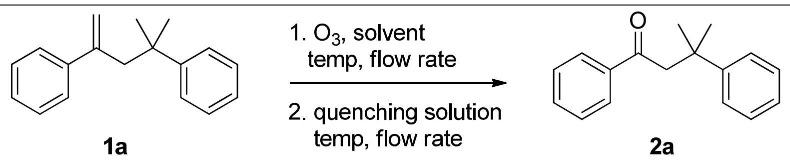
Users can set the excess of ozone for the desired ozonolysis reaction in Auto Mode (e.g. 50% excess means 1.5 eq. ozone). In order to accomplish this, the concentration (c[reactant] in mol/L) and the desired flow rate (v[reactant] in mL/min) of the reactant solution should also be given by the user. The system calculates the molar amount of ozone (n[ozone] in mmol) by the following formula: n[ozone]=c[reactant]*v[reactant]*(100+e)/100. The necessary mass flow value (v[oxygen] in normal mL/min) of the oxygen gas is calculated and controlled real-time by the program using the following formula: v[oxygen]=const* n[ozone]*(300-X)/X, where X is the ozone content of oxygen leaving the built-in ozone-generator (w/w, measured continuously by built-in ozone sensor).

The cooled reaction loop is a 4 mL (reaction volume) 1 mm i.d. PTFE tube wrapped around a refrigeration unit. After passing through the reaction loop, the formed ozonide mixes with the quench reagent solution before being collect in product receiving flask. The instrument is capable of producing from 10mg-10g of product per day. Higher amounts may be generated by leaving the O-Cube™ to generate product continuously over longer periods of time.

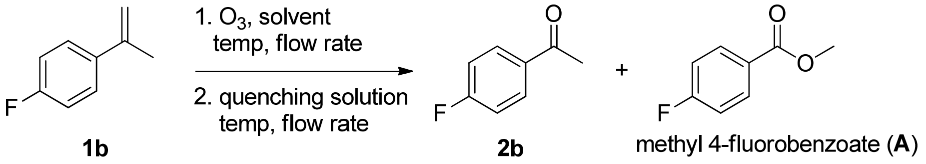
All flow ozonolysis experiments were performed in “single-pass” mode, without recirculation.

Flow Ozonolysis in the O-Cube. General Procedure: Stock solutions of the corresponding starting materials (0.05M, 20-25 mL) and quenching reagents in the appropriate solvents are prepared and placed in the respected reservoirs. The reaction parameters (temperature, flow rate and ozone concentration) are selected on the O-Cube control panel before the reaction is started. The reaction processing is initiated after the selected temperature is achieved. Initially, the instrument is processing only pure solvent until the set parameters are achieved. The ozone generator is initiated and the reaction mixture is mixed with the ozone flow after initial pre-cooling to the set reaction temperature. After processing through the reaction coil, the quenching solution is mixed with the reaction mixture and after passing the quench coil the reaction mixture is collected and an aliquot sample subjected to HPLC or GC-MS analysis. *(Caution! As ozonides and/or peroxides can be explosive and shock-sensitive, solvent was only removed when the solutions tested negative with peroxide test strips).* In cases where the crude reaction mixture tested positive for peroxide, either the type of quenching reagent or the concentration of the quenching reagent was changed in such a way so that in a following run no peroxide was observed. After completion of the reaction, the organic phase was removed and the aqueous phase was extracted with dichloromethane. In the cases where only organic phase was present, 20-40 mL of water were added prior the extraction. The combined organic phases are dried over $MgSO_4$, the solvent removed under vacuum and the residue purified by flash chromatography using a mixture of petroleum ether and ethyl acetate. All compounds described herein are literature known and NMR data are in agreement with the published data.

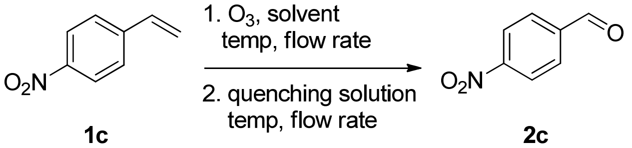
Table S1. Optimization Experiments in the Flow Ozonolysis of Styrenes **1a-d**. Shown is the variation of typical reaction parameters such as O_3 concentration, flow rate (ozonolysis and quench), ozonolysis temperature, quenching conditions, and quench temperature.



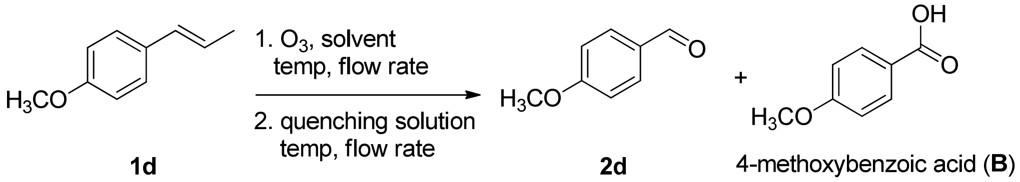
O_3, %	solvent	step 1 mL/min	temp. °C	quenching solution	step 2 mL/min	temp. °C	conv. % (GC-MS)
10	MeOH	1	-10	0.15M KI/MeOH	0.5	0	15
10	MeOH	0.5	-10	0.15M KI/MeOH	0.5	0	55
10	MeOH	0.5	0	0.15M KI/MeOH	0.5	10	>99
10	MeOH	1	0	0.15M $NaBH_4$/MeOH	0.5	10	>99
10	MeOH	1	rt	0.1M $NaBH_4$/MeOH	0.7	rt	>99
5	**MeOH**	**1**	**rt**	**0.1M $NaBH_4$/MeOH**	**0.7**	**rt**	**>99**



O_3, %	solvent	step 1 mL/min	temp. °C	quenching solution	step 2 mL/min	temp. °C	conv. % (GC-MS)	
							2b	**A**
5	MeOH	1	0	0.15M KI/MeOH	0.5	10	79	21
5	MeOH	1	-20	0.15M $NaBH_4$/MeOH	0.5	-10	92	8
5	MeOH	1	0	0.15M $NaBH_4$/MeOH	0.5	10	90	10
5	Me_2CO	0.5	0	5% H_2O/ Me_2CO	0.7	10	90	10
5	**Me_2CO**	**1**	**0**	**5% H_2O/ Me_2CO**	**0.7**	**10**	**>99**	-
5	MeOH	1	rt	0.17M H_2O_2/MeOH	0.5	rt	25	75
5	MeOH	1	rt	0.35M H_2O_2/MeOH	0.5	rt	26	74
5	MeOH	1	rt	1M H_2O_2/MeOH	0.5	rt	22	78
5	MeOH	1	rt	3M H_2O_2/MeOH	0.5	rt	28	72
5	MeOH	1	rt	5M H_2O_2/MeOH	0.5	rt	30	70



10	Me_2CO	1	10	5% H_2O/ Me_2CO	0.7	15	>99
10	Me_2CO	1	rt	5% H_2O/ Me_2CO	0.7	rt	>99
5	**Me_2CO**	**1**	**rt**	**5% H_2O/ Me_2CO**	**0.7**	**rt**	**>99**



O_3, %	solvent	step 1 mL/min	temp. °C	quenching solution	step 2 mL/min	temp. °C	conv. % (GC-MS)	
							2d	**B**
5	$CHCl_3$	1	10	0.15M $NaBH_4$/H_2O	1	15	78	22
5	**Me_2CO**	**1**	**10**	**5% H_2O/ Me_2CO**	**0.7**	**15**	**83**	**17**
5	Me_2CO	1	0	5% H_2O/ Me_2CO	0.7	10	65	35
5	Me_2CO	1	rt	5% H_2O/ Me_2CO	0.7	rt	78	22
8	Me_2CO	2	rt	5% H_2O/ Me_2CO	1	rt	65	35
5	MeOH	1	rt	0.15M H_2O_2/MeOH	0.7	rt	64	16
10	MeOH	1	5	3M H_2O_2/MeOH	0.9	10	77	23
10	MeOH	1	-10	5M H_2O_2/MeOH	0.9	0	77	23
10	MeOH	0.3	-20	3M H_2O_2/MeOH	1	-10	48	52
10	MeOH	0.2	rt	5M H_2O_2/MeOH	0.9	rt	50	50
10	MeOH	0.5	rt	3M H_2O_2/MeOH	0.6	rt	51	49

Products/Conditions:

3-Methyl-1,3-diphenylbutan-1-one (2a).[S2] a) Ozonolysis: 0.05 M of **1a** in methanol, 5% O_3, 1 mL/min flow rate, rt. b) Quenching: 0.1 M $NaBH_4$ in methanol, 0.7 mL/min flow rate, rt. Colorless oil (215 mg, 90 %), ^1H NMR (300 MHz, $CDCl_3$): δ ppm 7.86 (d, J = 7.1 Hz, 2H), 7.52 (t, J = 7.3 Hz, 1H), 7.39 (m, 4H), 7.31 (t, J = 7.6 Hz, 2H), 7.19 (t, J = 7.2 Hz, 1H), 3.34 (s, 2H), 1.54 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): 199.0, 148.9, 138.2, 132.7, 128.4, 128.2, 128.0, 125.8, 125.4, 50.9, 37.5, 29.1; MS (pos. APCI) m/z: 238 (100, M+1).

4-Fluoroacetophenone (2b).[S2] a) Ozonolysis: 0.05 M of **1b** in acetone, 5% O_3, 1 mL/min flow rate, 0 °C; b) Quenching: 5% H_2O/acetone (v/v), 0.7 mL/min flow rate, 10 °C; colorless oil (157 mg, 91 %), ^1H NMR (300 MHz, $CDCl_3$): δ ppm 8.01-7.96 (m, 2H), 7.13 (t, *J* = 8.6 Hz, 2H), 2.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.4, 165.8 (d, *J* = 254.6 Hz), 133.6 (d, *J* = 3.0 Hz), 130.9 (d, *J*= 9.3 Hz), 115.6 (d, *J* = 21.9 Hz), 26.5; MS (pos. APCI) m/z: 138 (100, M+1).

4-Nitrobenzaldehyde (2c).[S3] a) Ozonolysis: 0.05 M of **1c** in acetone, 5% O_3, 1 mL/min flow rate, rt. b) Quenching: 5% H_2O/acetone (v/v), 0.7 mL/min flow rate, rt; light yellow solid (157 mg, 84 %), mp. 106-108 °C, ^1H NMR (300 MHz, $CDCl_3$): δ ppm 10.15 (s, 1 H), 8.41 (d, *J* = 8.6 Hz, 2 H), 8.09 (d, *J* = 8.8 Hz, 2 H).; ^{13}C NMR (75 MHz, $CDCl_3$): δ190.3, 151.1, 140.0, 130.5, 124.3; MS (pos. APCI) m/z: 151 (100, M+1).

4-Methoxybenzaldehyde (2d).[S4] a) Ozonolysis: 0.05 M of **1d** in acetone, 5% O_3, 1 mL/min flow rate, 10°C. b) Quenching: 5% H_2O/acetone (v/v), 0.7 mL/min flow rate, 15°C. Colorless oil (98 mg, 72 %), ^1H NMR (300 MHz, $CDCl_3$): δ ppm 9.88 (s, 1 H), 7.84 (d, *J* = 8.8 Hz, 2 H), 7.0 (d, *J* = 8.7 Hz, 2 H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.8, 164.6, 131.9, 129.9, 114.3, 55.6; MS (pos. APCI) m/z: 136 (100, M+1).

4-Methoxybenzoic acid.[S4] a) Ozonolysis: 0.05 M of **2d** in $CHCl_3$, 50% O_3, 0.5 mL/min flow rate, 10°C. b) Quenching: 0.15 M H_2O_2 in water, 0.5 mL/min flow rate, 15°C. white solid (120 mg, 79%), mp. 186-188 °C; ^1H NMR (300 MHz, (DMSO-*d6*): δ ppm 12.62 (s, 1H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, DMSO-*d6*): δ

167.4, 163.2, 131.8, 123.4, 114.2, 55.8; MS (pos. APCI) m/z: 152 (100, M+1).

Attempted direct preparation of 4-methoxybenzoic acid from **2d** and ozone led to 50% selectivity for the acid (50% aldehyde remaining), see Table S1.

4-Fluorobenzoic acid methyl ester. [S5] a) Ozonolysis: 0.05 M of **1b** in methanol, 5% O_3, 1 mL/min flow rate, rt. b) Quenching: 1M H_2O_2 in methanol, 0.5 mL/min flow rate, rt, colorless oil (194 mg, 72 %); ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 8.06 (dd, *J* = 8.9 Hz, 5.4 Hz, 2H), 7.11 (dd, *J* = 8.8 Hz, 8.8 Hz, 2H), 3.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 165.7 (d, *J* = 253 Hz), 132.1(d, *J* = 9.3 Hz), 126.4 (d, *J* = 2.99 Hz),, 115.5 (d, *J* = 21.9 Hz), 52.2.; MS (pos. APCI) m/z: 154 (100, M+1).

Nopinone (4).[S6] a) Ozonolysis: 0.05 M of β-pinene (**3**) in acetone, 5% O_3, 1 mL/min flow rate, rt. b) Quenching: 5% H_2O/acetone, 0.7 mL/min flow rate, rt; colorless oil (97 mg, 70%), ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 2.49–2.65 (m, 3H), 2.35 (ddd, *J* = 2.2 Hz, 8.9 Hz, 19.1 Hz, 1H), 2.24–2.25 (m, 1H), 1.96–2.06 (m, 2H), 1.59 (d, J= 9.9 Hz, 1H), 1.34 (s, 3H), 0.86 (s, 3H),. ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.6, 57.7, 41.0, 40.2, 32.7, 25.7, 25.3, 21.9, 21.3; MS (pos. APCI) m/z: 138 (100, M+1).

Benzophenone (7).[S2] a) Ozonolysis: 0.05 M of **5** in chloroform, 10% O_3, 1 mL/min flow rate, rt. b) Quenching: 1.5 M H_2O_2 in chloroform, 0.5 mL/min flow rate, rt, white solid (157 mg, 86 %), m.p. 47-49 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 7.82 (d, *J* = 6.9 Hz, 4H), 7.61 (t, *J* = 7.4 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.7, 137.6, 132.4, 130.0, 128.3; MS (pos. APCI) m/z: 182 (100, M+1).

1-Nitrooctane (9).[S7] a) Ozonolysis: 0.05 M of **8** in ethyl acetate, 10% O_3 (3 equiv), 1 mL/min flow rate, rt. b) Quenching: 1.5 M H_2O_2 in water, 0.5 mL/min flow rate, rt; Colorless oil (117 mg, 73 %), ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 4.37 (t, *J*=7.0 Hz, 2H), 1.96-2.06 (m, 2 H), 1.29-1.71 (m, 10 H), 0.86 ppm (t, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 75.7, 31.8, 29.2, 28.5, 27.4, 26.2, 22.6, 14.1; MS (pos. APCI) m/z: 1 (100, M+1).

Methyl phenyl sulfoxide (11).[S8] a) Ozonolysis: 0.05 M of thioanisol (**10**) in methanol, 5% O_3, 1 mL/min flow rate, rt. b) Quenching: 0.1 M $NaBH_4$ in methanol, 0.7 mL/min flow rate, rt; colorless oil (147 mg, 84 %), ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 7.62–7.65 (m, 2H), 7.49–7.55 (m, 3H), 2.71 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.62, 131.07, 129.37, 123.50, 43.92; MS (pos. APCI) m/z: 140 (100, M+1).

Methyl phenyl sulfone (12).[S9] a) Ozonolysis: 0.05 M of thioanisol (**11**) in methanol, 10% O_3 (4 equivalent), 0.5 mL/min flow rate, -20°C. b) Quenching: 5 M H_2O_2 in methanol, 0.5 mL/min flow rate, -10°C; colorless crystals (136 mg, 87 %) mp. 85-87 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 7.94–7.97 (2H, m), 7.65-7.71 (m, 1H), 7.56−7.61 (m, 2H), 3.09 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.30, 133.86, 129.45, 127.34, 44.5; MS (pos. APCI) m/z: 156 (100, M+1).

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S1 For details see: http://www.thalesnano.com/products/o-cube.

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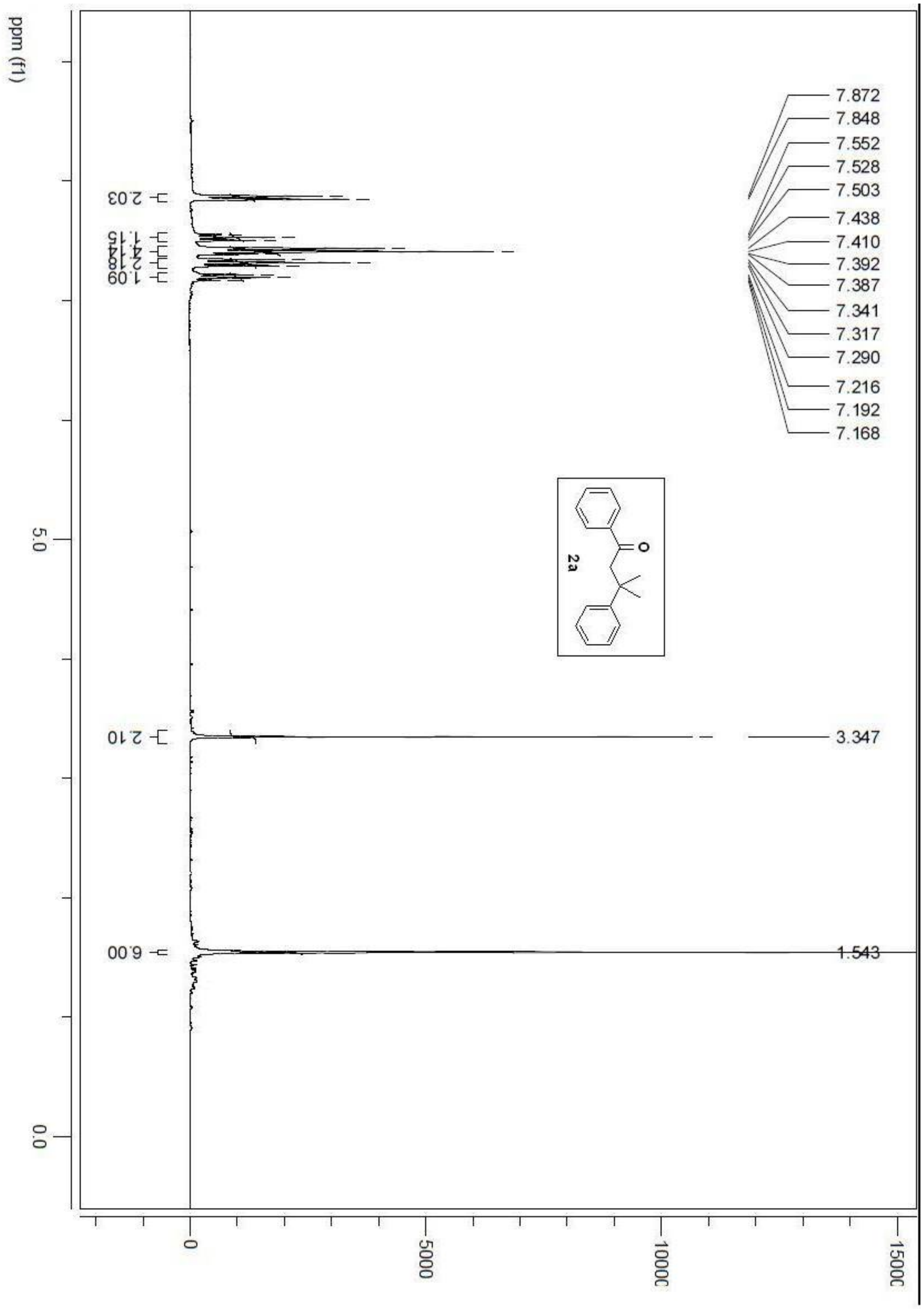
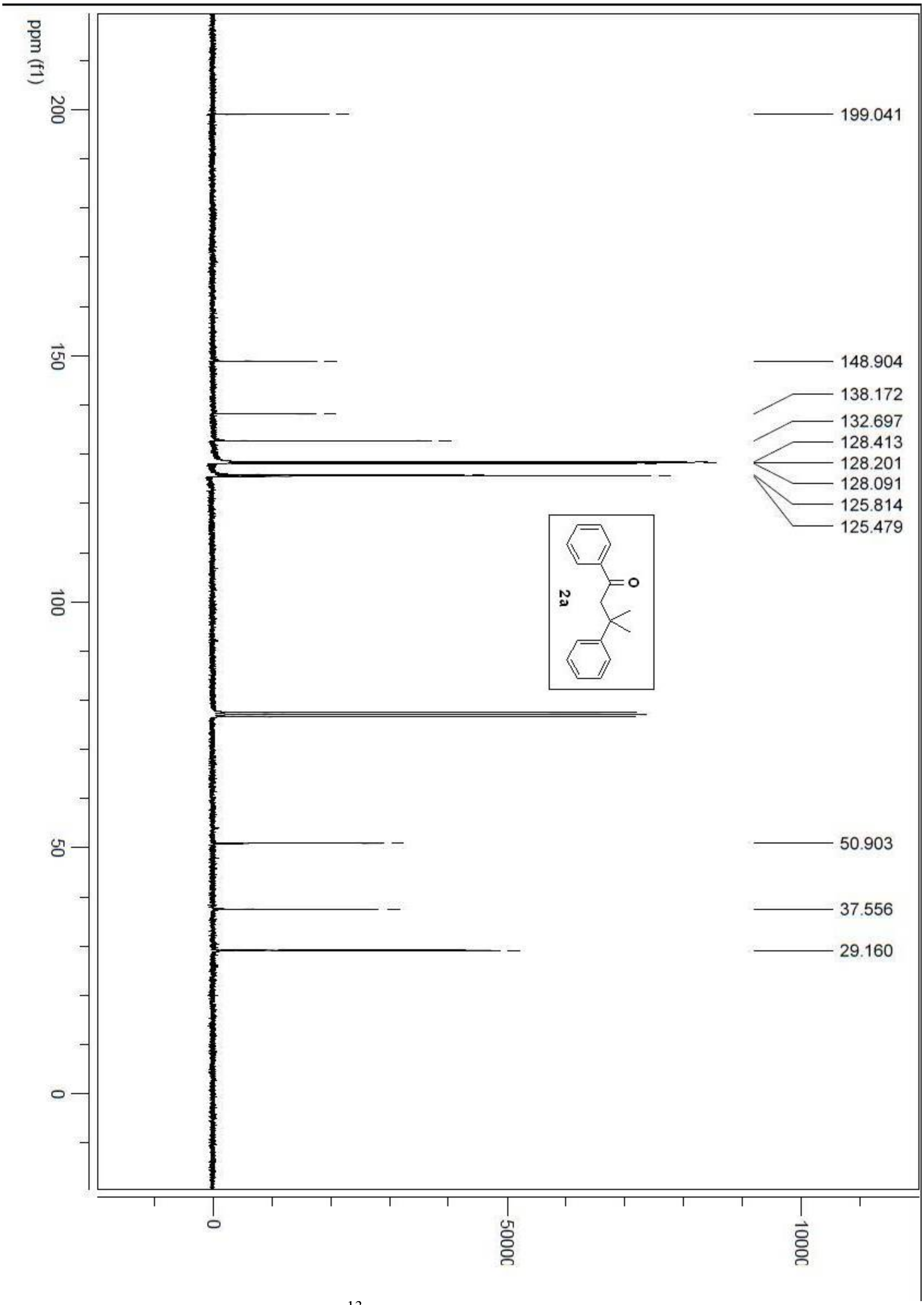


^{1}H NMR spectra of **2a**



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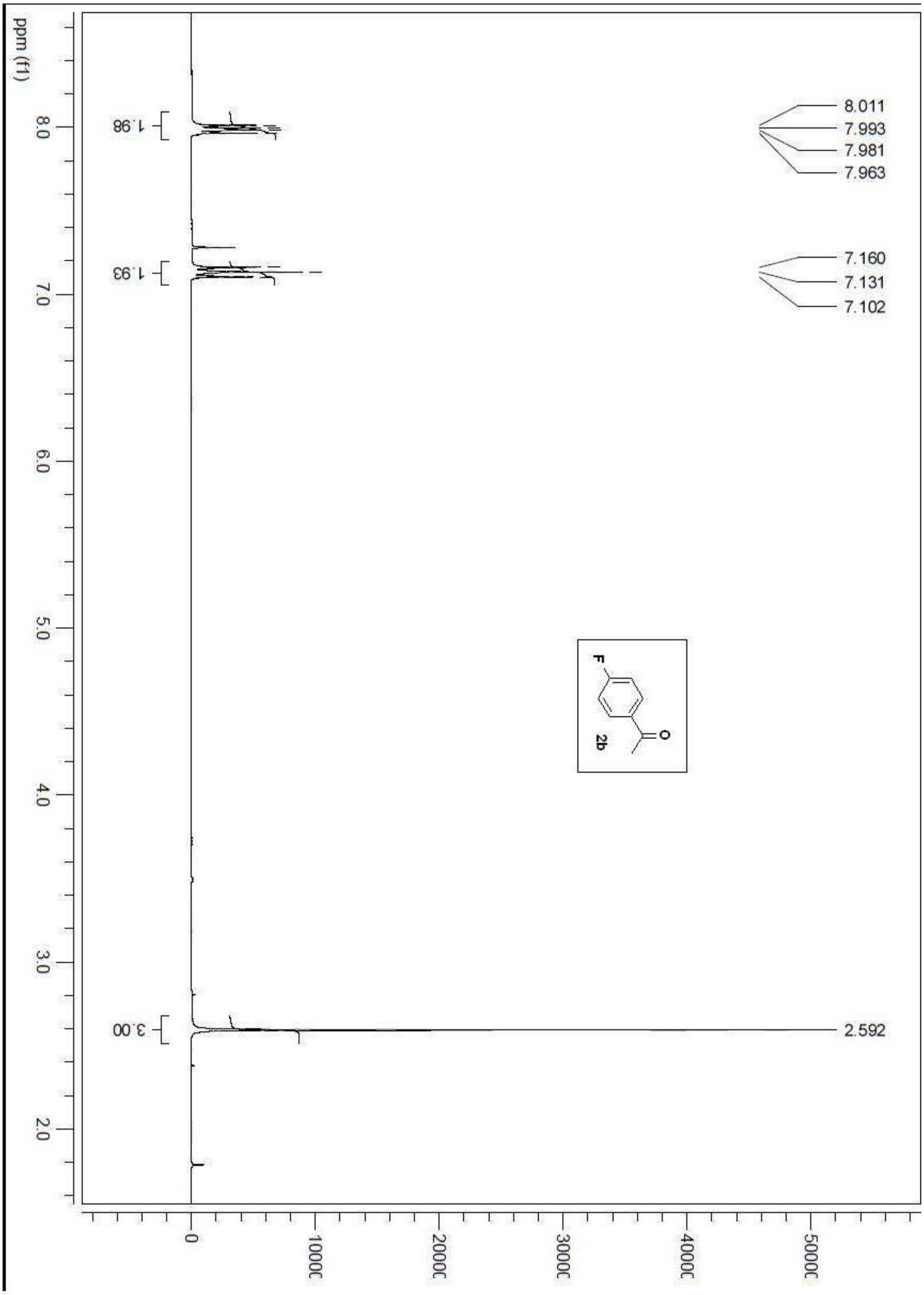

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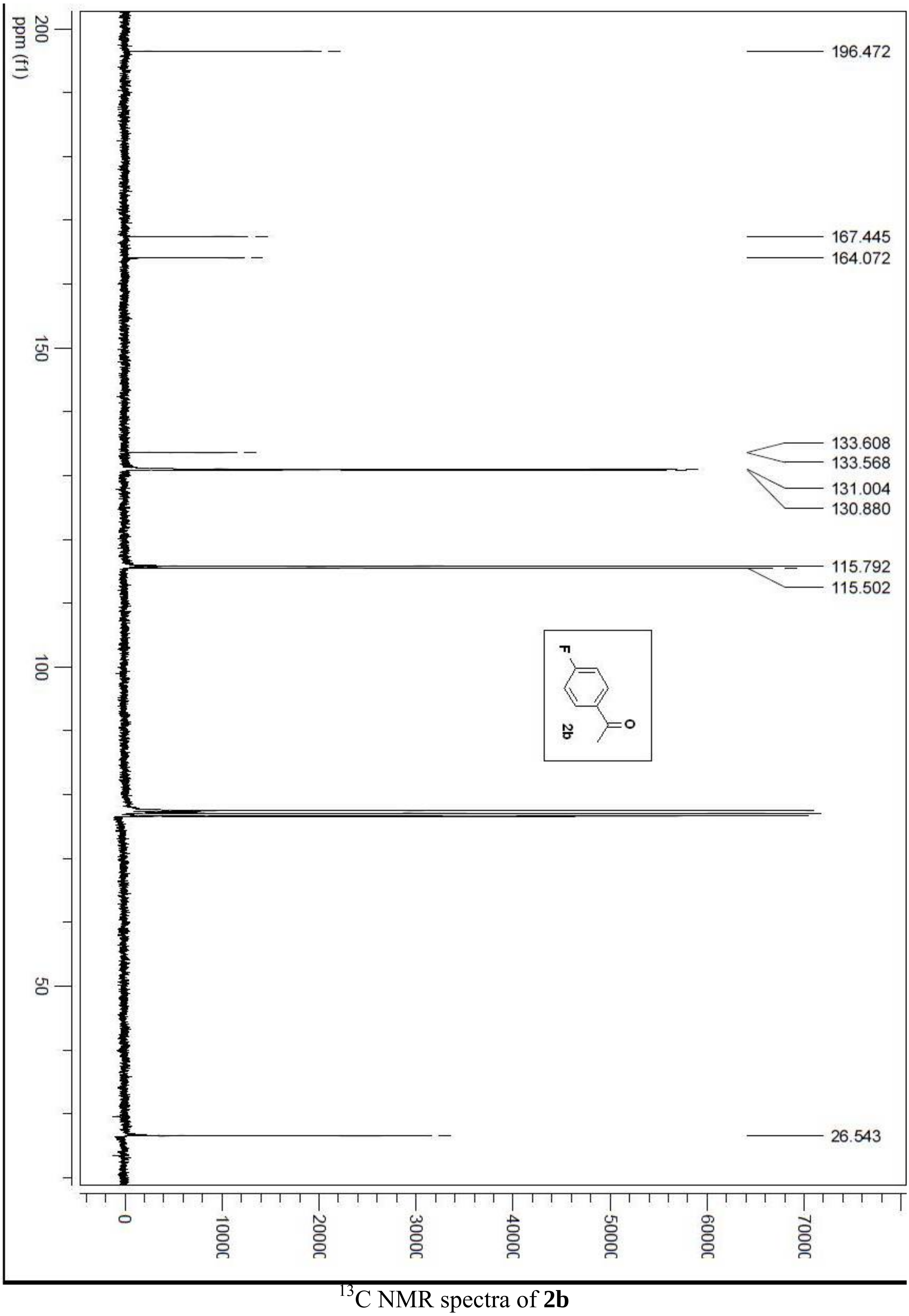

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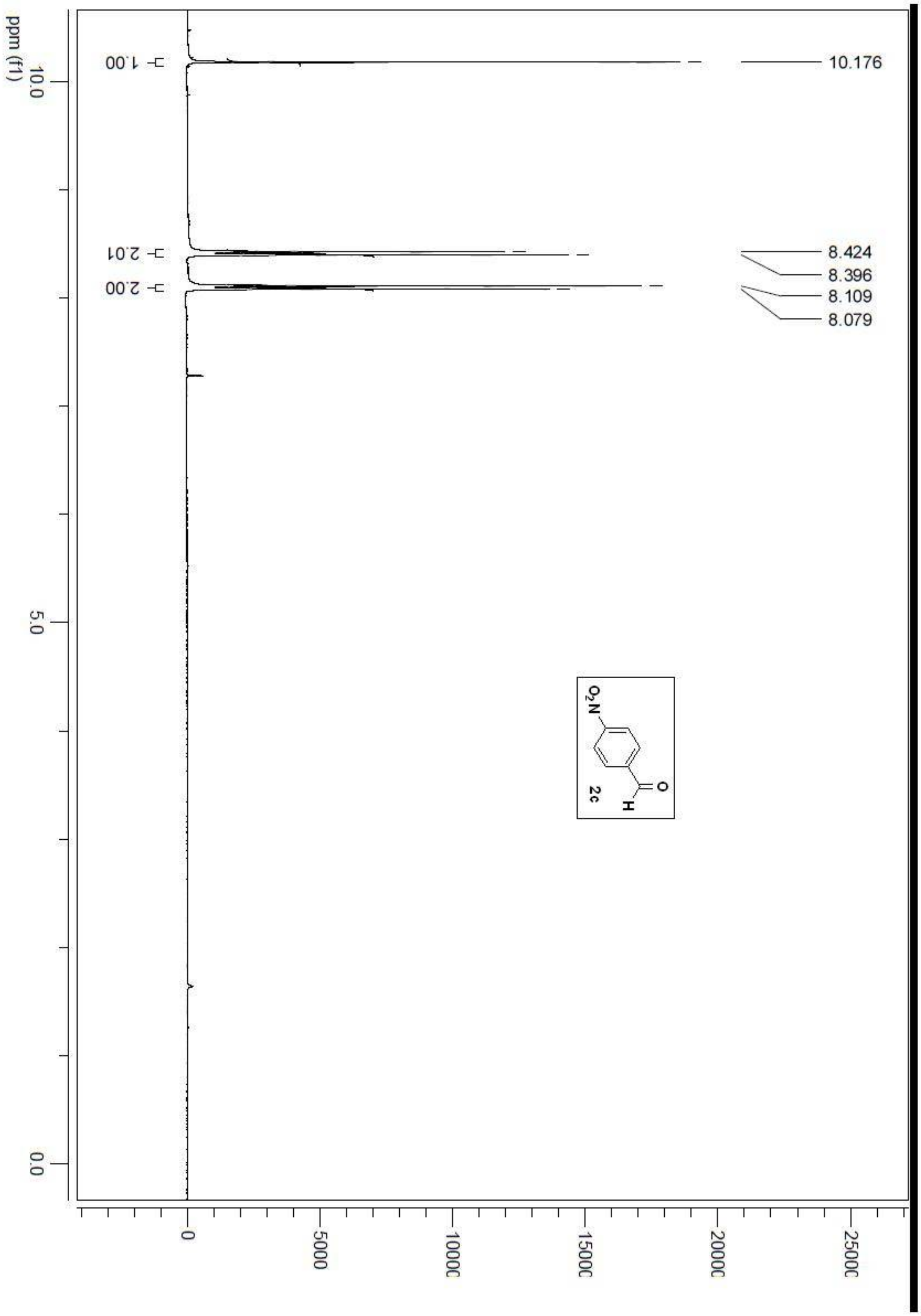

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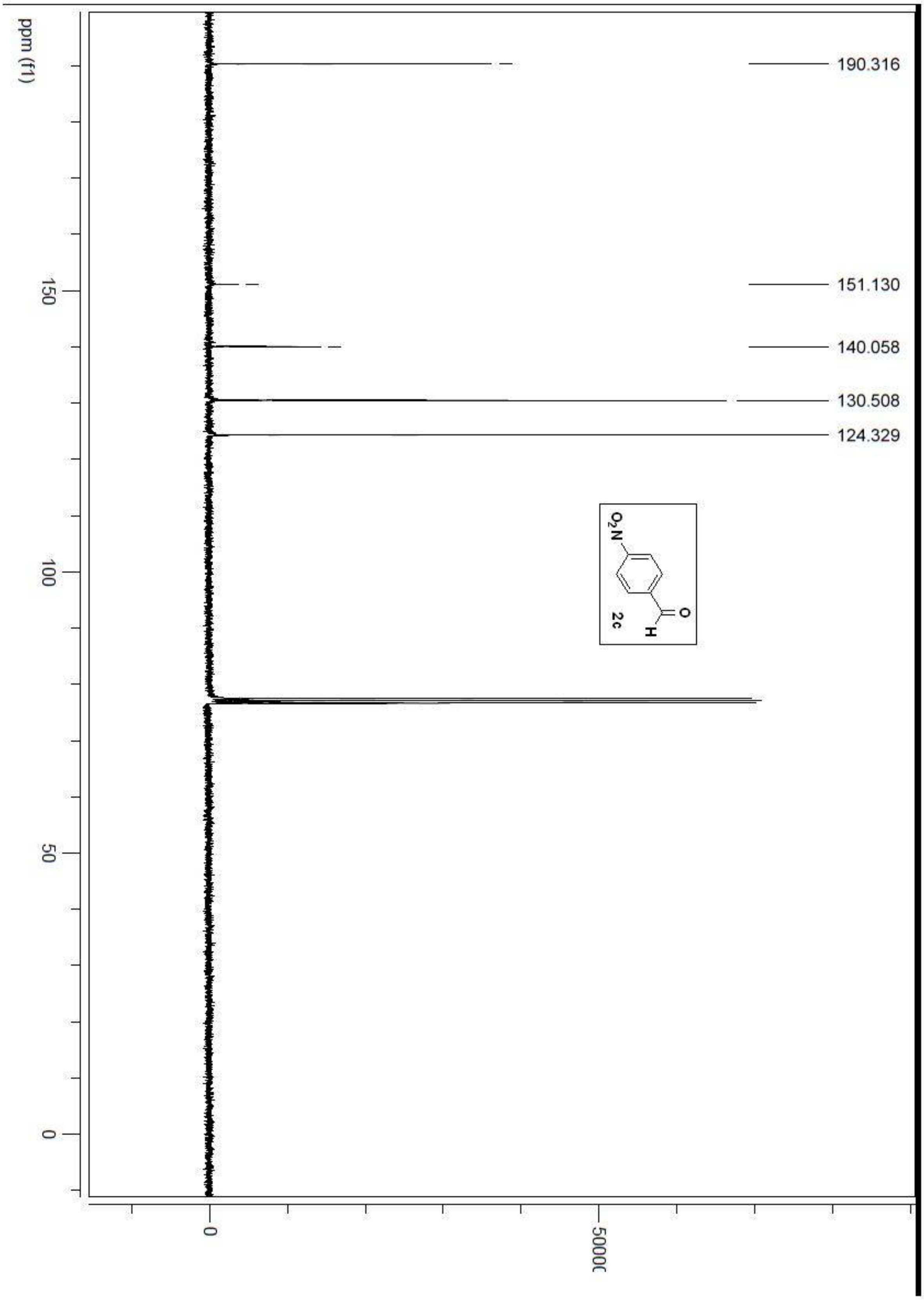

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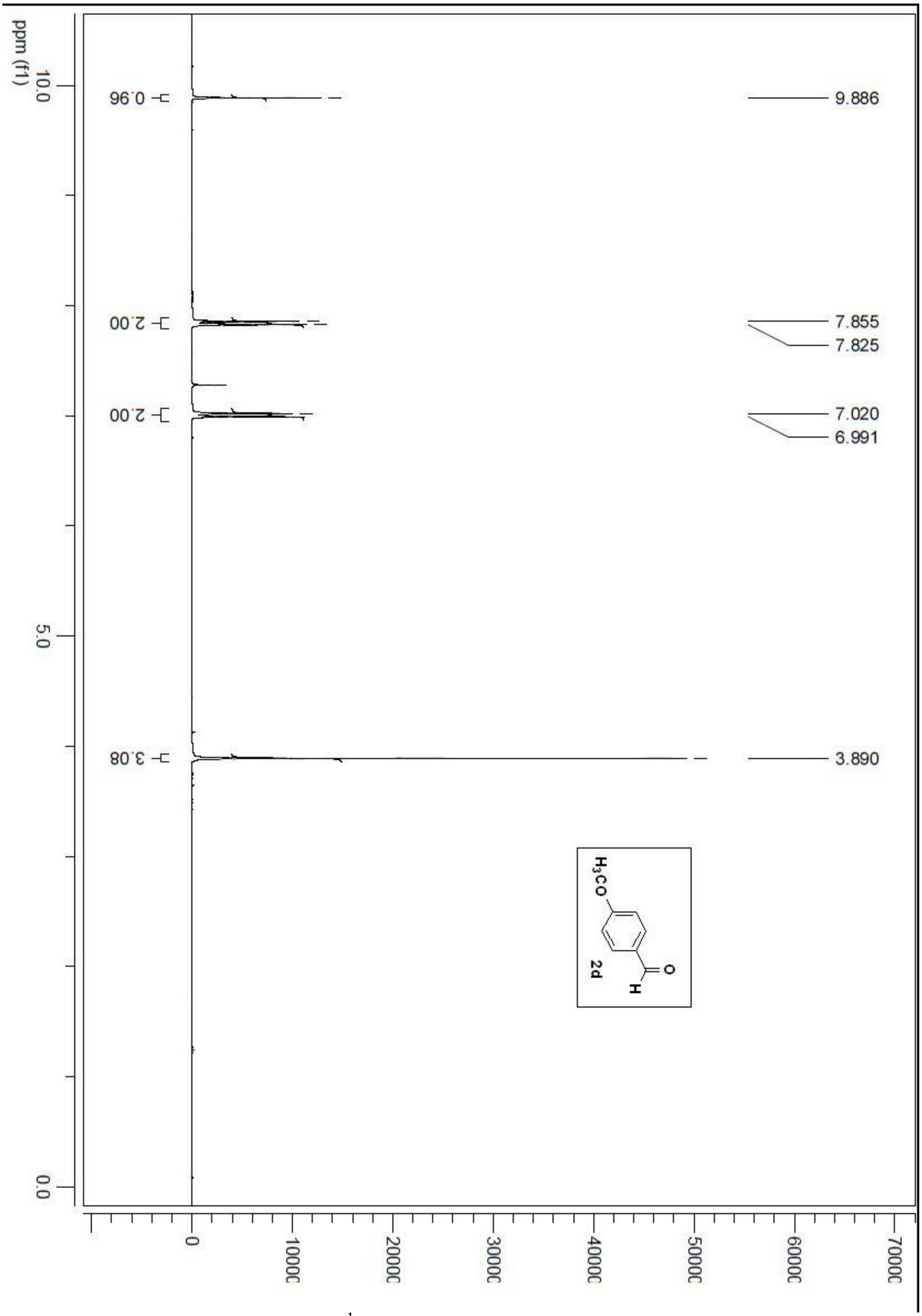

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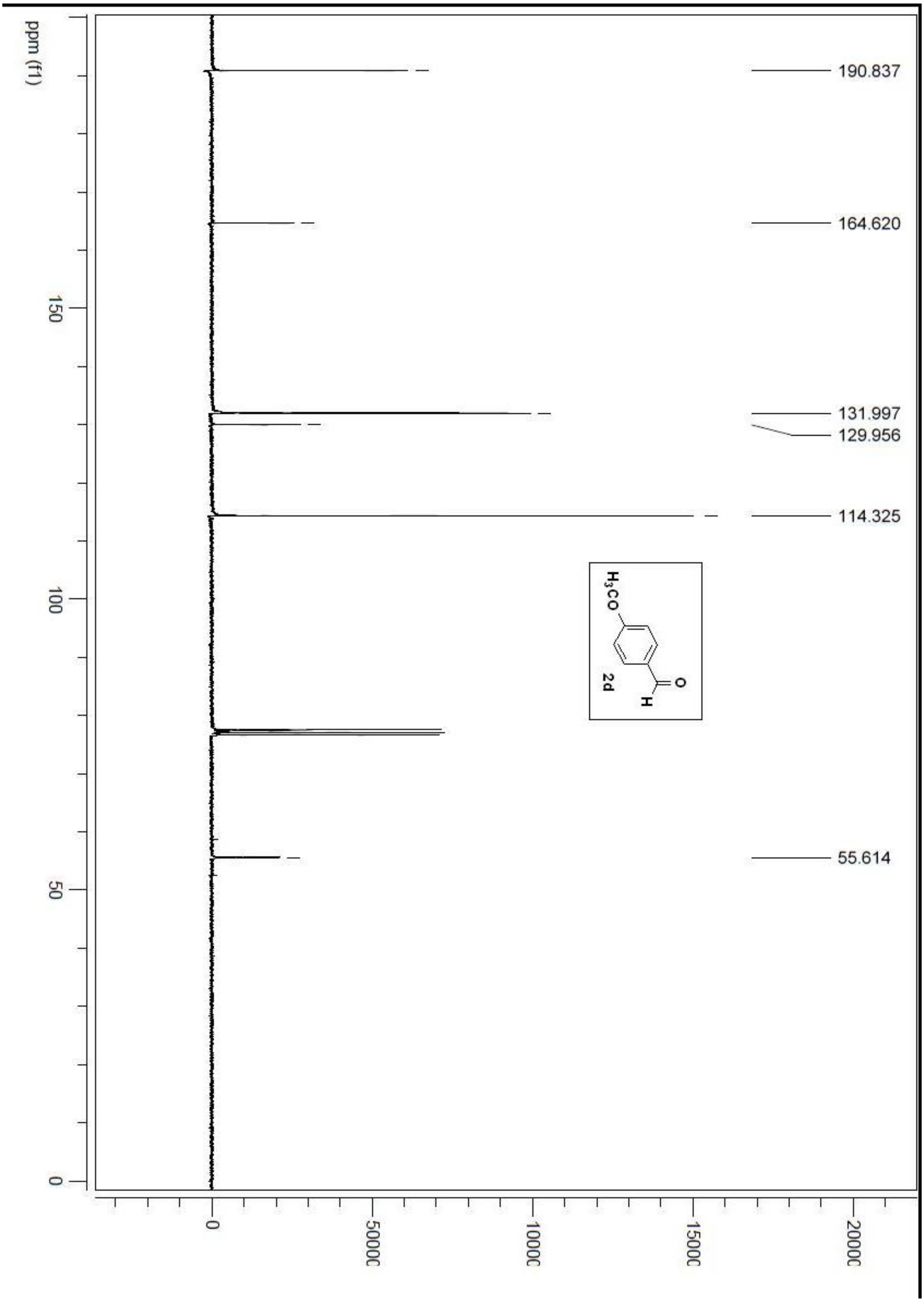

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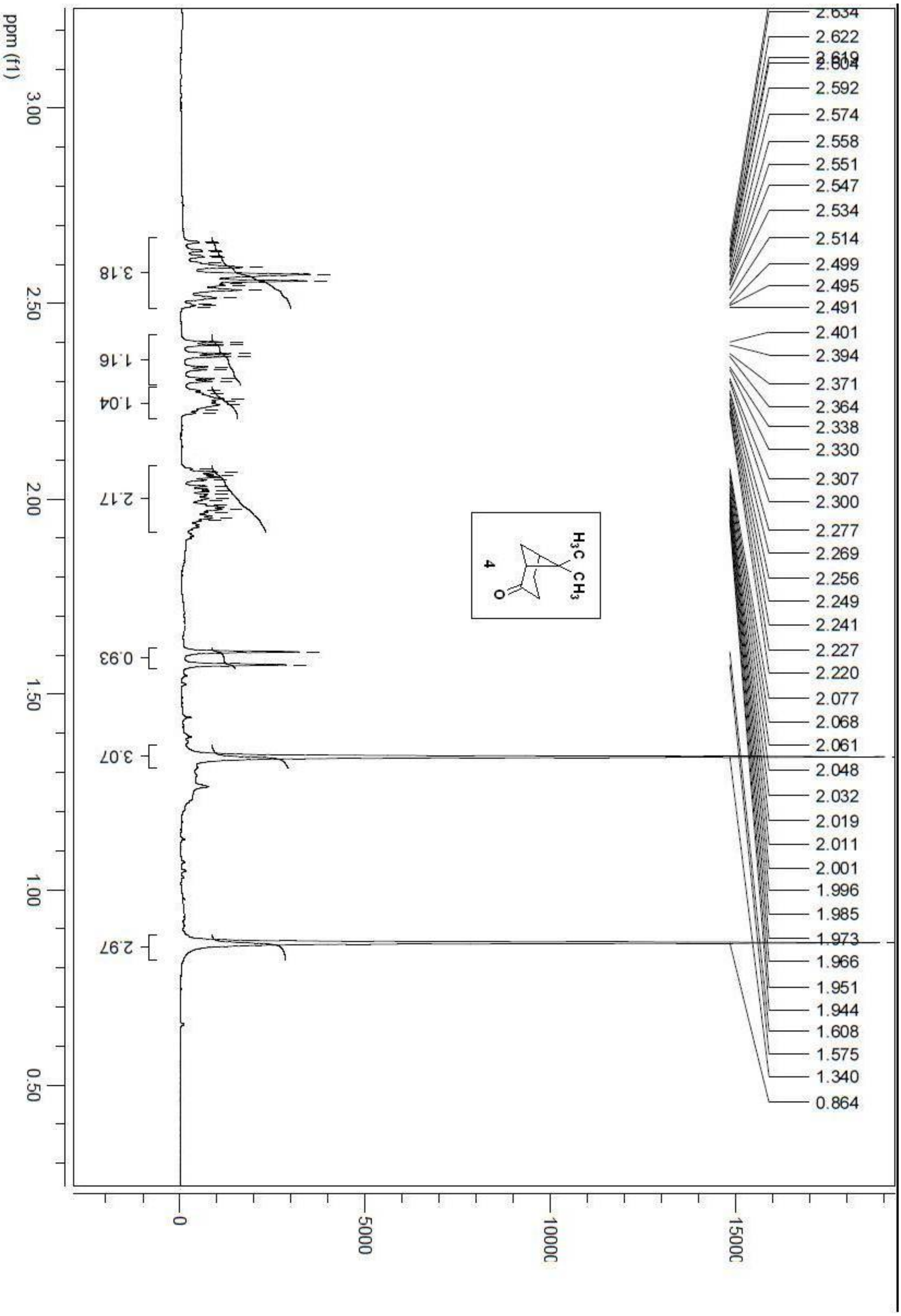

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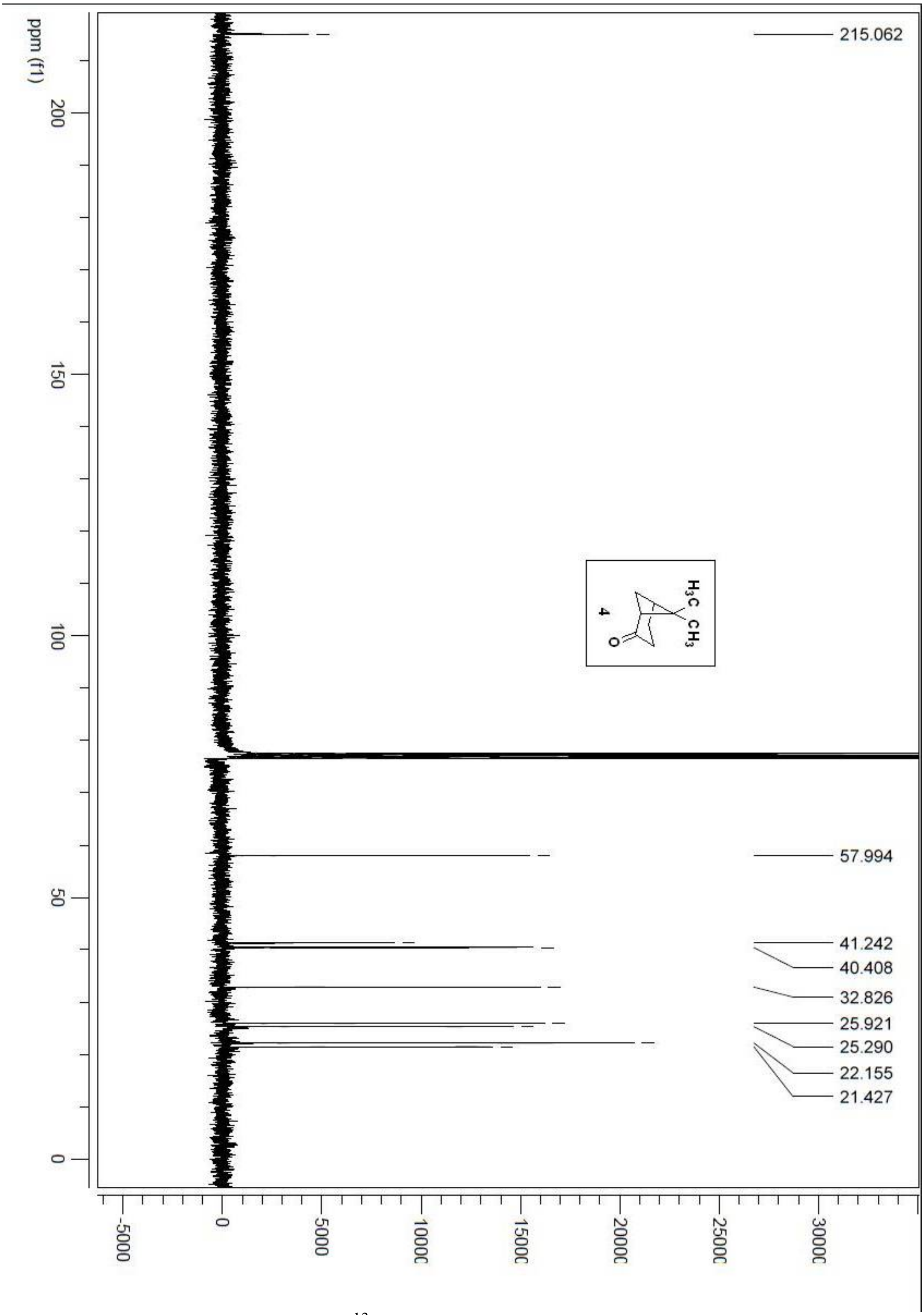

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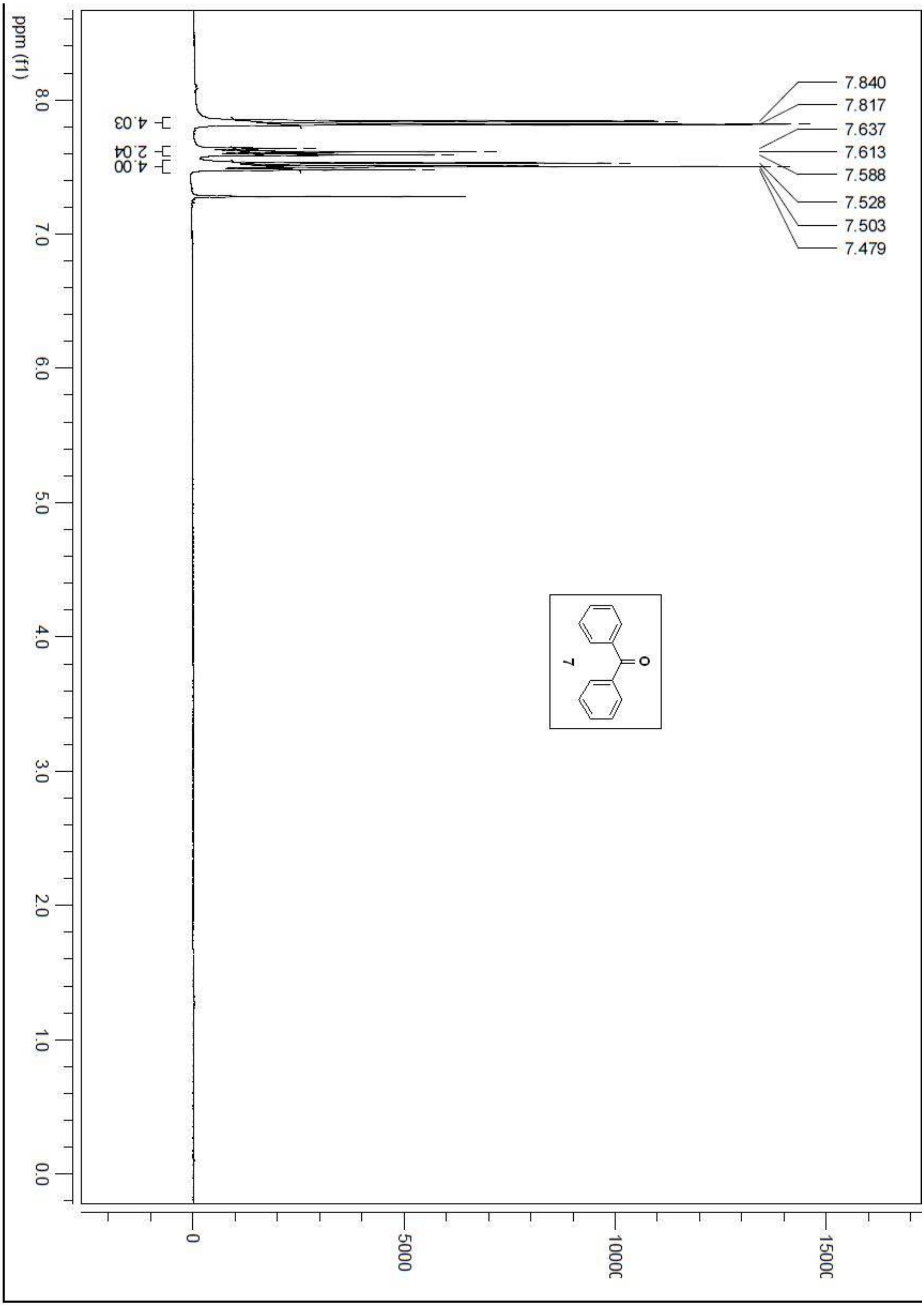

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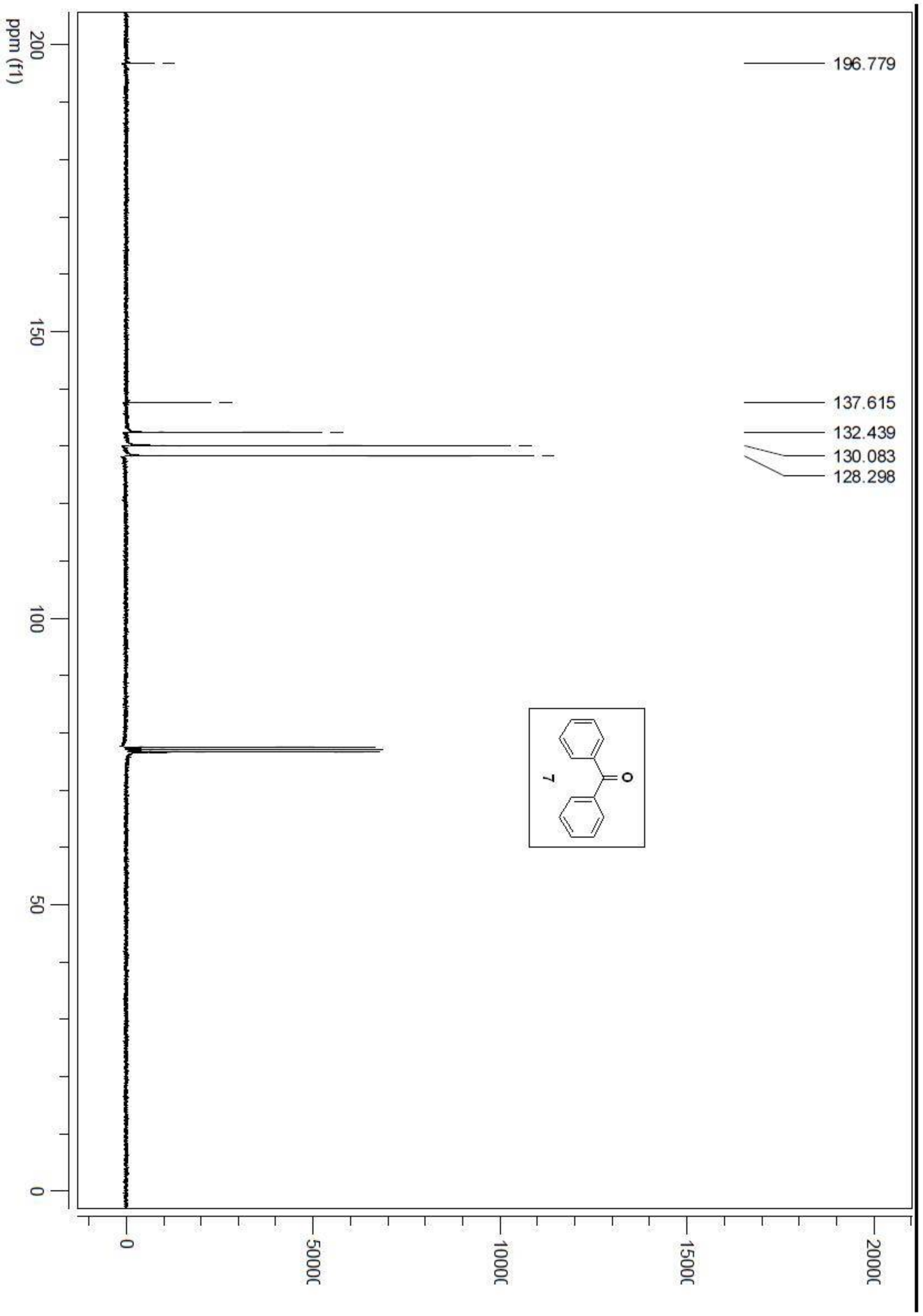

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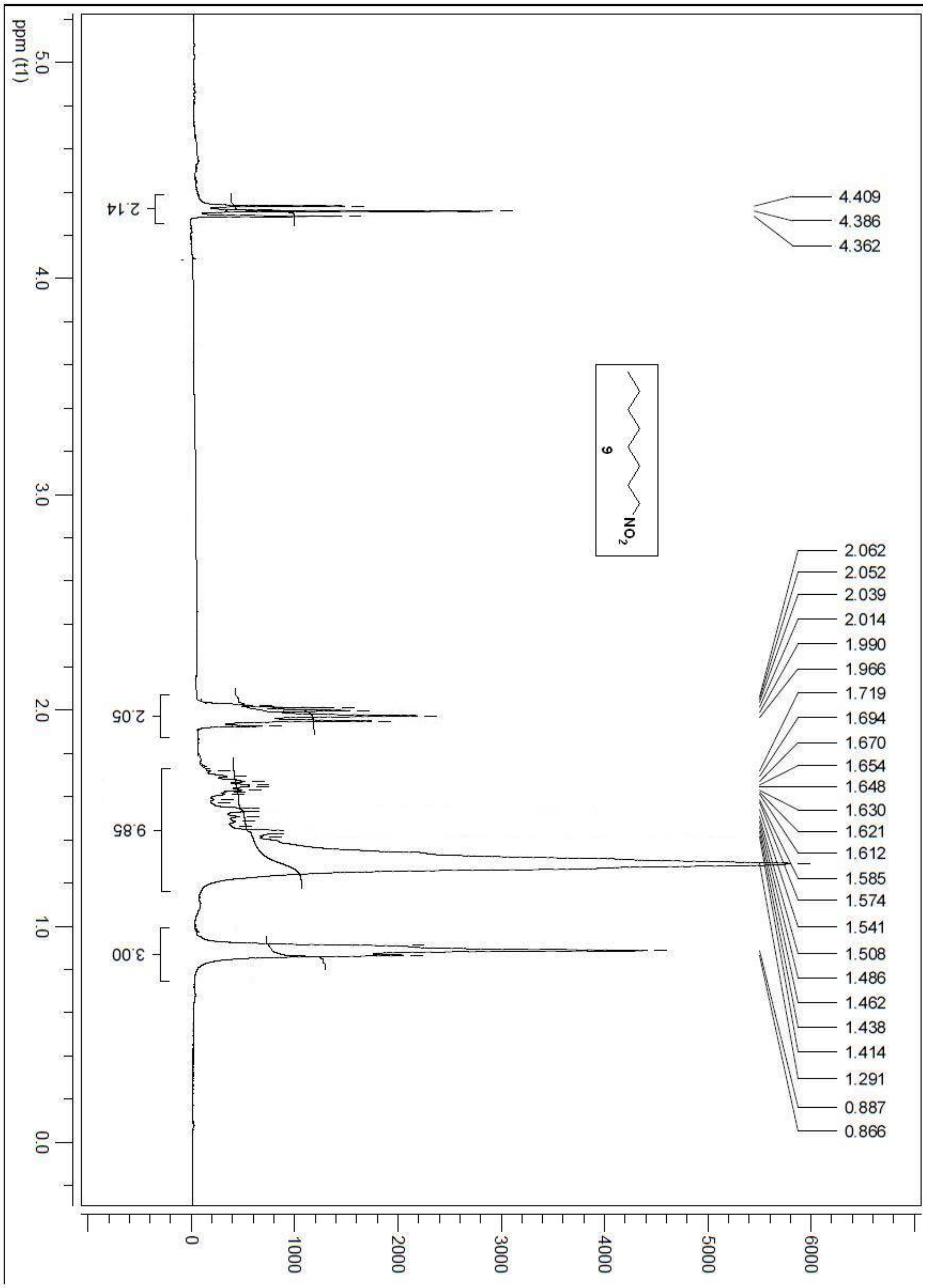

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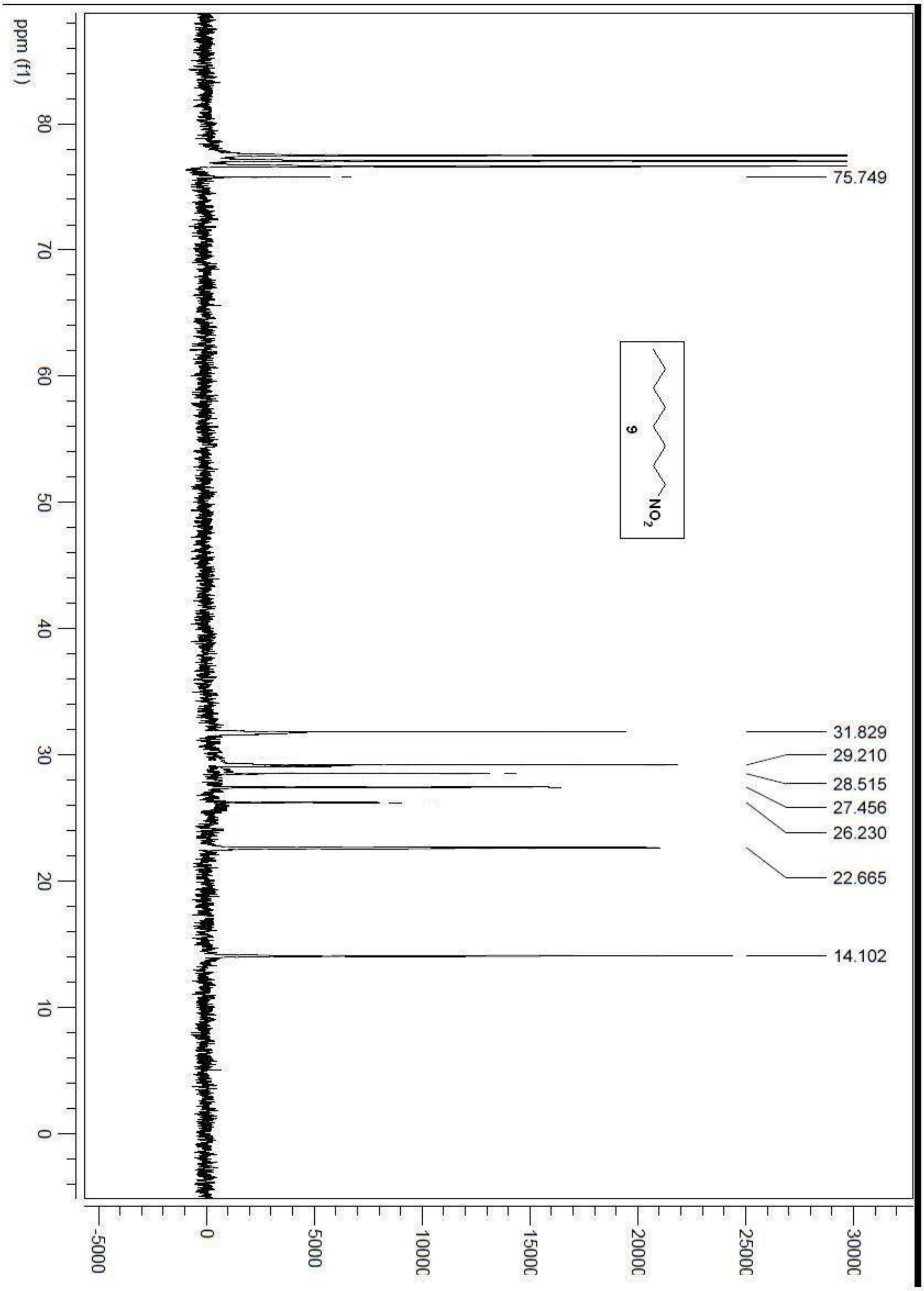
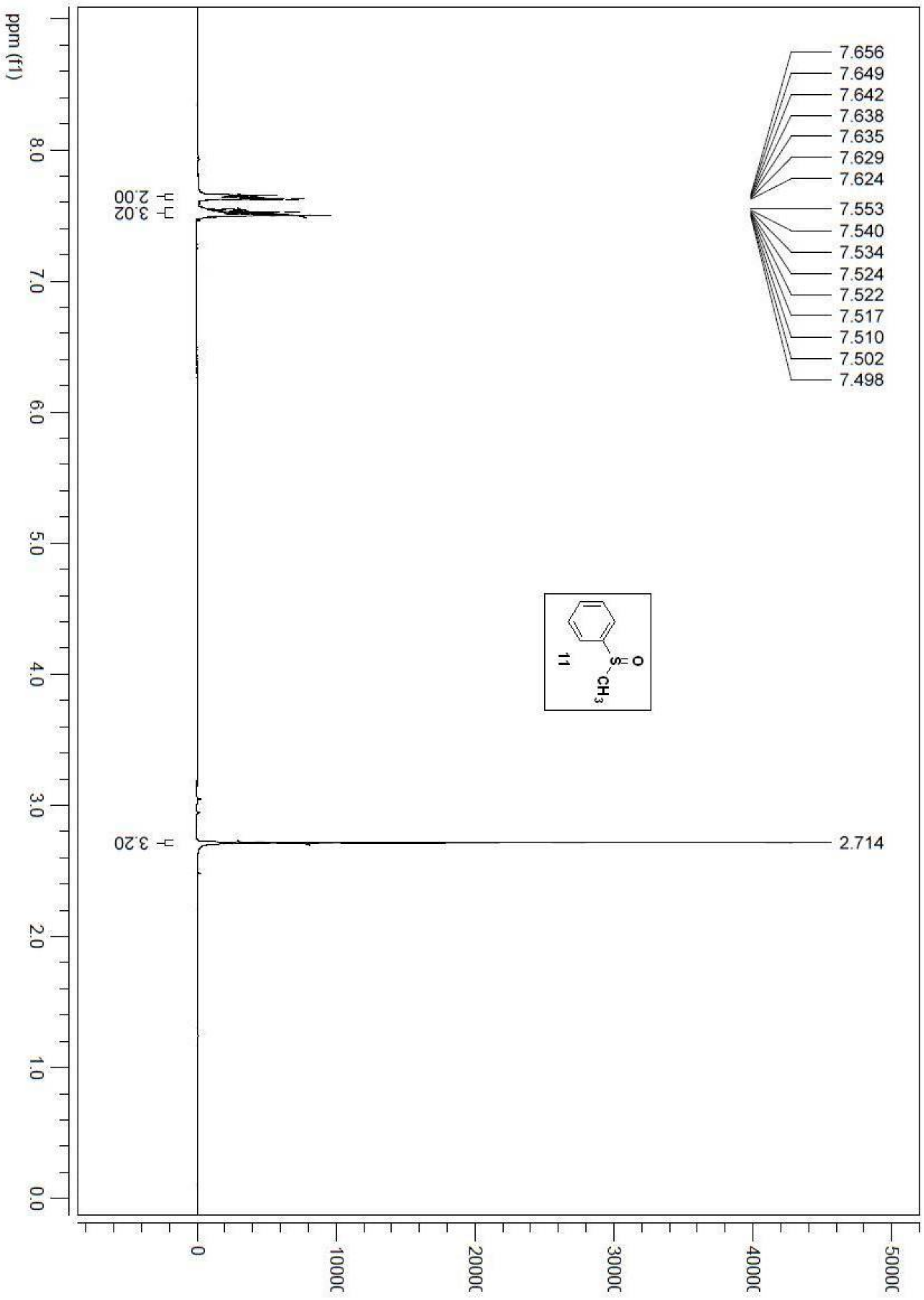


^{13}C NMR spectra of **9**



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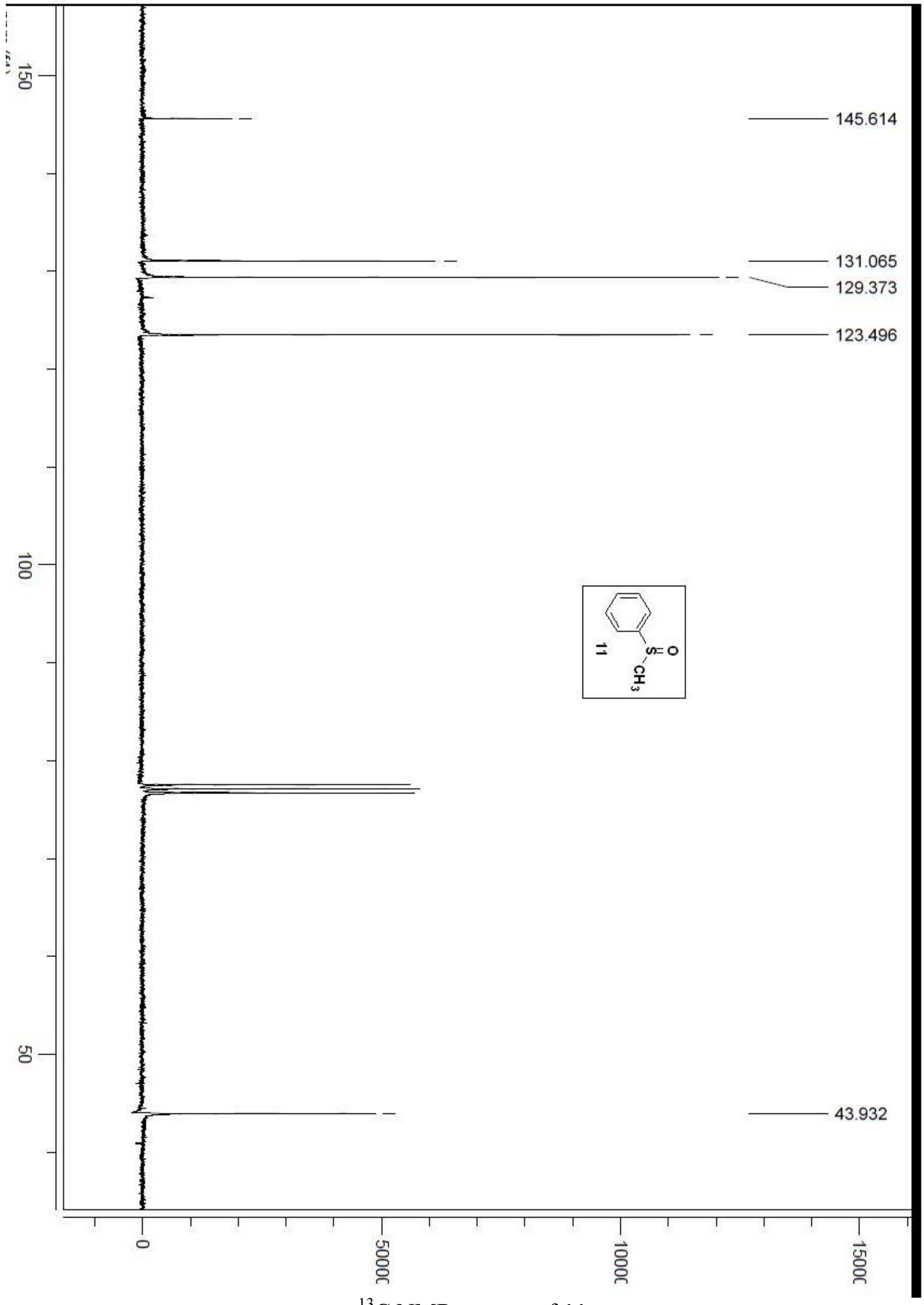
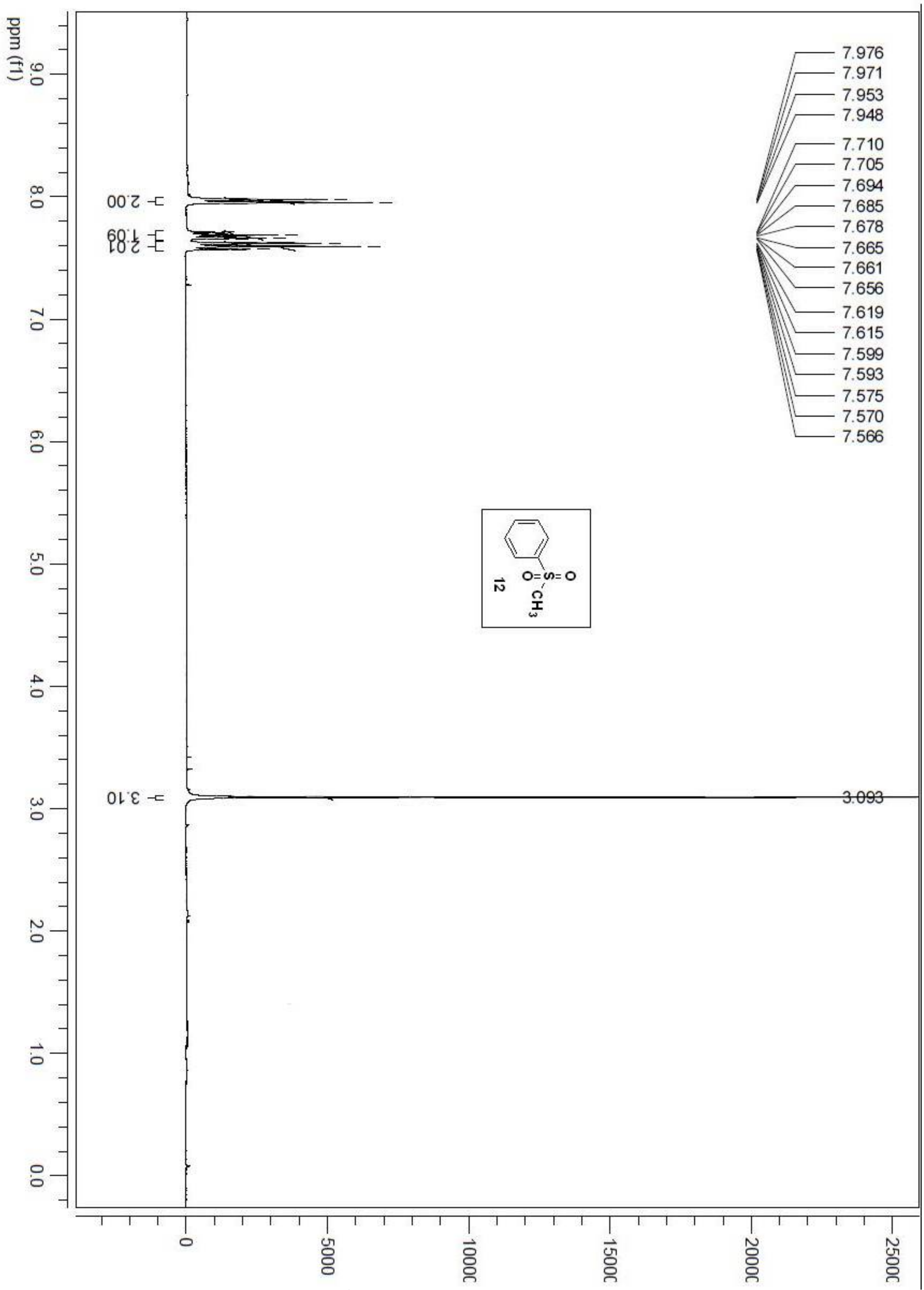
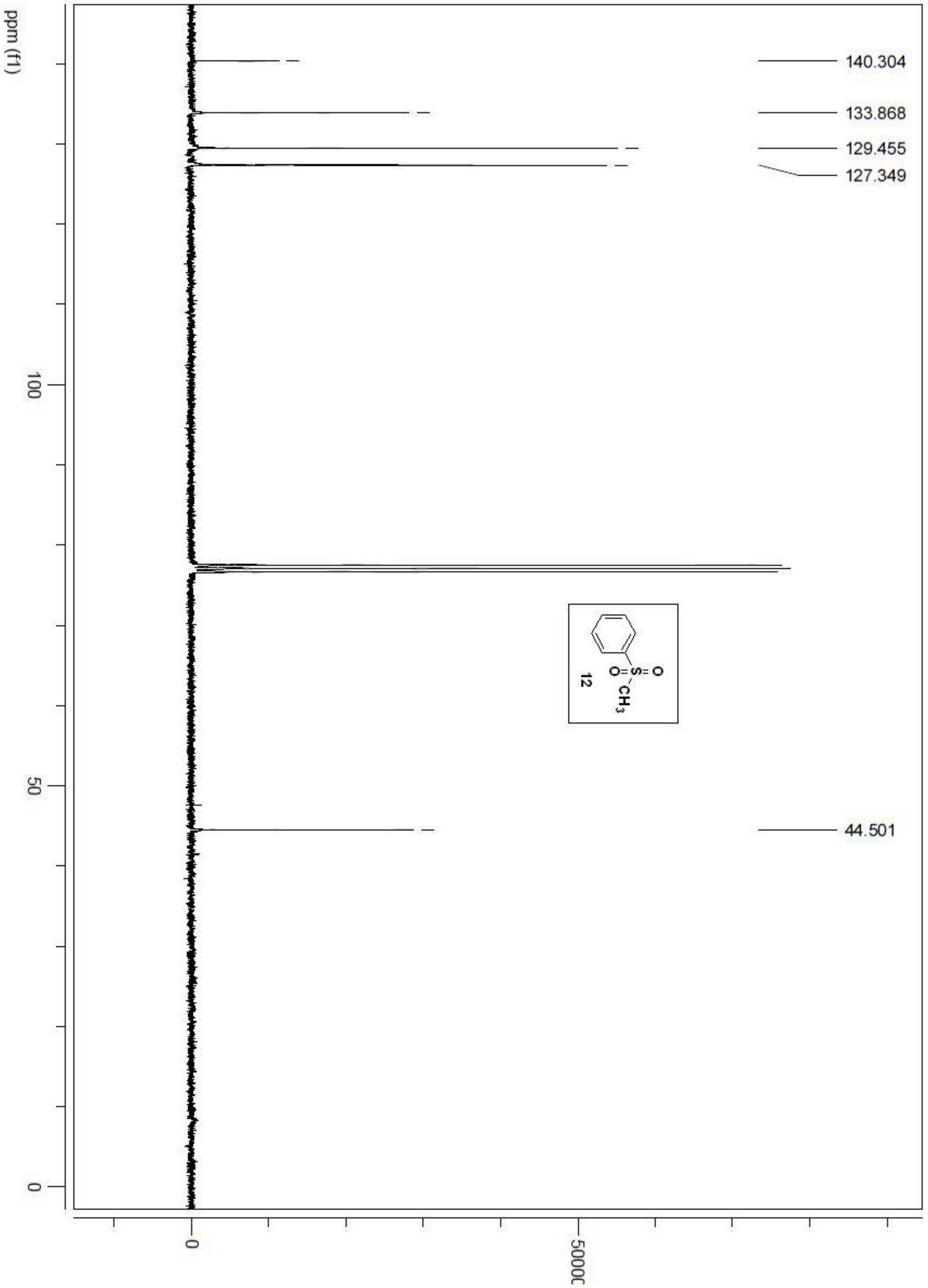


^{13}C NMR spectra of **11**



^{1}H NMR spectra of **12**



^{13}C NMR spectra of **12**