IAPP and the shared molecular origins of leakage and toxicity

(supporting information)

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BIOPHYSICAL ASSAYS

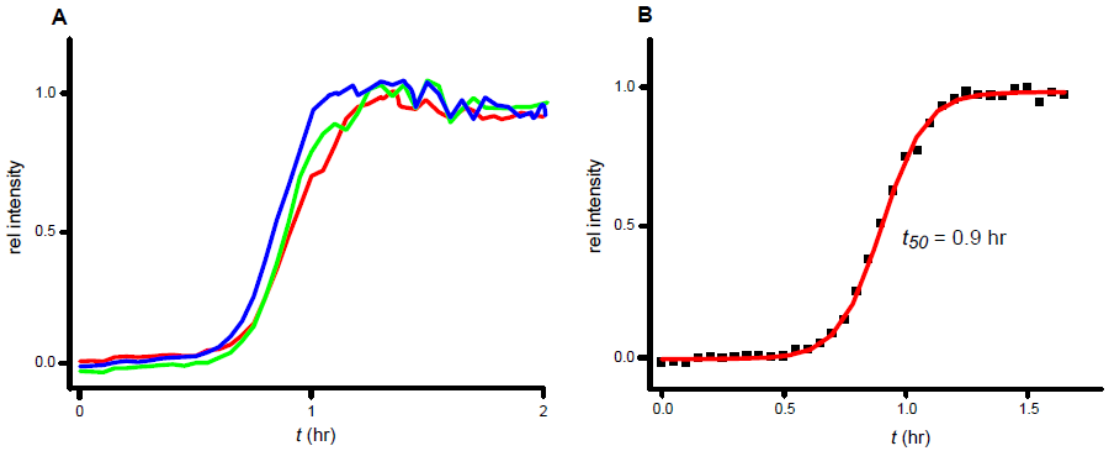


Figure S1, Related to Figure 2. Reproducibility and fit quality for amyloid conversion kinetics (A) Normalized data for time dependent assay of the kinetics of lipid catalyzed (DOPG:DOPC, 1:1, 630 μM, 100 nm) fibrillation of 10 μM IAPP. Each trace represents individual experiment for the kinetics of lipid catalyzed IAPP fibrillation. (B) A representative sigmoidal fit to calculate the reaction midpoint, t_{50}.

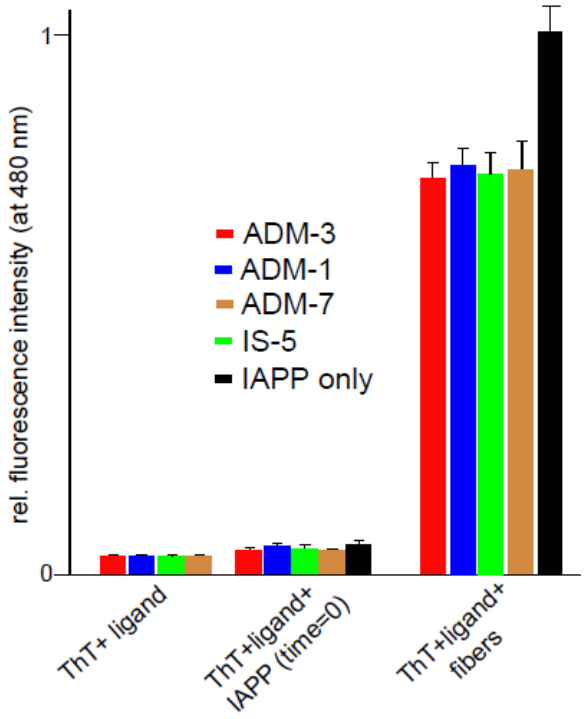


Figure S2, Related to Figure 1. Effect of small molecules on ThT fluorescence intensity. Fluorescence of 5 μM ThT in the presence of 100 μM (i.e. more than is used in data shown in main text) of each of the indicated compounds. Shown are ThT and compound in our standard reaction buffer (left) and in the presence of 10 μM IAPP and 630 μM lipid before (middle) and after (right) conversion of IAPP to amyloid. Experiments were conducted at least in triplicate with errors reported as standard deviations (SD).

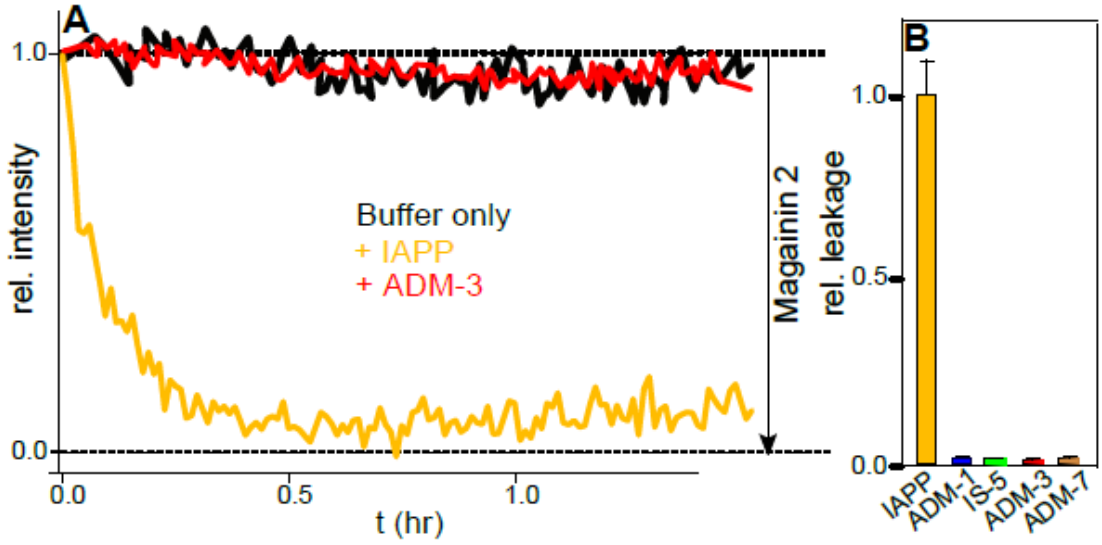


Figure S3, Related to Figure 5. Effect of small molecules on liposome leakage. (A) 100 μM of our compounds (ADM- 3 is shown) were assayed in our leakage assay (see Materials and Methods). For reference, leakage induced by 5 μM IAPP is also shown. (B) Statistics from single exponential fits to data represented in (A). Data in (A, B) is renormalized using magainin 2 to establish the full dynamic range of the assay. All kinetic experiments were conducted at least in triplicate with errors reported as standard deviations (SD).

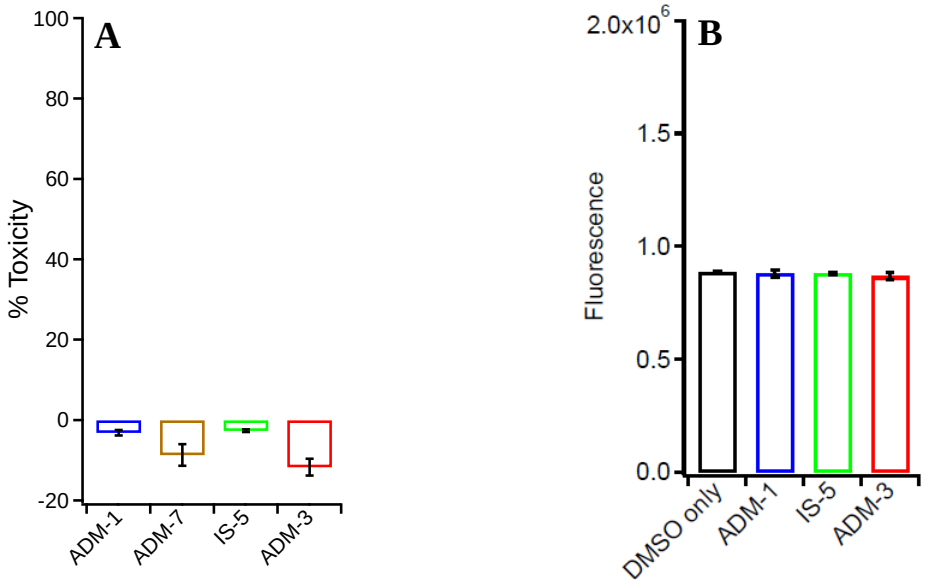


Figure S4, Related to Figure 4. Intrinsic toxicity of small molecules and interference with the viability assay. (A) INS-1 cells were incubated with 13 μM of each of the indicated small molecules in a manner matched to that used for data shown in the main text. Viability was then assayed using CTB assay and compared to carrier only controls. No toxicity was evident. (B) In our assays, CTB reagent is added 48 h after the addition of the small molecule. Nevertheless, we assayed the potential effect of small molecule on the CTB reagent as follows. Small molecules (13 μM) were incubated for 4 h in media with CTB reagent in 24 well plates (i.e. using vessels matched to the cell based experiments). Fluorescence response remained unchanged compared with DMSO carrier. Error bars represent the standard error of the mean of four replicates.

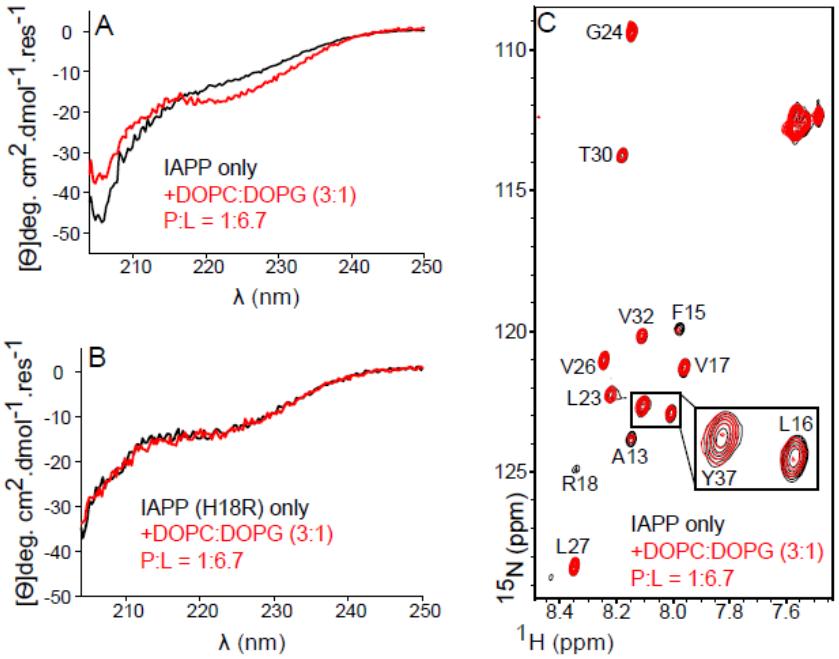
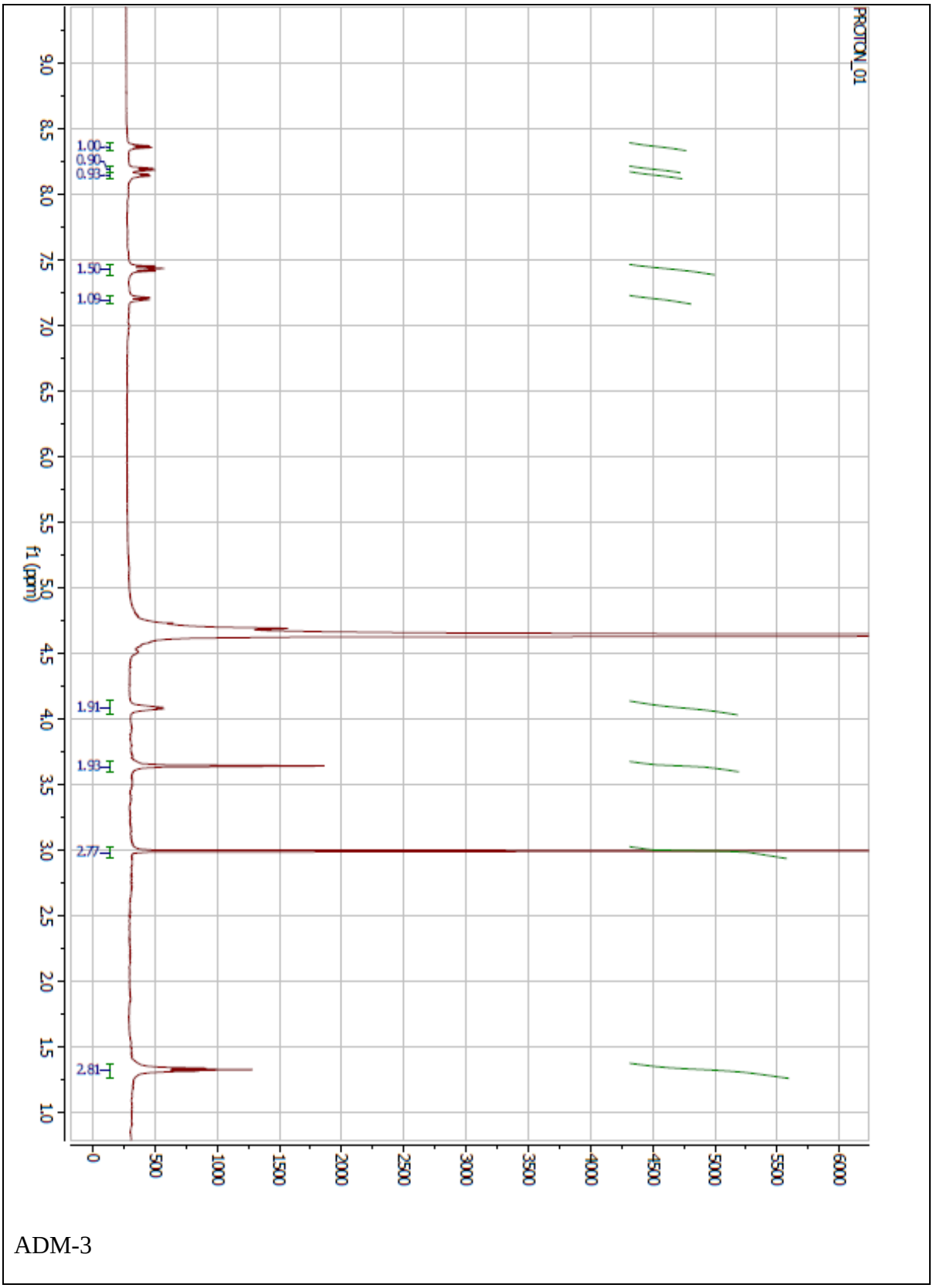


Figure S5, Related to Figure 6. Characterization of IAPP membrane binding at low anionicity. CD spectra of 60 μM human IAPP (A) or human IAPP H18R (B) in the absence (black) and presence (red) of 400 μM lipid membrane at the indicated stoichiometry of DOPC:DOPG. (C) NMR (^{15}N HSQC) of 50 μM rat IAPP in the absence (black) or presence (red) of lipid bilayer at 1:6.7 (IAPP:lipid), and DOPC:DOPG at 3:1. Many resonances are lost compared to Fig. 6D due to chemical exchange with solvent protons. (inset) A three-fold magnification of residues from the α-helical subdomain (L16), and the C-terminus (Y37). Buffer conditions (A-C), 20 mM Tris·HCl, 100 mM NaCl, pH 7.4.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8.0
7.5
7.0
6.5
6.0
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5.0
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4.0
3.5
3.0
2.5
2.0
1.5
1.0
0
500
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2000
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3000
3500
4000
4500
5000
5500
6000
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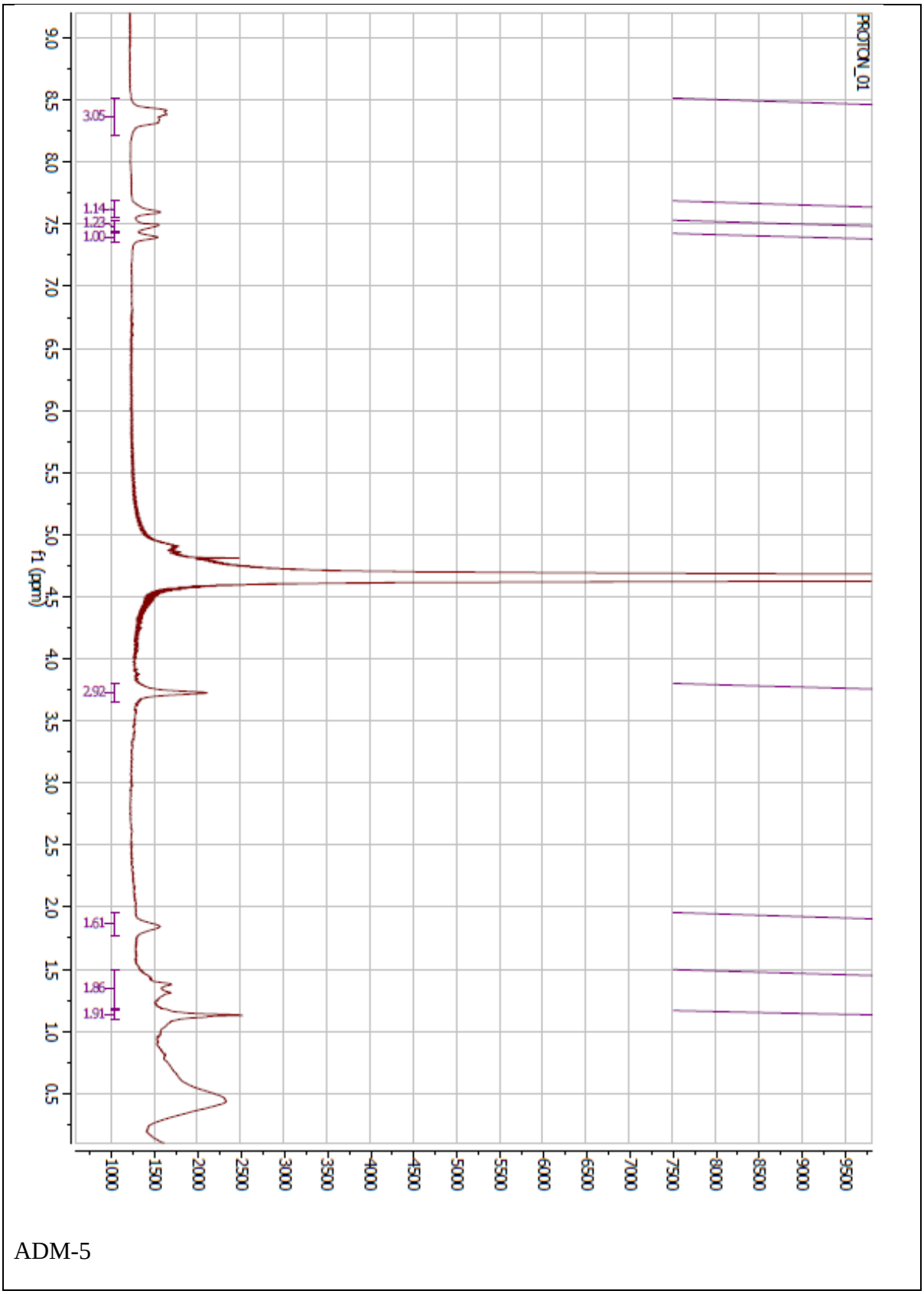
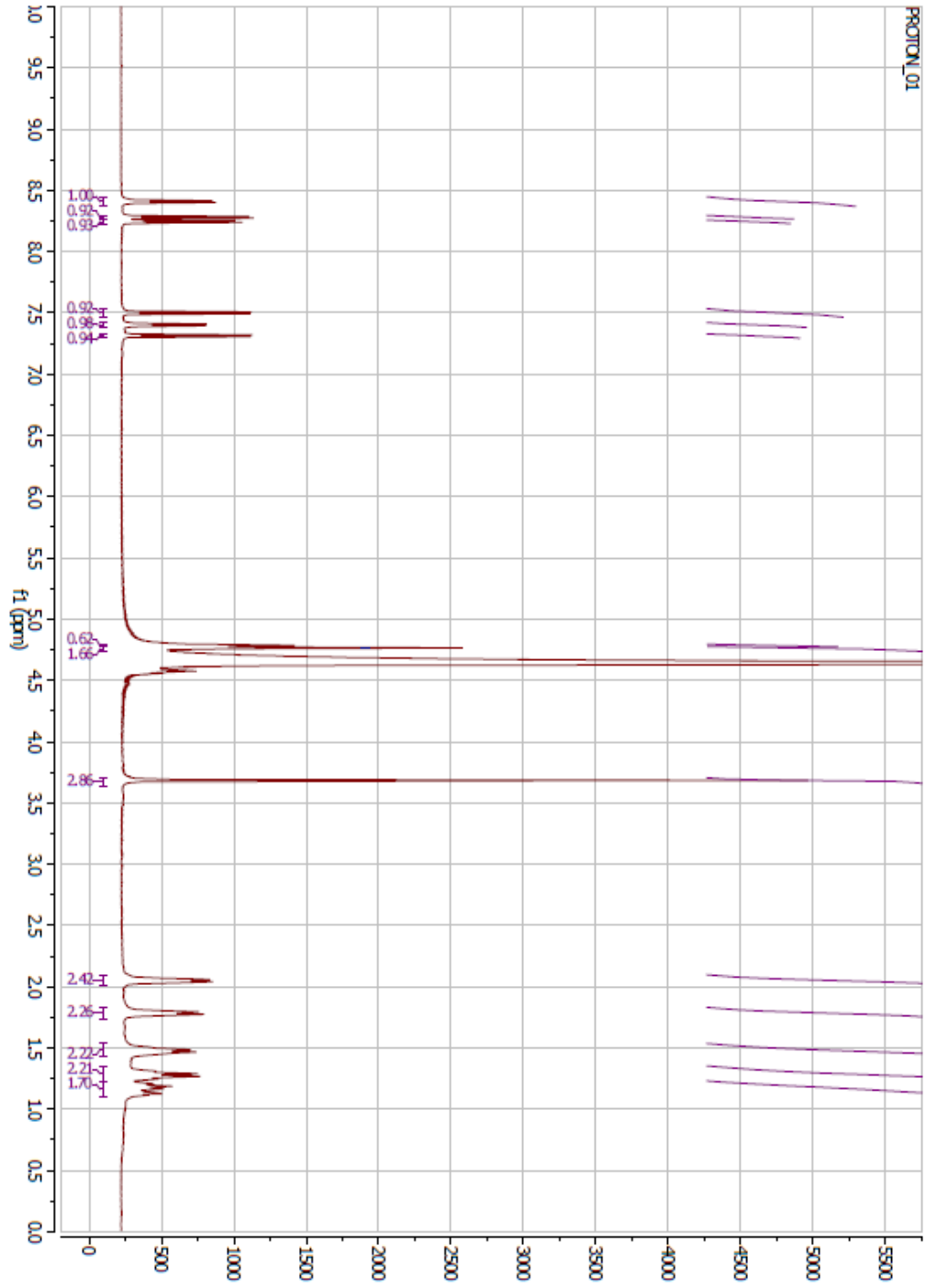
0.90
0.93
1.50
1.09
1.91
1.93
2.77
2.81

ADM-3



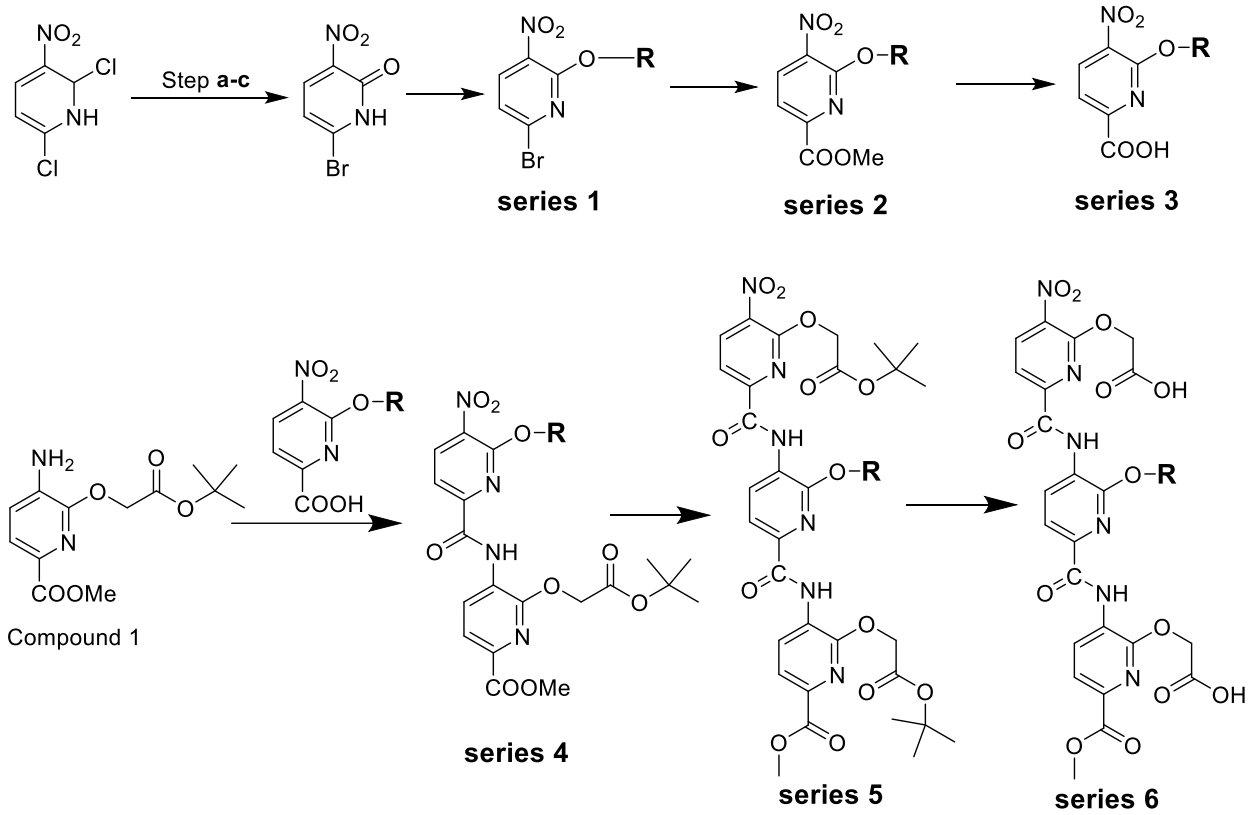
ADM-5



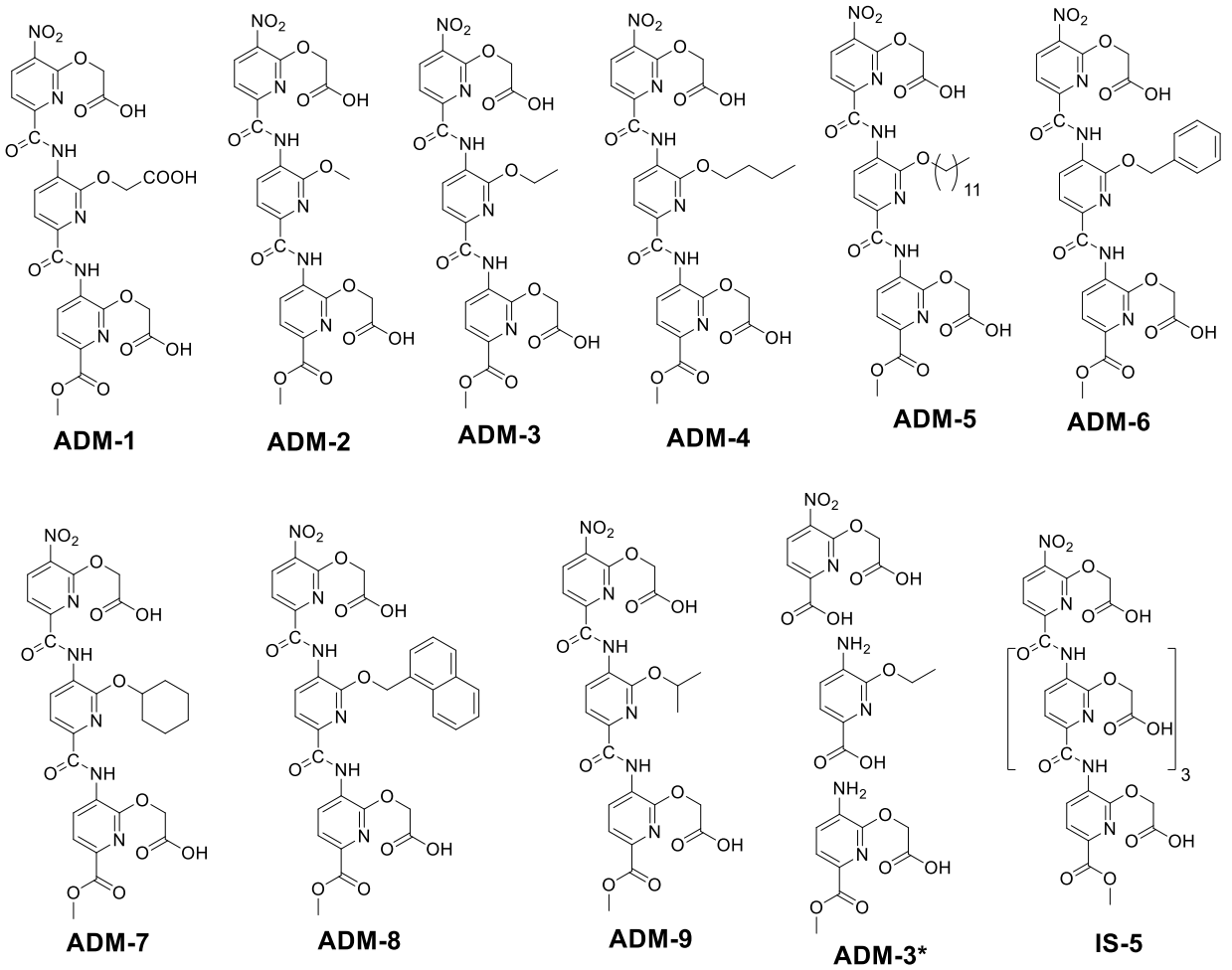
ADM-7

Figure S5D, Related to Figure 7. 1D 1H NMR spectra of ADM-3, ADM-5, and ADM-7 under solution kinetic assay conditions. Conditions were 100 μM small molecule, 100 mM Tris·HCl, 100 mM NaCl, pH 7.4.

SYNTHESIS AND CHARACTERIZATION



Scheme S1. Synthetic route for the synthesis of intermediates and tripyridylamide analogs.



Scheme S2. Chemical Structures of oligopyridylamides used in study.

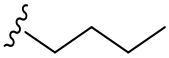
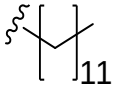
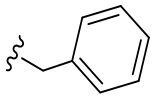
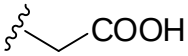
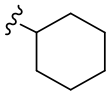
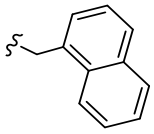
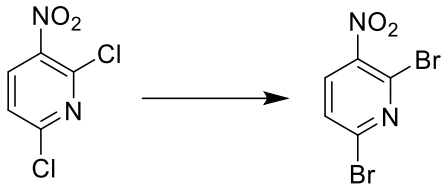
-R	series 1	series 2	series 3	series 4	series 5	series 6
CH_3	58	57	59	75	59	77
	87	62	73	80	62	78
	83	62	73	69	60	75
	85	56	73	72	68	79
	87	65	72	76	71	80
	77	66	68	78	62	69
	**64***	68	60	71	63	81
	68	70	72	58	54	69
	74	68	54	65	62	66

Table S1. % yield of the compounds (series 1, 2, 3, 4, 5, and 6) synthesized in scheme 1. * Reaction was not carried out using microwave.

Synthesis and Characterization of precursor compounds in Scheme 1 (step a-c):

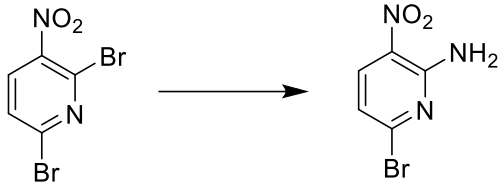
Step a: Synthesis and characterization of 2,6-dibromo-3-nitropyridine:



A solution of 2,6-dichloro-3-nitropyridine (19.1 g, 100 mmol) in 33% HBr in AcOH (200 mL) was refluxed for 24 h. Hot water (200 mL) was added slowly to the reaction and then allowed to cool down to r.t. Cold water (1 L) was added to this reaction mixture and stirred for 2 h. The light brown precipitate was filtered, washed with cold water (3×300 mL), and dried under vacuum overnight (24.2 g, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 7.96 (d, *J* = 8.3 Hz, 1H), 7.71 – 7.60 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.3, 143.9, 135.5, 133.5, 127.9. MS-ESI (*m/z*): calculated for $C_5H_2N_2O_2Br_2$ $(M)^+$: 278.9, found 279.1.

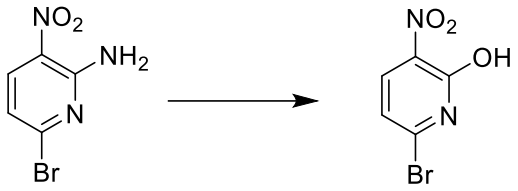
Step b: Synthesis and characterization of 6-bromo-3-nitropyridin-2-amine:



To a solution of 2M NH3 in ethanol (300 mL), 2,6-dibromo-3-nitropyridine (23.3 g, 82.8 mmol) was added in four portions at 0 °C in 30 min. The reaction was stirred for 24 h at r.t. under inert atmosphere. The reaction mixture was poured in cold water (1 L) to allow complete precipitation. The reaction mixture was then stirred at 0 °C for 2 h after which the precipitate was filtered and washed with cold water (3×300 mL). The yellow precipitate was then dried overnight under vacuum (15.1 g, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.19 (d, *J* = 8.6 Hz, 1H), 6.94 – 6.84 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.9, 147.8, 137.6, 136.9, 117.6. MS-ESI (*m/z*): calculated for $C_5H_4N_3O_2Br$ (M): 217.0, found 217.1.

Step c: Synthesis and characterization of 6-bromo-3-nitropyridin-2-ol:



To a solution of 6-bromo-3-nitropyridin-2-amine (6.1 g, 27.8 mmol) in conc. H_2SO_4 (38 mL), a solution of $NaNO_2$ (4.8 g, 69.5 mmol) in 18 mL of water was added drop-wise at 0 °C over 30 min. The solution was stirred for 2 h at 0 °C after which water (100 mL) was added and the reaction mixture was allowed to warm at r.t. The mixture was stirred for 1 h and then cooled down to 0 °C. The resulting yellow precipitate was filtered, washed with water (3×100 mL), and dried over vacuum overnight (4.8 g, 77%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.47 – 8.39 (d, *J* = 8.3 Hz, 1H), 7.13 – 7.01 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 156.7, 141.1, 139.1, 133.3, 117.5. MS-ESI (*m/z*): calculated for $C_5H_3N_2O_3Br$ (M): 217.9, found 218.1.

Series 1: General method for synthesis of O-alkyl derivatives of 2-bromo-6-hydroxy-5-nitropyridine.

To a mixture of 2-bromo-6-hydroxy-5-nitropyridine (1 mmol) in hexane (dry, 3 mL), alkyl iodide (2 mmol) and silver carbonate (1.2 mmol) were added. The mixture was irradiated at 120 °C for 12 min. with constant stirring in a 5 mL capped glass vial in Microwave (100-120 W). The reaction mixture was cooled, filtered, and dried over rotovap. Column chromatography (0 to 10% ethyl acetate in hexane, v/v) afforded the desired product as yellow oil or solid depends on individual compound (see Table S1 for % yield).

***Synthesis of (6-Bromo-3-nitro-pyridin-2-yloxy)-acetic acid tert-butyl ester.**

To a solution of 2-bromo-6-hydroxy-5-nitropyridine (10 mmol) in acetone (75 mL), sodium carbonate (15 mmol), sodium iodide (2.5 mmol), and *tert*-butyl-bromoacetate (12 mmol) were added and the reaction was stirred overnight at 70 °C under inert atmosphere. The volatiles were removed on rotovap. The mixture was dissolved in ethylacetate (150 mL) and successfully washed (2 × 30 mL) with water, 0.5 M HCl, and brine. The organic layer dried over sodium sulphate and column chromatography (0 to 30% ethyl acetate in hexane, v/v) afforded the desired product as a yellow solid (88%).

Series 2: General method for synthesis of 2-methyl ester-6-(O-alkyl)-5-nitropyridine.

To a solution of 2-bromo-6-(O-alkyl)-5-nitropyridine (1 mmol) in DMF (10 mL, anhydrous), PPh_3 (20.3 mg, 0.08 mmol), and $Pd(OAC)_2$ (3.5 mg, 0.015 mmol) were added and the reaction mixture was stirred for 10 min in inert atmosphere. Anhydrous methanol (10 mL) and triethylamine (0.65, 7.82 mmol) were added to the reaction mixture and again stirred for 10 min under inert atmosphere. The reaction mixture was stirred constantly in a pressure reactor at 80 °C under the atmosphere of

CO (g) (450 psi) for 15 h. The reaction mixture was filtered through celite and volatiles were evaporated on rotovap. Column chromatography (0 to 20% ethyl acetate in hexane, v/v) afforded the desired product as a yellow solid (see Table S1 for % yield).

Series 3: General method for saponification of 2-methyl ester-6-(O-alkyl)-5-nitropyridine.

The O-alkylated pyridone (1 mmol) was dissolved in tetrahydrofuran (18 mL) and cooled at 0 °C on ice followed by the addition of LiOH (0.04 g, 1 mmol) in water (18 mL). The solution was stirred for one h and then dried over rotovap for about 1/3 of the total volume. The reaction solution was diluted with water (10 mL) and acidified with hydrochloric acid (dil.) to pH 3-4 and extracted with ethyl acetate (3×25 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated on rotovap to afford the desired product as a yellow solid. The % yield varied with individual 2-carboxylic acid-6-(O-alkyl)-5-nitropyridine (see Table S1 for % yield).

Series 4: General method for synthesis of arylamide dimers.

To a solution of 2-carboxylic acid-6-(O-alkyl)-5-nitropyridine (0.5 mmol) in dichloromethane (10 mL, anhydrous), triethylamine (1 mmol) and 2-chloro-1-methylpyridinium iodide (0.48 mmol) were added and the reaction stirred for 20 min. at 50 °C. Compound **1** (0.35 mmol) in dichloromethane (10 mL, anhydrous) was added and the resulting reaction mixture was refluxed for 4 h. The reaction mixture was cooled and the volatiles were removed on rotovap. Column chromatography (0 to 20% ethylacetate in hexane, v/v) afforded the desired product as a yellow solid (see Table S1 for % yield).

General method for synthesis of amino arylamide dimers.

To a solution of nitro arylamide dimer (0.1 mmol) in tetrahydrofuran (10 mL), Pd/C (10% by wt.) was added and the reaction started with constant stirring in the atmosphere of H_2 (g) at room temperature. The progress of the reaction was monitored using TLC. The disappearance of the starting material confirms the completion of the reaction. The reaction mixture was filtered and the filterate was dried over rotovap to afford the desired product as a yellow solid, which is used in next step without further characterization.

Series 5: General method for synthesis of Nitro arylamide trimer.

To a solution of compound **2-R** (0.25 mmol) in dichloromethane (5 mL, anhydrous), triethylamine (0.5 mmol) and 2-chloro-1-methylpyridinium iodide (0.24 mmol) were added and the reaction stirred for 20 min. at 50 °C. Amino arylamide dimer (0.17 mmol) in dichloromethane (5 mL, anhydrous) was added and the resulting reaction mixture was refluxed for 4 h. The reaction mixture was cooled and the volatiles were removed on rotovap. Column chromatography (0 to 35% ethylacetate in hexane, v/v) afforded the desired product as a yellow solid (see Table S1 for % yield).

Series 6: General method for deprotection (O-tert butyl ester to O-CH_2-COOH) of Nitro arylamide trimer.

A solution of Nitro arylamide trimer (0.05 mmol) in DCM:TFA:TES (80:15:5) was stirred for 3 h at room temperature. The volatiles were removed on rotovap and the solid was washed with cold diethyl ether (3× 3 mL) which results in a brownish colored compound (see Table S1 for % yield).

Note: The starting material and product for compounds in series 1, 2, 4, and 5 were very difficult to separate using flash column chromatography because of their close R_f values (retention factor). Compounds in series 3 were synthesized via saponification and extraction of series 2 (without using column chromatography). Consequently, these compounds carried impurity in form of the starting material which can be seen in their ^{1}H-NMRs and ^{13}C-NMRs. The % yield for all of these compounds have been revised after accounting for the impurity using ^{1}H-NMRs. The % of the impurities were determined by calculating the area of their ^{1}H-NMR peaks with respect the compounds peaks.

SERIES 1:

O-Ethyl

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08 – 8.02 (d, *J*=8.2, 1H), 7.15 – 7.07 (d, *J*=8.2, 1H), 4.55 – 4.47 (q, *J*=7.1, 2H), 1.42 – 1.37 (t, *J*=7.1, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 165.0, 146.6, 136.6, 135.0, 112.9, 64.2, 53.5. MS-ESI (*m/z*): calculated for $C_7H_7N_2O_3Br$ (M): 246.0, found 246.1.

O-Cyclohexane

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.05 – 7.99 (d, *J*=8.2, 1H), 7.10 – 7.03 (d, *J*=8.2, 1H), 5.28 – 5.20 (tt, *J*=7.9, 3.7, 1H), 1.93 – 1.82 (m, 2H), 1.80 – 1.69 (m, 2H), 1.69 – 1.58 (m, 2H), 1.44 – 1.30 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.7, 155.2, 137.5, 136.4, 117.1, 76.7, 31.1, 25.4, 23.1. MS-ESI (*m/z*): calculated for $C_{11}H_{13}N_2O_3Br$ (M): 300.0, found 300.3.

O-Methyl

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.17 – 8.13 (d, *J*=8.2, 1H), 7.24 – 7.19 (d, *J*=8.2, 1H), 4.17 – 4.11 (s, 3H), 4.08 – 3.98 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 156.0, 143.6, 137.1, 132.8, 120.8, 55.8. MS-ESI (*m/z*): calculated for $C_6H_5N_2O_3Br$ (M): 232.0, found 232.2.

O-*tert* butyl ester

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.26 – 8.00 (d, *J*=8.2, 1H), 7.26 – 6.98 (d, *J*=8.4, 1H), 4.98 – 4.71 (s, 2H), 1.49 – 1.28 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.32, 155.08, 152.64, 137.89, 132.23, 117.64, 82.77, 64.51, 27.99. MS-ESI (*m/z*): calculated for $C_{11}H_{13}N_2O_3Br$ (M): 332.0, found 332.1.

O-Benzyl

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.14 (d, *J* = 8.2 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.41 – 7.35 (m, 2H), 7.35 – 7.32 (m, 1H), 7.19 (d, *J* = 8.2 Hz, 1H), 5.56 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 169.34, 166.51, 155.25, 140.71, 138.47, 128.56, 128.54, 127.92, 127.78, 82.77, 72.25. MS-ESI (*m/z*): calculated for $C_{12}H_9N_2O_3Br$ (M): 308.0, found 308.2.

O-Naphthalene

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.19 – 8.14 (d, *J*=8.2, 1H), 8.02 – 7.98 (d, *J*=1.4, 1H), 7.90 – 7.80 (m, 3H), 7.64 – 7.59 (dd, *J*=8.6, 1.7, 1H), 7.52 – 7.47 (m, 2H), 7.23 – 7.18 (d, *J*=8.2, 1H), 5.79 – 5.71 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.28, 143.44, 137.57, 137.02, 133.08, 132.70, 132.56, 128.33, 128.04, 127.66, 127.28, 126.28, 125.59, 120.81, 116.81, 70.06. MS-ESI (*m/z*): calculated for $C_{16}H_{11}N_2O_3Br$ (M): 358.0, found 358.2.

O-Dodecane

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.20 – 8.05 (d, *J*=8.2, 1H), 7.22 – 7.11 (d, *J*=8.2, 1H), 4.56 – 4.41 (t, *J*=6.6, 2H), 1.87 – 1.78 (p, *J*=6.9, 2H), 1.50 – 1.41 (m, 2H), 1.36 – 1.19 (m, 19H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 165.2, 153.8, 138.6, 126.5, 112.8, 71.0, 40.6, 32.0, 29.9, 29.7, 29.7, 29.7, 29.6, 29.4, 26.3, 22.7, 14.1. MS-ESI (*m/z*): calculated for $C_{17}H_{27}N_2O_3Br$ (M): 386.1, found 386.3.

O-Propyl

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.15 – 8.01 (d, *J*=8.2, 1H), 7.19 – 7.09 (d, *J*=8.1, 1H), 5.58 – 5.42 (p, *J*=6.2, 1H), 1.46 – 1.39 (d, *J*=6.2, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 164.6, 138.6, 130.9, 128.8, 102.9, 71.1, 22.0. MS-ESI (*m/z*): calculated for $C_8H_9N_2O_3Br$ (M): 260.0, found 260.1.

O-Butyl

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.16 – 8.07 (d, *J*=8.2, 1H), 7.22 – 7.12 (d, *J*=8.2, 1H), 4.53 – 4.46 (t, *J*=6.5, 2H), 1.86 – 1.76 (p, *J*=5.2, 2H), 1.57 – 1.46 (sex, *J*=4.8, 2H), 1.01 – 0.93 (t, *J*=7.4, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 165.3, 157.3, 138.7, 138.6, 102.6, 67.6, 30.8, 19.2, 13.8.

MS-ESI (*m/z*): calculated for $C_7H_7N_2O_3Br$ (M): 274.0, found 274.1.

SERIES 2:

O-Butyl

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.25 – 8.19 (d, *J*=8.0, 1H), 7.74 – 7.67 (d, *J*=8.1, 1H), 4.54 – 4.44 (t, *J*=6.5, 2H), 3.94 – 3.90 (s, 3H), 1.81 – 1.68 (m, 2H), 1.50 – 1.38 (m, 2H), 0.96 – 0.86 (t, *J*=7.4, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.8, 155.9, 148.6, 136.1, 135.5, 117.6, 68.1, 53.1, 30.6, 19.1, 13.7. MS-ESI (*m/z*): calculated for $C_{11}H_{14}N_2O_5$ (M): 254.1, found 254.1.

O-Ethyl

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 – 8.11 (d, *J*=8.0, 1H), 7.80 – 7.61 (d, *J*=8.0, 1H), 4.70 – 4.44 (q, *J*=7.1, 2H), 4.00 – 3.84 (s, 3H), 1.45 – 1.34 (t, *J*=7.1, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 163.7, 155.5, 148.5, 136.1, 135.4, 117.6, 64.2, 53.0, 14.1. MS-ESI (*m/z*): calculated for $C_9H_{10}N_2O_5$ (M): 226.1, found 226.1.

O-Methyl

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.41 – 8.25 (d, *J*=8.1, 1H), 7.88 – 7.73 (d, *J*=8.0, 1H), 4.23 – 4.16 (s, 3H), 4.02 – 3.98 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 163.7, 156.0, 148.6, 136.1, 135.7, 118.0, 55.1, 53.1. MS-ESI (*m/z*): calculated for $C_8H_8N_2O_5$ (M): 212.0, found 211.9.

O-Dodecane

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.25 – 8.18 (d, *J*=8.0, 1H), 7.73 – 7.67 (d, *J*=8.0, 1H), 4.54 – 4.44 (t, *J*=6.6, 2H), 3.96 – 3.88 (s, 3H), 1.83 – 1.68 (m, 2H), 1.45 – 1.33 (m, 2H), 1.33 – 1.10 (s, 19H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 163.8, 155.9, 148.5, 136.1, 135.4, 117.6, 76.8, 68.4, 53.1, 31.9, 29.6, 29.6, 29.5, 29.5, 29.3, 29.3, 29.2, 28.5, 25.8, 22.6, 14.0. MS-ESI (*m/z*): calculated for $C_{19}H_{30}N_2O_5$ (M): 366.2, found 366.2.

O-Benzyl

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.20 – 8.10 (d, *J*=8.2, 1H), 7.24 – 7.17 (d, *J*=8.2, 1H), 6.14 – 6.00 (ddt, *J*=17.2, 10.7, 5.4, 1H), 5.57 – 5.47 (dd, *J*=17.3, 1.5, 1H), 5.39 – 5.30 (dt, *J*=10.5, 1.4, 1H), 5.07 – 4.99 (dt, *J*=5.4, 1.5, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 163.7, 155.4, 148.5, 136.1, 135.8, 135.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 118.1, 77.3, 69.4, 53.2. MS-ESI (*m/z*): calculated for $C_{14}H_{12}N_2O_5$ (M): 288.1, found 288.1.

O-*tert* butyl ester

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.38 – 8.26 (d, *J*=8.1, 1H), 7.81 – 7.73 (d, *J*=8.1, 1H), 4.97 – 4.91 (s, 2H), 3.94 – 3.86 (s, 3H), 1.41 – 1.37 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.5, 163.3, 154.6, 148.2, 136.1, 135.7, 118.8, 82.4, 64.0, 53.0, 27.9, 27.9. MS-ESI (*m/z*): calculated for $C_{13}H_{16}N_2O_7$ (M): 312.1, found 312.2.

O-Naphthalene

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.36 – 8.30 (d, *J*=8.0, 1H), 8.09 – 8.02 (s, 1H), 7.90 – 7.76 (m, 4H), 7.69 – 7.62 (dd, *J*=8.5, 1.8, 1H), 7.52 – 7.45 (m, 2H), 5.87 – 5.77 (s, 2H), 4.09 – 3.99 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 165.7, 164.9, 146.3, 137.0, 135.3, 133.2, 133.2, 132.7, 128.5, 128.0, 127.9, 127.7, 126.5, 126.4, 126.3, 126.0, 70.1, 53.5. MS-ESI (*m/z*): calculated for $C_{18}H_{14}N_2O_5$ (M): 338.1, found 338.3.

O-Cyclohexane

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.34 – 8.19 (d, *J*=8.0, 1H), 7.80 – 7.69 (d, *J*=8.0, 1H), 5.51 – 5.36 (tt, *J*=7.7, 3.6, 1H), 4.05 – 3.92 (s, 3H), 2.03 – 1.90 (m, 2H), 1.86 – 1.76 (m, 2H), 1.76 – 1.64 (m, 2H), 1.59 – 1.36 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 163.9, 155.4, 148.6, 136.5, 135.4, 117.3, 71.8, 53.2, 31.2, 25.6, 23.4. MS-ESI (*m/z*): calculated for $C_{13}H_{16}N_2O_5$ (M): 280.1, found 280.1.

O-Propyl

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.23 – 8.13 (d, *J*=8.0, 1H), 7.71 – 7.63 (d, *J*=8.0, 1H), 5.62 – 5.47 (p, *J*=6.2, 1H), 3.96 – 3.86 (s, 3H), 1.39 – 1.32 (d, *J*=6.2, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 164.0, 155.4, 148.6, 136.5, 135.4, 117.3, 71.8, 53.1, 21.8. MS-ESI (*m/z*): calculated for $C_{10}H_{12}N_2O_5$ (M): 240.1, found 240.1.

SERIES 3:

O-Dodecane

^{1}H NMR (400 MHz, DMSO) δ = 8.61 – 8.50 (d, *J*=7.9, 1H), 7.86 – 7.74 (d, *J*=8.0, 1H), 4.61 – 4.42 (t, *J*=6.4, 2H), 1.84 – 1.66 (p, *J*=6.7, 2H), 1.47 – 1.09 (m, 21H). ^{13}C NMR (126 MHz, $cdcl_3$) δ 162.5, 155.6, 146.6, 137.2, 136.7, 116.8, 69.0, 31.9, 29.6, 29.6, 29.5, 29.3, 29.2, 28.5, 25.9, 22.7, 14.1. MS-ESI (*m/z*): calculated for $C_{18}H_{28}N_2O_5$ (M): 352.2, found 352.2.

O-Cyclohexane

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.40 – 8.31 (d, *J*=8.0, 1H), 7.92 – 7.85 (d, *J*=8.0, 1H), 5.42 – 5.32 (dq, *J*=7.9, 3.9, 1H), 2.02 – 1.91 (m, 2H), 1.89 – 1.68 (m, 4H), 1.61 – 1.38 (m, 4H). ^{13}C NMR (126

MHz, cdcl$_3$) δ 162.2, 155.0, 146.3, 137.7, 136.8, 116.4, 62.8, 31.0, 25.3, 23.0. MS-ESI (*m/z*): calculated for $C_{12}H_{14}N_2O_5$ (M): 266.1, found 266.2.

O-Naphthalene

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.47 – 8.37 (d, *J*=7.9, 1H), 7.91 – 7.78 (m, 5H), 7.53 – 7.40 (m, 5H), 5.81 – 5.62 (m, 2H). ^{13}C NMR (151 MHz, cdcl$_3$) δ 165.7, 164.9, 146.3, 136.9, 135.3, 133.2, 133.1, 132.7, 128.5, 128.0, 127.9, 127.7, 126.5, 126.4, 126.0, 113.1, 70.1. MS-ESI (*m/z*): calculated for $C_{17}H_{12}N_2O_5$ (M): 324.1, found 324.1.

O-*tert* butyl ester

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.54 – 8.42 (d, *J*=7.9, 1H), 8.06 – 7.92 (d, *J*=8.0, 1H), 5.02 – 4.91 (s, 2H), 1.48 – 1.42 (s, 9H). ^{13}C NMR (151 MHz, cdcl$_3$) δ 166.4, 162.7, 154.6, 146.4, 137.3, 125.5, 118.5, 83.5, 64.9, 27.9. MS-ESI (*m/z*): calculated for $C_{12}H_{14}N_2O_7$ (M): 298.1, found 298.1.

O-Methyl

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.46 – 8.37 (d, *J*=8.0, 1H), 8.00 – 7.94 (d, *J*=7.9, 1H), 4.25 – 4.18 (s, 3H). ^{13}C NMR (151 MHz, cdcl$_3$) δ 162.6, 155.8, 146.6, 137.7, 136.9, 117.4, 55.5. MS-ESI (*m/z*): calculated for $C_7H_6N_2O_5$ (M): 199.0, found 199.0.

O-Butyl

^{1}H NMR (500 MHz, $CDCl_3$) δ = 10.06 – 9.47 (s, 1H), 8.45 – 8.30 (d, *J*=8.0, 1H), 7.98 – 7.84 (d, *J*=8.0, 1H), 4.60 – 4.51 (t, *J*=6.4, 2H), 1.90 – 1.81 (m, 2H), 1.59 – 1.48 (m, 2H), 1.04 – 0.96 (t, *J*=7.4, 3H). ^{13}C NMR (151 MHz, cdcl$_3$) δ 163.8, 155.7, 146.7, 137.1, 136.5, 117.2, 68.6, 30.5, 19.1, 13.7. MS-ESI (*m/z*): calculated for $C_{10}H_{12}N_2O_5$ (M): 240.1, found 240.1.

O-Ethyl

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.51 – 8.21 (d, *J*=8.0, 1H), 8.03 – 7.81 (d, *J*=8.0, 1H), 4.75 – 4.52 (q, *J*=7.1, 2H), 1.58 – 1.44 (t, *J*=7.0, 3H). ^{13}C NMR (151 MHz, $cdcl_3$) δ 164.3, 155.5, 146.9, 137.0, 136.4, 117.4, 64.7, 14.1. MS-ESI (*m/z*): calculated for $C_8H_8N_2O_5$ (M): 212.0, found 212.1.

O-Benzyl

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.40 – 8.26 (d, *J*=7.9, 1H), 7.91 – 7.82 (d, *J*=7.9, 1H), 7.44 – 7.38 (m, 2H), 7.36 – 7.30 (m, 3H), 5.57 – 5.50 (s, 2H). ^{13}C NMR (151 MHz, $cdcl_3$) δ 164.0, 155.2, 147.0, 137.0, 136.6, 135.1, 128.8, 128.5, 127.7, 117.9, 70.0. MS-ESI (*m/z*): calculated for $C_{13}H_{10}N_2O_5$ (M^+): 275.1, found 275.1.

O-propyl

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.51 – 8.21 (d, *J*=7.7, 1H), 8.01 – 7.74 (d, *J*=7.9, 1H), 5.64 – 5.35 (m, 1H), 1.62 – 1.37 (d, *J*=5.6, 6H). ^{13}C NMR (151 MHz, $cdcl_3$) δ 162.9, 155.1, 146.4, 137.6, 136.6, 116.7, 72.6, 21.7. MS-ESI (*m/z*): calculated for $C_9H_{10}N_2O_5$ (M^+): 227.1, found 227.1.

SERIES 4:

O-Dodecane

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.77 – 0.99 (t, *J*=6.7, 6H), 1.44 – 1.52 (s, 9H), 1.52 – 1.58 (s, 3H), 1.88 – 1.96 (m, 1H), 3.86 – 3.91 (m, 2H), 3.86 – 4.16 (s, 3H), 4.92 – 5.07 (s, 2H), 7.48 – 7.59 (m, 1H), 7.80 – 7.93 (d, *J*=8.0, 1H), 7.94 – 7.99 (d, *J*=8.0, 1H), 8.01 – 8.08 (m, 1H), 8.26 – 8.50 (d, *J*=8.0, 1H), 8.65 – 9.09 (d, *J*=8.2, 1H), 10.24 – 10.53 (s, 1H). MS-ESI (*m/z*): calculated for $C_{31}H_{44}N_4O_9$ (M): 616.7, found 616.9.

O-Benzyl

^{1}H NMR (400 MHz, $CDCl_3$) δ =1.38-1.45 (s, 9H), 3.53-4.21 (s, 3H), 4.75-5.43 (s, 2H), 5.66-5.98 (s, 2H), 7.30-7.45 (m, 3 H), 7.53-7.65 (m, 2H), 7.85-7.94 (d, *J* = 8.2 Hz, 1H), 7.96-8.08 (d, *J* = 8.1 Hz, 1H), 8.32-8.56 (d, *J* = 8.0 Hz, 1H), 8.81-9.15 (d, *J* = 8.1 Hz, 1H), 10.30-10.61 (s, 1H). MS-ESI (*m/z*): calculated for $C_{26}H_{26}N_4O_9$ (M): 538.2, found 538.2.

O-Naphthalene

^{1}H NMR (400 MHz, $CDCl_3$) δ =1.34-1.39 (s, 9H), 3.82-4.05 (s, 3H), 4.92-5.14 (s, 2H), 5.82-6.16 (s, 2H), 7.44-7.52 (m, 2H), 7.65-7.72 (dd, *J*=8.3, 1.8, 1H), 7.80-7.91 (m, 4H), 7.98-8.04 (d, *J*=8.0, 1H), 8.05-8.08 (s, 1H), 8.35-8.53 (d, *J*=8.1, 1H), 8.78-9.21 (d, *J*=8.1, 1H), 10.22-10.69 (s, 1H). MS-ESI (*m/z*): calculated for $C_{30}H_{28}N_4O_9$ (M): 588.3, found 588.8.

O-Methyl

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.13 – 1.80 (s, 9H), 3.76 – 4.12 (s, 3H), 4.21 – 4.55 (s, 3H), 4.77 – 5.18 (s, 2H), 7.83 – 7.91 (d, *J*=8.1, 1H), 7.96 – 8.05 (d, *J*=7.9, 1H), 8.39 – 8.50 (d, *J*=8.0, 1H), 8.84 – 9.02 (d, *J*=8.1, 1H), 10.43 – 10.54 (s, 1H). MS-ESI (*m/z*): calculated for $C_{20}H_{22}N_4O_9$ (M^{+1}): 463.1, found 462.9.

O-Butyl

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.49 – 1.53 (s, 9H), 1.55 – 1.66 (m, 2H), 1.67 – 1.78 (m, 2H), 1.83 – 1.91 (m, 2H), 3.64 – 3.98 (s, 3H), 4.56 – 4.86 (t, *J*=6.1, 2H), 4.88 – 5.08 (s, 2H), 7.76 – 7.93 (d, *J*=8.1, 1H), 7.90 – 8.08 (d, *J*=8.0, 1H), 8.27 – 8.52 (d, *J*=8.0, 1H), 8.82 – 9.12 (d, *J*=8.1, 1H), 10.07 – 10.66 (s, 1H). MS-ESI (*m/z*): calculated for $C_{23}H_{28}N_4O_9$ (M^{+1}): 505.2, found 504.9.

O-Ethyl

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.48 – 1.53 (s, 9H), 1.52 – 1.62 (t, *J*=6.9, 3H), 3.87 – 4.00 (s, 3H), 4.71 – 4.84 (q, *J*=7.0, 2H), 4.91 – 5.13 (s, 2H), 7.81 – 7.92 (d, *J*=8.0, 1H), 7.92 – 8.01 (d,

J=8.0, 1H), 8.23 – 8.50 (d, *J*=8.0, 1H), 8.60 – 9.09 (d, *J*=8.1, 1H), 10.03 – 10.94 (s, 1H). MS-ESI (*m/z*): calculated for $C_{21}H_{24}N_4O_9$ (M^{+1}): 477.1, found 476.9.

O-Cyclohexane

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.39 – 1.56 (s, 9H), 1.78 – 1.92 (s, 2H), 1.97 – 2.09 (m, 1H), 3.68 – 4.11 (s, 3H), 4.82 – 5.19 (s, 2H), 5.37 – 5.56 (m, 1H), 7.84 – 7.91 (d, *J*=8.1, 1H), 7.92 – 8.00 (d, *J*=8.0, 1H), 8.24 – 8.51 (d, *J*=8.0, 1H), 8.67 – 9.18 (d, *J*=8.1, 1H), 9.90 – 10.81 (s, 1H). MS-ESI (*m/z*): calculated for $C_{25}H_{30}N_4O_9$ (M^{+1}): 531.2, found 531.1.

O-Propyl

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.49 – 1.51 (s, 9H), 1.51 – 1.55 (d, *J*=6.2, 7H), 3.92 – 3.96 (s, 3H), 5.01 – 5.07 (s, 2H), 5.67 – 5.78 (p, *J*=6.2, 1H), 7.87 – 7.91 (d, *J*=8.2, 1H), 7.93 – 7.98 (d, *J*=8.0, 1H), 8.01 – 8.07 (dd, *J*=8.2, 1.4, 1H), 8.37 – 8.39 (d, *J*=4.0, 1H), 8.66 – 9.16 (d, *J*=8.1, 1H), 10.30 – 10.46 (s, 1H). MS-ESI (*m/z*): calculated for $C_{22}H_{26}N_4O_9$ (M^{+1}): 491.1, found 490.9.

SERIES 5:

O-Dodecane

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.31 – 1.45 (s, 8H), 1.44 – 1.61 (s, 11H), 1.88 – 2.12 (d, *J*=7.6, 2H), 3.80 – 3.98 (s, 3H), 4.61 – 4.79 (t, *J*=6.5, 2H), 4.89 – 5.04 (s, 2H), 5.03 – 5.25 (s, 2H), 7.84 – 7.91 (d, *J*=8.2, 1H), 7.95 – 8.00 (d, *J*=8.1, 1H), 8.01 – 8.06 (m, 1H), 8.07 – 8.13 (d, *J*=8.0, 1H), 8.44 – 8.65 (d, *J*=8.0, 1H), 8.82 – 9.13 (dd, *J*=8.1, 4.7, 2H), 10.01 – 10.20 (s, 1H), 10.30 – 10.59 (s, 1H). MS-ESI (*m/z*): calculated for $C_{43}H_{58}N_6O_{13}$ (M^{+1}): 866.9, found 866.9.

O-Benzyl

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.25 – 1.32 (d, *J*=4.7, 21H), 3.82 – 3.93 (s, 5H), 4.40 – 4.58 (s, 2H), 4.83 – 4.97 (s, 2H), 5.63 – 5.72 (s, 3H), 7.28 – 7.38 (t, *J*=6.8, 4H), 7.50 – 7.59 (d, *J*=6.2, 3H), 7.76 – 7.85 (d, *J*=8.1, 2H), 7.89 – 8.01 (dd, *J*=8.1, 3.4, 3H), 8.36 – 8.47 (d, *J*=8.0, 2H), 8.77 – 9.03 (dd, *J*=13.9, 8.1, 3H), 9.93 – 10.12 (s, 1H), 10.42 – 10.50 (s, 1H). MS-ESI (*m/z*): calculated for $C_{38}H_{40}N_6O_{13}$ (M^{+1}): 789.2, found 789.0.

O-Butyl

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.43 – 1.45 (s, 11H), 1.50 – 1.61 (d, *J*=7.8, 1H), 1.87 – 2.05 (m, 2H), 3.73 – 3.97 (s, 4H), 4.51 – 4.78 (t, *J*=6.4, 3H), 4.88 – 4.96 (s, 2H), 4.98 – 5.12 (s, 2H), 7.74 – 7.85 (d, *J*=8.2, 1H), 7.87 – 7.97 (d, *J*=8.1, 1H), 7.94 – 8.11 (d, *J*=8.0, 1H), 8.30 – 8.49 (d, *J*=8.0, 1H), 8.82 – 8.95 (dd, *J*=8.1, 4.0, 2H), 9.86 – 10.14 (s, 1H), 10.29 – 10.59 (s, 1H). MS-ESI (*m/z*): calculated for $C_{35}H_{42}N_6O_{13}$ (M^{+1}): 755.2, found 754.9.

O-Ethyl

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.33 – 1.36 (s, 4H), 1.43 – 1.46 (s, 4H), 1.56 – 1.63 (t, *J*=7.0, 1H), 3.73 – 3.93 (s, 2H), 4.66 – 4.76 (q, *J*=7.1, 1H), 4.93 – 4.98 (s, 1H), 5.02 – 5.12 (s, 1H), 7.72 – 7.83 (d, *J*=8.1, 0H), 7.88 – 7.93 (d, *J*=8.1, 0H), 7.99 – 8.05 (d, *J*=8.1, 0H), 8.37 – 8.51 (d, *J*=8.0, 1H), 8.78 – 9.01 (dd, *J*=8.1, 4.3, 1H), 9.92 – 10.25 (s, 1H), 10.28 – 10.58 (s, 1H). MS-ESI (*m/z*): calculated for $C_{33}H_{38}N_6O_{13}$ (M^{+1}): 727.2, found 727.0.

O-Propyl

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.33 – 1.35 (s, 7H), 1.43 – 1.45 (s, 8H), 1.51 – 1.55 (d, *J*=6.2, 6H), 3.69 – 3.94 (s, 3H), 4.91 – 5.01 (s, 2H), 5.00 – 5.10 (s, 2H), 5.52 – 5.76 (dt, *J*=12.3, 6.2, 1H), 7.76 – 7.84 (d, *J*=8.2, 1H), 7.86 – 7.92 (d, *J*=8.1, 1H), 7.99 – 8.06 (d, *J*=8.0, 1H), 8.41 – 8.48 (d,

J=8.1, 1H), 8.85 – 8.96 (dd, *J*=8.1, 3.6, 2H), 10.01 – 10.11 (s, 1H), 10.30 – 10.43 (s, 1H). MS-ESI (*m/z*): calculated for $C_{34}H_{40}N_6O_{13}$ (M^{+1}): 741.3, found 741.3.

O-Methyl

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.27 – 1.38 (s, 9H), 1.40 – 1.50 (s, 14H), 3.78 – 3.99 (s, 4H), 4.15 – 4.32 (s, 3H), 4.89 – 5.00 (s, 3H), 4.98 – 5.14 (s, 2H), 7.70 – 7.85 (d, *J*=7.9, 1H), 7.86 – 7.96 (d, *J*=8.1, 1H), 7.97 – 8.04 (d, *J*=8.0, 1H), 8.37 – 8.50 (d, *J*=8.0, 1H), 8.70 – 9.03 (m, 3H), 10.04 – 10.15 (s, 1H), 10.40 – 10.46 (s, 1H). MS-ESI (*m/z*): calculated for $C_{32}H_{36}N_6O_{13}$ (M^{+1}): 713.2, found 713.0.

O-Cyclohexane

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.33 – 1.43 (s, 9H), 1.45 – 1.54 (s, 12H), 1.62 – 1.81 (s, 1H), 1.82 – 2.00 (m, 2H), 2.21 – 2.38 (s, 1H), 3.77 – 4.01 (s, 4H), 4.96 – 5.05 (s, 3H), 5.07 – 5.17 (s, 2H), 5.21 – 5.47 (d, *J*=3.6, 1H), 7.82 – 7.90 (d, *J*=8.1, 1H), 7.91 – 8.03 (d, *J*=8.1, 1H), 8.04 – 8.16 (d, *J*=8.0, 1H), 8.45 – 8.55 (d, *J*=8.1, 1H), 8.89 – 9.00 (dd, *J*=8.1, 3.2, 2H), 9.96 – 10.07 (s, 1H), 10.23 – 10.33 (s, 1H). MS-ESI (*m/z*): calculated for $C_{37}H_{44}N_6O_{13}$ (M^{+1}): 781.2, found 781.0.

O-Naphthalene

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.21 – 1.25 (s, 7H), 1.25 – 1.33 (s, 8H), 3.86 – 4.07 (s, 4H), 4.24 – 4.36 (s, 2H), 4.83 – 5.00 (t, *J*=5.6, 3H), 5.84 – 5.89 (s, 2H), 7.39 – 7.52 (m, 2H), 7.62 – 7.71 (dd, *J*=8.3, 1.8, 1H), 7.72 – 7.88 (m, 5H), 7.90 – 8.01 (dd, *J*=8.1, 6.6, 2H), 8.00 – 8.08 (s, 1H), 8.36 – 8.43 (d, *J*=8.1, 1H), 8.81 – 9.06 (dd, *J*=15.6, 8.1, 3H), 9.98 – 10.10 (s, 1H), 10.45 – 10.59 (s, 1H). MS-ESI (*m/z*): calculated for $C_{42}H_{42}N_6O_{13}$ (M^{+1}): 839.2, found 838.9.

SERIES 6:

ADM-1

The characterization of ADM-1 (referred as IS-3) is published elsewhere[1].

[1]Saraogi, I., Hebda, J.A., Becerril, J., Estroff, L.A., Miranker, A.D., and Hamilton, A.D. (2010) Synthetic **α**-helix mimetics as agonists and antagonists of islet amyloid polypeptide aggregation. Angew. Chem. Int. Ed. *49*, 736-739.

ADM-2

^{1}H NMR (500 MHz, DMSO) δ = 3.69 – 3.86 (s, 3H), 4.01 – 4.33 (s, 3H), 4.97 – 5.08 (s, 2H), 5.09 – 5.24 (s, 2H), 7.68 – 7.83 (t, *J*=9.0, 2H), 7.89 – 8.01 (d, *J*=6.9, 1H), 8.60 – 8.67 (s, 1H), 8.67 – 8.78 (d, *J*=7.0, 2H), 9.99 – 10.15 (s, 1H), 10.20 – 10.31 (s, 1H). MS-ESI (*m/z*): calculated for $C_{24}H_{20}N_6O_{13}$ (M+H): 601.1167, found 601.1163. Anal. Calcd for $C_{24}H_{20}N_6O_{13}$: C, 48.01; H, 3.36; N, 14.00; O, 34.64. Found: C, 48.24; H, 3.45; N, 13.83.

ADM-3

^{1}H NMR (500 MHz, DMSO) δ = 1.41 – 1.56 (t, *J*=7.0, 3H), 3.56 – 3.73 (s, 3H), 4.43 – 4.62 (d, *J*=7.0, 2H), 4.84 – 4.95 (s, 2H), 4.99 – 5.12 (s, 2H), 7.52 – 7.60 (s, 1H), 7.61 – 7.69 (d, *J*=8.0, 1H), 7.77 – 7.89 (d, *J*=8.0, 1H), 8.39 – 8.51 (m, 1H), 8.54 – 8.61 (s, 1H), 8.42 – 8.95 (d, *J*=8.0, 1H), 9.58 – 10.07 (s, 1H), 9.99 – 10.20 (s, 1H); MS-ESI (*m/z*): calculated for $C_{25}H_{22}N_6O_{13}$ (M+H): 615.1323, found 615.1323. Anal. Calcd for $C_{24}H_{22}N_6O_{13}$: C, 48.87; H, 3.61; N, 13.68; O, 33.85. Found: C, 49.01; H, 3.77; N, 13.54.

ADM-4

^{1}H NMR (500 MHz, DMSO) δ = 0.79 – 1.03 (t, *J*=7.4, 3H), 1.37 – 1.55 (q, *J*=7.6, 2H), 1.81 – 1.97 (p, *J*=7.4, 2H), 3.62 – 3.87 (s, 3H), 4.52 – 4.62 (t, *J*=7.8, 2H), 4.96 – 5.06 (s, 2H), 5.11 – 5.20 (s, 2H), 7.72 – 7.84 (s, 2H), 7.89 – 7.99 (d, *J*=8.3, 1H), 8.66 – 8.71 (d, *J*=8.1, 1H), 8.74 – 8.81 (s, 2H),

10.00 – 10.13 (s, 1H), 10.21 – 10.41 (s, 1H). MS-ESI (*m/z*): calculated for $C_{27}H_{26}N_6O_{13}$ (M+H): 643.1636, found 643.1633. Anal. Calcd for $C_{27}H_{26}N_6O_{13}$: C, 50.47; H, 4.08; N, 13.08; O, 32.37. Found: C, 50.63; H, 3.93; N, 13.21.

ADM-5

^{1}H NMR (500 MHz, DMSO) δ = 1.02 – 1.20 (m, 14H), 1.22 – 1.34 (m, 2H), 1.34 – 1.44 (m, 2H), 1.80 – 1.95 (t, *J*=6.1, 2H), 3.57 – 3.70 (s, 3H), 4.42 – 4.63 (t, *J*=7.1, 2H), 4.76 – 5.07 (s, 4H), 7.32 – 7.50 (d, *J*=8.0, 1H), 7.58 – 7.70 (d, *J*=7.9, 1H), 7.70 – 7.91 (d, *J*=8.1, 1H), 8.37 – 8.60 (s, 1H), 8.44 – 8.86 (d, *J*=8.0, 2H), 9.53 – 10.15 (s, 2H). MS-ESI (*m/z*): calculated for $C_{35}H_{42}N_6O_{13}$ (M+H): 755.2888, found 755.2886. Anal. Calcd for $C_{35}H_{42}N_6O_{13}$: C, 55.70; H, 5.61; N, 11.14; O, 27.56. Found: C, 55.75; H, 5.48; N, 11.10.

ADM-6

^{1}H NMR (500 MHz, DMSO) δ = 3.55 – 3.68 (s, 3H), 4.86 – 5.00 (s, 4H), 5.49 – 5.63 (s, 2H), 7.12 – 7.22 (t, *J*=7.5, 2H), 7.44 – 7.50 (d, *J*=7.8, 2H), 7.59 – 7.68 (d, *J*=11.7, 2H), 7.72 – 7.81 (d, *J*=7.8, 1H), 8.43 – 8.55 (m, 2H), 8.58 – 8.68 (d, *J*=7.2, 2H), 9.95 – 10.02 (s, 1H), 10.07 – 10.13 (s, 1H). MS-ESI (*m/z*): calculated for $C_{30}H_{24}N_6O_{13}$ (M+H): 677.1480, found 677.1476. Anal. Calcd for $C_{30}H_{24}N_6O_{13}$: C, 53.26; H, 3.58; N, 12.42; O, 30.74. Found: C, 53.40; H, 3.62; N, 12.25.

ADM-7

^{1}H NMR (400 MHz, DMSO) δ = 1.23 – 1.35 (m, 2H), 1.36 – 1.50 (q, *J*=12.4, 2H), 1.55 – 1.76 (m, 2H), 1.76 – 1.86 (m, 2H), 2.13 – 2.24 (m, 2H), 3.71 – 3.87 (s, 3H), 5.00 – 5.08 (s, 2H), 5.10 – 5.15 (m, 1H), 5.14 – 5.33 (s, 2H), 7.73 – 7.88 (m, 2H), 7.89 – 7.98 (d, *J*=8.1, 1H), 8.64 – 8.75 (m, 1H), 8.74 – 8.90 (m, 2H), 9.87 – 10.04 (s, 1H), 10.07 – 10.19 (d, *J*=5.2, 1H), 13.05-13.55 (s, br, 2H). MS-ESI (*m/z*): calculated for $C_{29}H_{28}N_6O_{13}$ (M+H): 669.1793, found 669.1794. Anal. Calcd for $C_{29}H_{28}N_6O_{13}$: C, 52.10; H, 4.22; N, 12.57; O, 31.11. Found: C, 52.21; H, 4.28; N, 12.34.

ADM-8

^{1}H NMR (500 MHz, DMSO-d_6) δ 3.77 – 3.88 (s, 3H), 4.96 – 5.08 (s, 4H), 5.11 – 5.22 (s, 2H), 7.15 – 7.21 (s, 1H), 7.46 – 7.64 (m, 3H), 7.78 – 7.85 (d, *J* = 8.1 Hz, 2H), 7.92 – 8.00 (d, *J* = 8.1 Hz, 2H), 8.53 – 8.64 (br, s, 1H), 8.65 – 8.76 (d, *J* = 8.1 Hz, 2H), 10.20 – 10.42 (br, s, 2H). MS-ESI (*m/z*): calculated for $C_{34}H_{26}N_6O_{13}$ (M+H): 727.1636, found 727.1634. Anal. Calcd for $C_{29}H_{28}N_6O_{13:}$ C, 56.20; H, 3.61; N, 11.57; O, 28.62. Found: C, 56.51; H, 3.74; N, 11.39.

ADM-9

^{1}H NMR (500 MHz, DMSO) δ = 1.52 – 1.56 (d, *J*=6.1, 8H), 3.82 – 3.84 (s, 3H), 5.07 – 5.10 (s, 2H), 5.19 – 5.22 (s, 2H), 5.42 – 5.50 (m, 1H), 7.80 – 7.87 (d, *J*=8.0, 2H), 7.95 – 8.01 (d, *J*=8.1, 1H), 8.69 – 8.76 (d, *J*=8.1, 1H), 8.77 – 8.84 (m, 2H), 10.04 – 10.13 (s, 1H), 10.31 – 10.41 (s, 1H). MS-ESI (*m/z*): calculated for $C_{26}H_{24}N_6O_{13}$ (M+H): 629.1480, found 629.1478. Anal. Calcd for $C_{26}H_{24}N_6O_{13:}$ C, 49.69; H, 3.85; N, 13.37; O, 33.09. Found: C, 49.94; H, 4.01; N, 13.17.

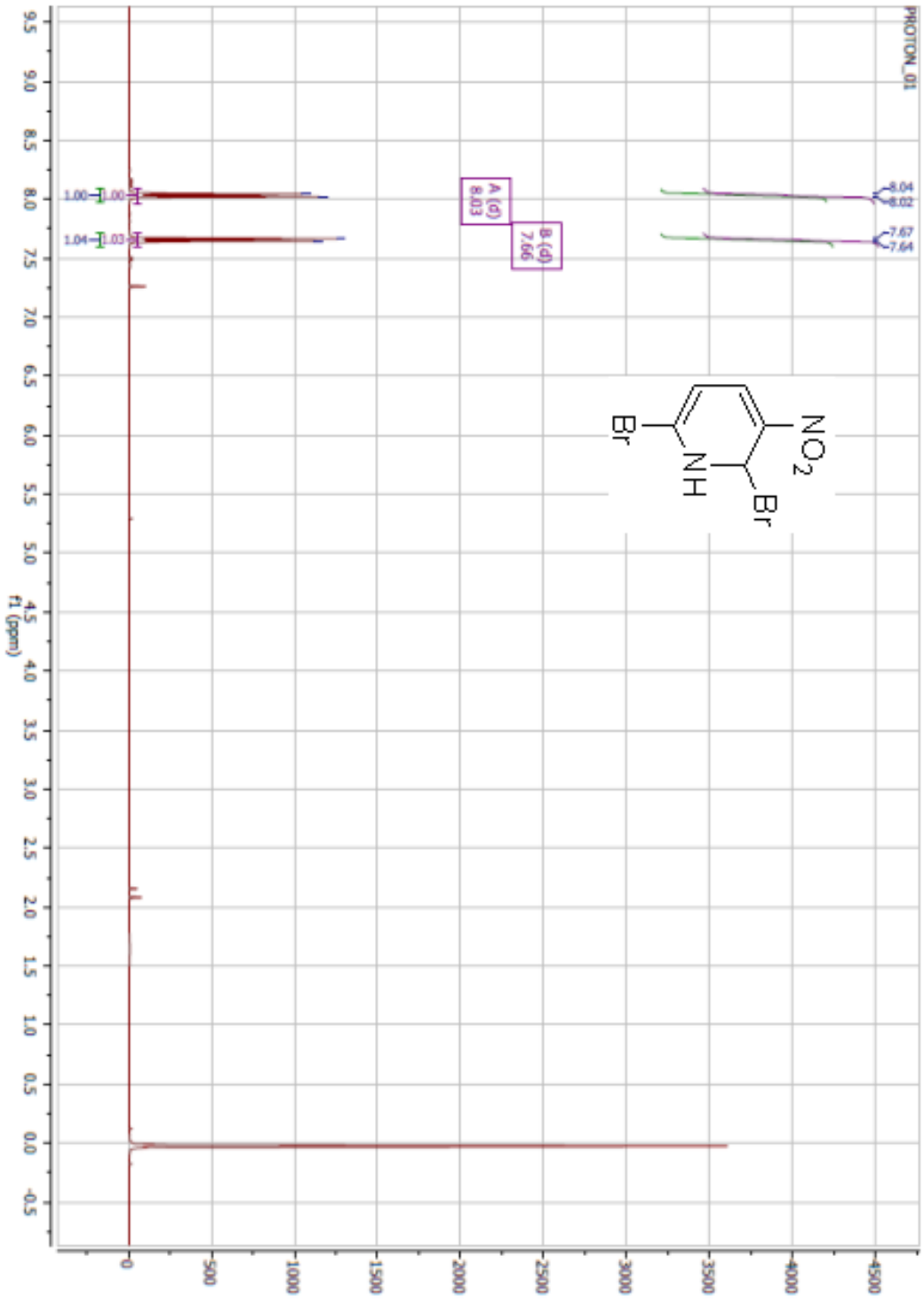


Figure S6. ^{1}H-NMR of 2,6-dibromo-3-nitropyridine (in $CDCl_3$).

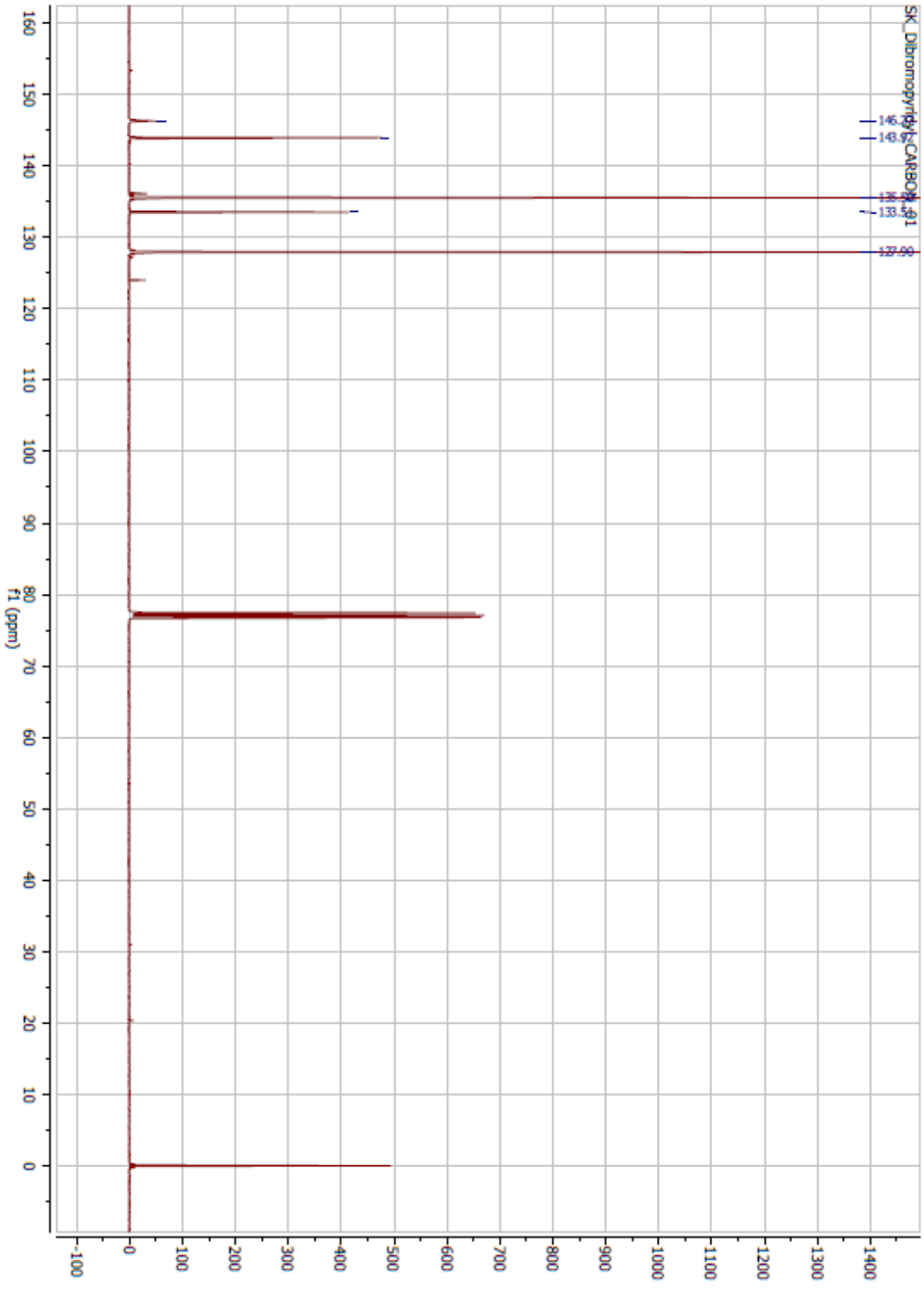


Figure S7. ^{13}C-NMR of 2,6-dibromo-3-nitropyridine (in $CDCl_3$).

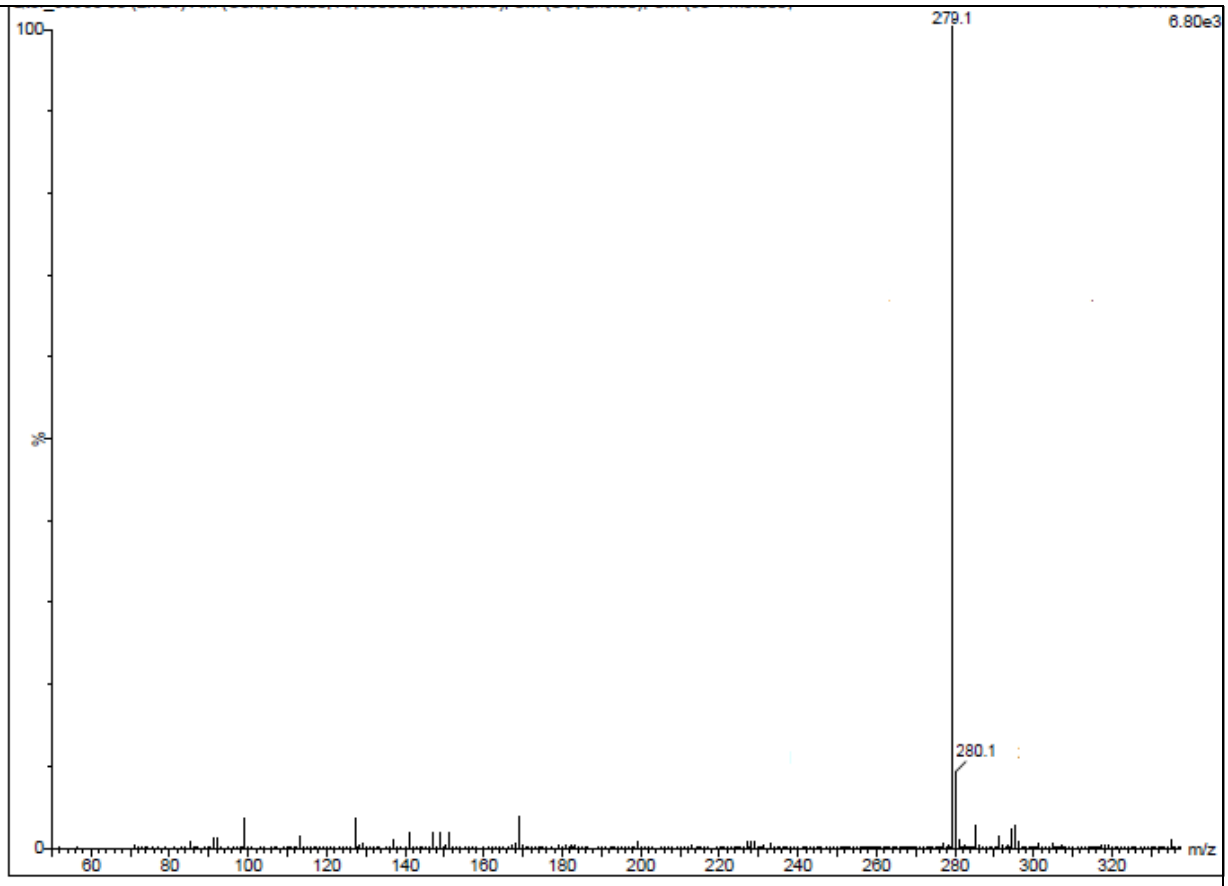


Figure S8. MS-ESI of 2,6-dibromo-3-nitropyridine.

Figure S9. ^{1}H-NMR of 6-dibromo-3-nitropyridin-2-amine (in $CDCl_3$).

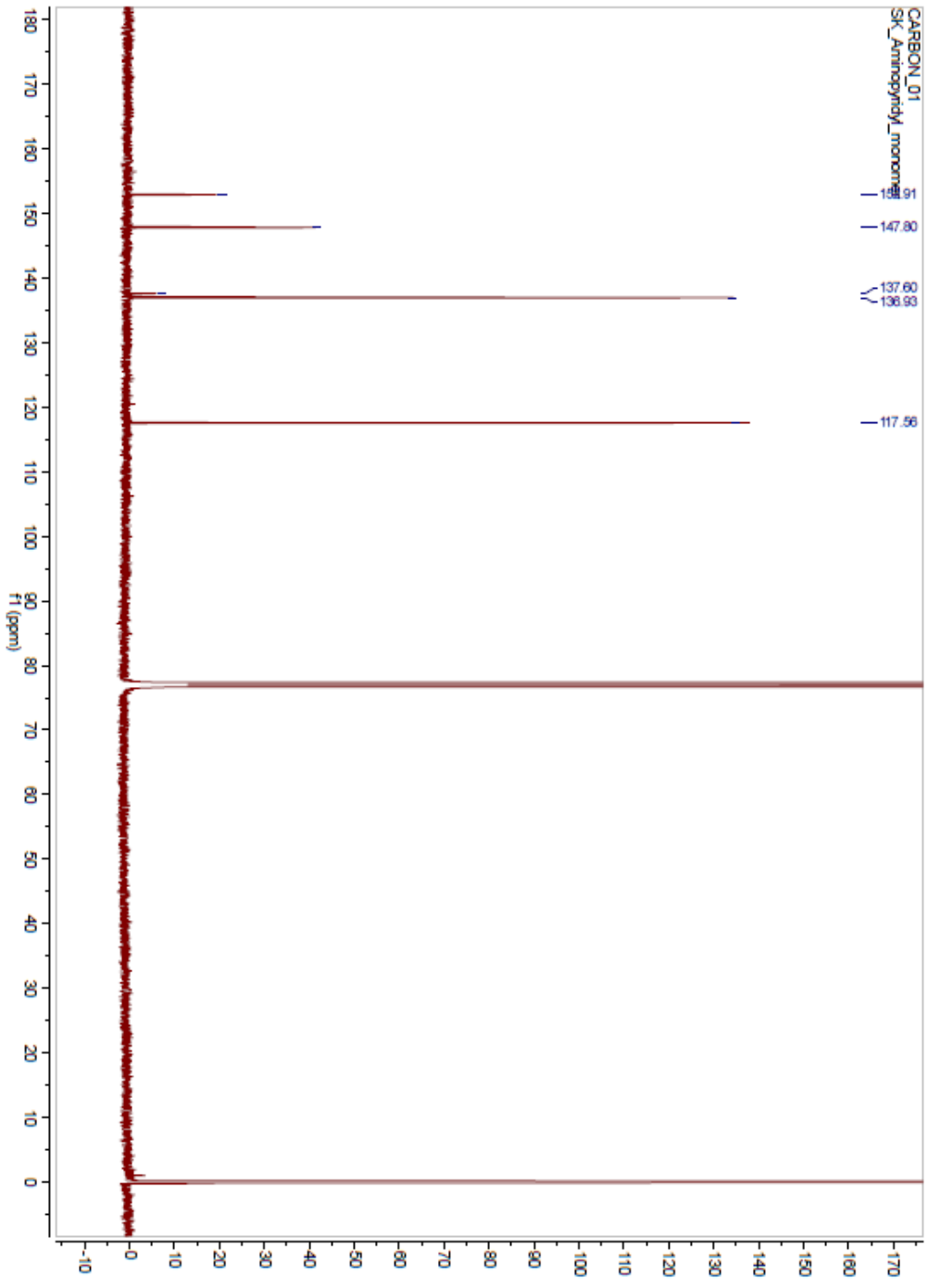


Figure S10. ^{13}C-NMR of 6-dibromo-3-nitropyridin-2-amine (in $CDCl_3$).

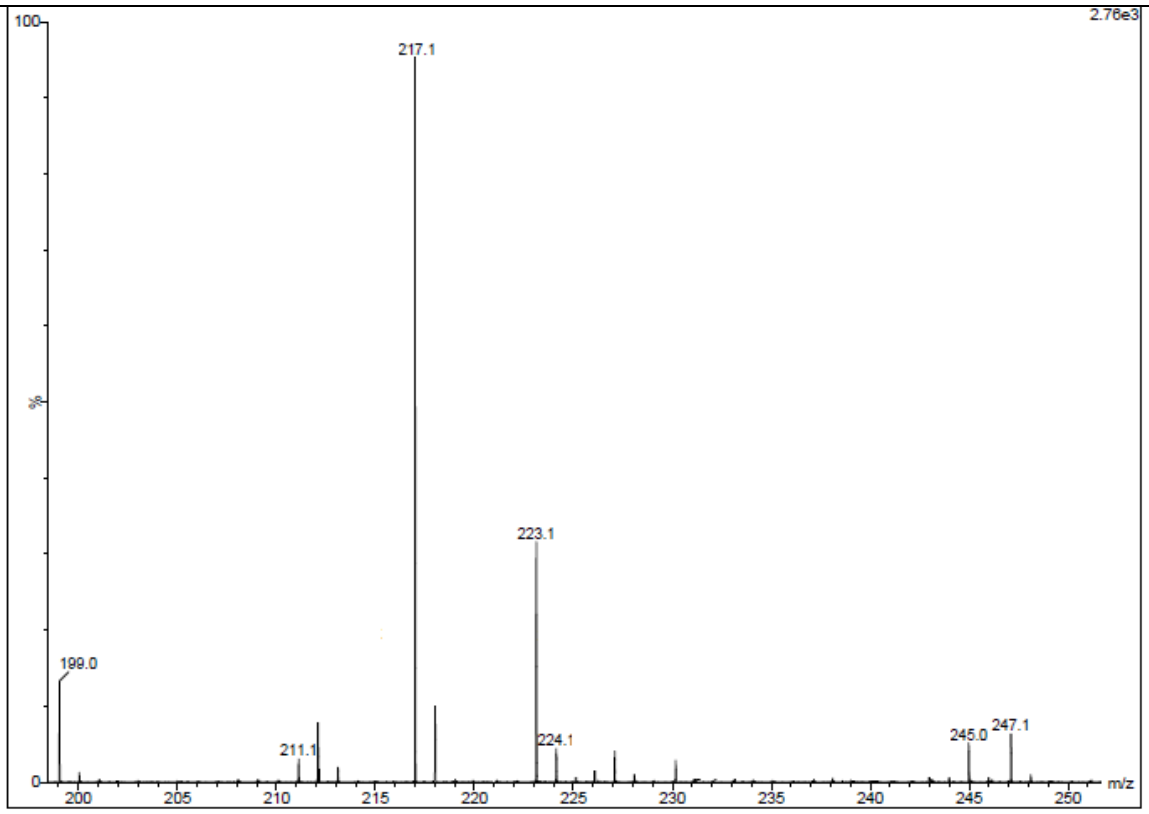


Figure S11. MS-ESI of 6-dibromo-3-nitropyridin-2-amine.

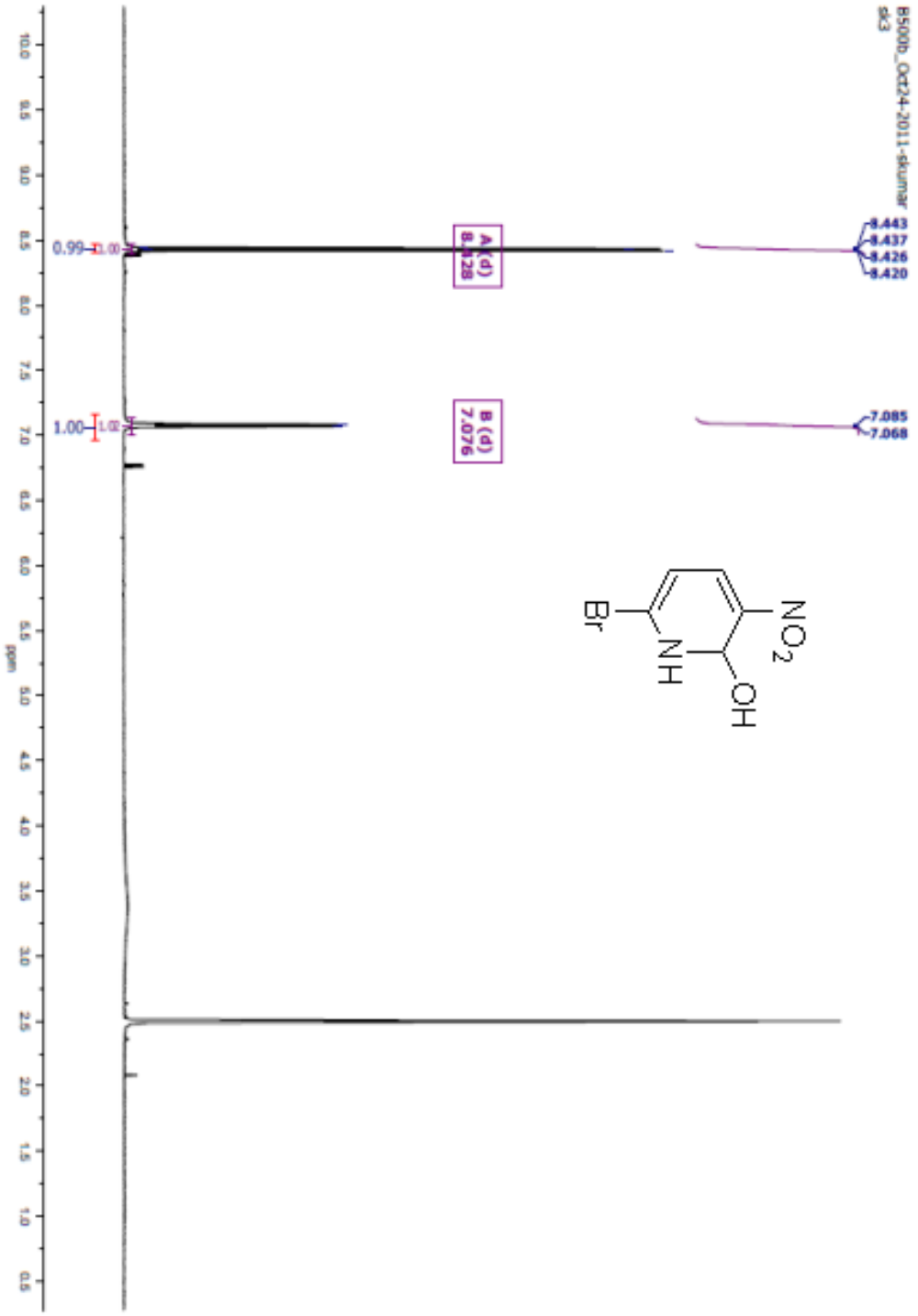


Figure S12. ^{1}H-NMR of 6-dibromo-3-nitropyridin-2-ol [in $(CD_3)_2SO$].

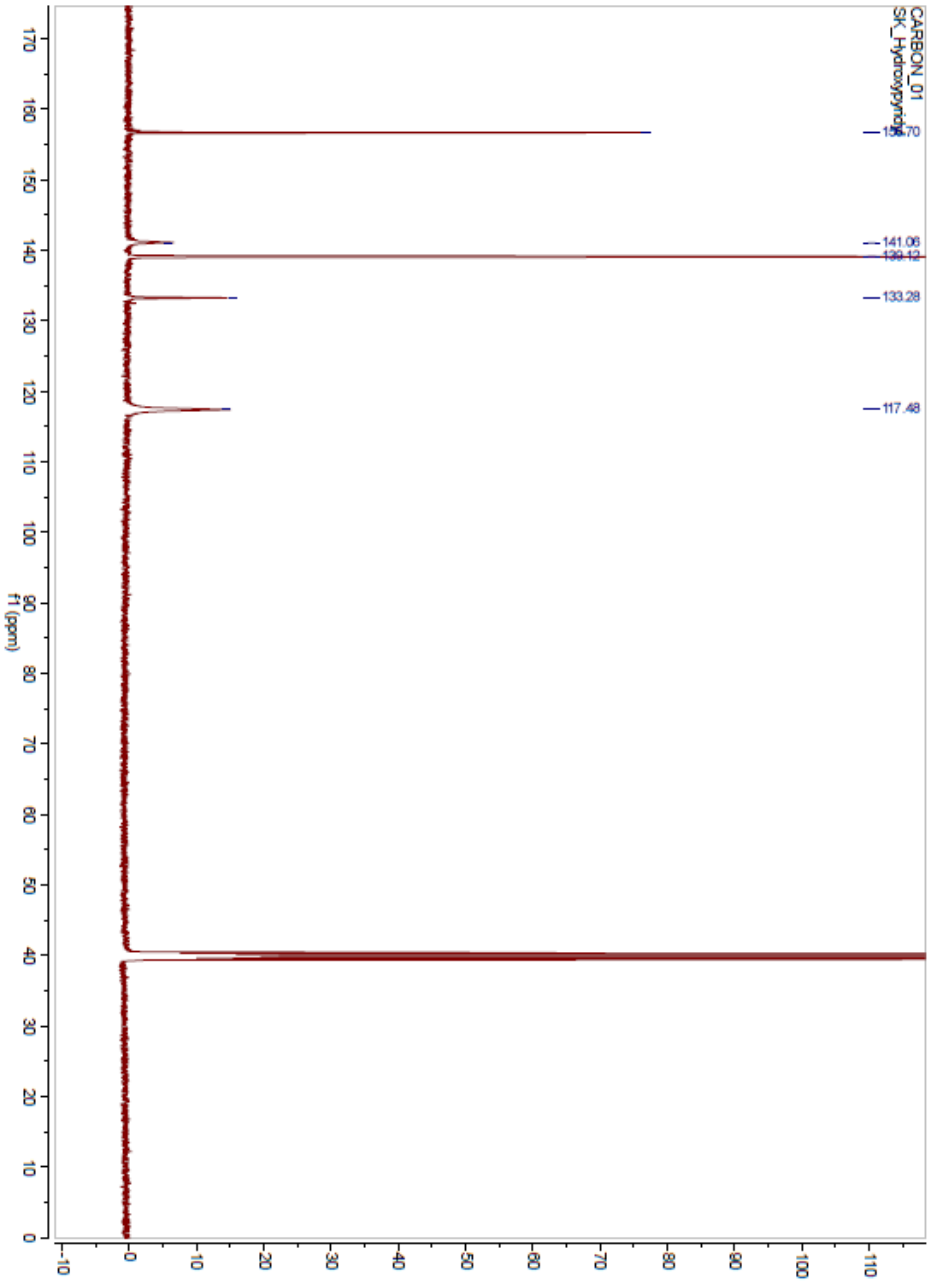


Figure S13. ^{13}C-NMR of 6-dibromo-3-nitropyridin-2-ol [in $(CD_3)_2SO$].

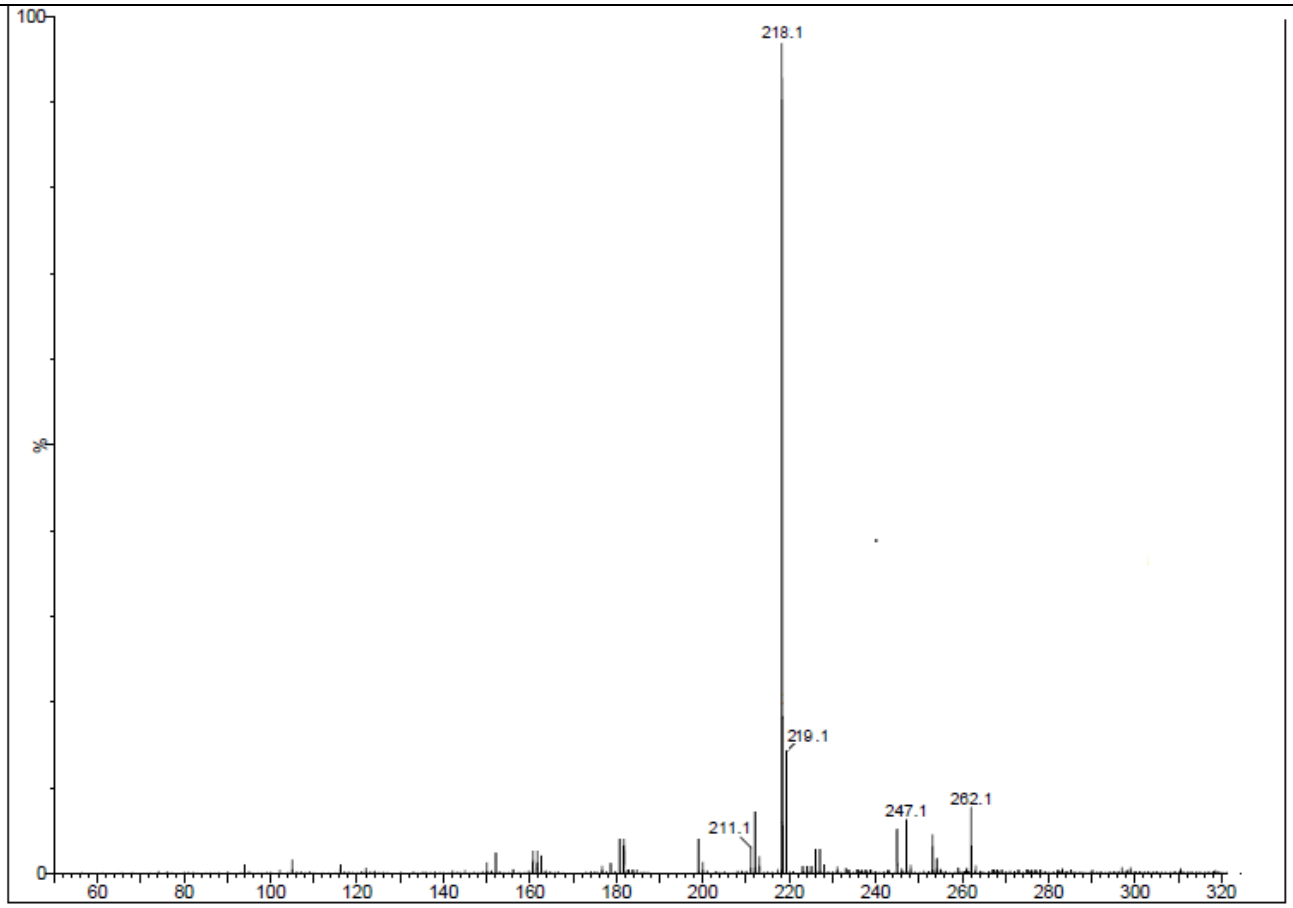


Figure S14. MS-ESI of 6-dibromo-3-nitropyridin-2-ol.

Series 1.

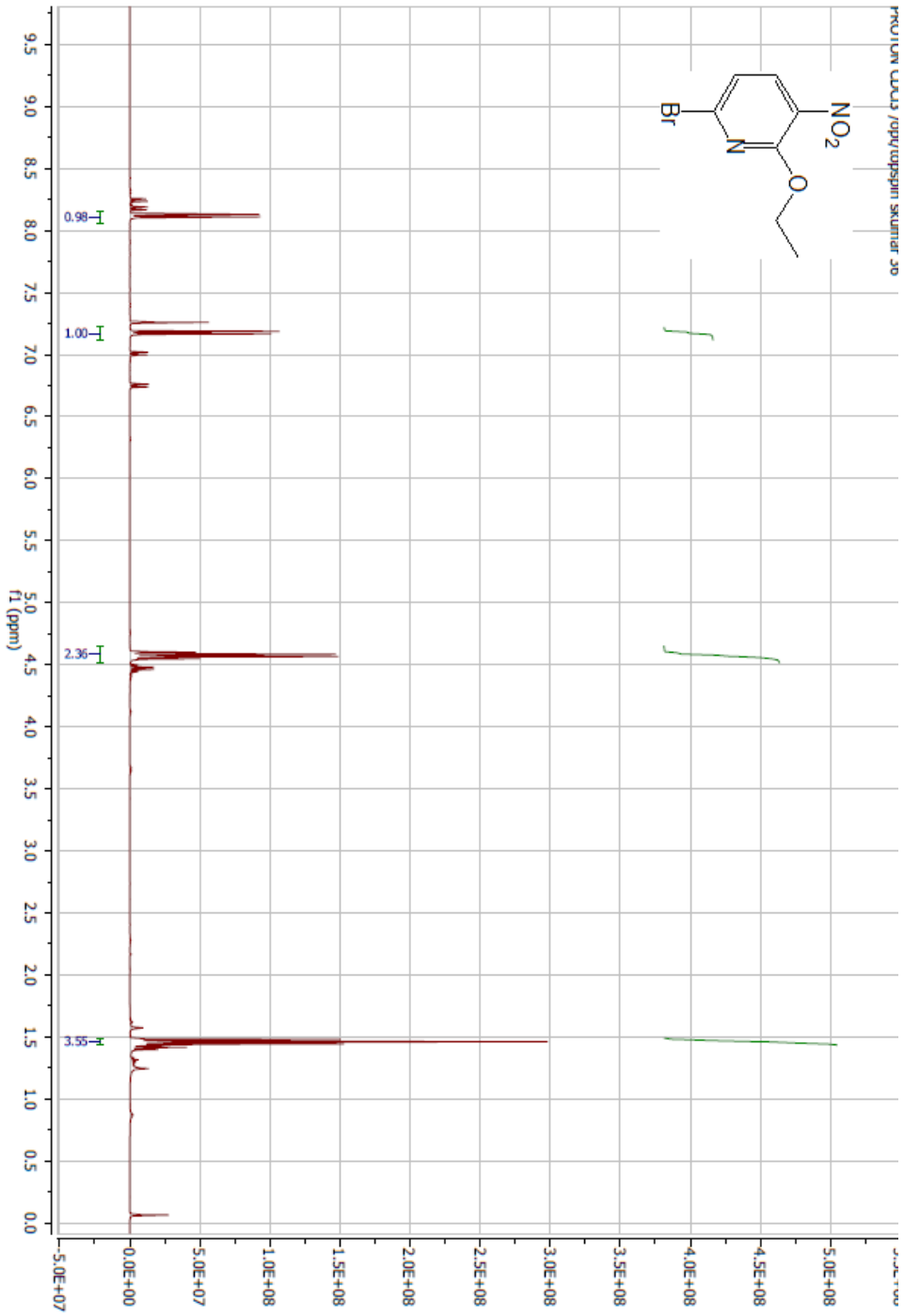


Figure S15. ^{1}H-NMR of O-Ethyl (in $CDCl_3$).

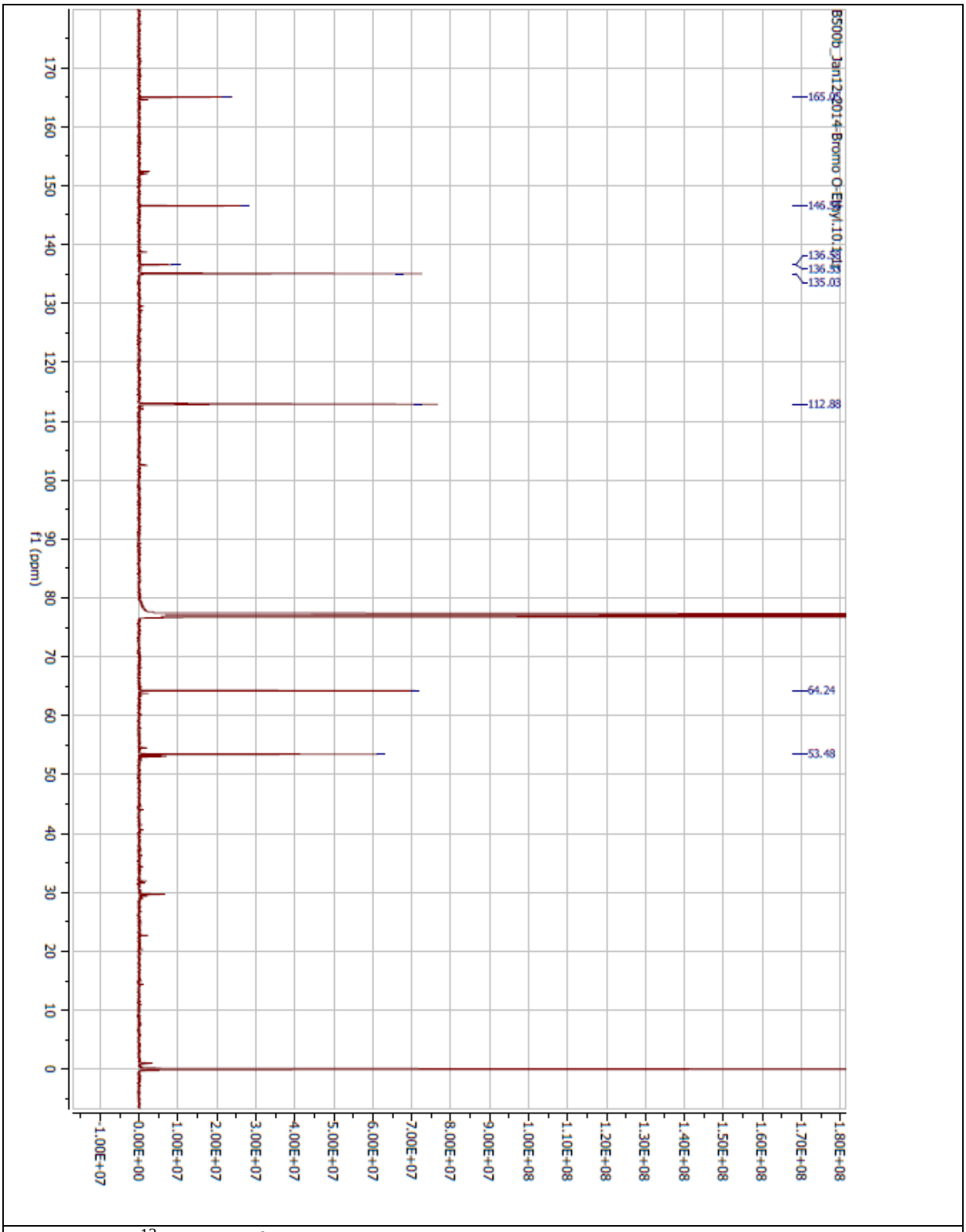


Figure S16. ^{13}C-NMR of O-Ethyl (in $CDCl_3$).

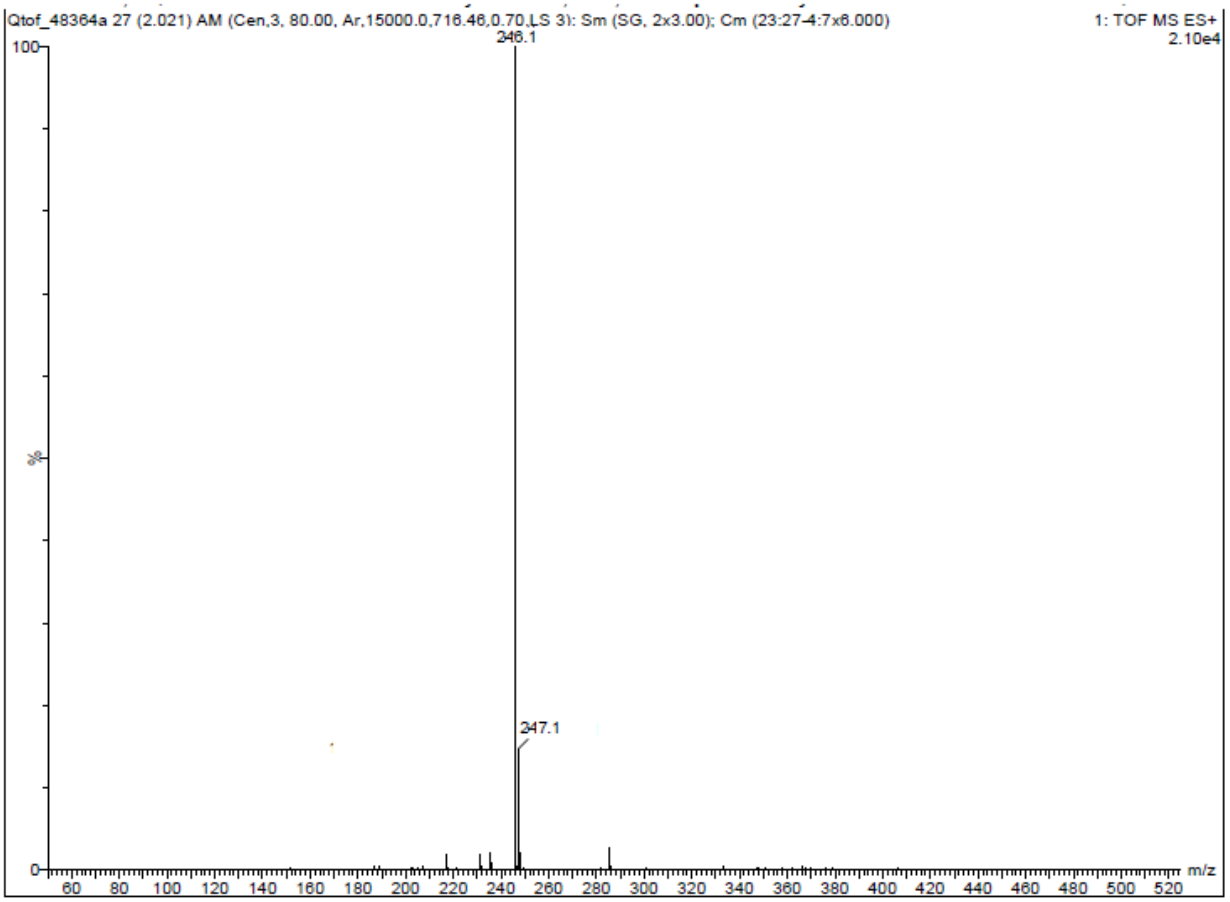


Figure S17. ESI-MS of O-Ethyl.

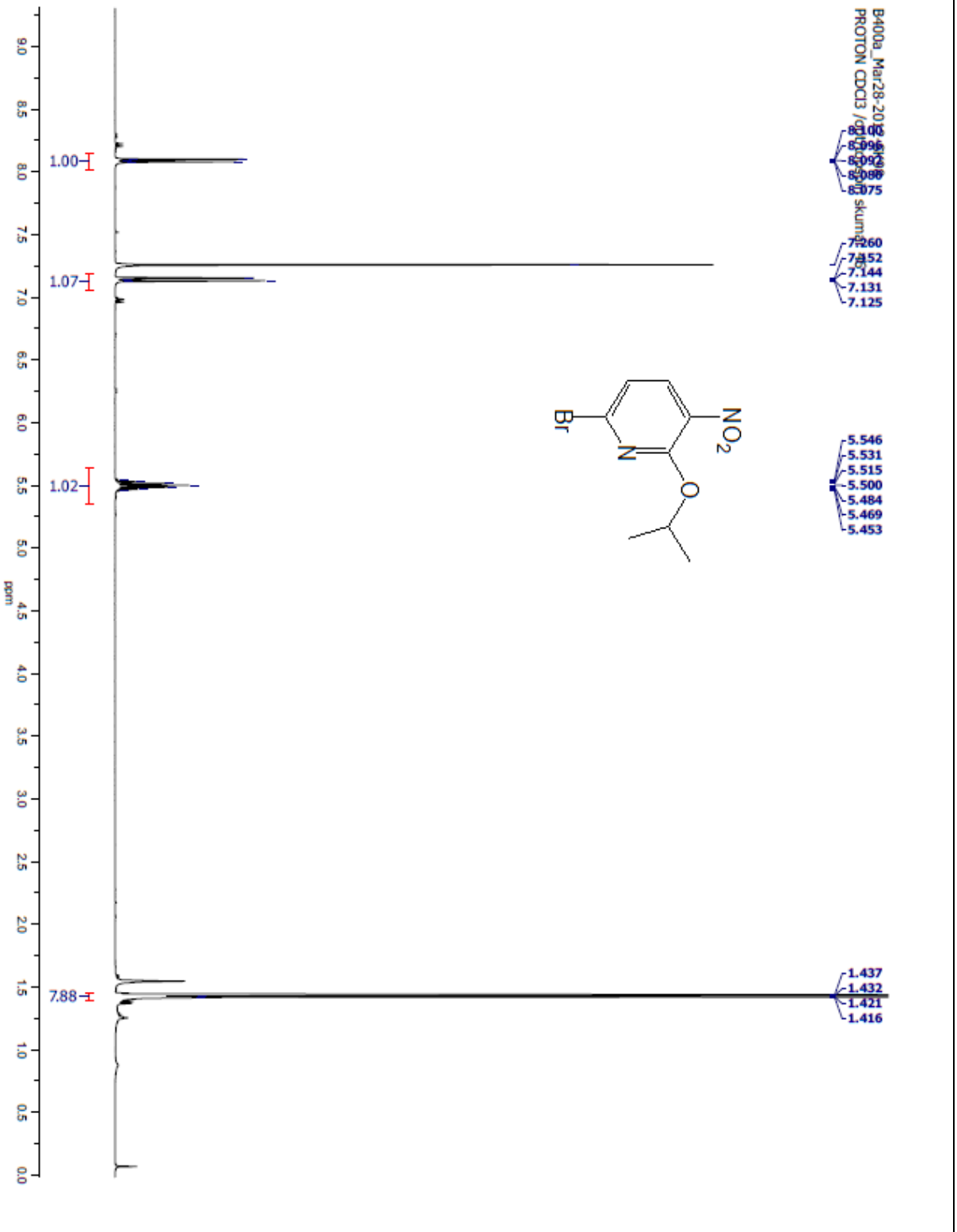


Figure S18. ^{1}H-NMR of O-Propyl (in $CDCl_3$).

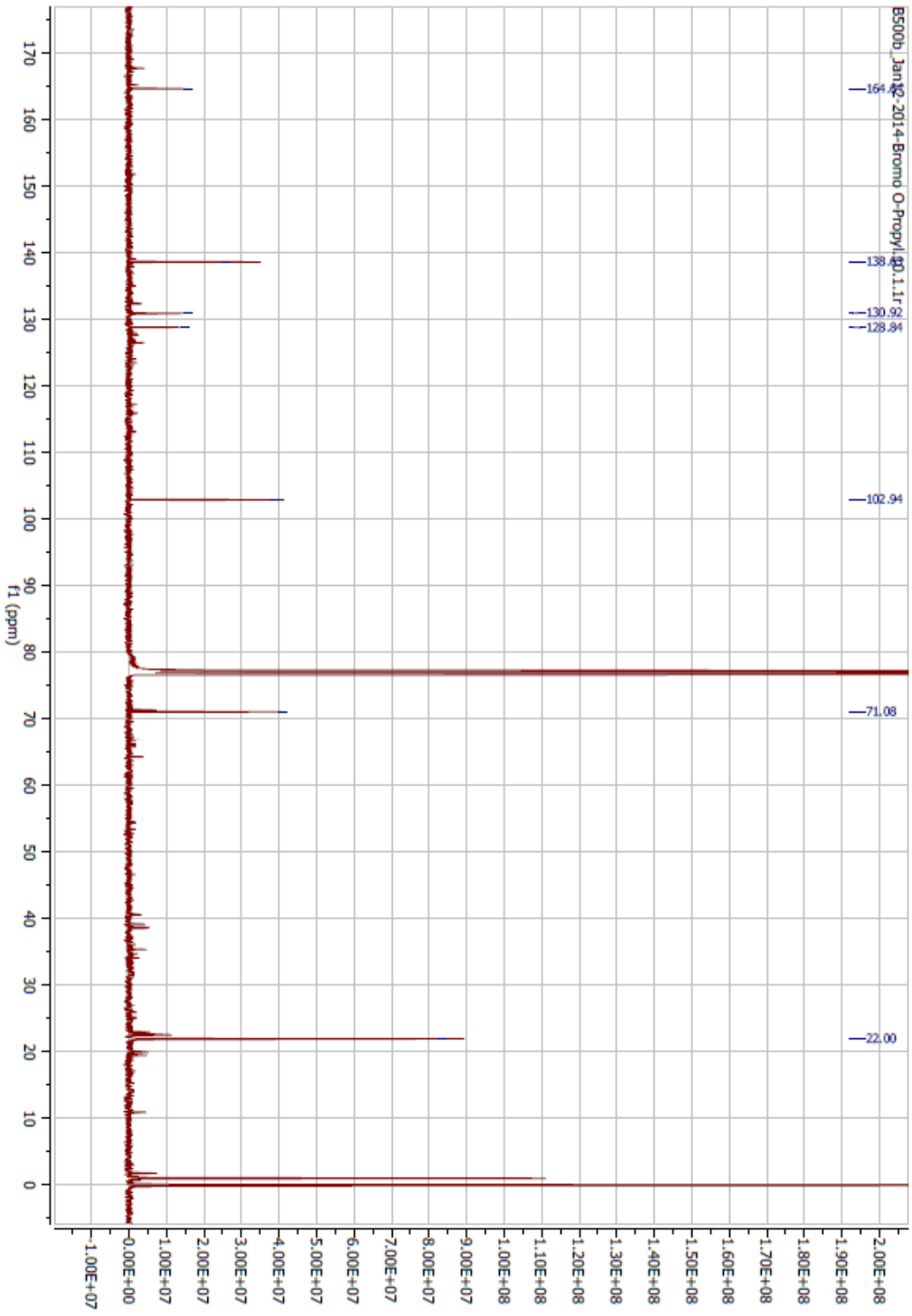


Figure S19. ^{13}C-NMR of O-Propyl (in $CDCl_3$).

Figure S20. ESI-MS of O-Propyl.

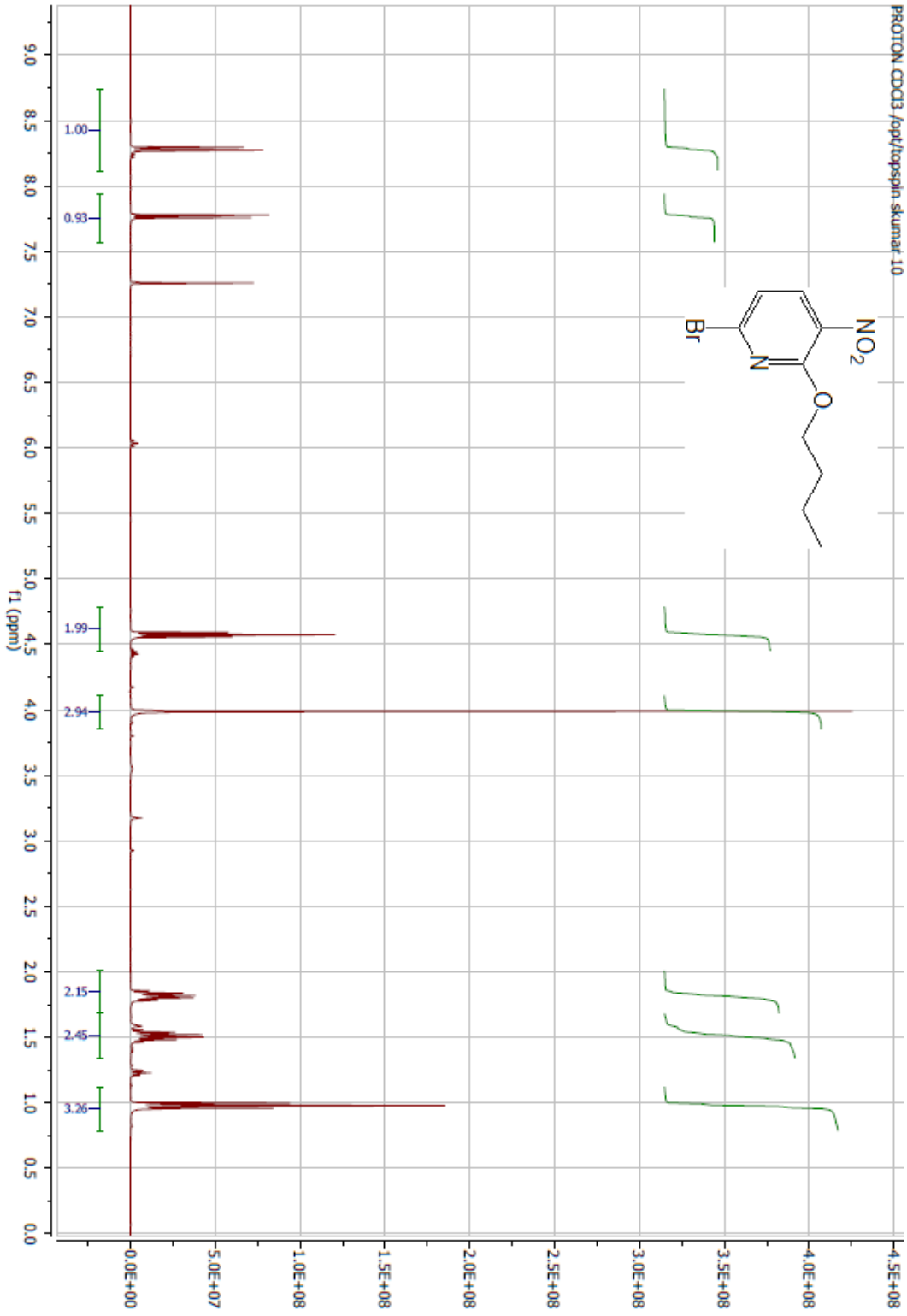


Figure S21. ^{1}H-NMR of O-Butyl (in $CDCl_3$).

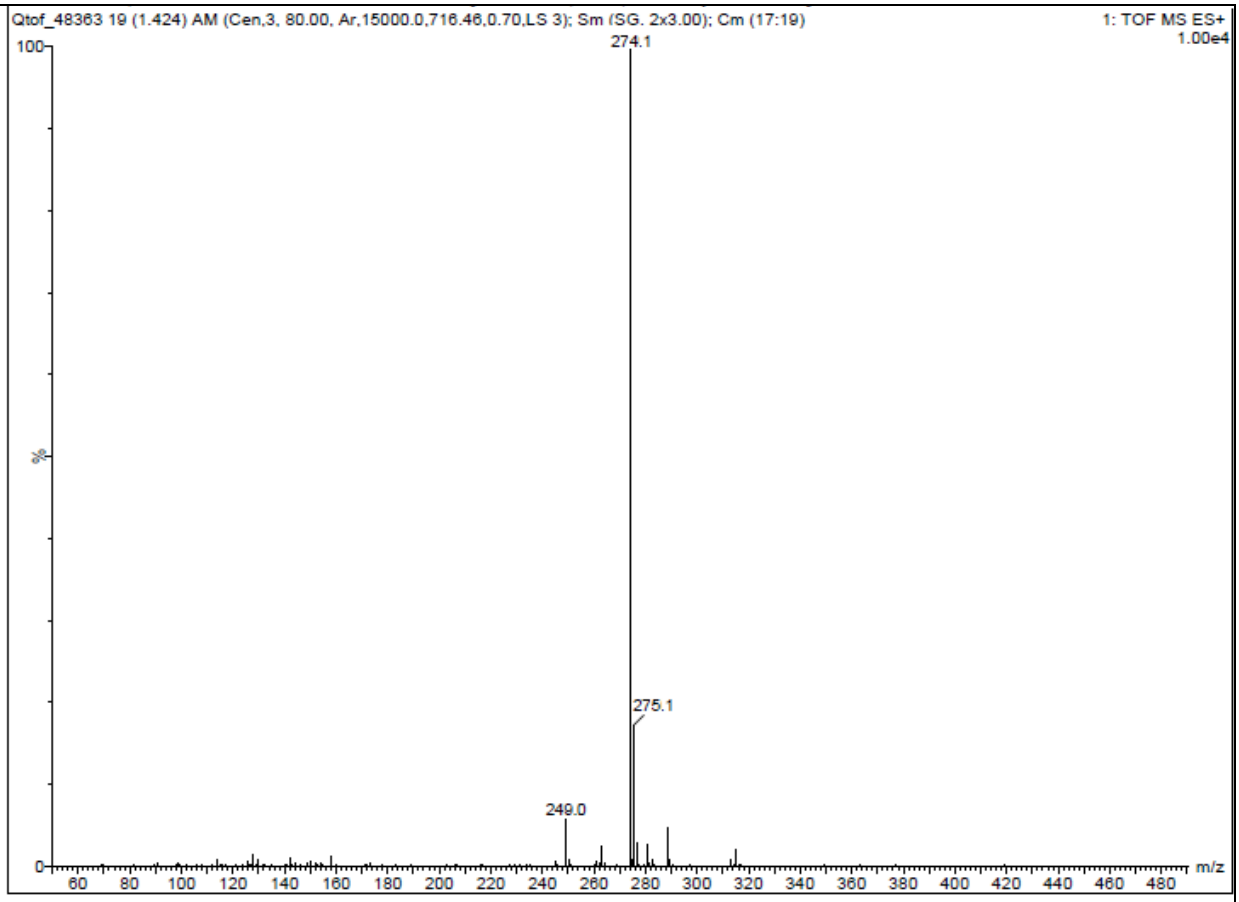


Figure S22. MS-ESI of O-Butyl.

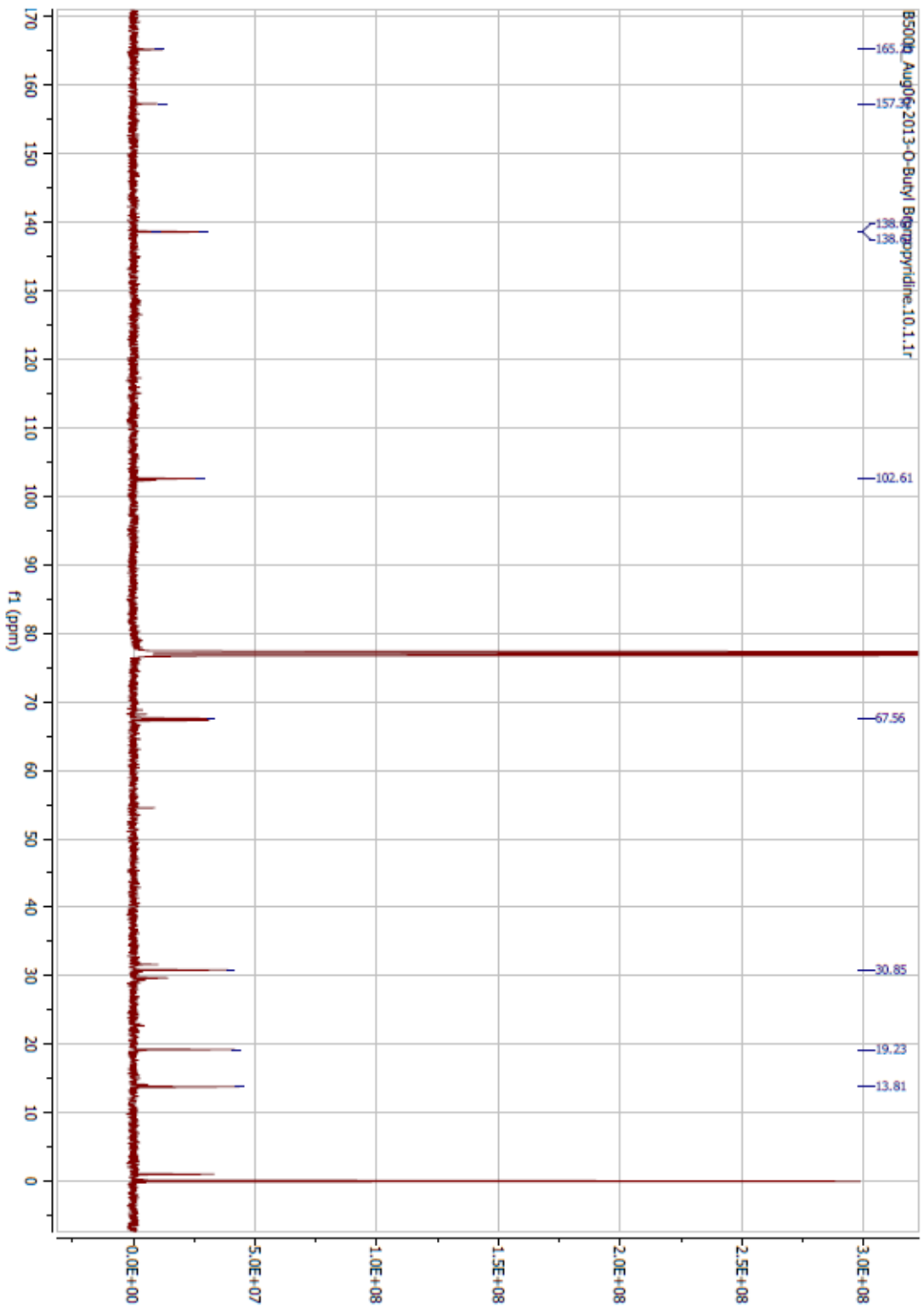


Figure S23. ^{13}C-NMR of O-Butyl (in $CDCl_3$).

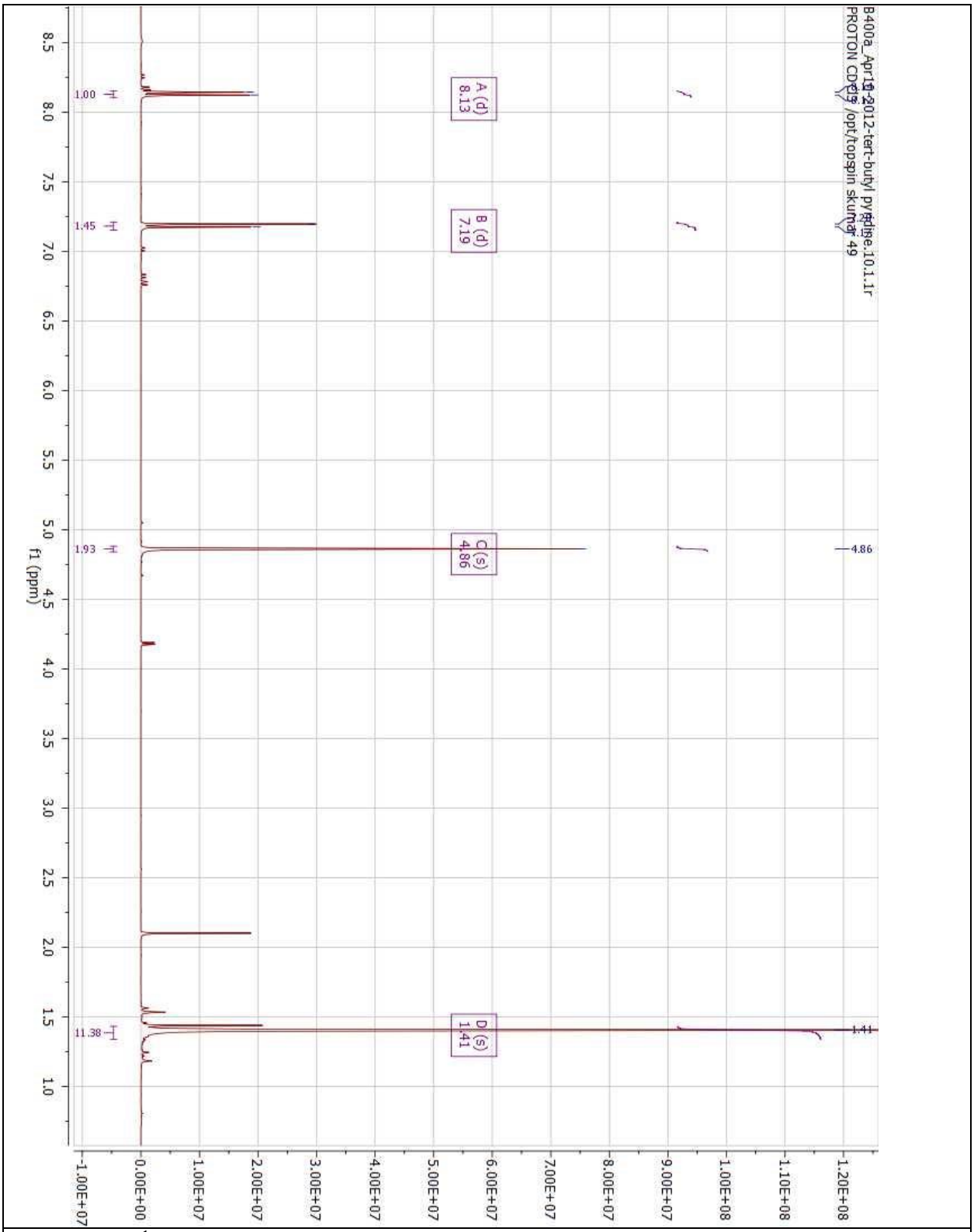


Figure S24. ^{1}H-NMR of O-*tert* butyl ester (in $CDCl_3$).

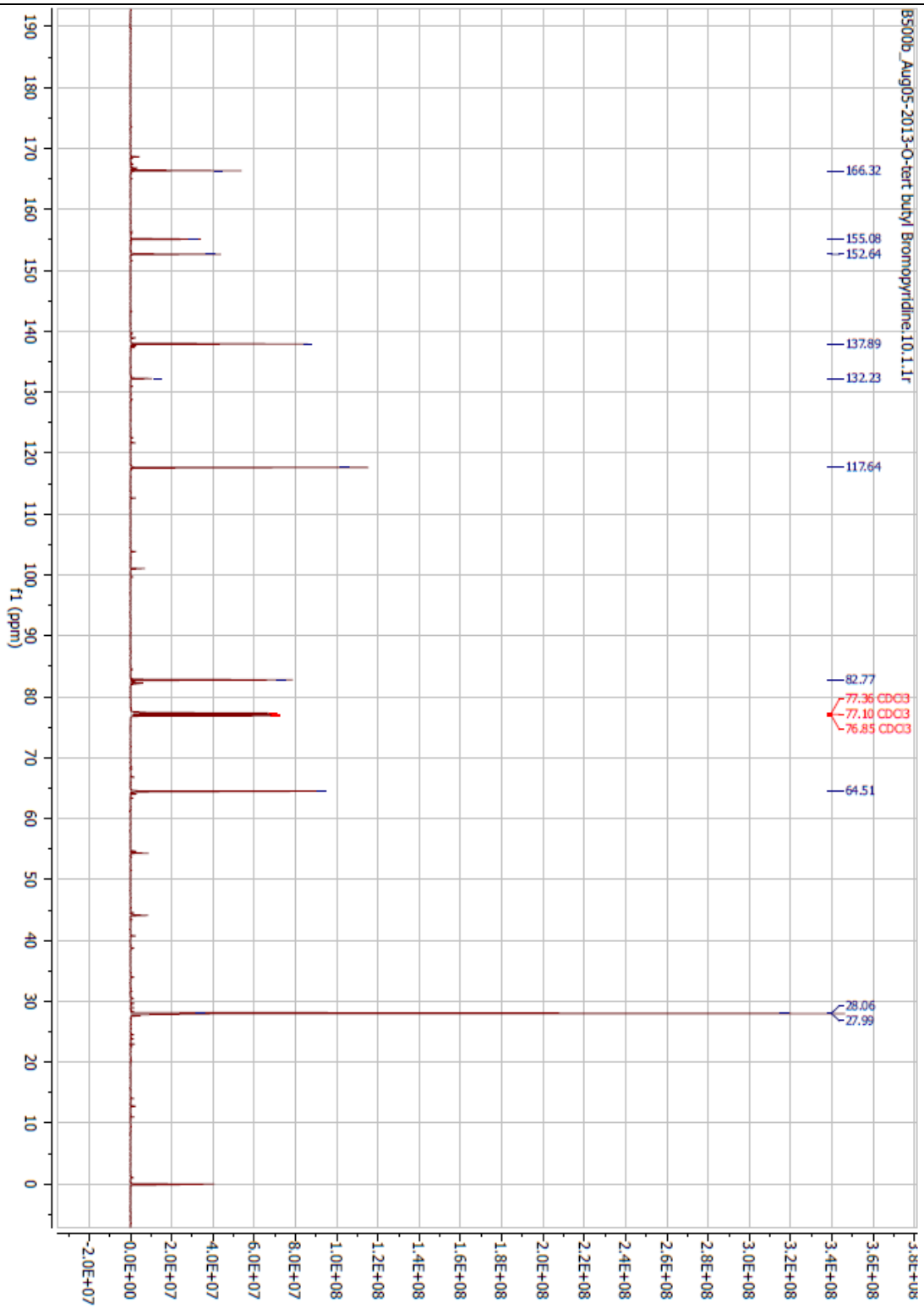


Figure S25. ^{13}C-NMR of O-*tert* butyl ester (in $CDCl_3$).

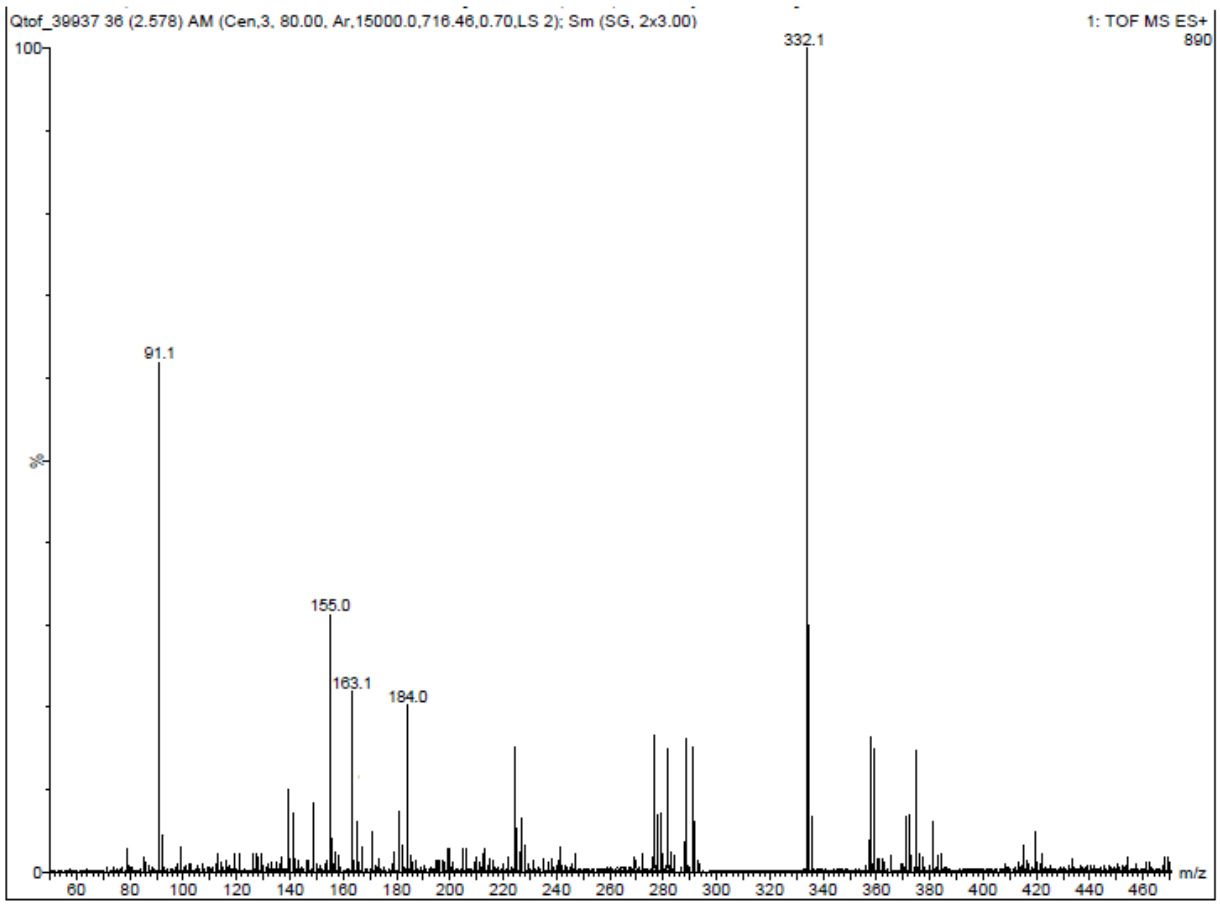


Figure S26. MS-ESI of O-*tert* butyl ester.

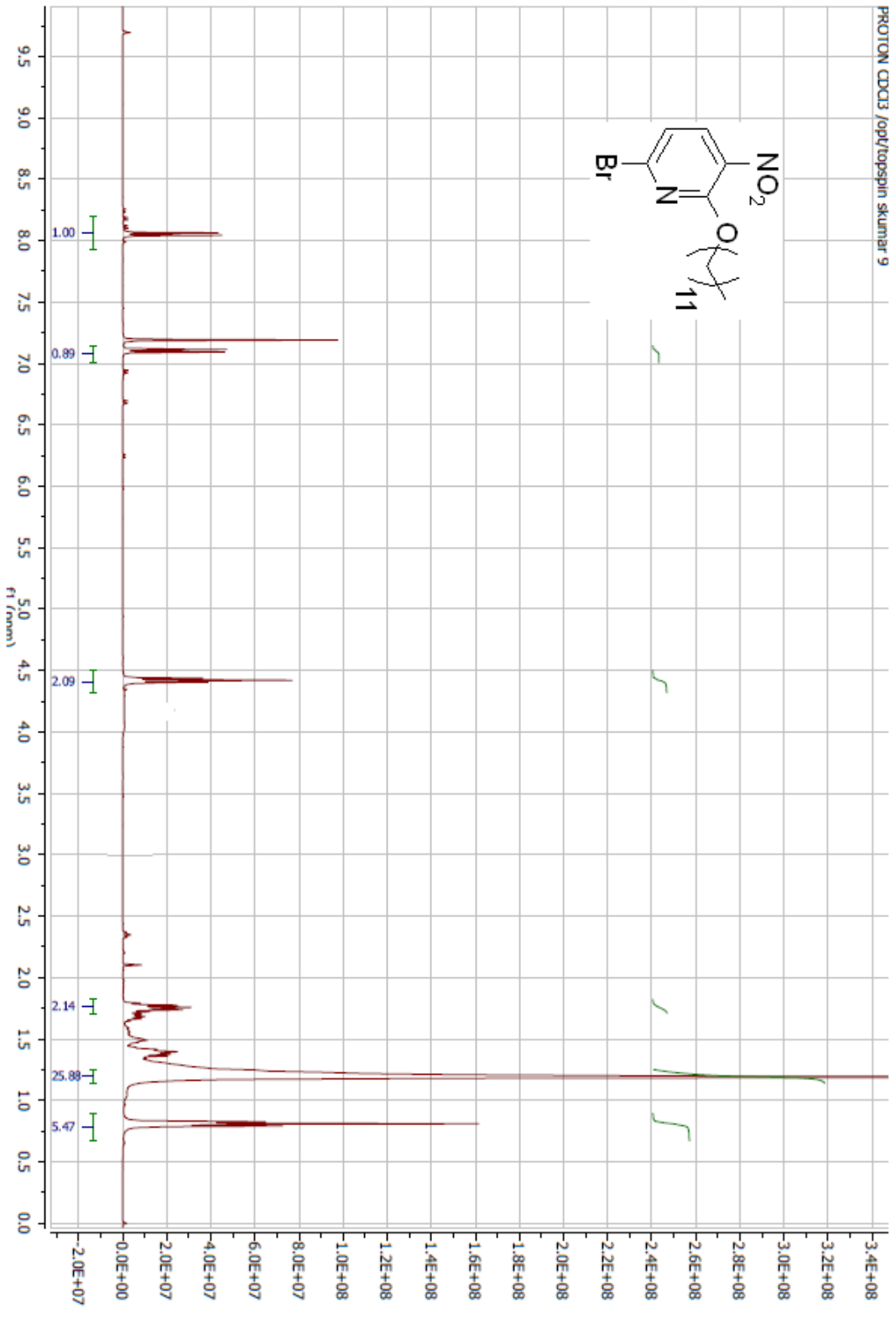


Figure S27. ^{1}H-NMR of O-Dodecane (in $CDCl_3$).

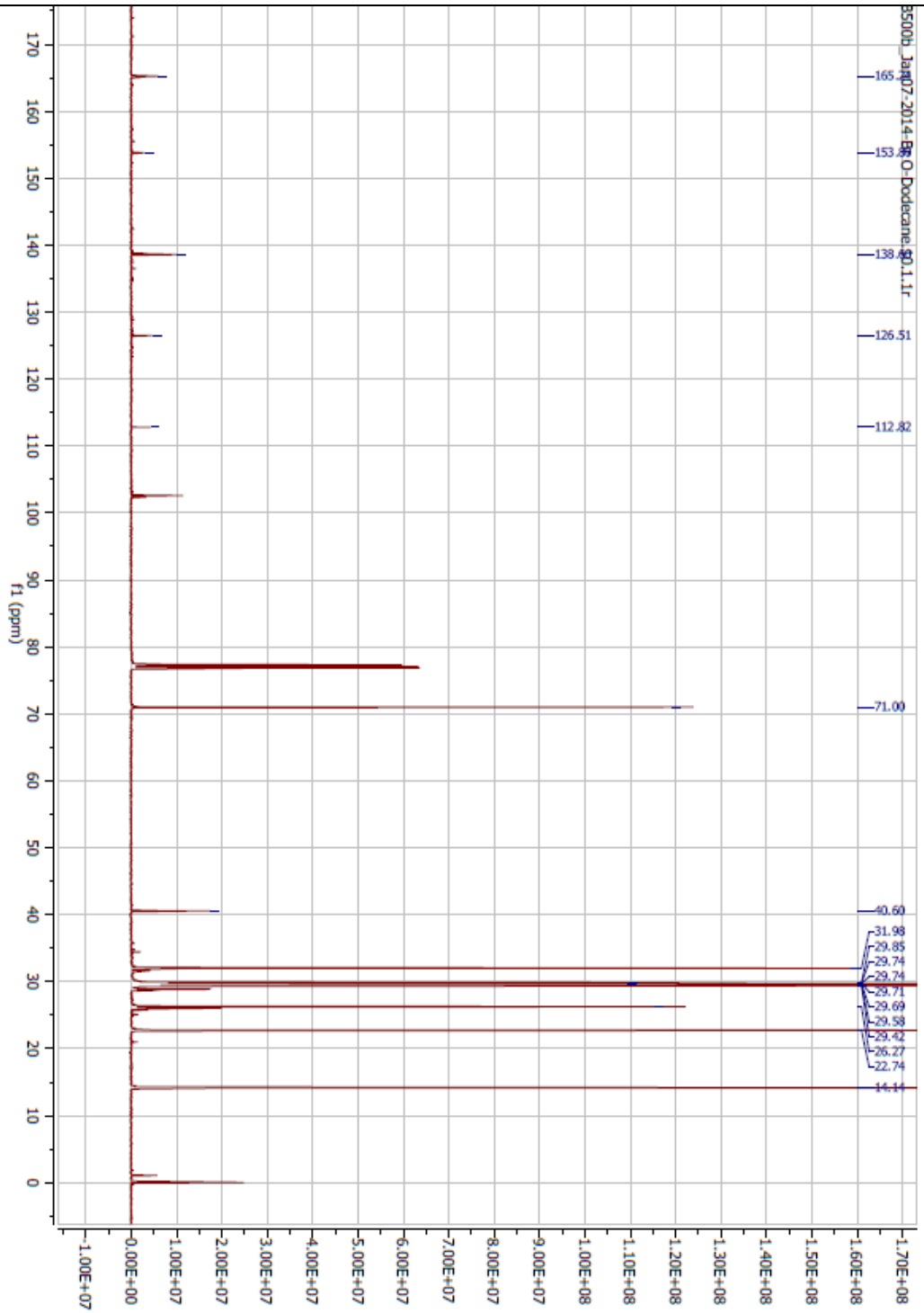


Figure S28. ^{13}C-NMR of O-Dodecane (in $CDCl_3$).

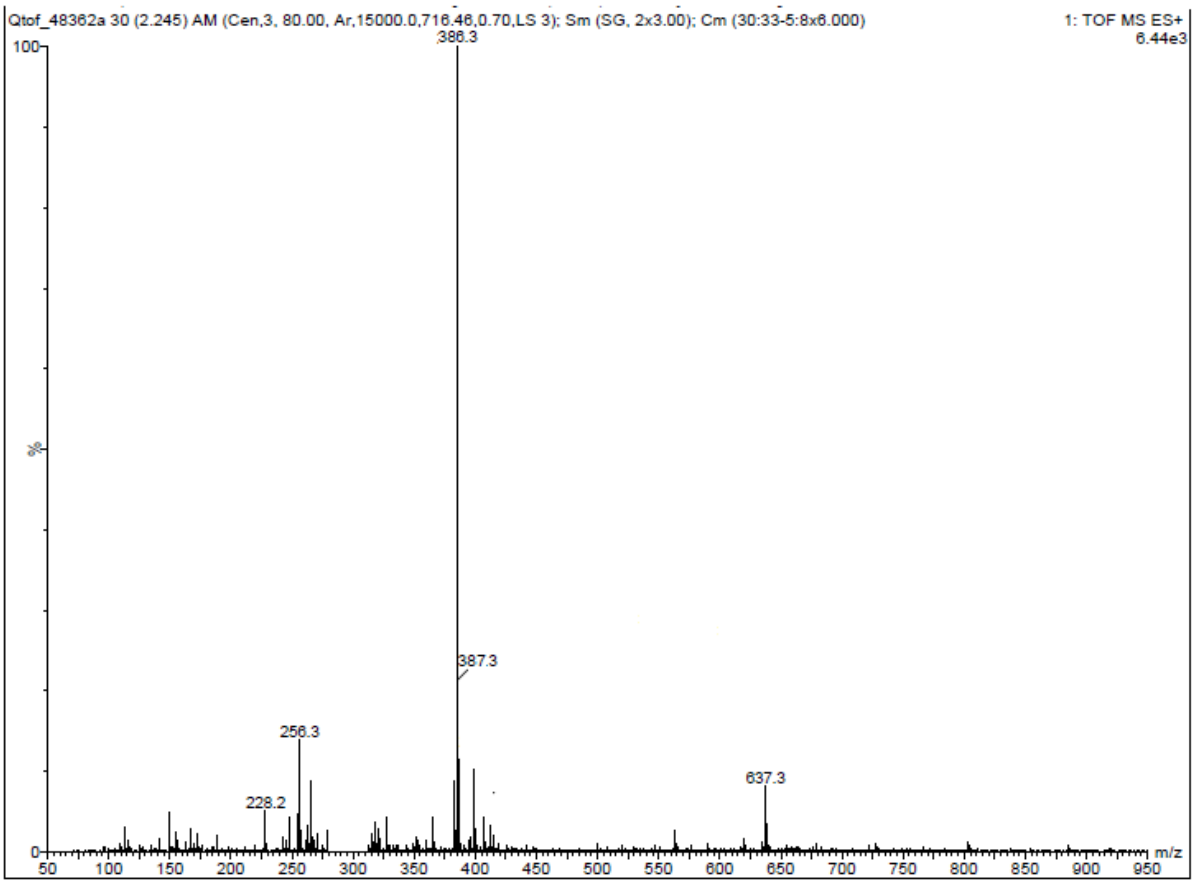


Figure S29. MS-ESI of O-Dodecane.

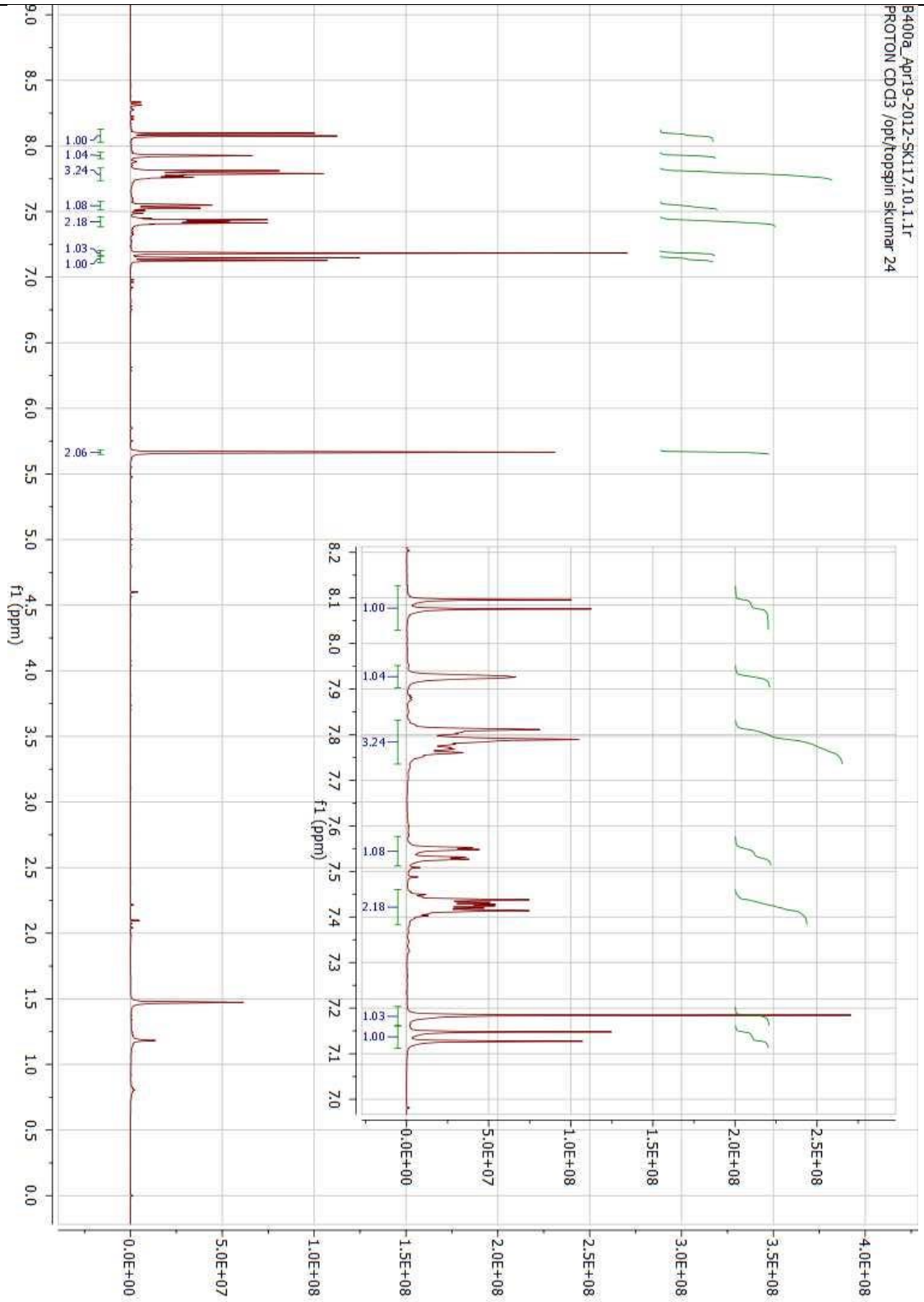


Figure S30. ^{1}H-NMR of O-Naphthalene (in $CDCl_3$).

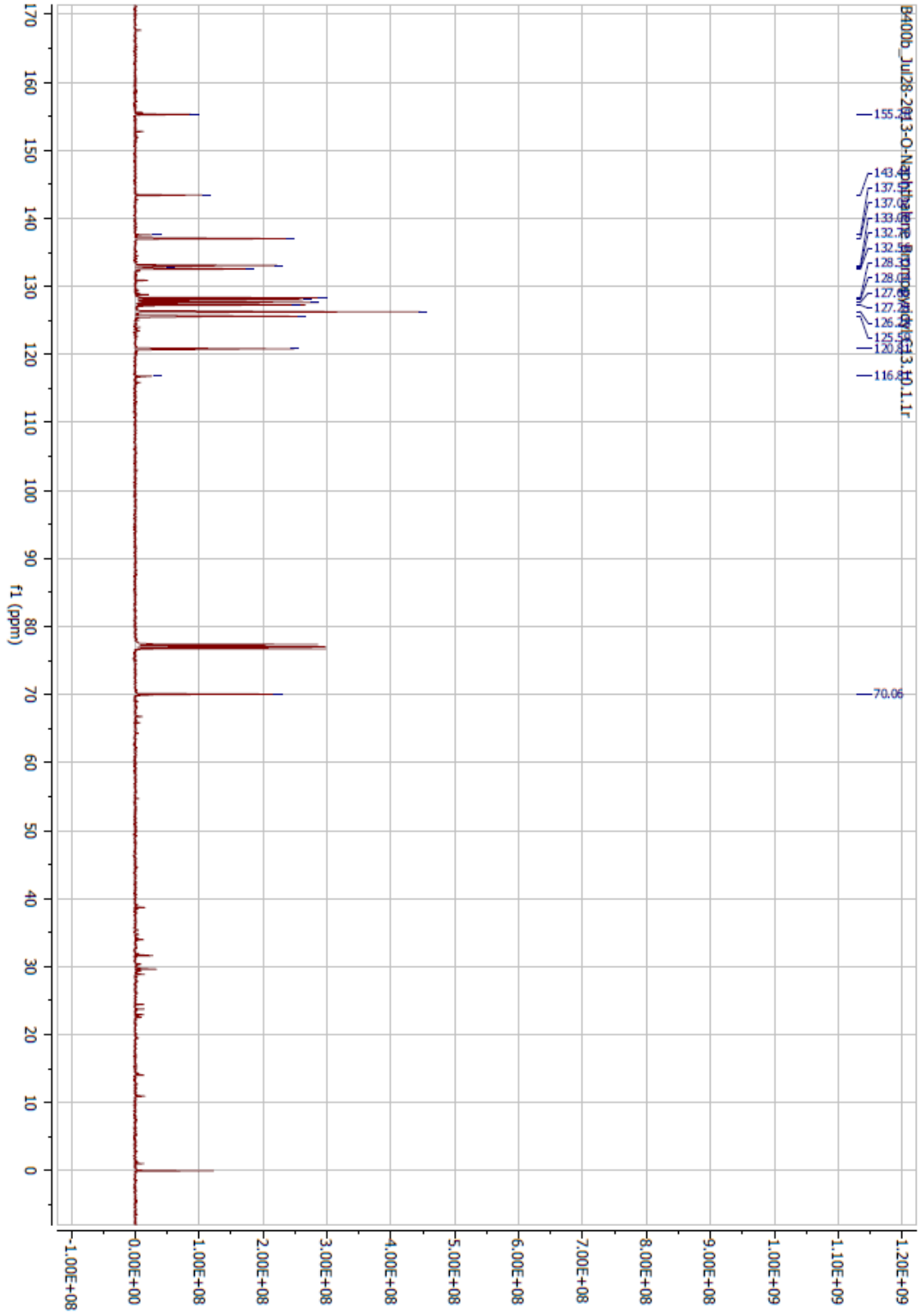


Figure S31. ^{13}C-NMR of O-Naphthalene (in $CDCl_3$).

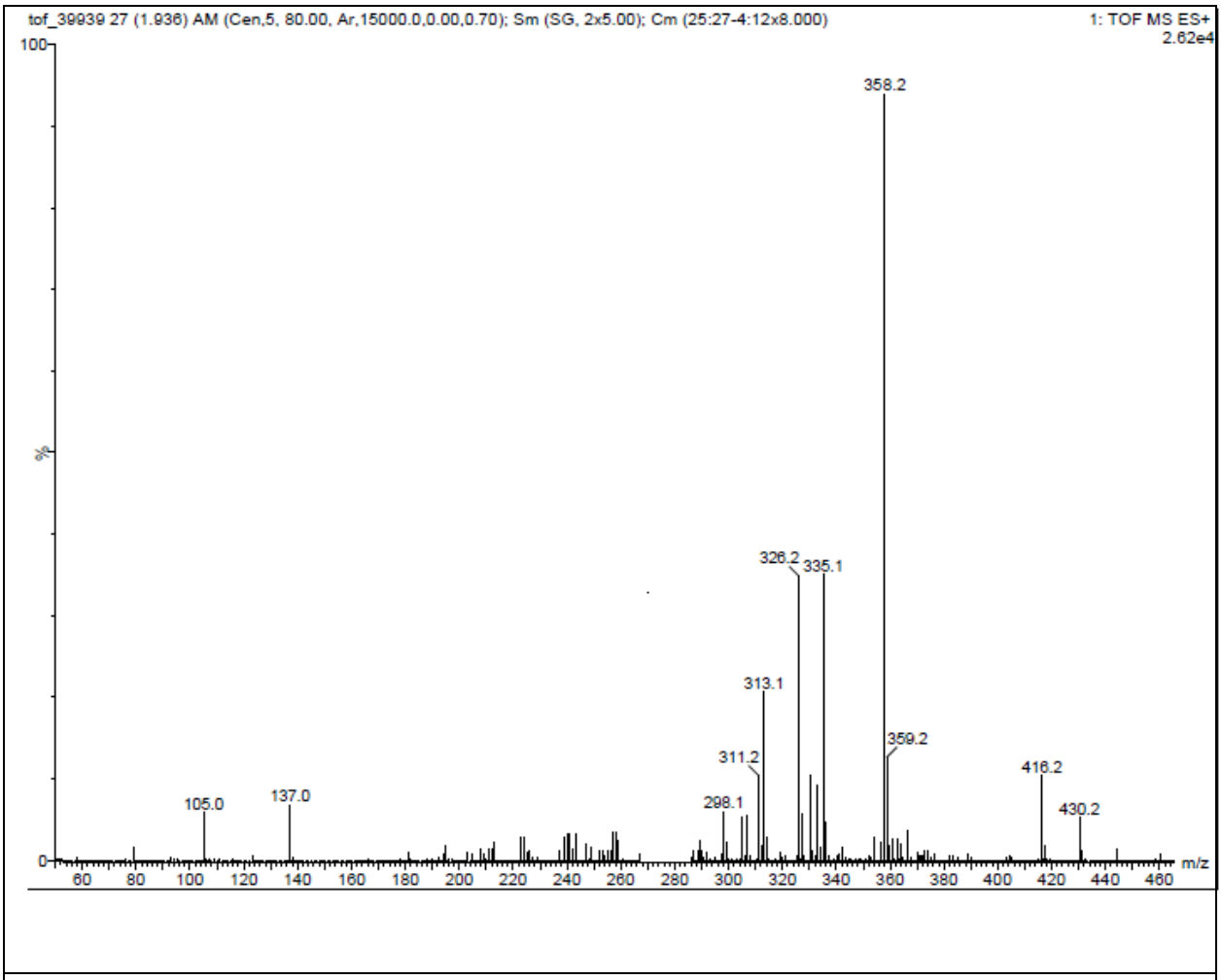


Figure S32. MS-ESI of O-Naphthalene.

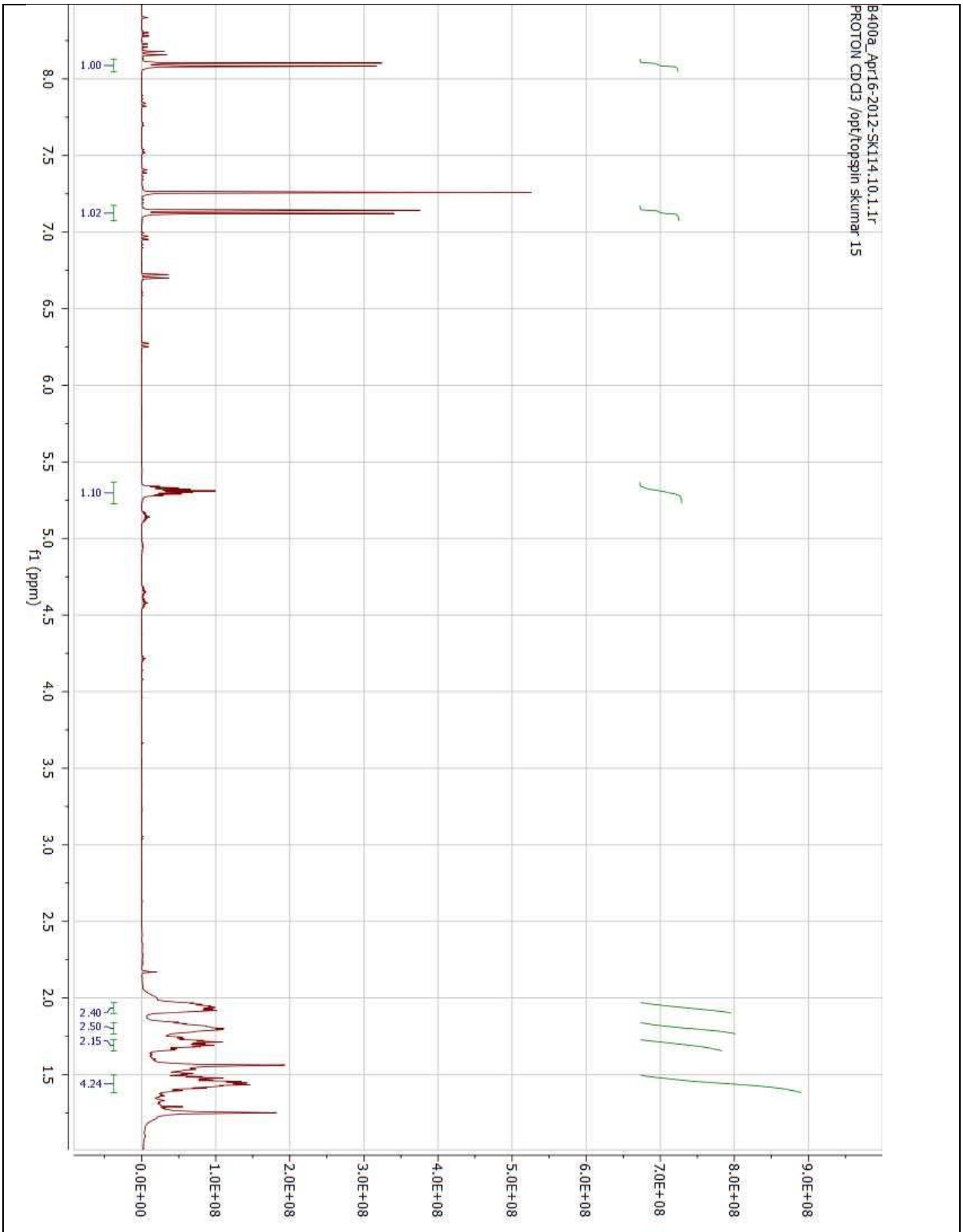


Figure S33. ^{1}H-NMR of O-Cyclohexane (in $CDCl_3$).

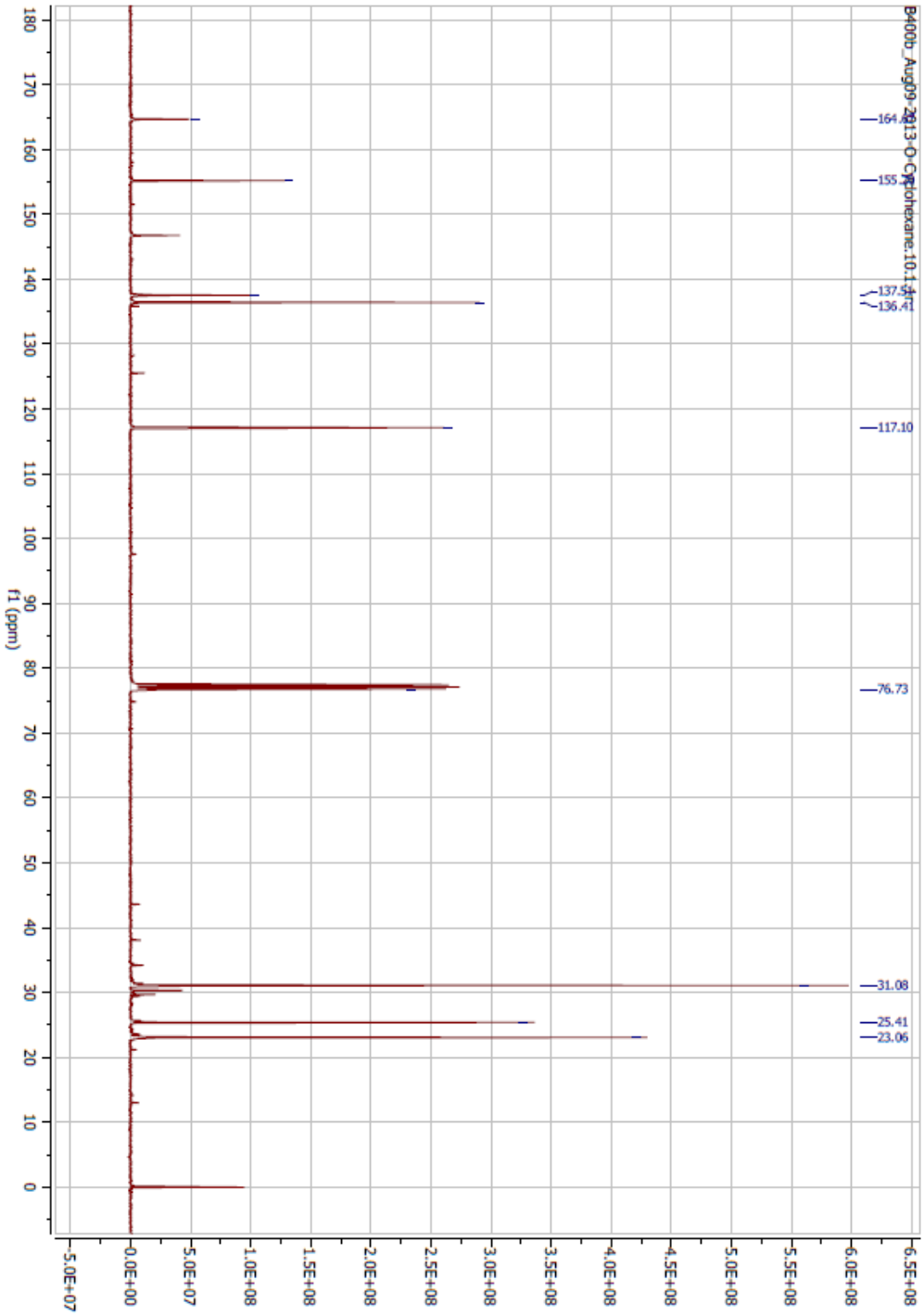


Figure S34. ^{13}C-NMR of O-Cyclohexane (in $CDCl_3$).

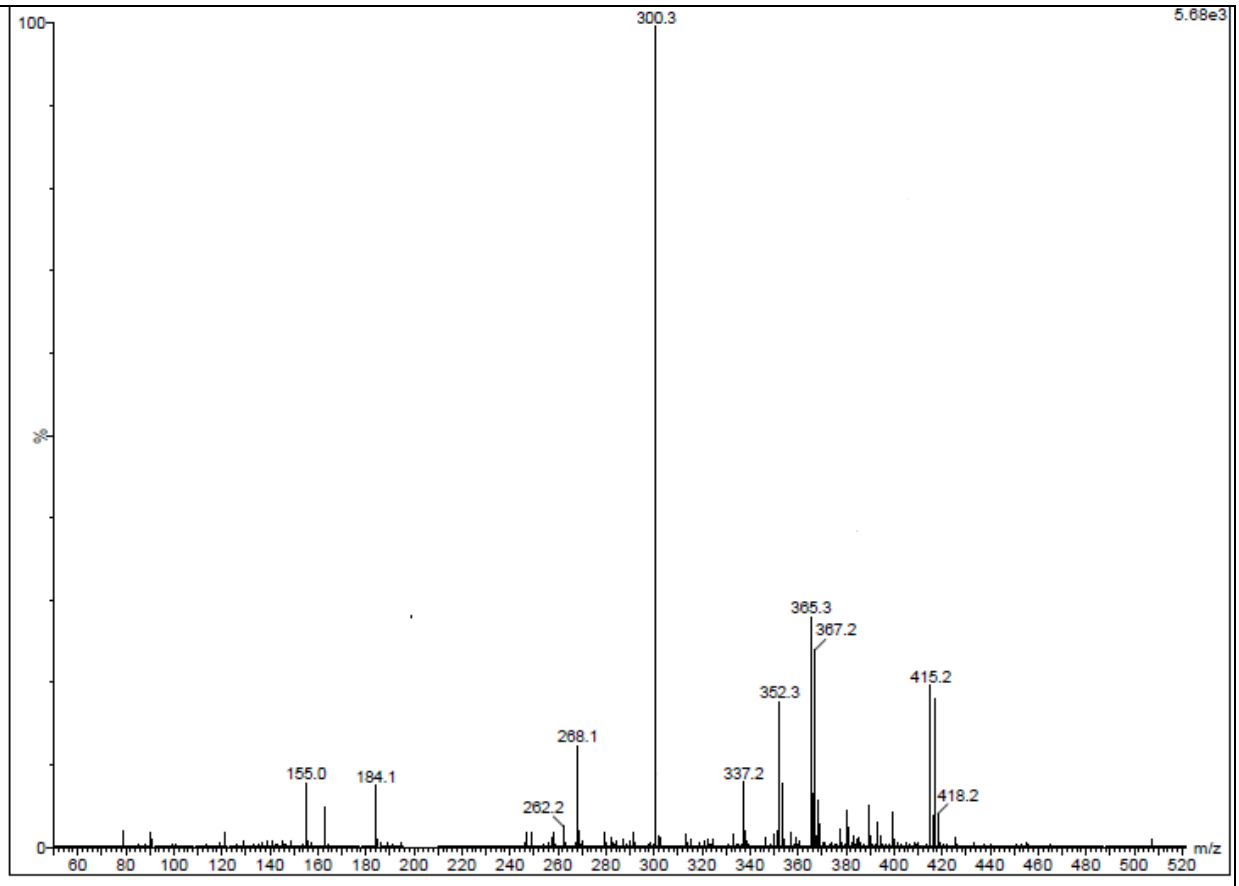


Figure S35. MS-ESI of O-Cyclohexane.

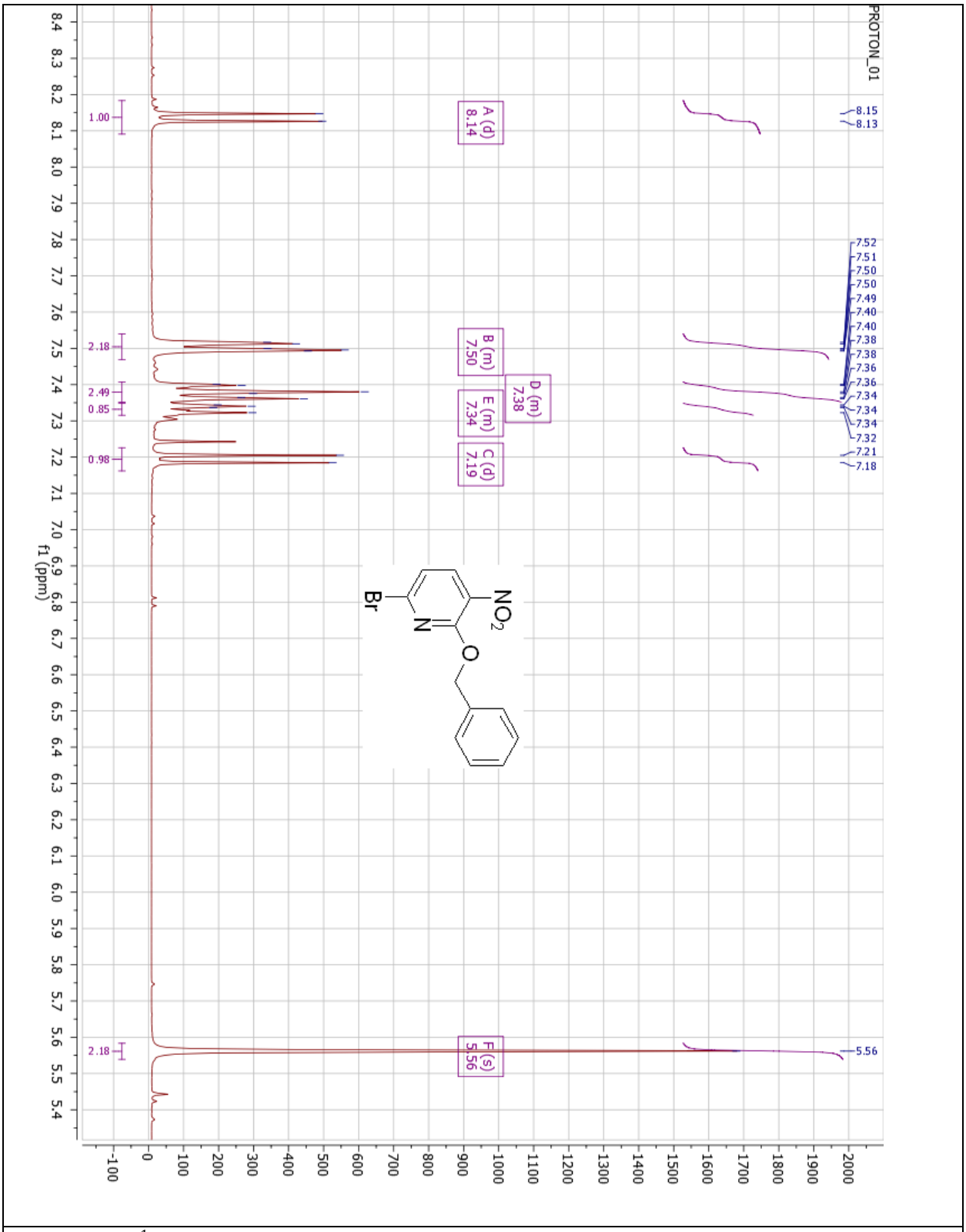


Figure S36. ^{1}H-NMR of O-Benzyl (in $CDCl_3$).

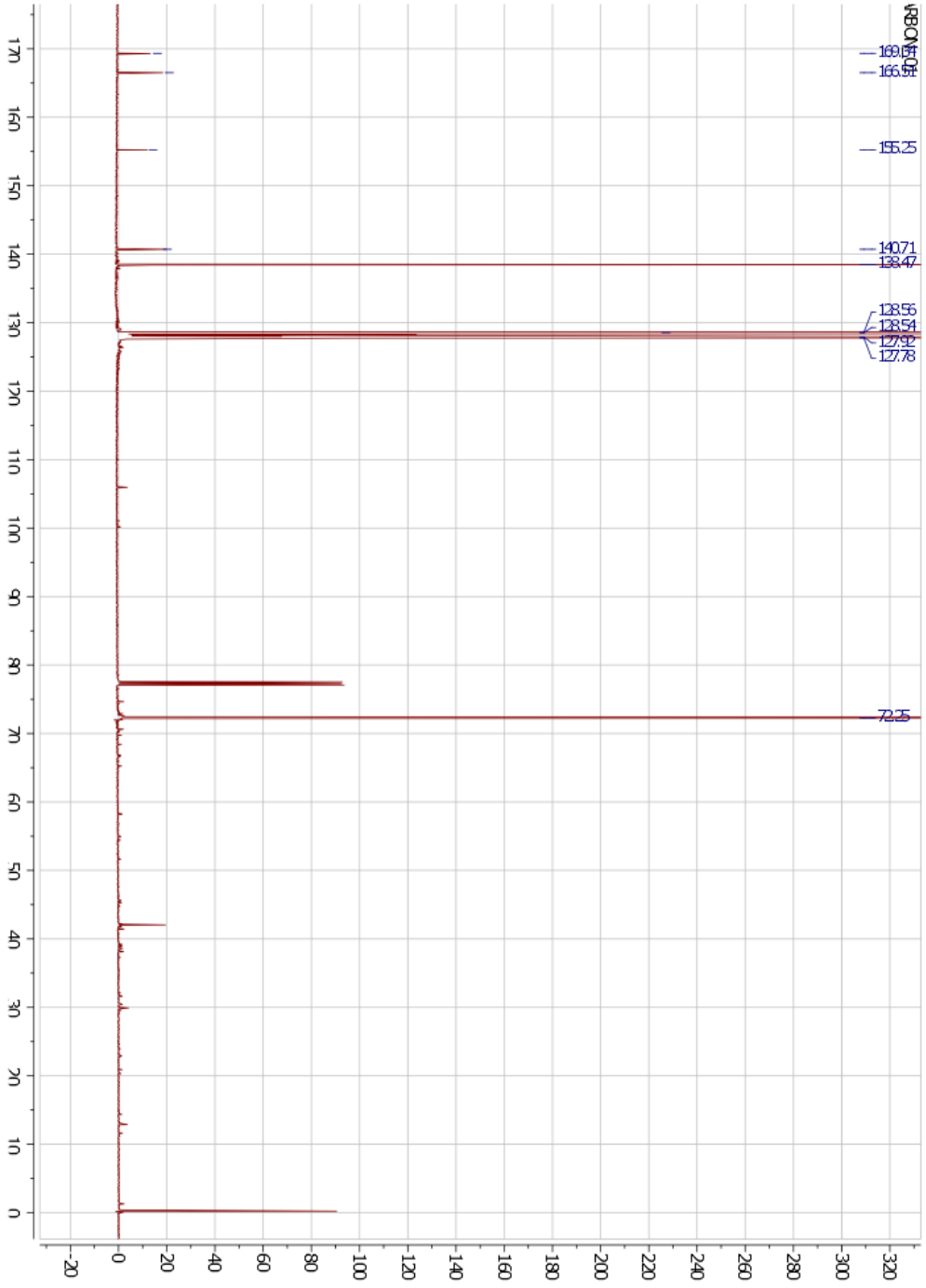


Figure S37. ^{13}C-NMR of O-Benzyl (in $CDCl_3$).

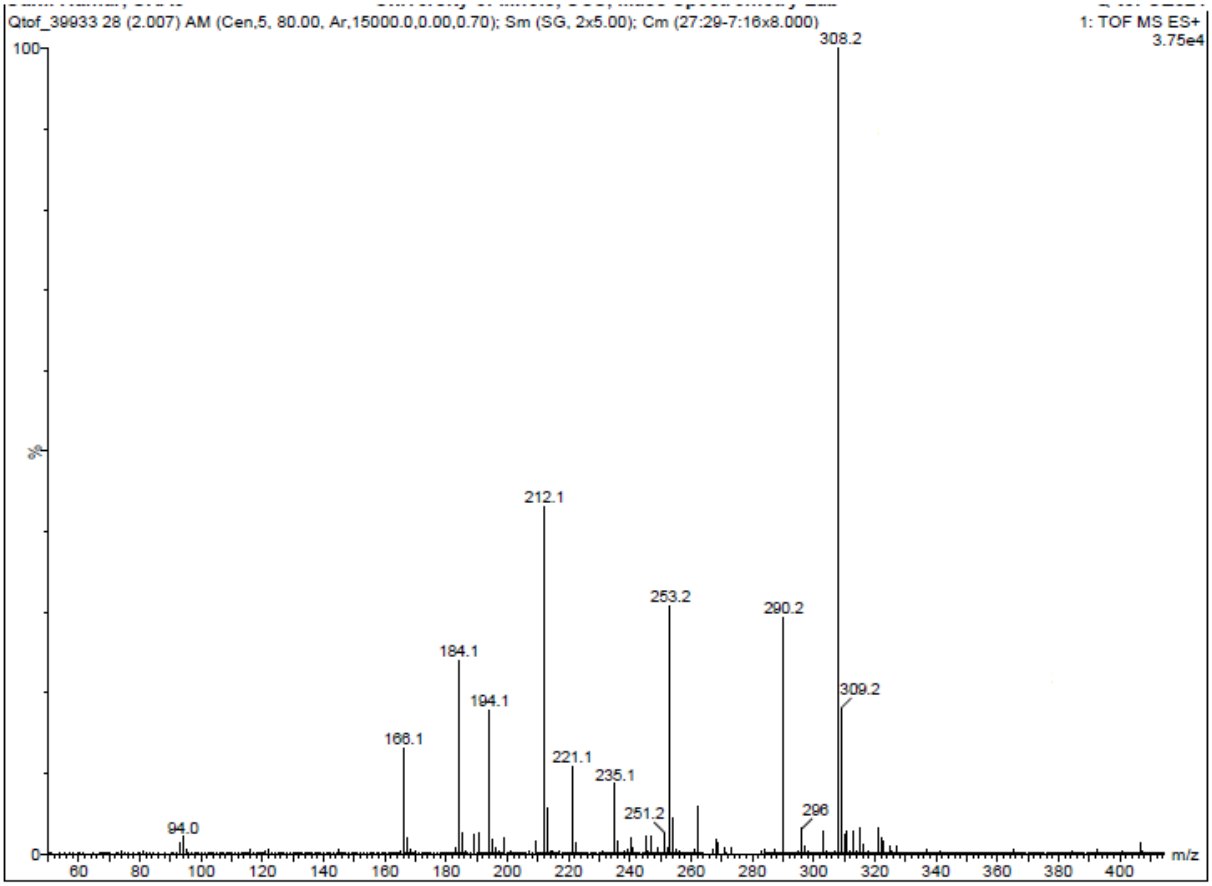


Figure S38. MS-ESI of O-Benzyl.

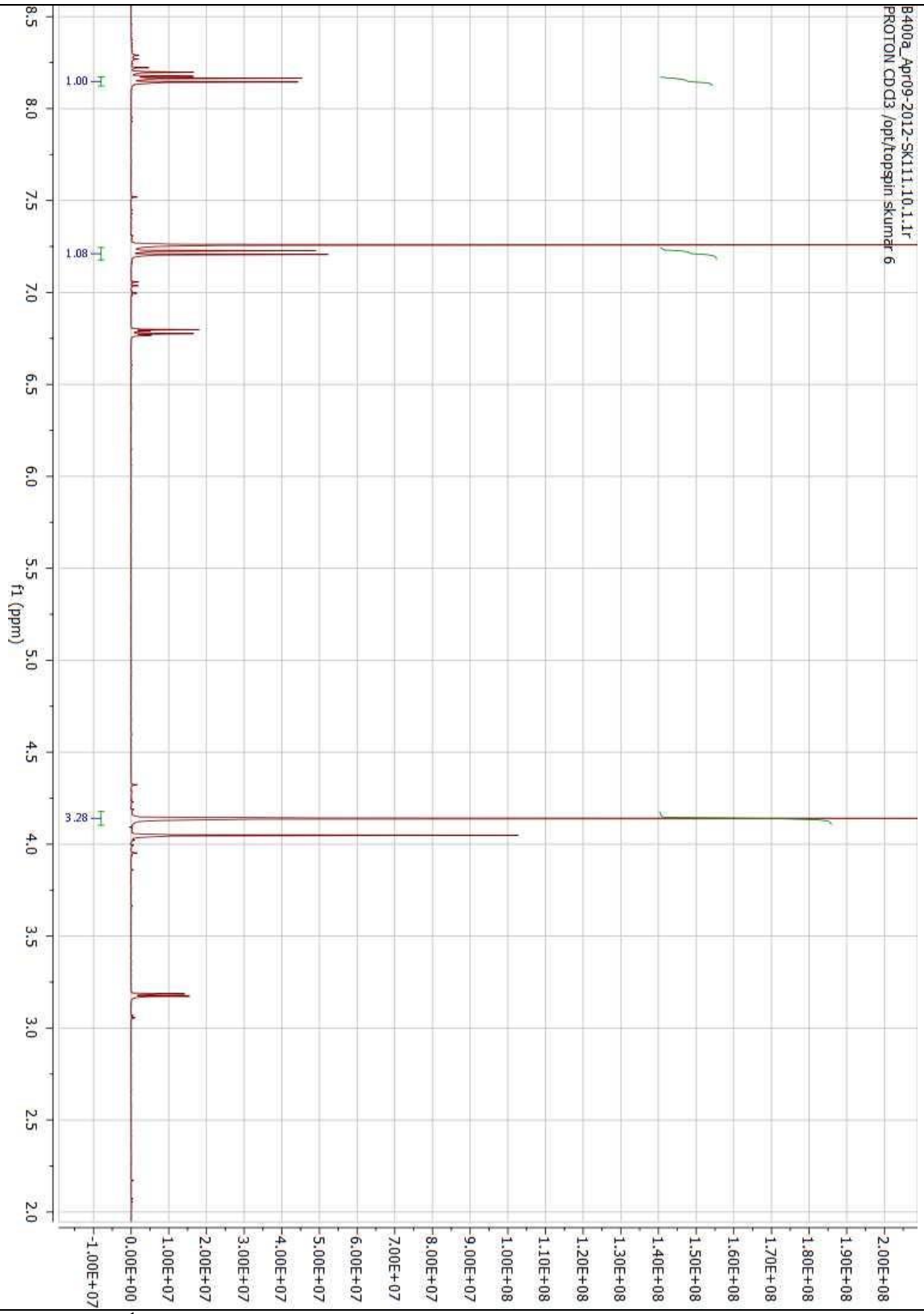


Figure S39. ^{1}H-NMR of O-Methyl (in $CDCl_3$).

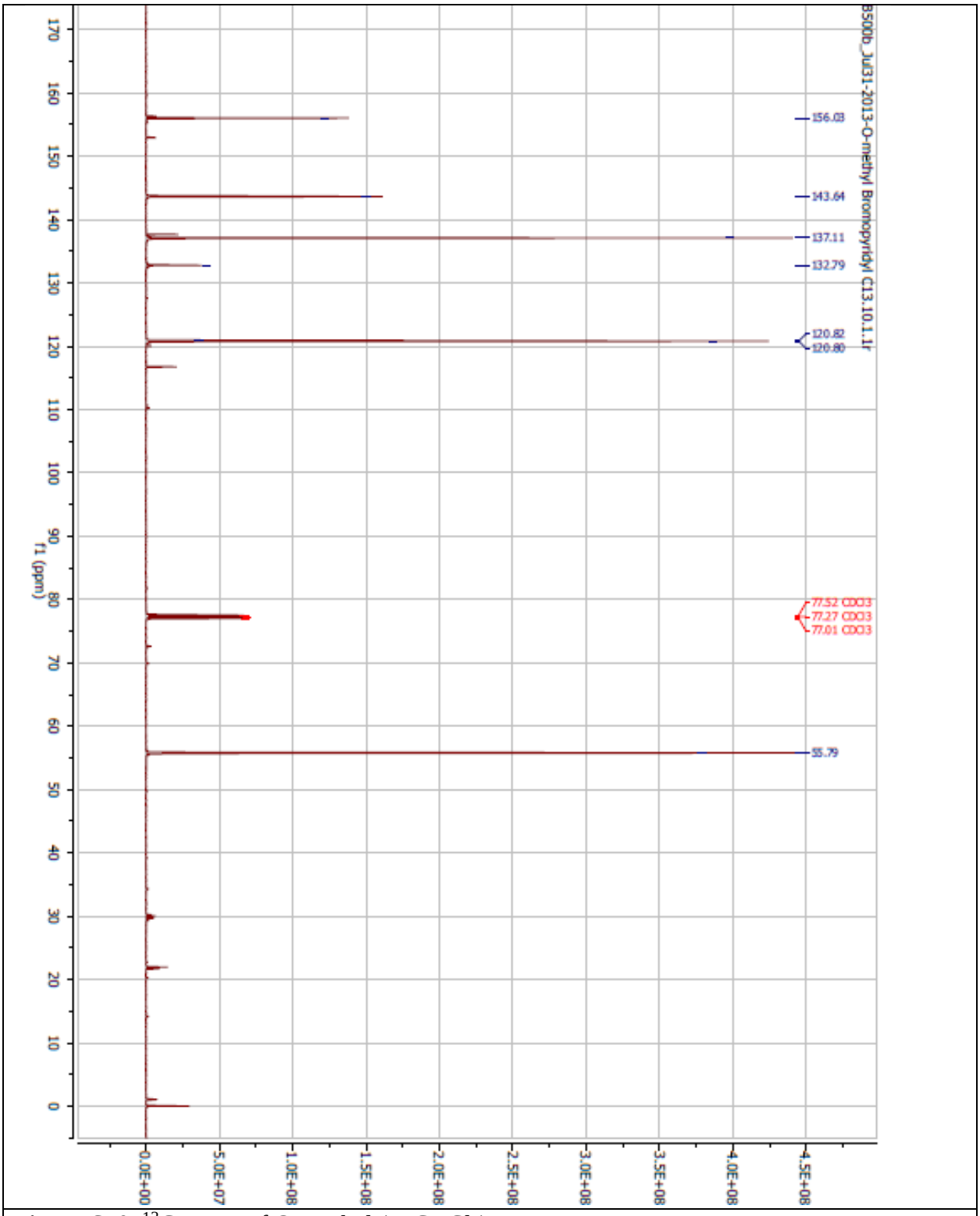


Figure S40. ^{13}C-NMR of O-Methyl (in $CDCl_3$).

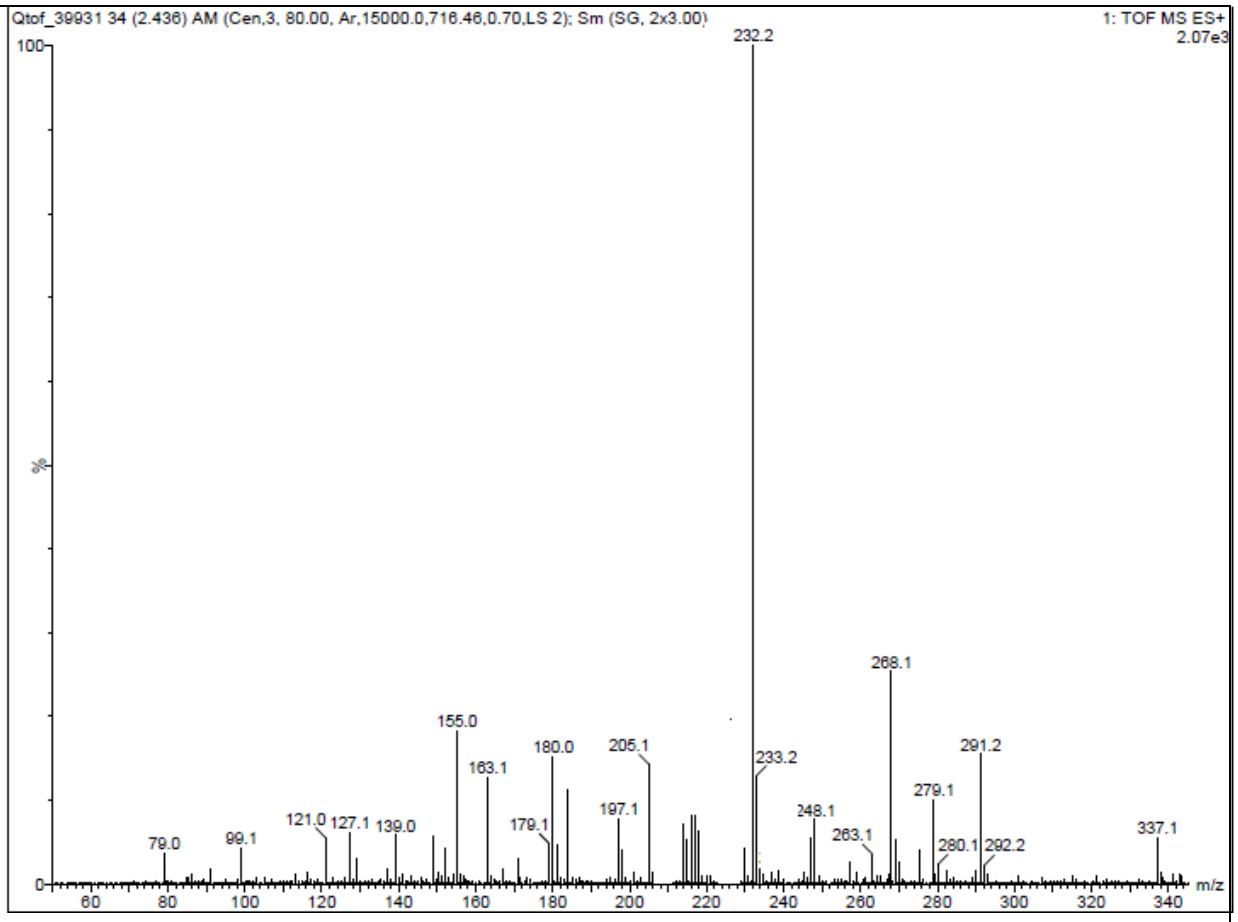


Figure S41. MS-ESI of O-Methyl.

Series 2.

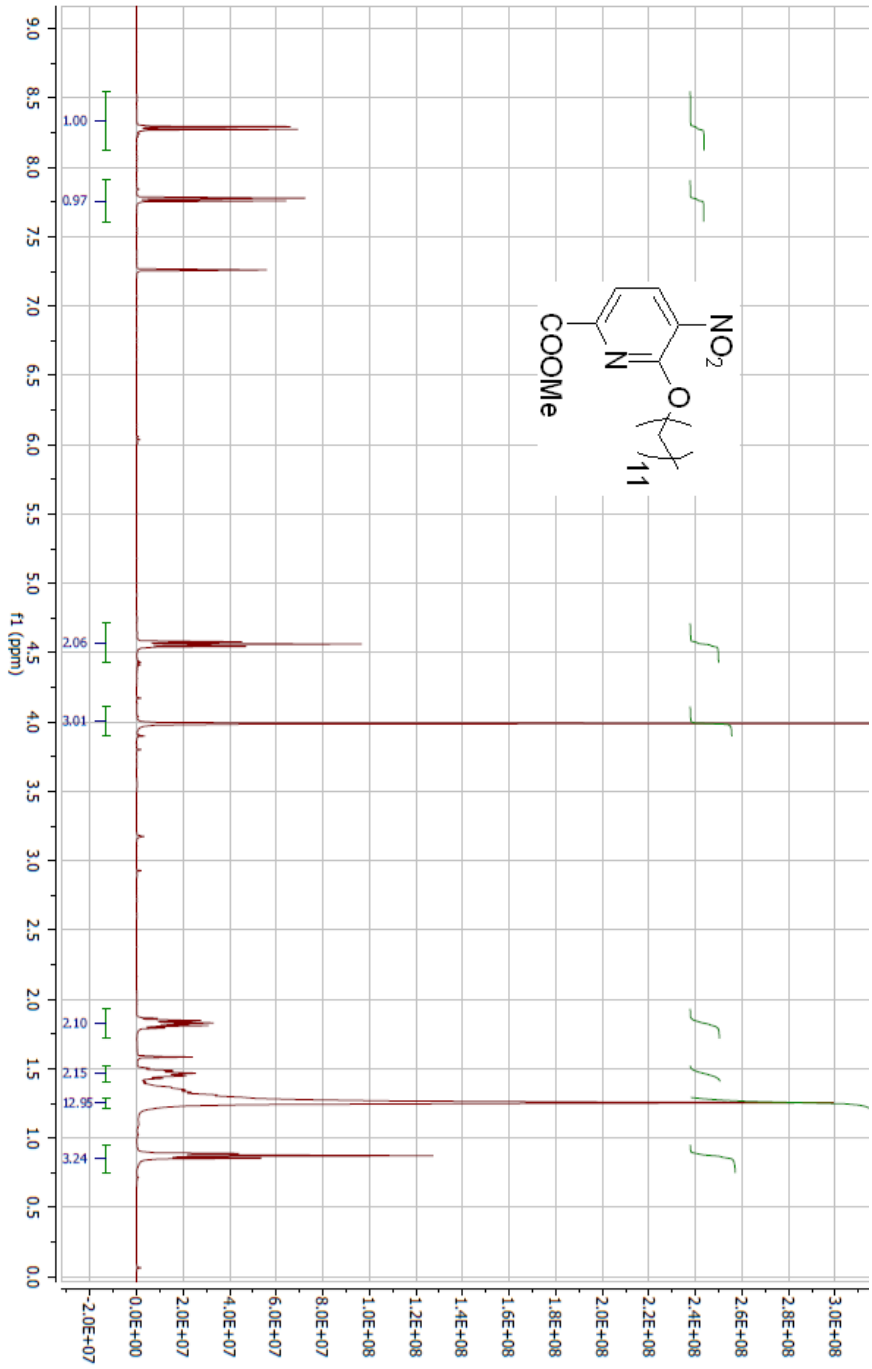


Figure S42. ^{1}H-NMR of O-Dodecane (in $CDCl_3$).

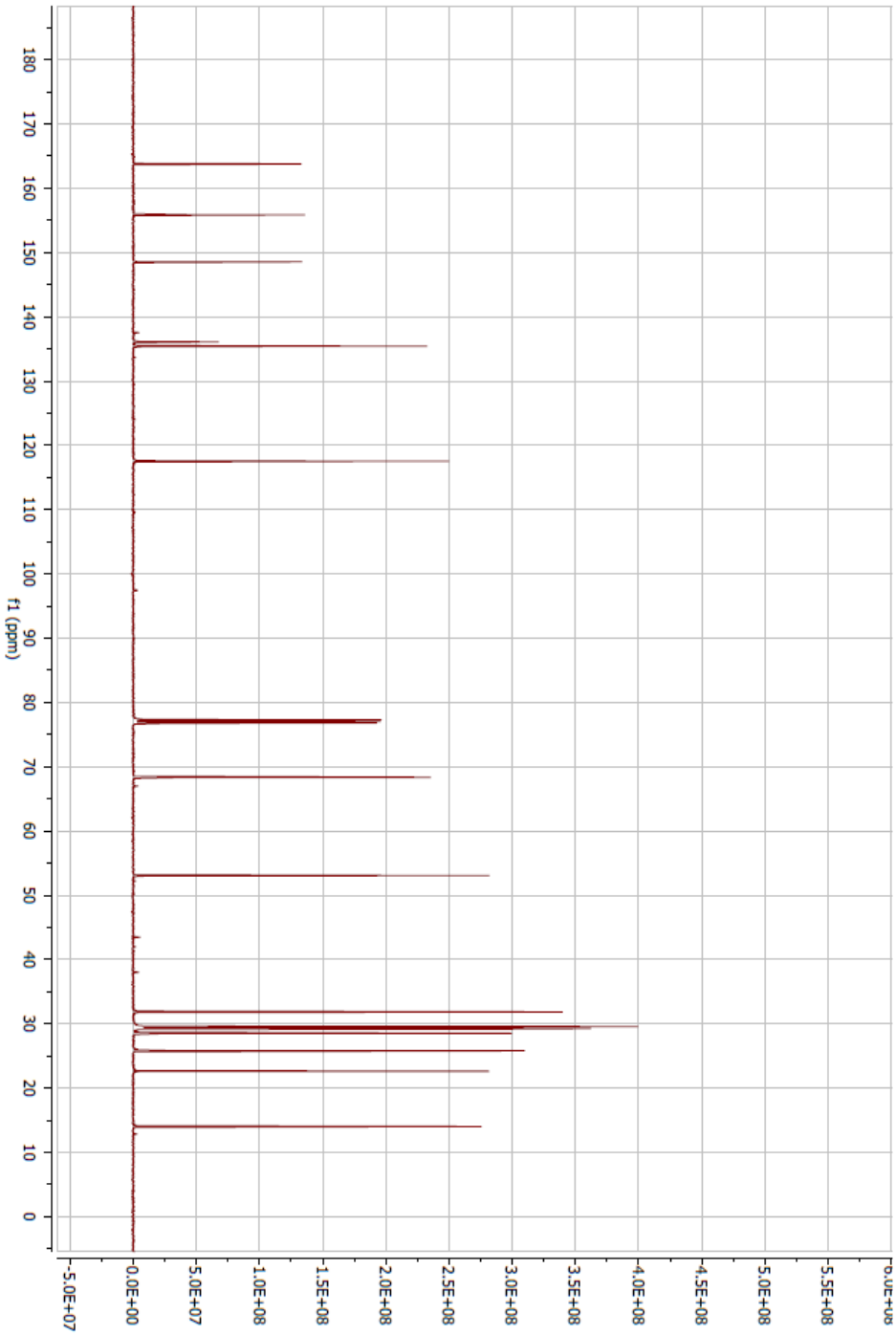


Figure S43. ^{13}C-NMR of O-Dodecane (in $CDCl_3$).

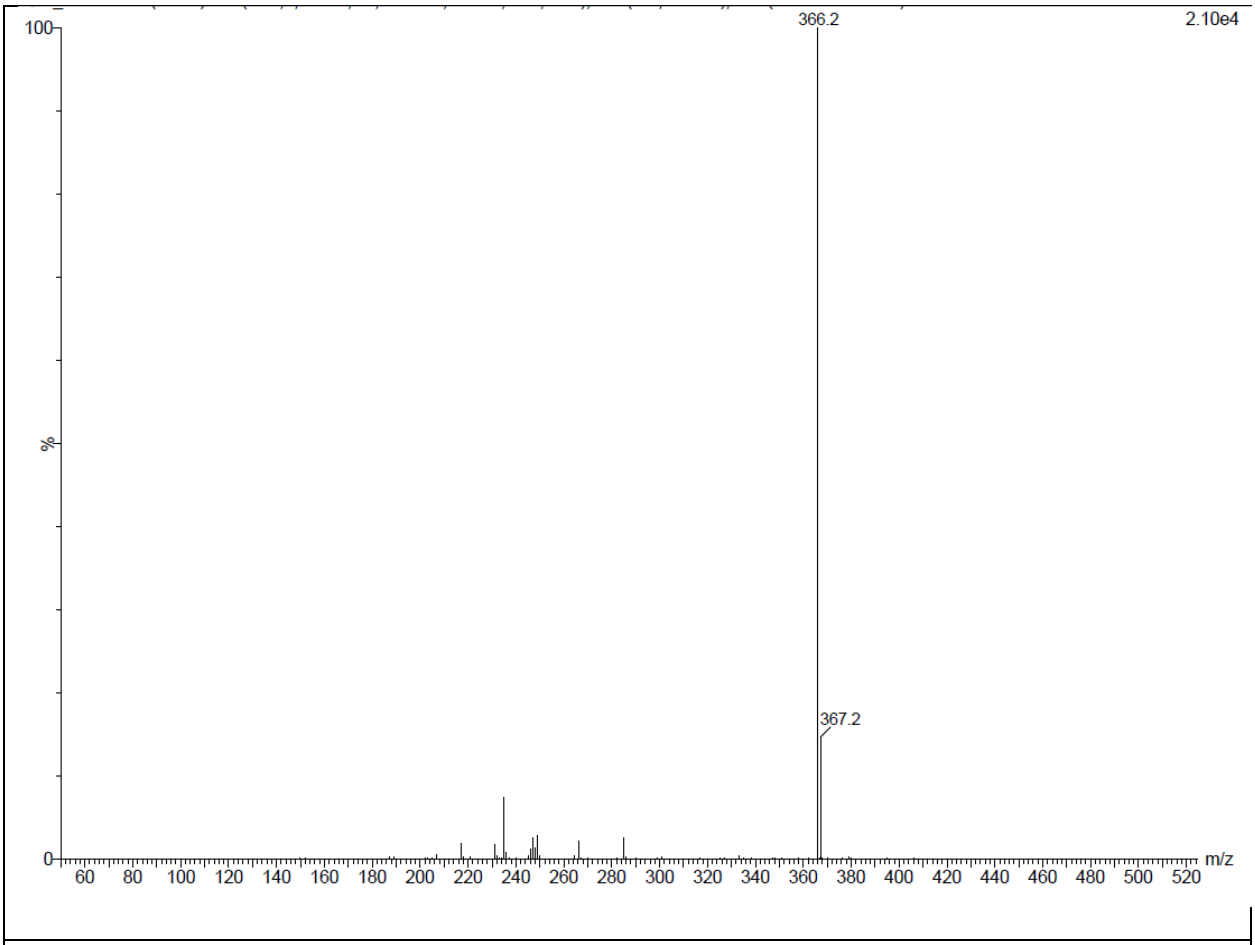


Figure S44. MS-ESI of O-Dodecane (in $CDCl_3$).

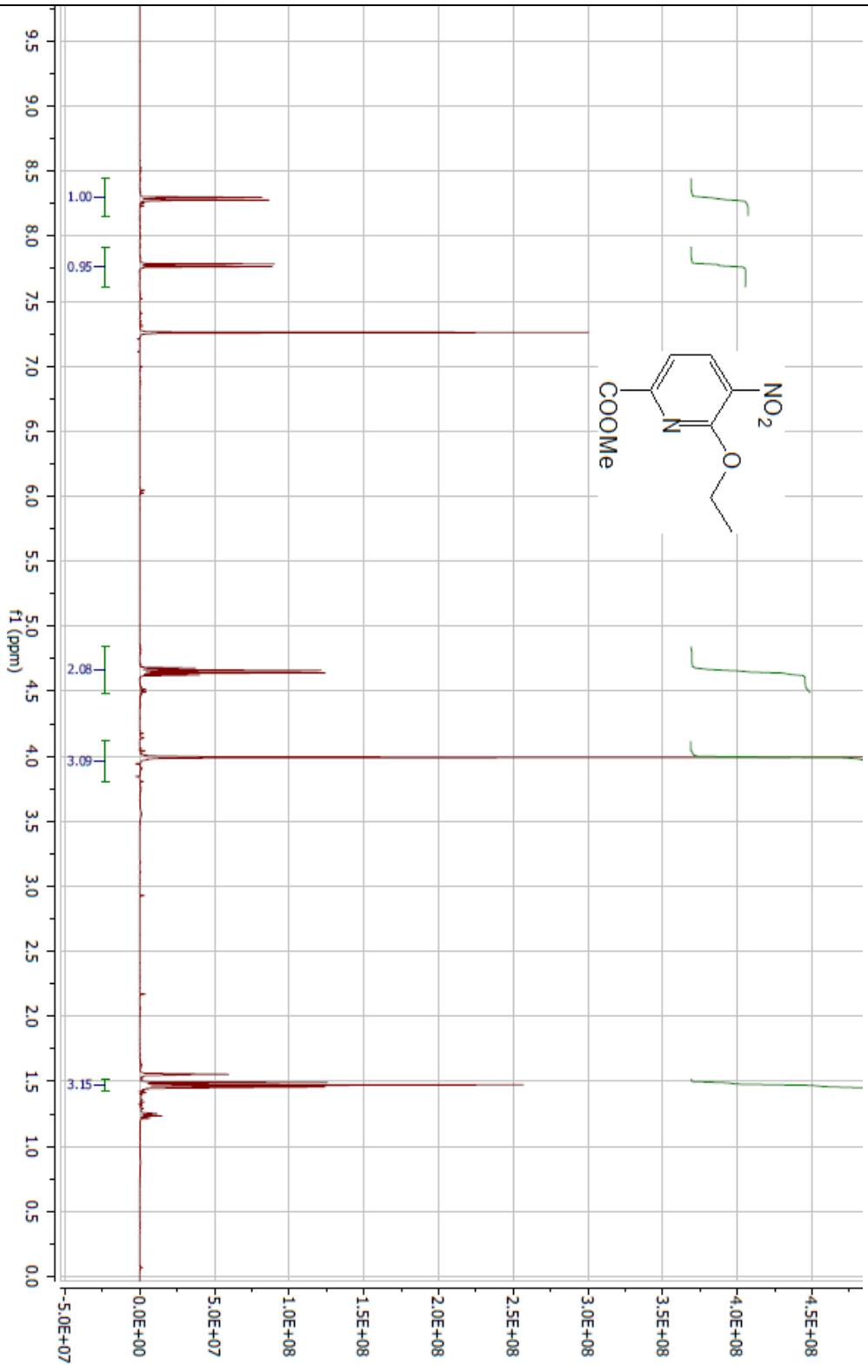


Figure S45. ^{1}H-NMR of O-Ethyl (in $CDCl_3$).

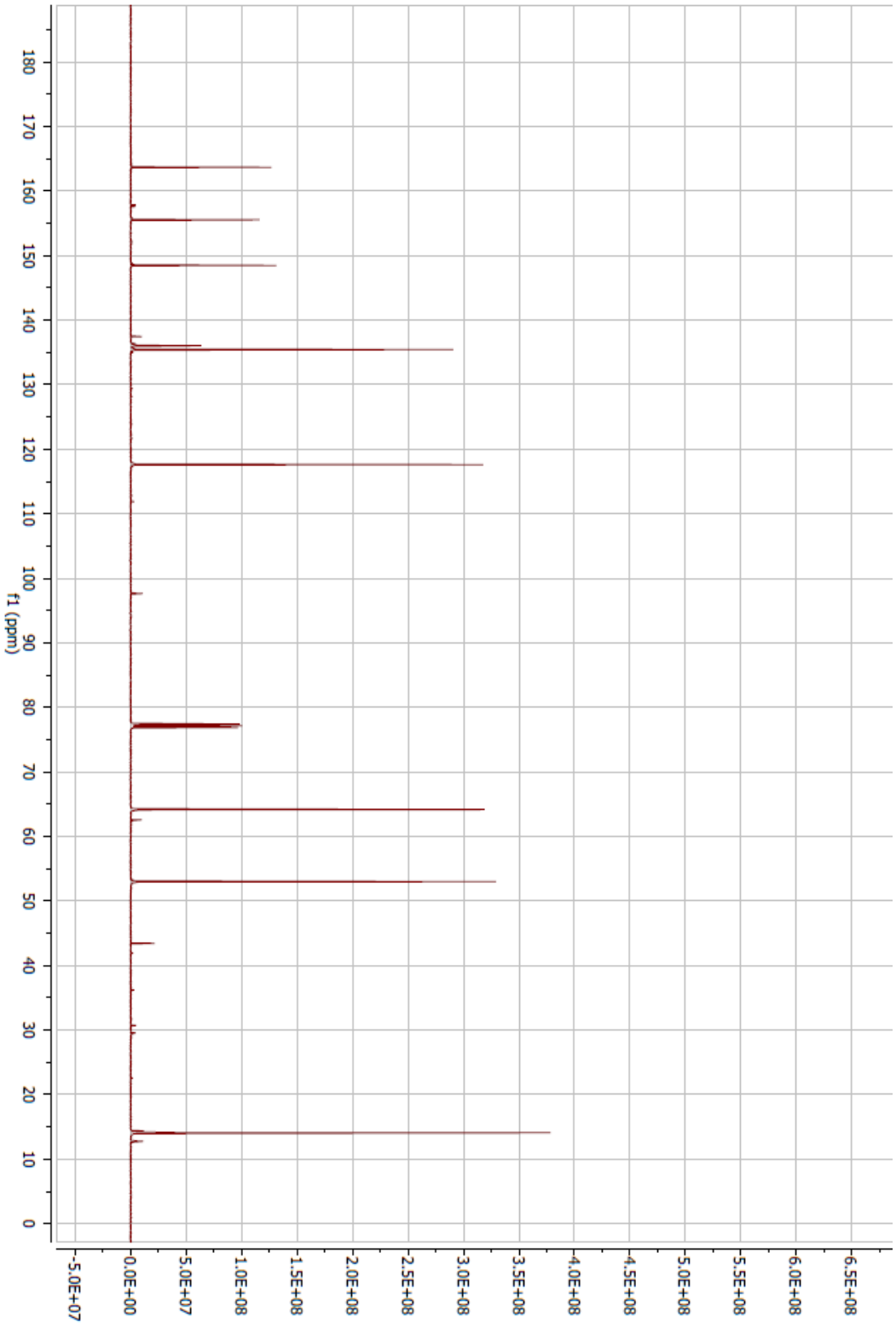


Figure S46. ^{13}C-NMR of O-Ethyl (in $CDCl_3$).

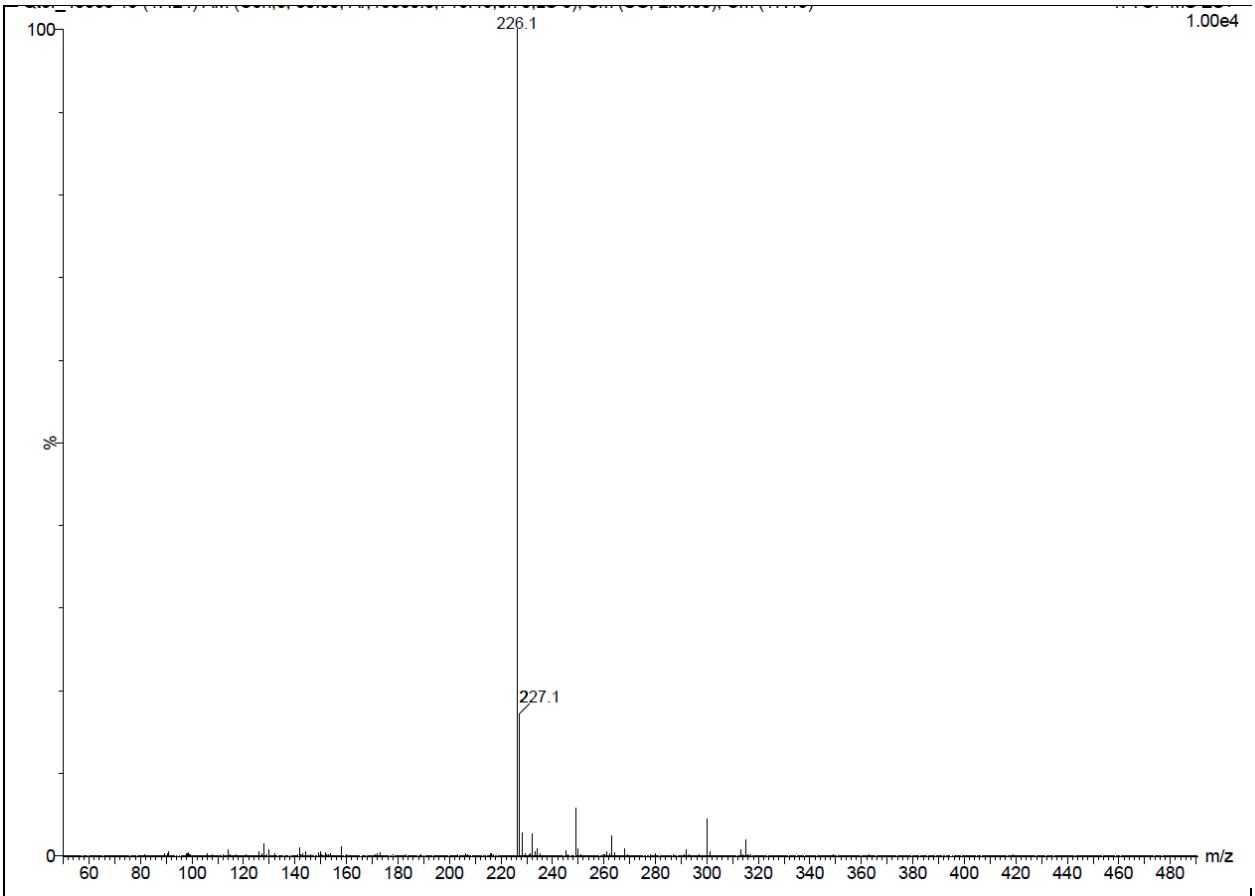


Figure S47. MS-ESI of O-Ethyl (in $CDCl_3$).

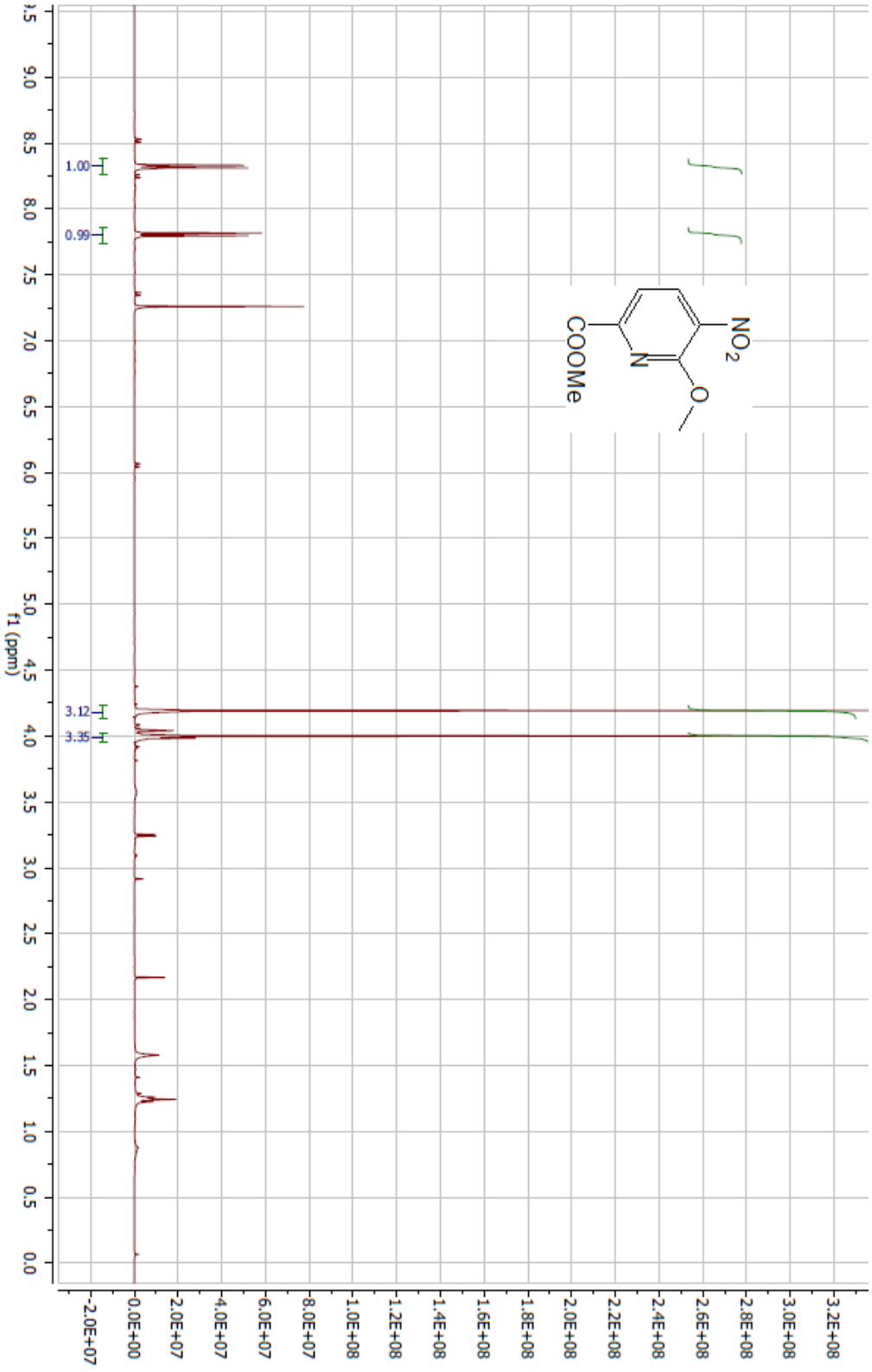


Figure S48. ^{1}H-NMR of O-Methyl (in $CDCl_3$).

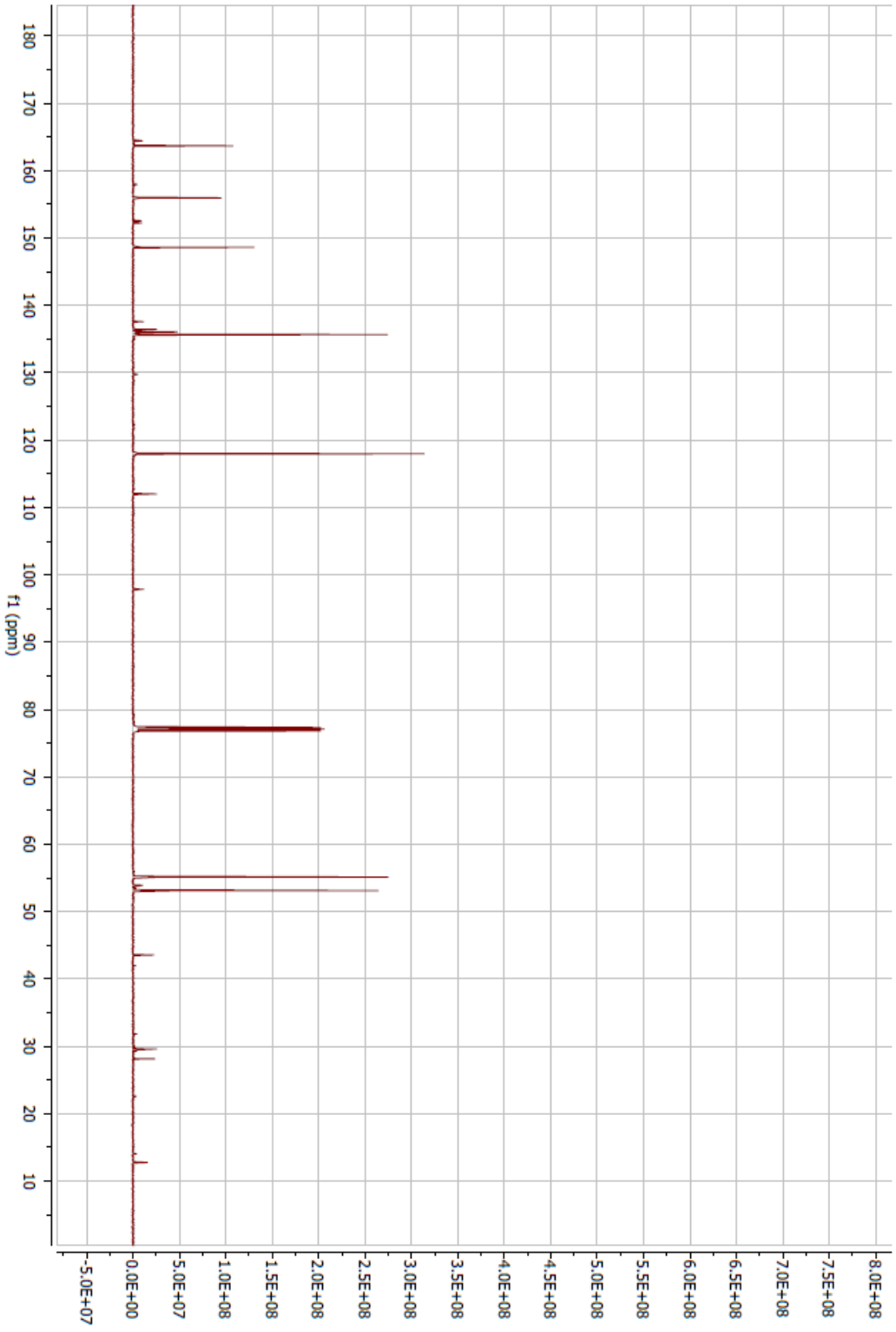


Figure S49. ^{13}C-NMR of O-Methyl (in $CDCl_3$).

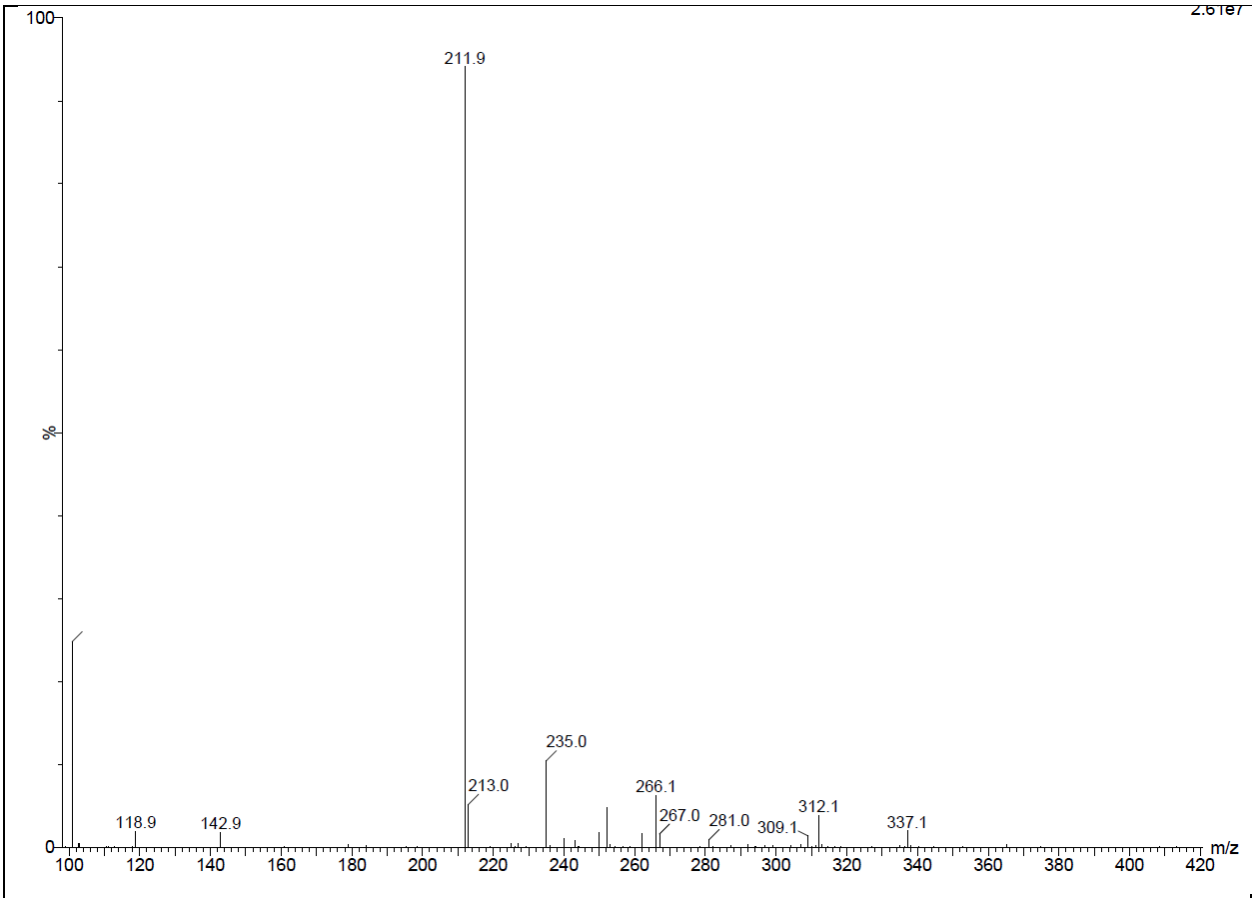


Figure S50. MS-ESI of O-Methyl (in $CDCl_3$).

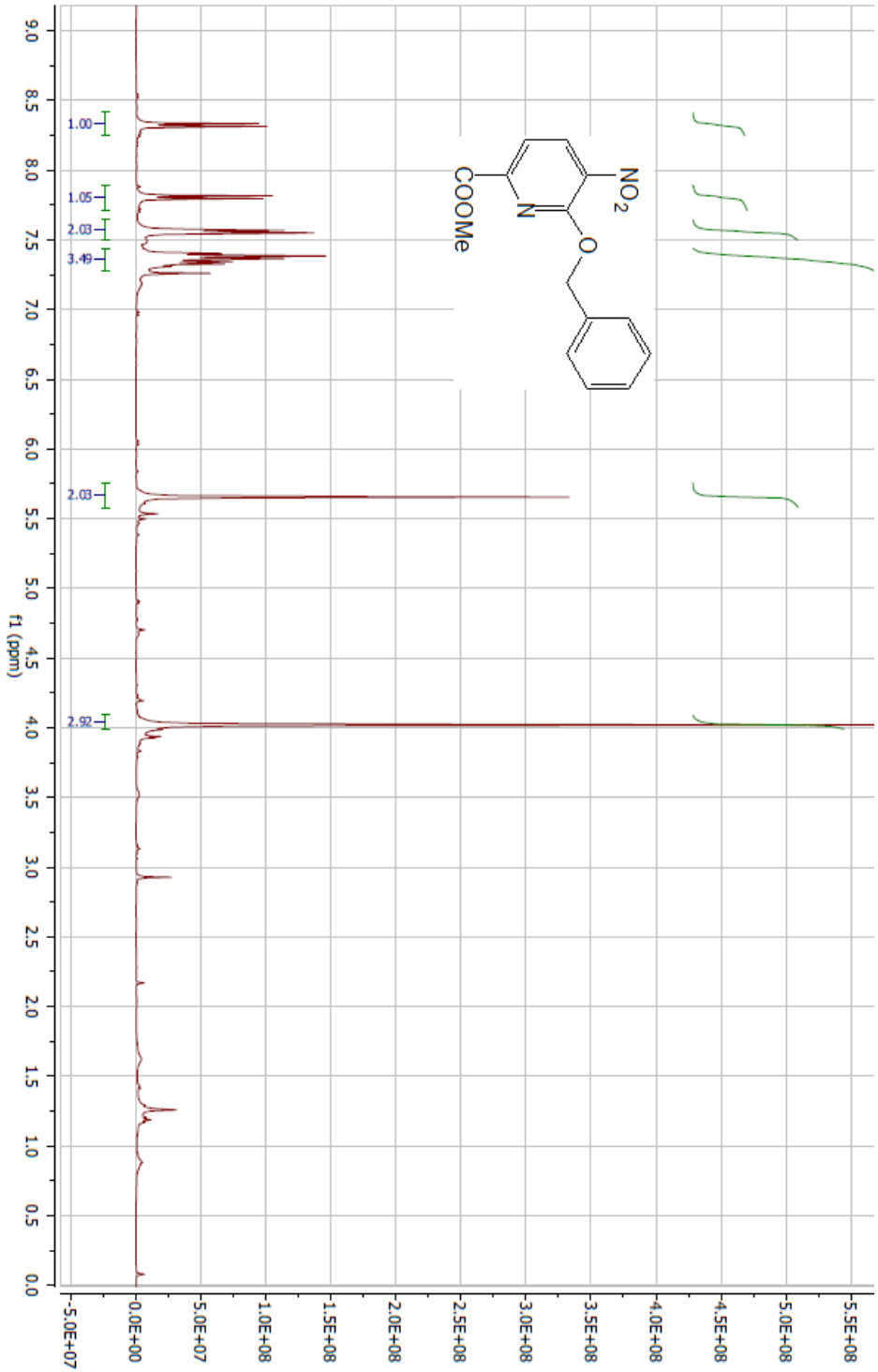


Figure S51. ^{1}H-NMR of O-Benzyl (in $CDCl_3$).

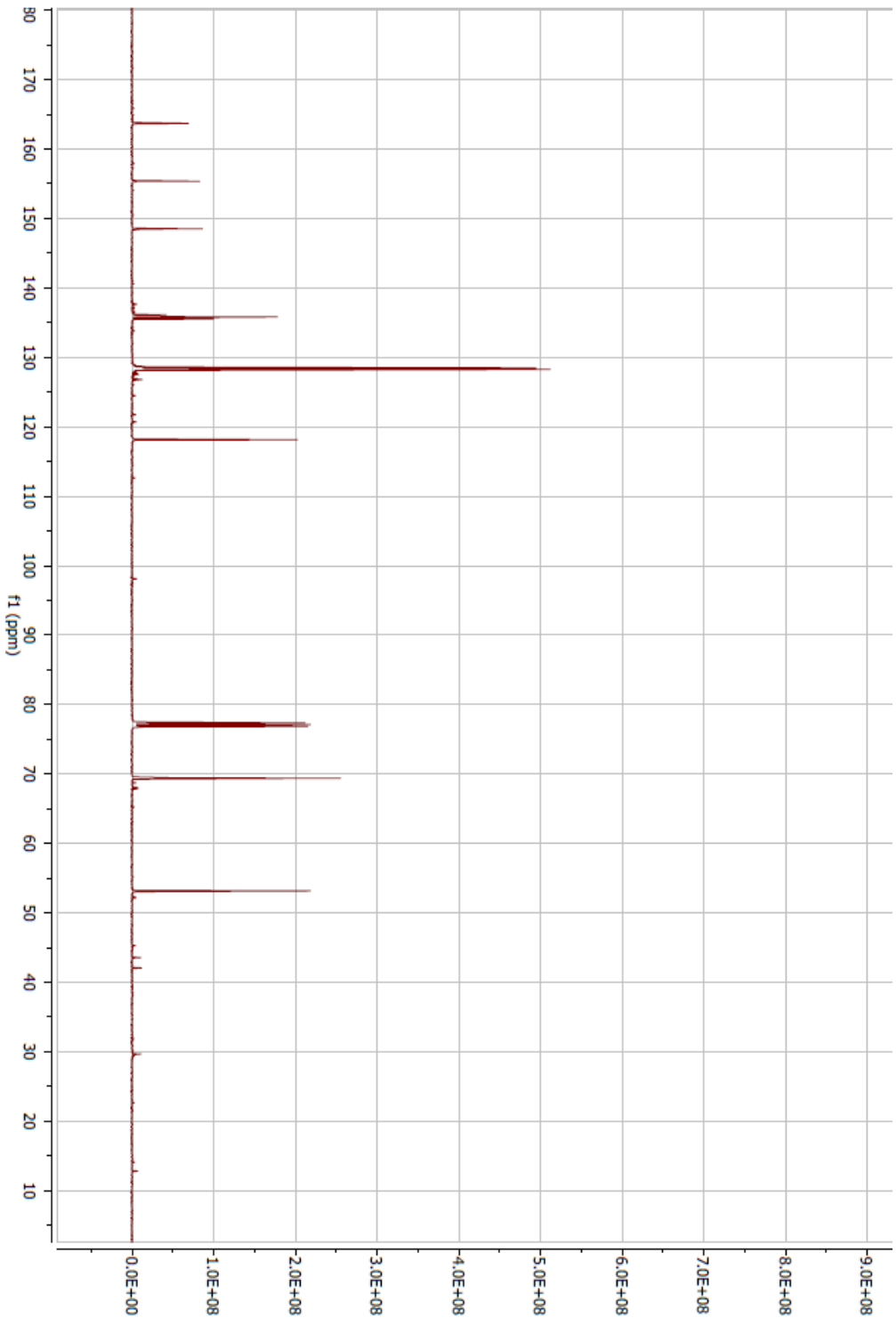


Figure S52. ^{13}C-NMR of O-Benzyl (in $CDCl_3$).

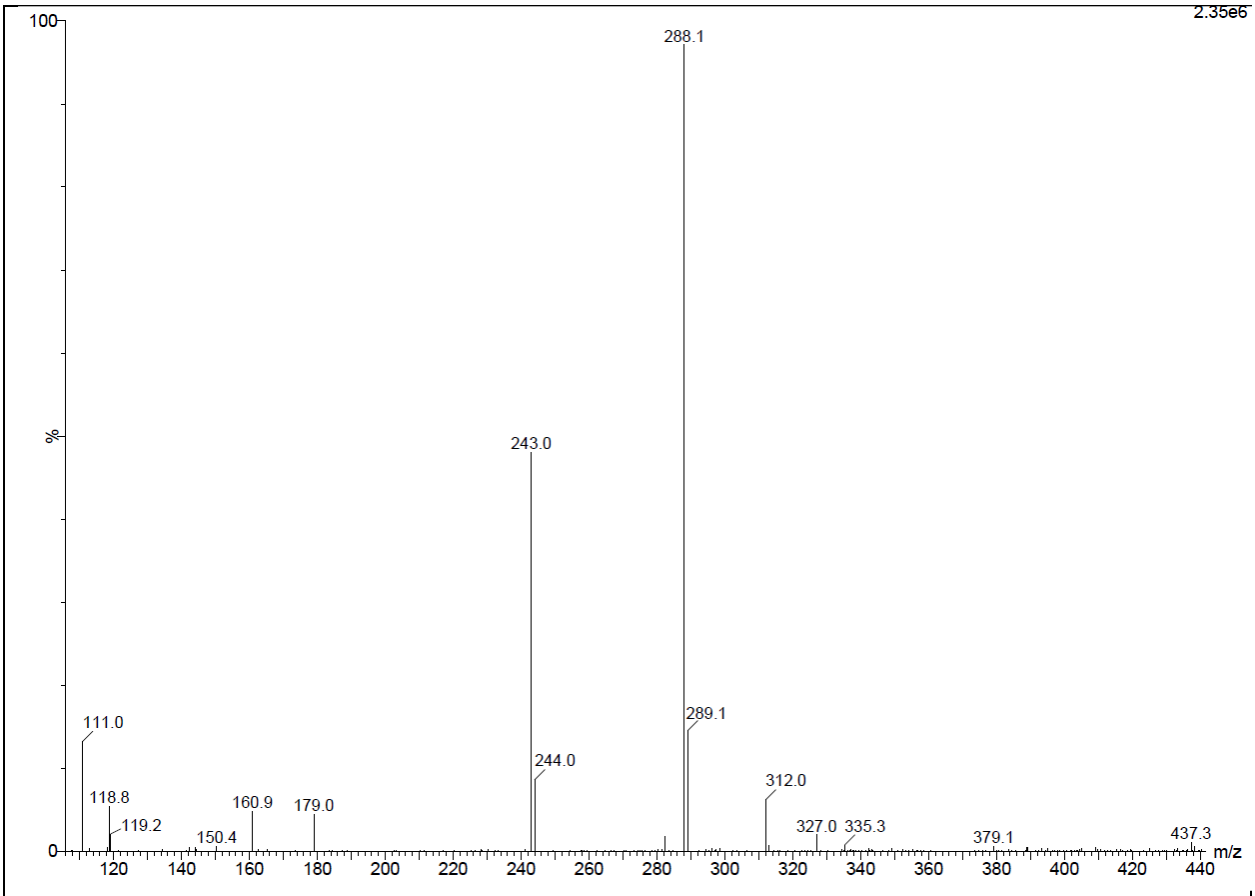


Figure S53. MS-ESI of O-Benzyl (in $CDCl_3$).

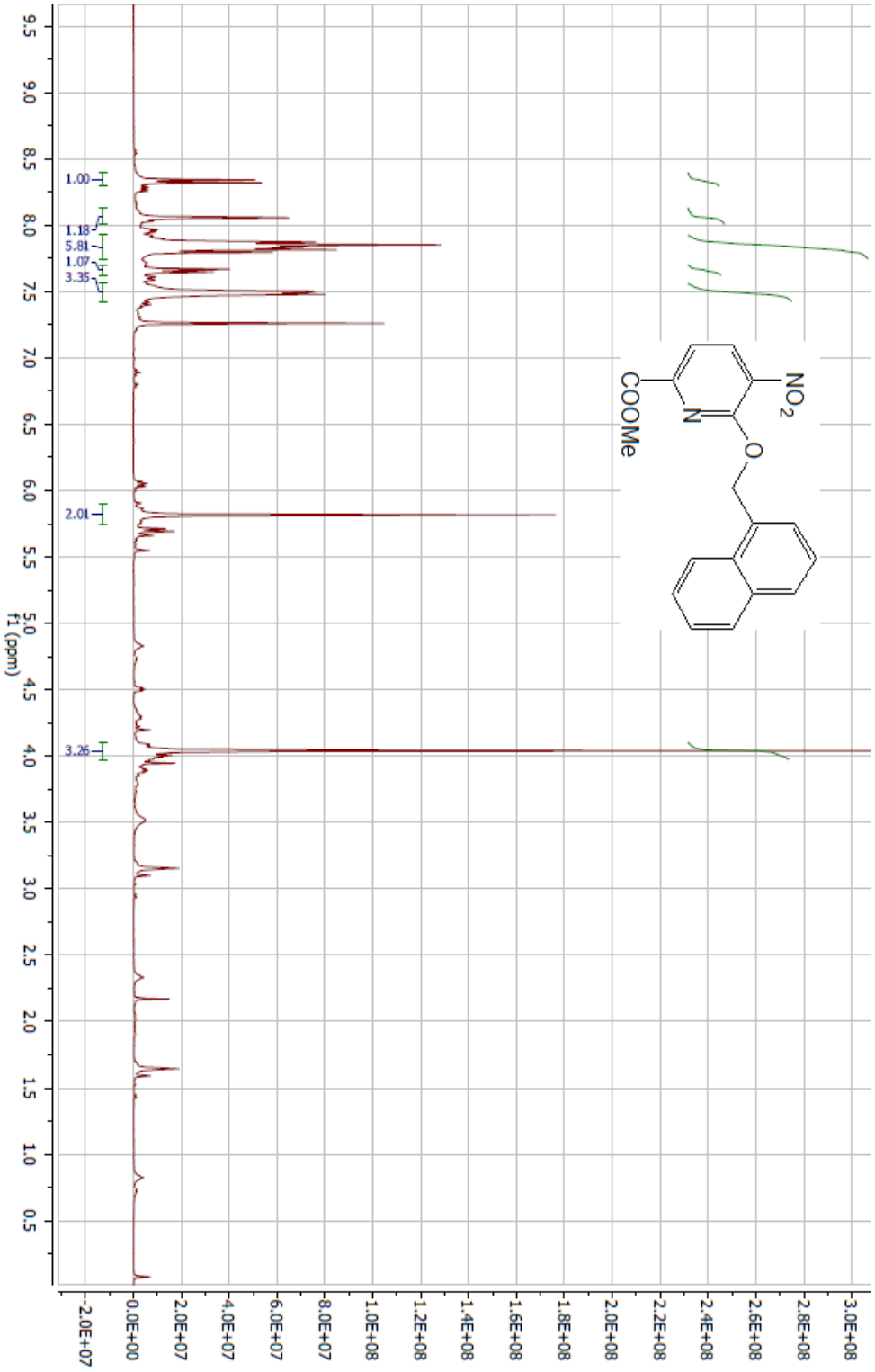


Figure S54. ^{1}H-NMR of O-Naphthalene (in $CDCl_3$).

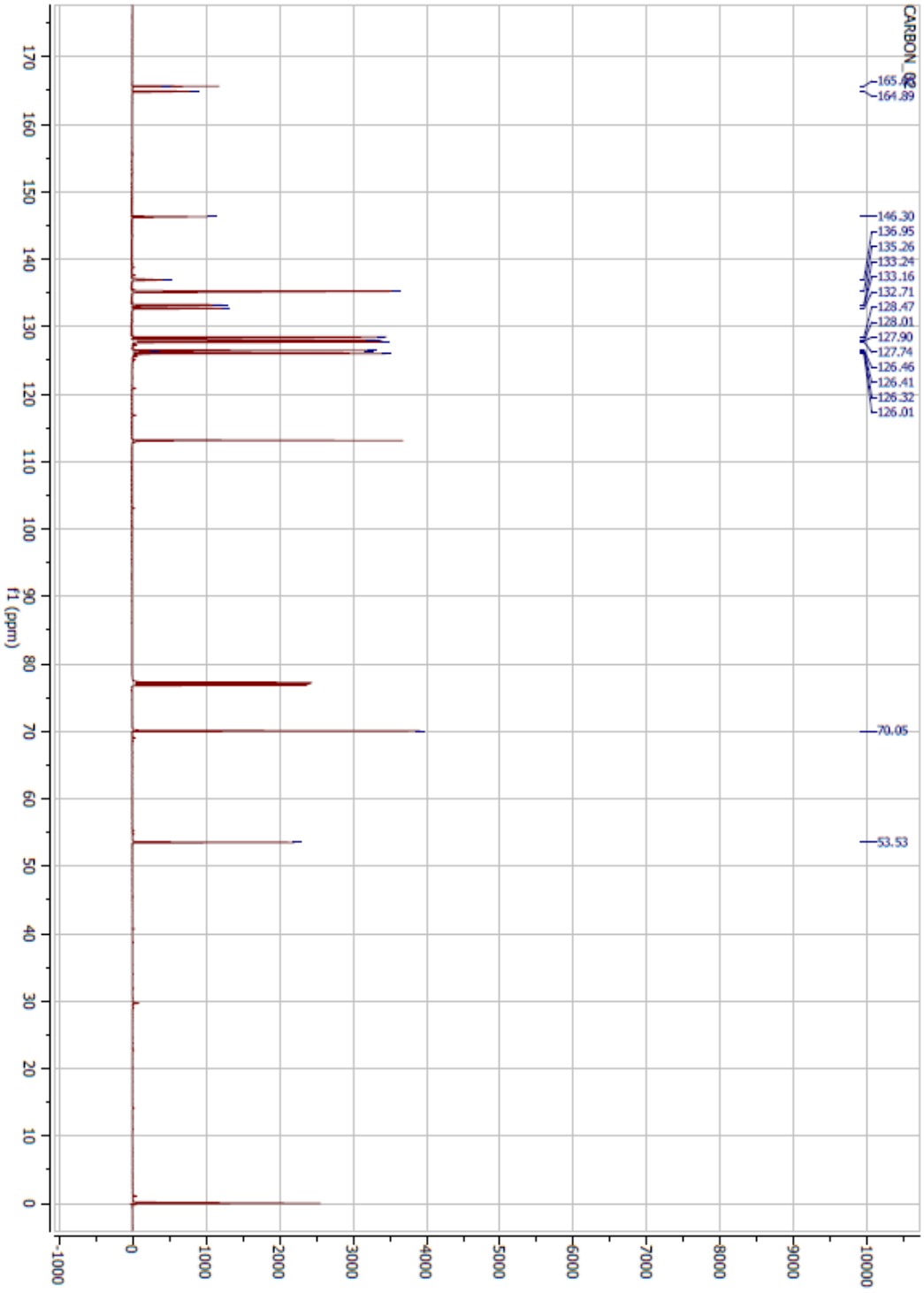


Figure S55. ^{13}C-NMR of O-Naphthalene (in $CDCl_3$).

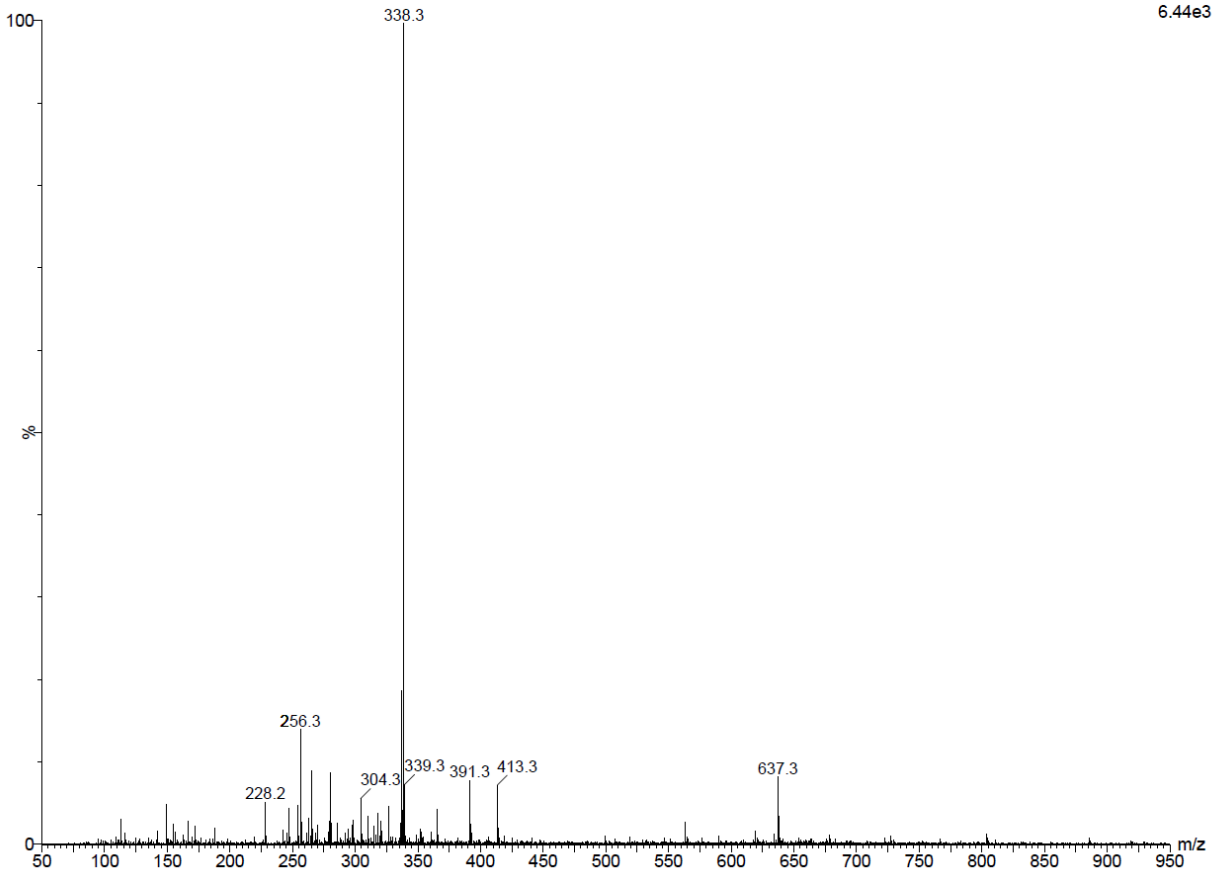


Figure S56. MS-ESI of O-Naphthalene (in $CDCl_3$).

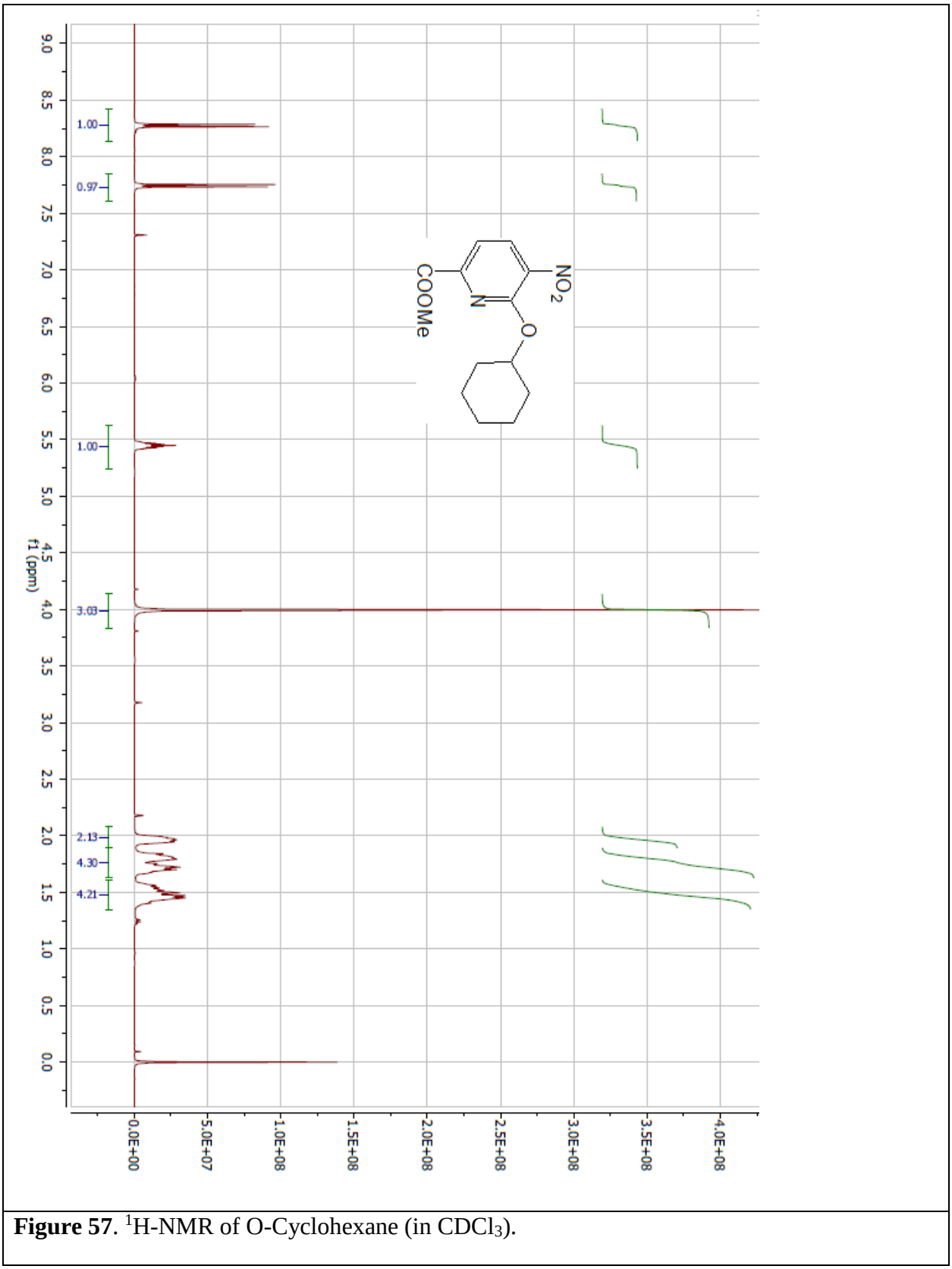


Figure 57. ^{1}H-NMR of O-Cyclohexane (in $CDCl_3$).

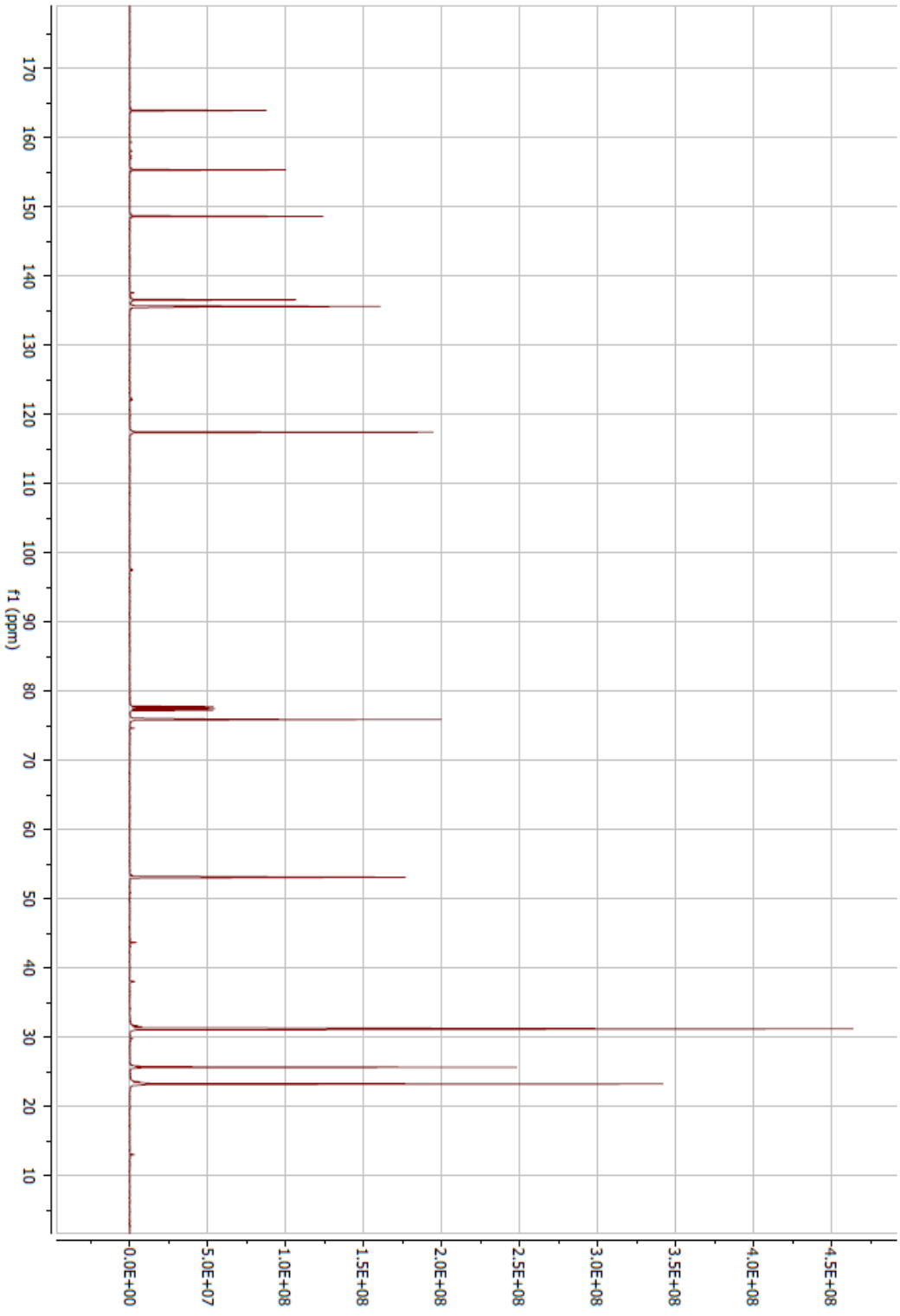


Figure S58. ^{13}C-NMR of O-Cyclohexane (in $CDCl_3$).

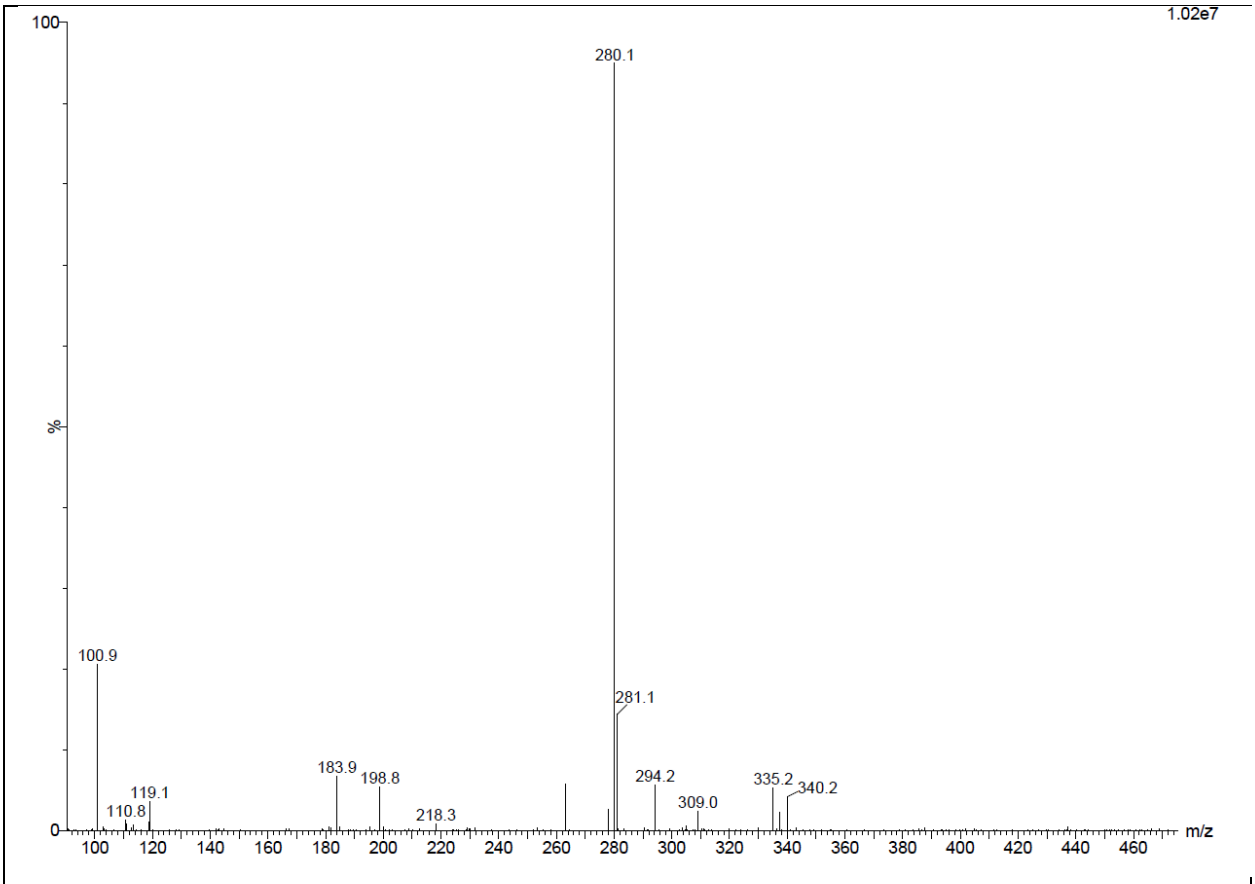


Figure S59. MS-ESI of O-Cyclohexane (in $CDCl_3$).

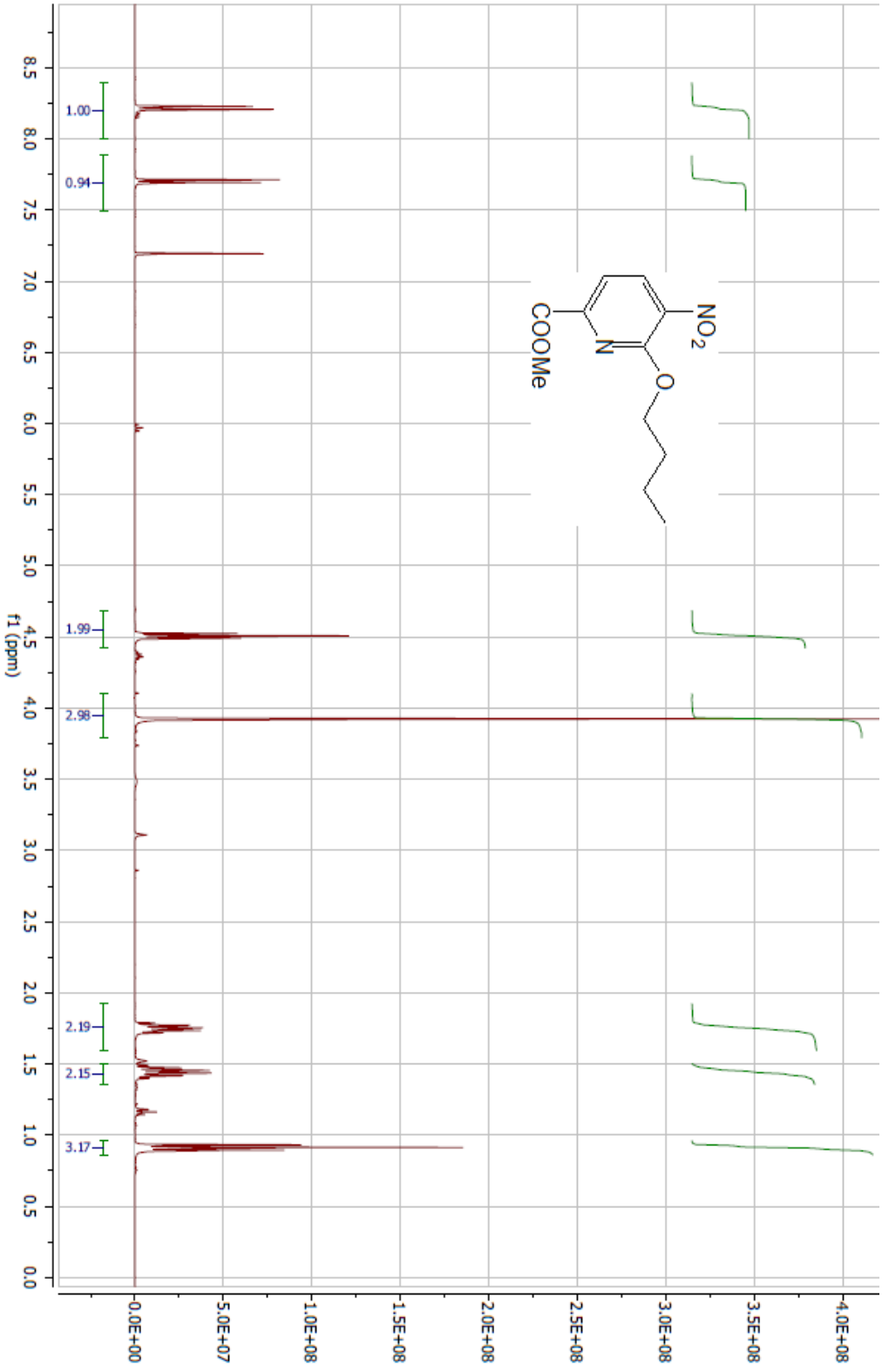


Figure S60. ^{1}H-NMR of O-Butyl (in $CDCl_3$).

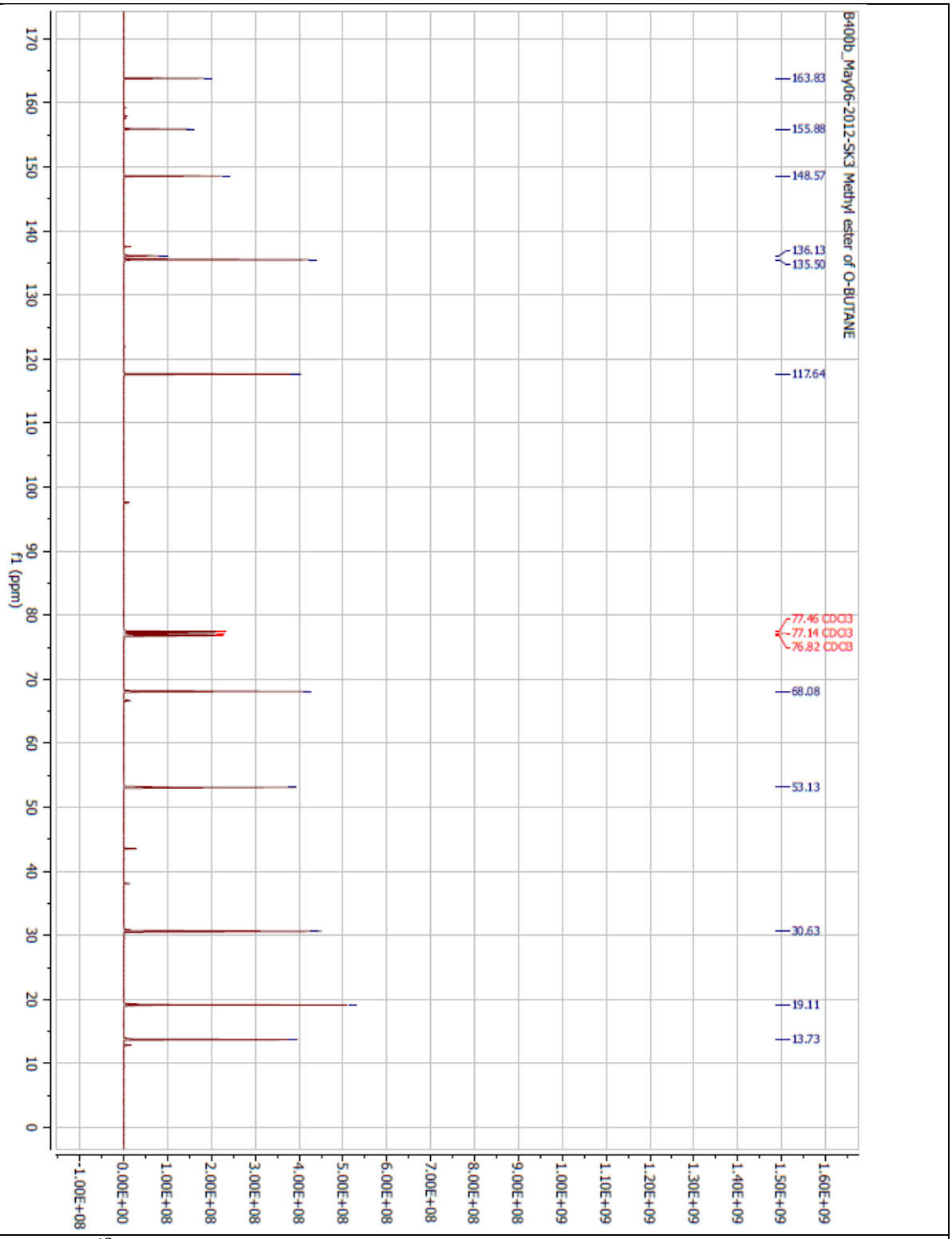


Figure S61. ^{13}C-NMR of O-Butyl (in $CDCl_3$).

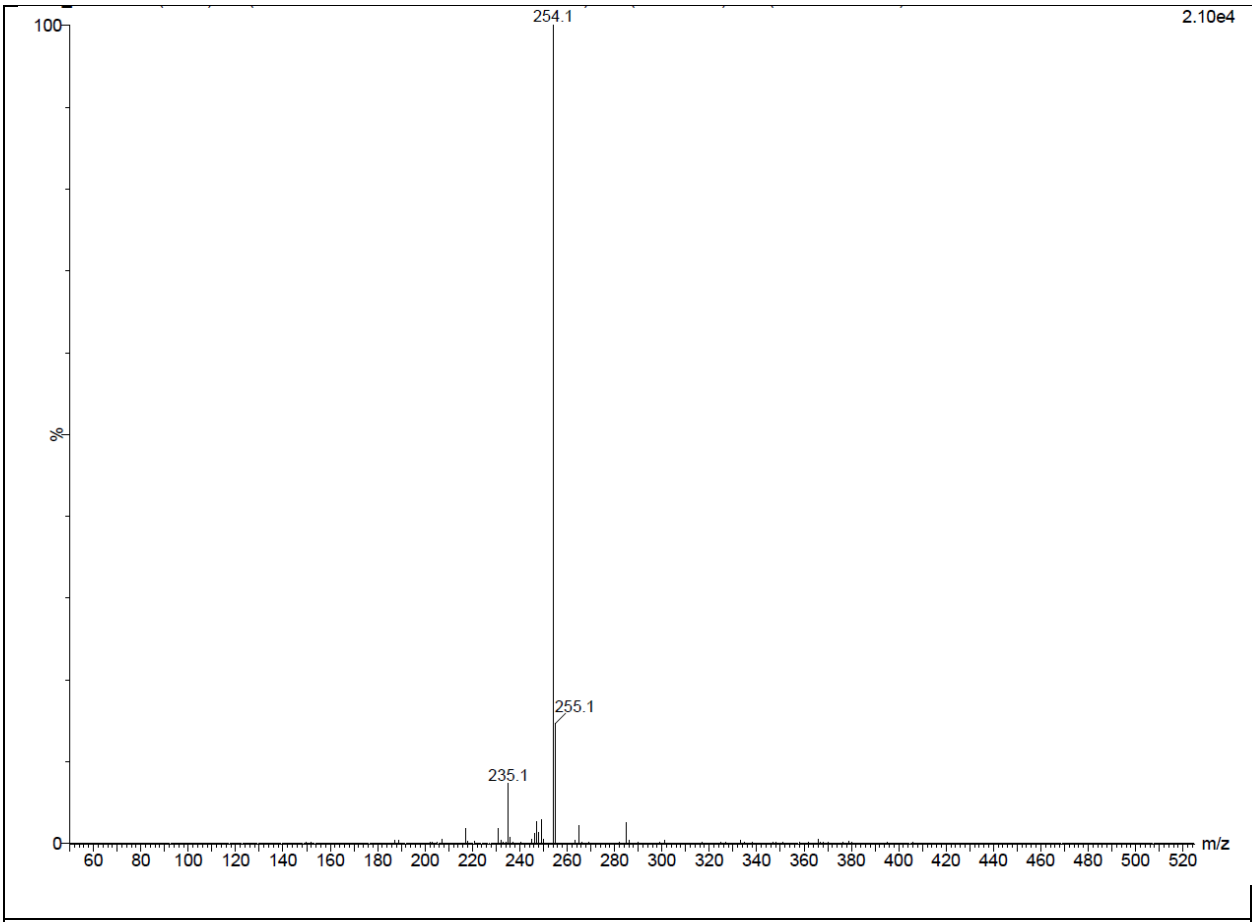


Figure S62. MS-ESI of O-Butyl (in $CDCl_3$).

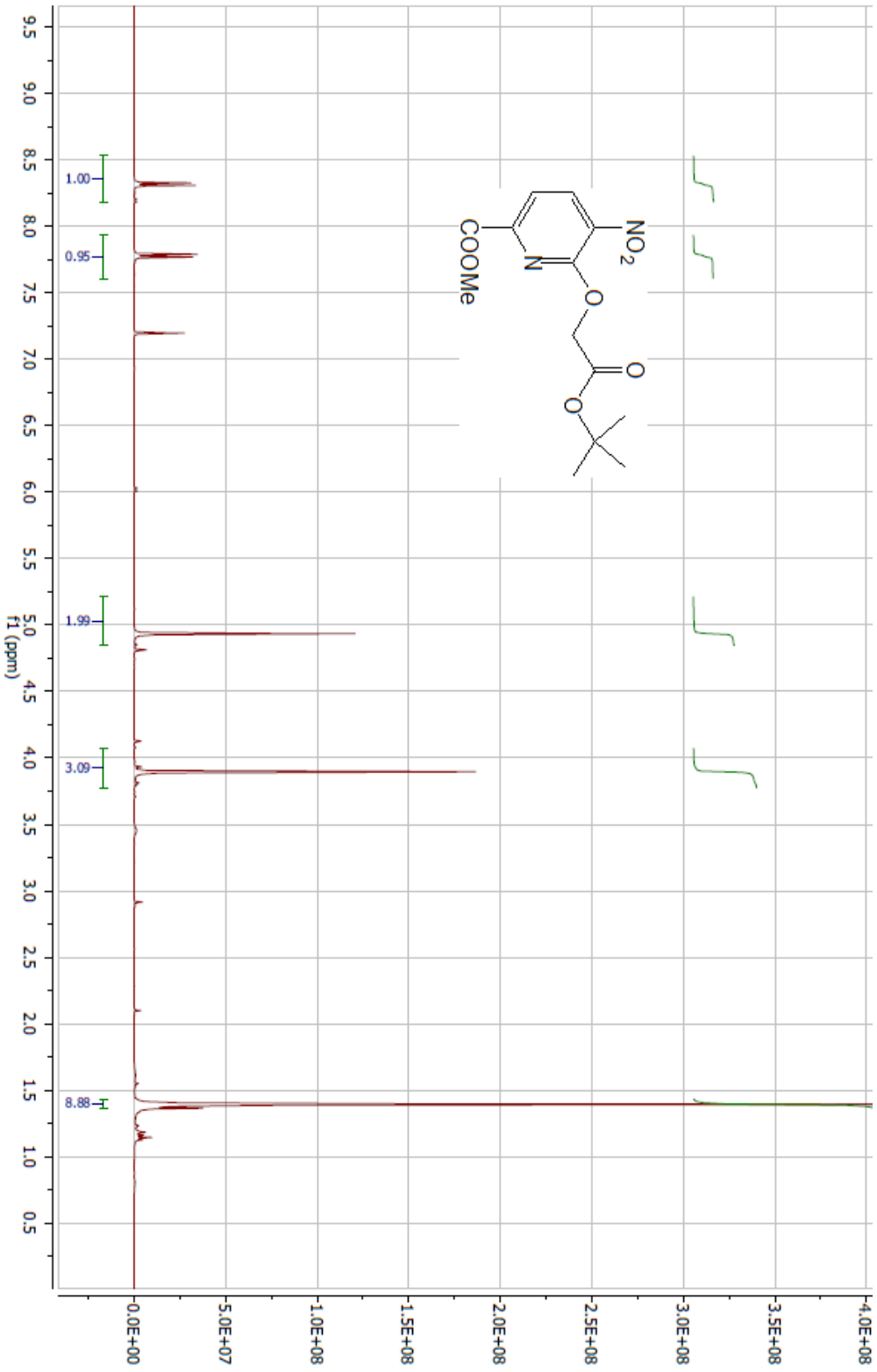


Figure S63. ^{1}H-NMR of O-*tert* butyl ester (in $CDCl_3$).

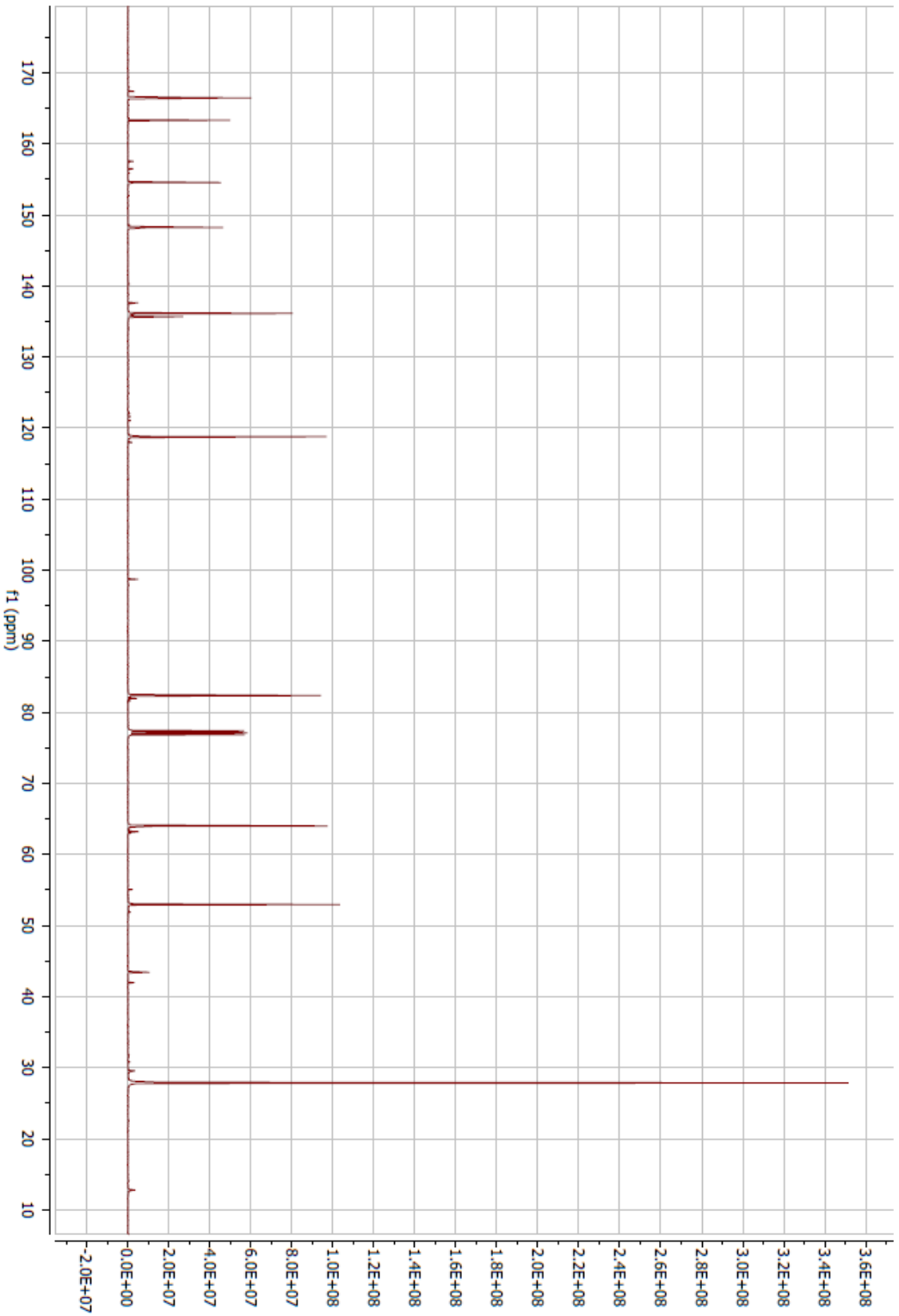


Figure S64. ^{13}C-NMR of O-*tert* butyl ester (in $CDCl_3$).

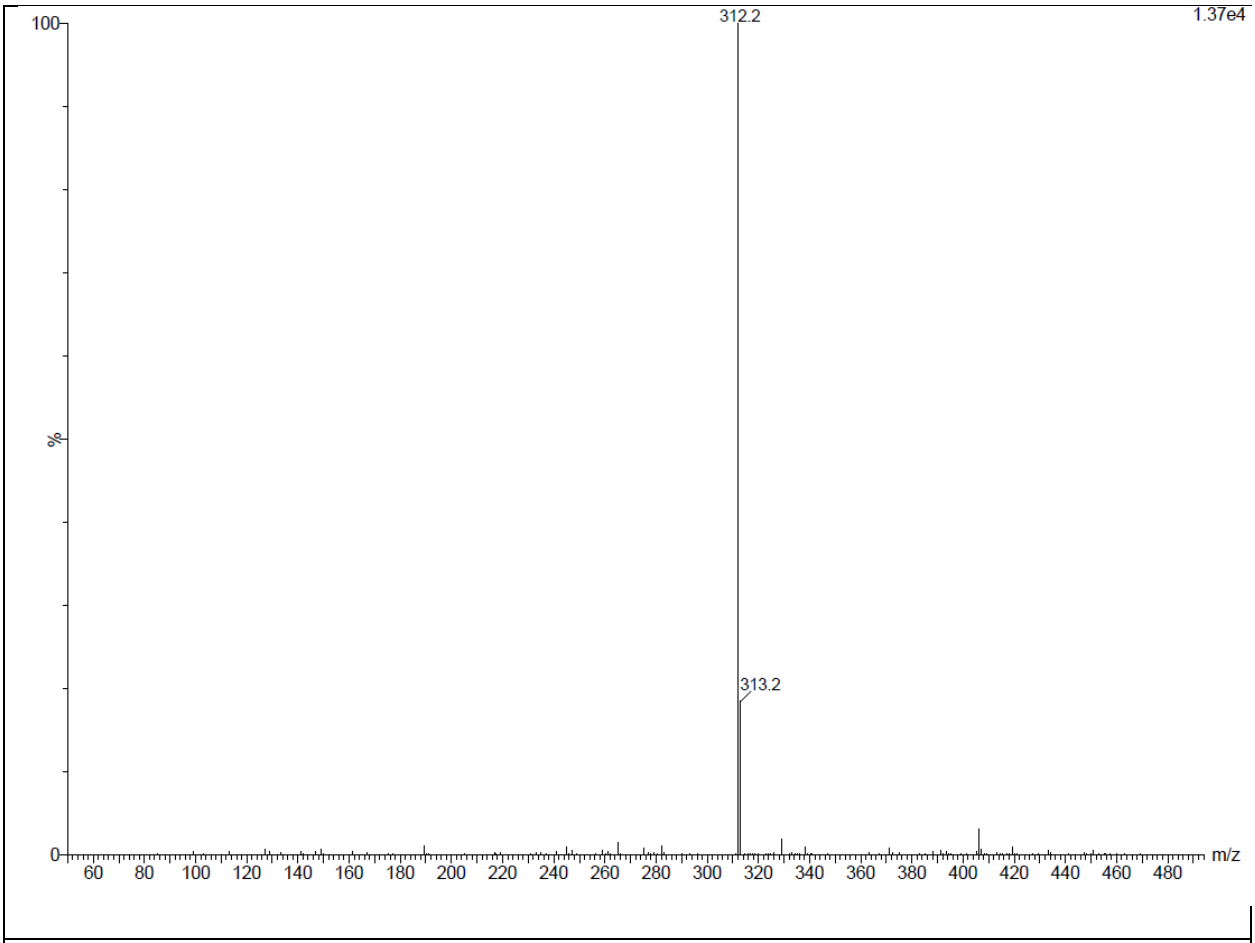


Figure S65. MS-ESI of O-*tert* butyl ester (in $CDCl_3$).

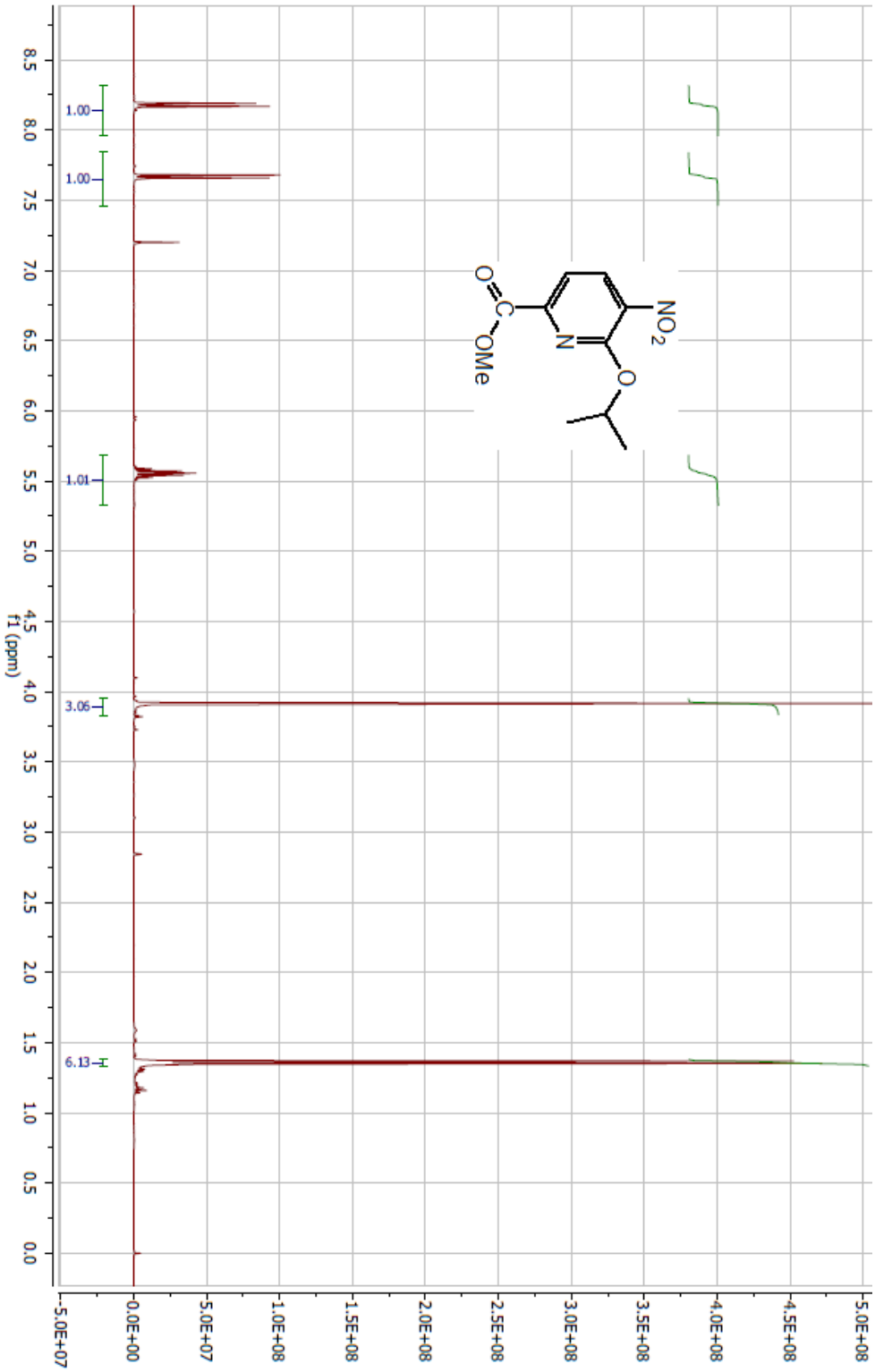


Figure S66. ^{1}H-NMR of O-Propyl (in $CDCl_3$).

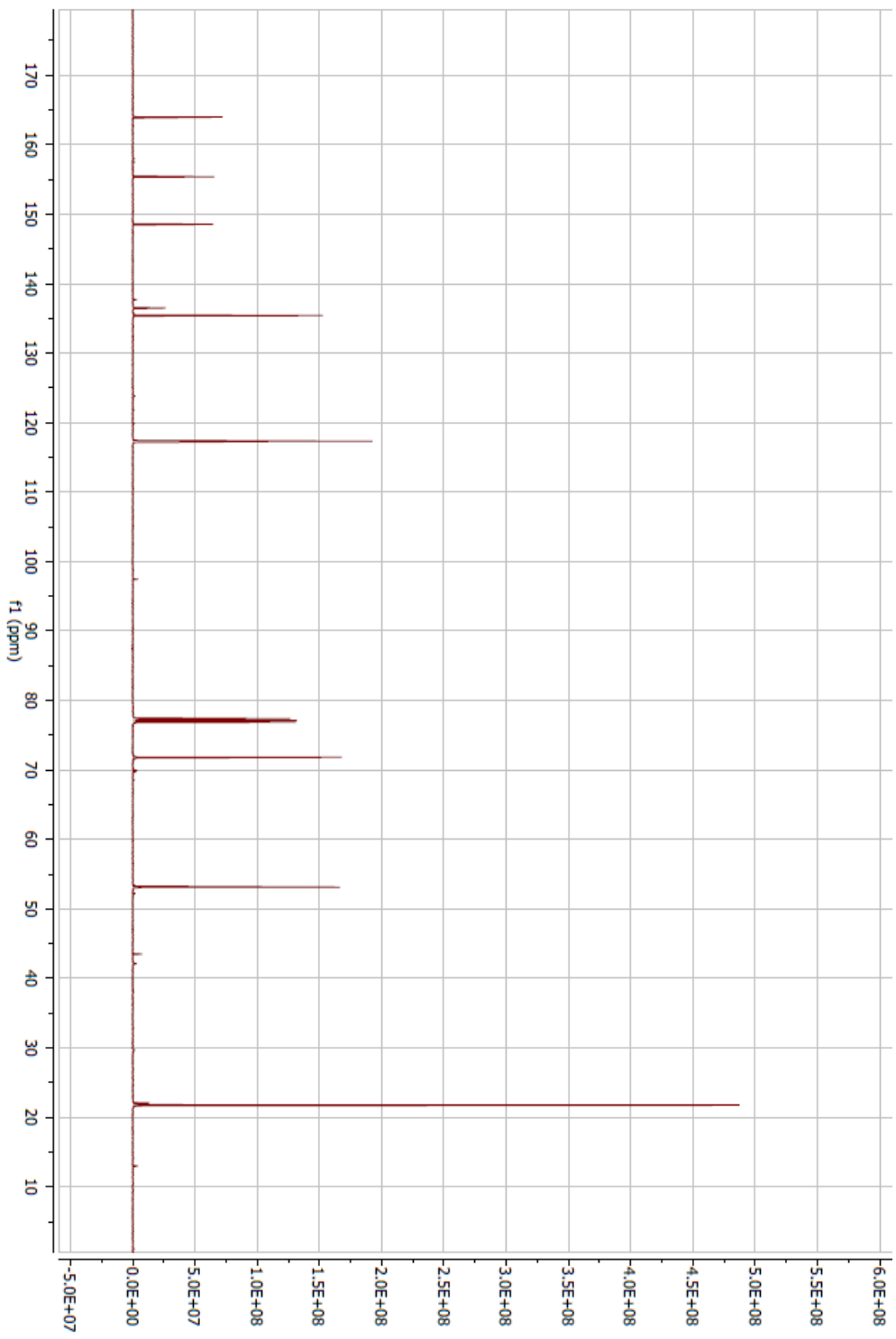


Figure S67. ^{13}C-NMR of O-Propyl (in $CDCl_3$).

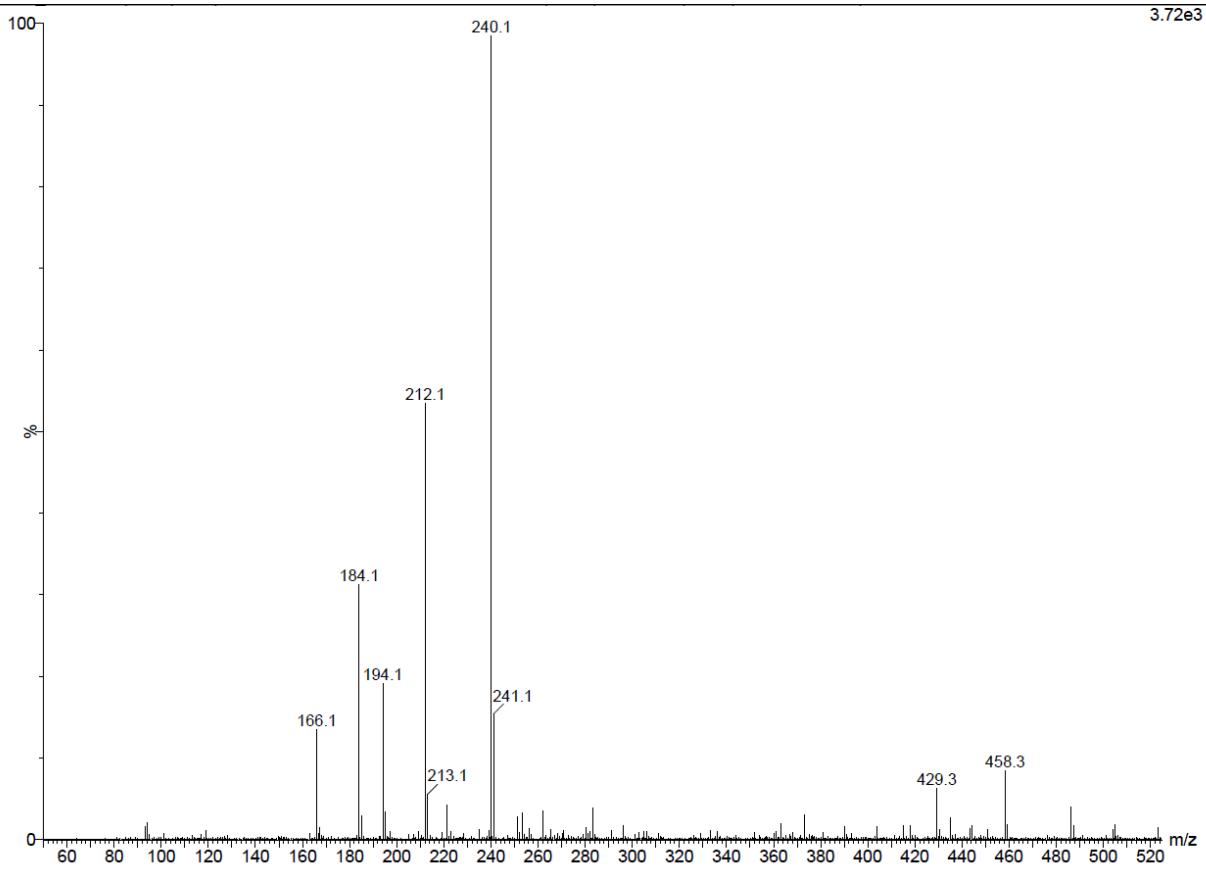


Figure S68. MS-ESI of O-Propyl (in $CDCl_3$).

Series 3:

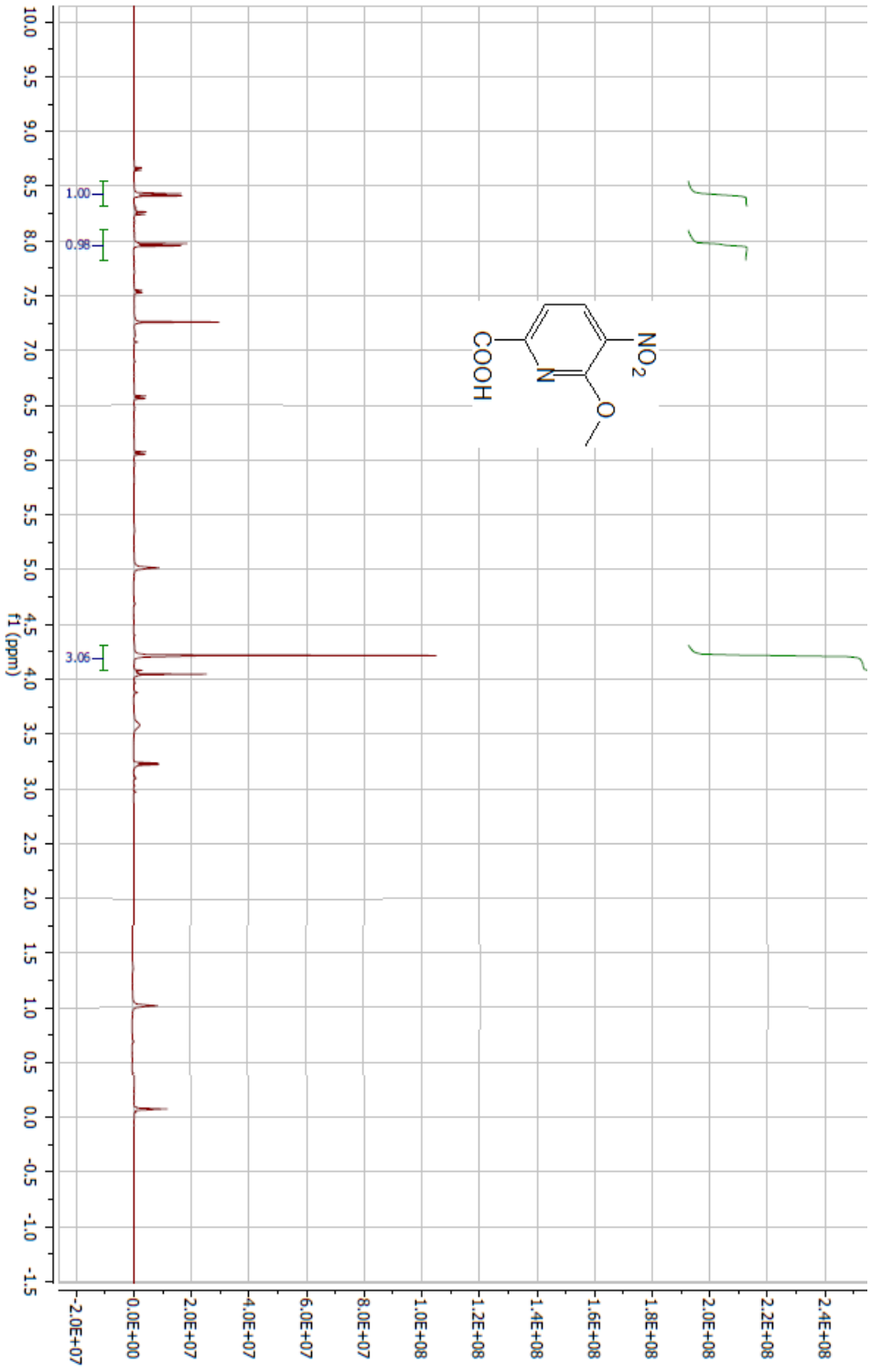


Figure S69. ^{1}H-NMR of O-Propyl (in $CDCl_3$).

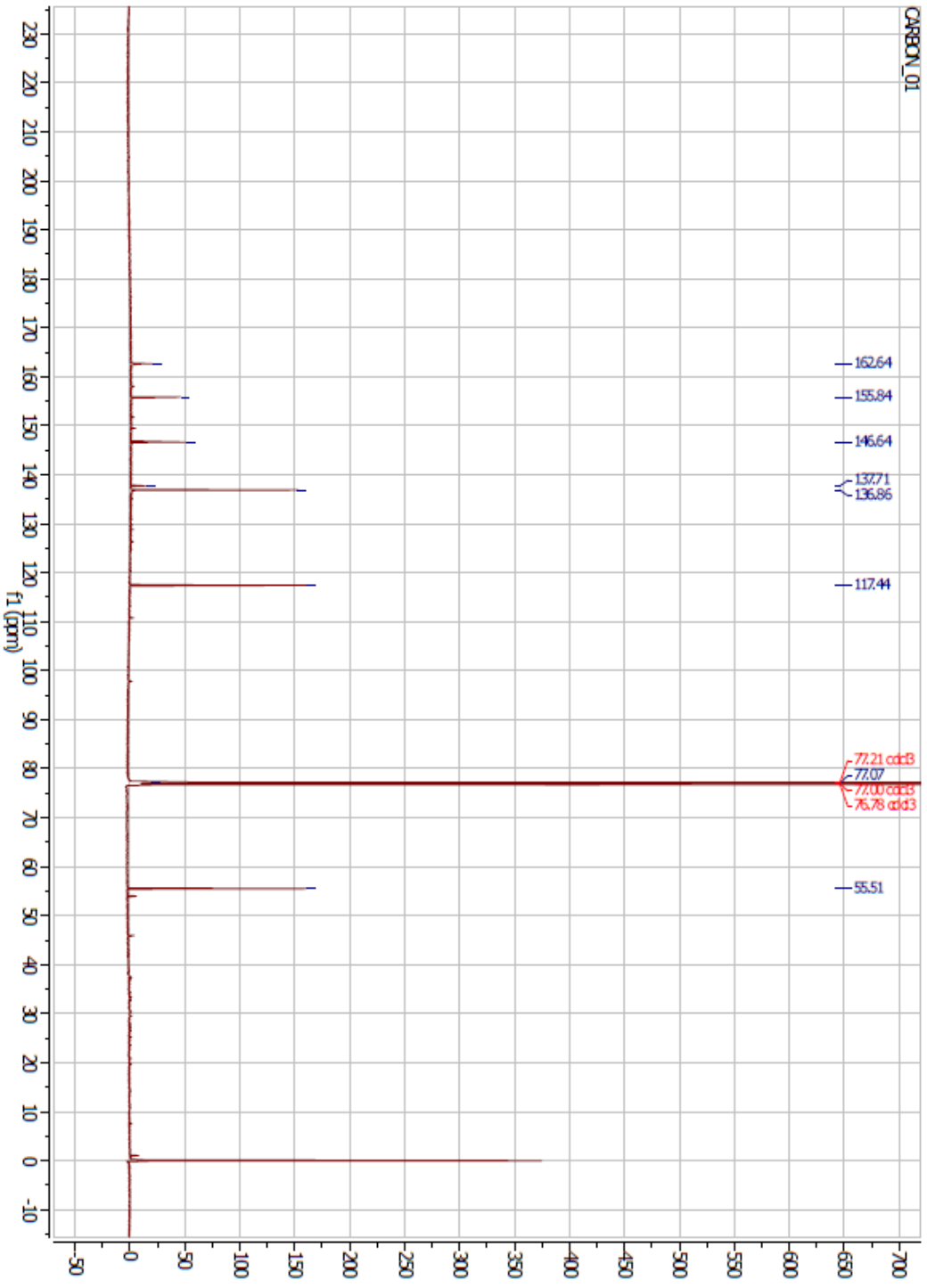


Figure S70. ^{13}C-NMR of O-Propyl (in $CDCl_3$).

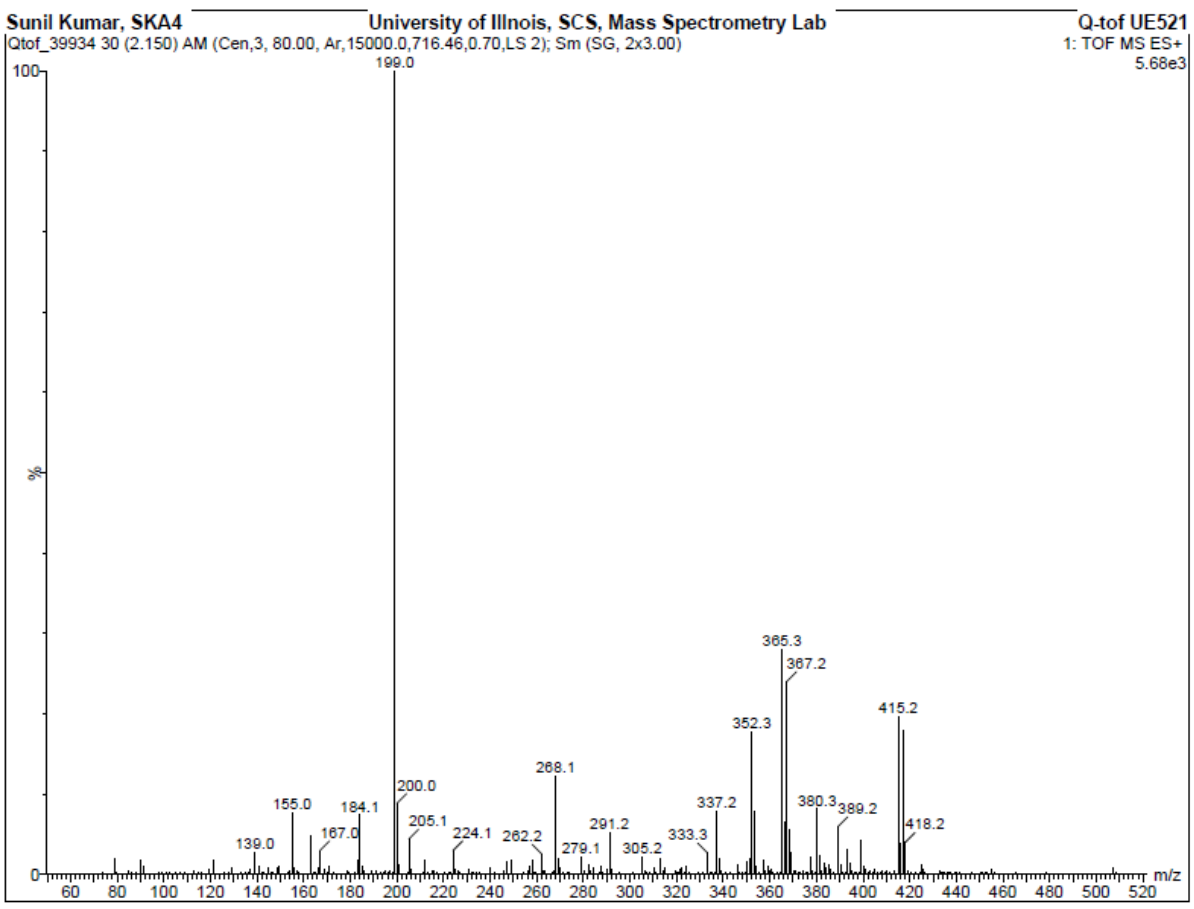


Figure S71. MS-ESI of O-Propyl.

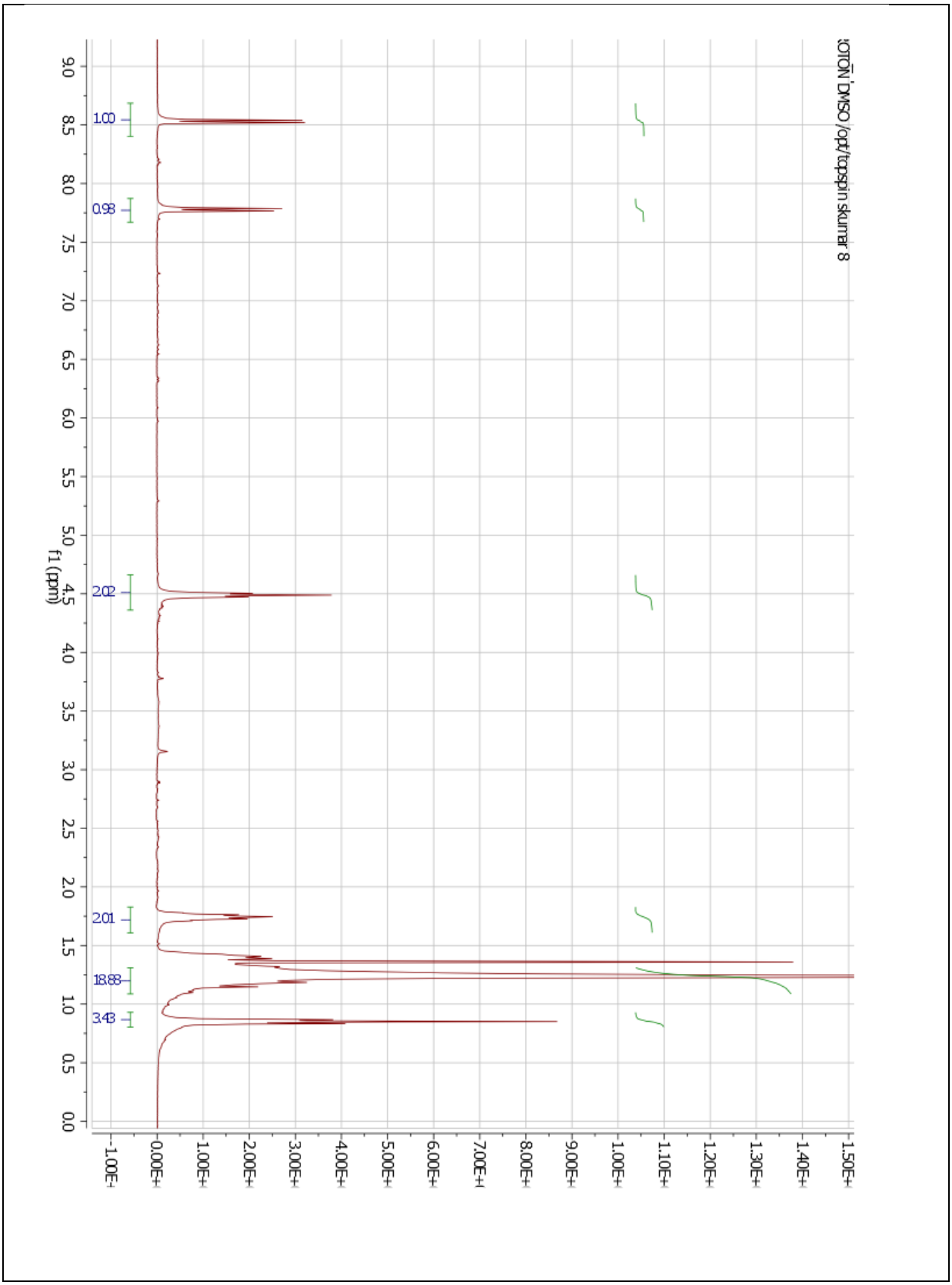

1.00
0.98
2.02
2.01
18.88
3.43
f1 (ppm)
DMSO /opt/topspin skumar 8

Figure S72. ^{1}H-NMR of O-Dodecane (in $CDCl_3$).

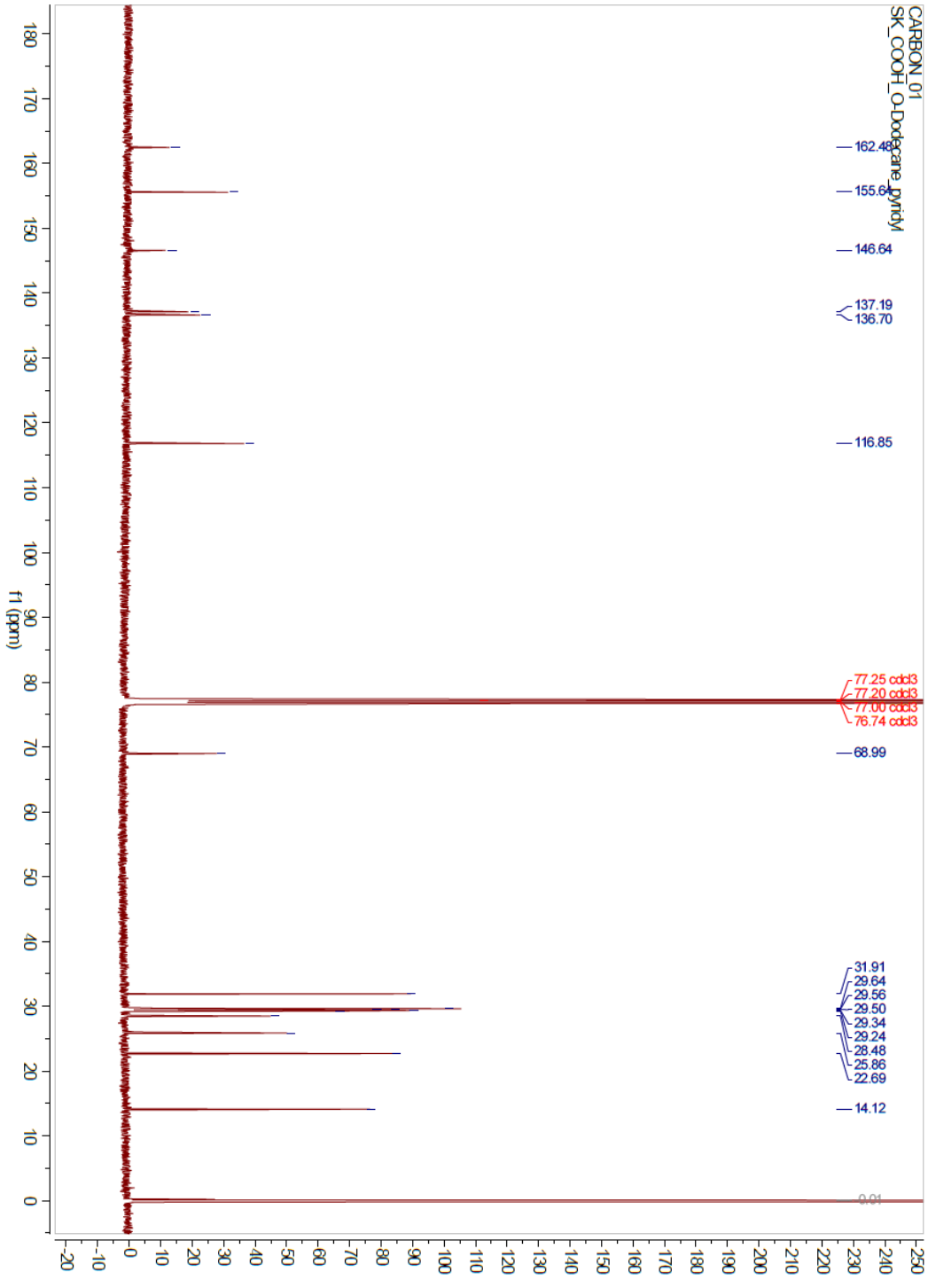


Figure S73. ^{13}C-NMR of O-Dodecane (in $CDCl_3$).

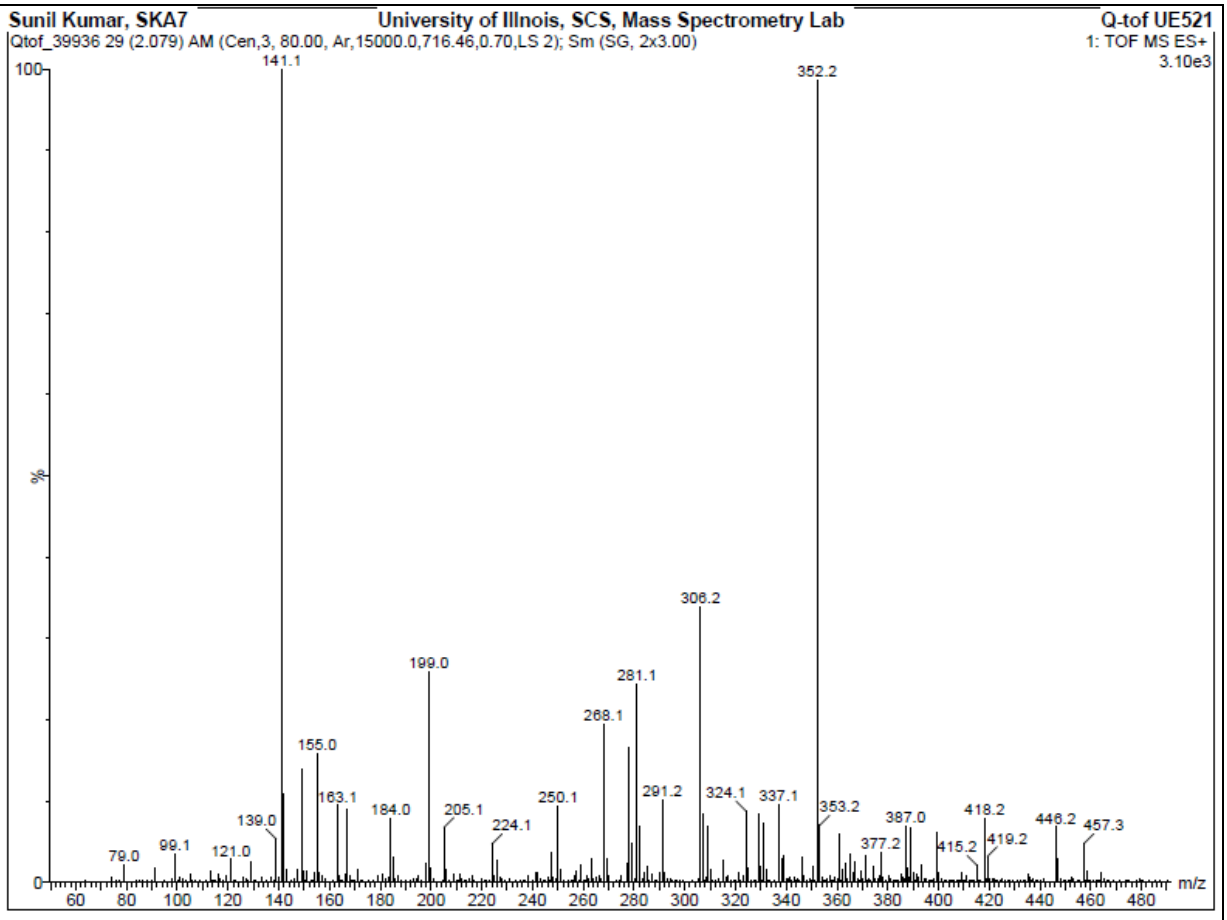


Figure S74. MS-ESI of O-Dodecane.

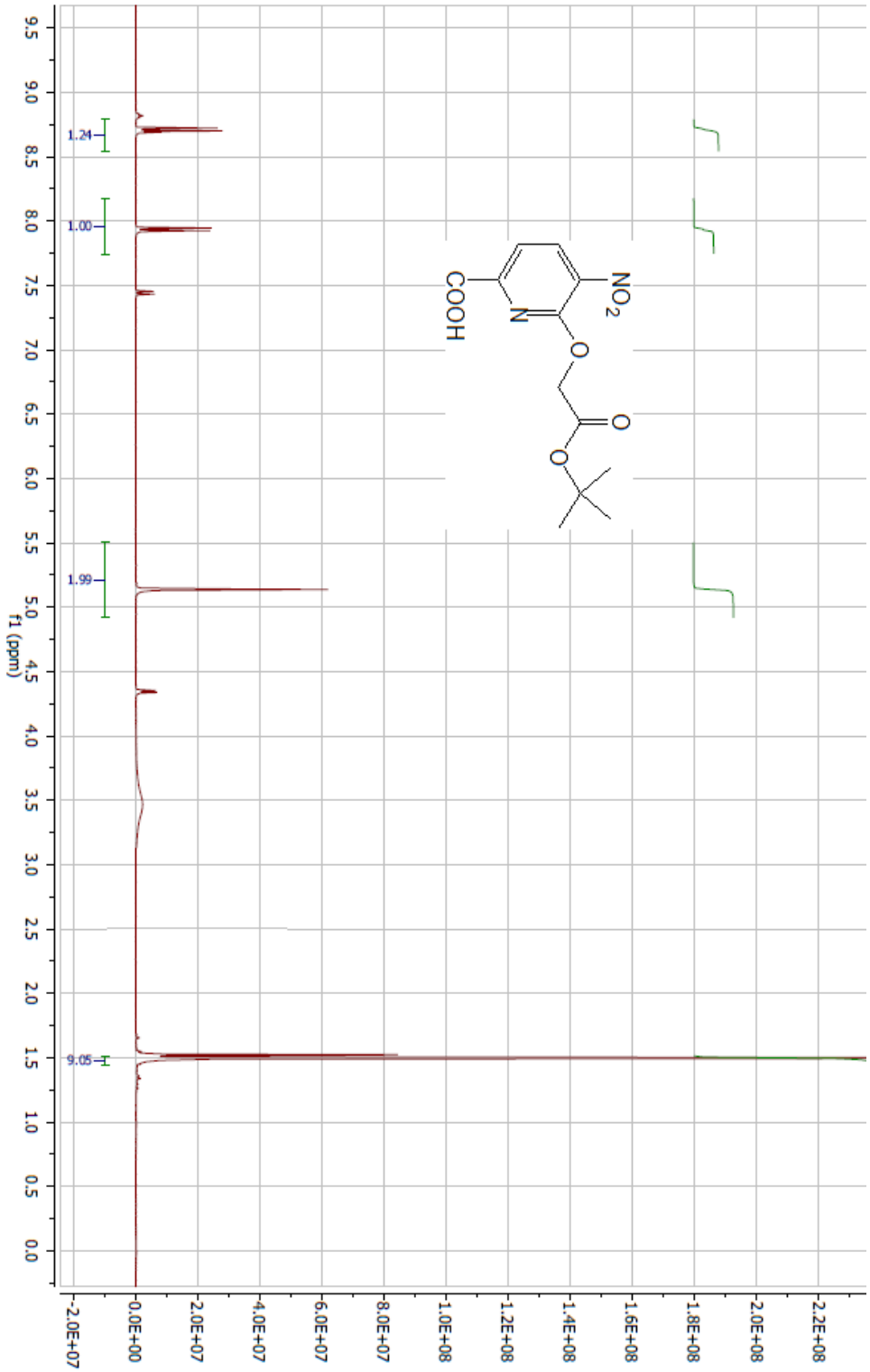


Figure S75. ^{1}H-NMR of O-*tert* butyl ester (in $CDCl_3$).

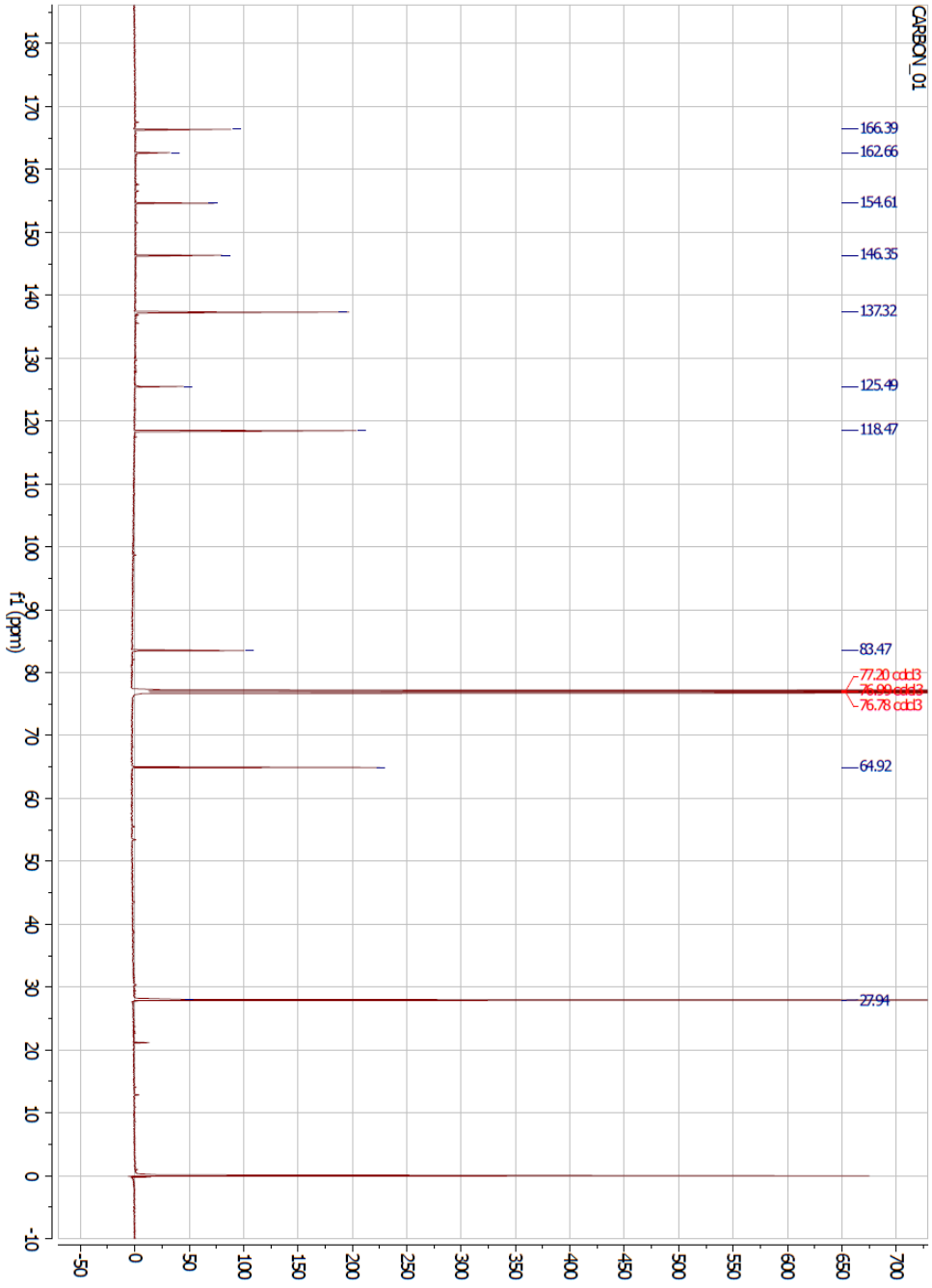


Figure S76. ^{13}C-NMR of O-*tert* butyl ester (in $CDCl_3$).

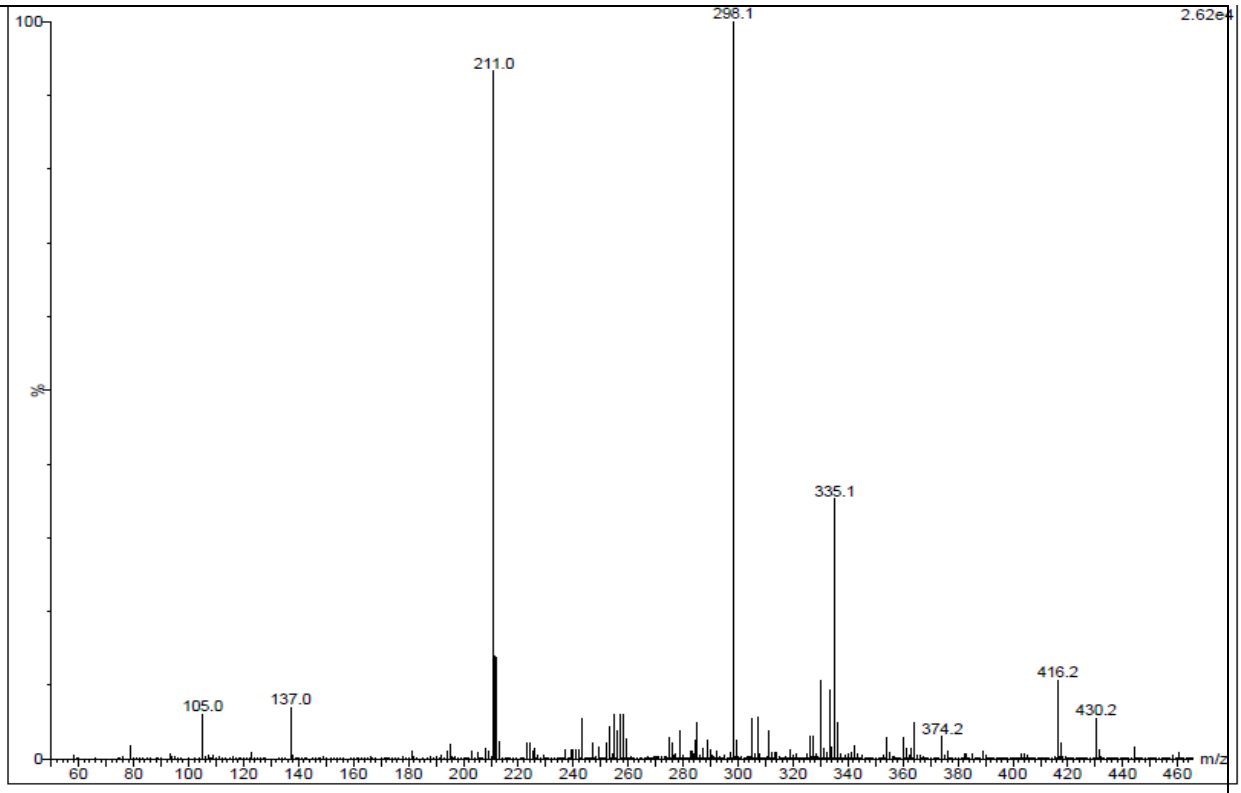


Figure S77. MS-ESI of O-*tert* butyl ester.

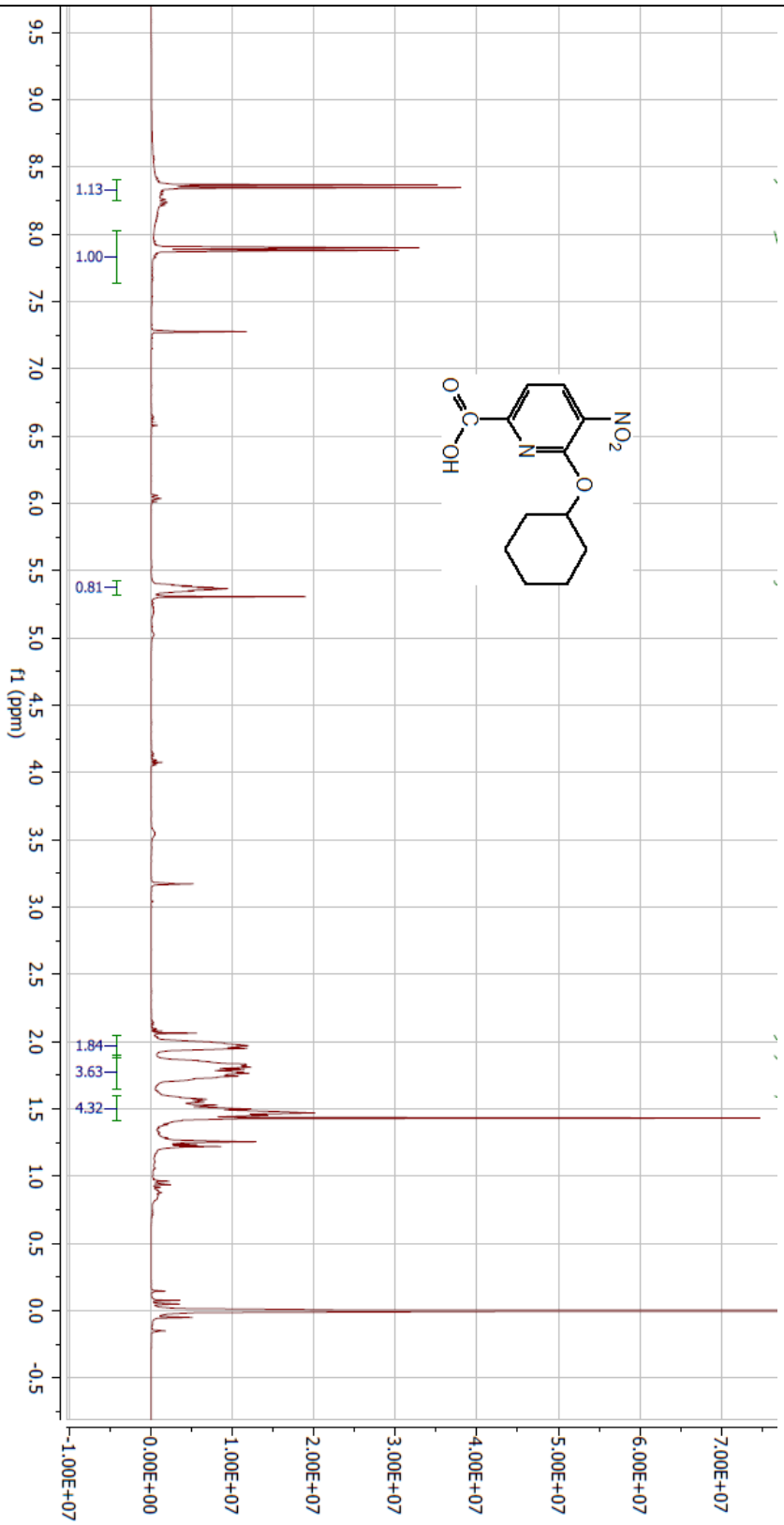


Figure S78. ^{1}H-NMR of O-Cyclohexane (in $CDCl_3$).

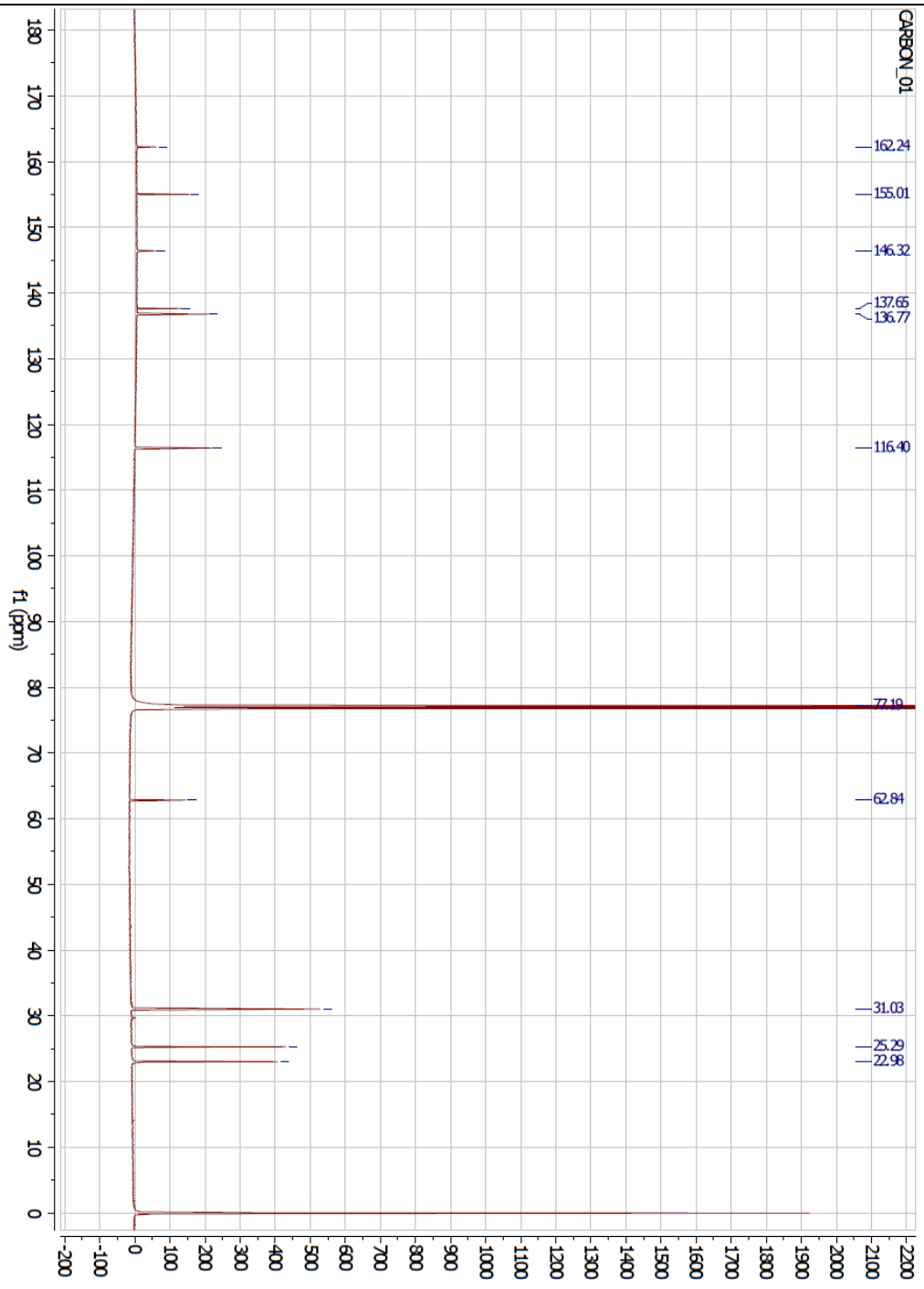


Figure S79. ^{13}C-NMR of O-Cyclohexane (in $CDCl_3$).

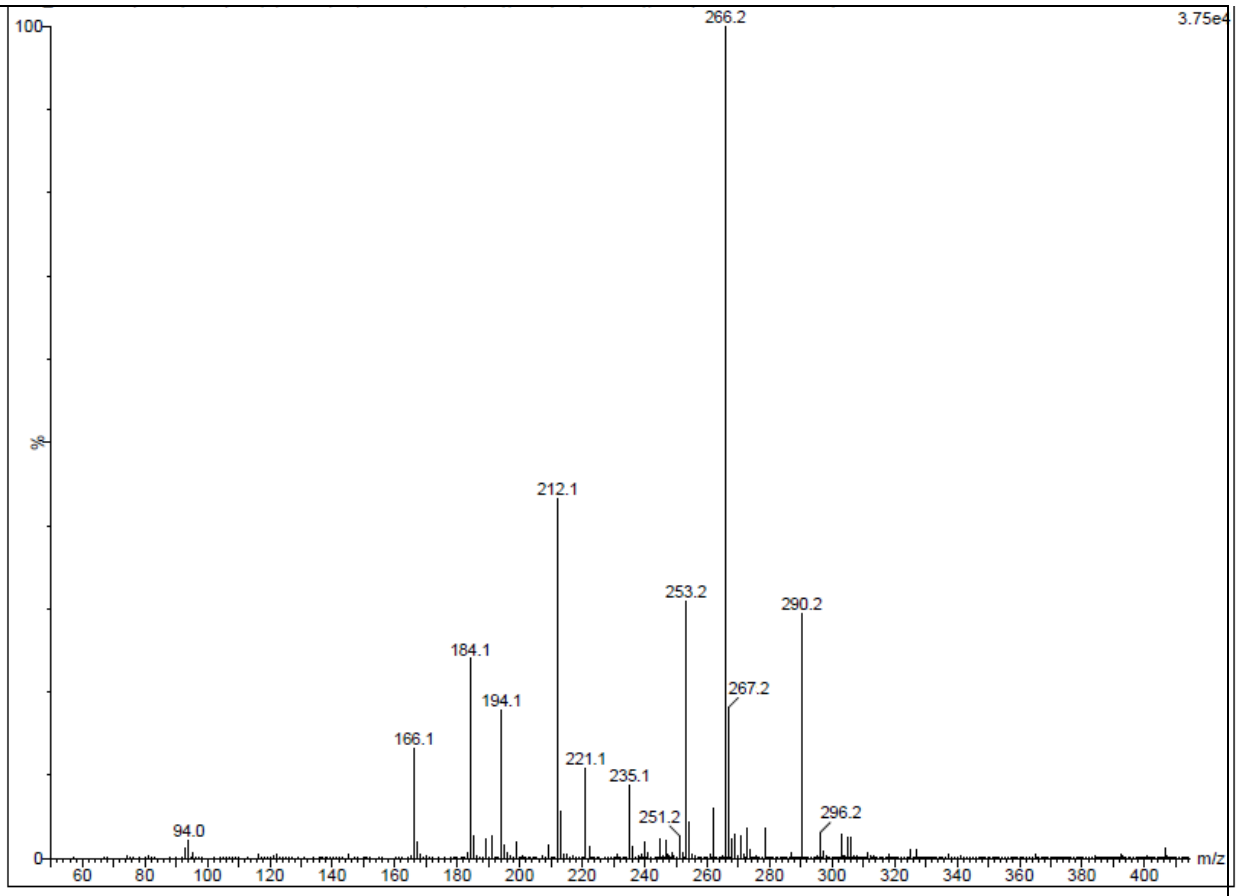


Figure S80. MS-ESI of O-Cyclohexane.

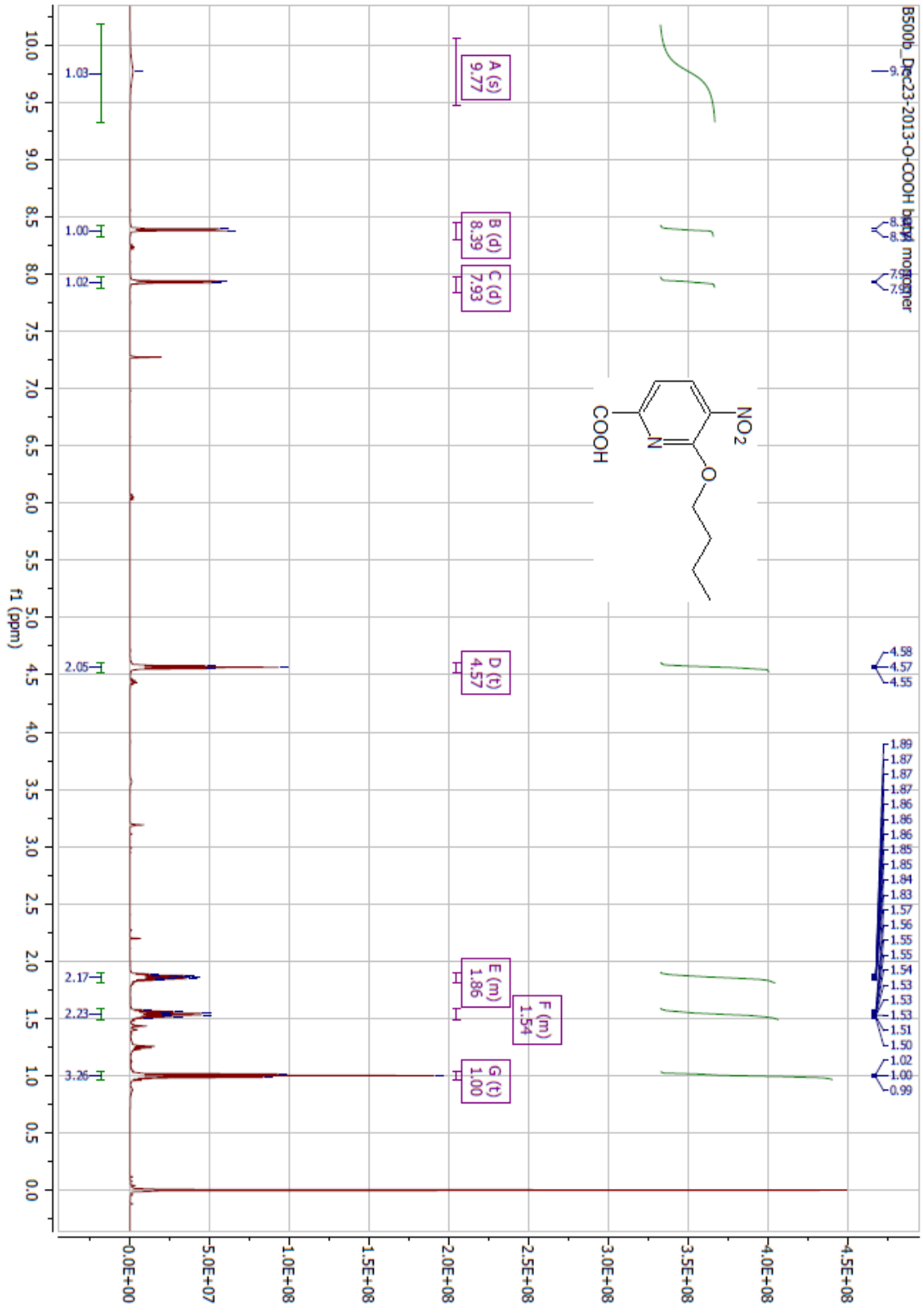


Figure S81. ^{1}H-NMR of O-Butyl (in $CDCl_3$).

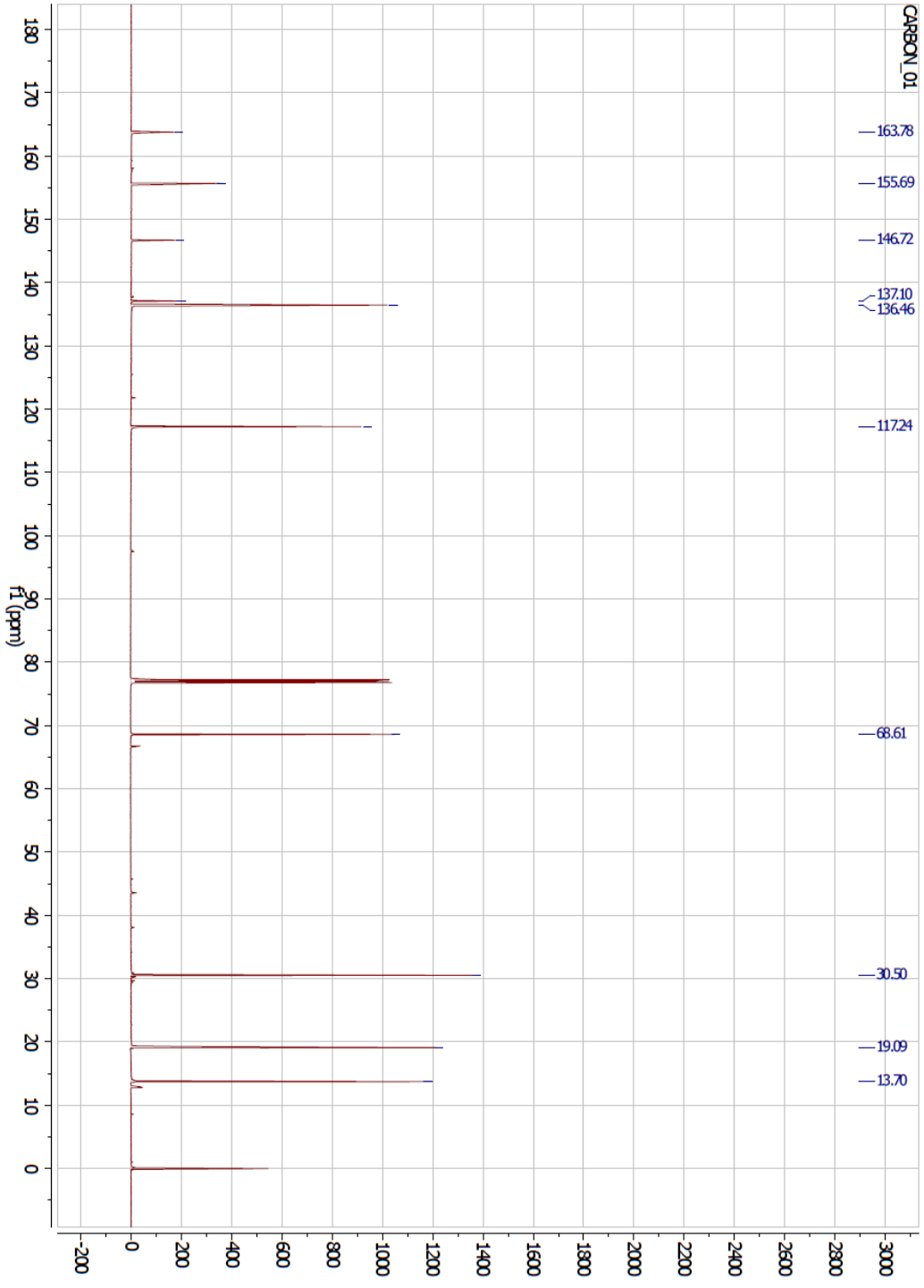


Figure S82. ^{13}C-NMR of O-Butyl (in $CDCl_3$).

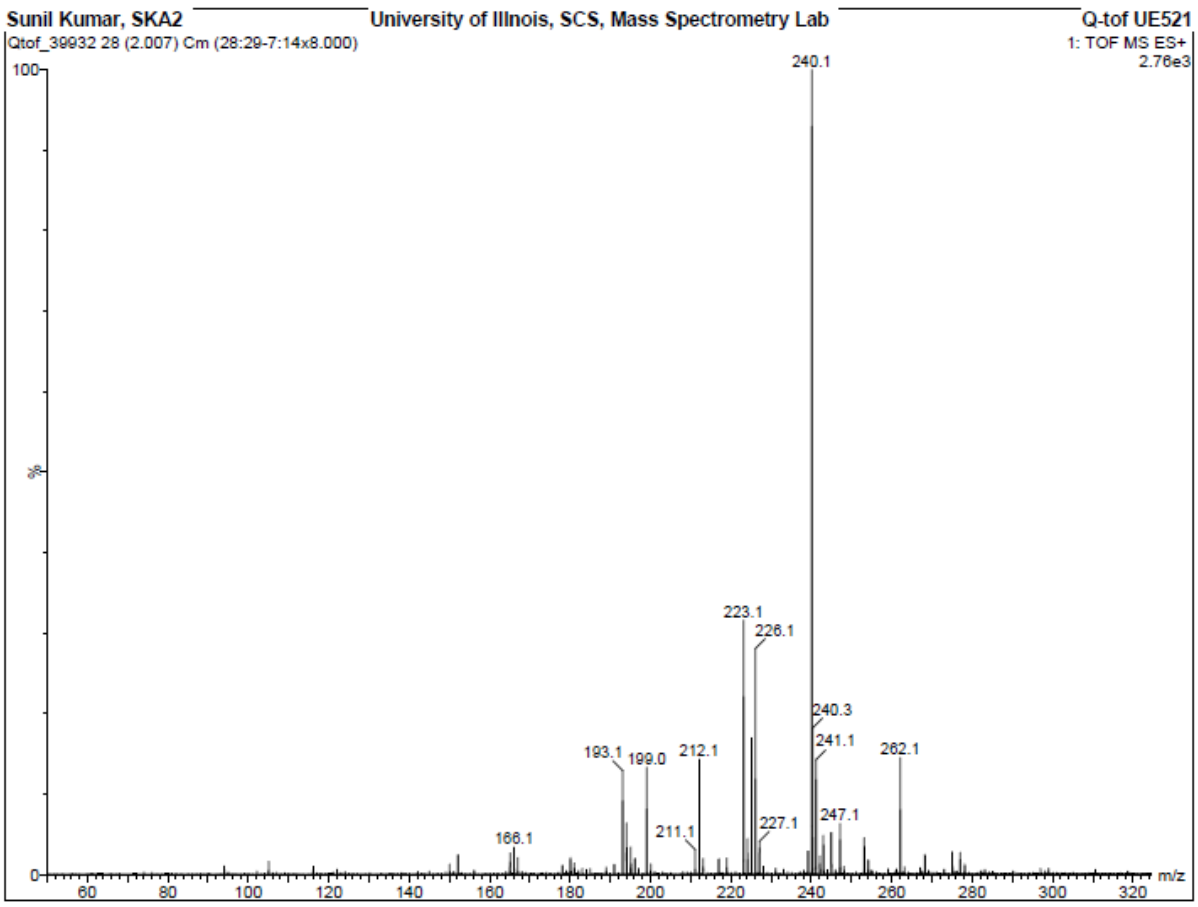


Figure S83. MS-ESI of O-Butyl.

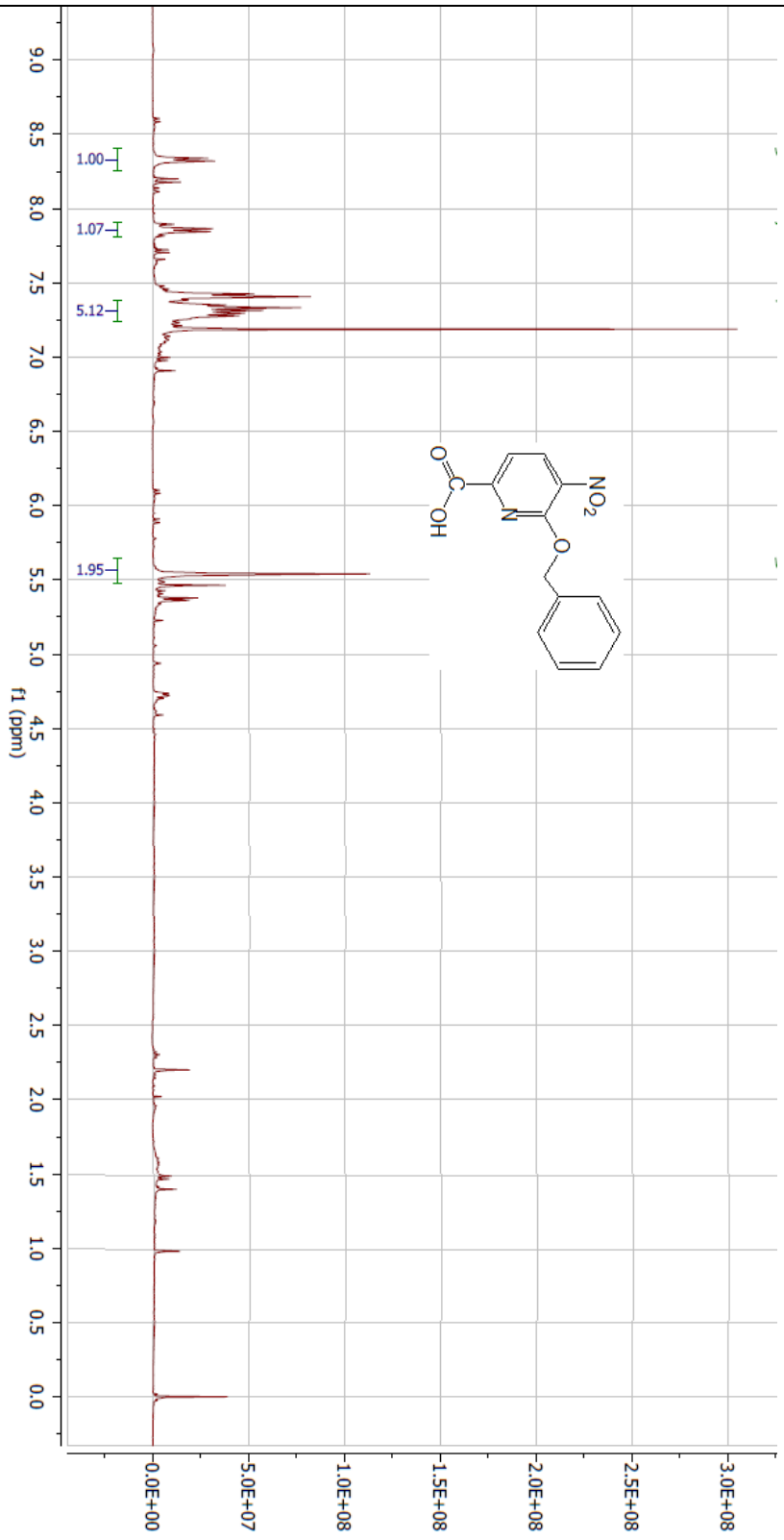


Figure S84. ^{1}H-NMR of O-Benzyl (in $CDCl_3$).

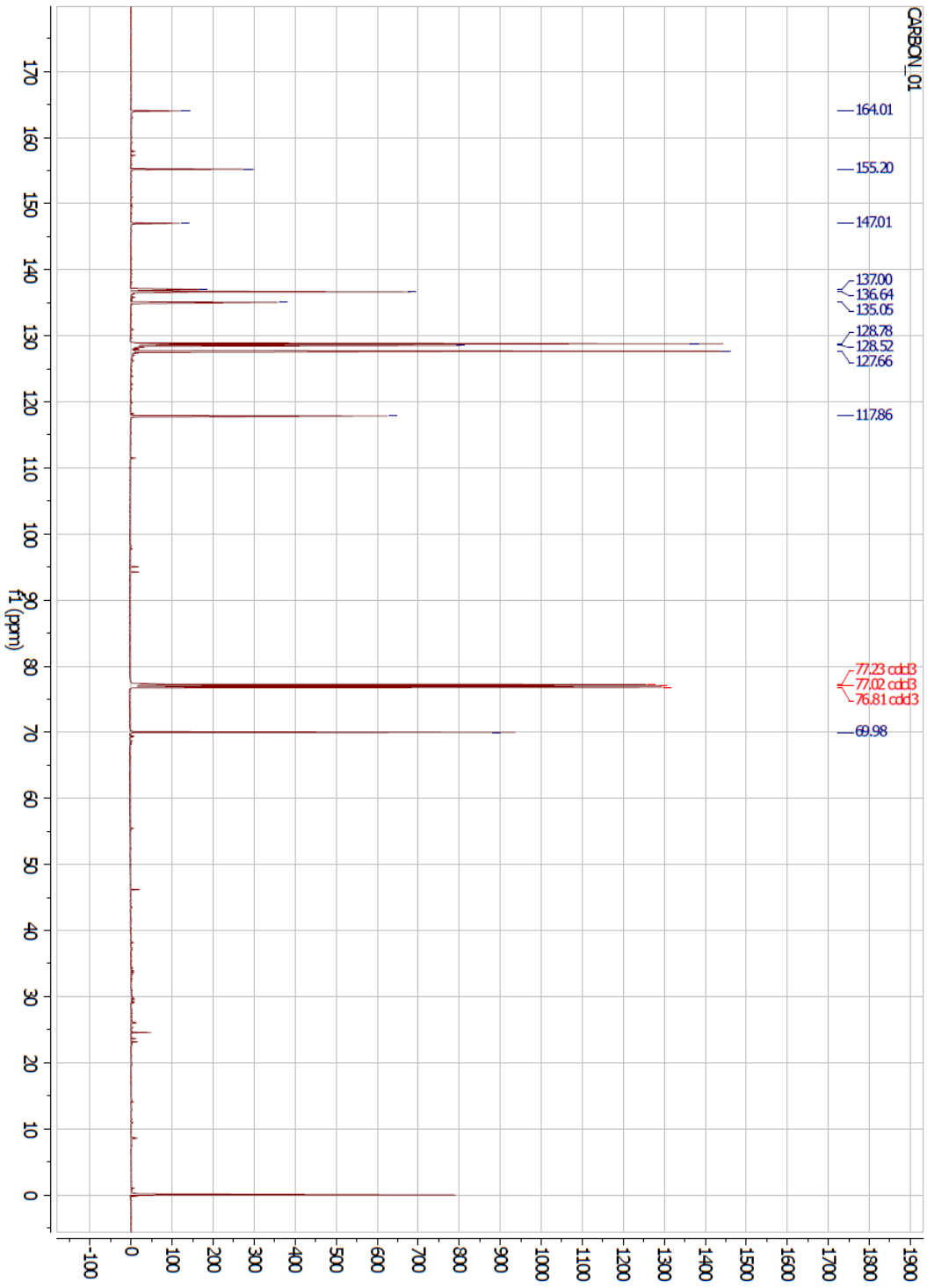


Figure S85. ^{13}C-NMR of O-Benzyl (in $CDCl_3$).

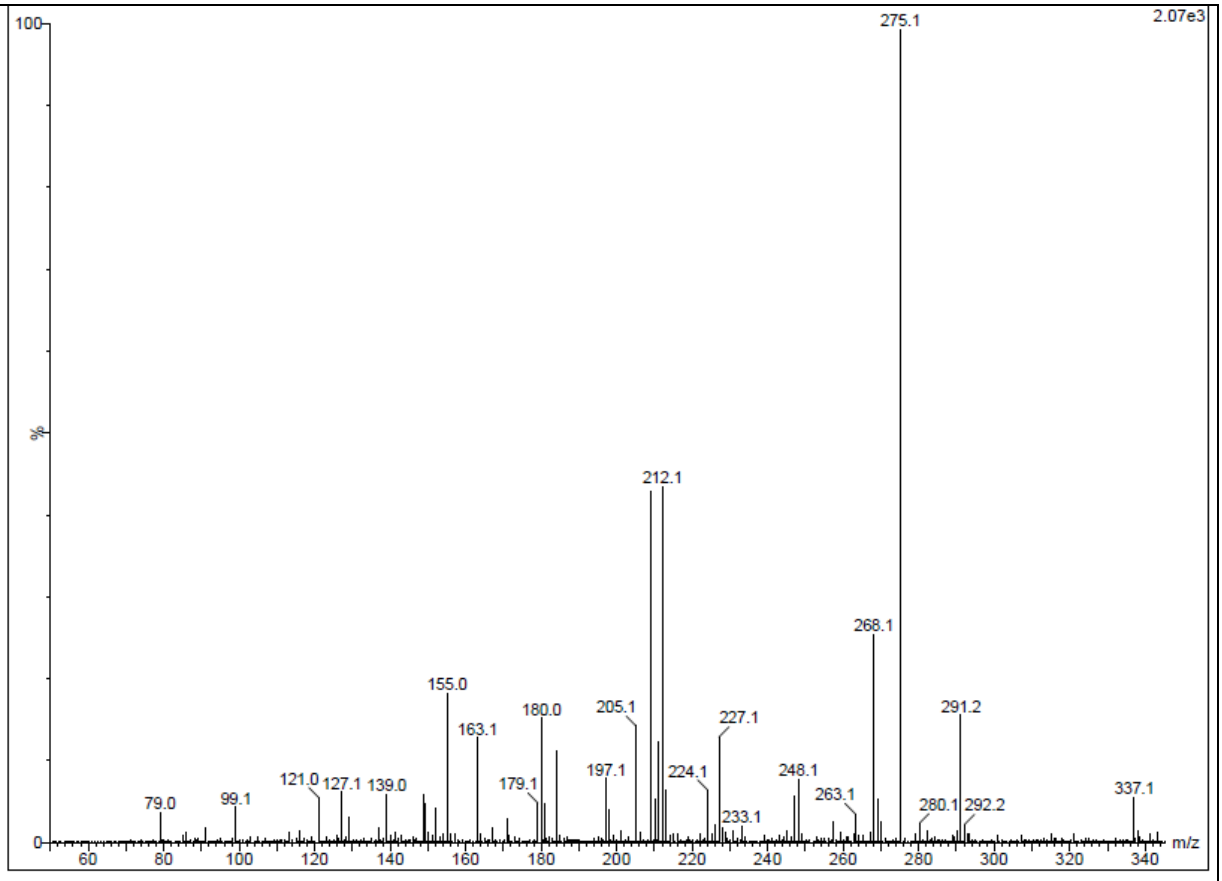


Figure S86. MS-ESI of O-Benzyl.

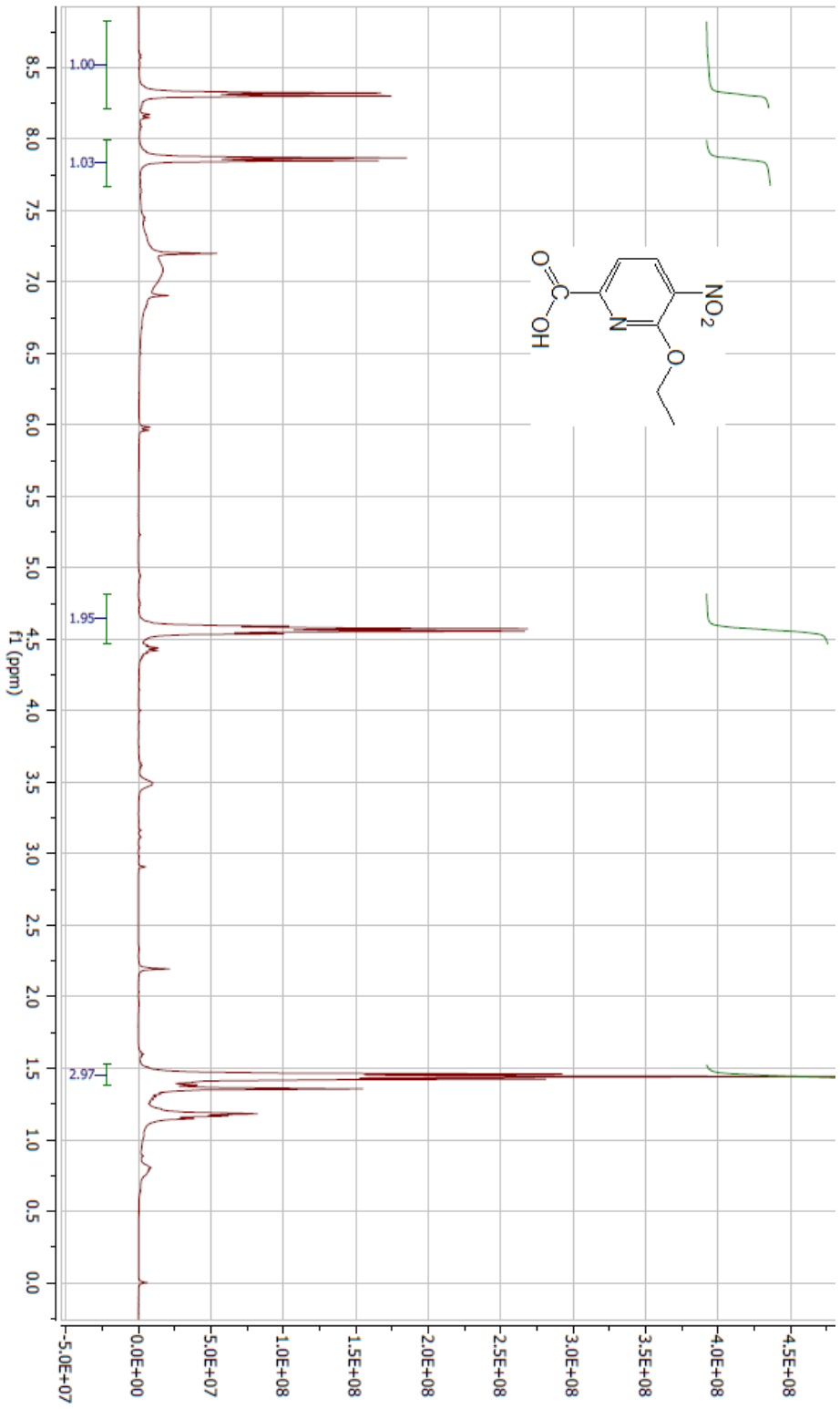


Figure S87. ^{1}H-NMR of O-Ethyl (in $CDCl_3$).

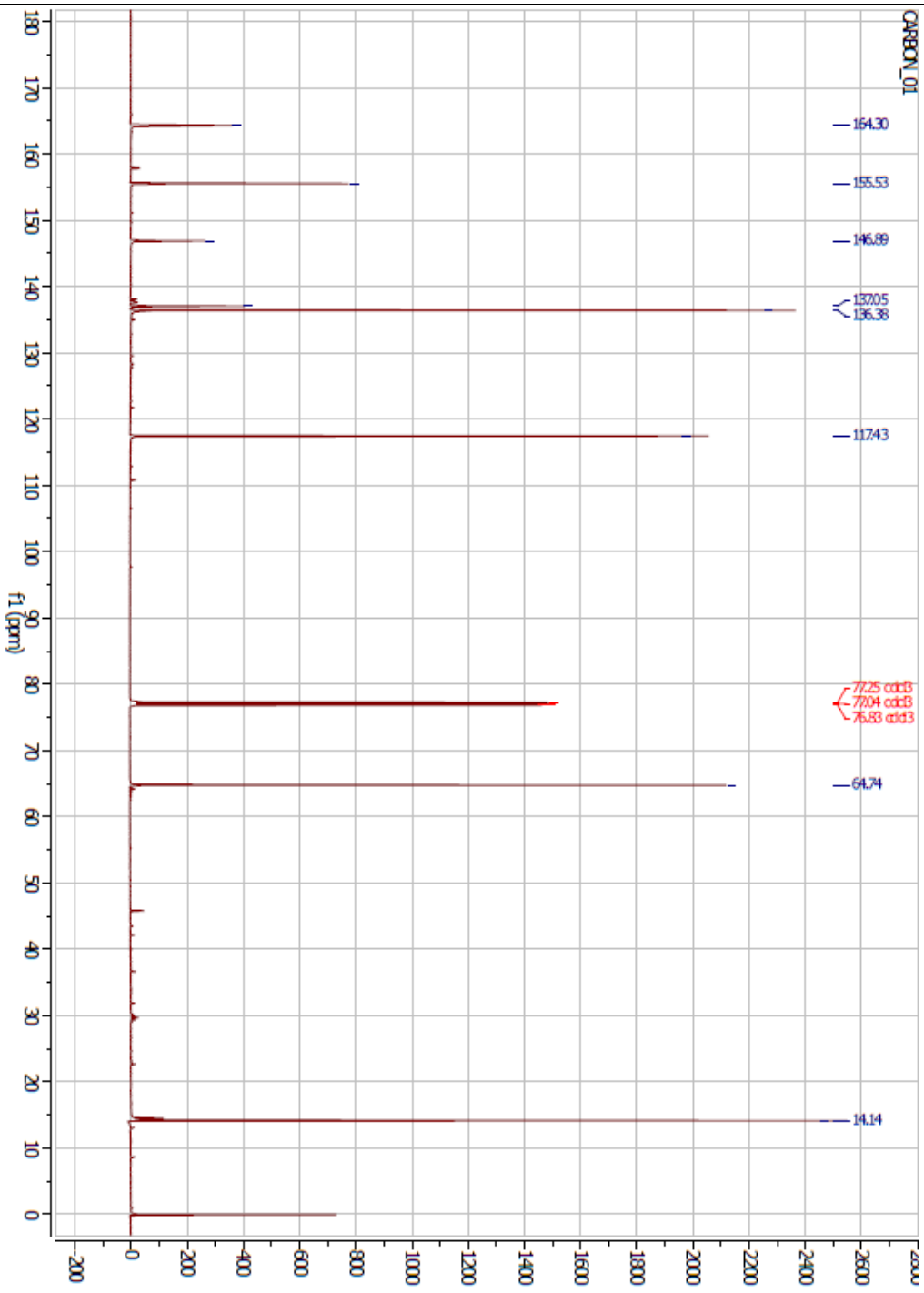


Figure S88. ^{13}C-NMR of O-Ethyl (in $CDCl_3$).

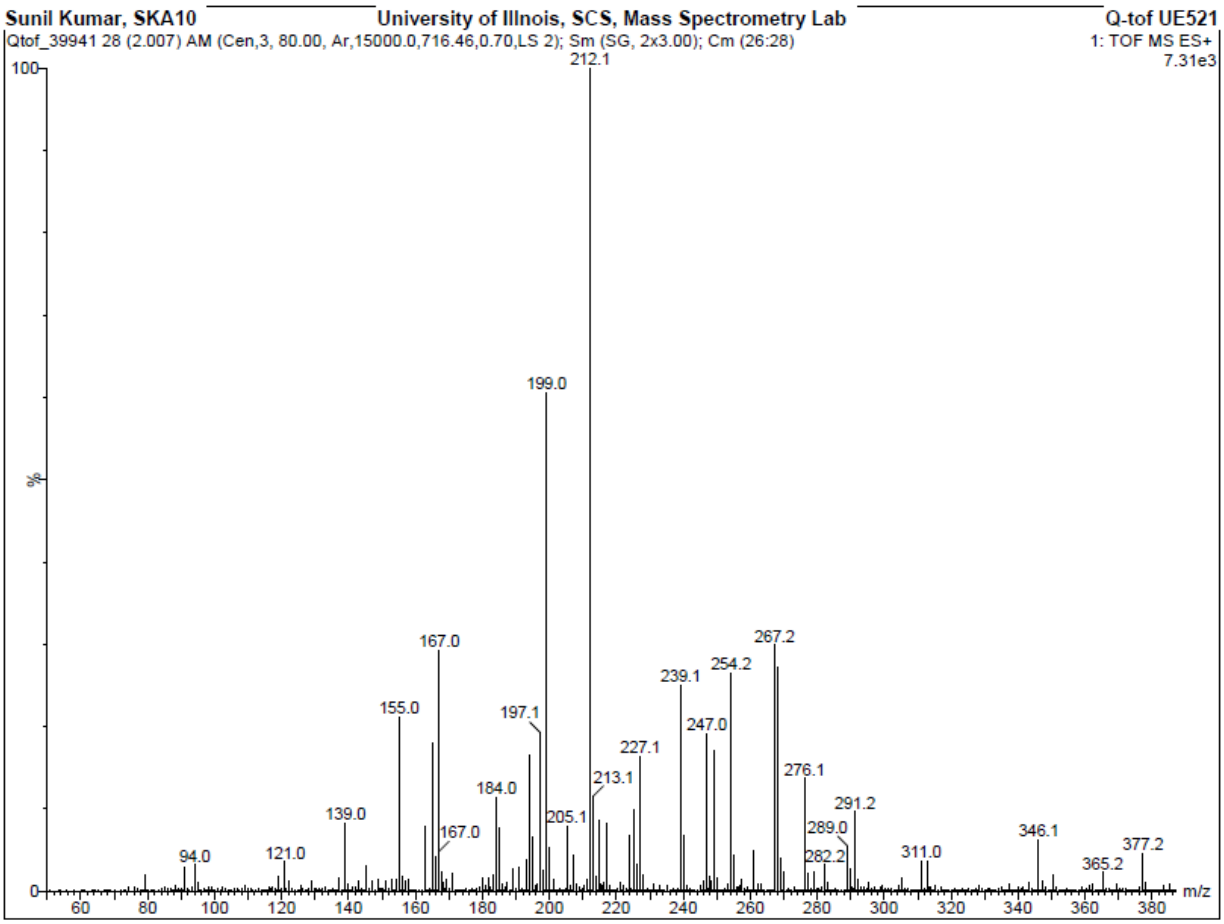


Figure S89. MS-ESI of O-Ethyl.

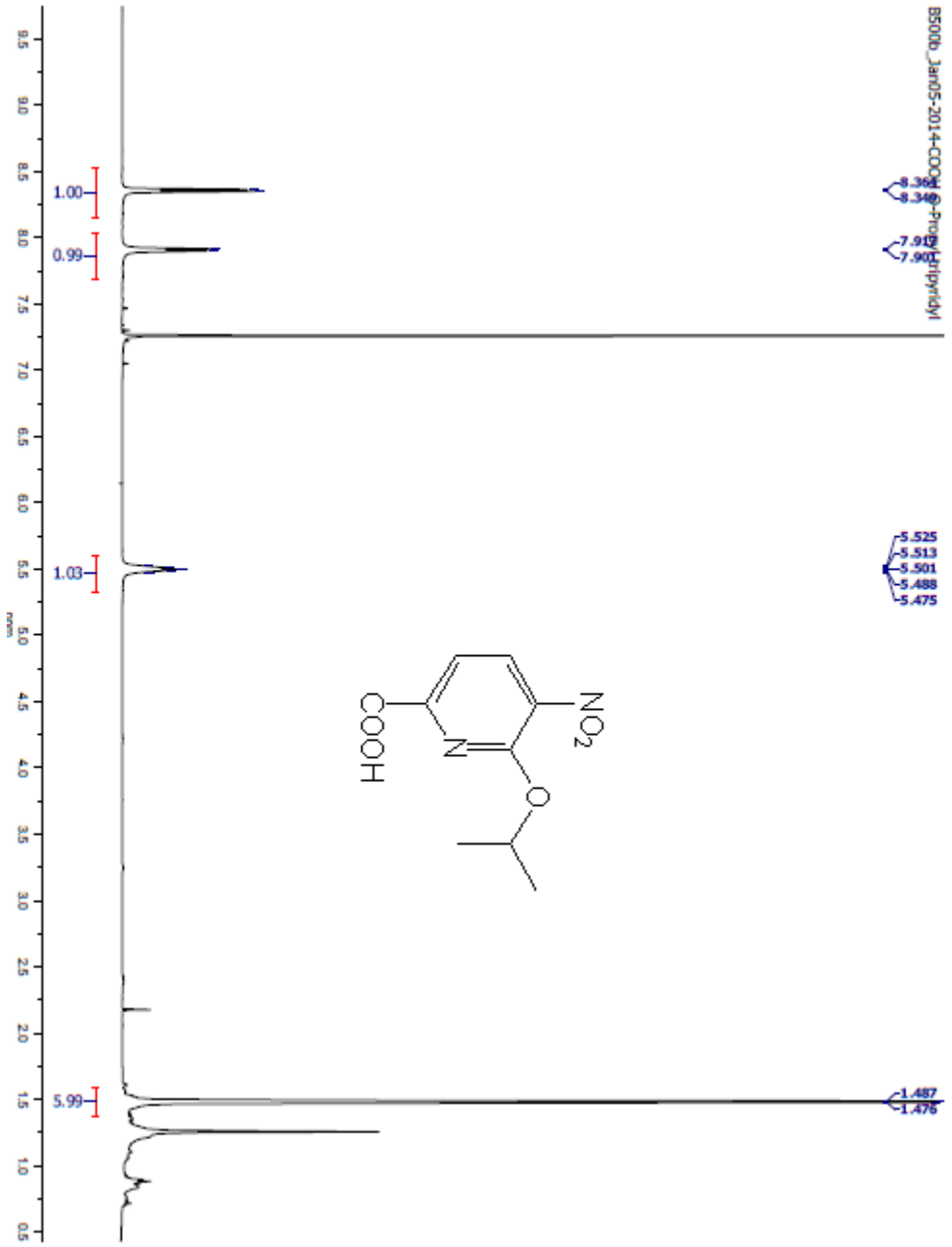


Figure S90. ^{1}H-NMR of O-Propyl (in $CDCl_3$).

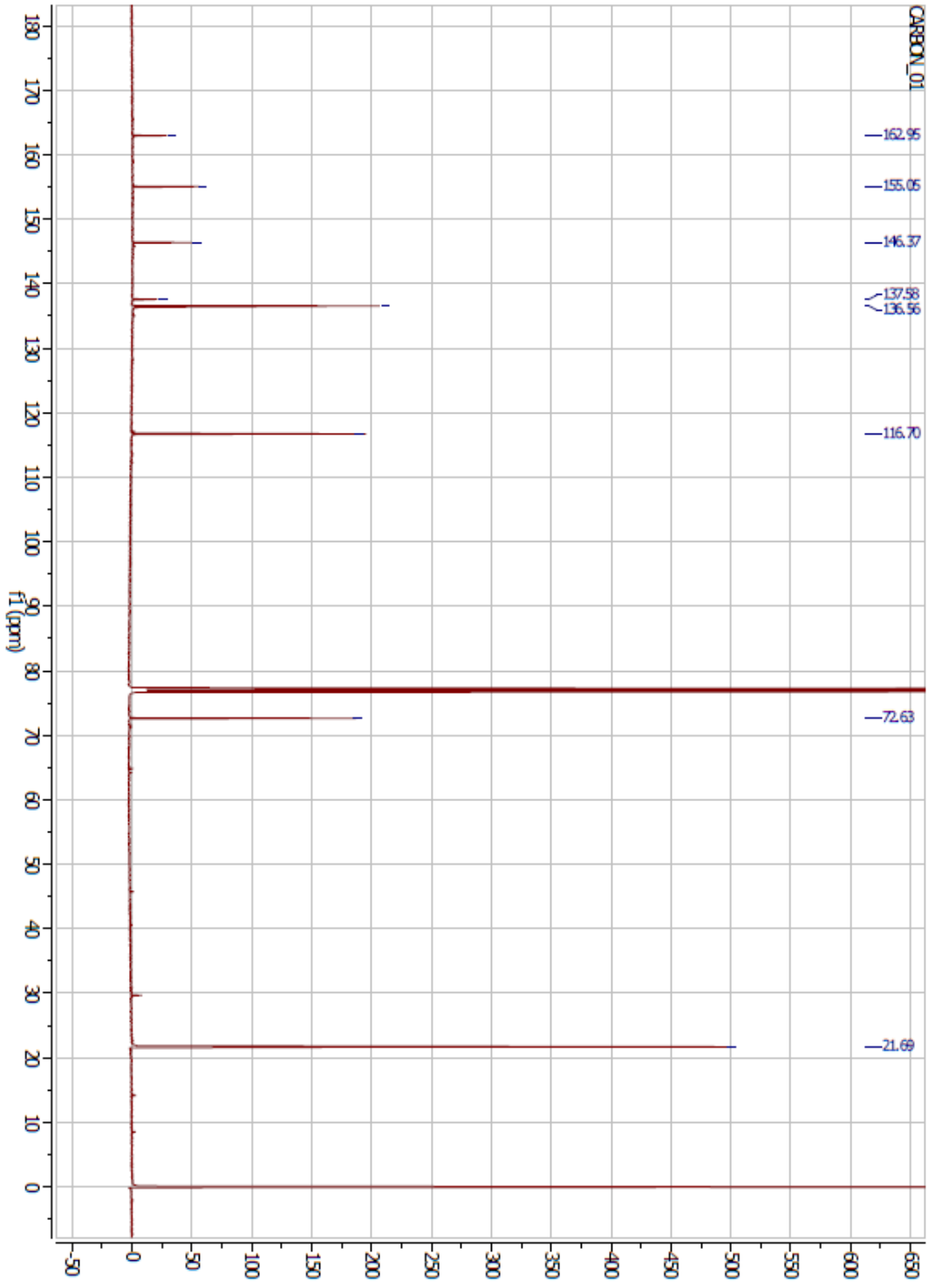


Figure S91. ^{13}C-NMR of O-Propyl (in $CDCl_3$).

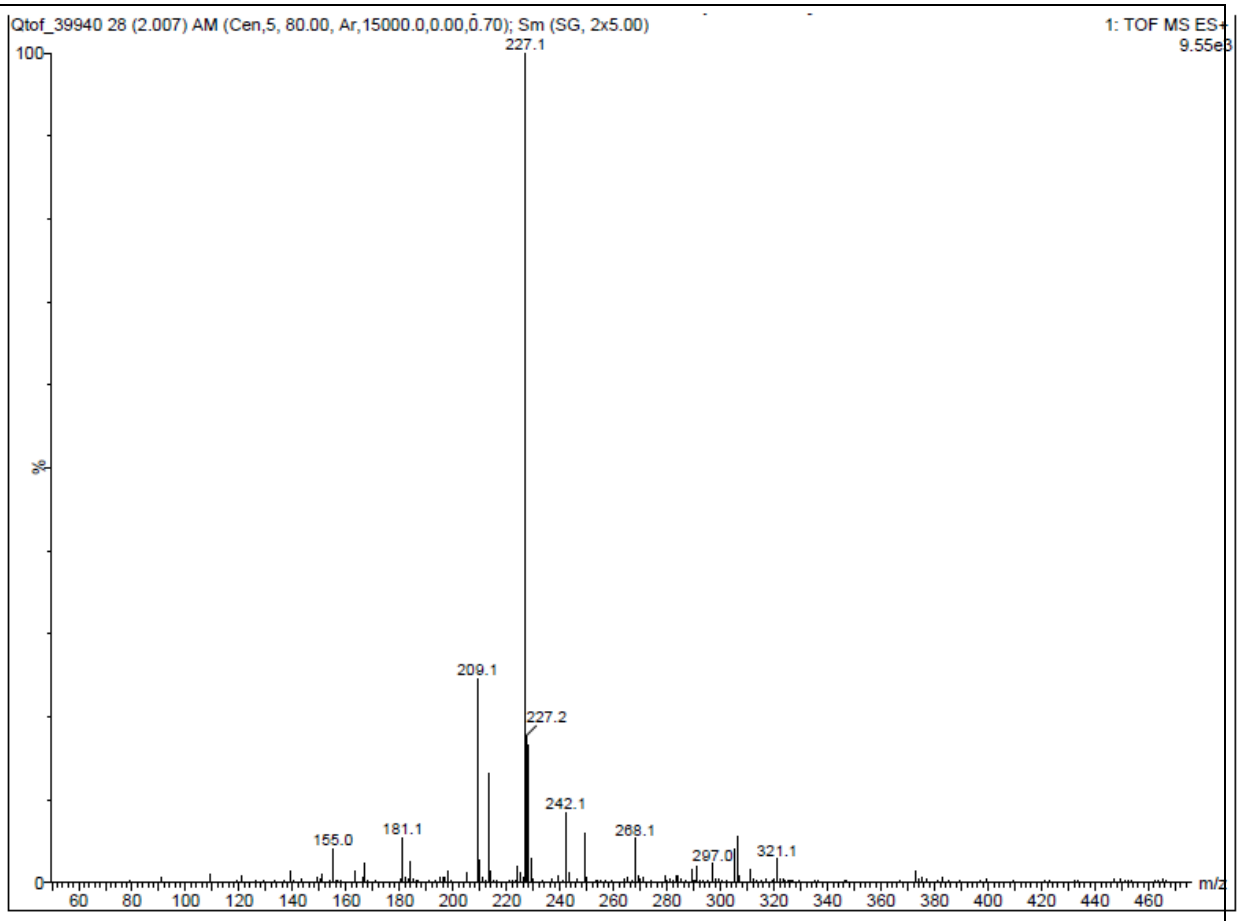


Figure S92. MS-ESI of O-Propyl.

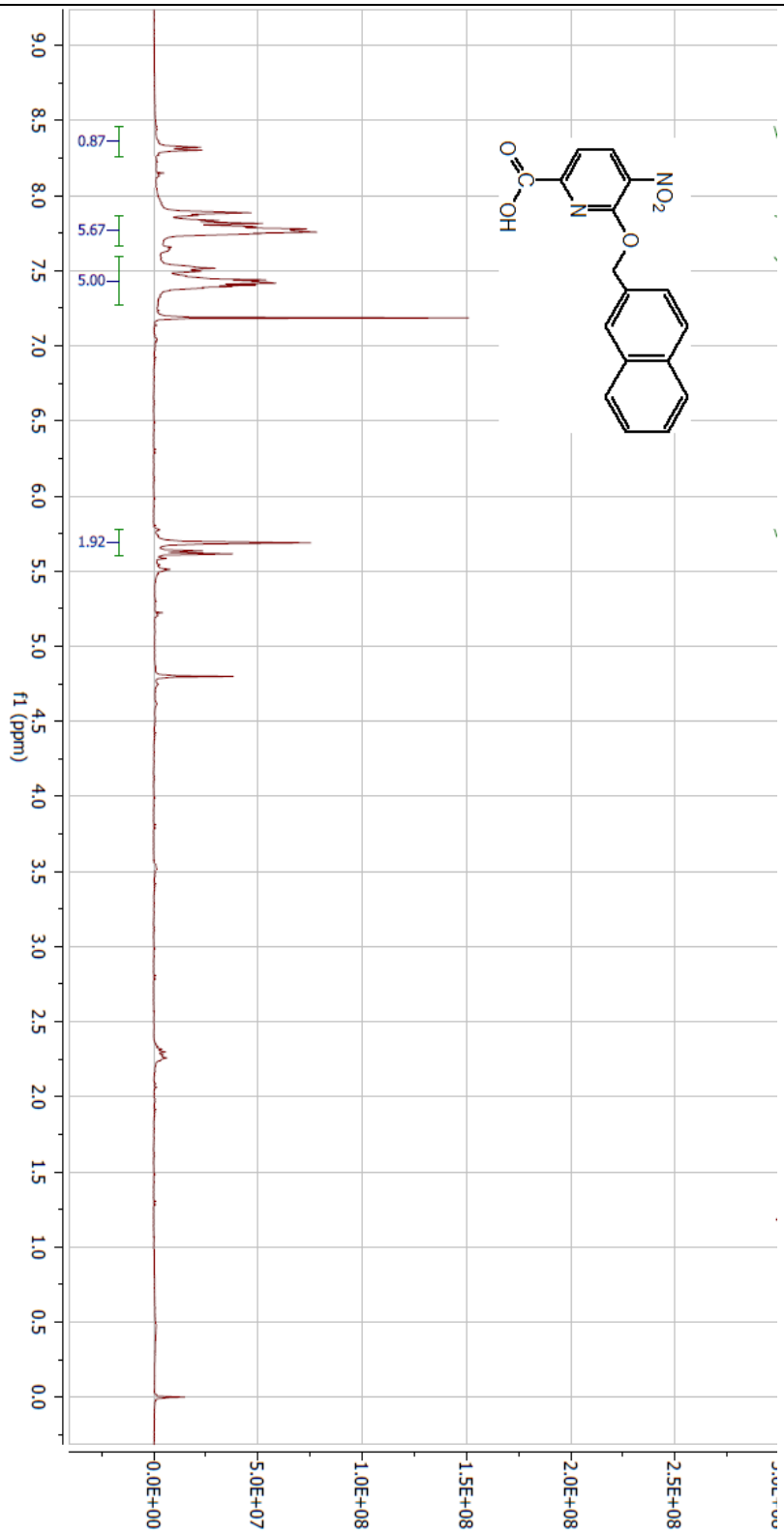


Figure S93. ^{1}H-NMR of O-Naphthalene (in $CDCl_3$).

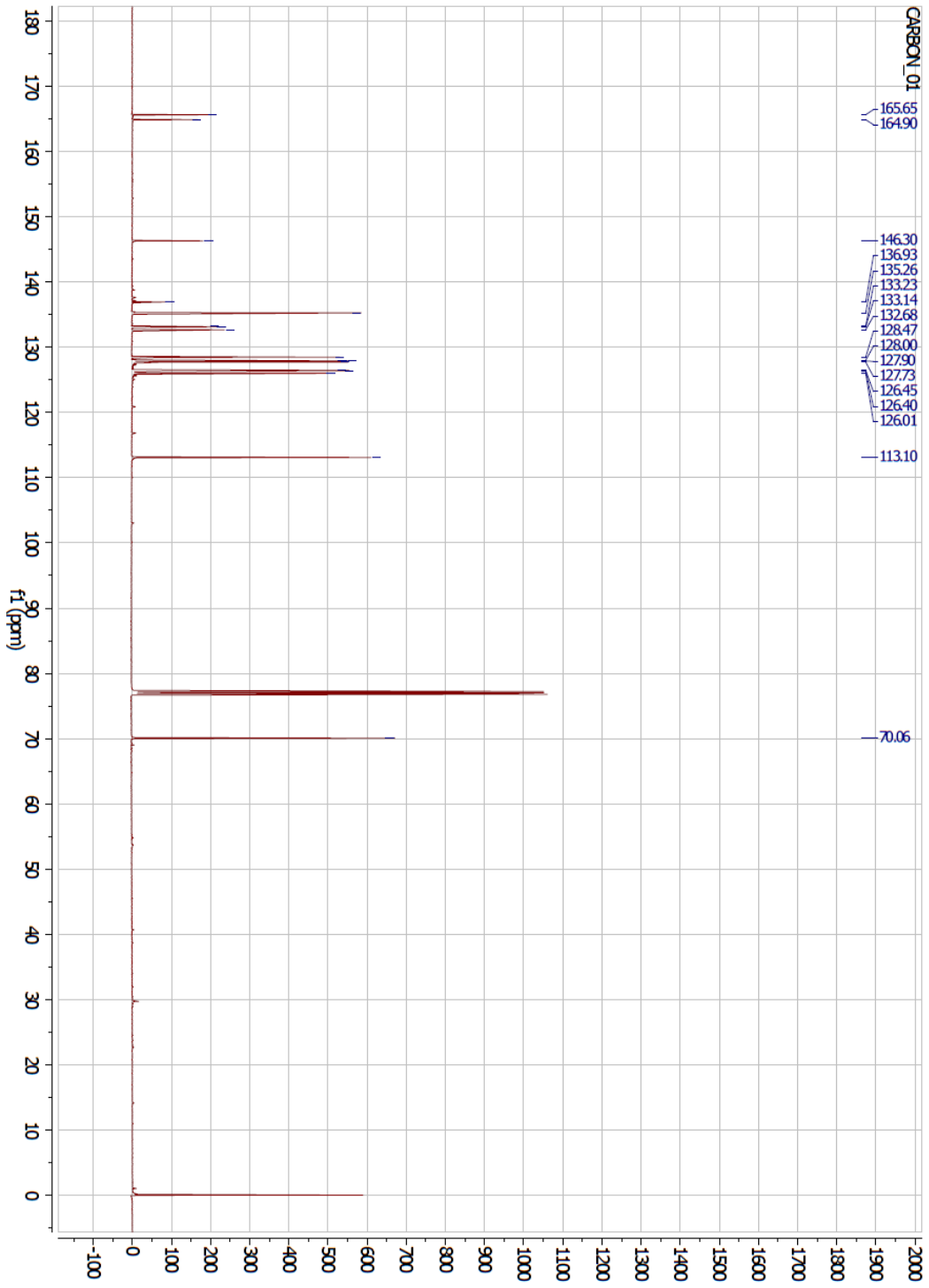


Figure S94. ^{13}C-NMR of O-Naphthalene (in $CDCl_3$).

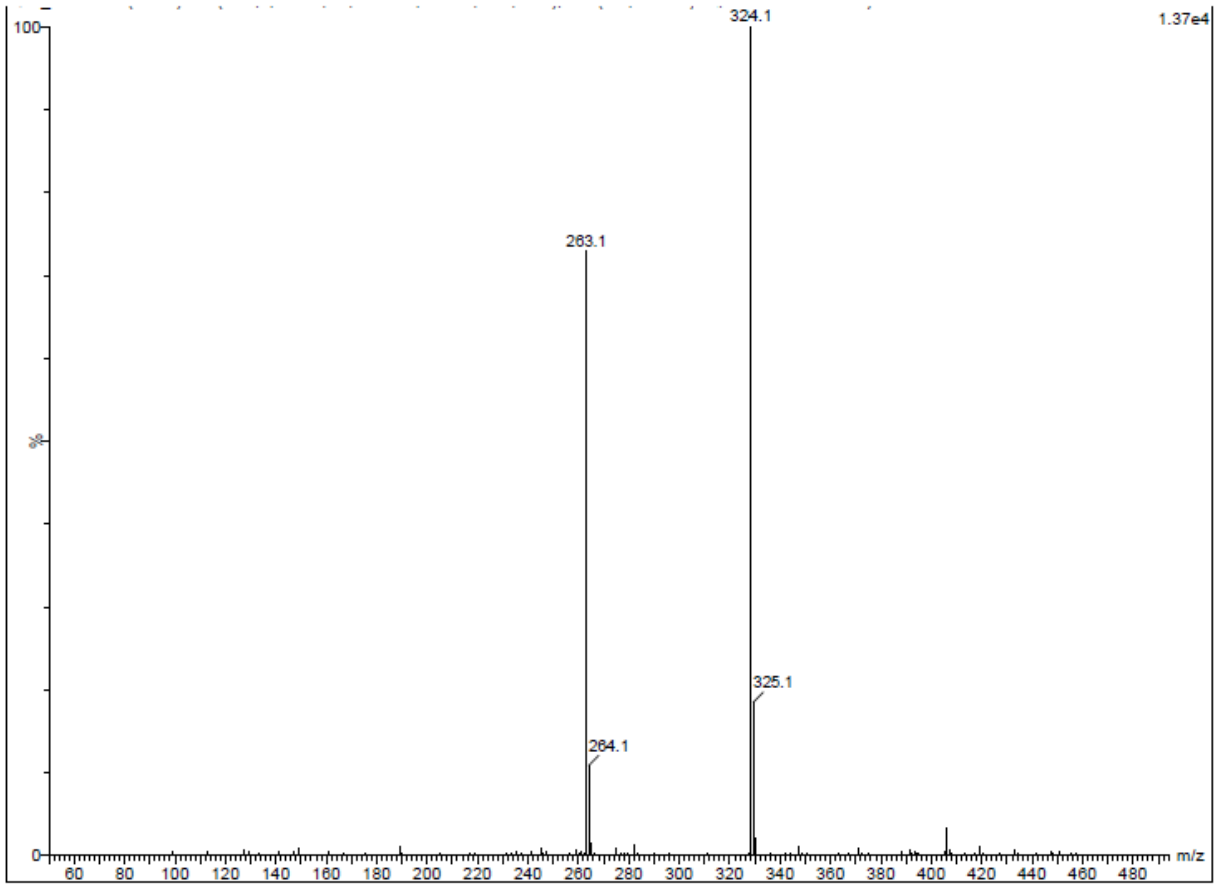


Figure S95. MS-ESI of O-Naphthalene.

Series 4:

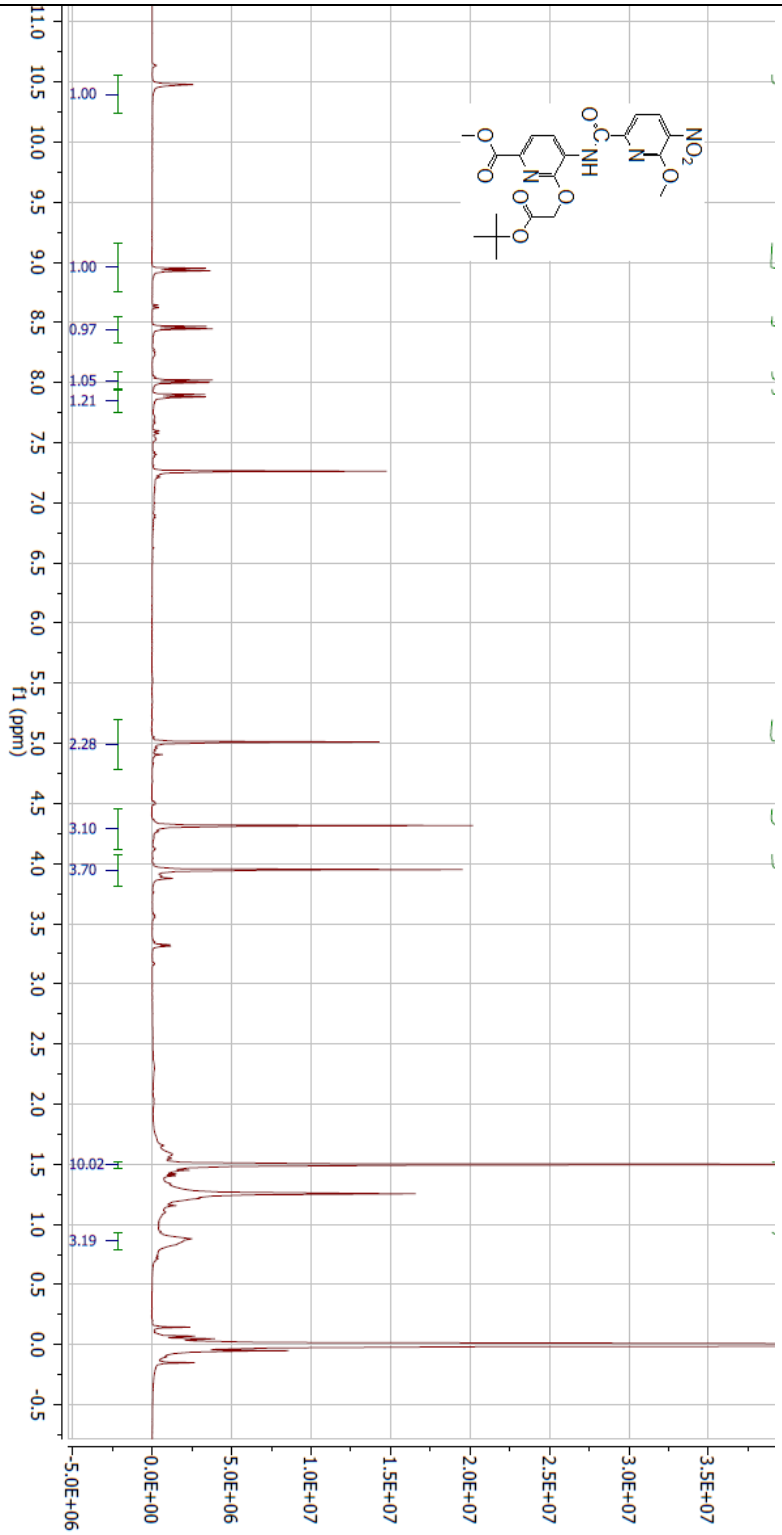


Figure S96. ^{1}H-NMR of O-Ethyl (in $CDCl_3$).

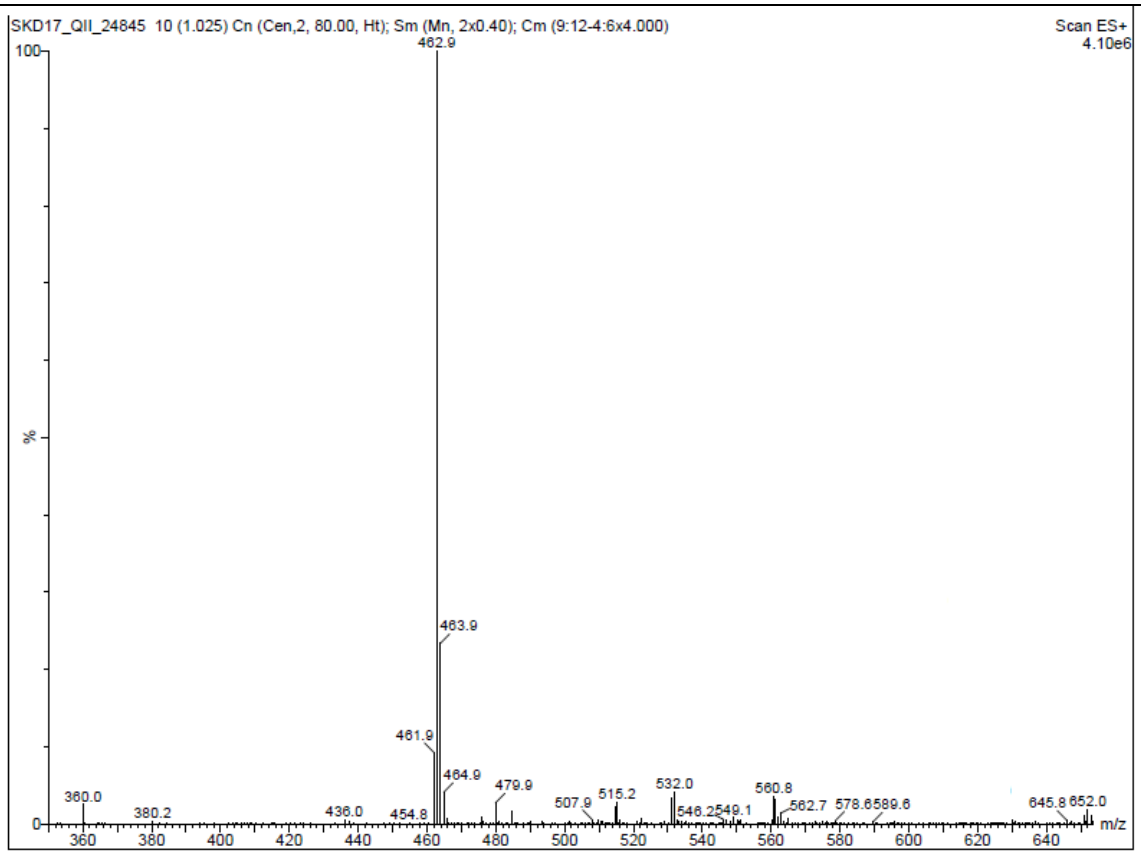


Figure S97. MS-ESI of O-Ethyl.

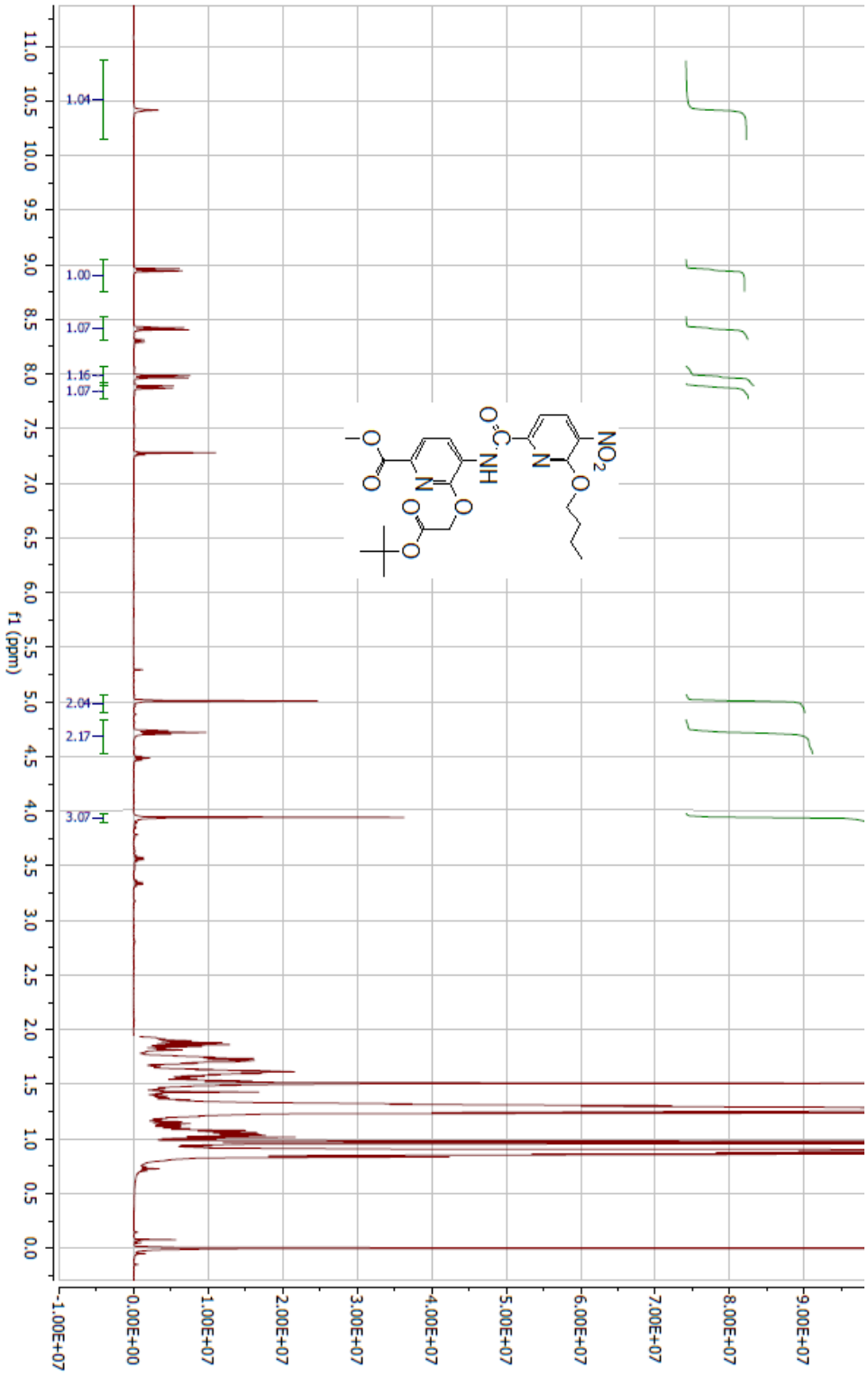


Figure S98. ^{1}H-NMR of O-Butyl (in $CDCl_3$).

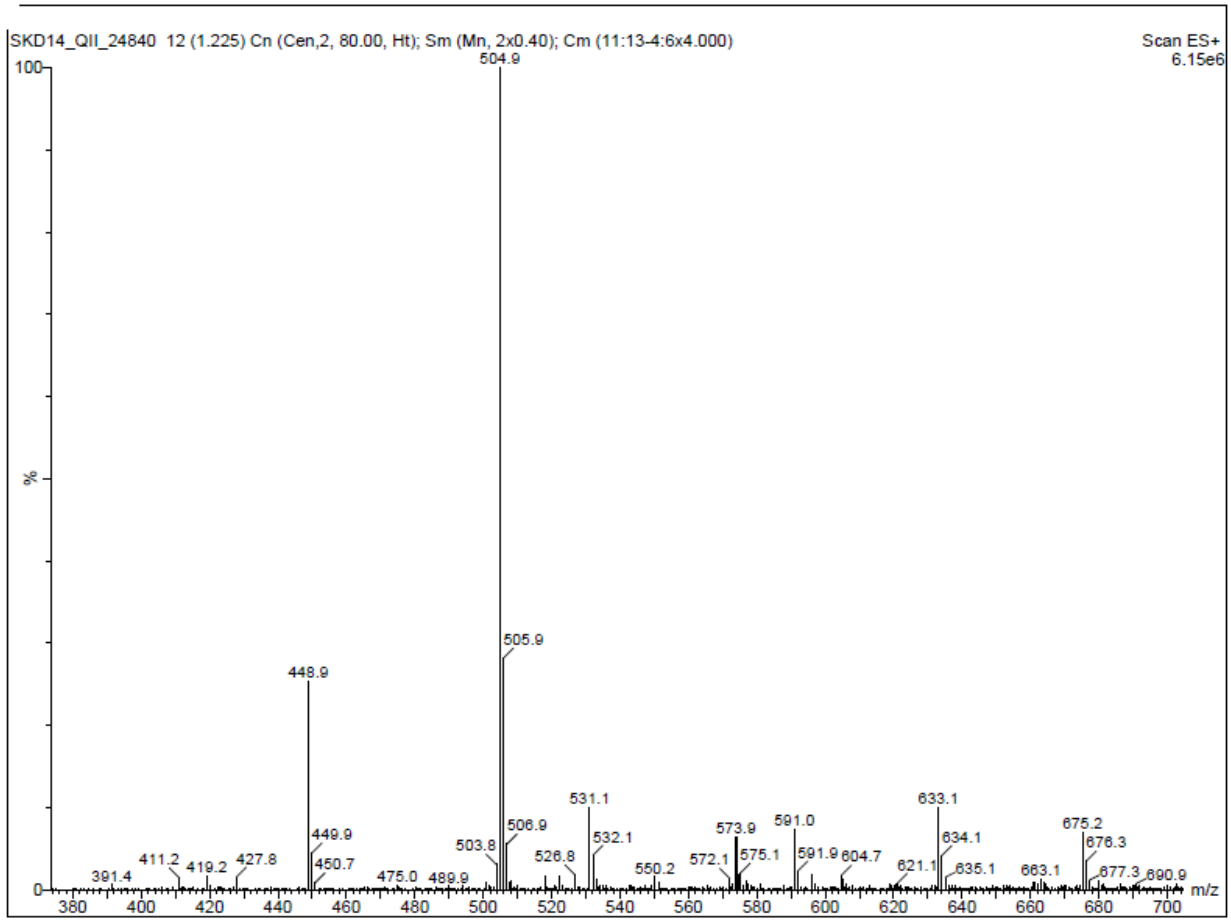


Figure S99. MS-ESI of O-Butyl.

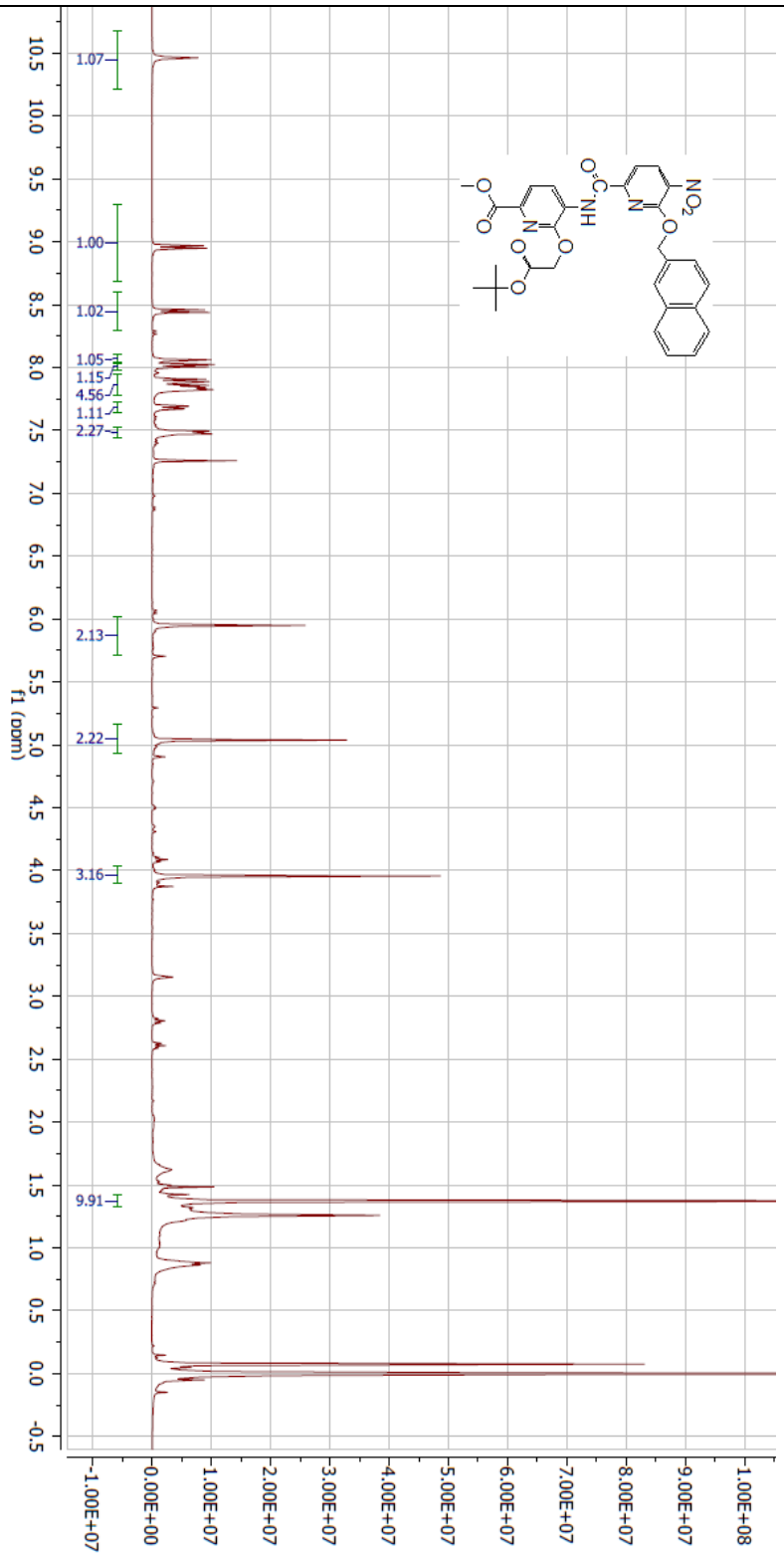


Figure S100. ^{1}H-NMR of O-Naphthalene (in $CDCl_3$).

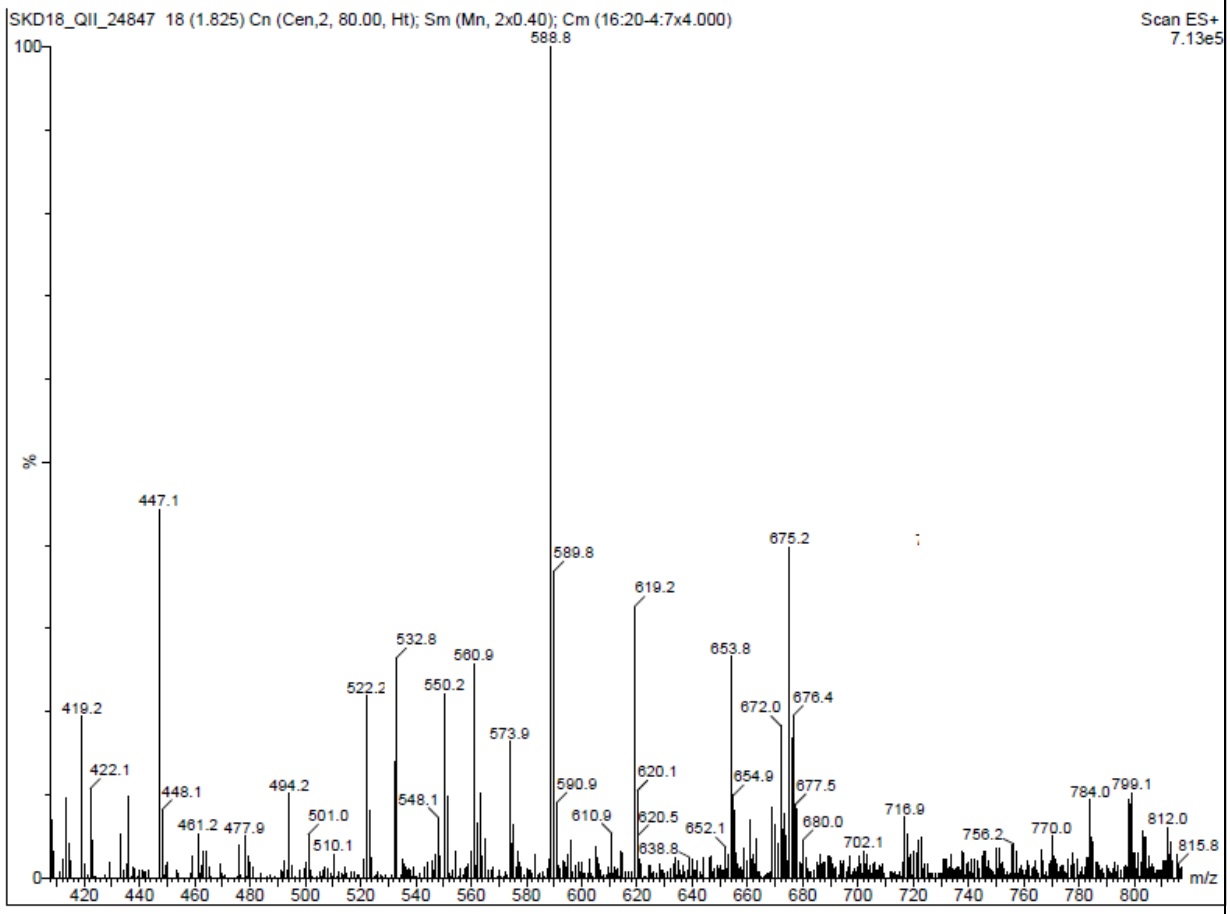


Figure S101. MS-ESI of O-Naphthalene.

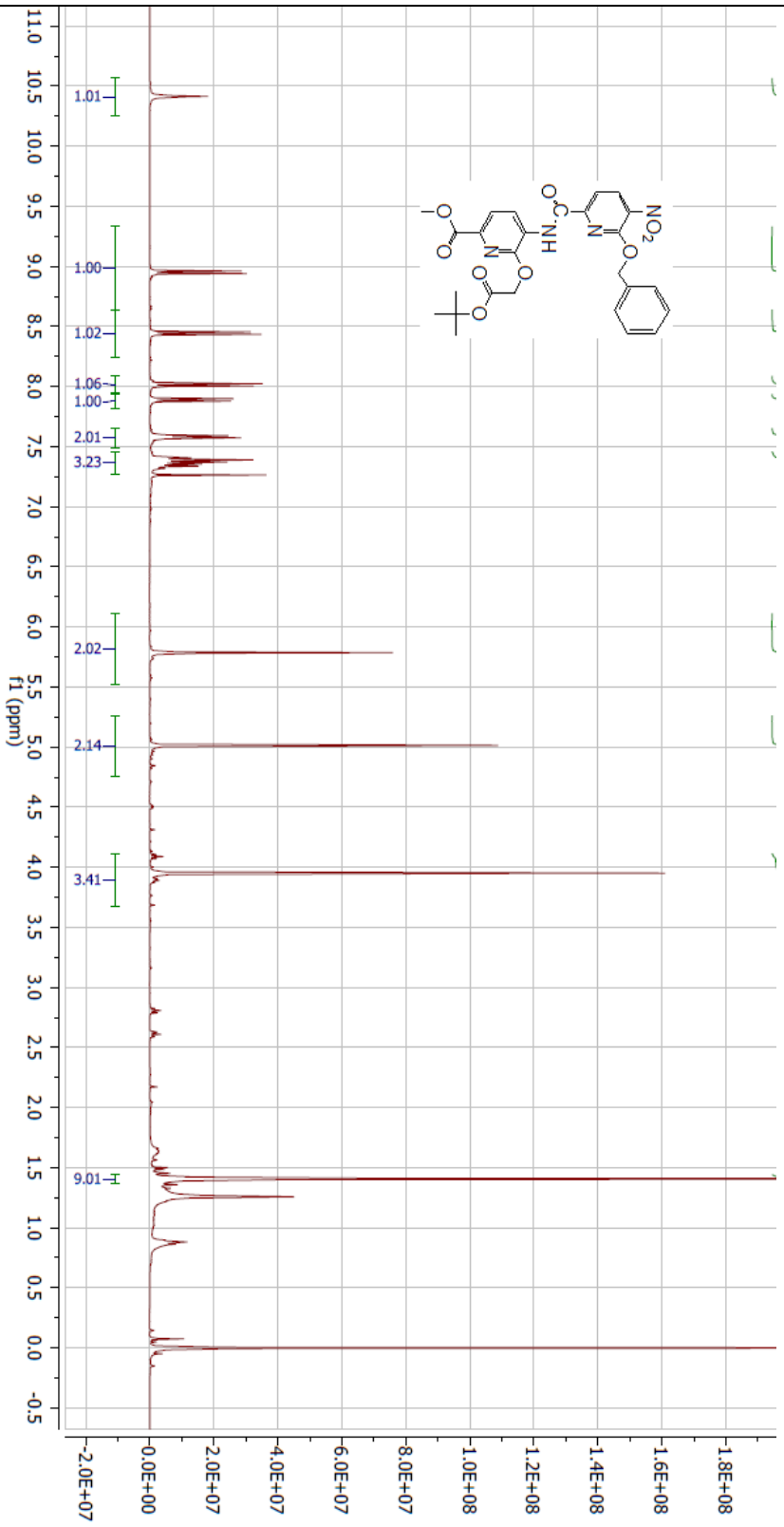


Figure S102. ^{1}H-NMR of O-Benzyl (in $CDCl_3$).

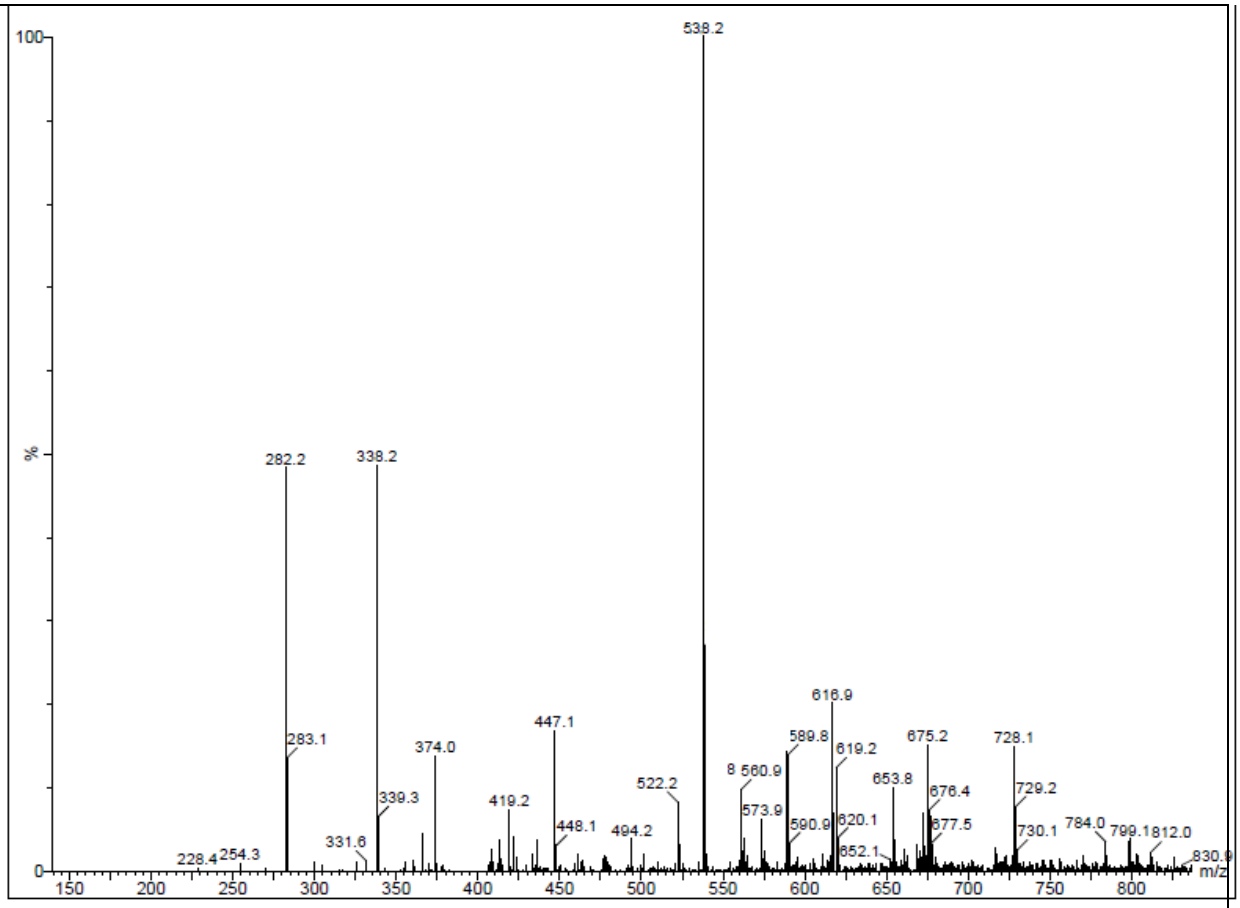


Figure S103. MS-ESI of O-Benzyl.

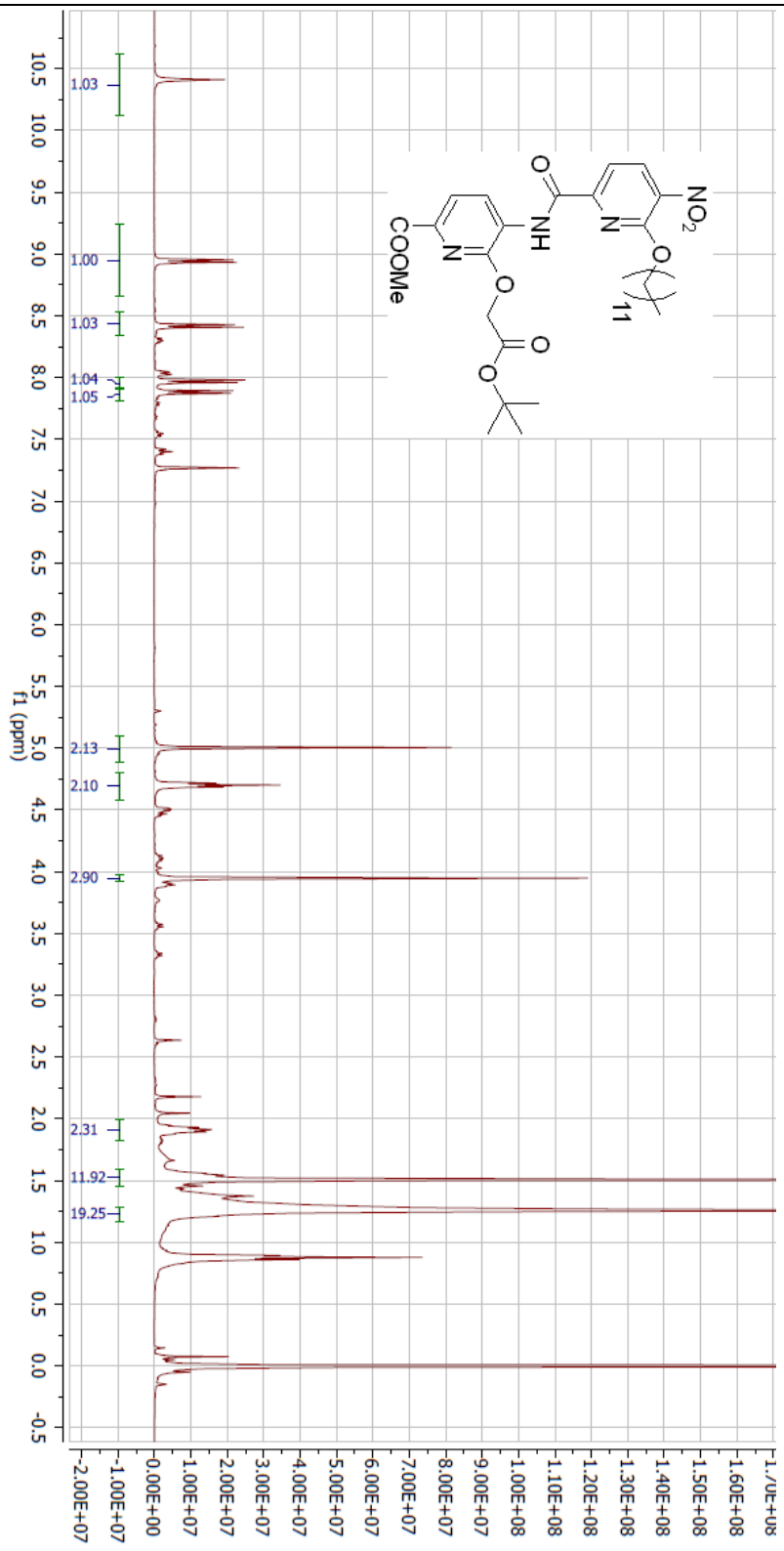


Figure S104. ^{1}H-NMR of O-Dodecane (in $CDCl_3$).

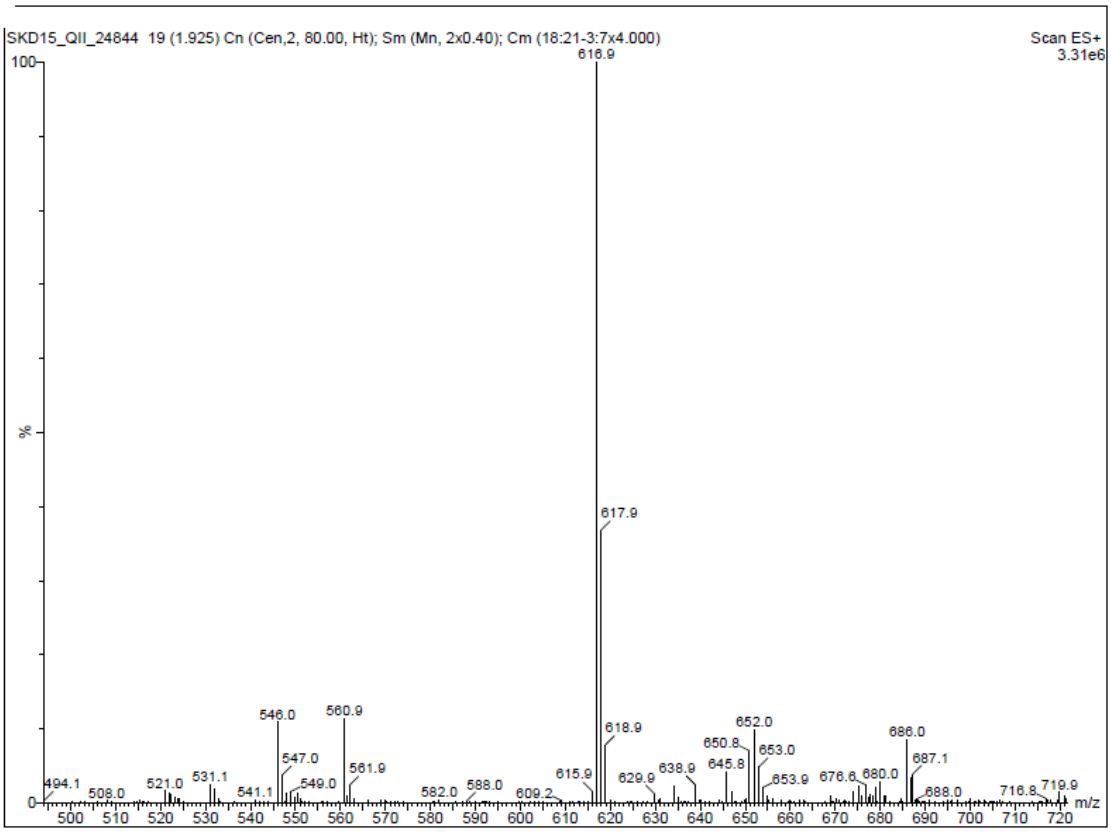


Figure S105. MS-ESI of O-Dodecane.

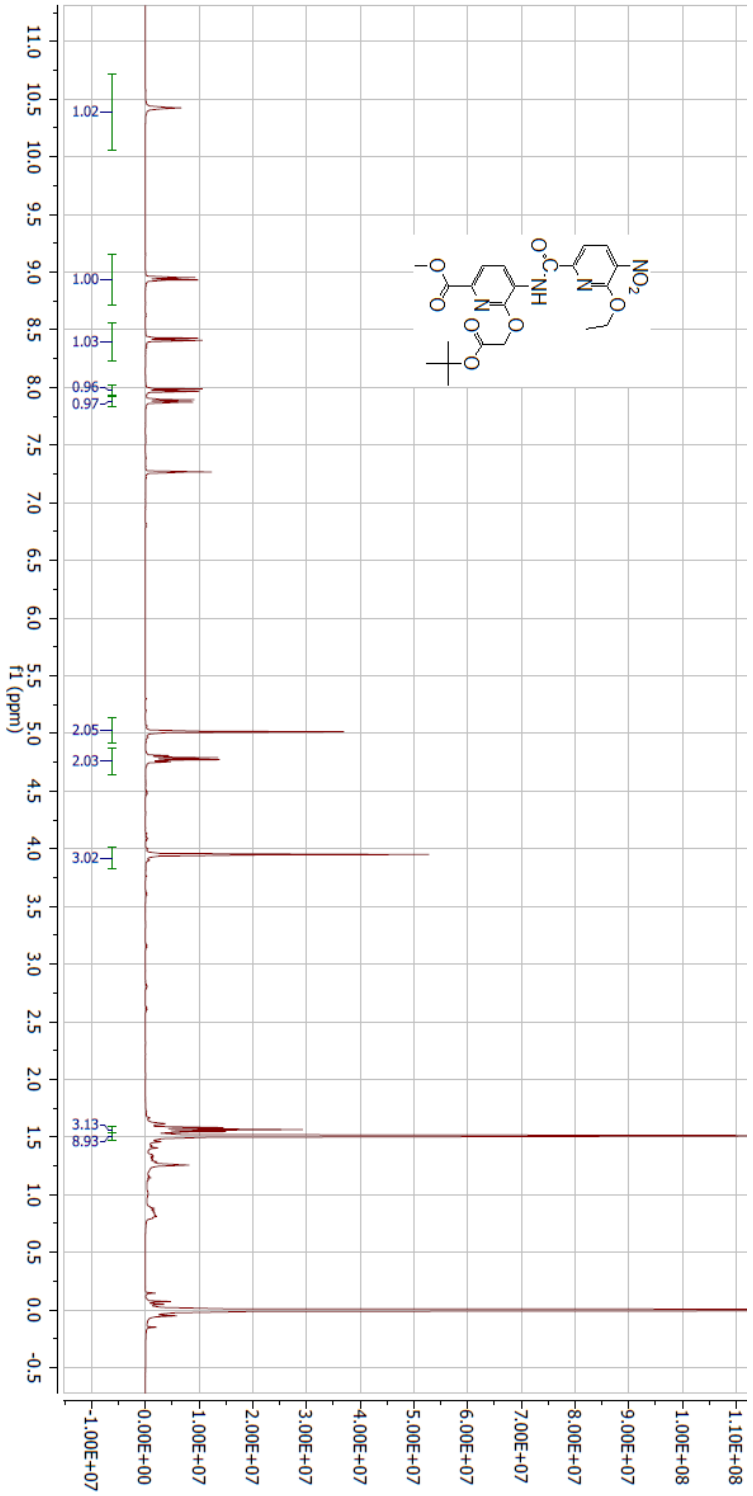


Figure S106. ^{1}H-NMR of O-Ethyl (in $CDCl_3$).

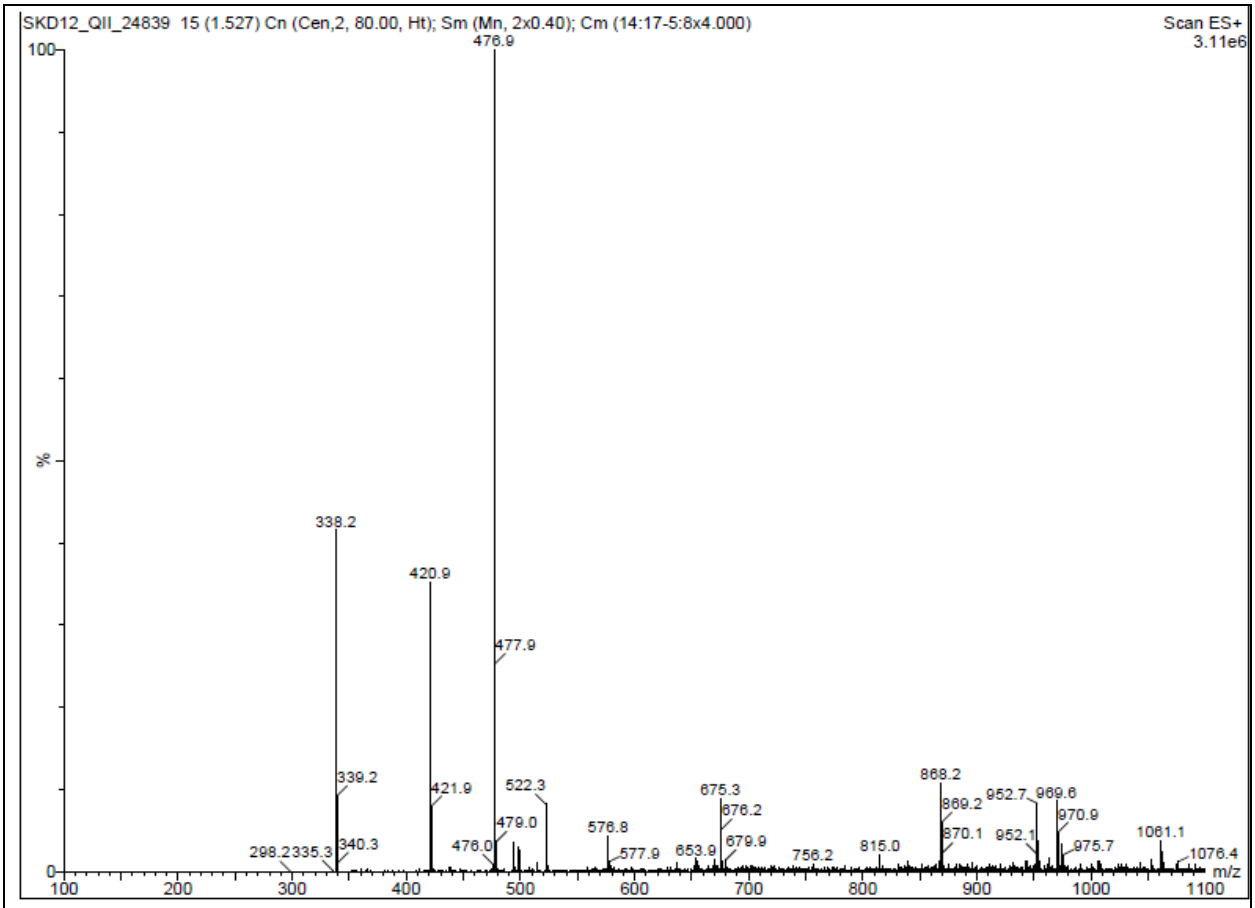


Figure S107. MS-ESI of O-Ethyl.

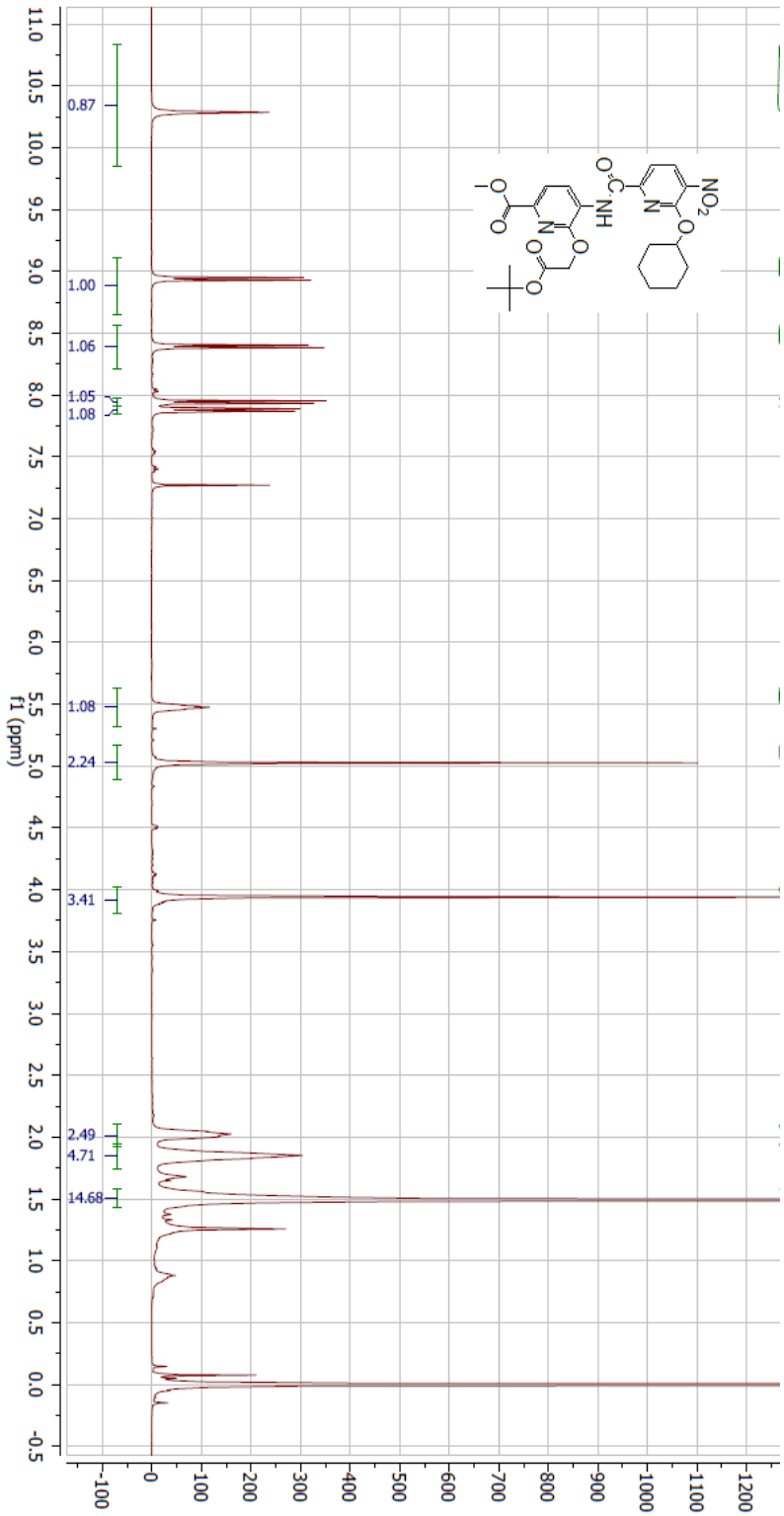


Figure S108. ^{1}H-NMR of O-Cyclohexane (in $CDCl_3$).

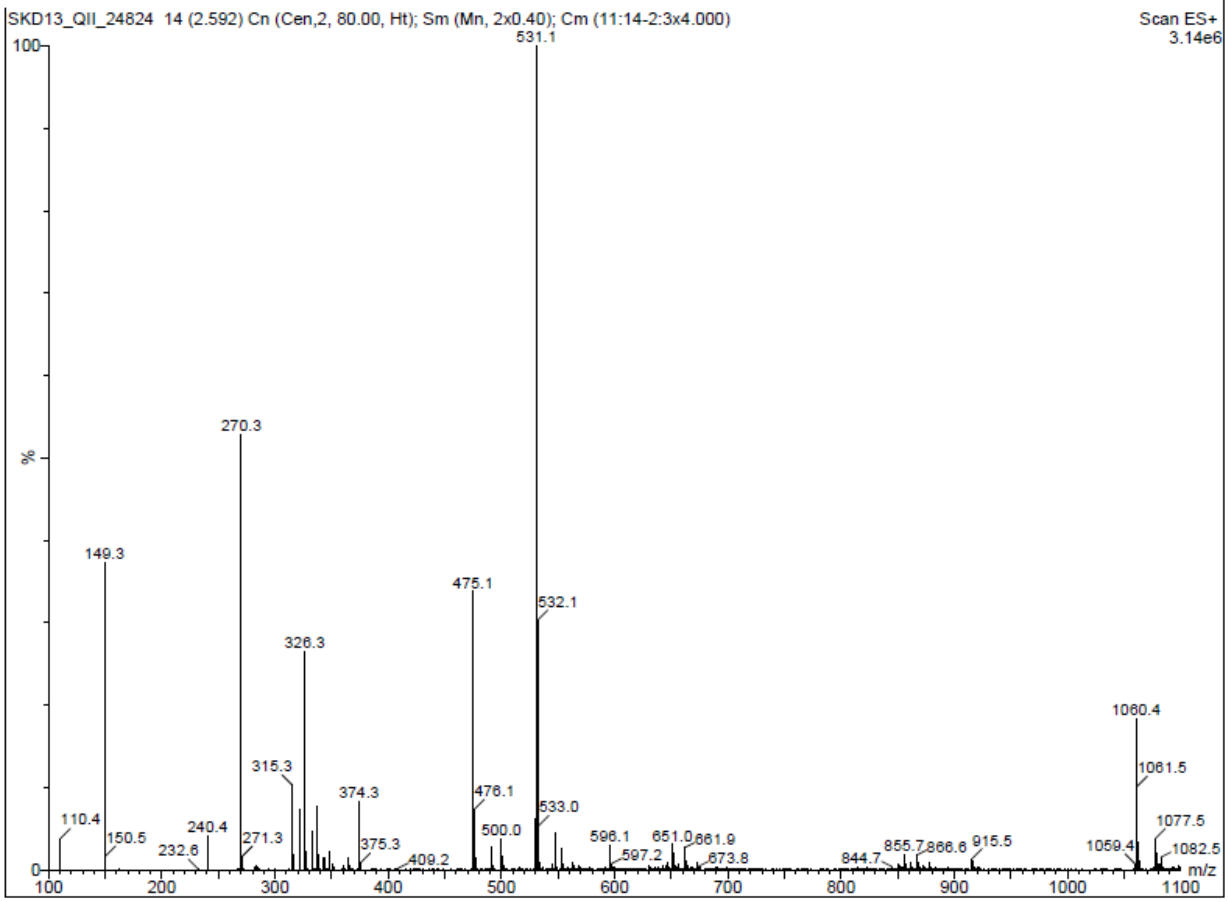


Figure S109. MS-ESI of O-Cyclohexane.

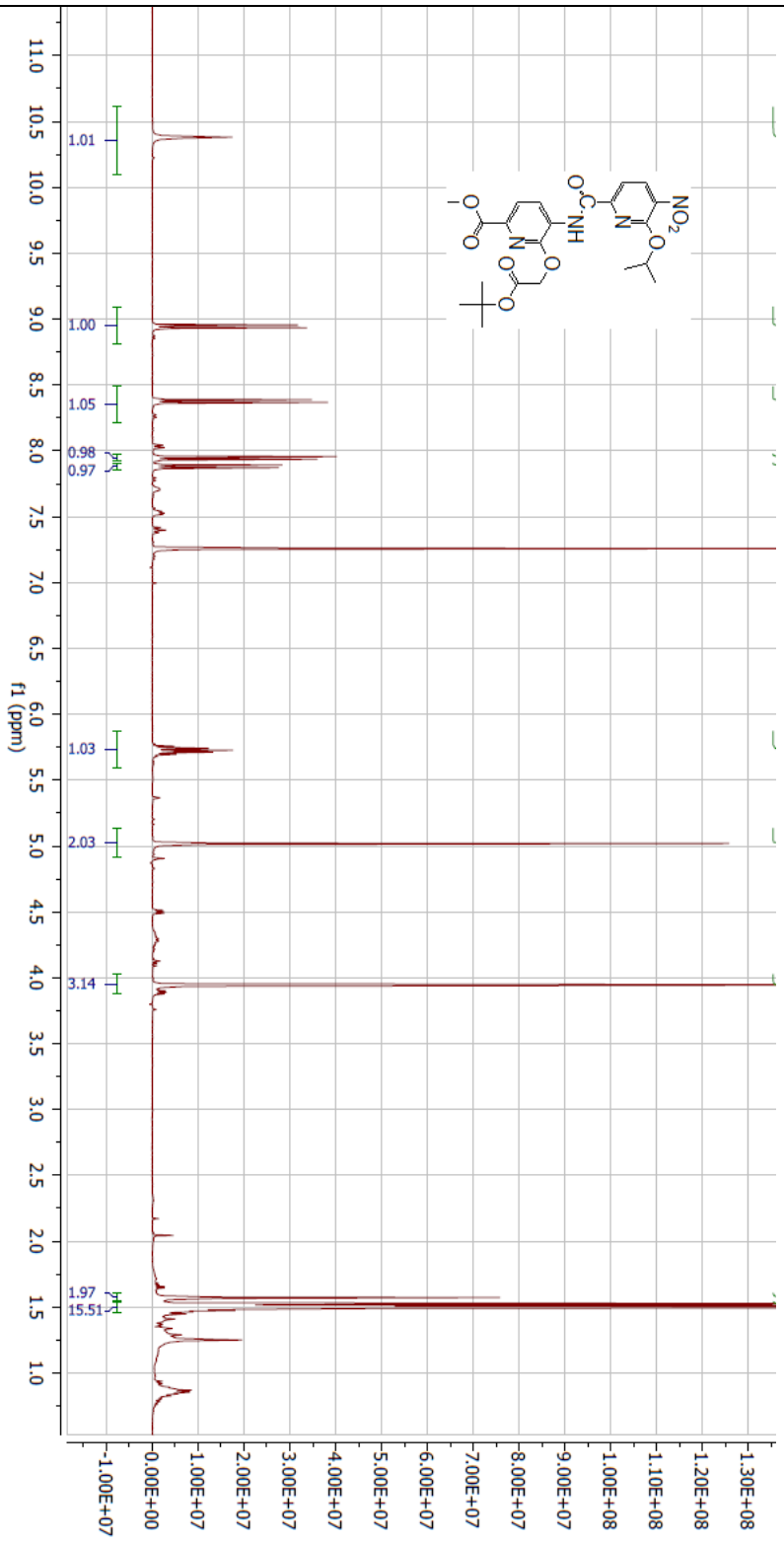


Figure S110. ^{1}H-NMR of O-Propyl (in $CDCl_3$).

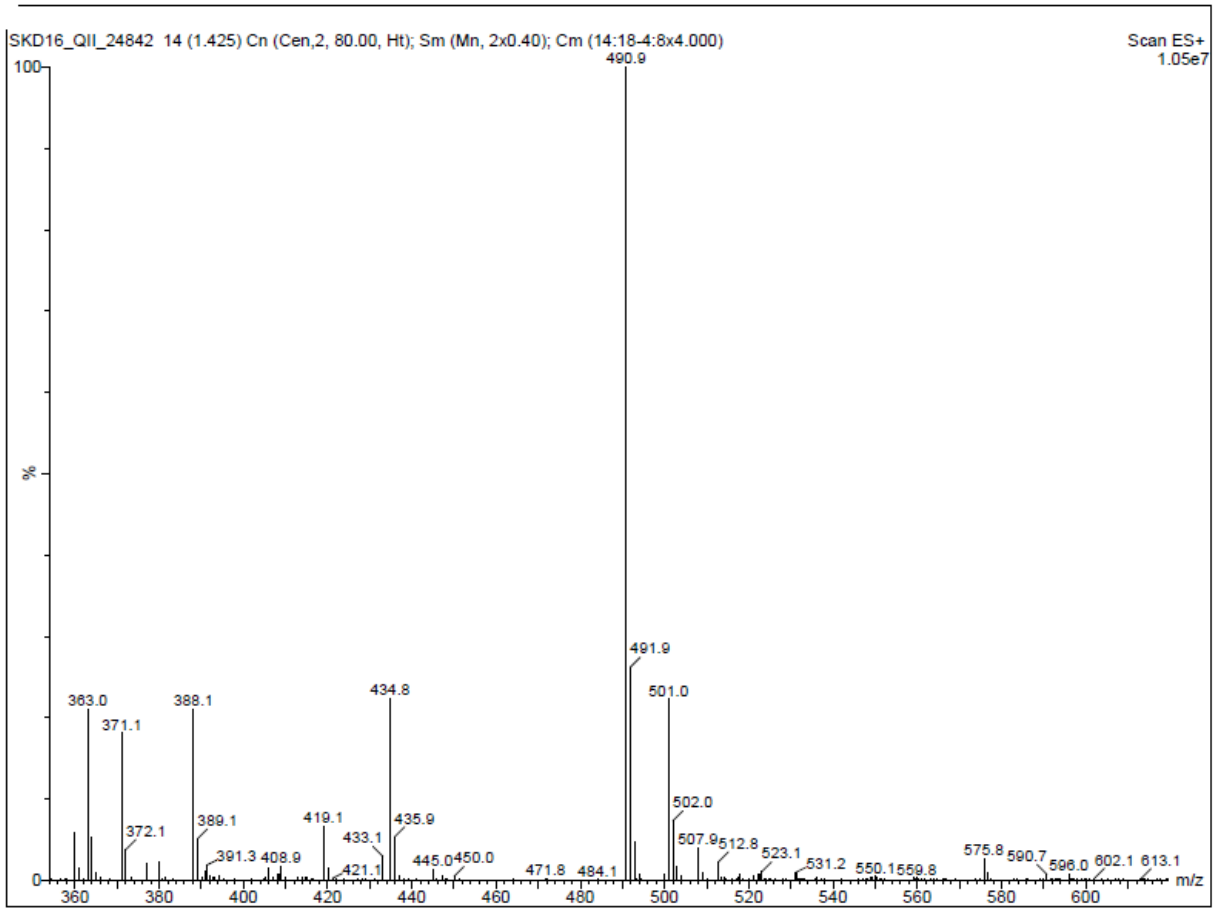


Figure S111. MS-ESI of O-Propyl.

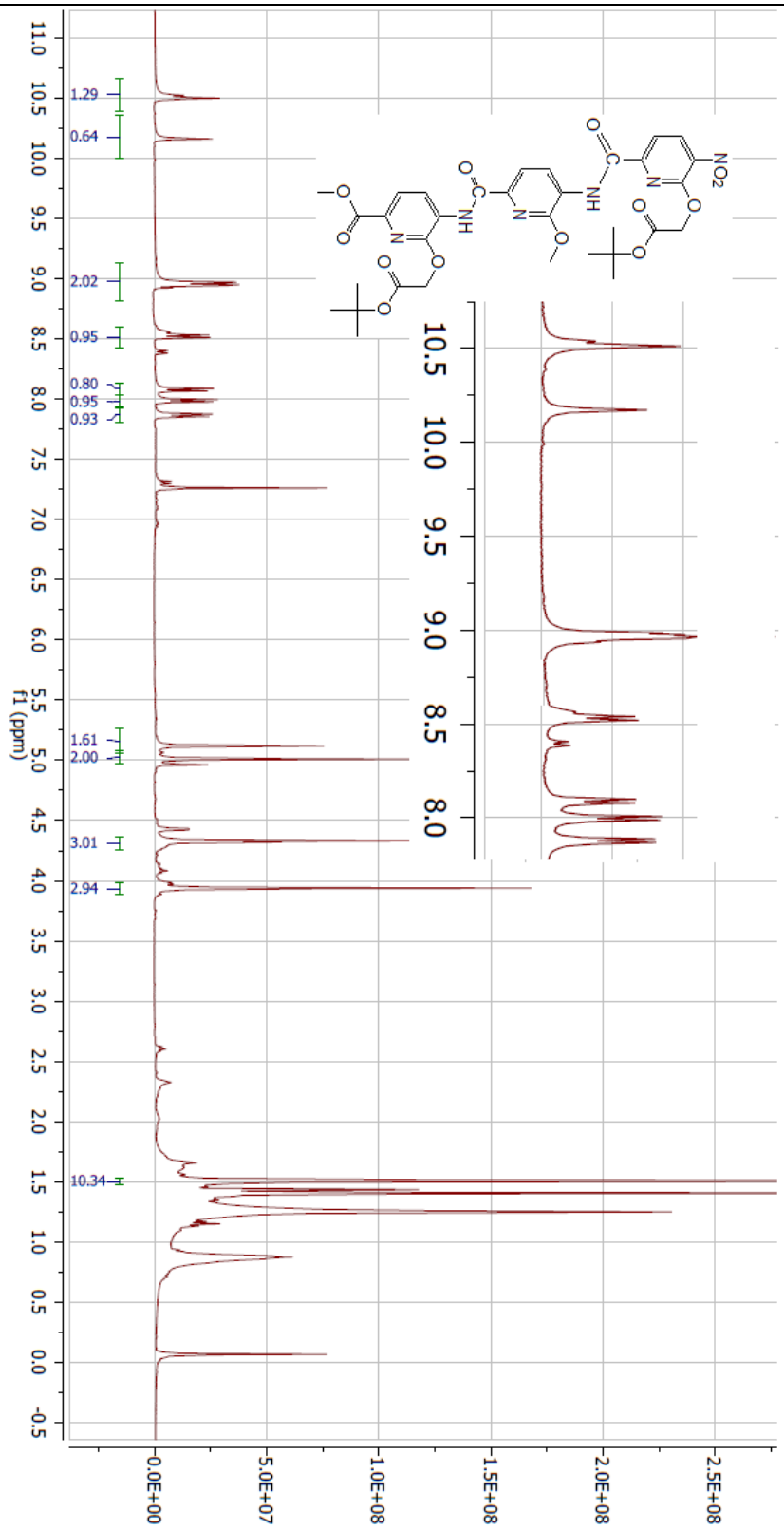


Figure S112. ^{1}H-NMR of O-Methyl (in $CDCl_3$).

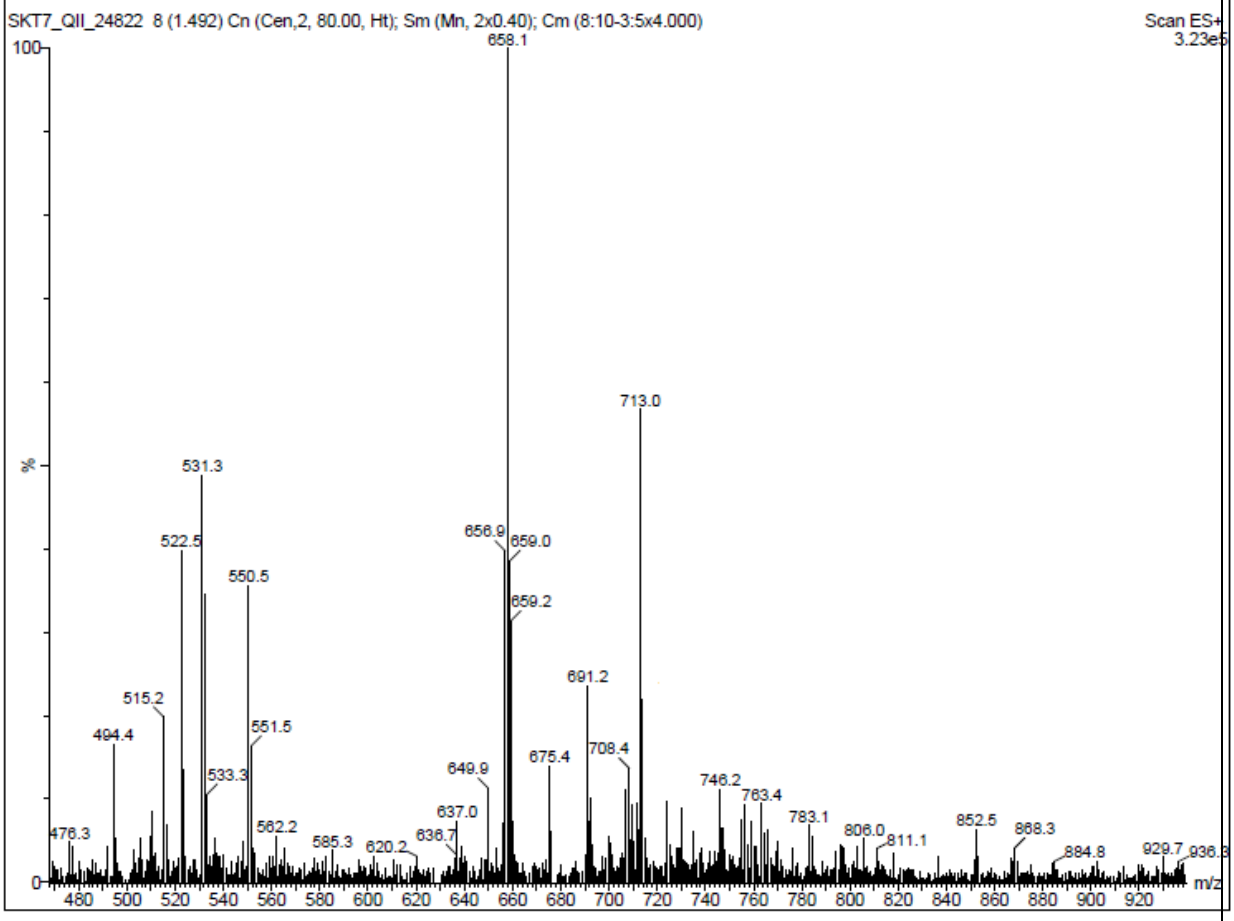


Figure S113. MS-ESI of O-Methyl.

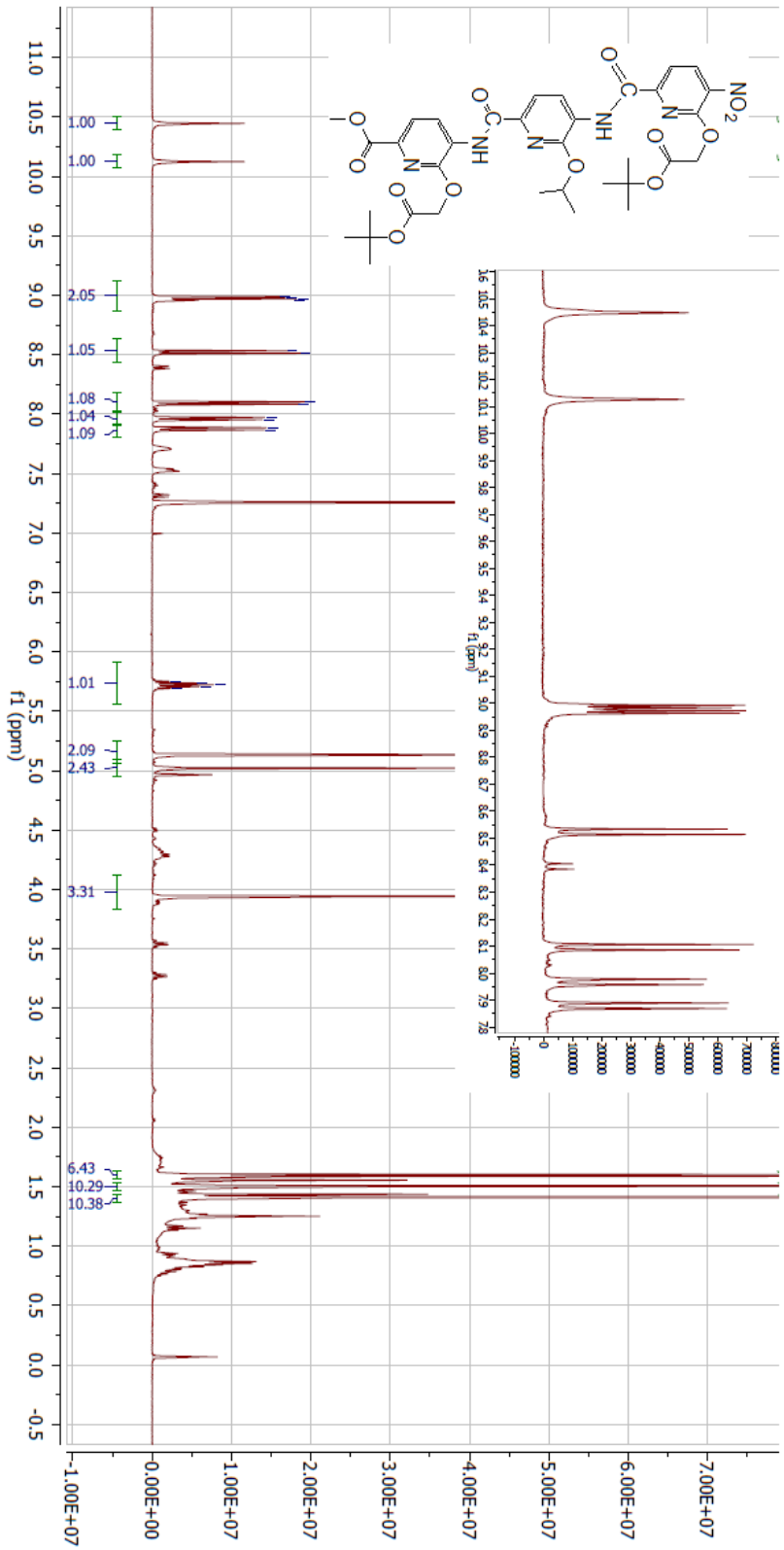


Figure S114. ^{1}H-NMR of O-Propyl (in $CDCl_3$).

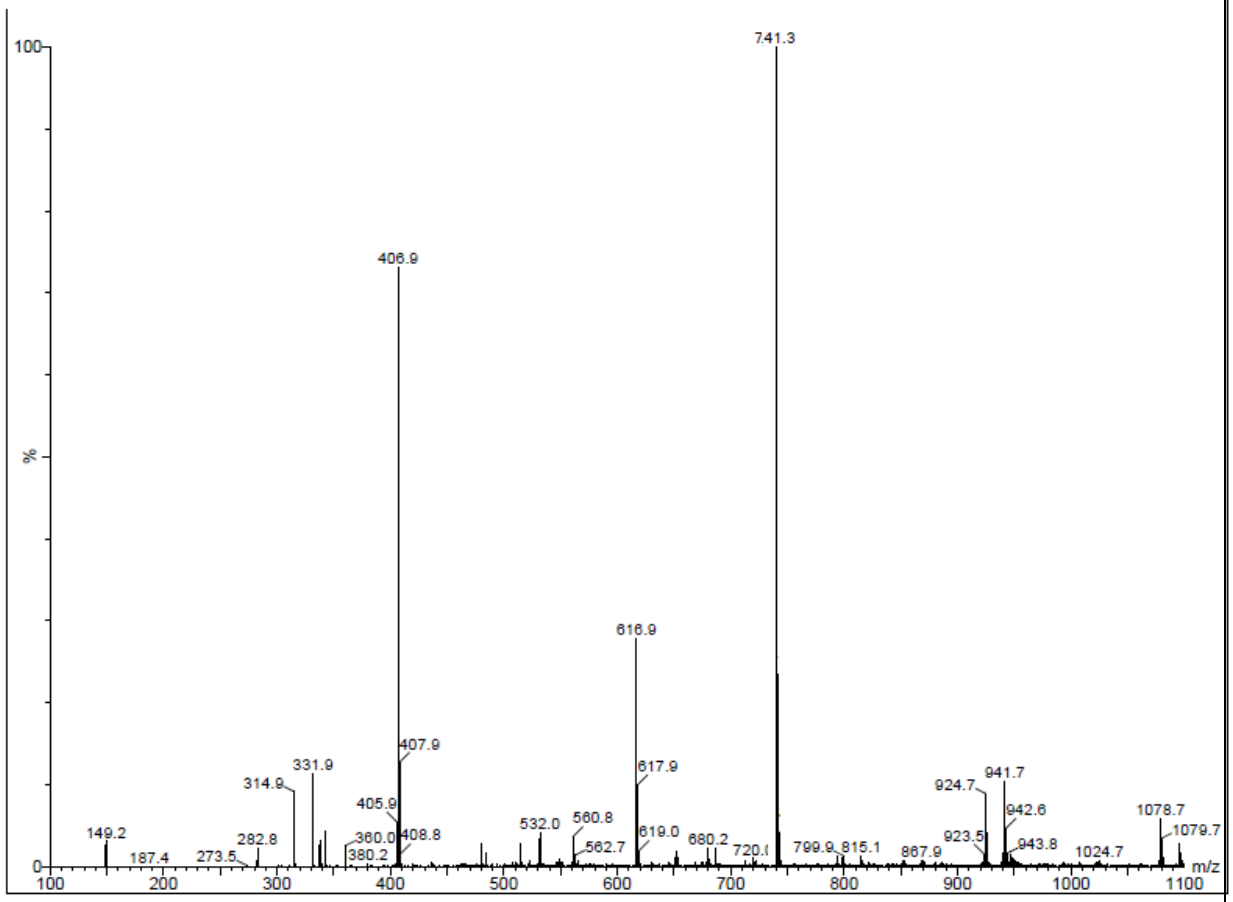


Figure S115. MS-ESI of O-Methyl.

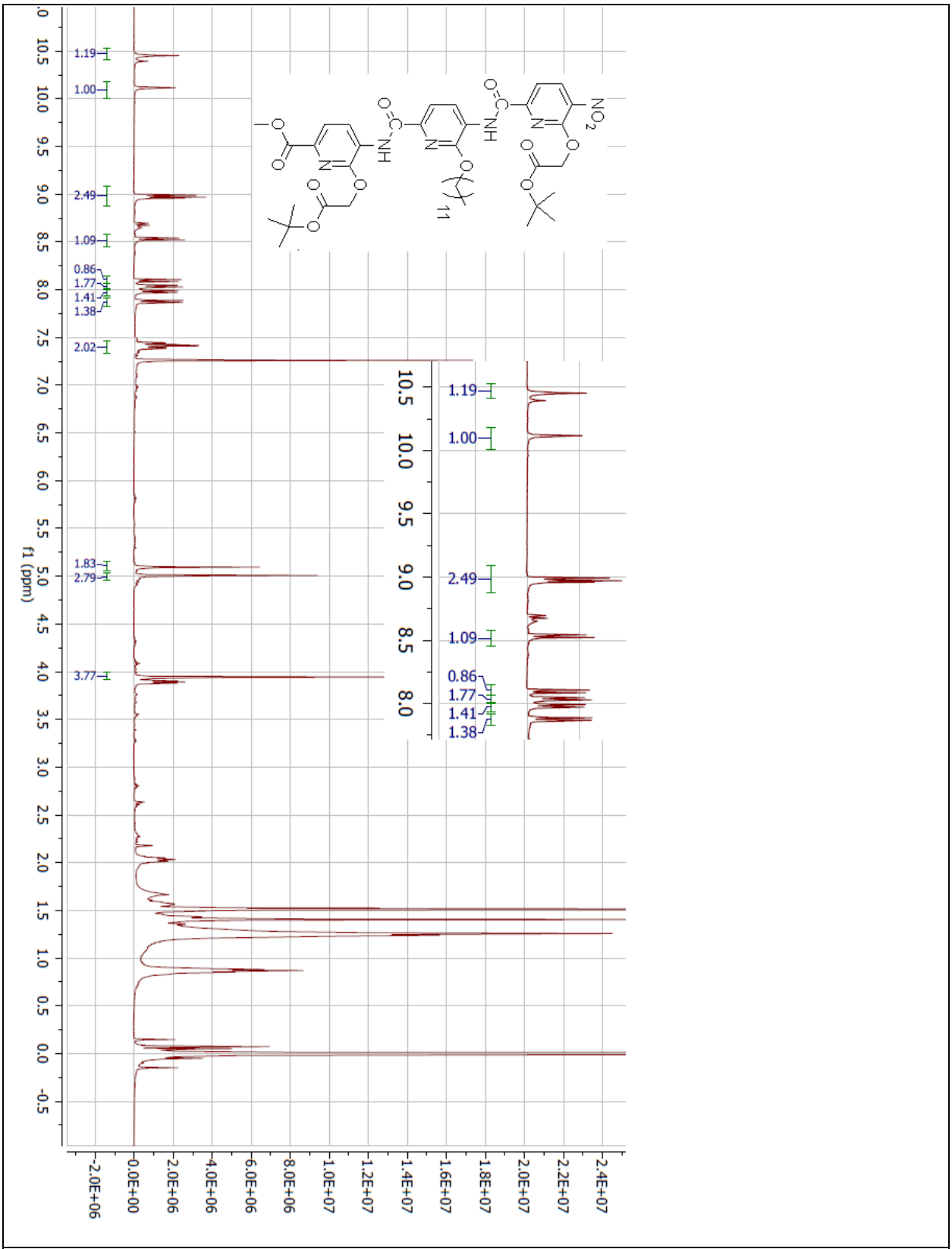


Figure S116. ^{1}H-NMR of O-Dodecane (in $CDCl_3$).

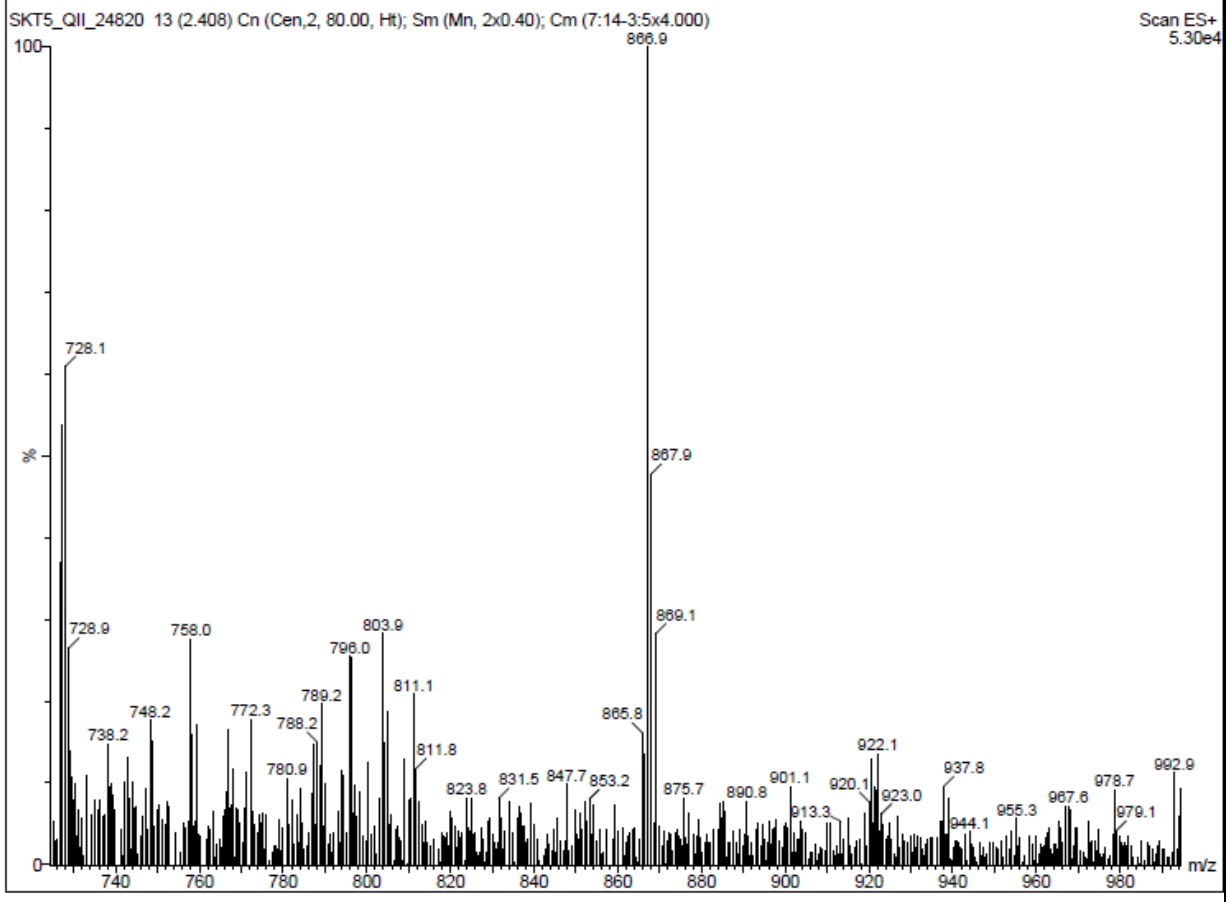


Figure S117. MS-ESI of O-Dodecane.

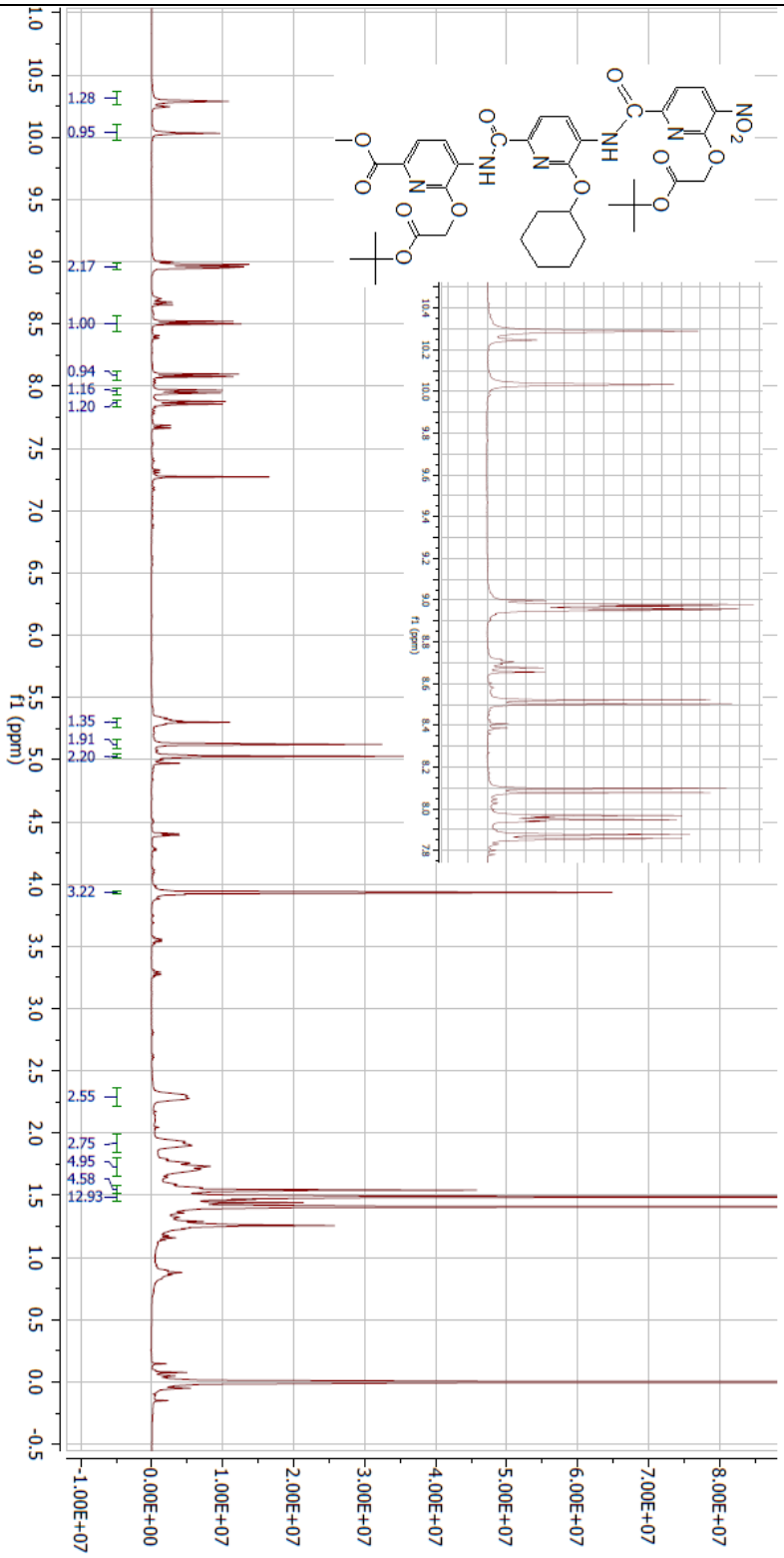


Figure S118. ^{1}H-NMR of O-Cyclohexane (in $CDCl_3$).

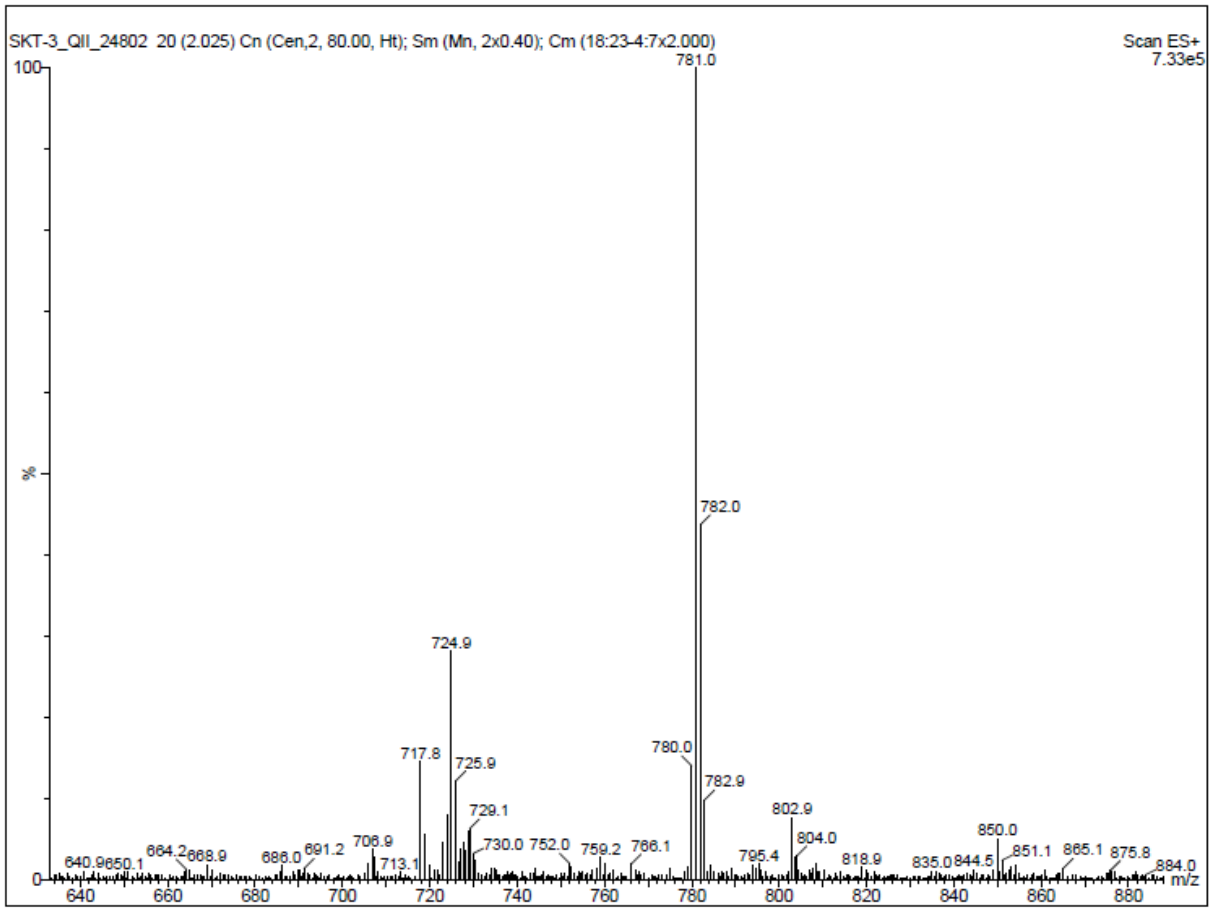


Figure S119. MS-ESI of O-Dodecane.

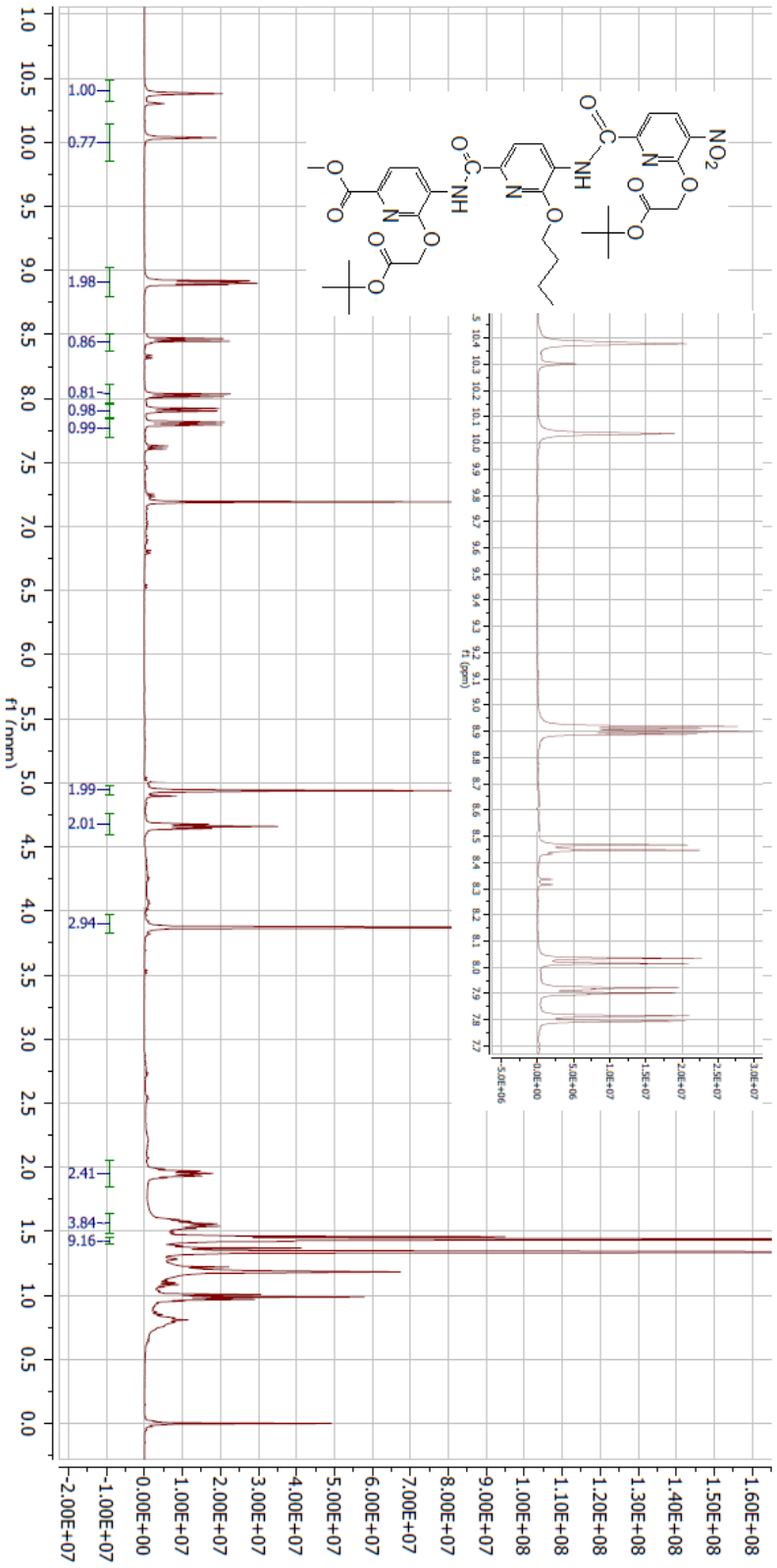


Figure S120. ^{1}H-NMR of O-Butyl (in $CDCl_3$).

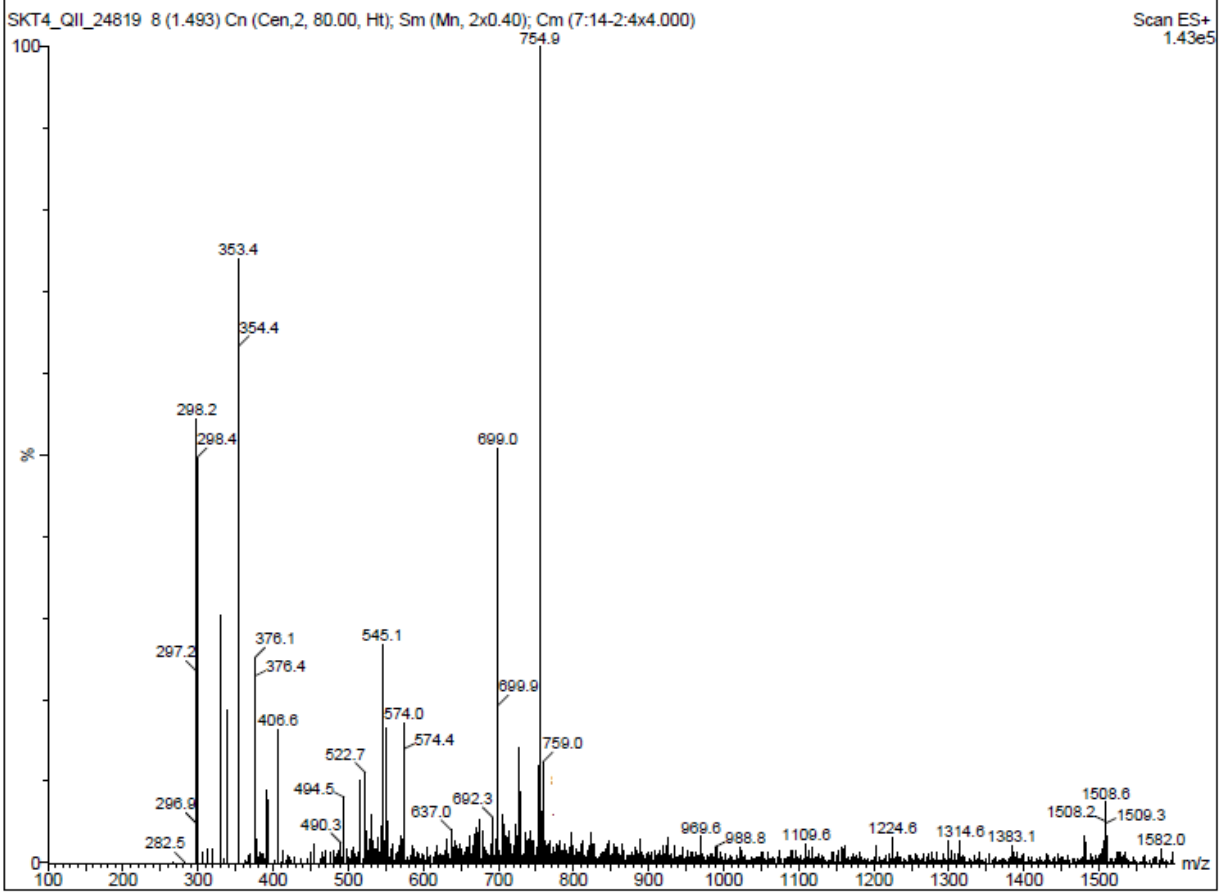


Figure S121. MS-ESI of O-Butyl.

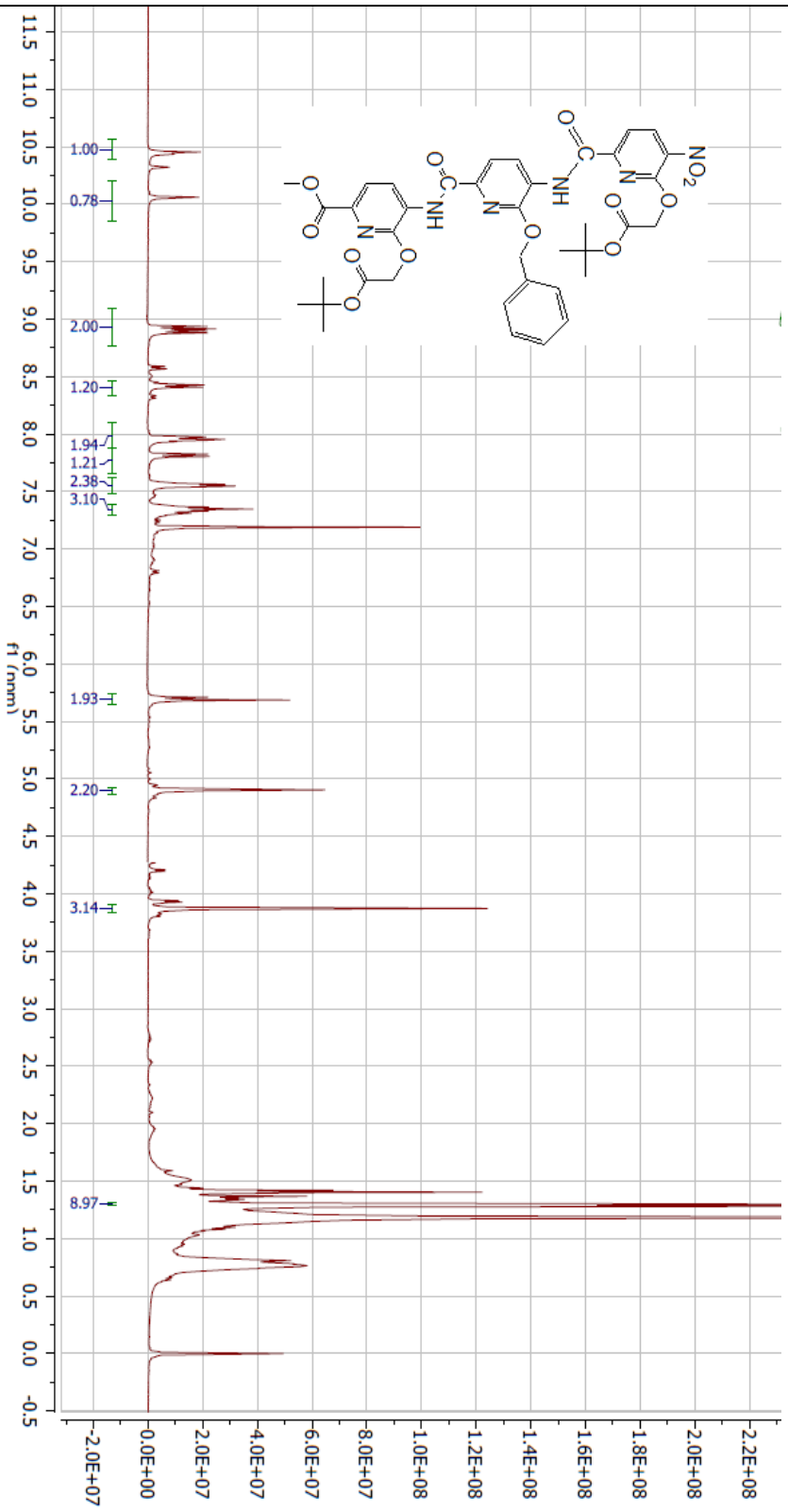


Figure S122. ^{1}H-NMR of O-Benzyl (in $CDCl_3$).

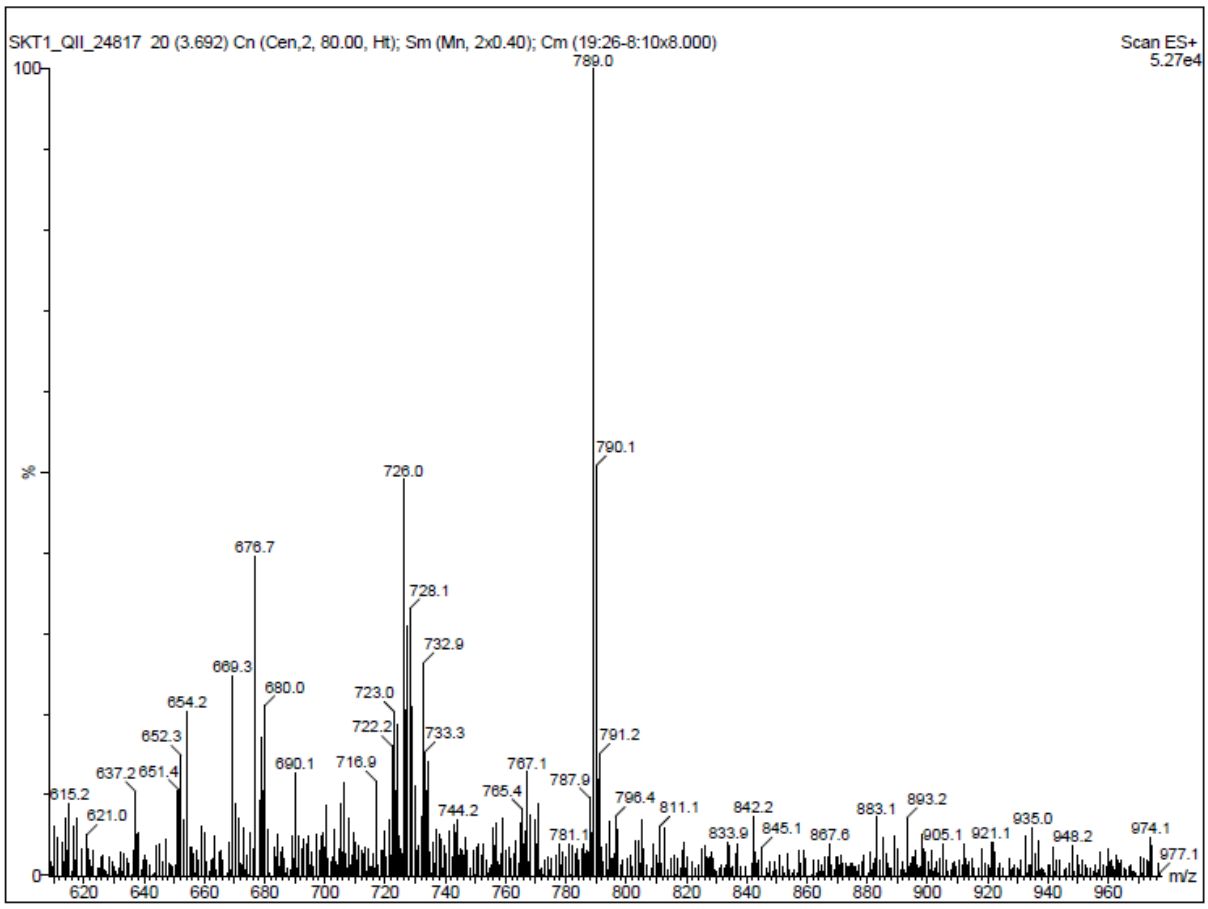


Figure S123. MS-ESI of O-Benzyl.

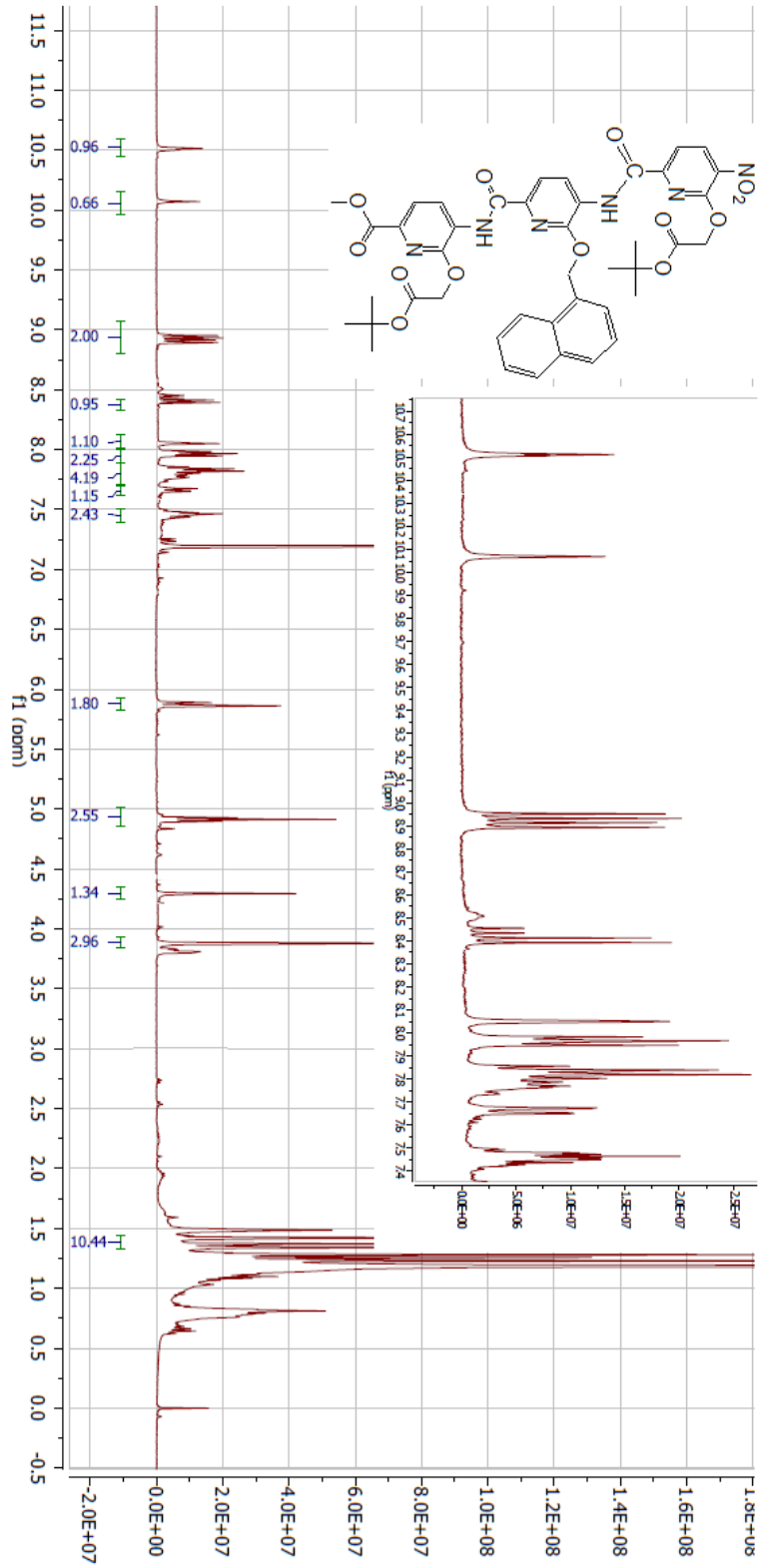


Figure S124. ^{1}H-NMR of O-Naphthalene (in $CDCl_3$).

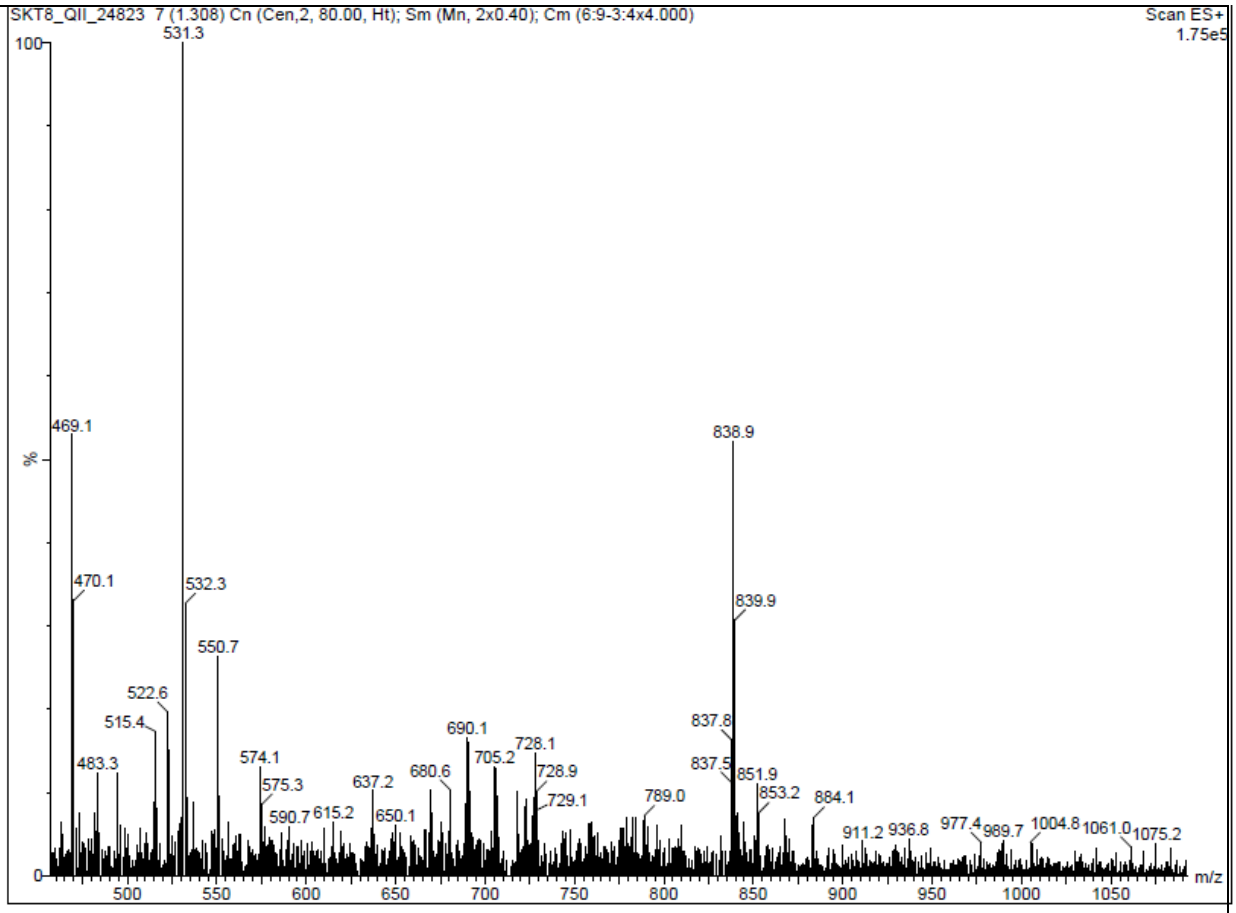


Figure S125. MS-ESI of O-Naphthalene.

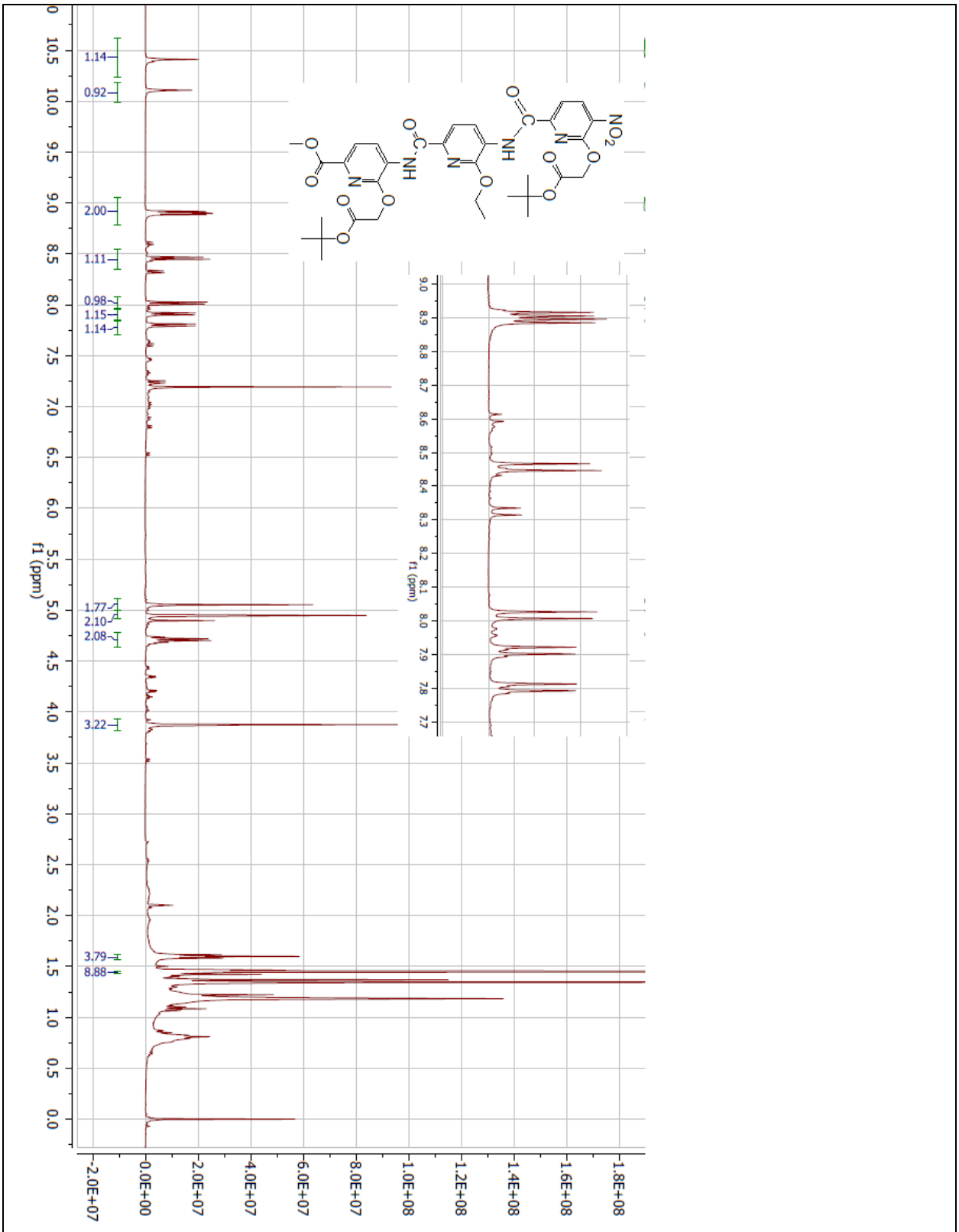


Figure S126. ^{1}H-NMR of O-Ethyl (in $CDCl_3$).

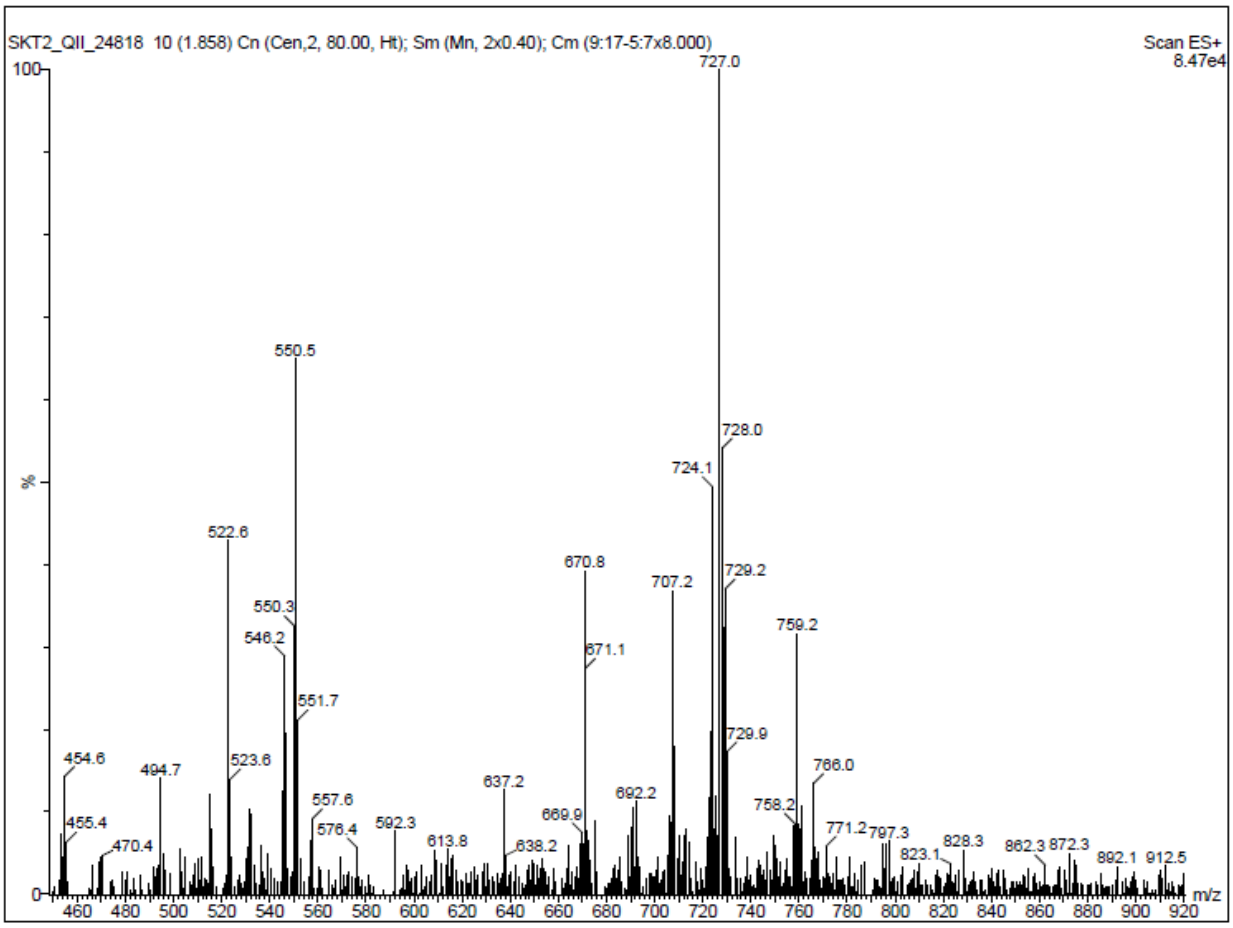


Figure S127. MS-ESI of O-Ethyl.

Series 6:

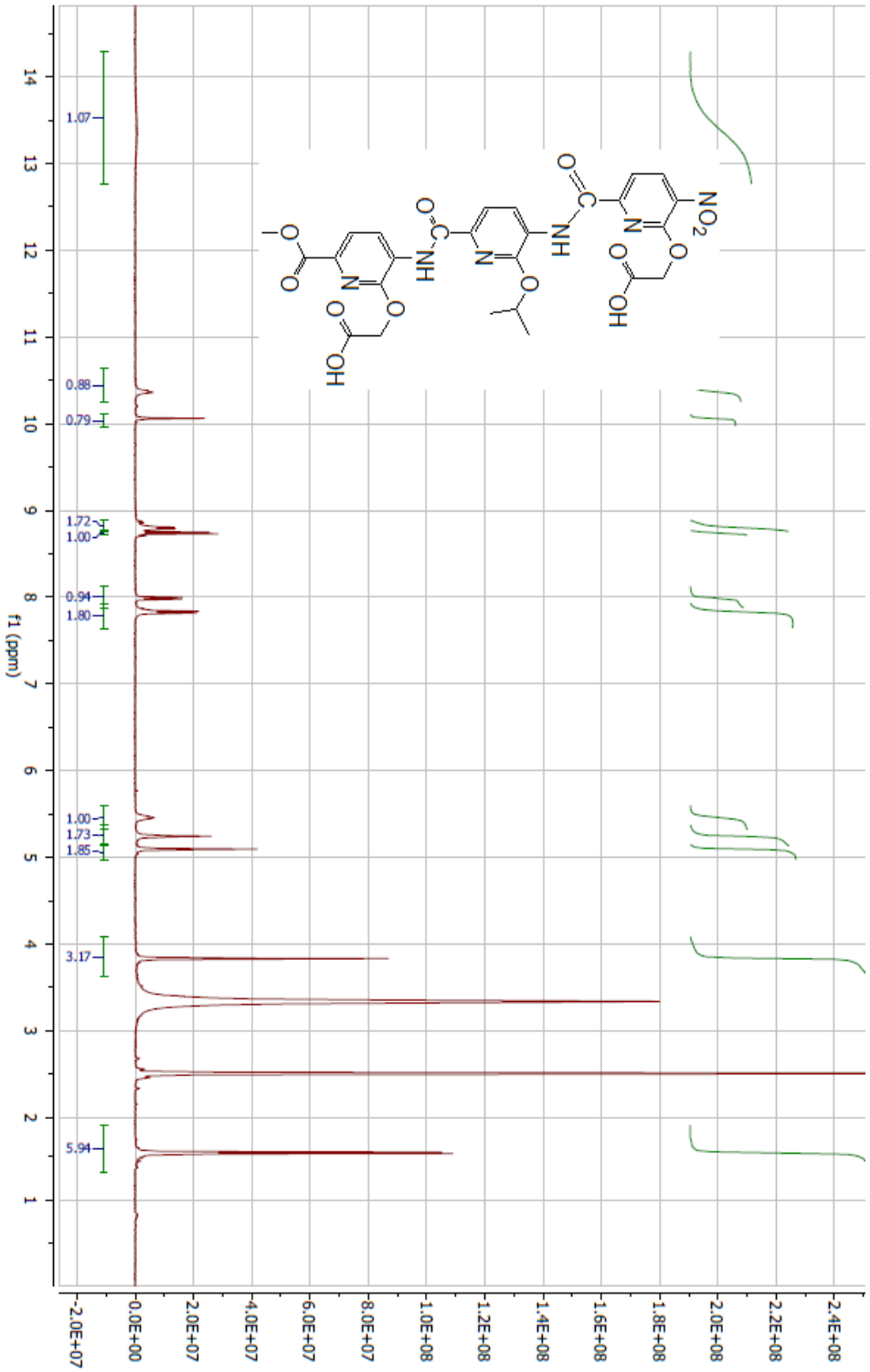


Figure S128. ^{1}H-NMR of ADM-9 [in $(CD_3)_2SO$].

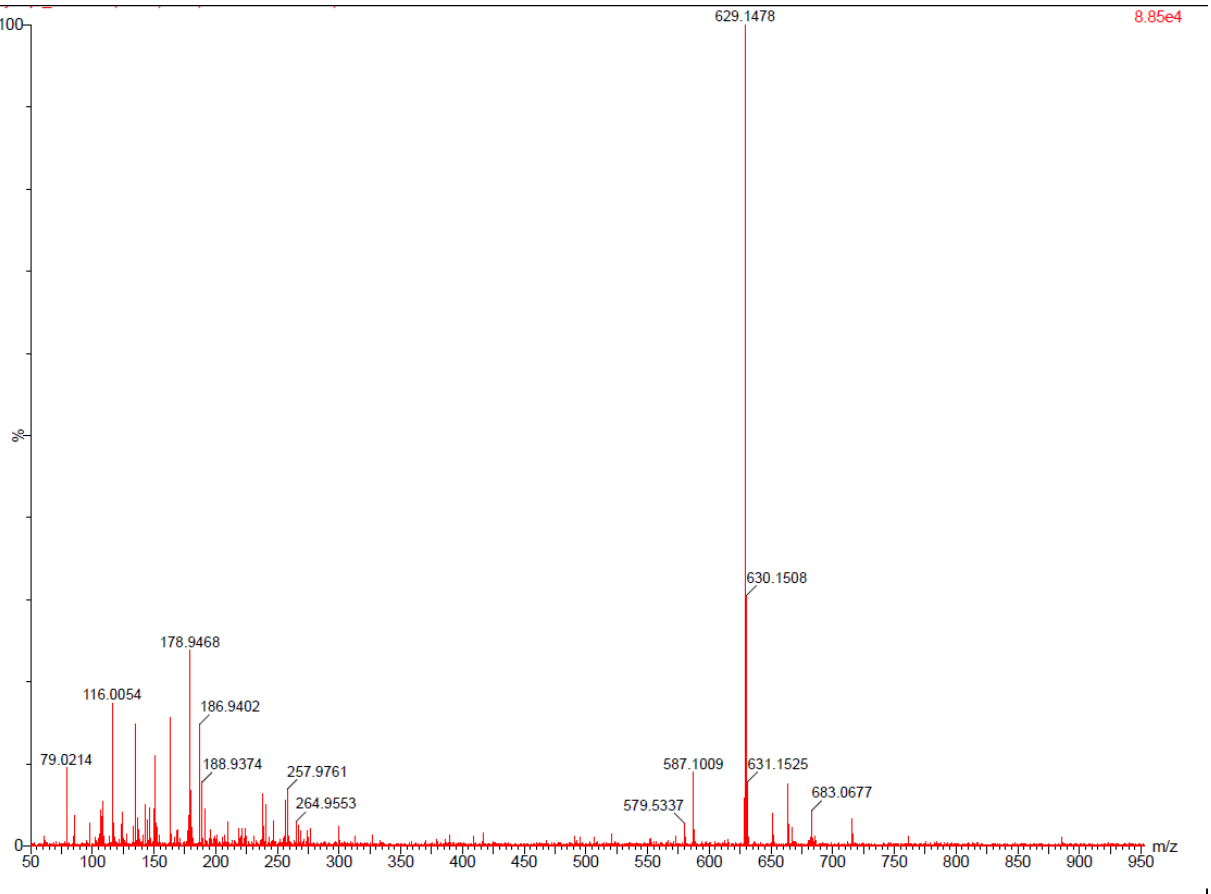


Figure S129. MS-ESI of ADM-9.

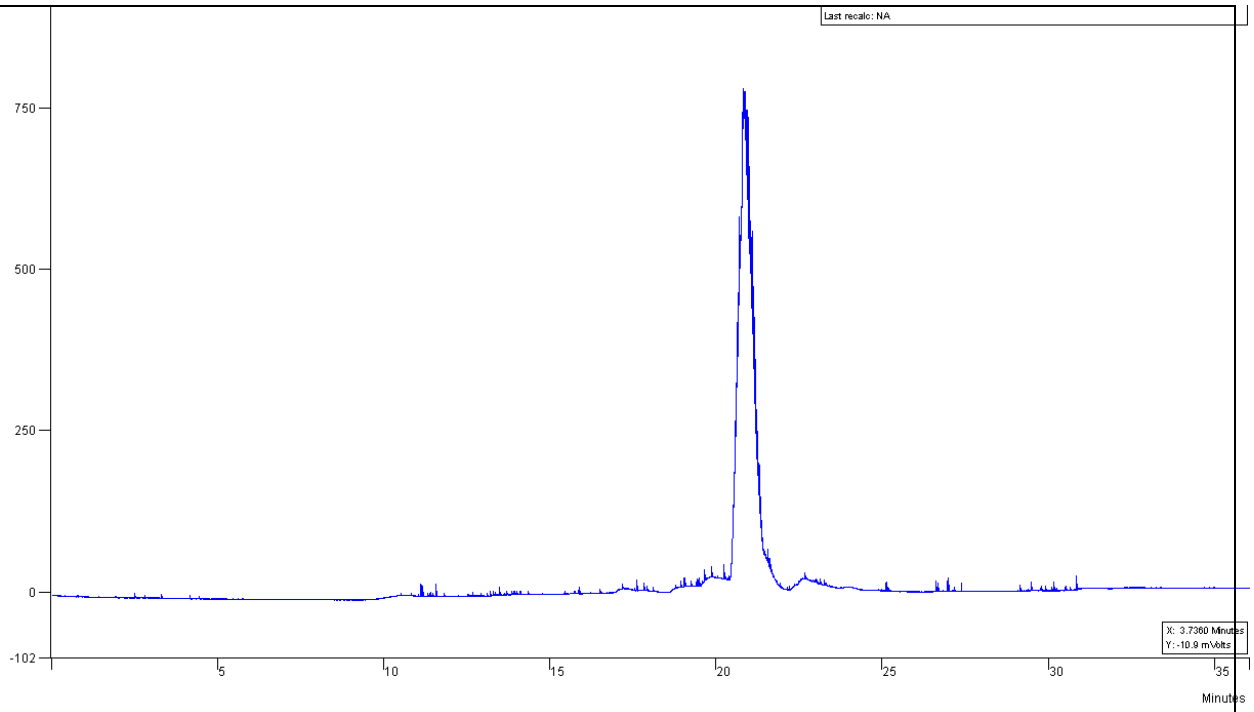


Figure S130. RP-HPLC of ADM-9.

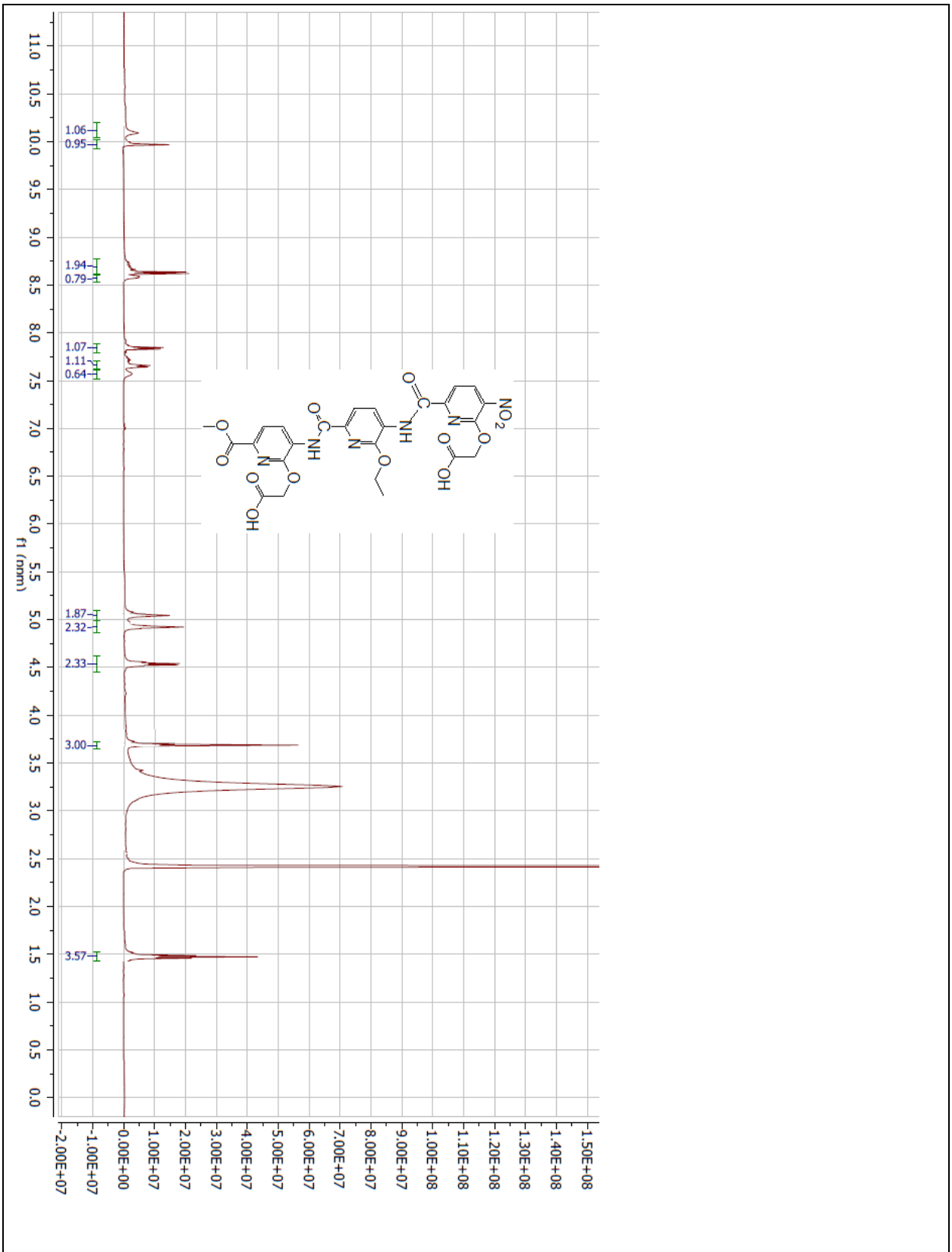


Figure S131. ^{1}H-NMR of ADM-3 [in $(CD_3)_2SO$].

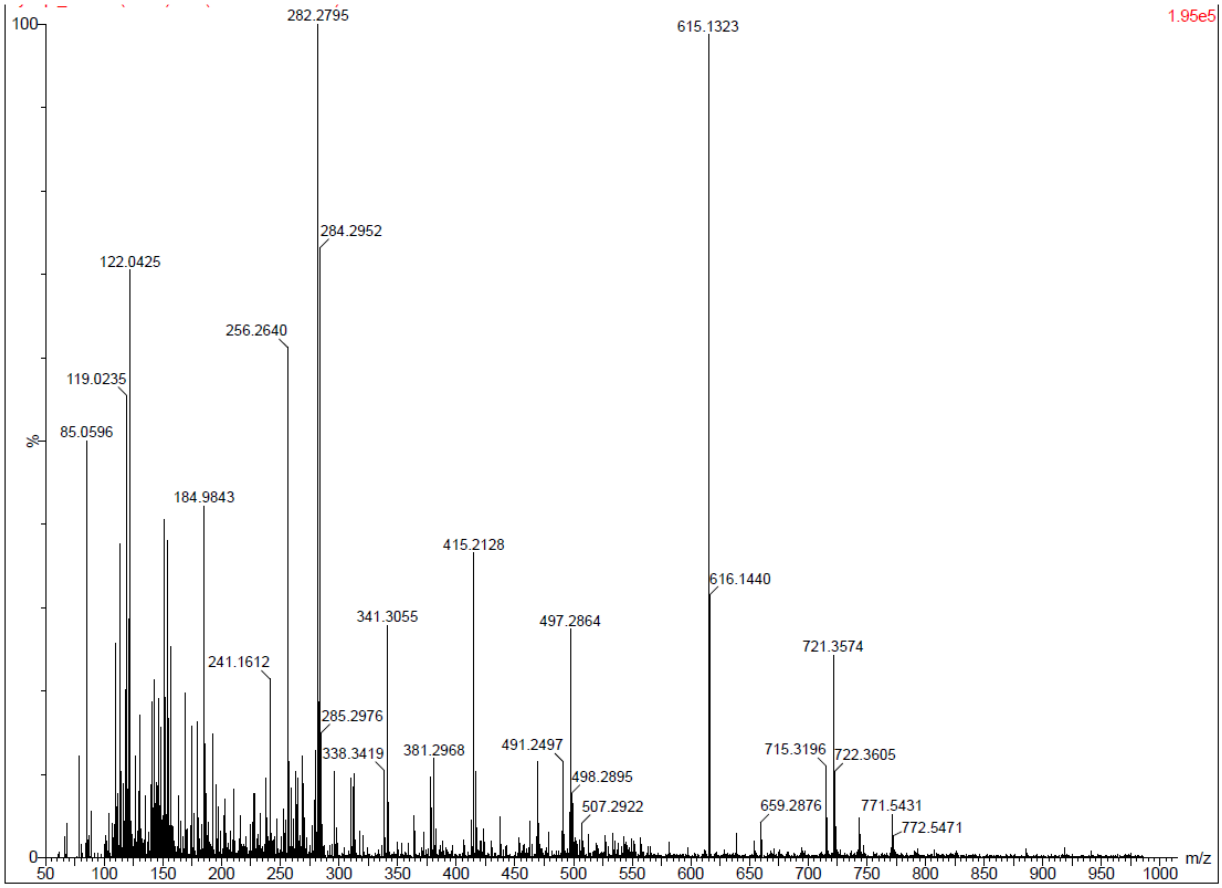


Figure S132. MS-ESI of ADM-3.

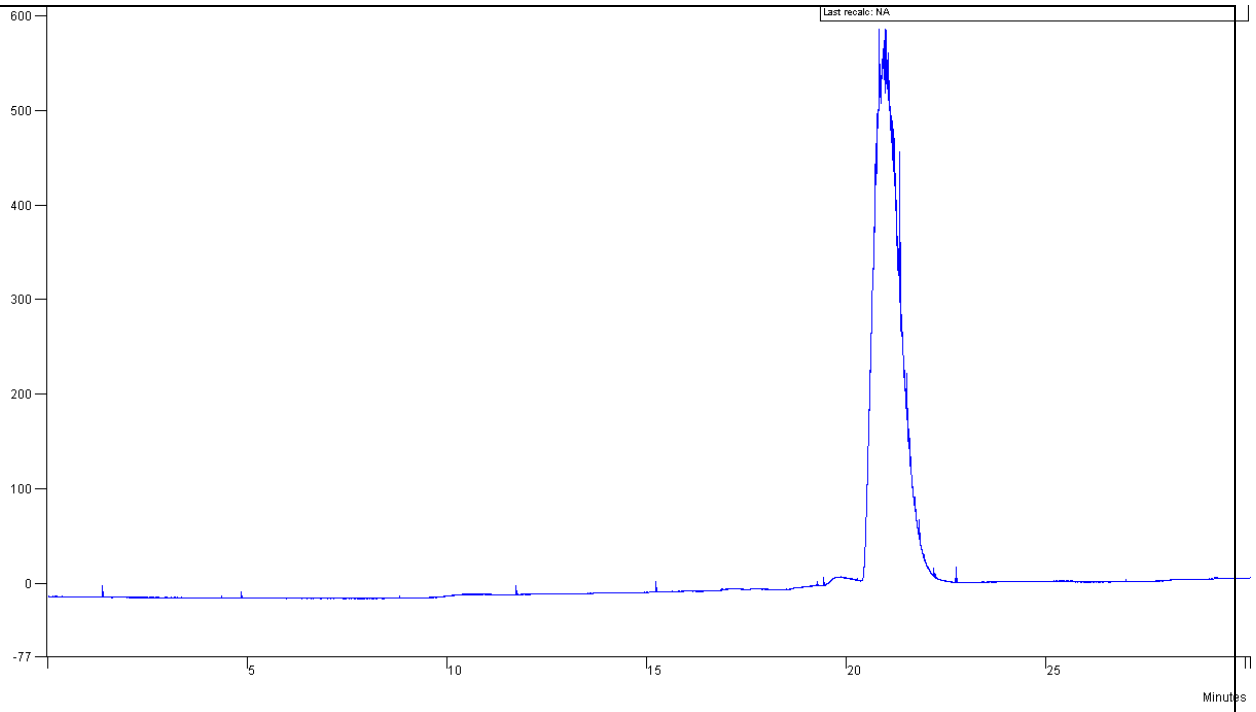


Figure S133. RP-HPLC of ADM-3.

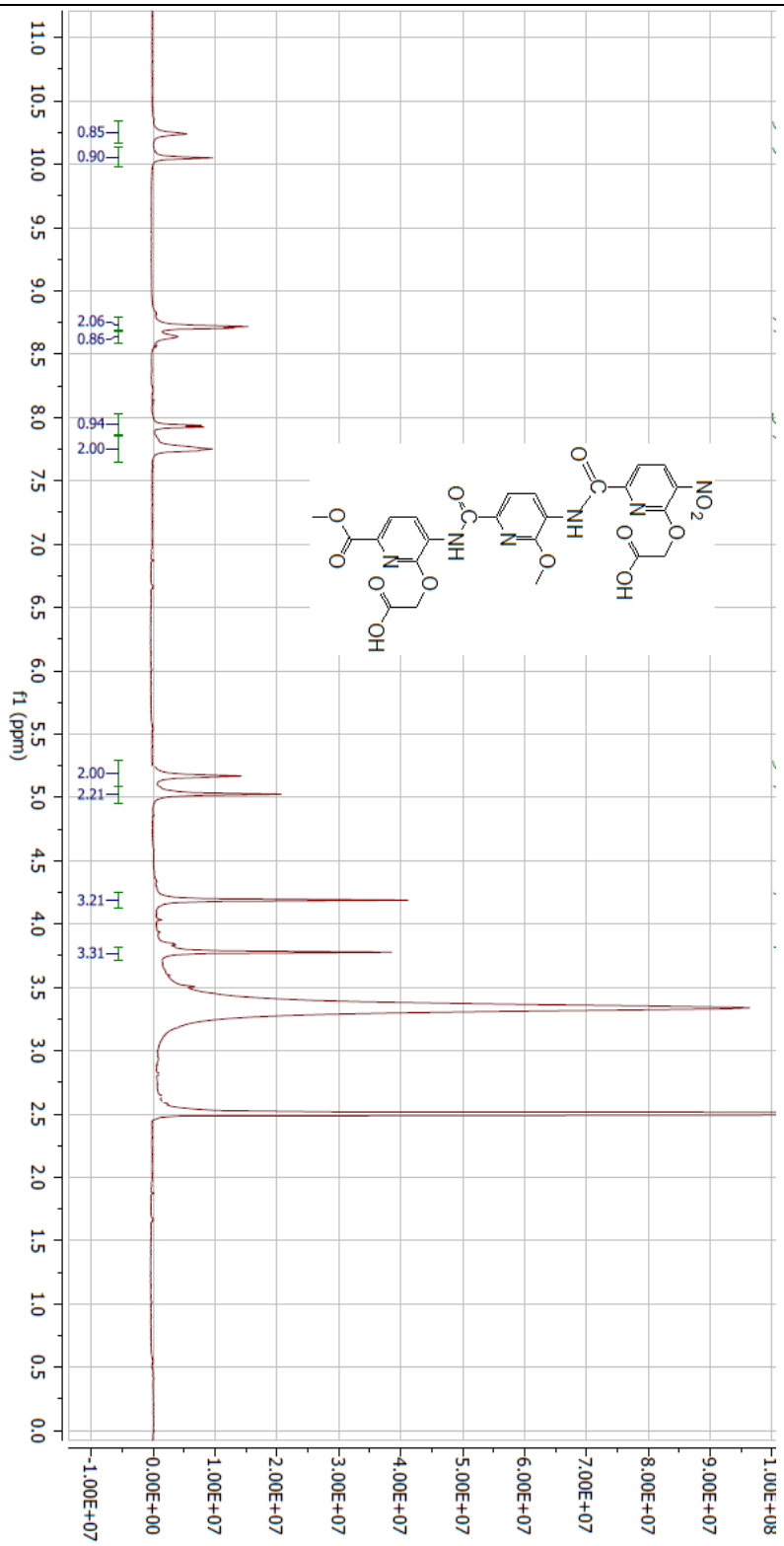


Figure S134. ^{1}H-NMR of ADM-2 [in $(CD_3)_2SO$].

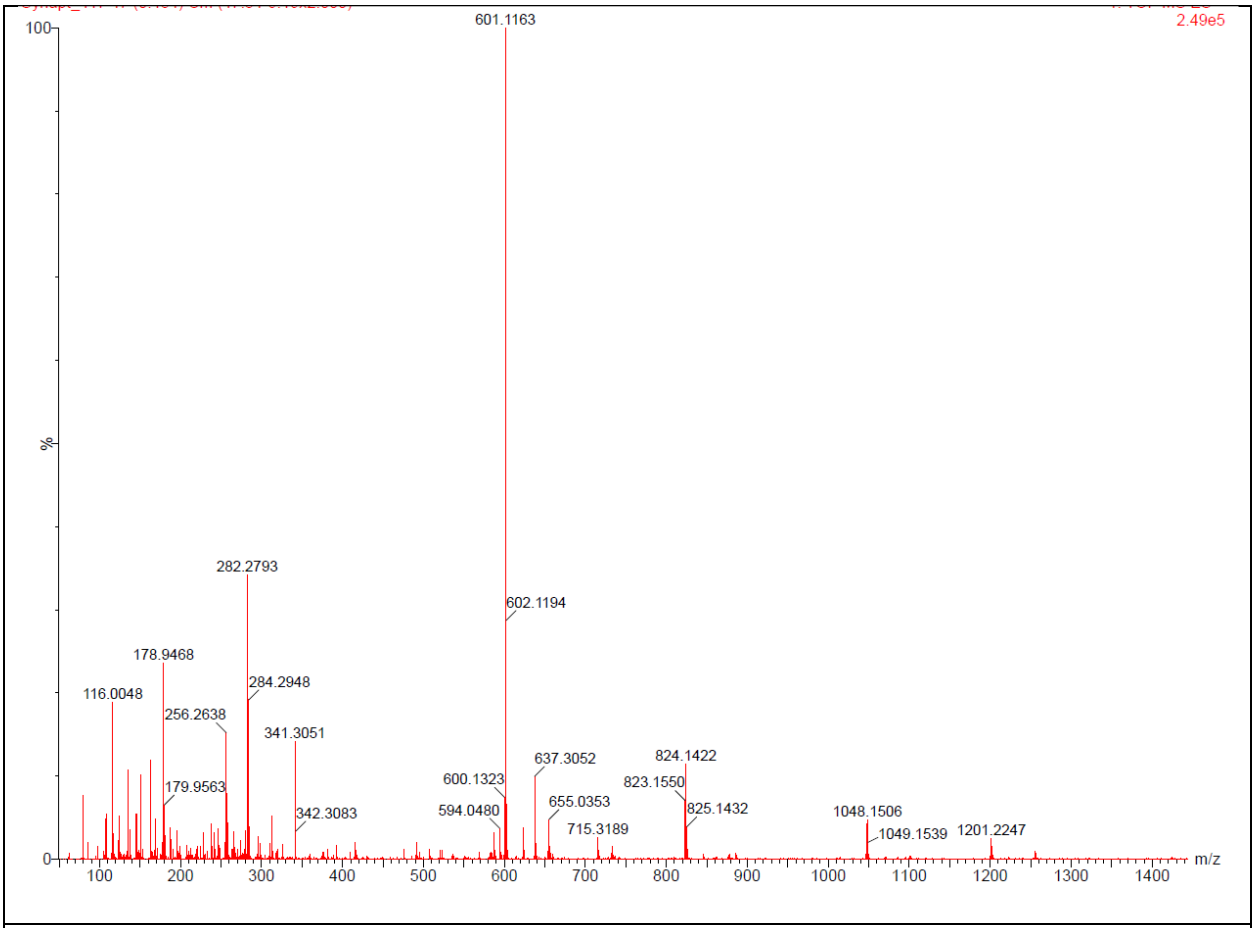


Figure S135. MS-ESI of ADM-2.

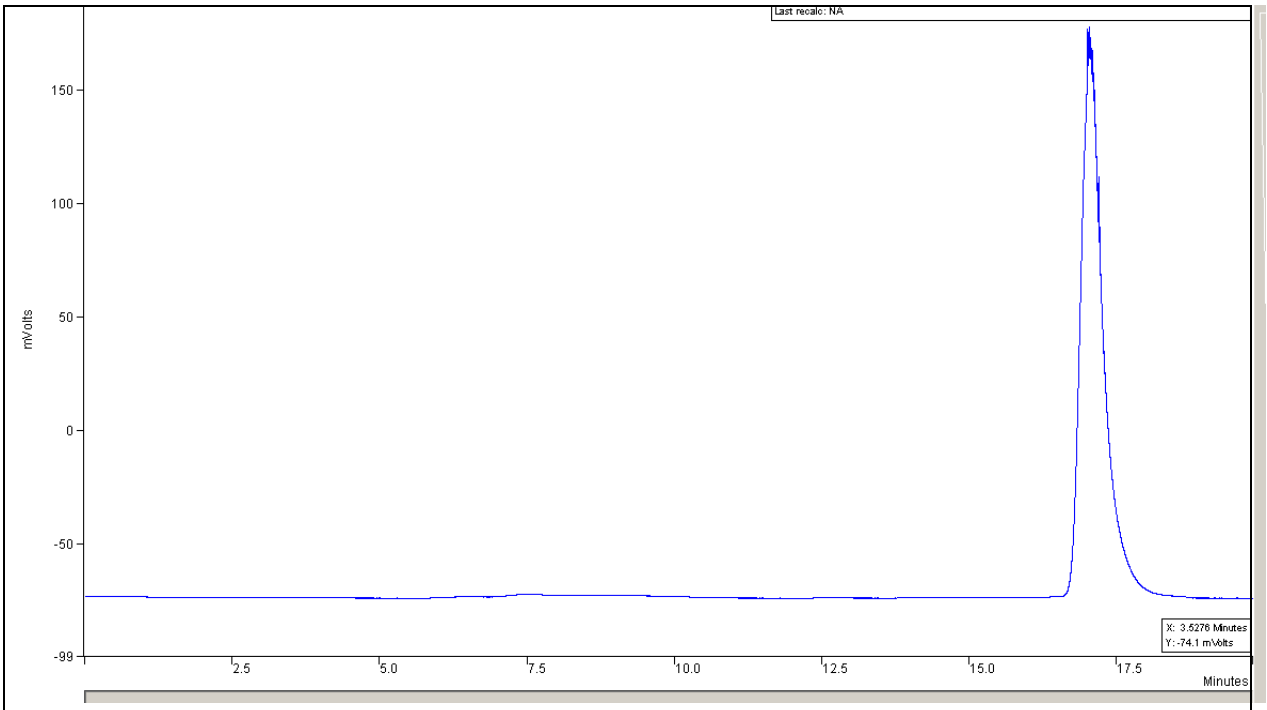


Figure S136. RP-HPLC of ADM-2.

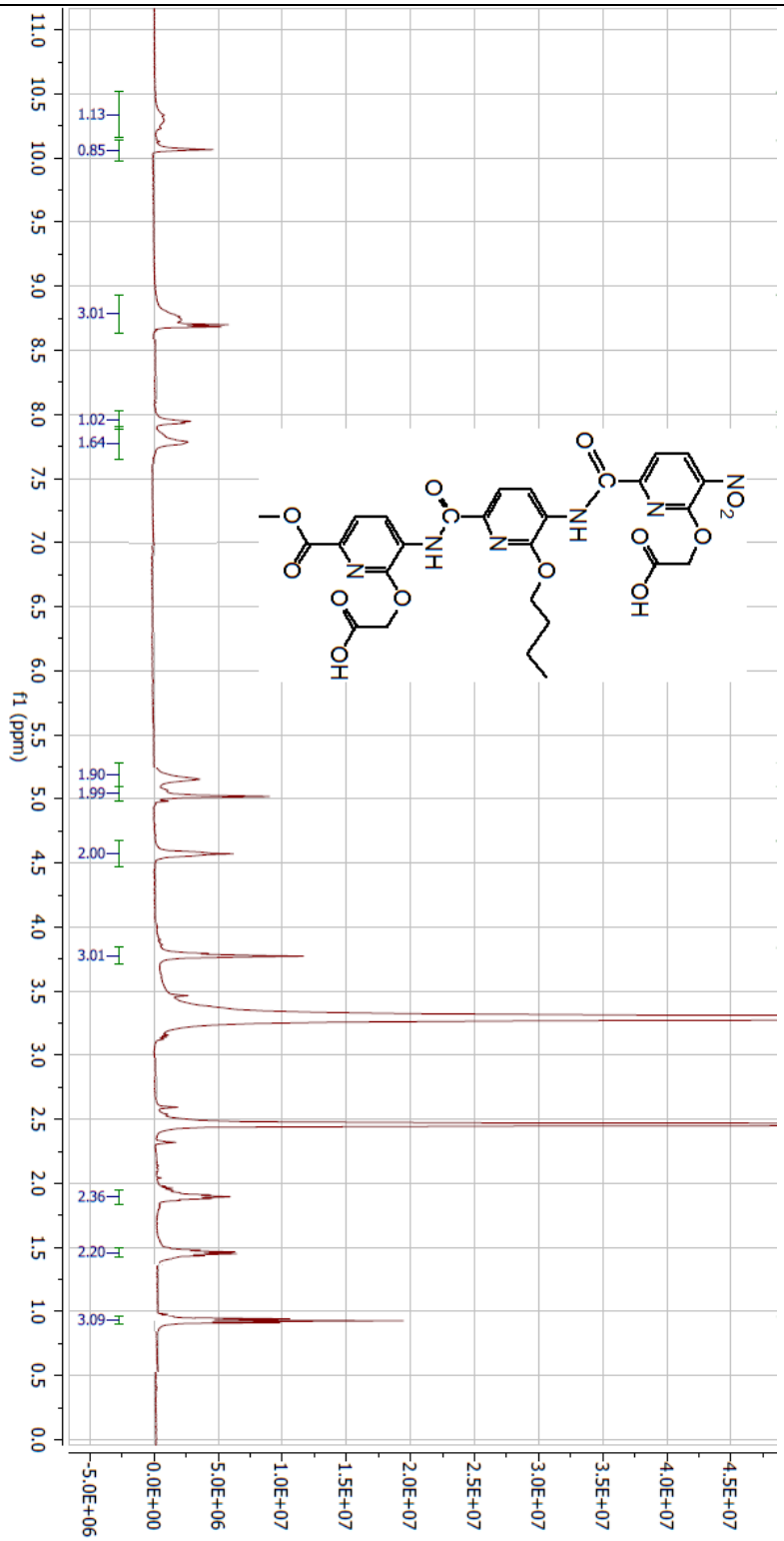


Figure S137. ^{1}H-NMR of AMD-4 [in $(CD_3)_2SO$].

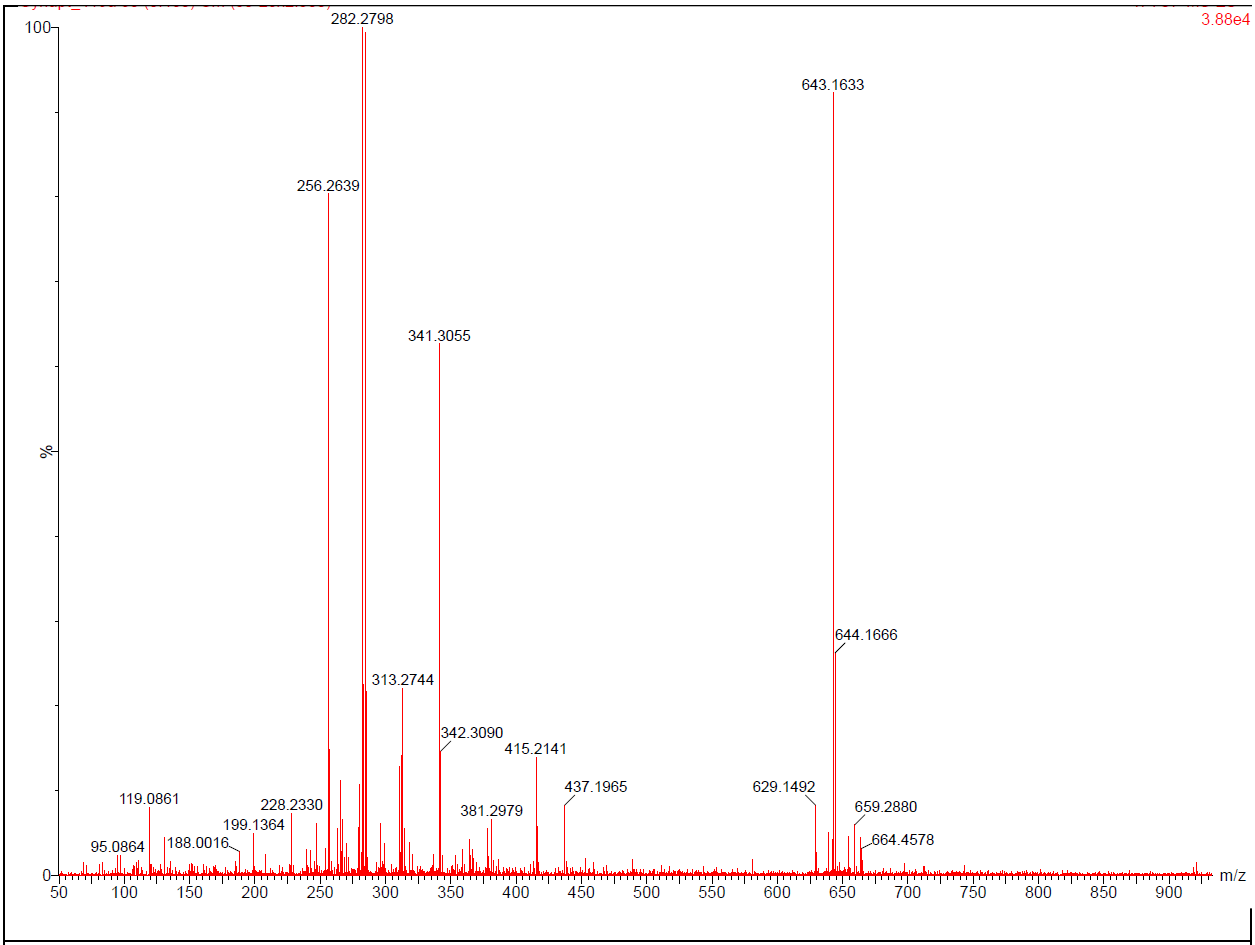


Figure S138. MS-ESI of ADM-4.

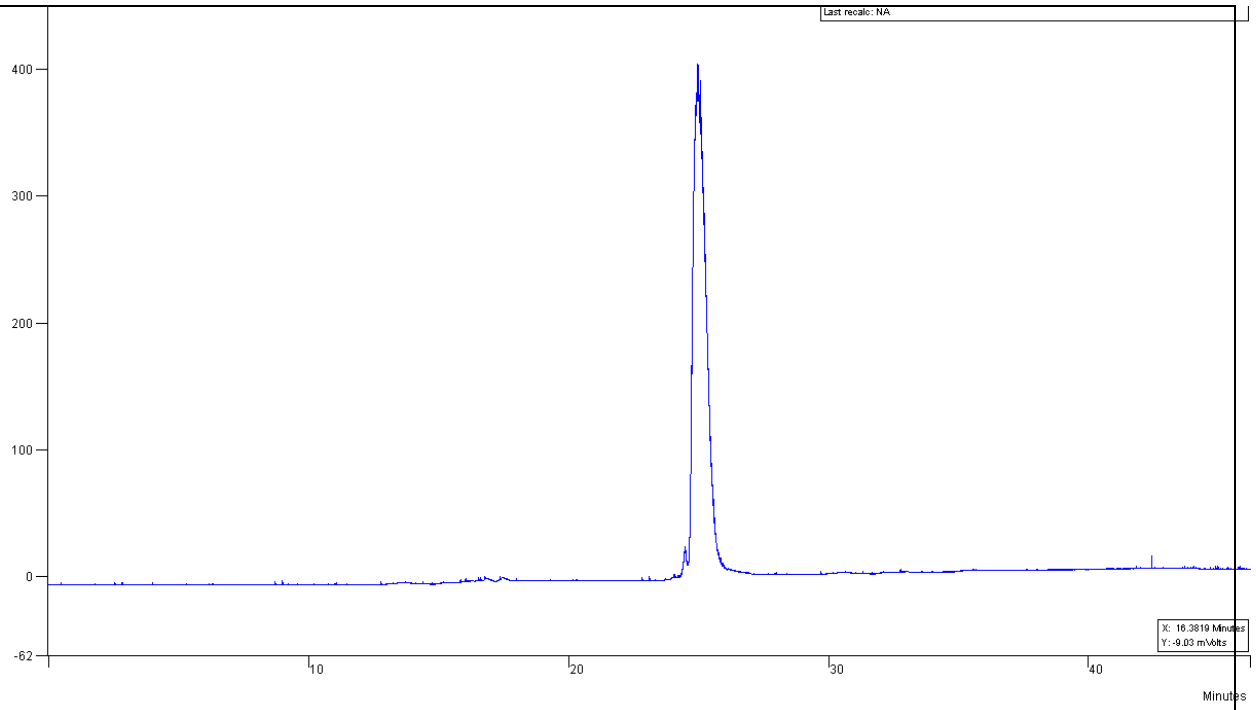


Figure S139. RP-HPLC of ADM-4.

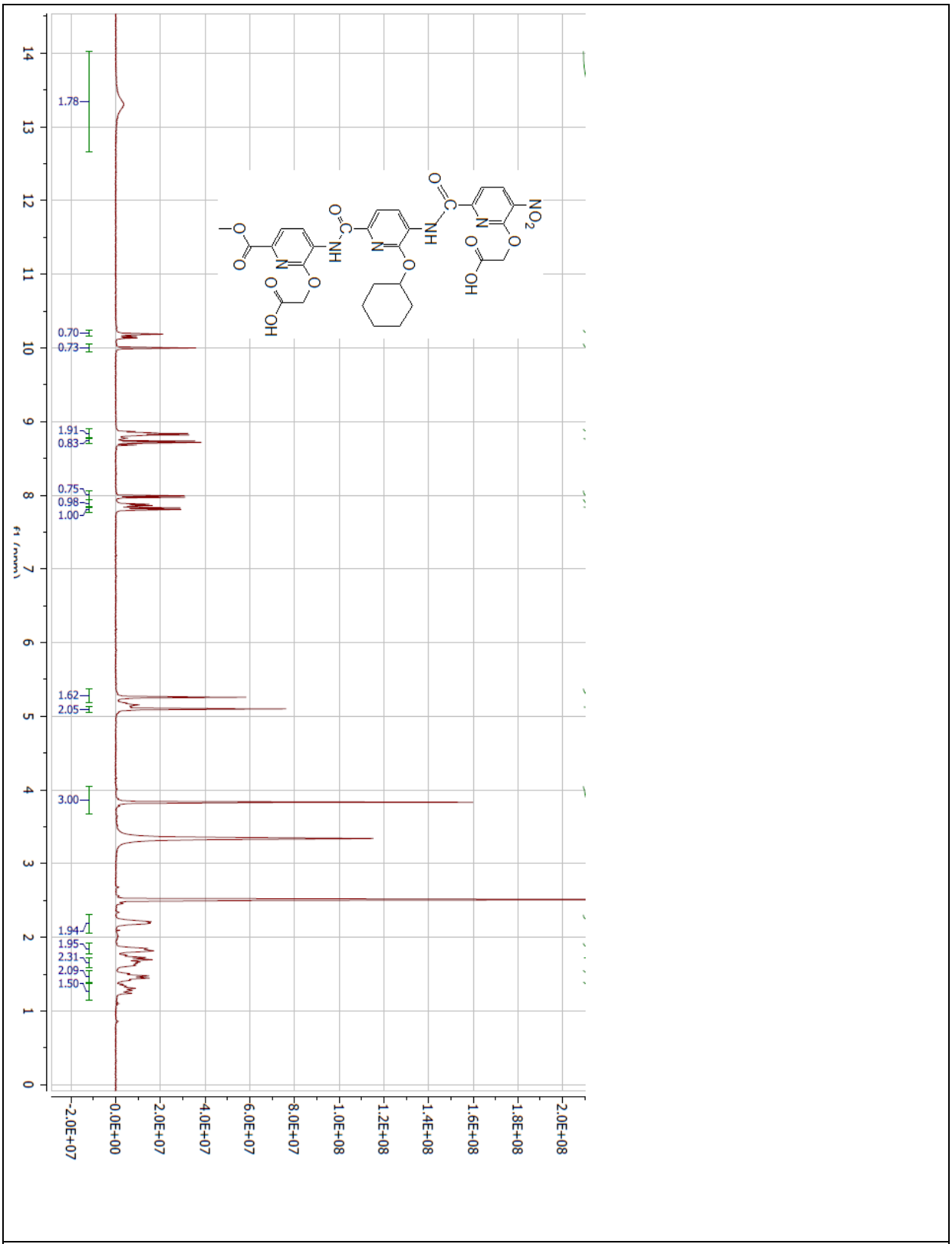


Figure S140. ^{1}H-NMR of ADM-7 [in $(CD_3)_2SO$].

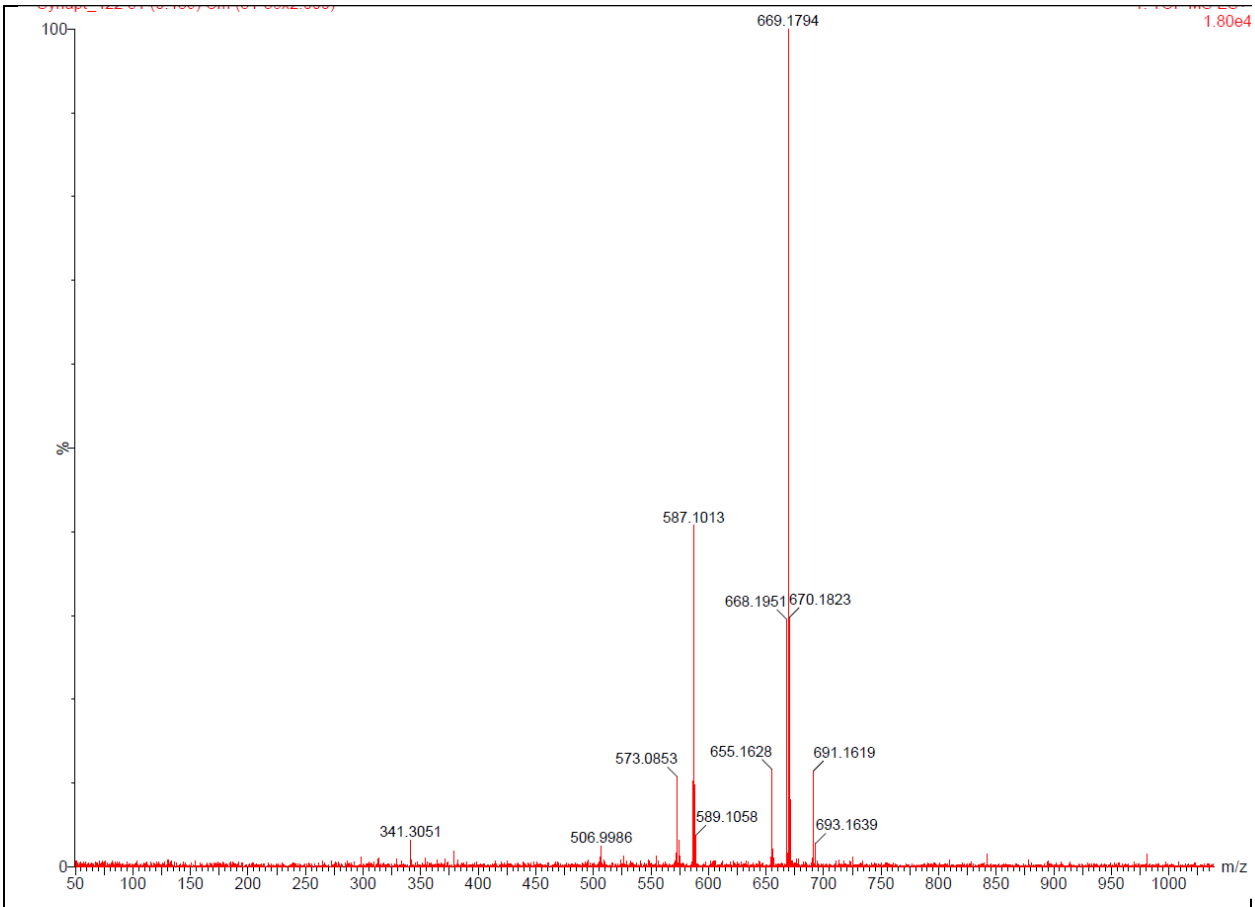


Figure S141. MS-ESI of ADM-7.

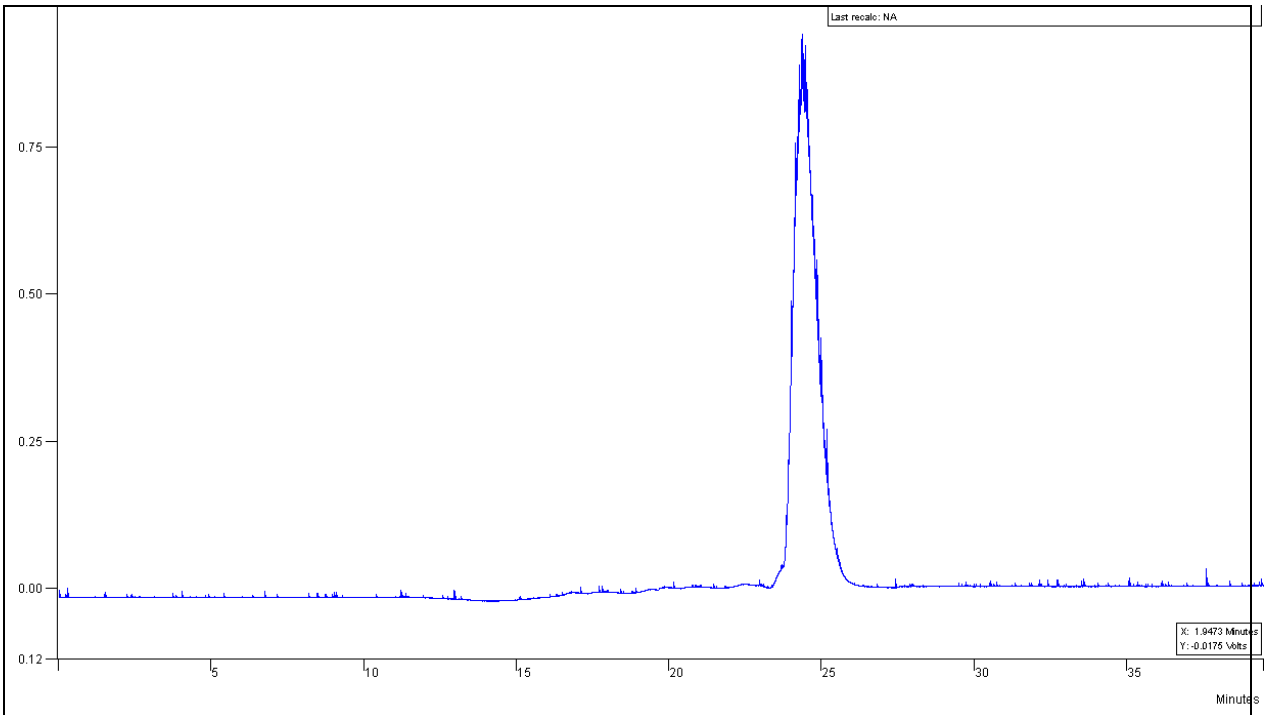


Figure S142. RP-HPLC of ADM-7.

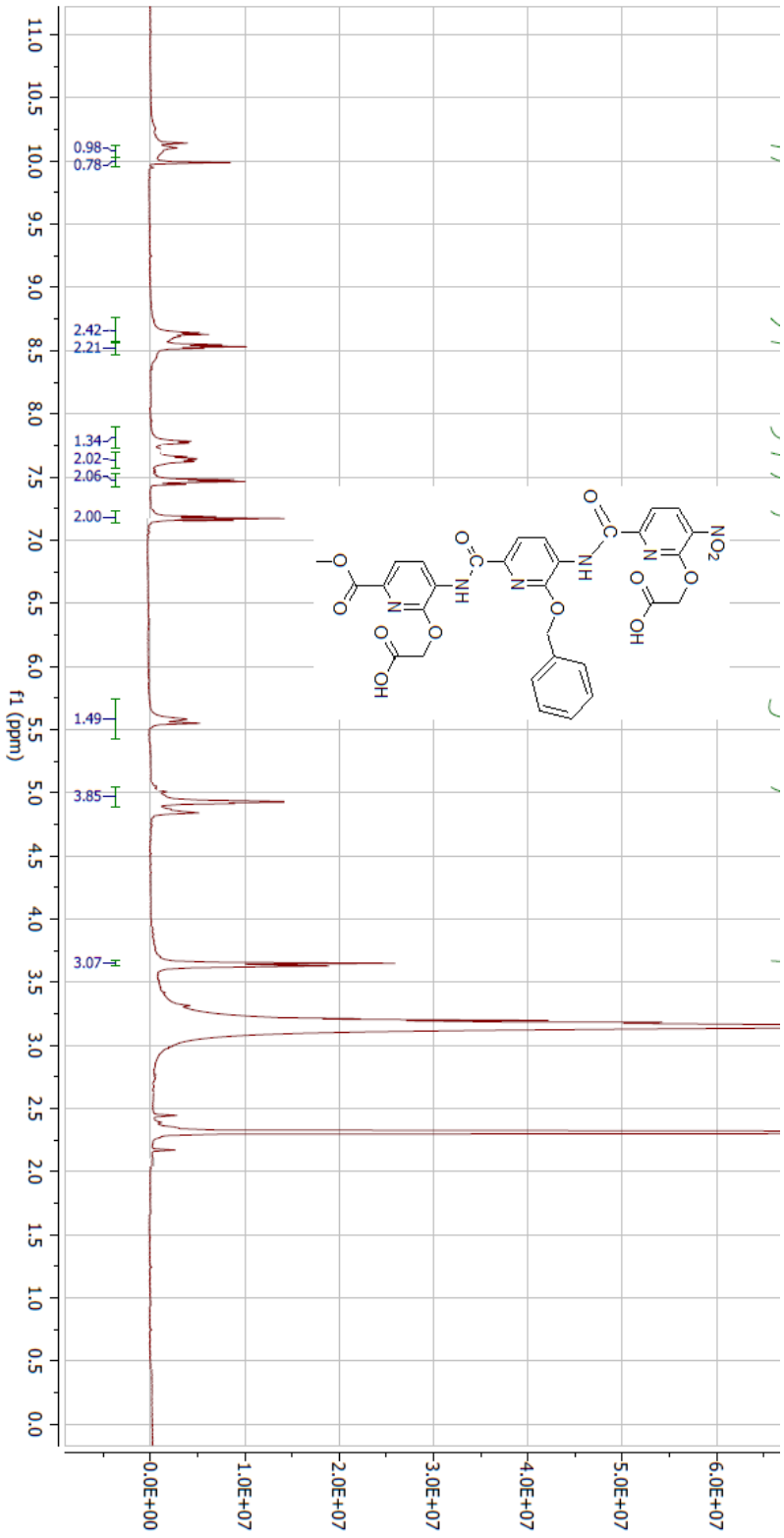


Figure S143. ^{1}H-NMR of ADM-6 [in $(CD_3)_2SO$].

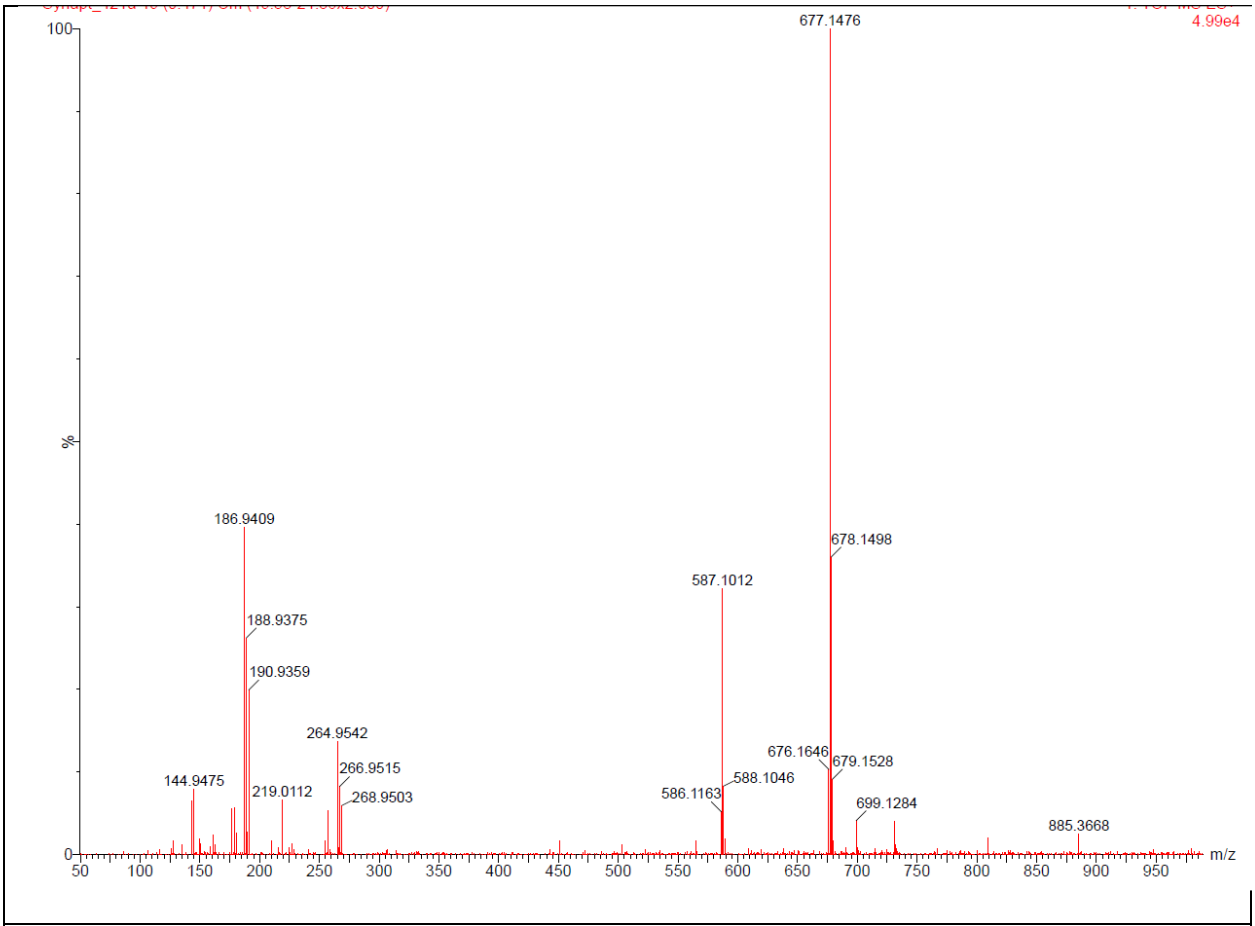


Figure S144. MS-ESI of ADM-6.

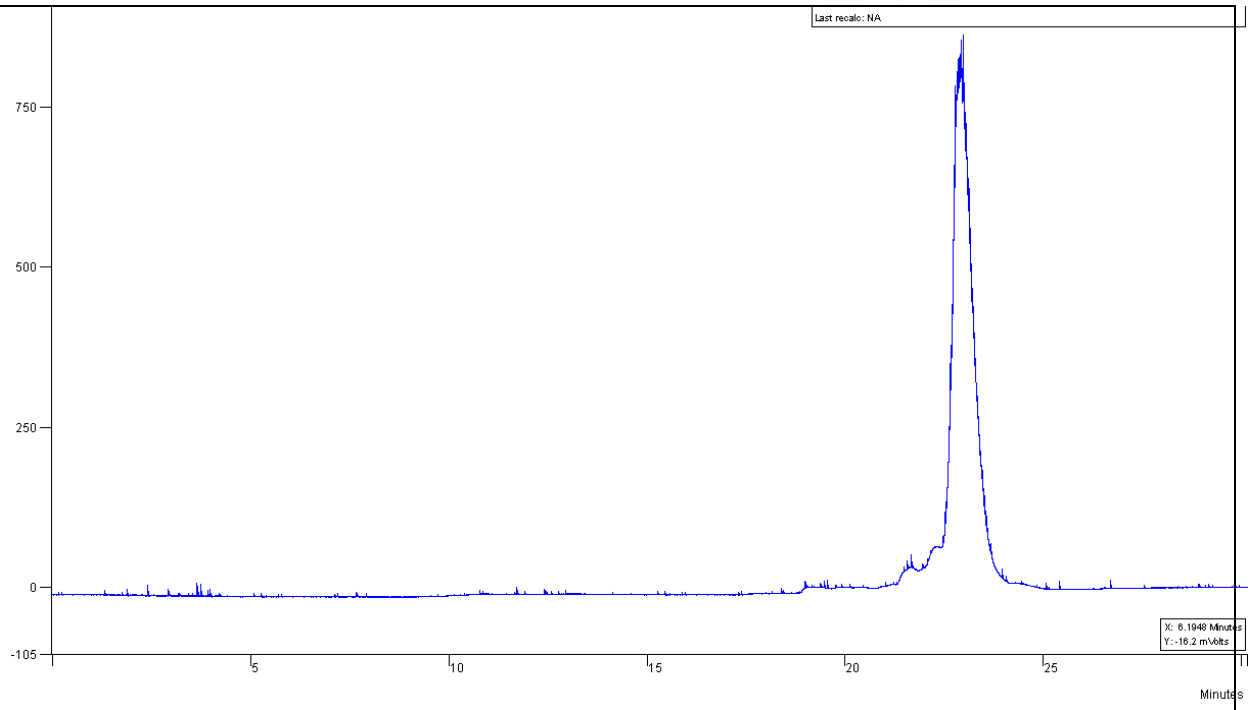


Figure S145. RP-HPLC of ADM-6.

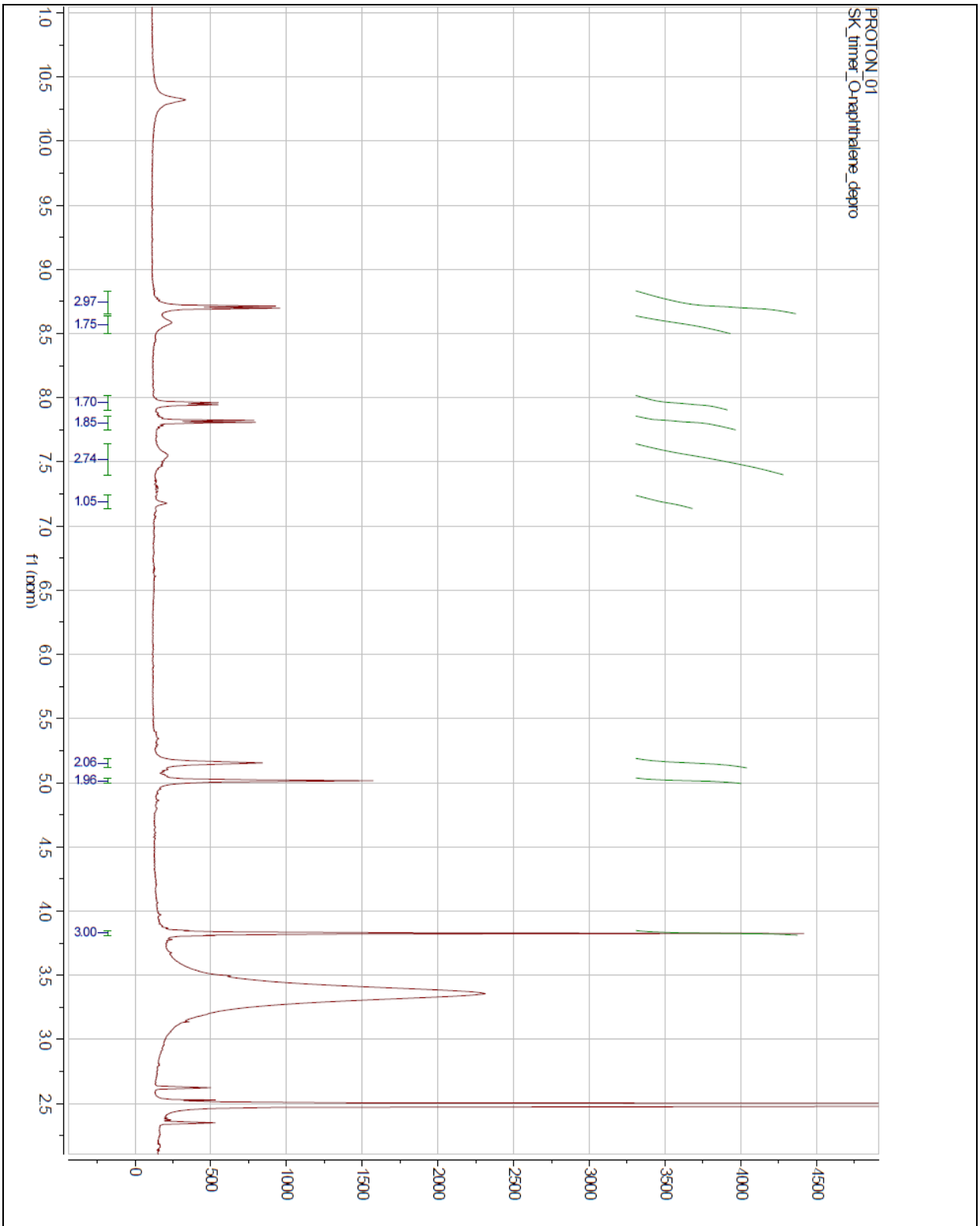


Figure S146. ^{1}H-NMR of ADM-8 [in $(CD_3)_2SO$].

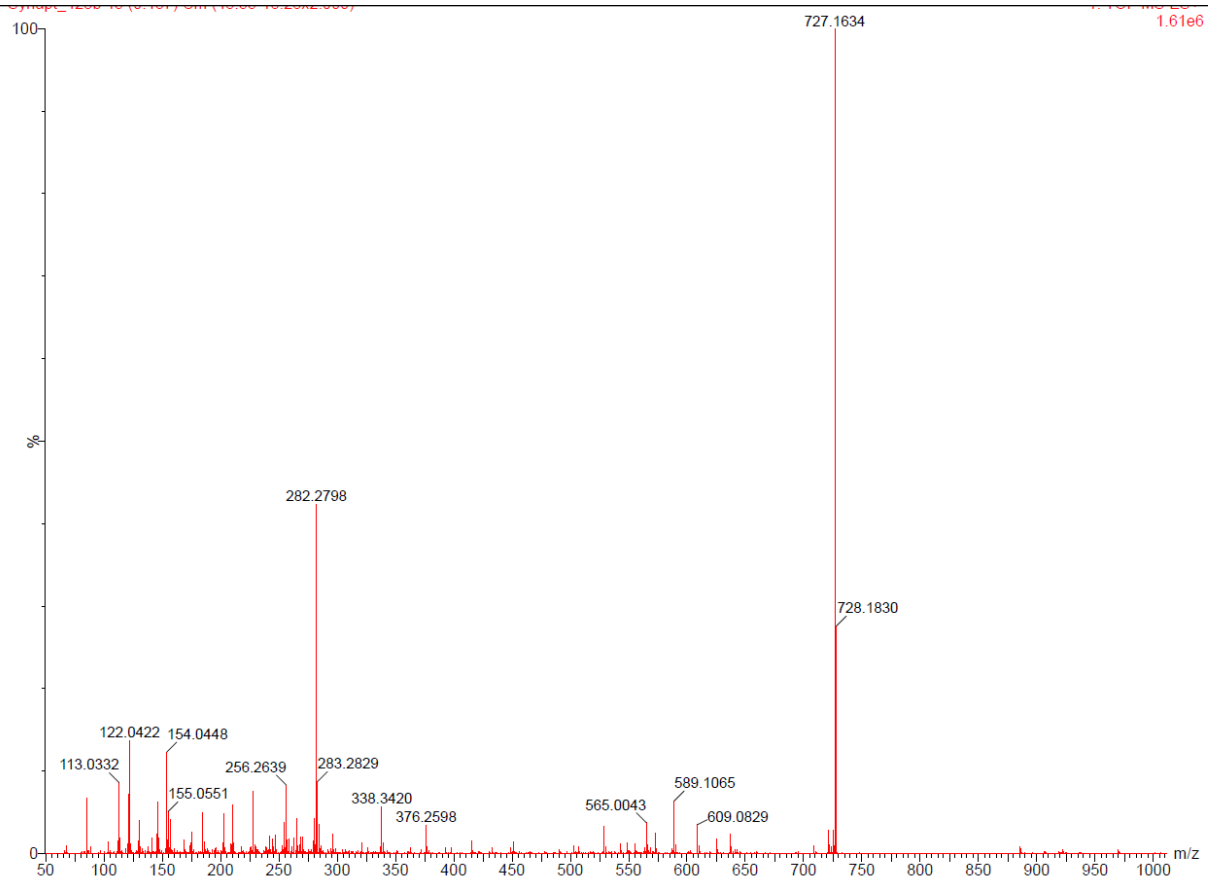


Figure S147. MS-ESI of ADM-8.

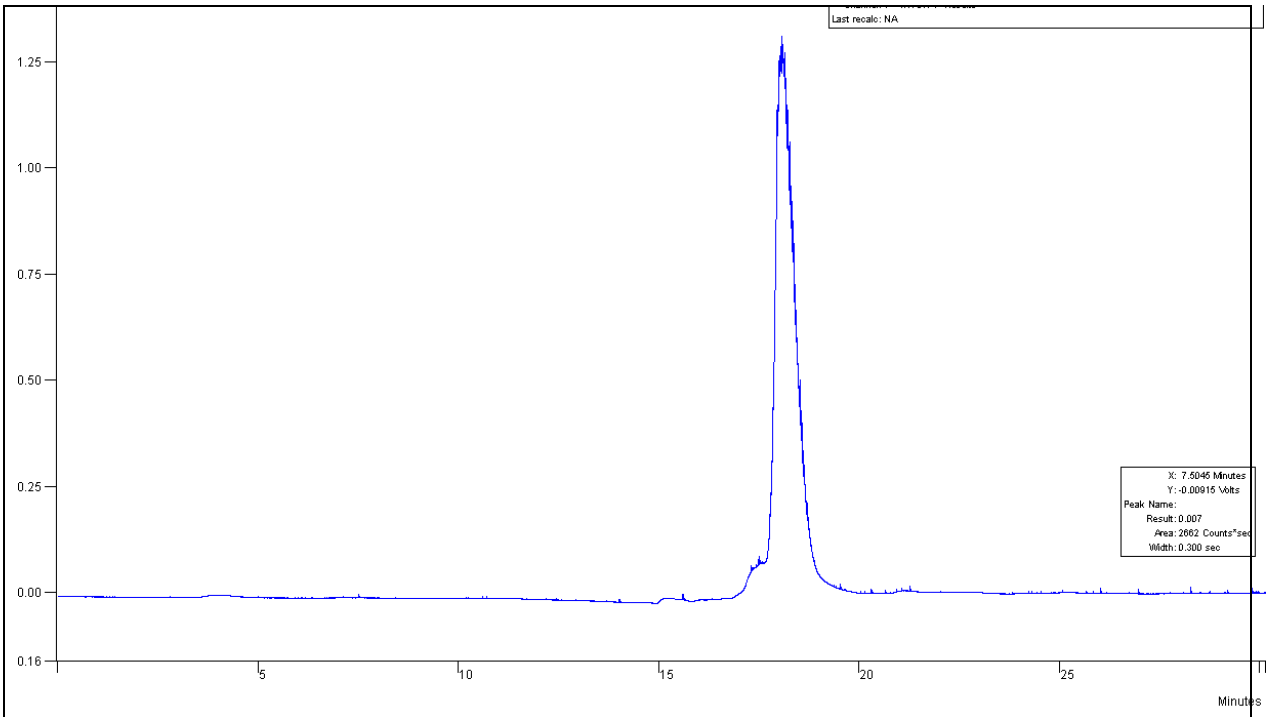


Figure S148. RP-HPLC of ADM-8.

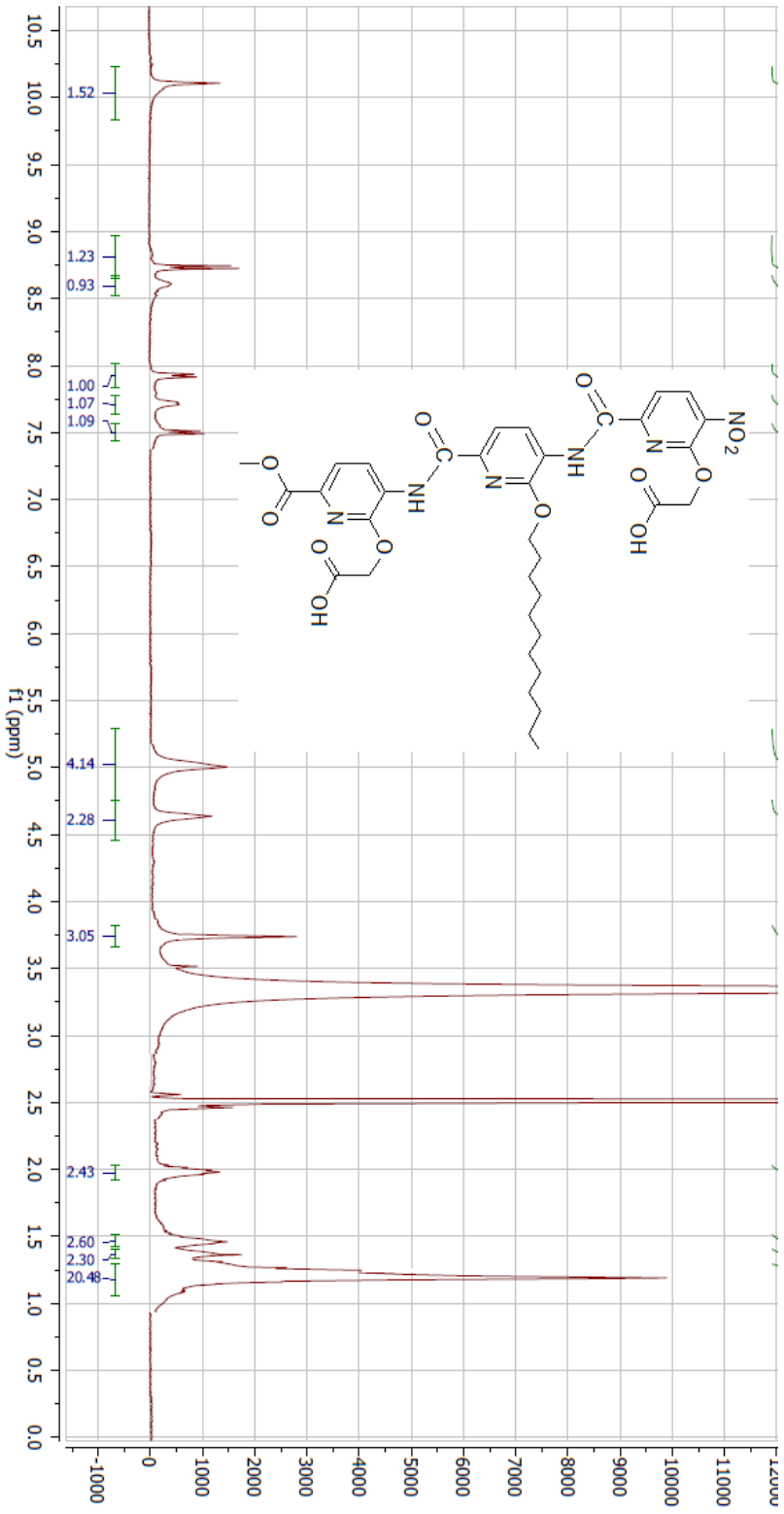


Figure S149. ^{1}H-NMR of ADM-5 [in $(CD_3)_2SO$].

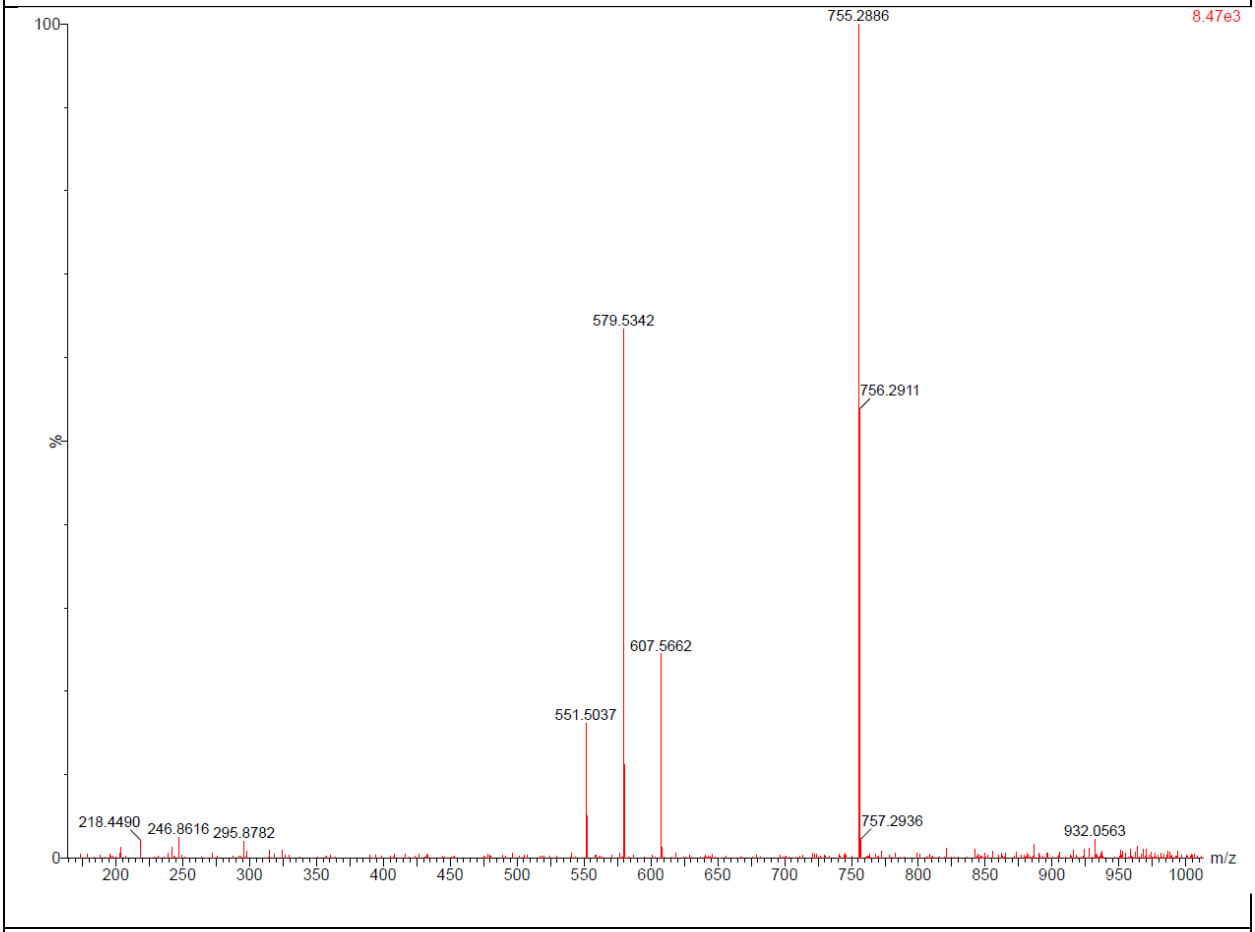


Figure S150. MS-ESI of ADM-5.

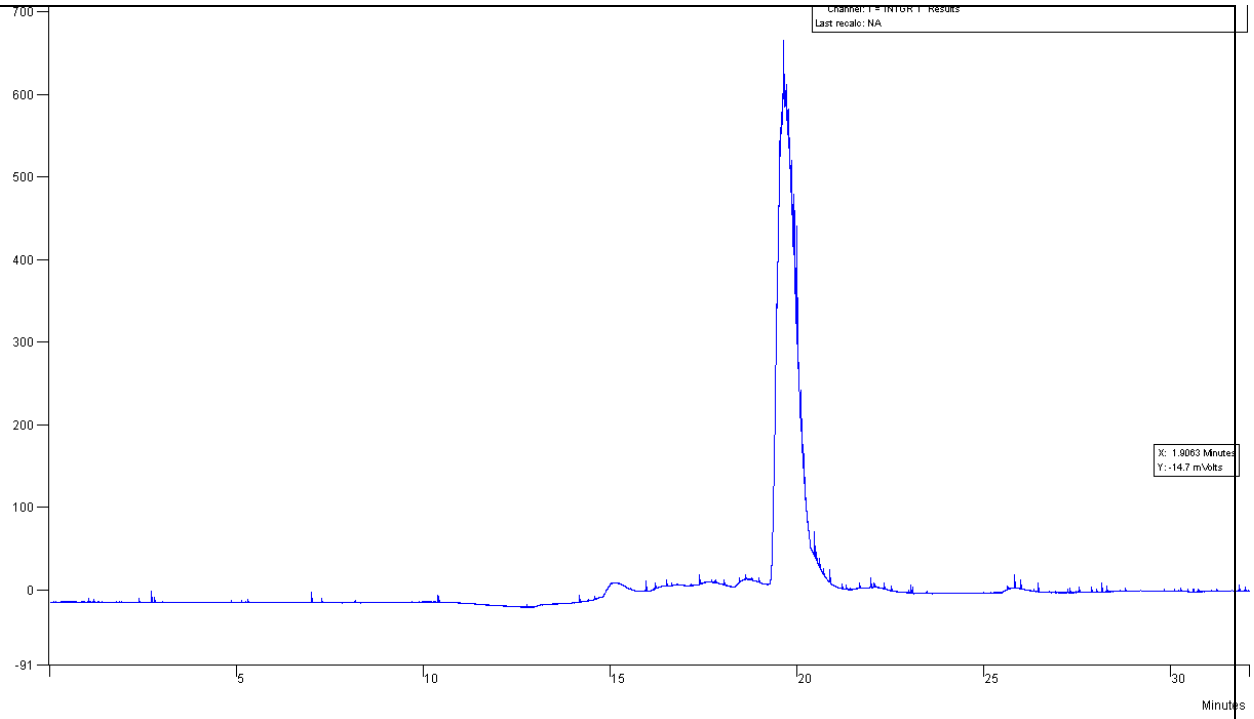


Figure S151. RP-HPLC of ADM-5.

CRYSTALLOGRAPHIC DATA

Crystals were examined under immersion oil and placed on a MiTeGen mount, then transferred onto an AFC11 goniometer with a 93 K N_2 stream bathing the crystal. Low-temperature diffraction data (ω-scans) were collected with a Rigaku MicroMax-007HF source (Cu *K*α; λ = 1.54178 Å) coupled to a Saturn994+ CCD detector. The structures were solved by direct methods using SHELXS and refined against F^2 on all data by full-matrix least squares with SHELXL.(1) All non-hydrogen atoms were refined anisotropically. Unless otherwise noted, hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the *U* value of the atoms to which they are linked (1.5 times for methyl groups). CCDC numbers **1005071** (*tert*-butyl analog of ADM-5) and **1005072** (*tert*-butyl analog of ADM-7) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

Tert-butyl ester analog of ADM-5

Crystal growth

Tert-butyl analog of ADM-5 (4.0 mg, 4.6 mmol) was dissolved in a mixture of ethylacetate/hexane (1:1, (v,v), 2 mL) in a 5 mL glass vial. Colorless crystals suitable for X-ray crystallography grew within 2 days at room temperature.

Crystal refinement

The atoms H3 and H5 were freely refined. The atom O4 is disordered across two positions and denoted by the suffixes A and B. The atom occupancies freely refined to 0.53(0.14) and 0.47(0.14), respectively.

Tert-butyl ester analog of ADM-5

Crystal Data for $C_{43}H_{58}N_6O_{13}$ (*M* = 866.95): triclinic, space group P-1 (no. 2), *a* = 10.9793(4) Å, *b* = 11.6232(5) Å, *c* = 18.9281(13) Å, *α* = 85.997(6)°, *β* = 81.209(6)°, *γ* = 69.708(5)°, *V* = 2238.6(2) $Å^3$, *Z* = 2, *T* = 93 K, μ(CuKα) = 0.795 mm^{-1}, *Dcalc* = 1.286 g/mm^3, 35289 reflections measured ($4.724 \leq 2\Theta \leq 133.158$), 7649 unique ($R_{int}$ = 0.2070, R_{sigma} = 0.2955) which were used

in all calculations. The final R_1 was 0.0951 ($I > 2\sigma(I)$) and wR_2 was 0.2724 (all data).

Tert-butyl ester analog of ADM-5

Crystal growth

Tert-butyl analog of ADM-7 (5.2 mg, 6.66 μmol) was dissolved in a mixture of ethylacetate/hexane (1:1, (v,v), 2 mL) in a 5 mL glass vial. Colorless crystals suitable for X-ray crystallography grew within 2 days at room temperature.

Crystal refinement

Two crystallographically independent molecules were refined in the asymmetric unit. These two models are related by a pseudo inversion center. The reflection list did not support the assignment of a higher symmetry space group.

Tert-butyl ester analog of ADM-7

Crystal Data for $C_{37}H_{44}N_6O_{13}$ (M = 780.78): triclinic, space group P-1 (no. 2), a = 16.0057(4) Å, b = 16.5652(5) Å, c = 17.9631(13) Å, α = 105.865(7)°, β = 104.047(7)°, γ = 110.924(8)°, V = 3960.3(4) Å^3, Z = 4, T = 93 K, μ(CuKα) = 0.843 mm^{-1}, *Dcalc* = 1.310 g/mm^3, 70183 reflections measured ($13.208 \leq 2\Theta \leq 108.488$), 9485 unique ($R_{int}$ = 0.1508, R_{sigma} = 0.1140) which were used in all calculations. The final R_1 was 0.0912 ($I > 2\sigma(I)$) and wR_2 was 0.2623 (all data).

Table S2. Crystal data and structure refinement for *Tert*-butyl ester analog of ADM-5.

Empirical formula	$C_{43}H_{58}N_6O_{13}$

Formula weight	866.95	
Temperature	93(2) K	
Wavelength	1.54187 Å	
Crystal system	Triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	a = 10.9793(4) Å	α = 85.997(6)°
	b = 11.6232(5) Å	β = 81.209(6)°
	c = 18.9281(13) Å	γ = 69.708(5)°
Volume	2238.6(2) $Å^3$	
Z	2	
Density (calculated)	1.286 Mg/m^3	
Absorption coefficient	0.795 mm^{-1}	
F(000)	924	
Crystal color	Colorless	
Crystal size	0.180 x 0.100 x 0.030 mm^3	
Θ range for data collection	2.362 to 66.579°	
Index ranges	$-12 \le h \le 13$, $-12 \le k \le 13$, $-22 \le l \le 22$	
Reflections collected	35289	
Independent reflections	7649 [R(int) = 0.2070]	
Completeness to θ = 66.579 °	96.7 %	

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.977 and 0.870
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7649 / 20 / 585
Goodness-of-fit on F^2	0.880
Final R indices [I>2σ(I) = 2809 data]	R1 = 0.0951, wR2 = 0.2116
R indices (all data)	R1 = 0.2084, wR2 = 0.2724
Largest diff. peak and hole	0.268 and -0.267 e.$Å^{-3}$

Table S3. Hydrogen bonds for *Tert*-butyl ester analog of ADM-5

	Distances (Å)			Angels (°)
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(D-H...A)
C(2) -H(2)...O(13)#1	0.95	2.54	3.090(7)	117.1
C(3) -H(3A)...O(13)#1	0.95	2.44	3.046(7)	121.8
C(9) -H(9A)...O(4A)	0.98	2.32	2.93(5)	119.0
C(10)-H(10A)...O(8)#2	0.98	2.54	3.430(9)	151.4
C(10)-H(10C)...O(4A)	0.98	2.54	3.07(4)	113.4
C(10)-H(10C)...O(4B)	0.98	2.31	2.85(5)	113.8
N(3)-H(3)...O(7)	0.85(6)	2.14(6)	2.602(6)	114(5)
C(14)-H(14)...O(6)	0.95	2.39	2.962(6)	118.4

C(18)-H(18A)...O(10)	0.99	2.47	3.097(7)	121.3
N(5)-H(5)...N(4)	0.81(7)	2.18(7)	2.622(7)	115(6)
C(32)-H(32)...O(8)	0.95	2.34	2.906(7)	117.9
C(39)-H(39A)...O(10)	0.98	2.44	3.016(7)	117.1
C(40)-H(40C)...O(10)	0.98	2.49	3.012(8)	113.2

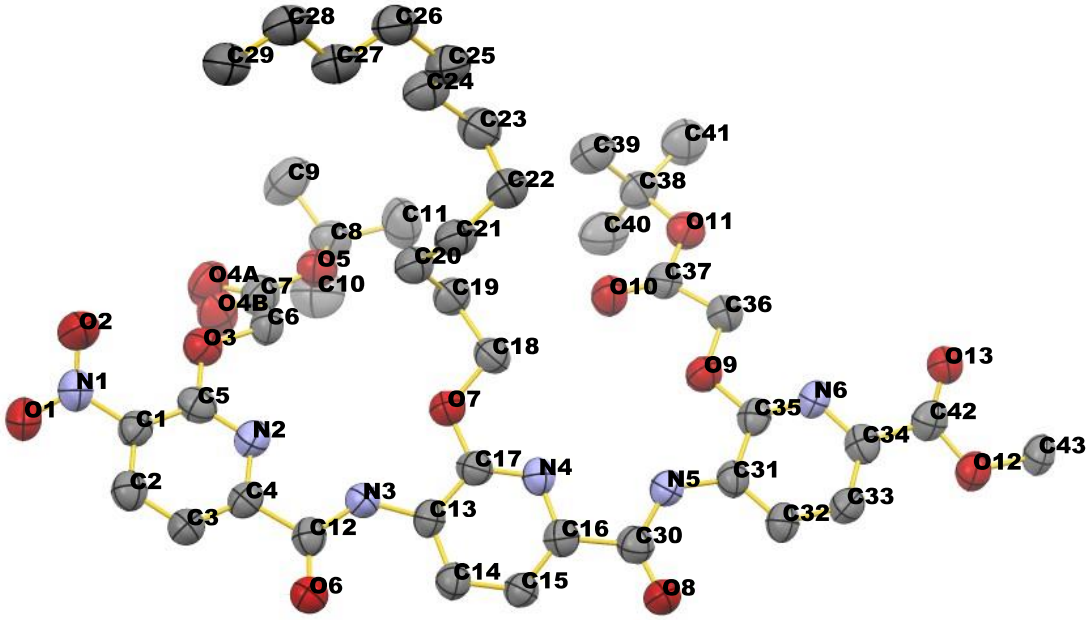


Figure S125. The numbering scheme of ***Tert*-butyl ester analog of ADM-5**. All atoms shown are depicted with 50% thermal contours. The hydrogen atoms are omitted for clarity.

***Tert*-butyl ester analog of ADM-7**

Crystal growth

Tert-butyl analog of ADM-7 (3.5 mg, 4.5 mmol) was dissolved in a mixture of ethylacetate/hexane (1:1, (v,v), 2 mL) in a 5 mL glass vial. Colorless crystals suitable for X-ray crystallography grew within 2 days at room temperature.

Crystal refinement

Two crystallographically independent molecules were refined in the asymmetric unit. These two models are related by a pseudo inversion center. The reflection list did not support the assignment of a higher symmetry space group.

Table S4. Crystal data and structure refinement for *tert*-butyl ester analog of ADM-7.

Empirical formula	$C_{37}H_{44}N_6O_{13}$	
Formula weight	780.78	
Temperature	93(2) K	
Wavelength	1.54187 Å	
Crystal system	Triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	a = 16.0057(4) Å	α = 105.865(7)°
	b = 16.5652(5) Å	β = 104.047(7)°
	c = 17.9631(13) Å	γ = 110.924(8)°
Volume	3960.3(4) Å^3	
Z	4	

Density (calculated)	1.310 Mg/m^3
Absorption coefficient	0.843 mm^{-1}
F(000)	1648
Crystal color	Colorless
Crystal size	0.080 x 0.020 x 0.020 mm^3
Θ range for data collection	6.604 to 54.244°
Index ranges	$-16 \le h \le 16$, $-17 \le k \le 17$, $-18 \le l \le 17$
Reflections collected	70183
Independent reflections	9485 [R(int) = 0.1508]
Completeness to θ = 54.244°	98.2 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.983 and 0.931
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9485 / 0 / 1023
Goodness-of-fit on F^2	0.911
Final R indices [I>2σ(I) = 4533 data]	R1 = 0.0912, wR2 = 0.2295
R indices (all data)	R1 = 0.1552, wR2 = 0.2623
Largest diff. peak and hole	0.819 and -0.295 $e.Å^{-3}$

Table S5. Hydrogen bonds for *tert*-butyl ester analog of ADM-7

	Distances (Å)			Angels (°)
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(D-H...A)
C(3)-H(3A)...O(13)#1	0.95	2.38	3.103(8)	132.4
C(6)-H(6B)...O(17)#2	0.99	2.57	3.353(7)	136.0
C(9)-H(9B)...O(15)#3	0.98	2.50	3.177(9)	126.3
C(10)-H(10A)...O(4)	0.98	2.39	2.957(8)	116.4
C(10)-H(10B)...O(16)#3	0.98	2.62	3.567(8)	161.9
C(11)-H(11C)...O(4)	0.98	2.45	3.016(8)	116.3
C(14)-H(14)...O(6)	0.95	2.25	2.862(8)	121.1
C(19)-H(19B)...N(4)	0.99	2.64	3.154(7)	112.2
C(19)-H(19B)...O(21)	0.99	2.46	3.396(7)	157.7
C(23)-H(23A)...O(8)#4	0.99	2.57	3.522(7)	162.5
C(23)-H(23B)...O(4)	0.99	2.47	3.426(8)	161.6
N(5)-H(8)...N(4)	0.88	2.20	2.645(8)	111.2
C(26)-H(26)...O(8)	0.95	2.30	2.886(7)	119.5
C(33)-H(33A)...O(10)	0.98	2.38	2.927(8)	114.8
C(34)-H(34C)...O(10)	0.98	2.44	2.962(9)	112.5
C(37)-H(37B)...O(25)#5	0.98	2.52	3.354(8)	142.4
C(39)-H(39)...O(23)#5	0.95	2.38	3.143(10)	137.0

C(40)-H(40)...O(25)#5	0.95	2.36	3.072(8)	131.4
C(43)-H(43A)...O(4)#6	0.99	2.46	3.256(7)	137.5
C(46)-H(46B)...O(3)#4	0.98	2.60	3.548(8)	162.5
C(46)-H(46C)...O(17)	0.98	2.43	3.004(8)	117.3
C(48)-H(48A)...O(17)	0.98	2.44	3.023(9)	117.3
N(9)-H(7)...N(8)	0.88	2.27	2.700(8)	110.3
C(51)-H(51)...O(19)	0.95	2.26	2.861(8)	120.6
C(52)-H(52)...O(10)	0.95	2.31	3.140(7)	145.1
C(56)-H(56A)...N(10)	0.99	2.65	3.153(8)	111.7
C(60)-H(60B)...O(21)#3	0.99	2.44	3.247(8)	137.9
N(11)-H(5)...N(10)	0.88	2.24	2.677(8)	110.4
C(63)-H(63)...O(21)	0.95	2.26	2.862(8)	120.3
C(67)-H(67A)...O(19)#3	0.99	2.60	3.545(9)	159.1
C(74)-H(74B)...O(13)#1	0.98	2.59	3.468(8)	148.5

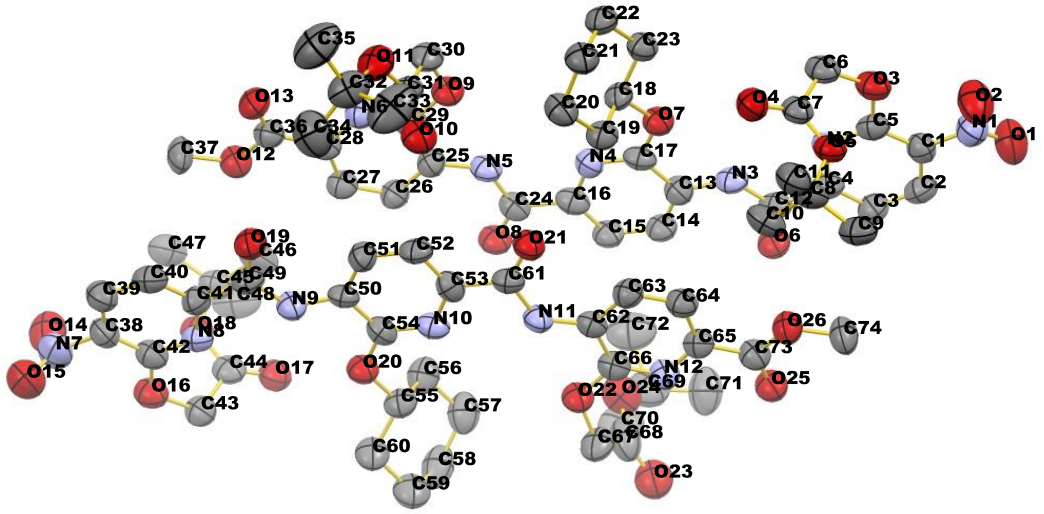


Figure S126. The numbering scheme of *tert*-butyl ester analog of ADM-7. All atoms shown are depicted with 50% thermal contours. The hydrogen atoms are omitted for clarity.