

Photochemical synthesis of benzo[*d*]imidazole-4-carboxylic acids from 3-(dialkylamino)-2-nitrobenzaldehydes

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S1. Reagents and methods.

NMR spectra ^1H , ^{13}C were recorded on a Bruker Fourier 300 (Bruker, USA). Chemical shifts were reported relative to solvents residue peaks (2.50 ppm for ^1H and 39.52 ppm for ^{13}C in $\text{DMSO}-d_6$ and 7.26 ppm for ^1H and 77.16 ppm for ^{13}C in CDCl_3).

High-resolution mass spectra (HRMS) spectra were recorded on Orbitrap LTQ XL system (Thermo Fisher Scientific, USA) using electrospray ionization (ESI).

Melting points were measured on a SMP 30 apparatus (Stuart Scientific, Great Britain).

Photoinduced processes were performed on EvoluChem™ PhotoRedOx box using 365 nm (LG, HCK1012-01-006, 25 mW/cm²), 380 nm (LG, HCK1012-01-013, 8 mW/cm²), 405 nm (LG, HCK1012-01-010, 28 mW/cm²), 425 nm (EPILED, HCK1012-01-012, 33 mW/cm²) and 450 nm (LG, HCK1012-01-002, 34 mW/cm²) light-emitting diode (LED) lamp from EvoluChem™ (HepatoChem, USA).

Commercially available reagents were used without additional purification. Merck Kieselgel 60 was used for flash chromatography. Thin-layer chromatography (TLC) was performed on silica gel 60 F254 aluminium plates (Merck, Germany).

S2. Optimization of solvent.

Compound **1b** (3 mg, 0.013 mmol) was dissolved in solvent (1 mL). Vials with obtained solutions were irradiated with 365 nm LED lamp in Evoluchem™ PhotoRedOx box with stirring for 6 h. Then solvents were removed in vacuum, the residues were weighed and analyzed by ¹H NMR in DMSO-*d*₆. The overall aromatic signal from 6.00 ppm to 9.00 ppm (3H) was used as a standard (300%). The quantity of components was assessed using the following signals:

- singlet from 9.91 ppm to 9.96 ppm (1H) for substrate **1b**;
- triplet from 7.35 ppm to 7.44 ppm (1H) for product **2b**;

Results are presented in Table S1.

Table S1. Solvent screening results for compound **1b**.

No	Solvent	Remained 1b , %	2b , %	Comments
1	DMSO	53	traces	
2	DMF	87	0	
3	PhMe	3	71	
4	PhH	0	90	
5	DCM	27	44	
6	1,4-Dioxane	0	33	c.m.*
7	EtOAc	55	35	
8	PhCl	39	22	c.m.*
9	Py	7	11	c.m.*
10	CH ₃ CN	44	41	

*a complex mixture of a large number of difficult to identify compounds.

S3. Kinetic study.

Compound **1b** (3 mg) was dissolved in 1 mL of CD₃CN in a Schlenk vessel. The mixture was degassed under vacuum and filled with argon three times. Next, part of the solution (0.65 mL) was transferred to argon filled NMR tube and sealed. The mixture was analyzed by ¹H NMR (starting point). NMR tube with this solution was irradiated with 365 nm LED lamp. Finally, the residue was analyzed by ¹H NMR. TMS signal was used as an internal standard - for all spectra its integral area was set on equal value. Initial integral area of **1b** singlet signal was determined as 100%. The yields of components were determined using the following integral areas:

- singlet from 9.83 ppm to 9.95 ppm (1H) for substrate **1b**;
- singlet from 5.05 ppm to 5.10 ppm (2H) for product **2b**.

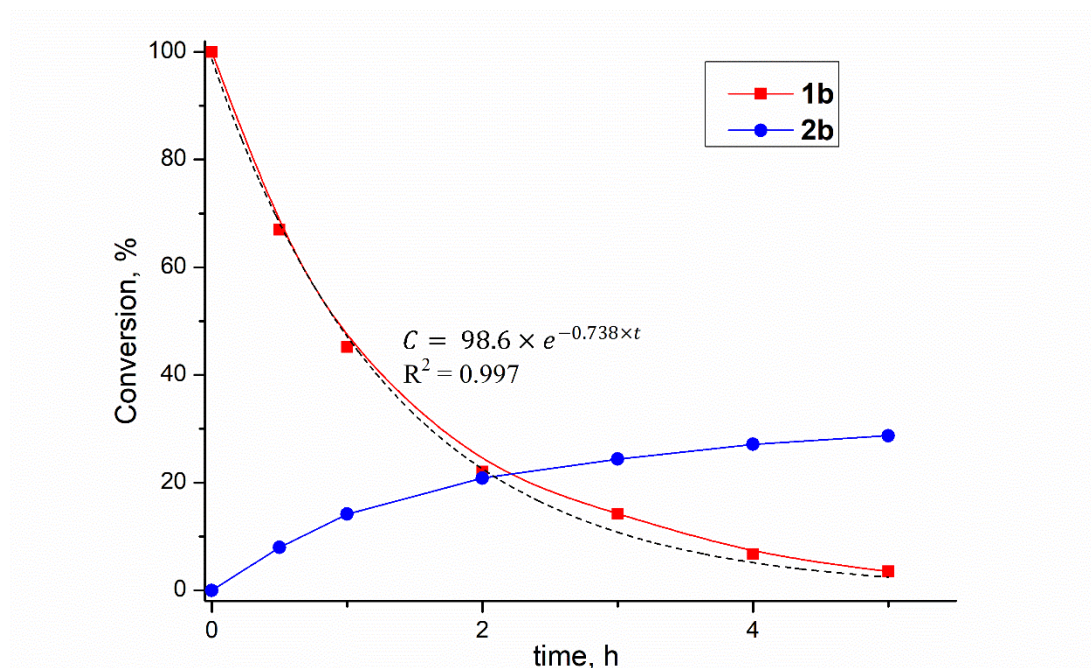


Figure S1. Kinetic study of compound **1b**.

S4. Wavelength study.

Compound **1b** (15 mg) was dissolved in 5 mL of CD₃CN in a Schlenk vessel. The mixture was degassed under vacuum and filled with argon three times. Next, parts of the solution (0.65 mL) were transferred to five argon filled NMR tubes and sealed. The mixtures were analyzed by ¹H NMR (starting point). NMR tubes with this solution were irradiated for 3 h with different LED lamps. Finally, all the residues were analyzed by ¹H NMR similarly to the mentioned above.

Table S2. Wavelength screening results for compound **1b**.

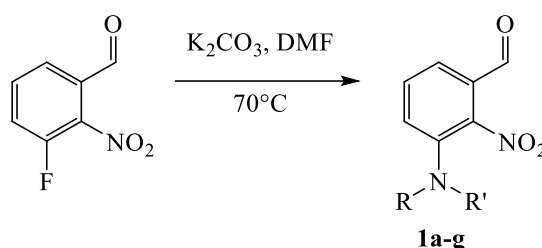
Wavelength	2b , yield	1b , remained
365 nm	24%	14%
380 nm	13%	32%
405 nm	10%	66%
425 nm	4%	91%
450 nm	0%	100%

S5. Temperature study.

Compound **1b** (9 mg) was dissolved in 3 mL of CD₃CN in a Schlenk vessel. The mixture was degassed under vacuum and filled with argon three times. Next, parts of the solution (0.65 mL) were transferred to three argon filled NMR tubes and sealed. The mixtures were analyzed by ¹H NMR (starting point). NMR tubes with this solution were irradiated for 1 h with 365 nm LED lamp in a glass bath with distilled water, with the temperature inside controlled using a magnetic stirrer with a thermocouple. Finally, all the residues were analyzed by ¹H NMR similarly to the mentioned above.

Table S3. Temperature screening results for compound **1b**.

Temperature	2b , yield	1b , remained
25 °C	38%	27%
40 °C	26%	12%
60 °C	32%	7%

S6. General synthetic procedure for 2-nitro-3-(dialkylamino)benzaldehydes (1a-g).

3-Fluoro-2-nitrobenzaldehyde (85 mg, 0.5 mmol) was dissolved in dry DMF (2 mL). The corresponding dialkylamine (0.6 mmol, 1.2 eq.) and K_2CO_3 (104 mg, 0.75 mmol, 1.5 eq.) were added subsequently. The resulting mixture was stirred at 70°C for 20 h. Then it was cooled to room temperature, diluted with EtOAc (100 mL), washed with saturated KCl solution (4×50 mL) and dried over Na_2SO_4 . All volatiles were removed in vacuo, and the residue was purified by flash chromatography (eluent – hexane-EtOAc mixture, 19:1).

3-(Dimethylamino)-2-nitrobenzaldehyde 1a: yield 72 mg (74%), orange oil. ^1H NMR (300 MHz, CDCl_3) δ : 2.88 (s, 6H, CH_3), 7.38 (d, 1H, Ar, J 8.3 Hz), 7.41–7.47 (d, 1H, Ar, J 7.4 Hz), 7.53 (t, 1H, Ar, J 7.8 Hz), 9.93 (s, 1H, COH). ^{13}C NMR (75 MHz, CDCl_3) δ : 43.1 (2C, CH_3), 121.8 (Ar), 125.6 (Ar), 129.0 (Ar), 131.2 (Ar), 142.8 (Ar), 145.5 (Ar), 187.7 (COH). HRMS (ESI), m/z : 195.0768 $[\text{M}+\text{H}]^+$, (calc. for $\text{C}_9\text{H}_{11}\text{N}_2\text{O}_3^+$, m/z : 195.0764).

3-Morpholino-2-nitrobenzaldehyde 1b: yield 94 mg (80%), light brown solid, mp 152–154°C. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ : 2.88–2.95 (m, 4H, $\text{N}-\text{CH}_2$), 3.61–3.68 (m, 4H, $\text{O}-\text{CH}_2$), 7.80–7.95 (m, 3H, Ar), 9.93 (s, 1H, COH). ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ : 52.6 (2C, $\text{N}-\text{CH}_2$), 66.4 (2C, $\text{O}-\text{CH}_2$), 127.2 (Ar), 129.7 (Ar), 130.2 (Ar), 132.1 (Ar), 144.4 (Ar), 144.6 (Ar), 189.6 (COH). HRMS (ESI), m/z : 237.0870 $[\text{M}+\text{H}]^+$, (calc. for $\text{C}_{11}\text{H}_{13}\text{N}_2\text{O}_4^+$, m/z : 237.0870).

2-Nitro-3-(piperidin-1-yl)benzaldehyde 1c: yield 110 mg (94%), orange oil. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ : 1.44–1.61 (m, 6H, $\text{CH}_2-\text{CH}_2-\text{CH}_2$), 2.83–2.92 (m, 4H, $\text{N}-\text{CH}_2$), 7.75–7.87 (m, 3H, Ar), 9.91 (s, 1H, COH). ^{13}C NMR (75 MHz, CDCl_3) δ : 23.8 (CH_2), 26.1 (2C, CH_2), 54.0 (2C, CH_2), 124.9 (Ar), 128.0 (Ar), 128.9 (Ar), 131.2 (Ar), 146.5 (Ar), 146.8 (Ar), 187.2 (COH). HRMS (ESI), m/z : 235.1080 $[\text{M}+\text{H}]^+$, (calc. for $\text{C}_{12}\text{H}_{15}\text{N}_2\text{O}_3^+$, m/z : 235.1077).

3-(Azepan-1-yl)-2-nitrobenzaldehyde 1d: yield 89 mg (72%), orange oil. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ : 1.48–1.59 (m, 4H, $\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2$), 1.60–1.73 (m, 4H, $\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2$), 3.18 (m, 4H, $\text{N}-\text{CH}_2$), 7.53 (dd, 1H, Ar, J 6.3, 2.2 Hz), 7.62–7.72 (m, 2H, Ar), 9.88 (s, 1H, COH). ^{13}C NMR (75 MHz, CDCl_3) δ : 27.4 (2C, $\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2$), 28.7 (2C, $\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2$), 53.0 (2C, $\text{N}-\text{CH}_2$), 120.6 (Ar), 126.2 (Ar), 129.1 (Ar), 130.9 (Ar), 141.7 (Ar), 145.6 (Ar), 188.0 (COH). HRMS (ESI), m/z : 249.1236 $[\text{M}+\text{H}]^+$, (calc. for $\text{C}_{13}\text{H}_{17}\text{N}_2\text{O}_3^+$, m/z : 249.1234).

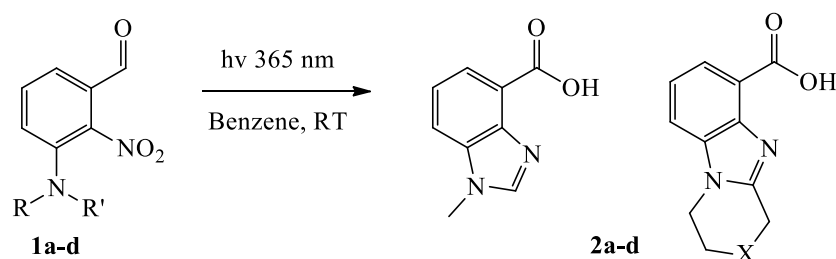
2-Nitro-3-(pyrrolidin-1-yl)benzaldehyde 1e: yield 98 mg (89%), yellow solid, mp 78–80°C. ^1H NMR (300 MHz, CDCl_3) δ : 1.96–2.04 (m, 4H, CH_2-CH_2), 3.28–3.36 (m, 4H, $\text{N}-\text{CH}_2$), 7.10 (dd, 1H, Ar, J 8.6,

0.8 Hz), 7.18 (dd, 1H, Ar, J 7.3, 0.9 Hz), 7.43 (td, 1H, Ar, J 7.6, 0.6 Hz), 9.91 (s, 1H, COH). ^{13}C NMR (75 MHz, CDCl_3) δ : 25.5 (2C, $\text{CH}_2\text{--CH}_2$), 49.0 (2C, N- CH_2), 117.5 (Ar), 121.6 (Ar), 129.5 (Ar), 130.9 (Ar), 136.5 (Ar), 140.8 (Ar), 188.4 (COH). HRMS (ESI), m/z : 221.0922 $[\text{M}+\text{H}]^+$, (calc. for $\text{C}_{11}\text{H}_{13}\text{N}_2\text{O}_3^+$, m/z : 221.0921).

3-(Diethylamino)-2-nitrobenzaldehyde 1f: yield 92 mg (83%), light brown solid, mp 55–57°C. ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ : 0.87 (t, 6H, $\text{CH}_2\text{--CH}_3$, J 7.1 Hz), 2.96 (q, 4H, $\text{CH}_2\text{--CH}_3$, J 7.2 Hz), 7.77–7.85 (m, 1H, Ar), 7.86–7.93 (m, 2H, Ar), 9.91 (s, 1H, COH). ^{13}C NMR (75 MHz, CDCl_3) δ : 12.6 (2C, $\text{CH}_2\text{--CH}_3$), 48.4 (2C, $\text{CH}_2\text{--CH}_3$), 125.8 (Ar), 127.8 (Ar), 130.6 (Ar), 131.0 (Ar), 144.2 (2C, Ar), 187.2 (COH). HRMS (ESI), m/z : 223.1078 $[\text{M}+\text{H}]^+$, (calc. for $\text{C}_{11}\text{H}_{15}\text{N}_2\text{O}_3^+$, m/z : 223.1077).

3-(Benzyl(ethyl)amino)-2-nitrobenzaldehyde 1g: yield 36 mg (25%), yellow oil. ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ : 0.87 (t, 3H, $\text{CH}_2\text{--CH}_3$, J 7.1 Hz), 2.94 (q, 2H, $\text{CH}_2\text{--CH}_3$, J 7.2 Hz), 4.12 (s, 2H, $\text{CH}_2\text{--Ph}$), 7.18–7.34 (m, 5H, Ph), 7.77 (t, 1H, Ar, J 7.7 Hz), 7.85 (dd, 1H, Ar, J 7.6, 1.5 Hz), 7.90 (dd, 1H, Ar, J 8.0, 1.5 Hz), 9.90 (s, 1H, COH). ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ : 12.2 ($\text{CH}_2\text{--CH}_3$), 47.7 ($\text{CH}_2\text{--CH}_3$), 57.8 ($\text{CH}_2\text{--Ph}$), 127.2 (2C, Ar), 128.3 (4C, Ph), 129.9 (Ph), 131.3 (Ar), 132.1 (Ar), 137.7 (Ph), 143.2 (Ar), 145.5 (Ar), 189.6 (COH). HRMS (ESI), m/z : 285.1236 $[\text{M}+\text{H}]^+$, (calc. for $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}_3^+$, m/z : 285.1234).

S7. General synthetic procedure for benzo[d]imidazole-4-carboxylic acids (2a-d).



The corresponding aldehyde **1a-d** (0.2 mmol) was dissolved in benzene (~15 mL, resulting concentration of substrate **1**: 3 mg/mL). Obtained solution was irradiated with 365 nm LED lamp with stirring for 24 h. The reaction progress was monitored by TLC (eluent – hexane-EtOAc mixture, 1:1). After the reaction completion, the mixture was filtered, resulting solution was collected, all volatiles were removed in vacuo. The residue was washed with Et_2O (3×1 mL), filtered and dried under reduced pressure.

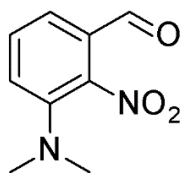
1-Methyl-1H-benzo[d]imidazole-4-carboxylic acid 2a: yield 35 mg (98%), black solid, mp 112–114°C. ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ : 3.93 (s, 3H, CH_3), 7.44 (t, 1H, Ar, J 7.7 Hz), 7.84 (d, 1H, Ar, J 7.5 Hz), 7.93 (d, 1H, Ar, J 8.4 Hz), 8.50 (s, 1H, HetAr). ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ : 31.3 (CH_3), 115.7 (Ar), 119.9 (Ar), 122.5 (Ar), 124.1 (Ar), 134.9 (Ar), 141.7 (Ar), 145.8 (HetAr), 166.2 (COOH). HRMS (ESI), m/z : 177.0659 $[\text{M}+\text{H}]^+$, (calc. for $\text{C}_9\text{H}_9\text{N}_2\text{O}_2^+$, m/z : 177.0659).

3,4-Dihydro-1H-benzo[4,5]imidazo[2,1-c][1,4]oxazine-9-carboxylic acid 2b: yield 33 mg (75%), pink solid, mp >250°C (with decomp.). ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ : 4.19 (m, 2H, $-\text{CH}_2-$), 4.29 (m, 2H, $-\text{CH}_2-$), 5.05 (s, 2H, $\text{CH}_2\text{--O}$), 7.35–7.43 (m, 1H, Ar), 7.78–7.90 (m, 2H, Ar). ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ : 42.1 (N- CH_2), 63.2 (N- $\text{CH}_2\text{--CH}_2\text{--O}$), 64.2 ($\text{CH}_2\text{--O}$), 114.9 (Ar), 119.6 (Ar), 121.7 (Ar), 124.4 (Ar), 134.6 (Ar), 140.9 (Ar), 149.9 (HetAr), 166.3 (COOH). HRMS (ESI), m/z : 219.0766 $[\text{M}+\text{H}]^+$, (calc. for $\text{C}_{11}\text{H}_{11}\text{N}_2\text{O}_3^+$, m/z : 219.0764).

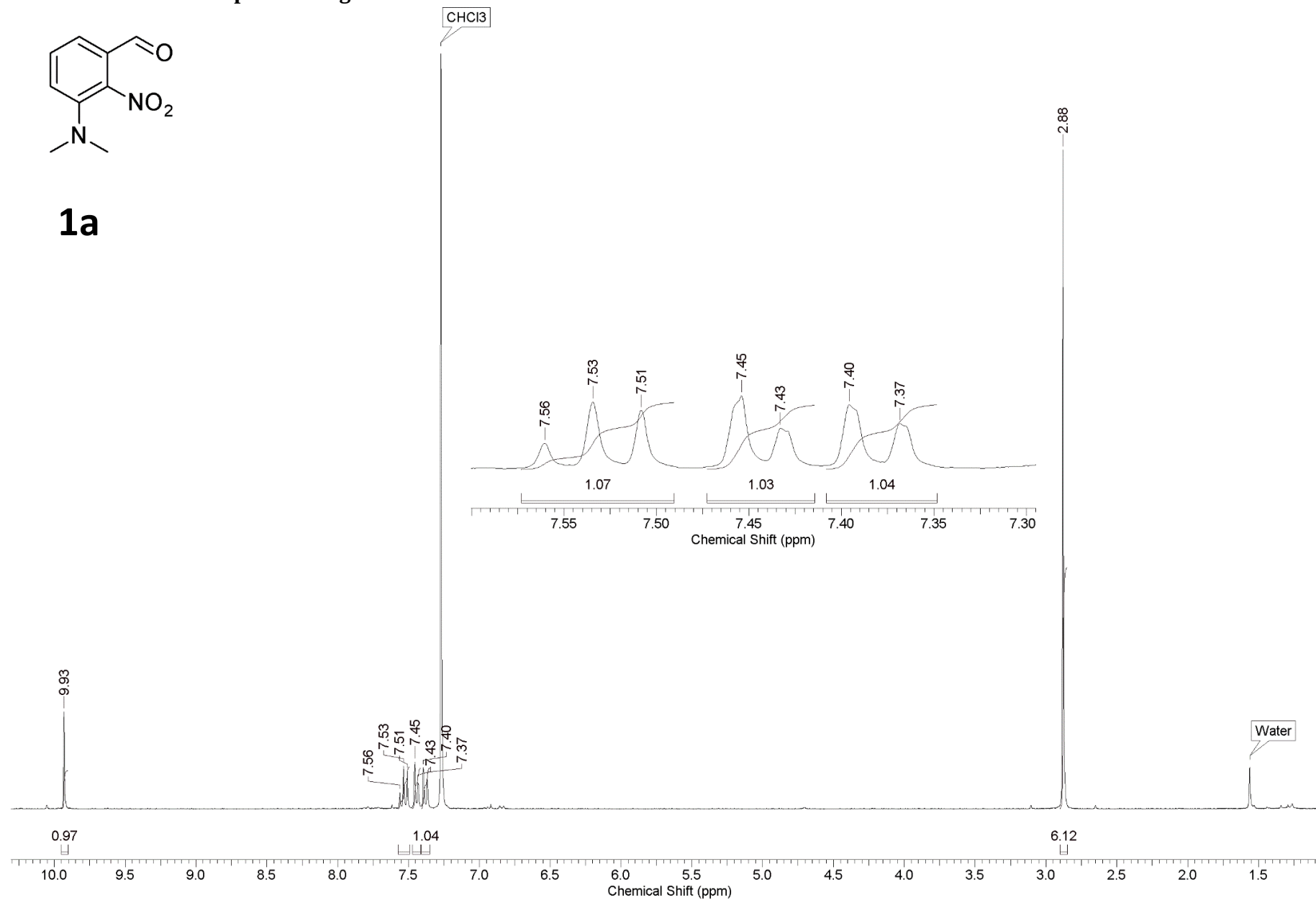
1,2,3,4-Tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine-6-carboxylic acid 2c: yield 31 mg (72%), brown solid, mp 138–140°C. ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ : 1.90–2.03 (m, 2H, $-\text{CH}_2-$), 2.03–2.14 (m, 2H, $-\text{CH}_2-$), 3.03–3.12 (m, 2H, $-\text{CH}_2-$), 4.15–4.26 (m, 2H, N- CH_2), 7.36 (t, 1H, Ar, J 7.8 Hz), 7.76–7.88 (m, 2H, Ar). ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ : 19.6 ($-\text{CH}_2-$), 21.6 ($-\text{CH}_2-$), 24.6 ($-\text{CH}_2-$), 42.6 (N-

$\underline{\text{CH}_2-}$), 115.0 (Ar), 118.1 (Ar), 121.6 (Ar), 123.9 (Ar), 134.6 (Ar), 141.0 (Ar), 153.7 (HetAr), 166.1 ($\underline{\text{COOH}}$). HRMS (ESI), m/z : 217.0974 $[\text{M}+\text{H}]^+$, (calc. for $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}_2^+$, m/z : 217.0972).
7,8,9,10-Tetrahydro-6H-benzo[4,5]imidazo[1,2-a]azepine-4-carboxylic acid 2d: yield 36 mg (78%), brown solid, mp 118–120°C. ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ : 1.67–1.82 (m, 4H, $-\underline{\text{CH}_2-}$), 1.84–1.96 (m, 2H, $-\underline{\text{CH}_2-}$), 3.10–3.19 (m, 2H, $-\underline{\text{CH}_2-}$), 4.29–4.44 (m, 2H, $\text{N}-\underline{\text{CH}_2}$), 7.37 (t, 1H, Ar, J 7.8 Hz), 7.77 (d, 1H, Ar, J 7.4 Hz), 7.91 (d, 1H, Ar, J 8.1 Hz). ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ : 24.7 ($-\underline{\text{CH}_2-}$), 27.9 ($-\underline{\text{CH}_2-}$), 28.9 ($-\underline{\text{CH}_2-}$), 29.9 ($-\underline{\text{CH}_2-}$), 44.4 ($\text{N}-\underline{\text{CH}_2}$), 115.0 (Ar), 118.6 (Ar), 121.9 (Ar), 123.5 (Ar), 135.8 (Ar), 140.6 (Ar), 159.2 (HetAr), 166.1 ($\underline{\text{COOH}}$). HRMS (ESI), m/z : 231.1130 $[\text{M}+\text{H}]^+$, (calc. for $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_2^+$, m/z : 231.1128).

S8. NMR and HRMS spectra images.

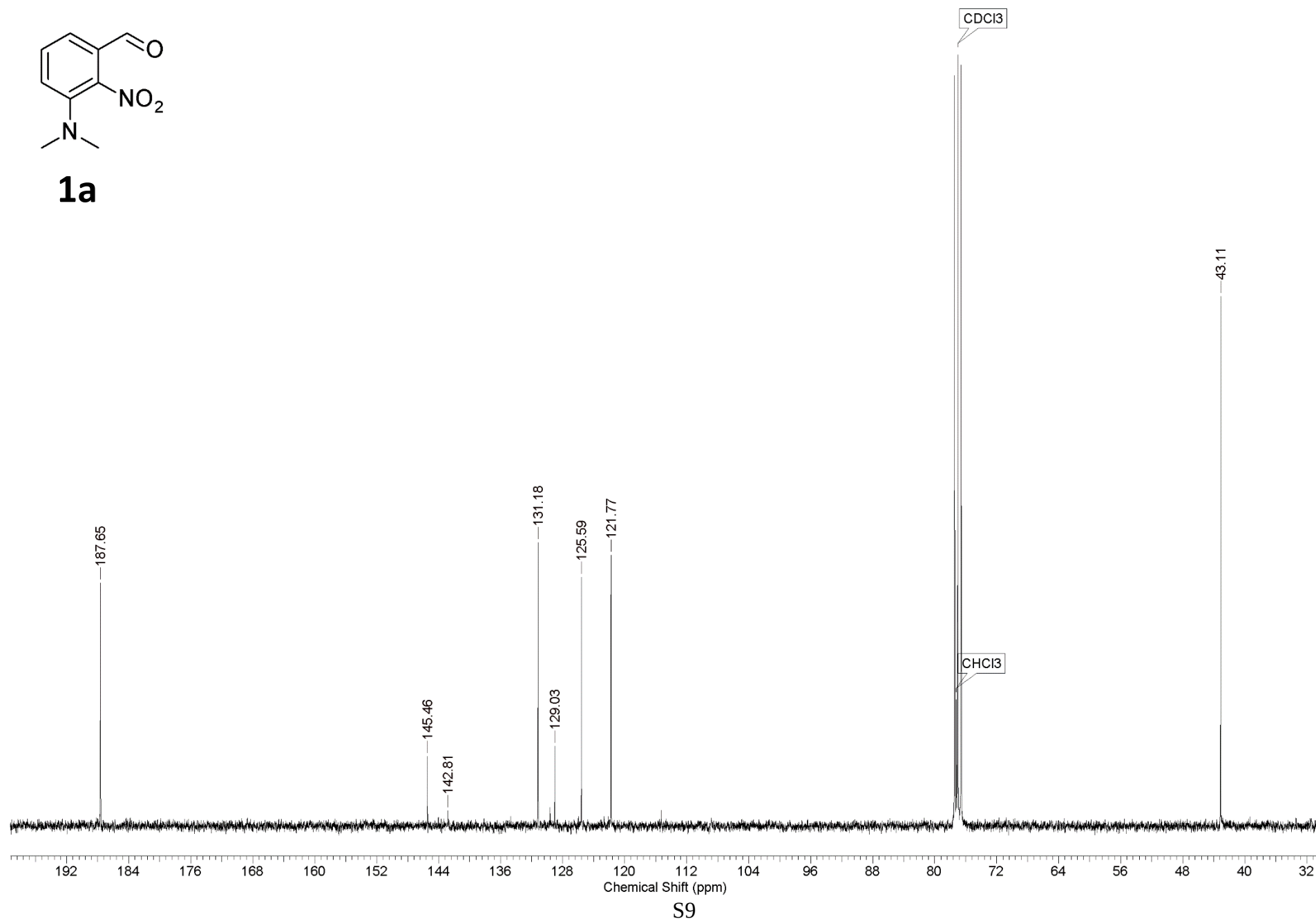


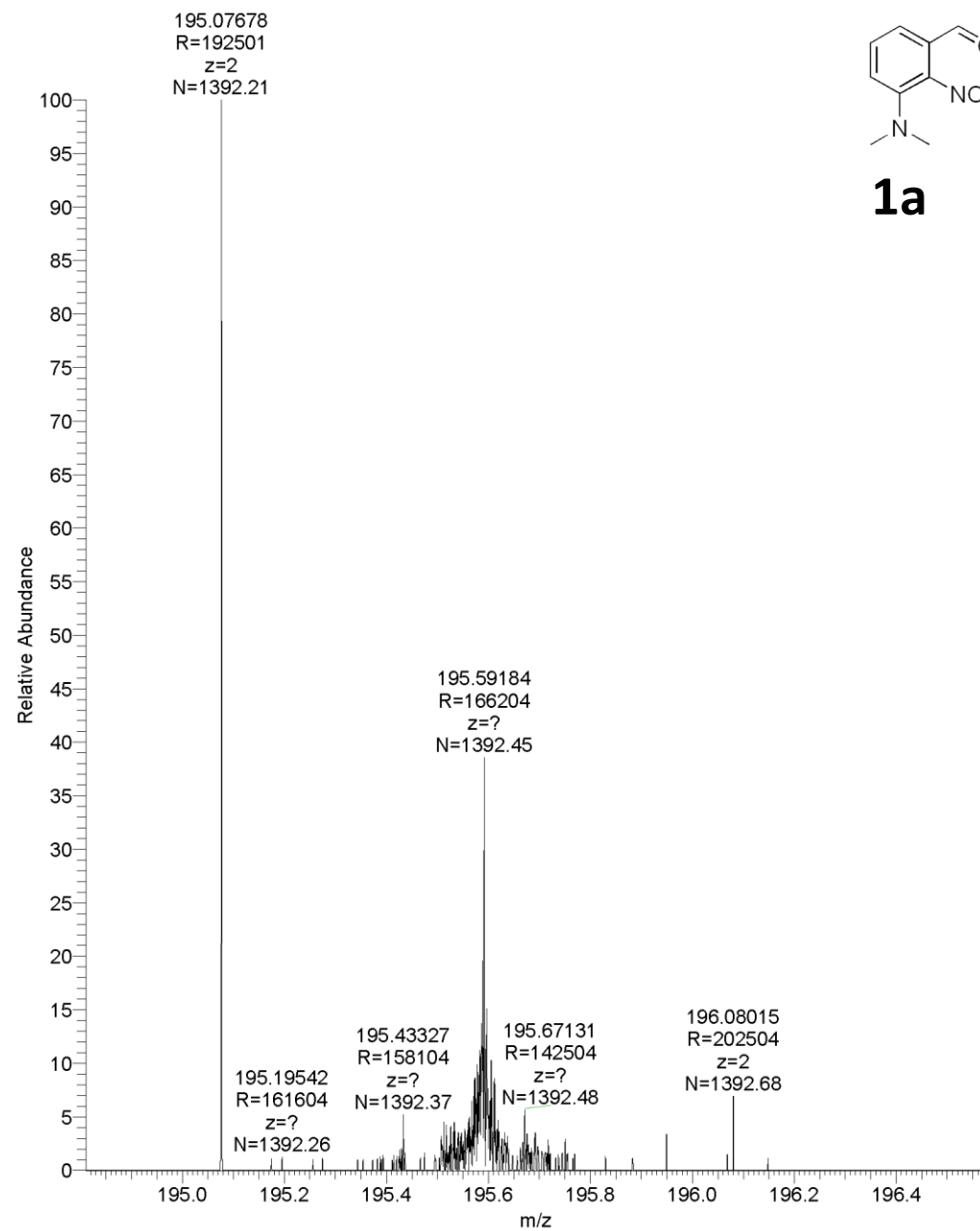
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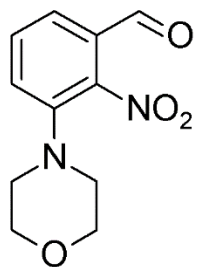


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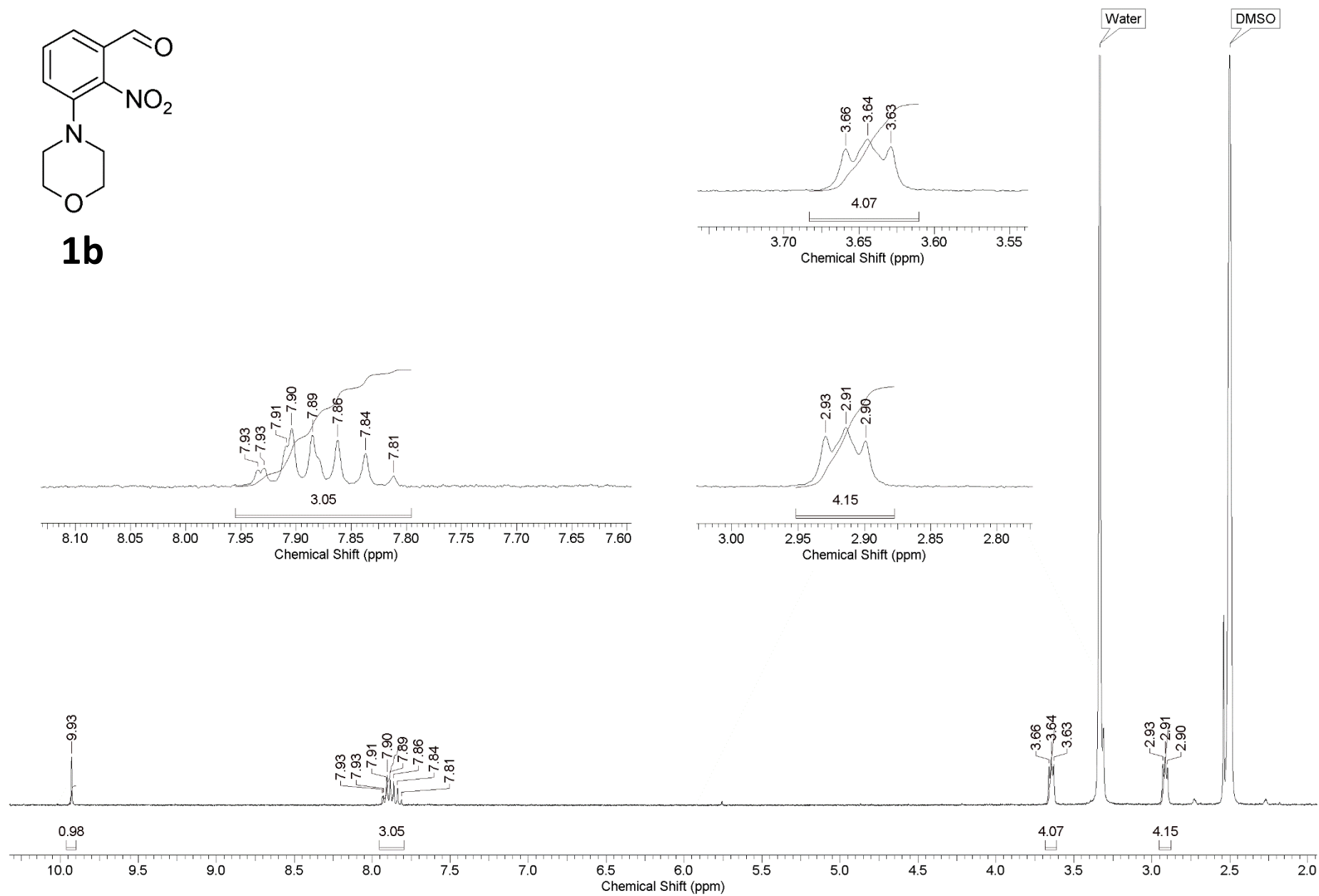


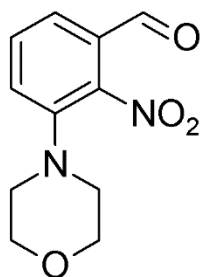


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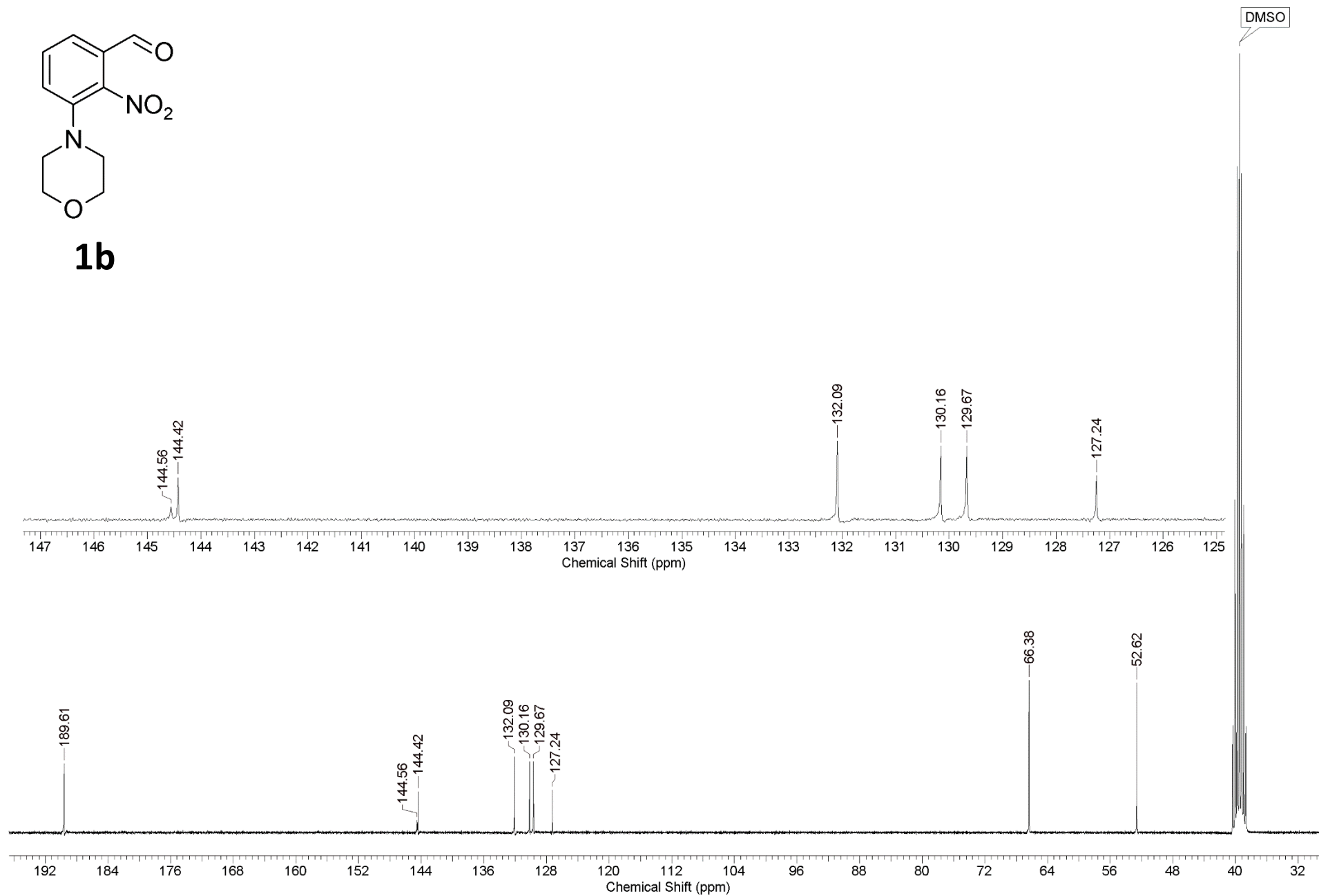


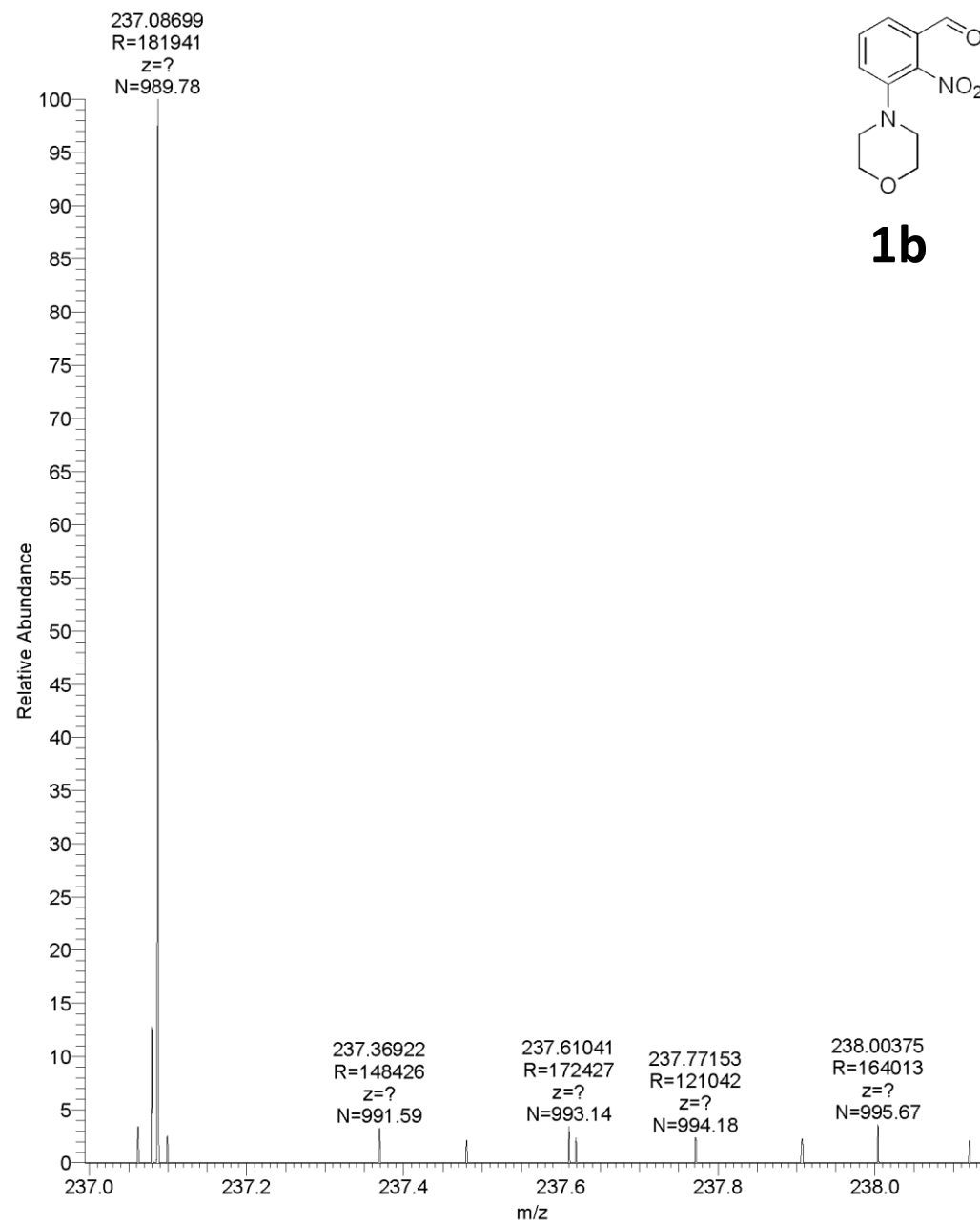
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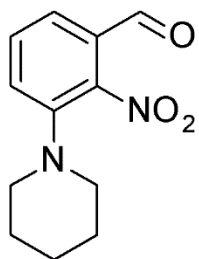


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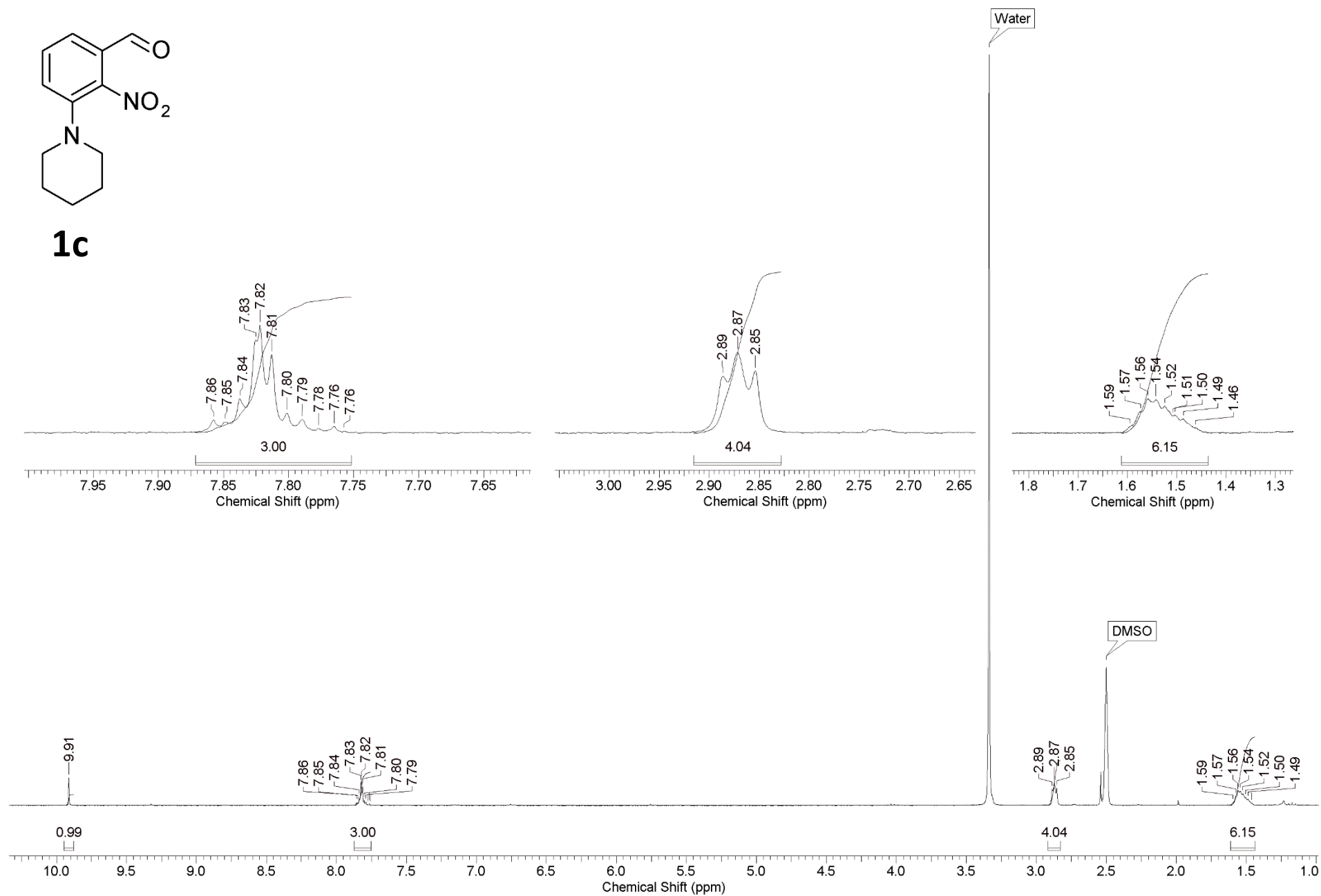


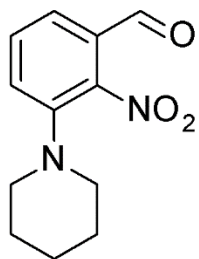


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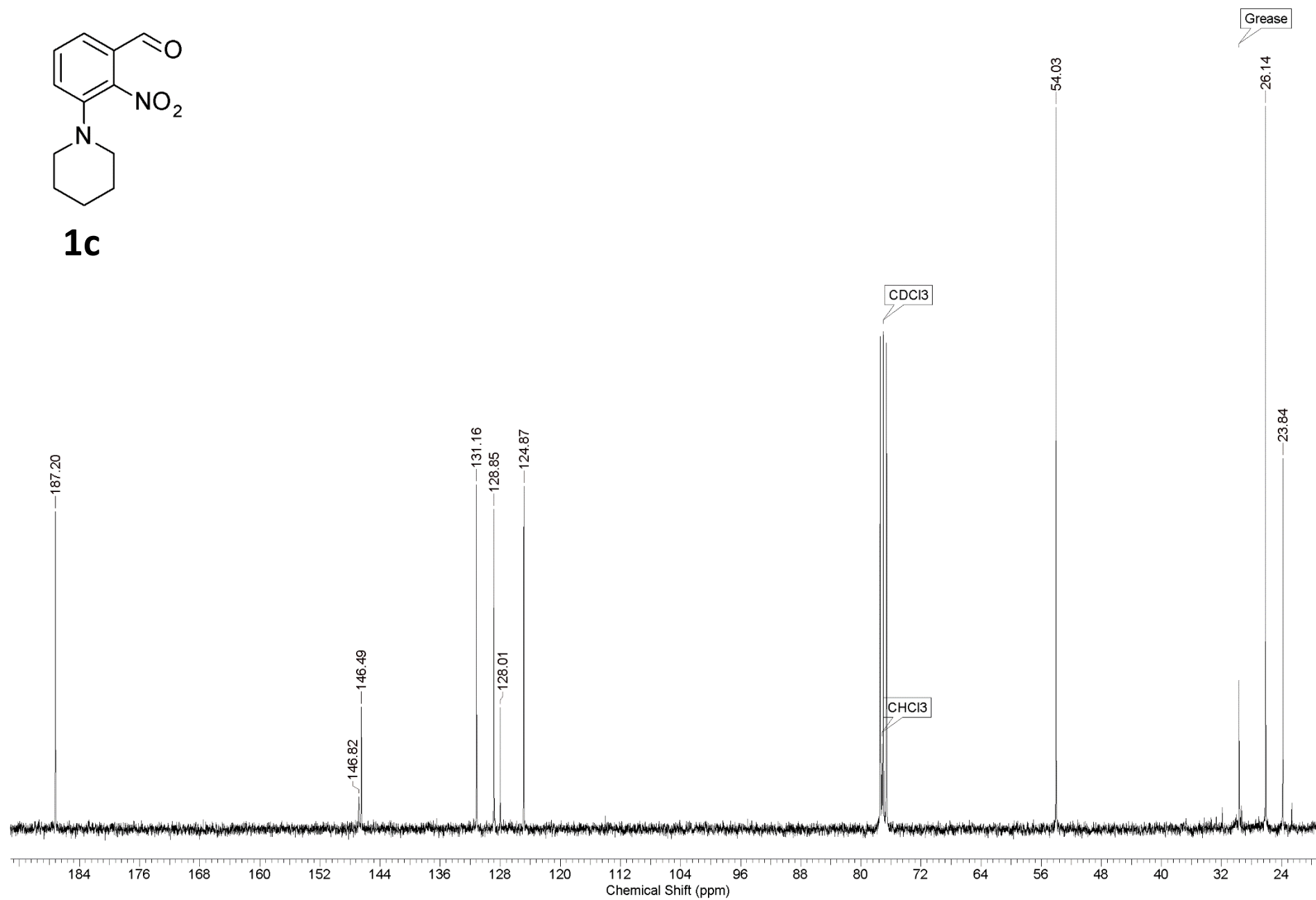


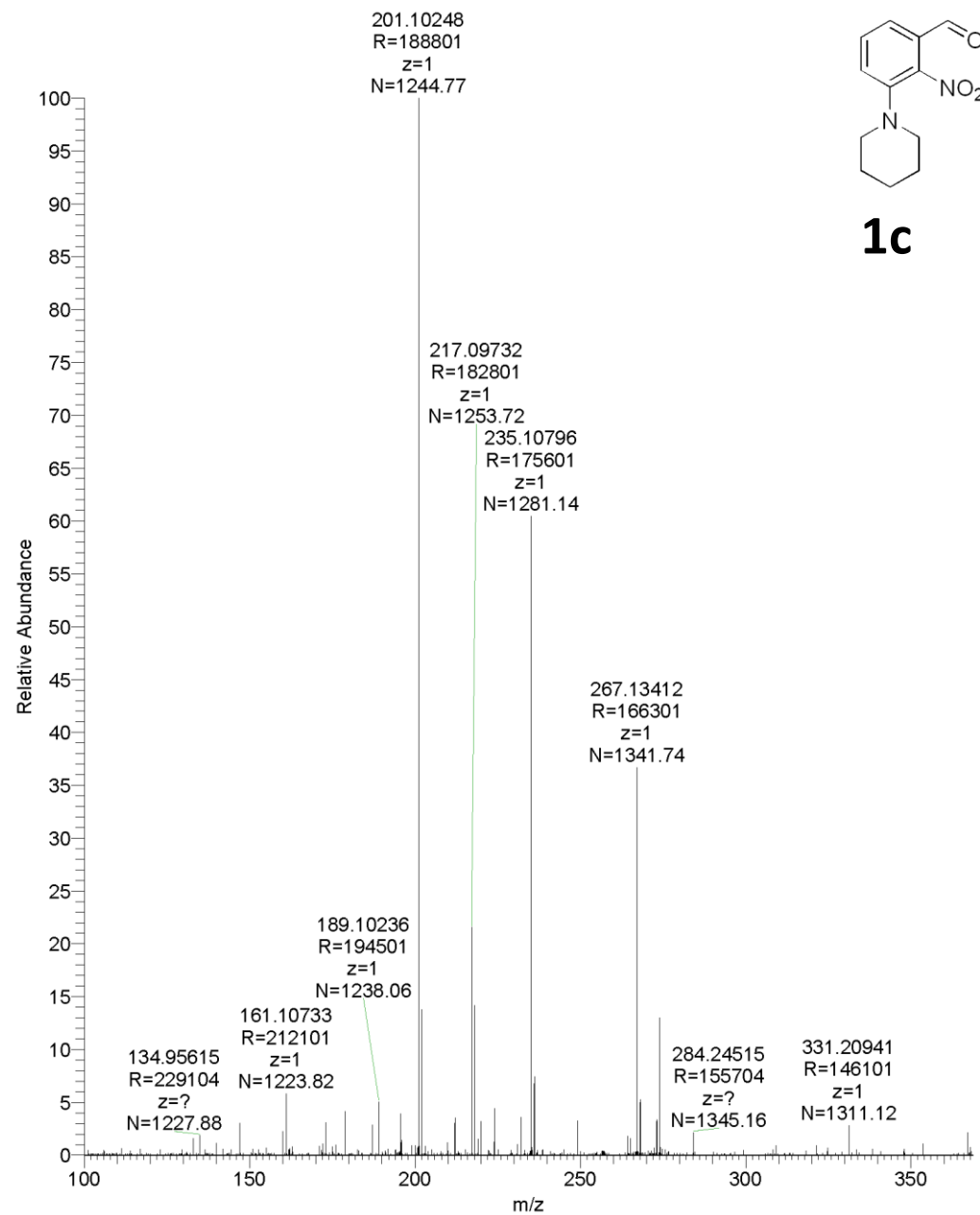
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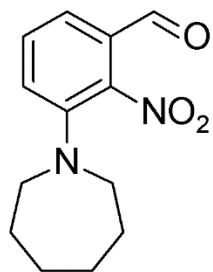




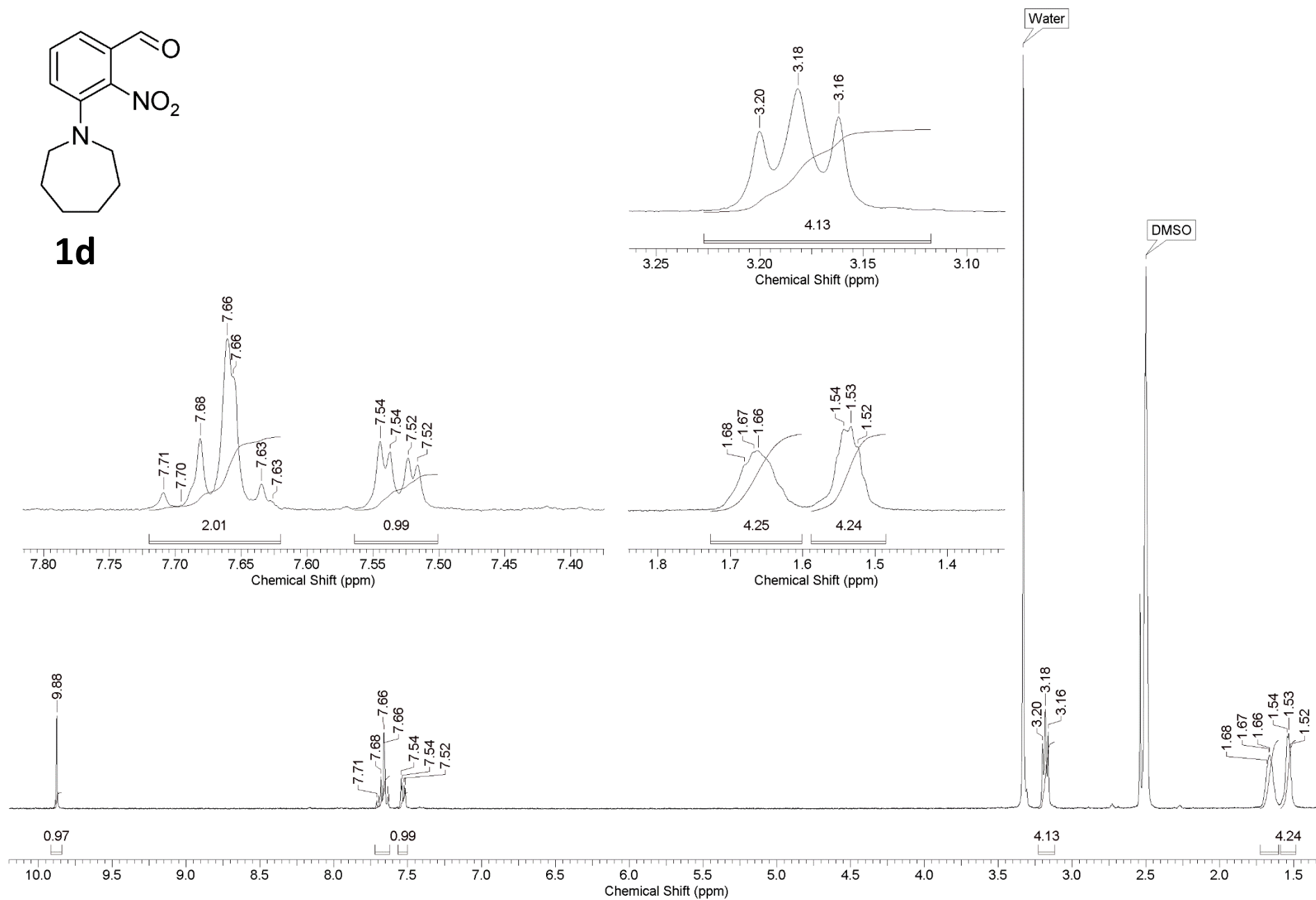
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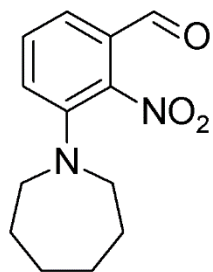




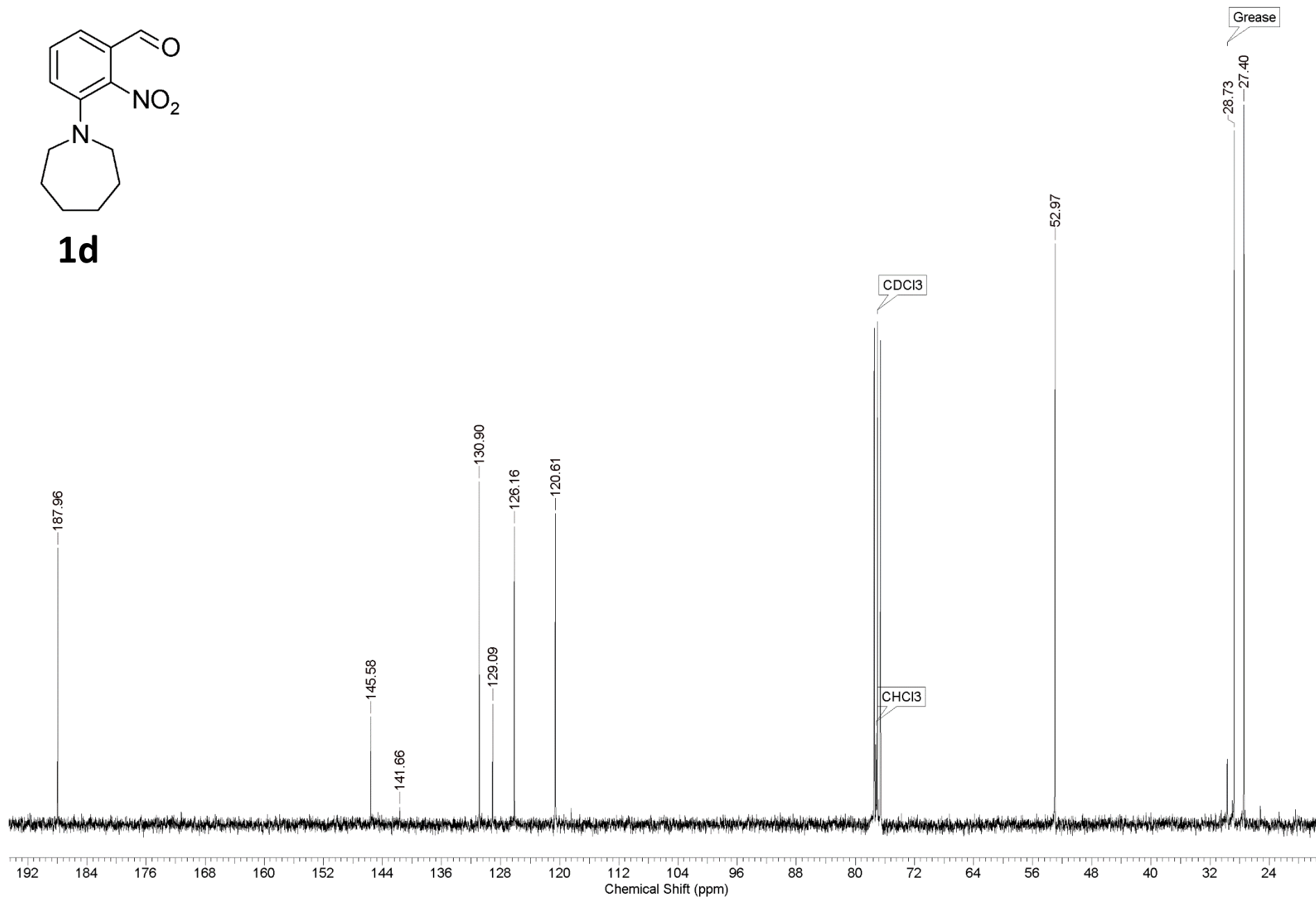


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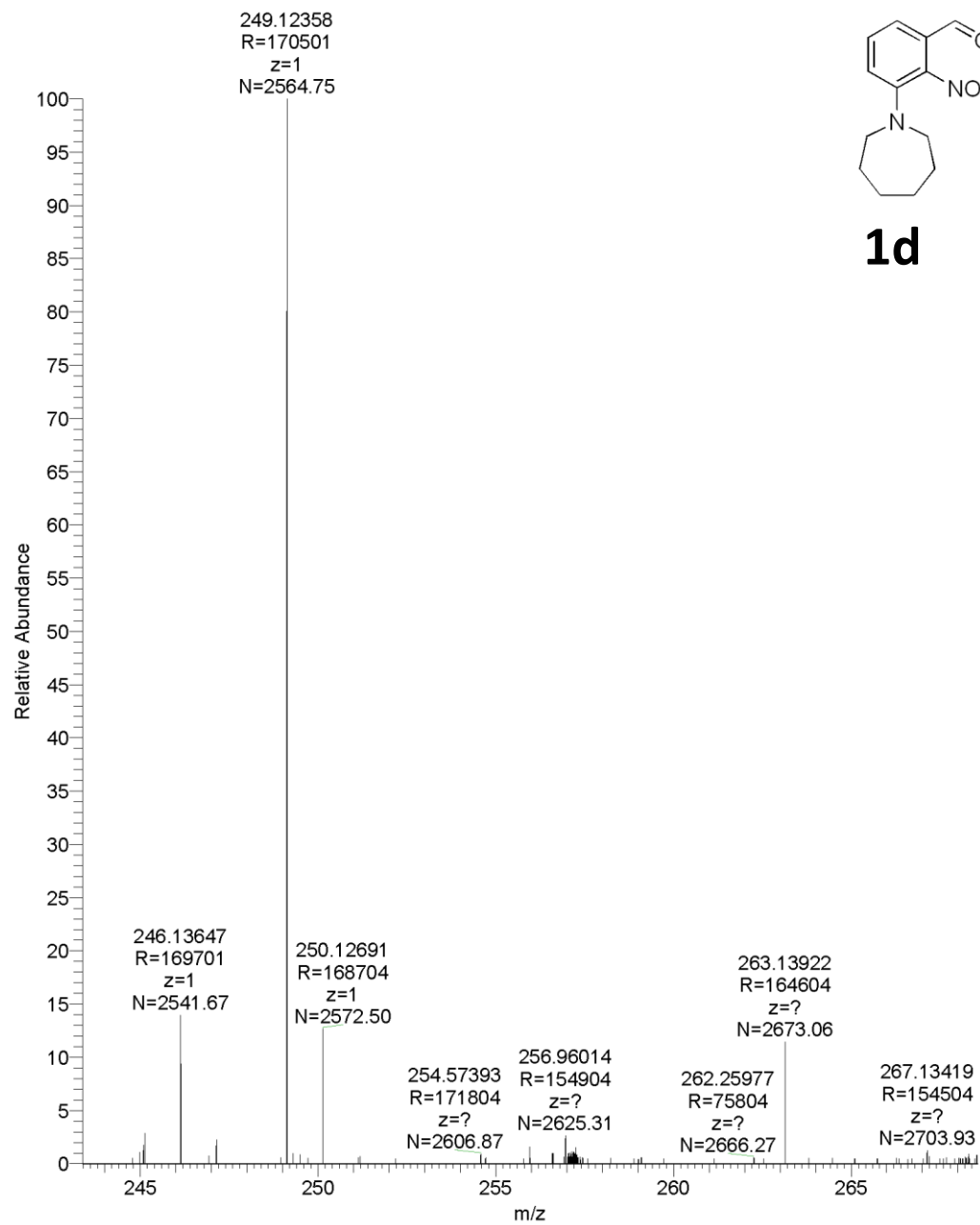




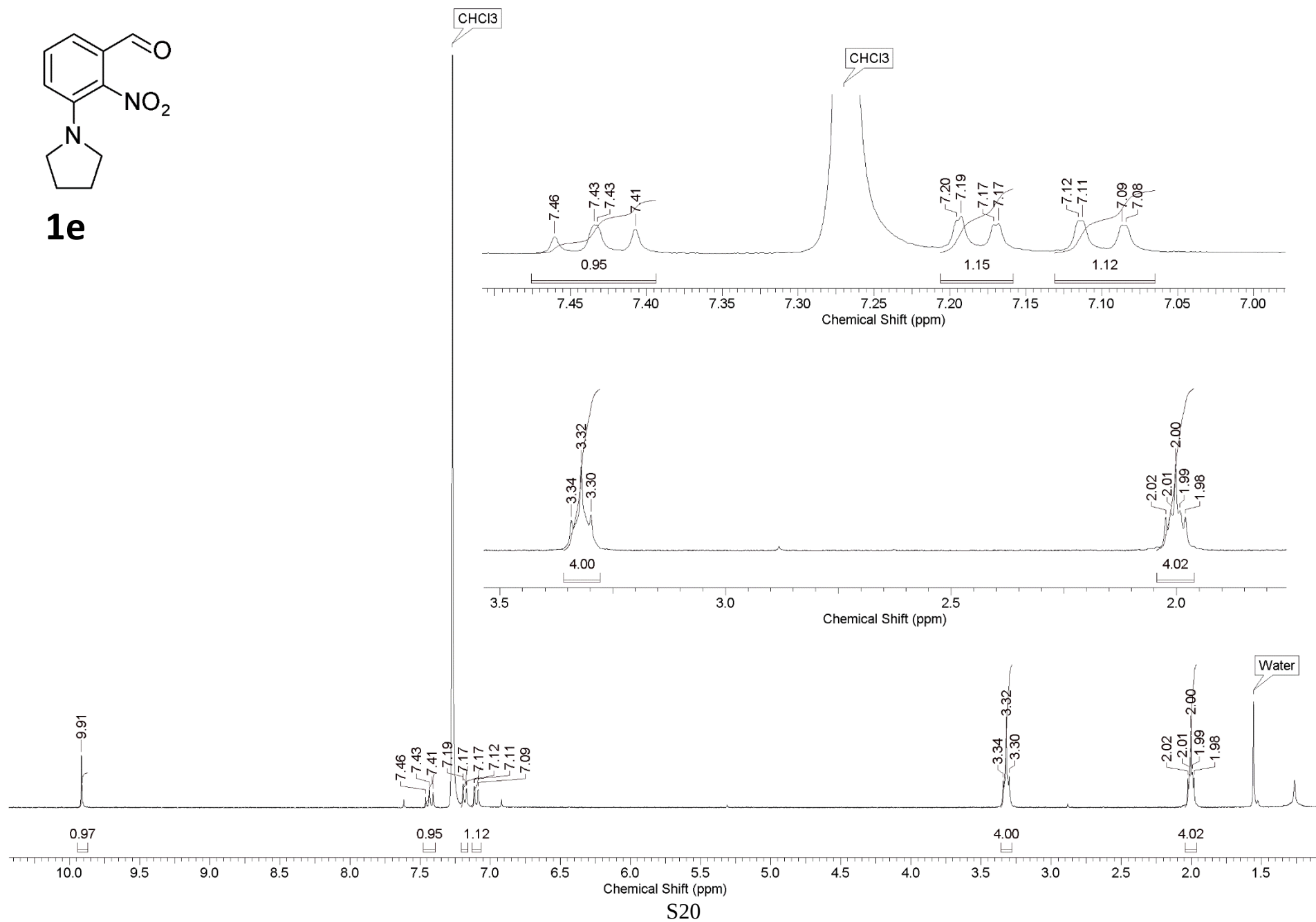
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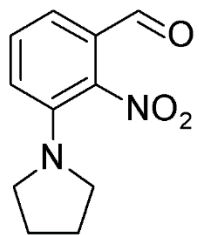


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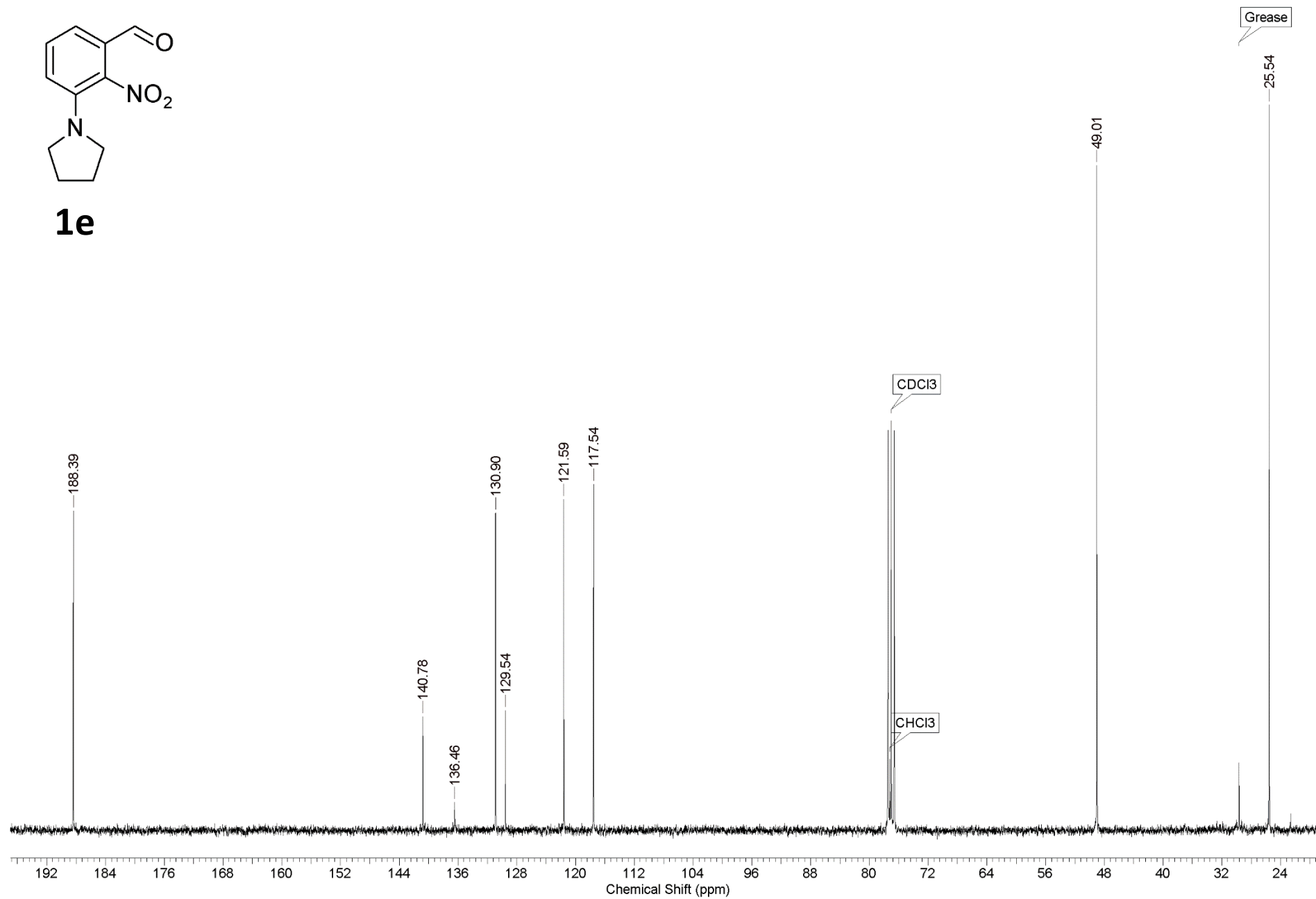


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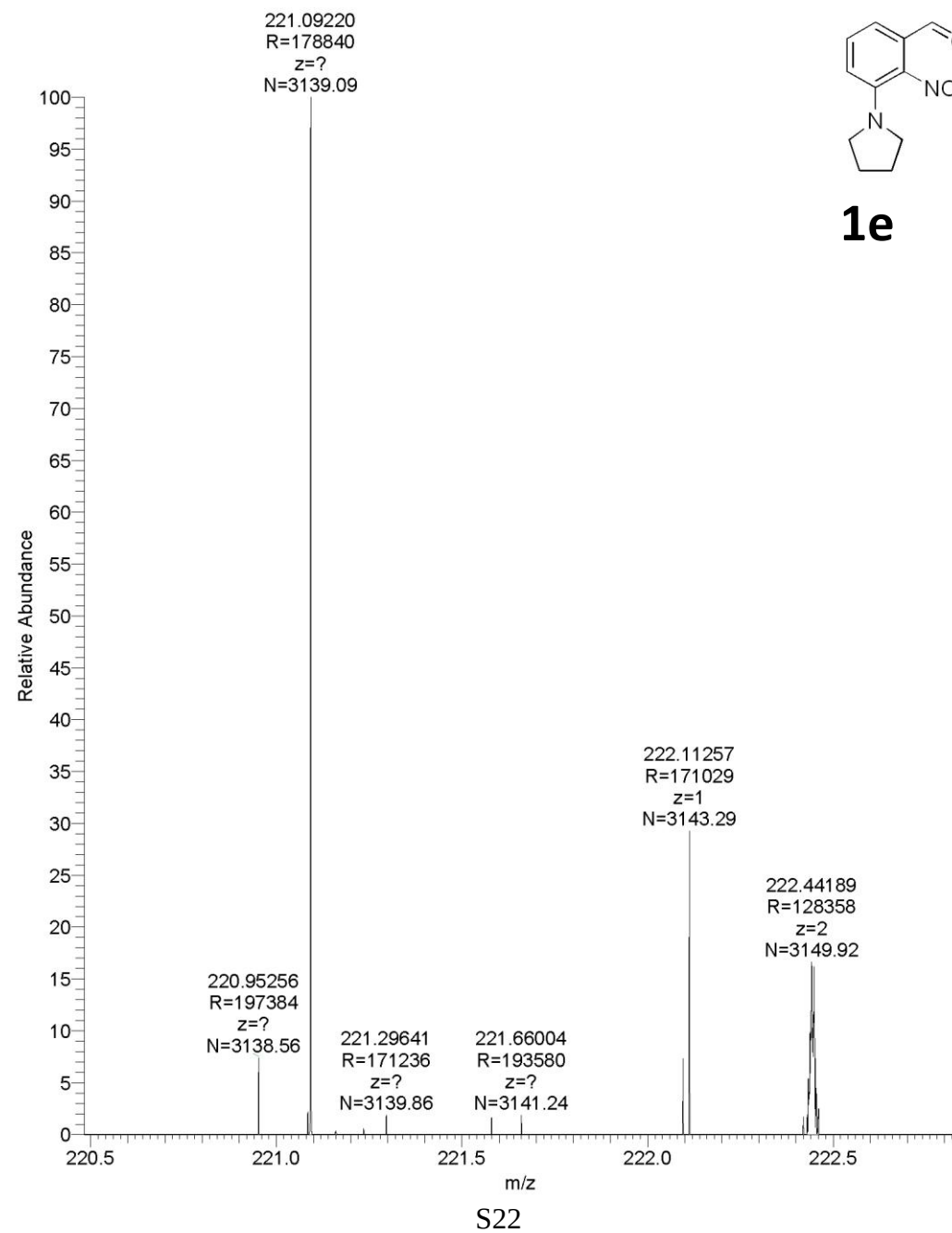


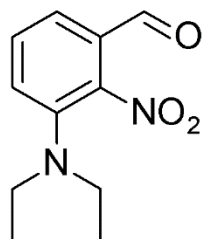


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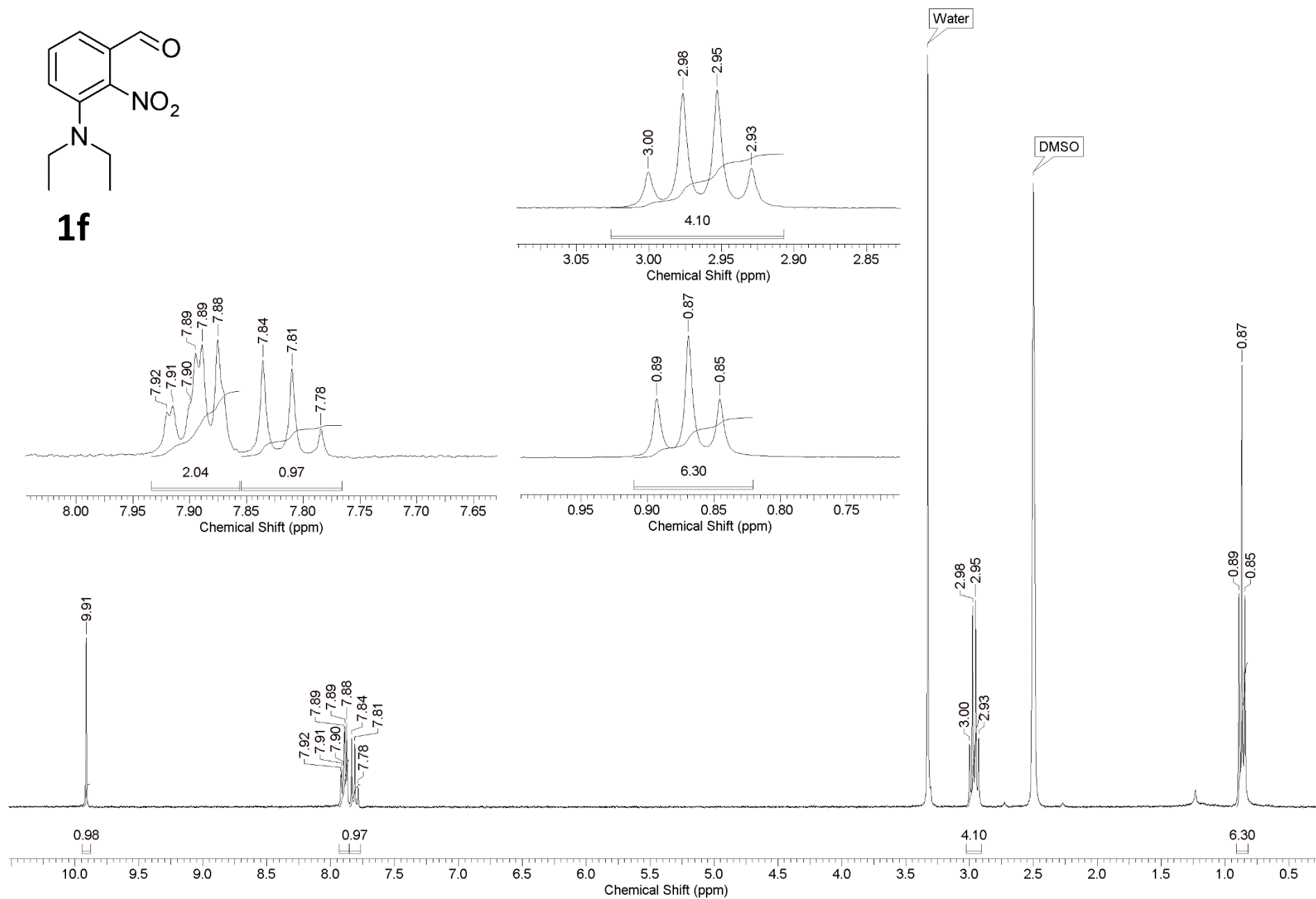


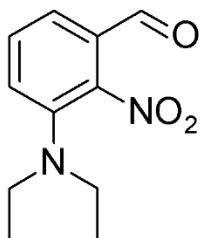
S21



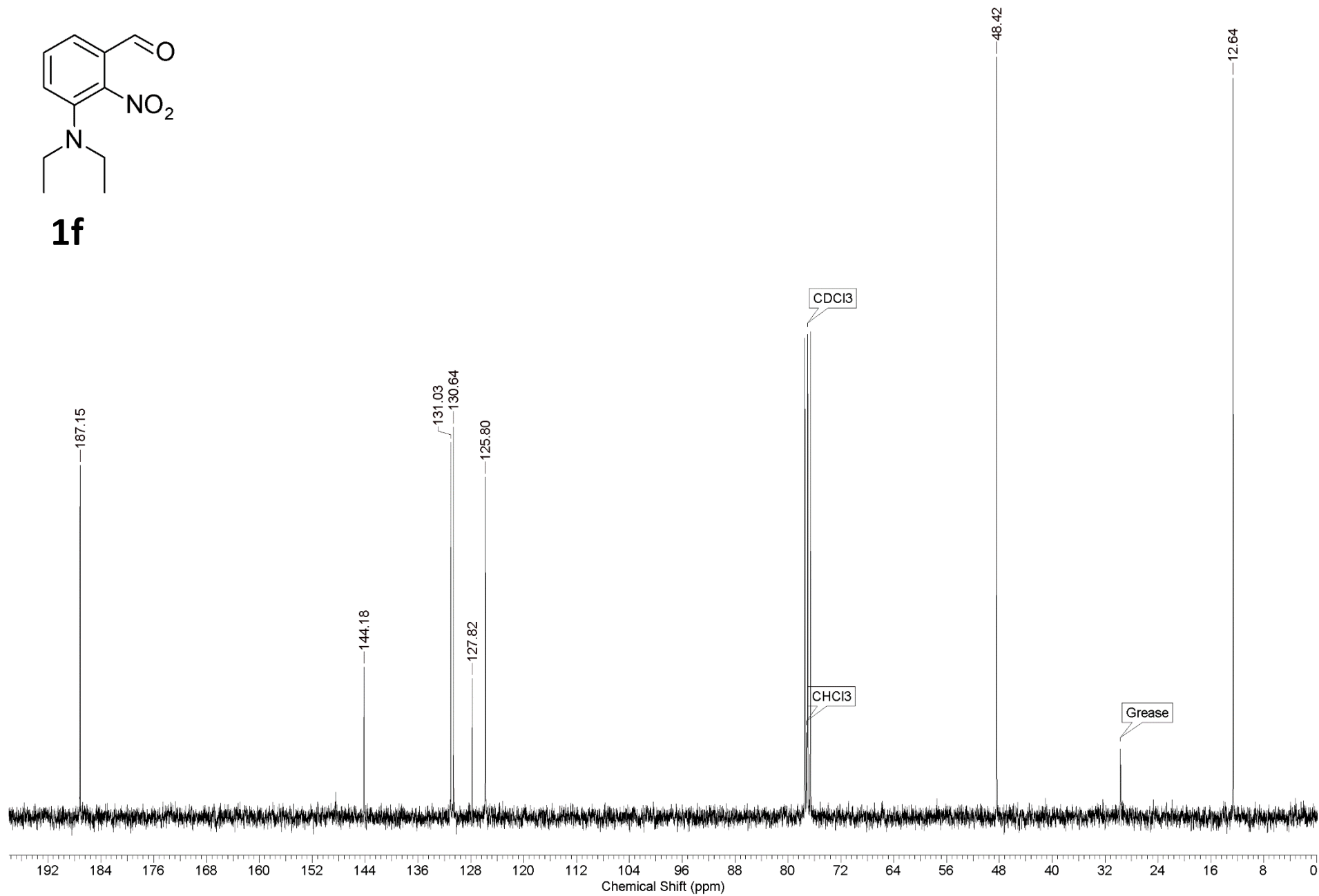


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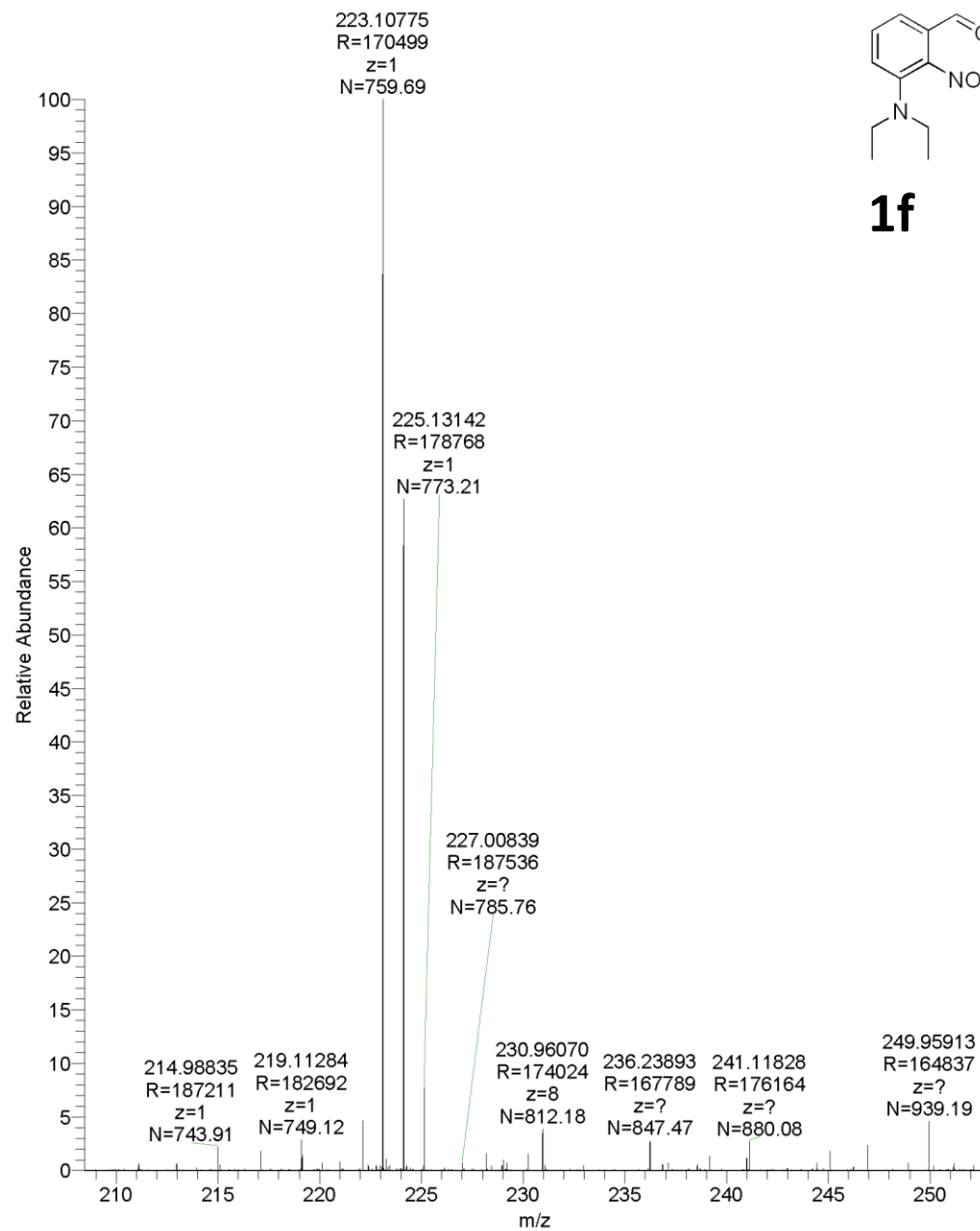




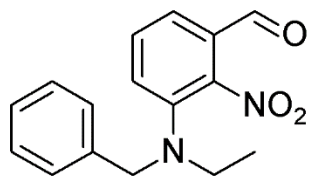
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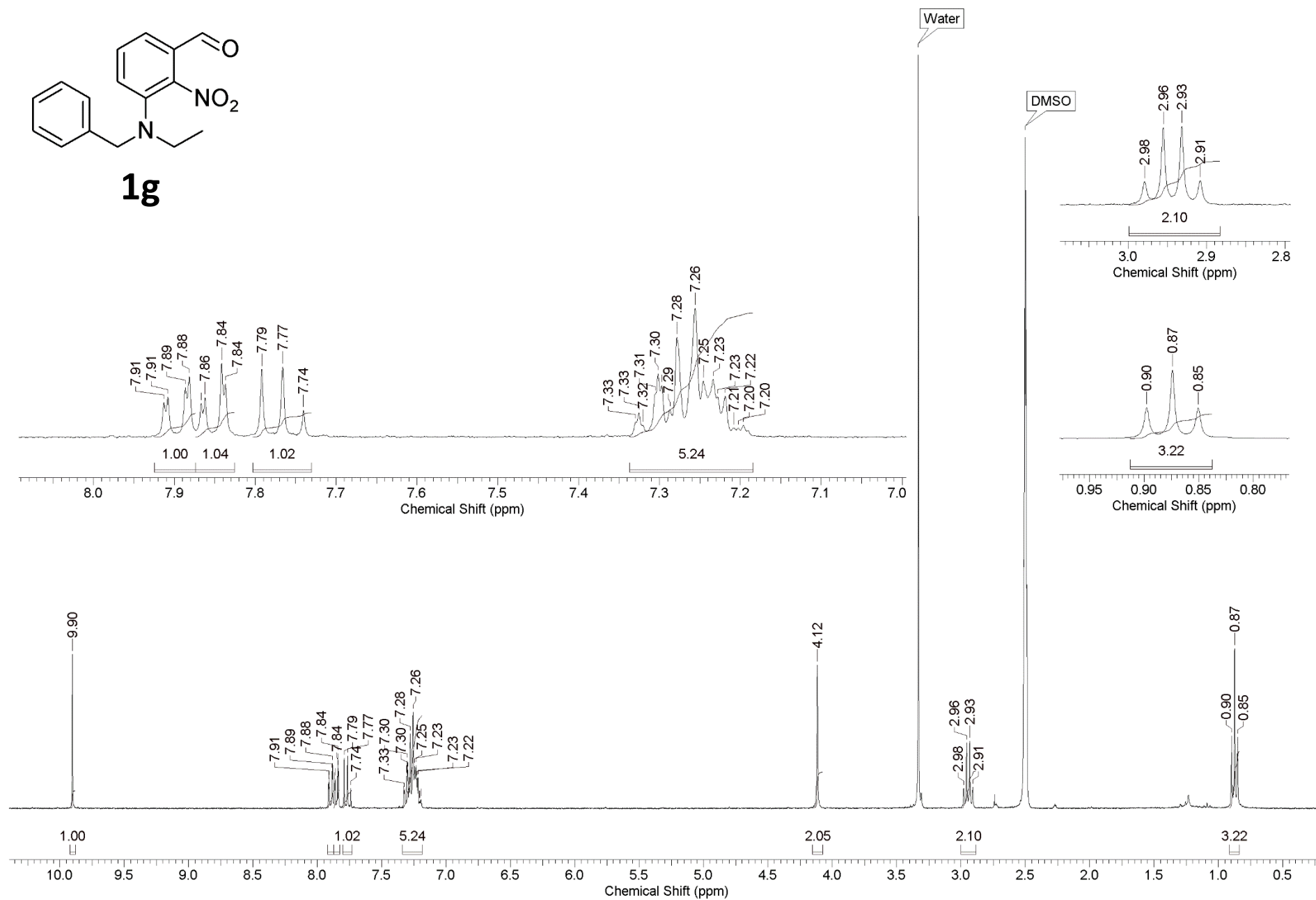
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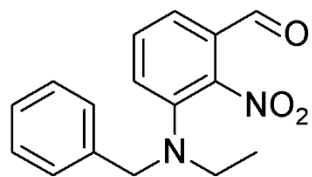


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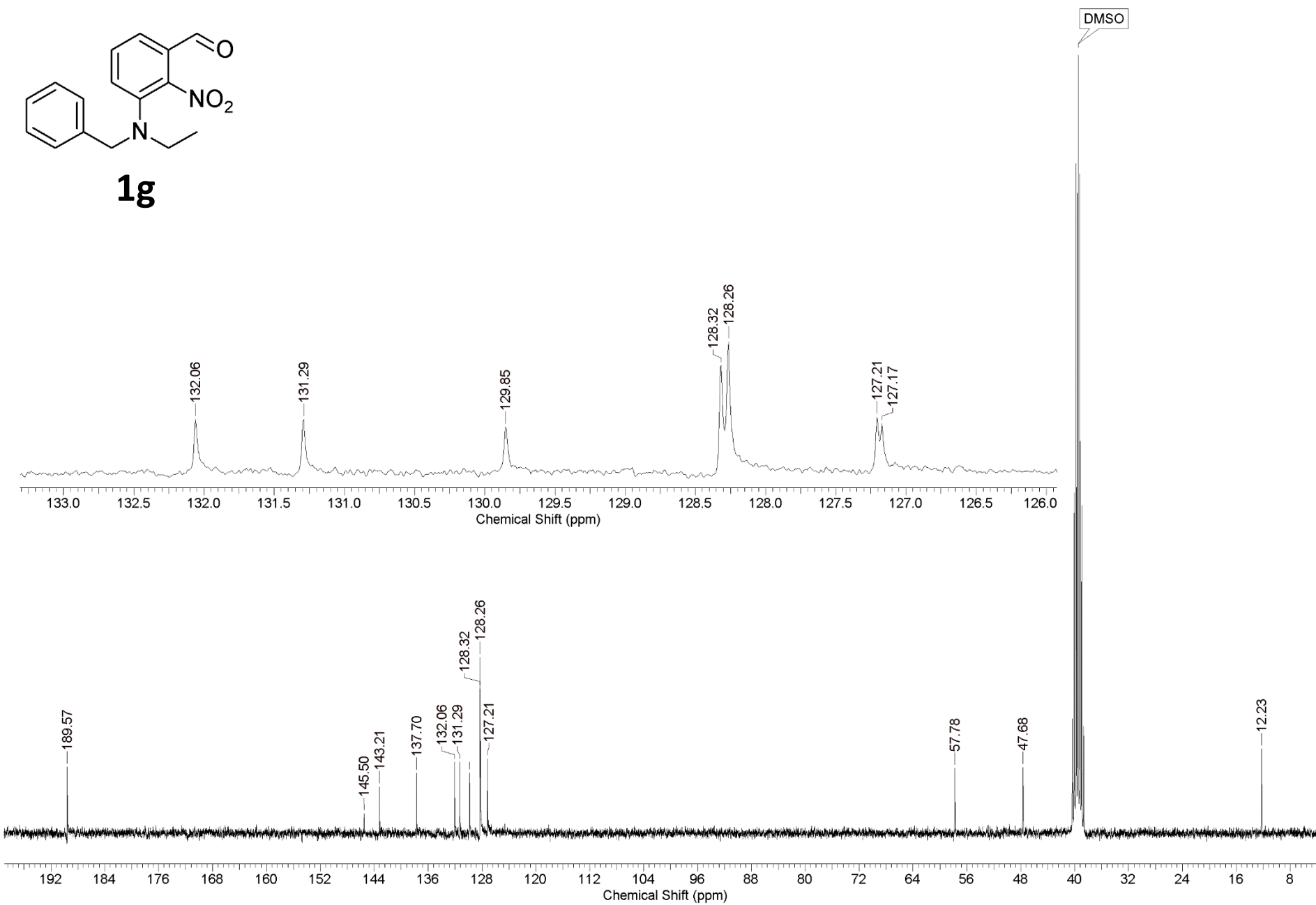


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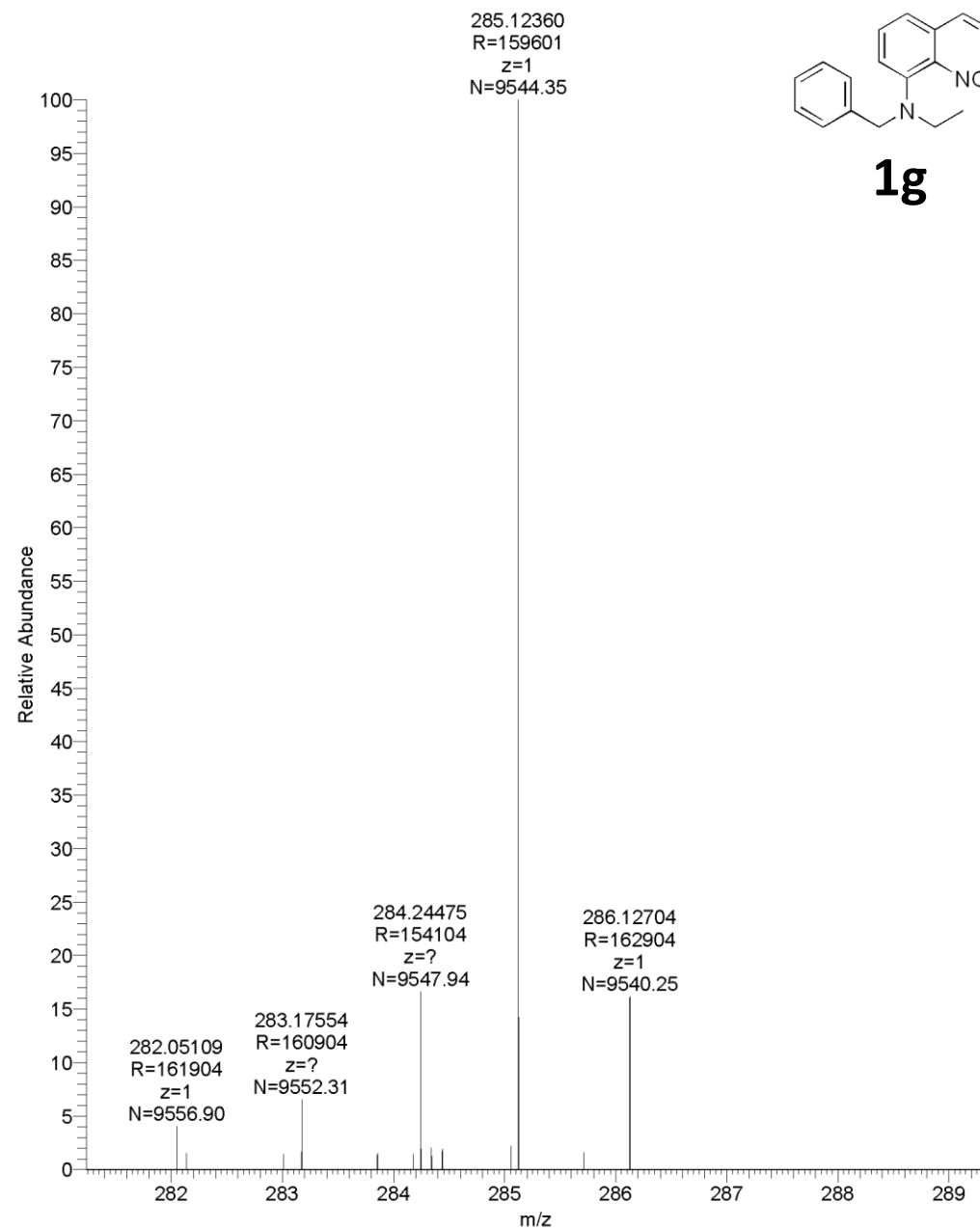




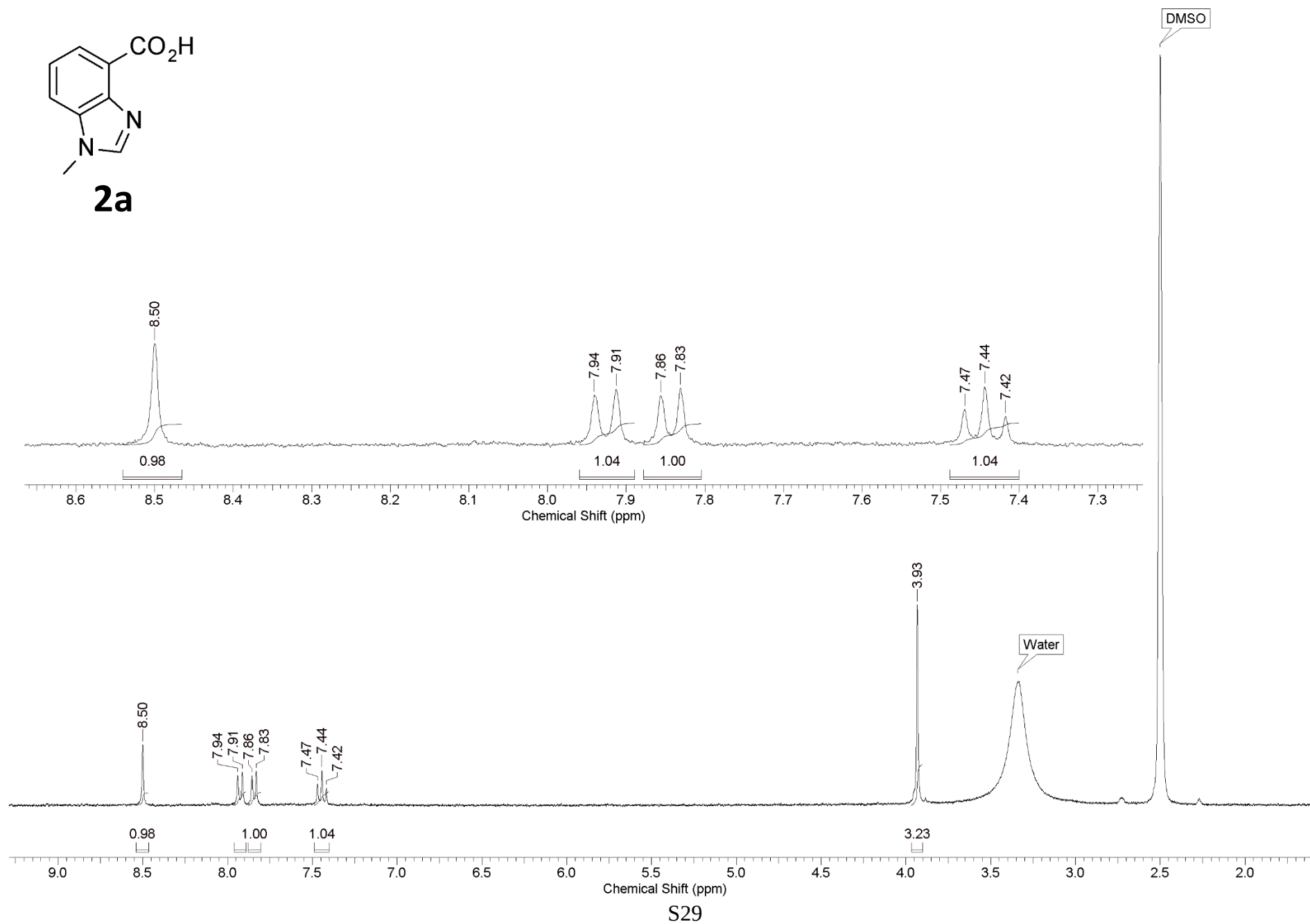
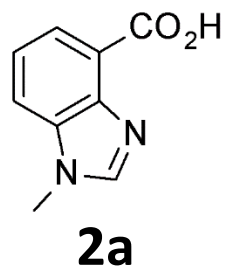
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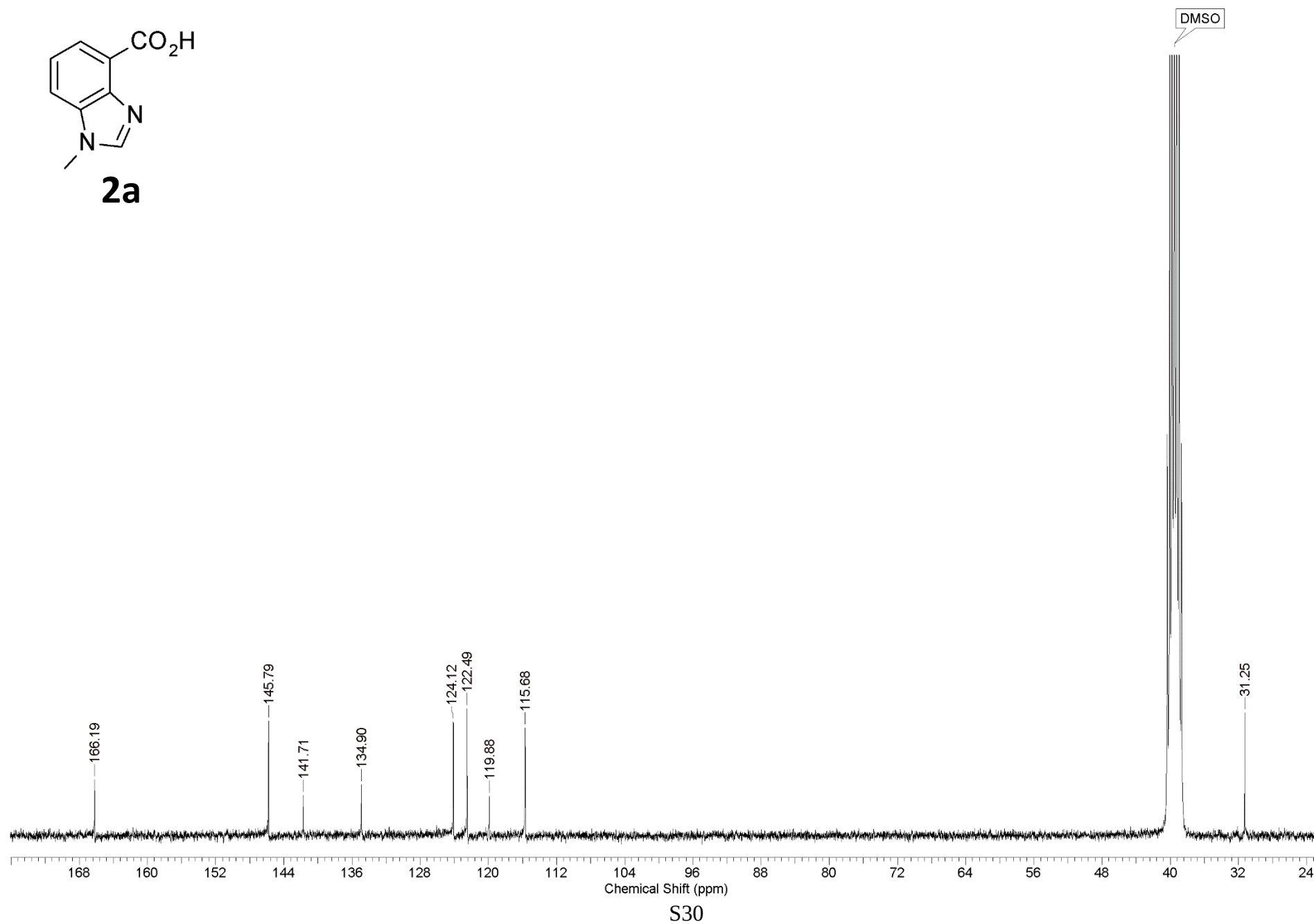
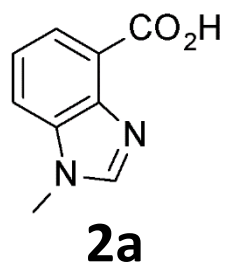


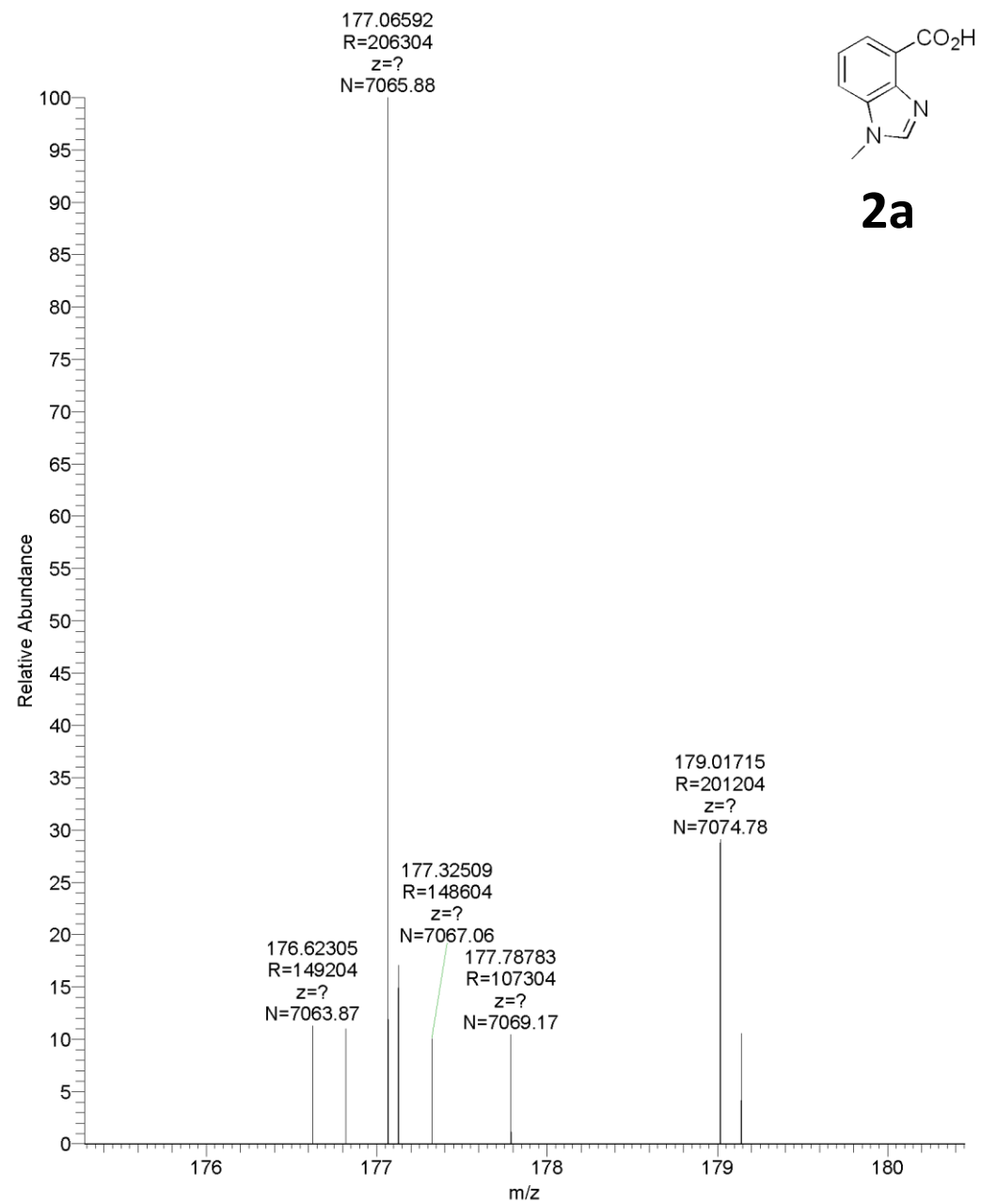
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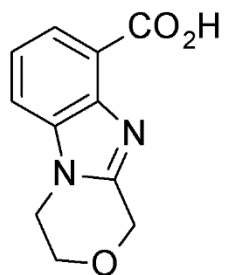
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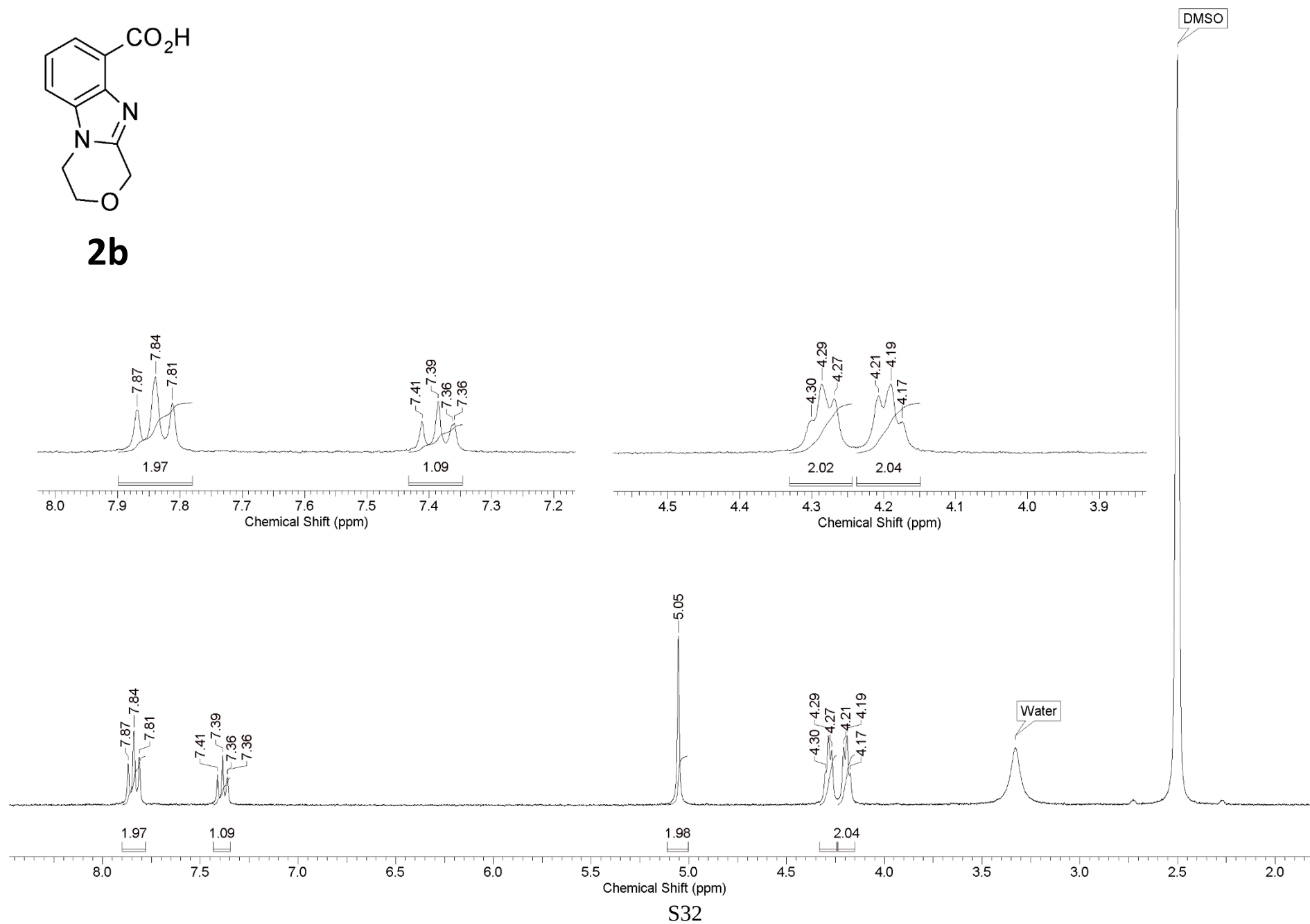


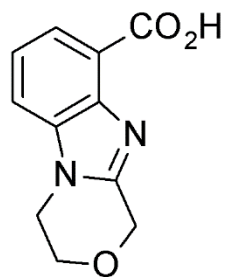


S31

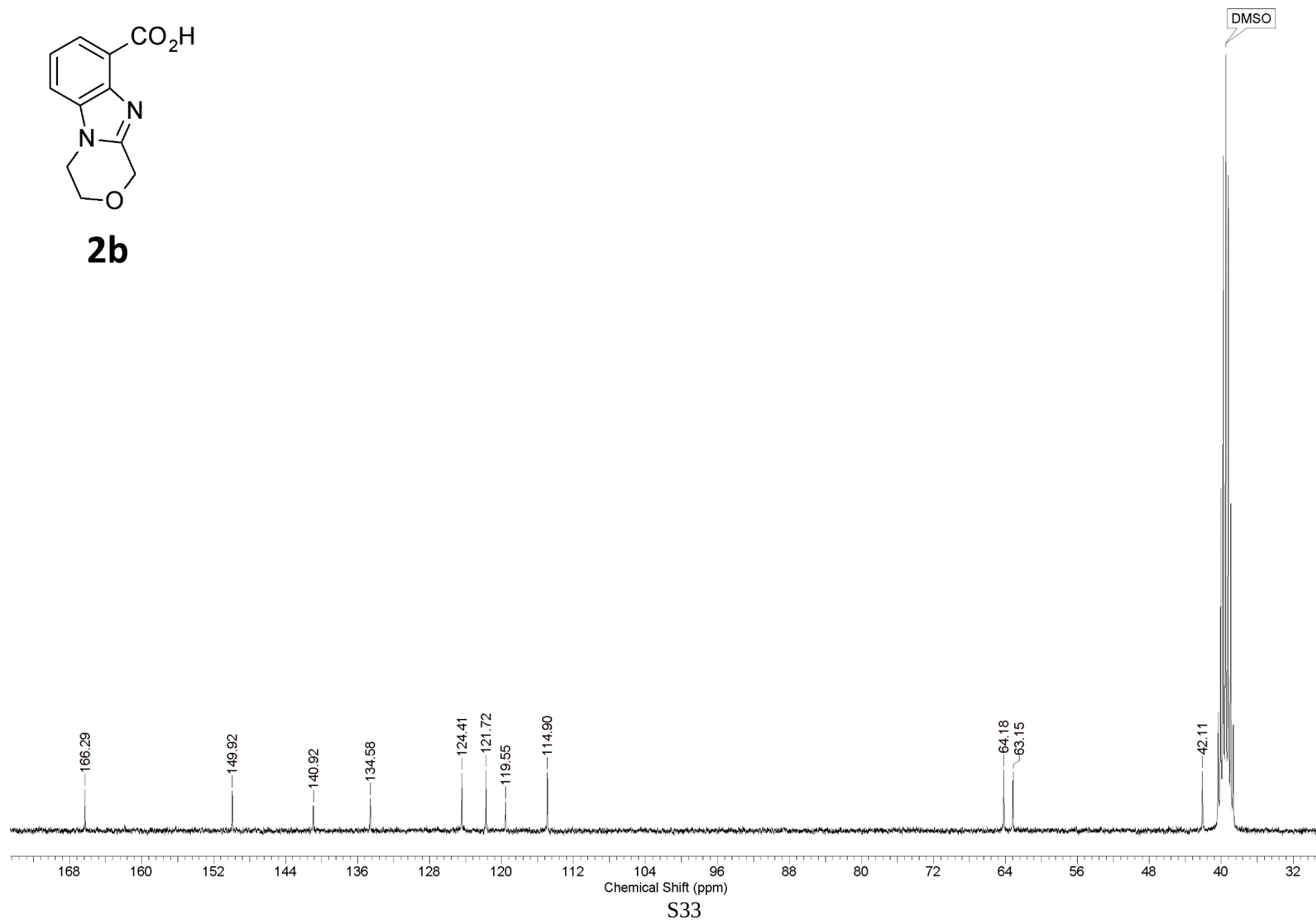


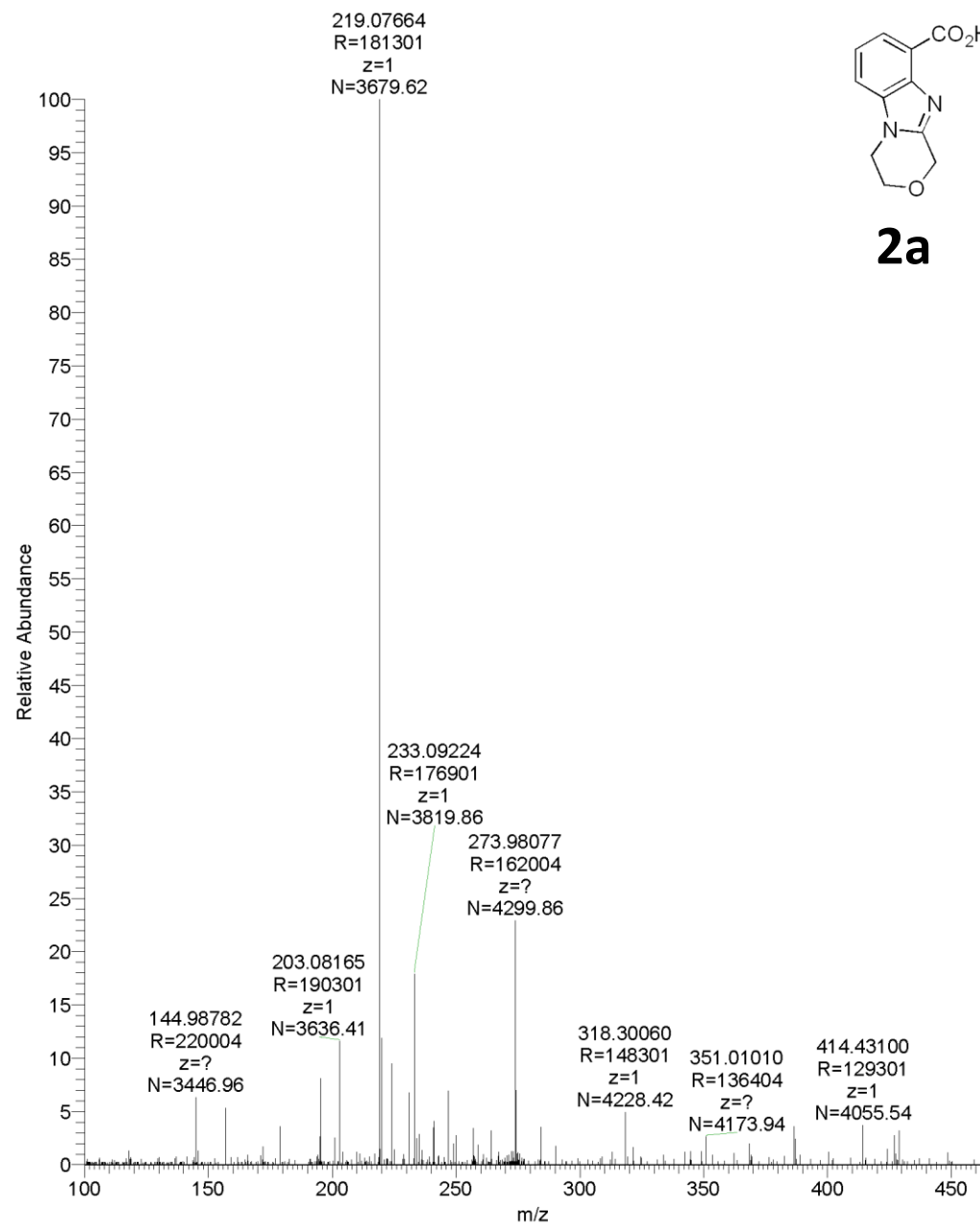
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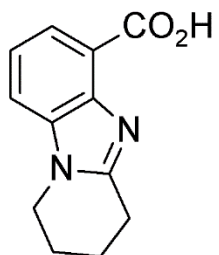




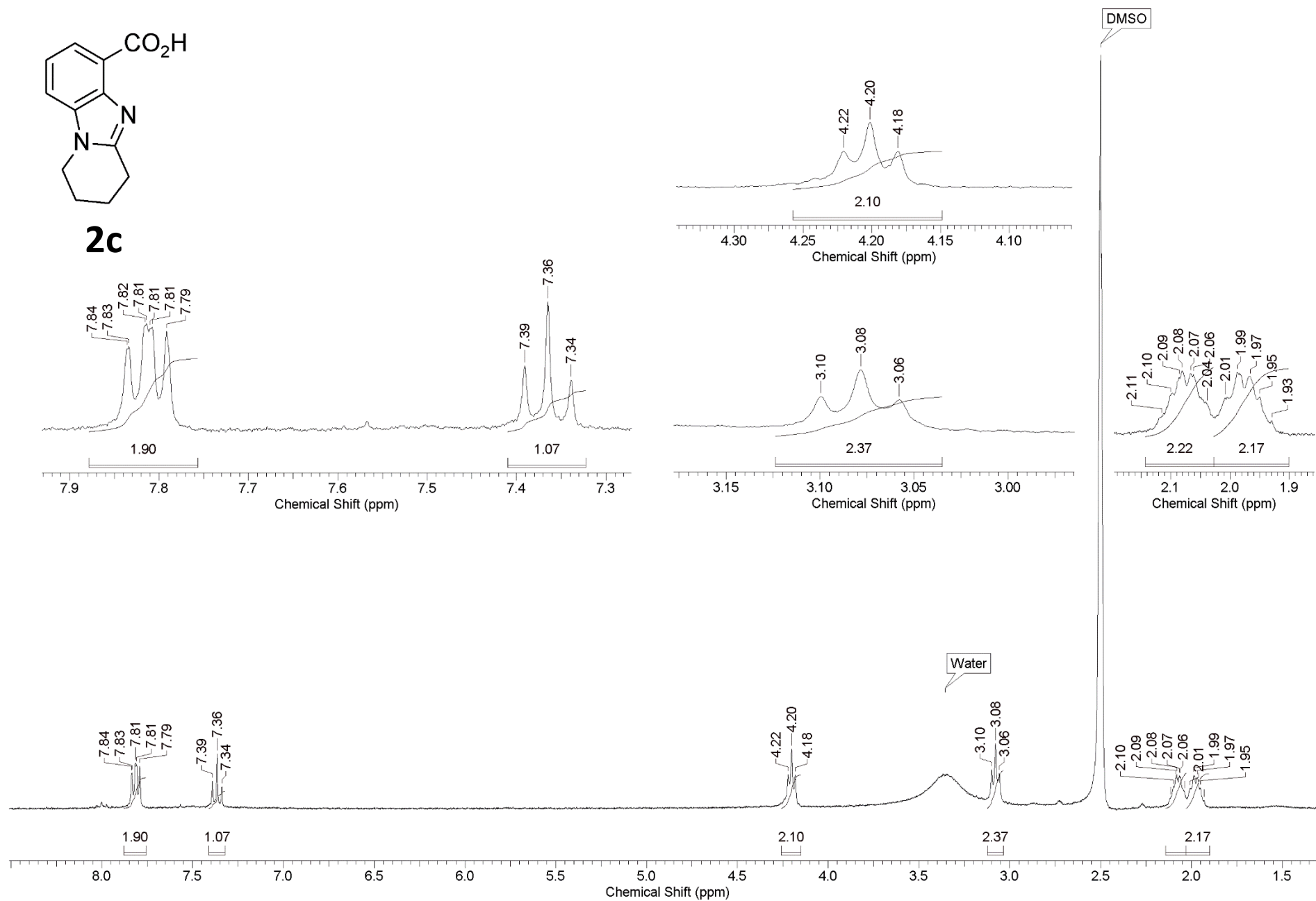
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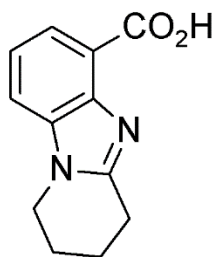




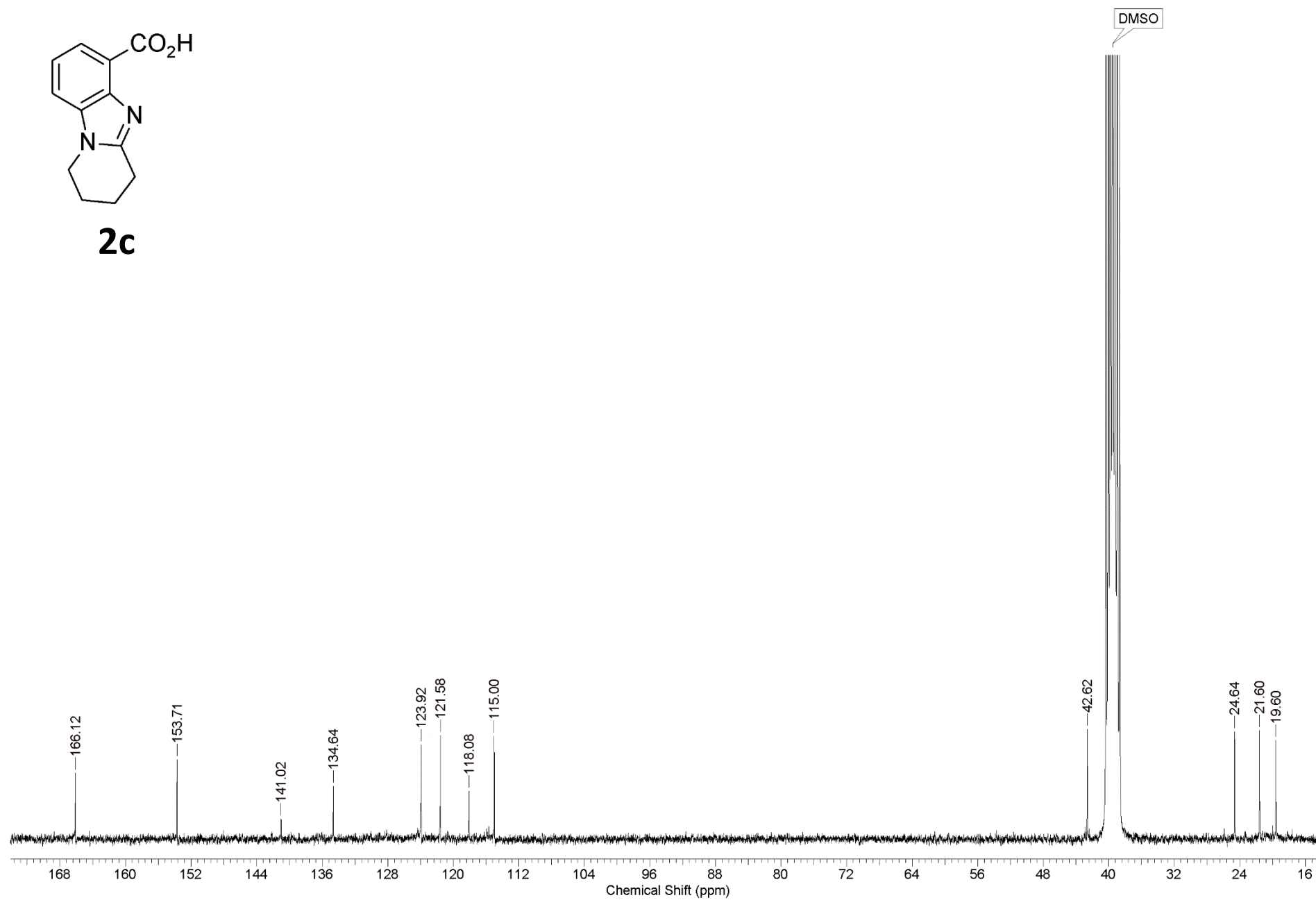
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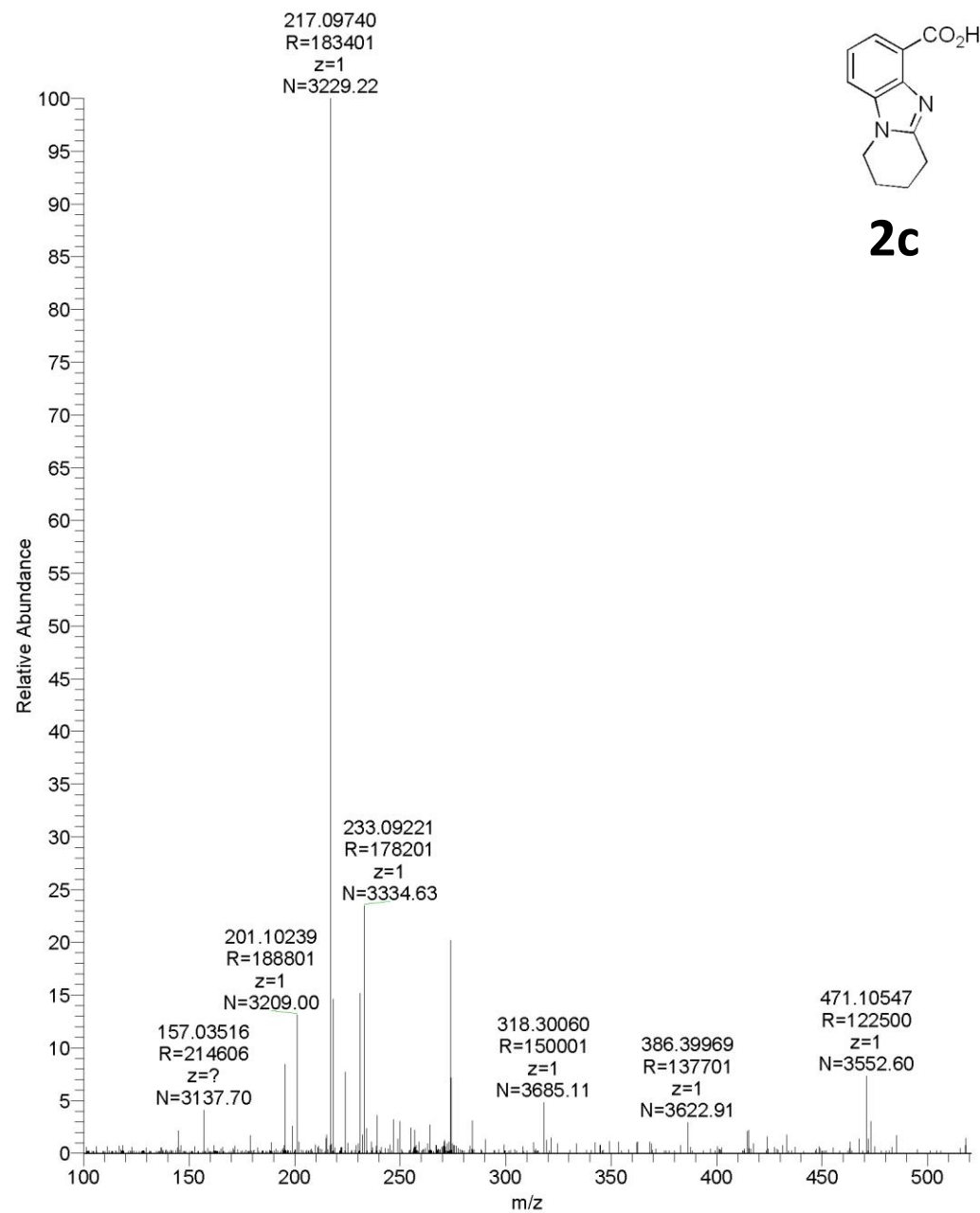


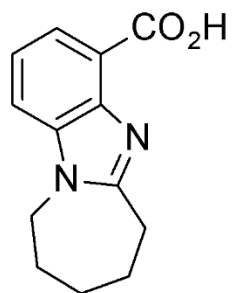
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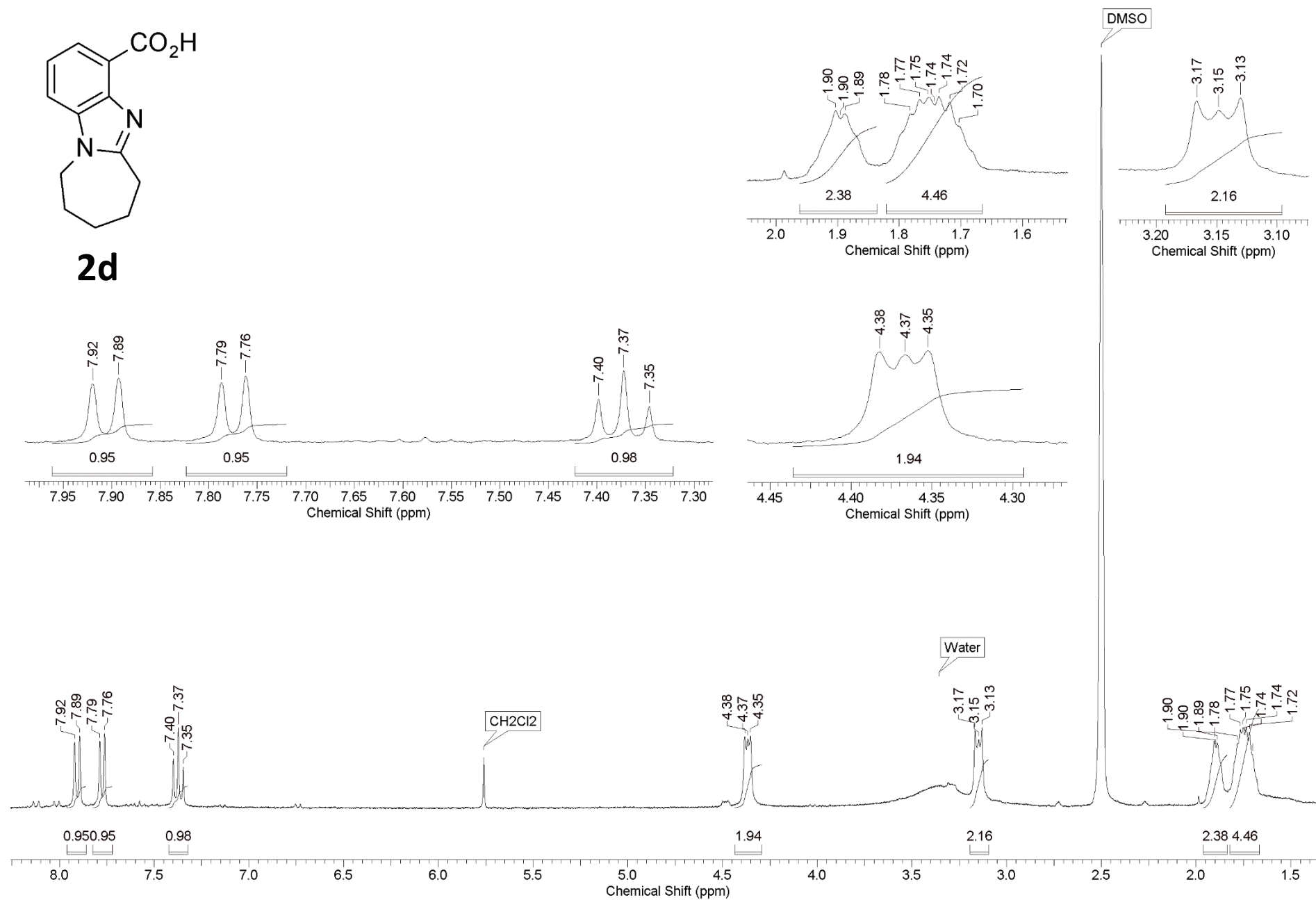
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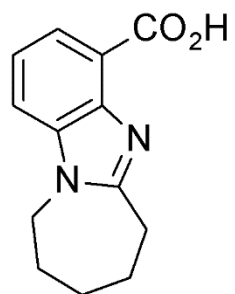




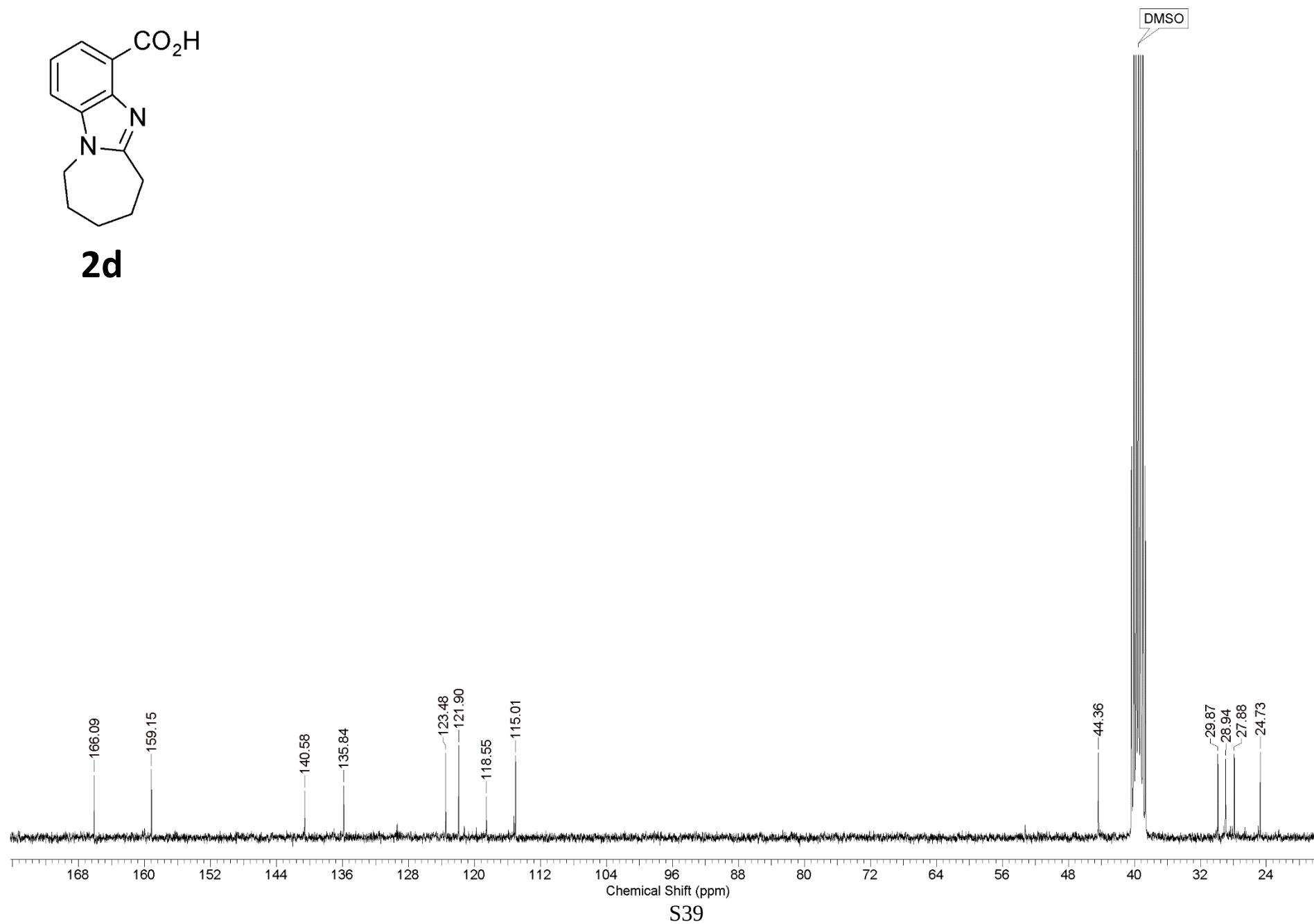
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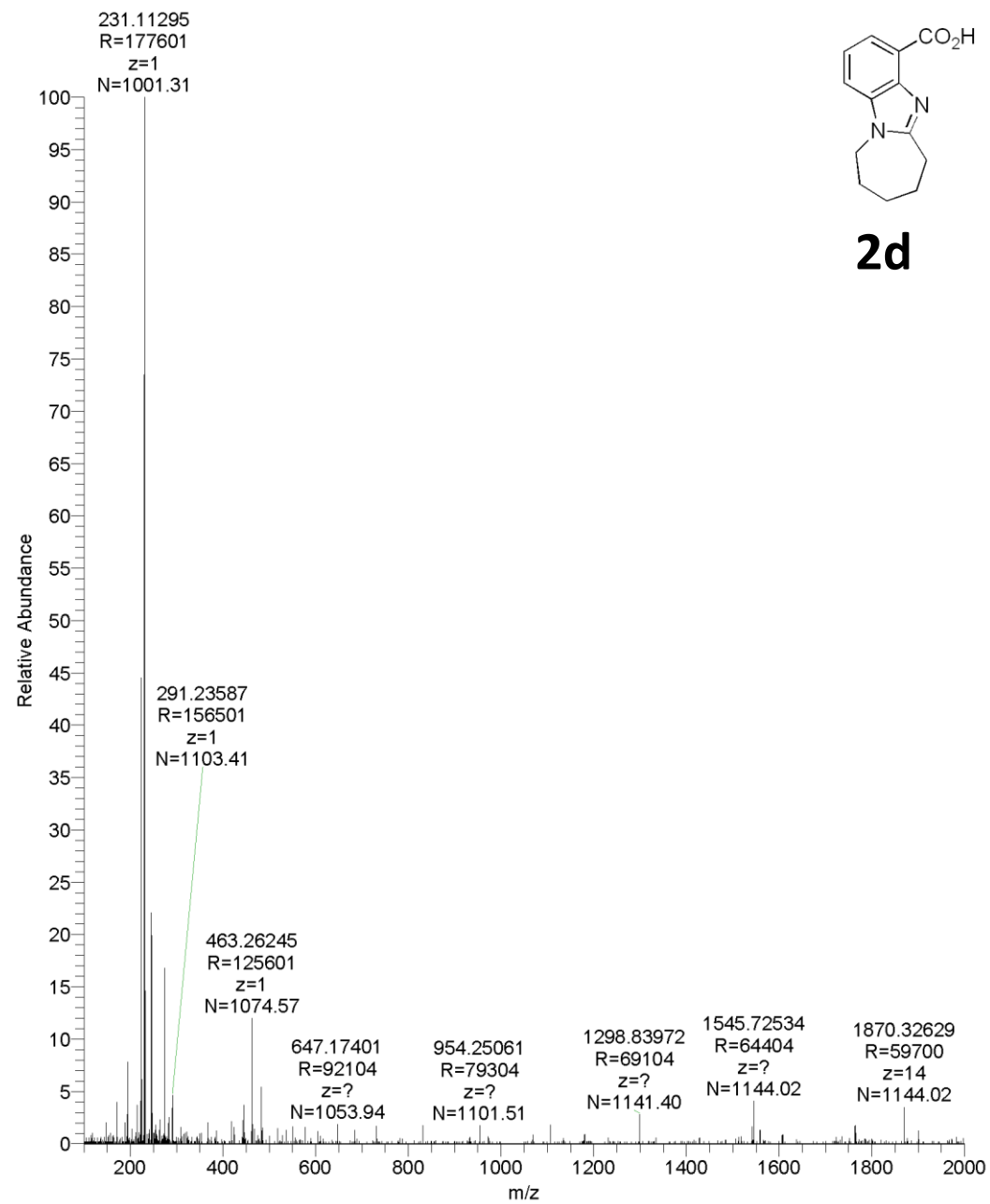


S38



2d





S40