

Diaryl α -nitrostilbenes as nitro-substituted analogues of combretastatins: synthesis and biological evaluation in the sea urchin embryo model

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Chemistry. Materials and methods. Melting points were measured using a Boetius melting point apparatus and were uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-500 instrument [working frequencies of 500.13 MHz (^1H) and of 125.76 MHz (^{13}C), respectively]. Chemical shift values were reported in parts per million (ppm) and referenced to the appropriate NMR solvent peaks. Spin–spin coupling constants (*J*) were reported in Hertz (Hz). NMR spectra were prepared using original software designed at N. D. Zelinsky Institute of Organic Chemistry RAS (Moscow, Russian Federation). Low resolution mass spectra (*m/z*) were recorded on a Finnigan MAT/INCOS 50 mass spectrometer at 70 eV using direct probe injection. High resolution mass spectra (HRMS) were measured on a Bruker micrOTOF II instrument using electrospray ionization (ESI). Elemental analysis was performed on the automated Perkin-Elmer 2400 CHN microanalyzer. Thin layer chromatography (TLC) analysis was performed using Merck 60 F₂₅₄ plates. Flash chromatography was accomplished using Silica (Acros, 0.035–0.070 mm, 60 Å). [(*E*)-2-Nitroprop-1-en-1-yl]benzene **3** was

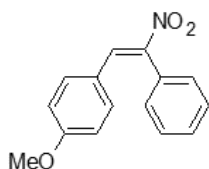
purchased from Sigma-Aldrich. Solvents and reagents were purified by standard procedures. Isoapiol **5a** and isodillapiol **5b** were synthesized according to published protocol.^{S1}

N-Methyl Schiff bases (general procedure) were prepared using a modified published protocol.^{S2} Methylamine hydrochloride (38 mmol) was suspended in methanol (5 mL) when heated to about 40 °C, and then the corresponding aldehyde (15 mmol) was added in portions with stirring at room temperature. Then NaHCO₃ (38 mmol) was added in portions for ~ 20 min, stirred for 2 h, and left overnight. The reaction mixture was decanted, the precipitate was washed twice with ethyl acetate, the extracts were combined and evaporated *in vacuo*. The residue was dissolved in dichloromethane (12 mL), washed with water (6 mL), dried with MgSO₄, and the solvent was evaporated *in vacuo*. The *N*-methyl Schiff bases were obtained as crystals or oils with a purity of 95–100% (according to NMR) and were used without purification in the reaction with aryl nitromethanes.

(*E*)-1,2-Diaryl-1-nitroethylenes **1** (general procedure). Acetic acid (48 mmol, 2.88 mL) was added dropwise to a mixture of aryl nitromethane (12 mmol) and the methyl Schiff base of the corresponding aldehyde (13.2 mmol) in acetonitrile (6.22 mL), and stirred overnight at room temperature. The volatile substances were evaporated, the crude product was diluted with dichloromethane (20 mL), washed with water, the organic layer was dried over MgSO₄, and evaporated *in vacuo*. The residue was triturated with a small amount of hot methanol and cooled. The resulting yellow crystals of 1,2-diaryl-1-nitroethylenes **1** were filtered, washed with cooled methanol, and dried in air. According to nomenclature, both targeted nitrostilbenes **1a–v** and nitroethylenes **4a,b** are *trans* (*E*)-isomers. However, the *cis*-diaryl topology for the aryl rings in **1a–v** as well as for aryl and methyl groups in **4a,b** is preserved, allowing their consideration as *Z*-isomers by nomenclature.

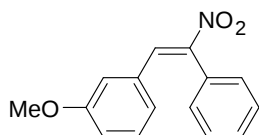
In the NMR spectra, the hydrogen and carbon atoms in the Ar² ring are indicated by the apostrophe (').

(*E*)-2-(4-Methoxyphenyl)-1-phenyl-1-nitroethylene (**1a**).



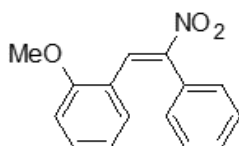
Yellow crystals; 2.175 g (71%); mp 147–149 °C (lit.^{S3} mp 147–149 °C); ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.32 (s, 1H, HC=), 7.57–7.52 (m, 3H, H-3, 4, 5), 7.42–7.37 (m, 2H, H-2, 6), 7.12 (d, *J* = 8.9 Hz, 2H, H-2', 4'), 6.86 (d, *J* = 8.9 Hz, 2H, H-3', 5'), 3.74 (s, 3H, OMe).

(*E*)-2-(3-Methoxyphenyl)-1-phenyl-1-nitroethylene (**1b**).



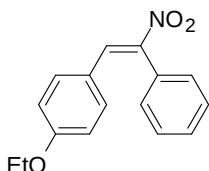
Yellow crystals; 1.9 g (61%); mp 77–80 °C (lit.^{S4} mp 78 °C); ¹H NMR (500 MHz, CDCl₃) δ 8.19 (s, 1H, HC=), 7.51–7.46 (m, 3H, H-3,4,5), 7.36–7.33 (m, 2H, H-2,6), 7.15 (t, *J* = 8.0 Hz, 1H, H-5'), 6.85 (dd, *J* = 8.3, 2.6 Hz, 1H, H-6'), 6.78 (dd, *J* = 7.6, 1.4 Hz, 1H, H-4'), 6.51 (t, *J* = 2.1 Hz, 1H, H-2'), 3.48 (s, 3H, OMe); ¹³C NMR (126 MHz, CDCl₃) δ 159.4, 149.6, 134.7, 132.3, 130.6 (2C), 130.0, 129.7, 129.2 (2C), 124.4, 117.7, 117.6, 114.7, 54.8.

(*E*)-2-(2-Methoxyphenyl)-1-phenyl-1-nitroethylene (**1c**).



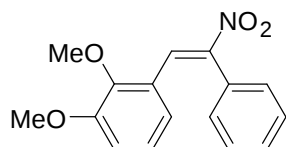
Yellow crystals; 2.14 g (70%); mp 116–118 °C (lit.^{S5} mp 115–116 °C); ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.61 (s, 1H, CH=), 7.46 – 7.41 (m, 3H, H-3,4,5), 7.31 (d, *J* = 7.5 Hz, 2H, H-2,6), 7.27 (td, *J* = 8.0, 1.7 Hz, 1H, H-5'), 6.88 (d, *J* = 8.3 Hz, 1H, H-3'), 6.69 (dd, *J* = 7.9, 1.7 Hz, 1H, H-6'), 6.62 (t, *J* = 7.6 Hz, 1H, H-4), 3.89 (s, 3H, OMe); ¹³C NMR (126 MHz, DMSO-*d*₆) δ 159.6, 150.2, 132.9, 131.7, 131.3 (2C), 131.1, 130.5, 130.4, 129.7 (2C), 129.1, 121.0, 111.6, 56.4.

(*E*)-2-(4-Ethoxyphenyl)-1-phenyl-1-nitroethylene (**1d**).



Yellow crystals; 2.10 g (65%); mp 148–149 °C (lit.^{S6} mp 147–149 °C); ¹H NMR (600 MHz, CDCl₃) δ 8.22 (s, 1H, CH=), 7.49 (m, 3H, H-2, 4, 6), 7.33 (m, 2H, H-3, 5), 7.02 (d, *J* = 8.8 Hz, 2H, H-2',6'), 6.72 (d, *J* = 8.8 Hz, 2H, H-3',5'), 3.99 (q, *J* = 7.0 Hz, 2H, OCH₂), 1.38 (t, *J* = 7.0 Hz, 3H, CH₃); ¹³C NMR (151 MHz, CDCl₃) δ 161.2, 147.3, 135.1, 133.2 (2C), 131.1, 130.6 (2C), 129.9, 129.3 (2C), 123.4, 114.8 (2C), 63.7, 14.6.

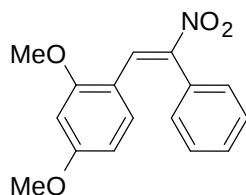
(*E*)-2-(2,3-Dimethoxyphenyl)-1-phenyl-1-nitroethylene (**1e**).



Yellow solid; 0.68 g (20%); mp 89–90 °C (MeOH) (lit.^{S5} mp 88–90 °C); ¹H NMR (CDCl₃, 500 MHz) δ 8.54 (1H, s, H-2), 7.45 (3H, m, Ar), 7.31 (2H, d, *J* = 6.9 Hz, Ar), 6.87 (1H, d, *J* = 8.1 Hz, Ar), 6.72 (1H, t, *J* = 8.1 Hz, Ar), 6.25 (1H, d, *J* = 8.0 Hz, Ar), 3.95 (3H, s, OCH₃), 3.86 (3H, s, OCH₃); ¹³C NMR (CDCl₃, 125.76 MHz) δ 55.8, 61.6, 114.4, 121.6, 123.6, 125.6, 128.9, 129.5,

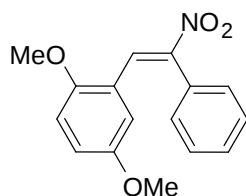
129.8, 130.6, 149.5, 150.4, 152.7; EIMS m/z 286 $[M + H]^+$ (4), 285 $[M]^+$ (24), 224 (49), 181 (12), 165 (10), 152 (28), 91 (36), 77 (18), 63 (12), 51 (22), 39 (19), 30 (24), 15 (100).

(E)-2-(2,4-Dimethoxyphenyl)-1-phenyl-1-nitroethylene (**1f**).



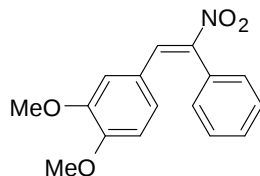
Yellow solid; 1.27 g (37%); mp 113–114 °C (MeOH) (lit.^{S5} mp 114–115 °C); ^1H NMR (CDCl_3 , 500 MHz) δ 8.65 (1H, s, H-2), 7.46 (3H, m, Ar), 7.32 (2H, m, Ar), 6.60 (1H, d, J = 8.8 Hz, Ar), 6.42 (1H, d, J = 1.6 Hz, Ar), 6.17 (1H, dd, J = 8.8 Hz, J = 1.7 Hz, Ar), 3.89 (3H, s, OCH_3), 3.76 (3H, s, OCH_3); ^{13}C NMR (CDCl_3 , 125.76 MHz) δ 55.4, 55.7, 98.0, 105.3, 113.0, 129.1, 129.5, 129.6, 130.6, 131.6, 147.2, 160.7, 163.4; EIMS m/z 286 $[M + H]^+$ (10), 285 $[M]^+$ (43), 224 (42), 209 (39), 165 (16), 152 (18), 91 (100), 77 (29), 63 (18), 51 (24), 39 (16), 30 (12), 15 (50).

(E)-2-(2,5-Dimethoxyphenyl)-1-phenyl-1-nitroethylene (**1g**).



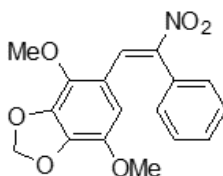
Yellow solid; 2.33 g (68%); mp 124–125 °C (MeOH) (lit.^{S5} mp 124 °C); ^1H NMR (CDCl_3 , 500 MHz) δ 8.62 (1H, s, H-2), 7.47 (3H, m, Ar), 7.35 (2H, m, Ar), 6.83 (2H, m, Ar), 6.20 (1H, s, Ar), 3.86 (3H, s, OCH_3), 3.25 (3H, s, OCH_3); ^{13}C NMR (CDCl_3 , 125.76 MHz) δ 55.0, 56.2, 112.2, 113.7, 119.5, 120.3, 129.1, 129.5, 129.7, 130.7, 131.1, 149.2, 152.7, 153.6; EIMS m/z 286 $[M + H]^+$ (6), 285 $[M]^+$ (38), 224 (83), 181 (25), 165 (26), 152 (53), 91 (57), 77 (19), 63 (20), 51 (20), 30 (26), 15 (100).

(E)-2-(3,4-Dimethoxyphenyl)-1-phenyl-1-nitroethylene (**1h**).



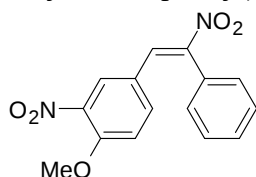
Yellow crystals; 3.18 g (94%); mp 100–102 °C (lit.^{S7} mp 102–103 °C); ^1H NMR (600 MHz, CDCl_3) δ 8.22 (s, 1H, HC=), 7.54–7.49 (m, 3H, H-3,4,5), 7.37 (d, J = 6.9 Hz, 2H, H-2,6), 6.94 (dd, J = 8.3, 2.1 Hz, 1H, H-6'), 6.78 (d, J = 8.4 Hz, 1H, H-5'), 6.39 (d, J = 2.1 Hz, 1H, H-2'), 3.86 (s, 3H, OMe), 3.39 (s, 3H, OCH_3); ^{13}C NMR (151 MHz, CDCl_3) δ 151.6, 148.7, 147.3, 135.3, 131.3, 130.9 (2C), 129.9, 129.4 (2C), 127.2, 123.8, 112.1, 110.8, 55.9, 55.1.

(*E*)-2-(2,5-Dimethoxy-3,4-methylenedioxyphenyl)-1-phenyl-1-nitroethylene (**1i**).



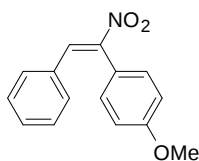
Orange crystals; 2.87 g (75%); mp 142–143 °C (lit.^{S3} mp 142–144 °C) ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.44 (1H, s, CH=); 7.36–7.60 (5H, m Ph), 6.08 (2H, s, OCH₂O), 5.84 (1H, s, H-6'), 3.98 (3H, s, OMe), 3.18 (3H, s, OCH₃); ¹³C NMR (126 MHz, DMSO-*d*₆) δ 147.8, 139.9, 138.6, 138.5, 138.2, 131.1, 130.7 (2C), 129.9, 129.4 (2C), 128.6, 116.0, 108.2, 102.7, 60.6, 55.3.

(*E*)-2-(4-Methoxy-3-nitrophenyl)-1-phenyl-1-nitroethylene (**1j**).



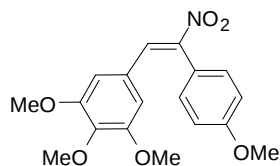
Yellow crystals; 2.84 g (79%); mp 162–166 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.15 (s, 1H, HC=), 7.56–7.51 (m, 4H, H-2', H-3,4,5), 7.33 (dd, *J* = 7.5, 1.7 Hz, 2H, H-2,6), 7.26 (dd, *J* = 8.7, 2.4 Hz, 1H, H-6'), 6.95 (d, *J* = 8.9 Hz, 1H, H-5'), 3.93 (d, 3H, OMe); ¹³C NMR (126 MHz, CDCl₃) δ 154.2, 149.8, 139.5, 136.4, 132.0, 130.5, 130.3 (2C), 129.7, 129.6 (2C), 128.0, 123.6, 113.7, 56.7; HRMS (ESI/QTOF) *m/z*: [M+NH₄]⁺ Calc. for C₁₅H₁₆N₃O₅ 318.1084; Found 318.1093; [M+Na]⁺ Calc. for C₁₅H₁₂N₂O₅Na 323.0638; F 323.0646; [M+K]⁺ Calc. for C₁₅H₁₂N₂O₅K 339.0378; Found 339.0382.

(*E*)-1-(4-Methoxyphenyl)-2-phenyl-1-nitroethylene (**1k**).



Yellow crystals; 2.24 g (73%); mp 102–103 °C (lit.^{S6} mp 100–102 °C); ¹H NMR (500 MHz, CDCl₃) δ 8.17 (s, 1H, CH=), 7.31 (t, *J* = 7.3 Hz, 1H, H-4'), 7.26 – 7.21 (m, 4H, H-2',3',5',6'), 7.13 (d, *J* = 7.3 Hz, 2H, H-2,6), 6.99 (d, *J* = 8.7 Hz, 2H, H-3,5), 3.87 (s, 3H, OCH₃); ¹³C NMR (126 MHz, CDCl₃) δ 160.8, 149.7, 134.3, 132.1 (2C), 131.5, 131.1 (2C), 130.6, 128.7 (2C), 122.5, 114.7 (2C), 55.3; HRMS (ESI/QTOF) *m/z*: [M+NH₄]⁺ Calc. for C₁₅H₁₇N₂O₃ 273.1234; Found 273.1240; [M+Na]⁺ Calc. for C₁₅H₁₃NO₃Na 278.0788; Found 278.0785.

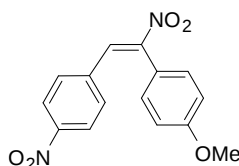
(*E*)-1-(4-Methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-1-nitroethylene (**1l**)



Yellow crystals; 2.94 g (71%); mp 136–138 °C (lit.^{S3} mp 136–138 °C); *R*_f = 0.48 (benzene); ¹H NMR (500 MHz, CDCl₃) δ 8.14 (s, 1H, CH=), 7.29 (d, *J* = 8.5 Hz, 2H, H-2,6), 7.02 (d, *J* = 8.5

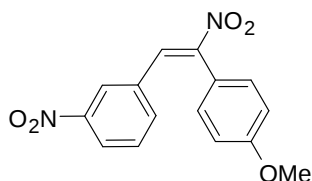
Hz, 2H, H-3,5), 6.40 (s, 2H, H-2',6'), 3.86 (s, 3H, OCH₃), 3.84 (s, 3H, OMe), 3.61 (s, 6H, 2OCH₃); ¹³C NMR (126 MHz, DMSO-*d*₆) δ 160.5, 152.6 (2C), 148.3, 139.8, 134.7, 132.3 (2C), 126.4, 122.7, 114.8 (2C), 109.0 (2C), 60.2, 55.5 (2C), 55.4.

(E)-1-(4-Methoxyphenyl)-2-(4-nitrophenyl)-1-nitroethylene (**1m**).



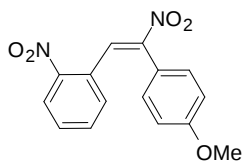
Yellow crystals; 2.38 g (66 %); mp 134–136 °C (lit.^{S3} mp 133–135 °C); ¹H NMR (500 MHz, CDCl₃) δ 8.13 (s, 1H, HC=), 8.09 (d, *J* = 8.2 Hz, 2H, H-3',5'), 7.30 (d, *J* = 8.4 Hz, 2H, H-2',6'), 7.23 (d, *J* = 7.9 Hz, 2H, H-2,6), 6.99 (d, *J* = 8.0 Hz, 2H, H-3,5), 3.88 (s, 3H, OCH₃); ¹³C NMR (126 MHz, DMSO-*d*₆) δ 160.6, 152.0, 147.7, 138.3, 132.1 (2C), 131.6 (2C), 131.5, 123.5 (2C), 121.3, 114.6 (2C), 55.2; HRMS (ESI/QTOF) *m/z*: [M+Na]⁺ Calc. for C₁₅H₁₂N₂O₅ 323.0638; Found 323.0647.

(E)-1-(4-Methoxyphenyl)-2-(3-nitrophenyl)-1-nitroethylene (**1n**).



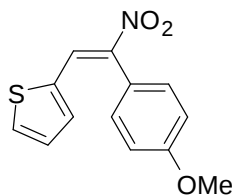
Yellow crystals; 1.95 g (54%); mp 160–166 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.17–8.14 (m, 2H, H-2',5'), 8.00 (s, 1H, HC=), 7.45 – 7.41 (m, 2H, H-4',6'), 7.25 (d, *J* = 8.4 Hz, 2H, 2,6), 7.01 (d, *J* = 8.8 Hz, 2H, H-3,5), 3.88 (s, 3H, OCH₃); ¹³C NMR (126 MHz, CDCl₃) δ 161.4, 152.1, 148.3, 136.0, 133.4, 131.9 (2C), 131.2, 129.7, 125.4, 124.7, 121.1, 115.0 (2C), 55.5; HRMS (ESI/QTOF) *m/z*: [M+Na]⁺ Calc. for C₁₅H₁₂N₂O₅Na 323.0638; Found 323.0632.

(E)-1-(4-Methoxyphenyl)-2-(2-nitrophenyl)-1-nitroethylene (**1o**).



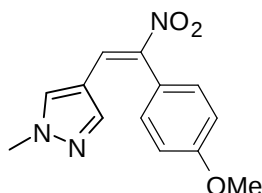
Yellow crystals; 2.23 g (62%); mp 82–85 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.37 (s, 1H, HC=), 8.14 (d, *J* = 8.0 Hz, 1H, H-3'), 7.47 (t, *J* = 7.7 Hz, 1H, H-5'), 7.41 (t, *J* = 7.7 Hz, 1H, H-4'), 7.14 (d, *J* = 8.3 Hz, 2H, H-2,6), 7.03 (d, *J* = 7.6 Hz, 1H, H-6'), 6.83 (d, *J* = 8.3 Hz, 2H, H-3,5), 3.79 (s, 3H, OCH₃); ¹³C NMR (126 MHz, CDCl₃) δ 160.8, 151.8, 148.1, 133.5, 132.3 (2C), 131.6, 130.8, 130.0, 128.8, 124.9, 120.8, 114.1 (2C), 55.3; HRMS (ESI/QTOF) *m/z*: [M+Na]⁺ Calc. for C₁₅H₁₂N₂O₅Na 323.0638; Found 323.0635; [M+K]⁺ Calc. for C₁₅H₁₂N₂O₅K 339.0378; Found 339.0375.

(*E*)-1-(4-Methoxyphenyl)-2-(2-thienyl)-1-nitroethylene (**1p**).



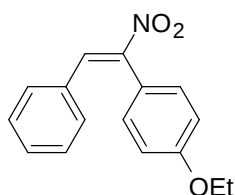
Yellow crystals; 1.98 g (63%); mp 145–147 °C (lit.^{S3} mp 145–147 °C); ¹H NMR (500 MHz, CDCl₃) δ 8.48 (1H, s, CH=), 7.39 (1H, d, *J* = 5.0 Hz, H-5'), 7.36 (1H, d, *J* = 3.5 Hz, H-3'), 7.28 (2H, d, *J* = 8.5 Hz, H-2,6), 7.06 (2H, d, *J* = 8.5 Hz, H-3,5), 7.01 (1H, t, *J* = 4.5 Hz, H-4'), 3.91 (3H, s, OMe); ¹³C NMR (500 MHz, DMSO-*d*₆) δ 55.3, 115.0 (2C), 121.6, 127.8, 129.6, 132.6 (2C), 134.9, 135.1, 137.9, 146.0, 160.9.

(*E*)-1-(4-Methoxyphenyl)-2-(1-methyl-pyrazol-4-yl)nitroethylene (**1q**).



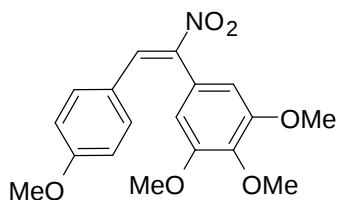
Yellow crystals; 1.369 g (44%); mp 151–153 °C (lit.³ mp 151–153 °C); ¹H NMR (500 Hz, CDCl₃) δ 8.15 (1H, s, CH=), 7.25 (2H, d, *J* = 8.5 Hz, H-2,6), 7.14 (1H, s, H-3'), 7.04 (2H, d, *J* = 8.5 Hz, H-3,5), 6.98 (1H, s, H-4'), 3.92 (3H, s, OMe), 3.82 (3H, s, N-Me); ¹³C NMR (126 MHz, DMSO-*d*₆) δ 160.2, 145.3, 140.0, 134.0, 131.6 (2C), 127.6, 123.1, 114.7 (2C), 114.0, 55.2, 38.75.

(*E*)-1-(4-Ethoxyphenyl)-2-phenyl-1-nitroethylene (**1r**).



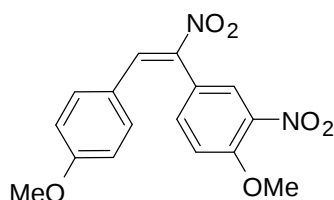
Yellow crystals; 2.197 g (68%); mp 98–100 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.16 (s, 1H, HC=), 7.31 (t, *J* = 7.3 Hz, 1H, H-4'), 7.27–7.22 (m, 4H, H-3', 5', 2, 6), 7.13 (d, *J* = 7.3 Hz, 2H, H-2',6'), 6.97 (d, *J* = 8.7 Hz, 2H, H-3,5), 4.09 (q, *J* = 7.0 Hz, 2H, OCH₂), 1.46 (t *J* = 7.0 Hz, 3H, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ 160.3, 149.8, 134.3, 132.1 (2C), 131.6, 131.1 (2C), 130.6, 128.7 (2C), 122.3, 115.2 (2C), 63.7, 14.8; HRMS (ESI/QTOF) *m/z*: [M+H]⁺ Calc. for C₁₆H₁₆NO₃ 270.1125; Found 270.1134; [M+Na]⁺ Calc. for C₁₆H₁₅NO₃Na 292.0944; Found 292.0949; [M+K]⁺ Calc. for C₁₆H₁₅NO₃K 308.0684; Found 308.0685.

(*E*)-1-(3,4,5-Trimethoxyphenyl)-2-(4-methoxyphenyl)-1-nitroethylene (**1s**).



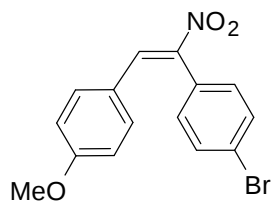
Yellow crystals; 3.067 g (74%); mp 142–146 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.19 (s, 1H, HC=), 7.09 (d, J = 7.8 Hz, 2H, H-2',6'), 6.78 (d, J = 8.9 Hz, 2H, H-3',5'), 6.54 (s, 2H, H-2,6), 3.94 (s, 3H, OCH_3), 3.81 (s, 6H, 2OCH_3), 3.80 (s, 3H, OCH_3); ^{13}C NMR (126 MHz, CDCl_3) δ 161.9, 154.1 (2C), 147.2, 139.3, 134.9, 133.4 (2C), 126.2, 123.5, 114.4 (2C), 107.5 (2C), 61.0, 56.3 (2C), 55.4; HRMS (ESI/QTOF) m/z : $[\text{M}+\text{H}]^+$ Calc. for $\text{C}_{18}\text{H}_{20}\text{NO}_6$ 346.1285; Found 346.1277; $[\text{M}+\text{Na}]^+$ Calc. for $\text{C}_{18}\text{H}_{19}\text{NO}_6\text{Na}$ 368.1105; Found 368.1098.

(*E*)-1-(4-Methoxy-3-nitrophenyl)-2-(4-methoxyphenyl)-1-nitroethylene (**1t**).



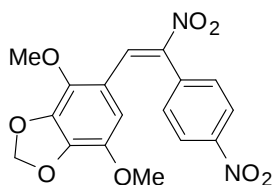
Yellow crystals; 1.982 g (50%); mp 114–117 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.28 (s, 1H, HC=), 7.85 (d, J = 2.2 Hz, 1H, H-2), 7.52 (dd, J = 8.7, 2.2 Hz, 1H, H-6), 7.22 (d, J = 8.7 Hz, 1H, H-5), 7.09 (d, J = 8.9 Hz, 2H, H-2',6'), 6.80 (d, J = 8.9 Hz, 2H, H-3',5'), 4.05 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3); ^{13}C NMR (126 MHz, CDCl_3) δ 162.2, 153.8, 144.6, 139.9, 136.8, 136.3, 133.2 (2C), 128.3, 123.1, 122.9, 114.6 (2C), 114.3, 56.7, 55.4; HRMS (ESI/QTOF) m/z : $[\text{M}+\text{H}]^+$ Calc. for $\text{C}_{16}\text{H}_{15}\text{N}_2\text{O}_6$ 331.0925; Found 331.0920; $[\text{M}+\text{NH}_4]^+$ Calc. for $\text{C}_{16}\text{H}_{18}\text{N}_3\text{O}_6$ 348.1190; Found 348.1183; $[\text{M}+\text{K}]^+$ Calc. for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_6\text{K}$ 369.0483; Found 369.0475.

(*E*)-1-(4-Bromophenyl)-2-(4-methoxyphenyl)-1-nitroethylene (**1u**).



Yellow crystals; 3.088 g (77 %); mp 107–110 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.24 (s, 1H, HC=), 7.63 (d, J = 8.3 Hz, 2H, H-2,6), 7.21 (d, J = 8.3 Hz, 2H, H-3,5), 7.06 (d, J = 8.8 Hz, 2H, H-2',6'), 6.78 (d, J = 8.9 Hz, 2H, H-3',5'), 3.79 (s, 3H, OCH_3); ^{13}C NMR (126 MHz, CDCl_3) δ 162.0, 146.2, 135.6, 133.2 (2C), 132.6 (2C), 132.4 (2C), 130.0, 124.4, 123.2, 114.5 (2C), 55.4; HRMS (ESI/QTOF) m/z : $[\text{M}+\text{H}]^+$ Calc. for $\text{C}_{15}\text{H}_{12}\text{BrNO}_3$ 334.0073, 336.0053; Found 334.0068, 336.0052.

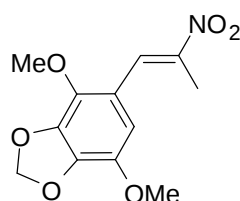
(*E*)-1-(4-Nitrophenyl)-2-(2,5-dimethoxy-3,4-methylenedioxyphenyl)-1-nitroethylene (**1v**).



Yellow crystals; 1.168 g (26 %); mp 139–141 °C ; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.66 (s, 1H, CH=), 8.36 (d, J = 8.7 Hz, 2H, H-3,5), 7.58 (d, J = 8.7 Hz, 2H, H-2,6), 6.04 (s, 2H, OCH_2O), 5.82 (s, 1H, H-6'), 4.05 (s, 3H, OMe), 3.33 (s, 3H, OMe); ^{13}C NMR (126 MHz, $\text{DMSO}-d_6$, APT) δ 148.5 (+), 146.1(+), 140.7 (+), 139.0 (+), 138.6 (+), 138.1 (+), 133.0 (-), 131.0 (-), 124.6 (-), 115.9 (+), 109.0 (-), 103.2 (+), 60.9 (-), 56.0 (-); HRMS (ESI/QTOF) m/z : $[\text{M}+\text{Na}]^+$ Calc. for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_8\text{Na}$ 397.0642; Found 397.0654.

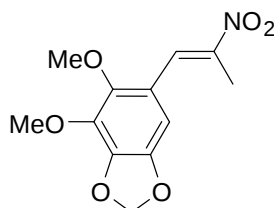
Synthesis of (*E*)-2-aryl-1-methyl-1-nitroethylenes **4a,b** (general procedure).^{S8} Tetranitromethane (4 mmol) in acetone (1 mL) was added dropwise at 0 °C to a stirred solution of isoapiol **5a** or isodillapiol **5b** (4 mmol) and pyridine (4.8 mmol) in acetone (3 mL). The mixture was stirred for 1.5 h, poured into water (20 mL) and extracted with ether (15 mL). The ether extract was washed with 33% aq. KOH (3 × 5 mL) and water (5 mL), dried with Na₂SO₄, and evaporated to dryness. The residue was recrystallized from EtOH.

(*E*)-1-(2,5-Dimethoxy-3,4-methylenedioxyphenyl)-2-nitropropene (**4a**).



Yellow crystals; 0.748 g (70%); mp 111–112 °C (lit.^{S8} mp 110–111 °C); ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.07 (s, 1H, HC=), 6.71 (s, 1H, H-6), 6.10 (s, 2H, OCH₂O), 3.90 (s, 3H, OMe), 3.82 (s, 3H, OMe), 2.36 (s, 3H, Me). ¹³C NMR (126 MHz, CDCl₃) δ 146.9, 139.2, 138.9, 138.3, 137.9, 129.5, 118.2, 109.3, 102.2, 60.3, 57.2, 14.4.

(*E*)-1-(2,3-Dimethoxy-4,5-methylenedioxyphenyl)-2-nitropropene (**4b**).



Yellow crystals; 0.662 g (61%); mp 93–94 °C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.07 (s, 1H, HC=), 6.80 (s, 1H, H-6), 6.11 (s, 2H, OCH₂O), 3.98 (s, 3H, OMe), 3.76 (s, 3H, OMe), 2.35 (s, 3H, Me). ¹³C NMR (126 MHz, CDCl₃) δ 147.3, 146.0, 145.0, 139.7, 137.8, 129.3, 119.0, 102.0, 101.9, 62.1, 60.2, 14.3. Calc for C₁₂H₁₃NO₆ C, 53.93; H, 4.90; N, 5.24. Found C, 53.80; H, 4.99; N, 5.37.

Single crystal X-ray diffraction data.

X-ray data for compound **1i** were at 100 K on the 'Belok/XSA' beamline ($\lambda = 0.9626$ Å, ϕ -scans) of the Kurchatov Synchrotron Radiation Source (Moscow, Russian Federation).^{S9,S10} Diffraction patterns were collected using Mardtb goniometer equipped with Rayonix SX165 2D positional sensitive CCD detector at 100 K. In total, 300 frames were collected with oscillation range of 1°. The data were indexed, integrated and scaled; absorption correction was applied using the XDS program package.^{S11} X-ray diffraction data for compound **4a** were collected at 100 K on a four-circle Rigaku Synergy S diffractometer equipped with a HyPix6000HE area-detector (kappa geometry, shutterless ω -scan technique), using graphite monochromatized Cu K α -radiation. The intensity data were integrated and corrected for absorption and decay by the CrysAlisPro program.^{S12} The structures were solved by direct methods using SHELXT^{S13}] and refined on F^2 using SHELXL-2018^{S14} in the OLEX2 program.^{S15} All non-hydrogen atoms were refined with individual anisotropic displacement parameters. All hydrogen atoms were placed in ideal calculated positions and refined as riding atoms with relative isotropic displacement parameters. The Mercury program suite^{S16} was used for molecular graphics. A rotating group model was applied for methyl groups.

The geometry of the molecules **1i** and **4a** in crystals is close due to the realization of one type of isomer; the differences lie in slight rotations of different functional groups. 1,3-Dioxole ring in **1i** adopts an *envelope* conformation, with the C2 carbon atom deviating from the mean plane passes through the other atoms of the five-member ring by 0.238(2) Å, while in the crystal of **4a** benzo[d][1,3]dioxole is almost flat with the deviation of carbon atom C2 from the plane by -0.0923(16)Å. Methoxy groups O7–C17 (**1i**) and O7–C12 (**4a**) are in plane of 3,4-methylenedioxybenzene system, the corresponding dihedral angles are 3.88(19)° and -2.59(16)°. The second methoxy group O4–C8 is rotated by 48.77(9)° and 28.04(16)° relative to the parent benzene ring. Nitro-substituent in the crystals of two molecules is coplanar to the plane of the double bond, whereas the dihedral angles C9-C10-N1-O9 corresponding to the turning of the group are -2.21(17)° and 9.90(15)° for compound **1i** and **4a**, respectively. Due to the steric factors (compound **1i**: intramolecular interaction C-H...pi; compound **4a**: the repulsion between methyl substituent and hydrogen atom H6), plane of the double bond is twisted by 20.65(6)° and 19.33(10)° relative to the basal plane of the central benzo[d][1,3]dioxole bicycle.

Table S1. Crystallographic data for compounds **1i** and **4a**.

Parameters	1i	4a
Empirical formula	C ₁₇ H ₁₅ NO ₆	C ₁₂ H ₁₃ NO ₆
FW	329.30	267.23
T, K	100.0(2)	100.00(10)
Radiation (λ), Å	0.96260	1.54184
Crystal size, mm	0.20×0.20×0.25	0.14×0.18×0.21
Crystal system	monoclinic	triclinic
Space group	<i>C</i> 2/ <i>c</i>	<i>P</i> $\bar{1}$
<i>a</i> , Å	21.841(4)	7.0546(3)
<i>b</i> , Å	6.7692(14)	7.4861(3)
<i>c</i> , Å	21.035(4)	11.6392(5)
α , deg.	90	106.729(4)
β , deg.	90.50(3)	91.932(4)
γ , deg.	90	97.698(4)
<i>V</i> , Å ³	3109.8(10)	581.67(4)
<i>Z</i>	8	2
<i>d</i> _c , g · cm ⁻³	1.407	1.526
<i>F</i> (000)	1376	280
μ , mm ⁻¹	0.227	1.061
2 θ _{max} , deg.	76.88	80.612
Index range	-28 ≤ <i>h</i> ≤ 28 -8 ≤ <i>k</i> ≤ 8 -25 ≤ <i>l</i> ≤ 26	-9 ≤ <i>h</i> ≤ 8 -9 ≤ <i>k</i> ≤ 9 -13 ≤ <i>l</i> ≤ 14
no. of rflns collected	22356	13644
no. of unique rflns [<i>R</i> _{int}]	3377 [0.1136]	2509 [0.0268]
no. of rflns with <i>I</i> > 2 σ (<i>I</i>)	2775	2336
data / restraints / parameters	3377 / 0 / 220	2509 / 0 / 175
<i>R</i> ₁ ; <i>wR</i> ₂ (<i>I</i> > 2 σ (<i>I</i>))	0.0546; 0.1314	0.0329; 0.0881
<i>R</i> ₁ ; <i>wR</i> ₂ (all data)	0.0625; 0.1373	0.0347; 0.0895
GOF on <i>F</i> ²	1.069	1.068
<i>T</i> _{min} ; <i>T</i> _{max}	0.939; 0.949	0.735; 1.000
ρ _{max} ; ρ _{min} , eÅ ⁻³	0.347; -0.289	0.266; -0.228

Phenotypic sea urchin embryo assay.^{S17}

Adult sea urchins, *Paracentrotus lividus* L. (Echinidae), were collected from the Mediterranean Sea on the Cyprus coast and kept in an aerated seawater tank. Gametes were obtained by intracoelomic injection of 0.5 M KCl. Eggs were washed with filtered seawater and fertilized by adding drops of diluted sperm. Embryos were cultured at room temperature (18–23 °C) under gentle agitation with a motor-driven plastic paddle (60 rpm) in filtered seawater. The embryos were observed with a Biolam light microscope (LOMO, St. Petersburg, Russian Federation). For treatment with the test compounds, 5 mL aliquots of embryo suspension were transferred to six-well plates and incubated as a monolayer at a concentration up to 2000 embryos/mL. Stock solutions of tested molecules were prepared in DMSO at 10 mM concentration followed by a 10-fold dilution with 96% EtOH. This procedure enhanced the solubility of the test compounds in the salt-containing medium (seawater), as evidenced by microscopic examination of the samples. The maximal tolerated concentrations of DMSO and EtOH in the *in vivo* assay were determined to be 0.05% and 1%, respectively. Higher concentrations of either DMSO (>0.1%) or EtOH (>1%) caused nonspecific alterations and retardation of the sea urchin embryo development independent of the treatment stage. CA2 and CA4 (synthesized as reported previously^{S1, S18}), isoapiol **5a**, and isodillapiol **5b** served as reference compounds. Stock solutions of **5a** and **5b** were prepared at 20 mM concentration in DMSO and 95% EtOH, respectively. Biological effects were assessed by exposing fertilized eggs (8–15 min postfertilization, 45–55 min before the first mitotic cycle completion) and hatched free-swimming blastulae (8–10 h postfertilization) to 2-fold decreasing concentrations of the compound. The antiproliferative activity was estimated quantitatively as minimum effective (threshold) concentration (MEC), resulting in cleavage alteration or full mitotic arrest followed by embryo mortality before hatching. For microtubule-destabilizing activity, the compounds were tested on blastulae just after hatching (8–10 h after fertilization), which originated from the same embryo culture. Embryo spinning was observed after 15 min to 20 h of exposure, depending on the structure and concentration of the compound. Embryo spinning together with the lack of forward movement served as an evidence of the microtubule-destabilizing mode of action of a molecule. Video illustrations are available at <http://www.chemical-block.com>. In the absence of embryo spinning, developmental alteration and embryo death were interpreted as compound systemic toxicity, which was estimated quantitatively as minimum effective concentration (MEC) causing developmental defects or embryo death. Embryonic development was monitored until the beginning of active feeding at four-arm pluteus stage (33–36 h postfertilization). Microphotographs were obtained using an AmScope binocular microscope with an MU500 digital camera (United Scopes LLC, Irvine, CA, USA). The sea urchin embryo assay data are available free of charge *via* the Internet at <http://www.zelinsky.ru>.

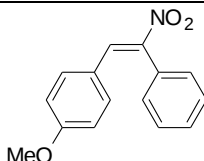
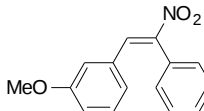
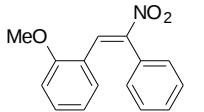
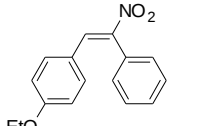
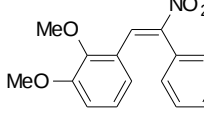
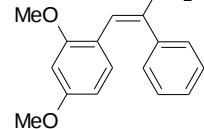
Experiments with the sea urchin embryos fulfil the requirements of biological ethics. The artificial spawning does not cause animal death, embryos develop outside the female organism, and both postspawned adult sea urchins and the excess of intact embryos are returned to the sea, their natural habitat.

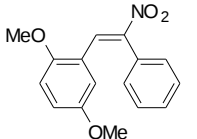
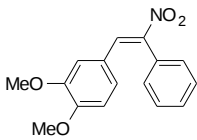
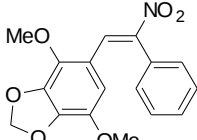
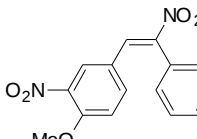
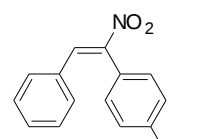
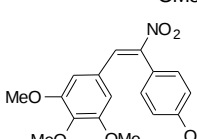
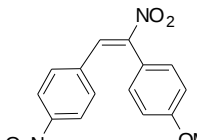
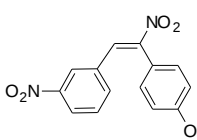
Structure-activity relationship for compounds 1a–v and 3-5.

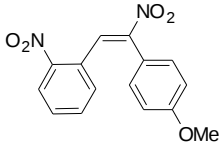
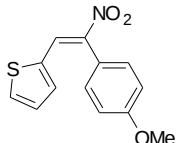
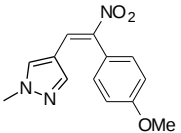
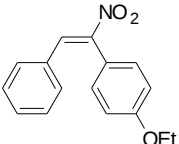
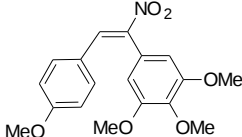
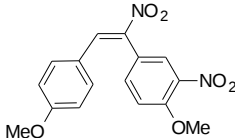
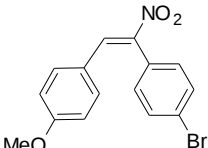
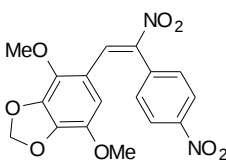
In the series of DNSs featuring phenyl ring B, compounds **1e–h** with different positions of two methoxy substituents in the ring A displayed similar toxicity. The same activity was found for **1c** with 2-methoxybenzene ring A, whereas compound **1b** with 3-methoxybenzene ring A showed weak antitubulin effect. Introduction of 4-methoxy-, 4-ethoxy-, and tetraalkoxy-substituted ring A yielded antitubulin molecules **1a**, **1d**, and **1i**, respectively, whereas stilbene **1k** with unsubstituted ring A and 4-methoxybenzene ring B showed only systemic toxicity. Comparative analysis of DNSs featuring 3,4,5-trimethoxybenzene and 4-methoxybenzene fragments suggested that 3,4,5-trimethoxybenzene as the ring B (**1s**) was favourable for microtubule destabilizing activity, whereas the same moiety as the ring A (**1l**) displayed only systemic toxicity. Introduction of 4-nitro group in the ring B (**1i** versus **1v**) eliminated the antitubulin effect while maintaining systemic toxicity. Moving the nitro group from 2-position (**1o**) to position 3 (**1n**) or position 4 (**1m**) of the ring A markedly reduced antitubulin effect and, conversely, increased systemic toxicity. Noticeably, the most potent compounds with tubulin-unrelated toxicity featured nitro group in position 3 (**1j** and **1n**) or position 4 (**1m**) in the ring A, or in position 3 in the ring B (**1t**). Based on these results, it was suggested that systemic toxicity of tested DNSs could be related to the presence of 3-nitro- or 4-nitrogroups in aryl moieties. Presumably, developmental impairment and embryo death due to systemic toxicity might hinder the detection of the antitubulin activity, especially when systemic toxicity occurred at lower concentrations than microtubule destabilizing effects, such as formation of tuberculate arrested eggs and embryo spinning.

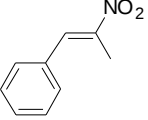
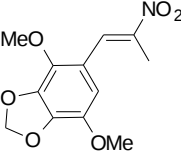
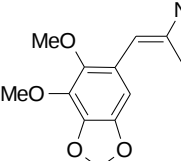
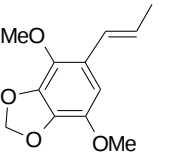
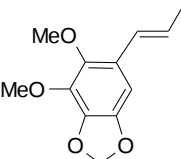
Next, the impact of nitroethylene fragment into biological effect was assessed in a series of styrenes **3,4** (Table S2). In the sea urchin embryo assay, compound **3** featuring phenyl ring and nitro-substituted double bond showed moderate microtubule destabilizing activity together with systemic toxicity. Introduction of nitro group into weakly toxic isoapiol **5a** and isodillapiol **5b** not only enhanced systemic toxicity, but also endowed the resulting compounds **4a** and **4b** with antitubulin activity, which was confirmed by embryo spinning. Noticeably, all three monoaryl nitrostyrenes **3-5** equally disrupted cleavage and induced blastulae spinning. Their close structural analogues without the nitro group, isoapiol **5a** and isodillapiol **5b**, failed to produce embryo spinning and showed only weak toxicity. Besides, isoapiol **5a** selectively inhibited cleavage (cell division) without any effect on post-hatching differentiation and morphogenesis, suggesting tubulin-unrelated antiproliferative activity.

Table S2. Structures of DNSs **1a–v**, nitrostyrenes **3,4**, isoapiol **5a**, and isodillapiol **5b^a** and their effects on the sea urchin *Paracentrotus lividus* embryos.

Compound ^a	Yield (%)	Minimum effective concentration (MEC, μM) ^b					Mode of action
		Fertilized egg treatment		Hatched blastula treatment			
		Cleavage alteration	Cleavage arrest	Embryo spinning	Morphological anomalies	Embryo mortality	
1a 	74	2	4 TE ^c	4	1	4	Microtubule-destabilizing activity; systemic toxicity
1b 	61	1	2 TE ^c	>4	1	2	Weak microtubule-destabilizing activity; systemic toxicity
1c 	70	2	>4	>4	2	>4	Systemic toxicity
1d^d 	65	~2	~4	~2	~1	~2	Microtubule-destabilizing activity; systemic toxicity
1e 	20	2	>4	>4	2	4	Systemic toxicity
1f 	37	2	>4	>4	2	4	Systemic toxicity

1g		68	2	>4	>4	2	4	Systemic toxicity
1h		93	1	4	>5	1	2	Systemic toxicity
1i^d		75	~2	~4	~1	~1	~2	Microtubule-destabilizing activity; systemic toxicity
1j		79	1	2	>4	0.5	1	Systemic toxicity
1k		73	2	4	>4	2	4	Systemic toxicity
1l		71	1	4	>4	1	4	Systemic toxicity
1m		66	1	2	>4	0.5	1	Systemic toxicity
1n		54	1	2	>4	0.5	1	Systemic toxicity

1o		62	0.2	1 TE ^c	1	1	2	Microtubule-destabilizing activity; systemic toxicity
1p		63	0.2	2	2	0.2	4	Microtubule-destabilizing activity; systemic toxicity
1q		44	2	>4	>4	1	>4	Systemic toxicity
1r		68	1	2 TE ^c	>4	1	2	Weak microtubule-destabilizing activity; systemic toxicity
1s		74	1	2	2	1	2	Microtubule-destabilizing activity; systemic toxicity
1t		50	4	>4	>4	0.5	4	Systemic toxicity
1u^d		77	~2	>4	>4	~1	~2	Systemic toxicity
1v		25	2	>4	>4	2	2	Systemic toxicity

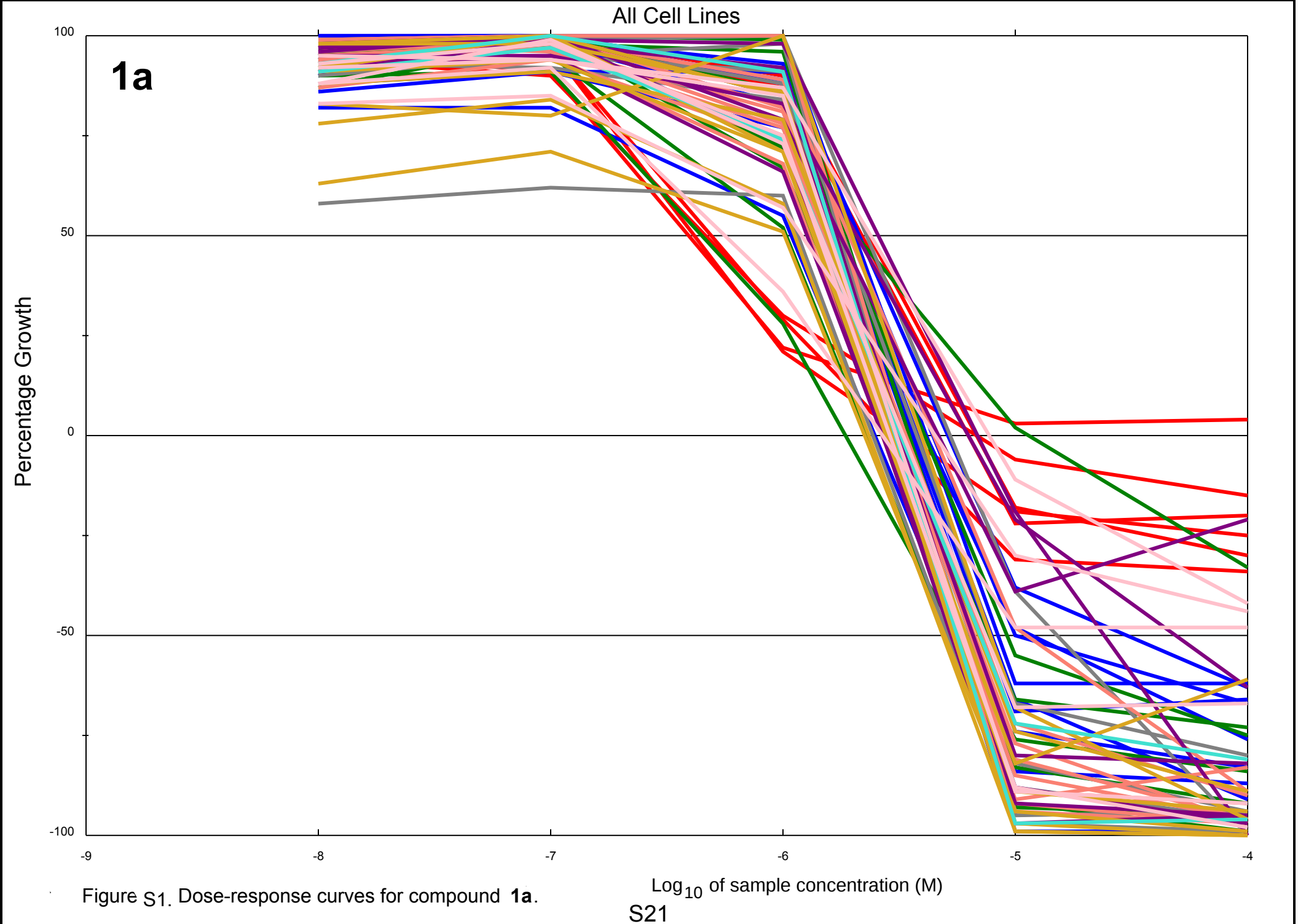
3		-	2	4	4	1	>4	Microtubule-destabilizing activity; systemic toxicity
4a		-	2	4	4	2	4	Microtubule-destabilizing activity; systemic toxicity
4b		-	2	4	4	2	5	Microtubule-destabilizing activity; systemic toxicity
5a		-	2	8	>10	>10	>10	Tubulin-unrelated antiproliferative activity
5b		-	20	80	>100	40	100	Systemic toxicity
CA2	Figure 1	-	0.002	0.01 TE ^c	0.05	0.01	0.04 ^e	Microtubule-destabilizing activity
CA4	Figure 1	-	0.002	0.01 TE ^c	0.05	0.005	0.05 ^e	Microtubule-destabilizing activity

^a Previously published compounds: **1a**, **1i**, **1m**, **1p**, and **1q**,^{S3,S19} **1l**,^{S3,S19,S20} **5a** and **5b**.^{S1} ^b The sea urchin embryo assay was conducted as described previously.^{S17} Fertilized eggs and hatched blastulae were exposed to 2-fold decreasing concentrations of compounds. Duplicate measurements showed no differences in MEC values. ^c TE: tuberculate arrested eggs typical for microtubule destabilizing agents. ^d MEC values were approximate due to compound precipitation in seawater. ^e Embryo mortality was observed after 25 h of exposure.

References

- S1. V. V. Semenov, A. S. Kiselyov, I. Y. Titov, I. K. Sagamanova, N. N. Ikizalp, N. B. Chernysheva, D. V. Tsyganov, L. D. Konyushkin, S. I. Firgang, R. V. Semenov, I. B. Karmanova, M. M. Raihstat and M. N. Semenova, *J. Nat. Prod.*, 2010, **73**, 1796;
<https://doi.org/10.1021/np1004278>.
- S2. N. S. Radulović, A. B. Miltojević and R. D. Vukićević, *C. R. Chim.*, 2013, **16**, 257;
<https://doi.org/10.1016/j.crci.2013.01.010>.
- S3. N. B. Chernysheva, A. S. Maksimenko, F. A. Andreyanov, V. P. Kislyi, Y. A. Strelenko, V. N. Khrustalev, M. N. Semenova and V. V. Semenov, *Tetrahedron*, 2017, **73**, 6728;
<https://doi.org/10.1016/j.tet.2017.10.016>.
- S4. B. Reichert and W. Hoffmann, *Arch. Pharm.*, 1936, **274**, 153;
<https://doi.org/10.1002/ardp.19362740301>.
- S5. E. A. Silyanova, A. V. Samet, L. K. Salamandra, V. N. Khrustalev and V. V. Semenov, *Eur. J. Org. Chem.*, 2020, 2093; <https://doi.org/10.1002/ejoc.202000099>.
- S6. E. A. Silyanova, V. I. Ushkarov, A. V. Samet, A. S. Maksimenko, I. A. Koblov, V. P. Kislyi, M. N. Semenova and V. V. Semenov, *Mendeleev Commun.*, 2022, **32**, 120;
<https://doi.org/10.1016/j.mencom.2022.01.039>.
- S7. B. Reichert and W. Kuhn, *Ber. Dtsch. Chem. Ges.*, 1941, **74**, 328;
<https://doi.org/10.1002/cber.19410740304>.
- S8. E. Schmidt, R. Schumacher, W. Bäjén and A. Wagner, *Ber. Dtsch. Chem. Ges.*, 1922, **55**, 1751;
<https://doi.org/10.1002/cber.19220550629>.
- S9. V. A. Lazarenko, P. V. Dorovatovskii, Y. V. Zubavichus, A. S. Burlov, Y. V. Koshchienko, V. G. Vlasenko and V. N. Khrustalev, *Crystals*, 2017, **7**, 325; <https://doi.org/10.3390/cryst7110325>.
- S10. R. D. Svetogorov, P. V. Dorovatovskii and V. A. Lazarenko, *Cryst. Res. Technol.*, 2020, **55**, 1900184; <https://doi.org/10.1002/crat.201900184>.
- S11. W. Kabsch, *Acta Crystallogr., Sect. D: Struct. Biol.*, 2010, **66**, 125;
<https://doi.org/10.1107/S0907444909047337>.
- S12. *CrysAlisPro. version 1.171.41.106a*, Rigaku Oxford Diffraction, 2021.
- S13. G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 2015, **71**, 3;
<https://doi.org/10.1107/S2053273314026370>.
- S14. G. M. Sheldrick, *Acta Crystallogr., Sect. C*, 2015, **71**, 3;
<https://doi.org/10.1107/S2053229614024218>.

- S15. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Cryst.*, 2009, **42**, 339; <https://doi.org/10.1107/S0021889808042726>.
- S16. C. F. Macrae, I. Sovago, S. J. Cottrell, P. T. A. Galek, P. McCabe, E. Pidcock, M. Platings, G. P. Shields, J. S. Stevens, M. Towler and P. A. Wood, *J. Appl. Crystallogr.*, 2020, **53**, 226; <https://doi.org/10.1107/S1600576719014092>.
- S17. M. N. Semenova, D. V. Demchuk, D. V. Tsyganov, N. B. Chernysheva, A. V. Samet, E. A. Silyanova, V. P. Kislyi, A. S. Maksimenko, A. E. Varakutin, L. D. Konyushkin, M. M. Raihstat, A. S. Kiselyov and V. V. Semenov, *ACS Comb. Sci.*, 2018, **20**, 700; <https://doi.org/10.1021/acscombsci.8b00113>.
- S18. G. R. Pettit, S. B. Singh, M. R. Boyd, E. Hamel, R. K. Pettit, J. M. Schmidt and F. Hogan, *J. Med. Chem.*, 1995, **38**, 1666; <https://doi.org/10.1021/jm00010a011>.
- S19. N. B. Chernysheva, A. S. Maksimenko, F. A. Andreyanov, V. P. Kislyi, Y. A. Strelenko, V. N. Khrustalev, M. N. Semenova and V. V. Semenov, *Eur. J. Med. Chem.*, 2018, **146**, 511; <https://doi.org/10.1016/j.ejmech.2018.01.070>.
- S20. K. Rorig, *J. Org. Chem.*, 1950, **15**, 391; <https://doi.org/10.1021/jo01148a025>.



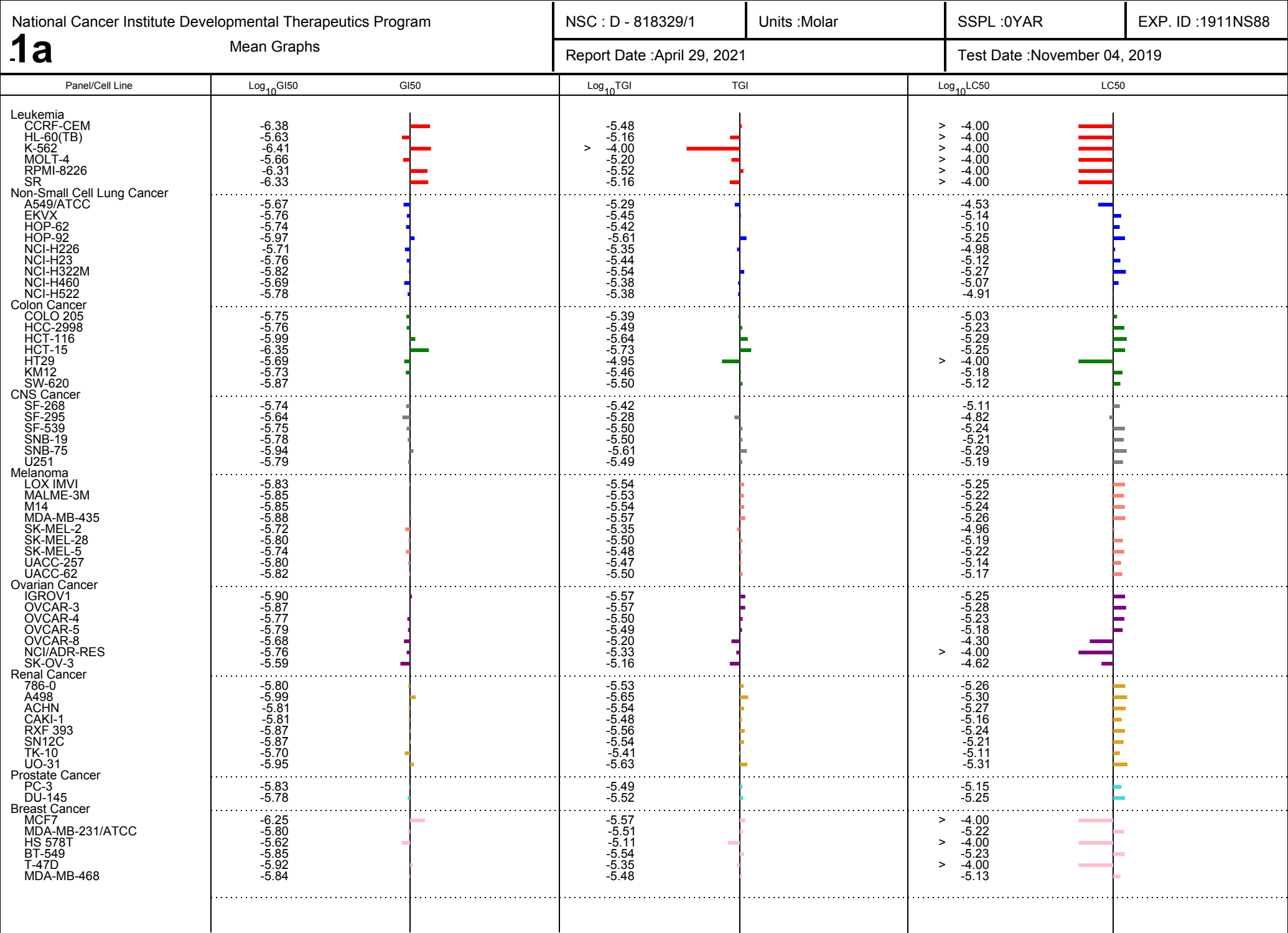
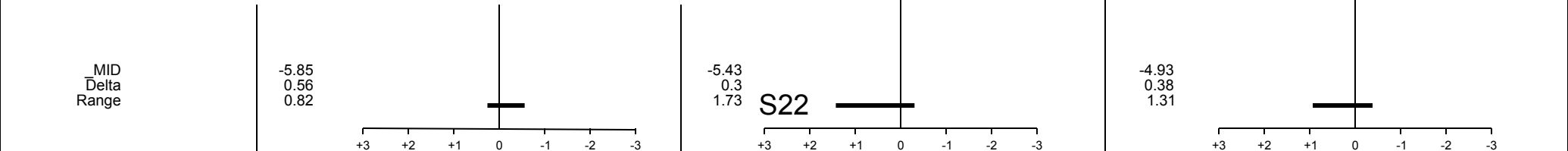
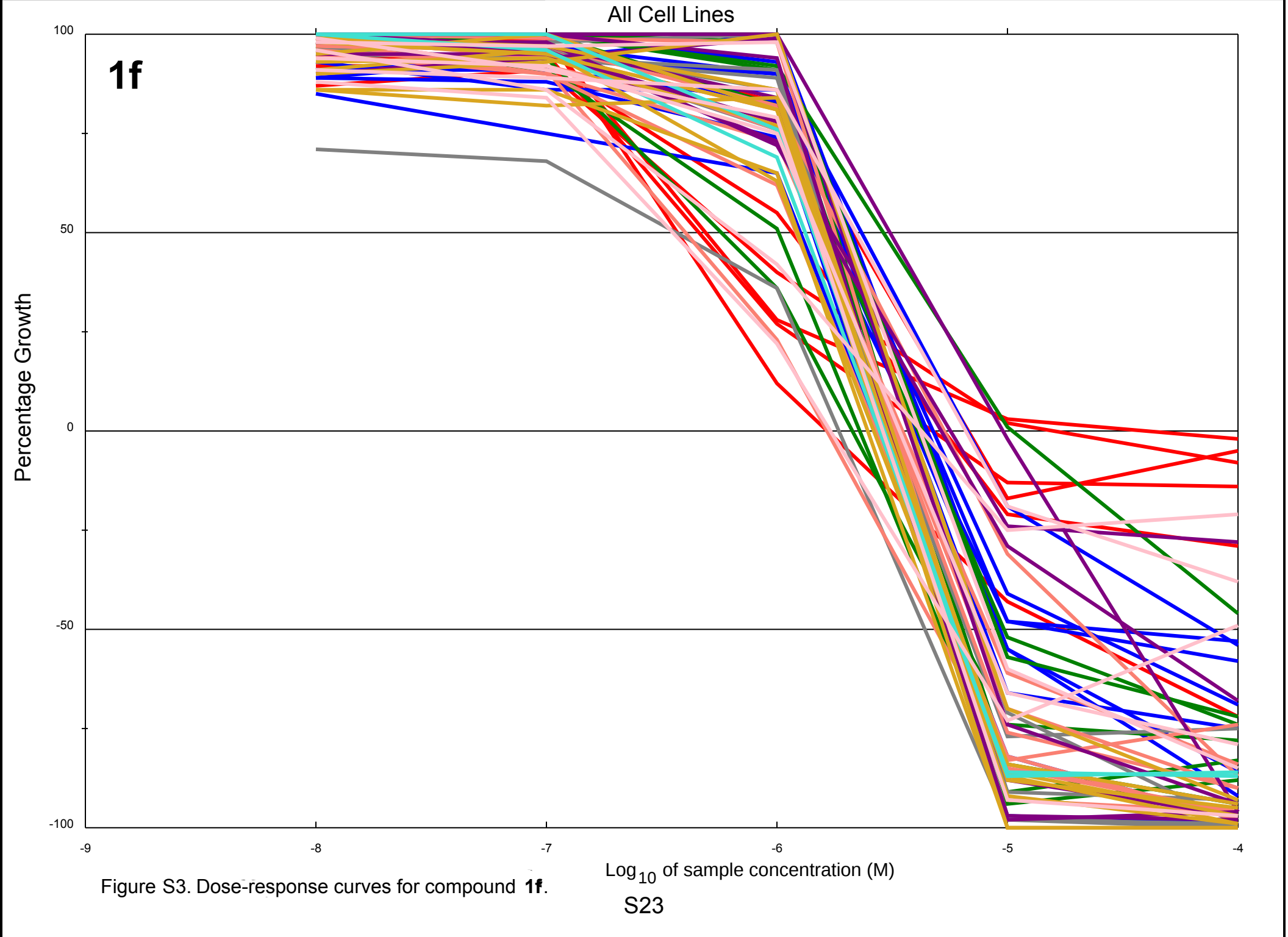
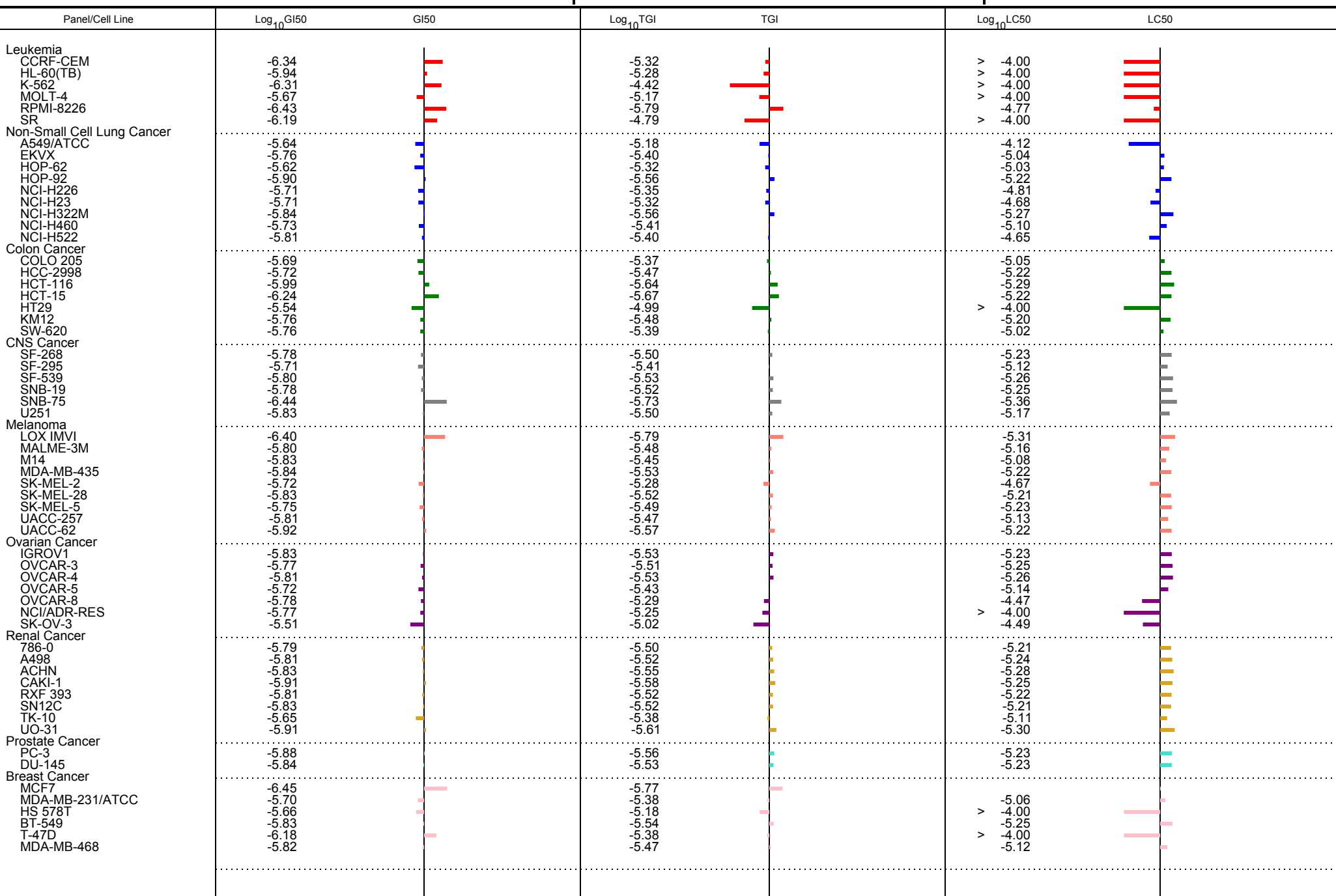
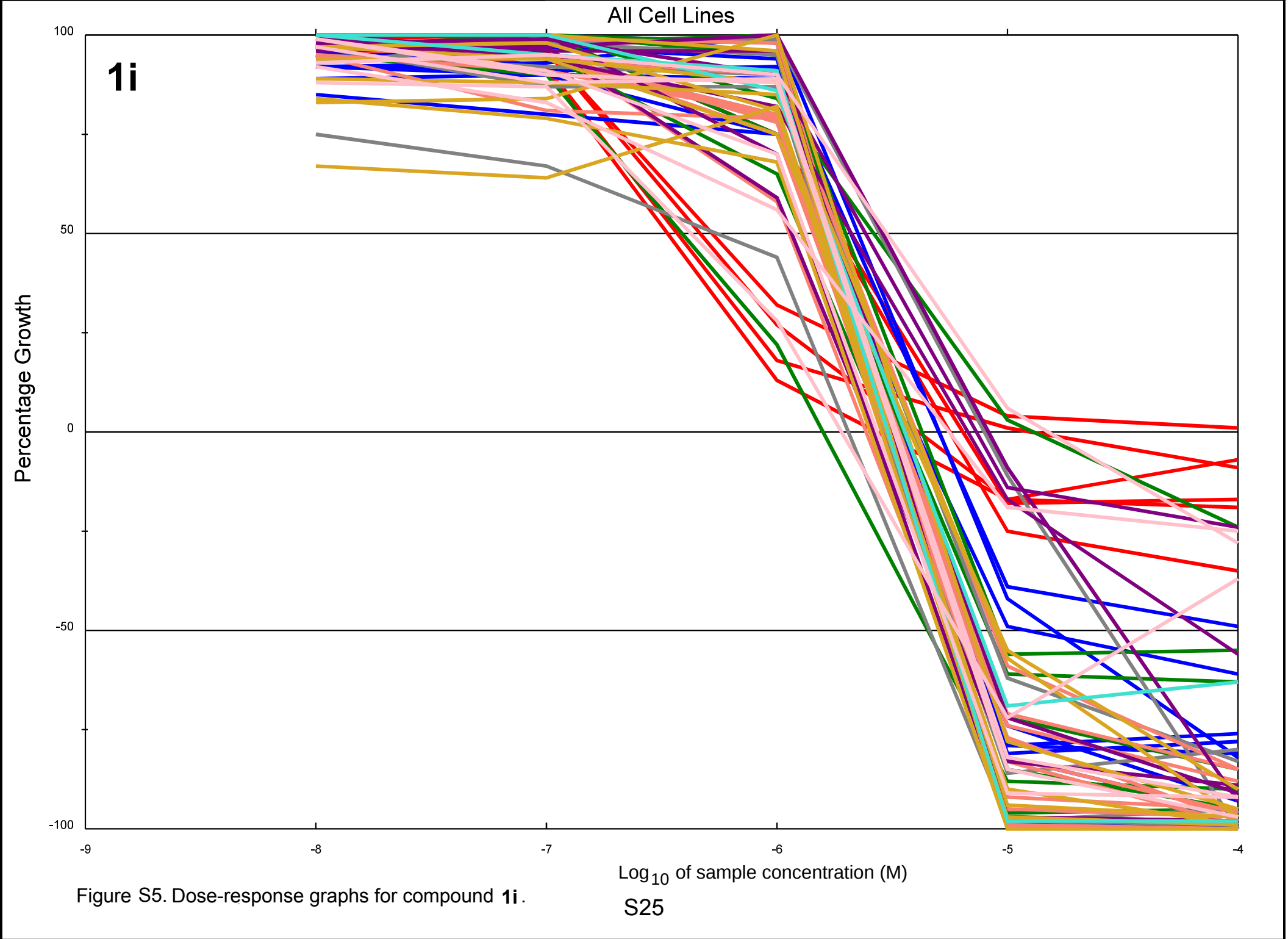


Figure S2. Mean graphs for compound 1a.









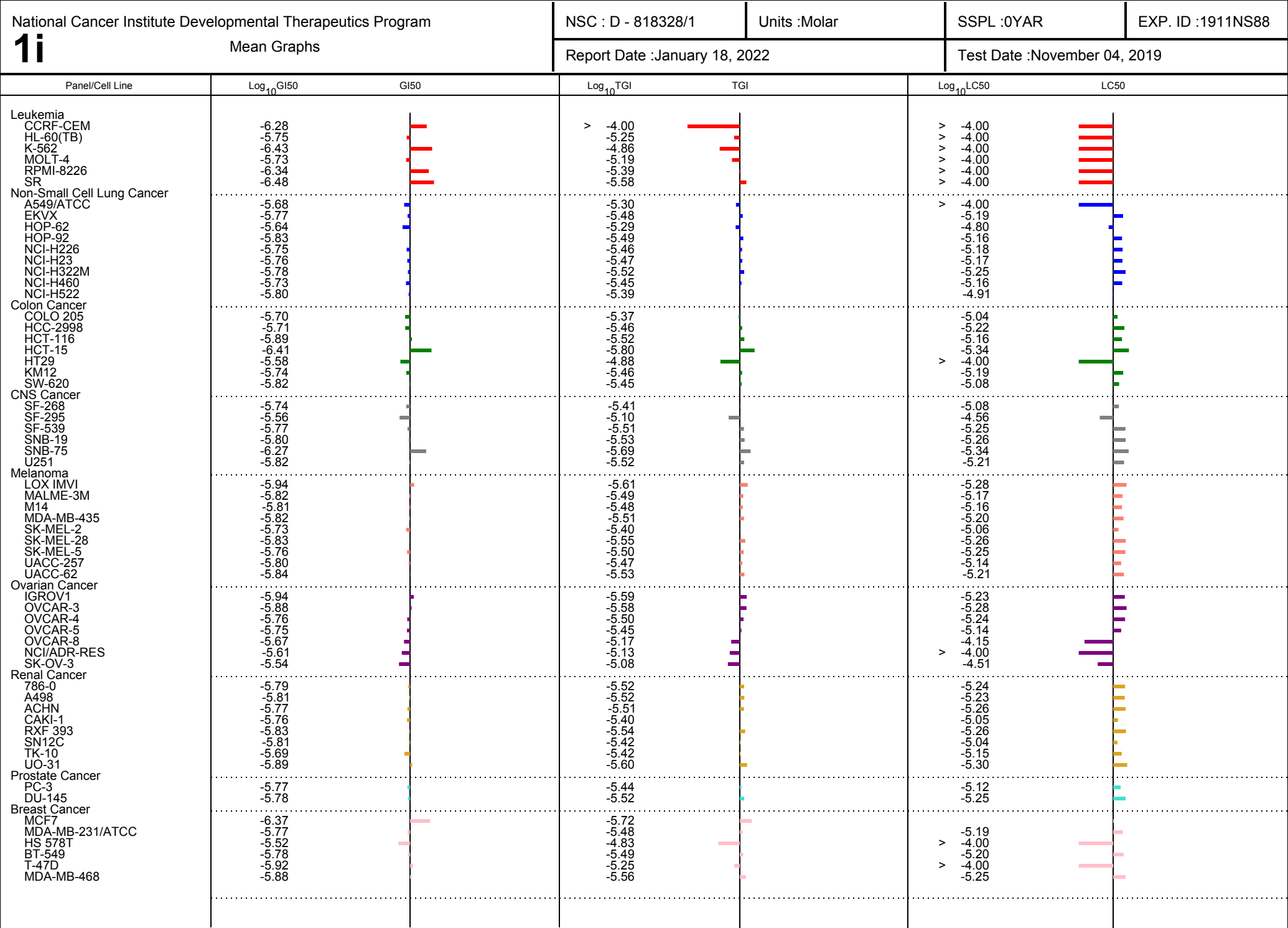
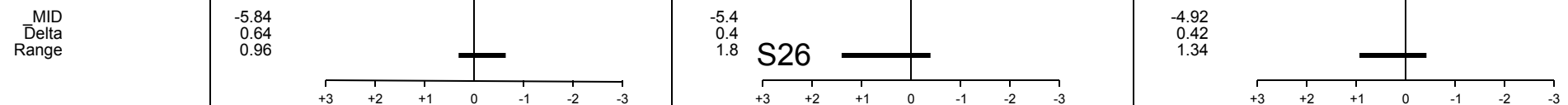
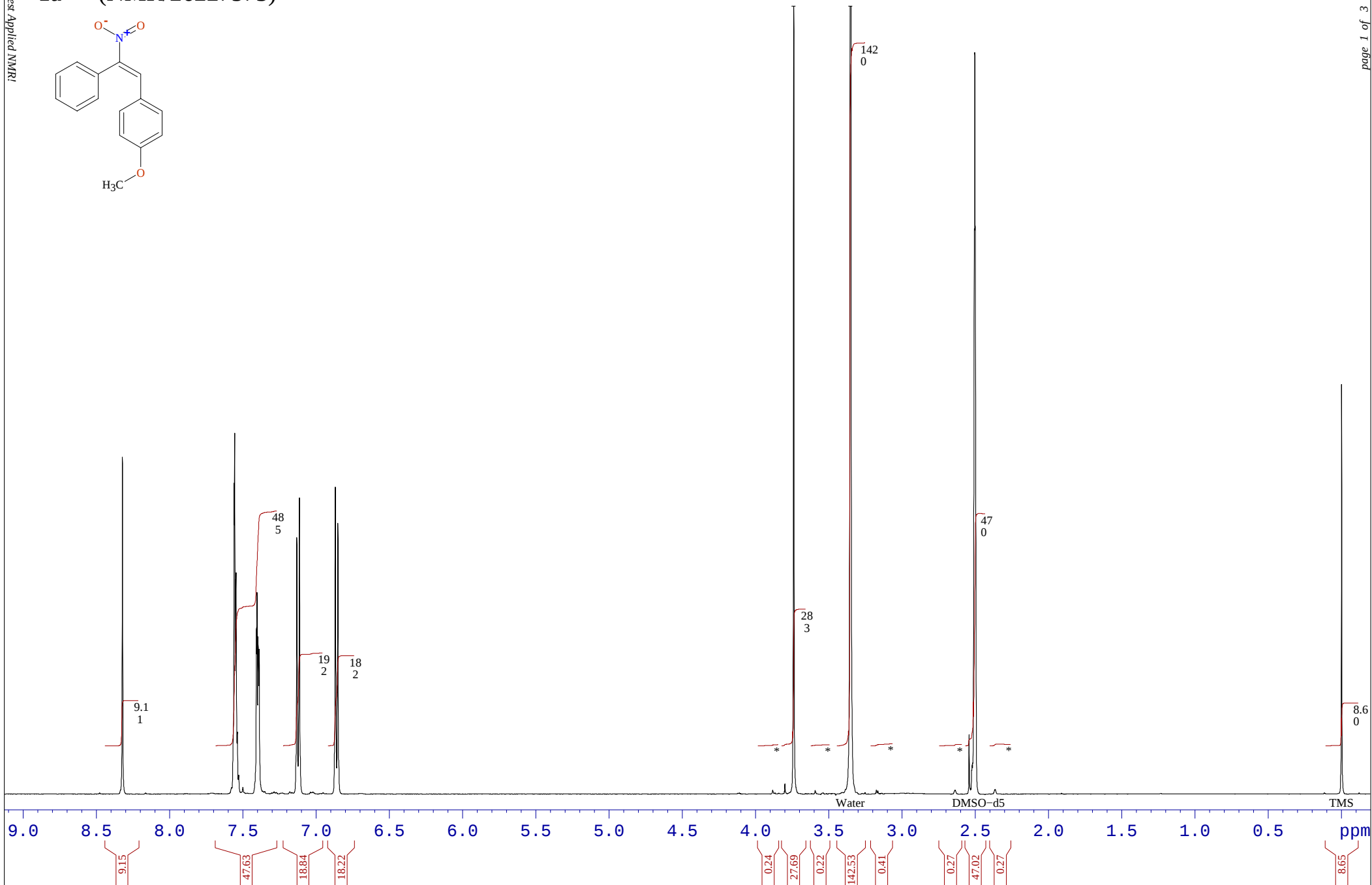
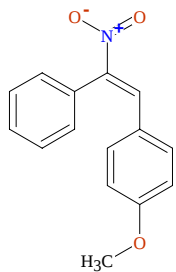


Figure S6. Mean graphs for compound 1i.

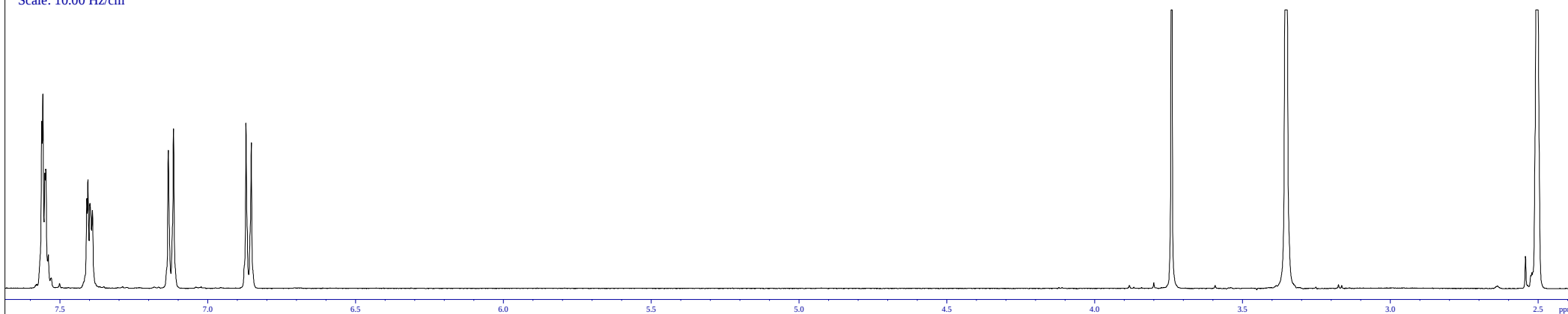
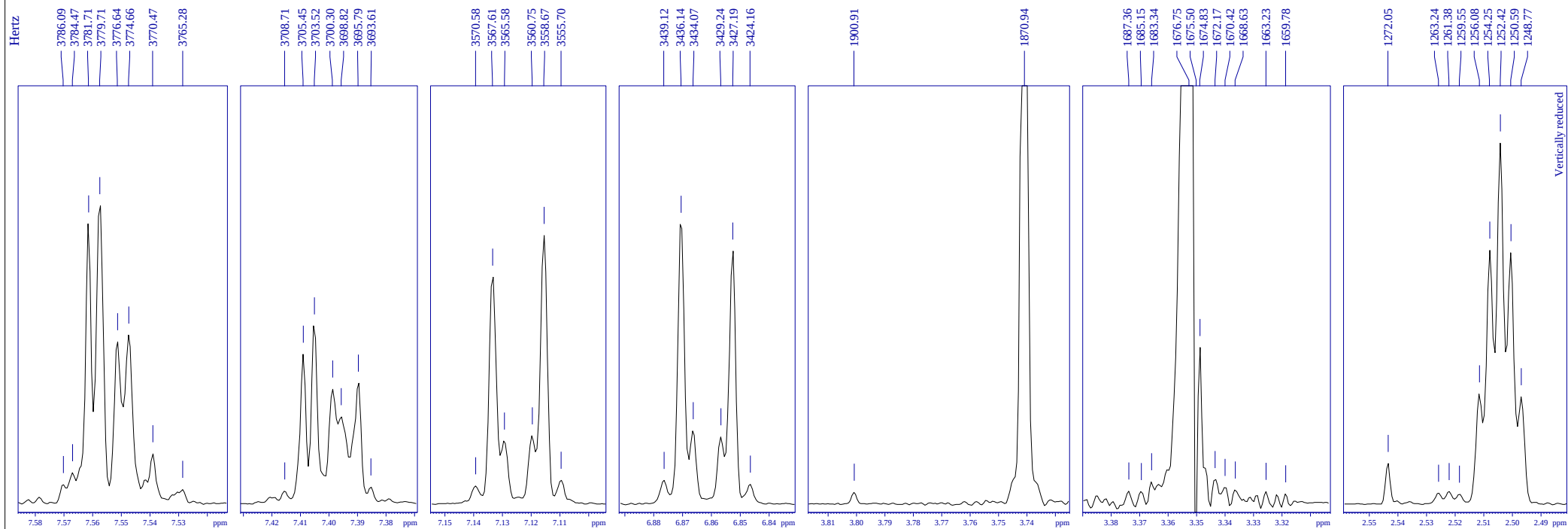


1a (NMR/26227573)

Found protons = 13 impurity* < 0.1 %



1a (NMR/26227573)

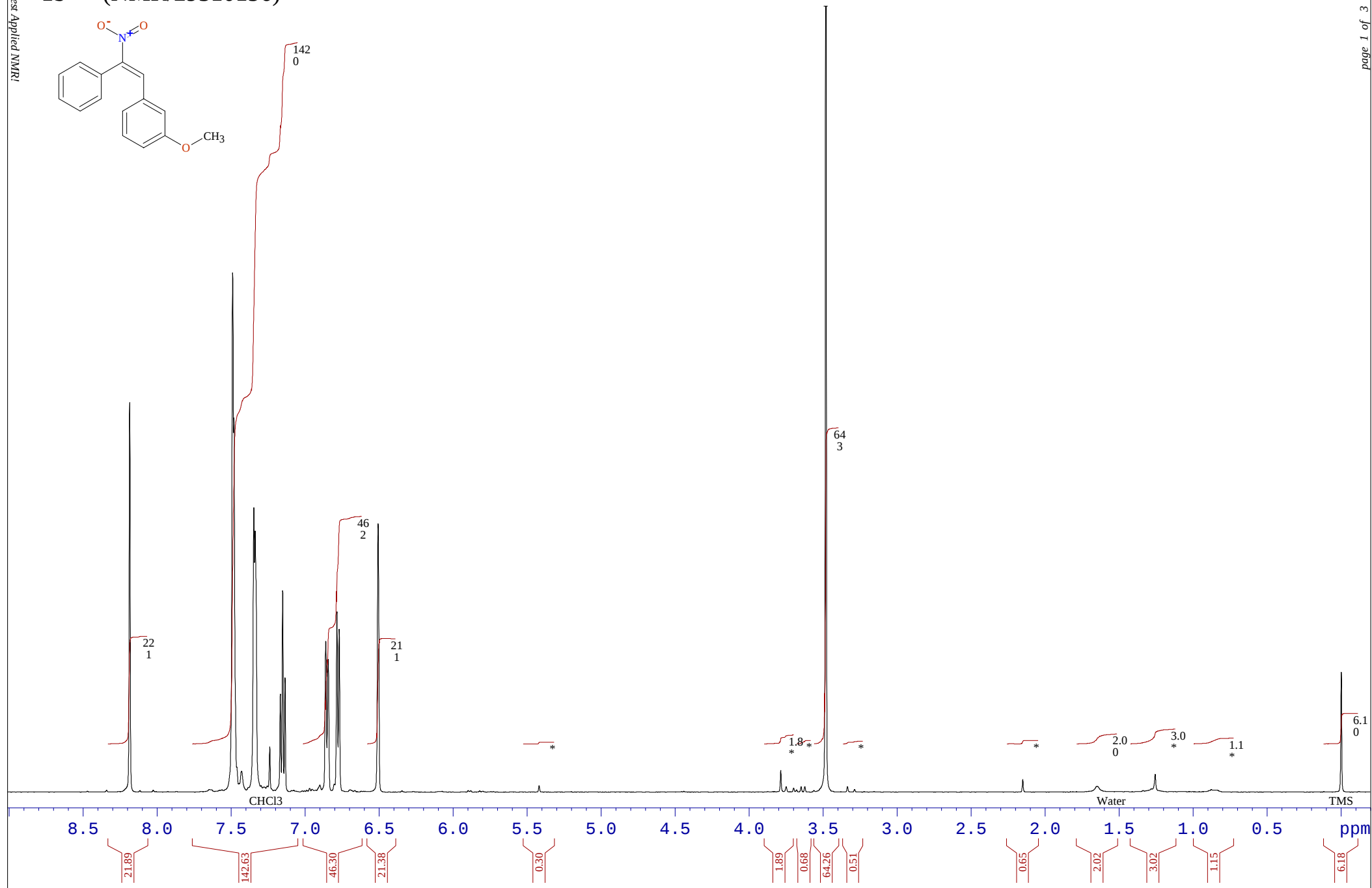
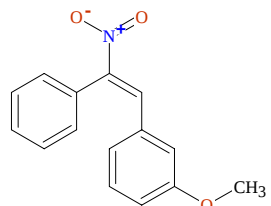


Peaks List

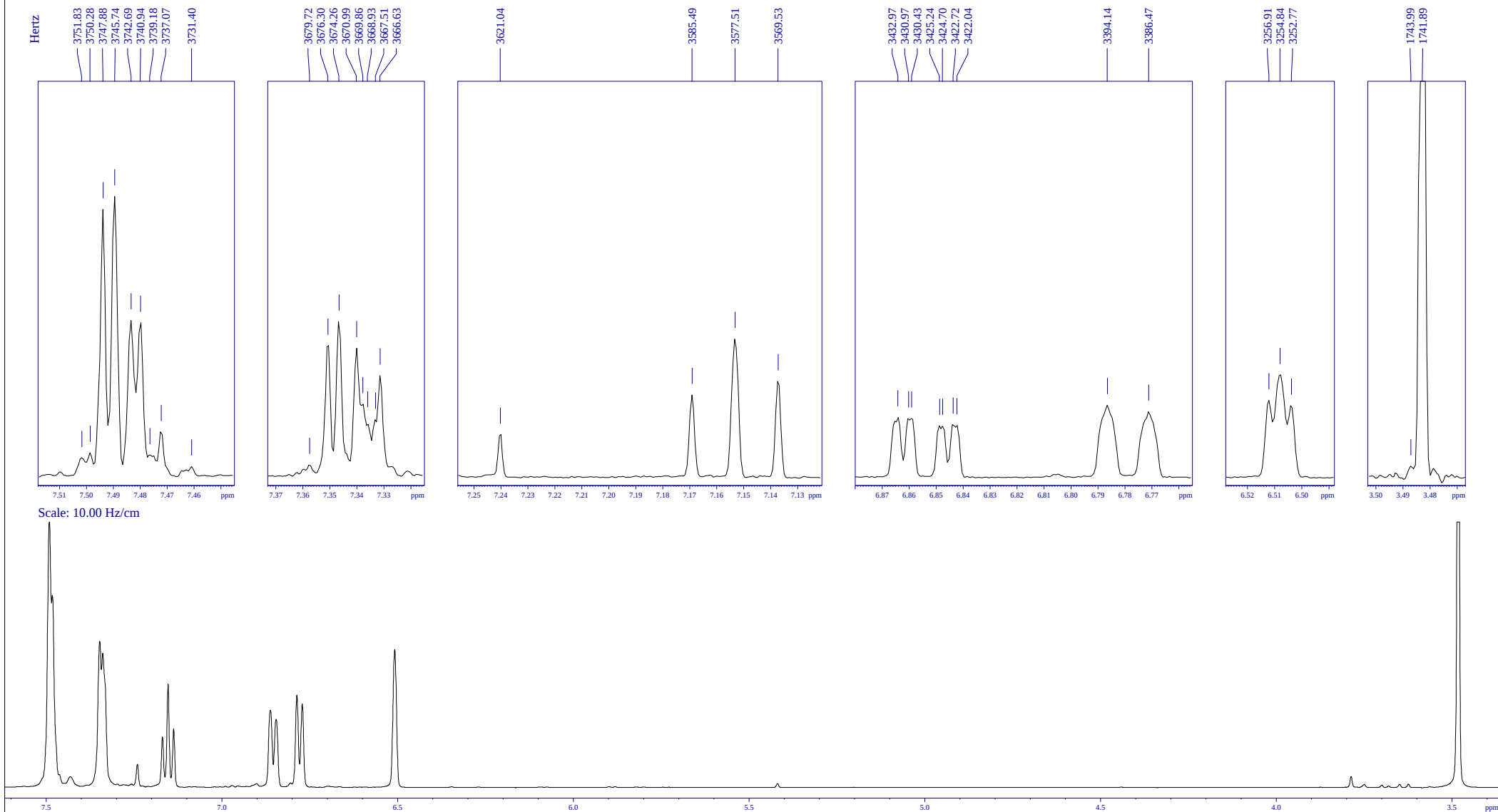
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7	17114.2	3774.663	3.29
8	17127.9	3770.475	0.98
9	17144.9	3765.279	0.29
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12	17347.3	3703.520	3.51
13	17357.9	3700.299	2.23
14	17362.7	3698.818	1.70
15	17372.6	3695.794	2.40
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17	17782.9	3570.582	0.35
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19	17799.3	3565.584	1.23
20	17815.1	3560.750	1.32
21	17822.0	3558.668	5.21
22	17831.7	3555.702	0.47
23	18213.7	3439.117	0.46
24	18223.4	3436.144	5.59
25	18230.3	3434.066	1.43
26	18246.1	3429.235	1.30
27	18252.8	3427.188	4.94
28	18262.7	3424.161	0.39
29	23254.1	1900.906	0.23
30	23352.3	1870.938	23.97
31	23953.9	1687.356	0.25
32	23961.1	1685.149	0.24
33	23967.0	1683.344	0.43
34	23988.6	1676.746	122.49
35	23992.7	1675.498	-2.40
36	23994.9	1674.833	3.04
37	24003.6	1672.167	0.48
38	24009.4	1670.424	0.33
39	24015.2	1668.631	0.27
40	24032.9	1663.230	0.25
41	24044.2	1659.780	0.20
42	25314.7	1272.054	1.33
43	25343.6	1263.244	0.35
44	25349.7	1261.380	0.41
45	25355.7	1259.554	0.32
46	25367.1	1256.075	3.55
47	25373.1	1254.253	8.17
48	25379.1	1252.424	11.61
49	25385.1	1250.594	8.08
50	25391.0	1248.772	3.45
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Found protons = 7 impurity* = 4.1 %

1b (NMR/29310156)



1b (NMR/29310156)

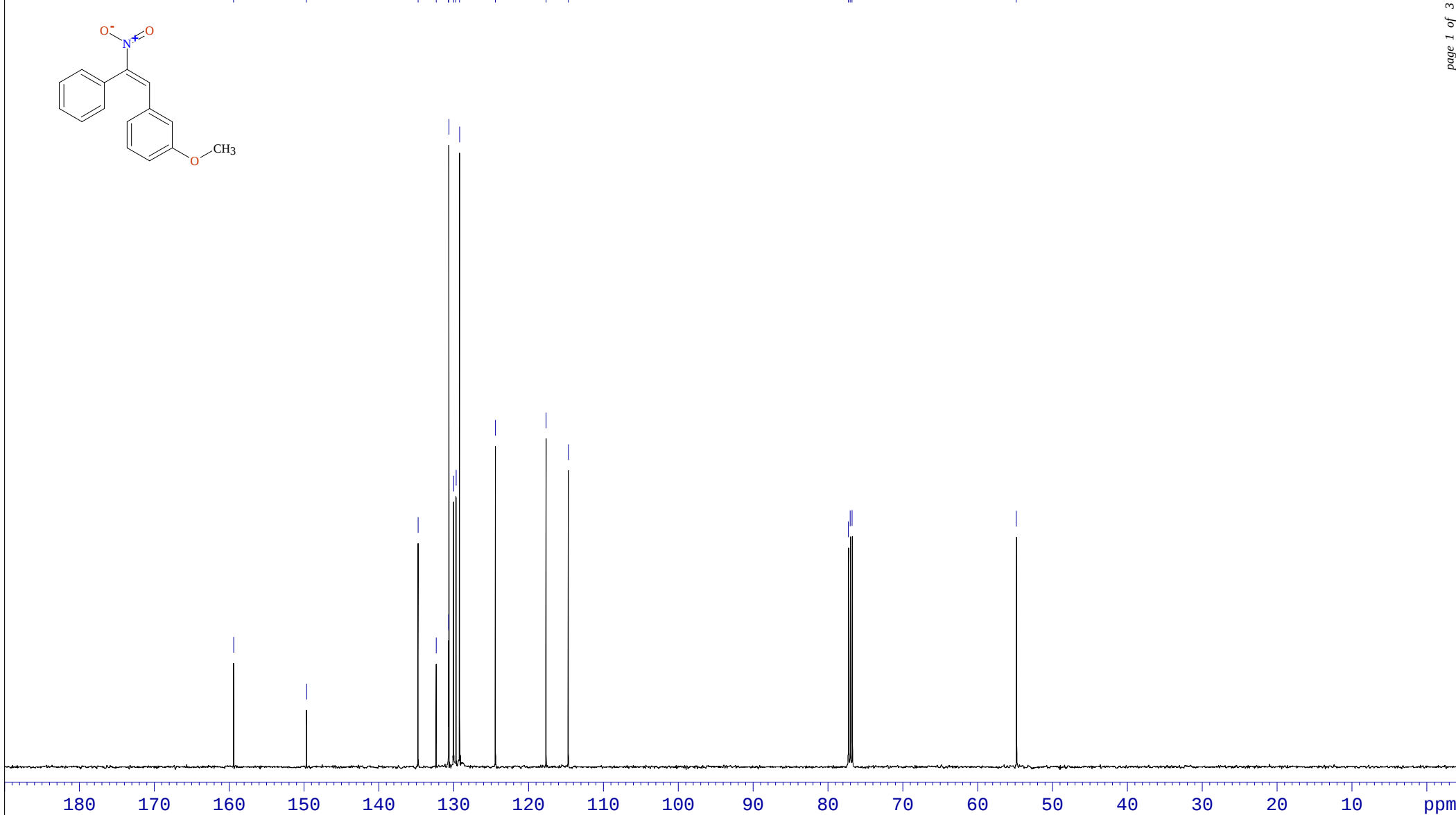
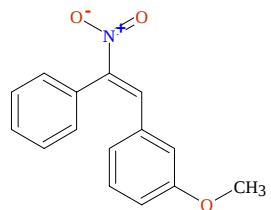


1b (NMR/29310156)

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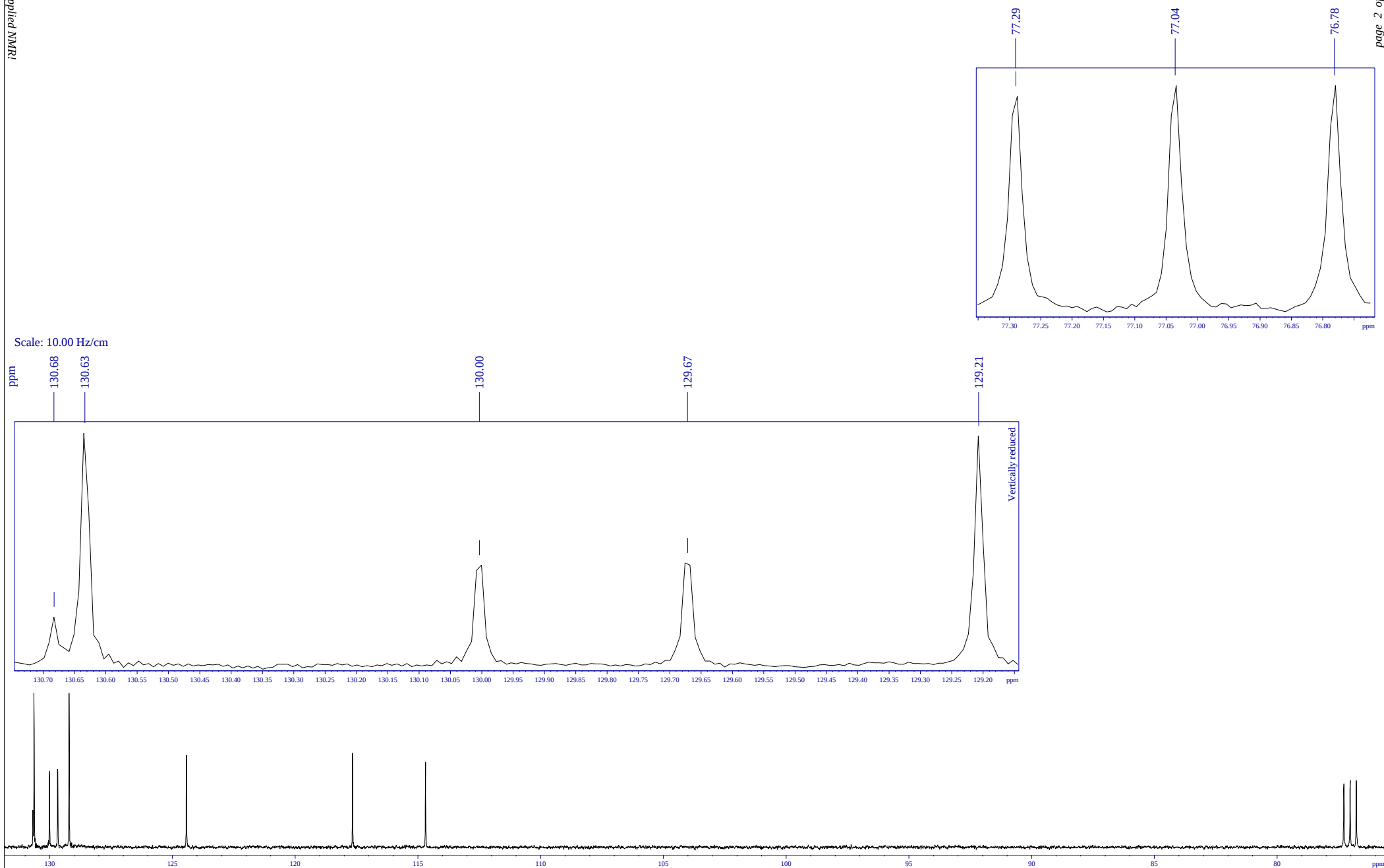
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4	17165.0	3747.878	7.4938	5.49
5	17172.0	3745.736	7.4895	5.75
6	17181.9	3742.692	7.4834	3.22
7	17187.7	3740.936	7.4799	3.21
8	17193.5	3739.179	7.4764	0.46
9	17200.4	3737.071	7.4722	0.96
10	17219.0	3731.399	7.4609	0.23
11	17388.3	3679.718	7.3575	0.27
12	17399.5	3676.295	7.3507	2.83
13	17406.2	3674.257	7.3466	3.21
14	17416.9	3670.986	7.3401	2.65
15	17420.6	3669.861	7.3378	1.53
16	17423.6	3668.933	7.3360	1.11
17	17428.3	3667.506	7.3331	1.20
18	17431.2	3666.630	7.3314	2.10
19	17580.6	3621.044	7.2402	0.92
20	17697.1	3585.495	7.1691	1.69
21	17723.2	3577.507	7.1532	2.85
22	17749.4	3569.526	7.1372	2.02
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24	18203.4	3430.971	6.8602	1.23
25	18205.2	3430.435	6.8591	1.21
26	18222.2	3425.240	6.8487	1.06
27	18223.9	3424.704	6.8476	1.05
28	18230.4	3422.718	6.8437	1.12
29	18232.6	3422.044	6.8423	1.09
30	18324.1	3394.141	6.7865	1.48
31	18349.2	3386.474	6.7712	1.35
32	18773.8	3256.905	6.5121	1.59
33	18780.6	3254.835	6.5080	2.12
34	18787.3	3252.767	6.5038	1.49
35	23238.9	1894.242	3.7875	0.45
36	23731.3	1743.987	3.4871	0.24
37	23738.2	1741.888	3.4829	25.51
38	25919.0	1076.370	2.1522	0.30
39	29446.0	-0.000	-0.0000	2.81

1b (NMR/29310156)



S33

1b (NMR/29310156)



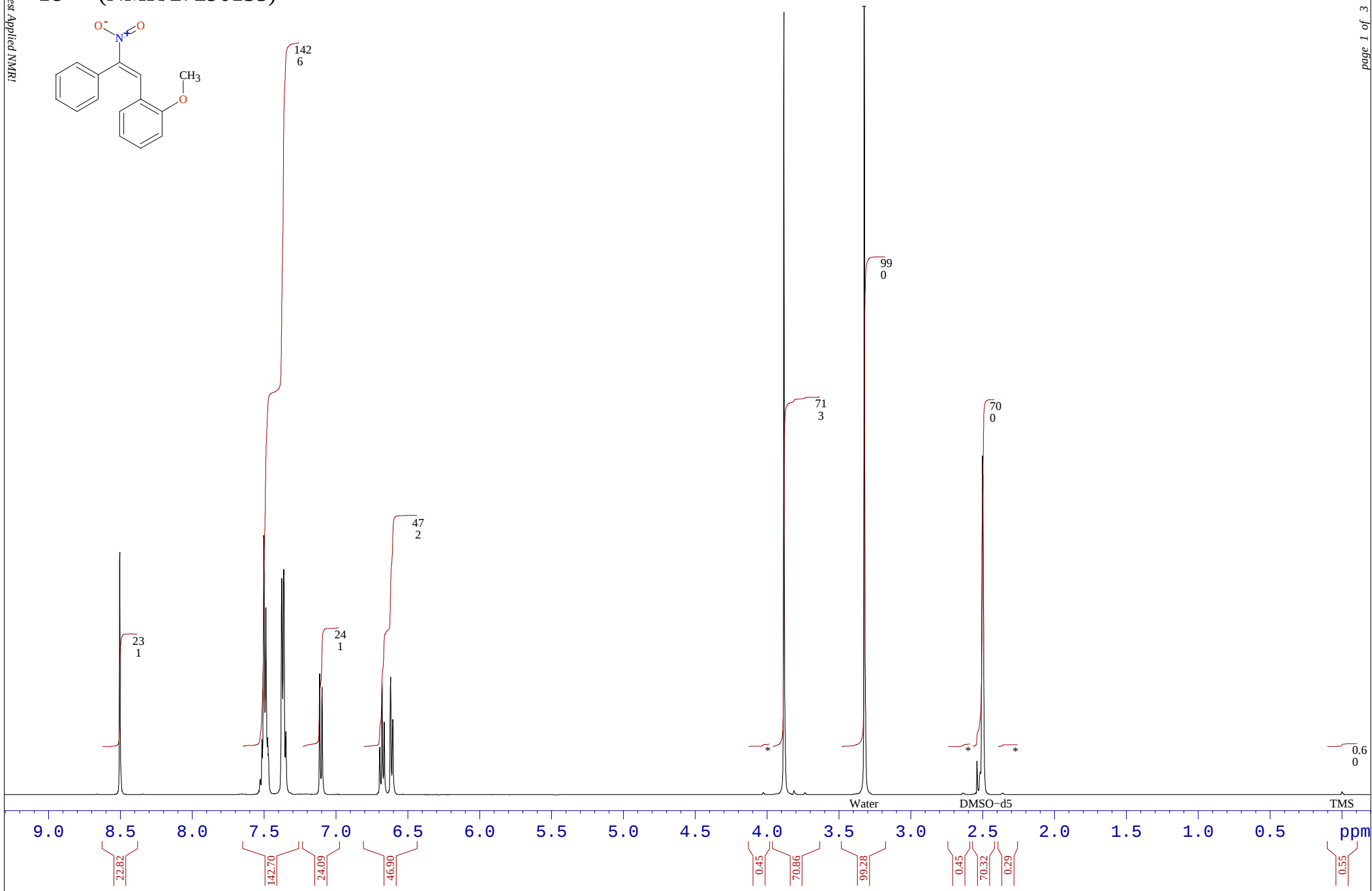
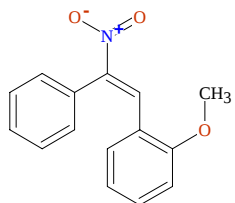
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Peaks List

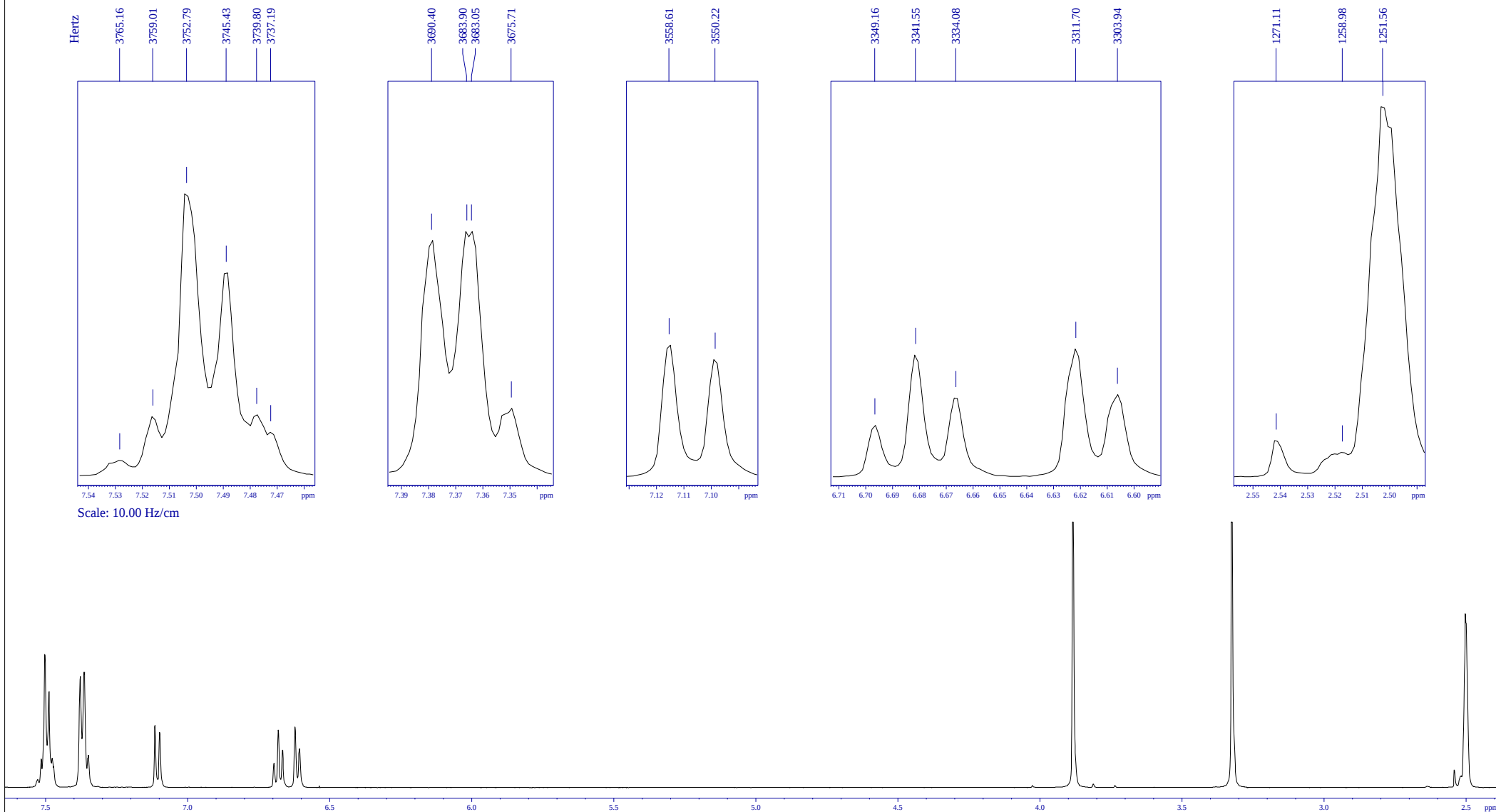
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4	13567.7	16642.080	132.3344	2.19
5	13776.0	16434.342	130.6825	2.49
6	13782.2	16428.172	130.6334	12.00
7	13861.6	16348.990	130.0038	5.49
8	13903.5	16307.196	129.6714	5.66
9	13962.1	16248.771	129.2069	11.70
10	14565.0	15647.485	124.4256	6.18
11	15418.2	14796.570	117.6593	6.42
12	15793.1	14422.671	114.6861	5.74
13	20508.7	9719.801	77.2898	4.40
14	20540.7	9687.812	77.0355	4.57
15	20572.8	9655.827	76.7811	4.53
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1c (NMR/27290135)

Found protons = 13 impurity* < 0.1 %



1c (NMR/27290135)

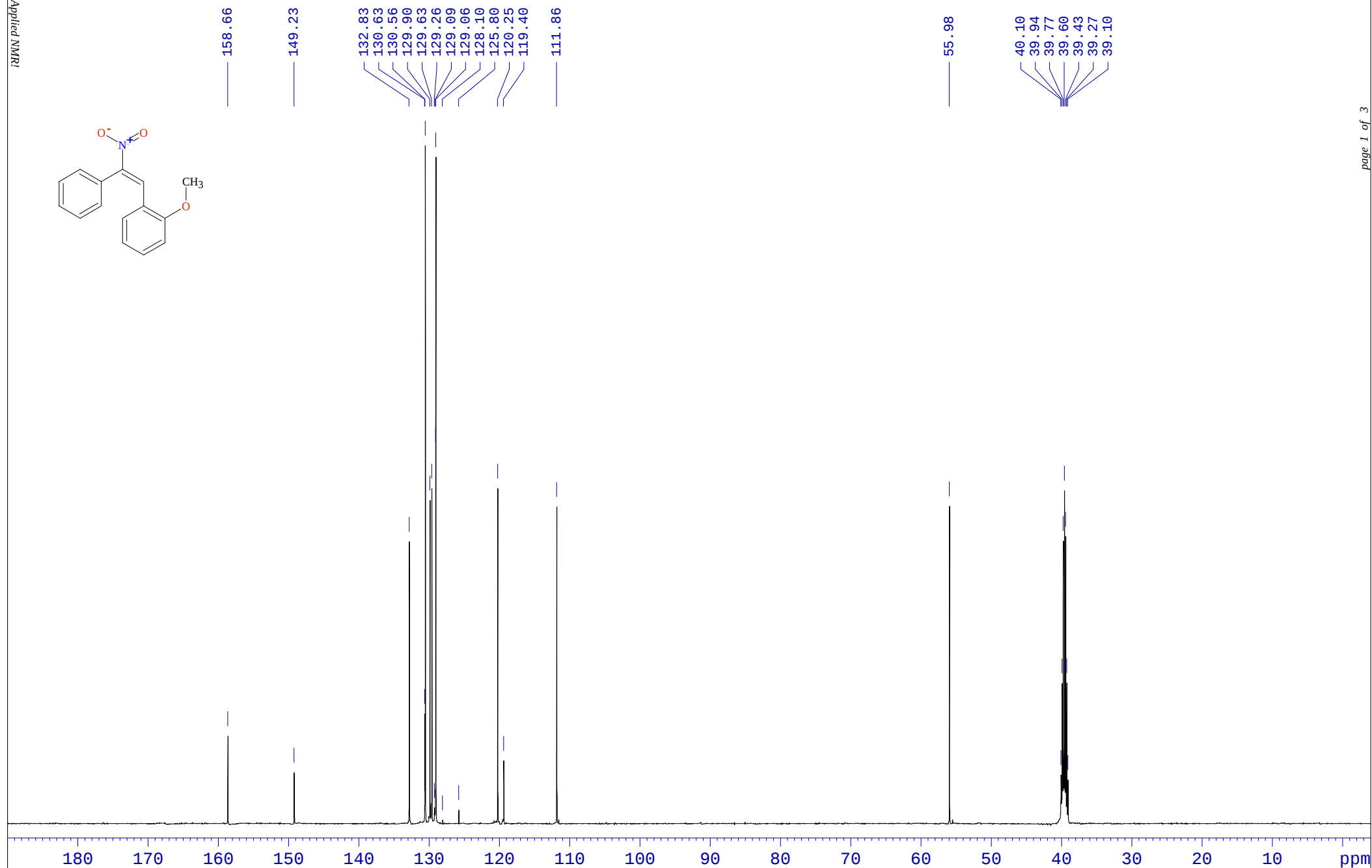
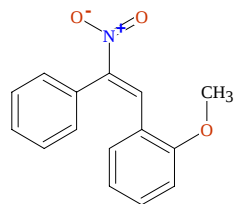


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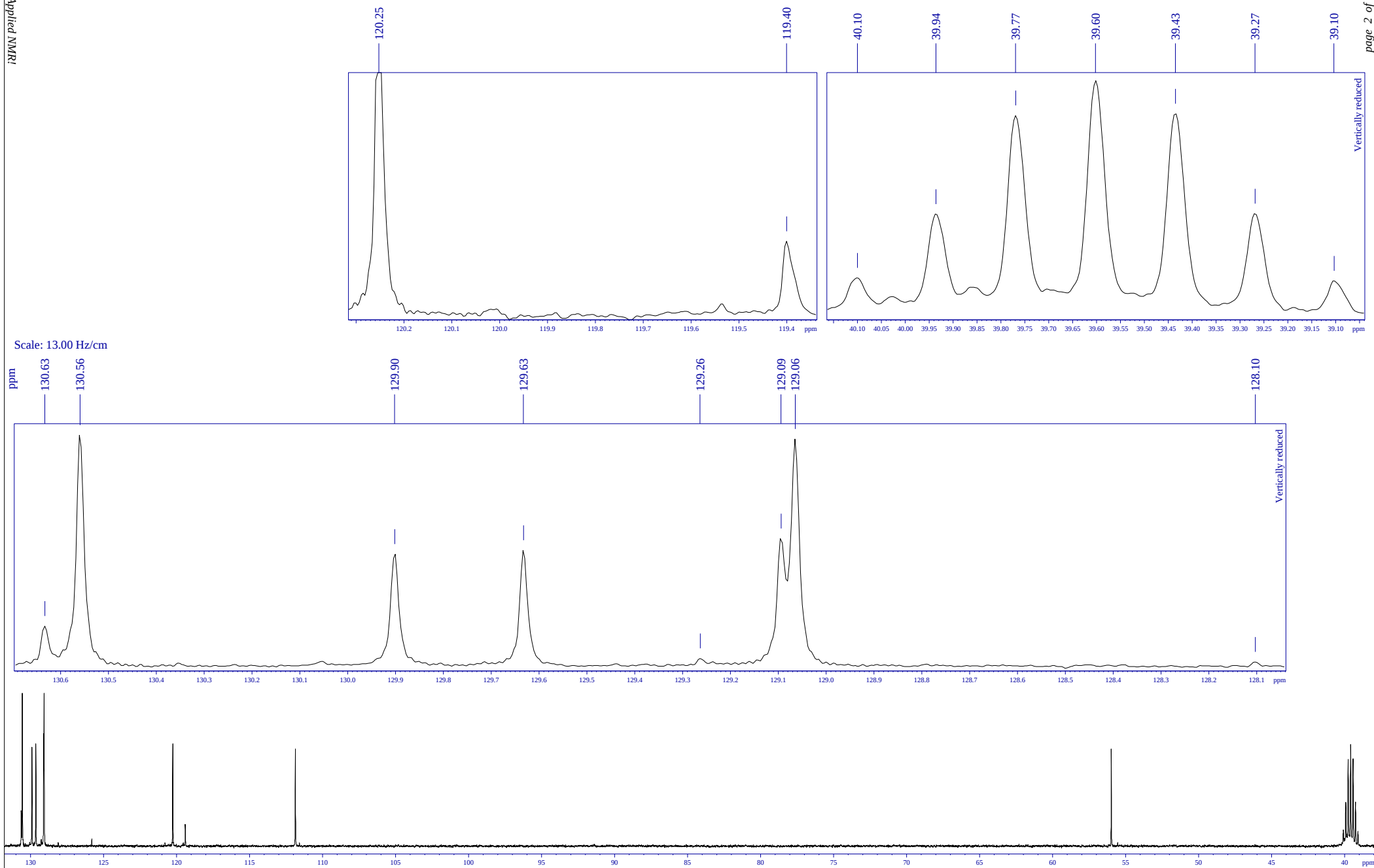
Peaks List

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3	8580.3	3759.006	7.5161	1.14
4	8590.5	3752.794	7.5036	5.38
5	8602.5	3745.435	7.4889	3.87
6	8611.8	3739.796	7.4776	1.16
7	8616.0	3737.194	7.4724	0.84
8	8692.7	3690.404	7.3789	4.40
9	8703.3	3683.896	7.3659	4.58
10	8704.7	3683.045	7.3642	4.55
11	8716.8	3675.711	7.3495	1.28
12	8908.6	3558.615	7.1154	2.49
13	8922.4	3550.223	7.0986	2.21
14	9251.8	3349.162	6.6966	0.97
15	9264.2	3341.553	6.6814	2.28
16	9276.5	3334.082	6.6664	1.50
17	9313.1	3311.704	6.6217	2.38
18	9325.9	3303.937	6.6062	1.53
19	11555.9	1942.831	3.8847	15.80
20	12013.8	1663.336	3.3258	23.81
21	12656.5	1271.105	2.5415	0.73
22	12676.3	1258.979	2.5173	0.47
23	12688.5	1251.563	2.5025	6.99

1c (NMR/27290135)



1c (NMR/27290135)



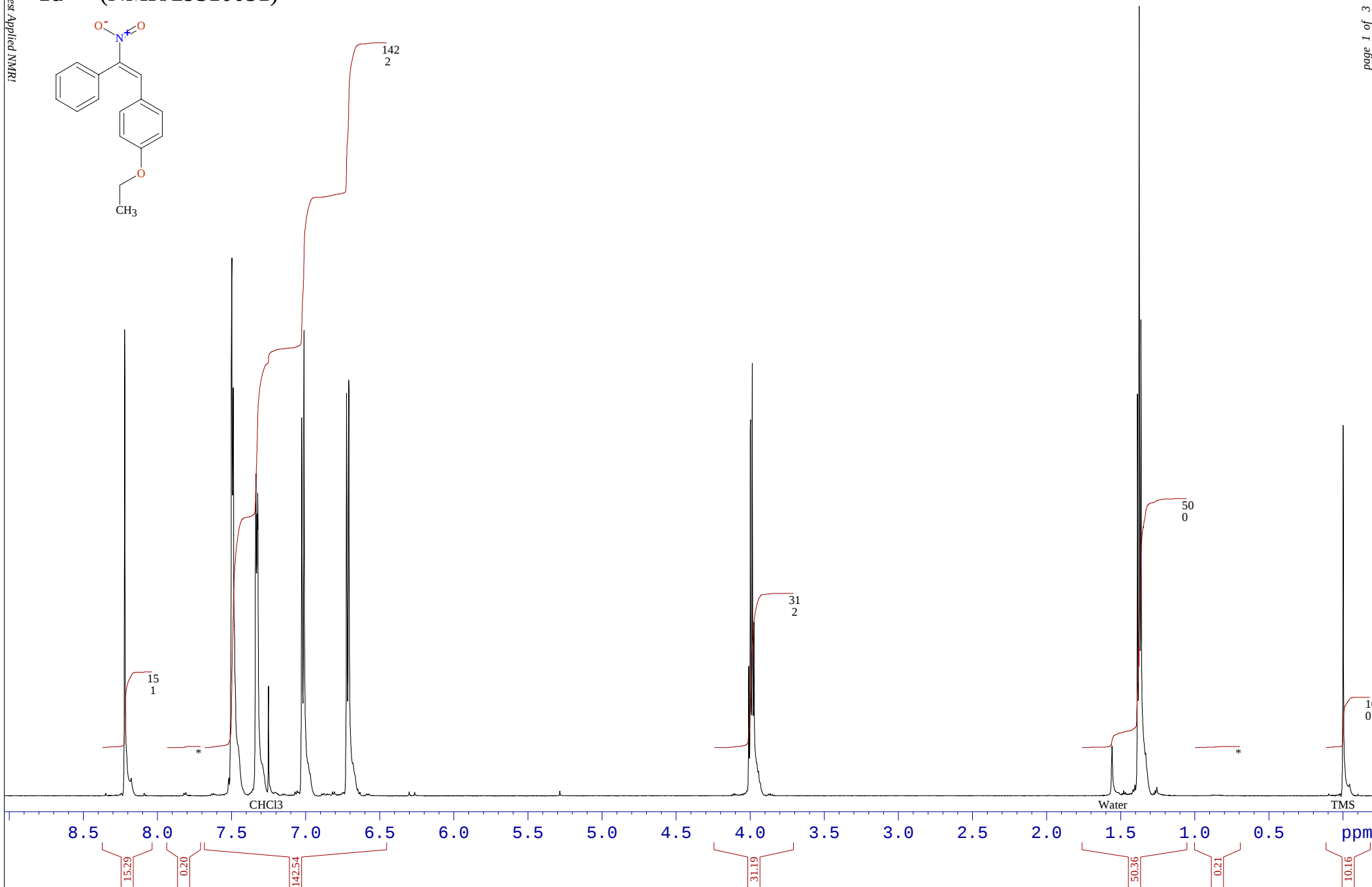
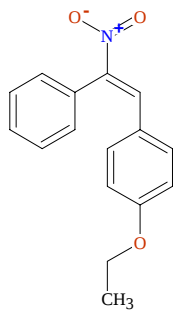
1c (NMR/27290135)

Peaks List

#	Address [points]	Frequency [Hz]	Frequency [ppm]	Intensity [cm]
1	18703.4	19953.293	158.6644	2.01
2	21175.2	18767.242	149.2332	1.22
3	25473.2	16704.869	132.8336	5.91
4	26050.0	16428.115	130.6329	2.40
5	26069.3	16418.854	130.5593	14.00
6	26241.7	16336.146	129.9016	6.79
7	26312.2	16302.291	129.6324	6.99
8	26409.0	16255.838	129.2630	0.47
9	26453.3	16234.584	129.0940	7.73
10	26461.1	16230.869	129.0645	13.60
11	26713.1	16109.943	128.1029	0.26
12	27317.1	15820.127	125.7983	0.47
13	28770.7	15122.634	120.2520	7.04
14	28993.9	15015.521	119.4003	1.47
15	30971.1	14066.776	111.8561	6.60
16	45616.6	7039.364	55.9755	6.73
17	49777.3	5042.885	40.1000	1.10
18	49820.4	5022.234	39.9358	2.98
19	49864.1	5001.266	39.7690	5.88
20	49907.9	4980.220	39.6017	6.91
21	49951.7	4959.243	39.4349	5.95
22	49995.3	4938.304	39.2684	2.99
23	50038.6	4917.519	39.1031	1.01

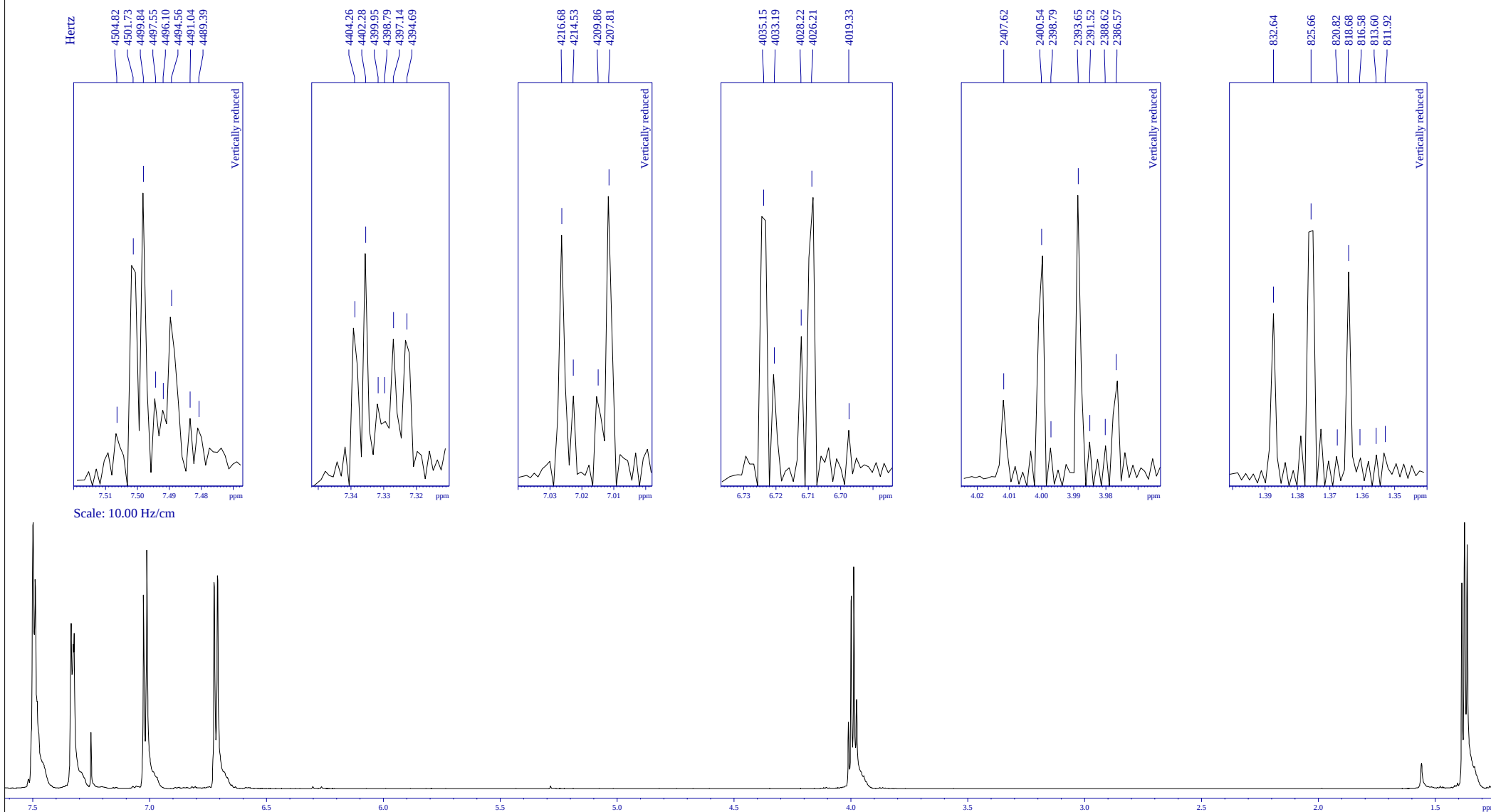
Found protons = 5 impurity* < 0.1 %

1d (NMR/29310051)



S42

1d (NMR/29310051)

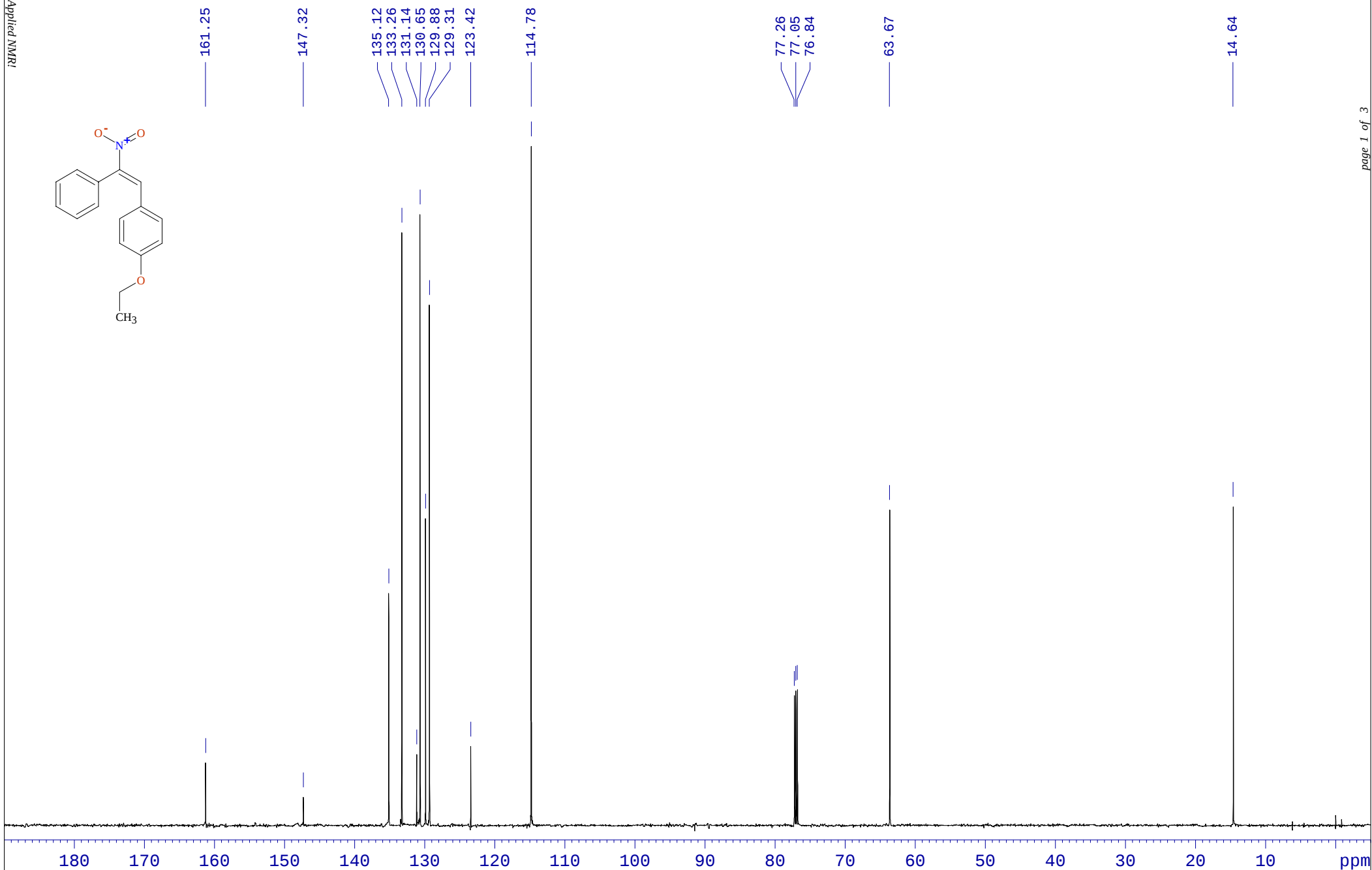
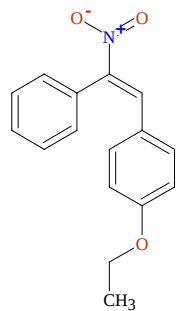


1d (NMR/29310051)

Peaks List

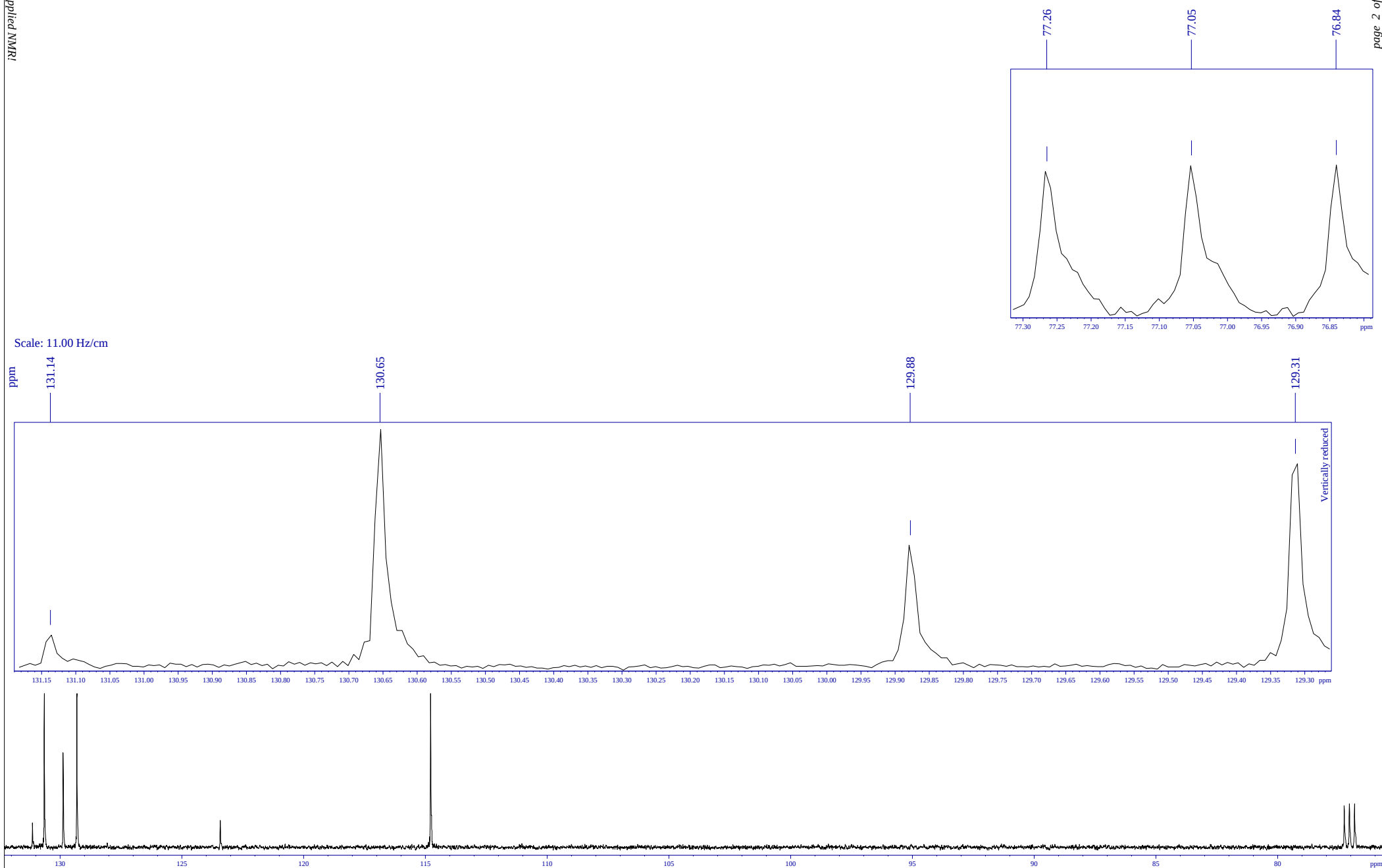
#	Address [points]	Frequency [Hz]	Intensity [ppm]	Intensity [cm]
1	7995.3	4933.977	8.2215	7.99
2	8580.3	4504.816	7.5064	1.34
3	8584.5	4501.729	7.5013	7.00
4	8587.0	4499.841	7.4981	8.26
5	8590.2	4497.554	7.4943	2.34
6	8592.2	4496.095	7.4919	1.98
7	8594.2	4494.557	7.4893	4.79
8	8599.0	4491.044	7.4835	1.73
9	8601.3	4489.392	7.4807	1.51
10	8717.3	4404.260	7.3388	4.00
11	8720.0	4402.282	7.3355	5.51
12	8723.2	4399.948	7.3317	1.86
13	8724.8	4398.794	7.3297	1.40
14	8727.0	4397.139	7.3270	3.42
15	8730.4	4394.687	7.3229	3.58
16	8789.1	4351.624	7.2511	2.74
17	8973.0	4216.675	7.0263	7.00
18	8976.0	4214.529	7.0227	2.36
19	8982.3	4209.864	7.0149	2.53
20	8985.1	4207.806	7.0115	8.21
21	9220.5	4035.154	6.7238	7.22
22	9223.2	4033.186	6.7205	2.61
23	9229.9	4028.218	6.7122	3.49
24	9232.7	4026.213	6.7089	7.34
25	9242.1	4019.331	6.6974	1.18
26	11439.1	2407.616	4.0118	2.61
27	11448.7	2400.539	4.0000	7.86
28	11451.1	2398.792	3.9971	1.01
29	11458.1	2393.654	3.9886	9.52
30	11461.0	2391.523	3.9850	1.21
31	11465.0	2388.617	3.9802	1.08
32	11467.7	2386.571	3.9768	3.38
33	13586.0	832.641	1.3874	9.23
34	13595.5	825.658	1.3758	16.00
35	13602.1	820.818	1.3677	1.24
36	13605.0	818.680	1.3642	11.56
37	13607.9	816.583	1.3607	1.14
38	13611.9	813.603	1.3557	1.32
39	13614.2	811.921	1.3529	1.50
40	14721.0	-0.001	-0.0000	9.19

1d (NMR/29310051)



S45

1d (NMR/29310051)



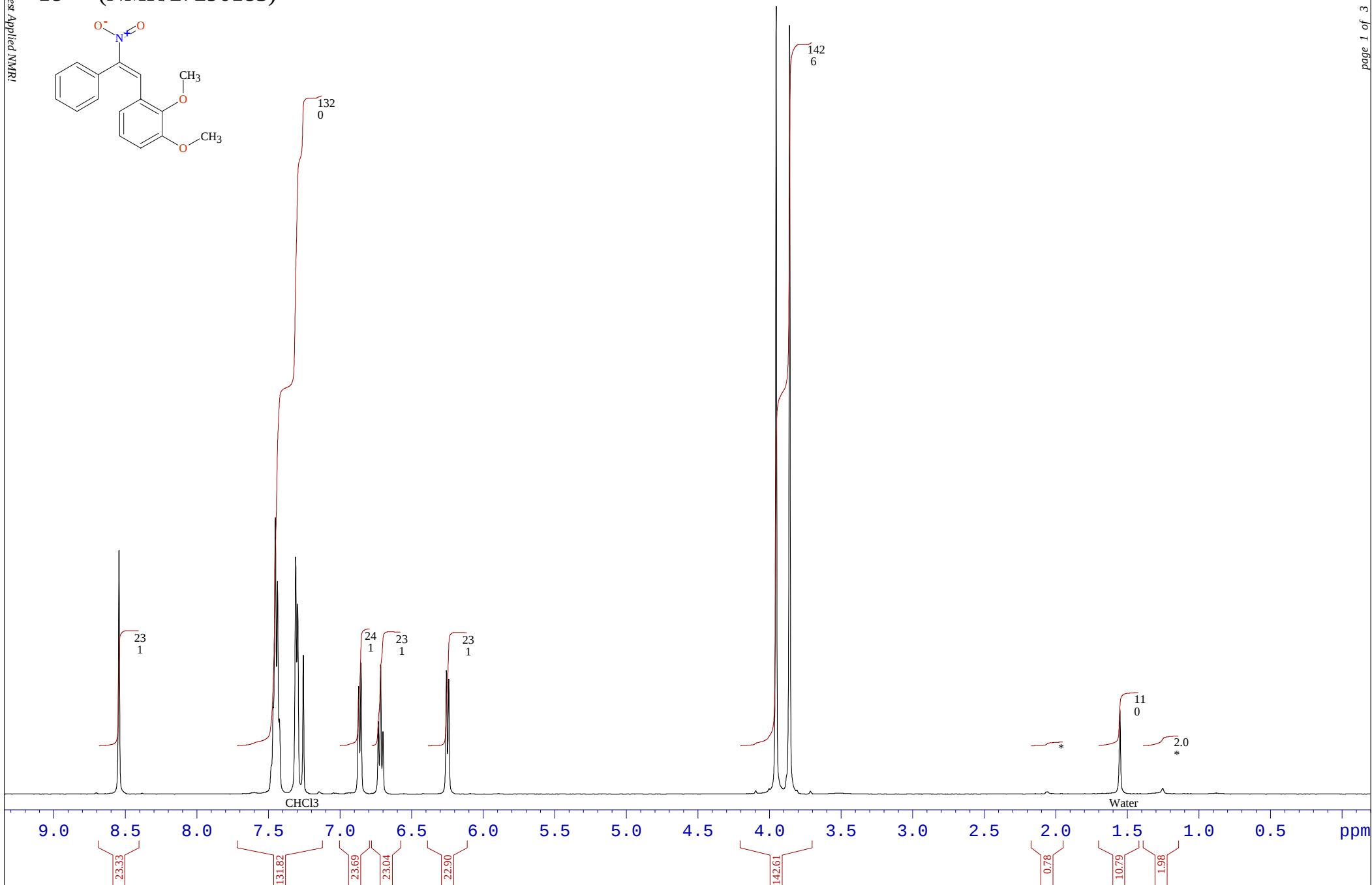
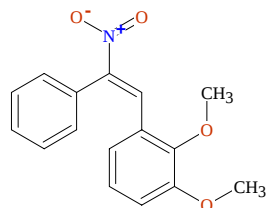
1d (NMR/29310051)

Peaks List

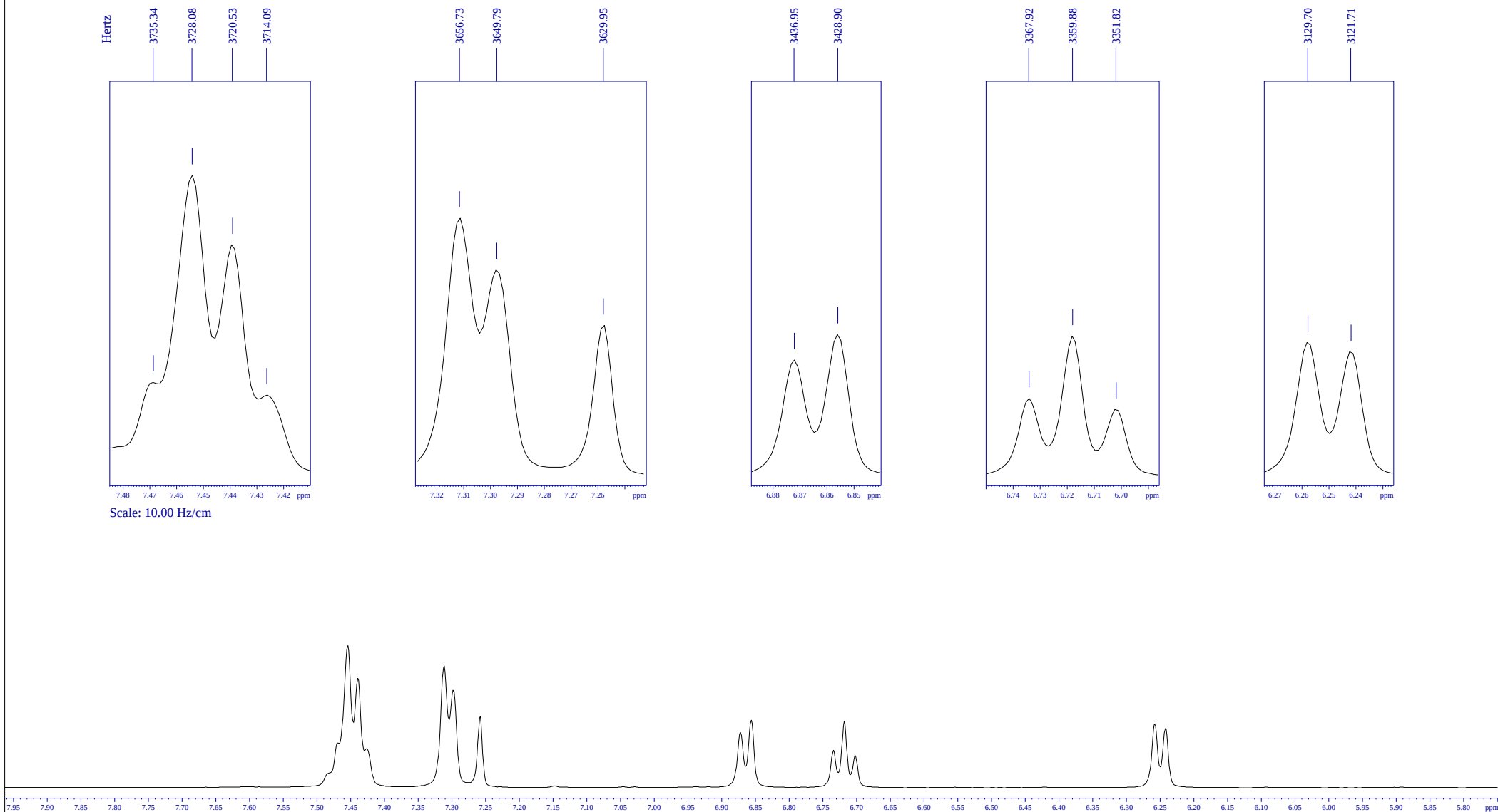
#	Address [points]	Frequency [Hz]	Intensity [ppm]	Intensity [cm]
1	11046.4	24333.666	161.2539	1.54
2	12810.5	22230.674	147.3178	0.76
3	14354.2	20390.400	135.1227	4.88
4	14590.4	20108.834	133.2569	12.71
5	14858.8	19788.953	131.1371	1.66
6	14919.9	19716.070	130.6541	12.36
7	15018.2	19598.896	129.8776	6.40
8	15089.6	19513.803	129.3137	11.11
9	15835.1	18625.137	123.4247	1.79
10	16928.7	17321.357	114.7849	14.00
11	21678.3	11659.469	77.2648	2.83
12	21705.1	11627.489	77.0528	2.90
13	21732.0	11595.432	76.8404	2.90
14	23398.9	9608.373	63.6726	6.52
15	29605.1	2209.907	14.6446	6.59

1e (NMR/27290183)

Found protons = 10 impurity* = 0.3 %



1e (NMR/27290183)

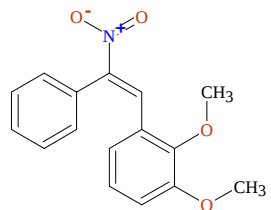


1e (NMR/27290183)

Peaks List

#	Address	Frequency		Intensity
	[points]	[Hz]	[ppm]	[cm]
1	7734.5	4273.947	8.5457	4.99
2	8617.0	3735.340	7.4687	1.76
3	8628.9	3728.083	7.4542	5.59
4	8641.3	3720.532	7.4391	4.31
5	8651.8	3714.092	7.4263	1.53
6	8745.8	3656.726	7.3116	4.80
7	8757.2	3649.791	7.2977	3.84
8	8789.7	3629.953	7.2580	2.83
9	9105.9	3436.954	6.8721	2.18
10	9119.1	3428.902	6.8560	2.65
11	9219.0	3367.921	6.7341	1.46
12	9232.1	3359.878	6.7180	2.62
13	9245.3	3351.821	6.7019	1.27
14	9609.3	3129.702	6.2578	2.51
15	9622.4	3121.711	6.2418	2.34
16	11496.8	1977.647	3.9543	16.00
17	11573.1	1931.065	3.8611	15.54
18	13464.2	776.851	1.5533	1.73

1e (NMR/27290183)



152.66
150.40
149.45

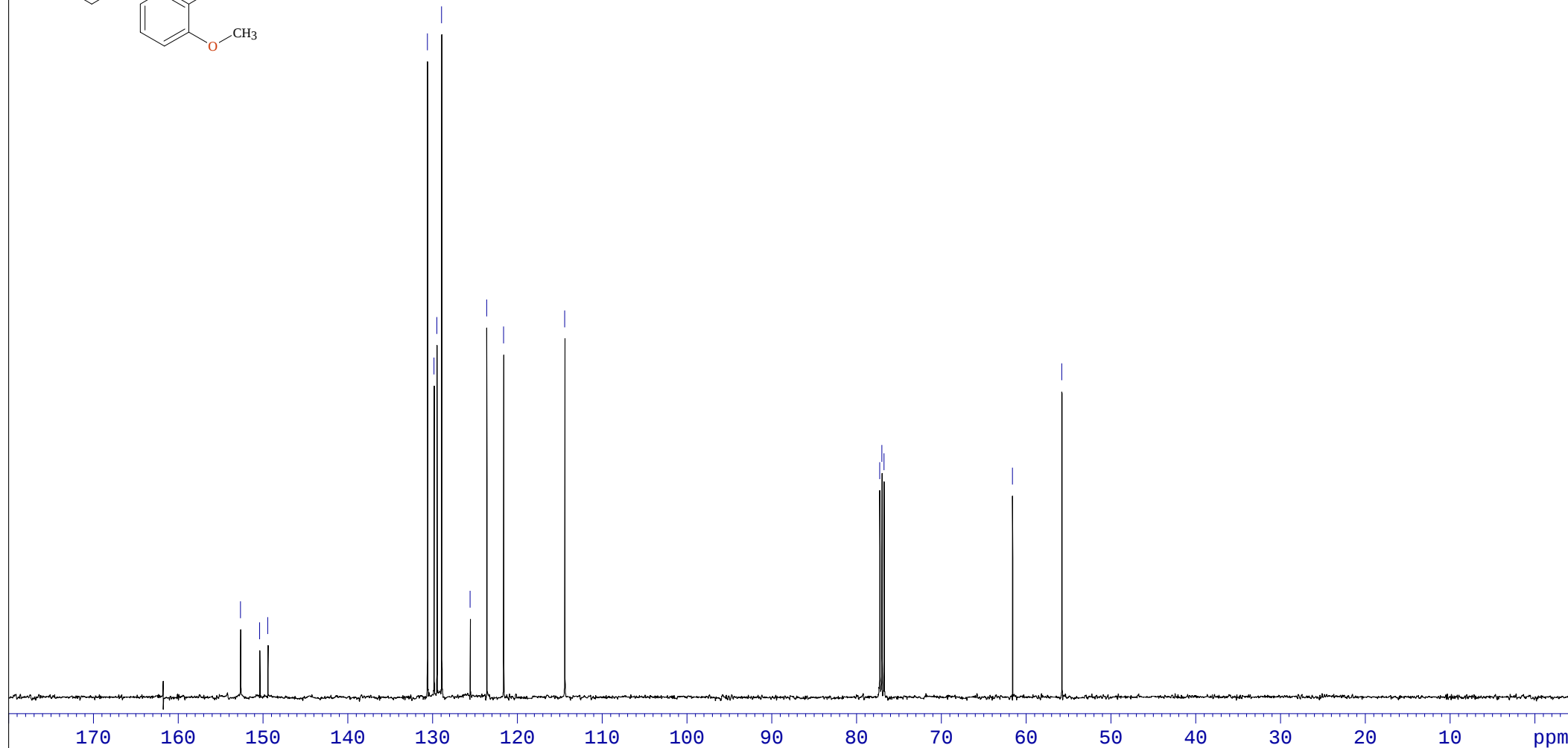
130.61
129.84
129.50
128.95
125.58
123.62
121.63

114.43

77.27
77.02
76.76

61.62

55.80

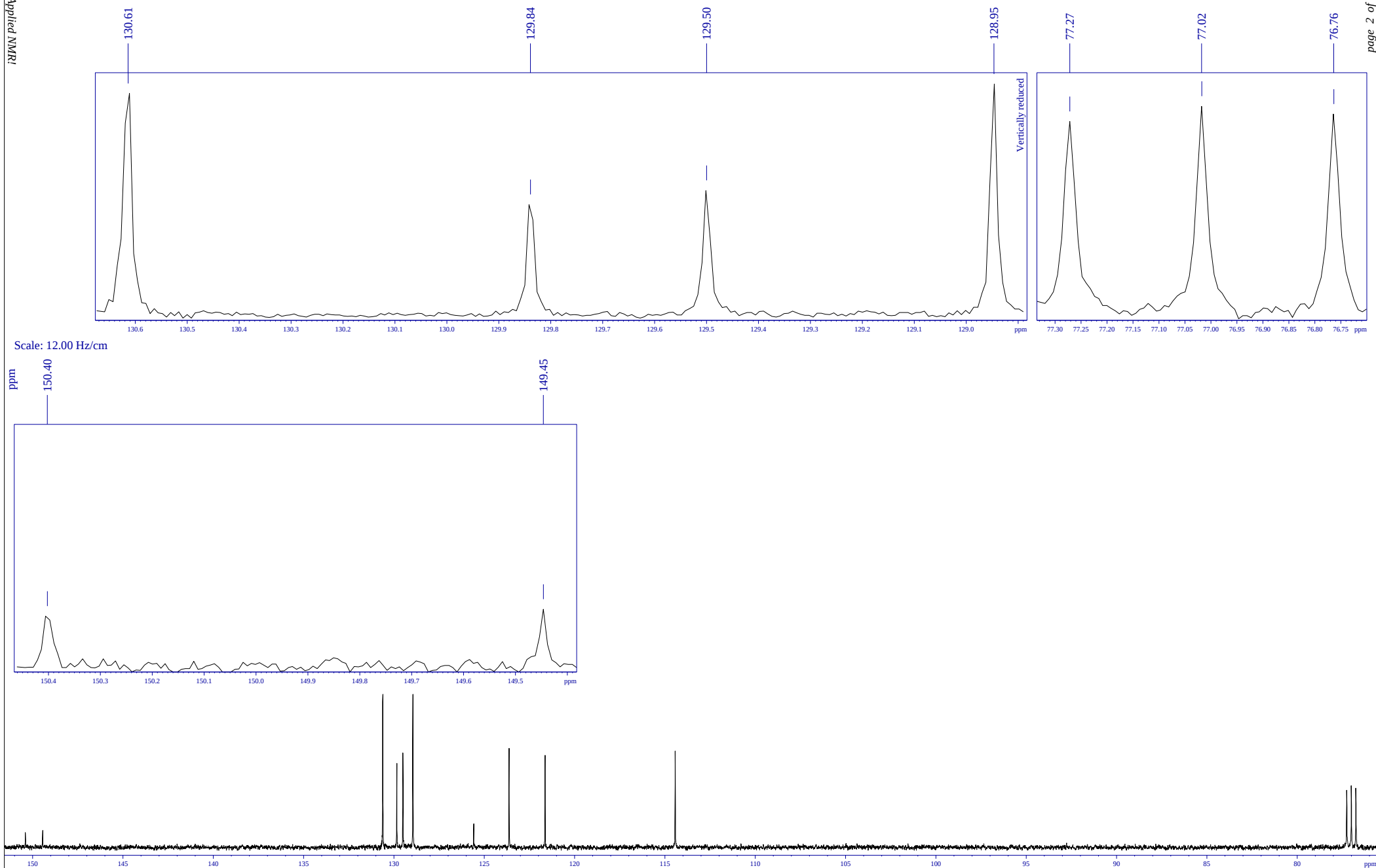


S51

1e (NMR/27290183)

The Best Applied NMR!

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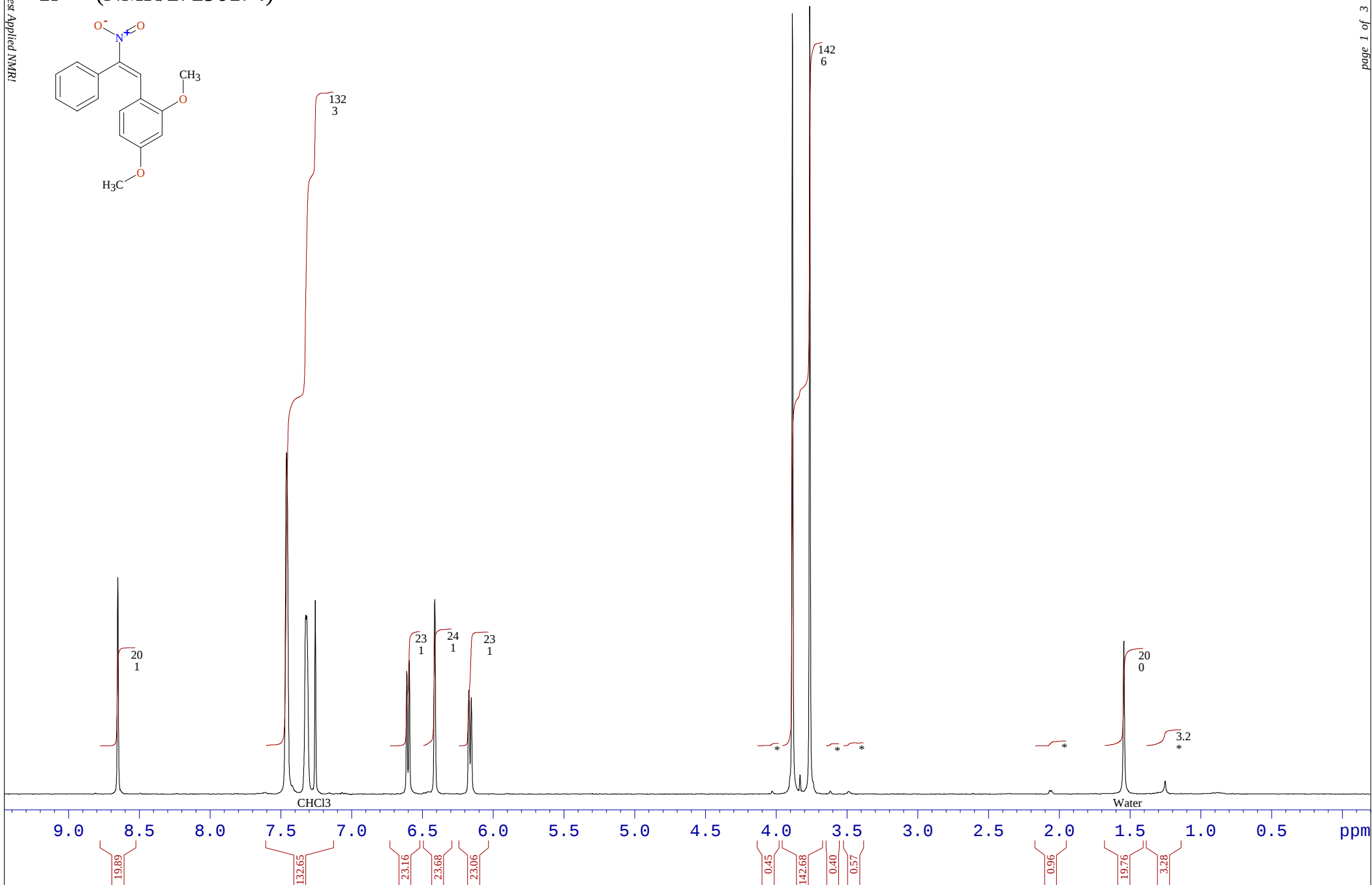
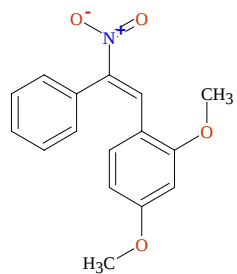
1e (NMR/27290183)

Peaks List

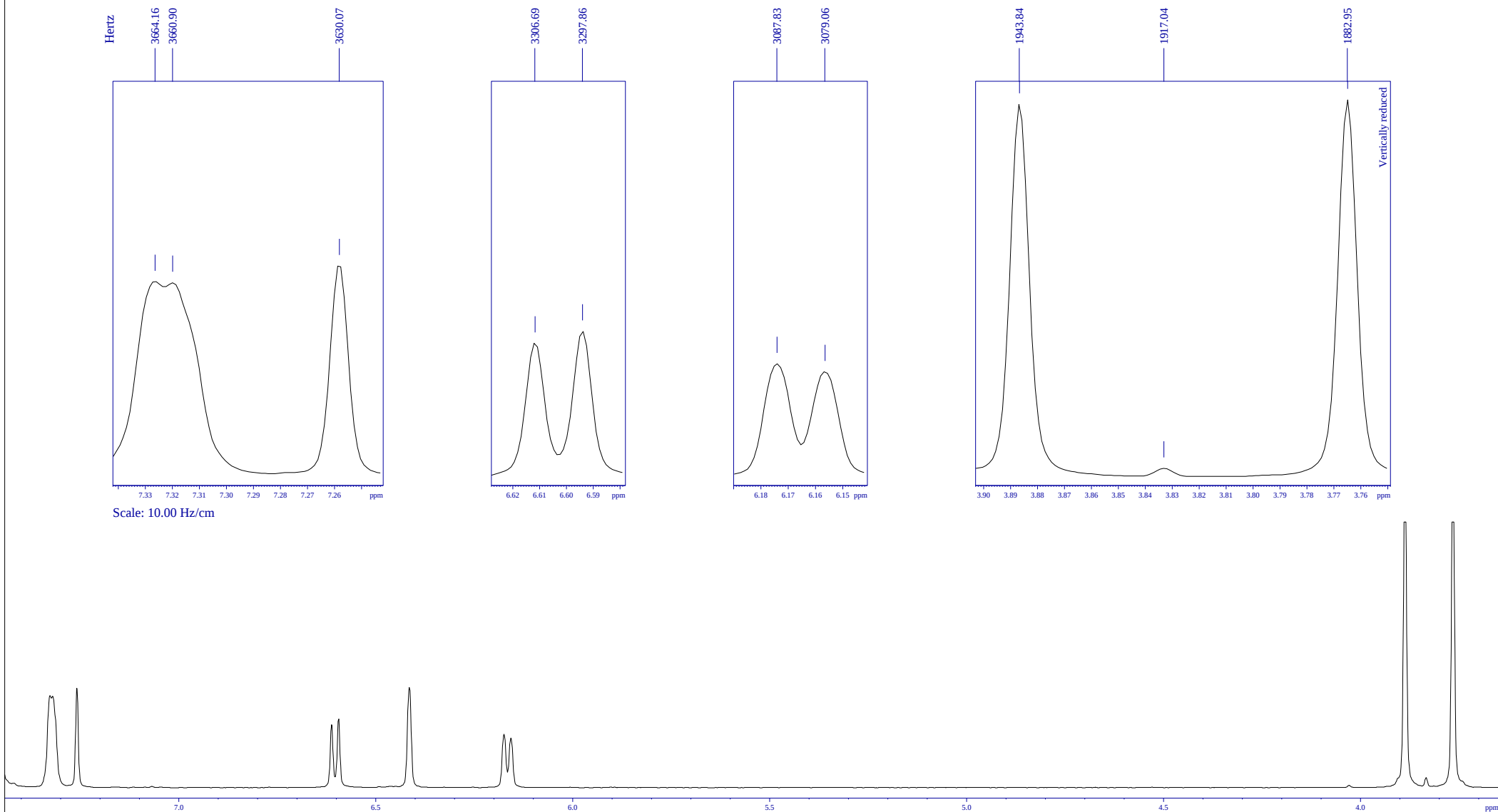
#	Address [points]	Frequency		Intensity
		[Hz]	[ppm]	[cm]
1	11004.7	19198.172	152.6599	1.51
2	11289.4	18914.230	150.4021	1.08
3	11409.9	18794.012	149.4461	1.16
4	13784.7	16425.693	130.6137	12.00
5	13882.3	16328.271	129.8390	6.00
6	13925.1	16285.624	129.4999	6.47
7	13994.9	16216.034	128.9465	12.00
8	14419.4	15792.694	125.5802	1.71
9	14666.1	15546.624	123.6235	6.79
10	14917.3	15296.099	121.6314	6.52
11	15825.9	14389.981	114.4262	6.62
12	20511.0	9717.511	77.2716	3.89
13	20543.0	9685.561	77.0176	4.19
14	20575.0	9653.590	76.7634	4.03
15	22485.2	7748.604	61.6153	3.85
16	23218.5	7017.294	55.8001	6.10

1f (NMR/27290174)

Found protons = 13 impurity* = 0.5 %



1f (NMR/27290174)

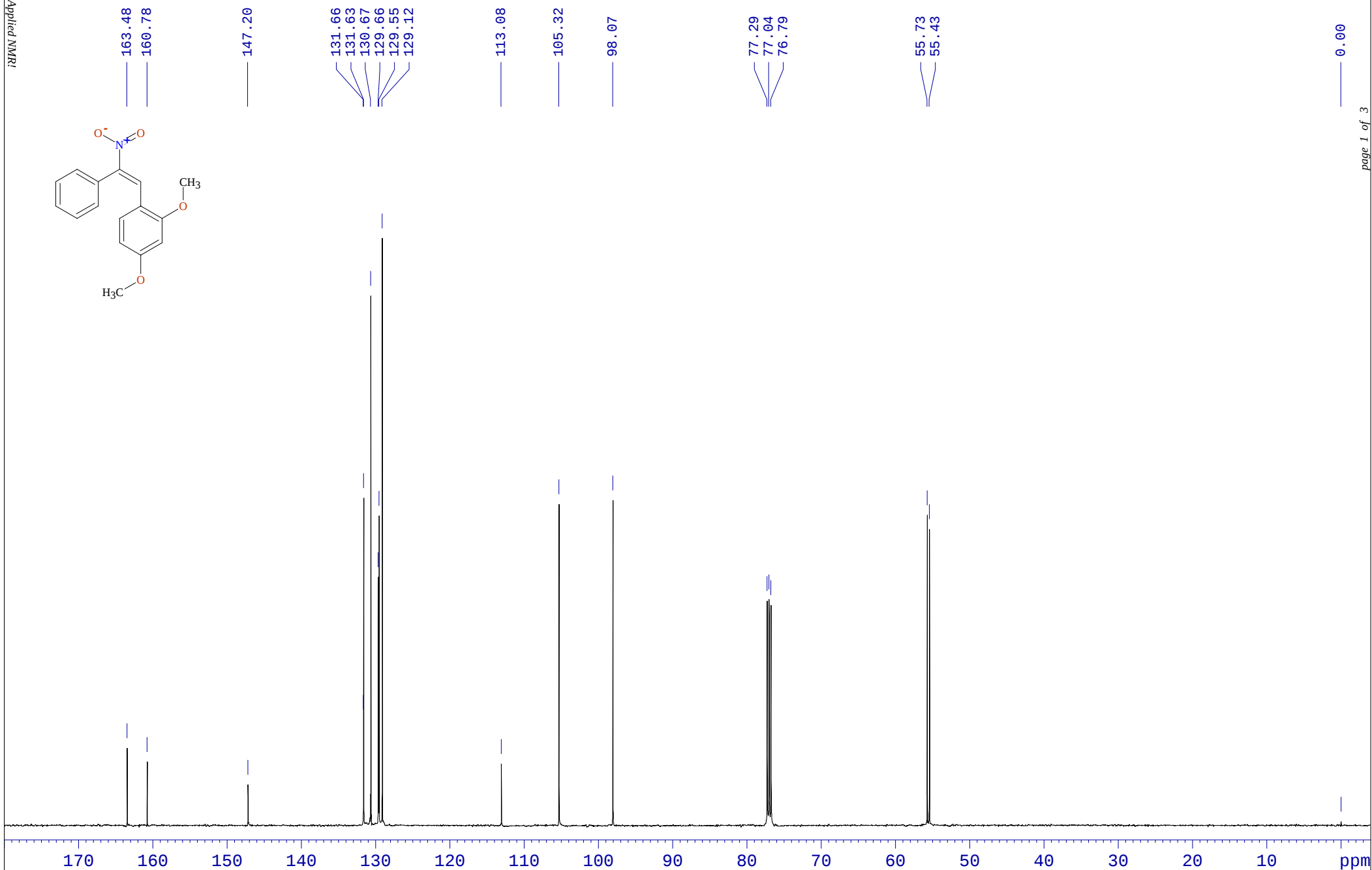
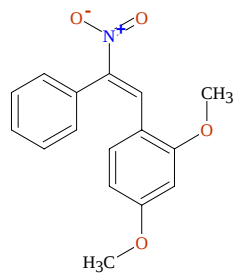


1f (NMR/27290174)

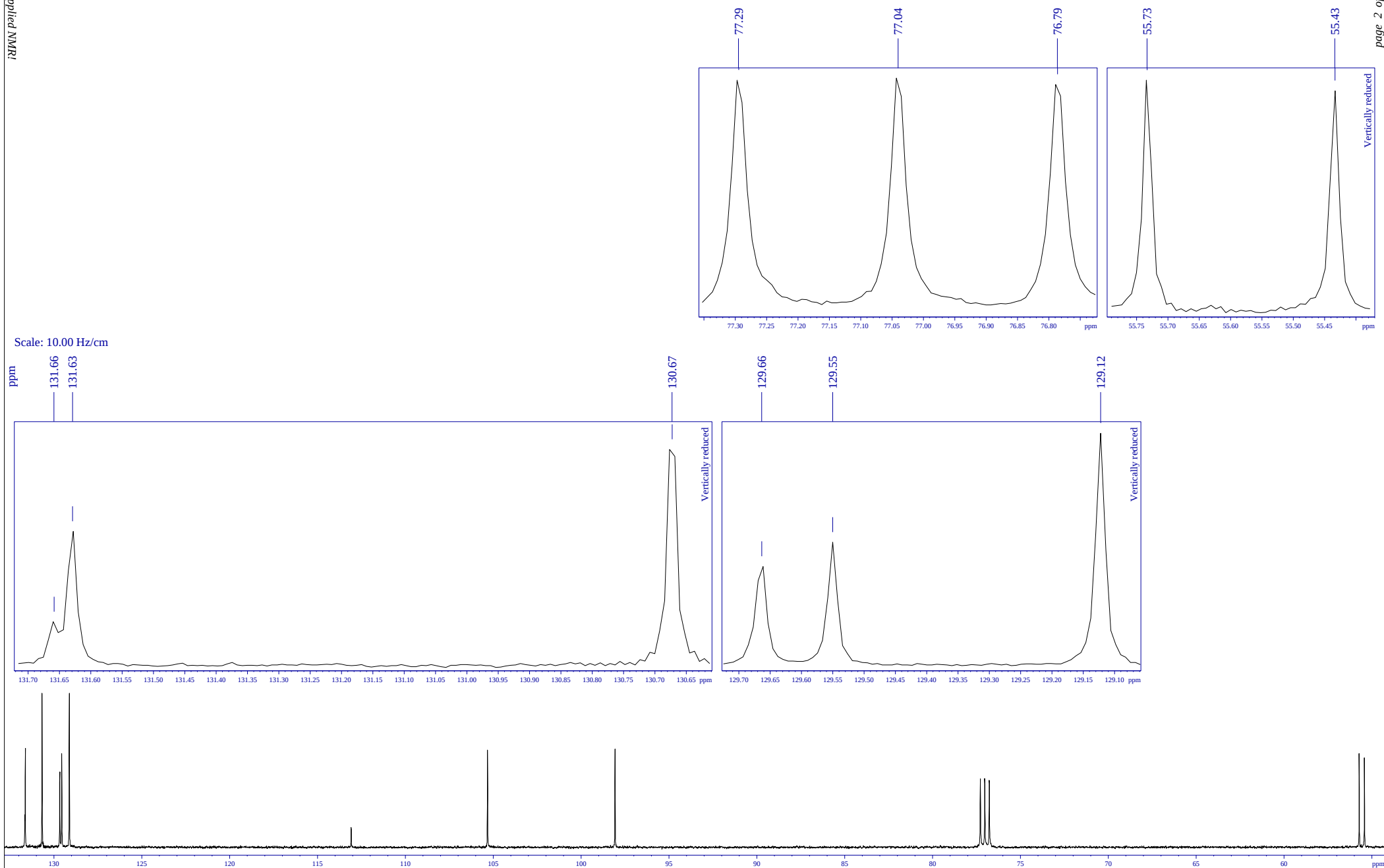
Peaks List

#	Address [points]	Frequency [Hz]	Intensity [ppm]	Intensity [cm]
1	7645.7	4328.166	8.6541	4.41
2	8622.4	3732.025	7.4621	6.94
3	8733.6	3664.156	7.3264	3.63
4	8739.0	3660.898	7.3199	3.61
5	8789.5	3630.065	7.2582	3.98
6	9319.3	3306.690	6.6117	2.50
7	9333.8	3297.861	6.5940	2.72
8	9481.0	3208.021	6.4144	3.95
9	9677.9	3087.830	6.1741	2.11
10	9692.2	3079.058	6.1565	1.96
11	11552.2	1943.838	3.8867	15.85
12	11596.1	1917.035	3.8331	0.39
13	11651.9	1882.949	3.7649	16.00
14	13470.7	772.900	1.5454	3.12
15	13710.1	626.747	1.2532	0.27

1f (NMR/27290174)



1f (NMR/27290174)



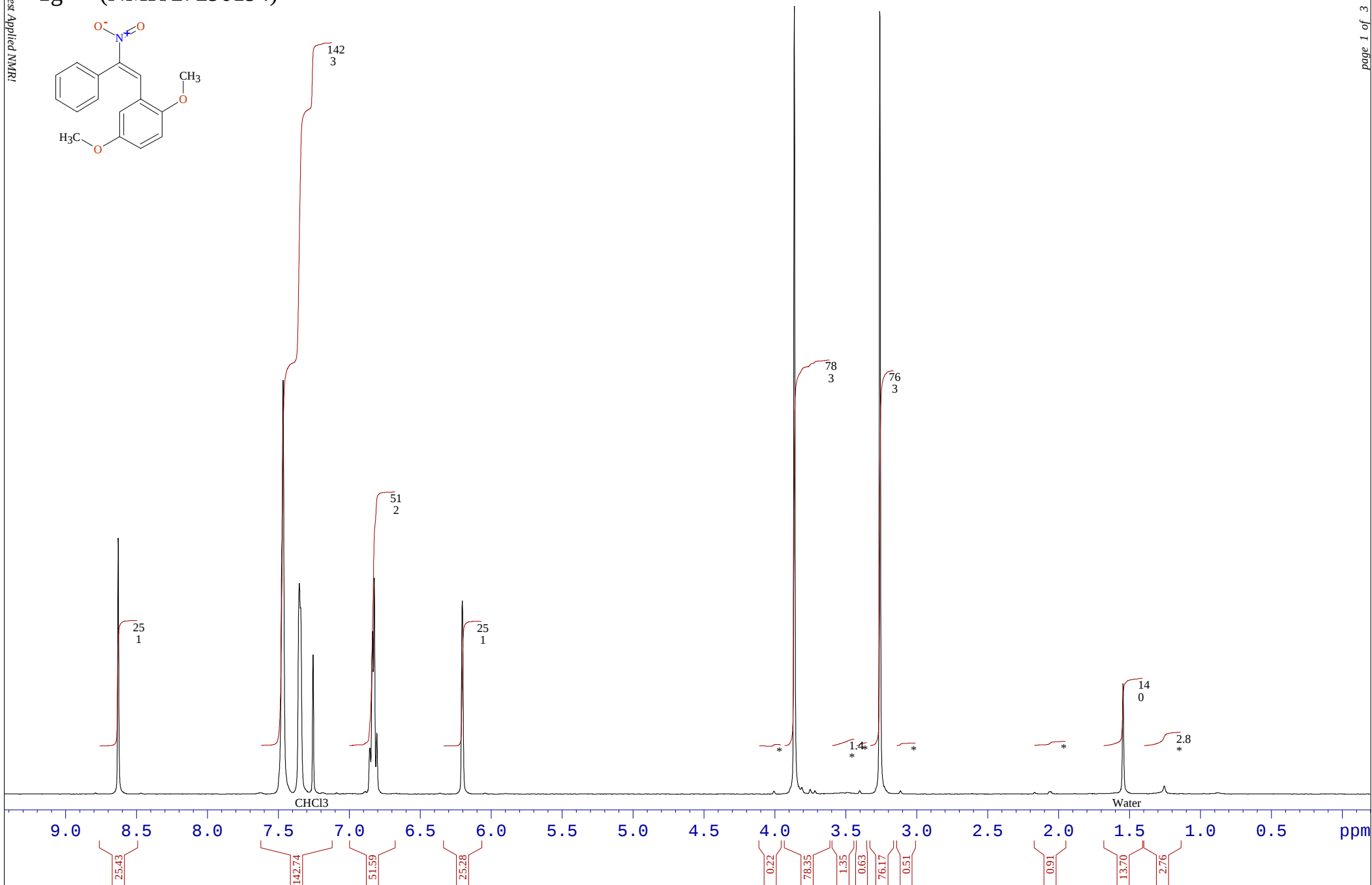
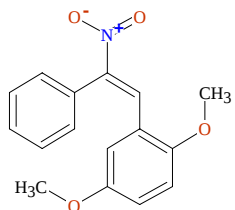
1f (NMR/27290174)

Peaks List

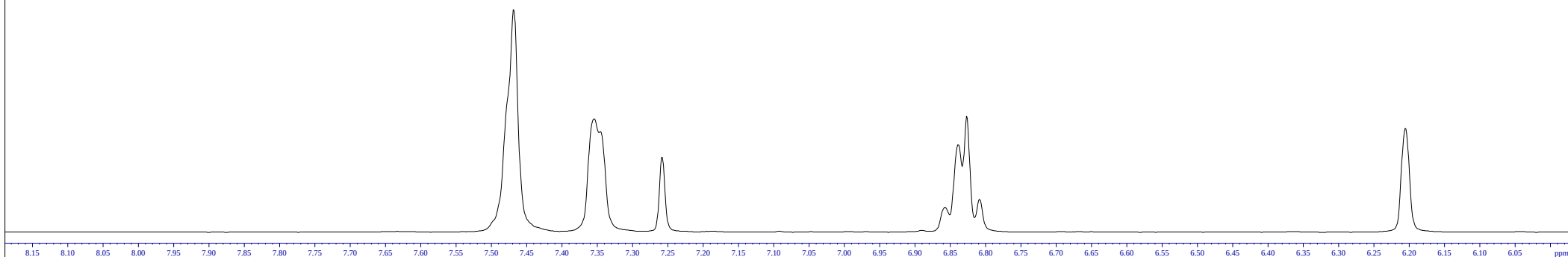
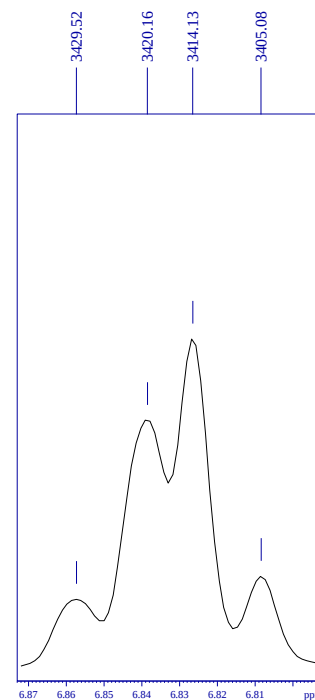
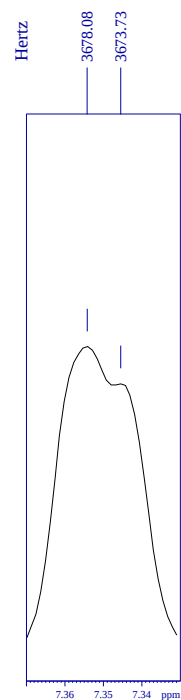
#	Address	Frequency		Intensity
	[points]	[Hz]	[ppm]	[cm]
1	9646.6	20558.754	163.4790	1.76
2	9986.5	20219.783	160.7835	1.50
3	11698.8	18512.146	147.2048	0.95
4	13659.1	16557.082	131.6585	2.22
5	13662.8	16553.391	131.6291	6.82
6	13783.5	16433.090	130.6725	11.65
7	13910.7	16306.186	129.6634	5.29
8	13925.0	16291.935	129.5501	6.37
9	13979.0	16238.108	129.1221	12.00
10	16001.4	14221.136	113.0835	1.43
11	16980.1	13245.092	105.3222	6.63
12	17895.1	12332.496	98.0655	6.74
13	20514.3	9720.381	77.2945	4.74
14	20546.3	9688.435	77.0404	4.80
15	20578.4	9656.461	76.7862	4.71
16	23233.1	7008.882	55.7332	6.43
17	23270.9	6971.185	55.4334	6.12
18	30260.9	0.001	0.0000	0.30

1g (NMR/27290194)

Found protons = 13 impurity* = 0.6 %



1g (NMR/27290194)



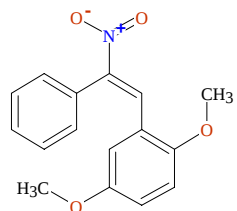
S61

1g (NMR/27290194)

Peaks List

#	Address [points]	Frequency [Hz]	Frequency [ppm]	Intensity [cm]
1	7664.2	4316.858	8.6315	5.20
2	8617.4	3735.070	7.4682	8.41
3	8710.8	3678.076	7.3542	4.27
4	8717.9	3673.728	7.3455	3.78
5	8789.6	3629.985	7.2581	2.85
6	9118.0	3429.519	6.8573	0.93
7	9133.4	3420.161	6.8385	3.30
8	9143.3	3414.126	6.8265	4.38
9	9158.1	3405.083	6.8084	1.24
10	9652.4	3103.395	6.2052	3.92
11	11570.1	1932.932	3.8649	15.99
12	12064.4	1631.186	3.2615	16.00
13	13469.0	773.905	1.5474	2.24

1g (NMR/27290194)



153.62
152.73
149.22

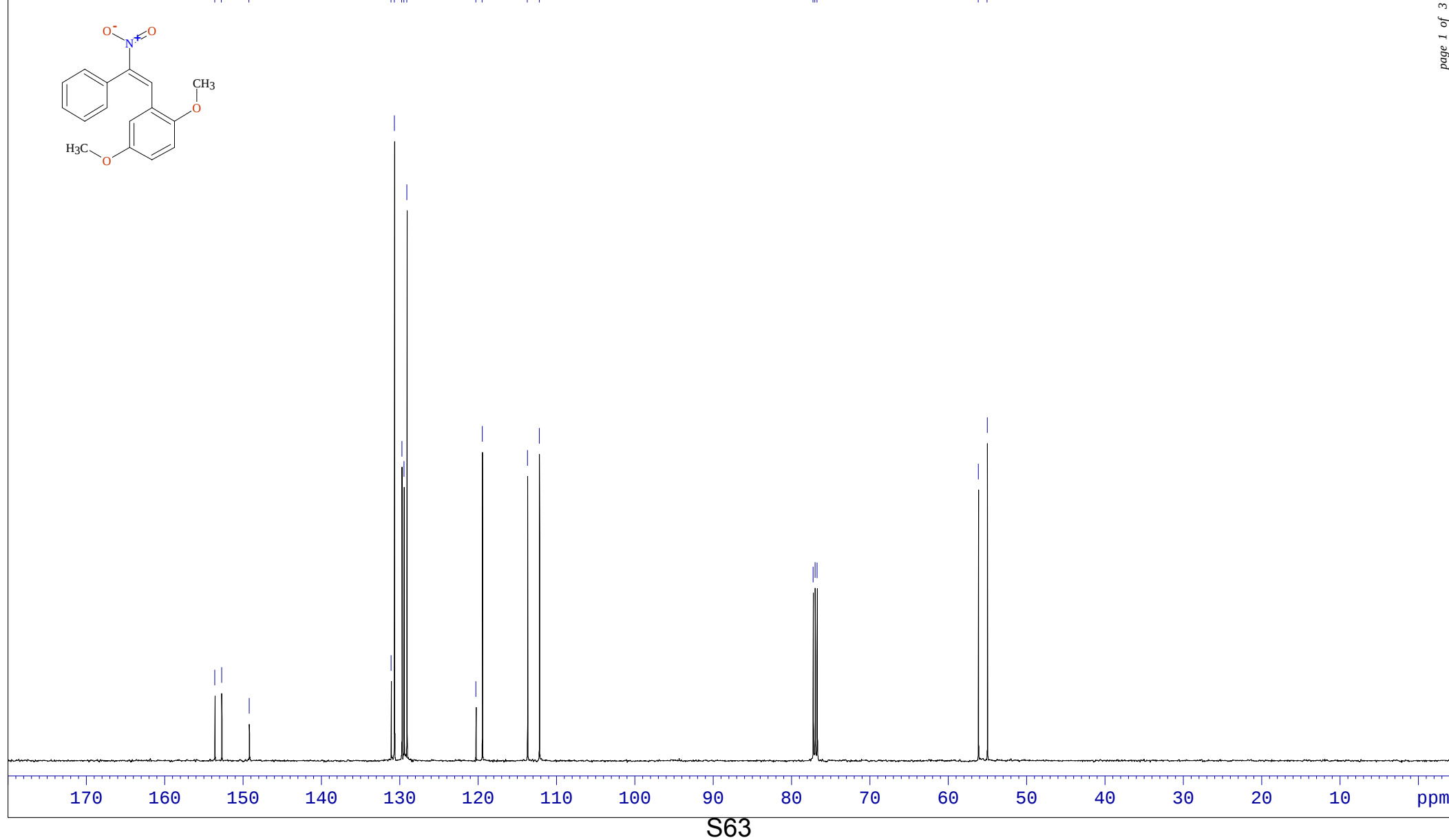
131.11
130.69
129.72
129.46
129.10

120.29
119.47

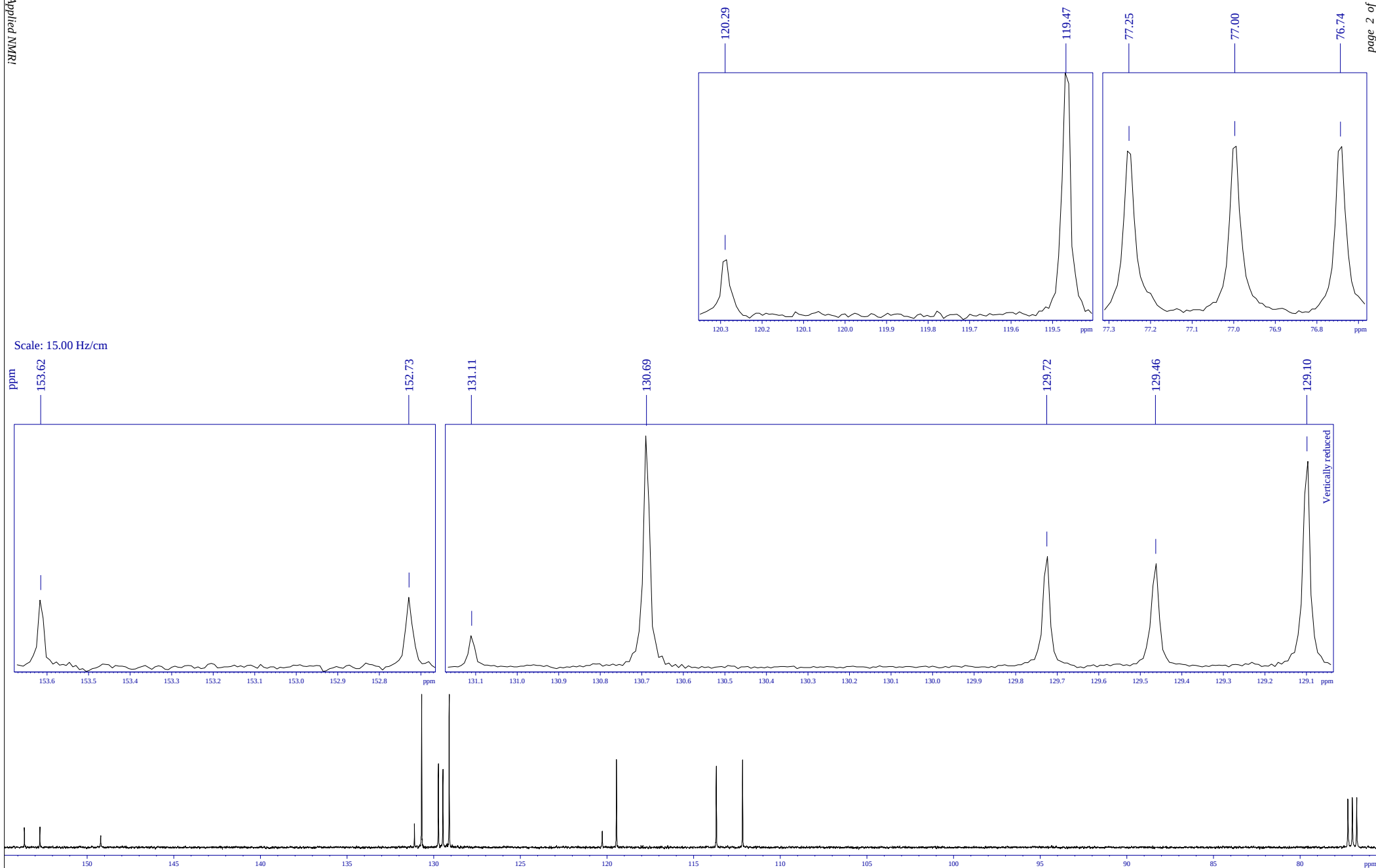
113.70
112.19

77.25
77.00
76.74

56.16
55.02



1g (NMR/27290194)

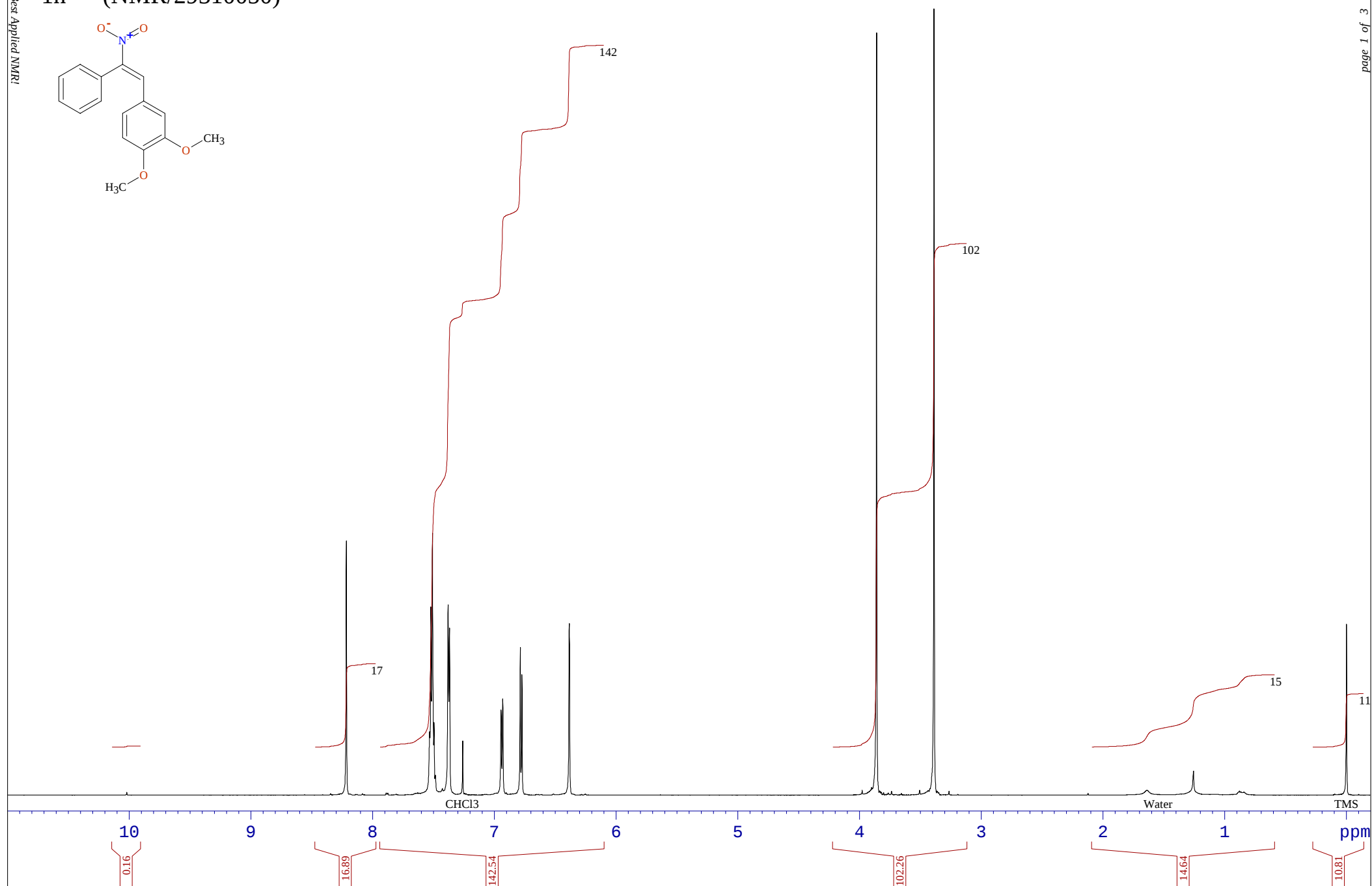
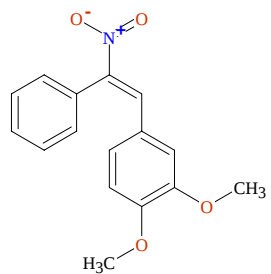


1g (NMR/27290194)

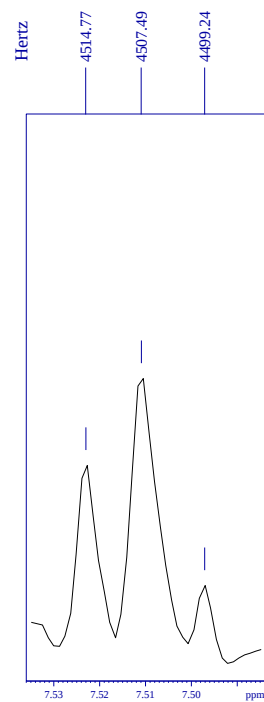
Peaks List

#	Address [points]	Frequency [Hz]	Intensity [cm]
1	10884.2	19318.314	1.36
2	10996.0	19206.807	1.38
3	11439.0	18765.061	0.80
4	13722.1	16488.057	1.61
5	13775.2	16435.141	12.00
6	13896.7	16313.924	5.82
7	13929.8	16280.957	5.37
8	13975.7	16235.164	10.89
9	15086.6	15127.284	1.16
10	15190.2	15023.926	6.04
11	15916.9	14299.220	5.52
12	16108.2	14108.432	5.98
13	20513.5	9715.021	3.41
14	20545.5	9683.019	3.51
15	20577.6	9651.071	3.48
16	23172.5	7063.110	5.66
17	23317.0	6919.044	6.11

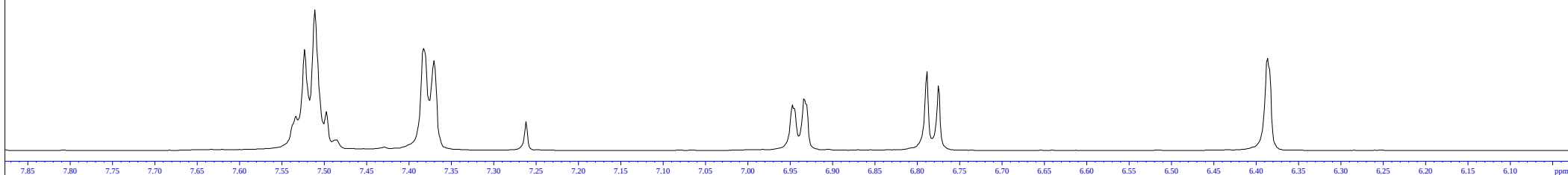
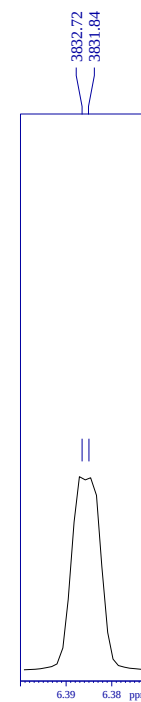
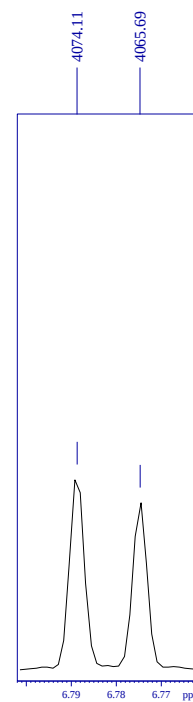
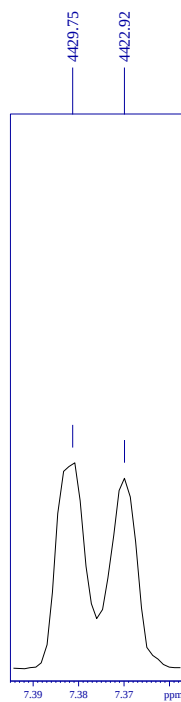
1h (NMR/29310050)



1h (NMR/29310050)



Scale: 10.00 Hz/cm



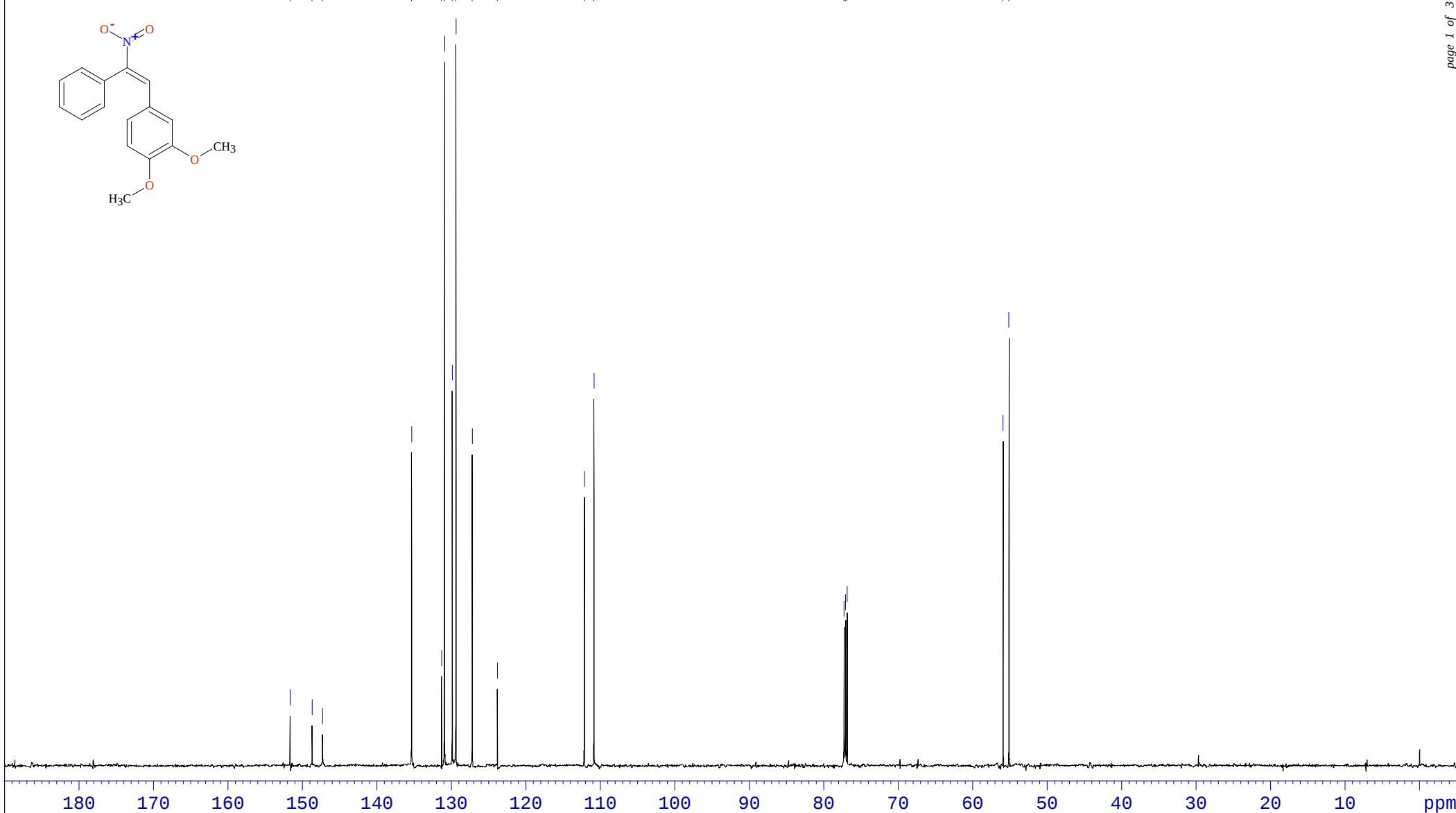
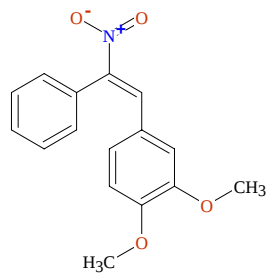
S67

1h (NMR/29310050)

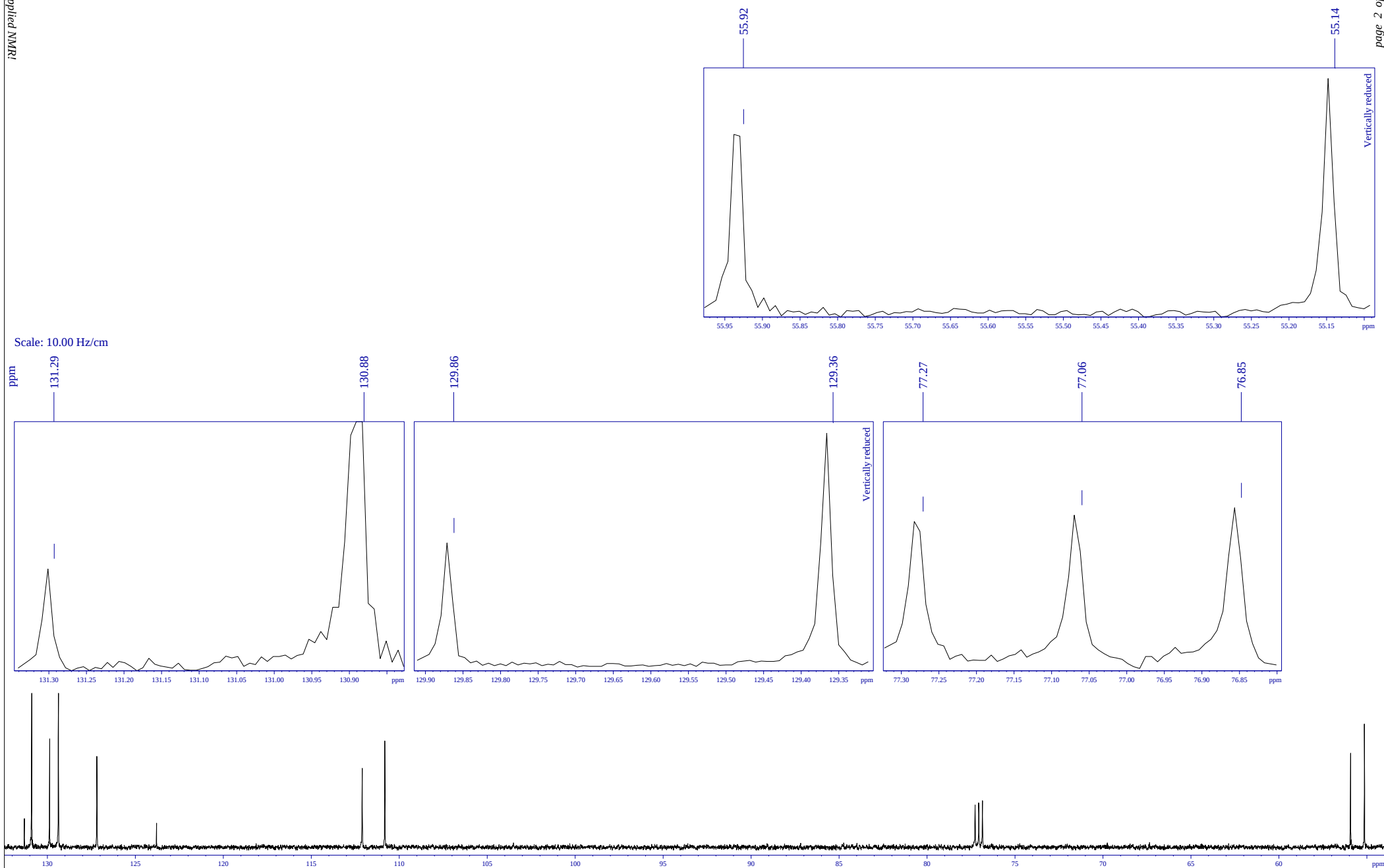
Peaks List

#	Address [points]	Frequency [Hz]	Frequency [ppm]	Intensity [cm]
1	8008.4	4931.705	8.2177	4.96
2	8576.7	4514.765	7.5230	2.94
3	8586.6	4507.489	7.5109	4.19
4	8597.9	4499.241	7.4971	1.20
5	8692.6	4429.748	7.3813	2.98
6	8701.9	4422.920	7.3699	2.72
7	8790.6	4357.854	7.2615	1.06
8	9048.2	4168.862	6.9466	1.24
9	9049.6	4167.827	6.9449	1.32
10	9059.3	4160.765	6.9331	1.55
11	9060.8	4159.610	6.9312	1.55
12	9177.4	4074.115	6.7887	2.79
13	9188.9	4065.691	6.7747	2.38
14	9506.4	3832.718	6.3865	2.80
15	9507.6	3831.845	6.3850	2.75
16	11572.1	2317.368	3.8614	16.00
17	11958.6	2033.851	3.3890	15.20
18	14731.0	-0.002	-0.0000	3.67

1h (NMR/29310050)



1h (NMR/29310050)



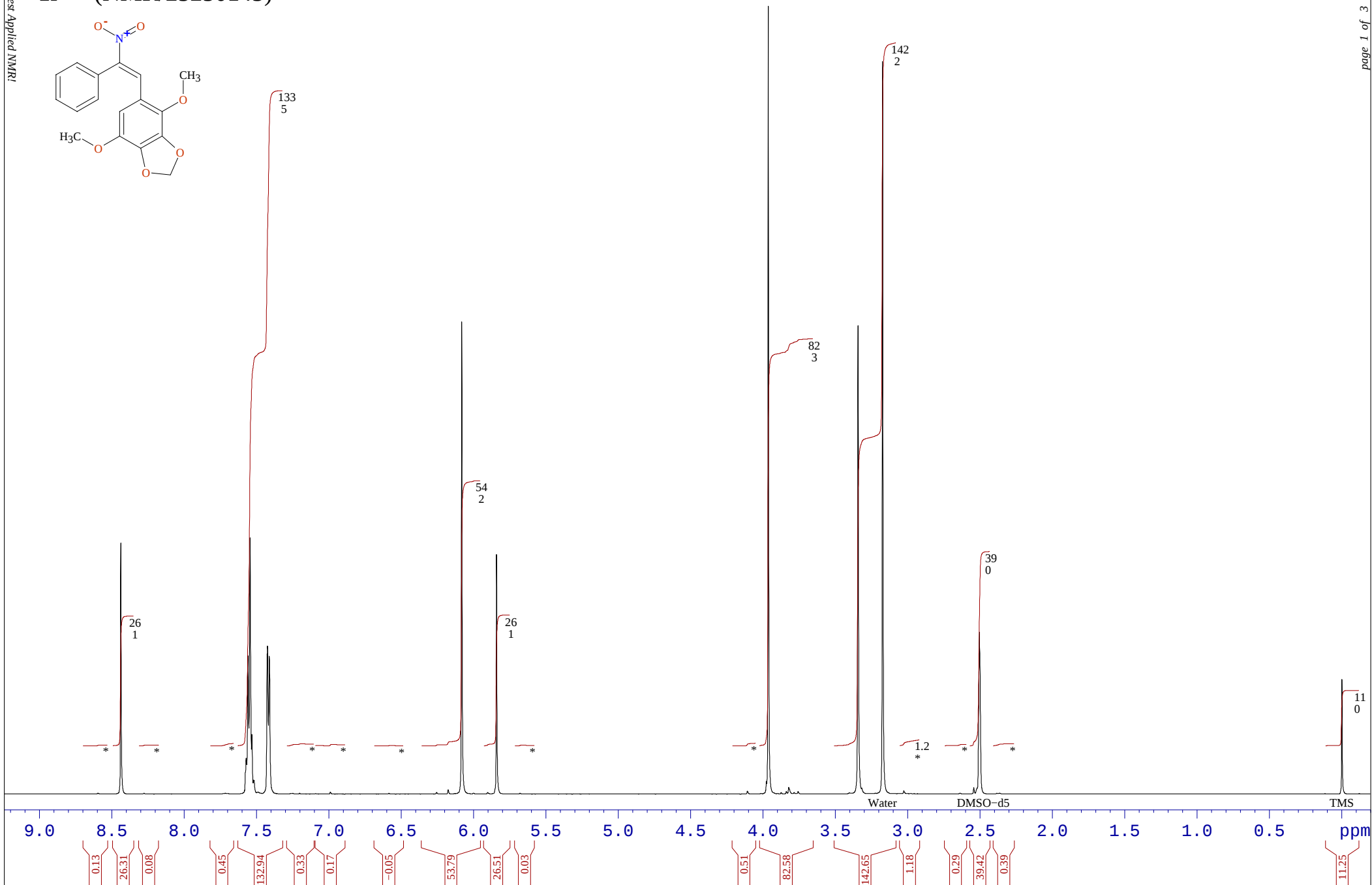
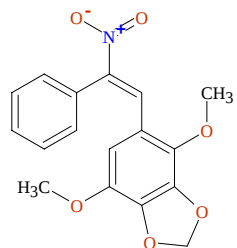
1h (NMR/29310050)

Peaks List

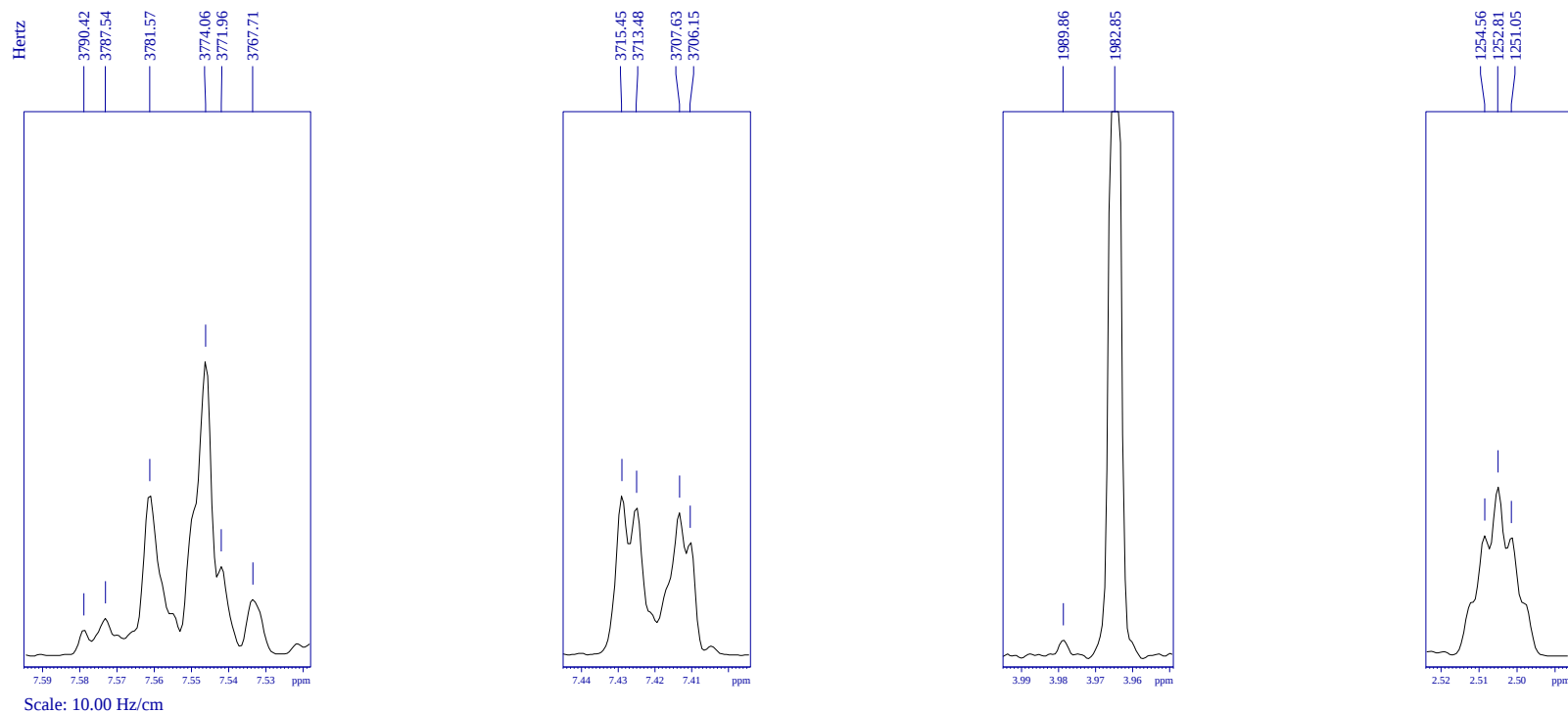
#	Address [points]	Frequency [Hz]	Intensity [cm]
1	12262.3	22884.129	1.28
2	12636.7	22437.900	1.03
3	12814.0	22226.531	0.85
4	14328.9	20420.561	6.22
5	14837.9	19813.797	1.95
6	14890.1	19751.551	13.79
7	15019.1	19597.877	7.39
8	15082.9	19521.729	14.00
9	15359.4	19192.100	6.53
10	15786.5	18683.016	1.80
11	17266.4	16918.834	5.59
12	17429.1	16724.842	7.29
13	21676.4	11661.746	2.99
14	21703.1	11629.841	3.03
15	21730.0	11597.817	3.16
16	24378.5	8440.571	6.94
17	24478.0	8321.916	8.39

1i (NMR/25250145)

Found protons = 14 impurity* = 0.9 %



1i (NMR/25250145)

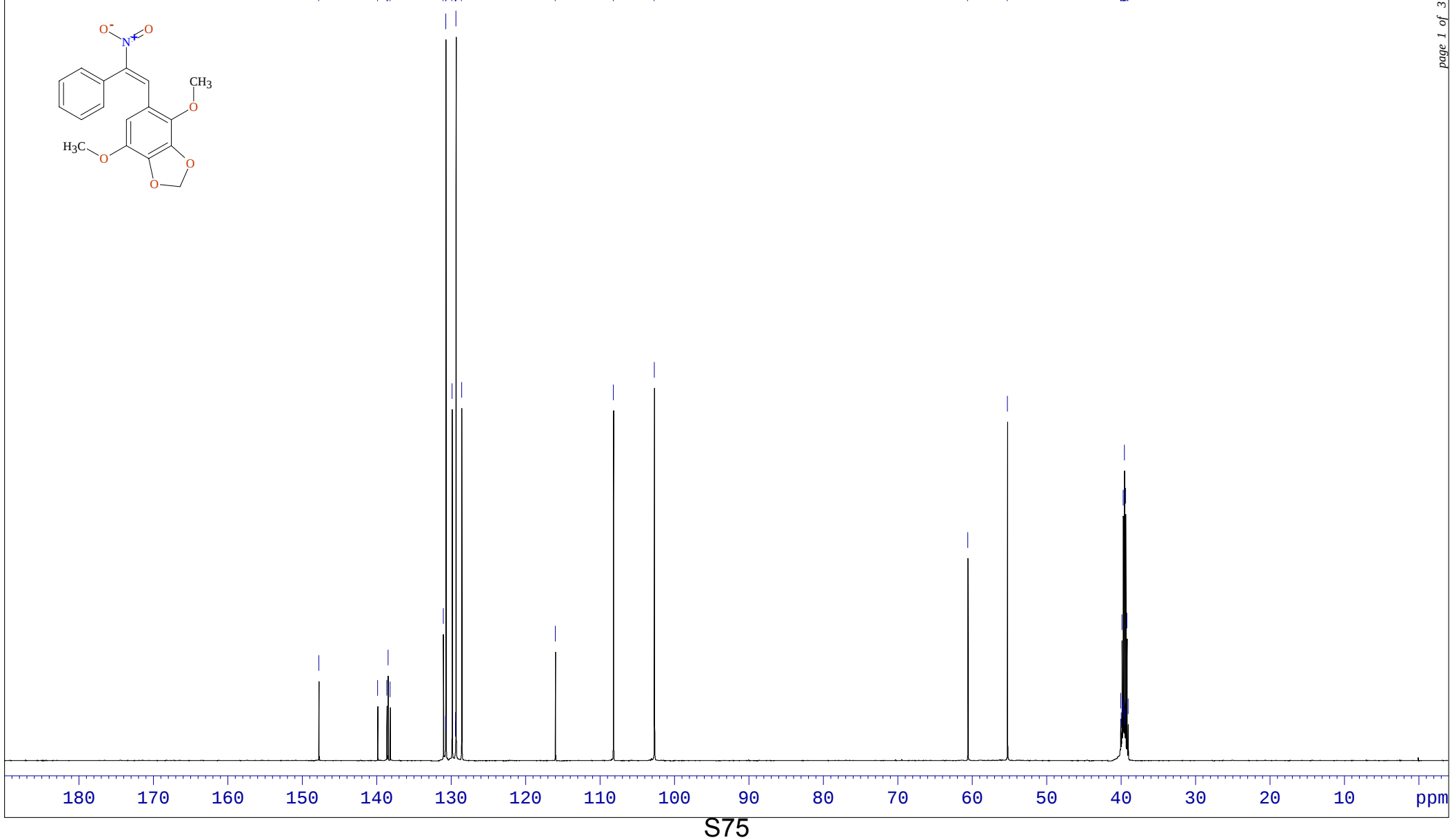
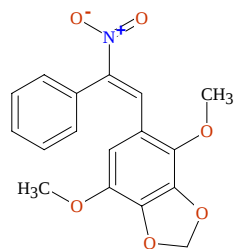


1i (NMR/25250145)

Peaks List

#	Address [points]	Frequency [Hz]	Intensity [cm]
1	15654.8	4220.658	8.4391
2	17064.6	3790.416	7.5789
3	17074.0	3787.542	7.5731
4	17093.6	3781.567	7.5612
5	17118.2	3774.060	7.5462
6	17125.0	3771.959	7.5420
7	17139.0	3767.711	7.5335
8	17310.2	3715.445	7.4290
9	17316.7	3713.481	7.4250
10	17335.8	3707.631	7.4133
11	17340.7	3706.151	7.4104
12	19515.5	3042.438	6.0833
13	19909.5	2922.202	5.8429
14	22964.6	1989.863	3.9787
15	22987.6	1982.845	3.9647
16	24004.4	1672.543	3.3442
17	24282.3	1587.724	3.1746
18	25374.1	1254.557	2.5085
19	25379.8	1252.811	2.5050
20	25385.6	1251.052	2.5015
21	29485.0	0.002	0.0000

1i (NMR/25250145)



page 2 of 3

Vertically reduced

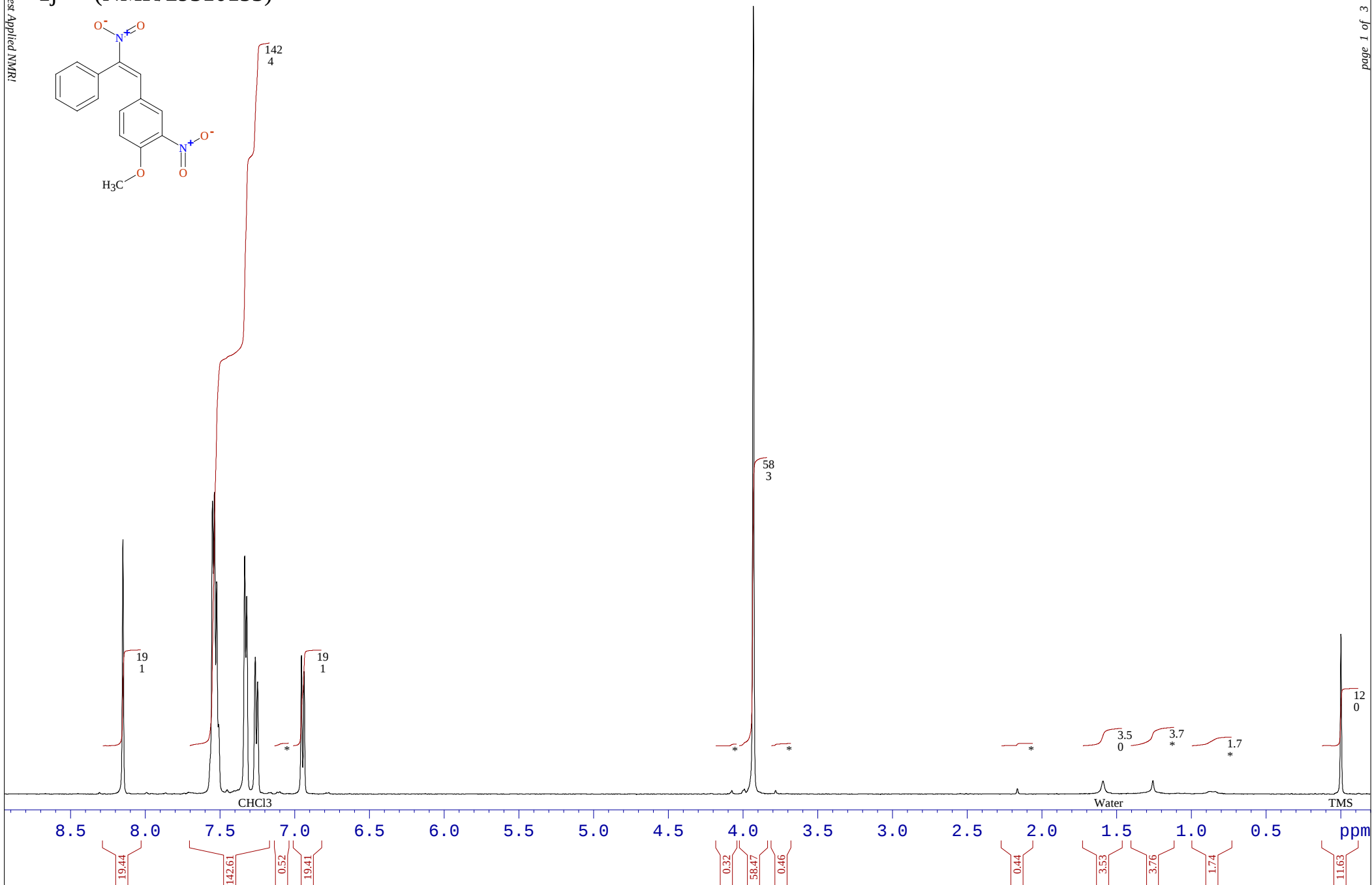
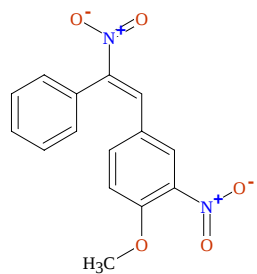
1i (NMR/25250145)

Peaks List

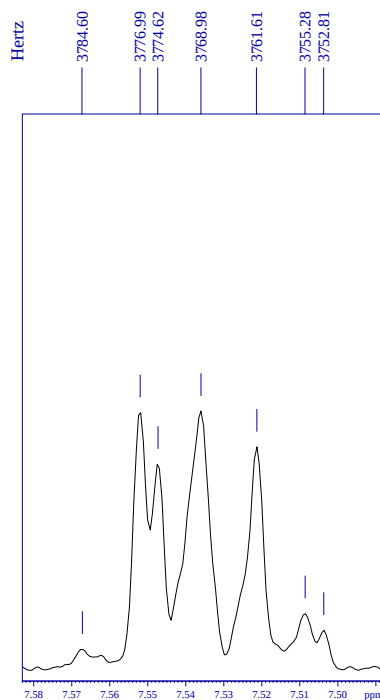
#	Address [points]	Frequency [Hz]	Frequency [ppm]	Intensity [cm]
1	21555.5	18584.754	147.7821	1.63
2	23624.6	17591.898	139.8871	1.15
3	23947.7	17436.871	138.6543	1.15
4	23994.2	17414.562	138.4769	1.72
5	24064.5	17380.820	138.2086	1.11
6	25938.6	16481.576	131.0580	2.54
7	26026.5	16439.398	130.7227	14.00
8	26039.2	16433.324	130.6743	0.39
9	26247.3	16333.434	129.8800	6.77
10	26365.2	16276.893	129.4304	0.32
11	26369.3	16274.885	129.4145	0.48
12	26382.3	16268.680	129.3651	13.79
13	26585.4	16171.206	128.5900	6.84
14	29881.9	14589.419	116.0120	2.15
15	31925.7	13608.765	108.2140	6.75
16	33367.3	12916.999	102.7133	7.17
17	44404.2	7621.096	60.6014	3.93
18	45798.4	6952.129	55.2819	6.59
19	49786.8	5038.359	40.0640	0.87
20	49807.0	5028.652	39.9868	0.47
21	49830.6	5017.327	39.8967	2.35
22	49850.6	5007.746	39.8205	0.73
23	49874.3	4996.362	39.7300	4.70
24	49894.4	4986.698	39.6532	0.66
25	49918.0	4975.370	39.5631	5.53
26	49937.8	4965.875	39.4876	0.51
27	49961.8	4954.382	39.3962	4.73
28	50005.6	4933.365	39.2291	2.38
29	50049.1	4912.460	39.0629	0.76

1j (NMR/29310153)

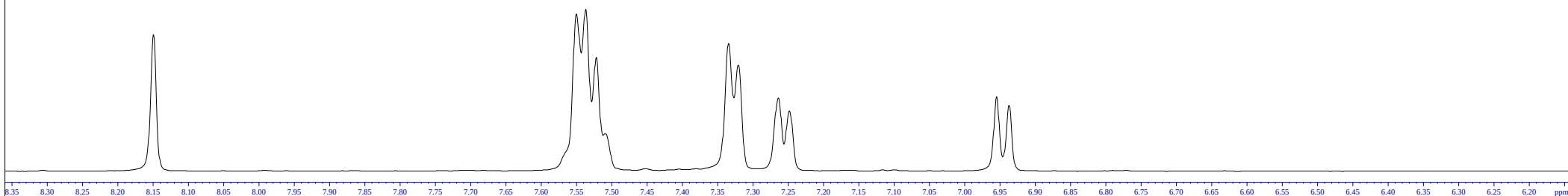
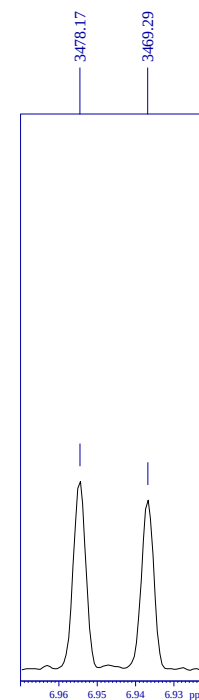
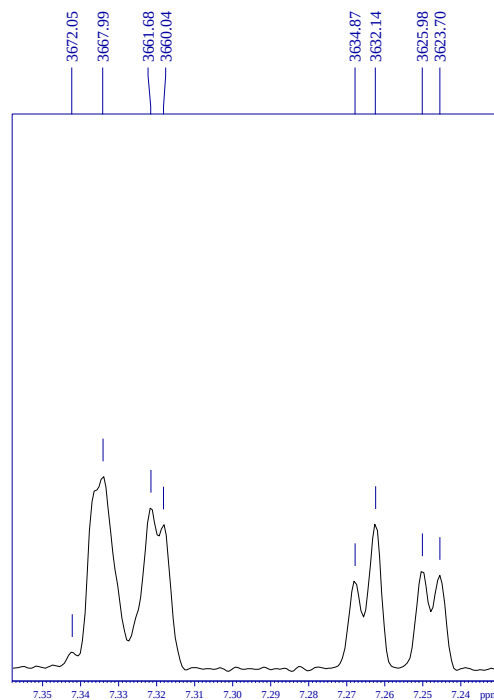
Found protons = 9 impurity* = 1.9 %



1j (NMR/29310153)



Scale: 10.00 Hz/cm

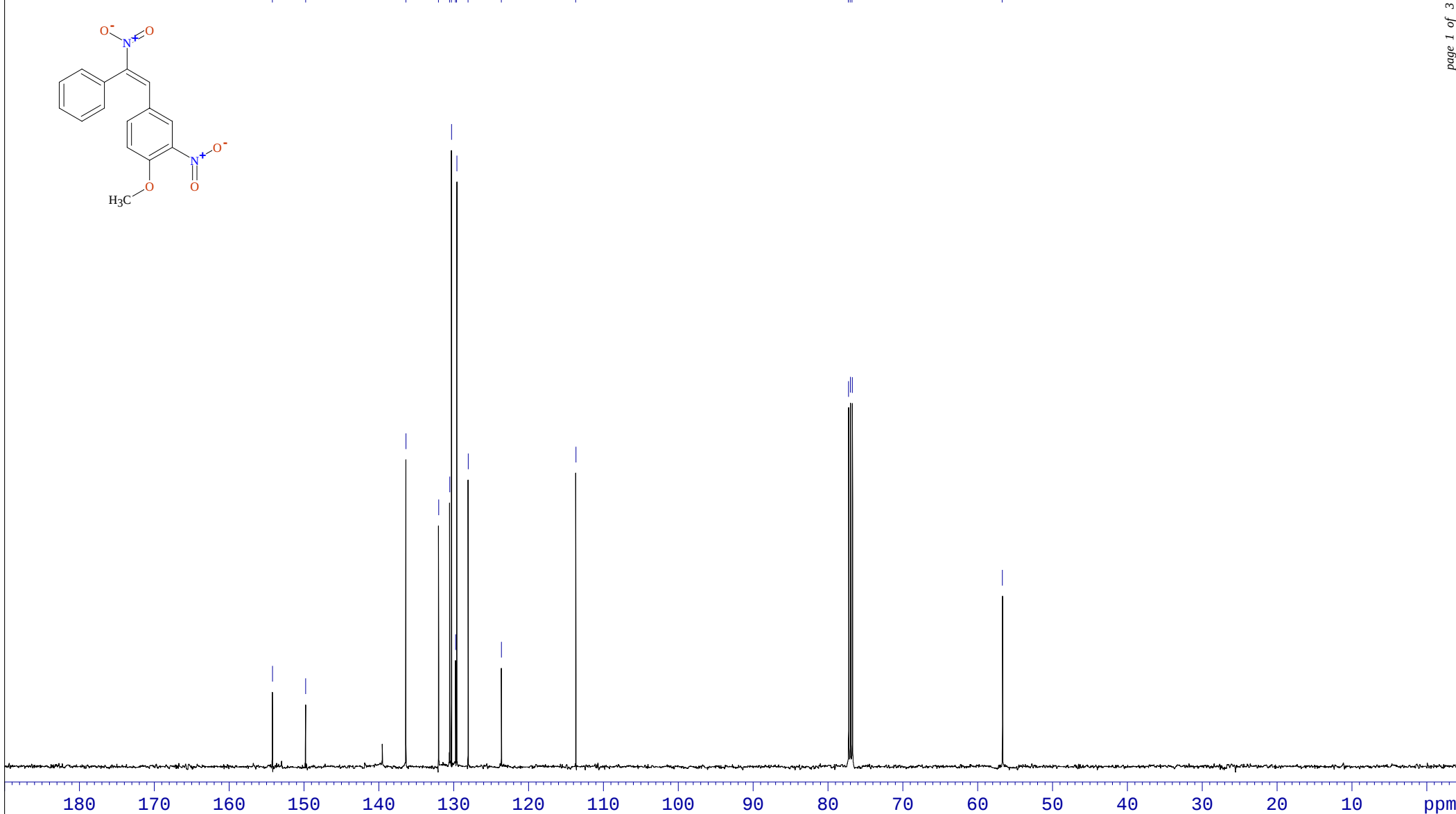
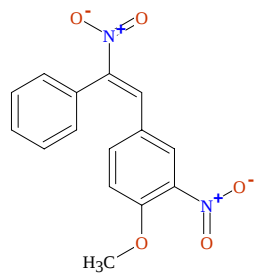


1j (NMR/29310153)

Peaks List

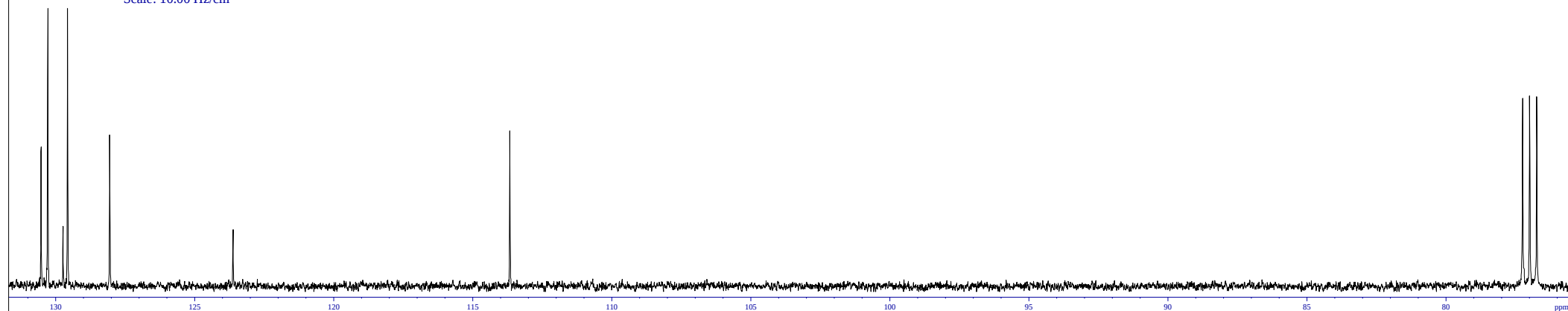
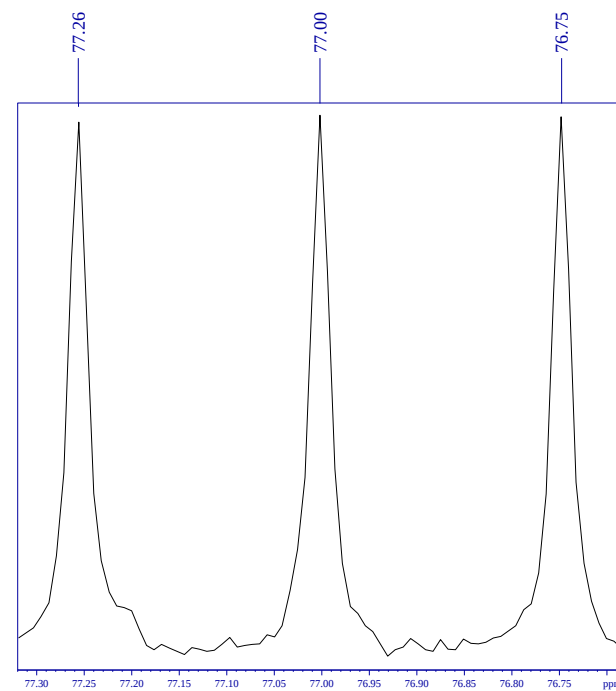
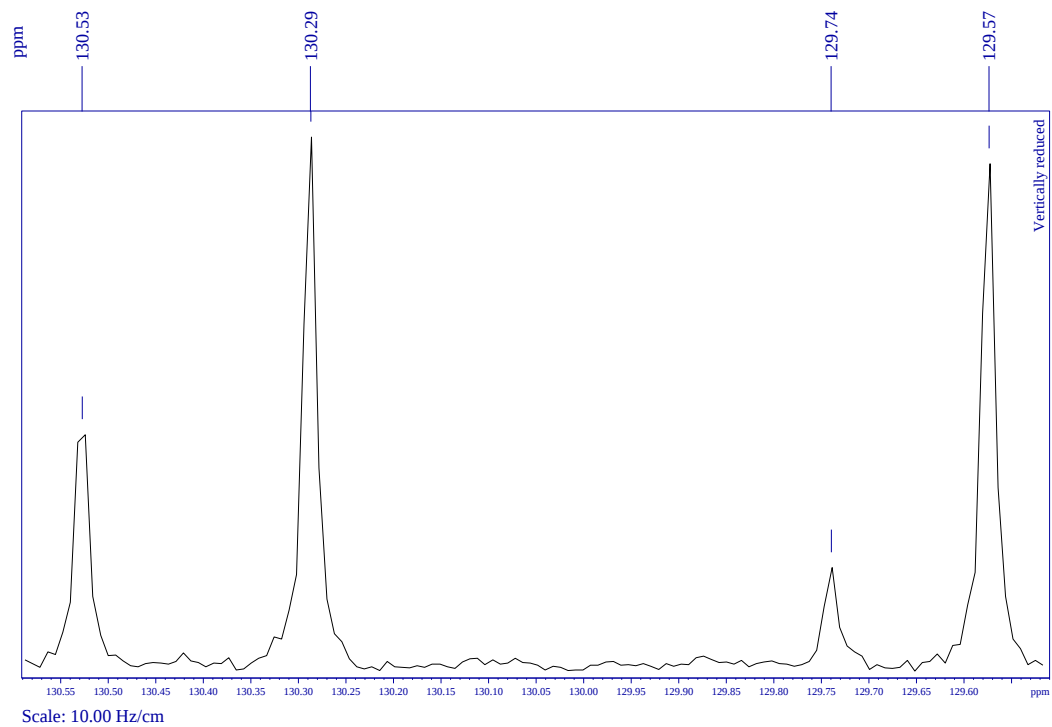
#	Address [points]	Frequency [Hz]	Intensity [ppm]	Intensity [cm]
1	16125.0	4075.623	8.1491	4.71
2	17078.6	3784.598	7.5672	0.28
3	17103.6	3776.985	7.5520	3.53
4	17111.3	3774.618	7.5473	2.81
5	17129.8	3768.982	7.5360	3.51
6	17153.9	3761.615	7.5213	3.02
7	17174.7	3755.279	7.5086	0.77
8	17182.8	3752.812	7.5037	0.54
9	17447.4	3672.048	7.3422	0.24
10	17460.7	3667.994	7.3341	2.63
11	17481.4	3661.682	7.3215	2.22
12	17486.8	3660.041	7.3182	1.97
13	17569.3	3634.867	7.2678	1.21
14	17578.2	3632.144	7.2624	1.98
15	17598.4	3625.978	7.2501	1.35
16	17605.9	3623.699	7.2455	1.29
17	18082.7	3478.170	6.9545	2.57
18	18111.8	3469.288	6.9368	2.31
19	23035.4	1966.747	3.9325	16.00
20	29480.0	0.002	0.0000	3.45

1j (NMR/29310153)



S81

1j (NMR/29310153)



S82

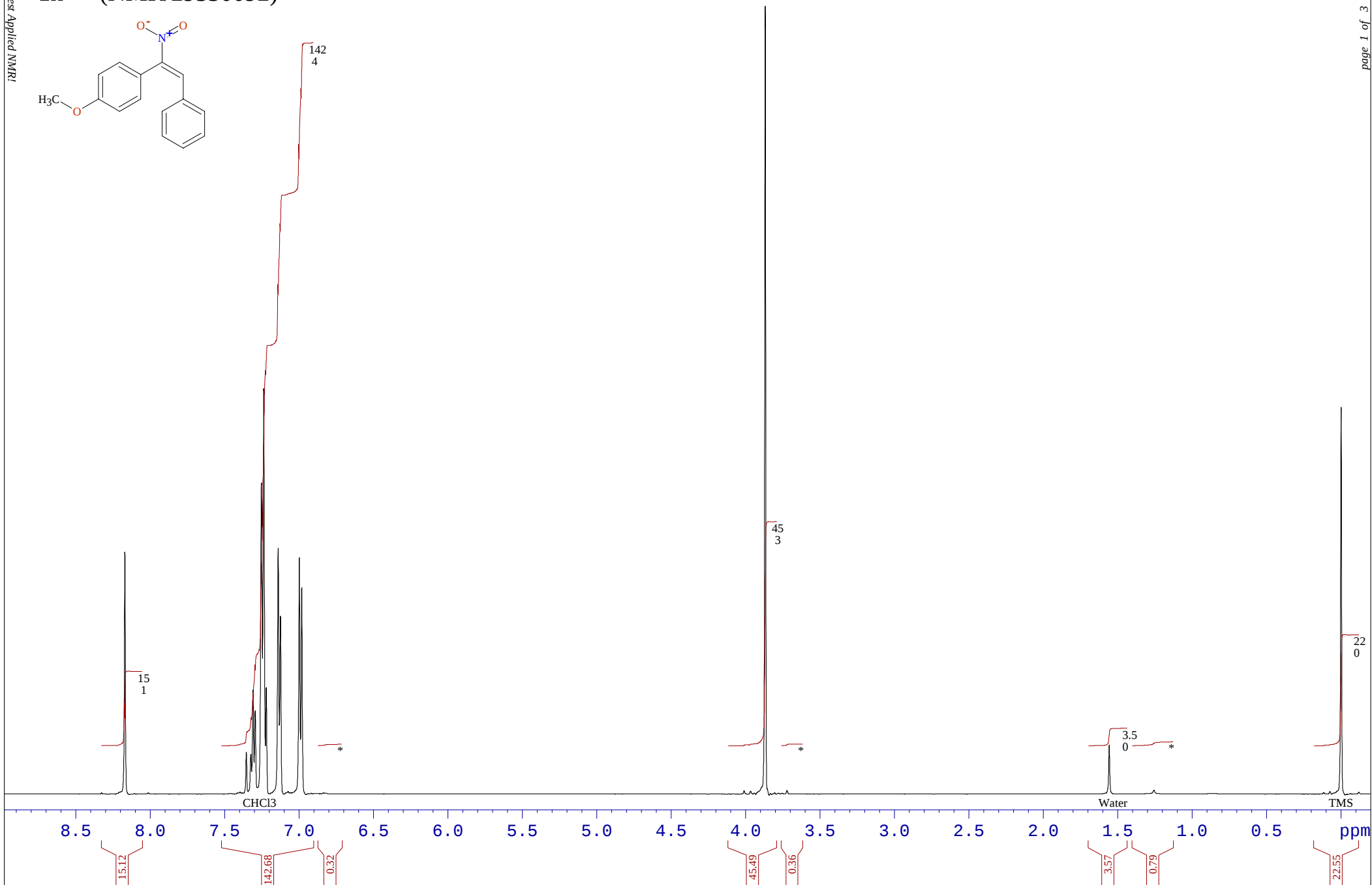
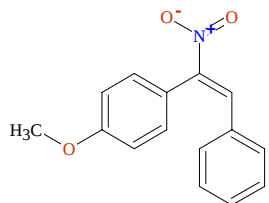
1j (NMR/29310153)

Peaks List

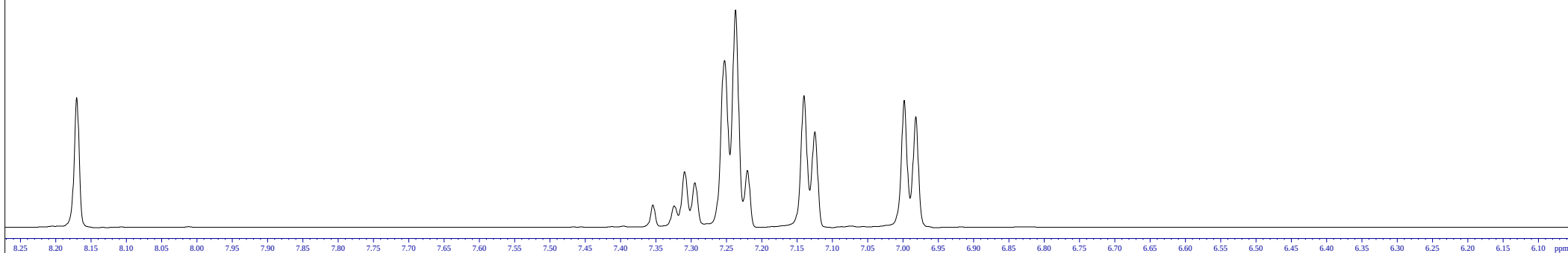
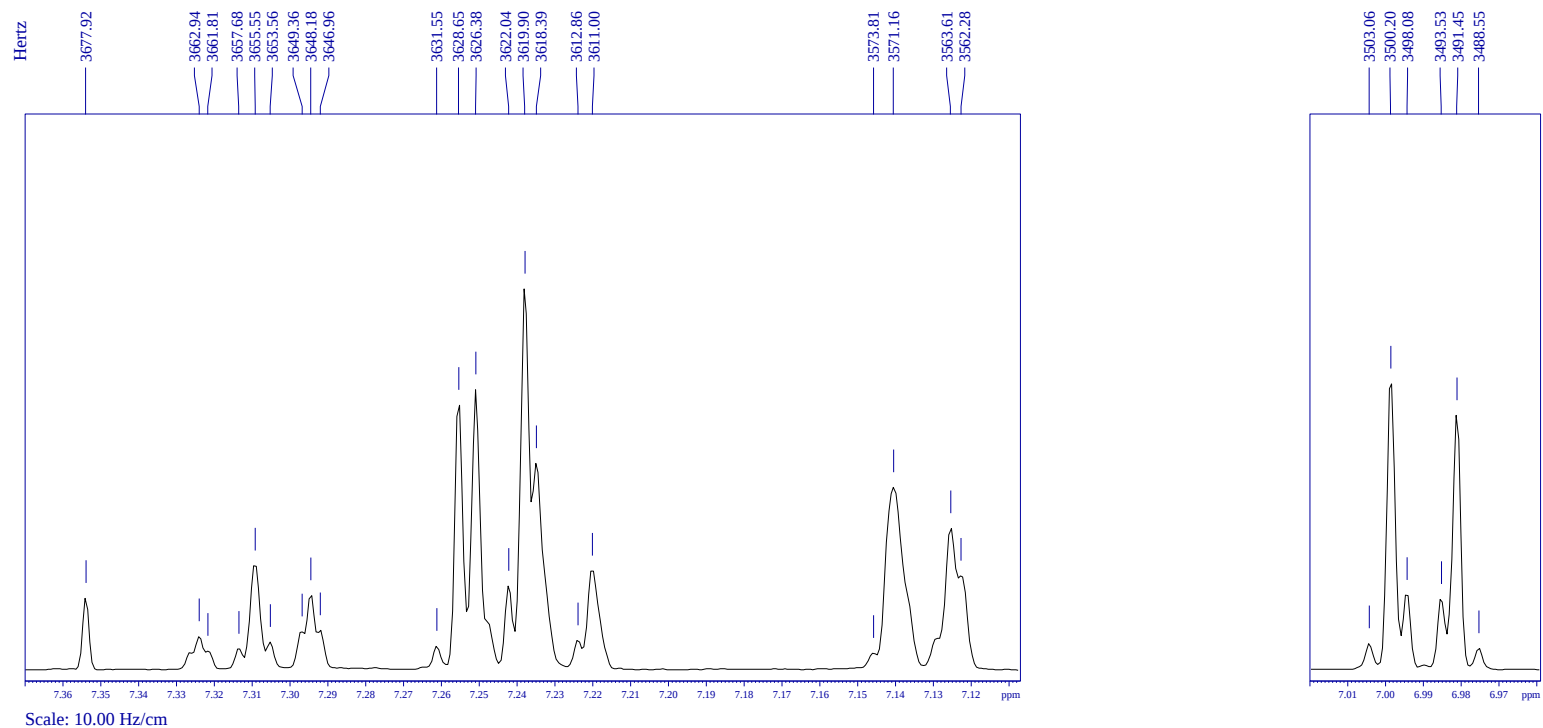
#	Address [points]	Frequency [Hz]	Frequency [ppm]	Intensity [cm]
1	10809.7	19392.684	154.2066	1.74
2	11367.9	18835.980	149.7798	1.43
3	13058.0	17150.391	136.3764	6.05
4	13609.4	16600.438	132.0033	5.04
5	13795.5	16414.832	130.5273	5.61
6	13825.9	16384.600	130.2869	12.00
7	13894.9	16315.752	129.7395	2.24
8	13915.8	16294.886	129.5736	11.47
9	14106.9	16104.304	128.0581	5.68
10	14665.9	15546.811	123.6250	2.12
11	15921.7	14294.395	113.6661	6.01
12	20512.9	9715.542	77.2560	7.03
13	20545.0	9683.537	77.0015	7.12
14	20577.0	9651.609	76.7476	7.10
15	23104.6	7130.899	56.7034	3.52

1k (NMR/29330092)

Found protons = 8 impurity* = 0.2 %



1k (NMR/29330092)



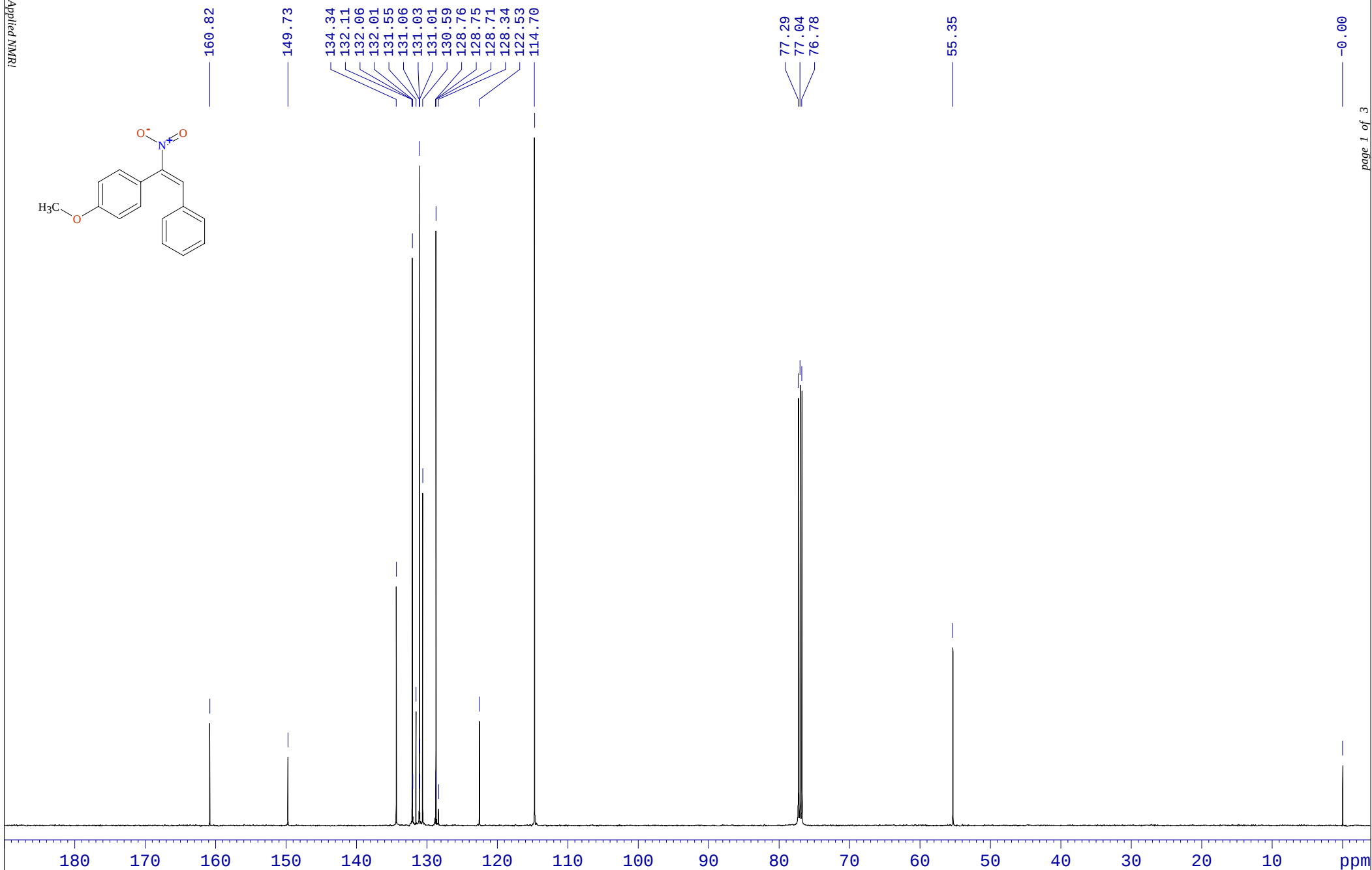
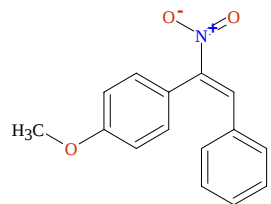
S85

1k (NMR/29330092)

Peaks List

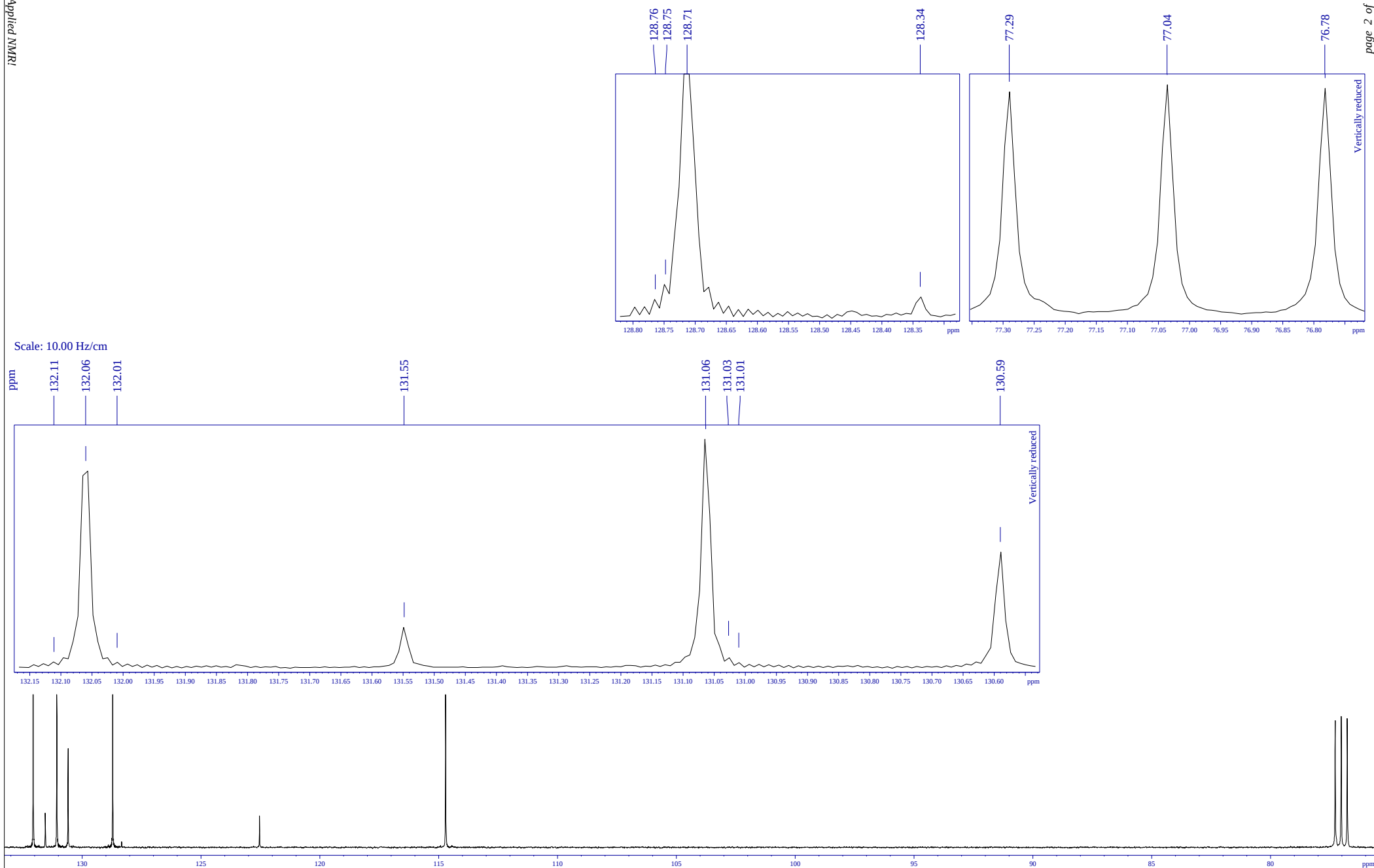
#	Address [points]	Frequency [Hz]	Frequency [ppm]	Intensity [cm]
1	16072.8	4086.053	8.1700	3.33
2	17410.2	3677.922	7.3539	0.93
3	17459.3	3662.938	7.3240	0.44
4	17463.0	3661.812	7.3217	0.24
5	17476.5	3657.679	7.3135	0.28
6	17483.5	3655.553	7.3092	1.38
7	17490.0	3653.560	7.3052	0.36
8	17503.8	3649.357	7.2968	0.49
9	17507.6	3648.182	7.2945	0.98
10	17511.7	3646.957	7.2920	0.52
11	17562.1	3631.546	7.2612	0.31
12	17571.6	3628.650	7.2554	3.49
13	17579.1	3626.380	7.2509	3.62
14	17593.3	3622.044	7.2422	1.10
15	17600.3	3619.902	7.2379	4.99
16	17605.2	3618.392	7.2349	2.68
17	17623.4	3612.865	7.2239	0.39
18	17629.5	3610.997	7.2201	1.31
19	17751.3	3573.807	7.1458	0.22
20	17760.0	3571.160	7.1405	2.35
21	17784.8	3563.610	7.1254	1.83
22	17789.1	3562.275	7.1227	1.21
23	17983.2	3503.058	7.0043	0.34
24	17992.6	3500.196	6.9986	3.80
25	17999.5	3498.078	6.9943	1.00
26	18014.4	3493.530	6.9852	0.94
27	18021.2	3491.447	6.9811	3.31
28	18030.7	3488.545	6.9753	0.28
29	23120.4	1935.308	3.8696	16.00
30	26908.3	779.322	1.5582	0.65
31	29462.0	-0.001	-0.0000	8.73

1k (NMR/29330092)



1k (NMR/29330092)

The Best Applied NMR!



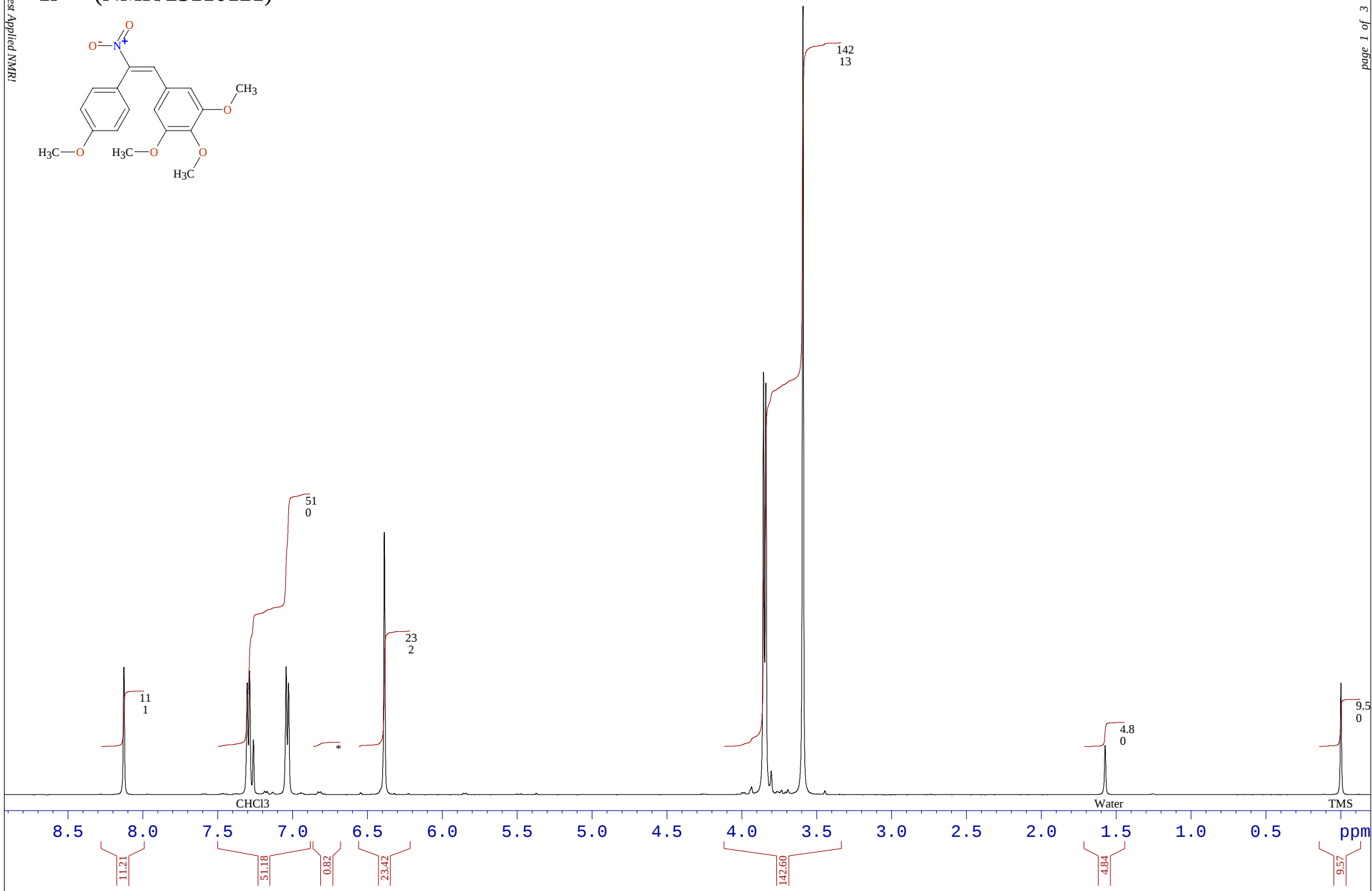
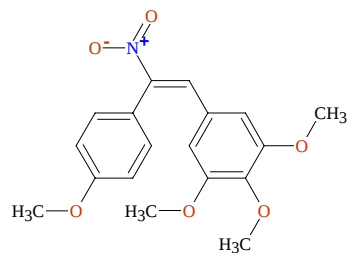
1k (NMR/29330092)

Peaks List

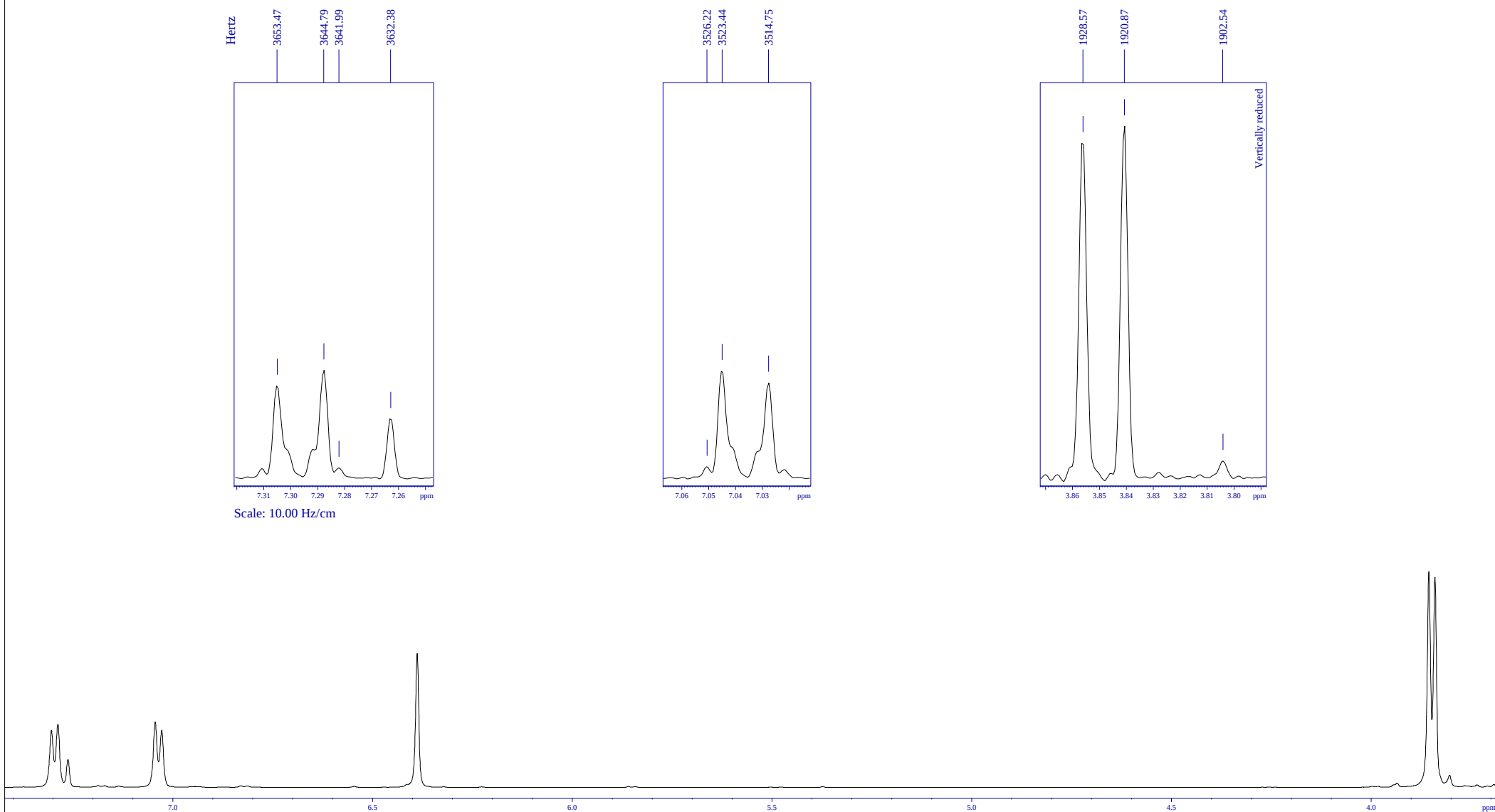
#	Address [points]	Frequency [Hz]	Intensity [cm]
1	9981.9	20224.461	2.15
2	11381.0	18829.127	1.45
3	13321.5	16893.877	5.17
4	13602.1	16613.998	0.33
5	13608.5	16607.580	12.52
6	13614.9	16601.230	0.31
7	13673.1	16543.229	2.37
8	13734.2	16482.283	13.61
9	13738.8	16477.654	0.59
10	13740.9	16475.590	0.30
11	13793.9	16422.736	6.85
12	14024.1	16193.095	0.35
13	14026.2	16191.024	0.66
14	14030.6	16186.608	12.77
15	14077.8	16139.542	0.40
16	14809.9	15409.432	2.18
17	15797.0	14424.980	14.00
18	20514.9	9719.823	8.75
19	20546.9	9687.874	9.00
20	20579.0	9655.926	8.87
21	23281.4	6960.783	3.74
22	30261.0	-0.004	1.28

11 (NMR/23110121)

Found protons = 16 impurity* < 0.1 %



11 (NMR/23110121)



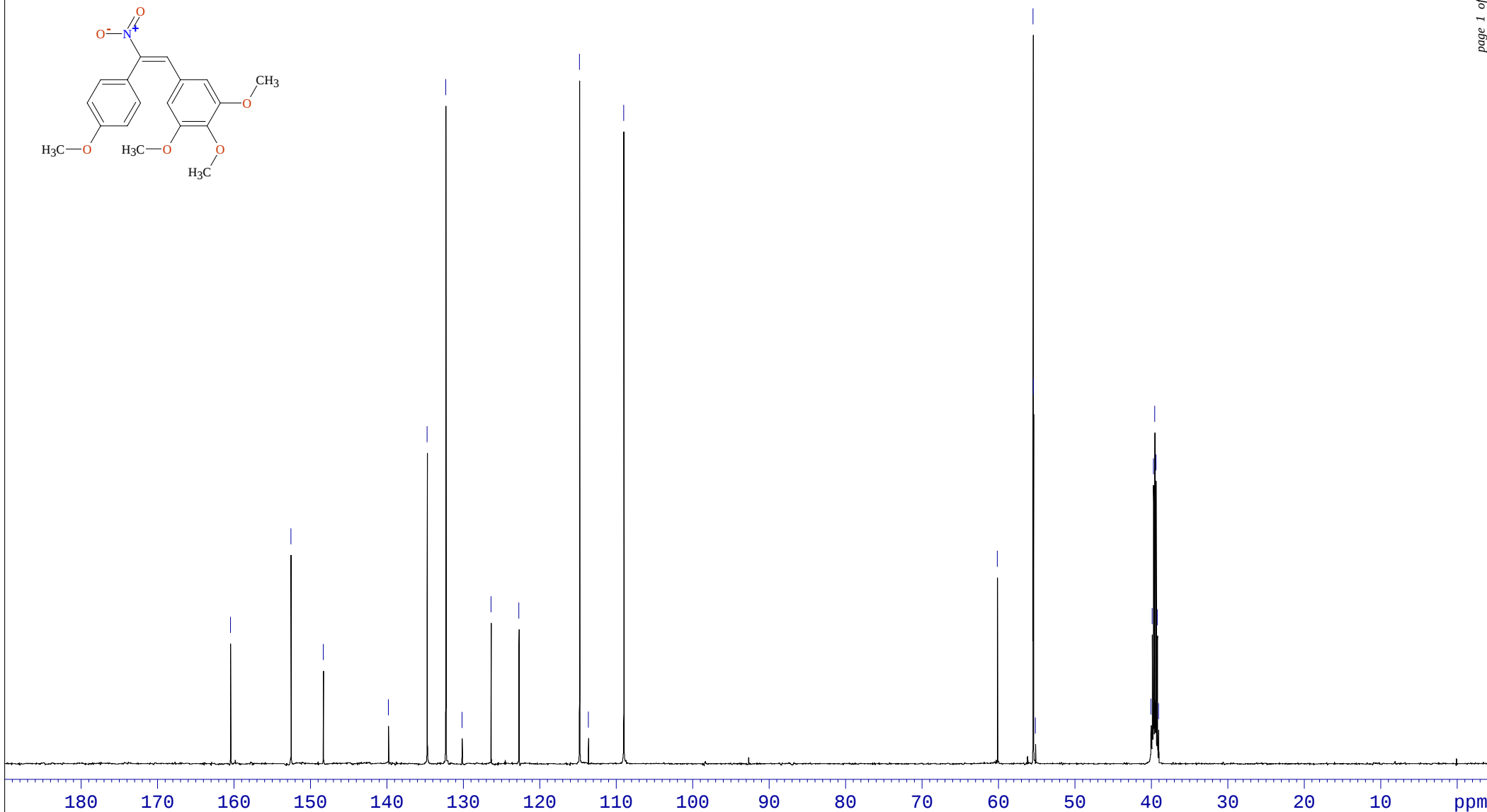
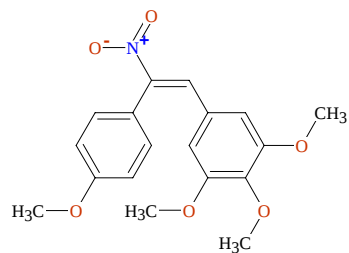
S91

11 (NMR/23110121)

Peaks List

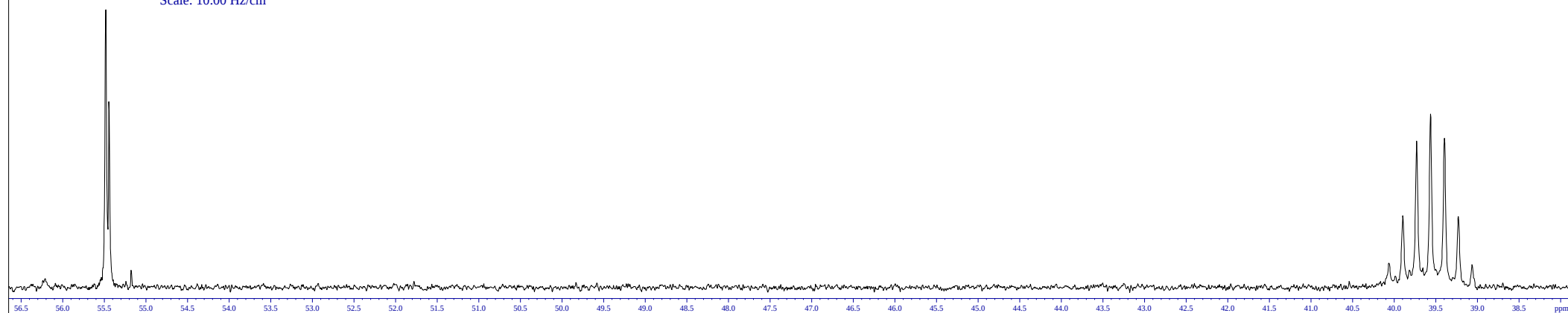
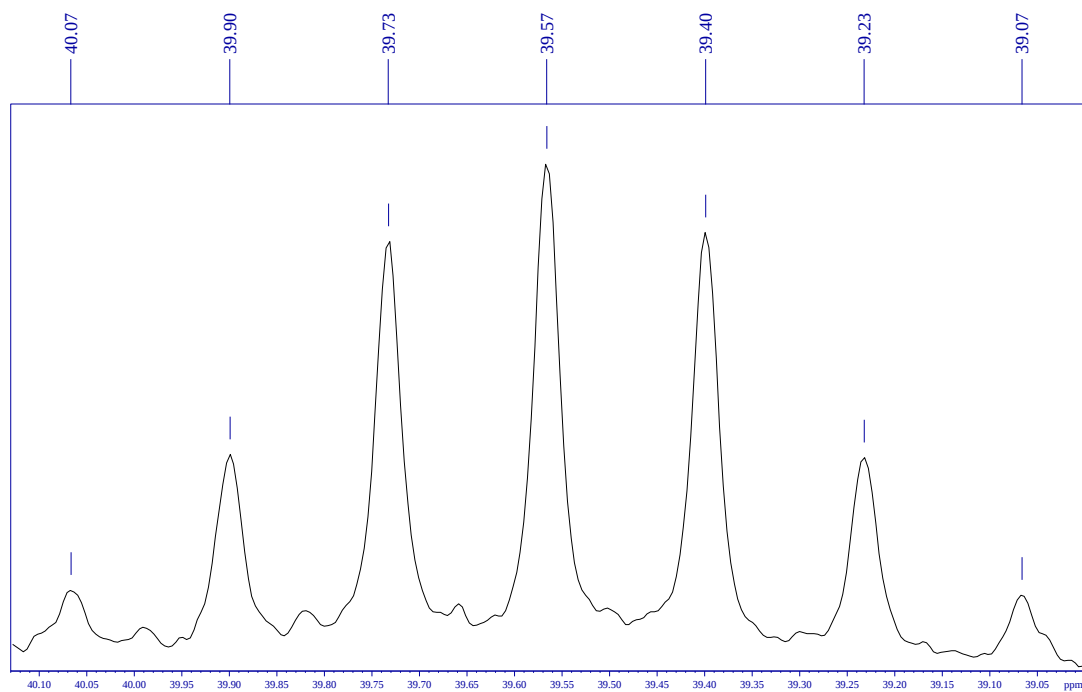
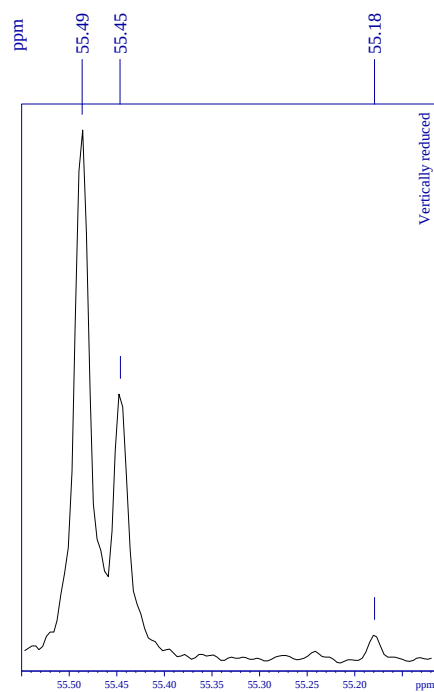
#	Address [points]	Frequency [Hz]	Intensity [ppm]	Intensity [cm]
1	16163.2	4064.895	8.1277	2.44
2	17511.3	3653.467	7.3050	1.84
3	17539.8	3644.786	7.2877	2.14
4	17548.9	3641.993	7.2821	0.20
5	17580.4	3632.379	7.2629	1.19
6	17928.3	3526.224	7.0506	0.23
7	17937.4	3523.438	7.0450	2.14
8	17965.9	3514.748	7.0277	1.89
9	19013.5	3195.037	6.3884	5.01
10	23163.5	1928.568	3.8561	8.43
11	23188.7	1920.872	3.8407	8.75
12	23248.8	1902.543	3.8041	0.43
13	23594.7	1796.983	3.5930	16.00
14	26902.4	787.523	1.5746	0.83
15	29483.0	0.002	0.0000	2.42

11 (NMR/23110121)



S93

11 (NMR/23110121)



S94

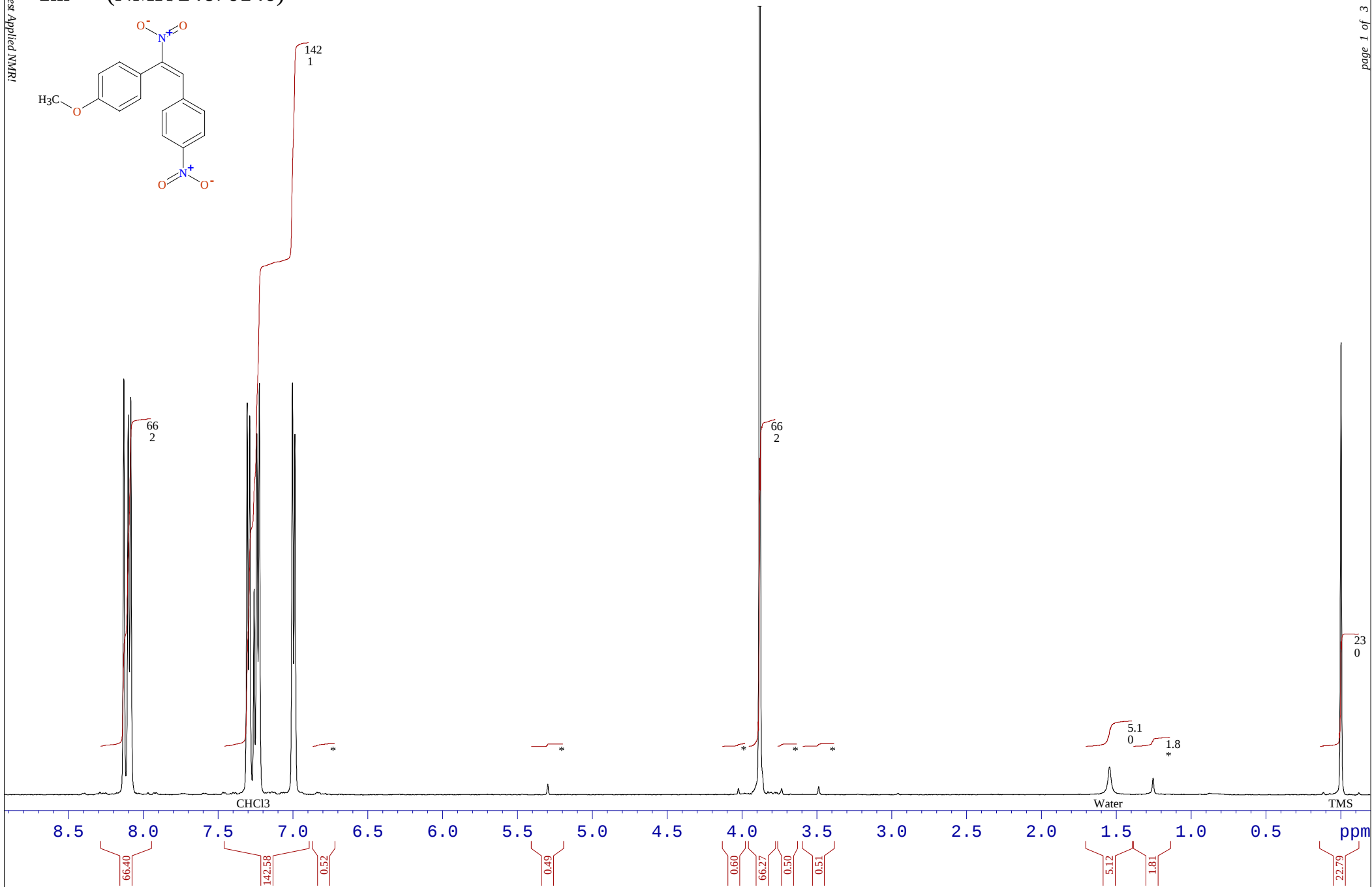
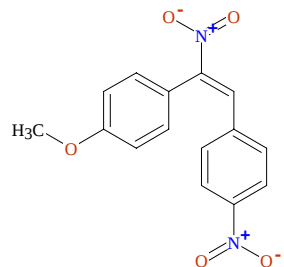
11 (NMR/23110121)

Peaks List

#	Address [points]	Frequency [Hz]	Frequency [ppm]	Intensity [cm]
1	18232.8	20179.107	160.4600	2.65
2	20304.9	19184.832	152.5538	4.28
3	21413.3	18652.996	148.3247	2.12
4	23644.8	17582.205	139.8100	1.06
5	24971.7	16945.510	134.7471	6.20
6	25612.4	16638.076	132.3025	12.86
7	26170.3	16370.372	130.1738	0.72
8	27163.6	15893.773	126.3840	3.02
9	28117.1	15436.230	122.7457	2.90
10	30195.9	14438.755	114.8139	13.08
11	30501.3	14292.213	113.6487	0.76
12	31713.1	13710.762	109.0251	12.14
13	44520.4	7565.351	60.1581	3.91
14	45744.8	6977.849	55.4864	14.00
15	45755.3	6972.798	55.4462	7.07
16	45825.3	6939.221	55.1792	0.66
17	49786.1	5038.676	40.0665	0.91
18	49830.0	5017.633	39.8992	2.69
19	49873.7	4996.667	39.7325	5.52
20	49917.3	4975.735	39.5660	6.53
21	49961.1	4954.720	39.3989	5.61
22	50004.8	4933.746	39.2321	2.66
23	50048.3	4912.873	39.0661	0.85

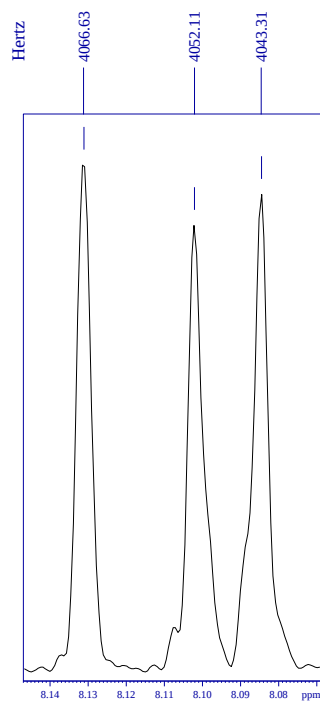
1m (NMR/24670140)

Found protons = 5 impurity* = 1.0 %

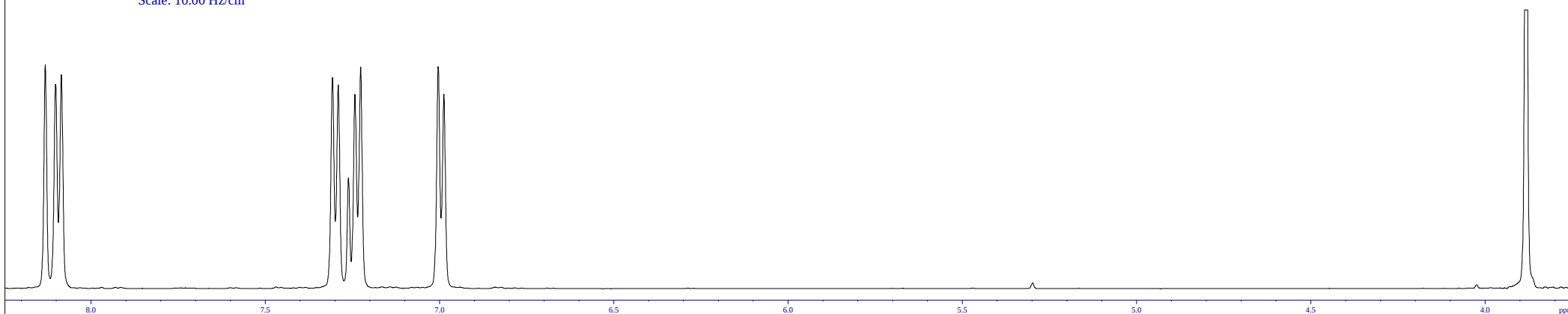
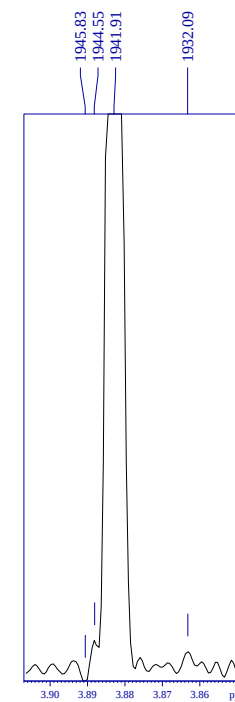
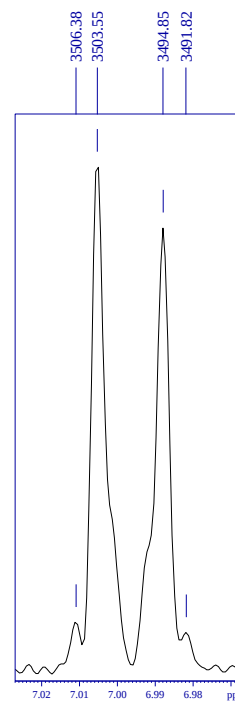
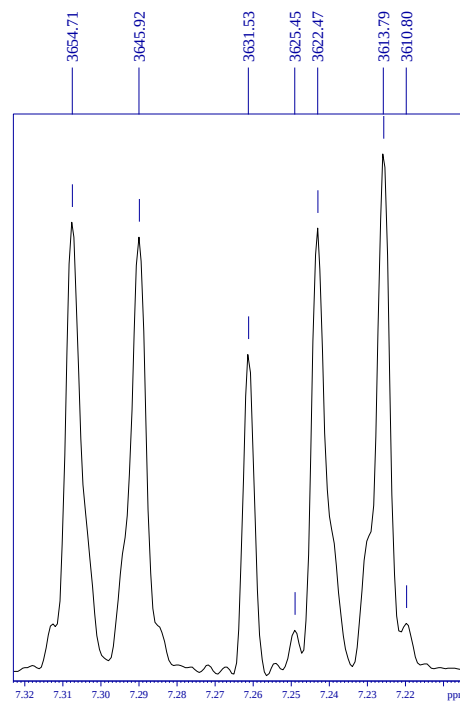


S96

1m (NMR/24670140)



Scale: 10.00 Hz/cm



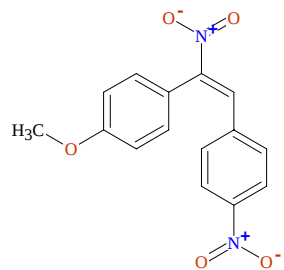
S97

1m (NMR/24670140)

Peaks List

#	Address [points]	Frequency [Hz]	Intensity [ppm]	Intensity [cm]
1	16153.5	4066.628	8.1311	6.95
2	16201.0	4052.113	8.1021	6.05
3	16229.9	4043.314	8.0845	6.48
4	17503.2	3654.709	7.3075	6.11
5	17532.0	3645.918	7.2899	5.89
6	17579.2	3631.528	7.2612	4.31
7	17599.1	3625.455	7.2490	0.54
8	17608.9	3622.466	7.2430	6.01
9	17637.3	3613.787	7.2257	7.08
10	17647.1	3610.805	7.2197	0.63
11	17989.3	3506.379	7.0109	0.65
12	17998.6	3503.548	7.0053	6.93
13	18027.1	3494.851	6.9879	6.02
14	18037.0	3491.824	6.9818	0.51
15	20794.9	2650.177	5.2990	0.25
16	23102.9	1945.827	3.8906	-0.21
17	23107.1	1944.548	3.8881	0.40
18	23115.7	1941.911	3.8828	26.69
19	23147.9	1932.087	3.8632	0.25
20	26945.0	773.297	1.5462	0.27
21	27423.3	627.351	1.2544	0.24
22	29479.0	-0.003	-0.0000	9.45

1m (NMR/24670140)

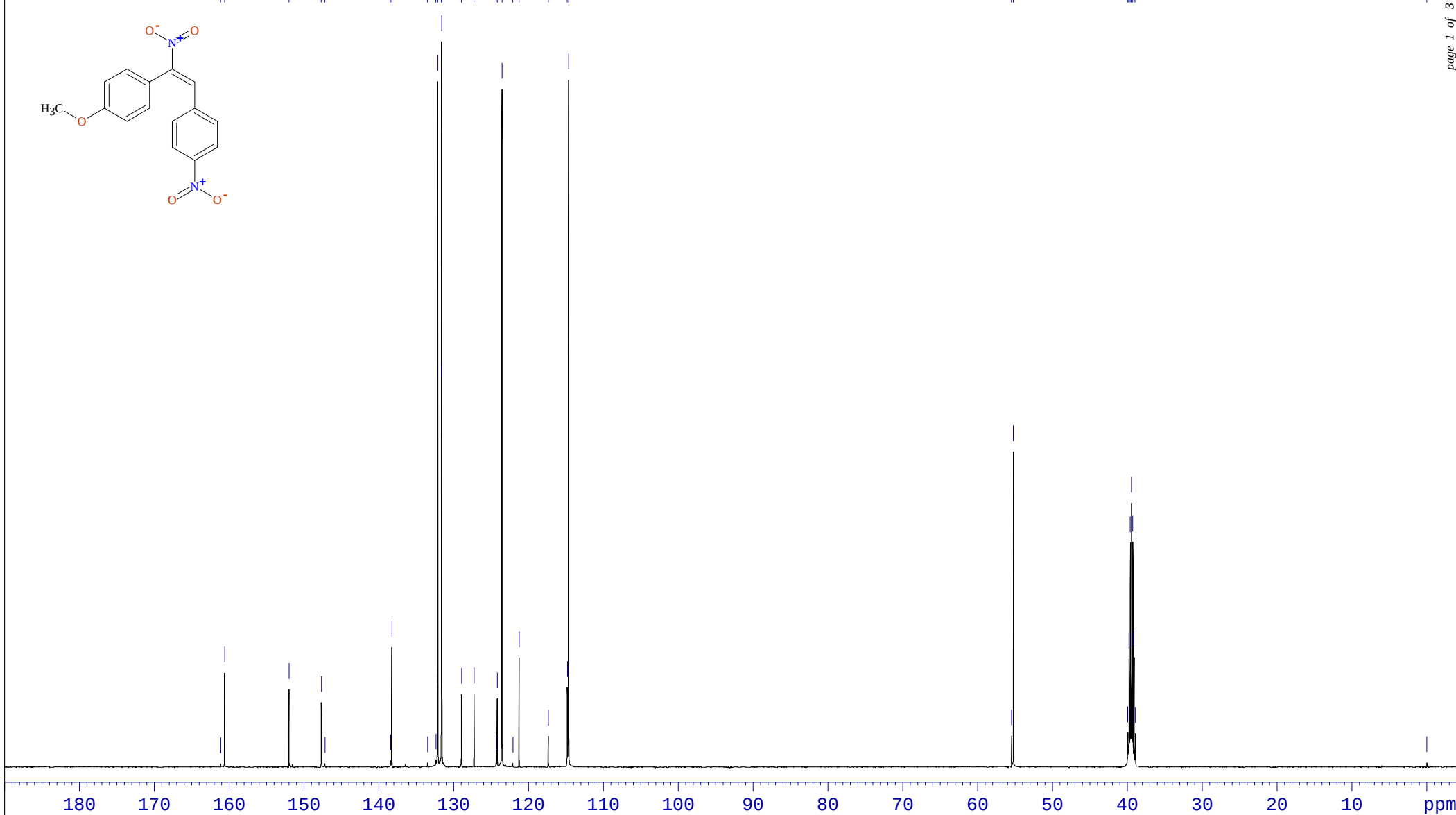


161.12
160.59
151.99
147.66
147.19
138.42
138.25
133.48
132.36
132.11
131.60
131.57
128.94
127.27
124.32
124.17
123.54
122.08
121.25
117.35
114.80
114.64

55.47
55.24

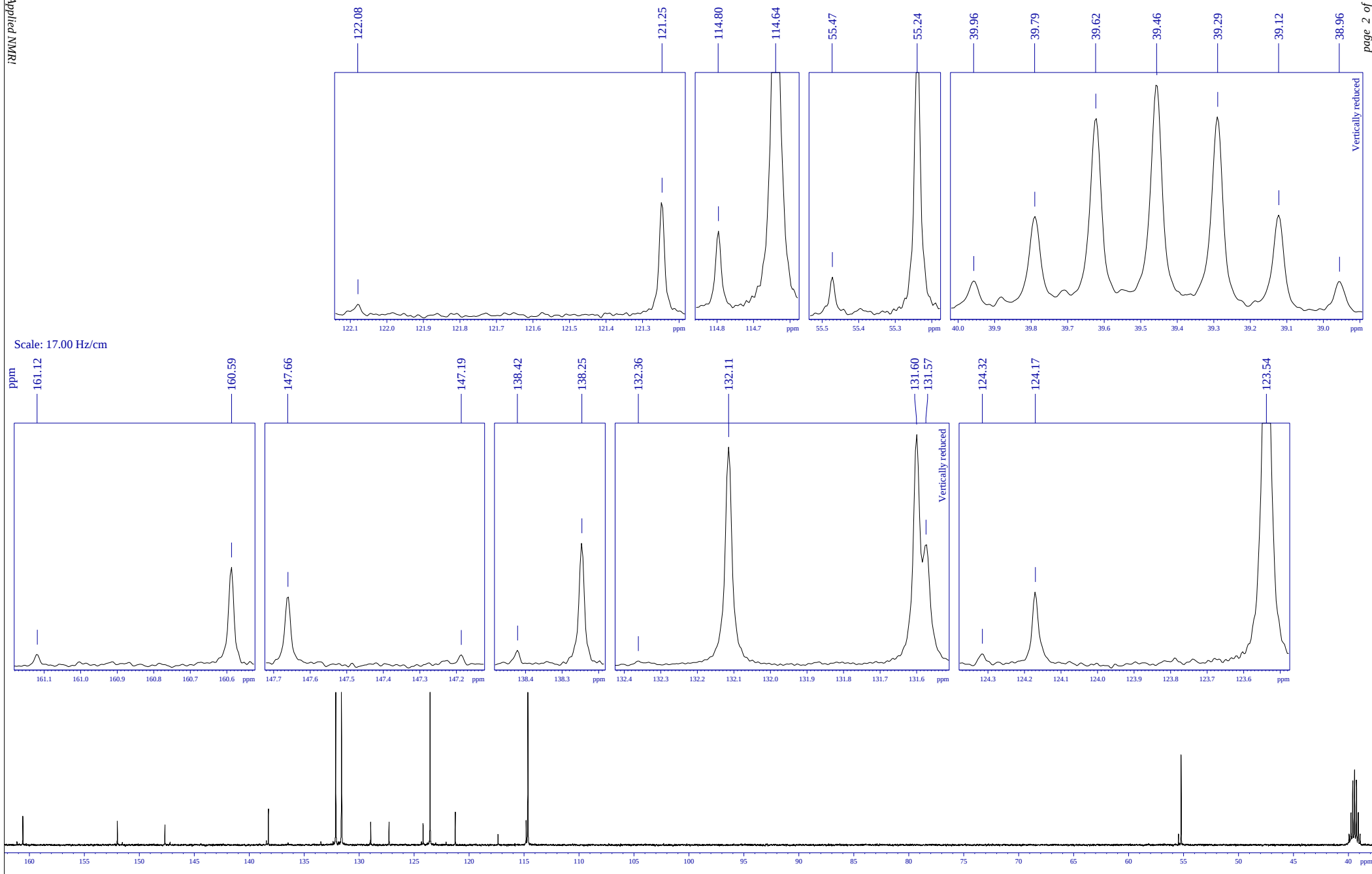
39.96
39.79
39.62
39.46
39.29
39.12
38.96

-0.00



S99

1m (NMR/24670140)



S100

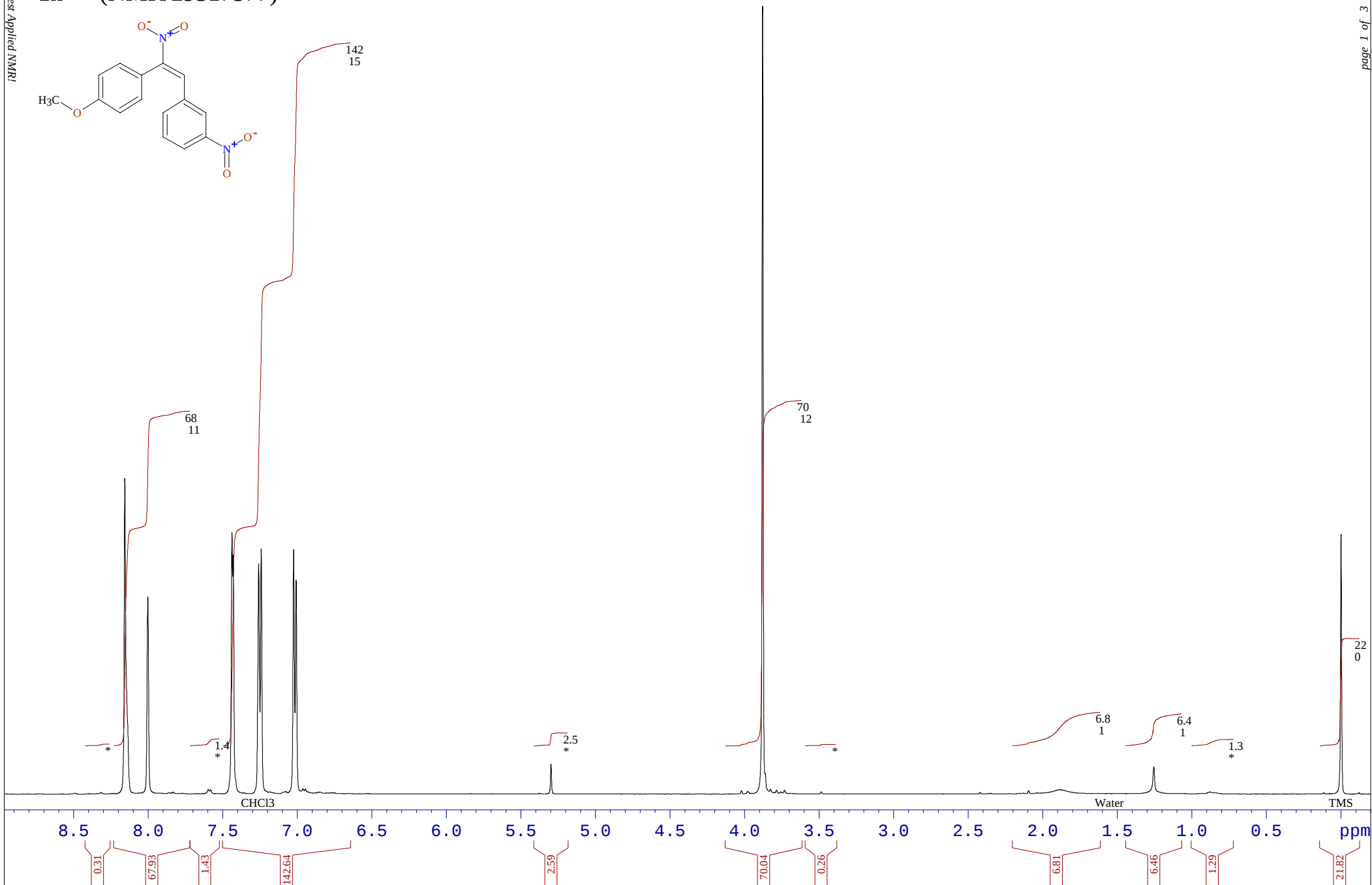
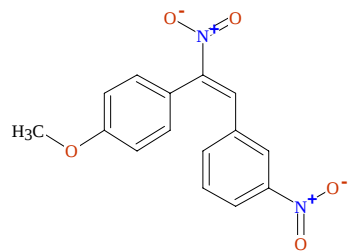
1m (NMR/24670140)

Peaks List

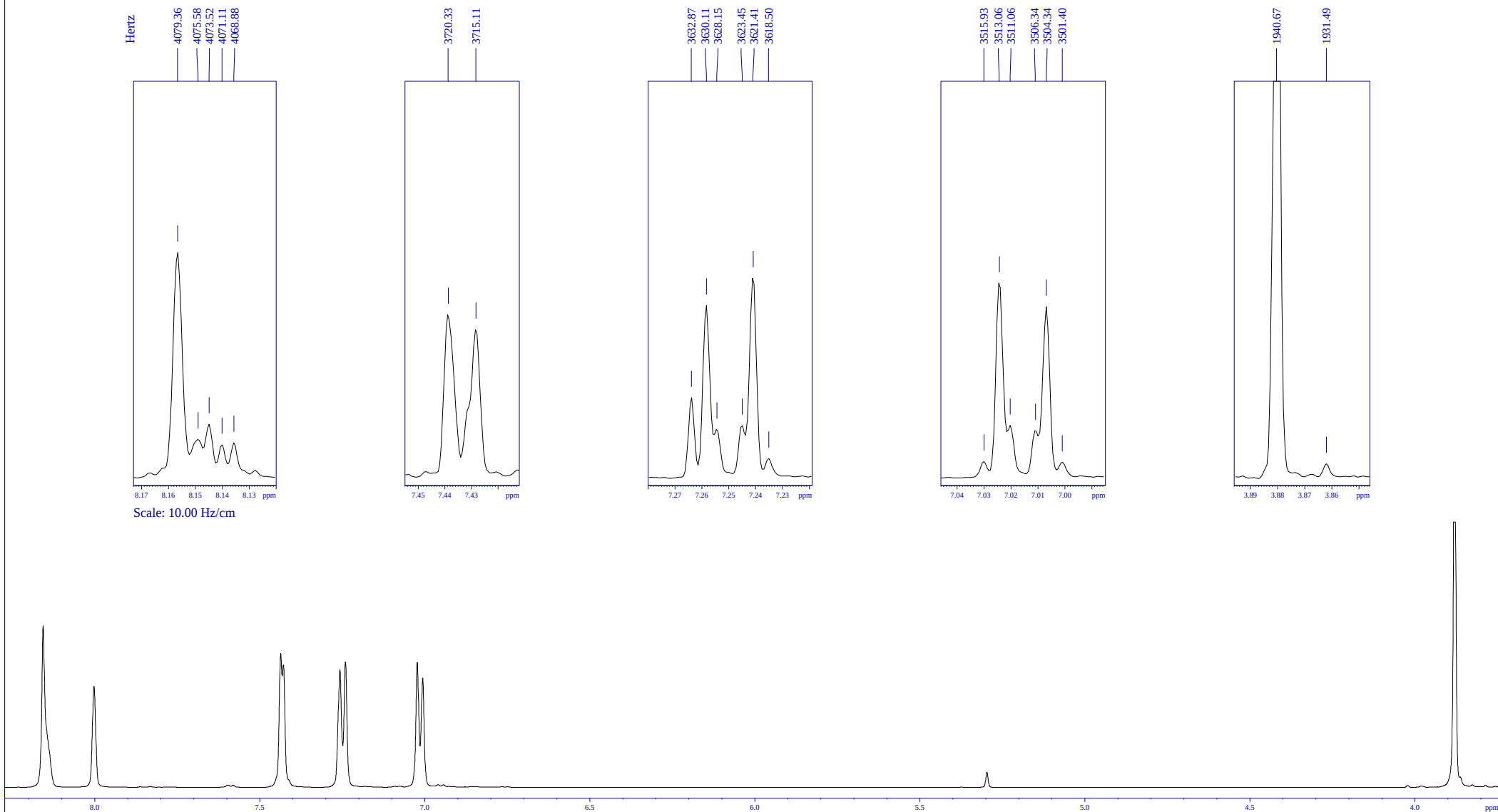
#	Address [points]	Frequency		Intensity [cm]
		[Hz]	[ppm]	
1	18030.5	20261.939	161.1187	0.22
2	18169.8	20195.092	160.5871	1.99
3	20423.4	19113.744	151.9885	1.67
4	21557.6	18569.502	147.6608	1.41
5	21681.8	18509.883	147.1867	0.21
6	23979.0	17407.621	138.4217	0.30
7	24025.1	17385.490	138.2458	2.47
8	25274.5	16786.000	133.4787	0.24
9	25567.3	16645.482	132.3614	0.26
10	25632.1	16614.408	132.1143	13.21
11	25766.8	16549.746	131.6001	14.00
12	25773.6	16546.516	131.5744	7.38
13	26464.2	16215.140	128.9394	1.57
14	26901.1	16005.467	127.2721	1.58
15	27676.1	15633.613	124.3152	0.23
16	27714.1	15615.364	124.1701	1.48
17	27879.9	15535.831	123.5377	13.08
18	28262.2	15352.389	122.0790	0.21
19	28480.3	15247.715	121.2466	2.29
20	29500.4	14758.255	117.3545	0.74
21	30170.9	14436.527	114.7962	1.69
22	30212.1	14416.750	114.6390	13.25
23	45718.9	6976.045	55.4720	0.76
24	45779.9	6946.768	55.2392	6.19
25	49785.1	5024.909	39.9570	0.76
26	49828.9	5003.915	39.7901	2.21
27	49872.6	4982.909	39.6230	4.43
28	49916.4	4961.895	39.4559	5.20
29	49960.1	4940.934	39.2893	4.45
30	50004.0	4919.885	39.1219	2.24
31	50047.5	4899.000	38.9558	0.75
32	60257.3	-0.004	-0.0000	0.26

1n (NMR/29317577)

Found protons = 40 impurity* = 1.1 %



1n (NMR/29317577)



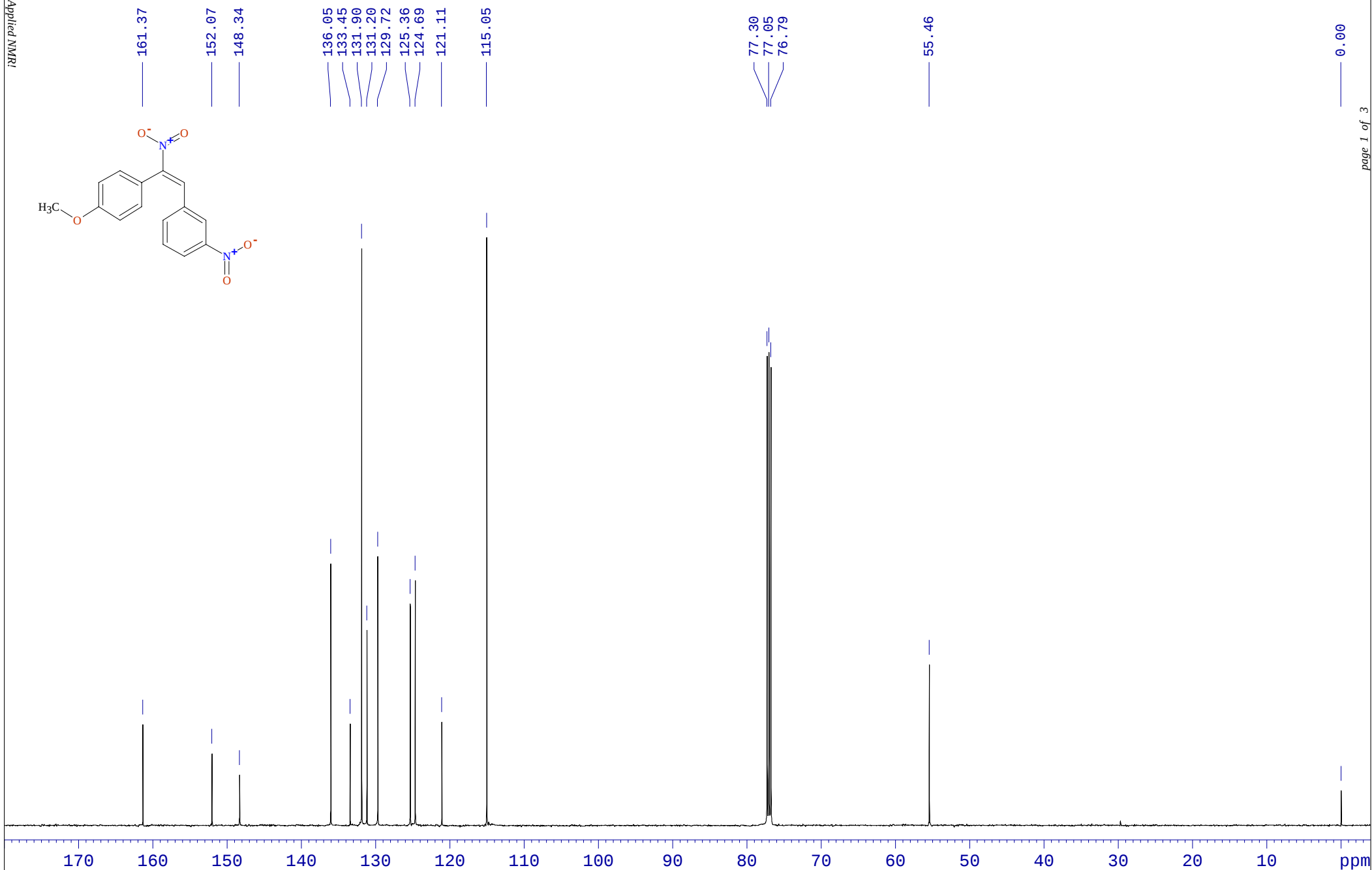
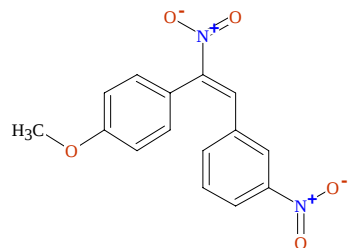
S103

1n (NMR/29317577)

Peaks List

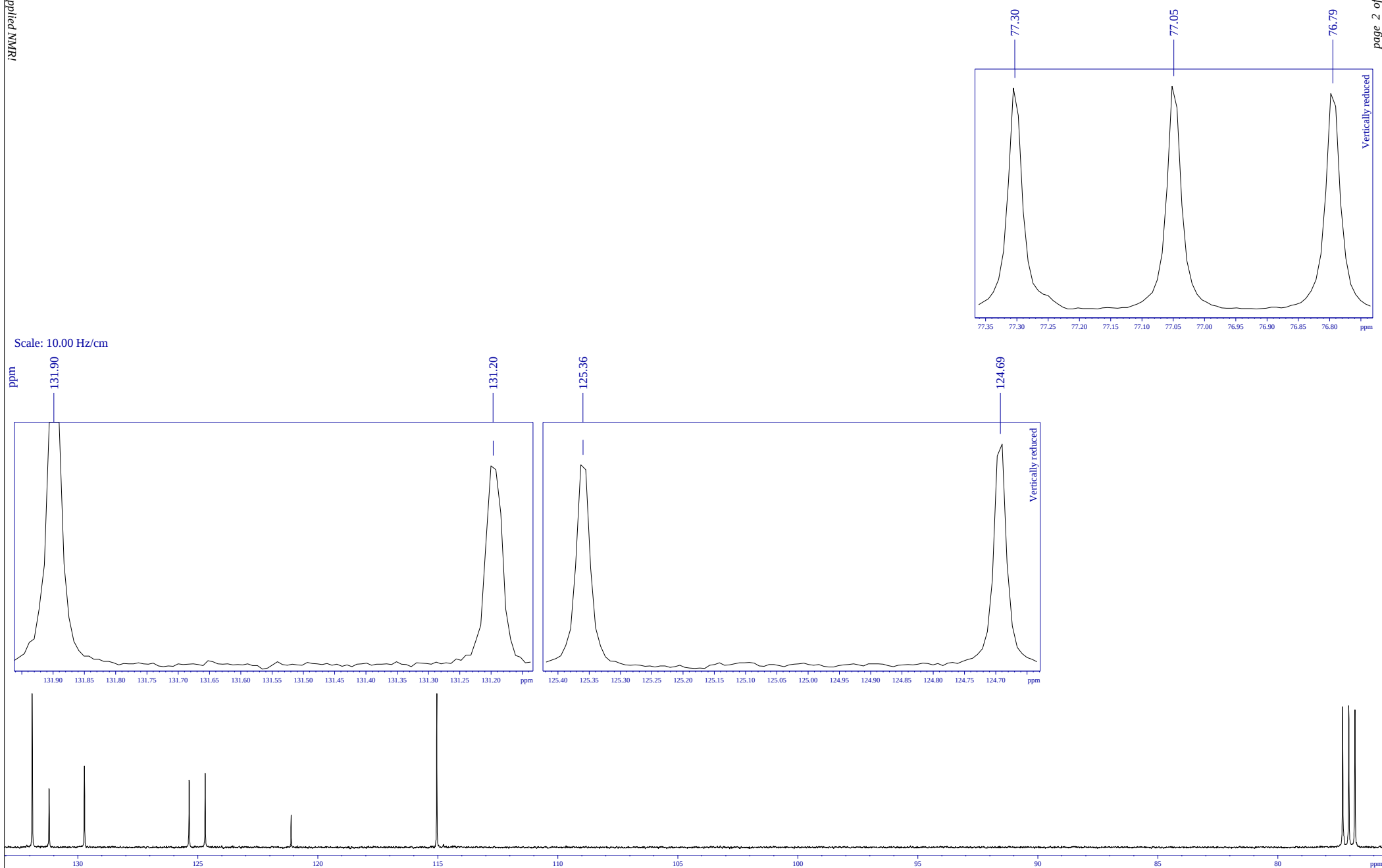
#	Address [points]	Frequency [Hz]	Intensity [cm]
1	16114.8	4079.357	8.1566
2	16127.1	4075.581	8.1490
3	16133.9	4073.516	8.1449
4	16141.8	4071.115	8.1401
5	16149.1	4068.883	8.1357
6	16367.4	4002.258	8.0024
7	17291.2	3720.329	7.4387
8	17308.3	3715.115	7.4283
9	17577.8	3632.870	7.2639
10	17586.9	3630.111	7.2583
11	17593.3	3628.152	7.2544
12	17608.7	3623.445	7.2450
13	17615.4	3621.409	7.2409
14	17624.9	3618.500	7.2351
15	17961.0	3515.928	7.0300
16	17970.4	3513.062	7.0243
17	17977.0	3511.057	7.0203
18	17992.4	3506.337	7.0109
19	17999.0	3504.339	7.0069
20	18008.6	3501.398	7.0010
21	20800.3	2649.460	5.2975
22	23122.8	1940.669	3.8803
23	23152.9	1931.492	3.8620
24	27424.1	628.037	1.2557
25	29482.0	0.002	0.0000

1n (NMR/29317577)



S105

1n (NMR/29317577)



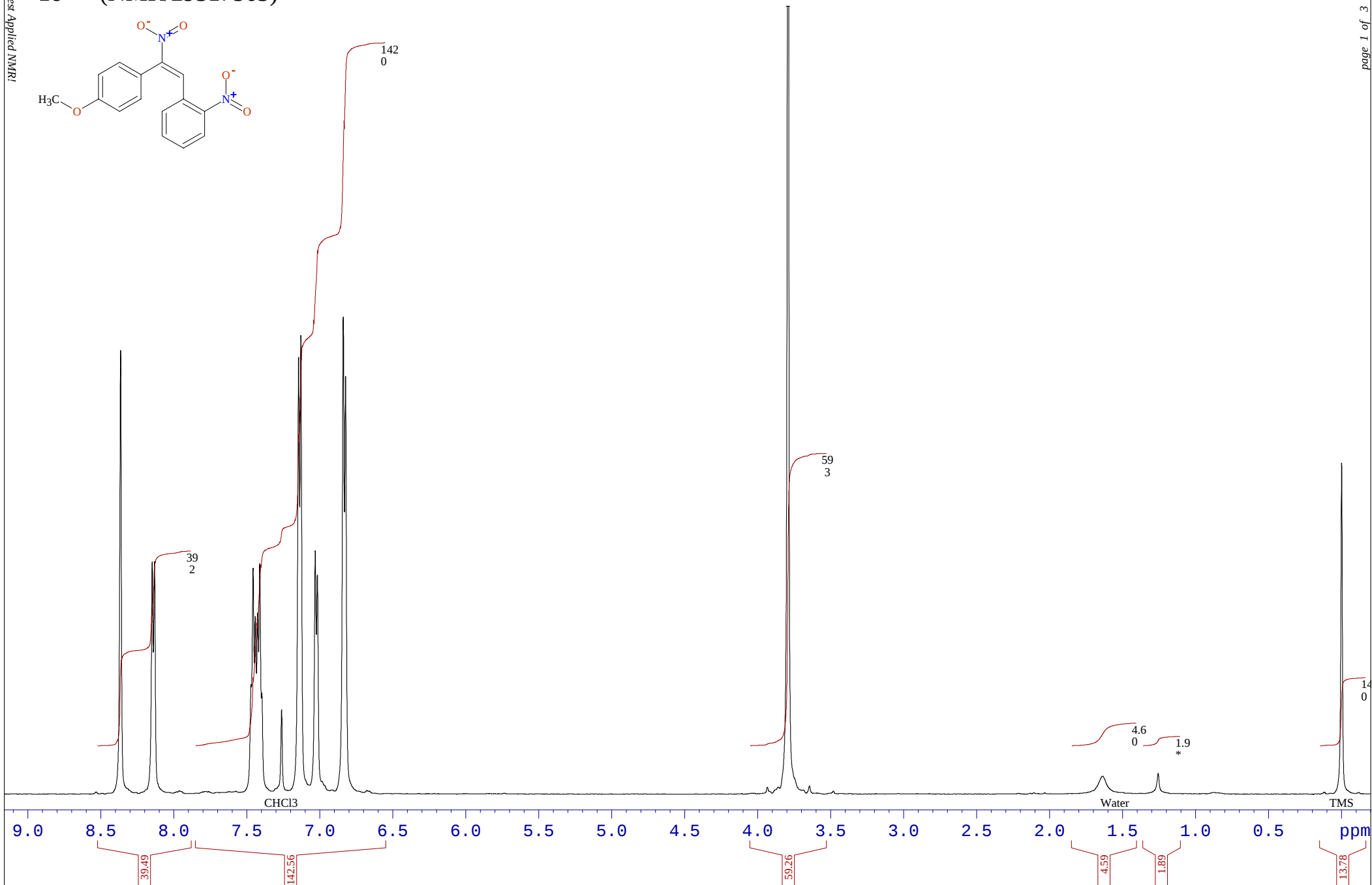
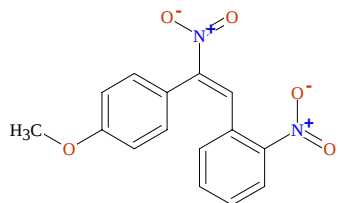
1n (NMR/29317577)

Peaks List

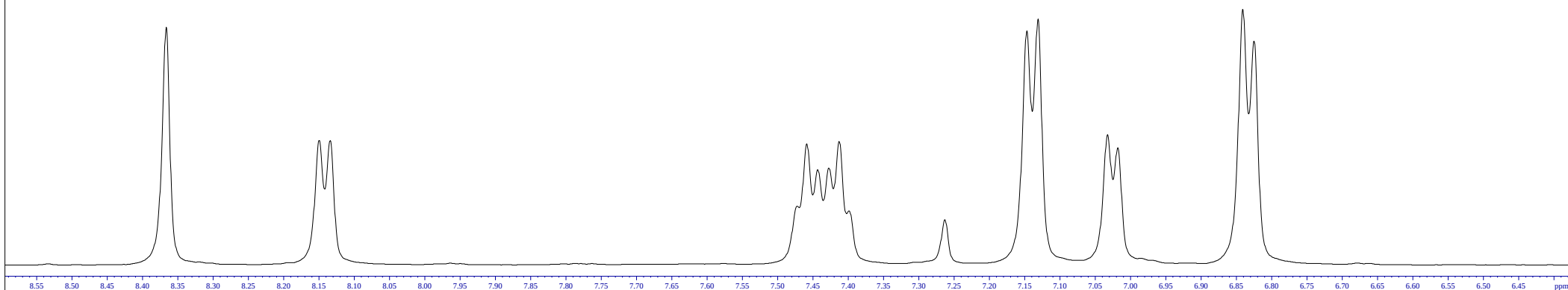
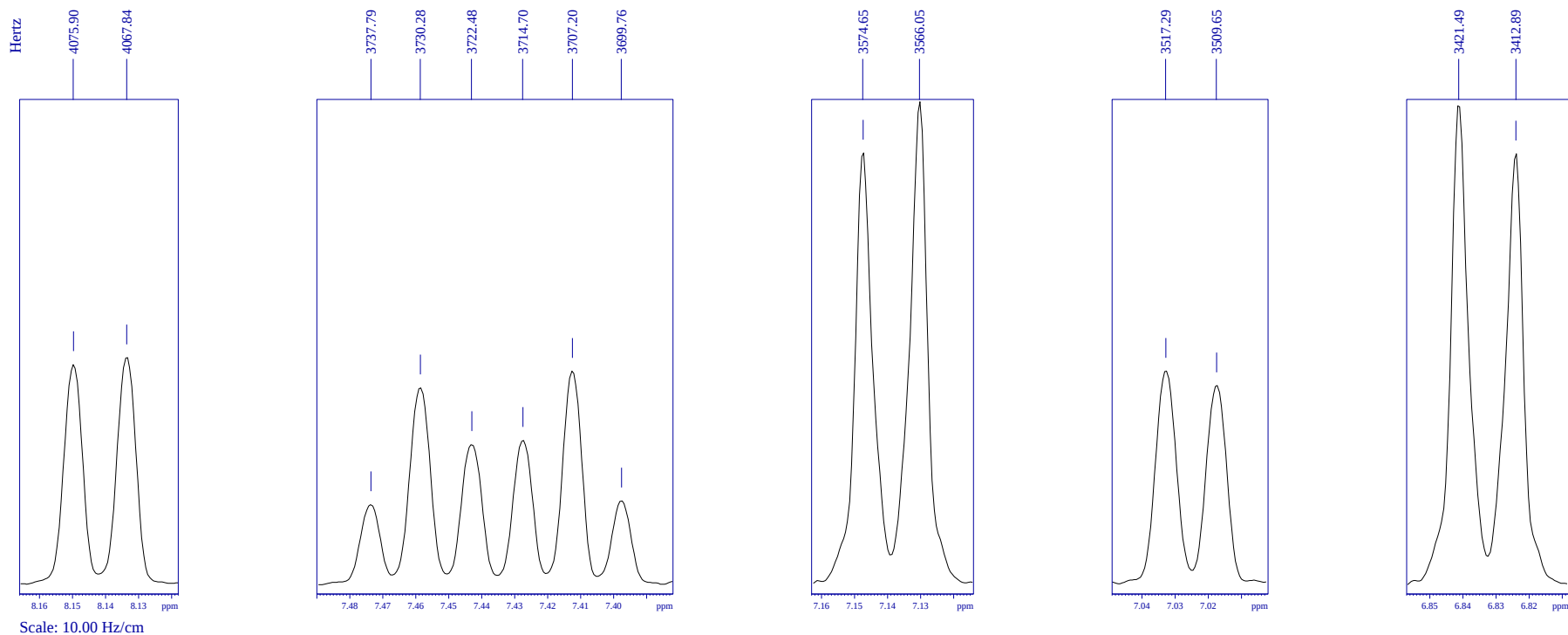
#	Address [points]	Frequency [Hz]	Intensity [cm]
1	9914.2	20293.023	161.3659
2	11086.9	19123.477	152.0659
3	11556.4	18655.270	148.3428
4	13105.8	17109.955	136.0548
5	13434.7	16782.018	133.4471
6	13630.0	16587.232	131.8983
7	13718.5	16498.998	131.1966
8	13904.0	16313.911	129.7249
9	14454.5	15764.979	125.3599
10	14538.6	15681.068	124.6926
11	14989.9	15231.023	121.1140
12	15753.9	14469.016	115.0546
13	20514.3	9721.480	77.3032
14	20546.3	9689.521	77.0491
15	20578.4	9657.546	76.7948
16	23268.4	6974.750	55.4618
17	30262.0	0.004	0.0000

1o (NMR/29317563)

Found protons = 5 impurity* = 1.3 %



1o (NMR/29317563)

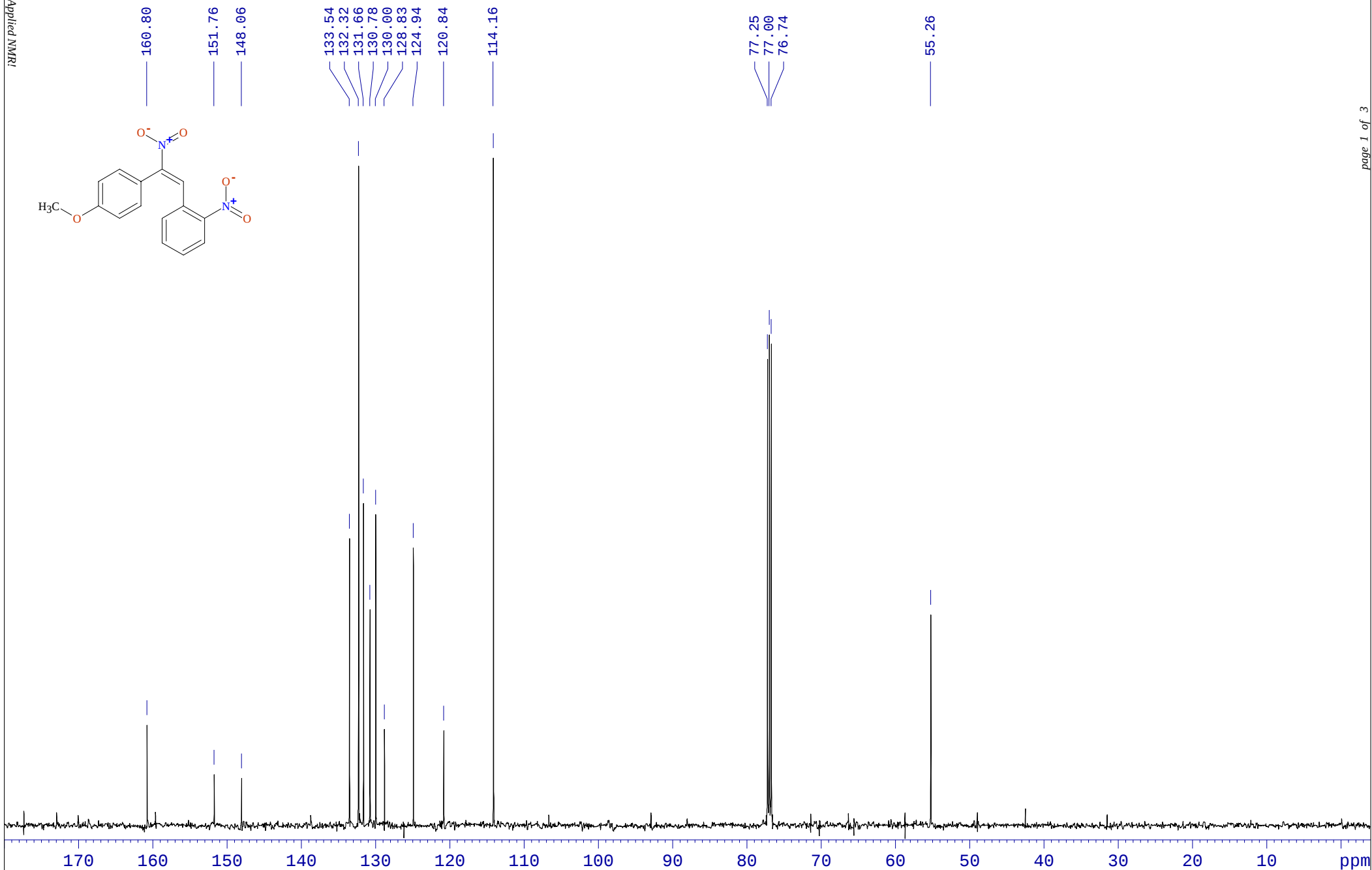
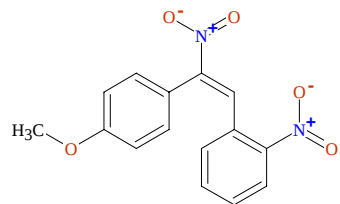


1o (NMR/29317563)

Peaks List

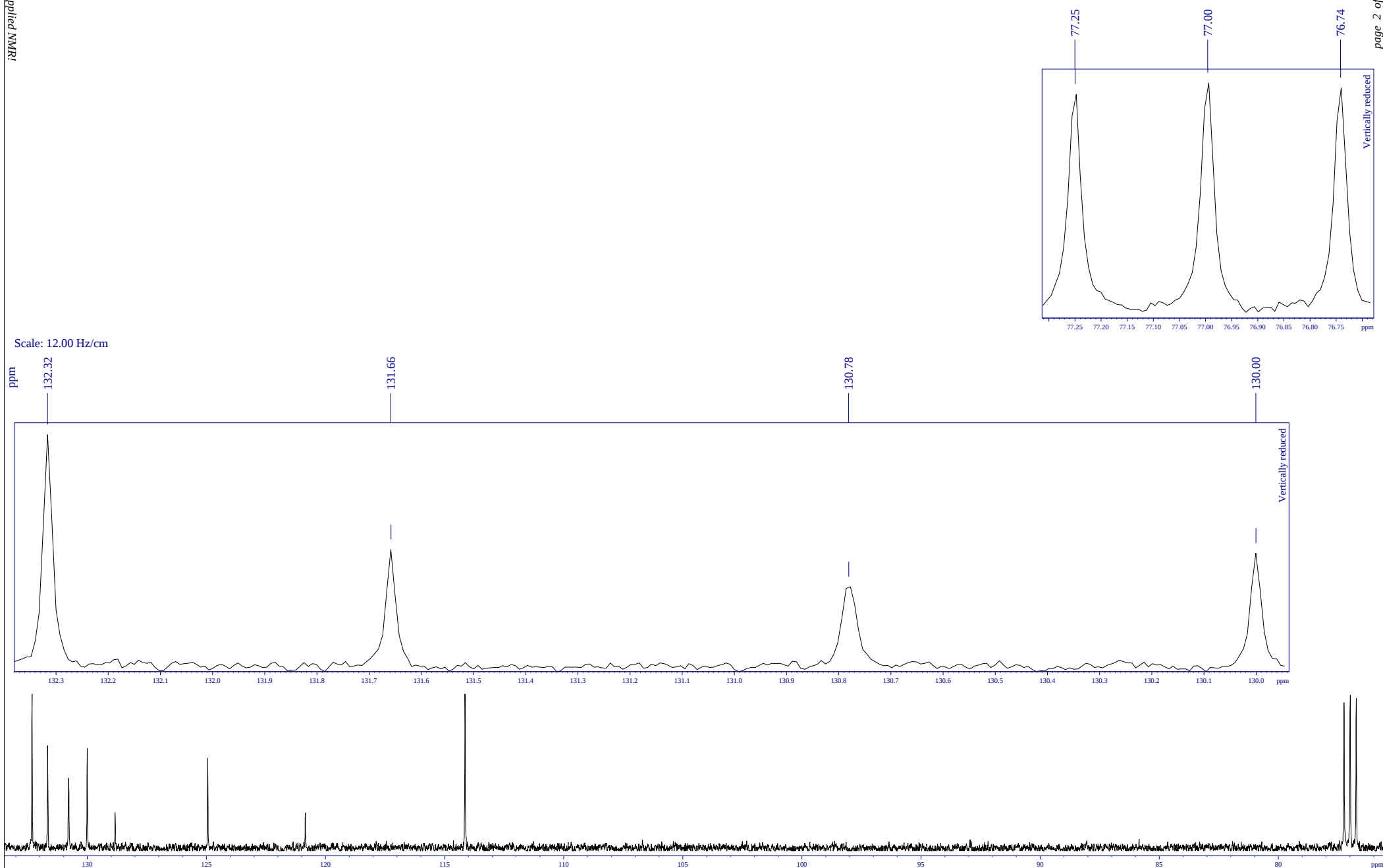
#	Address [points]	Frequency [Hz]	Intensity [cm]
1	15771.4	4184.156	7.96
2	16126.1	4075.896	3.38
3	16152.5	4067.835	3.50
4	17234.0	3737.791	1.23
5	17258.6	3730.276	3.03
6	17284.2	3722.483	2.15
7	17309.7	3714.705	2.22
8	17334.3	3707.198	3.28
9	17358.6	3699.762	1.29
10	17579.5	3632.344	1.75
11	17768.6	3574.647	6.67
12	17796.8	3566.054	7.43
13	17956.6	3517.290	3.29
14	17981.6	3509.650	3.06
15	18270.5	3421.488	7.42
16	18298.7	3412.888	6.65
17	23265.8	1897.026	28.00
18	27422.2	628.595	0.27
19	29482.0	0.002	6.83

1o (NMR/29317563)



S111

1o (NMR/29317563)



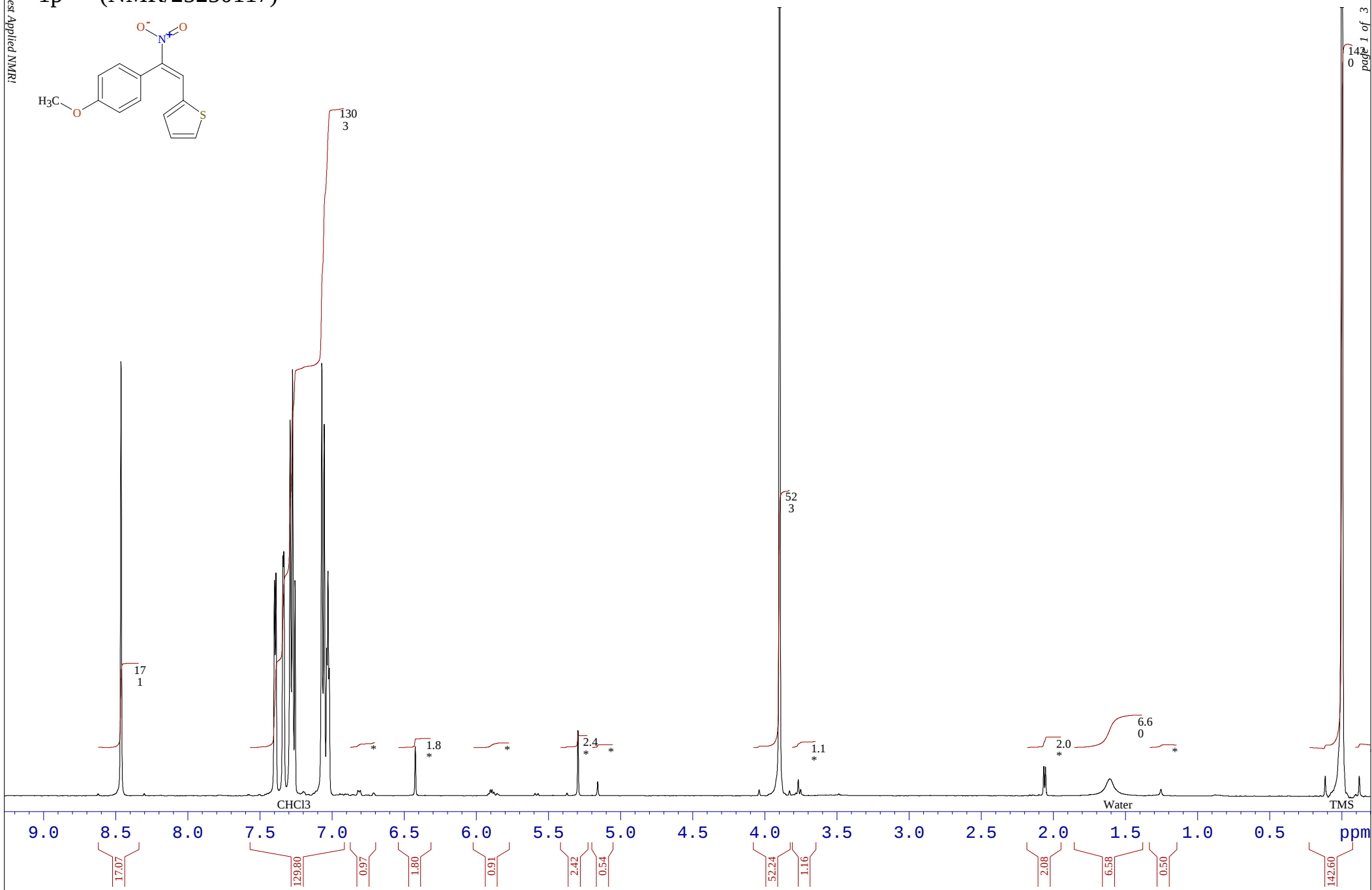
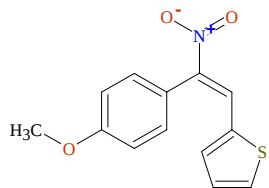
1o (NMR/29317563)

Peaks List

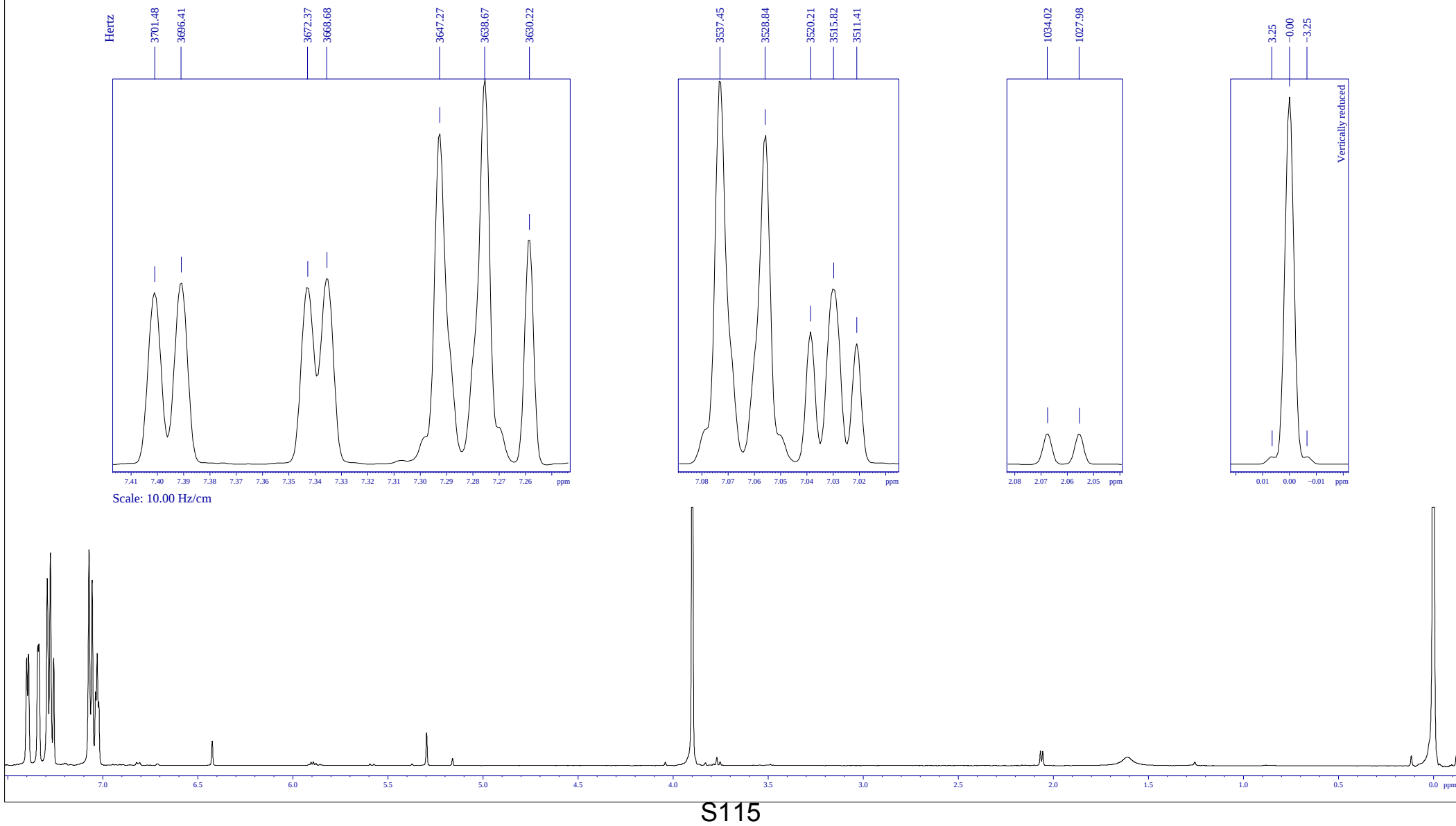
#	Address [points]	Frequency		Intensity
		[Hz]	[ppm]	[cm]
1	9978.2	20221.910	160.8004	2.52
2	11117.8	19085.383	151.7630	1.50
3	11584.5	18619.963	148.0621	1.33
4	13416.2	16793.193	133.5360	6.31
5	13570.0	16639.756	132.3159	13.81
6	13653.0	16557.031	131.6581	6.97
7	13763.6	16446.701	130.7808	4.85
8	13862.0	16348.567	130.0004	6.75
9	14010.1	16200.855	128.8259	2.42
10	14500.3	15711.943	124.9381	6.28
11	15016.7	15196.954	120.8430	2.45
12	15859.9	14356.018	114.1561	14.00
13	20513.7	9714.764	77.2498	10.07
14	20545.7	9682.812	76.9957	10.54
15	20577.8	9650.828	76.7414	10.26
16	23286.8	6949.138	55.2581	4.77

1p (NMR/25250117)

Found protons = 7 impurity* = 7.7 %



1p (NMR/25250117)

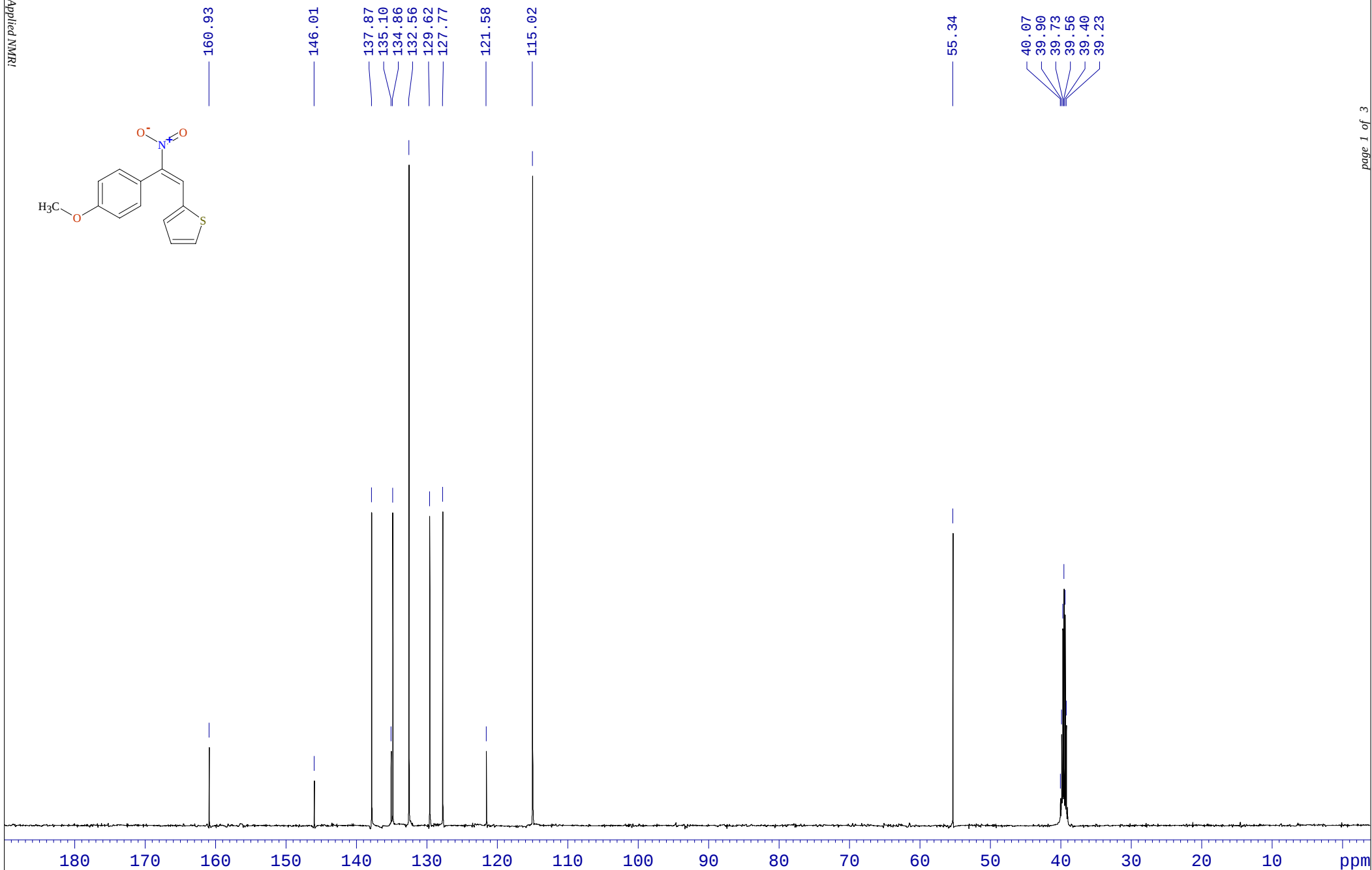
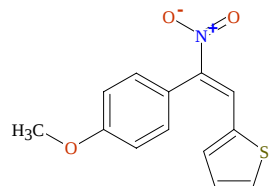


1p (NMR/25250117)

Peaks List

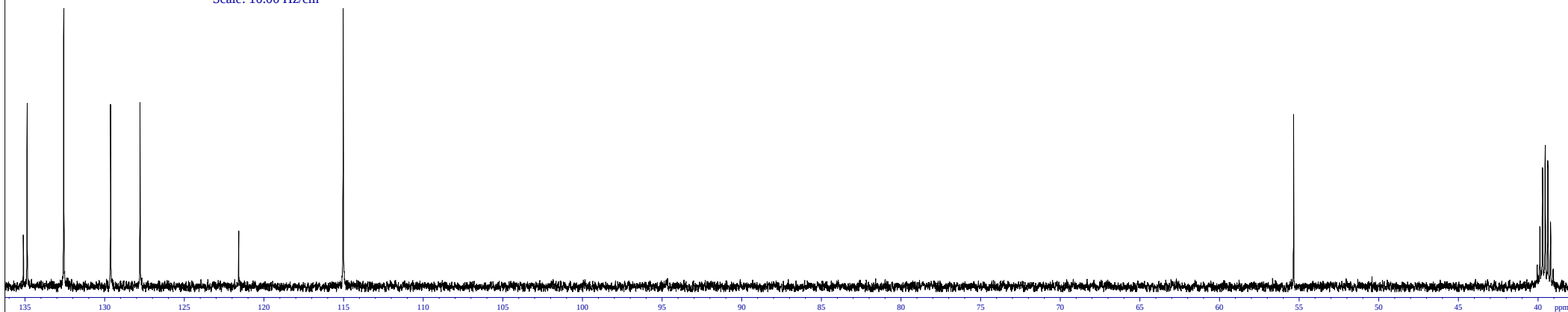
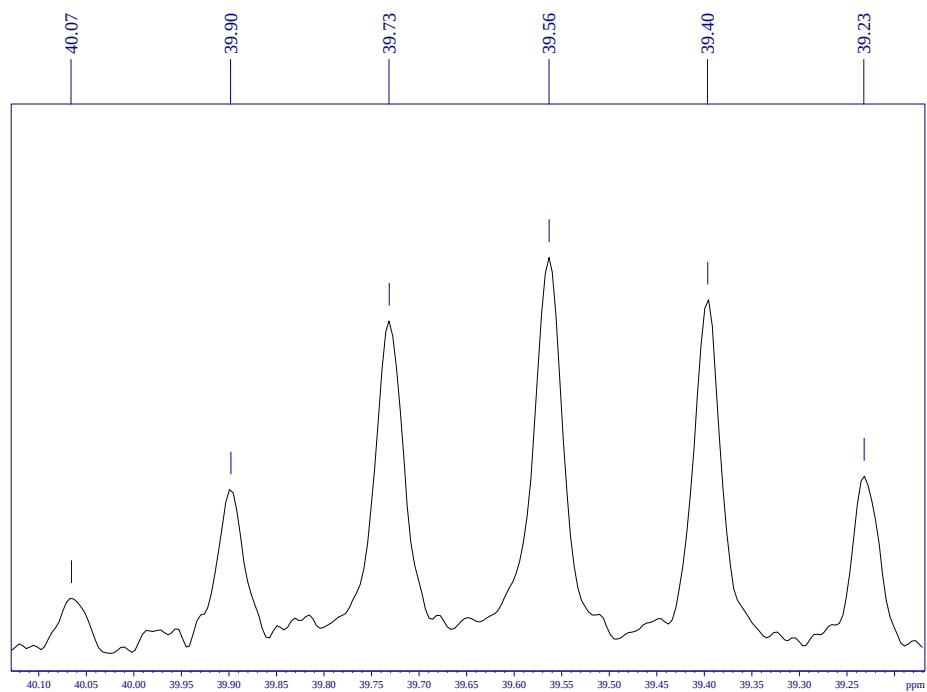
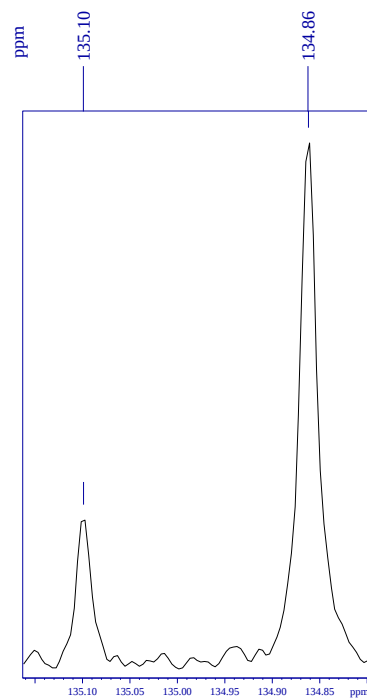
#	Address [points]	Frequency [Hz]	Intensity [cm]
1	15601.0	4233.395	7.55
2	17344.0	3701.476	3.27
3	17360.6	3696.412	3.47
4	17439.4	3672.369	3.38
5	17451.5	3668.683	3.56
6	17521.6	3647.269	6.35
7	17549.8	3638.673	7.45
8	17577.5	3630.216	4.34
9	17881.5	3537.451	7.39
10	17909.7	3528.843	6.30
11	17938.0	3520.214	2.52
12	17952.4	3515.815	3.35
13	17966.8	3511.408	2.31
14	18944.2	3213.132	1.00
15	20792.8	2648.991	1.34
16	21016.0	2580.869	0.29
17	23083.2	1950.003	27.84
18	23294.7	1885.455	0.31
19	26084.7	1034.019	0.58
20	26104.5	1027.977	0.58
21	29282.0	58.296	0.39
22	29462.4	3.246	1.60
23	29473.0	-0.003	79.07
24	29483.6	-3.251	1.60
25	29669.3	-59.911	0.39

1p (NMR/25250117)



S117

1p (NMR/25250117)



S118

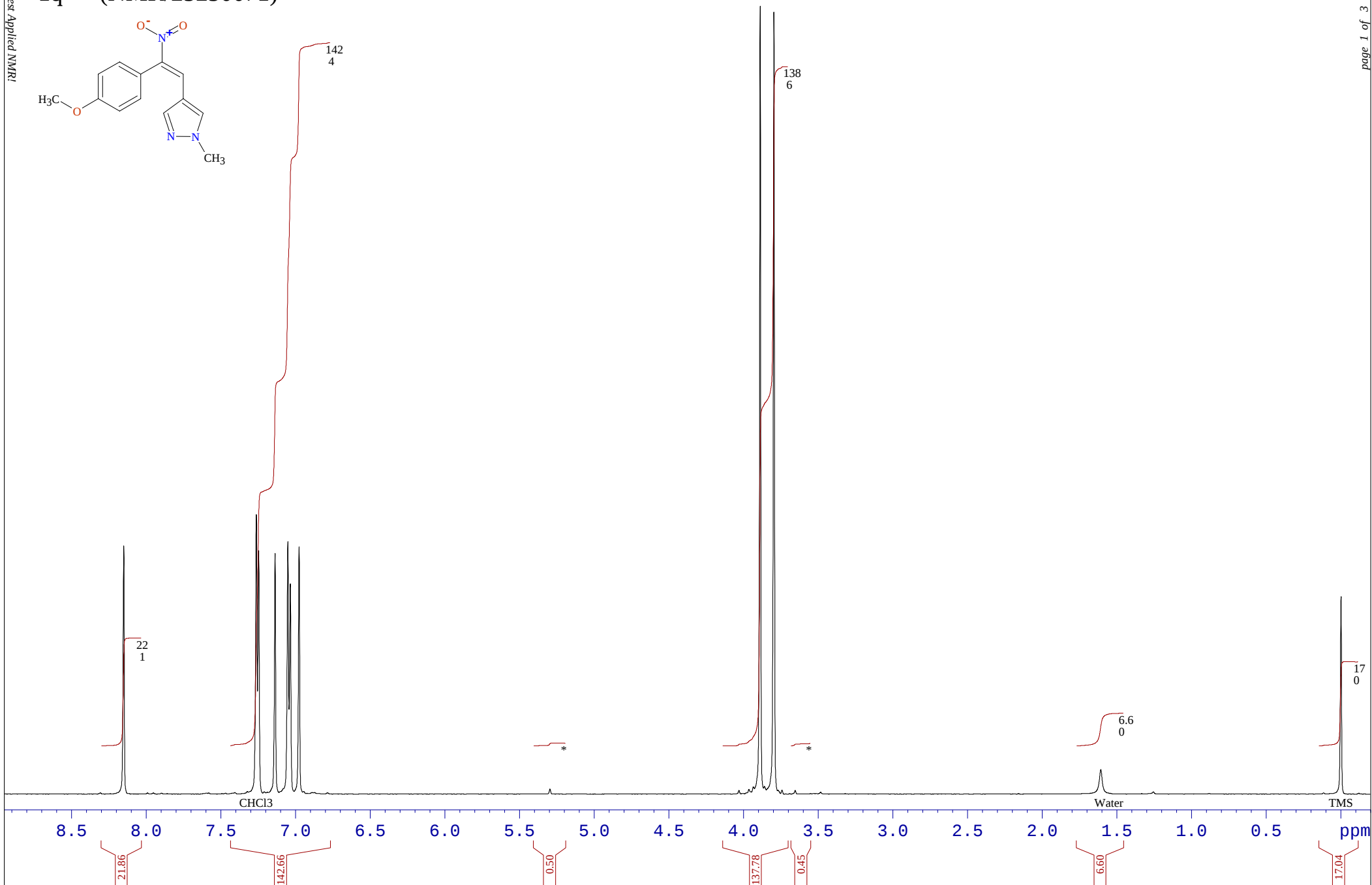
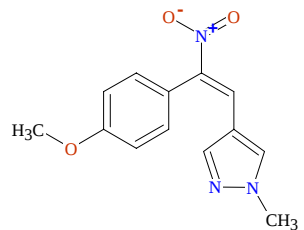
1p (NMR/25250117)

Peaks List

#	Address [points]	Frequency [Hz]	Intensity [cm]
1	18109.6	20238.225	160.9301
2	22020.9	18361.404	146.0060
3	24153.5	17338.109	137.8690
4	24879.6	16989.742	135.0989
5	24941.7	16959.938	134.8619
6	25544.8	16670.523	132.5605
7	26315.2	16300.845	129.6209
8	26799.3	16068.566	127.7739
9	28423.9	15289.049	121.5753
10	30142.5	14464.390	115.0178
11	45783.6	6959.214	55.3382
12	49786.3	5038.569	40.0656
13	49830.3	5017.468	39.8979
14	49873.9	4996.541	39.7314
15	49918.0	4975.378	39.5632
16	49961.7	4954.401	39.3964
17	50004.8	4933.721	39.2319

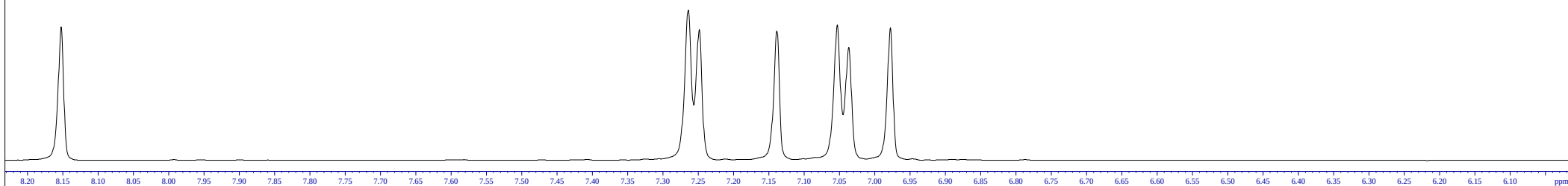
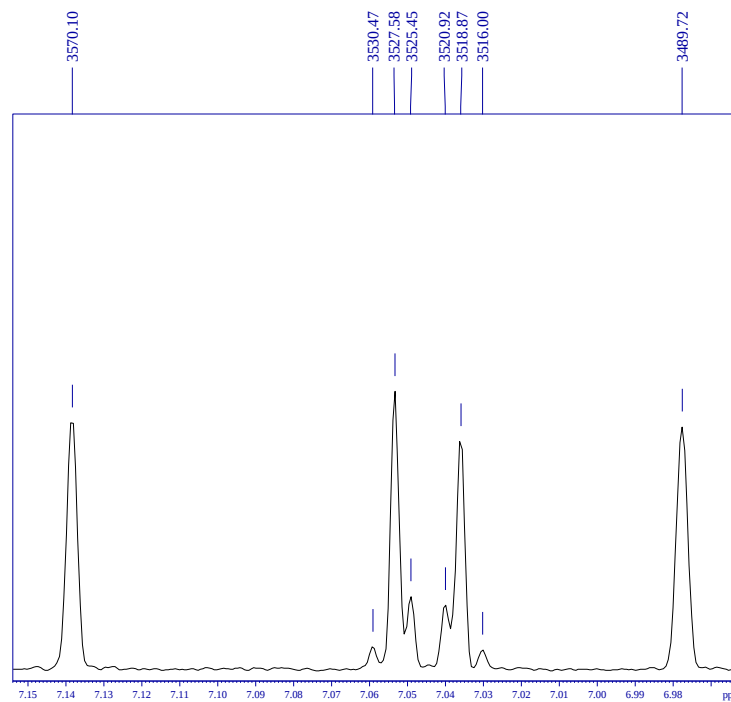
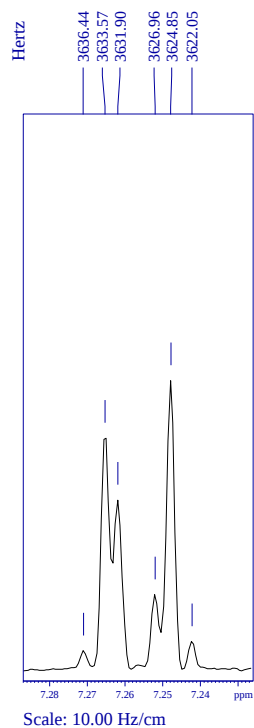
1q (NMR/25250071)

Found protons = 11 impurity* < 0.1 %



S120

1q (NMR/25250071)



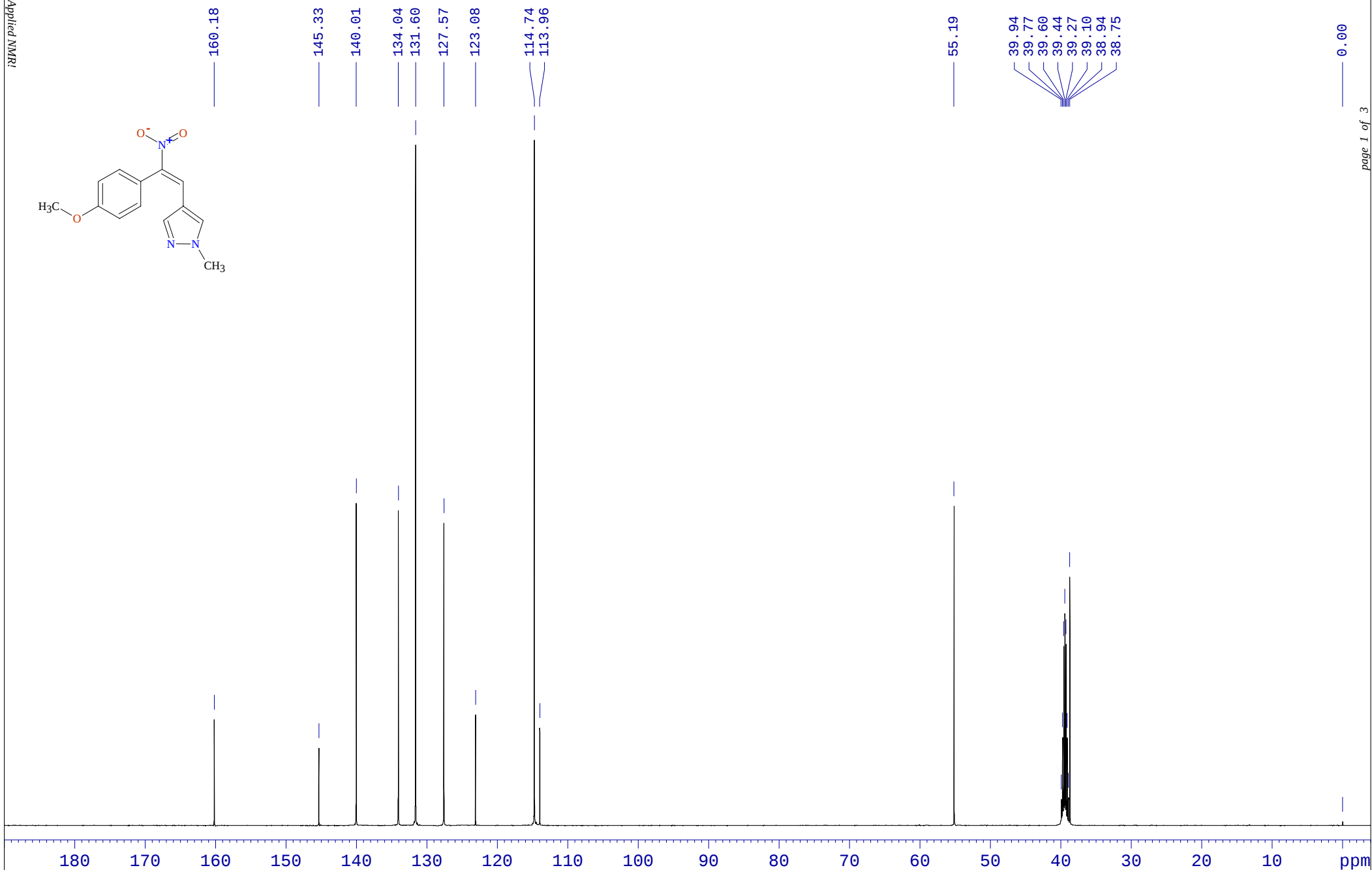
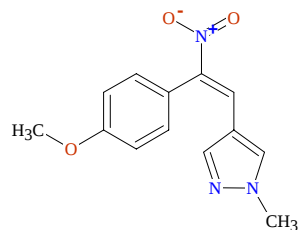
S121

1q (NMR/25250071)

Peaks List

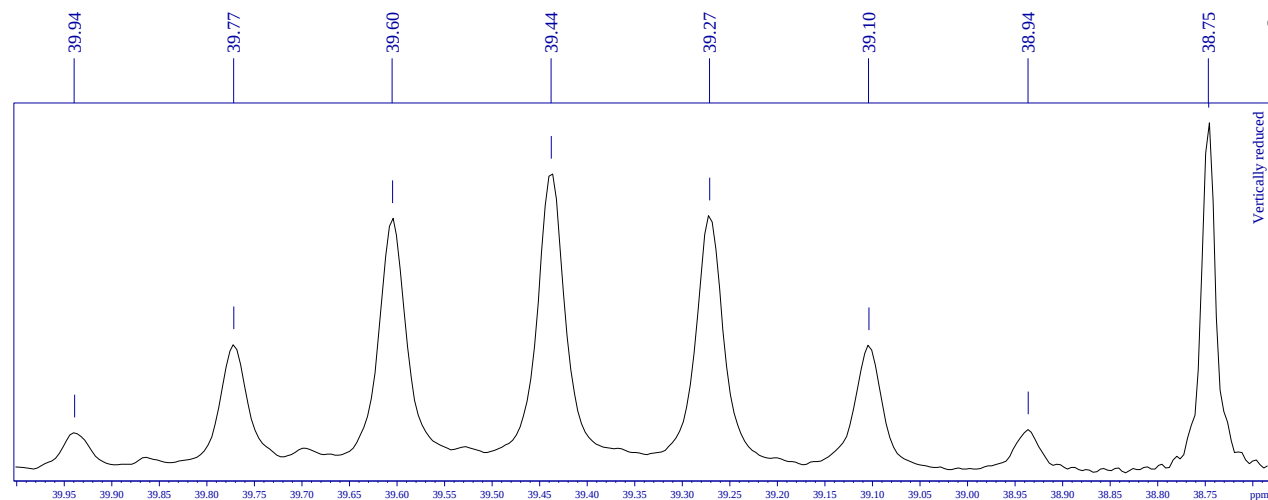
#	Address	Frequency		Intensity
	[points]	[Hz]	[ppm]	[cm]
1	16121.3	4077.065	8.1520	4.27
2	17565.1	3636.436	7.2710	0.27
3	17574.5	3633.571	7.2653	3.39
4	17580.0	3631.904	7.2619	2.40
5	17596.2	3626.960	7.2520	1.07
6	17603.1	3624.853	7.2478	4.10
7	17612.3	3622.053	7.2422	0.41
8	17782.5	3570.103	7.1383	3.57
9	17912.4	3530.468	7.0591	0.33
10	17921.8	3527.583	7.0533	3.96
11	17928.8	3525.452	7.0491	1.05
12	17943.7	3520.919	7.0400	0.93
13	17950.4	3518.868	7.0359	3.30
14	17959.8	3516.003	7.0302	0.28
15	18045.9	3489.719	6.9776	3.44
16	23106.7	1945.280	3.8895	16.00
17	23257.3	1899.324	3.7977	14.78
18	29481.0	0.002	0.0000	4.52

1q (NMR/25250071)

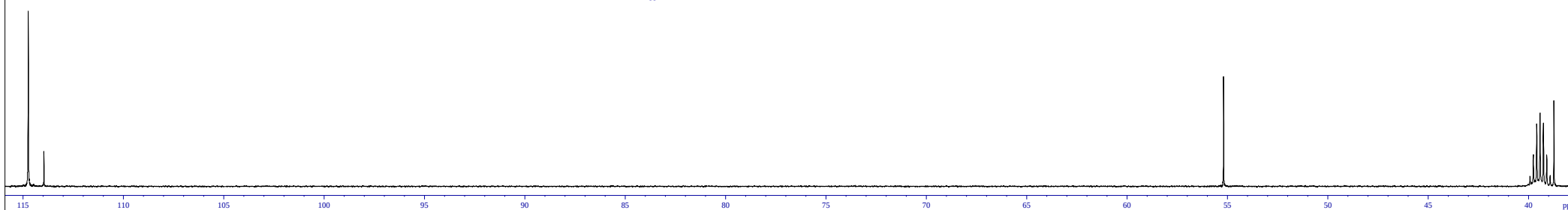
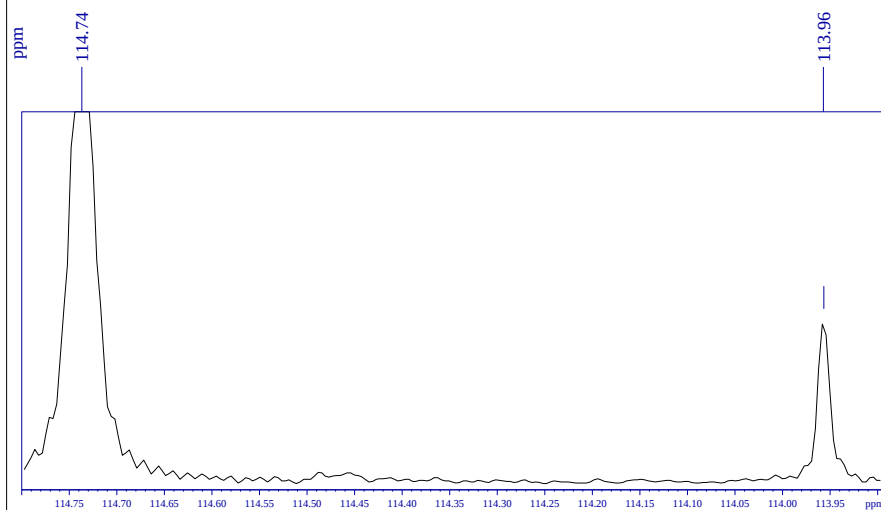


S123

1q (NMR/25250071)



Scale: 10.00 Hz/cm



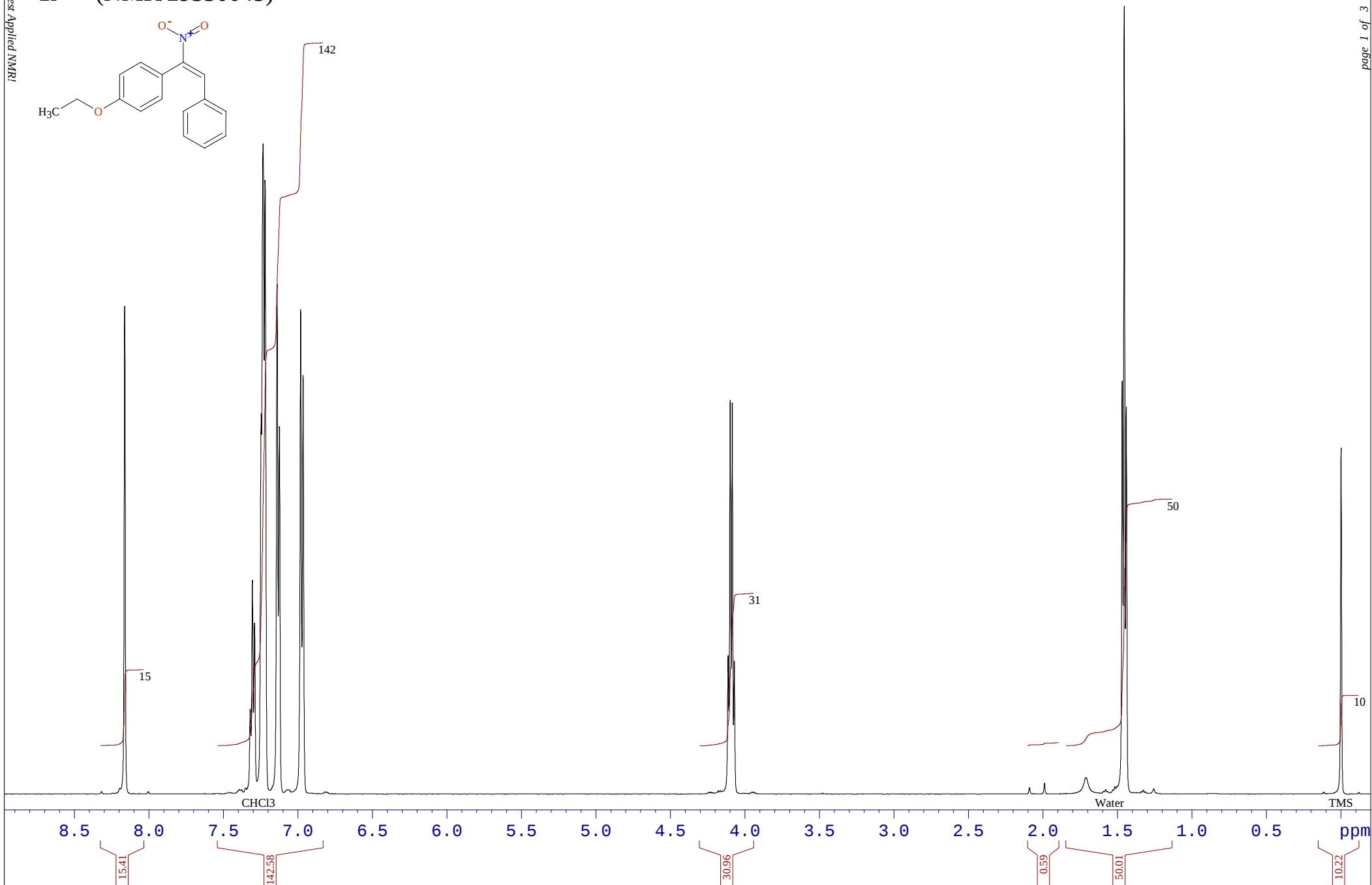
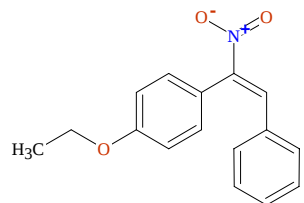
S124

1q (NMR/25250071)

Peaks List

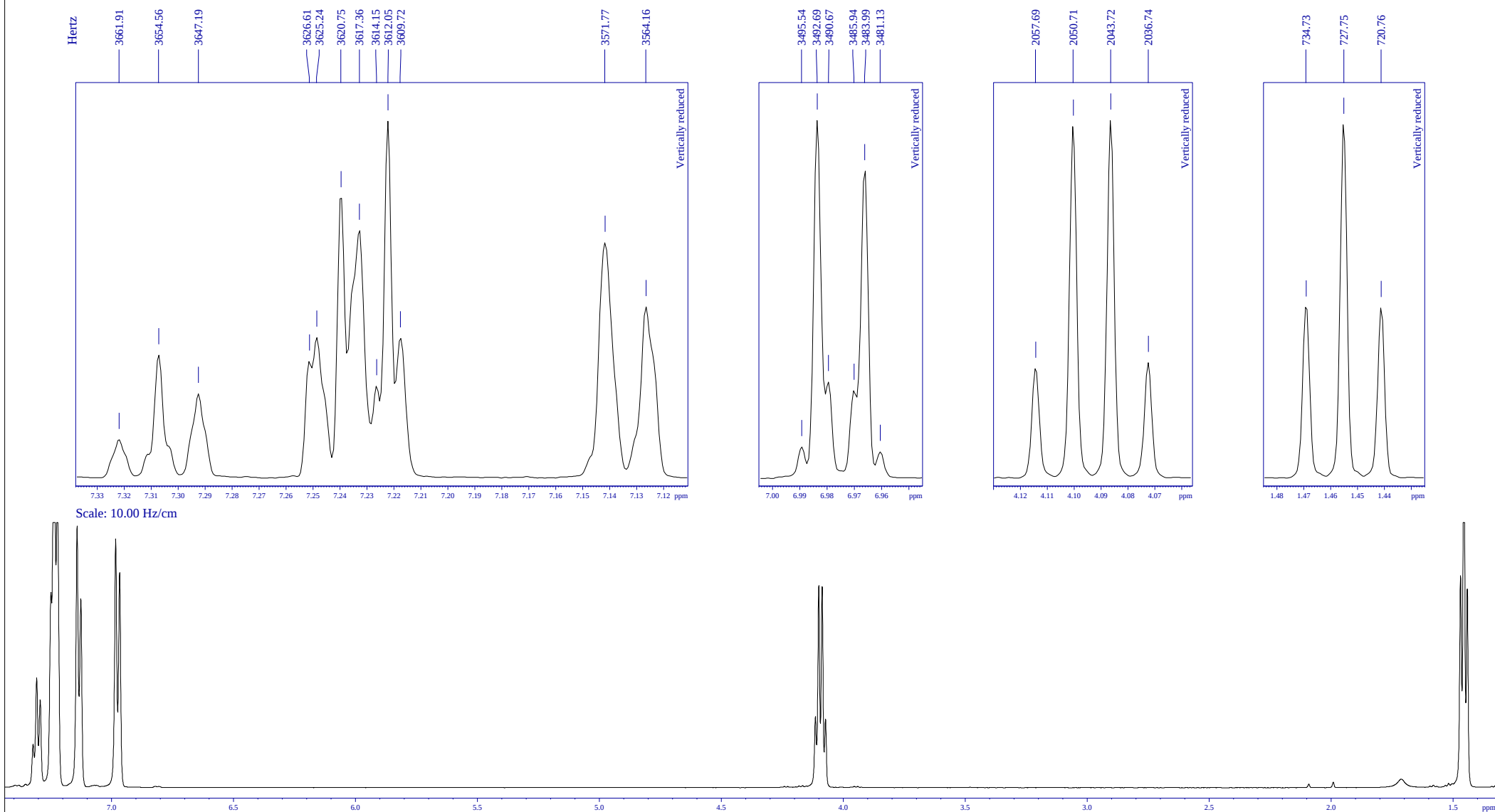
#	Address [points]	Frequency		Intensity
		[Hz]	[ppm]	[cm]
1	18272.2	20144.223	160.1826	2.27
2	22165.1	18276.275	145.3291	1.69
3	23557.8	17607.973	140.0149	6.67
4	25124.0	16856.459	134.0390	6.49
5	25764.1	16549.314	131.5967	13.92
6	26820.0	16042.683	127.5680	6.24
7	27995.7	15478.541	123.0821	2.40
8	30182.9	14429.016	114.7365	14.00
9	30387.3	14330.940	113.9566	2.12
10	45790.2	6940.065	55.1859	6.63
11	49786.2	5022.661	39.9391	0.60
12	49830.1	5001.604	39.7717	1.89
13	49873.8	4980.604	39.6047	3.75
14	49917.6	4959.608	39.4378	4.43
15	49961.2	4938.656	39.2712	3.79
16	50005.1	4917.594	39.1037	1.88
17	50049.0	4896.530	38.9362	0.65
18	50098.8	4872.666	38.7464	5.18
19	60253.6	0.003	0.0000	0.21

1r (NMR/29330045)



S126

1r (NMR/29330045)

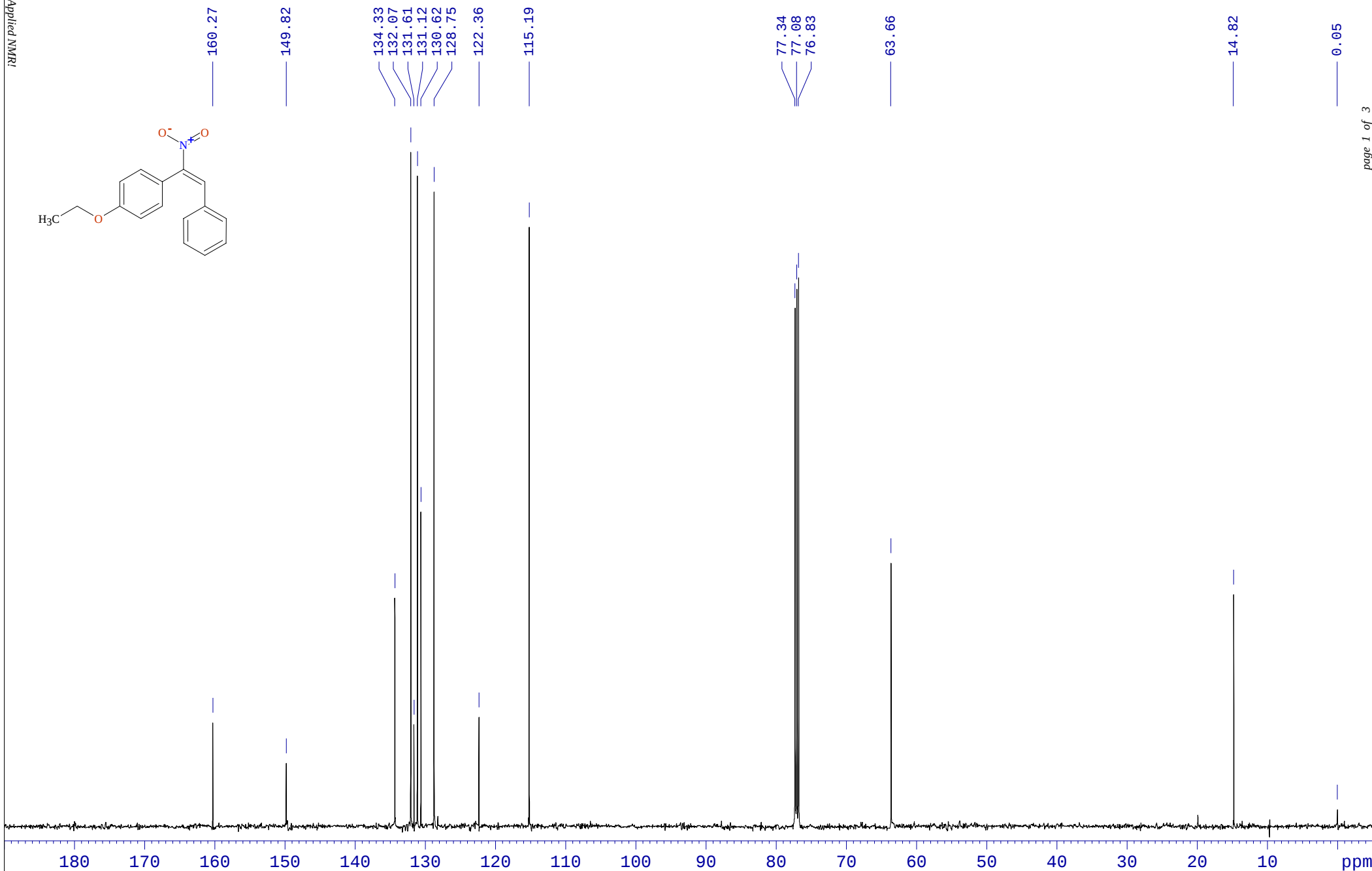
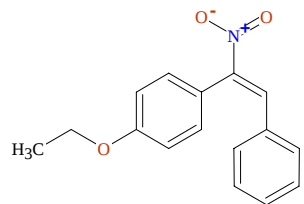


1r (NMR/29330045)

Peaks List

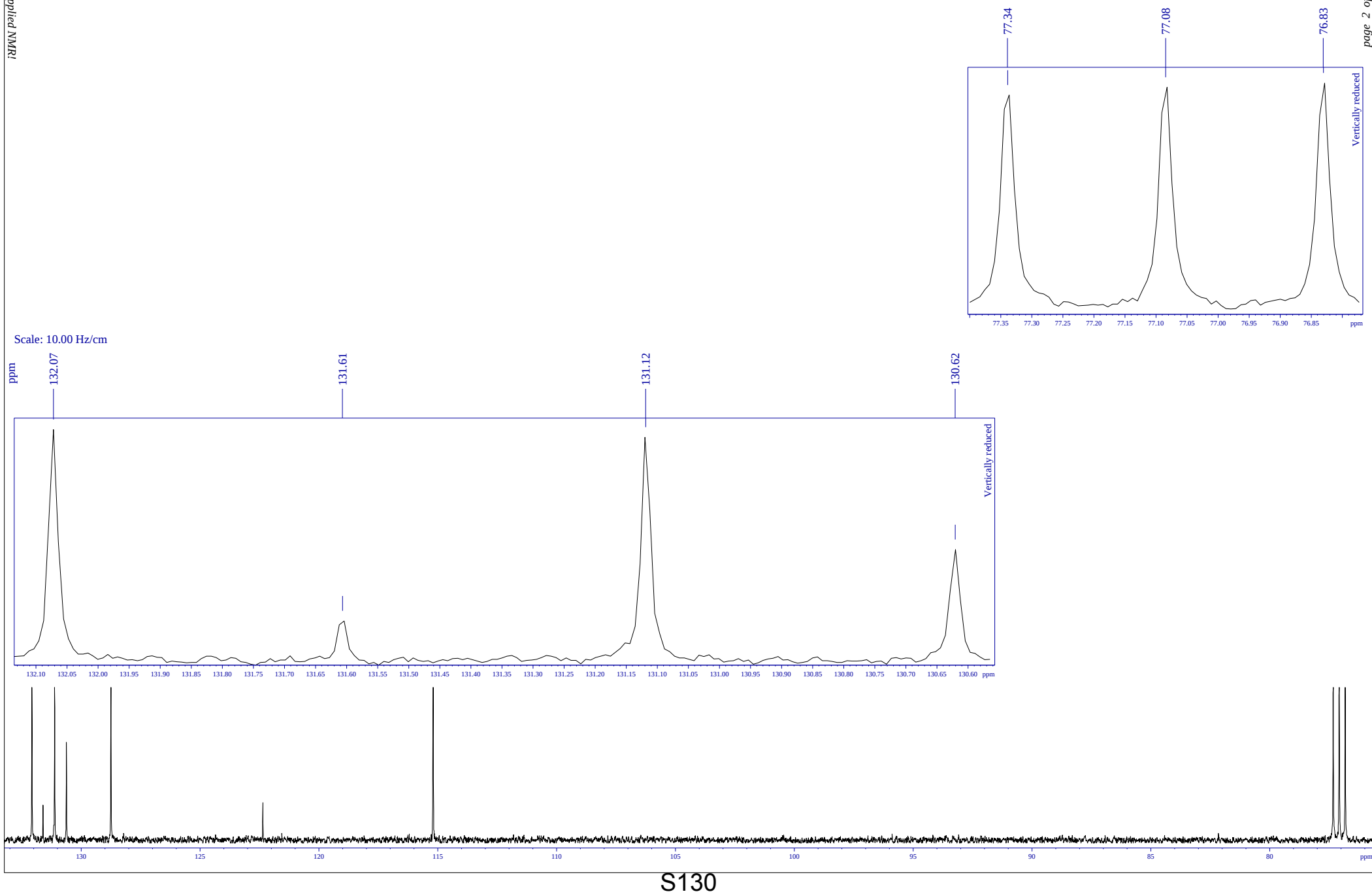
#	Address [points]	Frequency [Hz]	Intensity [cm]
1	16083.9	4082.974	8.1638
2	17463.7	3661.909	7.3219
3	17487.7	3654.556	7.3072
4	17511.9	3647.189	7.2925
5	17579.3	3626.615	7.2513
6	17583.8	3625.237	7.2486
7	17598.5	3620.754	7.2396
8	17609.6	3617.360	7.2328
9	17620.2	3614.146	7.2264
10	17627.0	3612.050	7.2222
11	17634.7	3609.715	7.2176
12	17759.0	3571.767	7.1417
13	17784.0	3564.158	7.1265
14	18008.8	3495.538	6.9893
15	18018.1	3492.690	6.9836
16	18024.8	3490.671	6.9795
17	18040.3	3485.938	6.9701
18	18046.7	3483.990	6.9662
19	18056.0	3481.131	6.9605
20	22720.3	2057.693	4.1143
21	22743.2	2050.708	4.1003
22	22766.1	2043.722	4.0864
23	22789.0	2036.738	4.0724
24	26200.3	995.700	1.9909
25	27055.4	734.725	1.4691
26	27078.3	727.748	1.4551
27	27101.2	720.763	1.4412
28	29463.0	-0.002	-0.0000

1r (NMR/29330045)



S129

1r (NMR/29330045)



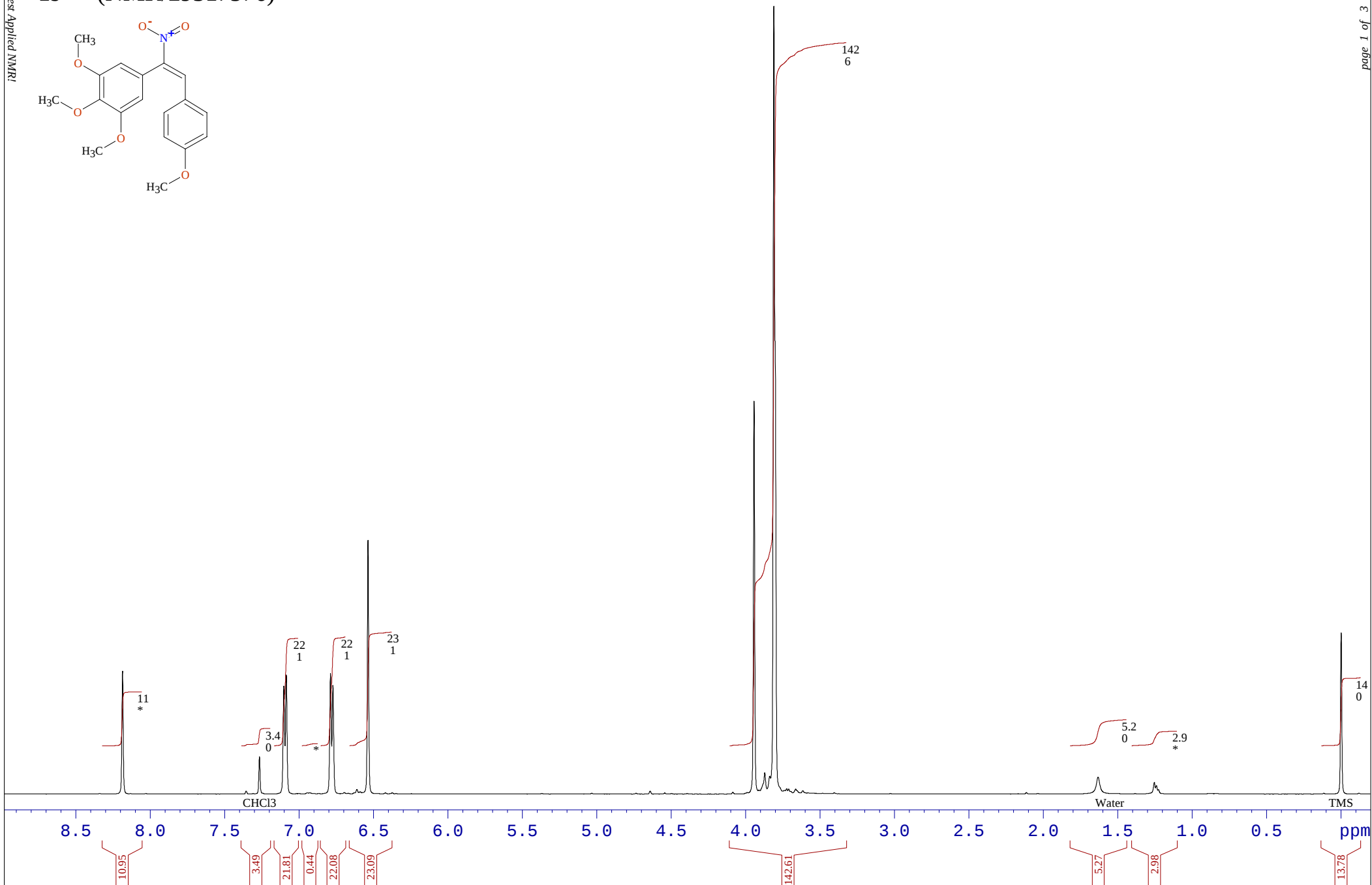
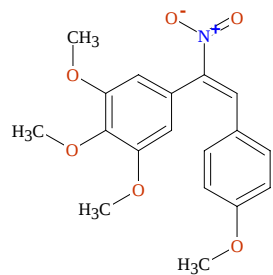
1r (NMR/29330045)

Peaks List

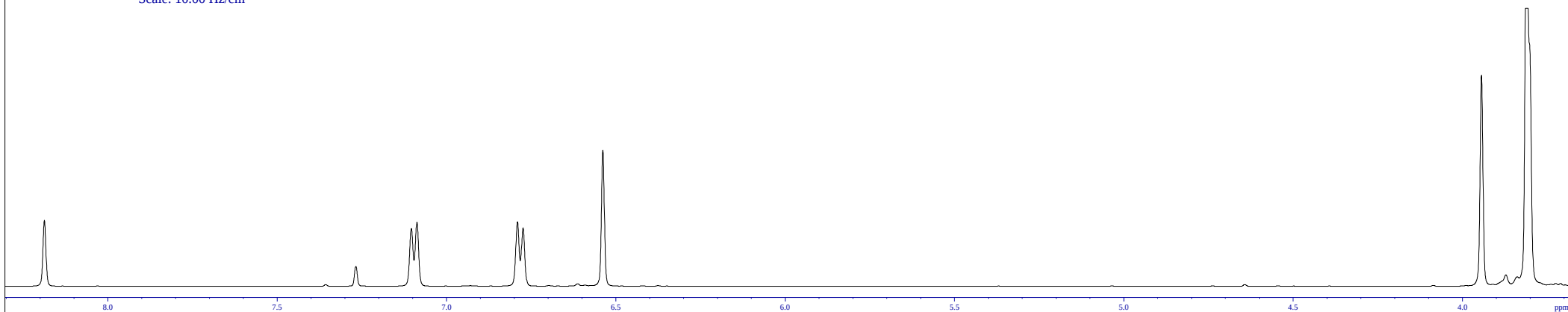
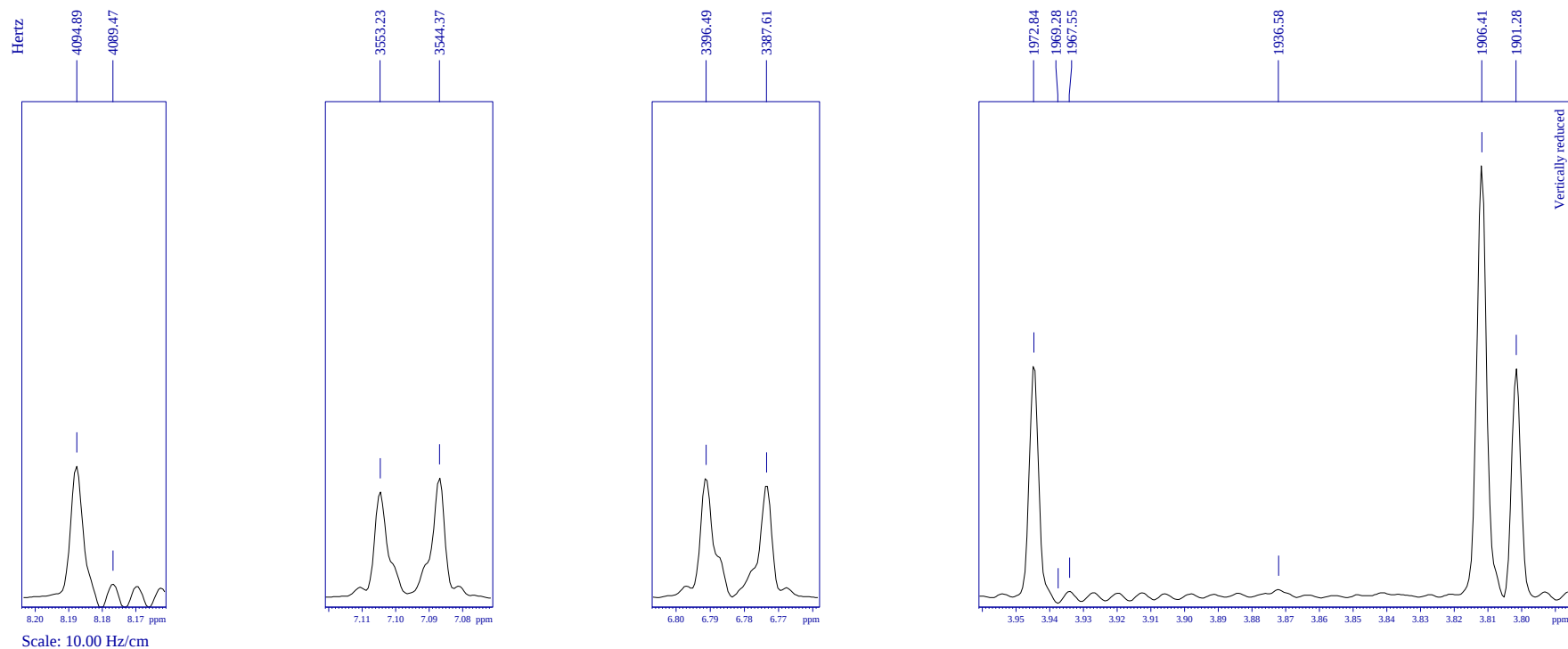
#	Address [points]	Frequency		Intensity [cm]
		[Hz]	[ppm]	
1	10056.0	20155.410	160.2717	2.47
2	11374.5	18840.453	149.8154	1.67
3	13327.2	16893.072	134.3302	5.01
4	13612.0	16609.049	132.0717	14.00
5	13670.6	16550.549	131.6066	2.53
6	13732.1	16489.201	131.1187	13.63
7	13794.9	16426.557	130.6206	6.72
8	14031.1	16190.991	128.7474	13.33
9	14837.0	15387.310	122.3567	2.58
10	15740.6	14486.187	115.1912	13.34
11	20513.6	9725.970	77.3389	11.20
12	20545.7	9693.978	77.0845	11.48
13	20577.8	9662.021	76.8304	11.64
14	22239.0	8005.201	63.6557	5.70
15	28396.5	1864.328	14.8247	5.27
16	30259.9	5.935	0.0472	0.66

1s (NMR/29317576)

Found protons = 9 impurity* = 0.6 %



1s (NMR/29317576)



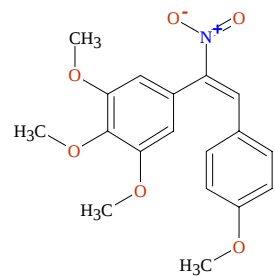
S133

1s (NMR/29317576)

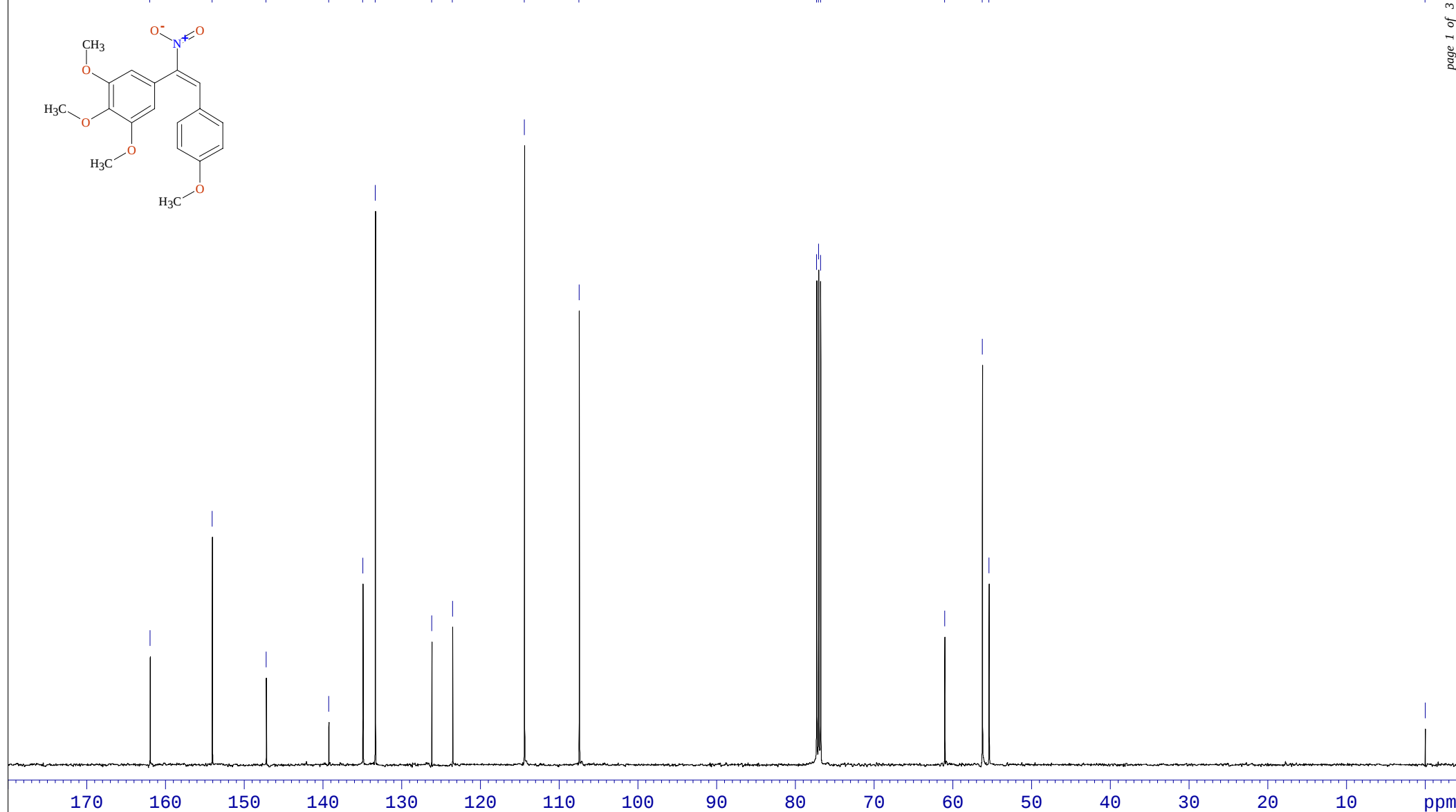
Peaks List

#	Address [points]	Frequency [Hz]	Intensity [ppm]	Intensity [cm]
1	16070.9	4094.885	8.1876	2.13
2	16088.6	4089.465	8.1768	0.21
3	17578.1	3634.909	7.2679	0.88
4	17845.8	3553.233	7.1046	1.71
5	17874.8	3544.369	7.0869	1.94
6	18359.4	3396.486	6.7912	1.95
7	18388.5	3387.611	6.7735	1.83
8	18773.9	3269.985	6.5383	5.41
9	23024.4	1972.838	3.9447	8.72
10	23036.1	1969.279	3.9375	-0.22
11	23041.7	1967.552	3.9341	0.21
12	23143.2	1936.578	3.8721	0.29
13	23242.1	1906.414	3.8118	16.00
14	23258.9	1901.280	3.8016	8.49
15	29489.0	0.001	0.0000	3.75

1s (NMR/29317576)

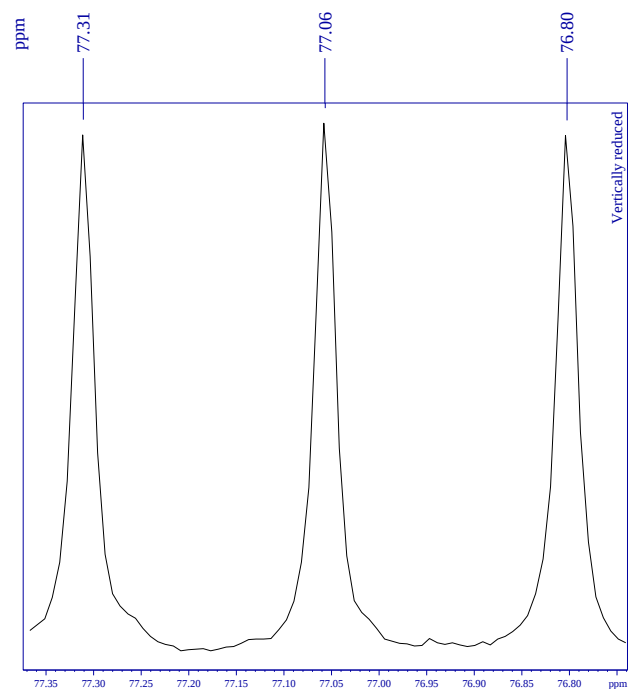


161.96
154.08
147.22
139.27
134.94
133.36
126.19
123.54
114.42
107.46
77.31
77.06
76.80
61.04
56.26
55.41
0.00

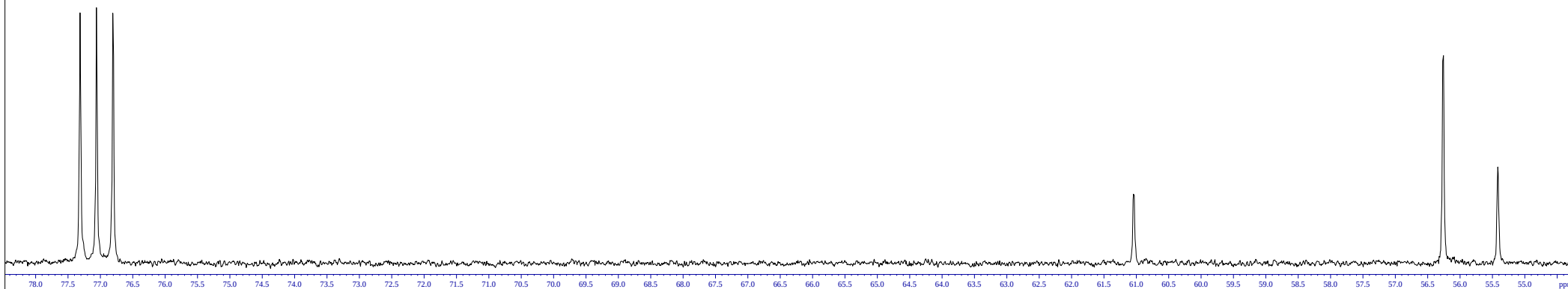
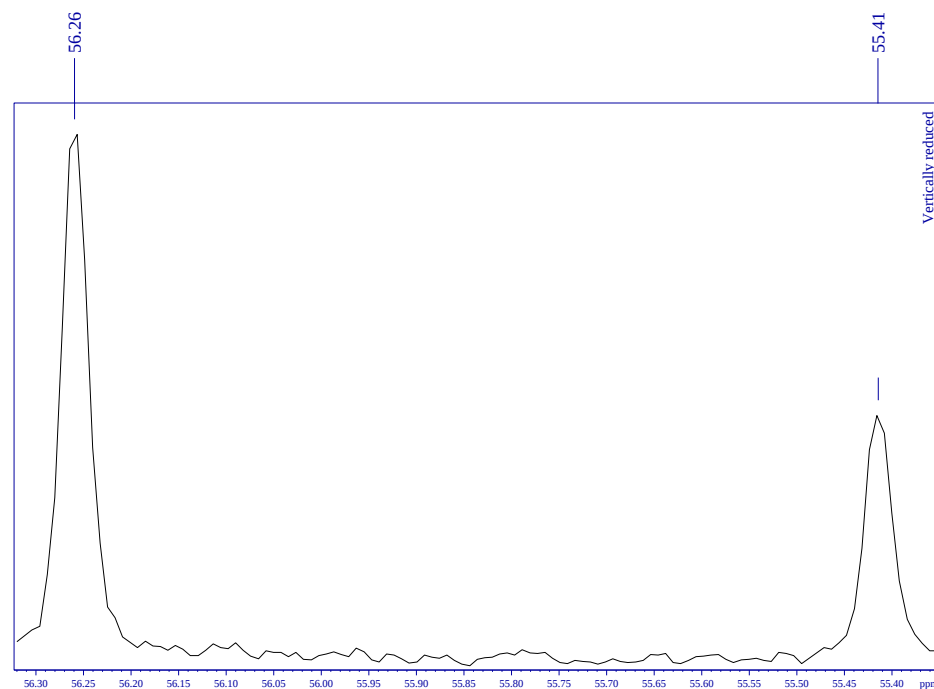


S135

1s (NMR/29317576)



Scale: 10.00 Hz/cm



S136

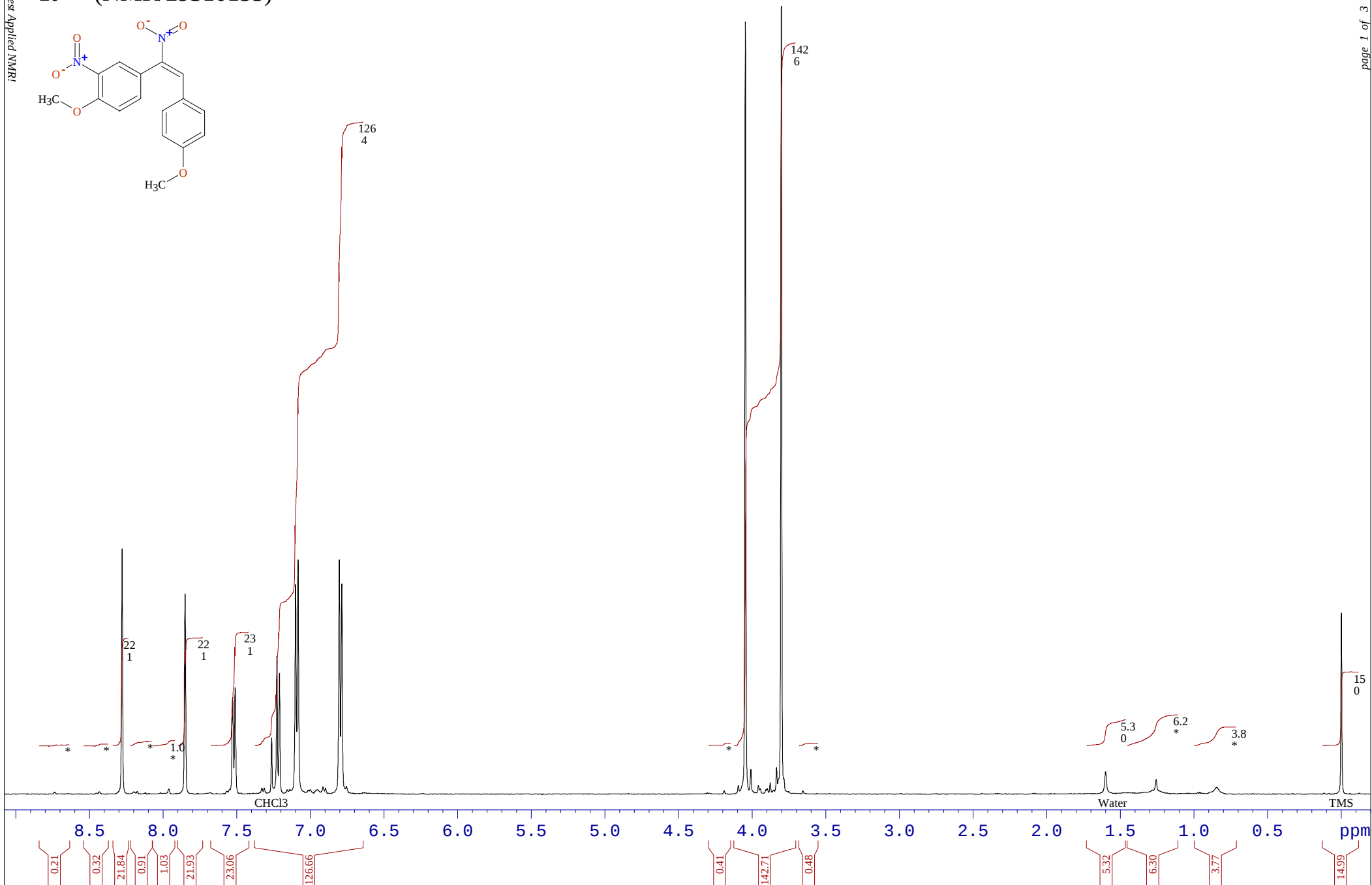
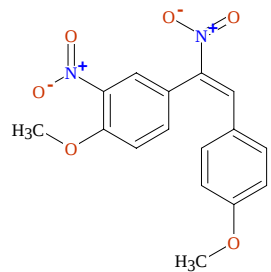
1s (NMR/29317576)

Peaks List

#	Address [points]	Frequency [Hz]	Intensity [cm]
1	9839.5	20368.207	2.39
2	10834.2	19376.219	4.58
3	11699.2	18513.584	1.84
4	12700.8	17514.688	0.99
5	13247.7	16969.205	3.60
6	13446.1	16771.406	10.65
7	14350.8	15869.120	2.55
8	14684.8	15535.977	2.81
9	15834.2	14389.742	12.00
10	16711.9	13514.413	8.79
11	20514.1	9722.438	9.33
12	20546.1	9690.465	9.56
13	20578.2	9658.512	9.37
14	22566.3	7675.730	2.58
15	23168.6	7075.060	7.89
16	23275.2	6968.788	3.60
17	30262.8	0.000	0.86

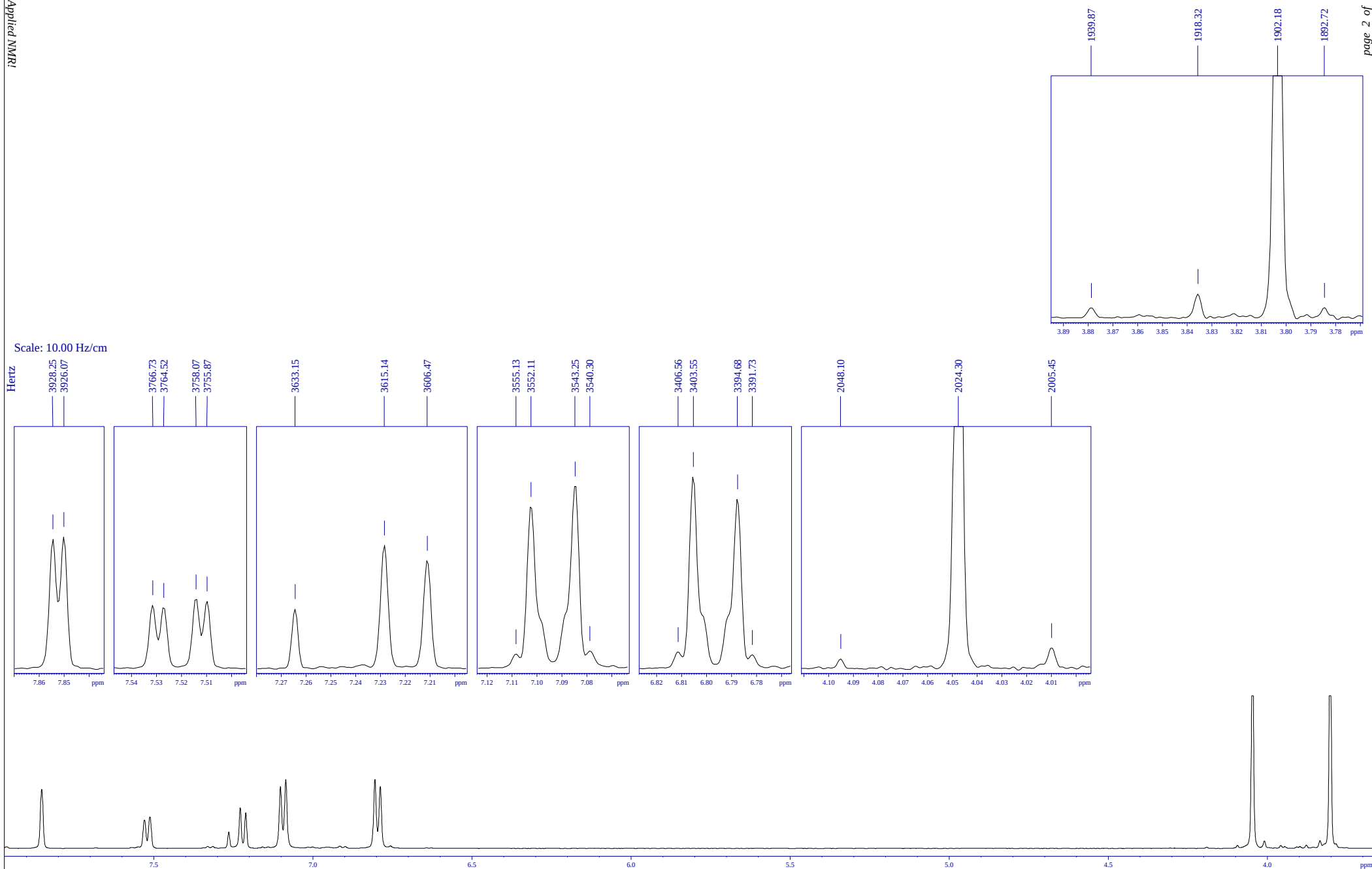
1t (NMR/29310155)

Found protons = 13 impurity* = 2.9 %



1t (NMR/29310155)

The Best Applied NMR!

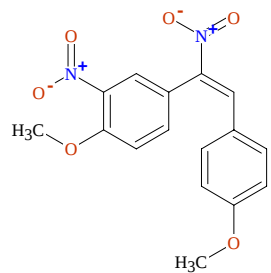


1t (NMR/29310155)

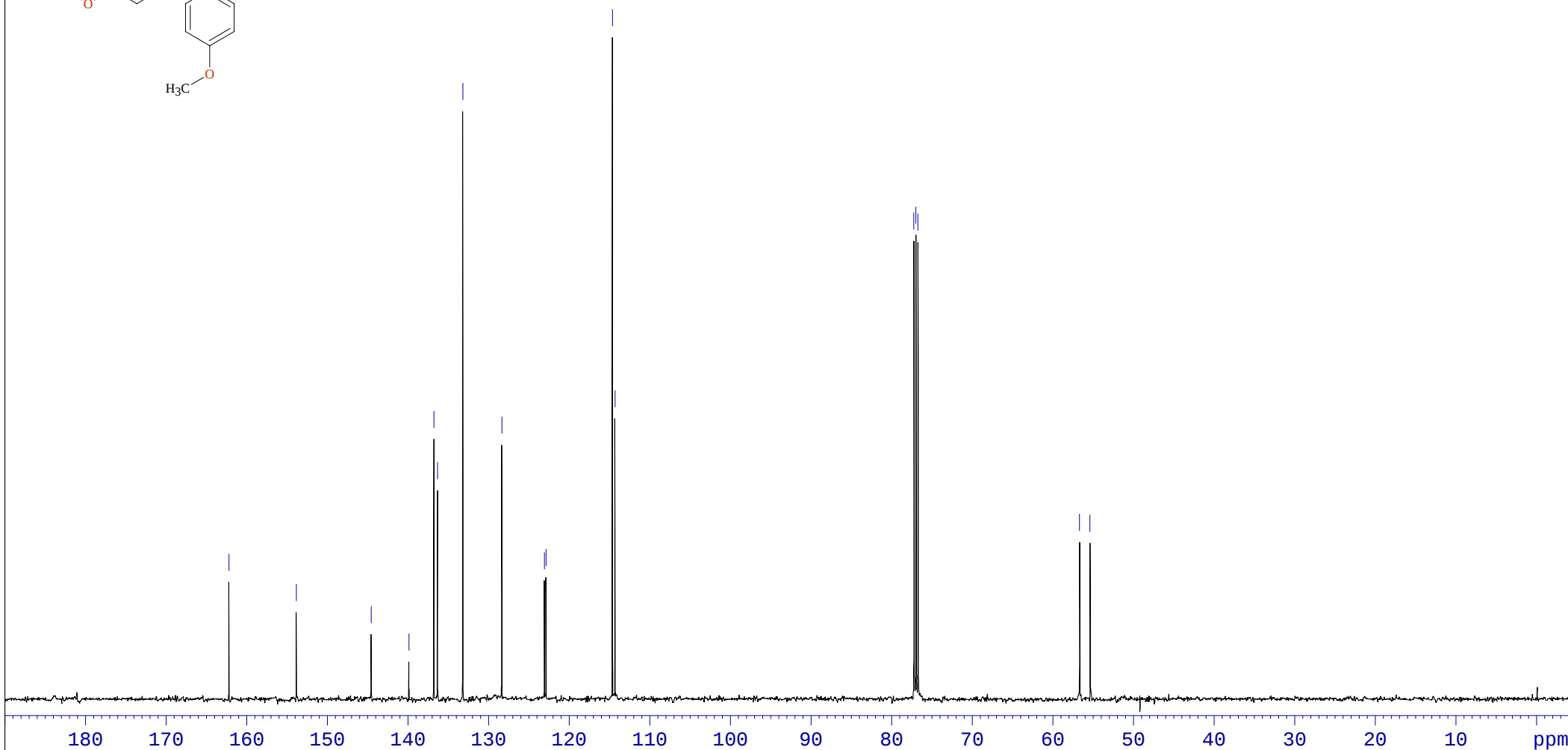
Peaks List

#	Address [points]	Frequency [Hz]	Intensity [cm]
1	15915.8	4140.982	8.2798
2	16612.9	3928.249	7.8545
3	16620.1	3926.073	7.8501
4	17142.2	3766.732	7.5315
5	17149.4	3764.519	7.5271
6	17170.5	3758.074	7.5142
7	17177.8	3755.871	7.5098
8	17579.9	3633.151	7.2644
9	17638.9	3615.145	7.2284
10	17667.3	3606.471	7.2111
11	17835.5	3555.132	7.1084
12	17845.4	3552.115	7.1024
13	17874.5	3543.246	7.0847
14	17884.2	3540.297	7.0788
15	18322.4	3406.562	6.8114
16	18332.2	3403.553	6.8053
17	18361.3	3394.682	6.7876
18	18371.0	3391.726	6.7817
19	22773.8	2048.102	4.0951
20	22851.8	2024.300	4.0475
21	22913.5	2005.451	4.0099
22	23128.4	1939.874	3.8787
23	23199.1	1918.317	3.8356
24	23251.9	1902.185	3.8034
25	23282.9	1892.725	3.7845
26	26861.4	800.656	1.6009
27	29485.0	0.002	0.0000

1t (NMR/29310155)

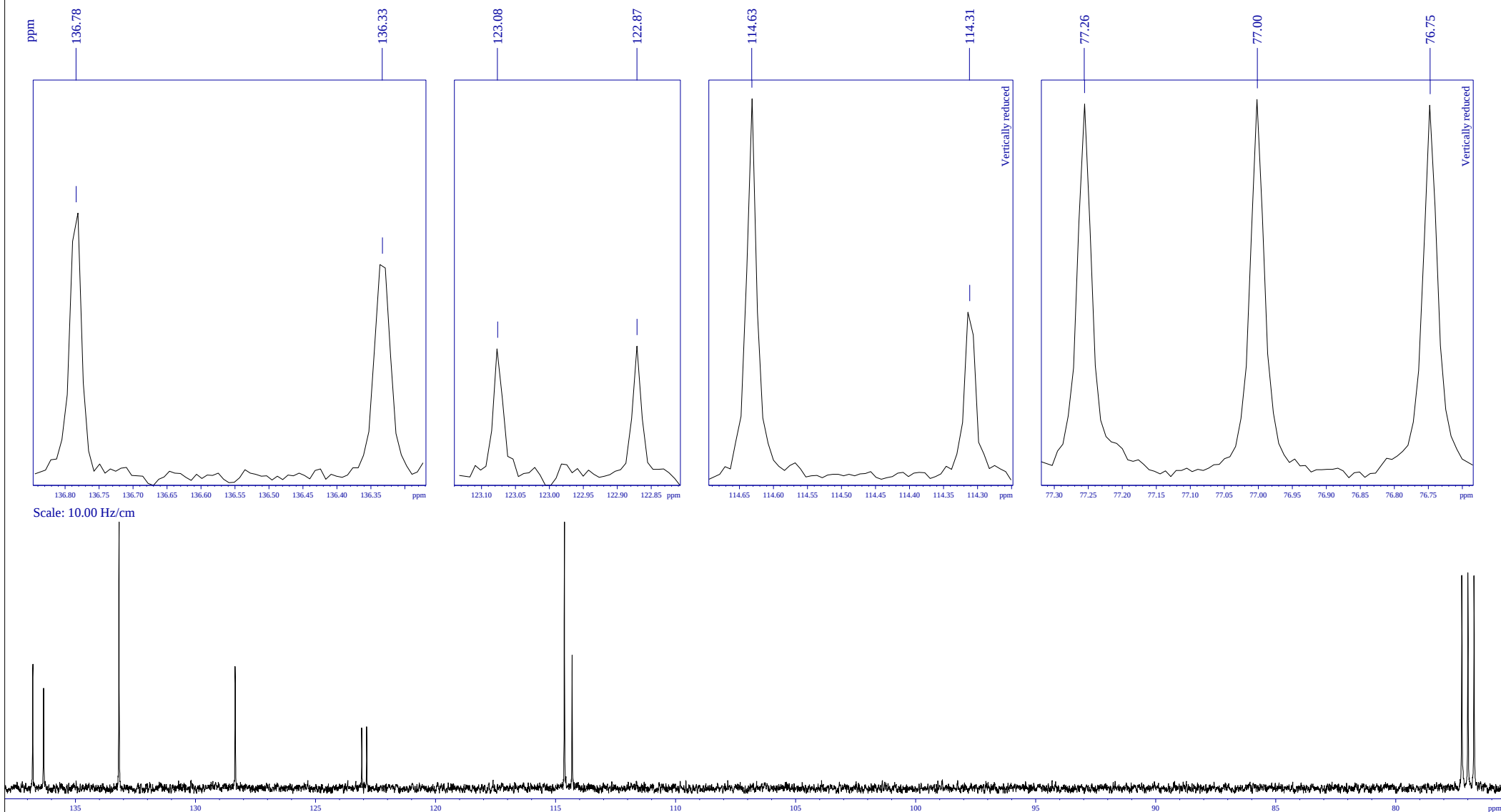


162.21
153.85
144.56
139.88
136.78
136.33
133.19
128.35
123.08
122.87
114.63
114.31
77.26
77.00
76.75
56.70
55.41



S141

1t (NMR/29310155)



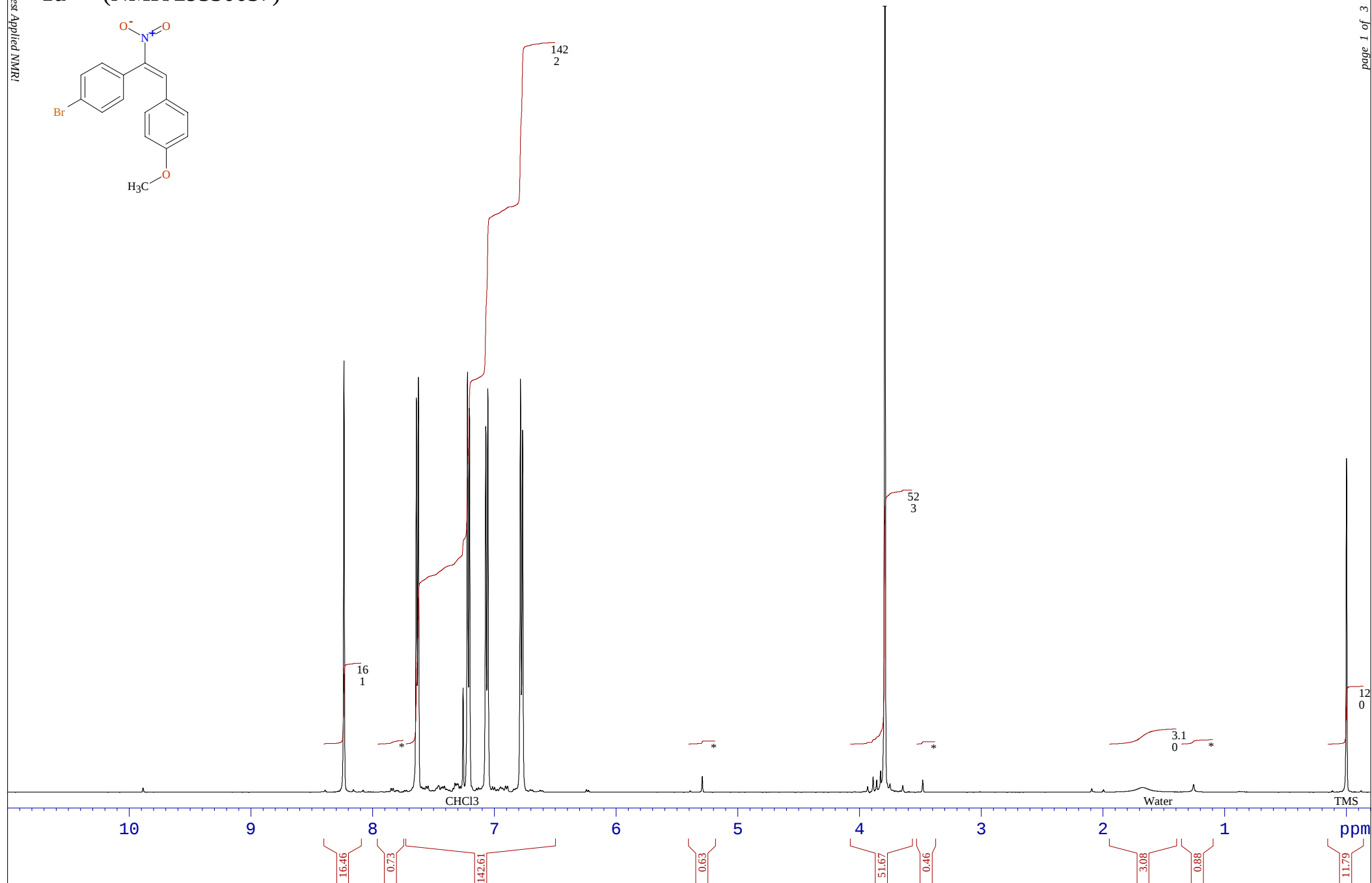
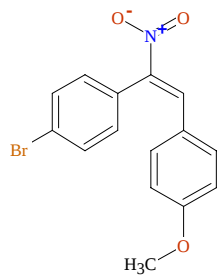
1t (NMR/29310155)

Peaks List

#	Address [points]	Frequency [Hz]	Intensity [cm]
1	9801.0	20398.590	2.36
2	10854.4	19348.045	1.94
3	12025.6	18179.984	1.45
4	12616.7	17590.553	0.91
5	13006.6	17201.611	5.11
6	13063.5	17144.941	4.11
7	13459.8	16749.699	10.91
8	14070.3	16140.838	4.91
9	14735.1	15477.787	2.39
10	14761.0	15451.979	2.42
11	15799.9	14415.831	12.00
12	15840.3	14375.559	5.46
13	20513.0	9715.479	8.38
14	20545.0	9683.529	8.49
15	20577.1	9651.576	8.37
16	23104.6	7130.878	3.07
17	23267.8	6968.116	3.07

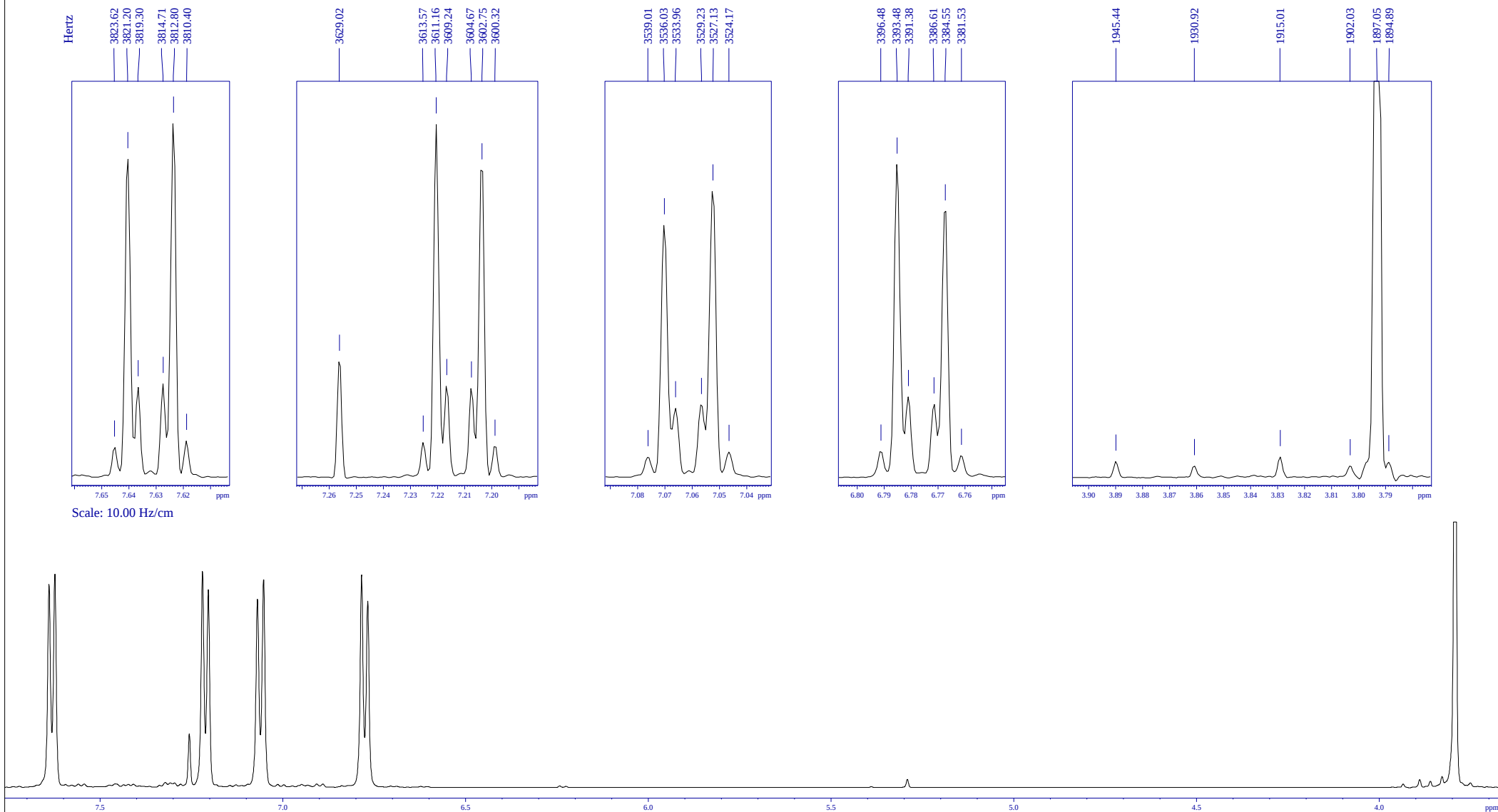
1u (NMR/29330037)

Found protons = 6 impurity* = 1.4 %



S144

1u (NMR/29330037)



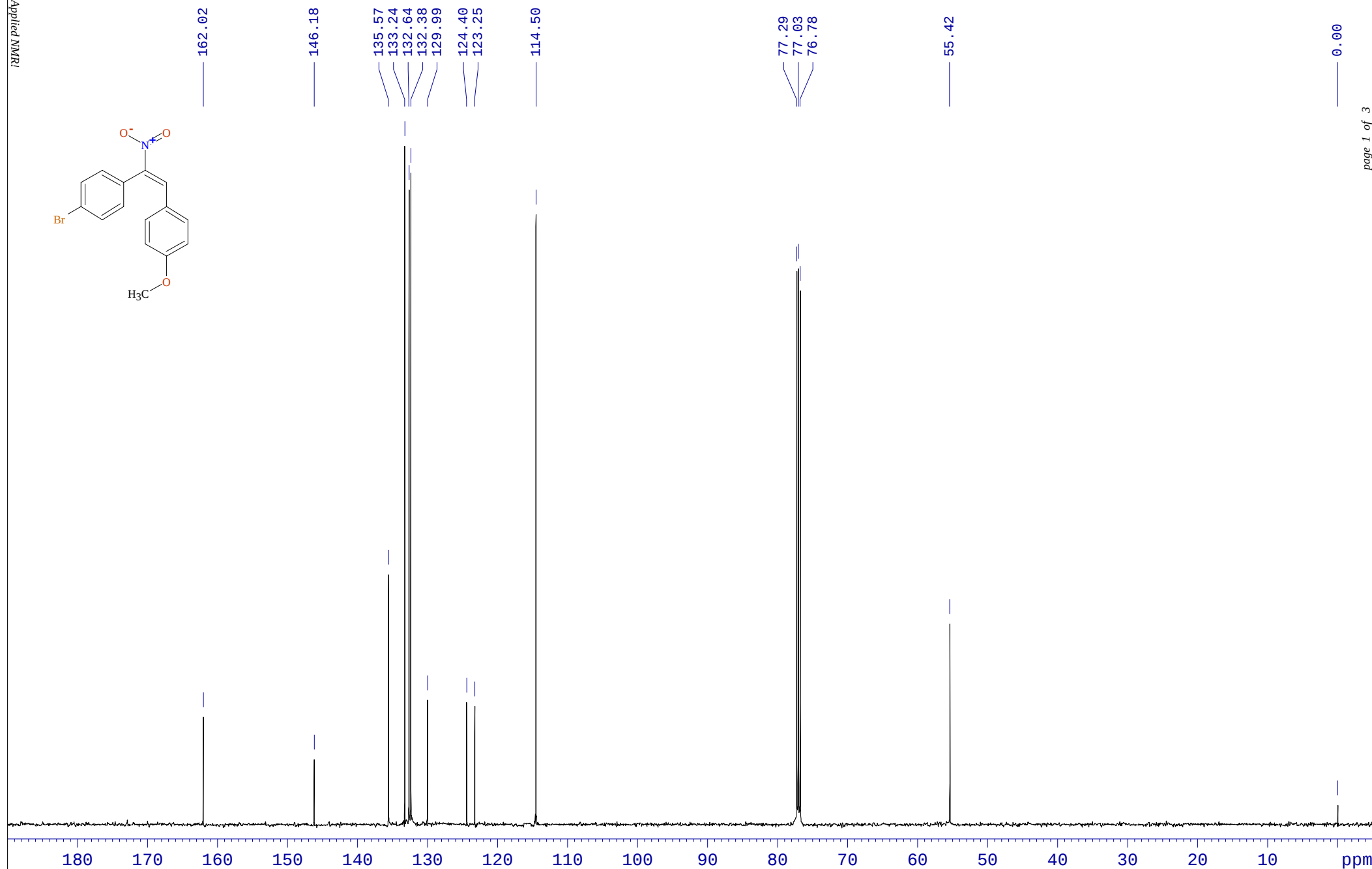
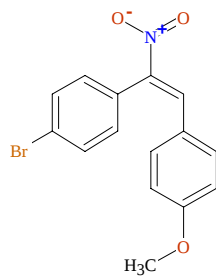
S145

1u (NMR/29330037)

Peaks List

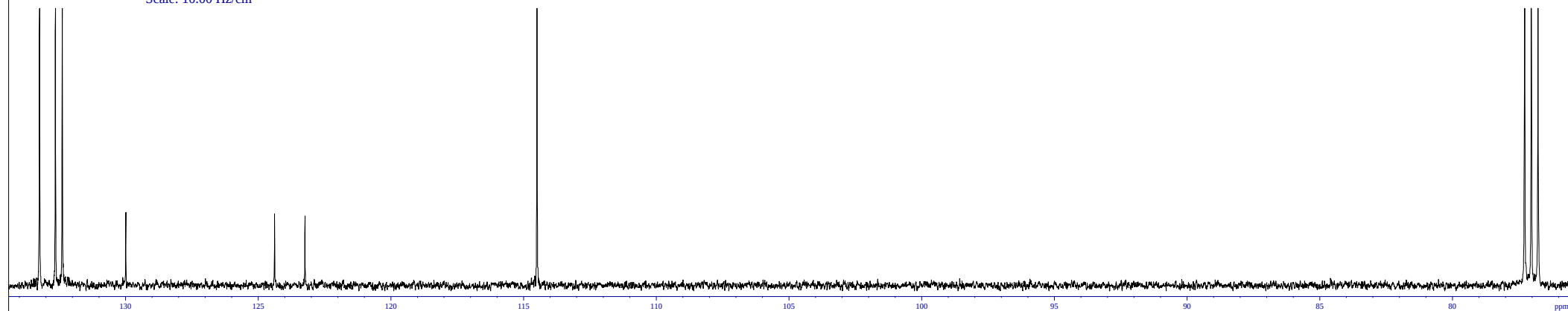
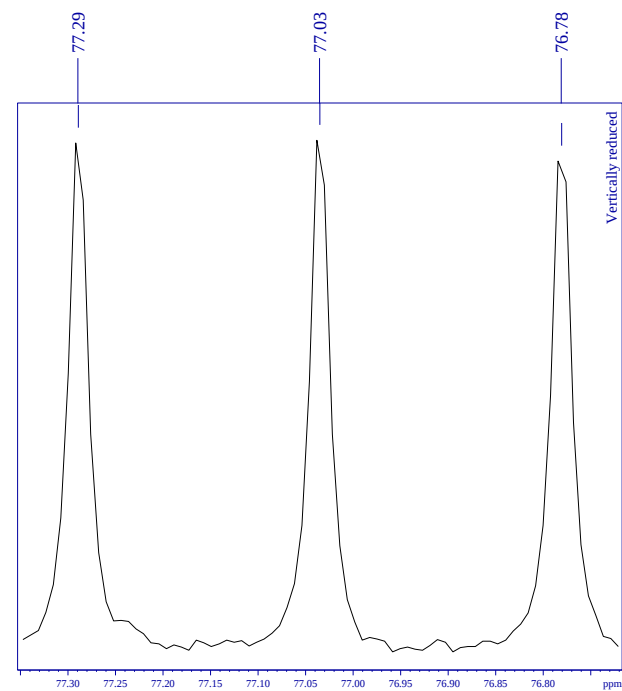
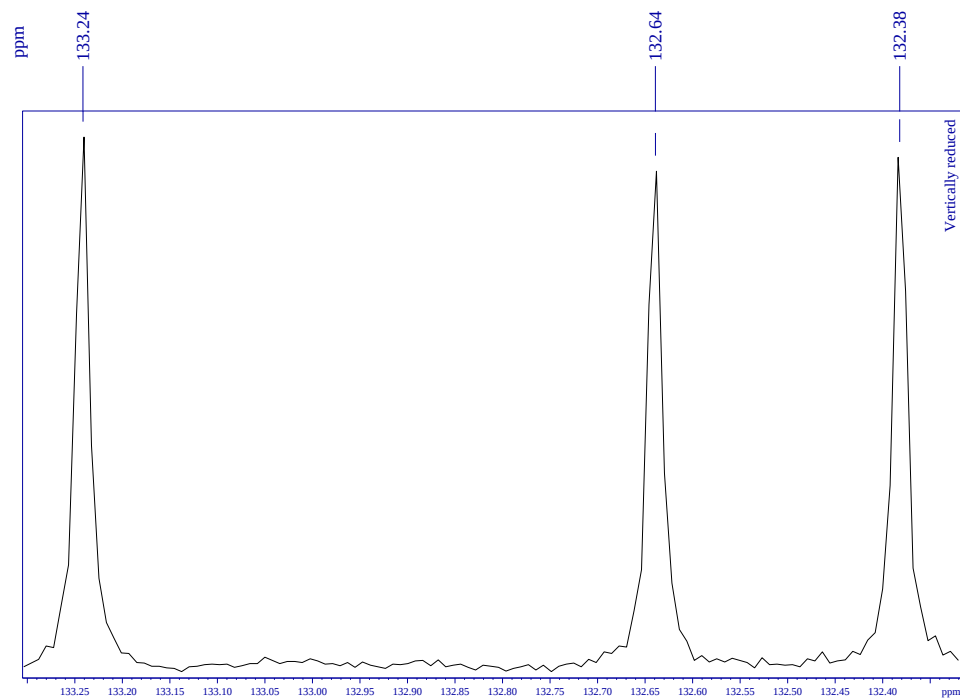
#	Address [points]	Frequency [Hz]	Intensity [ppm]	Intensity [cm]
1	15976.3	4118.565	8.2350	6.03
2	16942.8	3823.622	7.6453	0.60
3	16950.7	3821.204	7.6404	6.43
4	16956.9	3819.300	7.6366	1.79
5	16972.0	3814.707	7.6274	1.85
6	16978.2	3812.804	7.6236	7.06
7	16986.1	3810.403	7.6188	0.73
8	17580.4	3629.020	7.2562	2.40
9	17631.1	3613.569	7.2253	0.69
10	17638.9	3611.165	7.2205	7.00
11	17645.2	3609.240	7.2166	1.83
12	17660.2	3604.669	7.2075	1.78
13	17666.5	3602.754	7.2036	6.33
14	17674.5	3600.318	7.1988	0.64
15	17875.4	3539.014	7.0762	0.41
16	17885.1	3536.031	7.0702	5.00
17	17891.9	3533.963	7.0661	1.37
18	17907.4	3529.226	7.0566	1.47
19	17914.3	3527.129	7.0524	5.73
20	17924.0	3524.169	7.0465	0.51
21	18342.4	3396.483	6.7912	0.53
22	18352.2	3393.478	6.7852	6.26
23	18359.1	3391.380	6.7810	1.60
24	18374.7	3386.613	6.7715	1.46
25	18381.5	3384.546	6.7673	5.47
26	18391.4	3381.534	6.7613	0.44
27	20800.9	2646.217	5.2911	0.37
28	23097.2	1945.442	3.8899	0.32
29	23144.8	1930.919	3.8608	0.23
30	23196.9	1915.008	3.8290	0.41
31	23239.4	1902.032	3.8031	0.23
32	23255.7	1897.054	3.7931	28.05
33	23262.8	1894.894	3.7888	0.31
34	23765.2	1741.586	3.4823	0.27
35	29472.0	-0.002	-0.0000	7.79

1u (NMR/29330037)



S147

1u (NMR/29330037)



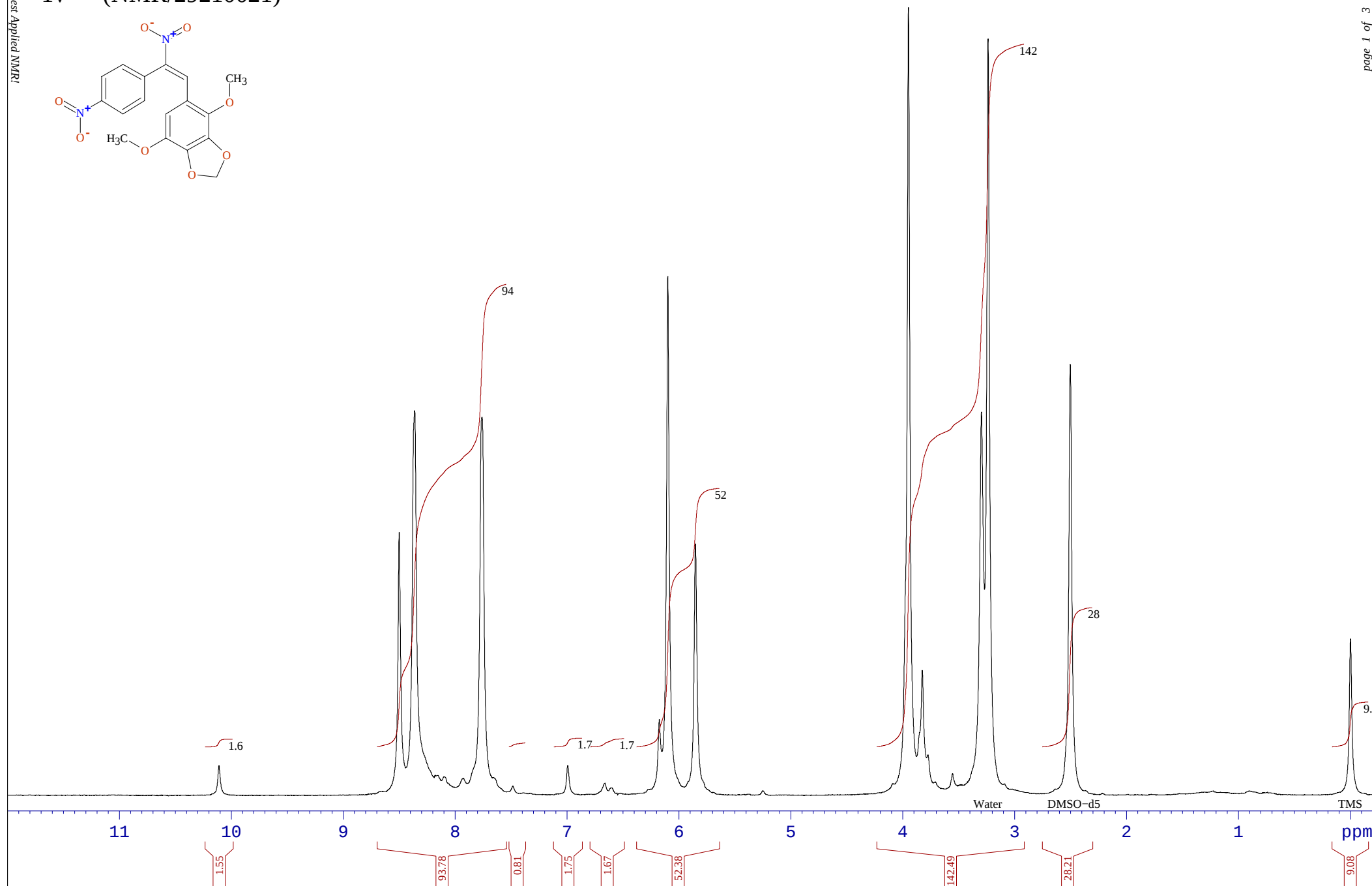
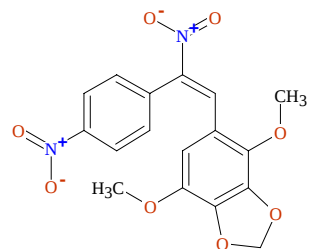
S148

1u (NMR/29330037)

Peaks List

#	Address	Frequency		Intensity
	[points]	[Hz]	[ppm]	[cm]
1	9829.8	20375.477	162.0216	2.48
2	11827.7	18382.951	146.1774	1.60
3	13165.1	17049.115	135.5710	5.28
4	13458.9	16756.141	133.2414	14.00
5	13534.8	16680.402	132.6391	13.21
6	13567.2	16648.086	132.3821	13.62
7	13869.0	16347.154	129.9892	2.74
8	14573.9	15644.105	124.3987	2.70
9	14718.8	15499.637	123.2499	2.69
10	15821.5	14399.830	114.5045	13.50
11	20514.3	9719.706	77.2891	11.65
12	20546.3	9687.751	77.0350	11.79
13	20578.4	9655.763	76.7806	11.45
14	23272.1	6969.349	55.4188	4.28
15	30260.3	0.005	0.0000	0.62

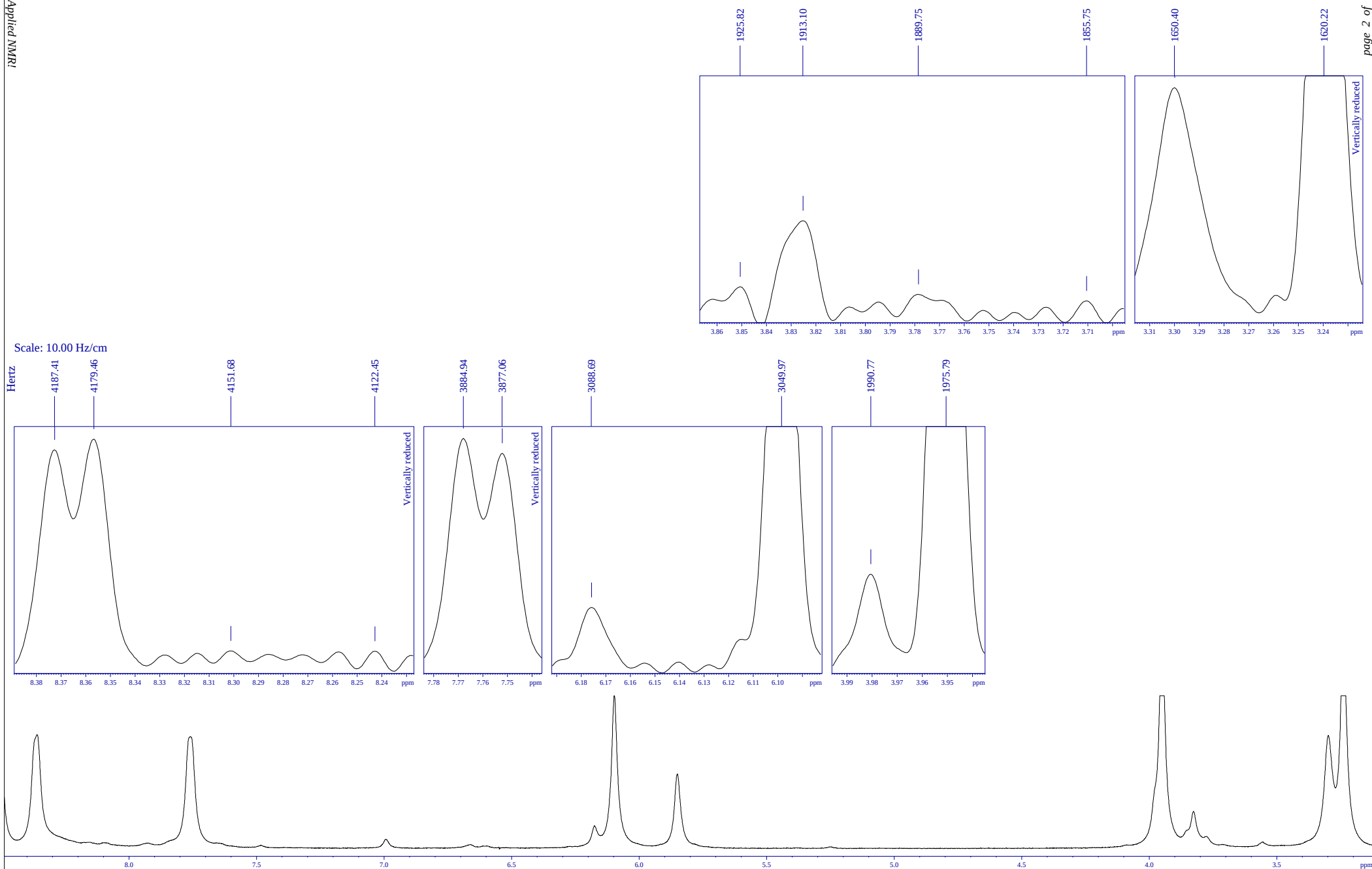
1v (NMR/29210021)



S150

1v (NMR/29210021)

The Best Applied NMR!

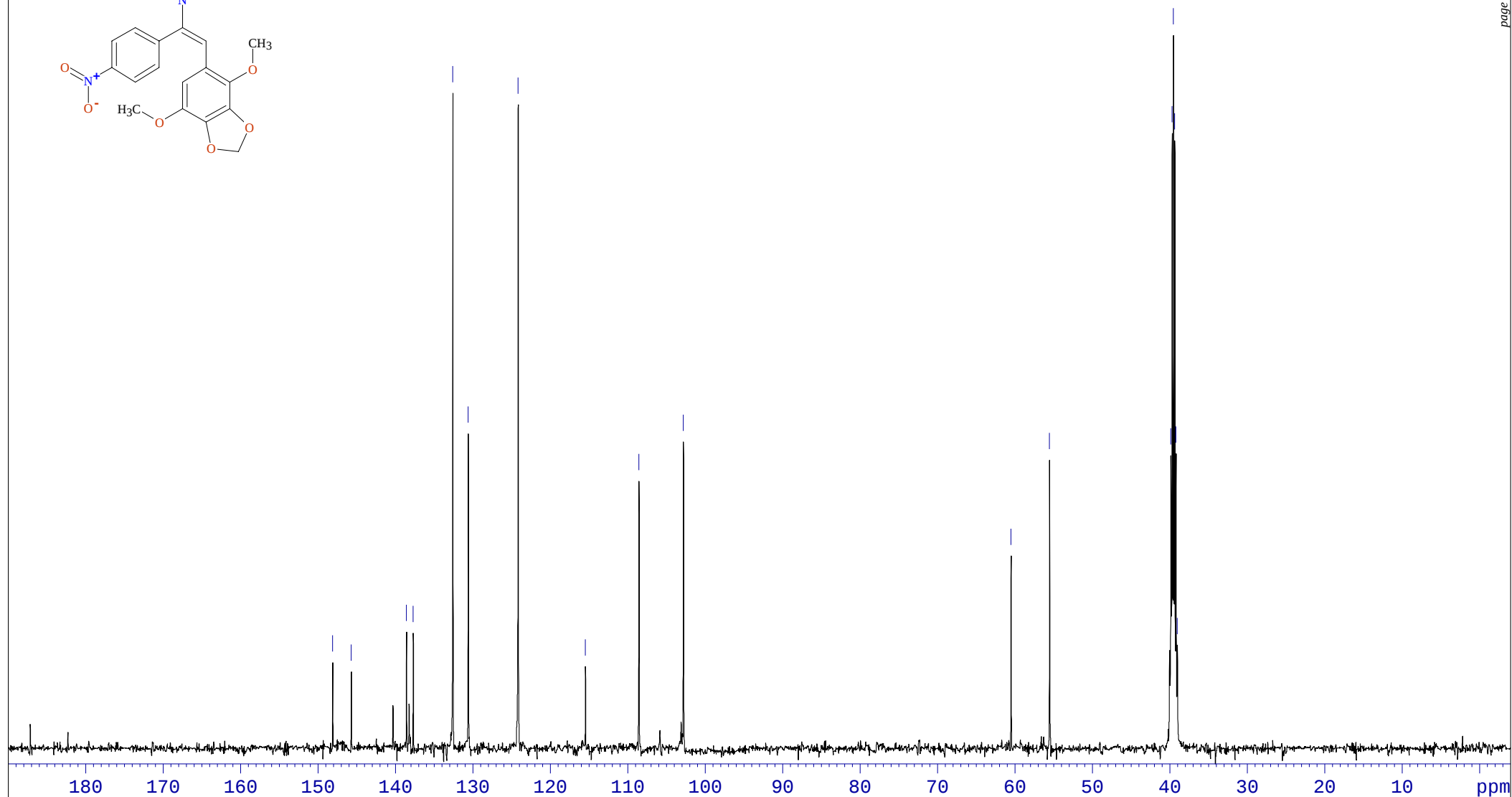
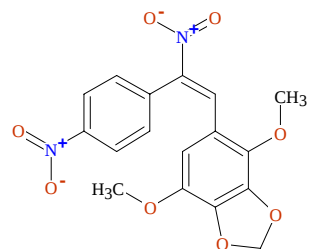


1v (NMR/29210021)

Peaks List

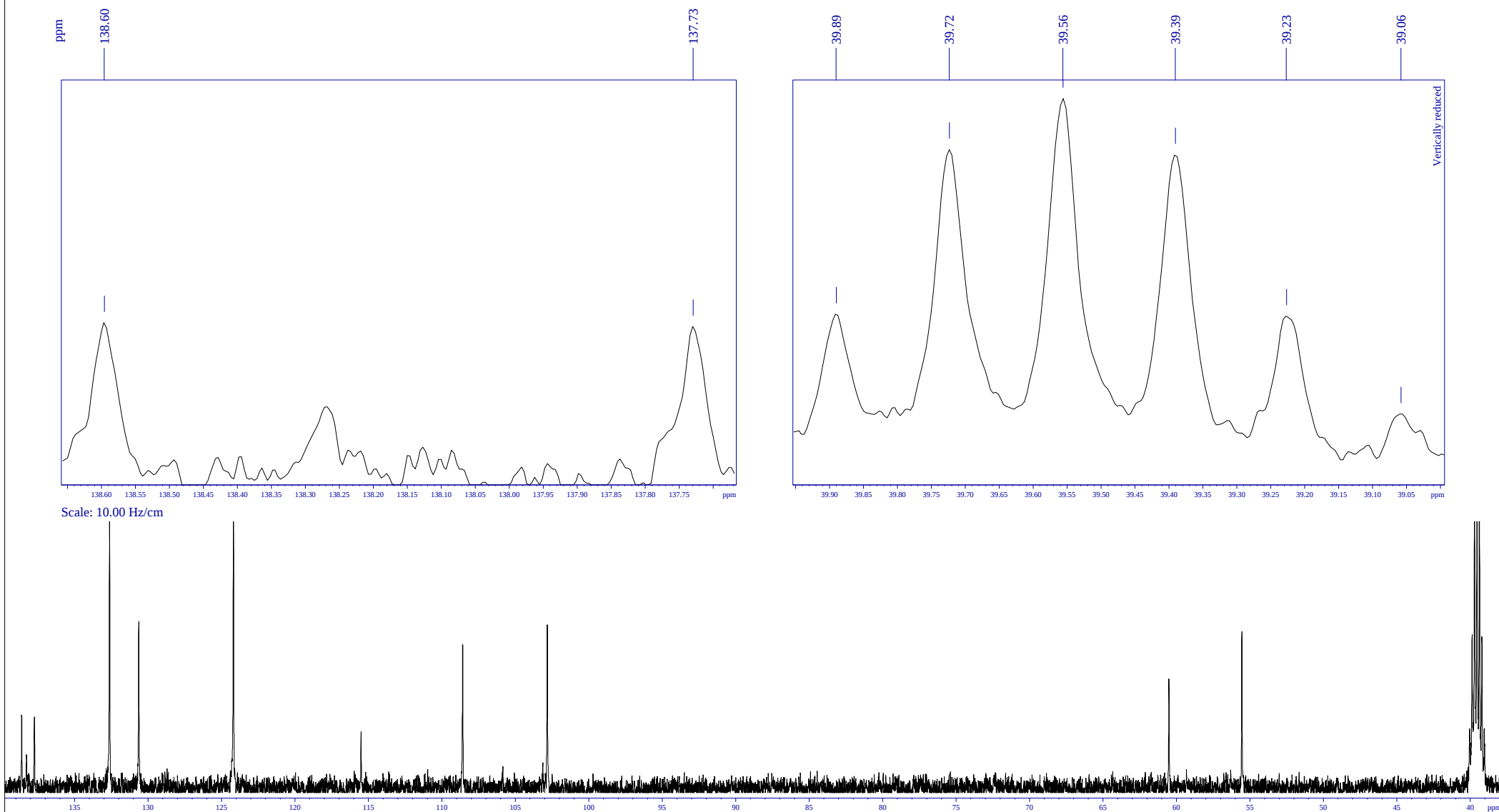
#	Address [points]	Frequency		Intensity
		[Hz]	[ppm]	[cm]
1	12929.1	5056.156	10.1097	0.60
2	15568.7	4250.620	8.4990	5.42
3	15775.9	4187.406	8.3726	5.06
4	15801.9	4179.458	8.3567	5.31
5	15892.9	4151.683	8.3012	0.41
6	15988.7	4122.455	8.2428	0.40
7	16767.0	3884.938	7.7679	5.39
8	16792.8	3877.058	7.7521	5.05
9	18037.0	3497.368	6.9929	0.62
10	19376.1	3088.691	6.1758	1.24
11	19503.0	3049.973	6.0984	10.49
12	19907.0	2926.680	5.8518	4.59
13	22973.8	1990.766	3.9805	1.92
14	23022.9	1975.785	3.9505	16.00
15	23186.6	1925.820	3.8506	0.63
16	23228.3	1913.100	3.8252	1.97
17	23304.8	1889.751	3.7785	0.48
18	23416.2	1855.747	3.7105	0.35
19	23671.9	1777.729	3.5545	0.46
20	23949.5	1693.005	3.3851	0.34
21	24089.1	1650.398	3.2999	5.28
22	24188.0	1620.219	3.2396	13.88
23	25393.1	1252.456	2.5043	7.55
24	29497.2	-0.003	-0.0000	3.29

1v (NMR/29210021)



S153

1v (NMR/29210021)

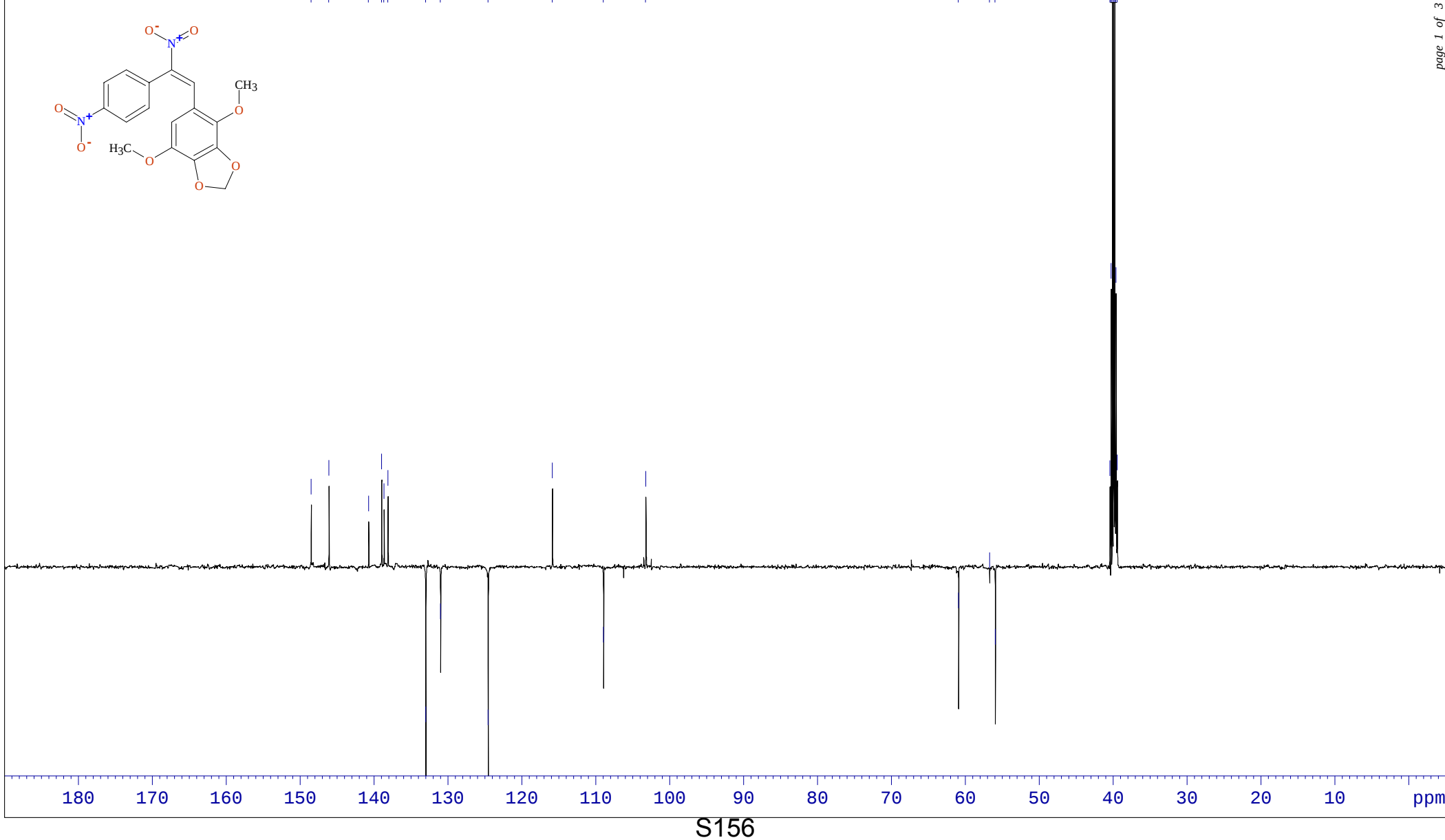
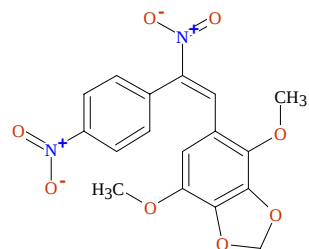


1v (NMR/29210021)

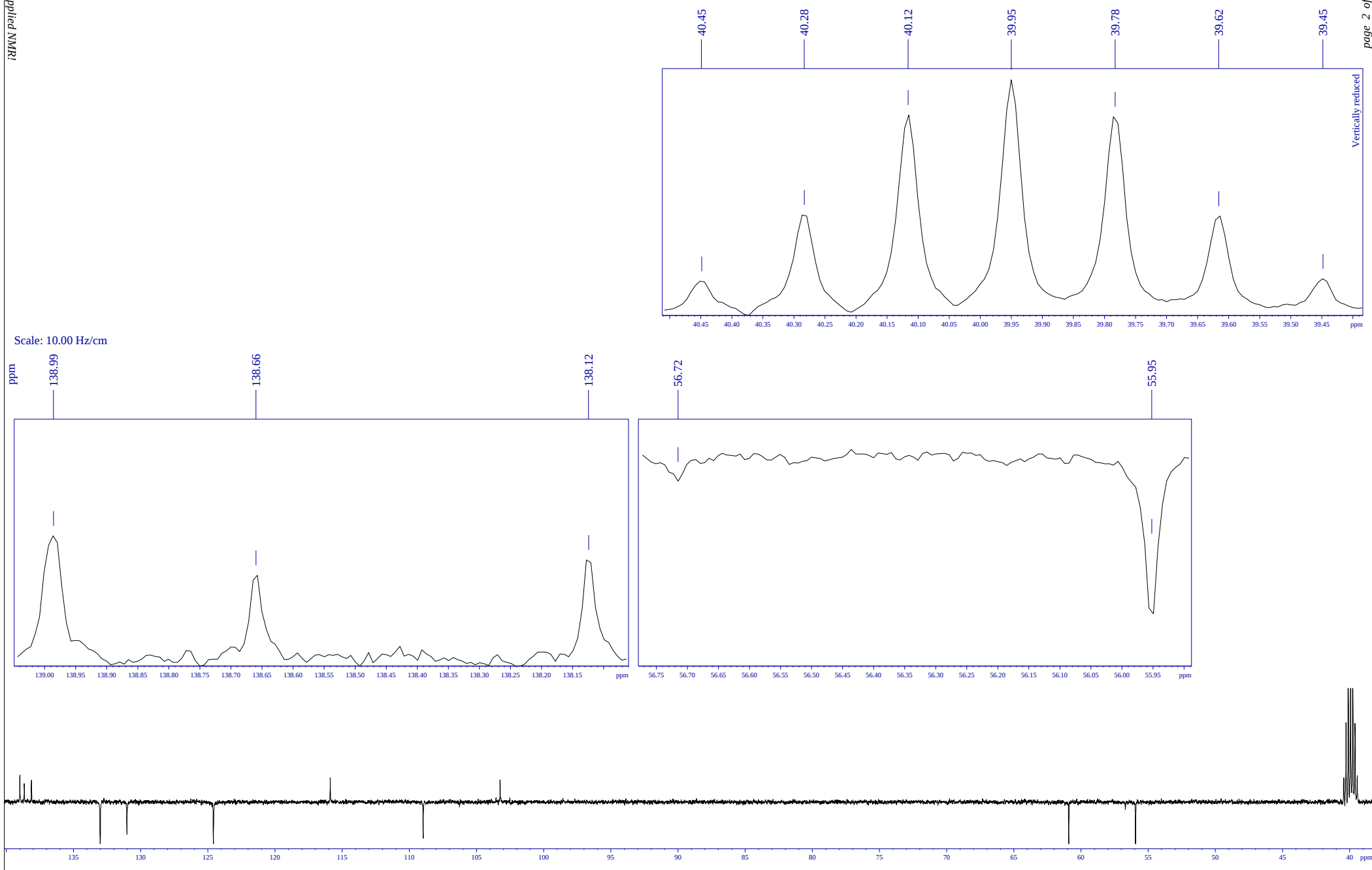
Peaks List

#	Address [points]	Frequency [Hz]	Frequency [ppm]	Intensity [cm]
1	21465.0	18628.164	148.1273	2.31
2	22094.8	18325.945	145.7241	2.09
3	23963.1	17429.480	138.5956	2.85
4	24190.1	17320.549	137.7294	2.78
5	25531.0	16677.150	132.6132	13.06
6	26052.5	16426.926	130.6235	6.62
7	27741.5	15616.479	124.1790	12.71
8	30019.0	14523.671	115.4892	2.20
9	31831.4	13654.006	108.5738	5.66
10	33334.4	12932.784	102.8388	6.46
11	44423.3	7611.922	60.5284	4.30
12	45725.2	6987.250	55.5611	6.15
13	49832.4	5016.485	39.8900	6.04
14	49876.0	4995.534	39.7234	12.11
15	49919.9	4974.472	39.5560	14.00
16	49963.3	4953.646	39.3904	11.94
17	50006.2	4933.069	39.2267	5.96
18	50050.4	4911.860	39.0581	2.33

1v (NMR/29210021)



1v (NMR/29210021)



1v (NMR/29210021)

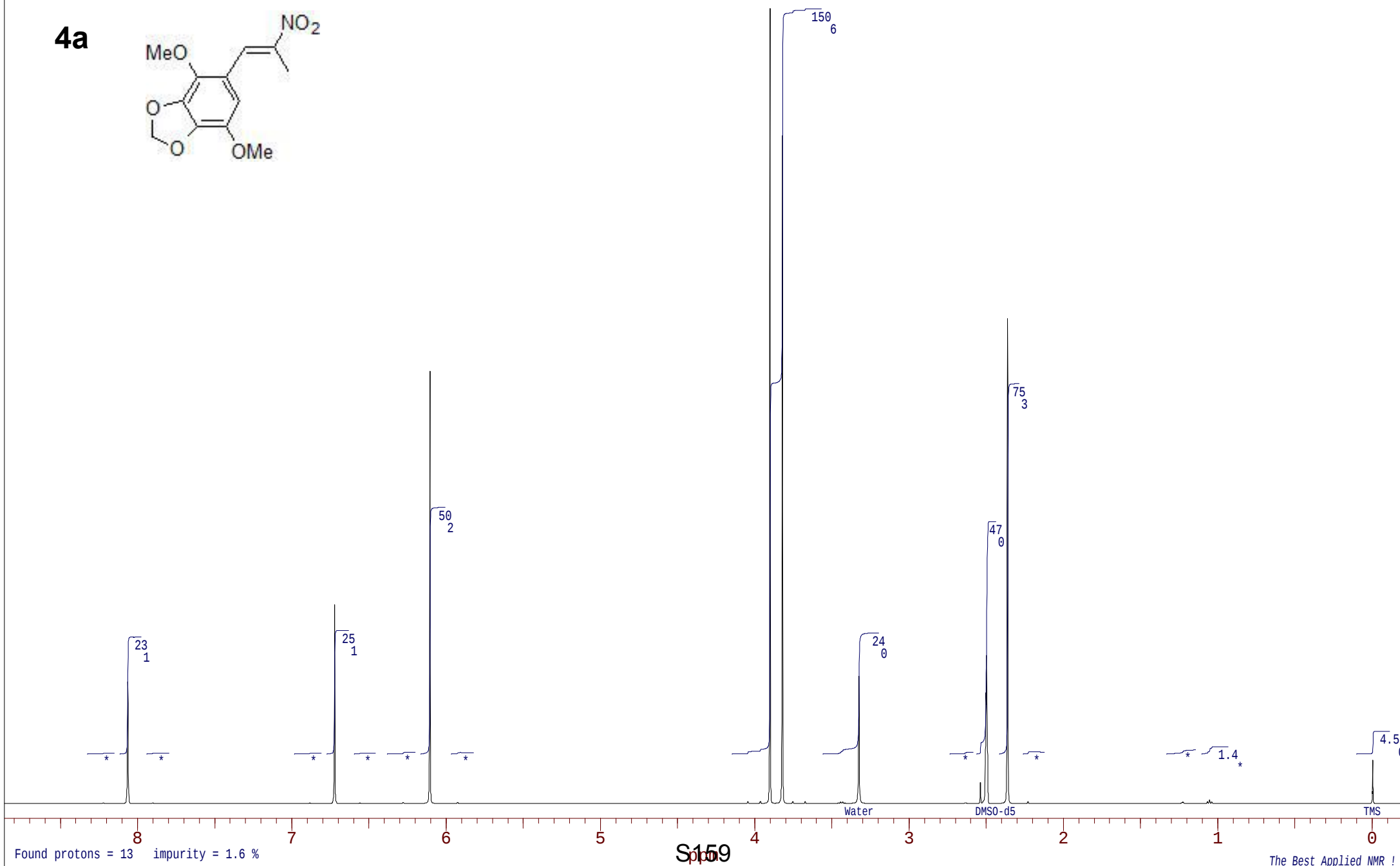
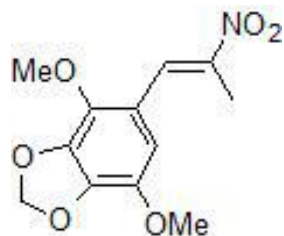
Peaks List

#	Address [points]	Frequency [Hz]	Intensity [cm]
1	9955.3	18677.455	1.94
2	10291.2	18375.092	2.39
3	11042.4	17698.852	1.48
4	11287.1	17478.539	2.54
5	11332.6	17437.543	1.80
6	11407.4	17370.184	2.15
7	12122.1	16726.824	-6.01
8	12400.8	16475.982	-3.06
9	13300.0	15666.459	-5.73
10	14514.4	14573.250	2.38
11	15481.4	13702.678	-3.51
12	16281.1	12982.824	2.10
13	22191.9	7661.726	-3.98
14	22780.0	7132.361	-0.69
15	22886.6	7036.401	-4.54
16	25052.4	5086.717	2.31
17	25075.4	5065.935	7.62
18	25098.8	5044.915	15.32
19	25122.1	5023.971	17.98
20	25145.3	5003.002	15.31
21	25168.7	4982.008	7.46
22	25192.1	4960.900	2.49

NMR/17210119



4a





/DEMC SA-001

146.893

139.154

138.904

138.345

137.874

129.513

118.184

109.302

102.210

77.475

77.256

77.051

76.627

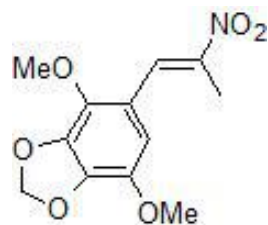
60.346

57.172

14.371

-0.007

4a



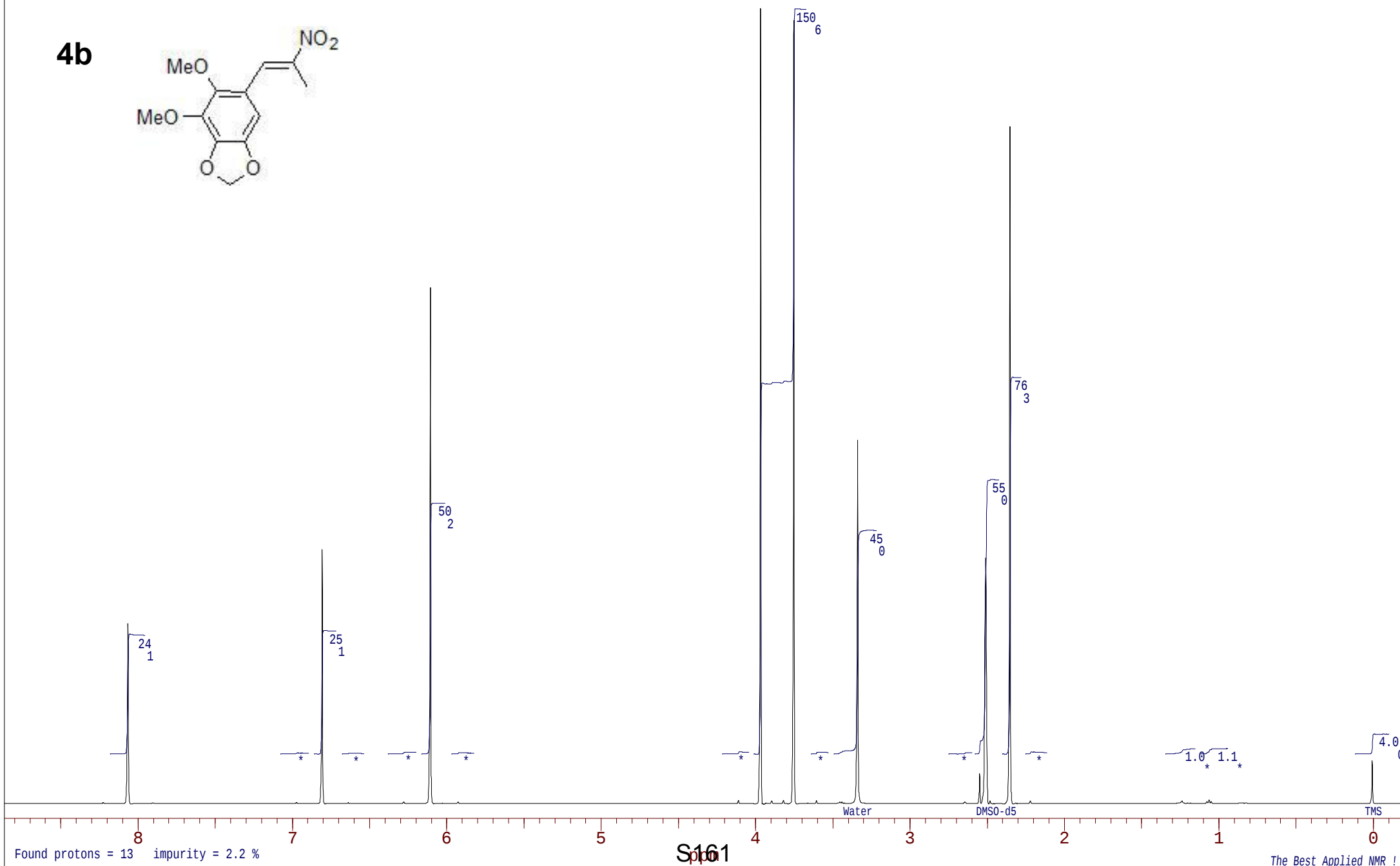
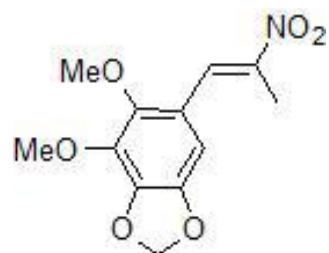
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

S160

NMR/16307502



4b

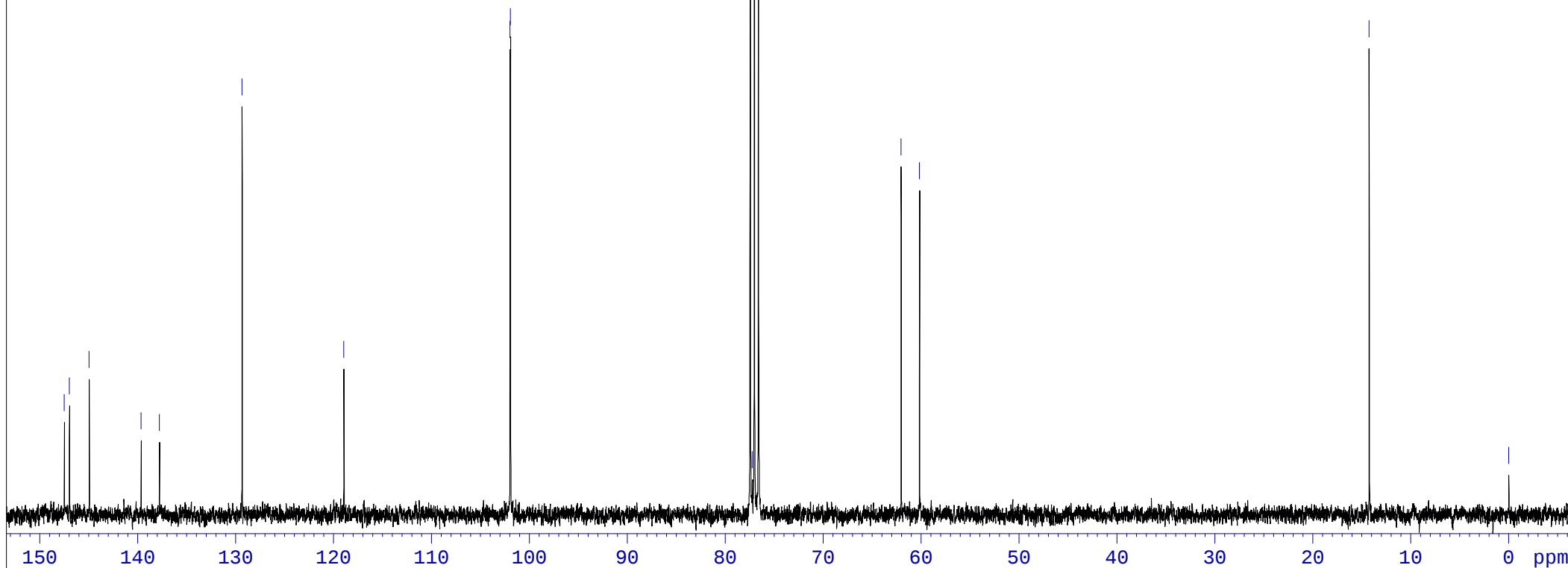
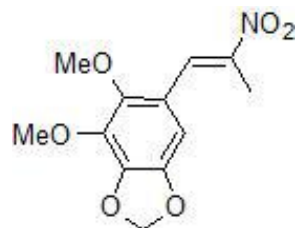




/DEMC SA-002

147.503
146.978
144.968
139.655
137.786
129.349
118.957
101.983
101.943
77.470
77.248
77.046
76.623
62.050
60.172
14.258
-0.006

4b



S162