

A comparative evaluation of monomethoxy substituted *o*-diarylazoles as antiproliferative microtubule destabilizing agents

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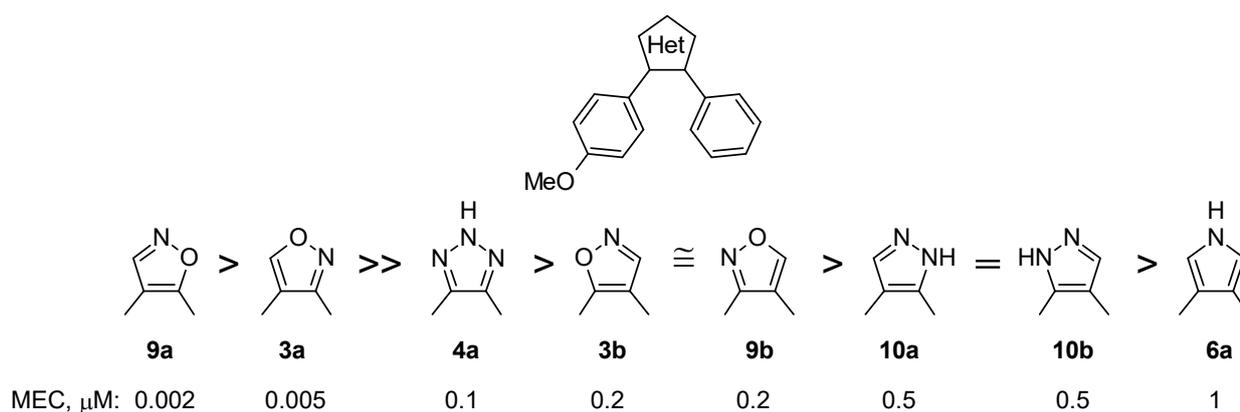


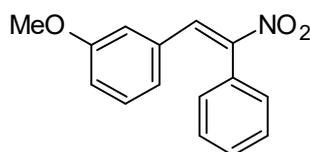
Figure S1. Comparative activity of monomethoxy substituted *o*-diarylazoles. MEC: minimal effective concentration for antimitotic antitubulin effect in the phenotypic sea urchin embryo assay.

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-600 instrument [working frequency of 600 MHz], Bruker DRX-500 instrument [working frequencies of 500.13 MHz (^1H) and of 125.76 MHz (^{13}C), respectively], and Bruker AVANCE-II [working frequencies of 300.13 MHz (^1H), and of 75.47 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 maXis and micrOTOF II instruments 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). All solvents and reagents were purified according to standard procedures.

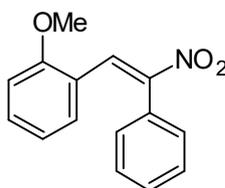
Synthesis of 1,2-diaryl-1-nitroethylenes 1 (general procedure). Acetic acid (108 mmol, 6.18 mL) was added dropwise to a mixture of phenylnitromethane (27 mmol) and methyl Schiff base of the corresponding aldehyde [S1] (29.7 mmol) in acetonitrile (14 mL) and stirred overnight. Then the volatiles were evaporated, the crude product was washed with water and extracted with dichloromethane (2 × 25 mL), the organic layers were combined, dried over MgSO₄, and the organic solvent was removed *in vacuo*. The residue was triturated with a small amount of methanol, and the resulting yellow crystals were filtered, washed with cooled methanol, and left to dry in the air to afford 1,2-diaryl-1-nitroethylenes **1** as yellow crystals.

(E)-2-(3-Methoxyphenyl)-1-nitro-1-phenyl-ethene (1c).



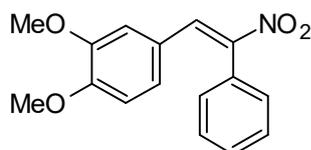
Yellow crystals; 4.2 g (61%); mp 77–79 °C (lit. [S2] 78 °C); ¹H NMR (500 MHz, CDCl₃) δ 8.19 (s, 1H, HC=), 7.52–7.45 (m, 3H, H-2,4,6), 7.36–7.31 (m, 2H, H-3,5), 7.15 (t, *J* = 8.0 Hz, 1H, H-5'), 6.85 (dd, *J* = 8.3, 2.6 Hz, 1H, H-6'), 6.78 (d, *J* = 7.6, 1H, H-4'), 6.51 (s, 1H, H-2), 3.48 (s, 3H, OCH₃); ¹³C NMR (125.76 MHz, CDCl₃) δ 159.4, 149.6, 134.8, 132.3, 130.7, 130.6 (2C), 130.0, 129.7, 129.2 (2C), 124.4, 117.7, 114.7, 54.8.

(E)-2-(2-Methoxyphenyl)-1-nitro-1-phenyl-ethene (1d).



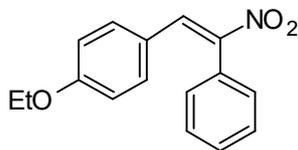
Yellow crystals; 4.2 g (61%); mp 116–118 °C (lit. [S3] 115–116 °C); ¹H NMR (600 MHz, CDCl₃) δ 8.61 (s, 1H, HC=), 7.53–7.38 (m, 3H, H-2,4,6), 7.33–7.29 (m, 2H, H-3,5), 7.27 (t, *J* = 7.5, 1H, H-4'), 6.88 (d, *J* = 8.3 Hz, 1H, H-6'), 6.69 (d, *J* = 7.9, 1H, H-3'), 6.62 (t, *J* = 7.6 Hz, 1H, H-5'), 3.89 (s, 3H, OCH₃); ¹³C NMR (150.9 MHz, CDCl₃) δ 159.6, 150.2, 132.9, 131.7, 131.39, 131.35 (2C), 131.1, 130.5, 130.4, 129.7 (2C), 121.04, 111.6, 56.4.

(E)-2-(3,4-Dimethoxyphenyl)-1-nitro-1-phenyl-ethene (1e).



Yellow crystals; 7.0 g (91%); mp 102–103 °C (lit. [S4] 102–103 °C); ¹H NMR (600 MHz, CDCl₃) δ 8.22 (s, 1H, HC=), 7.57–7.45 (m, 3H, H-2,4,6), 7.37 (d, *J* = 7.7 Hz, 2H, H-3,5), 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, OCH₃), 3.39 (s, 3H, OCH₃); ¹³C NMR (150.9 MHz, CDCl₃) 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-(4-Ethoxyphenyl)-1-nitro-1-phenyl-ethene (**1h**).

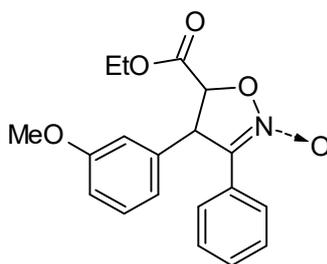


Yellow crystals; 4.07 g (56%); mp 147–149 °C (lit. [S5] 145 °C); ¹H NMR (600 MHz, CDCl₃) δ 8.21 (s, 1H, HC=), 7.50 (m, 3H, H-2,4,6), 7.33 (m, 2H, H-3,5), 7.02 (d, *J* = 8.7 Hz, 2H, H-2',6'), 6.72 (d, *J* = 8.8 Hz, 2H, H-3',5'), 3.99 (q, *J* = 7.0 Hz, 2H, OCH₂), 1.37 (t, *J* = 7.0 Hz, 3H, CH₃); ¹³C NMR (150.9 MHz, CDCl₃) δ 161.3, 147.3, 135.1, 133.3 (2C), 131.1, 130.7 (2C), 129.9, 129.3 (2C), 123.4, 114.8 (2C), 63.7, 14.6.

Synthesis of 3,4-diaryl-5-ethoxycarbonyl-4,5-dihydroisoxazole 2-oxides 2 (general procedure).

Triethylamine (1.8 mL) was added dropwise to a suspension of 1-(2-ethoxy-2-oxoethyl)pyridine-1-ium bromide (6.5 mmol) and nitroethylene **1** (4.3 mmol) in dry acetonitrile (5–10 mL). The mixture was stirred at room temperature for 1 h. Acetonitrile was removed *in vacuo*, the crude product was suspended in water (~10 mL), and extracted with dichloromethane (2 × 15 mL). The organic layers were combined and dried over MgSO₄, the solvent was evaporated *in vacuo*. The resulting oil was crystallized from ethanol, and the precipitate was filtered, washed with little cooled ethanol, and dried in air to afford 3,4-diaryl-5-ethoxycarbonyl-4,5-dihydroisoxazole 2-oxides **2a–d,f–h** as white crystals and **2e** as an oil.

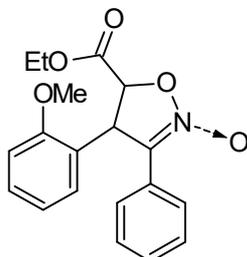
5-(Ethoxycarbonyl)-4-(3-methoxyphenyl)-3-phenyl-4,5-dihydroisoxazole 2-oxide (**2c**).



White crystals; 0.97 g (66%); mp 116–118 °C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.91 (d, *J* = 7.7 Hz, 2H, H-2,6), 7.47–7.35 (m, 3H, H-3,4,5), 7.31 (t, *J* = 7.9 Hz, 1H, H-5'), 6.96–6.88 (m, 3H, H-2',4',6'), 5.41 (d, *J* = 2.6 Hz, 1H, iso H-4), 5.13 (d, *J* = 2.6 Hz, 1H, iso H-5), 4.26 (q, *J* = 7.1 Hz, 2H, OCH₂), 3.74 (s, 3H, OCH₃), 1.27 (t, *J* = 7.1 Hz, 3H, CH₃); ¹³C NMR (125.76 MHz, DMSO-*d*₆) δ 168.7, 159.8, 140.3, 130.6, 129.7, 128.8 (2C), 126.6 (2C), 125.4, 119.2, 115.0, 113.4, 113.3, 77.7, 61.8, 55.2, 52.7,

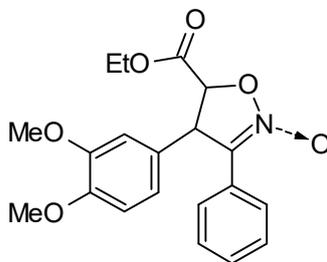
14.0; HRMS (ESI/QTOF) m/z : $[M+H]^+$ Calcd for $C_{19}H_{20}NO_5$ 342.1336; Found 342.1337; $[M+NH_4]^+$ Calcd for $C_{19}H_{23}N_2O_5$ 359.1601; Found 359.1601; $[M+Na]^+$ Calcd for $C_{19}H_{19}NO_5Na$ 364.1155; Found 364.1155; $[M+K]^+$ Calcd for $C_{19}H_{19}NO_5K$ 380.0895; Found 380.0892.

5-(Ethoxycarbonyl)-4-(2-methoxyphenyl)-3-phenyl-4,5-dihydroisoxazole 2-oxide (2d).



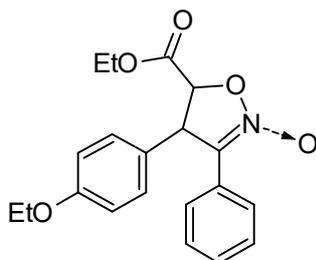
White crystals, 0.91 g (71%); mp 101–103 °C; 1H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, $J = 8.5$ Hz, 2H, H-2,6), 7.37–7.25 (m, 4H, H-3,4,5,4'), 7.12 (dd, $J = 7.3, 1.7$ Hz, 1H, H-6'), 6.95 (d, $J = 8.3$ Hz, 1H, H-3'), 6.88 (t, $J = 7.5$ Hz, 1H, H-5'), 5.48 (d, $J = 2.8$ Hz, 1H, iso H-4), 4.80 (d, $J = 3.0$ Hz, 1H, iso H-5), 4.32 (m, 2H, OCH_2), 3.93 (s, 3H, OCH_3), 1.34 (t, $J = 6.8$ Hz, 3H, CH_3); ^{13}C NMR (150.9 MHz, APT, $CDCl_3$) δ 169.2(-), 156.4(-), 129.9(+), 129.6(+), 128.8(2C,+), 128.4(+), 126.8(2C,+), 126.0(-), 125.97(-), 121.3(+), 114.7(-), 111.1(+), 78.5(+), 62.3(-), 55.8(+), 48.2(+), 14.2(+); HRMS (ESI/QTOF) m/z : $[M+H]^+$ Calcd for $C_{19}H_{20}NO_5$ 342.1336; Found 342.1334; $[M+Na]^+$ Calcd for $C_{19}H_{19}NO_5Na$ 364.1155; Found 364.1153; $[M+K]^+$ Calcd for $C_{19}H_{19}NO_5K$ 380.0895; Found 380.0891.

4-(3,4-Dimethoxyphenyl)-5-(ethoxycarbonyl)-3-phenyl-4,5-dihydroisoxazole 2-oxide (2e).



Dark oil, 1.52 g (95%); 1H NMR (500 MHz, $DMSO-d_6$) δ 7.91 (d, $J = 7.2$ Hz, 2H, H-2,6), 7.46 – 7.39 (m, 3H, H-3,4,5), 7.01 (d, $J = 2.1$ Hz, 1H, H-2'), 6.94 (d, $J = 8.3$ Hz, 1H, H-5'), 6.86 (dd, $J = 8.3, 2.1$ Hz, 1H, H-6'), 5.35 (d, $J = 2.8$ Hz, 1H, iso H-4), 5.11 (d, $J = 2.7$ Hz, 1H, iso H-5), 4.25 (m, 2H, OCH_2), 3.74 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 1.27 (t, $J = 7.1$ Hz, 3H, CH_3); ^{13}C NMR (125.76 MHz, $DMSO-d_6$) δ 168.8, 149.2, 148.7, 131.0, 129.6, 128.8(2C), 126.6(2C), 125.5, 119.4, 115.1, 112.3, 111.0, 78.0, 61.8, 55.6, 52.5, 55.51, 14.0; HRMS (ESI/QTOF) m/z : $[M+H]^+$ Calcd for $C_{20}H_{22}NO_6$ 372.1442; Found 372.1434; $[M+NH_4]^+$ Calcd for $C_{20}H_{25}N_2O_6$ 389.1707; Found 389.1700; $[M+Na]^+$ Calcd for $C_{20}H_{21}NO_6Na$ 394.1261; Found 394.1256; $[M+K]^+$ Calcd for $C_{20}H_{21}NO_6K$ 410.1000; Found 410.1001.

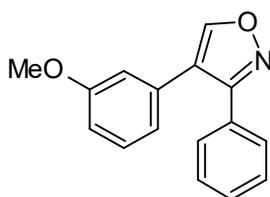
5-(Ethoxycarbonyl)-4-(4-ethoxyphenyl)-3-phenyl-4,5-dihydroisoxazole 2-oxide (**2h**).



White crystals; 1.06 g (70%); mp 92–94 °C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.89 (d, *J* = 7.1 Hz, 2H, H-2,6), 7.44–7.35 (m, 3H, H-3,4,5), 7.28 (d, *J* = 8.5 Hz, 2H, H-2',6'), 6.93 (d, *J* = 8.5 Hz, 2H, H-3',5'), 5.36 (d, *J* = 2.5 Hz, 1H, iso H-4), 5.07 (d, *J* = 2.5 Hz, 1H, iso H-5), 4.26 (d, *J* = 7.3 Hz, 2H, COOCH₂), 3.98 (q, *J* = 7.0 Hz, 2H, OCH₂), 1.31–1.24 (m, 6H, CH₃); ¹³C NMR (125.76 MHz, DMSO-*d*₆) δ 168.8, 158.4, 130.5, 129.6, 128.8 (2C), 128.5 (2C), 126.6 (2C), 125.4, 115.2 (2C), 115.1, 78.0, 63.1, 61.8, 52.1, 14.6, 14.0; HRMS (ESI/QTOF) *m/z*: [M+H]⁺ Calcd for C₂₀H₂₂NO₅ 356.1492; Found 356.1491; [M+NH₄]⁺ Calcd for C₂₀H₂₅N₂O₅ 373.1758; Found 373.1752; [M+Na]⁺ Calcd for C₂₀H₂₁NO₅Na 378.1312; Found 378.1306.

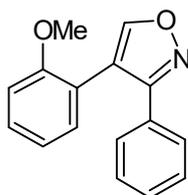
Synthesis of 3,4-diarylisoxazoles 3 (general procedure). A solution of isoxazoline **2** (1.17 mmol) in 2% ethanolic NaOH (7.5 mL) was stirred at 60 °C for 10 min, and then water (1 mL) was added. The mixture was stirred at 60 °C for 6 h and left overnight at room temperature. Then ethanol was evaporated *in vacuo*, water (3–5 mL) was added to the crude product, which was extracted with dichloromethane (2 × 10 mL). The organic layers were combined, washed with water, dried with MgSO₄, and the solvent was evaporated *in vacuo*. Further purification was performed by column chromatography on silica gel with gradient elution (benzene–benzene-ethyl acetate) to afford isoxazoles **3** as solids or oils.

3-Phenyl-4-(3-methoxyphenyl)isoxazole (**3c**).



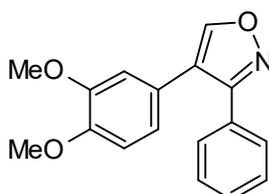
Yellowish oil; 0.103 g (35%); ¹H NMR (500 MHz, CDCl₃) δ 8.51 (s, 1H, iso H-5), 7.52 (m, 2H, H-2,6), 7.44–7.31 (m, 3H, H-3,4,5), 7.25 (t, *J* = 7.3 Hz, 1H, H-5'), 6.88 (dd, *J* = 8.3, 2.6 Hz, 1H, H-6'), 6.84 (dt, *J* = 7.6, 1.2 Hz, 1H, H-4'), 6.77 (t, *J* = 2.1 Hz, 1H, H-2'), 3.71 (s, 3H); ¹³C NMR (125.76 MHz, CDCl₃) δ 160.2, 159.8, 156.3, 130.3, 129.8, 129.7, 128.8 (2C), 128.6 (2C), 121.2, 120.2, 114.4, 113.7, 55.2; HRMS (ESI/QTOF) *m/z*: [M+H]⁺ Calcd for C₁₆H₁₄NO₂ 252.1019; Found 252.1017; [M+Na]⁺ Calcd for C₁₆H₁₃NO₂Na 274.0838; Found 274.0836.

3-Phenyl-4-(2-methoxyphenyl)isoxazole (3d).



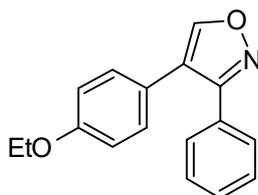
Yellowish oil; 0.085 g (29%), ^1H NMR (500 MHz, CDCl_3) δ 8.55 (s, 1H, iso H-5), 7.47 (m, 2H, H-2,6), 7.39–7.27 (m, 4H, H-3,4,5,4'), 7.15 (dd, $J = 7.4, 1.7$ Hz, 1H, H-6'), 6.91 (m, 2H, H-3',5'), 3.55 (s, 3H, OCH_3); ^{13}C NMR (125.76 MHz, CDCl_3) δ 160.9, 157.3, 156.9, 131.1, 129.8, 129.7, 129.3, 128.4 (2C), 128.0 (2C), 120.7, 118.1, 115.9, 111.2, 55.2; HRMS (ESI/QTOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{14}\text{NO}_2$ 252.1019; Found 252.1026; $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{16}\text{H}_{13}\text{NO}_2\text{Na}$ 274.0838; Found 274.0845.

3-Phenyl-4-(3,4-dimethoxyphenyl)isoxazole (3e).



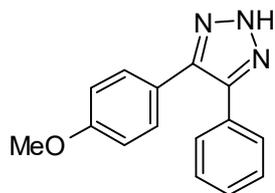
Off-white crystals; 0.082 g (25%); mp 86–88 °C (lit. [S6] 97.5–98.5 °C); ^1H NMR (500 MHz, CDCl_3) δ 8.49 (s, 1H, iso H-5), 7.52 (m, 2H, H-2,6), 7.45–7.34 (m, 3H, H-3,4,5), 6.85 (s, 2H, H-5',6'), 6.69 (s, 1H, H-2'), 3.90 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3); ^{13}C NMR (125.76 MHz, CDCl_3) δ 160.2, 155.8, 148.98, 148.95, 129.6, 128.79 (2C), 128.75, 128.6 (2C), 121.4, 121.3, 120.1, 112.1, 111.4, 56.0, 55.8; HRMS (ESI/QTOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{16}\text{NO}_3$ 282.1125; Found 282.1126; $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_3\text{Na}$ 304.0944; Found 304.0942.

3-Phenyl-4-(4-ethoxyphenyl)isoxazole (3h).



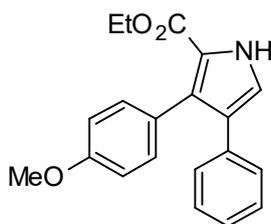
Off-white crystals; 0.099 g (32%); mp 74–76 °C; $R_f = 0.6$ (benzene); ^1H NMR (600 MHz, CDCl_3) δ 8.44 (s, 1H, iso H-5), 7.50 (d, $J = 7.7$ Hz, 2H, H-2,6), 7.43–7.31 (m, 3H, H-3,4,5), 7.15 (d, $J = 8.5$ Hz, 2H, H-2',6'), 6.86 (d, $J = 8.5$ Hz, 2H, H-3',5'), 4.03 (q, $J = 7.0$ Hz, 2H, OCH_2), 1.42 (t, $J = 7.0$ Hz, 3H, OCH_3); ^{13}C NMR (150.9 MHz, APT, CDCl_3) δ 159.7 (-), 158.4 (-), 155.3 (+), 129.6 (2C, +), 129.0 (+), 128.3 (-), 128.2 (2C, +), 128.1 (2C,+), 120.5 (-), 119.5 (-), 114.2 (2C,+), 63.0 (-), 14.3 (+); HRMS (ESI/QTOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{16}\text{NO}_2$ 266.1176; Found 266.1173; $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_2\text{Na}$ 288.0995; Found 288.0988.

4-(4-Methoxyphenyl)-5-phenyl-1,2,3-triazole (**4a**) [S7,S8].



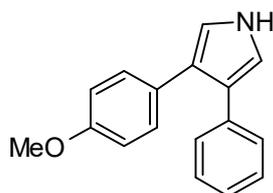
All experiments were performed in a well-ventilated fume hood and behind a blast shield. 1,2-Diarylnitroethylene **1a** (200 mg, 0.78 mmol) and NaN₃ (76 mg, 1.18 mmol) were stirred in DMF (6 mL), and then *p*-TsOH (67 mg, 0.39 mmol) was added carefully to the mixture. The mixture was stirred at 60 °C in air for 1 h. Then the mixture was cooled to room temperature, quenched with H₂O (20 mL), and extracted with EtOAc (3 × 20 mL). The organic layers were dried over anhydrous Na₂SO₄ and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc, 3:1) [S9]. Colorless oil; 0.143 g (73%); ¹H NMR (500 MHz, CDCl₃) δ 11.95 (s, 1H, NH), 7.57 (m, 2H, Ar), 7.48 (d, *J* = 8.3 Hz, 2H, Ar), 7.37 (m, 3H, Ar), 6.91 (d, *J* = 8.4 Hz, 2H, Ar), 3.73 (s, 3H, OCH₃); EIMS *m/z* (%): 251 [M]⁺ (100), 152 (16), 77 (64), 63 (69), 51 (91), 39 (48), 28 (54), 15 (47).

Ethyl 3-(4-methoxyphenyl)-4-phenyl-1H-pyrrole-2-carboxylate (**5a**) [S10].



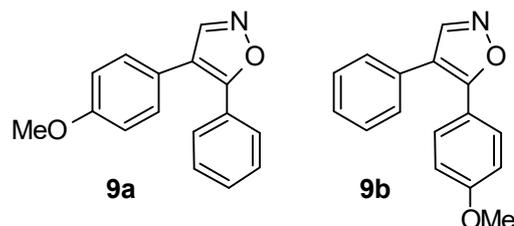
Freshly calcined potassium carbonate (276 mg, 2 mmol) was added to a suspension of 1,2-diarylnitroethylene **1a** [S11] (255 mg, 1 mmol) and ethyl isocyanoacetate (113 mg, 1 mmol) in ethanol (2 mL) and the mixture was stirred at room temperature for 12 h until the disappearance of the starting diarylnitroethylene **1a** (TLC control: hexane–EtOAc, 3:1). The reaction mixture was diluted with water (up to 15 mL), neutralized with HCl, filtered, washed with water (3 × 5 mL), and dried [S12]. White solid; 0.268 g (86 %); mp 129–131 °C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.95 (s, 1H, NH), 7.23 (d, *J* = 2.8 Hz, 1H; CHpyr), 7.16 (m, 2H, Ar), 7.07 (m, 5H, Ar), 6.84 (d, *J* = 8.4 Hz, 2H, Ar), 4.07 (q, *J* = 7.1 Hz, 2H, CH₂), 3.73 (s, 3H, OCH₃), 1.09 (t, *J* = 7.1 Hz, 3H, CH₃); EIMS *m/z* (%): 321 [M]⁺ (40), 275 (78), 204 (26), 176 (15), 77 (14), 29 (100), 15 (31).

3-(4-Methoxyphenyl)-4-phenyl-1H-pyrrole (**6a**) [S13].



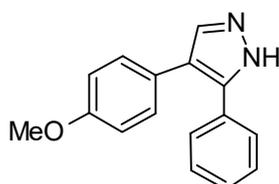
Suspension of ethyl 3-(4-methoxyphenyl)-4-phenyl-1*H*-pyrrole-2-carboxylate **5a** (200 mg, 0.32 mmol) and NaOH (128 mg, 3.2 mmol) in ethanol (3 mL) was boiled for 4 h until the disappearance of the starting pyrrole. The reaction mixture was diluted with water (up to 15 mL), filtered, washed with water (5 mL), and dried to afford white solid; 0.063 g (79%); mp 107–109 °C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.25 (s, 1H, NH), 7.27 (m, 4H, Ar), 7.19 (m, 3H, Ar), 6.91 (s, 1H, CHpyr), 6.86 (s, 1H, CHpyr), 6.82 (d, *J* = 7.9 Hz, 2H; Ar), 3.80 (s, 3H, OCH₃); EIMS *m/z* (%): 249 [M]⁺ (100), 234 (16), 178 (12), 15 (15).

Synthesis of 4,5-diarylloxazoles 9. These were published previously [S11].



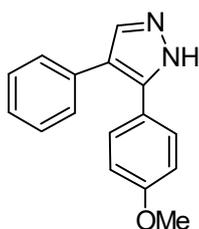
Synthesis of o-diarylpyrazoles 10 (general procedure). A mixture of dimethylacetal **8** [S11] (0.90 g, 3 mmol), hydrazine hydrate (195 mg, 3.9 mmol) and 0.4 mL conc. HCl was refluxed for 2 h and evaporated *in vacuo* to dryness. The residue was dissolved in EtOAc (40 mL), the solution was washed with 5% aq. NaHCO₃ (50 mL) and water (50 mL), dried with MgSO₄, evaporated, and the residue triturated with MeOH (3 mL). The resulting suspension was kept at 0–5 °C for 2 h, the crystalline precipitate filtered off, washed with cold MeOH (2 mL), and dried.

4-(4-Methoxyphenyl)-3-phenylpyrazole (10a).



Yellowish crystals, 378 mg (51%); mp 129–130 °C (lit. [S14] 131–132 °C; lit. [S15] 126–127 °C); ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.0 (br.s, 1H, NH), 7.8 (br.s, 1H, H-5), 7.45–7.30 (m, 5H, Ar), 7.17 (d, *J* = 8.6 Hz, 2H, Ar), 6.88 (d, *J* = 8.6 Hz, 2H, Ar), 3.71 (s, 3H, OCH₃); ¹³C NMR (125 MHz, DMSO-*d*₆) δ 157.9, 129.3 (2C), 128.5 (2C), 127.8 (2C), 127.6, 125.7, 118.6, 114.0 (2C), 55.0.

3-(4-Methoxyphenyl)-4-phenylpyrazole (10b).



Yellowish crystals, 411 mg (55%); mp 125–126 °C (lit. [S14] 127–127.5 °C); ¹H NMR (500 MHz, DMSO-*d*₆) δ 13.0 (br.s, 1H, NH), 7.8 (br.s, 1H, H-5), 7.35-7.20 (m, 7H, Ar); 6.92 (d, *J* = 8.5 Hz, 2H, Ar); 3.76 (s, 3H, OCH₃); ¹³C NMR (125 MHz, DMSO-*d*₆) δ 159.0, 133.7, 129.2 (2C), 128.5 (2C), 128.0 (2C), 126.2, 118.4, 114.0 (2C), 55.1.

Biology. Phenotypic sea urchin embryo assay [S16]. 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 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, Russia). 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 compounds 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 alteration and retardation of the sea urchin embryo development independent of the treatment stage. Combretastatin A-4 (synthesized as reported previously [S17,S18]) served as a positive control. The antiproliferative activity was assessed by exposing fertilized eggs (8–15 min after fertilization, 45–55 min before the first mitotic cycle completion) to 2-fold decreasing concentrations of the compound. Cleavage alteration and arrest were clearly detected at 2.5–5.5 h after fertilization, when control embryos reached 8-cell and early blastula stages, respectively. The effects were estimated quantitatively as a minimal effective concentration (MEC), resulting in cleavage alteration and embryo death before hatching or full mitotic arrest. At these concentrations all tested microtubule destabilizers caused 100% cleavage alteration and embryo death before hatching, whereas at 2-fold lower concentrations the compounds failed to produce any effect. For microtubule-destabilizing activity, the compounds were tested on free-swimming 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 treatment, depending on the structure and concentration of the compound. Both spinning and lack of forward movement were interpreted to be the result of the microtubule-destabilizing activity of a molecule. Video illustrations are available at <http://www.chemical-block.com>. The sea urchin embryo assay data are available free of charge via the Internet at <http://www.zelinsky.ru>. Experiments with the

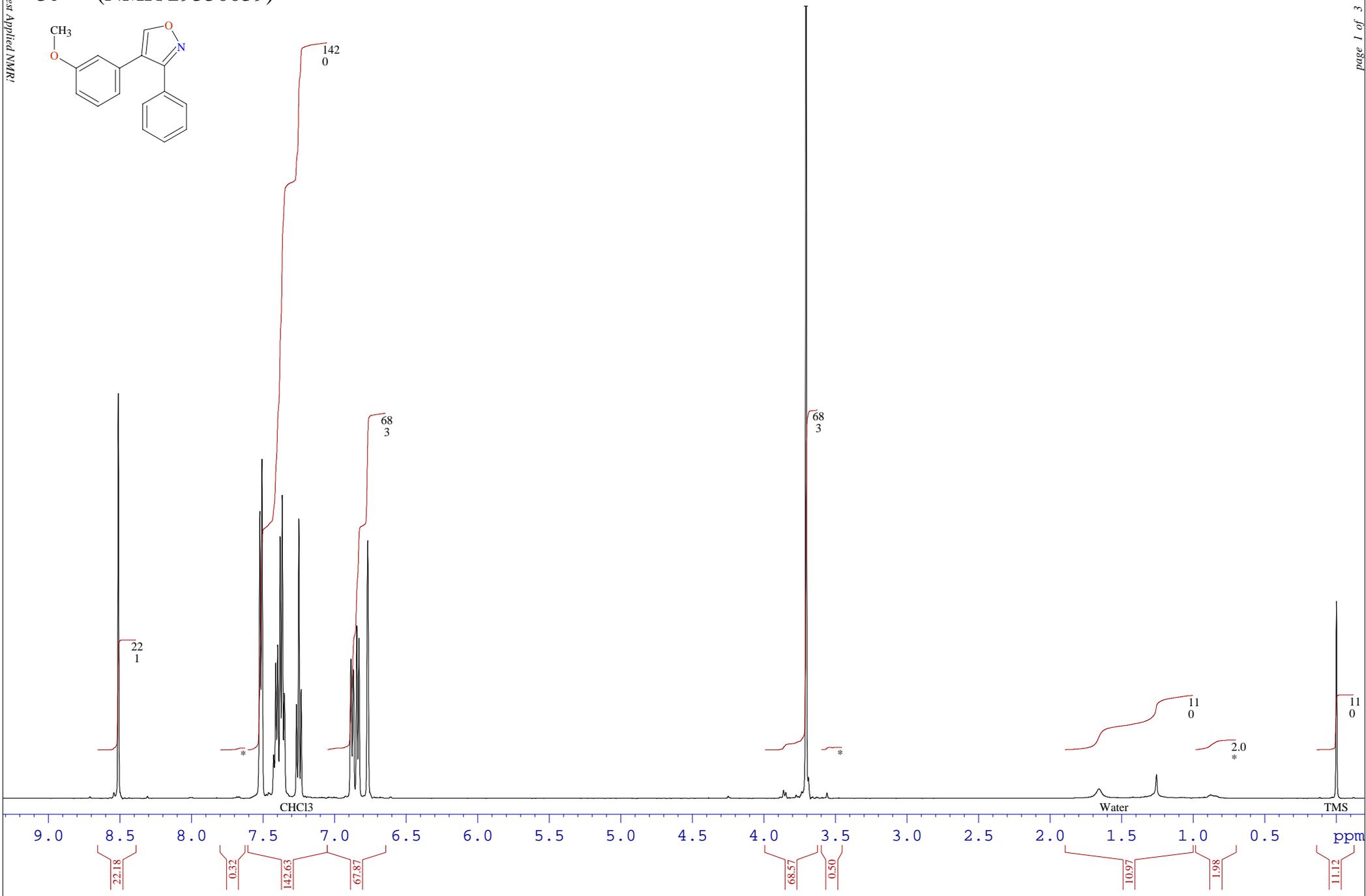
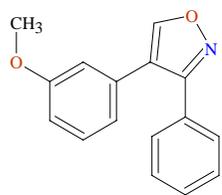
sea urchin embryos fulfill the requirements of biological ethics. The artificial spawning does not cause animal death, embryos develop outside the female organism, and both post spawned adult sea urchins and the excess of intact embryos are returned to the sea, their natural habitat.

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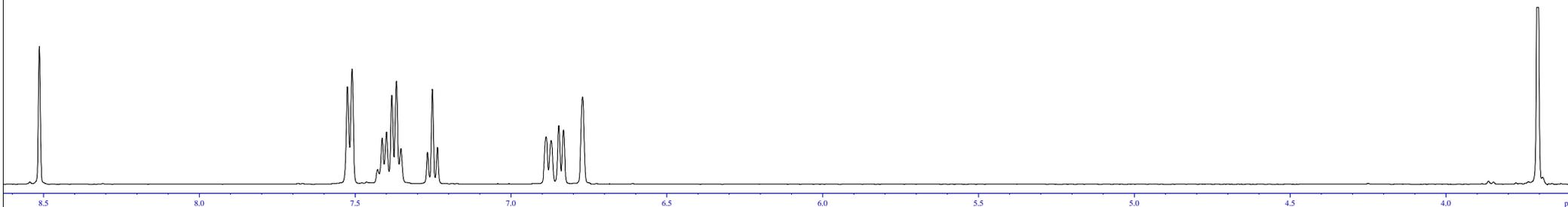
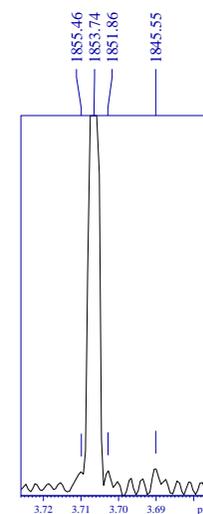
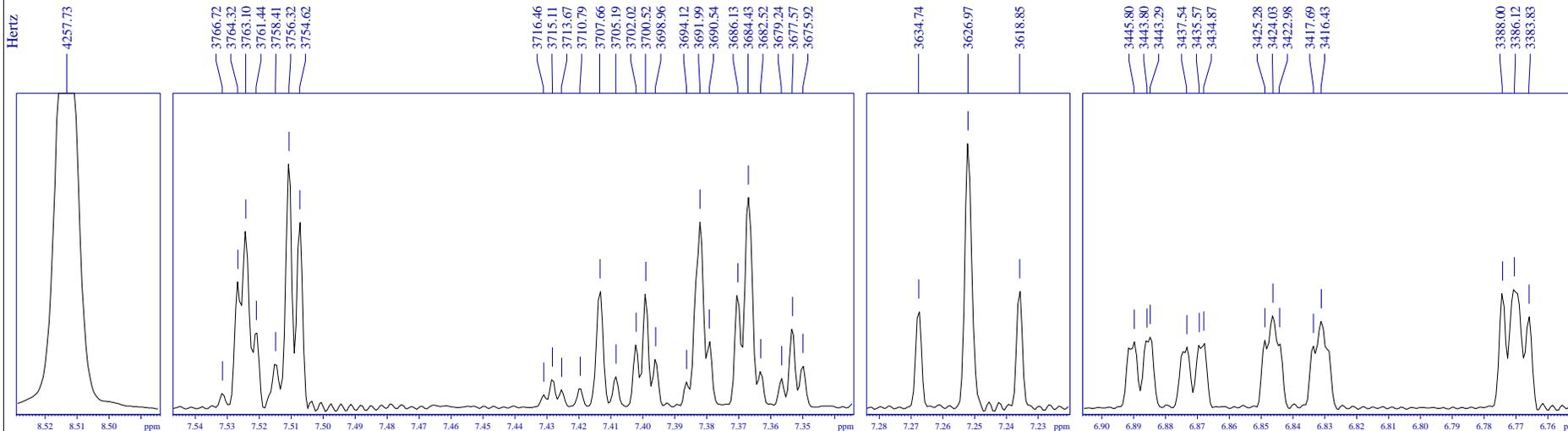
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3c (NMR/29330039)

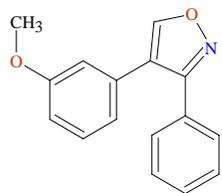
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3	15518.3	4255.884	8.5096	0.33
4	15520.8	4255.121	8.5080	-0.28
5	15523.3	4254.368	8.5065	0.27
6	15525.9	4253.562	8.5049	-0.28
7	15528.5	4252.771	8.5033	0.24
8	15531.1	4251.996	8.5018	-0.22
9	15533.7	4251.179	8.5001	0.24
10	17121.2	3766.715	7.5315	0.25
11	17129.1	3764.318	7.5267	2.14
12	17133.1	3763.101	7.5242	2.99
13	17138.5	3761.436	7.5209	1.33
14	17148.4	3758.412	7.5149	0.77
15	17155.3	3756.317	7.5107	4.21
16	17160.8	3754.623	7.5073	3.16
17	17285.9	3716.457	7.4310	0.23
18	17290.3	3715.105	7.4283	0.50
19	17295.0	3713.669	7.4254	0.31
20	17304.5	3710.787	7.4196	0.35
21	17314.7	3707.663	7.4134	2.00
22	17322.8	3705.188	7.4084	0.54
23	17333.2	3702.023	7.4021	1.08
24	17338.1	3700.517	7.3991	1.94
25	17343.2	3698.962	7.3960	0.84
26	17359.1	3694.119	7.3863	0.44
27	17366.1	3691.988	7.3821	3.16
28	17370.8	3690.543	7.3792	1.14
29	17385.3	3686.131	7.3703	1.94
30	17390.8	3684.435	7.3670	3.58
31	17397.1	3682.524	7.3631	0.63
32	17407.8	3679.244	7.3566	0.51
33	17413.3	3677.569	7.3532	1.37
34	17418.7	3675.919	7.3499	0.72
35	17553.7	3634.741	7.2676	1.67
36	17579.1	3626.973	7.2521	4.50
37	17605.8	3618.849	7.2358	2.00
38	18172.8	3445.796	6.8898	1.13
39	18179.4	3443.795	6.8858	1.16
40	18181.0	3443.286	6.8848	1.21
41	18199.9	3437.537	6.8733	1.03
42	18206.3	3435.568	6.8694	1.08
43	18208.6	3434.869	6.8680	1.12
44	18240.0	3425.279	6.8488	1.15
45	18244.1	3424.028	6.8463	1.57
46	18247.6	3422.979	6.8442	1.12
47	18264.9	3417.688	6.8336	1.06
48	18269.0	3416.429	6.8311	1.47
49	18362.2	3388.002	6.7742	1.95
50	18368.3	3386.123	6.7705	2.03
51	18375.9	3383.833	6.7659	1.55
52	23384.0	1855.456	3.7099	0.24
53	23389.7	1853.742	3.7065	24.15
54	23395.8	1851.864	3.7028	0.26
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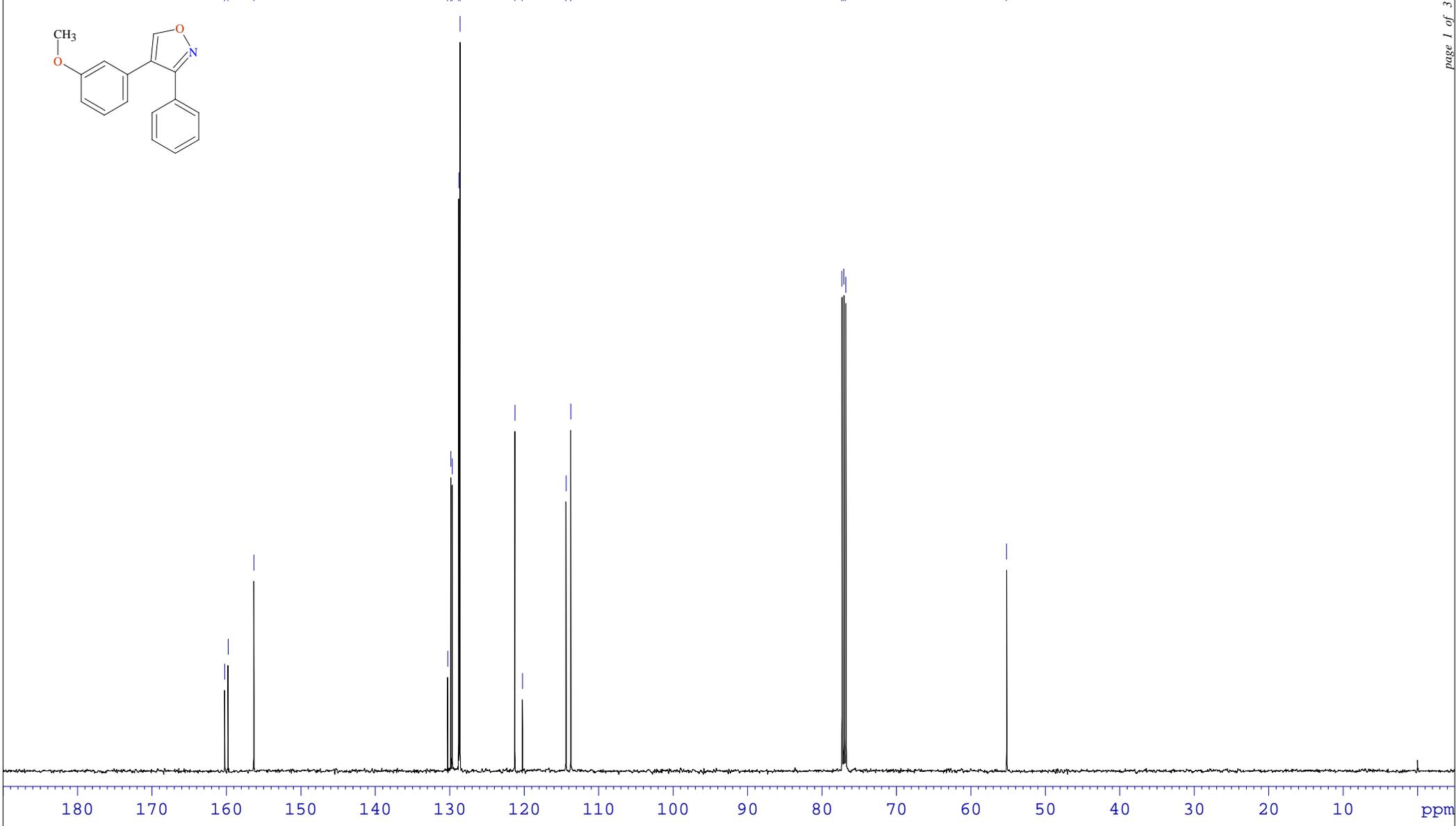
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77.33
77.07
76.82

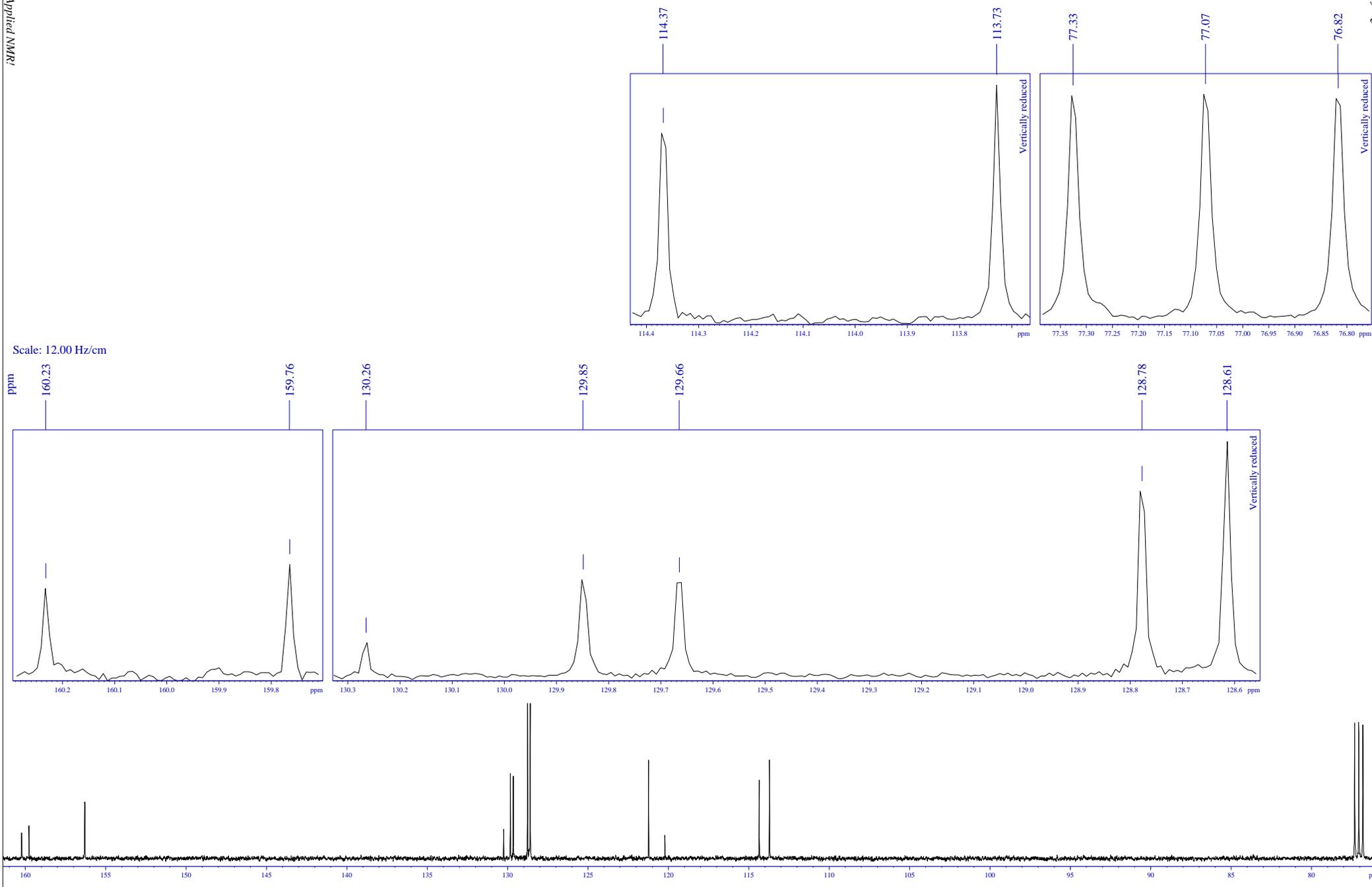
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3c (NMR/29330039)

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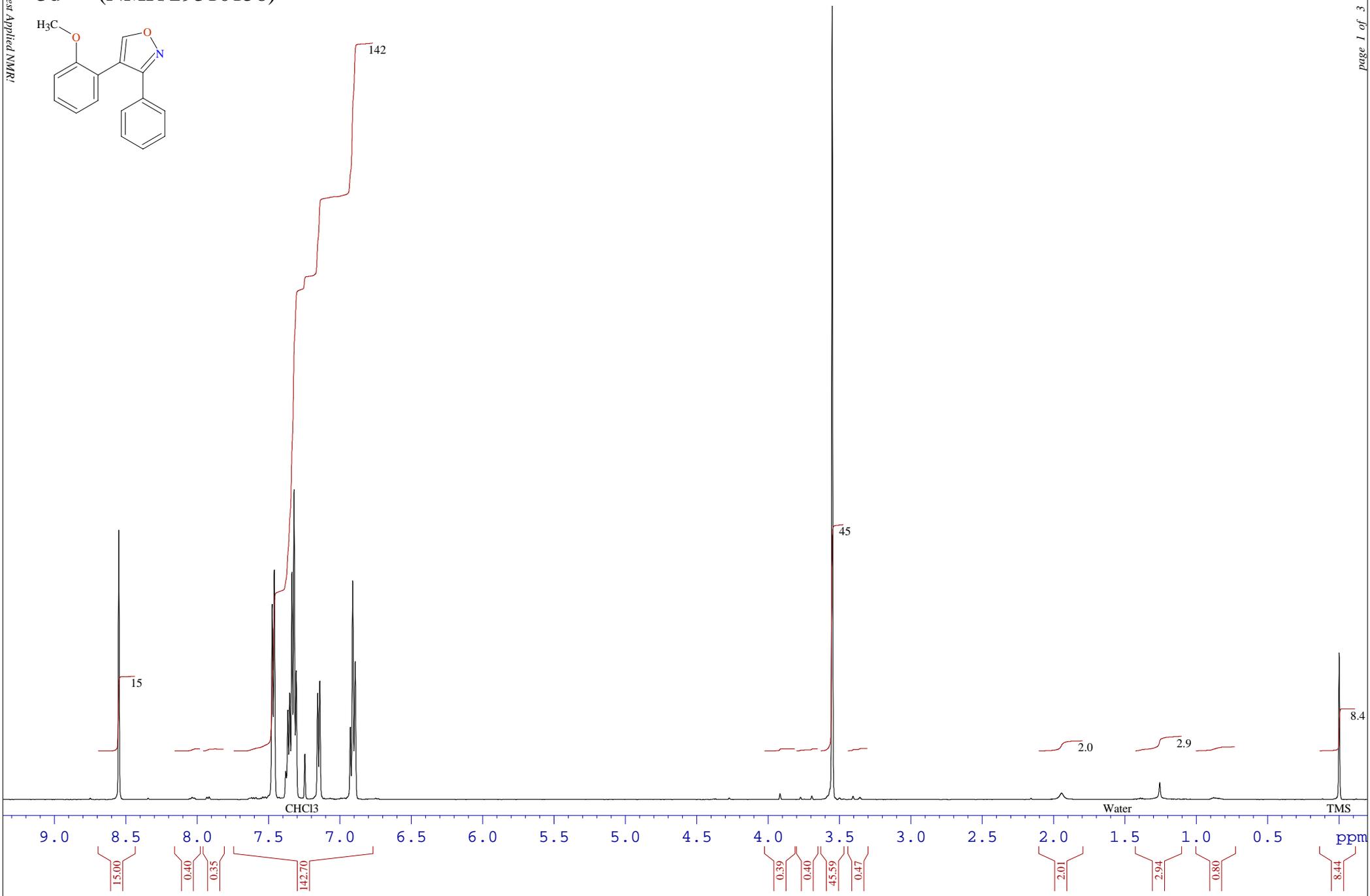
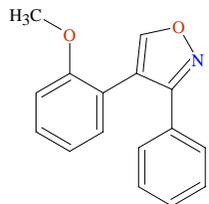


3c (NMR/29330039)

Peaks List

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4	13839.8	16381.840	130.2650	2.03
5	13892.3	16329.516	129.8489	5.90
6	13915.5	16306.323	129.6645	6.05
7	14027.4	16194.758	128.7774	11.66
8	14047.9	16174.243	128.6142	14.00
9	14977.0	15247.690	121.2465	6.64
10	15105.2	15119.877	120.2301	1.58
11	15844.4	14382.623	114.3677	5.62
12	15925.0	14302.246	113.7285	6.66
13	20515.3	9724.271	77.3254	9.45
14	20547.4	9692.322	77.0714	9.56
15	20579.4	9660.338	76.8170	9.51
16	23302.6	6944.486	55.2211	4.14

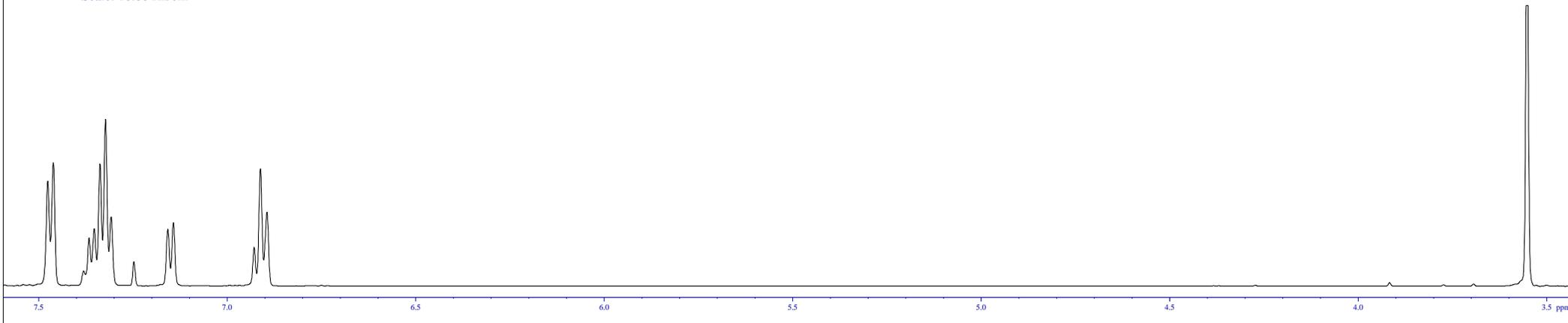
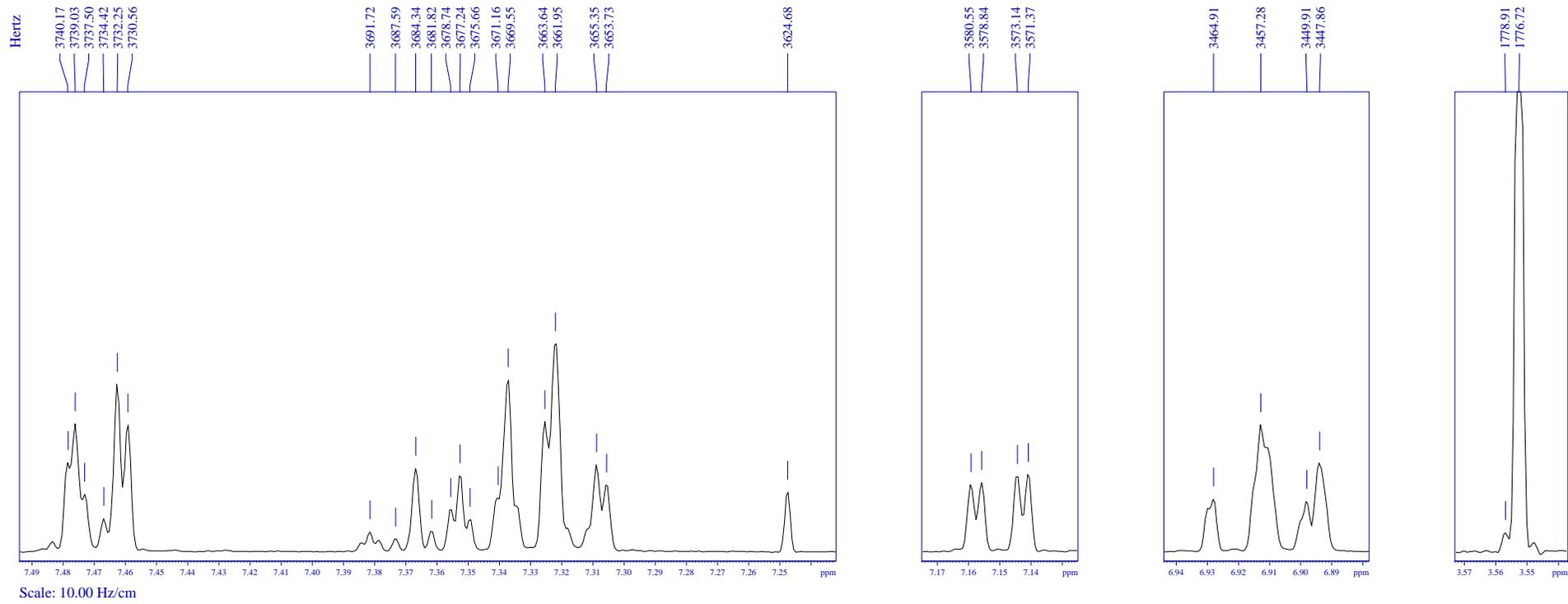
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3d (NMR/29310158)

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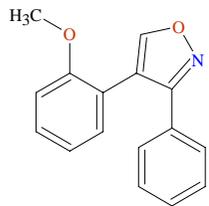


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3	17204.0	3739.026	7.4761	2.13
4	17209.0	3737.500	7.4731	0.96
5	17219.1	3734.416	7.4669	0.56
6	17226.2	3732.252	7.4626	2.80
7	17231.7	3730.564	7.4592	2.14
8	17359.0	3691.724	7.3815	0.33
9	17372.5	3687.587	7.3733	0.22
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11	17391.4	3681.821	7.3617	0.35
12	17401.5	3678.744	7.3556	0.73
13	17406.4	3677.236	7.3526	1.30
14	17411.6	3675.661	7.3494	0.56
15	17426.3	3671.163	7.3404	0.90
16	17431.6	3669.552	7.3372	2.92
17	17451.0	3663.644	7.3254	2.17
18	17456.5	3661.946	7.3220	3.52
19	17478.1	3655.353	7.3088	1.45
20	17483.4	3653.734	7.3056	1.14
21	17578.6	3624.681	7.2475	1.02
22	17723.3	3580.550	7.1592	1.13
23	17728.9	3578.840	7.1558	1.16
24	17747.5	3573.142	7.1444	1.29
25	17753.3	3571.367	7.1409	1.31
26	18102.2	3464.912	6.9280	0.88
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30	23626.9	1778.915	3.5569	0.32
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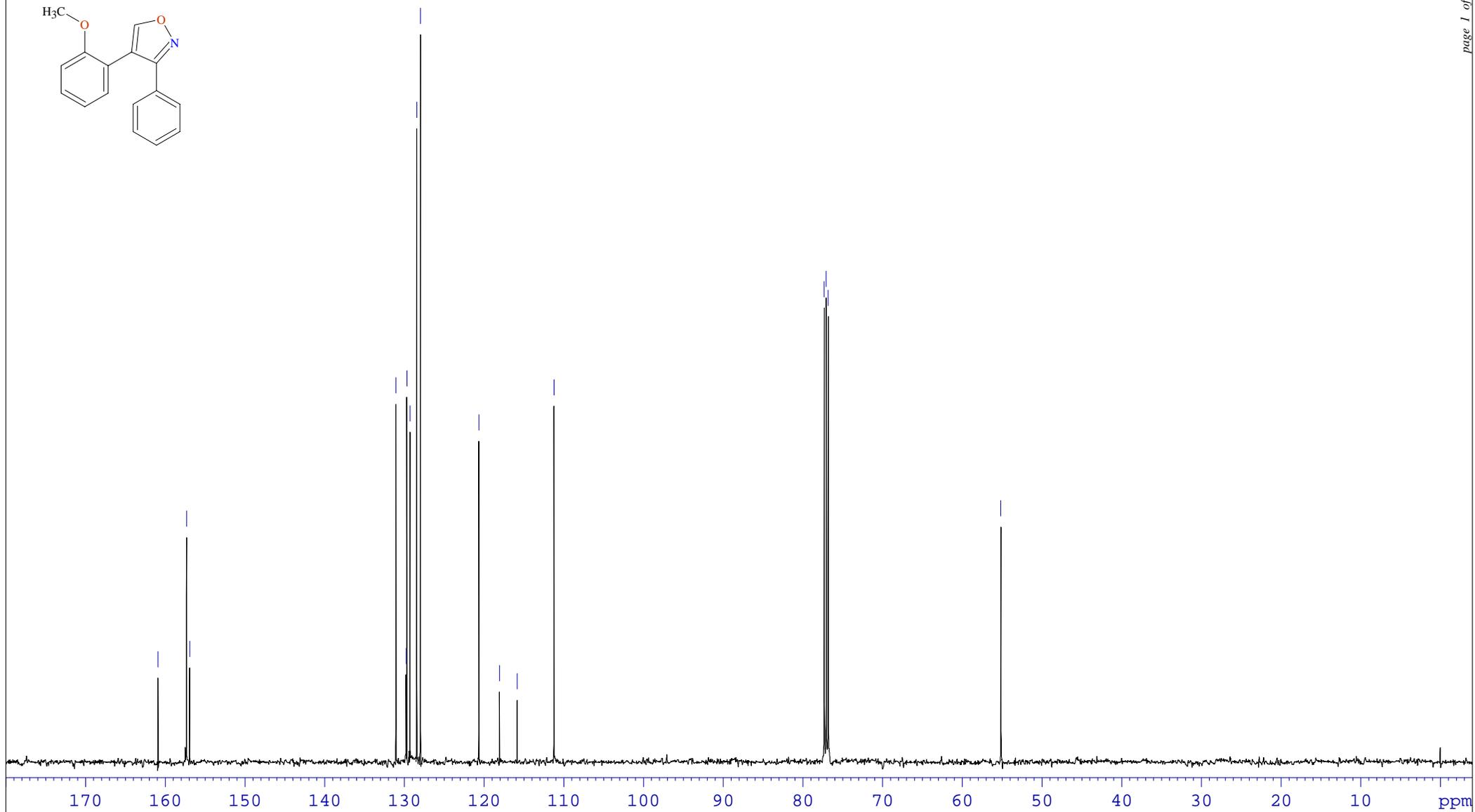


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76.84

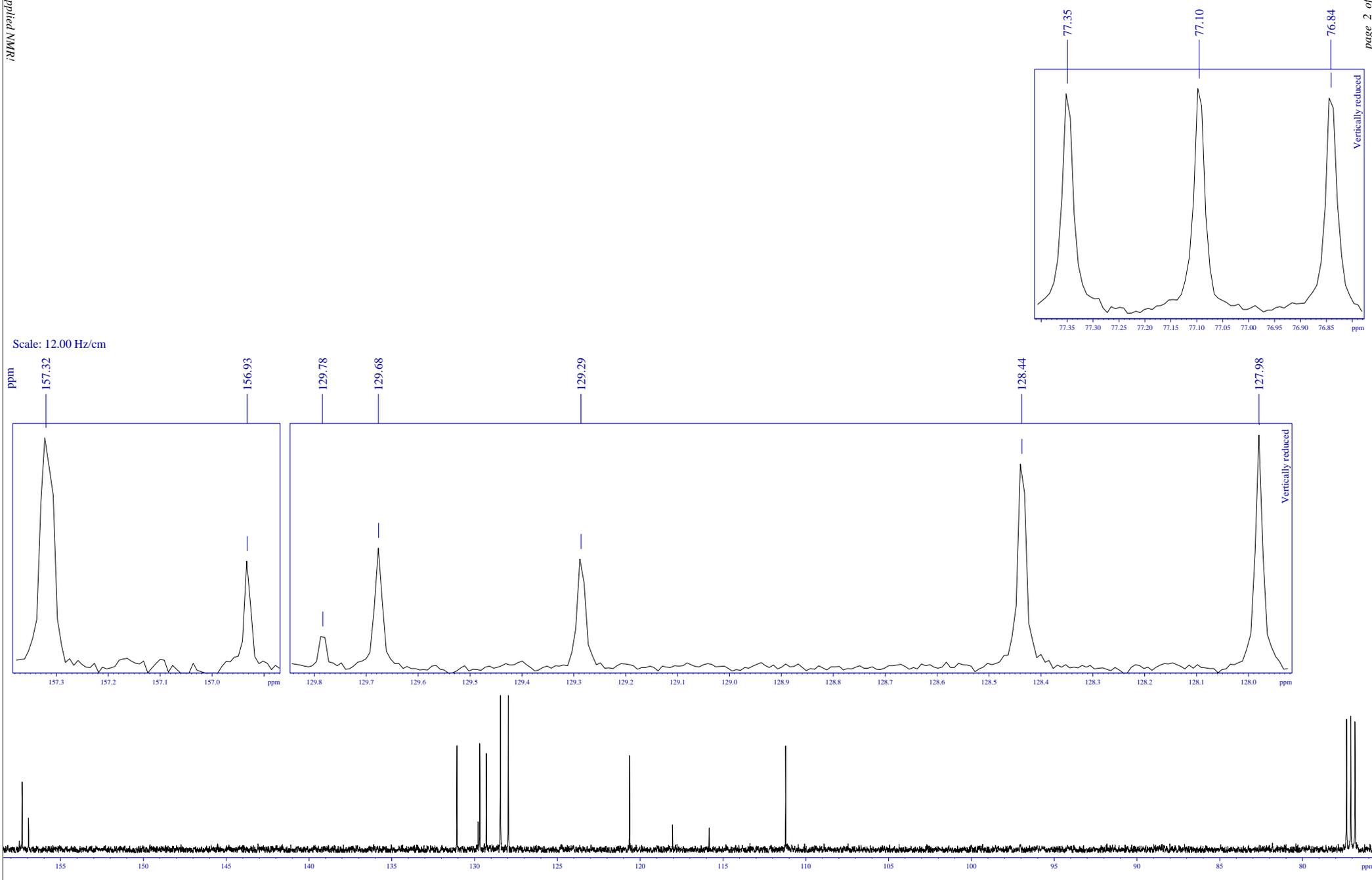
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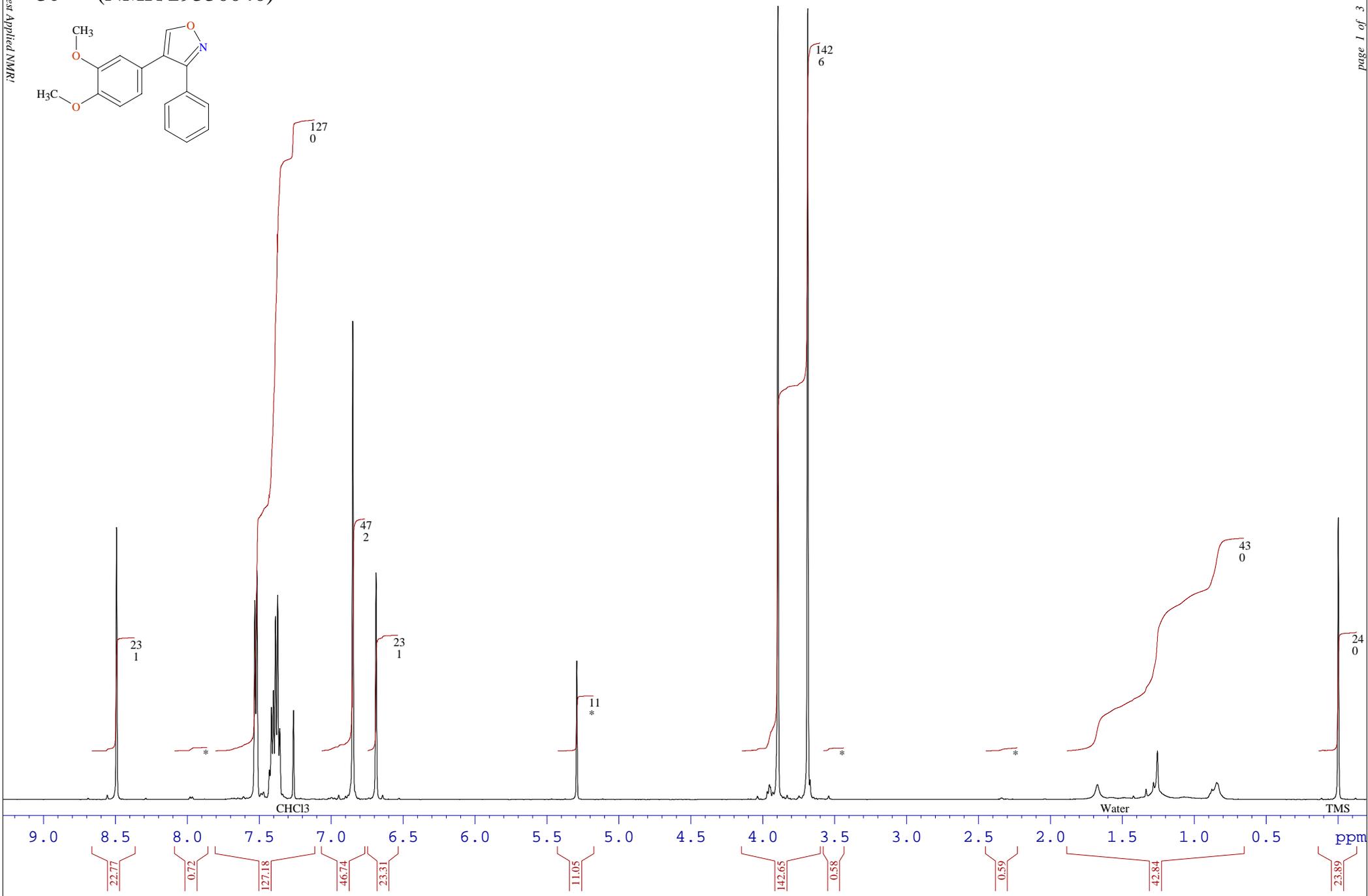
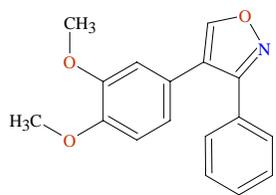
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Peaks List

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3	10477.1	19735.441	156.9322	2.16
4	13739.9	16481.410	131.0568	7.10
5	13900.5	16321.323	129.7838	2.06
6	13914.0	16307.809	129.6763	7.21
7	13963.2	16258.711	129.2859	6.72
8	14070.3	16151.916	128.4367	12.82
9	14128.0	16094.406	127.9794	14.00
10	15051.8	15173.071	120.6531	6.50
11	15378.8	14847.012	118.0604	1.75
12	15657.6	14568.962	115.8494	1.61
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14	20512.3	9727.286	77.3494	9.13
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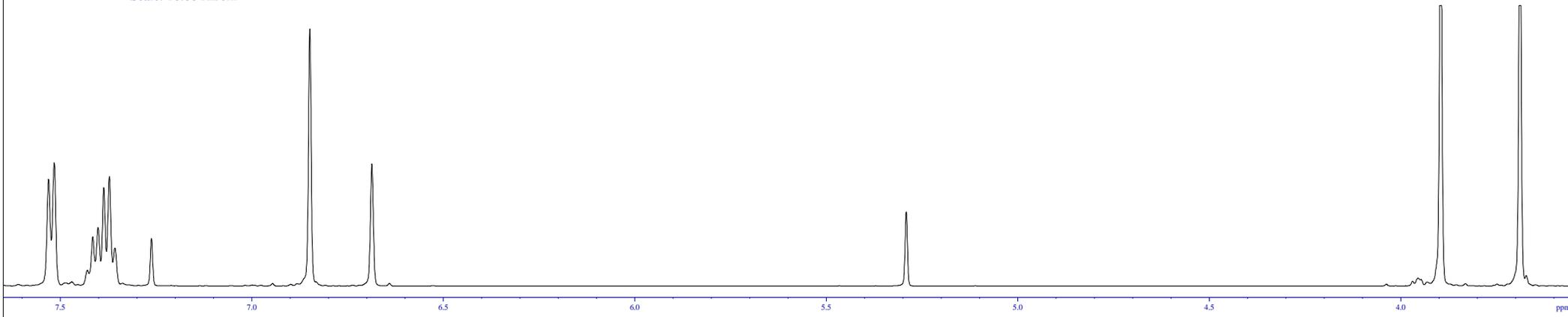
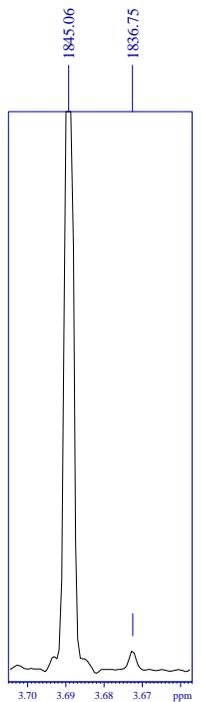
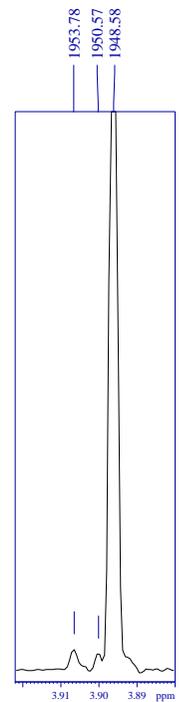
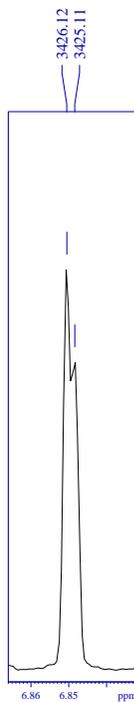
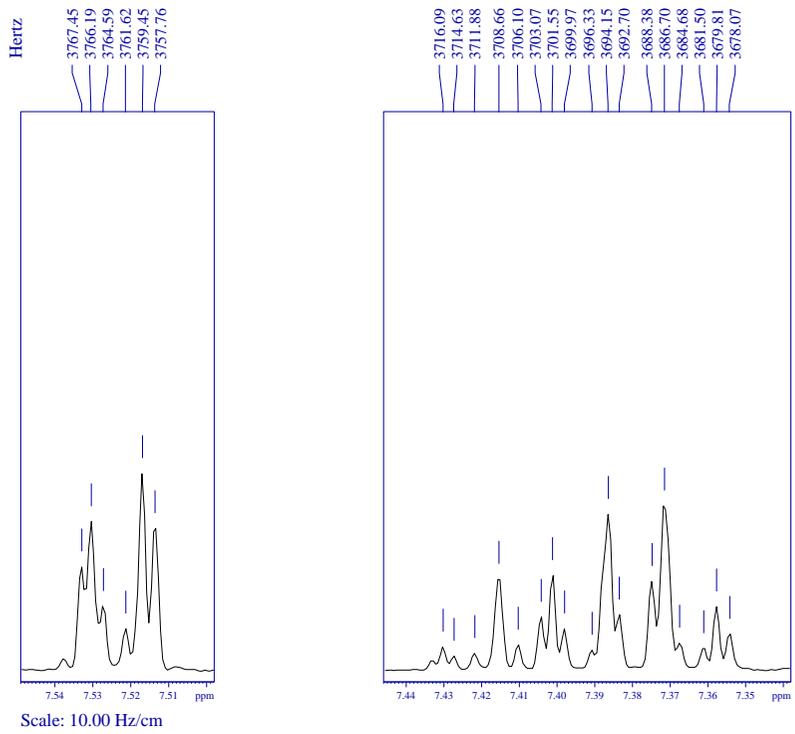
3e (NMR/29330040)



3e (NMR/29330040)

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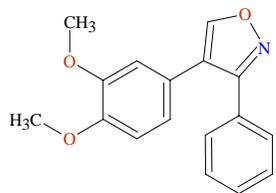


3e (NMR/29330040)

Peaks List

#	Address [points]	Frequency		Intensity [cm]
		[Hz]	[ppm]	
1	15564.8	4246.882	8.4916	6.14
2	17135.8	3767.447	7.5329	1.45
3	17140.0	3766.188	7.5304	2.07
4	17145.2	3764.591	7.5272	0.90
5	17154.9	3761.621	7.5213	0.58
6	17162.1	3759.447	7.5169	2.74
7	17167.6	3757.765	7.5136	2.04
8	17304.1	3716.088	7.4302	0.33
9	17308.9	3714.632	7.4273	0.20
10	17317.9	3711.880	7.4218	0.24
11	17328.5	3708.660	7.4154	1.32
12	17336.8	3706.103	7.4103	0.36
13	17346.8	3703.075	7.4042	0.75
14	17351.8	3701.545	7.4012	1.34
15	17356.9	3699.969	7.3980	0.58
16	17368.9	3696.328	7.3907	0.29
17	17376.0	3694.147	7.3864	2.17
18	17380.8	3692.700	7.3835	0.78
19	17394.9	3688.379	7.3748	1.24
20	17400.4	3686.699	7.3715	2.36
21	17407.0	3684.683	7.3675	0.38
22	17417.5	3681.499	7.3611	0.32
23	17423.0	3679.810	7.3577	0.89
24	17428.7	3678.071	7.3542	0.52
25	17580.1	3631.875	7.2619	2.10
26	18254.3	3426.123	6.8505	5.65
27	18257.6	3425.107	6.8484	4.35
28	18521.6	3344.543	6.6873	2.13
29	20808.4	2646.664	5.2920	3.19
30	23078.9	1953.776	3.9065	0.29
31	23089.4	1950.567	3.9001	0.24
32	23095.9	1948.576	3.8961	16.00
33	23435.1	1845.062	3.6892	14.94
34	23462.3	1836.752	3.6725	0.27
35	27421.5	628.518	1.2567	0.36
36	29481.0	0.002	0.0000	6.72

3e (NMR/29330040)

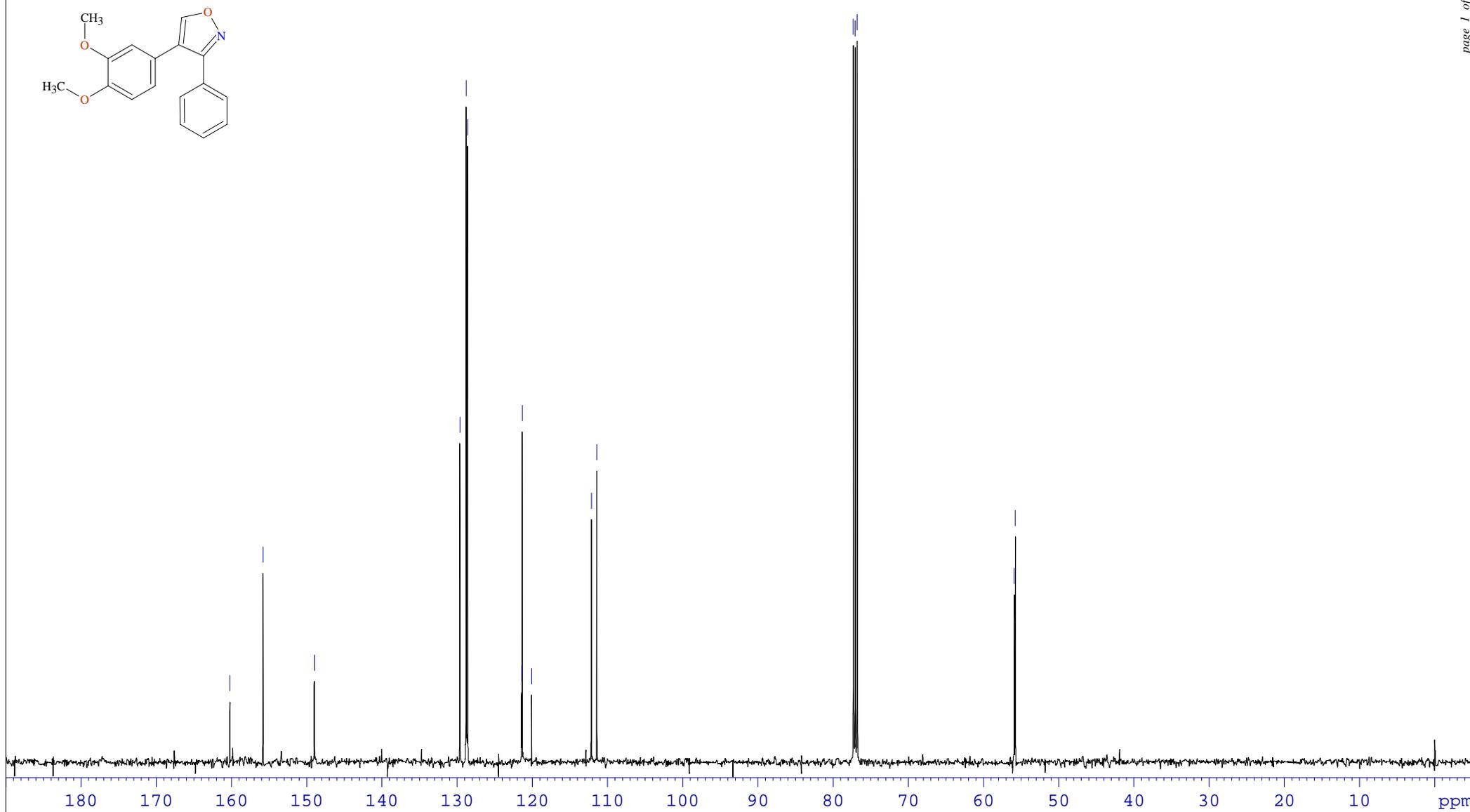


160.21
155.81
148.95

129.61
128.79
128.58
121.42
121.33
120.09
112.13
111.41

77.32
77.07
76.82

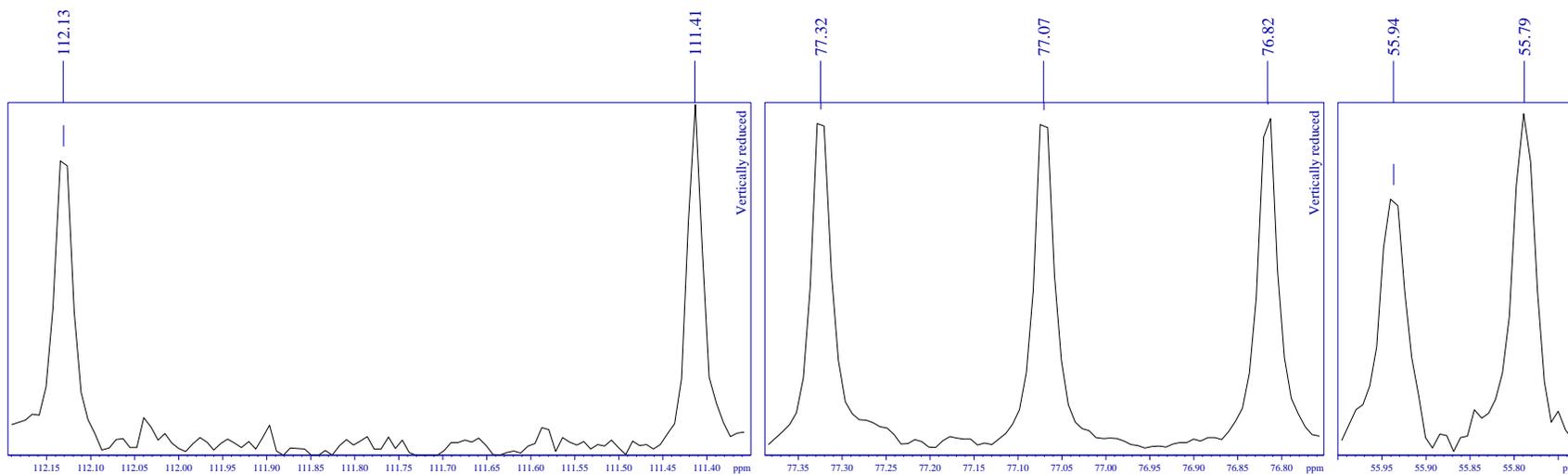
55.94
55.79



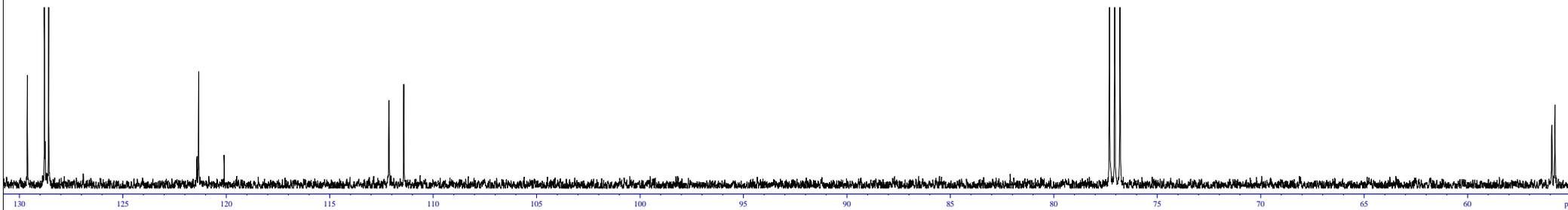
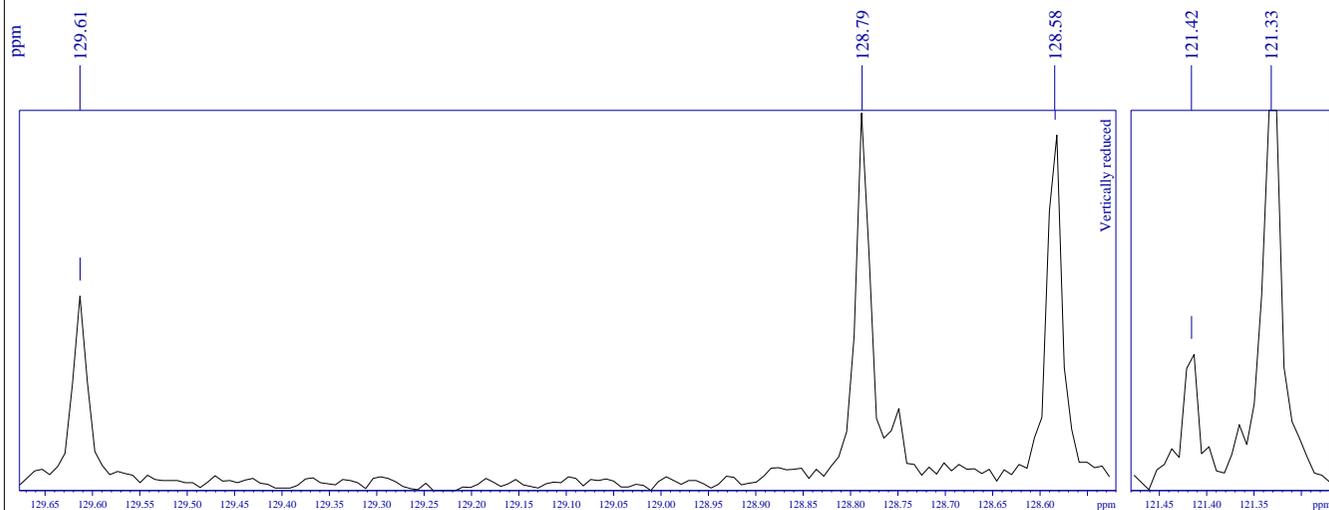
3e (NMR/29330040)

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Scale: 10.00 Hz/cm

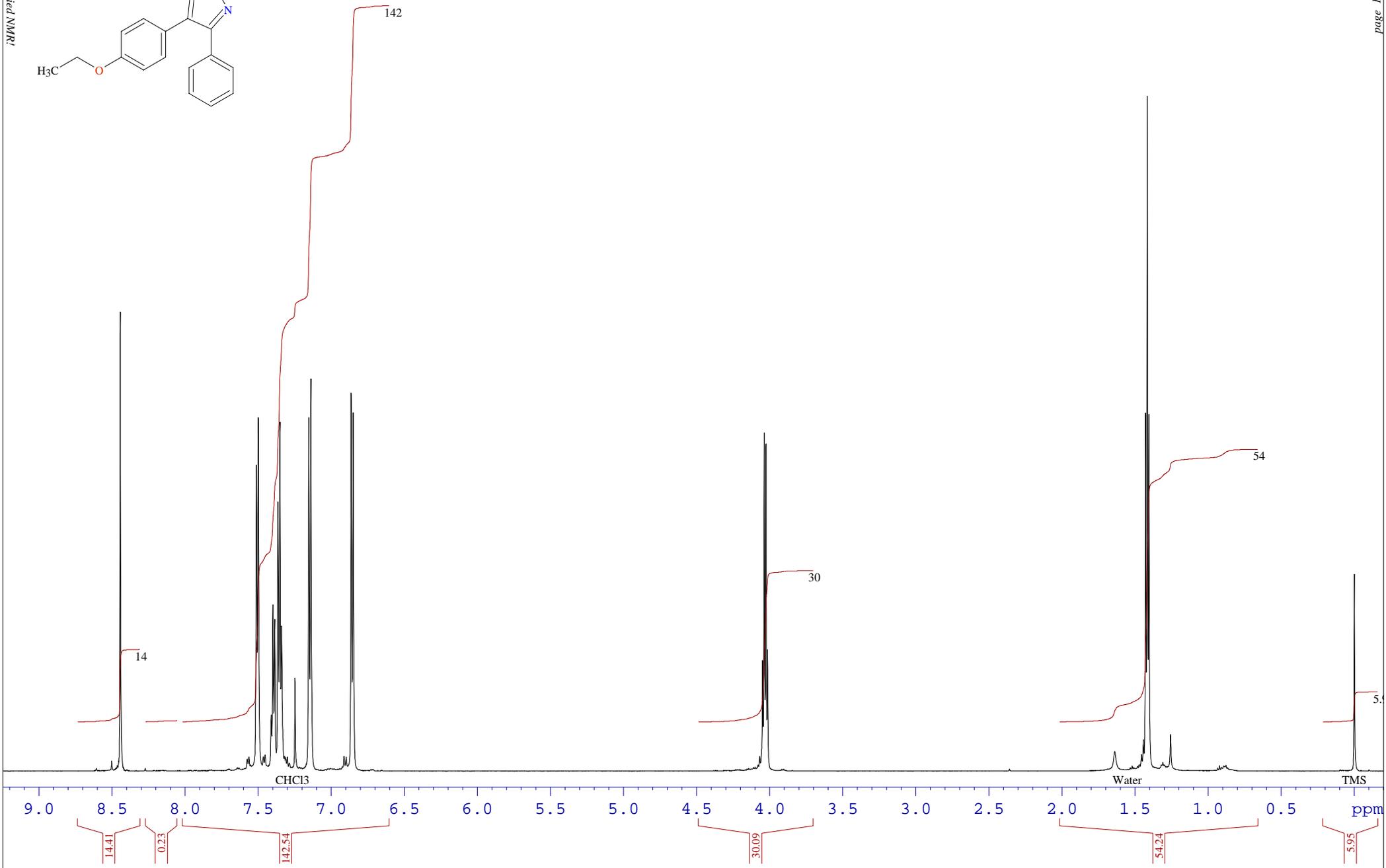
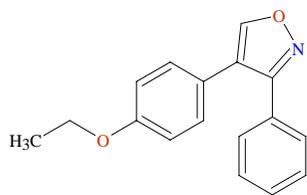


3e (NMR/29330040)

Peaks List

#	Address [points]	Frequency		Intensity
		[Hz]	[ppm]	[cm]
1	10063.8	20147.656	160.2100	1.57
2	10619.0	19593.939	155.8070	3.89
3	11483.2	18732.092	148.9537	1.91
4	13922.0	16299.843	129.6130	6.20
5	14026.1	16196.013	128.7874	12.33
6	14051.7	16170.449	128.5841	11.86
7	14955.6	15269.004	121.4160	1.72
8	14966.3	15258.394	121.3316	6.61
9	15122.2	15102.878	120.0950	1.72
10	16126.5	14101.316	112.1308	5.06
11	16216.9	14011.081	111.4132	5.72
12	20515.5	9724.121	77.3242	14.00
13	20547.5	9692.211	77.0705	13.98
14	20579.6	9660.171	76.8157	13.94
15	23212.4	7034.487	55.9368	3.43
16	23231.1	7015.823	55.7884	4.55

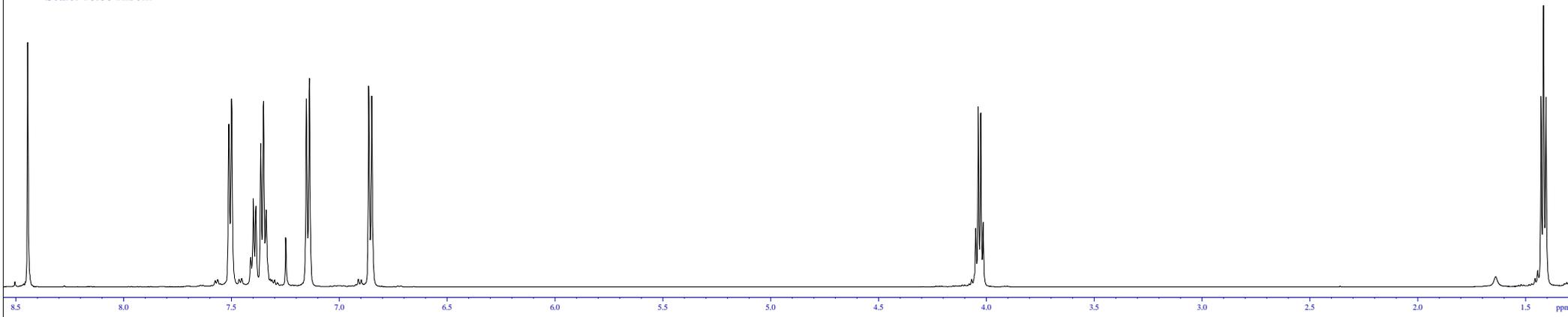
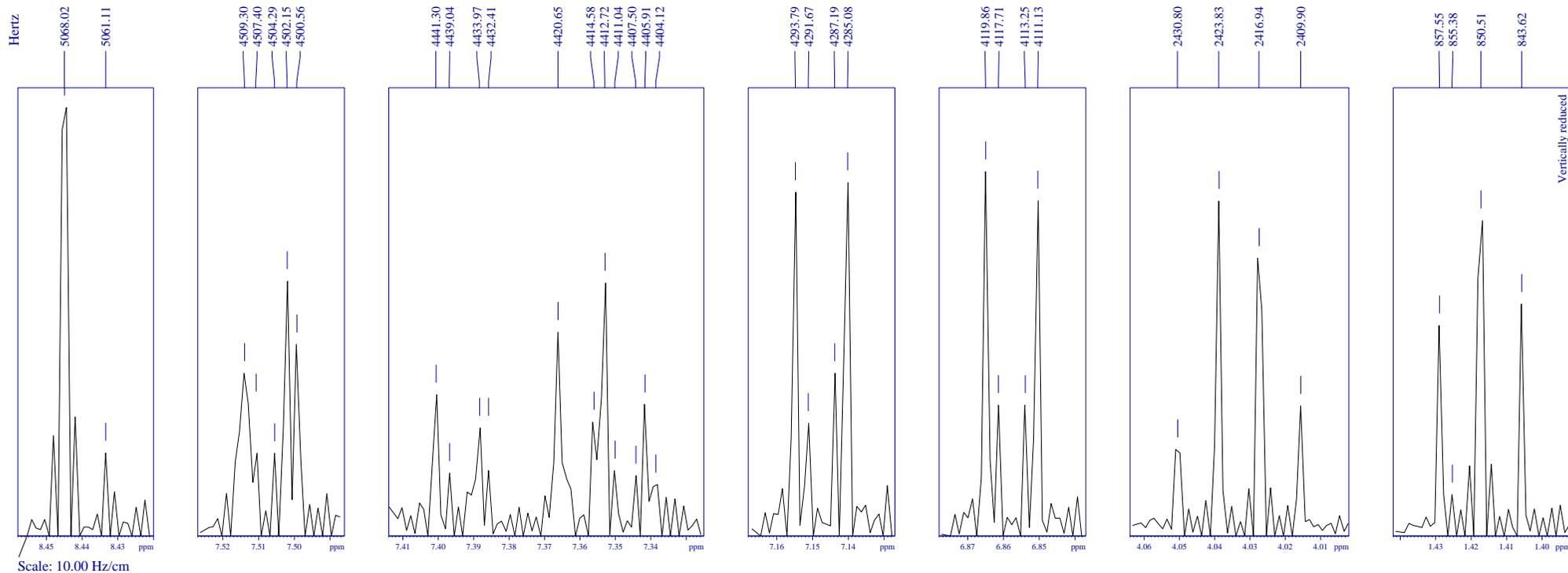
3h (NMR/29310149)



3h (NMR/29310149)

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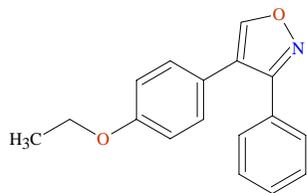


3h (NMR/29310149)

Peaks List

#	Address [points]	Frequency		Intensity [cm]
		[Hz]	[ppm]	
1	7811.5	5068.022	8.4449	10.10
2	7821.0	5061.107	8.4334	1.54
3	8573.2	4509.299	7.5139	3.21
4	8575.7	4507.402	7.5107	1.61
5	8580.0	4504.293	7.5055	1.53
6	8582.9	4502.151	7.5020	5.13
7	8585.1	4500.560	7.4993	3.79
8	8665.9	4441.297	7.4006	2.78
9	8668.9	4439.040	7.3968	1.12
10	8675.8	4433.969	7.3883	2.09
11	8678.0	4432.413	7.3858	1.17
12	8694.0	4420.649	7.3662	4.04
13	8702.3	4414.579	7.3560	2.31
14	8704.8	4412.716	7.3529	5.19
15	8707.1	4411.038	7.3501	1.18
16	8711.9	4407.502	7.3442	1.07
17	8714.1	4405.909	7.3416	2.56
18	8716.5	4404.119	7.3386	1.02
19	8789.3	4350.759	7.2497	2.00
20	8866.9	4293.792	7.1548	6.96
21	8869.8	4291.674	7.1512	2.22
22	8875.9	4287.187	7.1438	3.20
23	8878.8	4285.076	7.1402	7.35
24	9104.0	4119.864	6.8650	7.36
25	9107.0	4117.710	6.8614	2.53
26	9113.0	4113.246	6.8539	2.53
27	9115.9	4111.126	6.8504	6.79
28	11406.5	2430.802	4.0505	1.79
29	11416.0	2423.833	4.0388	6.76
30	11425.4	2416.937	4.0274	6.05
31	11434.9	2409.903	4.0156	2.51
32	13551.0	857.548	1.4289	8.01
33	13554.0	855.375	1.4253	1.29
34	13560.6	850.513	1.4172	13.42
35	13570.0	843.619	1.4057	8.85
36	14720.0	0.001	0.0000	4.50

3h (NMR/29310149)



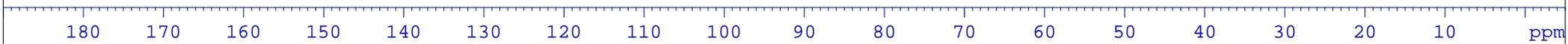
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155.30

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128.27
128.23
128.17
128.13
128.10
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126.38
120.45
119.46
114.56
114.23

76.76
76.54
76.33

63.00

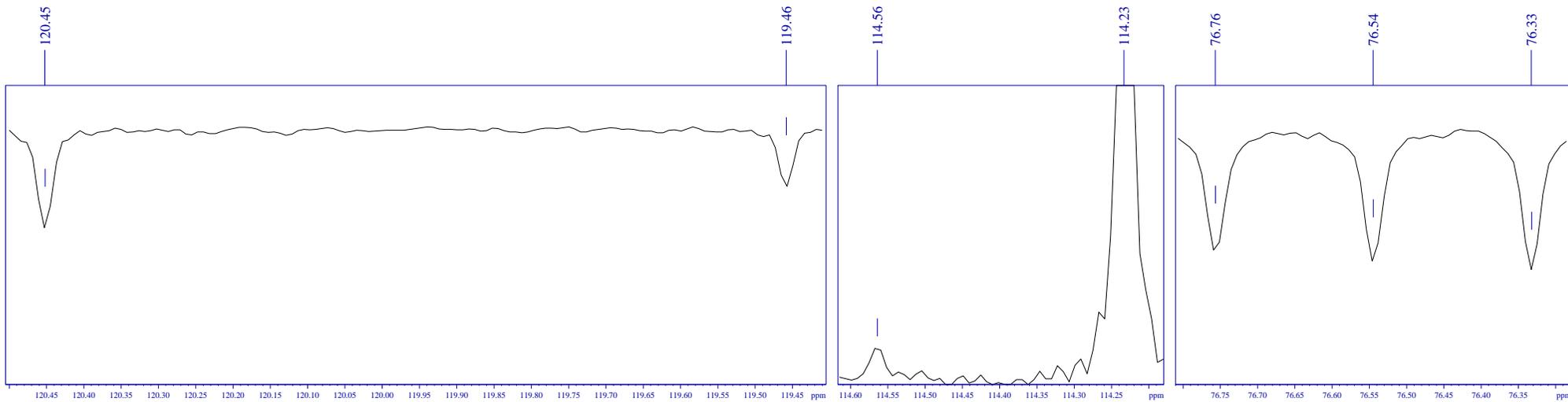
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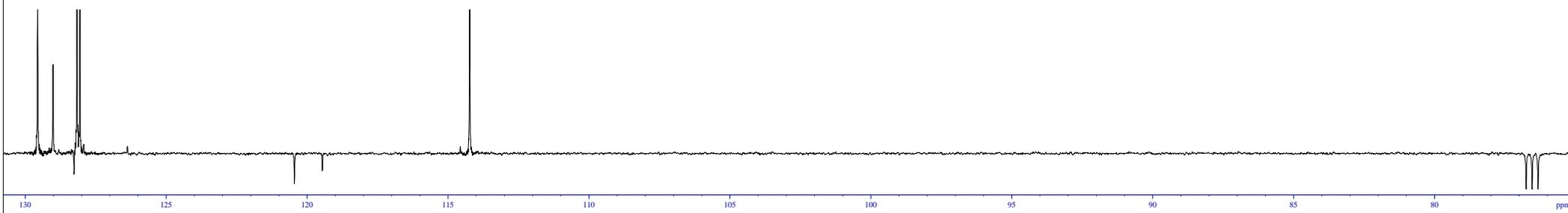
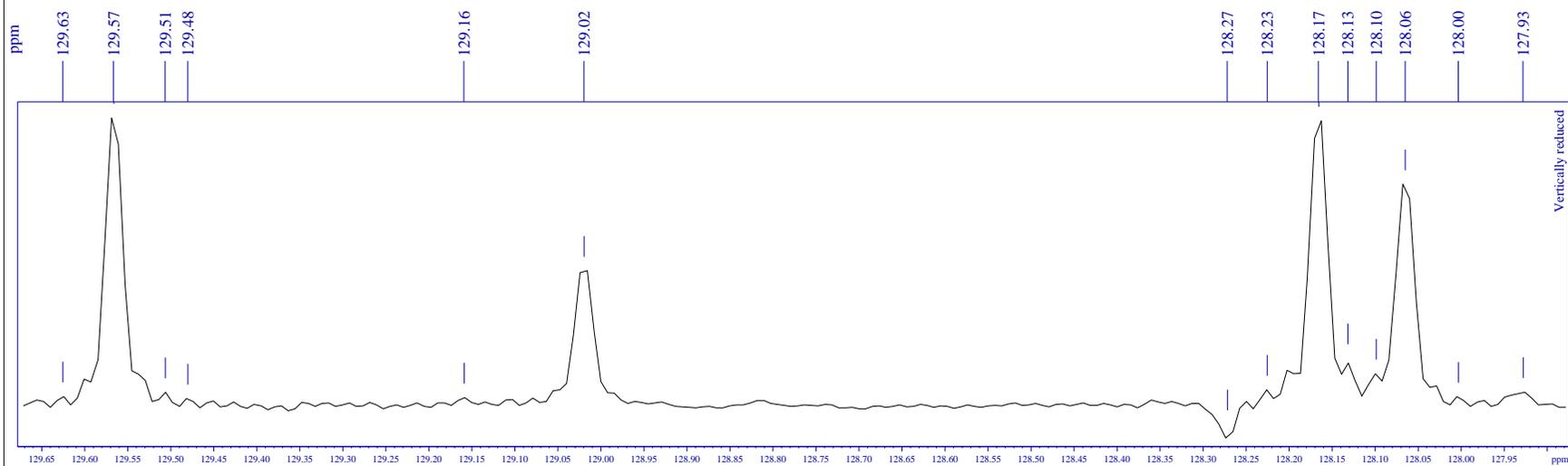
3h (NMR/29310149)

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Scale: 12.00 Hz/cm



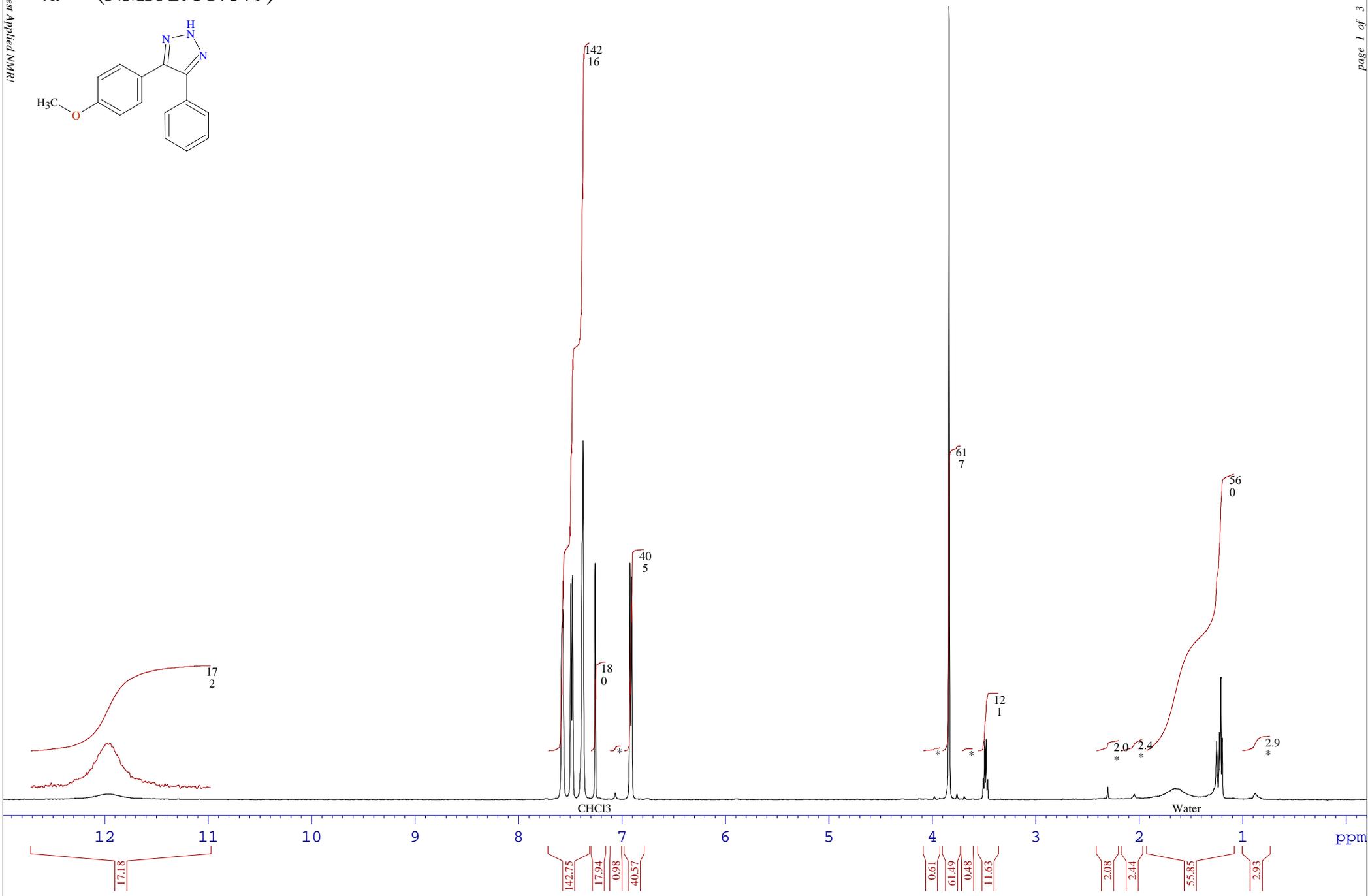
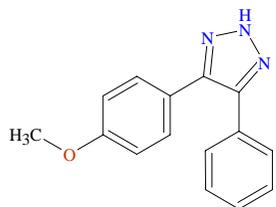
3h (NMR/29310149)

Peaks List

#	Address [points]	Frequency		Intensity [cm]
		[Hz]	[ppm]	
1	11182.6	24095.830	159.6777	-1.45
2	11350.2	23896.035	158.3537	-1.69
3	11736.5	23435.490	155.3018	4.55
4	14795.9	19788.457	131.1337	0.48
5	14986.8	19560.852	129.6254	0.48
6	14994.3	19551.914	129.5662	14.00
7	15001.9	19542.873	129.5063	0.67
8	15005.2	19538.924	129.4801	0.38
9	15045.9	19490.471	129.1590	0.42
10	15063.5	19469.412	129.0195	6.72
11	15158.2	19356.576	128.2717	-1.51
12	15164.0	19349.604	128.2255	0.79
13	15171.6	19340.557	128.1656	13.97
14	15175.9	19335.463	128.1318	2.06
15	15180.1	19330.465	128.0987	1.55
16	15184.4	19325.371	128.0650	10.81
17	15192.2	19316.039	128.0031	0.46
18	15201.7	19304.688	127.9279	0.69
19	15397.8	19070.965	126.3791	0.54
20	16148.1	18176.541	120.4519	-2.17
21	16273.9	18026.592	119.4582	-1.25
22	16893.4	17288.027	114.5639	0.51
23	16935.3	17238.100	114.2331	12.16
24	21679.3	11582.791	76.7566	-2.70
25	21706.1	11550.813	76.5447	-2.91
26	21733.0	11518.762	76.3323	-3.09
27	23420.6	9507.003	63.0008	-3.89
28	29584.5	2159.112	14.3080	2.35

4a (NMR/29317579)

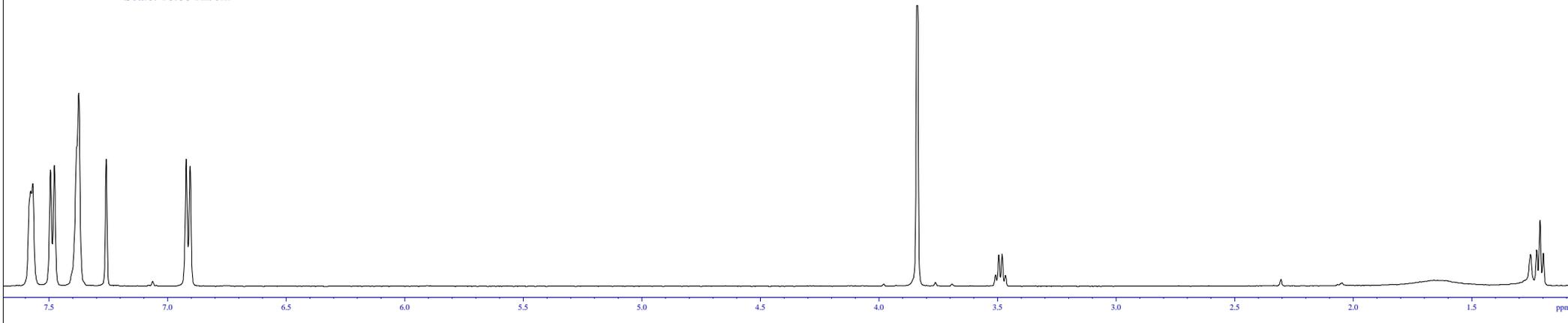
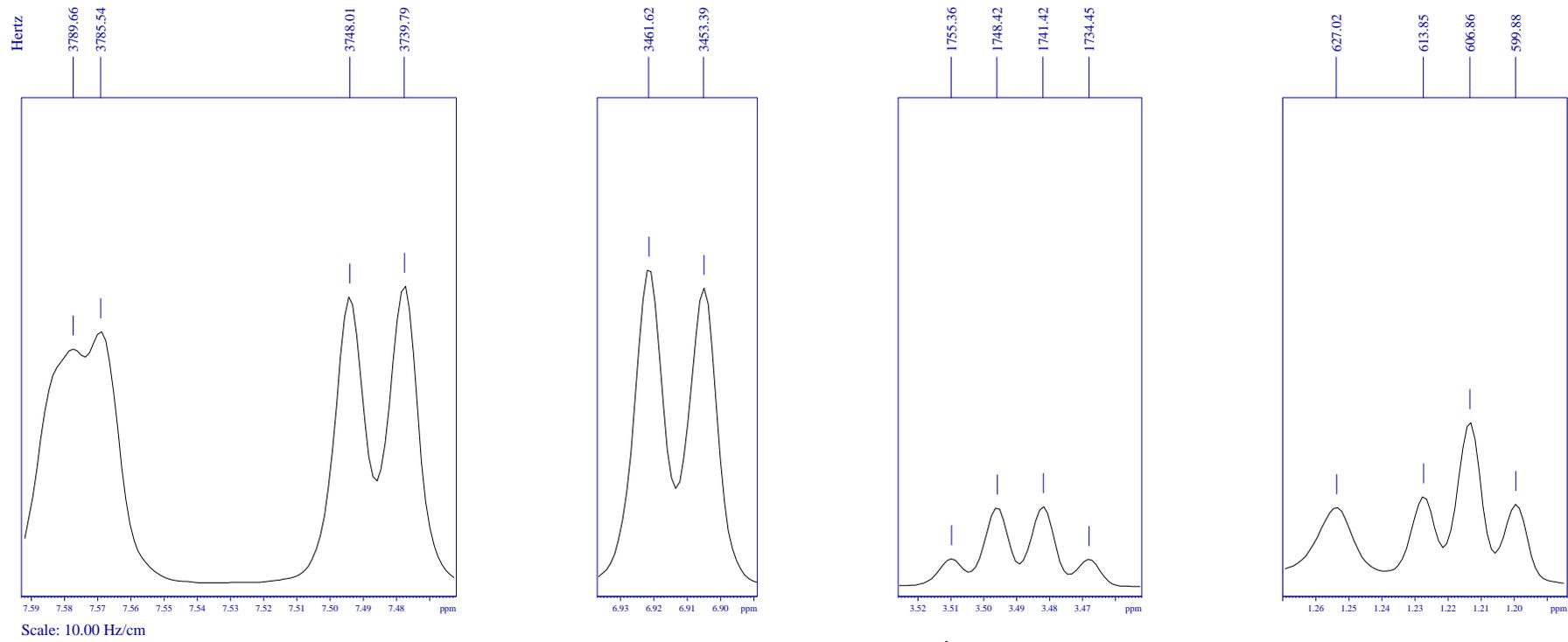
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4a (NMR/29317579)

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4a (NMR/29317579)

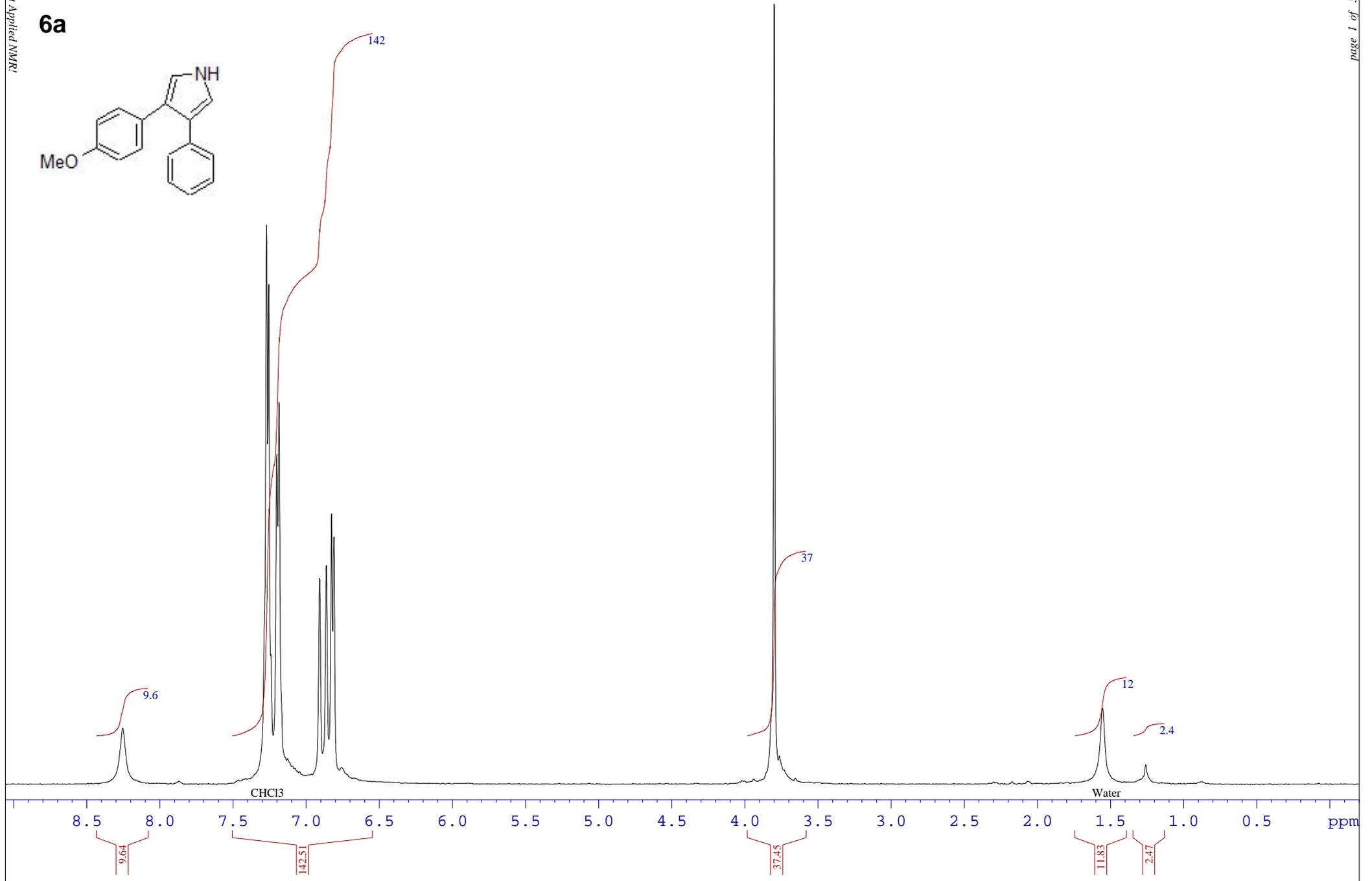
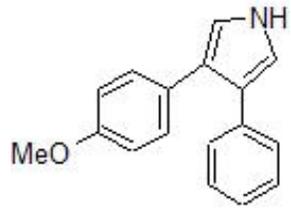
Peaks List

#	Address [points]	Frequency		Intensity [cm]
		[Hz]	[ppm]	
1	8528.0	3789.665	7.5774	3.54
2	8534.7	3785.544	7.5691	3.81
3	8596.2	3748.013	7.4941	4.33
4	8609.7	3739.794	7.4776	4.50
5	8693.7	3688.505	7.3751	7.18
6	8789.0	3630.330	7.2588	4.72
7	9065.4	3461.625	6.9215	4.77
8	9078.9	3453.387	6.9050	4.45
9	11590.3	1920.550	3.8401	16.00
10	11861.0	1755.359	3.5098	0.42
11	11872.4	1748.416	3.4959	1.18
12	11883.8	1741.423	3.4819	1.20
13	11895.2	1734.455	3.4680	0.41
14	12847.3	1153.334	2.3061	0.26
15	13376.1	830.603	1.6608	0.22
16	13709.7	627.020	1.2537	1.18
17	13731.2	613.849	1.2274	1.34
18	13742.7	606.861	1.2134	2.46
19	13754.1	599.882	1.1995	1.23

NMR/29330082



6a

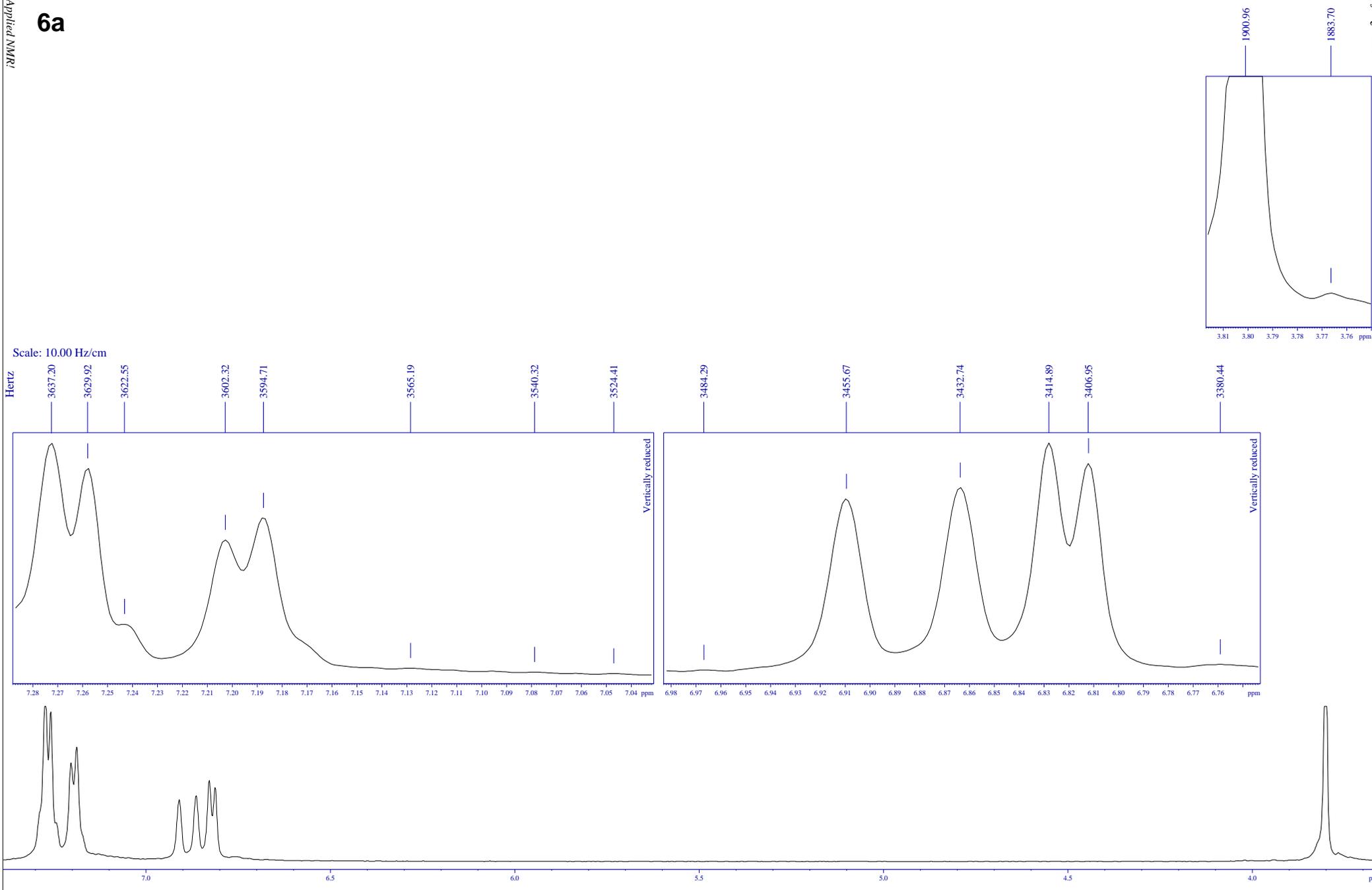


NMR/29330082

6a

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NMR/29330082

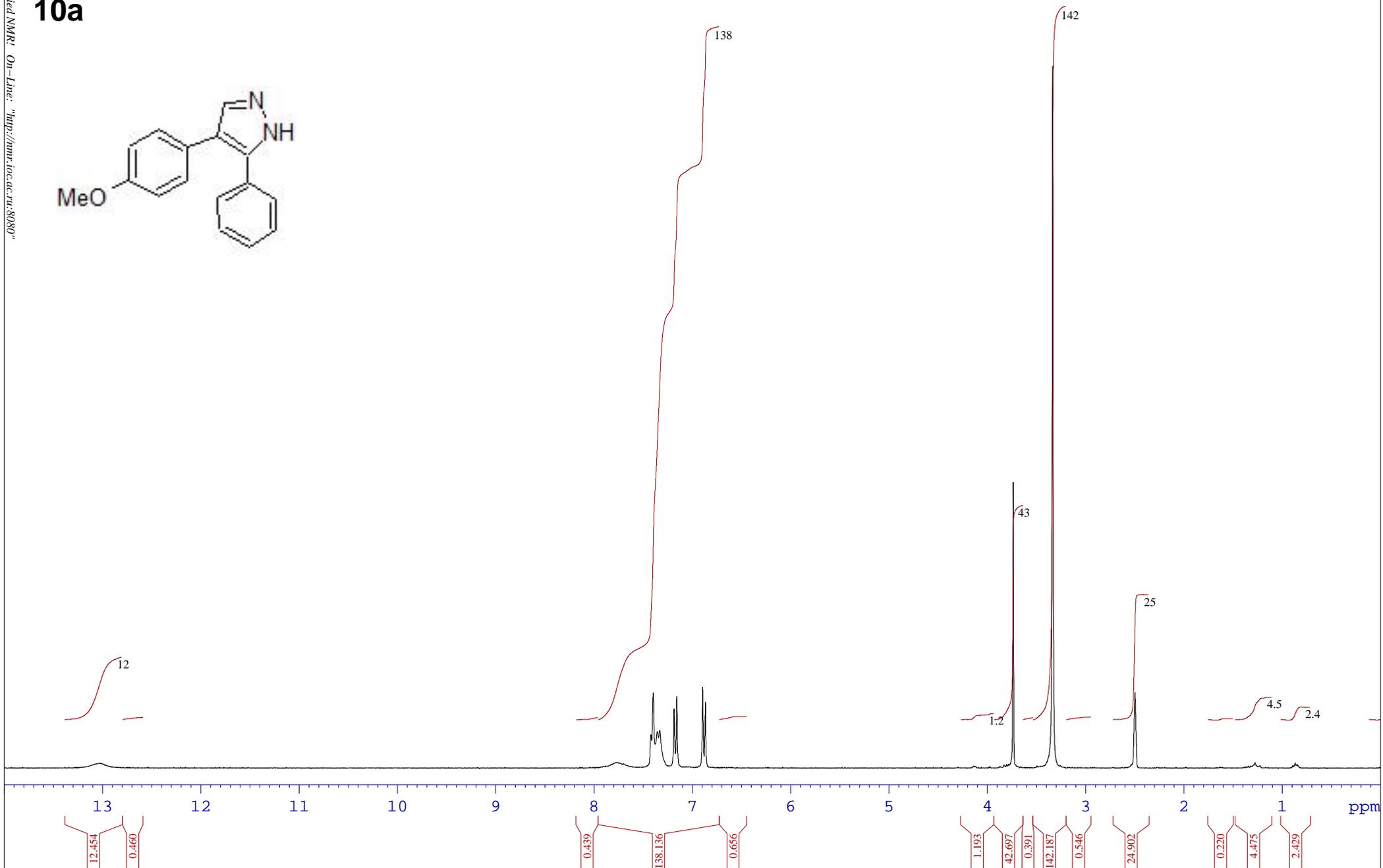
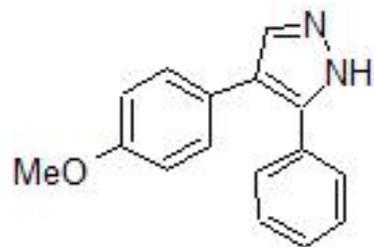
6a

Peaks List

#	Address [points]	Frequency		Intensity [cm]
		[Hz]	[ppm]	
1	7972.0	4129.016	8.2559	1.13
2	8777.8	3637.201	7.2725	11.28
3	8789.7	3629.922	7.2580	10.09
4	8801.8	3622.552	7.2432	2.62
5	8834.9	3602.325	7.2028	6.64
6	8847.4	3594.706	7.1875	7.72
7	8895.8	3565.194	7.1285	0.51
8	8936.5	3540.317	7.0788	0.32
9	8962.6	3524.409	7.0470	0.25
10	9028.3	3484.291	6.9668	0.20
11	9075.2	3455.669	6.9095	4.16
12	9112.8	3432.743	6.8637	4.42
13	9142.0	3414.892	6.8280	5.45
14	9155.0	3406.950	6.8121	4.98
15	9198.5	3380.442	6.7591	0.33
16	11622.4	1900.962	3.8009	15.82
17	11650.7	1883.697	3.7664	0.58
18	13462.6	777.805	1.5552	1.53
19	13704.5	630.171	1.2600	0.40

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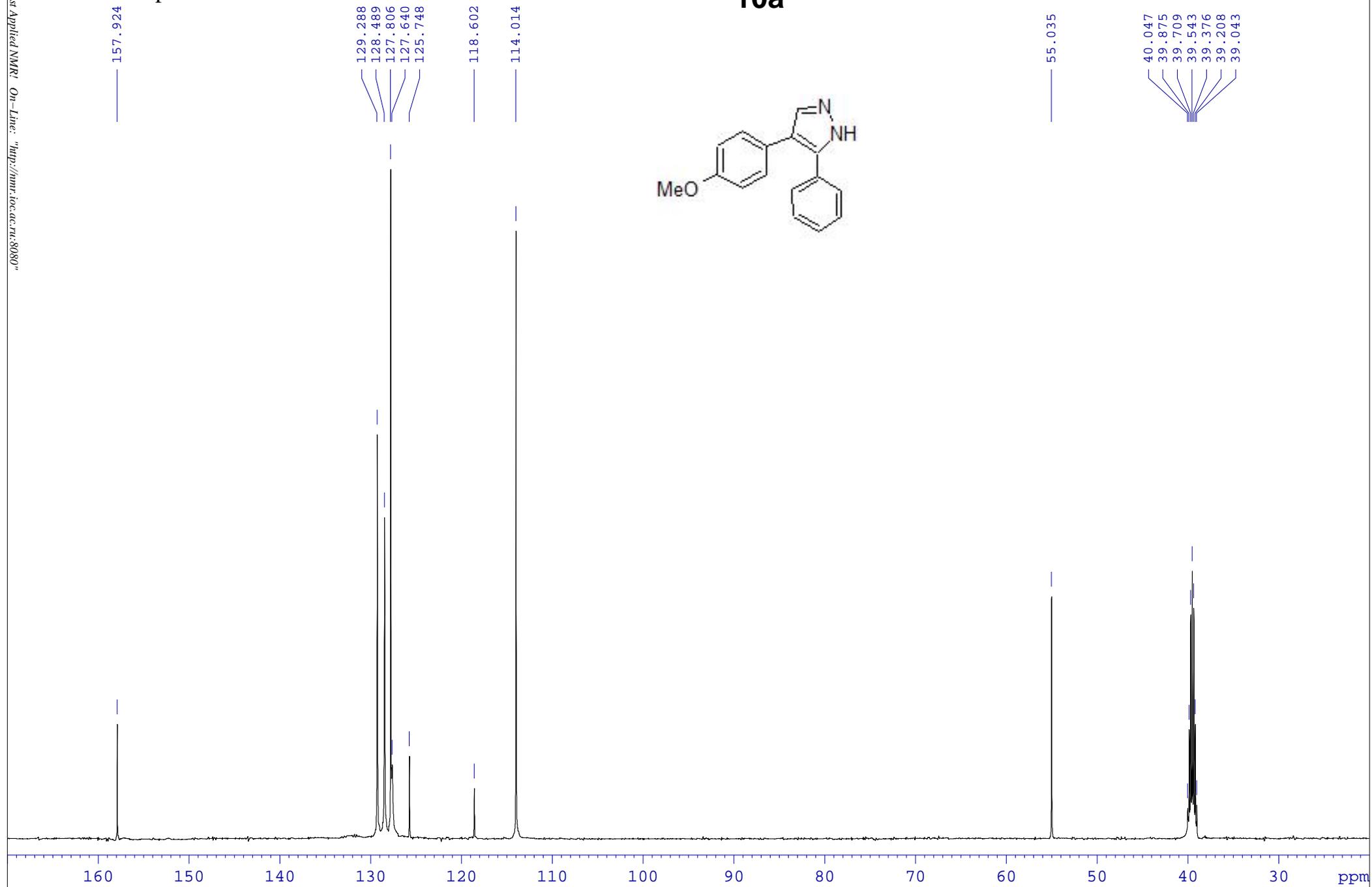
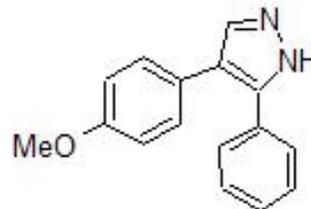
10a





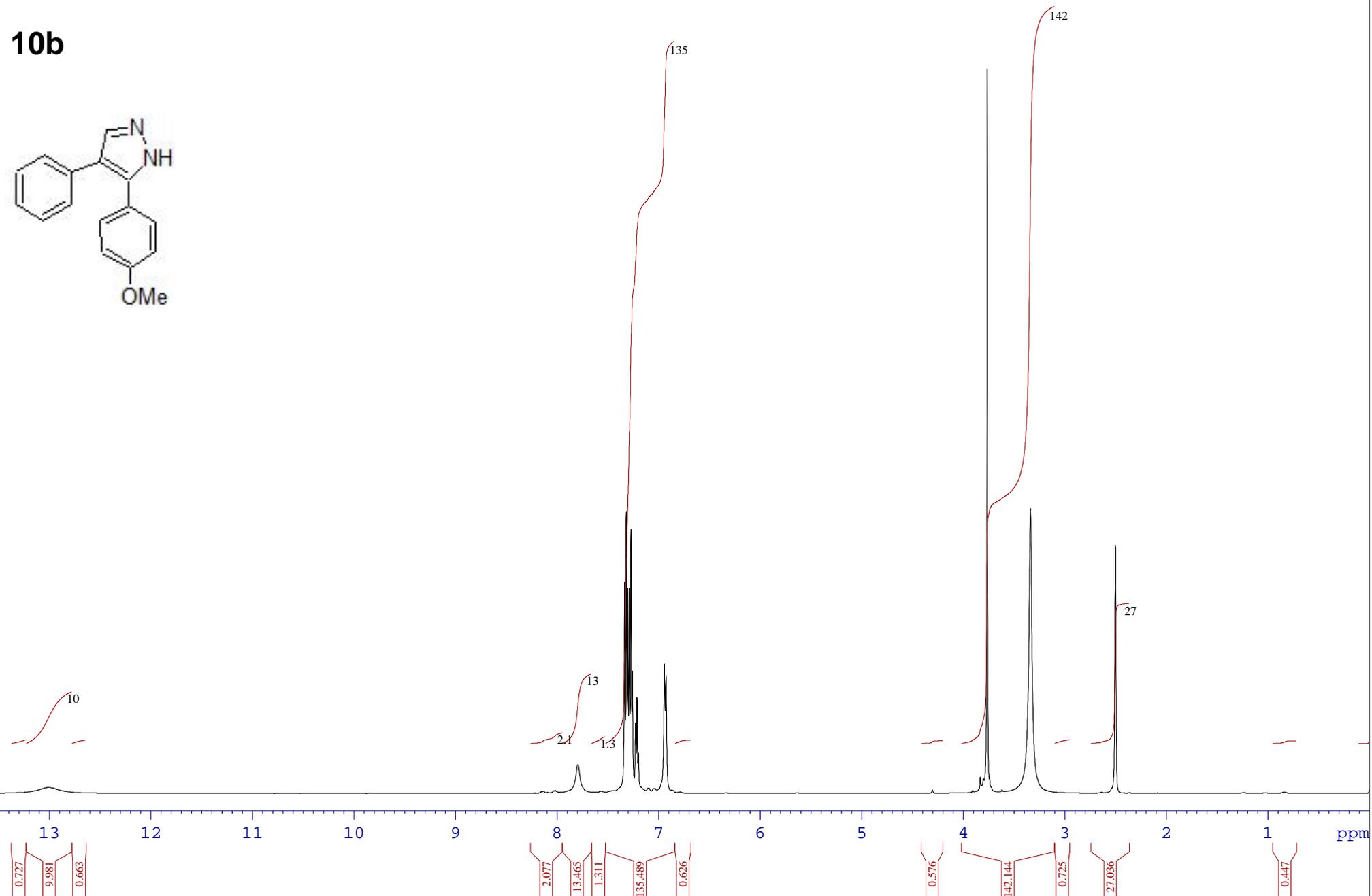
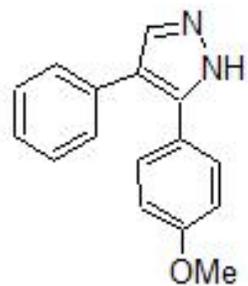
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10a



/UVIS Samp.475

10b





/UVIS Samp.508

