5-NITROISOXAZOLES IN S_NAR REACTIONS: ACCESS TO POLYSUBSTITUTED ISOXAZOLE DERIVATIVES

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SUPPORTING INFORMATION

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1. General Information.

NMR spectra were recorded on spectrometer Agilent 400-MR (400.0 MHz for ^{1}H; 100.6 MHz for ^{13}C, 162.0 MHz for ^{31}P, 376.3 MHz for ^{19}F) at r. t.; the chemical shifts δ were measured in ppm with respect to the $CDCl_3$ (^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.16 ppm), H_3PO_4 as external standard for ^{31}P and $CFCl_3$ as external standard for ^{19}F. Chemical shifts (δ) are given in ppm; J values are given in Hz. When necessary, assignments of signals in NMR spectra were made using 2D techniques. Accurate mass measurements (HRMS) were performed on a Bruker micrOTOF II instrument using electrospray ionization (ESI). The measurements were done in a positive ion mode (interface capillary voltage 4500 V) or in a negative ion mode (3200 V). Melting points (mp) are uncorrected. Analytical thin layer chromatography was carried out with Silufol silica gel plates (supported on aluminum); the detection was done by UV lamp (254 and 365 nm) and chemical staining (5% aqueous solution of $KMnO_4$). Column chromatography was performed on silica gel (230–400 mesh, Merck).

5-Nitroisoxazoles **1a-e,h**[1] and **1f**[2] were synthesized by described methods.

All other starting materials were commercially available.

All reagents except commercial products of satisfactory quality were purified by literature procedures prior to use.

2. Experimental Procedures.

*Methyl 4-methyl-5-nitroisoxazole-3-carboxylate (***1h***).* Triethylamine (0.56 mL, 0.40 g, 4 mmol) was added dropwise to a solution of tetranitromethane (0.6 mL, 0.98 g, 5 mmol) in 1,4-dioxane (4 mL) at 0 °C (ice bath). The reaction mixture was stirred for 5 min, and methyl crotonate (0.21 mL, 0.20 g, 2 mmol) in 1,4-dioxane (0.5 mL) was added dropwise. Then the cooling was removed, and the mixture was stirred at 70 °C for 2 h. The solvent was removed under reduced pressure, and the product was isolated by column chromatography. Yield: 0.26 g, 70%; colorless oil; R_f 0.29 (petroleum ether:EtOAc = 10:1) ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.60 (s, 3H, CH_3), 4.02 (s, 3H, CH_3O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.7 (CH_3), 53.5 (CH_3O), 115.8 (C), 157.1 (C), 159.1 (C), 162.2 (C-NO_2). Anal. calcd. for $C_6H_6N_2O_5$: C, 38.72; H, 3.25; N, 15.05. Found: C, 38.70; H, 3.26; N, 15.12.

General procedure 1. Amine (0.4 mmol) was added to the solution of 5-nitroisoxazole **1** (0.2 mmol) in CH_3CN (2 mL) and the resulting mixture was stirred at r. t. for 24 h. Then the mixture was poured into CH_2Cl_2 (30 mL) and it was washed sequentially with 10% HCl (2×15 mL), solution of $NaHCO_3$ (15 mL) and brine (15 mL). The organic layer was

dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure to give products **2** which required no additional purification.

General procedure 2. Nucleophile (0.2 mmol, in cases **2k,l,m** 0.1 mmol of nucleophiles are used) and DIPEA (0.2 mmol, 26 mg) were added to the solution of 5-nitroisoxazole **1** (0.2 mmol) in CH_3CN (2 mL). The resulting mixture was stirred at r. t. for 24 h. The solvent was removed under reduced pressure, and the residue was partitioned between water (20 mL) and CH_2Cl_2 (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3×10 mL), and the combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to give the product **2**.

General procedure 3. DIPEA (0.2 mmol) was added to the solution of 5-nitroisoxazole **1** (0.2 mmol) in corresponding alcohol (2 mL). The resulting mixture was stirred at r. t. for 48–72 h (TLC-monitoring). After the reaction was finished, the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL). The obtained solution was washed sequentially with 10% HCl (2×15 mL), solution of $NaHCO_3$ (15 mL) and brine (15 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give products **2** which required no additional purification.

*tert-Butyl 5-morpholinoisoxazole-3-carboxylate **(2a)***. **2a** was synthesized according to *GP1* starting from **1a** and morpholine**.** Yield: 49 mg, 96%; colorless solid; mp 118–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56 (s, 9H, $3CH_3$), 3.29–3.34 (m, 4H, $2CH_2$), 3.75–3.81 (m, 4H, $2CH_2$), 5.37 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1 ($3CH_3$), 46.7 ($2CH_2$), 65.9 ($2CH_2$), 79.4 (CH), 83.2 (C-O), 158.6 (C), 159.6 (C), 171.8 (C); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{12}H_{19}N_2O_4$: 255.1339; found: 255.1337.

*tert-Butyl 5-(butylamino)isoxazole-3-carboxylate **(2b)***. **2b** was synthesized according to *GP1* starting from **1a** and butylamine**.** Yield: 44 mg, 92%; light-yellow solid; mp 114–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, ^3J = 7.3 Hz, 3H, CH_3), 1.32–1.44 (m, 2H, CH_2), 1.56–1.63 (m, 2H, CH_2), 1.507 (s, 9H, $3CH_3$), 3.17 (dt, ^3J = 7.1 Hz, ^3J = 6.0 Hz, 2H, CH_2), 4.70 (br. t, ^3J = 6.0 Hz, 1H, NH), 5.30 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8 (CH_3), 20.0 (CH_2), 28.2 ($3CH_3$), 31.5 (CH_2), 44.5 (CH_2), 77.6 (CH), 83.1 (C-O), 158.6 (C), 159.9 (C), 171.1 (C); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{12}H_{21}N_2O_3$: 241.1547; found: 241.1552.

*tert-Butyl 5-(diethylamino)isoxazole-3-carboxylate **(2c)***. **2c** was synthesized according to *GP1* starting from **1a** and ethylamine**.** Yield: 45 mg, 94%; light-yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (t, ^3J = 7.2 Hz, 6H, $2CH_3$), 1.57 (s, 9H, $3CH_3$), 3.33 (q, ^3J = 7.2 Hz,

4H, $2CH_2$), 5.19 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.1 ($2CH_3$), 28.1 ($3CH_3$), 44.0 ($2CH_2$), 76.8 (CH), 82.9 (C-O), 158.6 (C), 160.1 (C), 170.7 (C); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{12}H_{21}N_2O_3$: 241.1547; found: 241.1550.

tert-Butyl 5-piperidin-1-ylisoxazole-3-carboxylate ***(2d)***. **2d** was synthesized according to *GP1* starting from **1a** and piperidine. Yield: 40 mg, 78%; Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 1.56 (s, 9H, $3CH_3$), 1.59-1.66 (m, 6H, $3CH_2$), 3.28-3.34 (m, 4H, $2CH_2$), 5.29 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.9 (CH_2), 24.9 ($2CH_2$), 28.1 ($3CH_3$), 47.7 ($2CH_2$), 78.5 (CH), 83.0 (C-O), 158.6 (C), 160.0 (C), 172.0 (C); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{13}H_{21}N_2O_3$: 253.1547; found: 253.1544.

tert-Butyl 5-(benzylamino)isoxazole-3-carboxylate ***(2e)***. **2e** was synthesized according to *GP1* starting from **1a** and benzylamine. Yield: 52 mg, 95%; white solid; mp 177–180 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 1.57 (s, 9H, $3CH_3$), 4.38 (d, ^3J = 5.9 Hz, 2H, CH_2), 5.12 (br.t, ^3J = 5.9 Hz, 1H, NH), 5.34 (s, 1H, CH), 7.27–7.39 (m, 5H, 5CH(Ar)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1 ($3CH_3$), 48.6 (CH_2), 78.5 (CH), 83.2 (C-O), 127.5 (2CH(Ar)), 128.1 (CH(Ar)), 129.0 (2CH(Ar)), 137.2 (C(Ar)), 158.6 (C), 159.8 (C), 170.8 (C); HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{15}H_{18}NaN_2O_3$: 297.1210; found: 297.1208.

tert-Butyl 5-phenoxyisoxazole-3-carboxylate ***(2g)***. **2g** was synthesized according to *GP2* starting from **1a** and phenol**.** Yield: 49 mg, 94%; white solid; mp 51–52 °C; R_f 0.38 (petroleum ether:EtOAc = 10:1) ^1H NMR (400 MHz, $CDCl_3$): δ 1.58 (s, 9H, $3CH_3$), 5.60 (s, 1H, CH), 7.17–7.22 (m, 2H, 2CH(Ar)), 7.25–7.31 (m, 1H, CH(Ar)), 7.39–7.45 (m, 2H, 2CH(Ar)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1 ($3CH_3$), 82.2 (CH), 83.8 (C-O), 119.2 (2CH(Ar)), 126.5 (CH(Ar)), 130.4 (2CH(Ar)), 154.4 (C(Ar)), 158.9 (C), 159.2 (C), 173.1 (C); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{16}NO_4$: 262.1074; found: 262.1077.

tert-Butyl 5-(3-aminophenoxy)isoxazole-3-carboxylate ***(2h)***. **2h** was synthesized according to *GP2* starting from **1a** and 3-aminophenol**.** Yield: 40 mg, 72%; light-yellow solid; mp 110–112 °C; R_f 0.18 (petroleum ether:EtOAc = 4:1) ^1H NMR (400 MHz, $CDCl_3$): δ 1.58 (s, 9H, $3CH_3$), 3.84 (br.s, 2H, NH_2), 5.62 (s, 1H, CH), 6.46–6.50 (m, 1H, CH(Ar)), 6.52–6.58 (m, 2H, 2CH(Ar)), 7.12–7.18 (m, 1H, CH(Ar)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1 ($3CH_3$), 82.2 (CH), 83.8 (C-O), 105.5 (CH(Ar)), 108.5 (CH(Ar)), 112.9 (CH(Ar)), 130.9 (CH(Ar)), 148.5 (C(Ar)), 155.5 (C(Ar)), 158.9 (C), 159.2 (C), 173.2 (C); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{17}N_2O_4$: 277.1183; found: 277.1184.

tert-Butyl 5-methoxyisoxazole-3-carboxylate ***(2i)***. **2i** was synthesized according to *GP3* starting from **1a** and methanol**.** Yield: 37 mg, 92%; white solid; mp 83–85 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 1.59 (s, 9H, $3CH_3$), 4.02 (s, 3H, CH_3), 5.58 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1 ($3CH_3$), 59.3 (CH_3), 78.1 (CH), 83.6 (C-O), 159.11 (C),

159.17 (C), 175.0 (C); HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_9H_{13}NaNO_4$: 222.0737; found: 222.0739.

*tert-Butyl 5-ethoxyisoxazole-3-carboxylate **(2j)***. **2j** was synthesized according to *GP3* starting from **1a** and ethanol**.** Yield: 38 mg, 89%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (t, ^3J = 7.1 Hz, 3H, CH_3), 1.57 (s, 9H, $3CH_3$), 4.26 (q, ^3J = 7.1 Hz, 2H, CH_2), 5.53 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4 (CH_3), 28.1 ($3CH_3$), 68.9 (CH_2), 78.4 (CH), 83.5 (C-O), 159.1 (C), 159.2 (C), 174.3 (C); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{10}H_{16}NO_4$: 214.1074; found: 214.1070.

*Di-tert-butyl 5,5'-[1,2-phenylenebis(oxy)]diisoxazole-3-carboxylate **(2k)*** **2k** was synthesized according to *GP2* starting from **1a** and 1,2-benzenediol**.** Yield: 34 mg, 76 %; yellowish oil; R_f = 0.32 (petroleum ether:EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58 (s, 18H, $6CH_3$), 5.66 (s, 2H, 2CH), 7.30–7.38 (m, 4H, 4CH(Ar)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1 ($6CH_3$), 82.8 (2CH), 84.0 (2C), 121.7 (2CH(Ar)), 127.9 (2CH(Ar)), 144.8 (2C), 158.6 (2C), 159.4 (2C), 171.7 (2C); HRMS (ESI) m/z $[M+NH_4]^+$ calcd for $C_{22}H_{28}N_3O_8^+$: 462.1875; found: 462.1871.

*Di-tert-butyl 5,5'-[1,3-phenylenebis(oxy)]diisoxazole-3-carboxylate **(2l)*** **2l** was synthesized according to *GP2* starting from **1a** and 1,3-benzenediol**.** Yield: 36 mg, 82 %; colorless solid; mp 101–104 °C; R_f = 0.42 (petroleum ether:EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59 (s, 18H, 6CH3), 5.76 (s, 2H, 2CH), 7.04–7.07 (m, 1H, CH(Ar)), 7.08-7.14 (m, 2H, 2CH(Ar)), 7.43-7.51 (m, 1H, CH(Ar)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1 (6CH3), 83.6 (2CH), 84.1 (2C), 110.1 (CH(Ar)), 116.3 (2CH(Ar)), 131.7 (CH(Ar)), 155.4 (2C), 158.6 (2C), 159.4 (2C), 171.6 (2C); HRMS (ESI) m/z $[M+NH_4]^+$ calcd for $C_{22}H_{28}N_3O_8^+$: 462.1872; found: 462.1871.

*Di-tert-butyl 5,5'-[1,4-phenylenebis(oxy)]diisoxazole-3-carboxylate **(2m)*** **2m** was synthesized according to *GP2* starting from **1a** and 1,4-benzenediol**.** Yield: 37 mg, 84 %; colorless solid; mp 175–178 °C; R_f = 0.14 (petroleum ether:EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58 (s, 18H, $6CH_3$), 5.68 (s, 2H, 2CH), 7.26 (s, 4H, 4CH(Ar)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1 ($6CH_3$), 82.8 (2CH), 84.1 (2C), 120.9 (4CH(Ar)), 151.9 (2C), 158.7 (2C), 159.3 (2C), 172.3 (2C); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{25}N_2O_8^+$: 445.1605; found: 445.1598.

*tert-Butyl 5-(phenylsulfanyl)isoxazole-3-carboxylate **(2n)***. **2n** was synthesized according to *GP2* starting from **1a** and benzenethiol**.** Yield: 47 mg, 85%; colorless oil; R_f 0.08 (petroleum ether:CH_2Cl_2 = 2:1) ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58 (s, 9H, $3CH_3$), 6.45 (s, 1H, CH), 7.34–7.42 (m, 3H, 3CH(Ar)), 7.45–7.54 (m, 2H, 2CH(Ar)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1 ($3CH_3$), 84.0 (C-O), 106.7 (CH), 129.4 (CH(Ar)), 129.8 (C(Ar)),

129.9 (2CH(Ar)), 132.8 (2CH(Ar)), 158.2 (C), 158.7 (C), 168.3 (C); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{16}NO_3S$: 278.0845; found: 278.0848.

tert-Butyl 5-(benzylsulfanyl)isoxazole-3-carboxylate ***(2o)***. **2o** was synthesized according to *GP2* starting from **1a** and phenylmethanethiol**.** Yield: 45 mg, 78%; colorless oil; R_f 0.23 (petroleum ether:EtOAc = 20:1) ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59 (s, 9H, $3CH_3$), 4.25 (s, 2H, CH_2), 6.40 (s, 1H, CH), 7.26–7.34 (m, 5H, 5CH(Ar)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1 ($3CH_3$), 38.1 (CH_2), 83.9 (C-O), 105.5 (CH), 128.1 (CH(Ar)), 128.9 (4CH(Ar)), 136.0 (C(Ar)), 158.2 (C), 158.8 (C), 167.7 (C); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{18}NO_3S$: 292.1002; found: 292.1004.

Methyl 5-morpholinoisoxazole-3-carboxylate ***(2r)***. **2r** was synthesized according to *GP1* starting from **1b** and morpholine**.** Yield: 42 mg, 98%; white solid; mp 137–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.30–3.35 (m, 4H, $2CH_2$), 3.74–3.80 (m, 4H, $2CH_2$), 3.89 (s, 3H, CH_3O). 5.42 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.6 ($2CH_2$), 52.7 (CH_3O), 65.8 ($2CH_2$), 79.3 (CH), 157.0 (C), 160.9 (C), 171.8 (C); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_9H_{13}N_2O_4$: 213.0870; found: 213.0878.

Methyl 5-phenoxyisoxazole-3-carboxylate ***(2s)***. **2s** was synthesized according to *GP2* starting from **1b** and phenol**.** Yield: 40 mg, 91%; colorless oil; R_f 0.20 (petroleum ether:EtOAc = 10:1) ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.93 (s, 3H, CH_3O), 5.66 (s, 1H, CH), 7.18–7.22 (m, 2H, 2CH(Ar)), 7.27–7.32 (m, 1H, CH(Ar)), 7.40–7.45 (m, 2H, 2CH(Ar)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.0 (CH_3O), 82.1 (CH), 119.3 (2CH(Ar)), 126.6 (CH(Ar)), 130.4 (2CH(Ar)), 154.3 (C-O), 157.7 (C), 160.2 (C), 173.4 (C); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{11}H_{10}NO_4$: 220.0604; found: 220.0604.

Methyl 5-(phenylsulfanyl)isoxazole-3-carboxylate ***(2t)***. **2t** was synthesized according to *GP2* starting from **1b** and benzenethiol**.** Yield: 44 mg, 93%; colorless oil; R_f 0.20 (petroleum ether:EtOAc = 10:1) ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.92 (s, 3H, CH_3O), 6.45 (s, 1H, CH), 7.34–7.42 (m, 3H, 3CH(Ar)), 7.47–7.54 (m, 2H, 2CH(Ar)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.0 (CH_3O), 106.1 (CH), 129.3 (C(Ar)), 129.6 (CH(Ar)), 129.9 (2CH(Ar)), 133.0 (2CH(Ar)), 156.6 (C), 160.0 (C), 169.2 (C); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{11}H_{10}NO_3S$: 236.0376; found: 236.0382.

1-(5-Morpholinoisoxazol-3-yl)ethanone ***(2u)***. **2u** was synthesized according to *GP1* starting from **1c** and morpholine**.** Purification by column chromatography (petroleum ether/ethyl acetate = 3:1) afforded the desired **2r**. Yield: 29 mg, 73%; white solid; mp 107–110 °C; R_f 0.28 (petroleum ether:EtOAc = 3:1) ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.54 (s, 3H, CH_3), 3.30–3.36 (m, 4H, $2CH_2$), 3.76–3.82 (m, 4H, $2CH_2$), 5.38 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.0 (CH_3), 46.8 ($2CH_2$), 65.9 ($2CH_2$), 76.9 (CH), 163.2 (C),

172.0 (C), 193.0 (C=O); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_9H_{13}N_2O_3$: 197.0921; found: 197.0926.

1-(5-(Phenylsulfanyl)isoxazol-3-yl)ethanone ***(2w)***. **2w** was synthesized according to *GP2* starting from **1c** and benzenethiol**.** Yield: 38 mg, 86%; colorless oil; R_f 0.41 (petroleum ether:EtOAc = 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.60 (s, 3H, CH_3), 6.41 (s, 1H, CH), 7.35–7.41 (m, 3H, 3CH(Ar)), 7.48–7.53 (m, 2H, 2CH(Ar)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.2 (CH_3), 103.9 (CH), 129.4 (C(Ar)), 129.6 (CH(Ar)), 129.9 (2CH(Ar)), 133.1 (2CH(Ar)), 162.4 (C), 169.0 (C), 191.7 (C); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{11}H_{10}NO_2S$: 220.0427; found: 220.0420.

(5-Morpholinoisoxazol-3-yl)(phenyl)methanone ***(2x)***. **2x** was synthesized according to *GP1* starting from **1d** and morpholine**.** Yield: 45 mg, 87%; light-yellow solid; mp 123–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.37–3.43 (m, 4H, $2CH_2$), 3.80–3.86 (m, 4H, $2CH_2$), 5.56 (s, 1H, CH), 7.46–7.53 (m, 2H, 2CH(Ar)), 7.59–7.65 (m, 1H, CH(Ar)), 8.23–8.28 (m, 2H, 2CH(Ar)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.8 ($2CH_2$), 66.0 ($2CH_2$), 79.4 (CH), 128.6 (2CH(Ar)), 130.7 (2CH(Ar)), 134.0 (CH(Ar)), 136.0 (C(Ar)), 163.1 (C), 171.4 (C), 186.7 (C=O); HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{14}H_{14}NaN_2O_3Na$: 281.0897; found: 281.0893.

5-Morpholinoisoxazole-3-carboxamide ***(2y)***. **2y** was synthesized according to *GP1* using THF as a solvent, starting from **1e** and morpholine**.** Yield: 34 mg, 87%; white solid; mp 138–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.32–3.37 (m, 4H, $2CH_2$), 3.78–3.83 (m, 4H, $2CH_2$), 5.50 (s, 1H, CH), 6.02 (br.s, 1H, NH_2), 6.73 (br.s, 1H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.7 ($2CH_2$), 65.9 ($2CH_2$), 78.6 (CH), 159.1 (C), 161.7 (C), 172.1 (C); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_8H_{12}N_3O_3$: 198.0873; found: 198.0878.

Diethyl (5-morpholinoisoxazol-3-yl)phosphonate ***(2z)***. **2z** was synthesized according to *GP1* starting from **1f** and morpholine. Yield: 53 mg, 92%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (dt, $^3J_{HH}$ = 7.1 Hz, $^4J_{PH}$ = 0.6 Hz, 6H, $2CH_3$), 3.32–3.37 (m, 4H, $2CH_2$), 3.76–3.82 (m, 4H, $2CH_2$), 4.16–4.29 (m, 4H, $2CH_2O$), 5.33 (d, $^3J_{PH}$ = 1.4 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.4 ($^3J_{CP}$ = 6.5 Hz, $2CH_3$), 46.8 ($2CH_2$), 63.6 ($^2J_{CP}$ = 5.9 Hz, $2CH_2$), 66.0 ($2CH_2$), 81.3 ($^2J_{CP}$ = 21.7 Hz, CH), 156.8 ($^1J_{CP}$ = 209.2 Hz, C), 171.5 ($^3J_{CP}$ = 12.0 Hz, C); ^{31}P NMR (162 MHz, $CDCl_3$): δ 5.40; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{11}H_{20}N_2O_5P$: 291.1104; found: 291.1102.

Diethyl (5-phenoxyisoxazol-3-yl)phosphonate ***(2za)***. **2za** was synthesized according to *GP2* starting from **1f** and phenol. Yield: 55 mg, 92%; colorless oil; R_f 0.20 (petroleum ether:EtOAc = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (dt, $^3J_{HH}$ = 7.0 Hz, $^4J_{PH}$ = 0.7

Hz, 6H, $2CH_3$), 4.16–4.30 (m, 4H, $2CH_2O$), 5.51 (d, $^3J_{PH}$ = 1.1 Hz, 1H, CH), 7.17–7.22 (m, 2H, 2CH(Ar)), 7.25–7.31 (m, 1H, CH(Ar)), 7.38–7.45 (m, 2H, 2CH(Ar)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.3 ($^3J_{CP}$ = 6.5 Hz, $2CH_3$), 63.8 ($^2J_{CP}$ = 5.9 Hz, $2CH_2$), 83.7 ($^2J_{CP}$ = 20.5 Hz, CH), 119.4 (2CH(Ar)), 126.4 (CH(Ar)), 130.4 (2CH(Ar)), 154.7 (C(Ar)), 158.2 ($^1J_{CP}$ = 211.6 Hz, C), 173.5 ($^3J_{CP}$ = 12.9 Hz, C); ^{31}P NMR (162 MHz, $CDCl_3$): δ 3.72; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{13}H_{17}NO_5P$: 298.0839; found: 298.0843.

Diethyl (5-(phenylsulfanyl)isoxazol-3-yl)phosphonate ***(2zb)***. **2zb** was synthesized according to *GP2* starting from **1f** and benzenethiol. Yield: 56 mg, 89%; colorless oil; R_f 0.23 (petroleum ether:EtOAc = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (dt, $^3J_{HH}$ = 7.1 Hz, $^4J_{PH}$ = 0.7 Hz, 6H, $2CH_3$), 4.13–4.28 (m, 4H, $2CH_2O$), 6.26 (d, $^3J_{PH}$ = 0.9 Hz, 1H, CH), 7.34–7.42 (m, 3H, 3CH(Ar)), 7.49–7.54 (m, 2H, 2CH(Ar)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.3 ($^3J_{CP}$ = 6.5 Hz, $2CH_3$), 63.9 ($^2J_{CP}$ = 5.9 Hz, $2CH_2$), 107.1 ($^2J_{CP}$ = 20.3 Hz, CH), 129.0 (C(Ar)), 129.8 (CH(Ar)), 130.0 (2CH(Ar)), 133.4 (2CH(Ar)), 156.4 ($^1J_{CP}$ = 210.8 Hz, C), 168.6 ($^3J_{CP}$ = 11.6 Hz, C); ^{31}P NMR (162 MHz, $CDCl_3$): δ 3.92; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{13}H_{16}NO_4PSNa$: 336.0430; found: 336.0430.

Adamantan-1-ylmethyl 5-morpholinoisoxazole-3-carboxylate ***(2zc)***. **2zc** was synthesized according to *GP1* starting from **1g** and morpholine**.** Yield: 62 mg, 90%; white solid; mp 102–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56–1.61 (m, 6H, $3CH_2$), 1.61–1.68 (m, 3H, $3CH_2$), 1.68–1.77 (m, 3H, $3CH_2$), 1.94–2.03 (m, 3H, 3CH), 3.31–3.38 (m, 4H, $2CH_2$), 3.76–3.82 (m, 4H, $2CH_2$), 3.93 (s, 2H, CH_2O), 5.43 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.0 (3CH), 33.5 (C), 36.9 ($3CH_2$), 39.3 ($3CH_2$), 46.7 ($2CH_2$), 65.9 ($2CH_2$), 75.1 (CH_2O), 79.3 (CH), 157.4 (C), 160.7 (C), 171.8 (C); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{19}H_{27}N_2O_4$: 347.1965; found: 347.1964.

Adamantan-1-ylmethyl 5-phenoxyisoxazole-3-carboxylate ***(2zd)***. **2zd** was synthesized according to *GP2* starting from **1g** and phenol**.** Yield: 61 mg, 87%; white solid; mp 115–117 °C; R_f 0.33 (petroleum ether:EtOAc = 20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57–1.61 (m, 6H, $3CH_2$), 1.63–1.69 (m, 3H, $3CH_2$), 1.69–1.76 (m, 3H, $3CH_2$), 1.96–2.03 (m, 3H, 3CH), 3.95 (s, 2H, CH_2O), 5.67 (s, 1H, CH), 7.18–7.24 (m, 2H, 2CH), 7.27–7.33 (m, 1H, CH), 7.40–7.47 (m, 2H, 2CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1 (3CH), 33.6 (C), 36.9 ($3CH_2$), 39.3 ($3CH_2$), 75.5 (CH_2O), 82.2 (CH), 119.2 (2CH(Ar)), 126.5 (CH(Ar)), 130.4 (2CH(Ar)), 154.4 (C(Ar)), 158.1 (C), 160.1 (C), 173.2 (C); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{24}NO_4$: 354.1700; found: 354.1697.

Adamantan-1-ylmethyl 5-(phenylsulfanyl)isoxazole-3-carboxylate ***(2ze)***. **2ze** was synthesized according to *GP2* starting from **1g** and benzenethiol. Yield: 63 mg, 85%; white solid; mp 73–74 °C; R_f 0.40 (petroleum ether:EtOAc = 20:1); ^{1}H NMR (400 MHz,

$CDCl_3$): δ 1.56–1.61 (m, 6H, $3CH_2$), 1.62–1.71 (m, 3H, $3CH_2$), 1.71–1.76 (m, 3H, $3CH_2$), 1.96–2.02 (m, 3H, 3CH), 3.95 (s, 2H, CH_2O), 6.51 (s, 1H, CH), 7.36–7.41 (m, 3H, 3CH), 7.48–7.54 (m, 2H, 2CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.0 (3CH), 33.6 (C), 36.9 ($3CH_2$), 39.2 ($3CH_2$), 75.5 (CH_2O), 106.5 (CH), 129.48 (CH), 129.54 (C), 129.9 (2CH), 132.9 (2CH), 157.0 (C), 159.9 (C), 168.5 (C); HRMS (ESI) m/z $[M+NH_4]^+$ calcd for $C_{21}H_{27}N_2O_3S$: 387.1737; found: 387.1735.

Methyl 4-methyl-5-morpholinoisoxazole-3-carboxylate ***(2zf).*** **2zf** was synthesized according to *GP1* starting from **1h** and morpholine at 80 °C for 6 h. Purification by column chromatography (petroleum ether/ethyl acetate = 4:1) afforded the desired **2zf**. Yield: 35 mg, 77%; white solid; mp 119–121 °C; R_f 0.16 (petroleum ether:EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.13 (s, 3H, CH_3), 3.35–3.40 (m, 4H, $2CH_2$), 3.77–3.83 (m, 4H, $2CH_2$), 3.92 (s, 3H, CH_3O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.8 (CH_3), 48.0 ($2CH_2$), 52.5 (CH_3O), 66.5 ($2CH_2$), 93.6 (C), 156.0 (C), 161.6 (C=O), 169.2 (C); HRMS (ESI) m/z $[M+K]^+$ calcd for $C_{10}H_{14}N_2O_4K$: 265.0585; found: 265.0583.

4-(3-Nitroisoxazol-5-yl)morpholine ***(2zg)***. **2zg** was synthesized according to *GP1* starting from **1i** and morpholine**.** Yield: 35 mg, 88%; yellow solid; mp 118–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.36–3.43 (m, 4H, $2CH_2$), 3.75–3.84 (m, 4H, $2CH_2$), 5.56 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.0 ($2CH_2$), 65.7 ($2CH_2$), 73.6 (CH), 168.0 (C-NO_2), 172.1 (C); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_7H_{10}N_3O_4$: 200.0666; found: 200.0670.

3-Nitro-5-phenoxyisoxazole ***(2zh)***. **2zh** was synthesized according to *GP2* starting from **1i** and phenol. Yield: 38 mg, 93%; colorless oil; R_f 0.31 (petroleum ether:EtOAc = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83 (s, 1H, CH), 7.23–7.28 (m, 2H, 2CH(Ar)), 7.34–7.40 (m, 1H, CH(Ar)), 7.46–7.53 (m, 2H, 2CH(Ar)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 77.4 (CH), 119.4 (2CH(Ar)), 127.8 (CH(Ar)), 130.7 (2CH(Ar)), 153.5 (C(Ar)), 167.5 (C-NO_2), 174.0 (C); HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_9H_6NaN_2O_4$: 229.0220; found: 229.0217.

3-Nitro-5-(phenylsulfanyl)isoxazole ***(2zi).*** **2zi** was synthesized according to *GP2* starting from **1i** and benzenethiol. Yield: 40 mg, 90%; colorless oil; R_f 0.35 (petroleum ether:CH_2Cl_2 = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.49 (s, 1H, CH), 7.42–7.51 (m, 3H, 3CH(Ar)), 7.58–7.64 (m, 2H, 2CH(Ar)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 99.6 (CH), 127.3 (C(Ar)), 130.4 (2CH(Ar)), 130.7 (CH(Ar)), 134.1 (2CH(Ar)), 167.6 (C-NO_2), 174.0 (C); HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_9H_6N_2O_3SNa$: 244.9991; found: 245.0005.

Methyl 5-{[1-(1-adamantyl)ethyl]amino}isoxazole-3-carboxylate ***(9)***. **9** was synthesized according to *GP2* starting from **1b** and **8** (rimantadine)**.** Purification by column chromatography (petroleum ether/ethyl acetate = 4:1) afforded the desired **9**. Yield: 47 mg, 86 %; white solid; mp 209-210 °C; R_f 0.38 (petroleum ether:EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (d, ^3J = 6.8 Hz, 3H, CH_3), 1.44–1.52 (m, 3H, $3CH_2$), 1.56–1.66 (m, 6H, $3CH_2$), 1.68–1.75 (m, 3H, $3CH_2$), 1.97–2.03 (m, 3H, 3CH), 2.97 (dt, ^3J = 6.8 Hz, ^3J = 10.0 Hz, 1H, CH), 3.91 (s, 3H, CH_3), 4.56 (br.d, ^3J = 10.0 Hz, 1H, NH), 5.34 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.9 (CH_3), 28.3 (3CH), 36.7 (C), 37.1 ($3CH_2$), 38.5 ($3CH_2$), 52.7 (CH_3O), 60.7 (CHN), 77.4 (CH), 157.1 (C), 161.3 (C), 171.5 (C); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{17}H_{25}N_2O_3$: 305.1860; found: 305.1853.

Methyl 5-(((8R,9S,13S,14S,17R)-17-ethynyl-17-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)oxy)isoxazole-3-carboxylate ***(11)***. **11** was synthesized according to *GP2* starting from **1b** and **10** (ethinylestradiol)**.** Purification by column chromatography (petroleum ether/ethyl acetate = 3:1) afforded the desired **11**. Yield: 66 mg, 78 %; white solid, mp 127-128 °C; R_f 0.16 (petroleum ether:EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (s, 3H, CH_3), 1.32–1.60 (m, 4H, $3CH_2$+CH), 1.66–1.86 (m, 3H, CH+$2CH_2$), 1.86-2.01 (m, 4H, $3CH_2$+OH), 2.21-2.45 (m, 3H, $2CH_2$+CH), 2.61 (s, 1H, HC≡), 2.82–2.93 (m, 2H, CH_2), 3.94 (s, 3H, CH_3O), 5.65 (s, 1H, CH), 6.88-6.93 (m, 1H, CH), 6.93-7.00 (m, 1H, CH), 7.30-7.36 (m, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.8 (CH_3), 22.9 (CH_2), 26.4 (CH_2), 27.0 (CH_2), 29.7 (CH_2), 32.8 (CH_2), 39.07 (CH_2), 39.12 (CH), 43.8 (CH), 47.2 (C), 49.6 (CH), 53.0 (CH_3), 74.3 (≡CH), 79.9 (≡C), 81.9 (CH), 87.5 (C), 116.3 (CH), 119.2 (CH), 127.3 (CH), 138.9 (C), 139.4 (C), 152.2 (C), 157.7 (C), 160.4 (C), 173.8 (C). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{25}H_{28}NO_5$: 422.1962; found: 422.1956.

Synthesis of tert-butyl 5-azidoisoxazole-3-carboxylate (2f). NaN_3 (0.25 mmol) was added to the solution of 5-nitroisoxazole **1a** (0.2 mmol) in CH_3CN (2 mL) and the resulting mixture was stirred at r. t. for 24 h. The mixture was poured into CH_2Cl_2 (30 mL) and it was washed with water (15 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give product **2f** which required no additional purification. Yield: 41 mg, 98%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56 (s, 9H, $3CH_3$), 6.01 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1 ($3CH_3$), 84.2 (C-O), 90.0 (CH), 158.4 (C), 159.4 (C), 162.5 (C); HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_8H_{10}N_4O_3Na$: 233.0645; found: 233.0649.

Synthesis of tert-butyl isoxazole-3-carboxylate (2p). 5-Nitroisoxazole **1a** (0.4 mmol) was dissolved in mixture of THF (2.6 mL) and water (0.8 mL) and cooled down to 0 ºC.

$NaBH_4$ (61 mg, 1.6 mmol) was added and the mixture was stirred at 0 ºC for 30 min. Then the mixture was warmed slowly up to r. t. and stirred for 2 h. NH_4Cl saturated solution (5 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give product **2p** which required no additional purification. Yield: 49 mg, 73%; brownish oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.61 (s, 9H, $3CH_3$), 6.71 (d, ^3J = 1.7 Hz, 1H, CH), 8.48 (d, ^3J = 1.7 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.2 ($3CH_3$), 83.9 (C-O), 105.3 (CH), 156.9 (C), 159.0 (C=O), 159.8 (CH); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_8H_{12}NO_3$: 170.0812; found: 170.0819.

General Procedure 4. Cerium (IV) ammonium nitrate (55 mg, 0.1 mmol) was added to a solution of isoxazole **2** (0.2 mmol) in $(CH_3CO)_2O$ (1 mL). The reaction mixture was stirred for 24 h, and then poured into water (30 mL) and neutralized with solution of $NaHCO_3$ (to pH 7–8). The product was extracted by CH_2Cl_2 (4×10 mL). The combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography.

*4-(3,4-Dinitroisoxazol-5-yl)morpholine **(3)***. **3** was synthesized according to *GP4* starting from **2zg.** Yield: 42 mg, 87%; yellow solid; mp 113–114 °C; R_f 0.23 (petroleum ether:EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (ps.s, 8H, $4CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.0 ($2CH_2$), 66.2 ($2CH_2$), 105.6 (C^4-NO_2), 162.3 (C^3-NO_2), 162.8 (C); Anal. calcd. for $C_7H_8N_4O_6$: C, 34.43; H, 3.30; N, 22.95. Found: C, 34.39; H, 3.19; N, 22.91.

*Methyl 5-morpholino-4-nitroisoxazole-3-carboxylate **(6)***. **6** was synthesized according to *GP4* starting from **2r.** Yield: 38 mg, 74%; light-yellow solid; mp 109–110 °C; R_f 0.14 (petroleum ether:EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81–3.85 (m, 4H, $2CH_2$), 3.85–3.89 (m, 4H, $2CH_2$), 4.00 (s, 3H, CH_3O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.0 ($2CH_2$), 54.0 (CH_3O), 66.4 ($2CH_2$), 111.4 (C-NO_2), 154.5 (C), 159.1 (C=O), 163.0 (C); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_9H_{12}N_3O_6$: 258.0721; found: 258.0717.

Synthesis of 4-(3-fluoro-4-nitroisoxazol-5-yl)morpholine (4a). Bu_4NF solution in THF (1 M, 0.4 mmol, 0.4 mL) was added to a solution of 3,4-dinitroisoxazole **3** (50 mg, 0.2 mmol) in CH_3CN (2 mL) and the resulting mixture was stirred at r. t. for 24 h. After the reaction was finished, the resulting mixture was filtered through silica gel and in addition the silica gel layer was washed with EtOAc (50 mL). The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography to give the product **4a**. Yield: 32 mg, 73%; white solid; mp 111–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.79–3.84 (m, 4H, $2CH_2$), 3.84–3.90 (m, 4H, $2CH_2$); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 48.3 ($2CH_2$), 66.3 ($2CH_2$), 103.0 ($^2J_{CF}$ = 20.1 Hz, C-NO_2), 163.6 (C), 163.0 ($^1J_{CF}$ = 269.0 Hz, C); ^{19}F NMR (376 MHz, $CDCl_3$): δ –117.12.

General procedure 5. A nucleophile (0.2 mmol) and DIPEA (0.2 mmol, 26 mg) were added to a solution of 3,4-dinitroisoxazole **3** (50 mg, 0.2 mmol) in CH_3CN (2 mL). The resulting mixture was stirred at r. t. for 24 h. After the reaction was finished, solvent was removed under reduced pressure, and the residue was partitioned between water and dichloromethane. The aqueous phase was extracted three times with CH_2Cl_2 (15 mL), and the combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to give the products **4b,c**.

4-(4-Nitro-3-phenoxyisoxazol-5-yl)morpholine ***(4b).*** **4b** was synthesized according to *GP5* with phenol**.** Yield: 48 mg, 83%; white solid; mp 110–111 °C; R_f 0.26 (petroleum ether:EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.72–3.79 (m, 4H, $2CH_2$), 3.82–3.89 (m, 4H, $2CH_2$), 7.22–7.31 (m, 3H, 3CH(Ar)), 7.37–7.44 (m, 2H, 2CH(Ar)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 48.3 ($2CH_2$), 66.4 ($2CH_2$), 105.5 (C-NO_2), 120.2 (2CH(Ar)), 126.3 (CH(Ar)), 129.9 (2CH(Ar)), 153.4 (C(Ar)), 164.4 (C), 165.5 (C). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{13}H_{14}N_3O_5$: 292.0928; found: 292.0928.

N-Benzyl-5-morpholin-4-yl-4-nitroisoxazol-3-amine ***(4c).*** **4c** was synthesized according to *GP5* with benzylamine. Yield: 40 mg, 65%; yellowish oil; R_f 0.13 (petroleum ether:EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.73–3.79 (m, 4H, $2CH_2$), 3.81–3.86 (m, 4H, $2CH_2$), 4.43 (d, ^3J = 5.9 Hz, 2H, CH_2-N) 6.39 (br.s, ^3J = 5.9 Hz, 2H, NH_2), 7.29–7.39 (m, 5H, 5CH(Ar)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.5 (CH_2), 48.6 ($2CH_2$), 66.5 ($2CH_2$), 106.5 (C-NO_2), 120.2 (3CH(Ar)), 128.9 (2CH(Ar)), 137.8 (C(Ar)), 158.7 (C), 164.4 (C). HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{17}N_4O_4$: 305.1244; found: 305.1243.

Synthesis of methyl 4-bromo-5-morpholinoisoxazole-3-carboxylate (5). NBS (36 mg, 0.2 mmol) was added to a solution of methyl 5-morpholinoisoxazole-3-carboxylate **2r** (42 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) and the resulting mixture was stirred at r. t. for 24 h. After the reaction was finished, the reaction mixture was quenched with water, extracted with CH_2Cl_2 (3×15 mL) and dried over anhydrous $MgSO_4$. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography to give the product **5**. Yield: 46 mg, 79%; white solid; mp 95–97 °C; R_f 0.22 (petroleum ether:EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.57–3.67 (m, 4H, $2CH_2$), 3.74–3.80 (m, 4H, $2CH_2$), 3.91 (s, 3H, CH_3O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.9 ($2CH_2$), 52.8 (CH_3O), 66.2 ($2CH_2$), 67.9 (C), 154.8 (C), 159.7 (C=O), 166.9 (C); HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_9H_{11}BrN_2O_4Na$: 312.9794; found: 312.9793.

Synthesis of (5-morpholinoisoxazol-3-yl)methanol (7). A solution of methyl 5-morpholinoisoxazole-3-carboxylate **2r** (85 mg, 0.4 mmol) in THF (2 mL) was gently added to a suspension of $LiAlH_4$ (30 mg, 0.8 mmol) in THF (1 mL) under argon atmosphere. The resulting mixture was stirred at r. t. for 3 h. After cooling down to 0 ºC, water (3 mL) was added to the reaction mixture. The resulting mixture was neutralized with 10% H_2SO_4 and extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give product **7** which required no additional purification. Yield: 51 mg, 69%; white solid; mp 79–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.24–3.34 (m, 4H, $2CH_2$), 3.74–3.83 (m, 4H, $2CH_2$), 4.57 (s, 2H, CH_2). 5.09 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.7 ($2CH_2$), 57.2 (CH_2), 66.0 ($2CH_2$), 77.6 (CH), 165.3 (C), 171.2 (C); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_8H_{13}N_2O_3$: 185.0921; found: 185.0923.

3. X-ray Diffraction Analysis.

Single crystals suitable for X-ray diffraction were obtained by slow evaporation of the solvent from a dichloromethane-*i-Pr*OH solution of **2zg** and petroleum ether-dichloromethane - for **4a**. Crystal data collection and refinement parameters of **2zg** and **4a** are summarized in Table S1. Intensity data were collected at 295 K on a CAD-4 diffractometer for **2zc** and STADI VARI Pilatus-100K for **4a** diffractometer using monochromated Cu Kα radiation, λ = 1.54186 Å. The data were corrected for decay, Lorentz, and polarization effects as well as absorption and beam corrections based on the multi-scan technique. The structures were solved by a combination of direct methods in *SHELXS*-97 and the difference Fourier technique, and refined by full-matrix least-squares procedures (*SHELXL-2015/1* or *SHELXL-2014/7*). Non hydrogen atoms were refined with anisotropic displacement parameters. The H-atoms were either located or calculated and subsequently treated with a riding model.

Table S1. Crystallographic data and structure refinement results of **2zg** and **4a**.

	2zg	**4a**
Empirical formula	$C_7H_9N_3O_4$	$C_7H_8FN_3O_4$
Formula weight	199.17	217.16
Temp, K	295(2)	295(2)
Crystal system	Monoclinic	Orthorhombic
Space group	$P2_1/n$	$P2_12_12_1$
a, Å	6.5806(19)	5.3356(14)
b, Å	12.0214(16)	8.561(3)
c, Å	10.9200(11)	19.632(6)
α, (°)	90	90
β, (°)	93.833(17)	90
γ, (°)	90	90
Volume, $Å^3$	861.9(3)	896.8(5)

Z	4	4
d_{calc}, g·cm^{-3}	1.535	1.608
λ, Å	1.54186	1.54186
μ, mm^{-1}	1.100	1.003
No. of data collected	1770	8235
No. of unique data/ number restraints/ number refined parameters	1770/0/127	1670/0/136
R_{int}	0.0230 (before absorption correction)	0.0671 (before absorption correction)
Goodness-of-fit on F^2	1.053	1.003
R_1, wR_2 ($I > 2$ (I))	0.0352, 0.0916	0.0533, 0.1307
R_1, wR_2 (all data)	0.0404, 0.0949	0.0588, 0.1343

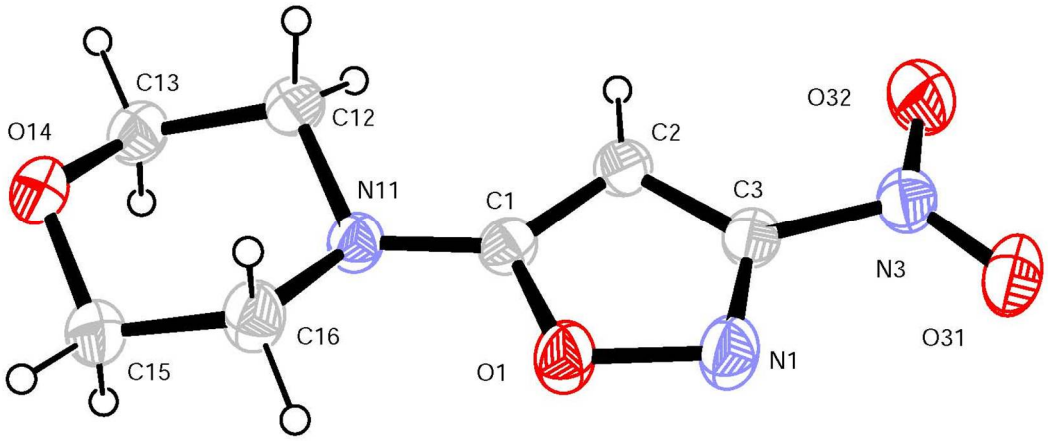

Figure S1. The molecular structure of compound **2zg.**

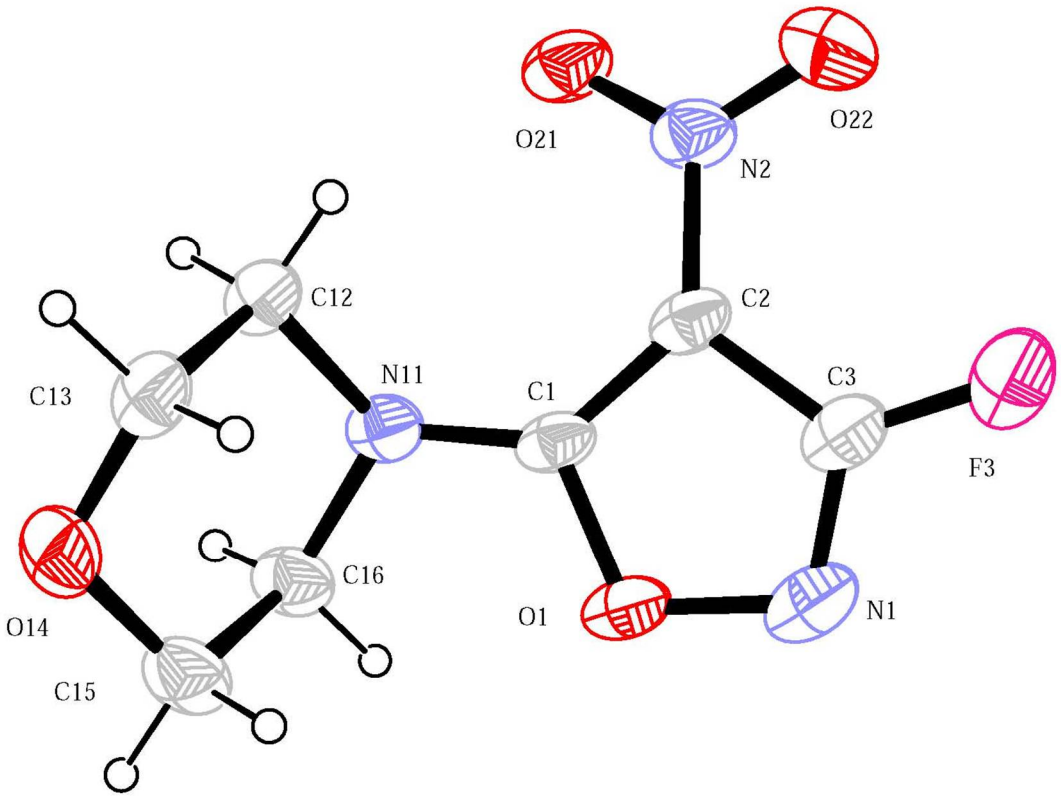

Figure S2. The molecular structure of compound **4a.**

4. DFT Studies

Computations were carried out using ORCA 4.0.1[3]. Structure optimizations were performed using the DFT functional B3LYP/G[4] in conjunction with Grimme's dispersion correction D3(BJ)[5] and def2-TZVP basis set[6] with the auxiliary basis: def2/J[7]. In all calculations, solvent effects were modeled using the conductor-like PCM (CPCM)[8] with CH_3CN as solvent. Convergence criteria were set tight for SCF calculations (TIGHTSCF). Thermodynamic properties were calculated at 298.15 K using QRRHO approach[9] for vibrational entropy correction. The nature of optimized intermediates and transition states was verified by frequency analysis. All the energies reported here are Gibbs free energies. Avogadro 1.2.0[10] was used to visualize the structure of the intermediates and FMOs. NBO Analysis was carried out with the JANPA package[11].

4.1 Computational Details

Orca DFT Key words for frequency and geometry optimization:

```
! B3LYP/G RIJCOSX D3BJ def2-TZVP def2/J  Opt TIGHTSCF NumFreq CPCM(acetonitrile)
------------
SCF SETTINGS
------------
Hamiltonian:
 Density Functional     Method          .... DFT(GTOs)
 Exchange Functional    Exchange        .... B88
   X-Alpha parameter    XAlpha          ....  0.666667
   Becke's b parameter  XBeta           ....  0.004200
 Correlation Functional Correlation     .... LYP
 LDA part of GGA corr.  LDAOpt          .... VWN-3
 Gradients option       PostSCFGGA      .... off
 Hybrid DFT is turned on
   Fraction HF Exchange ScalHFX         ....  0.200000
   Scaling of DF-GGA-X  ScalDFX         ....  0.720000
   Scaling of DF-GGA-C  ScalDFC         ....  0.810000
   Scaling of DF-LDA-C  ScalLDAC        ....  1.000000
   Perturbative correction              ....  0.000000
   NL short-range parameter             ....  4.800000
   RI-approximation to the Coulomb term is turned on
   Number of auxiliary basis functions  .... 943
   RIJ-COSX (HFX calculated with COS-X))....  on
--------------------
CPCM SOLVATION MODEL
--------------------
CPCM parameters:
  Epsilon                          ...      36.6000
  Refrac                           ...       1.3440
  Rsolv                            ...       1.3000
  Surface type                     ...    GEPOL SES
  Epsilon function type            ...         CPCM
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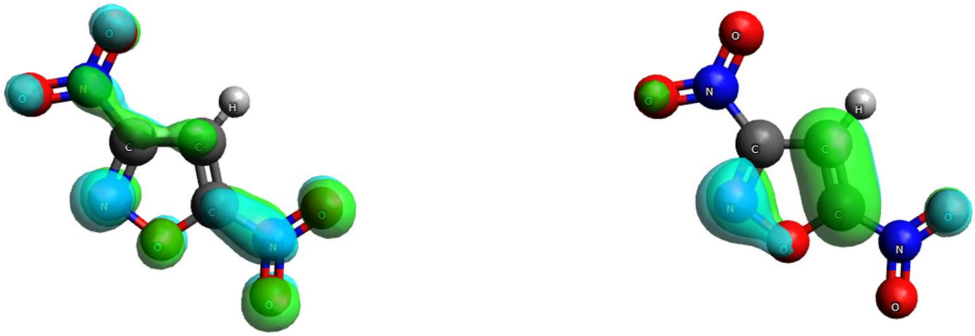
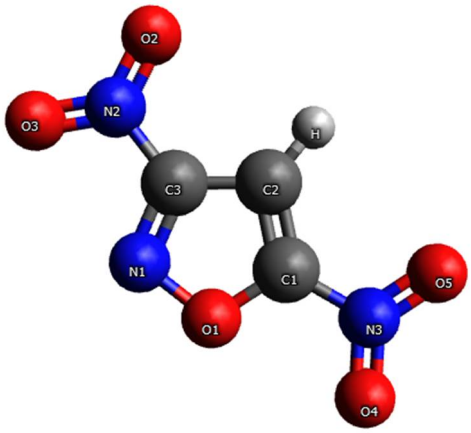
4.2. FMOs and Natural Atomic Charges



LUMO (-3.8 eV) HOMO (-9.0 eV)

Figure S3. The HOMO and LUMO of 3,5-dinitroisoxazole **1i**.

Table S2. Natural Atomic Charges of 3,5-dinitroisoxazole **1i**.



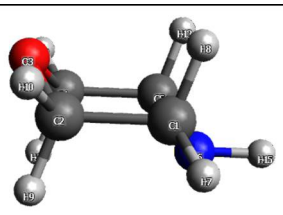
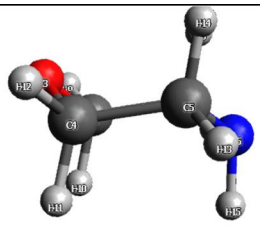
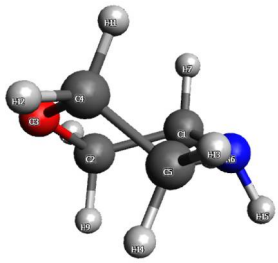
Atom	Nuclear charge	Electron population	NMB population	NPA charge
C1	6.0	5.6384994	5.6125959	0.3615006048
C2	6.0	6.2434817	6.2221182	-0.2434817216
C3	6.0	5.7972341	5.7696300	0.2027659057
O4	8.0	8.1984117	8.1730309	-0.1984116937
H5	1.0	0.7008934	0.6995262	0.2991066139
N6	7.0	7.0520019	7.0175768	-0.0520018779

N7	7.0	6.4890775	6.4462544	0.5109225092
O8	8.0	8.3464685	8.3278483	-0.3464684694
O9	8.0	8.3393528	8.3203240	-0.3393528142
N10	7.0	6.5064749	6.4632541	0.4935250838
O11	8.0	8.3421165	8.3233476	-0.3421165205
O12	8.0	8.3459876	8.3274860	-0.3459876186

4.3. Conformational analysis of morpholine.

Initial set of conformers was generated using RDKit program[12]. After the removal structures with the same energy three different conformers of morpholine were received (Table S3). The optimized geometry and the thermodynamic data were obtained with DFT (B3LYP-G/def2-TZVP/acetonitrile (CPCM)) method. According to conformational analysis morpholine has two the most stable conformations (M-1 and M-2) with similar energy (the difference in energy is approximately 0.22 kcal/mol). These conformations differ in the arrangement of the electron pair. For the discussion of mechanistic aspects of its S_NAr reaction we have chosen the conformation M-2 with the equatorial arrangement of the electron pair since in this case the nucleophile centre is in the less sterically hindered position.

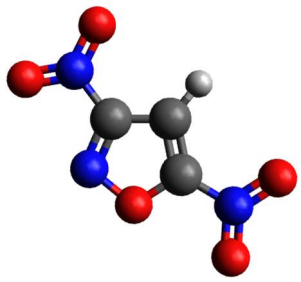
Table S3.

	M-1	M-2	M-3
			
G_{298}, Eh	-287.83437760	-287.83400852	-287.82456225
ΔG_{298}, kcal/mol	0	0.22	6.12

4.4. Cartesian Coordinates

List of Cartesian Coordinates of all the optimized structures

3,5-dinitroisoxazol (1i)



E = -655.31350770 Eh

ZPE = 0.06242156 Eh

G_{298} = -655.28424234 Eh

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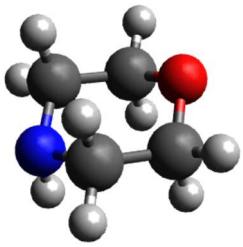
C	-0.00144312207226	0.82004247625121	0.00075720095120
C	-1.07238225821852	-0.09865450828682	0.00050018529167
O	0.67139953531082	-1.30930832637123	0.00121496679025
H	-0.02123998498240	1.89428728417557	0.00026145063089
N	-0.69493762152410	-1.35126416734175	0.00113074244717
N	-2.49773685143095	0.21350609448711	-0.00014245902392
O	-2.78781177063204	1.39665565070621	-0.00243390065067
O	-3.27756109800068	-0.71798773236244	-0.00009839032304
N	2.47684386611737	0.22334069354362	-0.00010446604073
O	3.20984349566437	-0.74869976511024	-0.00392565197158
O	2.82080336165192	1.39247910516781	0.00177165678454

Morpholine



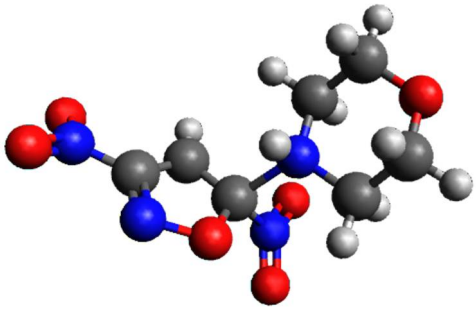
E = -287.94023799 Eh

ZPE = 0.13469347 Eh

G_{298} = -287.83400852 Eh

C	1.37391744103724	-0.07856127428074	0.22834599701949
C	0.62002845731733	1.21781127724598	0.48572397285763
O	-0.70921995492533	0.95570535056208	0.94240992952384
C	-1.44110438286694	0.16624891264655	0.00161327944536
C	-0.73393245049706	-1.15313306190920	-0.27167138979190
N	0.66212599385765	-0.97507037676792	-0.69037163313489
H	2.36031619763816	0.14557032858366	-0.18277886735300
H	1.51442682317989	-0.60483147147776	1.17699637448823
H	1.10449130437678	1.81138582393326	1.26164940201761
H	0.57616125673738	1.81286873816442	-0.43693431821445
H	-1.55758726471892	0.73308804580209	-0.93218607708058
H	-2.42702878480421	-0.00077559421954	0.43770324998057
H	-1.27122955966701	-1.70895280141674	-1.04215288580935
H	-0.74505993639801	-1.75517578239426	0.64188068607126
H	0.67391485973305	-0.56607811447188	-1.62011772001982

TS1



Imaginary mode -159.96

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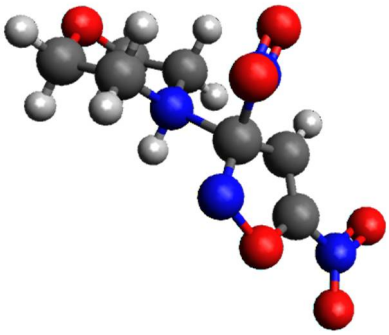
ZPE = 0.19936094 Eh

G_{298} = -943.08338653 Eh

C	-2.20626168263070	-0.31898752878354	-0.15474656144239
C	-1.25877960887897	0.01654100155075	0.79886230373977
C	-0.27558261255861	0.67037482580099	0.01349343827018
H	-1.24581770404088	-0.18398827821049	1.85190128732848
N	0.30157239019399	1.98207102187390	0.55967689329689
O	0.86163915901072	1.90462158155821	1.63902108948147
O	0.12331550792504	2.99604959138692	-0.08000238108021
N	-3.42370070440901	-1.07500032364425	0.11882862261771
O	-4.01739496261297	-1.57608547219571	-0.82044565092904
O	-3.76384473348853	-1.15858361484949	1.28859173043861
C	2.32216548225168	0.50668615239840	-0.84602757343956
C	1.68495185657984	-1.00667999431007	0.97780475199370
C	3.43417735663478	-0.46626733592081	-1.20254877023368
H	2.68429772862763	1.24506073158222	-0.13310690531264
H	1.93797056607437	1.00539017707455	-1.73397277539716
C	2.82606047641769	-1.91440554618481	0.54772365312413
H	2.01409747859106	-0.29004943662851	1.72428578683408

H	0.85140618149453	-1.58809781989878	1.36761016816422
H	4.28475403509789	0.08240119486391	-1.60251404694692
H	3.08249343854487	-1.17854797662707	-1.95809714521789
H	3.24171696648403	-2.41992195616241	1.41701843713636
H	2.45751172739454	-2.66801655628862	-0.15891422042745
N	1.20941999335062	-0.24212051407139	-0.20494905186290
O	3.88198211097192	-1.16570491516080	-0.04683603412251
H	0.85031180875218	-0.91098263517404	-0.88744920121214
O	-0.76193800357346	0.81725505417997	-1.24869774172043
N	-1.99579425220424	0.08709857184098	-1.38632010308070

TS2



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ZPE = 0.19894044 Eh

G_{298} = -943.07308742 Eh

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C	-0.23766691034106	0.50707408827252	-0.25744724673977
O	-2.09484146598267	-0.11891563465239	-1.33106015412569
H	-1.09559807236273	-0.04026905747118	1.78784659297479
N	-0.78236020215352	0.46239281805511	-1.49819929897316

N	0.34845663232436	1.97663234082676	0.14584791107778
O	0.72579833440584	2.11600927561823	1.29757978243310
O	0.31546507230498	2.85097675652283	-0.68995896340550
N	-3.51581248179050	-0.89125208191063	0.37675375704485
O	-4.29866129815588	-1.24060755311846	-0.49402227746778
O	-3.71273315066136	-0.98242064040420	1.58065838149574
C	2.34522465694228	0.32057856896756	-0.96584418562673
C	1.69075184317820	-0.84880234311135	1.09196983168394
C	3.51777158754424	-0.63917319311728	-1.07865526514221
H	2.64189474704585	1.19939295485499	-0.39738716834775
H	1.98258646689222	0.61758888780971	-1.94749196954267
C	2.89207211909215	-1.75626014530482	0.88662964993503
H	1.94499099561996	0.01257646368816	1.70305311705709
H	0.87287424979391	-1.39862118848238	1.55286451683677
H	4.35927671815470	-0.12713026049876	-1.54094335652470
H	3.24296465390968	-1.50156991764311	-1.69717664186542
H	3.28340010540188	-2.06630728613793	1.85341905446599
H	2.59464870744055	-2.64921475193178	0.32399585727696
N	1.22767752491333	-0.34258585126527	-0.23201992522973
O	3.94074331607002	-1.07817140830814	0.20438726929012
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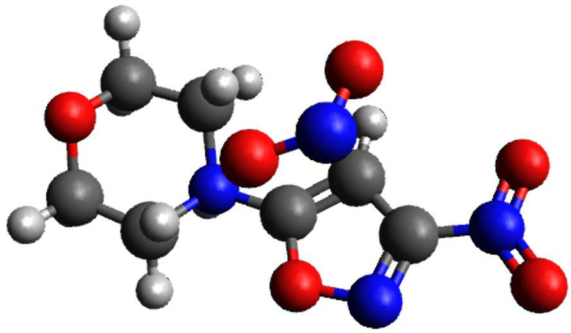
Pr1-H$^+$ + NO$_2^-$



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G_{298} = -943.10980071 Eh

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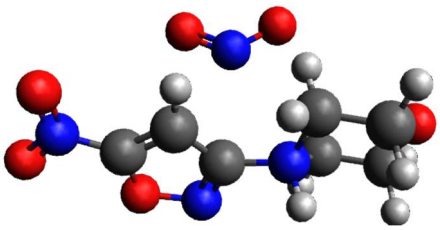
C	-0.14174038190255	-0.75426048866163	-0.26257946611839
H	-1.11955957516692	-0.68891413483468	1.70690762427785
N	-0.34030785577297	2.60310467081606	0.27177110334227
O	0.67781540559221	2.11000027211123	-0.28114604555749
O	-0.51757204478582	2.28847076424326	1.46716148831489
N	-3.56149299039983	0.10445425196009	0.22519817018922
O	-4.36372704969512	0.43468763824726	-0.62748431005071
O	-3.77687786926462	0.04385853937560	1.42358694080546
C	2.09746907581523	-0.49862614042829	-1.26218350611239
C	1.78120140430870	-0.57063411413299	1.22931610137749
C	3.56179094702508	-0.76389492649303	-0.99465034304372
H	1.87358663175838	0.56280374880945	-1.28850371471140
H	1.77231670236680	-0.98730331852305	-2.17515510247630
C	3.26878664481781	-0.83356003032055	1.31782708801870
H	1.54029871938179	0.49007402754135	1.25390185130646

H	1.24170572138148	-1.11230847738365	2.00138710742237
H	4.13936688702944	-0.27297191266531	-1.77524919869152
H	3.77541702494003	-1.83887604910248	-1.02116294397239
H	3.63311981932090	-0.39874020872952	2.24642019289696
H	3.47379947616996	-1.91055957294455	1.32603630264061
N	1.25829647661757	-1.06800801688259	-0.11770974643375
O	3.97000439190156	-0.21566772976541	0.24937053197312
H	1.36174104901052	-2.08877526168890	-0.13517126338759
O	-0.57959815909326	-0.54658859667364	-1.51548558629230
N	-1.90944767858338	-0.20338855572104	-1.47107421906650

Pr2-H^++NO_2^-



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ZPE = 0.19860373 Eh

G_{298} = -943.04891206 Eh

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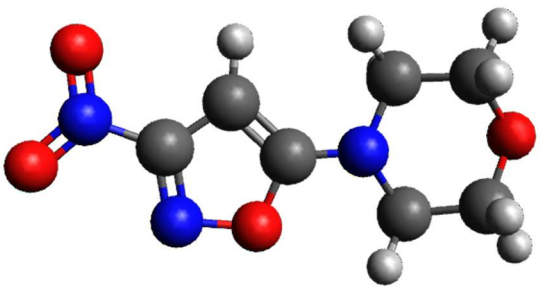
C	-0.21688002994065	-0.56593585670432	-0.48097089663057
O	-2.05407013274792	-0.24949773855658	-1.53104898846902
H	-1.11596663041806	-0.52454817995023	1.59210603538584
N	-0.69239439377619	-0.46041526661668	-1.69189744390572
N	0.23783868793182	1.80012222396474	0.76597763254706
O	1.36992448530655	2.28546607951597	1.00539653596667
O	-0.76640512392446	2.49479665242675	0.86444018028981

N	-3.66926909818503	-0.03278066946826	0.21511551467479
O	-4.49455834195756	0.20938585323681	-0.64716135772613
O	-3.86718581938946	-0.10103009489299	1.41946053663216
C	2.10811812220356	0.12547447413926	-1.12855123348529
C	1.73172126514702	-0.94161077392741	1.04660535843953
C	3.51925720906391	-0.43016914435240	-1.09366064790159
H	2.02523223776778	1.07149333721387	-0.59315294311141
H	1.71545752784466	0.20374316810939	-2.13838081998735
C	3.16749677851641	-1.43629746631763	0.99404167555357
H	1.66354395870889	0.06674818371659	1.45166572619281
H	1.09662546848858	-1.63208323029316	1.59777451022953
H	4.18697506071094	0.27143232895217	-1.58931453294633
H	3.57459135593235	-1.39025060295904	-1.63133608429982
H	3.56975923109718	-1.44624307271987	2.00553216263133
H	3.20596699223797	-2.46523657547957	0.60079555575253
N	1.21272362495182	-0.85051555168482	-0.36774758939027
O	3.99502876370397	-0.59095953641007	0.22759813598332
H	1.34817183430637	-1.76738769578485	-0.80635168901544

Pr1 (2zg)



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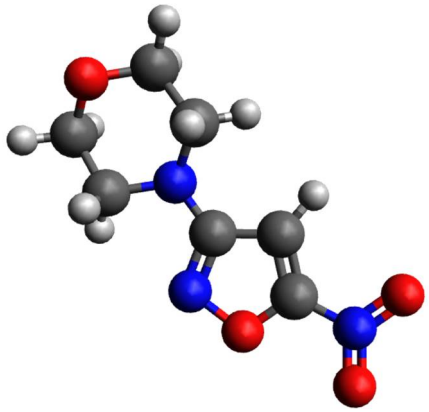
ZPE = 0.17511634 Eh

G_{298} = -737.35055135 Eh

C	-2.27632376156043	-0.38877604101243	-0.12066734030826
C	-1.15906713992489	-0.49496733600922	0.71357992506136
C	-0.11689311312173	-0.50913774002167	-0.19440033331559
H	-1.12835359993024	-0.54843518604845	1.78436396924500
N	-3.66598512583114	-0.32540593495601	0.31528205343988
O	-4.53880216227591	-0.28648676516622	-0.53387377378501
O	-3.86042613571321	-0.31568616810092	1.52106581418306
C	2.10053053781625	-0.20053570007131	-1.15142293284033
C	1.76216472190547	-0.49602653170407	1.29274015602986
C	3.48041156301356	-0.80491723622006	-0.95909158128172
H	2.16820408308771	0.89259611976623	-1.16823773129949
H	1.68942836423875	-0.54031169982579	-2.09876254035119
C	3.15156690849435	-1.09900593477598	1.34135640632076
H	1.79818563305879	0.55955546670880	1.58289220303094
H	1.11583505730391	-1.02755908609999	1.98872069886293
H	4.17199421131740	-0.36082183025796	-1.67250449897427
H	3.44566052969625	-1.88865325137932	-1.12321533510536
H	3.60944423586434	-0.88109153678096	2.30483672444276
H	3.09565758931874	-2.18554694618240	1.20424582236021
N	1.21217948211096	-0.62265972993731	-0.05941989980447
O	3.99249661995562	-0.53389873406587	0.34230439032418
O	-0.62078305751533	-0.40129895251166	-1.44981074139148
N	-2.01801544130921	-0.33069924534742	-1.40339145484378

Pr2



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ZPE = 0.17525233 Eh

G_{298} = -737.34492779 Eh

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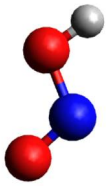
C	-1.16247751142655	-0.26986038684354	0.76680549115556
C	-0.17169218618667	-0.64480322368140	-0.19949660789894
O	-2.12526562585528	-0.81582677737064	-1.17304950370218
H	-1.03689874958947	0.04473587373618	1.78526519278688
N	-0.73678189509338	-0.95579616156894	-1.36167373314174
N	-3.66996409861052	-0.15043664330635	0.48677455343376
O	-4.54992757325882	-0.28853481678503	-0.34801256073745
O	-3.84100235725828	0.19630410917287	1.64682723273224
C	2.00307980302733	-0.96146320787640	-1.18764469896723
C	1.75786562159052	0.23519694967665	0.95592984552663
C	3.42540787010303	-1.28036838201892	-0.76760466496049
H	1.99492356053142	-0.08747148365252	-1.85067513373195
H	1.58630845352685	-1.80579455122387	-1.73476233665919
C	3.19647463176112	-0.14144585660641	1.25668319935255
H	1.72067730592229	1.25377268262302	0.55097235781112
H	1.18646047855105	0.20737482658103	1.88151062624458

H	4.06168839552184	-1.34692977383374	-1.64795518127267
H	3.45655347321700	-2.23674895928946	-0.23194775248642
H	3.65776499109857	0.63701077608331	1.86214489463397
H	3.23253817701791	-1.08979589768921	1.80532859040217
N	1.17381256463922	-0.70683265096861	-0.00797057965875
O	3.96329177883366	-0.25569578776626	0.06278158037347

HNO_2



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ZPE = 0.02008253 Eh

G_{298} = -205.80913549 Eh

N	0.78692669316288	3.27353197244875	-0.63587835117346
O	0.39621643579425	2.77272216688187	0.60617338450858
O	1.00212384098457	2.40635814783791	-1.39684529056083
H	0.24515303005829	3.57002771283147	1.14326025722572

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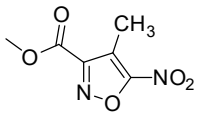
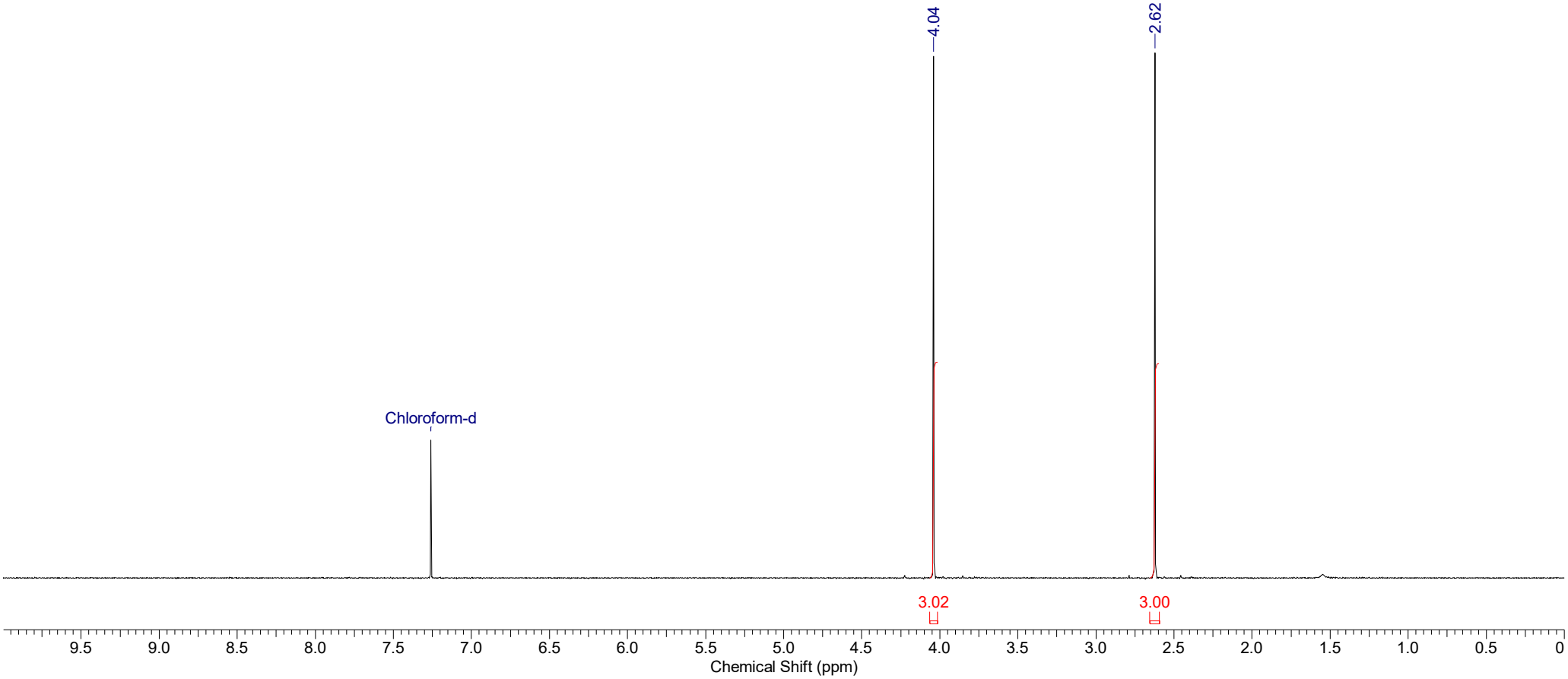
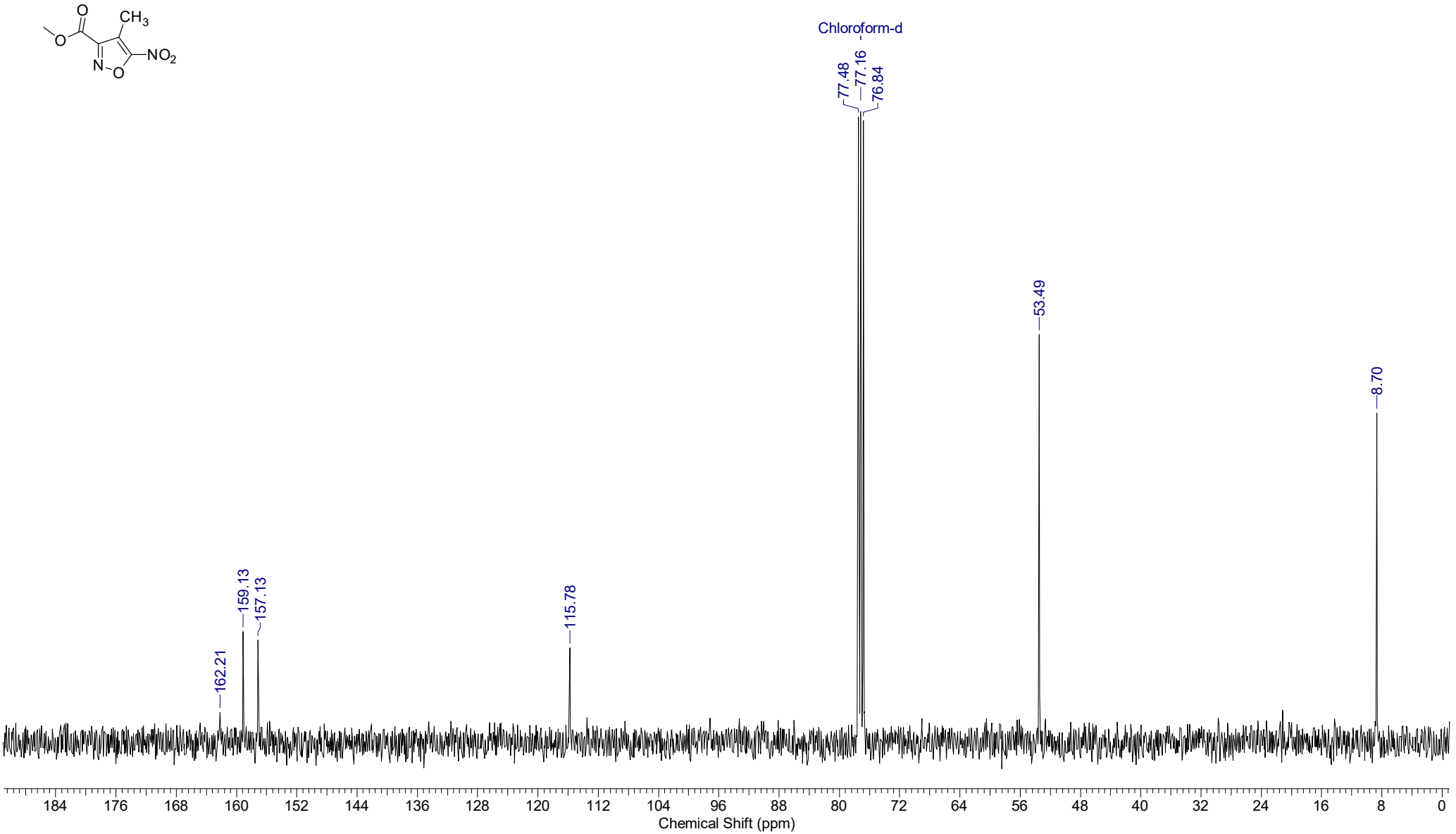
6. Copies of NMR Spectra

Methyl 4-methyl-5-nitroisoxazole-3-carboxylate **1g** (^{1}H NMR)

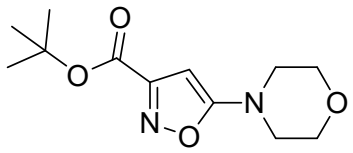


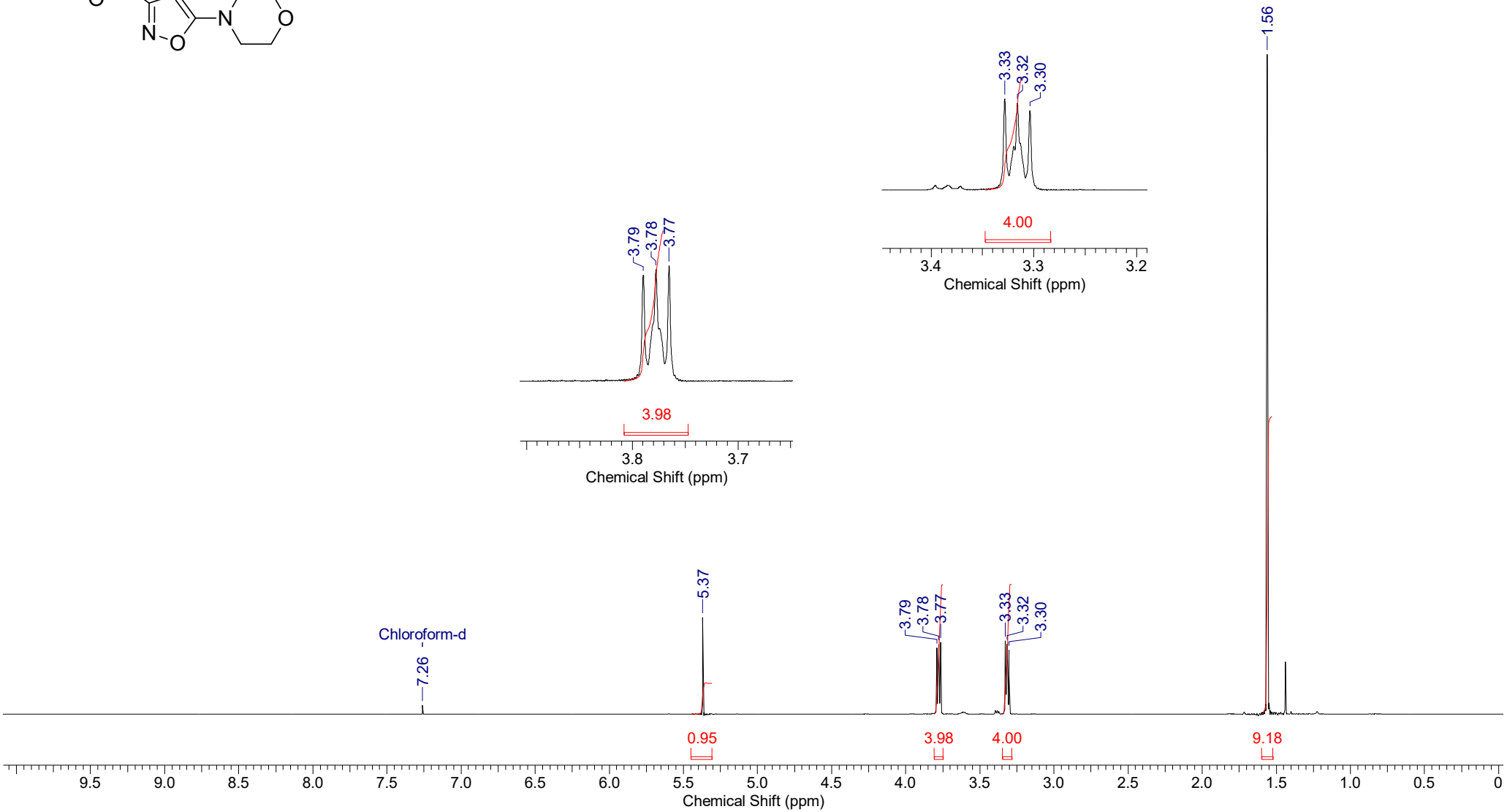


Methyl 4-methyl-5-nitroisoxazole-3-carboxylate **1g** (^{13}C NMR)

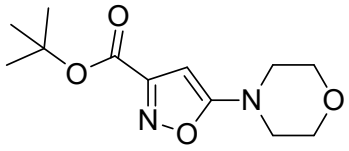


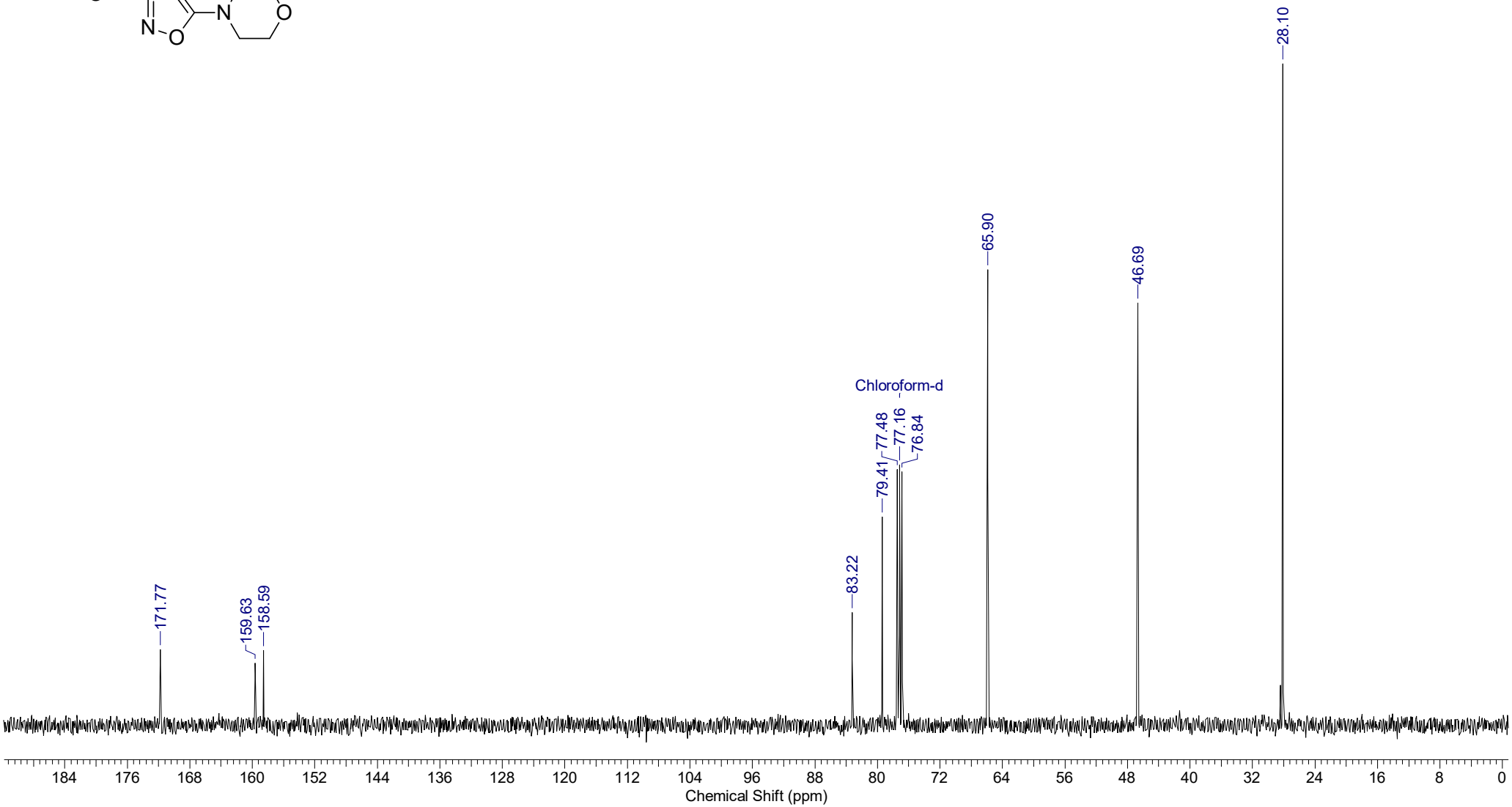
tert-Butyl 5-morpholinoisoxazole-3-carboxylate **2a** (^{1}H NMR)



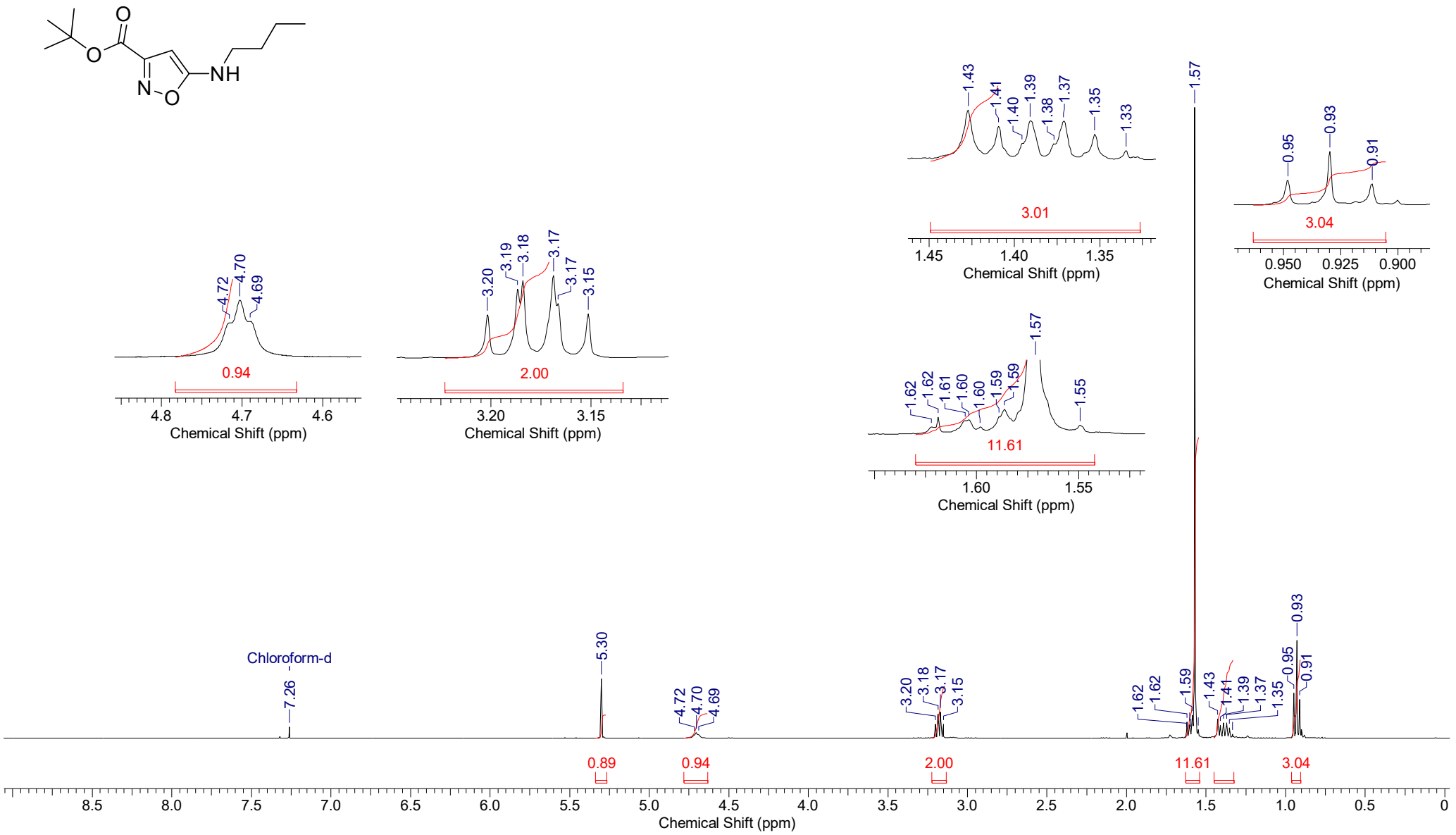


tert-Butyl 5-morpholinoisoxazole-3-carboxylate **2a** (^{13}C NMR)





tert-Butyl 5-(butylamino)isoxazole-3-carboxylate **2b** (^{1}H NMR)



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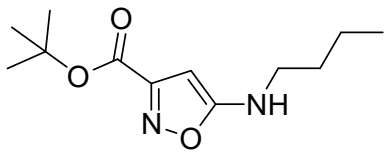
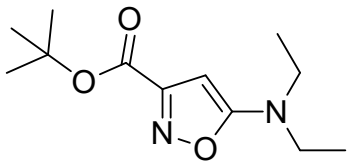
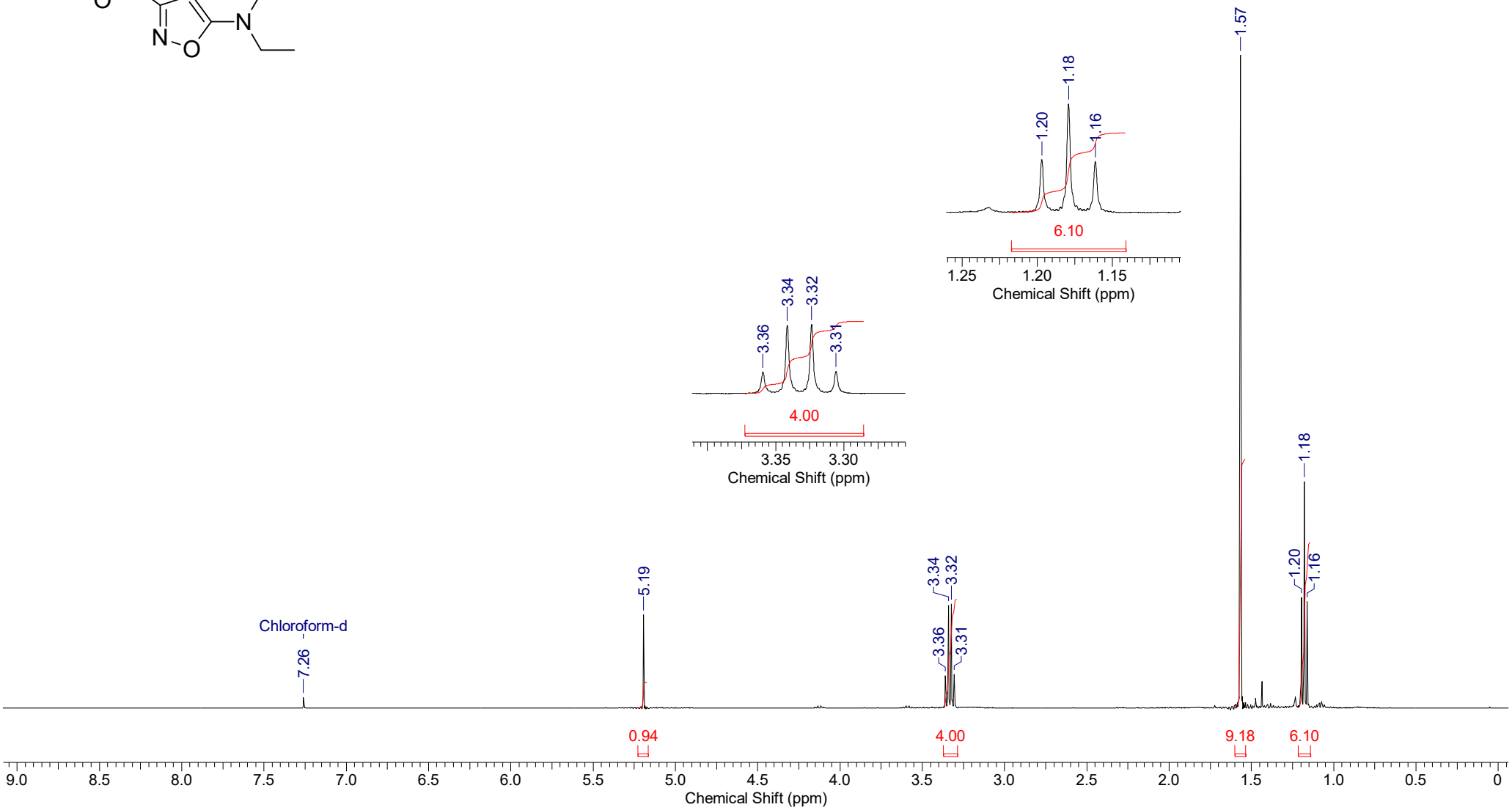
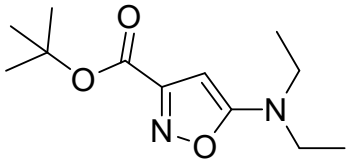


tert-Butyl 5-(diethylamino)isoxazole-3-carboxylate **2c** (^{1}H NMR)





tert-Butyl 5-(diethylamino)isoxazole-3-carboxylate **2c** (^{13}C NMR)



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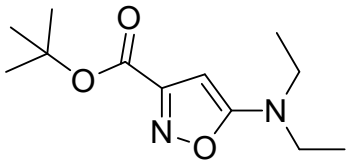
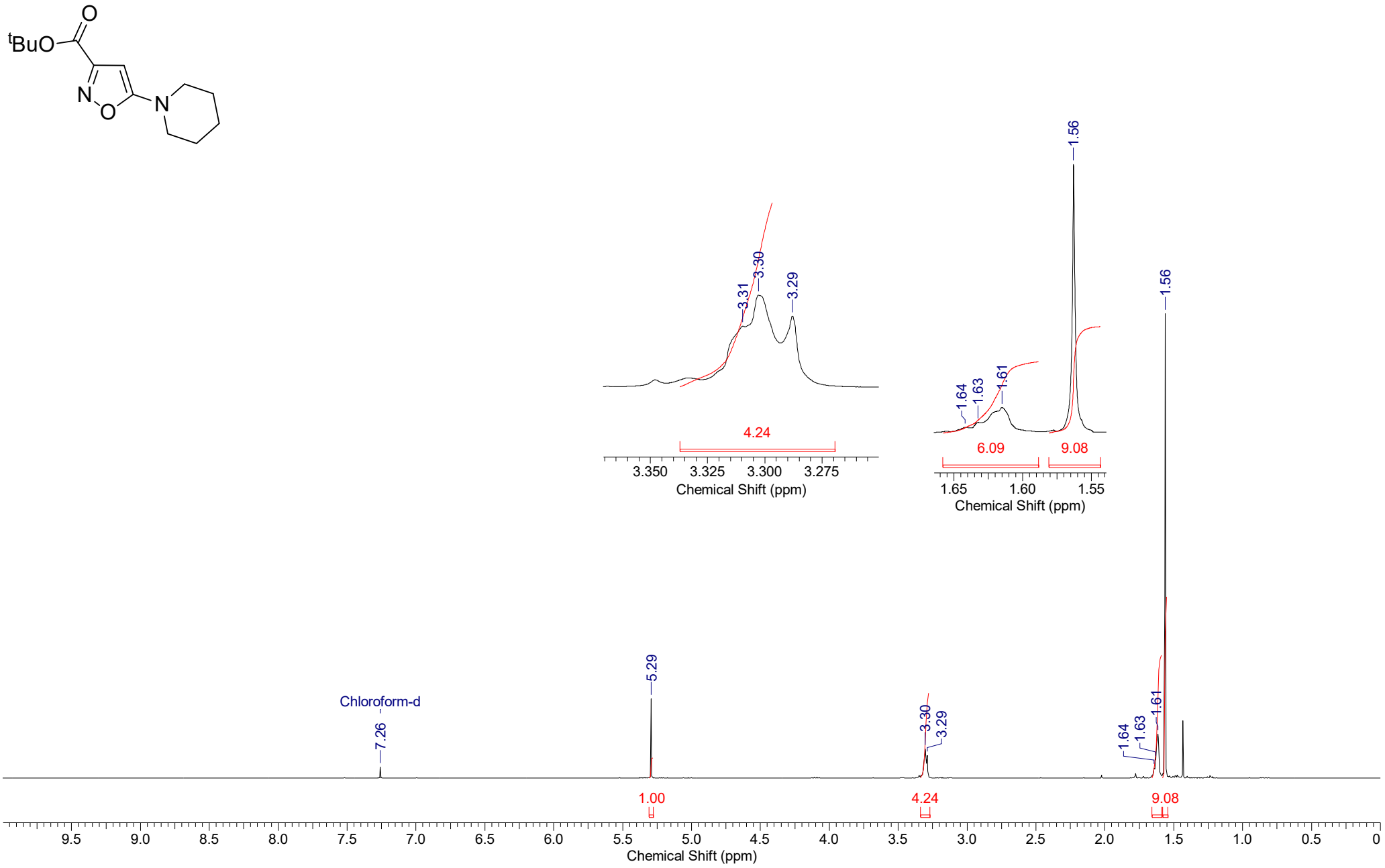


tert-Butyl 5-piperidine-1-ylisoxazole-3-carboxylate **2d** (^{1}H NMR)



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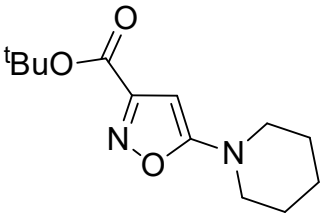

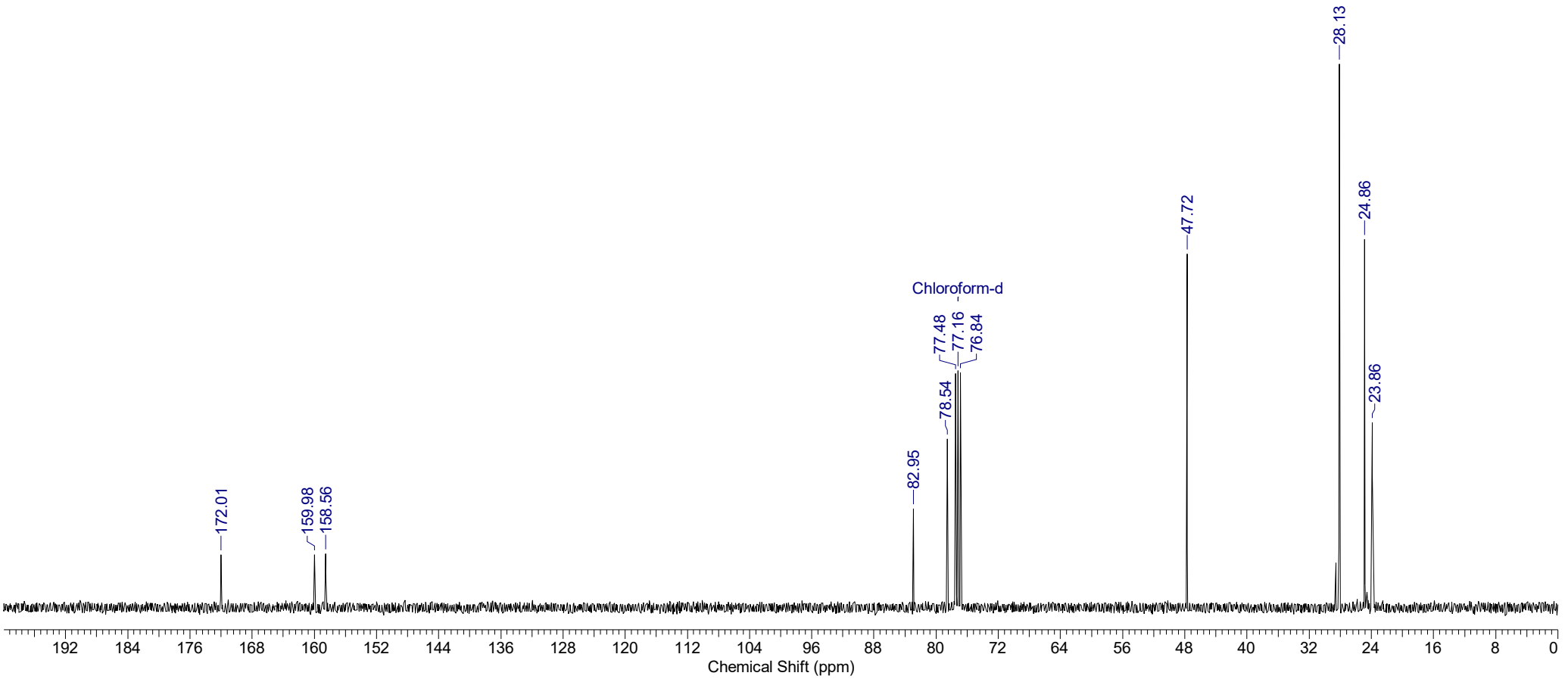

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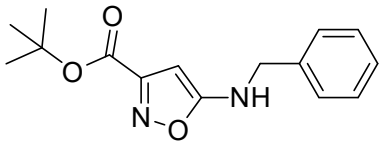

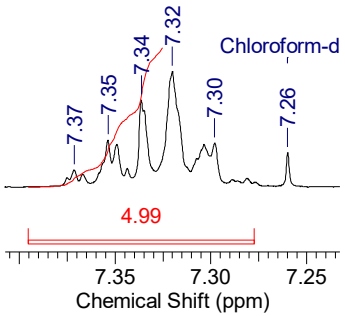

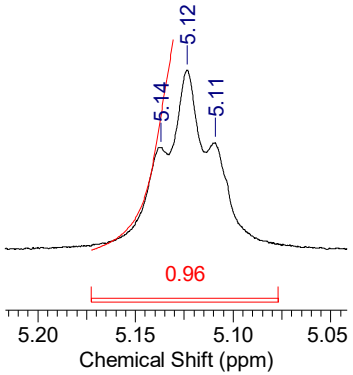

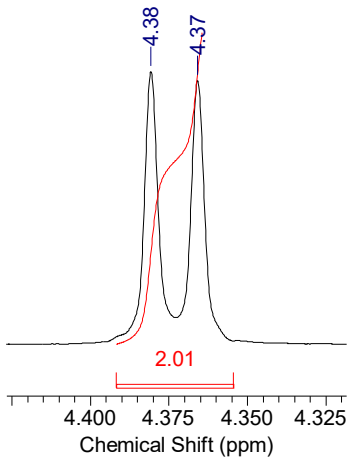

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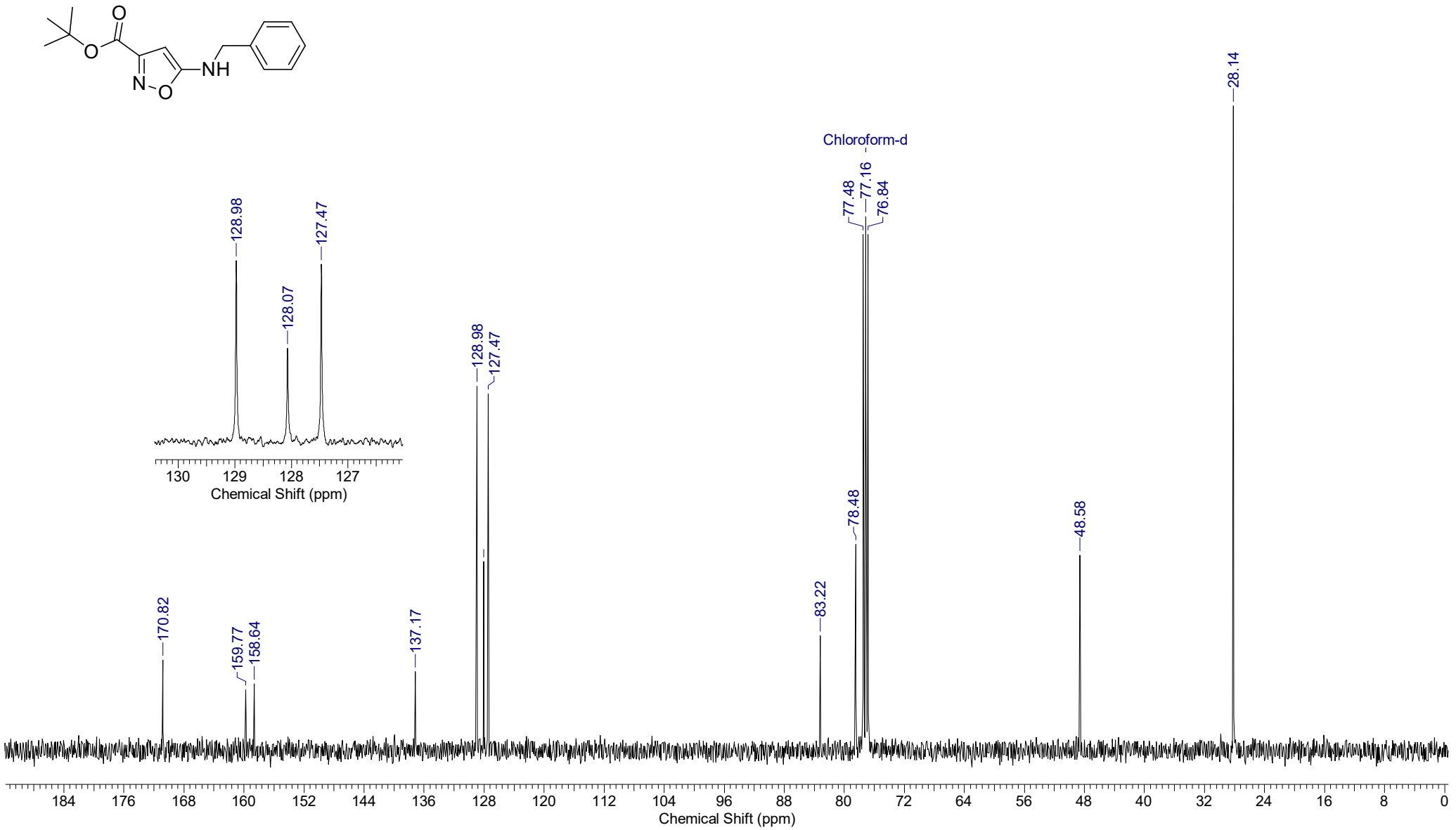

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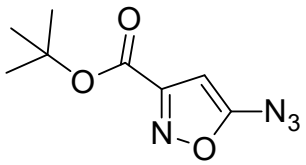

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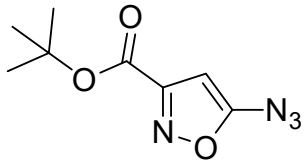
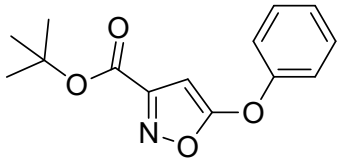


tert-Butyl 5-phenoxyisoxazole-3-carboxylate **2g** (^{1}H NMR)



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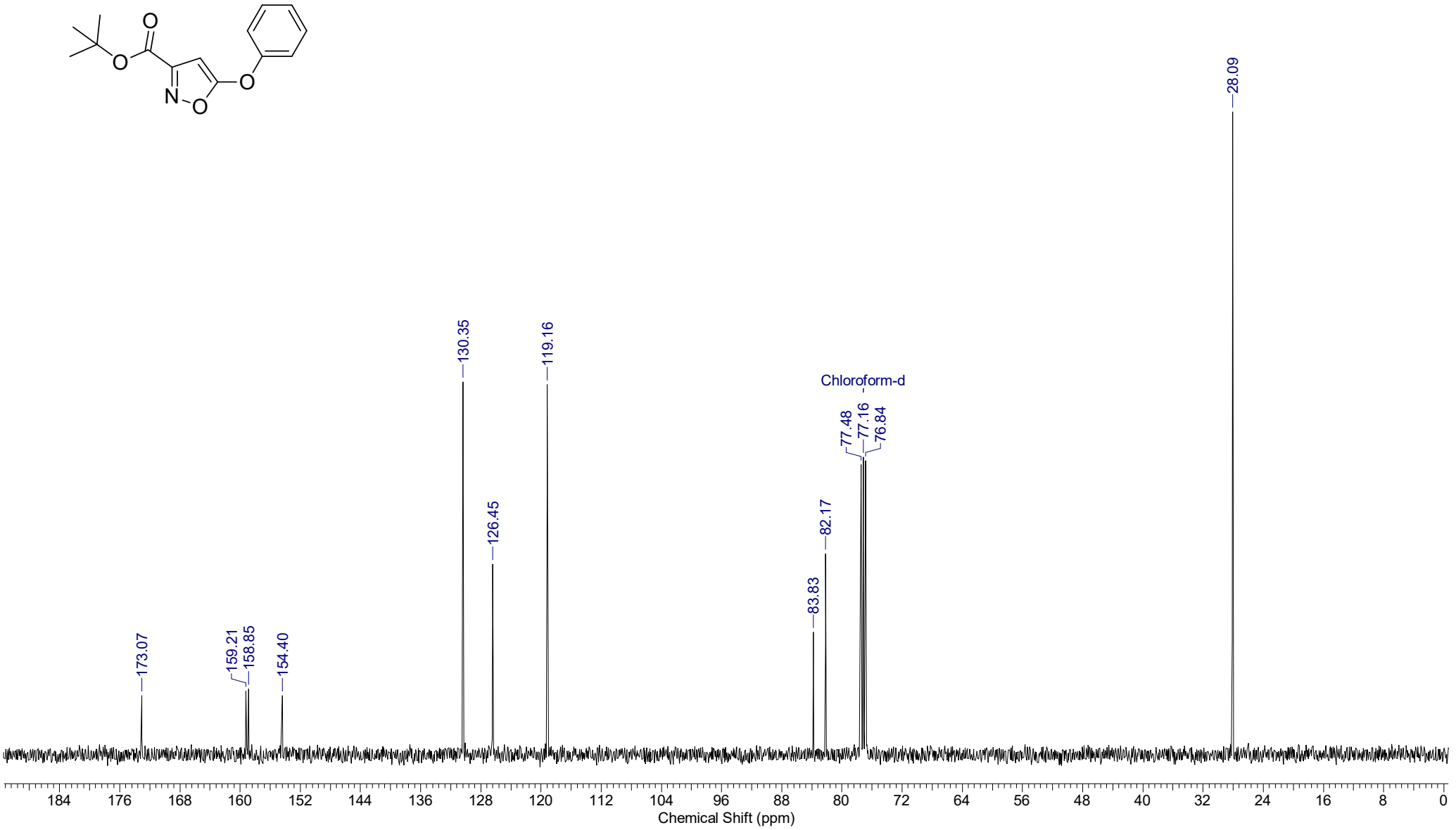

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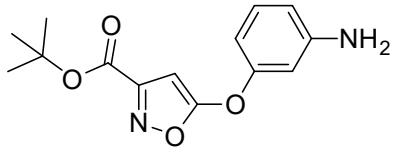
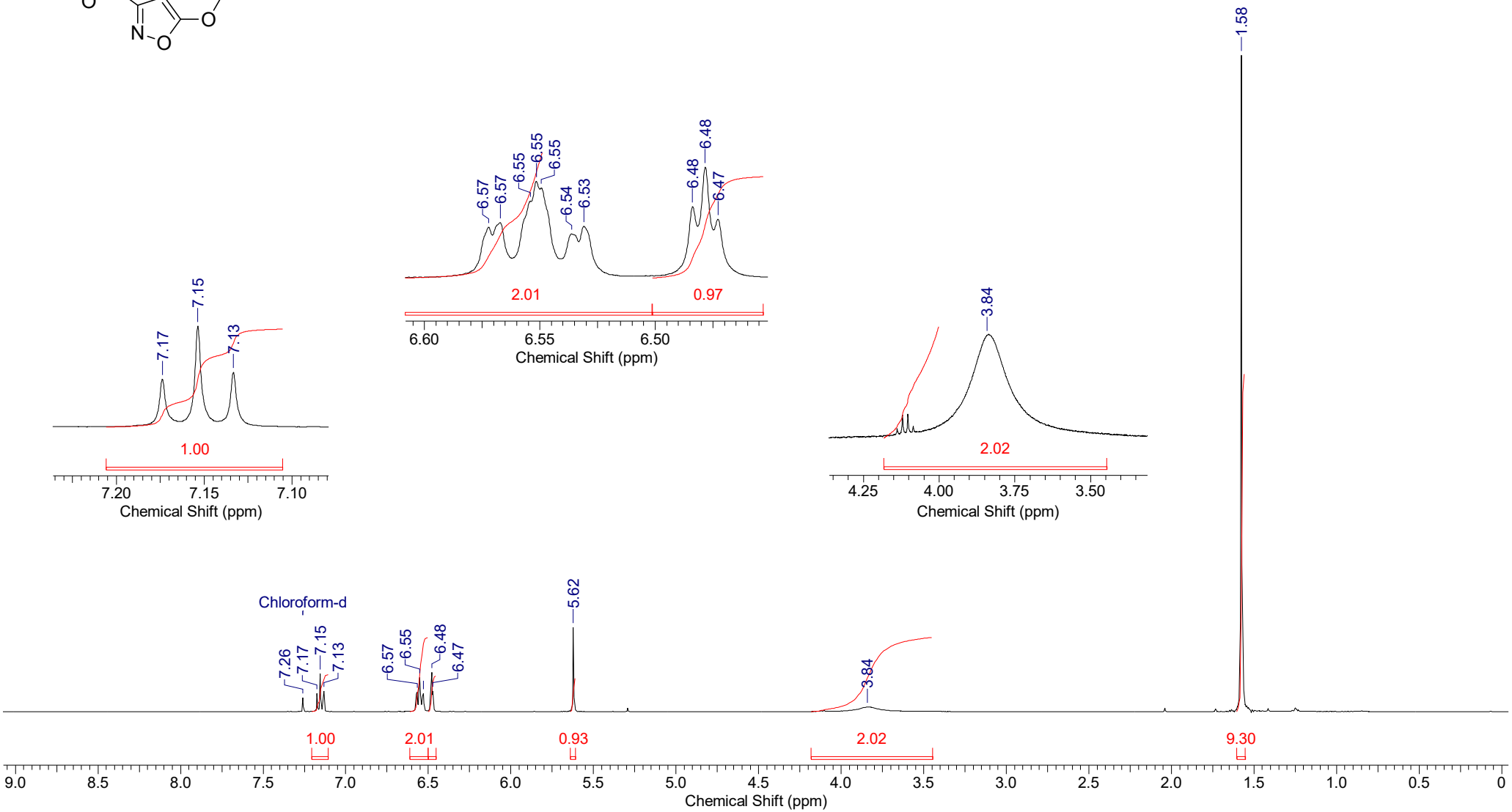
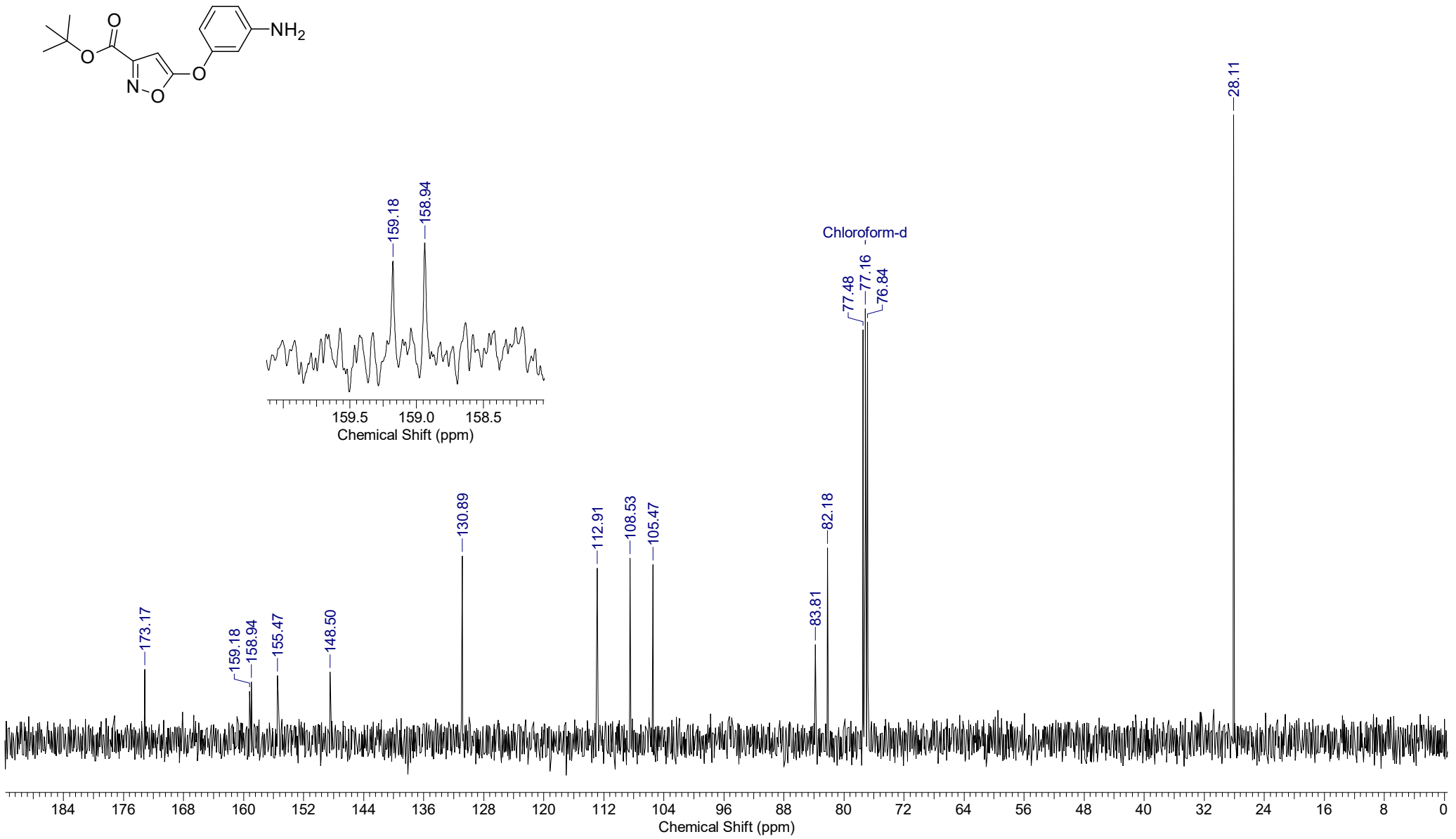




tert-Butyl 5-(3-aminophenoxy)isoxazole-3-carboxylate **2h** (^{13}C NMR)



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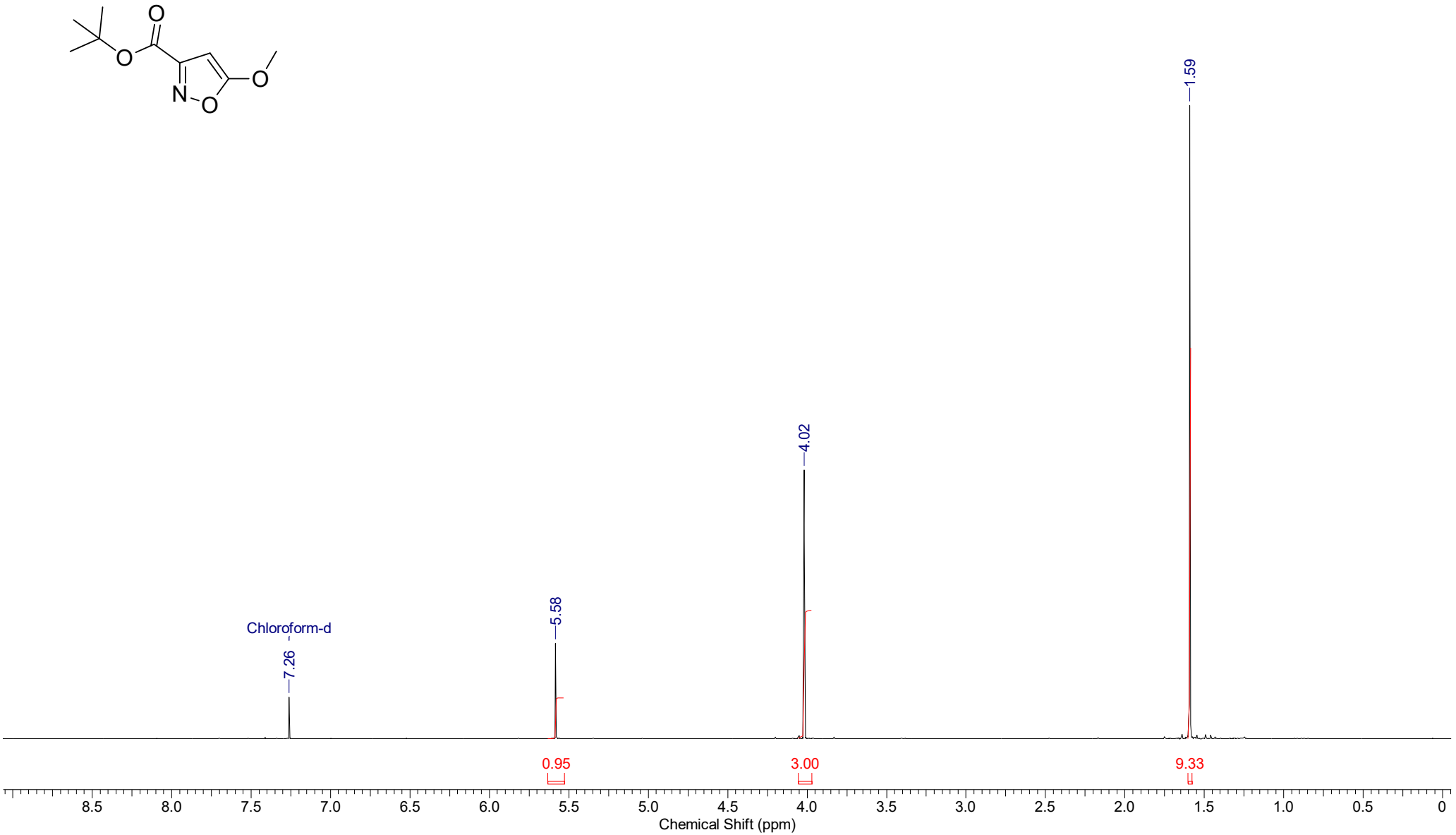
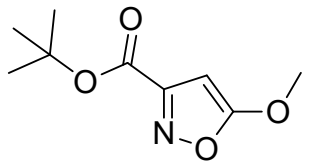
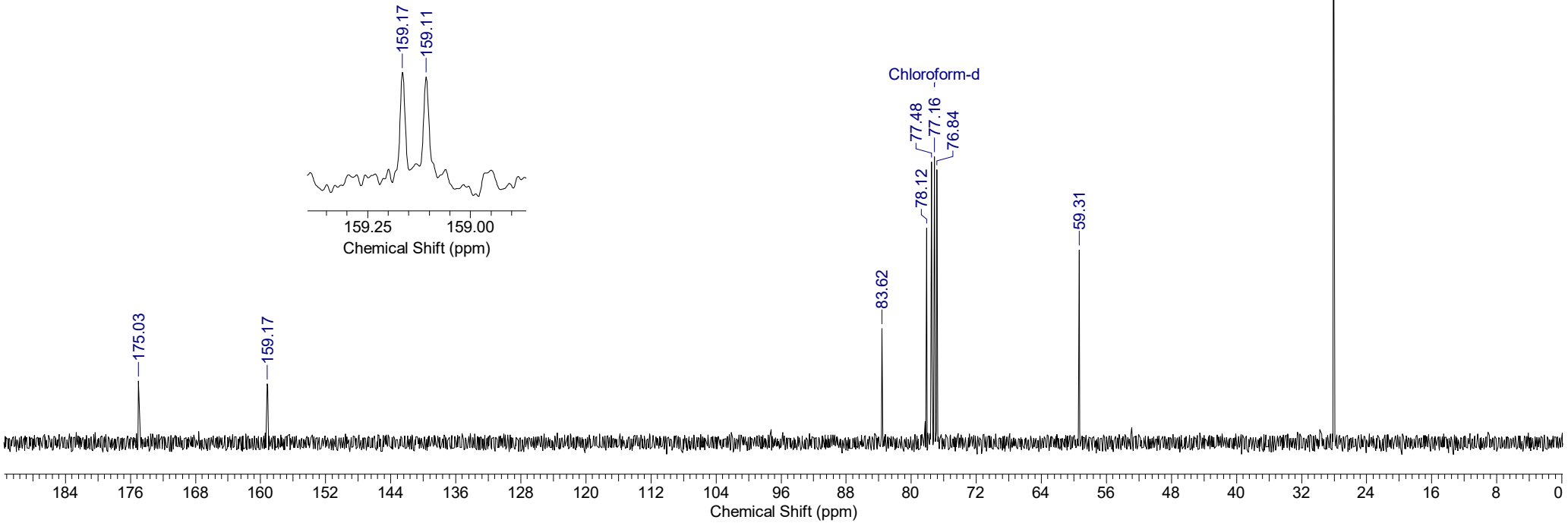
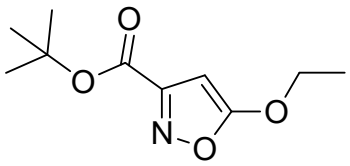


tert-Butyl 5-methoxyisoxazole-3-carboxylate **2i** (^{13}C NMR)

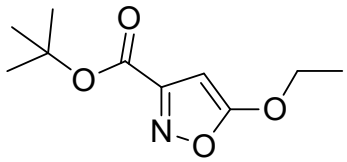




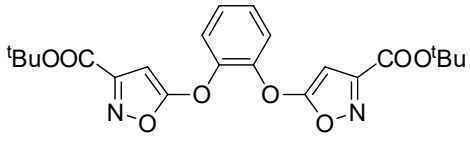
tert-Butyl 5-ethoxyisoxazole-3-carboxylate **2j** (^{1}H NMR)



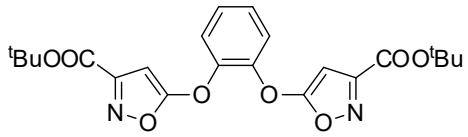
tert-Butyl 5-ethoxyisoxazole-3-carboxylate **2j** (^{1}H NMR)

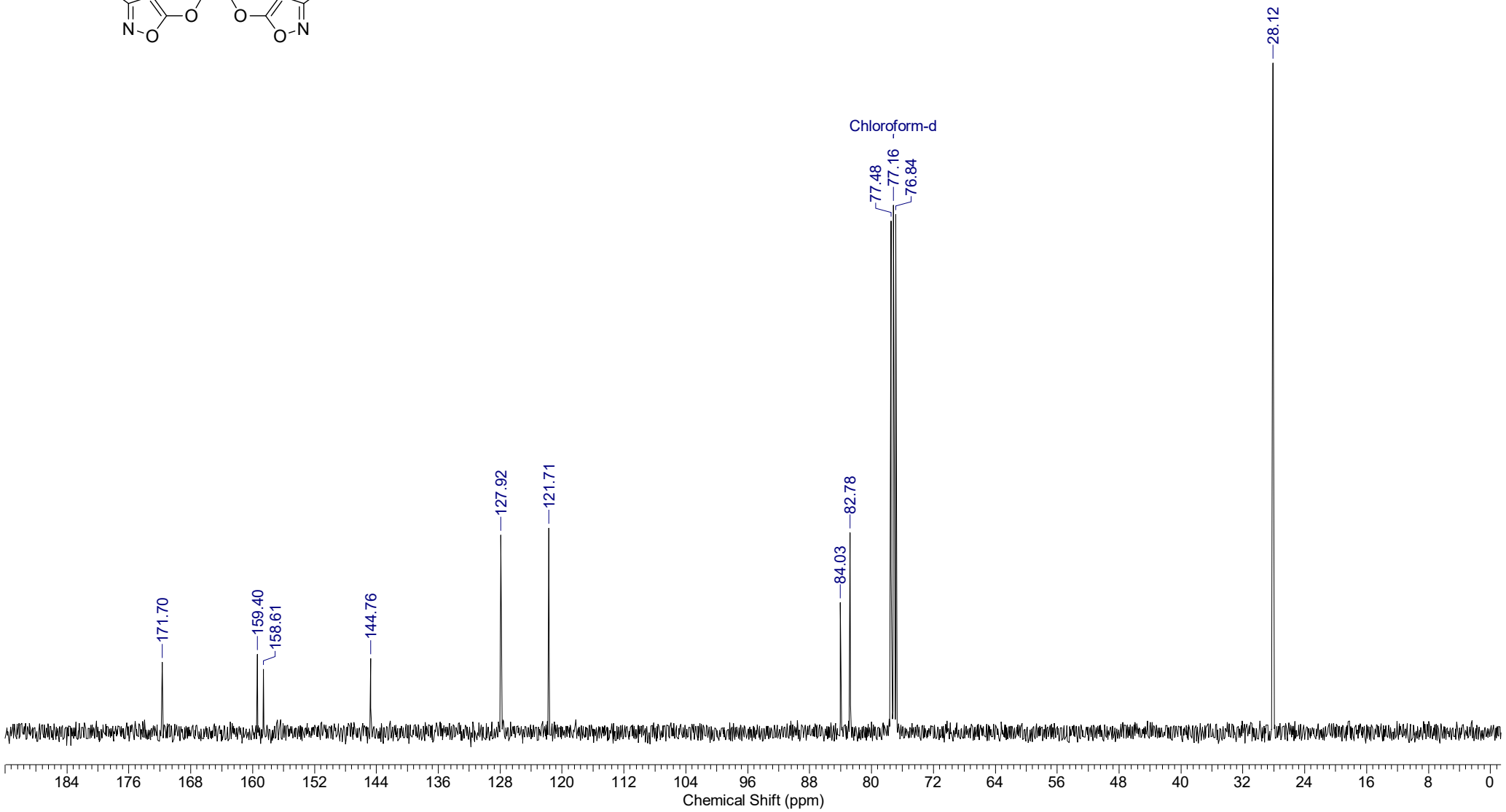


Di-tert-butyl 5,5'-[1,2-phenylenebis(oxy)]diisoxazole-3-carboxylate **2k** (^{1}H NMR)

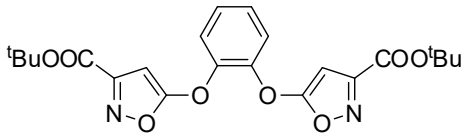


Di-tert-butyl 5,5'-[1,2-phenylenebis(oxy)]diisoxazole-3-carboxylate **2k** (^{13}C NMR)

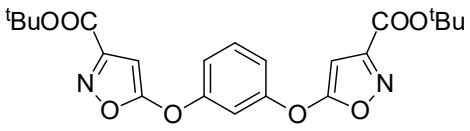




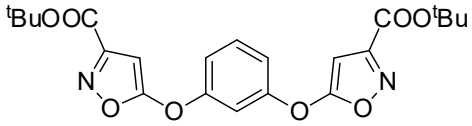
Di-tert-butyl 5,5'-[1,2-phenylenebis(oxy)]diisoxazole-3-carboxylate **2k** (APT)



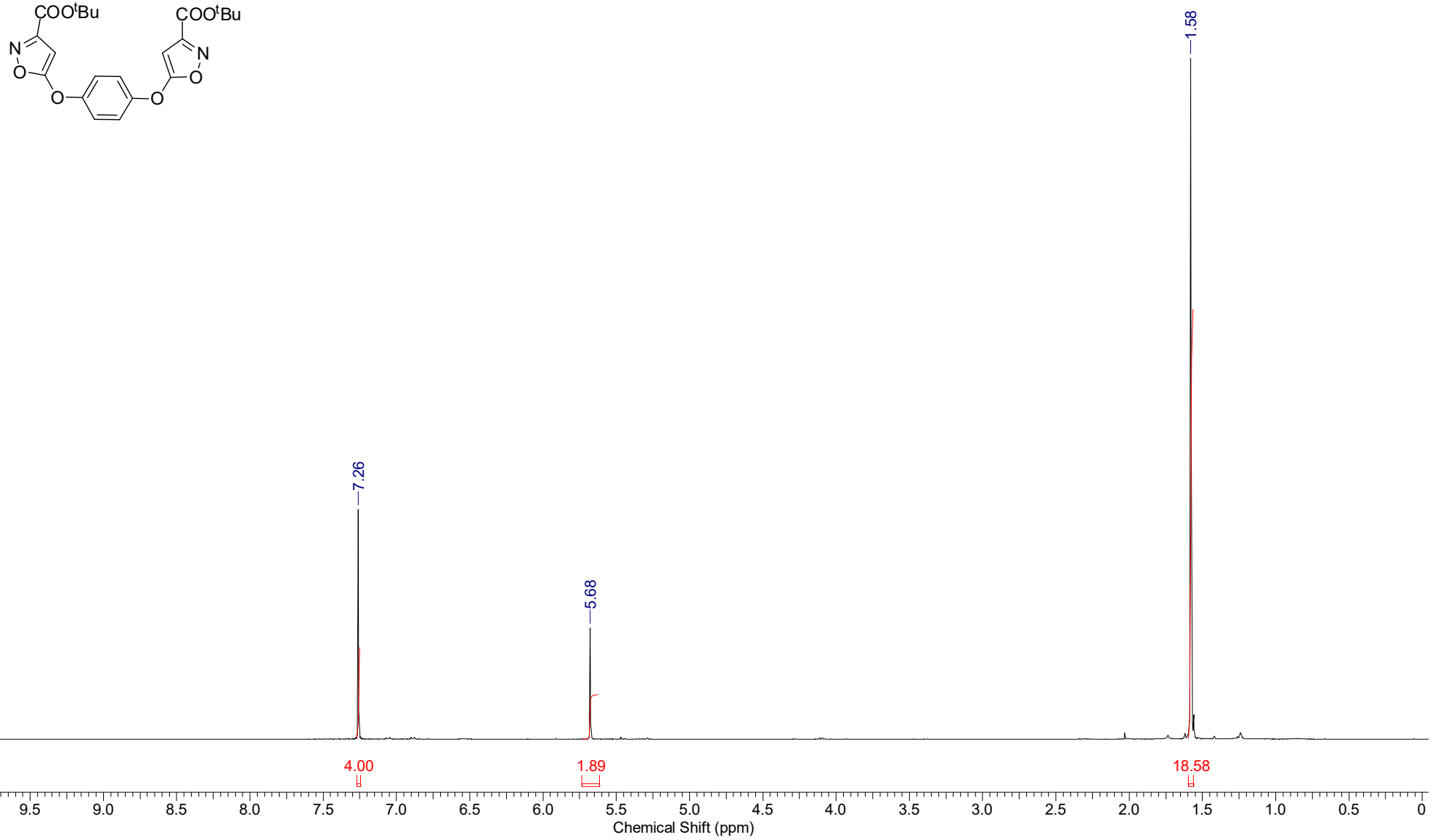
Di-tert-butyl 5,5'-[1,3-phenylenebis(oxy)]diisoxazole-3-carboxylate **2l** (^{1}H NMR)



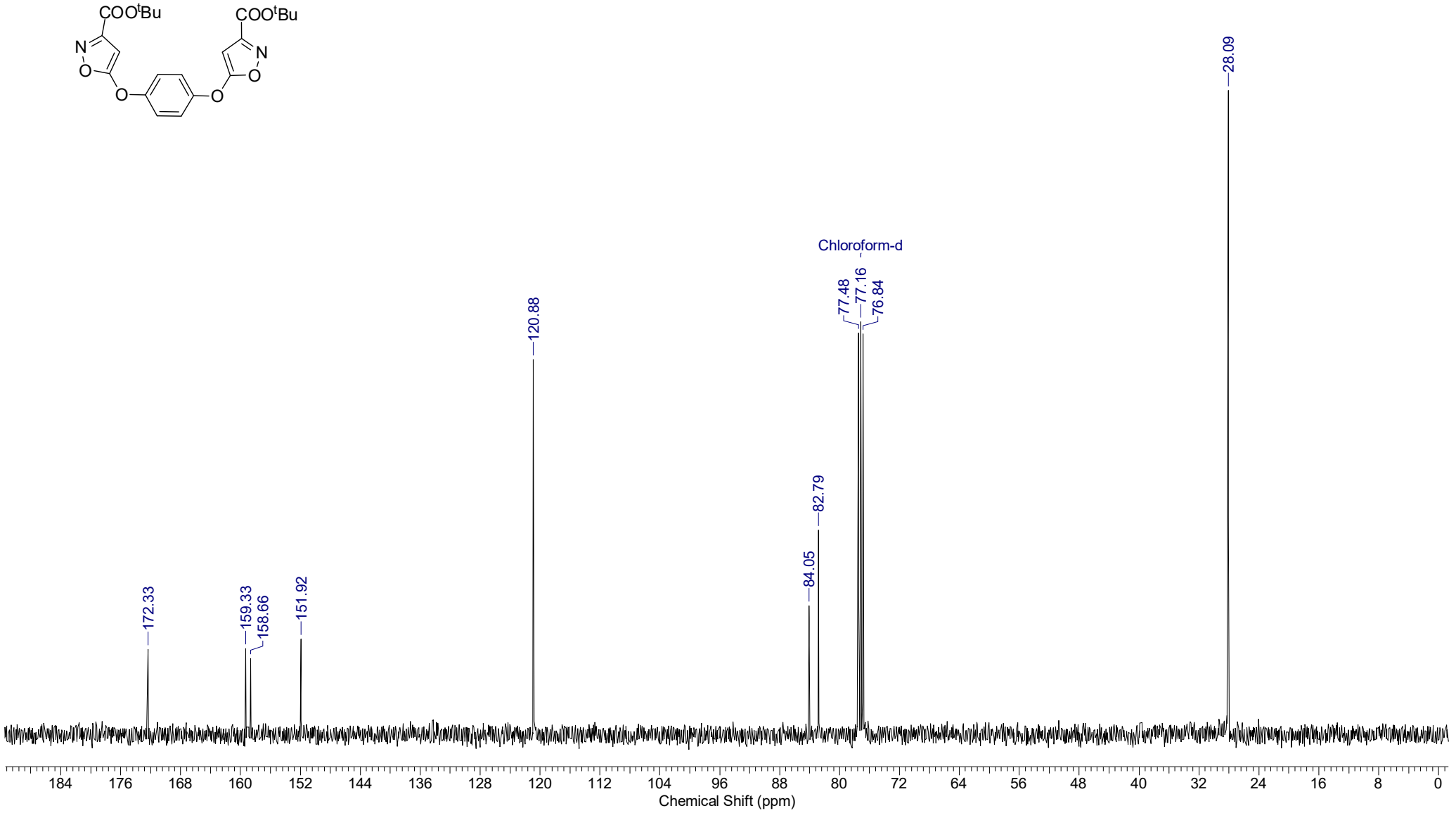
Di-tert-butyl 5,5'-[1,3-phenylenebis(oxy)]diisoxazole-3-carboxylate **2l** (^{13}C NMR)



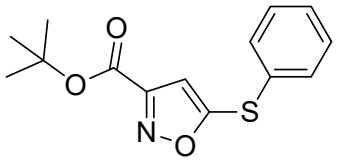
Di-tert-butyl 5,5'-[1,4-phenylenebis(oxy)]diisoxazole-3-carboxylate **2m** (^{1}H NMR)



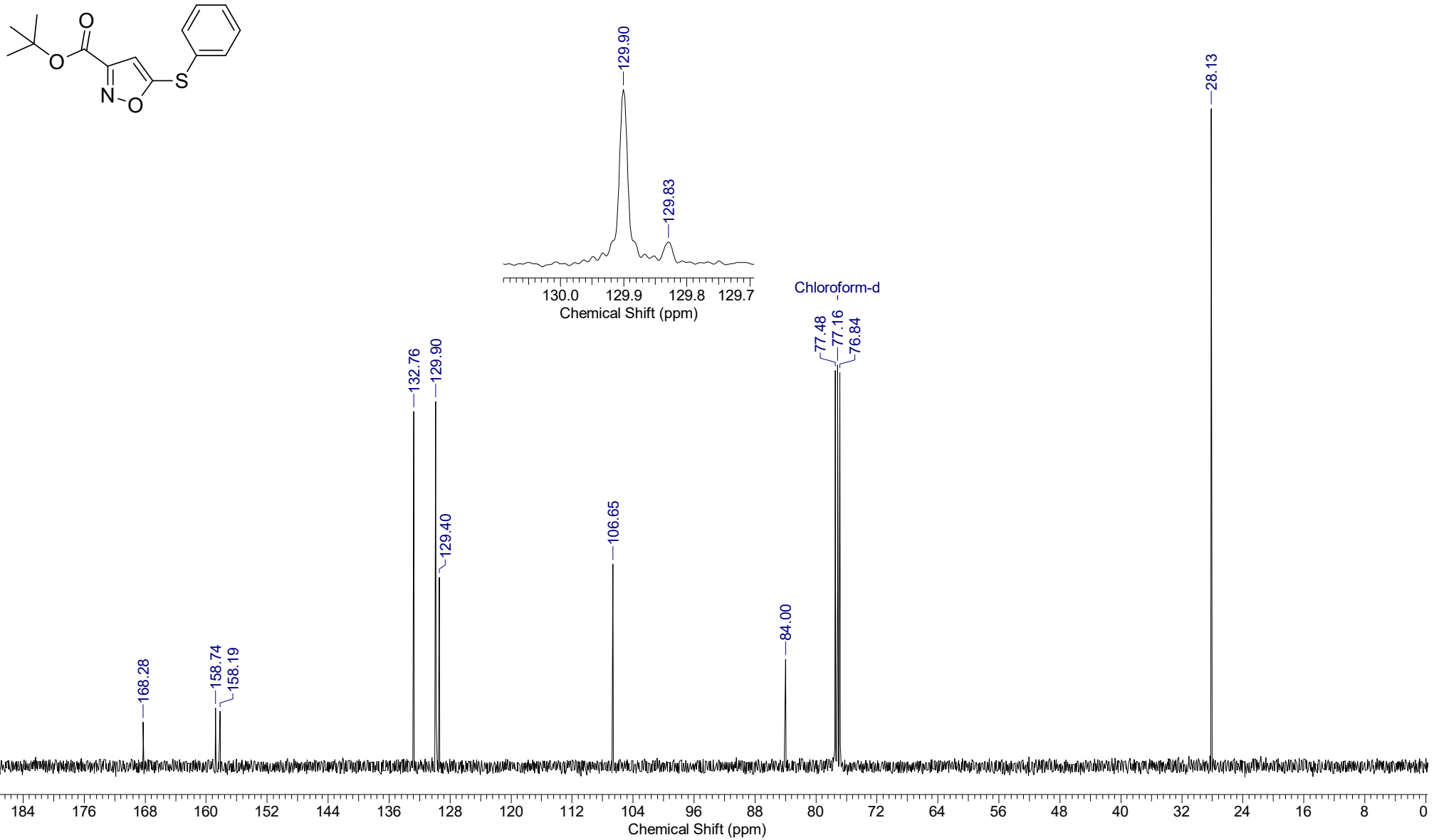
Di-tert-butyl 5,5'-[1,4-phenylenebis(oxy)]diisoxazole-3-carboxylate **2m** (^{13}C NMR)



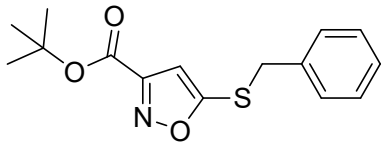
tert-Butyl 5-(phenylsulfanyl)isoxazole-3-carboxylate **2n** (^{1}H NMR)

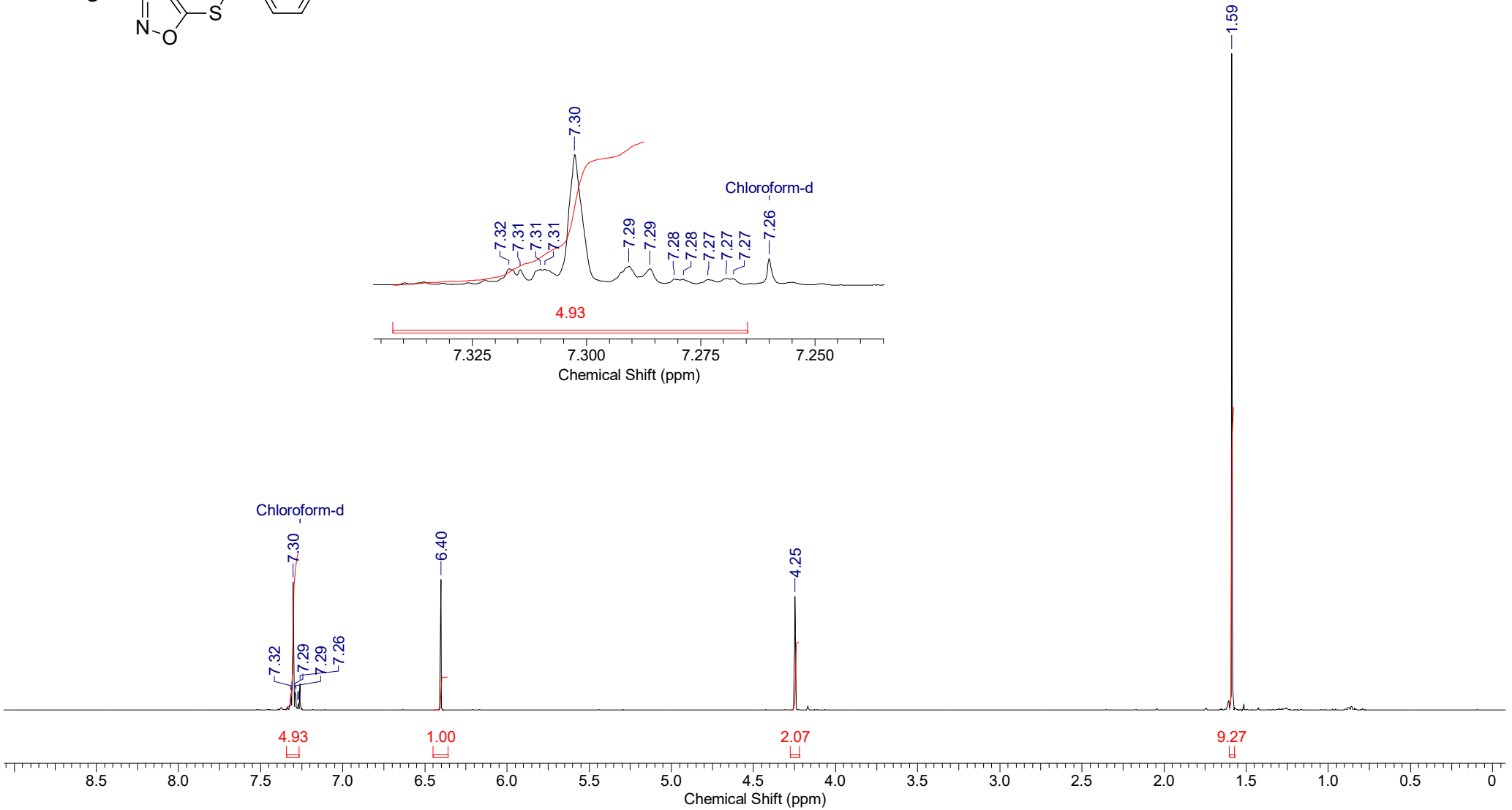


tert-Butyl 5-(phenylsulfanyl)isoxazole-3-carboxylate **2n** (^{13}C NMR)

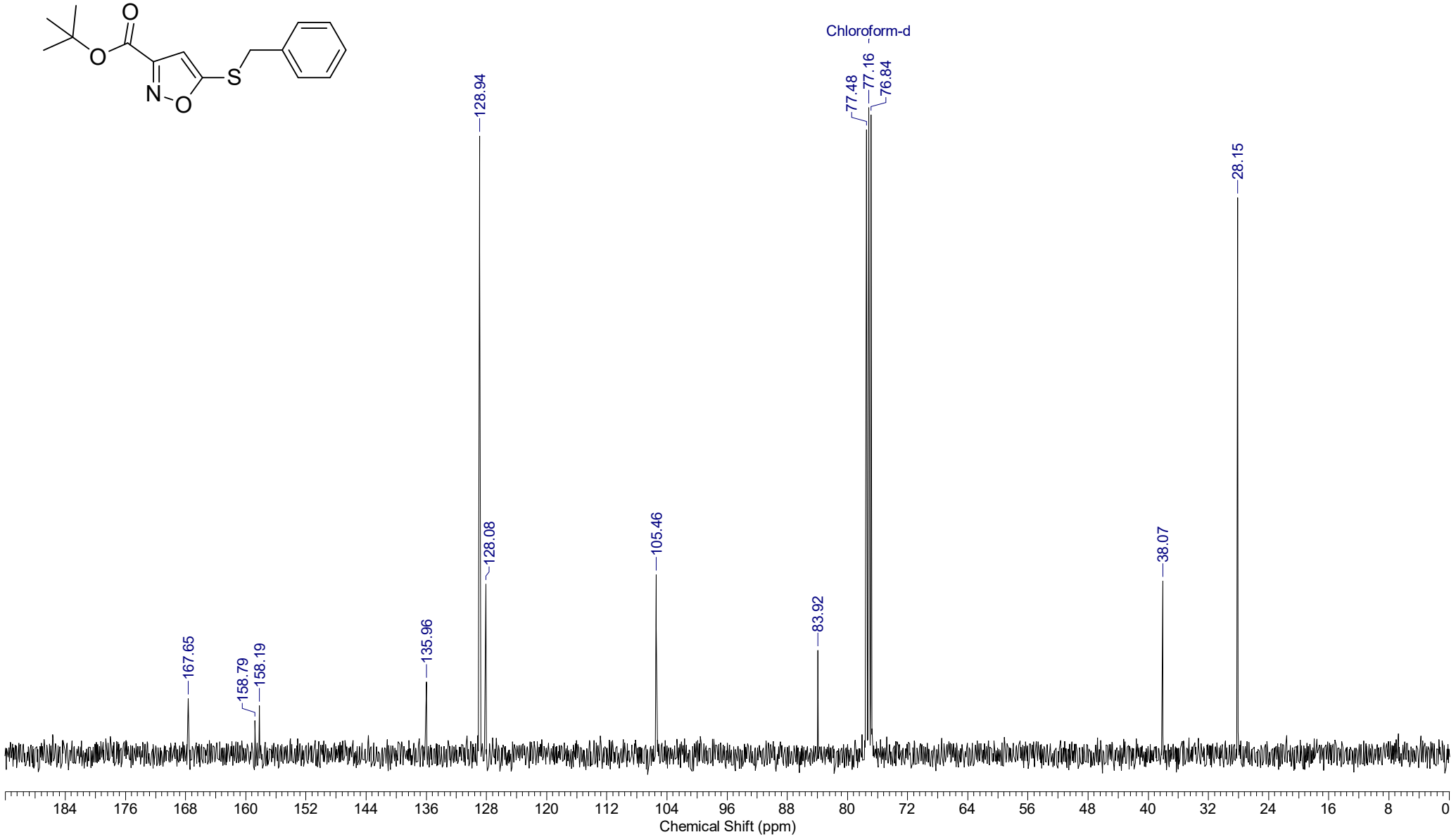


tert-Butyl 5-(benzylsulfanyl)isoxazole-3-carboxylate **2o** (^{1}H NMR)

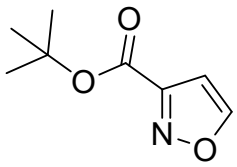




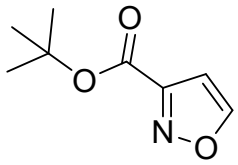
tert-Butyl 5-(benzylsulfanyl)isoxazole-3-carboxylate **2o** (^{13}C NMR)



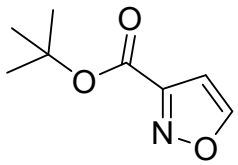
tert-Butyl isoxazole-3-carboxylate **2p** (^{1}H NMR)

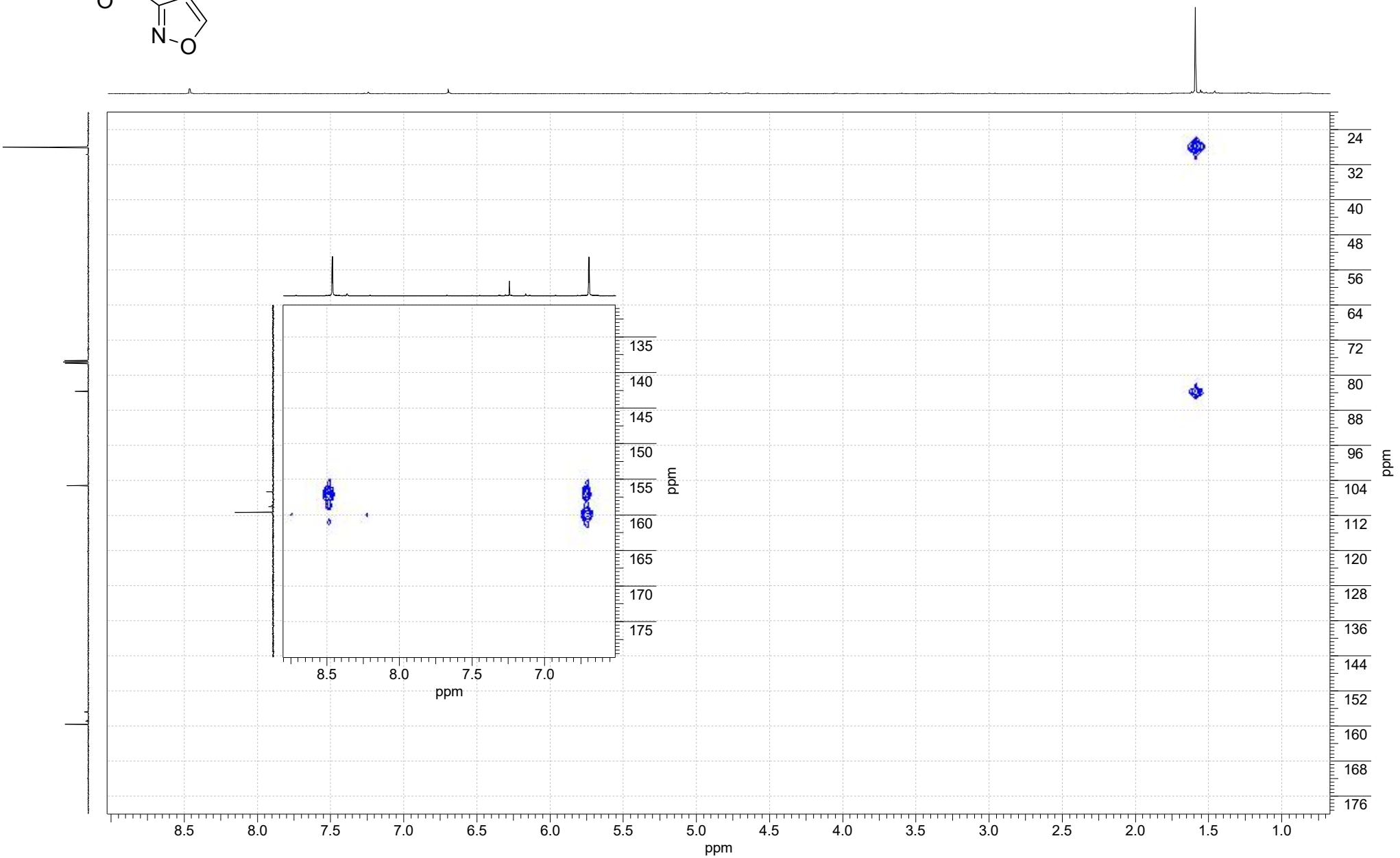


tert-Butyl isoxazole-3-carboxylate **2p** (^{13}C NMR)

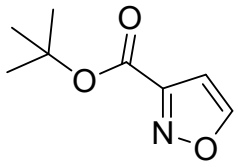


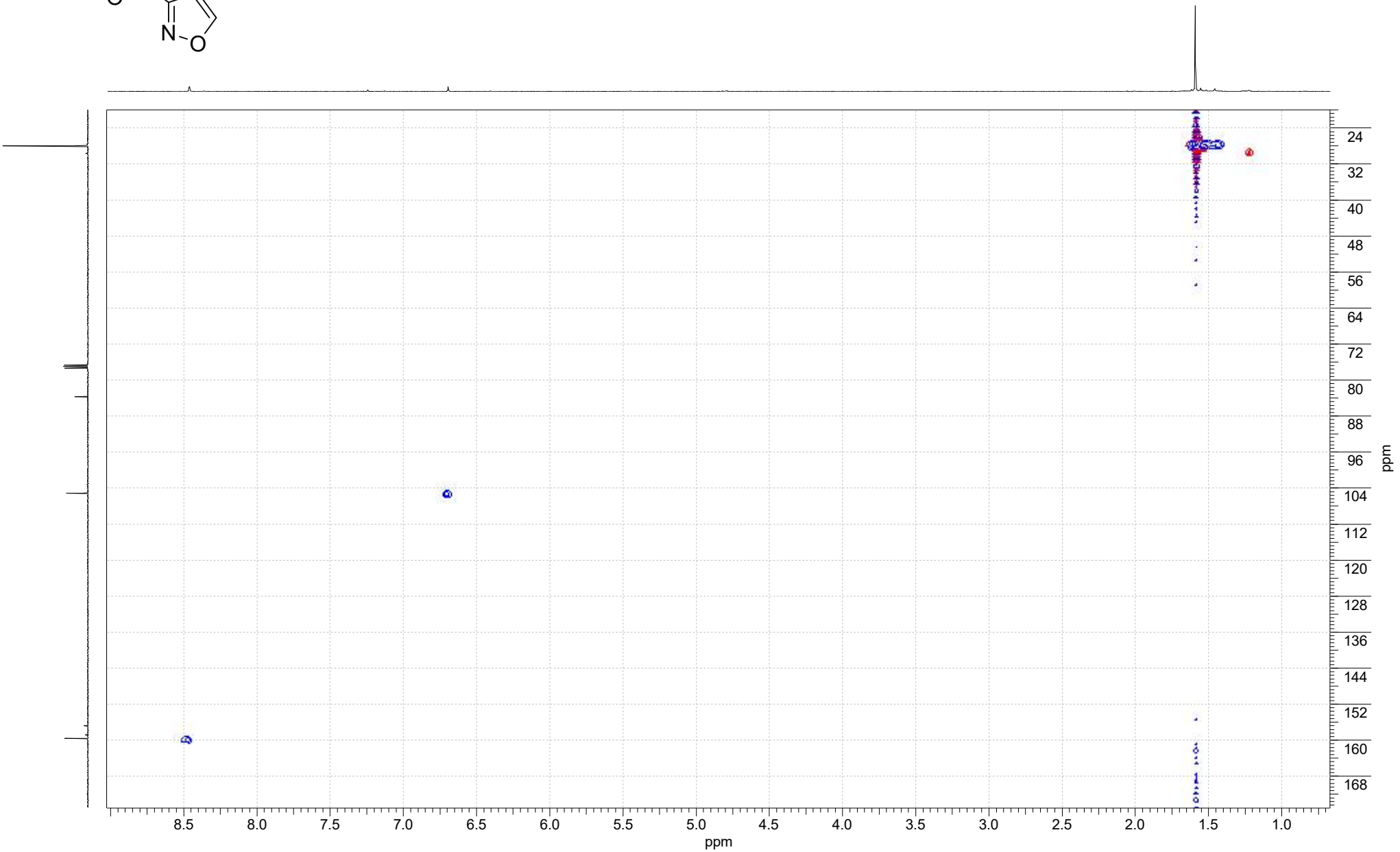
tert-Butyl isoxazole-3-carboxylate **2p** (HMBS)



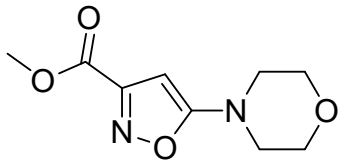


tert-Butyl isoxazole-3-carboxylate **2p** (HSQC)

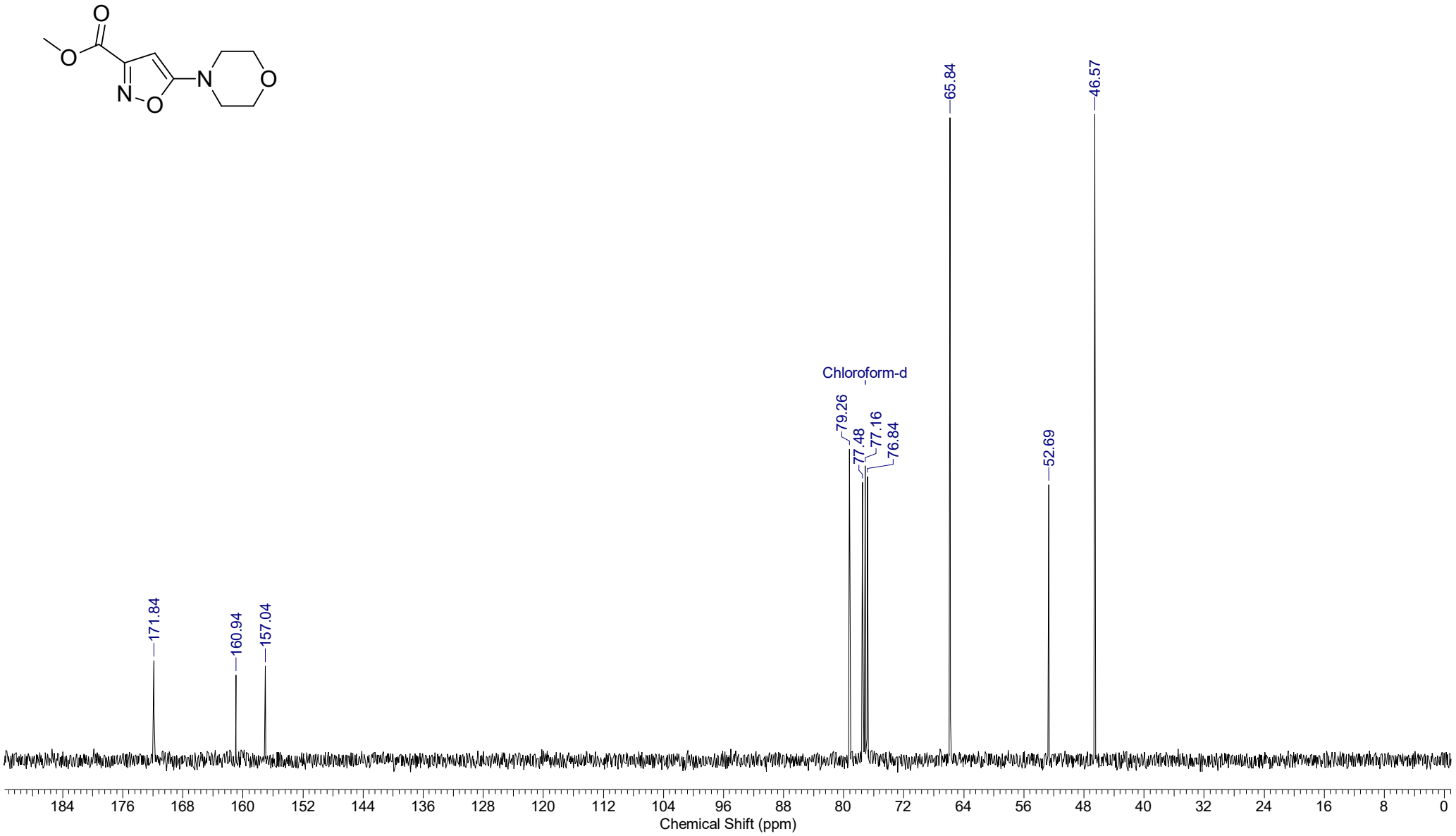




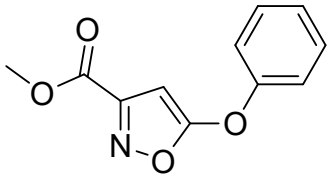
Methyl 5-morpholinoisoxazole-3-carboxylate **2r** (^{1}H NMR)



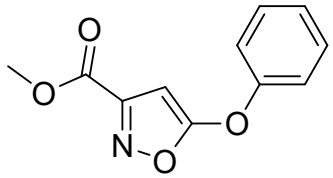
Methyl 5-morpholinoisoxazole-3-carboxylate **2r** (^{13}C NMR)



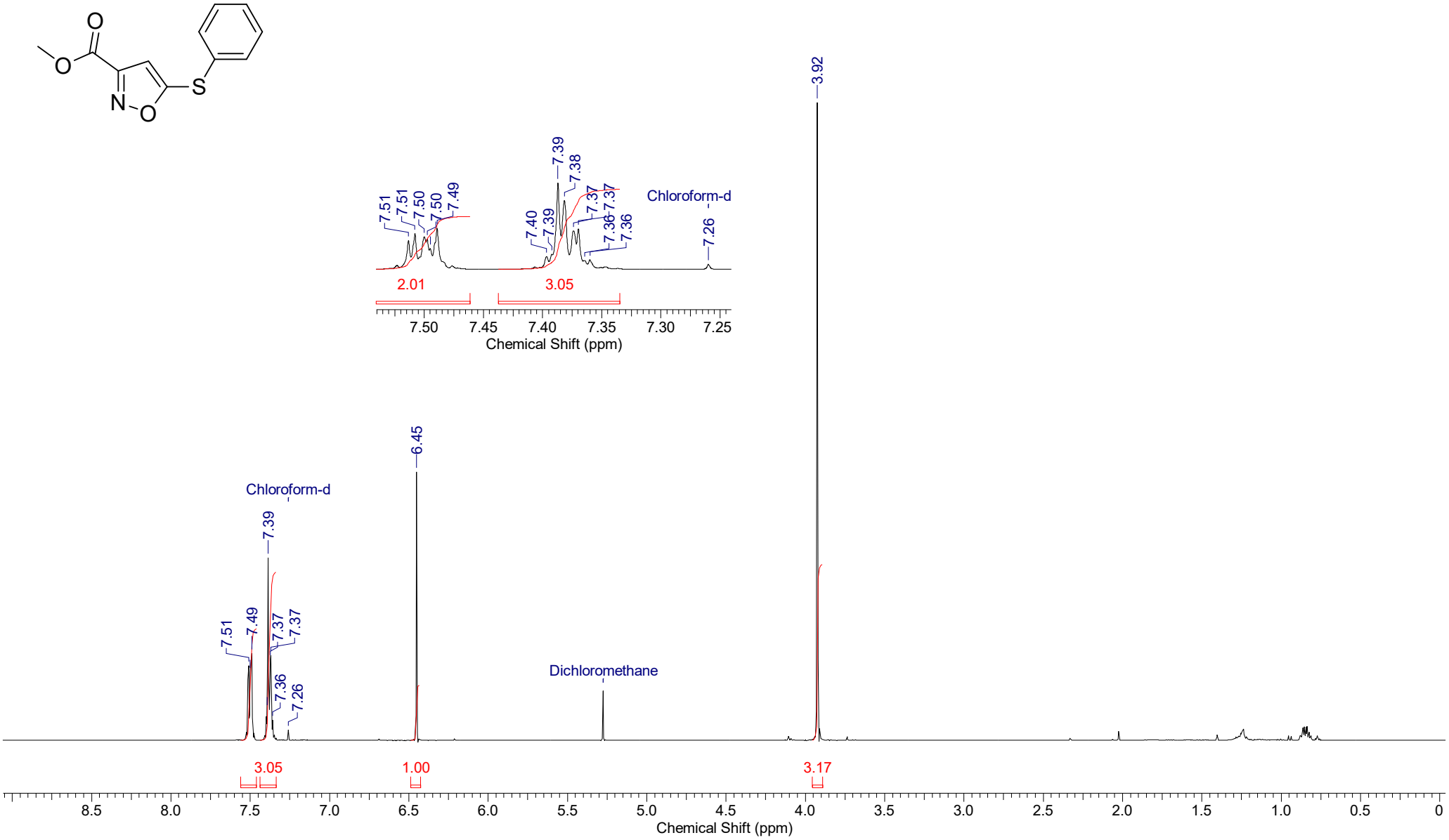
Methyl 5-phenoxyisoxazole-3-carboxylate **2s** (^{1}H NMR)



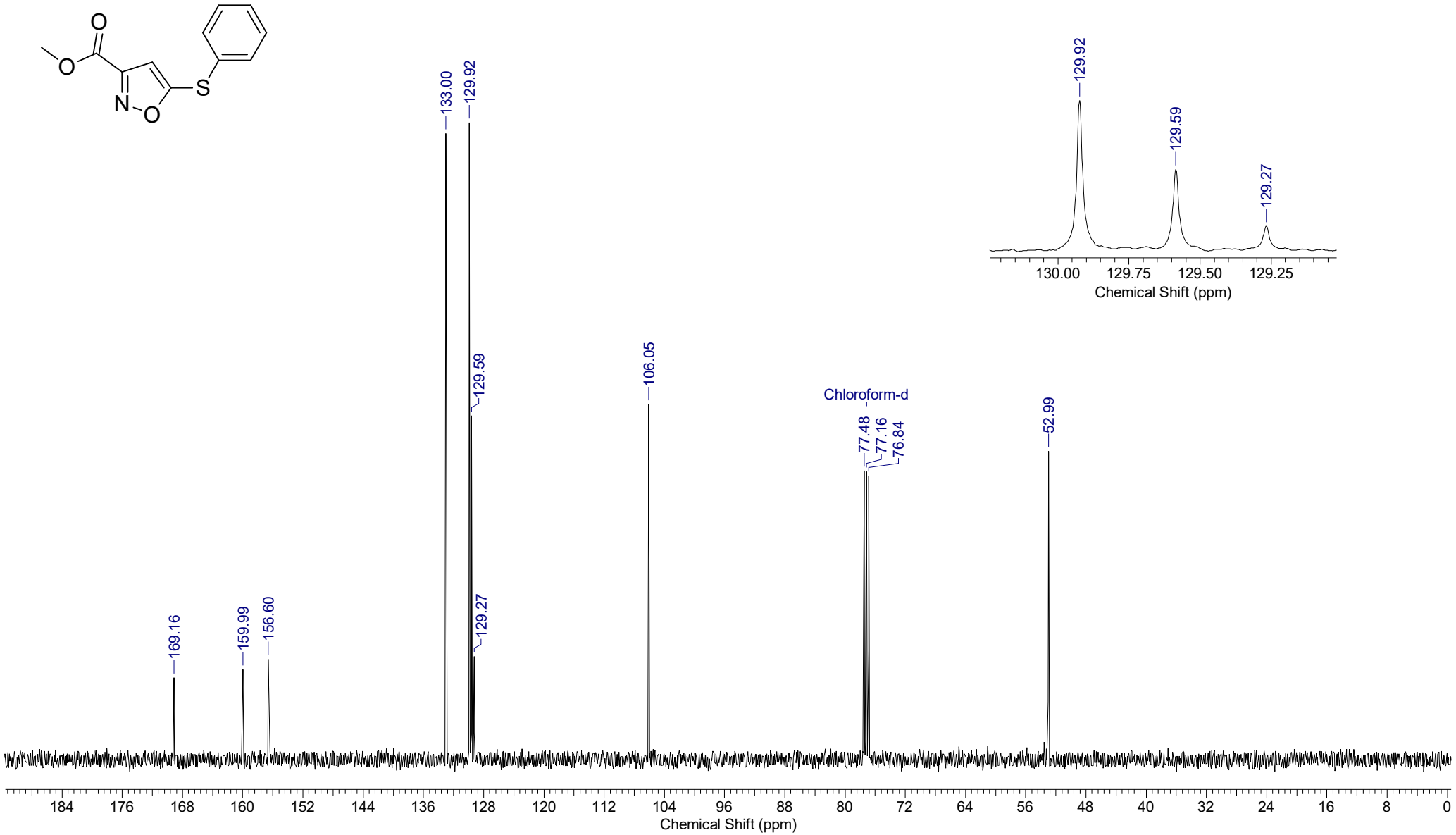
Methyl 5-phenoxyisoxazole-3-carboxylate **2s** (^{13}C NMR)



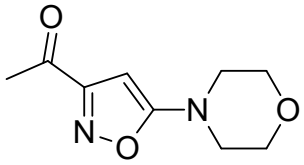
Methyl 5-(phenylsulfanyl)isoxazole-3-carboxylate **2t** (^{1}H NMR)



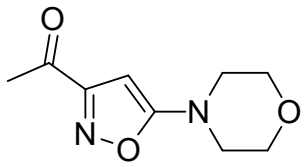
Methyl 5-(phenylsulfanyl)isoxazole-3-carboxylate **2t** (^{13}C NMR)



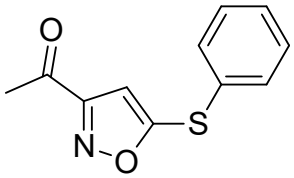
1-(5-Morpholinoisoxazol-3-yl)ethanone **2u** (^{1}H NMR)



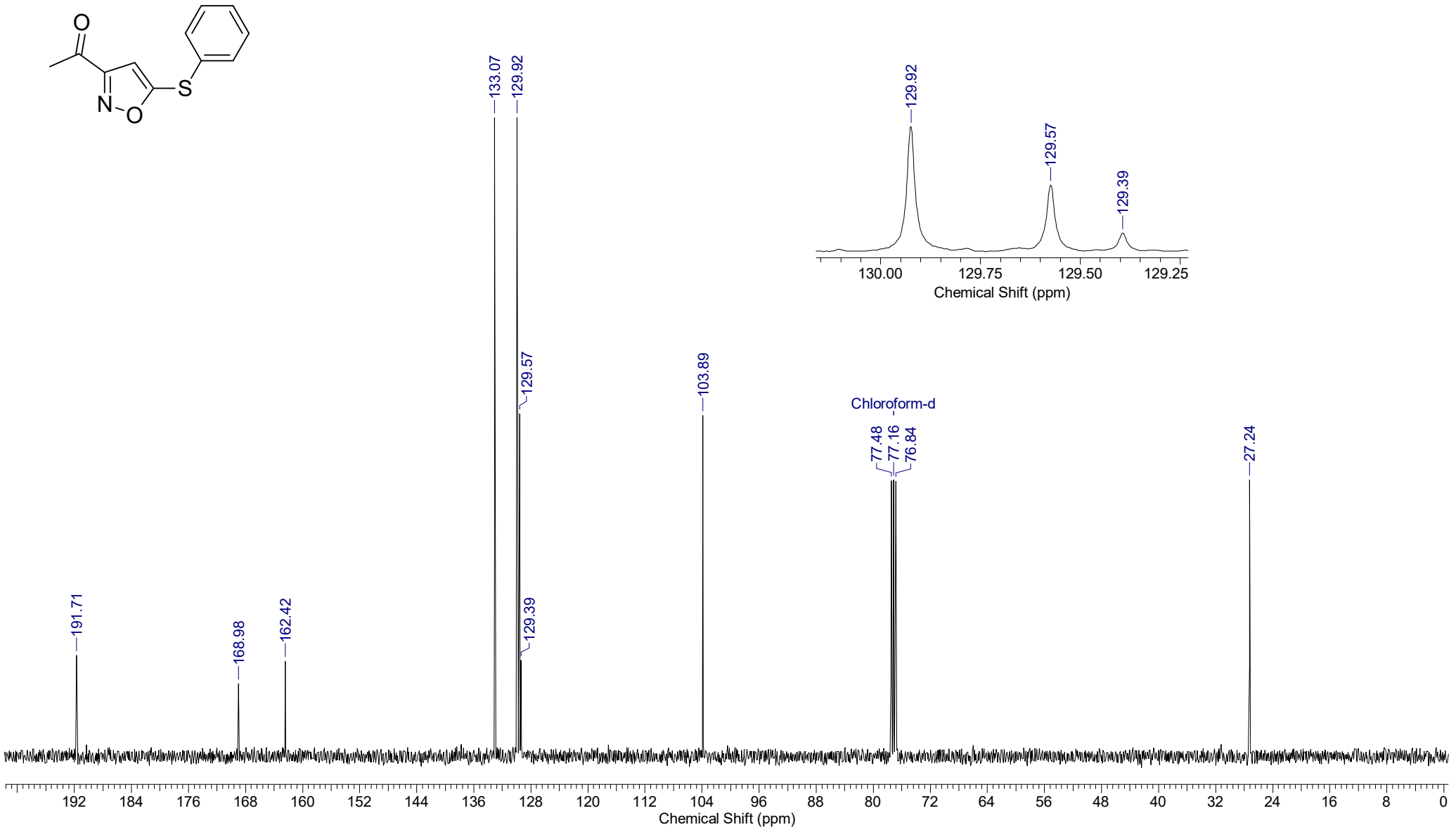
1-(5-Morpholinoisoxazol-3-yl)ethanone **2u** (^{13}C NMR)



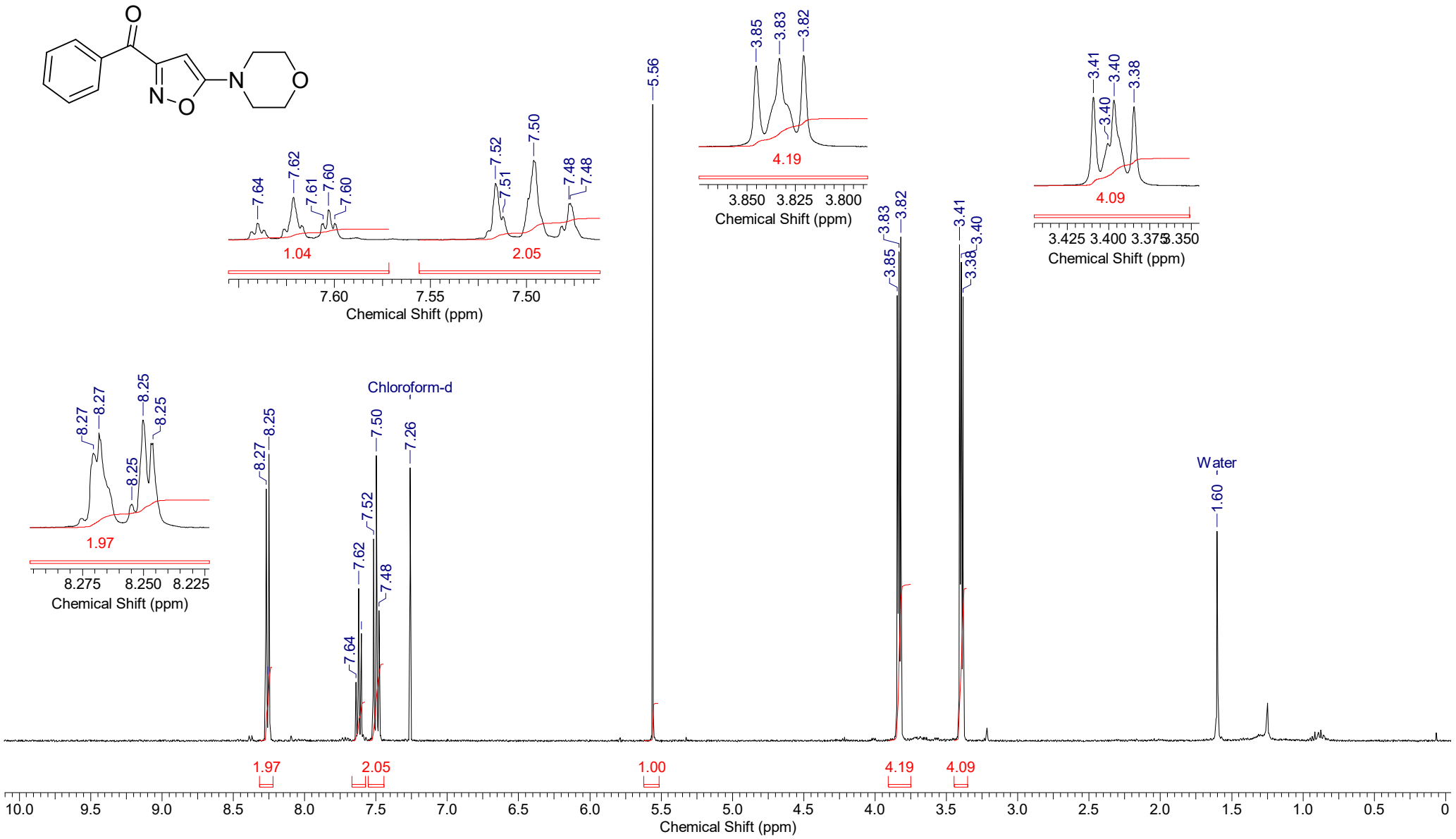
1-(5-(Phenylsulfanyl)isoxazol-3-yl)ethanone **2w** (^{1}H NMR)



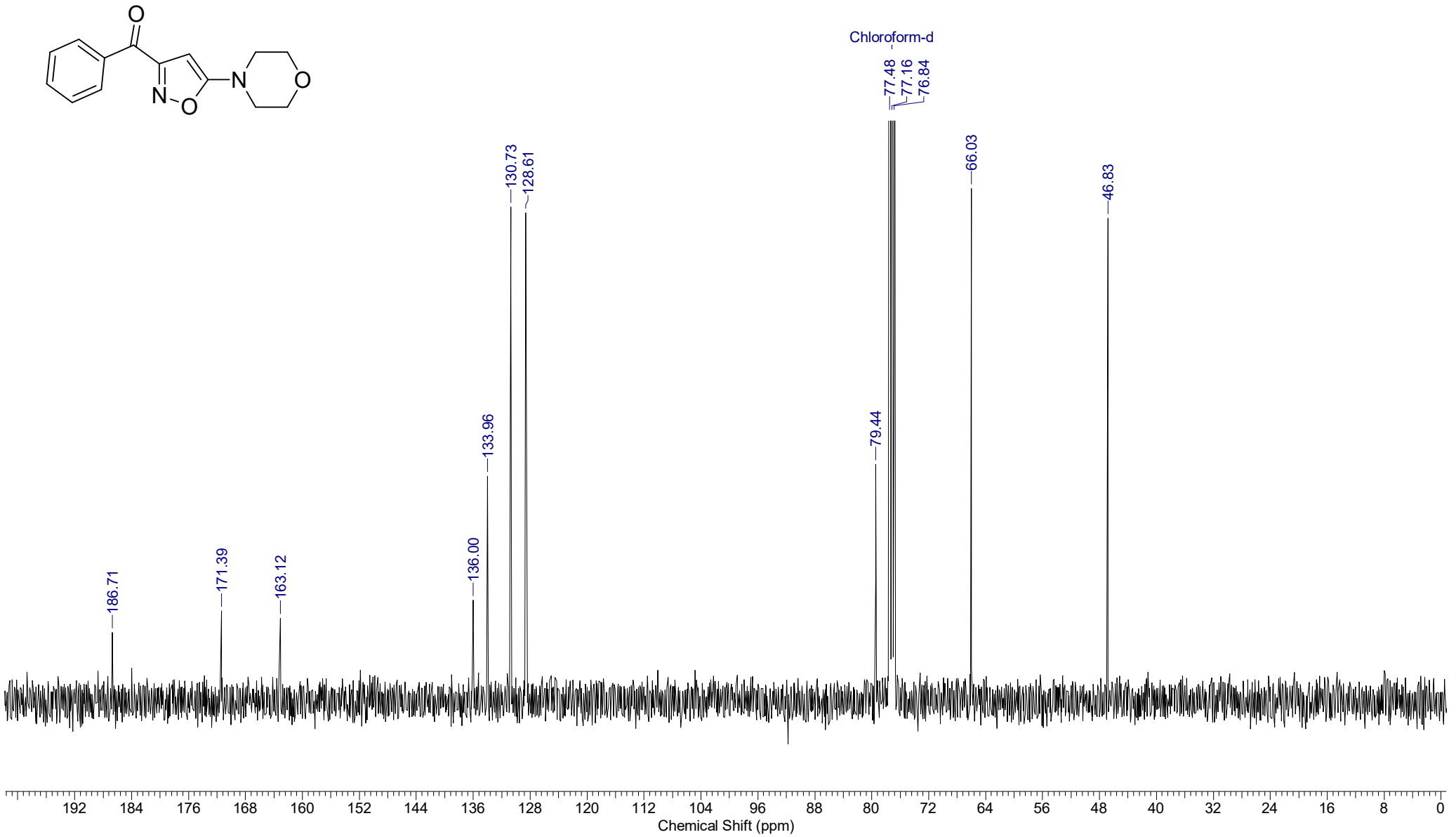
1-(5-(Phenylsulfanyl)isoxazol-3-yl)ethanone **2w** (^{13}C NMR)



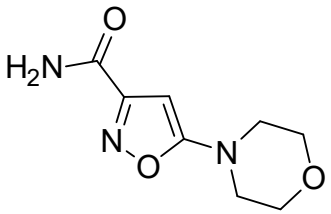
(5-Morpholinoisoxazol-3-yl)(phenyl)methanone **2x** (^{1}H NMR)

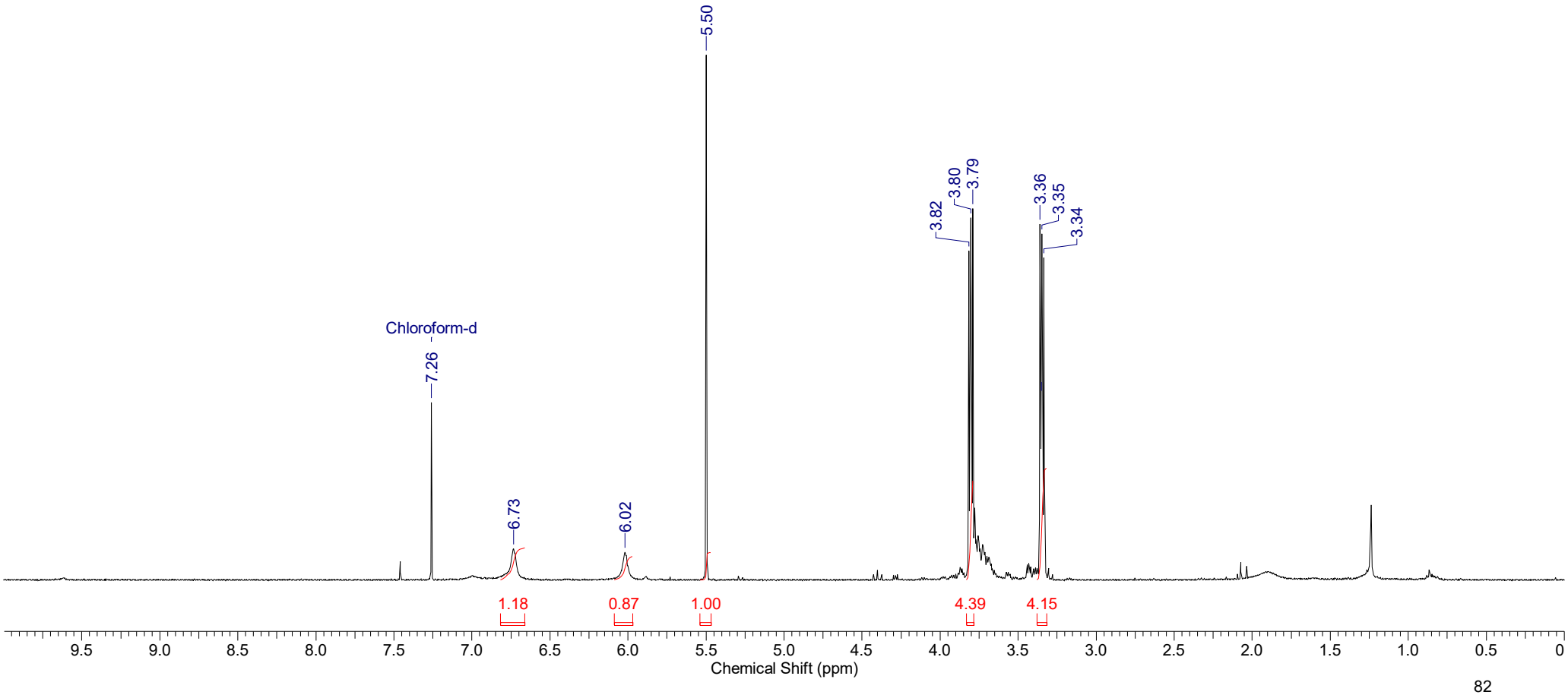


(5-Morpholinoisoxazol-3-yl)(phenyl)methanone **2x** (^{13}C NMR)

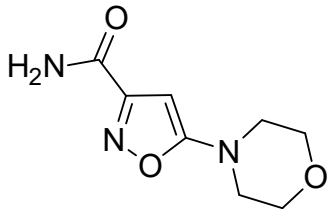


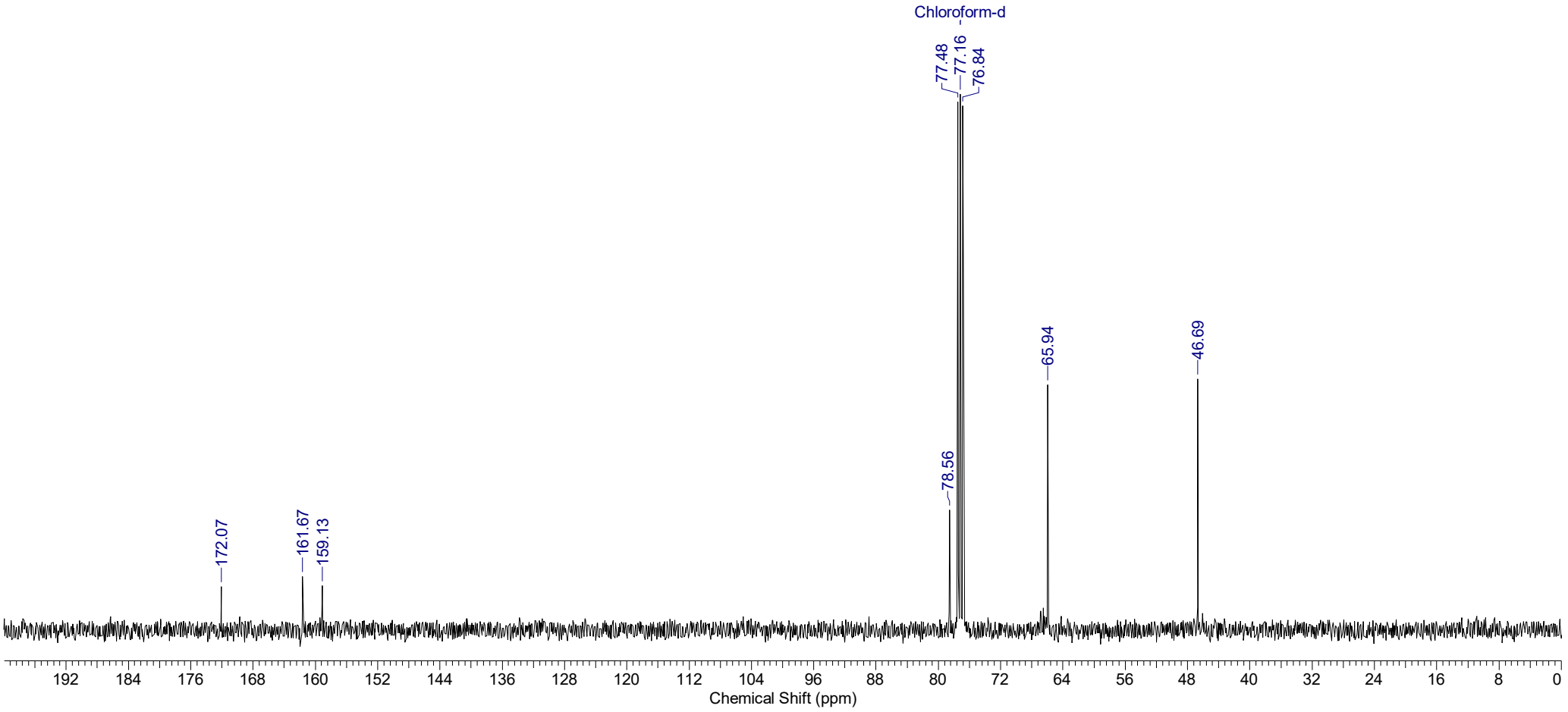
5-Morpholinoisoxazole-3-carboxamide **2y** (^{1}H NMR)



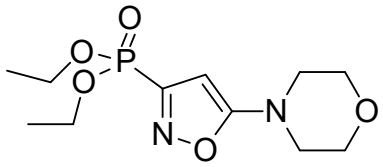


5-Morpholinoisoxazole-3-carboxamide **2y** (^{13}C NMR)

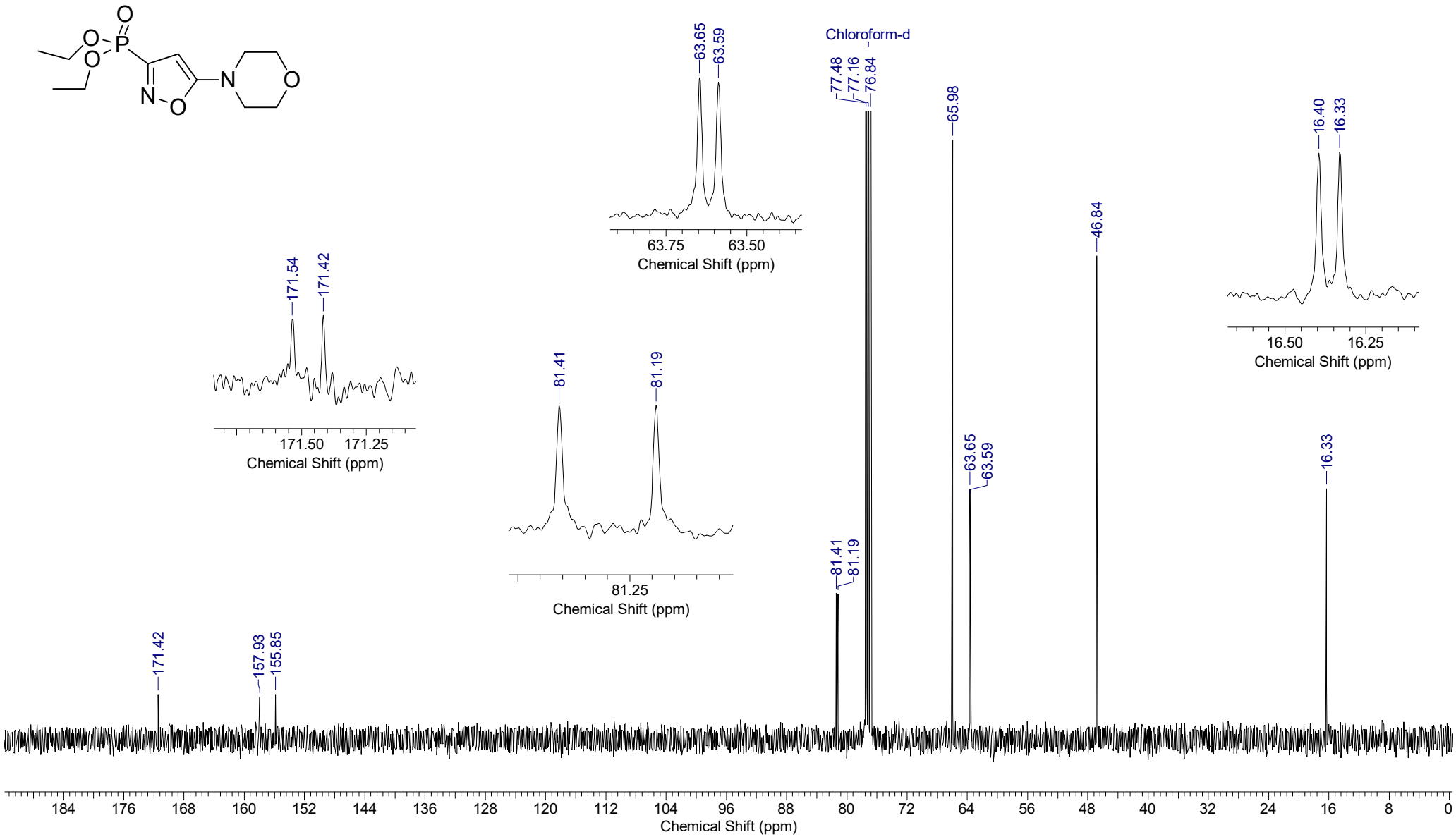




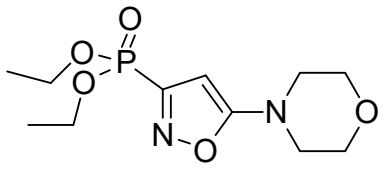
Diethyl (5-morpholinoisoxazol-3-yl)phosphonate **2z** (^{1}H NMR)



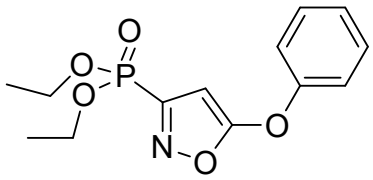
Diethyl (5-morpholinoisoxazol-3-yl)phosphonate **2z** (^{13}C NMR)



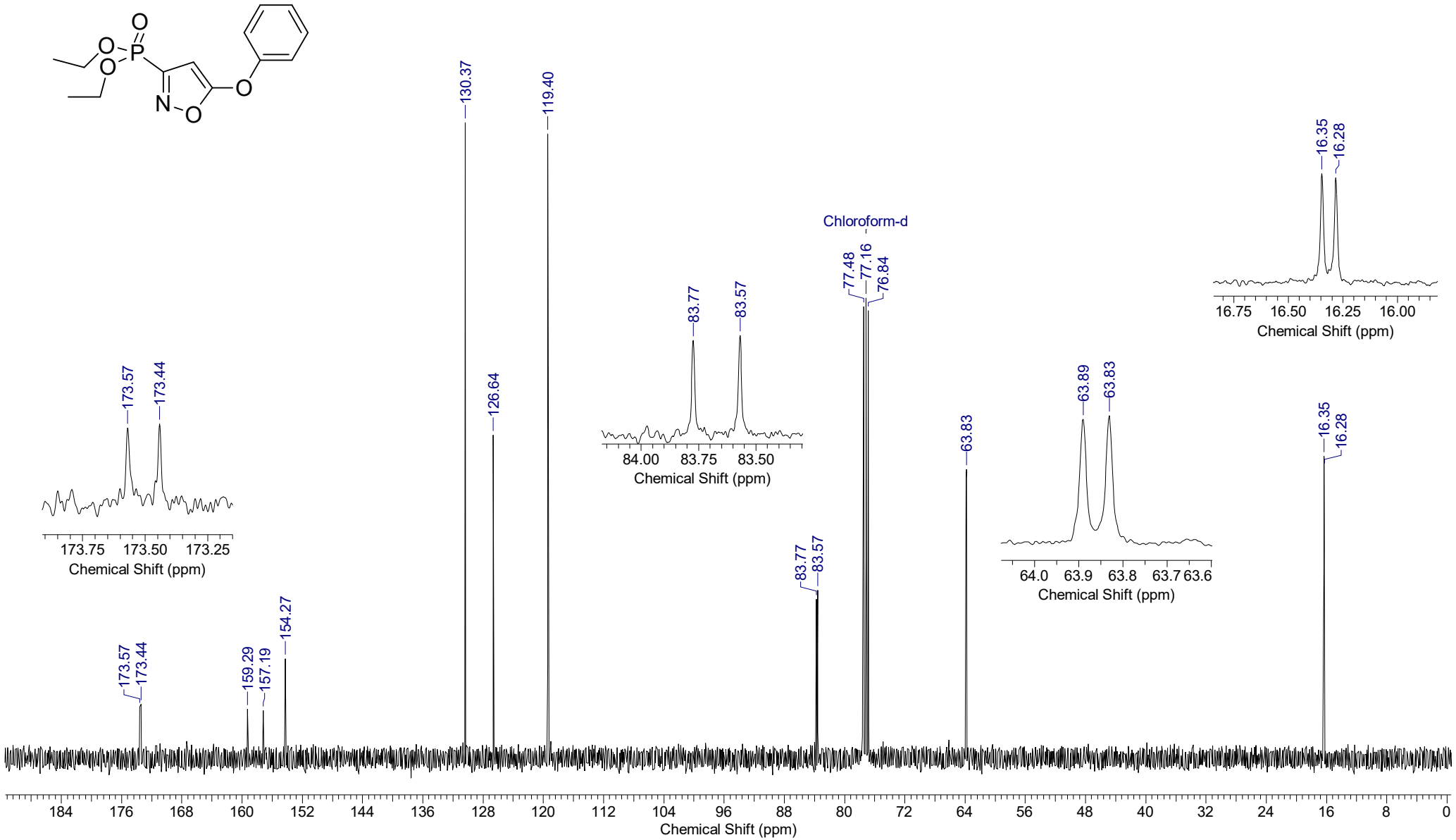
Diethyl (5-morpholinoisoxazol-3-yl)phosphonate **2z** (^{31}P NMR)



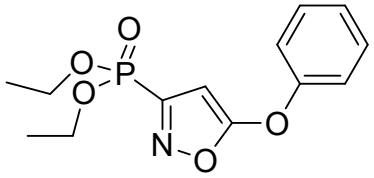
Diethyl (5-phenoxyisoxazol-3-yl)phosphonate **2za** (^{1}H NMR)



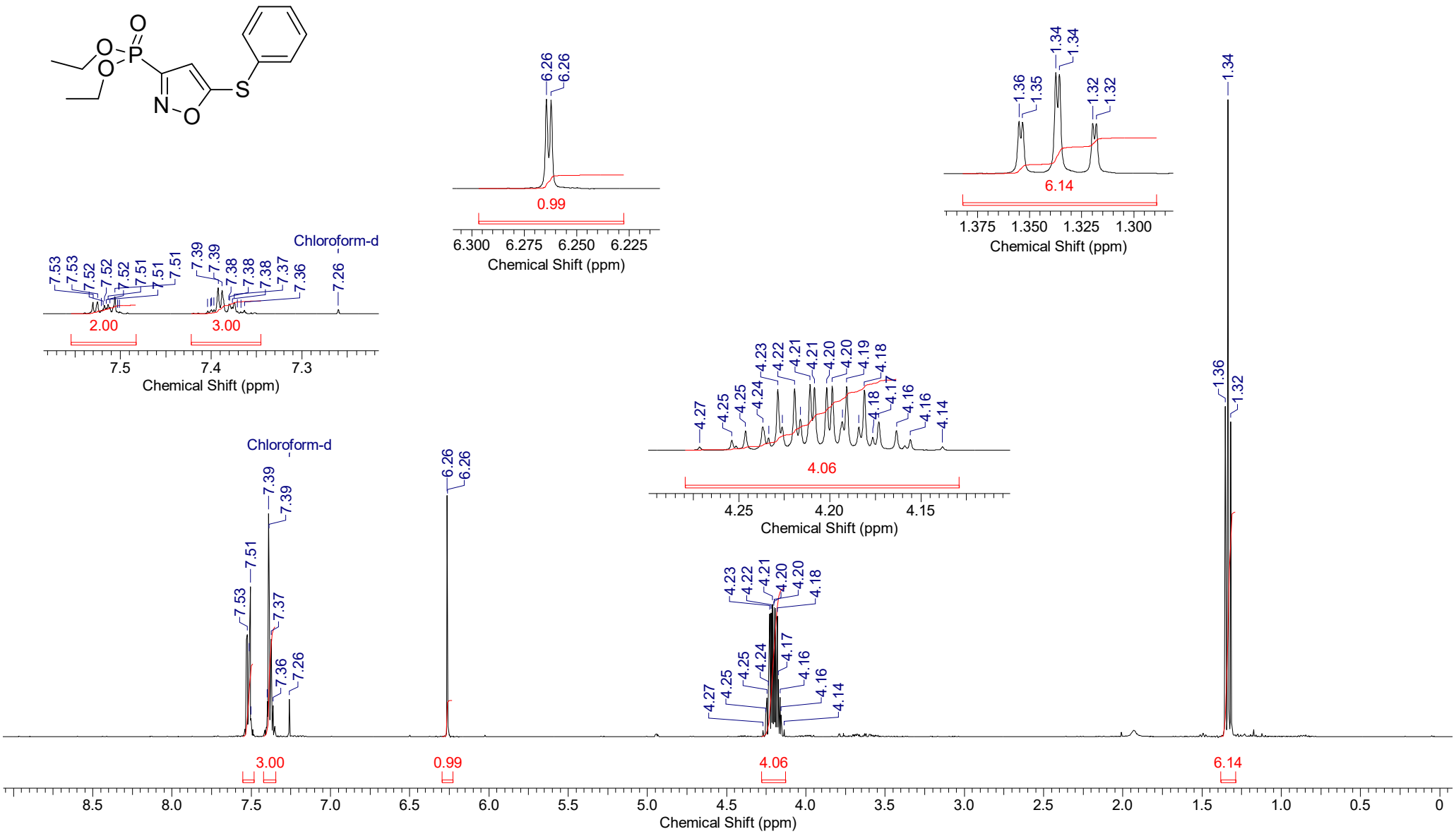
Diethyl (5-phenoxyisoxazol-3-yl)phosphonate **2za** (^{13}C NMR)



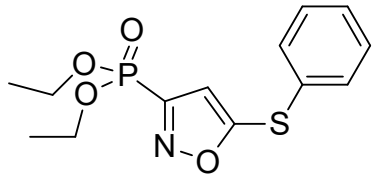
Diethyl (5-phenoxyisoxazol-3-yl)phosphonate **2za** (^{31}P NMR)



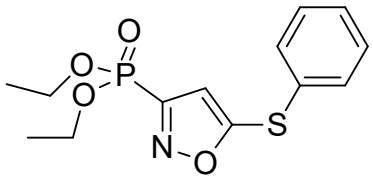
Diethyl (5-(phenylsulfanyl)isoxazol-3-yl)phosphonate **2zb** (^{1}H NMR)



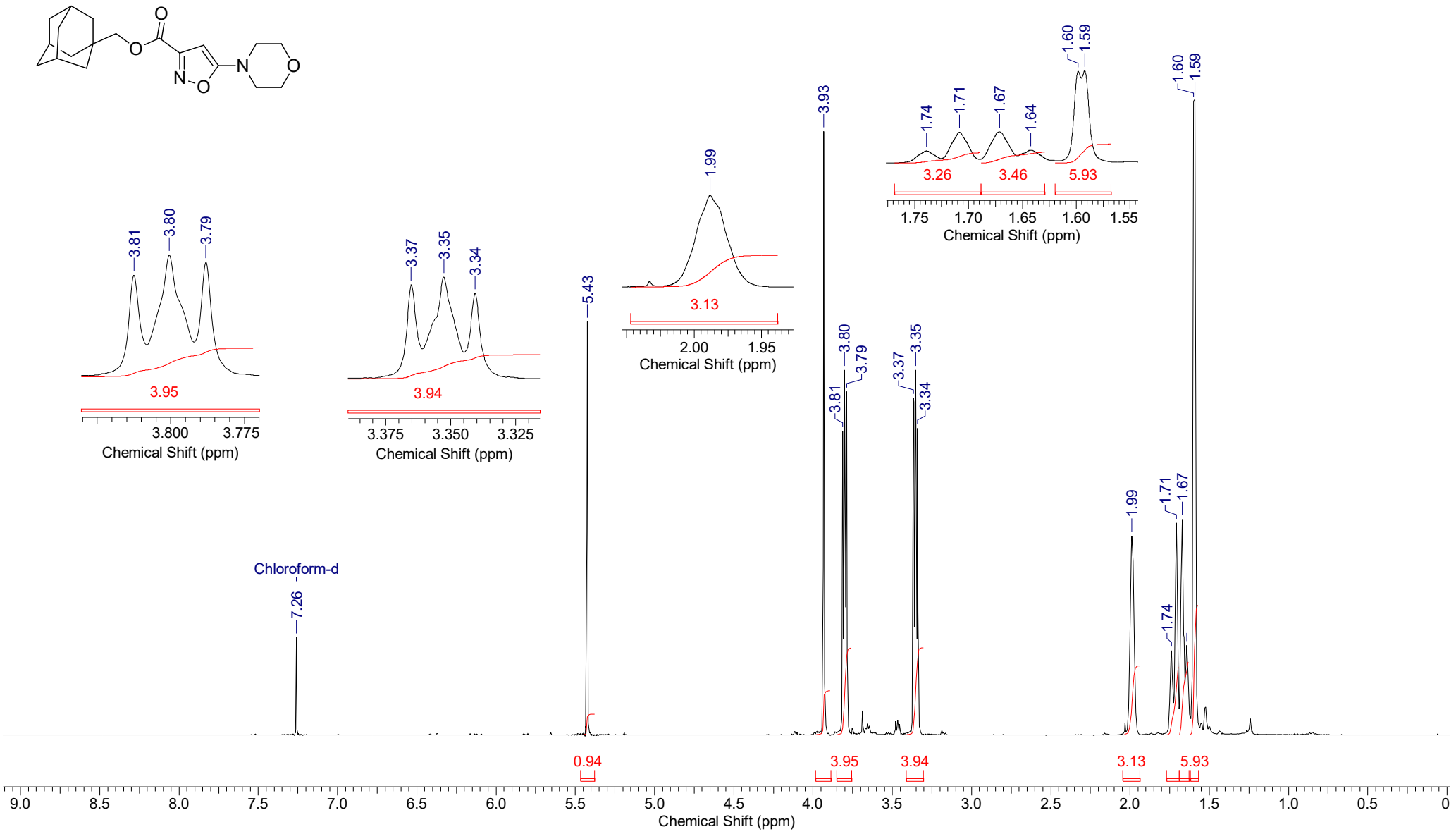
Diethyl (5-(phenylsulfanyl)isoxazol-3-yl)phosphonate **2zb** (^{13}C NMR)



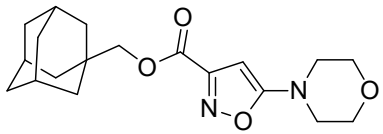
Diethyl (5-(phenylsulfanyl)isoxazol-3-yl)phosphonate **2zb** (^{31}P NMR)

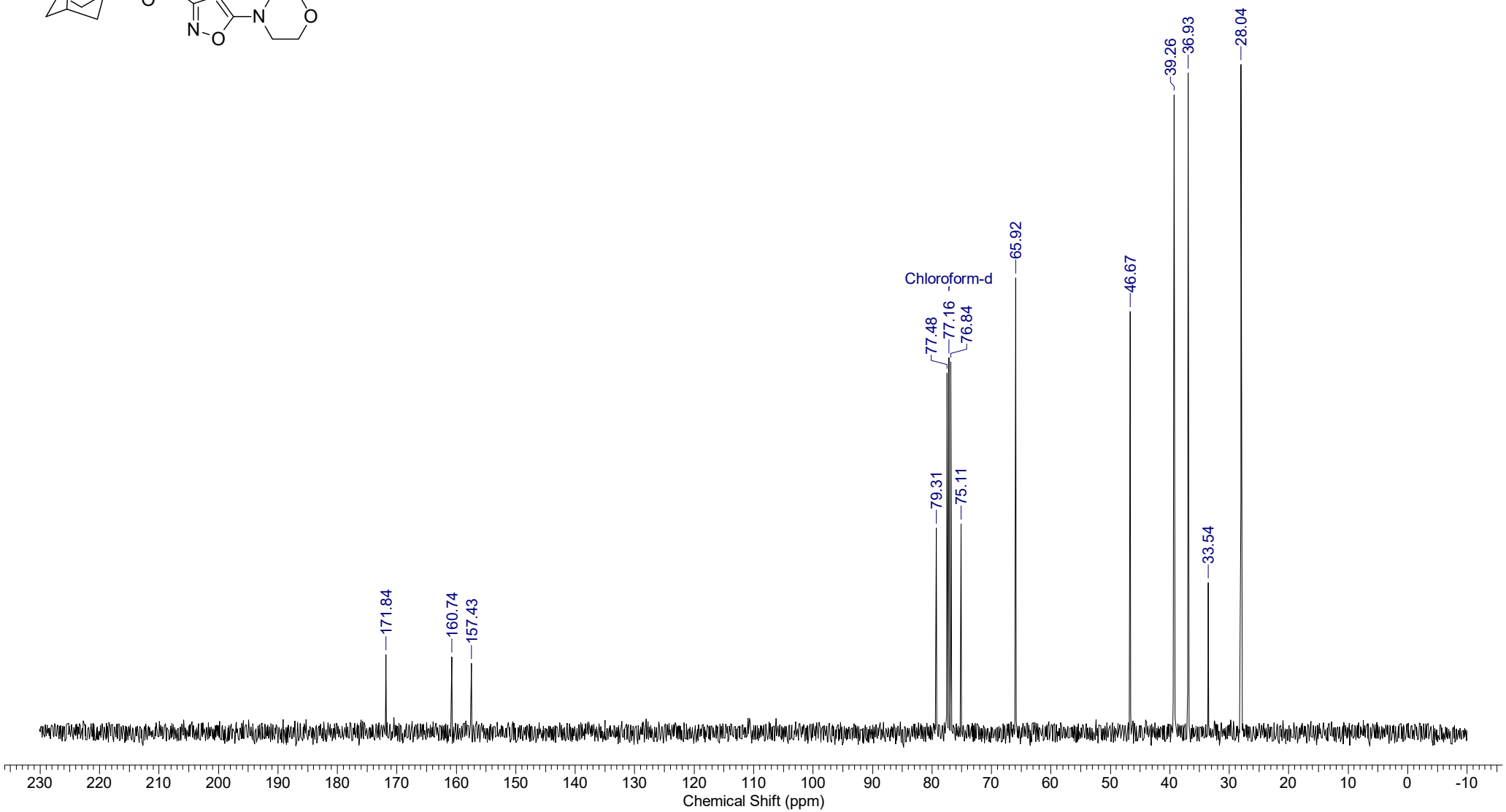


Adamantan-1-ylmethyl 5-morpholinoisoxazole-3-carboxylate **2zc** (^{1}H NMR)

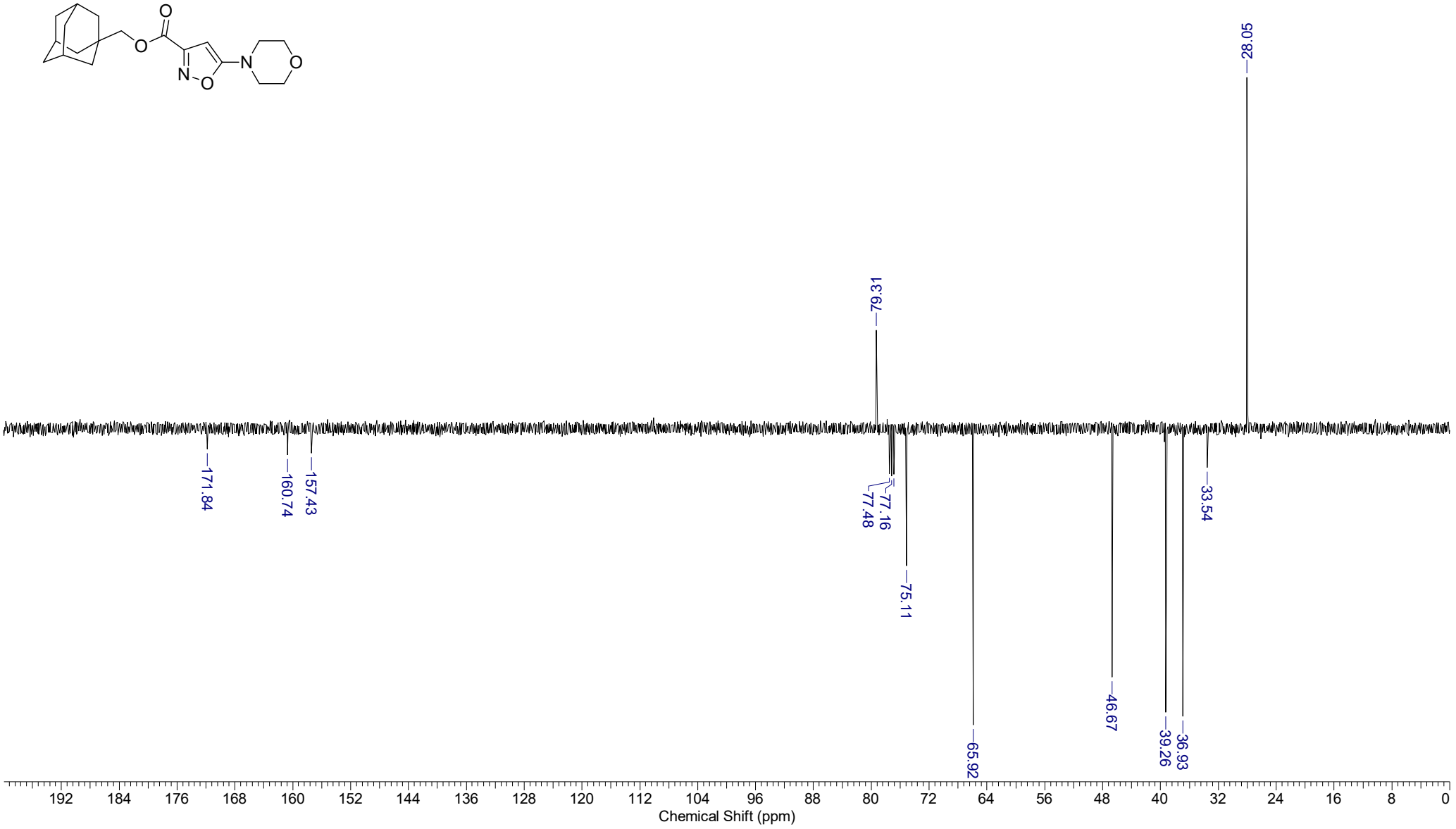


Adamantan-1-ylmethyl 5-morpholinoisoxazole-3-carboxylate **2zc** (^{1}H NMR)

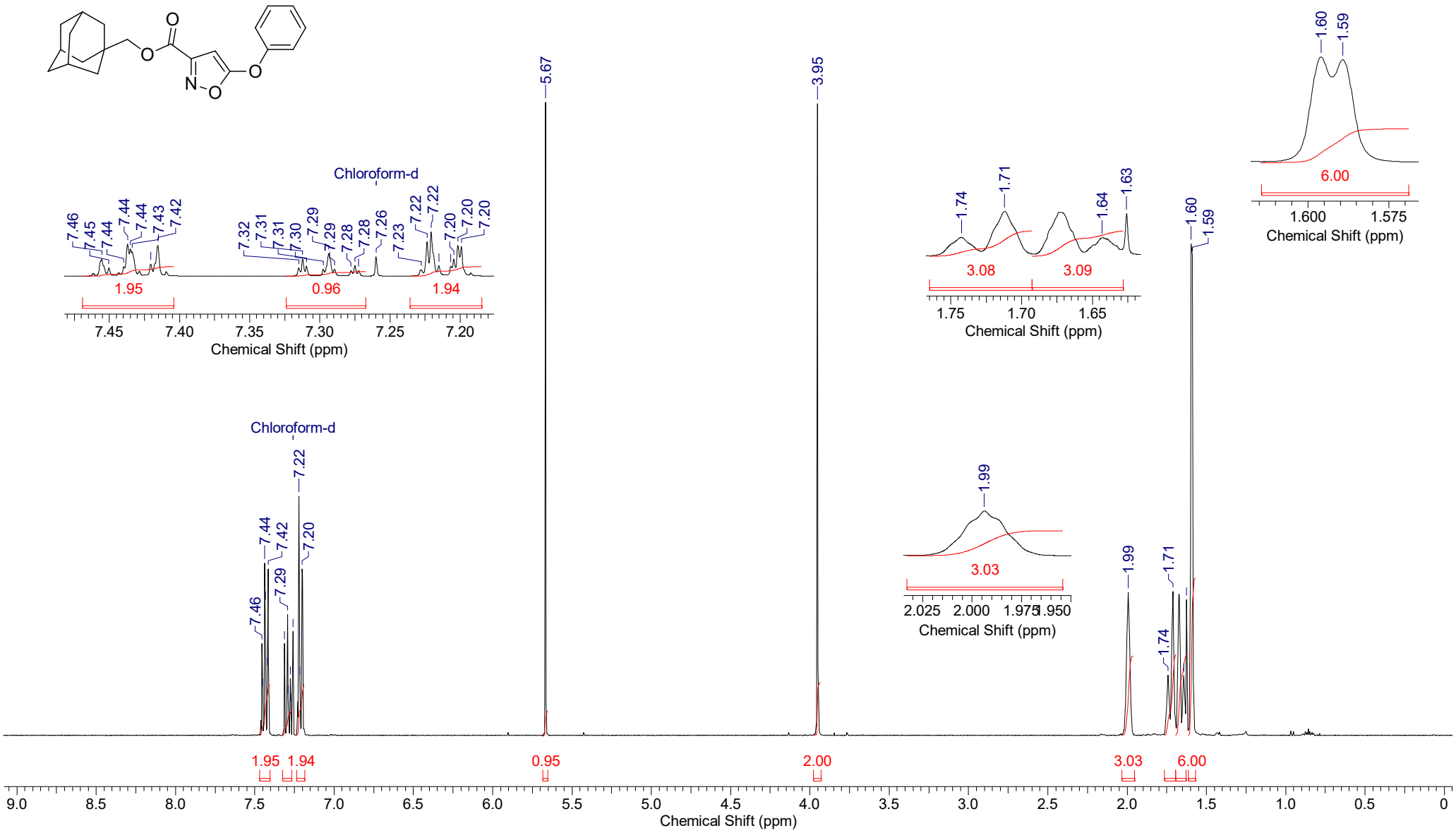




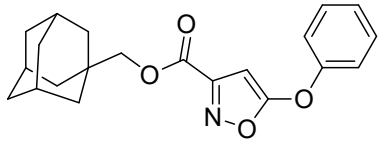
Adamantan-1-ylmethyl 5-morpholinoisoxazole-3-carboxylate **2zc** (APT)



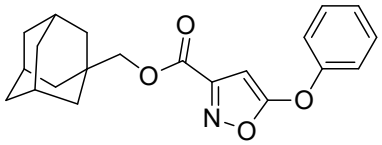
Adamantan-1-ylmethyl 5-phenoxyisoxazole-3-carboxylate **2zd** (^{1}H NMR)



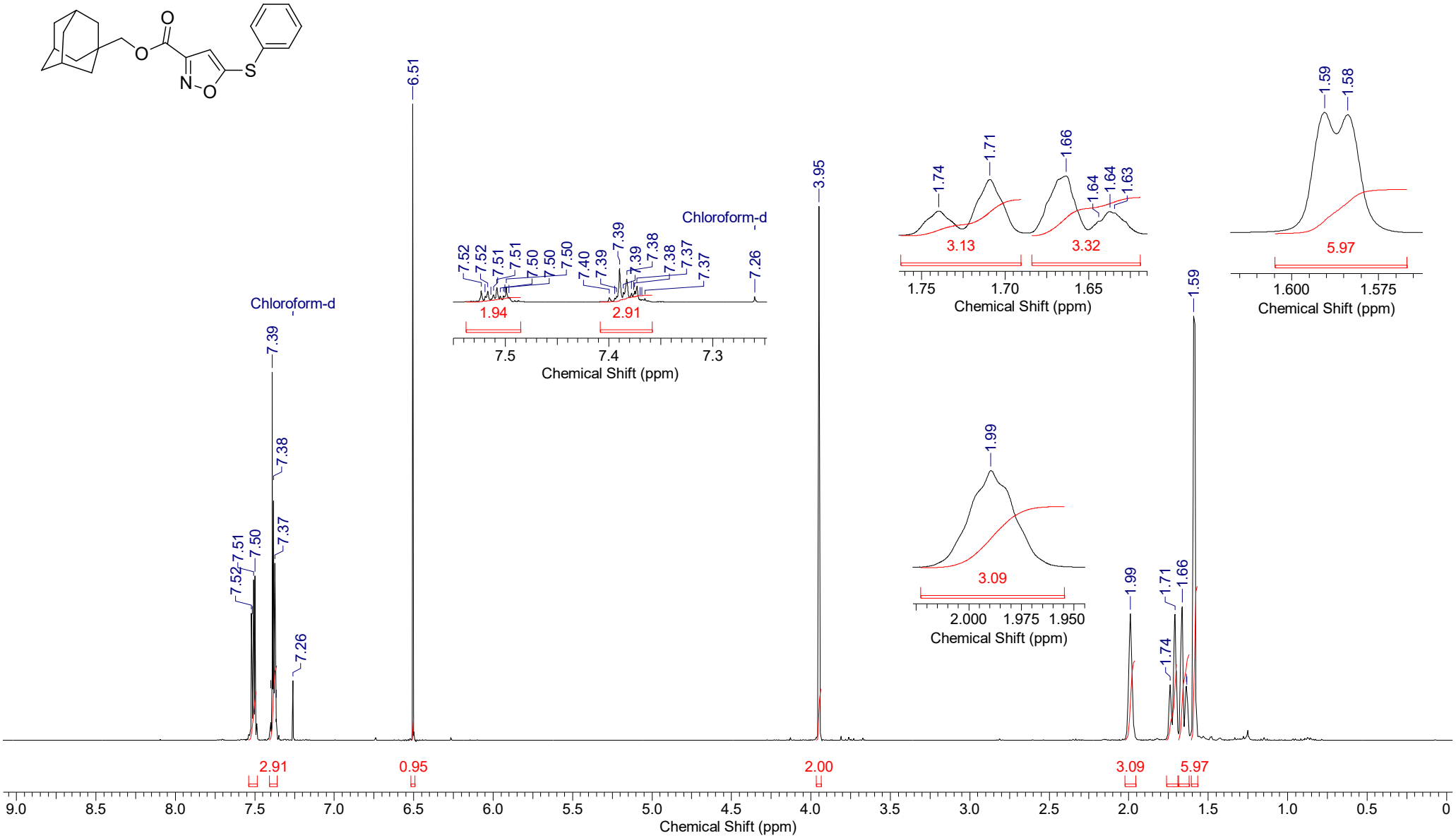
Adamantan-1-ylmethyl 5-phenoxyisoxazole-3-carboxylate **2zd** (^{13}C NMR)



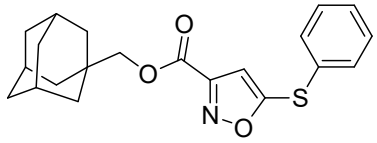
Adamantan-1-ylmethyl 5-phenoxyisoxazole-3-carboxylate **2zd** (APT)

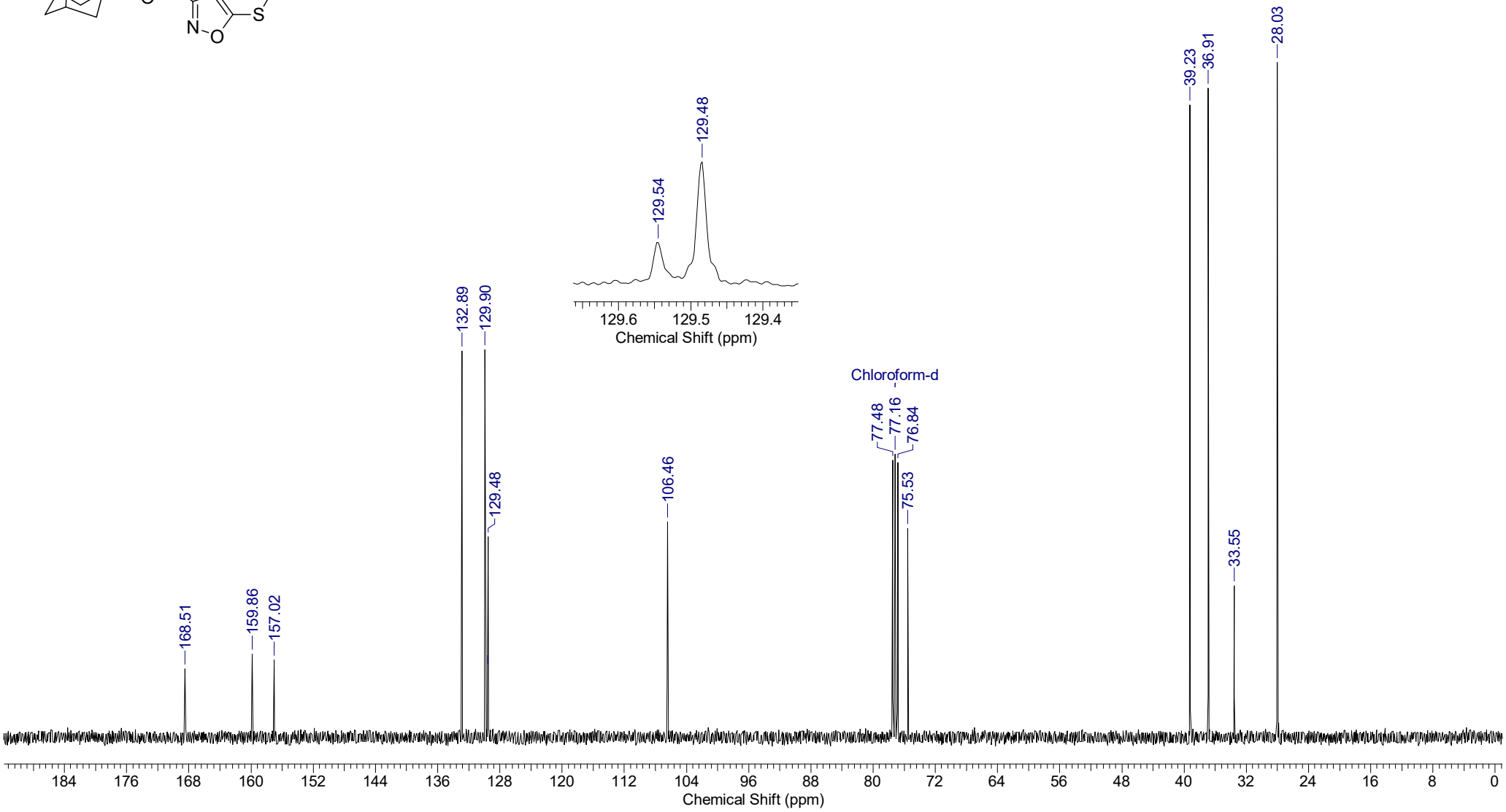


Adamantan-1-ylmethyl 5-(phenylsulfanyl)isoxazole-3-carboxylate **2ze** (^{1}H NMR)

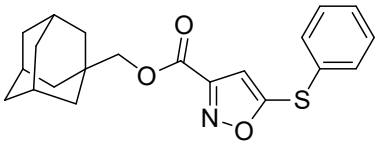


Adamantan-1-ylmethyl 5-(phenylsulfanyl)isoxazole-3-carboxylate **2ze** (^{13}C NMR)

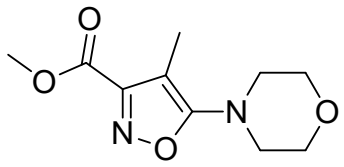




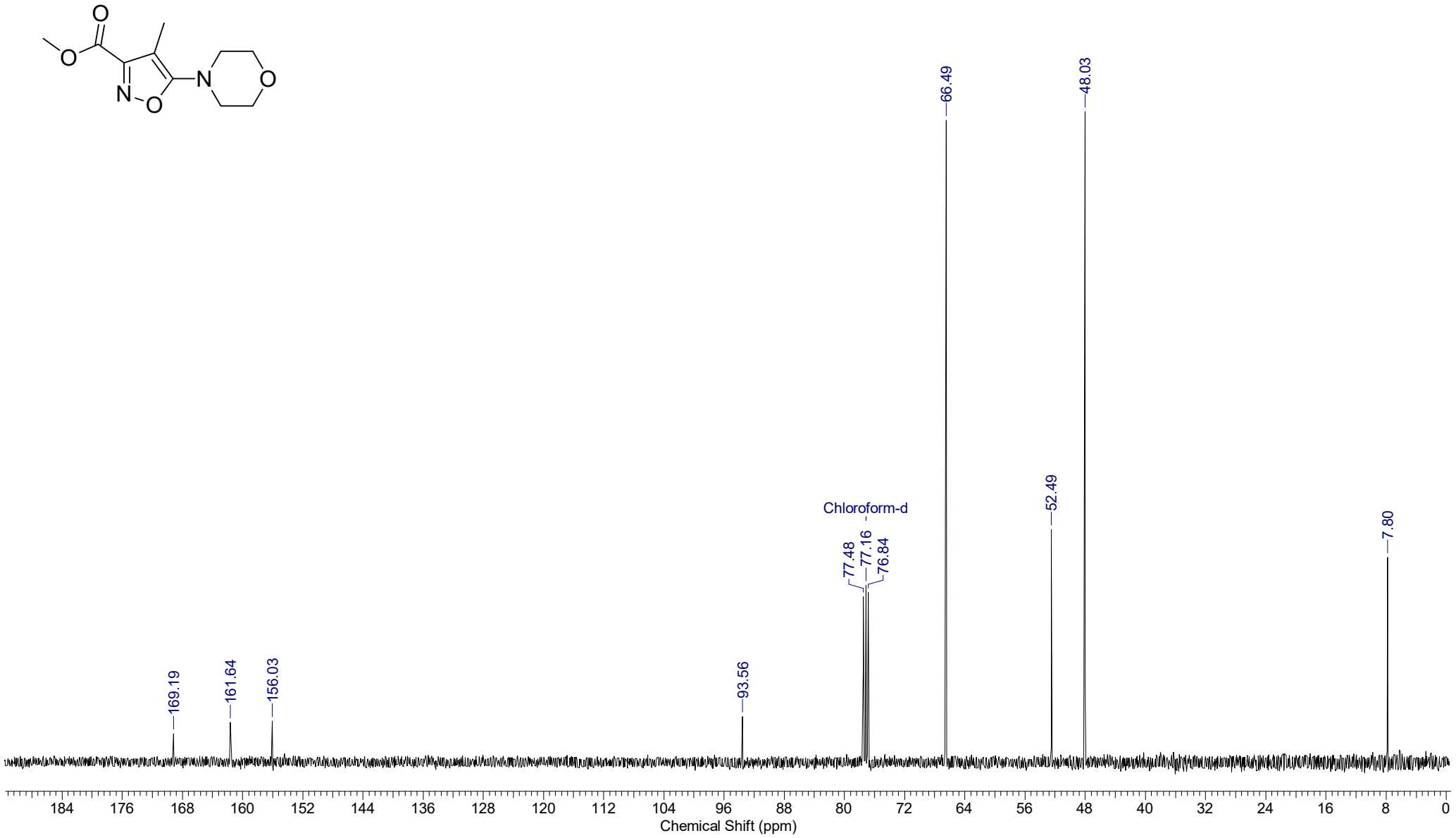
Adamantan-1-ylmethyl 5-(phenylsulfanyl)isoxazole-3-carboxylate **2ze** (APT)



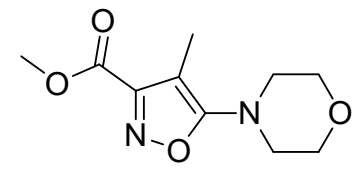
Methyl 4-methyl-5-morpholinoisoxazole-3-carboxylate **2zf** (^{1}H NMR)

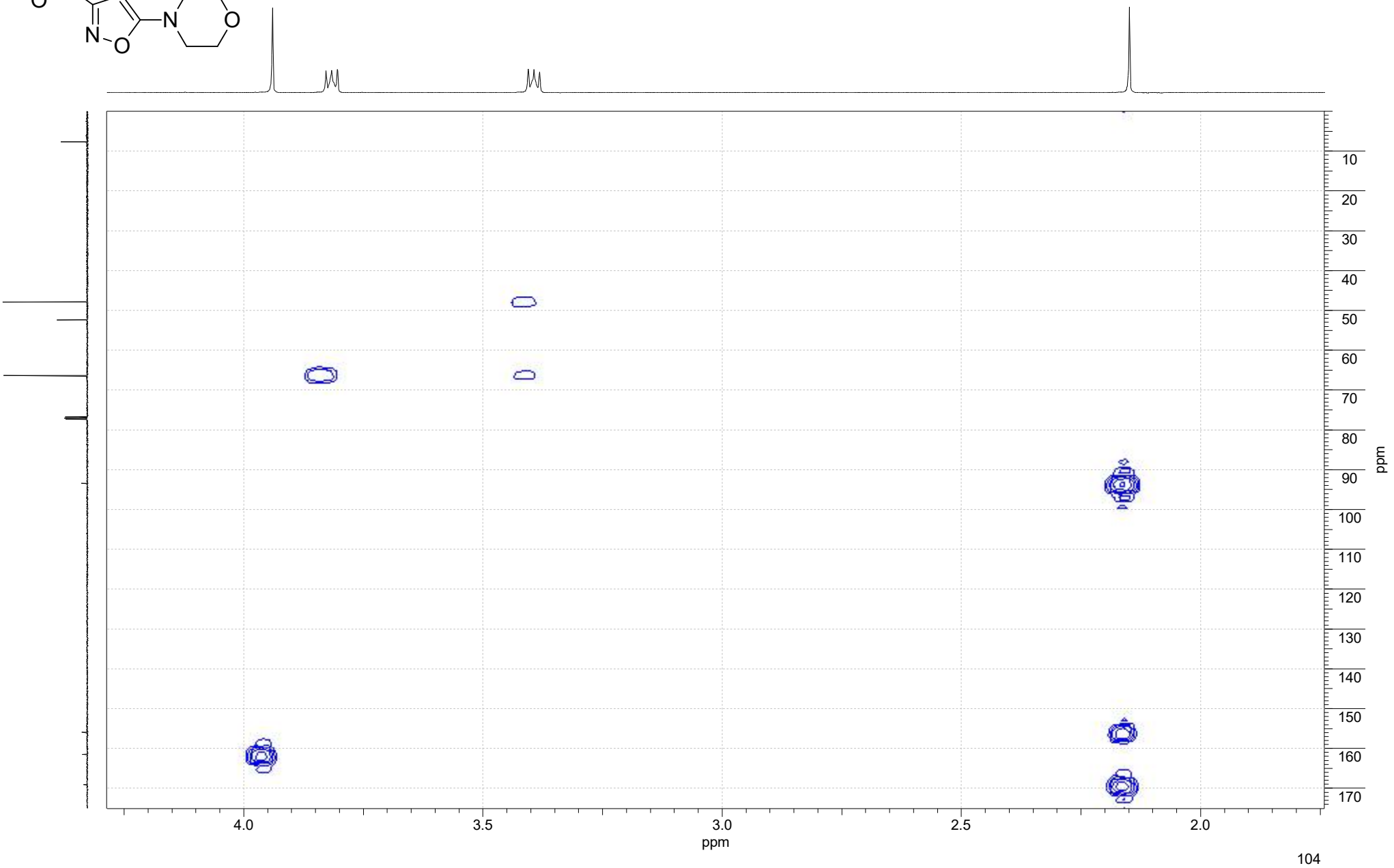


Methyl 4-methyl-5-morpholinoisoxazole-3-carboxylate **2zf** (^{13}C NMR)

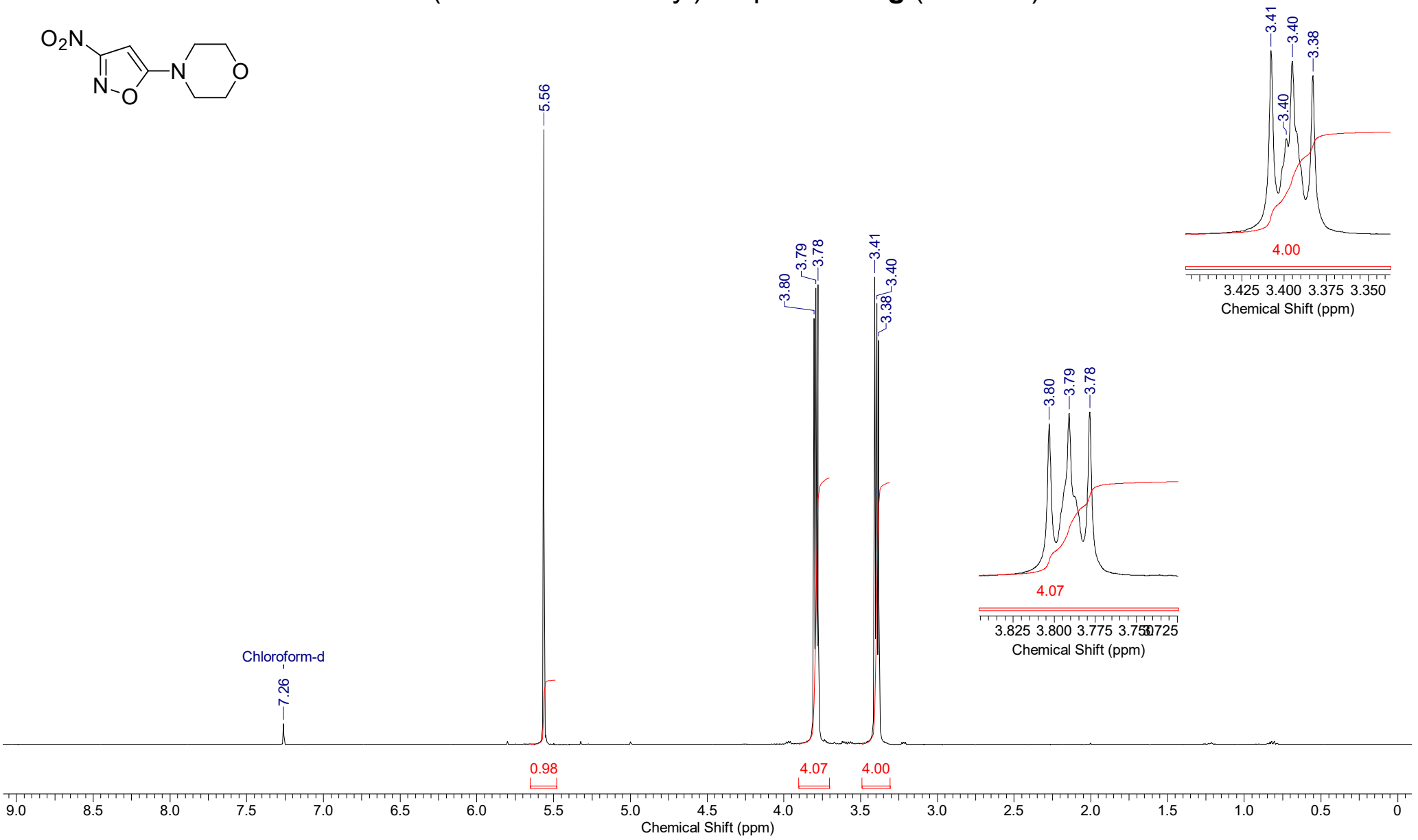


Methyl 4-methyl-5-morpholinoisoxazole-3-carboxylate **2zf** (HMBC)

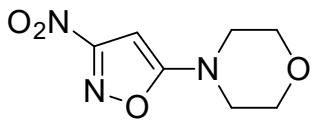


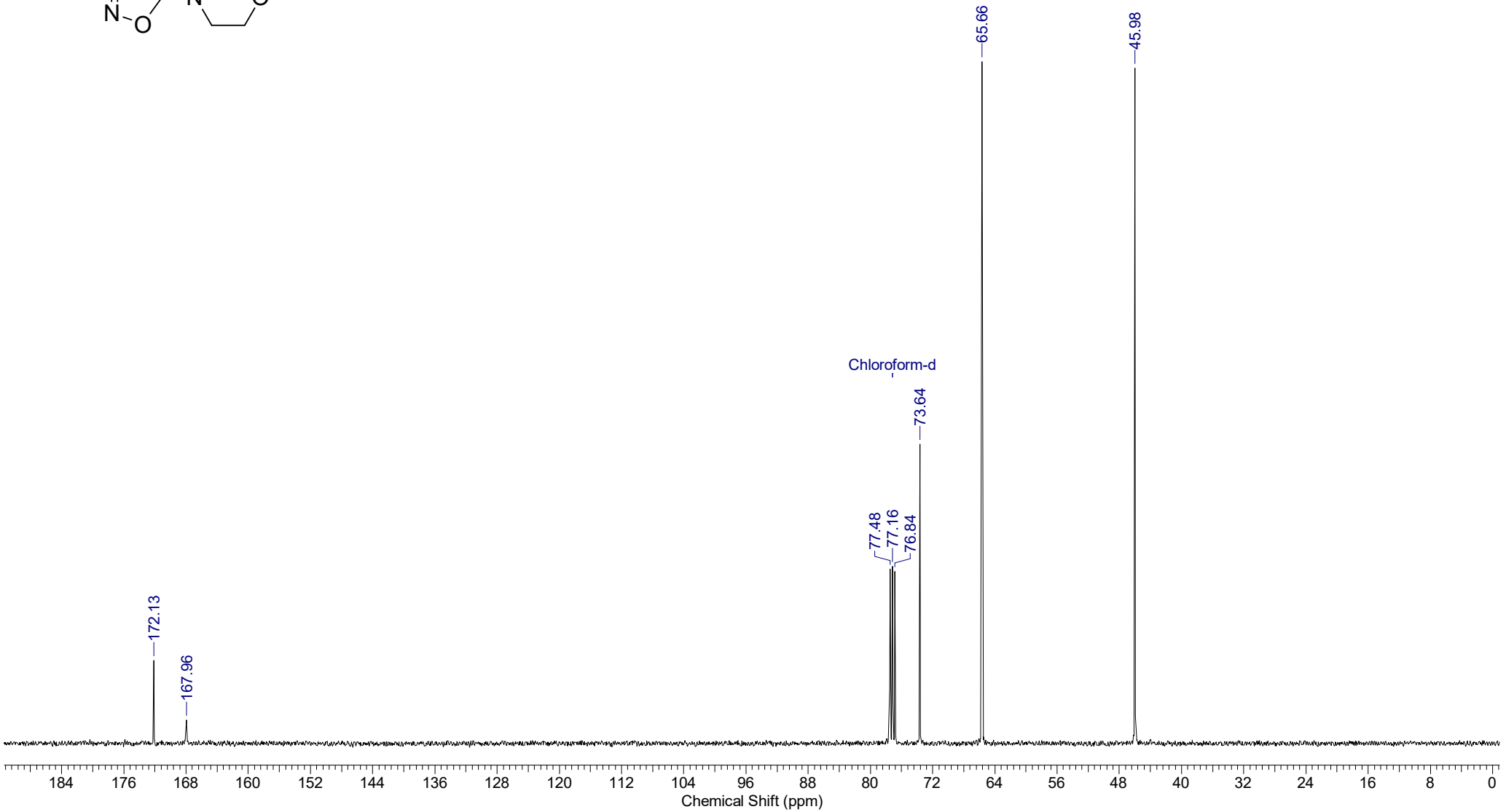


4-(3-Nitroisoxazol-5-yl)morpholine **2zg** (^{1}H NMR)

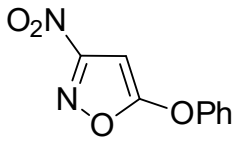


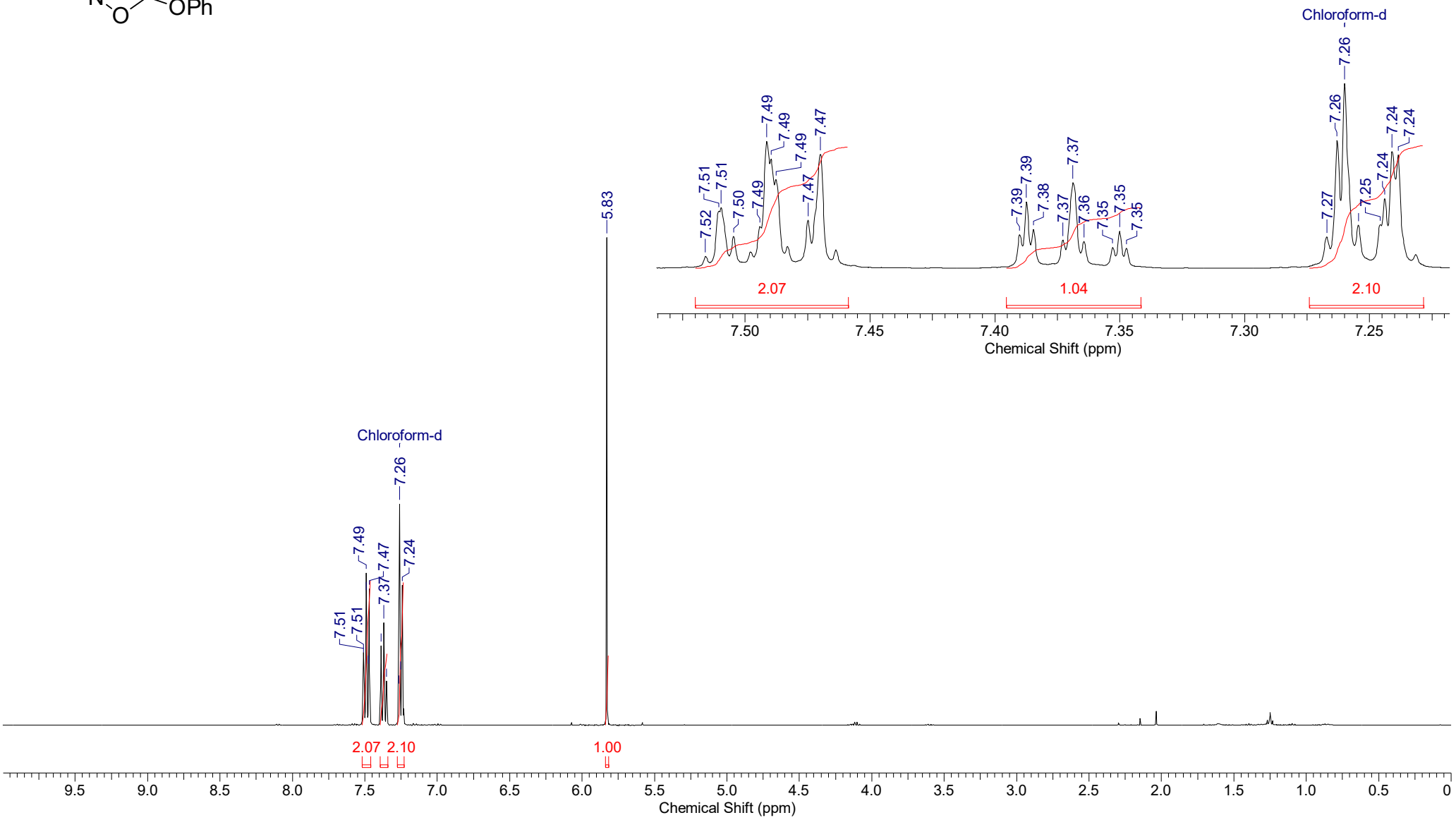
4-(3-Nitroisoxazol-5-yl)morpholine **2zg** (^{13}C NMR)



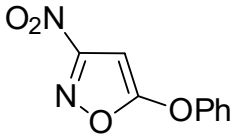


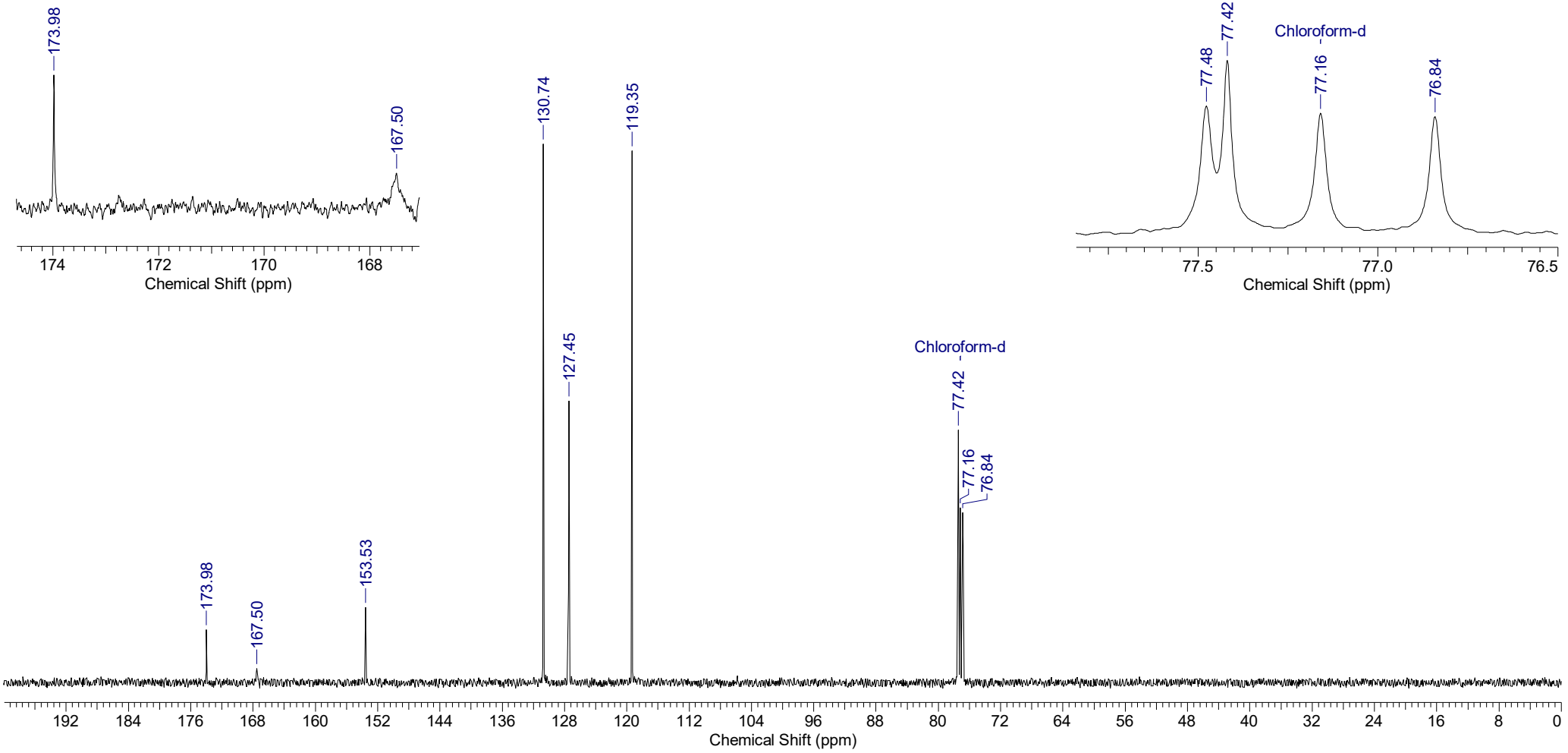
3-Nitro-5-phenoxyisoxazole **2zh** (^{1}H NMR)



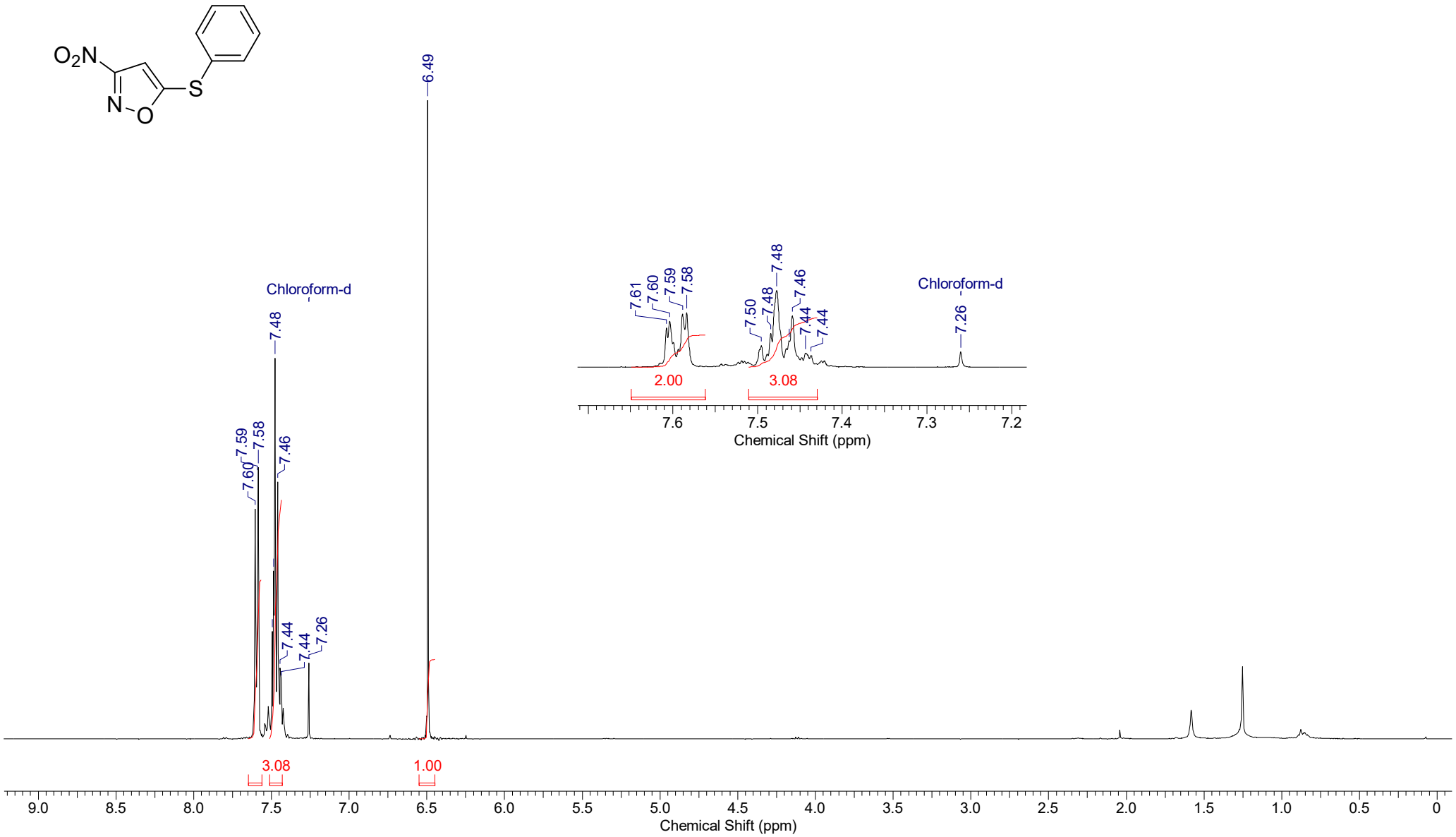


3-Nitro-5-phenoxyisoxazole **2zh** (^{13}C NMR)

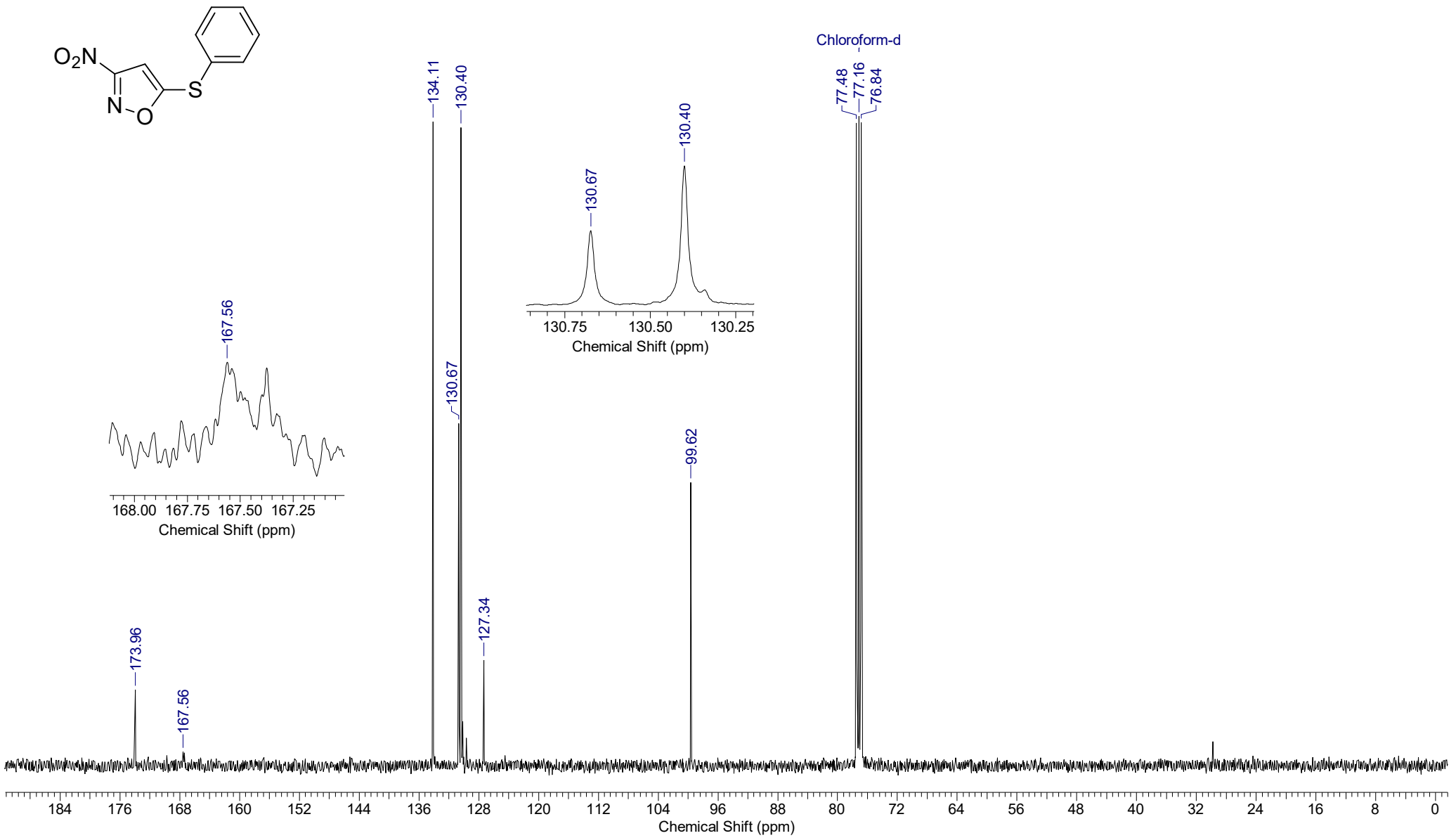




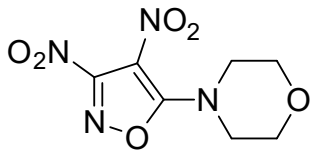
3-Nitro-5-(phenylsulfanyl)isoxazole **2zi** (^{1}H NMR)



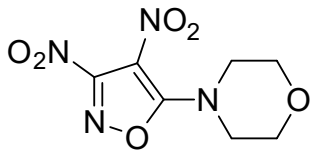
3-Nitro-5-(phenylsulfanyl)isoxazole **2zi** (^{13}C NMR)



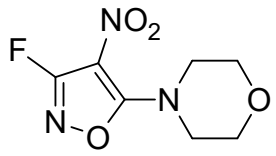
4-(3,4-Dinitroisoxazol-5-yl)morpholine **3** (^{1}H NMR)



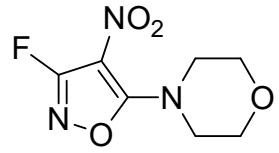
4-(3,4-Dinitroisoxazol-5-yl)morpholine **3** (^{13}C NMR)



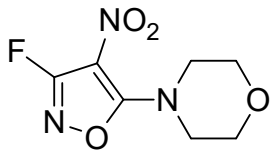
4-(3-Fluoro-4-nitroisoxazol-5-yl)morpholine **4a** (^{1}H NMR)



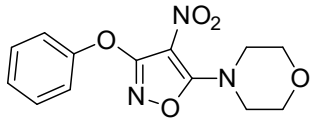
4-(3-Fluoro-4-nitroisoxazol-5-yl)morpholine **4a** (^{13}C NMR)

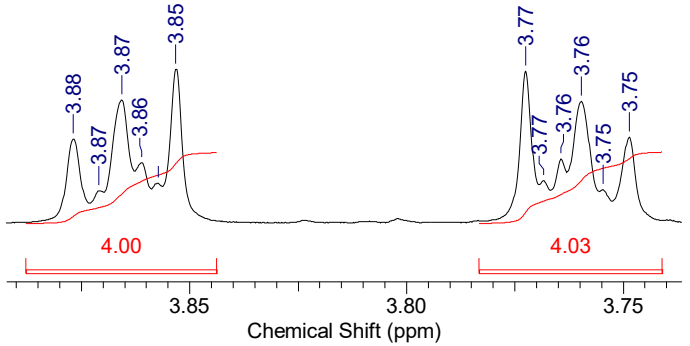


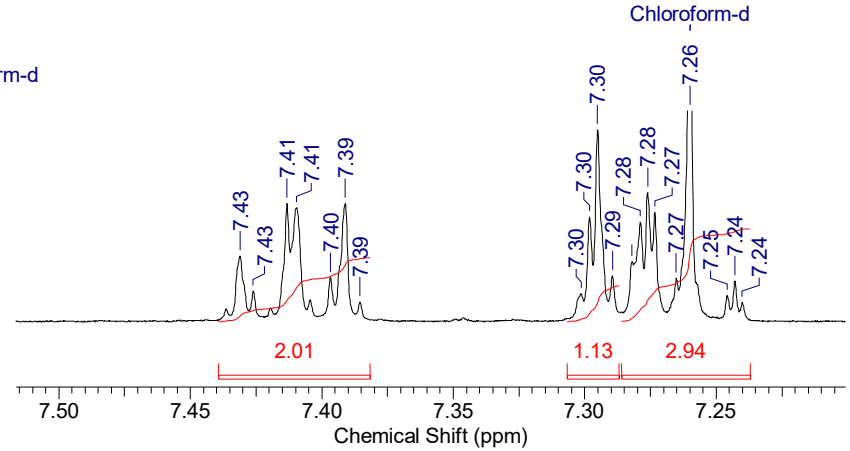
4-(3-Fluoro-4-nitroisoxazol-5-yl)morpholine **4a** (^{19}F NMR)

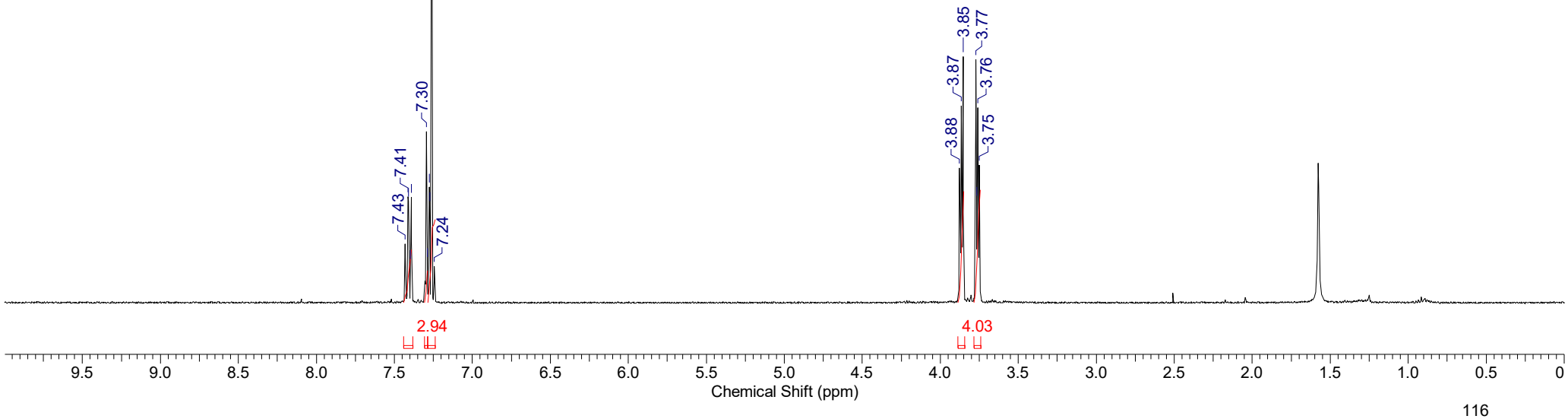


4-(4-Nitro-3-phenoxyisoxazol-5-yl)morpholine **4b** (^{1}H NMR)

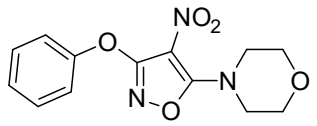




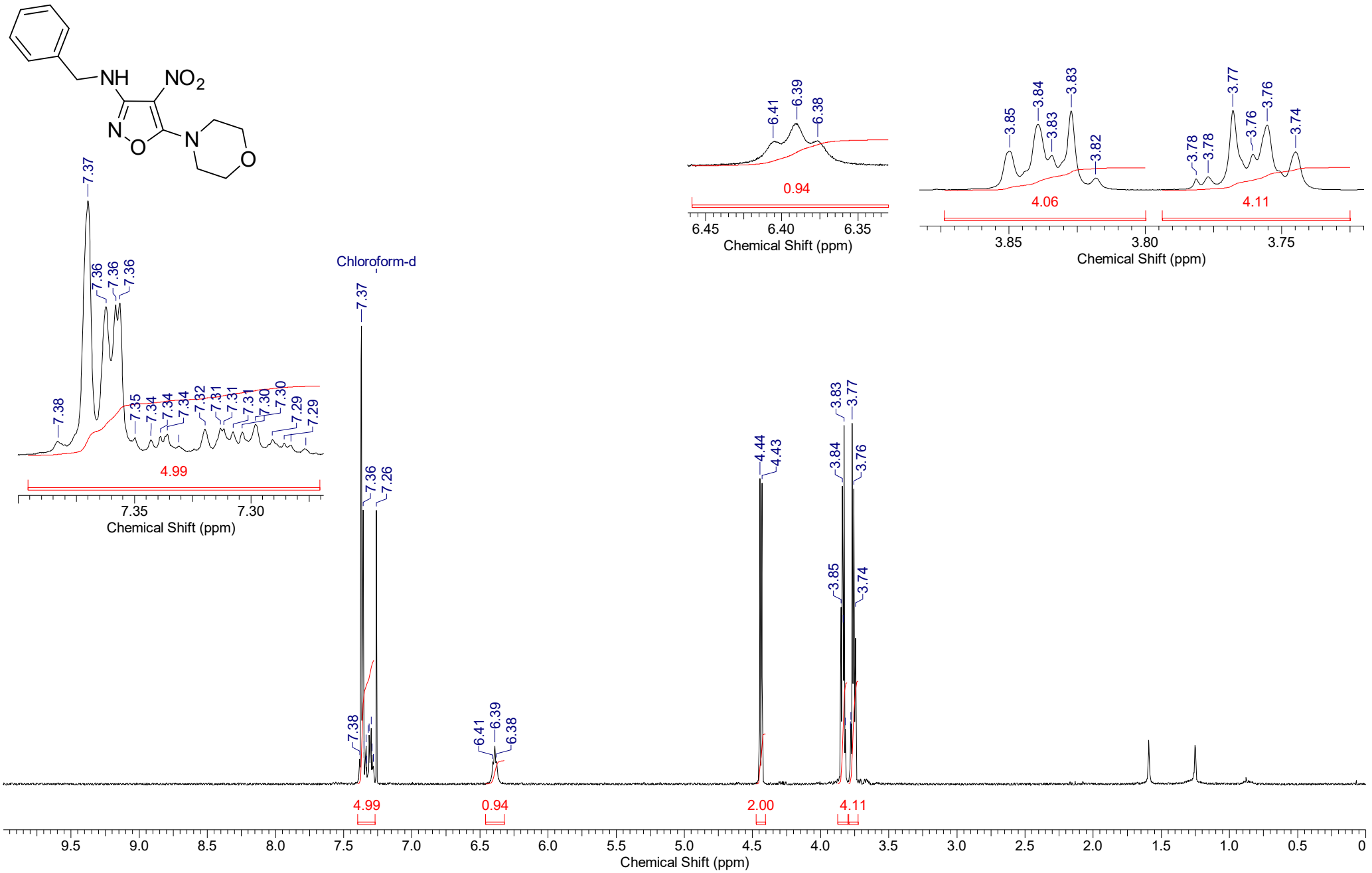




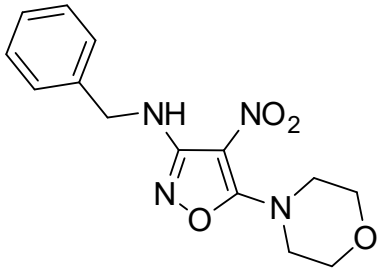
4-(4-Nitro-3-phenoxyisoxazol-5-yl)morpholine **4b** (^{13}C NMR)

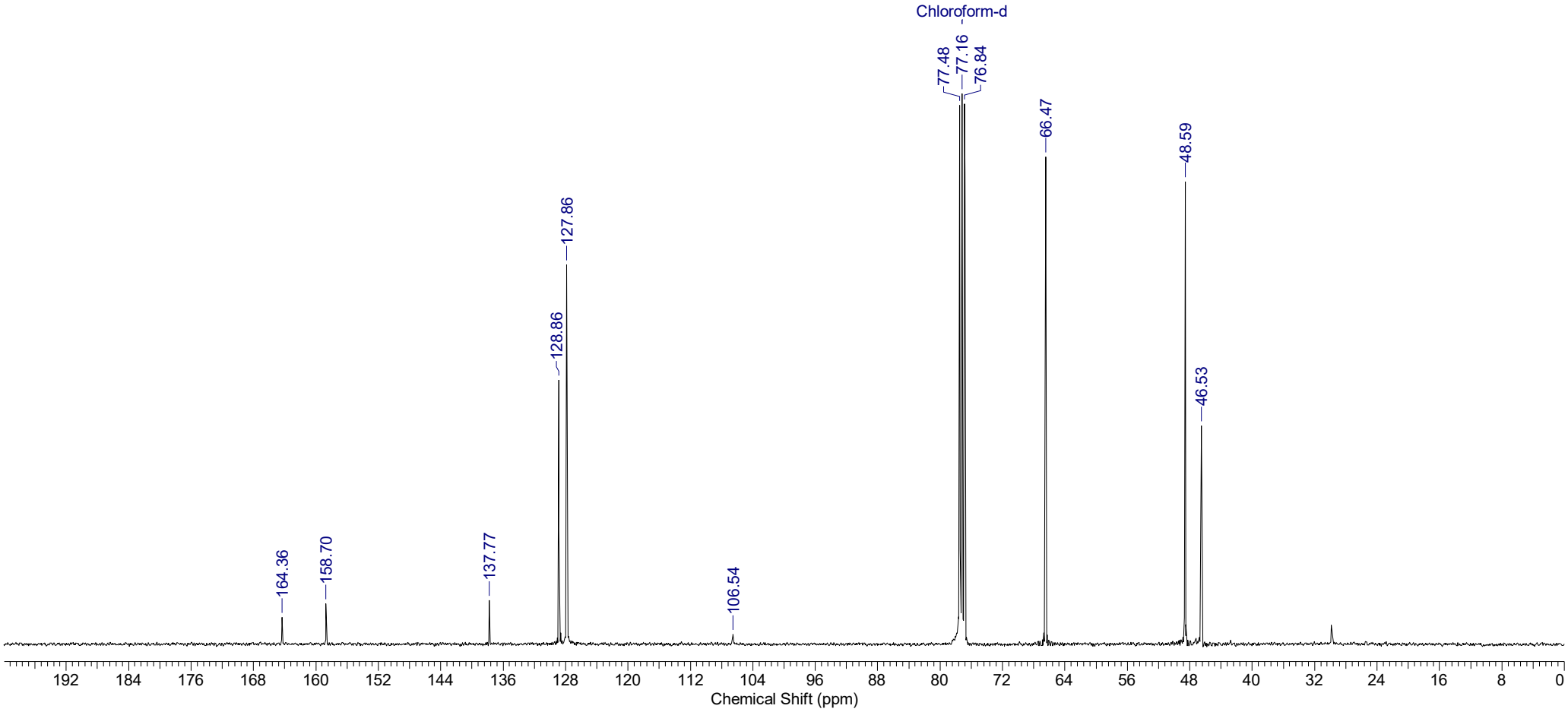


N-Benzyl-5-morpholin-4-yl-4-nitroisoxazole-3-amine **4c** (^{1}H NMR)

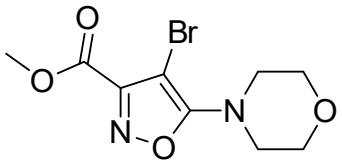


N-Benzyl-5-morpholin-4-yl-4-nitroisoxazole-3-amine **4c** (^{13}C NMR)

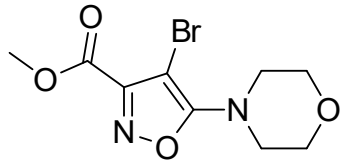




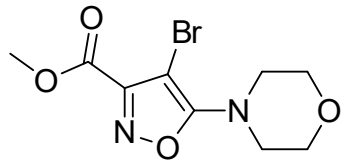
Methyl 4-bromo-5-morpholinoisoxazole-3-carboxylate **5** (^{1}H NMR)



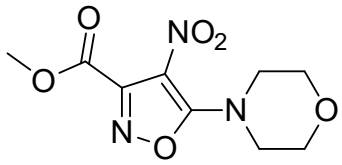
Methyl 4-bromo-5-morpholinoisoxazole-3-carboxylate **5** (^{13}C NMR)

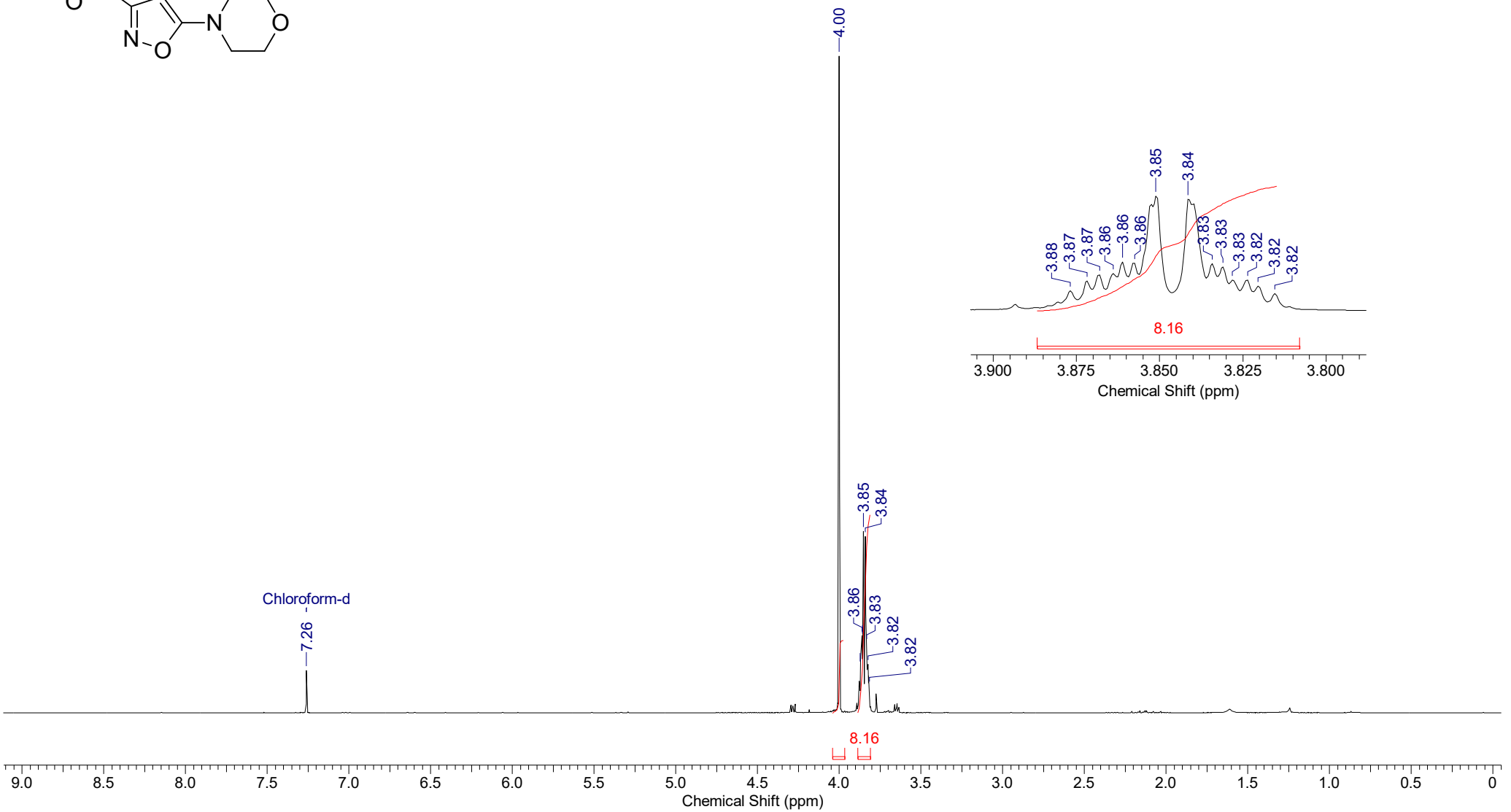


Methyl 4-bromo-5-morpholinoisoxazole-3-carboxylate **5** (APT)

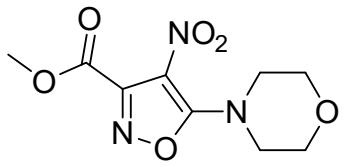


Methyl 5-morpholino-4-nitroisoxazole-3-carboxylate **6** (^{1}H NMR)

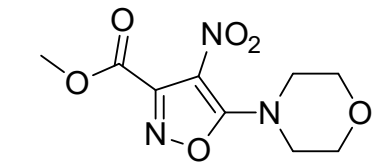




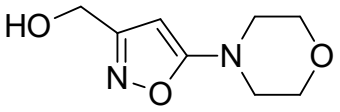
Methyl 5-morpholino-4-nitroisoxazole-3-carboxylate **6** (^{13}C NMR)

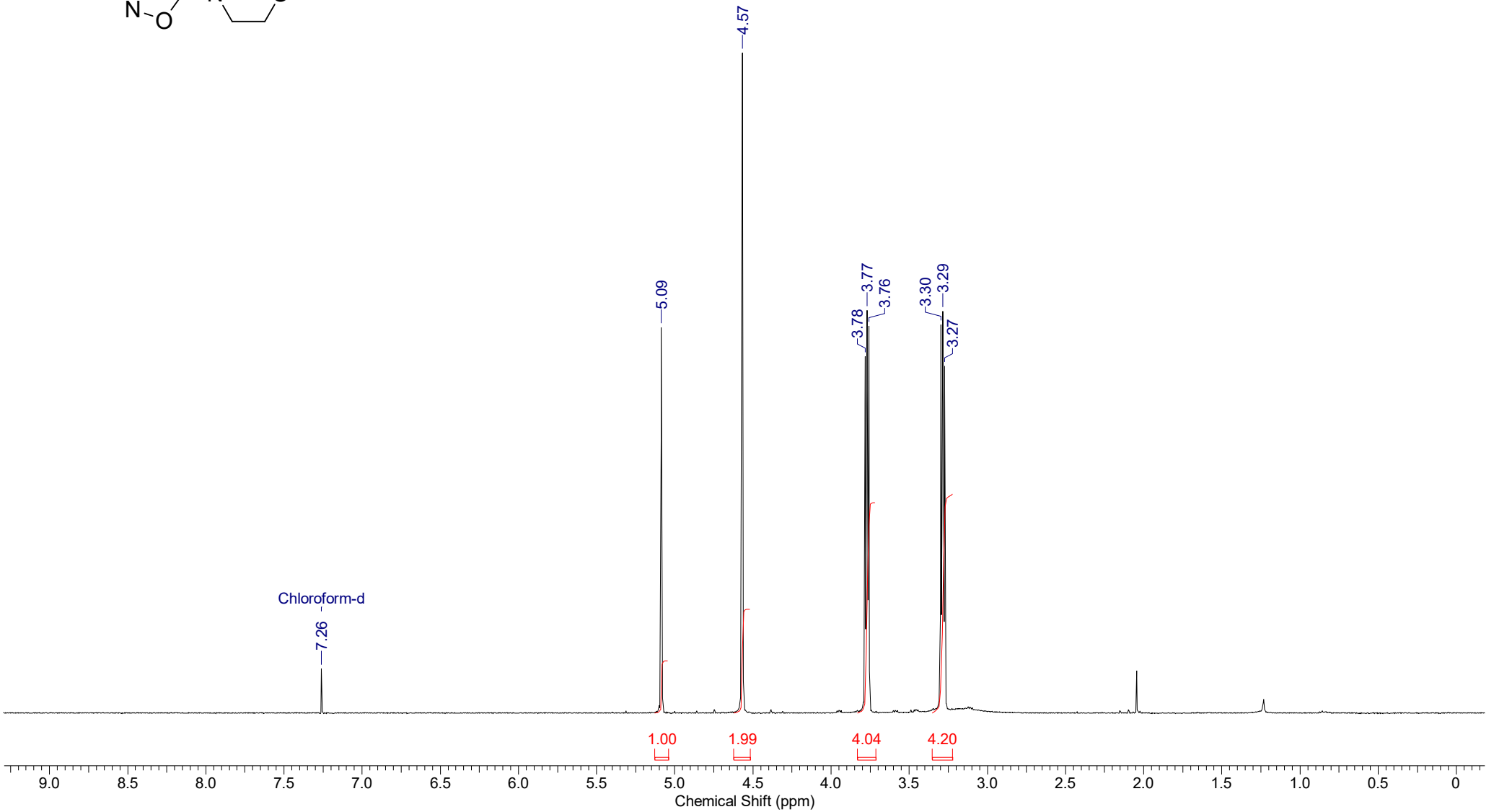


Methyl 5-morpholino-4-nitroisoxazole-3-carboxylate **6** (HMBC)

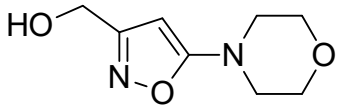


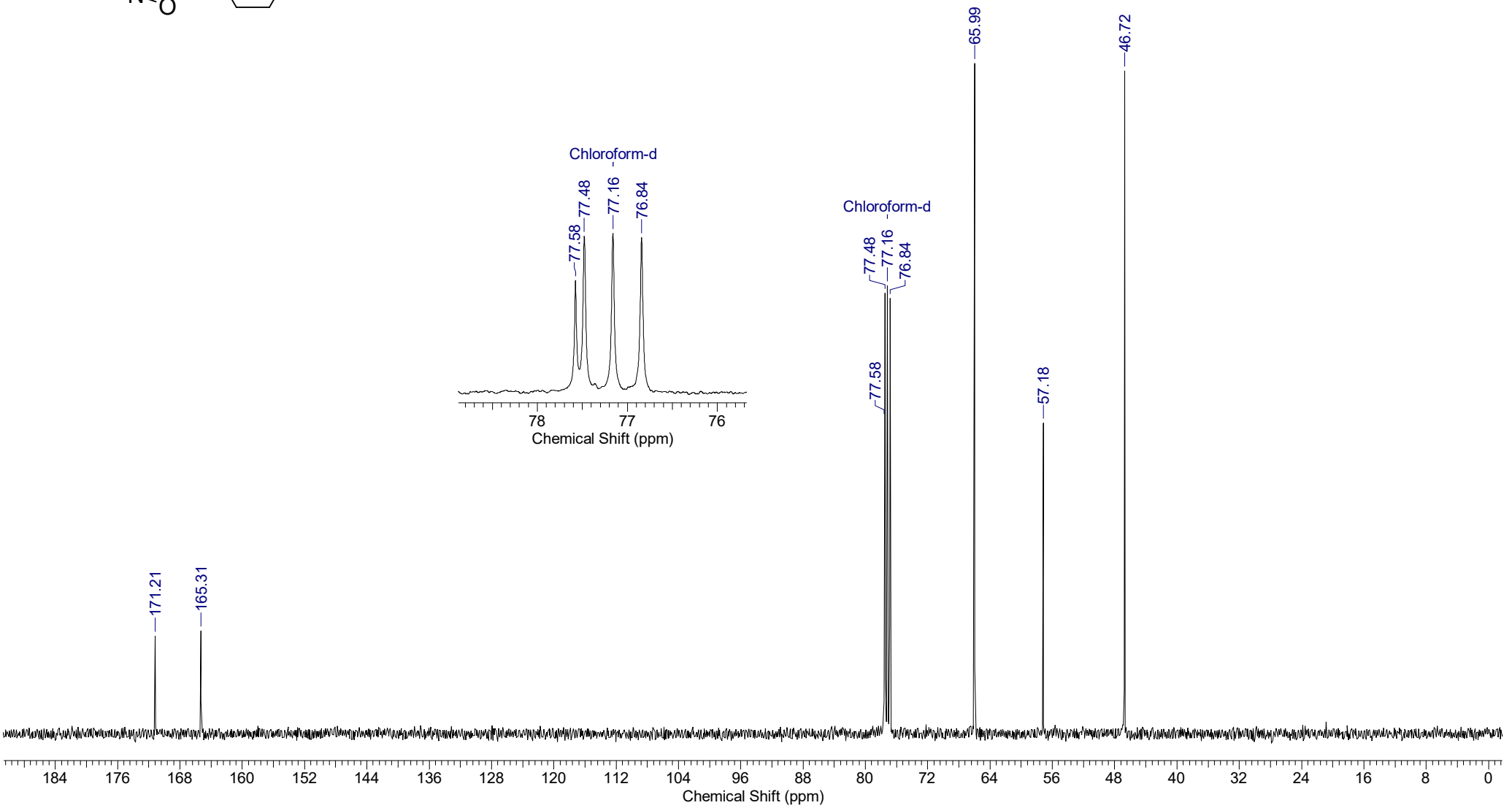
(5-Morpholinoisoxazol-3-yl)methanol **7** (^{1}H NMR)



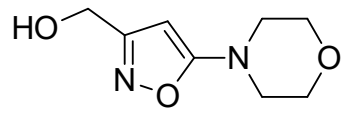


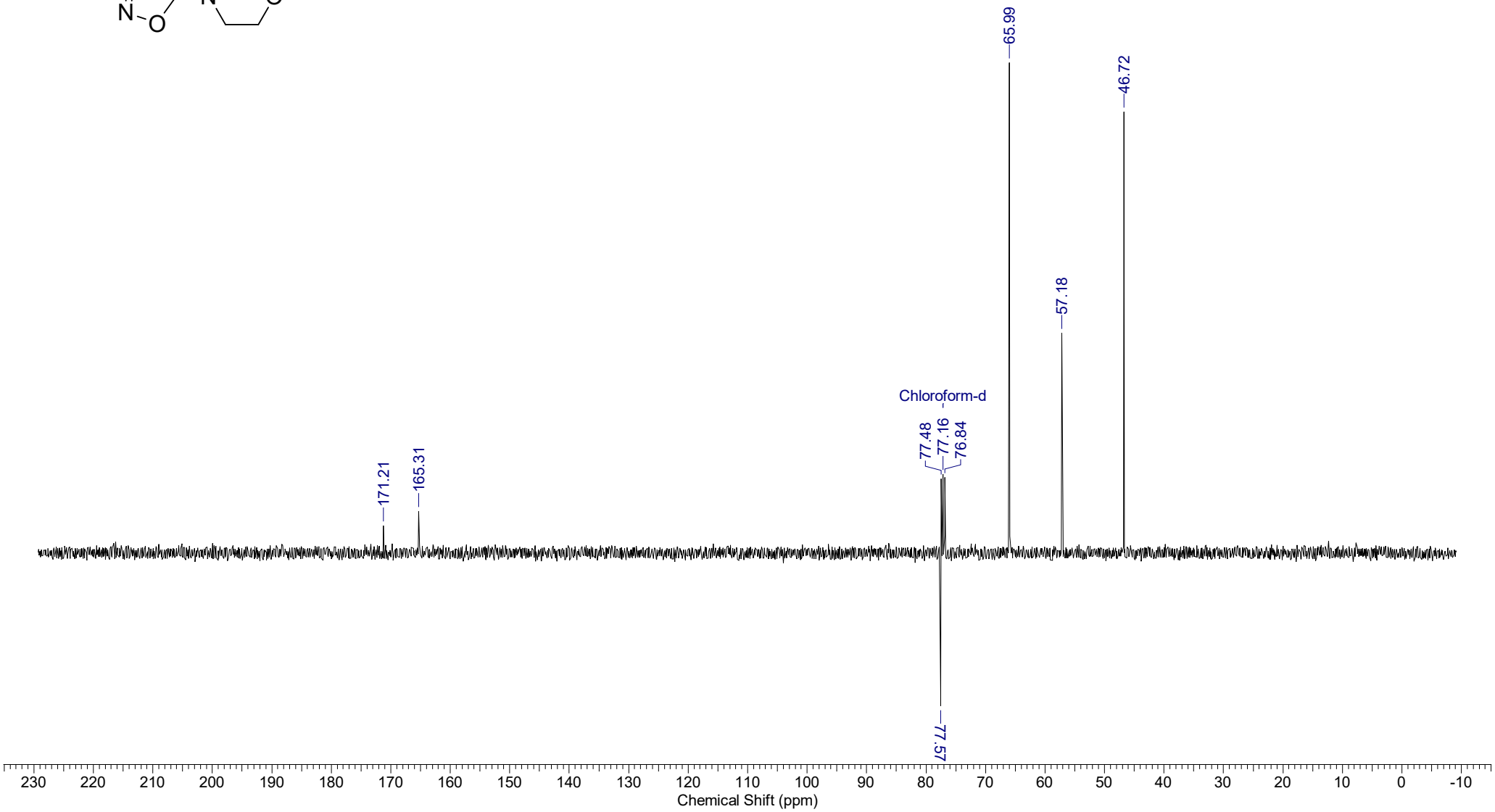
(5-Morpholinoisoxazol-3-yl)methanol **7** (^{13}C NMR)



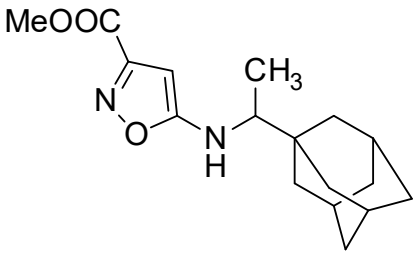


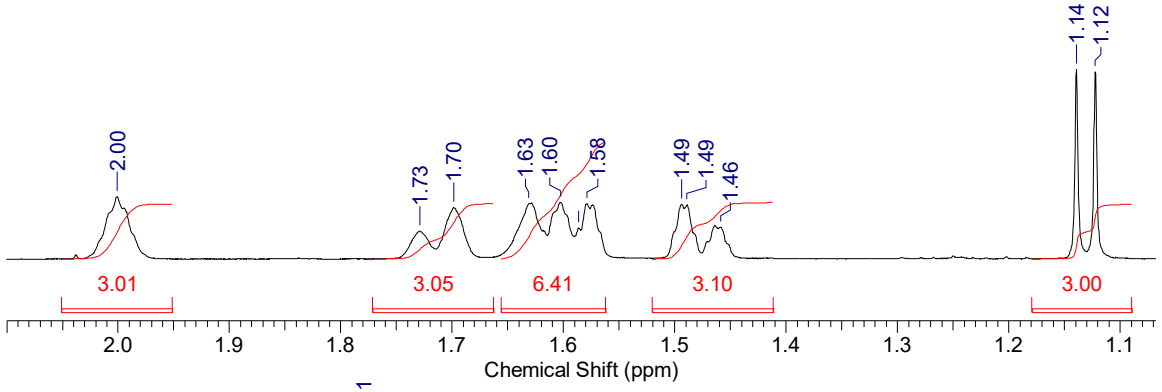
(5-Morpholinoisoxazol-3-yl)methanol **7** (APT)

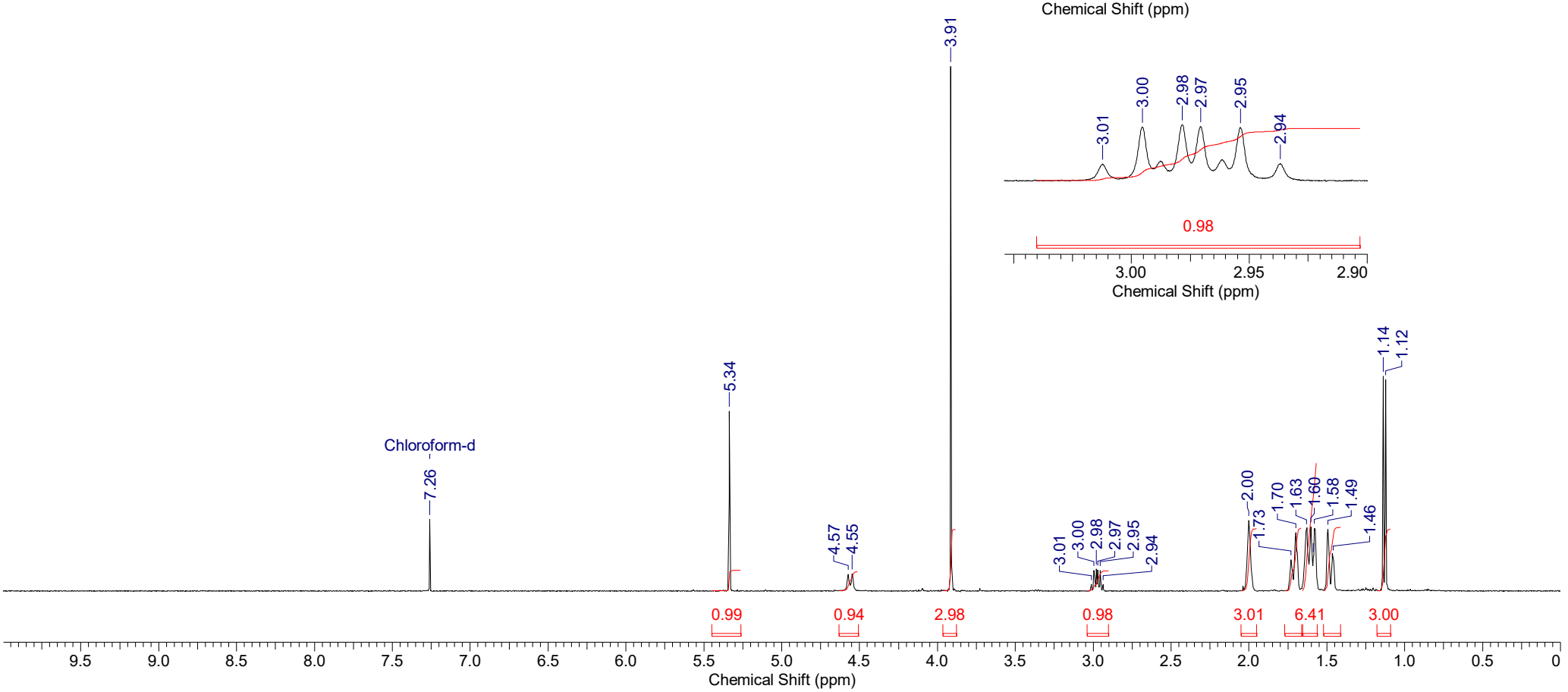




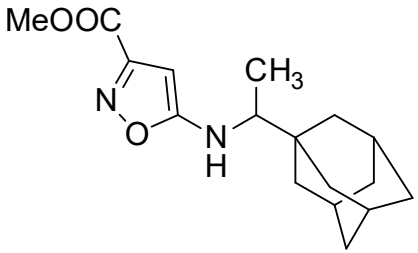
Methyl 5-{[1-(1-adamantyl)ethyl]amino}isoxazole-3-carboxylate **9** (^{1}H NMR)

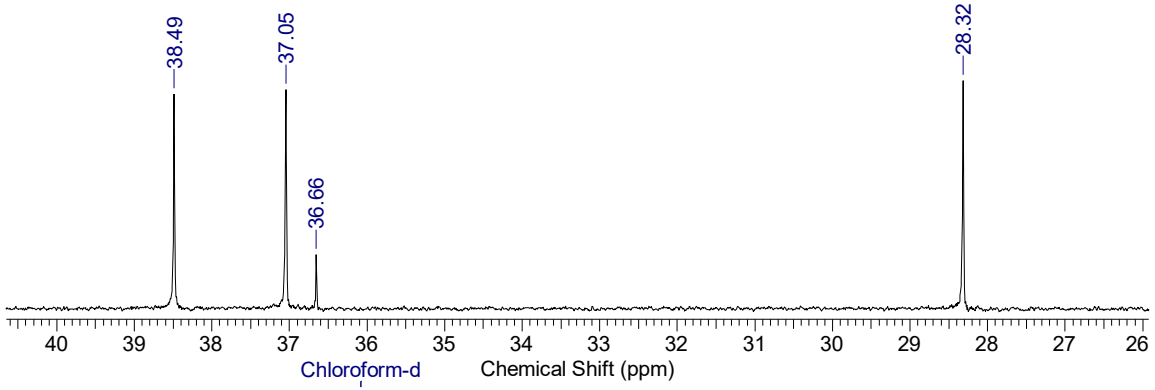


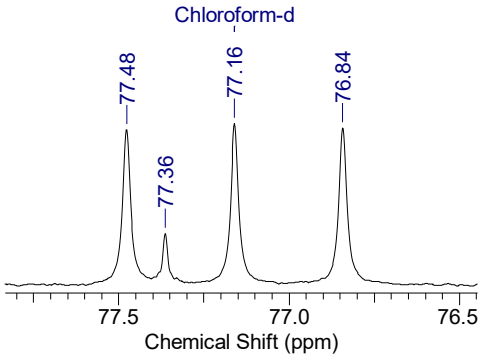




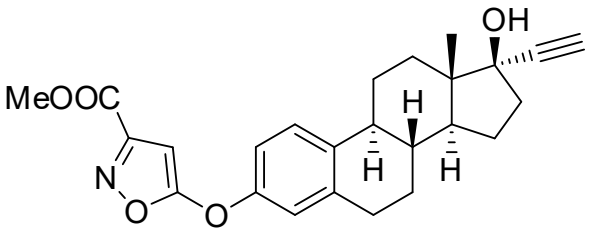
Methyl 5-{[1-(1-adamantyl)ethyl]amino}isoxazole-3-carboxylate **9** (^{13}C NMR)

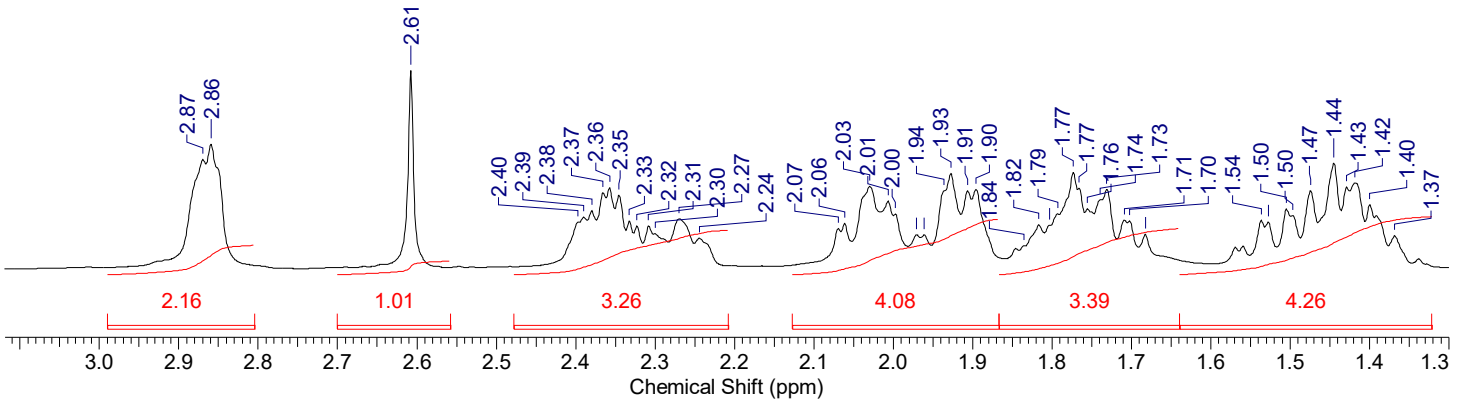


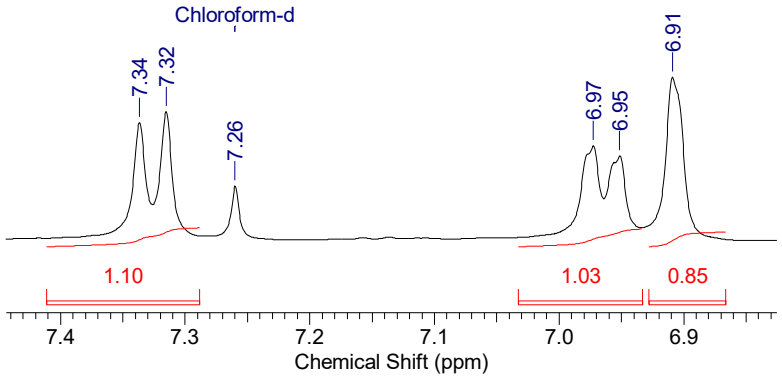




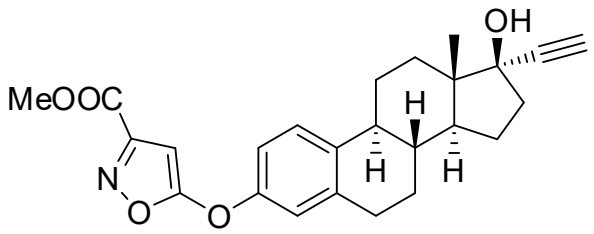
Methyl 5-(((8R,9S,13S,14S,17R)-17-ethynyl-17-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)oxy)isoxazole-3-carboxylate **11** (^{1}H NMR)

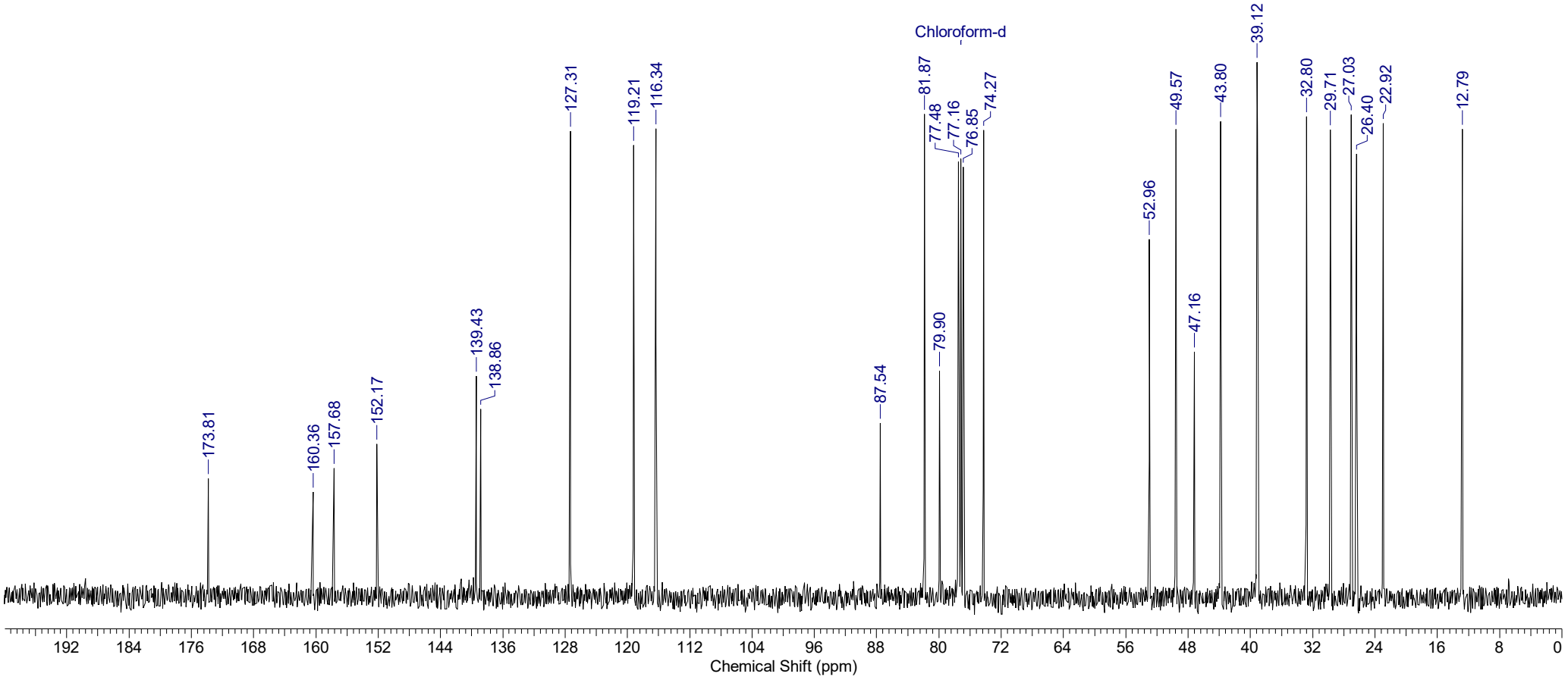




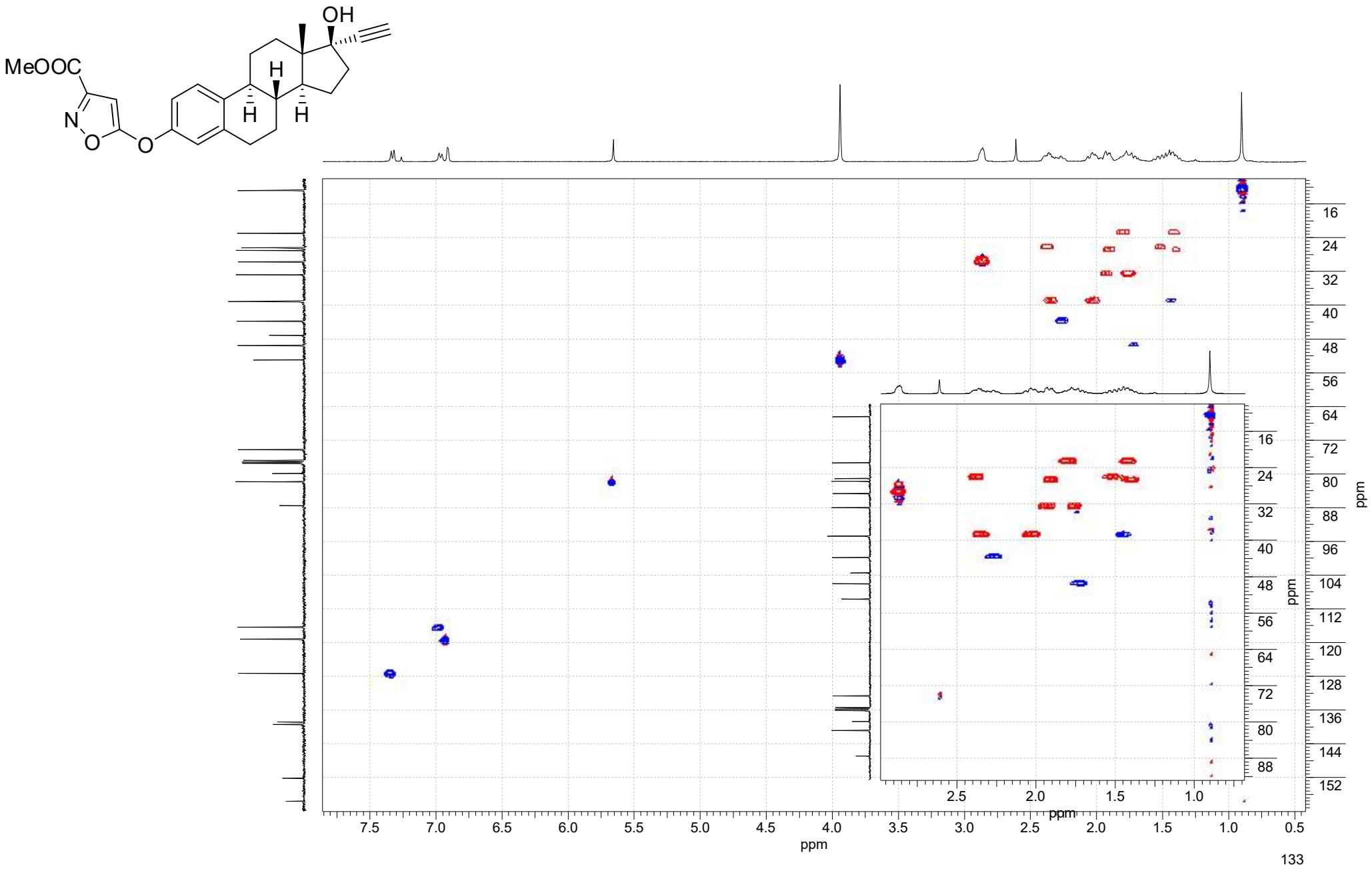


Methyl 5-(((8R,9S,13S,14S,17R)-17-ethynyl-17-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)oxy)isoxazole-3-carboxylate **11** (^{13}C NMR)





Methyl 5-(((8R,9S,13S,14S,17R)-17-ethynyl-17-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)oxy)isoxazole-3-carboxylate **11** (HSQC)



Methyl 5-(((8R,9S,13S,14S,17R)-17-ethynyl-17-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)oxy)isoxazole-3-carboxylate **11** (HMBC)