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Ball-Milling and Cheap Reagents Breathe Green Life into the One Hundred-Year-Old Hofmann reaction

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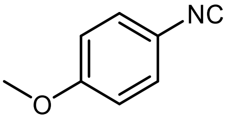
1. GENERAL METHODS AND MATERIALS

Commercially available reagents were purchased from Acros, Aldrich, Strem Chemicals, Alfa-Aesar, TCI Europe and used as received. The solvents were purchased from Aldrich or VWR International in sure/sealed^{TM} bottles over molecular sieves. Filtration of the resulting brown crude isocyanide residue loaded onto a short bed of silica gel was performed by using EcoChrome^{TM} MP Silica gel 60 Å, particle size 0.040–0.063 mm (230–400 mesh). All reactions were monitored by thin-layer chromatography (TLC) performed on glass-backed silica gel 60 F254, 0.2 mm plates (Merck), and compounds were visualized under UV light (254 nm) or using cerium ammonium molybdate solution with subsequent heating. The eluents were technical grade and distilled prior to use. A Spex 8000M Mixer/Mill®, ball-milling apparatus was used for all reactions. The reagents were milled using a zirconia-beaker (45 mL) equipped with balls (d = 10.0 mm) of the same material. ^{1}H and ^{13}C liquid NMR spectra were recorded on a Varian 400 and 500 MHz NMR spectrometer at 298 K and were calibrated using trimethylsylane (TMS). Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referred to the residual hydrogen in the solvent ($CHCl_3$, 7.27 ppm or DMSO 2.54 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br s = broad singlet), coupling constant (*J*) in Hertz and integration. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$, δ 77.0 ppm or δ DMSO-d_6 δ 39.5 ppm). To remove any trace of heptane, all NMR samples were first dissolved in DCM (approximately 1 mL) and then concentrated under vacuum with a rotary evaporator. ^{1}H NMR self-diffusion measurements were performed in $CDCl_3$ at 298 K on a Bruker Avance 300 MHz (7.05 T) spectrometer. A Bruker DIFF30 probe supplied by a Bruker Great 1/40 amplifier was used to measure the self-diffusion coefficients, *D*. The NMR sequence used was the Pulse-Gradient STimulated Echo (PGSTE). Experiments were performed varying the gradient strength (g) keeping, at the same time, the gradient pulse length (δ) and the gradient pulse intervals constant (Δ). *D* were extrapolated from the Stejskal-Tanner plot, i.e. the semi-logarithmic fitting of I/I_0 vs q^2t, where I and I_0 are the signals intensities in the presence and absence of the applied field gradient respectively, $q = \gamma g\delta$ is the scattering vector (γ being the gyromagnetic ratio of the observed nucleus), $t = (\Delta - \delta/3)$ is the diffusion time.[1] Errors on the self-diffusion coefficients were estimated to be around 2 % on the basis of repeated measurements. Deuterated NMR solvents were obtained from Aldrich. High-resolution mass spectra (HRMS) were recorded using an Electrospray Ionisation (ESI) spectrometer. Analysis of reaction mixture was determined by GC-MS (GC Agilent 6850, MS Agilent 5973) and equipped with HP5 universal capillary column (30 m length and 0.20 mm diameter, 0.11 film thickness) and a flame ionization detector (FID). GC oven temperature was programmed from 80 °C to 250 °C at the rate of 10 °C/min. He gas was used as a carrier gas. Temperatures of injection port and FID were kept constant at 300 °C. Retention times of different compounds were determined by injecting pure compound under identical conditions. Melting points were determined in an open capillary on a Büchi melting point apparatus and are uncorrected.

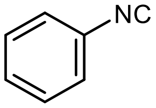
2. GENERAL PROCEDURE

4-methoxy aniline (615 mg, 5.0 mmol), sodium hydroxide (2.4 g, 60.0 mmol), chloroform (716 mg, 484 μL, 6.0 mmol) and sodium sulfate (1.0 g, 7.0 mmol) were transferred into a zirconia-milling beaker (45 ml) equipped with four balls (d = 10.0 mm) of the same material. The jar was shaken at 18Hz for 15 minutes in a Spex 8000M Mixer/Mill. Then an additional aliquot of chloroform (716 mg, 484 μL 6.0 mmol) was added and the mixture was subjected to grinding further for 15 minutes. Upon completion of the ball milling process (monitored by TLC and GC), the resulting brown solid was scratched off from the jar, loaded onto a short bed of silica gel (1 g) and washed with heptane/ethyl acetate (97/3) solution. The solvent was removed under reduced pressure, affording the desired product **2** as yellow solid, (419 mg, 63% yield).

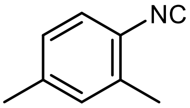
3. SUMMARY OF ^{1}H AND ^{13}C NMR AND HRMS DATA FOR ISOCYANIDES 2-30



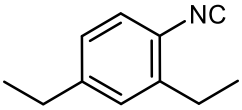
1-Isocyano-4-methoxybenzene, 2. yellow solid, (419 mg, 63% yield). M.p.: 31–32 °C (Lit.:[2] 30 °C); R_f = 0.45 (9:1 Heptane/AcOEt); IR (KBr) ν (cm^{-1}): 2969, 2123, 1606, 1504, 1249, 1024, 831; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.31 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.8 (t, J_{NC} = 5.2 Hz), 160.0, 128.0, 119.6 (t, J_{NC} = 13.5 Hz), 114.7, 55.7. Spectroscopic data are in agreement with those reported earlier.[2]



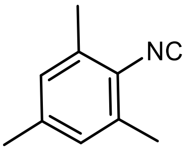
Isocyanobenzene (3). Yellow oil (284 mg, 55%); R_f = 0.57 (9:1 Heptane/AcOEt); IR (KBr) ν (cm^{-1}): 2972, 2123, 1611, 1512, 1261, 837; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41–7.36 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 164.1 (t, J_{NC} = 5.2 Hz), 129.5, 129.5, 126.8 (t, J_{NC} = 13.5 Hz), 126.5. Spectroscopic data are in agreement with those reported earlier.[3]



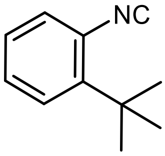
1-Isocyano-2,4-dimethylbenzene (4). Brown oil, (387 mg, 59%); R_f = 0.57 (9:1 Heptane/AcOEt); IR (KBr) ν (cm^{-1}): 2967, 2940, 2872, 2121, 1660, 1580, 1430, 801; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.21 (d, J = 7.8 Hz, 1H), 7.07 (s, 1H), 6.99 (d, J = 7.8 Hz, 1H), 2.38 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.9 (t, J_{NC} = 5.6 Hz), 139.6, 134.7, 131.2, 127.4, 126.4, 124.1 (t, J_{NC} = 13.2 Hz), 21.4, 18.6; HRMS (ESI): m/z calcd for $C_9H_{10}N$: 132.0813 $[M+H]^+$. Found: 132.0817.



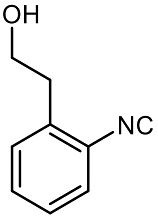
2,4-Diethyl-1-isocyanobenzene (5) Yellow oil, (517 mg, 65%); Rf = 0.53 (9:1 Heptane/AcOEt); IR (KBr) ν (cm^{-1}): 2970, 2942, 2880, 2120, 1667, 1585, 1459, 804; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (t, J = 7.6 Hz, 1H), 7.12 (d, J = 7.6 Hz, 2H), 2.80 (q, J = 7.5 Hz, 4H), 1.27 (t, J = 7.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.9 (t, J_{NC} = 5.5 Hz), 140.9, 129.2, 126.3, 125.4, 25.9, 14.0; HRMS (ESI): m/z calcd for $C_{11}H_{14}N$: 160.1126 $[M+H]^+$. Found: 160.1130.



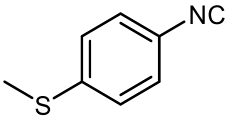
2-Isocyano-1,3,5-trimethylbenzene (6). Yellow oil (508 mg, 70 %); $R_f = 0.51$ (9:1 Heptane/AcOEt); IR (KBr) ν (cm^{-1}): 2970, 2942, 2880, 2120, 1667, 1585, 1459, 804; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.90 (s, 2H), 2.36 (s, 6H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.8 (t, $J_{NC} = 5.2$ Hz), 138.9, 134.7, 128.5, 124.3 (t, $J_{NC} = 12.5$ Hz), 21.2, 18.9. Spectroscopic data are in agreement with those reported earlier.[4]



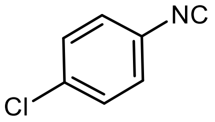
1-(*tert*-Butyl)-2-isocyanobenzene (7). Yellow oil (151 mg, 19%); $R_f = 0.52$ (9:1 Heptane/AcOEt); IR (KBr) *ν* (cm^{-1}): 2962, 2871, 2120, 1631, 749; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.28 (d, $J = 5.9$ Hz, 1H), 7.08 (t, $J = 6.1$ Hz, 1H), 6.86–6.74 (m, 1H), 6.68 (d, $J = 7.6$ Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.2 (t, $J_{NC} = 5.6$ Hz), 145.7, 130.2, 129.5, 127.0, 126.9, 125.4 (t, $J_{NC} = 12.4$ Hz), 35.1, 29.3; HRMS (ESI): m/z calcd for $C_{11}H_{14}N$: 160.1126 $[M+H]^+$. Found: 160.1123.



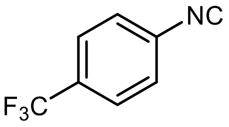
2-(2-Isocyanophenyl)ethan-1-ol (8). Colourless oil (132 mg, 18%); $R_f = 0.52$ (3:2 Heptane/AcOEt); IR (KBr) *ν* (cm^{-1}): 2962, 2932, 2844, 2863, 2142, 1667, 1465, 1380; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45–7.18 (m, 4H), 3.93 (t, $J = 6.5$ Hz, 2H), 3.04 (t, $J = 6.5$ Hz, 2H), 1.61 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.2, 135.5, 130.8, 129.6, 127.6, 127.2, 126.6 (t, $J_{NC} = 12.4$ Hz) 61.9, 35.7; HRMS (ESI): m/z calcd for $C_9H_{10}NO$: 148.0762 $[M+H]^+$. Found: 148.0759.



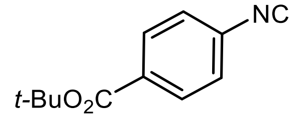
((4-Isocyanophenyl)(methyl)sulfane (9). Yellow oil (380 mg, 51%); $R_f = 0.21$ (9:1 Heptane/AcOEt). IR (KBr) *ν* (cm^{-1}): 2921, 2123, 1484, 1091, 812; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.28 (d, $J =$ (8.6 Hz, 2H), 7.21 (d, $J = 8.6$ Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.2, 141.4, 126.7, 126.5, 123.2, (t, $J_{NC} = 13.5$ Hz) 15.4; HRMS (ESI): m/z calcd for C_8H_8NS: 150.0377 $[M+H]^+$, found: 150.0379.



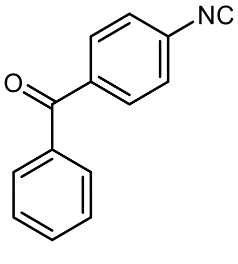
1-Chloro-4-isocyanobenzene (10). White solid (344 mg, 50%), m.p.: 71-72°C (Lit.:[5] 71°C); $R_f = 0.60$ (9:1 Heptane/AcOEt). IR (KBr) ν (cm^{-1}): 2124, 1650, 1488, 1403, 1090, 1020, 828; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, $J = 8.8$ Hz, 2H), 7.32 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.7, 135.6, 129.9, 127.8, 125.2 (t, $J_{NC} = 13.5$ Hz); Spectroscopic data are in agreement with those reported earlier.[6]



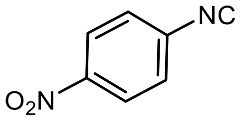
1-Isocyano-4-(trifluoromethyl)benzene (11). Brown oil (385 mg, 45%); $R_f = 0.67$ (9:1 Heptane/AcOEt); IR (KBr) ν (cm-1): 3038, 2935, 2261, 1615, 1504, 1323, 1218, 1130, 827. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.69 (d, $J = 8.1$ Hz, 2H), 7.51 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.0, 134.3 (q, $^2J_{CF} = 33$ Hz, $\underline{C}$(Ar)-CF_3), 132.0 (t, $J_{CN} = 15$ Hz, C(Ar)-NC), 129.6, 129.4 (dd, $J^1 = 7.6$ Hz, $J^2 = 3,8$ Hz), 125 (q, $^1J_{CF} = 273$ Hz). Spectroscopic data are in agreement with those reported earlier.[7]



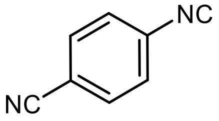
***tert*-Butyl 4-isocyanobenzoate (12)**. Brown oil (498 mg, 49%), $R_f = 0.42$ (9:1 Heptane/AcOEt); IR (KBr) ν (cm^{-1}): 3001, 2978, 2126, 1719, 1604, 1290, 1100, 768. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, $J = 8.5$ Hz, 2H), 7.37 (d, $J = 8.5$ Hz, 2H), 1.56 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 164.0, 132.8, 130.6, 129.5, 126.2, 82.0, 28.1; HRMS (ESI): m/z calcd for $C_{12}H_{14}NO_2$: 204.1024 $[M+H]^+$, found: 204.1025.



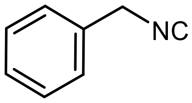
(4-Isocyanophenyl)(phenyl)methanone (13). White solid (445 mg, 43%), m.p.: 101–102 °C (*Lit.*:[8] 101 °C); $R_f = 0.44$ (9:1 Heptane/AcOEt); IR (KBr) ν (cm^{-1}): 3093, 3065, 2126, 1648, 1599, 1574, 1411, 1274, 694; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.84 (d, $J = 7.4$ Hz, 2H), 7.77 (d, $J = 7.4$ Hz, 2H), 7.63 (t, $J = 7.0$ Hz, 1H), 7.50 (t, $J = 7.0$ Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 195.0, 167.1, 138.3, 136.8, 133.2, 131.2, 130.1, 129.5, 128.7, 126.5. Spectroscopic data are in agreement with those reported earlier.[9]



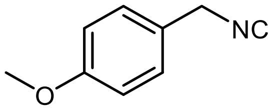
1-Isocyano-4-nitrobenzene (14). Yellow solid (185 mg, 25 %); m.p.: 109–110 °C (*Lit.*:[10] 110 °C); $R_f = 0.53$ (9:1 Heptane/AcOEt); IR (KBr) ν (cm^{-1}): 3067, 2132, 1545, 1354; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.31 (*d*, J = 8.9 Hz, 2H), 7.57 (*d*, J = 8.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.0 (t, J_{CN} = 10 Hz), 147.7, 131.4 (t, J_{CN} = 12.7 Hz), 127.7, 125.2. Spectroscopic data are in agreement with those reported earlier.[11]



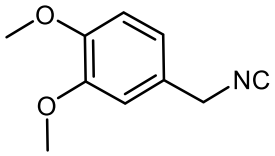
4-Isocyanobenzonitrile (15). White solid (186 mg, 29%), m.p.: 184-185 °C (*Lit*:[12] 180-185 °C); $R_f = 0.53$ (9:1 Heptane/AcOEt); IR (KBr) ν (cm^{-1}): 3093, 3045, 2235, 1607, 1501; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.73 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.1, 133.6, 129.9 (t, J_{NC} = 13.5 Hz.), 127.4, 117.3, 113.6. Spectroscopic data are in agreement with those reported earlier, CAS no: 2980-80-5.[13]



(Isocyanomethyl)benzene (16). Brown oil (328 mg, 56%); $R_f = 0.54$ (9:1 Heptane/AcOEt); IR (neat) ν (cm^{-1}) 3100, 2900, 2150, 1600, 1480, 1210, 690; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42-7.34 (m, 5H), 4.65 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 157.8 (t, J_{NC} = 5.6 Hz), 132.4, 129.0, 128.4, 126.6, 45.5 (t, J_{NC} = 6.9 Hz). Spectroscopic data are in agreement with those reported earlier, CAS no: 10340-91-7.[14]

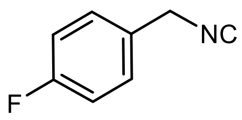


1-(Isocyanomethyl)-4-methoxybenzene (17). Yellow oil (361 mg, 49%); $R_f = 0.30$ (9:1 Heptane/AcOEt); IR (KBr) ν (cm^{-1}) 2939, 2838, 2148, 1681, 1510, 1247, 1029, 813; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.24 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 4.54 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) 159.7, 157.1 (t, J_{NC} = 5.1 Hz), 128.2, 124.6, 114.4, 55.4, 45.1 (t, J_{NC} = 6.7 Hz). Spectroscopic data are in agreement with those reported earlier.[15]

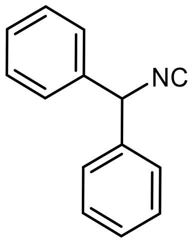


4-(Isocyanomethyl)-1,2-dimethoxybenzene (18). Yellow oil (416 mg, 67%); $R_f = 0.54$ (Heptane/AcOEt 8/2); IR (KBr) ν (cm^{-1}) 2836, 2153, 1596, 1514, 1025; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87-6.83 (m, 3H), 4.55(s, 2H), 3.88 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 157.4 (t,

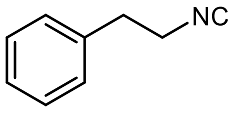
J_{NC} = 5.7 Hz), 149.5, 149.2, 124.9, 119.3, 111.4, 110.0, 56.1, 56.0, 45.4 (t, J_{NC} = 6.9 Hz); HRMS (ESI): m/z calcd for $C_{10}H_{12}NO_2$: 178.0868 [M+H]$^+$, found: 178.0871.



1-Fluoro-4-(isocyanomethyl)benzene (19). Yellow oil (304 mg, 45%); R_f = 0.39 (9:1 Heptane/AcOEt); IR (KBr) ν (cm^{-1}): 2932, 2262, 2153, 1607, 1507, 1222, 820; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33 (dd, J = 8.6, 5.1 Hz, 2H), 7.10 (t, J = 8.6 Hz, 2H), 4.61 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 163.0 (d, $^1J_{CF}$ = 247 Hz, C(Ar)-F, 158.0 (t, $^1J_{CN}$ = 5 Hz), 128.6 (d, J_{CF} = 8.8 Hz), 128.51, 116.0 (d, J_{CF} = 23 Hz), 44.8 (t, J_{CN} = 6.3 Hz); HRMS (ESI): m/z calcd for C_8H_7FN: 136.0562 [M+H]$^+$, found: 136.0560. Spectroscopic data are in agreement with those reported earlier.[2]

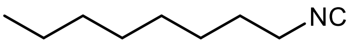


(Isocyanomethylene)dibenzene (20). White solid (396 mg, 41%), m.p.: 36–37 °C (Lit.:[7] 35–36 °C); R_f = 0.50 (9:1 Heptane/AcOEt). IR (KBr) ν (cm^{-1}) 3063, 3030, 2139, 1659, 1601, 1492, 1451, 1323, 700; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39–7.33 (m, 10H), 5.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.43, 137.69, 129.09, 128.59, 126.70, 62.09 (t, J_{NC} = 6.4 Hz); HRMS (ESI): m/z calcd for $C_{14}H_{12}N$: 194.0970 [M+H]$^+$, found: 194.0967

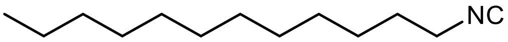


(2-Isocyanoethyl)benzene (21). Yellow oil (341 mg, 52%); R_f = 0.57 (9:1 Heptane/AcOEt); IR (neat) ν (cm^{-1}) 3025, 2915, 2146, 1635, 1452, 696; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 (t, J = 7.3 Hz, 2H), 7.29–7.26 (m, 1H), 7.23 (d, J = 7.3 Hz, 2H), 3.61 (tt, J = 7.2, 2.1 Hz, 2H), 2.99 (tt, J = 5.2, 2.1 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 156.6 (t, J_{NC} = 6.3 Hz), 136.7, 128.8, 128.7, 127.2, 42.9 (t, J_{NC} = 6.9 Hz), 35.6. Spectroscopic data are in agreement with those reported earlier.[16]

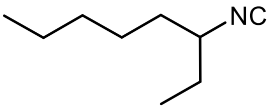
1-Isocyanoheptane (22). Yellow oil (394 mg, 63%); R_f = 0.7 (9:1 Heptane/AcOEt); IR (neat) ν (cm^{-1}): 2925, 2856, 2146, 1635, 1461, 1378, 725; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.37 (tt, J^1 = 8.6 Hz, J^2 =3.8 Hz, 2H), 1.70–1.65 (m, 2H), 1.44–1.40 (m, 2H), 1.34–1.25 (m, 6H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 155.8 (J_{NC} = 5.8 Hz), 41.7 (J_{NC} = 6.3 Hz), 31.7, 29.2, 28.5, 26.4, 22.6, 14.1; HRMS (ESI): m/z calcd for $C_8H_{16}N$: 126.1283 [M+H]$^+$, found: 126.1284. Spectroscopic data are in agreement with those reported earlier.[2]



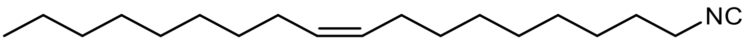
1-Isocyanooctane (23). Colourless oil (494 mg, 71%); $R_f = 0.53$ (9:1 Heptane/AcOEt); IR (KBr) ν (cm^{-1}): 2932, 2148, 1462; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.36 (tt, $J^1 = 6$Hz, $J^2 = 3$Hz, 2H), 1.70–1.62 (m, 2H), 1.47–1.40 (m, 2H), 1.30–1.26 (m, 8H), 0.88 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.7 (t, $J_{NC} = 6.0$ Hz), 41.7 (t, $J_{NC} = 6.0$ Hz), 31.8, 29.2, 29.1, 28.8, 26.4, 22.7, 14.2; HRMS (ESI): m/z calcd for $C_9H_{18}N$: 140.1439 [M+H]$^+$, found: 140.1437. Spectroscopic data are in agreement with those reported earlier. CAS no 70159-85-2 .



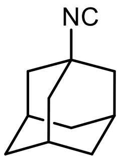
1-Isocyanododecane (24). Yellow oil (674 mg, 69%); $R_f = 0.54$ (9:1 Heptane/AcOEt); IR (KBr) ν (cm^{-1}): 3090, 2126, 1484, 1088, 823; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.39–3.34 (m, 2H), 1.69-1.64 (m, 2H), 1.45-1.40 (m, 2H), 1.32–1.26 (m, 16H), 0.87 (t, $J = 6.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.7, (t, $J_{NC} = 5.6$ Hz), 41.6 (t, $J_{NC} = 6.4$ Hz), 32.0, 29.7 (2C), 29.6, 29.5, 29.4, 29.2, 28.8, 26.4, 22.8, 14.2. Spectroscopic data are in agreement with those reported earlier: CAS no 36999-98-1.[17]



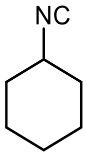
3-Isocyanooctane (25). Yellow oil (349 mg, 54%); $R_f = 0.54$ (9:1 Heptane/AcOEt); IR (KBr) ν (cm^{-1}) 3047, 2093, 2869, 2151, 1670, 1590, 1489, 1380, 1315, 752; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.34 (t, $J = 4.0$ Hz, 1H), 1.54–1.29 (m, 10H), 0.90 (t, $J = 7.1$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156,2 (t, $J_{NC} = 6.4$ Hz), 44.6 (t, $J_{NC} = 6.0$ Hz), 39.0, 30.7, 28.8, 24.1, 22.9, 14.1, 10.9; HRMS (ESI): m/z calcd for $C_9H_{18}N$: 140.1439 [M+H]$^+$, found: 140.1435.



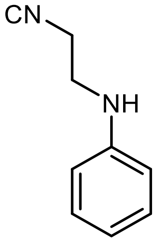
(*Z*)-1-isocyanoicos-9-ene (26). Yellow oil (708 mg, 51%); $R_f = 0.48$ (9:1 Heptane/AcOEt); IR (KBr) ν (cm^{-1}) 2927, 2854, 2146, 1635, 1465, 1350, 723; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.35 (dt, $J = 8.0$, 4.2 Hz, 2H), 3.39–3.36 (m, 2H), 2.06-1.98 (m, 2H), 1.69–1.66 (m, 2H), 1.45–1.42 (m, 2H), 1.27–1.26 (m, 22H), 0.88 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0 (t, $J_{CN} = 5.0$ Hz), 130.0, 129.7, 41.5 (t, $J_{CN} = 6.3$ Hz), 31.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.7, 27.3, 27.2, 26.4, 22.7, 14.1; HRMS (ESI): m/z calcd for $C_{19}H_{36}N$: 278.2848 [M+H]$^+$, found: 278.2850.



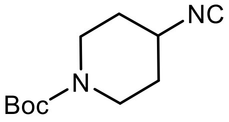
1-Adamantyl isocyanide (27) White solid (467 mg, 58%); m.p.: 189–190 °C, (*Lit.*:[18] 190–191 °C); $R_f = 0.62$ (9:1 Heptane/AcOEt); IR (KBr) ν (cm^{-1}) 2916, 2858, 2123, 1454, 1354, 1309, 1108, 1076,831. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.10–2.02 (m, 3H), 2.02 (d, $J = 3.1$ Hz, 6H), 1.70–1.63 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 151.8 (t, $J_{CN} = 5.0$ Hz), 54.4 (t, $J_{CN} = 6.3$ Hz), 43.7, 35.6, 28.9. Spectroscopic data are in agreement with those reported earlier: CAS no 22110-53-8.[19]



Isocyanocyclohexane, (28). Colourless oil (256 mg, 47%); $R_f = 0.6$ (9:1 Heptane/AcOEt); ^{1}H NMR (500 MHz, CDCl$_3$) δ: 3.61–3.58 (m, 1H), 1.88–1.86 (s, 2H), 1.78–1.65 (m, 4H), 1.50–1.34 (m, 4H); ^{13}C NMR (126 MHz, CDCl$_3$) δ: 154.1 (t, $J_{CN} = 5.0$ Hz), 51.7 (t, $J_{CN} = 6.3$ Hz), 32.7, 25.0, 23.0. Spectroscopic data are in agreement with those reported earlier, CAS no 931-53-3.



***N*-(2-isocyanoethyl)aniline (29).** Colourless oil (183 mg, 25%); $R_f = 0.41$ (9:1 Heptane/AcOEt); IR (KBr) ν (cm^{-1}): 2960, 2929, 2878, 2864, 2148, 1692, 1460, 1389; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.22 (t, J = 7.8 Hz, 2H), 6.78 (t, J = 7.3 Hz, 1H), 6.64 (d, J = 9.4 Hz, 2H), 4.02 (bs, 1H), 3.60 (t, J = 5.9 Hz, 2H), 3.50 (t, J = 5.9 Hz, 2H); ^{13}C NMR (126 MHz, CDCl$_3$) δ: 161.9, 147.9, 129.5, 118.0, 113.0, 43.8, 37.9; HRMS (ESI): m/z calcd for C_9H11N2: 147.0922 [M+H]+, found: 147.0917.



tert-Butyl 4-isocyanopiperidine-1-carboxylate (30). Colourless oil (568 mg, 54%); $R_f = 0.3$ (9:1 Heptane/AcOEt); IR (KBr) ν (cm^{-1}): 2974, 2931, 2862, 2140, 1678, 1423, 2236, 1129, 1033; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 3.84 (s, 1H), 3.63–3.55 (m, 2H), 3.45–3.40 (m, 2H), 1.90-1.79 (m, 2H), 1.82–1.79 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (126 MHz, CDCl$_3$) δ: 156.7 (t, $J_{CN} = 5.0$ Hz), 154.5, 80.1, 49.7 (t, $J_{CN} = 6.3$ Hz), 40.0, 31.5, 28.5; HRMS (ESI): m/z calcd for: $C_{11}H_{19}N_2O_2$: 211.1446 [M+H]$^+$, found: 211.1450.

Table S1. Self diffusion coefficients (D×10^9 m^2 s^{-1}) for all the signals in the ^1H NMR spectrum of the by-products from reaction reported in **Scheme 4** dissolved in $CDCl_3$.

ppm	0.88	1.28	3.80	3.83	6.85	6.88	7.00	7.03	7.30	7.33	8.00	8.46
D	1.21	1.97	0.81	1.35	1.17	1.17	0.75	0.71	1.37	1.35	0.81	0.71

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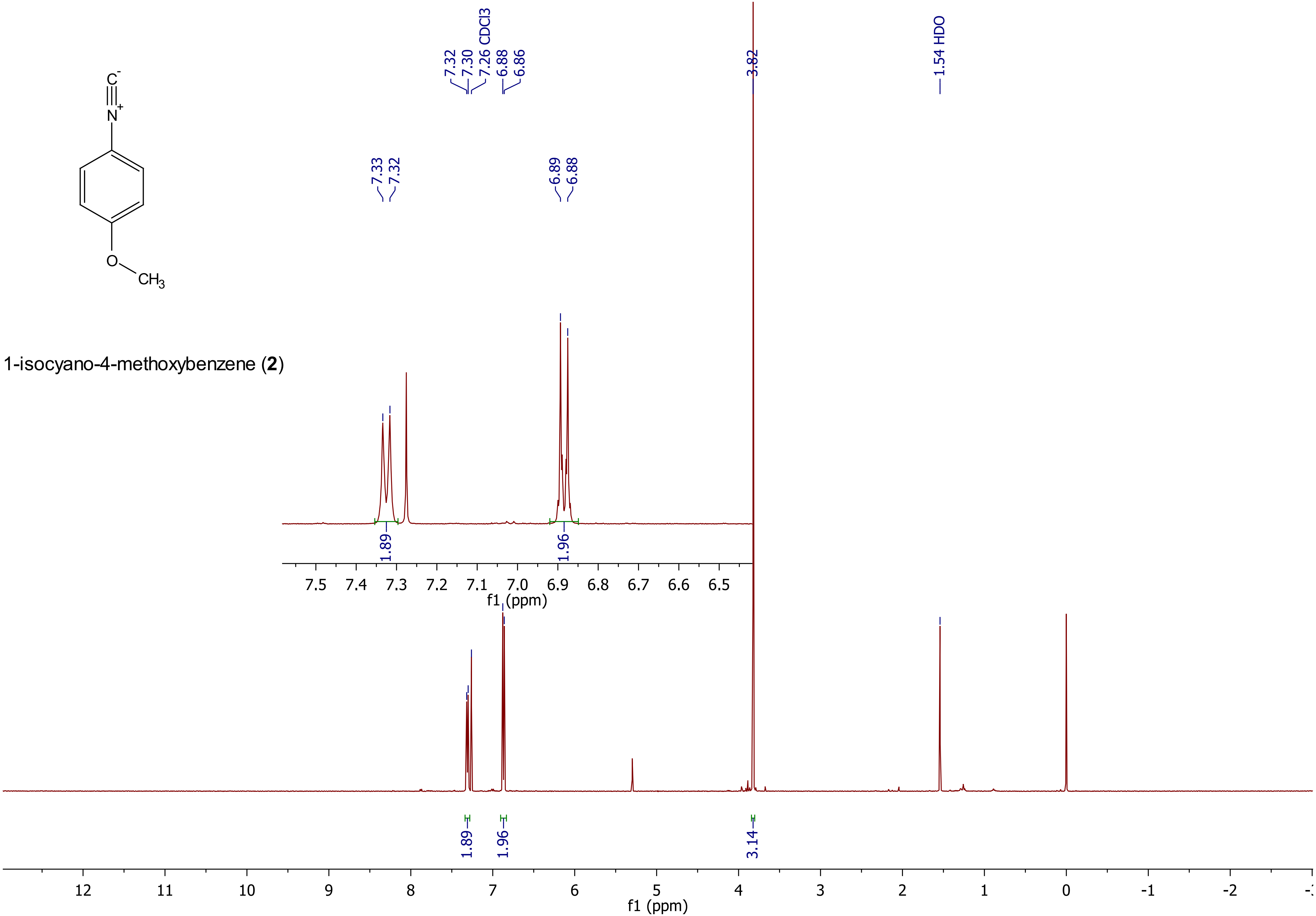
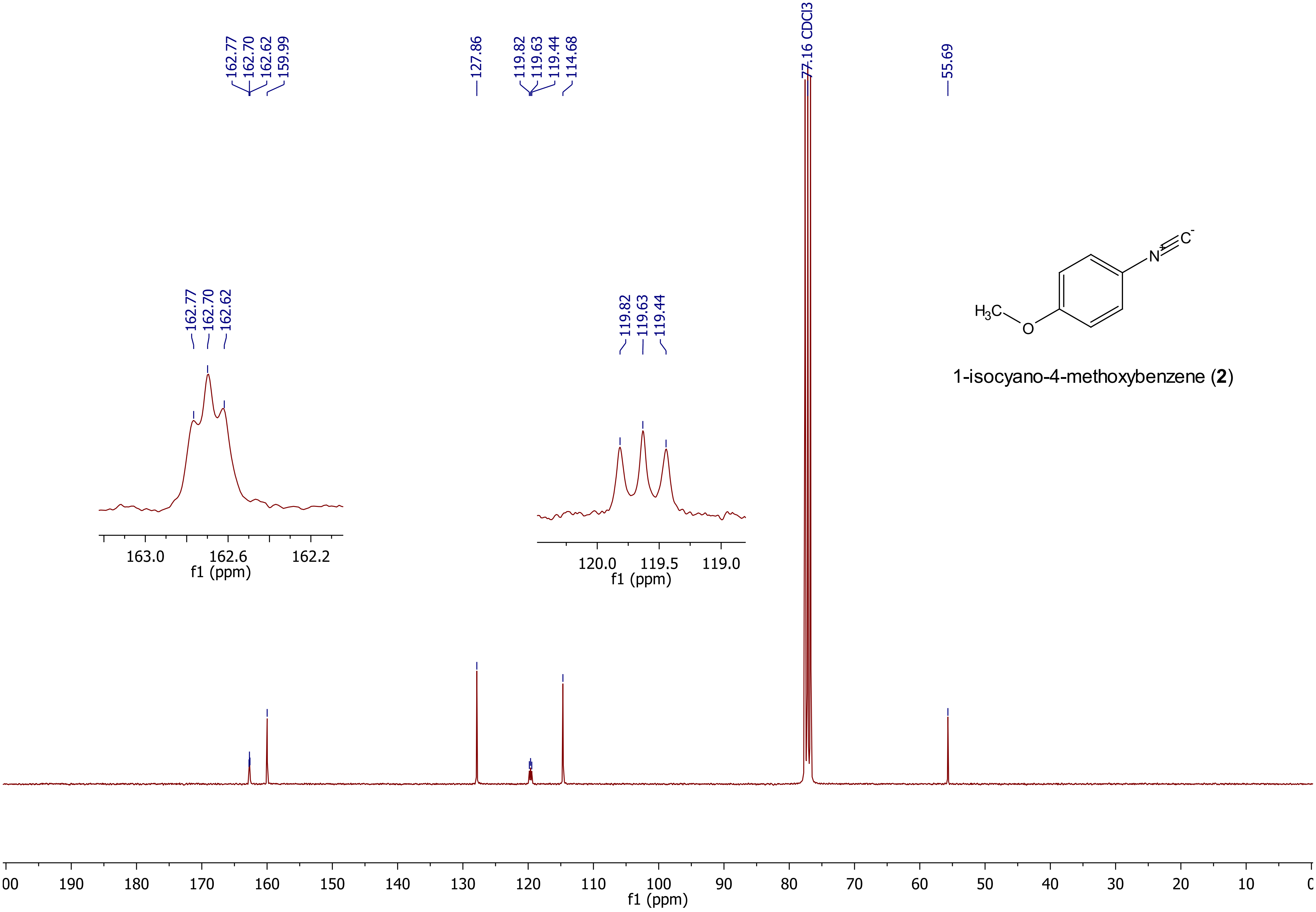
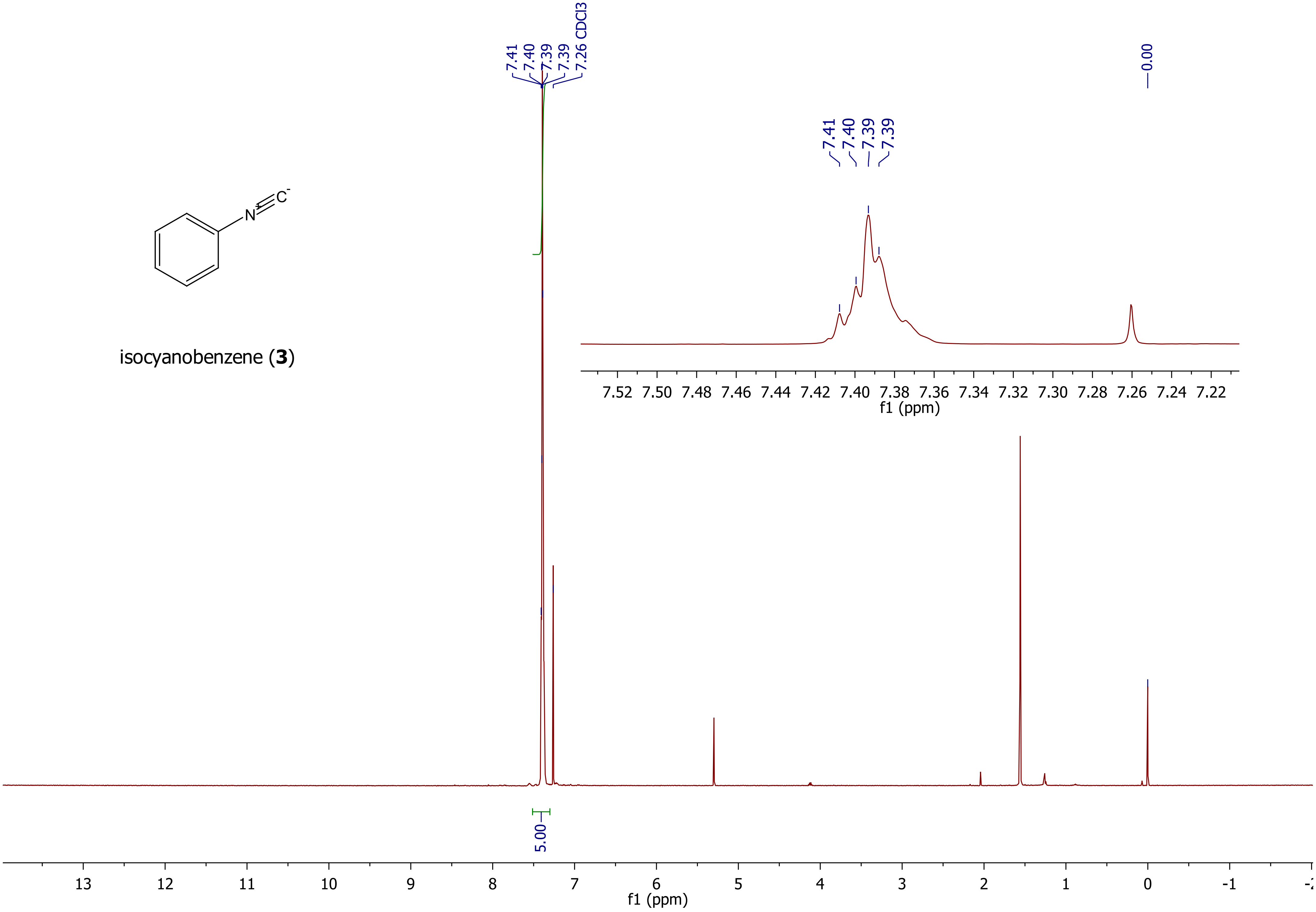


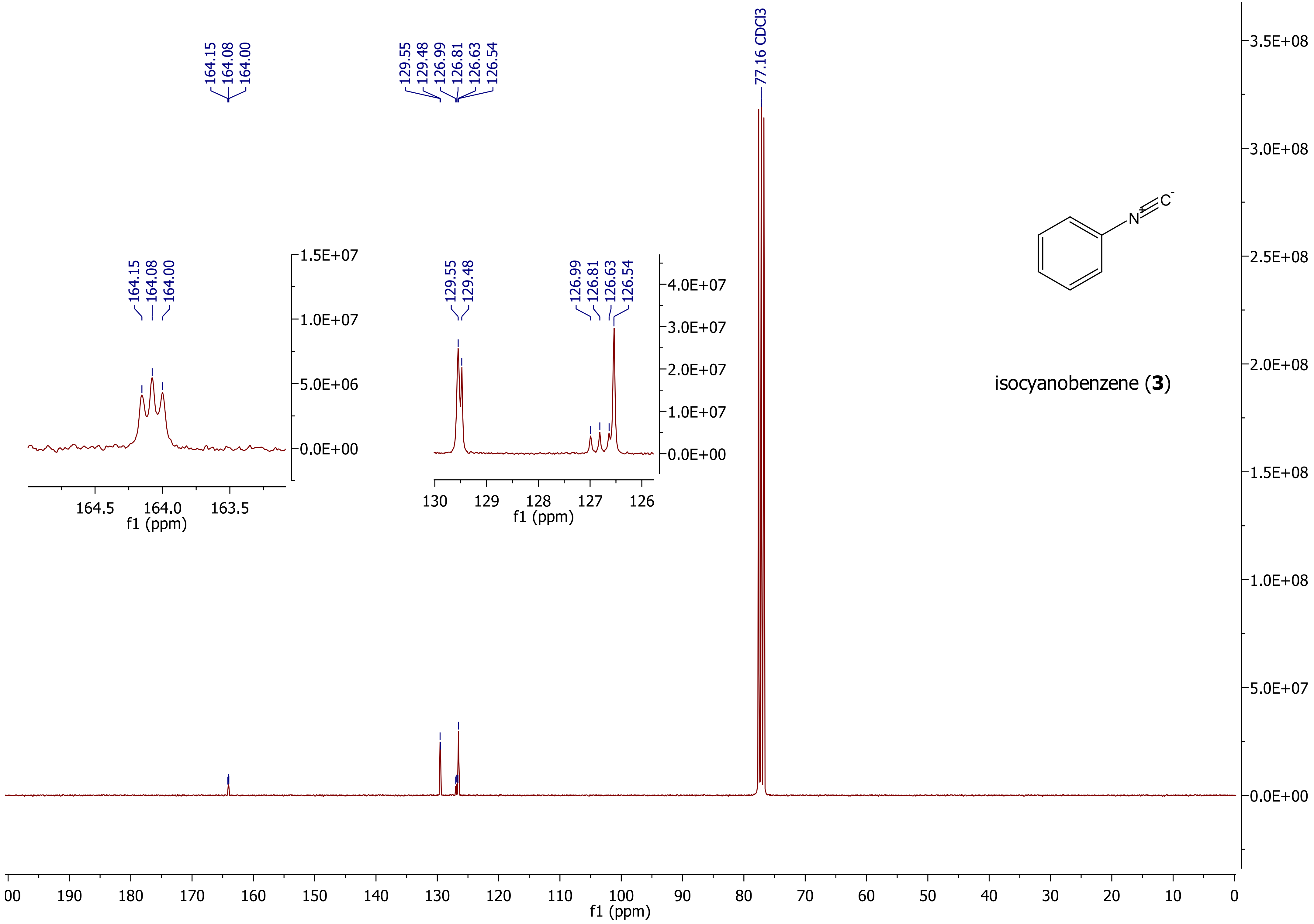
1-isocyano-4-methoxybenzene (**2**)



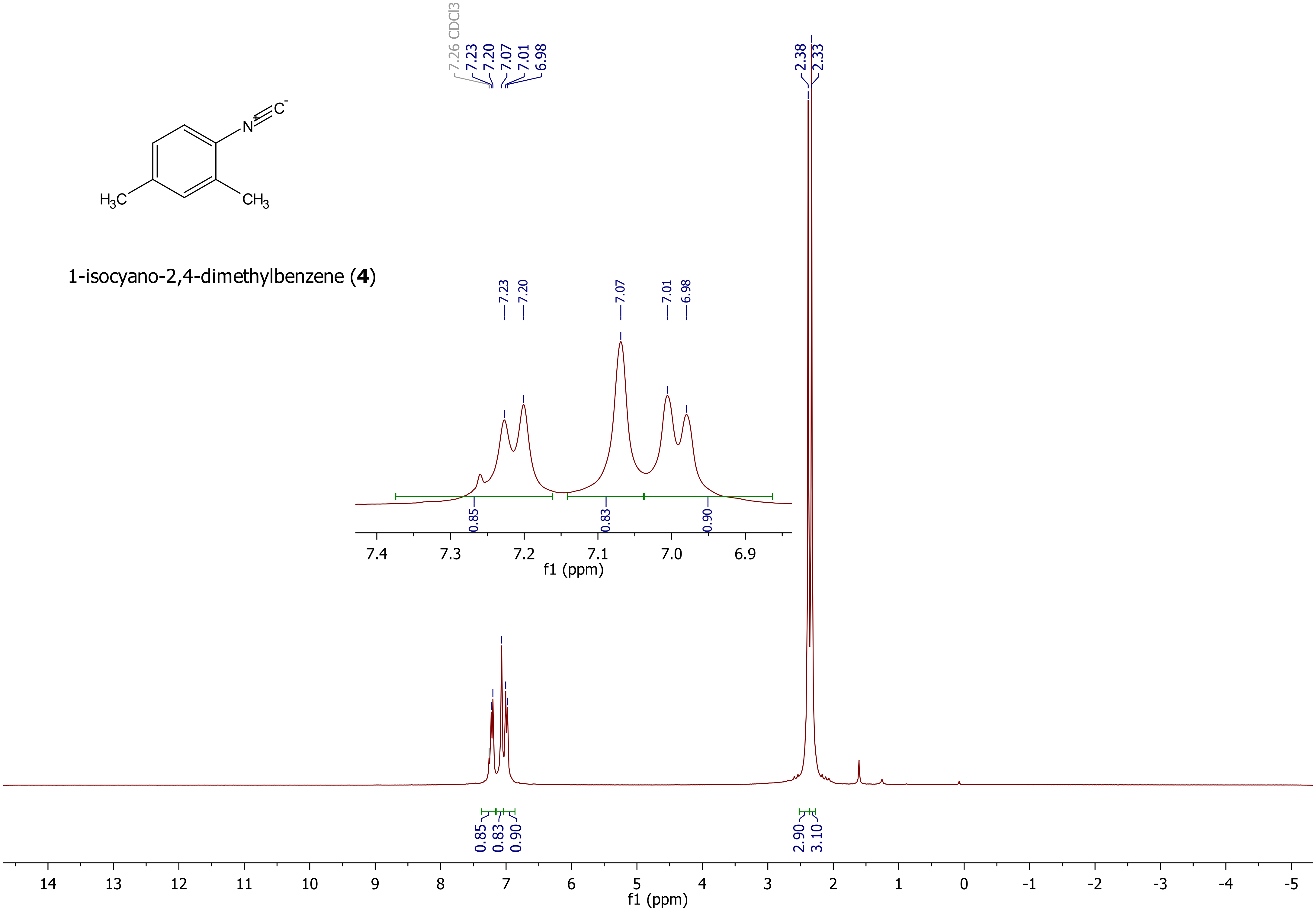
1-isocyano-4-methoxybenzene (**2**)



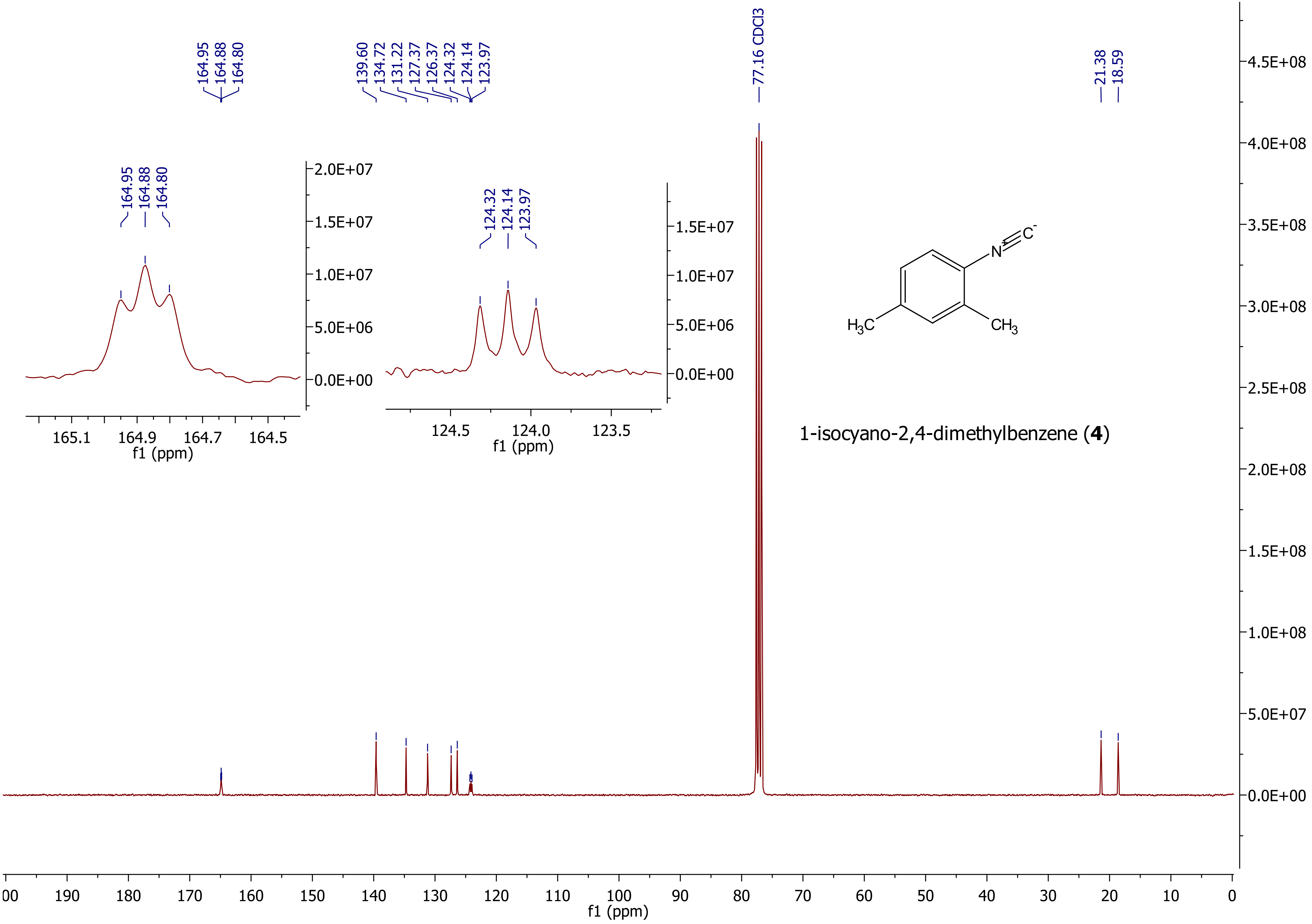
isocyanobenzene (**3**)



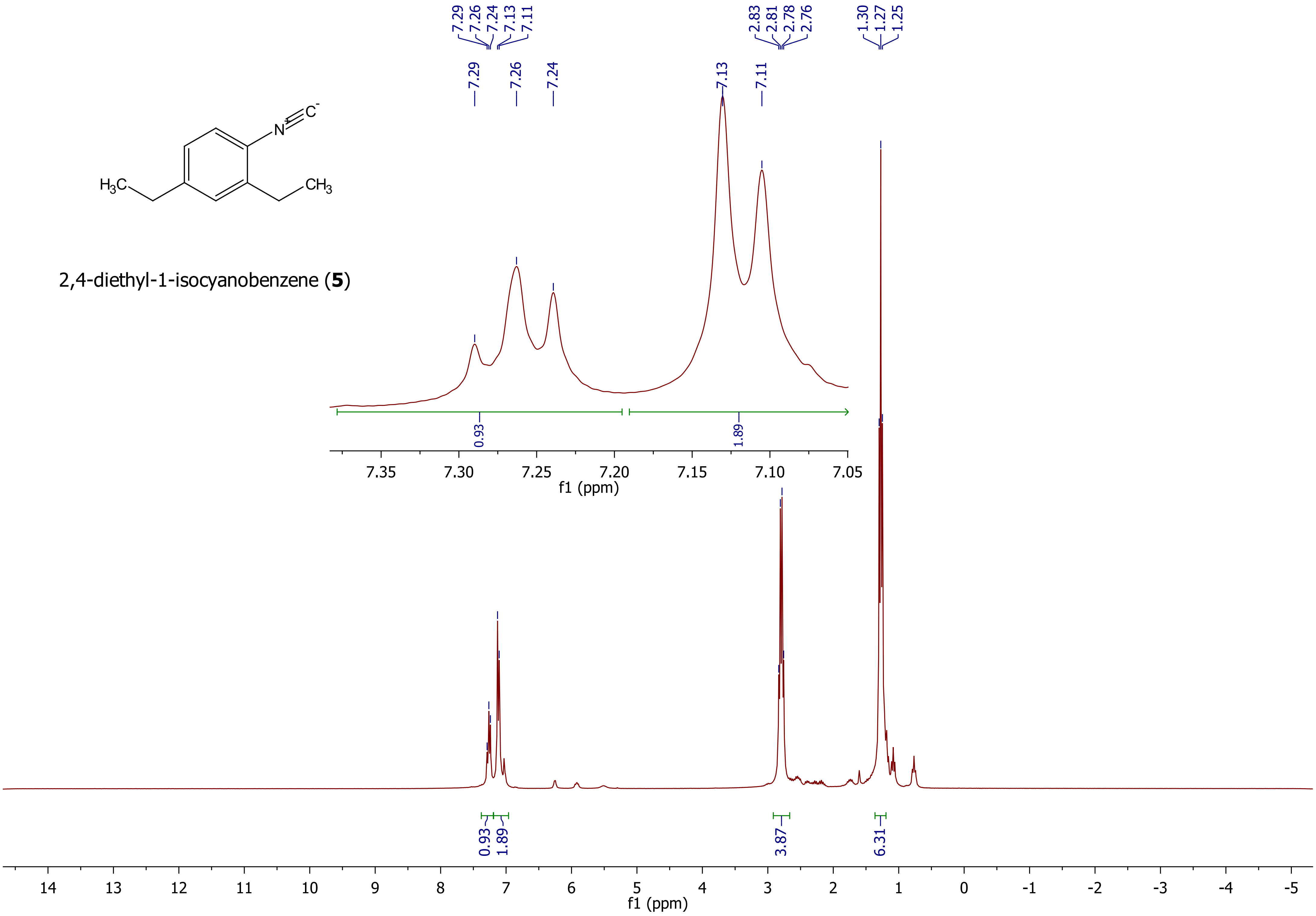
isocyanobenzene (**3**)



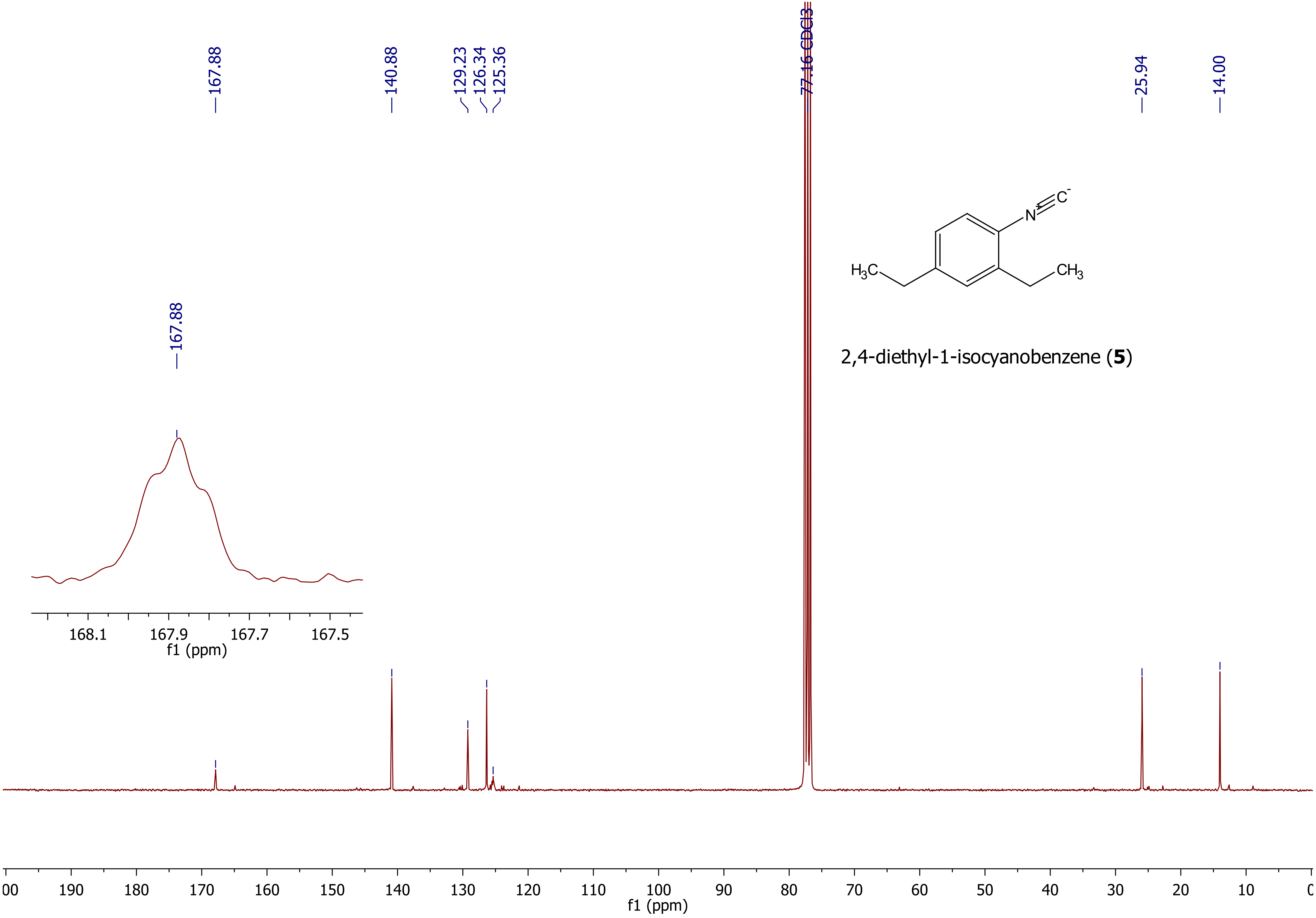
1-isocyano-2,4-dimethylbenzene (**4**)



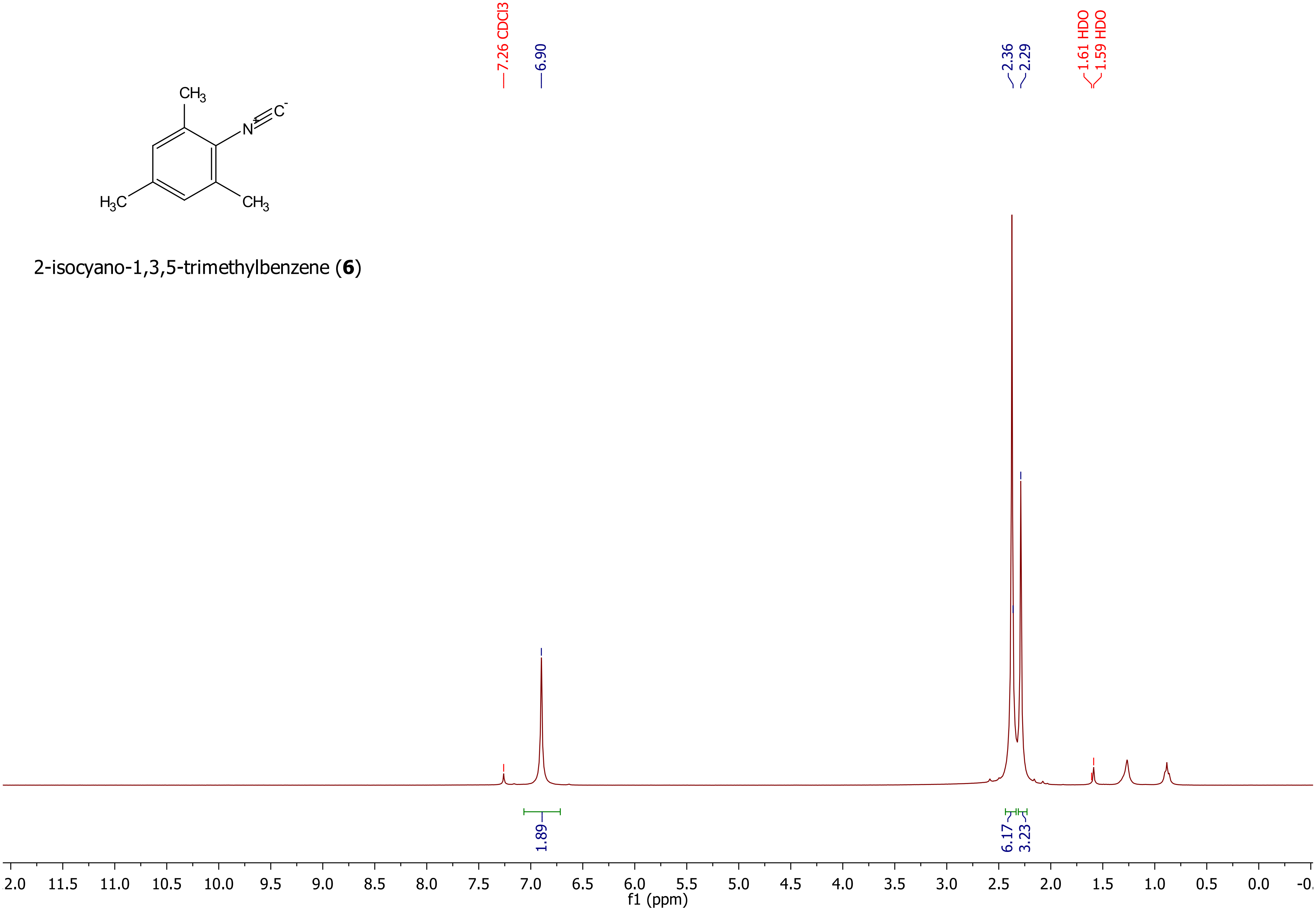
1-isocyano-2,4-dimethylbenzene (**4**)



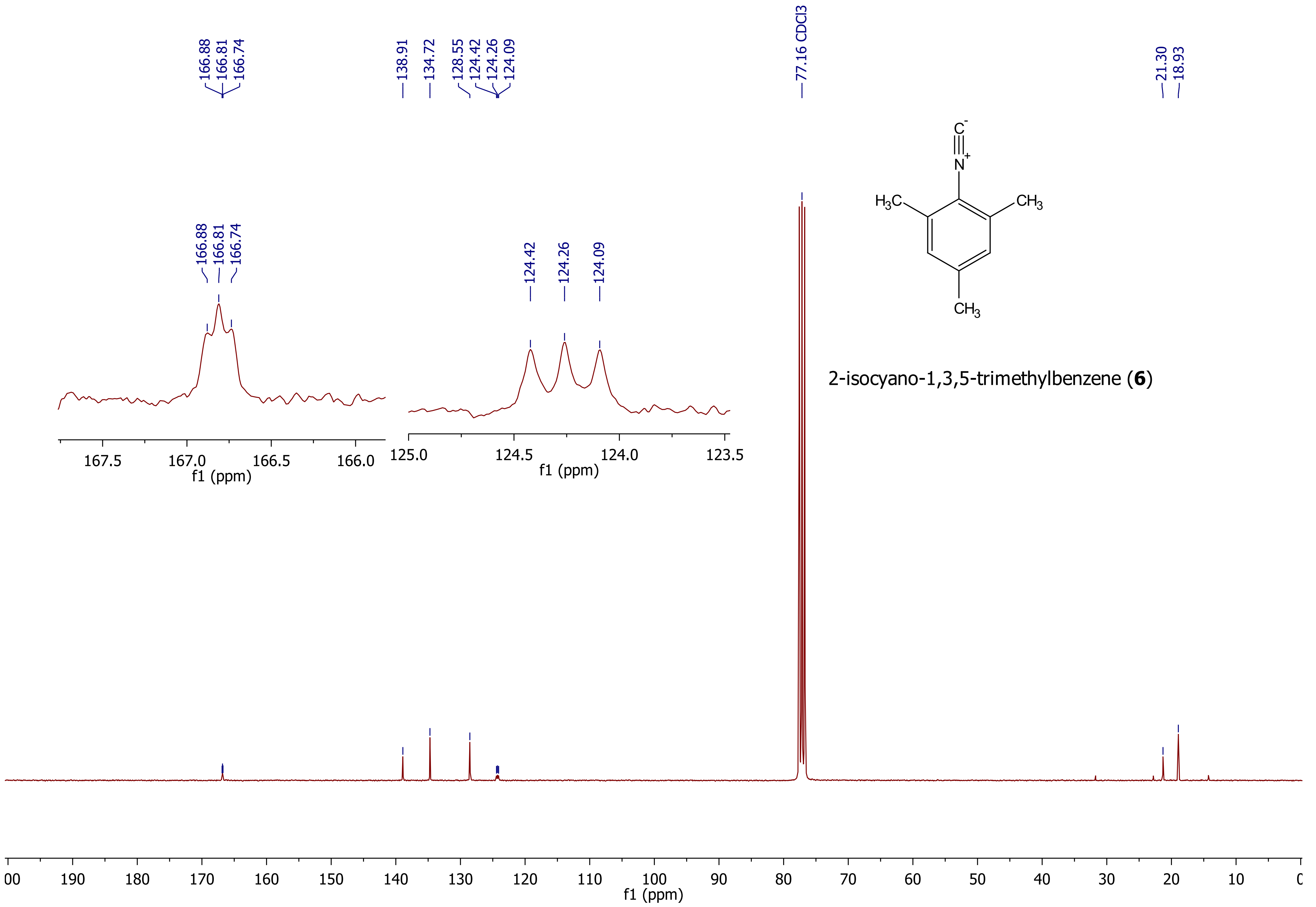
2,4-diethyl-1-isocyanobenzene (**5**)



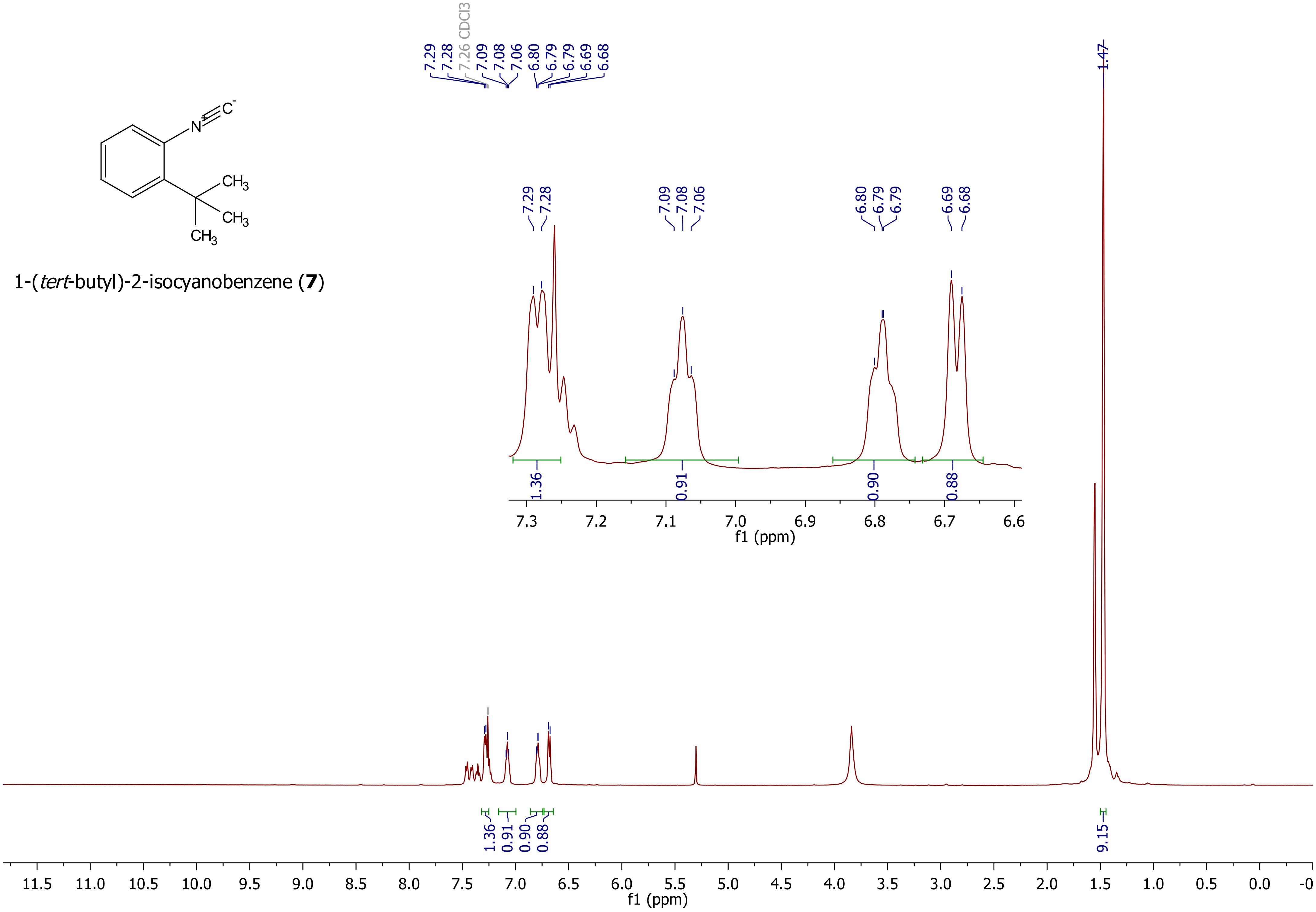
2,4-diethyl-1-isocyanobenzene (**5**)

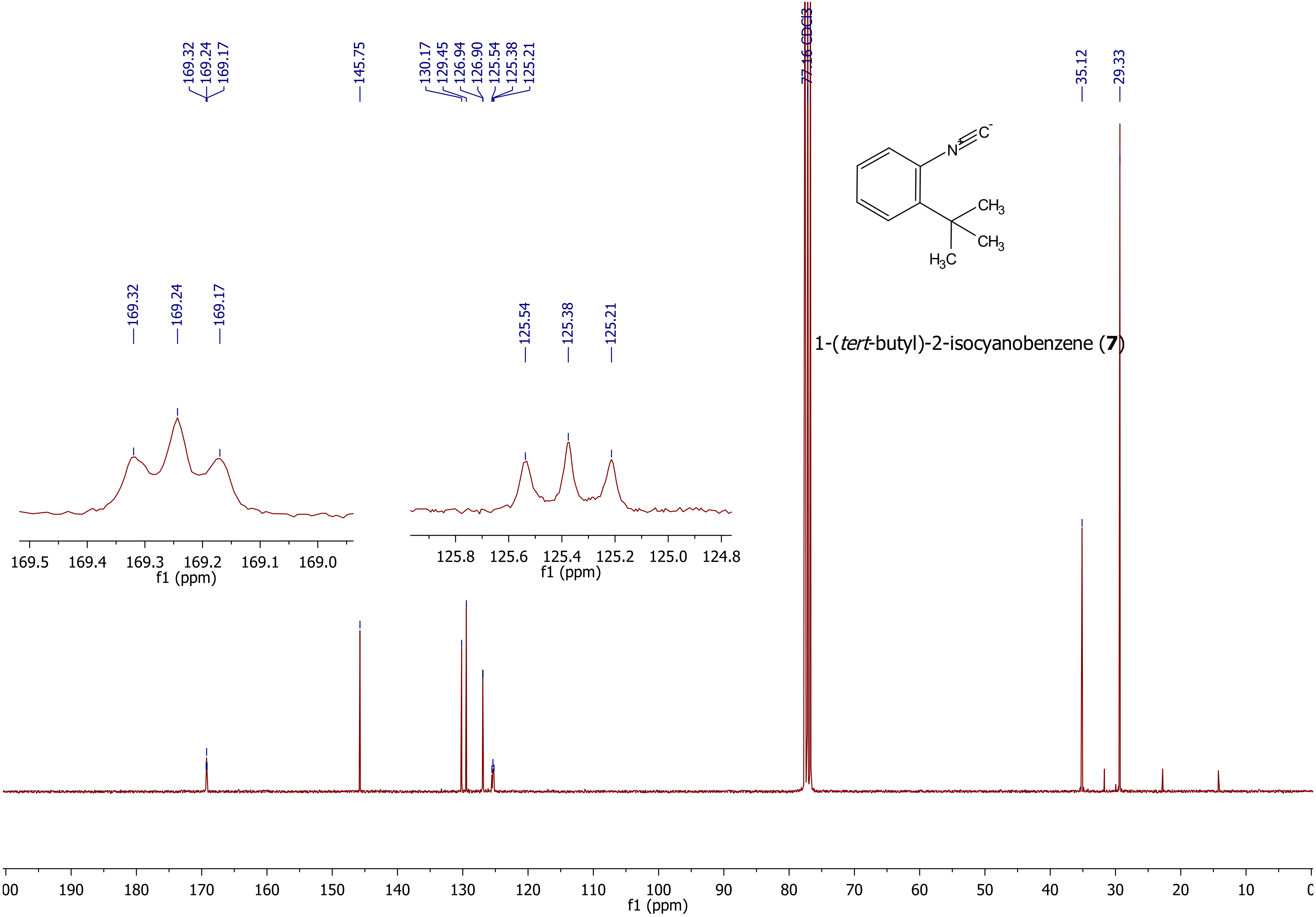


2-isocyano-1,3,5-trimethylbenzene (**6**)

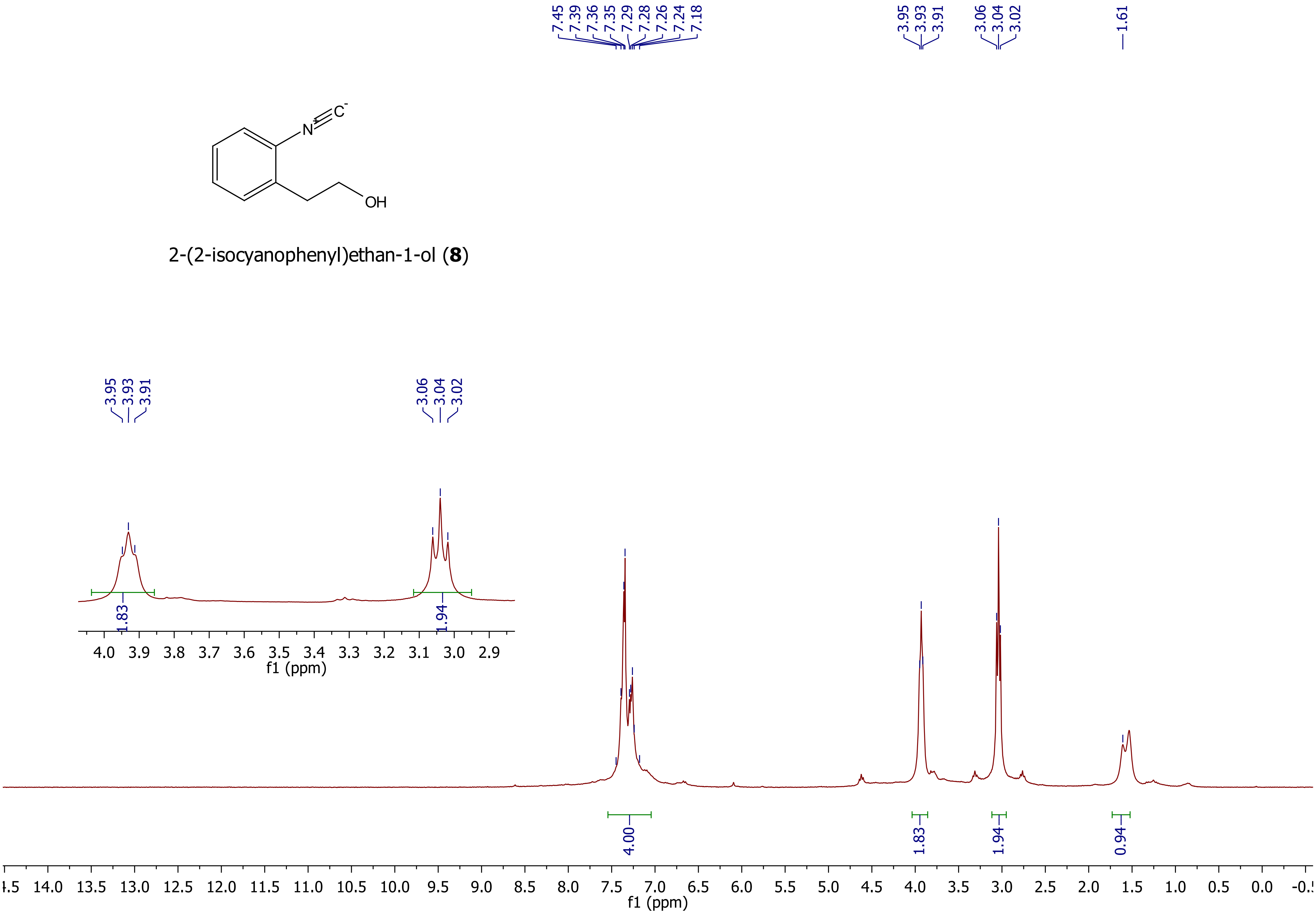


2-isocyano-1,3,5-trimethylbenzene (**6**)

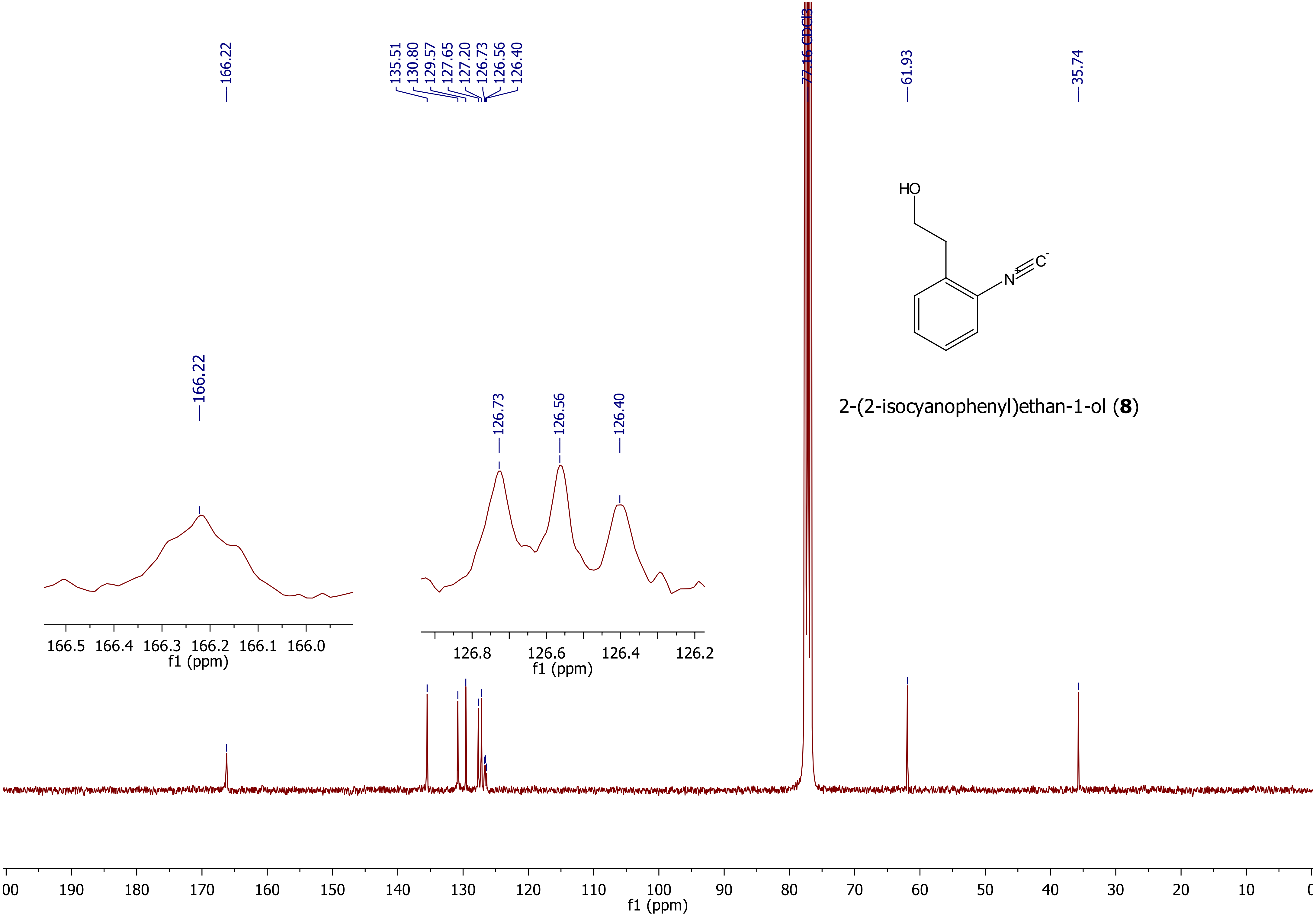

1-(*tert*-butyl)-2-isocyanobenzene (**7**)



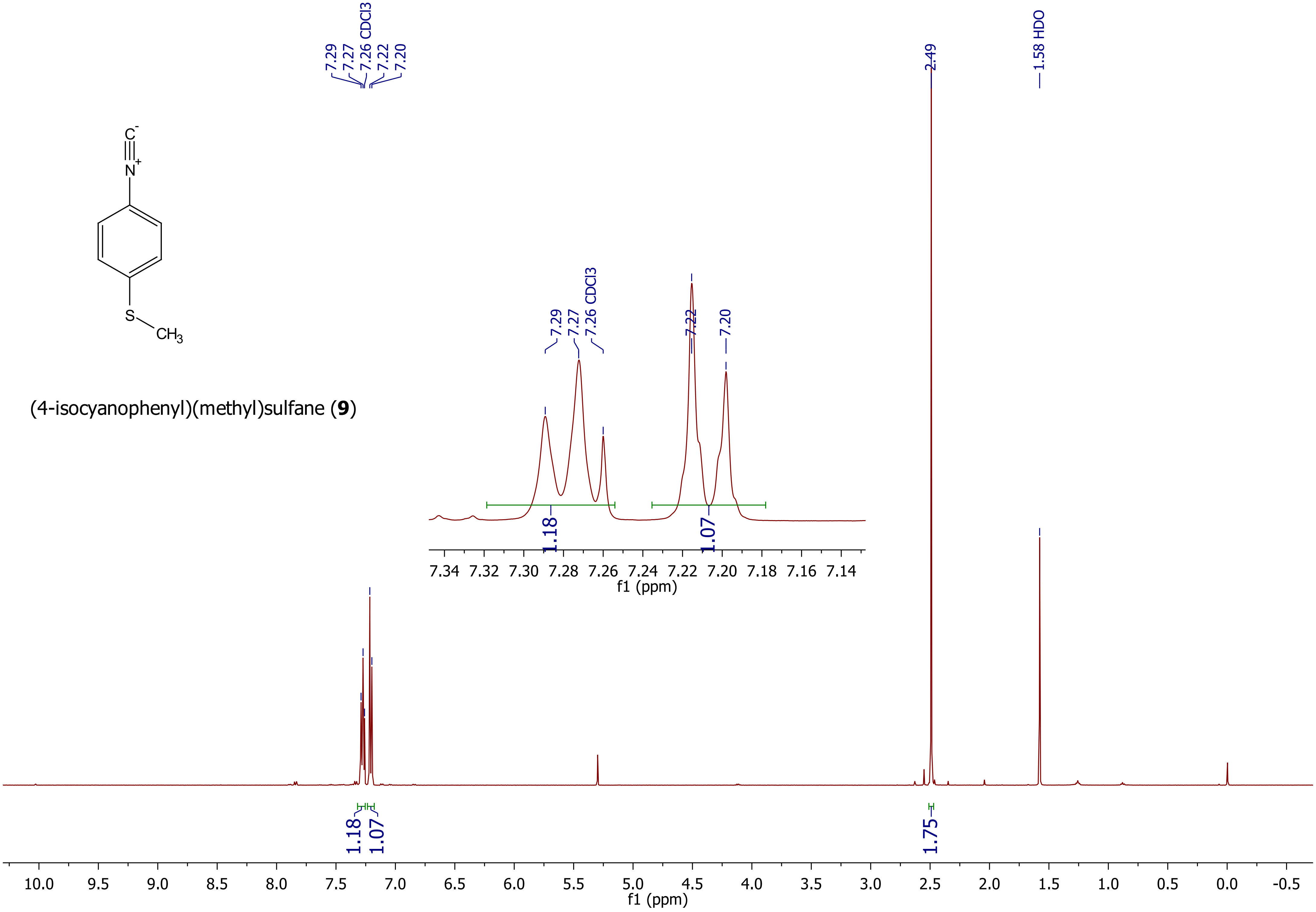
1-(*tert*-butyl)-2-isocyanobenzene (**7**)



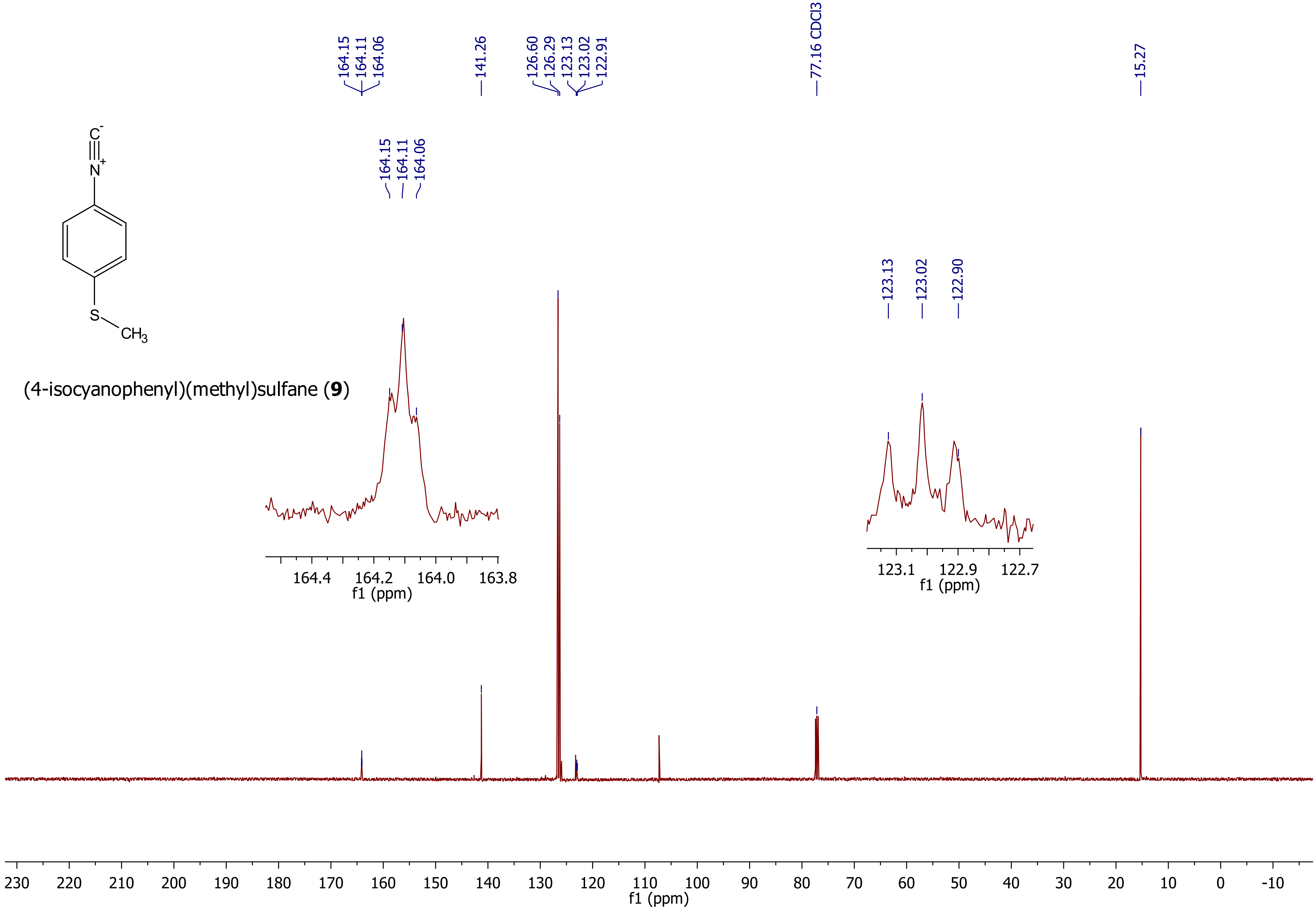
2-(2-isocyanophenyl)ethan-1-ol (**8**)

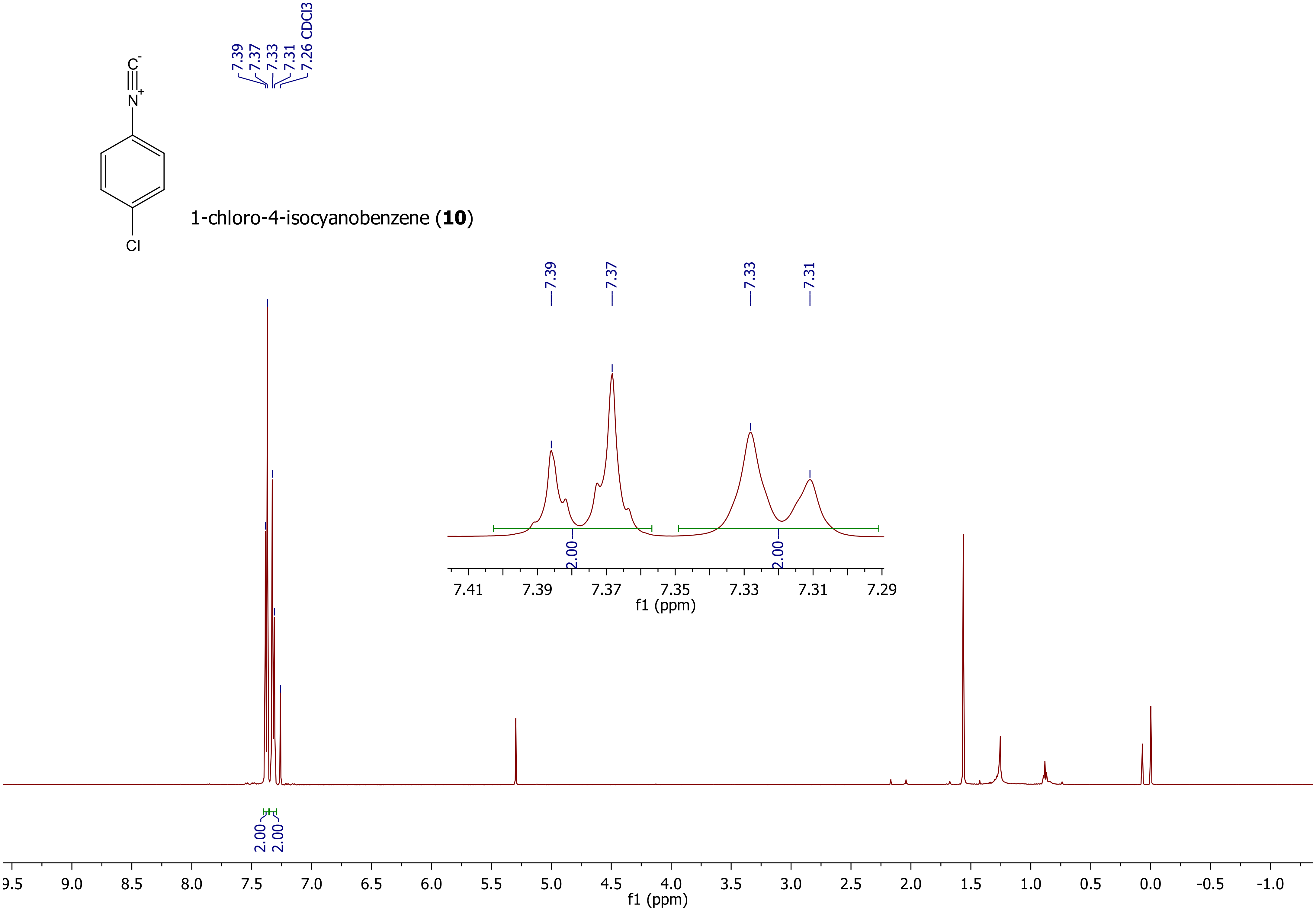


2-(2-isocyanophenyl)ethan-1-ol (**8**)

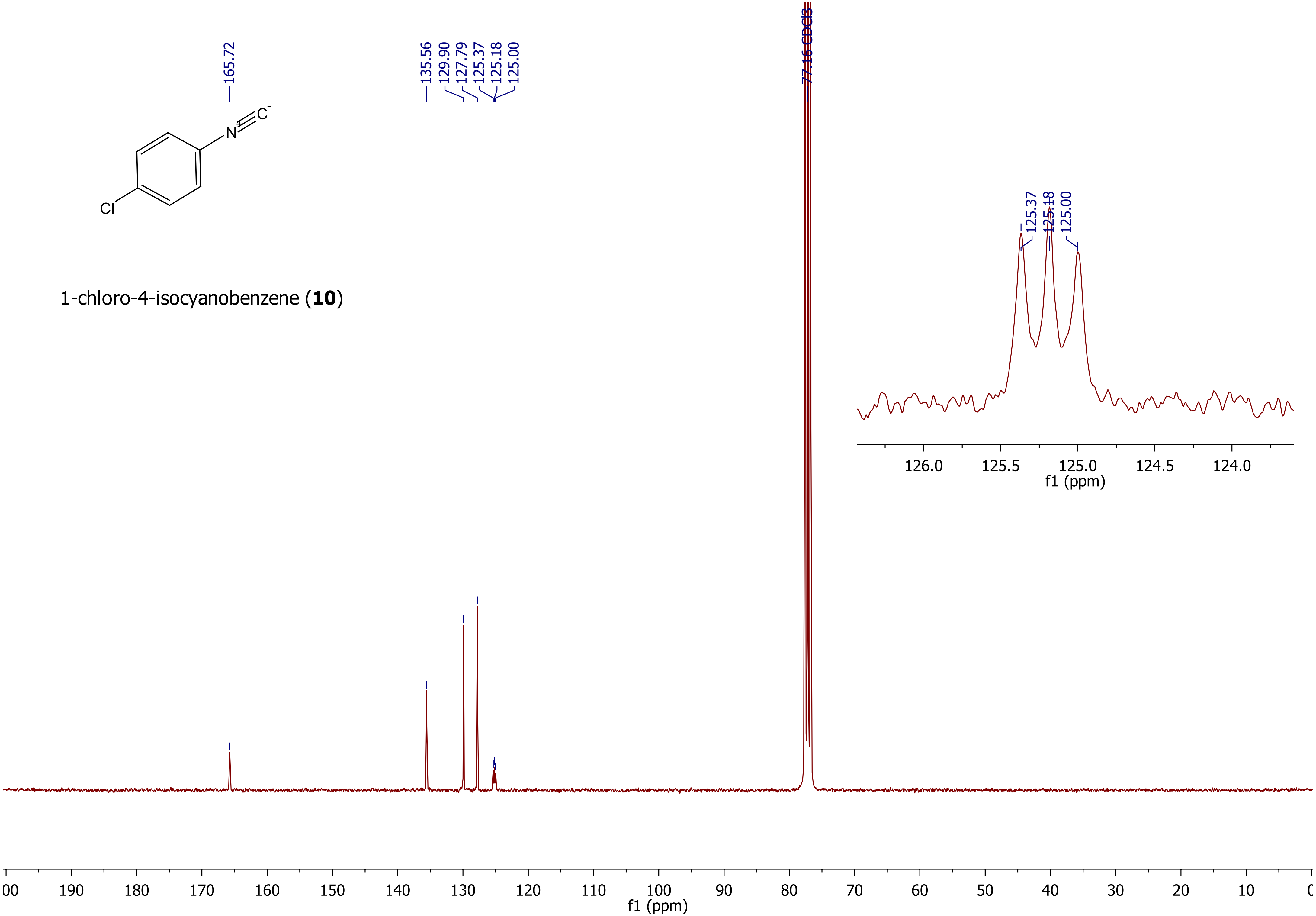


(4-isocyanophenyl)(methyl)sulfane (**9**)

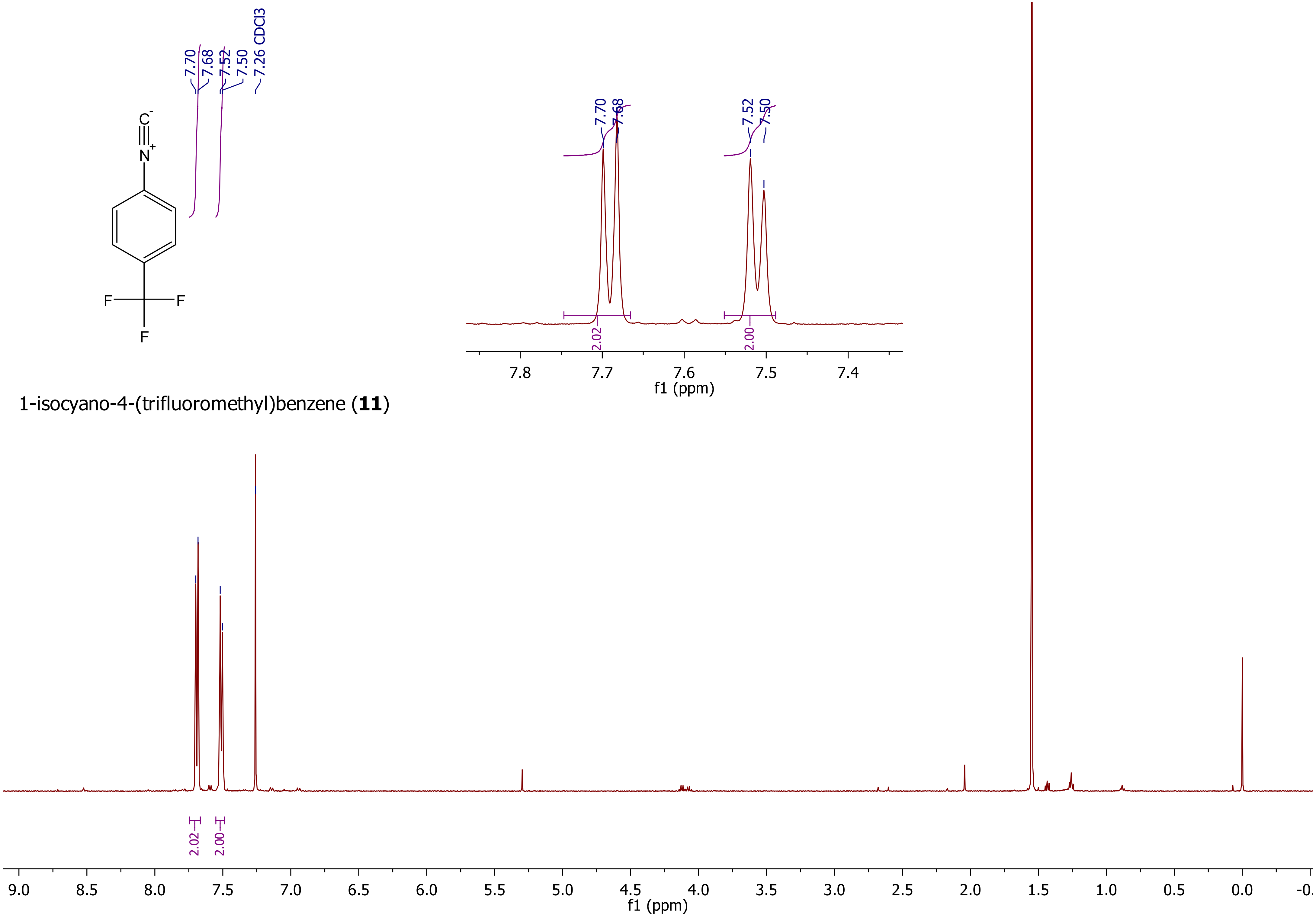

(4-isocyanophenyl)(methyl)sulfane (**9**)



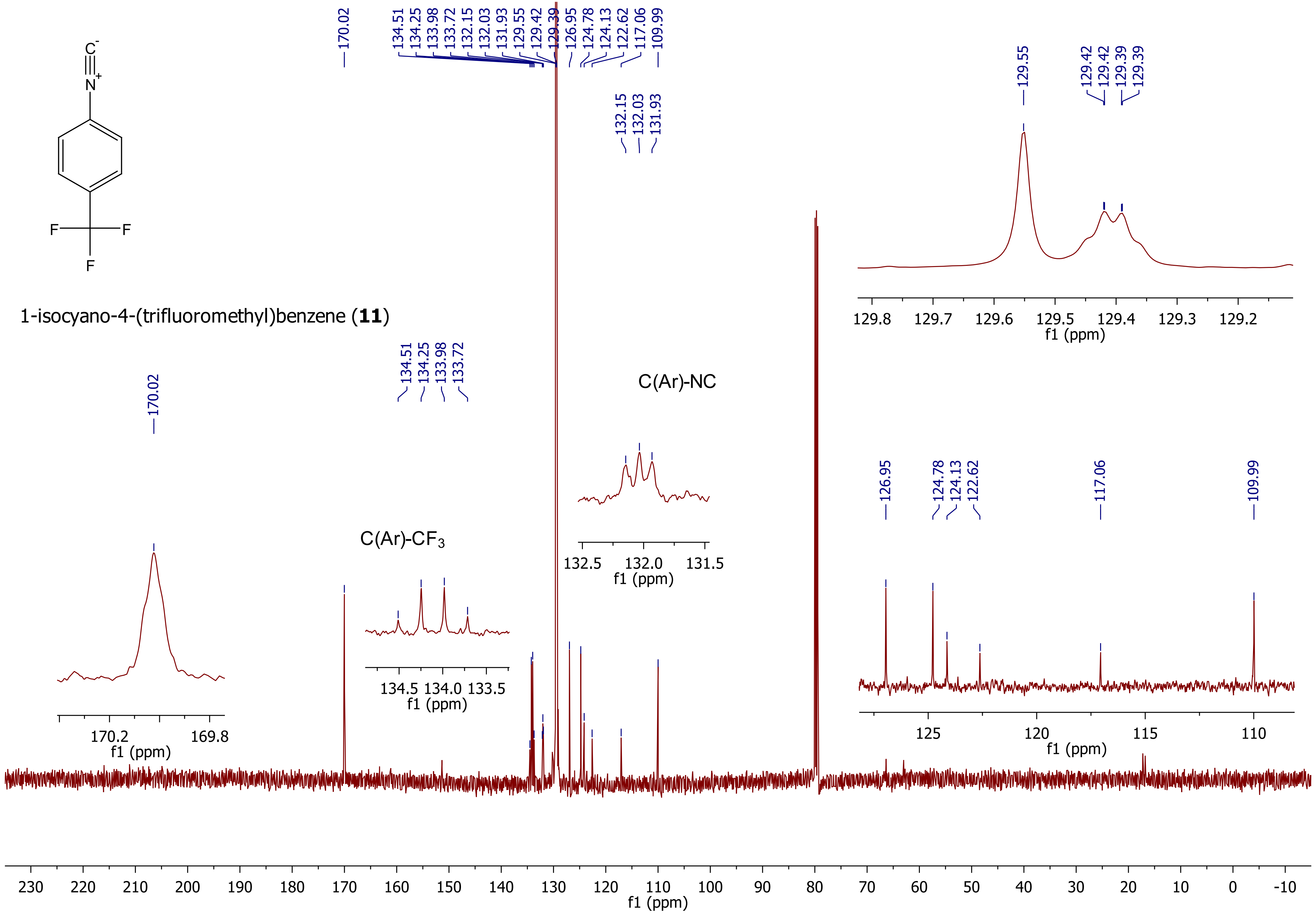
1-chloro-4-isocyanobenzene (**10**)



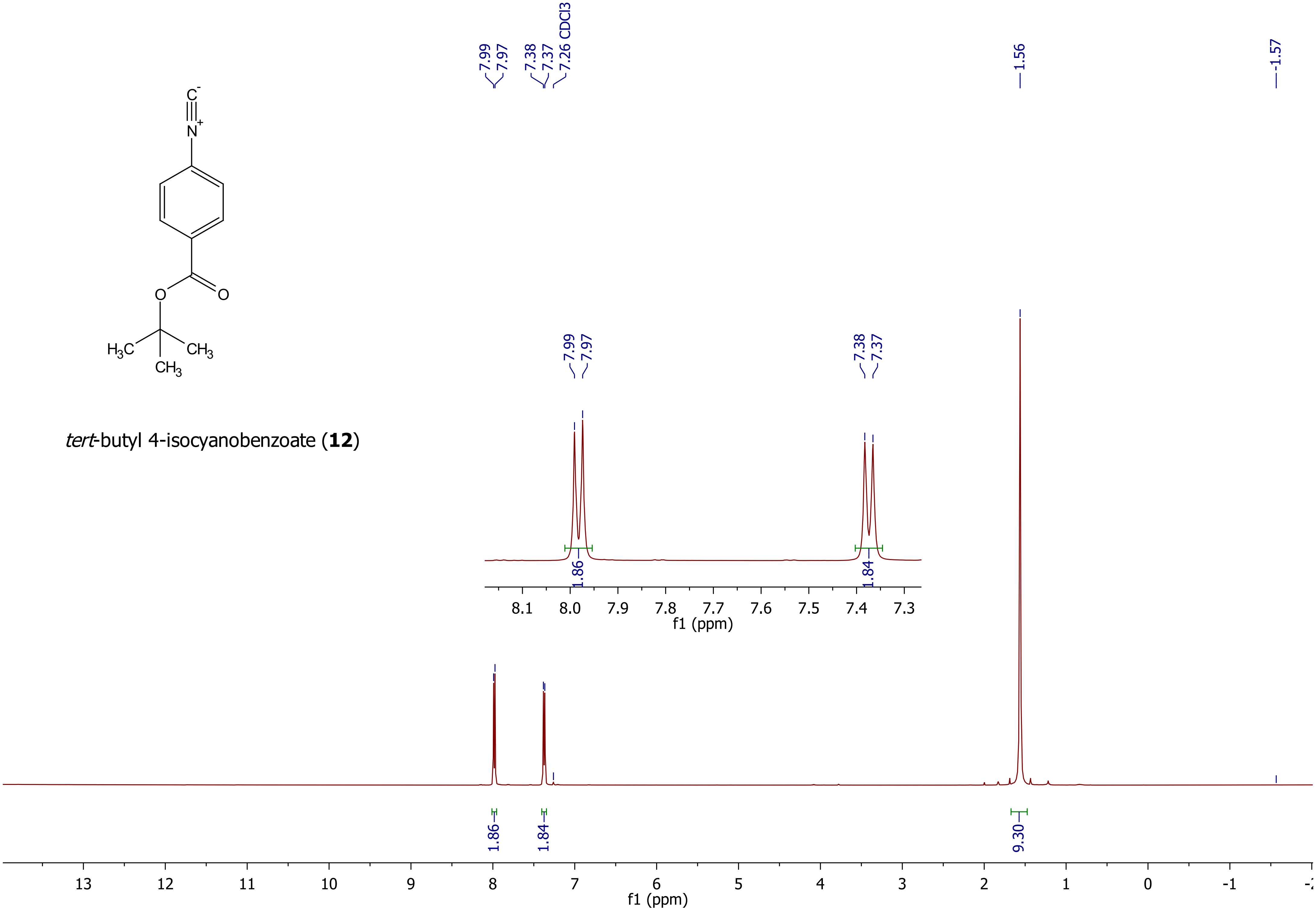
1-chloro-4-isocyanobenzene (**10**)



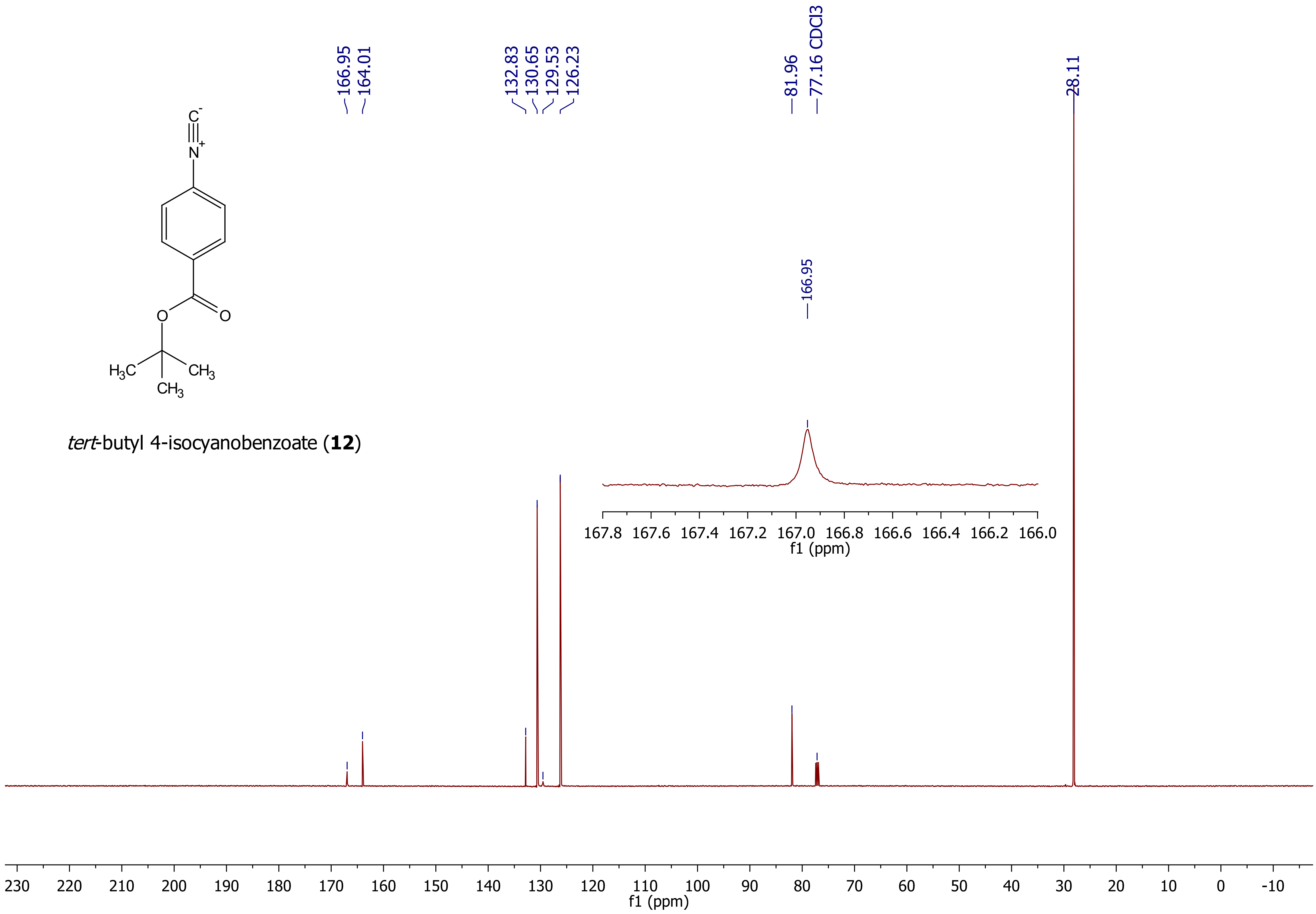
1-isocyano-4-(trifluoromethyl)benzene (**11**)



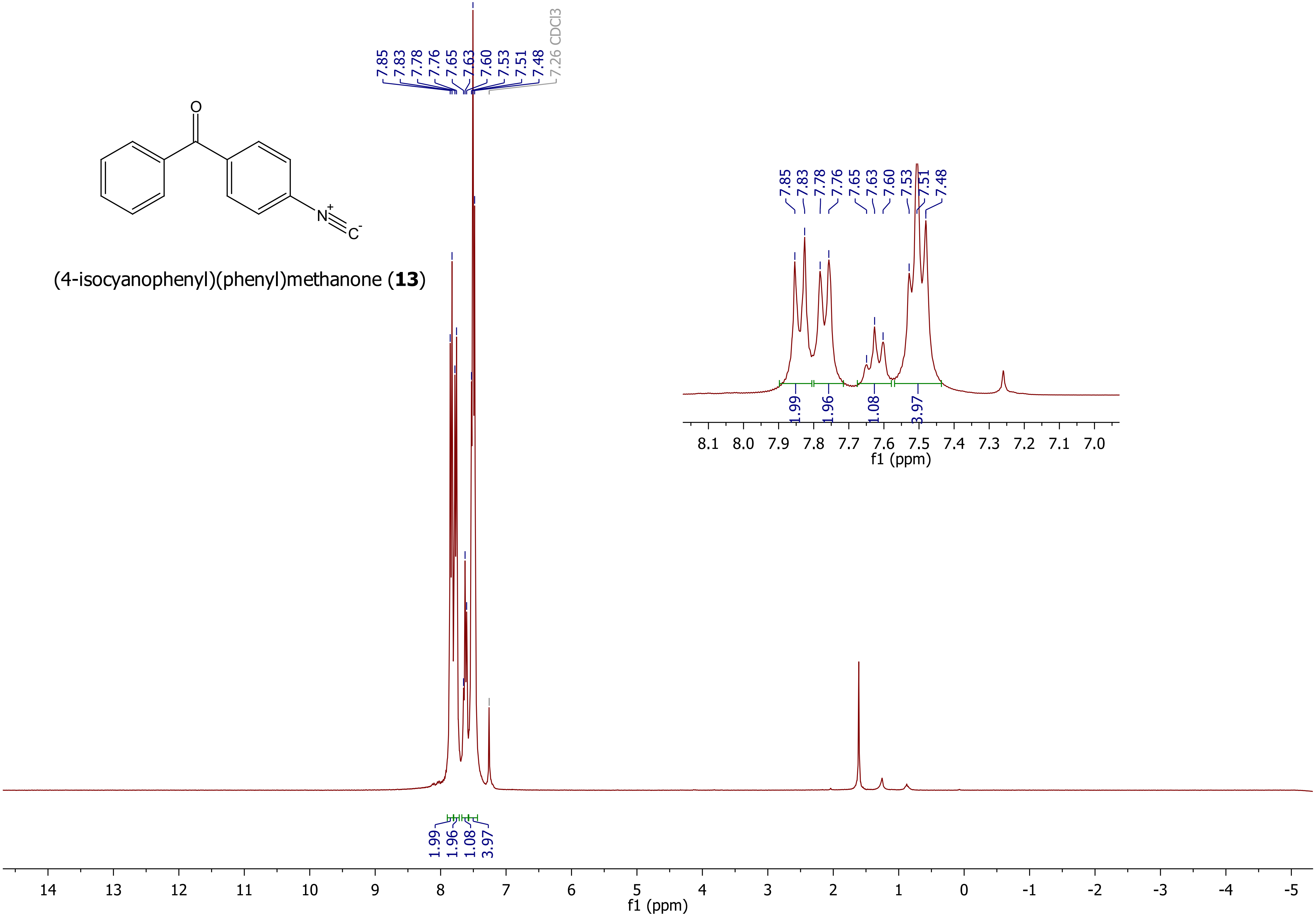
1-isocyano-4-(trifluoromethyl)benzene (**11**)



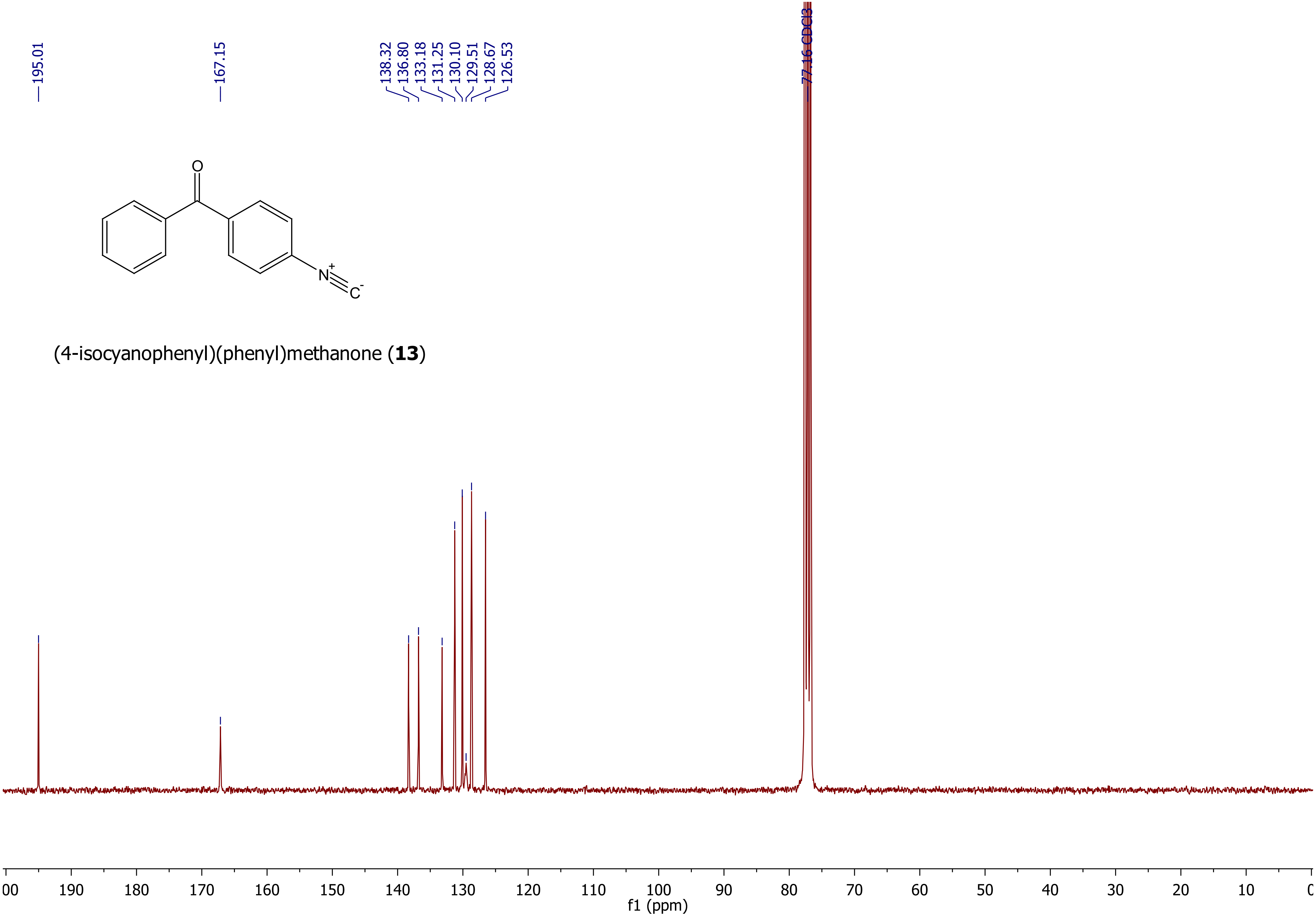
tert-butyl 4-isocyanobenzoate (**12**)



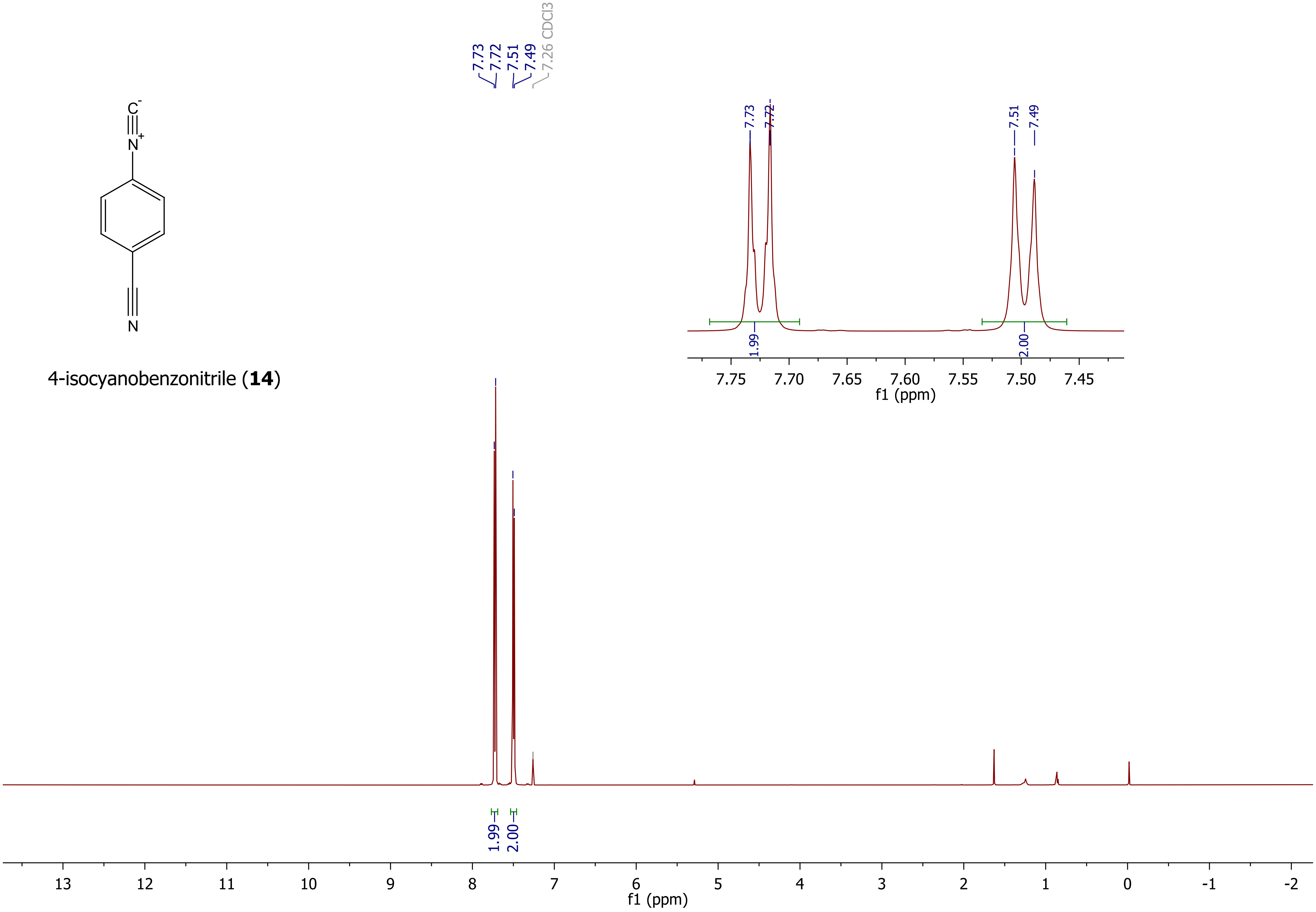
tert-butyl 4-isocyanobenzoate (**12**)



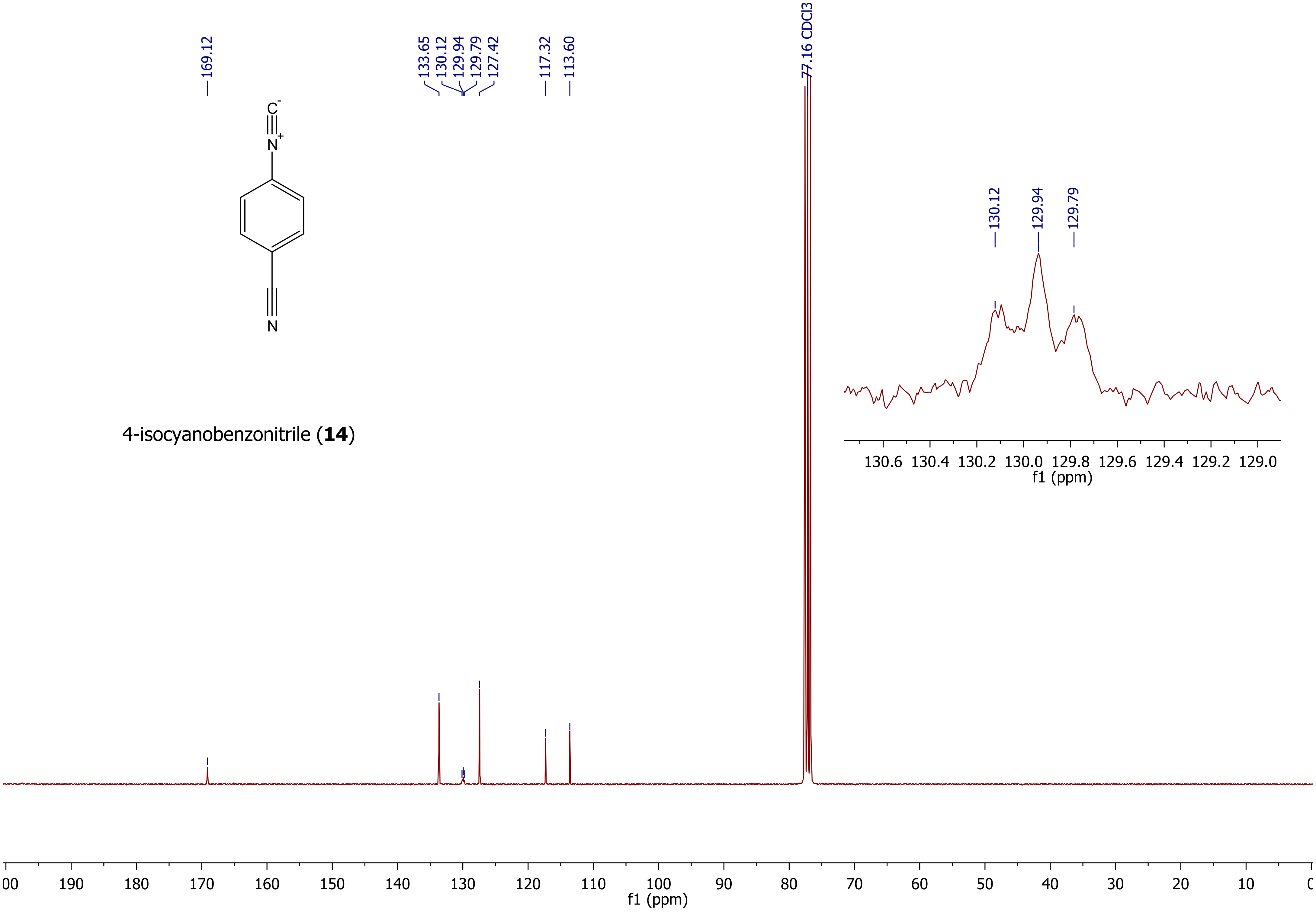
(4-isocyanophenyl)(phenyl)methanone (**13**)

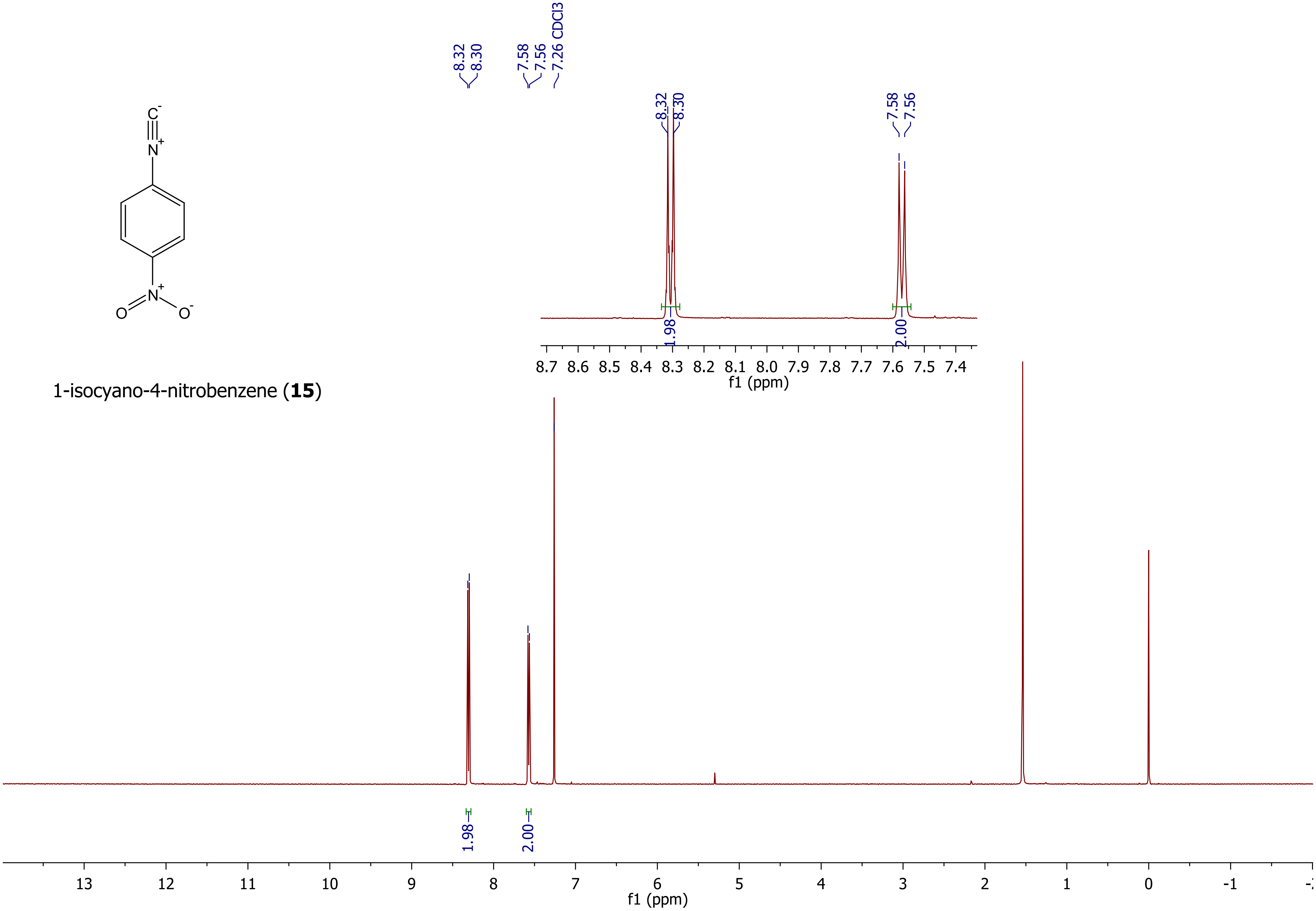


(4-isocyanophenyl)(phenyl)methanone (**13**)

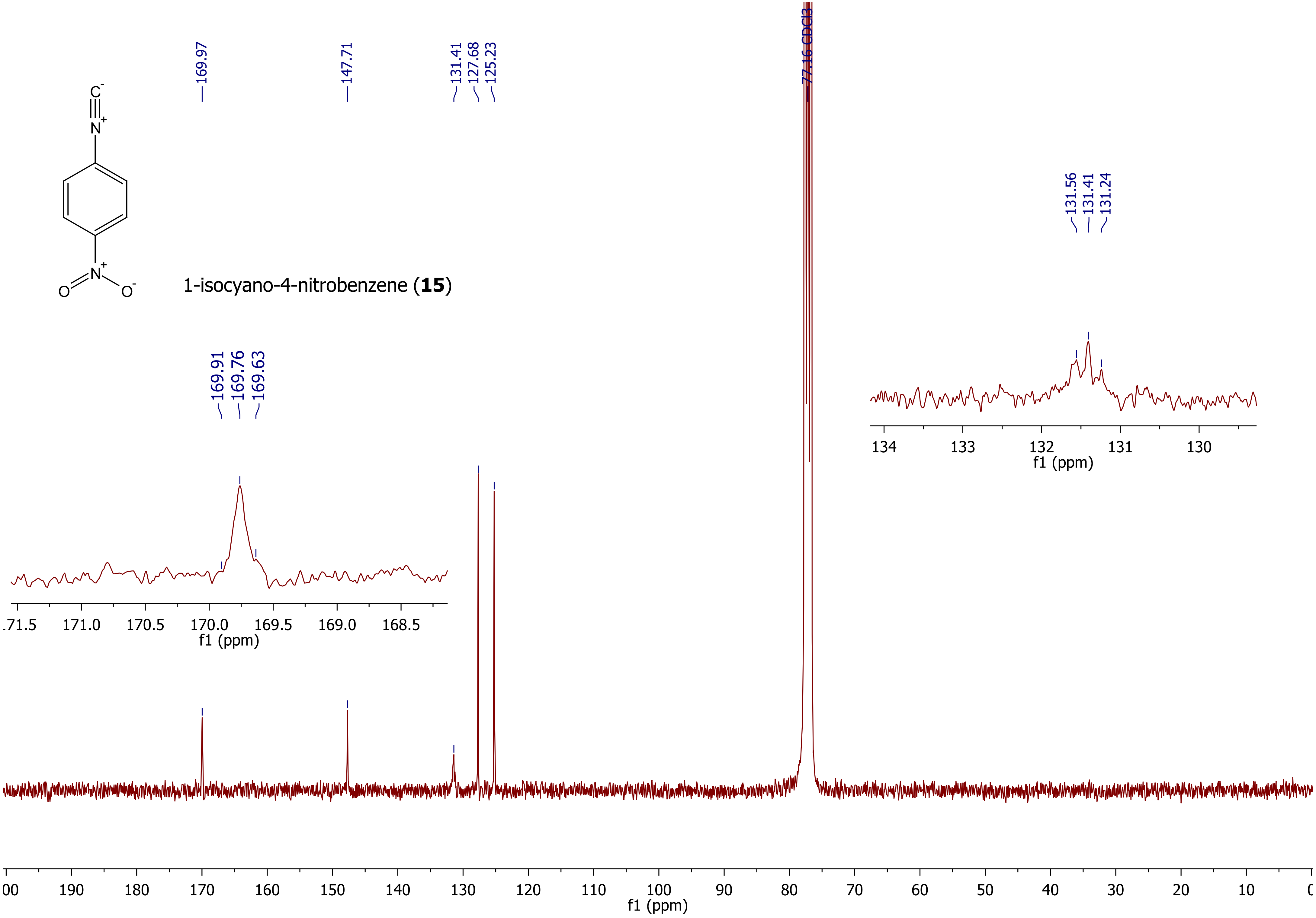


4-isocyanobenzonitrile (**14**)

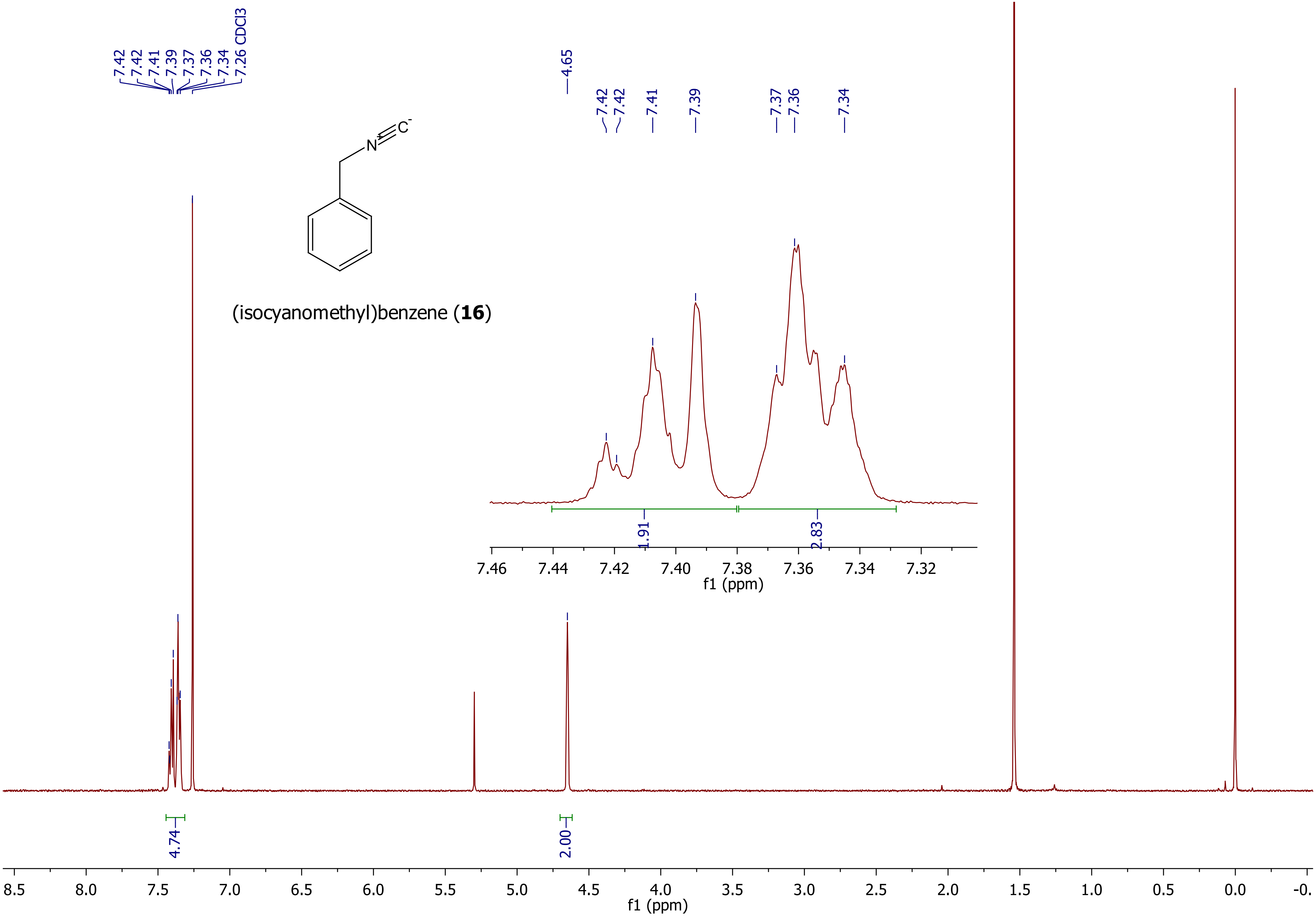

4-isocyanobenzonitrile (**14**)

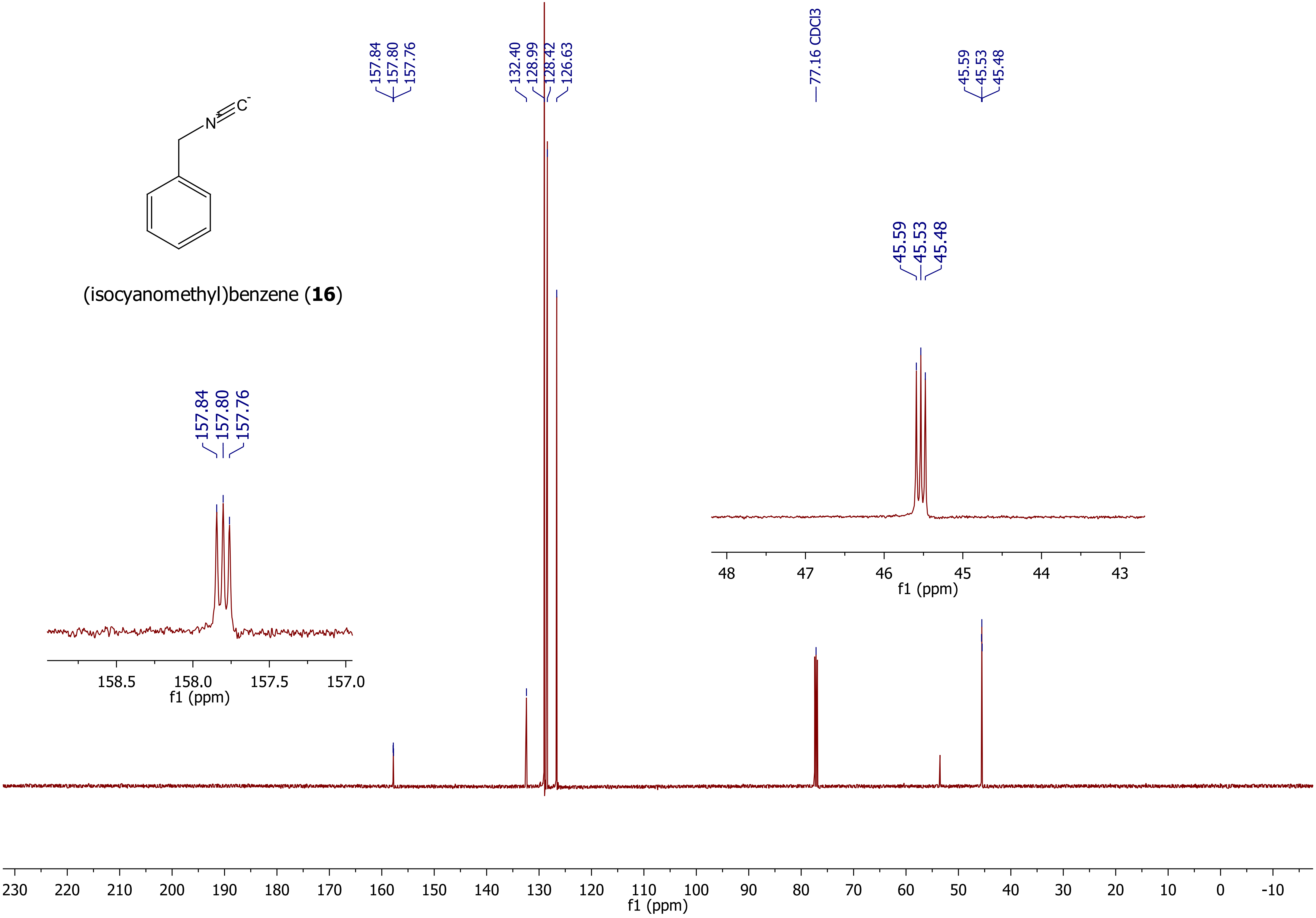


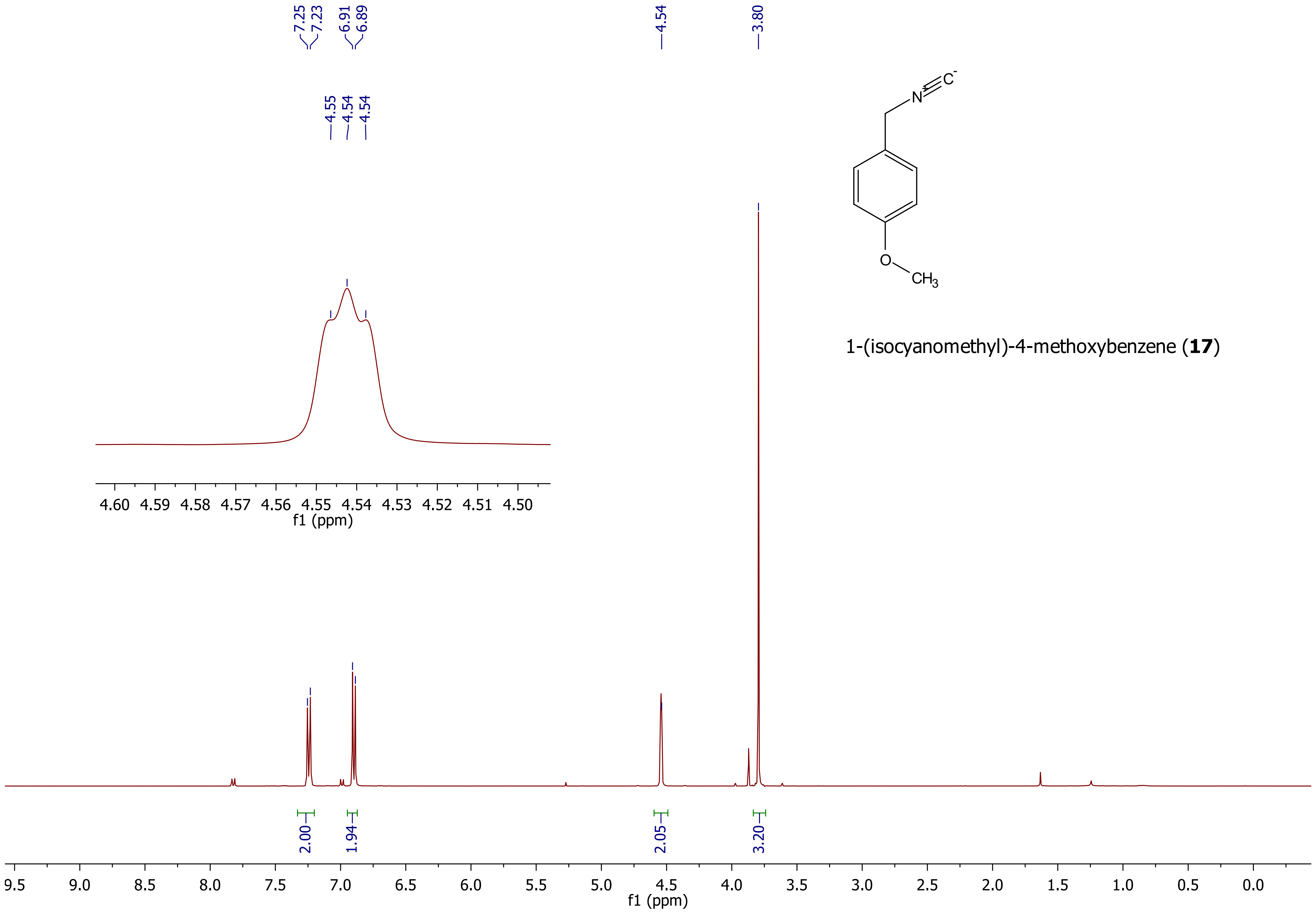
1-isocyano-4-nitrobenzene (**15**)



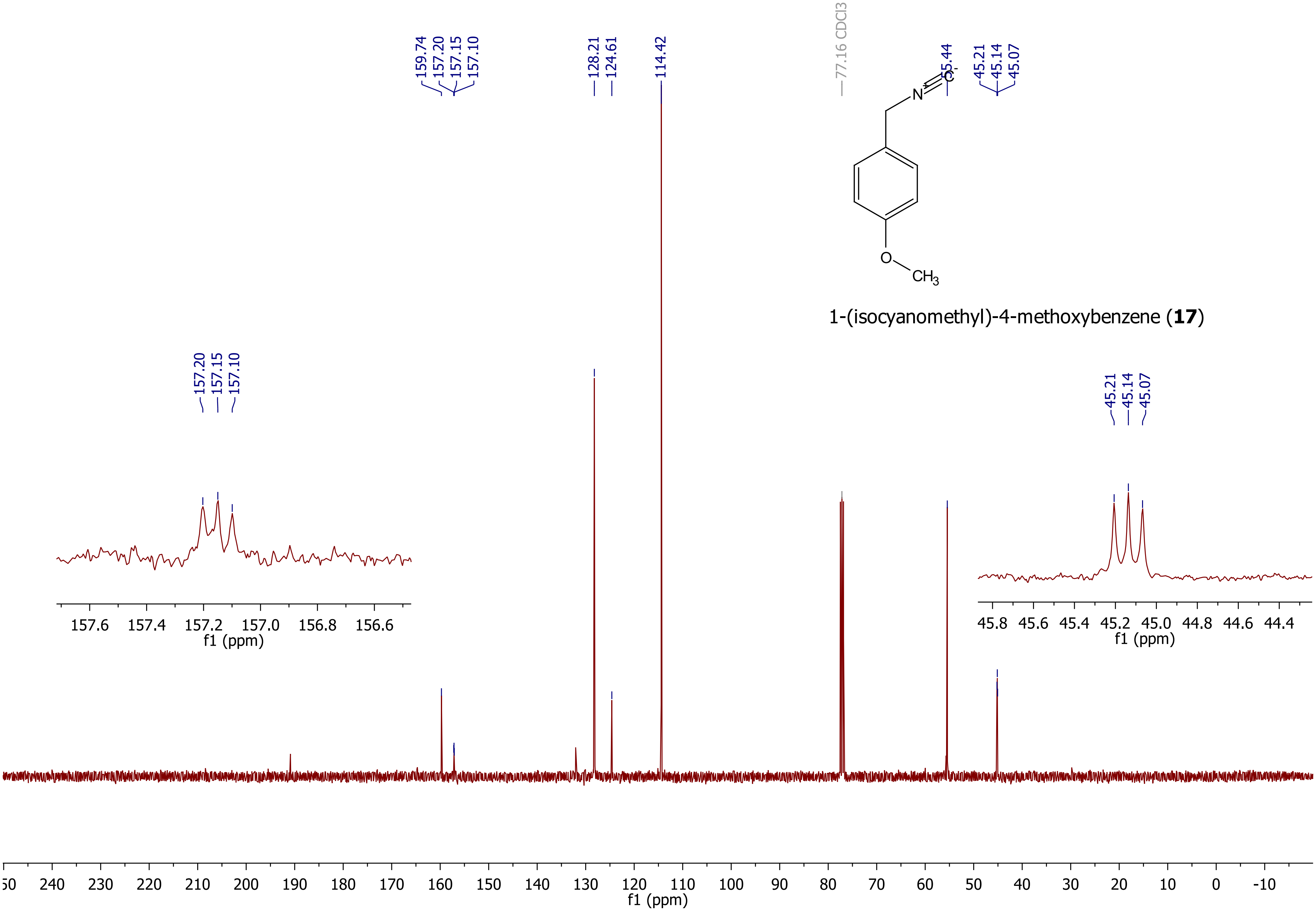
1-isocyano-4-nitrobenzene (**15**)


(isocyanomethyl)benzene (**16**)

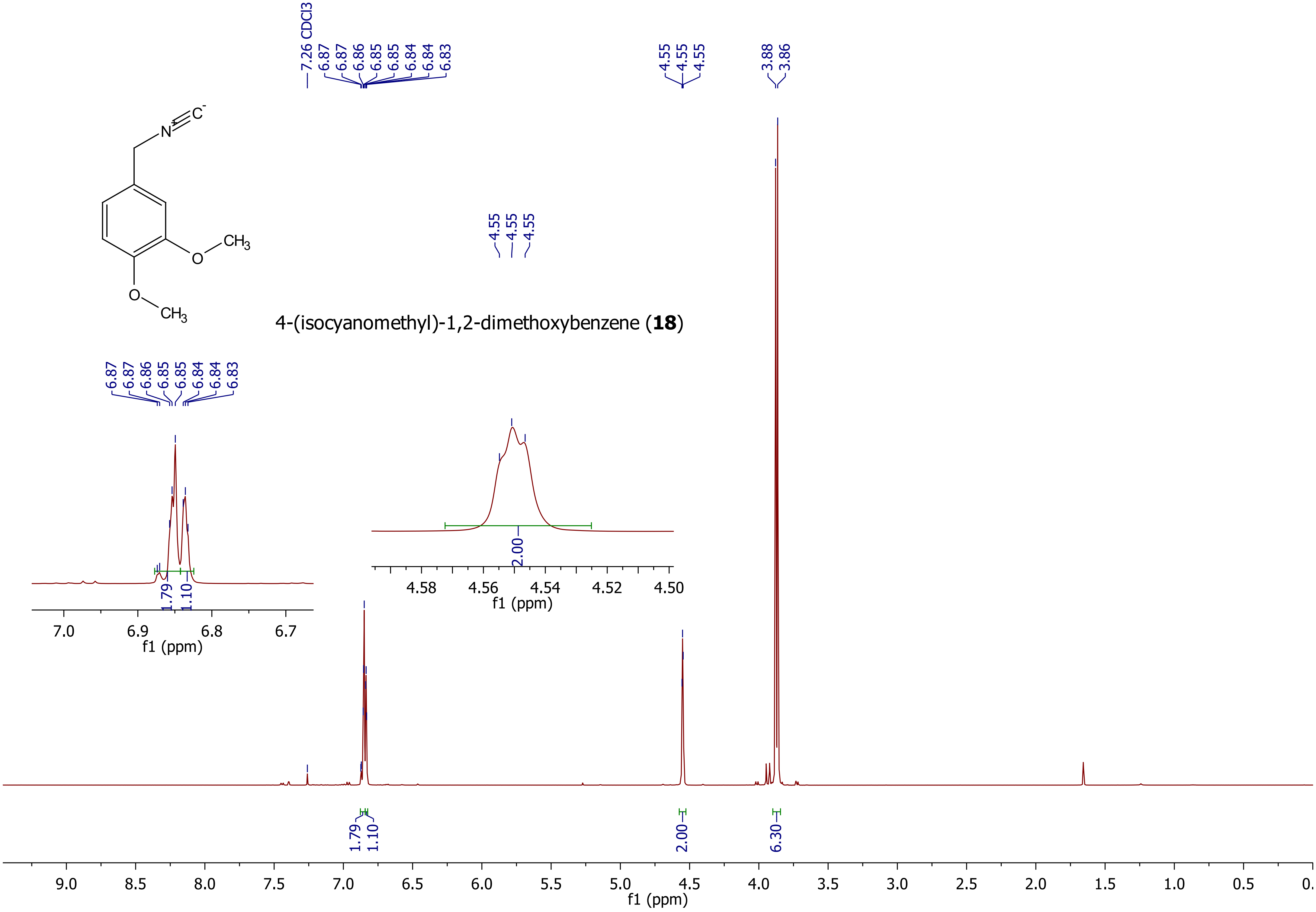

(isocyanomethyl)benzene (**16**)



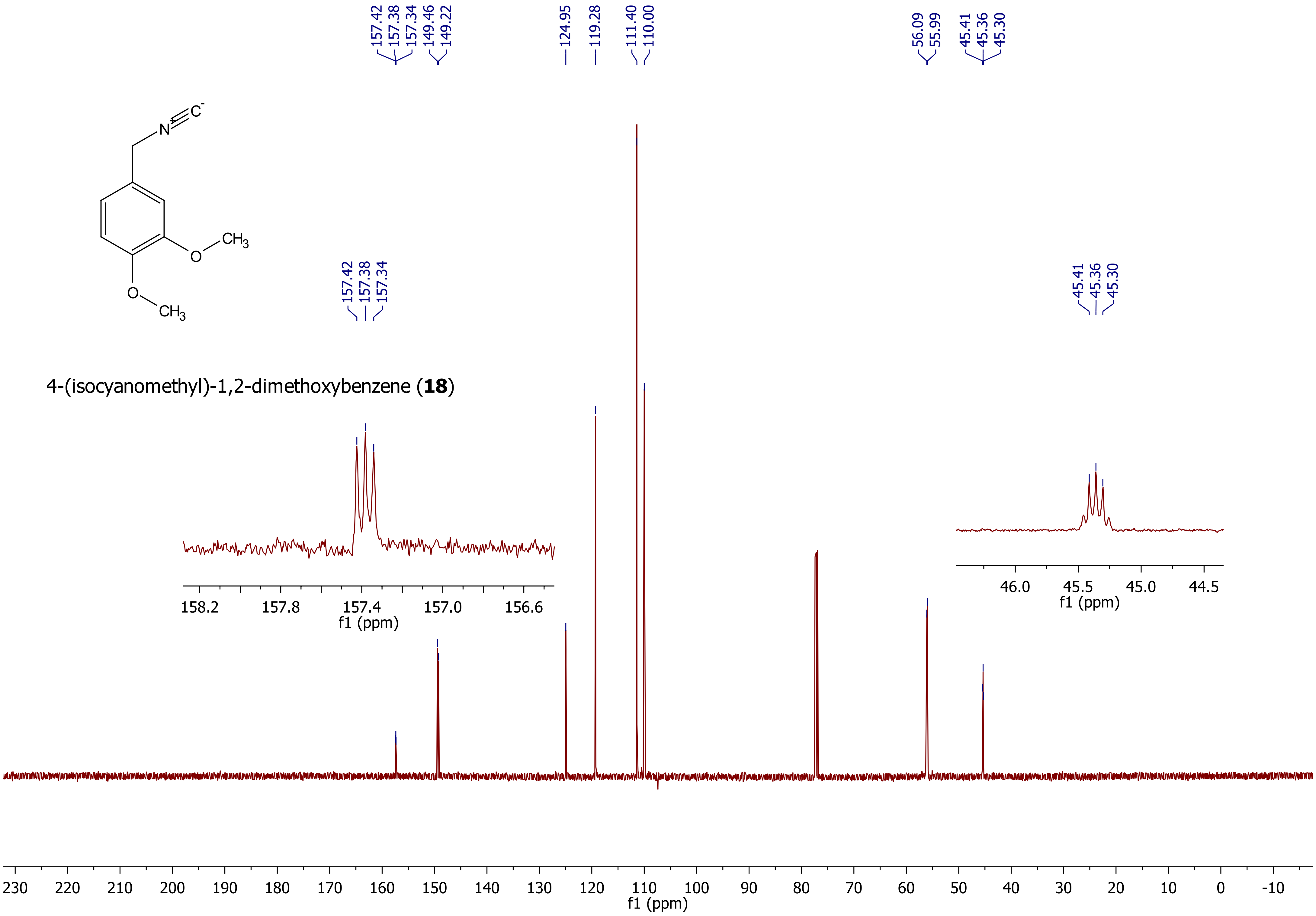
1-(isocyanomethyl)-4-methoxybenzene (**17**)



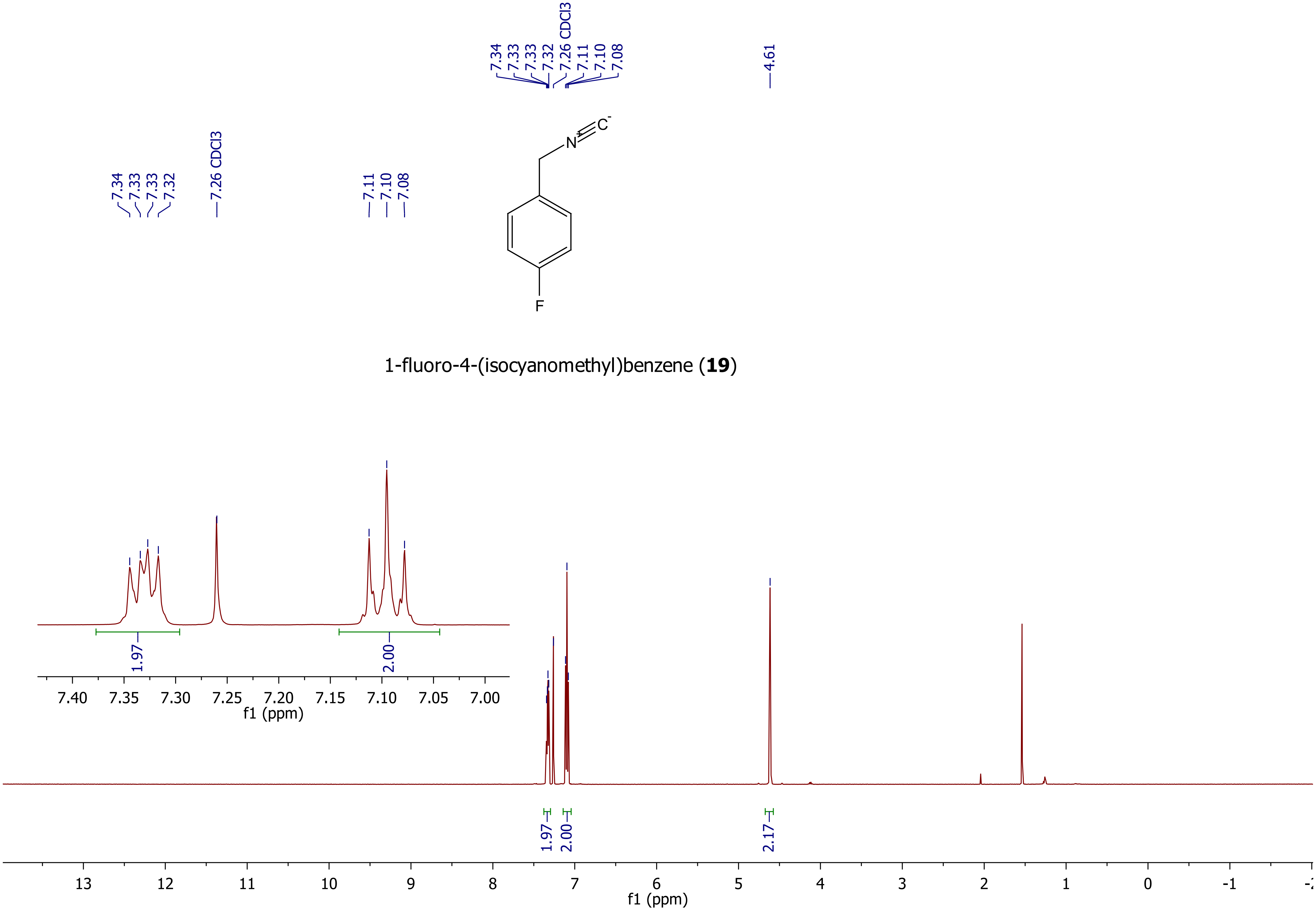
1-(isocyanomethyl)-4-methoxybenzene (**17**)



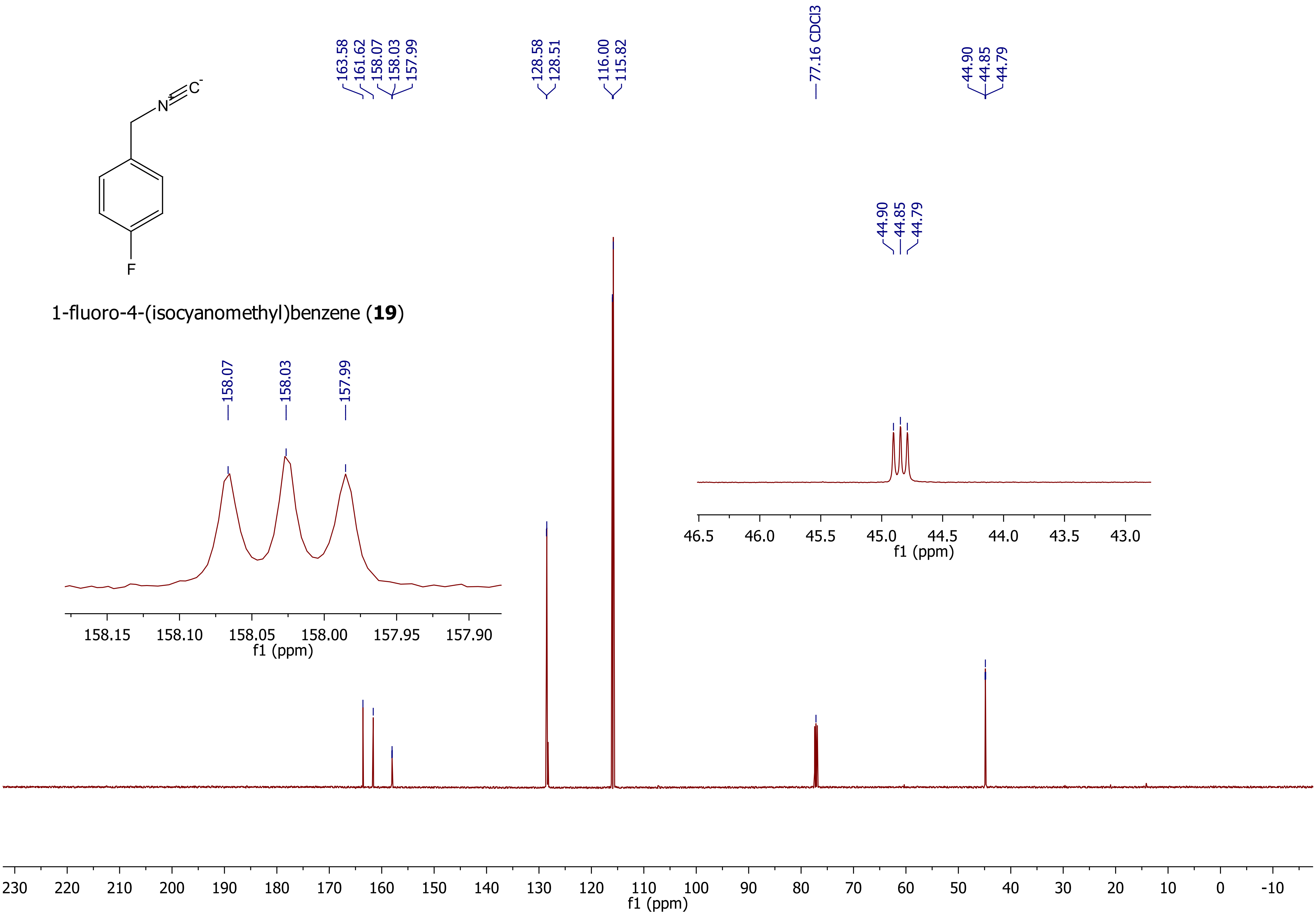
4-(isocyanomethyl)-1,2-dimethoxybenzene (**18**)



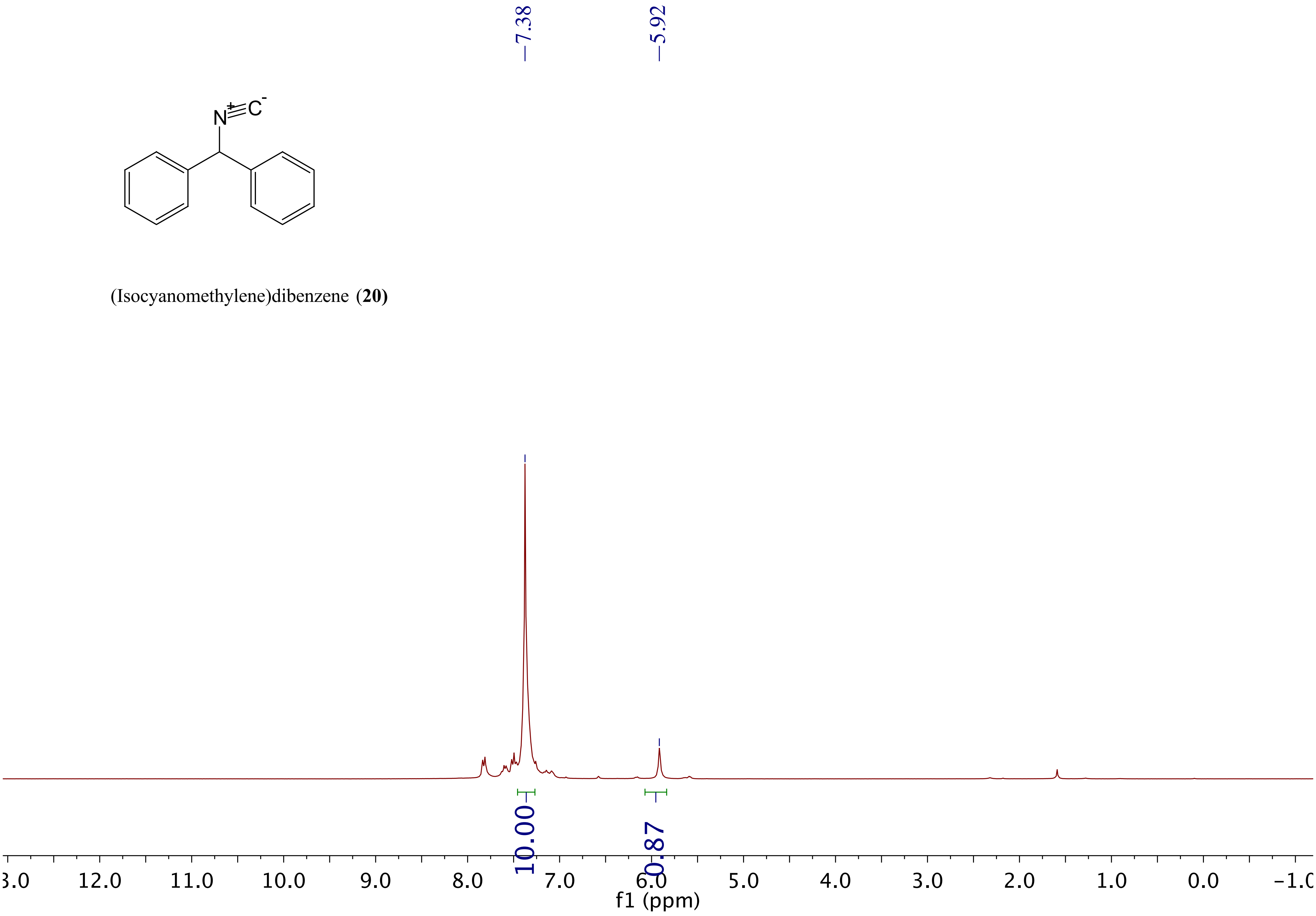
4-(isocyanomethyl)-1,2-dimethoxybenzene (**18**)



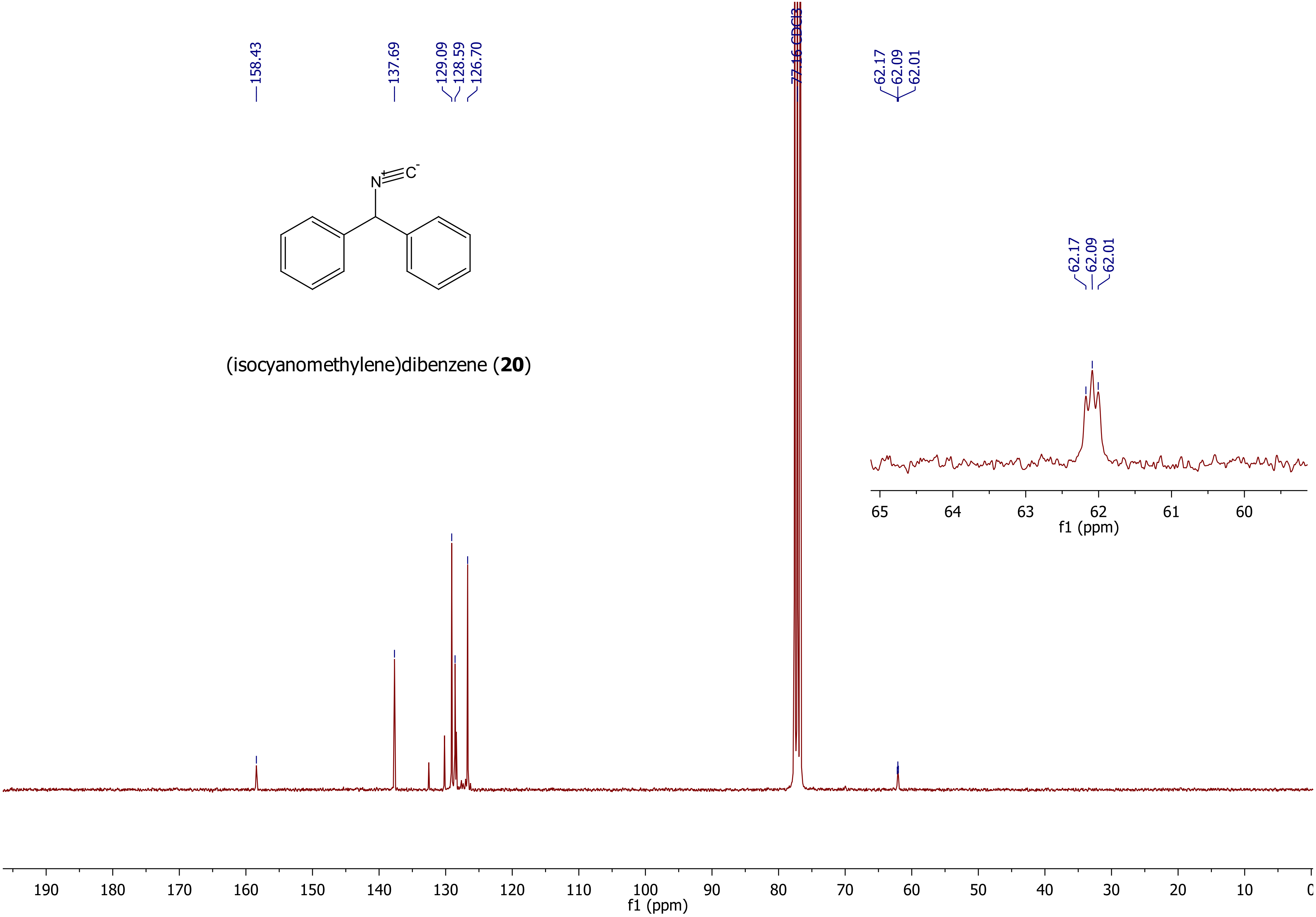
1-fluoro-4-(isocyanomethyl)benzene (**19**)



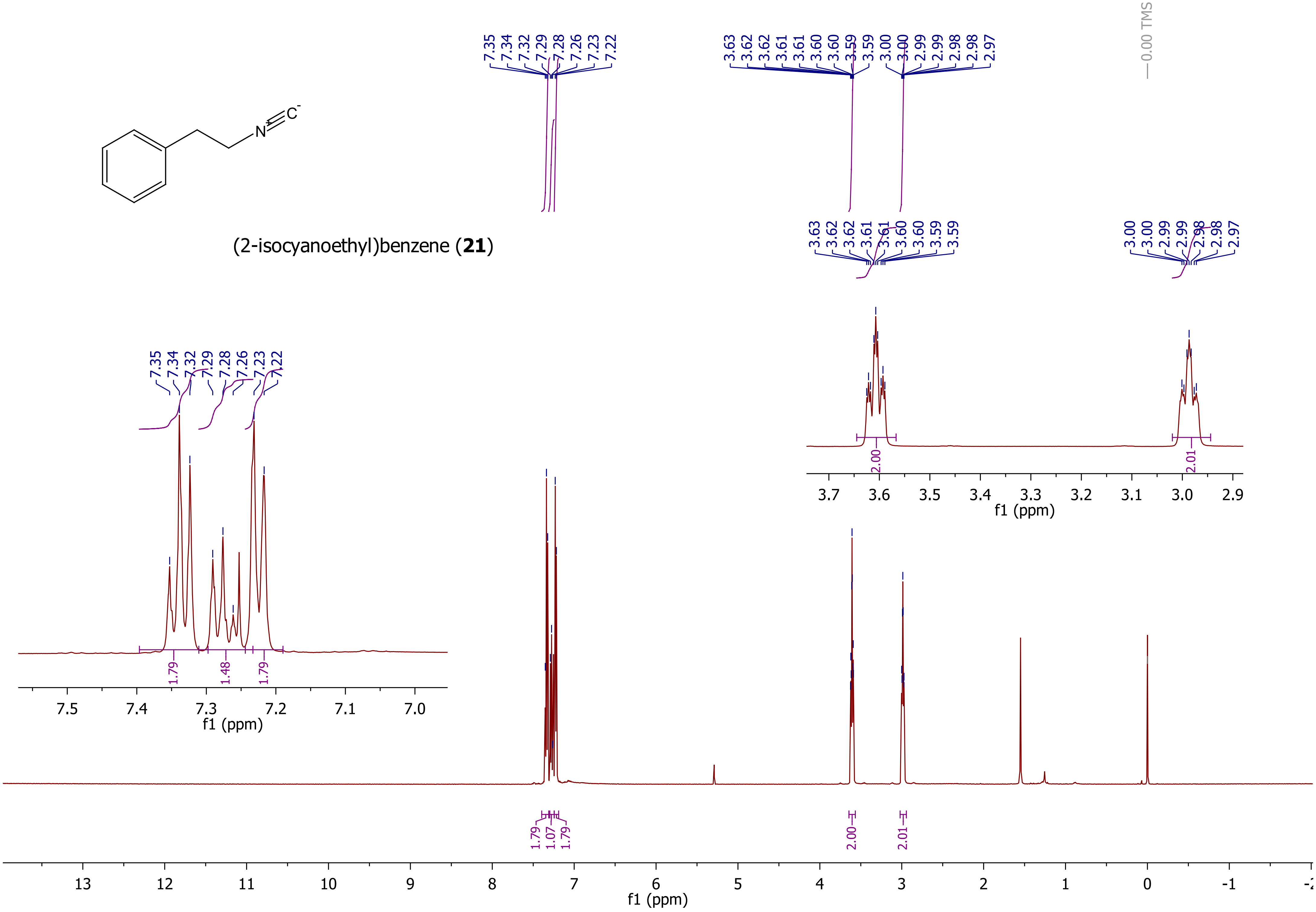
1-fluoro-4-(isocyanomethyl)benzene (**19**)

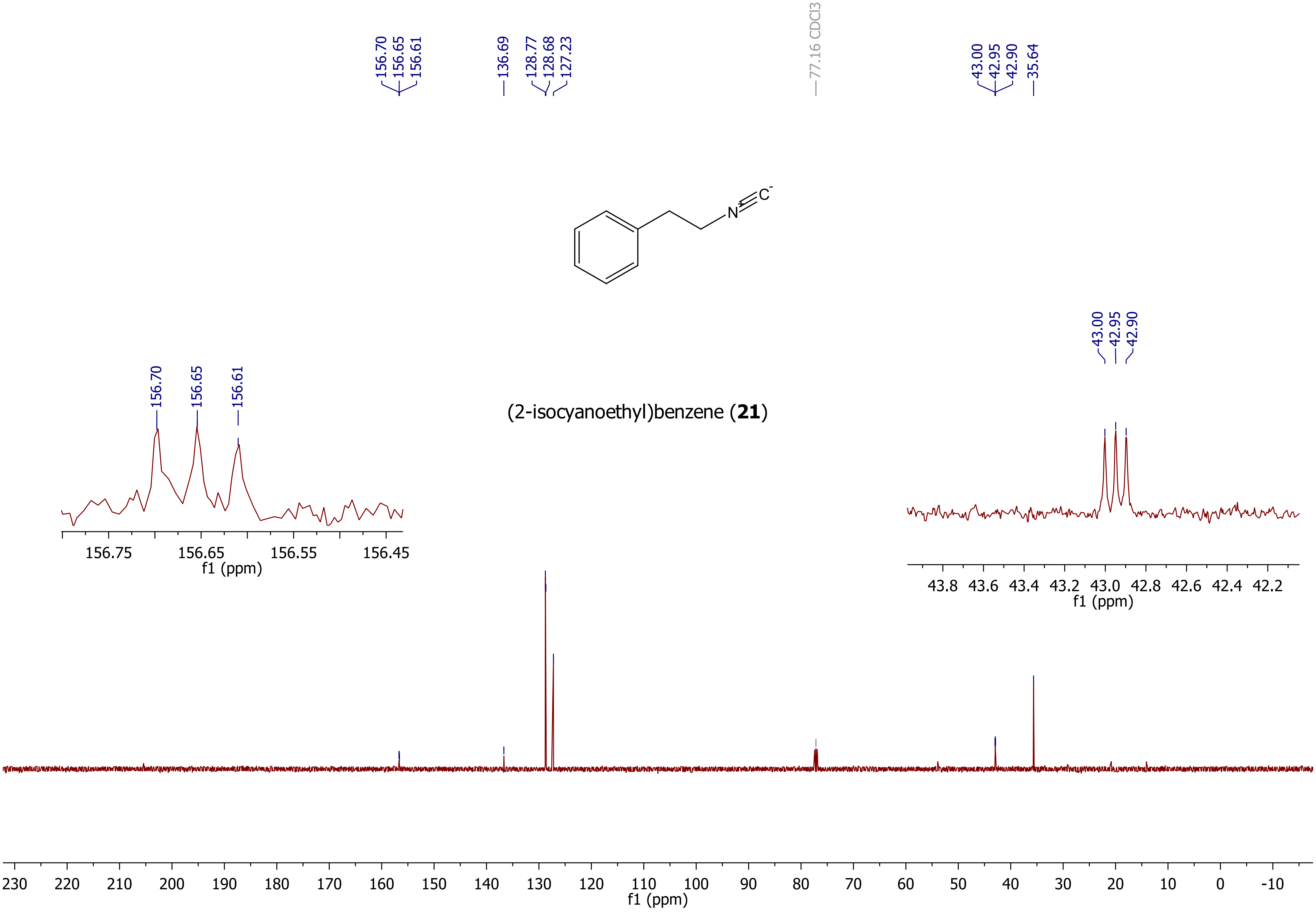


(Isocyanomethylene)dibenzene (**20**)

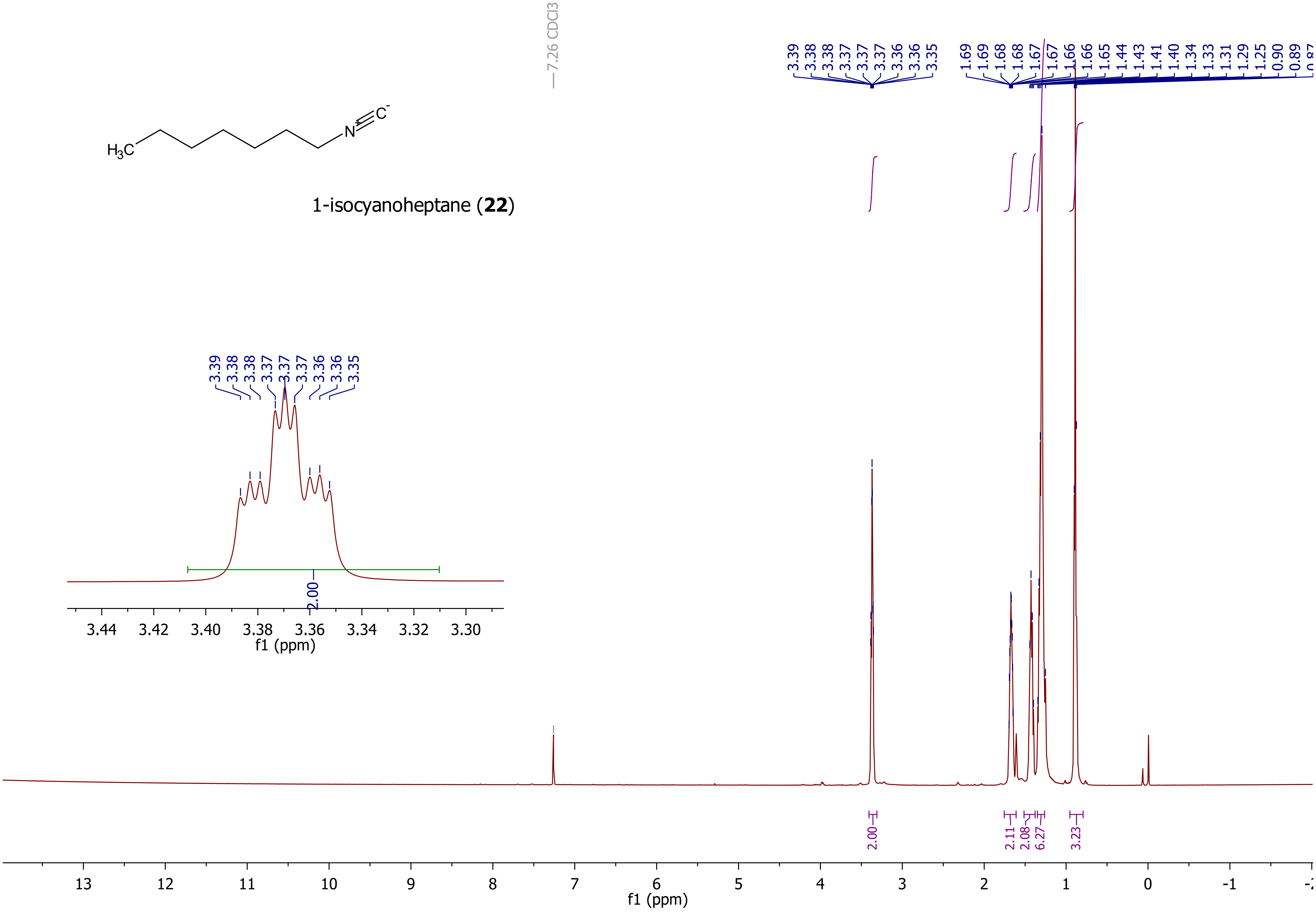


(isocyanomethylene)dibenzene (**20**)

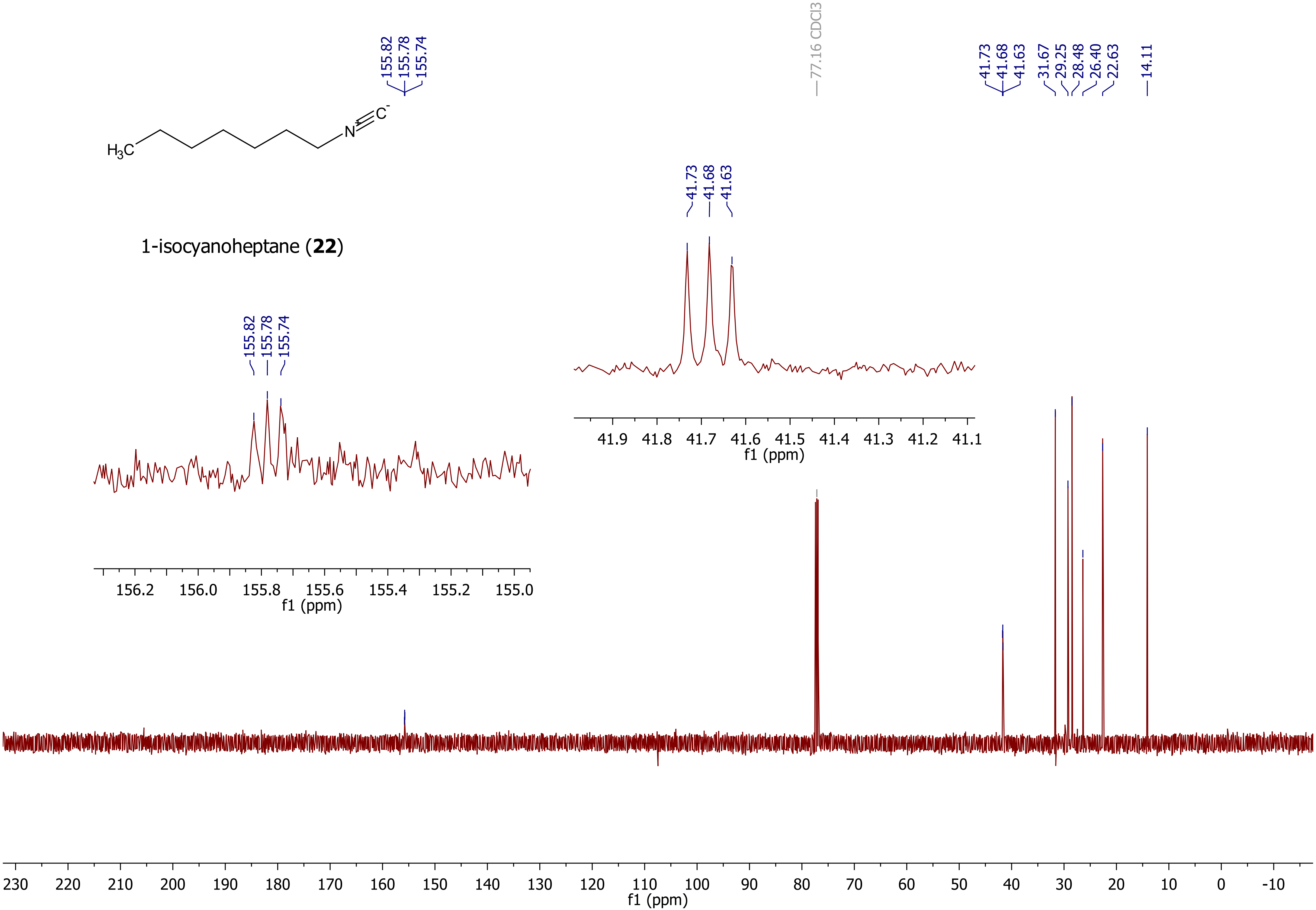

(2-isocyanoethyl)benzene (**21**)



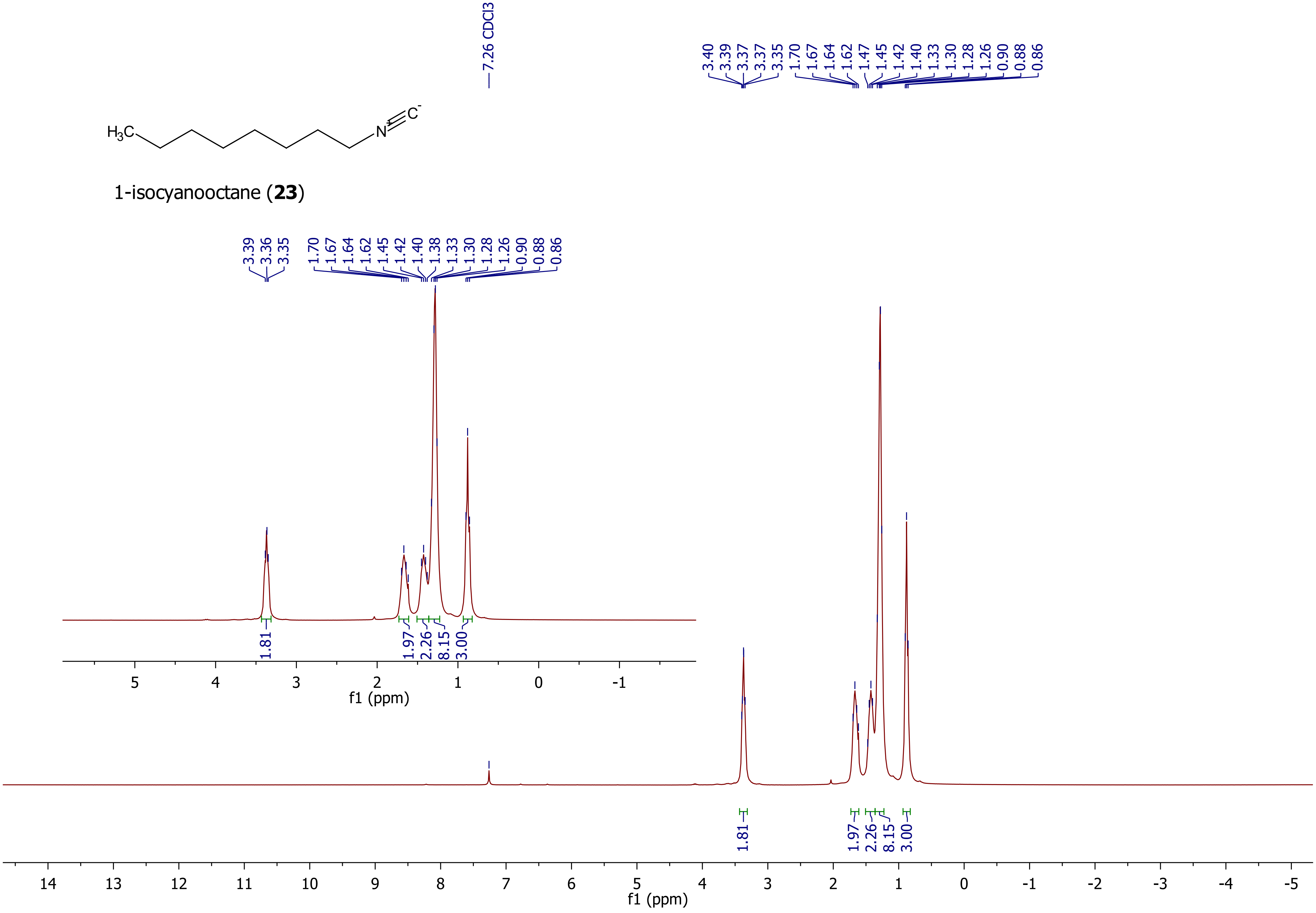
(2-isocyanoethyl)benzene (**21**)



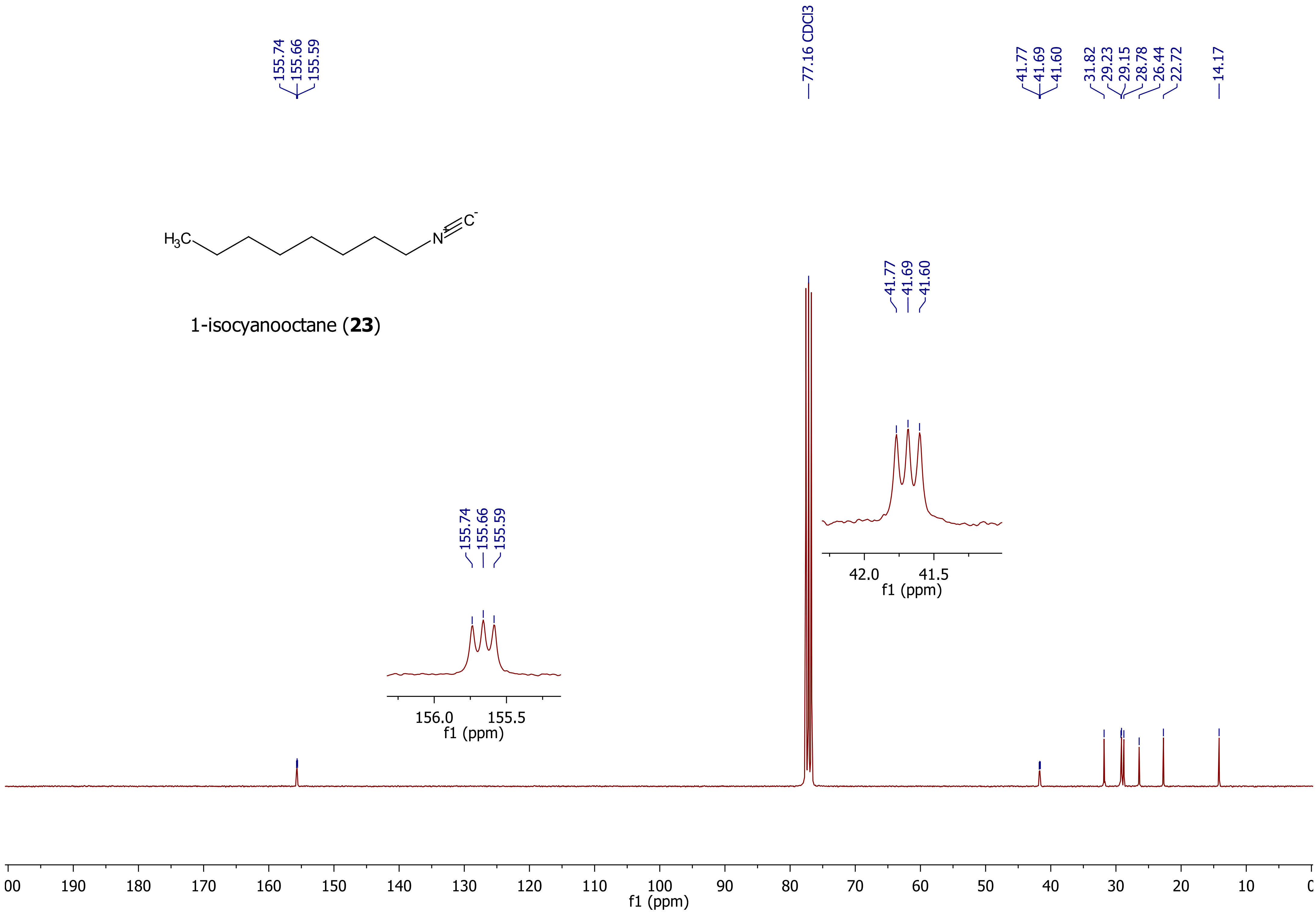
1-isocyanoheptane (**22**)



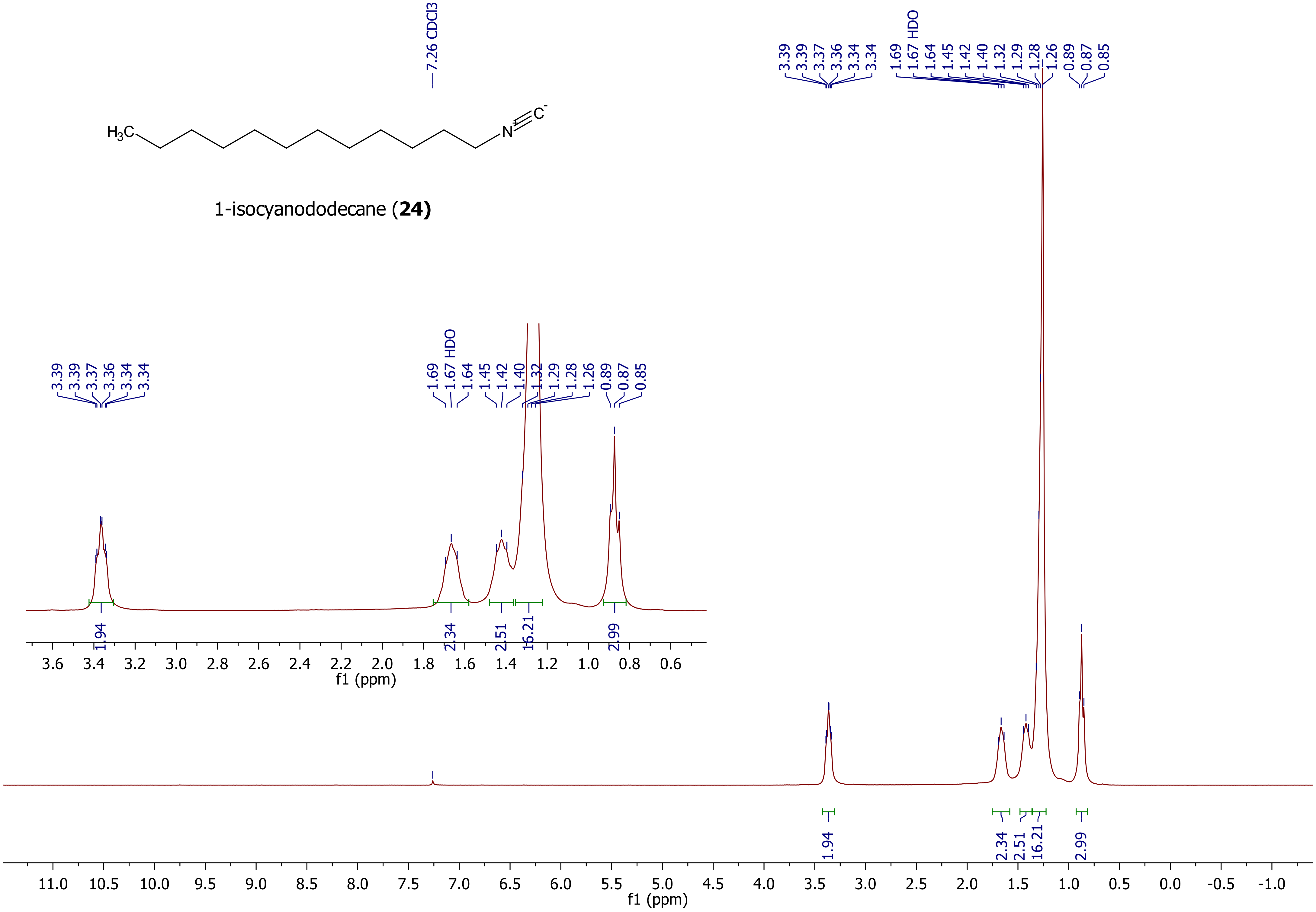
1-isocyanoheptane (**22**)

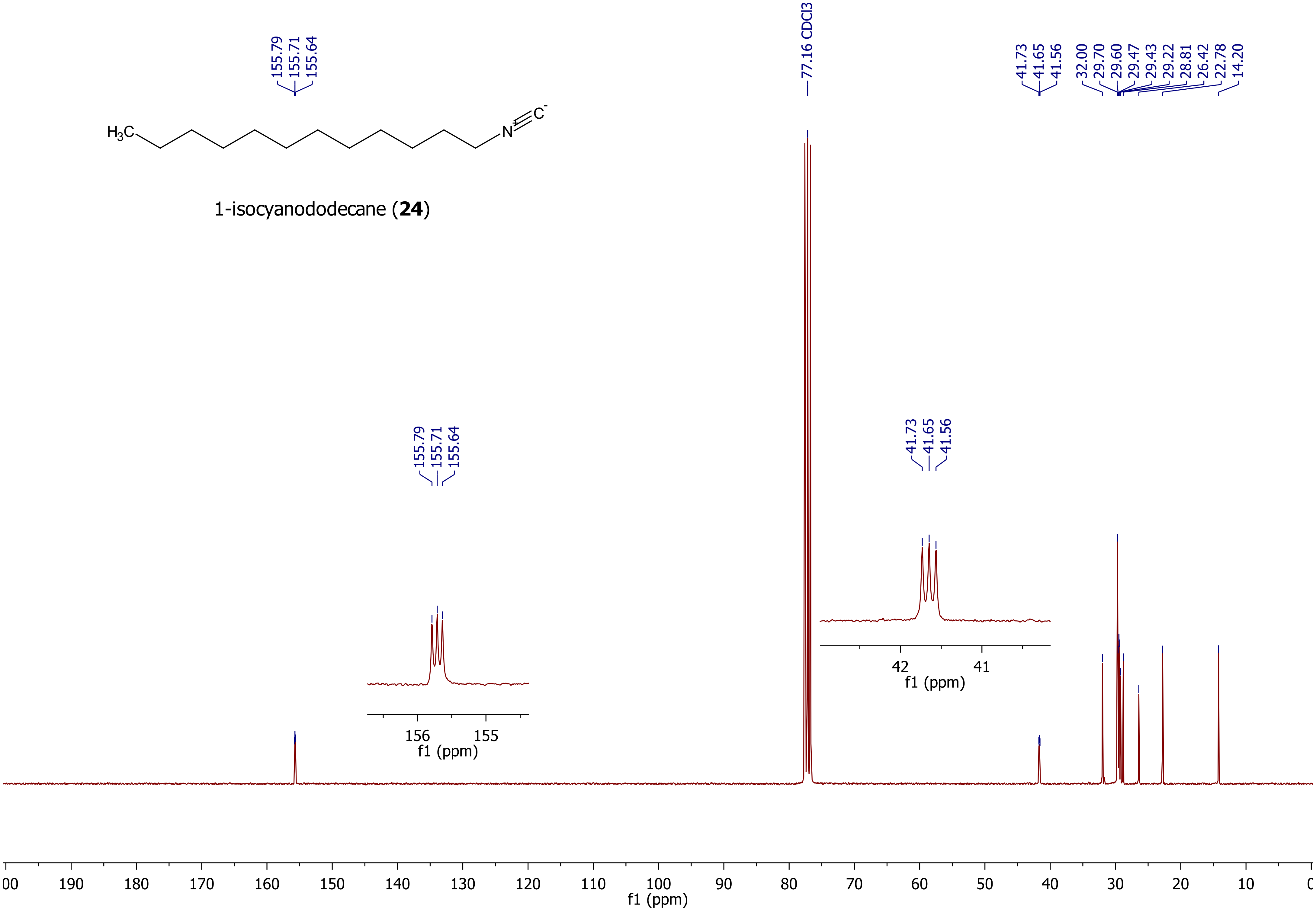


1-isocyanooctane (**23**)

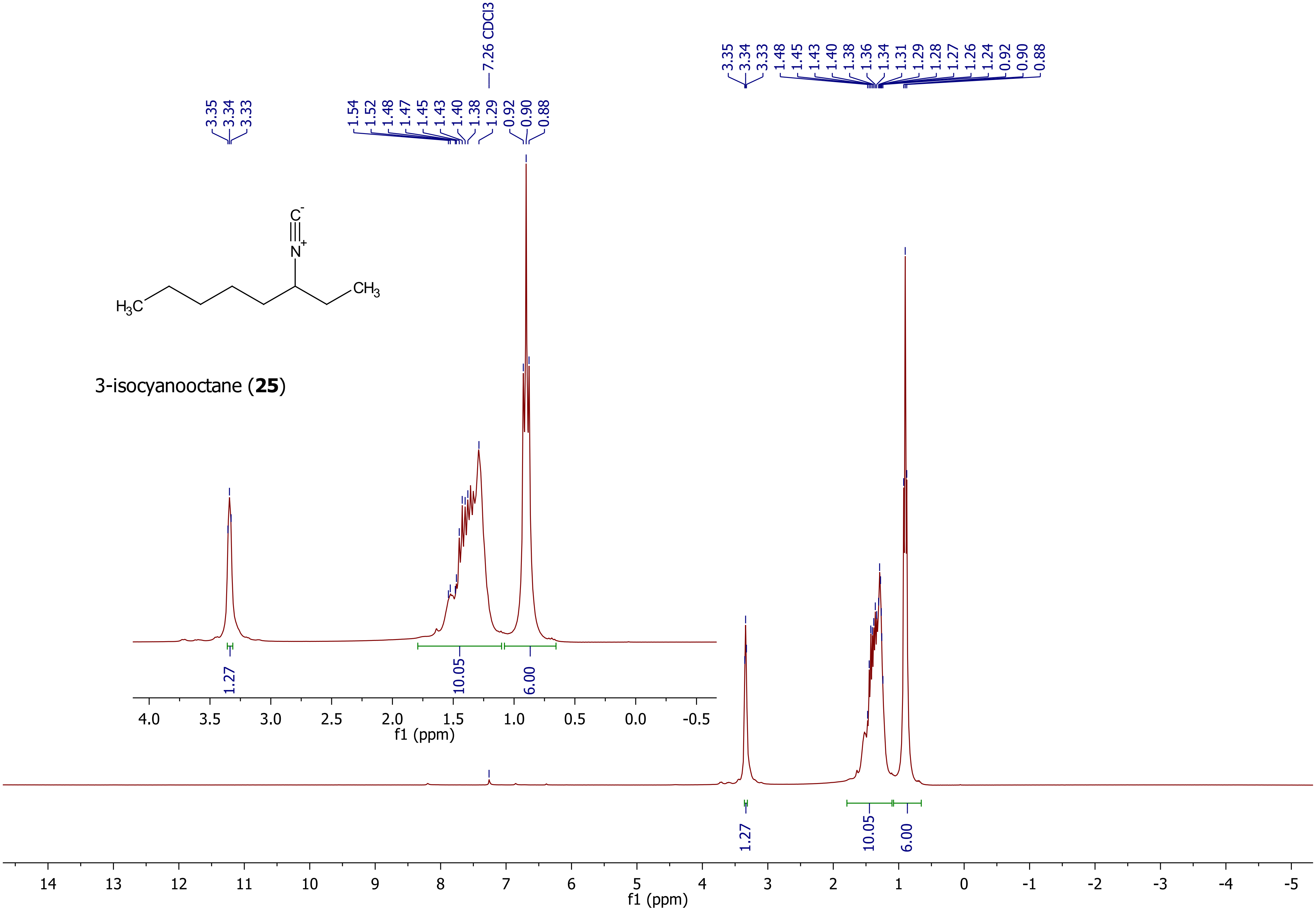


1-isocyanooctane (**23**)

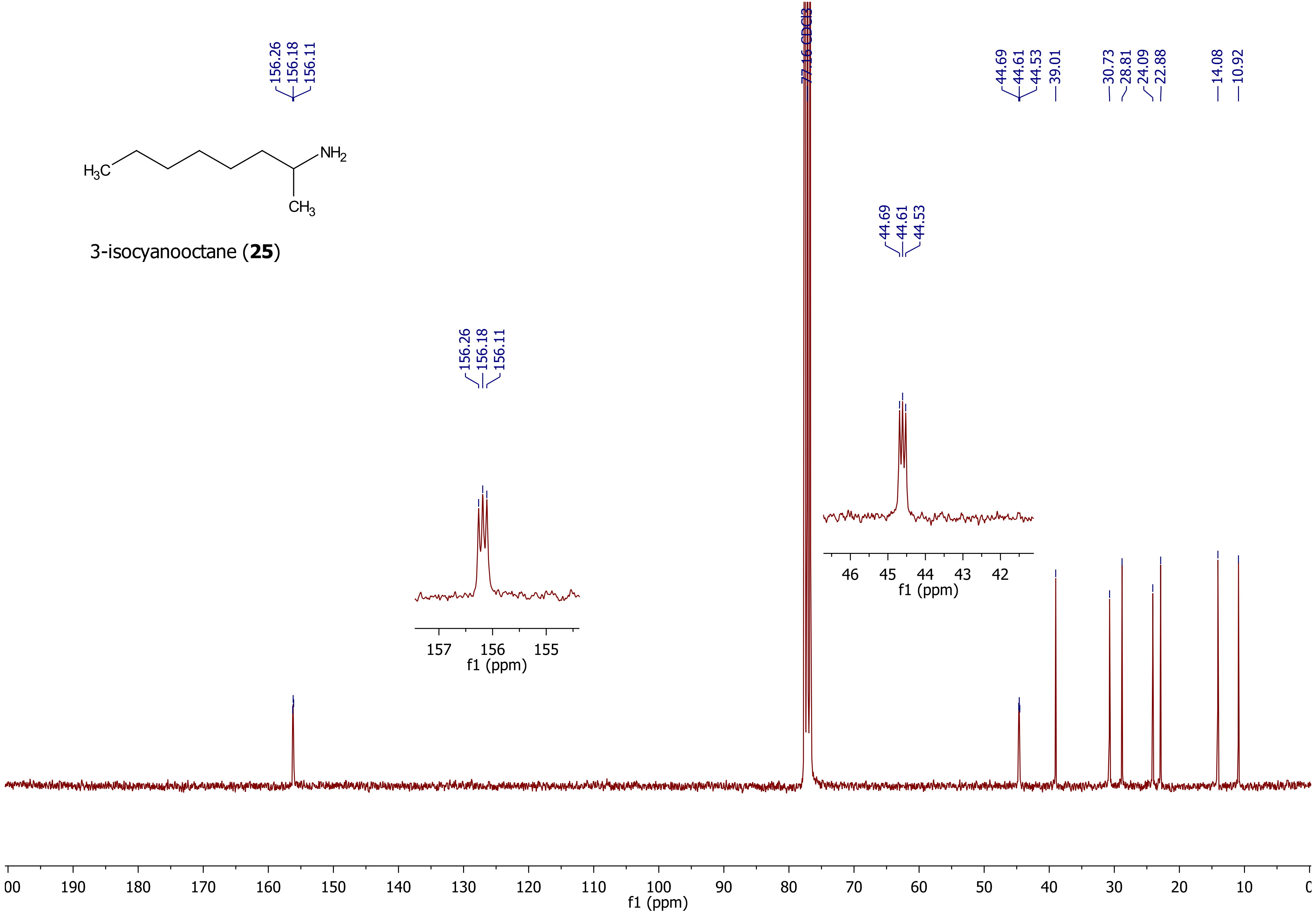

1-isocyanododecane (**24)**

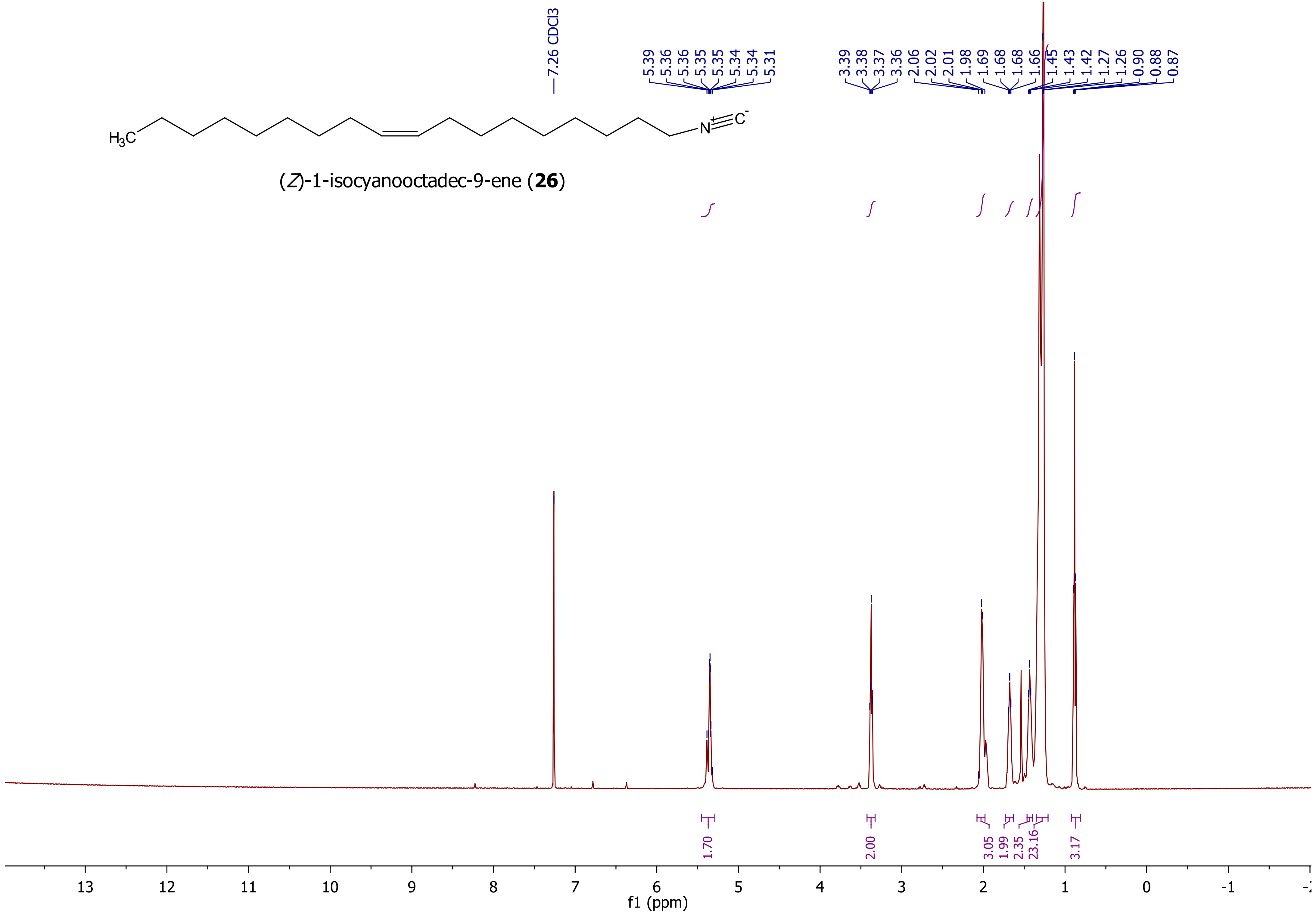


1-isocyanododecane (**24**)

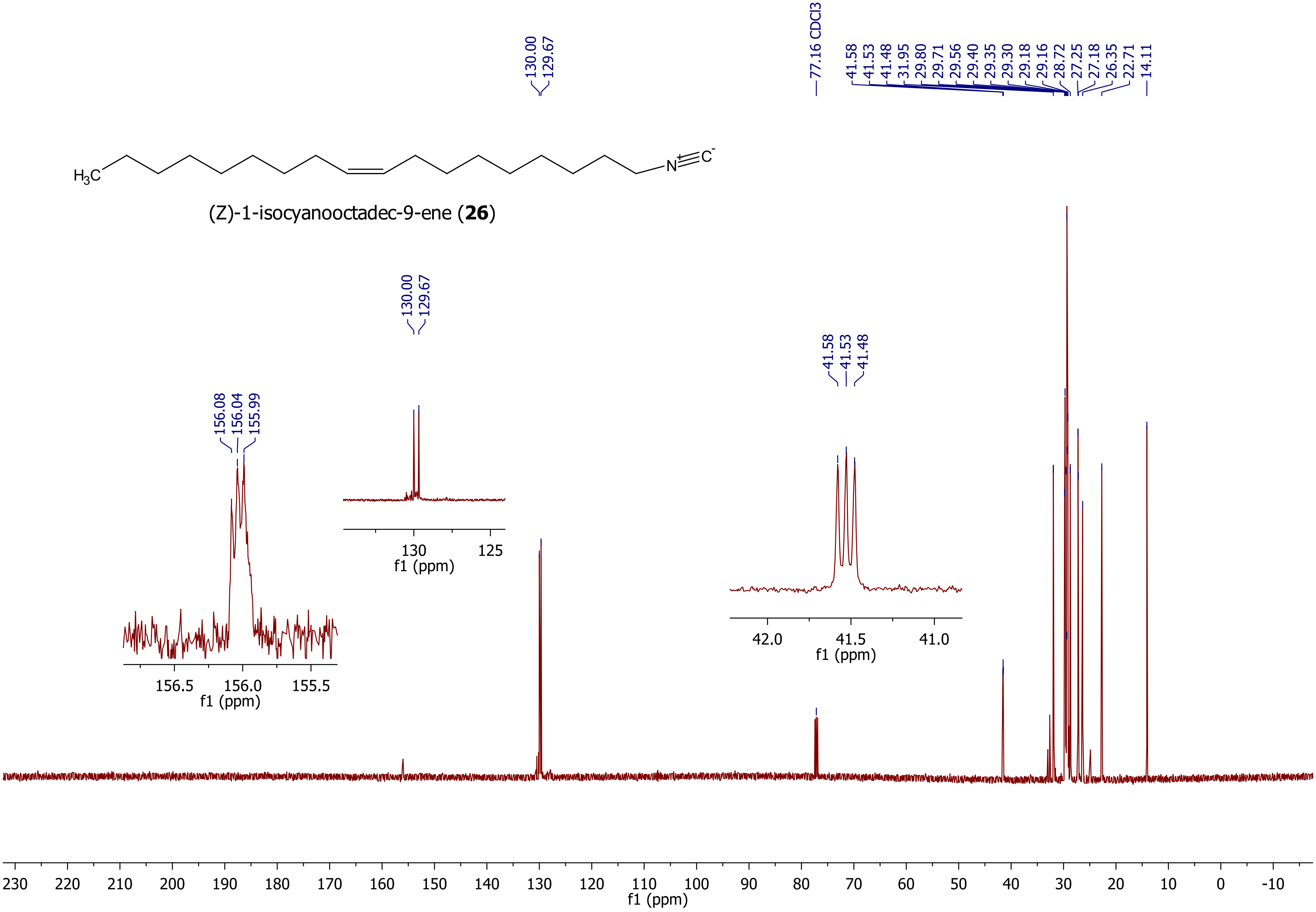


3-isocyanooctane (**25**)

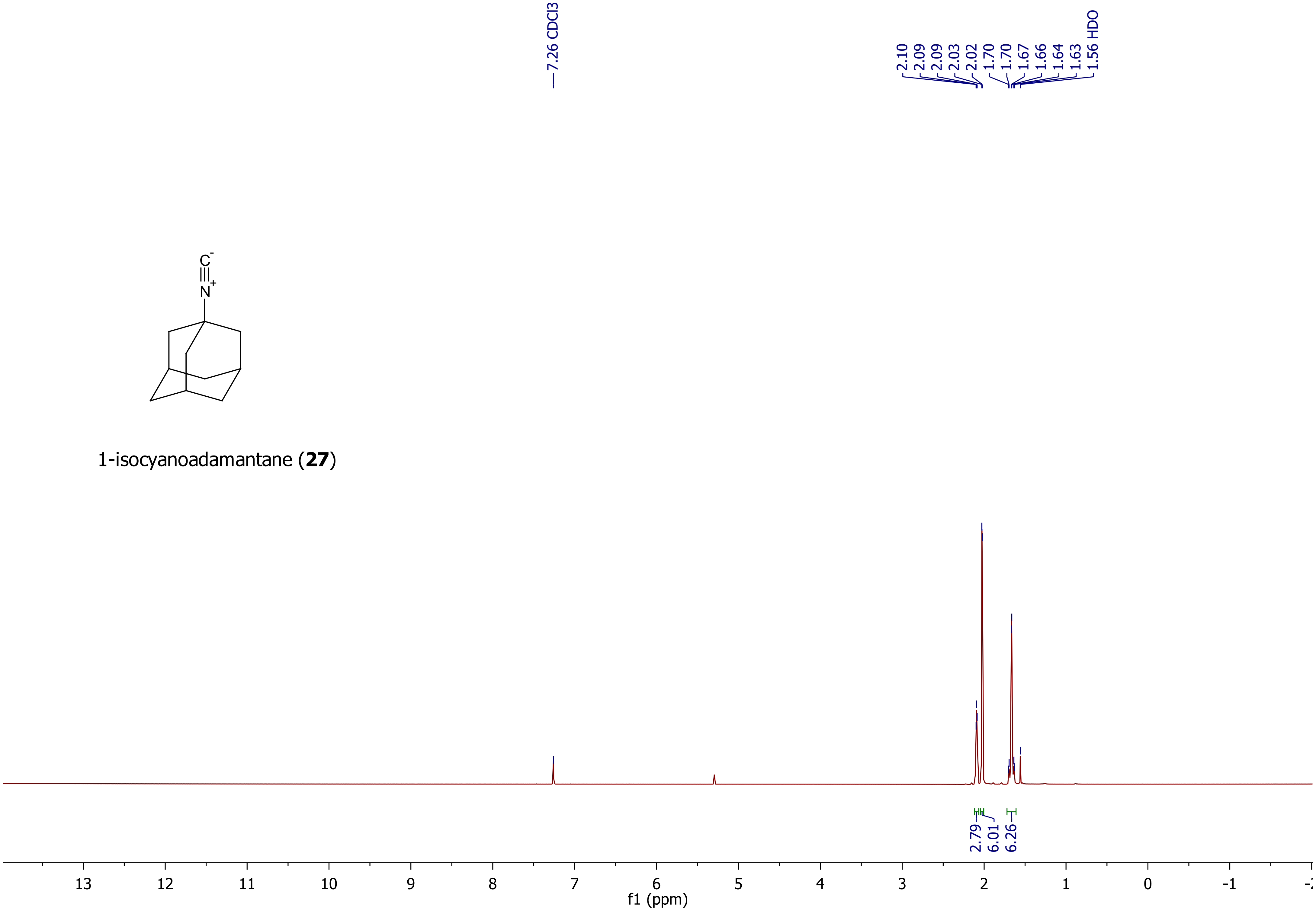

3-isocyanooctane (**25**)



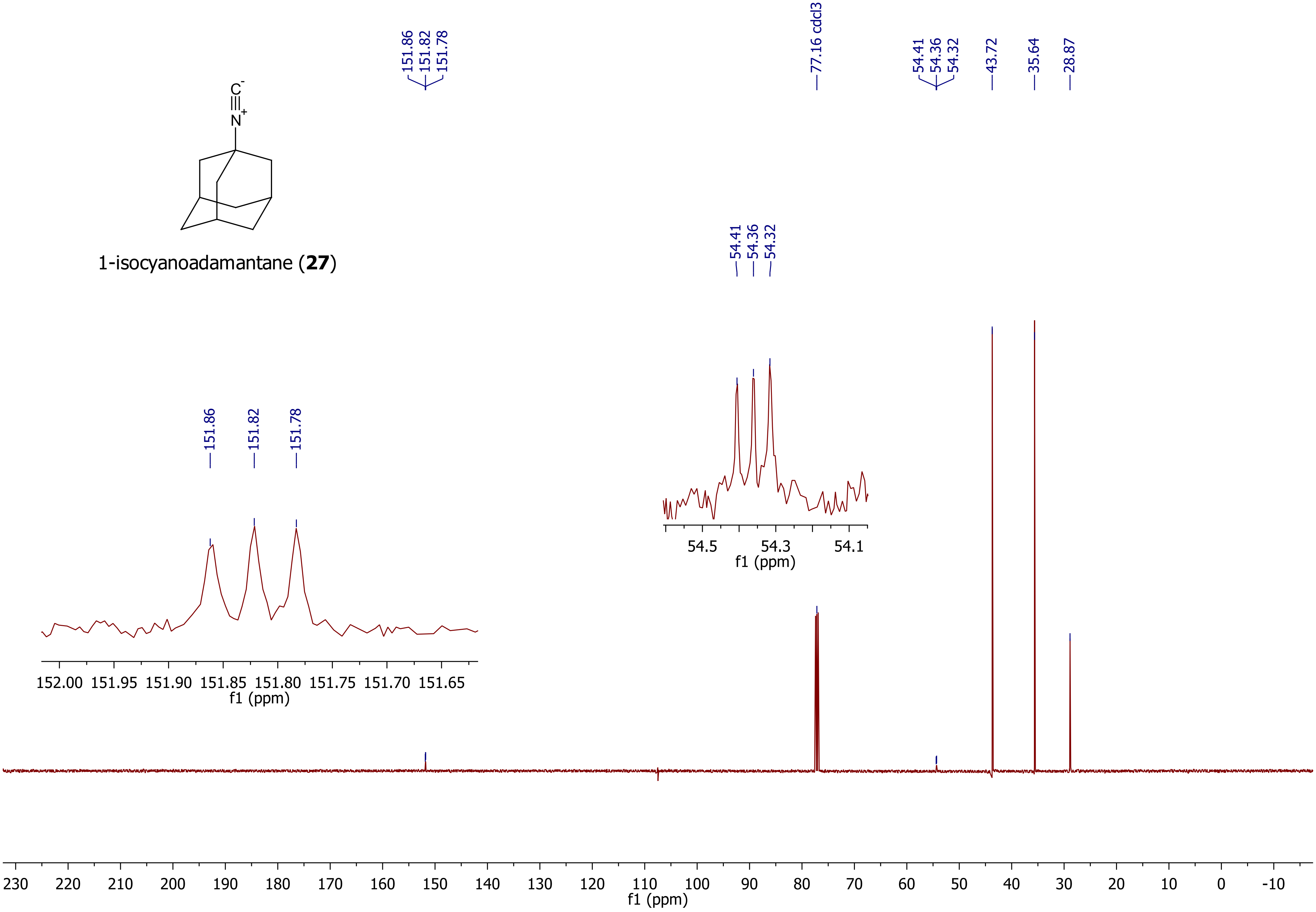
(*Z*)-1-isocyanooctadec-9-ene (**26**)

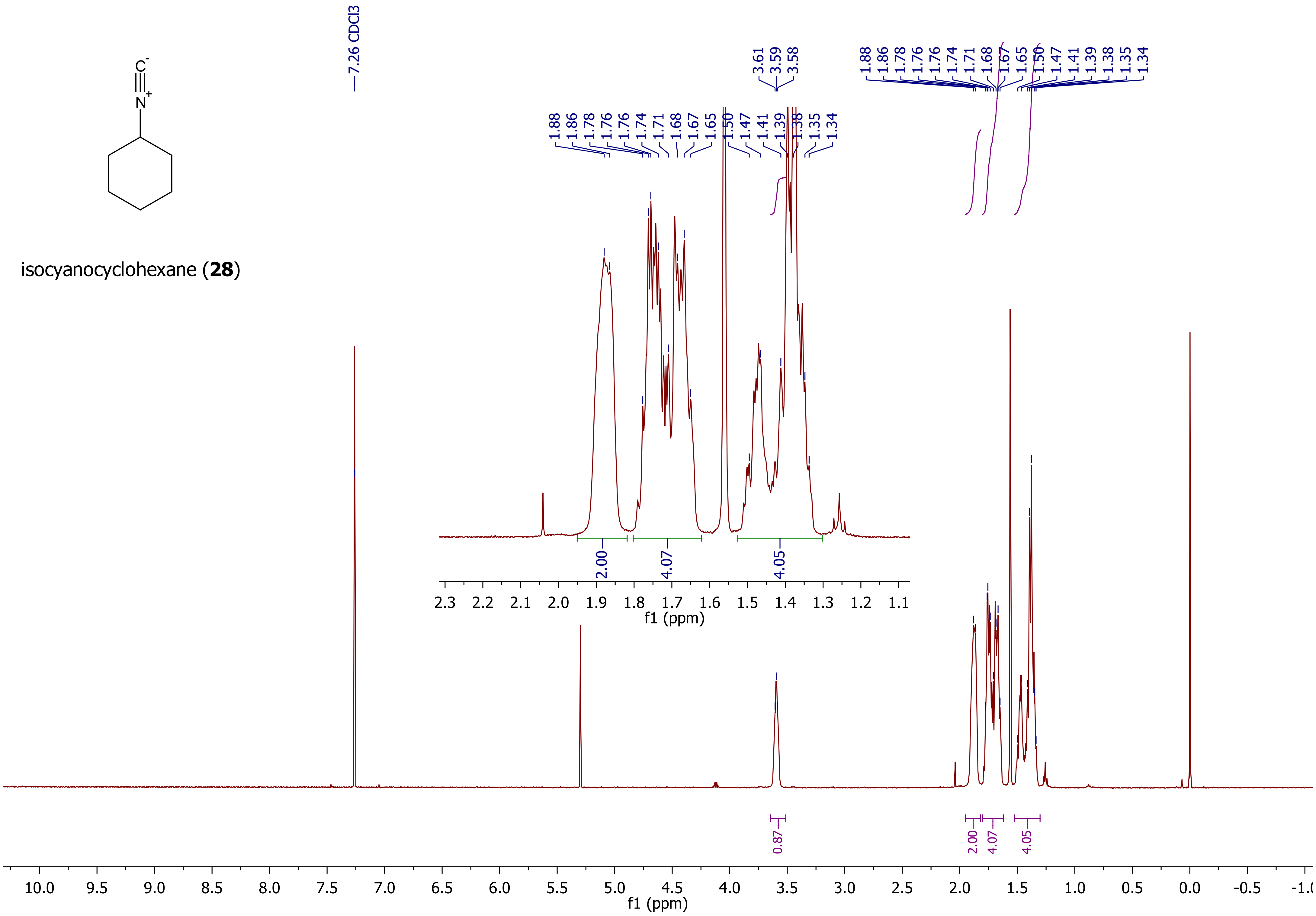


(Z)-1-isocyanooctadec-9-ene (**26**)

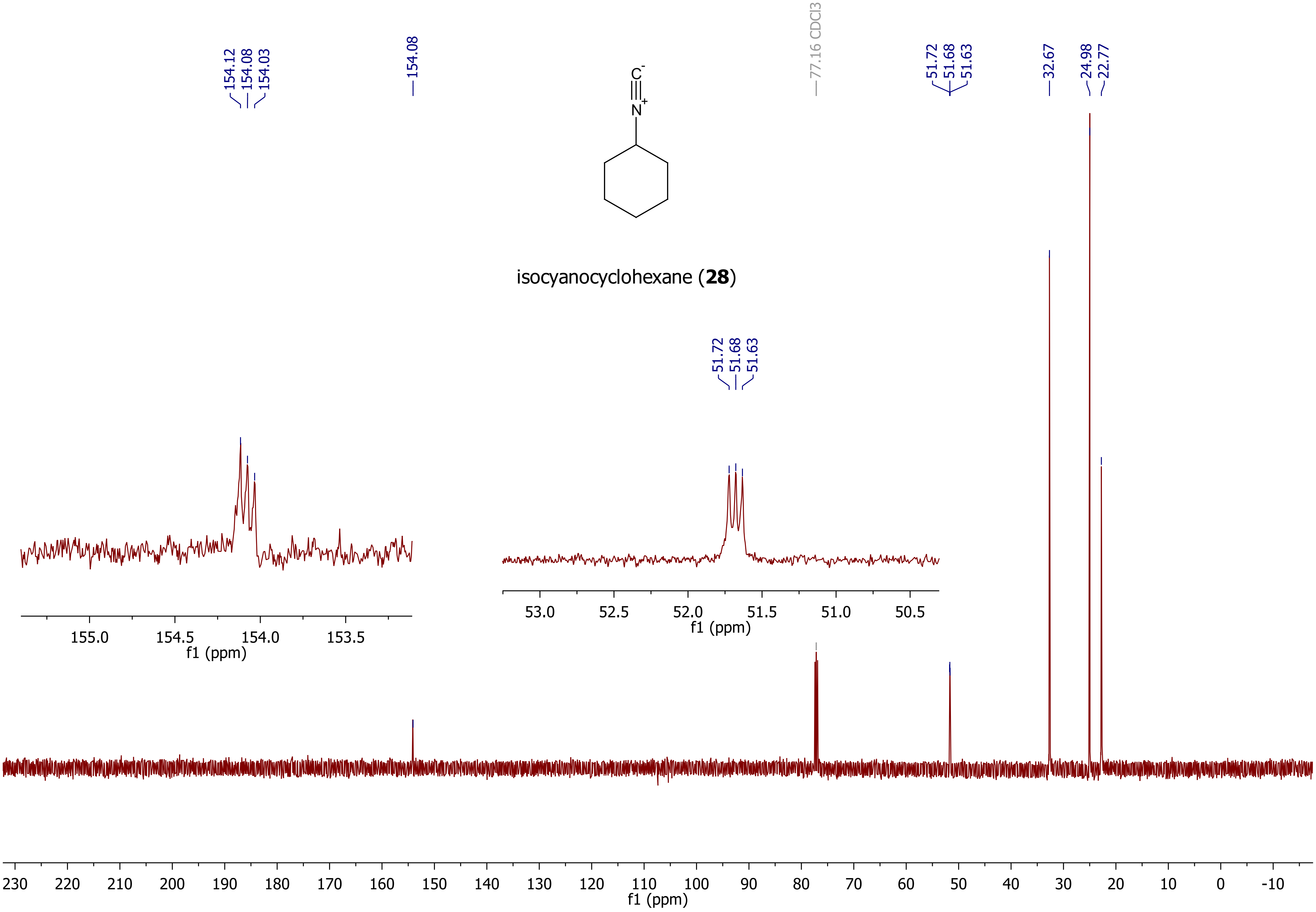


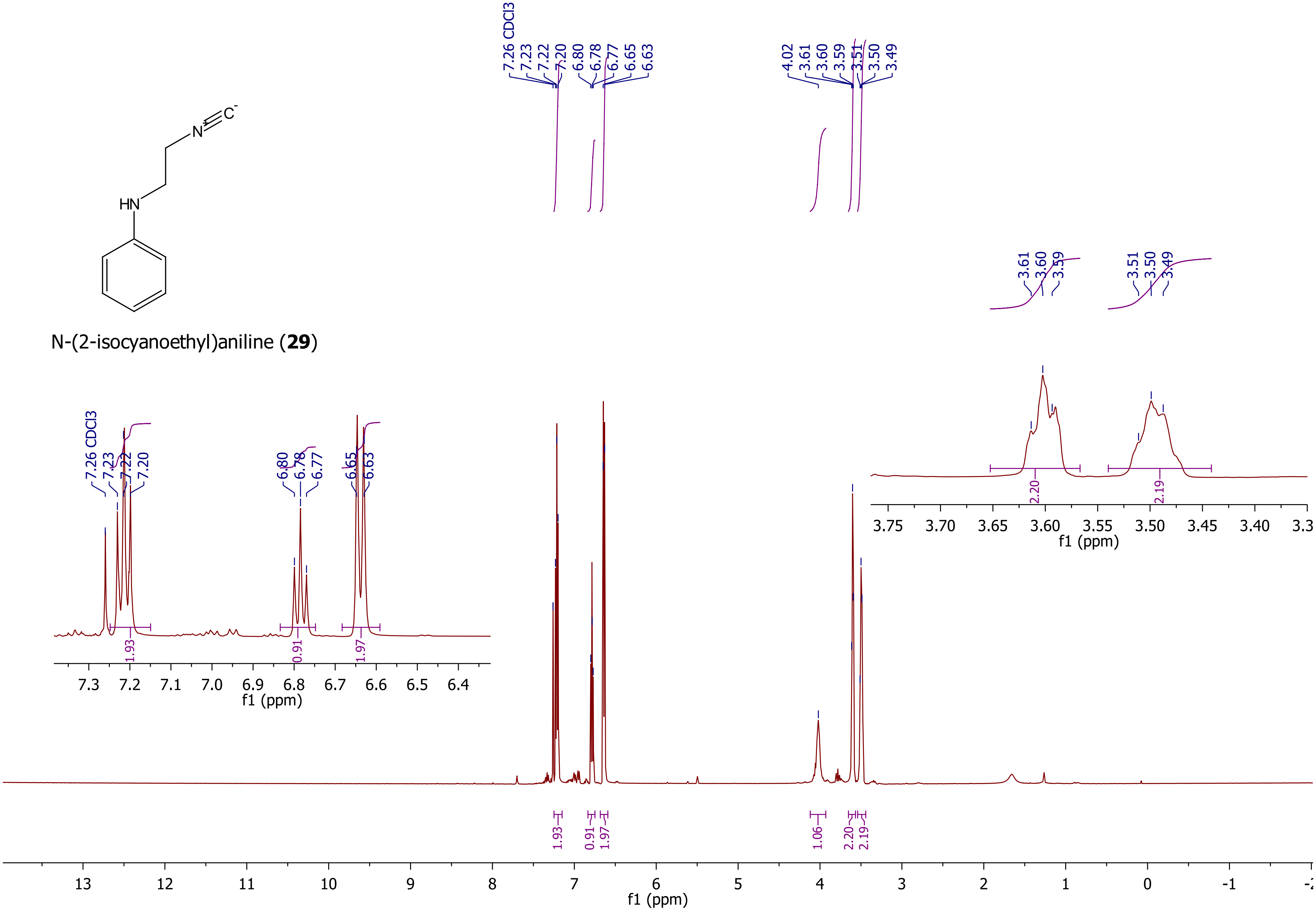
1-isocyanoadamantane (**27**)


1-isocyanoadamantane (**27**)

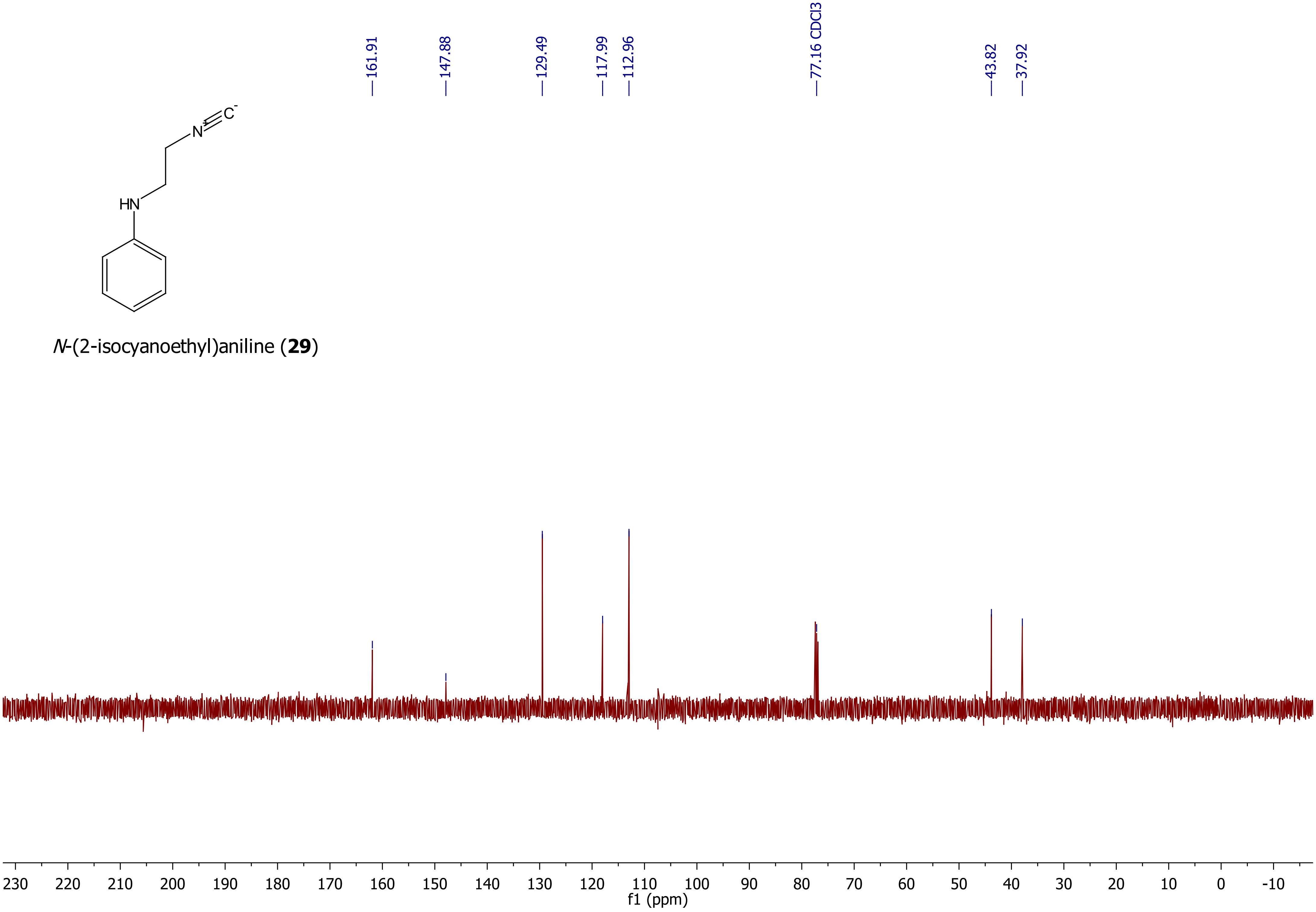


isocyanocyclohexane (**28**)

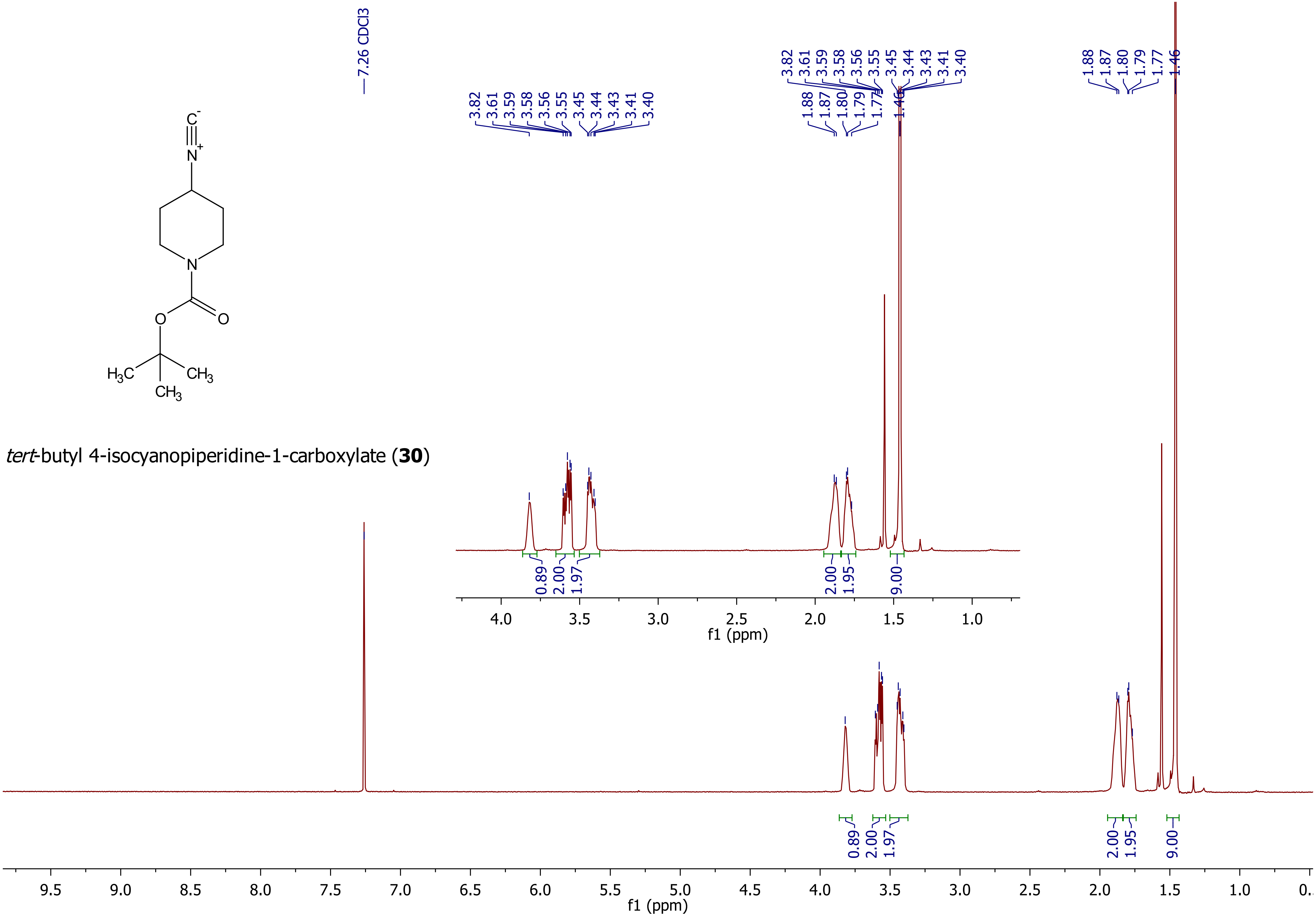

isocyanocyclohexane (**28**)



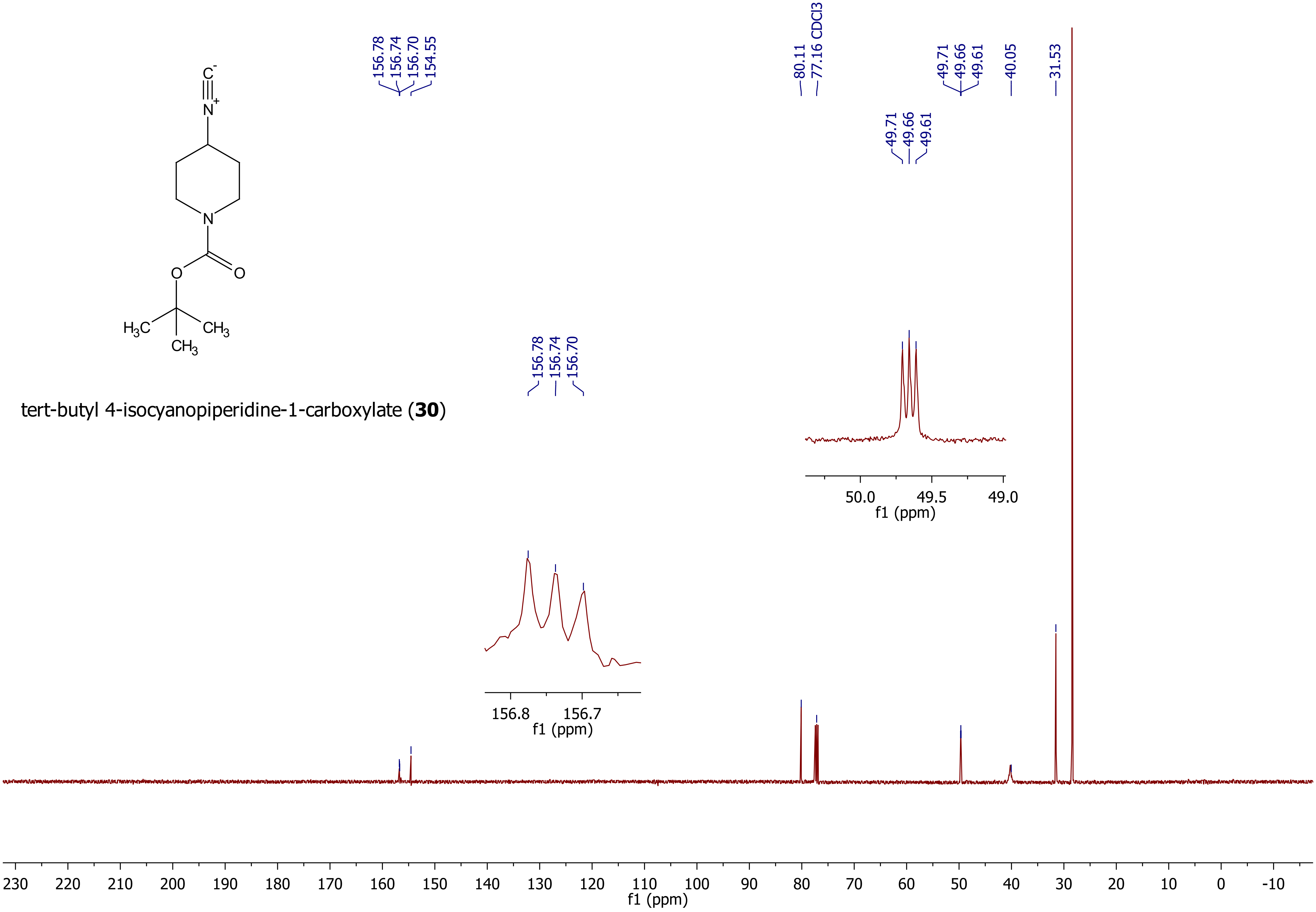
N-(2-isocyanoethyl)aniline (**29**)



N-(2-isocyanoethyl)aniline (**29**)



tert-butyl 4-isocyanopiperidine-1-carboxylate (**30**)



tert-butyl 4-isocyanopiperidine-1-carboxylate (**30**)