Electronic supplementary materials *Mendeleev Commun.*, 2023, **33**, 34–36

Synthesis of CF_3-substituted isoindolones *via* rhodium(III)-catalyzed carbenoid C–H functionalization of aryl hydroxamates

Daria V. Vorobyeva, Alexandra S. Bubnova, Anastasiya G. Buyanovskaya and Sergey N. Osipov

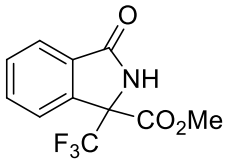
Table of contents

1. General information

All solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were distilled when necessary. Analytical TLC was performed with Merck silica gel 60 F 254 plates; visualization was accomplished with UV light or spraying with $Ce(SO_4)_2$ solution in 5% H_2SO_4. NMR spectra were obtained with Bruker AV-300, AV-400 and Inova-400 spectrometers operating at 300 and 400 MHz, respectively, for ^1H (TMS reference), at 101 MHz for ^{13}C, at 282 MHz and 376 MHz for ^{19}F (CCl_3F reference). Analytical data (C, H, N content) were obtained with a Carlo Erba model 1106 microanalyzer.

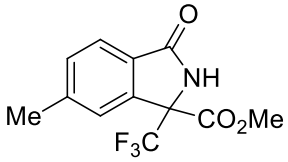
General procedure for C-H activation/annulation of aryl hydroxamates. A dried 10 ml Schlenk tube equipped with a magnetic stirrer was charged with the corresponding aryl hydroxamate (0.45 mmol), MeCN (2 ml), $[Cp^*RhCl_2]_2$ (7.0 mg, 11.3 μmol), CsOAc (0.03 g, 0.1 mmol) and the corresponding diazo compound (0.08 g, 0.5 mmol) under Ar. The reaction mixture was stirred at 30-70°C for 1.5-3 h until the completion of the reaction (TLC control). The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent petroleum ether/ethyl acetate) to give the desired product.

Methyl 3-oxo-1-(trifluoromethyl)isoindoline-1-carboxylate (2a).



Yield 91% as a white solid (eluent petroleum ether/ethyl acetate = 4:1). M.p. 133–135 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.91 (t, 2H, *J* = 6.8 Hz, Ar), 7.74-7.65 (m, 2H, Ar), 7.06 (s, 1H, NH), 3.92 (s, 3H, OCH_3). ^{13}C NMR (101 MHz $CDCl_3$): δ 170.4, 164.8, 137.3, 133.0, 131.4, 130.9, 124.8, 124.3, 122.7 (q, *J* = 284.8 Hz, CF_3), 68.8 (q, *J* = 31.5 Hz, >C<), 54.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ -74.51 (s, 3F, CF_3). Elemental analysis, calcd. for $C_{11}H_8F_3NO_3$ (%): C, 50.98; H, 3.11; N, 5.40; found: C, 50.91; H, 3.24; N, 5.36.

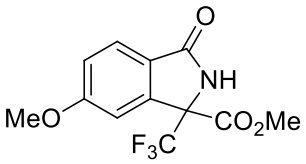
Methyl 6-methyl-3-oxo-1-(trifluoromethyl)isoindoline-1-carboxylate (2b).



Yield 84% as a white solid (eluent petroleum ether/ethyl acetate = 4:1). M.p. 193–195 °C.

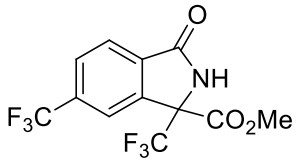
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, 1H, *J* = 7.6 Hz, Ar), 7.67 (s, 1H, Ar), 7.46 (d, 1H, *J* = 7.6 Hz, Ar), 6.74 (s, 1H, NH), 3.91 (s, 3H, OCH_3), 2.54 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.2, 164.9, 144.2, 137.6, 131.9, 128.7, 125.1, 124.1, 122.7 (q, *J* = 284.5 Hz, CF_3), 68.5 (q, *J* = 31.2 Hz, >C<), 54.2, 21.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ -74.57 (s, 3F, CF_3). Elemental analysis, calcd. for $C_{12}H_{10}F_3NO_3$ (%): C, 52.75; H, 3.69; N, 5.13%; found: C, 52.70; H, 3.82; N, 5.07.

Methyl 6-methoxy-3-oxo-1-(trifluoromethyl)isoindoline-1-carboxylate (2c).



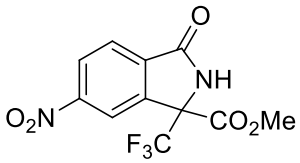
Yield 93% as a white solid (eluent petroleum ether/ethyl acetate = 3:1). M.p. 145–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, 1H, *J* = 8.8 Hz, Ar), 7.34 (s, 1H, Ar), 7.15 (dd, 1H, *J* = 8.4, 2.4 Hz, Ar), 6.89 (s, 1H, NH), 3.94 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.2, 164.8, 163.6, 139.5, 125.7, 123.7, 122.6 (q, *J* = 283.2 Hz, CF_3), 117.2, 109.8, 68.3 (q, *J* = 30.9 Hz, >C<), 55.8, 54.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ -74.65 (s, 3F, CF_3). Elemental analysis, calcd. for $C_{12}H_{10}F_3NO_4$ (%): C, 49.84; H, 3.49; N, 4.84; found: C, 49.97; H, 3.53; N, 4.89.

Methyl 3-oxo-1,6-bis(trifluoromethyl)isoindoline-1-carboxylate (2d).



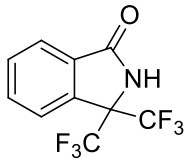
Yield 74% as a beige solid (eluent petroleum ether/ethyl acetate = 4:1). M.p. 155–157 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (s, 1H, Ar), 8.04 (d, 1H, *J*=7.5 Hz, Ar), 7.95 (d, 1H, *J* = 7.7 Hz, Ar), 7.14 (s, 1H, NH), 3.96 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.5, 163.9, 137.7, 135.1 (q, *J* = 33.1 Hz, *C*-CF_3), 134.6, 128.5-128.4 (m), 125.1, 122.3-122.2 (m), 123.2 (q, *J* = 271.6 Hz, CF_3), 122.3 (q, *J* = 283.6 Hz, CF_3), 68.7 (q, *J* = 31.6 Hz, >C<), 54.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ -74.40 (s, 3F, CF_3), -62.53 (s, 3F, CF_3). Elemental analysis, calcd. for $C_{12}H_7F_6NO_3$ (%): C, 44.05; H, 2.16; N, 4.28; found: C, 43.97; H, 2.33; N, 4.23.

Methyl 6-nitro-3-oxo-1-(trifluoromethyl)isoindoline-1-carboxylate (2e).



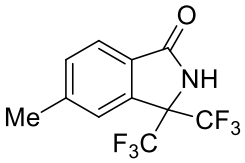
Yield 60% as a beige solid (eluent petroleum ether/ethyl acetate = 4:1). M.p. 200–203 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (s, 1H, Ar). 8.55 (dd, 1H, *J* = 8.4, 1.6 Hz, Ar), 8.09 (d, 1H, *J* = 8.3 Hz, Ar), 7.24 (s, 1H, NH), 3.99 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ 166.7, 163.8, 150.9, 138.3, 136.9, 126.8, 125.3, 122.8 (q, *J* = 284.4 Hz, CF_3), 120.1, 68.4 (q, *J* = 31.0 Hz, >C<), 54.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ -74.25 (s, 3F, CF_3). Elemental analysis, calcd. for $C_{11}H_7F_3N_2O_5$ (%) C, 43.43; H, 2.32; N, 9.21; found: C, 43.34; H, 2.31; N, 9.29.

3,3-Bis(trifluoromethyl)isoindolin-1-one (4a).



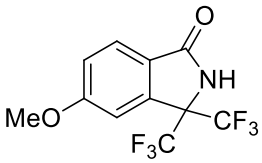
Yield 52% as a white solid (eluent petroleum ether/ethyl acetate = 15:1). M.p. 125–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (s, 1H, Ar), 7.96 (d, 1H, *J* = 7.2 Hz, Ar), 7.72-7.68 (m, 2H, Ar, 1H, NH). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.5. 135.1, 133.5, 131.8, 131.7, 125.0, 124.1, 122.0 (q, *J* = 283.0 Hz, CF_3), 67.6-66.5 (m). ^{19}F NMR (376 MHz, $CDCl_3$): δ -73.41 (s, 6F, 2 CF_3). Elemental analysis, calcd. for $C_{10}H_5F_6NO$ (%): C, 44.63; H, 1.87; N, 5.20; found: C, 44.77; H, 2.09; N, 5.30.

5-Methyl-3,3-bis(trifluoromethyl)isoindolin-1-one (4b).



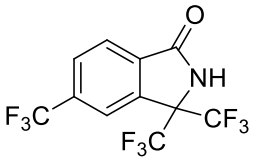
Yield 50% as amorphous solid (eluent petroleum ether/ethyl acetate = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 1H, Ar). 7.85 (d, 1H, *J* = 8.0 Hz, Ar), 7.54-7.52 (m, 1H, Ar, 1H, NH), 2.56 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.9. 144.9, 135.5, 132.6, 129.3-129.2 (m), 124.7, 124.4, 122.1 (q, *J* = 284.2 Hz, CF_3), 67.3-66.6 (m), 26.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ -73.36 (s, 6F, 2 CF_3). Elemental analysis, calcd. for $C_{11}H_7F_6NO$ (%): C, 46.66; H, 2.49; N, 4.95; found: C, 46.76; H, 2.58; N, 4.98.

5-Methoxy-3,3-bis(trifluoromethyl)isoindolin-1-one (4c).



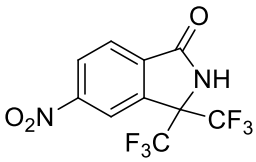
Yield 40% as a white solid (eluent petroleum ether/ethyl acetate = 8:1). M.p. 137–140 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, 1H, *J* = 8.4 Hz, Ar), 7.22-7.19 (m, 2H, Ar, 1H, NH), 3.95 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.2. 163.9, 137.3, 126.4, 124.0, 122.0 (q, *J* = 285.6 Hz, CF_3), 117.7, 109.3, 66.9-66.3 (m), 55.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ -73.54 (s, 6F, 2 CF_3). Elemental analysis, calcd. for $C_{11}H_7F_6NO_2$ (%): C, 44.16; H, 2.36; N, 4.68; found: C, 44.25; H, 2.37; N, 4.74.

3,3,5-Tris(trifluoromethyl)isoindolin-1-one (4d).



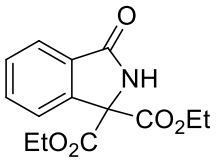
Yield 66% as a white solid (eluent petroleum ether/ethyl acetate = 15:1). M.p. 178–181 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, 1H, *J* = 8.0 Hz, Ar), 8.04 (d, 1H, *J* = 8.0 Hz, Ar), 8.00 (s, 1H, Ar), 7.73 (s, 1H, NH). ^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ 167.1, 135.9, 135.3, 134.7 (q, *J* = 32.9 Hz, *C*-CF_3), 129.9-129.8 (m), 125.8, 123.3 (q, *J* = 270.9 Hz, CF_3), 122.1 (q, *J* = 284.0 Hz, CF_3), 121.3, 67.6-66.3 (m). ^{19}F NMR (376 MHz, $CDCl_3$): δ -73.14 (s, 6F, 2 CF_3), -62.65 (s, 3F, CF_3). Elemental analysis, calcd. for $C_{11}H_4F_9NO$ (%): C, 39.19; H, 1.20; N, 4.15; found: C, 39.08; H, 1.27; N, 4.24.

5-Nitro-3,3-bis(trifluoromethyl)isoindolin-1-one (4e).



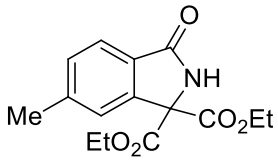
Yield 60% as a white solid (eluent petroleum ether/ethyl acetate = 15:1). M.p. 139–142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (dd, 1H, *J* = 8.4, 2.0 Hz, Ar), 8.61 (s, 1H, Ar), 8.19 (d, 1H, *J* = 8.0 Hz, Ar), 7.92 (s, 1H, NH). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.2, 151.2, 136.7, 136.0, 127.6, 126.4, 121.5 (q, *J* = 286.5 Hz, CF_3), 119.8, 67.9-66.6 (m). ^{19}F NMR (376 MHz, $CDCl_3$): δ -72.96 (s, 6F, 2 CF_3). Elemental analysis, calcd. for $C_{10}H_4F_6N_2O_3$ (%): C, 38.23; H, 1.28; N, 8.92; found: C, 38.27; H, 1.33; N, 8.98.

Diethyl 3-oxoisoindoline-1,1-dicarboxylate (6a).



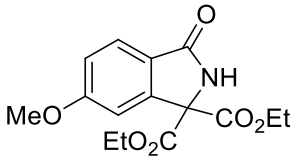
Yield 75% as a white solid (eluent petroleum ether/ethyl acetate = 2:1). M.p. 108–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (t, *J* = 8.7 Hz, 2H, Ar), 7.67 (t, *J* = 7.6 Hz, 1H, Ar), 7.59 (t, *J* = 7.5 Hz, 1H, Ar), 6.85 (s, 1H, NH), 4.31 (q, *J* = 7.1 Hz, 4H, 2 OCH_2), 1.32 (t, *J* = 7.1 Hz, 6H, 2 CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.6, 166.0, 139.9, 132.6, 130.6, 130.0, 125.2, 123.8, 70.5, 63.2, 13.9. Elemental analysis, calcd. for $C_{14}H_{15}NO_5$ (%): C, 60.64; H, 5.45; N, 5.05; found: C, 60.88; H, 5.53; N, 4.94.

Diethyl 6-methyl-3-oxoisoindoline-1,1-dicarboxylate (6b).



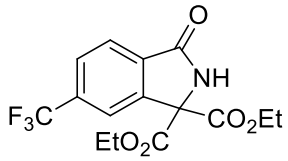
Yield 63% as a white solid (eluent petroleum ether/ethyl acetate = 2:1). M.p. 153–158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 7.8 Hz, 1H, Ar), 7.66 (s, 1H, Ar), 7.39 (d, *J* = 7.7 Hz, 1H, Ar), 6.75 (s, 1H, NH), 4.31 (q, *J* = 7.1 Hz, 4H, 2 OCH_2), 2.52 (s, 3H, OCH_3), 1.32 (t, *J* = 7.1 Hz, 6H, 2 CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.0, 166.2, 143.4, 140.3, 130.9, 128.2, 125.5, 123.5, 70.4, 63.0, 22.0, 13.8. Elemental analysis, calcd. for $C_{15}H_{17}NO_5$ (%): C, 61.85; H, 5.88; N, 4.81; found: C, 61.88; H, 6.14; N, 4.85.

Diethyl 6-methoxy-3-oxoisoindoline-1,1-dicarboxylate (6c).



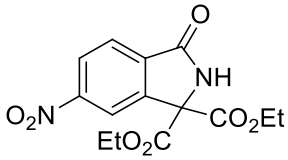
Yield 74% as a white solid (eluent petroleum ether/ethyl acetate = 2:1). M.p. 170–172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.4 Hz, 1H, Ar), 7.30 (d, *J* = 2.2 Hz, 1H, Ar), 7.05 (dd, *J* = 8.5, 2.1 Hz, 1H, Ar), 6.61 (s, 1H, NH), 4.27 (q, *J* = 7.1 Hz, 4H, 2 OCH_2), 3.89 (s, 3H, OCH_3), 1.28 (t, *J* = 7.2 Hz, 6H, 2 CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.6, 166.1, 163.3, 142.2, 125.1, 123.2, 116.6, 110.0, 70.2, 63.1, 55.7, 13.8. Elemental analysis, calcd. for $C_{15}H_{17}NO_6$ (%): C, 58.63; H, 5.58; N, 4.56; found: C, 58.88; H, 5.83; N, 4.27.

Diethyl 3-oxo-6-(trifluoromethyl)isoindoline-1,1-dicarboxylate (6d).



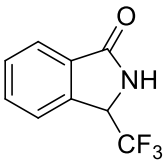
Yield 88% as a white solid (eluent petroleum ether/ethyl acetate = 2:1). M.p. 107–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 1H, NH), 8.08 (s, 1H, Ar), 7.93 (d, *J* = 7.9 Hz, 1H, Ar), 7.80 (d, *J* = 7.9 Hz, 1H, Ar), 4.28 (q, *J* = 7.1 Hz, 4H, 2 OCH_2), 1.26 (t, *J* = 7.1 Hz, 6H, 2 CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.4, 165.34, 140.4, 134.4 (q, *J* = 32.7 Hz, *C*-CF_3), 134.1, 127.3 (q, *J* = 3.7 Hz), 124.4, 123.4 (q, *J* = 274.1 Hz, CF_3), 122.7 (q, *J* = 3.9 Hz), 70.7, 63.5, 13.7. ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.50 (s, 3F, CF_3). Elemental analysis, calcd. for $C_{15}H_{14}F_3NO_5$ (%): C, 52.18; H, 4.09; N, 4.06; found: C, 51.99; H, 4.31; N, 3.94.

Diethyl 6-nitro-3-oxoisoindoline-1,1-dicarboxylate (6e).



Yield 60% as a white solid (eluent petroleum ether/ethyl acetate = 2:1). M.p. 124–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (s, 1H, Ar), 8.41 (d, *J* = 8.4 Hz, 1H, Ar), 8.17-8.11 (m, 1H, NH), 7.97 (d, *J* = 8.3 Hz, 1H, Ar), 4.30 (q, *J* = 7.0 Hz, 4H, 2 OCH_2), 1.29 (t, *J* = 7.0 Hz, 6H, 2 CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.4, 164.9, 150.6, 140.9, 136.0, 125.6, 125.0, 121.1, 70.5 63.8, 13.8. Elemental analysis, calcd. for $C_{14}H_{14}N_2O_7$ (%): C, 52.18; H, 4.38; N, 8.69; found: C, 51.93; H, 4.59; N, 8.61.

3-(Trifluoromethyl)isoindolin-1-one (7).



Isoindoline **2a** (0.15 g, 0.58 mmol) was dissolved in 5% KOH/MeOH-H_2O (1:1) (10 mL) and stirred at room temperature for 2 h. After evaporation of solvents under reduced pressure, water (8 mL) was added to a residue, the suspension was washed with diethyl ester (3*10 mL) before being acidified with HCl conc. until pH 3–4 and extracted with ethyl acetate (3* 7 mL). The ethyl acetate extracts were combined and dried over $MgSO_4$, filtered and evaporated to dryness. Yield 62% as a white solid. M.p. 146–148 °C. ^{1}H NMR (400 MHz, CD_3OD): δ 7.82 (d, 1H, *J* = 7.6 Hz, Ar), 7.73 – 7.61 (m, 3H, Ar), 5.36 (q, 1H, *J* = 6.8 Hz, CH). ^{13}C NMR (101 MHz, CD_3OD): δ 171.6, 138.4, 132.4, 132.1, 129.7, 124.1 (q, *J* = 279.5 Hz, CF_3), 123.8, 123.3, 57.2 (q, *J* = 33.2 Hz, >CH). ^{19}F NMR (376 MHz, CD_3OD): δ -74.10 (s, 3F, CF_3). Elemental analysis, calcd. for $C_9H_6F_3NO$ (%): C, 53.74; H, 3.01; N, 6.96; found: C, 53.90; H, 3.27; N, 6.74.

^{1}H NMR, ^{19}F NMR and ^{13}C NMR Spectra.

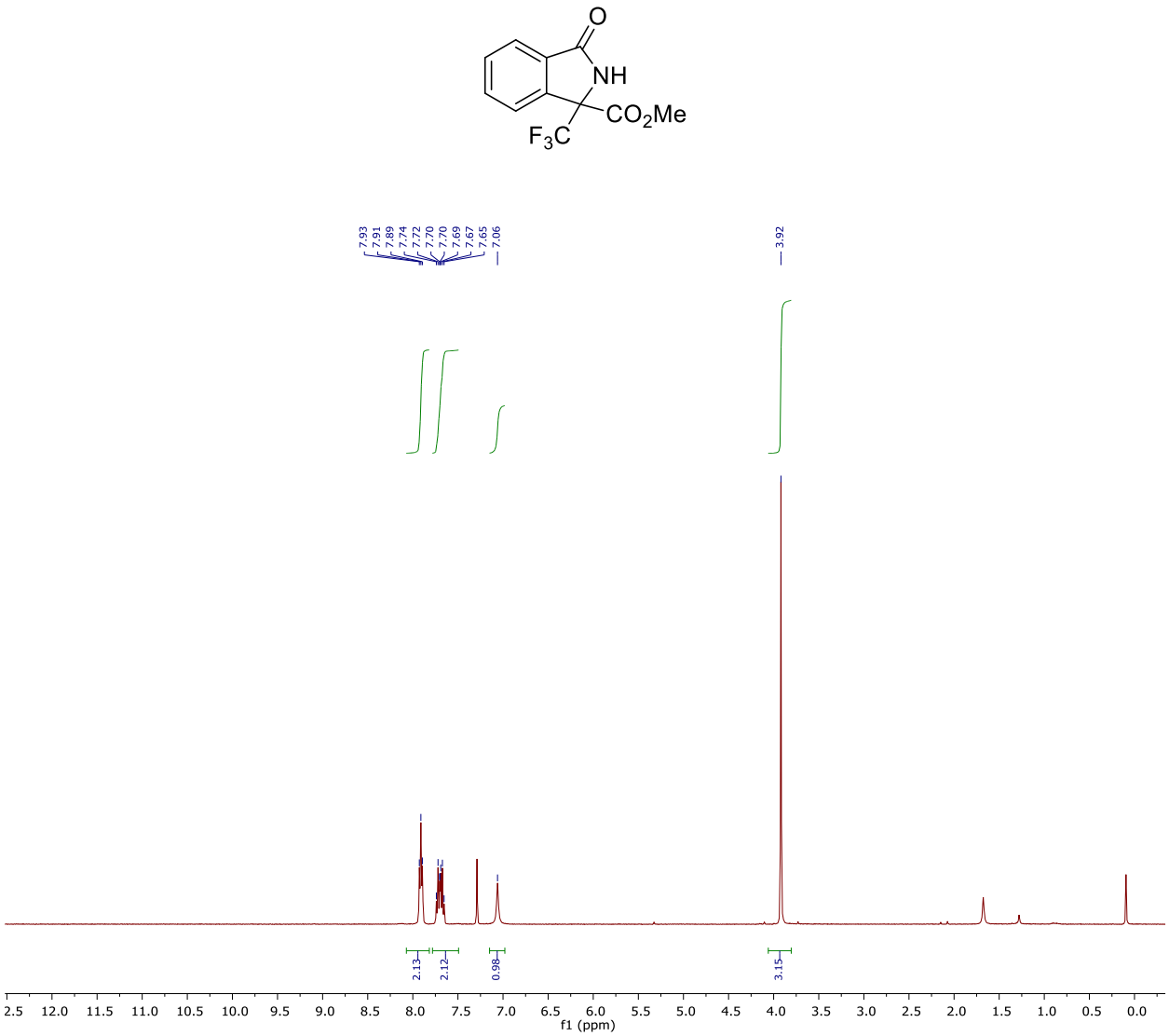


Figure S1 ^{1}H NMR spectrum of compound **2a** in $CDCl_3$

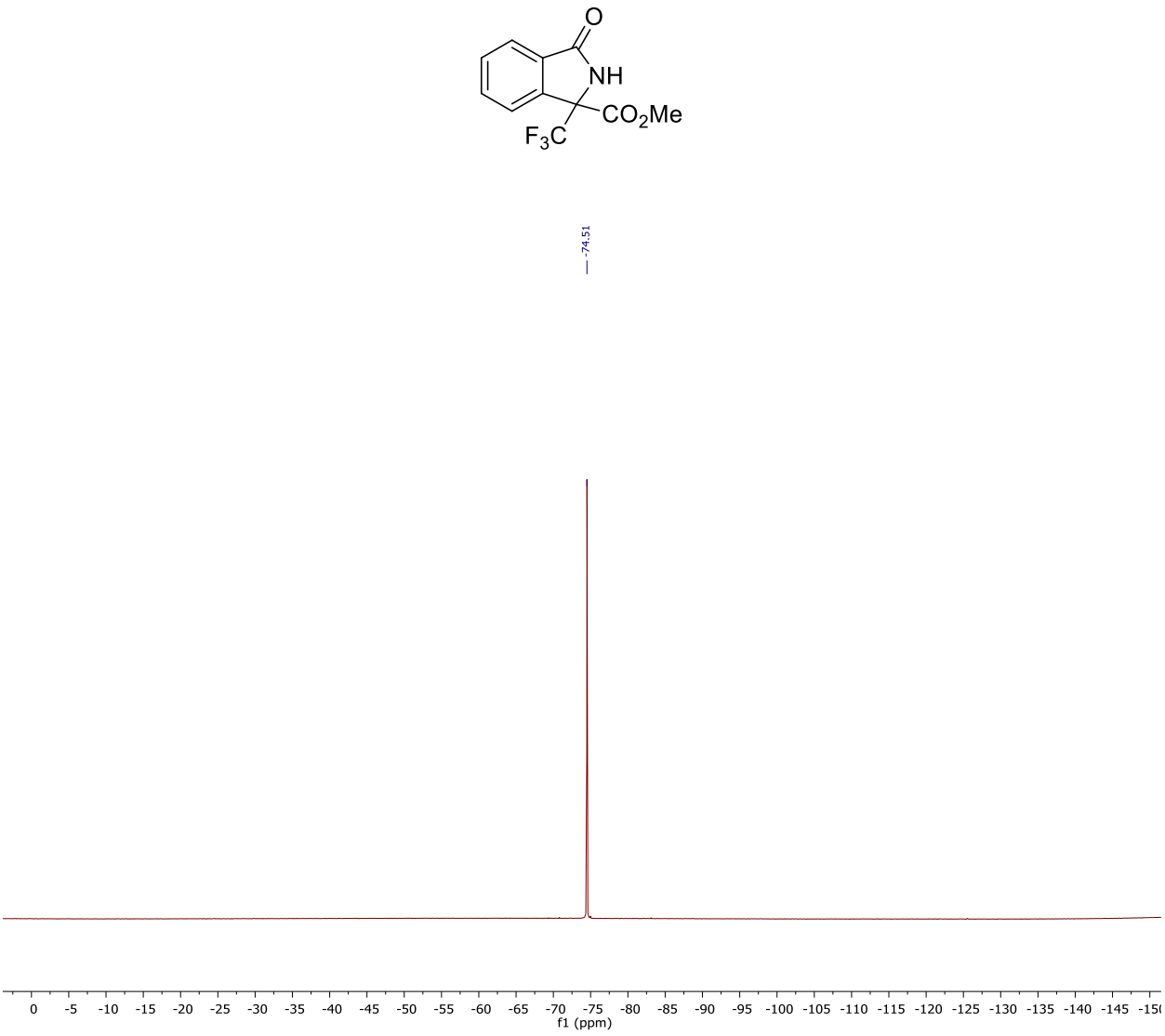


Figure S2 ^{19}F NMR spectrum of compound **2a** in $CDCl_3$

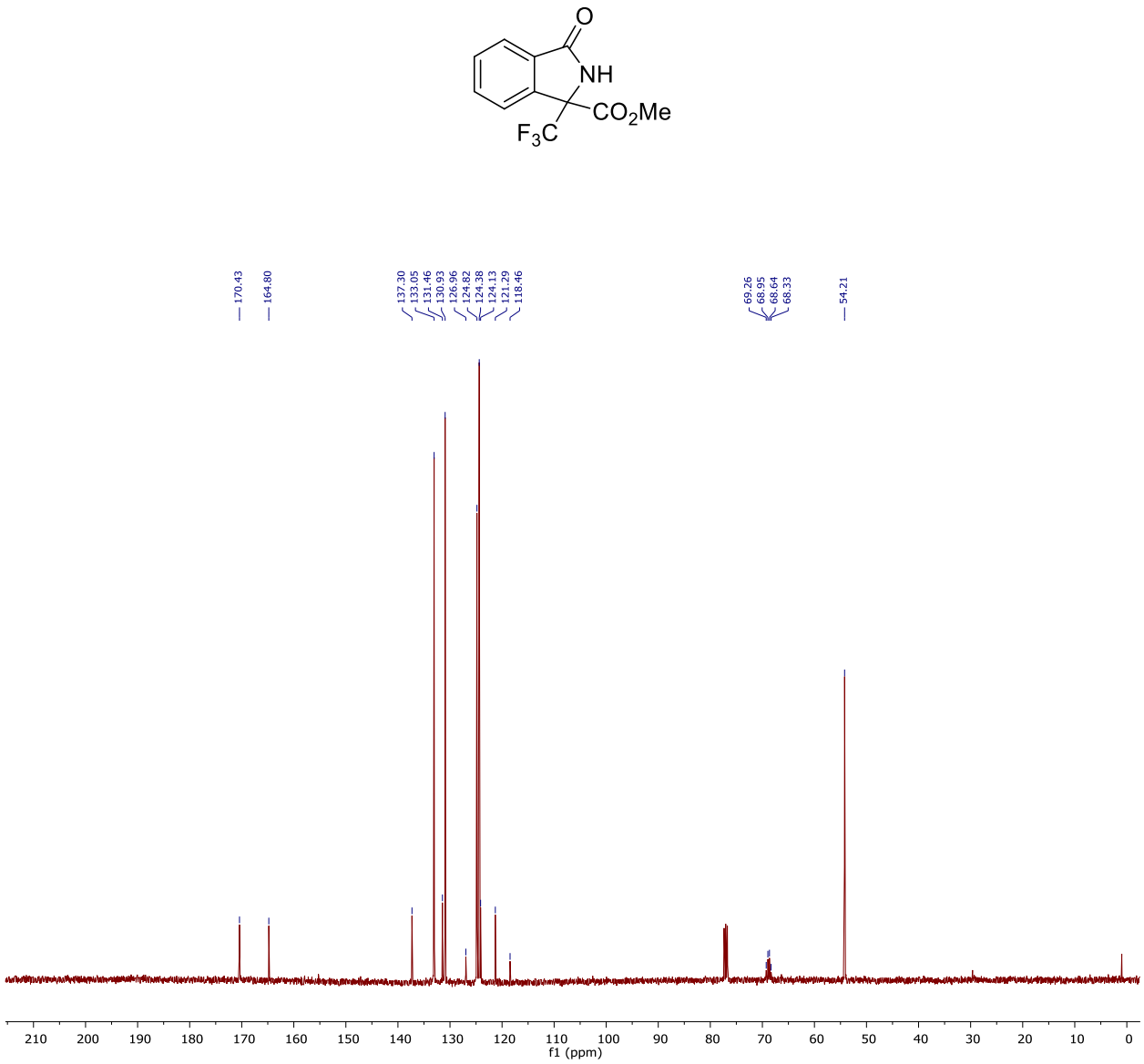


Figure S3 ^{13}C NMR spectrum of compound **2a** in $CDCl_3$

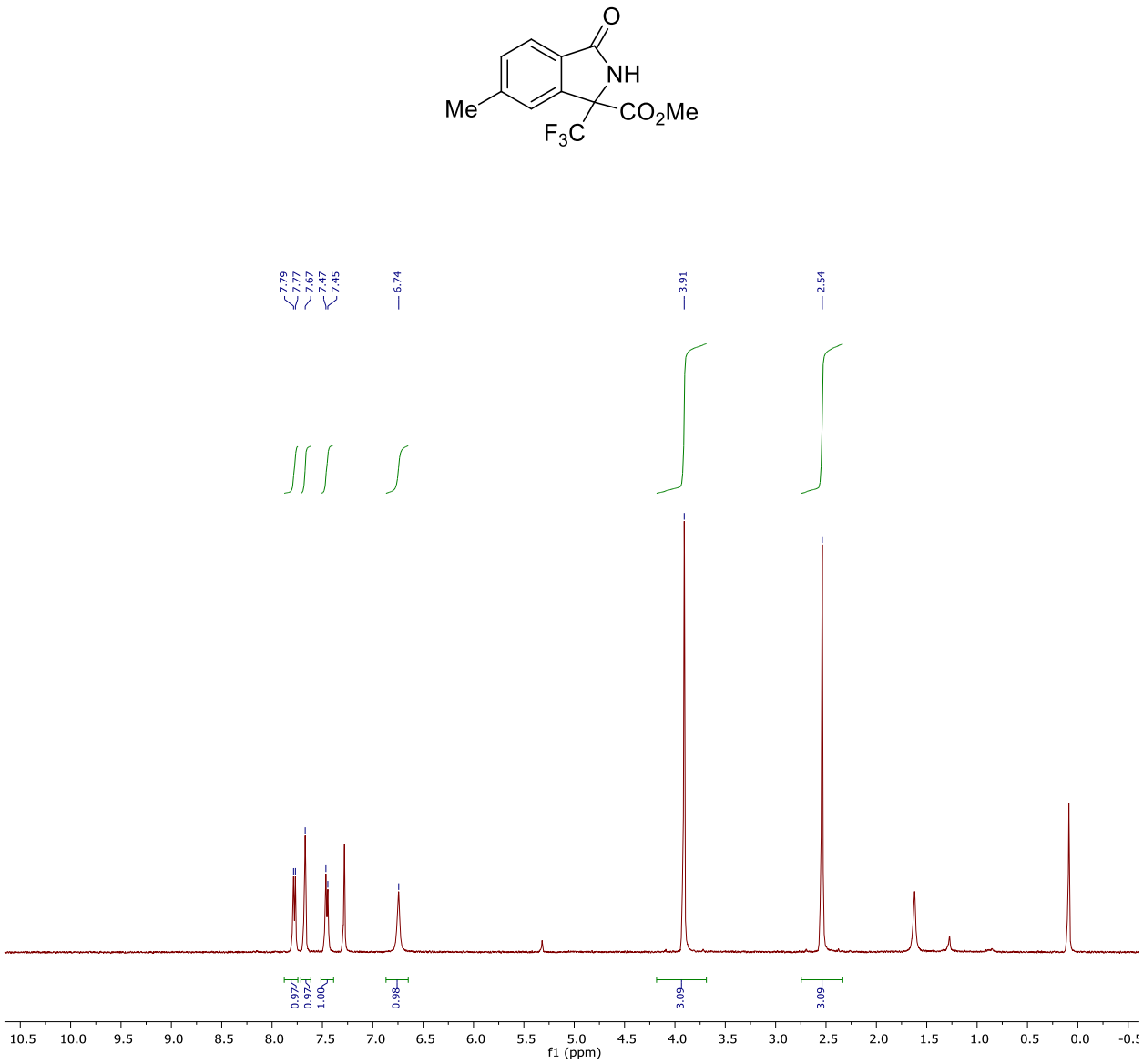


Figure S4 ^{1}H NMR spectrum of compound **2b** in $CDCl_3$

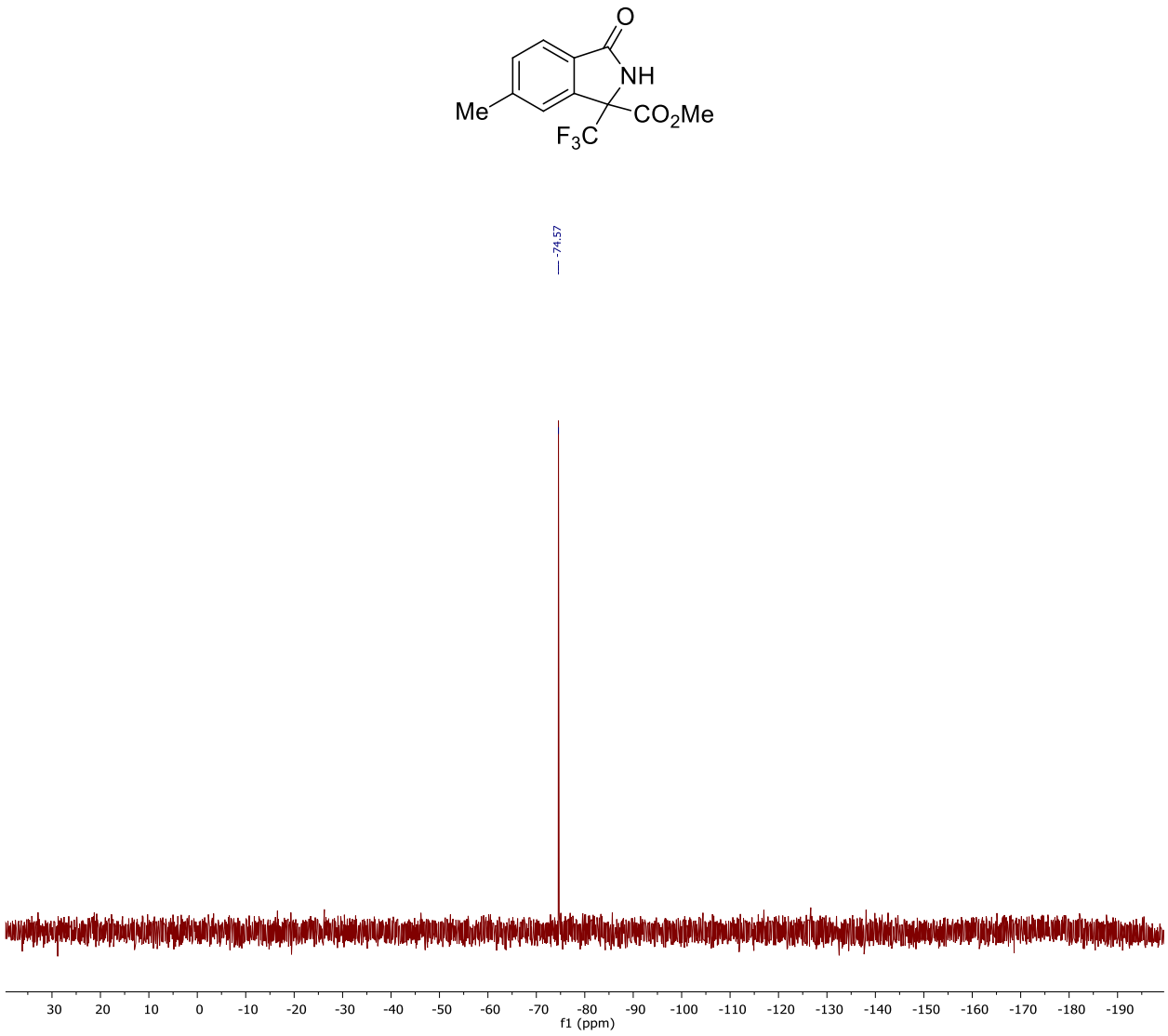


Figure S5 ^{19}F NMR spectrum of compound **2b** in $CDCl_3$

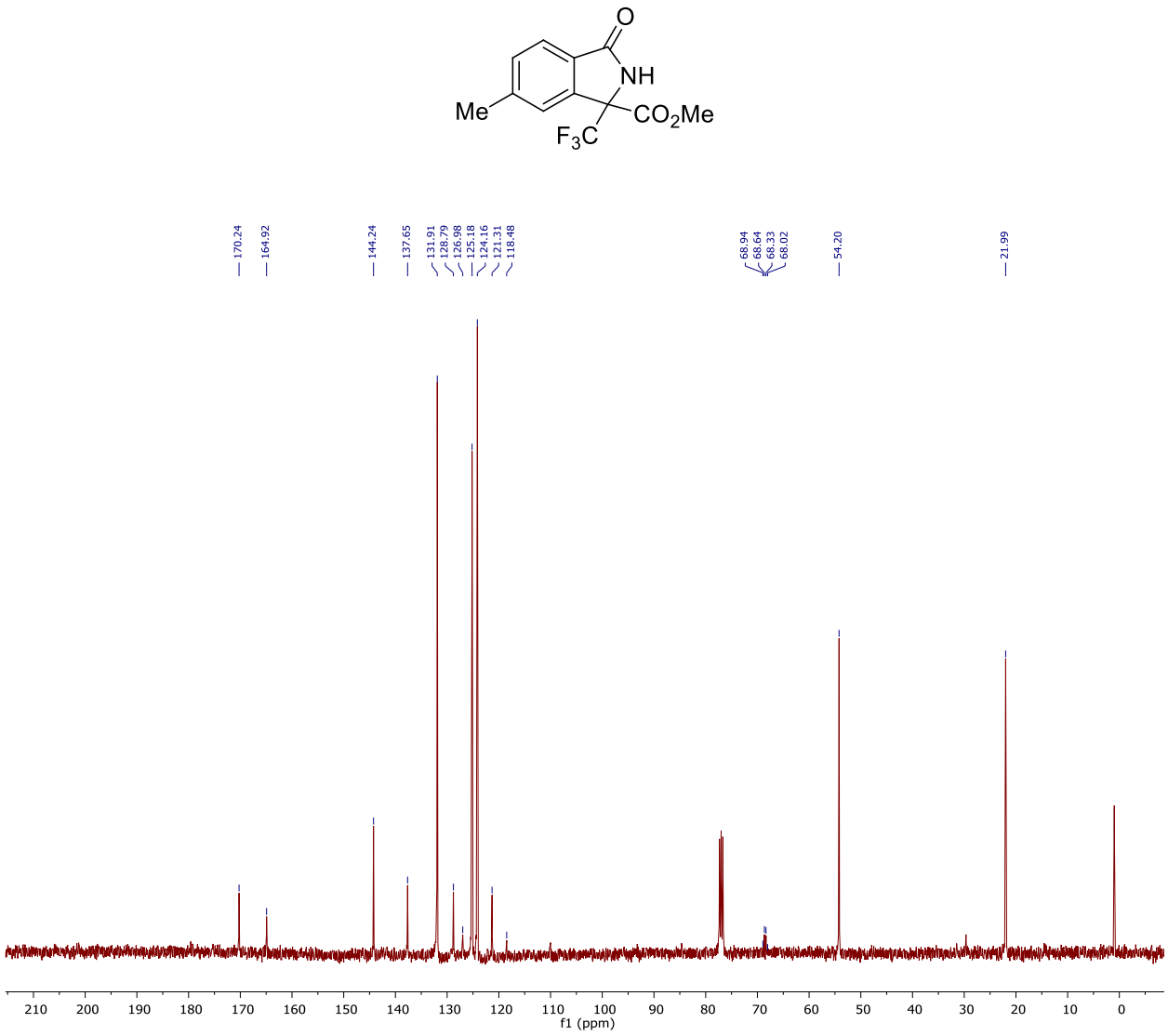


Figure S6 ^{13}C NMR spectrum of compound **2b** in $CDCl_3$

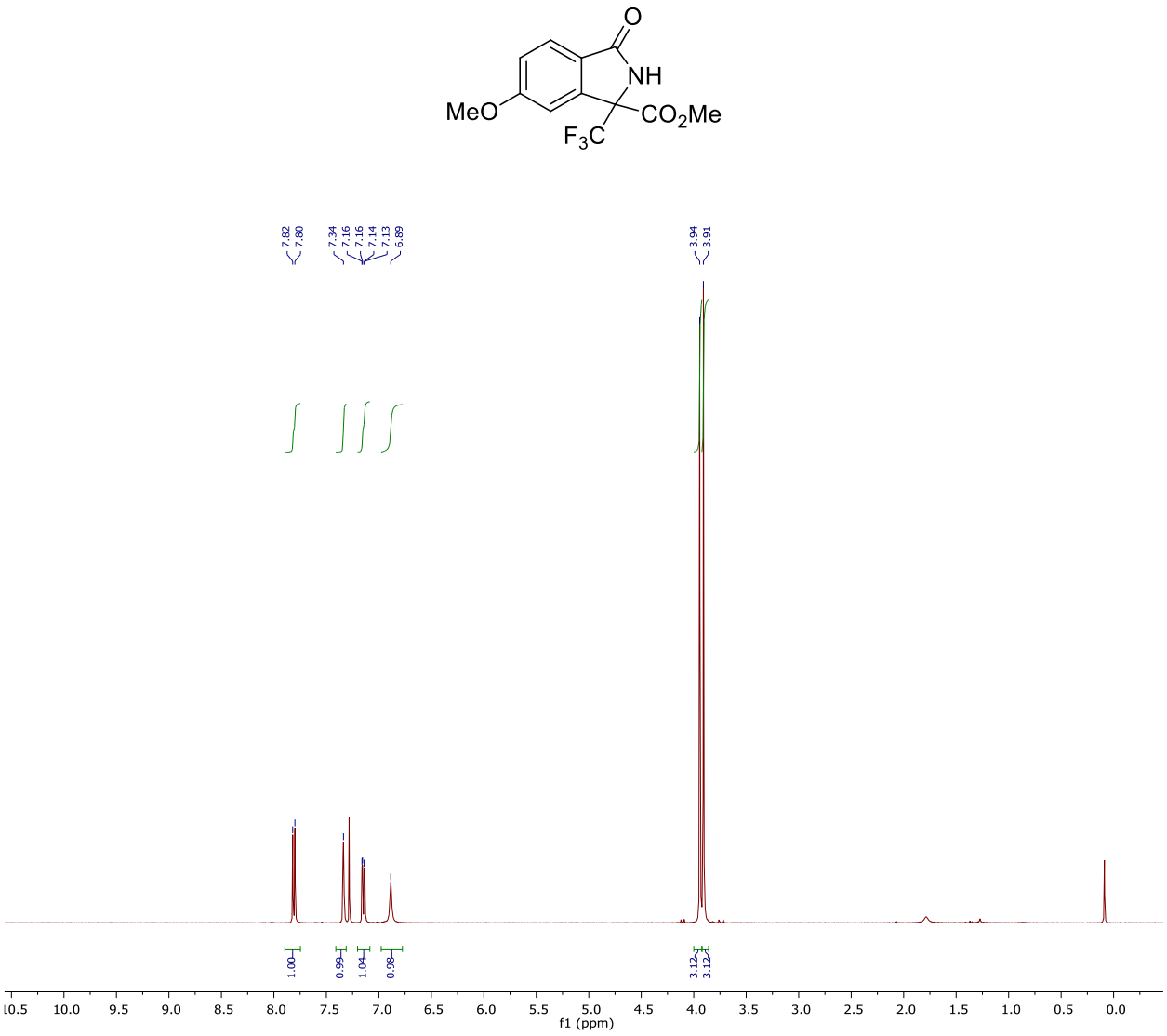


Figure S7 ^{1}H NMR spectrum of compound **2c** in $CDCl_3$

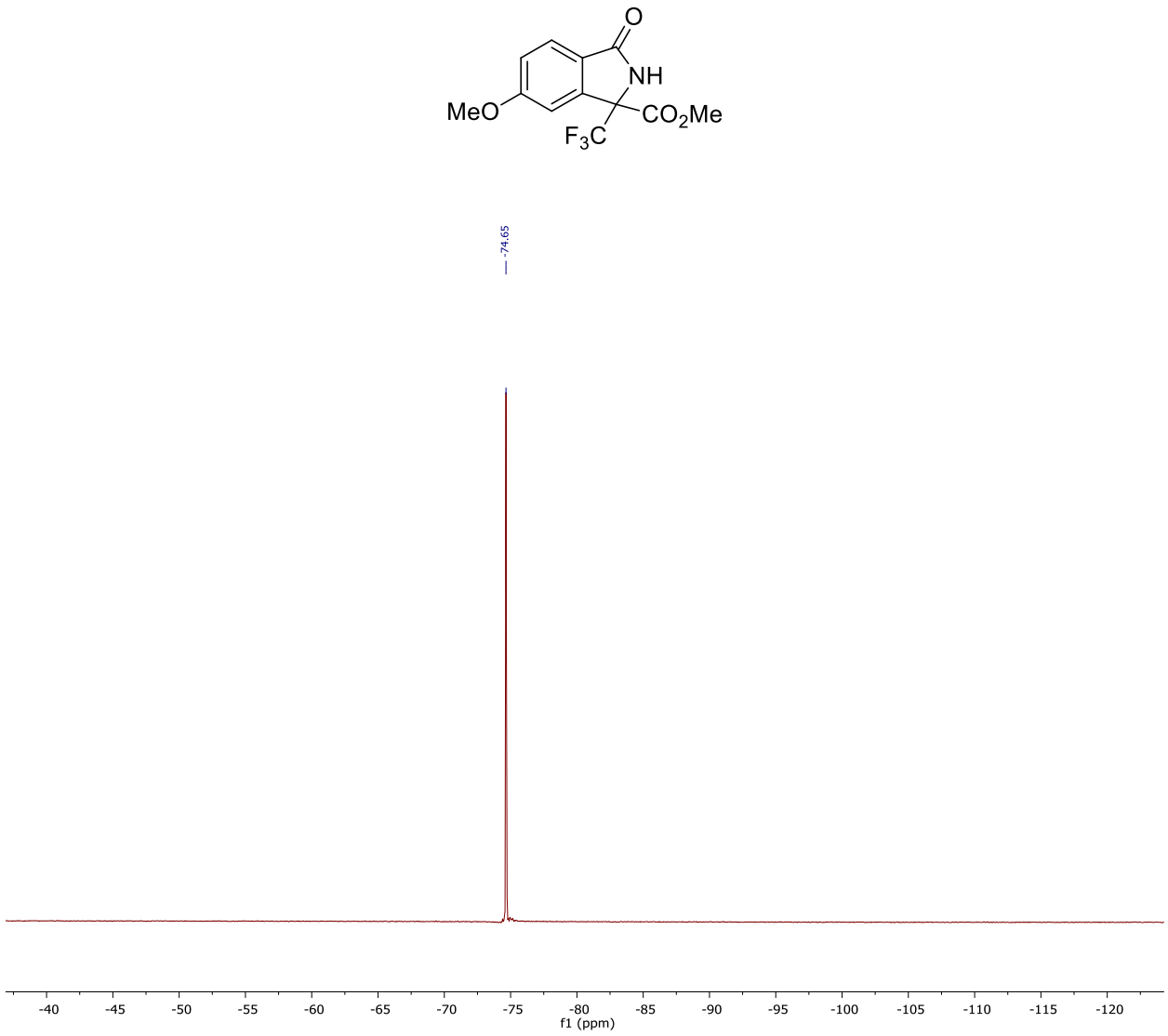


Figure S8 ^{19}F NMR spectrum of compound **2c** in $CDCl_3$

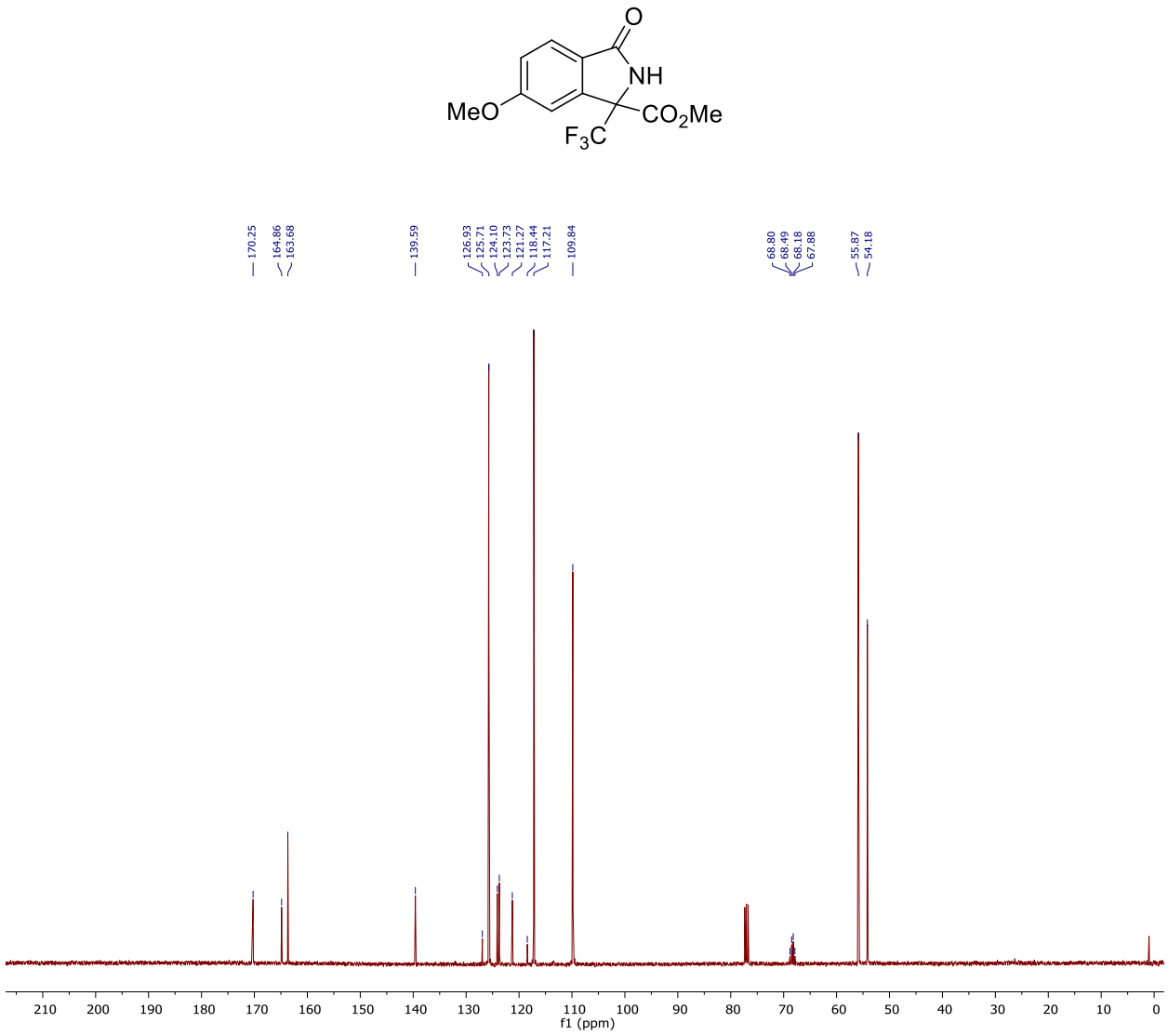


Figure S9 ^{13}C NMR spectrum of compound **2c** in $CDCl_3$

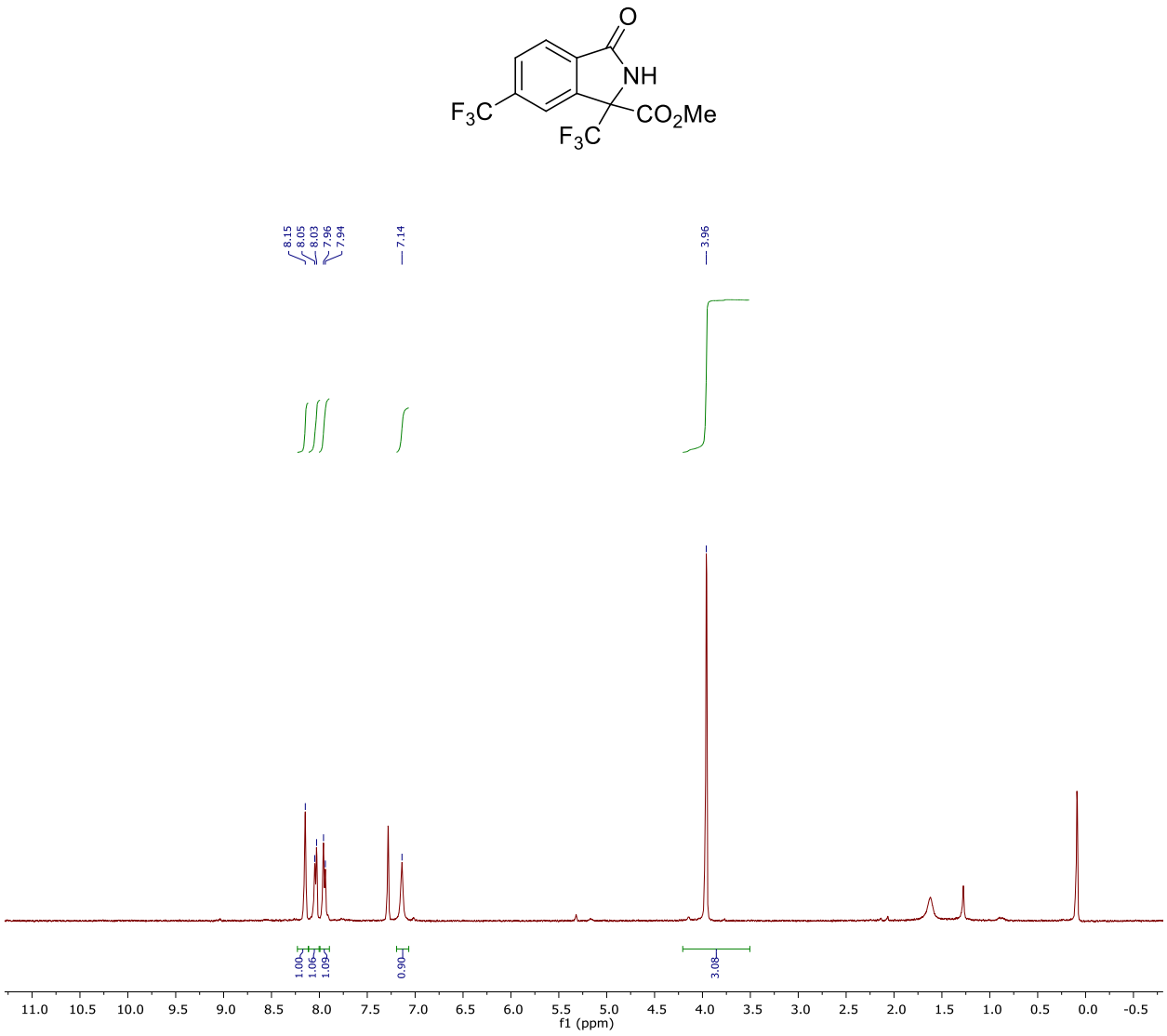


Figure S10 ^{1}H NMR spectrum of compound **2d** in $CDCl_3$

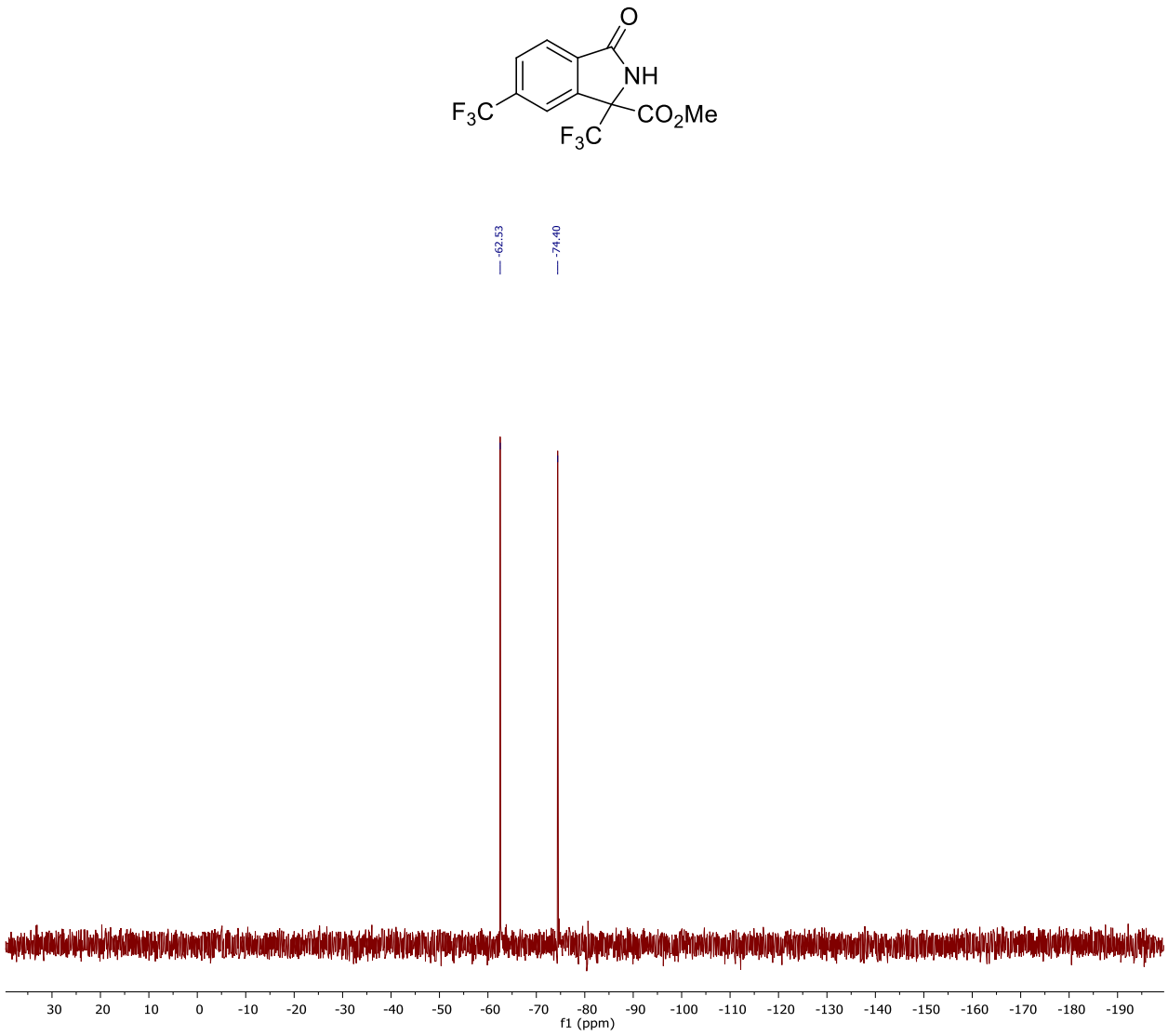


Figure S11 ^{19}F NMR spectrum of compound **2d** in $CDCl_3$

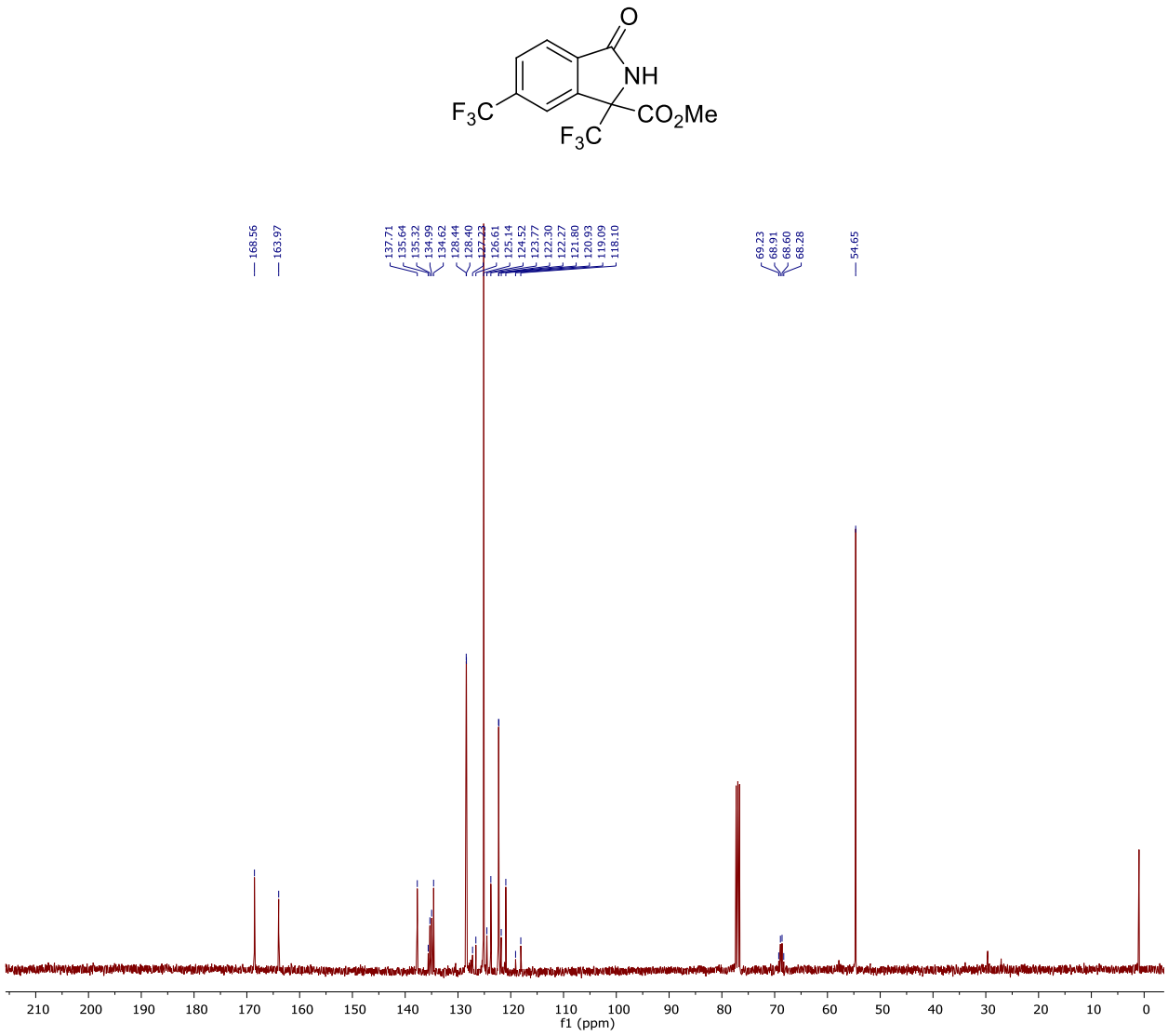


Figure S12 ^{13}C NMR spectrum of compound **2d** in $CDCl_3$

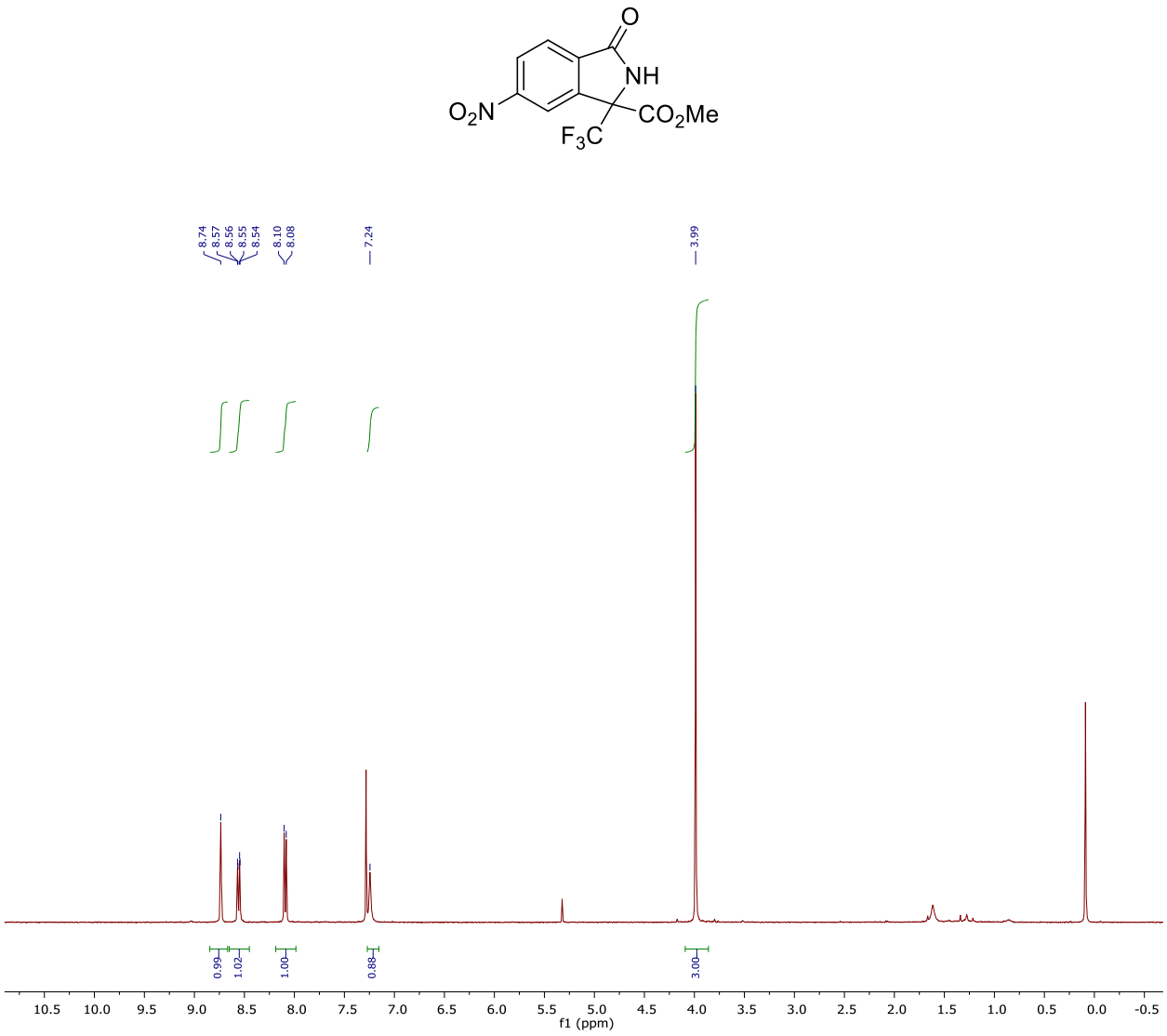


Figure S13 ^{1}H NMR spectrum of compound **2e** in $CDCl_3$

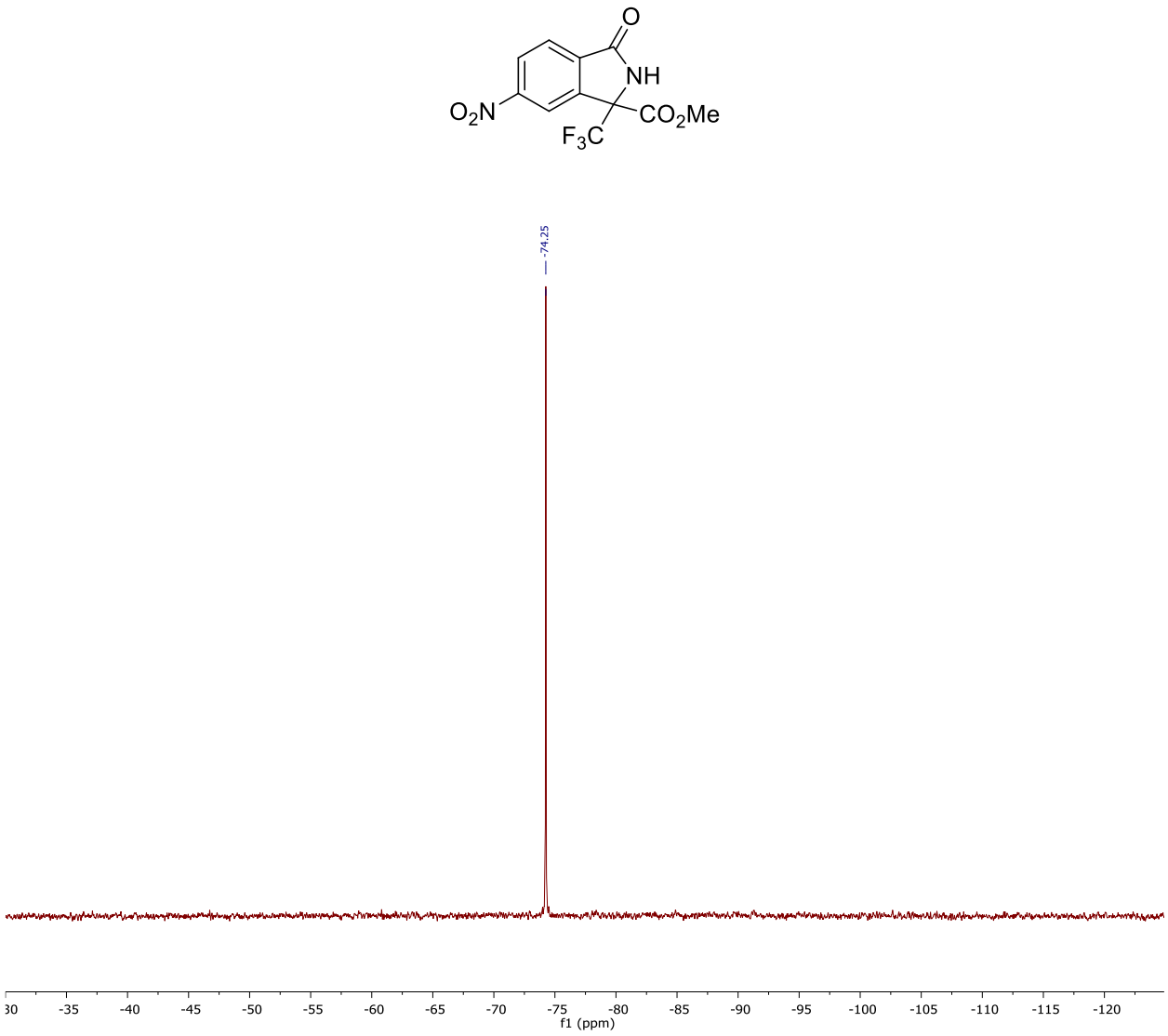


Figure S14 ^{19}F NMR spectrum of compound **2e** in $CDCl_3$

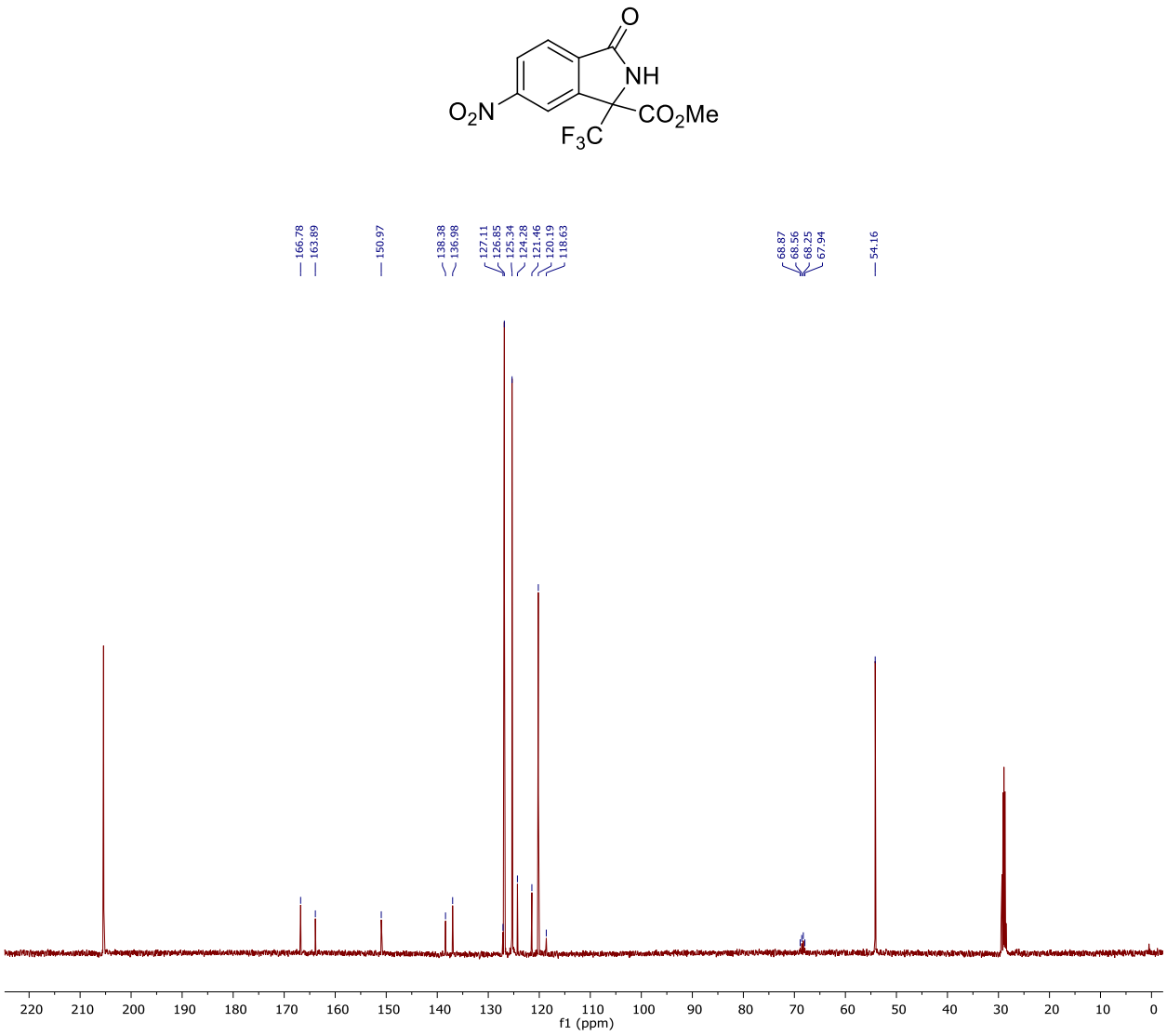


Figure S15 ^{13}C NMR spectrum of compound **2e** in $(CD_3)_2CO$

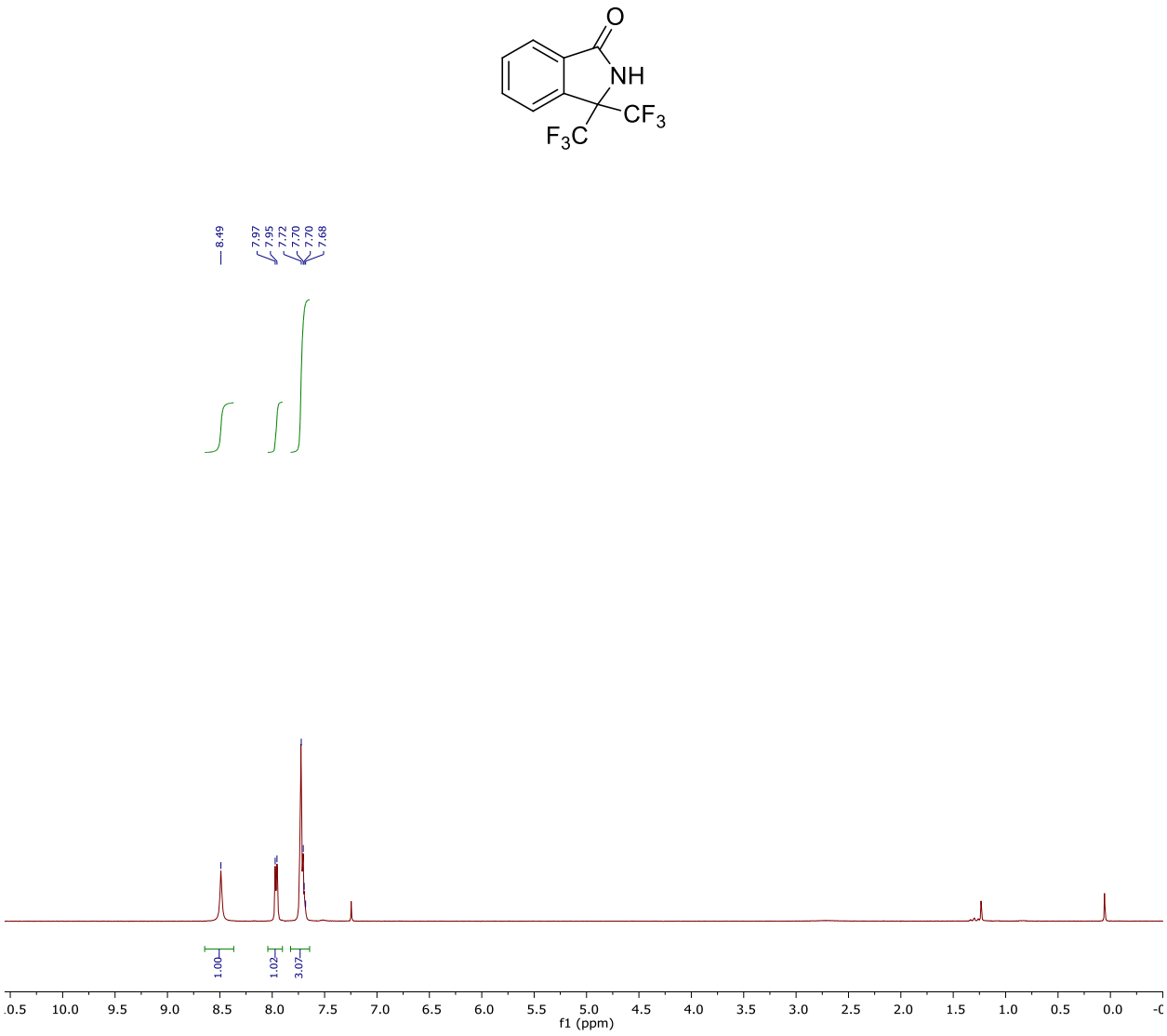


Figure S16 ^{1}H NMR spectrum of compound **4a** in $CDCl_3$

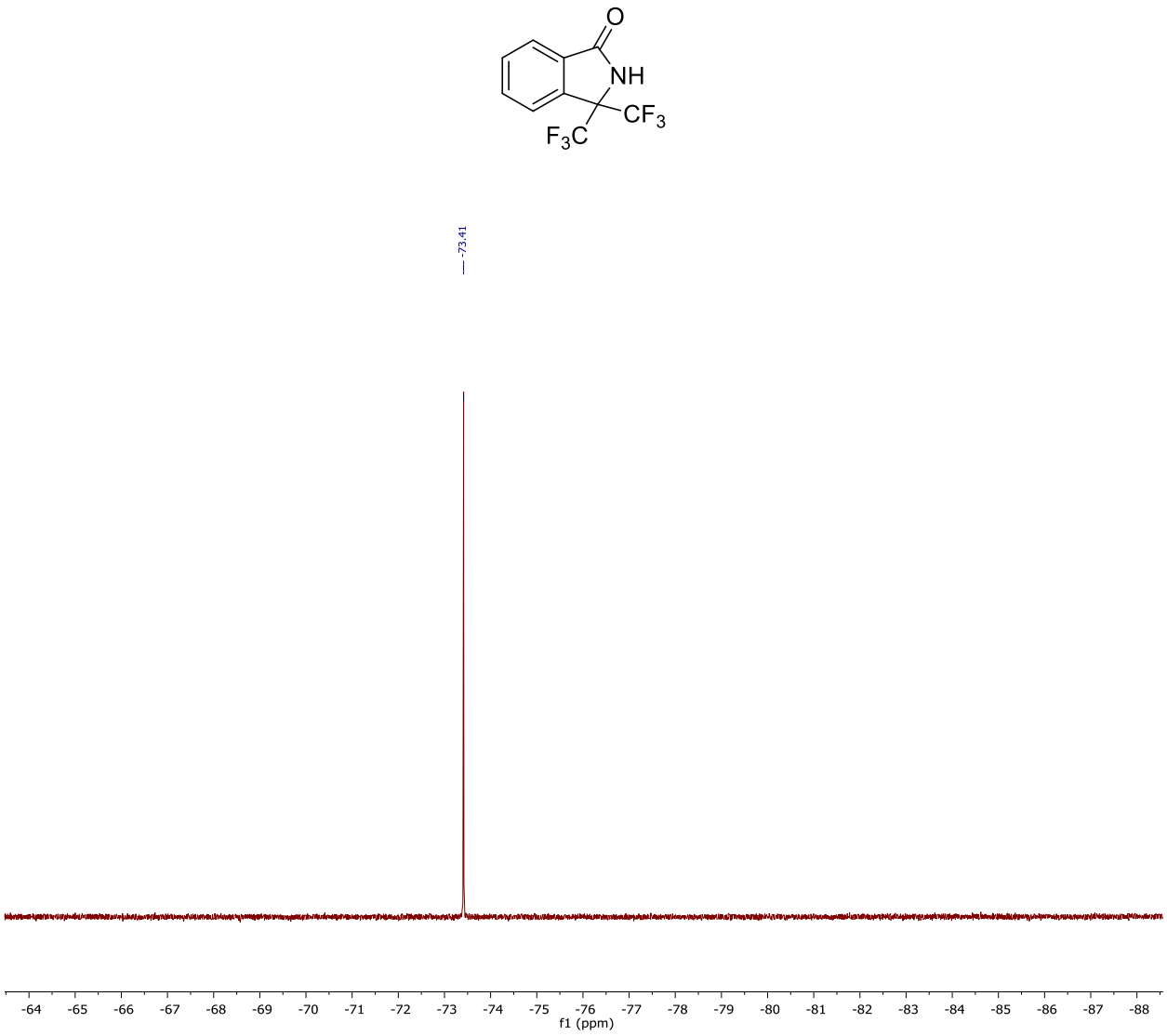


Figure S17 ^{19}F NMR spectrum of compound **4a** in $CDCl_3$

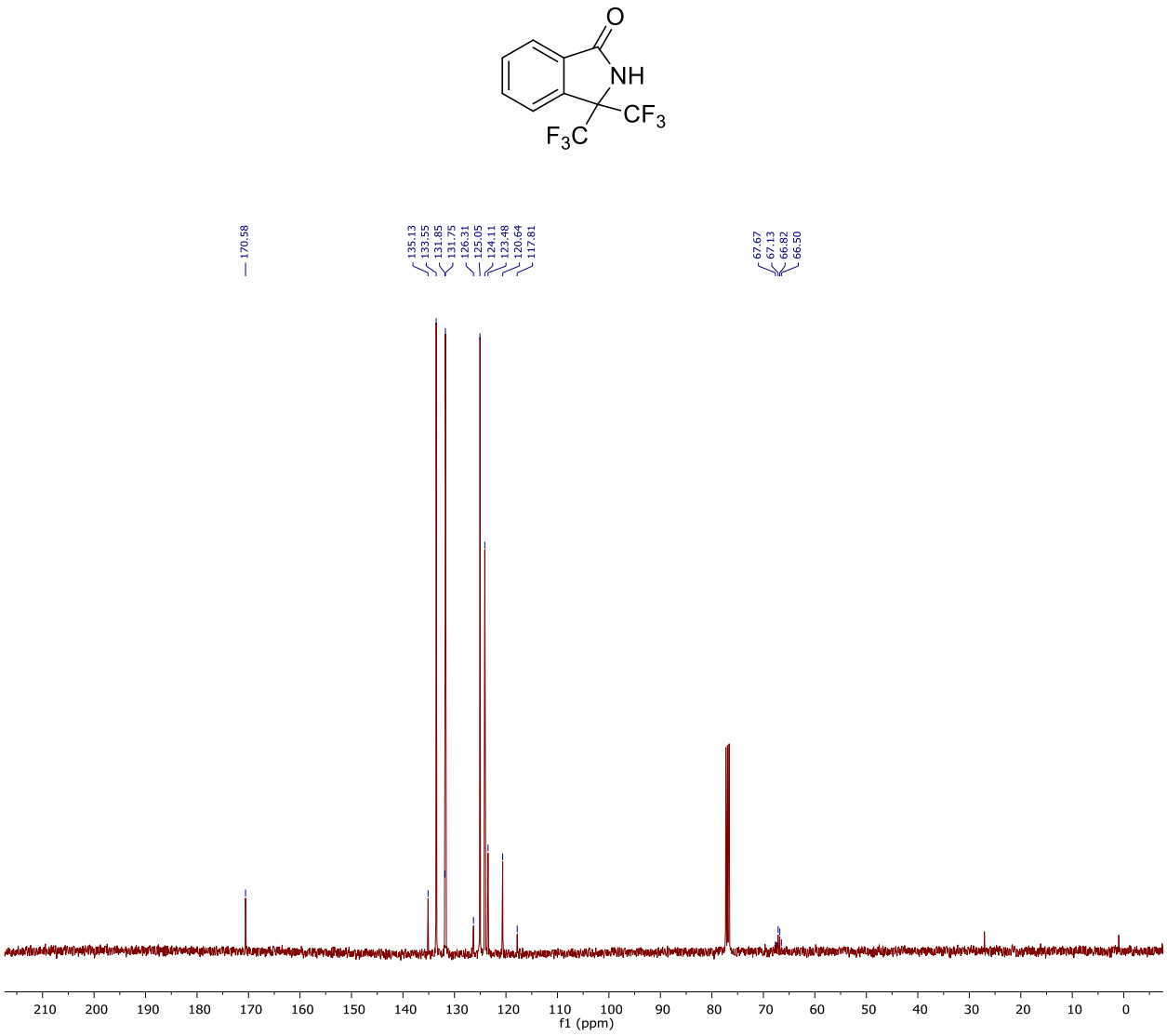


Figure S18 ^{13}C NMR spectrum of compound **4a** in $CDCl_3$

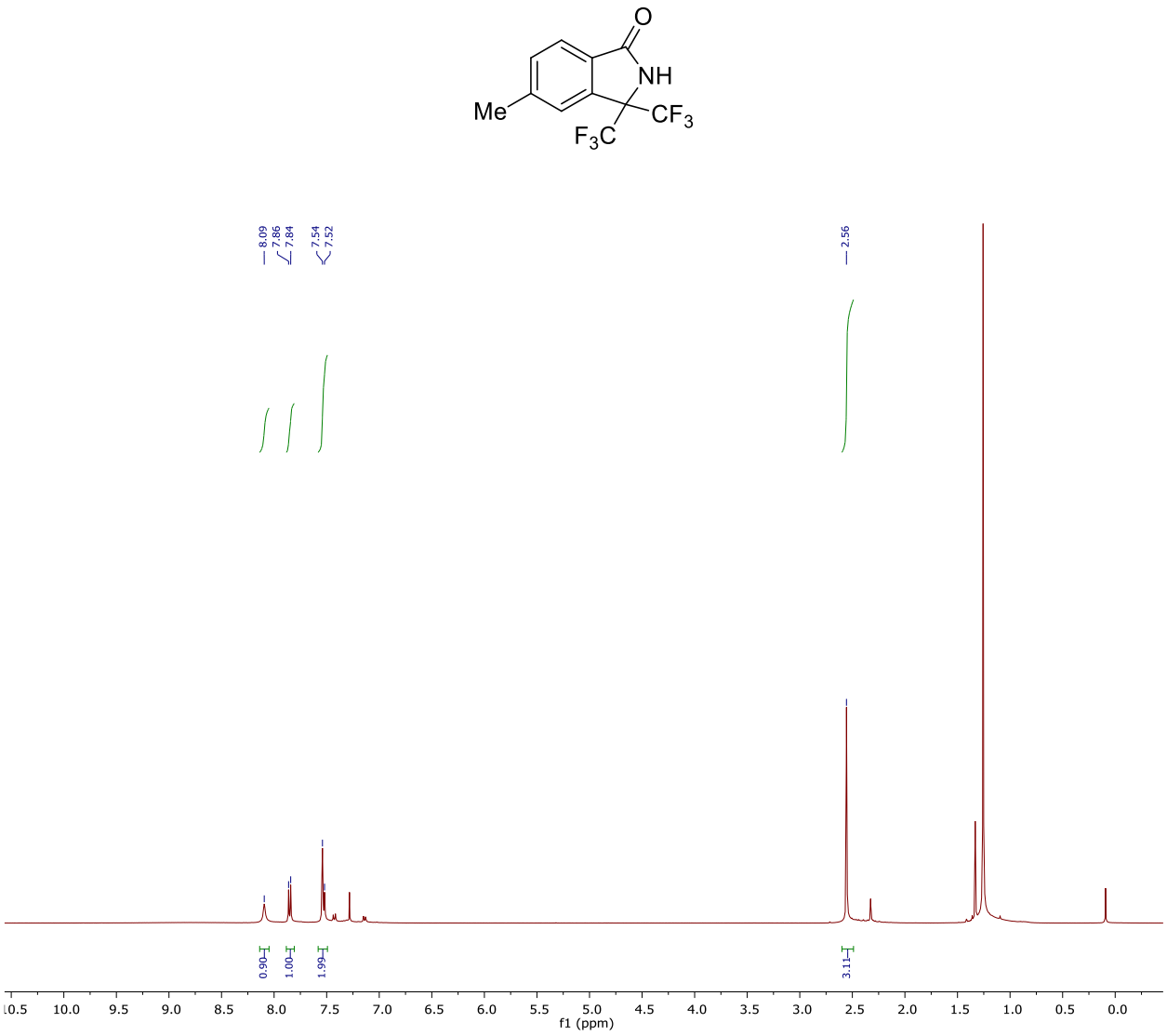


Figure S19 ^{1}H NMR spectrum of compound **4b** in $CDCl_3$

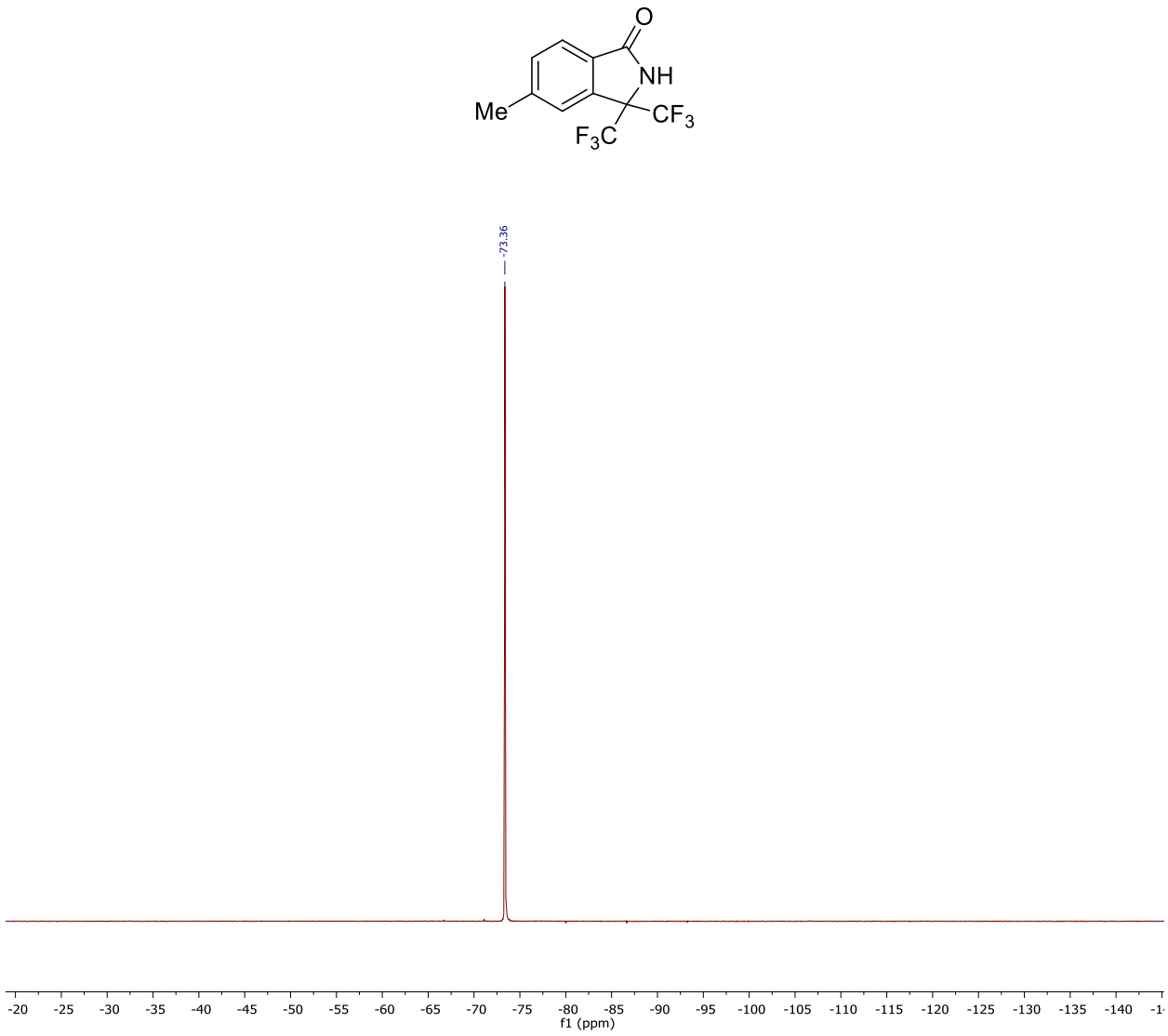


Figure S20 ^{19}F NMR spectrum of compound **4b** in $CDCl_3$

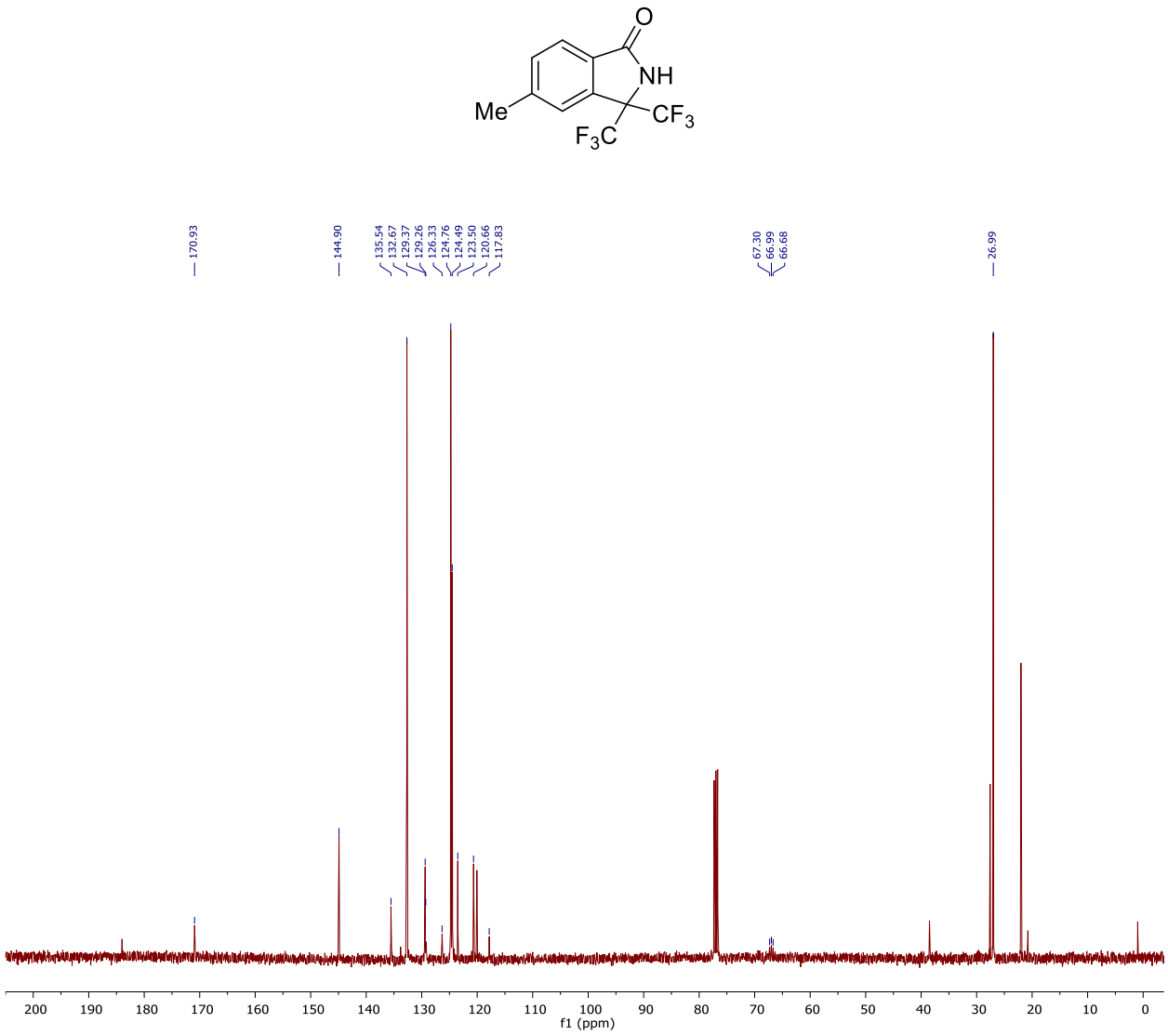


Figure S21 ^{13}C NMR spectrum of compound **4b** in $CDCl_3$

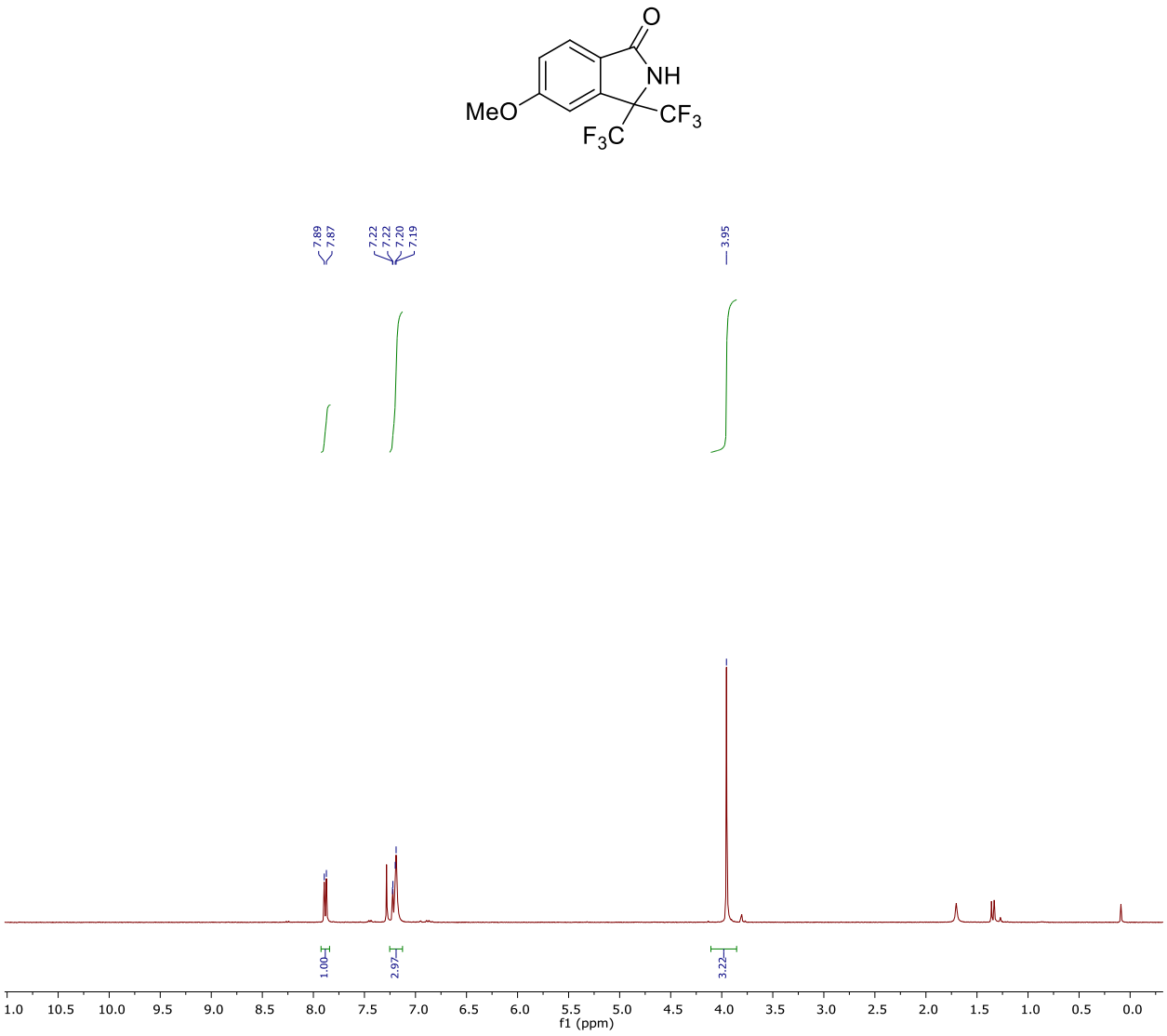


Figure S22 ^{1}H NMR spectrum of compound **4c** in $CDCl_3$

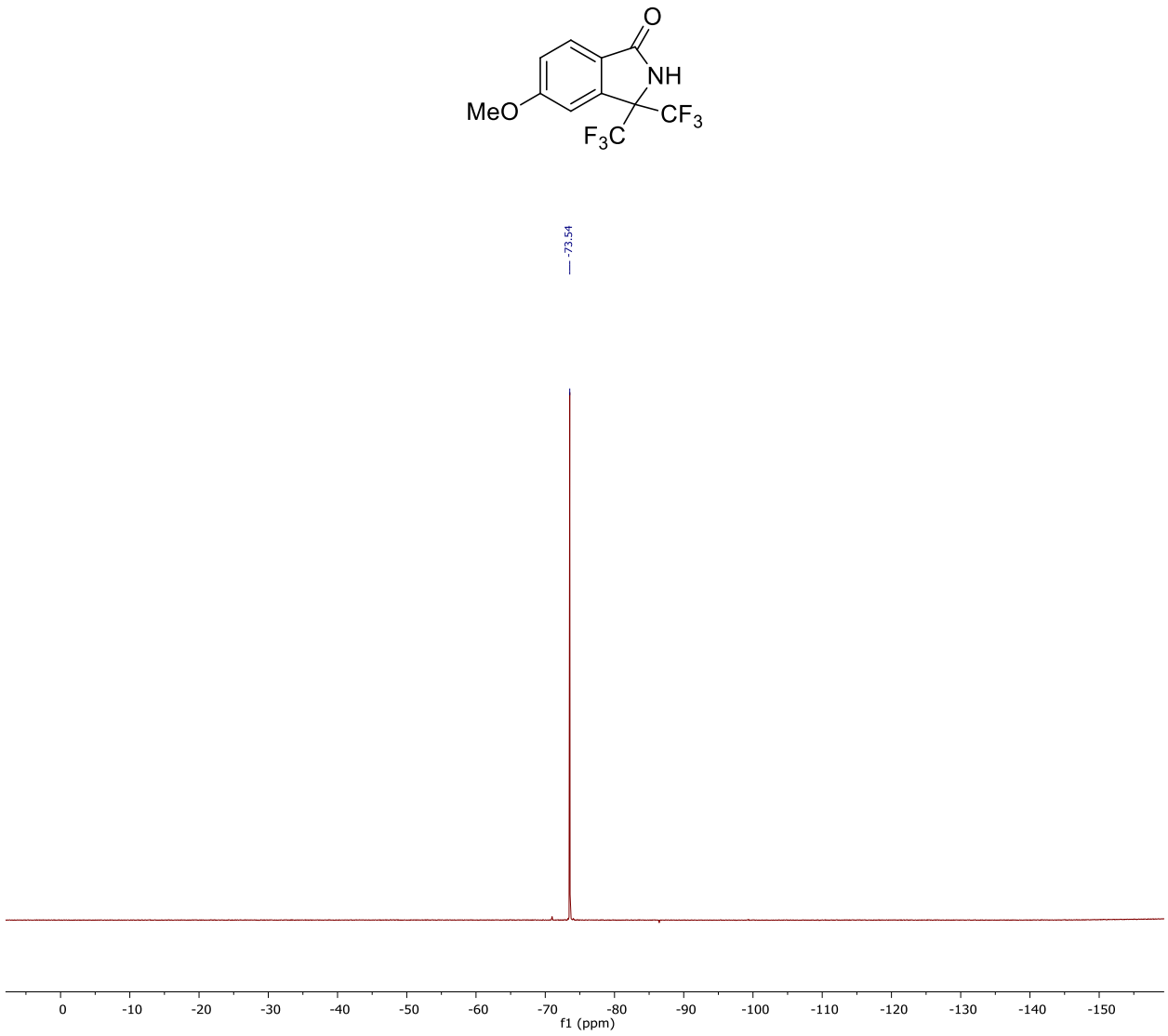


Figure S23 ^{19}F NMR spectrum of compound **4c** in $CDCl_3$

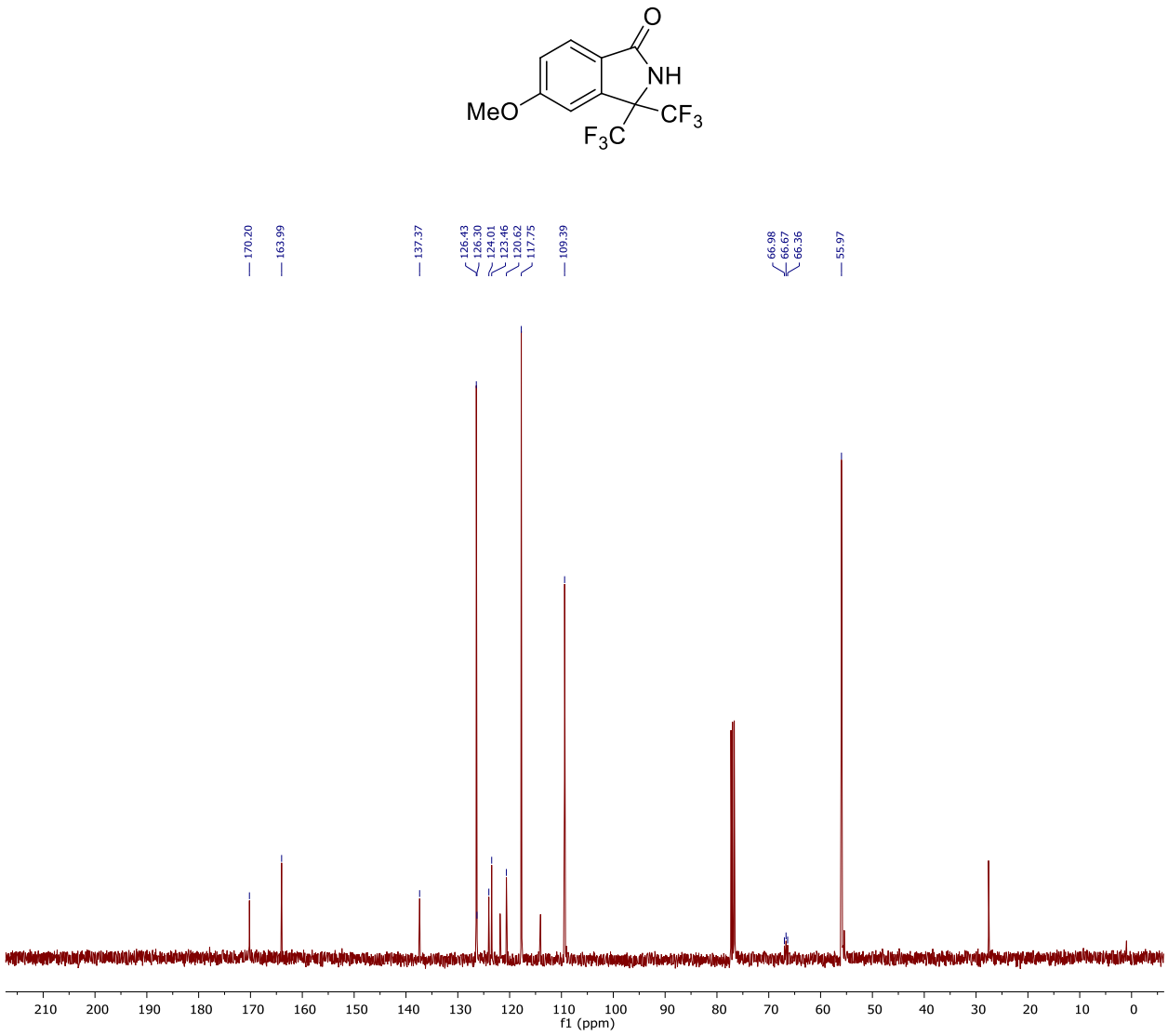


Figure S24 ^{13}C NMR spectrum of compound **4c** in $CDCl_3$

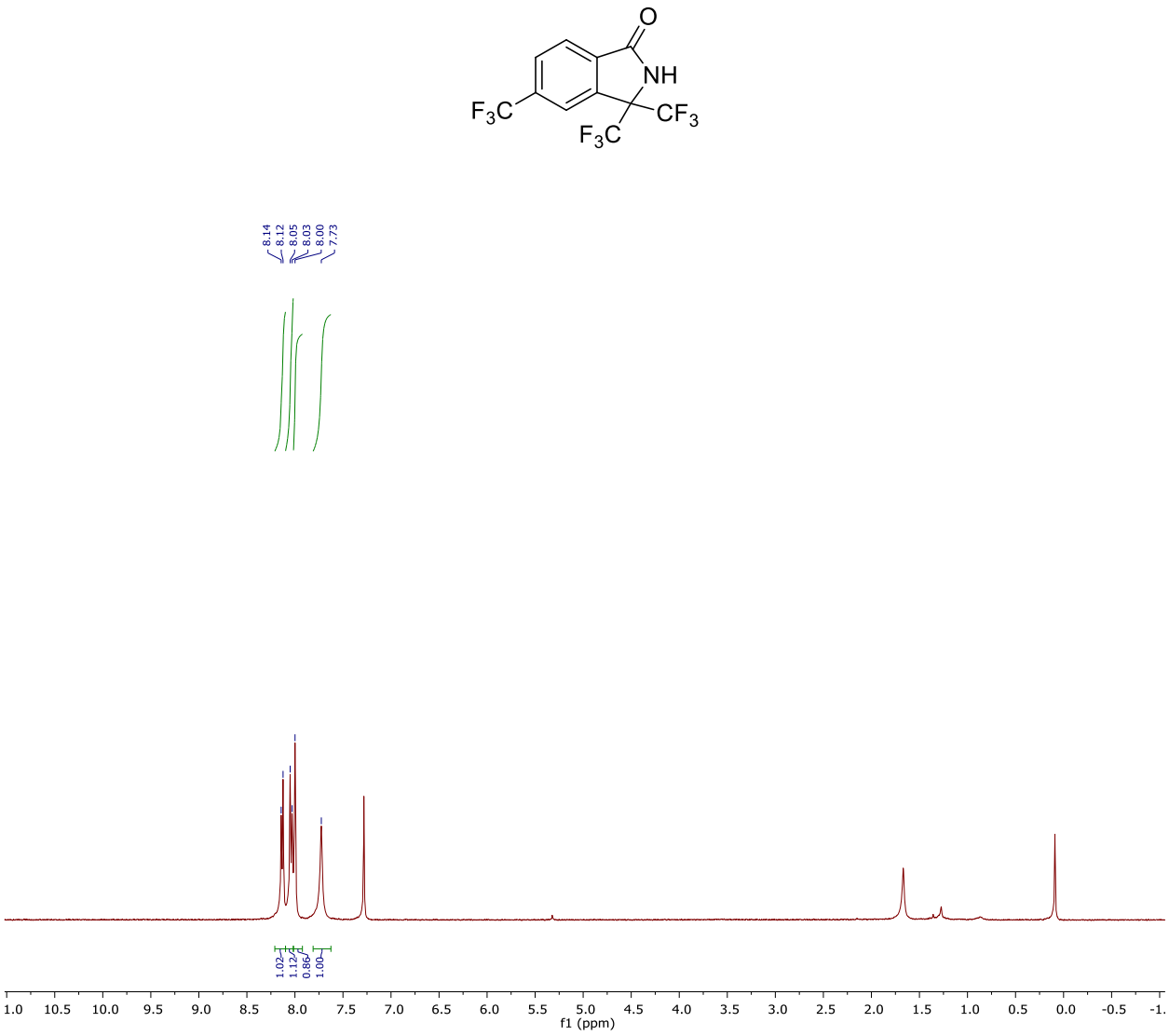


Figure S25 ^{1}H NMR spectrum of compound **4d** in $CDCl_3$

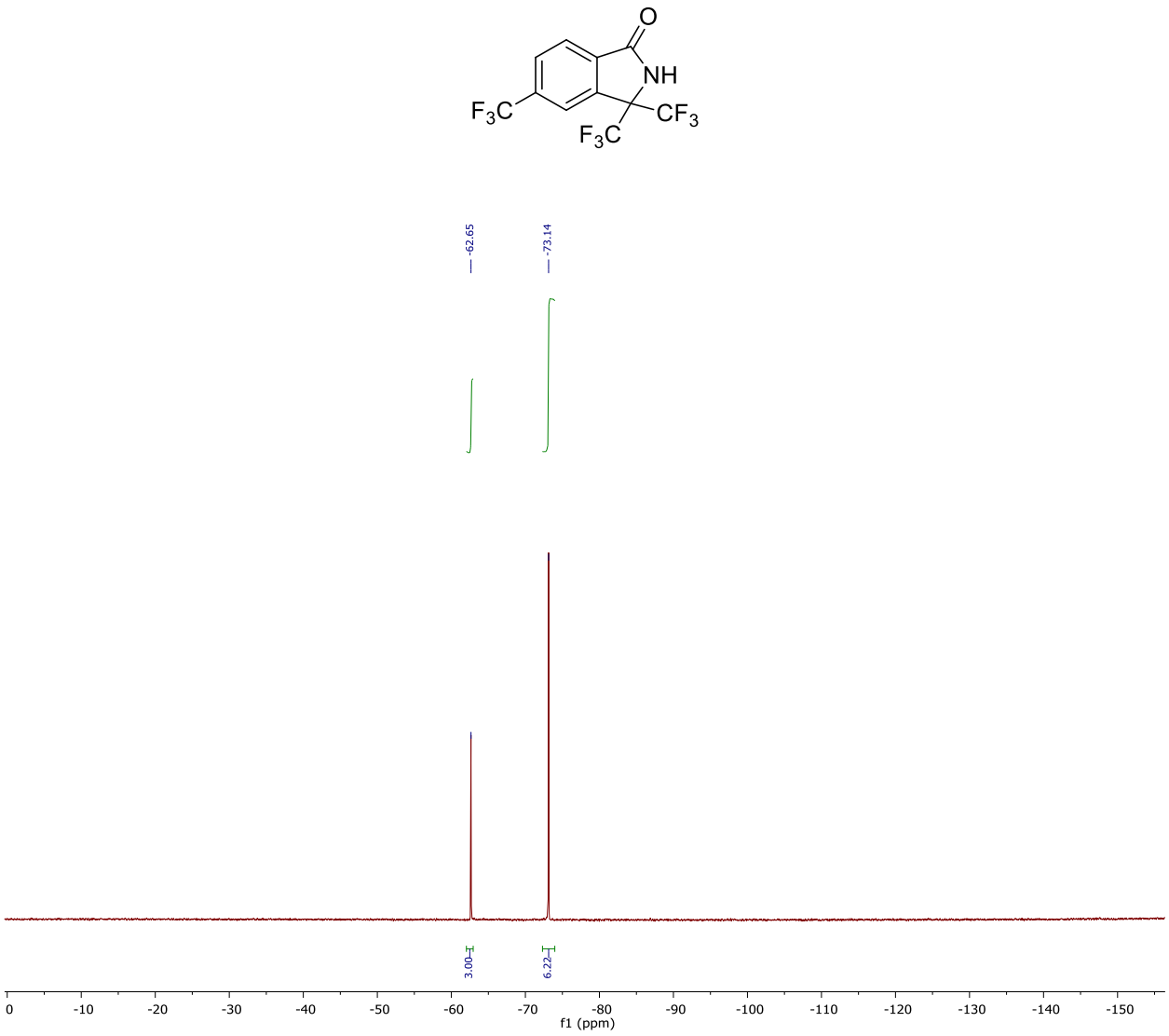


Figure S26 ^{19}F NMR spectrum of compound **4d** in $CDCl_3$

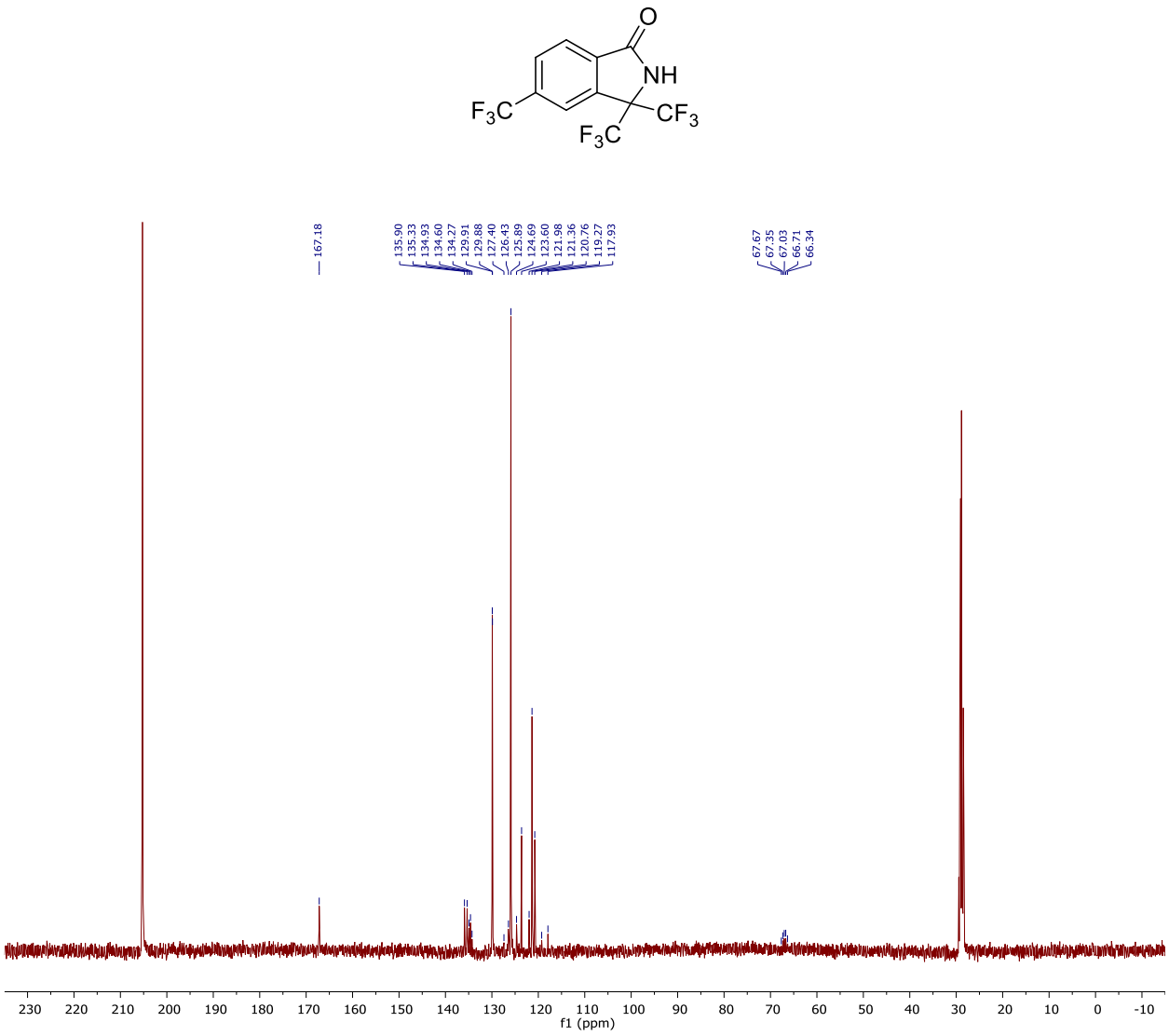


Figure S27 ^{13}C NMR spectrum of compound **4d** in $(CD_3)_2CO$

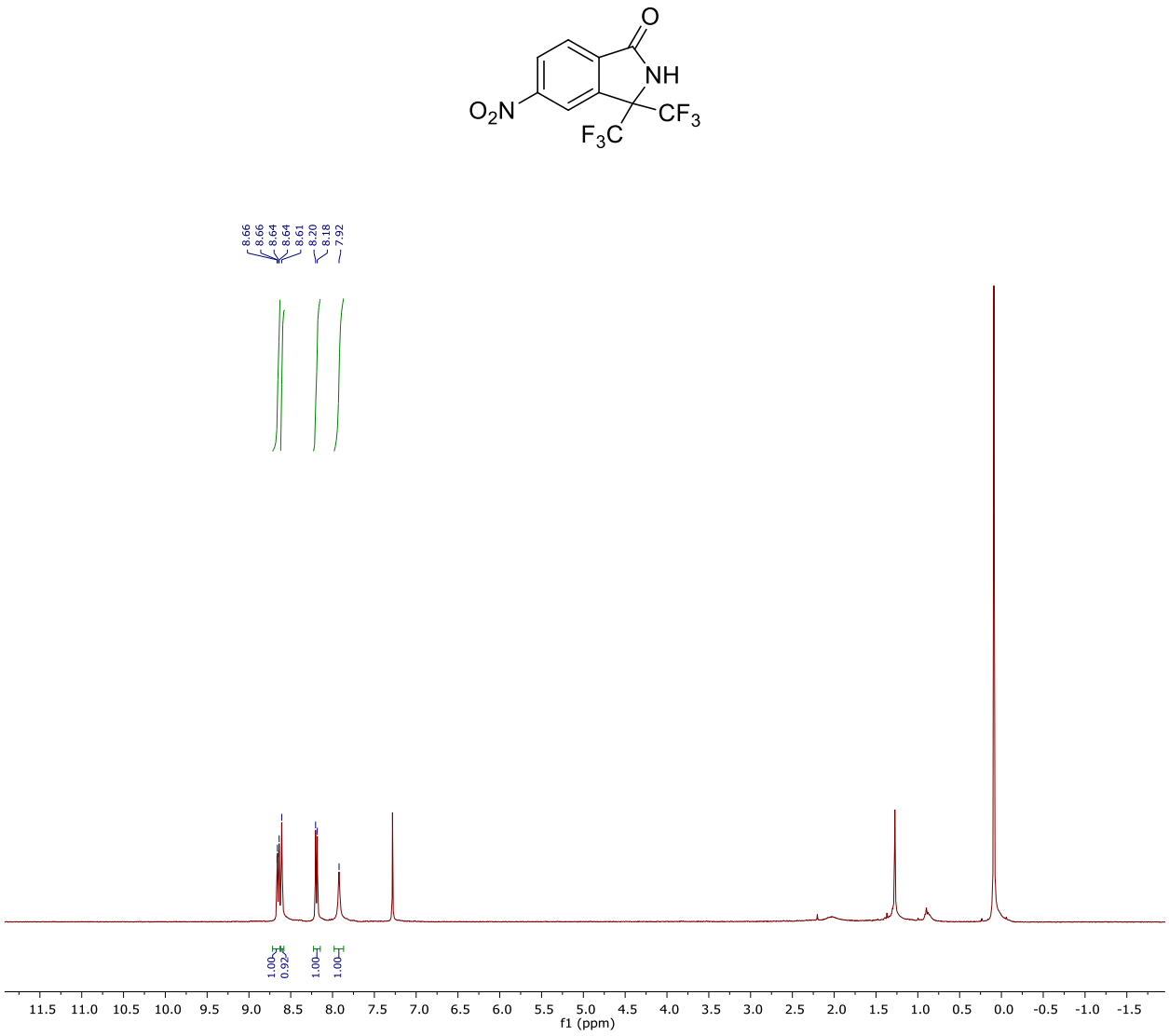


Figure S28 ^{1}H NMR spectrum of compound **4e** in $CDCl_3$

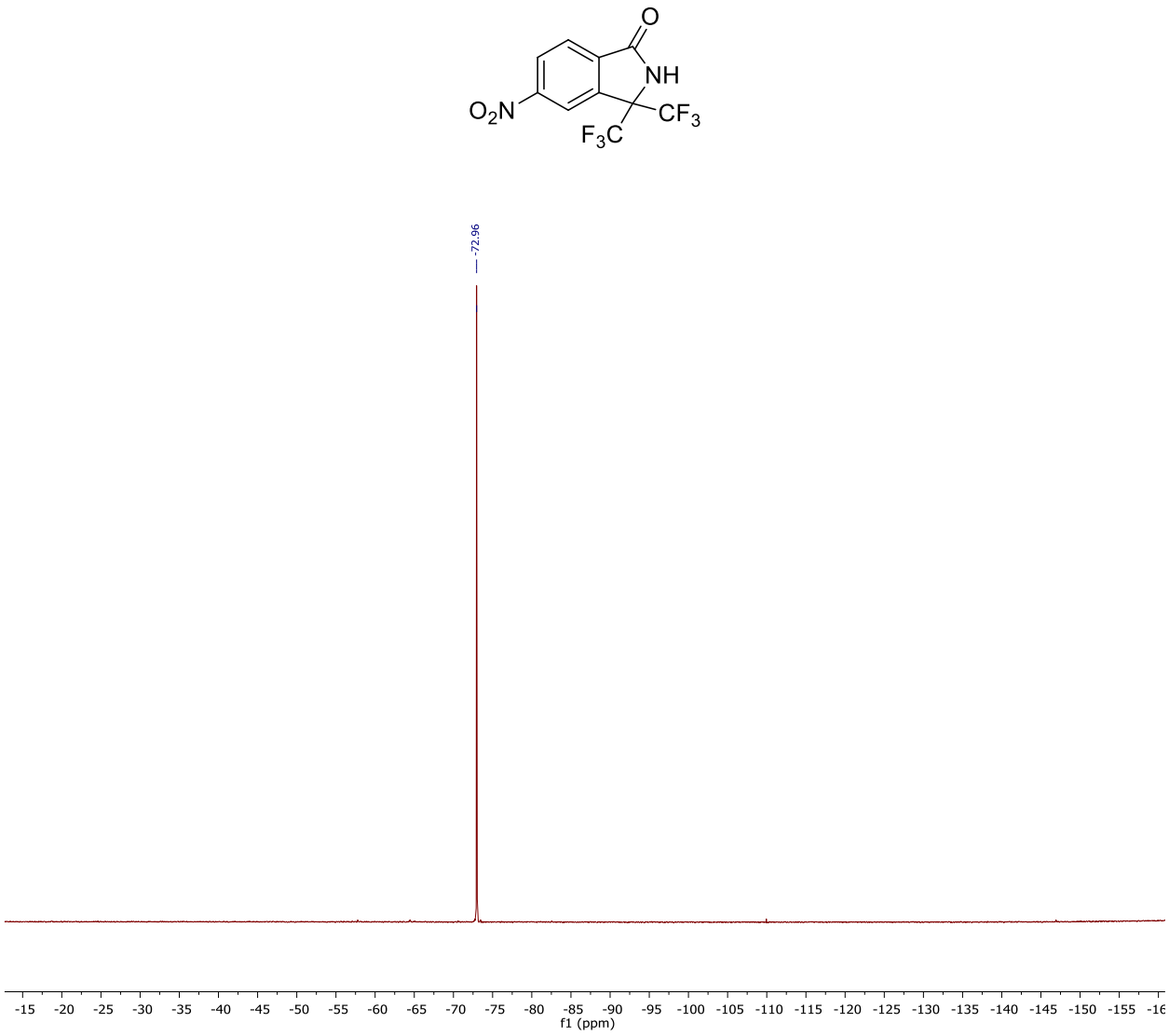


Figure S29 ^{19}F NMR spectrum of compound **4e** in $CDCl_3$

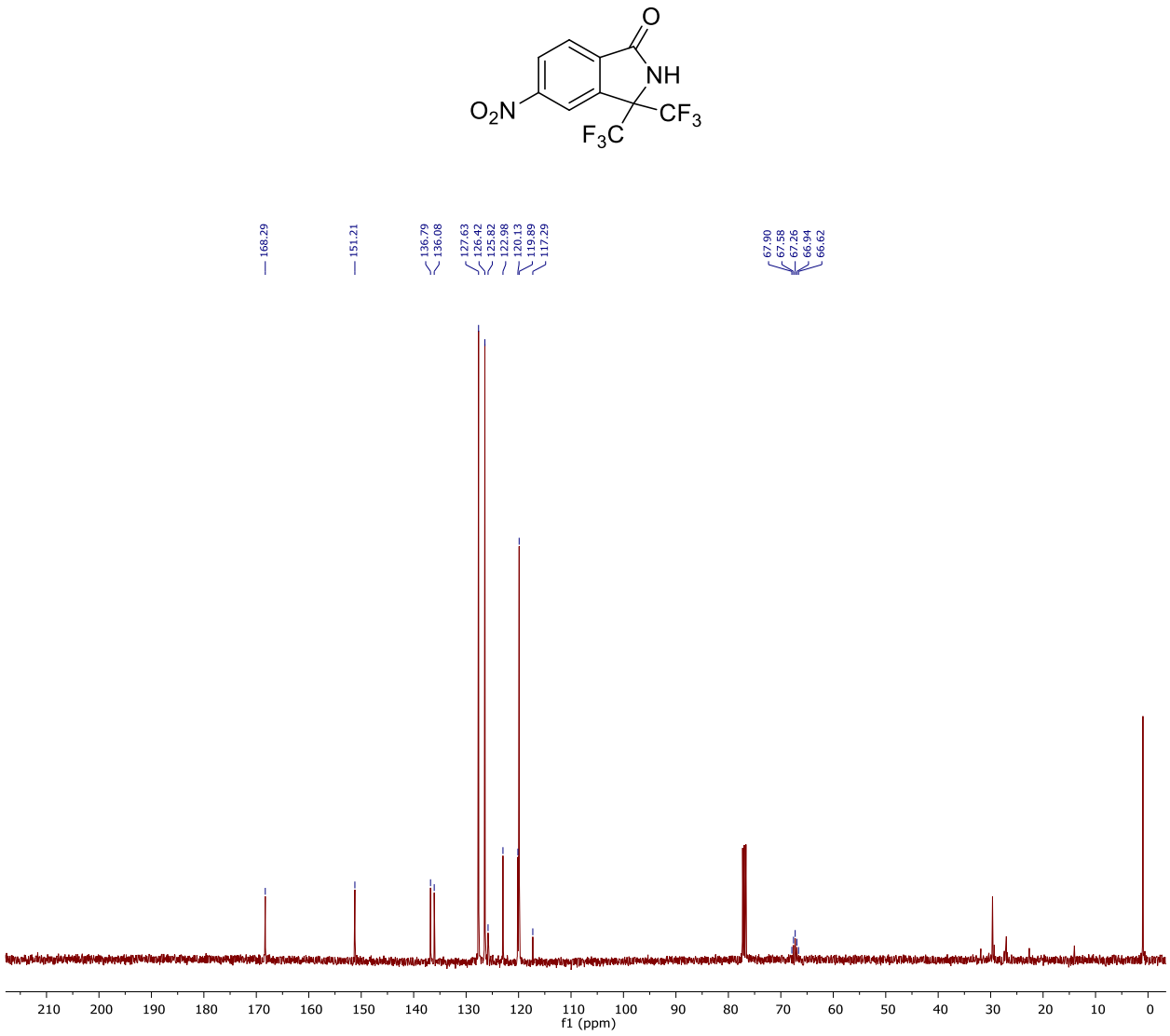


Figure S30 ^{13}C NMR spectrum of compound **4e** in $CDCl_3$

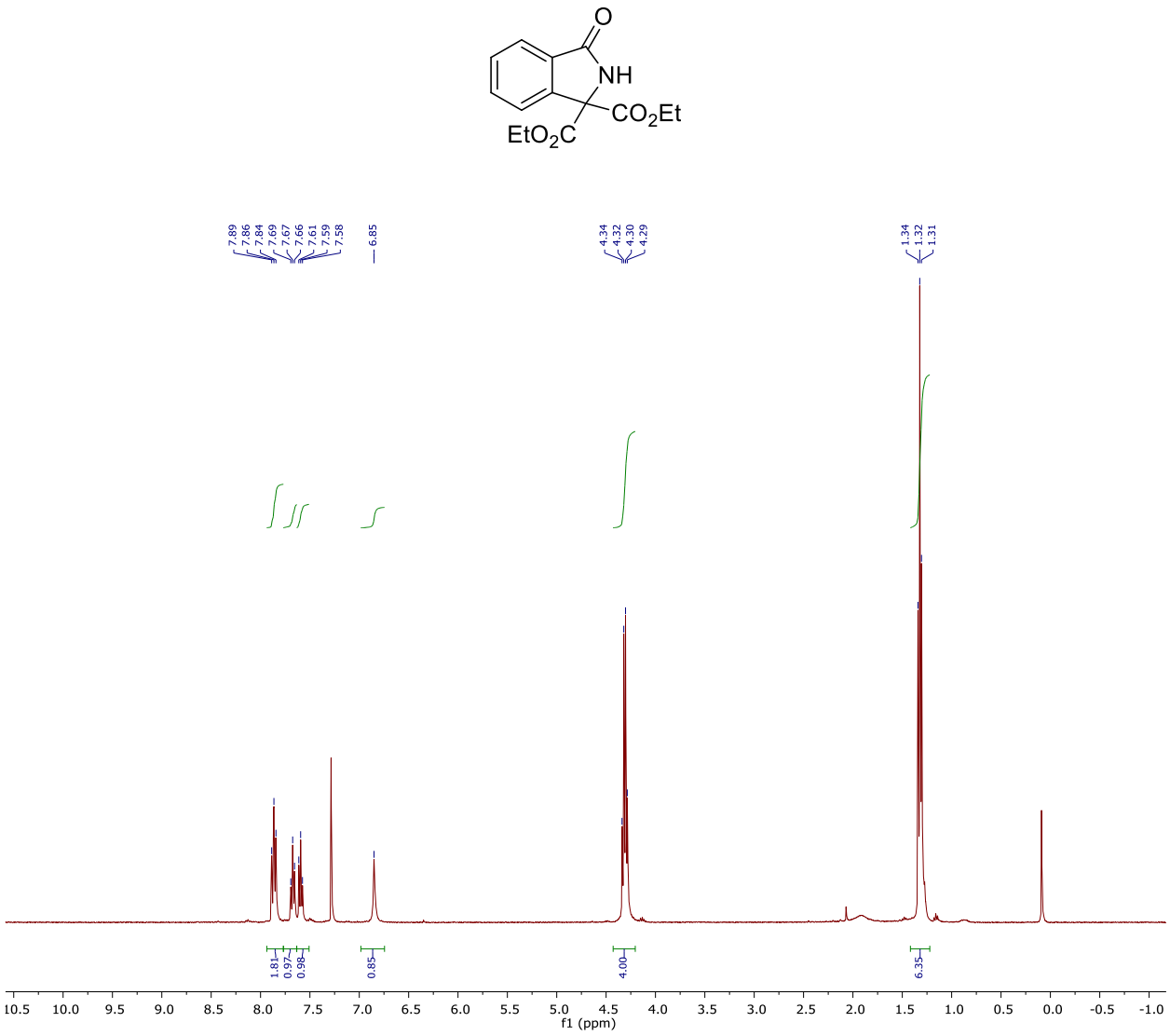


Figure S31 ^{1}H NMR spectrum of compound **6a** in $CDCl_3$

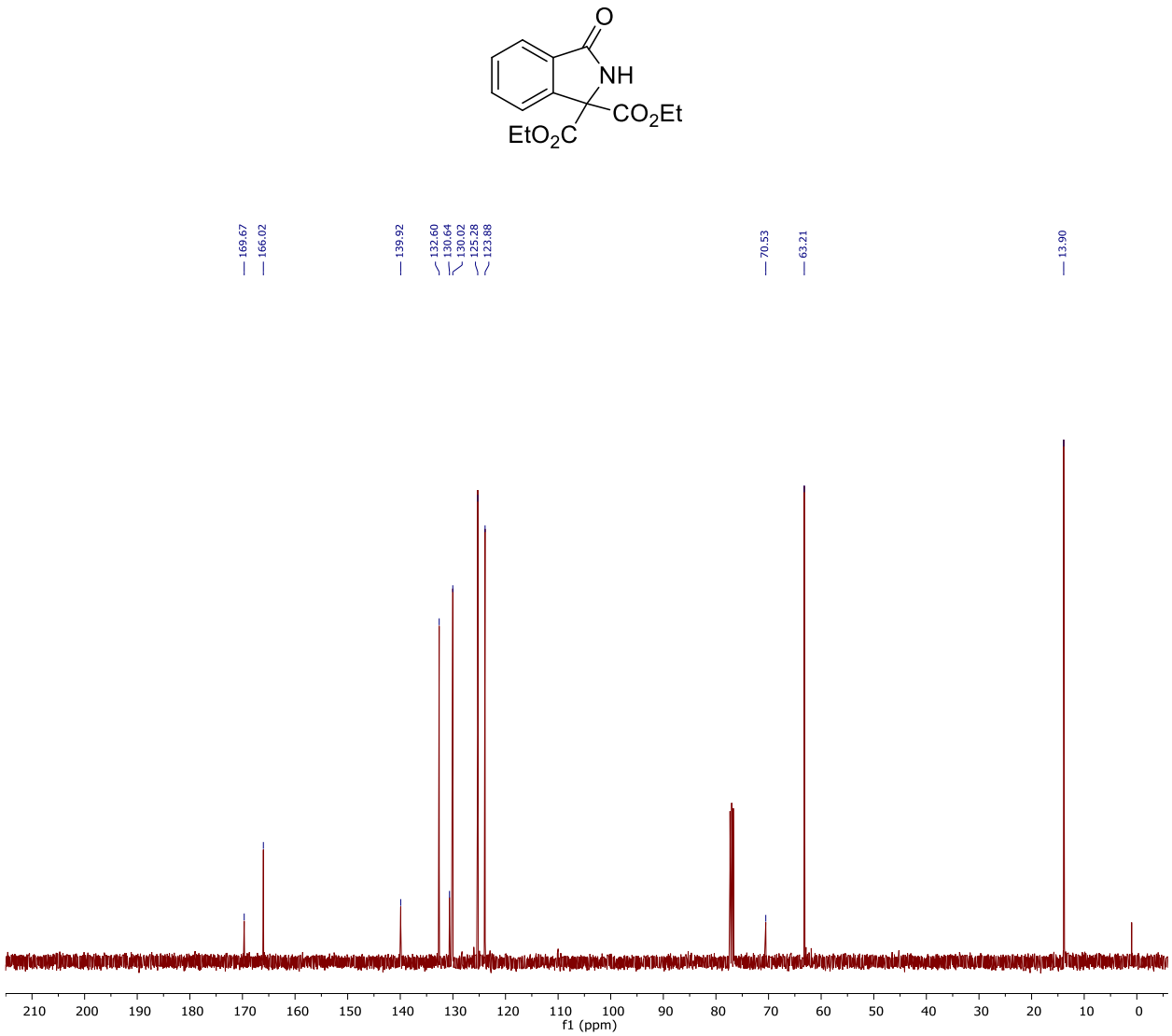


Figure S32 ^{13}C NMR spectrum of compound **6a** in $CDCl_3$

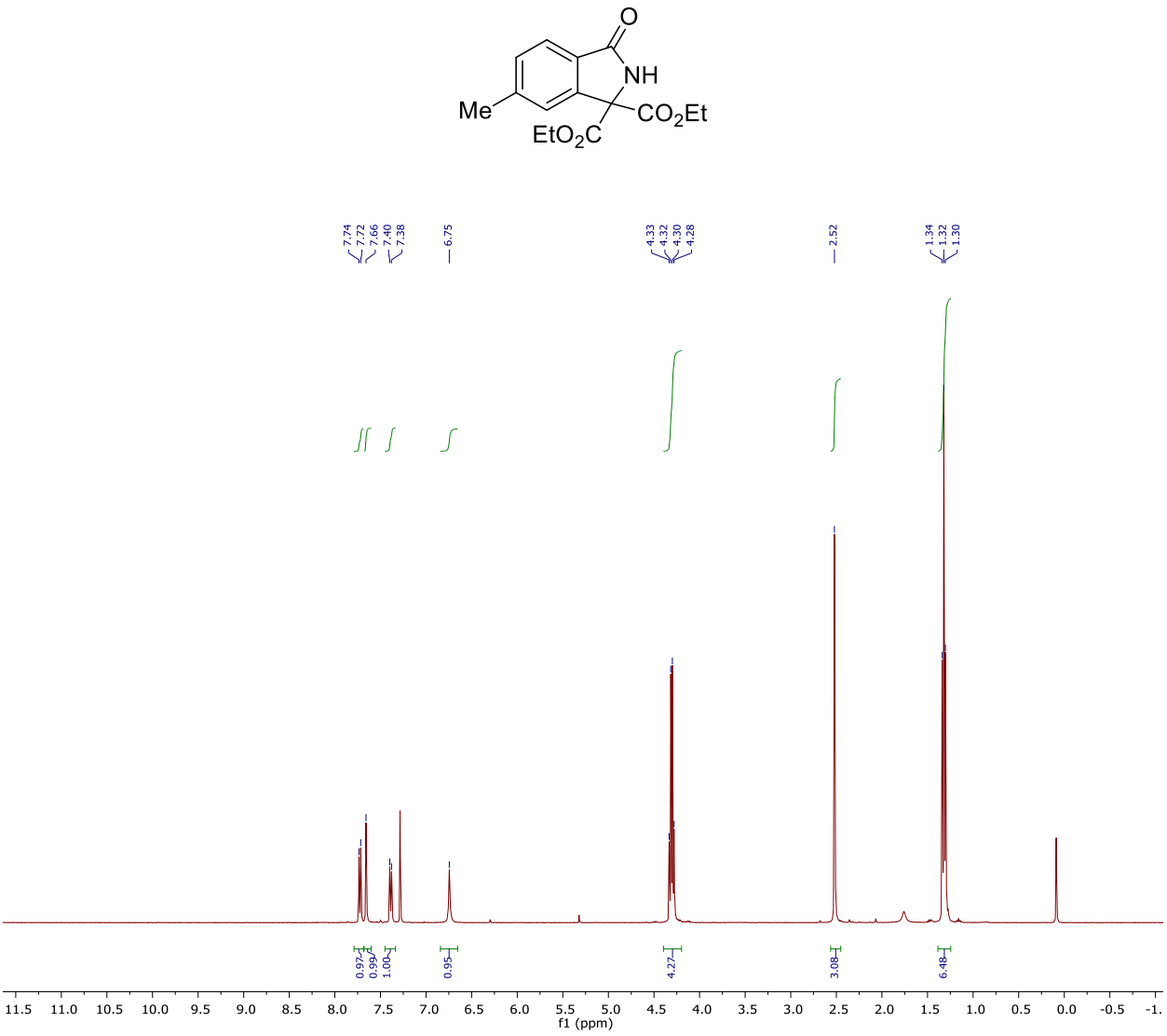


Figure S33 ^{1}H NMR spectrum of compound **6b** in $CDCl_3$

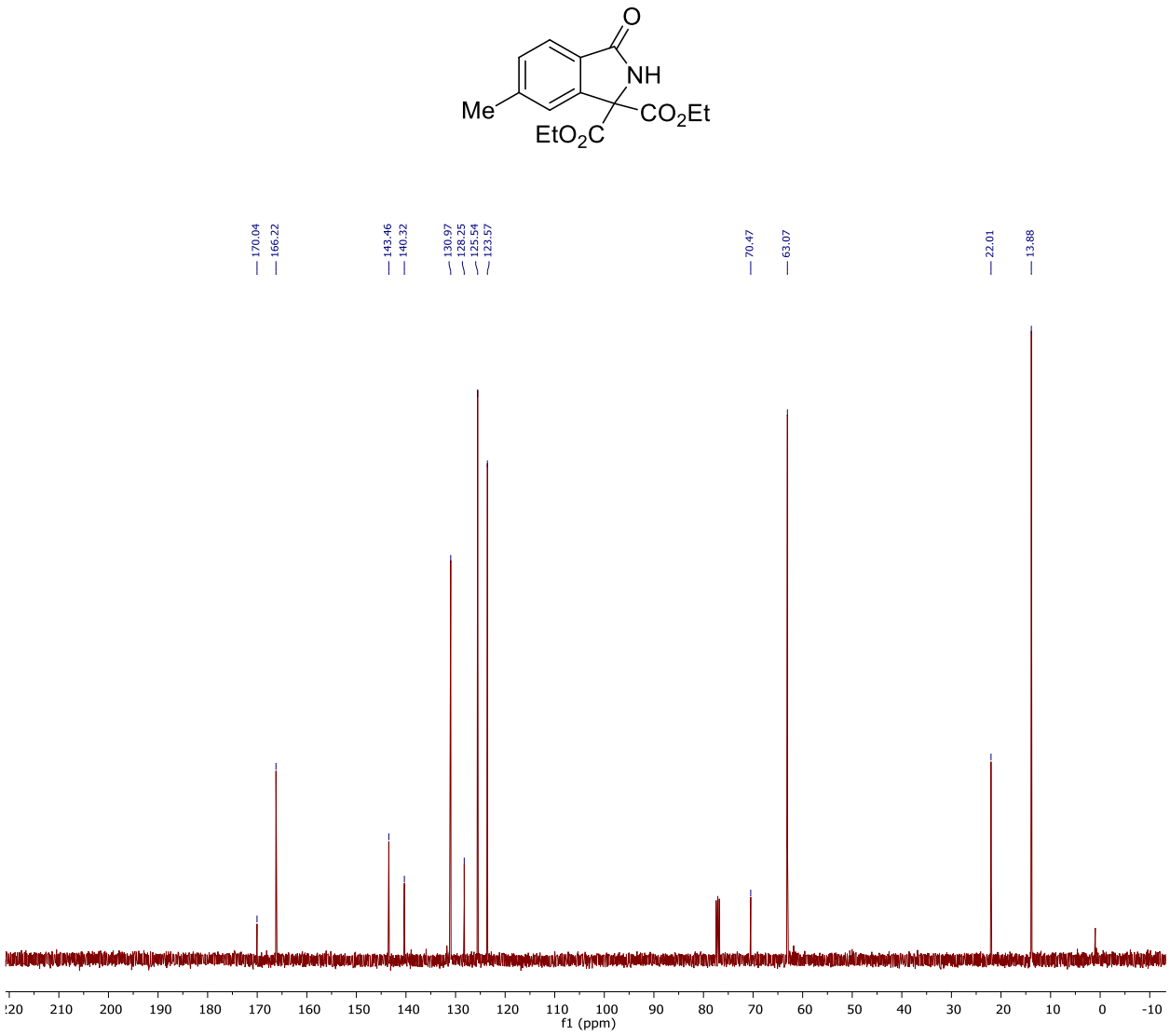


Figure S34 ^{13}C NMR spectrum of compound **6b** in $CDCl_3$

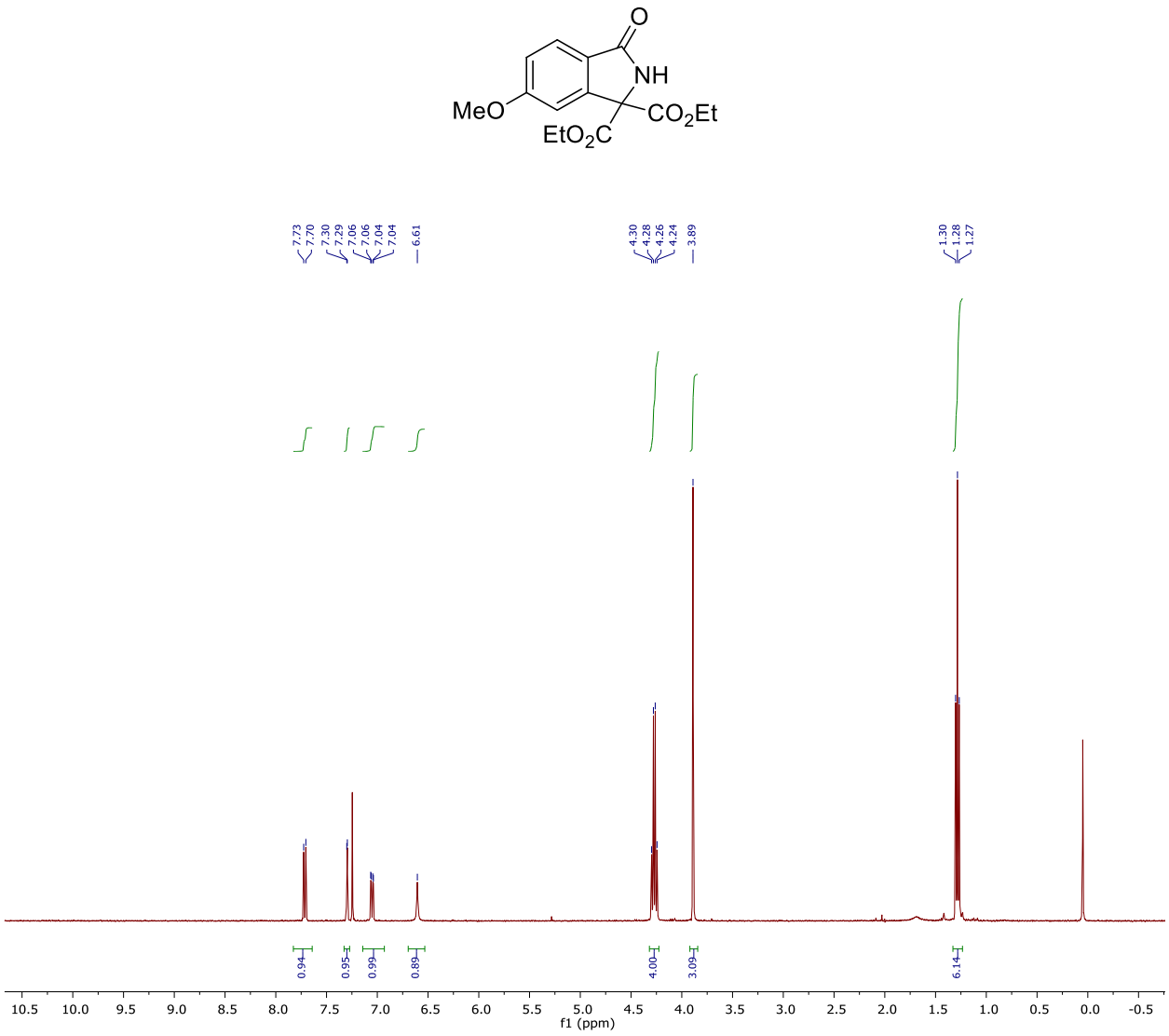


Figure S35 ^{1}H NMR spectrum of compound **6c** in $CDCl_3$

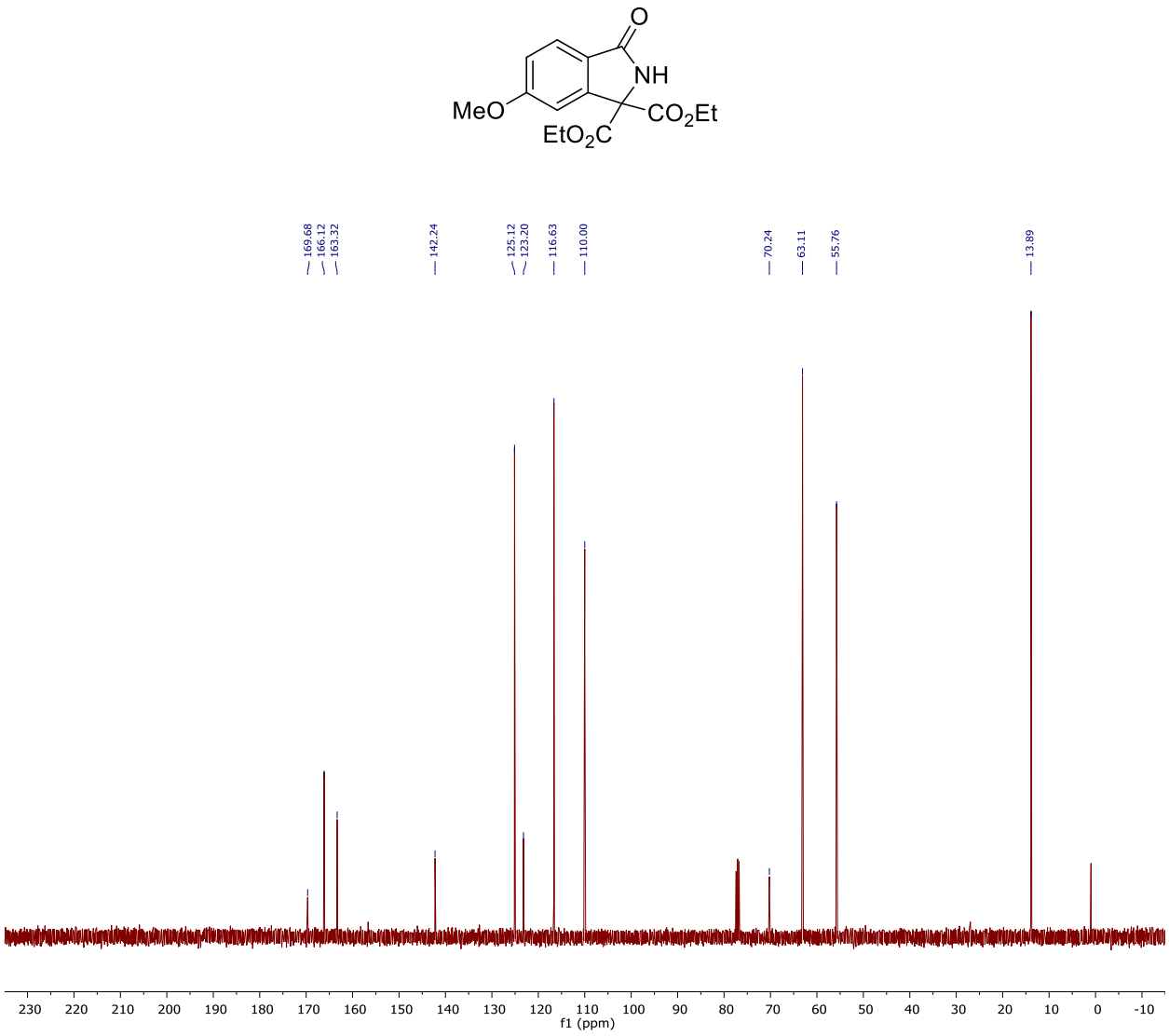


Figure S36 ^{13}C NMR spectrum of compound **6c** in $CDCl_3$

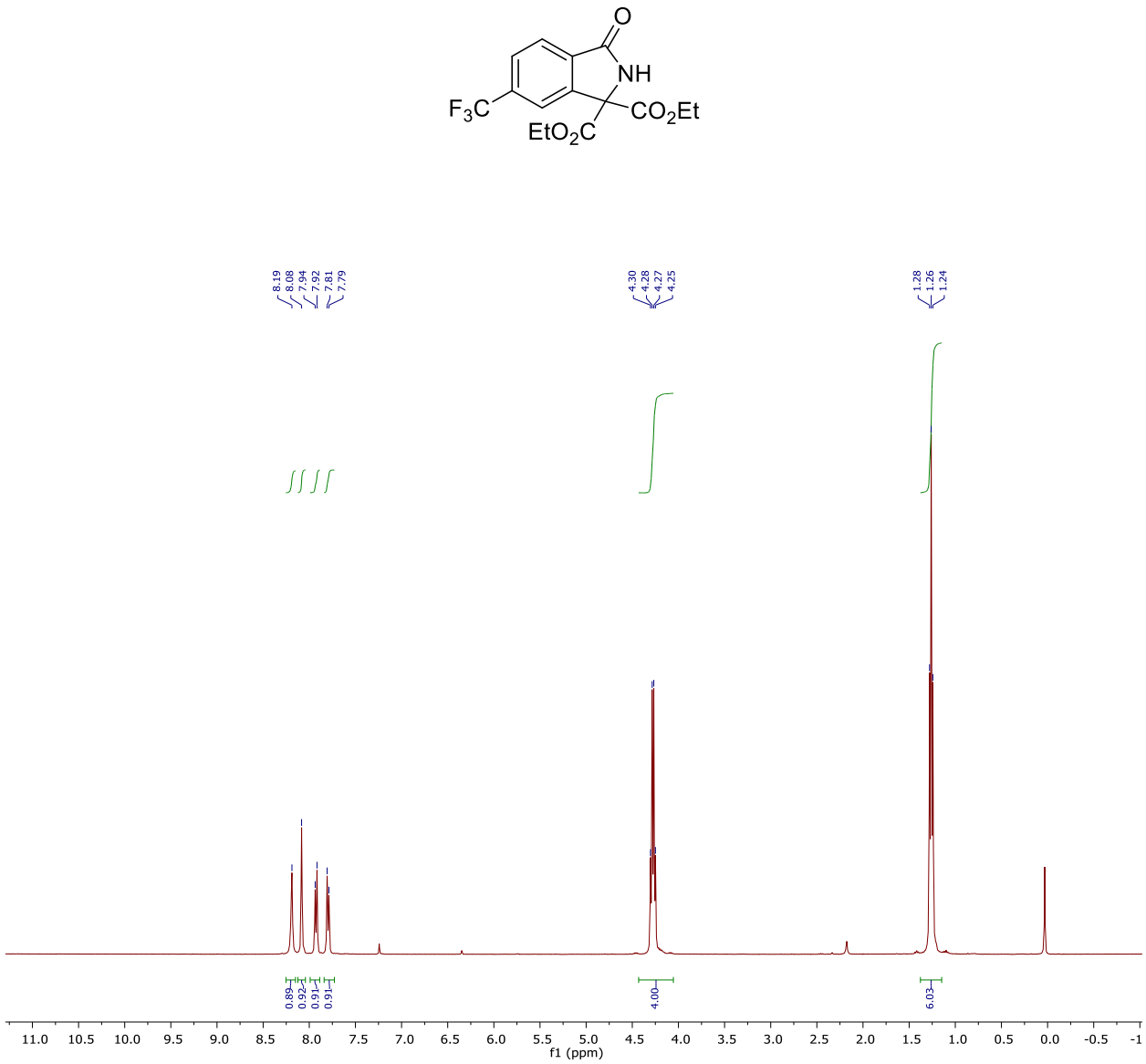


Figure S37 ^{1}H NMR spectrum of compound **6d** in $CDCl_3$

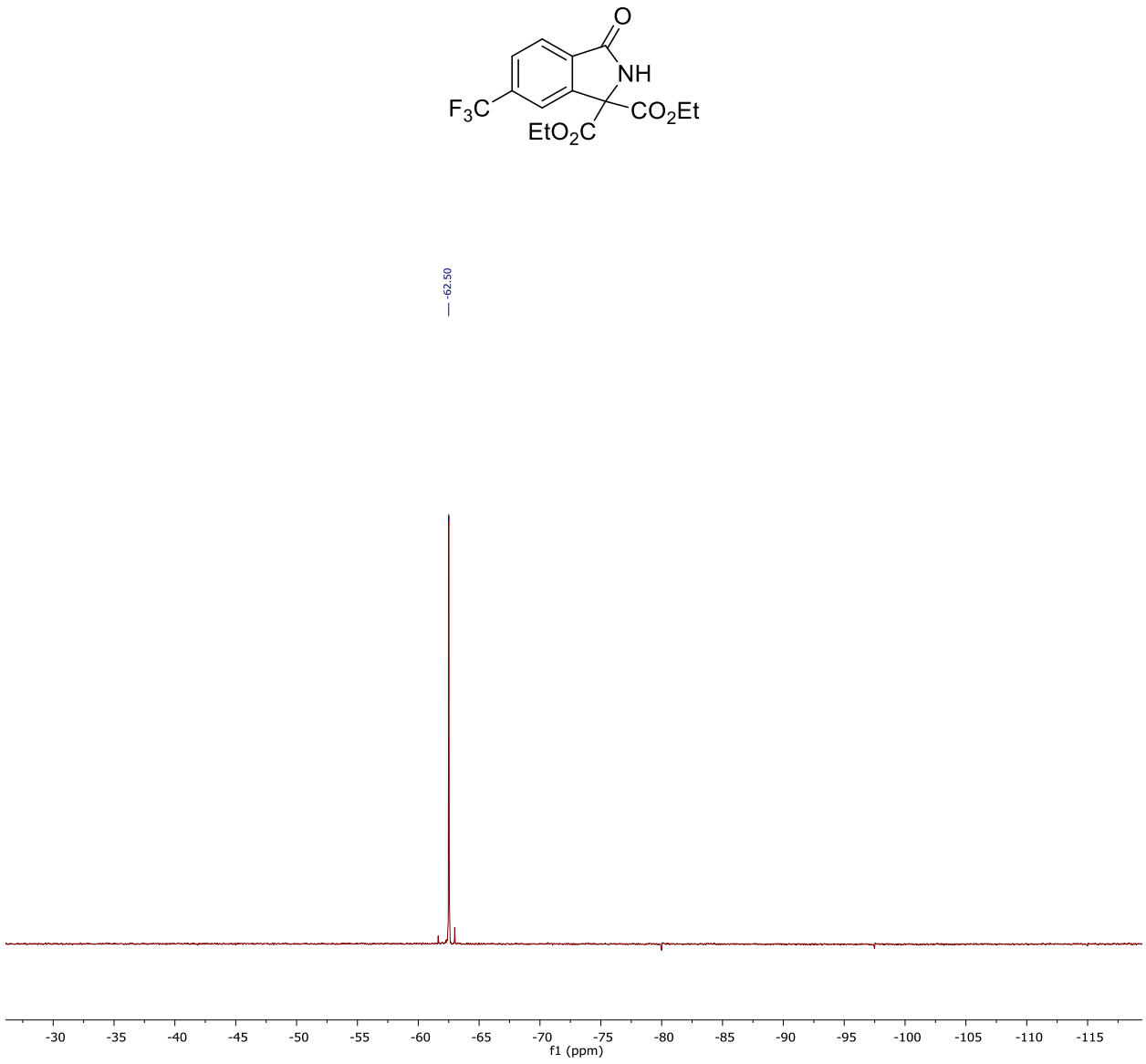


Figure S38 ^{19}F NMR spectrum of compound **6d** in $CDCl_3$

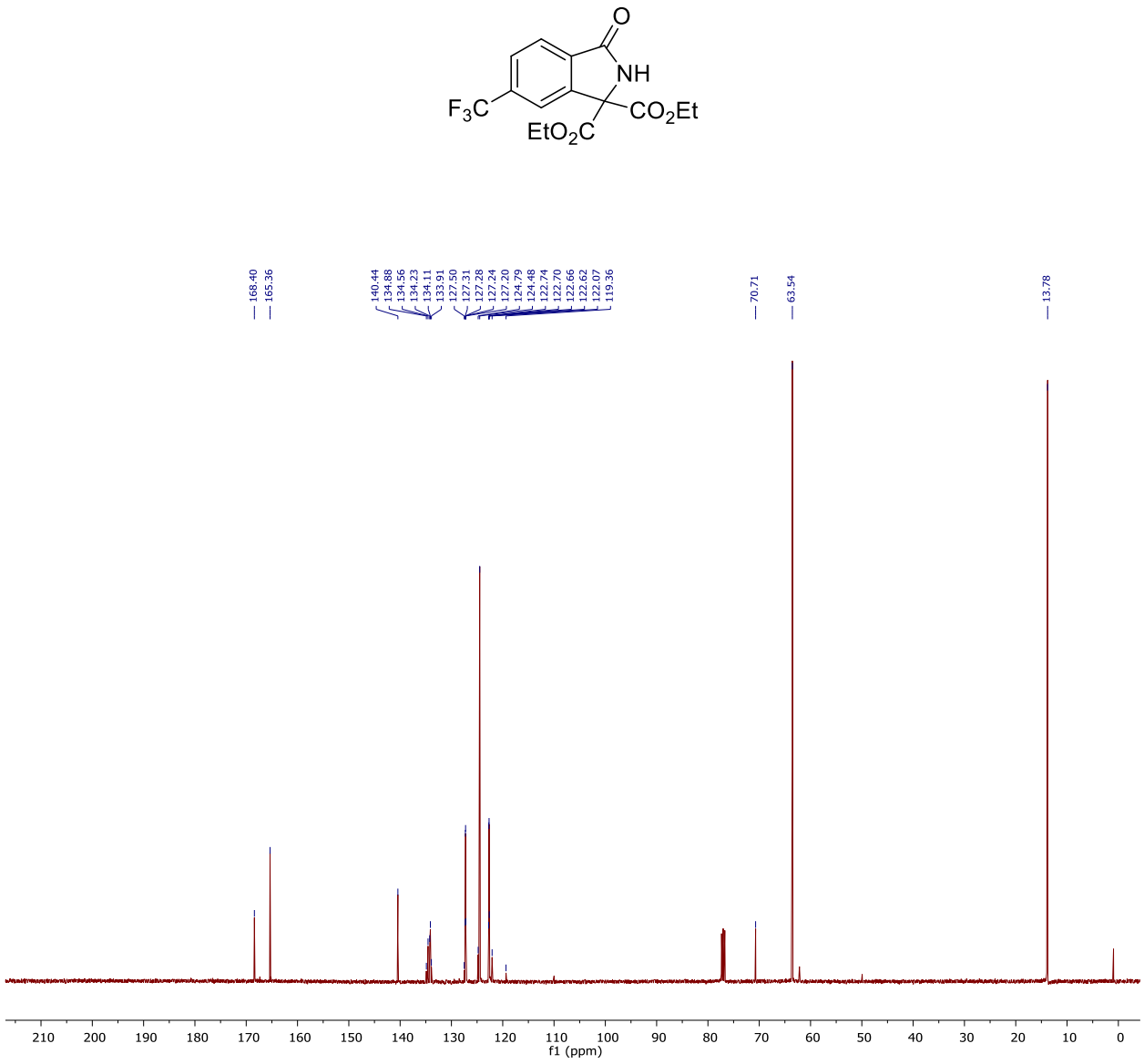


Figure S39 ^{13}C NMR spectrum of compound **6d** in $CDCl_3$

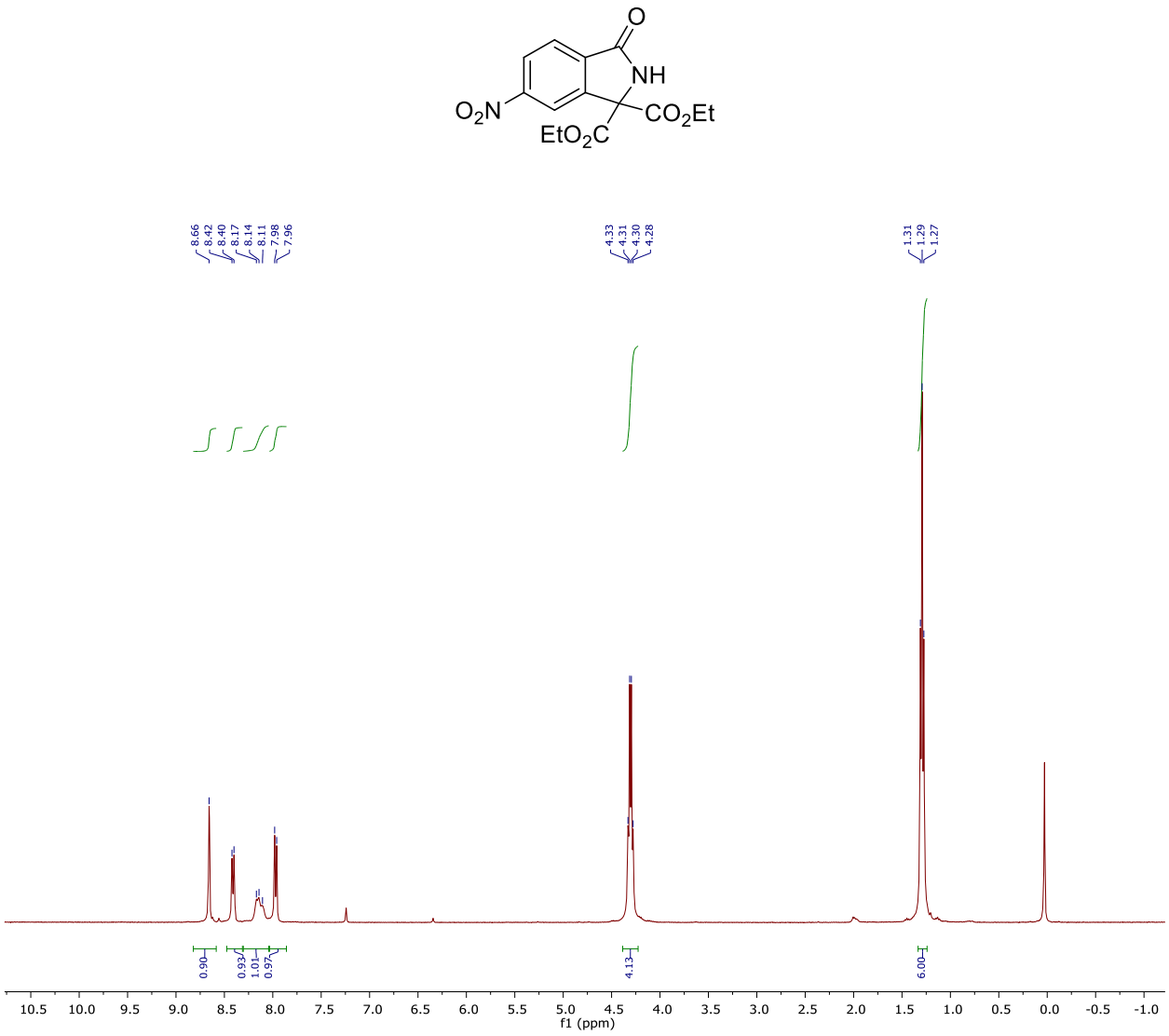


Figure S40 ^{1}H NMR spectrum of compound **6e** in $CDCl_3$

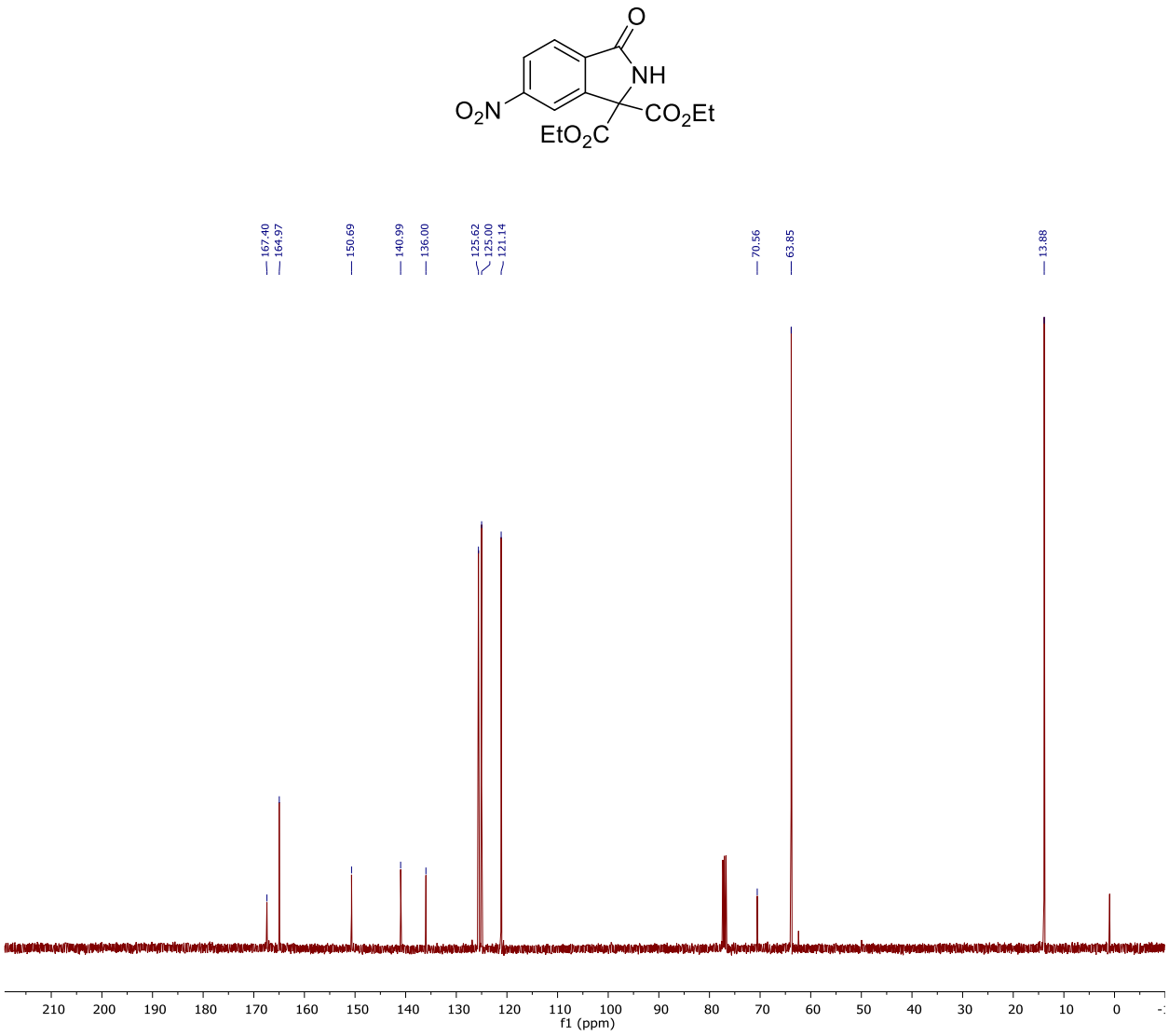


Figure S41 ^{13}C NMR spectrum of compound **6e** in $CDCl_3$

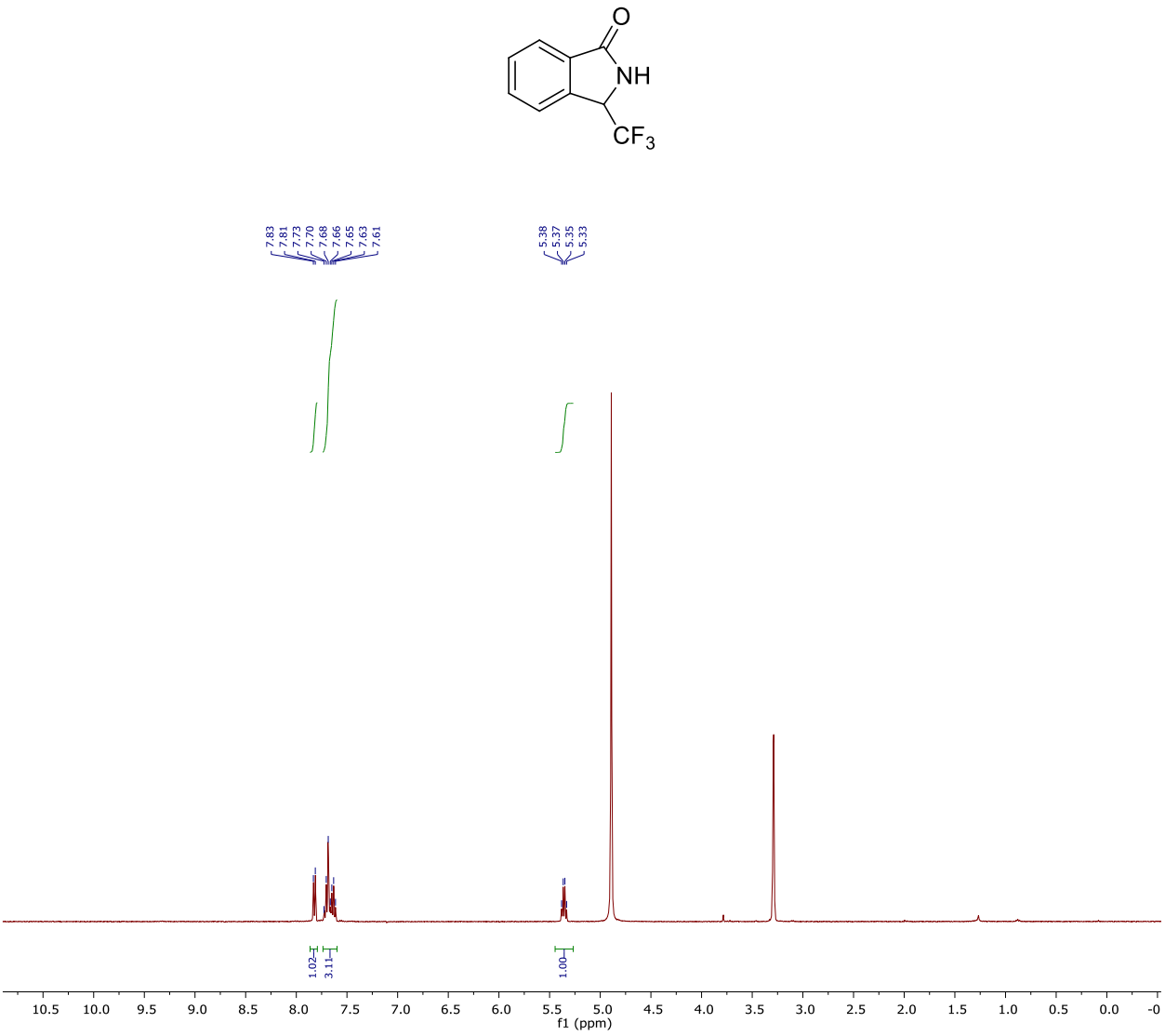


Figure S42 ^{1}H NMR spectrum of compound **7** in CD_3OD

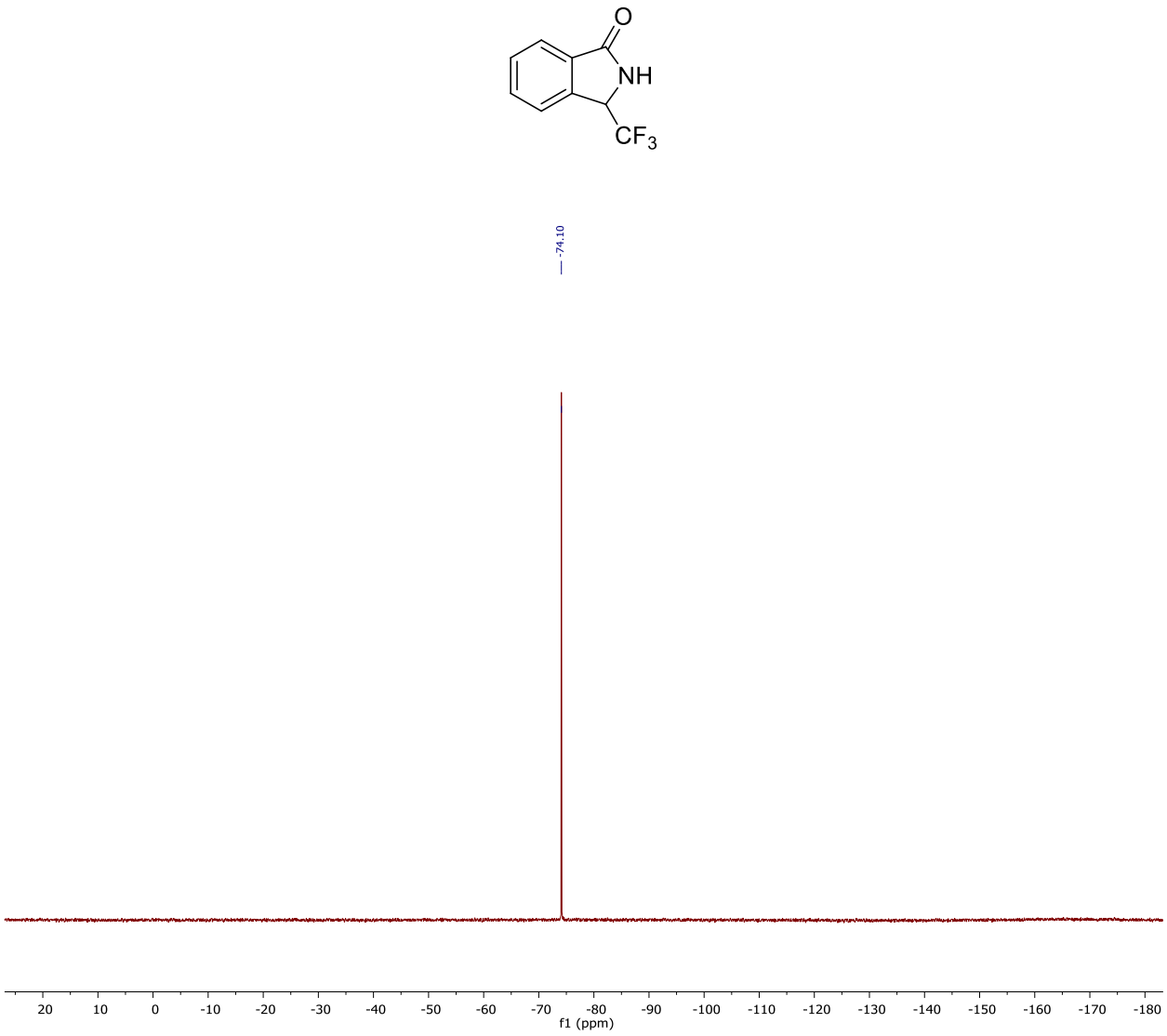


Figure S43 ^{19}F NMR spectrum of compound **7** in CD_3OD

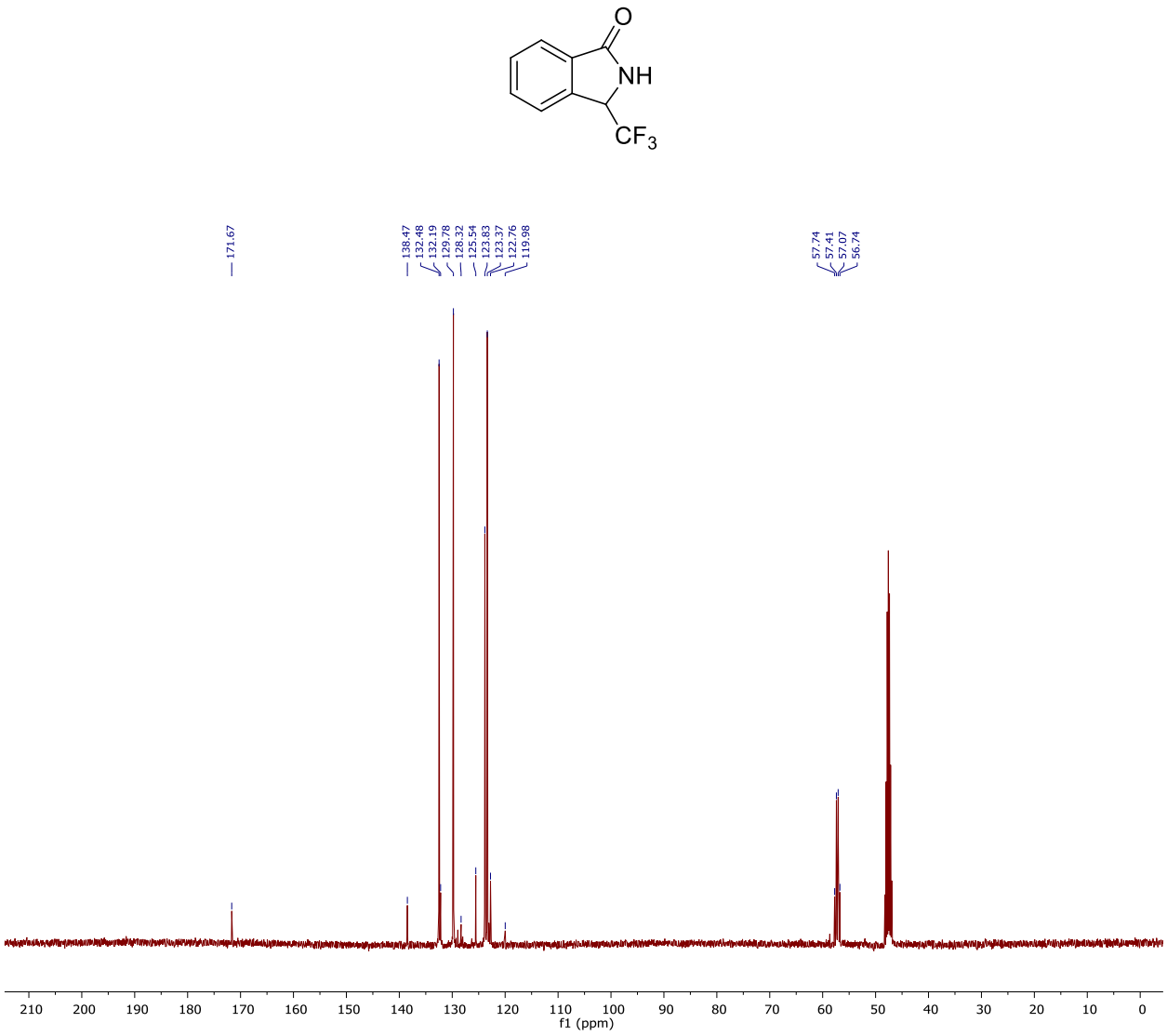


Figure S44 ^{13}C NMR spectrum of compound **7** in CD_3OD