

Quinazoline addition to indole hydrazone derivatives in TFA as a facile synthesis of trifluoroacetylhydrazide quinazoline σ -adducts

Yurii A. Azev, Olga S. Koptyaeva, Oleg S. Eltsov, Yulia. A. Yakovleva, Tat'yana A. Pospelova and Vasilii A. Bakulev

General. Unless otherwise indicated, all common reagents and solvents were used from commercial suppliers without further purification. The reaction progress and purity of the obtained compounds were controlled by TLC method on Sorbfil UV-254 plates, using visualization under UV light. Melting points were determined on a Stuart SMP10 melting point apparatus. ^1H , ^{13}C and ^{19}F NMR spectra were acquired on Bruker Avance-400 and Bruker Avance NEO-600 spectrometers in DMSO- d_6 solutions, using TMS as internal reference for ^1H and ^{13}C NMR or CFCl_3 for ^{19}F NMR. Mass-spectra (EI, 70eV) were recorded on MicrOTOF-Q instrument (Bruker Daltonics) at 250°C.

HRMS analysis was performed with a tandem quadrupole time-of-flight (Q-TOF) accurate mass detector Agilent 6545 Q-TOF LC-MS (Agilent Technologies, USA). QTOF instrument was operated with an electrospray ion source in positive ion mode. Nitrogen at 350°C, a flow rate of 10 dm³ min, was used as a drying gas. Sheath gas temperature was set at 400°C, sheath gas flow rate was 12 dm³ min. The nebulizer pressure was 40 psi, the capillary voltage 3500 V, the skimmer voltage 45 V, and the fragmentor voltage 90 V. Ions were scanned in the mass ranges 100–1000 Da. The TOF detector was operated in EDR (2 GHz) mode; the rate of acquisition was 1.5 spectra per second. Adjustment and operation of the instrument, as well as data processing were controlled by means of ‘MassHunter Workstation Software B.08.00’ software. Adjusting the mass spectrometer and correcting the mass measurement accuracy were carried out automatically in accordance with the instruction manual of the device and with the use of recommended standard solutions (Agilent, part. numbers G1969-85000 and G1969-85001).

Indole carbaldehyde hydrazones (general procedure). 2-Methyl-1*H*-indole-3-carbaldehyde (0.5 mmol) was dissolved in ethanol (3 ml). Then this solution was added to a mixture of the corresponding hydrazine and hydrochloric acid (0.02 ml) in water (3.0 ml). The resulting mixture was refluxed for 10 minutes and then was cooled. The resulting solid was filter off and dried. The crude hydrazones were used directly in the next step without additional purification.

2-Methyl-3-[[2-(4-nitrophenyl)hydrazineylidene]methyl]-1*H*-indole (2a). Yield 59%, m.p. 288–289 °C. $^1\text{H NMR}$ (600 MHz, DMSO- d_6 , δ , ppm): 2.54 (s, 3H, CH₃), 7.09 (br. s, 2H, H⁴), 7.12-7.15 (m, 2H, H⁵, H⁶), 7.37-7.33 (m, 1H, H⁷), 8.12-8.17 (m, 3H, H⁴, H⁵), 8.34 (s, 1H, H¹), 10.98 (s, 1H, N³H), 11.47 (s, 1H, N¹H). $^{13}\text{C NMR}$ (151 MHz, DMSO- d_6 , δ , ppm): 12.04 (s, CH₃), 108.08 (s, C³), 110.56 (s, C⁵), 111.41 (s, C⁷), 120.86 (s, C⁵), 121.11 (s, C⁴), 122.23 (s, C⁶), 125.68 (s, C^{3a}), 126.93 (s, C⁶), 136.18 (s, C^{7a}), 137.38 (s, C⁷), 139.65 (s, C²), 140.25 (s, C¹),

151.31 (s, C^{4'}). ¹⁵N NMR (61 MHz, DMSO-*d*₆, δ, ppm): 144.79 (s, N¹), 155.43 (s, N^{3'}), 303.13 (s, N^{2'}). MS (EI, 70 eV), *m/z* (*I*, %): 294 (M⁺, 100), 157 (86), 130 (64). HRMS (ESI-MS), *m/z*: 295.1203 [M+H]⁺ (calc. for C₁₆H₁₅N₄O₂, *m/z*: 295.1190).

2-Methyl-3-[[2-(*p*-tolyl)hydrazineylidene]methyl]-1*H*-indole (2b). Yield 61%, m.p. 143–144 °C. ¹H NMR (600 MHz, DMSO-*d*₆, δ, ppm): δ 2.21 (s, 3H, CH₃), 2.51 (s, 3H, C²CH₃), 6.94 (d, 2H, *J* = 7.9 Hz, H^{4'}), 7.03 (d, 2H, *J* = 8.1 Hz, H^{5'}), 7.10 (dd, *J* = 5.9, 3.1 Hz, 2H, H⁵, H⁶), 7.31 (dd, *J* = 5.6, 3.4 Hz, 1H, H⁷), 8.15 (s, 2H, H^{1'}, H⁴), 9.64 (br. s, 1H, N³H), 11.23 (s, 1H, N¹H). ¹³C NMR (151 MHz, DMSO-*d*₆, δ, ppm): 12.03 (s, CH₃), 20.73 (s, CH₃), 108.79 (s, C³), 111.14 (s, C⁷), 111.85 (s, C⁵), 120.25 (s, C⁵), 121.02 (s, C⁴), 121.77 (s, C⁶), 125.88 (s, C^{3a}), 126.24 (s, C⁷), 129.96 (s, C^{6'}), 134.61 (s, C^{1'}), 136.08 (s, C^{7a}), 136.76 (s, C²), 144.58 (s, C^{4'}). ¹⁵N NMR (61 MHz, DMSO-*d*₆, δ, ppm): 140.1 (s, N^{3'}), 140.5 (s, N¹), 311.7 (s, N^{2'}). MS (EI, 70 eV), *m/z* (*I*, %): 263 (M⁺, 100), 157 (68), 130 (41). HRMS (ESI-MS), *m/z*: 264.1506 [M+H]⁺ (calc. for C₁₇H₁₈N₃, *m/z*: 264.1495).

3-[[2-(4-Fluorophenyl)hydrazineylidene]methyl]-2-methyl-1*H*-indole (2c). Yield 68%, m.p. 133–134 °C. ¹H NMR (600 MHz, DMSO-*d*₆, δ, ppm): 2.51 (s, 3H, CH₃), 7.02 – 6.98 (m, 2H, H⁵, H⁶), 7.11 – 7.05 (m, 4H, H^{5'}, H^{6'}), 7.33 – 7.29 (m, 1H, H⁷), 8.14 – 8.11 (m, 1H, H⁴), 8.15 (s, 1H, H^{1'}), 9.75 (s, 1H, N³H), 11.23 (s, 1H, N¹H). ¹³C NMR (151 MHz, DMSO-*d*₆, δ, ppm): 12.01 (CH₃), 108.65 (s, C³), 111.16 (s, C⁷), 111.83 (s, C⁵), 120.98 (s, C⁵), 121.81 (s, C⁴), 122.34 (s, C⁶), 125.84 (s, C^{3a}), 126.75 (s, C⁷), 128.40 (s, C^{6'}), 135.17 (s, C^{1'}), 136.07 (s, C^{7a}), 136.98 (s, C²), 143.52 (s, C^{4'}). ¹⁵N NMR (61 MHz, DMSO-*d*₆, δ, ppm): 142.2 (s, N^{3'}), 147.4 (s, N¹), 315.2 (s, N^{2'}). ¹⁹F NMR (565 MHz, DMSO-*d*₆, δ, ppm): -127.76 (s). MS (EI, 70 eV), *m/z* (*I*, %): 267 (M⁺, 100), 157 (69), 130 (51). HRMS (ESI-MS), *m/z*: 268.1255 [M+H]⁺ (calc. for C₁₆H₁₅FN₃, *m/z*: 268.1245).

Reaction of quinazoline 1 with hydrazones 2a-c (general procedure). A mixture of quinazoline **1** (0.5 mmol) and the corresponding hydrazone **2** (0.5 mmol) in trifluoroacetic acid (3.0 ml) was refluxed for 65–70 h. The solvent was removed under reduced pressure. Water (2.0 ml) was added to the residue; the solid was filtered off. The resulting product **3** was analytically pure and no additional purification was required.

4-(2-Methyl-3-[[2-(4-nitrophenyl)-2-trifluoroacetylhydrazineylidene]methyl]-1*H*-indol-5-yl)-1,4-dihydroquinazolin-3-ium trifluoroacetate (3a). Yield 68%, m.p. 143–144 °C. ¹H NMR (600 MHz, DMSO-*d*₆, δ, ppm): 2.29 (s, 3H, H⁸), 6.26 (s, 1H, H^{4''}), 7.13 (d, *J* = 7.6 Hz, 1H, H^{5''}), 7.20 (d, *J* = 7.9 Hz, 1H, H^{8''}), 7.24 (t, *J* = 7.5 Hz, 1H, H^{6''}), 7.37 (t, *J* = 7.6 Hz, 1H, H^{7''}), 7.50 (d, *J* = 8.0 Hz, 2H, H⁷), 7.53 (s, 1H, H⁴), 7.55 (d, *J* = 8.1 Hz, 1H, H⁶), 7.76 (s, 1H, H^{1'}), 7.87 (d, *J* = 9.0 Hz, 2H, H^{Ar}), 8.41 (d, *J* = 8.9 Hz, 2H, H^{Ar}), 8.56 (s, 1H, H^{2''}), 11.12 (s, 2H, N¹H, N^{3''}H), 12.39 (s, 1H, COOH). ¹³C NMR (151 MHz, DMSO-*d*₆, δ, ppm): 12.22 (s, C⁸), 54.61 (s, C^{4''}), 116.39 (q, *J* = 288.7 Hz, CF₃), 117.61 (s, C^{8''}), 119.67 (s, C³), 121.93 (s, C^{4a''}), 124.75 (s, 2C^{Ar}), 125.51 (s, 2C^{Ar}), 127.62 (s, C⁶), 127.86 (s, C^{6''}), 128.60 (s, C^{5''}), 128.72 (s, C⁷), 129.86 (s, C^{8a''}), 130.05 (s, C^{7''}), 130.24 (s, C^{3a}), 130.46 (s, C⁴), 133.64 (s, C^{7a}), 137.63 (s, C²), 141.26 (s, C^{1'}), 142.44 (s, C⁵), 144.73 (s, C^{Ar}), 146.25 (s, C^{Ar}), 149.20 (s, C^{2''}), 155.83 (q, ²*J* = 36.3 Hz, COCF₃), 158.39 (q, ²*J* = 31.6 Hz, COOH). ¹⁹F NMR (565 MHz, DMSO-*d*₆, δ, ppm): -

73.53 (s), -74.00 (s). ^{15}N NMR (61 MHz, DMSO- d_6 , δ , ppm): 126.1 (s, $\text{N}^{1''}$, $\text{N}^{3''}$), 215.5 (s, N^1 , N^3), 304.2 (s, N^2), 369.2 (s, NO_2). MS (EI, 70 eV), m/z (*I*, %): 520 (M^+ , 15), 390 (31), 131 (100). HRMS (ESI-MS), m/z : 521.1565 [$\text{M}+\text{H}$] $^+$ (calc. for $\text{C}_{26}\text{H}_{20}\text{F}_3\text{N}_6\text{O}_3$, m/z : 521.1543).

4-(2-Methyl-3-[[2-(*p*-tolyl)-2-trifluoroacetylhydrazineylidene]methyl]-1*H*-indol-5-yl)-1,4-dihydroquinazolin-3-ium trifluoroacetate (3b). Yield 71%, m.p. 118–119 °C.

^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 2.15 (s, 3H, H^8), 2.39 (s, 3H, H^{Ar}), 6.25 (s, 1H, $\text{H}^{4''}$), 7.13 (d, $J = 8.0$ Hz, 1H, $\text{H}^{5''}$), 7.20 (d, $J = 8.0$ Hz, 1H, $\text{H}^{8''}$), 7.24 (t, $J = 8.0$ Hz, 1H, $\text{H}^{6''}$), 7.42 – 7.30 (m, 4H, $\text{H}^{4,6,7,7''}$), 7.43-7.48 (m, 2H, H^{Ar}), 7.50-7.54 (m, 2H, H^{Ar}), 7.60 (s, 1H, H^1), 8.55 (s, 2H, $\text{H}^{2''}$), 11.06 (s, 2H, N^1H , $\text{N}^{3''}\text{H}$), 12.35 (s, 1H, COOH). ^{13}C NMR (101 MHz, DMSO- d_6 , δ , ppm): 11.24 (s, C^8), 20.57 (s, C^8), 54.14 (s, $\text{C}^{4''}$), 111.33 (q, $J = 284.6$ Hz, CF_3), 117.10 (s, C^3), 117.39 (s, 2C^{Ar}), 117.79 (s, $\text{C}^{8''}$), 121.45 (s, $\text{C}^{4\text{a}''}$), 122.55 (s, C^6), 124.36 (s, 2C^{Ar}), 126.64 (s, $\text{C}^{6''}$), 127.35 (s, $\text{C}^{5''}$), 128.15 (s, C^7), 129.33 (s, $\text{C}^{8\text{a}''}$), 129.71 (s, $\text{C}^{3\text{a}}$), 130.44 (s, $\text{C}^{7''}$), 130.97 (s, $\text{C}^{7\text{a}}$), 132.98 (s, C^4), 136.19 (s, C^2), 136.95 (s, C^1), 137.35 (s, C^5), 138.86 (s, C^{Ar}), 141.84 (s, $\text{C}^{2''}$), 148.70 (s, C^{Ar}), 155.67 – 154.96 (m, COCF_3), 158.13 – 157.77 (m, COOH). ^{15}N NMR (61 MHz, DMSO- d_6 , δ , ppm): 128.3 (s, $\text{N}^{1''}$, $\text{N}^{3''}$), 221.7 (s, N^1 , N^3), 300.6 (s, N^2). ^{19}F NMR (376 MHz, DMSO- d_6 , δ , ppm): -73.65 (s), -74.00 (s). MS (EI, 70 eV), m/z (*I*, %): 489 (M^+ , 38), 359 (32), 131 (100). HRMS (ESI-MS), m/z : 490.1872 [$\text{M}+\text{H}$] $^+$ (calc. for $\text{C}_{27}\text{H}_{23}\text{F}_3\text{N}_5\text{O}$, m/z : 490.1849).

4-(3-[[2-(4-Fluorophenyl)-2-trifluoroacetylhydrazineylidene]methyl]-2-methyl-1*H*-indol-5-yl)-1,4-dihydroquinazolin-3-ium trifluoroacetate (3c). Yield 65%, m.p. 123–124 °C. ^1H NMR (400 MHz, DMSO- d_6 , δ , ppm): 2.16 (s, 3H, H^8), 6.25 (s, 1H, $\text{H}^{4''}$), 7.13 (d, $J = 8.0$ Hz, 1H, $\text{H}^{5''}$), 7.20 (d, $J = 8.0$ Hz, 1H, $\text{H}^{8''}$), 7.25 (t, $J = 8.0$ Hz, 1H, $\text{H}^{6''}$), 7.35 – 7.44 (m, 4H, $\text{H}^{4,6,7,7''}$), 7.50-7.55 (d.d, $J = 14.4$ Hz, $J = 2.8$ Hz, 2H, H), 7.56 (d, $J = 8.0$ Hz, 2H, H^{Ar}), 7.63 (s, 1H, H^1), 8.55 (s, 2H, $\text{H}^{2''}$), 11.08 (s, 2H, N^1H , $\text{N}^{3''}\text{H}$), 12.32 (s, 1H, COOH). ^{13}C NMR (101 MHz, DMSO- d_6 , δ , ppm): 11.14 (s, C^8), 54.14 (s, $\text{C}^{4''}$), 116.19 (q, $J = 286.3$ Hz, CF_3), 117.10 (s, $\text{C}^{8''}$), 117.54 (s, C^3), 121.44 (s, $\text{C}^{4\text{a}''}$), 126.64 (s, 2C^6 or 2C^5), 126.78 (s, 2C^6 or 2C^5), 127.37 (s, C^6), 128.09 (s, 2C^6 or 2C^5), 128.22 (s, 2C^6 or 2C^5), 128.87 (s, C^7), 129.35 (s, $\text{C}^{8\text{a}''}$), 129.56 (s, $\text{C}^{7''}$), 129.88 (s, $\text{C}^{3\text{a}}$), 130.33 (s, C^4), 130.97 (s, C^{Ar}), 133.03 (s, C^{Ar}), 135.77 (s, $\text{C}^{7\text{a}}$), 136.49 (s, C^2), 139.16 (s, C^1), 141.86 (s, C^5), 148.69 (s, $\text{C}^{2''}$), 155.64 – 154.97 (m, COCF_3), 158.18 – 157.59 (m, COOH). ^{19}F NMR (376 MHz, DMSO- d_6 , δ , ppm): -73.55 (s), -74.01 (s), -114.01 (s). ^{15}N NMR (61 MHz, DMSO- d_6 , δ , ppm): 127.5 (s, $\text{N}^{1''}$, $\text{N}^{3''}$), 218.1 (s, N^1 , N^3), 302.5 (s, N^2). MS (EI, 70 eV), m/z (*I*, %): 493 (M^+ , 35), 363 (18), 131 (100). HRMS (ESI-MS), m/z : 494.1619 [$\text{M}+\text{H}$] $^+$ (calc. for $\text{C}_{26}\text{H}_{19}\text{F}_4\text{N}_5\text{O}$, m/z : 494.1598).

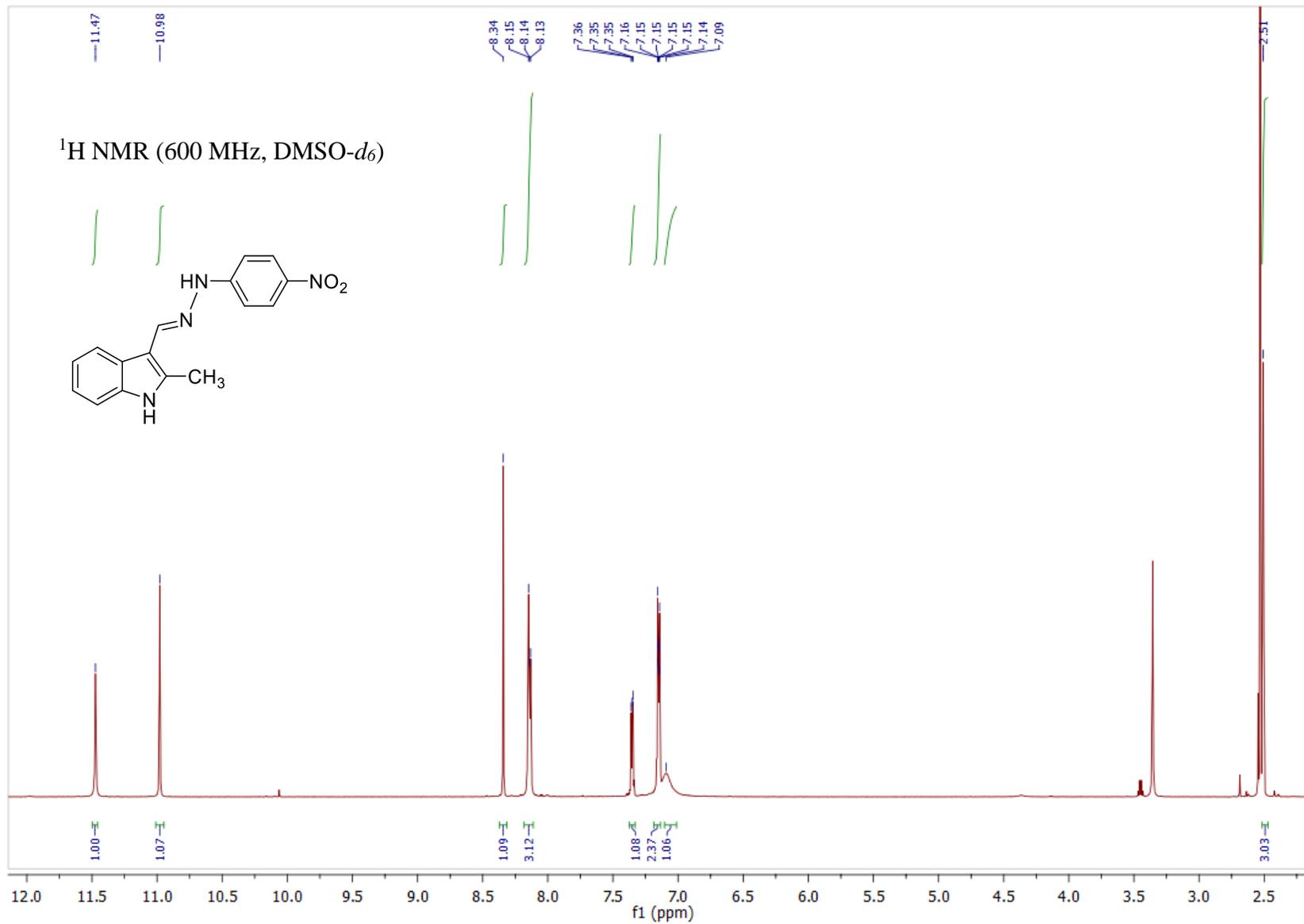


Figure S1

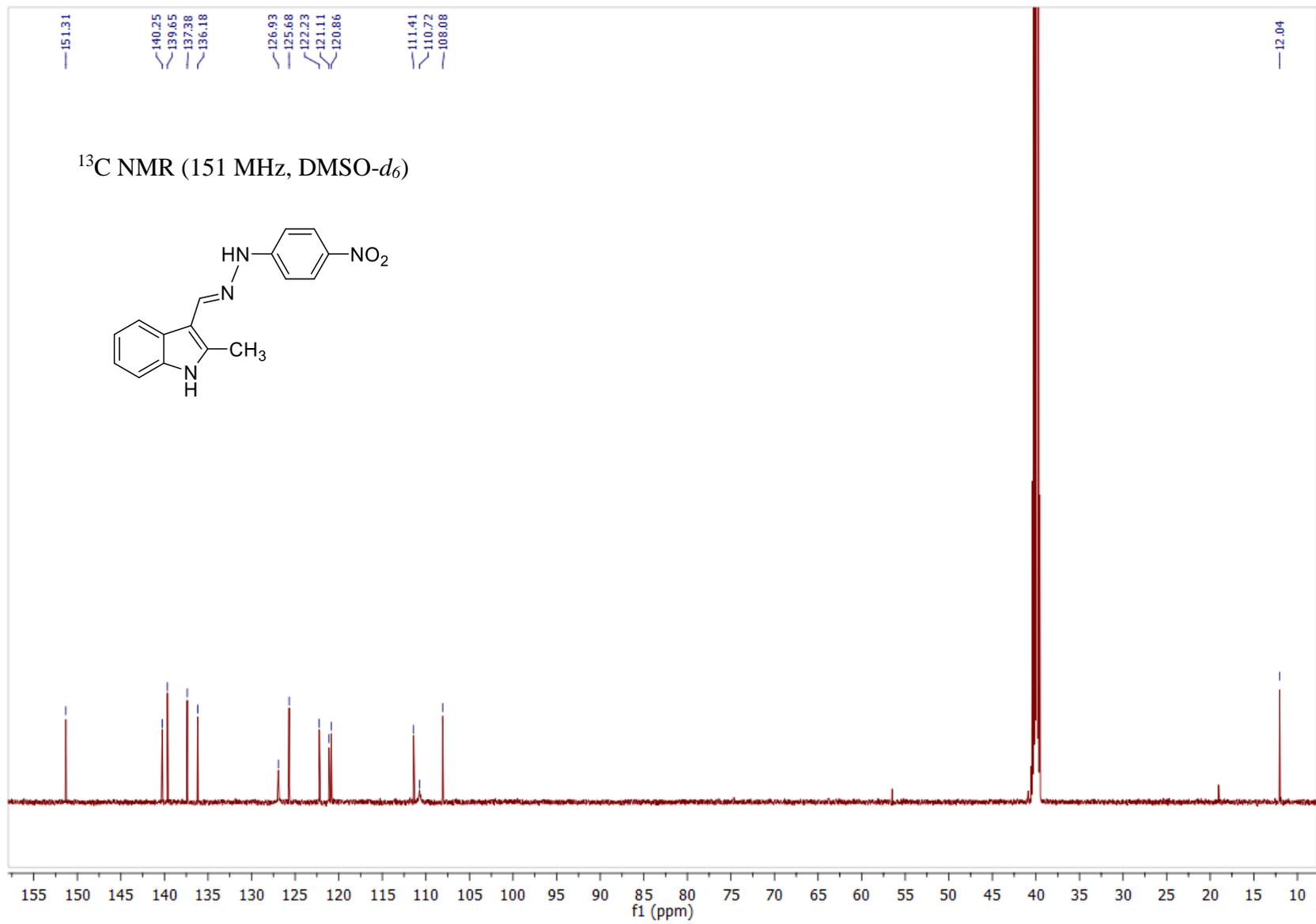


Figure S2

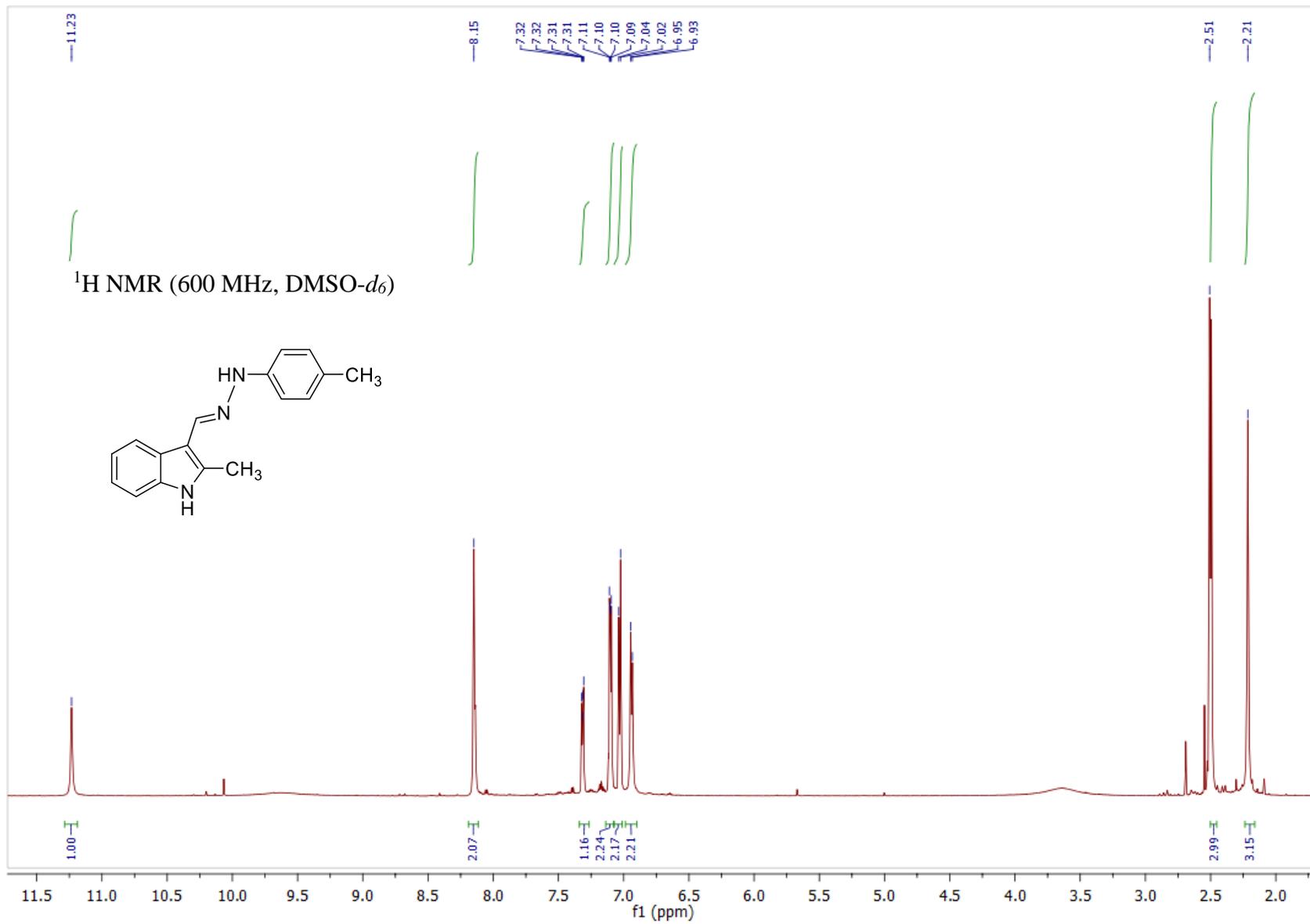


Figure S3

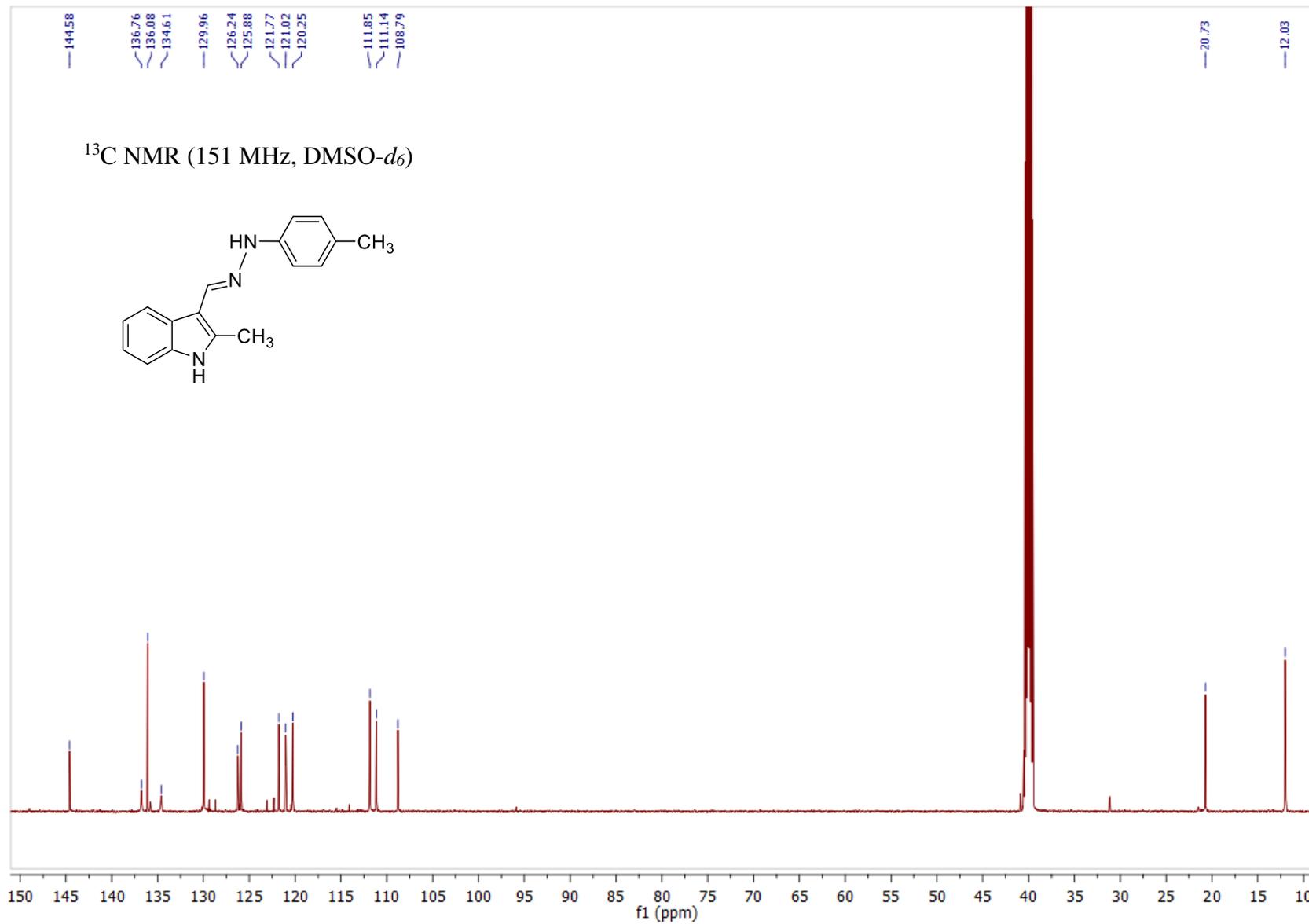


Figure S4

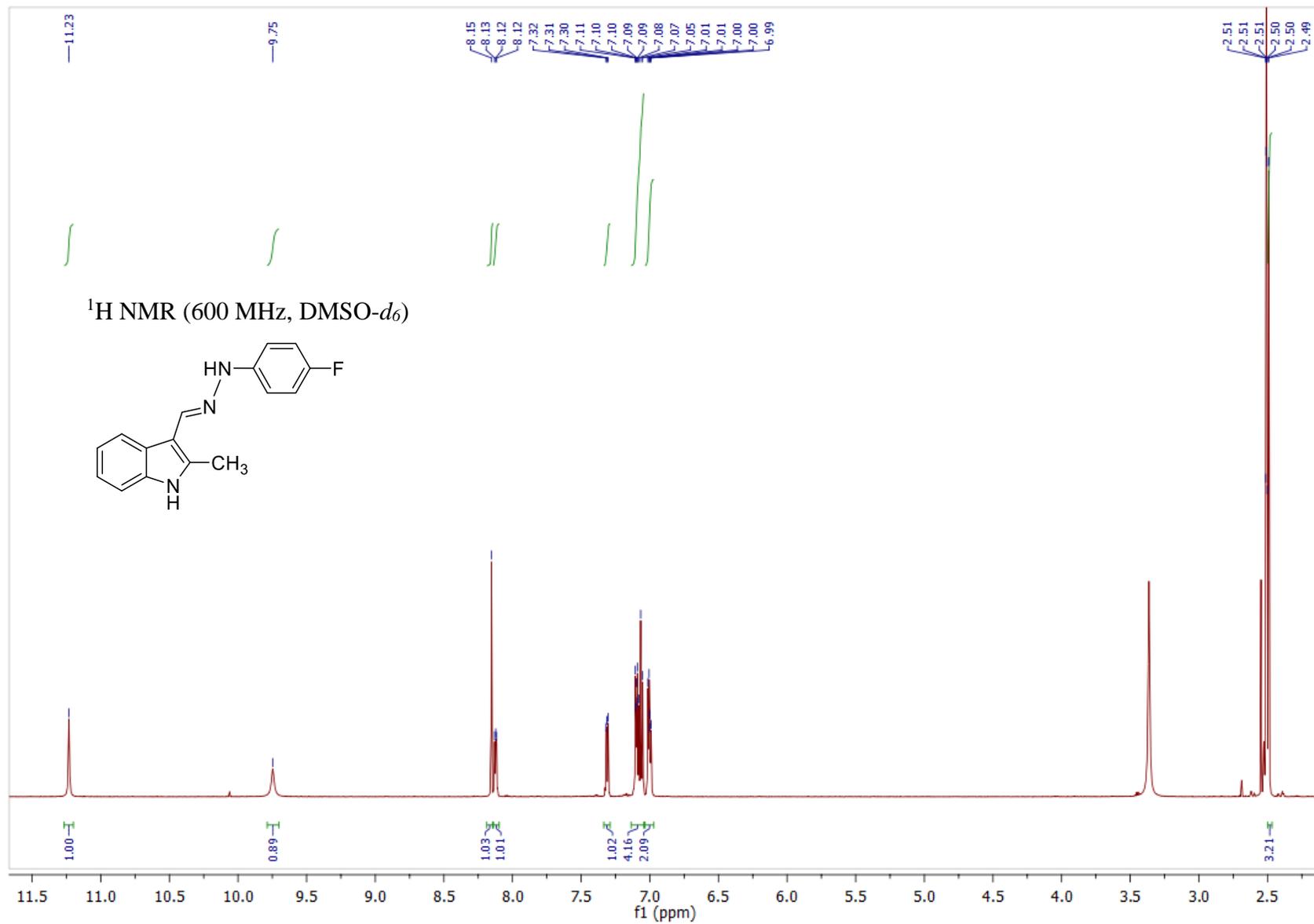


Figure S5

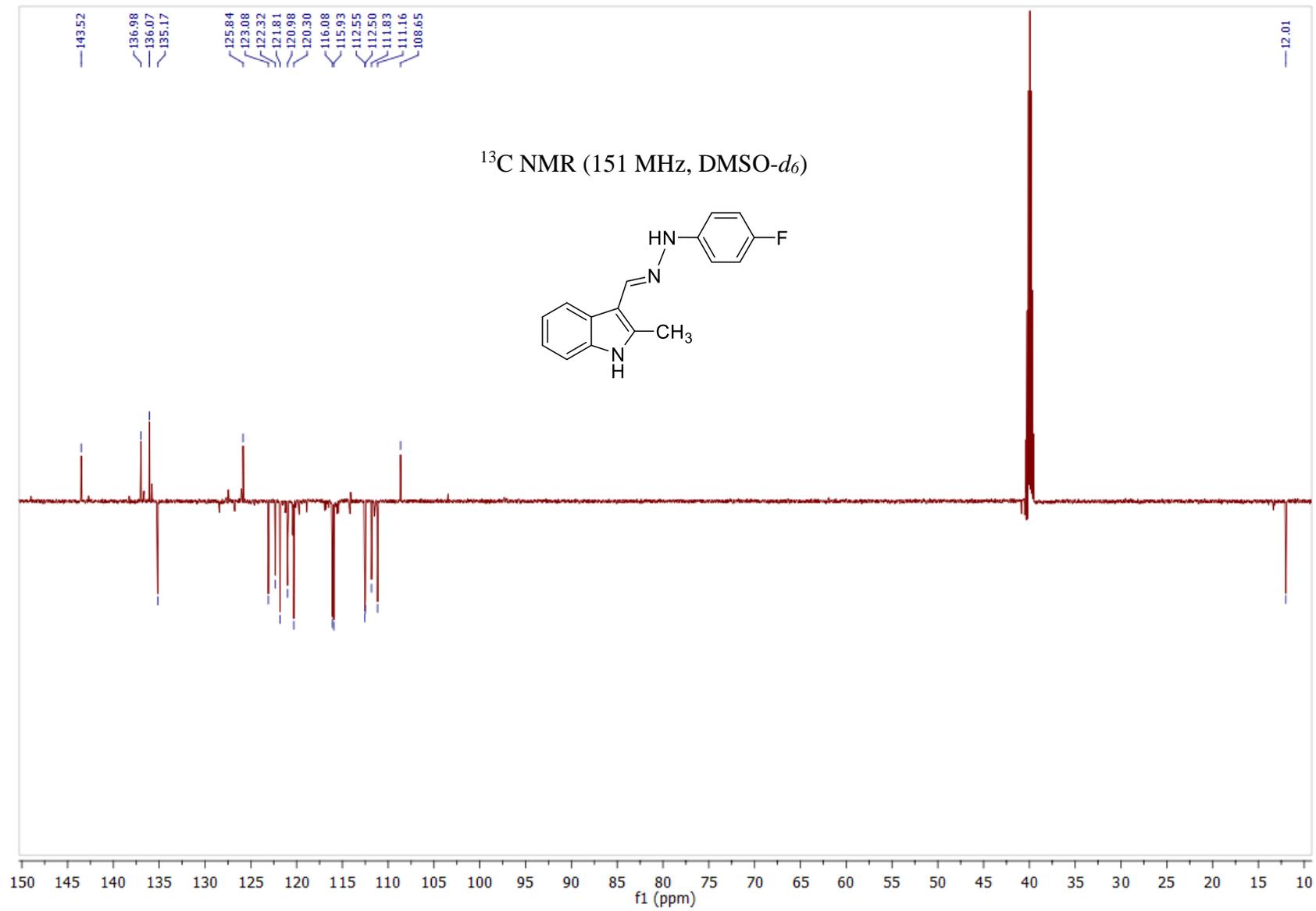


Figure S6

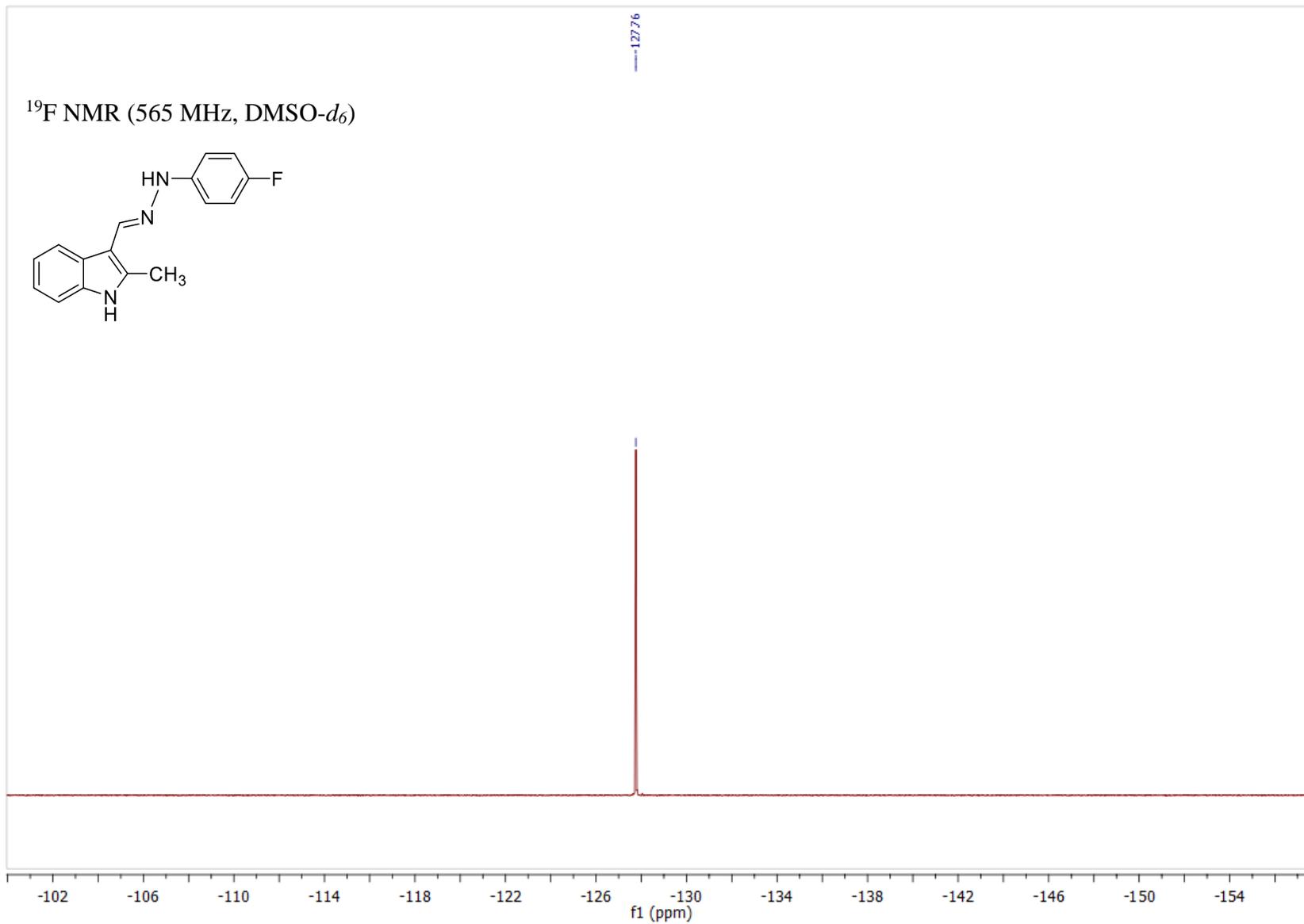


Figure S7

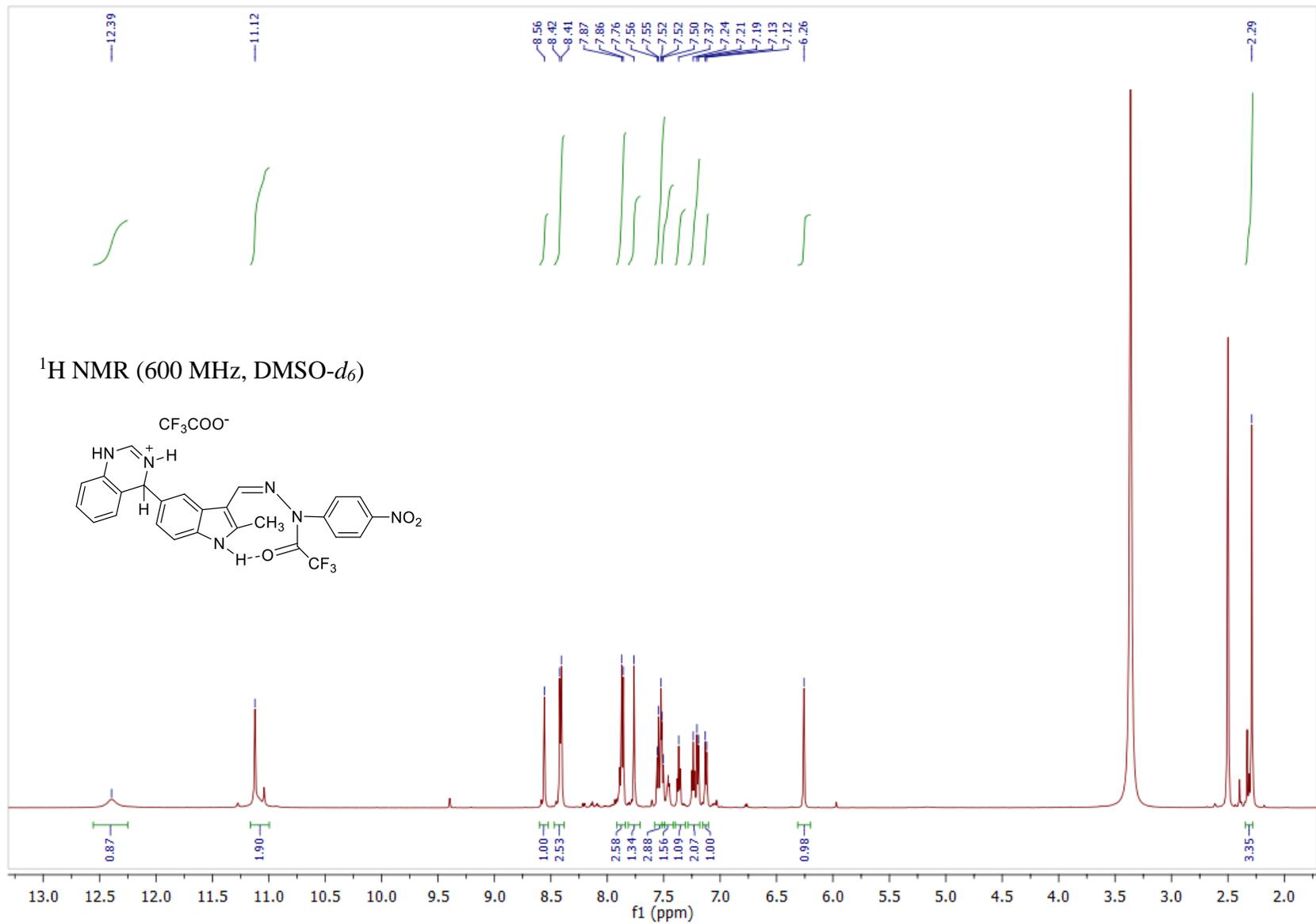


Figure S8

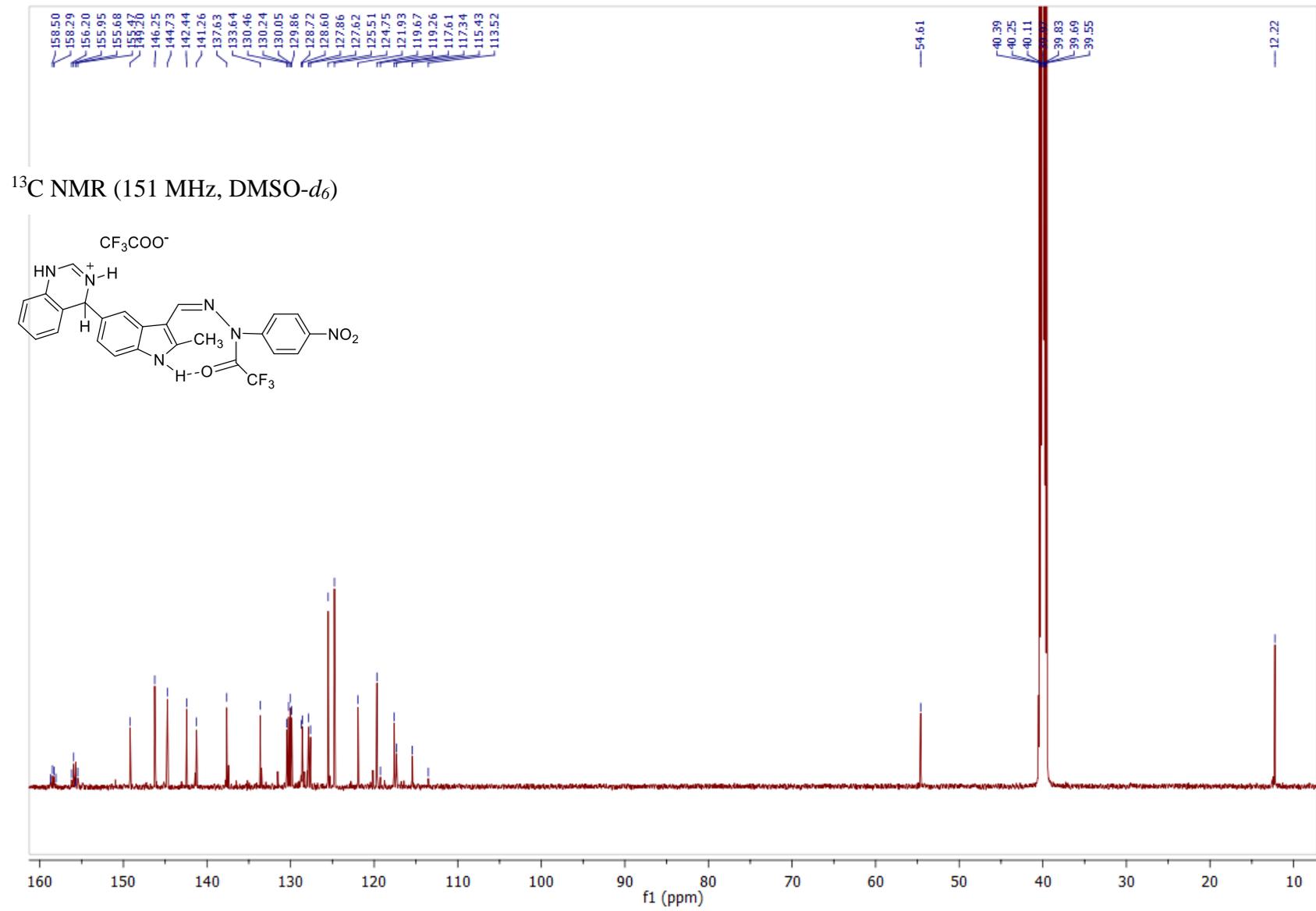


Figure S9

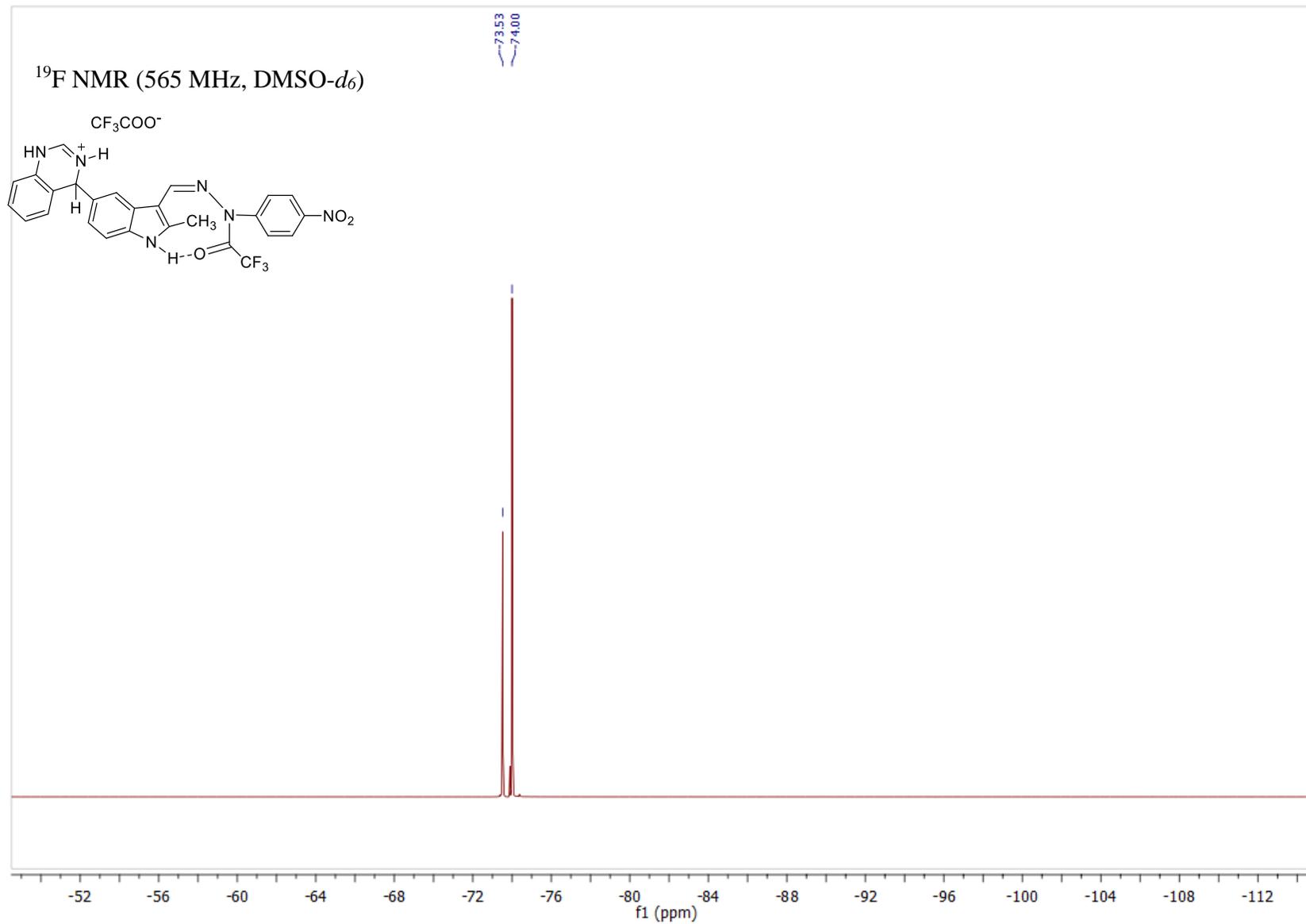


Figure S10

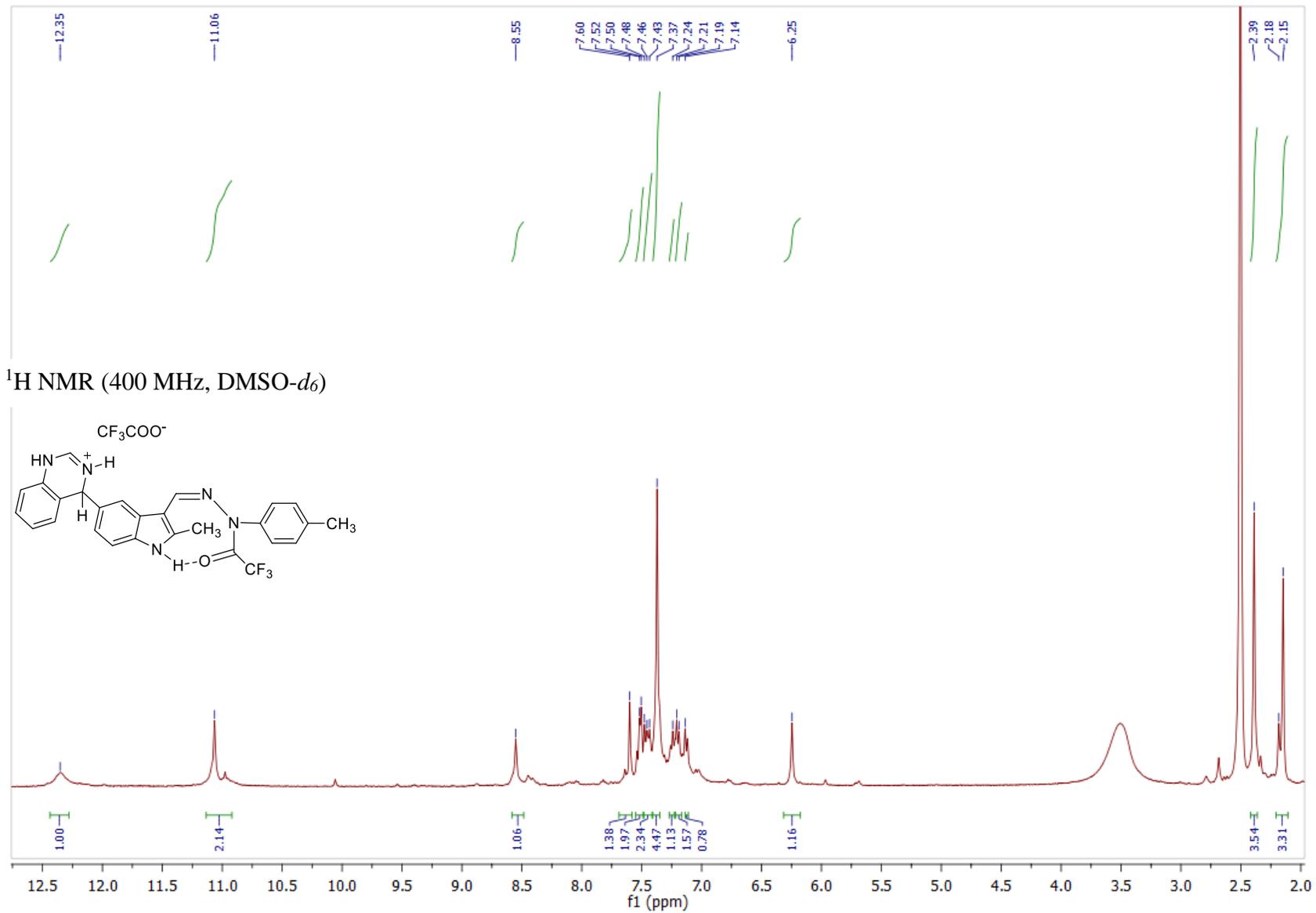


Figure S11

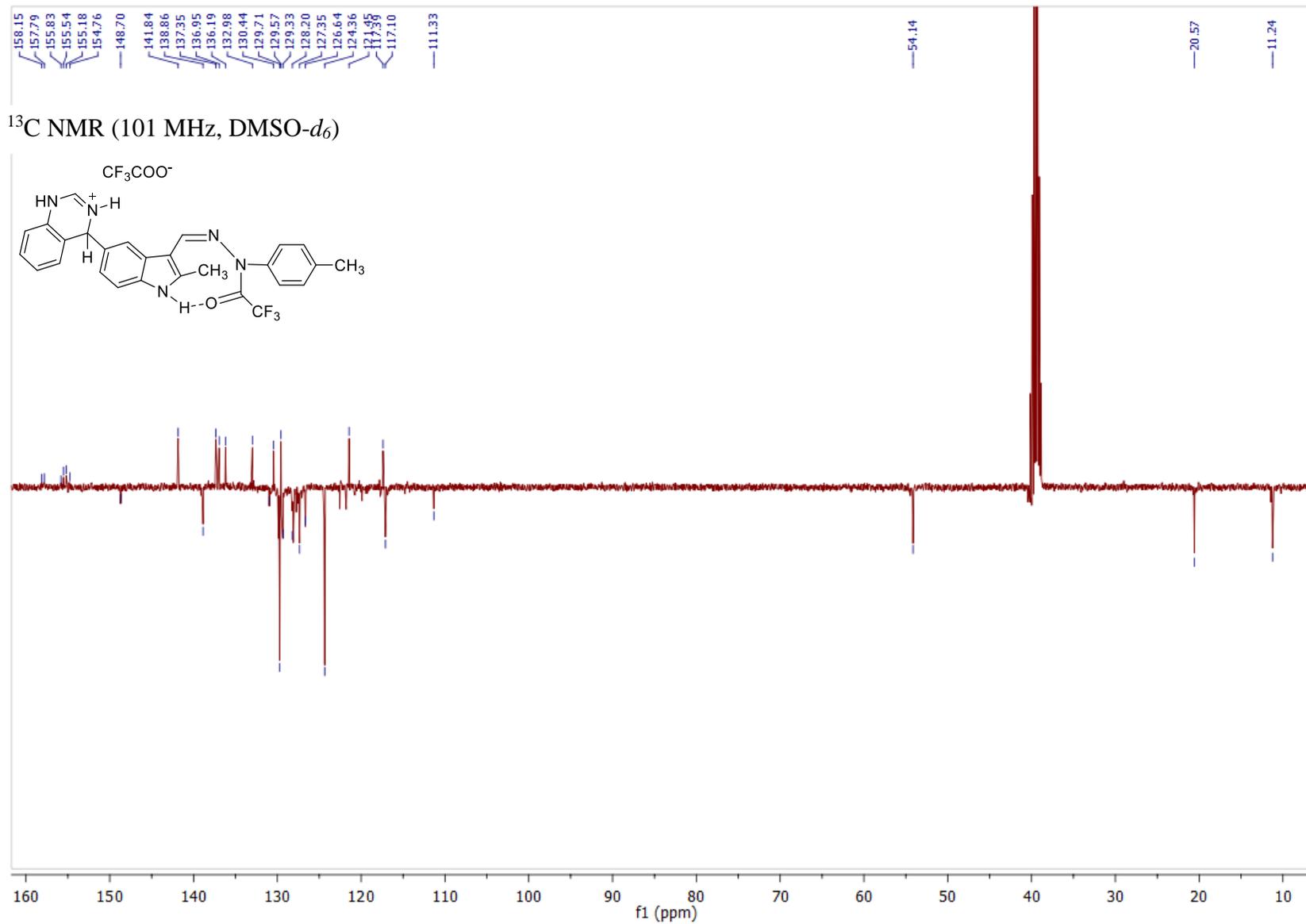


Figure S12

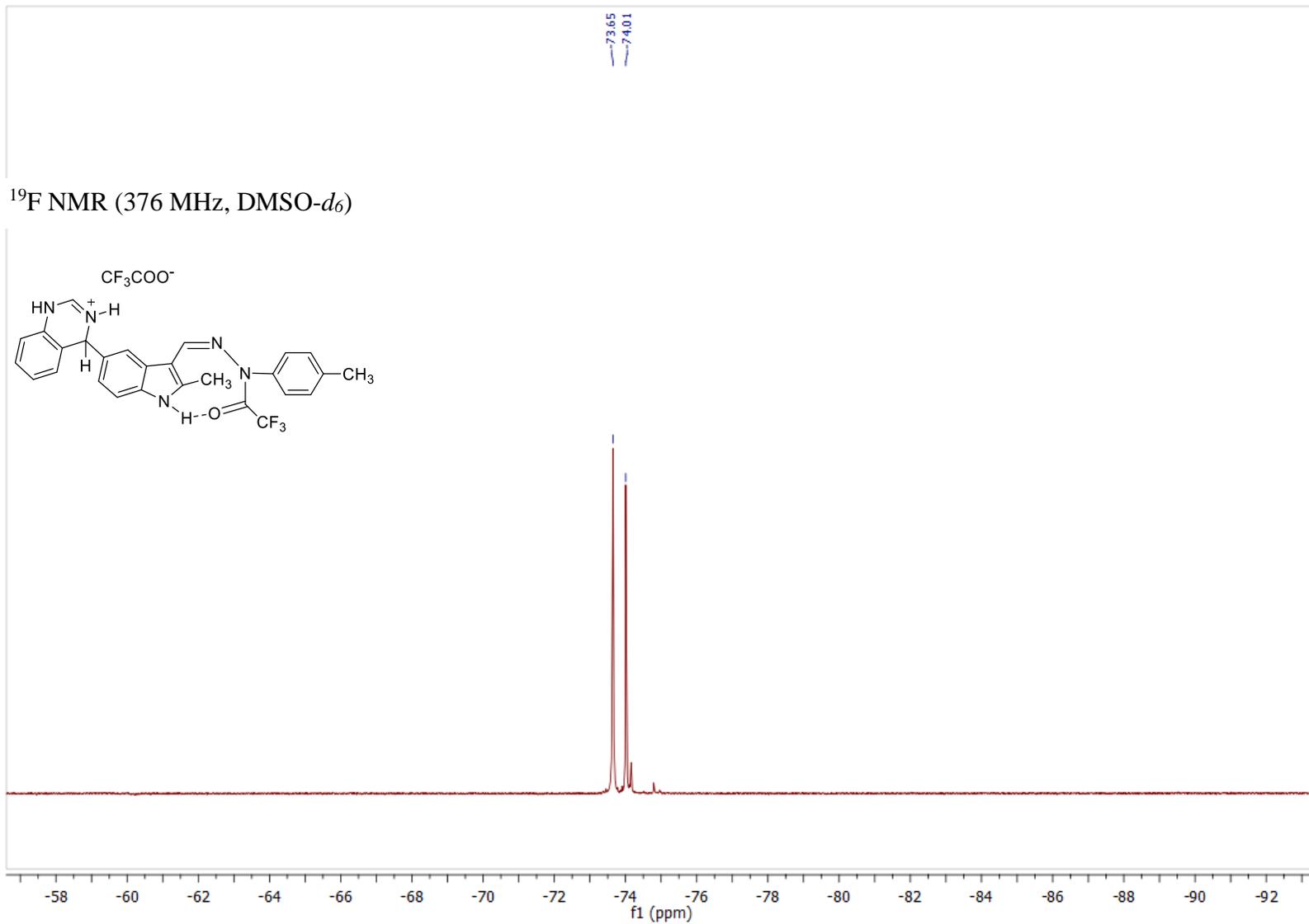


Figure S13

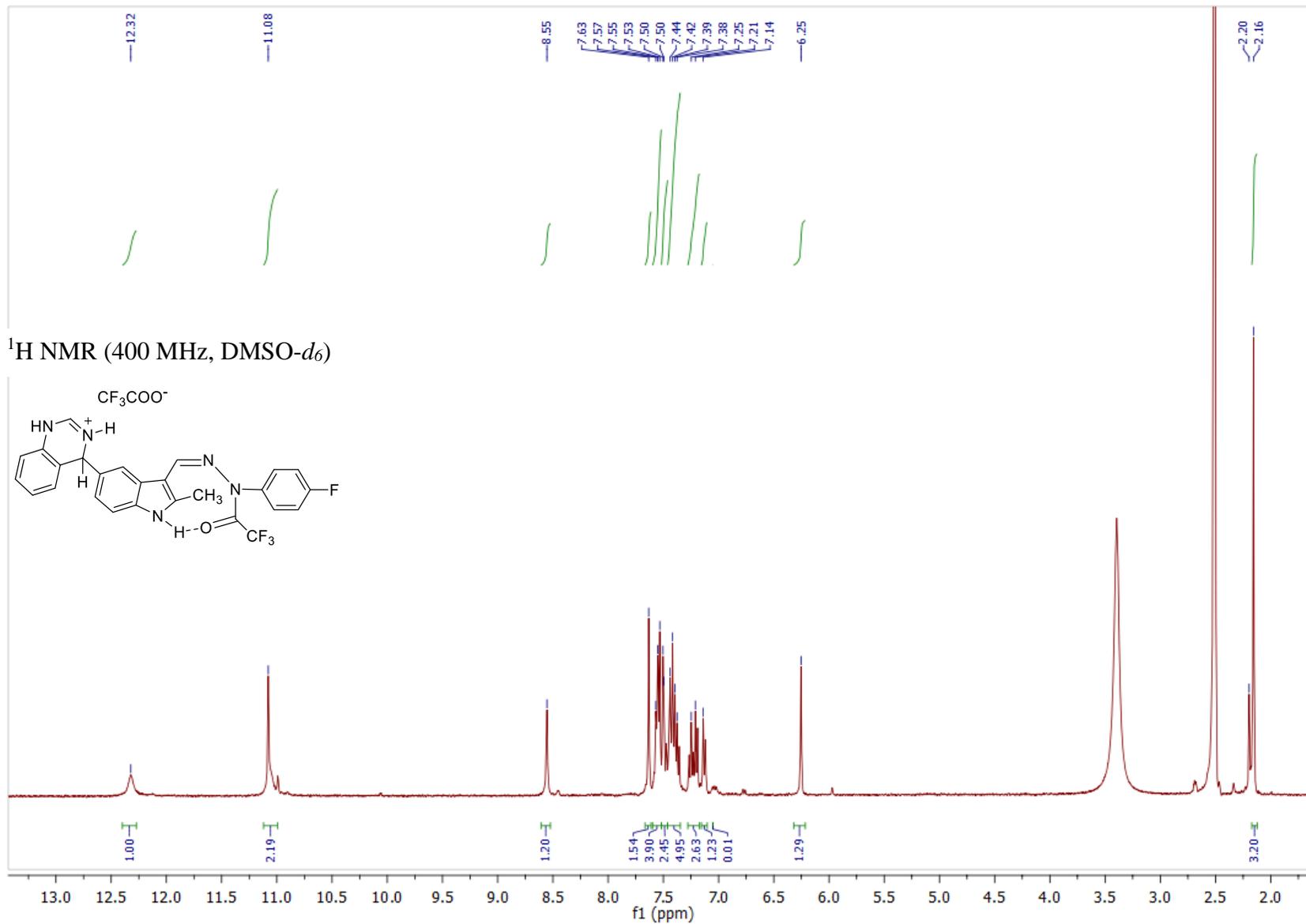


Figure S14

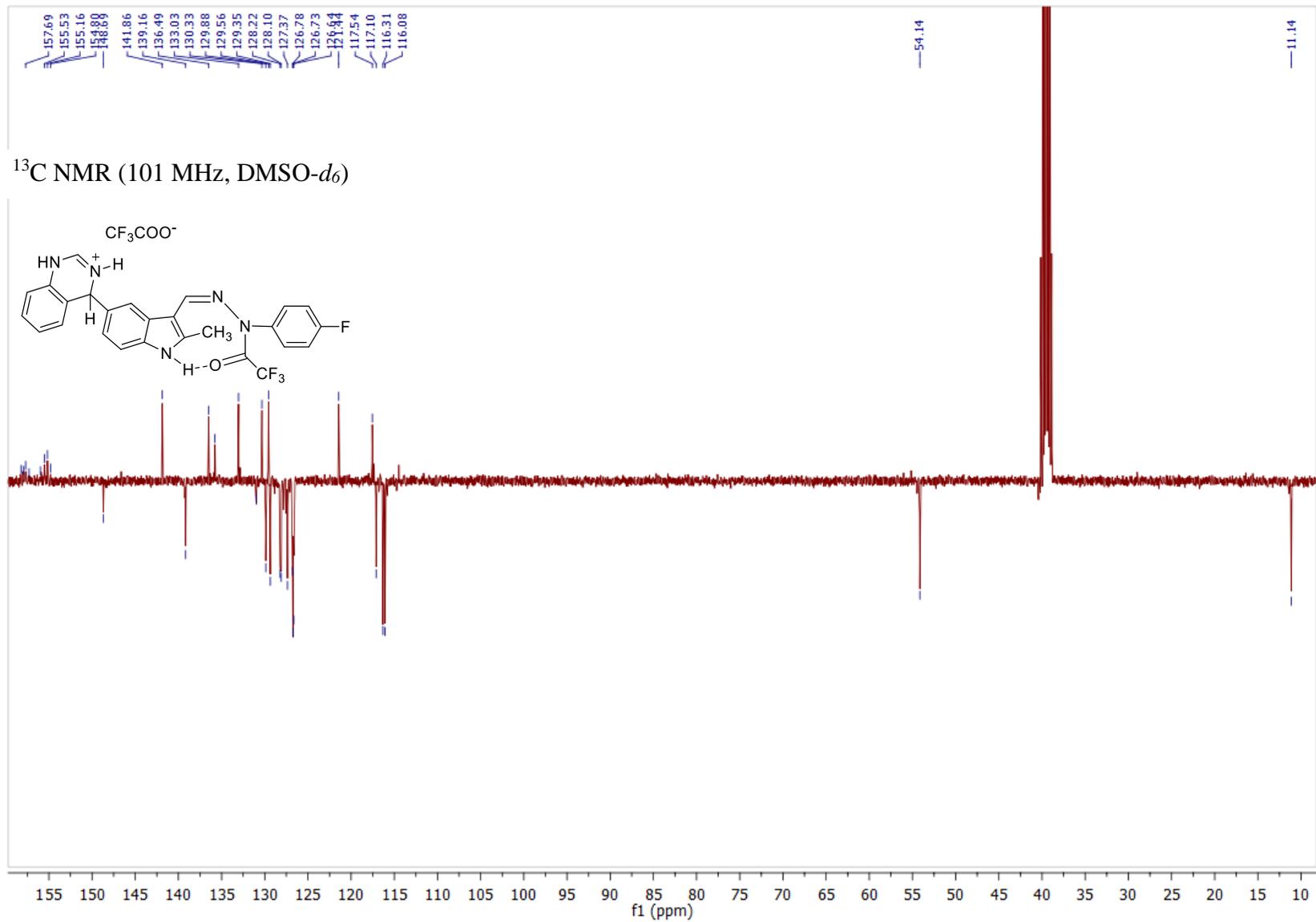


Figure S15

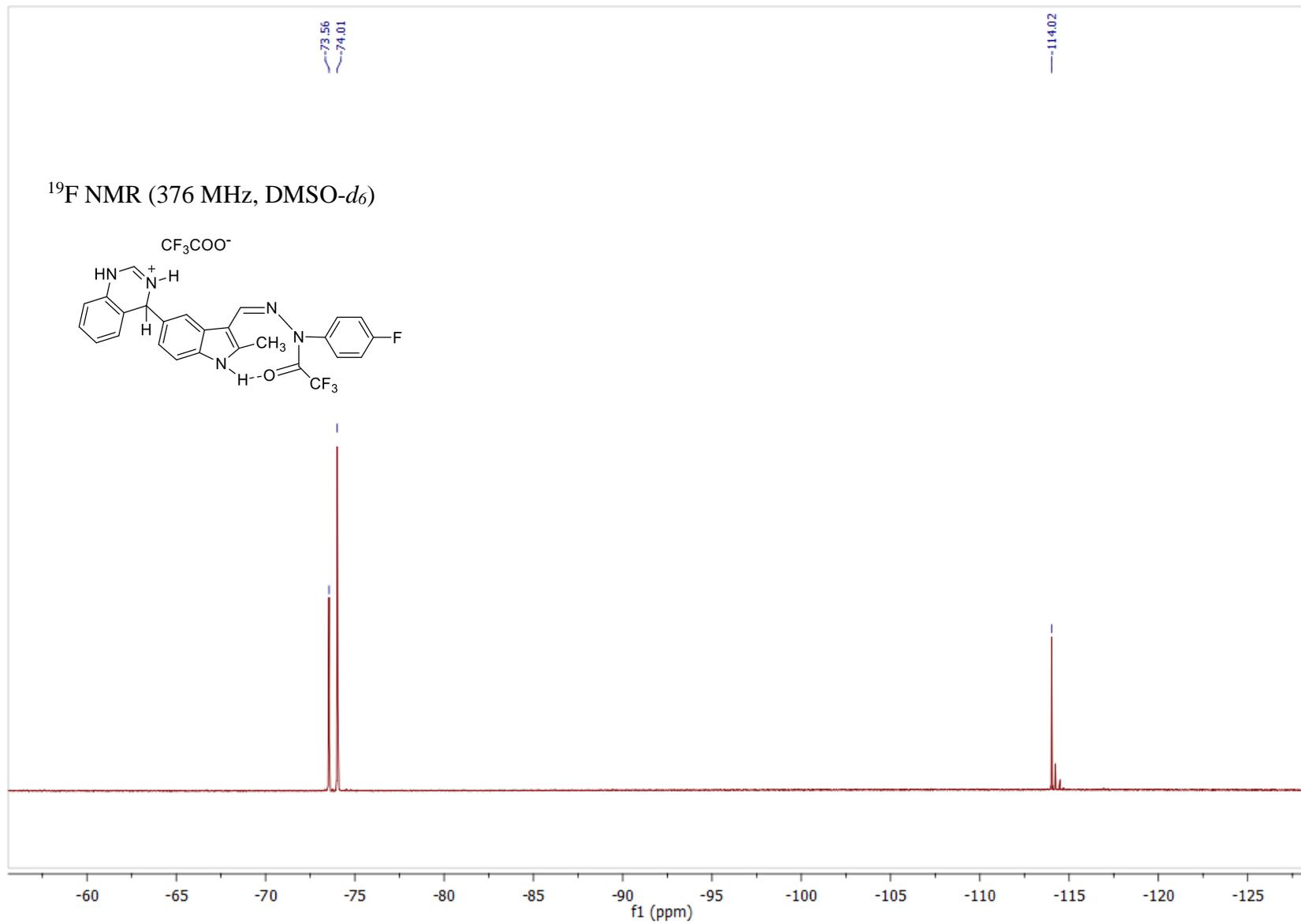


Figure S16