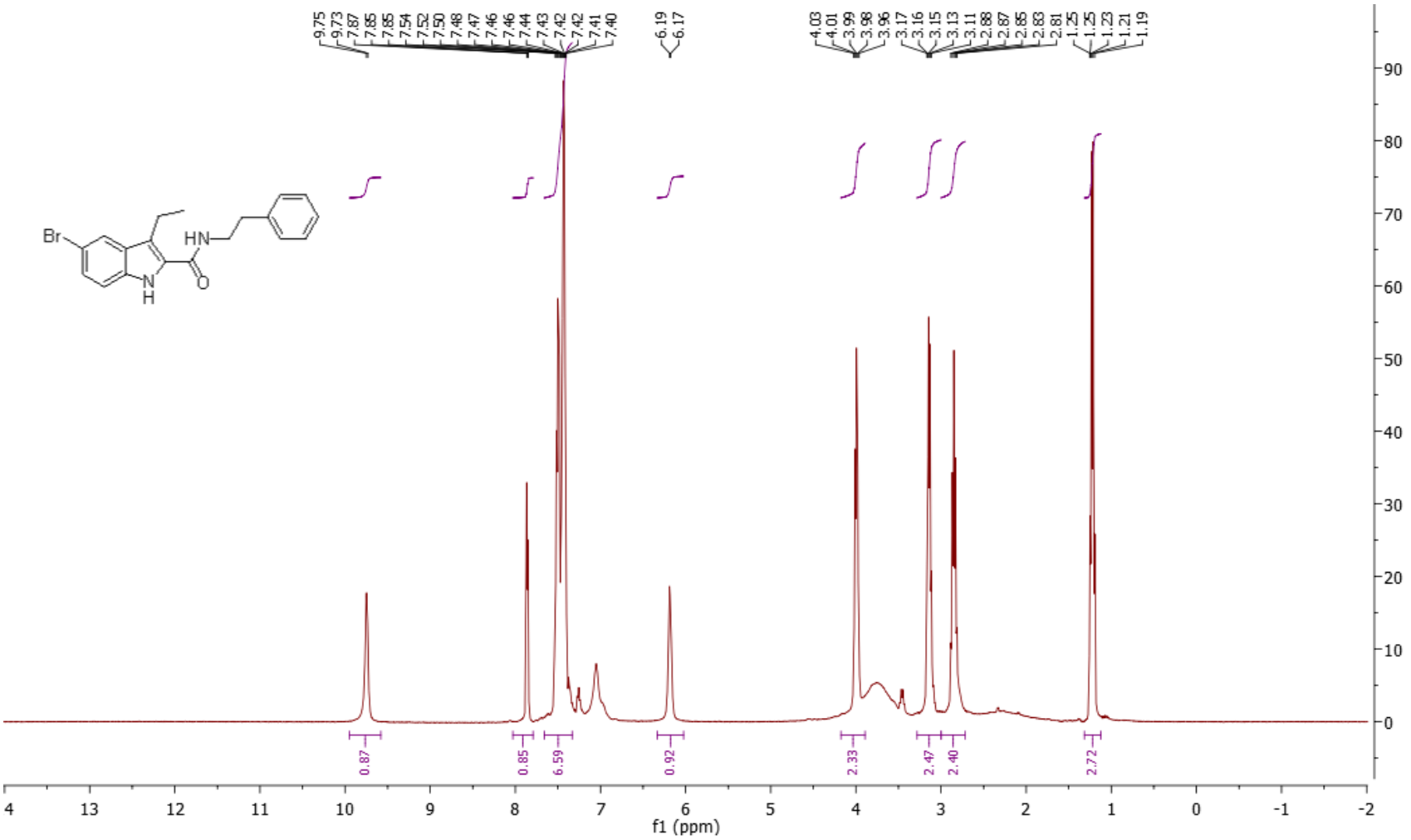
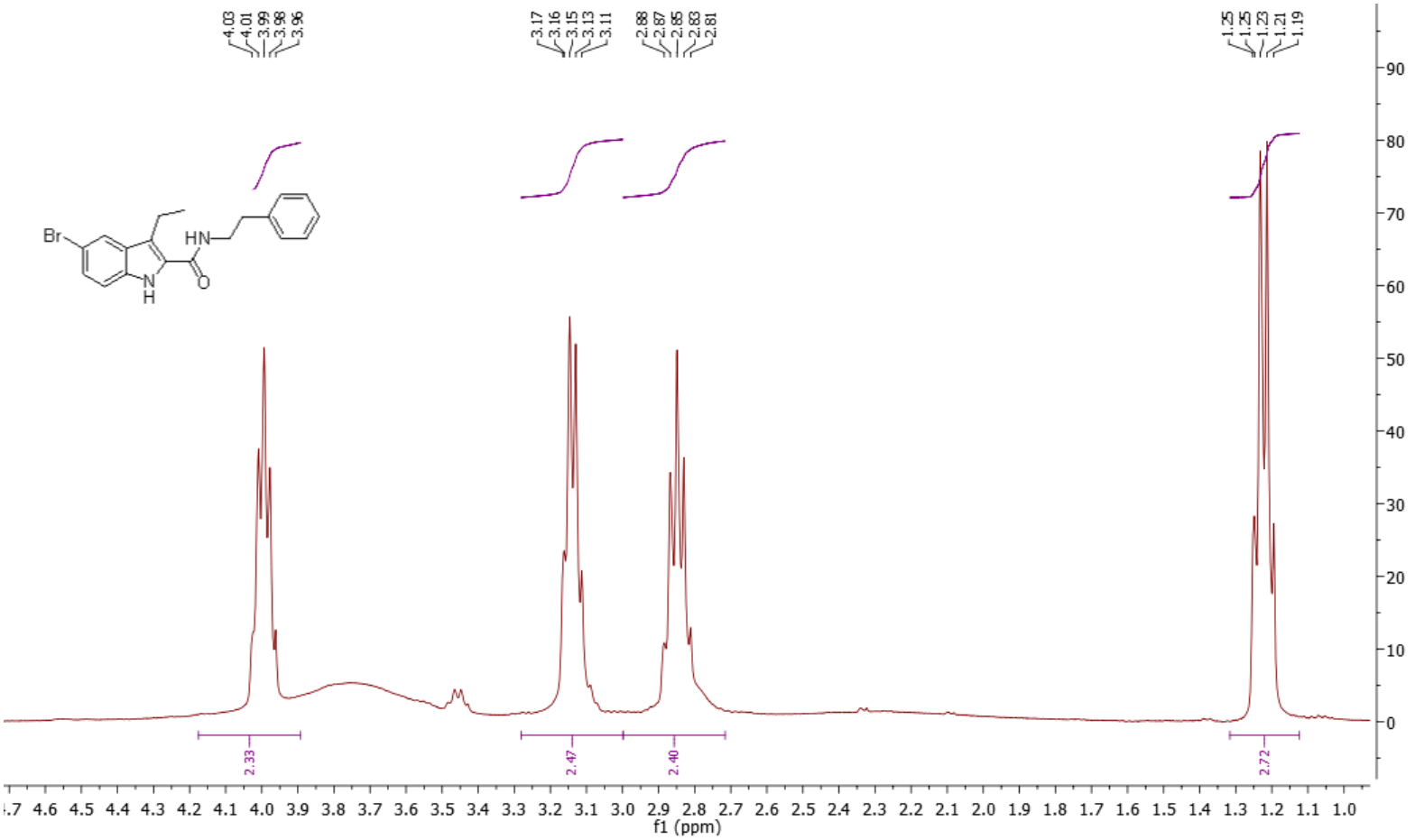
5a



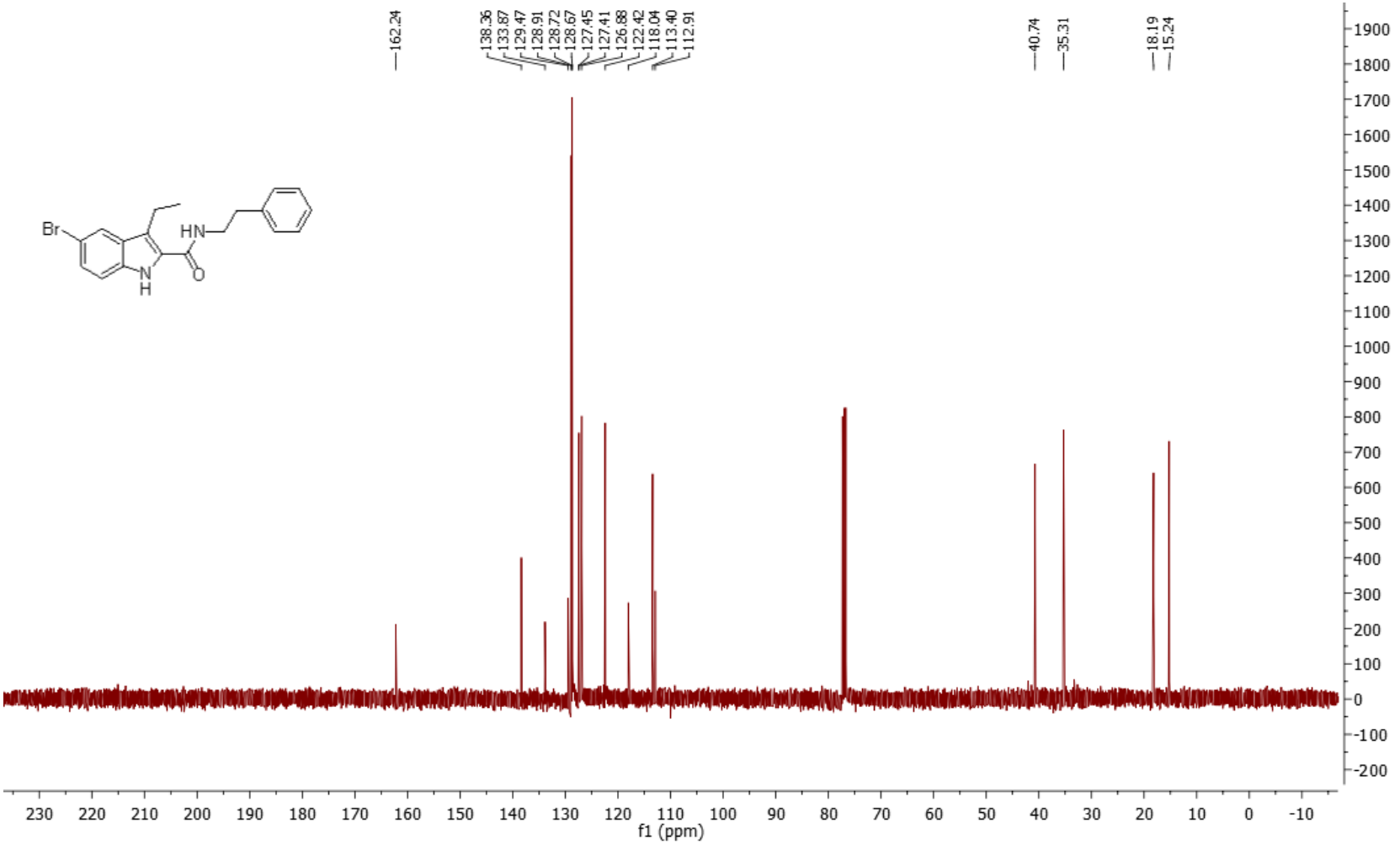
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.74 (s, 1H), 8.03 – 7.79 (m, 1H), 7.66 – 7.33 (m, 7H), 6.18 (s, 1H), 3.99 (q, J = 6.6 Hz, 2H), 3.14 (t, J = 7.3, 6.8 Hz, 2H), 2.85 (q, J = 7.6, 7.1 Hz, 2H), 1.22 (t, J = 7.6, 7.0 Hz, 3H).

5a



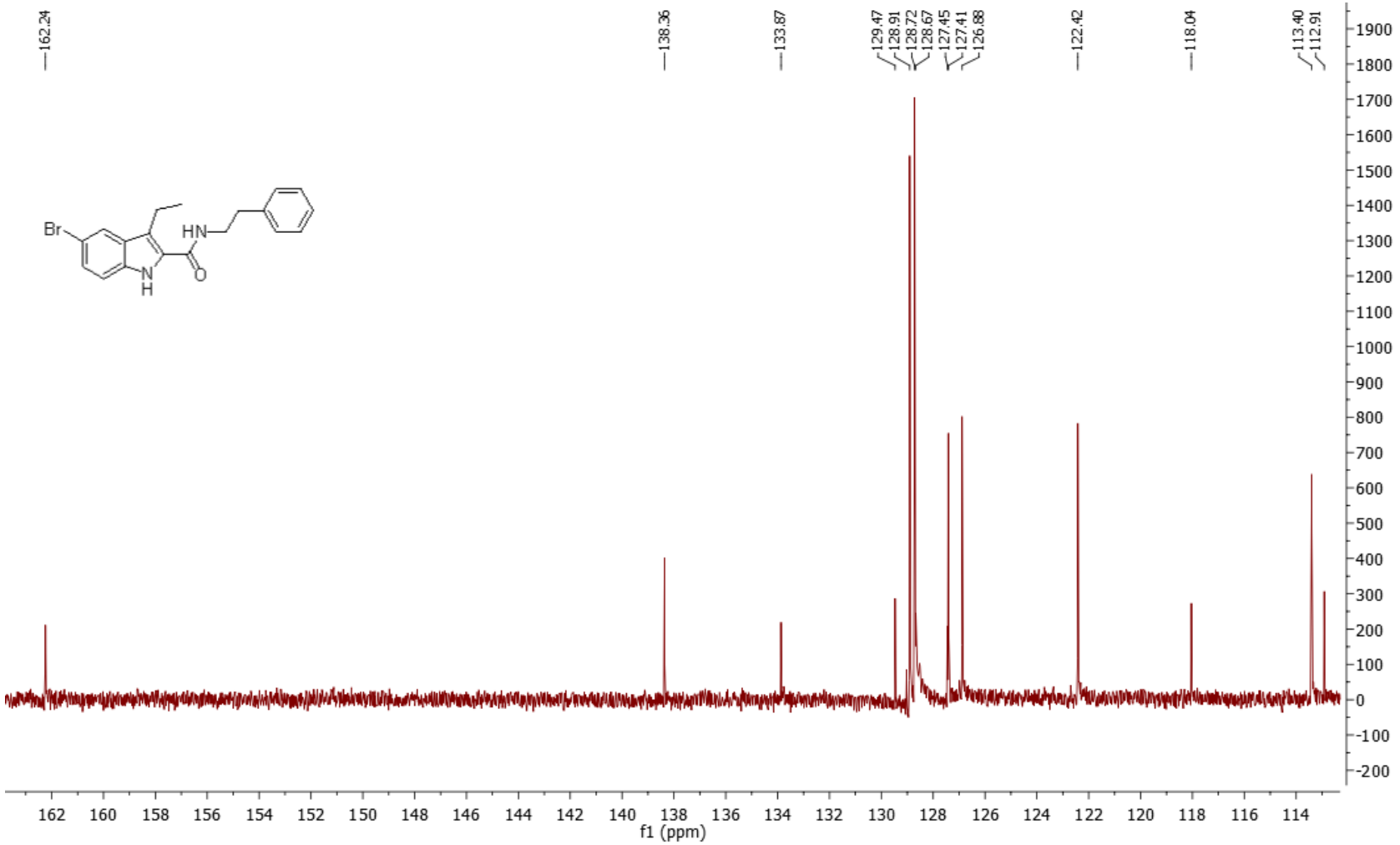
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.74 (s, 1H), 8.03 – 7.79 (m, 1H), 7.66 – 7.33 (m, 7H), 6.18 (s, 1H), 3.99 (q, J = 6.6 Hz, 2H), 3.14 (t, J = 7.3, 6.8 Hz, 2H), 2.85 (q, J = 7.6, 7.1 Hz, 2H), 1.22 (t, J = 7.6, 7.0 Hz, 3H).

5a



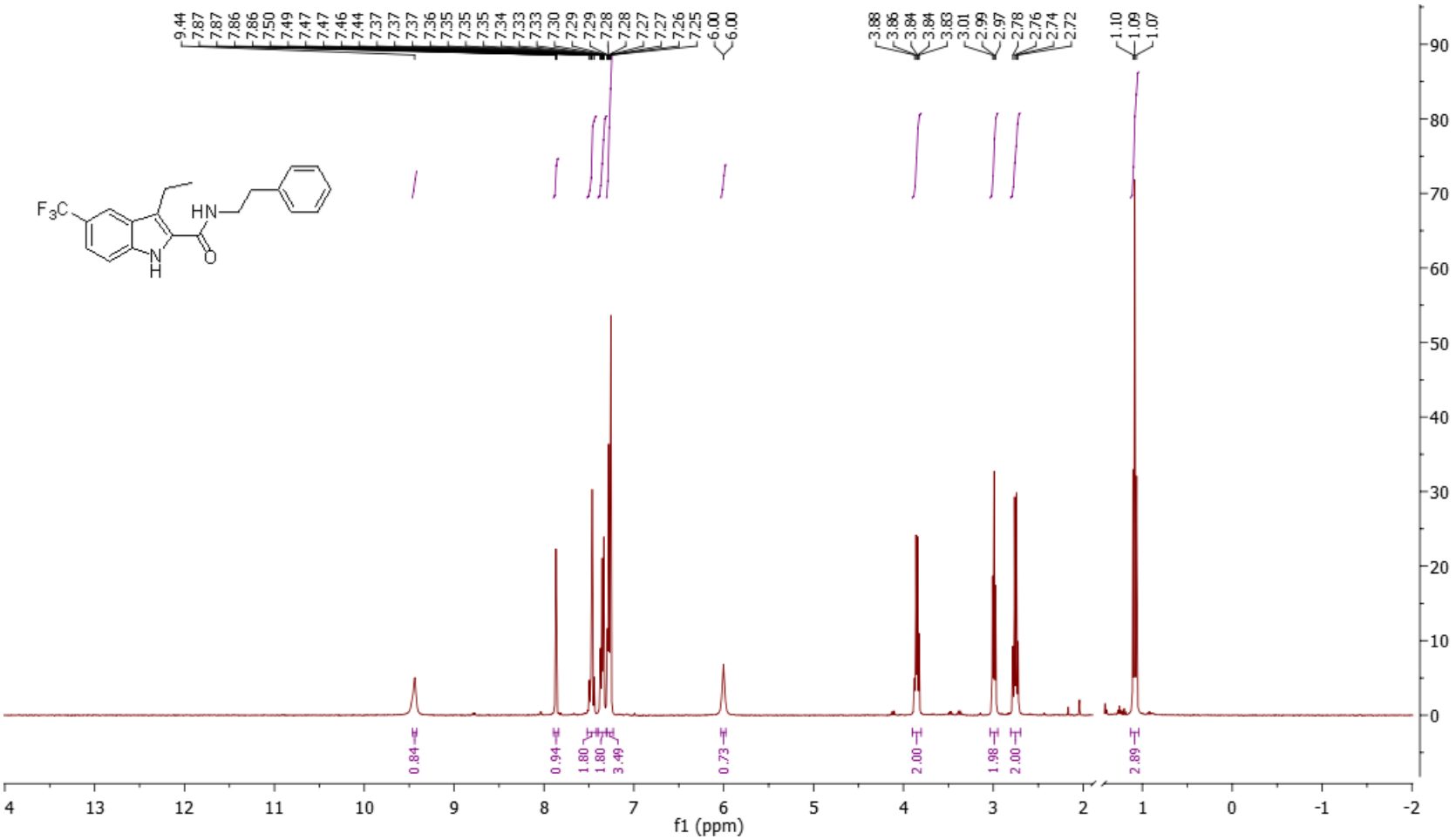
^{13}C NMR (101 MHz, cdcl$_3$) δ 162.24, 138.36, 133.87, 129.47, 128.91, 128.72, 127.45, 127.41, 126.88, 122.42, 118.04, 113.40, 112.91, 40.74, 35.31, 18.19, 15.24.

5a



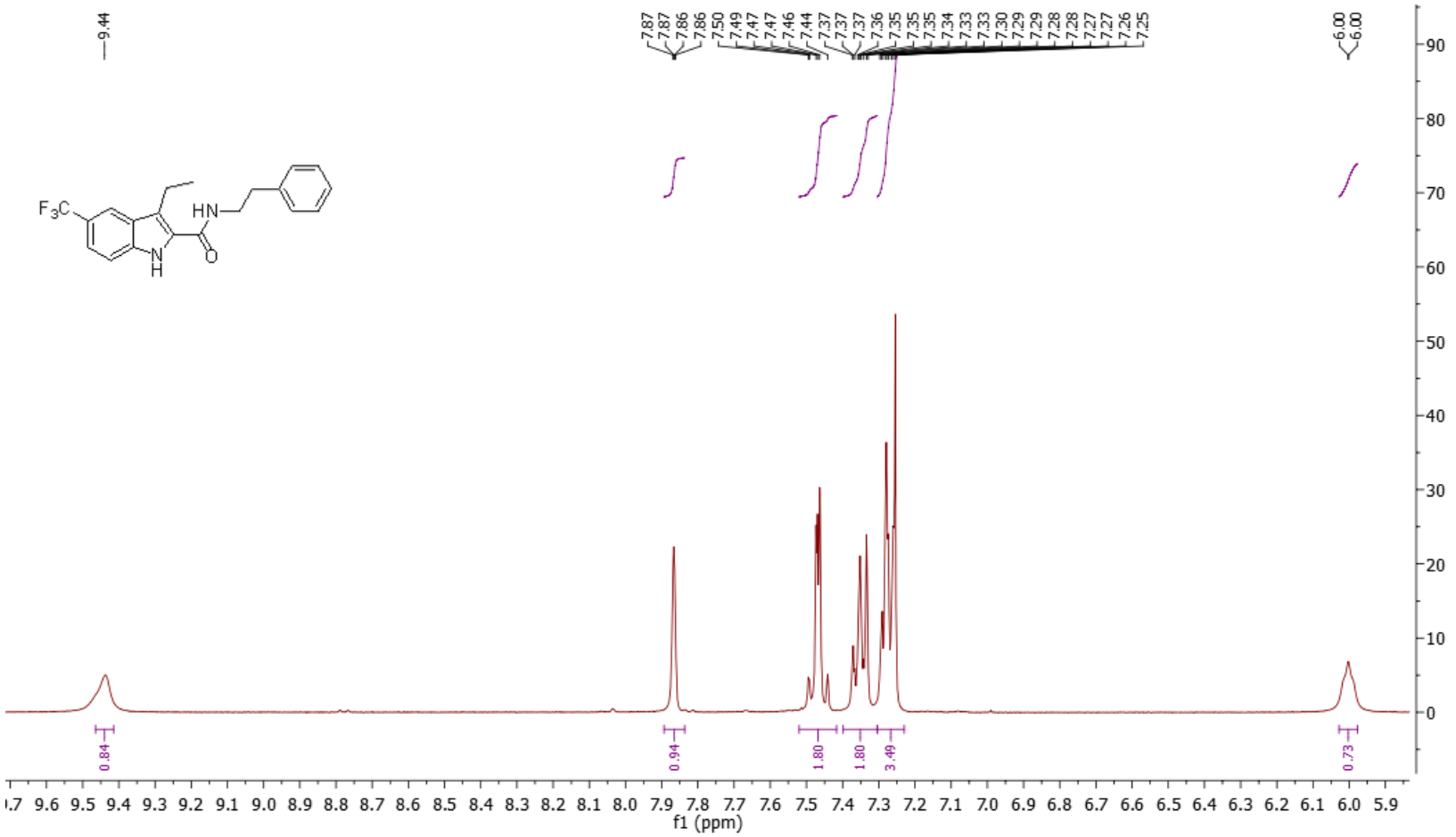
^{13}C NMR (101 MHz, cdcl$_3$) δ 162.24, 138.36, 133.87, 129.47, 128.91, 128.72, 127.45, 127.41, 126.88, 122.42, 118.04, 113.40, 112.91, 40.74, 35.31, 18.19, 15.24.

5b



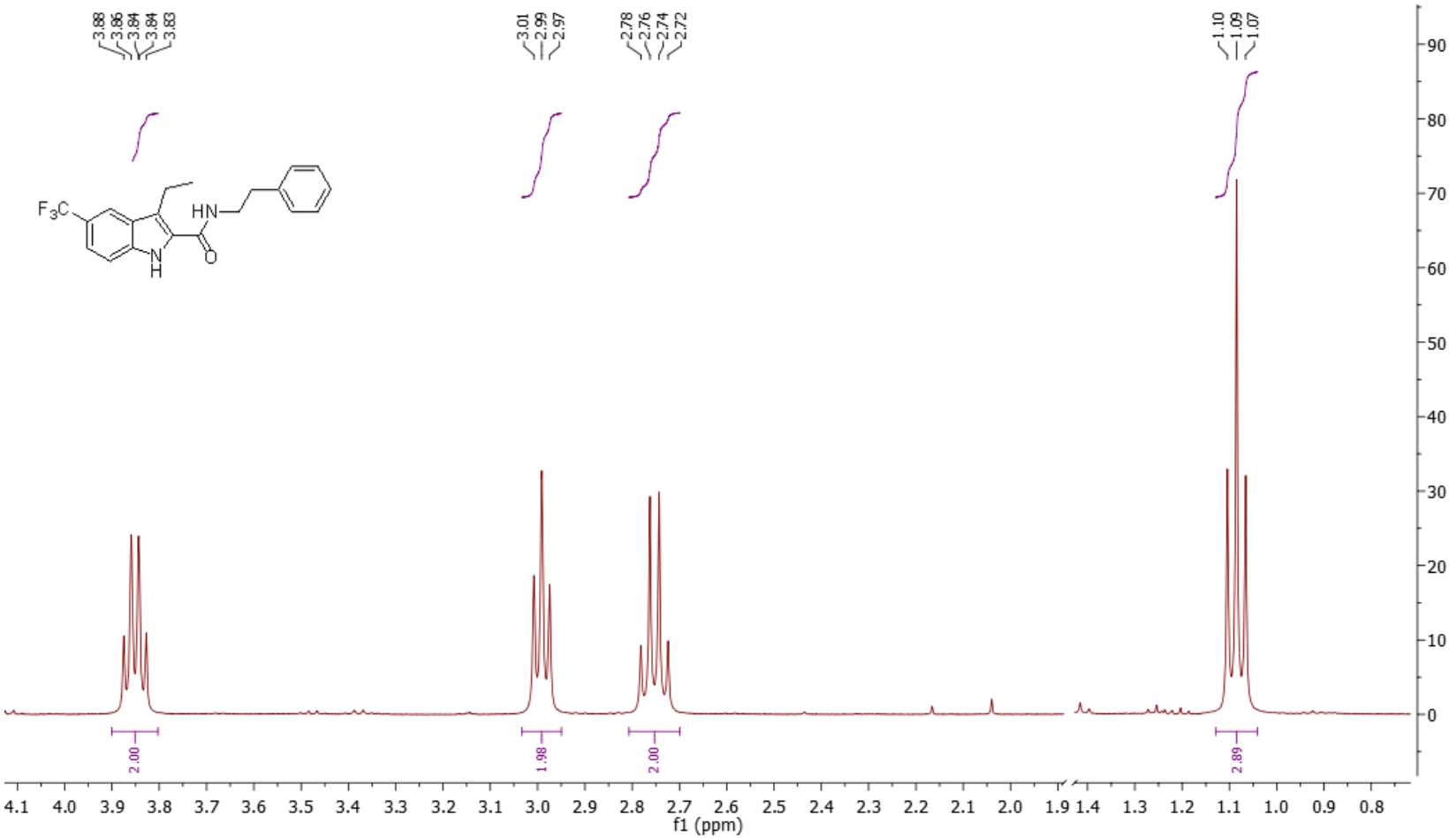
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.44 (s, 1H), 7.87 (s, 1H), 7.52 – 7.42 (m, 2H), 7.40 – 7.23 (m, 4H), 6.00 (s, 1H), 3.85 (q, J = 6.4 Hz, 2H), 2.99 (t, J = 6.6 Hz, 2H), 2.75 (q, J = 7.7 Hz, 2H), 1.08 (t, J = 7.7 Hz, 3H).

5b



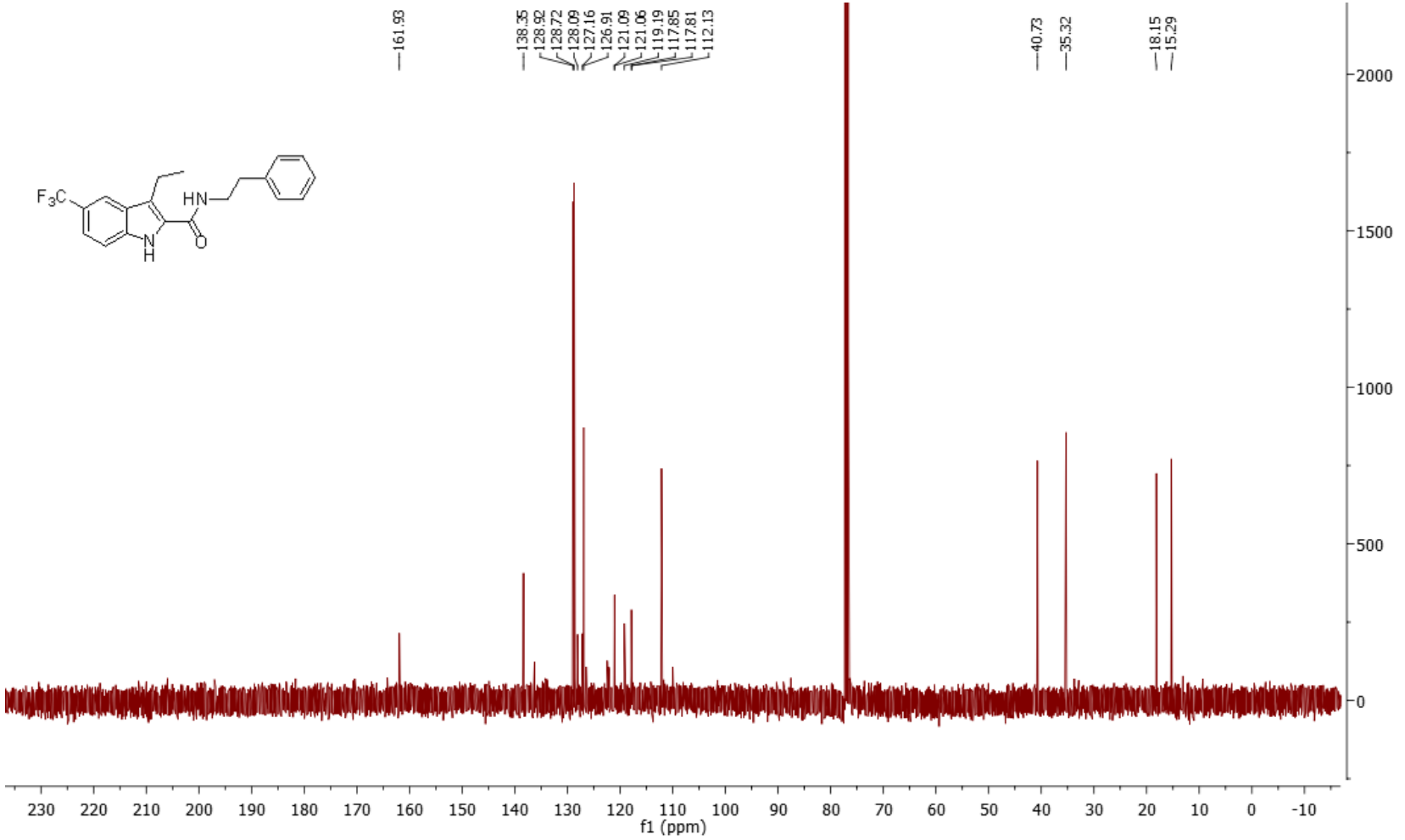
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.44 (s, 1H), 7.87 (s, 1H), 7.52 – 7.42 (m, 2H), 7.40 – 7.23 (m, 4H), 6.00 (s, 1H), 3.85 (q, J = 6.4 Hz, 2H), 2.99 (t, J = 6.6 Hz, 2H), 2.75 (q, J = 7.7 Hz, 2H), 1.08 (t, J = 7.7 Hz, 3H).

5b



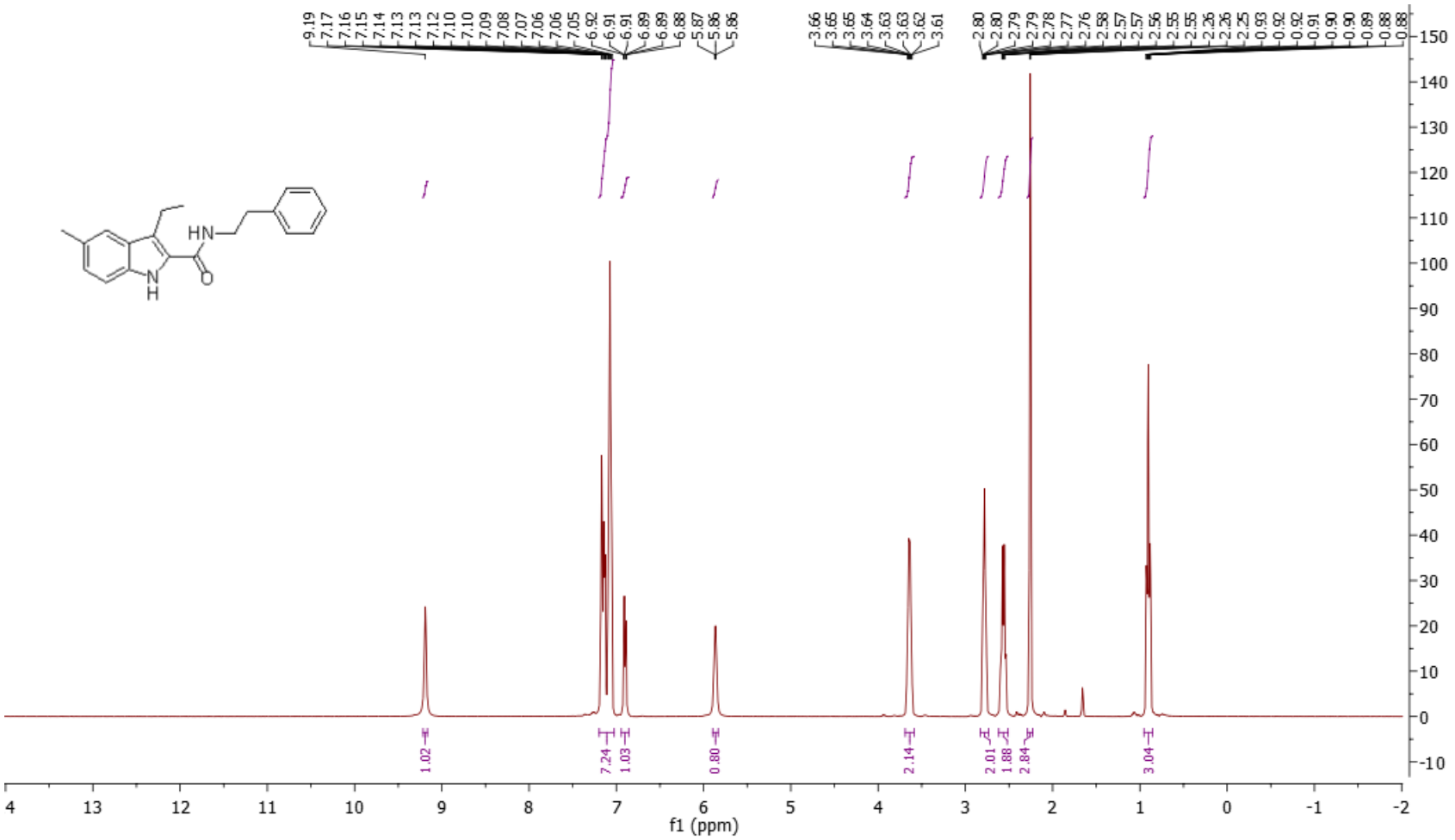
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.44 (s, 1H), 7.87 (s, 1H), 7.52 – 7.42 (m, 2H), 7.40 – 7.23 (m, 4H), 6.00 (s, 1H), 3.85 (q, J = 6.4 Hz, 2H), 2.99 (t, J = 6.6 Hz, 2H), 2.75 (q, J = 7.7 Hz, 2H), 1.08 (t, J = 7.7 Hz, 3H).

5b



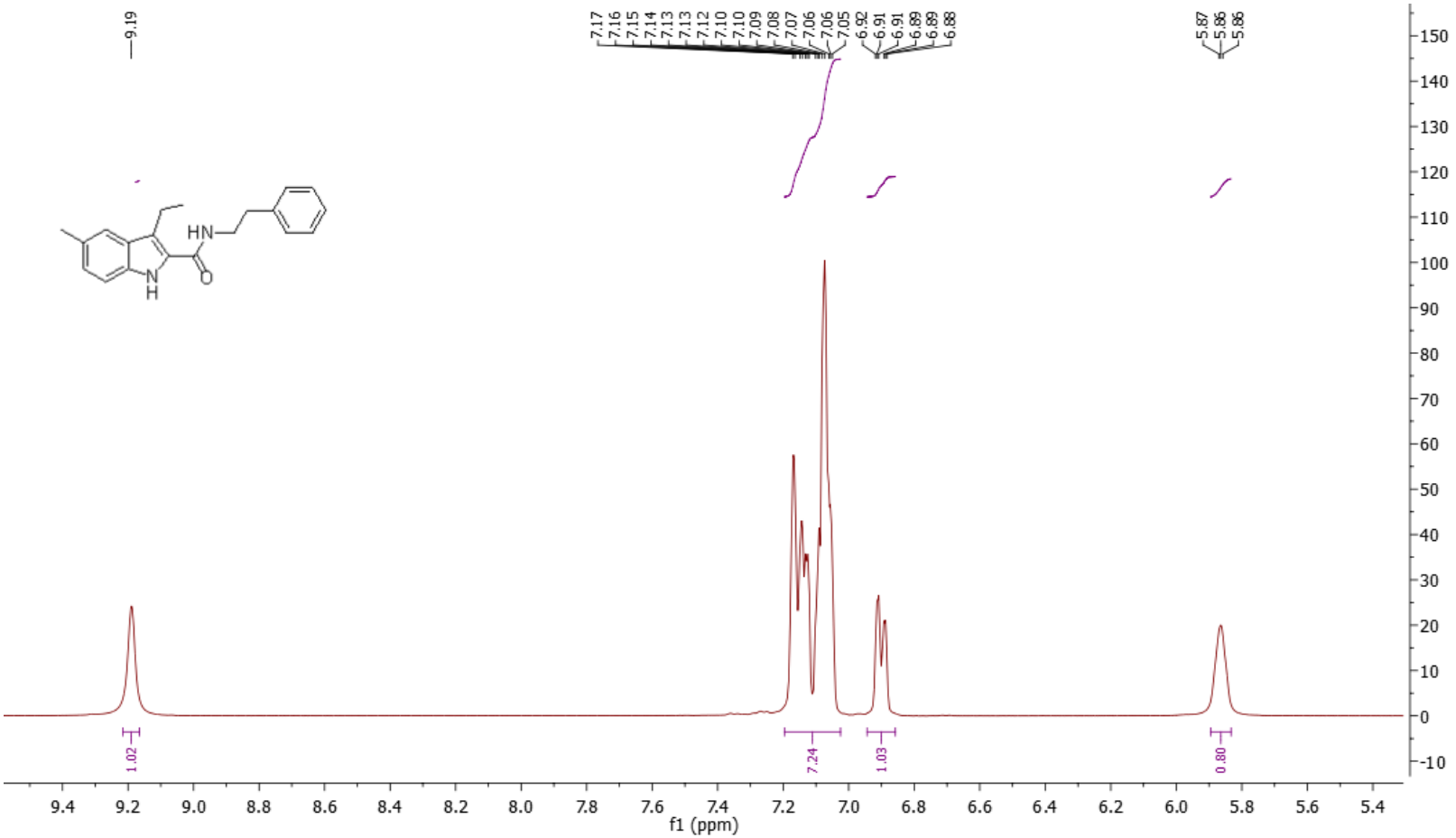
^{13}C NMR (101 MHz, cdcl$_3$) δ 161.93, 138.35, 128.92, 128.72, 128.09, 127.16, 126.91, 121.09, 121.06, 119.19, 117.85, 117.81, 112.13, 40.73, 35.32, 18.15, 15.29.

5c



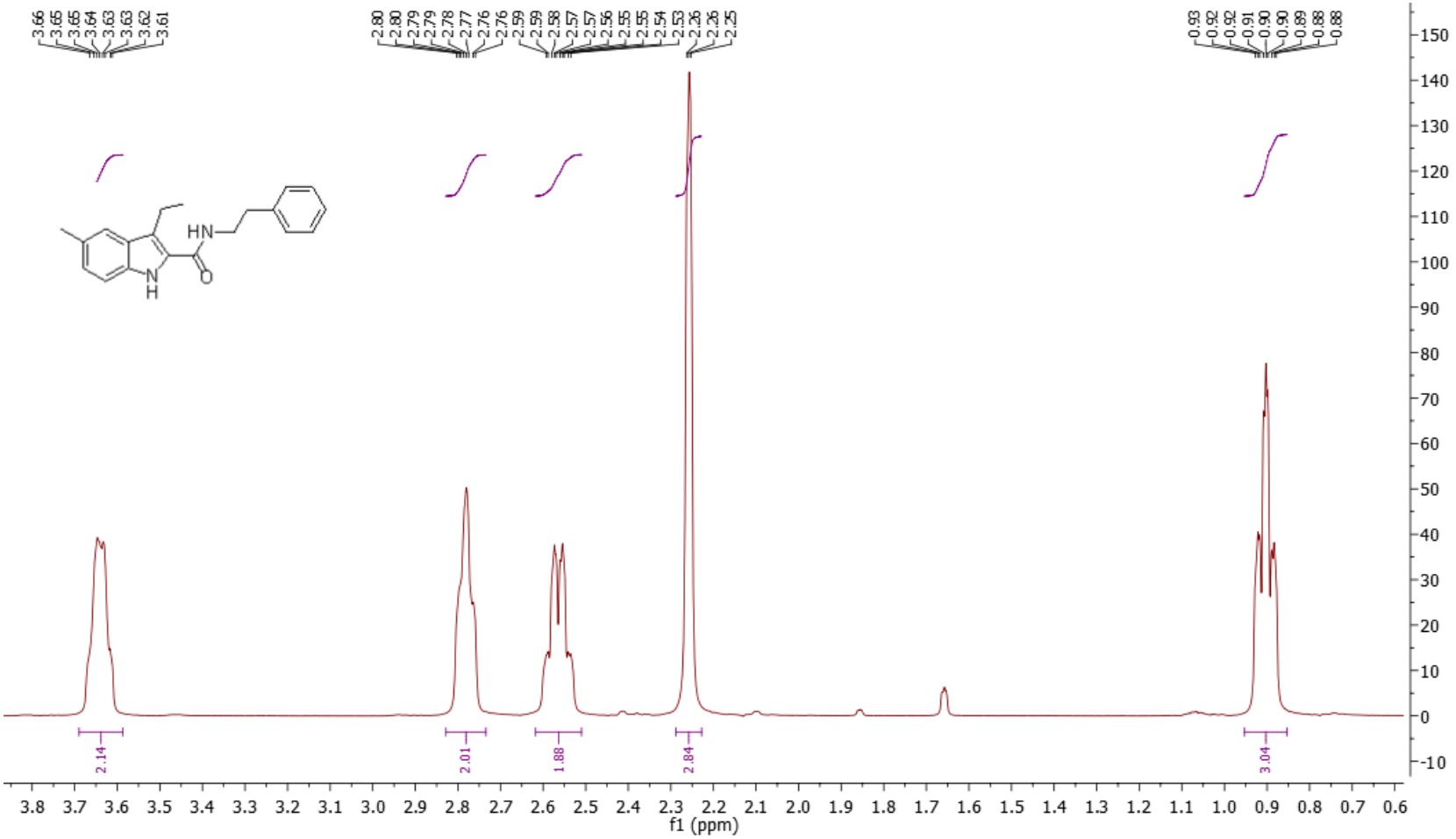
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.19 (s, 1H), 7.11 (m, 7H), 6.94 – 6.86 (m, 1H), 5.86 (s, 1H), 3.64 (q, J = 8.8 Hz, 2H), 2.78 (t, J = 8.3 Hz, 2H), 2.56 (q, J = 10.2 Hz, 2H), 2.26 (s, 3H), 0.90 (t, J = 7.7 Hz, 3H).

5c



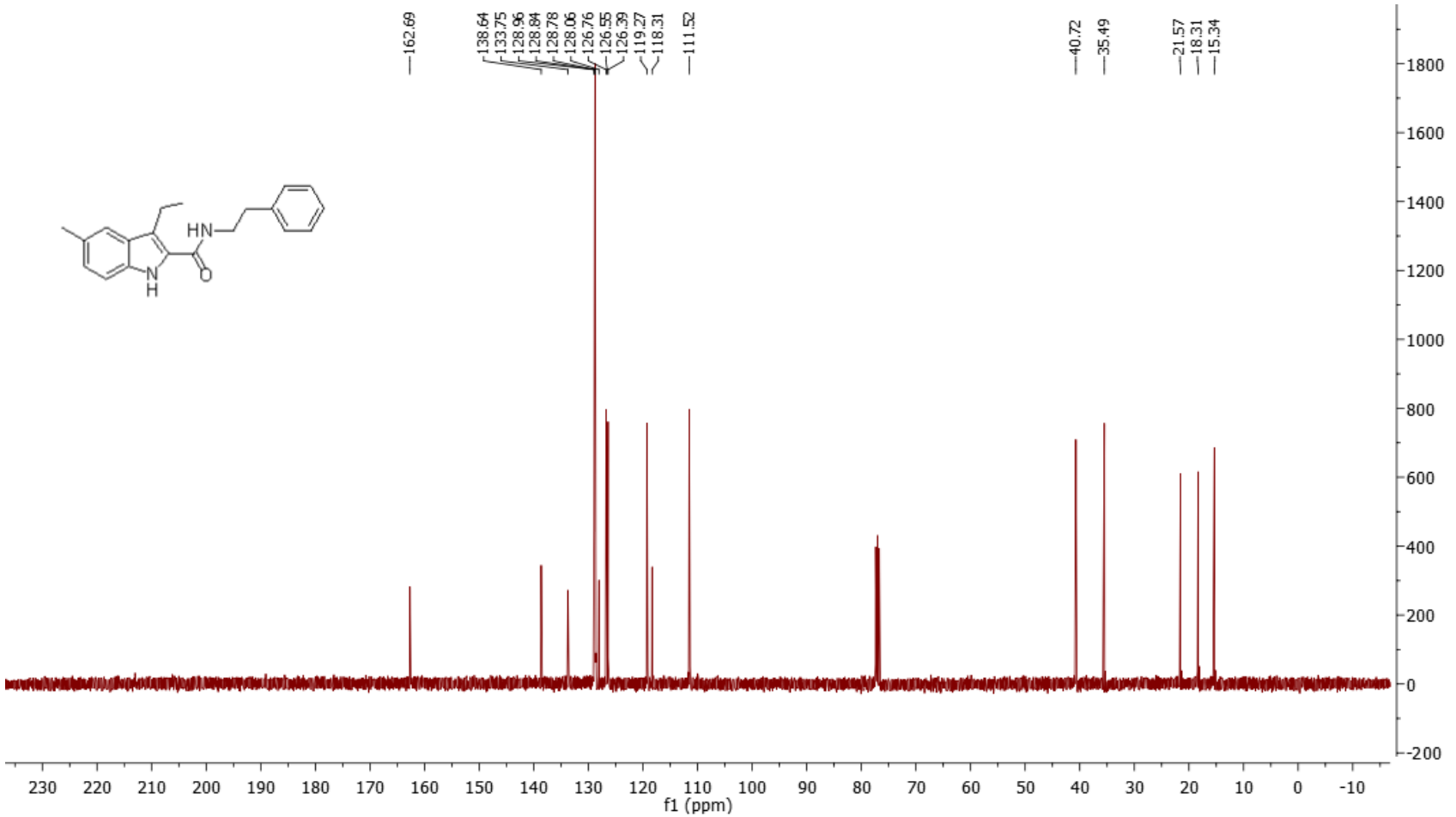
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.19 (s, 1H), 7.11 (m, 7H), 6.94 – 6.86 (m, 1H), 5.86 (s, 1H), 3.64 (q, J = 8.8 Hz, 2H), 2.78 (t, J = 8.3 Hz, 2H), 2.56 (q, J = 10.2 Hz, 2H), 2.26 (s, 3H), 0.90 (t, J = 7.7 Hz, 3H).

5c



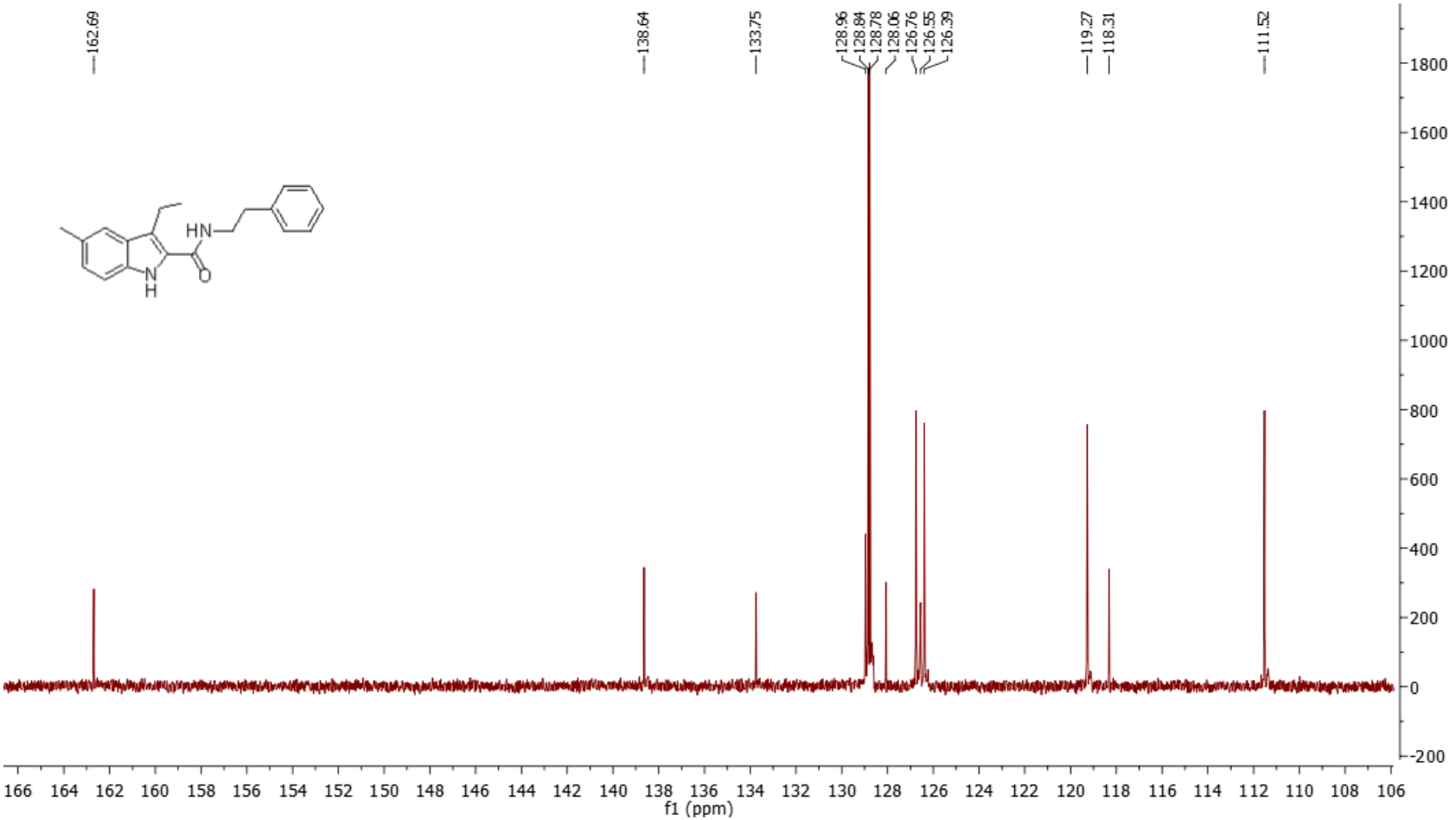
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.19 (s, 1H), 7.11 (m, 7H), 6.94 – 6.86 (m, 1H), 5.86 (s, 1H), 3.64 (q, J = 8.8 Hz, 2H), 2.78 (t, J = 8.3 Hz, 2H), 2.56 (q, J = 10.2 Hz, 2H), 2.26 (s, 3H), 0.90 (t, J = 7.7 Hz, 3H).

5c



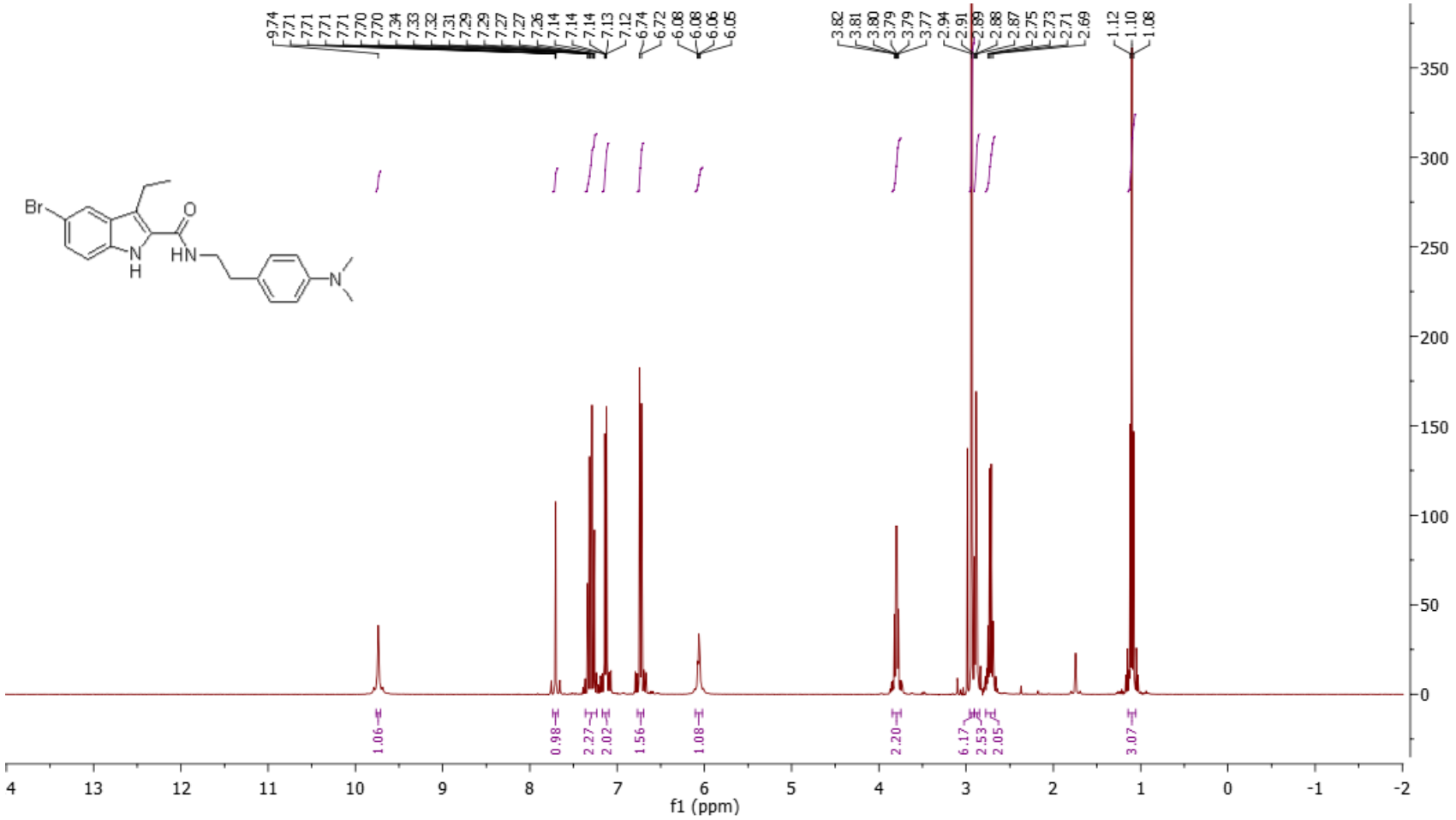
^{13}C NMR (101 MHz, cdcl$_3$) δ 162.69, 138.64, 133.75, 128.96, 128.84, 128.78, 128.06, 126.76, 126.55, 126.39, 119.27, 118.31, 111.52, 40.72, 35.49, 21.57, 18.31, 15.34.

5c



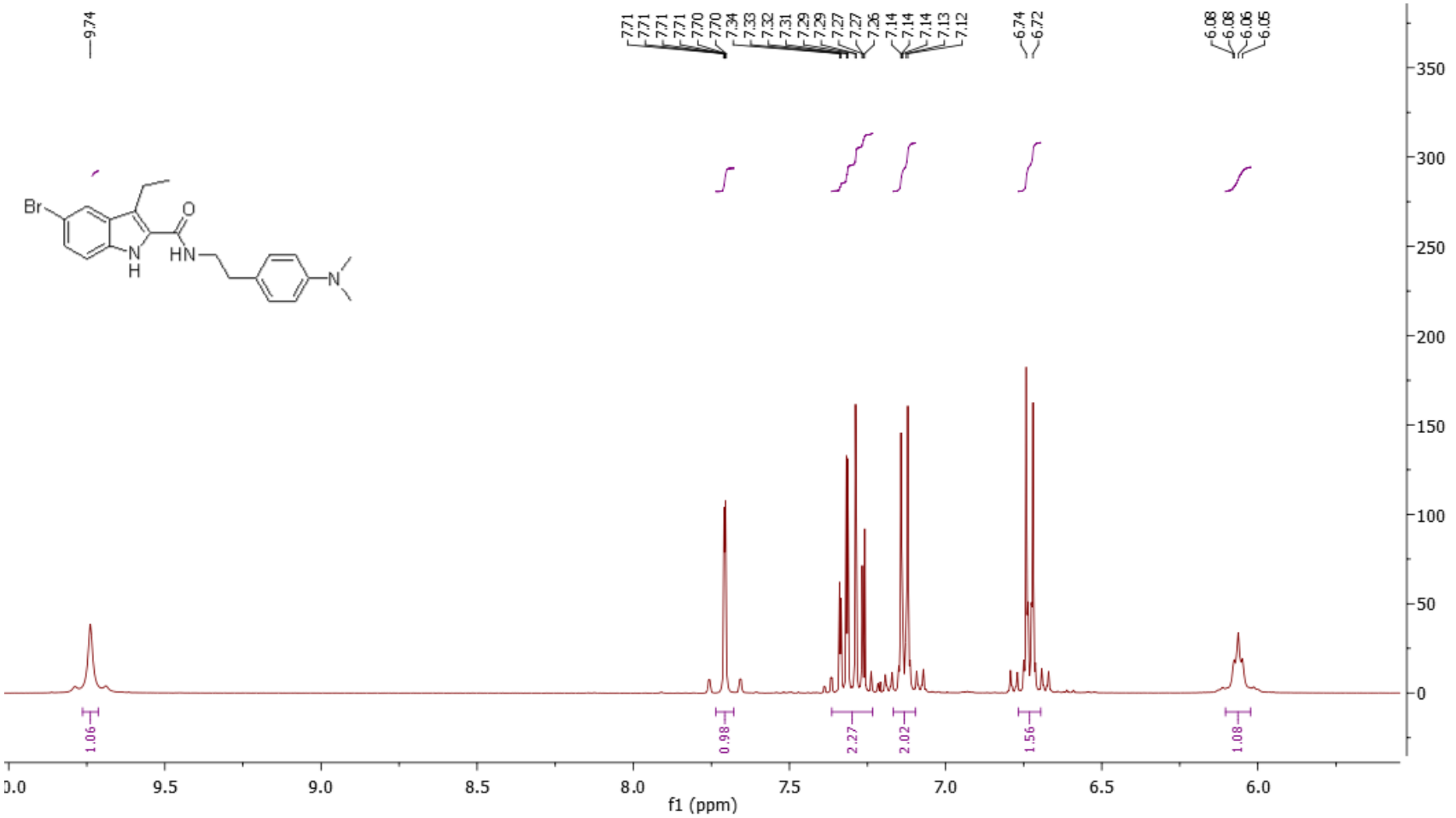
^{13}C NMR (101 MHz, cdcl$_3$) δ 162.69, 138.64, 133.75, 128.96, 128.84, 128.78, 128.06, 126.76, 126.55, 126.39, 119.27, 118.31, 111.52, 40.72, 35.49, 21.57, 18.31, 15.34.

5d



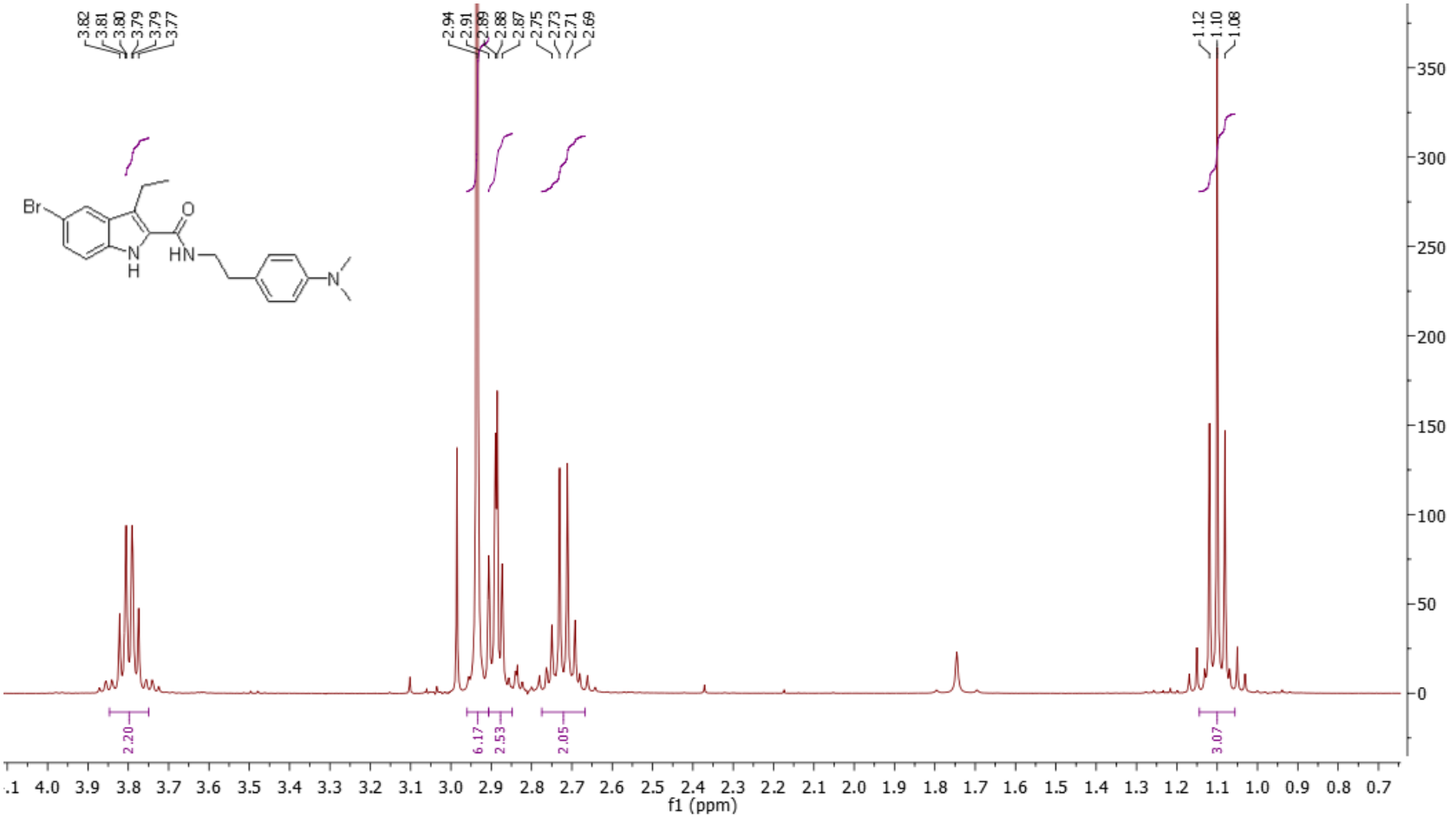
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.74 (s, 1H), 7.71 (d, J = 1.8 Hz, 1H), 7.36 – 7.23 (m, 2H), 7.13 (d, J = 8.6 Hz, 2H), 6.73 (d, J = 8.6 Hz, 2H), 6.06 (t, J = 5.6 Hz, 1H), 3.80 (q, J = 6.8 Hz, 2H), 2.94 (s, 6H), 2.89 (t, J = 6.8 Hz, 3H), 2.72 (q, J = 7.7 Hz, 2H), 1.10 (t, J = 7.7 Hz, 3H).

5d



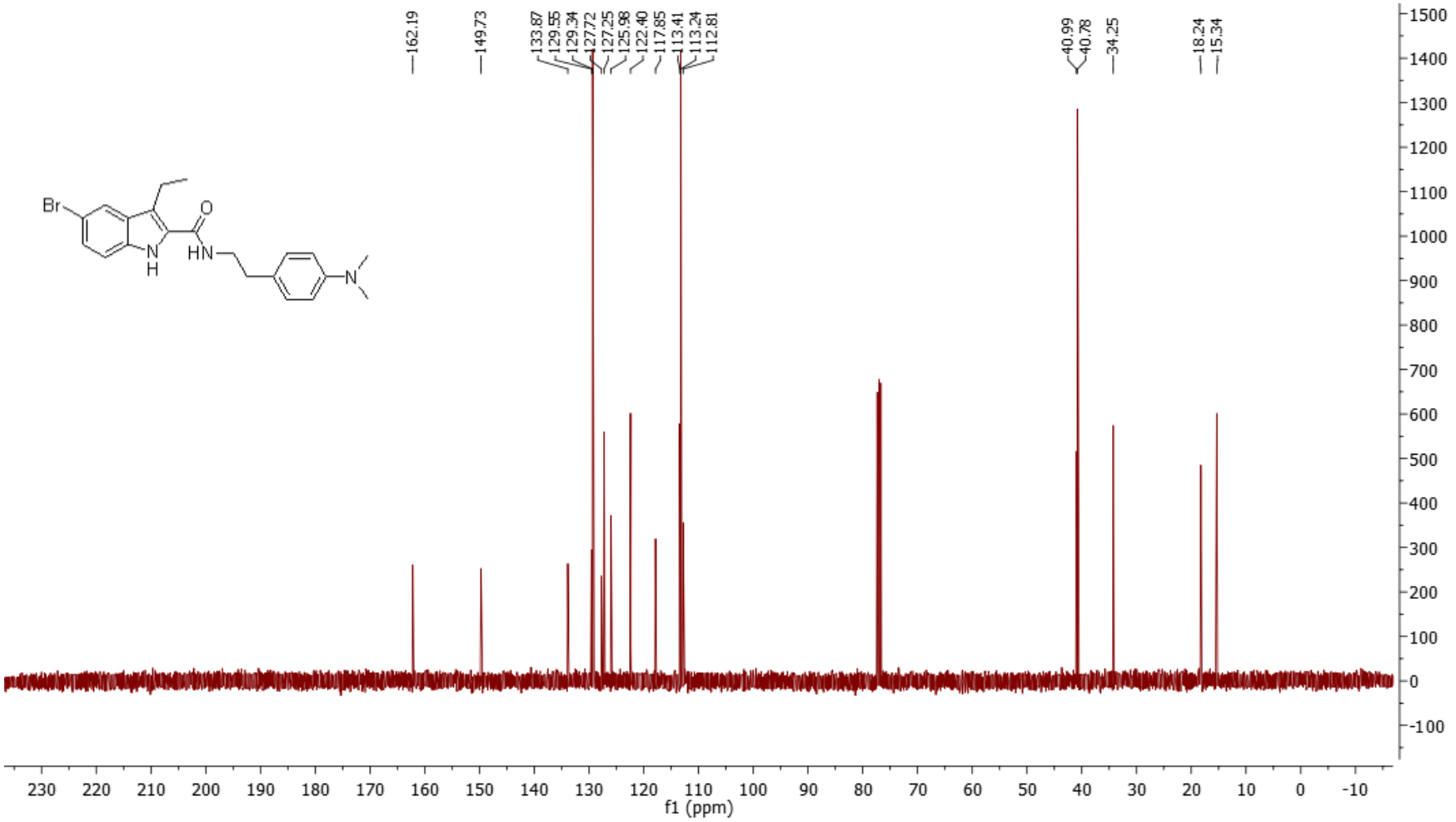
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.74 (s, 1H), 7.71 (d, *J* = 1.8 Hz, 1H), 7.36 – 7.23 (m, 2H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.73 (d, *J* = 8.6 Hz, 2H), 6.06 (t, *J* = 5.6 Hz, 1H), 3.80 (q, *J* = 6.8 Hz, 2H), 2.94 (s, 6H), 2.89 (t, *J* = 6.8 Hz, 3H), 2.72 (q, *J* = 7.7 Hz, 2H), 1.10 (t, *J* = 7.7 Hz, 3H).

5d



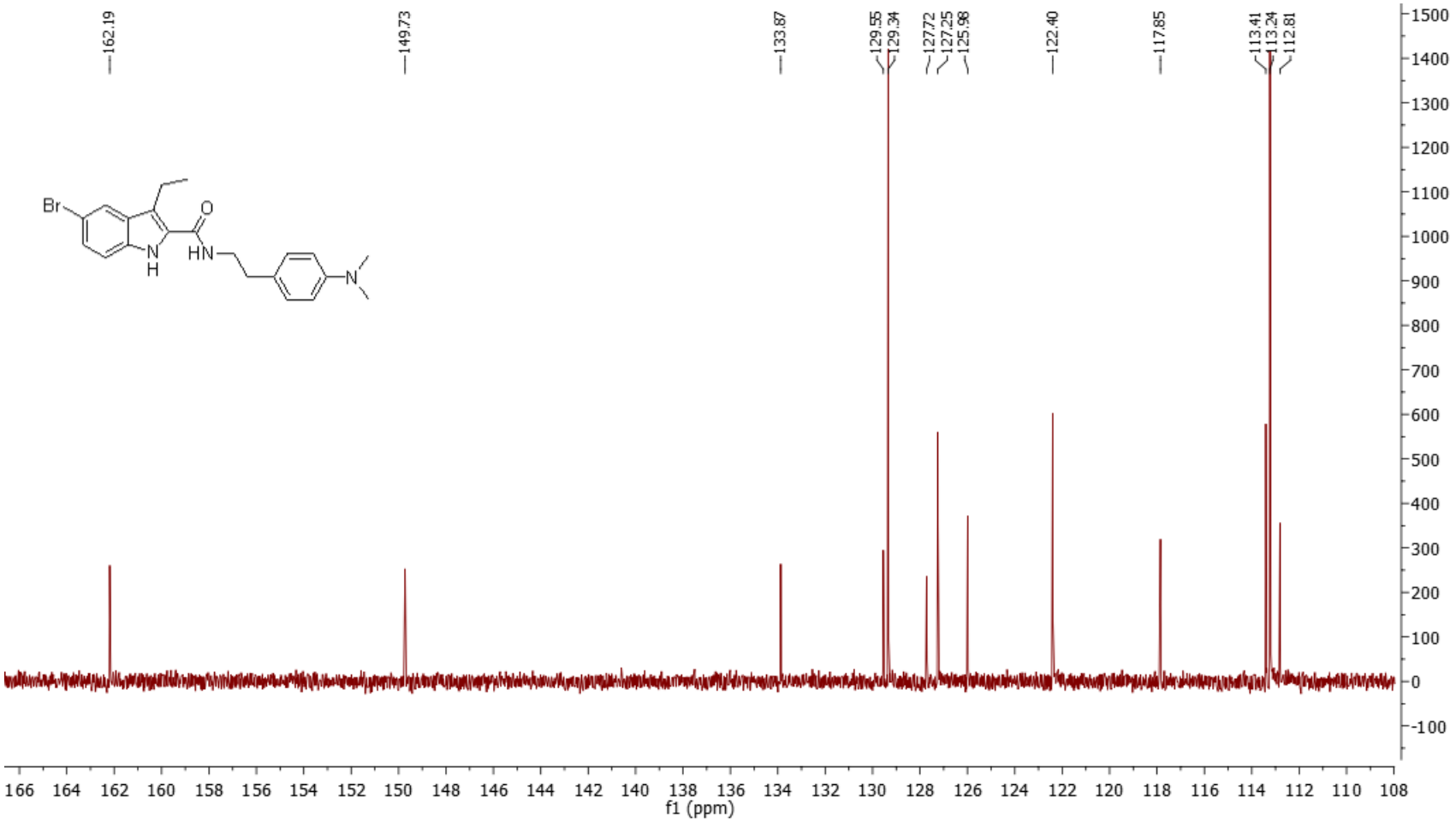
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.74 (s, 1H), 7.71 (d, *J* = 1.8 Hz, 1H), 7.36 – 7.23 (m, 2H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.73 (d, *J* = 8.6 Hz, 2H), 6.06 (t, *J* = 5.6 Hz, 1H), 3.80 (q, *J* = 6.8 Hz, 2H), 2.94 (s, 6H), 2.89 (t, *J* = 6.8 Hz, 3H), 2.72 (q, *J* = 7.7 Hz, 2H), 1.10 (t, *J* = 7.7 Hz, 3H).

5d



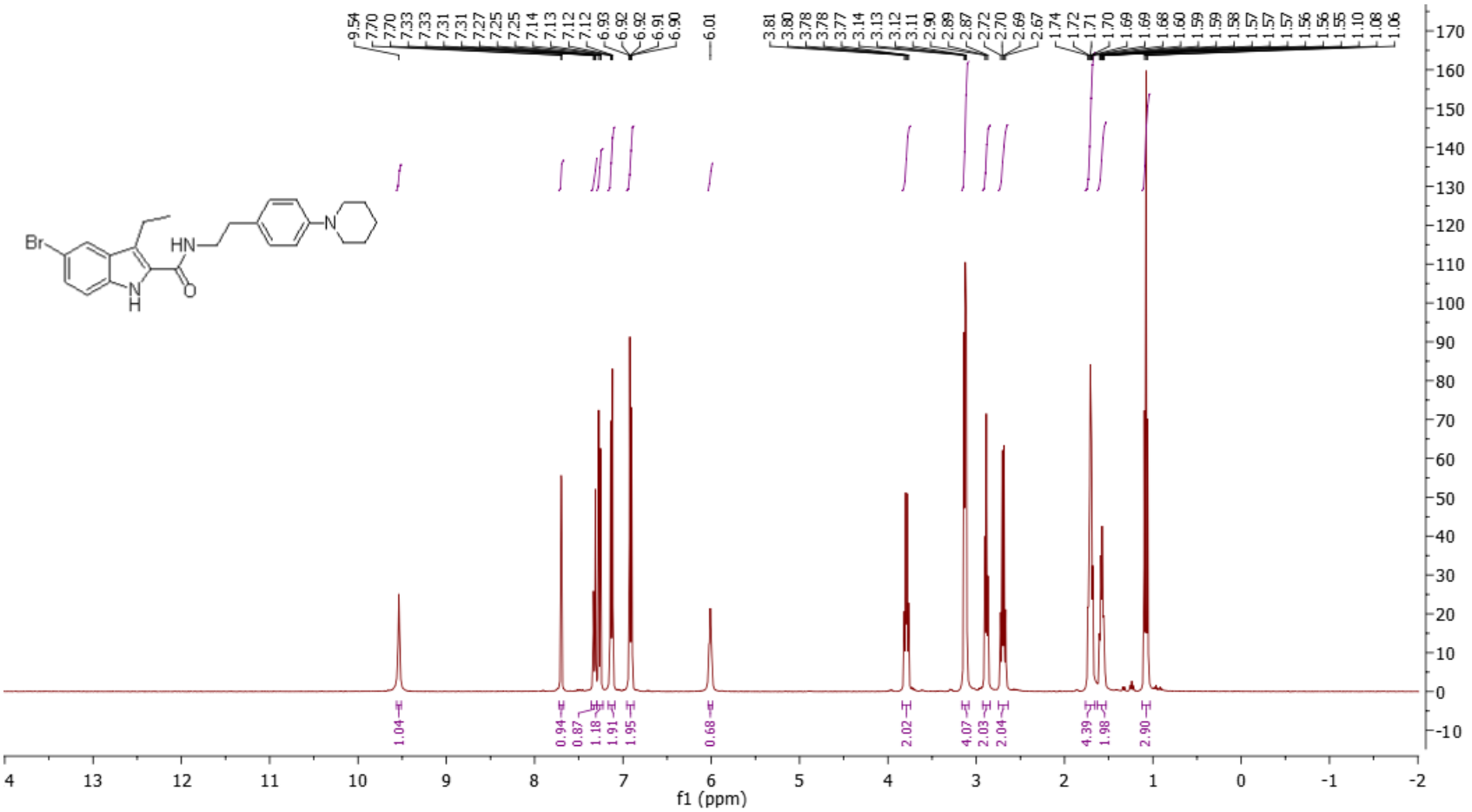
^{13}C NMR (101 MHz, cdcl$_3$) δ 162.19, 149.73, 133.87, 129.55, 129.34, 127.72, 127.25, 125.98, 122.40, 117.85, 113.41, 113.24, 112.81, 40.99, 40.78, 34.25, 18.24, 15.34.

5d



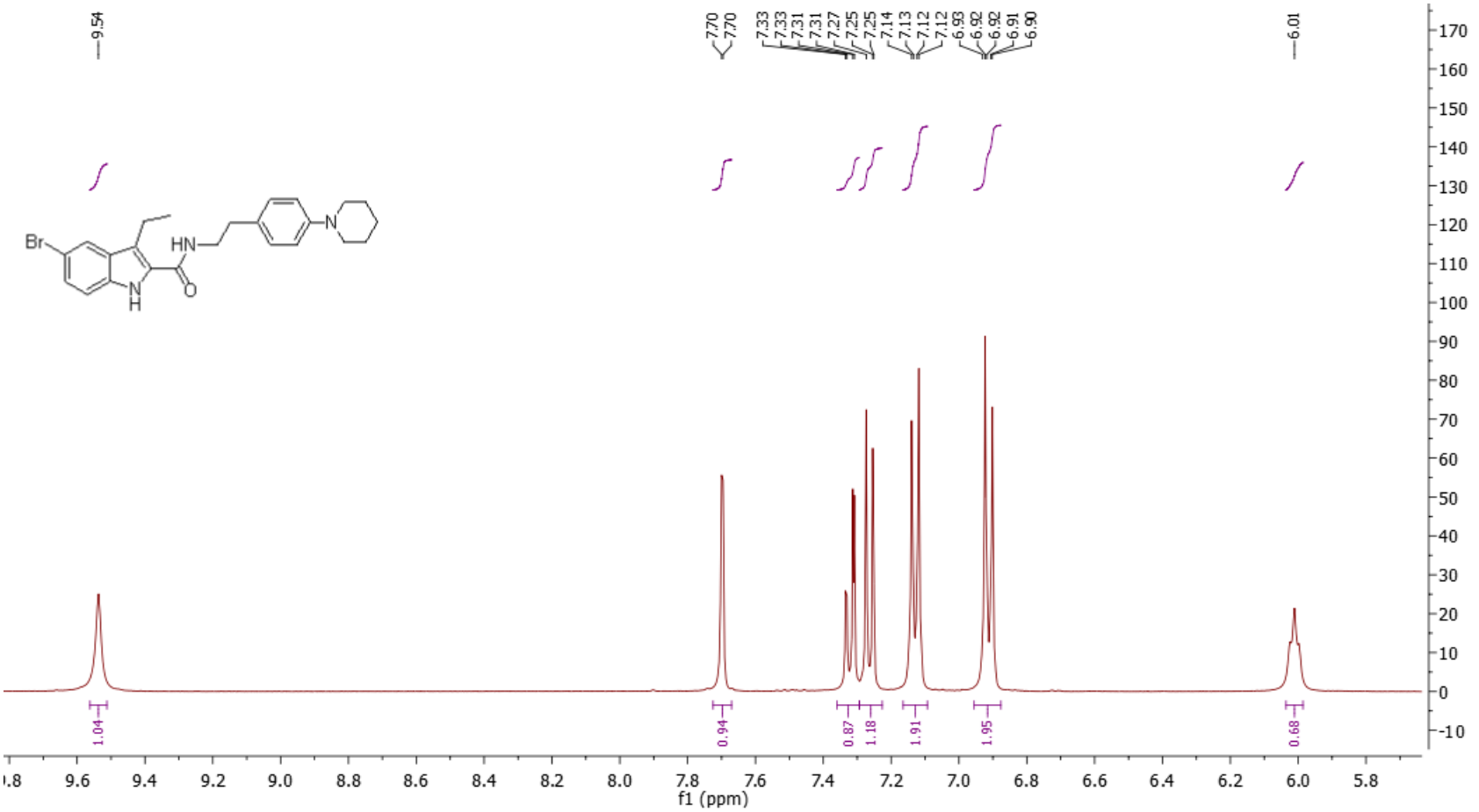
^{13}C NMR (101 MHz, cdcl$_3$) δ 162.19, 149.73, 133.87, 129.55, 129.34, 127.72, 127.25, 125.98, 122.40, 117.85, 113.41, 113.24, 112.81, 40.99, 40.78, 34.25, 18.24, 15.34.

5e



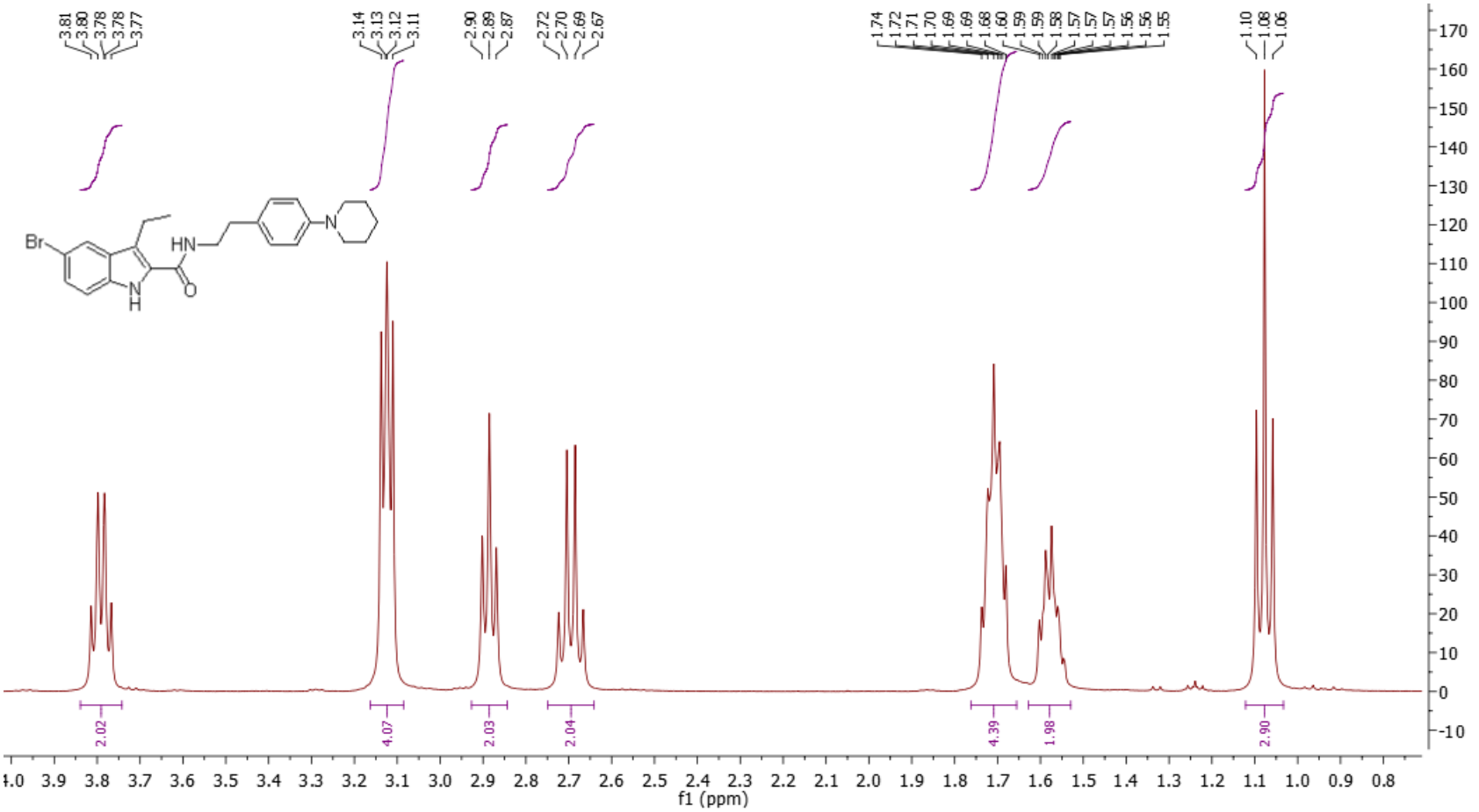
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.54 (s, 1H), 7.70 (d, *J* = 1.8 Hz, 1H), 7.32 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H) 7.13 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.01 (s, 1H), 3.78 (q, *J* = 6.5 Hz, 2H), 3.16 – 3.09 (m, 4H), 2.89 (t, *J* = 6.6 Hz, 2H), 2.69 (q, *J* = 7.7 Hz, 2H), 1.76 – 1.66 (m, 4H), 1.63 – 1.53 (m, 2H), 1.08 (t, *J* = 7.6 Hz, 3H).

5e



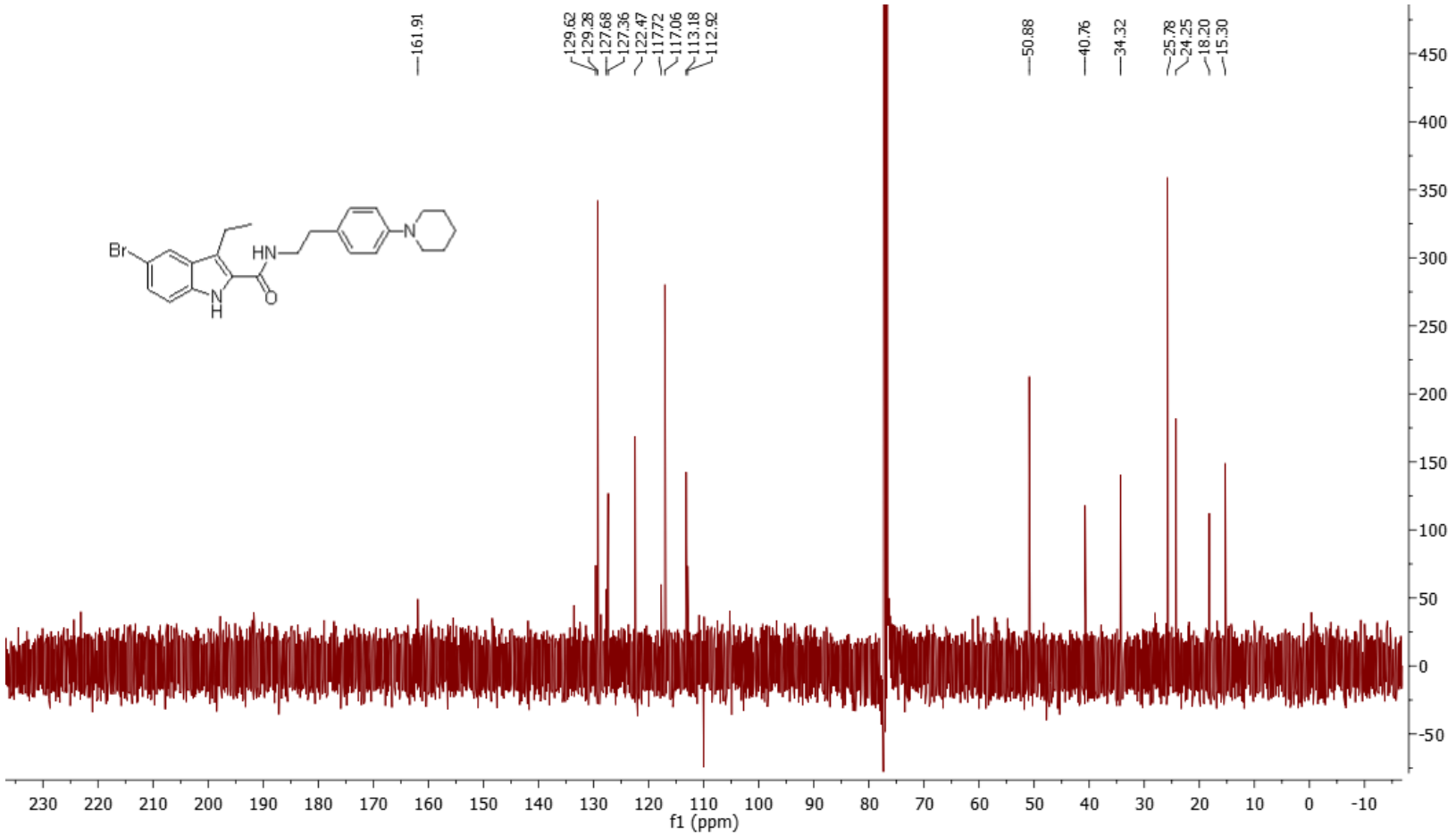
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.54 (s, 1H), 7.70 (d, *J* = 1.8 Hz, 1H), 7.32 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H) 7.13 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.01 (s, 1H), 3.78 (q, *J* = 6.5 Hz, 2H), 3.16 – 3.09 (m, 4H), 2.89 (t, *J* = 6.6 Hz, 2H), 2.69 (q, *J* = 7.7 Hz, 2H), 1.76 – 1.66 (m, 4H), 1.63 – 1.53 (m, 2H), 1.08 (t, *J* = 7.6 Hz, 3H).

5e



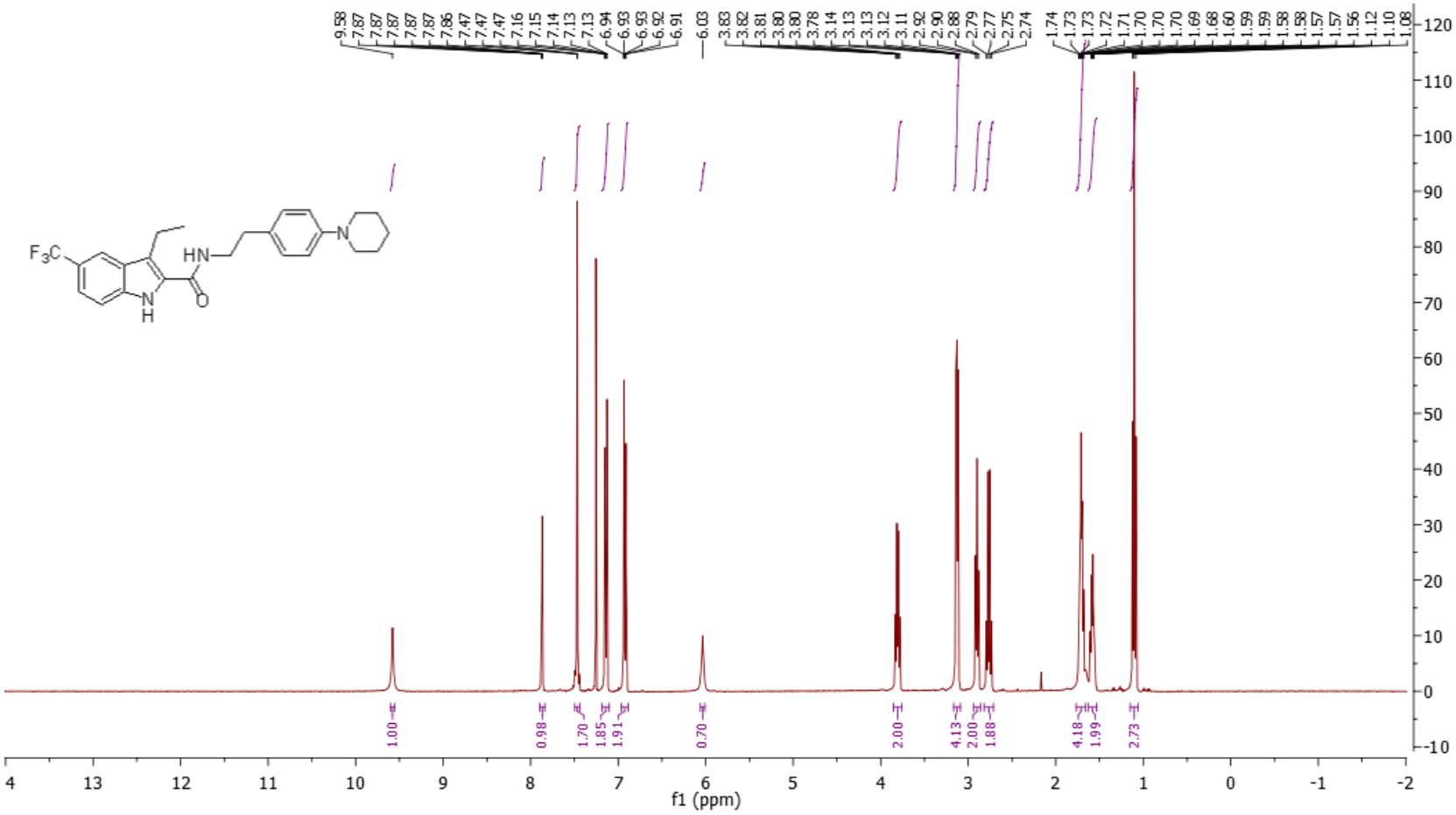
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.54 (s, 1H), 7.70 (d, *J* = 1.8 Hz, 1H), 7.32 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H) 7.13 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.01 (s, 1H), 3.78 (q, *J* = 6.5 Hz, 2H), 3.16 – 3.09 (m, 4H), 2.89 (t, *J* = 6.6 Hz, 2H), 2.69 (q, *J* = 7.7 Hz, 2H), 1.76 – 1.66 (m, 4H), 1.63 – 1.53 (m, 2H), 1.08 (t, *J* = 7.6 Hz, 3H).

5e



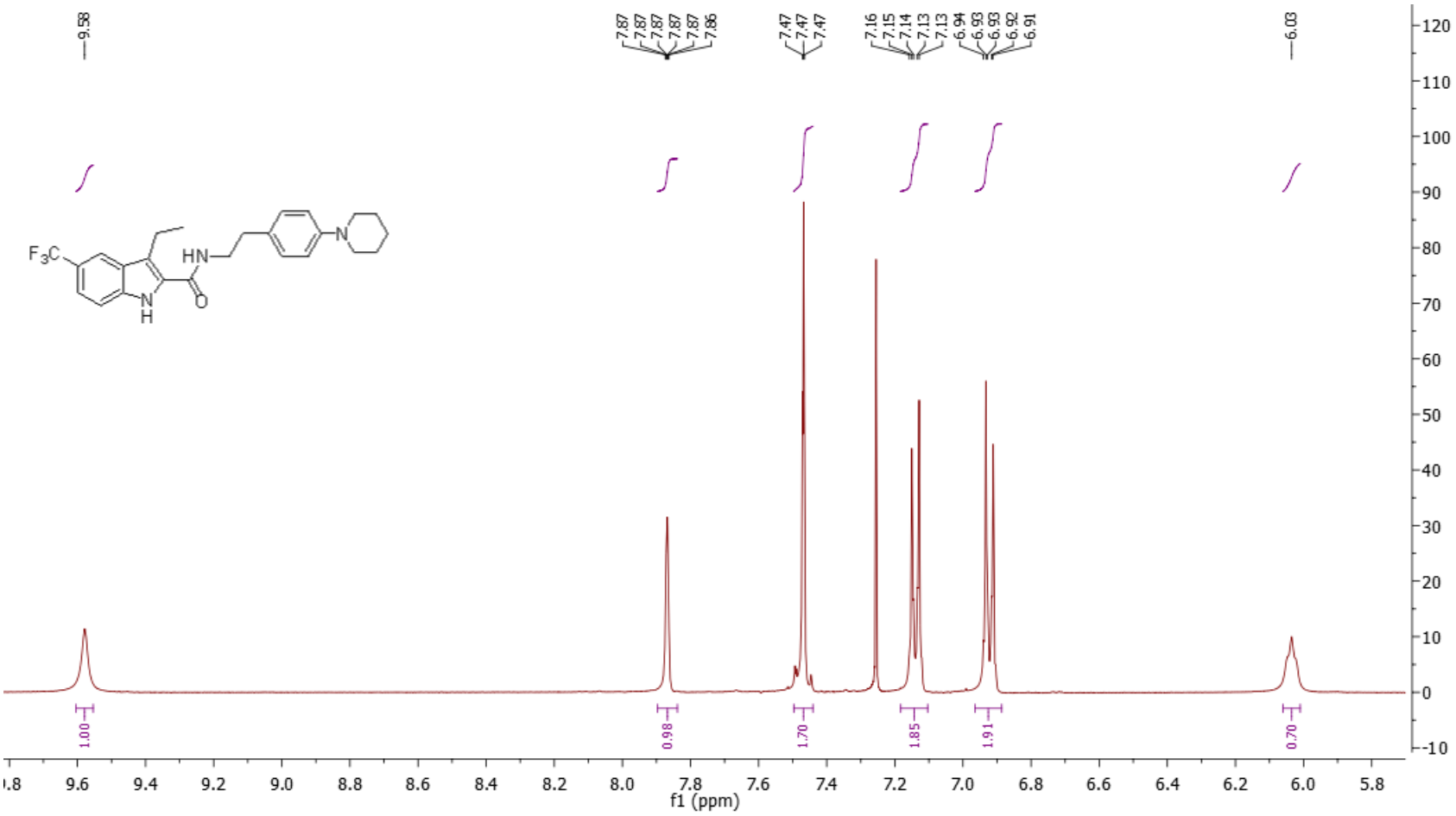
^{13}C NMR (101 MHz, cdcl$_3$) δ 161.91, 129.62, 129.28, 127.68, 127.36, 122.47, 117.72, 117.06, 113.18, 112.92, 50.88, 40.76, 34.32, 25.78, 24.25, 18.20, 15.30.

5f



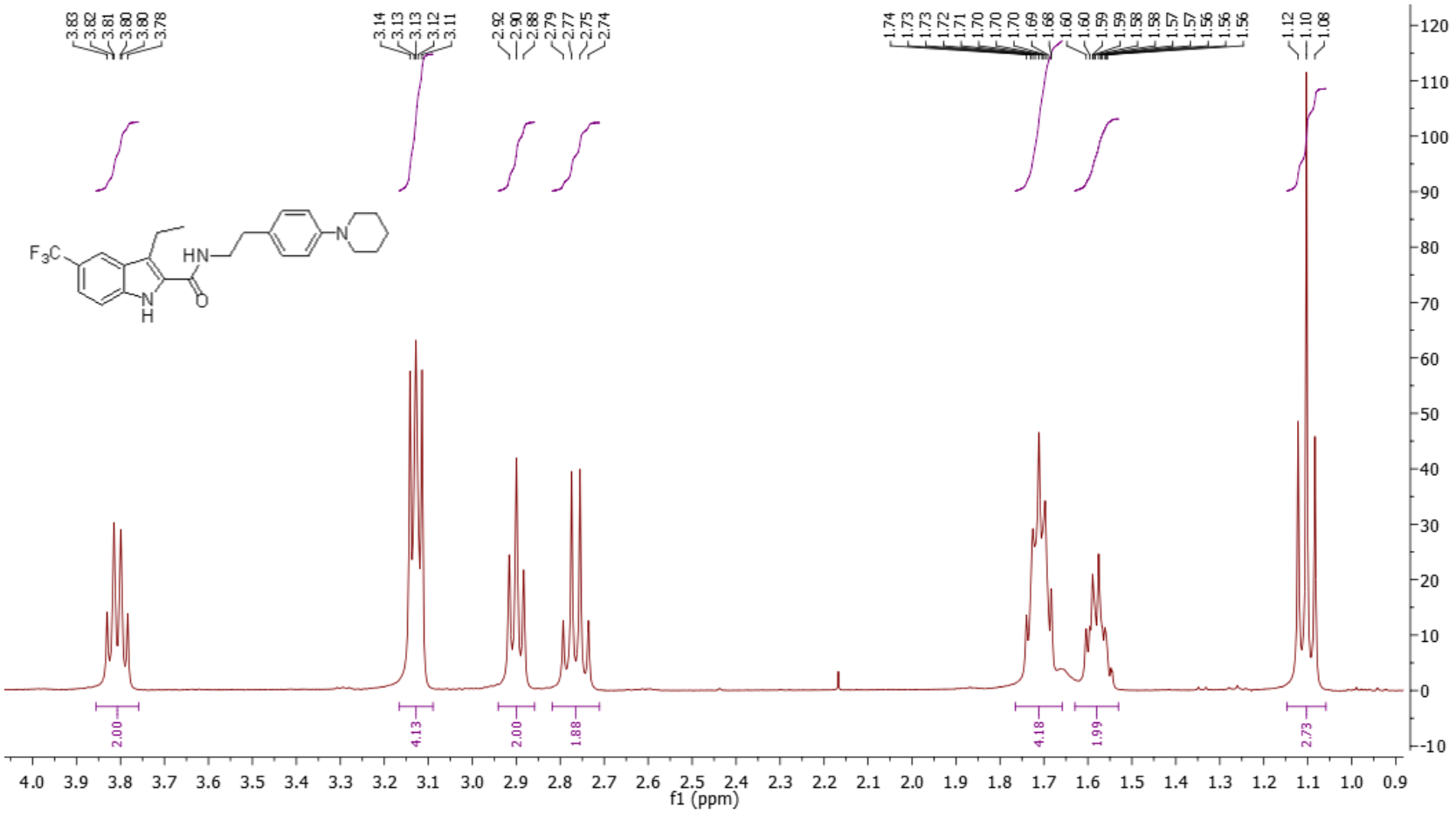
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.58 (s, 1H), 7.87 (s, 1H), 7.47 (d, J = 1.5 Hz, 2H), 7.14 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 6.03 (s, 1H), 3.81 (q, J = 6.5 Hz, 2H), 3.17 – 3.09 (m, 4H), 2.90 (t, J = 6.6 Hz, 2H), 2.76 (q, J = 7.7 Hz, 2H), 1.76 – 1.66 (m, 4H), 1.63 – 1.53 (m, 2H), 1.10 (t, J = 7.7 Hz, 3H).

5f



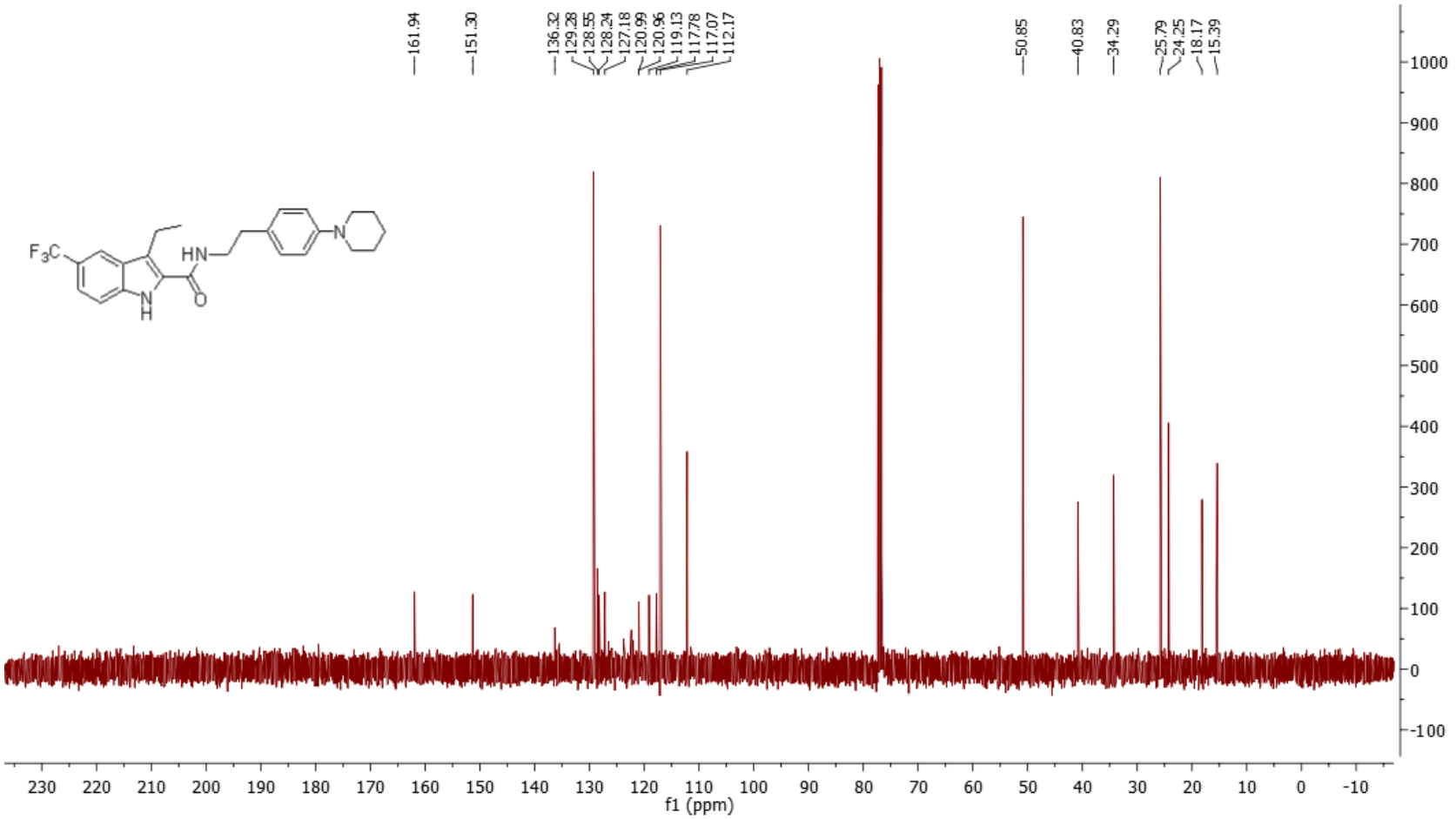
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.58 (s, 1H), 7.87 (s, 1H), 7.47 (d, J = 1.5 Hz, 2H), 7.14 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 6.03 (s, 1H), 3.81 (q, J = 6.5 Hz, 2H), 3.17 – 3.09 (m, 4H), 2.90 (t, J = 6.6 Hz, 2H), 2.76 (q, J = 7.7 Hz, 2H), 1.76 – 1.66 (m, 4H), 1.63 – 1.53 (m, 2H), 1.10 (t, J = 7.7 Hz, 3H).

5f



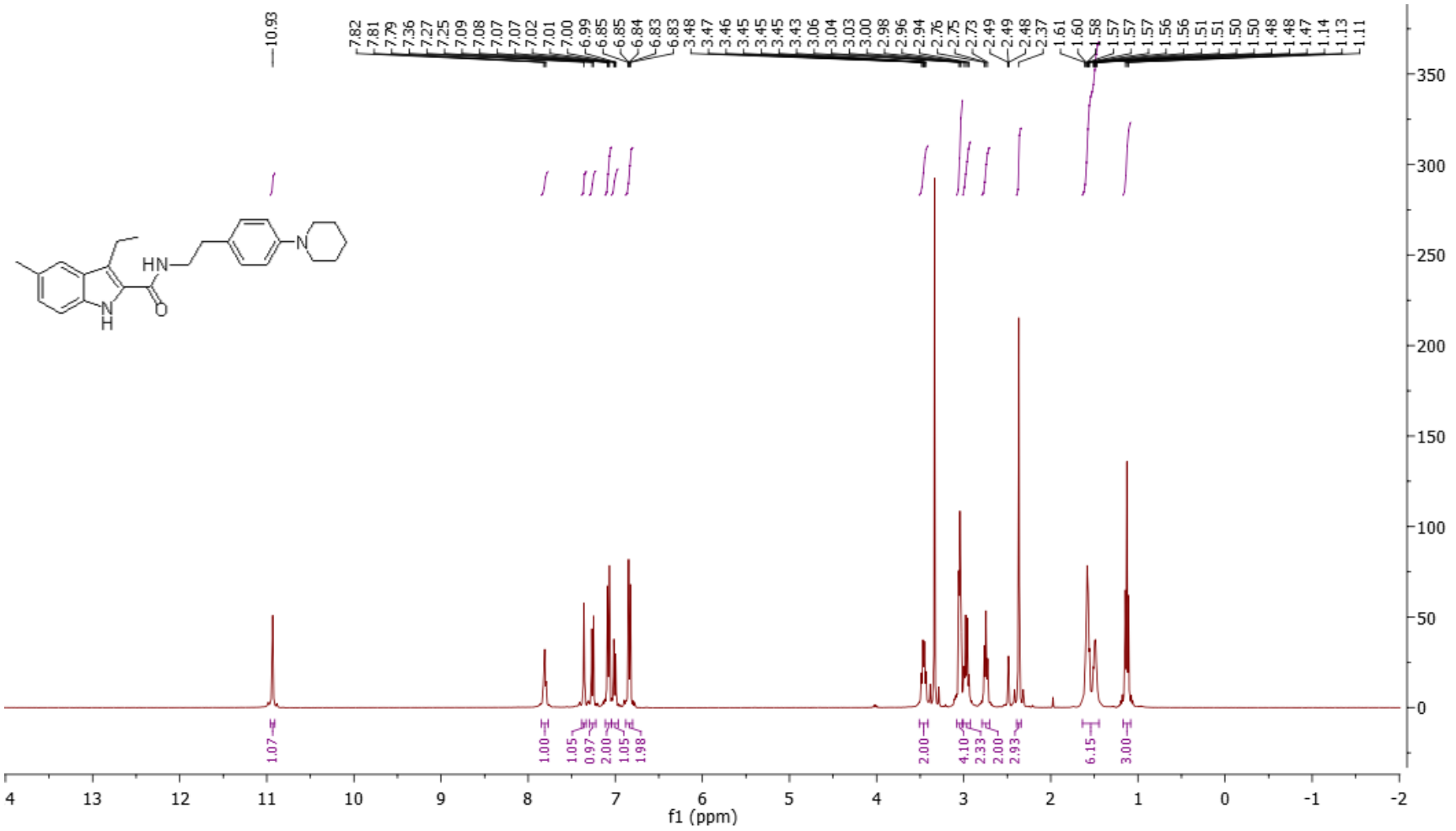
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.58 (s, 1H), 7.87 (s, 1H), 7.47 (d, J = 1.5 Hz, 2H), 7.14 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 6.03 (s, 1H), 3.81 (q, J = 6.5 Hz, 2H), 3.17 – 3.09 (m, 4H), 2.90 (t, J = 6.6 Hz, 2H), 2.76 (q, J = 7.7 Hz, 2H), 1.76 – 1.66 (m, 4H), 1.63 – 1.53 (m, 2H), 1.10 (t, J = 7.7 Hz, 3H).

5f



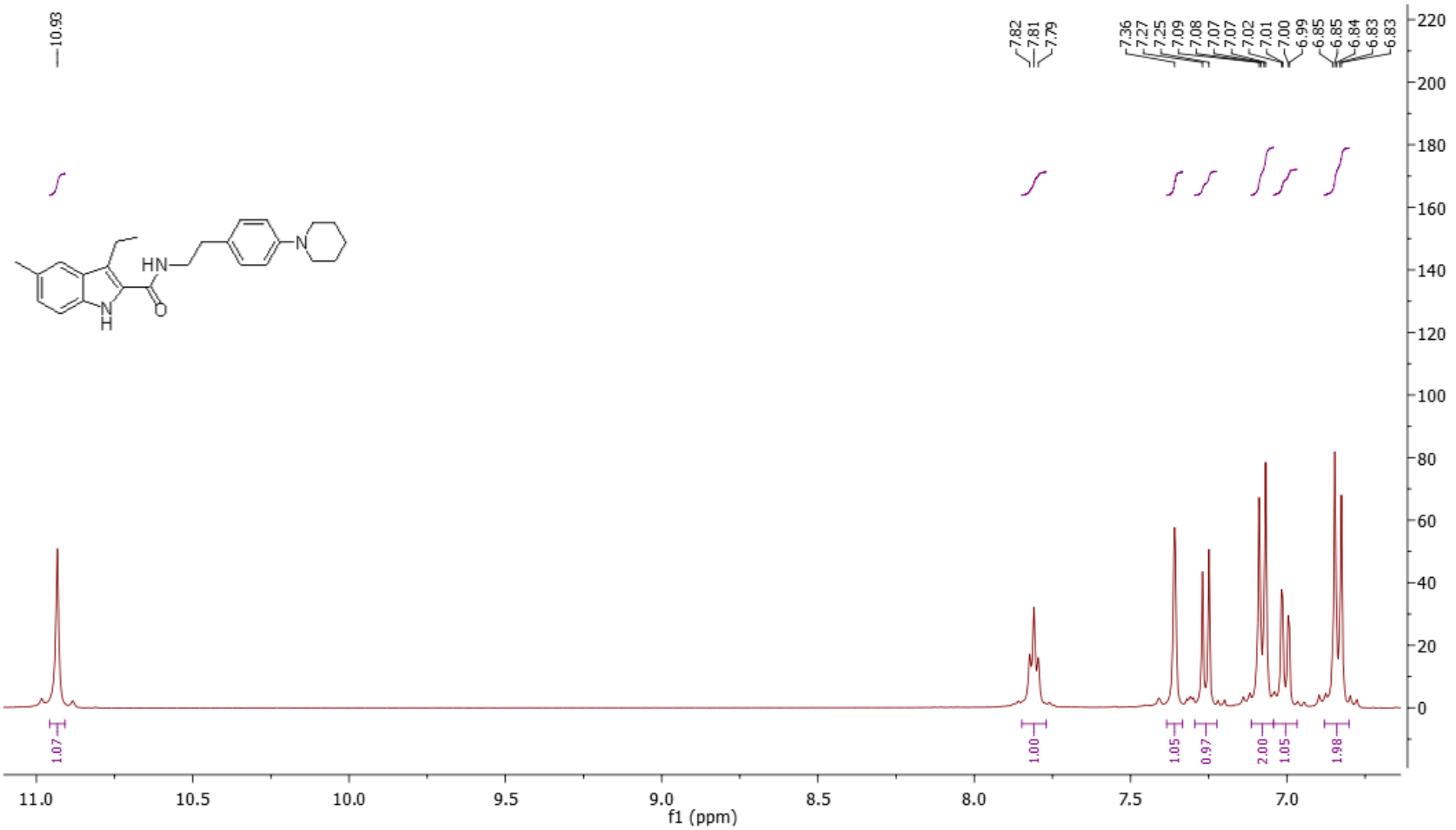
^{13}C NMR (101 MHz, cdcl$_3$) δ 161.94, 151.30, 136.32, 129.28, 128.55, 128.24, 127.18, 120.99, 120.96, 119.13, 117.78, 117.07, 112.17, 50.85, 40.83, 34.29, 25.79, 24.25, 18.17, 15.39.

5g



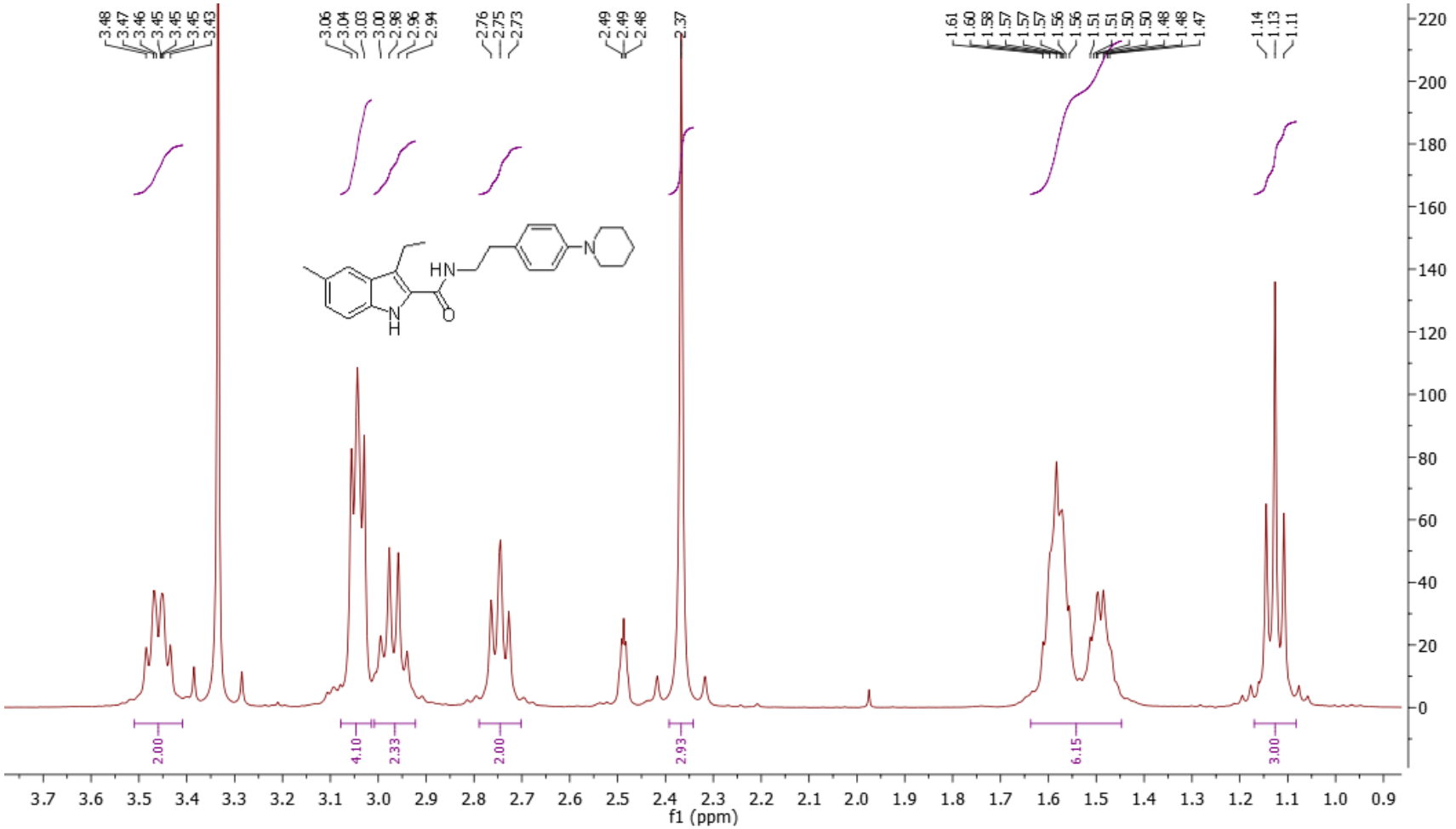
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 7.81 (t, J = 5.6 Hz, 1H), 7.36 (s, 1H), 7.26 (d, J = 8.3 Hz, 1H), 7.08 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.3 Hz, 1H), 6.83 (d, J = 8.7 Hz, 2H), 3.46 (q, J = 8.3 Hz, 2H), 3.04 (d, J = 5.2 Hz, 4H), 2.97 (q, J = 7.3 Hz, 2H), 2.75 (t, J = 7.4 Hz, 2H), 2.37 (s, 3H), 1.64 – 1.45 (m, 6H), 1.13 (t, J = 7.4 Hz, 3H).

5g



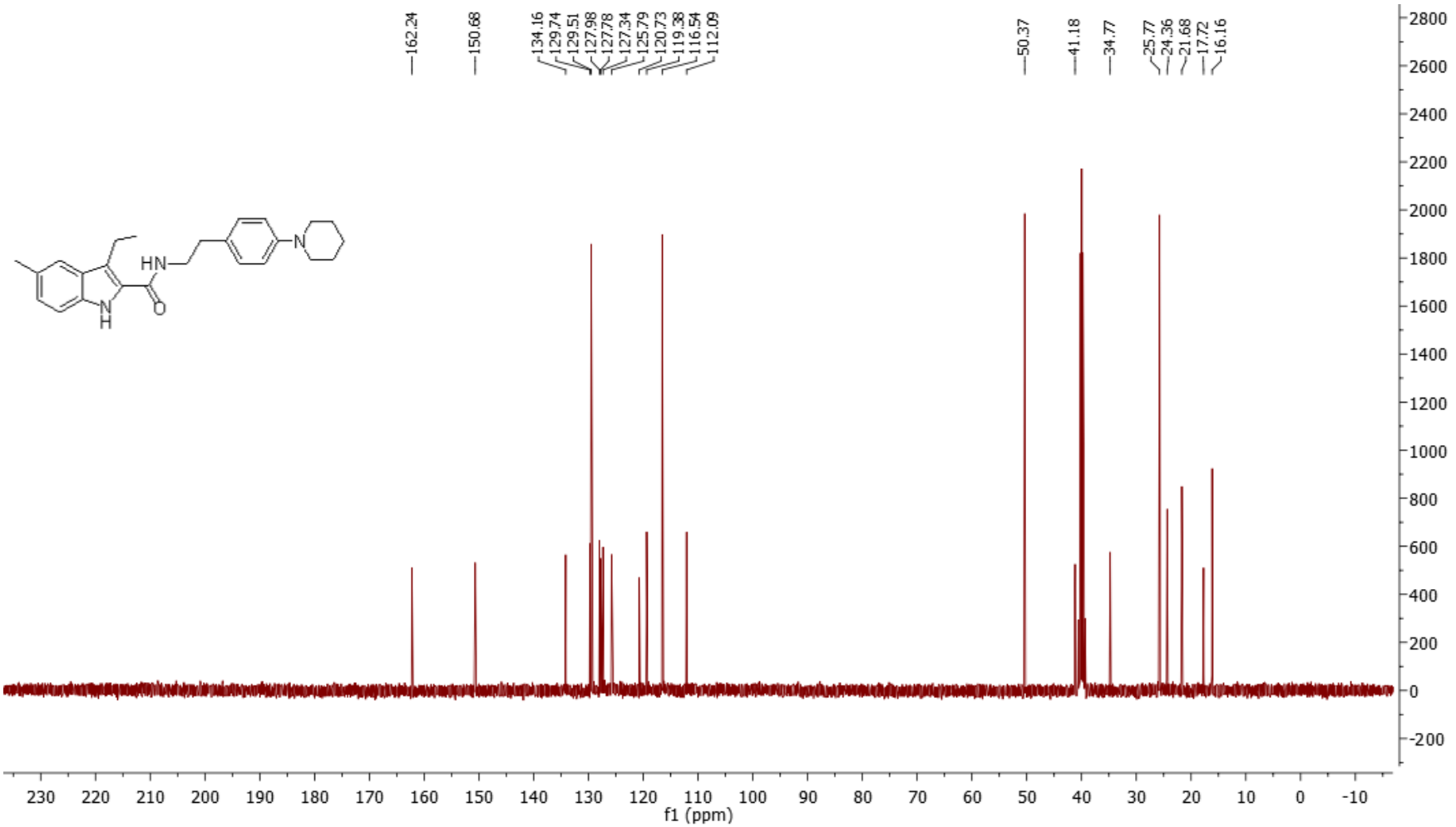
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 7.81 (t, J = 5.6 Hz, 1H), 7.36 (s, 1H), 7.26 (d, J = 8.3 Hz, 1H), 7.08 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.3 Hz, 1H), 6.83 (d, J = 8.7 Hz, 2H), 3.46 (q, J = 8.3 Hz, 2H), 3.04 (d, J = 5.2 Hz, 4H), 2.97 (q, J = 7.3 Hz, 2H), 2.75 (t, J = 7.4 Hz, 2H), 2.37 (s, 3H), 1.64 – 1.45 (m, 6H), 1.13 (t, J = 7.4 Hz, 3H).

5g



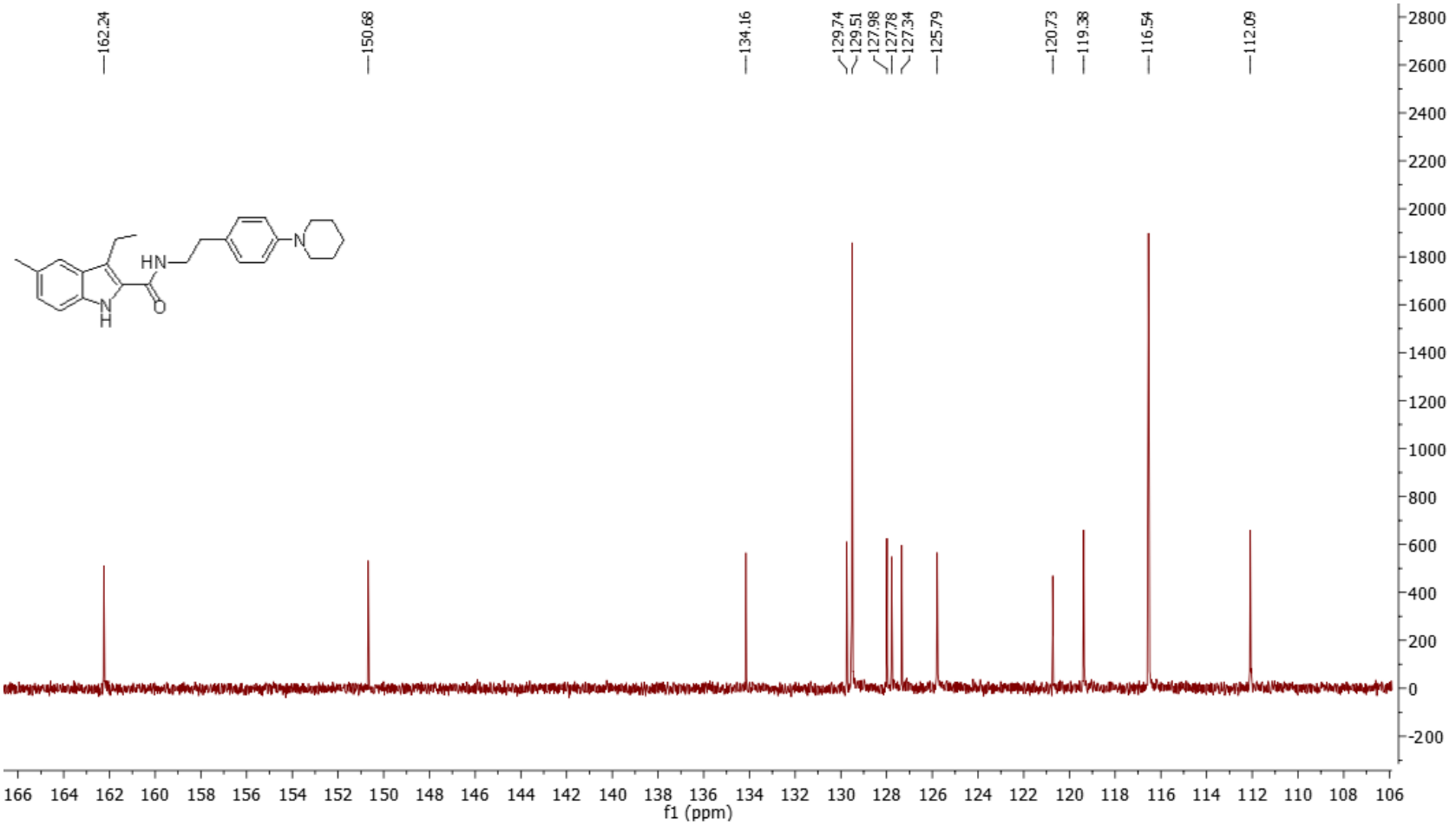
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 7.81 (t, J = 5.6 Hz, 1H), 7.36 (s, 1H), 7.26 (d, J = 8.3 Hz, 1H), 7.08 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.3 Hz, 1H), 6.83 (d, J = 8.7 Hz, 2H), 3.46 (q, J = 8.3 Hz, 2H), 3.04 (d, J = 5.2 Hz, 4H), 2.97 (q, J = 7.3 Hz, 2H), 2.75 (t, J = 7.4 Hz, 2H), 2.37 (s, 3H), 1.64 – 1.45 (m, 6H), 1.13 (t, J = 7.4 Hz, 3H).

5g



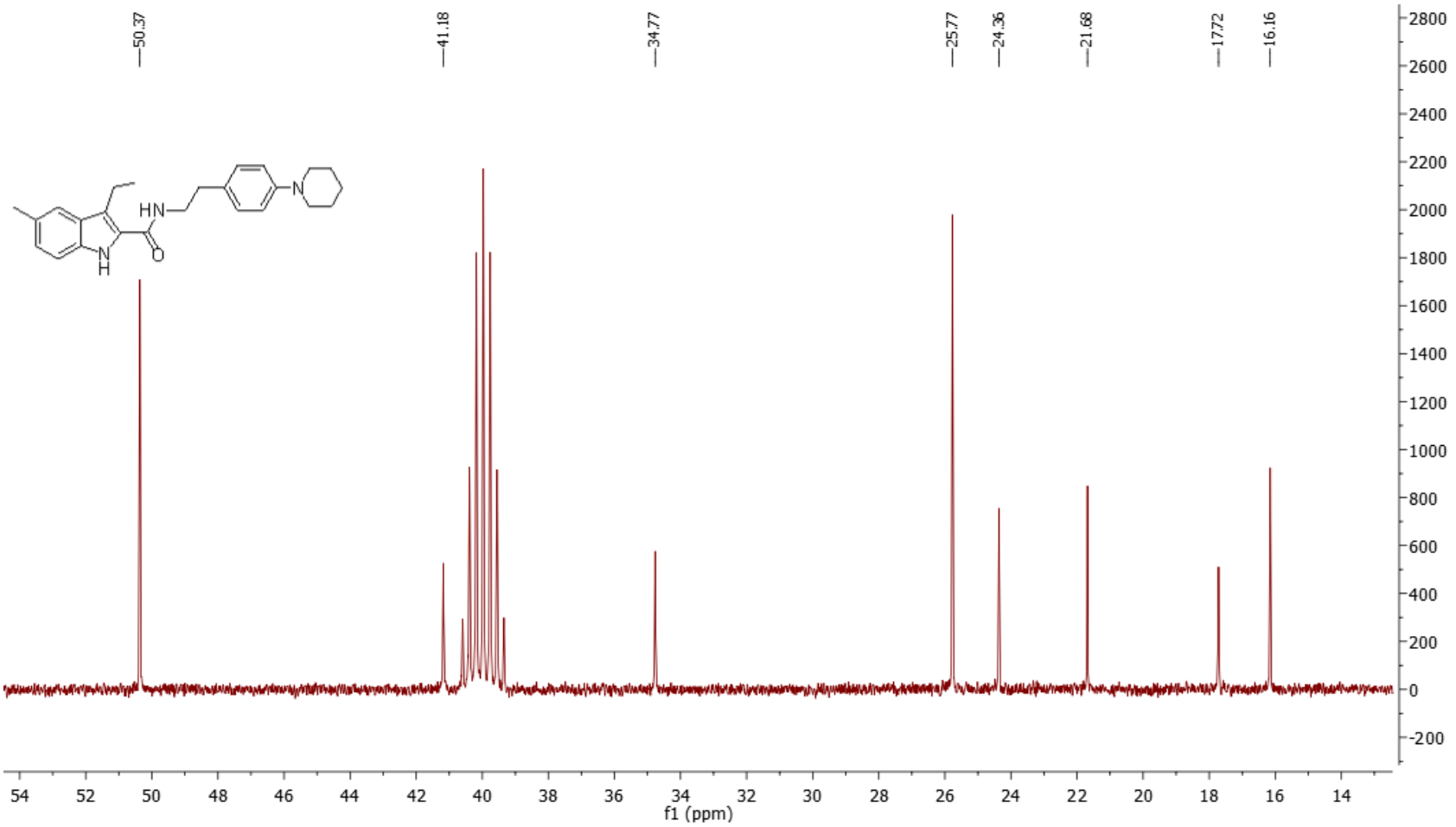
^{13}C NMR (101 MHz, dmso) δ 162.24, 150.68, 134.16, 129.74, 129.51, 127.98, 127.78, 127.34, 125.79, 120.73, 119.38, 116.54, 112.09, 50.37, 41.18, 34.77, 25.77, 24.36, 21.68, 17.72, 16.16.

5g



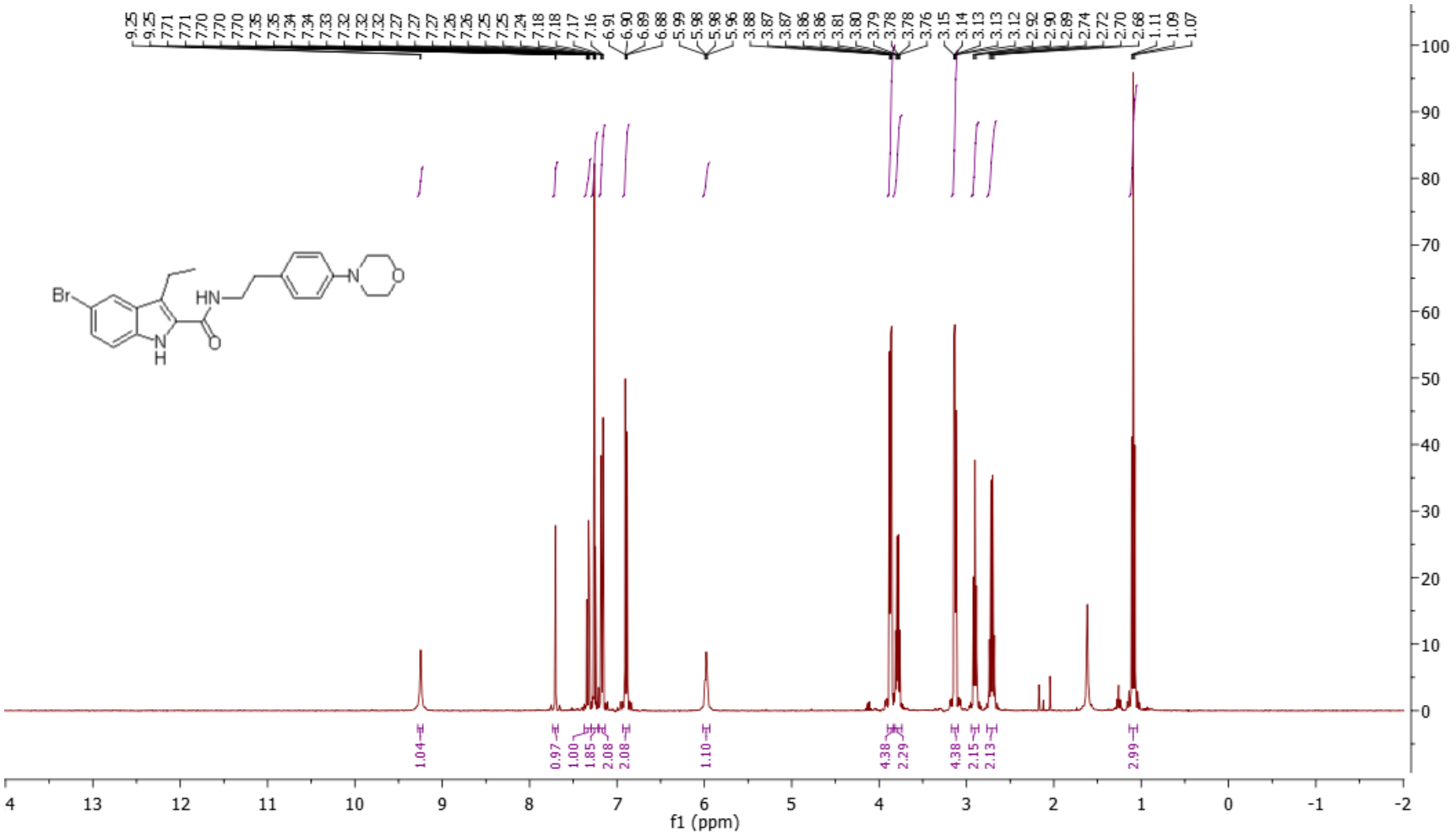
^{13}C NMR (101 MHz, dmso) δ 162.24, 150.68, 134.16, 129.74, 129.51, 127.98, 127.78, 127.34, 125.79, 120.73, 119.38, 116.54, 112.09, 50.37, 41.18, 34.77, 25.77, 24.36, 21.68, 17.72, 16.16.

5g



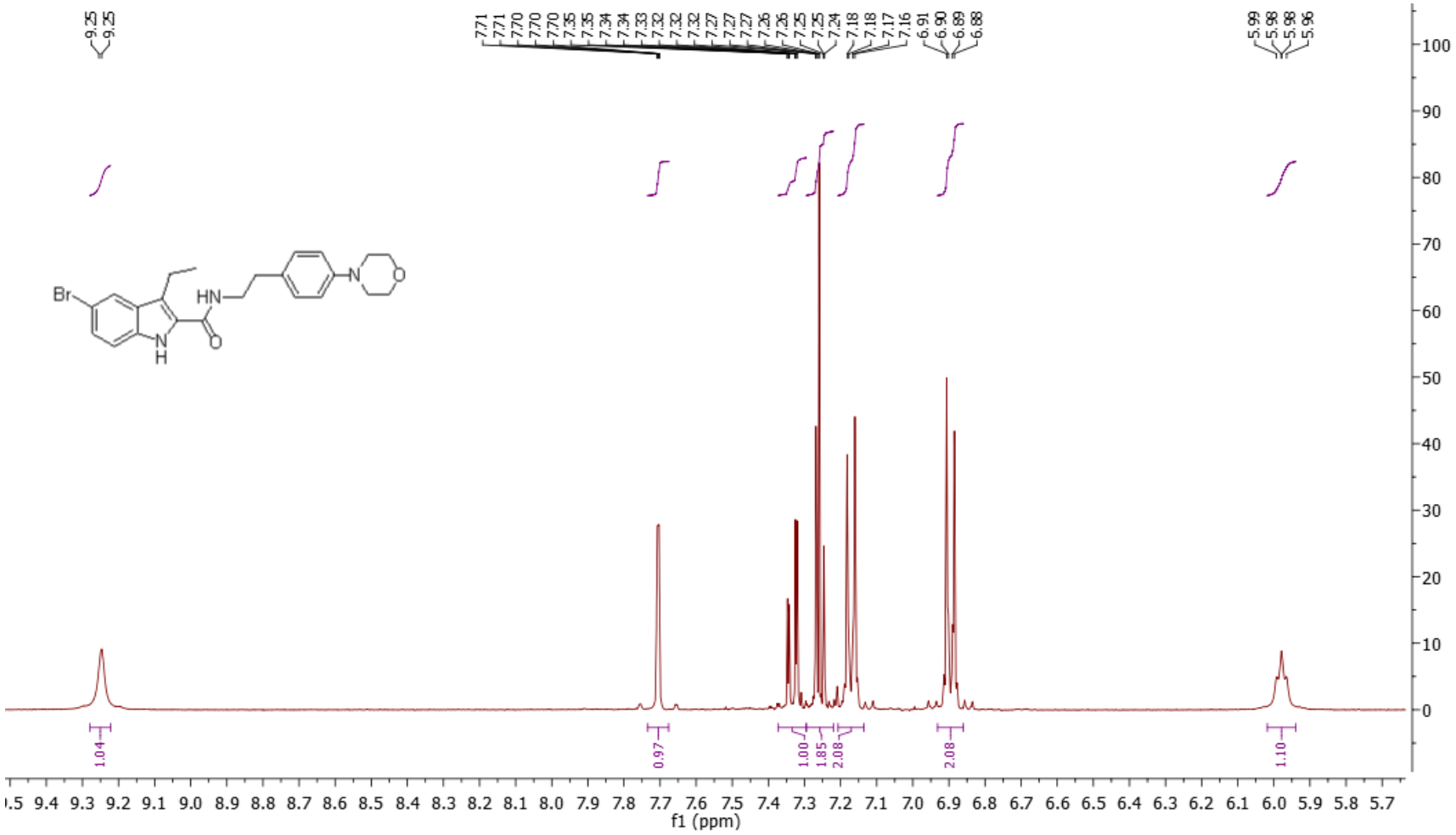
^{13}C NMR (101 MHz, dmso) δ 162.24, 150.68, 134.16, 129.74, 129.51, 127.98, 127.78, 127.34, 125.79, 120.73, 119.38, 116.54, 112.09, 50.37, 41.18, 34.77, 25.77, 24.36, 21.68, 17.72, 16.16.

5h



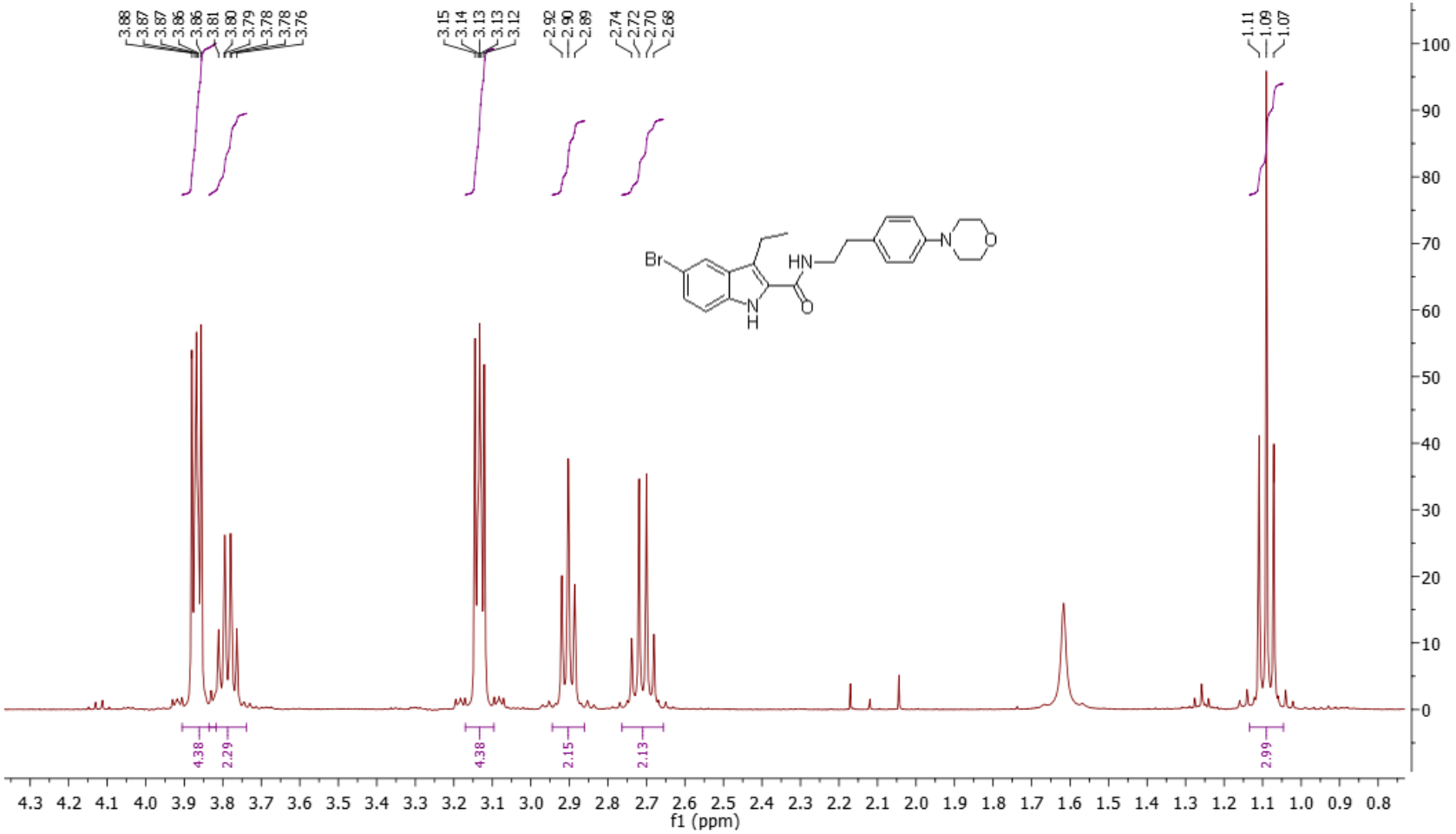
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.25 (s, 1H), 7.71 (d, J = 1.7 Hz, 1H), 7.33 (dd, J = 8.7, 1.9, Hz, 1H), 7.26 (m, 1H), 7.17 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 6.00 – 5.95 (t, J = 5.6 Hz, 1H), 3.91 – 3.82 (m, 4H), 3.79 (q, J = 6.7 Hz, 2H), 3.17 – 3.10 (m, 4H), 2.90 (t, J = 6.6 Hz, 2H), 2.71 (q, J = 7.7 Hz, 2H), 1.09 (t, J = 7.6 Hz, 3H).

5h



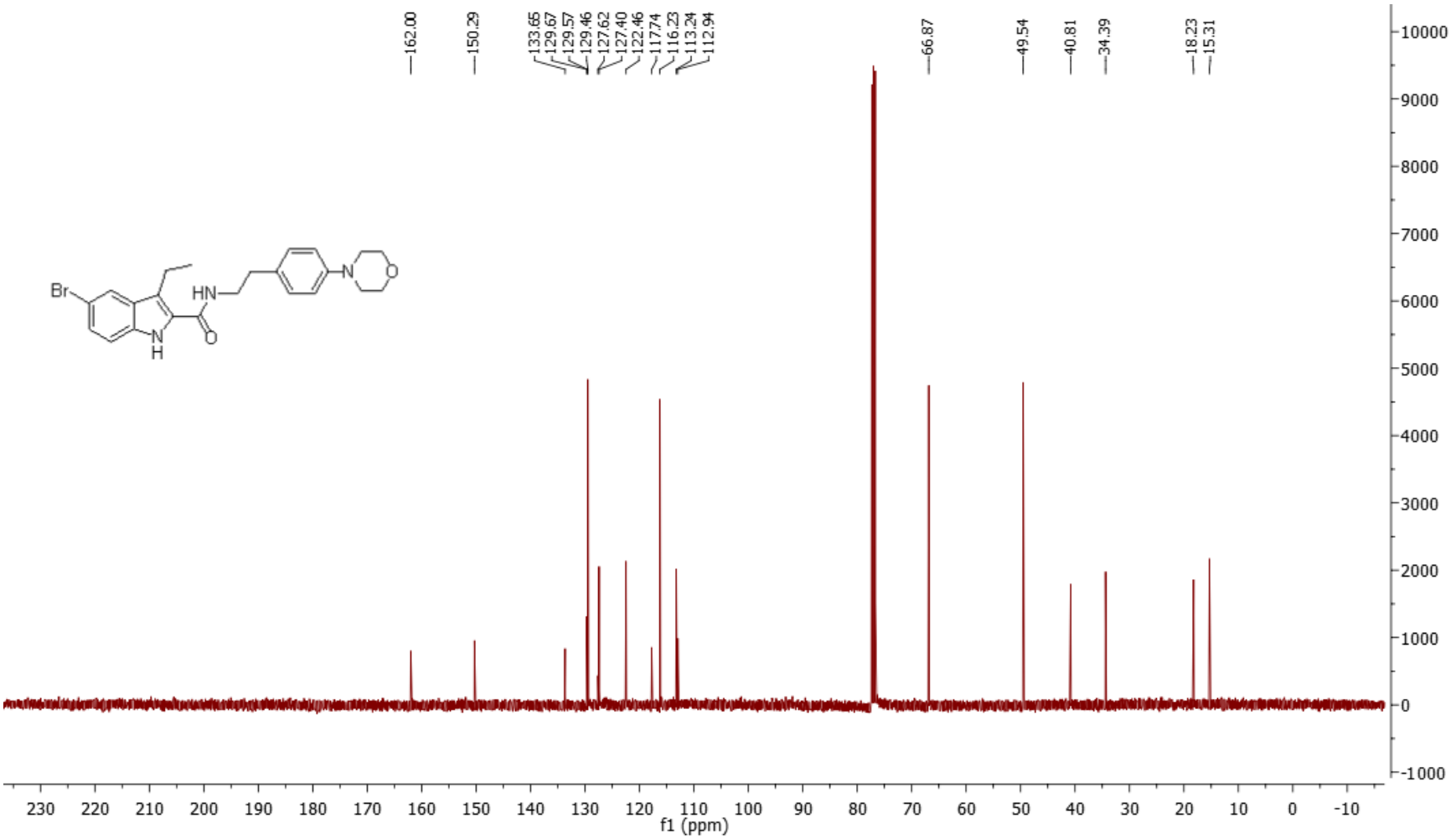
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.25 (s, 1H), 7.71 (d, *J* = 1.7 Hz, 1H), 7.33 (dd, *J* = 8.7, 1.9, Hz, 1H), 7.26 (m, 1H), 7.17 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.00 – 5.95 (t, *J* = 5.6 Hz, 1H), 3.91 – 3.82 (m, 4H), 3.79 (q, *J* = 6.7 Hz, 2H), 3.17 – 3.10 (m, 4H), 2.90 (t, *J* = 6.6 Hz, 2H), 2.71 (q, *J* = 7.7 Hz, 2H), 1.09 (t, *J* = 7.6 Hz, 3H).

5h



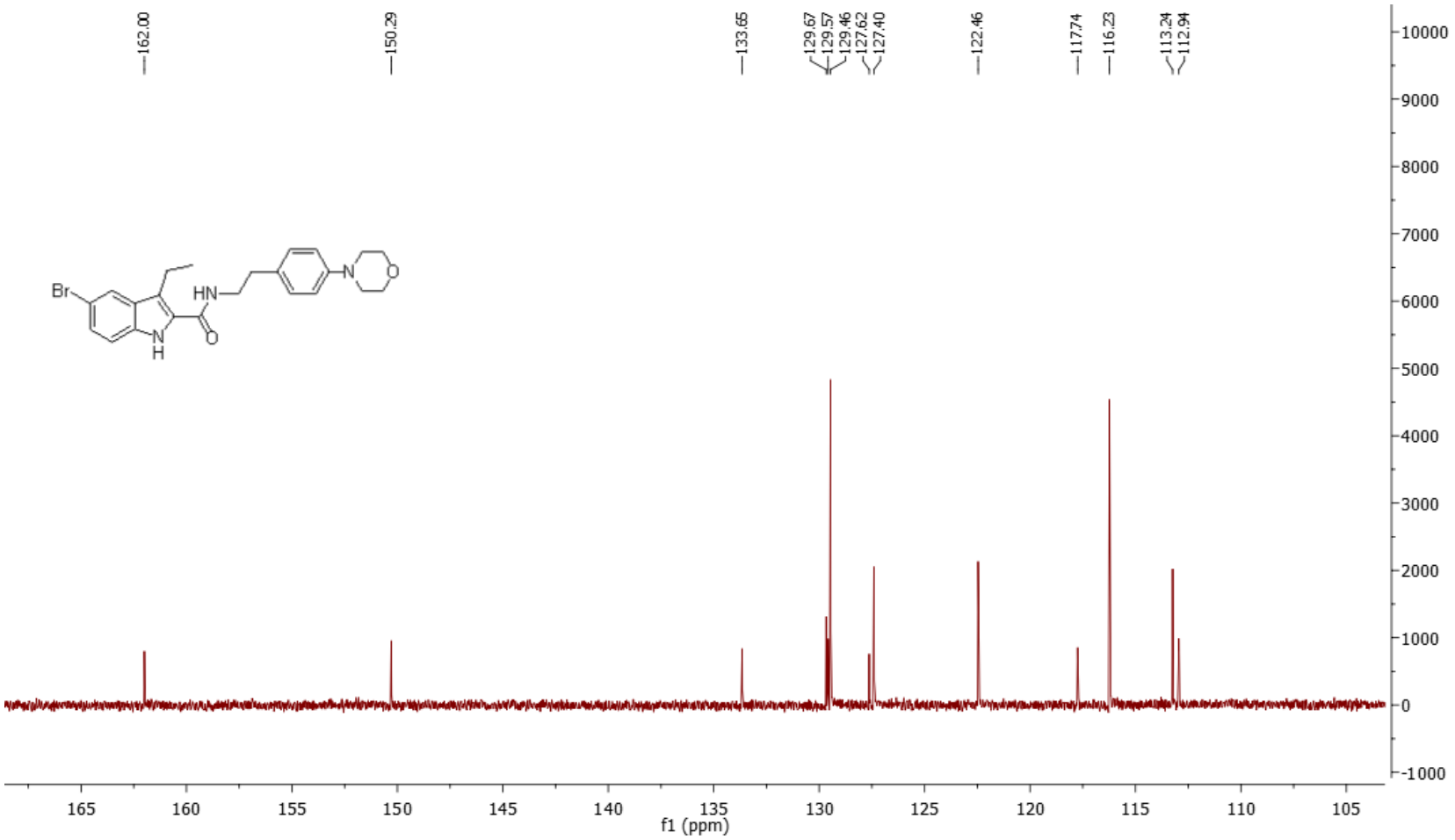
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.25 (s, 1H), 7.71 (d, J = 1.7 Hz, 1H), 7.33 (dd, J = 8.7, 1.9, Hz, 1H), 7.26 (m, 1H), 7.17 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 6.00 – 5.95 (t, J = 5.6 Hz, 1H), 3.91 – 3.82 (m, 4H), 3.79 (q, J = 6.7 Hz, 2H), 3.17 – 3.10 (m, 4H), 2.90 (t, J = 6.6 Hz, 2H), 2.71 (q, J = 7.7 Hz, 2H), 1.09 (t, J = 7.6 Hz, 3H).

5h



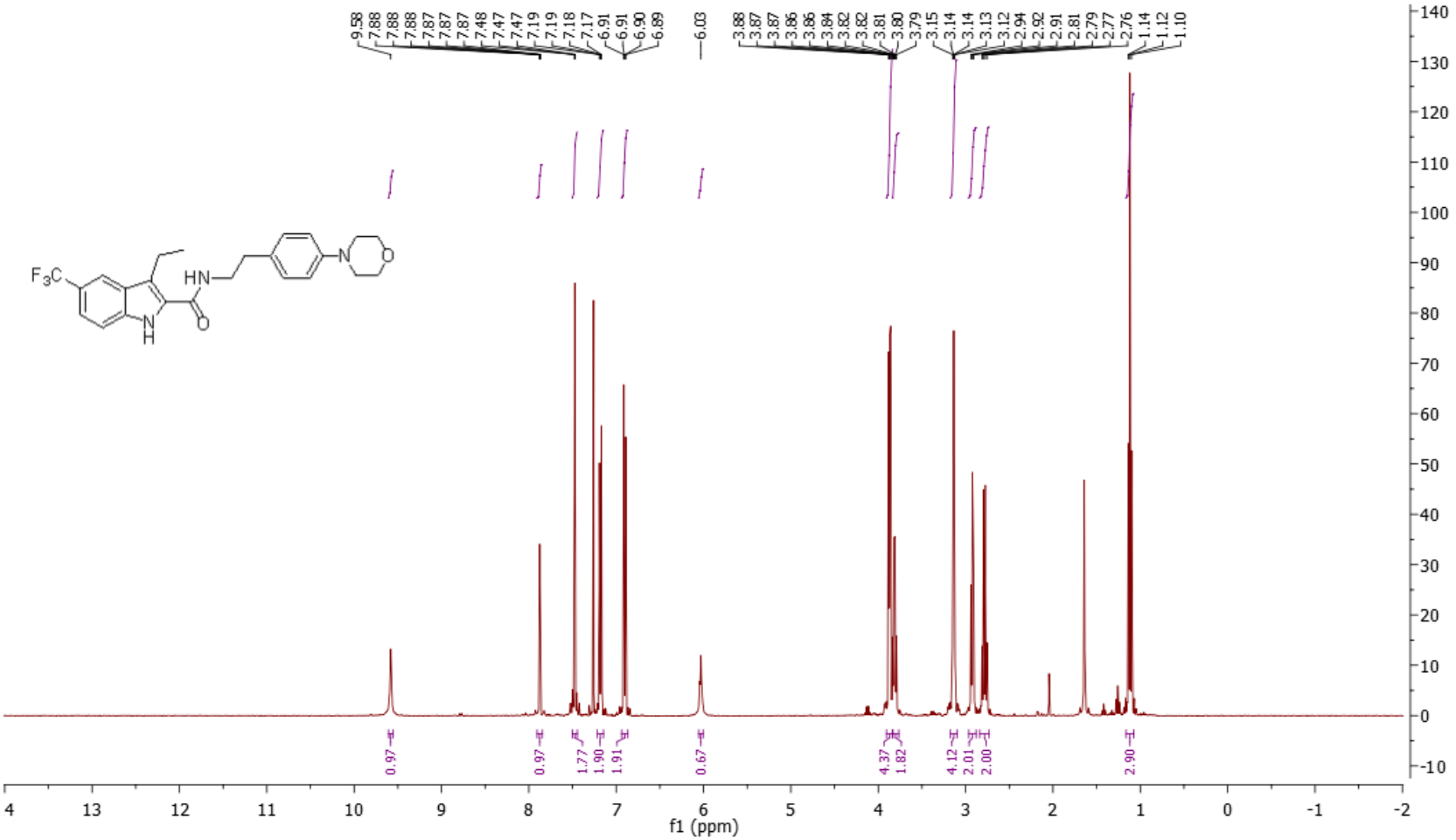
^{13}C NMR (101 MHz, cdcl$_3$) δ 162.00, 150.29, 133.65, 129.67, 129.57, 129.46, 127.62, 127.40, 122.46, 117.74, 116.23, 113.24, 112.94, 66.87, 49.54, 40.81, 34.39, 18.23, 15.31.

5h



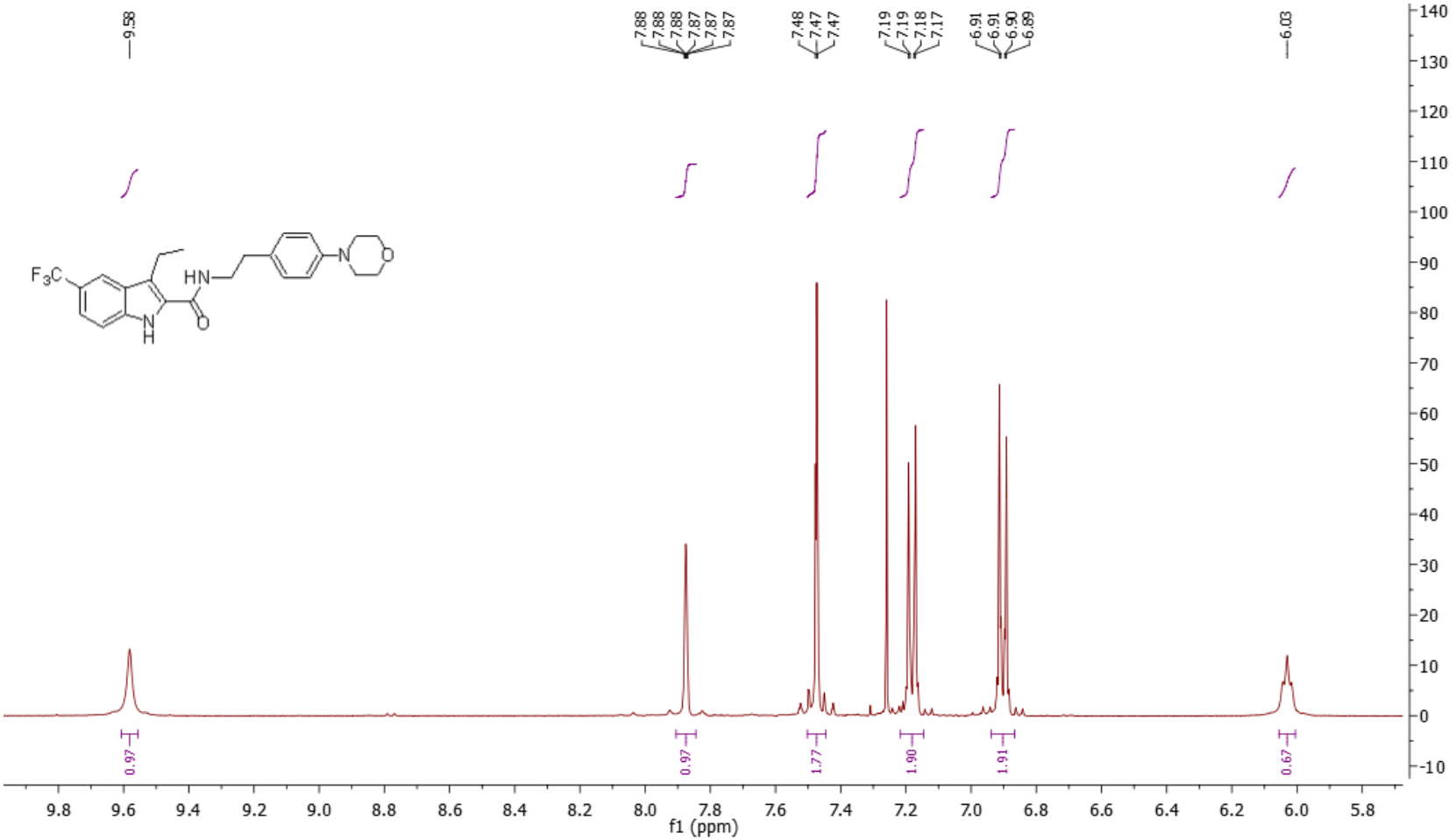
^{13}C NMR (101 MHz, cdcl$_3$) δ 162.00, 150.29, 133.65, 129.67, 129.57, 129.46, 127.62, 127.40, 122.46, 117.74, 116.23, 113.24, 112.94, 66.87, 49.54, 40.81, 34.39, 18.23, 15.31.

5i



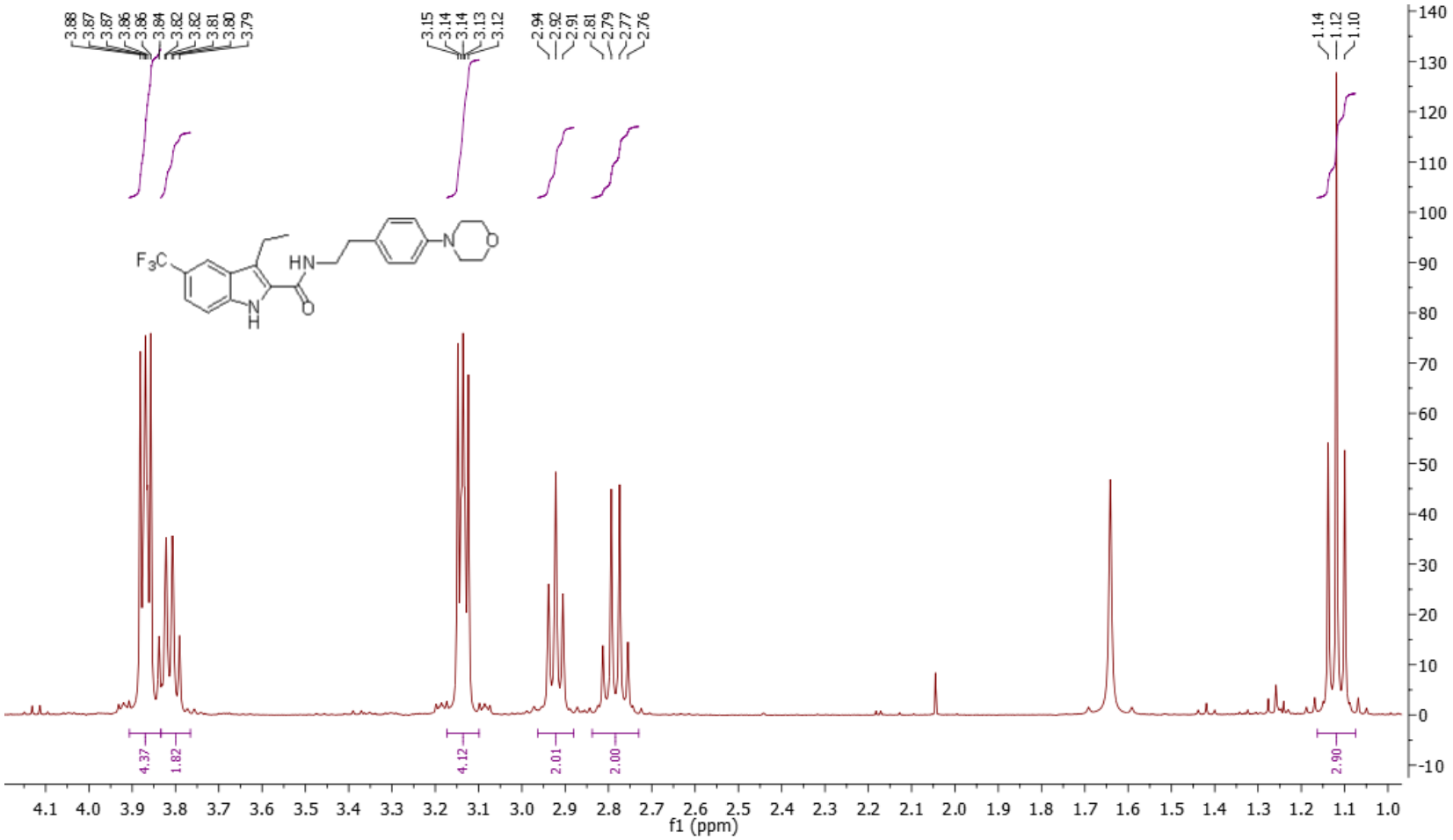
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.58 (s, 1H), 7.87 (s, 1H), 7.49 - 7.46 (m, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.03 (s, 1H), 3.91 – 3.83 (m, 4H), 3.80 (q, J = 6.4 Hz, 2H), 3.17 – 3.10 (m, 4H), 2.92 (t, *J* = 6.6 Hz, 2H), 2.78 (q, *J* = 7.7 Hz, 2H), 1.12 (t, *J* = 7.7 Hz, 3H).

5i



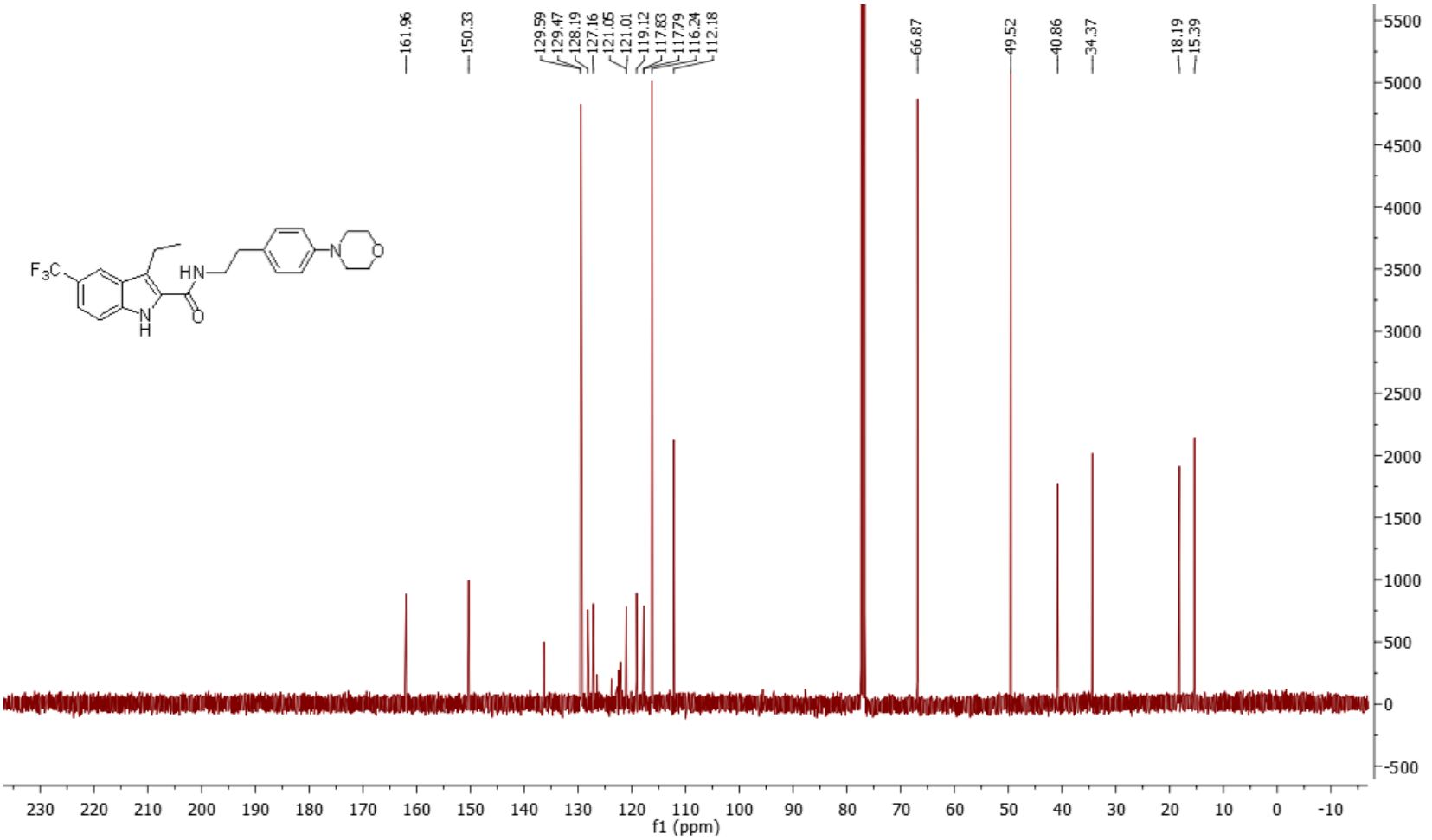
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.58 (s, 1H), 7.87 (s, 1H), 7.49 - 7.46 (m, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.03 (s, 1H), 3.91 – 3.83 (m, 4H), 3.80 (q, J = 6.4 Hz, 2H), 3.17 – 3.10 (m, 4H), 2.92 (t, *J* = 6.6 Hz, 2H), 2.78 (q, *J* = 7.7 Hz, 2H), 1.12 (t, *J* = 7.7 Hz, 3H).

5i



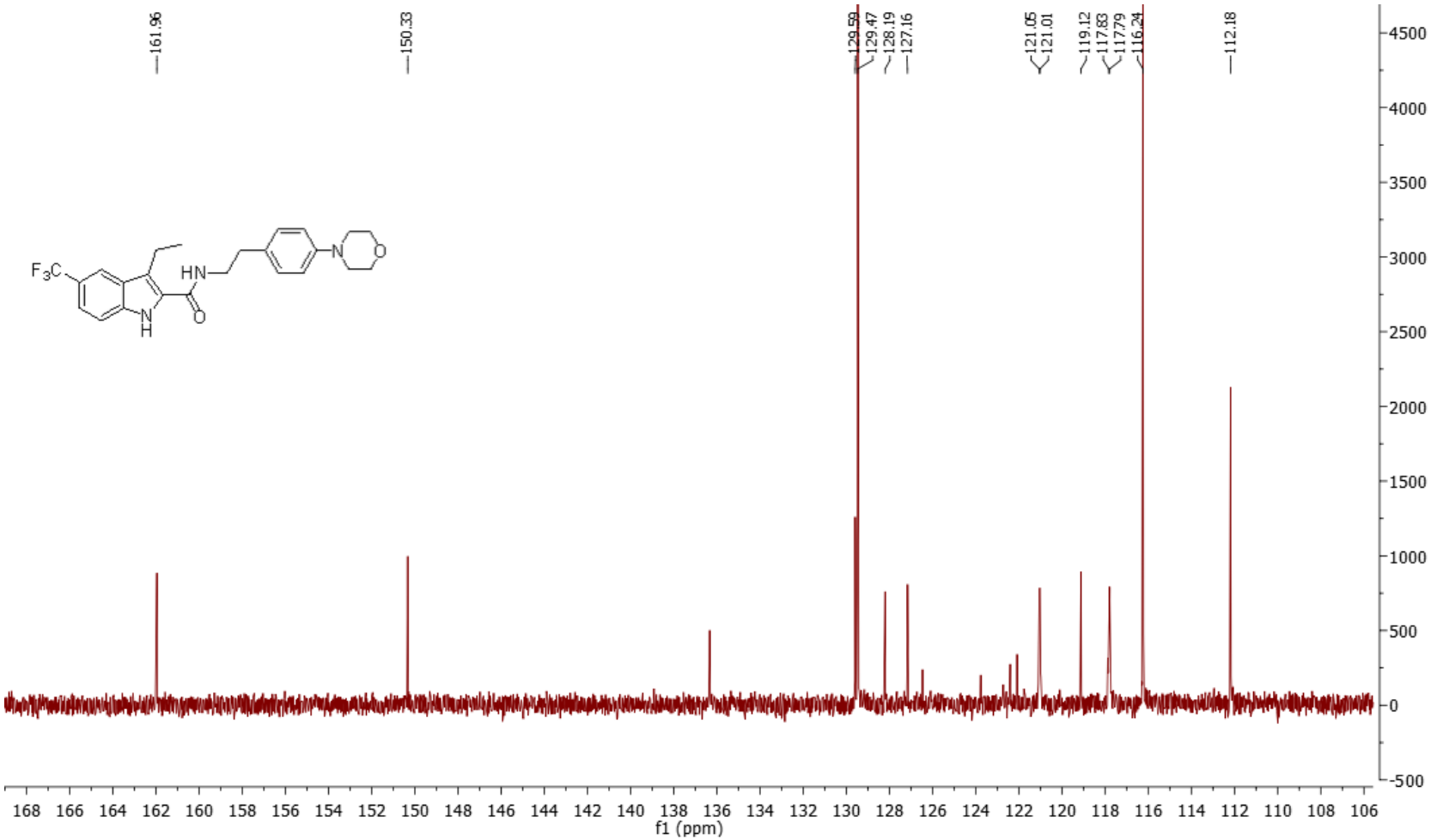
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.58 (s, 1H), 7.87 (s, 1H), 7.49 - 7.46 (m, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.03 (s, 1H), 3.91 – 3.83 (m, 4H), 3.80 (q, J = 6.4 Hz, 2H), 3.17 – 3.10 (m, 4H), 2.92 (t, *J* = 6.6 Hz, 2H), 2.78 (q, *J* = 7.7 Hz, 2H), 1.12 (t, *J* = 7.7 Hz, 3H).

5i



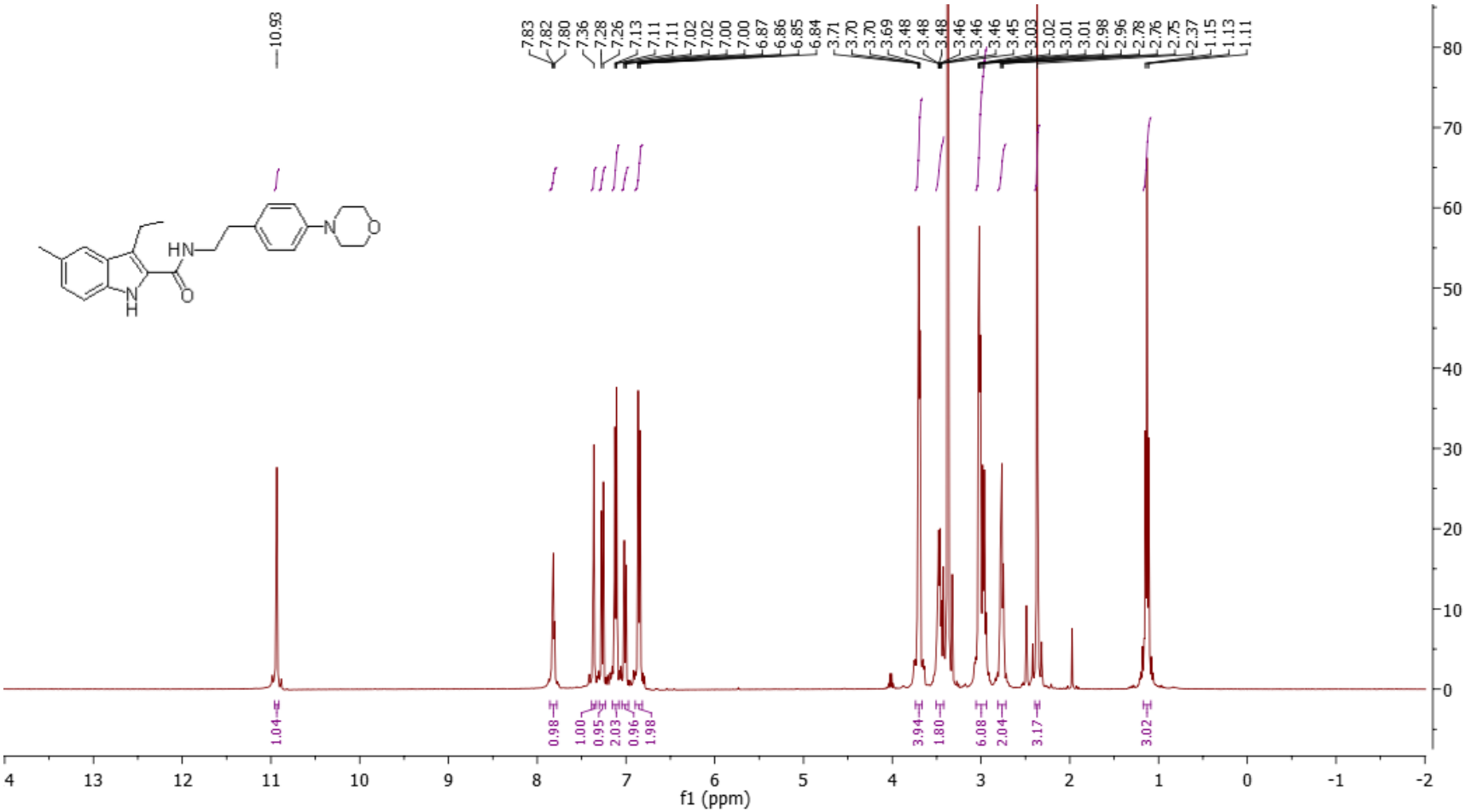
^{13}C NMR (101 MHz, cdcl$_3$) δ 161.96, 150.33, 129.59, 129.47, 128.19, 127.16, 121.05, 121.01, 119.12, 117.83, 117.79, 116.24, 112.18, 66.87, 49.52, 40.86, 34.37, 18.19, 15.39.

5i



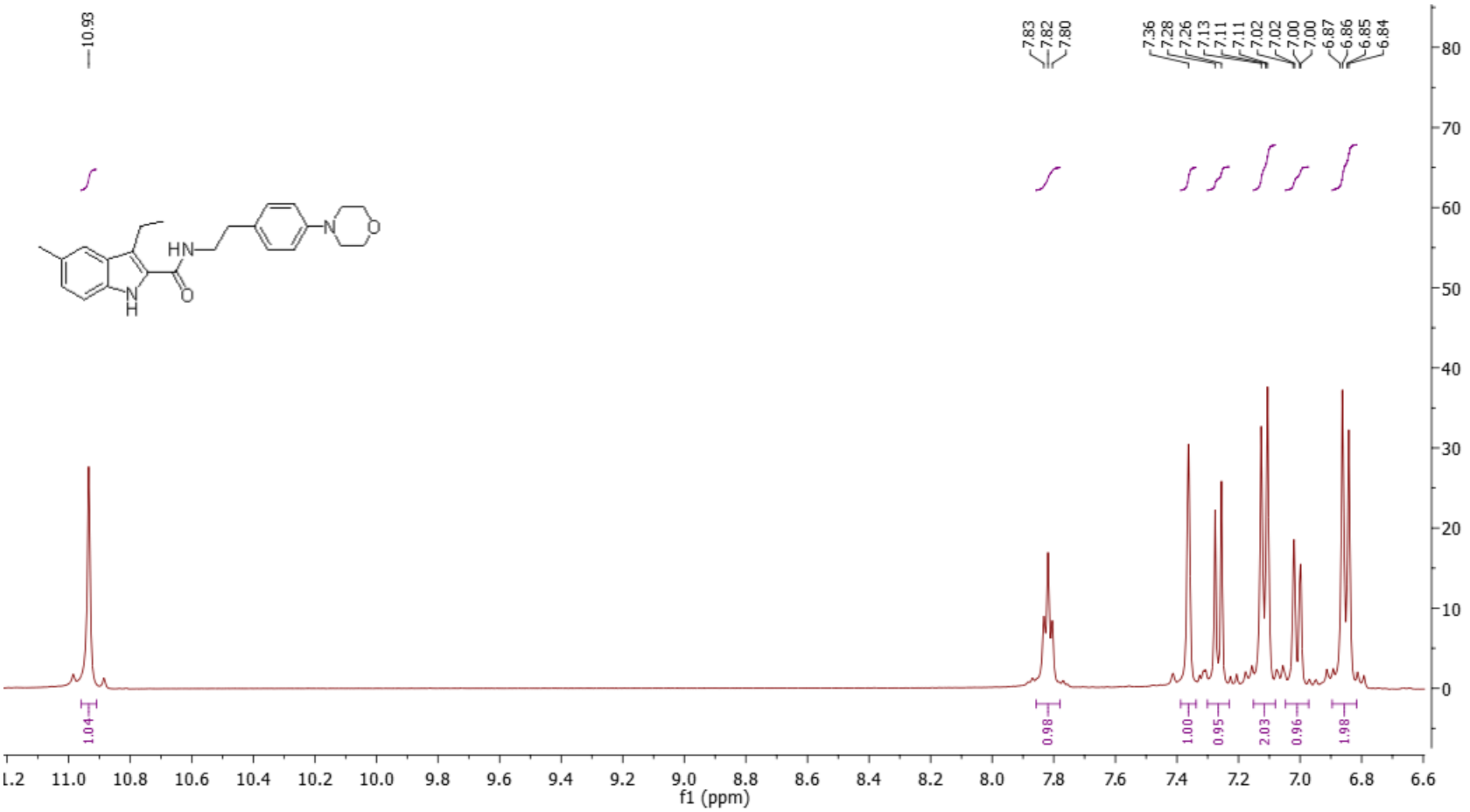
^{13}C NMR (101 MHz, cdcl$_3$) δ 161.96, 150.33, 129.59, 129.47, 128.19, 127.16, 121.05, 121.01, 119.12, 117.83, 117.79, 116.24, 112.18, 66.87, 49.52, 40.86, 34.37, 18.19, 15.39.

5j



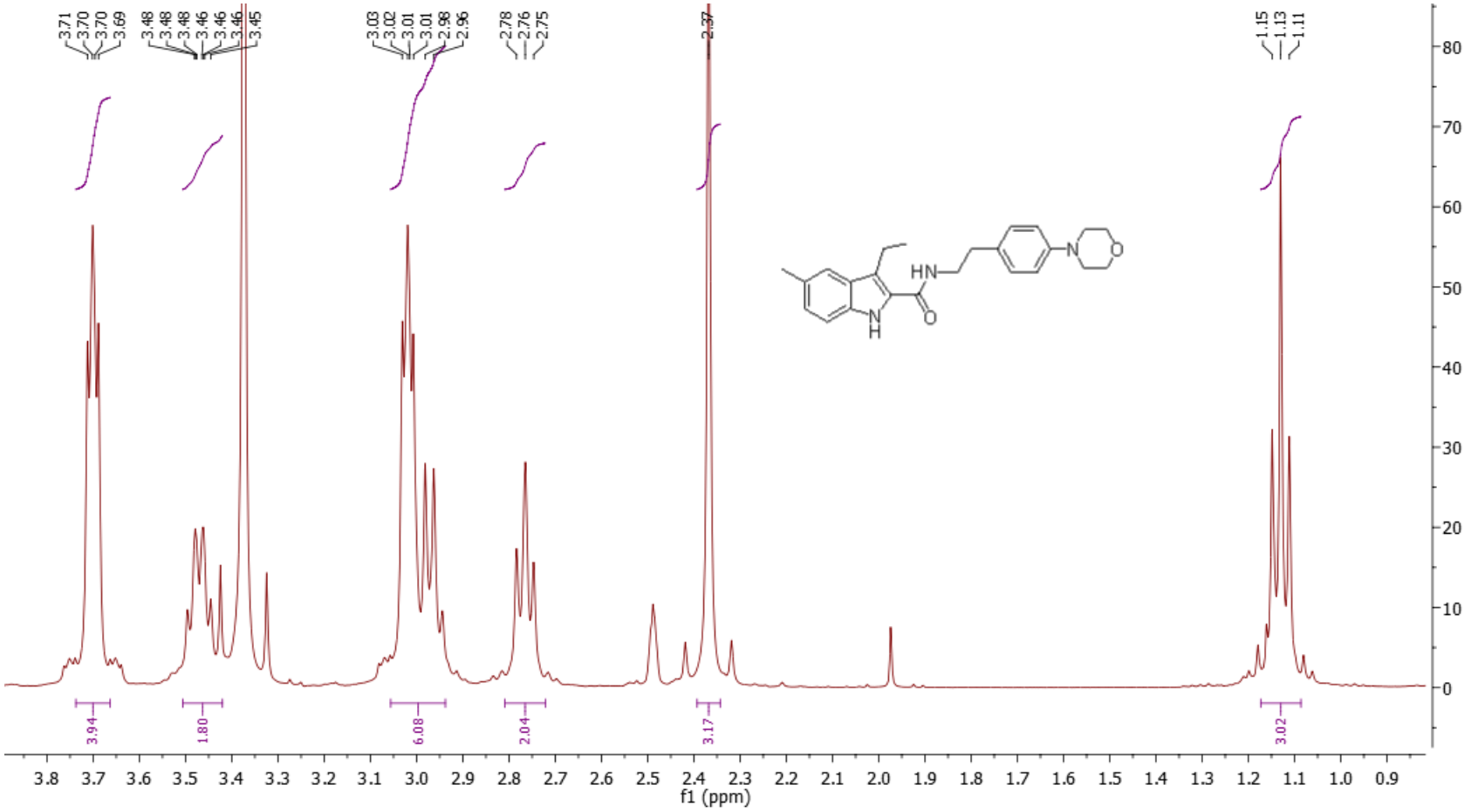
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 7.82 (t, J = 5.6 Hz, 1H), 7.36 (s, 1H), 7.27 (d, J = 8.3 Hz, 1H), 7.12 (d, J = 8.3 Hz, 2H), 7.01 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.3 Hz, 2H), 3.72 - 3.68 (m, 4H), 3.45 (q, J = 6.9 Hz, 2H), 3.06 – 2.94 (m, 6H), 2.77 (t, J = 7.4 Hz, 2H), 2.37 (s, 3H), 1.13 (t, J = 7.4 Hz, 3H).

5j



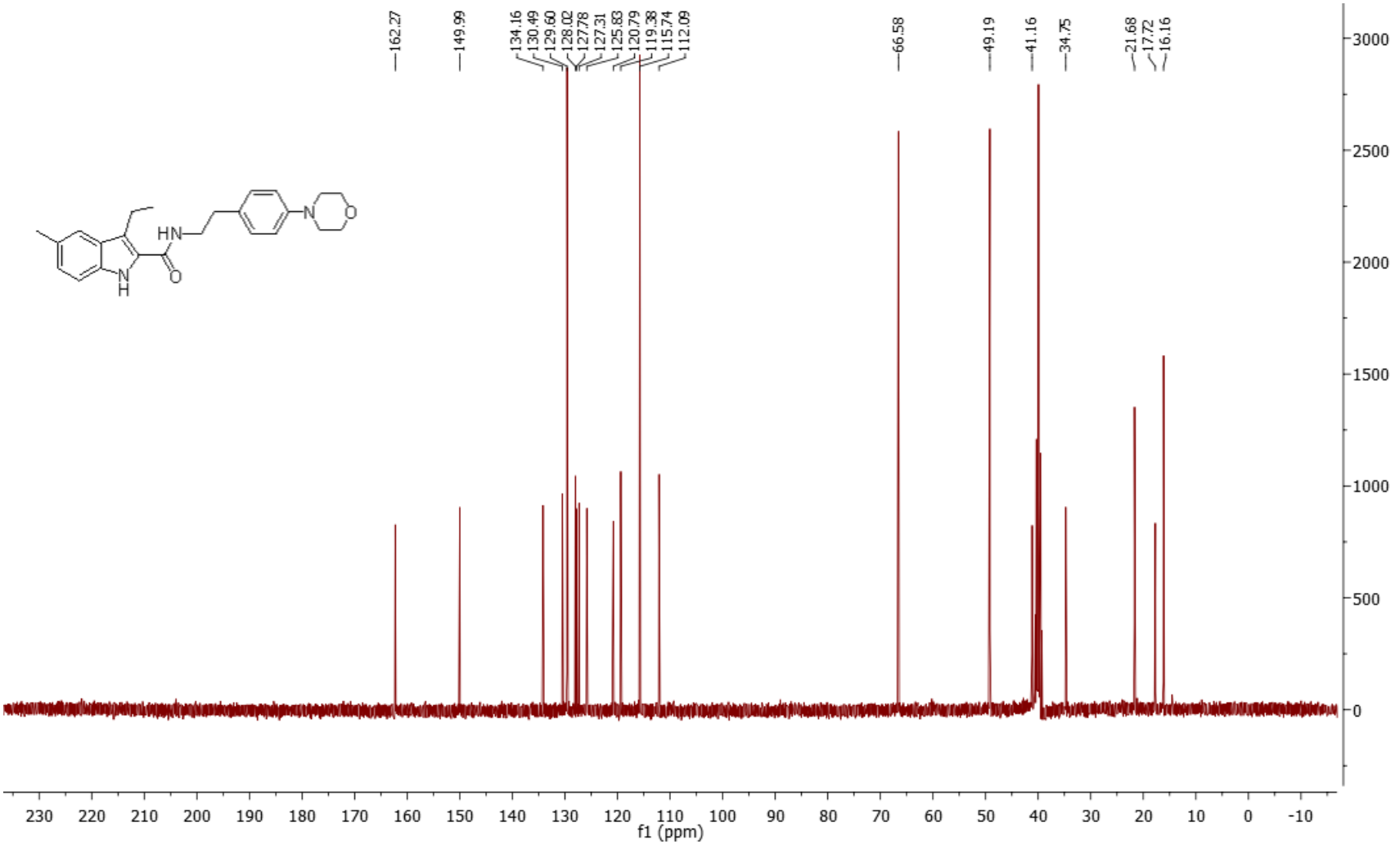
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 7.82 (t, J = 5.6 Hz, 1H), 7.36 (s, 1H), 7.27 (d, J = 8.3 Hz, 1H), 7.12 (d, J = 8.3 Hz, 2H), 7.01 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.3 Hz, 2H), 3.72 - 3.68 (m, 4H), 3.45 (q, J = 6.9 Hz, 2H), 3.06 – 2.94 (m, 6H), 2.77 (t, J = 7.4 Hz, 2H), 2.37 (s, 3H), 1.13 (t, J = 7.4 Hz, 3H).

5j



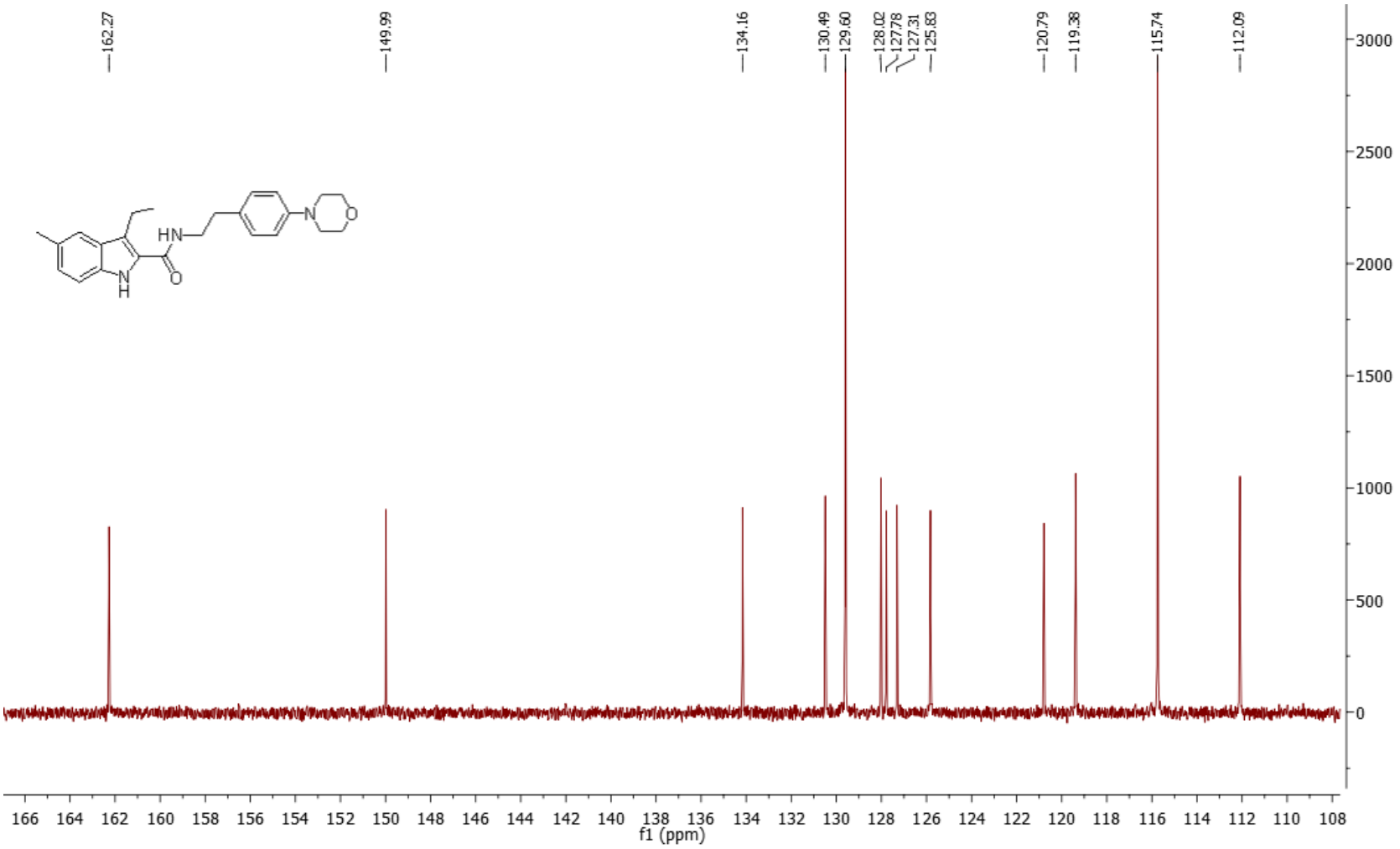
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 7.82 (t, J = 5.6 Hz, 1H), 7.36 (s, 1H), 7.27 (d, J = 8.3 Hz, 1H), 7.12 (d, J = 8.3 Hz, 2H), 7.01 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.3 Hz, 2H), 3.72 - 3.68 (m, 4H), 3.45 (q, J = 6.9 Hz, 2H), 3.06 – 2.94 (m, 6H), 2.77 (t, J = 7.4 Hz, 2H), 2.37 (s, 3H), 1.13 (t, J = 7.4 Hz, 3H).

5j



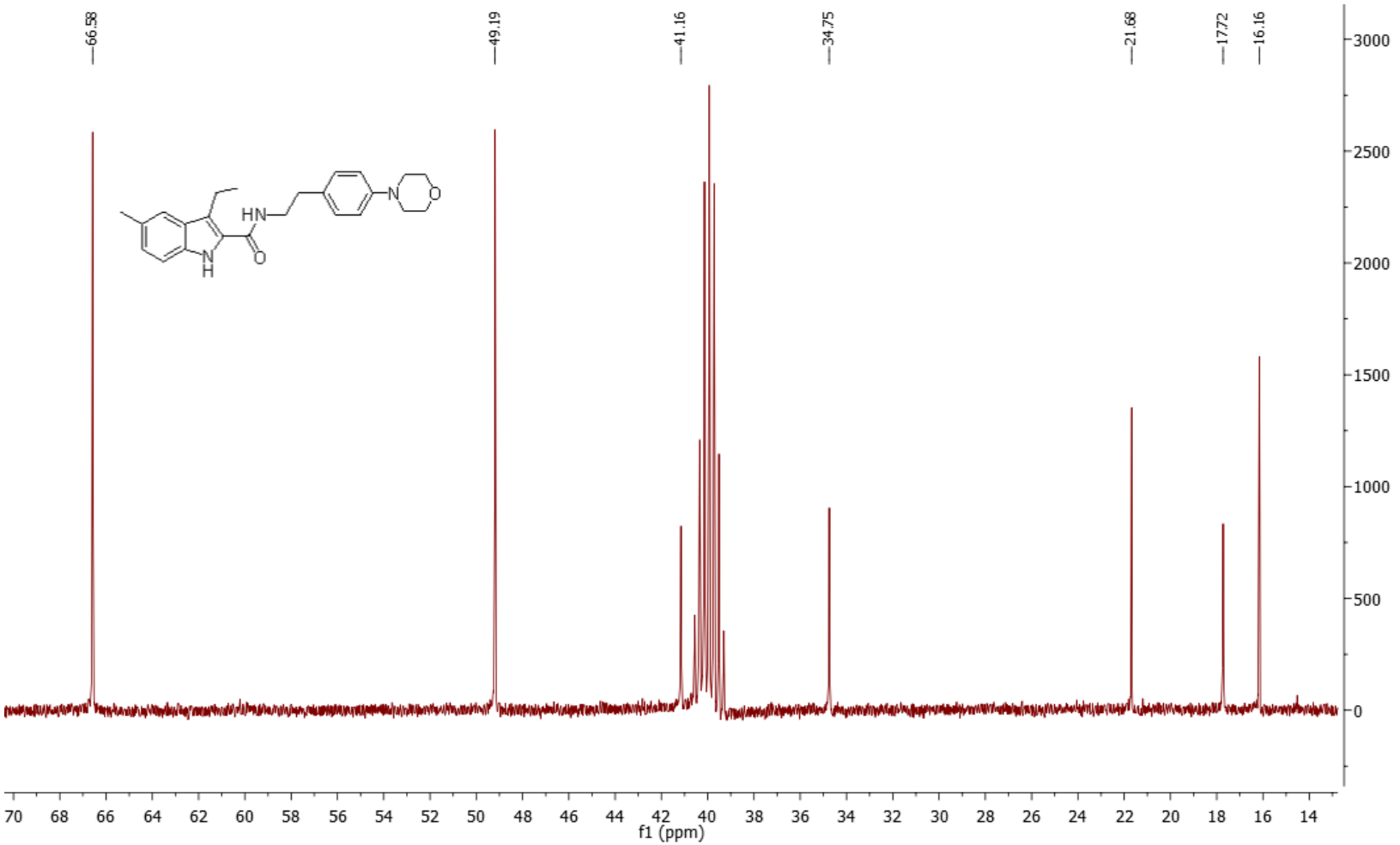
^{13}C NMR (101 MHz, dmso) δ 162.27, 149.99, 134.16, 130.49, 129.60, 128.02, 127.78, 127.31, 125.83, 120.79, 119.38, 115.74, 112.09, 66.58, 49.19, 41.16, 34.75, 21.68, 17.72, 16.16.

5j



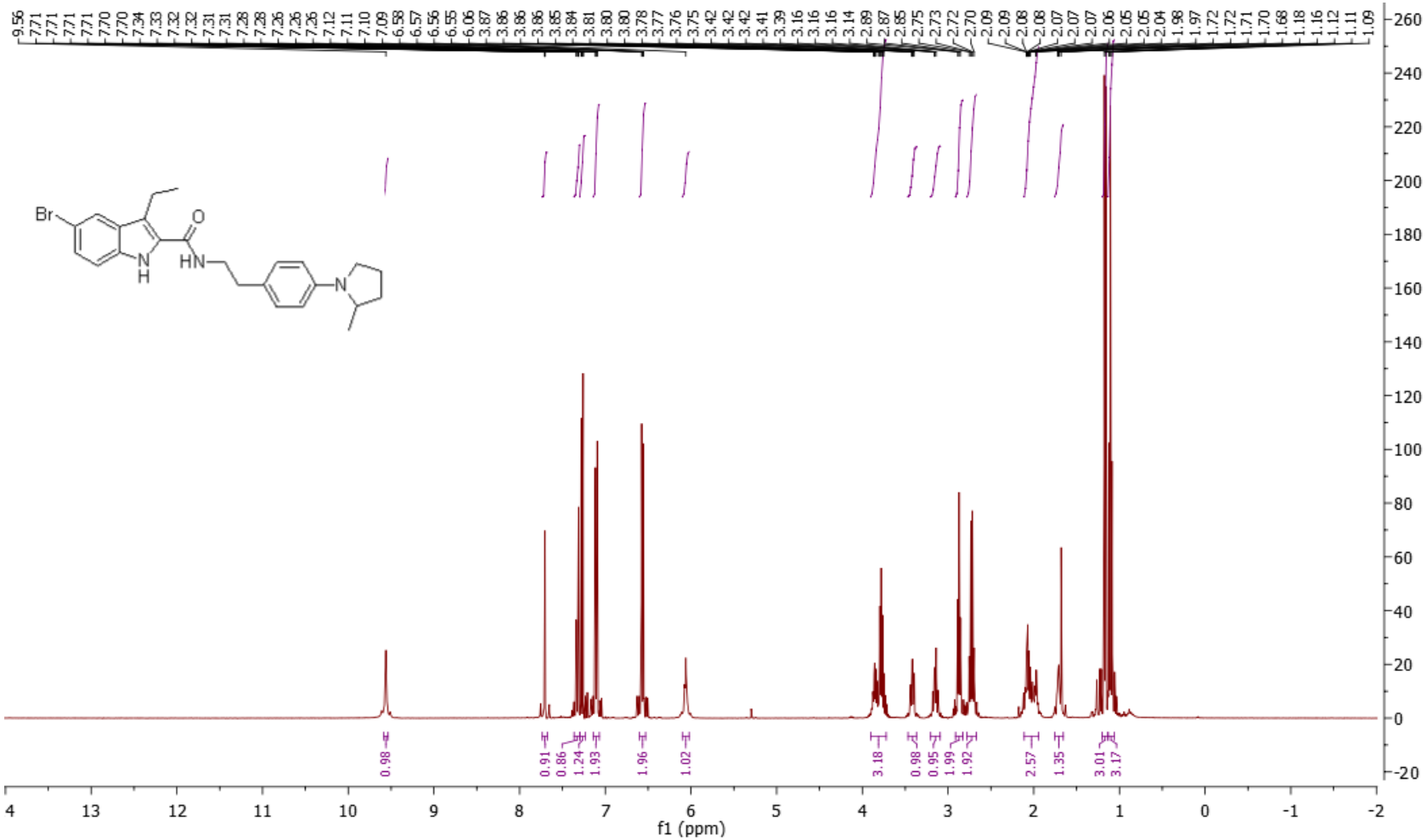
^{13}C NMR (101 MHz, dmso) δ 162.27, 149.99, 134.16, 130.49, 129.60, 128.02, 127.78, 127.31, 125.83, 120.79, 119.38, 115.74, 112.09, 66.58, 49.19, 41.16, 34.75, 21.68, 17.72, 16.16.

5j



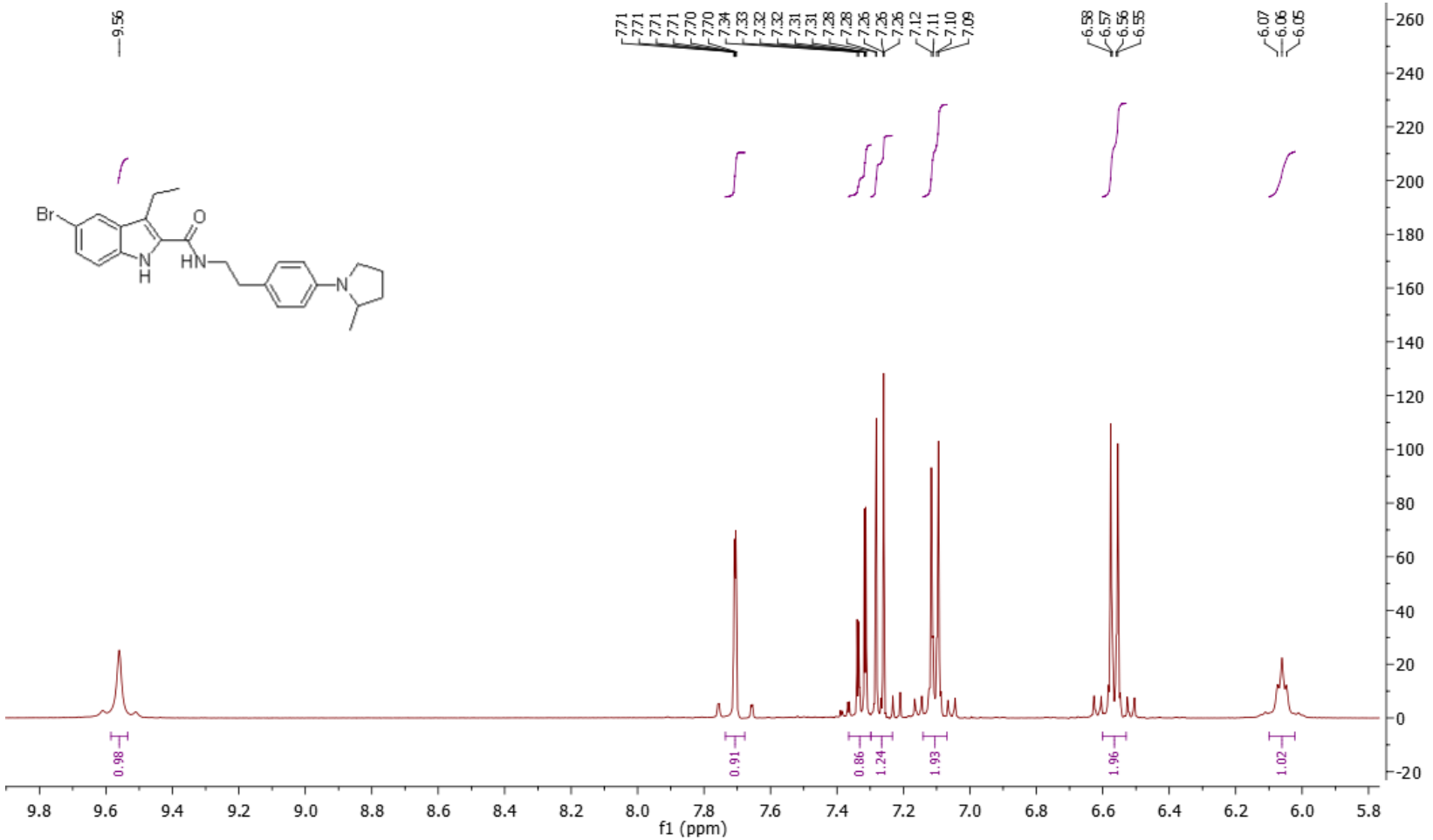
^{13}C NMR (101 MHz, dmso) δ 162.27, 149.99, 134.16, 130.49, 129.60, 128.02, 127.78, 127.31, 125.83, 120.79, 119.38, 115.74, 112.09, 66.58, 49.19, 41.16, 34.75, 21.68, 17.72, 16.16.

5k



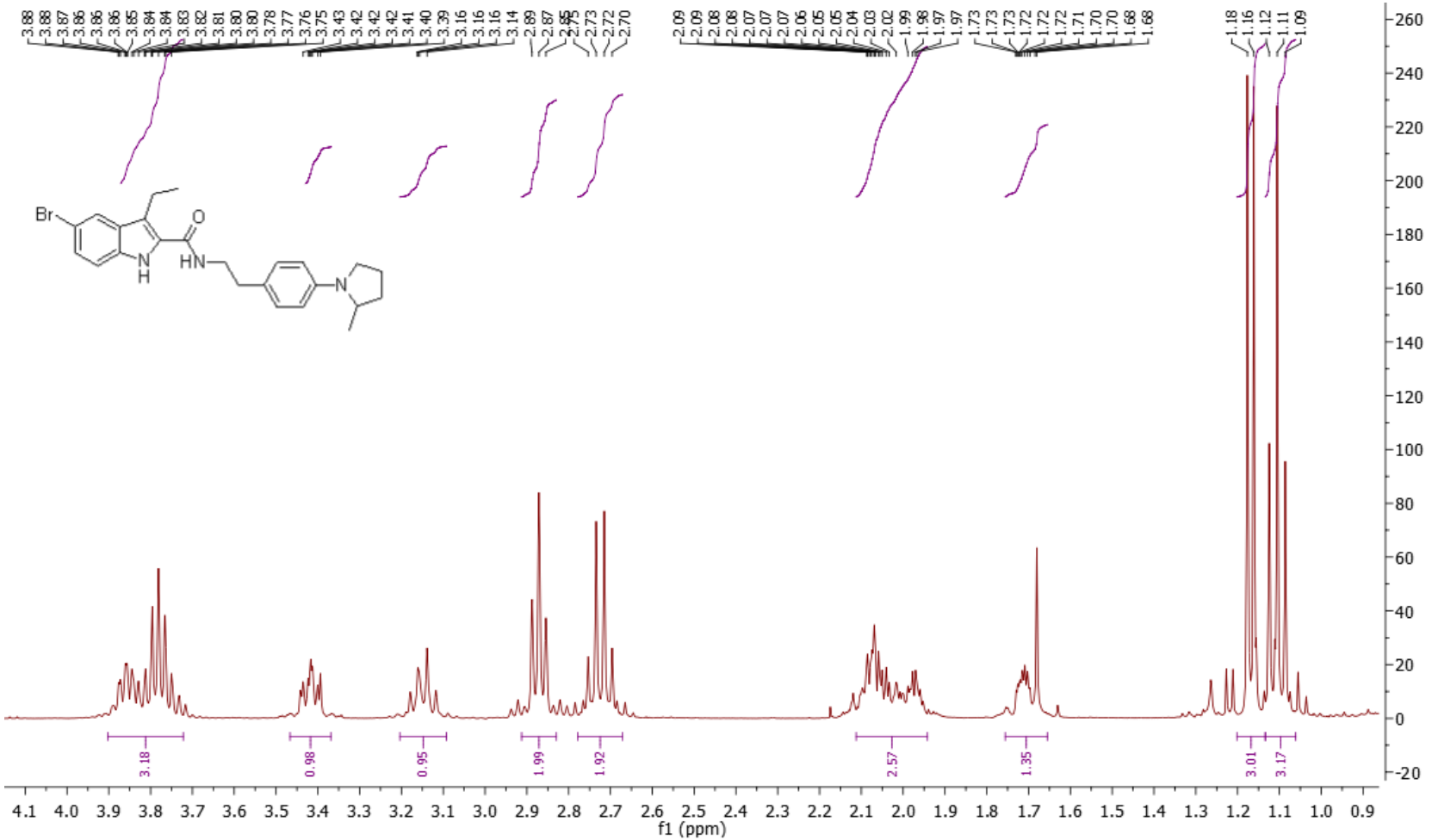
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.56 (s, 1H), 7.71 (d, J = 1.9 Hz, 1H), 7.32 (dd, J = 8.6, 2.0 Hz, 1H), 7.27 (d, J = 8.6 Hz, 1H), 7.10 (d, J = 8.6 Hz, 2H), 6.57 (d, J = 8.6 Hz, 2H), 6.06 (t, J = 5.6 Hz, 1H), 3.90 – 3.72 (m, 3H), 3.44 - 3.39 (m, 1H), 3.20 – 3.09 (m, 1H), 2.87 (t, J = 6.6 Hz, 2H), 2.72 (q, J = 7.7 Hz, 2H), 2.11 – 1.94 (m, 3H), 1.76 – 1.66 (m, 1H), 1.17 (d, J = 6.1 Hz, 3H), 1.11 (t, J = 7.7 Hz, 3H).

5k



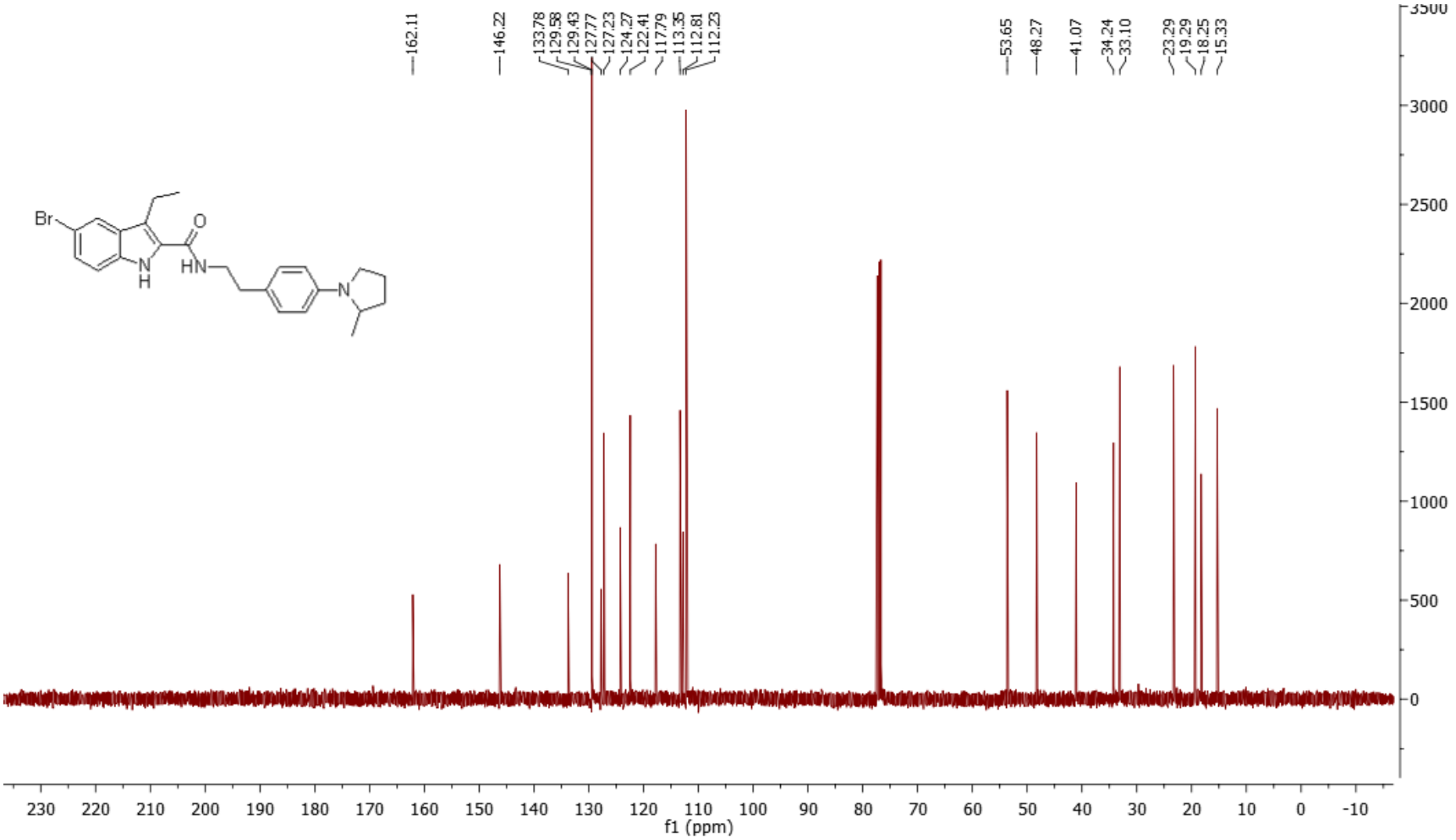
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.56 (s, 1H), 7.71 (d, J = 1.9 Hz, 1H), 7.32 (dd, J = 8.6, 2.0 Hz, 1H), 7.27 (d, J = 8.6 Hz, 1H), 7.10 (d, J = 8.6 Hz, 2H), 6.57 (d, J = 8.6 Hz, 2H), 6.06 (t, J = 5.6 Hz, 1H), 3.90 – 3.72 (m, 3H), 3.44 - 3.39 (m, 1H), 3.20 – 3.09 (m, 1H), 2.87 (t, J = 6.6 Hz, 2H), 2.72 (q, J = 7.7 Hz, 2H), 2.11 – 1.94 (m, 3H), 1.76 – 1.66 (m, 1H), 1.17 (d, J = 6.1 Hz, 3H), 1.11 (t, J = 7.7 Hz, 3H).

5k



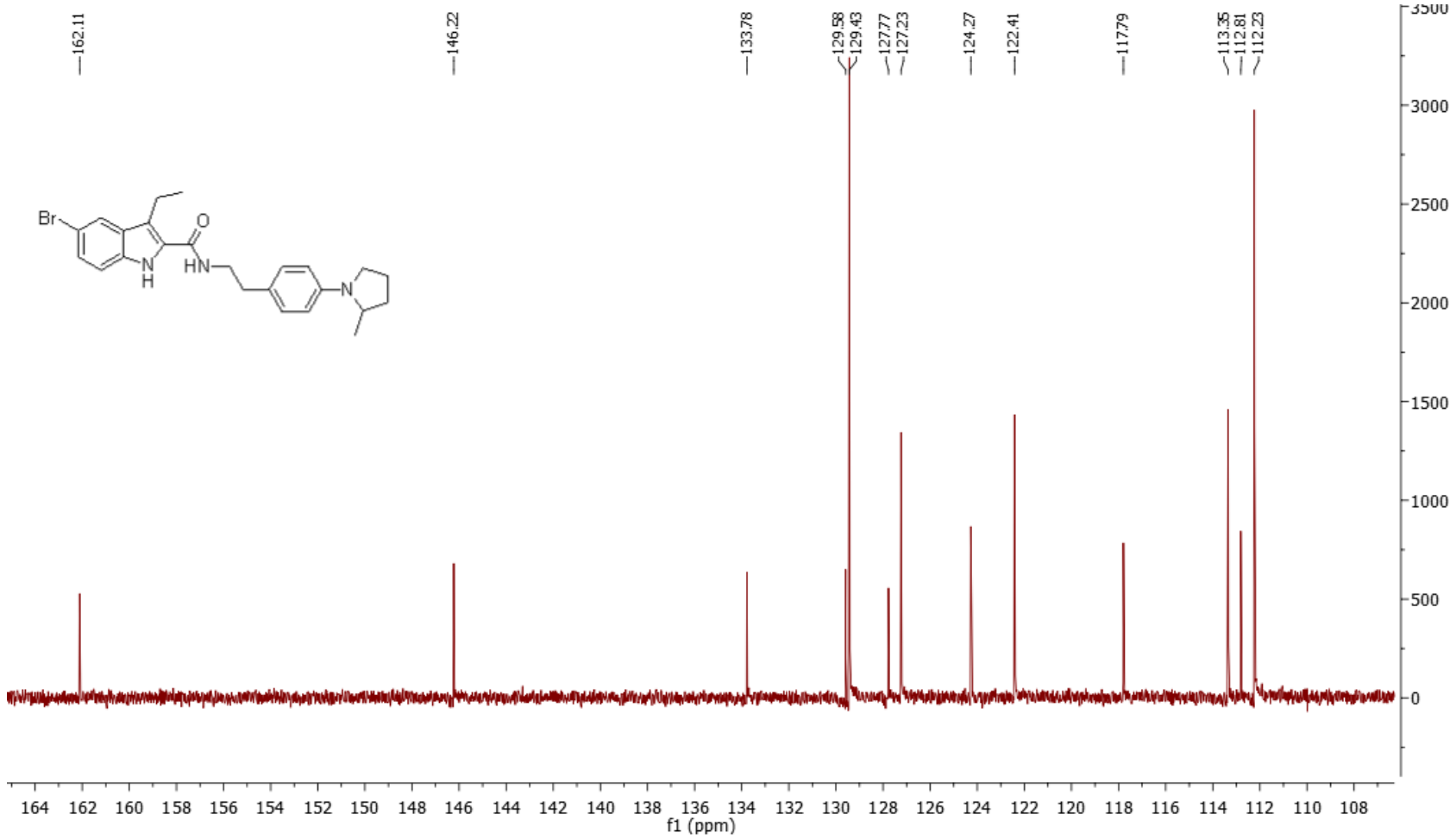
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.56 (s, 1H), 7.71 (d, *J* = 1.9 Hz, 1H), 7.32 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.27 (d, *J* = 8.6 Hz, 1H), 7.10 (d, *J* = 8.6 Hz, 2H), 6.57 (d, *J* = 8.6 Hz, 2H), 6.06 (t, *J* = 5.6 Hz, 1H), 3.90 – 3.72 (m, 3H), 3.44 - 3.39 (m, 1H), 3.20 – 3.09 (m, 1H), 2.87 (t, *J* = 6.6 Hz, 2H), 2.72 (q, *J* = 7.7 Hz, 2H), 2.11 – 1.94 (m, 3H), 1.76 – 1.66 (m, 1H), 1.17 (d, *J* = 6.1 Hz, 3H), 1.11 (t, *J* = 7.7 Hz, 3H).

5k



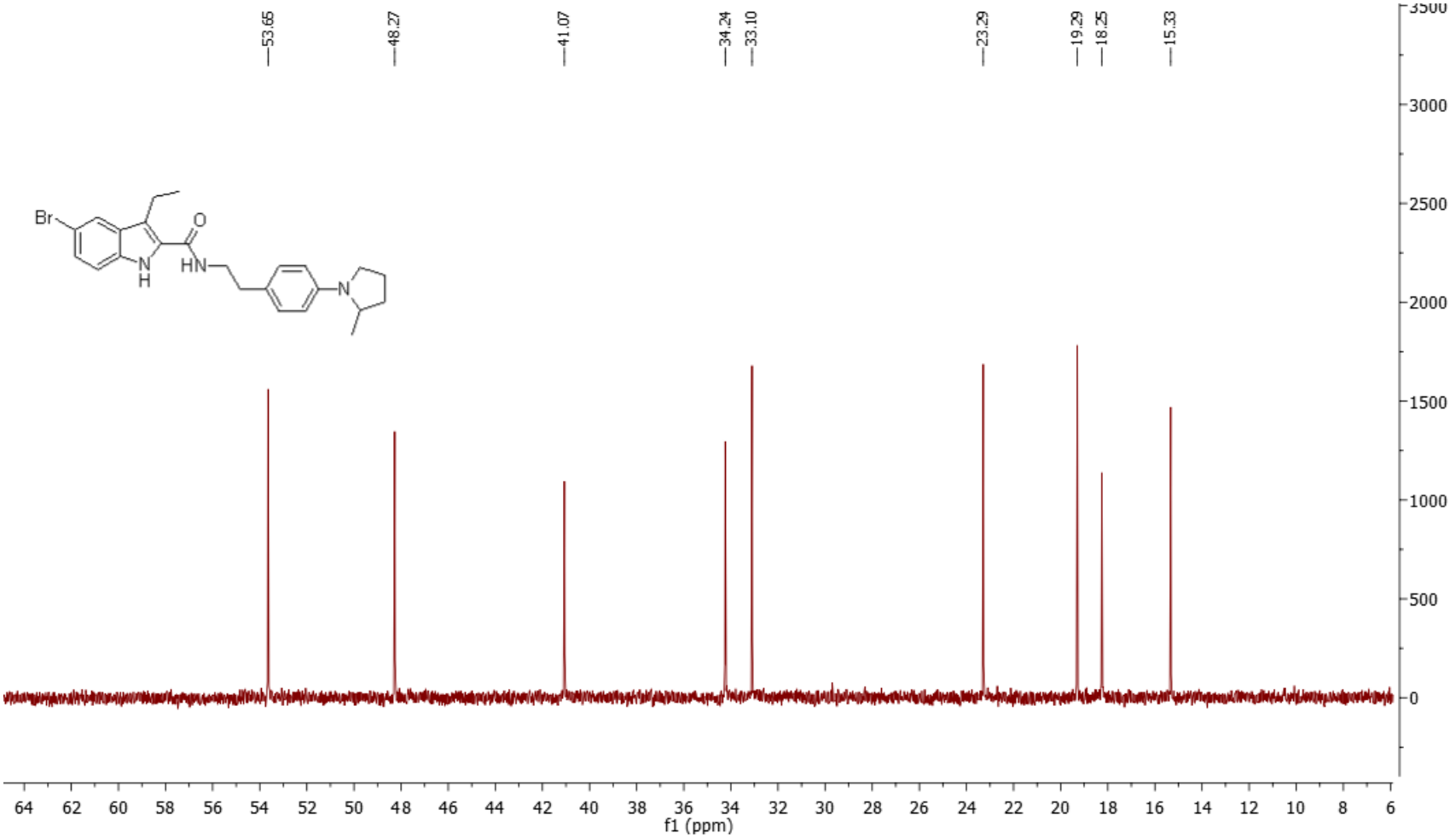
^{13}C NMR (101 MHz, cdcl$_3$) δ 162.11, 146.22, 133.78, 129.58, 129.43, 127.77, 127.23, 124.27, 122.41, 117.79, 113.35, 112.81, 112.23, 53.65, 48.27, 41.07, 34.24, 33.10, 23.29, 19.29, 18.25, 15.33.

5k



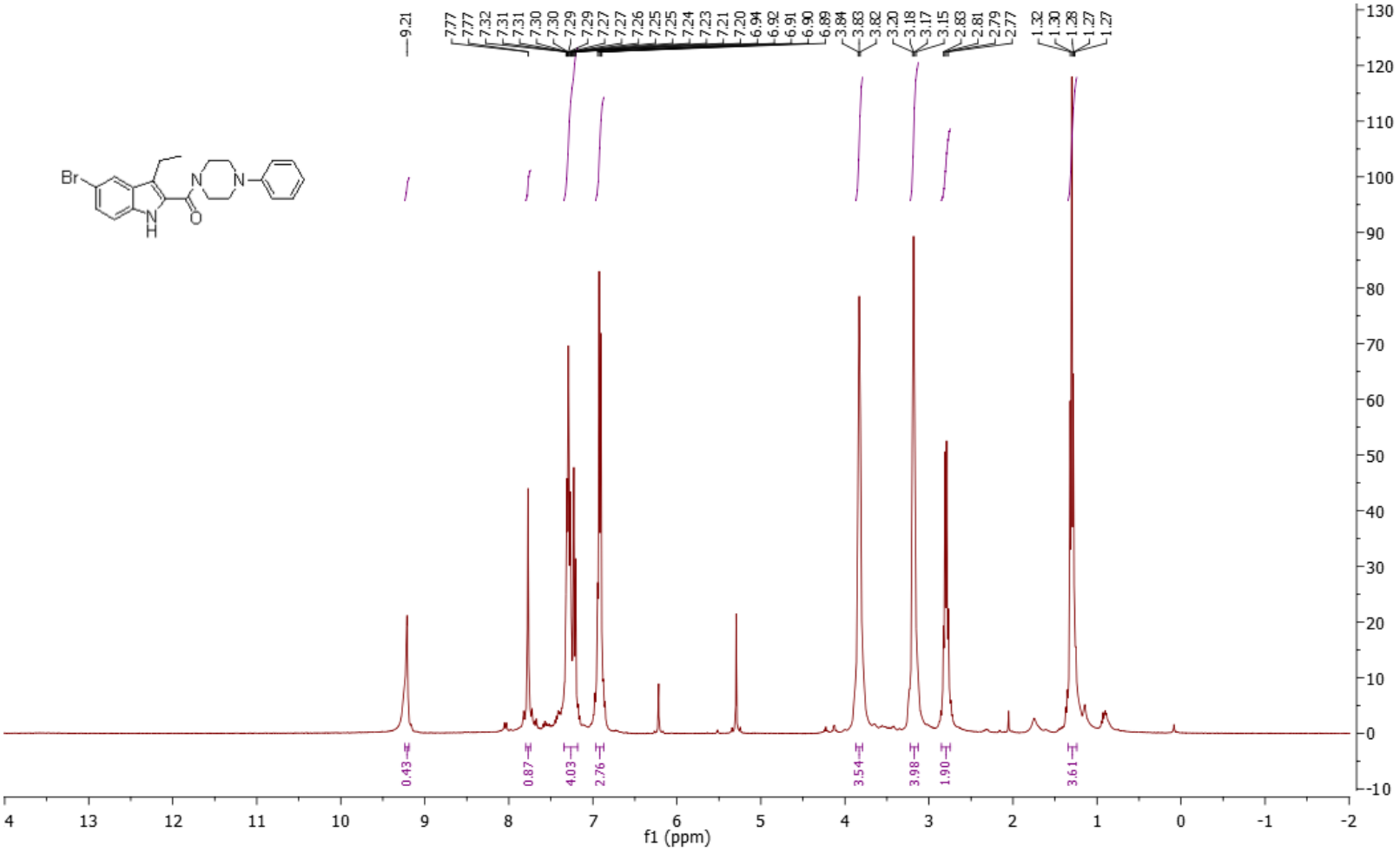
^{13}C NMR (101 MHz, cdcl$_3$) δ 162.11, 146.22, 133.78, 129.58, 129.43, 127.77, 127.23, 124.27, 122.41, 117.79, 113.35, 112.81, 112.23, 53.65, 48.27, 41.07, 34.24, 33.10, 23.29, 19.29, 18.25, 15.33.

5k



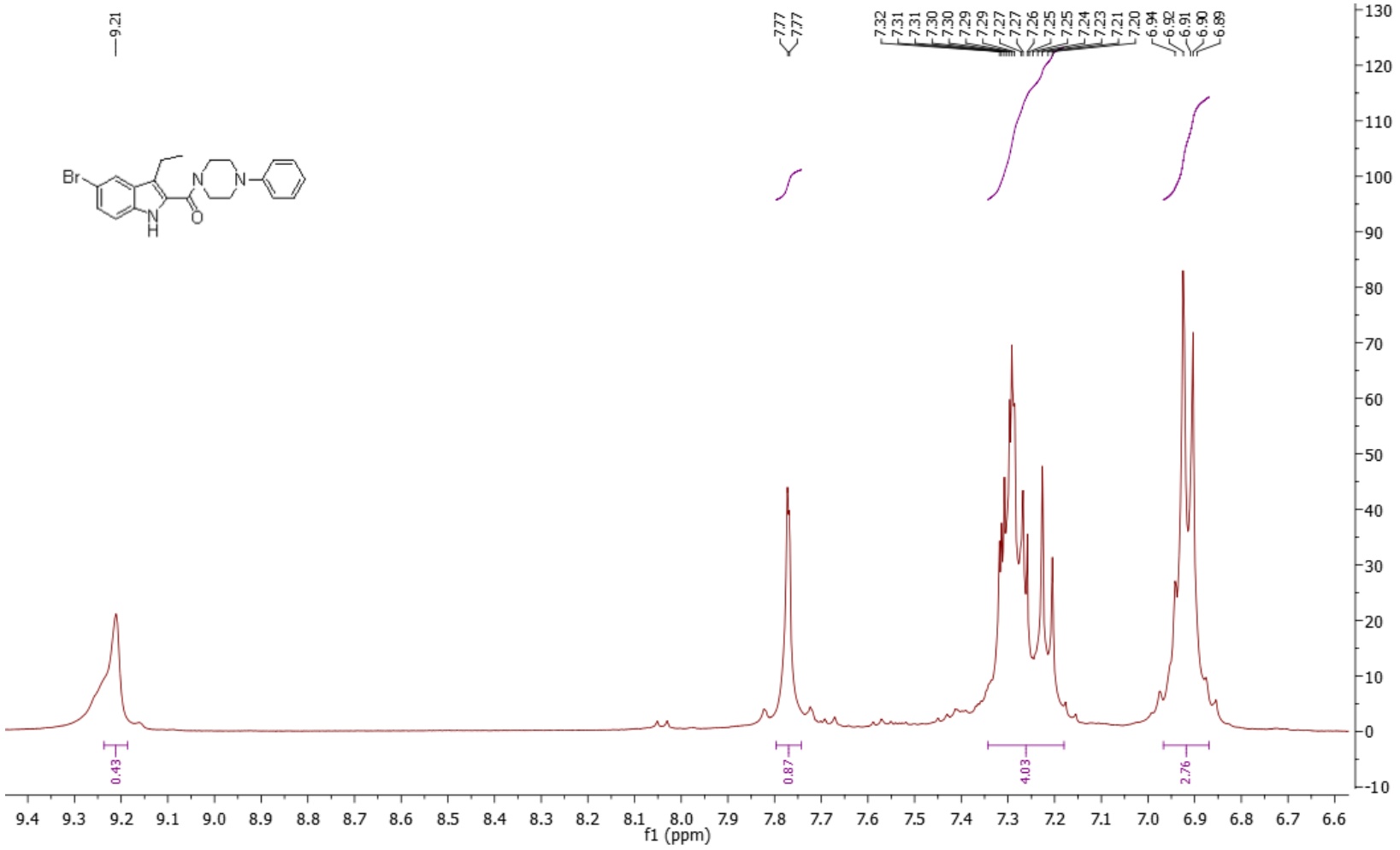
^{13}C NMR (101 MHz, cdcl$_3$) δ 162.11, 146.22, 133.78, 129.58, 129.43, 127.77, 127.23, 124.27, 122.41, 117.79, 113.35, 112.81, 112.23, 53.65, 48.27, 41.07, 34.24, 33.10, 23.29, 19.29, 18.25, 15.33.

6a



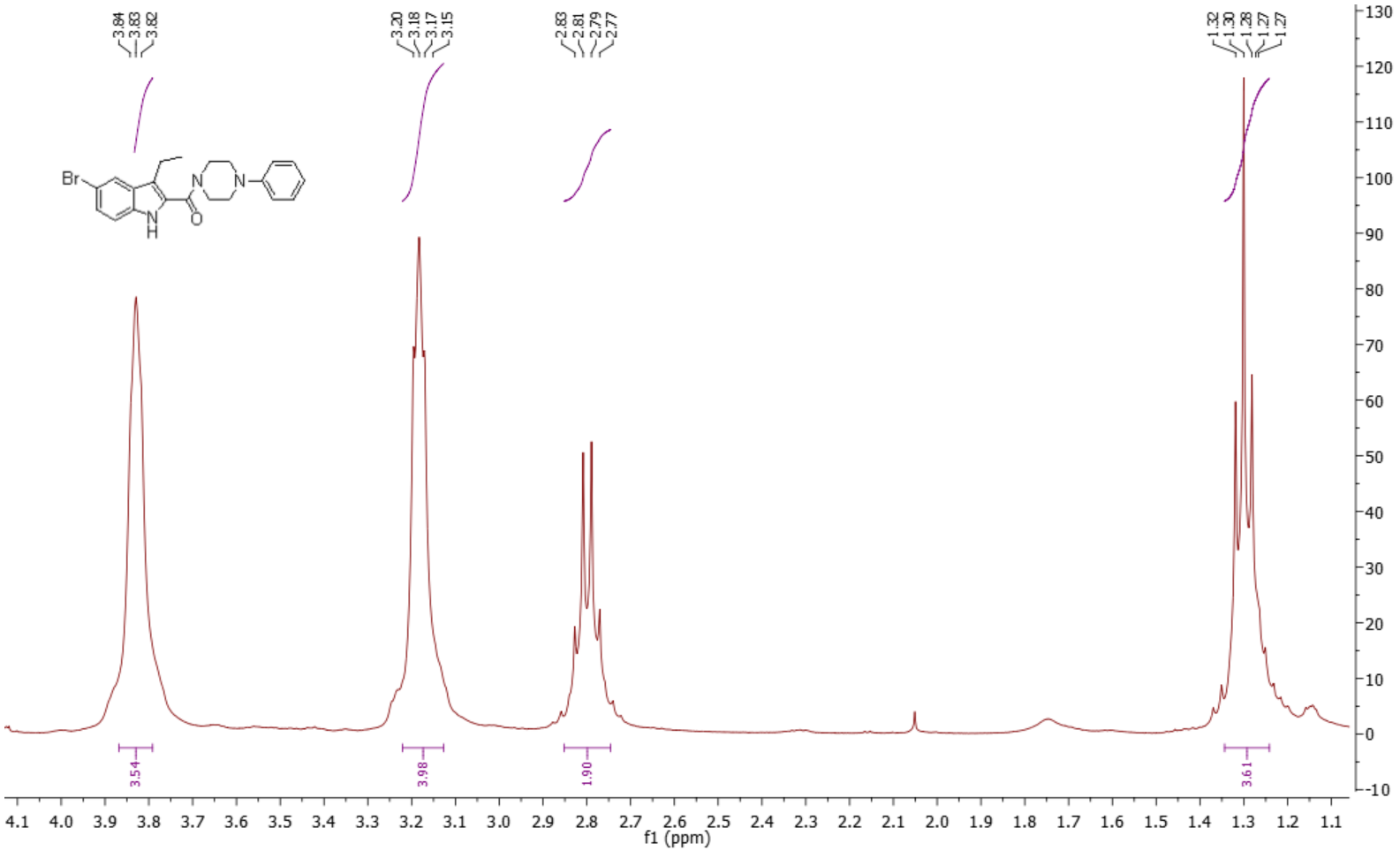
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.21 (s, 1H), 7.77 (s, 1H), 7.34 – 7.18 (m, 4H), 6.94 - 6.89 (m, 3H), 3.83 (t, J = 5.2 Hz, 4H), 3.17 (t, J = 7.4 Hz, 4H), 2.80 (q, J = 7.5 Hz, 2H), 1.30 (t, J = 7.4 Hz, 3H).

6a



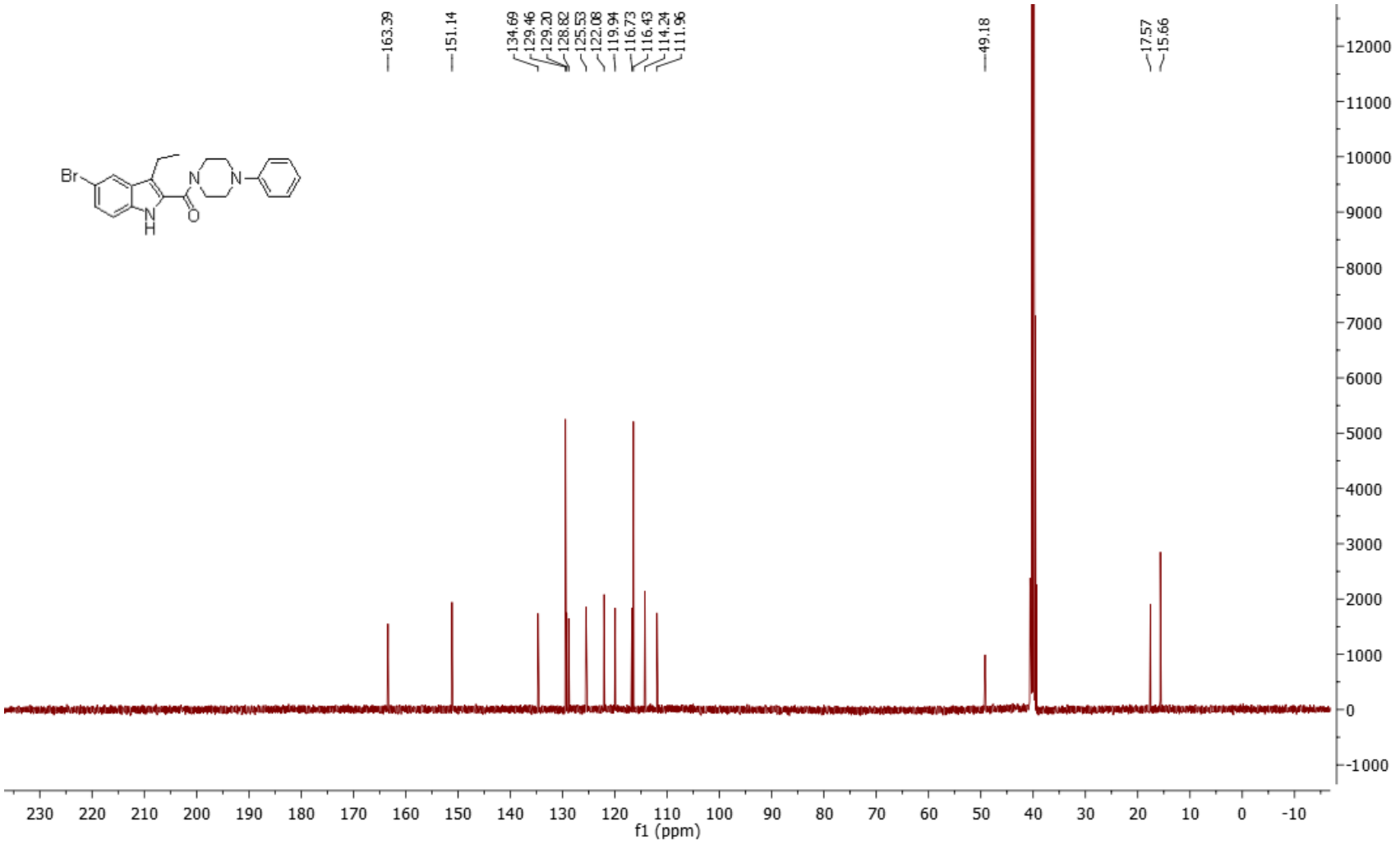
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.21 (s, 1H), 7.77 (s, 1H), 7.34 – 7.18 (m, 4H), 6.94 - 6.89 (m, 3H), 3.83 (t, J = 5.2 Hz, 4H), 3.17 (t, J = 7.4 Hz, 4H), 2.80 (q, J = 7.5 Hz, 2H), 1.30 (t, J = 7.4 Hz, 3H).

6a



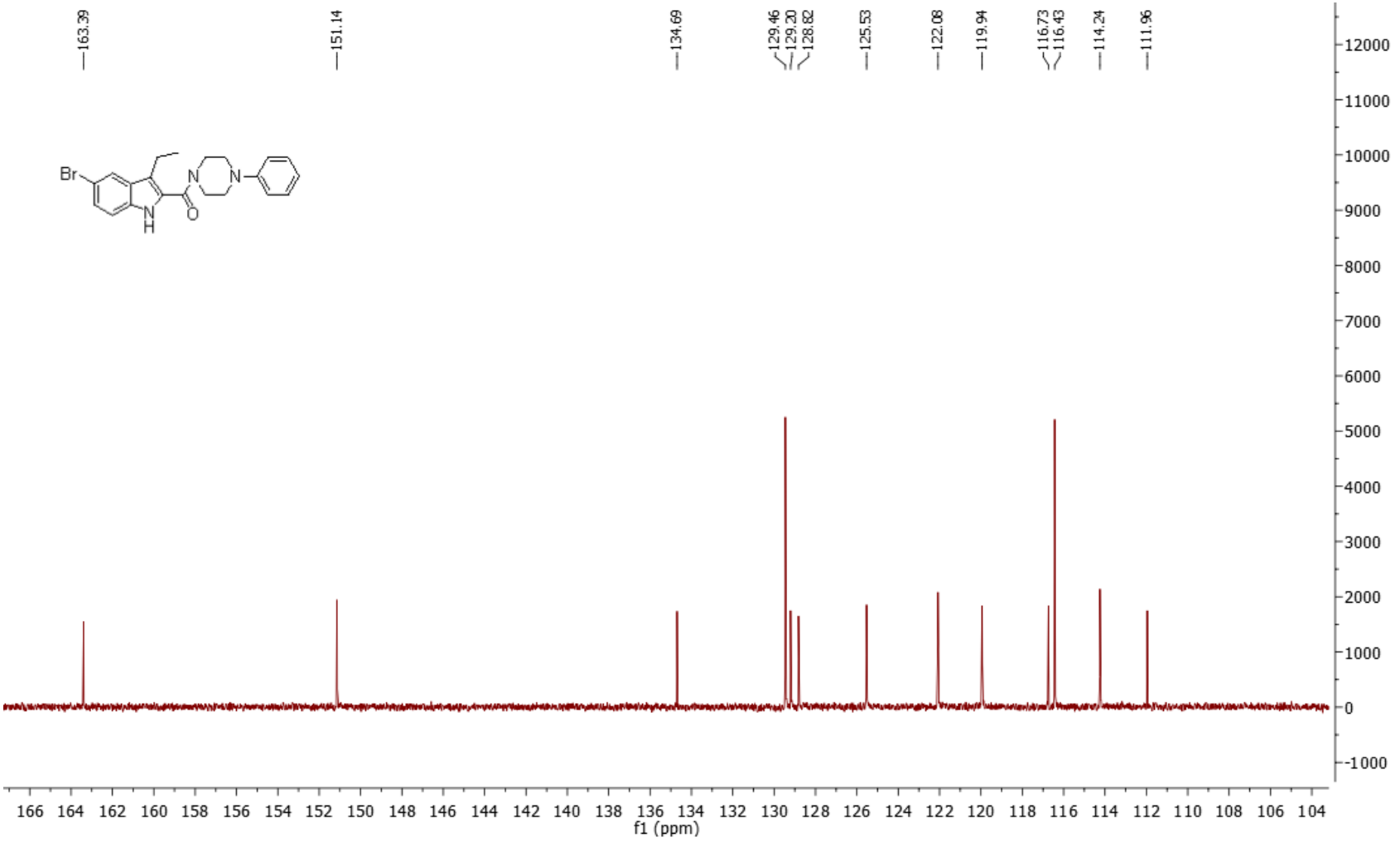
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.21 (s, 1H), 7.77 (s, 1H), 7.34 – 7.18 (m, 4H), 6.94 - 6.89 (m, 3H), 3.83 (t, J = 5.2 Hz, 4H), 3.17 (t, J = 7.4 Hz, 4H), 2.80 (q, J = 7.5 Hz, 2H), 1.30 (t, J = 7.4 Hz, 3H).

6a



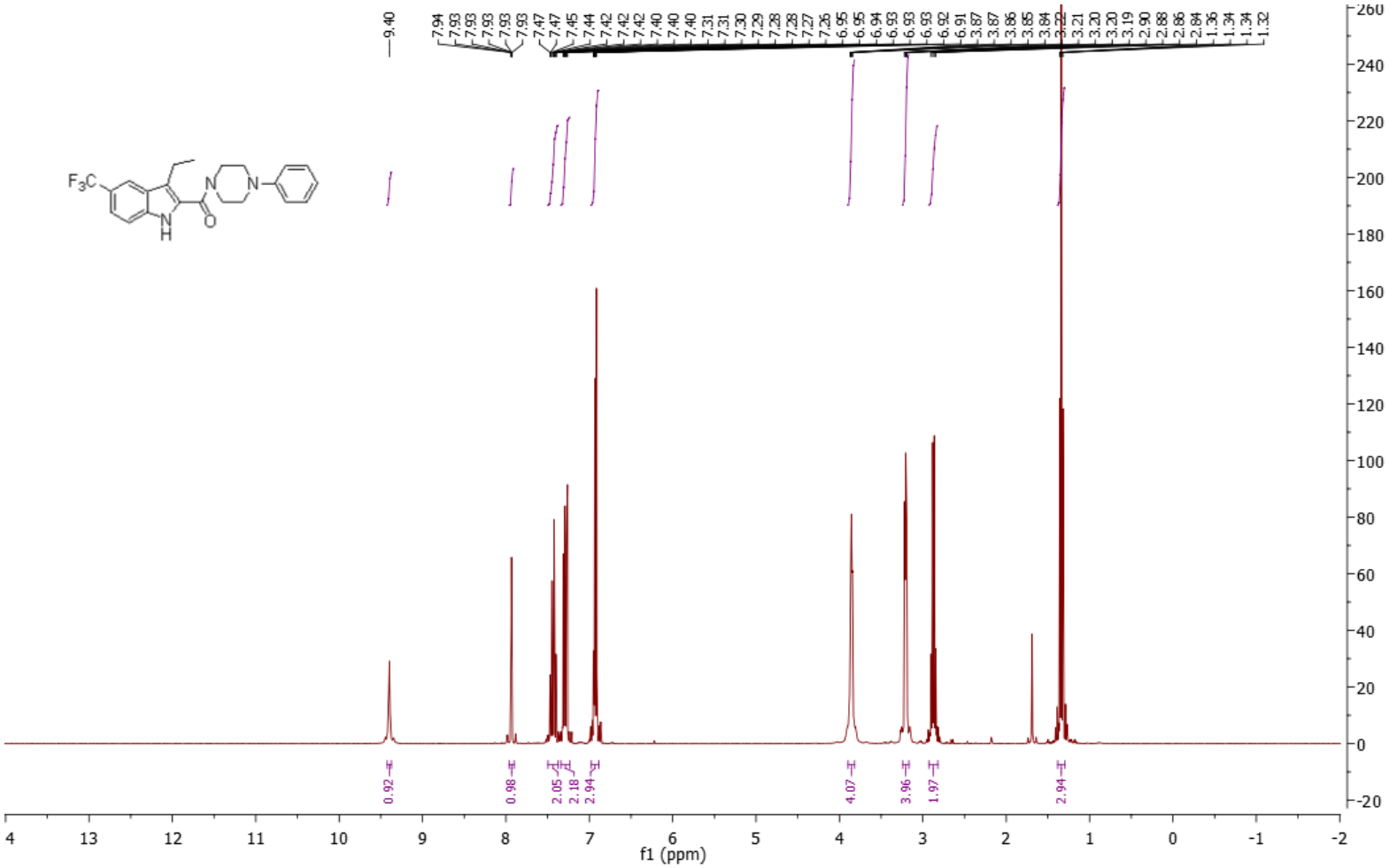
^{13}C NMR (101 MHz, dmso) δ 163.39, 151.14, 134.69, 129.46, 129.20, 128.82, 125.53, 122.08, 119.94, 116.73, 116.43, 114.24, 111.96, 49.18, 40.18, 17.57, 15.66.

6a



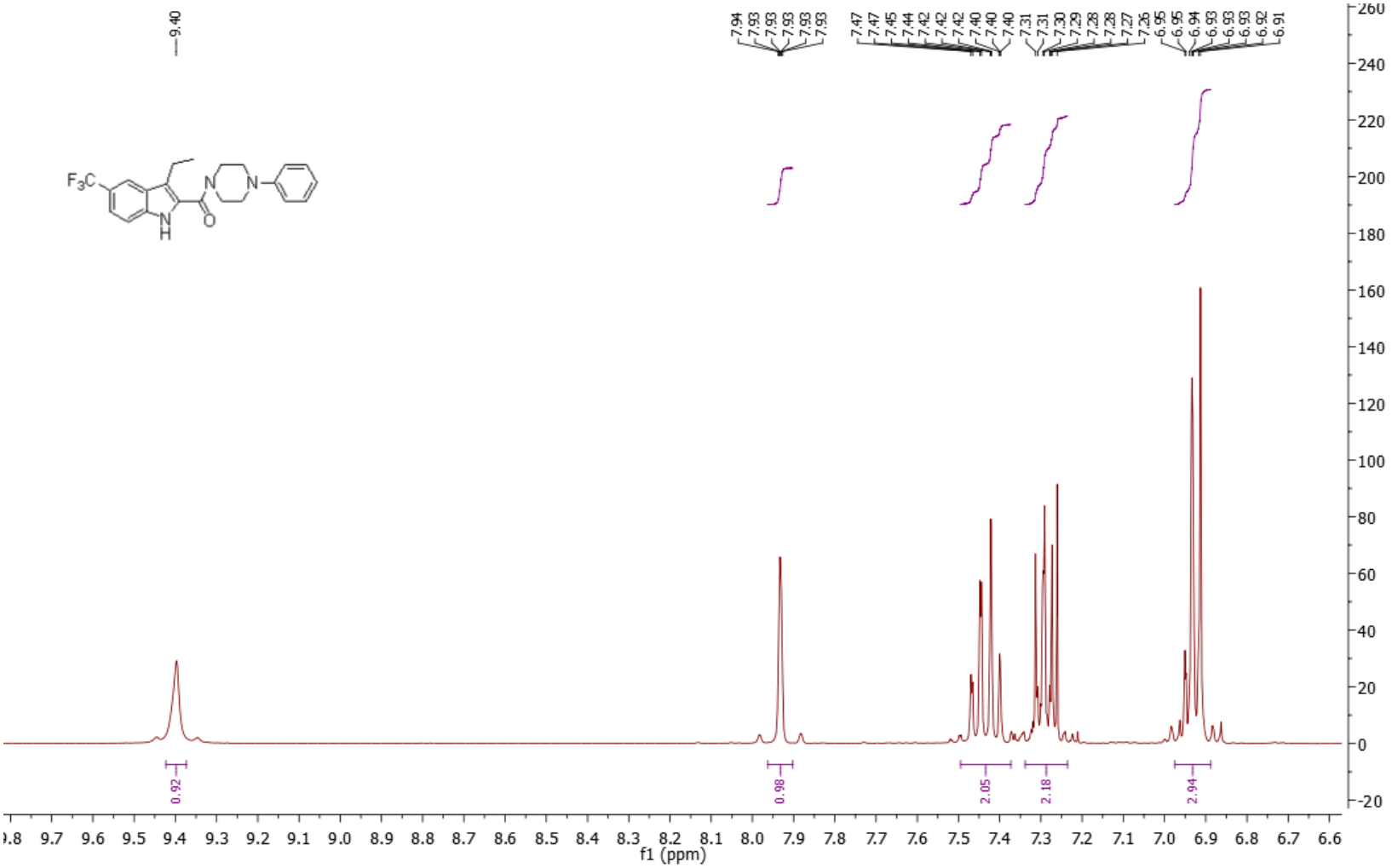
^{13}C NMR (101 MHz, dmso) δ 163.39, 151.14, 134.69, 129.46, 129.20, 128.82, 125.53, 122.08, 119.94, 116.73, 116.43, 114.24, 111.96, 49.18, 40.18, 17.57, 15.66.

6b



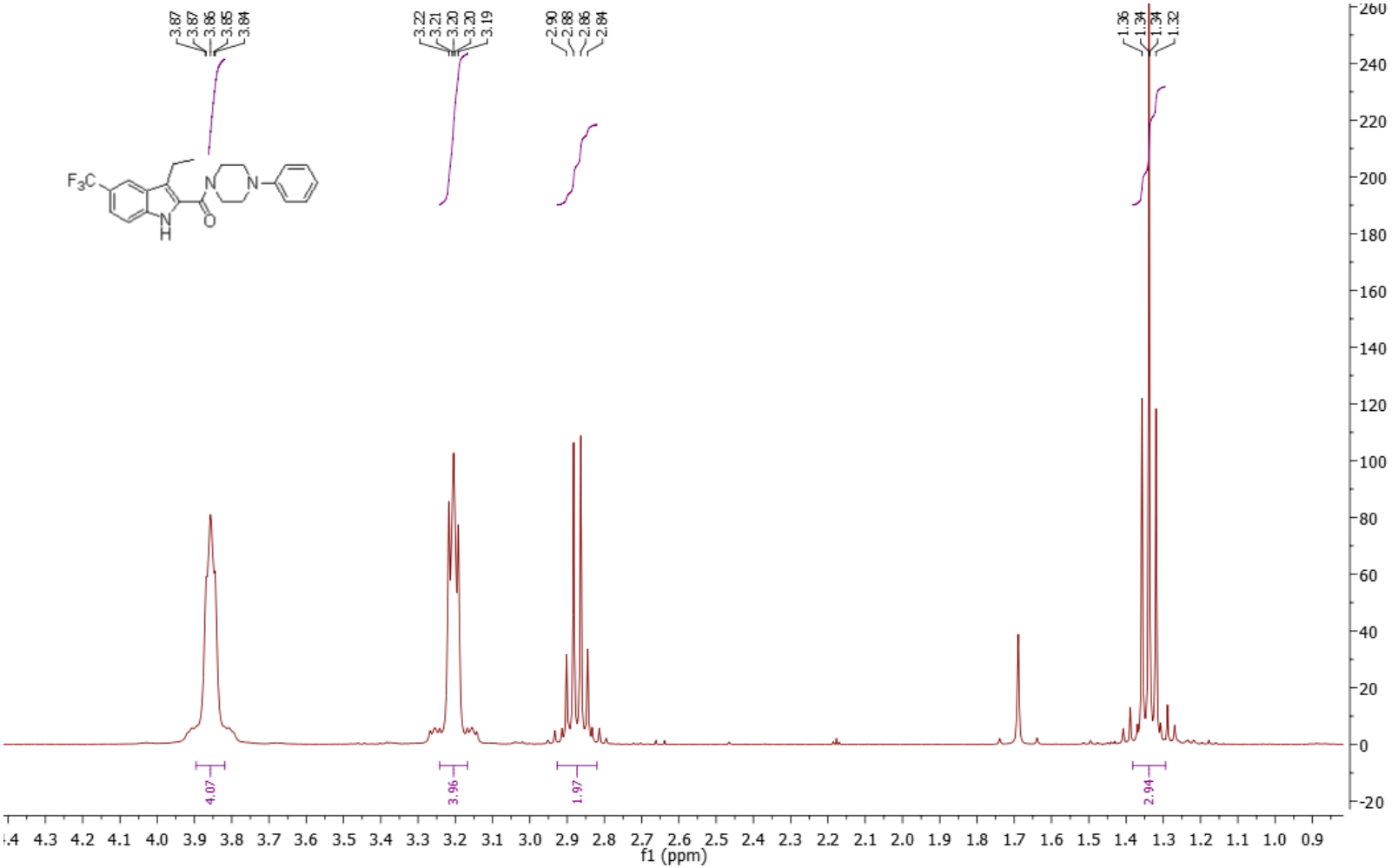
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.40 (s, 1H), 7.93 (s, 1H), 7.49 – 7.37 (m, 2H), 7.34 – 7.24 (m, 2H), 6.98 – 6.89 (m, 3H), 3.86 (t, J = 5.1 Hz, 4H), 3.20 (t, J = 5.3 Hz, 4H), 2.87 (q, J = 7.6 Hz, 2H), 1.34 (t, J = 7.7 Hz, 3H).

6b



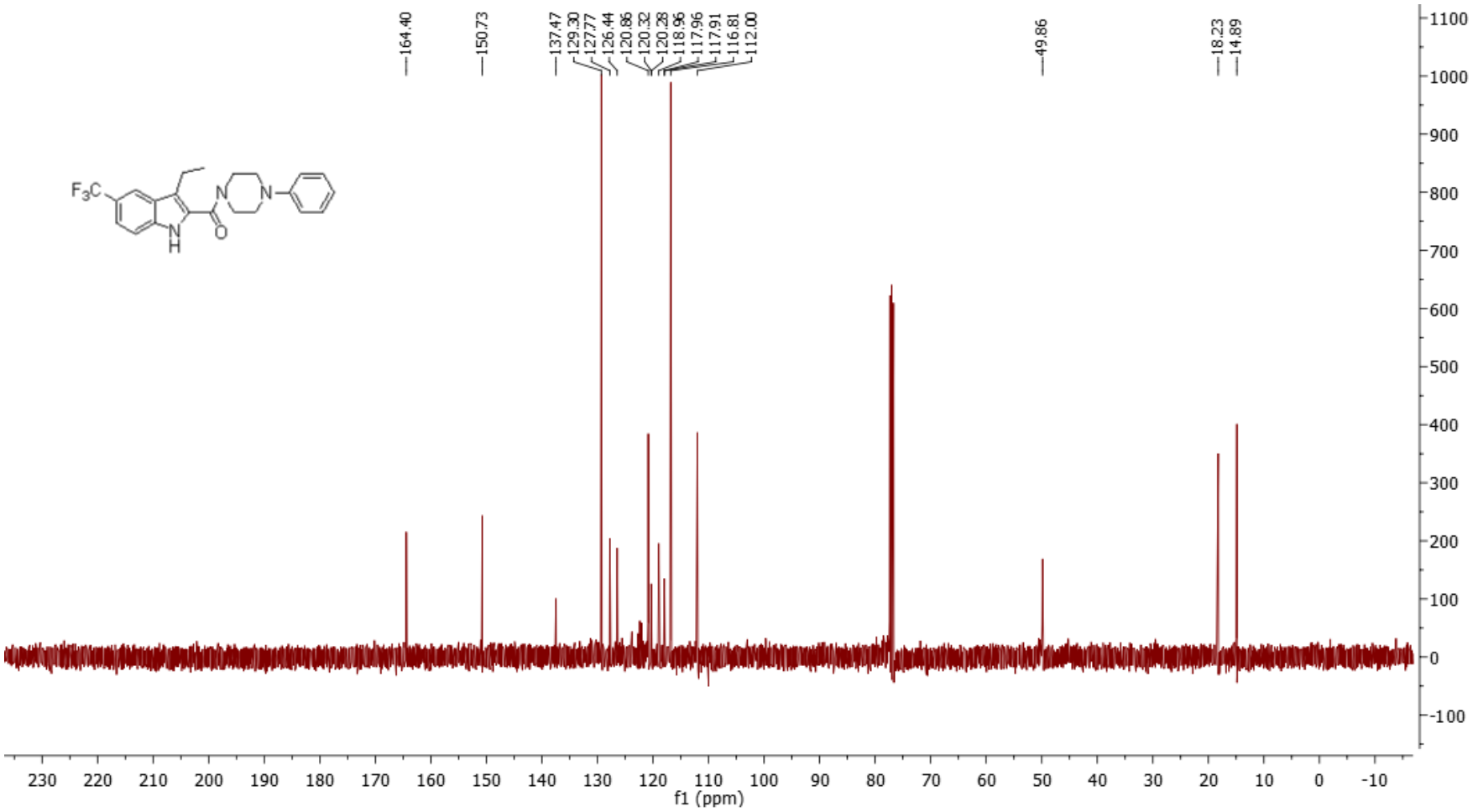
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.40 (s, 1H), 7.93 (s, 1H), 7.49 – 7.37 (m, 2H), 7.34 – 7.24 (m, 2H), 6.98 – 6.89 (m, 3H), 3.86 (t, J = 5.1 Hz, 4H), 3.20 (t, J = 5.3 Hz, 4H), 2.87 (q, J = 7.6 Hz, 2H), 1.34 (t, J = 7.7 Hz, 3H).

6b



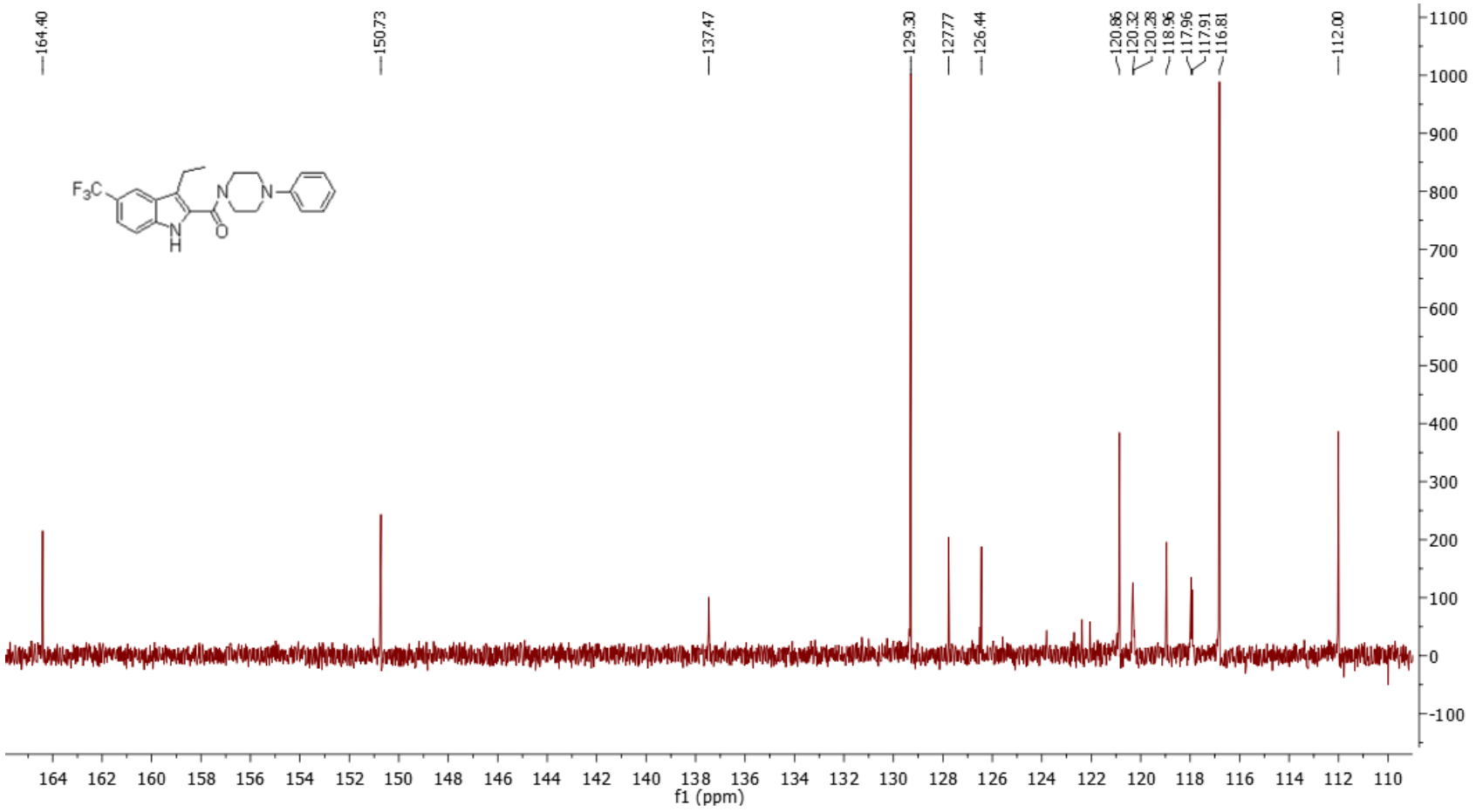
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.40 (s, 1H), 7.93 (s, 1H), 7.49 – 7.37 (m, 2H), 7.34 – 7.24 (m, 2H), 6.98 – 6.89 (m, 3H), 3.86 (t, J = 5.1 Hz, 4H), 3.20 (t, J = 5.3 Hz, 4H), 2.87 (q, J = 7.6 Hz, 2H), 1.34 (t, J = 7.7 Hz, 3H).

6b



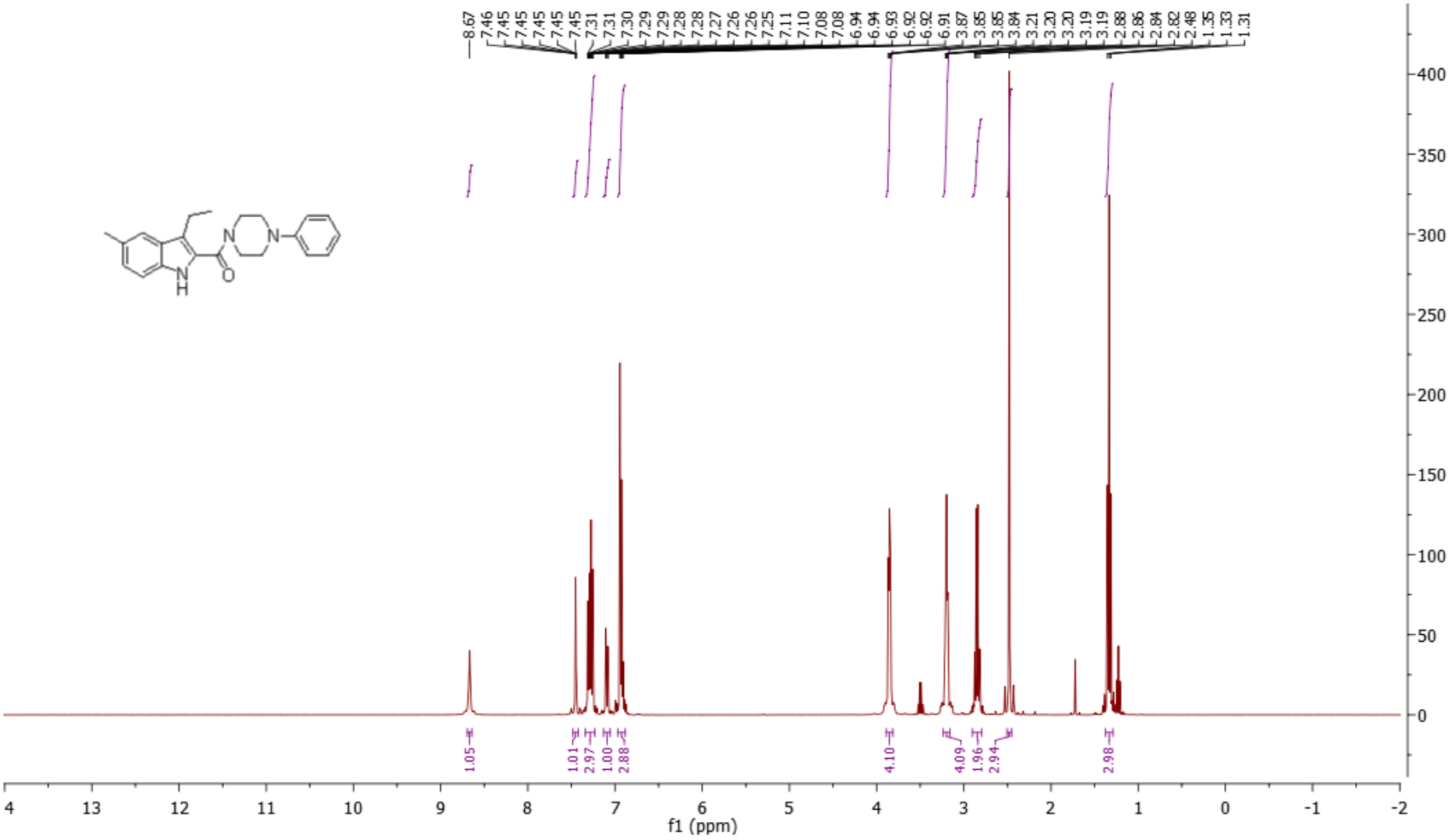
^{13}C NMR (101 MHz, cdcl$_3$) δ 164.40, 150.73, 137.47, 129.30, 127.77, 126.44, 120.86, 120.32, 120.28, 118.96, 117.96, 116.81, 112.00, 49.86, 18.23, 14.89.

6b



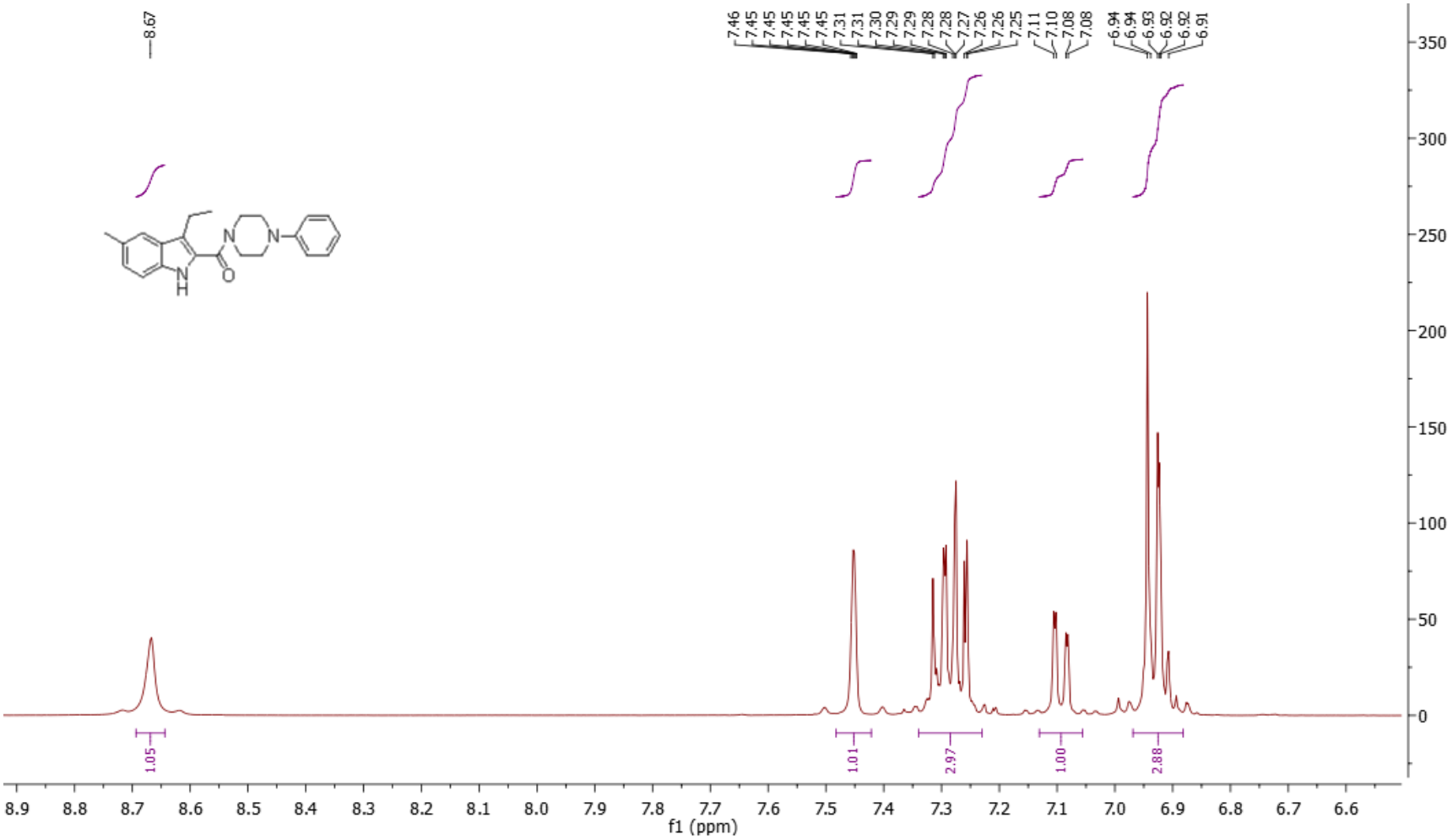
^{13}C NMR (101 MHz, cdcl$_3$) δ 164.40, 150.73, 137.47, 129.30, 127.77, 126.44, 120.86, 120.32, 120.28, 118.96, 117.96, 116.81, 112.00, 49.86, 18.23, 14.89.

6c



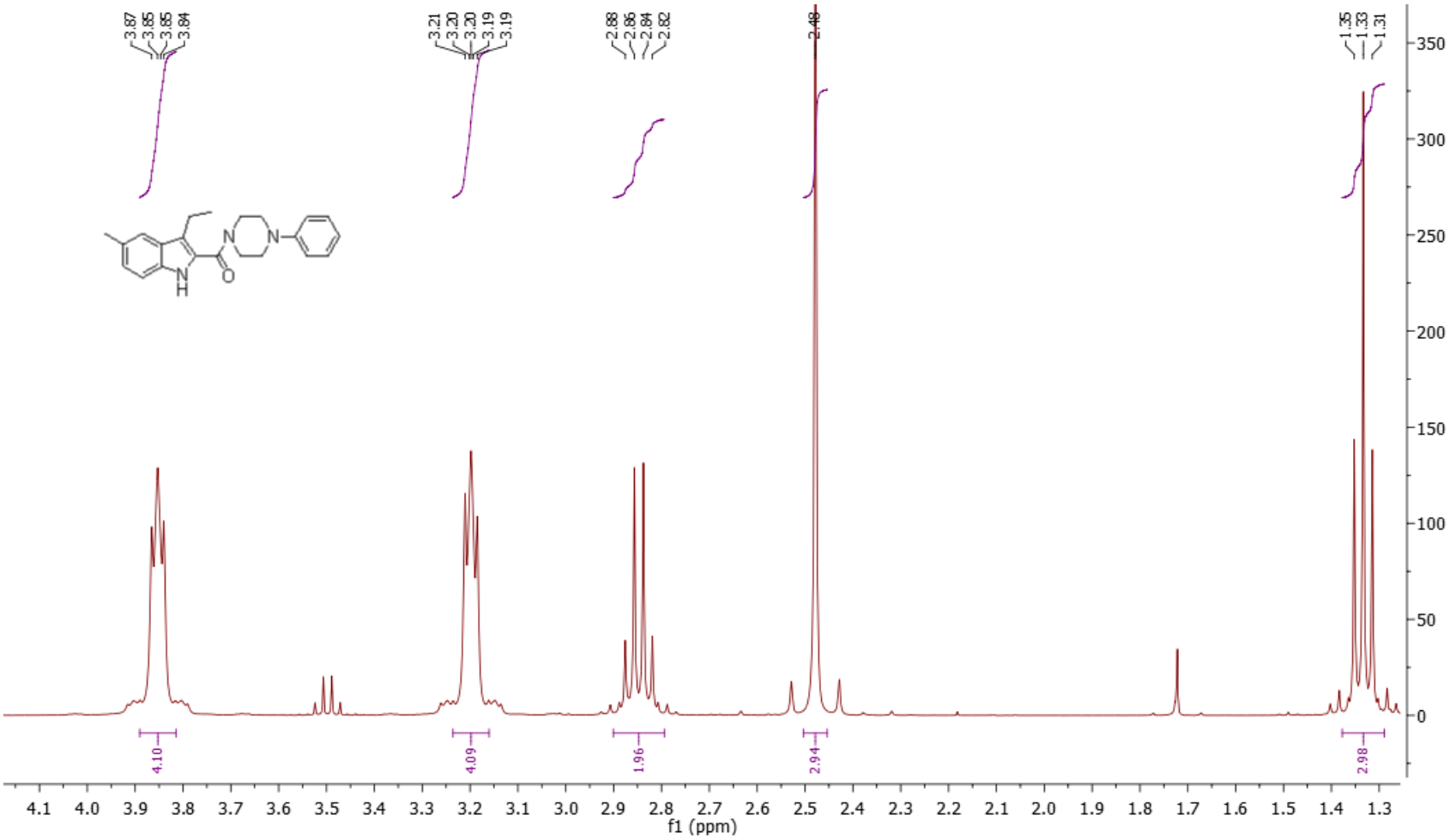
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 7.45 (s, 1H), 7.34 – 7.23 (m, 3H), 7.09 (dd, J = 8.3, 1.6 Hz, 1H), 6.97 – 6.88 (m, 3H), 3.85 (t, J = 6.5 Hz, 4H), 3.20 (t, J = 6.5 Hz, 4H), 2.85 (q, J = 7.6 Hz, 2H), 2.48 (s, 3H), 1.33 (t, J = 7.6 Hz, 3H).

6c



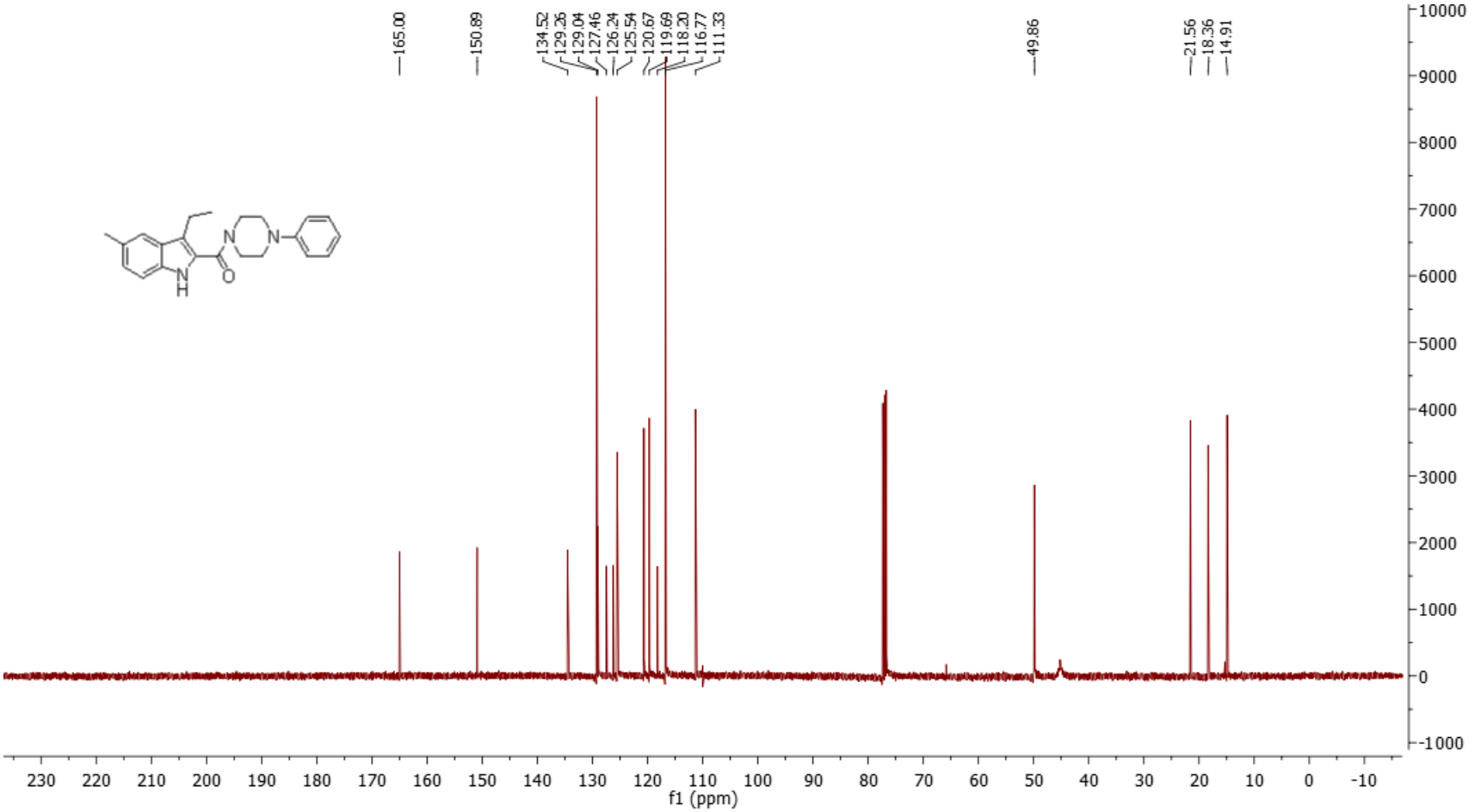
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 7.45 (s, 1H), 7.34 – 7.23 (m, 3H), 7.09 (dd, *J* = 8.3, 1.6 Hz, 1H), 6.97 – 6.88 (m, 3H), 3.85 (t, *J* = 6.5 Hz, 4H), 3.20 (t, *J* = 6.5 Hz, 4H), 2.85 (q, *J* = 7.6 Hz, 2H), 2.48 (s, 3H), 1.33 (t, *J* = 7.6 Hz, 3H).

6c



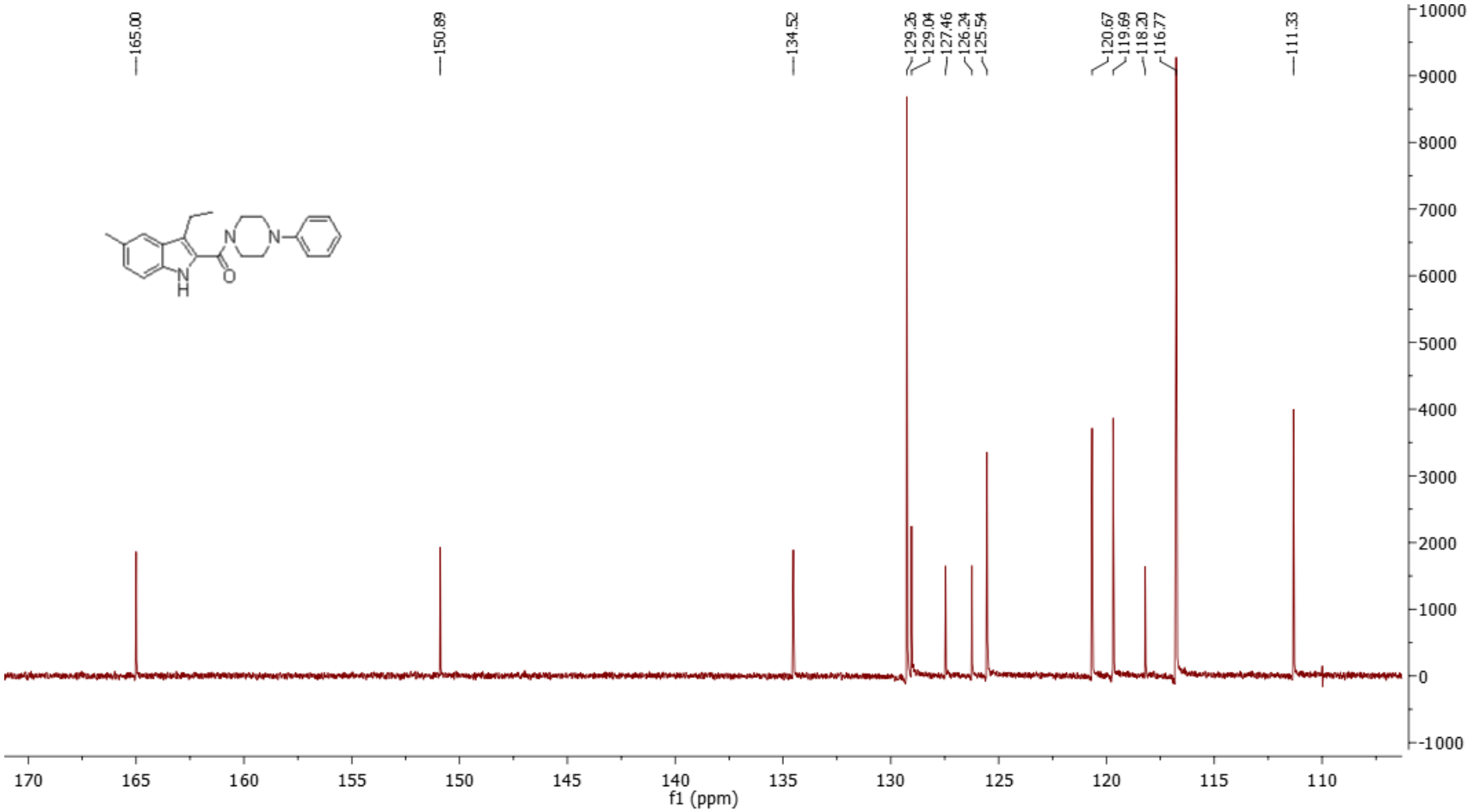
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 7.45 (s, 1H), 7.34 – 7.23 (m, 3H), 7.09 (dd, J = 8.3, 1.6 Hz, 1H), 6.97 – 6.88 (m, 3H), 3.85 (t, J = 6.5 Hz, 4H), 3.20 (t, J = 6.5 Hz, 4H), 2.85 (q, J = 7.6 Hz, 2H), 2.48 (s, 3H), 1.33 (t, J = 7.6 Hz, 3H).

6c



^{13}C NMR (101 MHz, cdcl$_3$) δ 165.00, 150.89, 134.52, 129.26, 129.04, 127.46, 126.24, 125.54, 120.67, 119.69, 118.20, 116.77, 111.33, 49.86, 21.56, 18.36, 14.91.

6c



^{13}C NMR (101 MHz, cdcl$_3$) δ 165.00, 150.89, 134.52, 129.26, 129.04, 127.46, 126.24, 125.54, 120.67, 119.69, 118.20, 116.77, 111.33, 49.86, 21.56, 18.36, 14.91.

Appendix A

Experimental procedures

General Details

All the chemicals used were of analytical grade and purified by standard methods prior to use. Silica gel column chromatography was carried out using kieselgel 60 (Merck). TLC analysis was performed on aluminium-backed plates coated with silica gel 60 F_{254} (Merck). Melting points were determined using a Gallen Kamp melting point apparatus and are uncorrected. Components were visualized using potassium permanganate solution and UV light. NMR Spectra were taken using a Varian Unity INOVA 400 MHz and Bruker AC250 MHz spectrometers for proton and carbon at university of Aberdeen. All numbers referring to NMR data obtained are in parts per million (ppm). High resolution mass spectrometric data were obtained using Thermo Instruments MS system (LTQ XL/LTQ Orbitrap Discovery) coupled to a Thermo Instruments HPLC system (Accela PDA detector, Accela PDA autosampler and Pump) at university of Aberdeen

General procedure for the synthesis of compounds 3a-c

To a stirred suspension of derivatives of *p*-chlorophenylhydrazine hydrochloride **1a-c** (2.793 mmol, 1 equiv) in absolute ethanol (20 mL), 2-oxo-butanoic acid **2** (0.5 g, 1.1 equiv) and *p*-toluenesulfonic acid monohydrate (PTSA) (2.66 g, 5 equiv) were added and the resulting reaction mixture was refluxed for 20 h. The residue after removal of ethanol under reduced pressure was extracted with DCM, washed twice with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and evaporated under reduced pressure to give crude product which was recrystallised from light petroleum and EtOAc to yield **3a-c**

General procedure for the synthesis of compounds 4a-c

To a solution of indole ester **3a-c** (1 equiv) in appropriate alcohol, (0.5 M) 5% NaOH (5 equiv) was added. The reaction mixture was kept at 40 ^{o}C with stirring overnight. The residue after removal of alcohol under reduced pressure was then taken into water, precipitated out at pH = 1 using 5% HCl. The precipitate was extracted with EtOAc, dried over $MgSO_4$ and evaporated under reduced pressure to give the corresponding carboxylic acids **4a-c**.

General procedure for the synthesis of compounds 5a-k and 6a-c

A mixture of indole-2-carboxylic acids **4a-c** (1 equiv), BOP (1.5 equiv), and DIPEA (2 equiv) in DCM (0.05 M) was stirred for 10 min at rt before addition of the appropriate amine (1.2 equiv) and the resulting reaction mixture was stirred overnight at rt. After removing of the solvent in vacuo, the residue was extracted with EtOAc, washed with 5% HCl, saturated $NaHCO_3$ solution, brine, dried over $MgSO_4$, and evaporated under reduced pressure to give a crude product, which was purified by flash chromatography on silica gel.

4.2. Biological evaluation

4.2.1. Cytotoxic activity using MTT Assay and evaluation of IC_{50}

All cell lines used were of American Type Culture Collection (ATCC)

4.2.1.1. MTT assay

MTT assay was carried out to study the effect of compounds on mammary epithelial cells (MCF-10A) [27]. The medium in which cells were propagated contained Dulbecco's modified Eagle's medium (DMEM)/ Ham's F-12 medium (1:1) supplemented with epidermal growth factor (20 ng/mL), hydrocortisone (500 ng/mL), insulin (10 μg/mL), 2 mM glutamine and 10% fetal calf serum. After every 2-3 days, the cells were passaged using trypsin ethylenediamine tetra acetic acid (EDTA). The cells were seeded at a density of 10^4 cells mL^{-1} in flat-bottomed culture plates containing 96 wells each. After 24 h, medium was removed from the plates and the compounds in (in 0.1% DMSO) were added (in 200 μL medium to yield a final concentration of 0.1% v/v) to the wells of plates. A single compound was designated with four wells followed by incubation of plates for 96h at 37°C. After incubation, medium was removed completely from the plates followed by addition of MTT (0.4 mg/mL in medium) to each well and subsequent incubation of plates for 3h. MTT (along with the medium) was removed and DMSO (150μL) was added to each well of the culture plates, followed by vortexing and subsequent measurement of absorbance (at 540 nm) using microplate reader. The data are shown as percentage inhibition of proliferation in comparison with controls containing 0.1% DMSO.

4.2.1.2. Assay for antiproliferative effect

To explore the antiproliferative potential of compounds MTT assay was performed according to previously reported procedure [28] using different cell lines To explore the antiproliferative potential of compounds propidium iodide fluorescence assay was performed using different cell lines. To calculate the total nuclear DNA, a fluorescent dye (propidium iodide, PI) is used which can attach to the DNA, thus offering a quick and precise technique. PI cannot pass through the cell membrane and its signal intensity can be considered as directly proportional to quantity of cellular DNA. Cells whose cell membranes are damaged or have changed permeability are counted as dead ones. The assay was performed by seeding the cells of different cell lines at a density of 3000-7500 cells/well (in 200µl medium) in culture plates followed by incubation for 24h at 37 °C in humidified 5% CO_2/95% air atmospheric conditions. The medium was removed; the compounds were added to the plates at 10 µM concentrations (in 0.1% DMSO) in triplicates, followed by incubation for 48 h. DMSO (0.1%) was used as control. After incubation, medium was removed followed by the addition of PI (25 µl, 50µg/mL in water/medium) to each well of the plates. At -80 °C, the plates were allowed to freeze for 24 h, followed by thawing at 25°C. A fluorometer (Polar-Star BMG Tech) was used to record the readings at excitation and emission wavelengths of 530 and 620 nm for each well. The percentage cytotoxicity of compounds was calculated using the following formula:

$$\% \text{ Cytotoxicity} = \frac{A_C - A_{TC}}{A_C} \times 100$$

Where A_{TC}= Absorbance of treated cells and A_C= Absorbance of control. Erlotinib was used as positive control in the assay.

4.2.1.3. EGFR inhibitory assay

EGFR-TK assay was performed to evaluate the inhibitory potency of novel compounds **20-23**, **28-31** and **33** against EGFR [29]. Baculoviral expression vectors including pBlueBacHis2B and pFASTBacHTc were used separately to clone 1.6 kb cDNA coding for EGFR cytoplasmic domain (EGFR-CD, amino acids 645–1186). 5′ upstream to the EGFR sequence comprised a sequence that encoded $(His)_6$. Sf-9 cells were infected for 72h for protein expression. The pellets of Sf-9 cells were solubilized in a buffer containing sodium vanadate (100 µM), aprotinin (10 µg/mL), triton (1%), HEPES buffer (50mM), ammonium molybdate (10 µM), benzamidine HCl (16 µg/mL), NaCl (10 mM), leupeptin (10 µg/mL) and pepstatin (10 µg/mL) at 0°C for 20 min at pH 7.4, followed by centrifugation for 20 min. To eliminate the non-specifically bound material, a Ni-NTA super flow packed column was used to pass through and wash the crude extract supernatant first with 10 mM and then with 100 mM imidazole. Histidine-linked proteins were first eluted with 250 and then with 500 mM imidazole subsequent to dialysis against NaCl (50 mM), HEPES (20 mM), glycerol (10%) and 1 µg/mL each of aprotinin, leupeptin and pepstatin for 120 min. The purification was performed either at 4 °C or on ice. To record autophosphorylation level, EGFR kinase assay was carried out on the basis of DELFIA/Time-Resolved Fluorometry. The compounds were first dissolved in DMSO absolute, subsequent to dilution to appropriate concentration using HEPES (25 mM) at pH 7.4. Each compound (10 µL) was incubated with recombinant enzyme (10 µL, 5 ng for EGFR, 1:80 dilution in 100 mM HEPES) for 10 min at 25^{o}C, subsequent to the addition of 5X buffer (10 µL, containing 2 mM $MnCl_2$, 100 µM Na_3VO_4, 20 mM HEPES and 1 mM DTT) and ATP-$MgCl_2$ (20 µL, containing 0.1 mM ATP and 50 mM $MgCl_2$) and incubation for 1h. The negative and positive controls were included

in each plate by the incubation of enzyme either with or without ATP-$MgCl_2$. The liquid was removed after incubation and the plates were washed thrice using wash buffer. Europium-tagged antiphosphotyrosine antibody (75 µL, 400 ng) was added to each well followed by incubation of 1h and then washing of the plates using buffer. The enhancement solution was added to each well and the signal was recorded at excitation and emission wavelengths of 340 at 615 nm. The autophosphorylation percentage inhibition by compounds was calculated using the following equation:

$$100\% - [(negative\ control)/(positive\ control) - (negative\ control)]$$

Using the curves of percentage inhibition of eight concentrations of each compound, IC_{50} was calculated. Majority of signals detected by antiphosphotyrosine antibody were from EGFR because the enzyme preparation contained low impurities.

4.2.1.4. CDK2 assay

Protein Kinase Assays. Human CDK2/A2 was purchased from New England Biolabs IC_{50} values for CDK2/A was determined according to the supplier's instructions (Upstate). CDK2/A were assayed at an ATP concentration of 12.5 µM [30].

4.3. Statistical analysis

Computerized Prism 5 program was used to statistically analyzed data using one-way ANOVA test followed by Tukey's as post ANOVA for multiple comparison at $P \leq .05$. Data were presented as mean ± SEM.

Experimental of MD Simulations

In-Silico molecular docking studies were performed within EGFR (Epidermal Growth Factor Receptor tyrosine kinase domain with 4-anilinoquinazoline inhibitor erlotinib) and CDK2 (Crystal structure of CDK2 with inhibitor dinaciclib) using Molecular Operating Environment Software (MOE® 2014.09) according to docking protocols

reported elsewhere [31]. Crystal structures of target proteins of both EGFR and CDK2 were obtained from protein data bank. Structure of study molecules were built using ChemDraw® Ultra software (v.8, 2003). Preparation of both target proteins and study molecules was done as reported before [32, 33]. Docking scores (S; kcal/mol), root-mean square deviation (RMSD; A).