A Robust Protocol for Pd(II)-catalyzed C-3 Arylation of (*1H*) Indazoles and Pyrazoles: Total Synthesis of Nigellidine Hydrobromide

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SUPPORTING INFORMATION

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General Information:

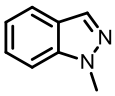
Unless otherwise noted, all reactions were run under air and were heated on hot plates with oil baths calibrated to an external thermometer. Prior to starting experiments, the hot plate was turned on, and the oil bath was allowed to equilibrate to the desired temperature over 30 minutes. All materials were used as received from commercial sources without further purification and all reagents were handled in air. ^{1}H and ^{13}C NMR spectra were recorded on Varian-Inova and Bruker AV (400 MHz and 100 MHz, respectively) instrument internally referenced to $SiMe_4$ or chloroform signals. The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. High resolution mass spectra were recorded at the Center for Mass Spectrometry, The Scripps Research Institute.

Experimental:

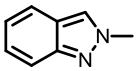
1. General Procedure for Substrate Synthesis:

(1) General Procedure for 1-Me-, Bn-, and SEM-indazole[1]:

To a suspended solution of NaH (6 mmol, 1.5 eq) in DMF (5 mL) and DMSO (2.5 mL), was added substituted indazole (4 mmol, 1.0 eq) in DMF (5 mL) at 0 °C under N_2 atmosphere. Then the reaction mixture was warmed to rt and stirred for 15 minutes. The solution was cooled back to 0 °C whereupon alkyl halide (6.4 mmol, 1.6 eq) was added dropwise to the stirred solution. Upon complete addition, the solution was stirred at rt overnight. The reaction was then quenched with saturated NH_4Cl and extracted with Et_2O. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in *vacuo*. The resulting residue was purified by silica gel column using hexane:ethyl acetate (4:1 to 1:1) as the eluent to give the corresponding protected 1H-indazole and 2H-indazole (the ratio is about 2:1 to 3:1).

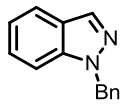


1-Methyl-1H-indazole[2]: white solid, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.39 (d, *J* = 3.6 Hz, 2H), 7.15 (dt, *J* = 7.9, 3.8 Hz, 1H), 4.07 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.77, 132.60, 126.10, 123.91, 120.96, 120.32, 108.80, 35.40.

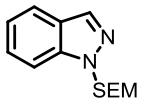


2-Methyl-2H-indazole[3]: white solid, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.05 (t, *J* = 8.0 Hz, 1H), 4.13 (s,

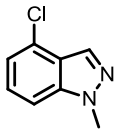
3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.87, 125.67, 123.36, 121.92, 121.43, 119.81, 117.02, 40.08.



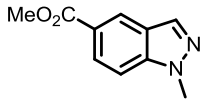
1-Benzyl-1H-indazole[4]: white solid, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.36 – 7.20 (m, 5H), 7.18 (d, *J* = 6.7 Hz, 2H), 7.14 – 7.10 (m, 1H), 5.58 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.49, 136.84, 133.32, 128.65, 127.67, 127.10, 126.32, 124.31, 121.09, 120.58, 109.23, 52.90.



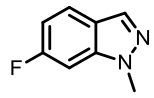
1-((2-(Trimethylsilyl)ethoxy)methyl)-1H-indazole[5]: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 5.75 (s, 2H), 3.55 (t, *J* = 8.0 Hz, 2H), 0.89 (t, *J* = 8.0 Hz, 2H), -0.07 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.69, 133.98, 126.68, 124.74, 121.22, 120.99, 109.93, 109.61, 77.61, 66.31, 17.70, -1.53.



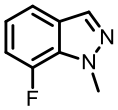
4-Chloro-1-methyl-1H-indazole[6]: yellow oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.29 – 7.24 (m, 2H), 7.12 – 7.07 (m, 1H), 4.05 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.70, 131.33, 126.70, 126.51, 123.18, 120.01, 107.47, 35.78



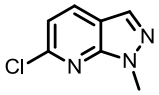
Methyl 1-methyl-1H-indazole-5-carboxylate: brown solid, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.07 (s, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 4.09 (s, 3H), 3.94 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.28, 141.53, 134.47, 127.04, 124.57, 123.63, 122.77, 108.61, 52.05, 35.68; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{10}H_{11}N_2O_2$ $[M+H]^+$ 191.0815, found 191.0820.



6-Fluoro-1-methyl-1H-indazole: white solid, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.64 (dd, *J* = 8.8, 5.1 Hz, 1H), 7.00 (d, *J* = 9.2 Hz, 1H), 6.90 (td, *J* = 9.0, 2.1 Hz, 1H), 4.00 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.06 (d, *J* = 243 Hz), 140.11 (d, *J* = 12.0 Hz), 132.91, 122.34 (d, *J* = 11.0 Hz), 120.77, 110.34 (d, *J* = 25.0 Hz), 94.50 (d, *J* = 26.0 Hz), 35.49; **HRMS** (ESI-TOF) *m/z* Calcd for $C_8H_8FN_2$ $[M+H]^+$ 151.0666, found 151.0668.

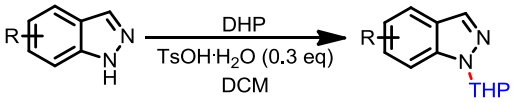


7-Fluoro-1-methyl-1H-indazole: yellow oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 2.3 Hz, 1H), 7.46 – 6.91 (m, 1H), 7.06 – 6.91 (m, 2H), 4.23 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.51(d, *J* = 246 Hz), 133.03 (d, *J* = 1.0 Hz), 129.37 (d, *J* = 12.0 Hz), 127.98 (d, *J* = 4.0 Hz), 120.78 (d, *J* = 5.0 Hz), 116.61 (d, *J* = 4.0 Hz), 110.58 (d, *J* = 17.0 Hz), 38.11 (d, *J* = 4.0 Hz); **HRMS** (ESI-TOF) *m/z* Calcd for $C_8H_8FN_2$ $[M+H]^+$ 151.0666, found 151.0665.

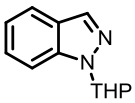


6-Chloro-1-methyl-1H-pyrazolo[3,4-b]pyridine: yellow solid, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.0 Hz, 1H), 8.01 (s, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 4.17 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.55, 149.61, 132.14, 132.04, 117.31, 114.08, 34.18; **HRMS** (ESI-TOF) *m/z* Calcd for $C_7H_7ClN_3$ $[M+H]^+$ 168.0328, found 168.0330.

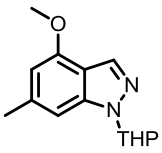
(2) General Procedure for 1-THP-indazole[7]:



To a solution of substituted indazole (10 mmol, 1.0 eq) in DCM (40 mL), was added *p*-toluenesulfonic acid (571 mg, 3 mmol, 0.3 eq), and dihydropyran (DHP, 30 mmol, 3.0 eq). The solution was then stirred at rt until TLC showed a complete conversion of starting material. The solution was further diluted with DCM, washed with saturated $NaHCO_3$. The separated organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in *vacuo*. The resulting residue was purified by silica gel column using hexane:ethyl acetate (6:1) as the eluent to give the sole 1-THP-1H-indazole.



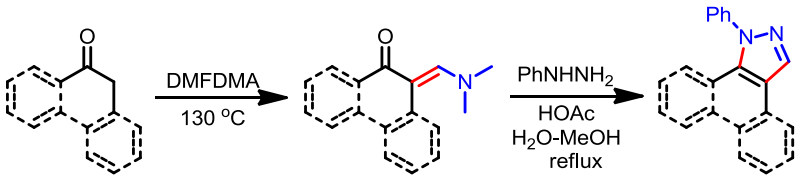
1-(Tetrahydro-2H-pyran-2-yl)-1H-indazole[7]: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.17 (t, *J* = 8.0 Hz, 1H), 5.73 (dd, *J* = 9.5, 2.7 Hz, 1H), 4.06-4.01 (m, 1H), 3.78 – 3.72 (m, 1H), 2.65 – 2.55 (m, 1H), 2.18 – 2.06 (m, 2H), 1.79 – 1.63 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.42, 133.86, 126.42, 124.62, 121.11, 120.95, 109.90, 85.18, 67.43, 29.36, 25.07, 22.60.



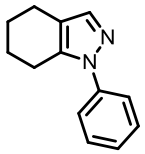
4-Methoxy-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole 7: white solid, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.94 (s, 1H), 6.32 (s, 1H), 5.63 (dd, *J* = 9.5, 2.7 Hz, 1H), 4.07

– 4.01 (m, 1H), 3.93 (s, 3H), 3.79 – 3.68 (m, 1H), 2.61 – 2.52 (m, 1H), 2.47 (s, 3H), 2.22 – 2.10 (m, 1H), 2.10 – 1.99 (m, 1H), 1.81 – 1.57 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.18, 141.71, 138.47, 131.60, 114.76, 102.37, 102.25, 85.16, 67.49, 55.27, 29.35, 25.11, 22.70, 22.47; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{14}H_{19}N_2O_2$ $[M+H]^+$ 247.1441, found 247.1450.

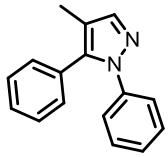
(3) General Procedure for Pyrazole Synthesis[8,9]:



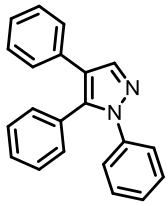
To a 35 mL sealed tube, were added N,N-dimethylformamide dimethyl acetal (DMFDMA) (1.0 mL, 7.5 mmol, 1.5 eq), and corresponding ketone (5 mmol, 1.0 eq) under N_2 atmosphere. The tube was capped and stirred at 130 °C overnight. The reaction mixture was cooled to rt and evaporated in *vacuo*. The residue was diluted with MeOH (13 mL) and transferred to a 50 mL flask, then HOAc (3.0 mL), H_2O (26 mL) and $PhNHNH_2$ (0.74 mL, 7.5 mmol) were added. The resulting mixture was heated to reflux overnight. After cooling, the mixture was evaporated to half volume in *vacuo*, and H_2O (20 mL) was added. The solution was extracted with DCM and the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in *vacuo*. The resulting residue was purified by silica gel column using hexane:ethyl acetate (10:1) as the eluent to give the product.



1-Phenyl-4,5,6,7-tetrahydro-1H-indazole[10]: brown oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 – 7.38 (m, 5H), 7.33 – 7.27 (m, 1H), 2.74 – 2.71 (m, 2H), 2.64 – 2.51 (m, 2H), 1.82– 1.77 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.04, 138.73, 138.10, 128.94, 126.49, 122.92, 117.66, 23.62, 23.10, 22.73, 20.67.

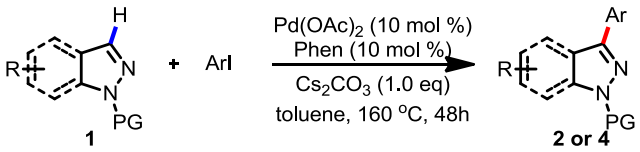


4-Methyl-1,5-diphenyl-1H-pyrazole[11]: white solid, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.41 – 7.32 (m, 3H), 7.32 – 7.16 (m, 7H), 2.15 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.12, 140.27, 139.78, 130.56, 129.79, 128.64, 128.39, 127.94, 126.71, 124.59, 116.35, 9.17.

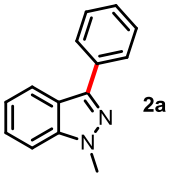


1,4,5-Triphenyl-1H-pyrazole[12]: white solid, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.35 – 7.18 (m, 13H), 7.15 (dt, *J* = 6.6, 1.7 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.95, 139.75, 139.20, 132.78, 130.44, 130.22, 128.69, 128.59, 128.44, 128.41, 127.96, 127.19, 126.37, 125.16, 122.42.

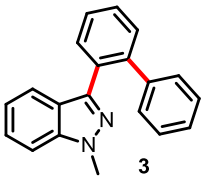
2. General Procedure for C-3 Arylation



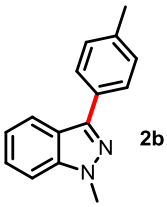
To a 35 mL sealed tube, were added $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), 1,10-phenanthroline (4.5 mg, 0.025 mmol), Cs_2CO_3 (82 mg, 0.25 mmol), aryl halide (0.25 mmol), indazole derivative (0.25 mmol), and toluene (1 mL). The tube was capped and stirred at 160 °C for 48-72 h. The reaction mixture was cooled to room temperature and diluted with EtOAc, filtered through a short pad of Celite, washed with EtOAc, and concentrated in *vacuo*. The resulting residue was purified by PTLC using hexanes:EtOAc (10:1 to 6:1, depending on different substrates) as the eluent.



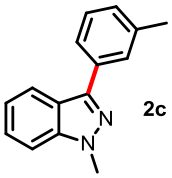
1-Methyl-3-phenyl-1H-indazole[13]: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.99 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.47 – 7.37 (m, 3H), 7.25 – 7.20 (m, 1H), 4.13 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.65, 141.38, 133.65, 128.75, 127.75, 127.32, 126.20, 121.56, 121.29, 120.85, 109.14, 35.48.



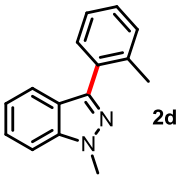
3-([1,1'-Biphenyl]-2-yl)-1-methyl-1H-indazole: white solid, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.3, 2.0 Hz, 1H), 7.98 – 7.94 (m, 2H), 7.56 – 7.45 (m, 8H), 7.44 – 7.39 (m, 1H), 7.28 – 7.21 (m, 1H), 3.68 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.86, 139.29, 138.77, 133.54, 129.89, 128.79, 128.14, 128.04, 127.85, 127.75, 127.61, 126.20, 122.66, 120.82, 120.42, 39.23; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{20}H_{17}N_2$ $[M+H]^+$ 285.1386, found 285.1390.



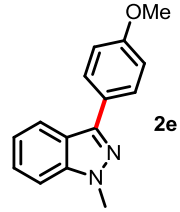
1-Methyl-3-(*p*-tolyl)-1H-indazole: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 2H), 7.45 – 7.39 (m, 2H), 7.33 (dd, *J* = 7.9, 0.7 Hz, 2H), 7.23 – 7.19 (m, 1H), 4.12 (s, 3H), 2.44 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.74, 141.36, 137.54, 130.78, 129.46, 127.21, 126.15, 121.56, 121.37, 120.69, 109.08, 35.44, 21.29; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{15}H_{15}N_2$ $[M+H]^+$ 223.1230, found 223.1239.



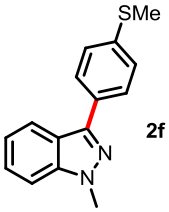
1-Methyl-3-(*m*-tolyl)-1H-indazole: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.2 Hz, 1H), 7.80 (s, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.46 – 7.38 (m, 3H), 7.24 – 7.20 (m, 1H), 4.13 (s, 3H), 2.47 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.83, 141.37, 138.43, 133.52, 128.64, 128.58, 127.95, 126.20, 124.50, 121.61, 121.39, 120.78, 109.12, 35.48, 21.52; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{15}H_{15}N_2$ $[M+H]^+$ 223.1230, found 223.1238.



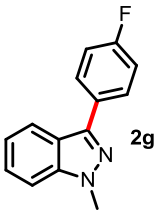
1-Methyl-3-(*o*-tolyl)-1H-indazole: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.2 Hz, 1H), 7.56 – 7.51 (m, 1H), 7.46 – 7.40 (m, 2H), 7.38 – 7.29 (m, 3H), 7.19 – 7.15 (m, 1H), 4.15 (s, 3H), 2.42 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.44, 140.61, 137.15, 132.35, 130.64, 130.47, 128.03, 126.13, 125.61, 122.97, 121.37, 120.42, 108.94, 35.46, 20.50; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{15}H_{15}N_2$ $[M+H]^+$ 223.1230, found 223.1237.



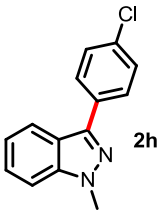
3-(4-Methoxyphenyl)-1-methyl-1H-indazole[13]: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.2 Hz, 1H), 7.93 – 7.87 (m, 2H), 7.45 – 7.37 (m, 2H), 7.22 – 7.18 (m, 1H), 7.08 – 7.02 (m, 2H), 4.11 (s, 3H), 3.88 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.37, 143.54, 141.35, 128.53, 126.32, 126.15, 121.46, 121.31, 120.61, 114.21, 109.06, 55.30, 35.40.



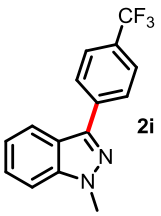
1-Methyl-3-(4-(methylthio)phenyl)-1H-indazole: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.90 (d, *J* = 7.9 Hz, 2H), 7.46 – 7.36 (m, 4H), 7.24 – 7.18 (m, 1H), 4.12 (s, 3H), 2.54 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.11, 141.39, 138.00, 130.55, 127.60, 126.83, 126.23, 121.48, 121.20, 120.86, 109.18, 35.49, 15.83; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{15}H_{15}N_2S$ $[M+H]^+$ 255.0950, found 255.0958.



3-(4-Fluorophenyl)-1-methyl-1H-indazole: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.3 Hz, 1H), 7.94 – 7.89 (m, 2H), 7.47 – 7.40 (m, 2H), 7.25 – 7.16 (m, 3H), 4.13 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.62 (d, *J* = 246 Hz), 142.09 (d, *J* = 146 Hz), 129.56 (d, *J* = 3.0 Hz), 129.07, 128.99, 126.54, 121.34, 121.11 (d, *J* = 1.0 Hz), 115.89, 115.68, 109.26, 35.47; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{14}H_{12}FN_2$ $[M+H]^+$ 227.0979, found 227.0979.

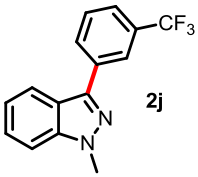


3-(4-Chlorophenyl)-1-methyl-1H-indazole: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.93 – 7.88 (m, 2H), 7.50 – 7.45 (m, 2H), 7.45 – 7.41 (m, 2H), 7.25 – 7.21 (m, 1H), 4.12 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.46, 141.42, 133.57, 132.19, 128.95, 128.46, 126.36, 121.40, 121.13, 121.01, 109.29, 35.56; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{14}H_{12}ClN_2$ $[M+H]^+$ 243.0683, found 243.0683.



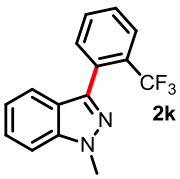
1-Methyl-3-(4-(trifluoromethyl)phenyl)-1H-indazole: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.8 Hz, 2H), 8.01 (d, *J* = 8.3 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.49 – 7.42 (m, 2H), 7.28 – 7.24 (m, 1H), 4.14 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.02, 141.48, 137.24 (q, *J* = 2.0 Hz), 129.47 (q, *J* = 32.0 Hz), 127.29, 126.46, 125.68 (d, *J* = 4.0 Hz), 122.92,

121.51, 121.47, 120.88, 109.43, 35.64; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{15}H_{12}F_3N_2$ $[M+H]^+$ 277.0947, found 277.0952.



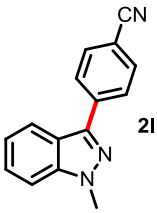
2j

1-Methyl-3-(3-(trifluoromethyl)phenyl)-1H-indazole: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.16 (d, *J* = 7.3 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.68 – 7.58 (m, 2H), 7.46 – 7.44 (m, 2H), 7.29 – 7.23 (m, 1H), 4.14 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.06, 141.47, 134.55, 131.19 (q, *J* = 32.0 Hz), 129.21, 126.46, 125.54, 124.31 (q, *J* = 4.0 Hz), 124.00 (q, *J* = 4.0 Hz), 122.83, 121.41, 121.39, 120.81, 109.40, 35.62; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{15}H_{12}F_3N_2$ $[M+H]^+$ 277.0947, found 277.0952.



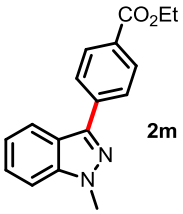
2k

1-Methyl-3-(2-(trifluoromethyl)phenyl)-1H-indazole: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 – 7.83 (m, 1H), 7.67 – 7.53 (m, 4H), 7.47 – 7.40 (m, 2H), 7.18 – 7.14 (m, 1H), 4.14 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.10, 140.42, 132.74, 131.84 (q, *J* = 2.0 Hz), 131.37, 129.91 (q, *J* = 31.0 Hz), 128.42, 126.60 (q, *J* = 4.0 Hz), 126.34, 125.30, 123.38, 120.82, 120.73, 108.92, 35.59; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{15}H_{12}F_3N_2$ $[M+H]^+$ 277.0947, found 277.0957.



2l

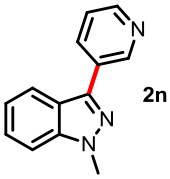
4-(1-Methyl-1H-indazol-3-yl)benzonitrile[13]: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.3 Hz, 2H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.50 – 7.42 (m, 2H), 7.29 – 7.25 (m, 1H), 4.15 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.52, 141.35, 138.25, 132.53, 127.37, 126.57, 121.78, 121.44, 120.71, 119.01, 110.83, 109.58, 35.76.



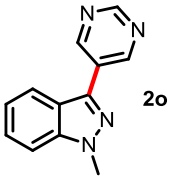
2m

Ethyl 4-(1-methyl-1H-indazol-3-yl)benzoate: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 – 8.14 (m, 2H), 8.08 – 8.03 (m, 2H), 8.02 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.29 – 7.18 (m, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.13 (s, 3H), 1.43 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100

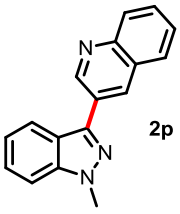
MHz, $CDCl_3$) δ 166.45, 142.36, 141.43, 138.02, 130.00, 129.36, 126.84, 126.37, 121.58, 121.39, 121.04, 109.35, 60.92, 35.62, 14.32; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{17}H_{17}N_2O_2$ $[M+H]^+$ 281.1284, found 281.1290.



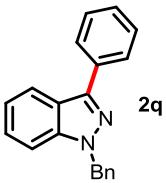
1-Methyl-3-(pyridin-3-yl)-1H-indazole[13]: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.24 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.64 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.26 (ddd, *J* = 7.9, 2.3, 1.7 Hz, 1H), 7.99 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.50 – 7.39 (m, 3H), 7.30 – 7.22 (m, 1H), 4.15 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.70, 148.26, 141.34, 140.45, 134.27, 129.72, 126.47, 123.63, 121.41, 120.74, 109.36, 35.61.



1-Methyl-3-(pyrimidin-5-yl)-1H-indazole: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.32 (s, 2H), 9.21 (s, 1H), 7.94 (d, *J* = 8.3 Hz, 1H), 7.52 – 7.42 (m, 2H), 7.31 – 7.25 (m, 1H), 4.15 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.43, 154.66, 141.37, 137.20, 128.07, 126.79, 122.00, 121.45, 120.29, 109.66, 35.83; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{12}H_{11}N_4$ $[M+H]^+$ 211.0978, found 211.0986.

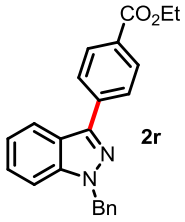


3-(1-Methyl-1H-indazol-3-yl)quinoline: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.58 (d, *J* = 2.2 Hz, 1H), 8.66 (s, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 8.6 Hz, 1H), 7.77 – 7.67 (m, 1H), 7.62 – 7.55 (m, 1H), 7.47 – 7.45 (m, 2H), 7.31 – 7.24 (m, 1H), 4.17 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.81, 147.44, 141.42, 140.61, 132.96, 129.34, 129.32, 128.04, 128.00, 126.97, 126.94, 126.55, 121.74, 121.53, 120.83, 109.46, 35.70; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{17}H_{14}N_3$ $[M+H]^+$ 260.1182, found 260.1185.

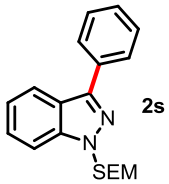


1-Benzyl-3-phenyl-1H-indazole[13]: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 – 8.01 (m, 1H), 8.01 – 7.97 (m, 2H), 7.54 – 7.46 (m, 2H), 7.42 – 7.35 (m, 1H), 7.35 – 7.31 (m, 2H), 7.31 – 7.21 (m, 5H), 7.18 (dt, *J* = 8.0, 3.9 Hz, 1H), 5.64 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.13,

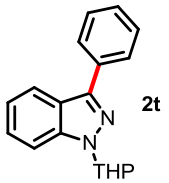
141.03, 136.84, 133.63, 128.76, 128.65, 127.85, 127.65, 127.49, 127.09, 126.33, 122.06, 121.38, 121.06, 109.60, 53.03.



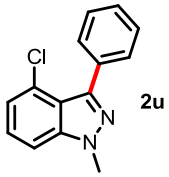
Ethyl 4-(1-benzyl-1H-indazol-3-yl)benzoate (Drug YD-3): colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 – 8.14 (m, 2H), 8.12 – 8.06 (m, 2H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.32 – 7.19 (m, 6H), 5.65 (s, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.46, 142.87, 141.08, 138.02, 136.53, 130.00, 129.46, 128.69, 127.76, 127.09, 127.03, 126.50, 122.07, 121.57, 121.14, 109.80, 60.93, 53.17, 14.33; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{23}H_{21}N_2O_2$ $[M+H]^+$ 357.1597, found 357.1581.



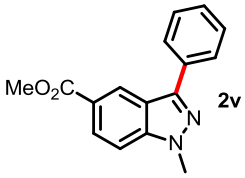
3-Phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (dt, *J* = 8.1, 1.0 Hz, 1H), 8.04 – 7.99 (m, 2H), 7.66 (dt, *J* = 8.5, 0.9 Hz, 1H), 7.59 – 7.52 (m, 2H), 7.52 – 7.42 (m, 2H), 7.33 – 7.25 (m, 1H), 5.84 (s, 2H), 3.77 – 3.59 (m, 2H), 1.06 – 0.89 (m, 2H), -0.01 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.81, 141.25, 133.37, 128.76, 128.07, 127.58, 126.69, 122.57, 121.64, 121.31, 109.92, 77.72, 66.40, 17.73, -1.47; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{19}H_{25}N_2OSi$ $[M+H]^+$ 325.1731, found 325.1740.



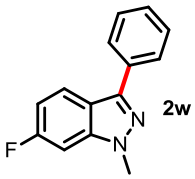
3-Phenyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 – 7.97 (m, 3H), 7.69 – 7.62 (m, 1H), 7.53 – 7.49 (m, 2H), 7.47 – 7.37 (m, 2H), 7.28 – 7.20 (m, 1H), 5.80 (dd, *J* = 9.3, 2.8 Hz, 1H), 4.15 – 4.04 (m, 1H), 3.81 – 3.75 (m, 1H), 2.72 – 2.67 (m, 1H), 2.31 – 2.07 (m, 2H), 1.86 – 1.60 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.52, 140.92, 133.57, 128.65, 127.91, 127.65, 126.41, 122.50, 121.54, 121.28, 110.37, 85.52, 67.43, 29.36, 25.13, 22.60; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{18}H_{19}N_2O$ $[M+H]^+$ 279.1492, found 279.1504.



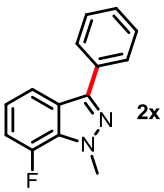
4-Chloro-1-methyl-3-phenyl-1H-indazole: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 – 7.71 (m, 2H), 7.51 – 7.44 (m, 3H), 7.35 (s, 1H), 7.34 (d, *J* = 3.0 Hz, 1H), 7.18 (dd, *J* = 5.6, 2.6 Hz, 1H), 4.14 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.72, 142.27, 133.00, 130.56, 128.04, 127.64, 127.28, 126.82, 121.52, 119.59, 107.81, 35.76; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{14}H_{12}ClN_2$ $[M+H]^+$ 243.0683, found 243.0685.



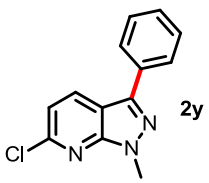
Methyl 1-methyl-3-phenyl-1H-indazole-5-carboxylate: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 1.5, 0.8 Hz, 1H), 8.09 (dd, *J* = 8.9, 1.5 Hz, 1H), 8.00 – 7.93 (m, 2H), 7.53 (ddt, *J* = 8.8, 7.0, 0.8 Hz, 2H), 7.46 – 7.42 (m, 1H), 7.39 (dd, *J* = 8.8, 0.8 Hz, 1H), 4.12 (s, 3H), 3.96 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.26, 145.51, 143.03, 132.75, 128.88, 128.30, 127.48, 127.09, 124.84, 123.07, 121.30, 108.86, 52.07, 35.67; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{16}H_{15}N_2O_2$ $[M+H]^+$ 267.1128, found 267.1129.



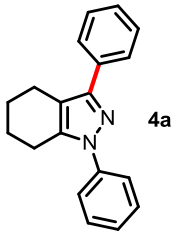
6-Fluoro-1-methyl-3-phenyl-1H-indazole: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 – 7.89 (m, 3H), 7.53 – 7.50 (m, 2H), 7.44 – 7.38 (m, 1H), 7.04 (dd, *J* = 9.1, 2.2 Hz, 1H), 6.97 (dt, *J* = 9.0, 2.2 Hz, 1H), 4.06 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.11 (d, *J* = 244 Hz), 144.06, 141.76 (d, *J* = 12.0 Hz), 133.11, 128.82, 128.06, 127.33, 122.79 (d, *J* = 10.9 Hz), 118.51, 110.71 (d, *J* = 25.7 Hz), 94.77 (d, *J* = 25.9 Hz), 35.57; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{14}H_{12}FN_2$ $[M+H]^+$ 227.0979, found 227.0988.



7-Fluoro-1-methyl-3-phenyl-1H-indazole: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 – 7.90 (m, 2H), 7.78 – 7.72 (m, 1H), 7.55 – 7.47 (m, 2H), 7.45 – 7.38 (m, 1H), 7.12 – 7.02 (m, 2H), 4.31 (d, *J* = 1.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.59 (d, *J* = 246 Hz), 144.34 (d, *J* = 1.5 Hz), 133.07, 130.95 (d, *J* = 12.4 Hz), 128.80, 128.05, 127.42, 125.63 (d, *J* = 4.2 Hz), 121.25 (d, *J* = 5.44 Hz), 117.00 (d, *J* = 4.3 Hz), 110.77 (d, *J* = 16.9 Hz), 38.31 (d, *J* = 4.5 Hz); **HRMS** (ESI-TOF) *m/z* Calcd for $C_{14}H_{12}FN_2$ $[M+H]^+$ 227.0979, found 227.0990.

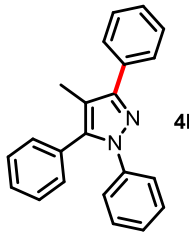


6-Chloro-1-methyl-3-phenyl-1H-pyrazolo[3,4-b]pyridine: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.0 Hz, 1H), 7.96 – 7.94 (m, 2H), 7.56 – 7.52 (m, 2H), 7.48 – 7.43 (m, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 4.21 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.51, 150.34, 143.00, 132.68, 132.11, 128.75, 128.60, 126.73, 117.35, 111.89, 33.55; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{13}H_{11}ClN_3$ $[M+H]^+$ 244.0642, found 244.0647.



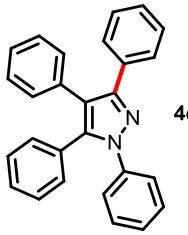
4a

1,3-Diphenyl-4,5,6,7-tetrahydro-1H-indazole: yellow oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 – 7.78 (m, 2H), 7.62 – 7.53 (m, 2H), 7.48 – 7.40 (m, 4H), 7.34 – 7.30 (m, 2H), 2.93 – 2.70 (m, 4H), 1.87 – 1.84 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.04, 140.02, 139.67, 134.10, 129.02, 128.40, 127.31, 126.92, 126.69, 123.39, 115.51, 23.94, 23.10, 22.75, 22.56; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{19}H_{19}N_2$ $[M+H]^+$ 275.1543, found 275.1542.



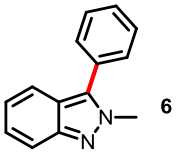
4b

4-Methyl-1,3,5-triphenyl-1H-pyrazole: white solid, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 – 7.79 (m, 2H), 7.52 – 7.48 (m, 2H), 7.43 – 7.38 (m, 4H), 7.37 – 7.22 (m, 7H), 2.29 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 151.20, 141.41, 140.15, 133.83, 130.69, 130.04, 128.63, 128.43, 128.38, 128.10, 127.85, 127.54, 126.69, 124.69, 114.12, 10.19; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{22}H_{19}N_2$ $[M+H]^+$ 311.1543, found 311.1547.



4c

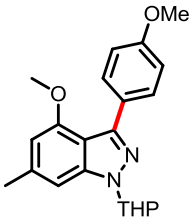
1,3,4,5-Tetraphenyl-1H-pyrazole: white solid, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 – 7.55 (m, 2H), 7.41 – 7.19 (m, 14H), 7.18 – 7.06 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.17, 141.33, 139.93, 133.10, 130.67, 130.40, 130.04, 128.72, 128.36, 128.22, 128.15, 128.10, 127.58, 127.17, 126.61, 125.28, 120.67; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{27}H_{21}N_2$ $[M+H]^+$ 373.1699, found 373.1703.



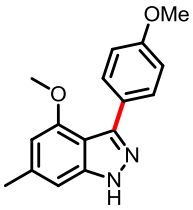
6

2-Methyl-3-phenyl-2H-indazole[14]: colorless oil, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.7 Hz, 1H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.59 – 7.50 (m, 4H), 7.53 – 7.44 (m, 1H), 7.34 – 7.30 (m, 1H), 7.13 – 7.04 (m, 1H), 4.19 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 147.99, 135.96, 129.63, 129.50, 128.93, 128.64, 126.19, 121.73, 121.11, 120.05, 116.92, 38.47.

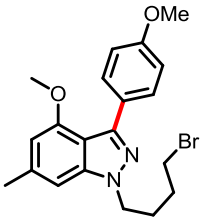
3. Total Synthesis of Nigellidine



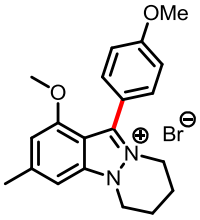
4-Methoxy-3-(4-methoxyphenyl)-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole 8: To a 100 mL sealed tube, were added $Pd(OAc)_2$ (74.8 mg, 0.333 mmol, 0.1 eq), 1,10-phenanthroline (180 mg, 1.0 mmol, 0.3 eq), Cs_2CO_3 (3.25 g, 10 mmol, 3.0 eq), 4-bromoanisole (1.7 mL, 13.32 mmol, 4.0 eq), indazole **7** (820 mg, 3.33 mmol), and toluene (13 mL). The tube was capped and stirred at 160 °C for 72 h. The reaction mixture was cooled to room temperature and diluted with EtOAc, filtered through a short pad of Celite, washed with EtOAc, and concentrated in *vacuo*. The resulting residue was purified by silica gel column using hexanes:EtOAc (6:1) as the eluent to give a white solid, 634 mg (54% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 – 7.86 (m, 2H), 7.01 – 6.94 (m, 3H), 6.36 (s, 1H), 5.68 (dd, *J* = 9.5, 2.8 Hz, 1H), 4.13 – 4.02 (m, 1H), 3.87 (s, 6H), 3.82 – 3.70 (m, 1H), 3.70 – 3.60 (m, 1H), 2.50 (s, 3H), 2.24 – 2.13 (m, 1H), 2.12 – 2.02 (m, 1H), 1.84 – 1.59 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.24, 153.90, 144.67, 143.31, 138.29, 130.82, 126.66, 113.10, 111.73, 102.60, 102.36, 85.31, 67.45, 55.20, 55.07, 29.23, 25.11, 22.68, 22.30; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{21}H_{25}N_2O_3$ $[M+H]^+$ 353.1860, found 353.1862.



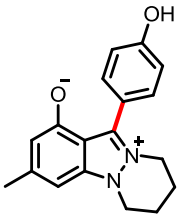
4-Methoxy-3-(4-methoxyphenyl)-6-methyl-1H-indazole 9: To a solution of compound **8** (0.46 g, 1.3 mmol, 1.0 eq) in MeOH (20 mL), was added AcCl (2.8 mL, 39 mmol, 30 eq) dropwise at 0 °C. The solution was heated to 55 °C for 2 h, then cooled to rt and evaporated in *vacuo*. The residue was diluted with EtOAc, washed with saturated $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and evaporated to give nearly pure product, white solid, 304 mg (87% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 – 7.86 (m, 2H), 7.05 – 6.97 (m, 2H), 6.46 – 6.37 (m, 1H), 6.30 (s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.39 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.41, 153.88, 145.59, 144.17, 138.42, 130.94, 126.74, 113.38, 110.41, 102.42, 102.06, 55.25, 55.10, 22.08; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{16}H_{17}N_2O_2$ $[M+H]^+$ 269.1284, found 269.1285.



1-(4-Bromobutyl)-4-methoxy-3-(4-methoxyphenyl)-6-methyl-1H-indazole 10: To a suspended solution of NaH (60% in mineral oil, 86 mg, 2.14 mmol, 2.0 eq) in DMF (2 mL) and DMSO (1 mL), was added compound **9** (287 mg, 1.07 mmol, 1.0 eq) in DMF (2 mL) at 0 °C under N_2 atmosphere. The mixture was stirred at rt for 20 min, then cooled back to 0 °C, and 1,4-dibromobutane (0.38 mL, 3.21 mmol, 3.0 eq) was added. The resulting mixture was stirred at rt overnight, quenched by saturated NH_4Cl, extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, evaporated in *vacuo*. The residue was purified by silica gel column using hexanes:EtOAc (6:1) as the eluent to give a colorless oil, 321 mg (74% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 – 7.79 (m, 2H), 7.01 – 6.93 (m, 2H), 6.76 (s, 1H), 6.32 (s, 1H), 4.36 (t, *J* = 6.8 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.42 (t, *J* = 6.6 Hz, 2H), 2.49 (s, 3H), 2.16 – 2.05 (m, 2H), 1.97 – 1.84 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.20, 154.12, 144.12, 143.26, 138.12, 130.65, 126.67, 113.25, 111.00, 101.86, 101.23, 55.26, 55.11, 47.71, 33.15, 29.85, 28.27, 22.36; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{20}H_{24}BrN_2O_2$ $[M+H]^+$ 403.1016, found 403.1012.



1-Methoxy-11-(4-methoxyphenyl)-3-methyl-6,7,8,9-tetrahydropyridazino[1,2-a]indazol-10-ium Bromide 11: To a 35 mL sealed tube, were added compound **10** (310 mg, 0.77 mmol, 1.0 eq) and acetonitrile (5 mL). The tube was capped and stirred at 110 °C overnight. The reaction mixture was cooled to room temperature and concentrated in *vacuo*. The resulting residue was recrystallized with DCM/Hexane to give a white solid, 250 mg (81% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 – 7.60 (m, 2H), 7.11 – 7.02 (m, 2H), 6.98 (s, 1H), 6.45 (s, 1H), 4.77 – 4.61 (m, 4H), 3.88 (s, 3H), 3.75 (s, 3H), 2.52 (s, 3H), 2.52 – 2.47 (m, 2H), 2.37 – 2.24 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.58, 154.68, 147.03, 143.21, 142.06, 132.35, 116.52, 113.97, 109.84, 105.65, 101.41, 55.67, 55.40, 48.81, 46.99, 23.05, 20.28, 19.36; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{20}H_{24}BrN_2O_2$ $[M+H]^+$ 403.1016, found 403.1023.



Nigellidine Hydrobromide 12:[15] To a solution of compound **11** (40.3 mg, 0.1 mmol, 1.0 eq) in DCM (6 mL), was added BBr_3 (1M in DCM, 0.6 mL, 0.6 mmol, 6.0 eq) dropwise at rt. The solution was stirred at rt for 4h, then quenched with slow addition of MeOH (2 mL), and anhydrous K_2CO_3 (1.0 g) with vigorous stirring. The solution was then filtered through a pad of Celite and washed with DCM. The e filtrate was concentrated in *vacuo* and the resulting residue was purified by column (DCM/MeOH = 4/1) to give a pale yellow solid, 28 mg (74% yield). The solid was dissolved in hot methanol, then kept in an open flask at room temperature until the crystals were formed. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.59 – 7.43 (m, 2H), 7.09 (s, 1H), 7.06 – 6.91 (m, 2H), 6.71 – 6.55 (m, 1H), 4.48 (t, J = 6.1 Hz, 2H), 4.39 (t, J = 5.8 Hz, 2H), 2.44 (s, 3H), 2.23 – 2.17 (m, 2H), 2.12 – 2.07 (m, 2H); **^{13}C NMR** (151 MHz, DMSO) δ 160.73, 154.48, 146.78, 143.94, 143.23, 133.39, 116.14, 116.10, 109.97, 109.89, 100.53, 49.16, 47.51, 23.24, 20.73, 20.08; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{18}H_{19}N_2O_2$ $[M\text{-}Br]^+$ 295.1441, found 295.1447.

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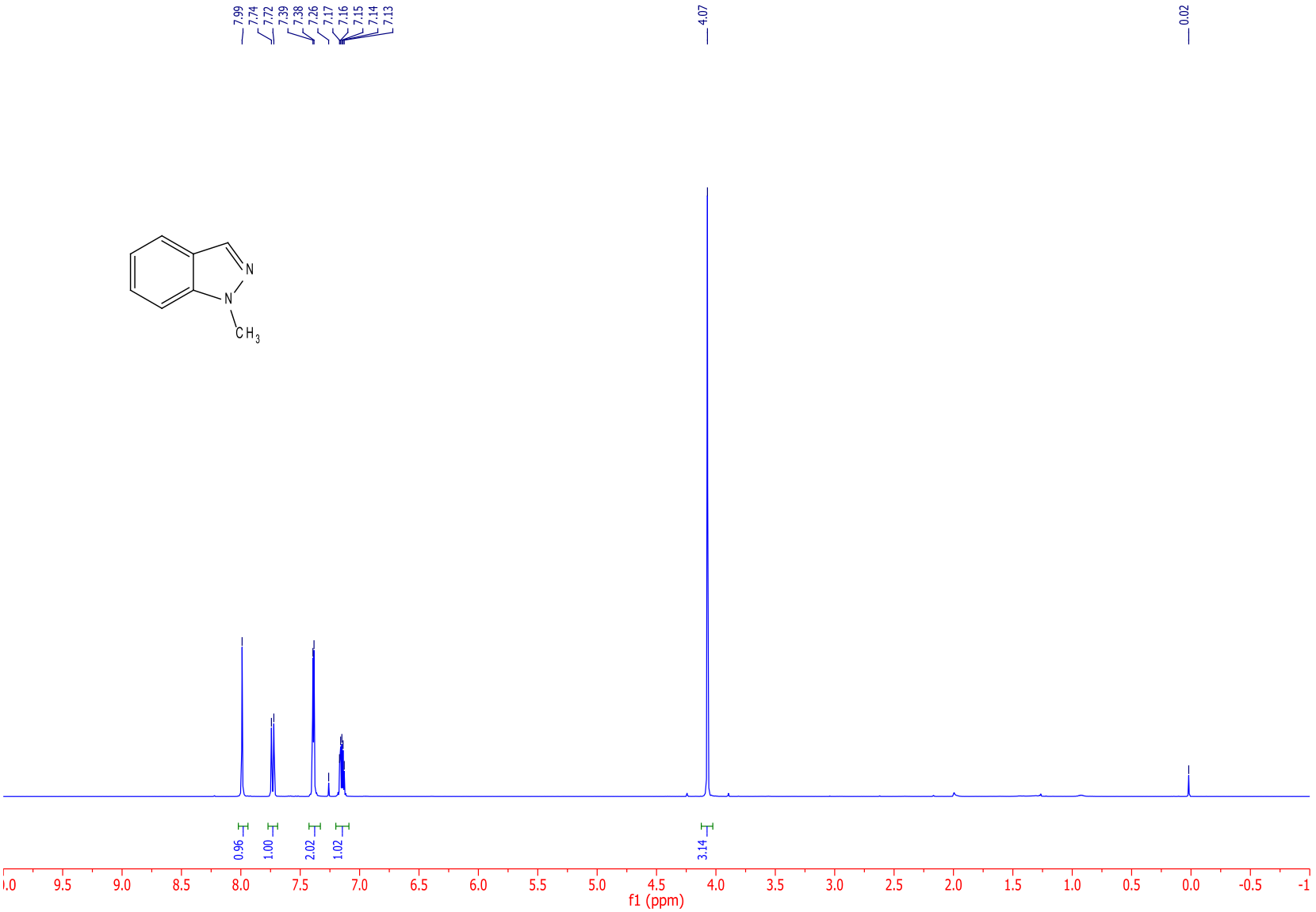

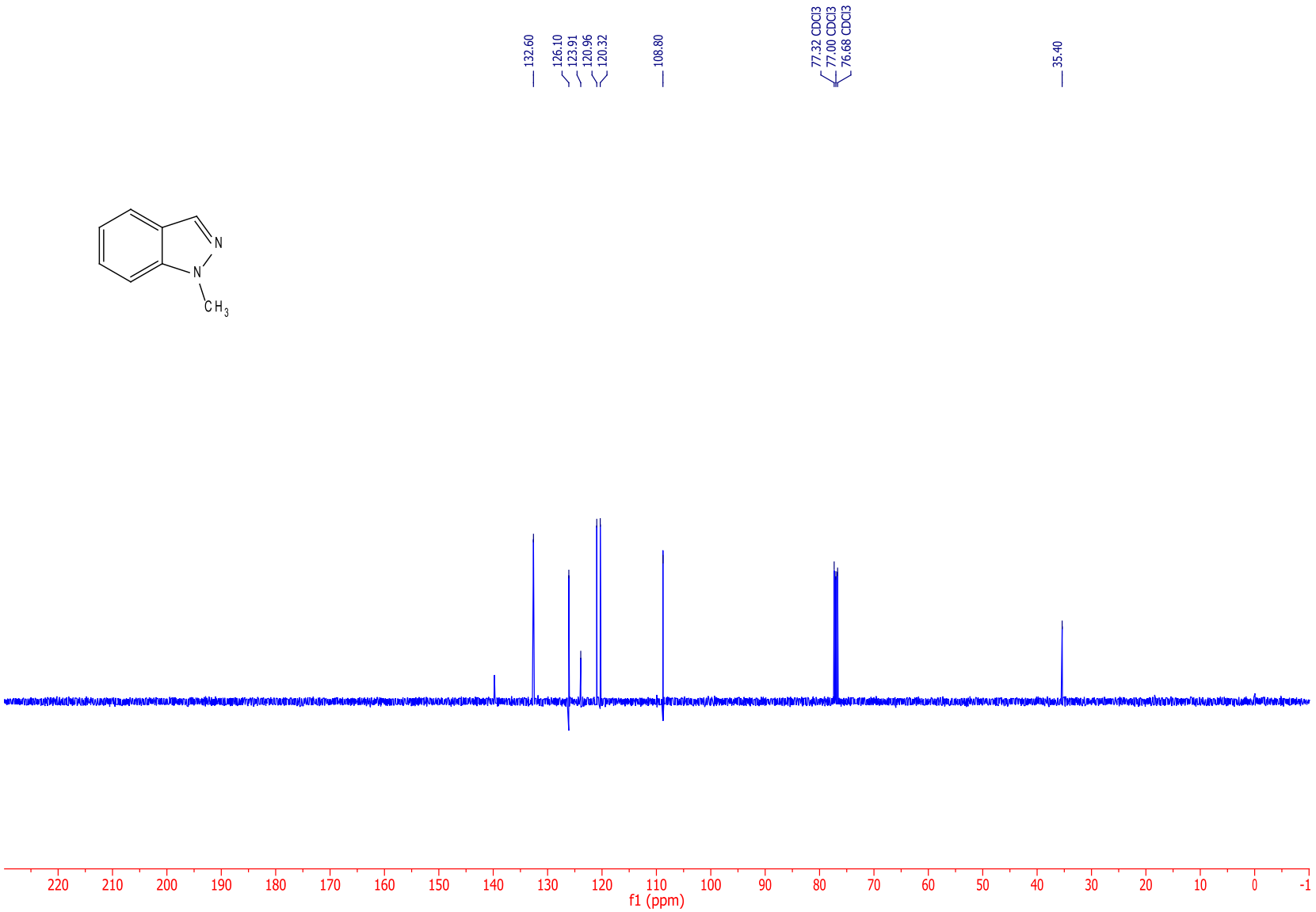

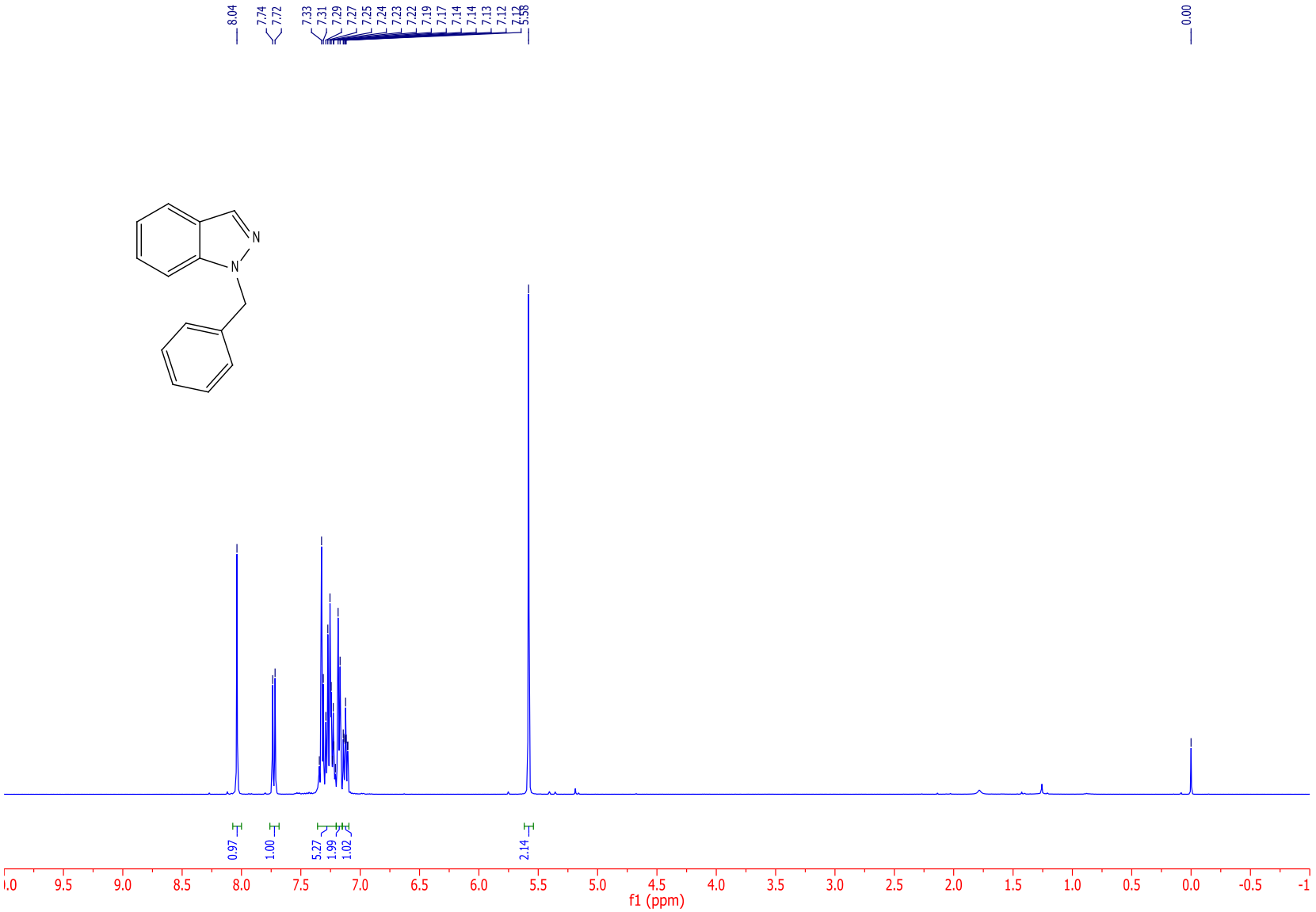

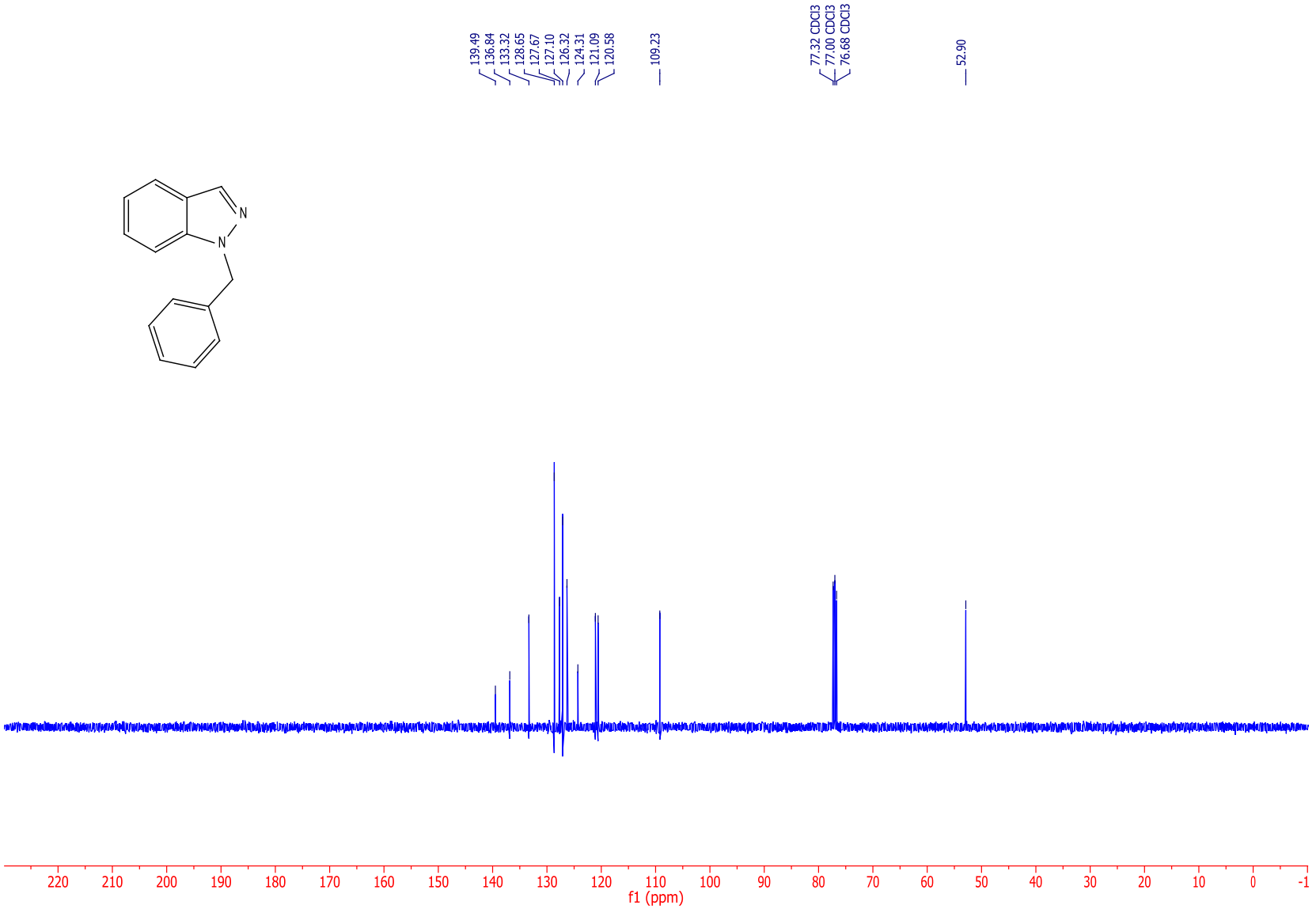

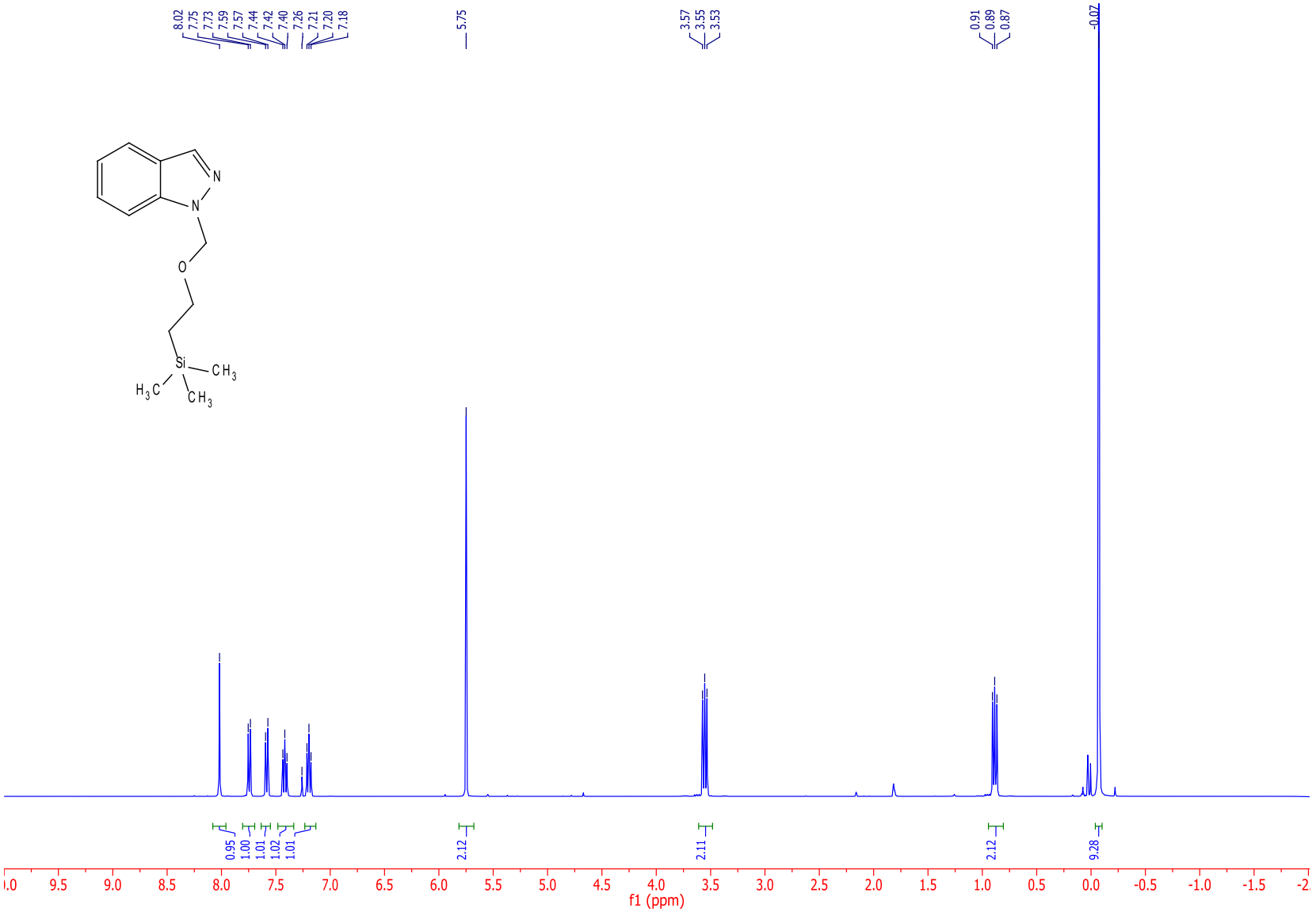

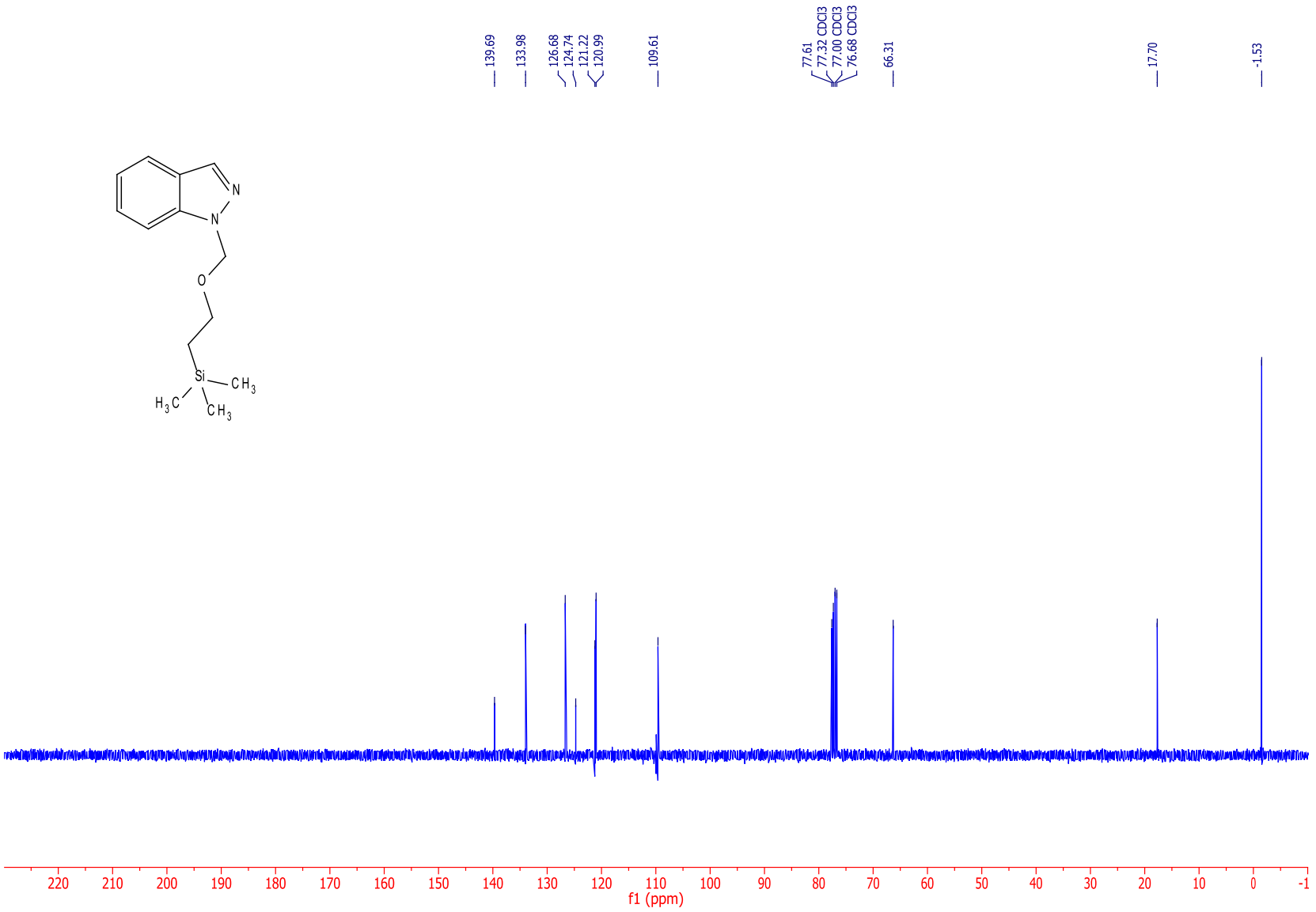

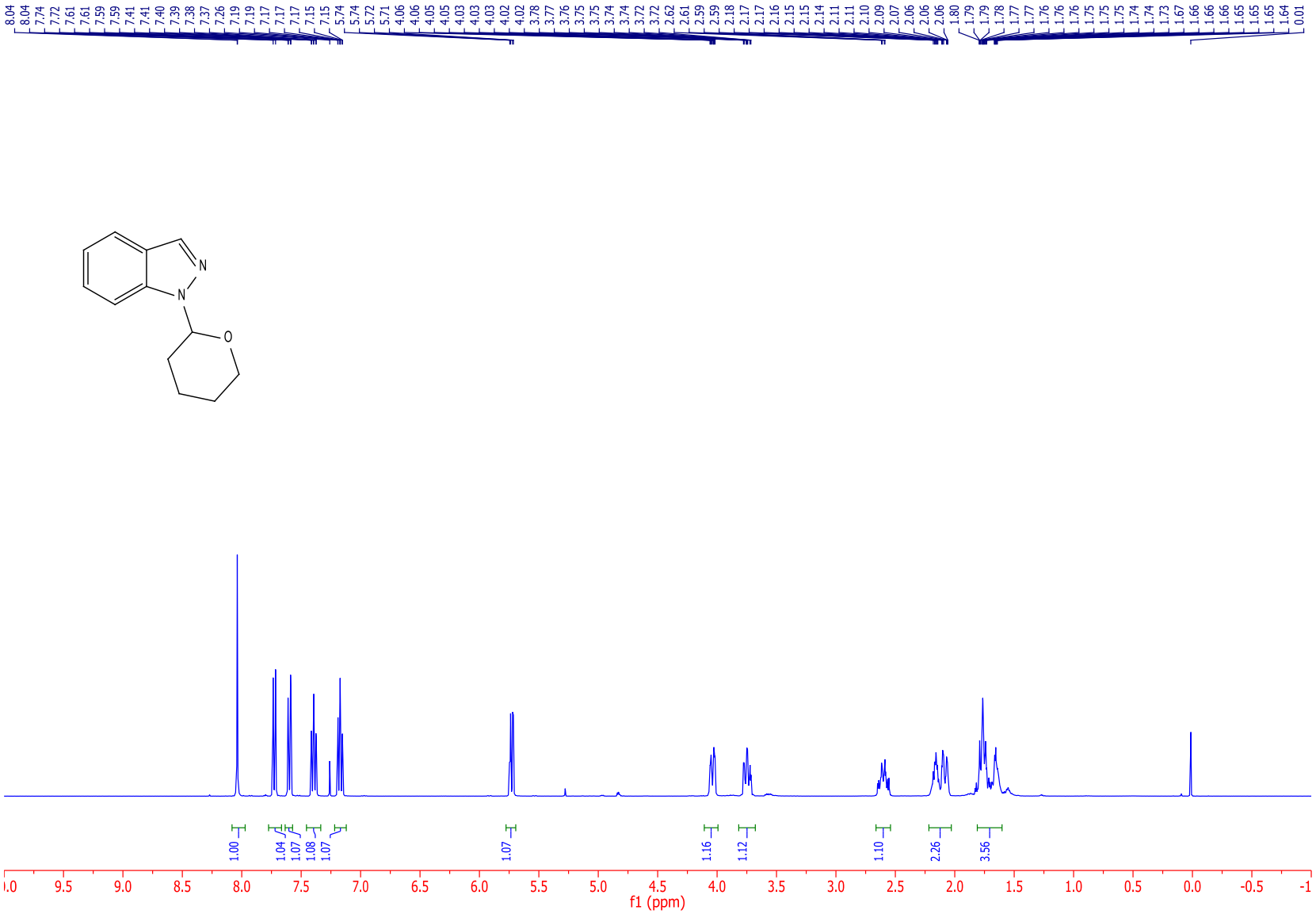

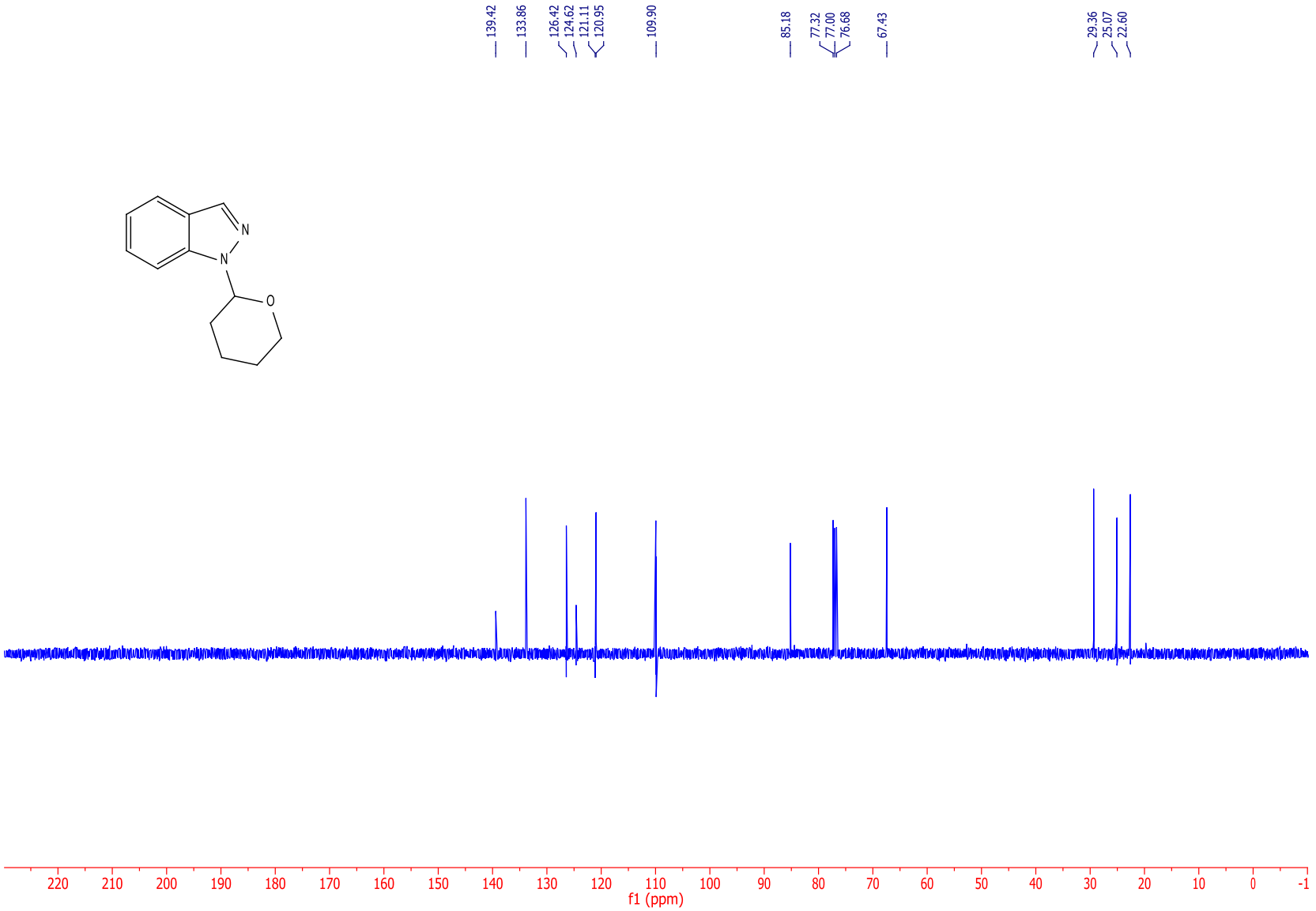

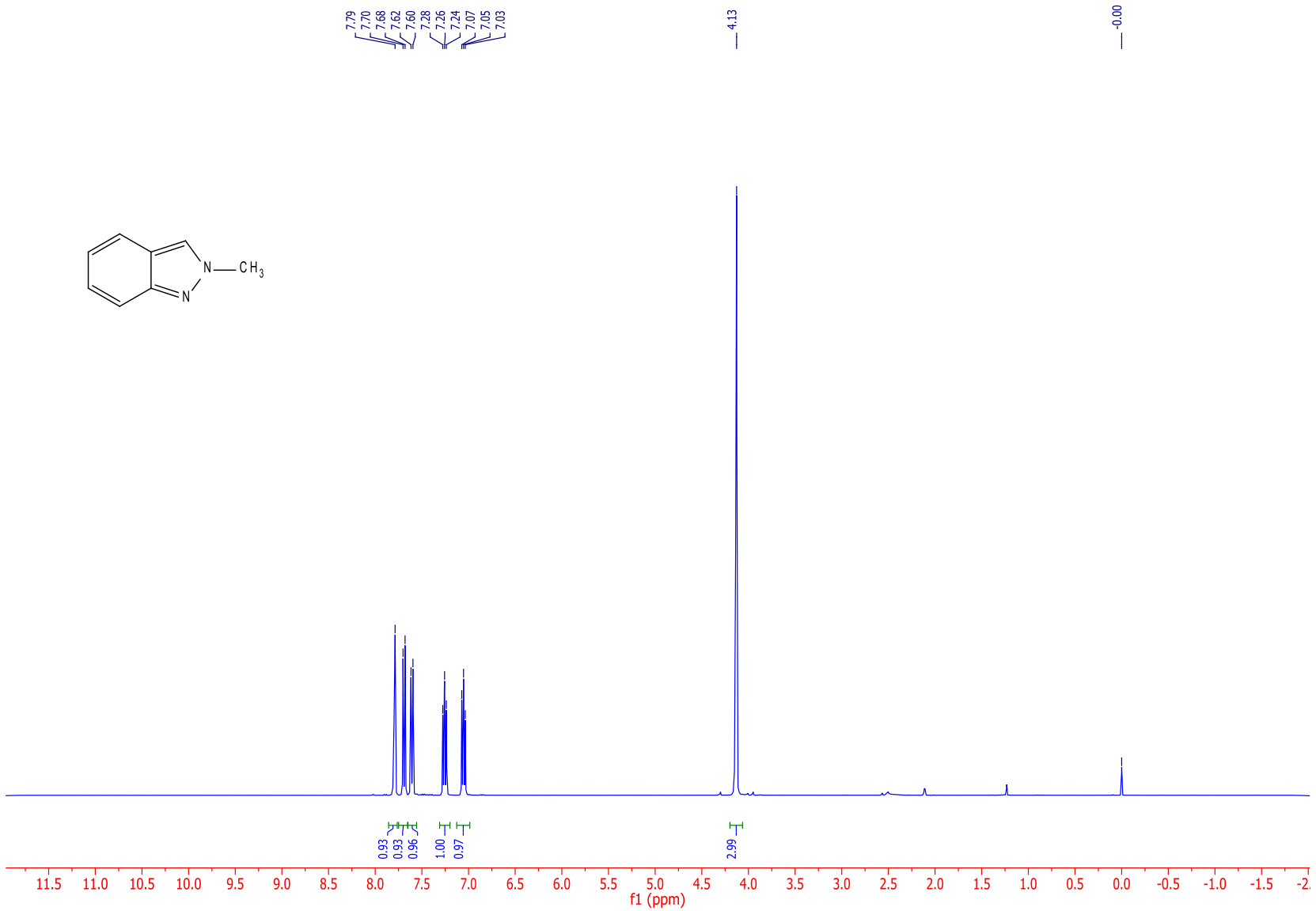

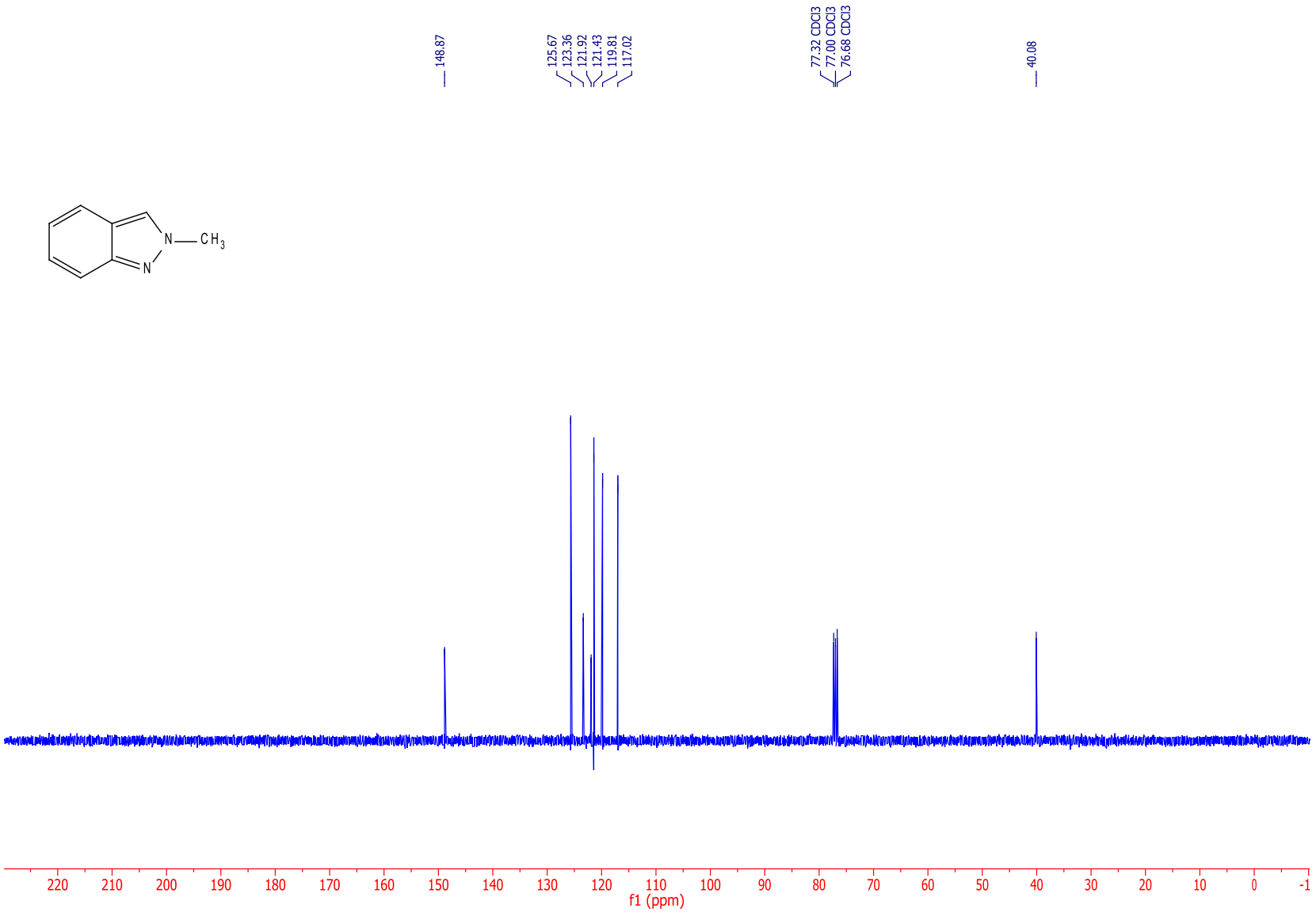

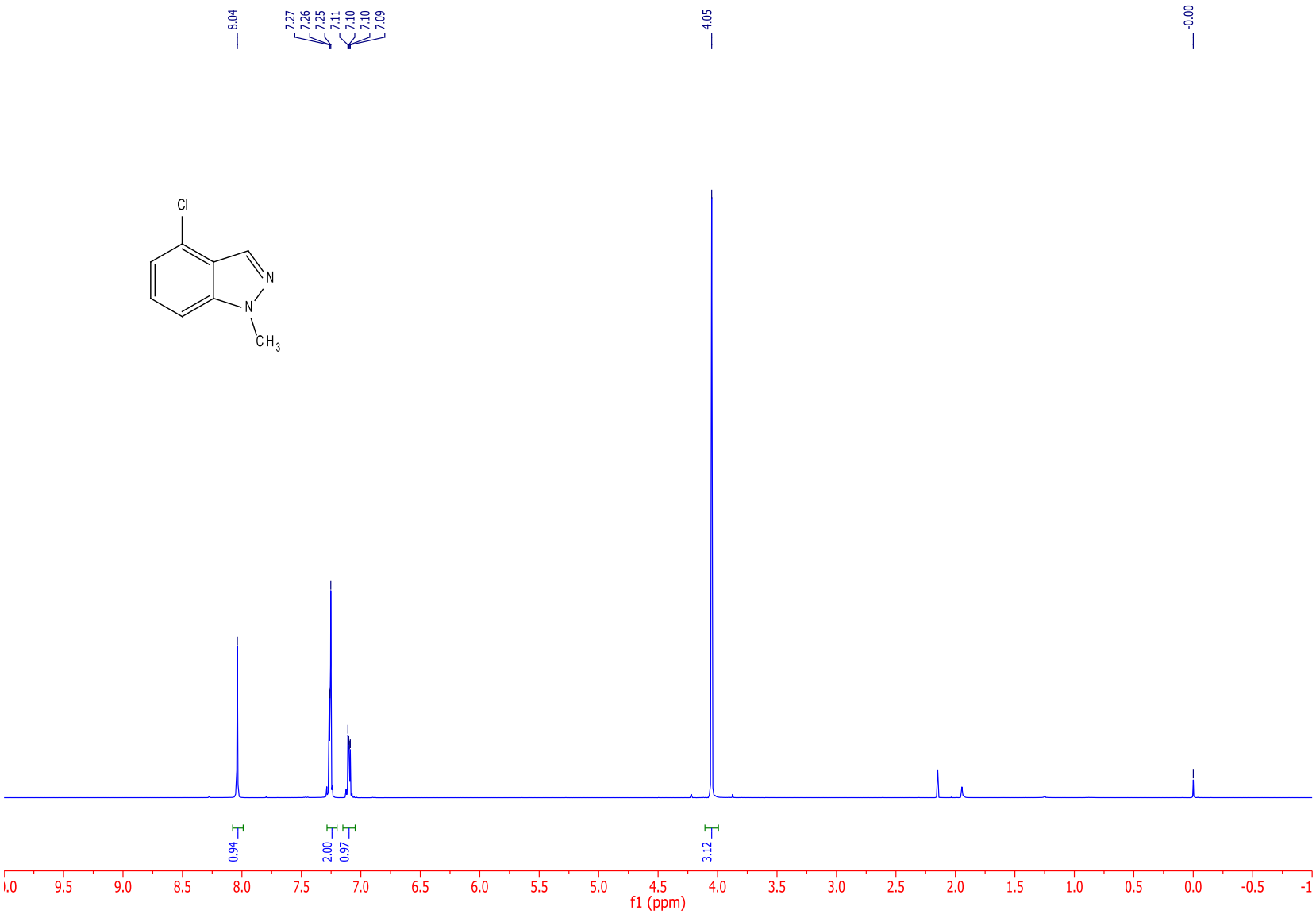

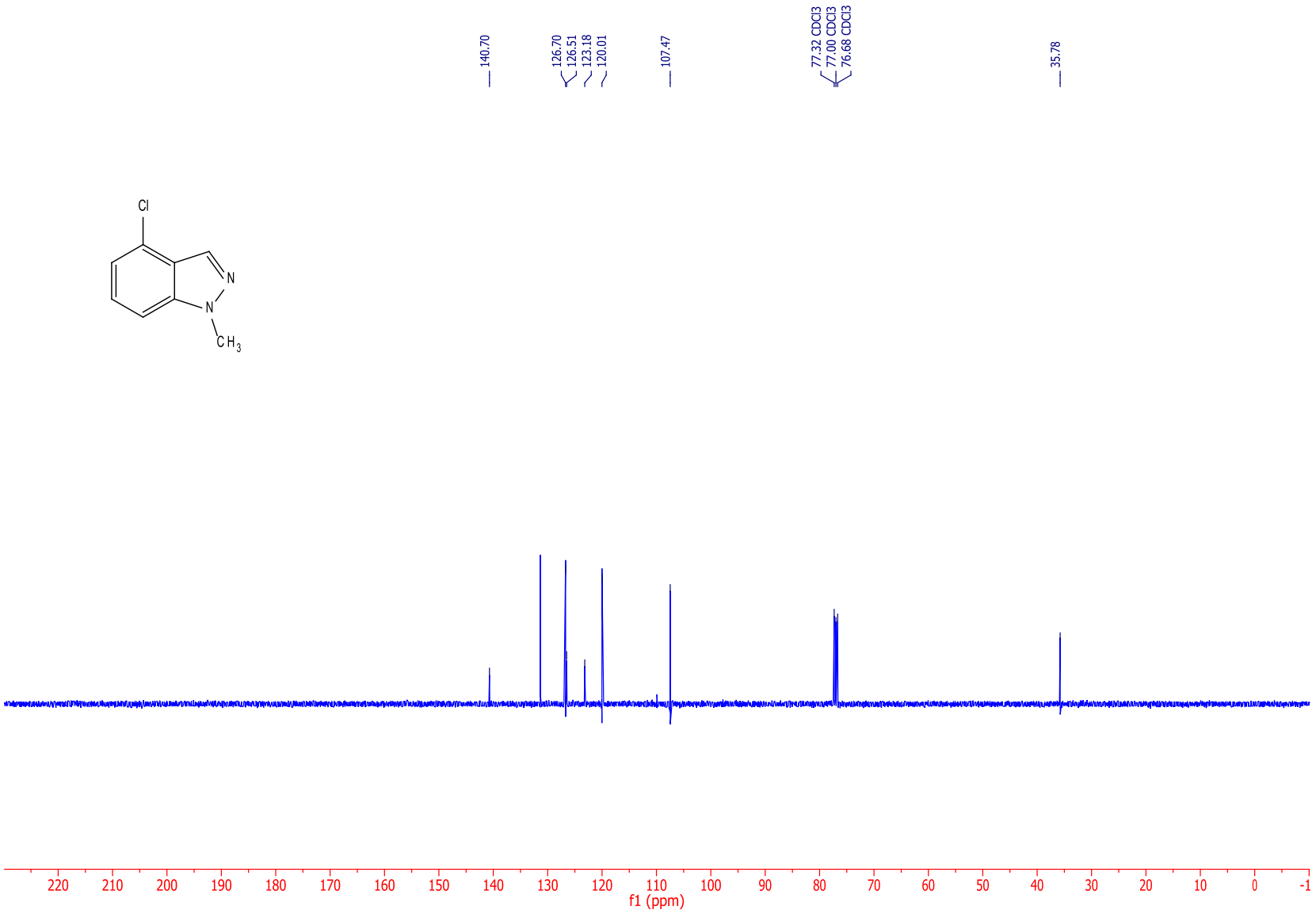

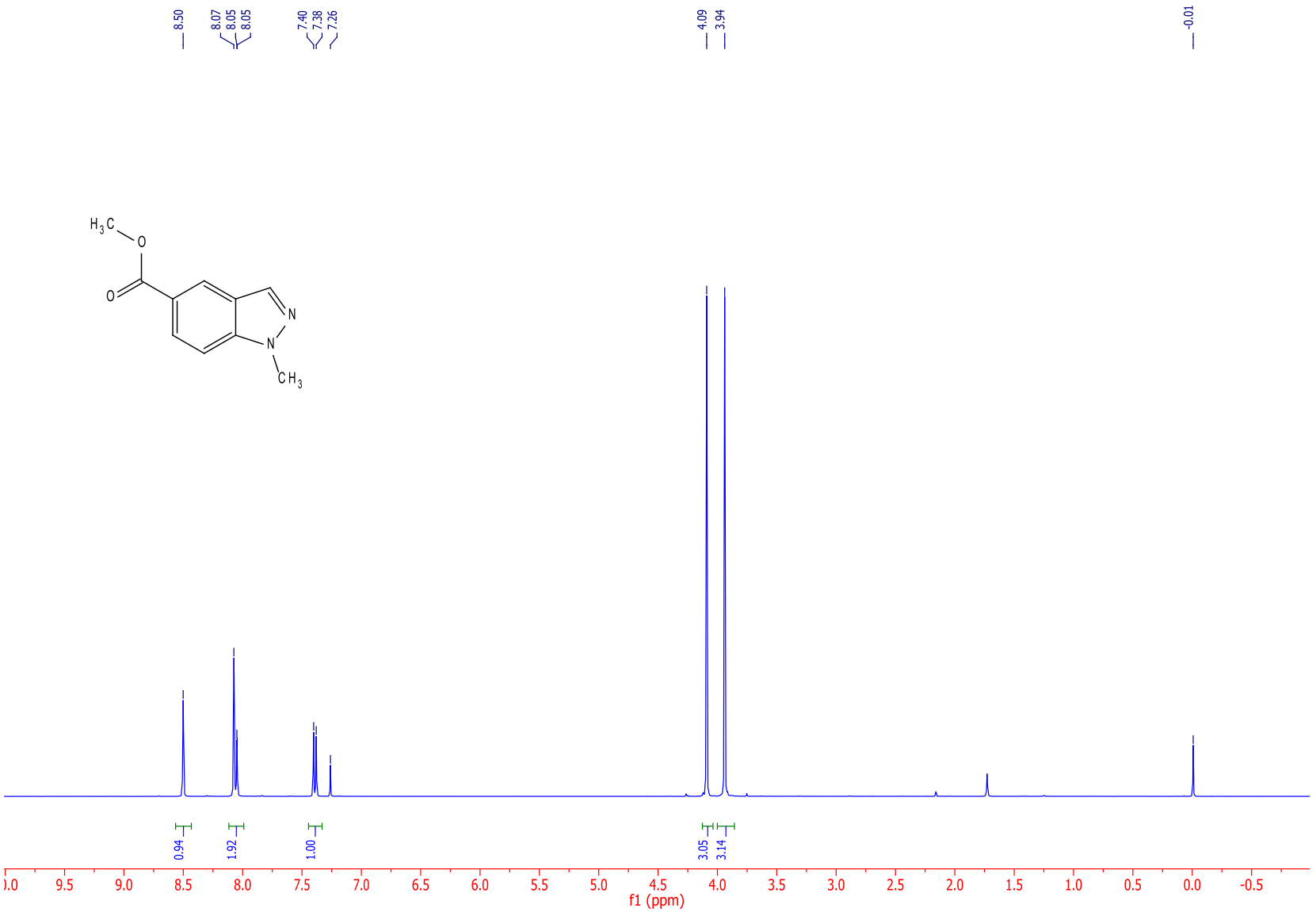

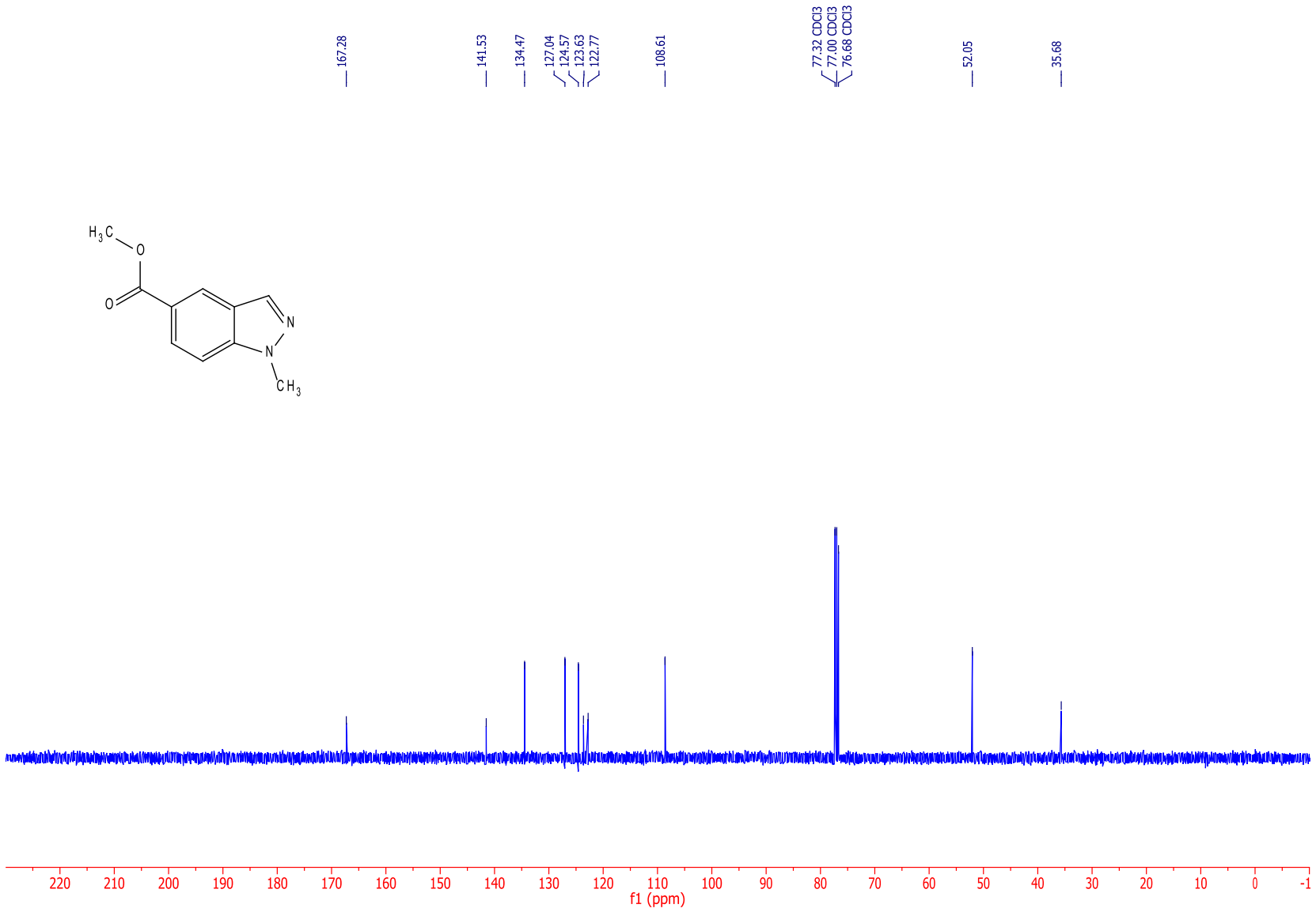

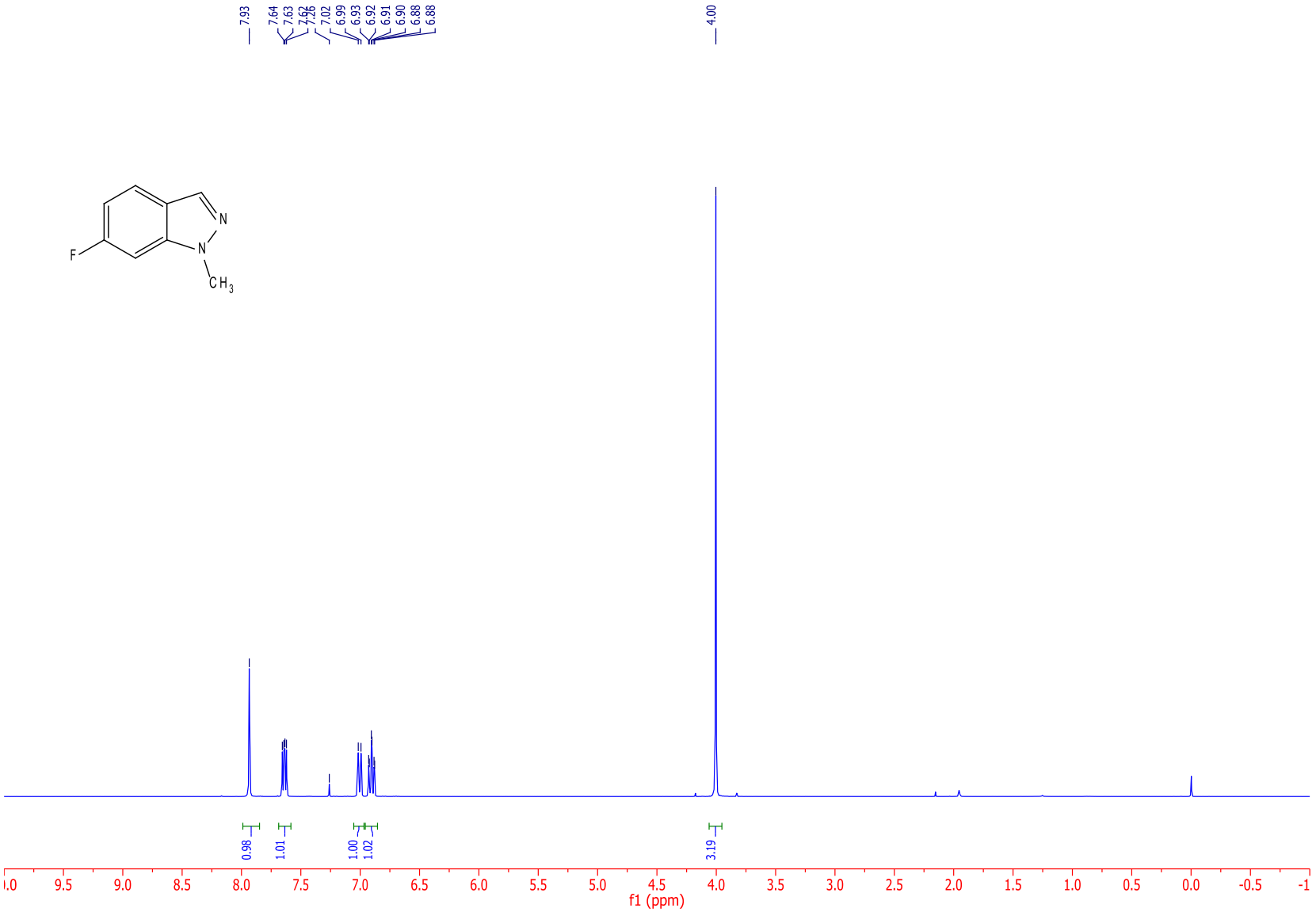

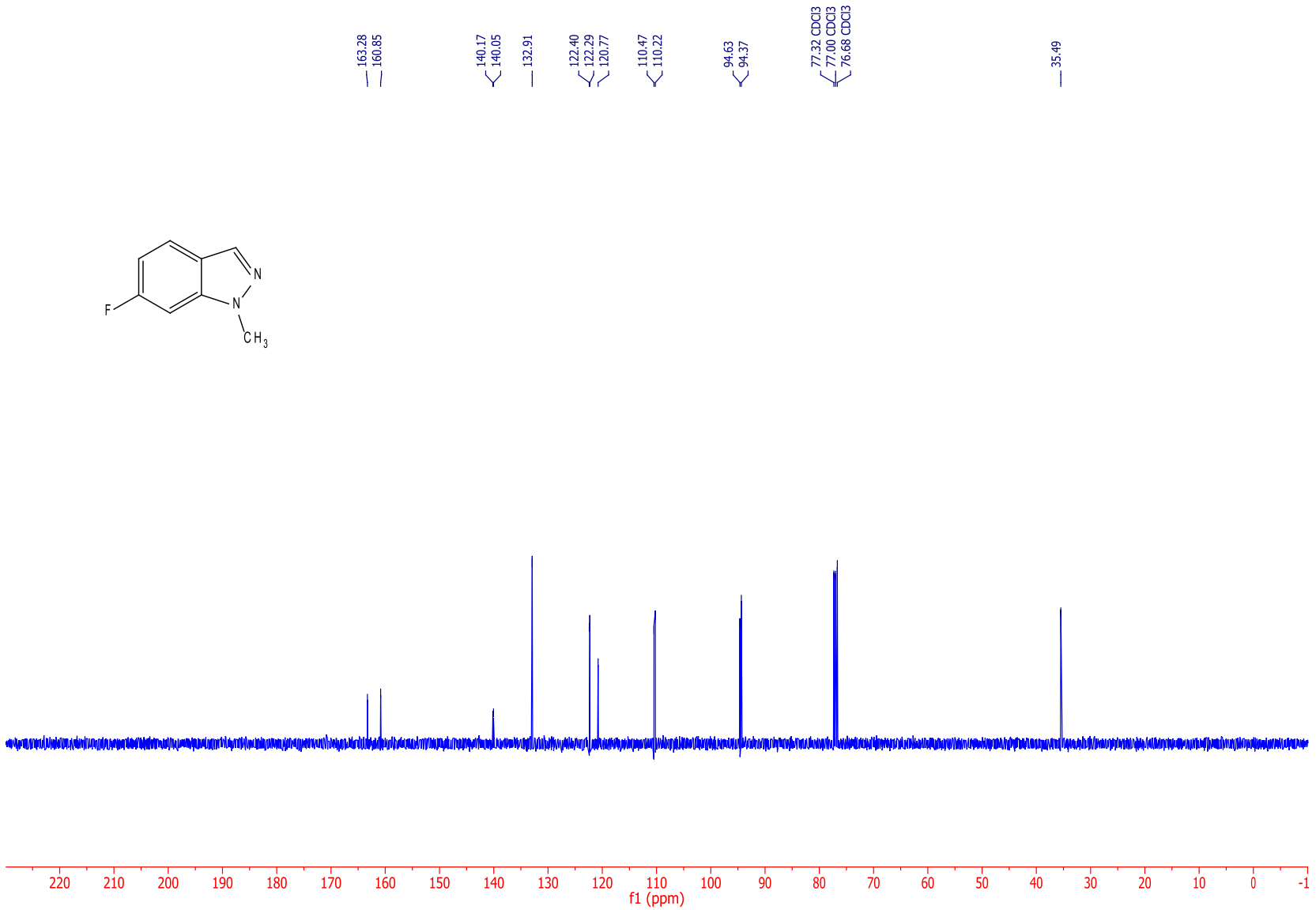

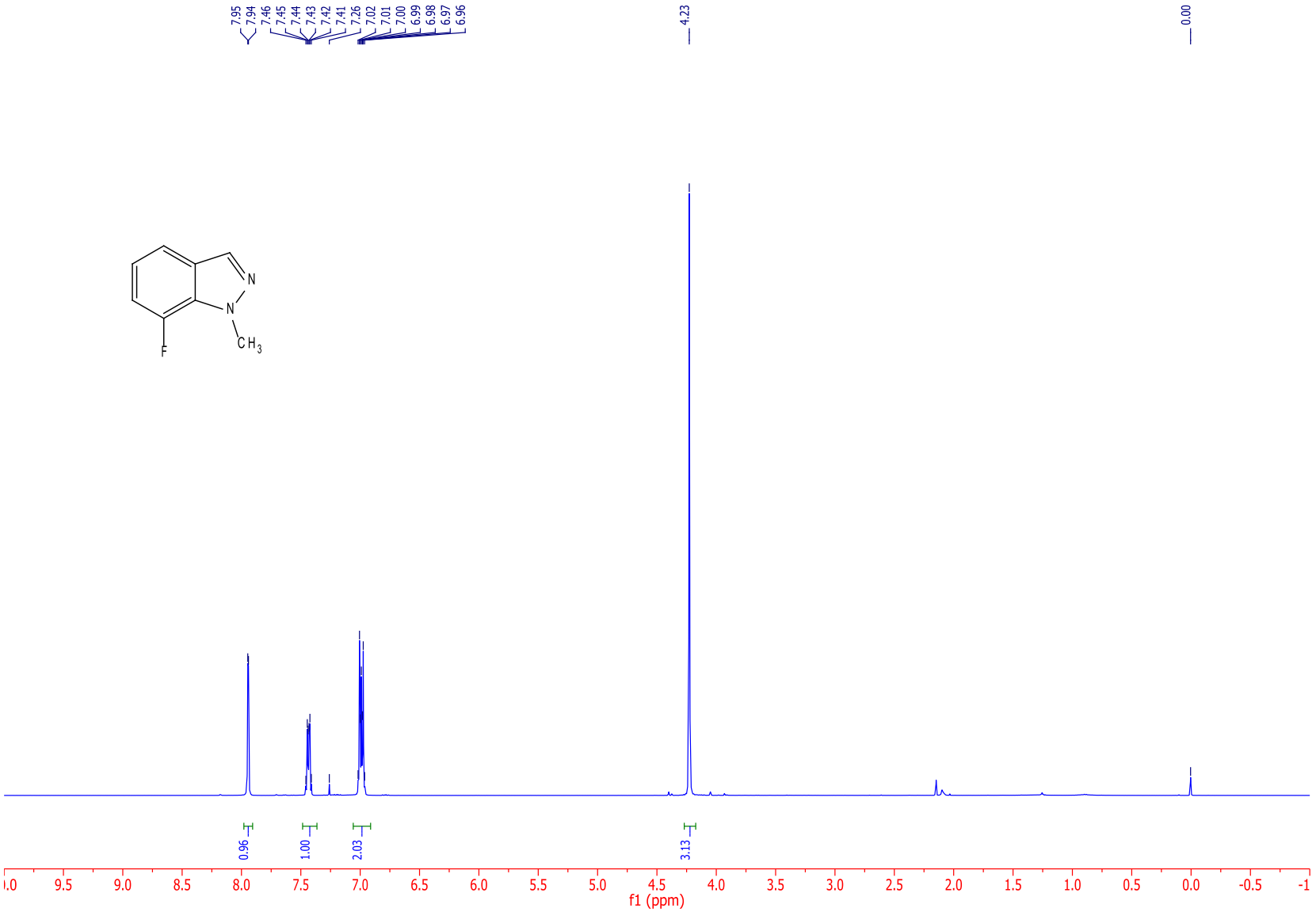

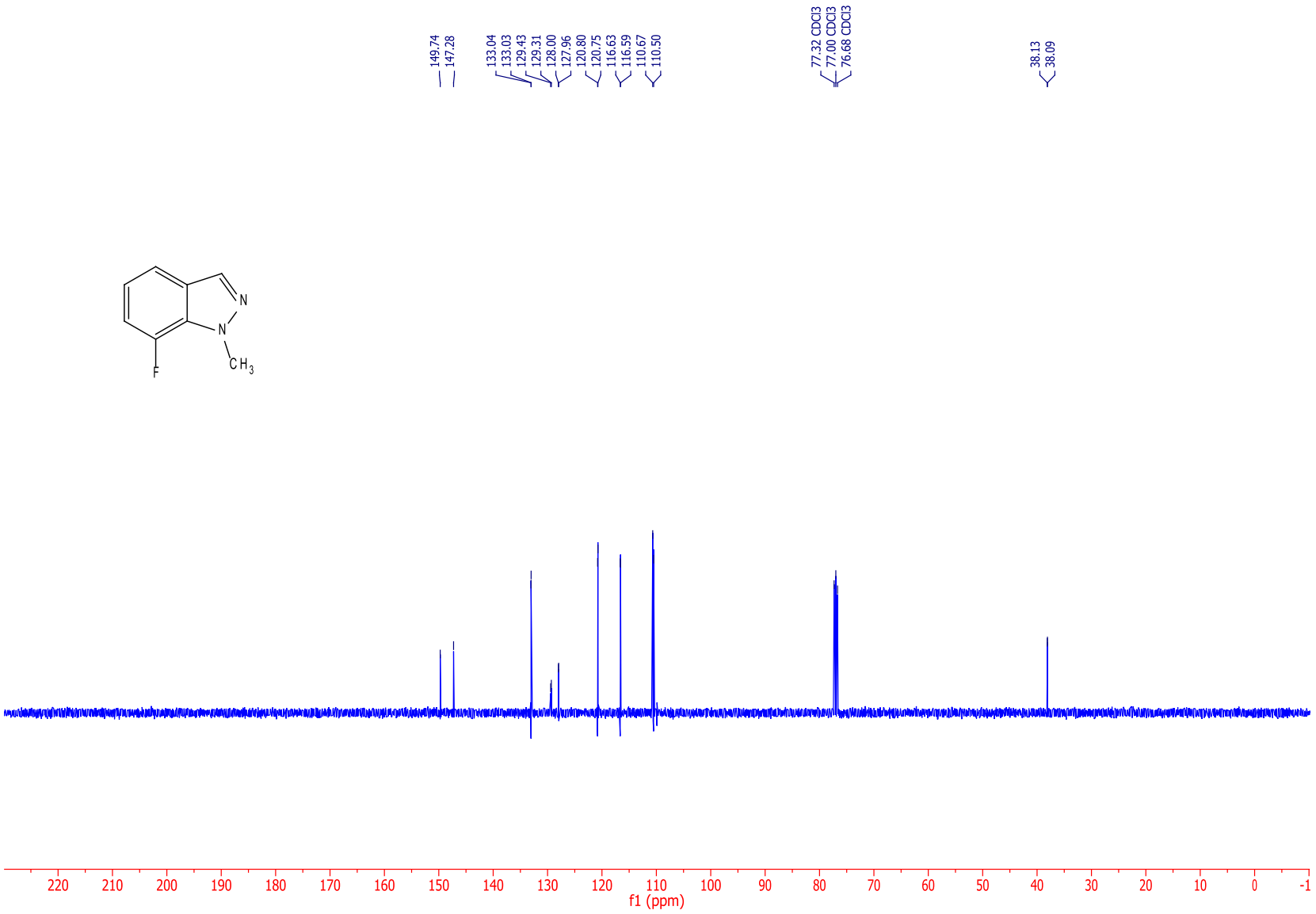

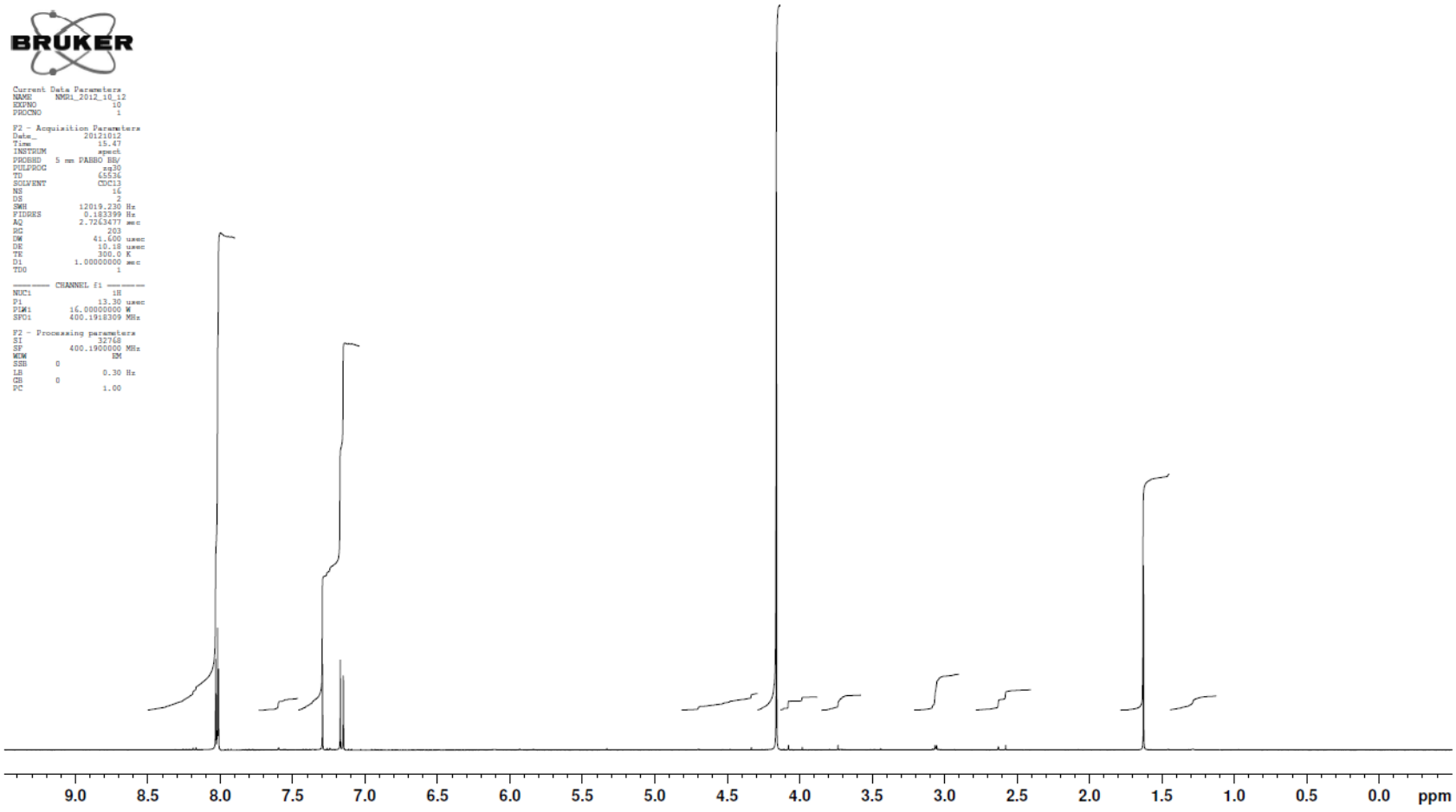
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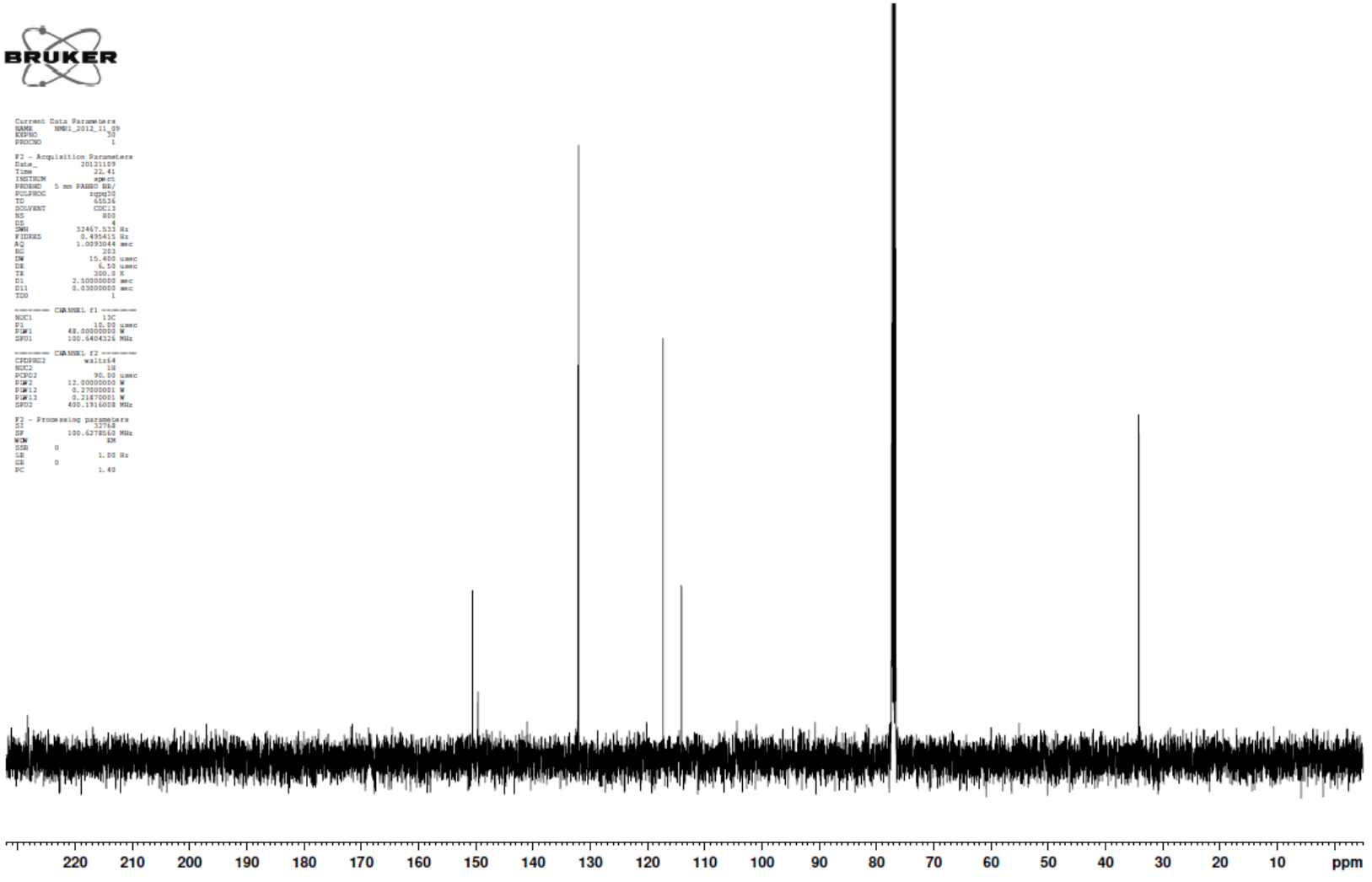
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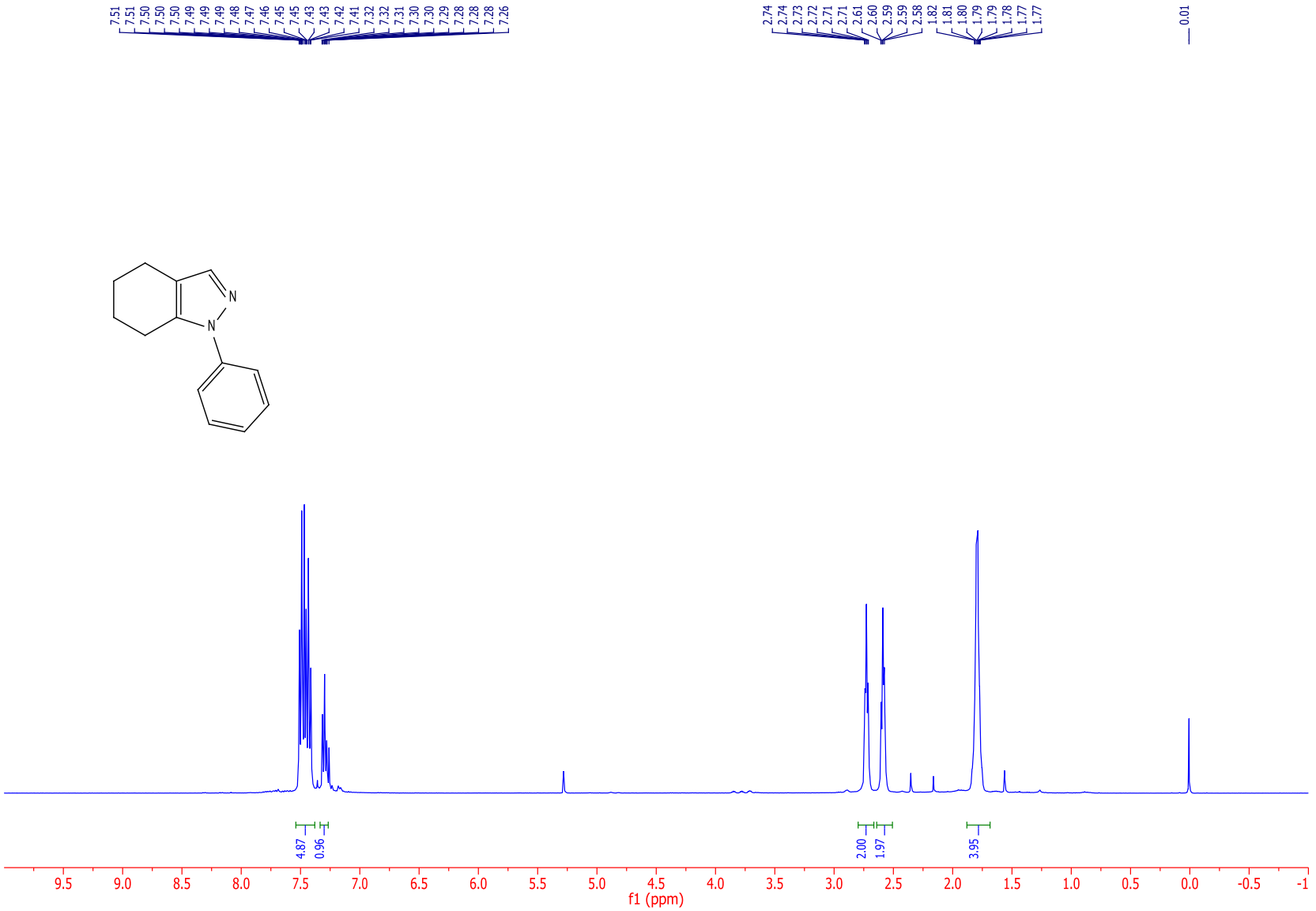

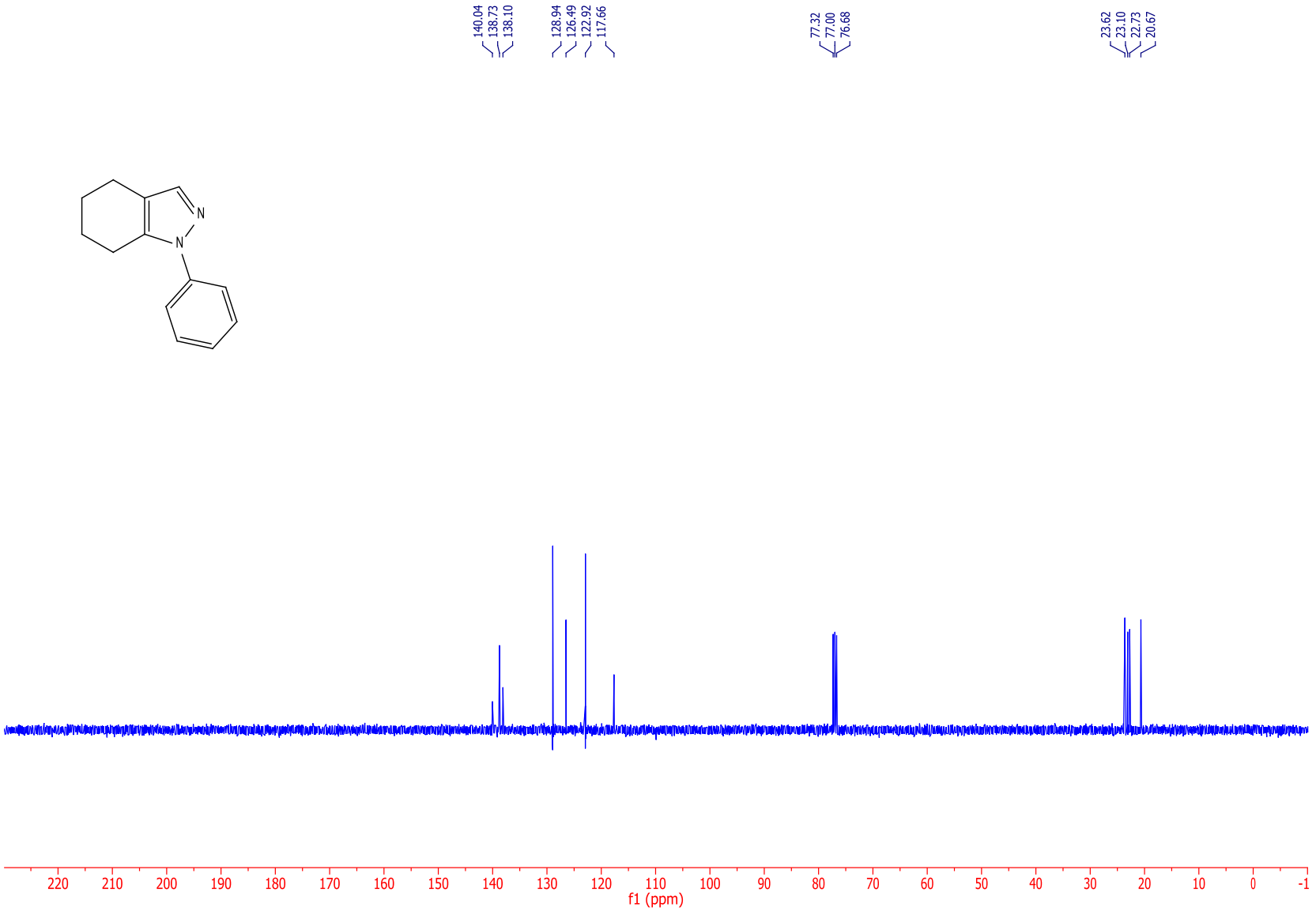

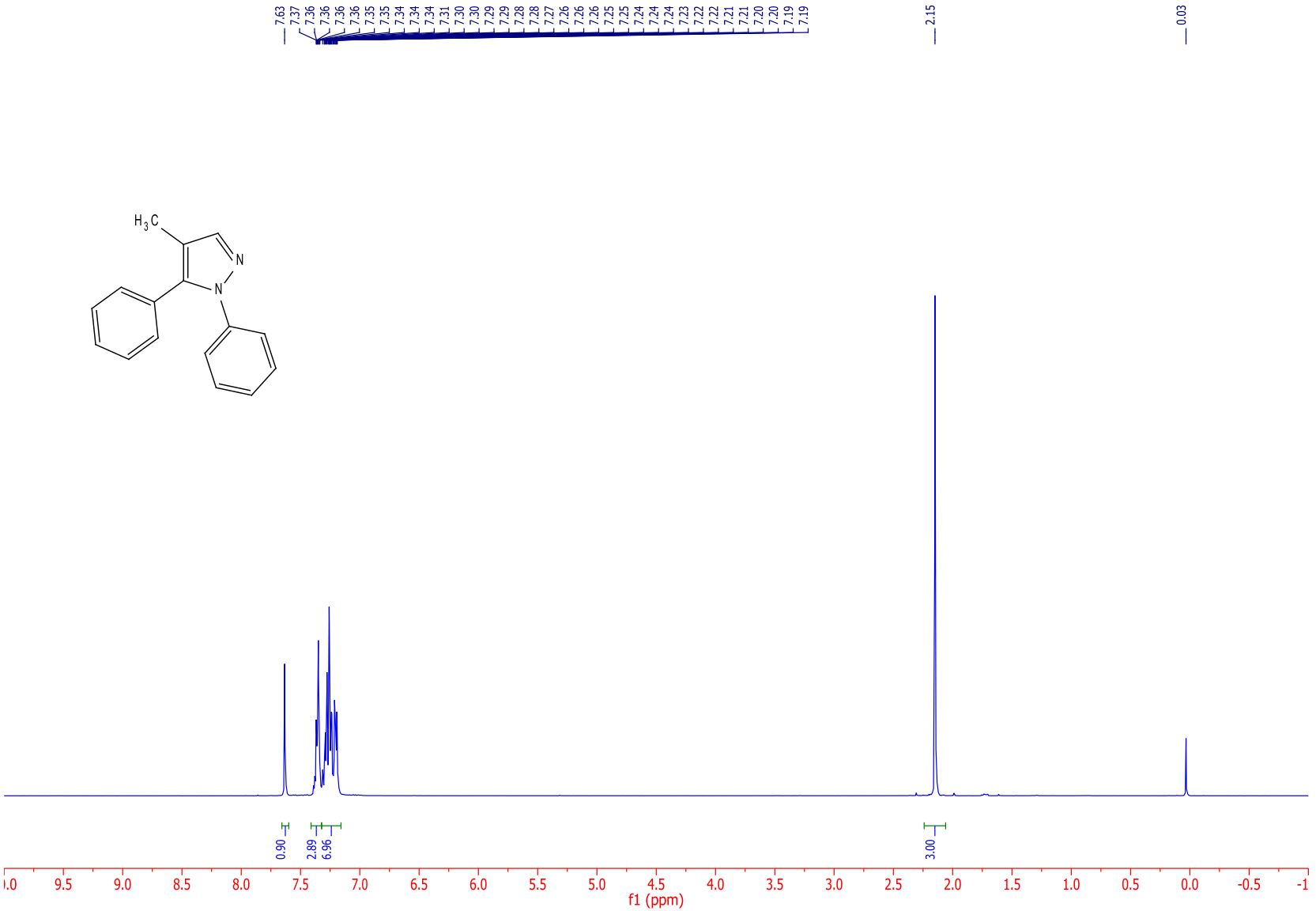

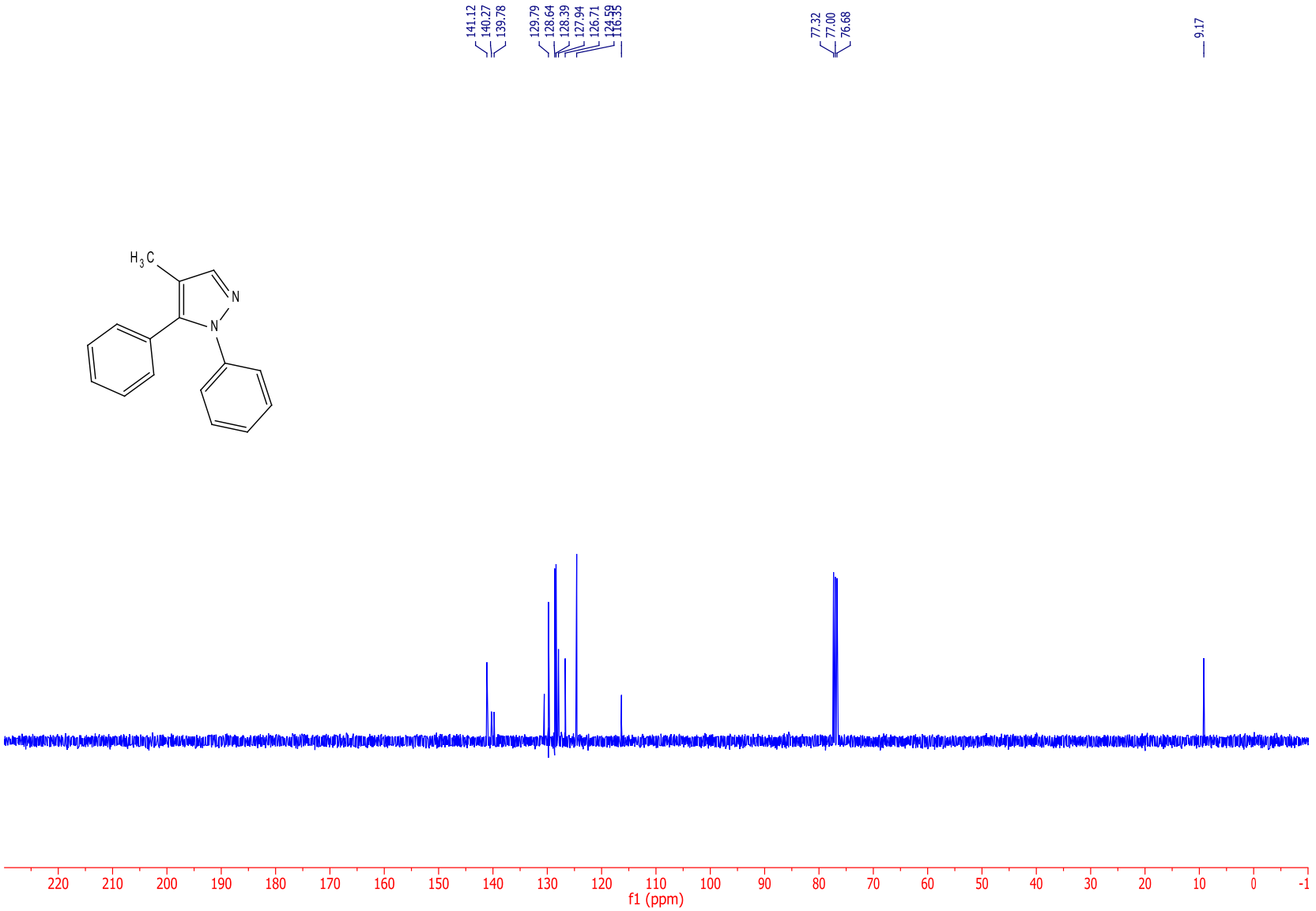

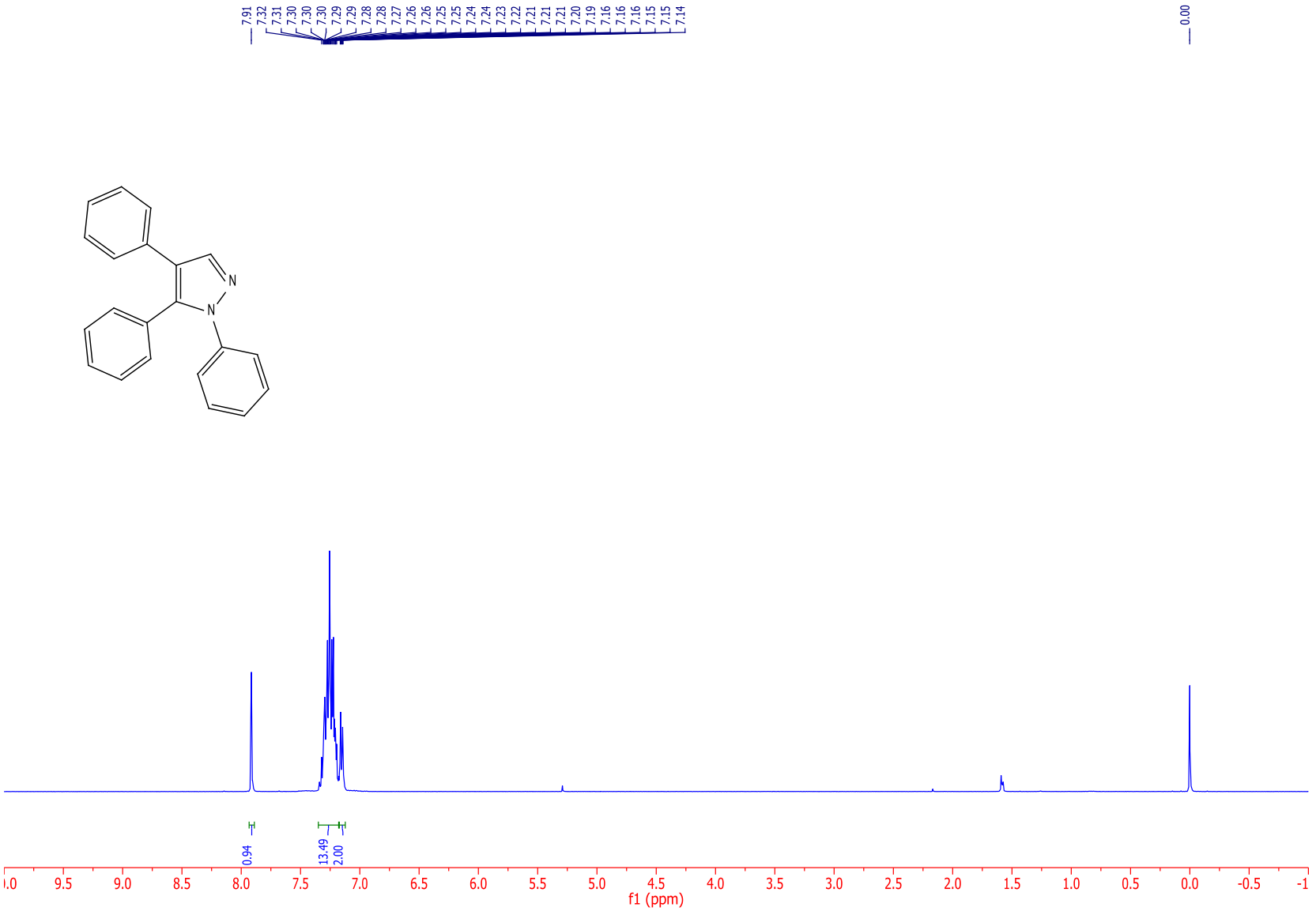

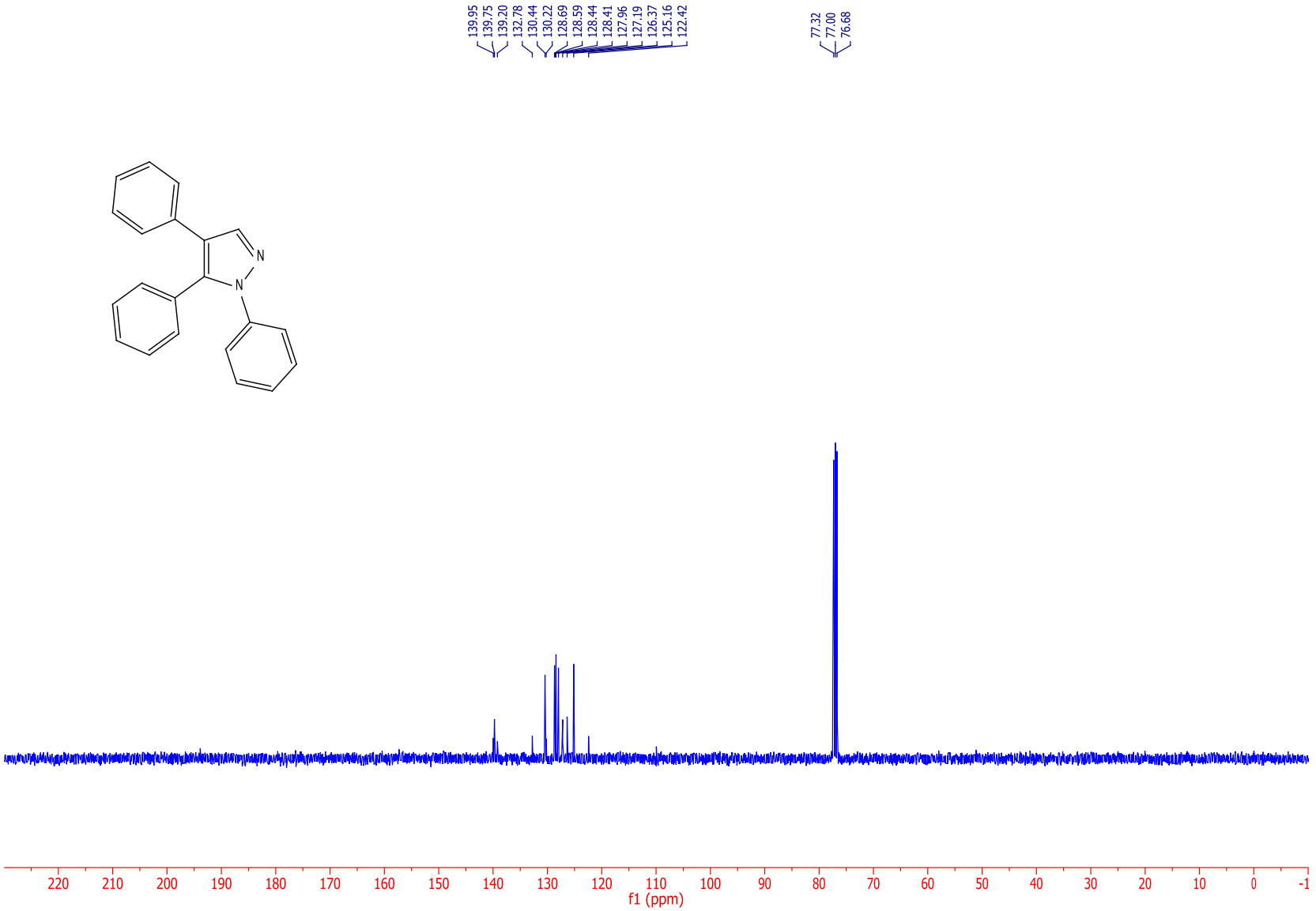

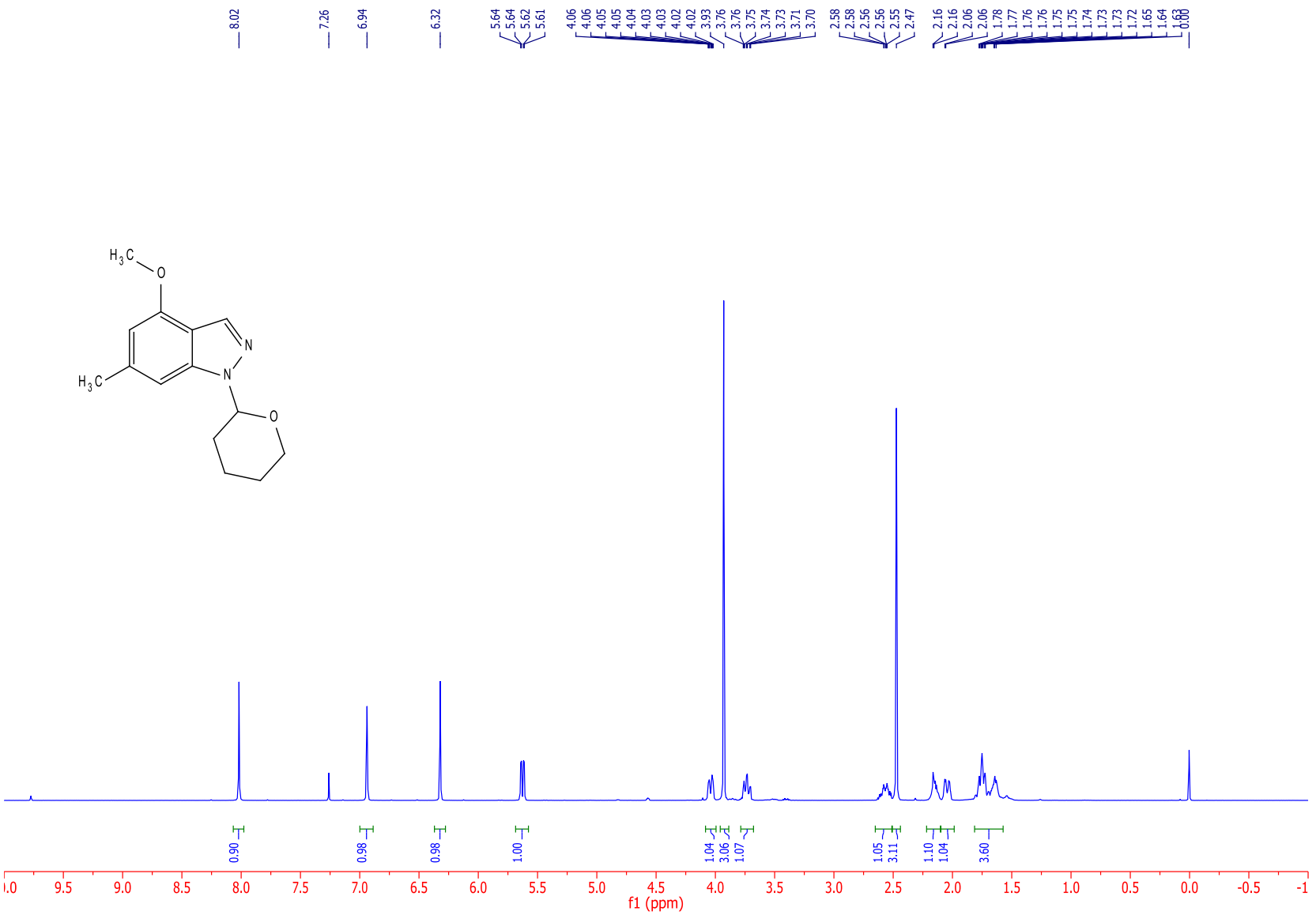

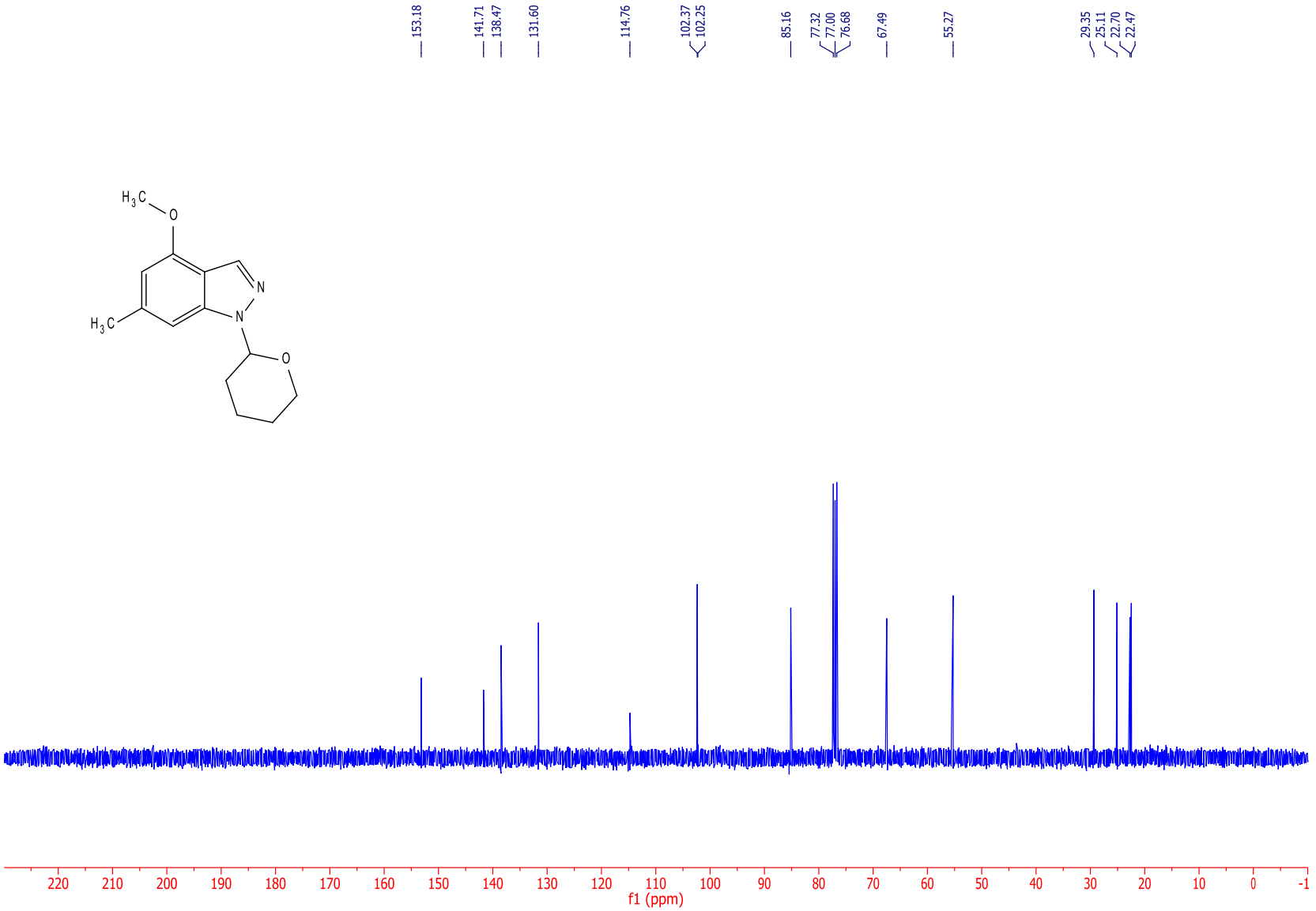

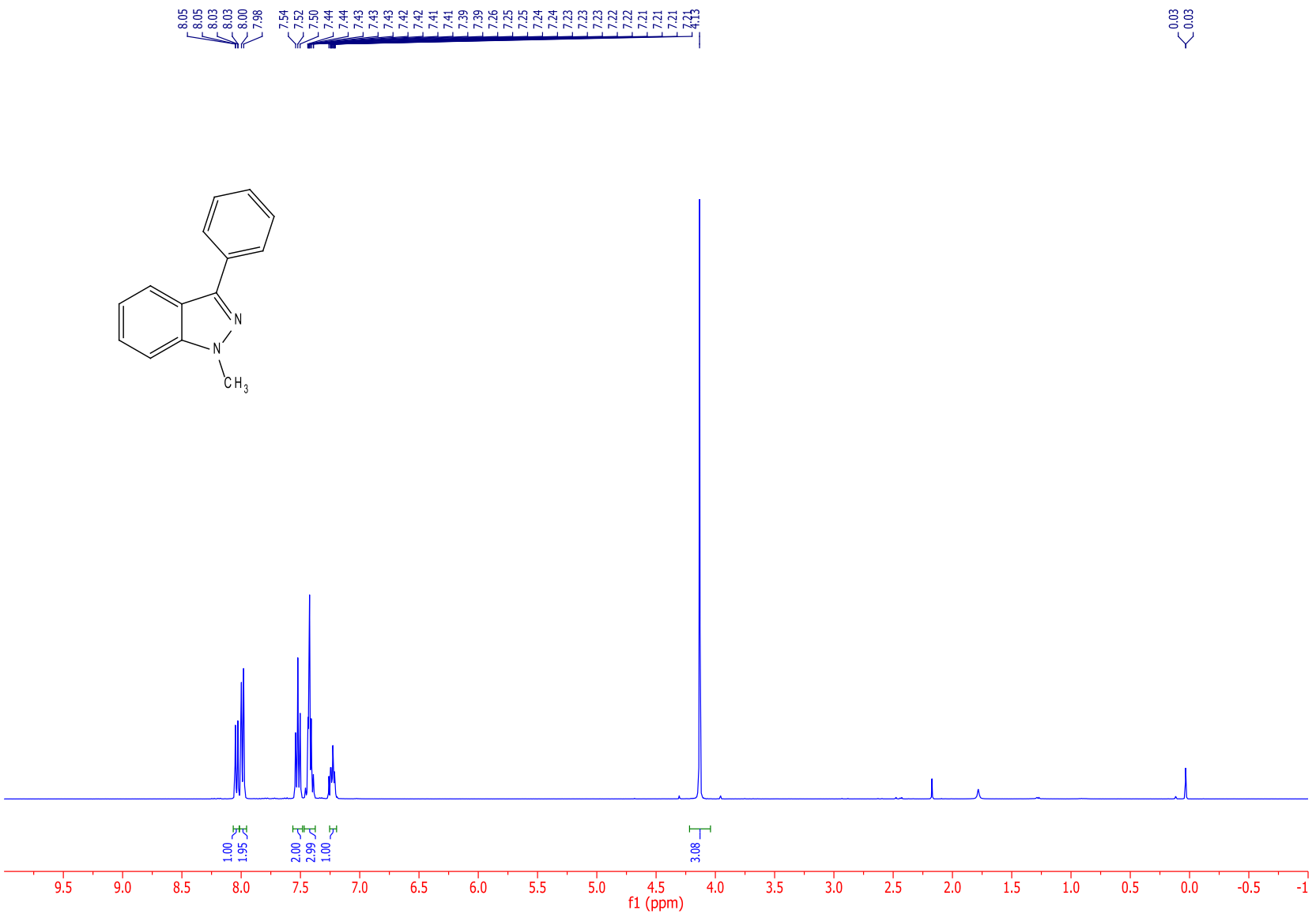

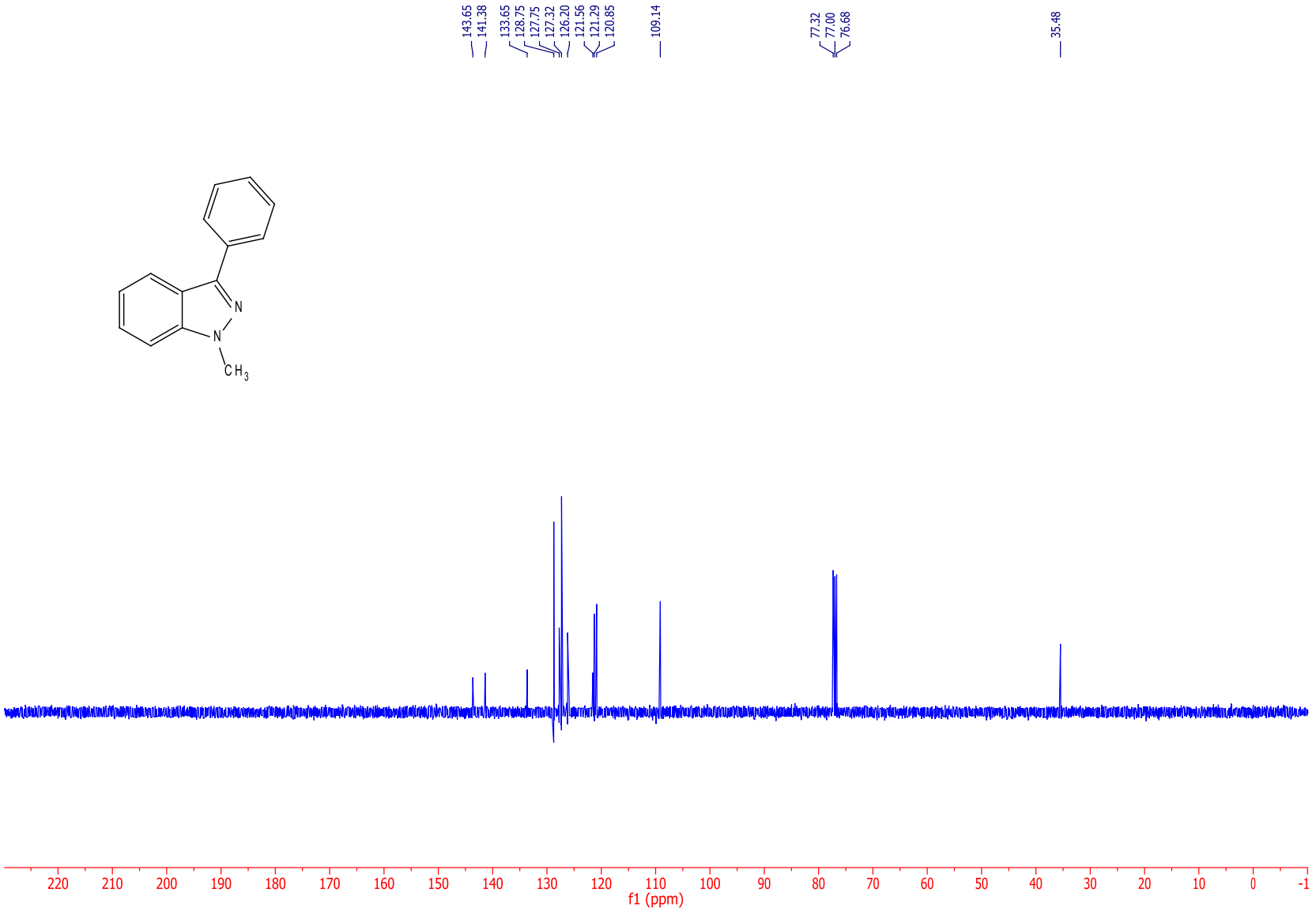

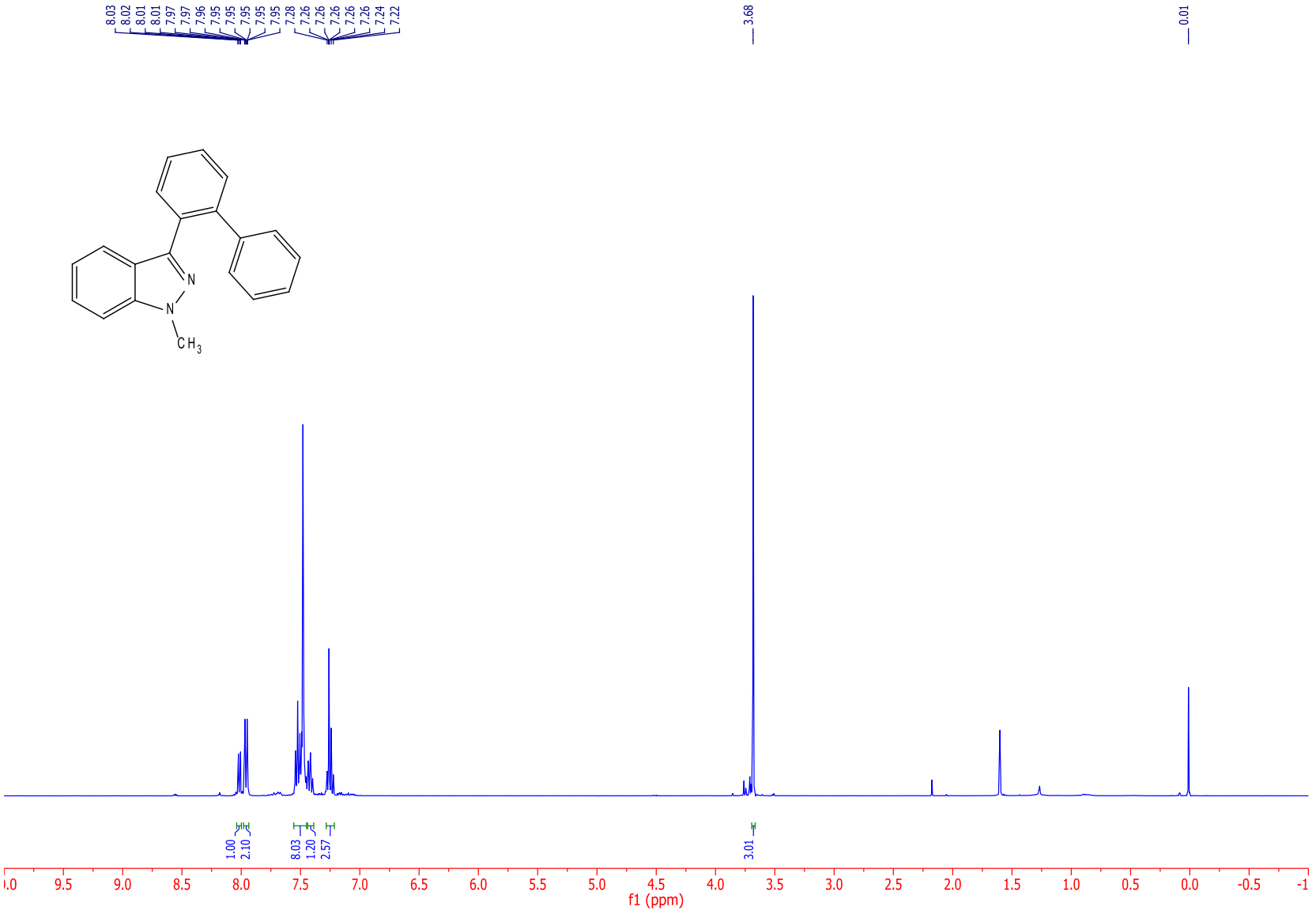

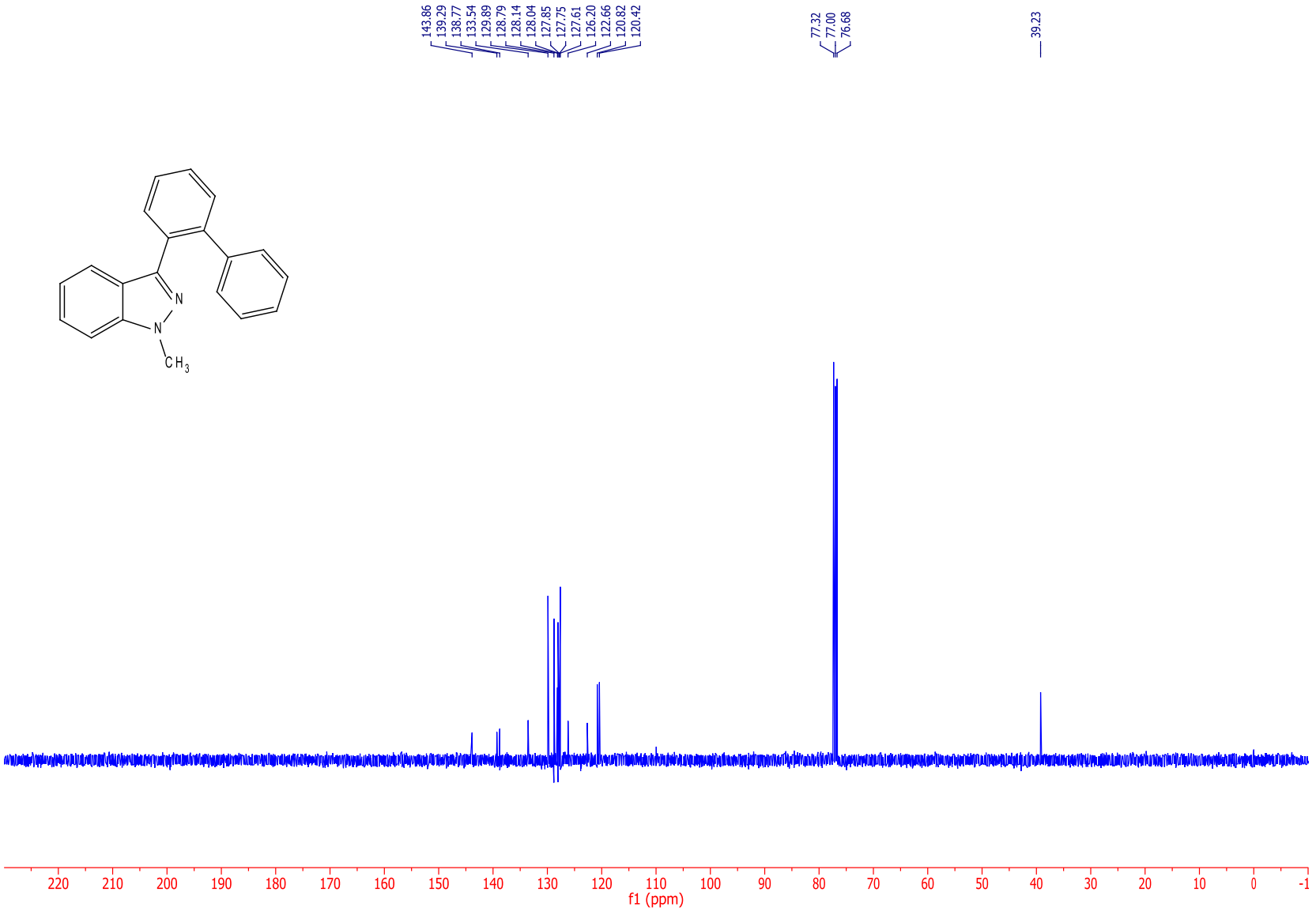

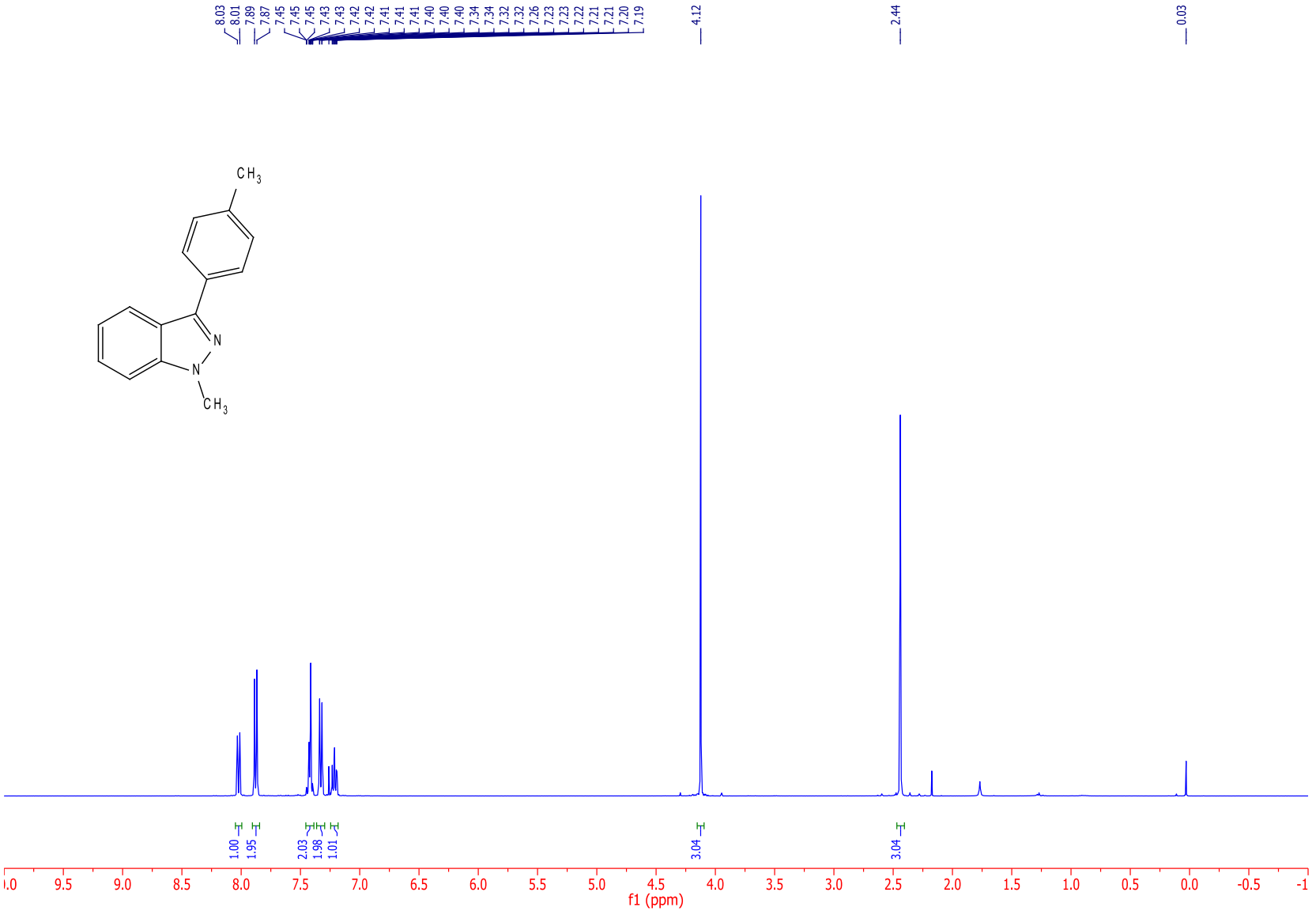

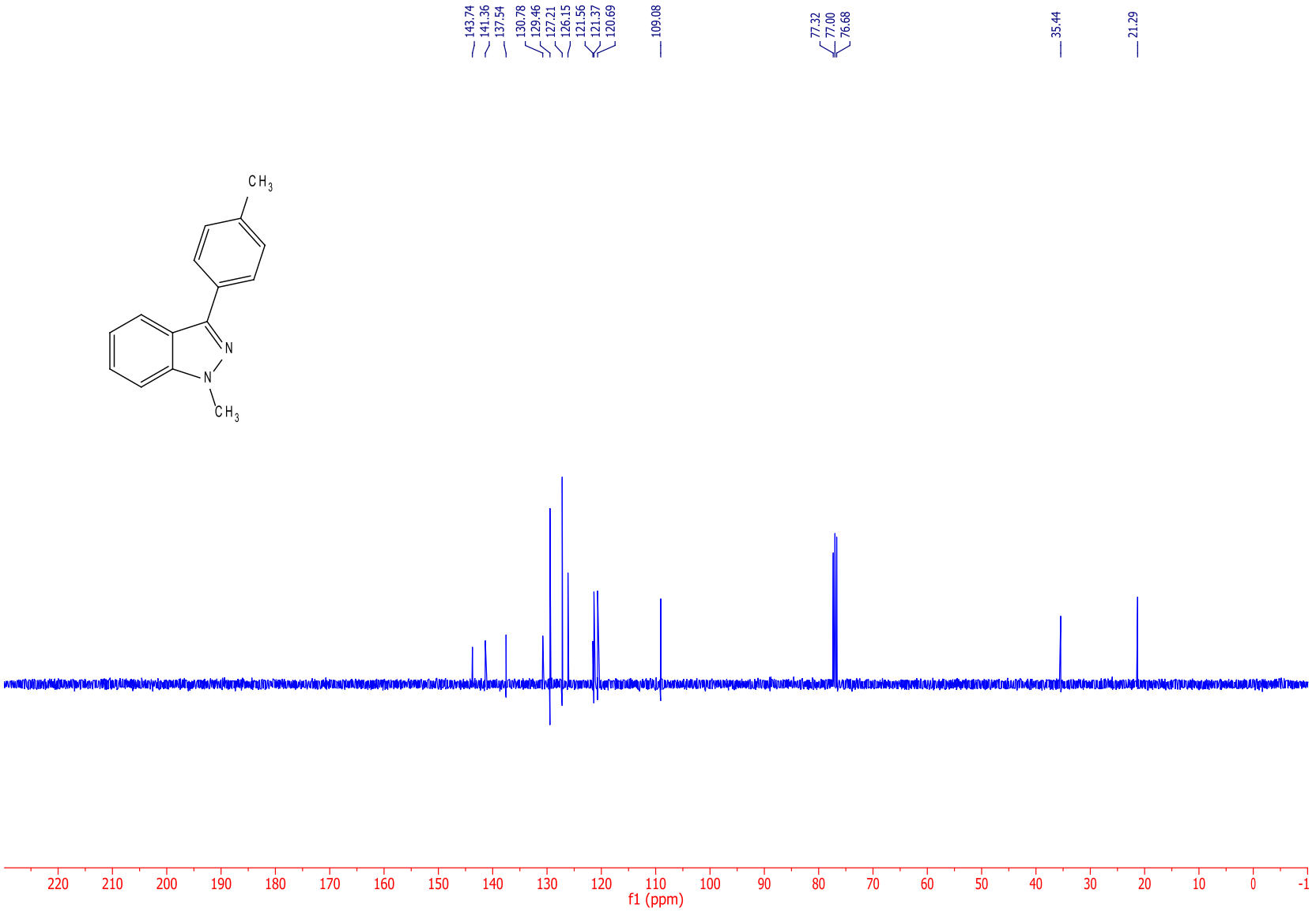

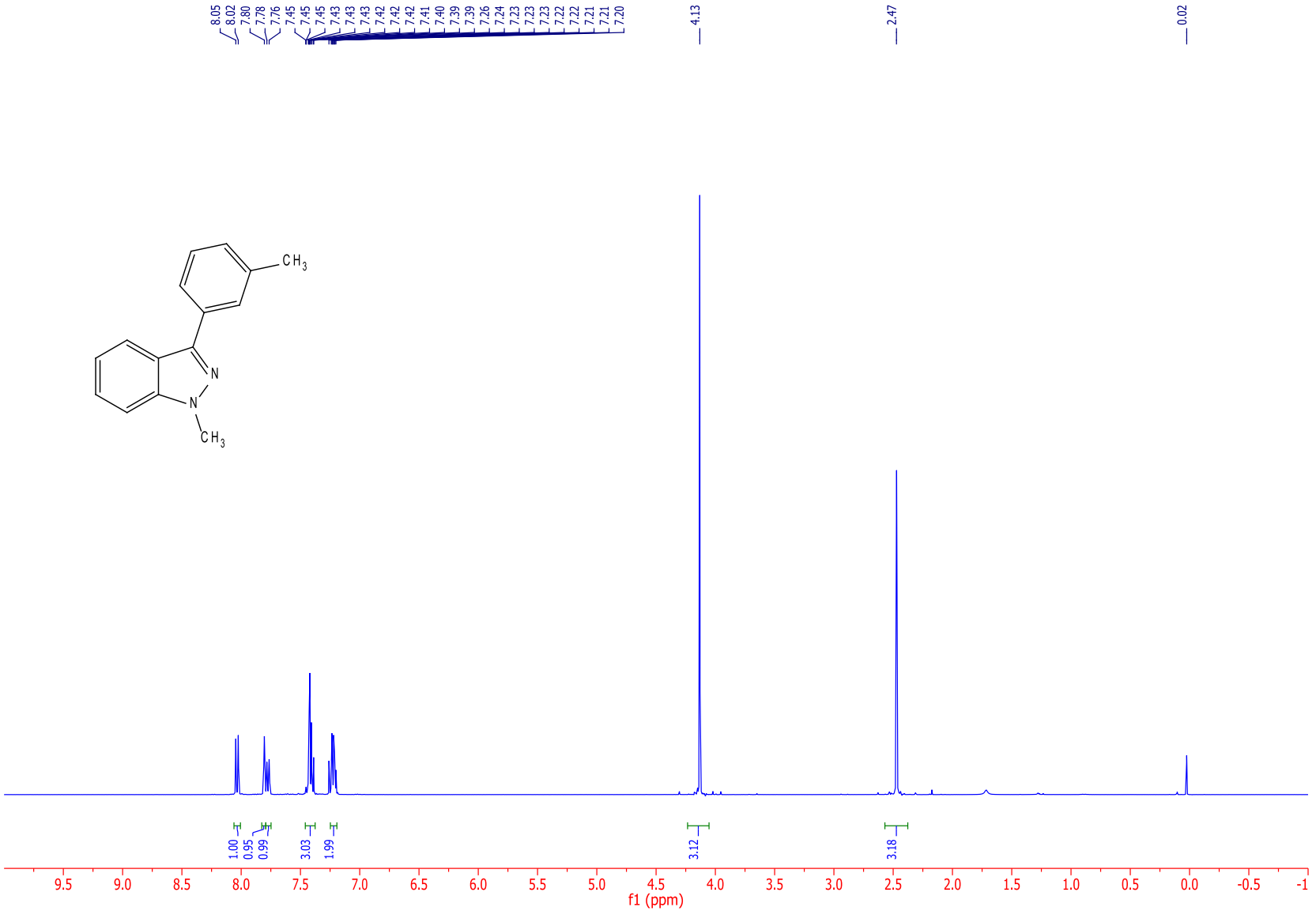

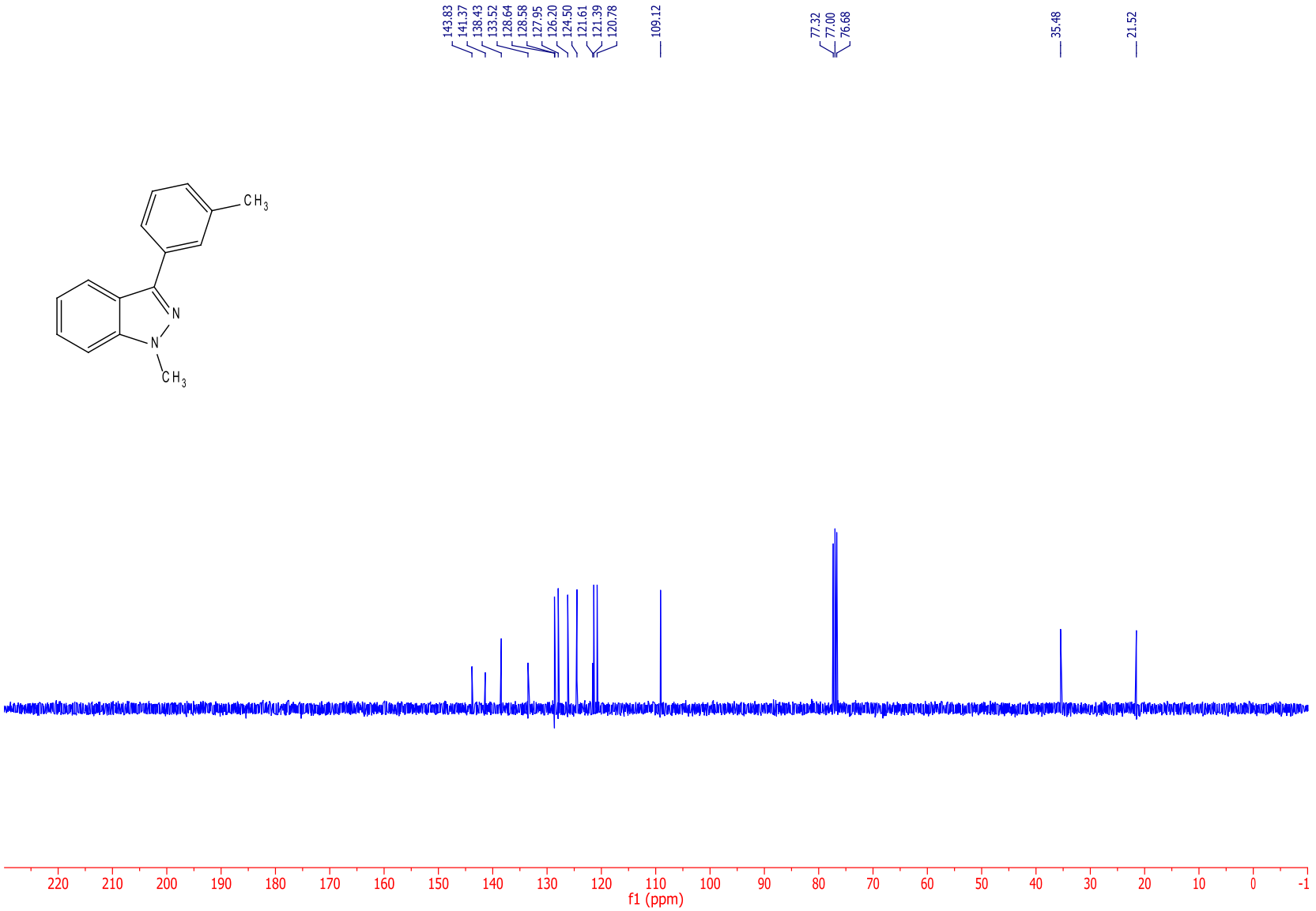

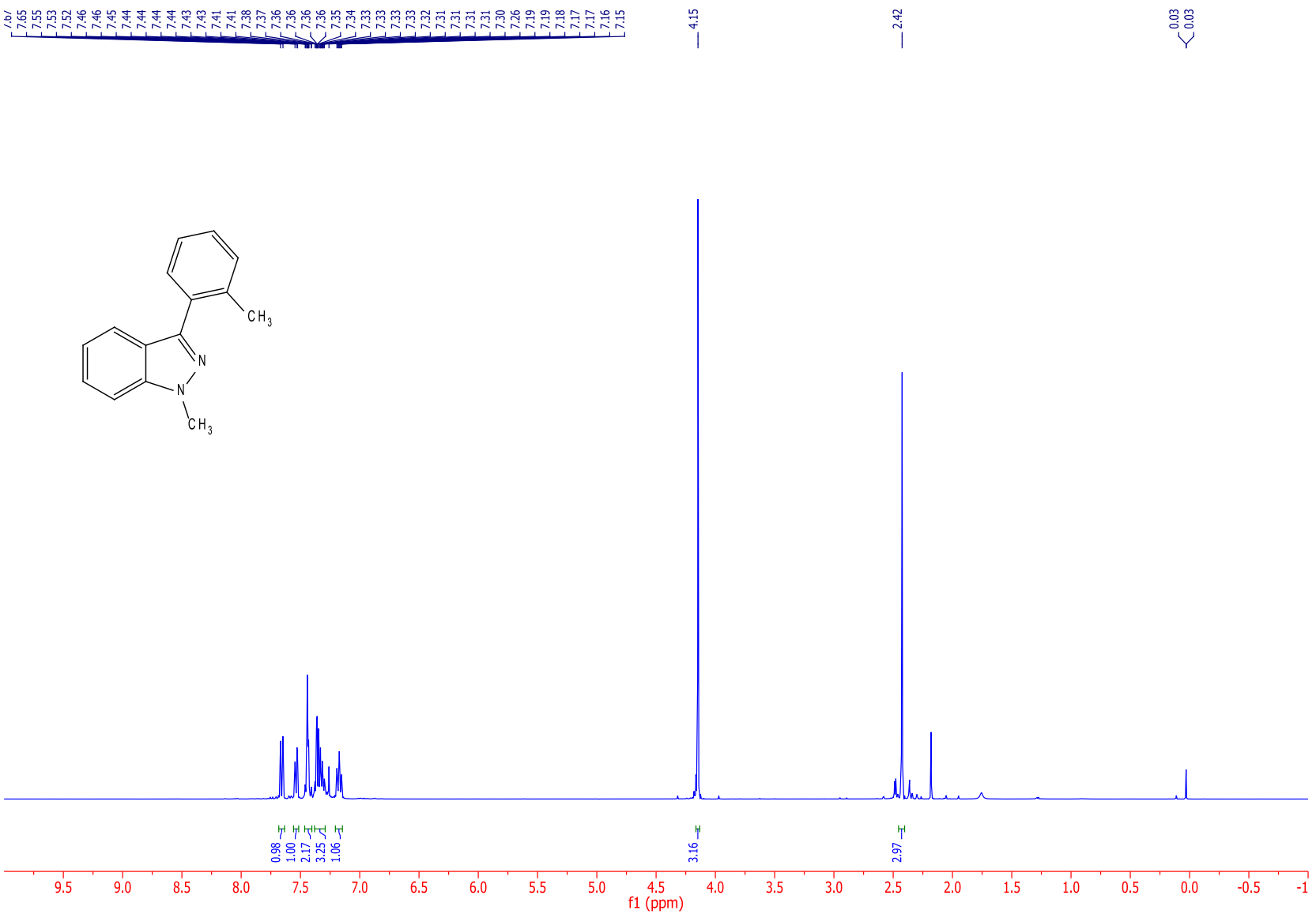

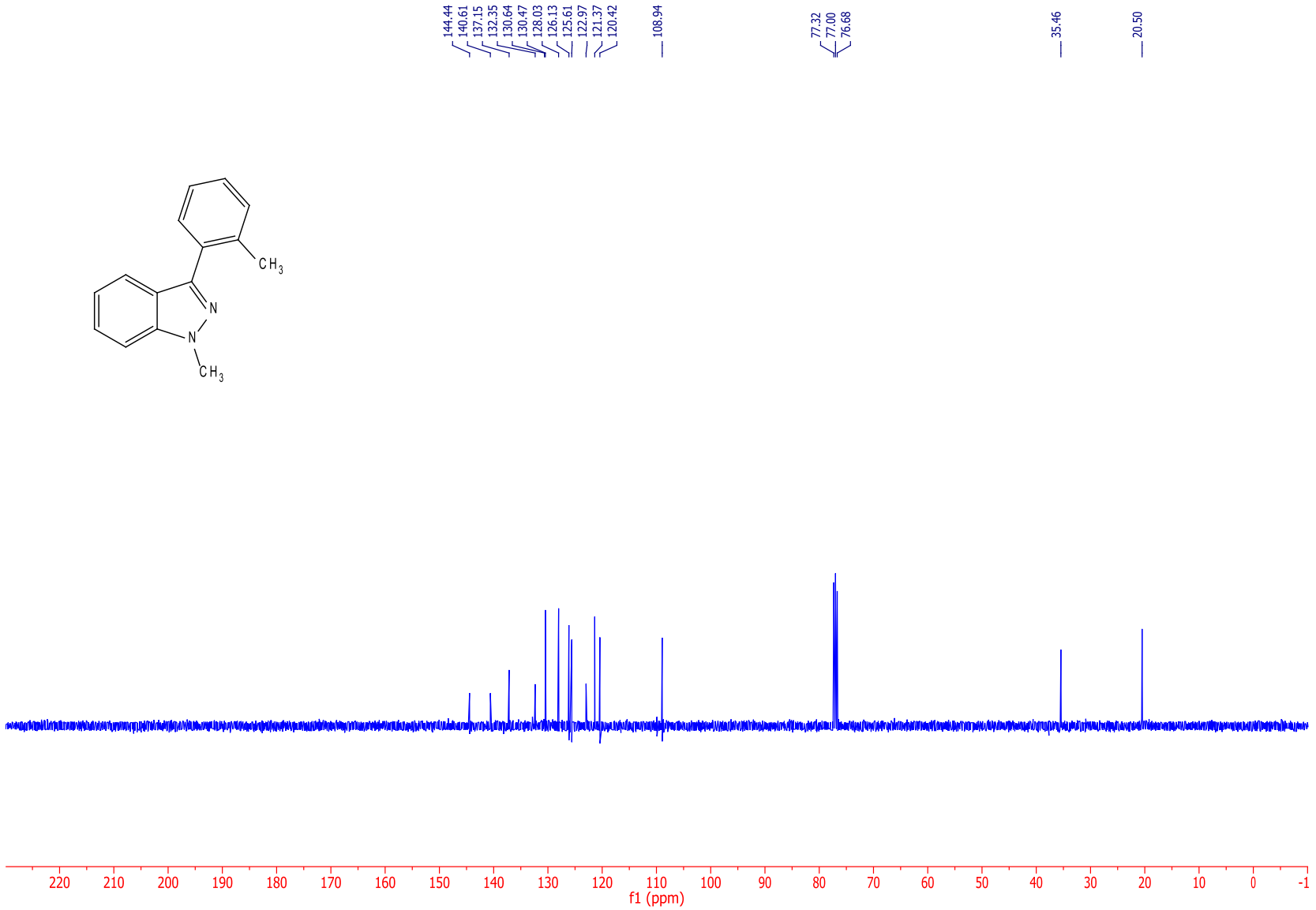

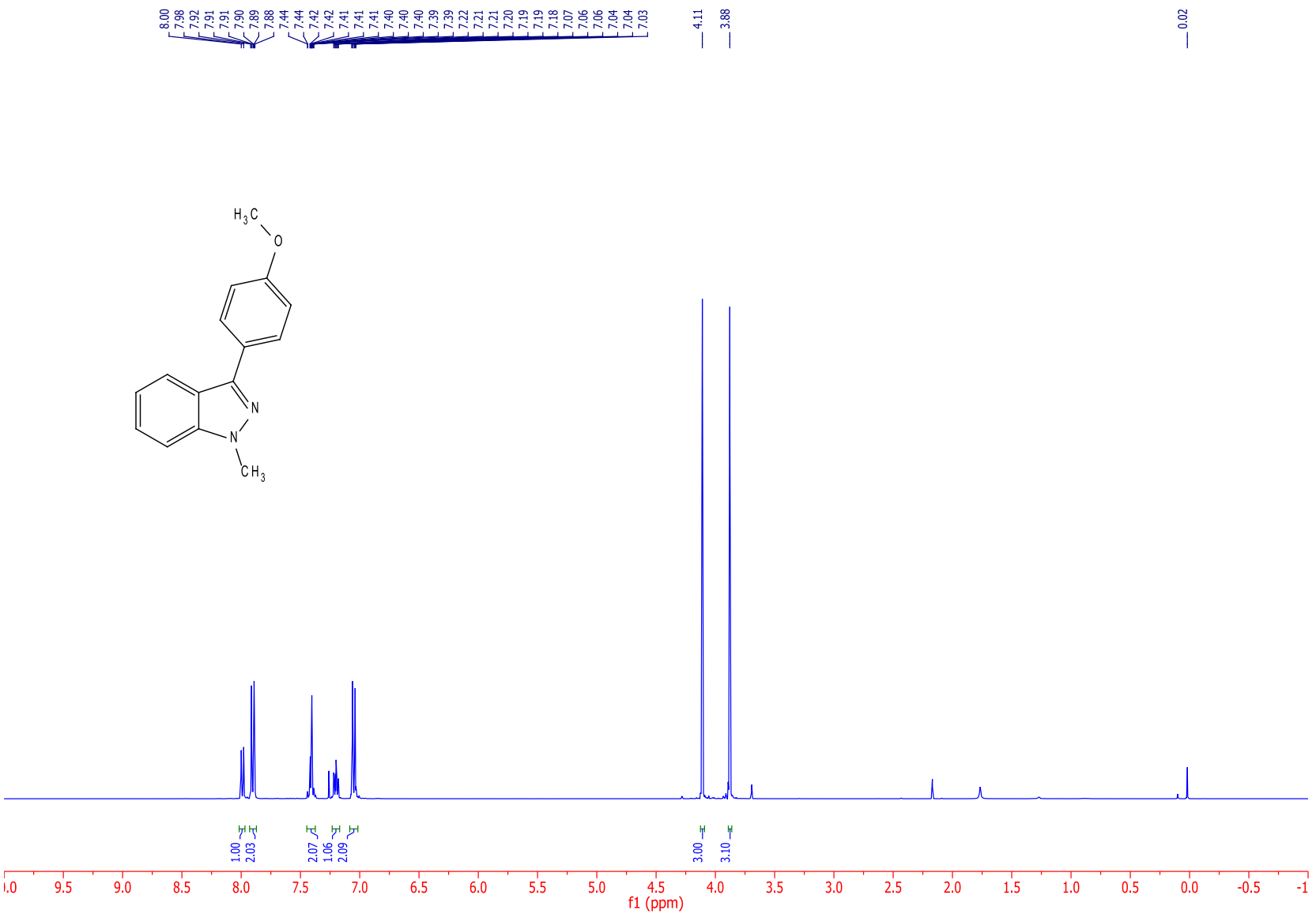

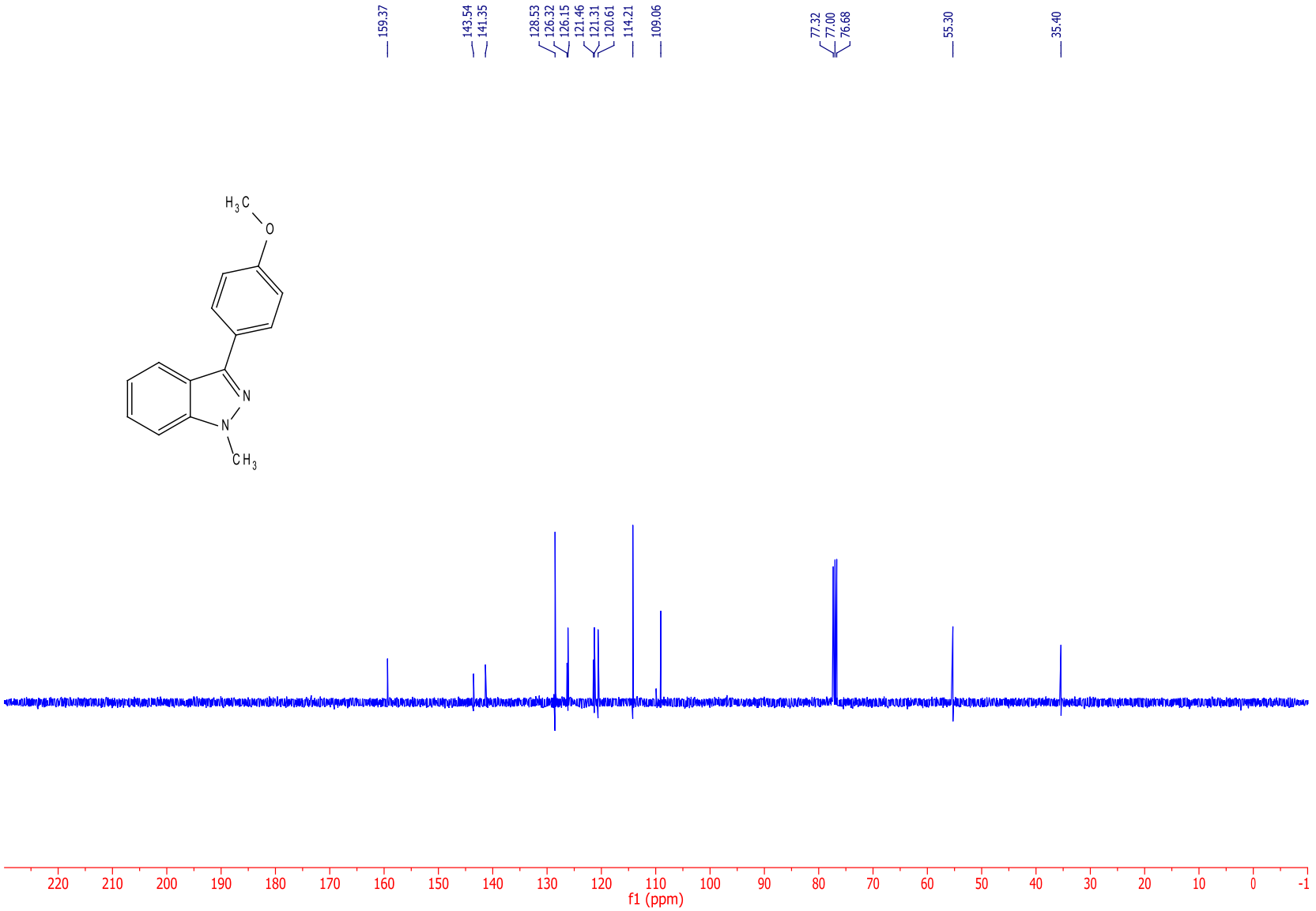

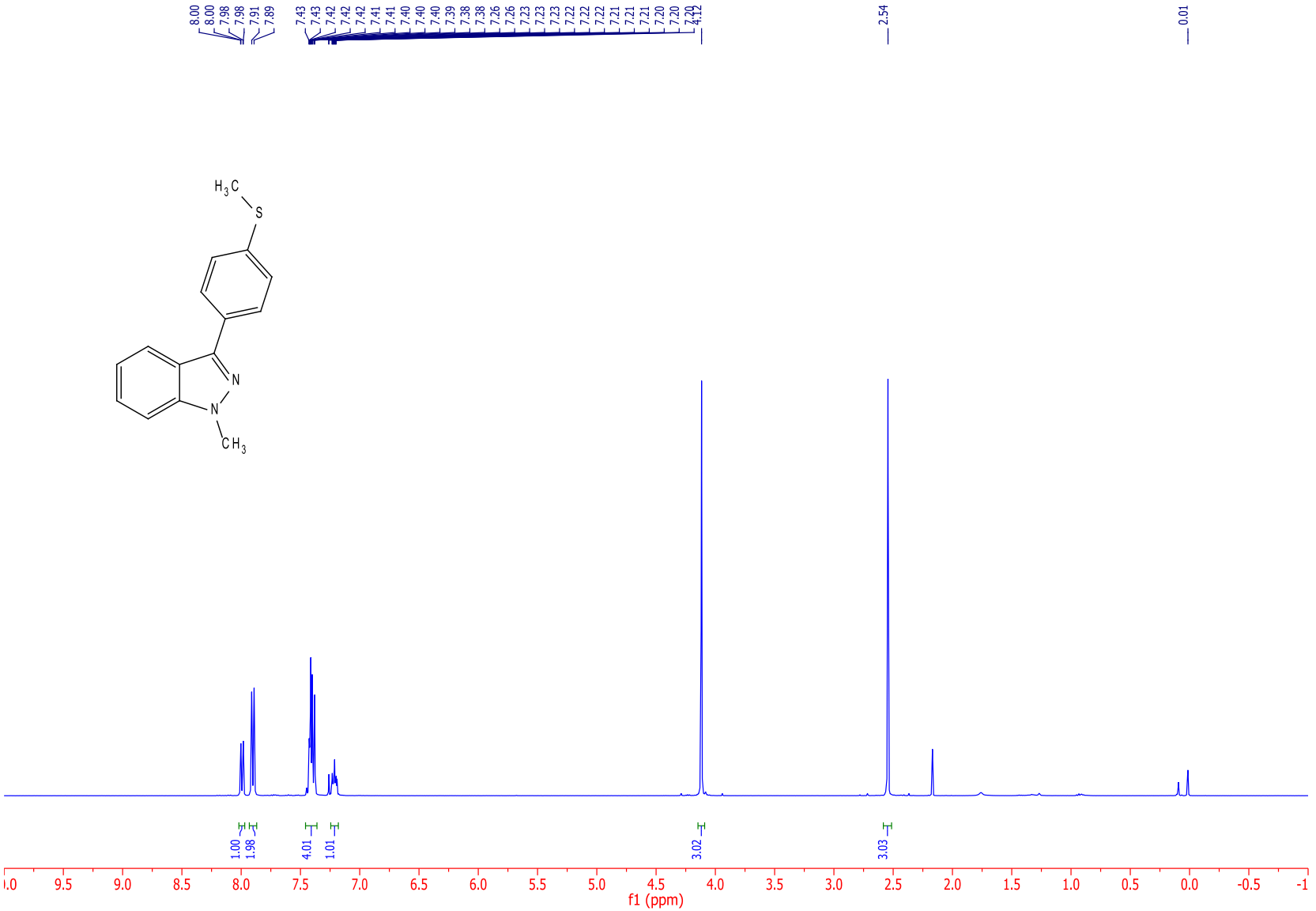

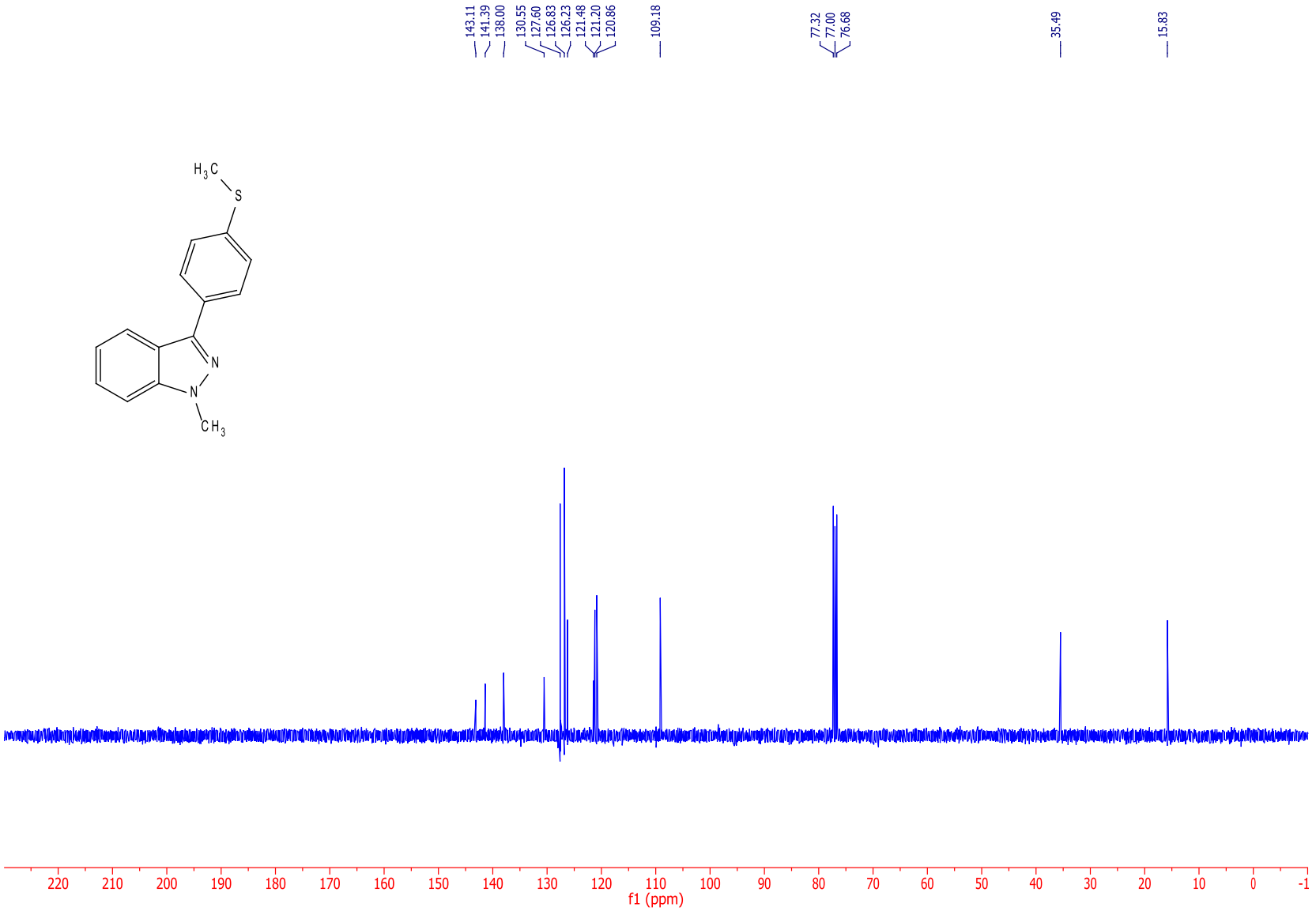

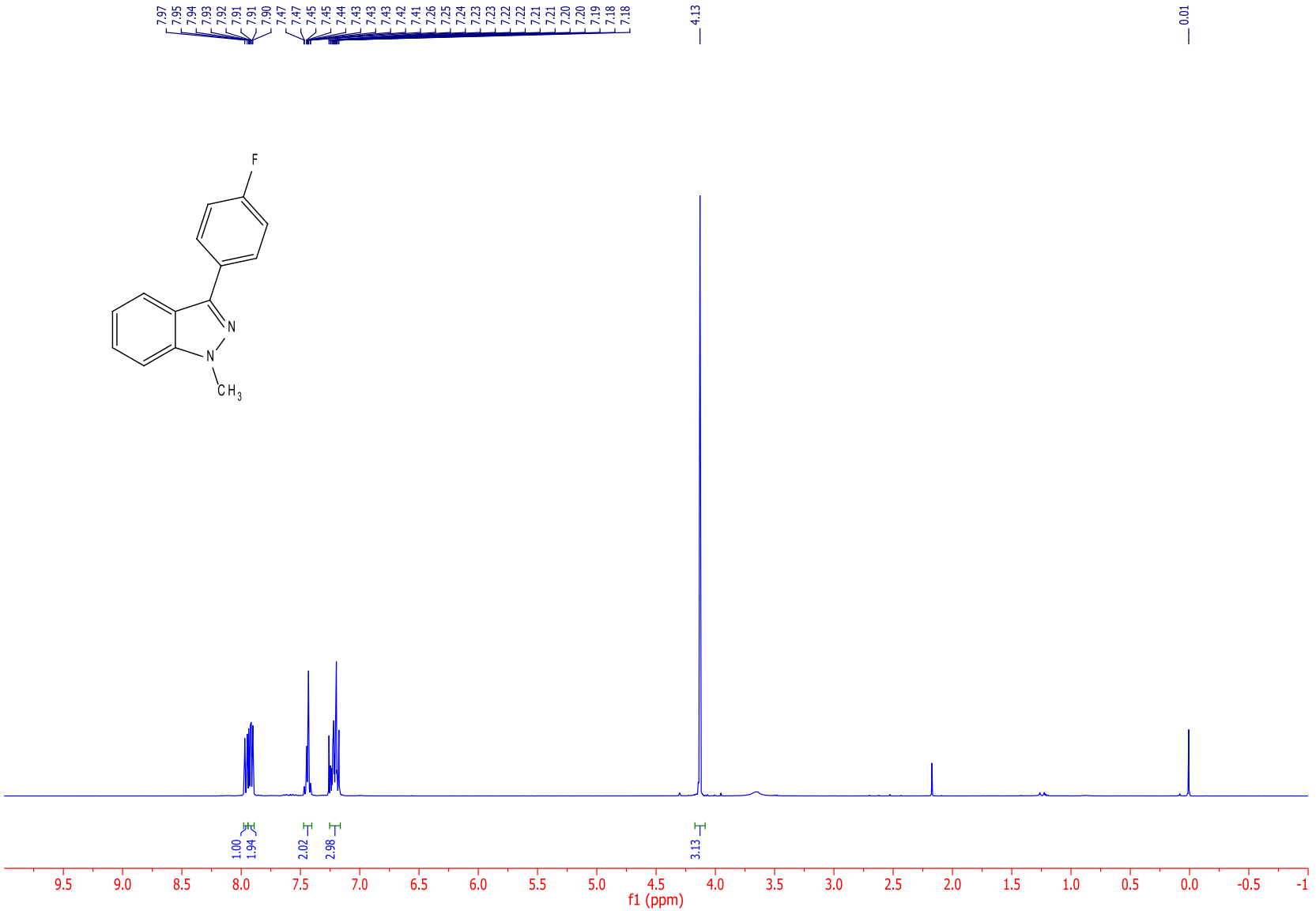

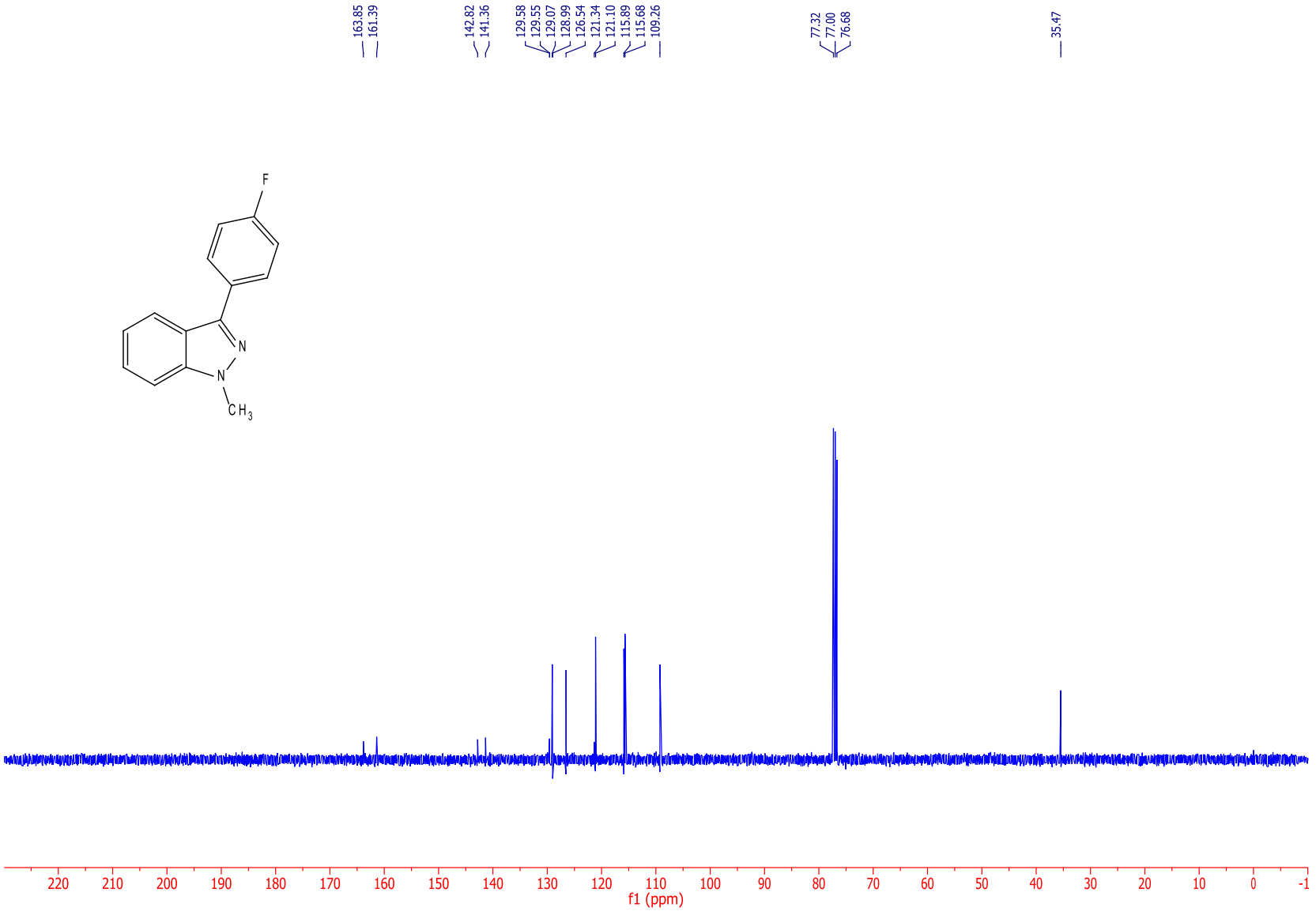

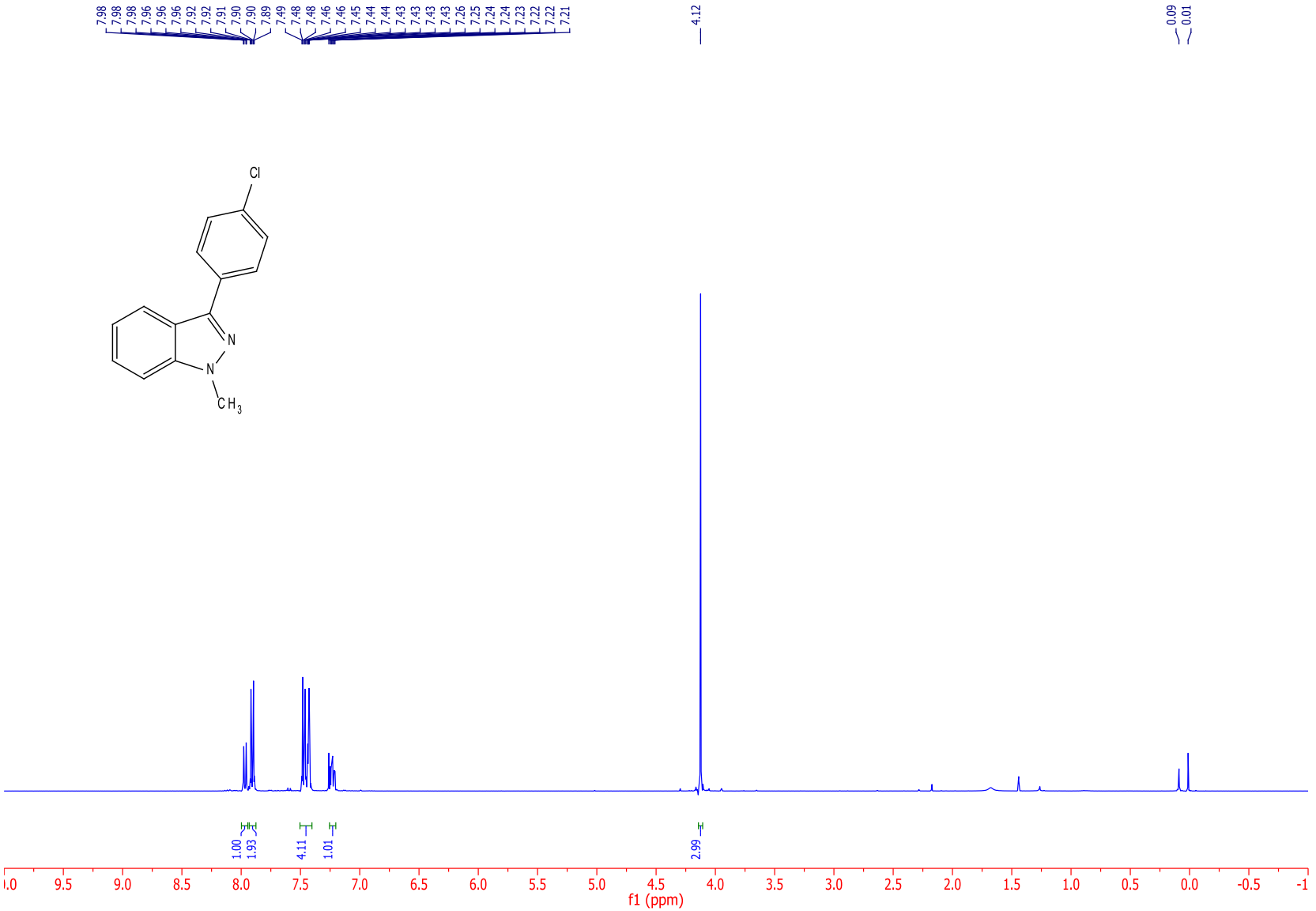

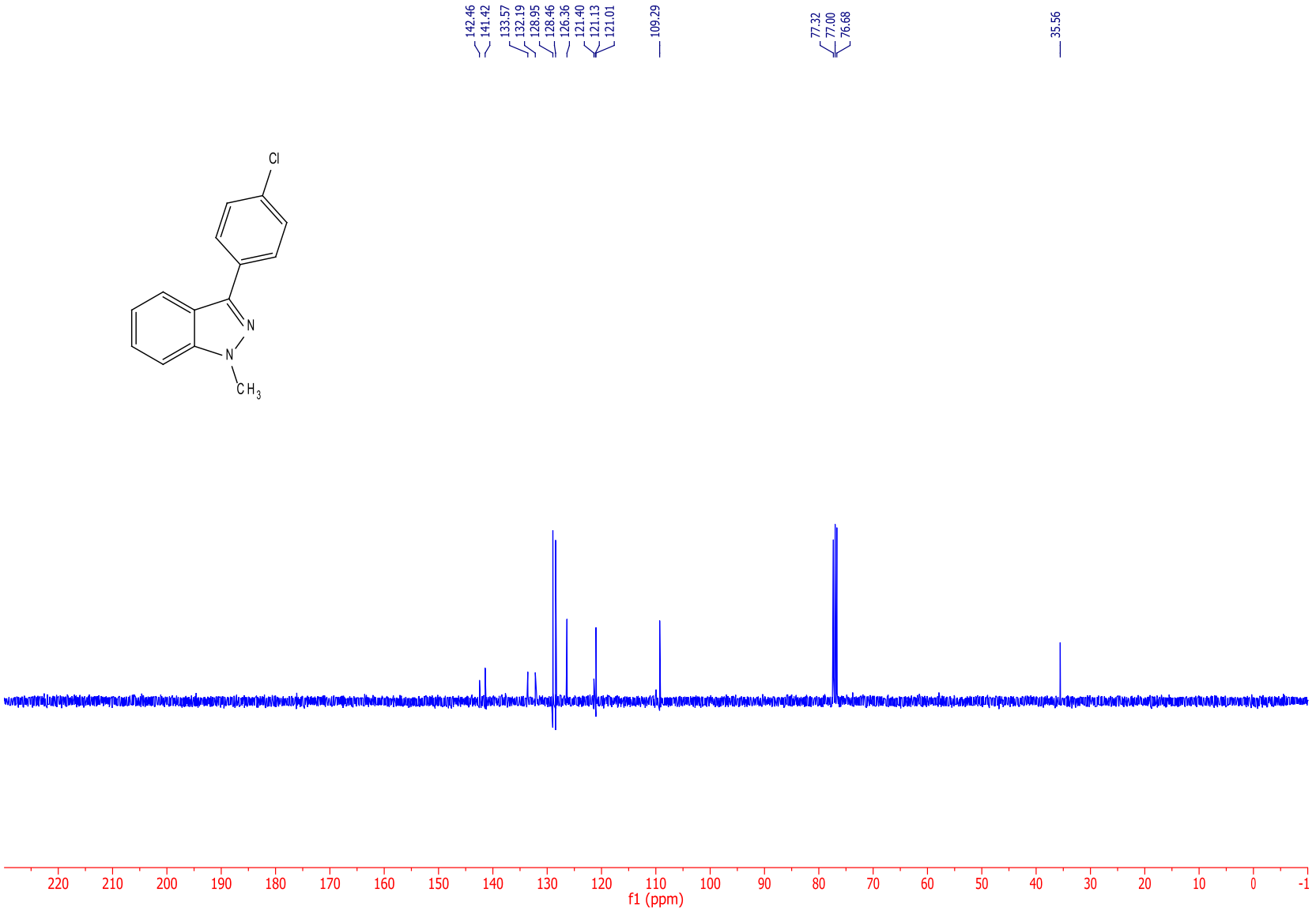

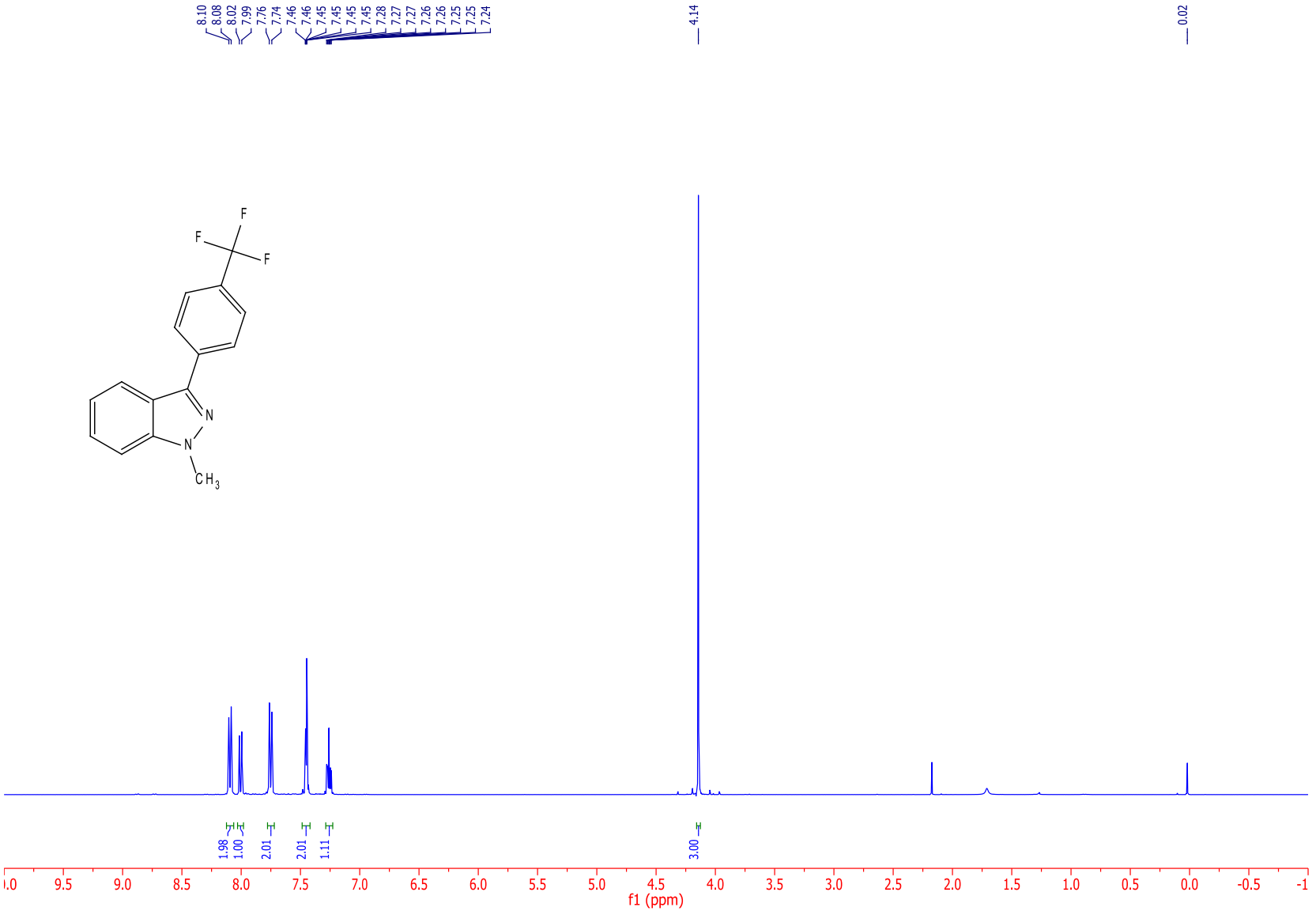

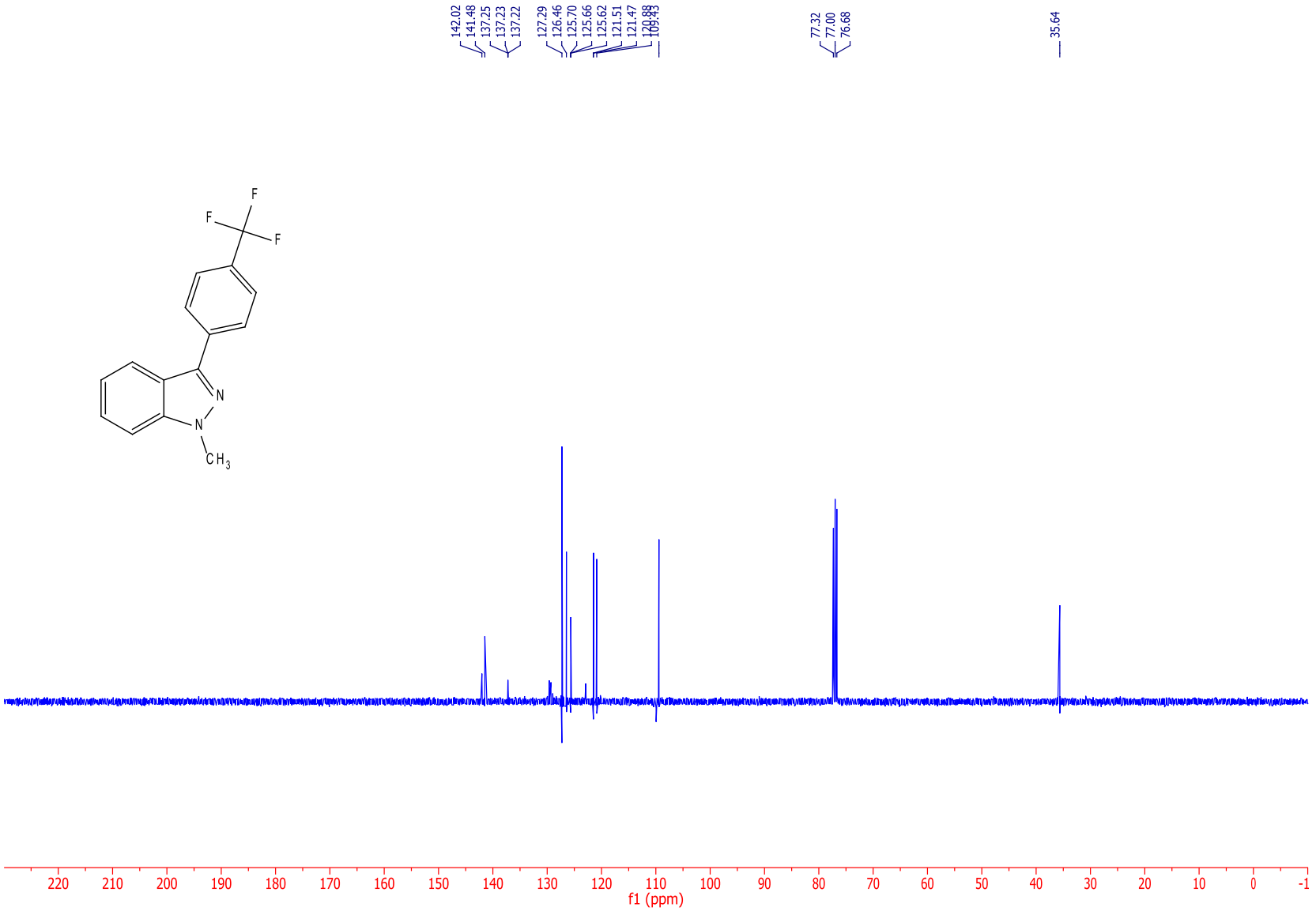

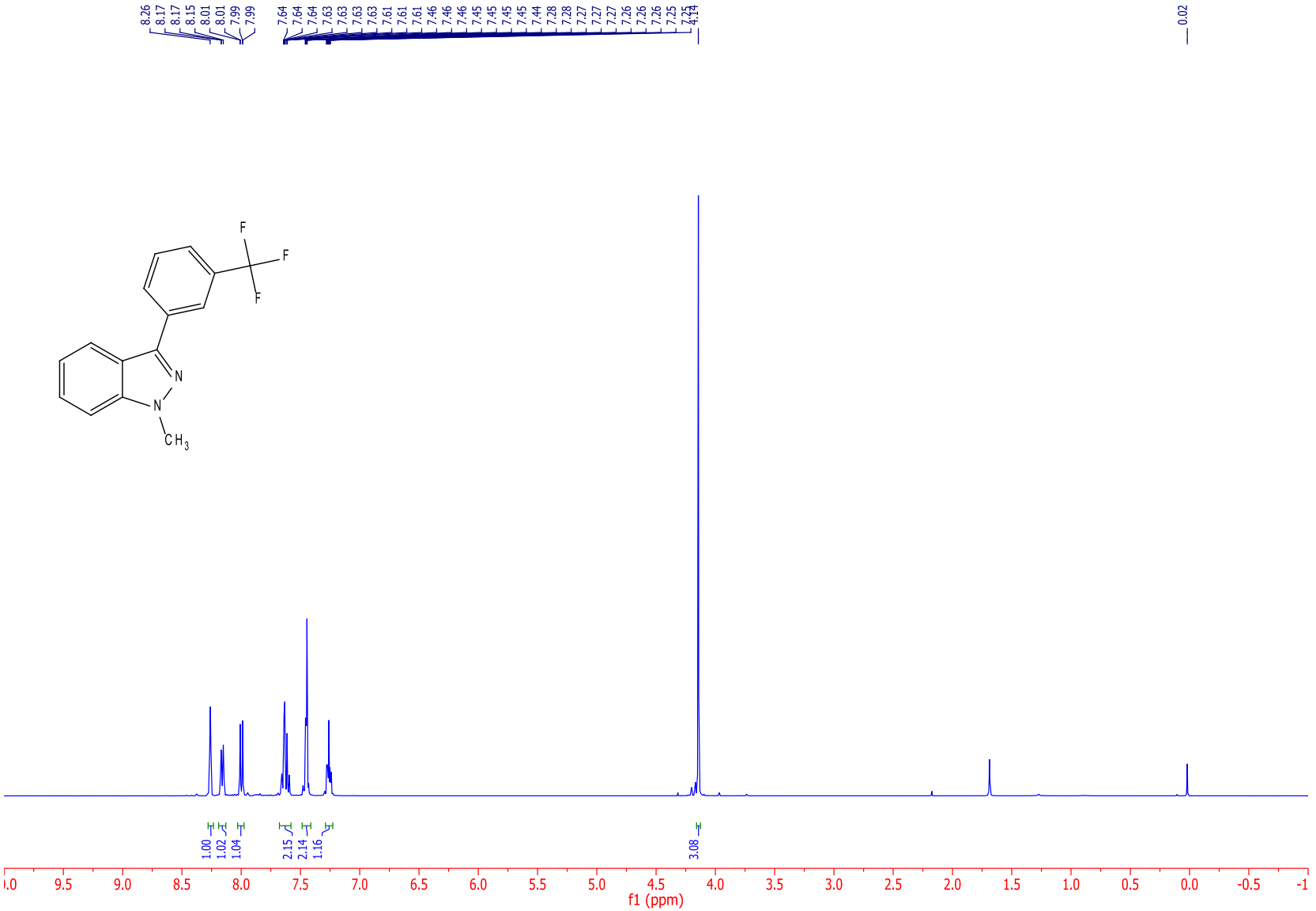

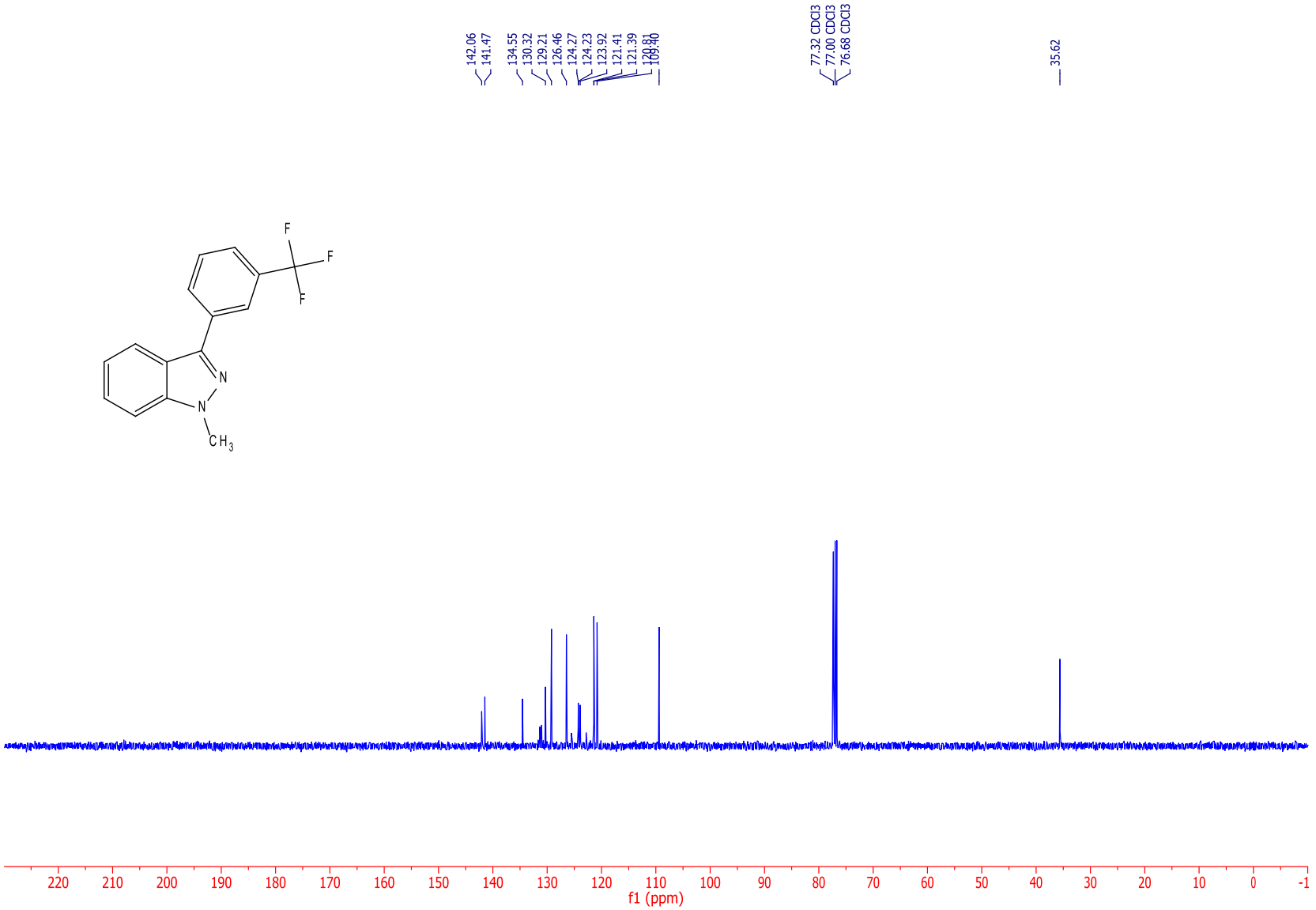

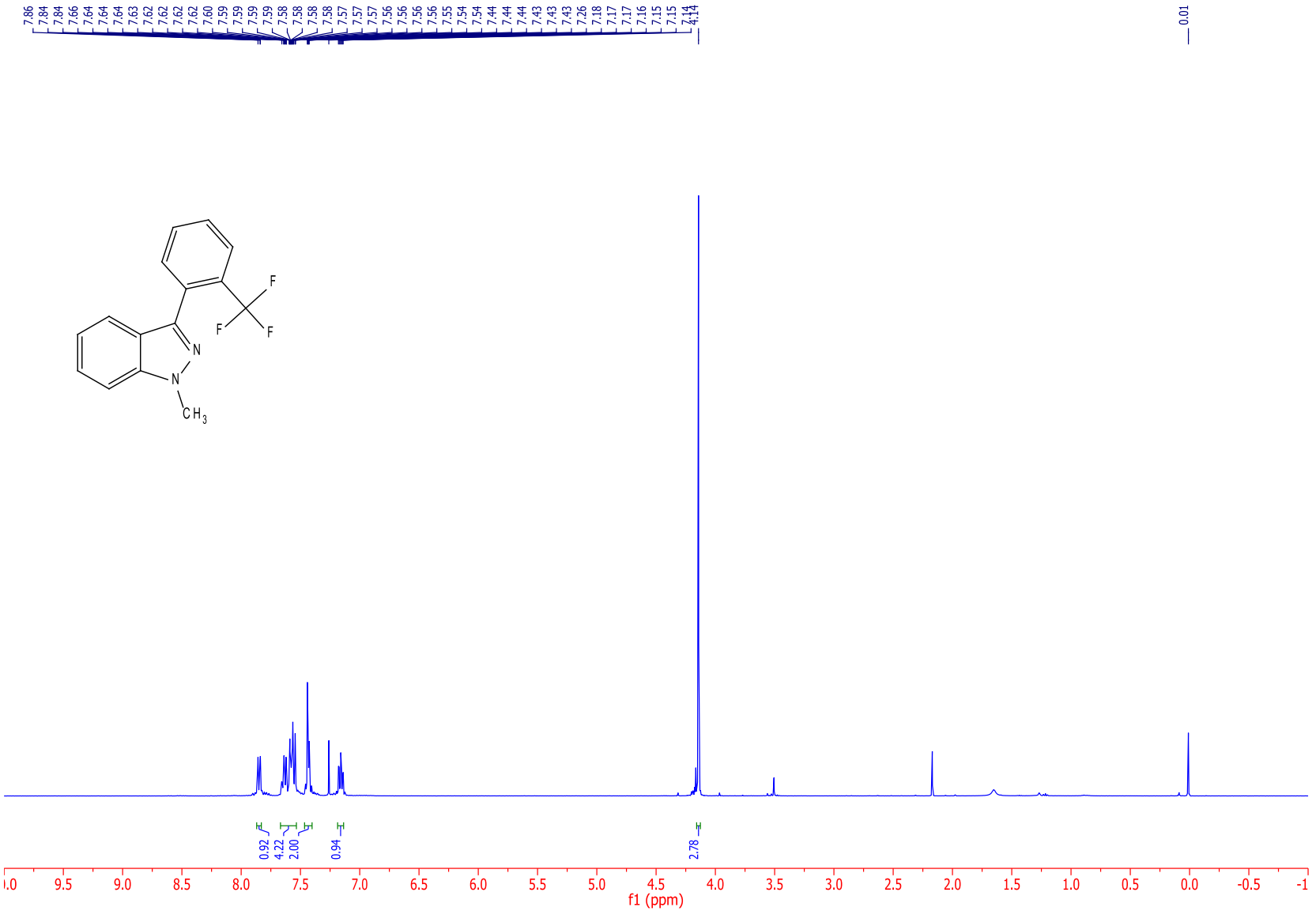

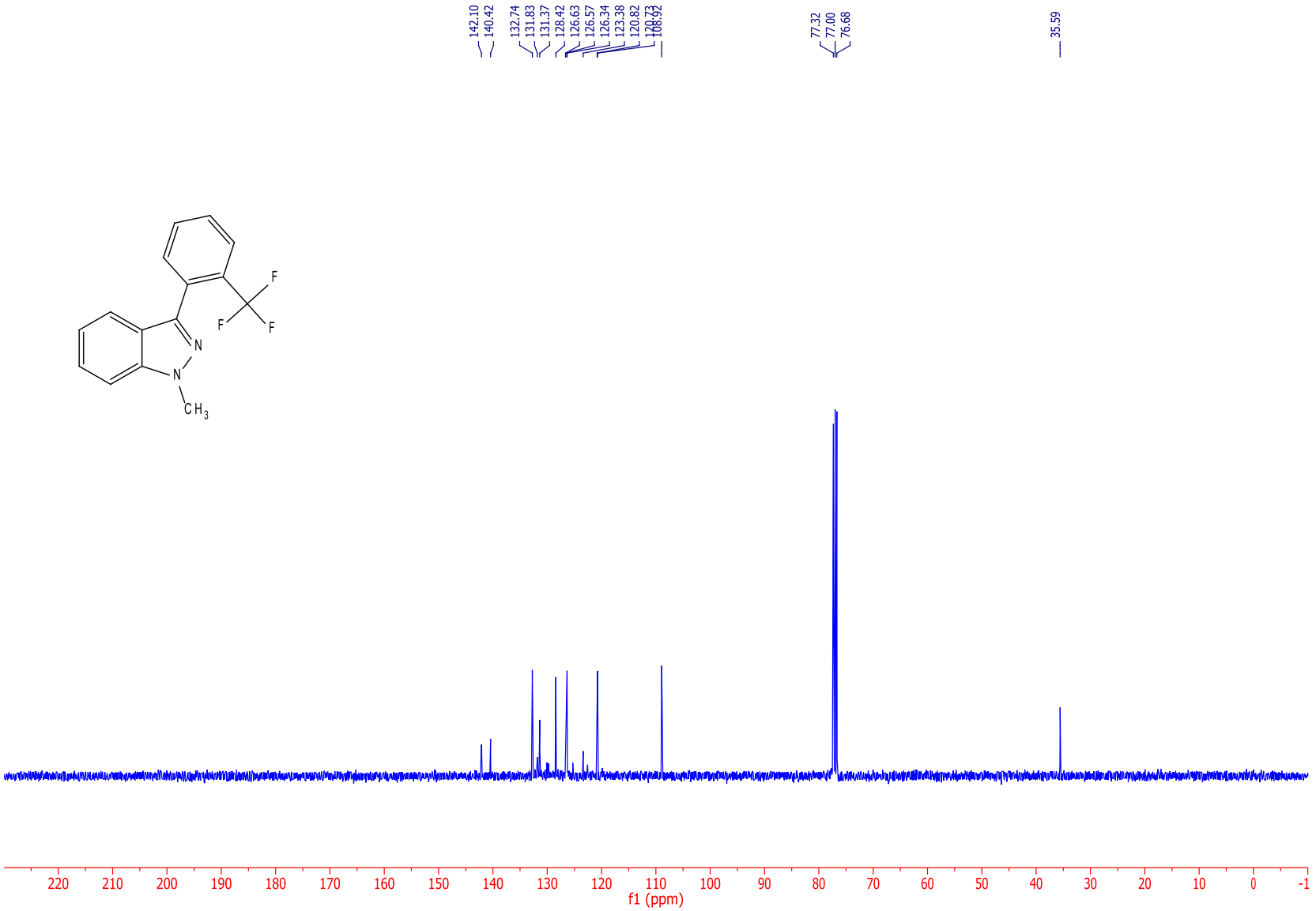

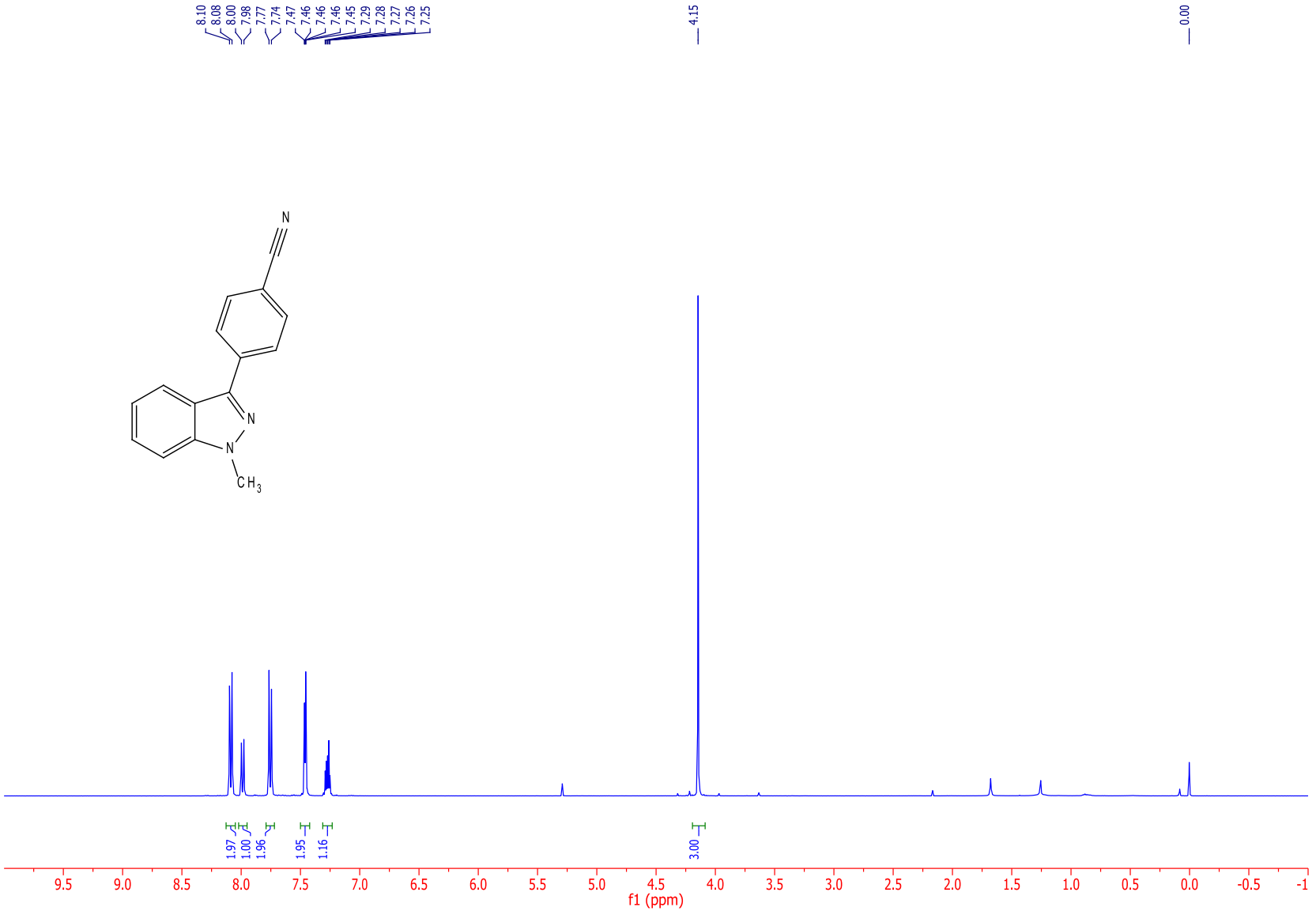

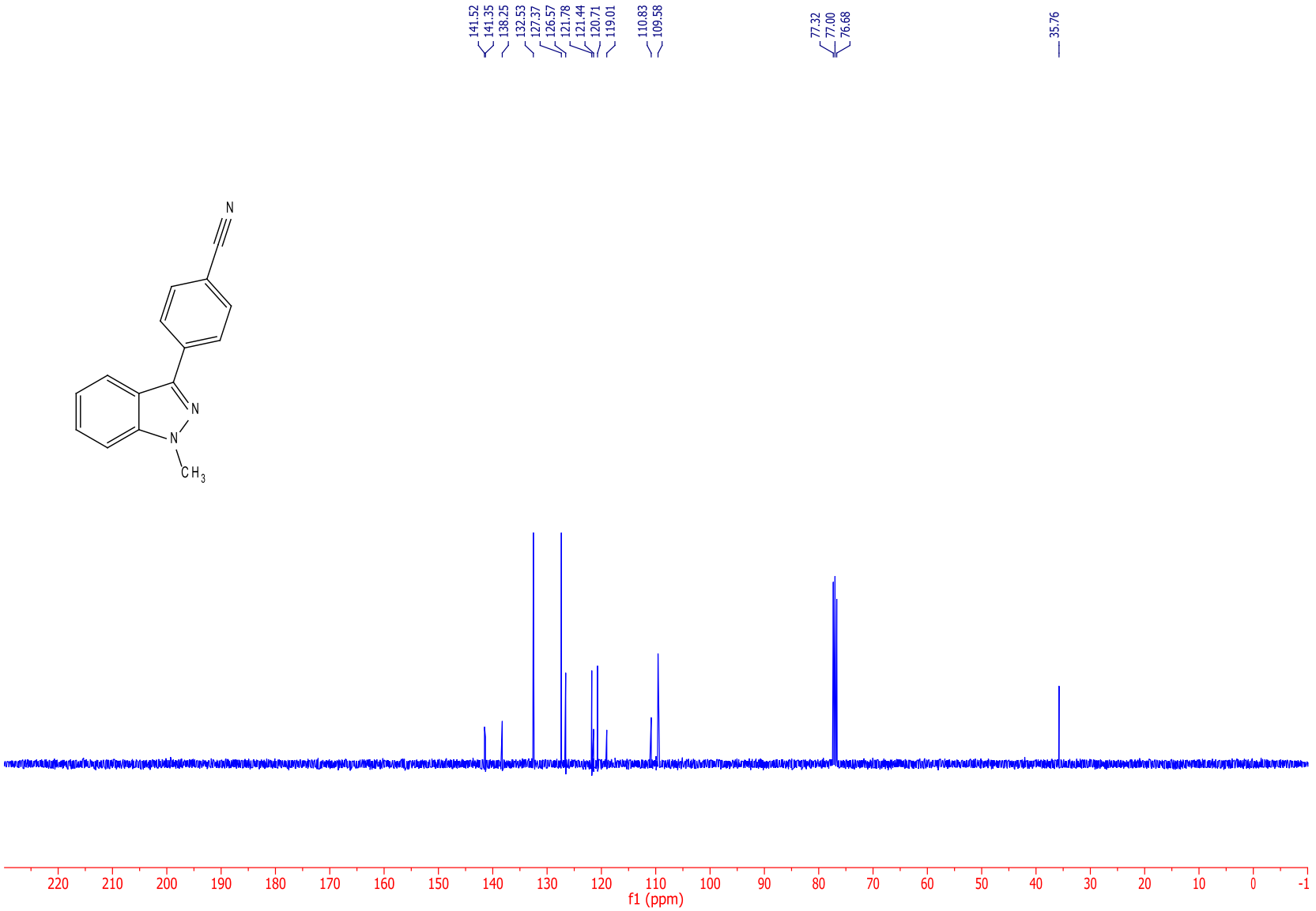

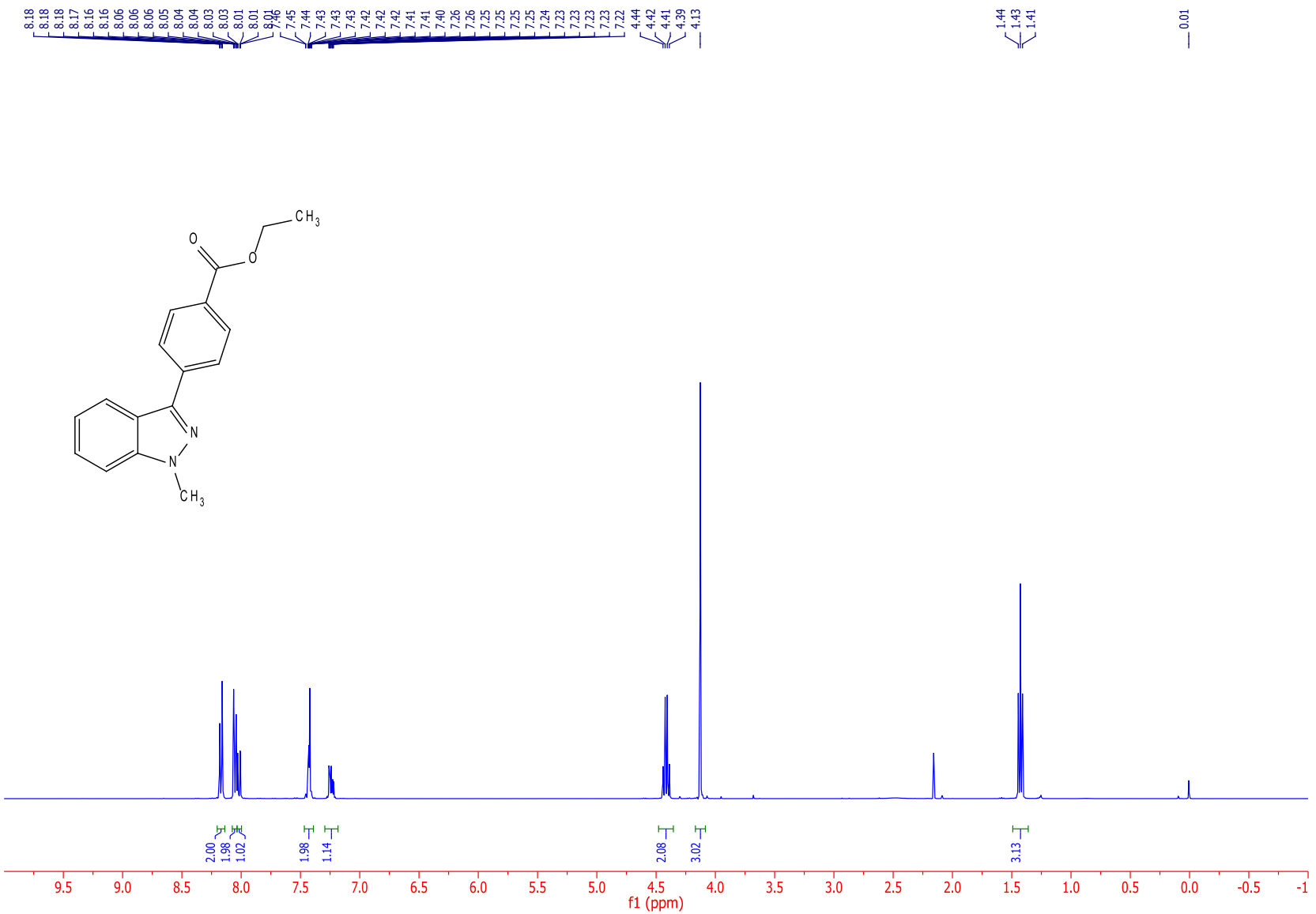

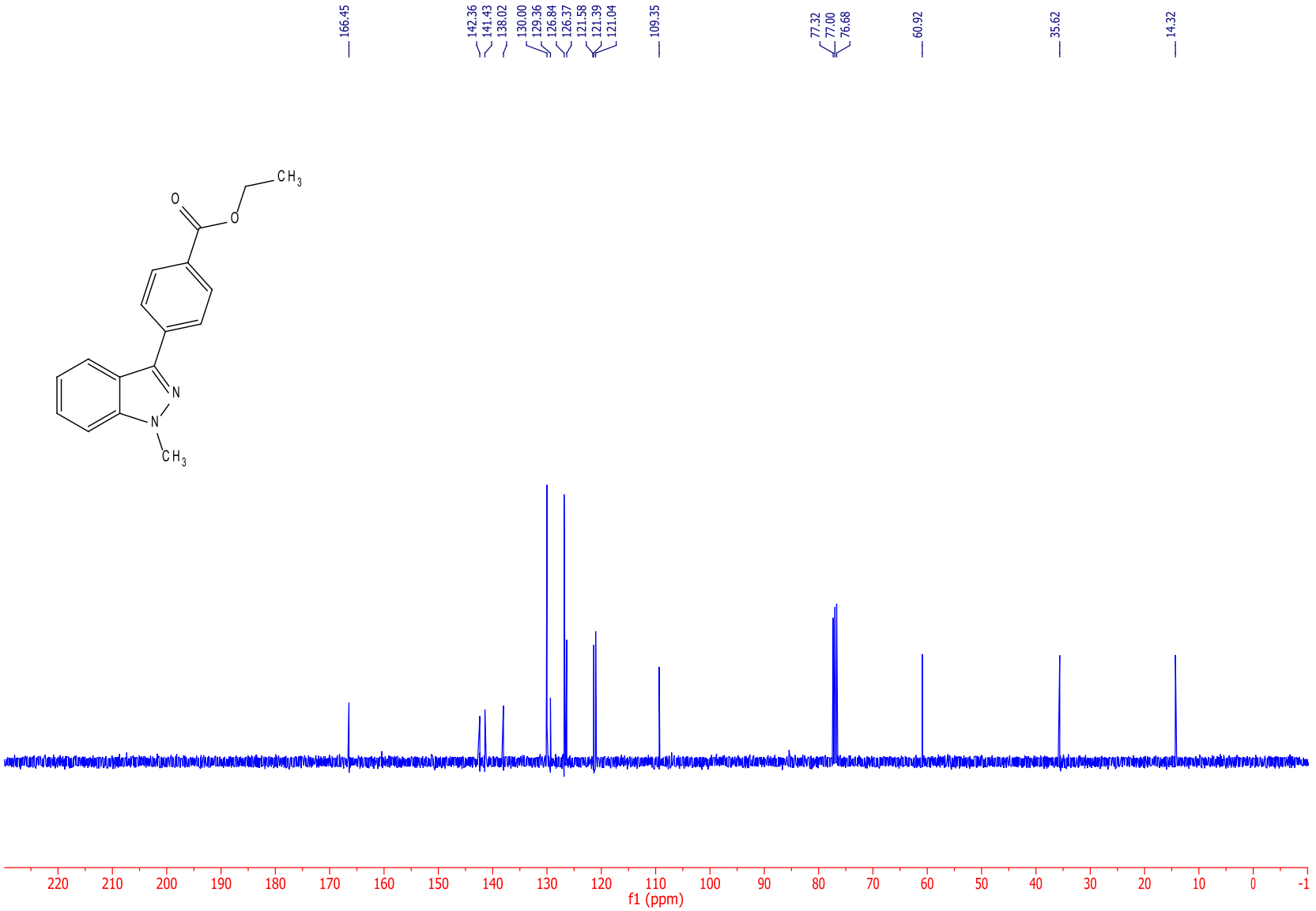

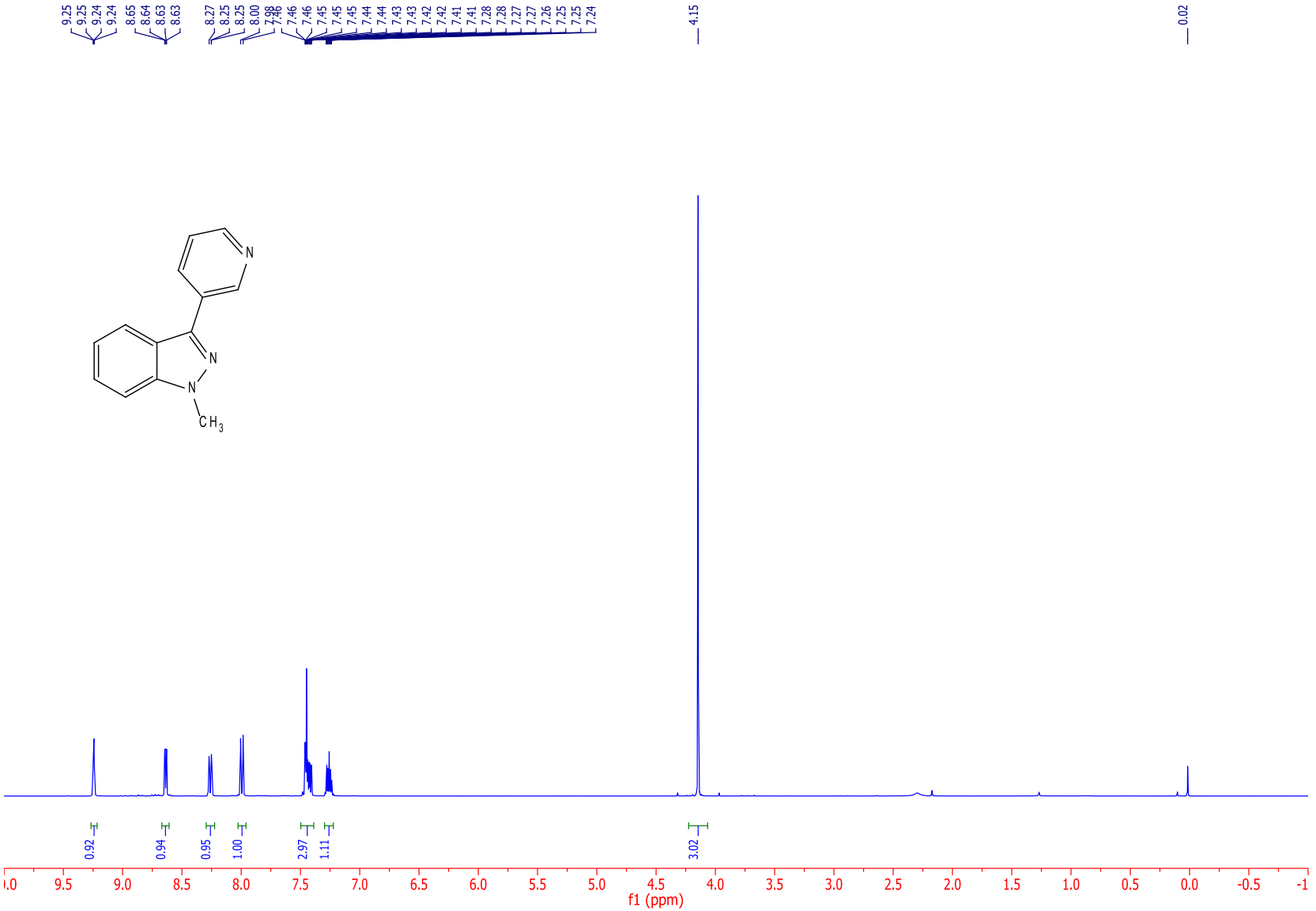

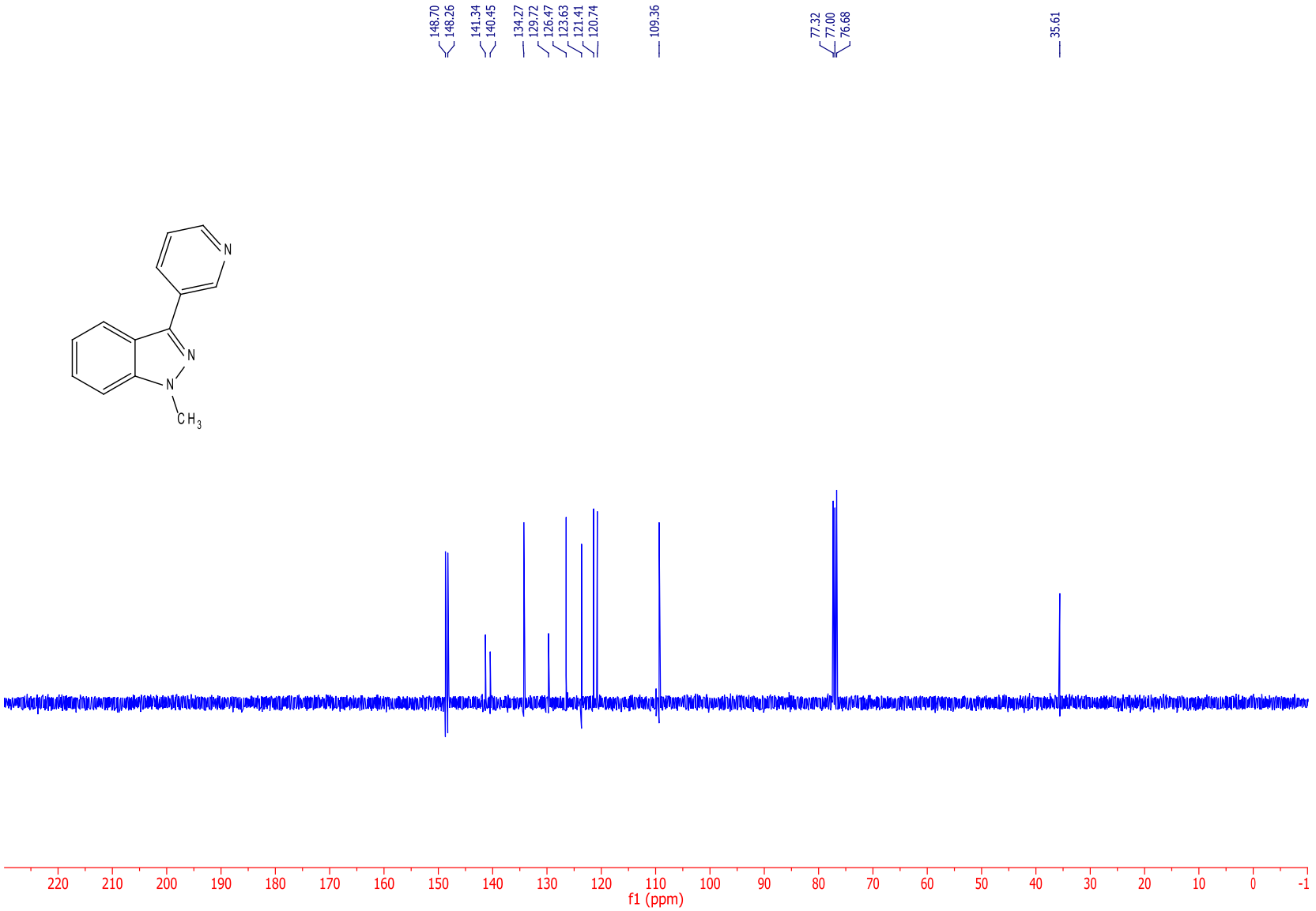

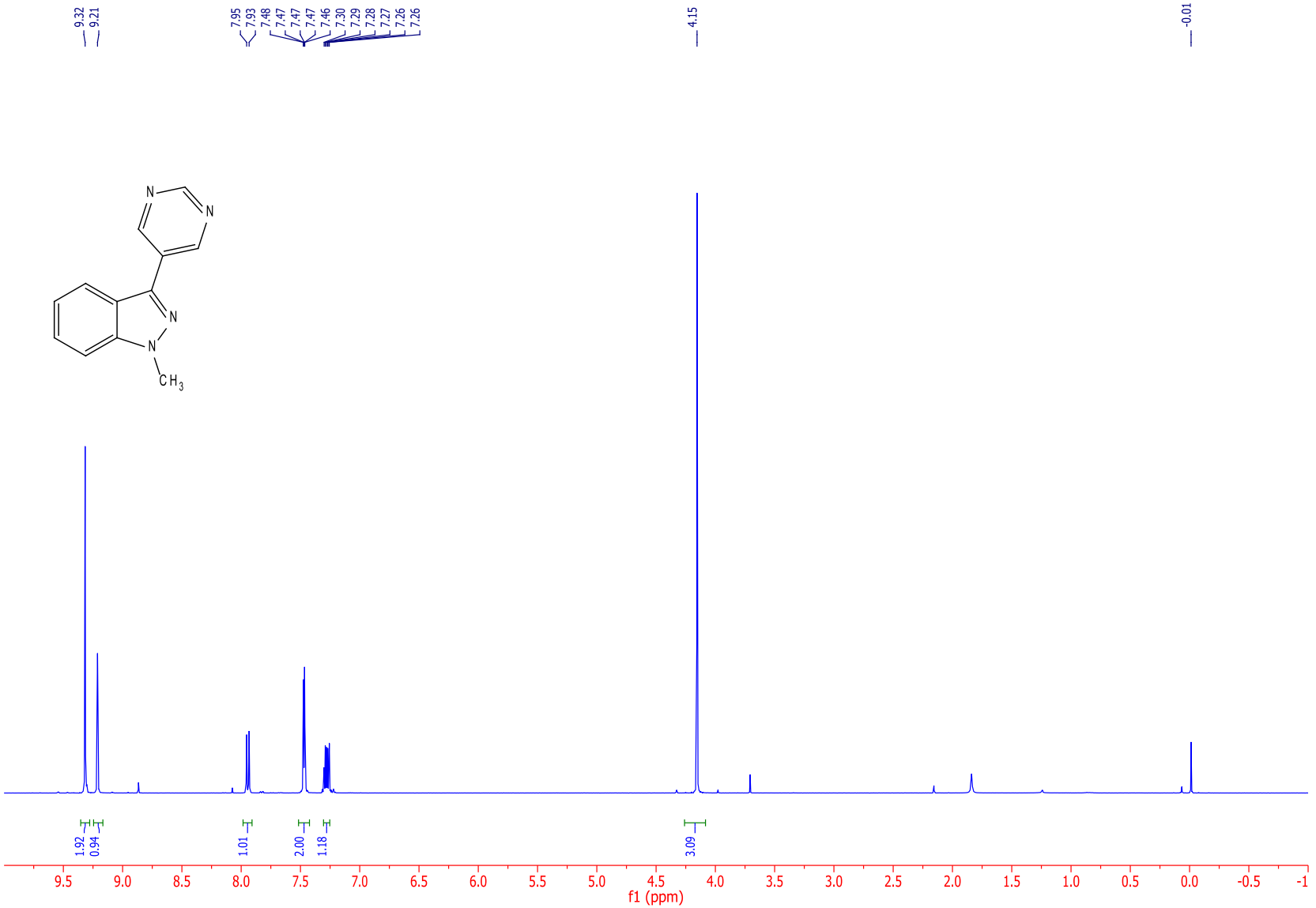

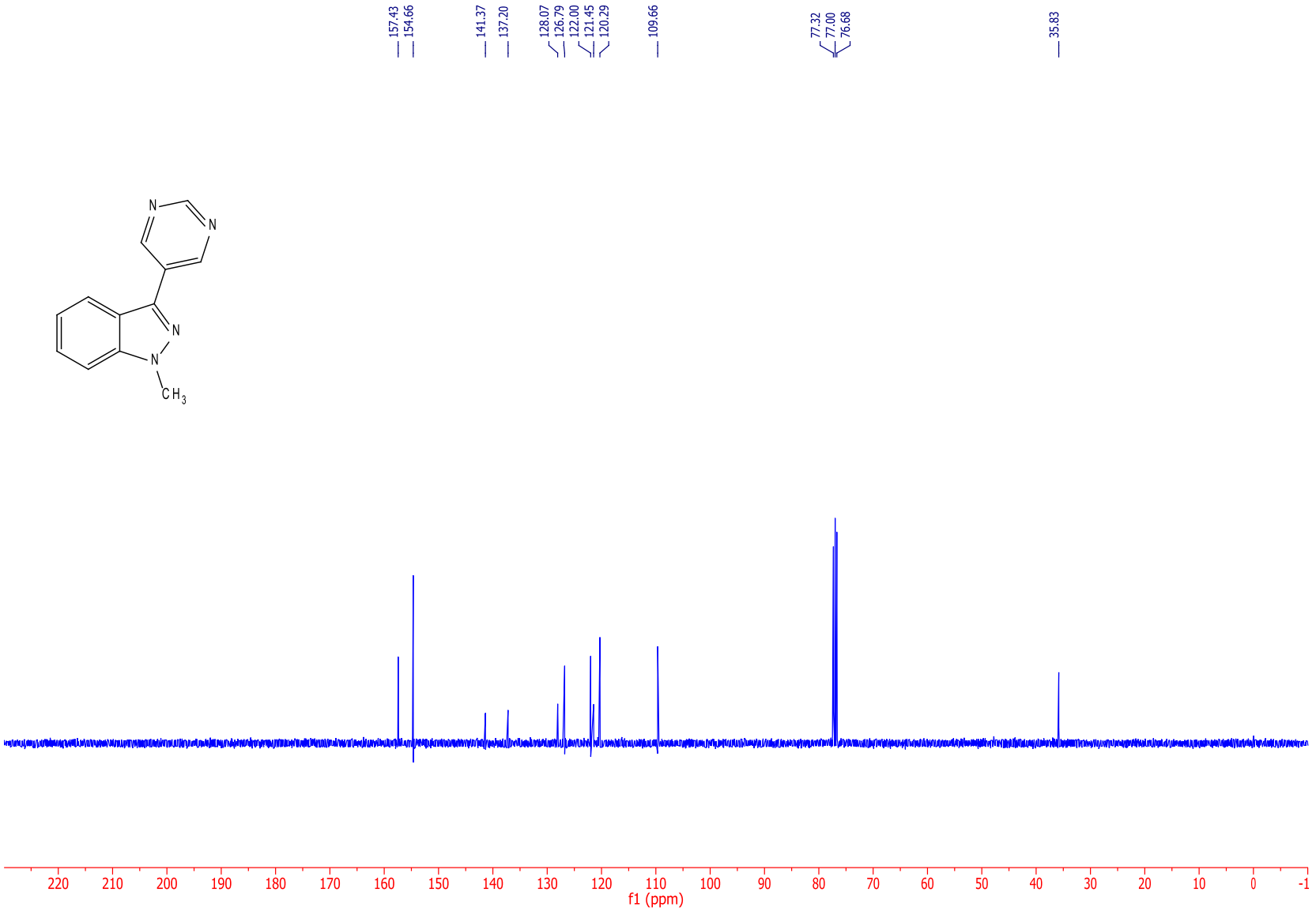

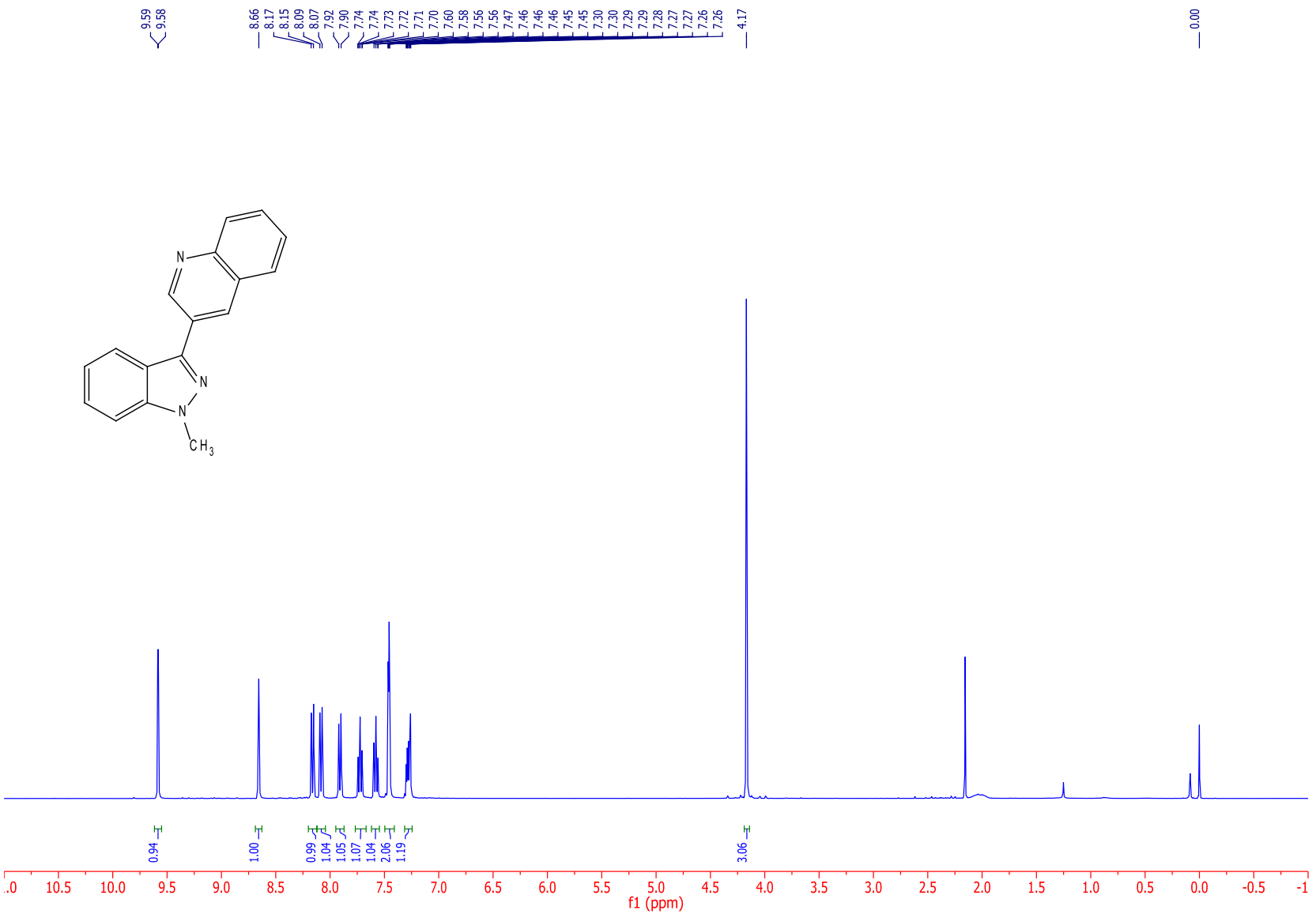

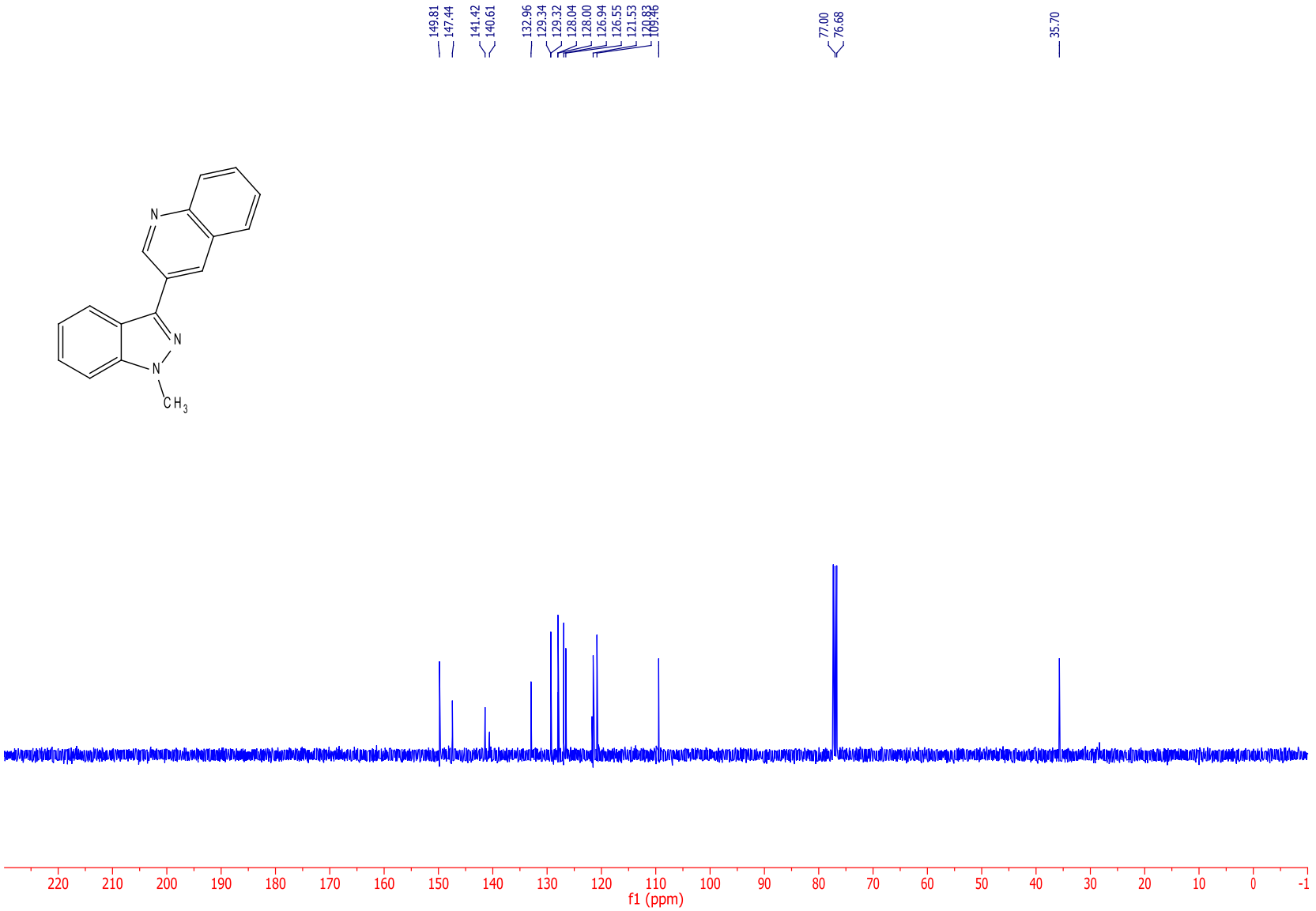

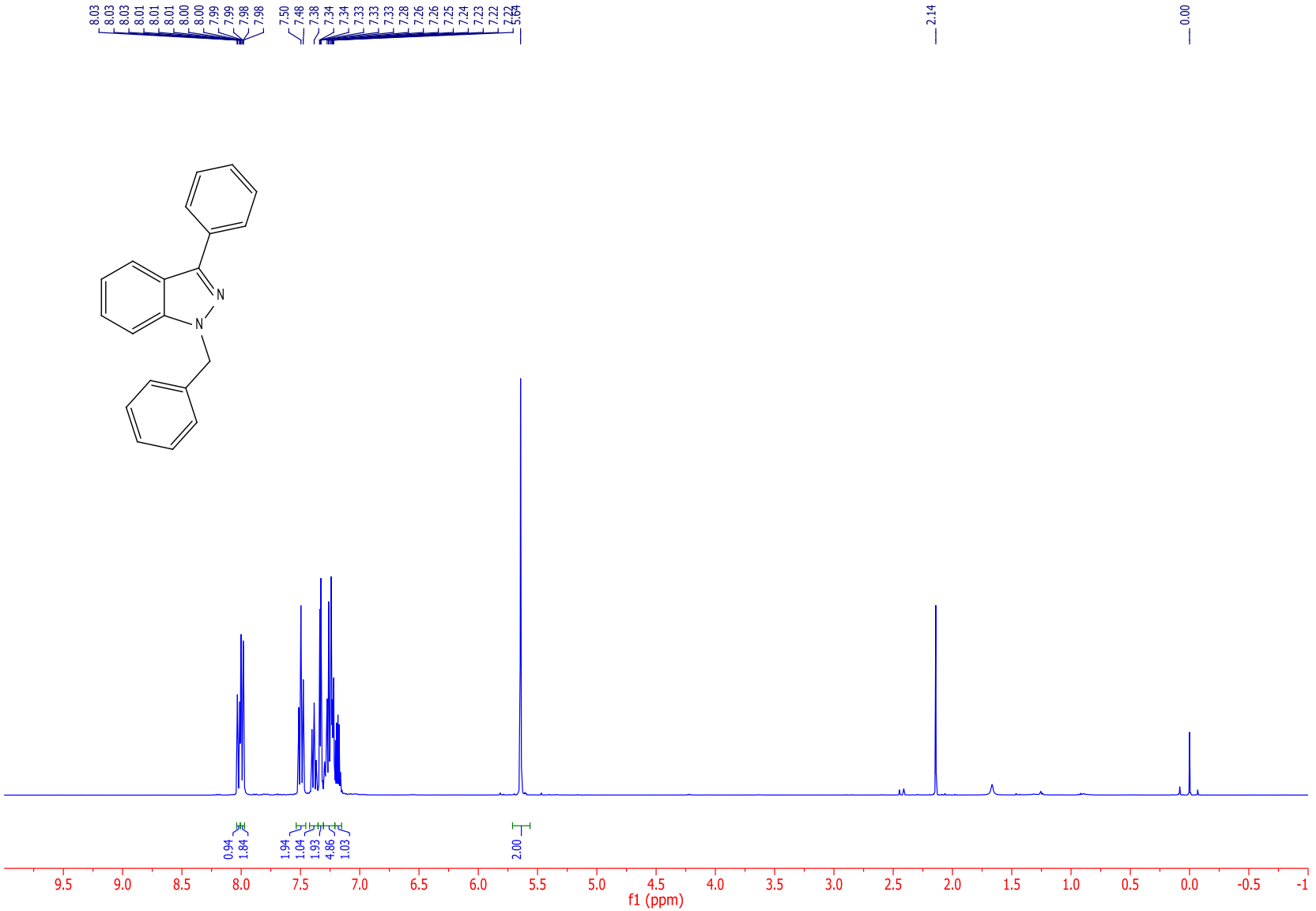

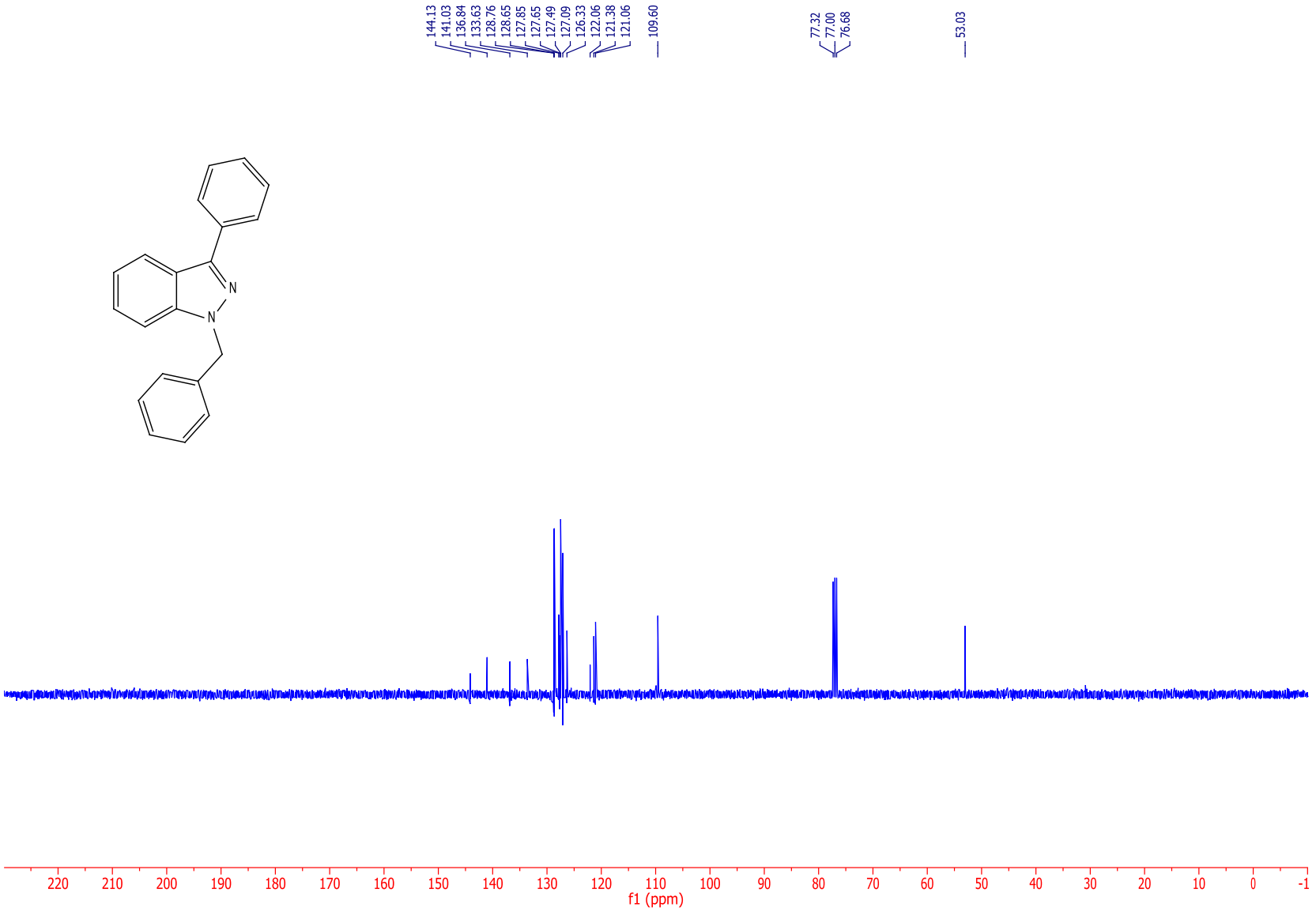

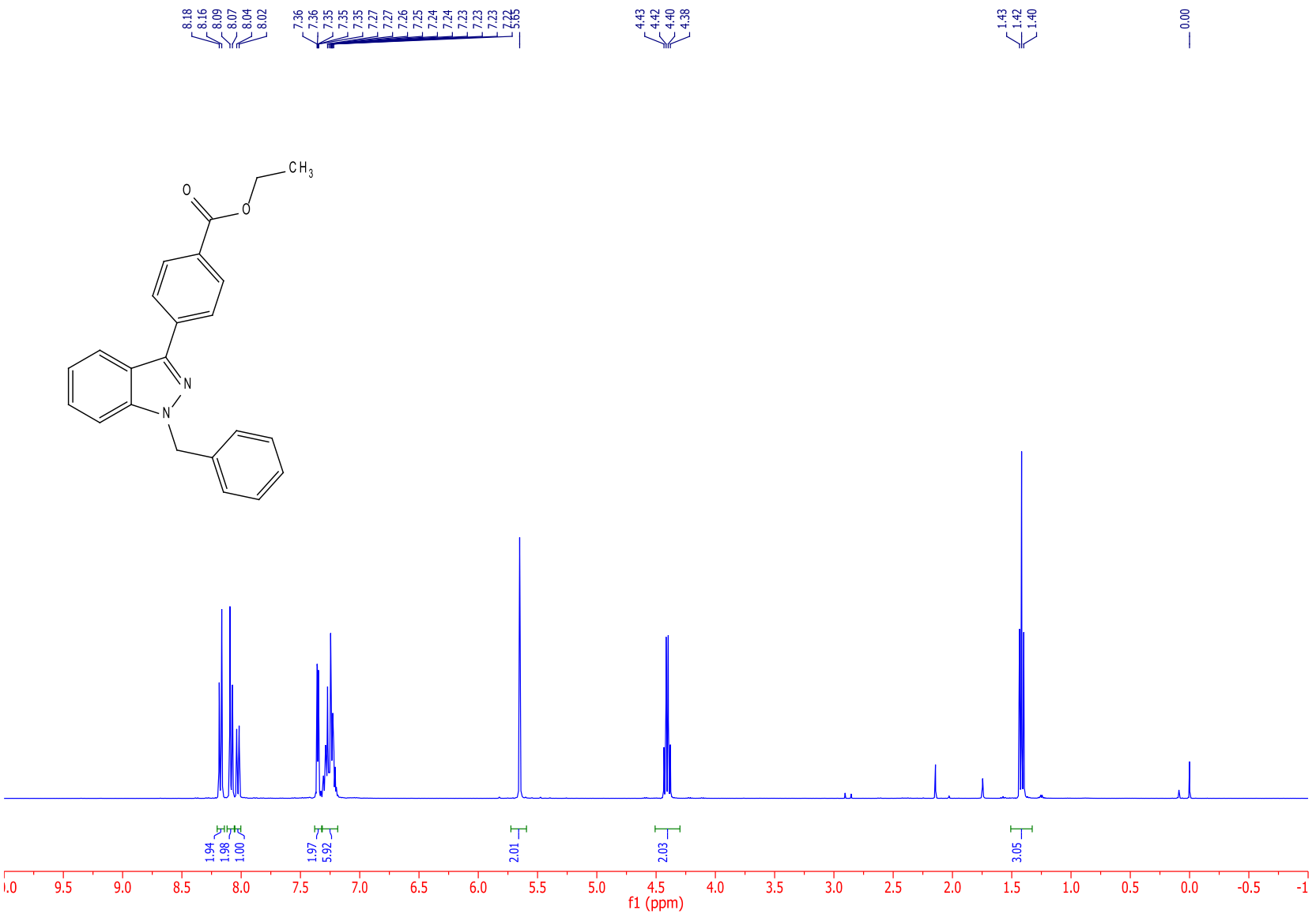

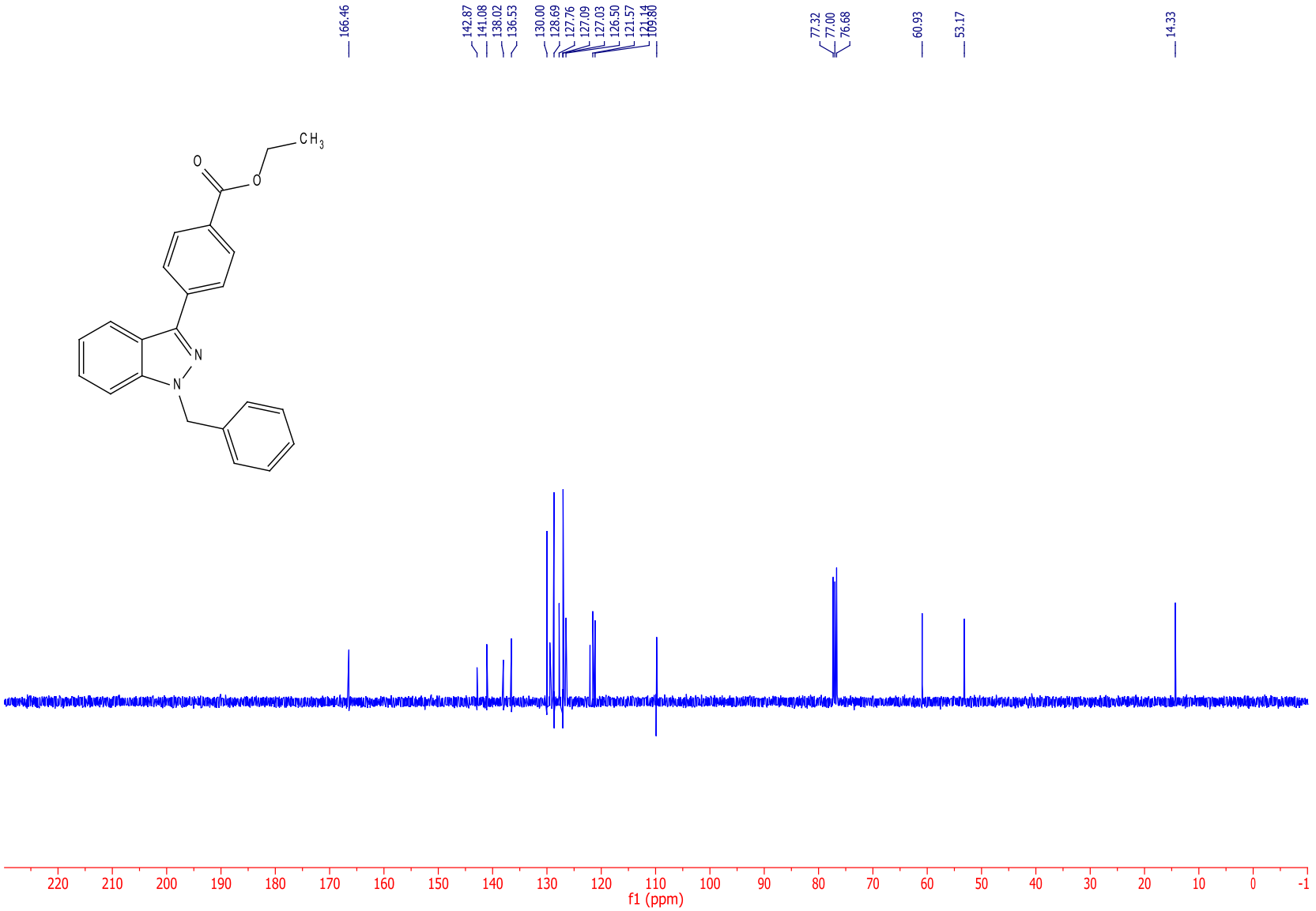

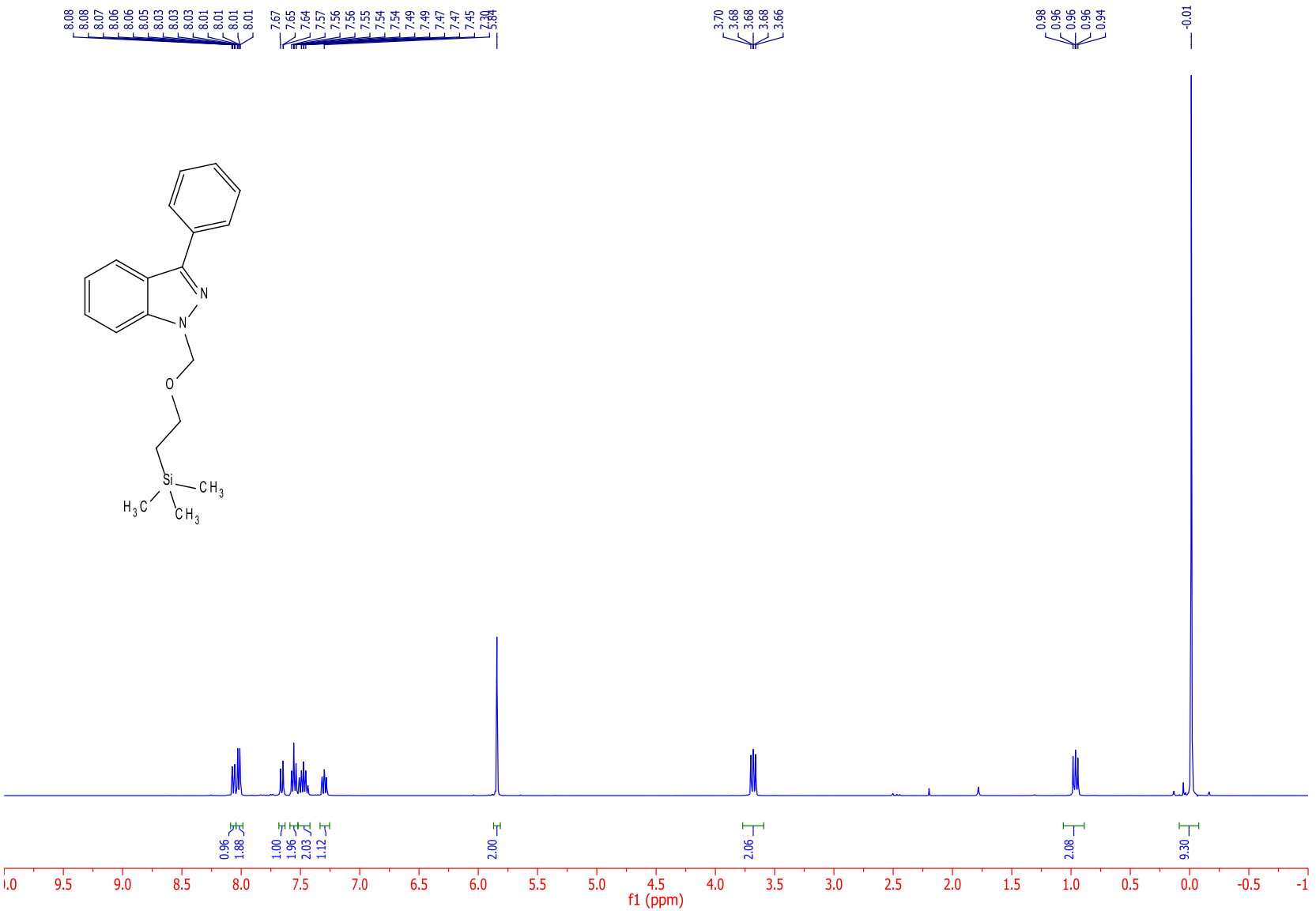

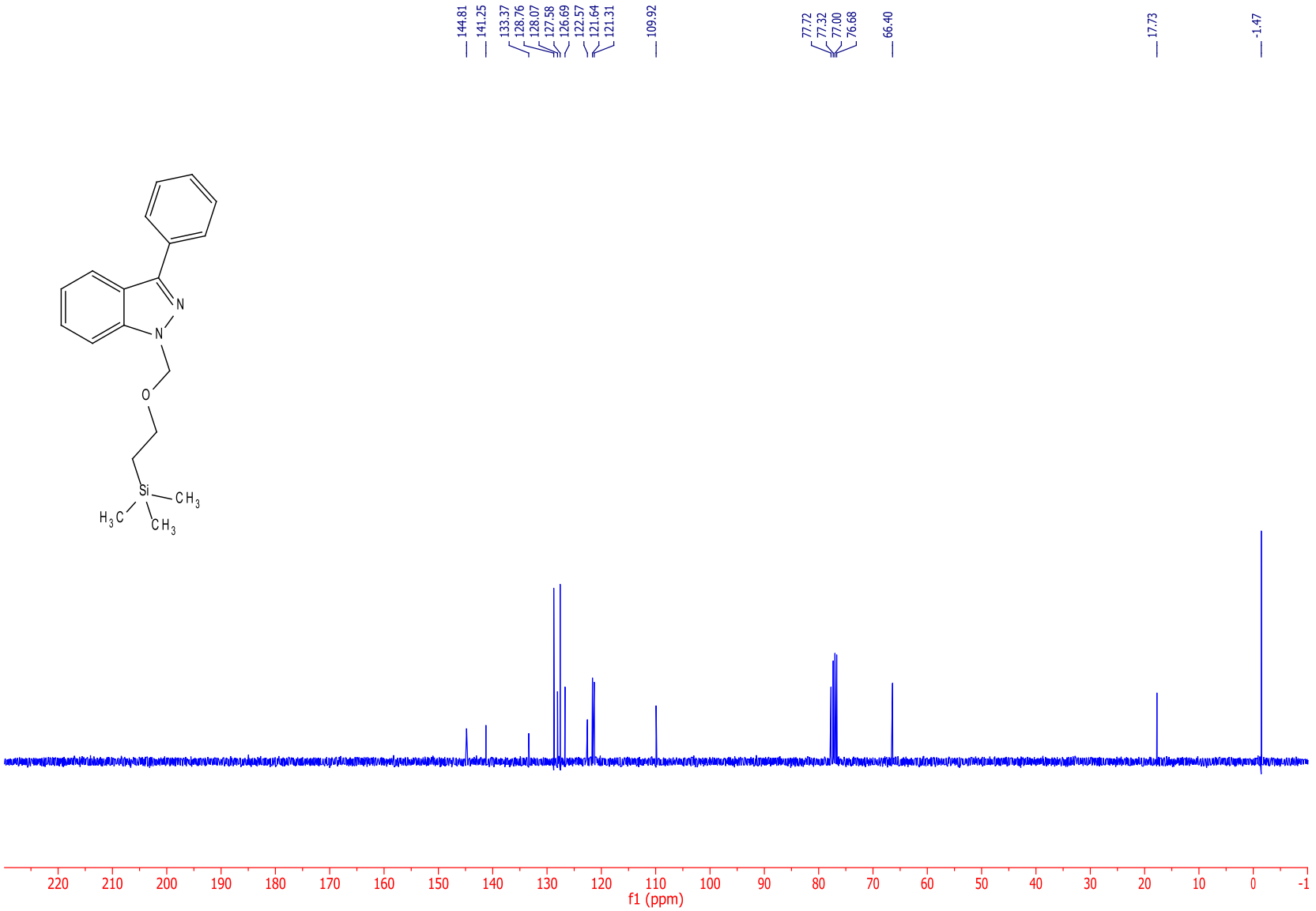

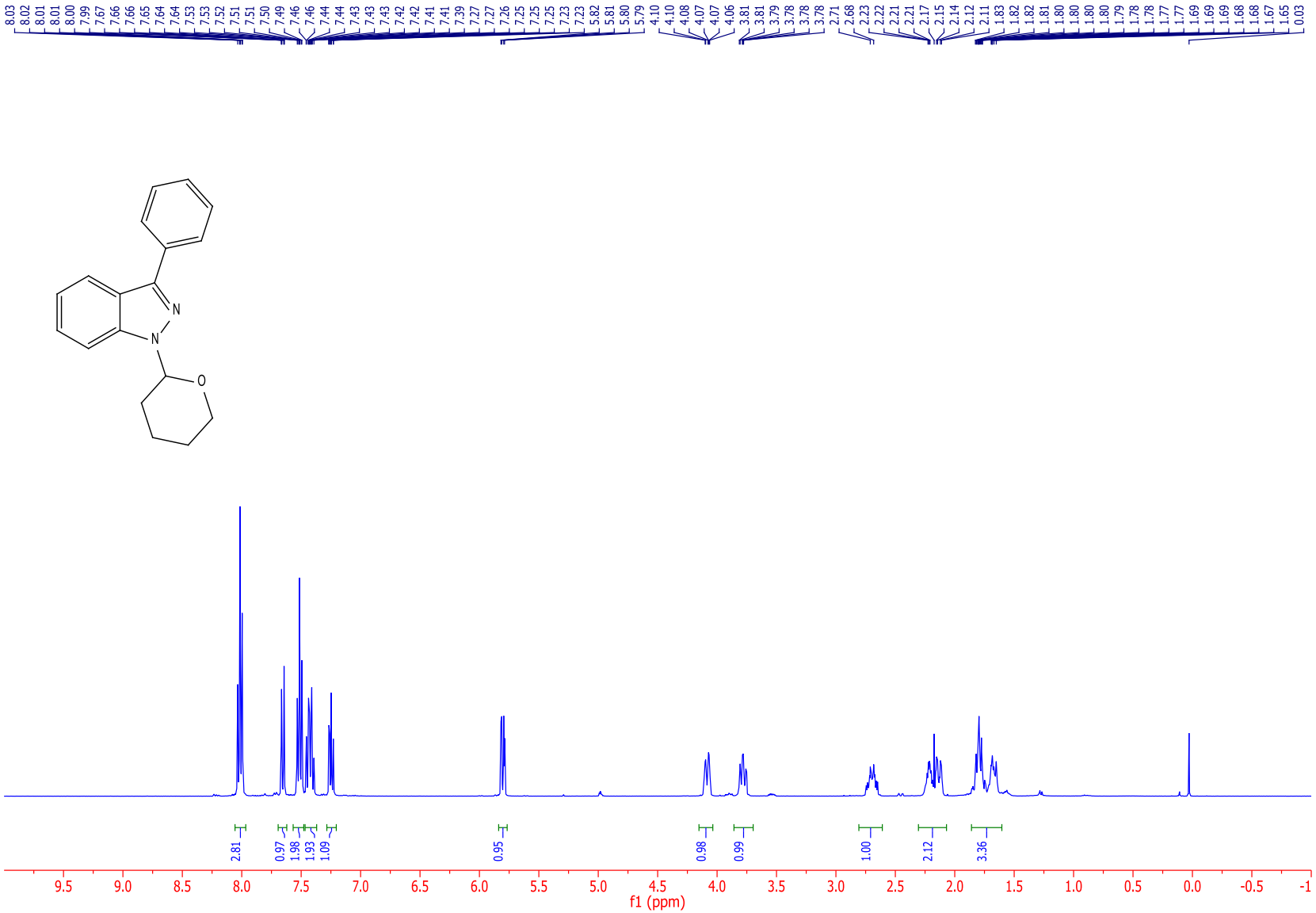

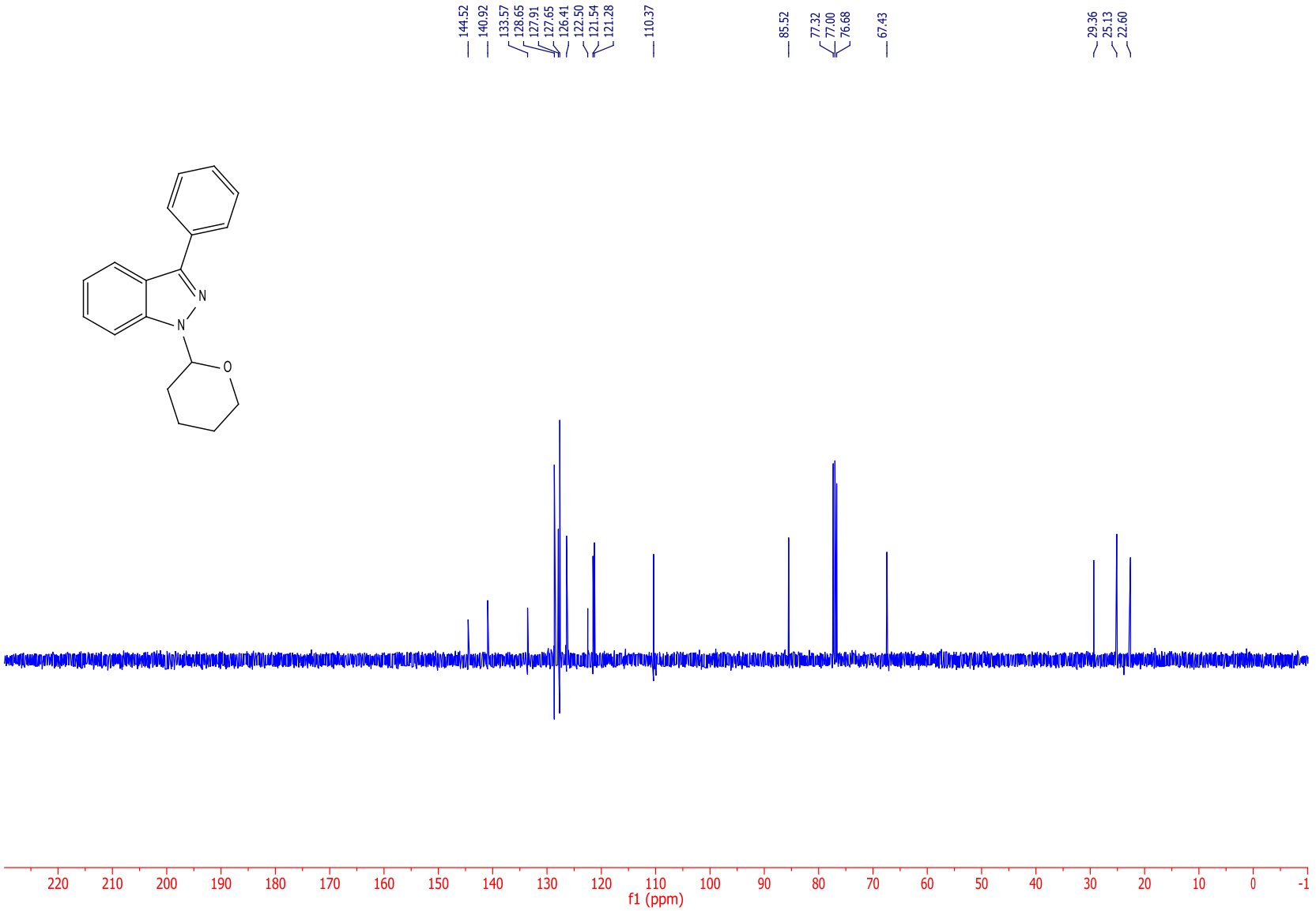

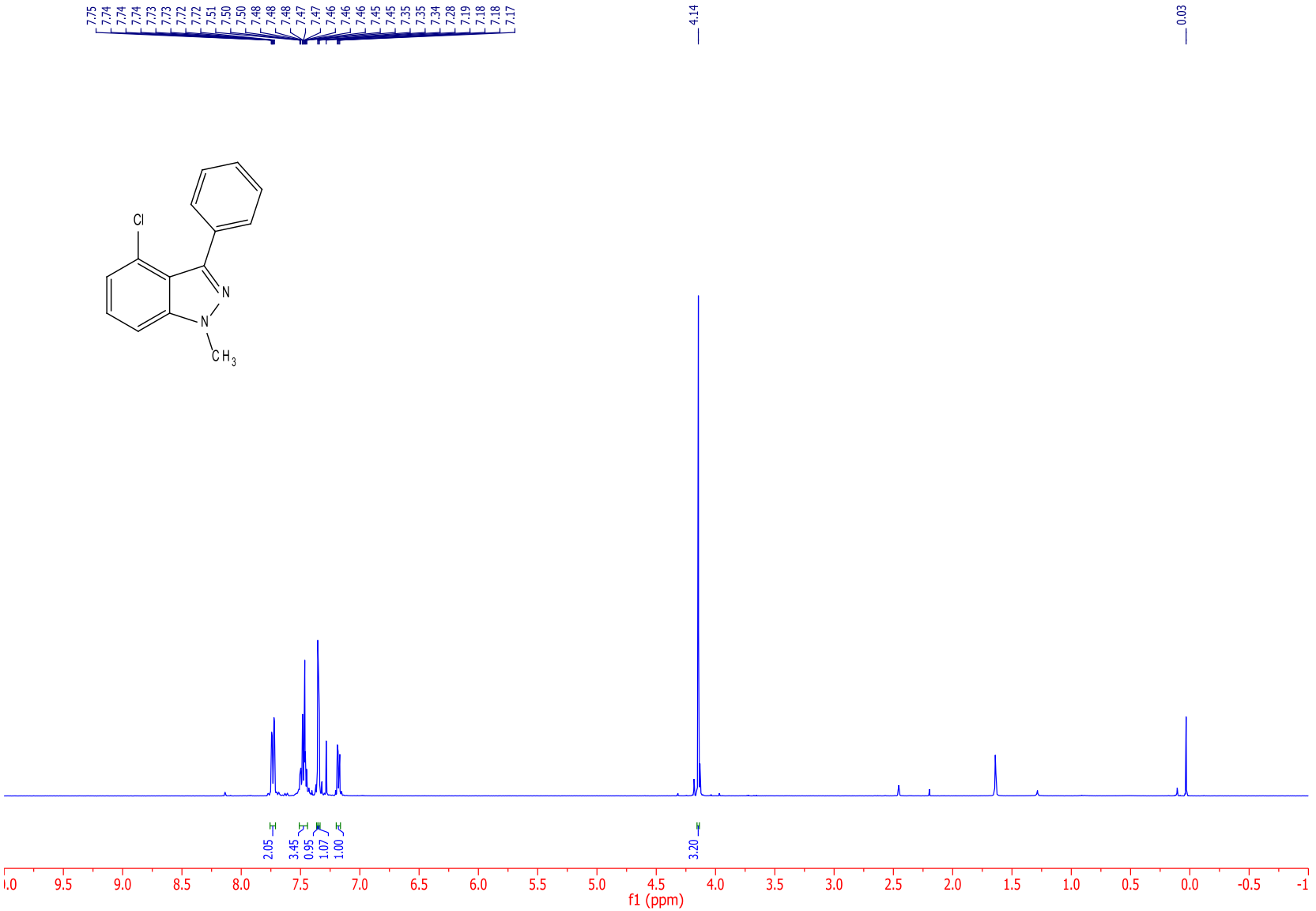

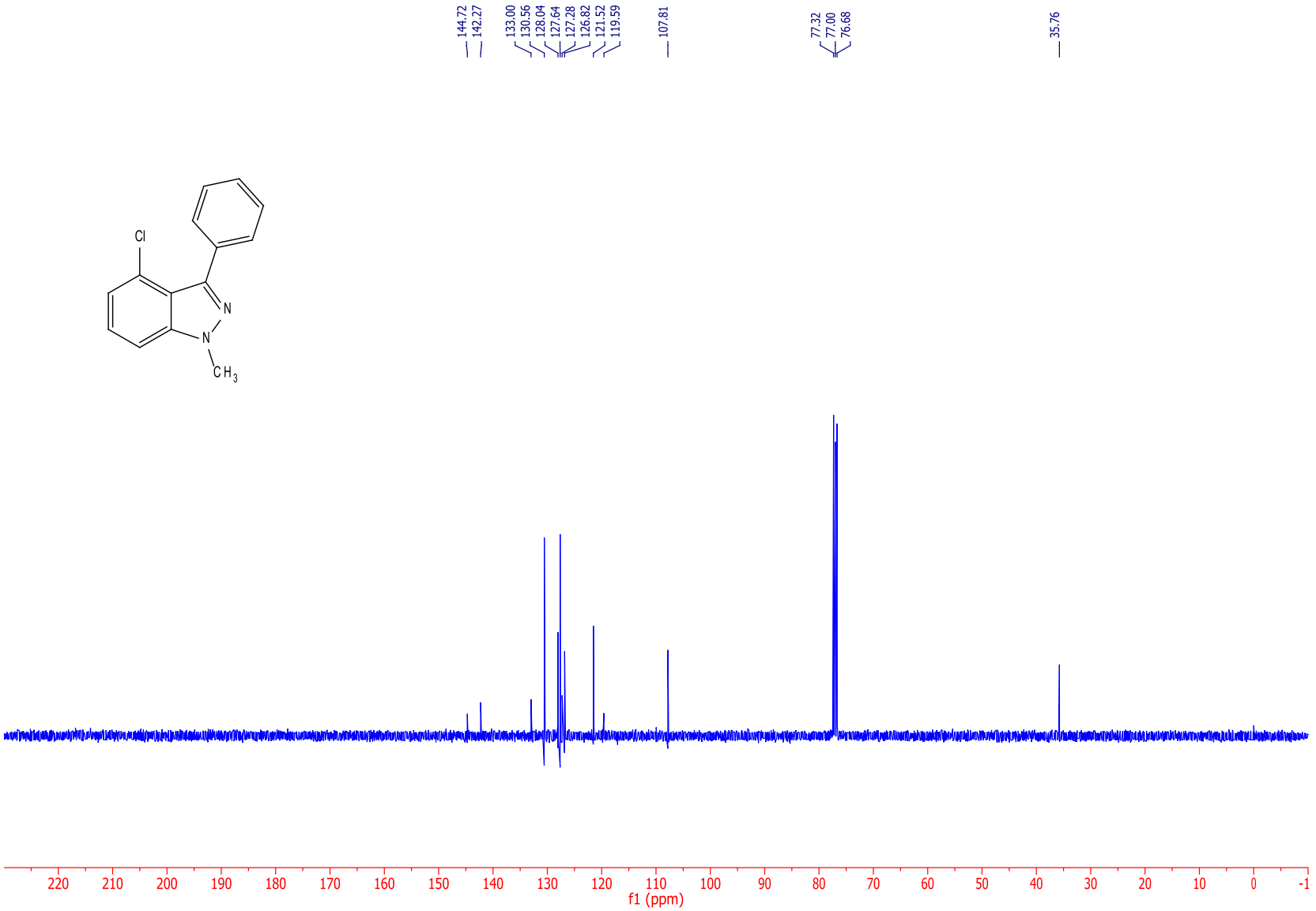

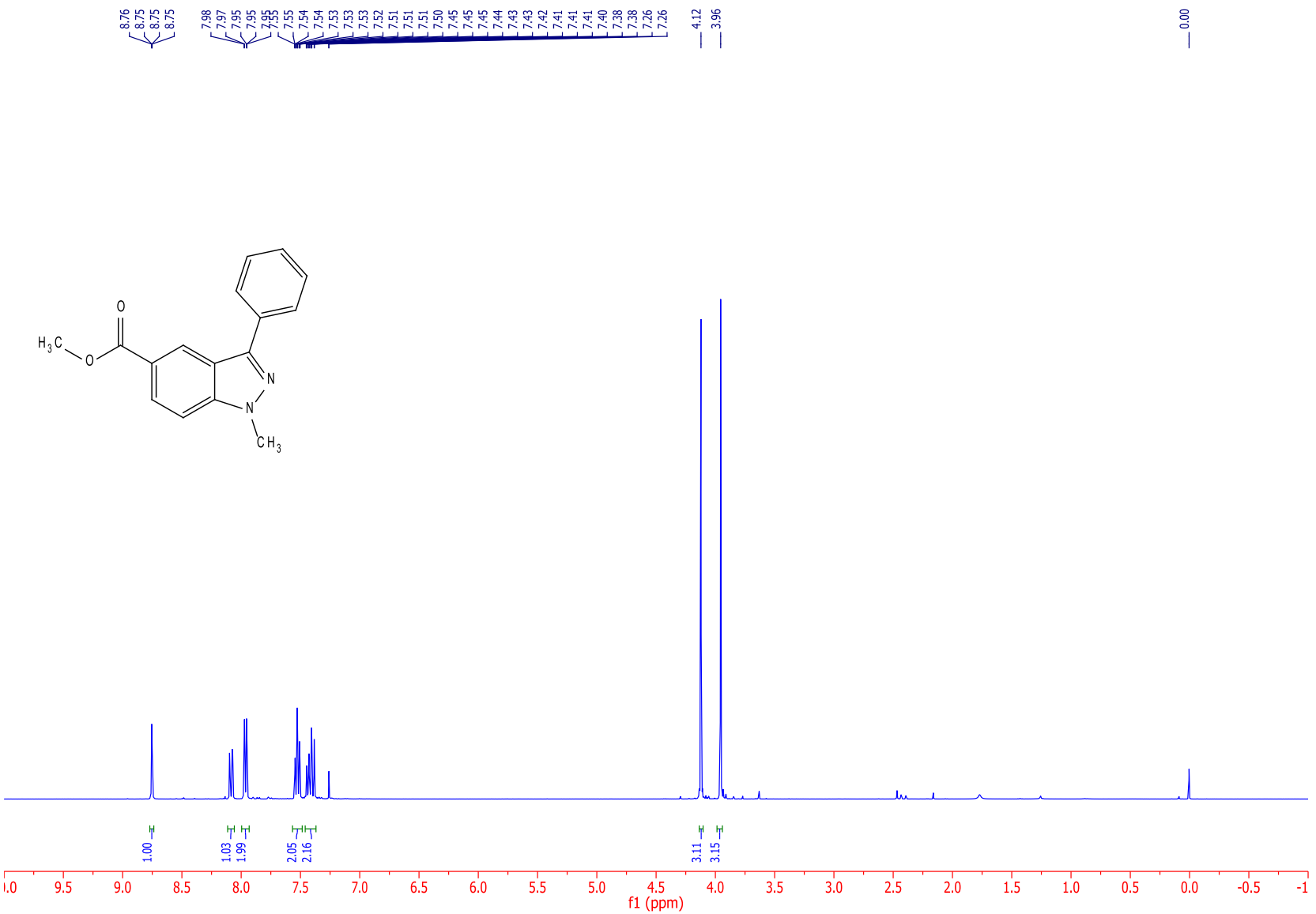

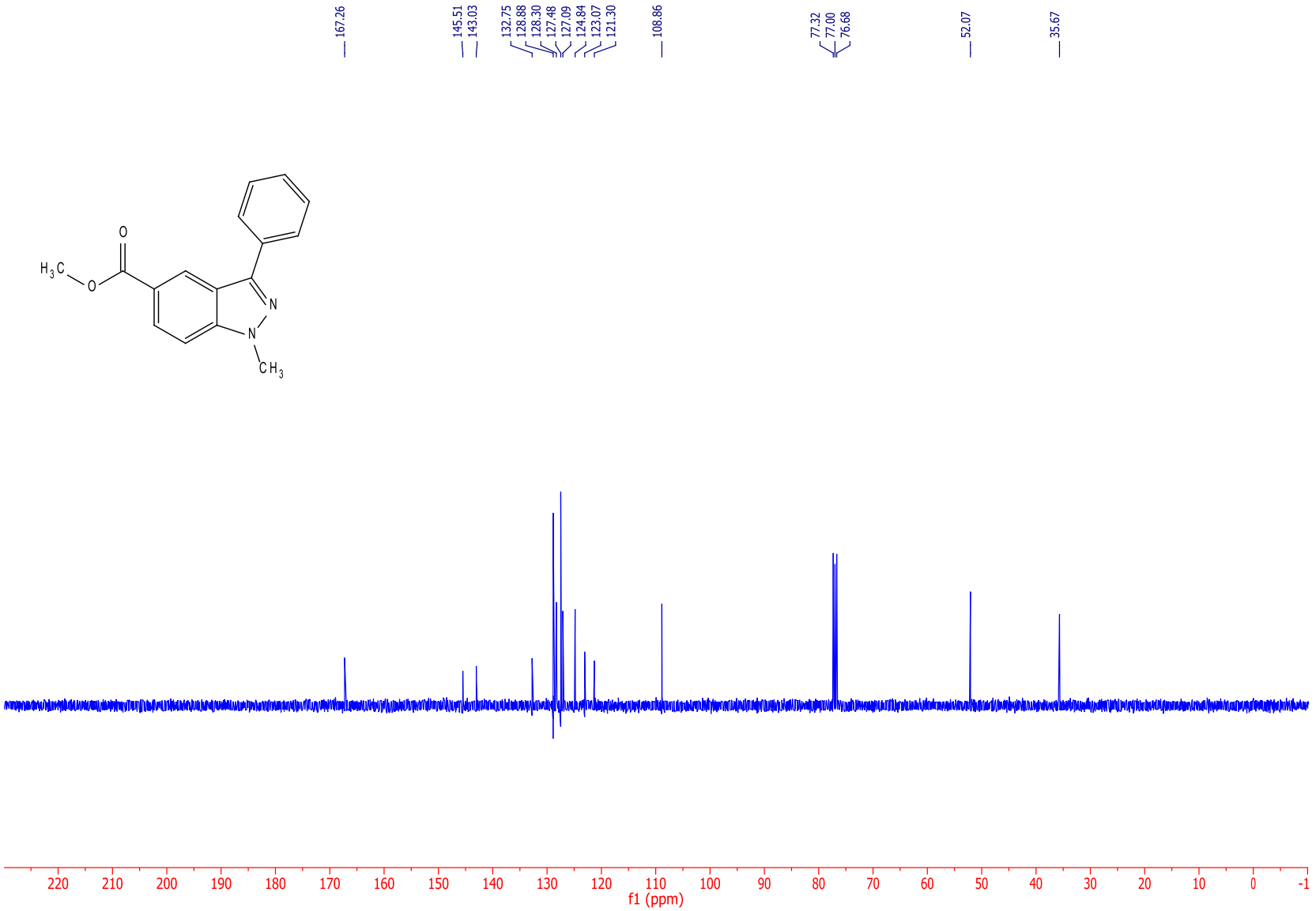

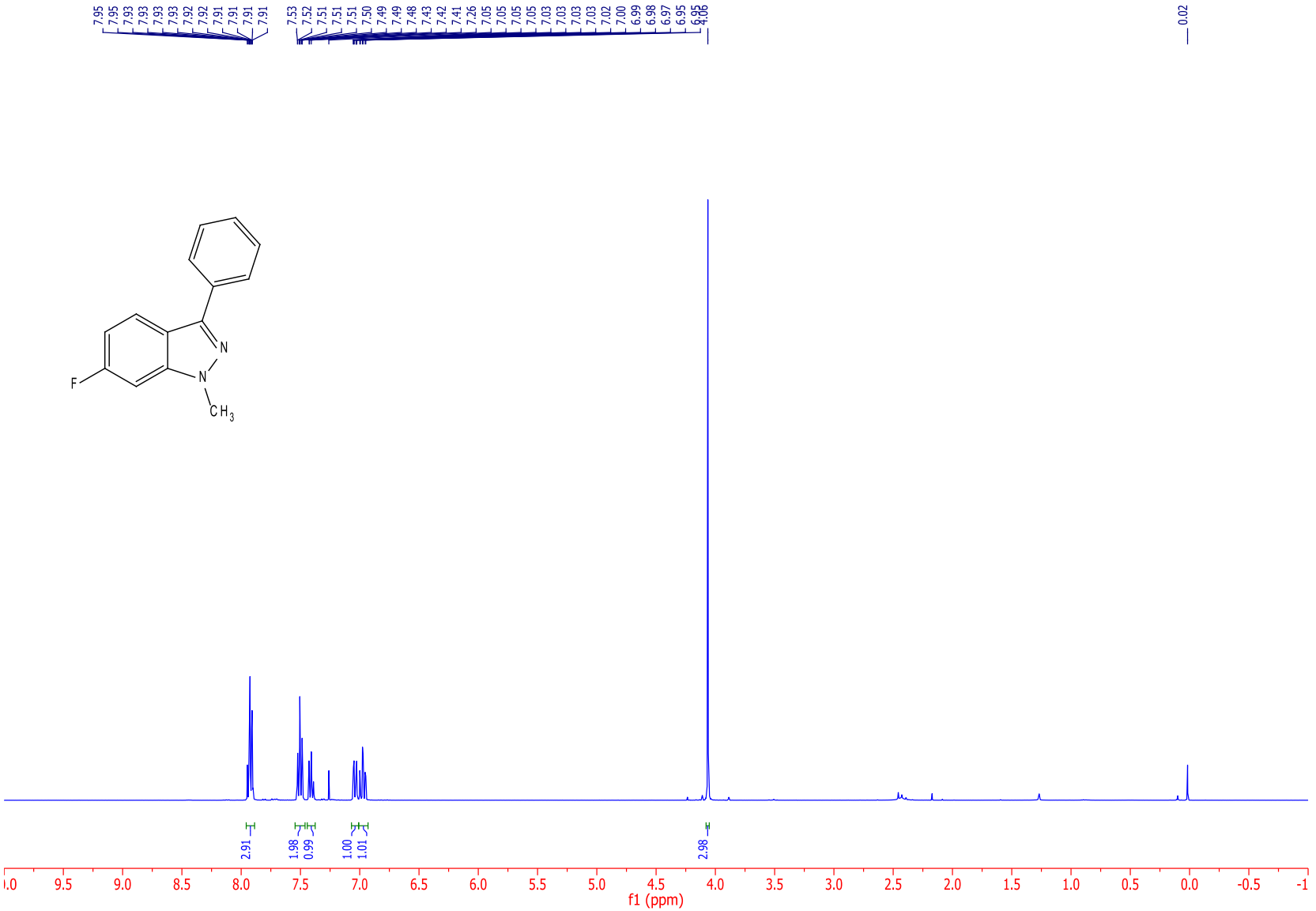

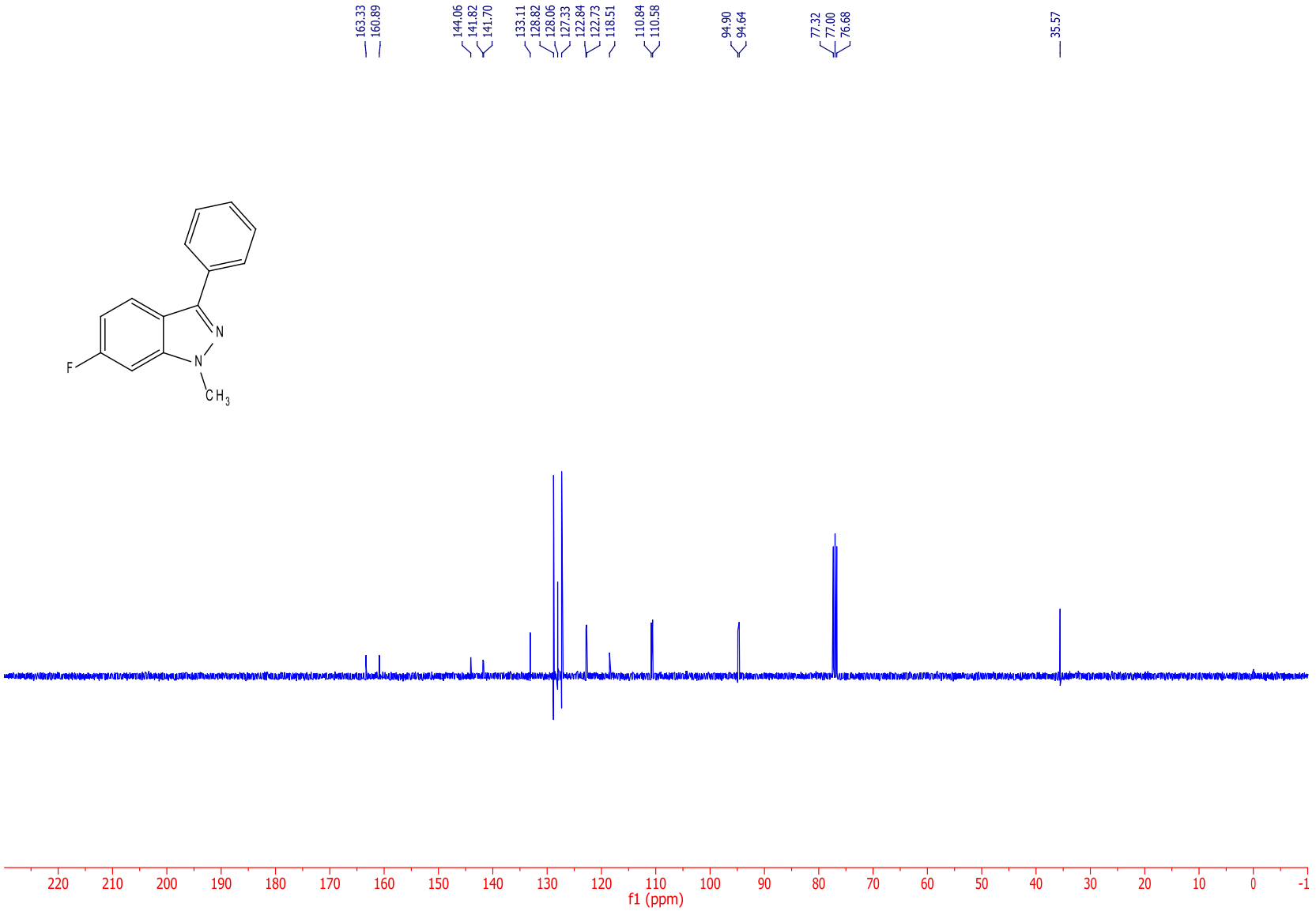

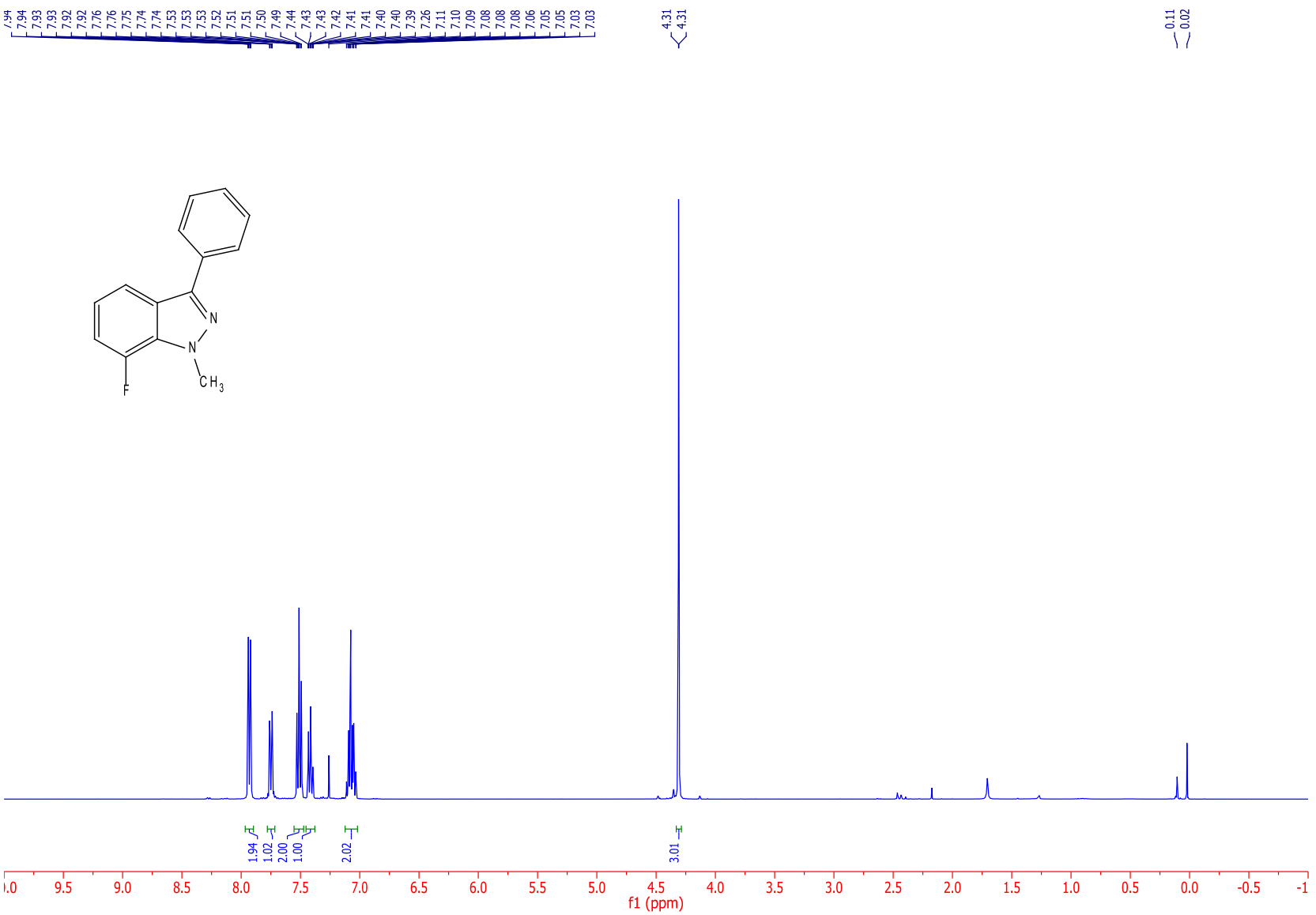

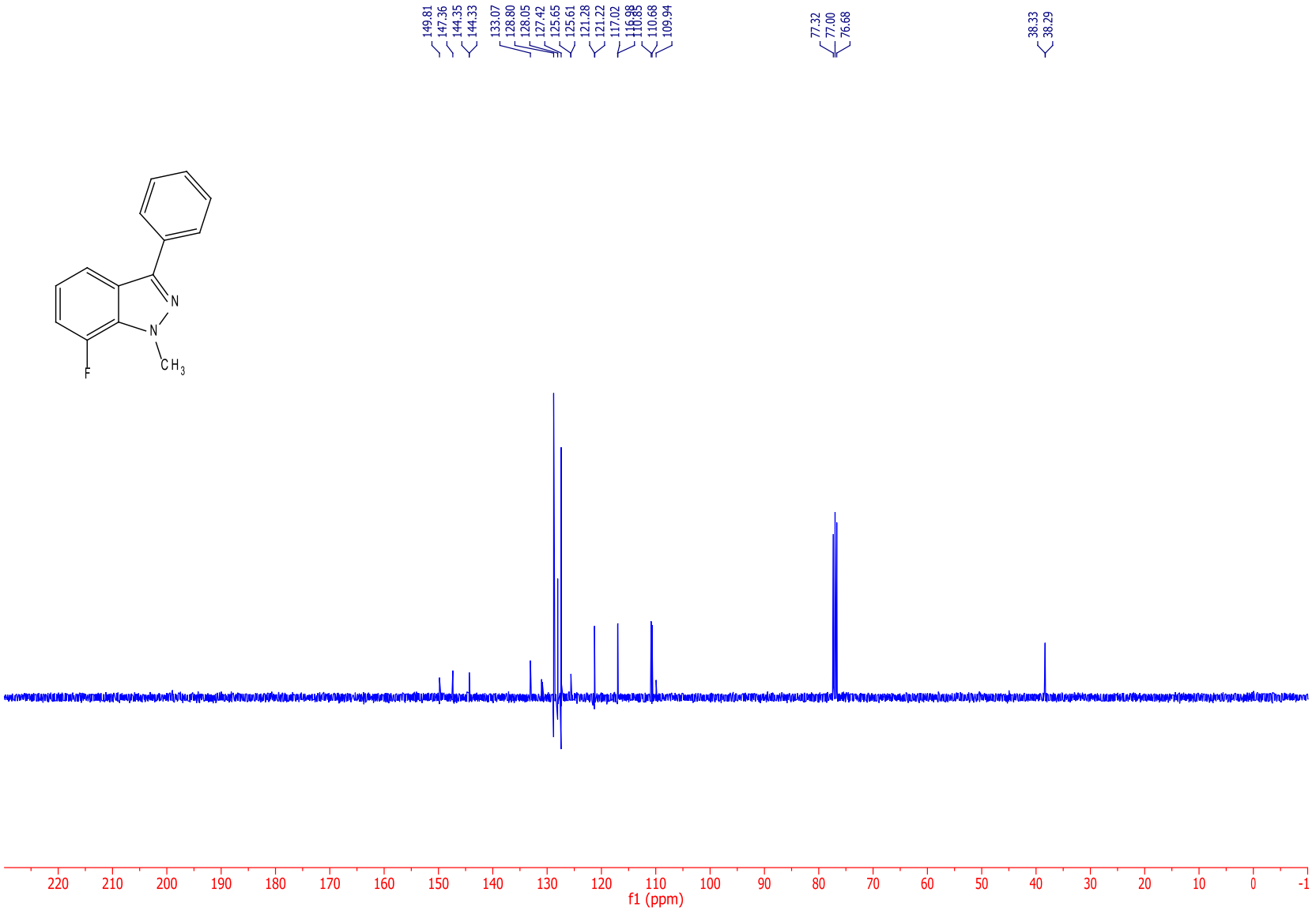

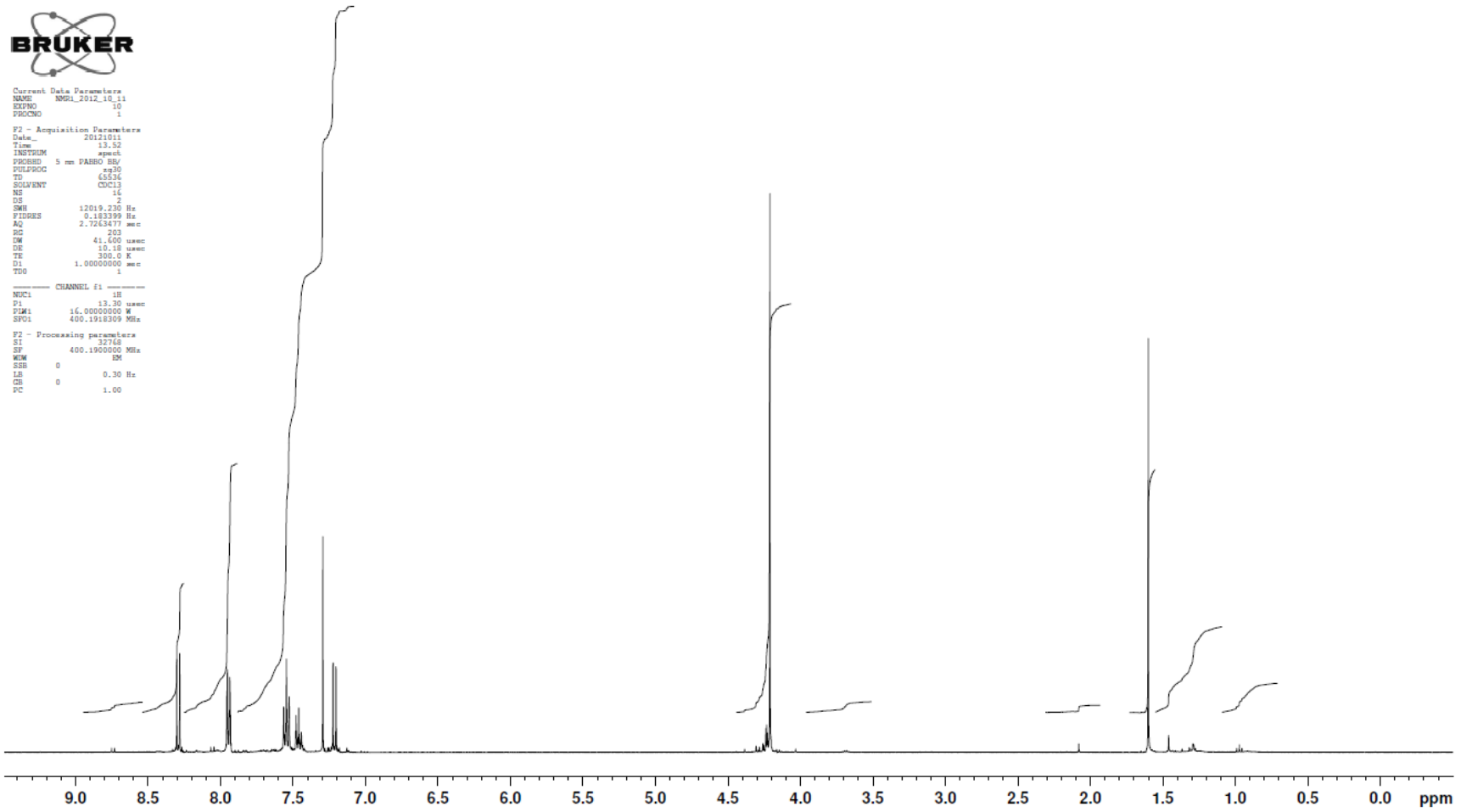

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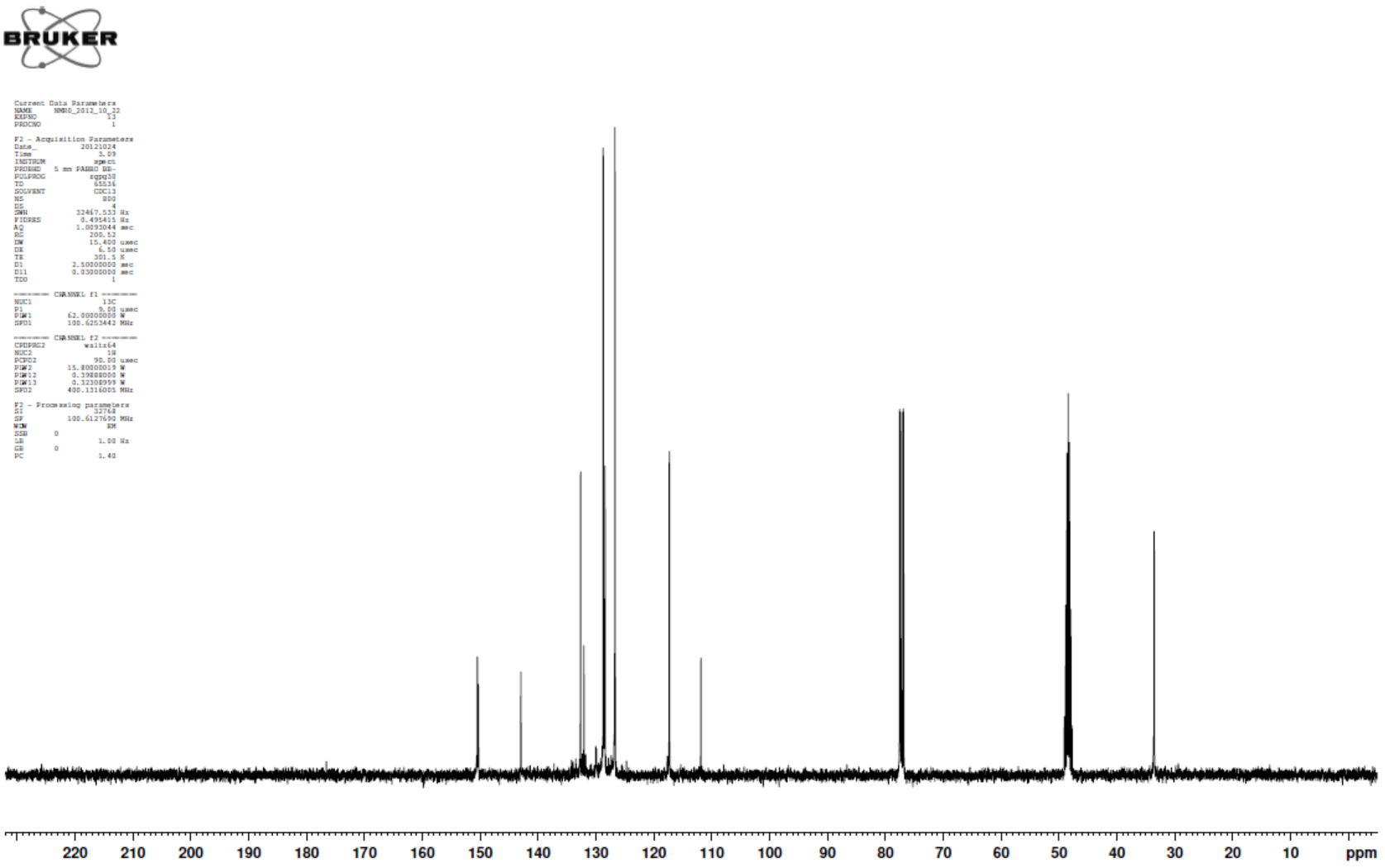

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