Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Metal-free regioselective C5-cyanoalkylation of the 8-aminoquinolineamides/sulfonamides via oxidative cross-dehydrogenative coupling with alkylnitriles

Fatemeh Doraghi,[a] Ebrahim Kianmehr,[*a] Alireza Foroumadi[*b]

a. School of Chemistry, College of Science, University of Tehran, Tehran 1417614411, Iran. E-mail: kianmehr@khayam.ut.ac.ir
b. Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran. E-mail: aforoumadi@yahoo.com

Contents

1. General information

Reagents were commercially available and solvents were used after purification. All reactions were carried out in an oil bath using sealed tubes (15 mL) and were monitored by thin-layer chromatography (TLC) using pre-coated silica gel plates GF254 plates. TLC plates were visualized by exposure to ultraviolet light (UV). Products were purified by flash column chromatography on 230–400 mesh silica gel, SiO_2.^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian INOVA-500 spectrometer (500 MHz, ^{1}H), and were referenced to the residual peaks of DMSO-d_6 at 2.50 ppm (^{1}H NMR) and DMSO-d_6 at 39.52 ppm (^{13}C NMR). Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet dd = doublet of doublet, and m = multiplet), coupling constant (Hz), and integration. IR spectra were recorded on Bruker Tensor 27 Equinox 55 infrared spectrophotometer (ν in cm^{-1}). Mass spectra were obtained using an Agilent 5975C VL MSD (Ion source: EI^+, 70 eV, 230 °C). GC-MS analysis were performed on an Agilent GC 7890A (Column: Rtx 5 MS, length = 30 m, I.D = 0.250 mm, Film thickness = 25 µm) and 5975C VL MSD (Ion source: EI^+, 70 eV, 230 °C). Temperature program: initial temperature = 45 ºC, initial time = 3 min, program rate = 10 ºC/min, final temperature = 270 ºC, final time = 30 min, split ratio = 100 mL/min and flow rate = 1 mL/min. Conditions: 1. injection port temperature: 230 ºC, 2. ion source temperature: 230 ºC, 3. carrier gas: He 99.999%, 4. sample volume: 0.3 µL. Elemental analysis (CHNS) was recorded on a Thermo Finnigan Flash EA 1112 elemental analyzer. Melting points were recorded with a micro melting point apparatus.

2. Experimental Section

2.1 General procedure for the synthesis of starting materials

Amides were prepared according to literature procedures from 8-aminoquinoline and acyl chlorides (Procedure A, C)[1] or carboxylic acids (Procedure B).[2]

2.1.1 Synthesis of *N*-(quinolin-8-yl)amides

Procedure A:

To a stirred solution of a carboxylic acid (5 mmol) and DMF (5 drops) in CH_2Cl_2 (10 mL), $(COCl)_2$ (1.5 equiv) was added dropwise. The solution was magnetically stirred at room temperature for 1-2 h. The solvent was then removed by evaporation under reduced pressure, and the resulting residue was dissolved in CH_2Cl_2 (10 mL). After that to a solution of 8-aminoquinoline (2.5 mmol) and *N*,*N*-dimethyl-4-aminopyridine (DMAP) (0.25 mmol) in CH_2Cl_2 (10 mL), NEt_3 (5 mmol) was added, and the resulting solution was cooled to 0 °C, acyl chloride (5 mmol) was added dropwise and the reaction mixture was stirred at room temperature overnight. The mixture was washed with saturated aqueous $NaHCO_3$ (5 mL), and CH_2Cl_2 (3×10 mL). The combined organic phase was washed with aqueous 1 M HCl (10 mL) and was dried over Na_2SO_4. After filtration and evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc) to give the desired product.

2.1.2 Synthesis of 2-methoxy-*N*-(quinolin-8-yl)benzamide and *N*-(quinolin-8-yl)isonicotinamide

Procedure B:

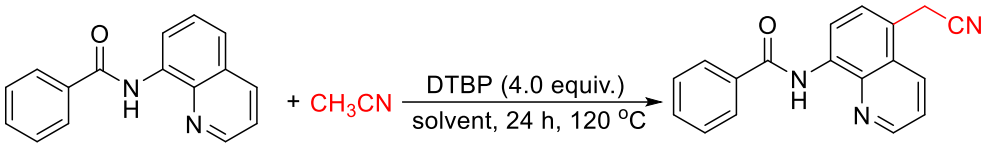
Acid (5 mmol) and NEt_3 (5 mmol) were dissolved in CH_2Cl_2 (10 mL), the flask was flushed with nitrogen and the resulting mixture was cooled to 0 °C. Ethyl chloroformate (10 mmol) was added dropwise and the solution was stirred at 0 °C for 1-2 h followed by dropwise addition of 8-aminoquinoline (2.5 mmol) solution in CH_2Cl_2 (10 mL). The resulting mixture was warmed up to room temperature and stirred overnight. The mixture was washed with saturated aqueous $NaHCO_3$ (5 mL), and CH_2Cl_2 (3×10 mL). The combined organic phase was washed with aqueous 1 M HCl (10 mL) and was dried over Na_2SO_4. After filtration and evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc) to give the desired product.

2.1.3 Synthesis of *N*-(quinolin-8-yl)sulfonamides

Procedure C:

To a stirred solution of 8-aminoquinoline (2.5 mmol) and DMAP (0.25 mmol) in CH_2Cl_2 (10 mL), NEt_3 (5 mmol) was added and the resulting solution was cooled to 0 °C. Sulfonyl chloride (5 mmol) in CH_2Cl_2 was added dropwise to the mixture and the reaction was stirred at room temperature overnight. The mixture was washed with saturated aqueous $NaHCO_3$ (5 mL), and CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with aqueous 1 M HCl (10 mL) and was dried over Na_2SO_4. After filtration and evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc) to give the desired product.

2.2 Optimization of solvent

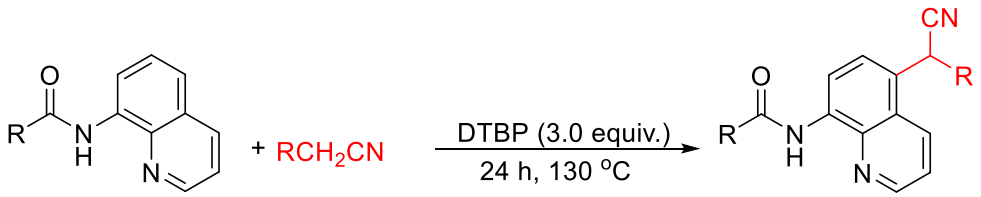


1a **2a** **3a**

Entry	Solvent	Yield (%)
1	Dimethyl sulfoxide	49
2	Methanol	33
3	Toluene	26
4	1,2-Dichloroethane	36
5	Chlorobenzene	22
6	Acetonitrile	64

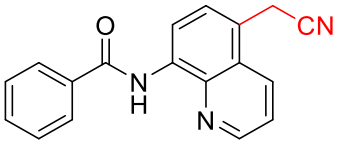
[a] Reaction conditions: **1a** (0.1 mmol), acetonitrile **2a** (10.0 equiv.), DTBP (4.0 equiv.), solvent (1 mL), stirred at 120 °C for 24 h.

2.3 General procedure for C5-cyanoalkylation of 8-aminoquinolineamides



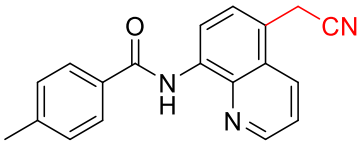
1 **2** **3**

In a 10 mL schlenk tube, the amide **1** (0.1 mmol), DTBP (3.0 equiv.) and alkylnitrile **2** (1 mL) was added. The tube was sealed and the resulting solution was heated in an oil bath at 130 °C with vigorous stirring for 24 h. Then the reaction mixture was cooled to room temperature. The mixture was poured into water (5 mL) and extracted with ethyl acetate (3 × 10 mL), and the combined organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under vacuum. The residue was purified by column chromatography on silica gel using petroleum ether/EtOAc (4:1) to give the desired product **3**.



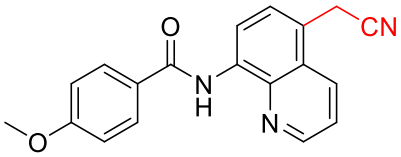
***N*-(5-(cyanomethyl)quinolin-8-yl)benzamide (3a)**

yellow solid, Yield: 82%, m.p. 131-133 °C; IR cm^{-1}: 3362, 2909, 2250, 1675, 1521, 1387, 1329, 1263, 1160, 1048, 900, 828, 788, 708, 651; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.51 (s, 2H), 7.63 (t, *J* = 7.2 Hz, 2H), 7.67 (d, *J* = 7.2 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.82 (dd, *J* = 8.5, 4.2 Hz, 1H), 8.04 (d, *J* = 7.2 Hz, 2H), 8.60 (d, *J* = 8.5 Hz, 1H), 8.72 (d, *J* = 7.9 Hz, 1H), 9.05 (d, *J* = 3.0 Hz, 1H), 10.71 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.69, 116.05, 118.89, 122.15, 122.69, 125.77, 127.05, 127.34, 129.06, 132.22, 132.95, 134.17, 134.31, 138.52, 149.31, 164.56. EI-MS *m/z* (%): 287 (M^+, 32), 105 (100), 43 (79), 77 (60), 138 (40), 167 (4), 210 (4). $C_{18}H_{13}N_3O$ (287): calcd. C, 75.25; H, 4.56; N, 14.63; found C, 75.61; H, 4.94; N, 14.23.



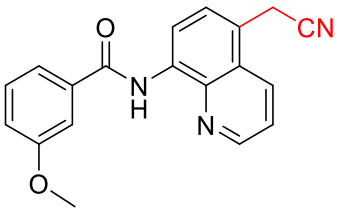
***N*-(5-(cyanomethyl)quinolin-8-yl)-4-methylbenzamide (3b)**

yellow solid, Yield: 79%, m.p. 157-159 °C; IR cm^{-1}: 3340, 2906, 2249, 1658, 1607, 1499, 1390, 1255, 1178, 1025, 832, 788, 758, 673; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.36 (s, 3H), 4.04 (s, 2H), 7.17 (d, *J* = 13.7 Hz, 2H), 7.62 (d, *J* = 7.2 Hz, 2H), 7.67 (m, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 8.3, 1H), 8.44 (d, *J* = 8.3 Hz, 1H), 8.63 (d, *J* = 7.6 Hz, 1H), 8.87 (d, *J* = 4.2 Hz, 1H), 10.22 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 18.91, 19.70, 116.26, 118.89, 122.32, 122.60, 125.78, 127.32, 128.14, 132.83, 133.69, 134.06, 135.09, 138.27, 138.38, 149.27, 168.09. EI-MS *m/z* (%): 301 (M^+, 3), 119 (100), 91 (59), 133 (54), 77 (34), 103 (27), 210 (10). $C_{19}H_{15}N_3O$ (301): calcd. C, 75.73; H, 5.02; N, 13.94; found C, 75.96; H, 5.41; N, 13.55.



***N*-(5-(cyanomethyl)quinolin-8-yl)-4-methoxybenzamide (3c)**

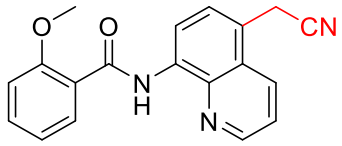
yellow solid, Yield: 91%, m.p. 174-175 °C; IR cm^{-1}: 3375, 2221, 1659, 1531, 1392, 1316, 1259, 1173, 996, 828, 761, 660; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.87 (s, 3H), 4.49 (s, 2H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.79 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 2H), 8.57 (d, *J* = 8.8 Hz, 1H), 8.69 (d, *J* = 7.9 Hz, 1H), 9.03 (d, *J* = 4.4 Hz, 1H), 10.60 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.67, 55.50, 114.26, 115.70, 118.89, 121.70, 122.61, 125.73, 126.39, 127.34, 128.97, 132.88, 134.33, 138.42, 149.17, 162.32, 163.97. EI-MS *m/z* (%): 317 (M^+, 55), 135 (100), 77 (54), 92 (45), 136 (31), 107 (21), 182 (5). $C_{19}H_{15}N_3O_2$ (317): calcd. C, 71.91; H, 4.76; N, 13.24; found C, 71.65; H, 4.52; N 13.50.



***N*-(5-(cyanomethyl)quinolin-8-yl)-3-methoxybenzamide (3d)**

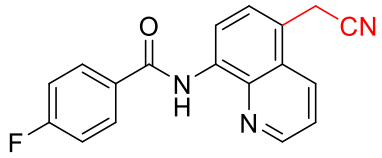
yellow solid, Yield: 79%, m.p. 179-182 °C; IR cm^{-1}: 3262, 2939, 2247, 1656, 1598, 1525, 1379, 1289, 1235, 1162, 1019, 908, 836, 748, 684; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.23 (s, 3H), 4.49 (s, 2H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.63 (t, *J* = 8.5 Hz, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.80 (dd, *J* = 8.5, 4.1 Hz, 1H), 8.17 (d, *J* = 9.2 Hz, 1H), 8.57 (d, *J* = 8.6 Hz, 1H), 8.86 (d, *J* = 7.9 Hz, 1H), 9.11 (d, *J* = 3.0 Hz, 1H), 12.44 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.67, 56.48, 112.66, 115.71, 118.64, 121.14, 121.45, 122.50, 125.72, 127.48,

131.50, 132.67, 132.99, 133.87, 135.23, 138.44, 149.30, 157.48, 162.59. EI-MS *m/z* (%): 317 (M^+, 23), 135 (100), 149 (94), 77 (57), 43 (41), 167 (41), 105 (18). $C_{19}H_{15}N_3O_2$ (317): calcd. C, 71.91; H, 4.76; N, 13.24; found C, 71.73; H, 4.52; N, 13.53.



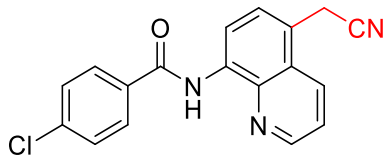
_N_-(5-(cyanomethyl)quinolin-8-yl)-2-methoxybenzamide (3e)

yellow solid, Yield: 72%, m.p. 168-170 °C; IR cm^{-1}: 3387, 2256, 1653, 1526, 1385, 1326, 1289, 1240, 992, 825, 759, 684; ^1H NMR (500 MHz, DMSO-d_6) δ 4.22 (s, 3H), 4.49 (s, 2H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.79 (dd, *J* = 8.4, 3.7 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 8.56 (d, *J* = 8.5 Hz, 1H), 8.86 (d, *J* = 8.0 Hz, 1H), 9.10 (d, *J* = 3.9 Hz, 1H), 12.43 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.66, 56.54, 112.73, 115.74, 118.94, 120.99, 121.18, 121.53, 122.56, 125.76, 127.52, 131.51, 132.75, 133.92, 135.22, 138.46, 149.38, 157.50, 162.62. EI-MS *m/z* (%): 317 (M^+, 13), 135 (100), 77 (62), 92 (33), 105 (32), 136 (19), 152 (12). $C_{19}H_{15}N_3O_2$ (317): calcd. C, 71.91; H, 4.76; N, 13.24; found C, 71.65; H, 4.84; N, 13.10.



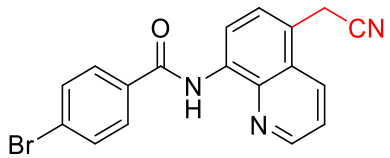
_N_-(5-(cyanomethyl)quinolin-8-yl)-4-fluorobenzamide (3f)

yellow solid, Yield: 83%, m.p. 144-145 °C; IR cm^{-1}: 3332, 2976, 2250, 2001, 1677, 1598, 1414, 1231, 1059, 798, 679; ^1H NMR (500 MHz, DMSO-d_6) δ 4.51 (s, 2H), 7.45 (t, *J* = 8.8 Hz, 2H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.81 (dd, *J* = 8.5, 4.2 Hz, 1H), 8.11 (dd, *J* = 8.7, 5.5 Hz, 2H), 8.59 (d, *J* = 8.5 Hz, 1H), 8.68 (d, *J* = 7.9 Hz, 1H), 9.04 (d, *J* = 4.1 Hz, 1H), 10.67 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.70, 115.92, 116.09, 116.35, 118.88, 122.30, 122.67, 125.78, 127.29, 129.88, 129.96, 132.92, 134.14, 138.63, 149.31, 163.61. EI-MS *m/z* (%): 305 (M^+, 43), 123 (100), 95 (72), 75 (28), 142 (17), 155 (17), 182 (7). $C_{18}H_{12}FN_3O$ (305): calcd. C, 70.81; H, 3.96; N, 13.76; found C, 70.98; H, 4.35; N, 13.47.



4-chloro-_N_-(5-(cyanomethyl)quinolin-8-yl)benzamide (3g)

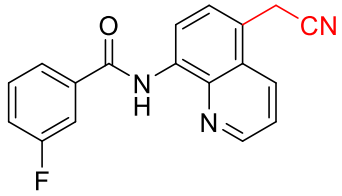
yellow solid, Yield: 77%, m.p. 171-173 °C; IR cm^{-1}: 3335, 2916, 2249, 1671, 1516, 1381, 1323, 1260, 1103, 1039, 901, 833, 791; ^1H NMR (500 MHz, DMSO-d_6) δ 4.51 (s, 2H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 7.9 Hz, 2H), 8.04 (dd, *J* = 8.5, 4.3 Hz, 1H), 8.57 (d, *J* = 8.0 Hz, 1H), 8.67 (d, *J* = 8.7 Hz, 1H), 8.96 (d, *J* = 2.7 Hz, 1H), 10.29 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.71, 116.26, 118.87, 122.62, 125.75, 126.05, 127.24, 128.92, 129.05. 130.76, 132.84, 134.22, 134.94, 138.63, 149.26, 166.32. EI-MS *m/z* (%): 321 (M^+ ^{35}Cl, 5), 323 (M^+ ^{37}Cl, 3), 139 (100), 153 (73), 111 (53), 167 (51), 182 (9), 210 (5). $C_{18}H_{12}ClN_3O$ (321): calcd. C, 67.19; H, 3.76; N, 13.06; found C, 67.45; H, 3.92; N, 12.90.



4-bromo-_N_-(5-(cyanomethyl)quinolin-8-yl)benzamide (3h)

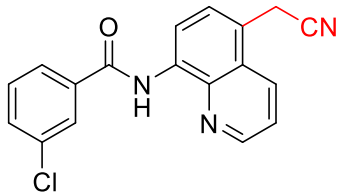
yellow solid, Yield: 71%, m.p. 177-179 °C; IR cm^{-1}: 3389, 2927, 2250, 1723, 1670, 1520, 1381, 1269, 1018, 823, 759, 700; ^1H NMR (500 MHz, DMSO-d_6) δ 4.52 (s, 2H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.63 (d, *J* = 6.8 Hz, 1H), 7.77

(d, *J* = 9.6 Hz, 2H), 8.04 (d, *J* = 7.4 Hz, 2H), 8.58 (d, *J* = 7.7 Hz, 1H), 8.72 (d, *J* = 8.9 Hz, 1H), 8.96 (d, *J* = 3.8 Hz, 1H), 10.37 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.76, 115.47, 115.78, 118.07, 119.41, 121.59, 122.37, 125.64, 126.82, 127.36, 128.77, 132.67, 134.25, 138.32, 148.83, 173.19. EI-MS *m/z* (%): 365 (M^+ ^{79}Br, 4), 367 (M^+ ^{81}Br, 4), 167 (100), 155 (83), 286 (71), 183 (54), 210 (43), 182 (33). $C_{18}H_{12}BrN_3O$ (365): calcd. C, 59.04; H, 3.30; N, 11.47; found C, 59.41; H, 3.36; N, 11.49.



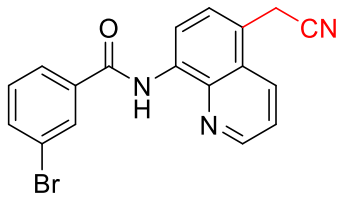
_N_-(5-(cyanomethyl)quinolin-8-yl)-3-fluorobenzamide (3i)

yellow solid, Yield: 88%, m.p. 166-168 °C; IR cm^{-1}: 3335, 2907, 2309, 1659, 1583, 1526, 1391, 1329, 1264, 1155, 1073, 860, 823, 746, 674; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.51 (s, 2H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.65-7.70 (m, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.80 (dd, *J* = 8.4, 4.6 Hz, 2H), 7.88 (d, *J* = 7.7 Hz, 1H), 8.59 (d, *J* = 8.4 Hz, 1H), 8.66 (d, *J* = 7.9 Hz, 1H), 9.05 (d, *J* = 3.8 Hz, 1H), 10.70 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.73, 114.13, 114.31, 116.68, 118.88, 119.04, 119.21, 122.58, 122.70, 123.11, 123.13, 125.79, 127.26, 131.23, 131.30, 132.91, 134.00, 138.72, 149.39, 161.27, 163.22, 163.43. EI-MS *m/z* (%): 305 (M^+, 30), 123 (100), 95 (87), 178 (45), 75 (32), 210 (26), 43 (13). $C_{18}H_{12}FN_3O$ (305): calcd. C, 70.81; H, 3.96; N, 13.76; found C, 70.88; H, 4.07; N, 13.82.



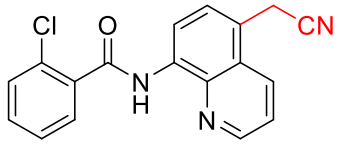
3-chloro-_N_-(5-(cyanomethyl)quinolin-8-yl)benzamide (3j)

yellow solid, Yield: 69%, m.p. 178-181 °C; IR cm^{-1}: 3335, 2928, 2250, 1671, 1571, 1524, 1386, 1254, 1166, 1087, 1024, 908, 836, 794, 738, 686; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.52 (s, 2H), 7.65 (t, *J* = 7.9 Hz, 1H), 7.70-7.76 (m, 2H), 7.81 (dd, *J* = 8.4, 4.0 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 8.05 (s, 1H), 8.59 (d, *J* = 8.7 Hz, 1H), 8.65 (d, *J* = 8.1 Hz, 1H), 9.05 (d, *J* = 4.0 Hz, 1H), 10.71 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.75, 116.62, 118.82, 122.60, 122.98, 125.63, 127.87, 128.82, 129.37, 130.56, 130.87, 131.91, 132.64, 133.77, 133.97, 138.66, 149.27, 166.06. EI-MS *m/z* (%): 321 (M^+ ^{35}Cl, 31), (M^+ ^{37}Cl, 11), 139 (100), 111 (66), 141 (37), 75 (31), 155 (20), 210 (18). $C_{18}H_{12}ClN_3O$ (321): calcd. C, 67.19; H, 3.76; N, 13.06; found C, 67.24; H, 4.01; N, 13.26.



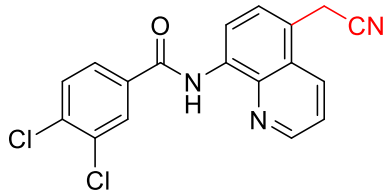
3-bromo-_N_-(5-(cyanomethyl)quinolin-8-yl)benzamide (3k)

yellow solid, Yield: 82%, m.p. 170-172 °C; IR cm^{-1}: 3335, 2952, 2597, 2250, 1667, 1526, 1391, 1299, 1252, 1057, 996, 937, 835, 791, 740, 688; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.50 (s, 2H), 7.56 (t, *J* = 7.9 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.78 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.84 (d, *J* = 7.7, 1H), 8.00 (d, *J* = 7.4 Hz, 1H), 8.15 (s, 1H), 8.56 (d, *J* = 8.4 Hz, 1H), 8.62 (d, *J* = 7.9 Hz, 1H), 9.02 (d, *J* = 2.8 Hz, 1H), 10.65 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.72, 116.75, 118.83, 122.17, 122.53, 122.60, 125.73, 126.03, 127.16, 129.97, 131.10, 132.82, 133.95, 134.81, 136.53, 138.70, 149.31, 163.19. EI-MS *m/z* (%): 365 (M^+ ^{79}Br, 22), 367 (M^+ ^{81}Br, 21), 183 (100), 185 (94), 155 (90), 157 (63), 76 (44), 210 (26). $C_{18}H_{12}BrN_3O$ (365): calcd. C, 59.04; H, 3.30; N, 11.47; found C, 59.25; H, 3.37; N, 11.48.



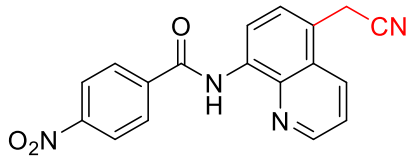
2-chloro-*N*-(5-(cyanomethyl)quinolin-8-yl)benzamide (3l)

yellow solid, Yield: 66%, m.p. 177-180 °C; IR cm^{-1}: 3355, 2903, 2250, 1672, 1590, 1522, 1387, 1327, 1232, 1121, 1041, 830, 786, 745, 661; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.52 (s, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.79 (dd, *J* = 8.3, 4.5 Hz, 2H), 8.58 (d, 8.6 Hz, 1H), 8.72 (d, *J* = 7.4 Hz, 1H), 8.97 (d, *J* = 4.1 Hz, 1H), 10.50 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.80, 116.24, 118.85, 122.67, 125.78, 127.65, 127.84, 129.32, 129.62, 130.18, 131.62, 131.98, 132.82, 134.12, 135.62, 138.35, 149.29, 166.82. EI-MS *m/z* (%): 321 (M^{+} ^{35}Cl, 68), 323 (M^{+} ^{37}Cl, 26), 139 (100), 141 (83), 111 (57), 140 (29), 113 (20), 75 (23). $C_{18}H_{12}ClN_3O$ (321): calcd. C, 67.19; H, 3.76; N, 13.06; found C, 67.02; H, 3.61; N, 12.66.



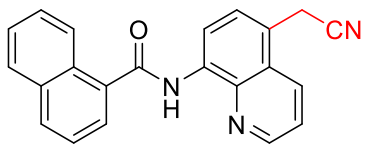
3,4-dichloro-*N*-(5-(cyanomethyl)quinolin-8-yl)benzamide (3m)

yellow solid, Yield: 55%, m.p. 166-169 °C; IR cm^{-1}: 3344, 2925, 2856, 2246, 1670, 1515, 1393, 1325, 1248, 1051, 946, 794, 669; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.52 (s, 2H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.79 (d, *J* = 9.3 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 8.24 (s, 1H), 8.55-8.64 (m, 2H), 9.04 (d, *J* = 2.8 Hz, 1H), 10.73 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.75, 117.28, 118.86, 122.64, 122.89, 127.16, 127.34, 129.41, 129.59, 130.15, 131.18, 131.80, 132.87, 133.95, 134.89, 138.93, 149.40, 162.67. EI-MS *m/z* (%): 355 (M^{+} $^{35}Cl_2$, 23), 357 (M^{+} ^{35}Cl, ^{37}Cl, 15), 359 (M^{+} $^{37}Cl_2$, 3), 173 (100), 175 (86), 145 (51), 147 (34), 109 (21), 210 (19). $C_{18}H_{11}C_{l2}N_3O$ (355): calcd. C, 60.69; H, 3.11; N, 11.80; found C, 60.63; H, 3.22; N, 11.89.



***N*-(5-(cyanomethyl)quinolin-8-yl)-4-nitrobenzamide (3n)**

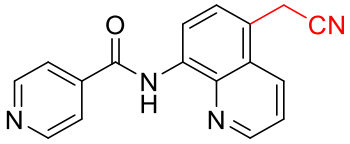
yellow solid, Yield: 67%, m.p. 136-138 °C; IR cm^{-1}: 2919, 2852, 2254, 1684, 1555, 1453, 1259, 1095, 903, 808, 725, 657; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.53 (s, 2H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.81 (dd, *J* = 8.6, 4.2 Hz, 1H), 8.27 (d, *J* = 8.8 Hz, 2H), 8.43 (d, *J* = 8.9 Hz, 2H), 8.60 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.68 (d, *J* = 7.9 Hz, 1H), 9.05 (d, *J* = 3.7 Hz, 1H), 10.84 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.77, 117.10, 122.73, 123.00, 123.64, 124.08, 127.22, 128.84, 132.94, 133.90, 136.06, 138.83, 139.93, 149.44, 150.24. 163.23. EI-MS *m/z* (%): 332 (M^{+}, 55), 150 (100), 210 (65), 104 (56), 164 (52), 76 (36), 183 (14). $C_{18}H_{12}N_4O_3$ (332): calcd. C, 65.06; H, 3.64; N, 16.86; found C, 65.33; H, 3.82; N, 16.92.



***N*-(5-(cyanomethyl)quinolin-8-yl)-1-naphthamide (3o)**

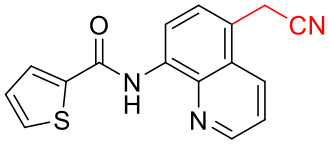
Cream solid, Yield: 80%, m.p. 153-156 °C; IR cm^{-1}: 3353, 2923, 2241, 1670, 1590, 1520, 1382, 1325, 1252, 1130, 1023, 909, 778, 662; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.53 (s, 2H), 7.61-7.64 (m, 2H), 7.65-7.68 (m, 1H), 7.77 (t, *J* = 7.7 Hz, 2H), 7.98 (d, *J* = 7.0 Hz, 1H), 8.04-8.08 (m, 1H), 8.15 (d, *J* = 8.2 Hz, 1H), 8.36-8.40 (m, 1H), 8.59 (d, *J* = 8.6 Hz, 1H), 8.81 (d, *J* = 7.8 Hz, 1H), 8.94 (d, *J* = 4.1 Hz, 1H), 10.48 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.74, 116.21, 118.89, 122.34, 122.61, 124.98, 125.18, 125.56, 125.76, 126.57, 127.31, 127.33, 128.49, 129.57, 131.08, 132.83, 133.37, 133.83, 134.39, 138.41, 149.22, 166.79. EI-MS *m/z* (%): 337 (M^{+}, 69),

155 (100), 127 (79), 156 (25), 169 (24), 126 (18), 210 (6). $C_{22}H_{15}N_3O$ (337): calcd. C, 78.32; H, 4.48; N, 12.46; found C, 78.34; H, 4.45; N, 12.40.



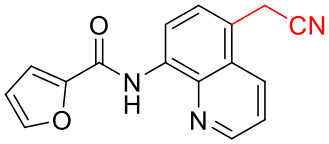
***N*-(5-(cyanomethyl)quinolin-8-yl)isonicotinamide (3p)**

orange solid, Yield: 71%, m.p. 189-191 °C; IR cm^{-1}: 3393, 2251, 1659, 1529, 1386, 1261, 997, 824, 758, 639; ^1H NMR (500 MHz, DMSO-d_6) δ 4.55 (s, 2H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.68 (dd, *J* = 8.2, 4.4 Hz, 1H), 7.95 (d, *J* = 5.8 Hz, 2H), 8.47 (d, *J* = 8.3 Hz, 1H), 8.68 (d, *J* = 7.6 Hz, 1H), 8.86 (d, *J* = 5.8 Hz, 2H), 8.98 (d, *J* = 4.1 Hz, 1H), 10.77 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 25.40, 116.52, 117.61, 121.09, 122.41, 123.16, 126.94, 127.87, 133.56, 136.77, 138.54, 141.49, 149.35, 150.66, 163.17. EI-MS *m/z* (%): 288 (M^+, 29), 106 (100), 78 (43), 52 (14), 262 (3), 210 (2), 182 (2). $C_{17}H_{12}N_4O$ (288): calcd. C, 70.82; H, 4.20; N, 19.43; found C, 71.01; H, 4.49; N, 19.31.



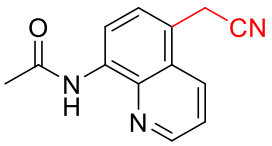
***N*-(5-(cyanomethyl)quinolin-8-yl)thiophene-2-carboxamide (3q)**

yellow solid, Yield: 68%, m.p. 143-145 °C; IR cm^{-1}: 3361, 3098, 2903, 2250, 1727, 1649, 1525, 1413, 1393, 1329, 1240, 1105, 1049, 827, 787, 721, 638; ^1H NMR (500 MHz, DMSO-d_6) δ 4.51 (s, 2H), 7.26-7.32 (m, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.81 (dd, *J* = 8.6, 4.2 Hz, 1H), 7.95 (d, *J* = 4.6 Hz, 1H), 8.00 (d, *J* = 3.6 Hz, 1H), 8.57-8.60 (m, 2H), 9.05 (d, *J* = 4.2 Hz, 1H), 10.59 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.71, 116.45, 118.85, 122.26, 122.67, 127.28, 128.18, 128.18, 128.52, 129.30, 132.46, 132.89, 134.65, 139.01, 149.32, 162.90. EI-MS *m/z* (%): 293 (M^+, 79), 111 (100), 125 (45), 83 (16), 142 (11), 182 (7), 210 (6). $C_{16}H_{11}N_3OS$ (293): calcd. C, 65.51; H, 3.78; N, 14.32; found C, 65.73; H, 3.80; N, 14.36.



***N*-(5-(cyanomethyl)quinolin-8-yl)furan-2-carboxamide (3r)**

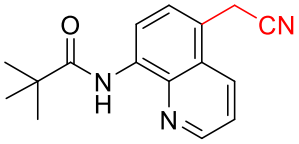
yellow solid, Yield: 75%, m.p. 141-143 °C; IR cm^{-1}: 3320, 2969, 2309, 2209, 1667, 1519, 1380, 1322, 1155, 1077, 1002, 823, 788; ^1H NMR (500 MHz, DMSO-d_6) δ 4.49 (s, 2H), 6.69 (d, *J* = 3.0 Hz, 1H), 7.61-7.65 (m, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.81 (dd, *J* = 8.4, 4.1 Hz, 1H), 8.06 (d, *J* = 1.3 Hz, 1H), 8.45 (d, *J* = 8.1 Hz, 1H), 8.58 (d, *J* = 8.3 Hz, 1H), 9.05 (d, *J* = 3.9 Hz, 1H), 10.68 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.67, 112.86, 115.71, 116.64, 118.84, 122.08, 122.45, 127.03, 127.81, 132.96, 133.39, 136.79, 146.21, 147.69, 149.27, 155.39. MS (EI): 277 (M^+, 55), 95 (100), 209 (82), 43 (26), 109 (21), 67 (13), 182 (7). $C_{16}H_{11}N_3O_2$ (277): calcd. C, 69.31; H, 4.00; N, 15.15; found C, 69.38; H, 4.36; N, 15.19.



***N*-(5-(cyanomethyl)quinolin-8-yl)acetamide (3s)**

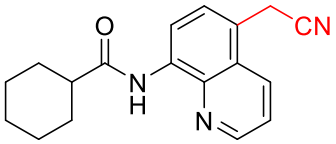
Cream solid, Yield: 79%, m.p. 99-101 °C; IR cm^{-1}: 3346, 2926, 2852, 2247, 1675, 1519, 1450, 1326, 1180, 941, 817, 674; ^1H NMR (500 MHz, DMSO-d_6) δ 2.28 (s, 3H), 4.44 (s, 2H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.73 (dd, *J* = 8.5, 4.2 Hz, 1H), 8.51 (d, *J* = 8.6 Hz, 1H), 8.58 (d, *J* = 8.0 Hz, 1H), 8.97 (d, *J* = 4.2 Hz, 1H), 10.13 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.64, 24.54, 115.97, 118.90, 121.29, 122.34, 125.67, 127.25, 132.58, 134.85, 138.27,

148.81, 169.00. EI-MS *m/z* (%): 225 (M^+, 28), 183 (100), 43 (77), 182 (55), 57 (43), 167 (25), 210 (13). $C_{13}H_{11}N_3O$ (225): calcd. C, 69.32; H, 4.92; N, 18.66; found C, 69.37; H, 5.11; N, 18.69.



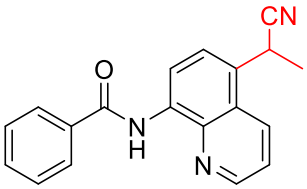
***N*-(5-(cyanomethyl)quinolin-8-yl)pivalamide (3t)**

Light yellow solid, Yield: 74%, m.p. 116-119 °C; IR cm^{-1}: 3361, 2963, 2255, 1730, 1676, 1521, 1380, 1323, 1148, 1030, 927, 832, 787, 655; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.33 (s, 9H), 4.45 (s, 2H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.75 (dd, *J* = 8.5, 4.5 Hz, 1H), 8.53 (d, *J* = 8.0 Hz, 1H), 8.61 (d, *J* = 7.9 Hz, 1H), 8.98 (d, *J* = 2.2 Hz, 1H), 10.18 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.63, 27.24, 37.68, 114.95, 118.86, 121.29, 122.53, 125.62, 127.31, 132.85, 134.24, 138.17, 149.11, 176.10. EI-MS *m/z* (%): 267 (M^+, 23), 57 (100), 210 (86), 41 (75), 266 (48), 182 (42), 224 (39). $C_{16}H_{17}N_3O$ (267): calcd. C, 71.89; H, 6.41; N, 15.72; found C, 71.98; H, 6.48; N, 16.10.



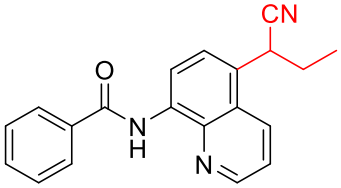
***N*-(5-(cyanomethyl)quinolin-8-yl)cyclohexanecarboxamide (3u)**

Cream solid, Yield: 93%, m.p. 128-131 °C; IR cm^{-1}: 3344, 2927, 2853, 2250, 1674, 1519, 1450, 1390, 1323, 1255, 942, 845, 790, 671; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.19-1.24 (m, 1H), 1.29-1.37 (m, 2H), 1.42-1.50 (m, 2H), 1.64-1.67 (m, 1H), 1.74-1.77 (m, 2H), 1.90-1.93 (m, 2H), 2.63-2.68 (m, 1H), 4.45 (s, 2H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.75 (dd, *J* = 8.5, 4.2 Hz, 1H), 8.52 (d, *J* = 8.5 Hz, 1H), 8.60 (d, *J* = 8.0 Hz, 1H), 8.99 (d, *J* = 4.0 Hz, 1H), 10.05 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.65, 25.10, 25.39, 29.31, 45.05, 115.65, 118.88, 121.21, 122.38, 125.66, 127.26, 132.66, 134.68, 138.26, 148.86, 174.37. EI-MS *m/z* (%): 293 (M^+, 36), 183 (100), 210 (91), 182 (44), 55 (44), 83 (30), 155 (15). $C_{18}H_{19}N_3O$ (293): calcd. C, 73.69; H, 6.53; N, 14.32; found C, 73.58; H, 6.88; N 14.29.



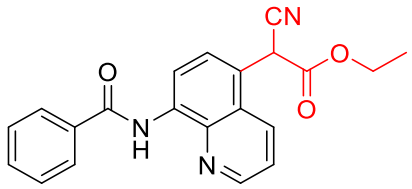
***N*-(5-(1-cyanoethyl)quinolin-8-yl)benzamide (4a)**

Light yellow solid, Yield: 57%, m.p. 127-129 °C; IR cm^{-1}: 3316, 3004, 2246, 1647, 1525, 1384, 1312, 1169, 1039, 940, 876, 807, 722, 635; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.69 (d, *J* = 7.1 Hz, 3H), 5.08 (q, *J* = 7.1 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 6.5 Hz, 1H), 7.63 (t, *J* = 7.4 Hz, 2H), 8.04 (d, *J* = 7.0 Hz, 2H), 8.69 (d, *J* = 8.9 Hz, 1H), 8.76 (d, *J* = 8.0 Hz, 1H), 9.04 (d, *J* = 4.1 Hz, 1H), 10.73 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 15.75, 28.86, 116.05, 120.32, 122.71, 125.44, 127.45, 128.17, 128.43, 128.86, 129.05, 131.91, 132.23, 132.48, 138.48, 149.21, 164.54. EI-MS *m/z* (%): 301 (M^+, 39), 105 (100), 77 (84), 51 (23), 142 (6), 224 (5), 180 (4). $C_{19}H_{15}N_3O$ (301): calcd. C, 75.73; H, 5.02; N, 13.94; found C, 75.87; H, 4.92; N, 14.03.



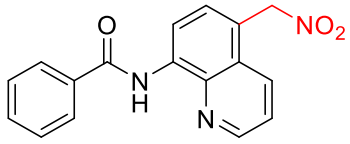
***N*-(5-(1-cyanopropyl)quinolin-8-yl)benzamide (4b)**

Light yellow solid, Yield: 26%, m.p. 119-121 °C; IR cm^{-1}: 3333, 2967, 2243, 1666, 1584, 1521, 1384, 1319, 1263, 1025, 896, 836, 791, 699; ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.95 (t, *J* = 7.3 Hz, 3H), 2.10-2.13 (m, 2H), 4.65 (m, 1H), 7.51 (d, *J* = 7.7 Hz, 2H), 7.71 (dd, *J* = 8.6, 4.5 Hz, 1H), 7.84-7.91 (m, 2H), 8.04 (d, *J* = 6.1 Hz, 3H), 8.36 (d, *J* = 8.1 Hz, 1H), 8.87 (d, *J* = 3.7 Hz, 1H), 10.19 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 10.05, 20.84, 29.56, 116.14, 120.90, 122.27, 123.72, 127.03, 127.49, 127.81, 128.39, 128.43, 129.03, 132.12, 135.97, 148.75, 150.02, 164.41. EI-MS *m/z* (%): 315 (M^+, 35), 105 (100), 275 (50), 77 (47), 238 (6), 142 (4), 290 (3). $C_{20}H_{17}N_3O$ (315): calcd. C, 76.17; H, 5.43; N, 13.32; found C, 75.88; H, 5.82; N, 12.93.



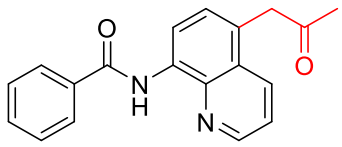
Ethyl 2-(8-benzamidoquinolin-5-yl)-2-cyanoacetate (4c)

yellow solid, Yield: 34%, m.p. 154-167 °C; IR cm^{-1}: 3336, 2982, 2231, 1743, 1674, 1522, 1378, 1227, 1095, 1015, 899, 849, 791, 696; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.23 (t, *J* = 7.1 Hz, 3H), 4.41 (q, *J* = 7.1 Hz, 2H), 6.29 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.60-7.66 (m, 2H), 7.68 (d, *J* = 6.4 Hz, 1H), 7.89 (dd, *J* = 8.9, 4.3 Hz, 1H), 8.05 (d, *J* = 7.3 Hz, 2H), 8.80 (d, *J* = 8.4 Hz, 1H), 8.94 (d, *J* = 8.7 Hz, 1H), 9.13 (d, *J* = 3.9 Hz, 1H), 10.86 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 14.37, 43.30, 64.01, 115.90, 120.91, 123.01, 123.57, 125.89, 127.09, 127.82, 128.40, 129.43, 131.54, 134.45, 136.57, 149.43, 149.99, 162.25, 163.57. EI-MS *m/z* (%): 359 (M^+, 10), 105 (100), 358 (39), 77 (26), 106 (8), 286 (2), 261 (1). $C_{21}H_{17}N_3O_3$ (359): calcd. C, 70.18; H, 4.77; N, 11.69; O; found C, 70.24; H, 4.93; N, 12.03.



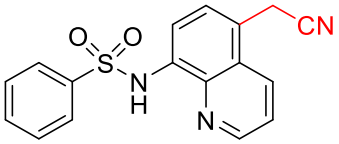
***N*-(5-(nitromethyl)quinolin-8-yl)benzamide (4f)**

Light yellow solid, Yield: 88%, m.p. 179-180 °C; IR cm^{-1}: 3366, 2915, 1667, 1525, 1370, 1322, 1261, 1186, 1069, 893, 830, 789, 695, 615; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.29 (s, 2H), 7.63 (t, *J* = 7.3 Hz, 2H), 7.66-7.70 (m, 1H), 7.78 (dd, *J* = 8.5, 4.1 Hz, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 8.04 (d, *J* = 7.3 Hz, 2H), 8.64 (d, *J* = 8.5 Hz, 1H), 8.76 (d, *J* = 7.9 Hz, 1H), 9.03 (d, *J* = 3.9 Hz, 1H), 10.78 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 75.76, 115.45, 121.35, 123.02, 127.03, 127.07, 129.06, 131.70, 132.30, 133. 25, 134.22, 135.71, 138.17, 149.23, 164.65. EI-MS *m/z* (%): 307 (M^+, 1), 105 (100), 261 (88), 77 (38), 262 (21), 155 (15), 156 (6). $C_{17}H_{13}N_3O_3$ (307): calcd. C, 66.44; H, 4.26; N, 13.67; found C, 66.02; H, 4.71; N, 14.05.



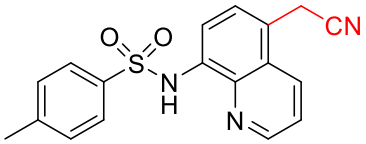
***N*-(5-(2-oxopropyl)quinolin-8-yl)benzamide (4g)**

Cream solid, Yield: 73%, m.p. 162-163 °C; IR cm^{-1}: 3362, 3051, 1705, 1662, 1525, 1387, 1323, 1260, 1157, 1069, 1001, 898, 830, 789, 696, 641; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.24 (s, 3H), 4.29 (s, 2H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.62 (t, *J* = 6.8 Hz, 2H), 7.65-7.68 (m, 2H), 8.03 (d, *J* = 7.5 Hz, 2H), 8.38-8.40 (m, 1H), 8.66 (d, *J* = 7.8 Hz, 1H), 8.96 (d, *J* = 3.8 Hz, 1H), 10.69 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 29.48, 46.27, 116.17, 122.02, 126.96, 126.98, 127.13, 128.62, 129.02, 132.09, 133.10, 134.10, 134.47, 138.40, 148.65, 164.41, 205.90. EI-MS *m/z* (%): 304 (M^+, 39), 105 (100), 261 (76), 77 (41), 155 (9), 43 (4), 184 (1). $C_{19}H_{16}N_2O_2$ (304): calcd. C, 74.98; H, 5.30; N, 9.20; found C, 75.27; H, 4.89; N, 8.81.



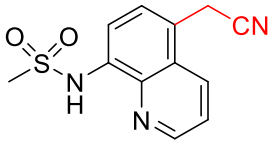
***N*-(5-(cyanomethyl)quinolin-8-yl)benzenesulfonamide (6a)**

Cream solid, Yield: 77%, m.p. 124-127 °C; IR cm^{-1}: 3177, 2924, 2316, 2255, 1667, 1582, 1505, 1473, 1370, 1305, 1162, 1090, 883, 832, 755, 723; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.42 (s, 2H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.54 (d, *J* = 7.3 Hz, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.69-7.71 (m, 2H), 7.93 (d, *J* = 7.6 Hz, 2H), 8.46 (d, *J* = 7.8 Hz, 1H), 8.91 (d, *J* = 3.3 Hz, 1H), 10.07 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.61, 115.93, 118.72, 122.59, 122.78, 125.95, 126.89, 126.93, 129.13, 132.61, 133.15, 133.78, 138.86, 139.28, 149.37. MS (EI): 323 (M^+, 19), 77 (100), 182 (81), 142 (75), 259 (74), 258 (62), 219 (28). $C_{17}H_{13}N_3O_2S$ (323): calcd. C, 63.14; H, 4.05; N, 12.99; found C, 63.38; H, 3.91; N, 12.67.



***N*-(5-(cyanomethyl)quinolin-8-yl)-4-methylbenzenesulfonamide (6b)**

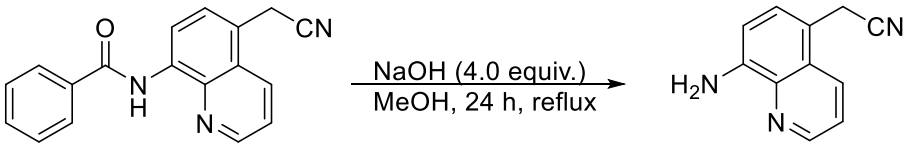
Light Yellow solid, Yield: 81%, m.p. 147-149 °C; IR cm^{-1}: 3244, 2924, 2256, 1593, 1504, 1473, 1418, 1356, 1301, 1159, 1089, 1062, 880, 825, 784, 662; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.26 (s, 3H), 4.41 (s, 2H), 7.27 (d, *J* = 7.2 Hz, 2H), 7.57 (d, *J* = 7.0 Hz, 1H), 7.67-7.72 (m, 2H), 7.82 (d, *J* = 6.8 Hz, 2H), 8.46 (d, *J* = 8.5 Hz, 1H), 8.92 (d, *J* = 4.7 Hz, 1H), 9.93 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.59, 20.86, 115.28, 118.73, 122.49, 122.63, 125.95, 126.94, 127.00, 129.60, 132.65, 133.85, 136.33, 138.65, 143.68, 149.36. MS (EI): 337 (M^+, 21), 273 (100), 91 (78), 142 (28), 272 (67), 182 (50), 155 (64). $C_{18}H_{15}N_3O_2S$ (337): calcd. C, 64.08; H, 4.48; N, 12.45; found C, 64.23; H, 4.52; N, 12.27.



***N*-(5-(cyanomethyl)quinolin-8-yl)methanesulfonamide (6c)**

Light Yellow solid, Yield: 73%, m.p. 118-121 °C; IR cm^{-1}: 3241, 2931, 2254, 1506, 1476, 1424, 1371, 1324, 1150, 1023, 887, 829, 761, 693; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.17 (s, 3H), 4.49 (s, 2H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.78 (dd, *J* = 8.4, 4.1 Hz, 1H), 8.57 (d, *J* = 8.3 Hz, 1H), 9.01 (d, *J* = 3.5 Hz, 1H), 9.45 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.61, 43.13, 116.25, 118.85, 122.46, 122.74, 126.18, 127.26, 133.03, 134.37, 138.93, 149.43. MS (EI): 261 (M^+, 42), 182 (100), 142 (87), 183 (63), 155 (52), 77 (31), 196 (11). $C_{12}H_{11}N_3O_2S$ (261): calcd. C, 55.16; H, 4.24; N, 16.08; found C, 55.50; H, 4.46; N, 16.32.

2.4 Removal of the acyl moiety

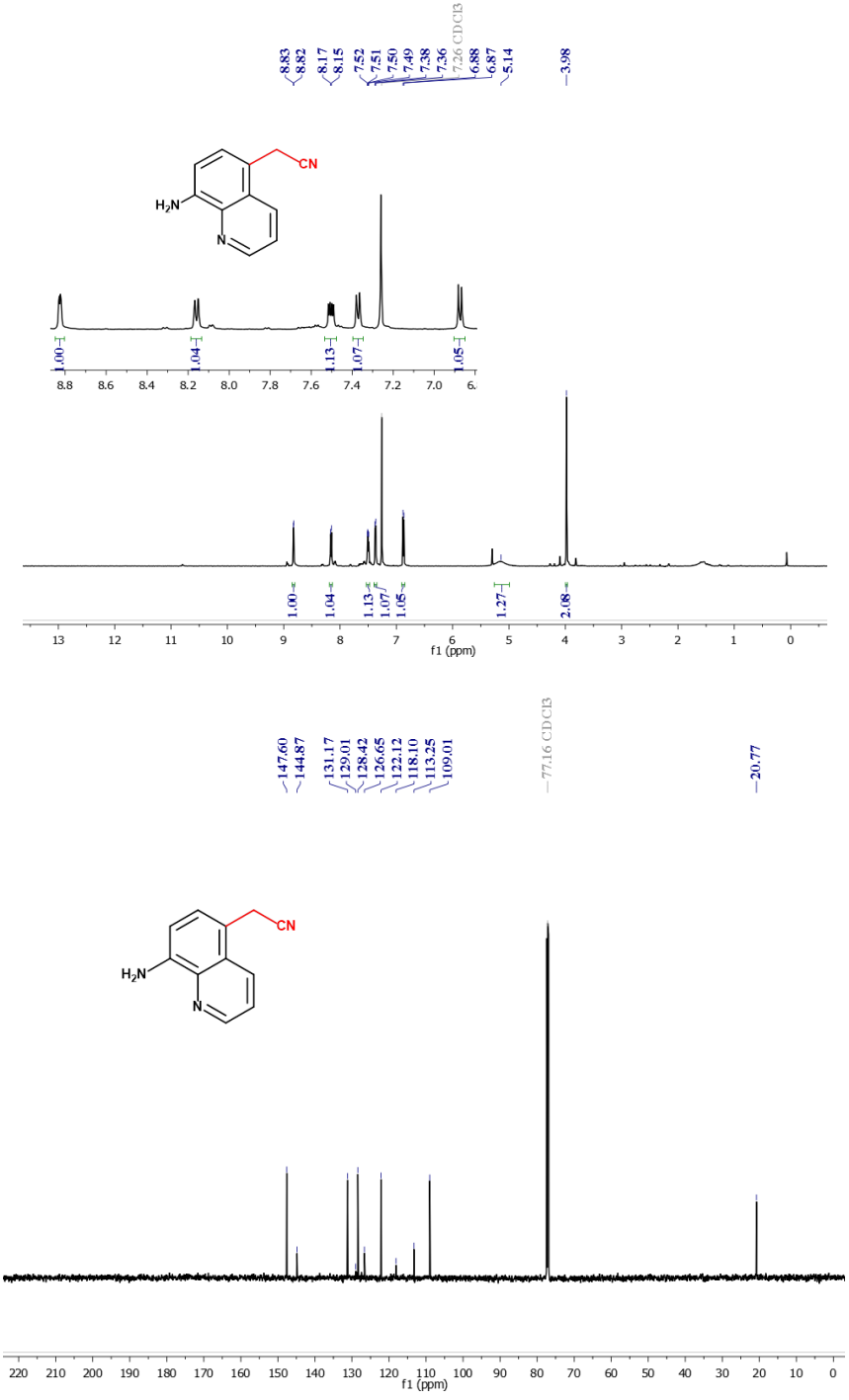


3a **13**, 63%

To a solution of **3a** (2 mmol) in methanol (10 mL), NaOH (4.0 equiv.) was added and the reaction mixture was refluxed for 24 h. Then, methanol was removed and the mixture was diluted with EtOAc (100 mL) and washed with aqueous 1 M HCl (3 × 20 mL). After filtration and evaporation of the solvent under reduced pressure, the desired product **13** was obtained through recrystallization in absolute ethanol (63% yield).

2-(8-aminoquinolin-5-yl)acetonitrile (13)

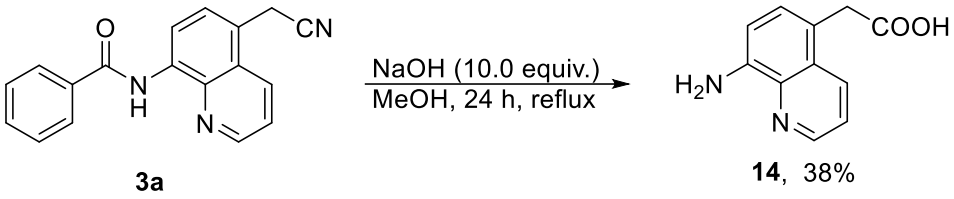
Cream solid, Yield: 63%, m.p. 145-147 °C; IR cm^{-1}: 3411, 3322, 2914, 2253, 1619, 1508, 1413, 1368, 1328, 1259, 1125, 1041, 926, 821, 776, 688; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.98 (s, 2H), 5.14 (br, 1H), 6.87 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.50 (dd, J = 8.5, 4.1 Hz, 1H), 8.15 (d, J = 9.8 Hz, 1H), 8.82 (d, J = 2.6 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 20.77, 109.01, 113.25, 118.10, 122.12, 126.65, 128.42, 129.01, 131.17, 144.87, 147.60. MS (EI): 183 (M^+, 97), 182 (100), 105 (29), 155 (19), 77 (18), 128 (7), 51 (6). $C_{11}H_9N_3$ (183): calcd. C, 72.11; H, 4.95; N, 22.94; found C, 72.50; H, 4.55; N, 23.32.



2.5 Conversion of the cyano group to the carboxylic acid group

To a solution of **3a** (2 mmol) in methanol (10 mL), NaOH (10.0 equiv.) was added and the reaction mixture was refluxed for 24 h. Then, methanol was removed from the mixture and the combined organic phase was diluted with EtOAc (100 mL) and washed with aqueous 1 M HCl (3 × 20 mL). After filtration

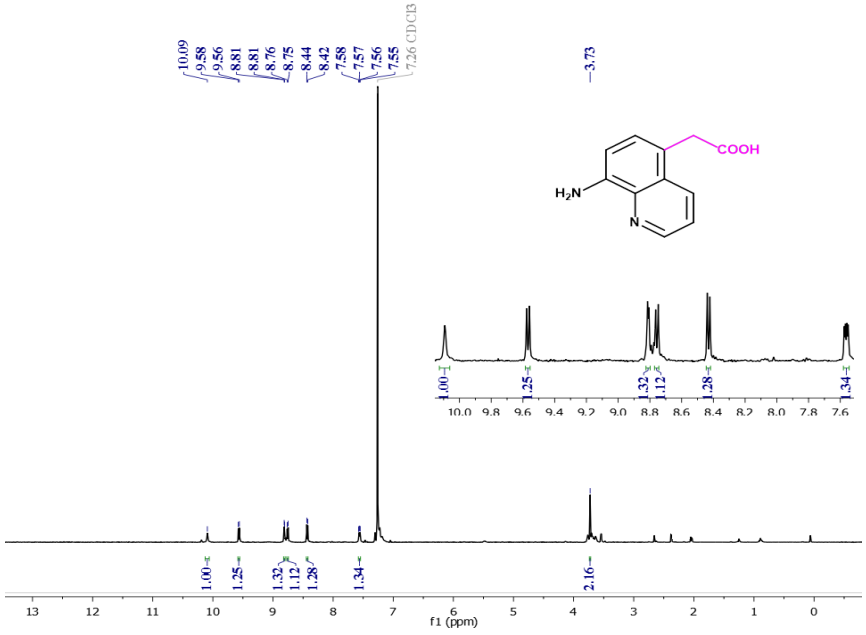
and evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc) to give the desired product **14** in 38% yield.



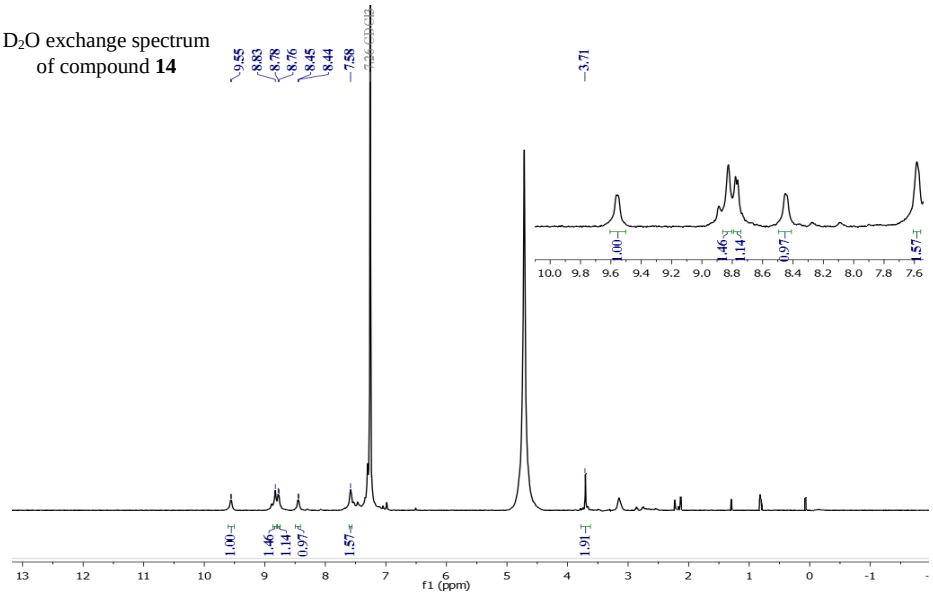
3a **14**, 38%

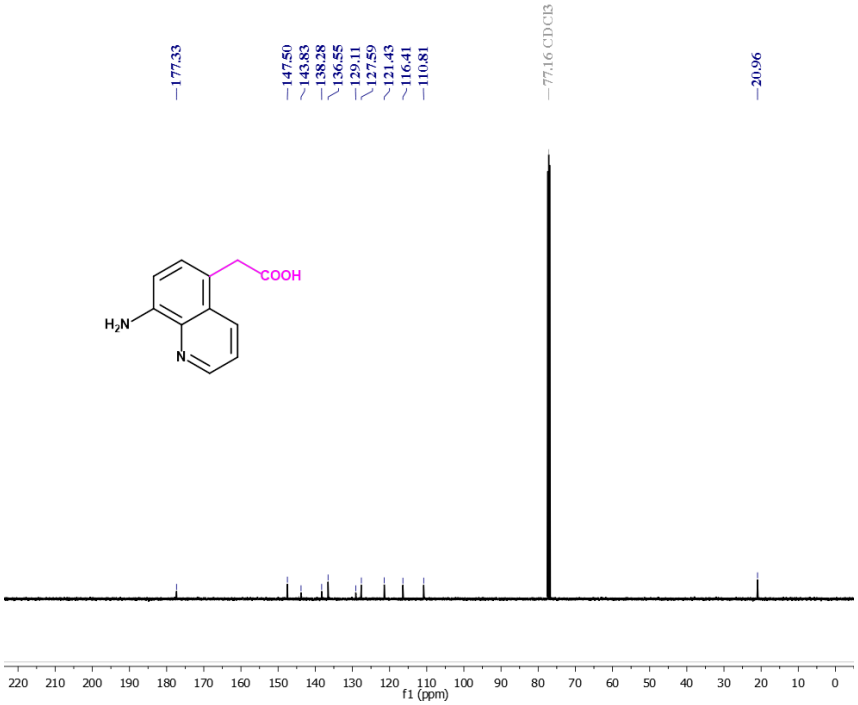
2-(8-aminoquinolin-5-yl)acetic acid (14)

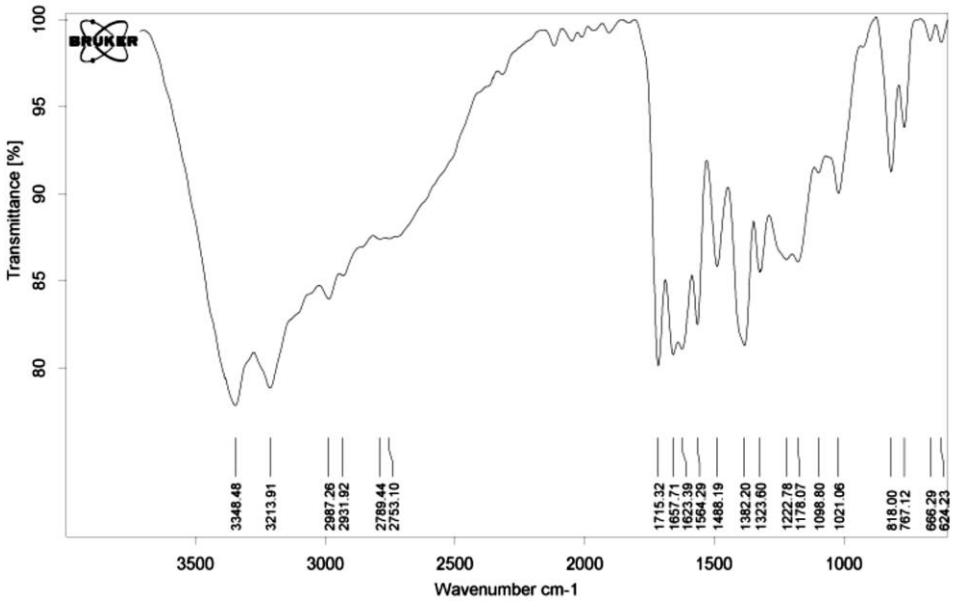
yellow oil, Yield: 38%, IR cm^{-1}: 3348, 3213, 2987, 2931, 2789, 2753, 1715, 1657, 1622, 1564, 1488, 1382, 1323, 1222, 1178, 1098, 1021, 818, 767, 666, 624; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.73 (s, 2H), 7.56 (dd, J = 8.6, 4.0 Hz, 1H), 8.43 (d, J = 8.2 Hz, 1H), 8.75 (d, J = 7.4 Hz, 1H), 8.81 (d, J = 4.1 Hz, 1H), 9.56 (d, J = 8.7 Hz, 1H), 10.09 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d6) δ 20.96, 110.81, 116.41, 121.43, 127.59, 129.11, 136.55, 138.28, 143.83, 147.50, 177.33. MS (EI): 202 (M^+, 28), 84 (100), 66 (62), 188 (59), 45 (37), 143 (26), 116 (20). $C_{11}H_{10}N_2O_2$ (202): calcd. C, 65.34; H, 4.98; N, 13.85; found C, 65.70; H, 5.28; N, 14.01.



D_2O exchange spectrum of compound **14**

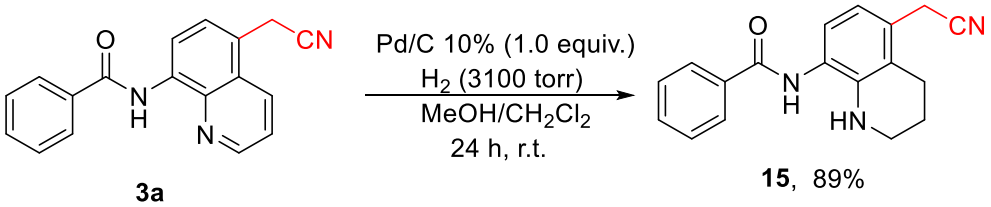






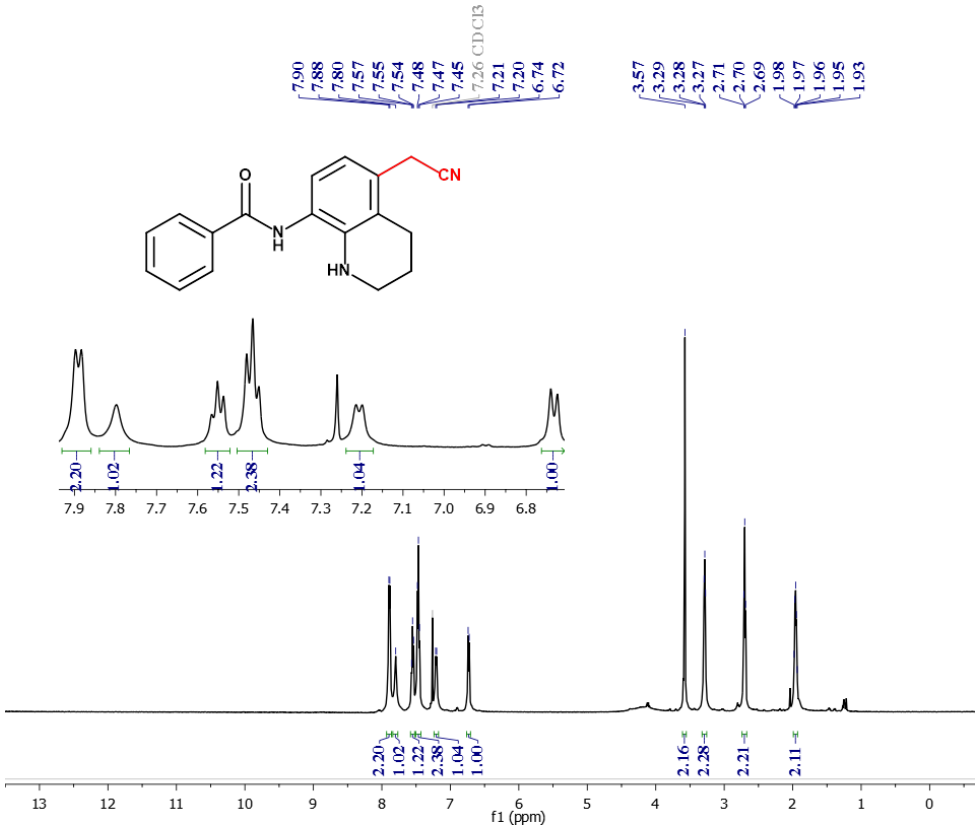
2.6 Reduction of the pyridine ring

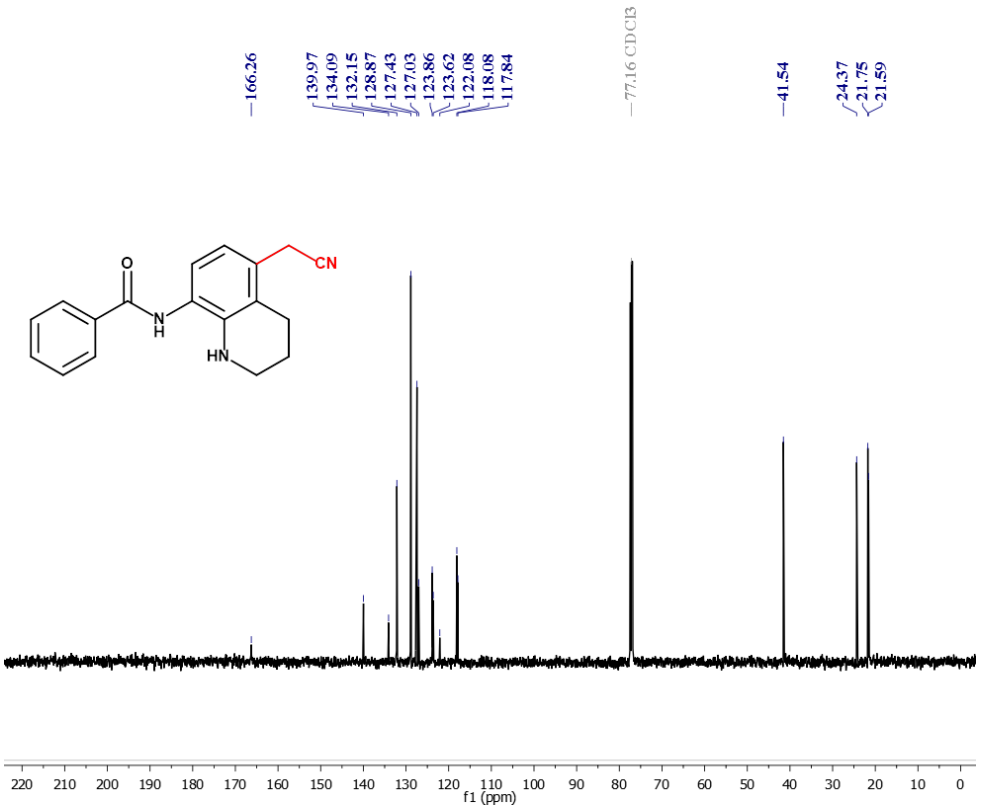
To a solution of **3a** (2 mmol) in methanol (5 mL) and CH_2Cl_2 (5 mL), Pd/C 10% (1.0 equiv.) was added, and the reaction mixture was stirred under H_2 (3100 torr) for 24 h. Then, the solvent was removed from the mixture and the desired product **15** was obtained through recrystallization in absolute ethanol (89% yield).



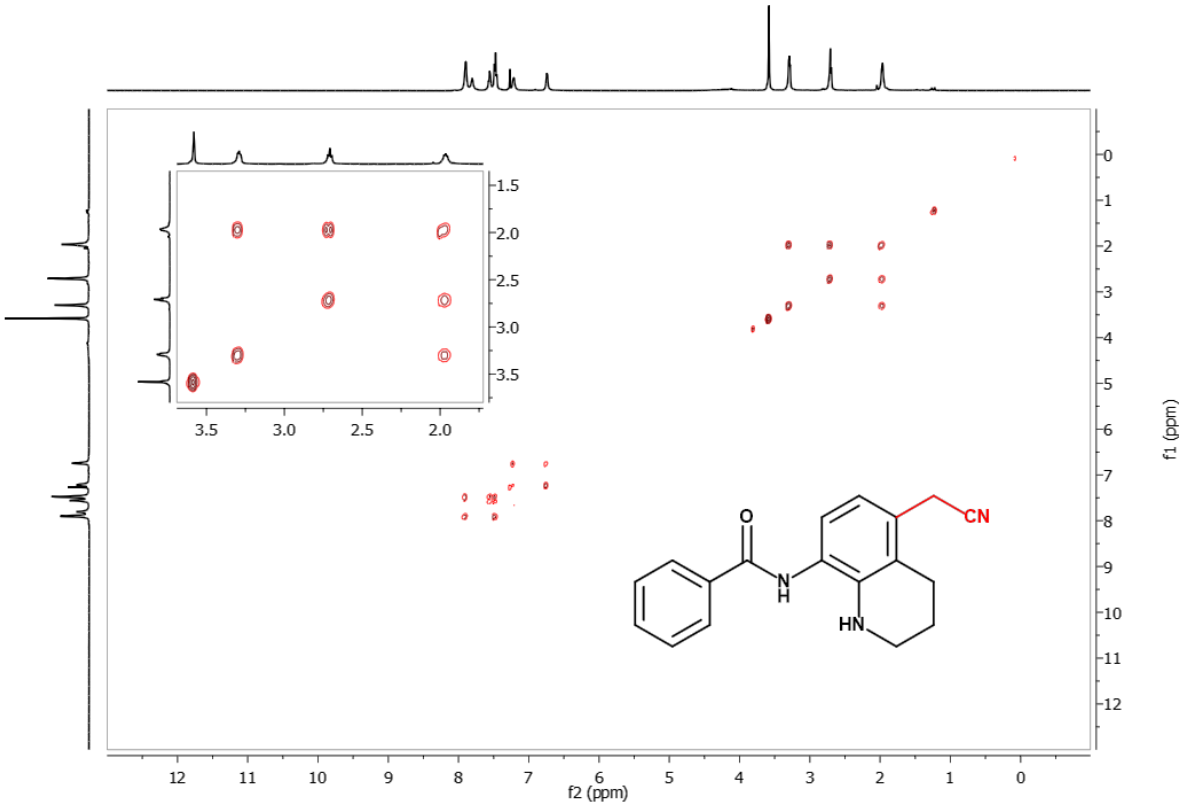
***N*-(5-(cyanomethyl)-1,2,3,4-tetrahydroquinolin-8-yl)benzamide (15)**

Goldish solid, Yield: 89%, m.p. 86-87 °C; IR cm^{-1}: 3371, 3387, 2922, 2850, 2245, 1637, 1587, 1515, 1446, 1315, 1267, 1192, 1074, 1024, 918, 894, 697; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.95 (dt, J = 11.5, 6.0 Hz, 2H), 2.70 (t, J = 6.3 Hz, 2H), 3.26-3.30 (m, 2H), 3.57 (s, 2H), 6.73 (d, J = 7.9 Hz, 1H), 7.20 (d, J = 7.4 Hz, 1H), 7.46 (t, J = 7.4 Hz, 2H), 7.55 (t, J = 7.1 Hz, 1H), 7.80 (s, 1H), 7.89 (d, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 21.59, 21.75, 24.37, 41.54, 117.84, 118.08, 122.08, 123.62, 123.86, 127.03, 127.43, 128.87, 132.15, 134.09, 139.97, 166.26. MS (EI): 291 (M^+, 50), 105 (100), 274 (51), 77 (45), 186 (26), 145 (17), 214 (5). $C_{18}H_{17}N_3O$ (291): calcd. C, 74.20; H, 5.88; N, 14.42; O; found C, 74.58; H, 6.28; N, 14.44.



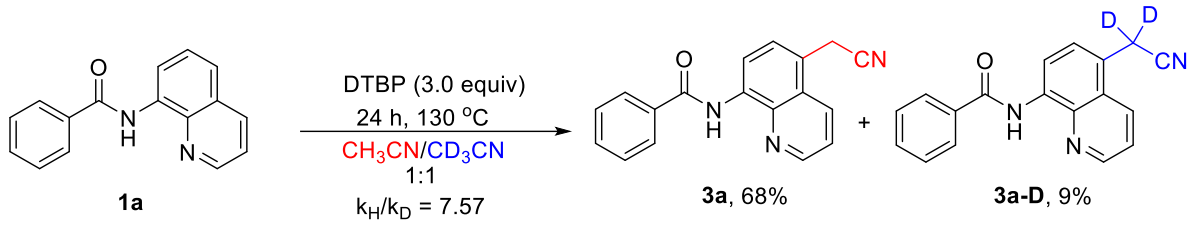


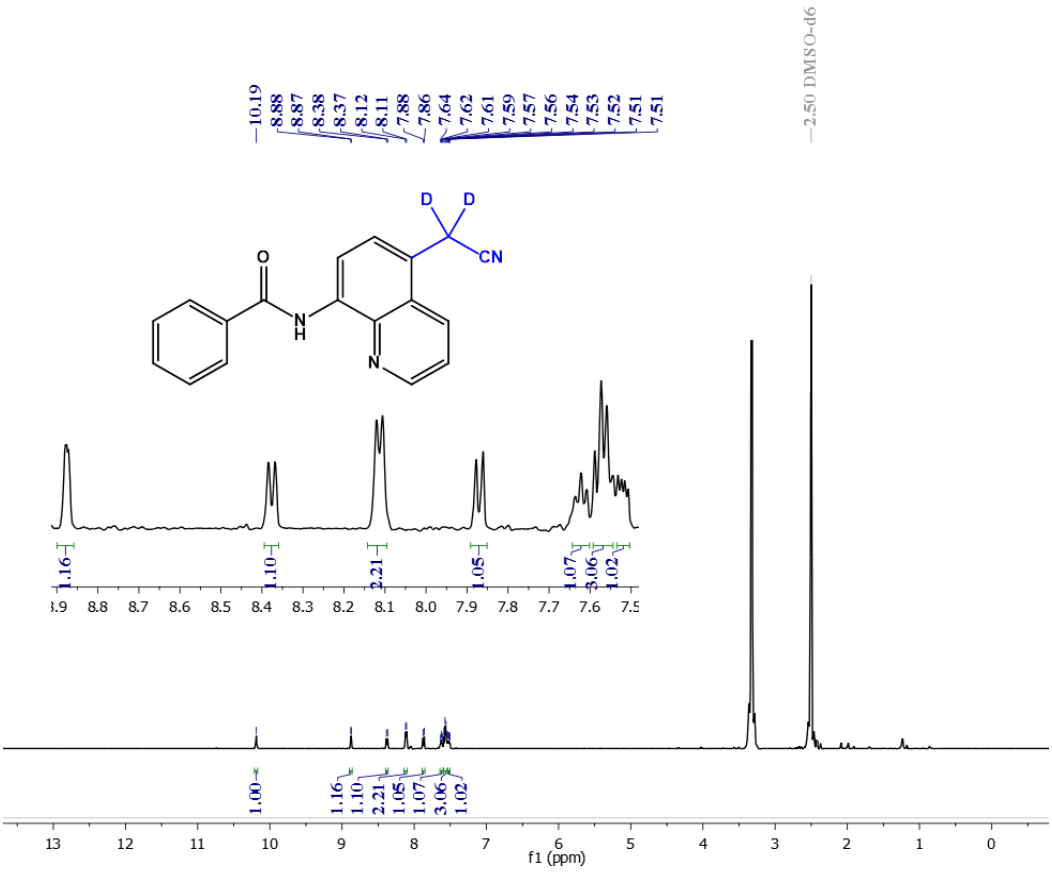
HH-COSY NMR spectrum of 15



2.7 Mechanistic studies

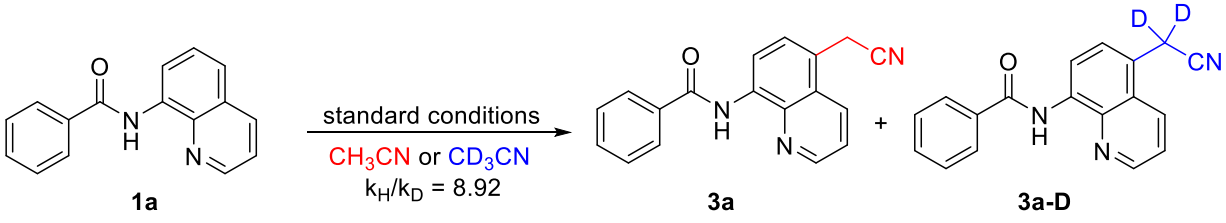
2.7.1 The kinetic isotopic effect studies on the solvent (competition reaction)

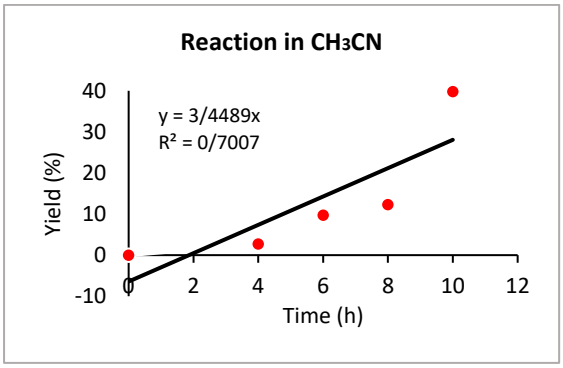


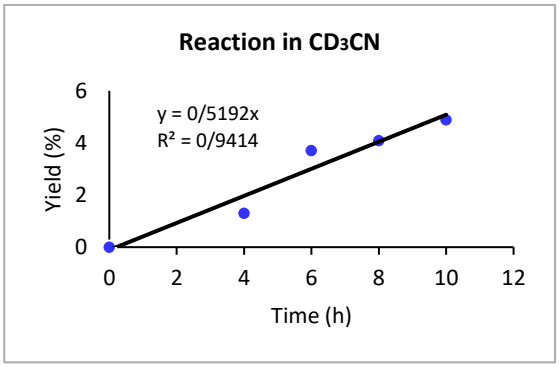


2.7.2 The kinetic isotopic effect studies on the solvent (parallel reaction)

Eight parallel sealed tubes were charged with *N*-(quinolin-8-yl)benzamide **1a** (0.1 mmol), DTBP (3.0 equiv.), and CH_3CN or CD_3CN (four experiments for each). The reactions were stirred at 130 °C for 24 h. Then the reaction mixture cooled to room temperature and was analyzed by GC-MS to record the yield of products **3a** or **3a-D**. A considerable intermolecular kinetic isotope effect (k_H/k_D = 8.92) showed that the C-H bond activation of acetonitrile contributes to the rate-limiting step.

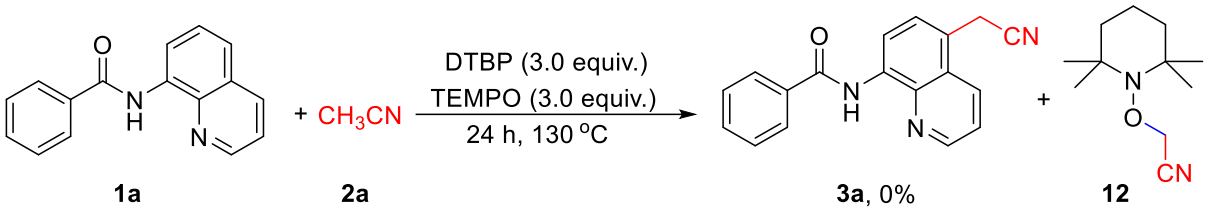




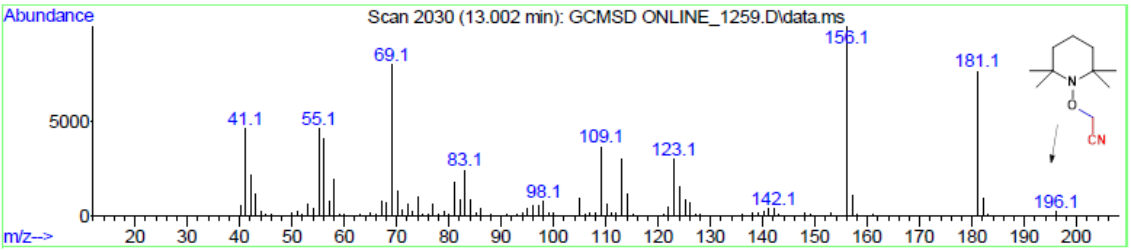


2.7.3 Trapping of the Reaction Intermediate

A 10 mL sealed tube was equipped with a magnetic stir bar and charged with *N*-(quinolin-8-yl)benzamide **1a** (0.1 mmol), DTBP (3.0 equiv.), TEMPO (3.0 equiv.) and CH_3CN **2a** (1 mL). The vessel was heated at 130 °C for 24 h and then it was cooled to room temperature. The mixture was analyzed by GC-MS. Product **3a** was not observed under the reaction conditions, and **12** was detected (1.8%).



1a **2a** **3a**, 0% **12**



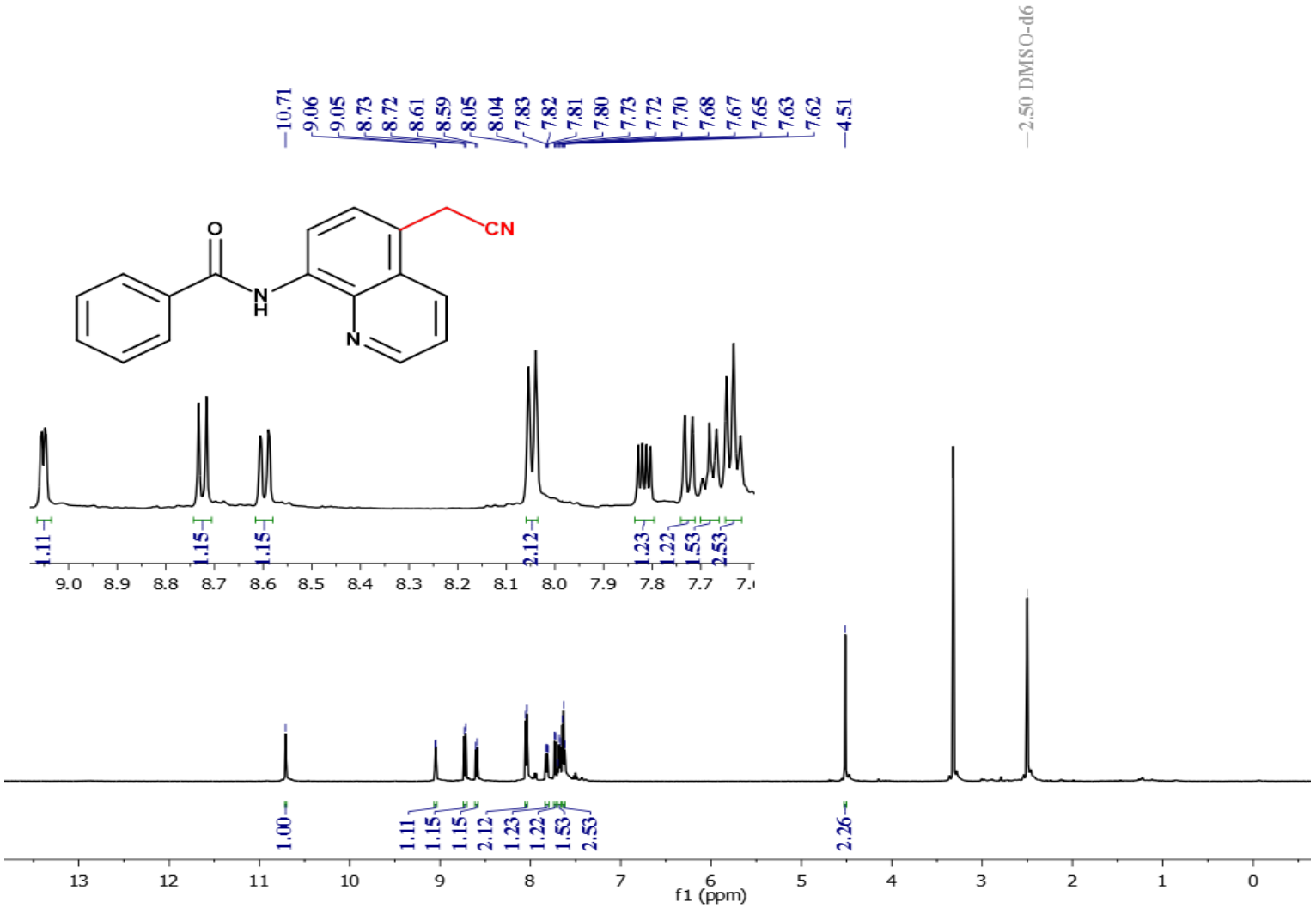
3. References

1 (a) M. Nishino, K. Hirano, T. Satoh, M. Miura, *Angew. Chem., Int. Ed.*, 2013, **52**, 4457; (b) Y. Aihara, N. Chatani, *Chem. Sci.*, 2012, **4**, 664.

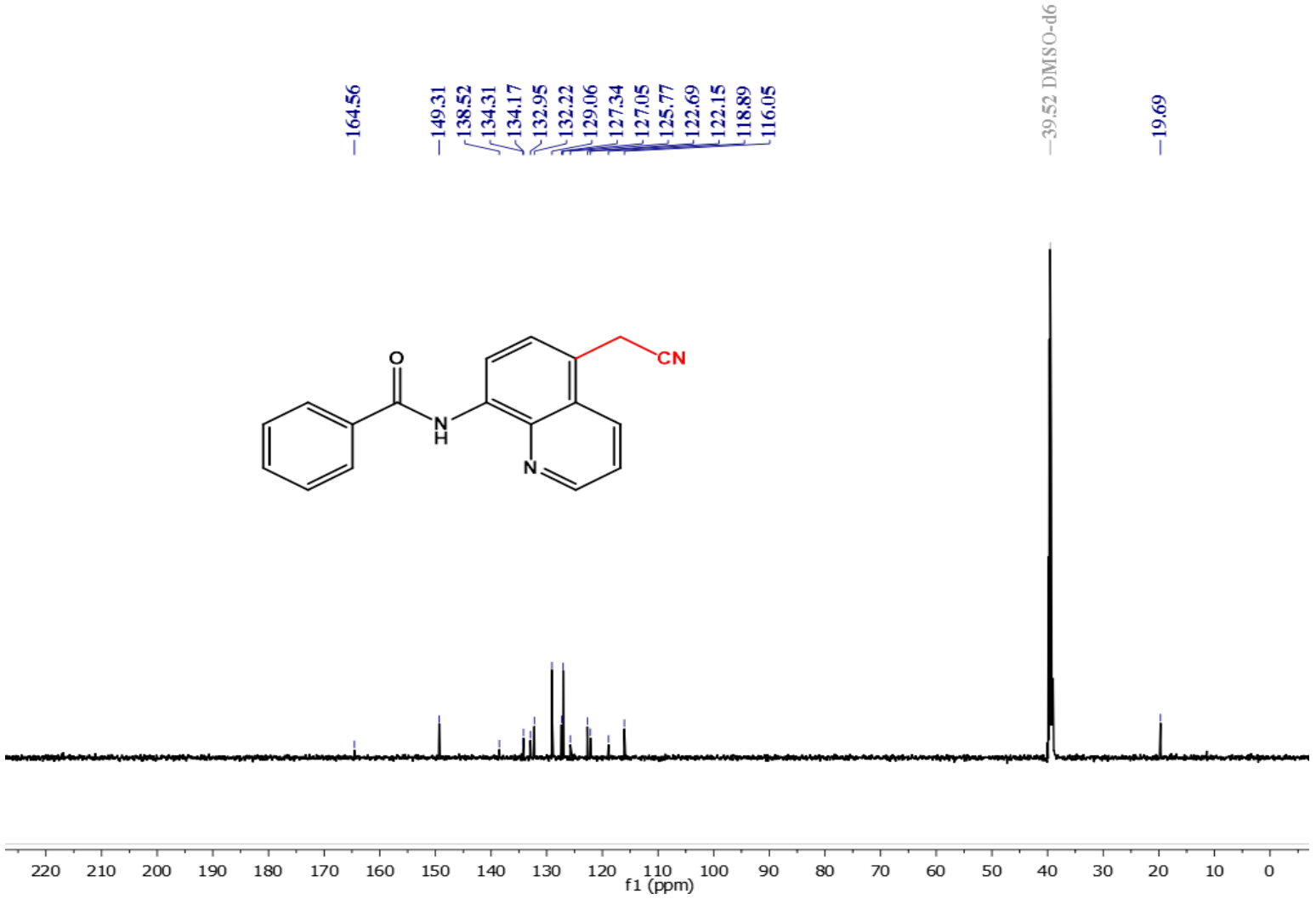
2 L. D. Tran, I. Popov, O. Daugulis, *J. Am. Chem. Soc.*, 2012, **134**, 18237.

4. ^{1}H and ^{13}C NMR spectra

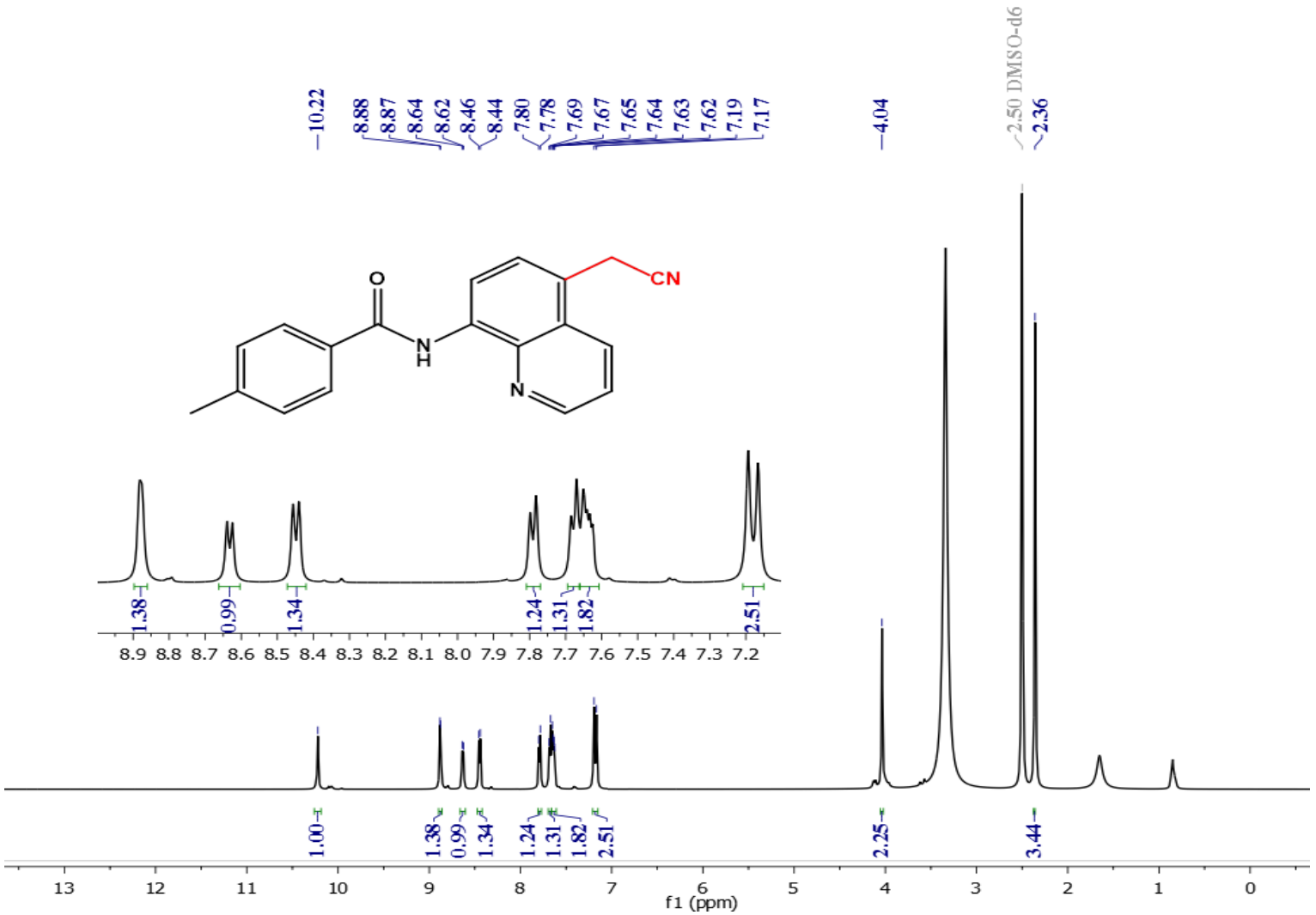
^{1}H NMR spectrum of 3a



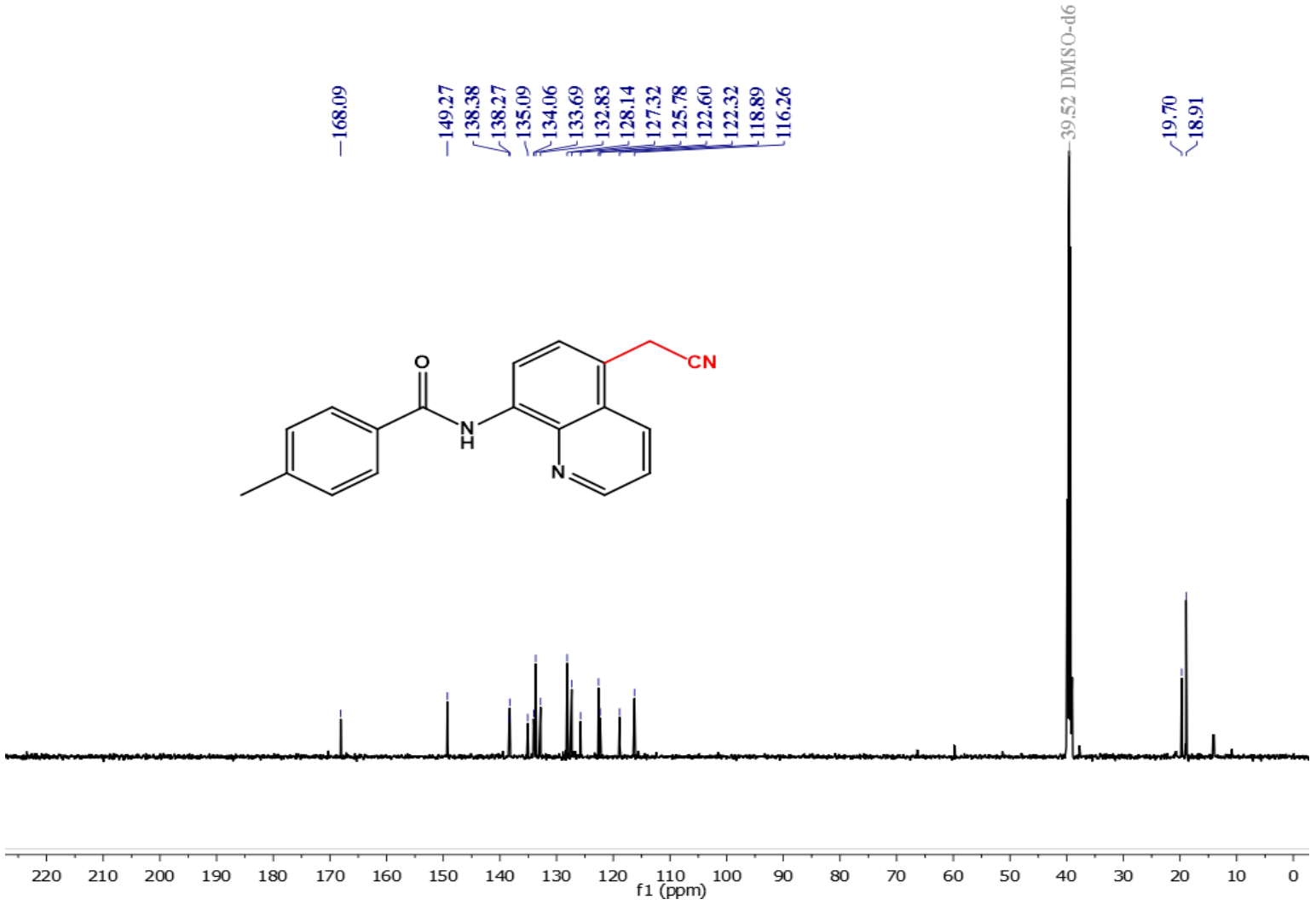
^{13}C NMR spectrum of 3a



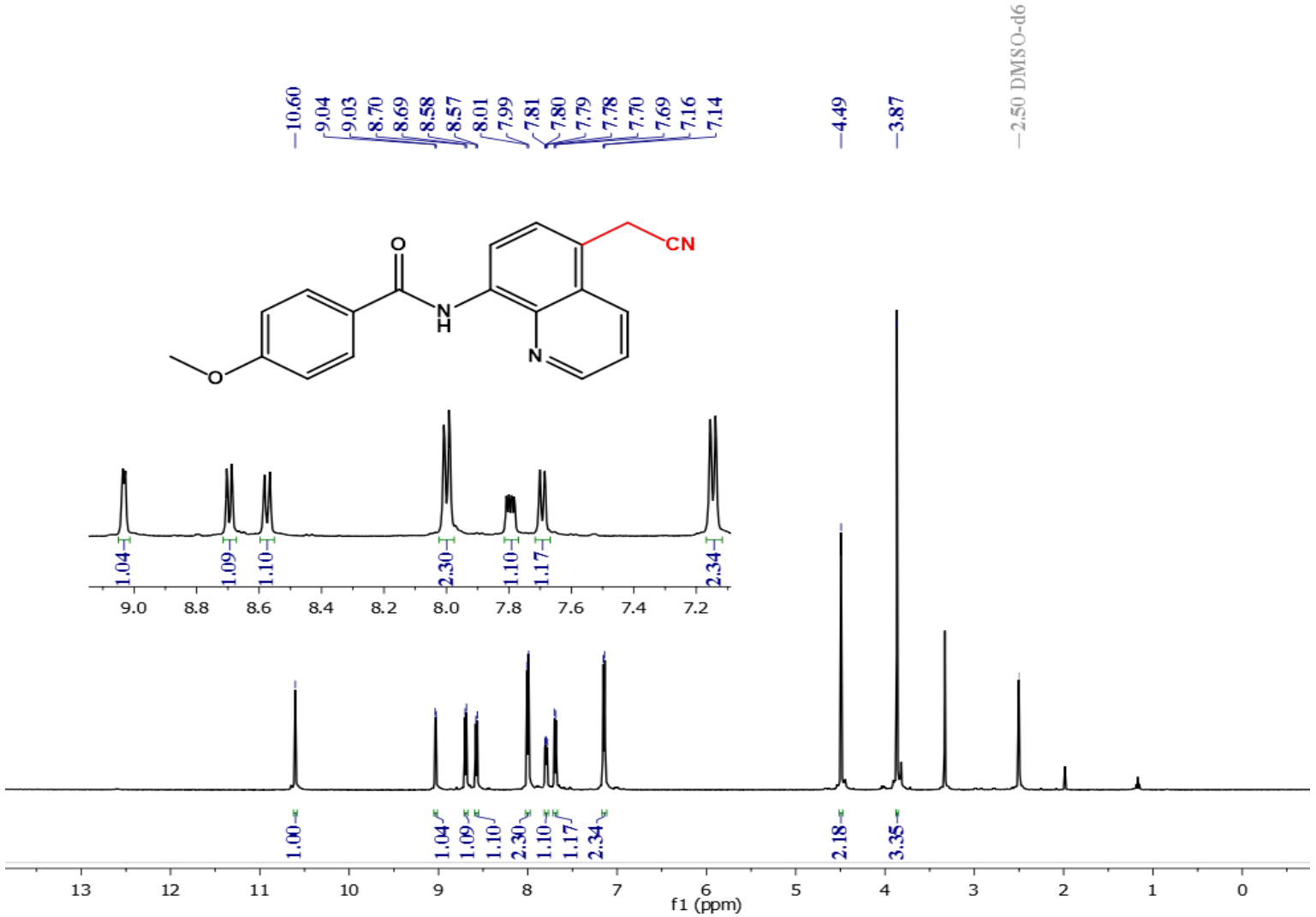
[1] H NMR spectrum of 3b



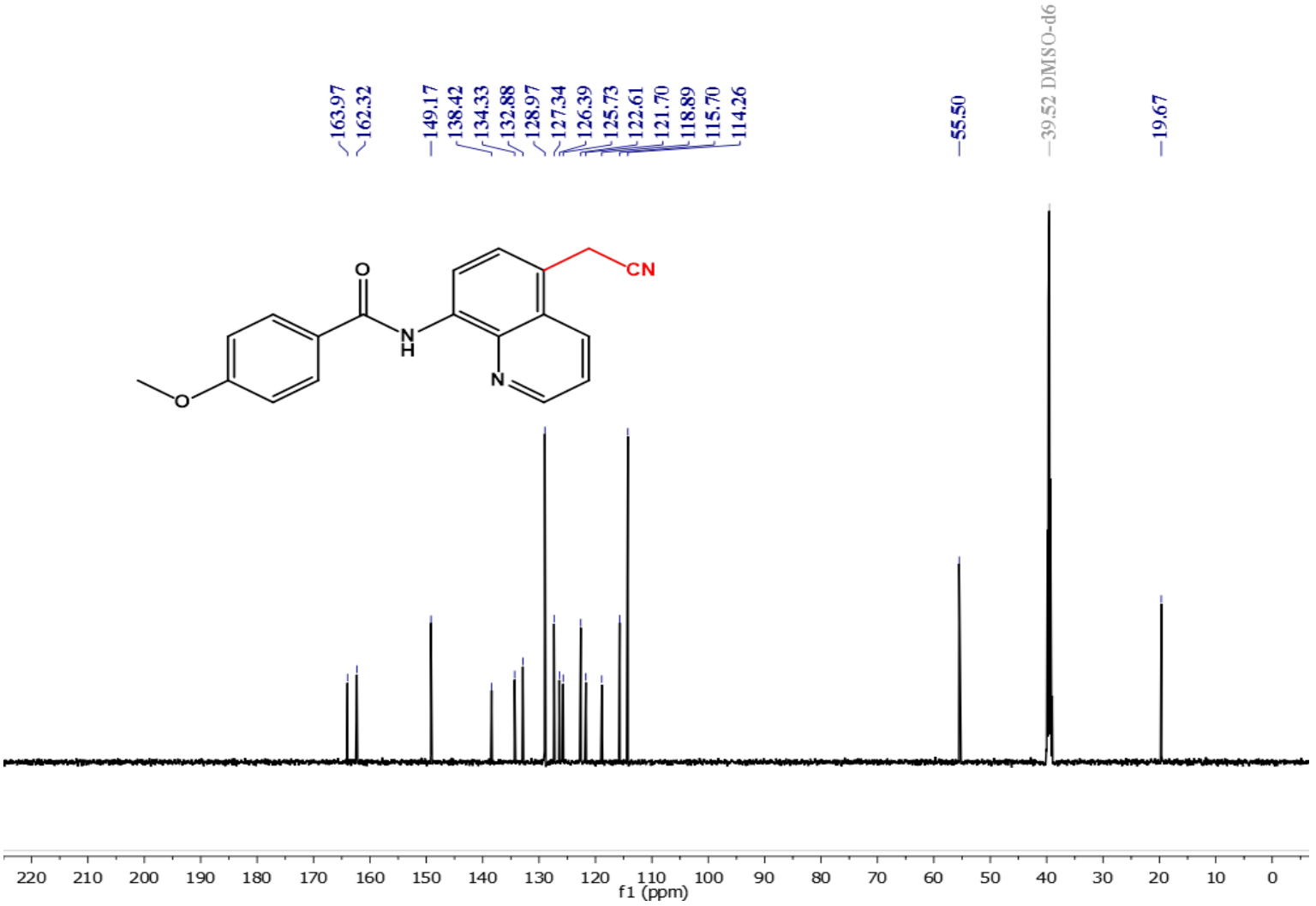
^{13}C NMR spectrum of 3b



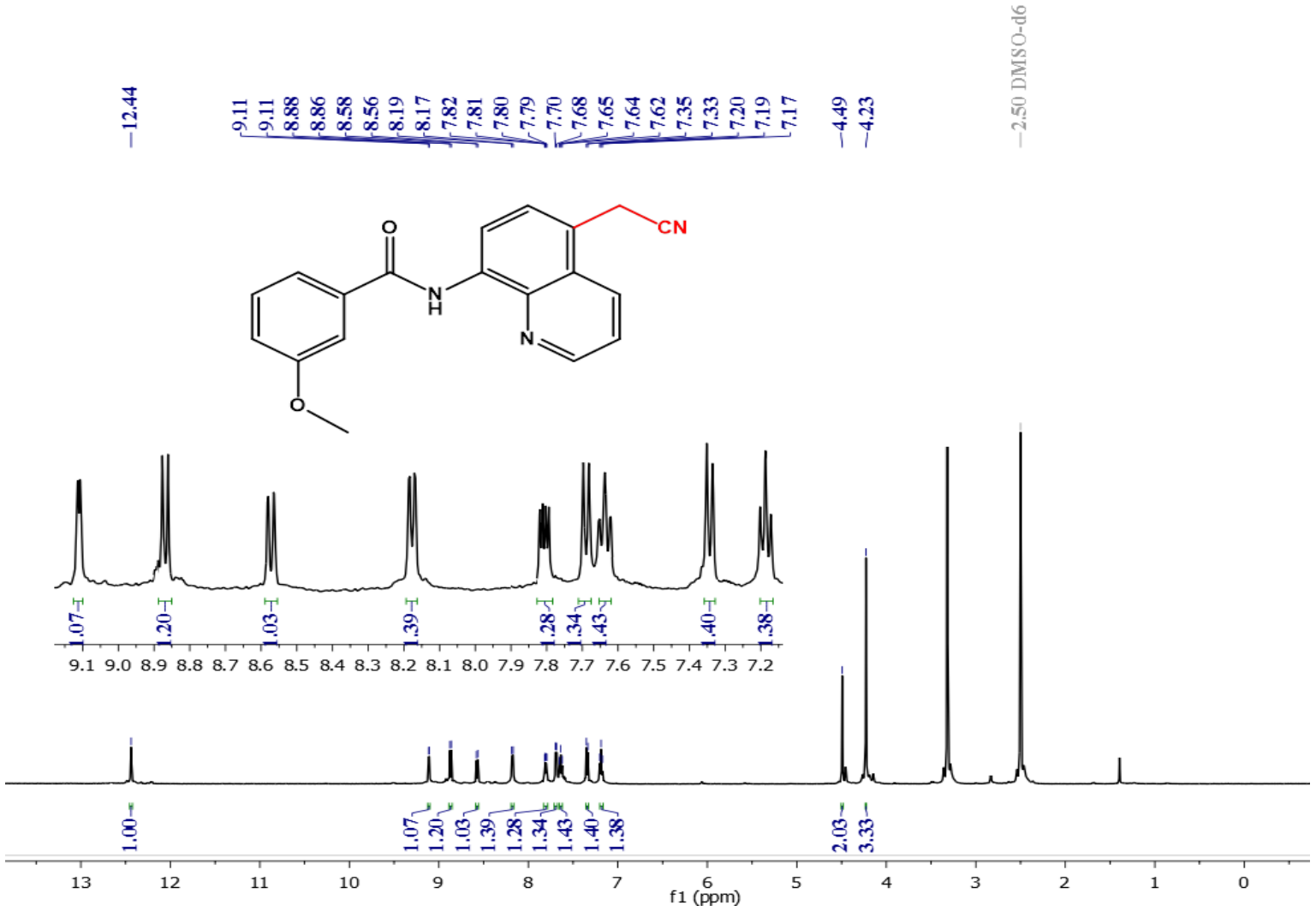
^{1}H NMR spectrum of 3c



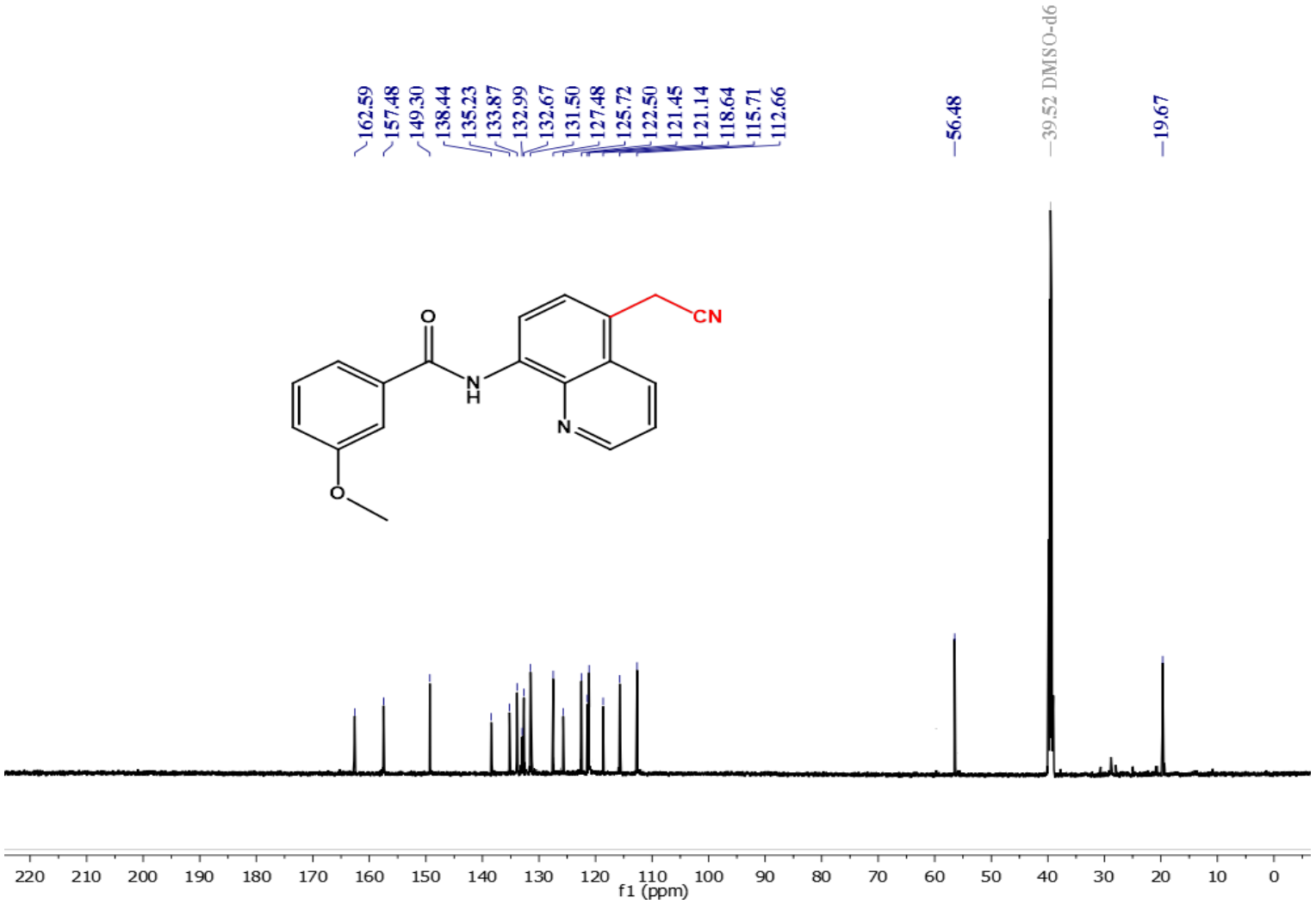
^{13}C NMR spectrum of 3c



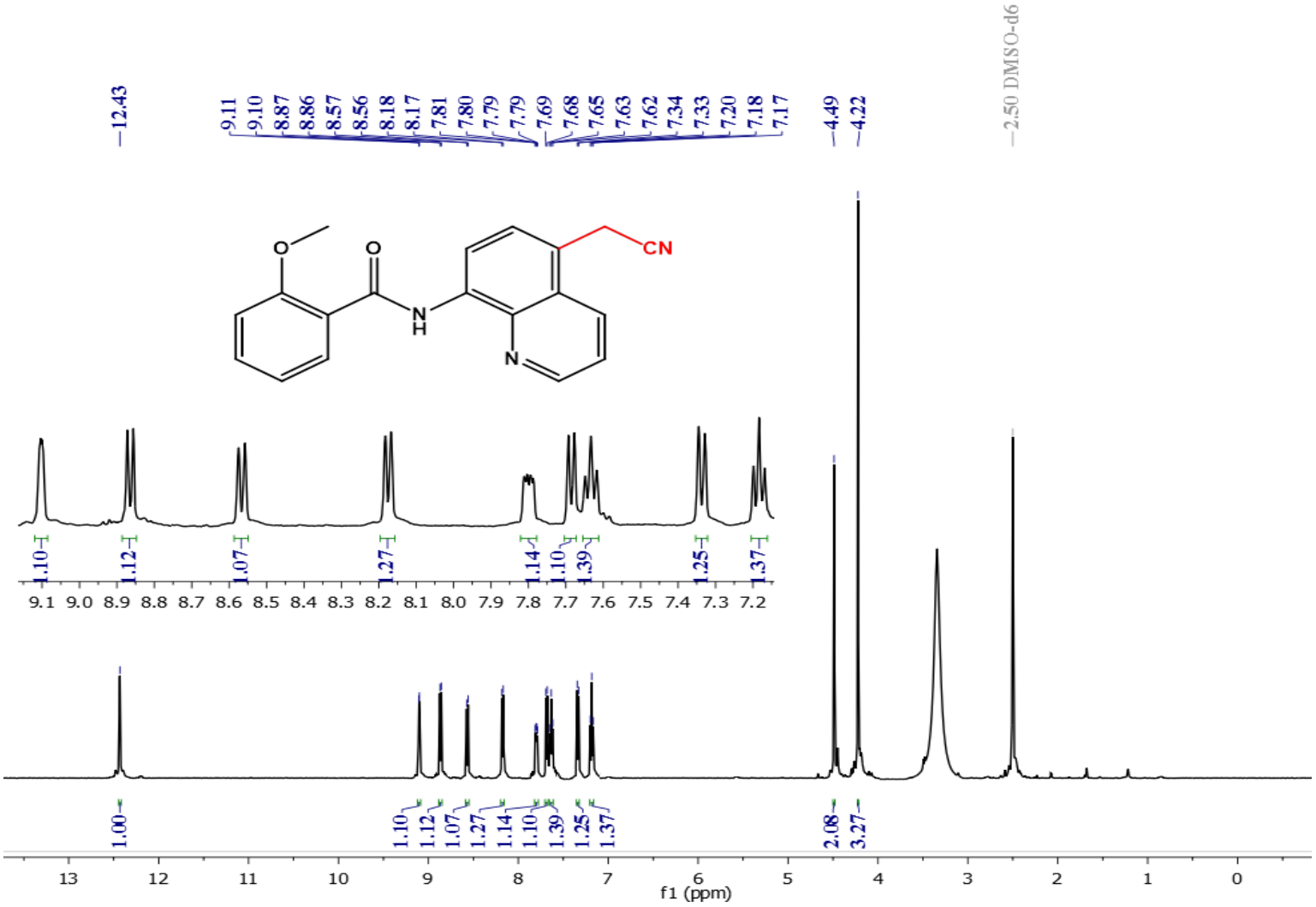
[1]H NMR spectrum of 3d



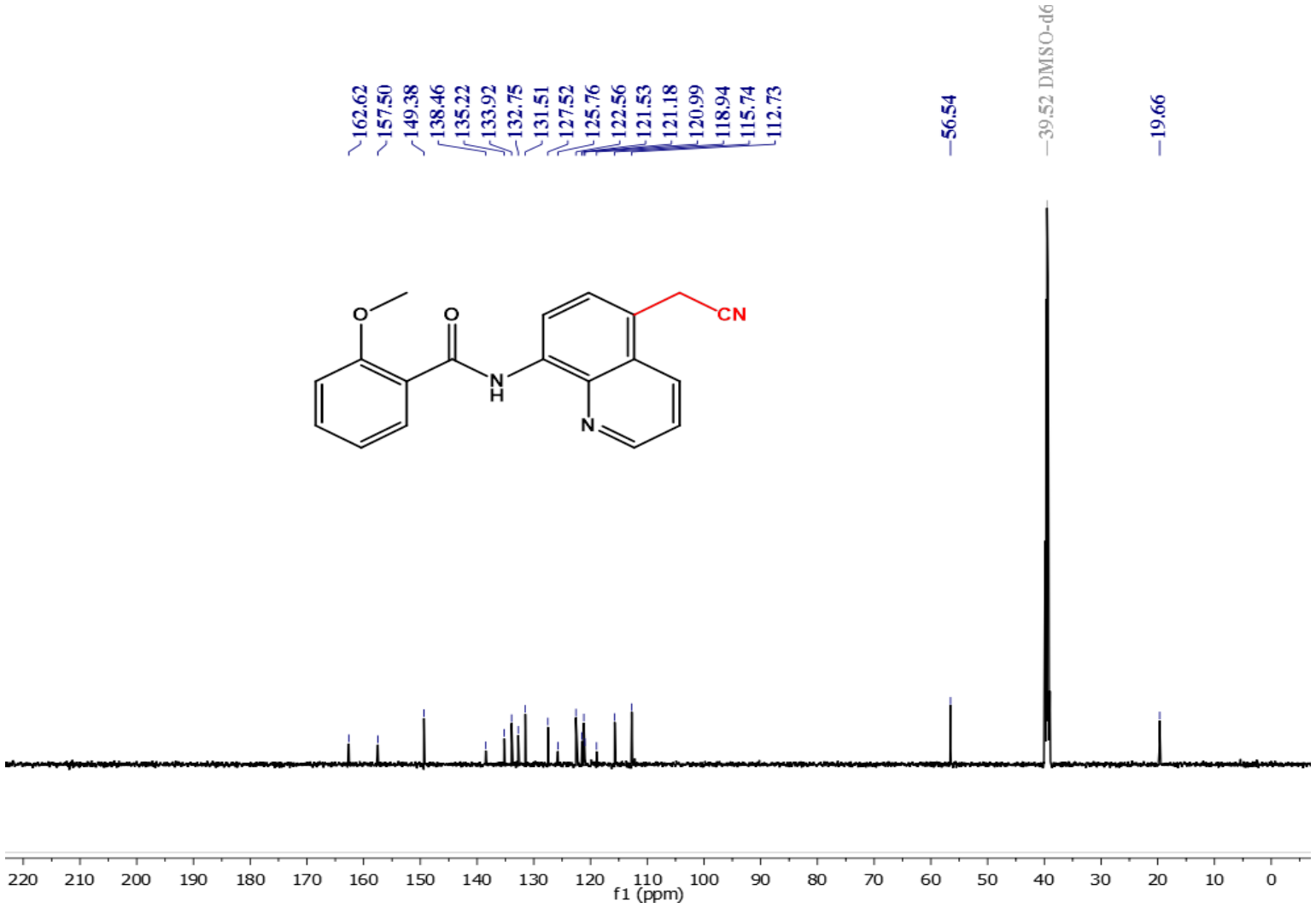
^{13}C NMR spectrum of 3d



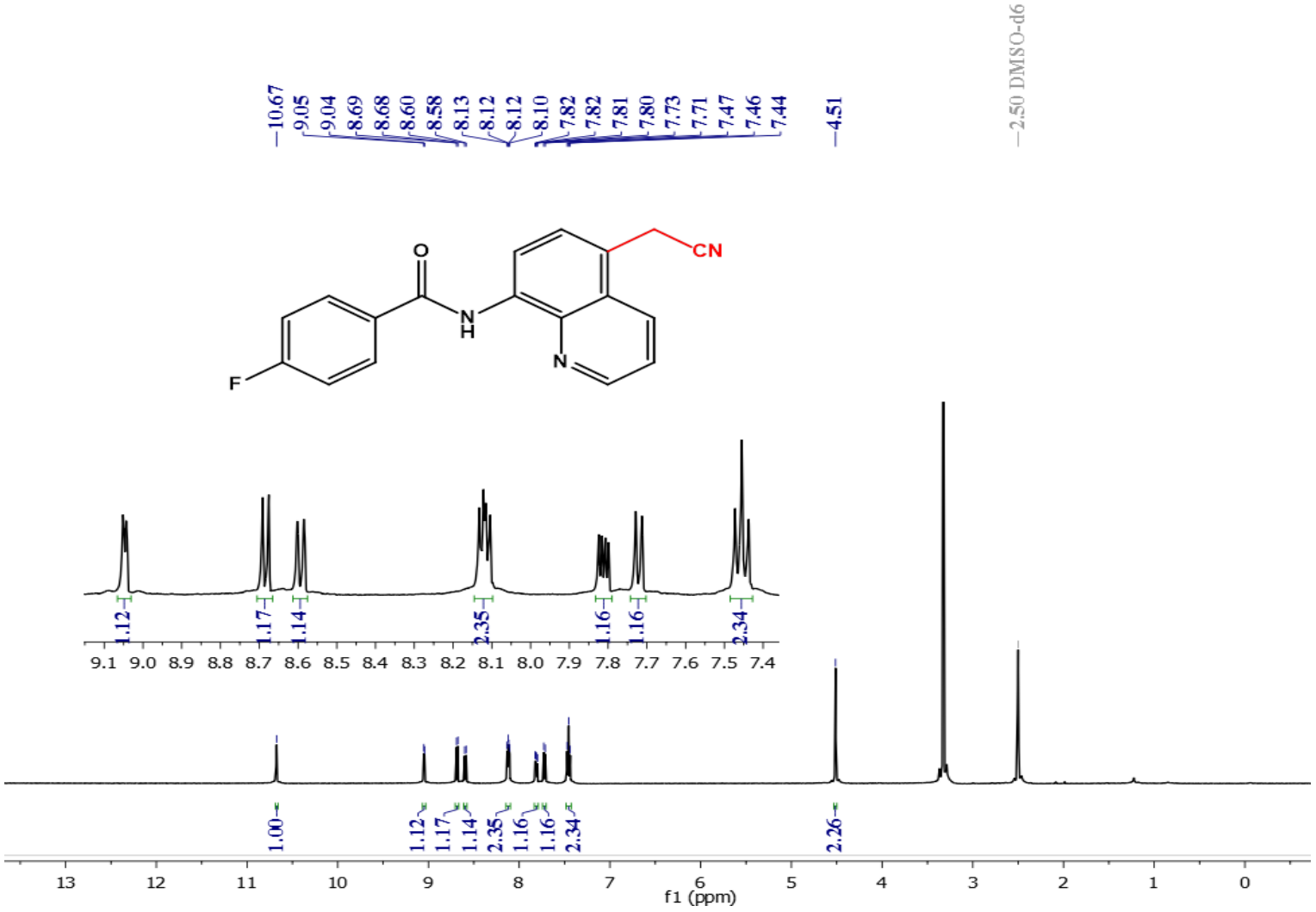
[1]H NMR spectrum of 3e



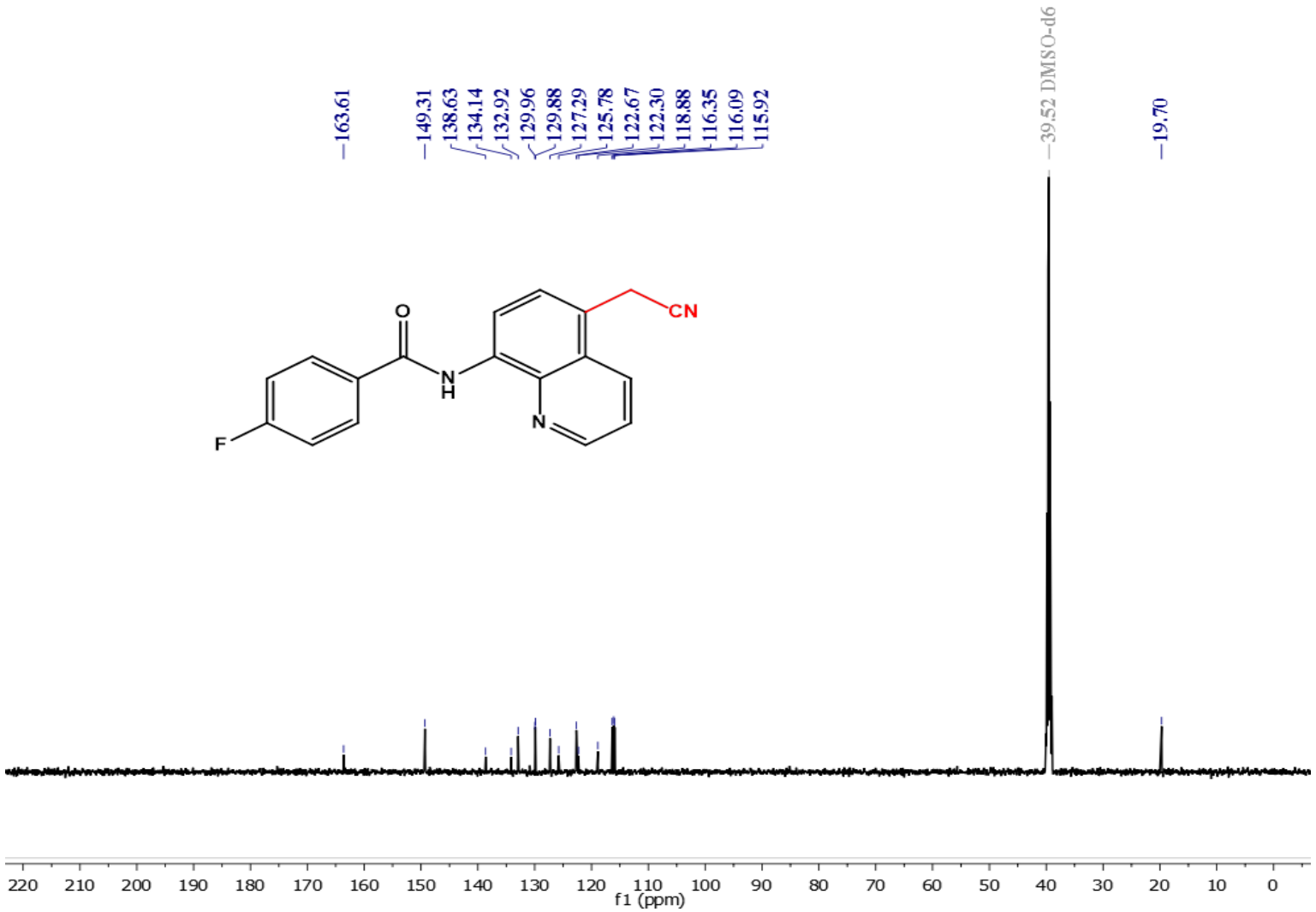
^{13}C NMR spectrum of 3e



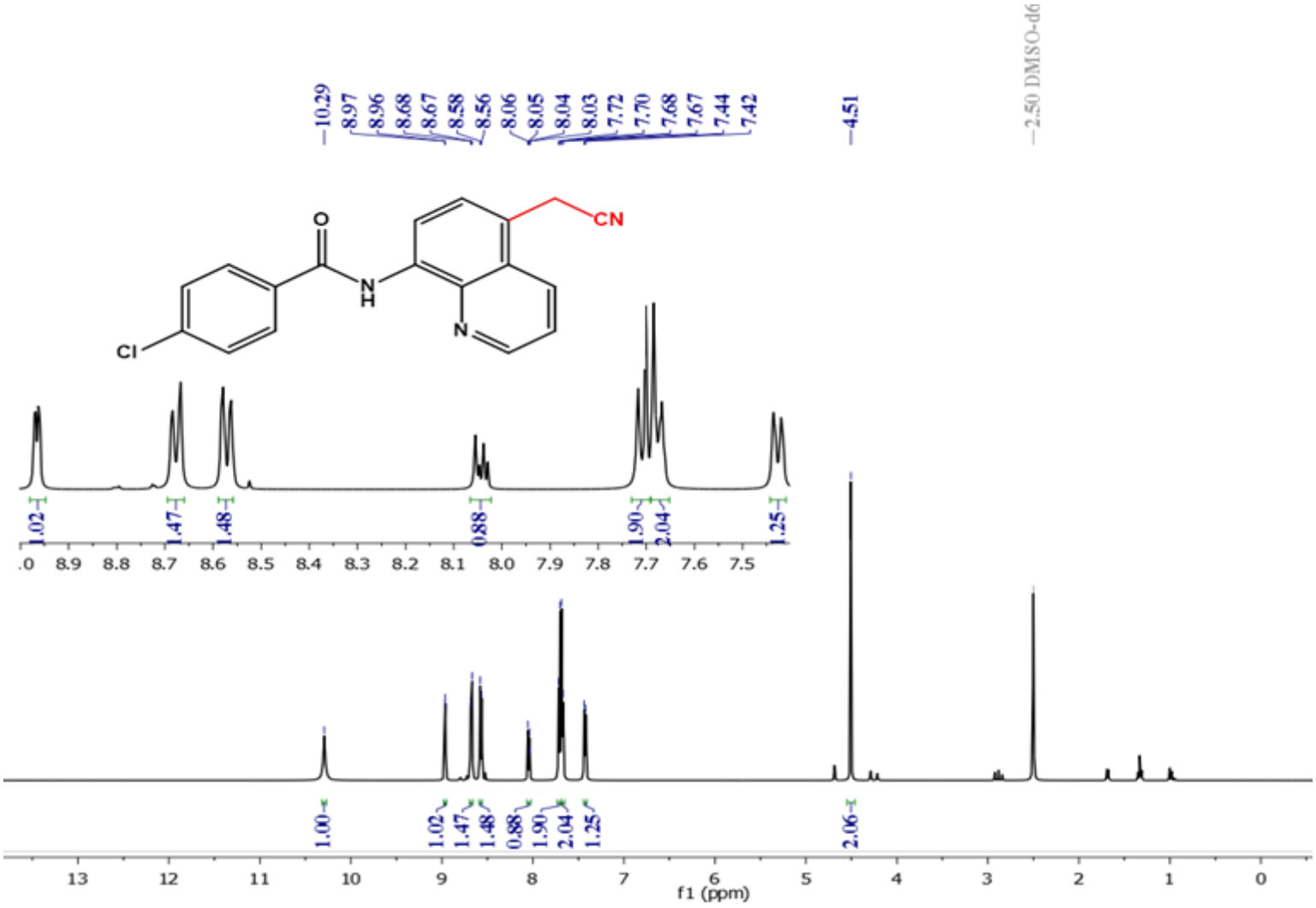
^{1}H NMR spectrum of 3f



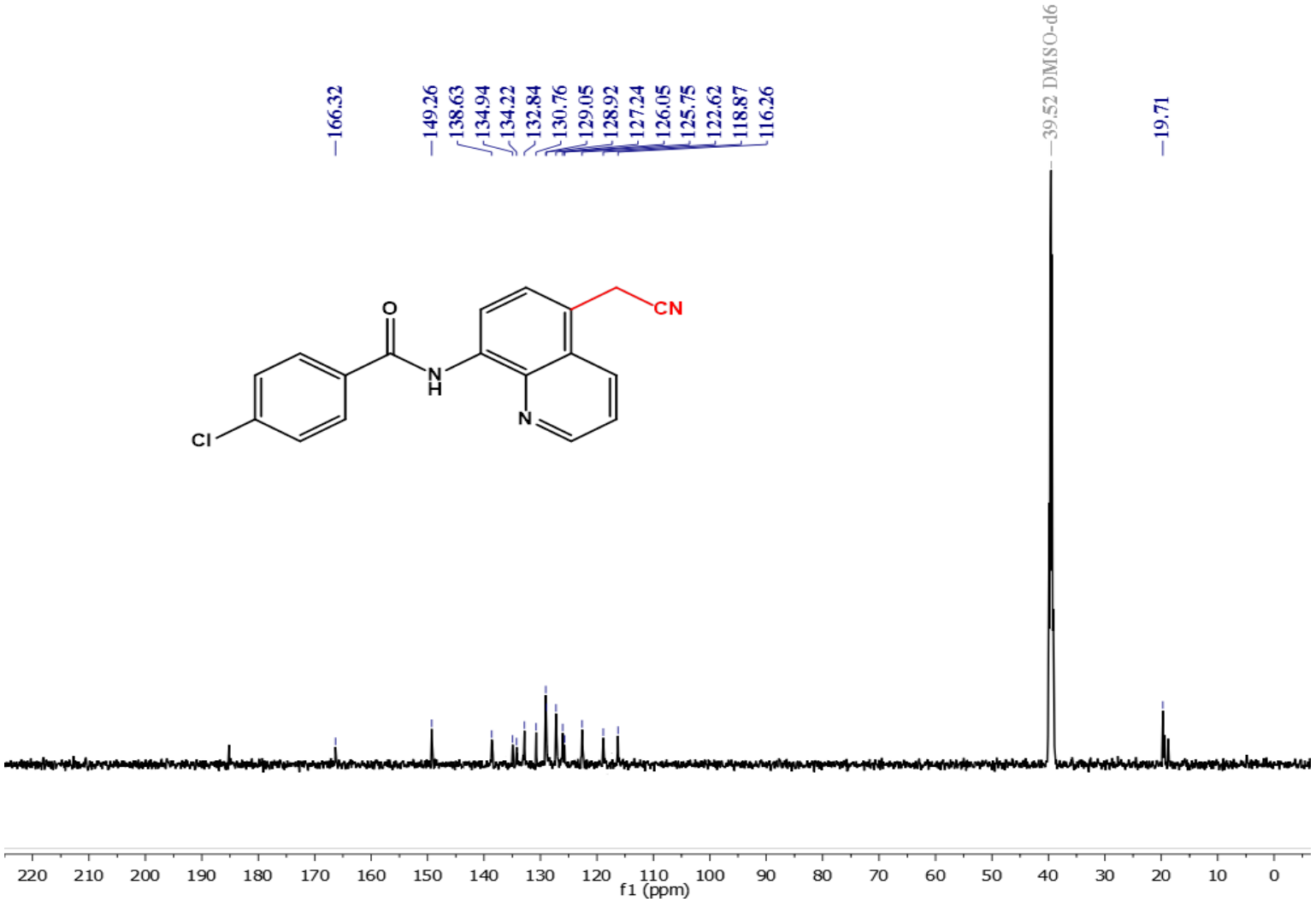
^{13}C NMR spectrum of 3f



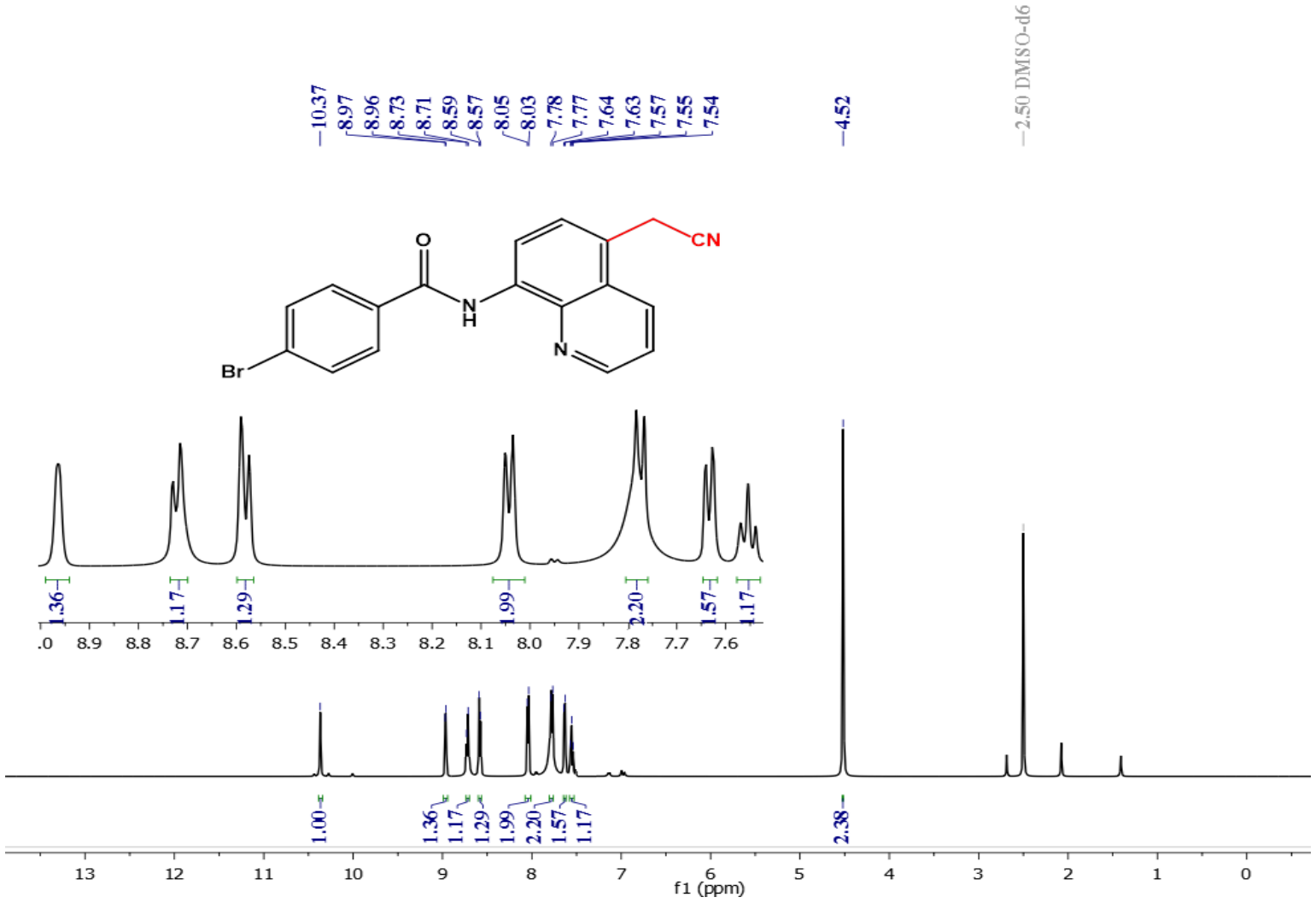
^{1}H NMR spectrum of 3g



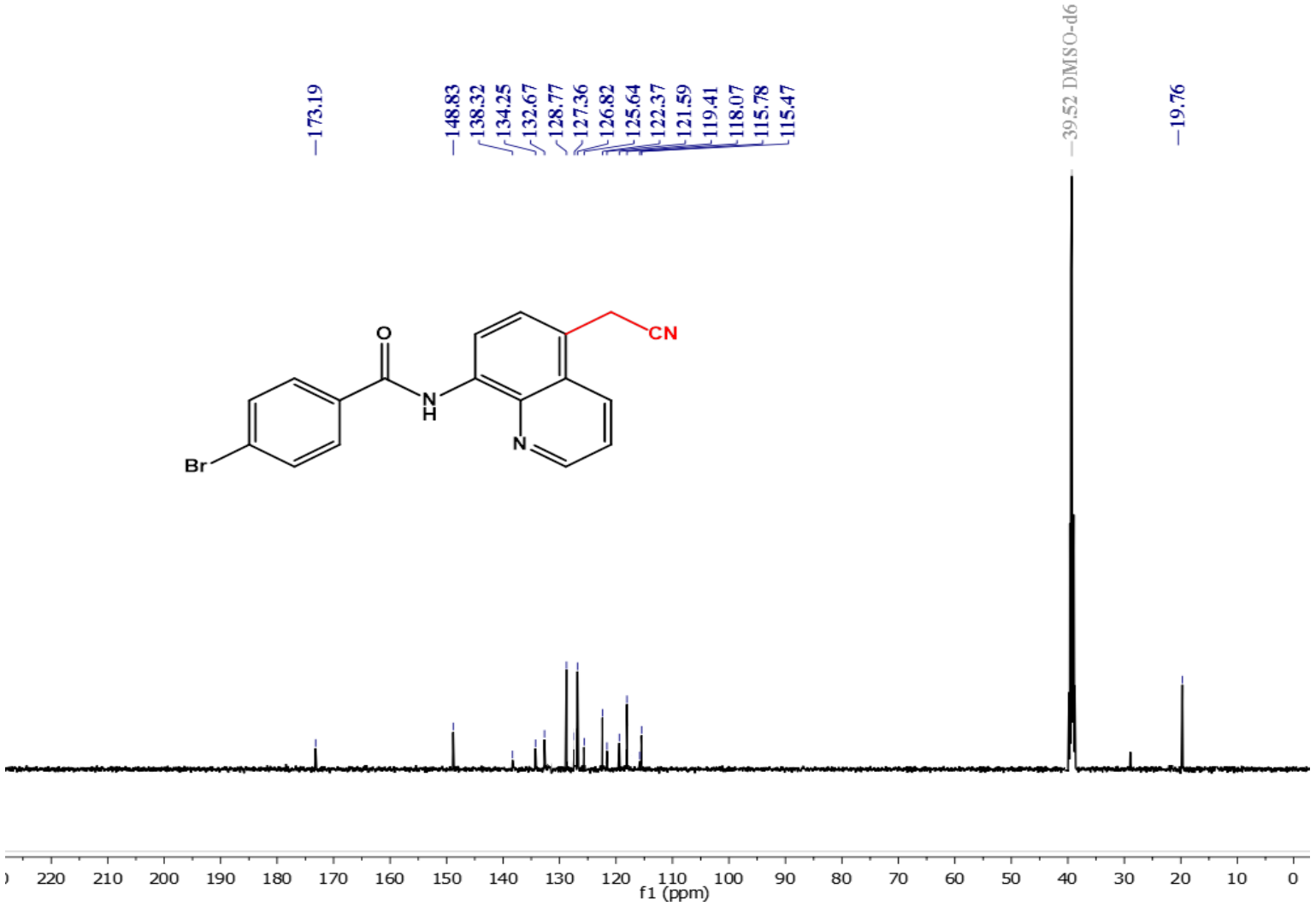
^{13}C NMR spectrum of 3g



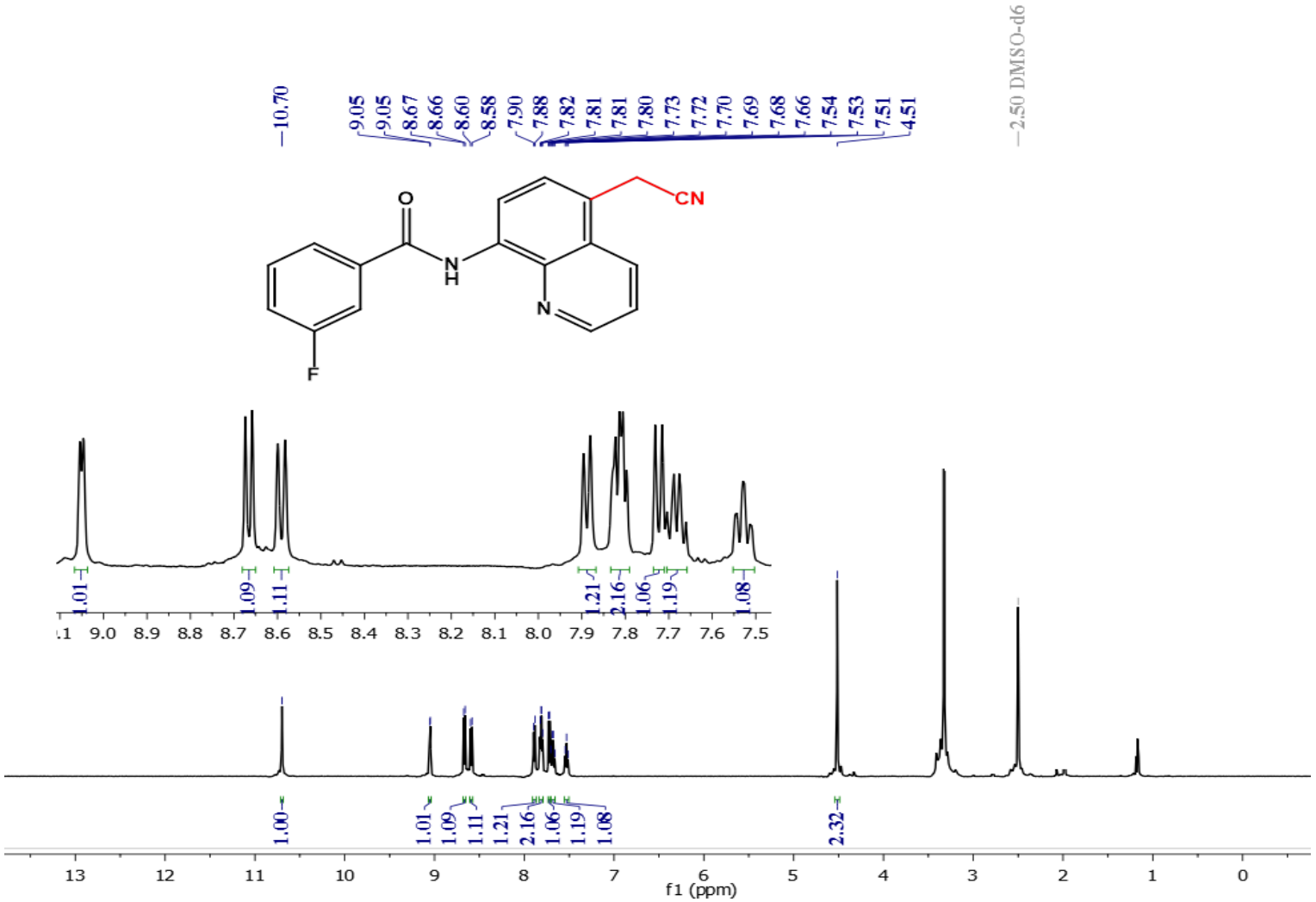
[1]H NMR spectrum of 3h



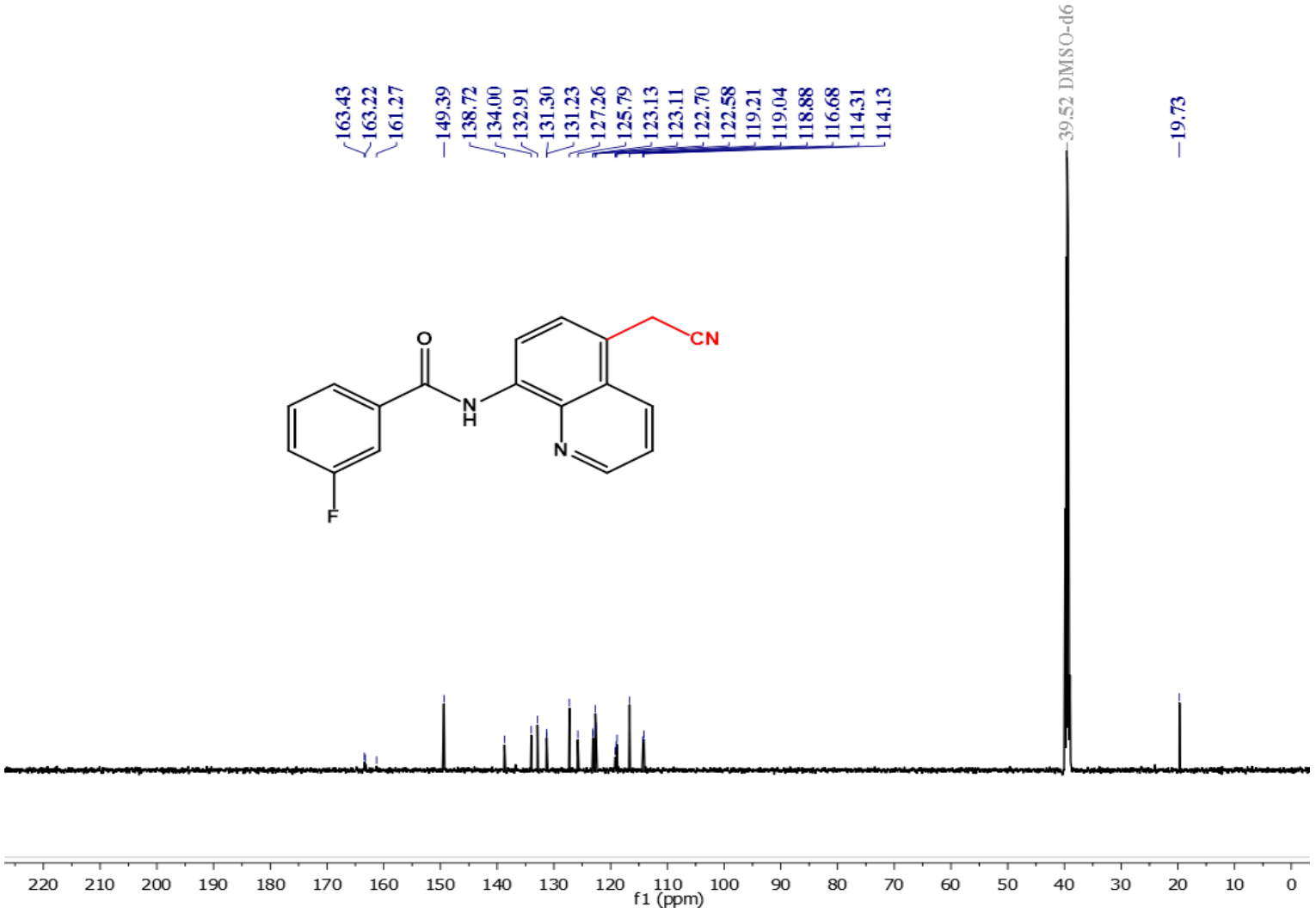
^{13}C NMR spectrum of 3h



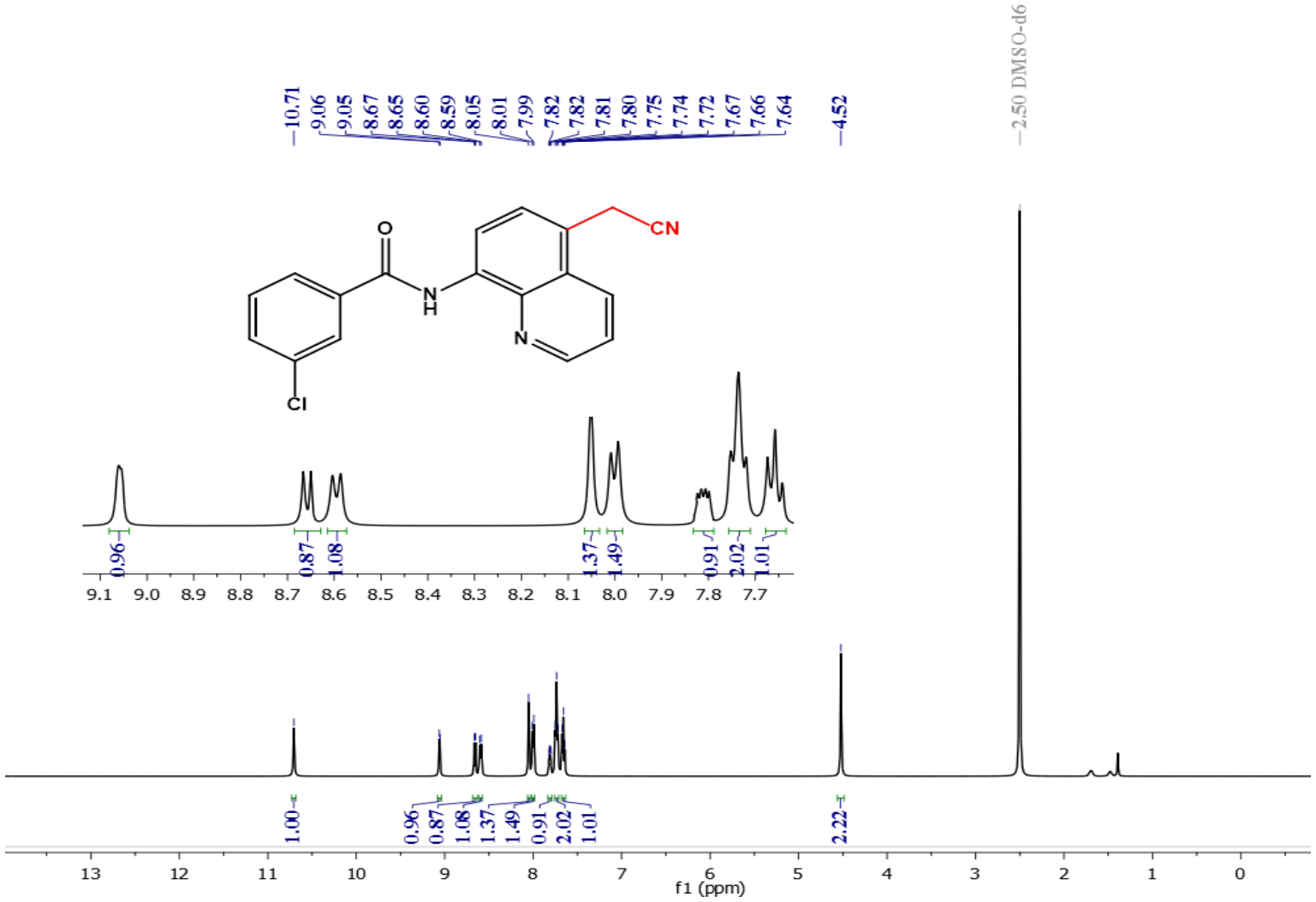
^{1}H NMR spectrum of 3i



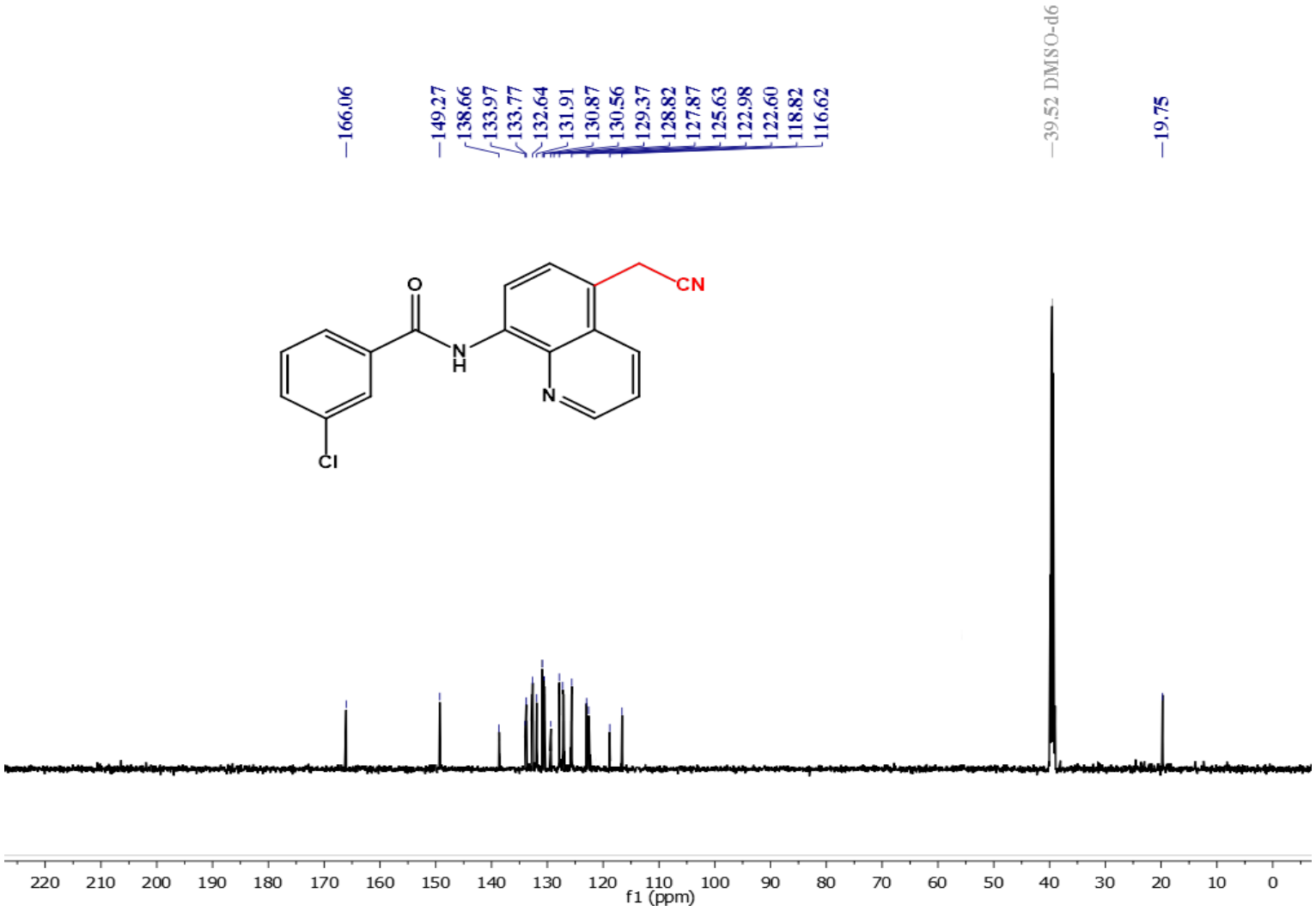
^{13}C NMR spectrum of 3i



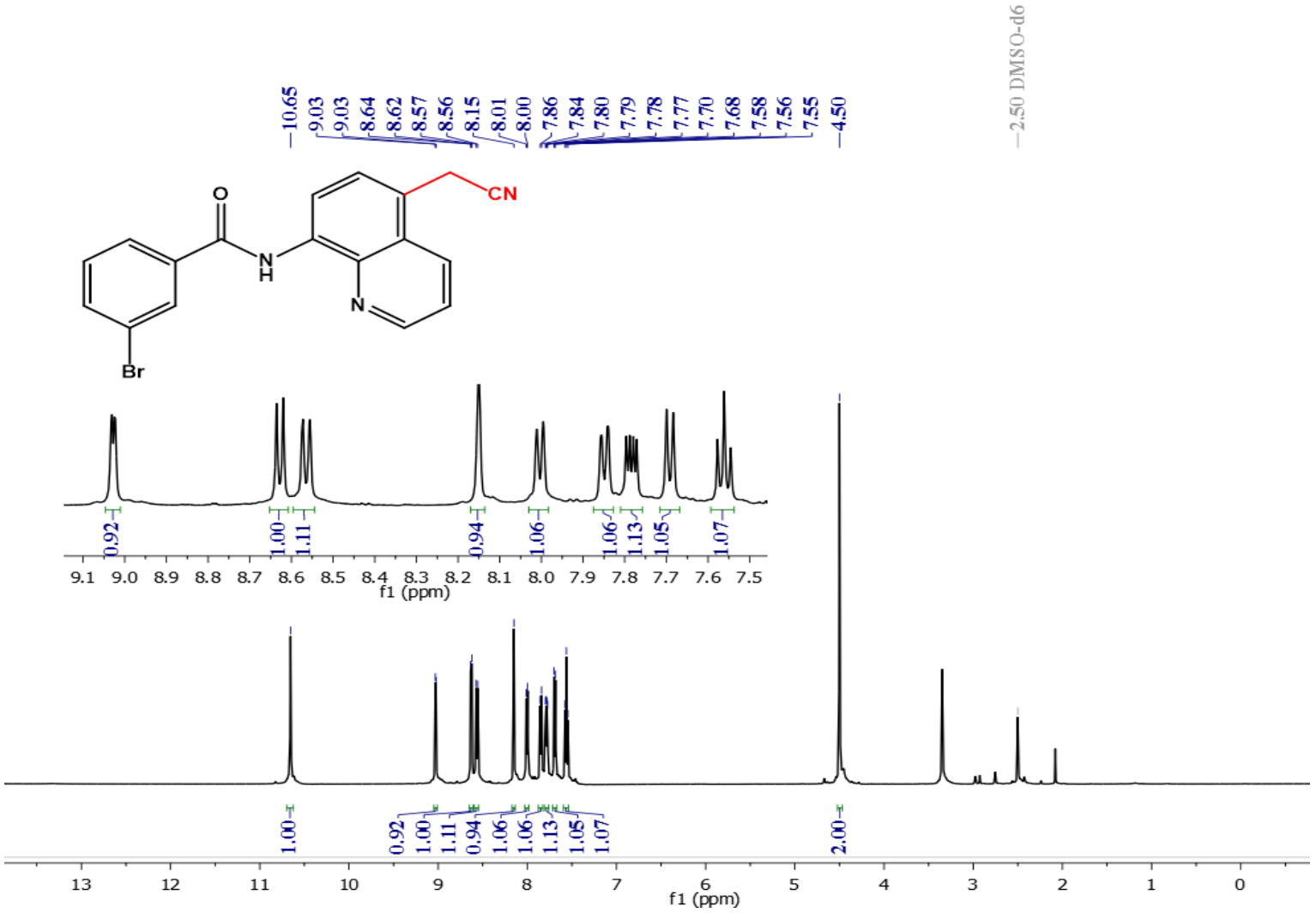
^{1}H NMR spectrum of 3j



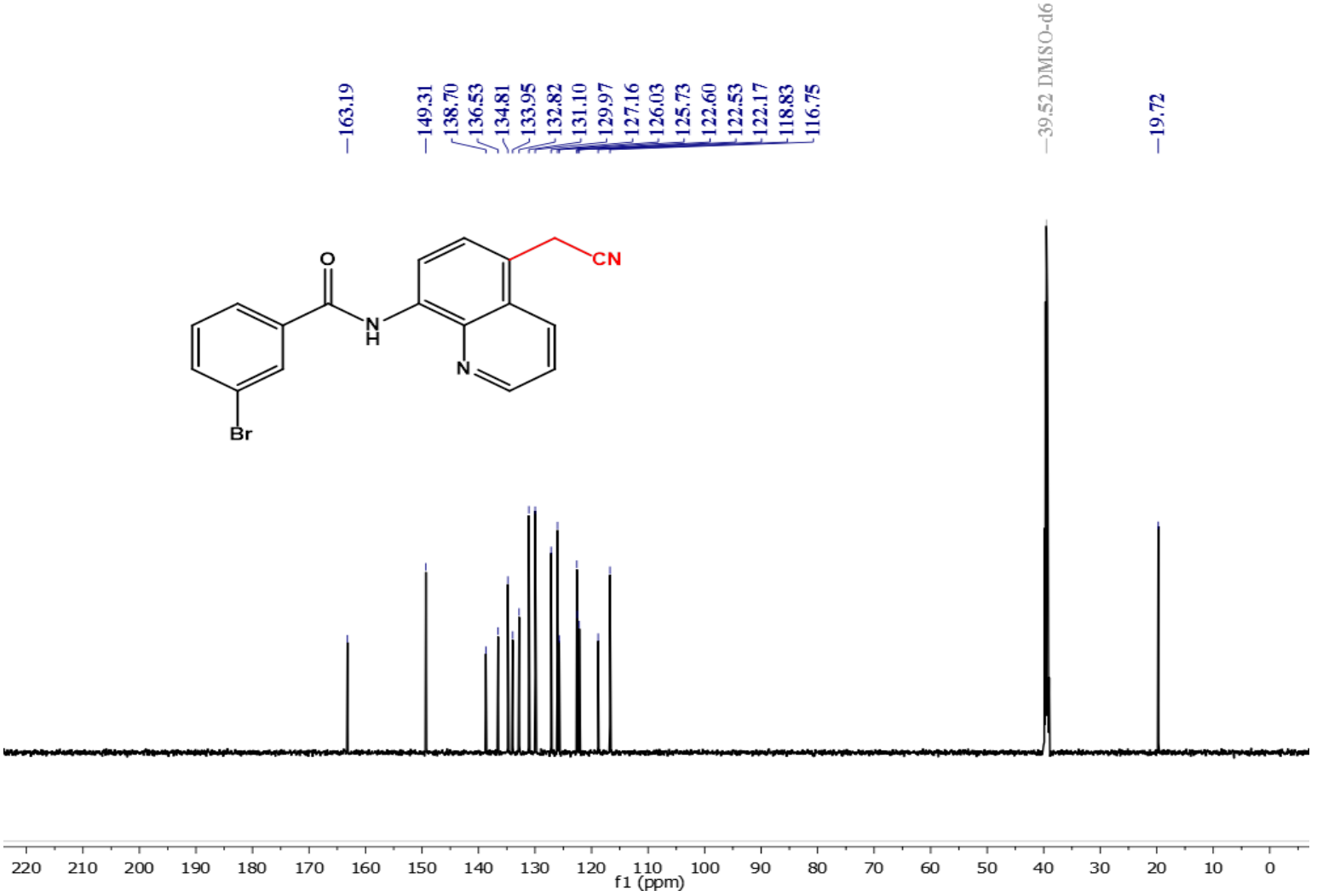
^{13}C NMR spectrum of 3j



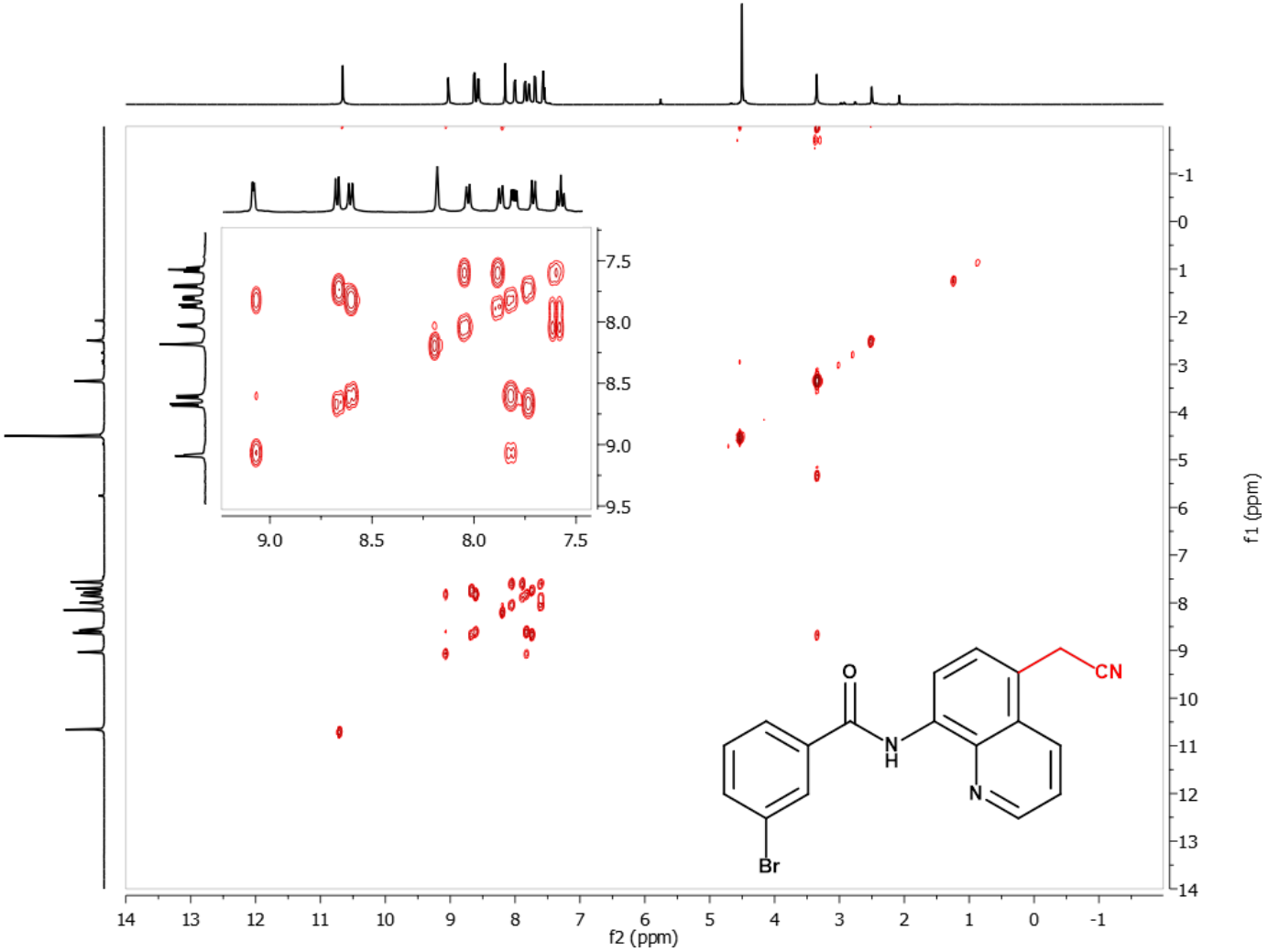
^{1}H NMR spectrum of 3k



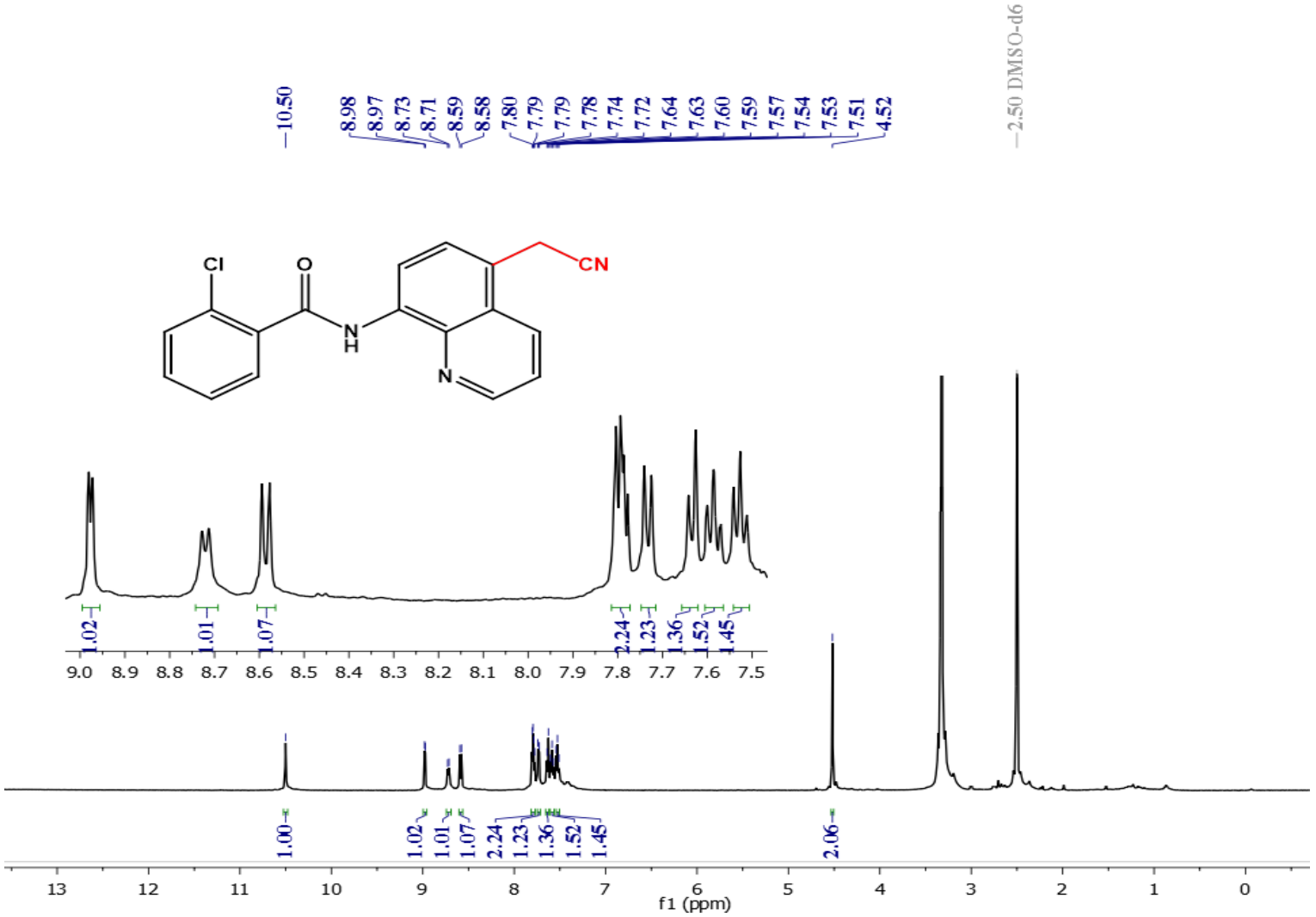
^{13}C NMR spectrum of 3k



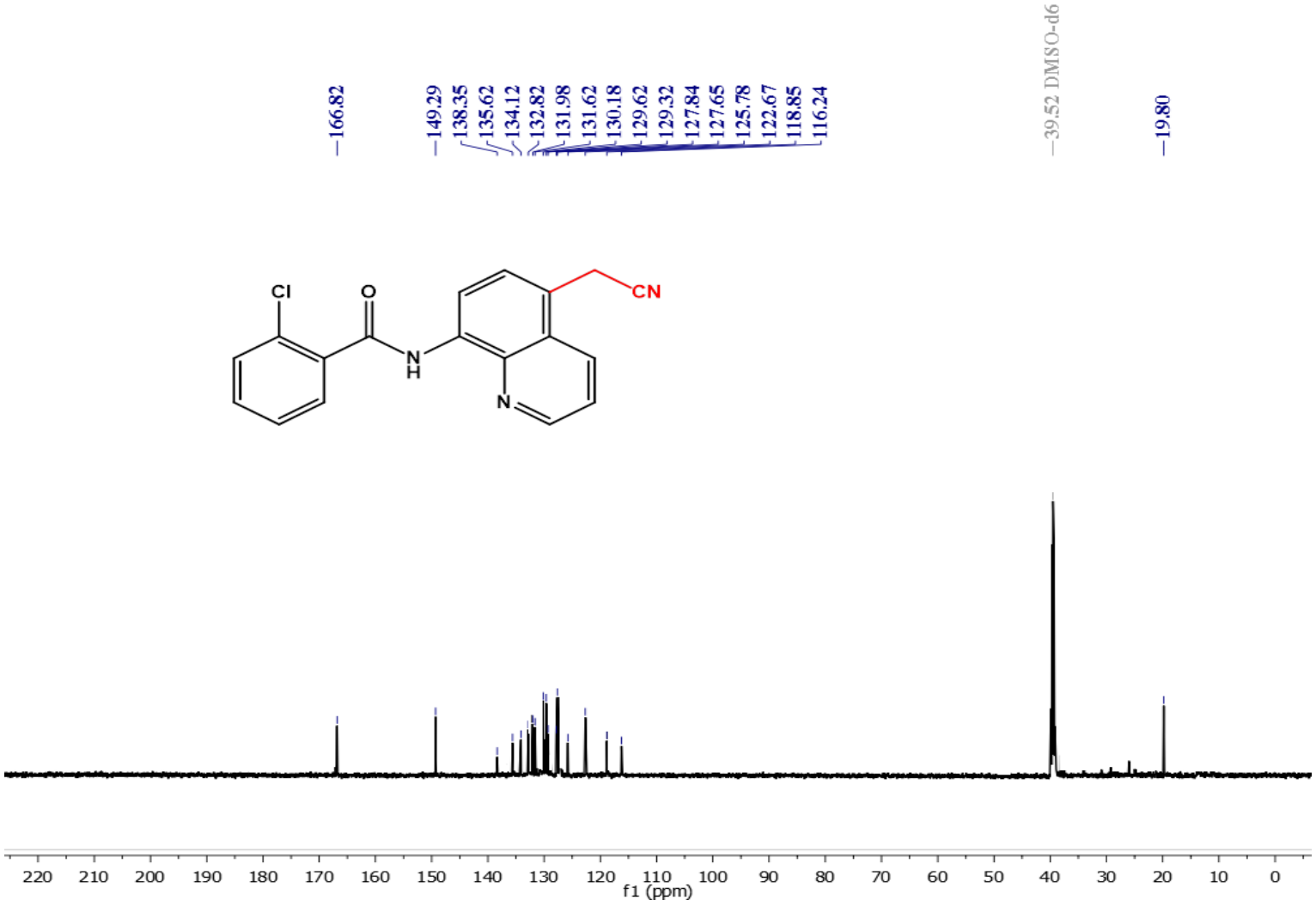
HH-COSY NMR spectrum of 3k



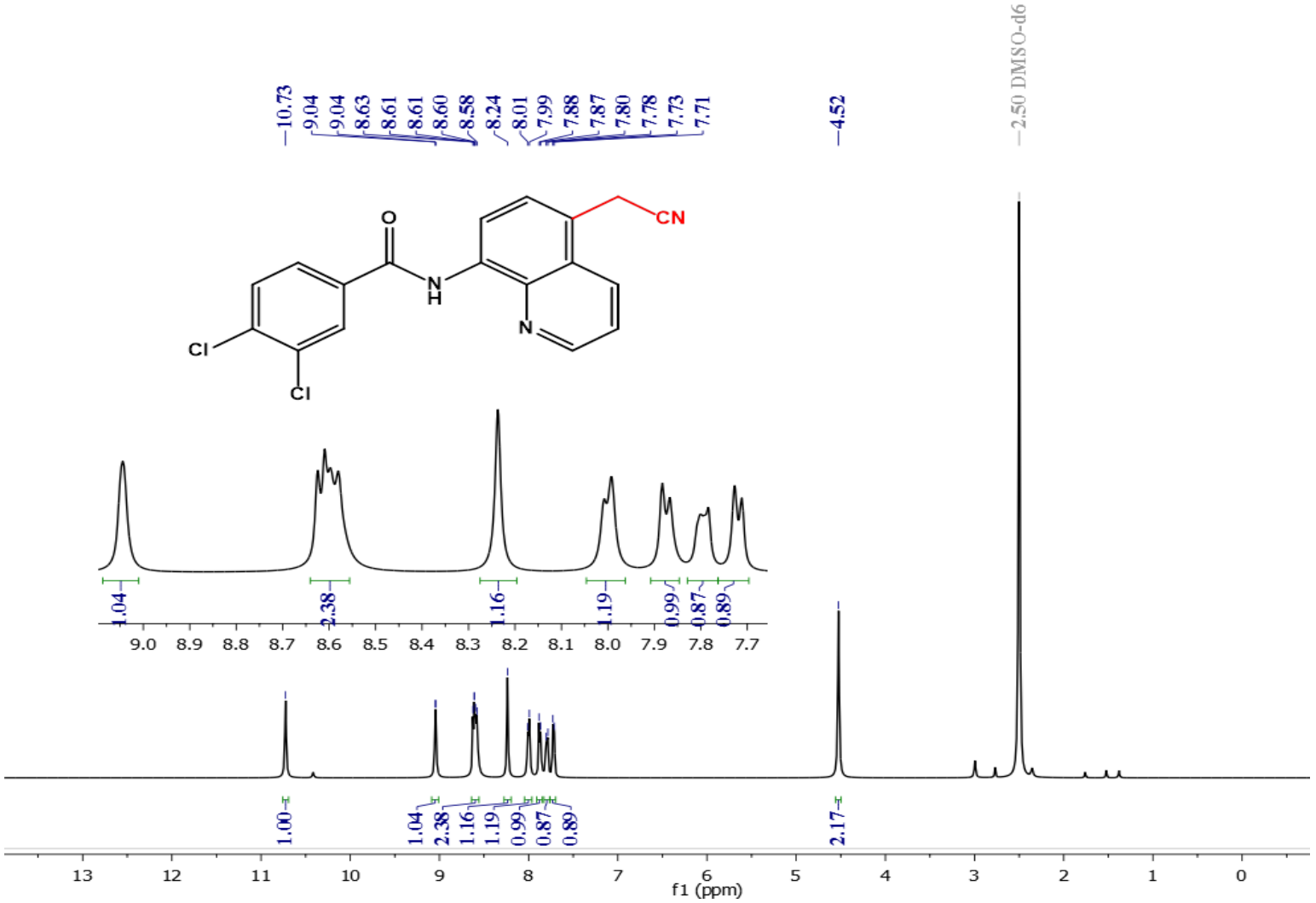
^{1}H NMR spectrum of 3l



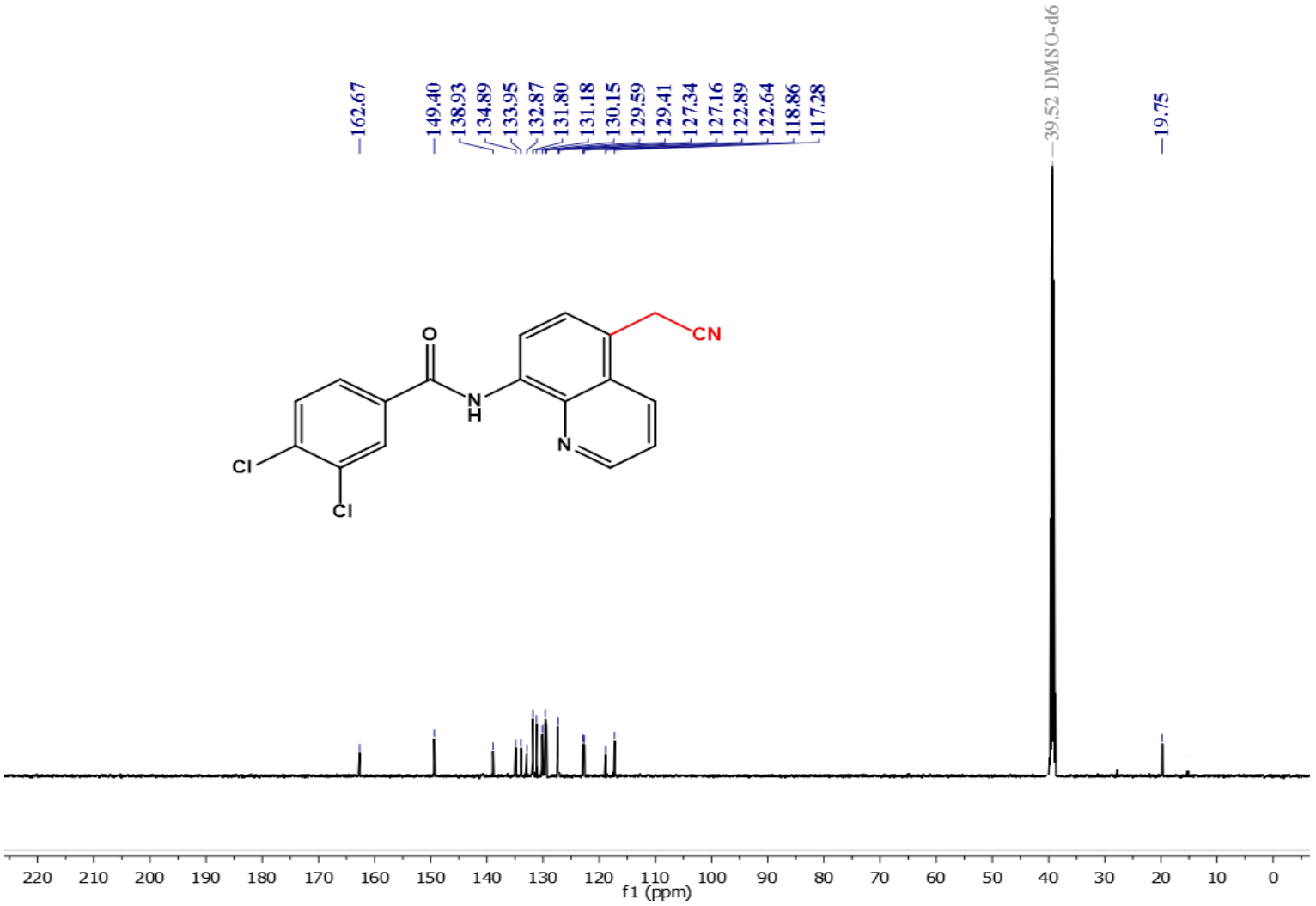
^{13}C NMR spectrum of 3l



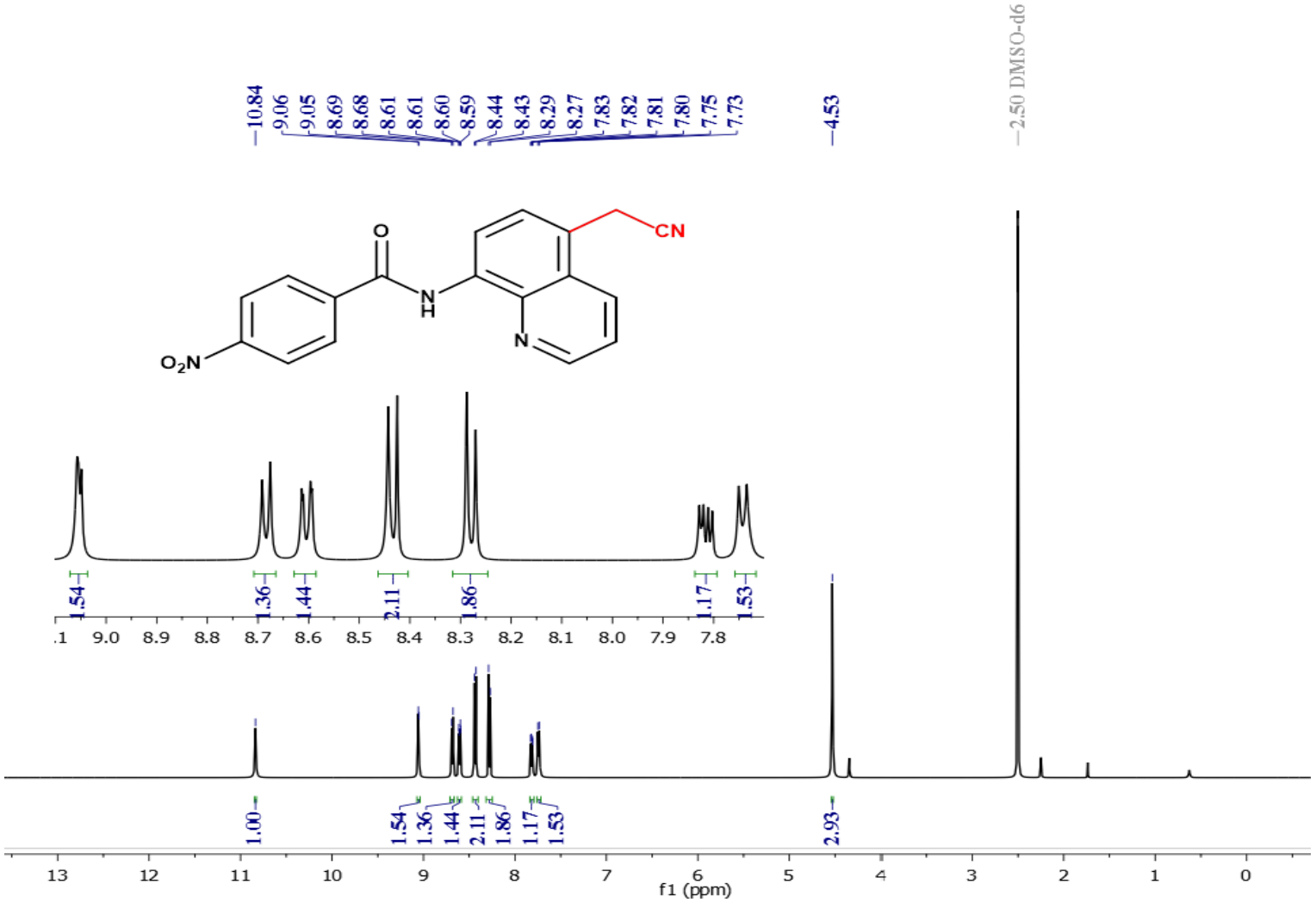
[1]H NMR spectrum of 3m



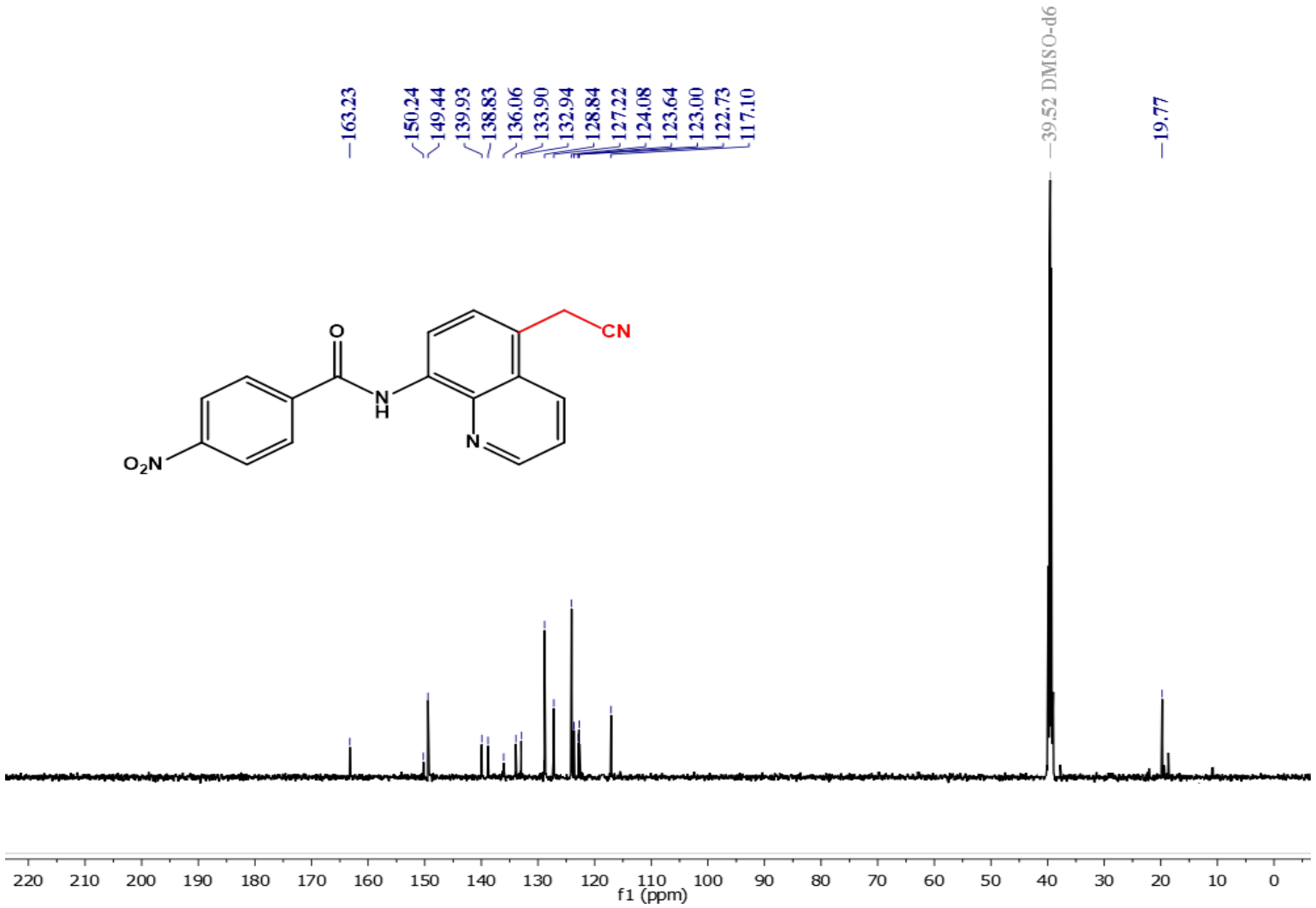
^{13}C NMR spectrum of 3m



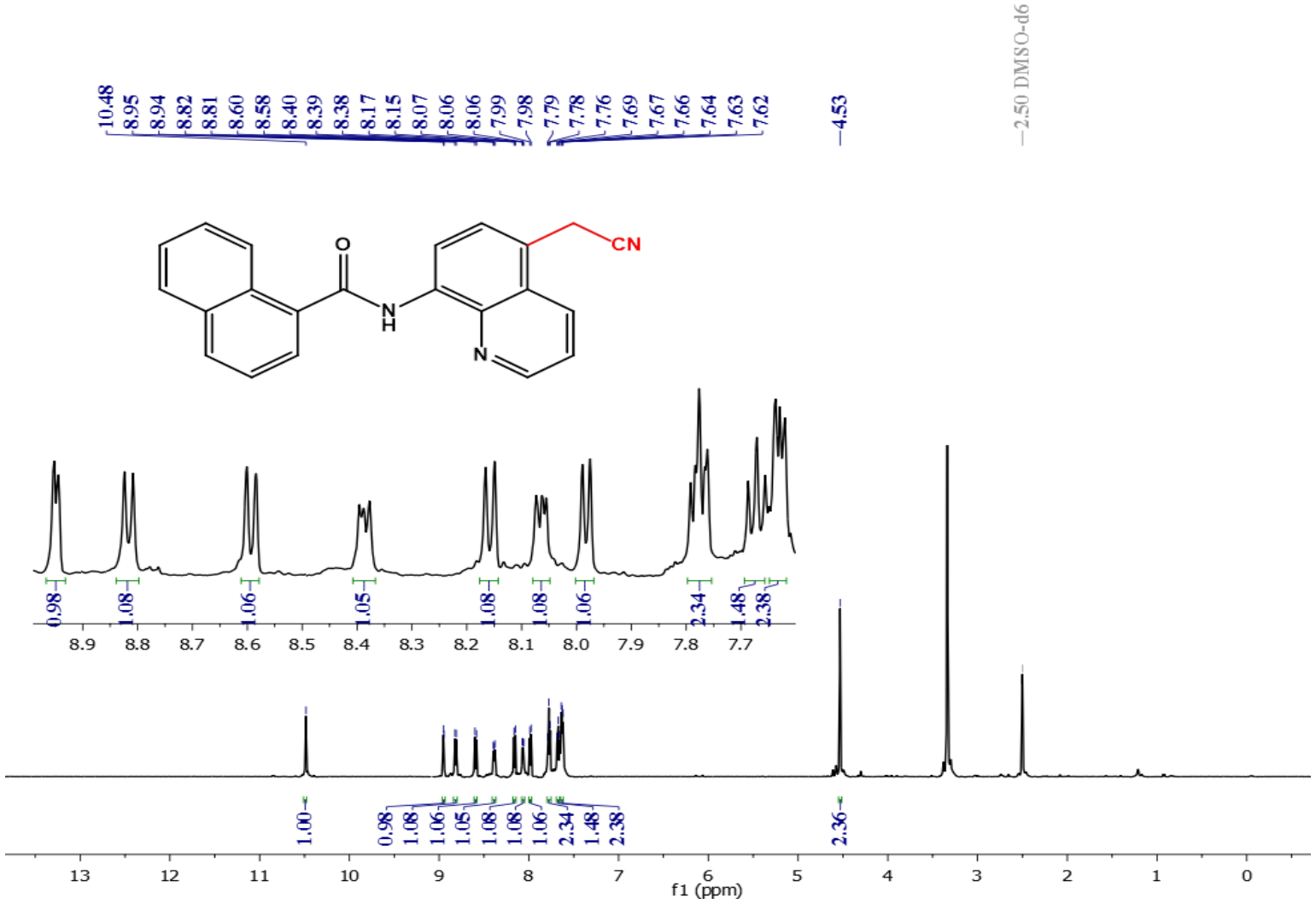
^{1}H NMR spectrum of 3n



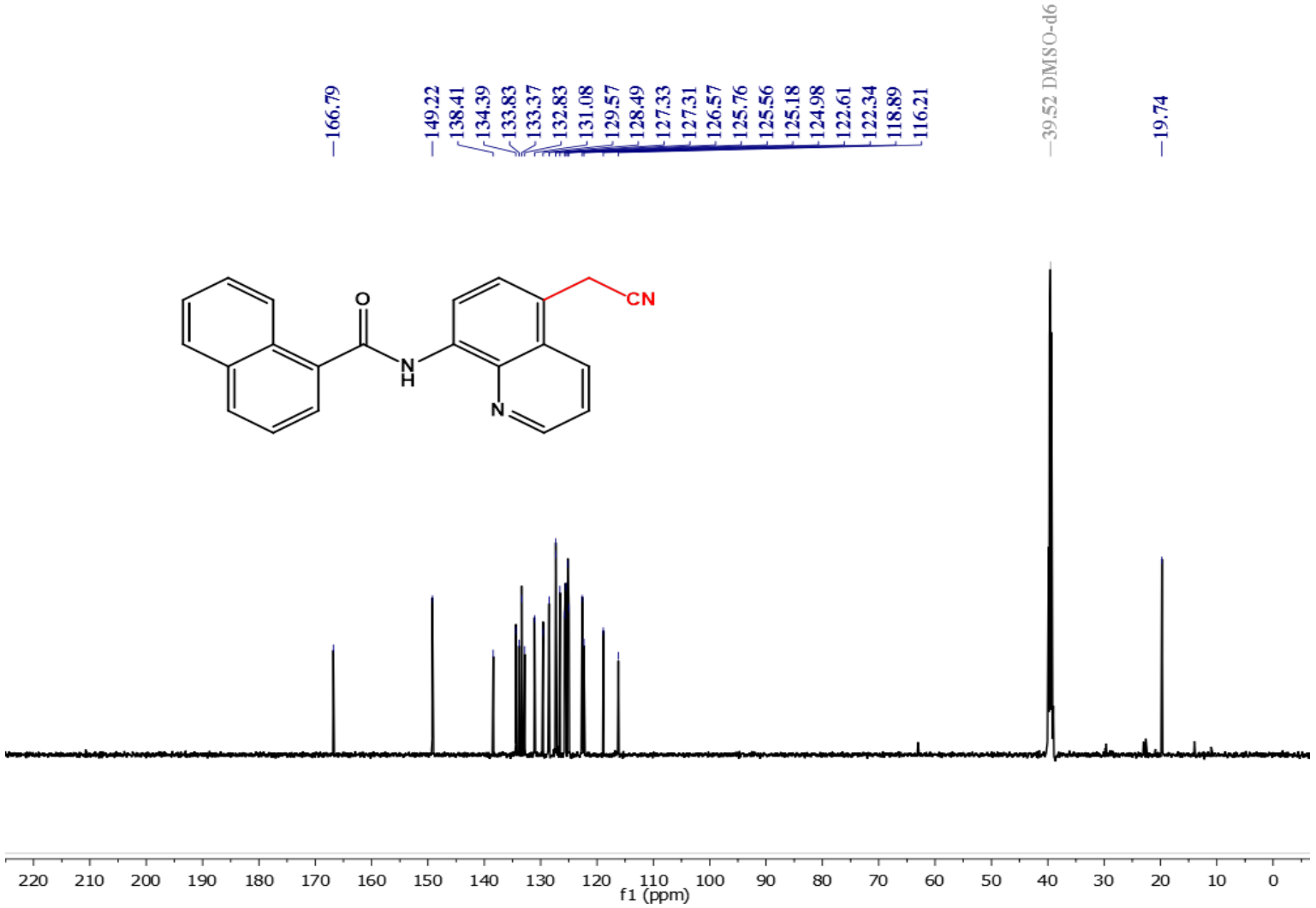
^{13}C NMR spectrum of 3n



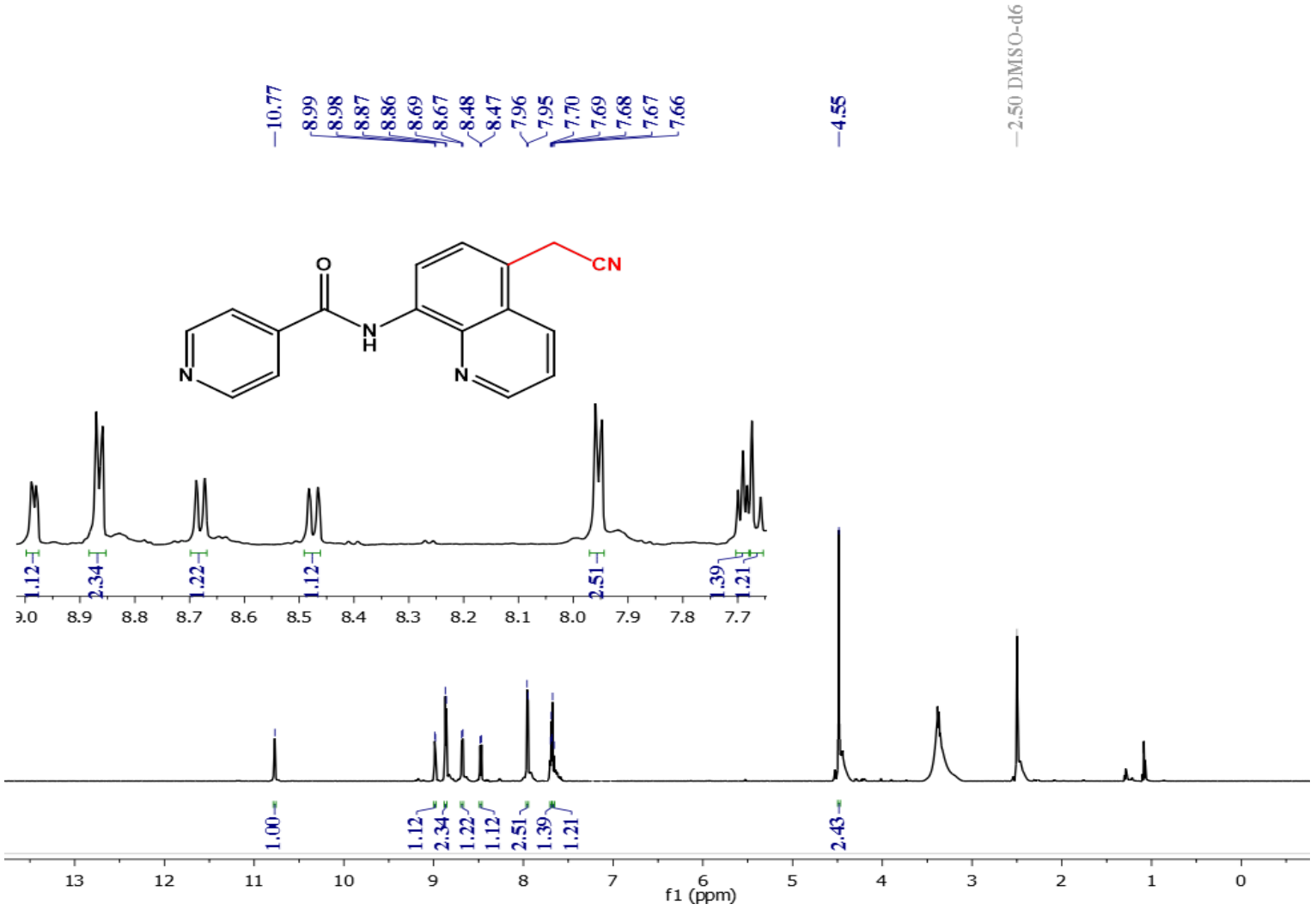
^{1}H NMR spectrum of 3o



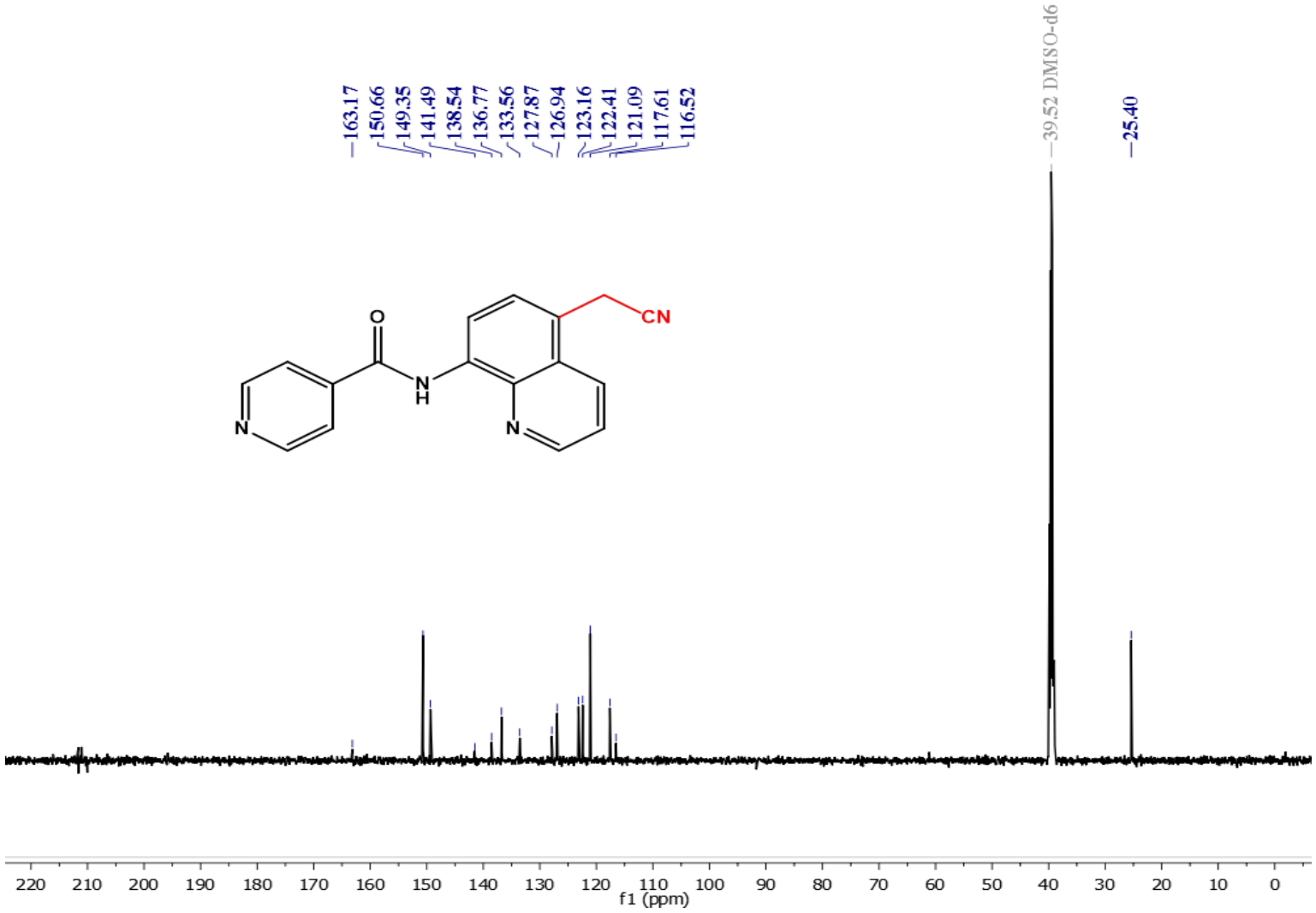
^{13}C NMR spectrum of 3o



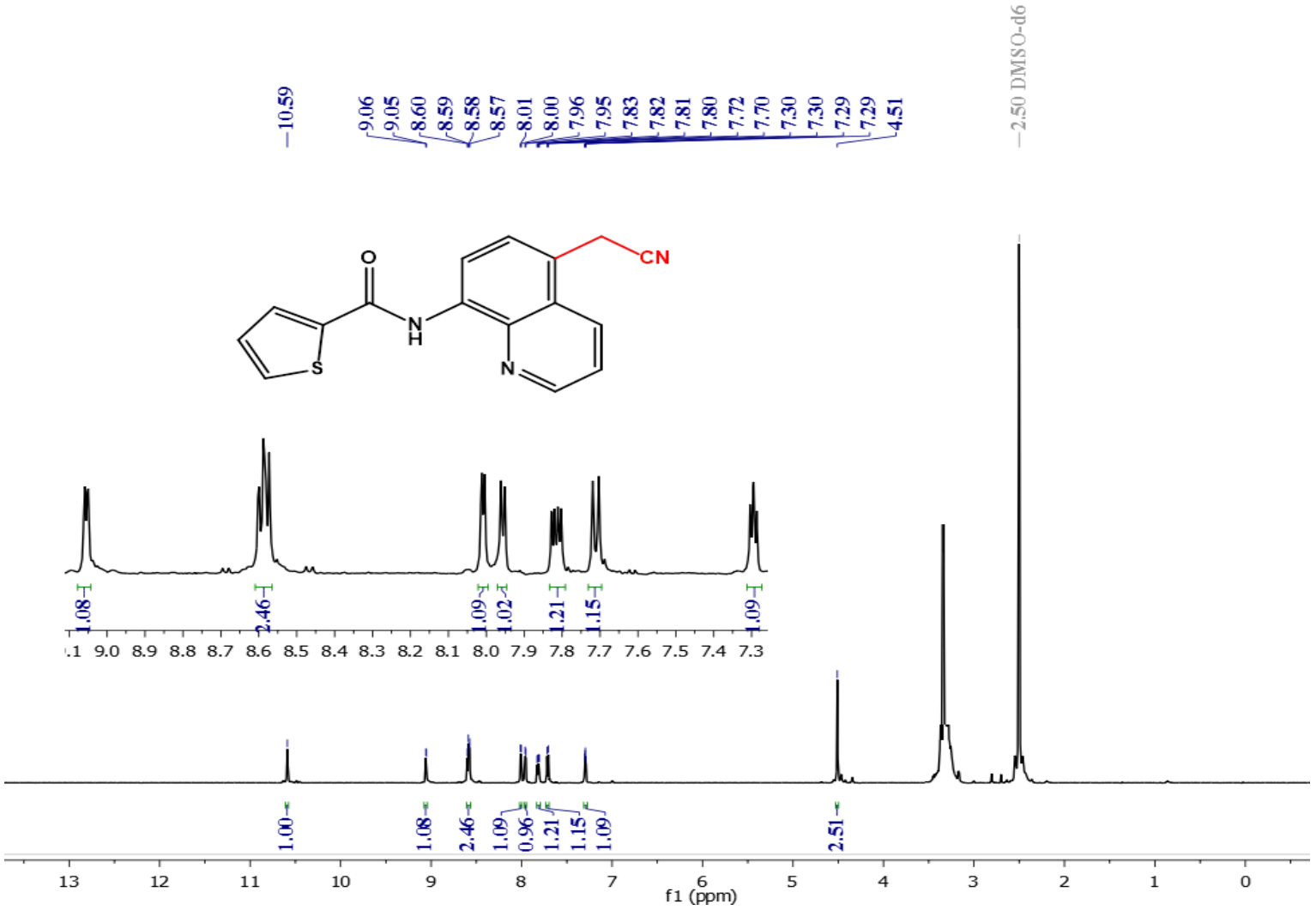
[1]H NMR spectrum of 3p



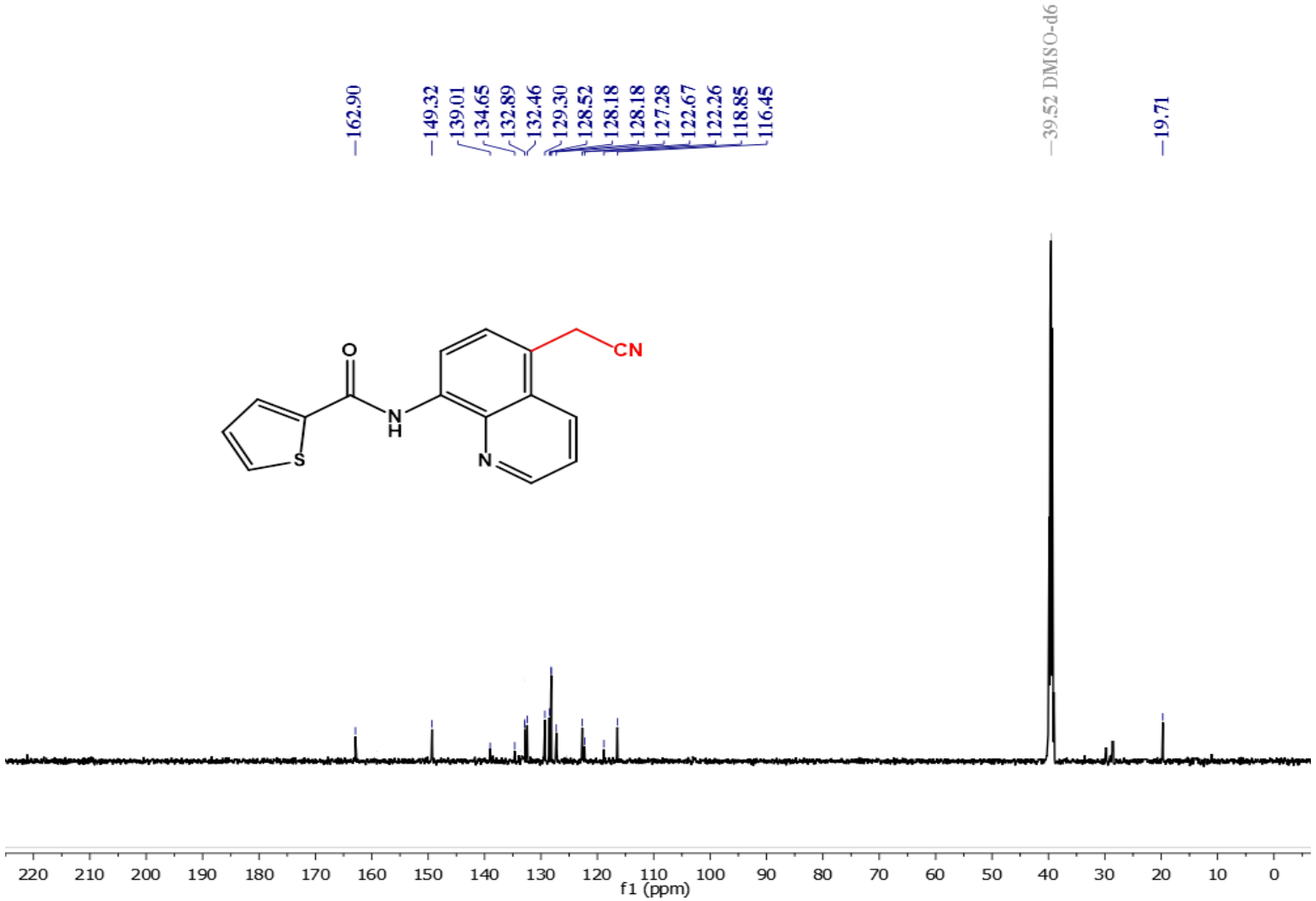
^{13}C NMR spectrum of 3p



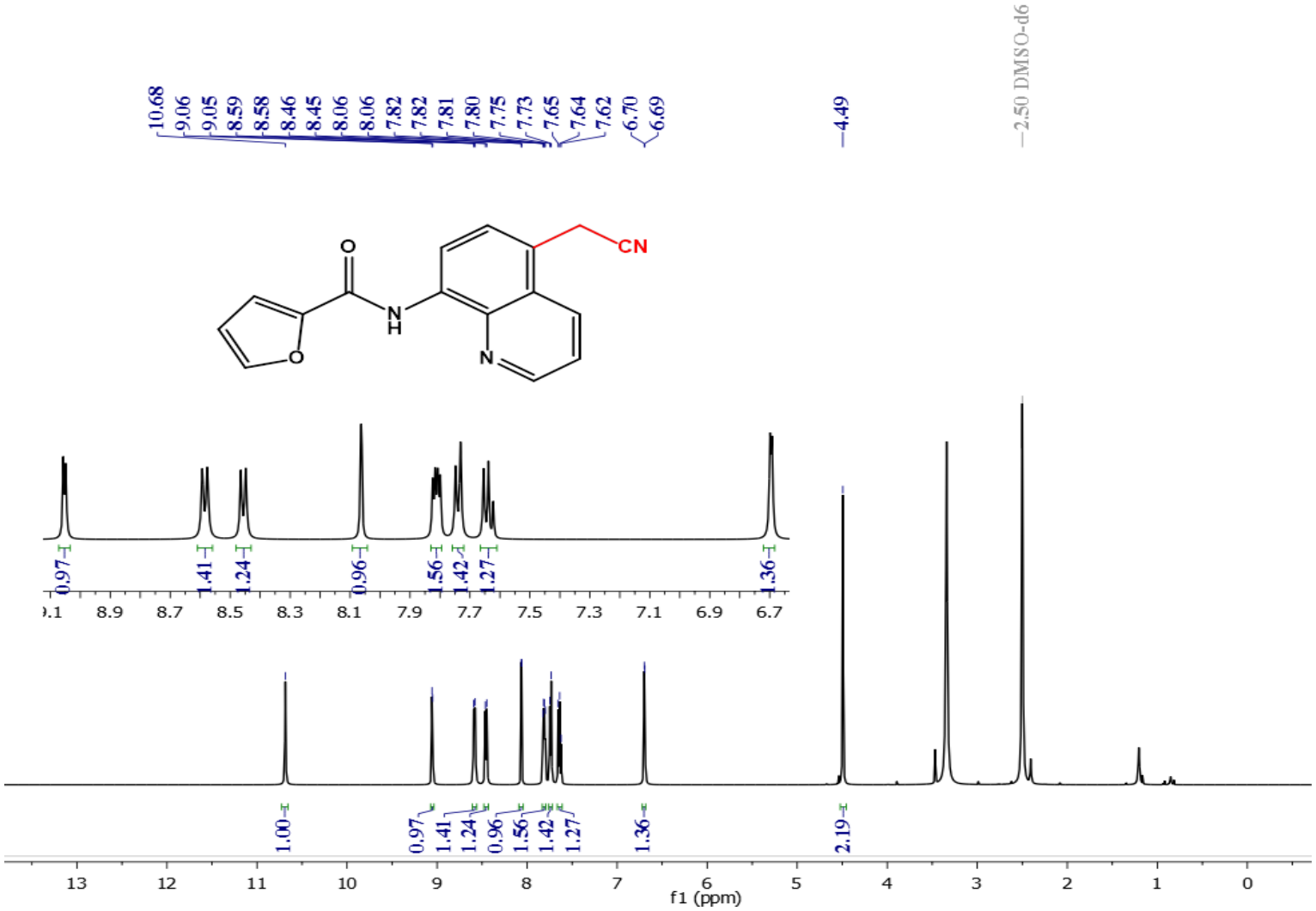
^{1}H NMR spectrum of 3q



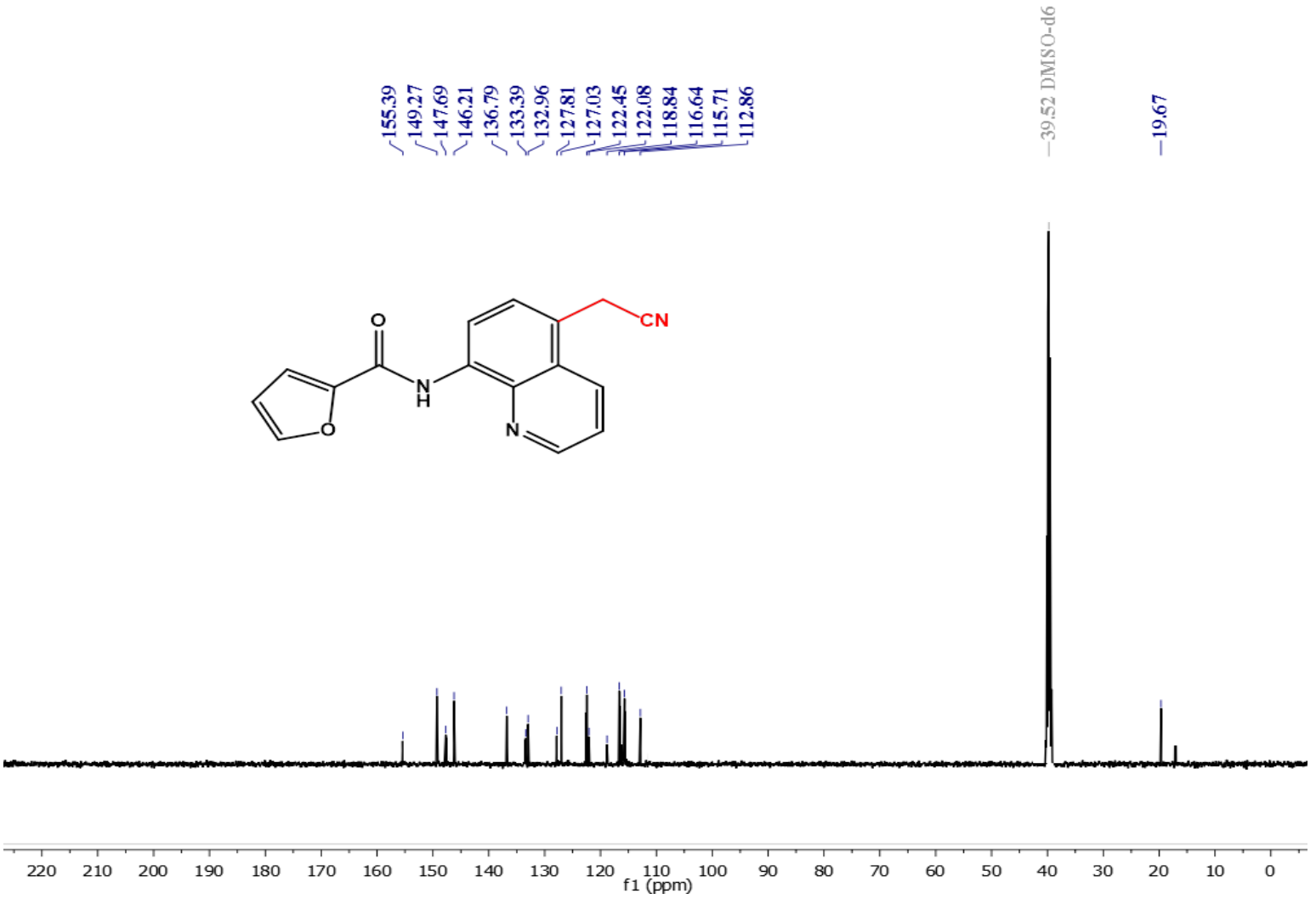
^{13}C NMR spectrum of 3q



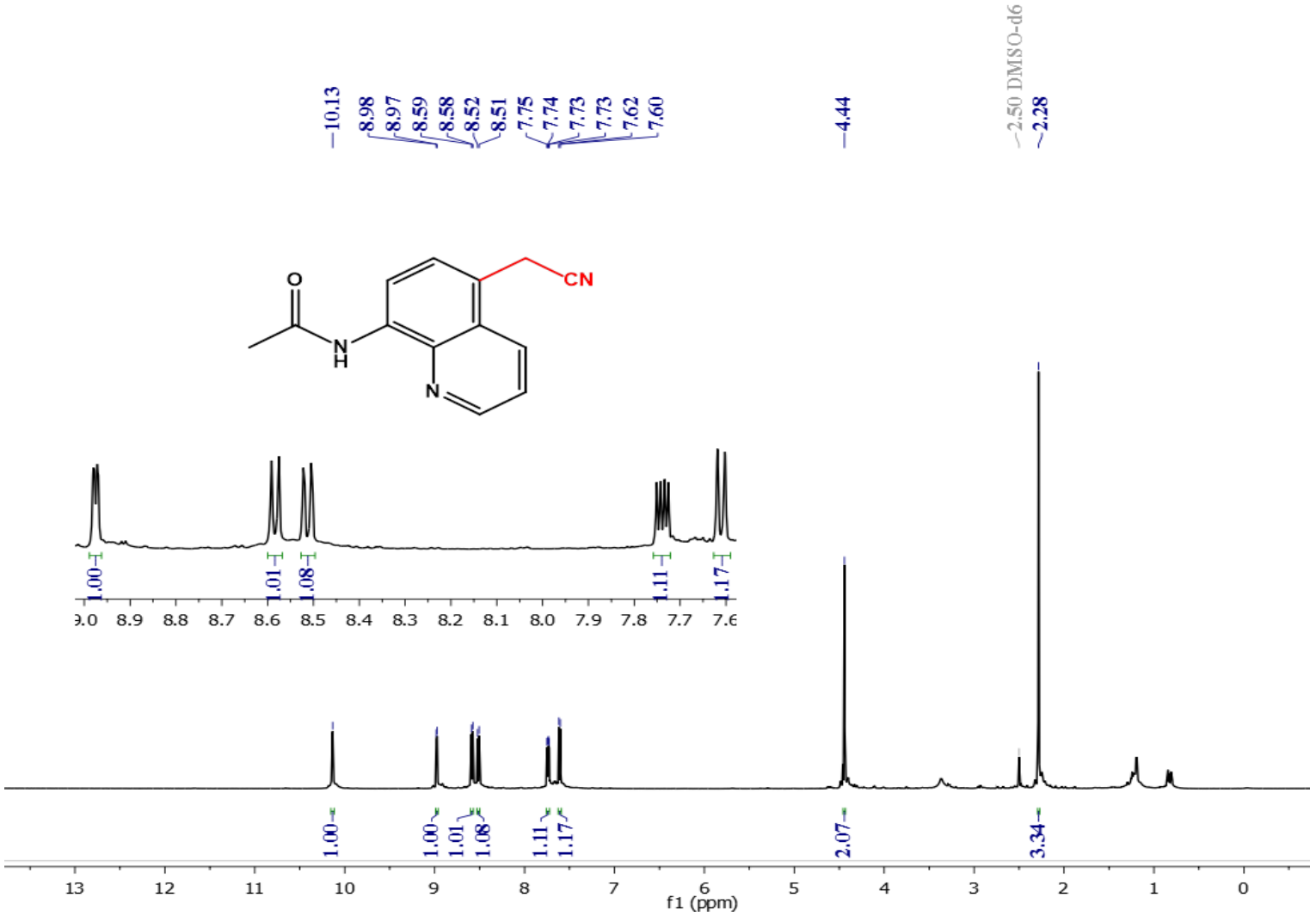
^{1}H NMR spectrum of 3r



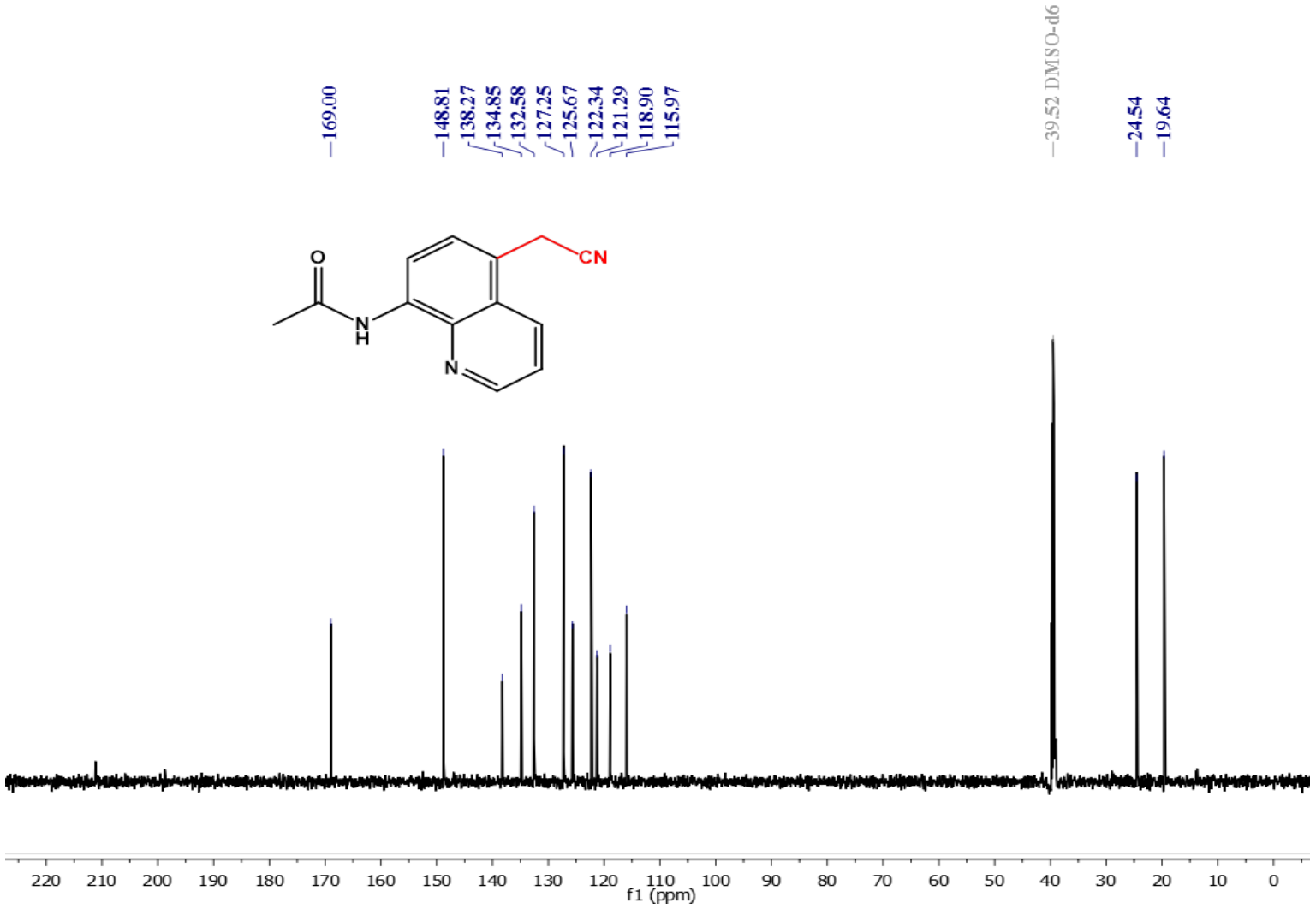
^{13}C NMR spectrum of 3r



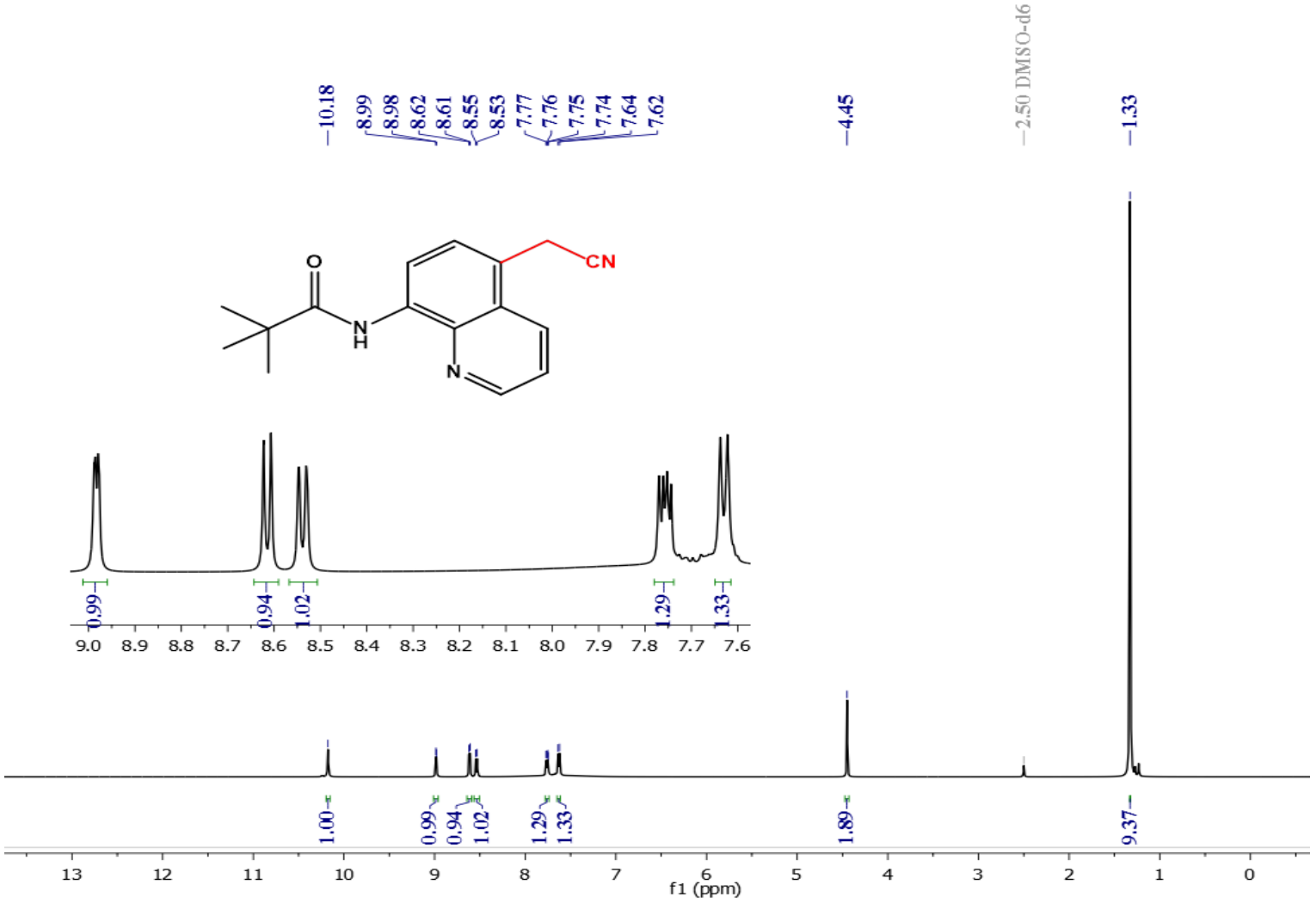
^{1}H NMR spectrum of 3s



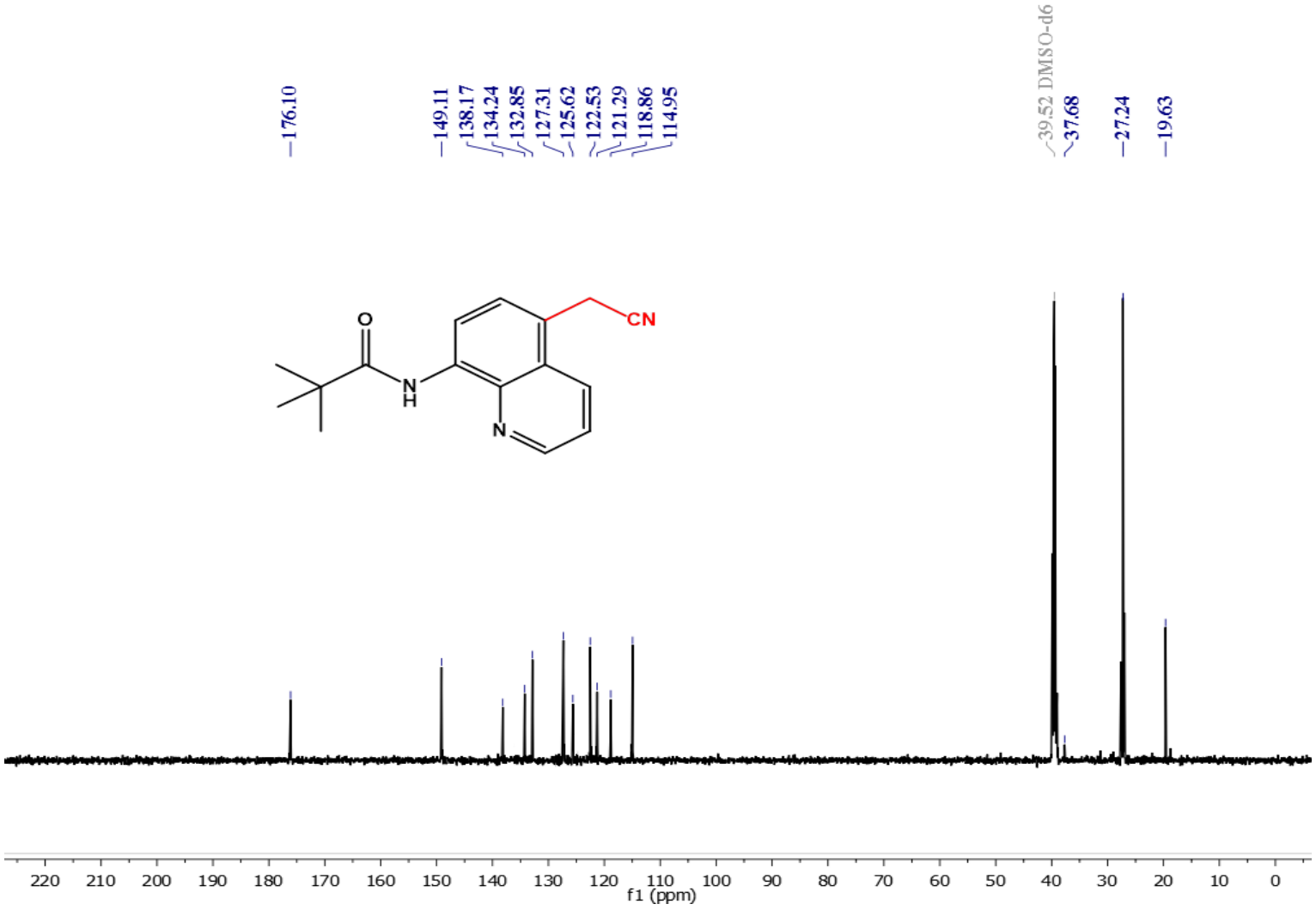
^{13}C NMR spectrum of 3s



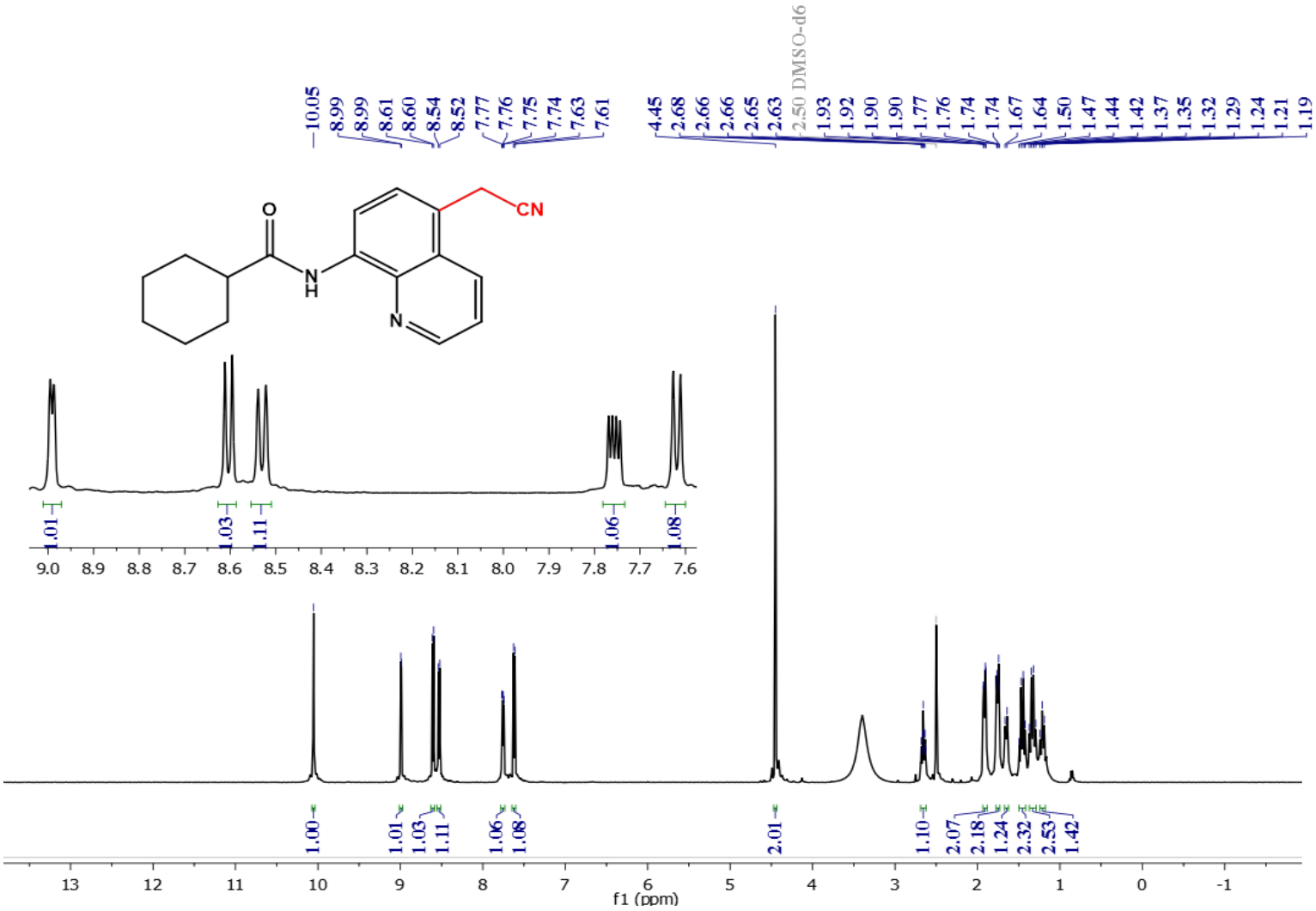
[1]H NMR spectrum of 3t



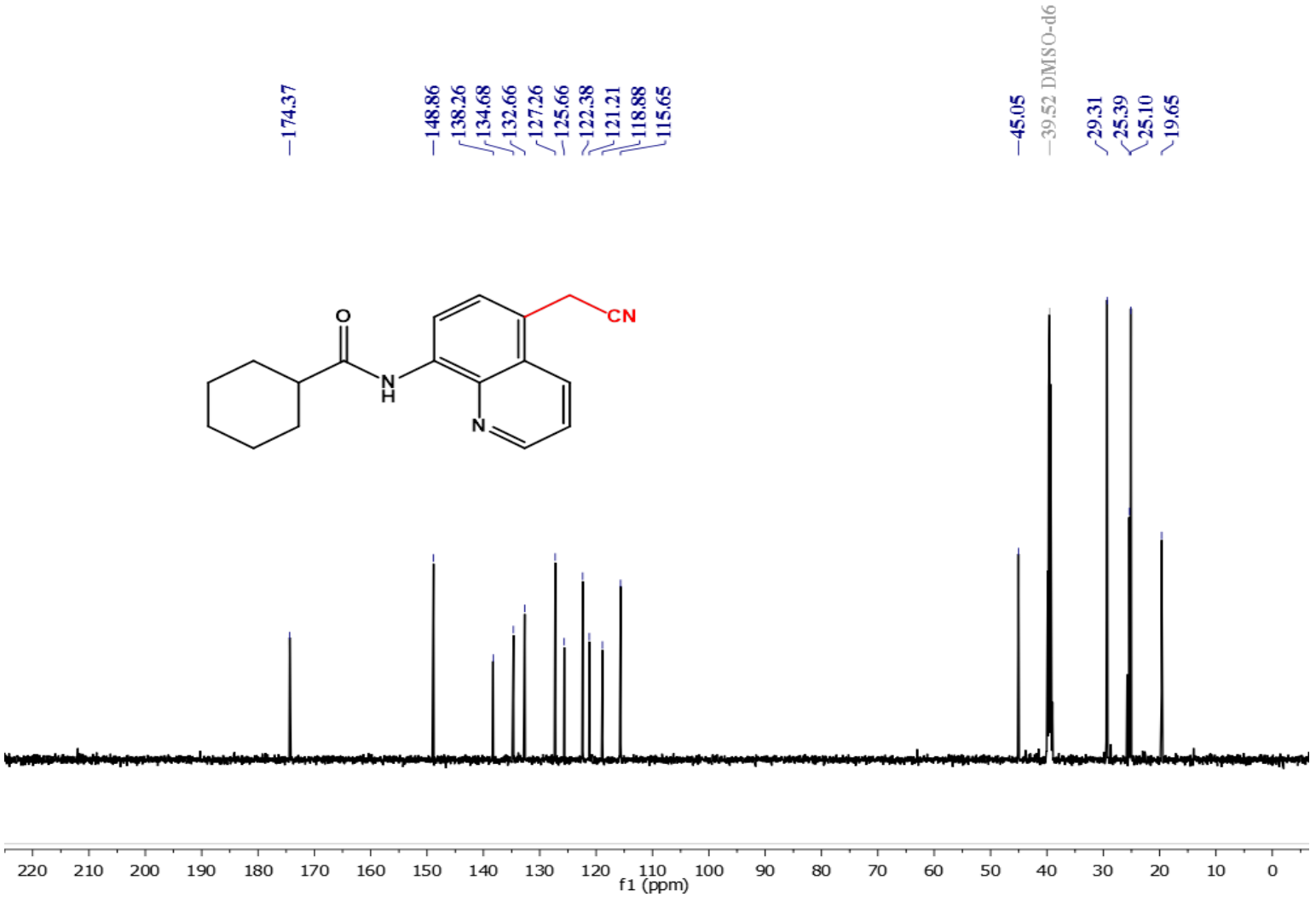
^{13}C NMR spectrum of 3t



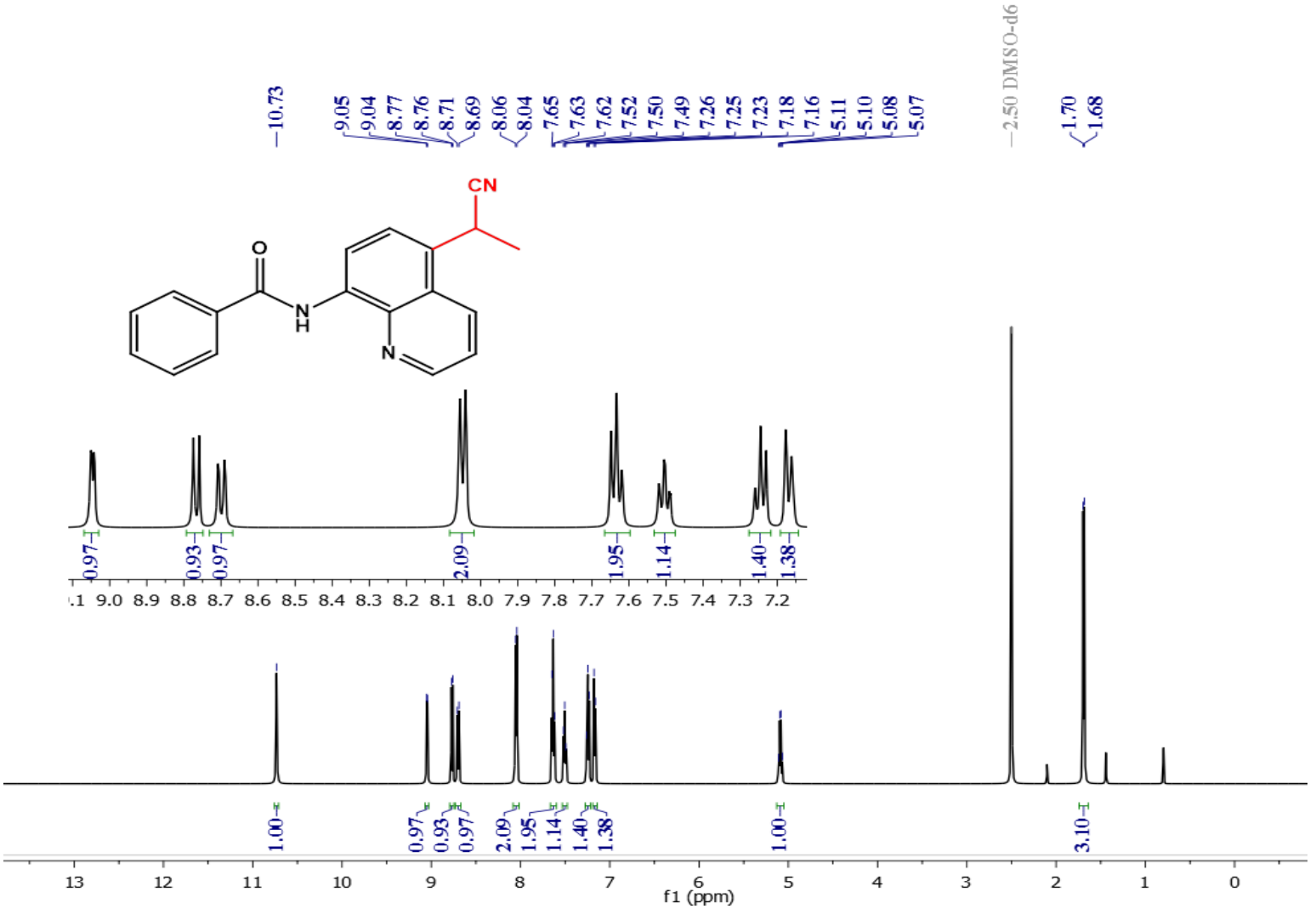
^{1}H NMR spectrum of 3u



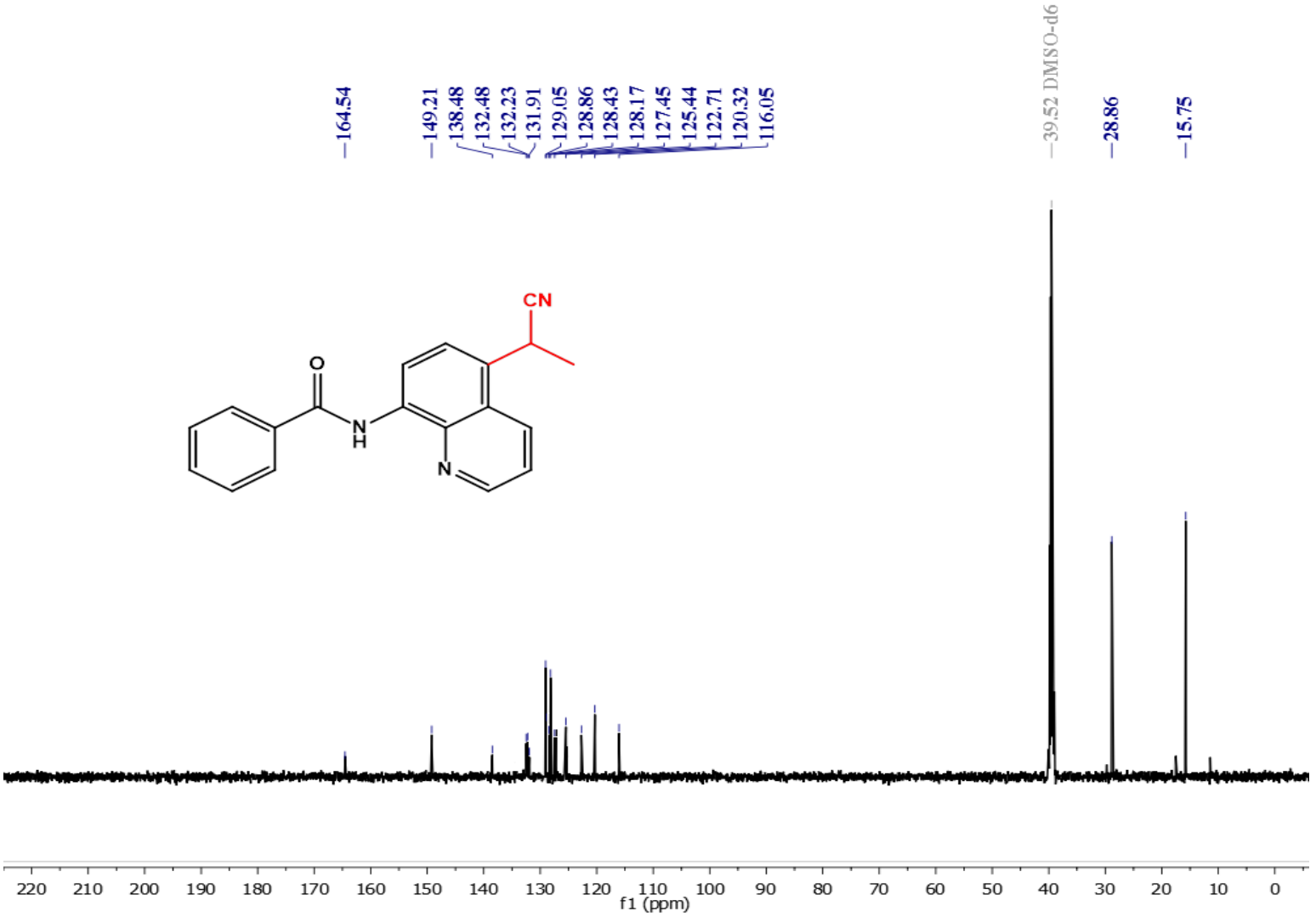
^{13}C NMR spectrum of 3u



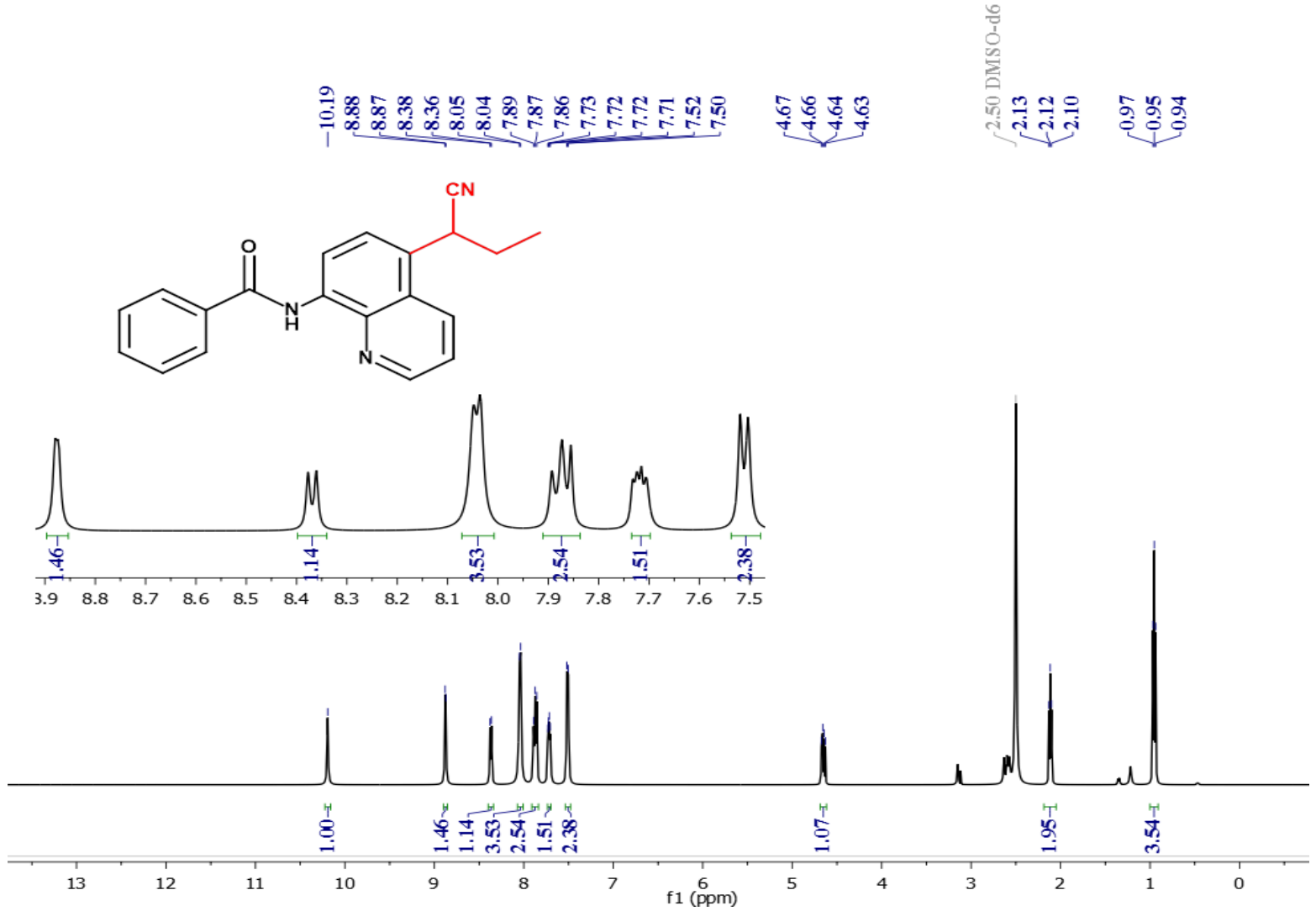
[1]H NMR spectrum of 4a



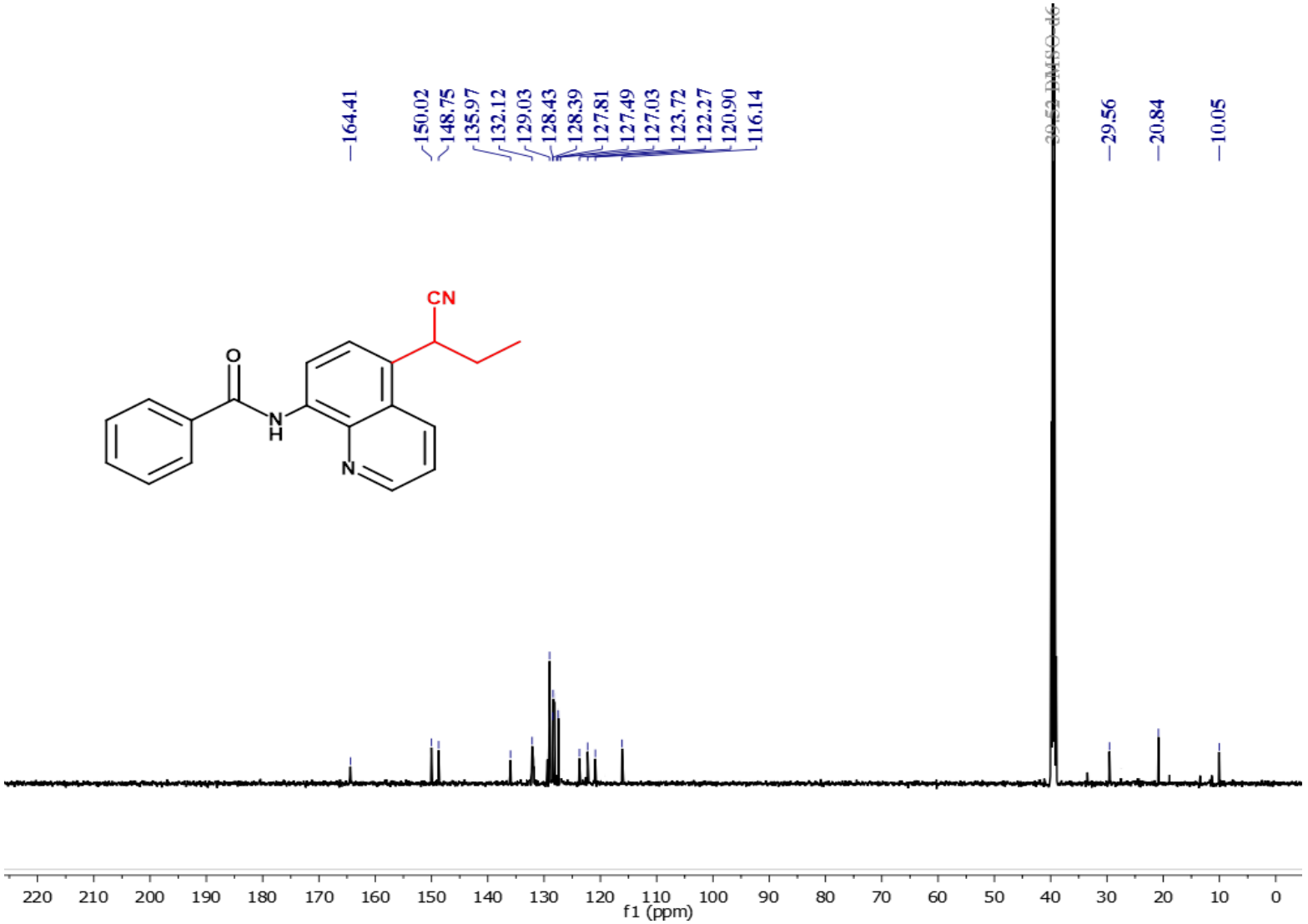
^{13}C NMR spectrum of 4a



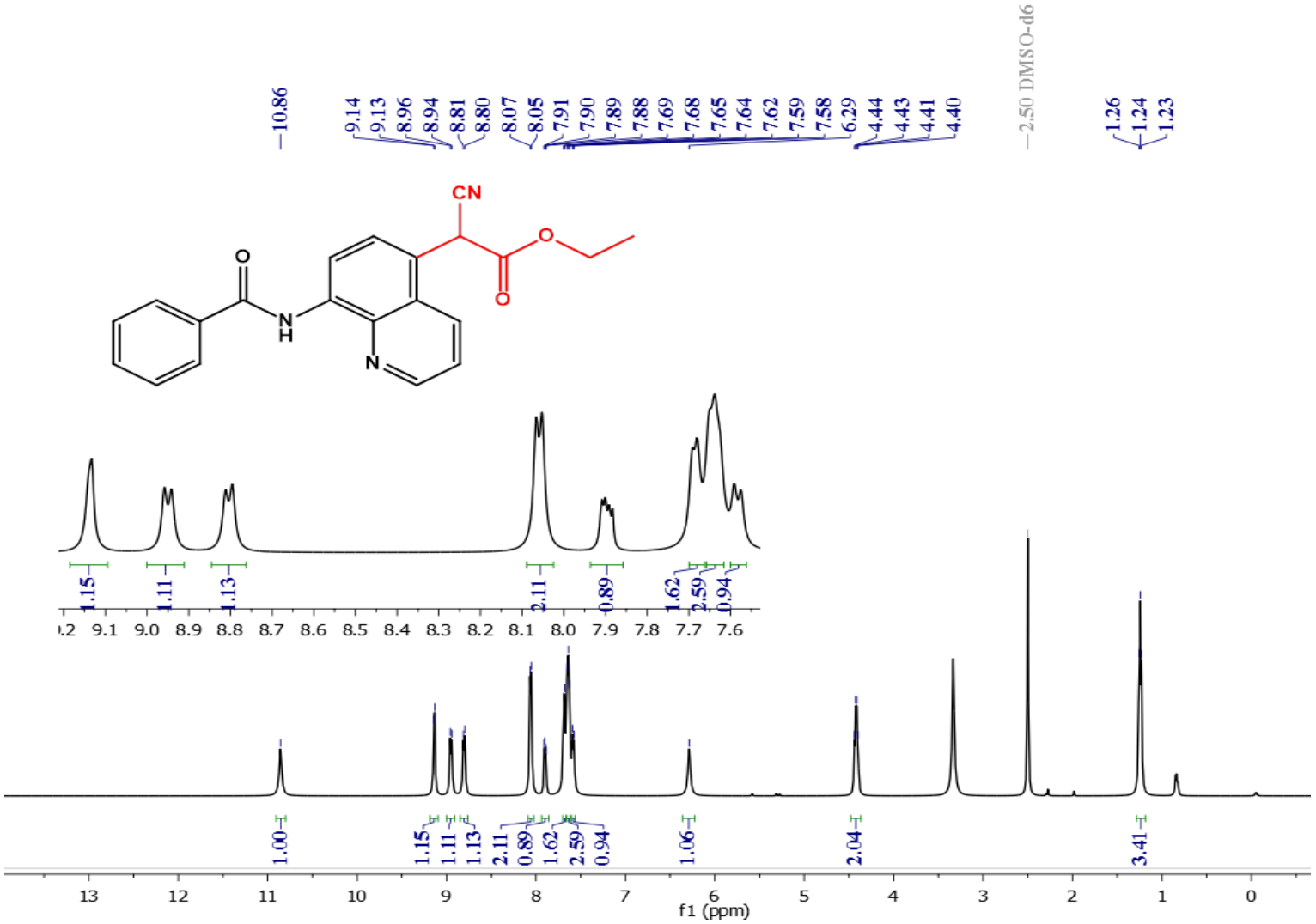
[1]H NMR spectrum of 4b



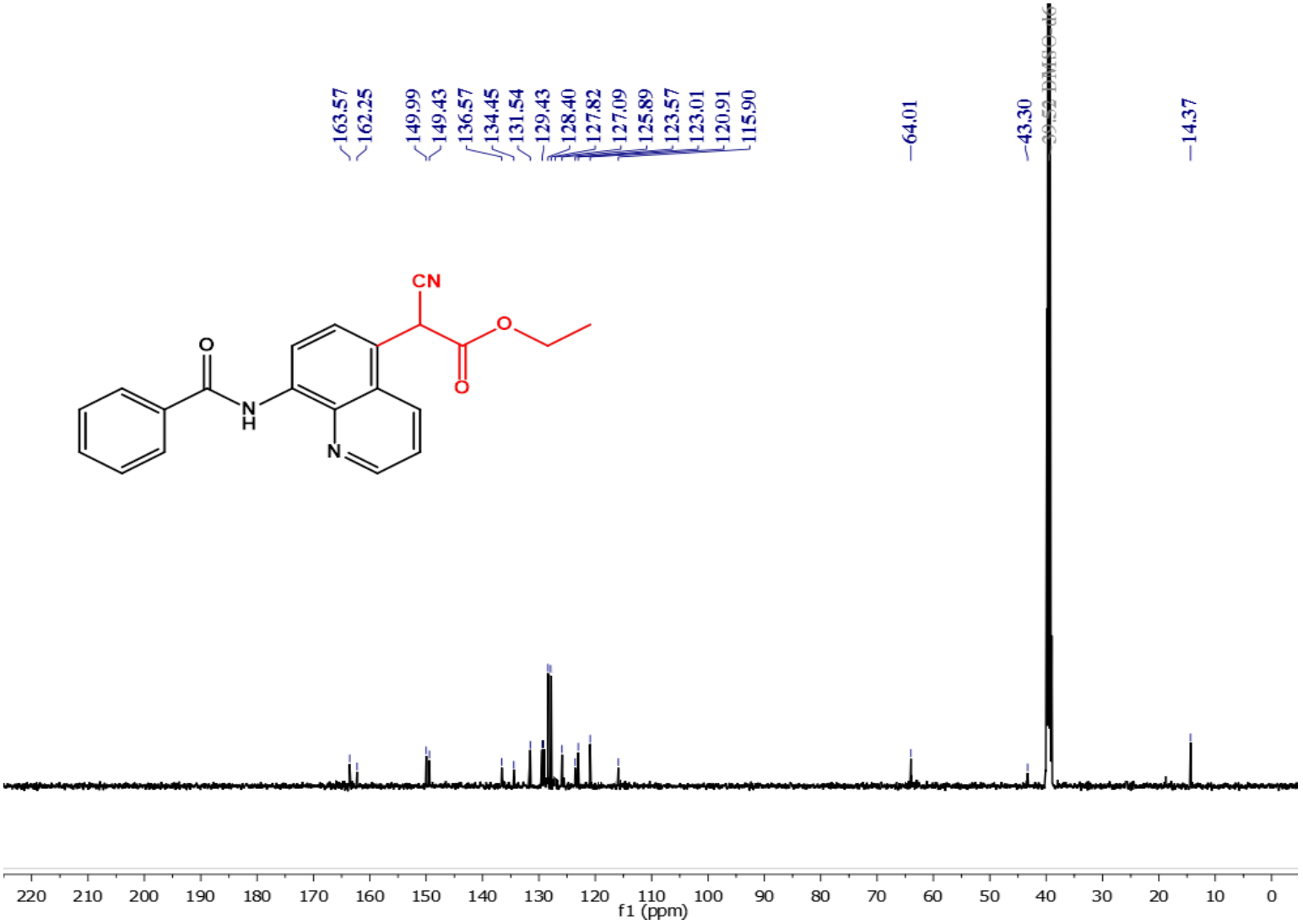
^{13}C NMR spectrum of 4b



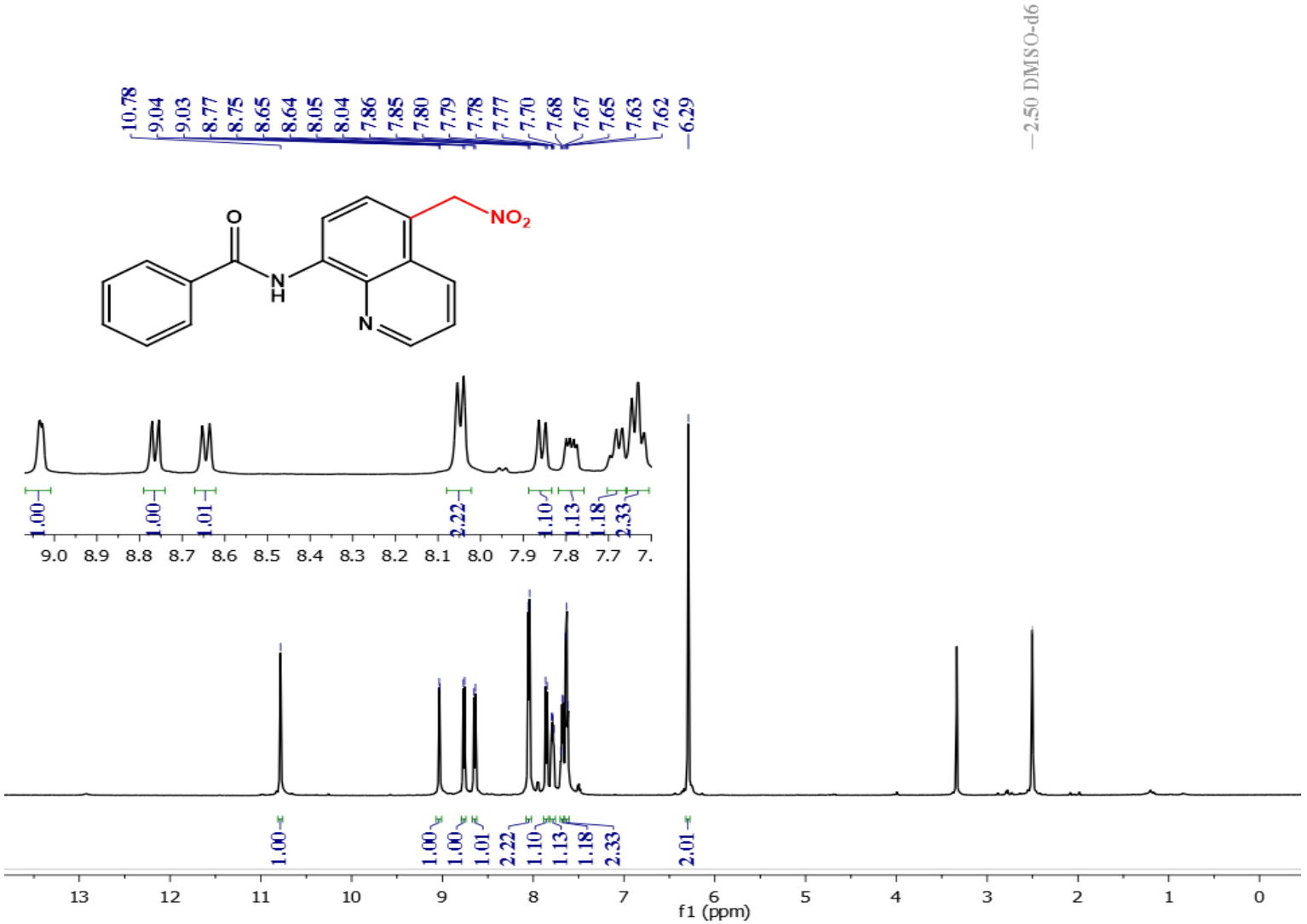
^{1}H NMR spectrum of 4c



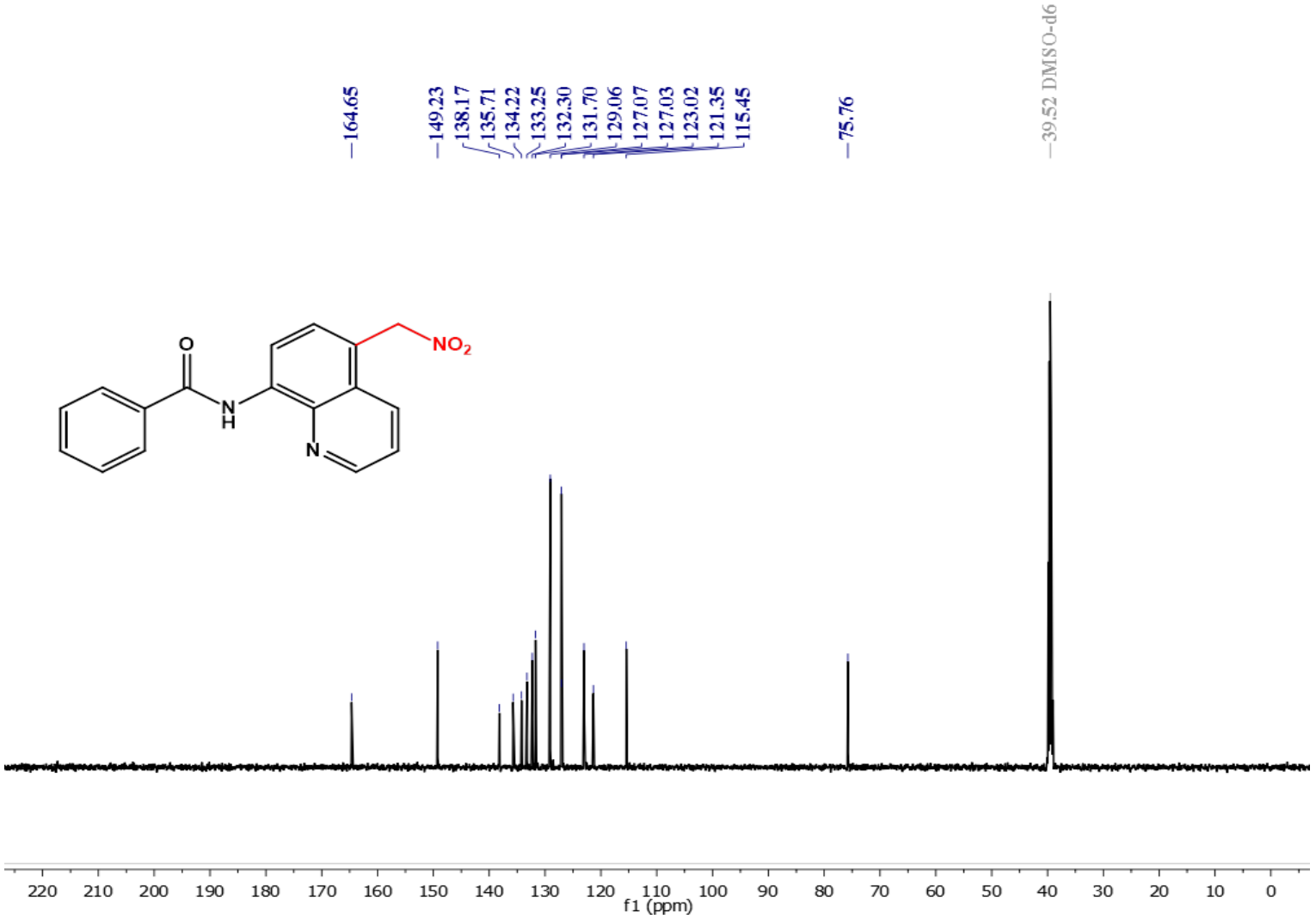
^{13}C NMR spectrum of 4c



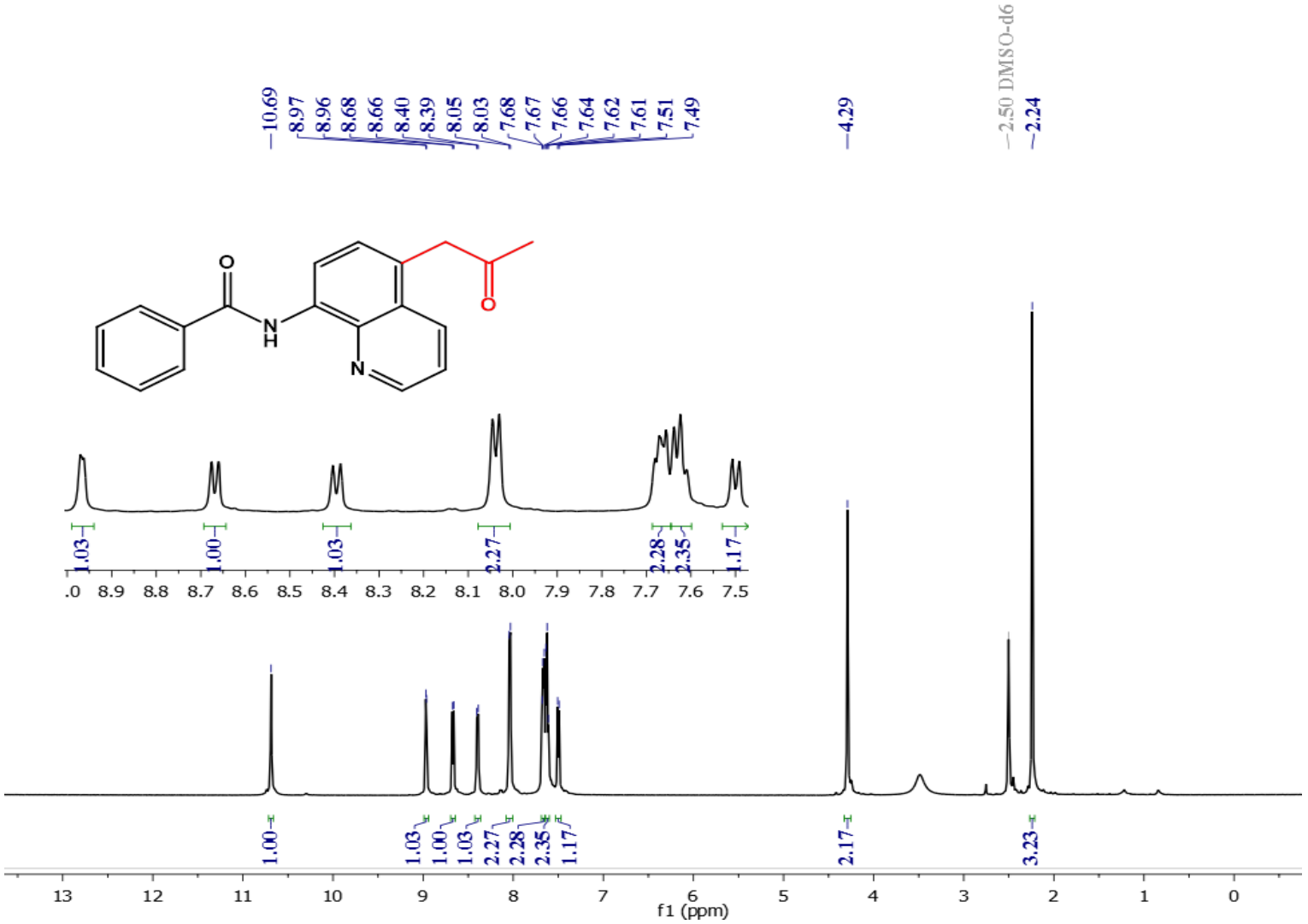
[1]H NMR spectrum of 4f



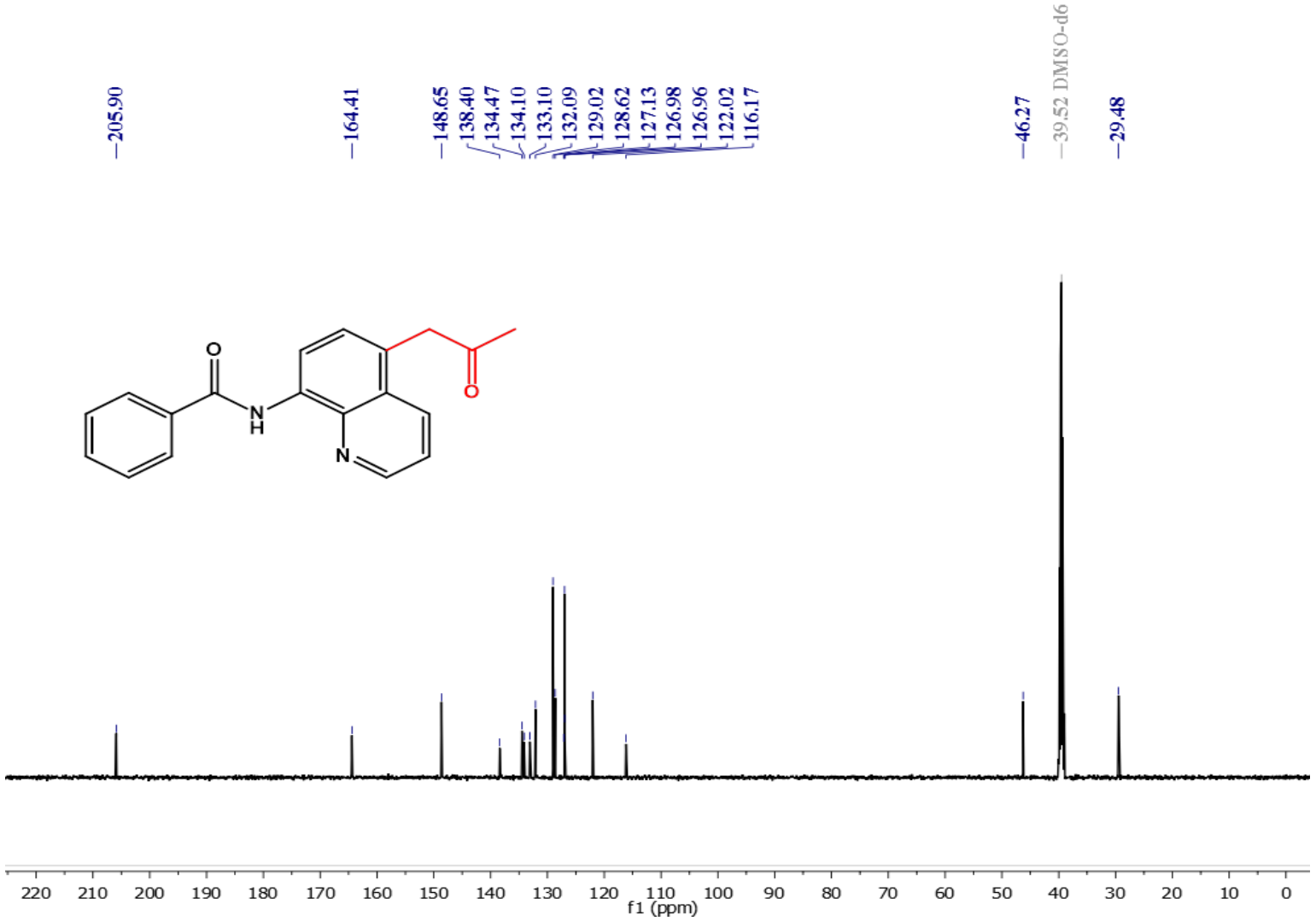
^{13}C NMR spectrum of 4f



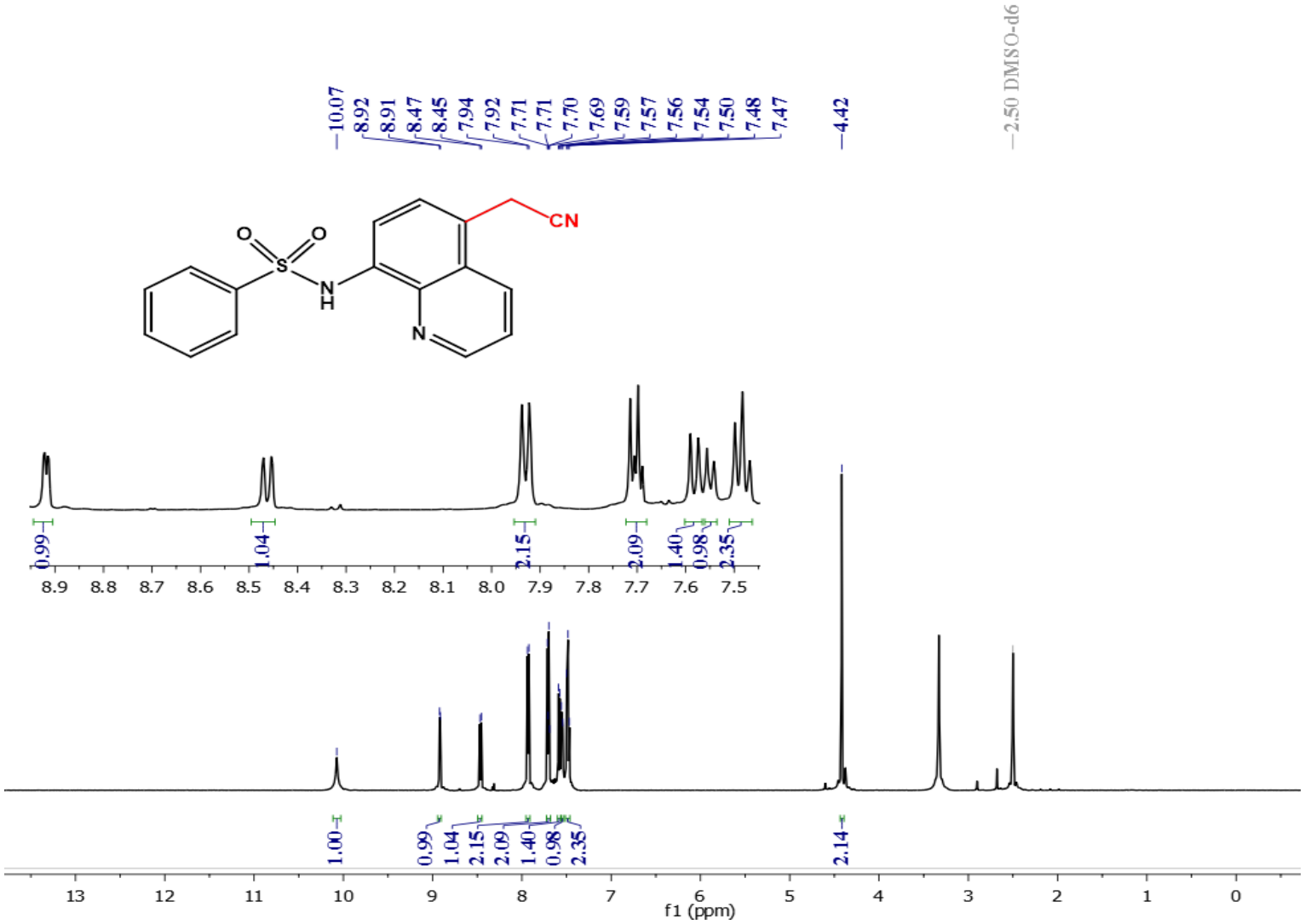
[1]H NMR spectrum of 4g



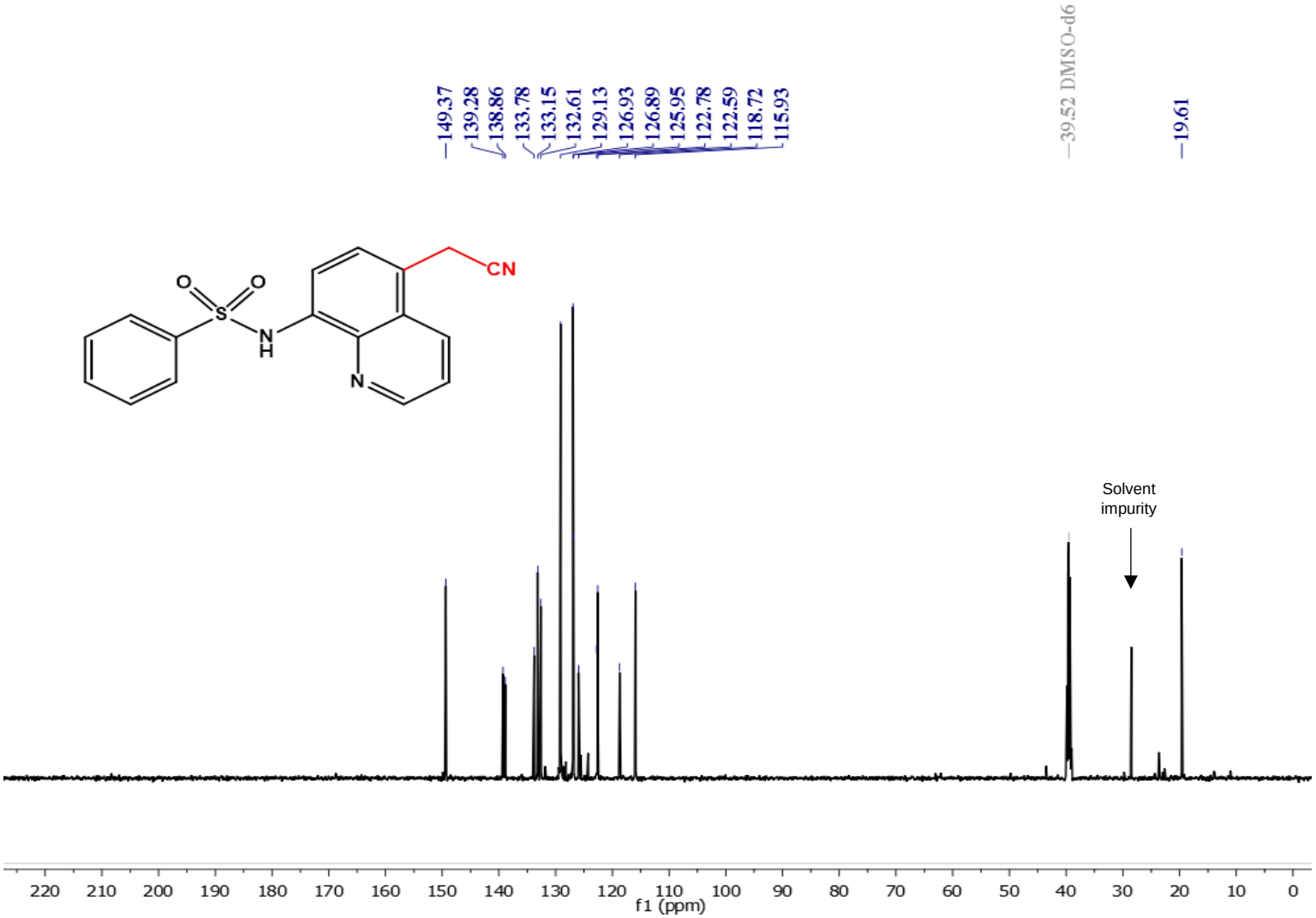
^{13}C NMR spectrum of 4g



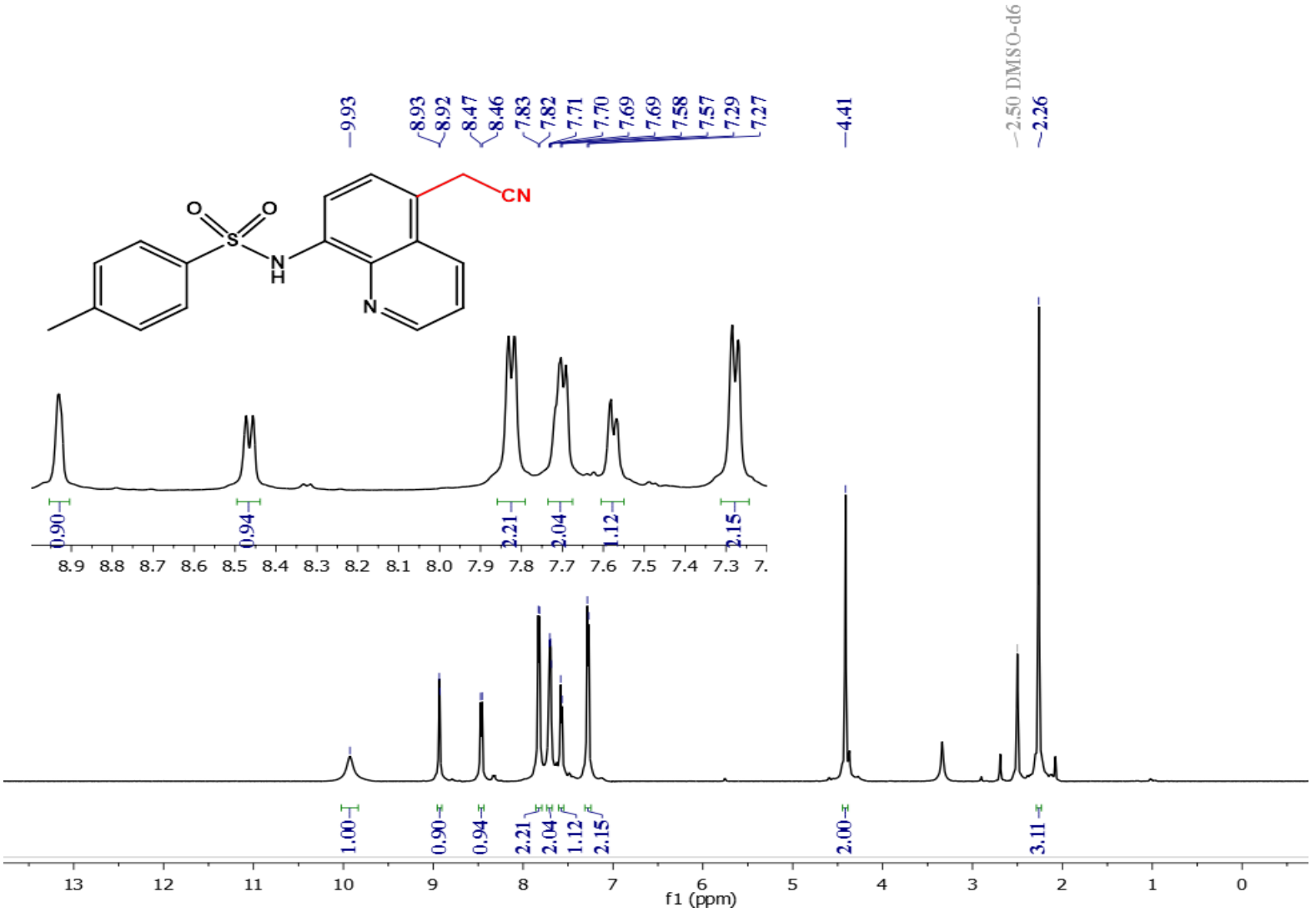
^{1}H NMR spectrum of 6a



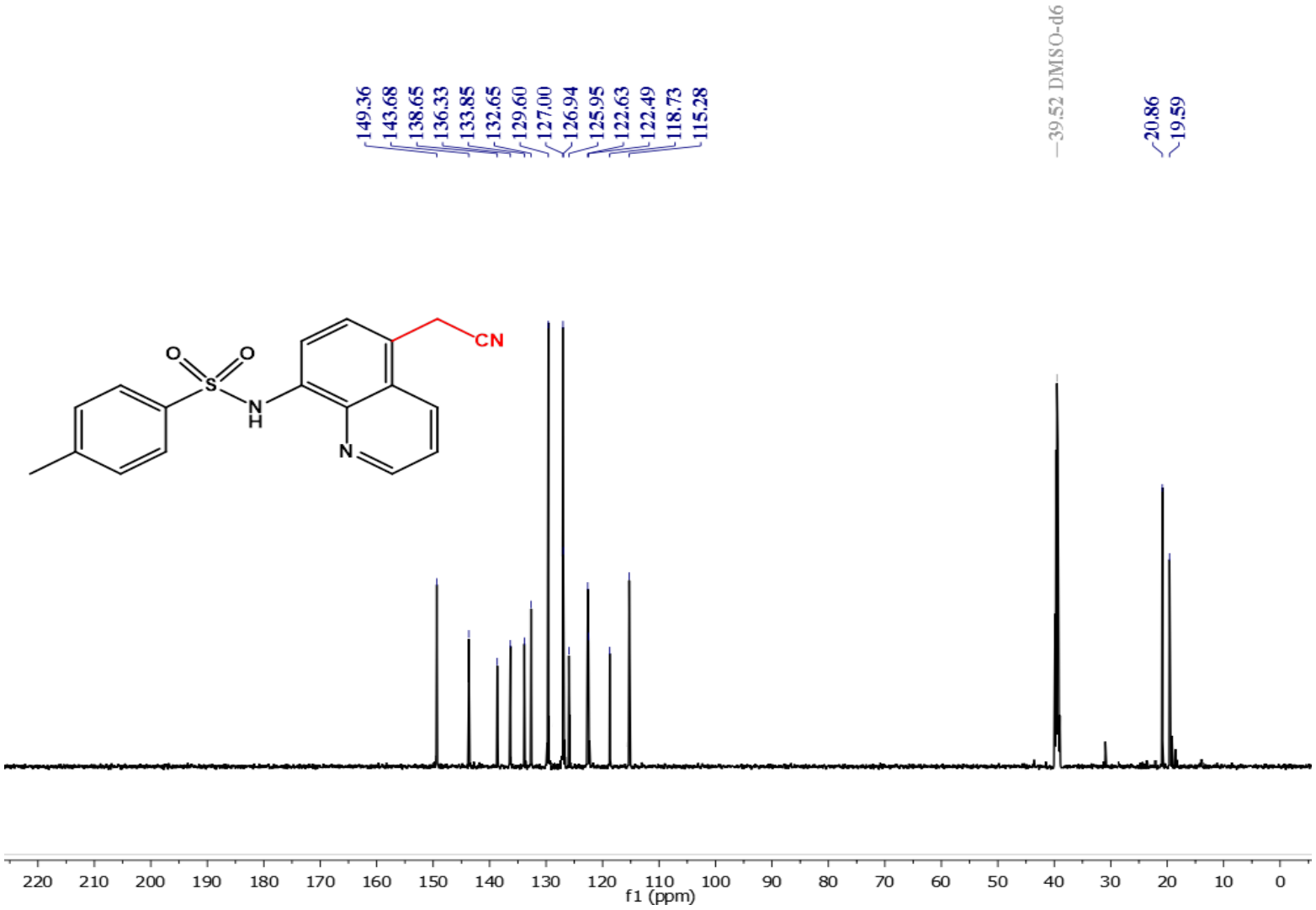
^{13}C NMR spectrum of 6a



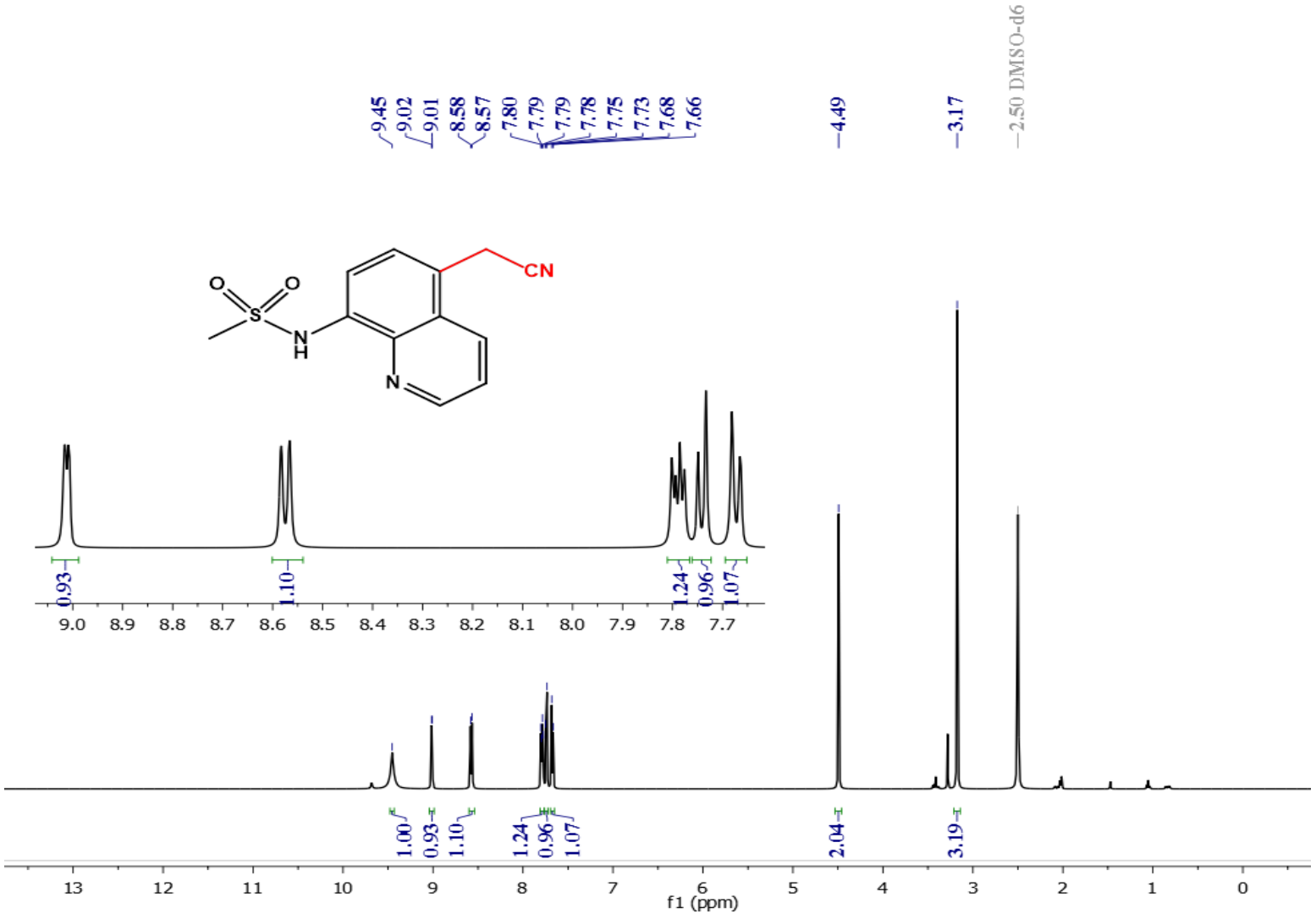
^{1}H NMR spectrum of 6b



^{13}C NMR spectrum of 6b



^{1}H NMR spectrum of 6c



^{13}C NMR spectrum of 6c