Electronic Supplementary Material (ESI) for Chemical Communications

An Expedient Pd/DBU Mediated Cyanation of Aryl/Heteroaryl Bromides With $K_4[Fe(CN)_6]$

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General information

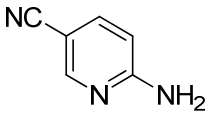
Unless otherwise noted, the reagents (chemicals) were purchased from commercial sources, and used without further purification. Water was deionized before used. Analytical thin layer chromatography (TLC) was HSGF 254 (0.15-0.2 mm thickness). Compound spots were visualized by UV light (254 nm). Column chromatography was performed on silica gel FCP 200-300. NMR spectra were run on 300 or 400 MHz instrument. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Low- and high-resolution mass spectra (LRMS and HRMS) were measured on spectrometer.

General procedure for palladium catalyzed cyanation of aryl/heteroaryl bromides

A vial equipped with a magnetic stir bar was charged with $Pd(PPh_3)_4$ (1-5% mmol), $K_4[Fe(CN)_6].3H_2O$ (0.4 mmol), aryl/heteroaryl bromides (1.0 mmol, if solid) and capped with septa. The vial was evacuated and backfilled with argon and the process was repeated three times. Under argon, aryl/heteroaryl bromides (1.0 mmol, if liquid), t-BuOH/H_2O (1:1) 3.0 mL and DBU (0.25 mmol) were charged successively to the vial via syringe, and then the resulting mixture was stirred at room temperature for 10 min. After that, the vial was kept in the pre-heated 85 °C oil bath for appropriate time. After the reaction was complete, the reaction mixture was cooled to room temperature and filtered. The cake was rinsed with methanol followed by dichloromethane. The filtrate obtained was concentrated in vacuum. The crude product was purified by silica gel column chromatography.

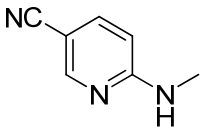
Characterization data of aryl/heteroaryl nitriles

2-Amino-5-cyanopyridine:



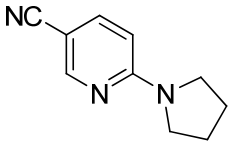
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (d, J = 2.0 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.03 (s, 2H), 6.48 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.56, 153.21, 139.34, 119.01, 107.78, 94.62. EI-MS m/z (M^+) 119; EI-HRMS calcd for (M^+) 119.0483, found 119.0480.

2-Methylamino-5-cyanopyridine:



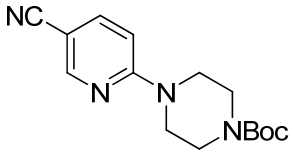
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (d, J = 2.0 Hz, 1H), 7.65 (s, 1H), 7.55 (s, 1H), 6.51 (d, J = 8.8 Hz, 1H), 2.81 (d, J = 4.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.47, 153.16, 138.23, 119.14, 108.93, 94.18, 27.56. EI-MS m/z (M^+) 133; EI-HRMS calcd for (M^+) 133.0640, found 133.0636.

2-(Pyrrolidin-1-yl)-5-cyanopyridine:



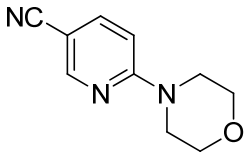
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 2.4 Hz, 1H), 7.55 (dd, J = 2.4, 8.8 Hz, 1H), 6.32 (d, J = 8.8 Hz, 1H), 3.48 (br, 4H), 2.03 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.71, 153.27, 139.17, 119.44, 106.37, 95.08, 47.10, 25.56. EI-MS m/z (M^+) 173; EI-HRMS calcd for (M^+) 173.0953, found 173.0950.

***tert*-Butyl 4-(5-Cyanopyridin-2-yl)piperazine-1-carboxylate:**



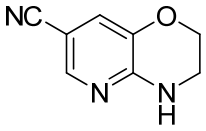
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 2.4 Hz, 1H), 7.62 (dd, *J* = 2.4, 8.8 Hz, 1H), 6.59 (d, *J* = 8.8 Hz, 1H), 3.71-3.62 (m, 4H), 3.58-3.49 (m, 4H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.36, 154.80, 152.80, 140.13, 118.67, 105.96, 96.91, 80.49, 44.35, 28.57. EI-MS *m*/*z* (M^+) 288; EI-HRMS calcd for (M^+) 288.1586, found 288.1582.

2-(4-Morpholinyl)-5-cyanopyridine:



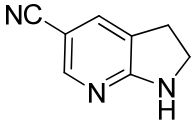
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, *J* = 2.4 Hz, 1H), 7.87 (dd, *J* = 2.4, 9.2 Hz, 1H), 6.93 (d, *J* = 9.2 Hz, 1H), 3.70-3.65 (m, 4H), 3.64-3.59 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.69, 152.80, 140.11, 118.66, 105.83, 97.16, 66.66, 44.88. EI-MS *m*/*z* (M^+) 189; EI-HRMS calcd for (M^+) 189.0902, found 189.0904.

3,4-Dihydro-2H-pyrido[3,2-b][1,4]oxazine-7-carbonitrile:



^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, *J* = 2.0 Hz, 1H), 7.93 (s, 1H), 7.28 (d, *J* = 1.0 Hz, 1H), 4.11 (t, *J* = 4.4 Hz, 2H), 3.48-3.45 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.48, 145.40, 137.39, 121.55, 118.52, 94.77, 63.46, 39.55. EI-MS *m*/*z* (M^+) 161; EI-HRMS calcd for (M^+) 161.0589, found 161.0594.

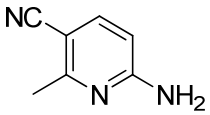
3,4-Dihydro-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile:



^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, *J* = 2.0 Hz, 1H), 7.62 (s, 2H), 7.45 (d, *J* =

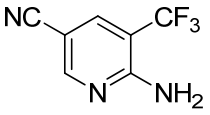
2.0 Hz, 1H), 3.57 (t, J = 8.8 Hz, 2H), 3.01 (t, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.06, 152.36, 131.42, 122.90, 119.47, 94.53, 43.13, 26.05. EI-MS m/z (M^+) 145; EI-HRMS calcd for (M^+) 145.0640, found 145.0634.

2-Amino-5-cyano-6-methylpyridine:



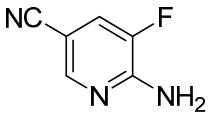
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J=8.4 Hz, 1H), 6.33 (d, J=8.4 Hz, 1H), 4.99 (s, 2H), 2.56 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.53, 159.68, 141.32, 118.65, 105.66, 97.56, 23.57. EI-MS m/z (M^+) 133; EI-HRMS calcd for (M^+) 133.0640, found 133.0639.

2-Amino-5-cyano-3-trifluoromethylpyridine:



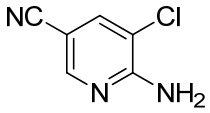
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (d, J = 2.0 Hz, 1H), 8.24 (s, 1H), 7.57 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.95, 156.51, 139.00, 124.50, 121.80, 117.54, 106.20, 105.88, 105.56, 105.24, 94.70. EI-MS m/z (M^+) 187; EI-HRMS calcd for (M^+) 187.0357, found 187.0357.

2-Amino-5-cyano-3-fluoropyridine:



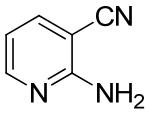
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.22-8.19 (m, 1H), 7.83 (dd, J = 1.8, 11.4 Hz, 1H), 7.37 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.50, 152.38, 148.90, 148.85, 145.43, 142.90, 122.79, 122.61, 117.68, 94.33. EI-MS m/z (M^+) 137; EI-HRMS calcd for (M^+) 137.0389, found 137.0387.

2-Amino-3-chloro-5-cyanopyridine:



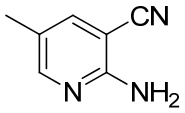
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (d, J = 1.8 Hz, 1H), 8.07 (d, J = 1.8 Hz, 1H), 7.41 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.86, 151.40, 138.63, 117.53, 112.64, 95.83. EI-MS m/z (M^+) 153; EI-HRMS calcd for (M^+) 153.0094, found 153.0086.

2-Amino-3-cyanopyridine:



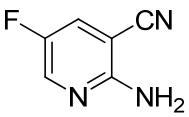
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (dd, J = 2.0, 4.8 Hz, 1H), 7.85 (dd, J = 2.0, 7.6 Hz, 1H), 6.87 (s, 2H), 6.63 (dd, J = 4.8, 7.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.94, 153.18, 142.22, 117.02, 111.91, 89.15. EI-MS m/z (M^+) 119; EI-HRMS calcd for (M^+) 119.0483, found 119.0491.

2-Amino-3-cyano-5-methylpyridine



^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, J = 2.0 Hz, 1H), 7.68 (d, J = 2.0 Hz, 1H), 6.62 (s, 2H), 2.10 (s, 3H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 158.32, 153.32, 141.84, 120.60, 117.15, 88.78, 16.36. EI-MS m/z (M^+) 133; EI-HRMS calcd for (M^+) 133.0640, found 133.0639.

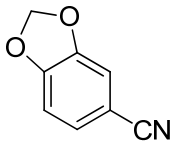
2-Amino-3-cyano-5-fluoropyridine:



^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (d, J=3.2, 1H), 7.98 (dd, J = 3.2, 8.4 Hz, 1H), 6.86 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.41, 151.72, 149.33, 141.50,

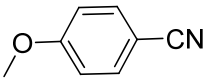
141.25, 128.74, 128.52, 115.90, 88.69, 88.64. EI-MS *m*/*z* (M^+) 137; EI-HRMS calcd for (M^+) 137.0389, found 137.0394.

Piperonylnitrile:



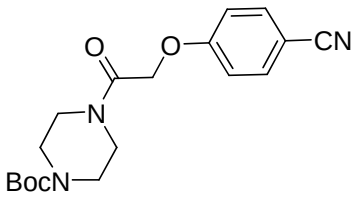
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46-7.36 (m, 2H), 7.10 (d, J = 8.0 Hz, 1H), 6.17 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.44, 147.81, 128.52, 118.90, 111.30, 109.35, 103.76, 102.47. EI-MS *m*/*z* (M^+) 147; EI-HRMS calcd for (M^+) 147.0320, found 147.0308.

4-Methoxybenzonitrile:



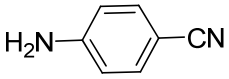
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.00, 134.13, 119.40, 114.91, 104.08, 55.71. EI-MS *m*/*z* (M^+) 133; EI-HRMS calcd for (M^+) 133.0528, found 133.0518.

***tert*-Butyl 4-(2-(4-Cyanophenoxy)acetyl)piperazine-1-carboxylate:**



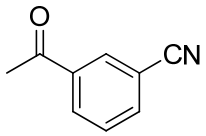
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H), 5.00 (s, 2H), 3.45 -3.31 (m, 8H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.31, 161.62, 153.79, 133.99, 119.12, 115.76, 103.02, 79.21, 65.67, 43.75, 41.04, 28.02. EI-MS *m*/*z* (M^+) 345; EI-HRMS calcd for (M^+) 345.1689, found 345.1697.

4-Aminobenzonitrile:



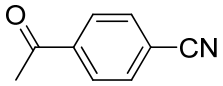
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38 (d, J = 8.4 Hz, 2H), 6.60 (d, J = 8.4 Hz, 2H), 6.13 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.01, 133.45, 120.69, 113.44, 95.51. EI-MS m/z (M^+) 118; EI-HRMS calcd for (M^+) 118.0531, found 118.0523.

3-Acetylbenzonitrile:



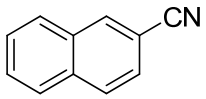
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.63-7.59 (m, 1H), 2.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.01, 137.91, 136.19, 132.40, 132.21, 129.88, 118.11, 113.36, 26.77. EI-MS m/z (M^+) 145; EI-HRMS calcd for (M^+) 145.0528, found 145.0528.

4-Acetylbenzonitrile:



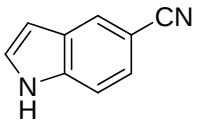
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J = 8.0 Hz, 2H), 8.01 (d, J = 8.0 Hz, 2H), 2.64 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.35, 139.84, 132.76, 128.76, 118.17, 115.13, 27.01. EI-MS m/z (M^+) 145; EI-HRMS calcd for (M^+) 145.0528, found 145.0529.

2-Naphthonitrile:



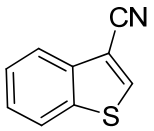
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 8.06 (t, J = 7.2 Hz, 2H), 7.78 (dd, J = 1.6, 8.4 Hz, 1H), 7.76-7.66 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 134.35, 134.27, 131.86, 129.33, 129.29, 128.48, 128.00, 127.75, 126.30, 119.17, 108.39. EI-MS m/z (M^+) 153; EI-HRMS calcd for (M^+) 153.0578, found 153.0587.

1*H*-indole-5-carbonitrile:



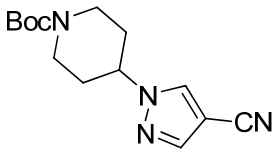
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.66 (s, 1H), 8.08 (s, 1H), 7.57-7.55 (m, 2H), 7.42 (dd, J = 1.6, 8.4 Hz, 1H), 6.58 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 137.61, 128.10, 127.42, 125.74, 123.67, 120.82, 112.68, 102.10, 100.90. EI-MS m/z (M^+) 142; EI-HRMS calcd for (M^+) 142.0531, found 142.0533.

Benzo[b]thiophene-3-carbonitrile:



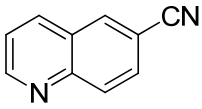
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.22 (dd, J = 1.2, 6.9 Hz, 1H), 7.95 (d, J = 7.2 Hz, 1H), 7.66-7.54 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.69, 137.75, 137.46, 126.39, 126.18, 123.04, 122.74, 114.54, 107.32. EI-MS m/z (M^+) 159; EI-HRMS calcd for (M^+) 159.0143, found 159.0152.

***tert*-butyl 4-(4-cyano-1H-pyrazol-1-yl)piperidine-1-carboxylate:**



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.81 (s, 1H), 4.36-4.22 (m, 3H), 2.89 (t, J = 12.4 Hz, 2H), 2.17-2.10 (m, 2H), 1.95-1.84 (m, 2H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.63, 142.28, 132.15, 113.62, 92.30, 80.38, 60.43, 42.67, 32.30, 28.58. EI-MS m/z (M^+) 276; EI-HRMS calcd for (M^+) 276.1586, found 276.1597.

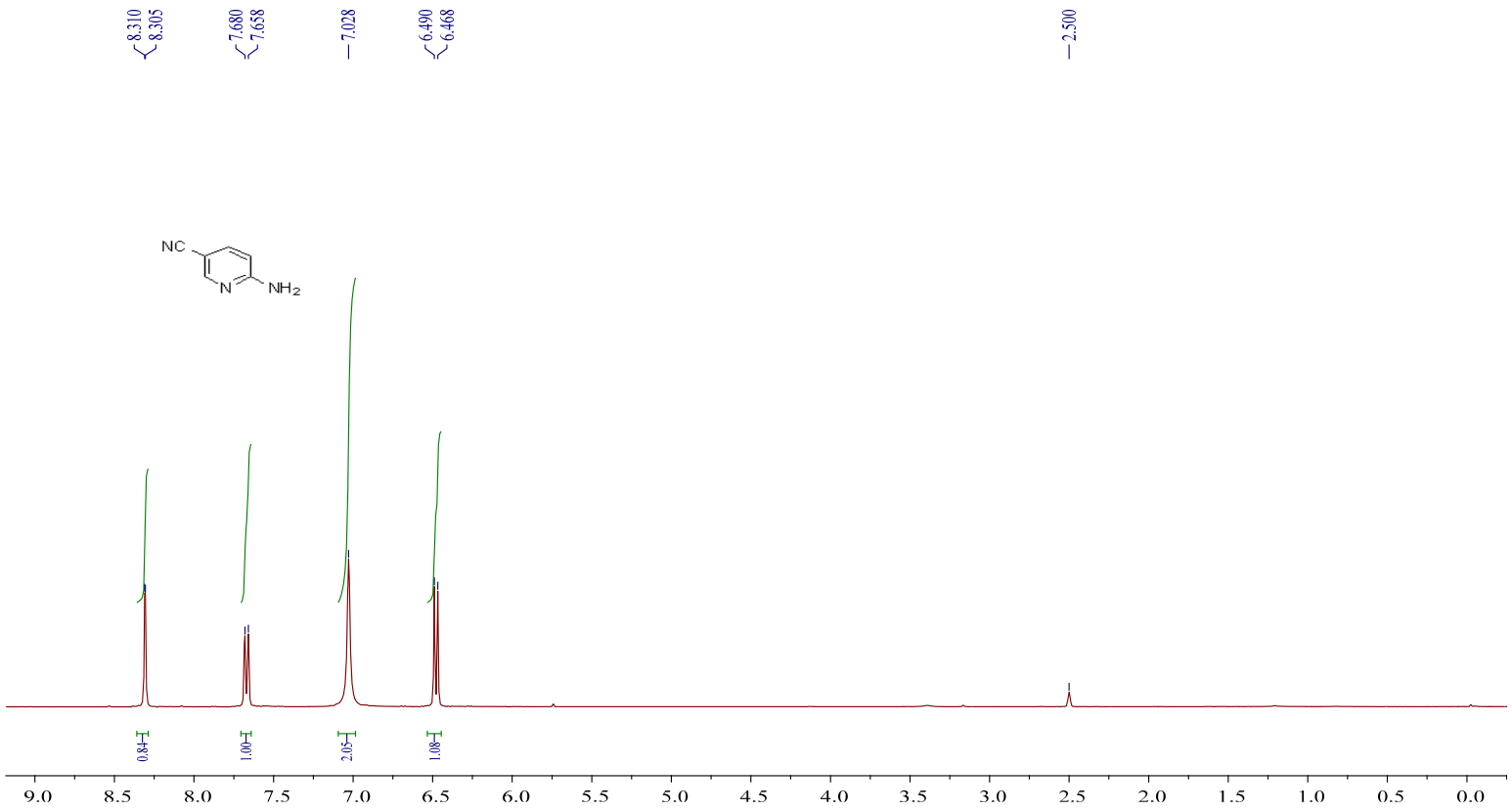
Quinoline-6-carbonitrile:



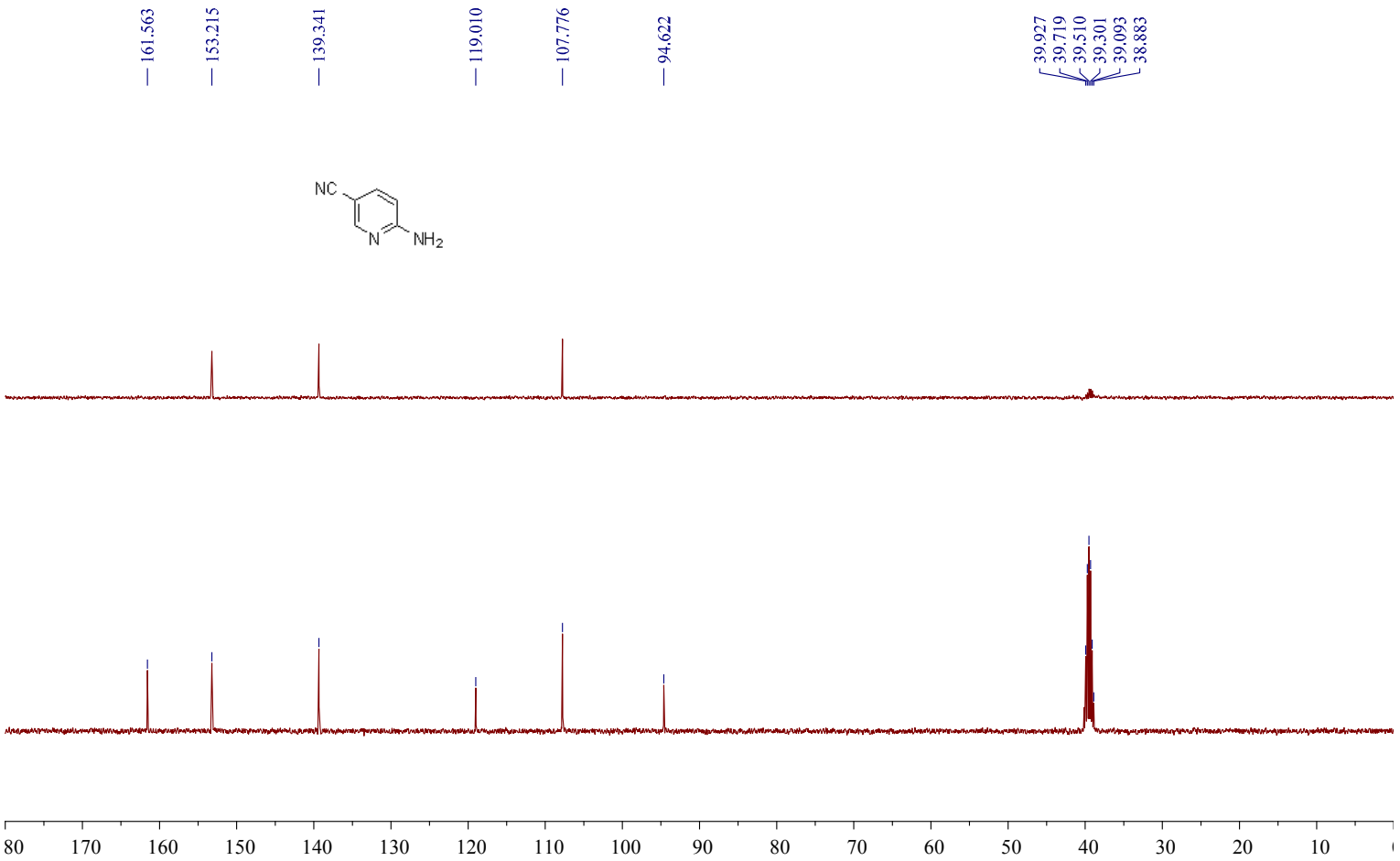
^{1}H NMR (300 MHz, DMSO-d_6) δ 9.07 (dd, J = 1.8, 4.2 Hz, 1H), 8.66 (d, J = 1.2 Hz,

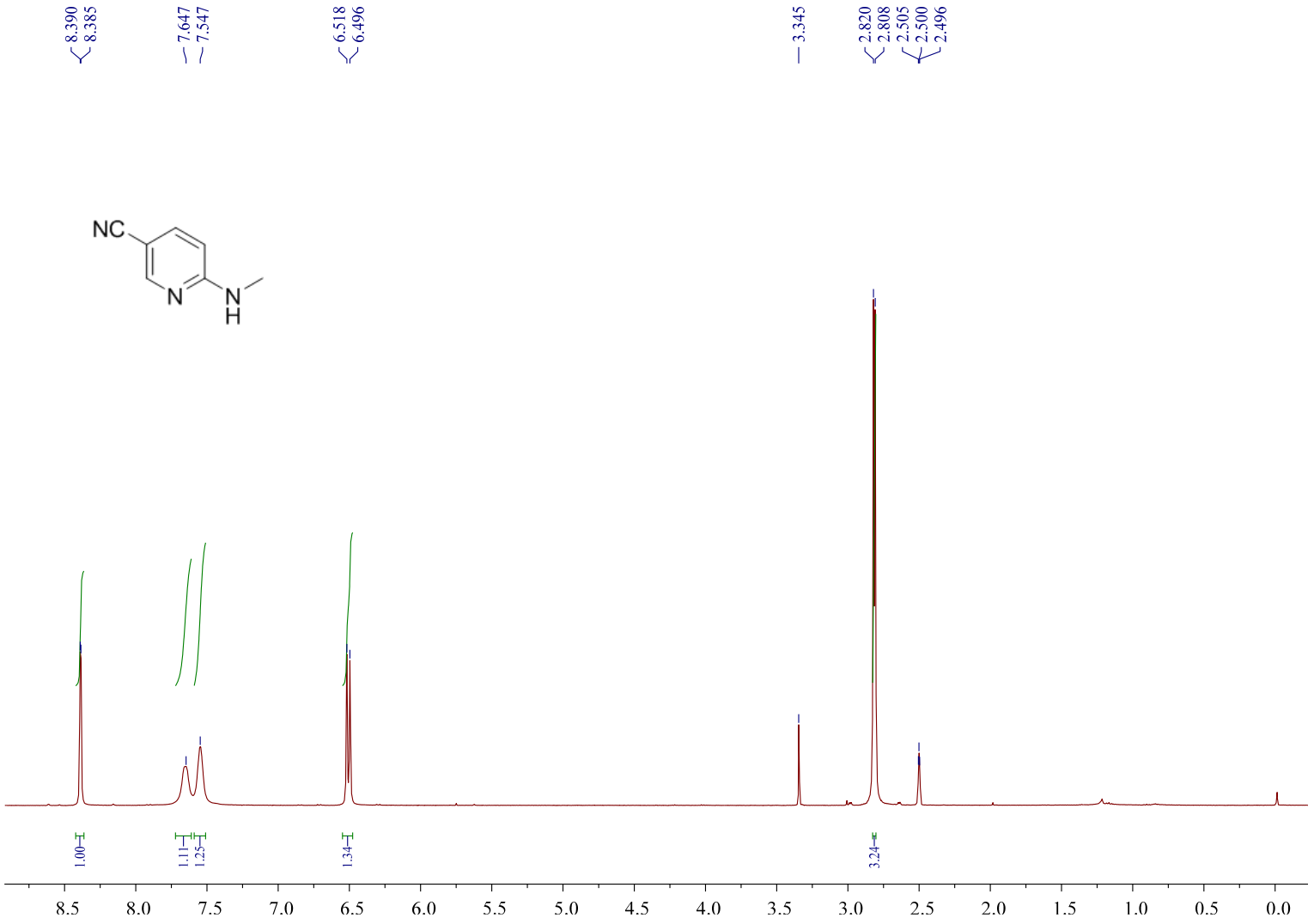
1H), 8.49 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* =8.4 Hz, 1H), 8.04 (dd, *J* = 1.8, 8.7 Hz, 1H), 7.69 (dd, *J* = 4.2, 8.4 Hz, 1H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 153.69, 148.50, 136.75, 135.04, 130.44, 130.16, 127.29, 123.07, 118.64, 109.11. EI-MS *m*/*z* (M^+) 154; EI-HRMS calcd for (M^+) 154.0531, found 154.0525.

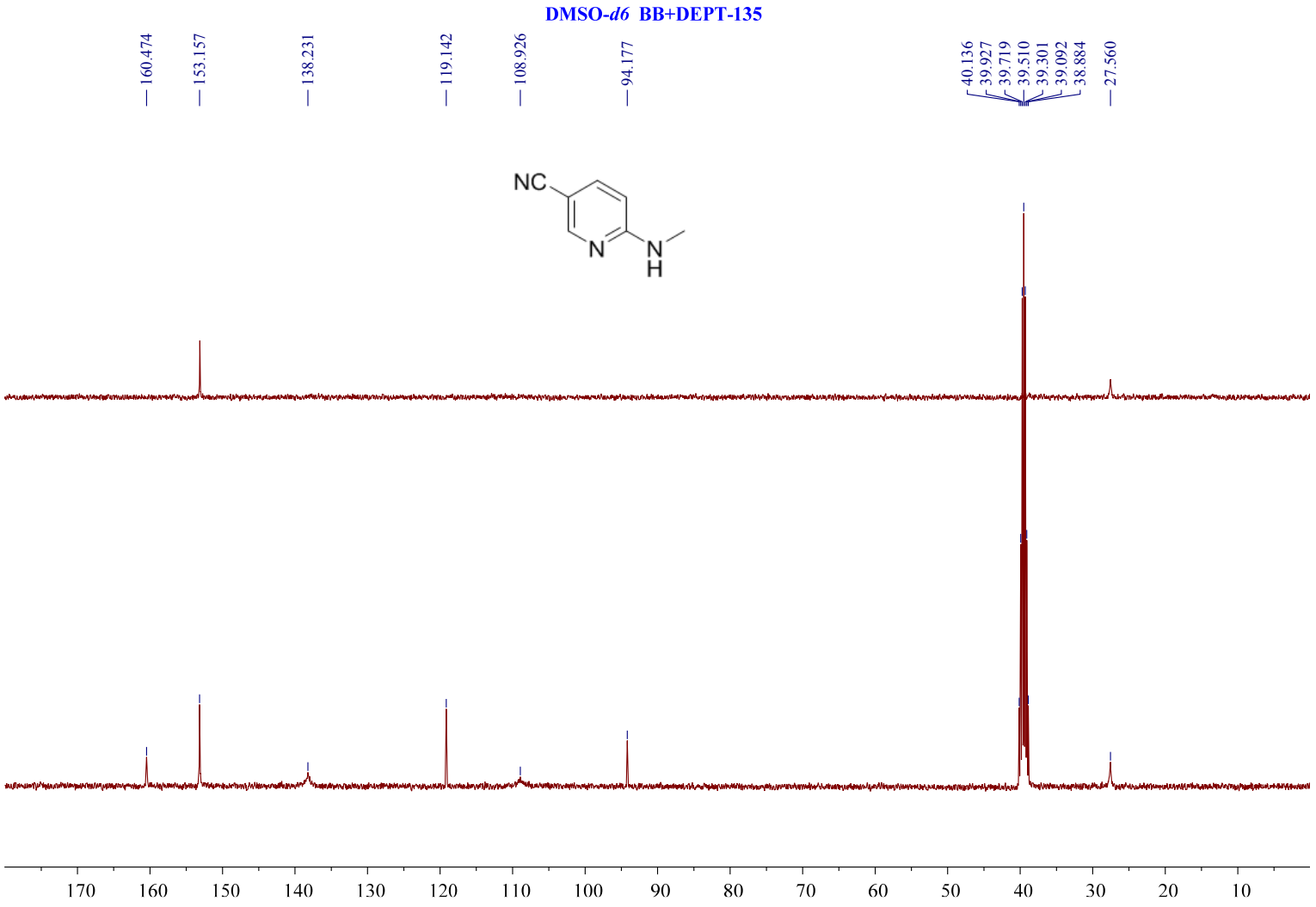
NMR spectra of isolated aryl/heteroaryl nitriles

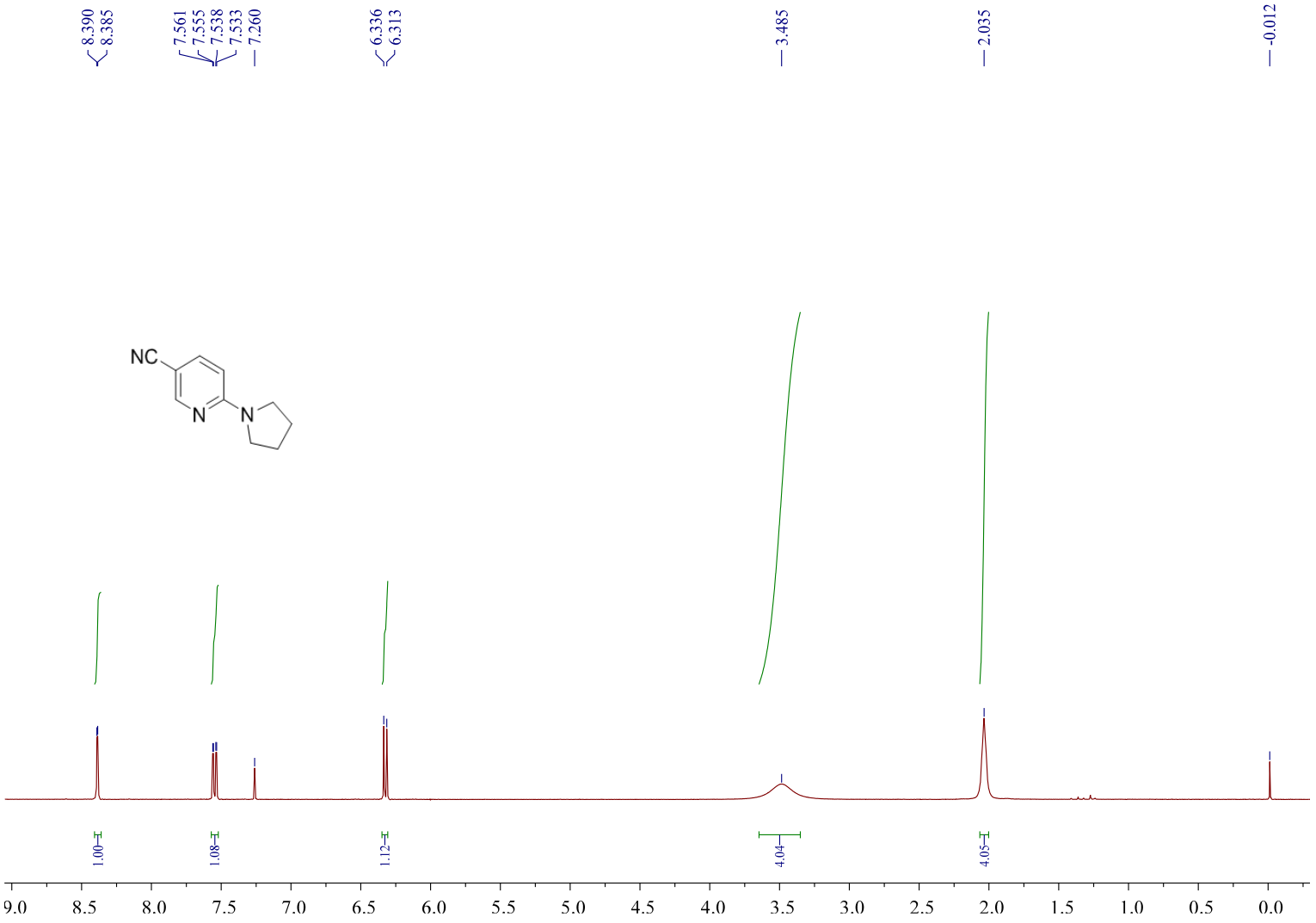


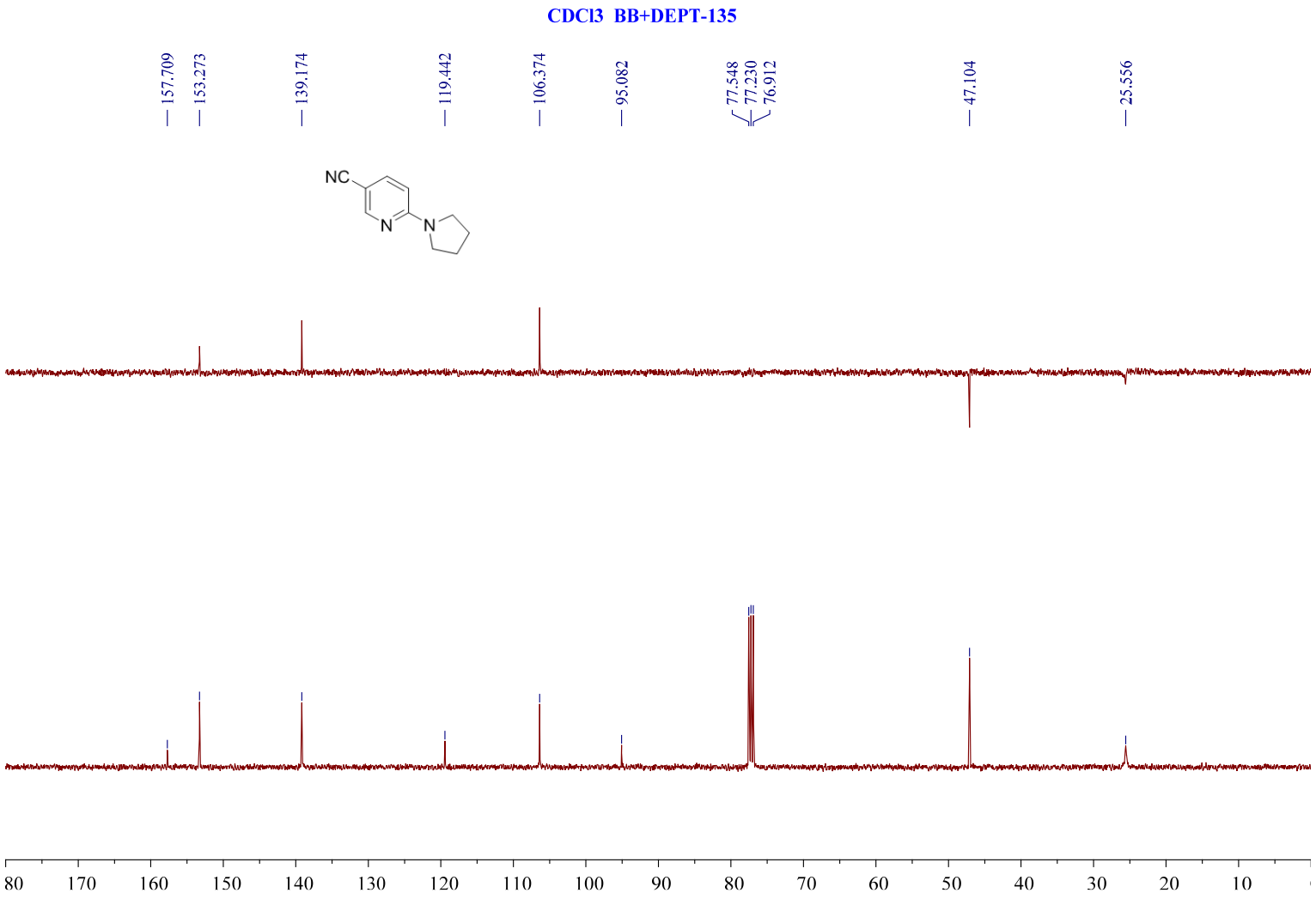
DMSO-*d6* BB+DEPT-135

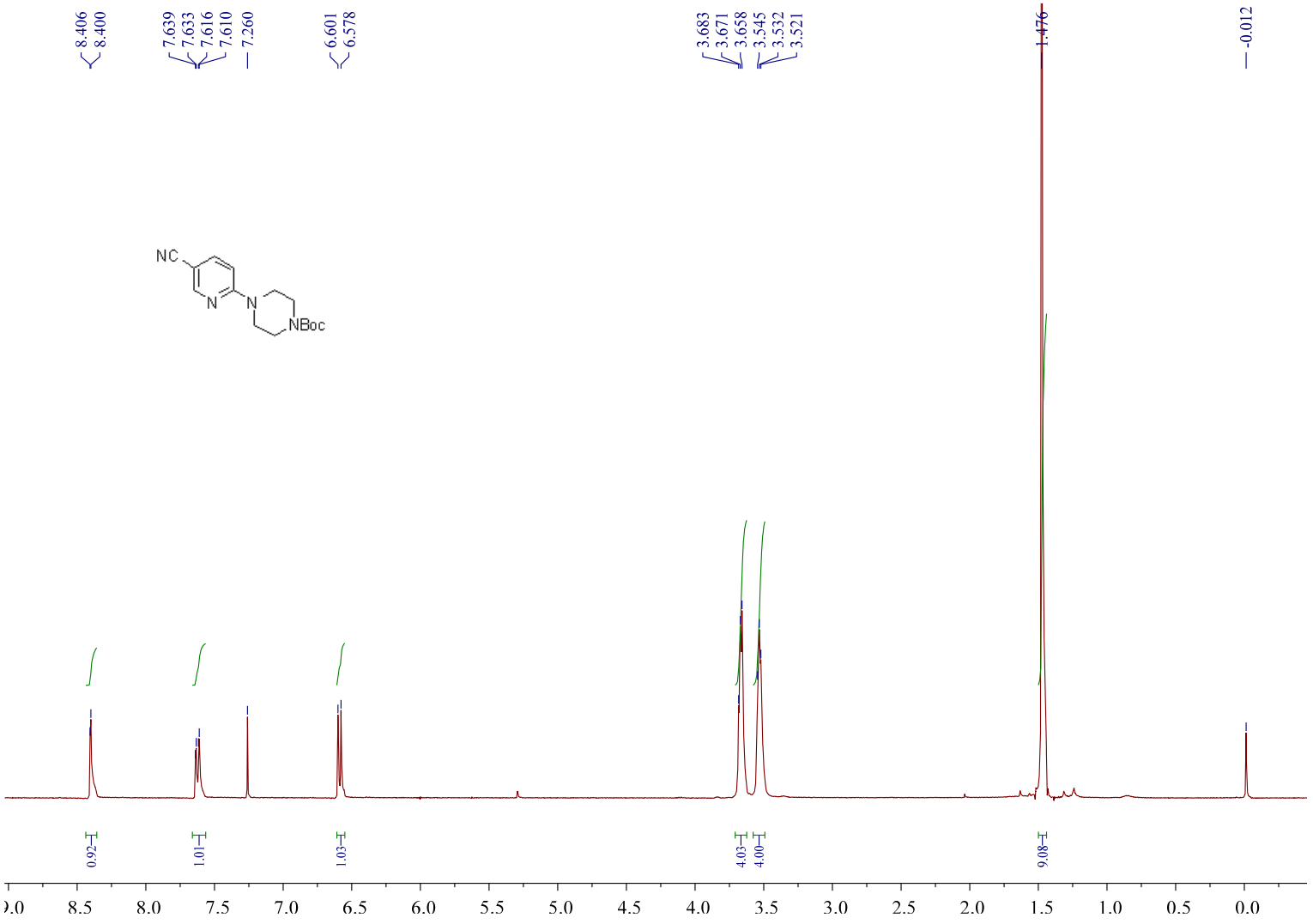


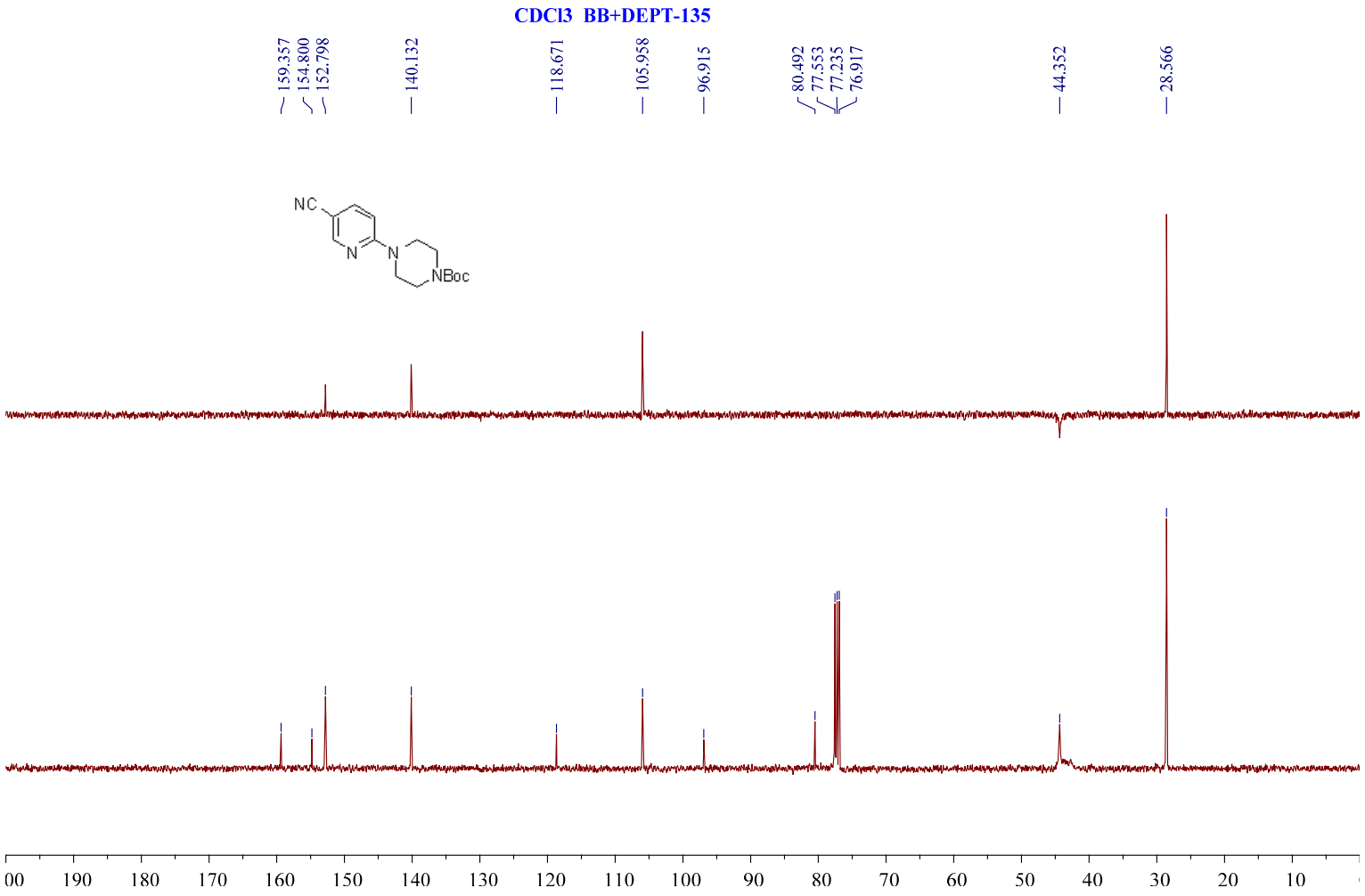


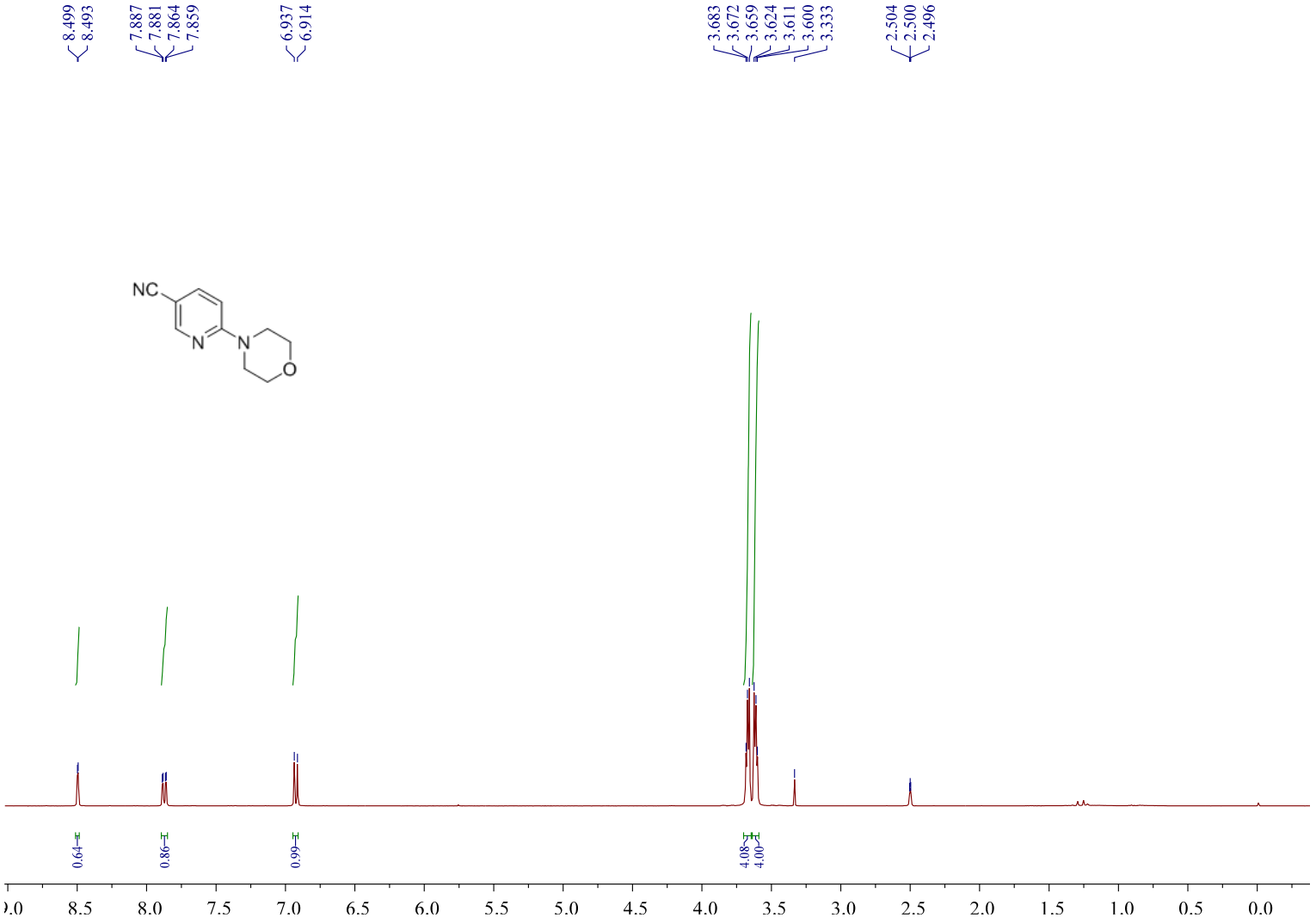


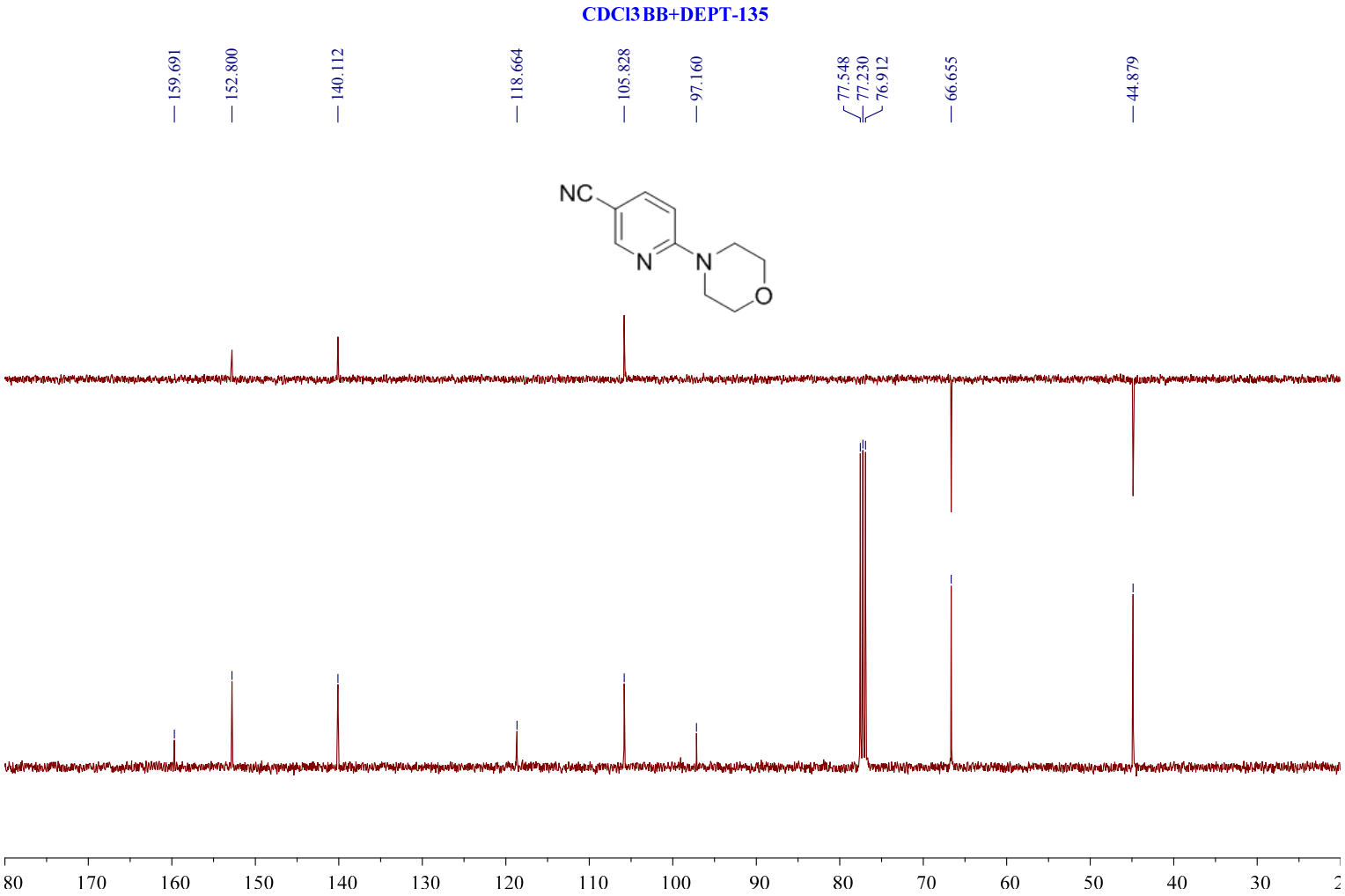


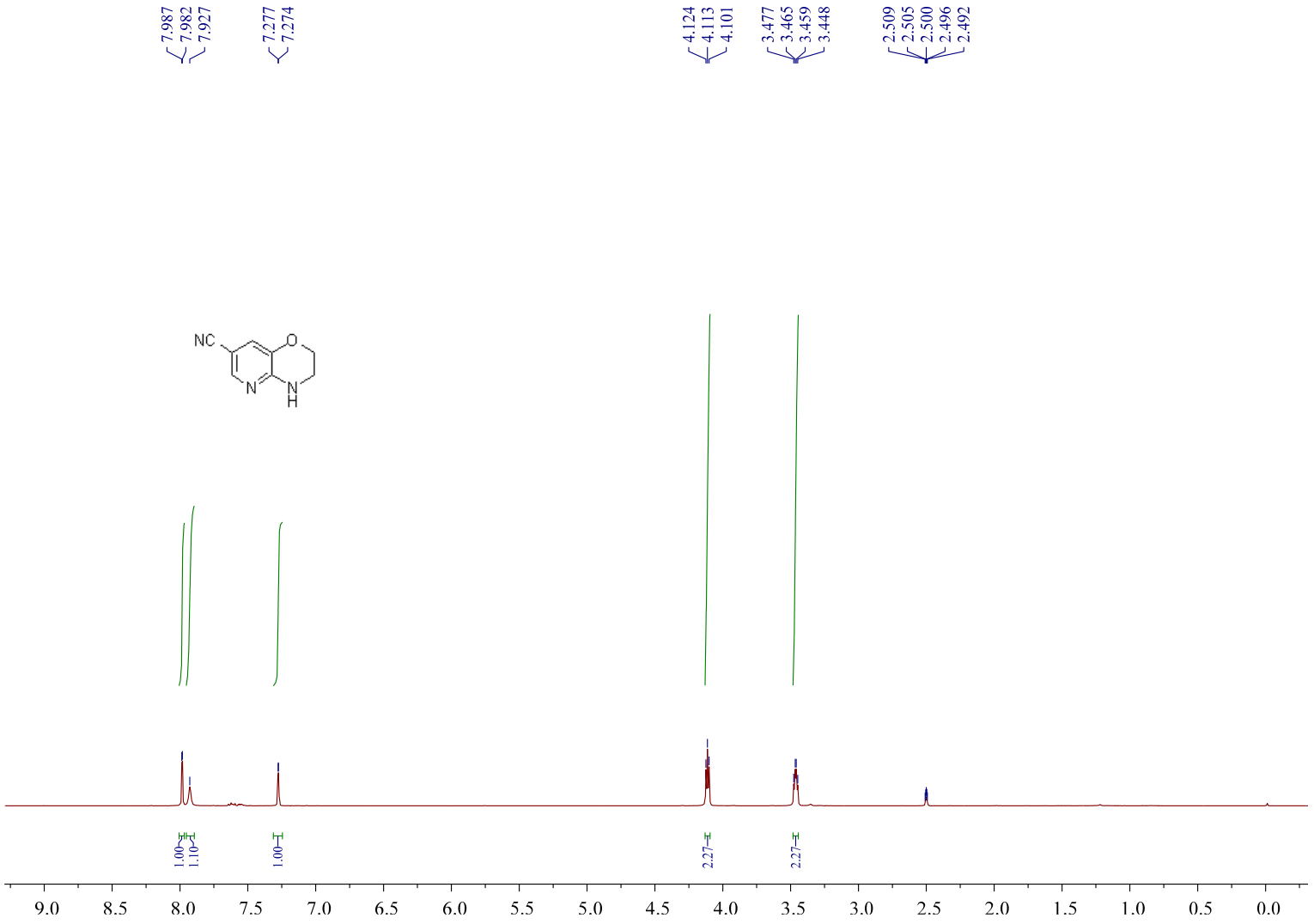




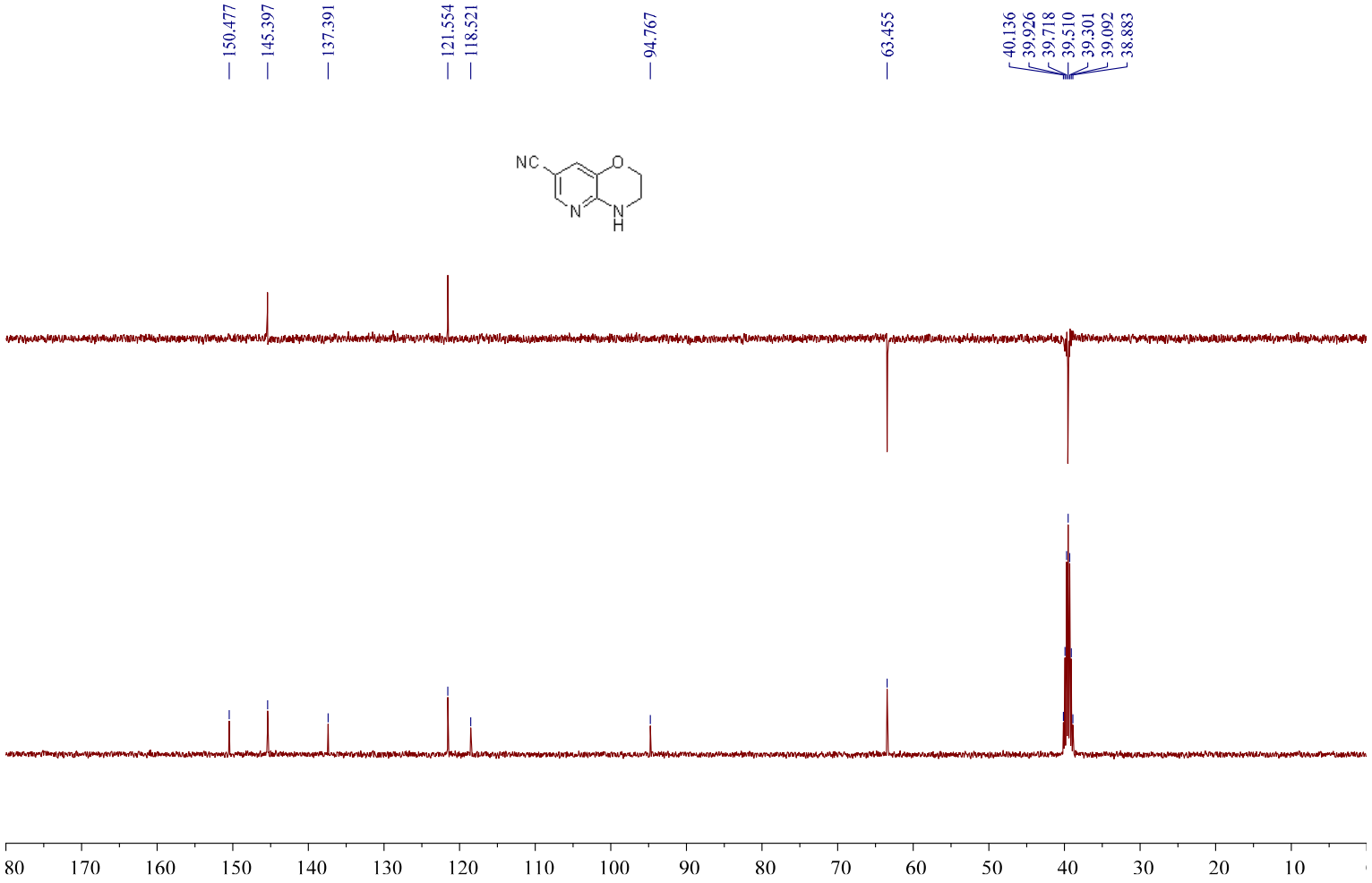


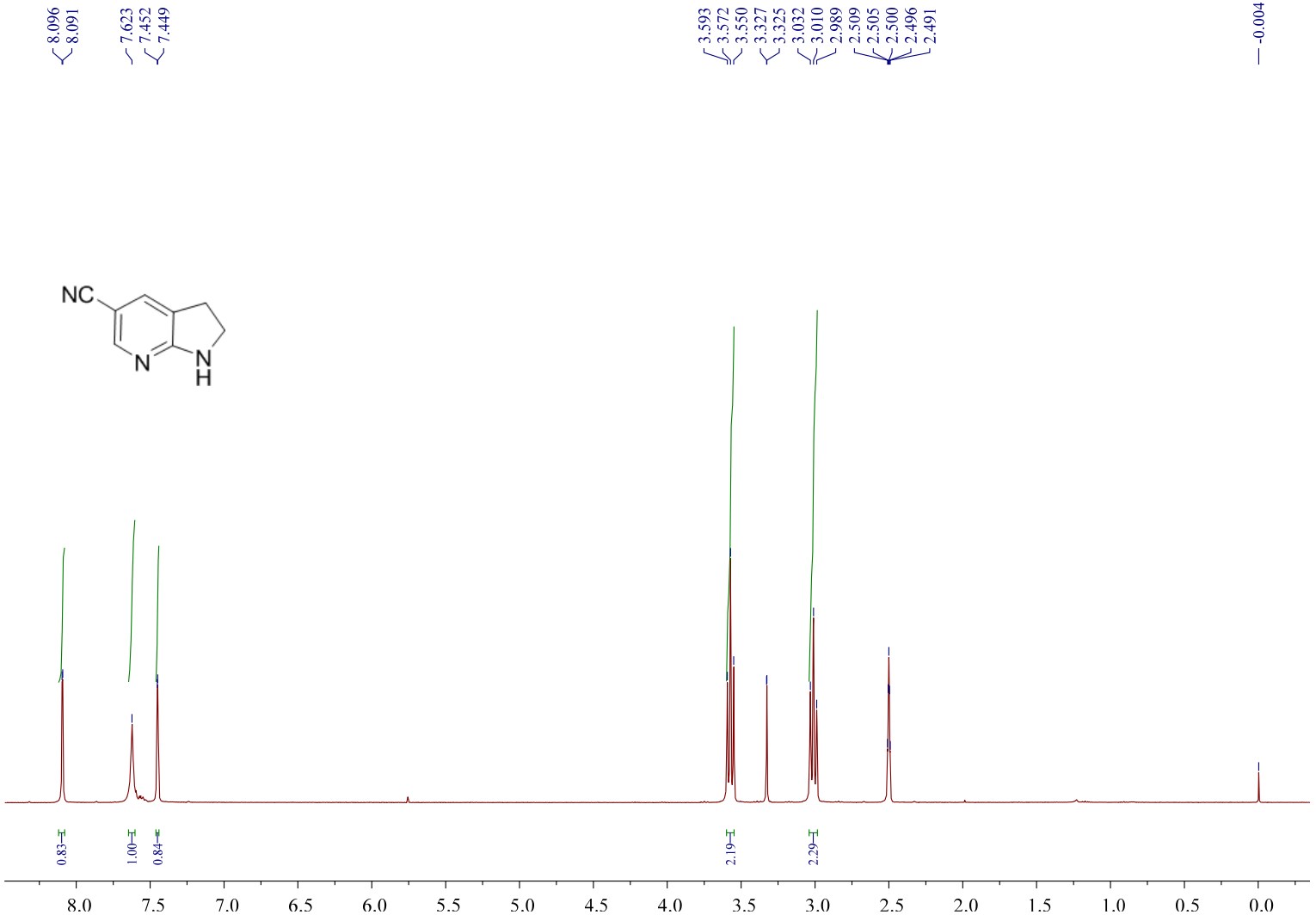


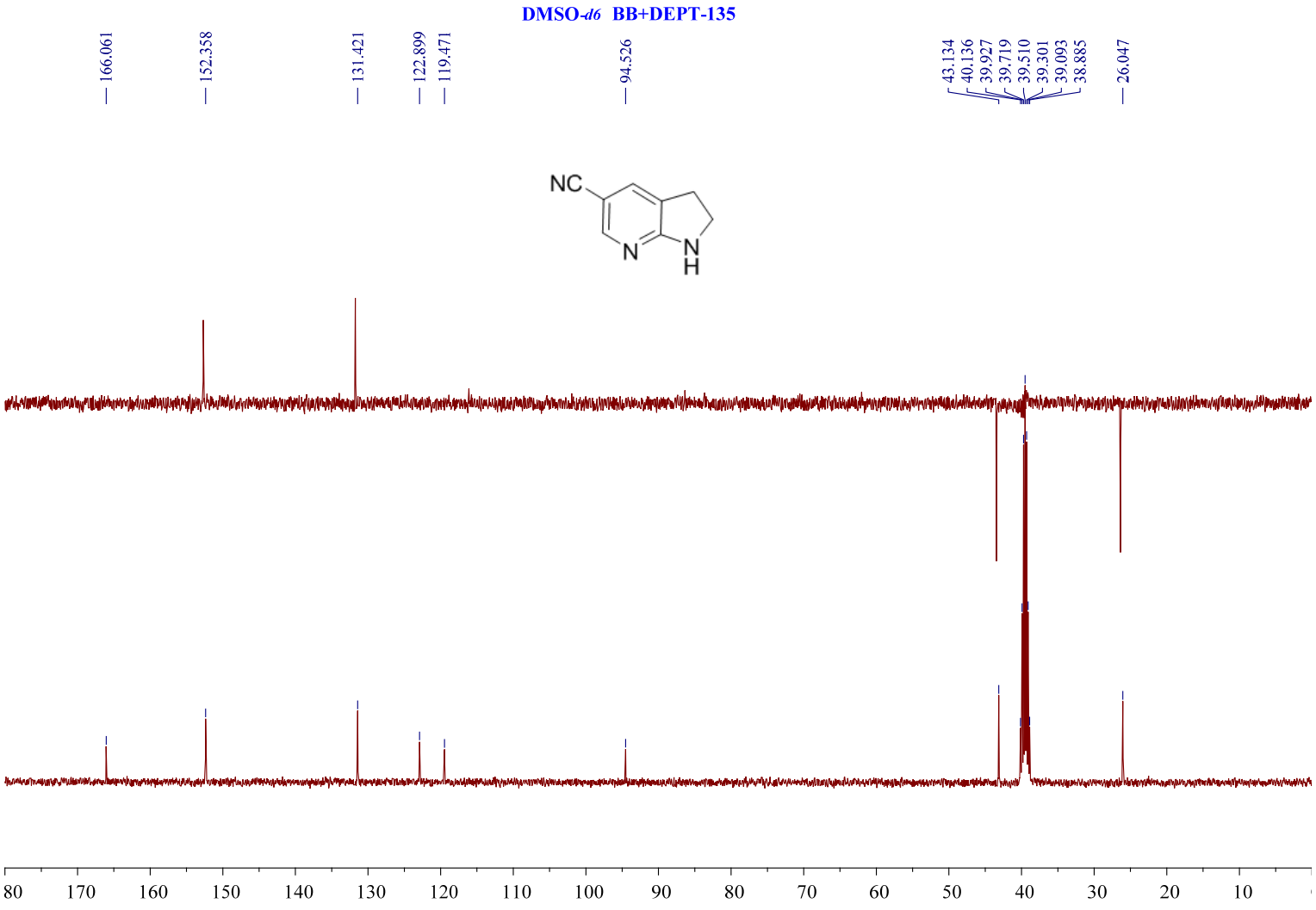


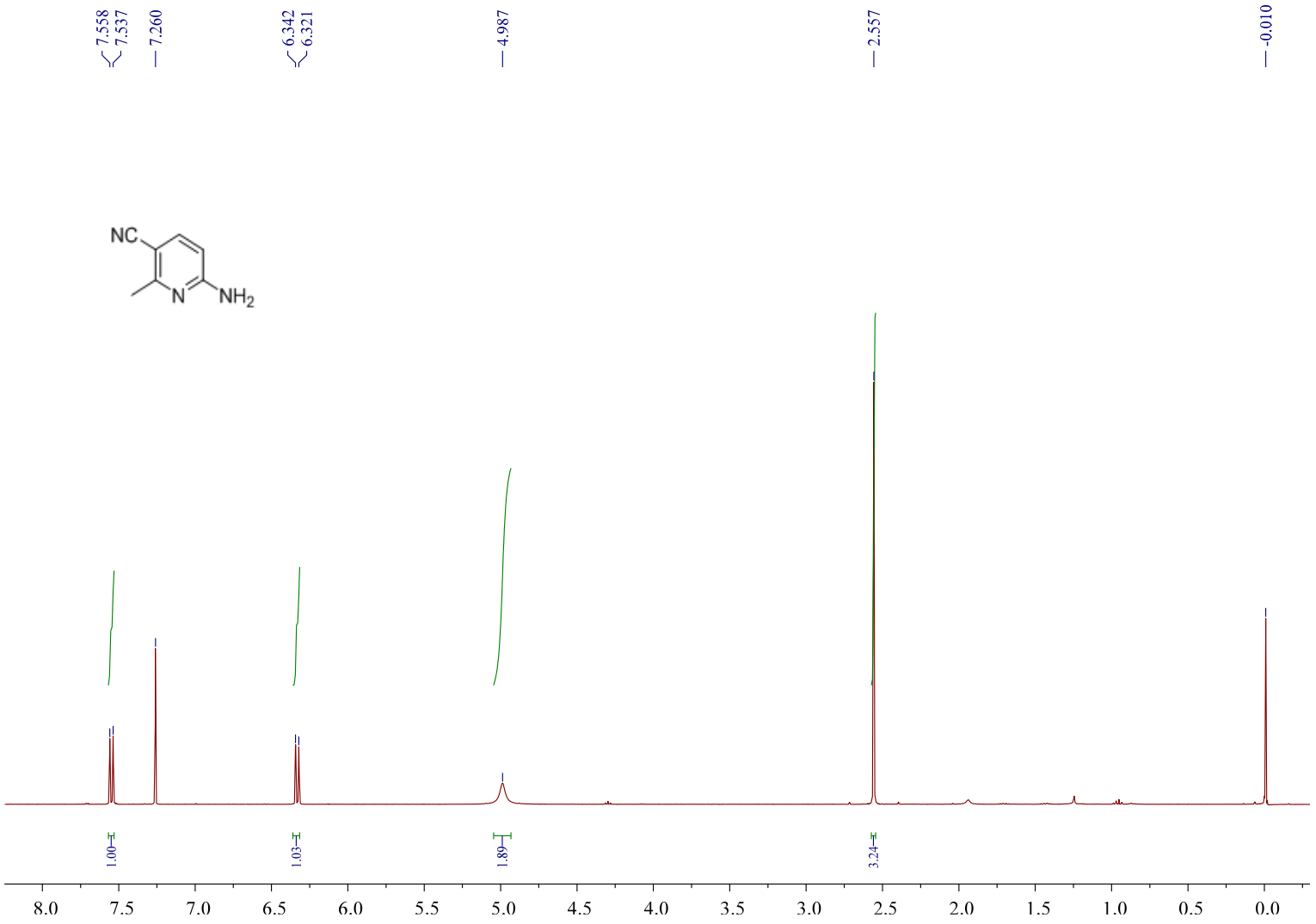


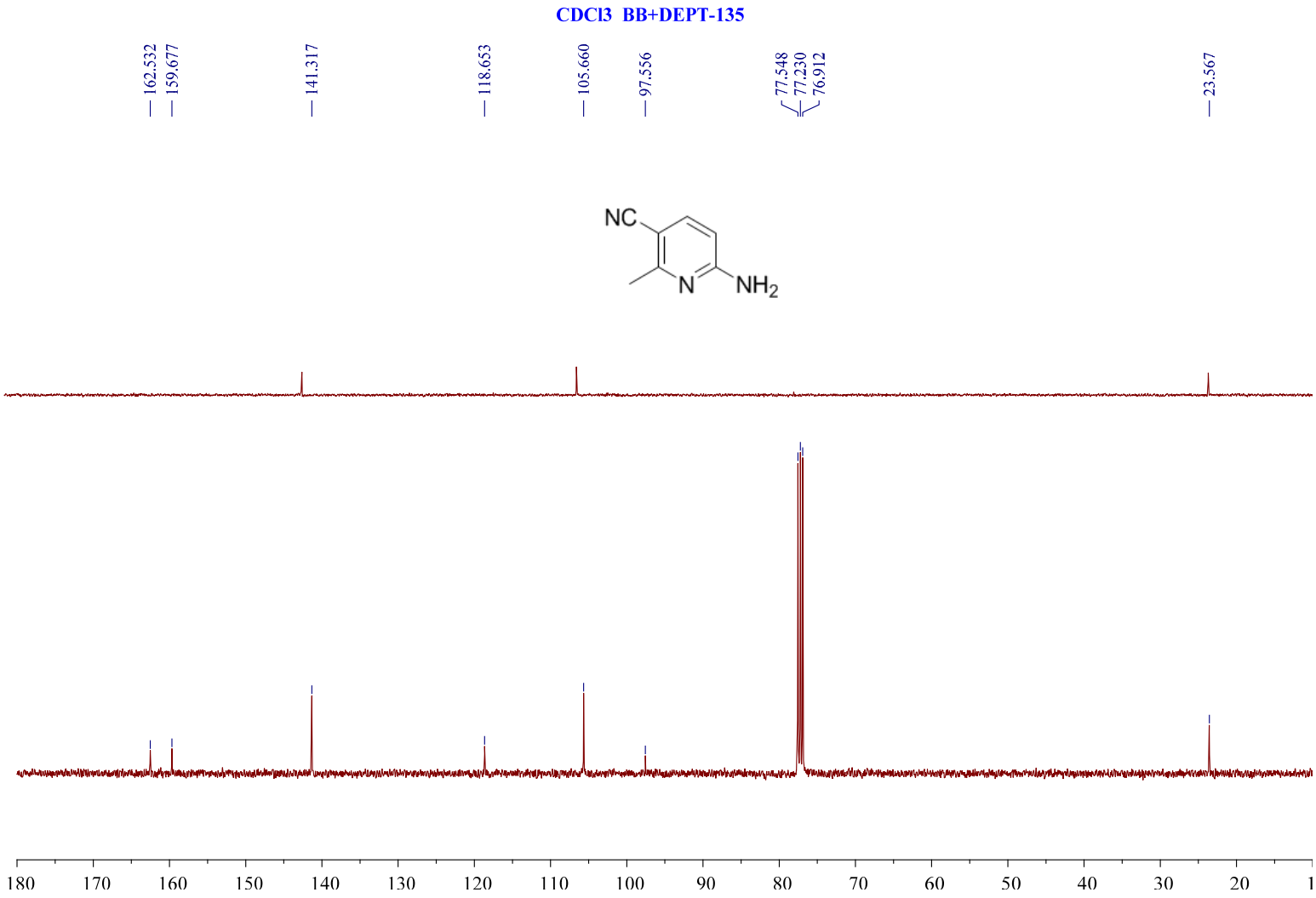
DMSO-*d6* BB+DEPT-135

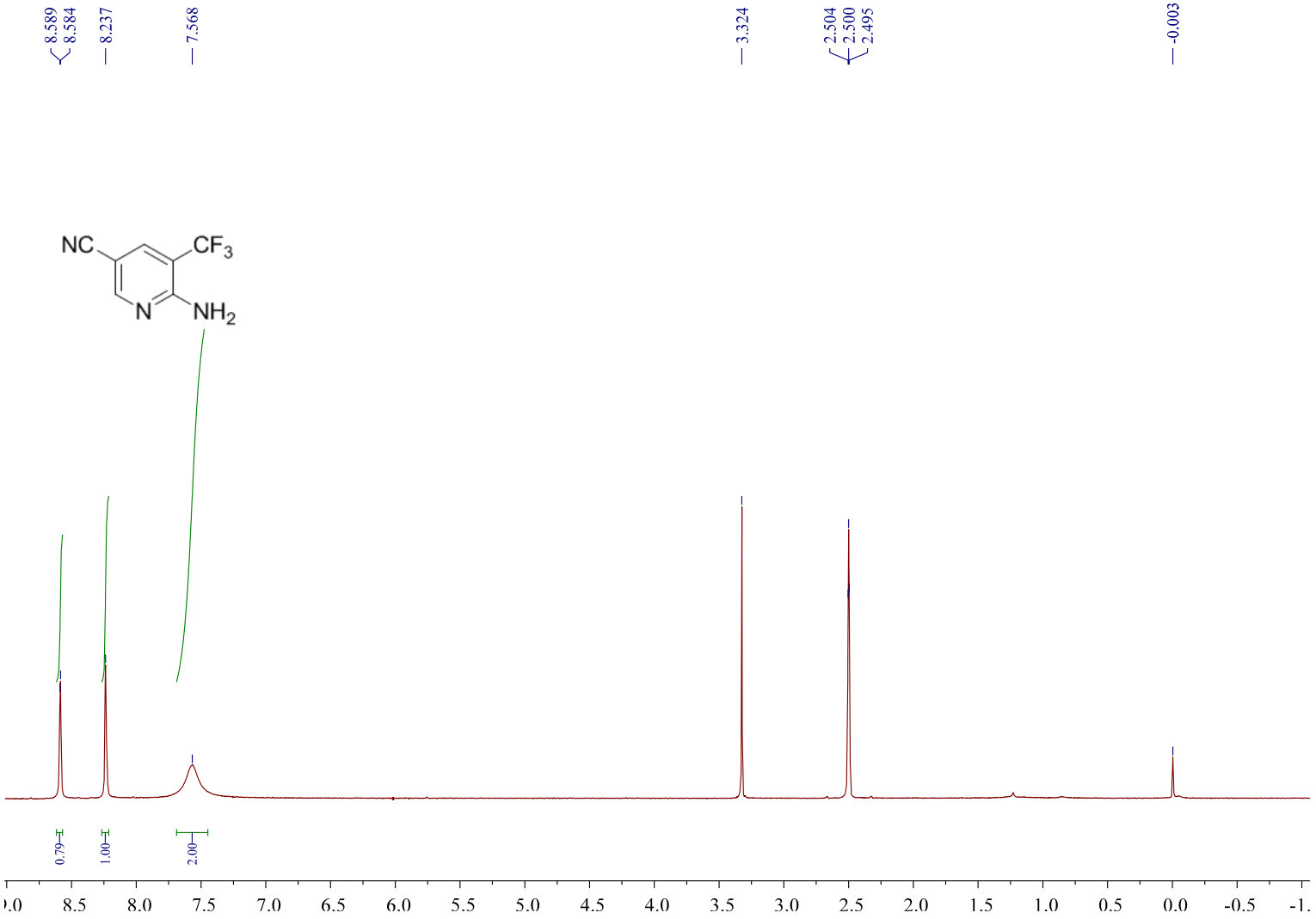


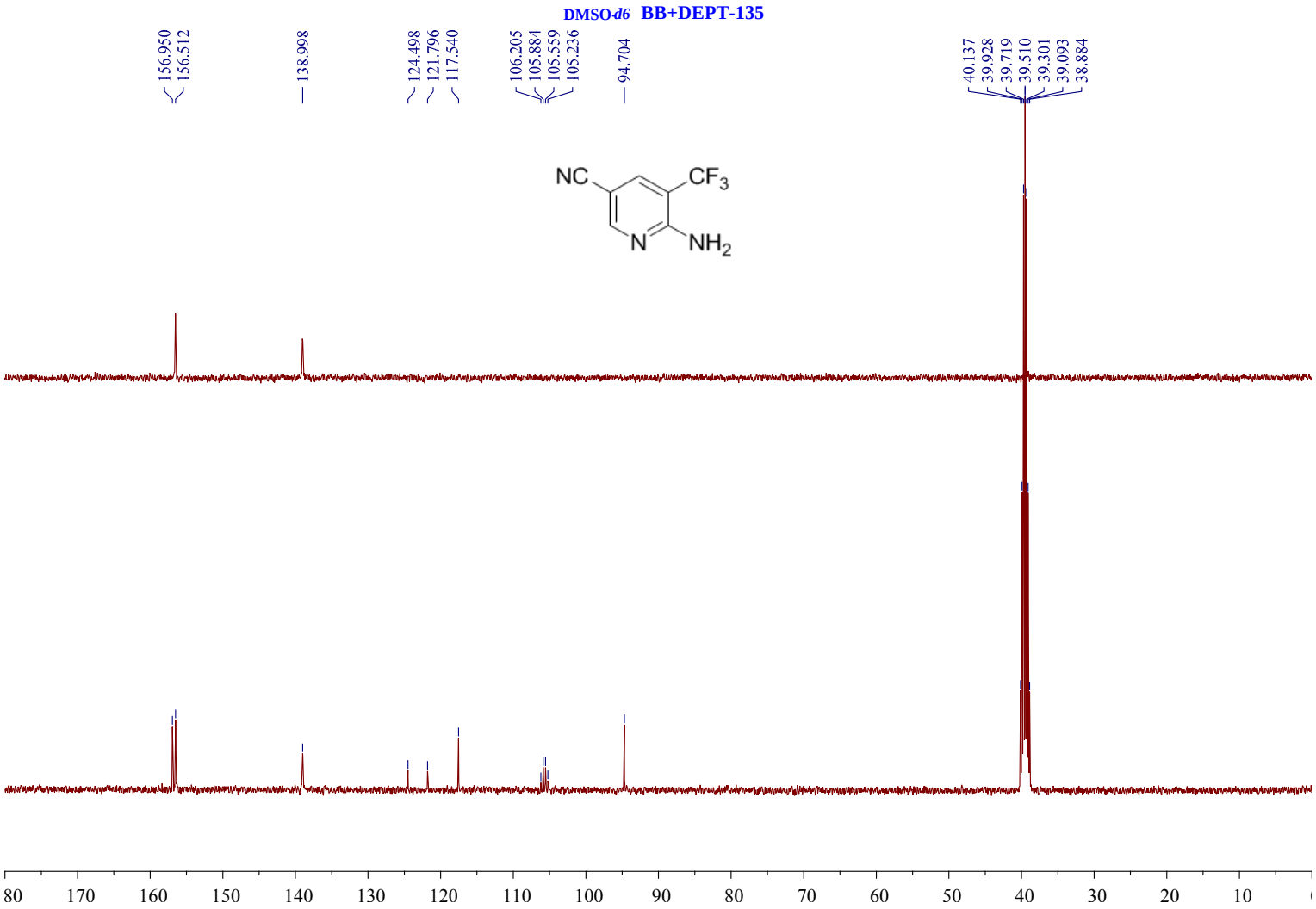


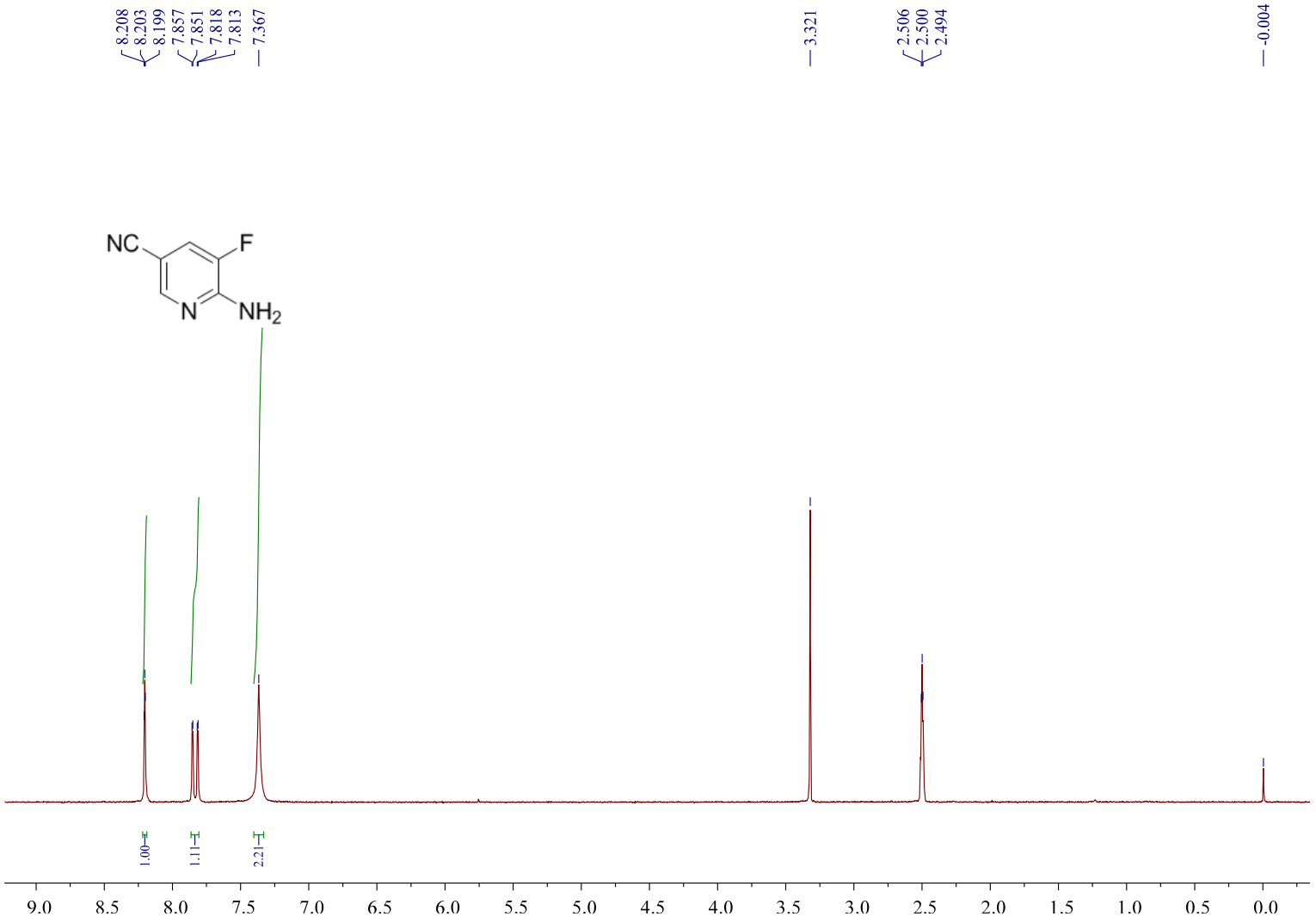


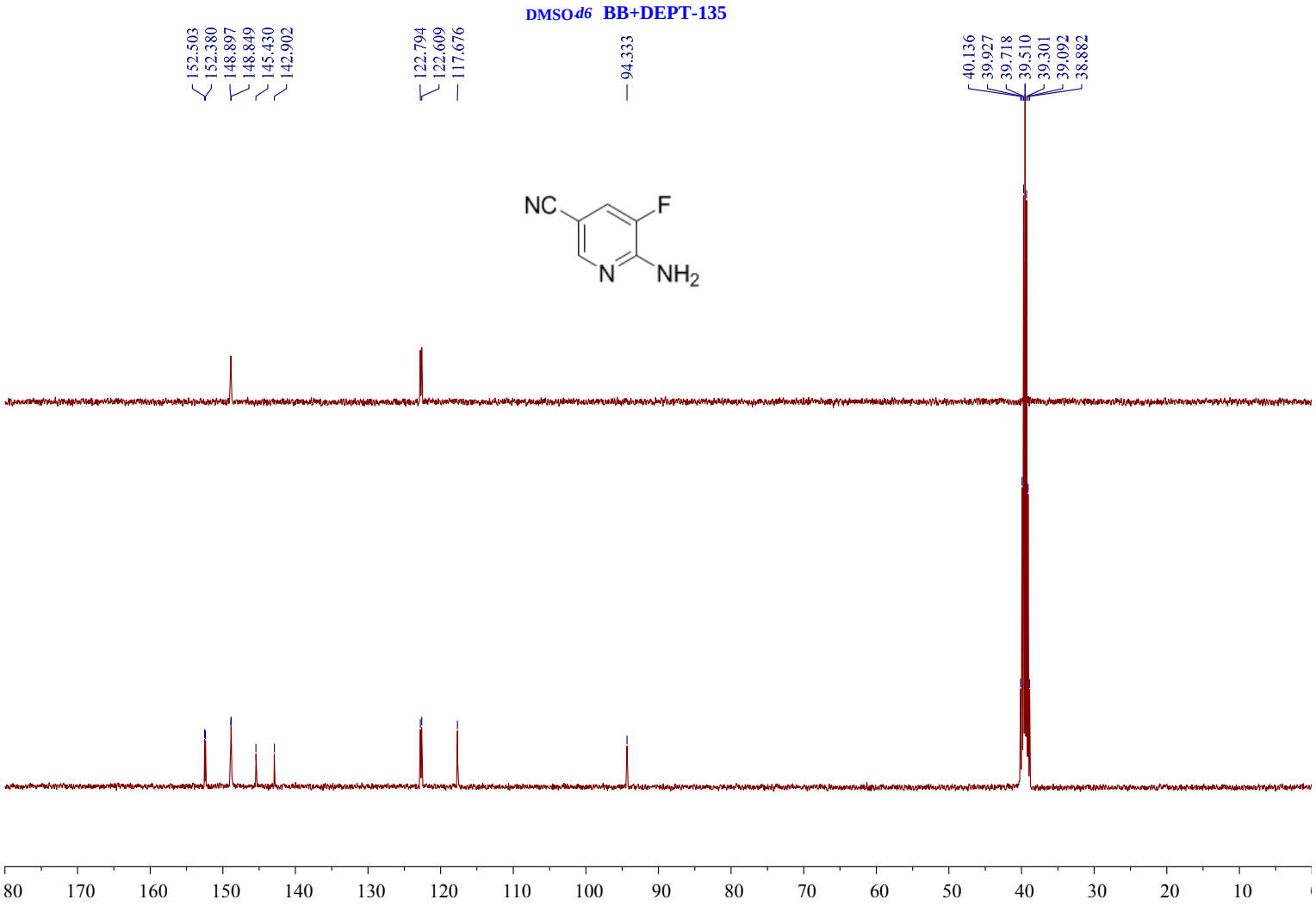


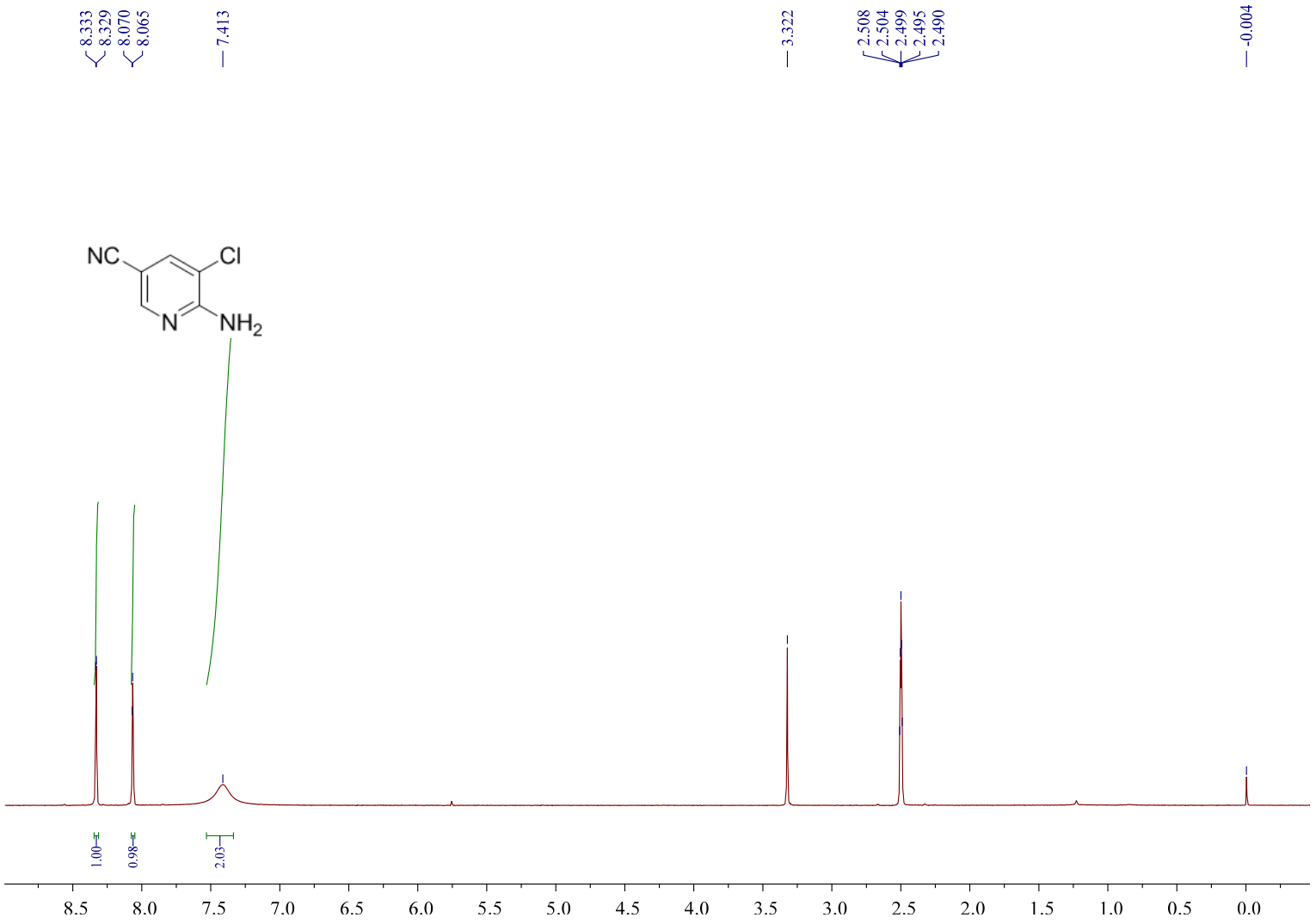


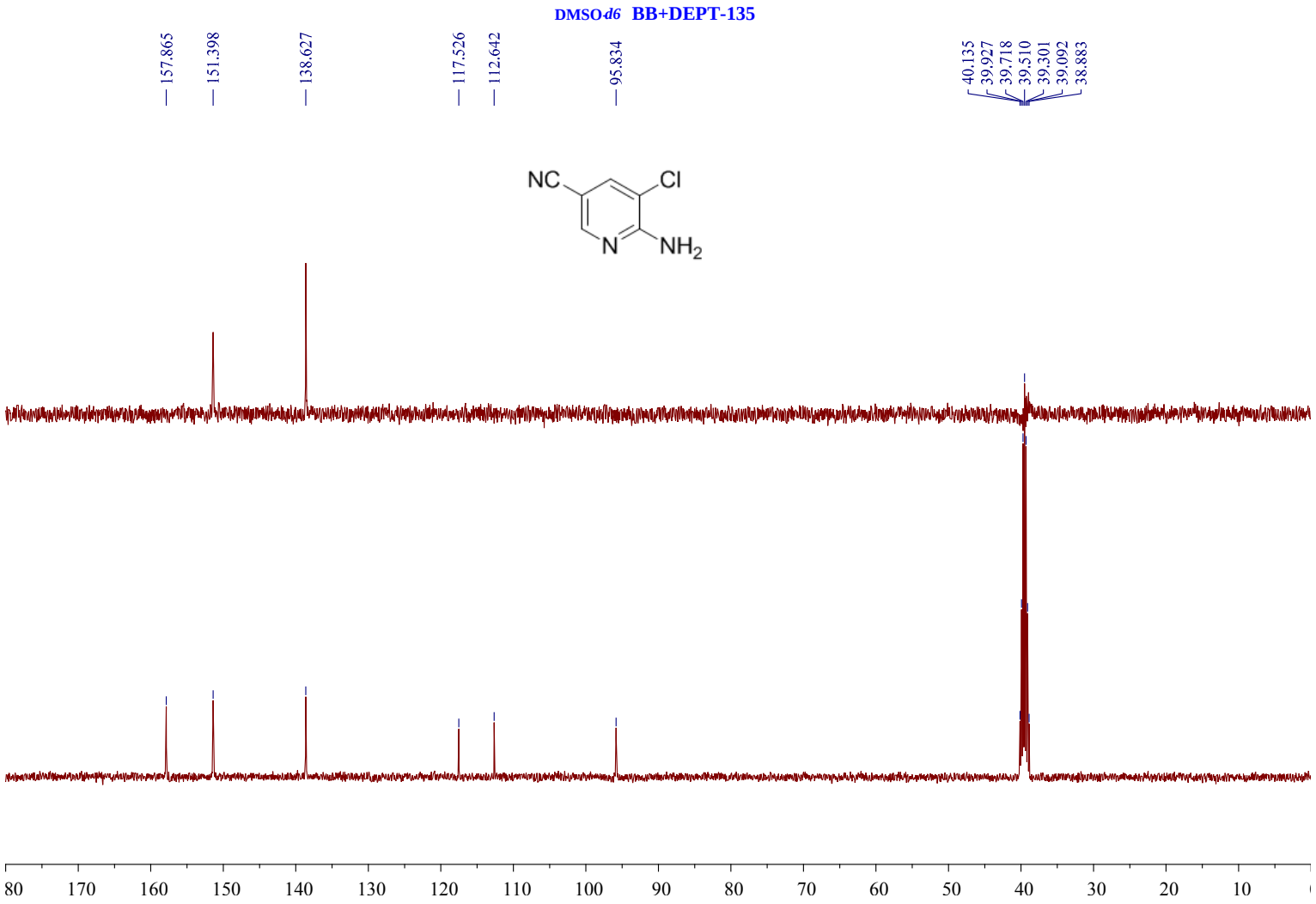


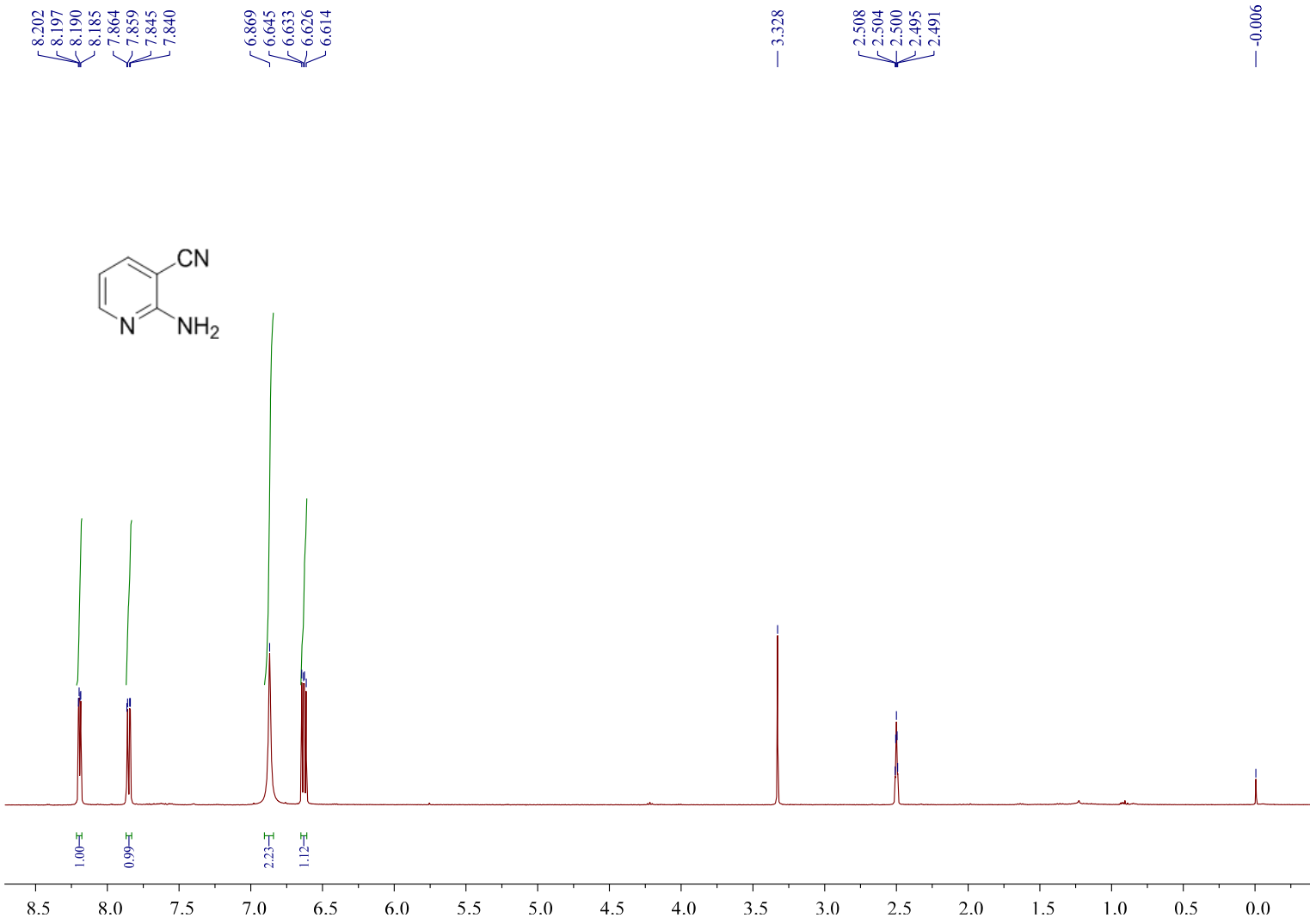


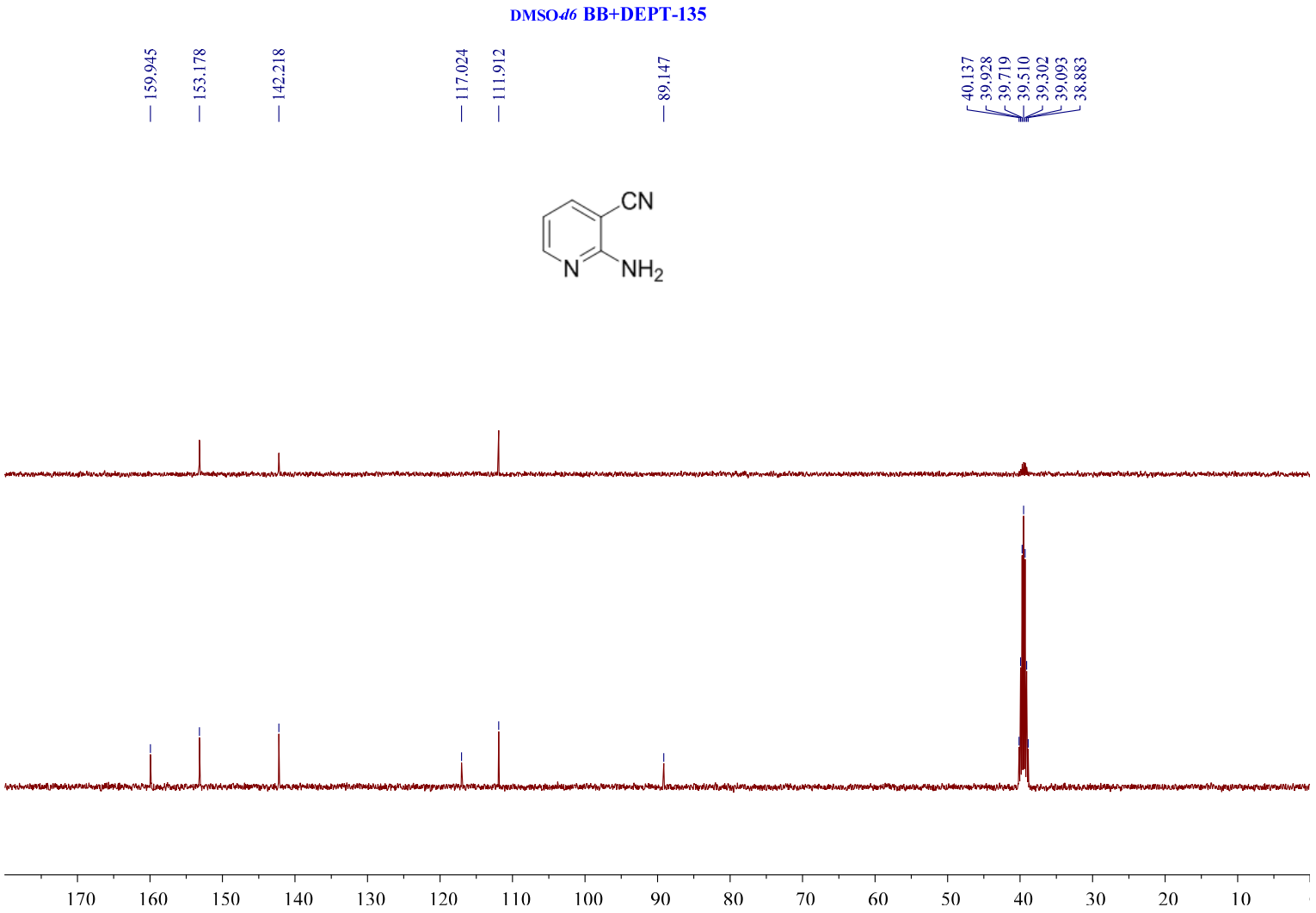


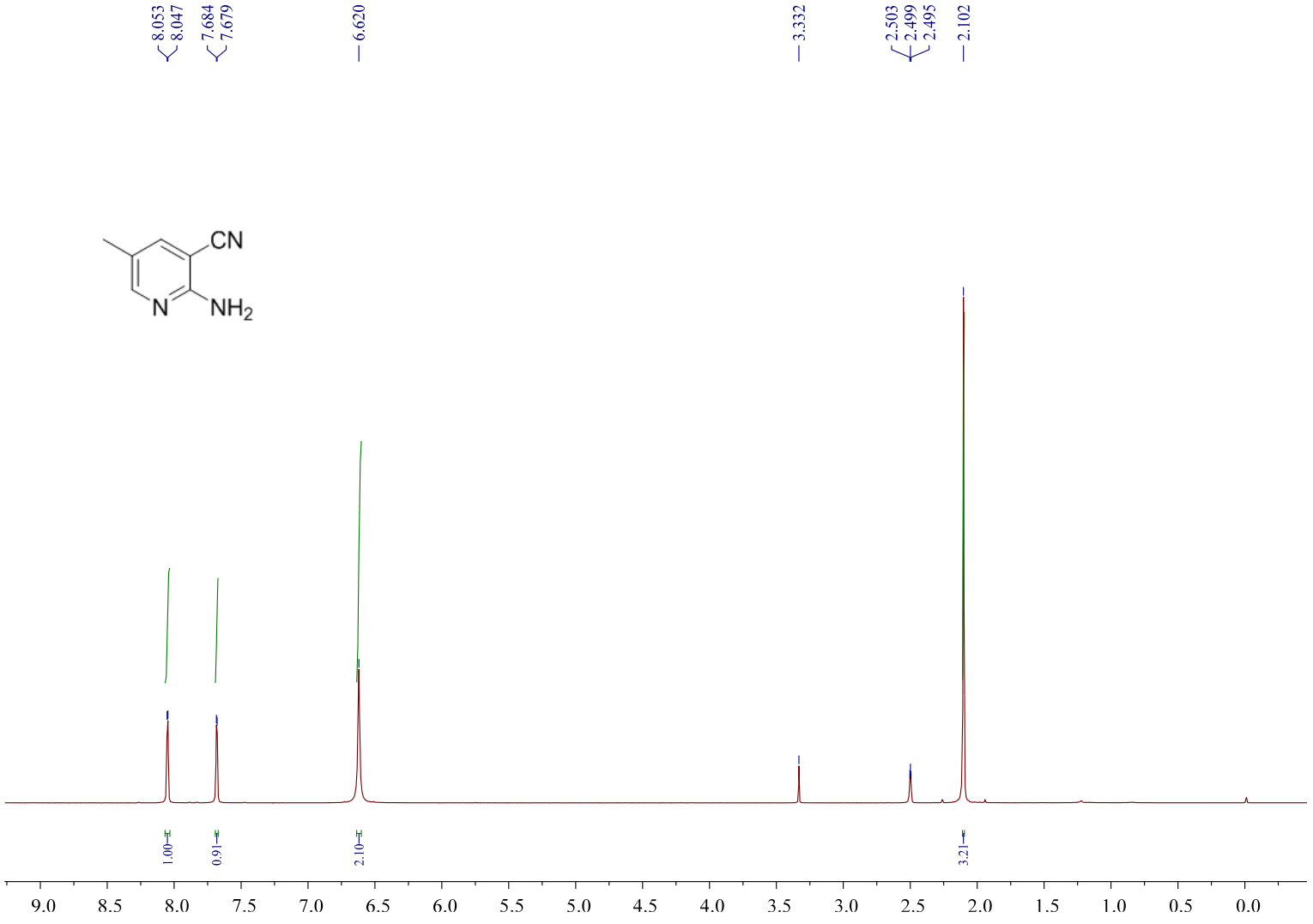


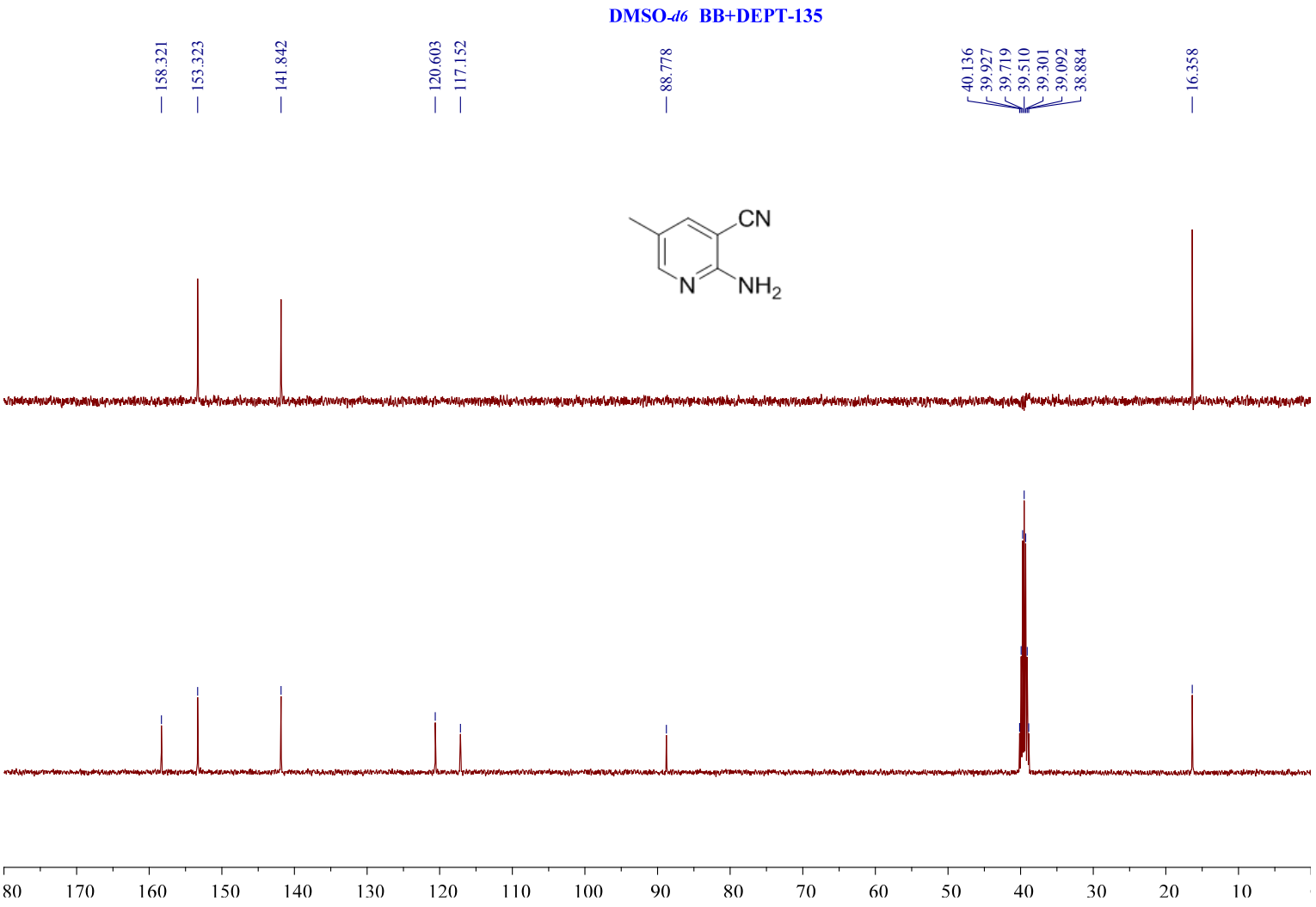


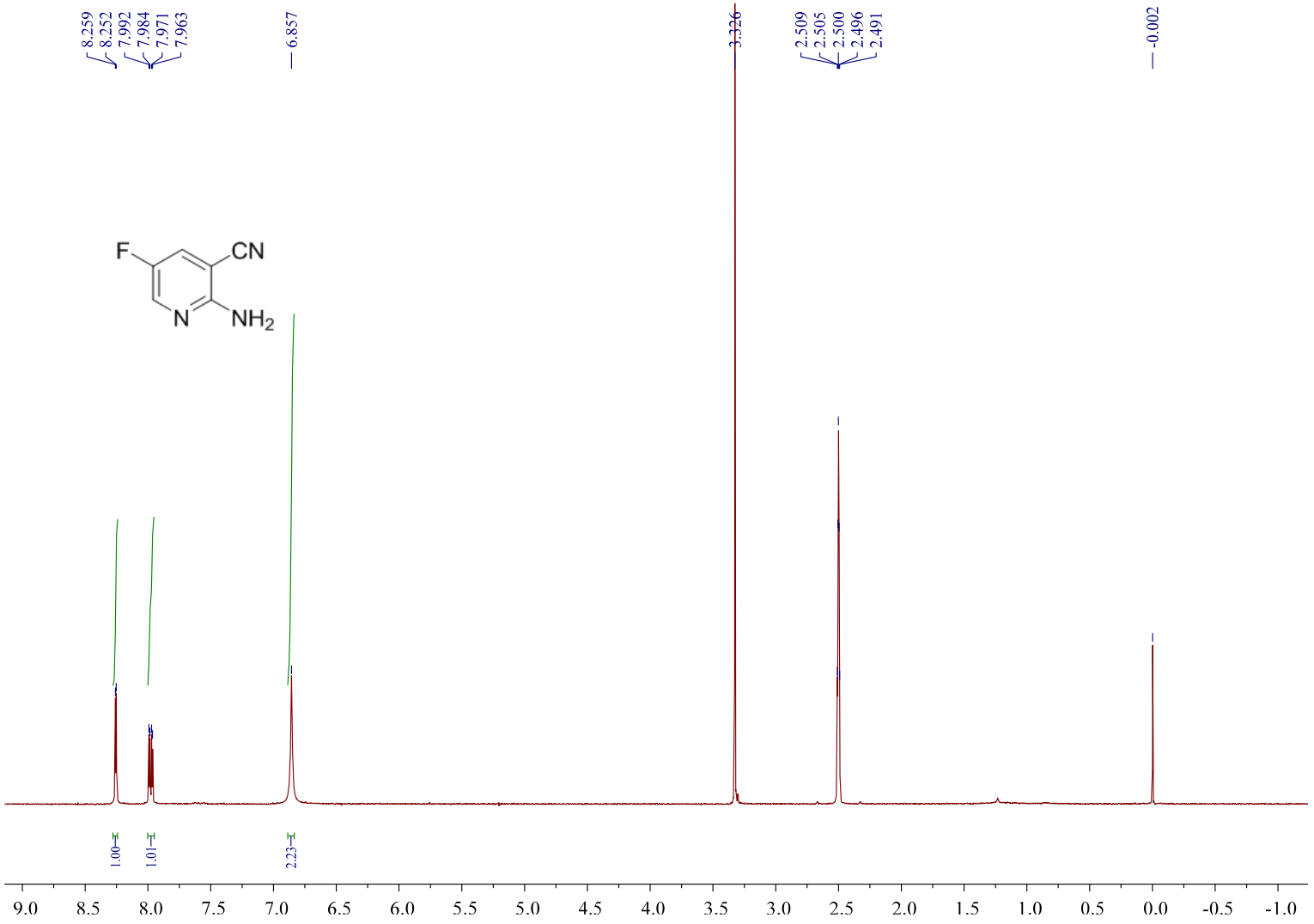


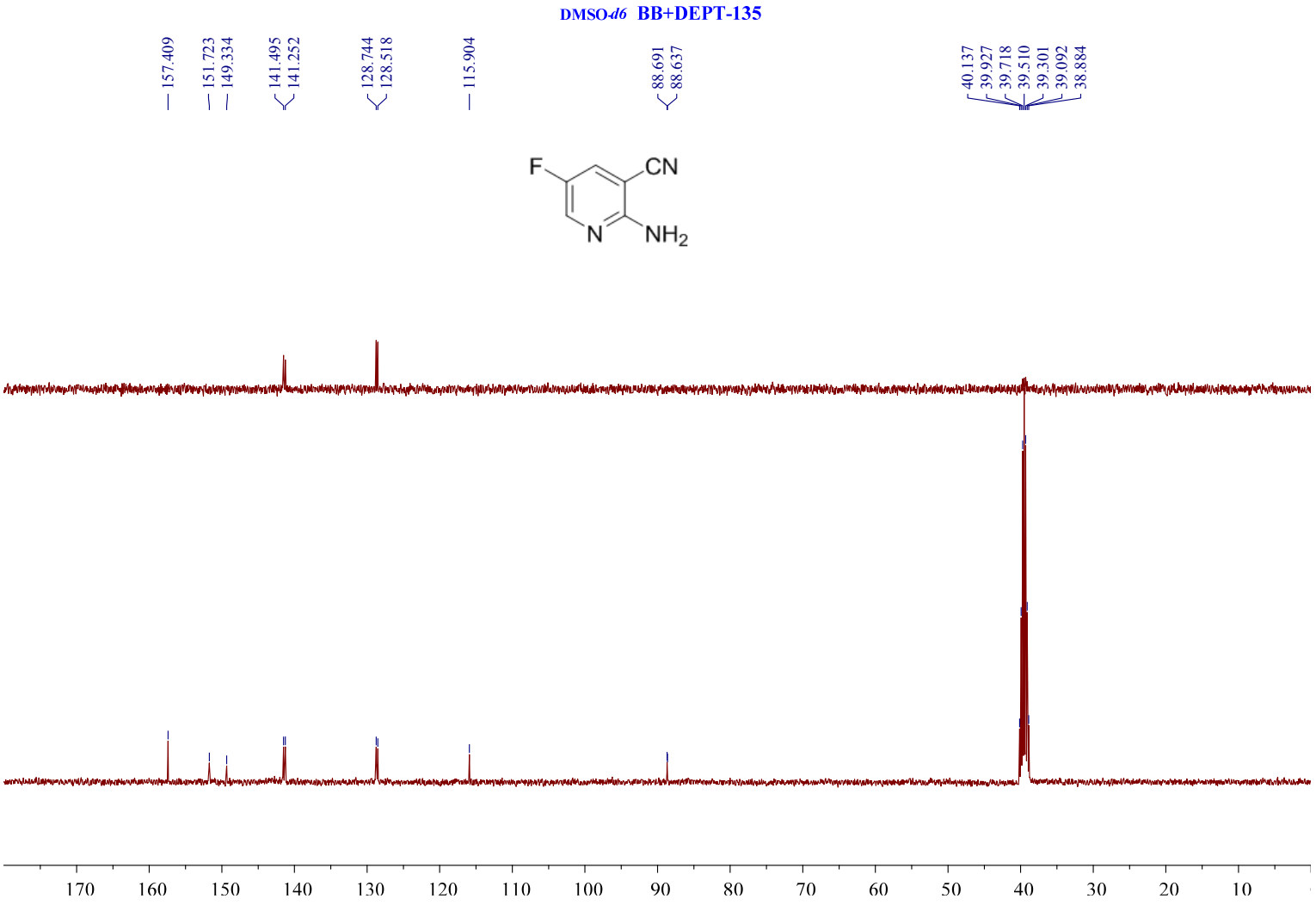


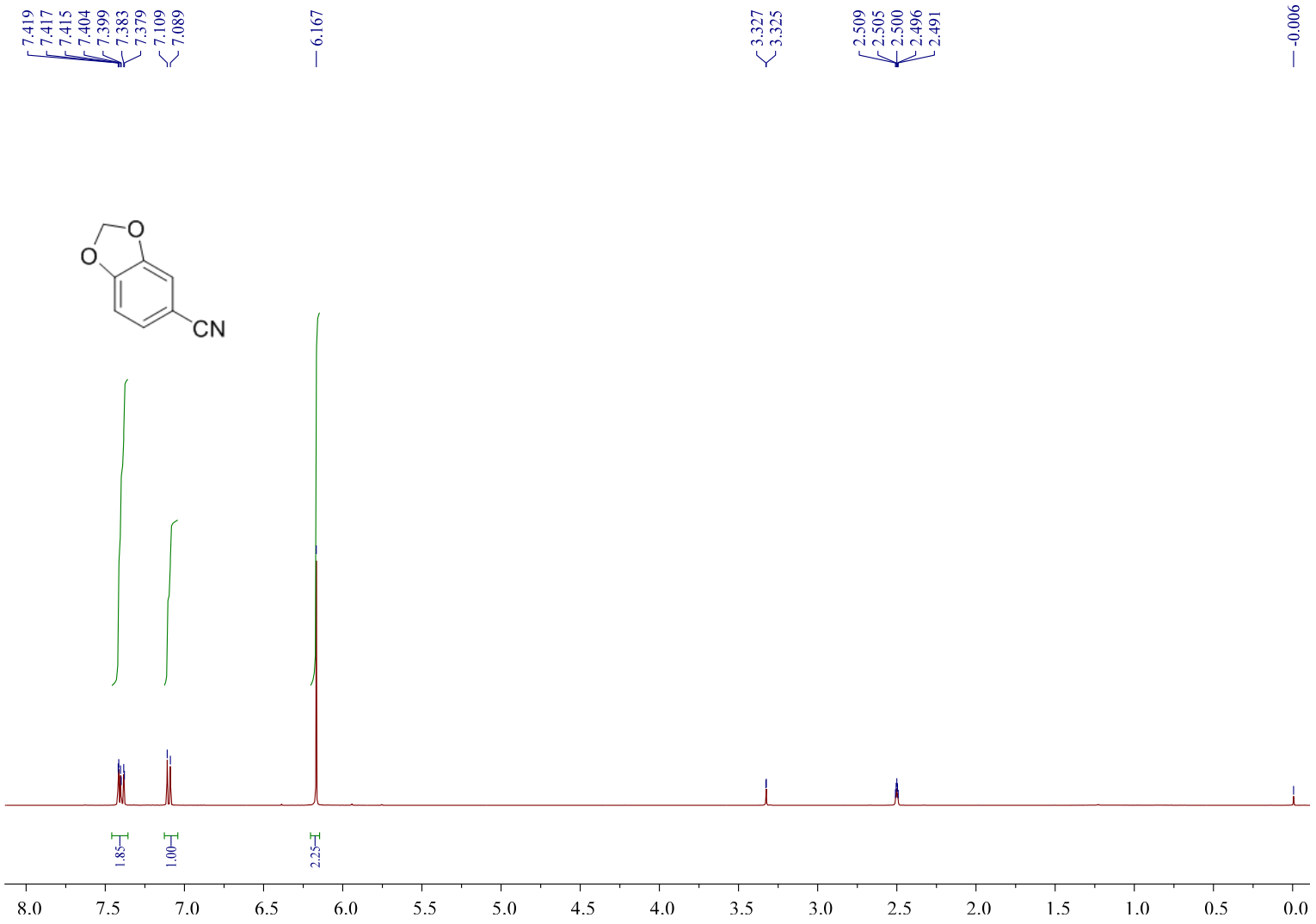


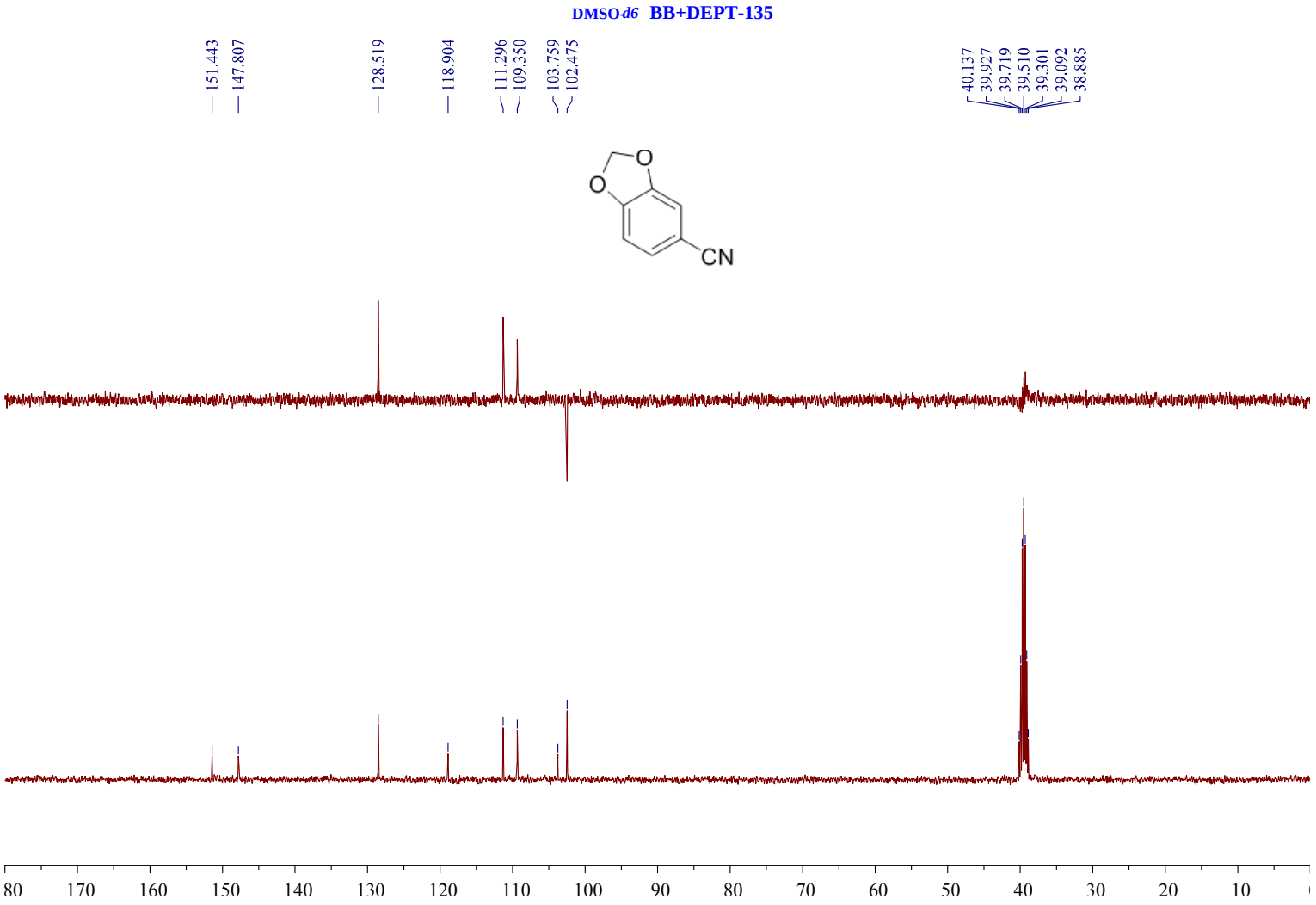


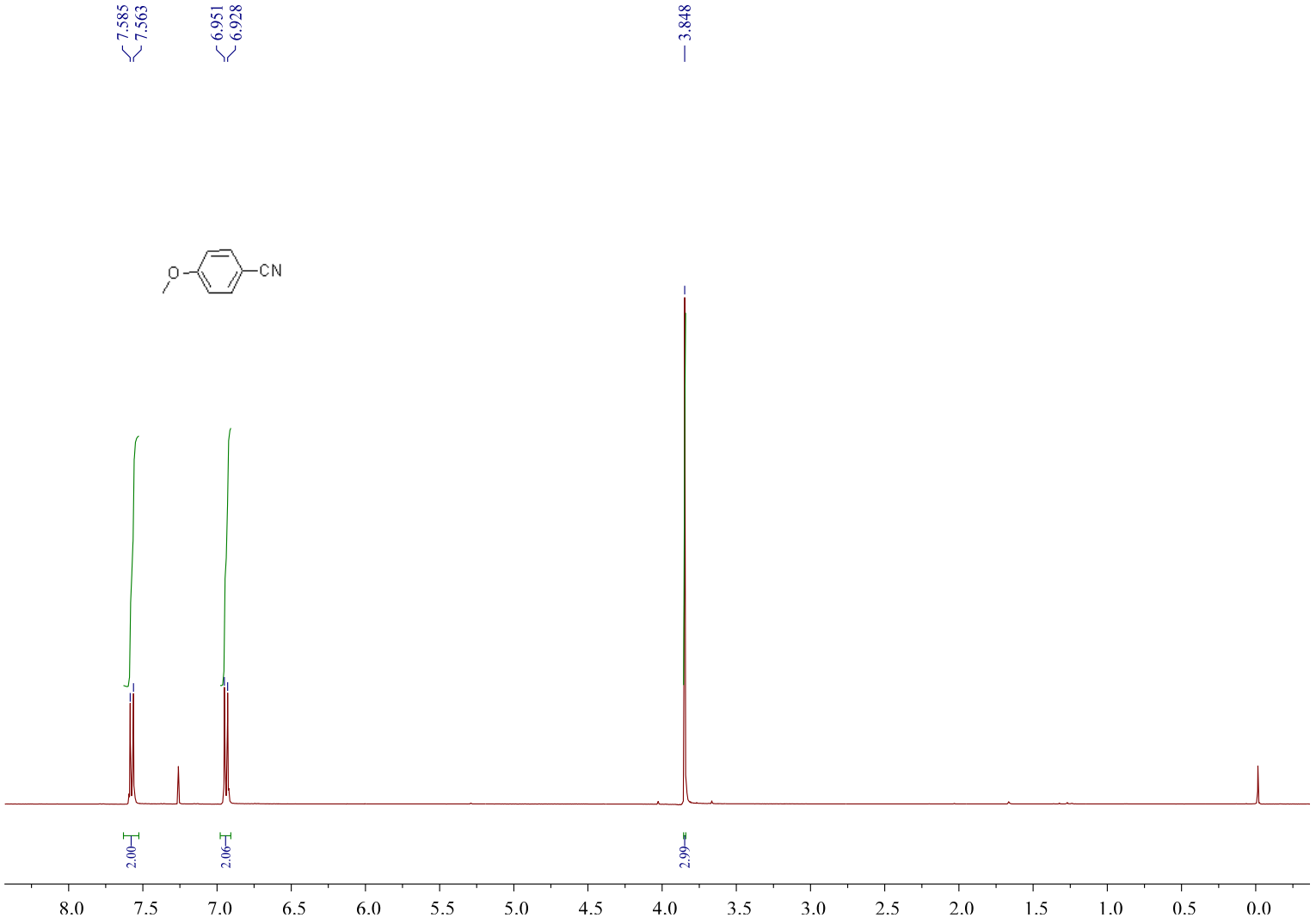


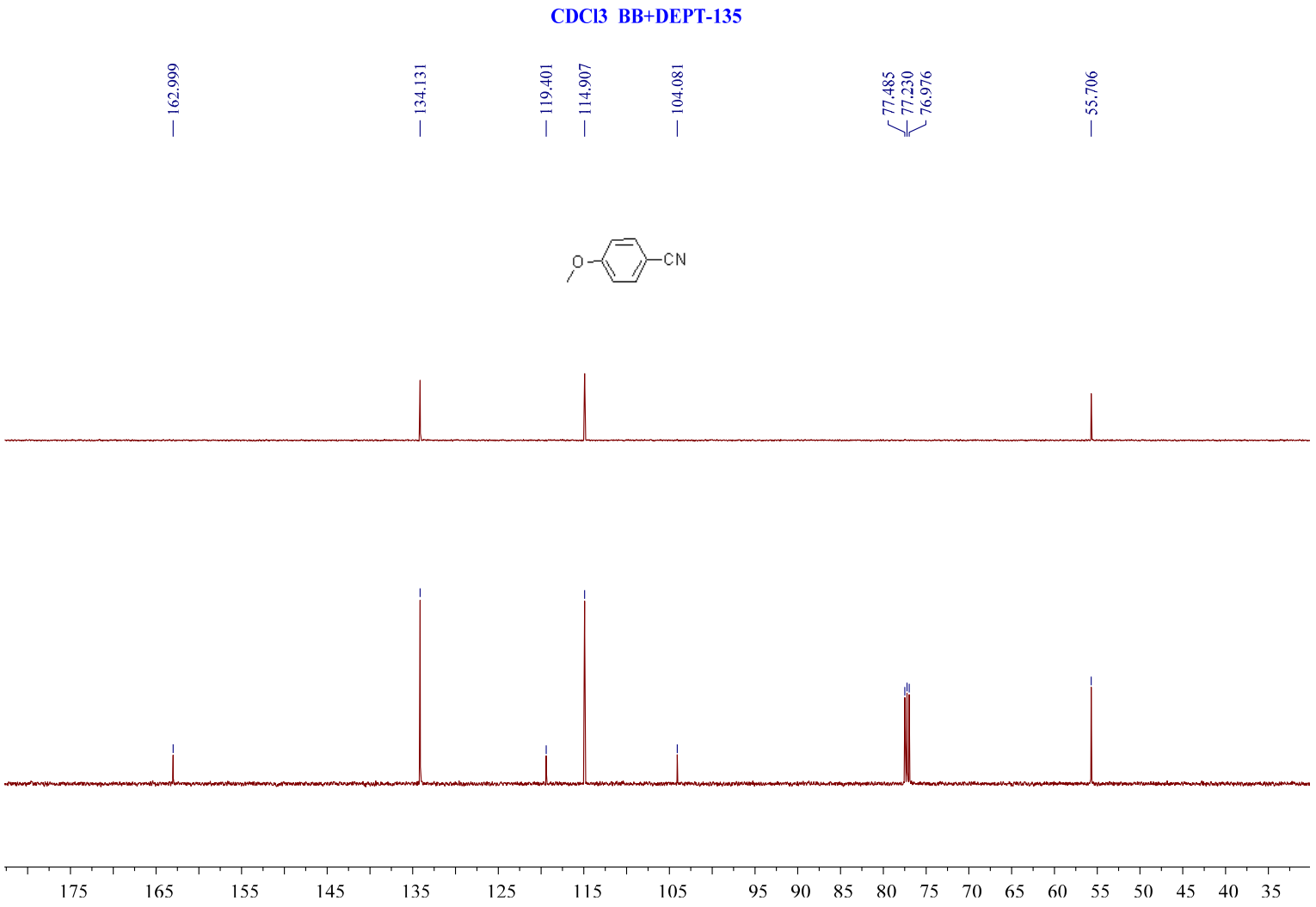


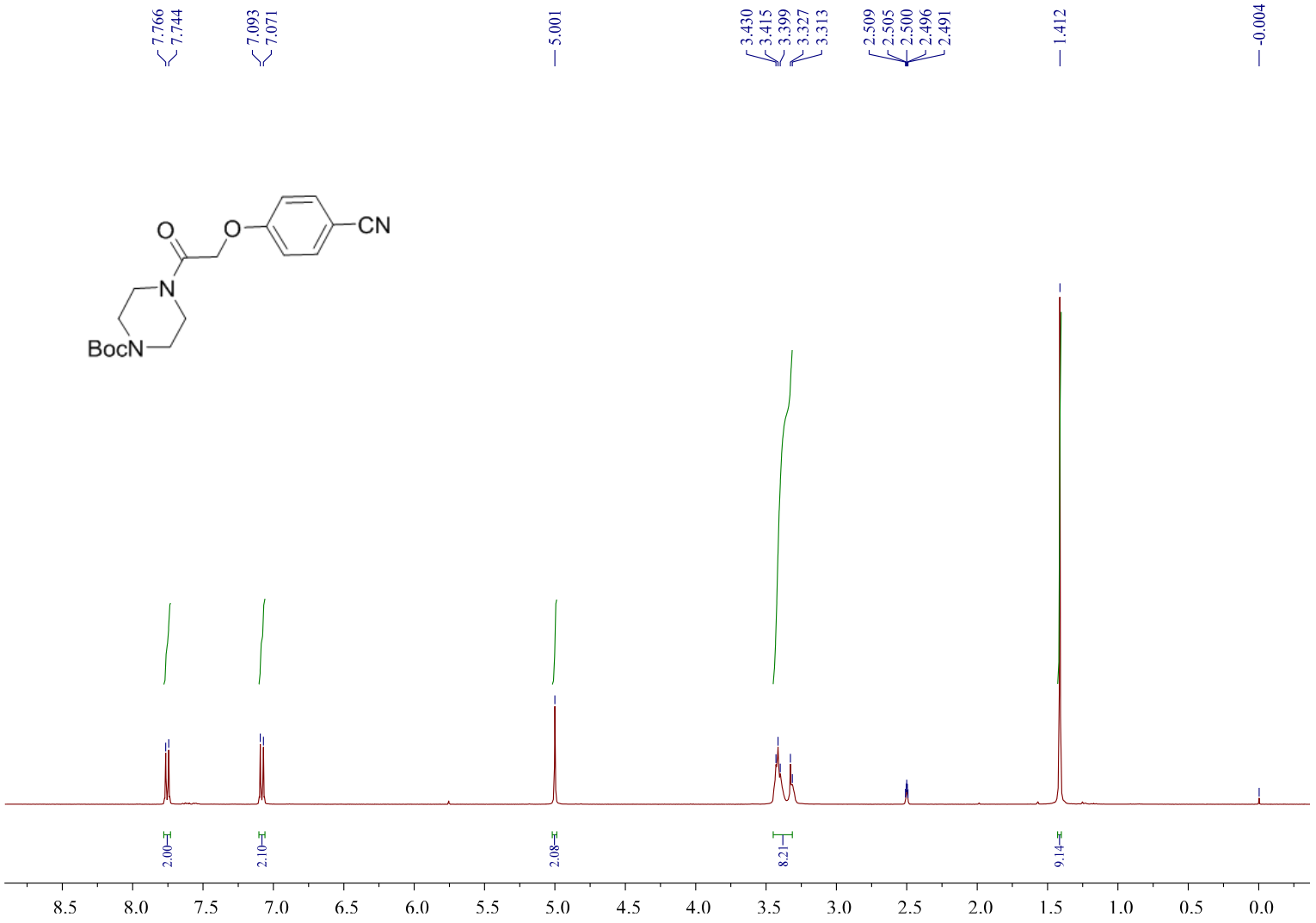


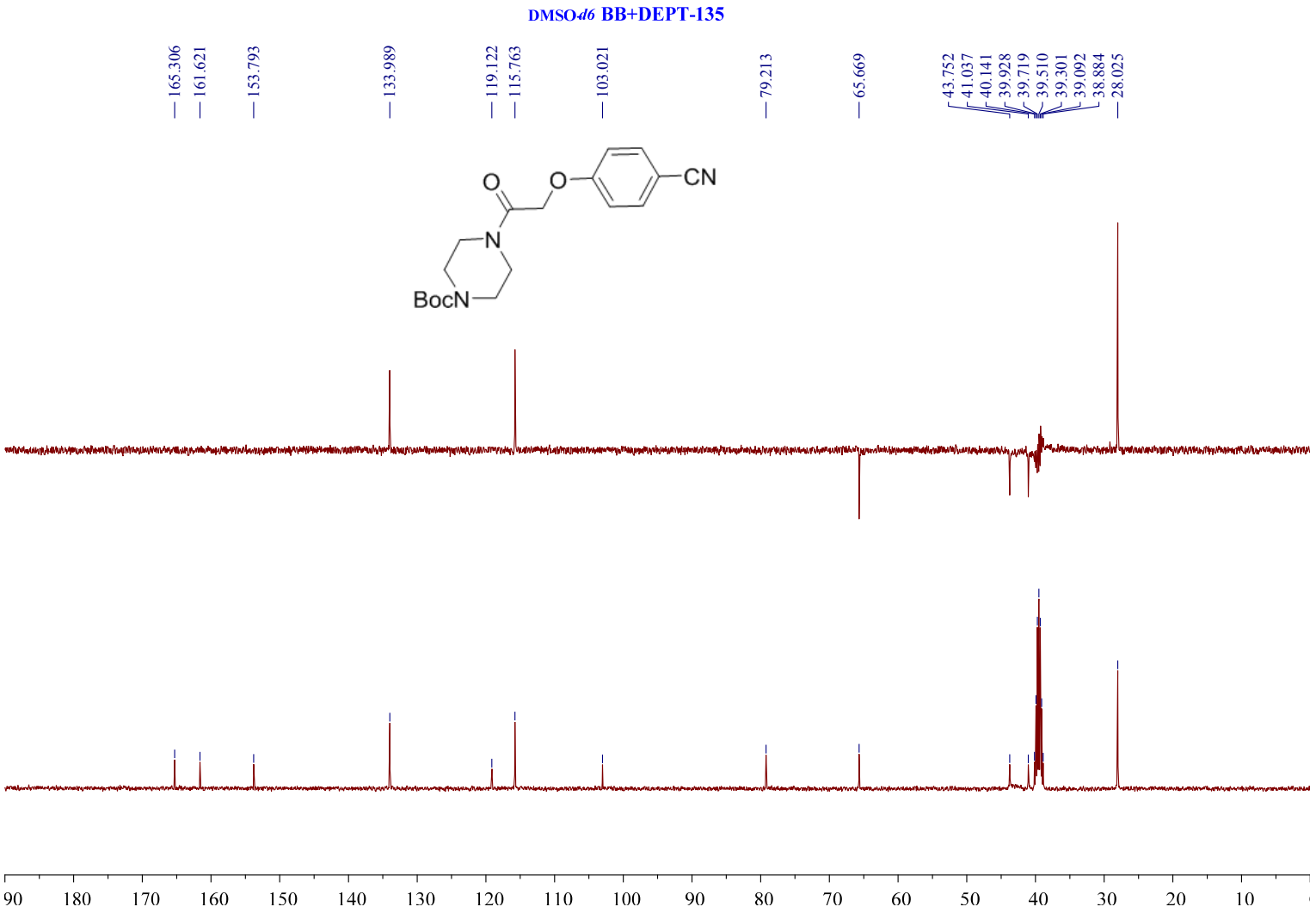


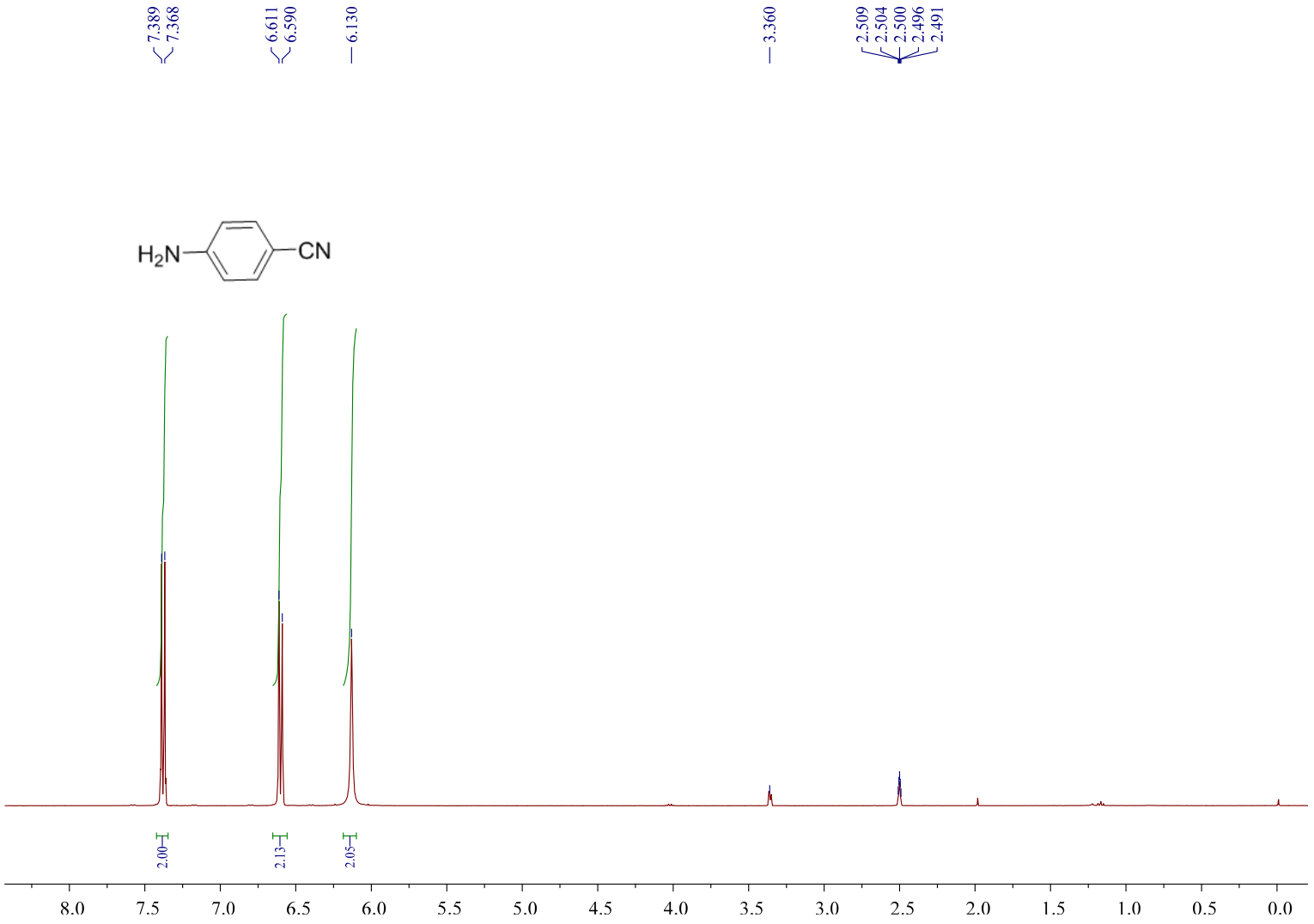


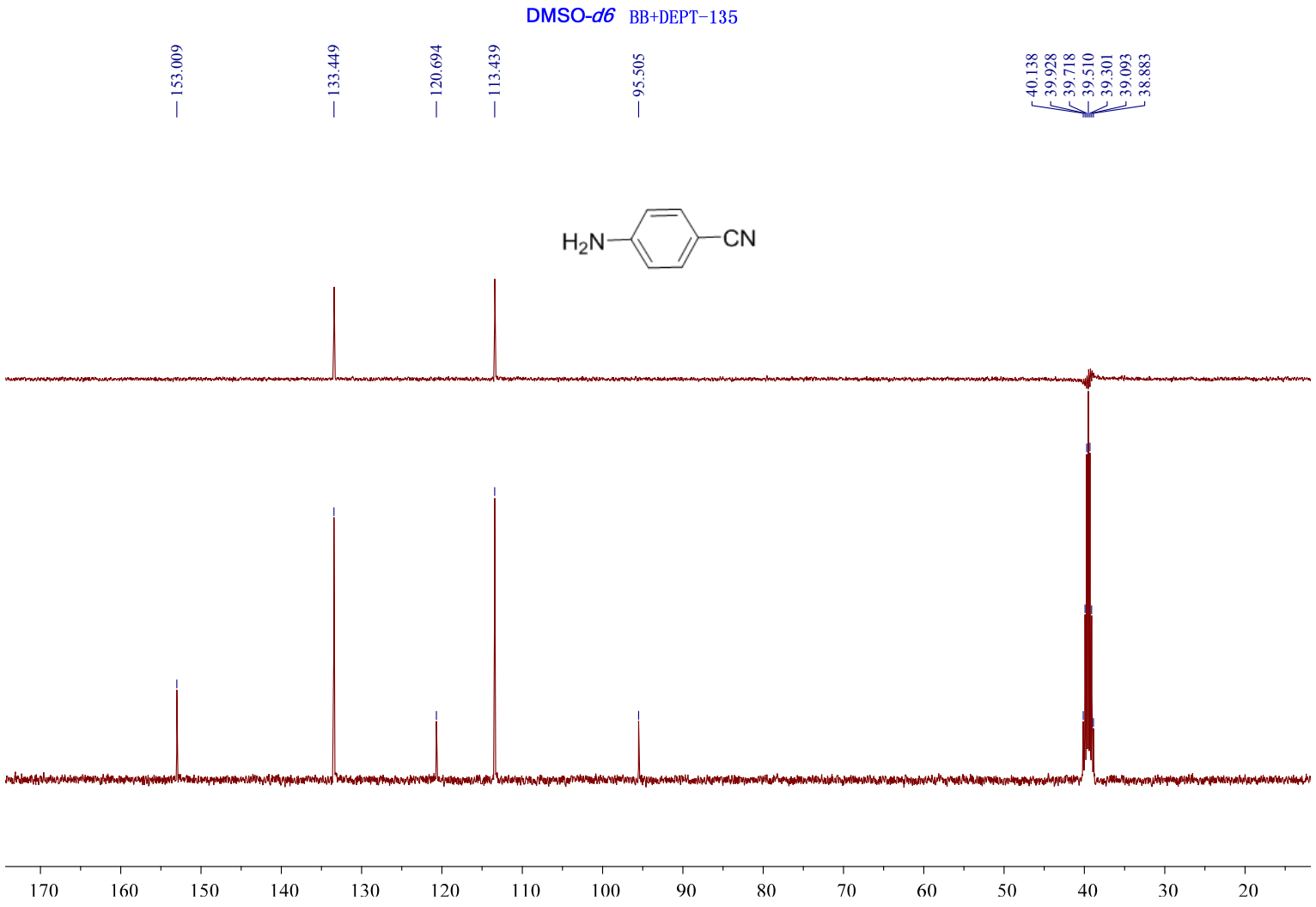


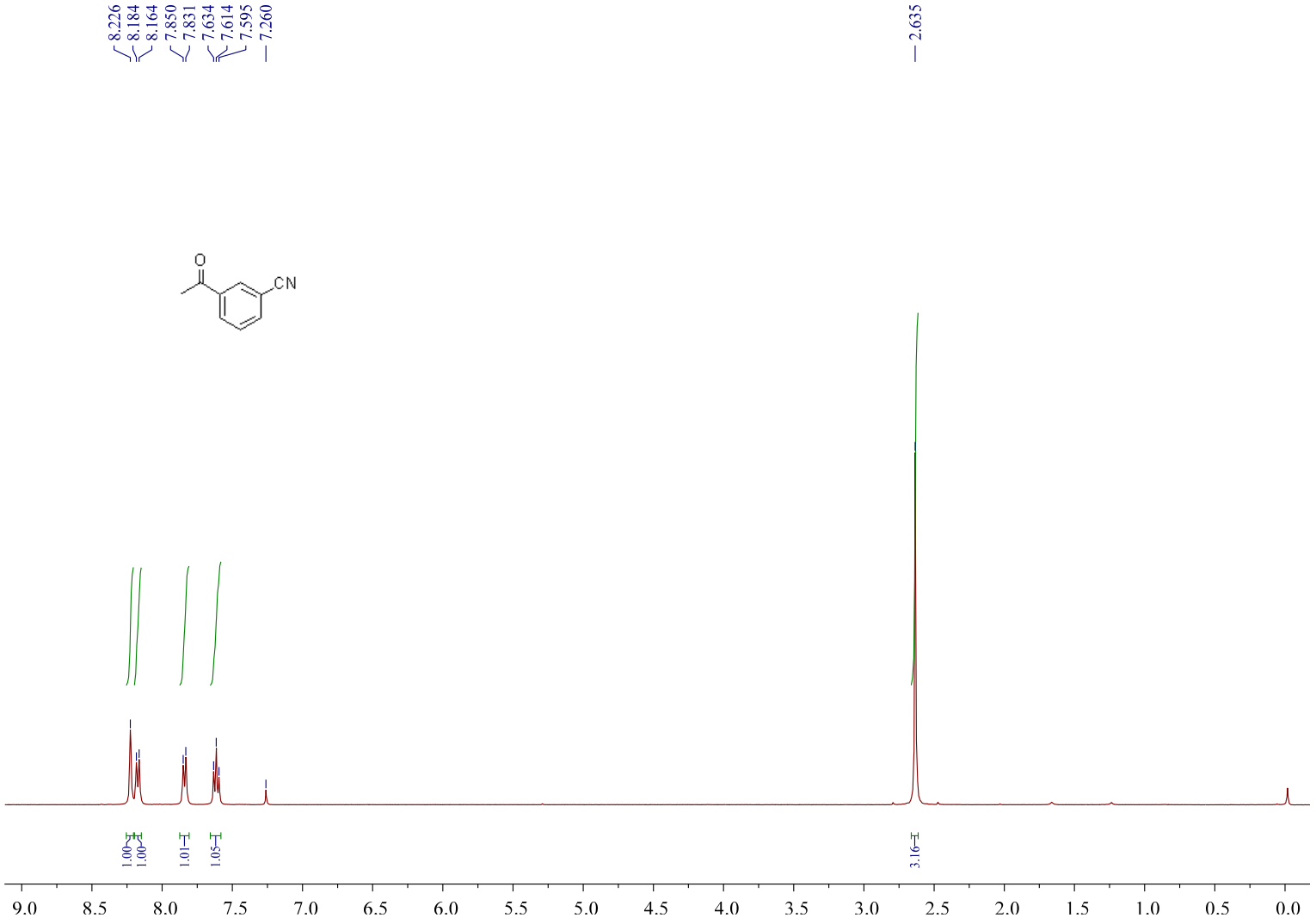


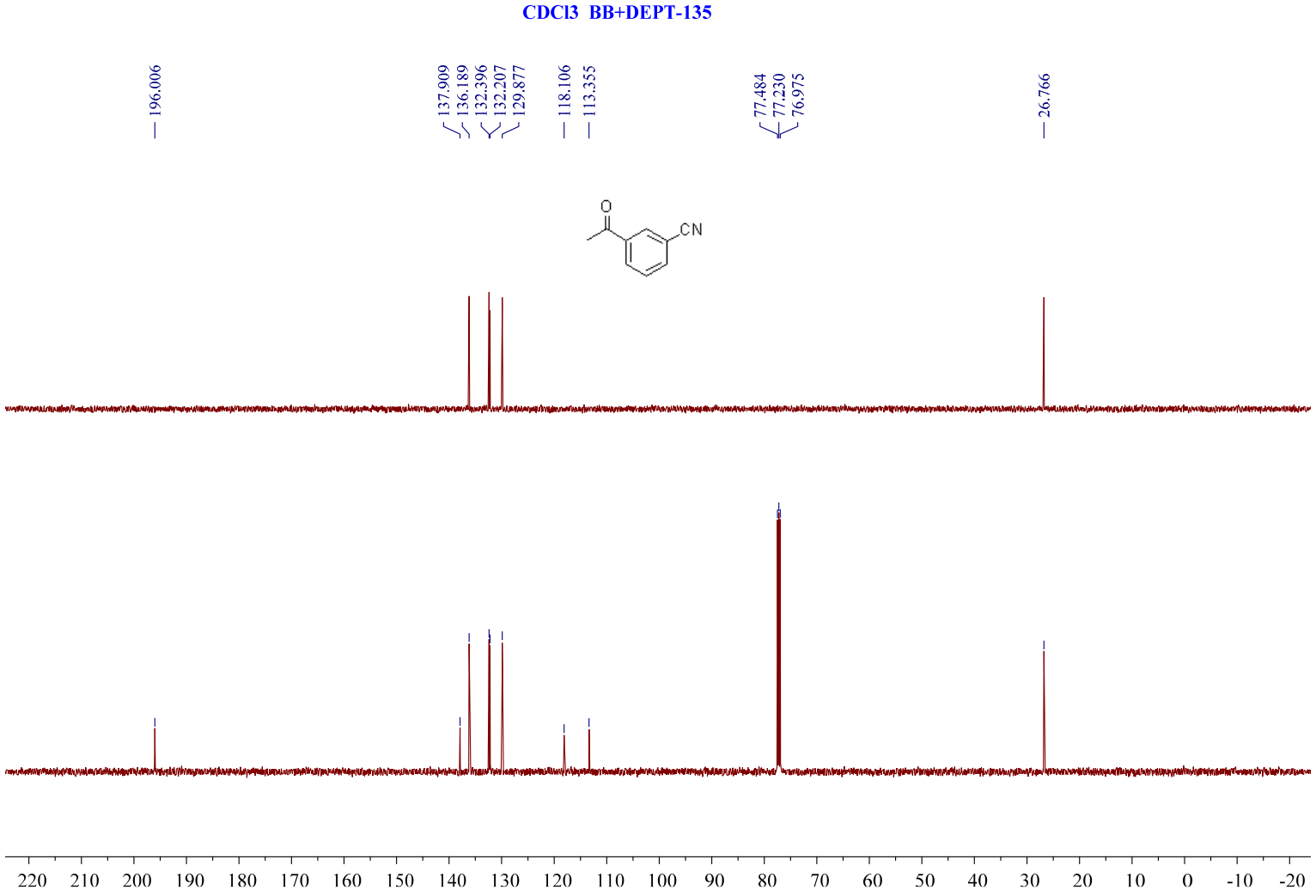


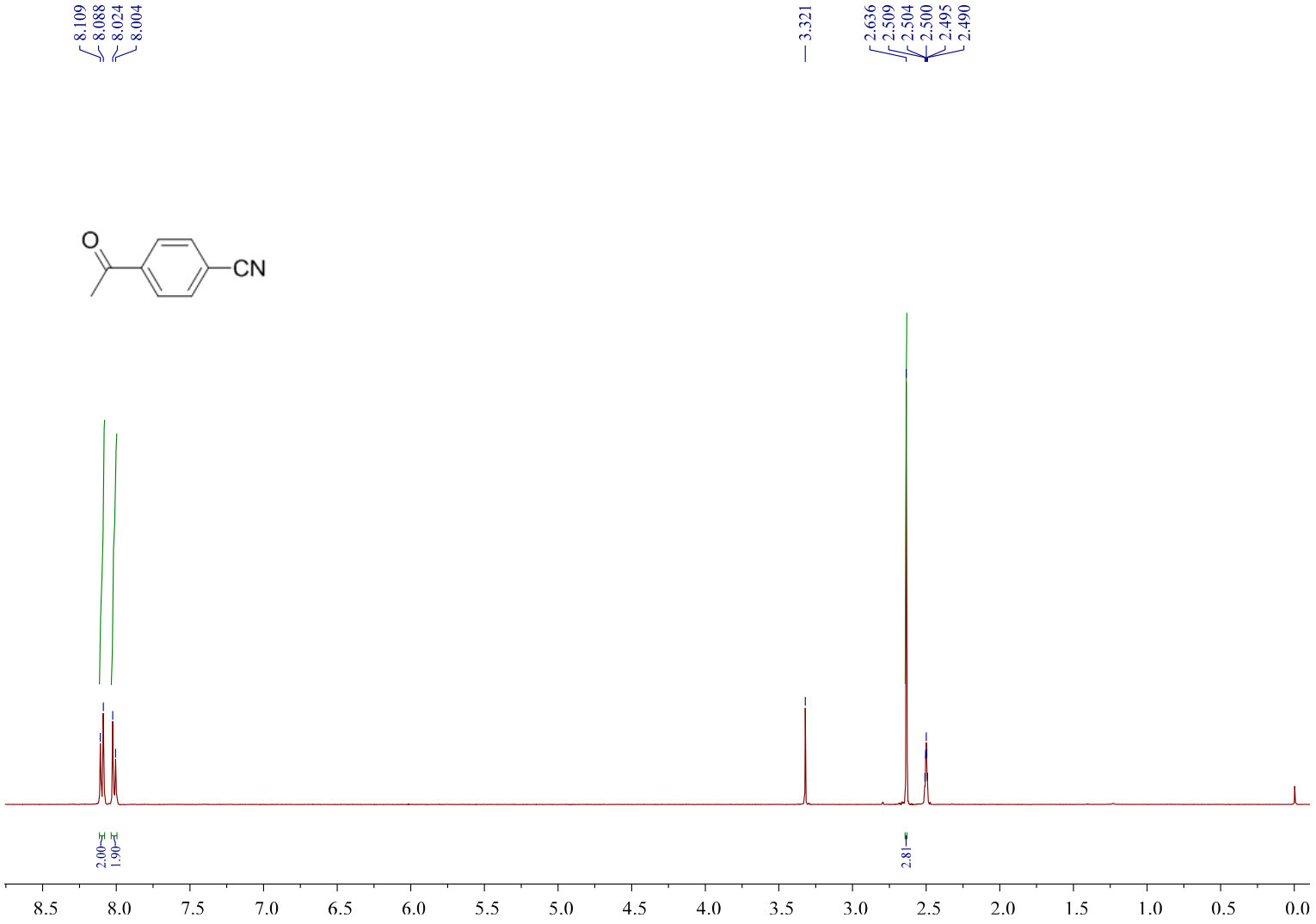


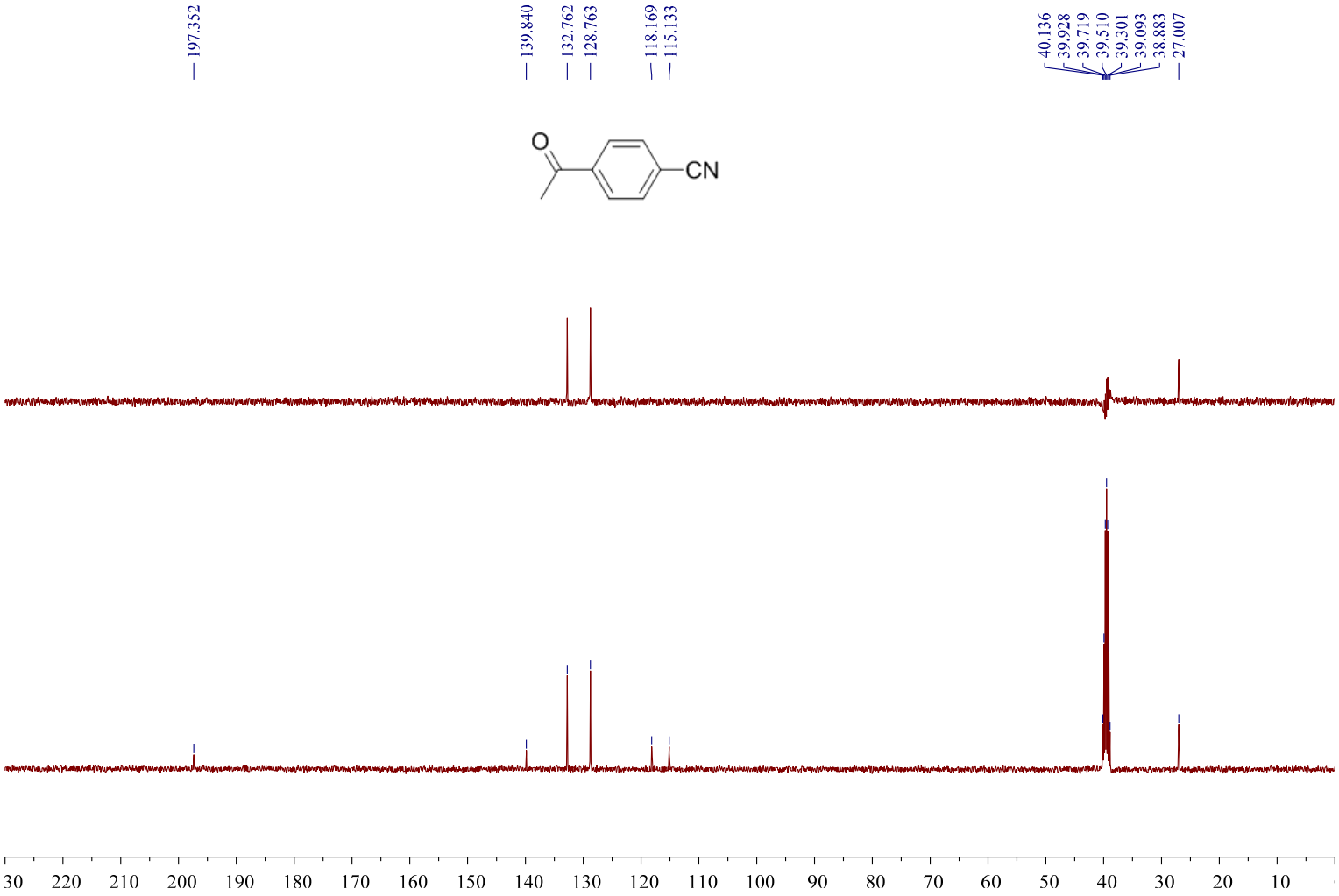


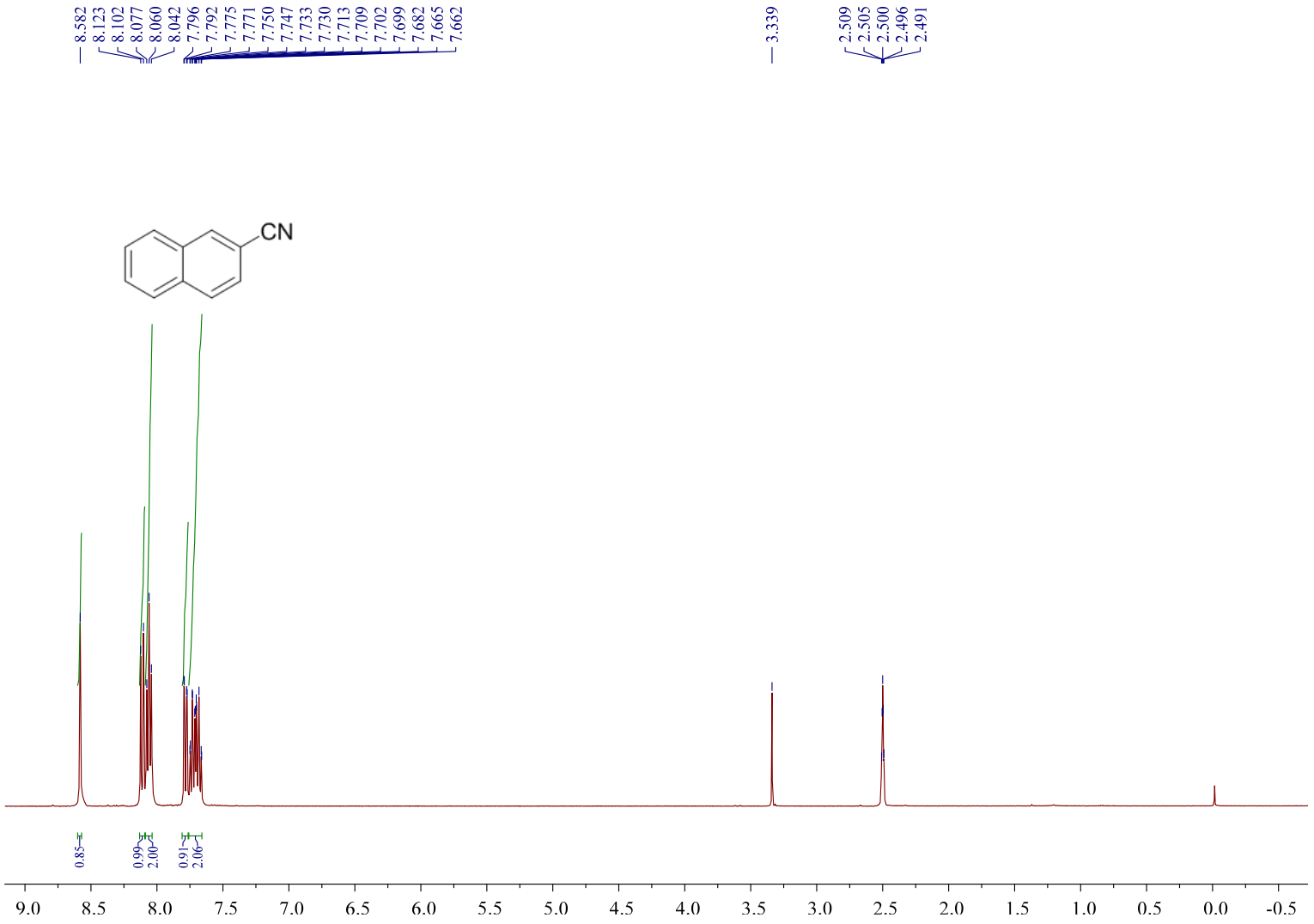


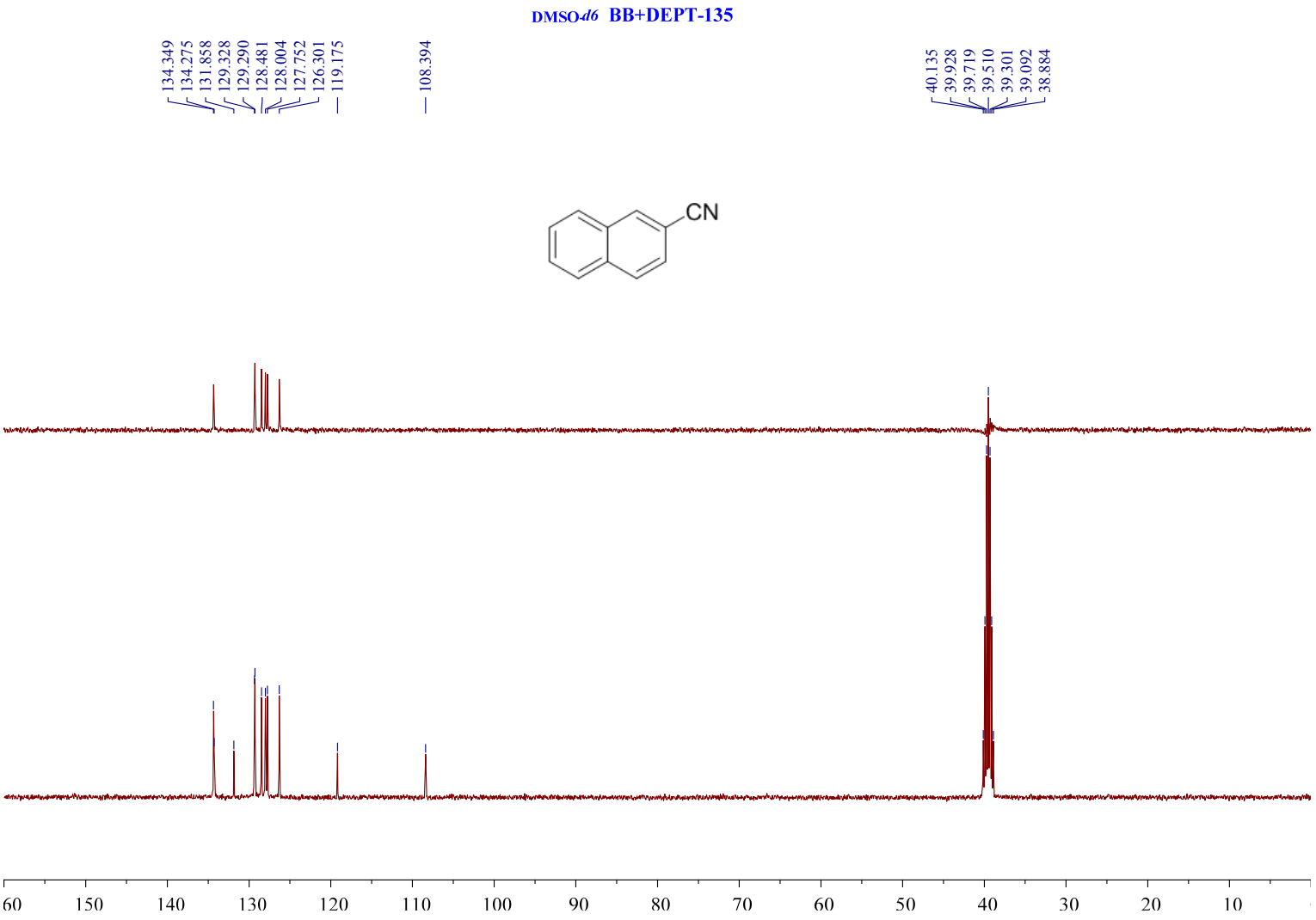


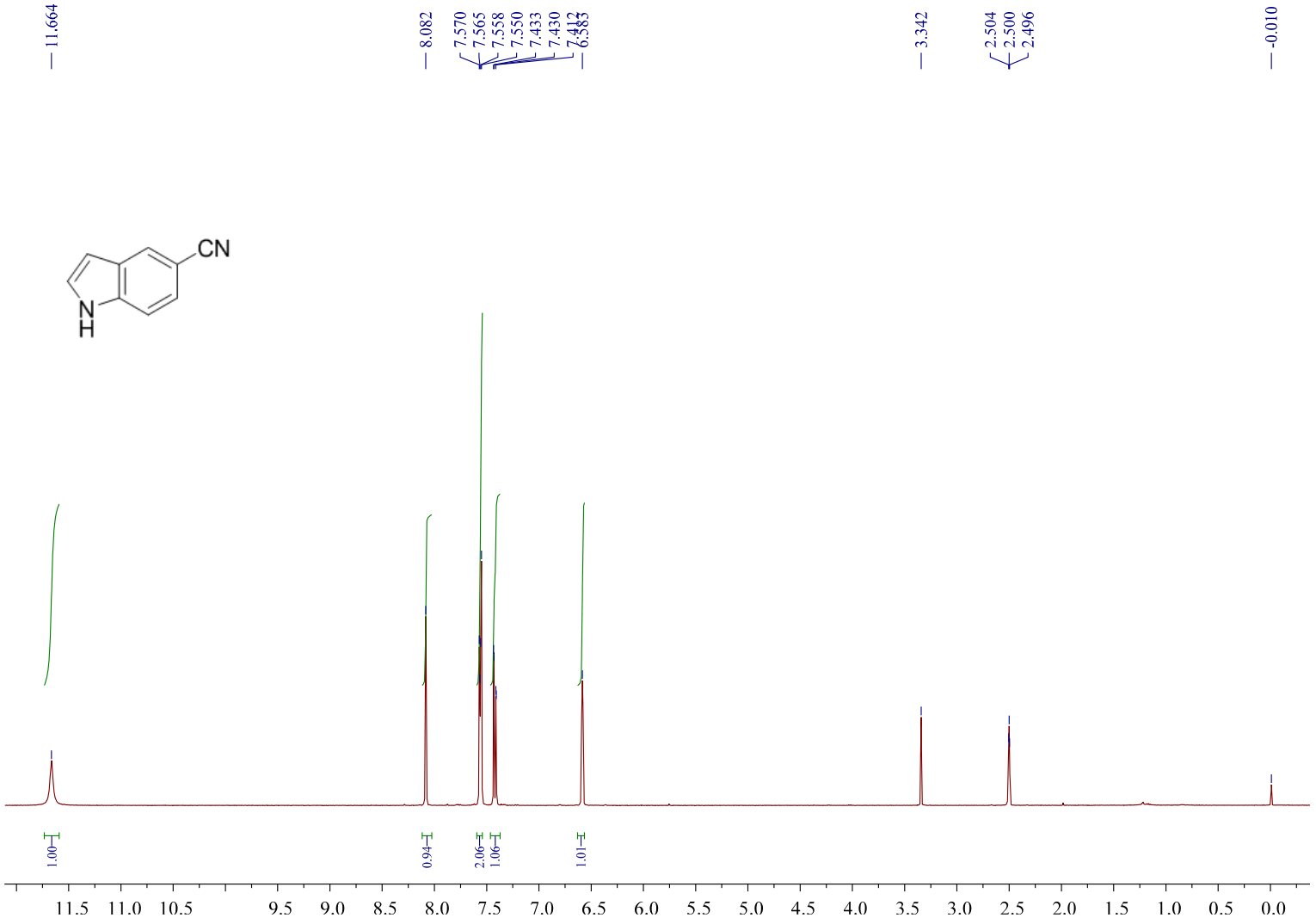


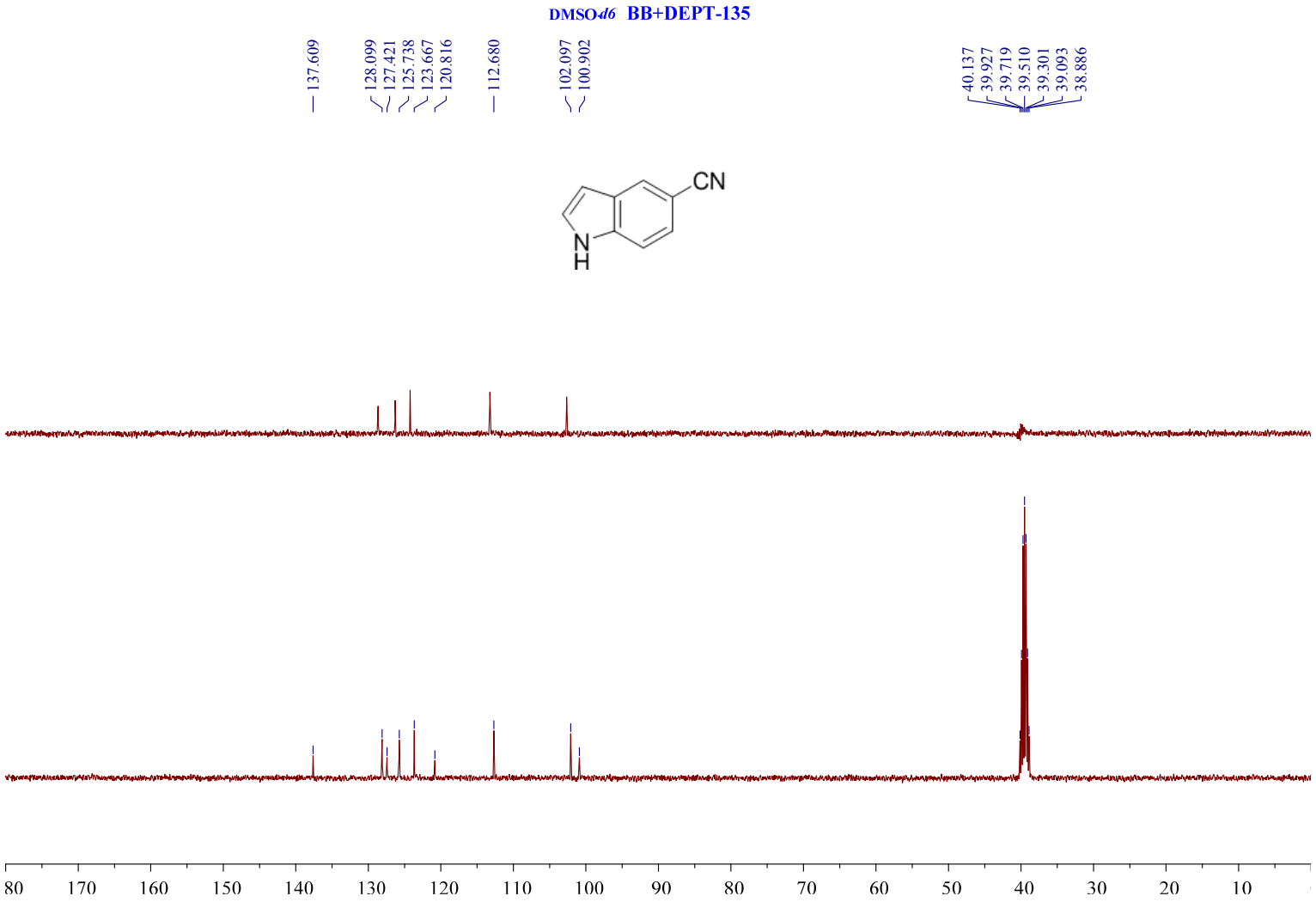


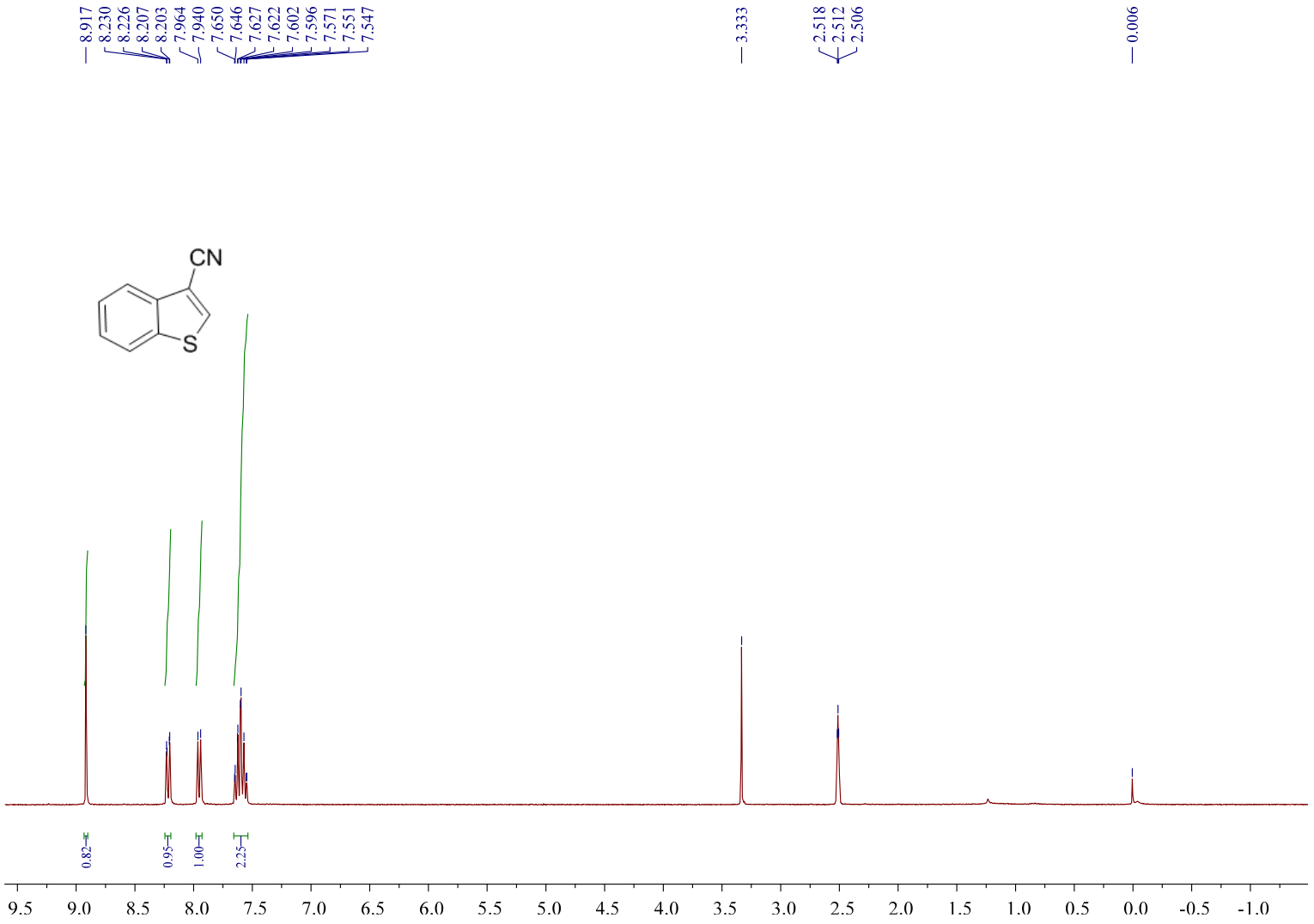


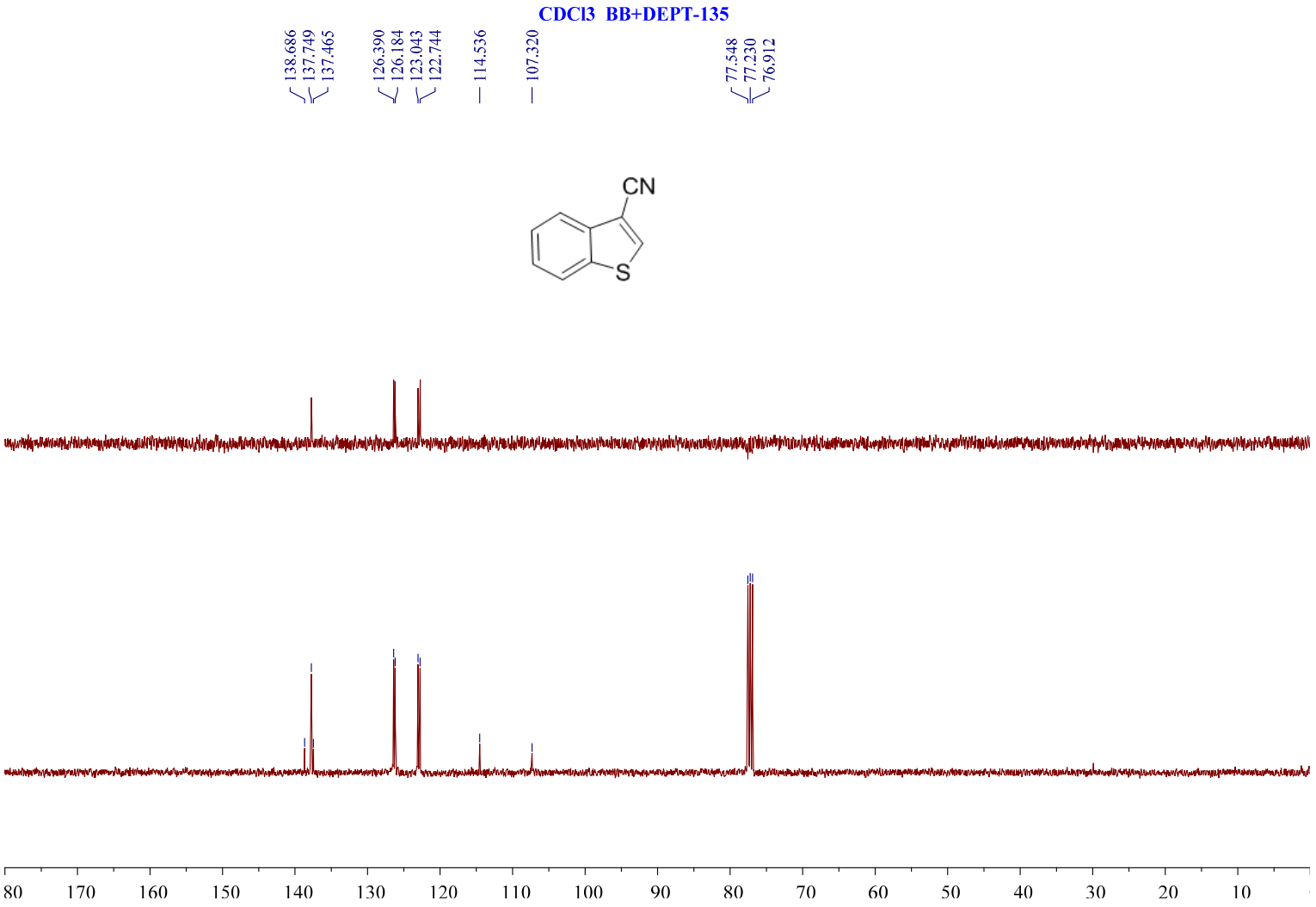








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107.320
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77.230
76.912
CN
S
80
170
160
150
140
130
120
110
100
90
80
70
60
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10