

Copper-Catalyzed Cyanation of Heterocycle C-H Bonds with Ethyl (ethoxymethylene)cynoacetate as a Cyanating Agent and its Mechanism

Ze-lin Li^a, Kang-kang Sun^a, and Chun Cai^{*a}

^a Chemical Engineering College, Nanjing University of Science and Technology, Nanjing 210094, People's Republic of China

Fax: (+86)-25-8431-5030; phone: (+86)-25-8431-5514; e-mail: c.cai@njust.edu.cn

1. General information	2
2. General procedure	2
3. Characterization data	3
4. NMR spectra	9

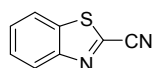
1. General information

All compounds are characterized by ^1H NMR, ^{13}C NMR and MS. Analytical thin-layer chromatography is performed on glass plates precoated with silica gel impregnated with a fluorescent indicator (254 nm), and the plates are visualized by exposure to ultraviolet light. ^1H NMR and ^{13}C NMR spectra are recorded on an AVANCE 500 Bruker spectrometer operating at 500 MHz and 125 MHz in CDCl_3 , respectively, and chemical shifts are reported in ppm. GC analyses are performed on an Agilent 7890A instrument (Column: Agilent 19091J-413:30 m \times 320 μm \times 0.25 μm , H, FID detection). GC-MS data was recorded on a 5975C Mass Selective Detector, coupled with a 7890A Gas Chromatograph (Agilent Technologies).

2. General procedure

General procedure for the synthesis of cyanating product: To a mixture of benzothiazoles (0.5 mmol) **1a**, $\text{Cu}(\text{OAc})_2$ (1.0 equiv.), DTBP (3.5 equiv.) and solvent (DMF =2.0 ml) in a reaction tube was then added additive KI (0.1 equiv.). The reaction mixture was stirred at 135°C for 24h in air. The reaction mixture was extracted with ethyl acetate (15 mL \times 3). The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford the desired products **3**.

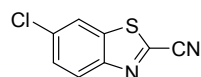
3.Characterization data



Formula: C₈H₄N₂S

Mass: 160

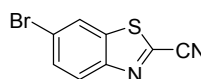
benzo[d]thiazole-2-carbonitrile (3a): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give **3a** as white solid (57.6mg, 72%). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.28 – 8.22 (m, 1H), 8.04 – 7.96 (m, 1H), 7.66 (pd, *J* = 7.2, 1.5 Hz, 2H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 151.3, 135.6, 134.4, 127.7, 127.0, 124.4, 120.8, 112.0. GC-MS (EI) *m/z*: 160.



Formula: C₈H₃ClN₂S

Mass: 194

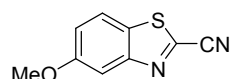
6-chlorobenzo[d]thiazole-2-carbonitrile (3b): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give **3b** as white solid (55.3mg, 57%). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.24 (d, *J* = 1.9 Hz, 1H), 7.93 (d, *J* = 8.7 Hz, 1H), 7.63 (dd, *J* = 8.7, 2.0 Hz, 1H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 152.1, 137.3, 133.5, 131.5, 128.4, 124.0, 121.6, 111.6. GC-MS (EI) *m/z*: 194.



Formula: C₈H₃BrN₂S

Mass: 238

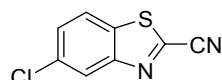
6-bromobenzo[d]thiazole-2-carbonitrile (3c): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give **3c** as white solid (63.1mg, 53%). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.16 (d, *J* = 1.8 Hz, 1H), 8.10 (d, *J* = 8.8 Hz, 1H), 7.78 (dd, *J* = 8.8, 1.9 Hz, 1H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 150.1, 135.8, 130.8, 126.0, 125.3, 123.4, 122.1, 111.6. GC-MS (EI) *m/z*: 238.



Formula: C₉H₆N₂OS

Mass: 190

5-methoxybenzo[d]thiazole-2-carbonitrile (3d): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give **3d** as white solid (64.6mg, 68%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.82 (d, *J* = 9.0 Hz, 1H), 7.63 (d, *J* = 2.4 Hz, 1H), 7.28 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.93 (s, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 159.3, 152.9, 126.5, 120.9, 119.1, 113.1, 112.1, 105.2, 54.8. GC-MS (EI) *m/z*: 190.

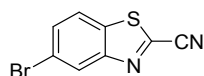


Formula: C₈H₃ClN₂S

Mass: 194

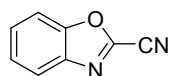
5-chlorobenzo[d]thiazole-2-carbonitrile (3e): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give **3e** as white solid (66.0mg, 68%). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.23 (d, *J* = 1.8 Hz, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.62 (dd, *J* = 8.7, 1.9 Hz, 1H). ¹³C NMR (126 MHz,

Chloroform-*d*) δ 152.1, 137.3, 133.5, 132.5, 128.4, 124.0, 121.6, 111.6. GC-MS (EI) *m/z*: 194.



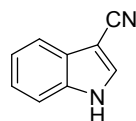
Formula: C₈H₃BrN₂S
Mass: 238

5-bromobenzo[d]thiazole-2-carbonitrile (3f): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give **3f** as white solid (66.6mg, 56%). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.15 (d, *J* = 1.8 Hz, 1H), 8.08 (d, *J* = 8.8 Hz, 1H), 7.76 (dd, *J* = 8.8, 1.8 Hz, 1H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 150.1, 135.9, 135.8, 130.8, 125.3, 123.4, 122.1, 111.6. GC-MS (EI) *m/z*: 238.



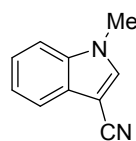
Formula: C₈H₄N₂O
Mass: 144

benzo[d]oxazole-2-carbonitrile (3g): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give **3g** as white solid (28.1mg, 39%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.91 (d, *J* = 8.1 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 1H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 149.5, 138.6, 136.3, 128.1, 125.6, 121.0, 110.6, 108.2. GC-MS (EI) *m/z*: 144.



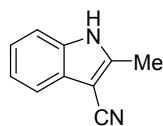
Formula: C₉H₆N₂
Mass: 142

1H-indole-3-carbonitrile (4a): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give **4a** as white solid (44.7mg, 63%). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.79 (s, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 3.0 Hz, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.43 – 7.34 (m, 2H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 133.9, 130.8, 126.0, 123.4, 121.5, 118.8, 114.8, 111.0, 86.7. GC-MS (EI) *m/z*: 142.



Formula: C₁₀H₈N₂
Mass: 156

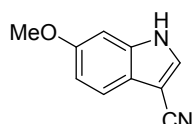
1-methyl-1H-indole-3-carbonitrile (4b): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give **4b** as white solid (53.0mg, 68%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 1.6 Hz, 1H), 7.47 – 7.32 (m, 3H), 3.89 (d, *J* = 1.6 Hz, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 135.0, 134.6, 126.8, 122.9, 121.2, 118.8, 115.0, 109.4, 84.5, 32.7. GC-MS (EI) *m/z*: 156.



Formula: C₁₀H₈N₂

Mass: 156

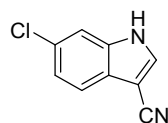
2-methyl-1H-indole-3-carbonitrile (4c): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give **4c** as white solid (47.6mg, 61%). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.42 (s, 1H), 7.69 – 7.63 (m, 1H), 7.39 – 7.33 (m, 1H), 7.25 (dd, *J* = 5.8, 2.5 Hz, 2H), 2.64 (s, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 143.4, 133.6, 126.7, 122.5, 121.1, 118.1, 115.2, 110.2, 85.1, 12.1. GC-MS (EI) *m/z*: 156.



Formula: C₁₀H₈N₂O

Mass: 172

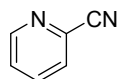
6-methoxy-1H-indole-3-carbonitrile (4d): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give **4d** as white solid (49.9mg, 58%). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.64 (s, 1H), 7.73 (d, *J* = 3.1 Hz, 1H), 7.40 (d, *J* = 8.9 Hz, 1H), 7.24 (d, *J* = 2.4 Hz, 1H), 7.03 (dd, *J* = 8.9, 2.4 Hz, 1H), 3.94 (s, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 155.1, 130.7, 128.6, 126.9, 115.0, 114.3, 111.9, 99.7, 86.5, 54.8. GC-MS (EI) *m/z*: 172.



Formula: C₉H₅ClN₂

Mass: 176

6-chloro-1H-indole-3-carbonitrile (4e): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give **4e** as white solid (44.9mg, 51%). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.74 (s, 1H), 7.81 – 7.71 (m, 2H), 7.53 (d, *J* = 1.7 Hz, 1H), 7.34 (dd, *J* = 8.6, 1.8 Hz, 1H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 134.2, 131.3, 129.6, 122.4, 119.7, 114.1, 113.4, 111.1, 87.3. GC-MS (EI) *m/z*: 176.

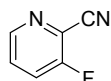


Formula: C₆H₄N₂

Mass: 104

picolinonitrile (5a): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give **5a** as white solid (36.9mg, 71%).

¹H NMR (500 MHz, Chloroform-*d*) δ 8.69 (d, *J* = 4.6 Hz, 1H), 7.90 – 7.84 (m, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.57 – 7.52 (m, 1H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 150.1, 136.3, 132.8, 127.6, 126.2, 116.3. GC-MS (EI) *m/z*: 104.

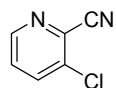


Formula: C₆H₃FN₂

Mass: 122

3-fluoropicolinonitrile (5b): The crude product was purified by column

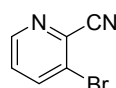
chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give **5b** as white solid (42.1mg, 69%). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.56 (dd, *J* = 4.1, 1.8 Hz, 1H), 7.73 – 7.49 (m, 2H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 161.4, 159.2, 146.1, 127.8, 123.7, 122.0, 112.0. GC-MS (EI) *m/z*: 122.



Formula: C₆H₃ClN₂

Mass: 138

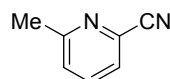
3-chloropicolinonitrile (5c): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give **5c** as white solid (46.2mg, 67%). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.62 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.89 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.52 (dd, *J* = 8.4, 4.6 Hz, 1H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 147.8, 136.6, 135.0, 132.3, 126.6, 113.7. GC-MS (EI) *m/z*: 138.



Formula: C₆H₃BrN₂

Mass: 182

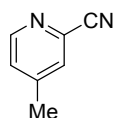
3-bromopicolinonitrile (5d): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give **5d** as white solid (57.3mg, 63%). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.66 (dd, *J* = 4.6, 1.4 Hz, 1H), 8.04 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.6 Hz, 1H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 148.1, 139.7, 134.3, 126.7, 123.6, 114.7. GC-MS (EI) *m/z*: 182.



Formula: C₇H₆N₂

Mass: 118

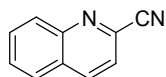
6-methylpicolinonitrile (5e): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give **5e** as white solid (36.6mg, 62%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.73 (t, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 2.62 (s, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 159.7, 136.1, 132.2, 125.9, 124.7, 116.4, 23.4. GC-MS (EI) *m/z*: 118.



Formula: C₇H₆N₂

Mass: 118

3-methylpicolinonitrile (5f): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give **5f** as white solid (40.1mg, 68%). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.55 (d, *J* = 5.0 Hz, 1H), 7.52 (s, 1H), 7.33 (d, *J* = 5.0 Hz, 1H), 2.43 (s, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 149.8, 147.8, 132.8, 128.4, 126.9, 116.4, 19.9. GC-MS (EI) *m/z*: 118.

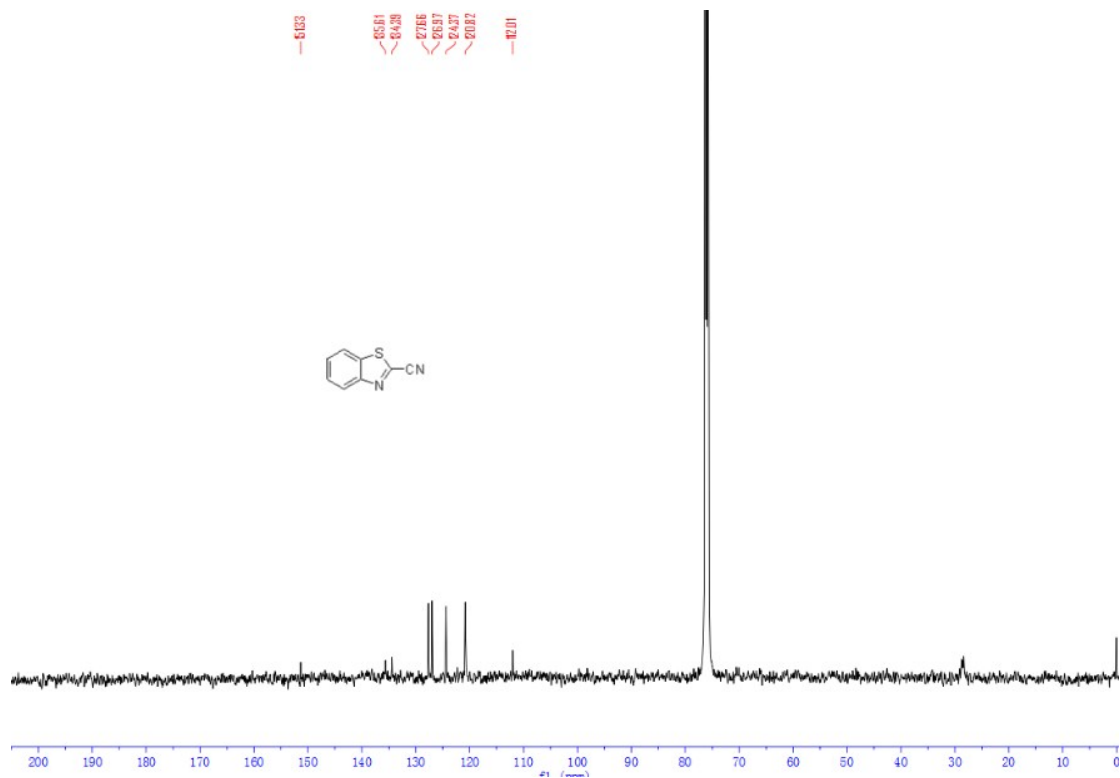
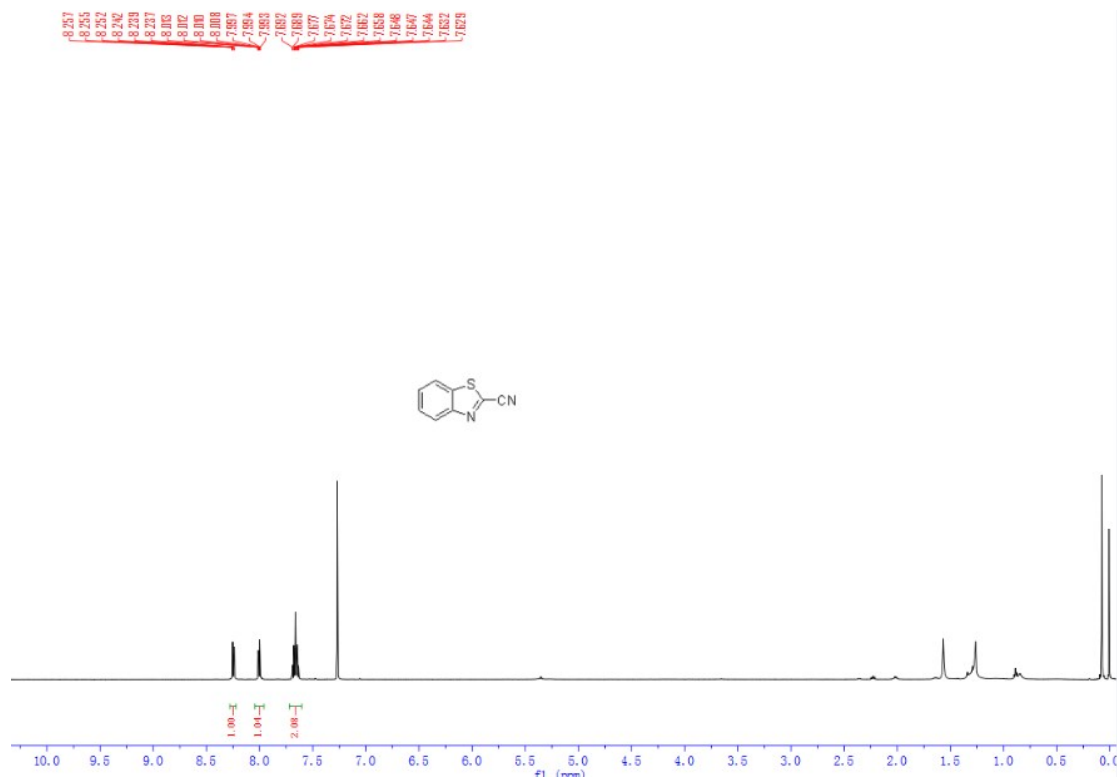


Formula: C₁₀H₆N₂

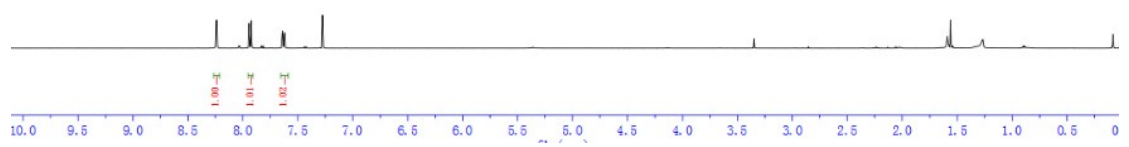
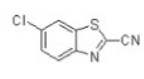
Mass: 154

quinoline-2-carbonitrile (5g): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 19:1) to give **5g** as white solid (51.6mg, 67%). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.32 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.86 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.75 – 7.69 (m, 2H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 147.3, 136.5, 132.7, 130.3, 129.1, 128.5, 127.7, 126.8, 122.4, 116.6. GC-MS (EI) *m/z*: 154.

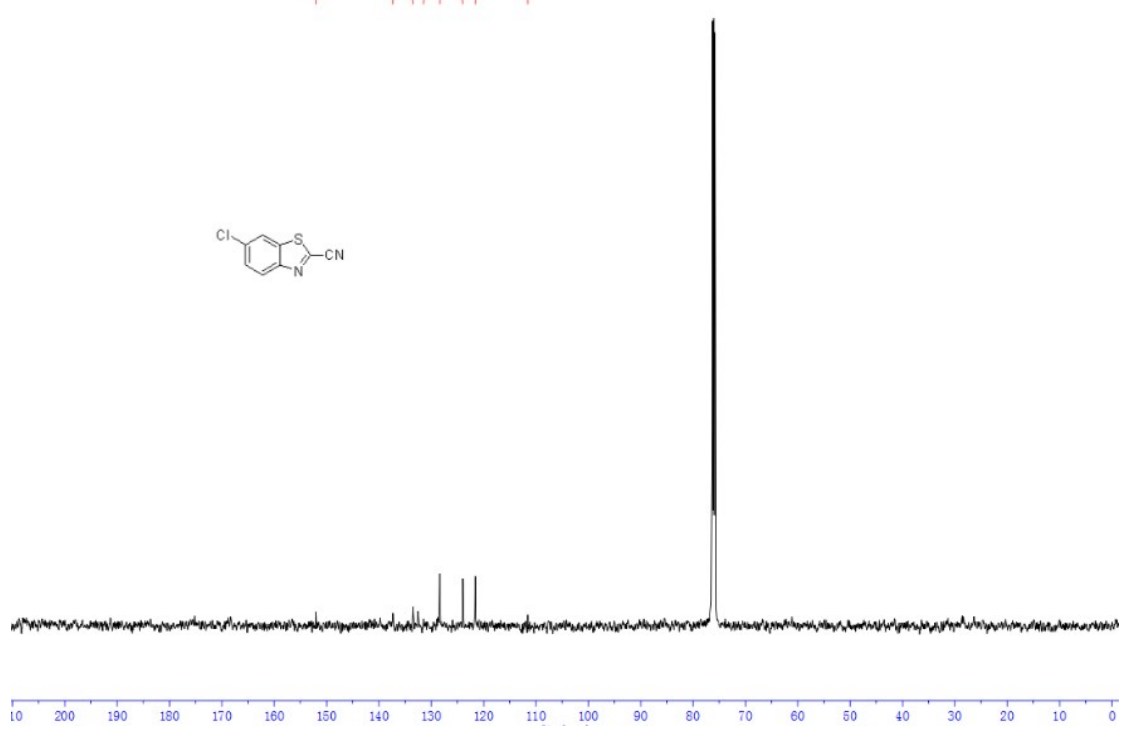
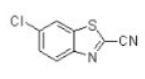
4. NMR spectra



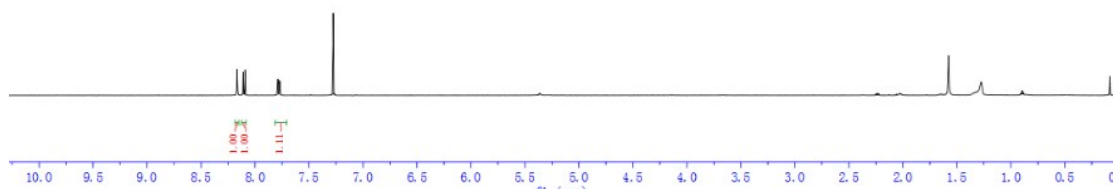
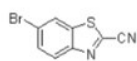
8.242
8.238
7.842
7.825
7.844
7.837
7.823
7.818



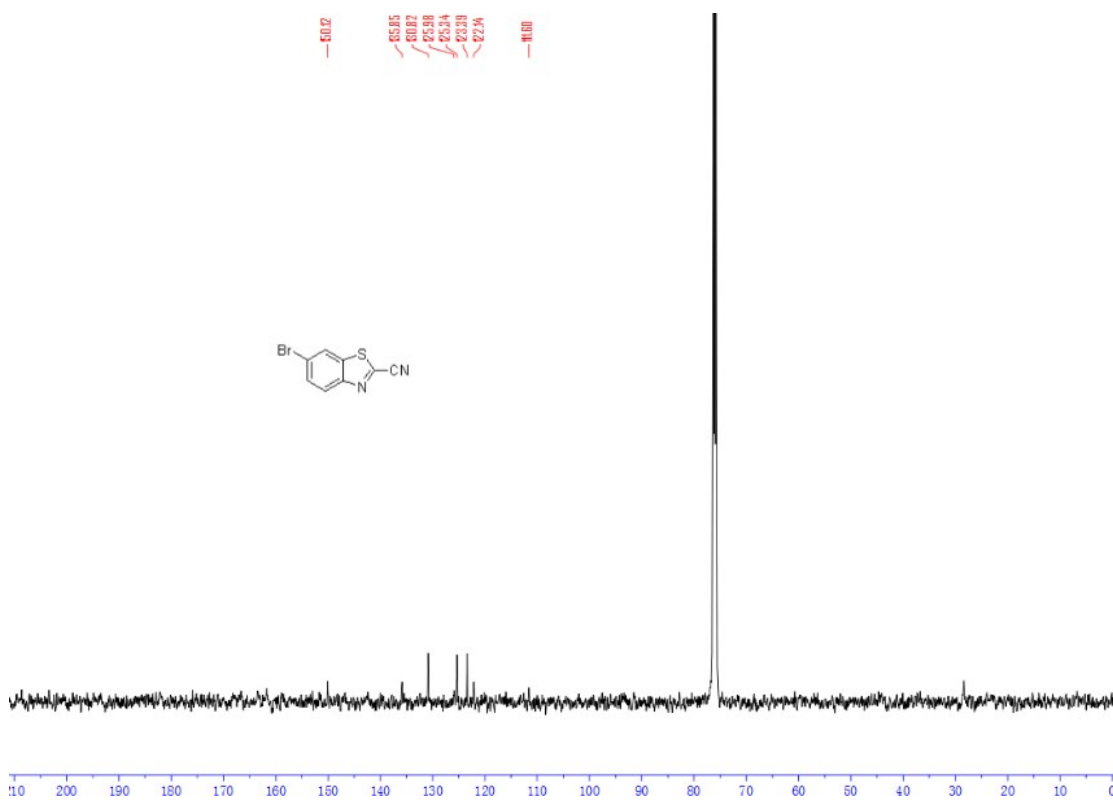
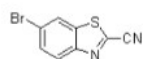
152.07
133.16
131.46
128.40
123.37
121.55
11.55



8.106
8.103
8.100
7.916
7.772
7.769

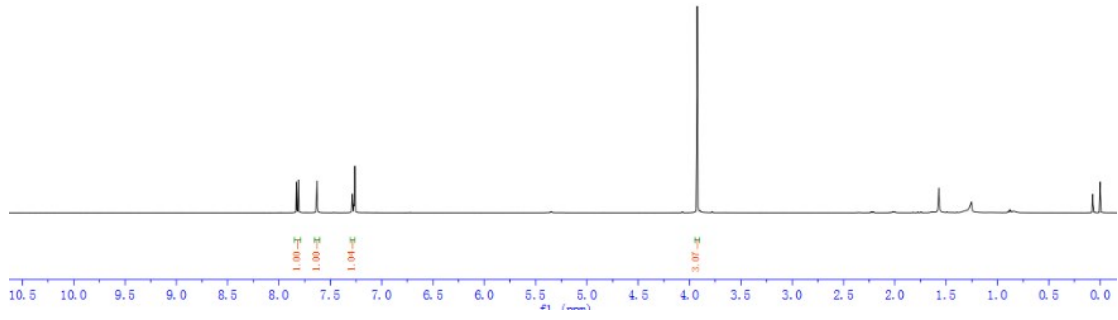
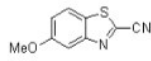


80.02
85.85
80.82
85.98
83.34
82.39
82.54
11.00



7.879
7.861
7.653
7.628
7.380
7.265
7.272
7.267

3.927



158.27

152.91

126.48

120.00

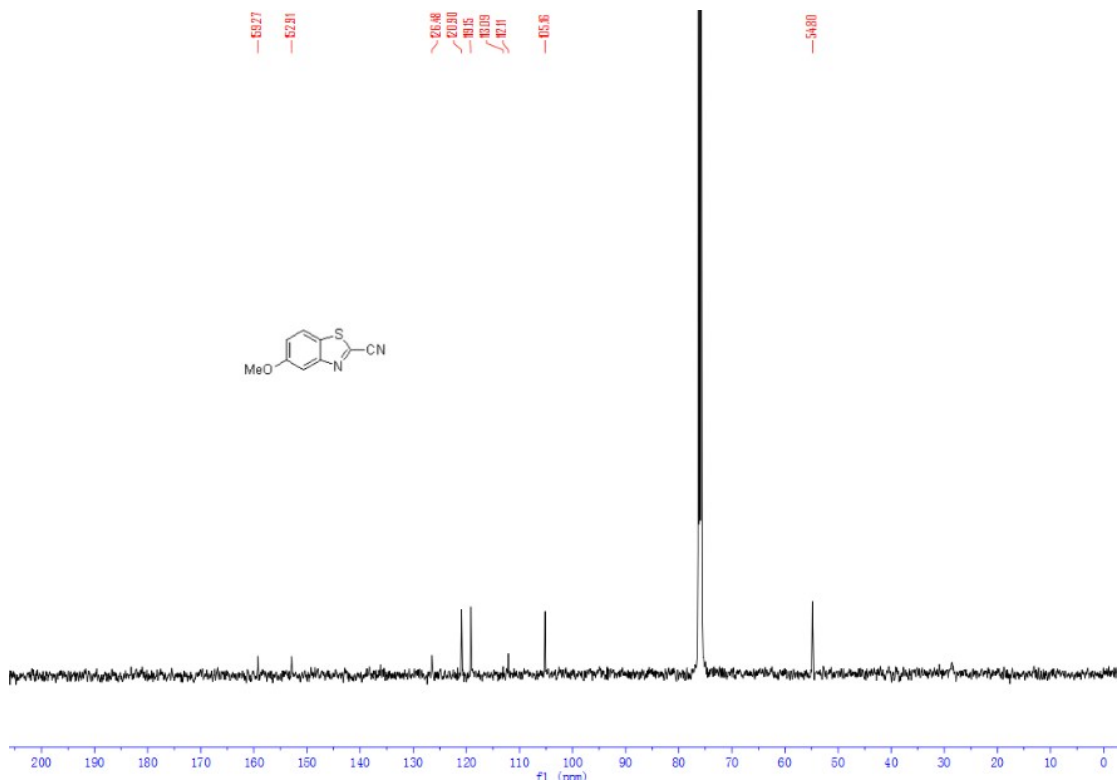
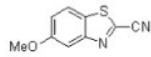
107.35

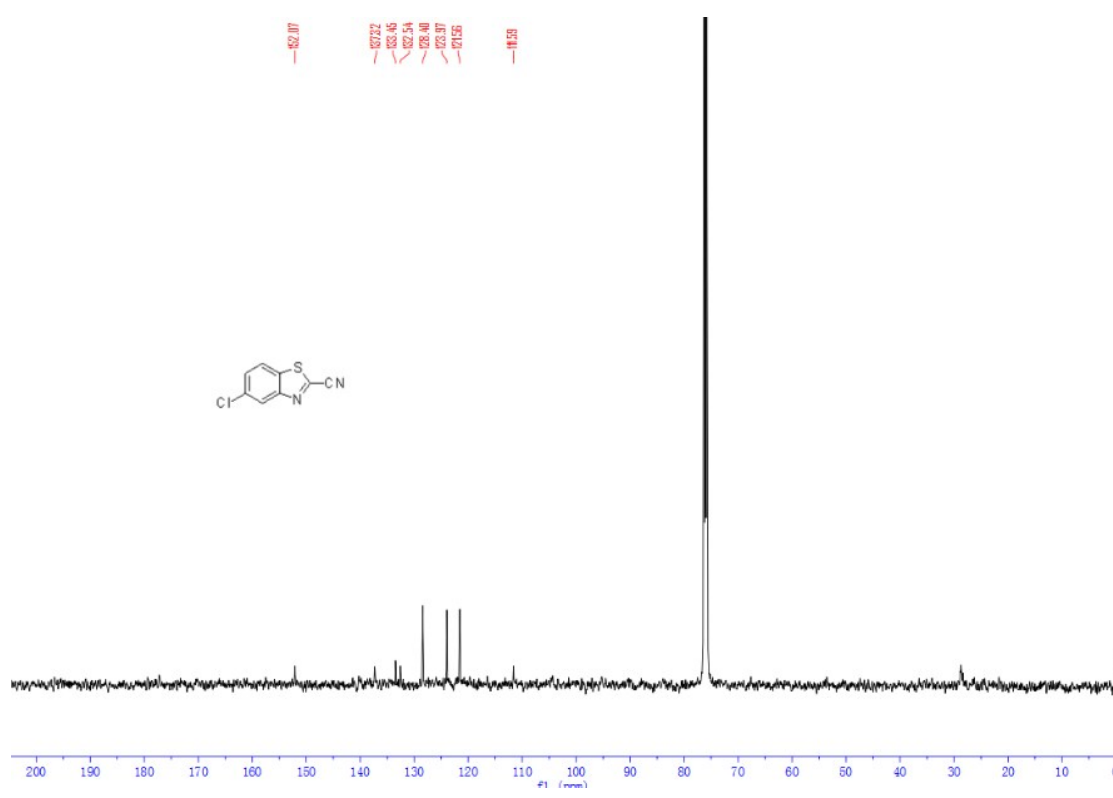
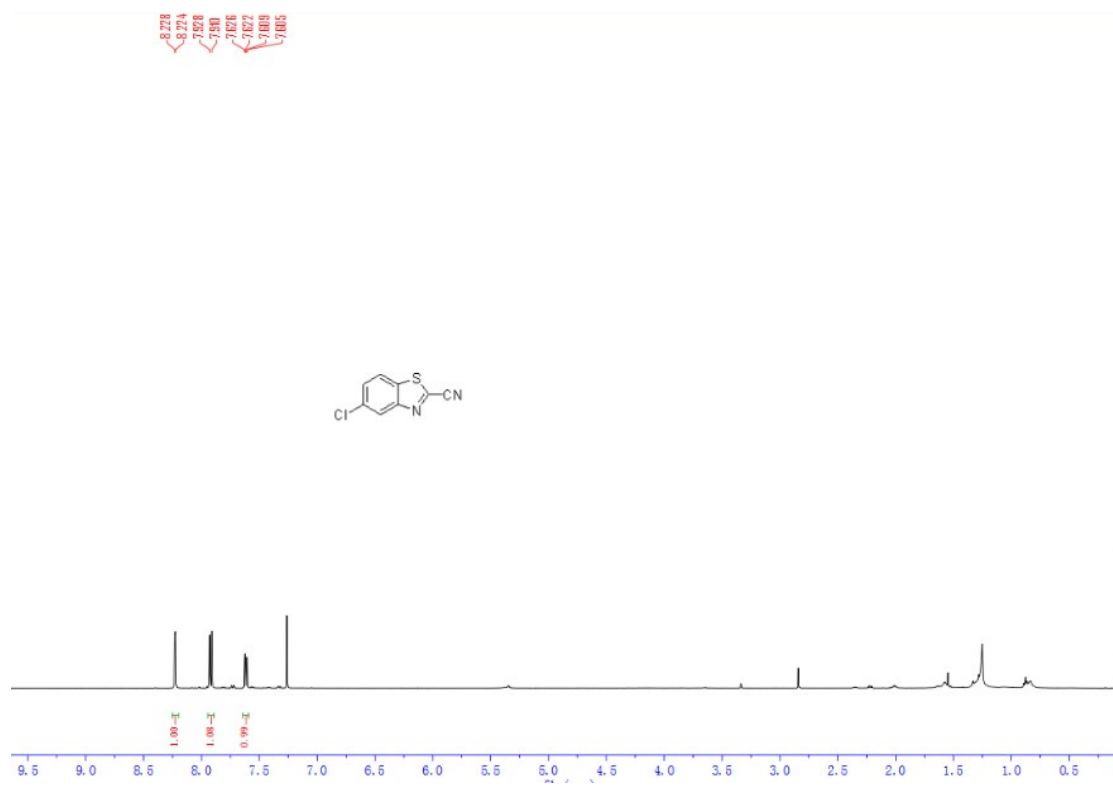
87.03

82.11

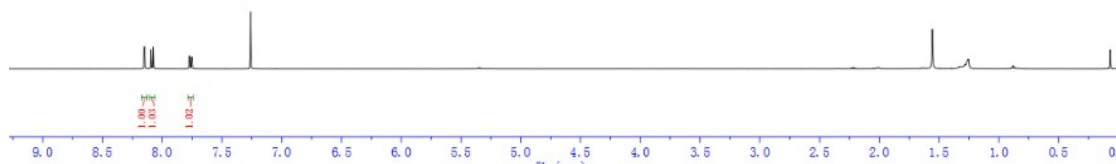
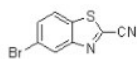
65.65

54.80

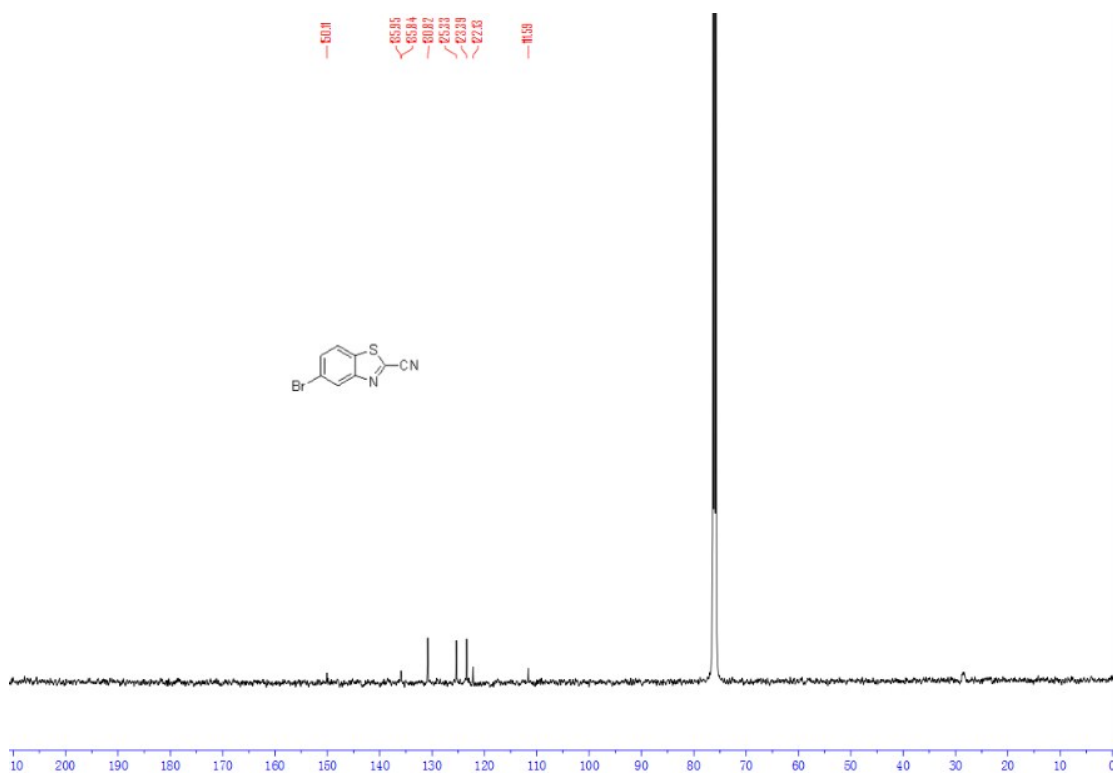
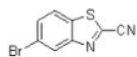




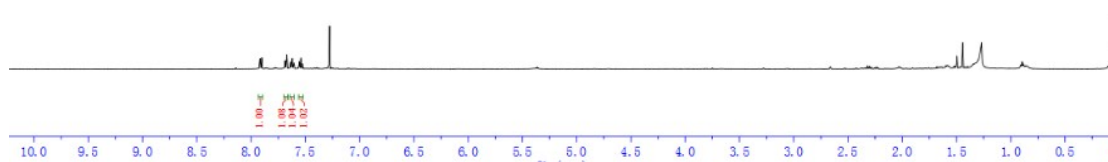
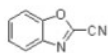
8.51
8.47
8.003
7.75
7.70
7.57
7.53



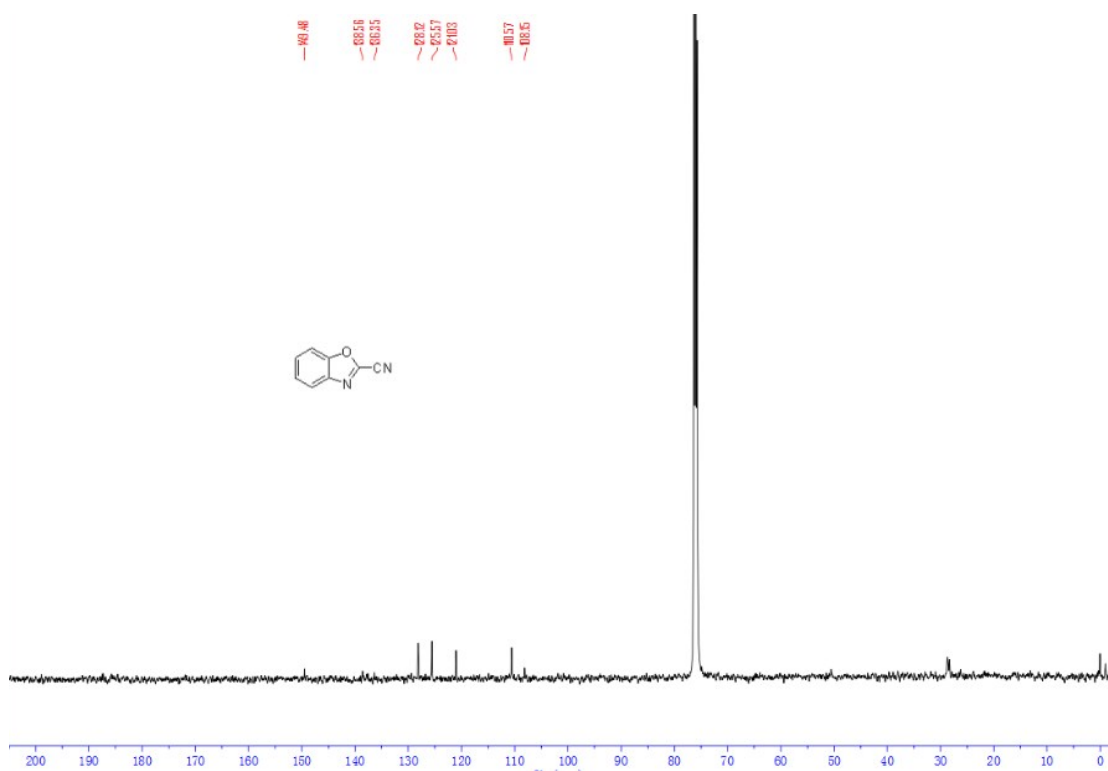
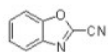
60.1
65.55
65.64
60.02
65.33
62.33
11.59



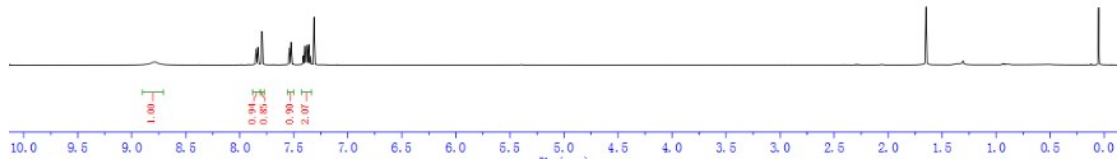
7.798
7.702
7.687
7.670
7.626
7.620
7.605
7.557
7.540
7.526



160.46
138.58
138.35
128.82
125.57
120.83
110.57
108.65

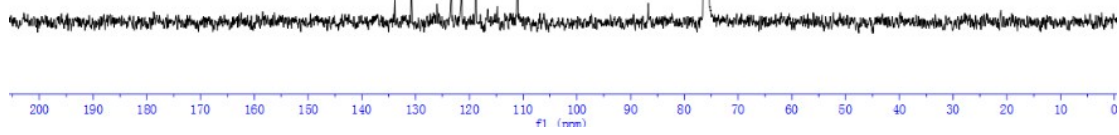


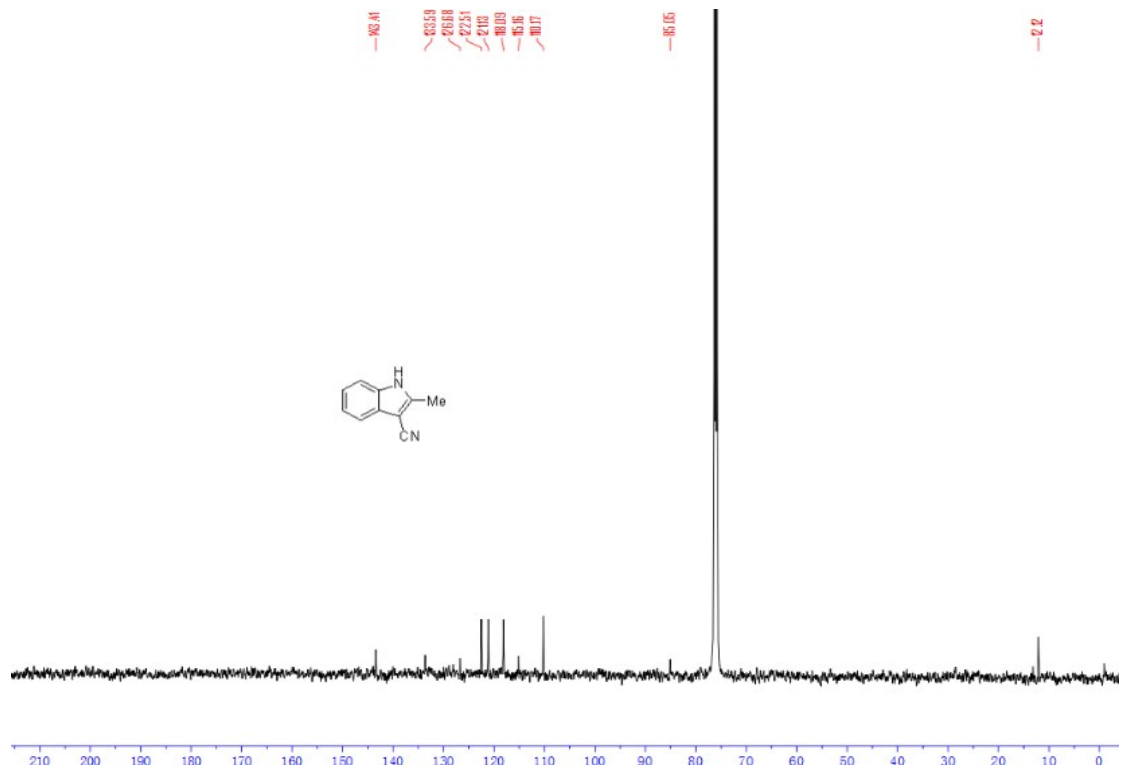
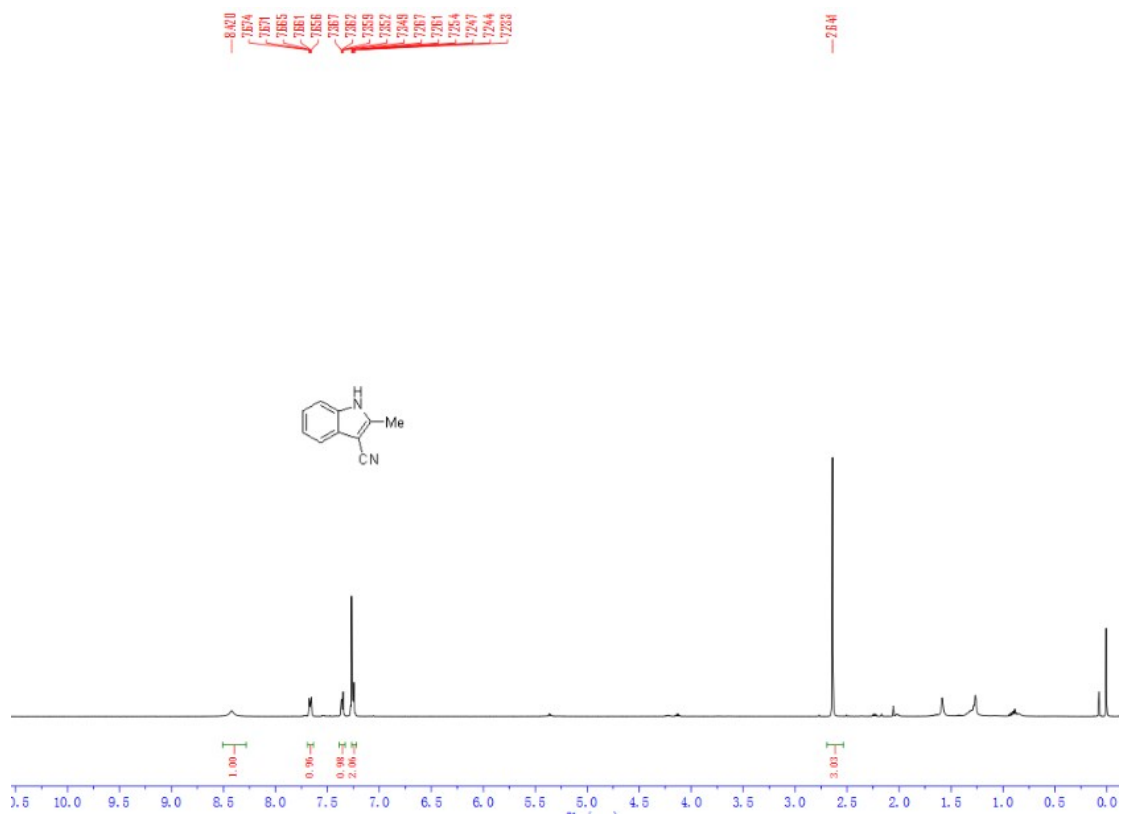
8.831
7.940
7.853
7.837
7.832
7.540
7.525
7.465
7.462
7.400
7.388
7.386
7.385
7.381
7.379
7.376
7.363
7.361
7.340
7.346

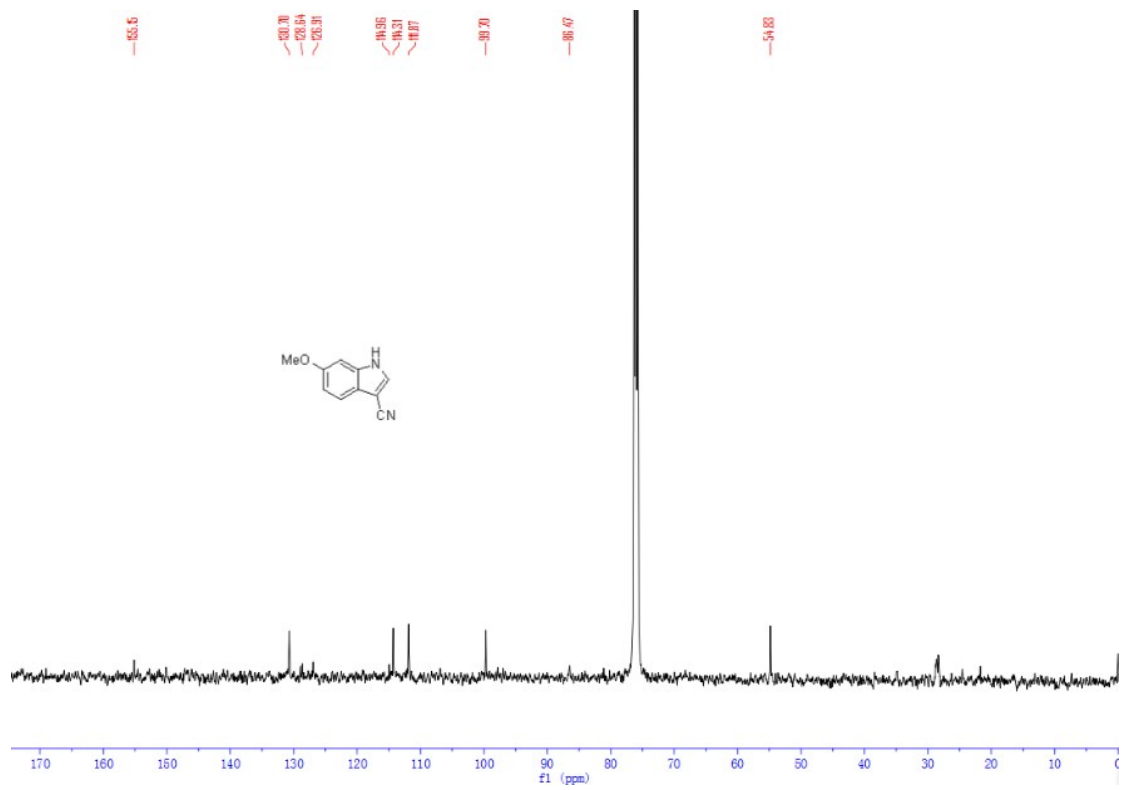
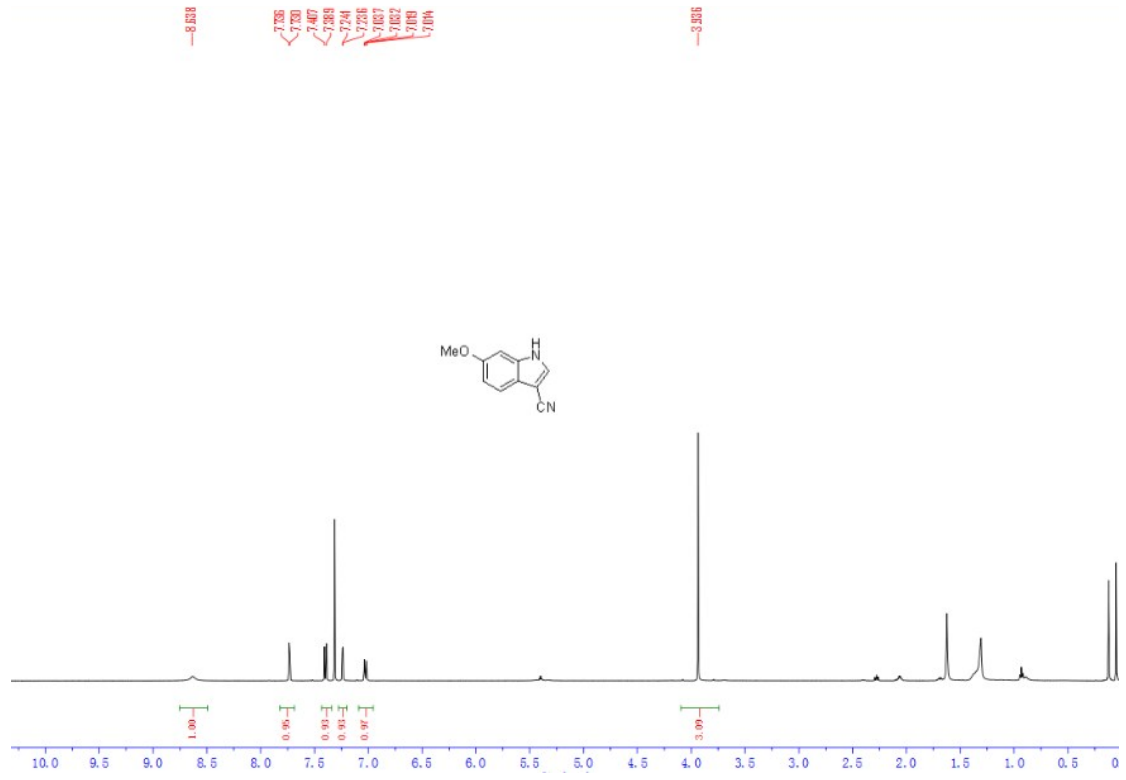


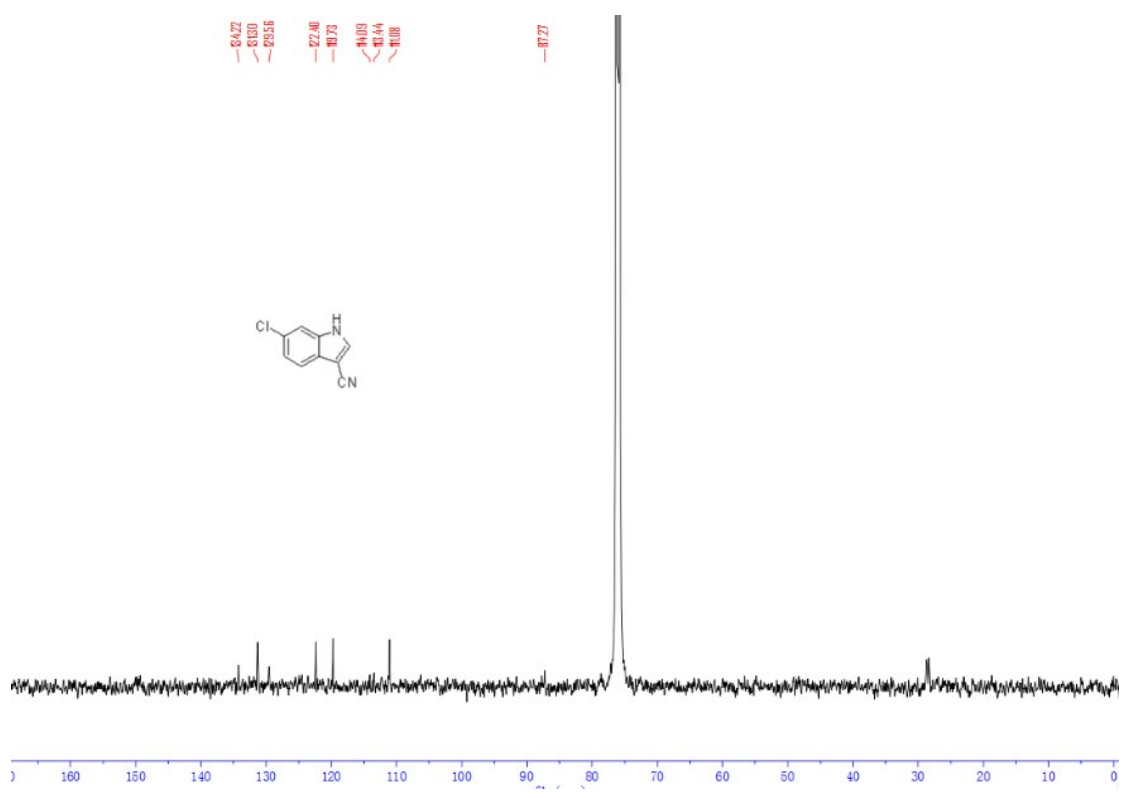
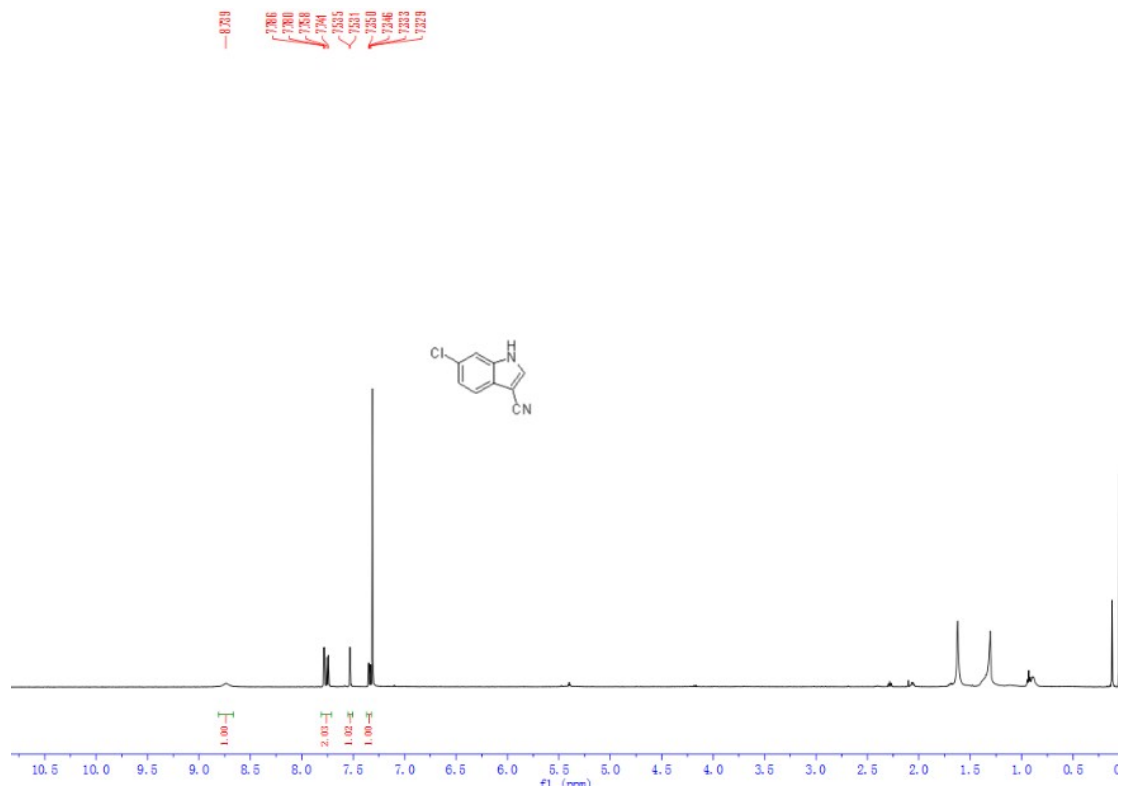
133.87
130.76
129.00
123.41
117.73
114.78
110.05

88.72

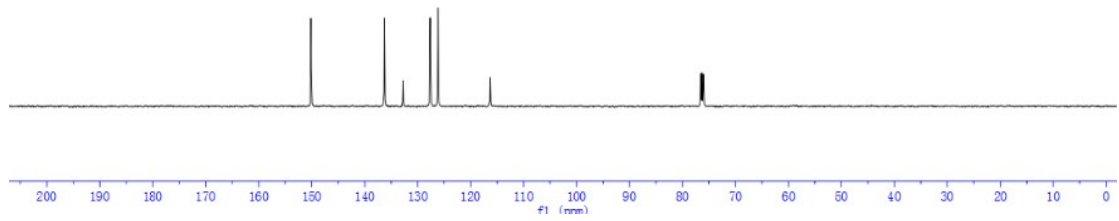
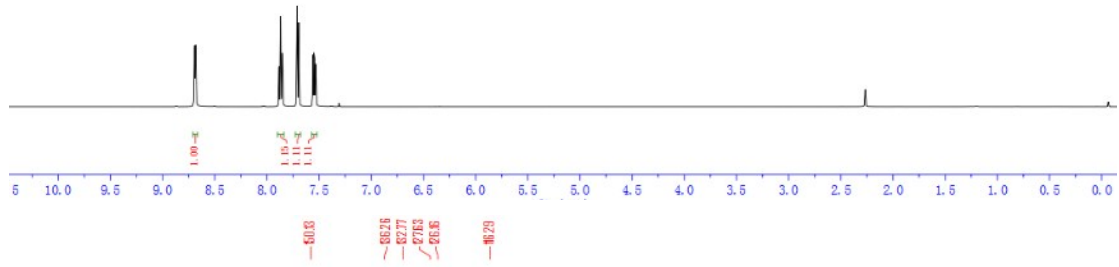


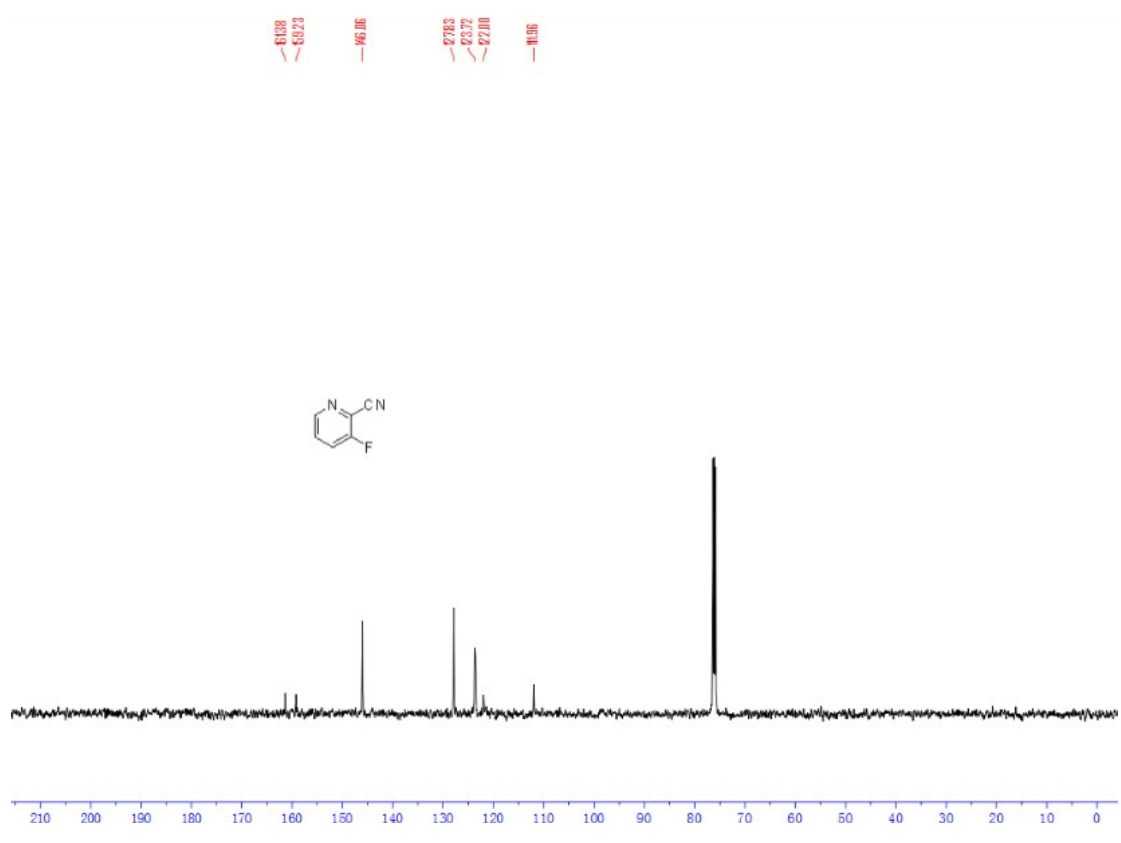
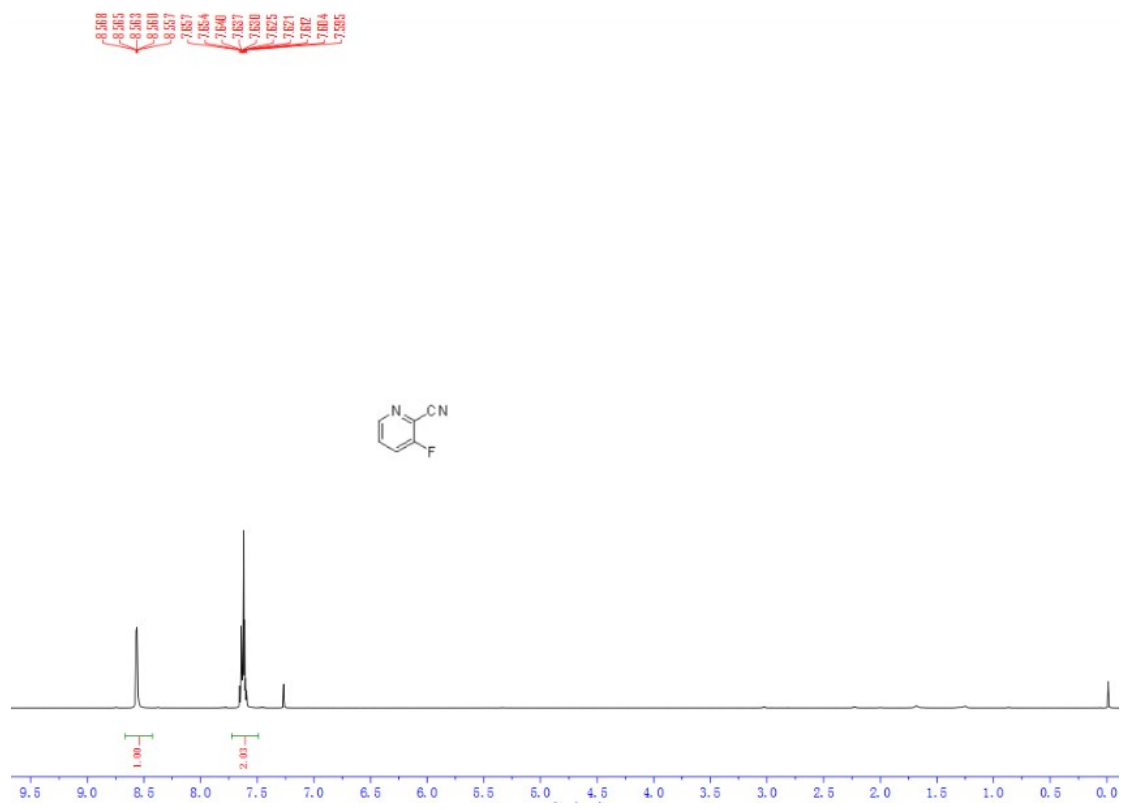


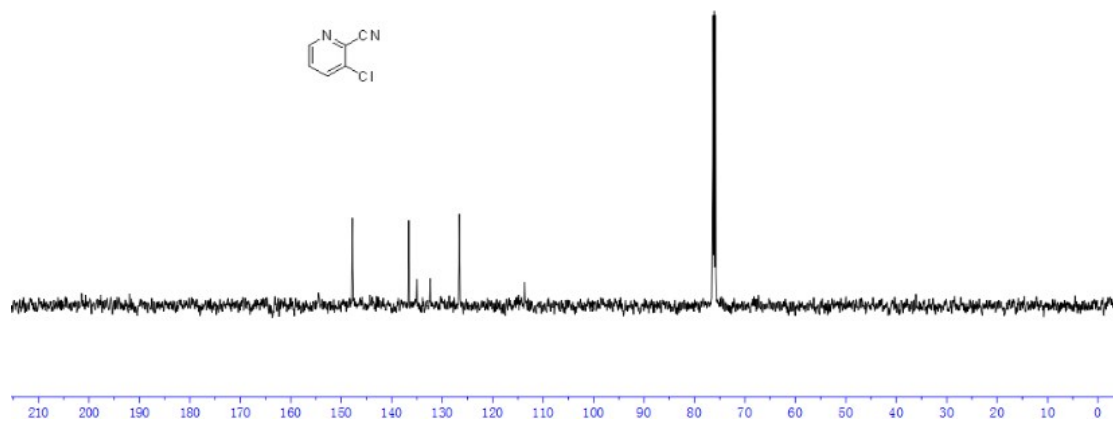
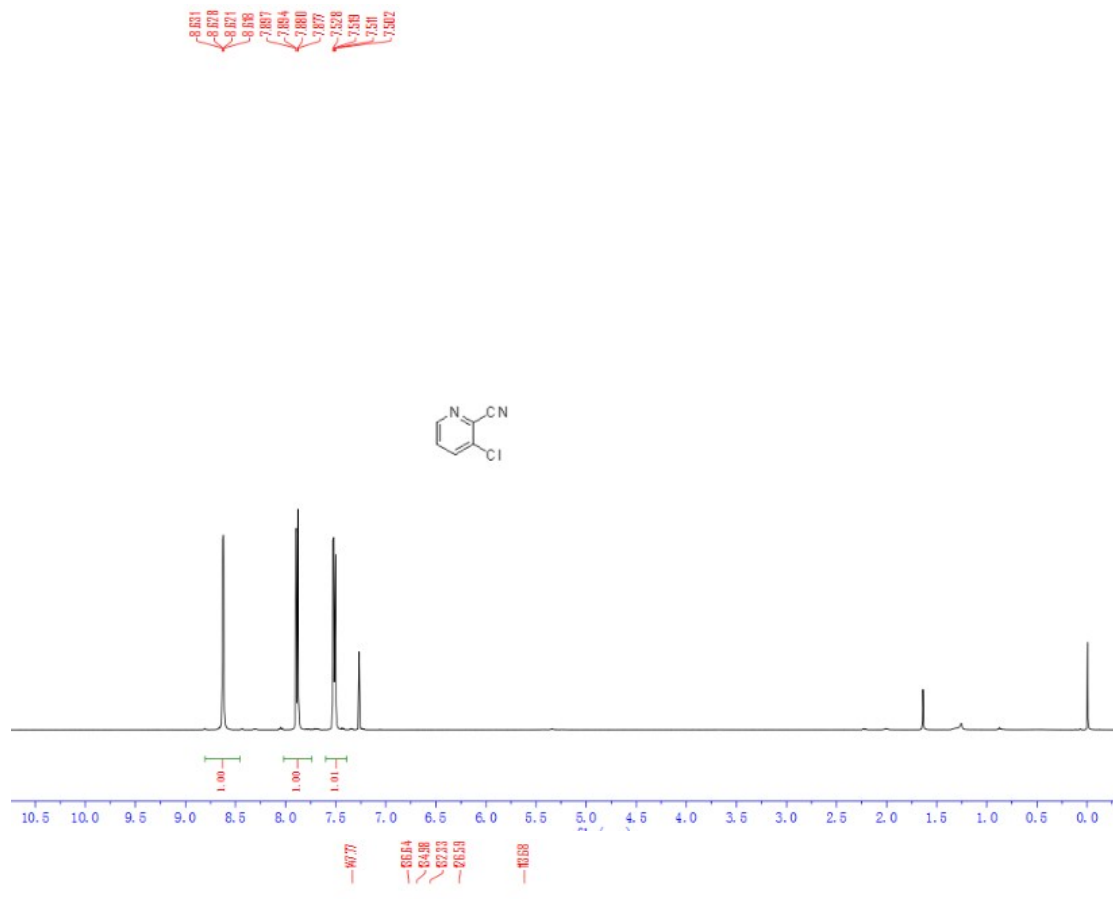


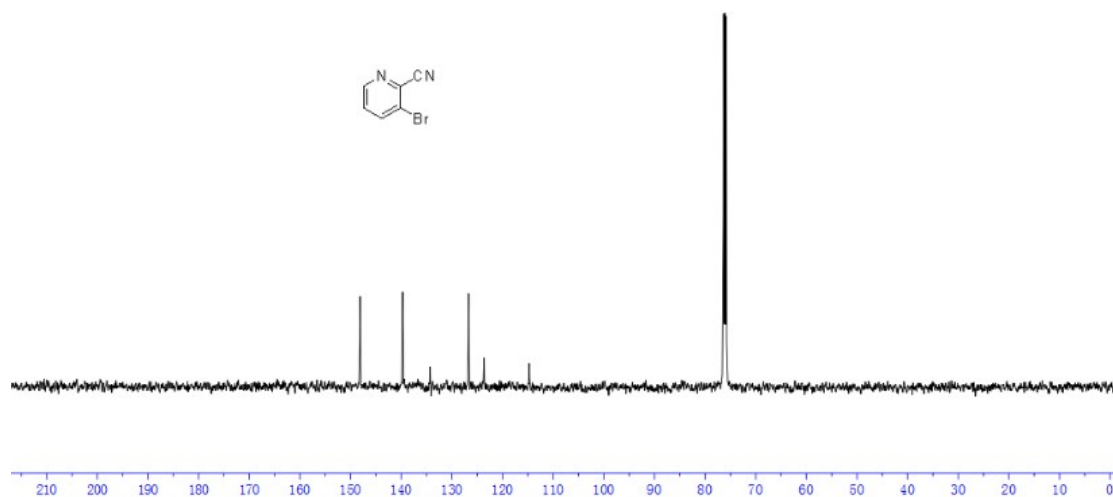
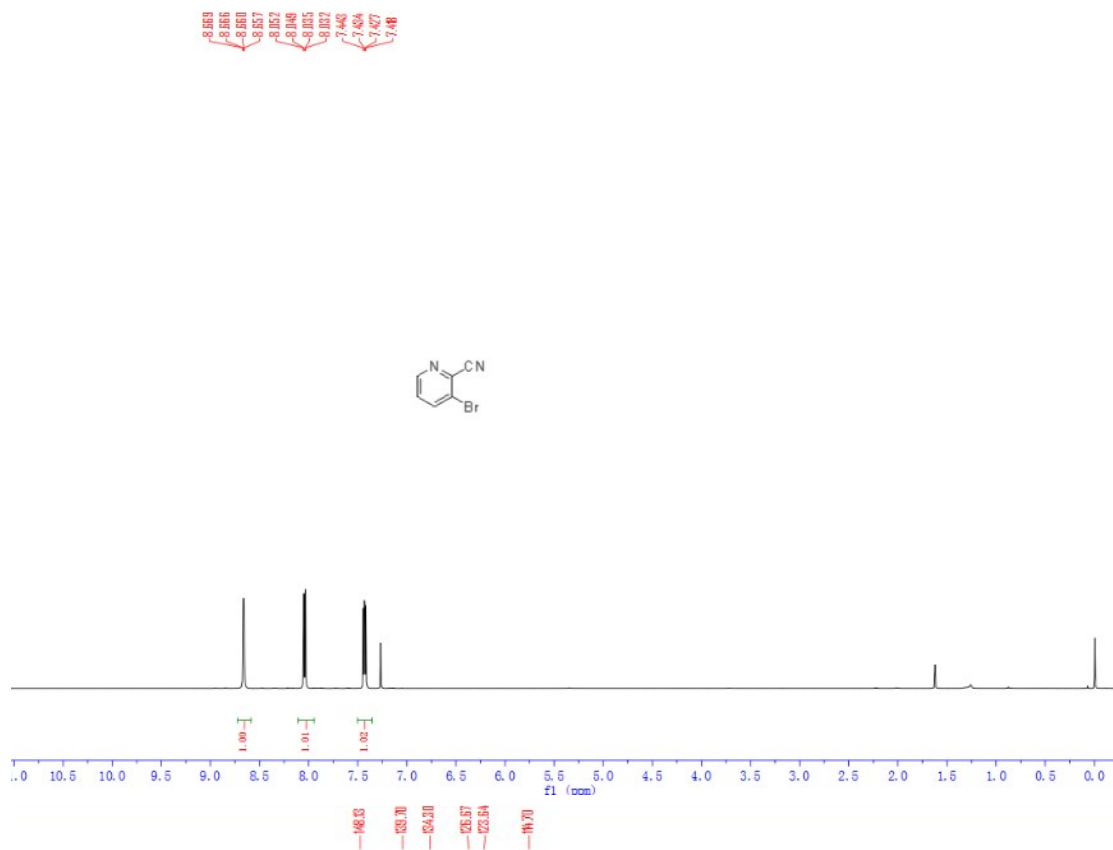


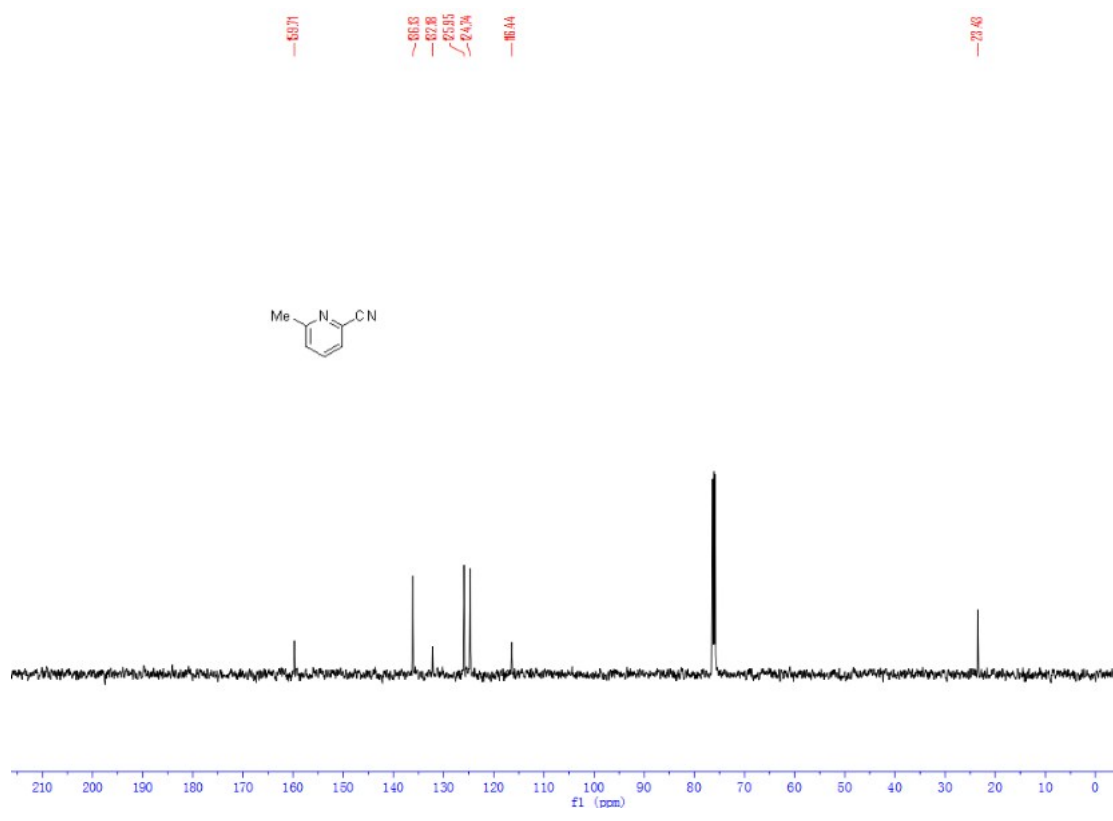
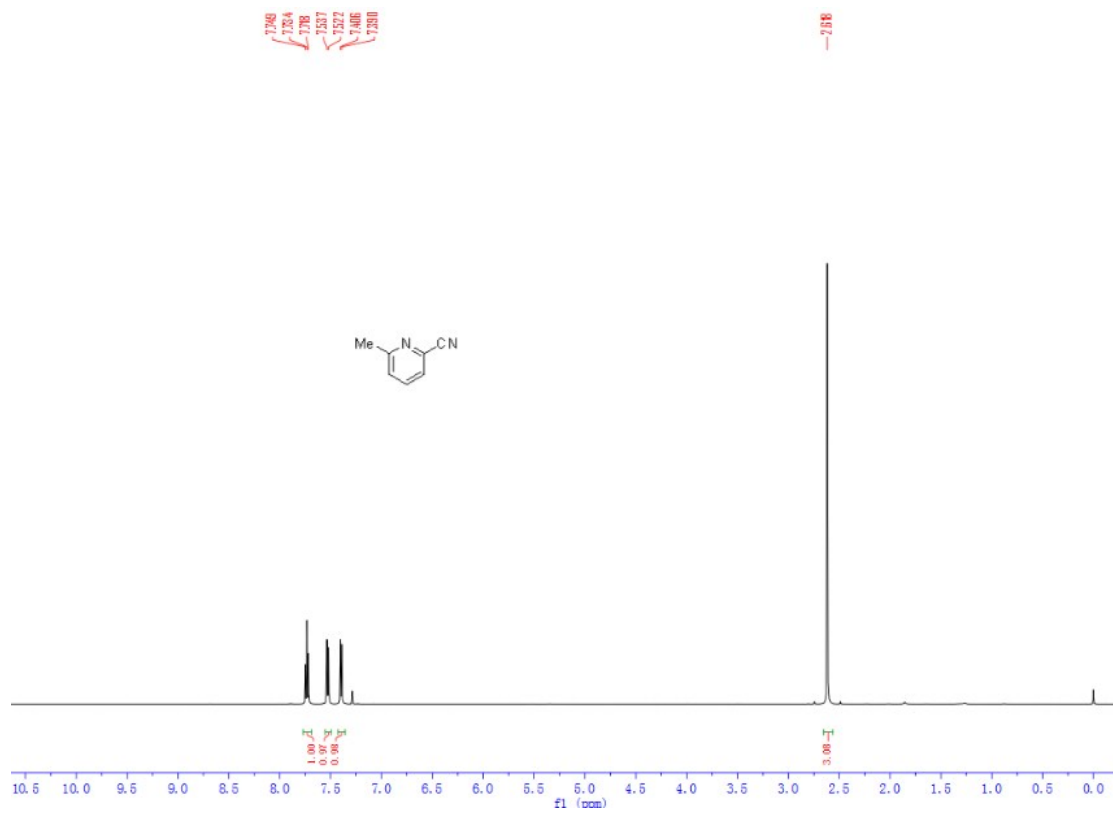
8819
8819
7888
7887
7885
7885
779
7566
7555
7555
7555
7554
7554
7553

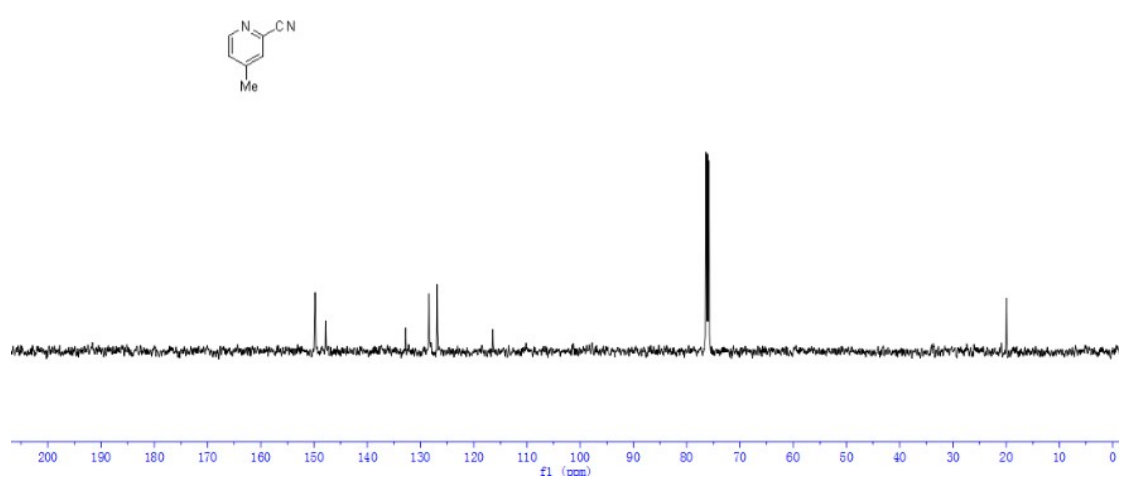
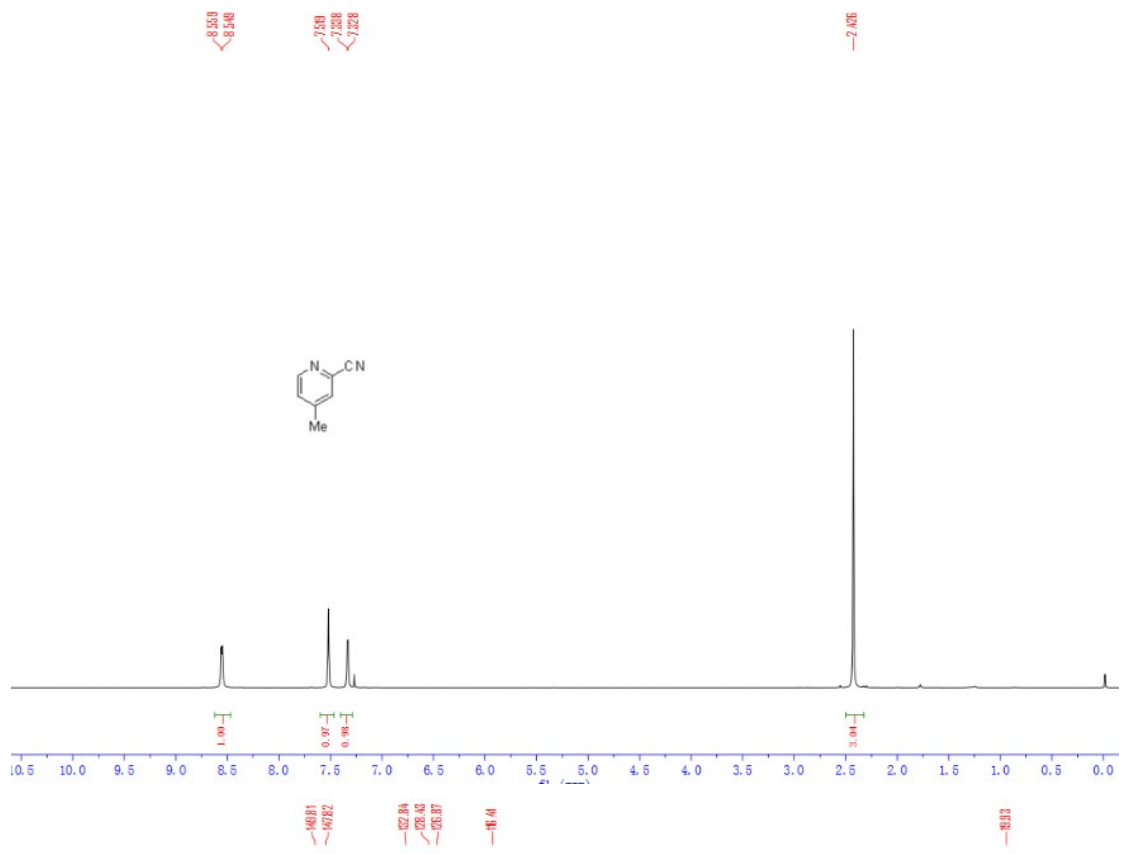




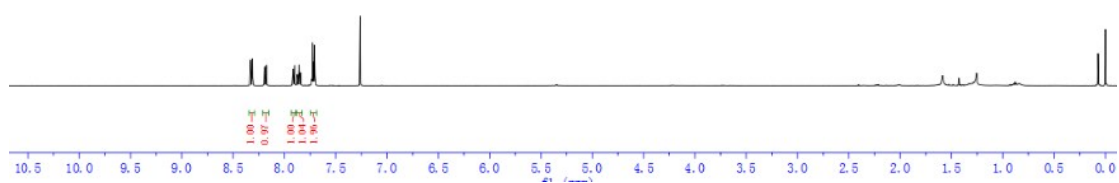
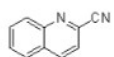








8.320
8.315
8.304
8.298
7.977
7.901
7.875
7.872
7.851
7.858
7.855
7.844
7.844
7.794
7.722
7.725
7.720
7.700
7.700
7.700
7.700
7.700
7.700



167.28
135.50
132.72
130.29
129.88
128.46
127.72
126.80
123.37
116.58

