

Cobalt(II)-Catalyzed Benzylic Oxidations with Potassium persulfate in TFA/TFAA

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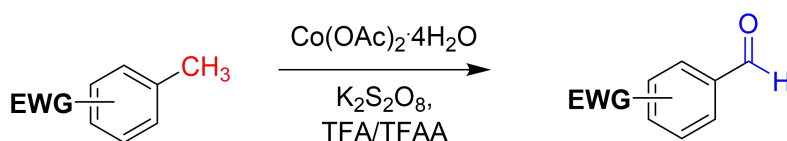
Content

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1. Reagent: Unless otherwise indicated, all solvents and organic reagents were obtained from commercially available sources and were used without further purification. Silica gel was used for column chromatography and was performed with 60 A mesh standard grade silica gel.

2. Instrument: The reaction process was monitored using thin layer chromatography (TLC) with silica gel plates (thickness = 0.20 mm, GF254) under UV light and LC-MS (Waters Acquity UPLC/ SQD). Mass spectra was obtained using a Waters Acquity UPLC-SQD mass spectrometer. High resolution mass spectra (HRMS) were recorded on an Agilent Technologies LC/MSD TOF spectrometer. ¹H NMR spectra was recorded on a Varian Mercury-400 or 500 MHz instrument, and ¹³C NMR spectra was recorded at 400 or 500 MHz on a Varian Mercury using CDCl₃ as a solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in parts per million relative to CDCl₃ (d 7.26), CD₃OD (d 3.31) and DMSO-d₆ (d 2.50) for ¹H NMR and relative to CDCl₃ (d 77.23), CD₃OD (d 49.51) and DMSO-d₆ (d 39.51) for ¹³C NMR with TMS as an internal standard. Abbreviations used for ¹H NMR splitting are as follows: s = singlet, brs = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, br m = broad multiplet.

3. General procedure for the synthesis of the desired compounds (2a – 2t)

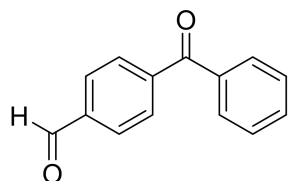


Substituted ketone, ester, and nitrotoluene (1.0 equiv.), Co(OAc)₂·4H₂O (20 %) and K₂S₂O₈ (1.5 equiv.) was dissolved in commercial TFA/TFAA (0.9 ml:0.1 ml) in a 15 mL sealed tube. Then the reaction mixture was stirred at 80°C-110°C for 7-16 h. The reaction was monitored by TLC and LC-MS. After completion of the reaction, the mixture was cooled down to room temperature, and the reaction was quenched by the addition of saturated NaHCO₃. The reaction mixture was diluted with 20 mL CH₂Cl₂, the organic phase was washed with sat. NaHCO₃ and brine (20 mL), dried

over Na₂SO₄ and concentrated on rotavapor under reduced pressure. Finally the residue was purified by silical gel column chromatography (Petroleum ether: Ethyl acetate = 10:1) to give the corresponding products.

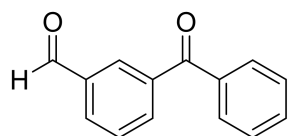
4. The analytic data

4-Benzoylbenzaldehyde (2a)



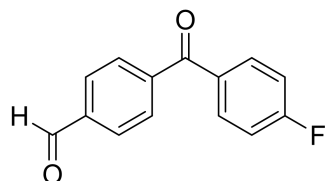
Isolated Yield: 32.8 mg, 78%; ¹H NMR (500 MHz, Chloroform-*d*) δ 10.13 (s, 1H), 8.00 (d, *J* = 7.8 Hz, 2H), 7.93 (d, *J* = 8.0 Hz, 2H), 7.81 (d, *J* = 7.6 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 196.0, 191.8, 138.6, 136.9, 133.3, 130.5, 130.3, 130.0, 129.7, 129.4, 128.7, 128.7. LRMS (ESI) calcd. for C₁₄H₁₀O₂ [M+H]: 211.25, found: 211.29.

3-Benzoylbenzaldehyde (2b)



Isolated Yield: 36.2 mg, 86%; ¹H NMR (500 MHz, Chloroform-*d*) δ 10.09 (s, 1H), 8.28 (s, 1H), 8.12 (d, *J* = 7.6 Hz, 1H), 8.08 (d, *J* = 7.7 Hz, 1H), 7.81 (d, *J* = 7.5 Hz, 2H), 7.68 (t, *J* = 7.7 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 2H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 195.6, 191.6, 138.7, 137.0, 136.5, 135.6, 133.1, 132.8, 131.5, 130.2, 129.4, 128.7. LRMS (ESI) calcd. for C₁₄H₁₀O₂ [M+H]: 211.25, found: 211.32.

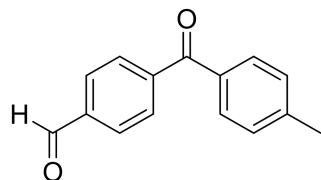
4-(4-Fluorobenzoyl) benzaldehyde (2c)



Isolated Yield: 36.9 mg, 81%; ¹H NMR (500 MHz, Chloroform-*d*) δ 10.13 (s, 1H), 8.01 (d, *J* = 7.9 Hz, 2H), 7.90 (d, *J* = 7.6 Hz, 2H), 7.86 (dd, *J* = 8.3, 5.3 Hz, 2H), 7.19

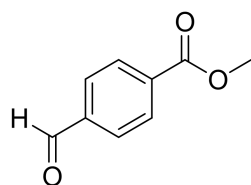
(t, $J = 8.3$ Hz, 2H). ^{13}C NMR (126 MHz, Chloroform- d) δ 194.4, 191.7, 166.9, 164.9, 142.6, 138.6, 133.1, 132.9, 132.9, 130.3, 129.7, 116.0, 115.8. LRMS (ESI) calcd. for $\text{C}_{15}\text{H}_{12}\text{O}_2$ [M+H]: 229.25, found: 229.27.

4-(4-Methylbenzoyl) benzaldehyde (2d)



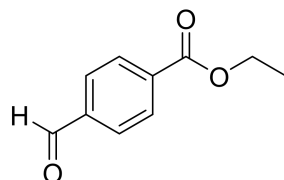
Isolated Yield: 37.6 mg, 84%; ^1H NMR (500 MHz, Chloroform- d) δ 10.13 (s, 1H), 7.99 (d, $J = 7.8$ Hz, 2H), 7.90 (d, $J = 7.9$ Hz, 2H), 7.72 (d, $J = 7.8$ Hz, 2H), 7.30 (d, $J = 7.8$ Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (126 MHz, Chloroform- d) δ 195.7, 191.8, 144.3, 143.1, 138.5, 134.5, 130.5, 130.3, 129.6, 129.4, 21.9. LRMS (ESI) calcd. for $\text{C}_{15}\text{H}_{12}\text{O}_2$ [M+H]: 225.25, found: 225.27.

Methyl 4-formylbenzoate (2e)



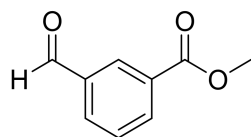
Isolated Yield: 20.6 mg, 63%; ^1H NMR (500 MHz, Chloroform- d) δ 10.09 (s, 1H), 8.18 (d, $J = 7.9$ Hz, 2H), 7.94 (d, $J = 7.9$ Hz, 2H), 3.95 (s, 3H). ^{13}C NMR (126 MHz, Chloroform- d) δ 197.3, 191.7, 170.8, 137.6, 134.6, 133.3, 129.2, 128.4, 65.9, 26.8. LRMS (ESI) calcd. for $\text{C}_9\text{H}_8\text{O}_3$ [M+H]: 165.16, found: 165.20.

Ethyl 4-formylbenzoate (2f)



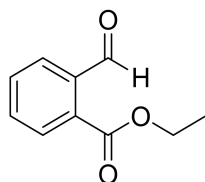
Isolated Yield: 23.4 mg, 66%; ^1H NMR (400 MHz, Chloroform- d) δ 10.09 (s, 1H), 8.18 (d, $J = 8.0$ Hz, 2H), 7.94 (d, $J = 8.1$ Hz, 2H), 4.41 (q, $J = 7.1$ Hz, 2H), 1.41 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, Chloroform- d) δ 191.8, 165.7, 139.2, 135.6, 130.3, 129.6, 61.7, 14.4. LRMS (ESI) calcd. for $\text{C}_9\text{H}_8\text{O}_3$ [M+H]: 179.18, found: 179.21.

Methyl 3-formylbenzoate (2g)



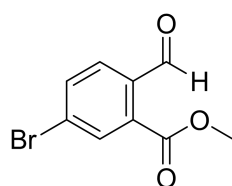
Isolated Yield: 20.9 mg, 64%; $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 10.07 (s, 1H), 8.52 (s, 1H), 8.29 (d, $J = 7.7$ Hz, 1H), 8.08 (d, $J = 8.1$ Hz, 1H), 7.62 (t, $J = 7.9$ Hz, 1H), 3.96 (s, 3H). $^{13}\text{C NMR}$ (126 MHz, Chloroform-*d*) δ 191.5, 136.7, 135.3, 133.2, 131.4, 129.4, 52.6. LRMS (ESI) calcd. for $\text{C}_{10}\text{H}_{10}\text{O}_3$ $[\text{M}+\text{H}]$: 165.16, found: 165.19.

Ethyl 2-formylbenzoate (2h)



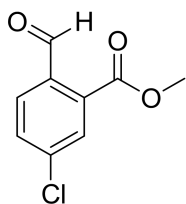
Isolated Yield: 23.4 mg, 66%; $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 10.63 (s, 1H), 7.96 (dt, $J = 20.2, 4.8$ Hz, 2H), 7.68 – 7.61 (m, 2H), 4.45 (q, $J = 7.2$ Hz, 2H), 1.43 (t, $J = 7.2$ Hz, 3H). $^{13}\text{C NMR}$ (126 MHz, Chloroform-*d*) δ 192.3, 165.5, 137.2, 133.1, 132.6, 132.4, 130.5, 128.5, 62.1, 14.4. LRMS (ESI) calcd. for $\text{C}_{10}\text{H}_{10}\text{O}_3$ $[\text{M}+\text{H}]$: 179.23, found: 179.22.

Methyl 5-bromo-2-formylbenzoate (2i)



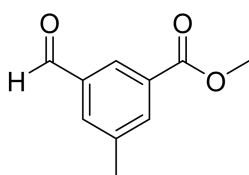
Isolated Yield: 36.4 mg, 75%; $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 10.58 (s, 1H), 8.13 (s, 1H), 7.81 (q, $J = 8.2$ Hz, 2H), 3.99 (s, 3H). $^{13}\text{C NMR}$ (126 MHz, Chloroform-*d*) δ 191.1, 165.5, 135.7, 133.6, 130.1, 128.2, 53.2. LRMS (ESI) calcd. for $\text{C}_9\text{H}_7\text{BrO}_3$ $[\text{M}+\text{H}]$: 244.09, found: 244.12.

Methyl 5-chloro-2-formylbenzoate (2j)



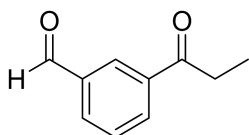
Isolated Yield: 28.4 mg, 72%; $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 10.58 (s, 1H), 7.96 (s, 1H), 7.91 (d, $J = 8.4$ Hz, 1H), 7.62 (d, $J = 8.4$ Hz, 1H), 3.99 (s, 3H). $^{13}\text{C NMR}$ (126 MHz, Chloroform-*d*) δ 191.2, 140.0, 135.6, 133.8, 133.0, 131.0, 130.4, 53.5. LRMS (ESI) calcd. for $\text{C}_9\text{H}_7\text{ClO}_3$ [M+H]: 199.70, found: 199.73.

Methyl 3-formyl-5-methylbenzoate (2k)



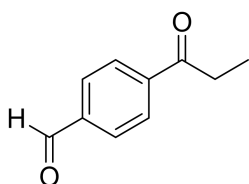
Isolated Yield: 24.7 mg, 65%; $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 10.04 (s, 1H), 8.32 (s, 1H), 8.11 (s, 1H), 7.88 (s, 1H), 3.95 (s, 3H), 2.48 (s, 3H). $^{13}\text{C NMR}$ (126 MHz, Chloroform-*d*) δ 192.0, 166.6, 139.9, 137.0, 136.3, 133.8, 131.5, 129.3, 52.8, 21.5. LRMS (ESI) calcd. for $\text{C}_{11}\text{H}_{12}\text{O}_3$ [M+H]: 179.23, found: 179.27.

3-Propionylbenzaldehyde (2l)



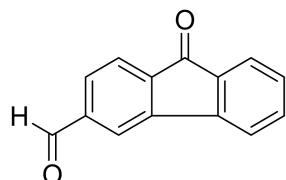
Isolated Yield: 20.4 mg, 63%; $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 10.10 (s, 1H), 8.45 (s, 1H), 8.23 (d, $J = 7.8$ Hz, 1H), 8.08 (d, $J = 7.6$ Hz, 1H), 7.65 (t, $J = 7.7$ Hz, 1H), 3.07 (q, $J = 7.3$ Hz, 2H), 1.26 (t, $J = 7.3$ Hz, 3H). $^{13}\text{C NMR}$ (126 MHz, Chloroform-*d*) δ 200.0, 191.7, 137.4, 134.4, 133.7, 133.6, 133.1, 129.9, 129.7, 129.4, 129.2, 32.2, 8.2. LRMS (ESI) calcd. for $\text{C}_{10}\text{H}_{10}\text{O}_3$ [M+H]: 163.20, found: 163.24.

4-Propionylbenzaldehyde (2m)



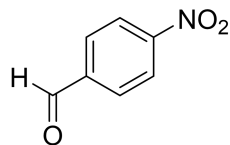
Isolated Yield: 21.8 mg, 67%; $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 10.09 (s, 1H), 8.09 (d, $J = 7.9$ Hz, 2H), 7.96 (d, $J = 7.9$ Hz, 2H), 3.04 (q, $J = 7.0$ Hz, 2H), 1.23 (t, $J = 7.3$ Hz, 3H). $^{13}\text{C NMR}$ (126 MHz, Chloroform-*d*) δ 200.3, 191.8, 141.2, 139.0, 129.9, 128.6, 32.5, 8.1. LRMS (ESI) calcd. for $\text{C}_{10}\text{H}_{10}\text{O}_2$ [M+H]: 163.21, found: 163.32.

9-Oxo-9H-fluorene-3-carbaldehyde (2n)



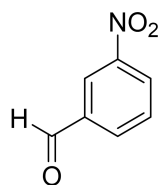
Isolated Yield: 28.7 mg, 69%; $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 10.10 (s, 1H), 8.05 (s, 1H), 7.83 (s, 2H), 7.72 (d, $J = 7.5$ Hz, 1H), 7.64 (d, $J = 7.6$ Hz, 1H), 7.58 (t, $J = 7.5$ Hz, 1H), 7.38 (t, $J = 7.5$ Hz, 1H). $^{13}\text{C NMR}$ (126 MHz, Chloroform-*d*) δ 192.9, 191.6, 145.1, 143.6, 141.1, 135.7, 134.2, 132.6, 130.1, 124.9, 124.7, 121.1, 119.7; LRMS (ESI) calcd. for $\text{C}_{15}\text{H}_8\text{O}_3$ [M+H]: 209.22, found: 209.25.

4-Nitrobenzaldehyde (2o)



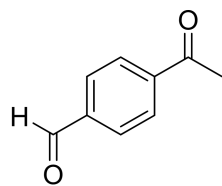
Isolated Yield: 18.4 mg, 61%; $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) 10.16 (s, 1H), 8.40 (d, $J = 8.1$ Hz, 2H), 8.08 (d, $J = 8.2$ Hz, 2H). $^{13}\text{C NMR}$ (126 MHz, Chloroform-*d*) δ 190.4, 151.3, 140.2, 130.6, 124.5. LRMS (ESI) calcd. for $\text{C}_7\text{H}_5\text{NO}_3$ [M+H]: 152.14, found: 152.17.

3-Nitrobenzaldehyde (2p)



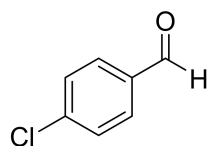
Isolated Yield: 18.4 mg, 61%; $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 10.12 (s, 1H), 8.71 (s, 1H), 8.49 (d, $J = 8.2$ Hz, 1H), 8.24 (d, $J = 7.5$ Hz, 1H), 7.77 (t, $J = 7.8$ Hz, 1H). $^{13}\text{C NMR}$ (126 MHz, Chloroform-*d*) δ 189.9, 148.9, 137.5, 134.8, 130.5, 128.7, 124.6. LRMS (ESI) calcd. for $\text{C}_7\text{H}_5\text{NO}_3$ [M+H]: 152.14, found: 152.16.

4-Acetylbenzaldehyde (2q)



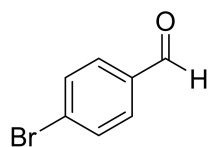
Isolated Yield: 20.7 mg, 70%; $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 10.10 (s, 1H), 8.09 (d, $J = 7.9$ Hz, 2H), 7.97 (d, $J = 7.8$ Hz, 2H), 2.65 (s, 3H). $^{13}\text{C NMR}$ (126 MHz, Chloroform-*d*) δ 197.6 , 191.8 , 141.3, 139.2 , 130.0 , 129.0 , 27.1 . LRMS (ESI) calcd. for $\text{C}_9\text{H}_8\text{O}_2$ [M+H]: 149.17, found: 149.18.

4-chlorobenzaldehyde (2r)



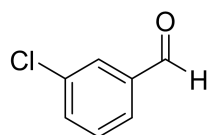
Isolated Yield: 22.4 mg, 82%; $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 9.92 (s, 1H), 7.76 (d, $J = 8.0$ Hz, 2H), 7.44 (d, $J = 8.0$ Hz, 2H). $^{13}\text{C NMR}$ (126 MHz, Chloroform-*d*) δ 190.77 , 140.84 , 134.73 , 130.86 , 129.40 . LRMS (ESI) calcd. for $\text{C}_7\text{H}_5\text{ClO}$ [M+H]: 140.00, found: 140.02.

4-bromobenzaldehyde (2s)

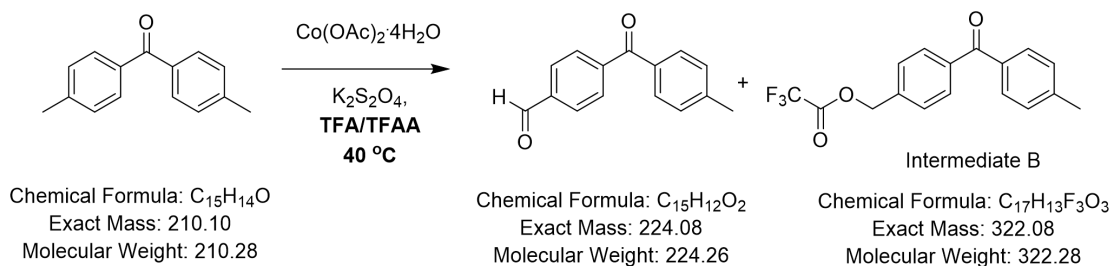


Isolated Yield: 32.8 mg, 90%; $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 9.93 (s, 1H), 7.70 (d, $J = 8.0$ Hz, 2H), 7.62 (d, $J = 8.0$ Hz, 2H). $^{13}\text{C NMR}$ (126 MHz, Chloroform-*d*) δ 191.03 , 135.11 , 132.43 , 130.97 , 129.72 . LRMS (ESI) calcd. for $\text{C}_7\text{H}_5\text{BrO}$ [M+H]: 183.95, found: 183.92.

3-chlorobenzaldehyde (2t)



Isolated Yield: 21.2 mg, 75%; $^1\text{H NMR}$ (500 MHz, Chloroform-*d*) δ 9.97 (s, 1H), 7.85 (s, 1H), 7.76 (d, $J = 7.5$ Hz, 1H), 7.59 (d, $J = 8.0$ Hz, 1H), 7.48 (t, $J = 7.9$ Hz, 1H). $^{13}\text{C NMR}$ (126 MHz, Chloroform-*d*) δ 190.93 , 137.96 , 135.59 , 134.51 , 130.50 , 129.42 , 128.09 . LRMS (ESI) calcd. for $\text{C}_7\text{H}_5\text{ClO}$ [M+H]: 140.00, found: 140.02.



When 4,4'-dimethyl-benzophenone was performed at the low temperature (40 °C), the corresponding intermediate B was observed by the LC-MS. We found that the intermediate B had the same retention time with the starting material, and the LC-MS data was presented as the following (see Figure 1 and Figure 2).

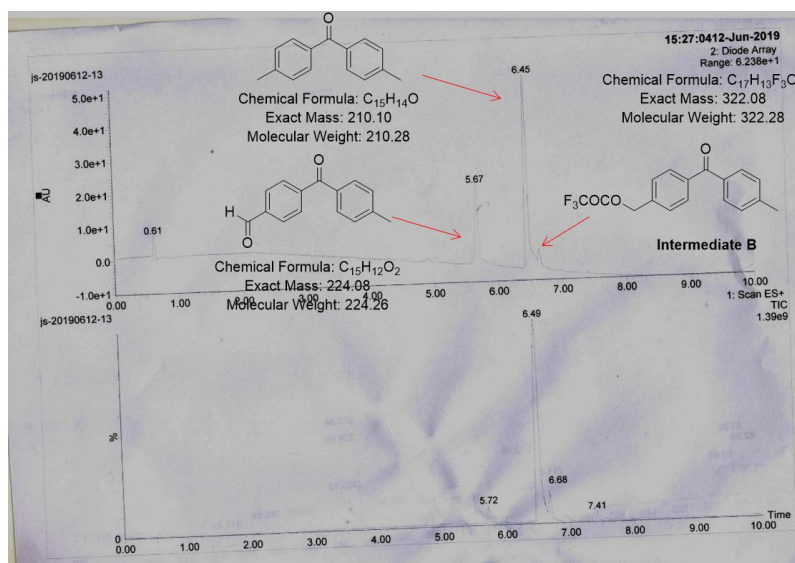


Figure 1 The liquid Chromatography of 4,4'-dimethyl-benzophenone oxidation

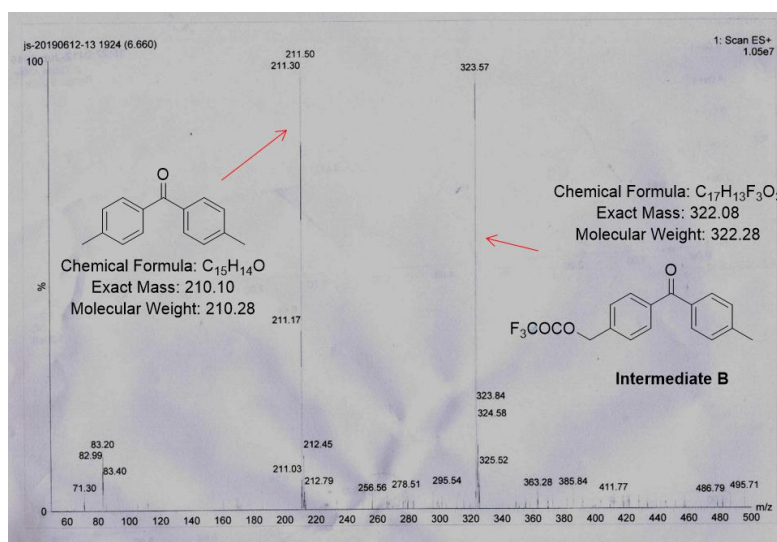
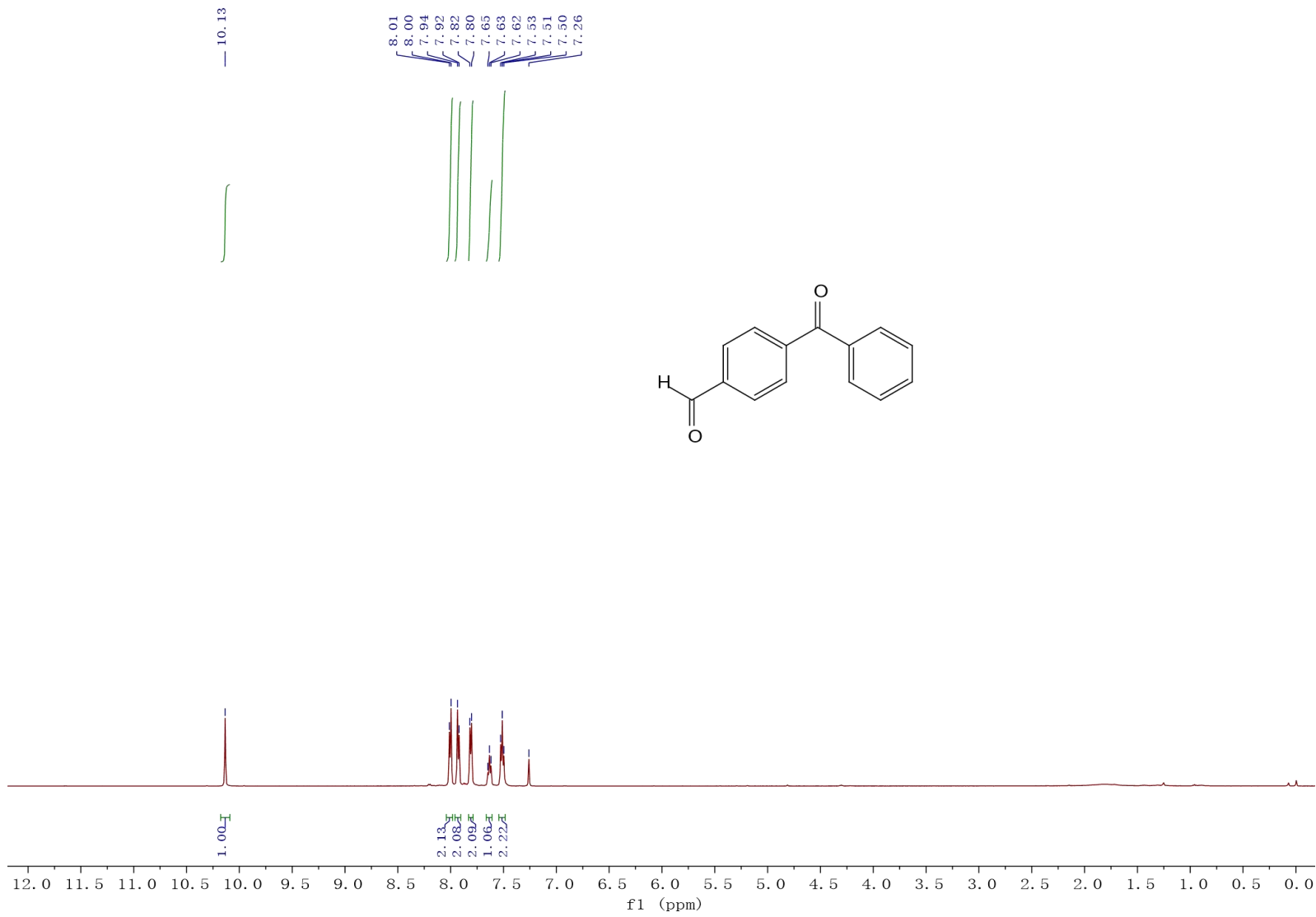
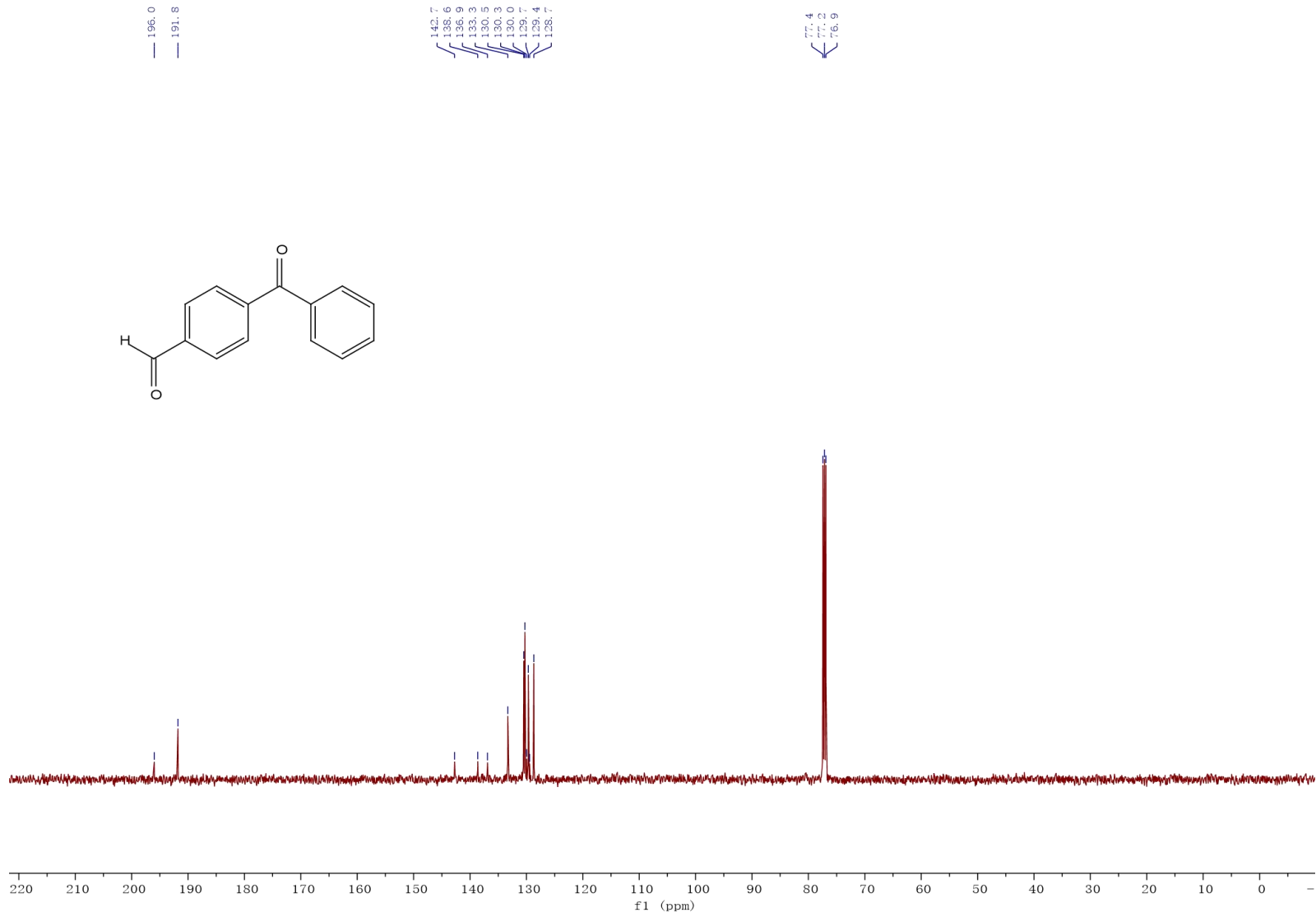
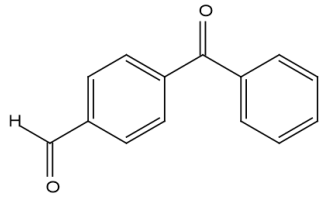
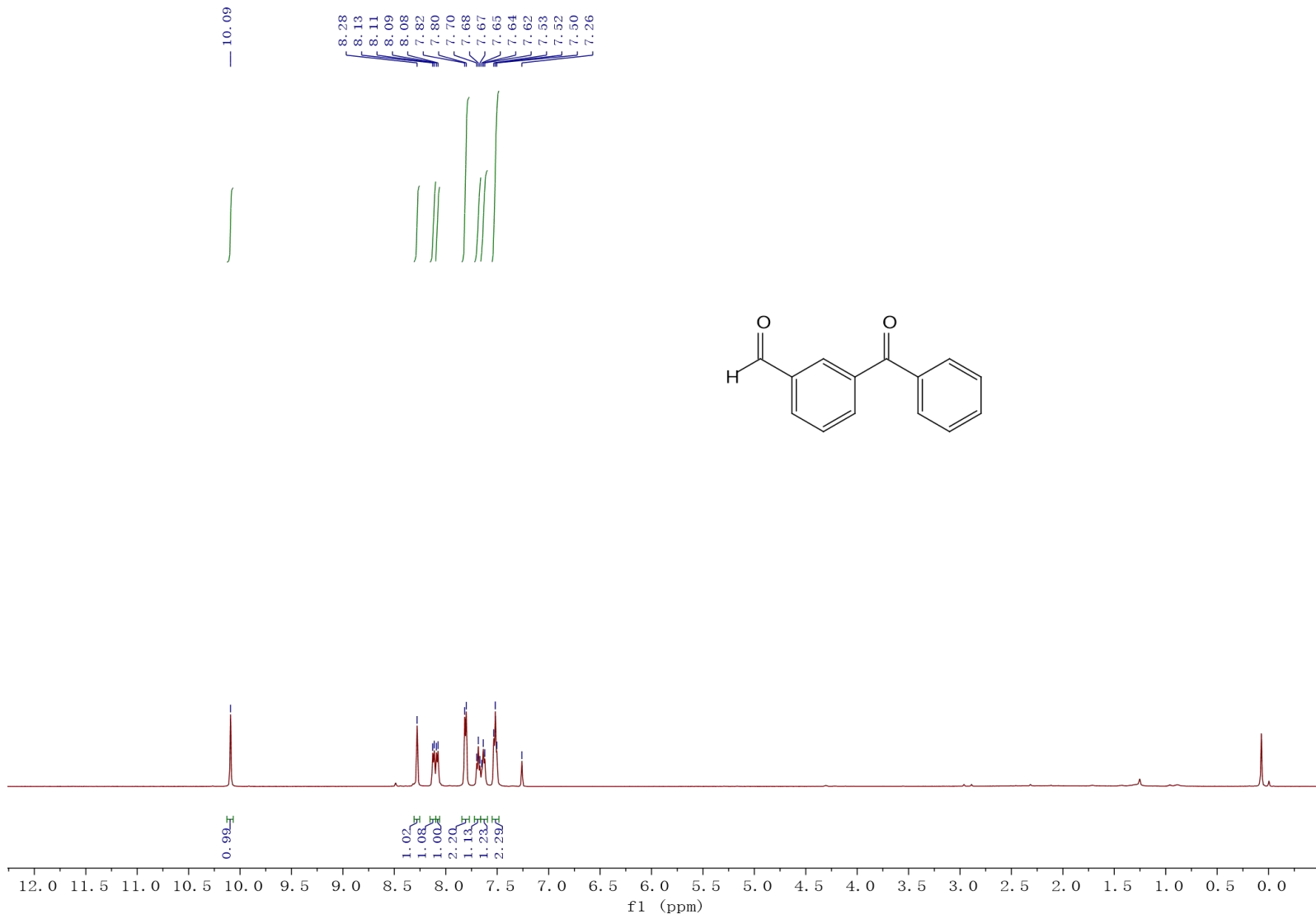
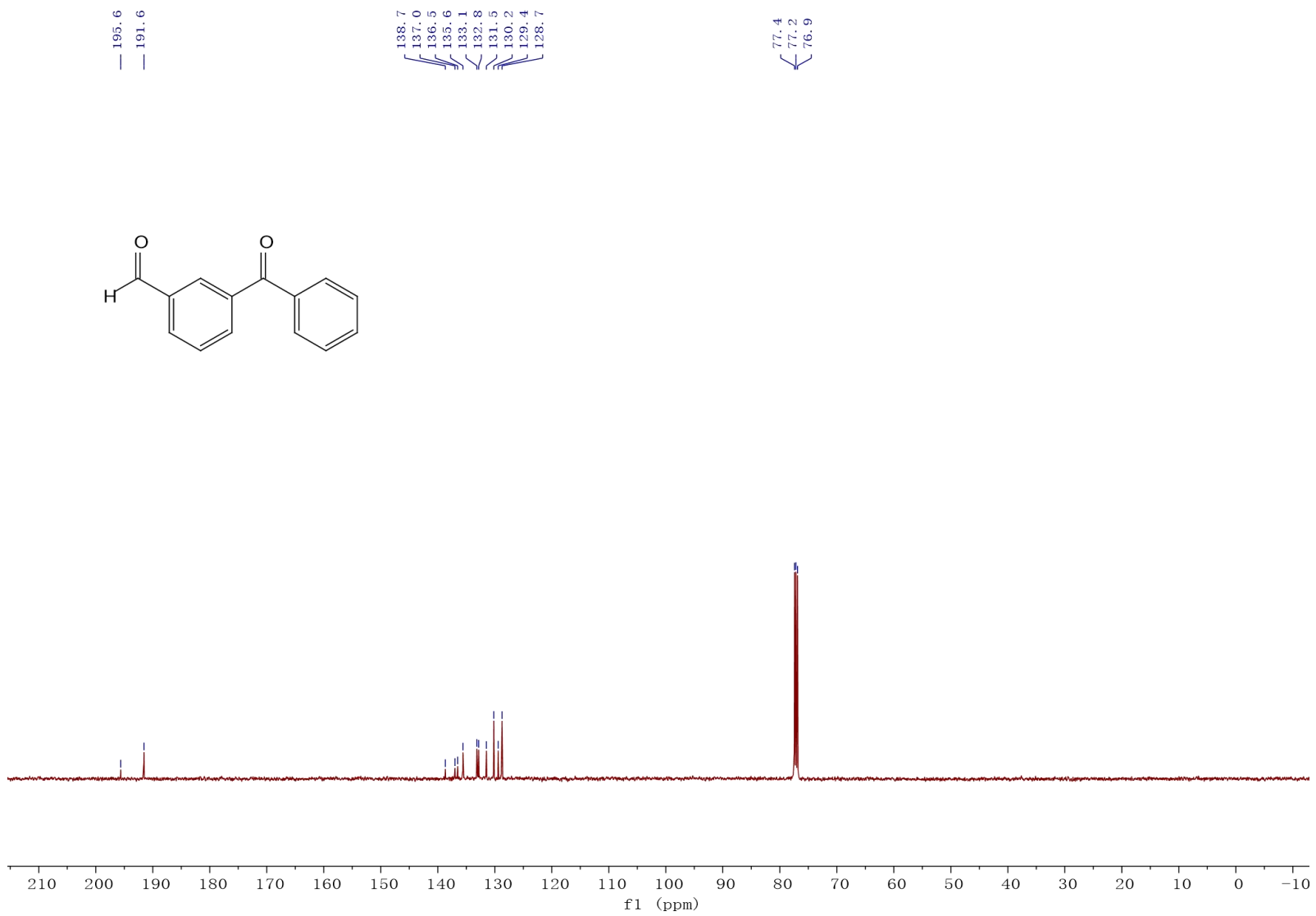
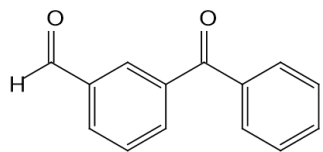


Figure 2 The MS data of 4,4'-dimethyl-benzophenone (6.66 min peak)

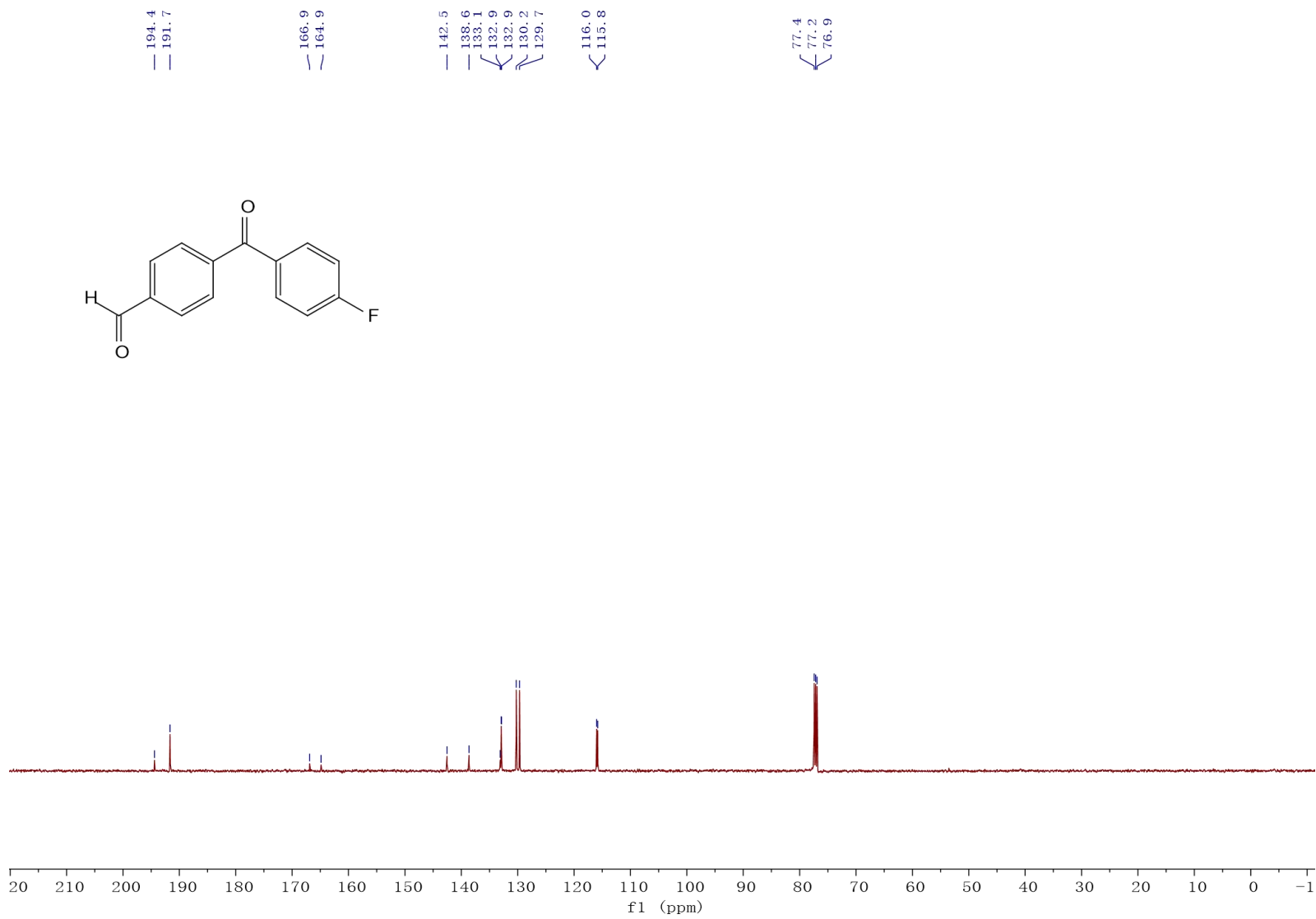
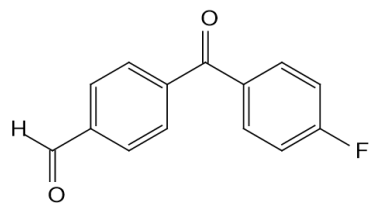


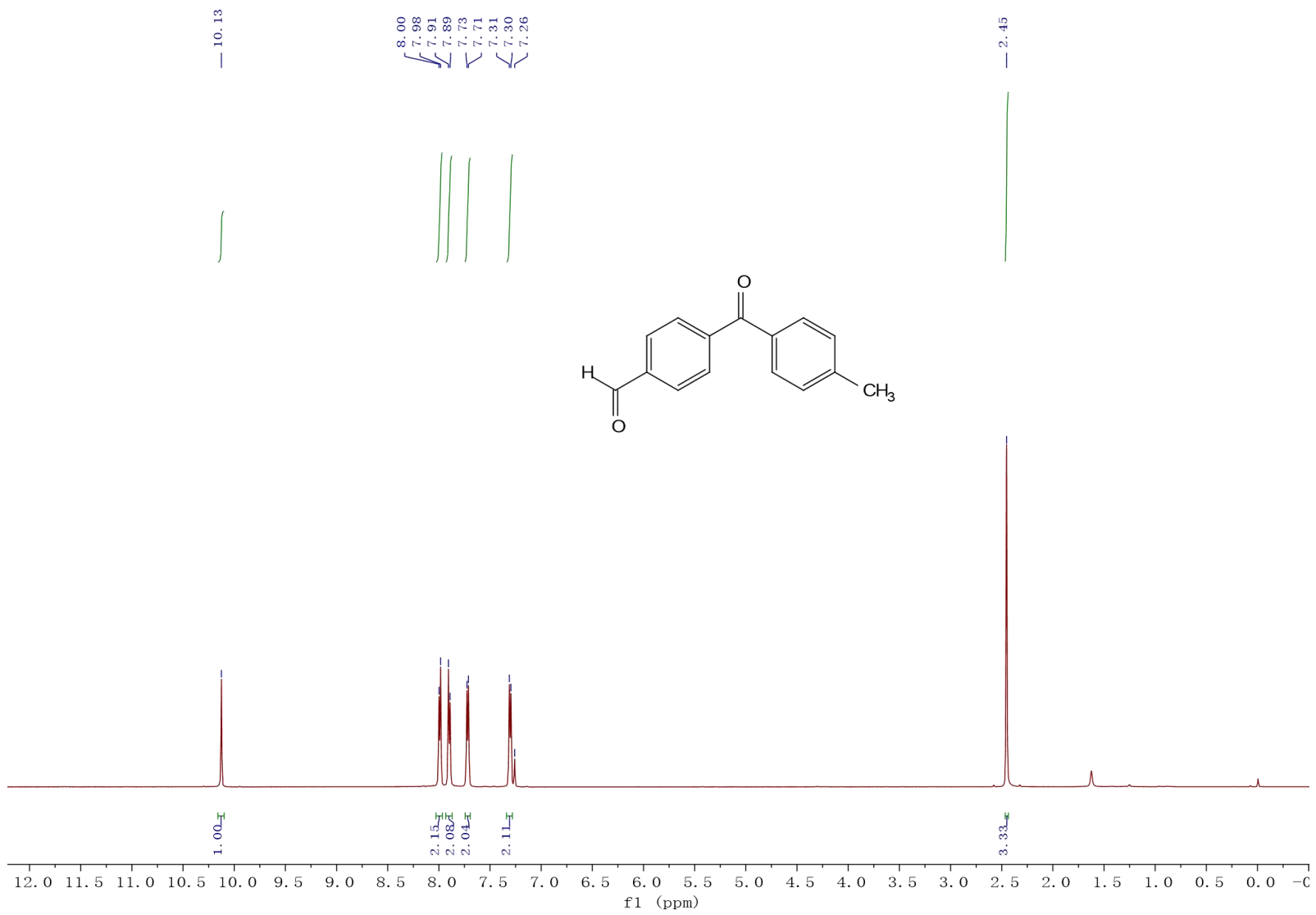


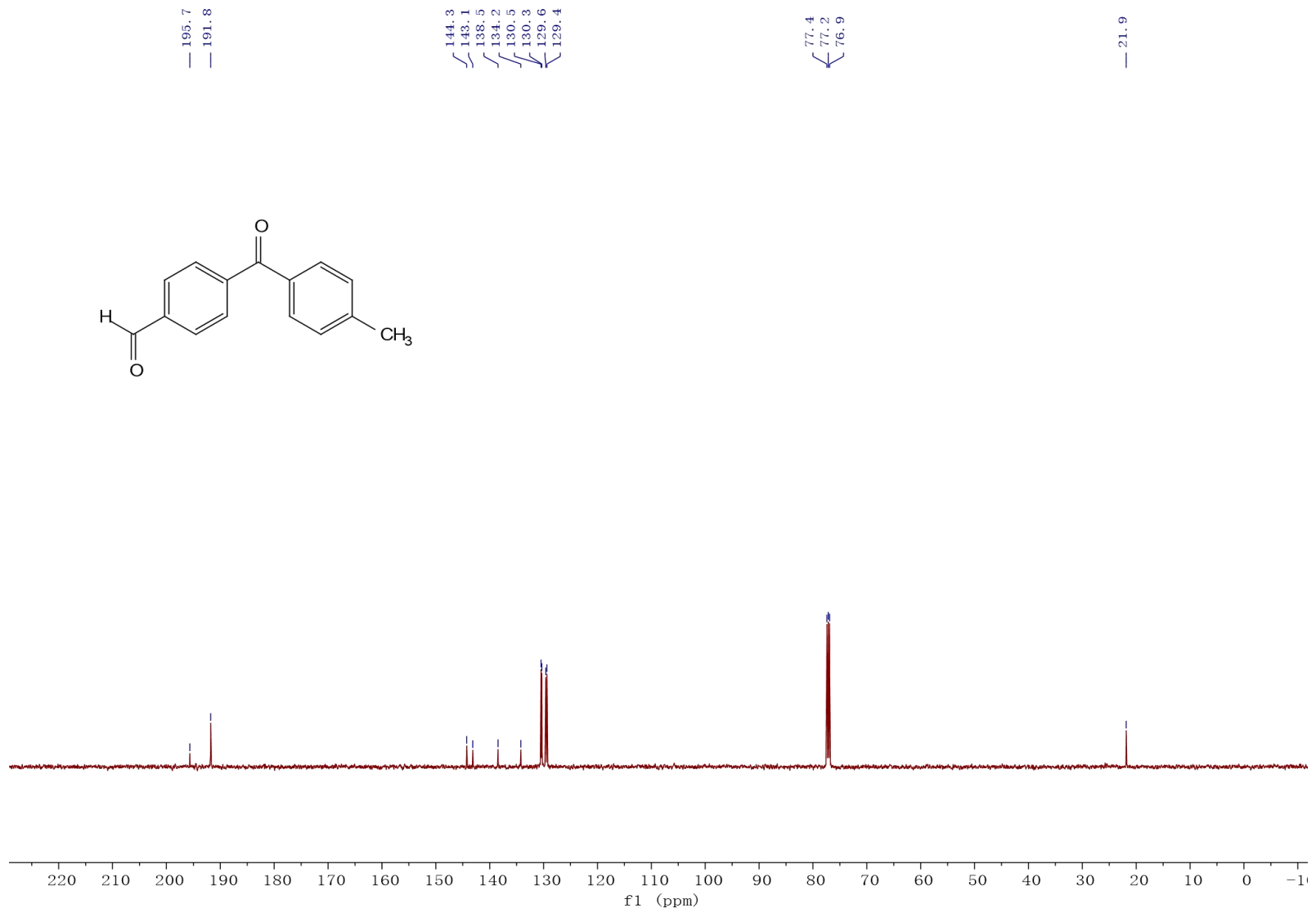


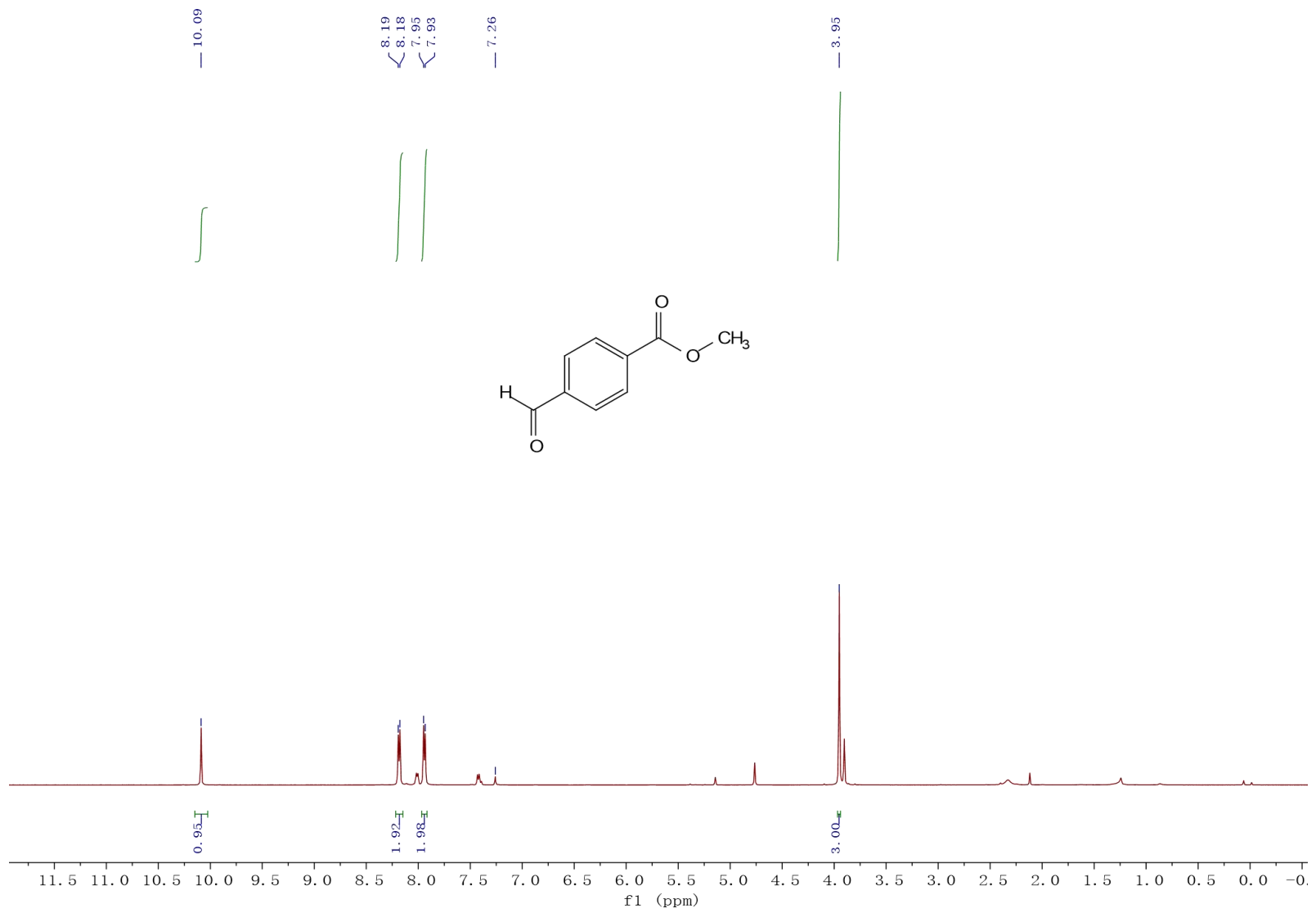


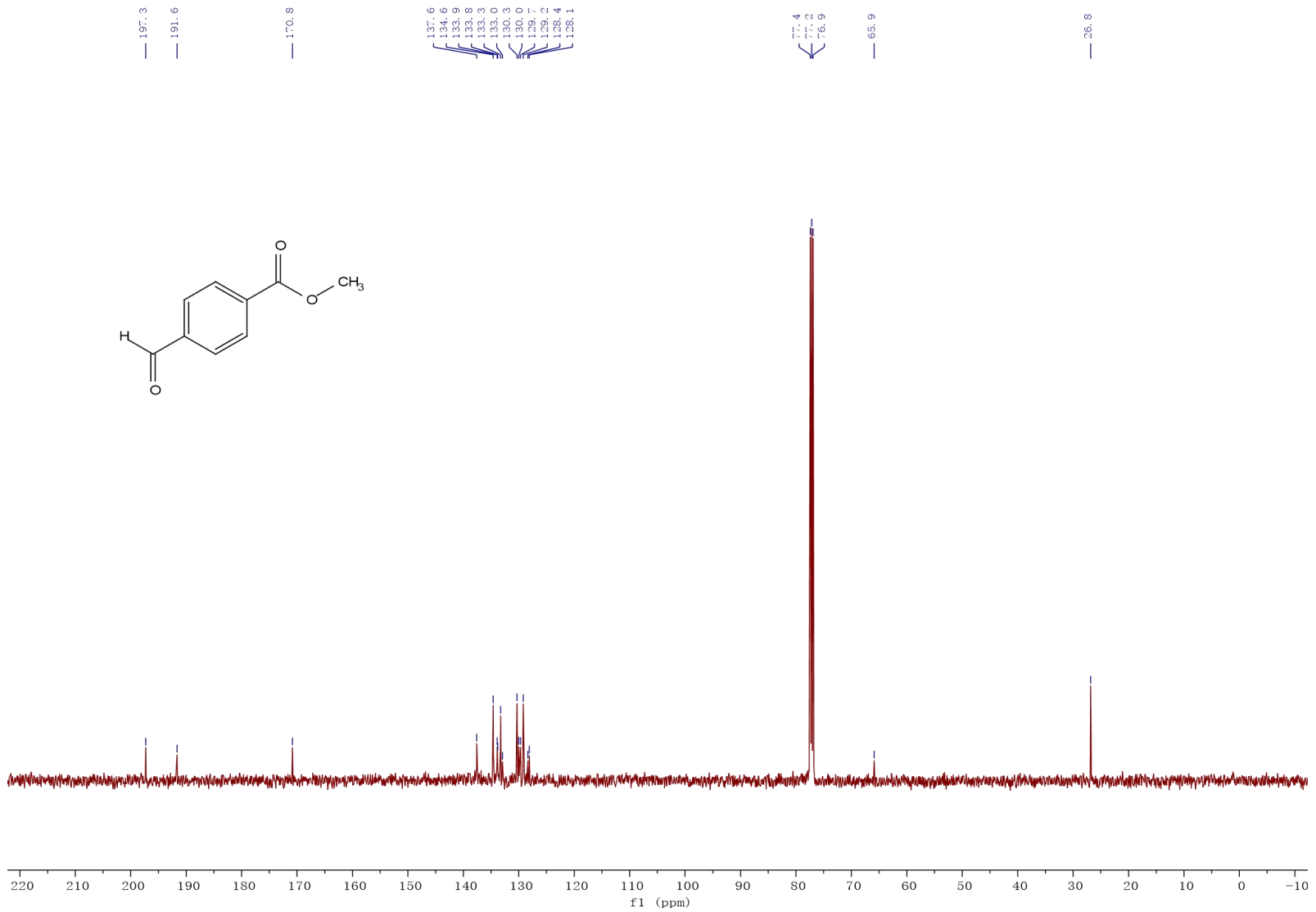
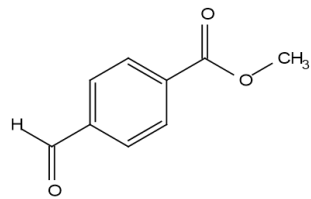


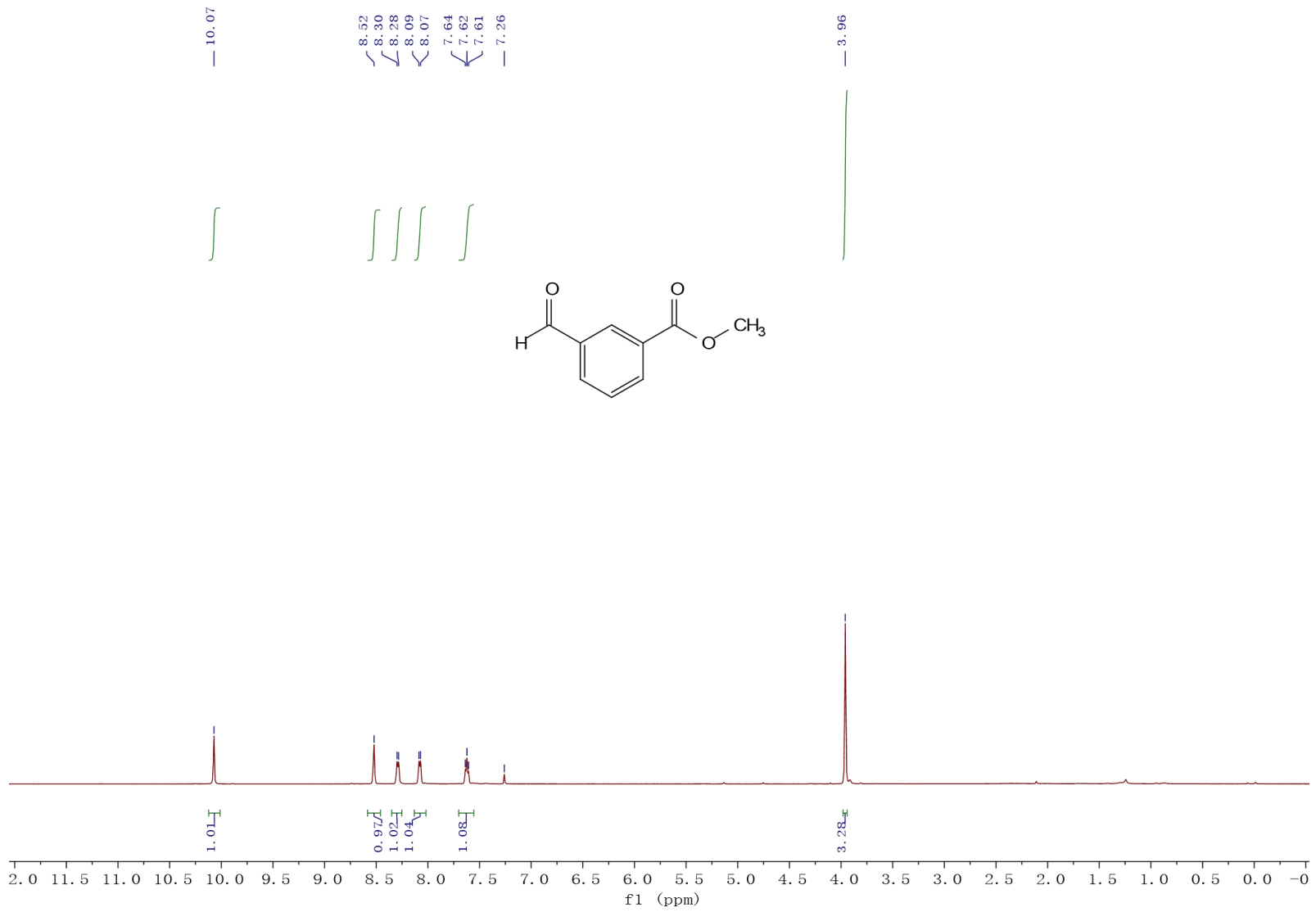


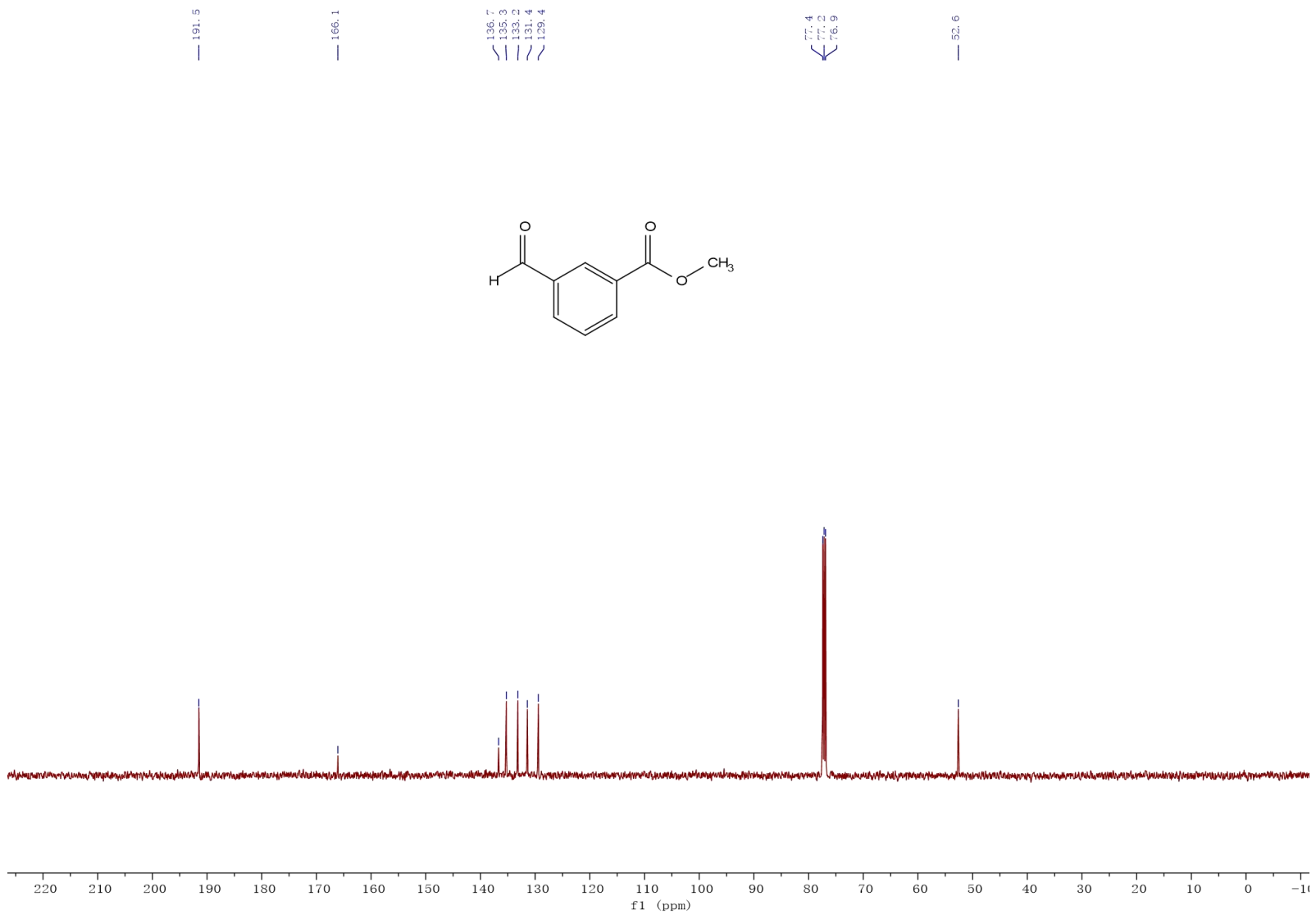


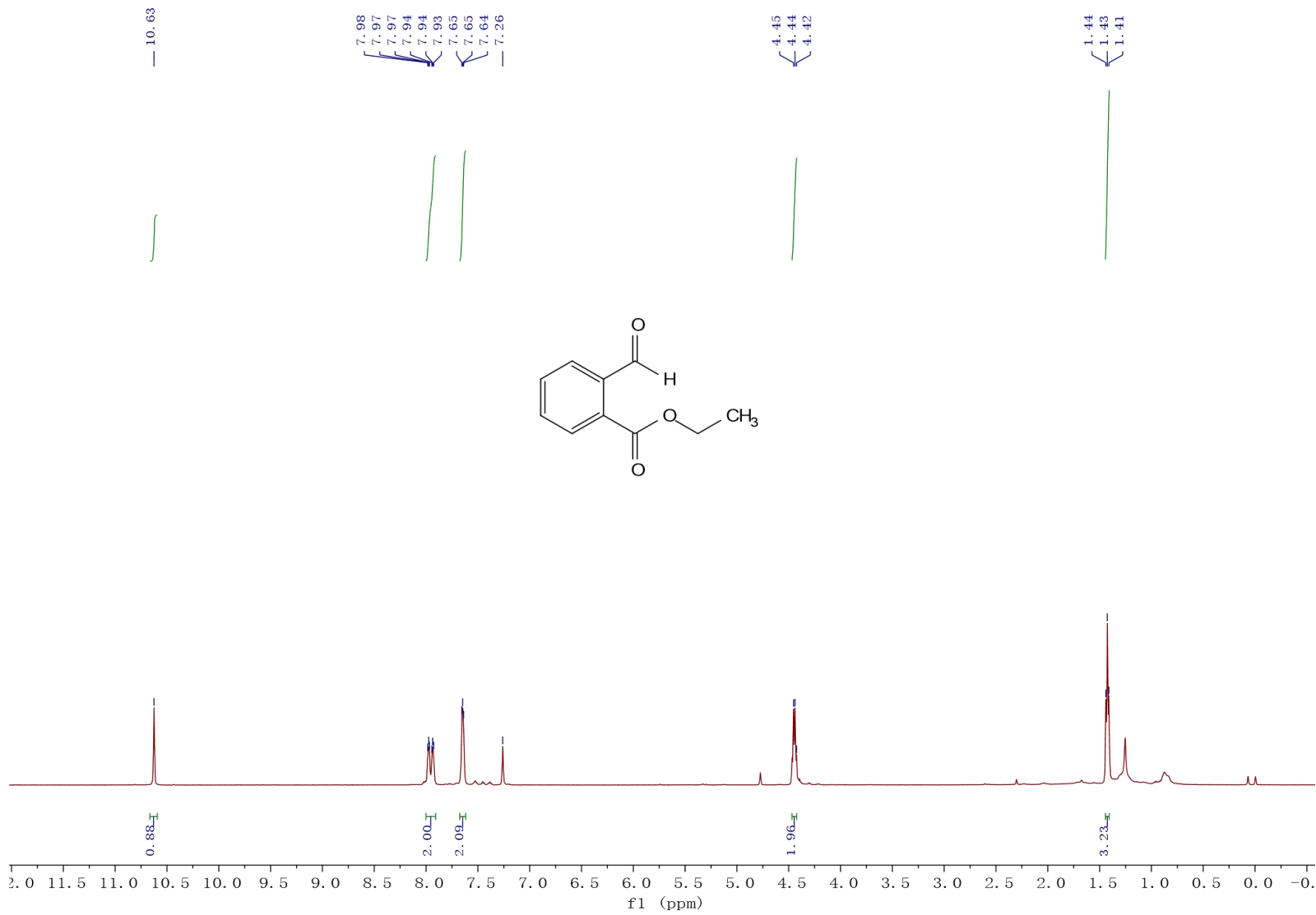


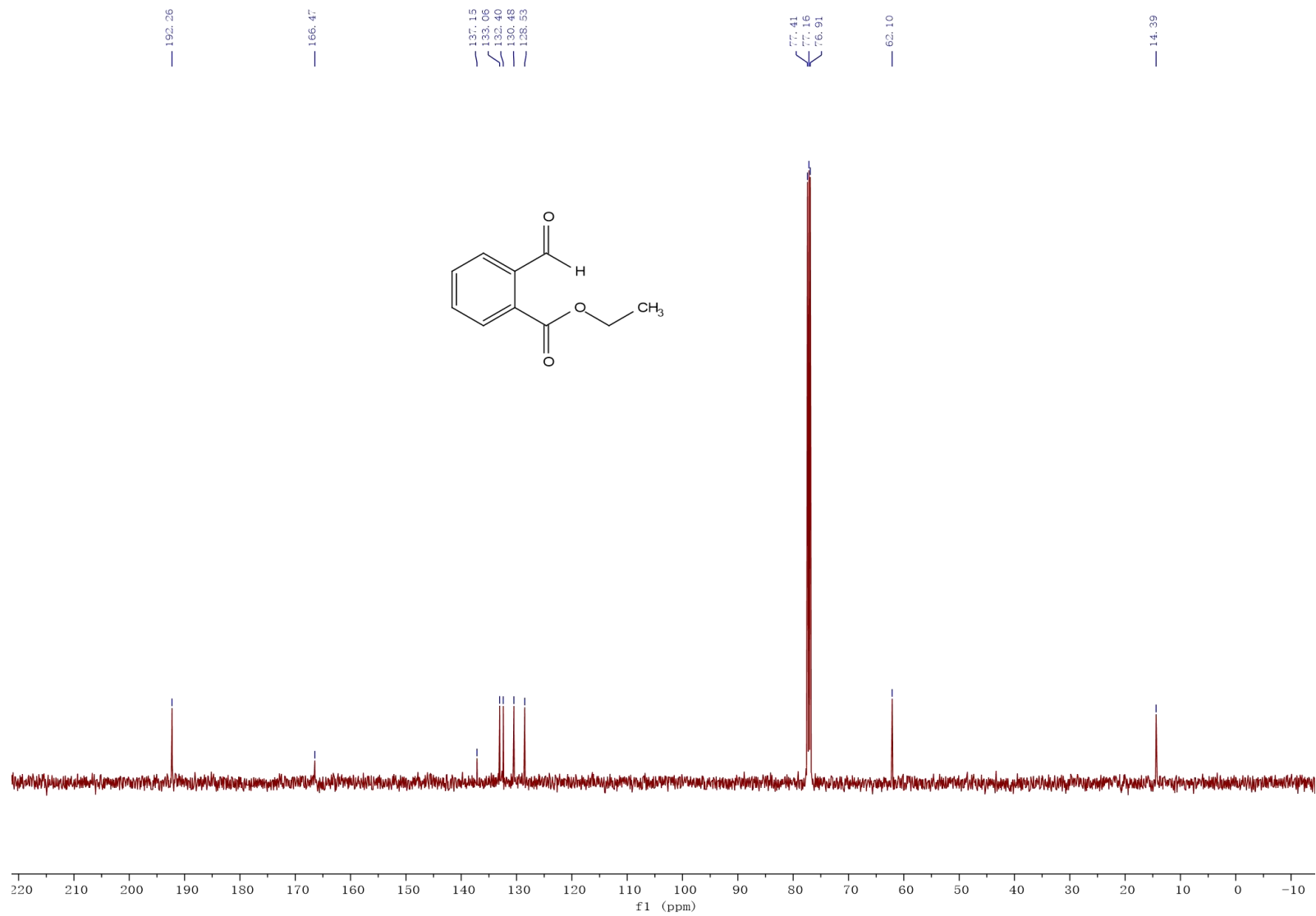


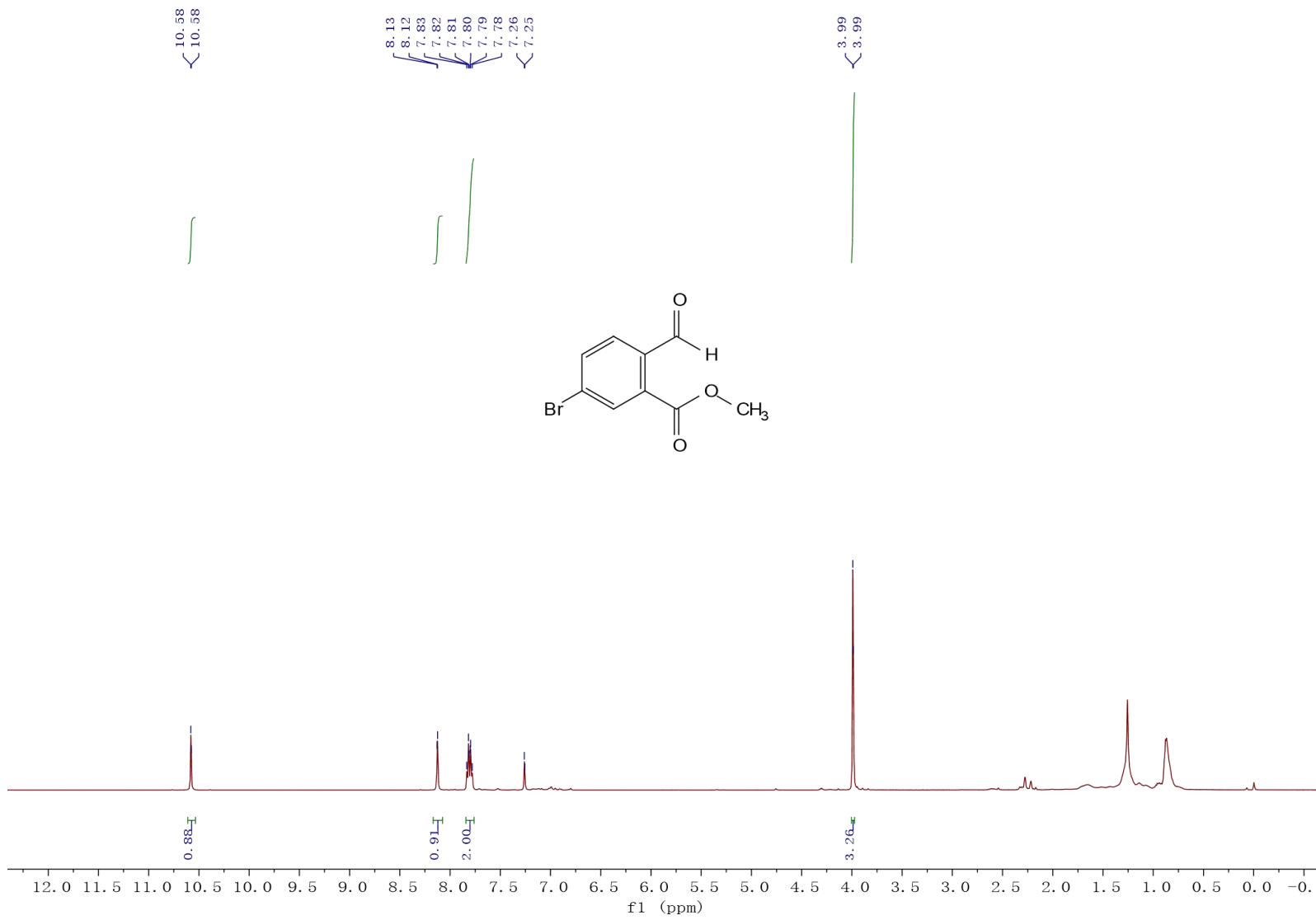


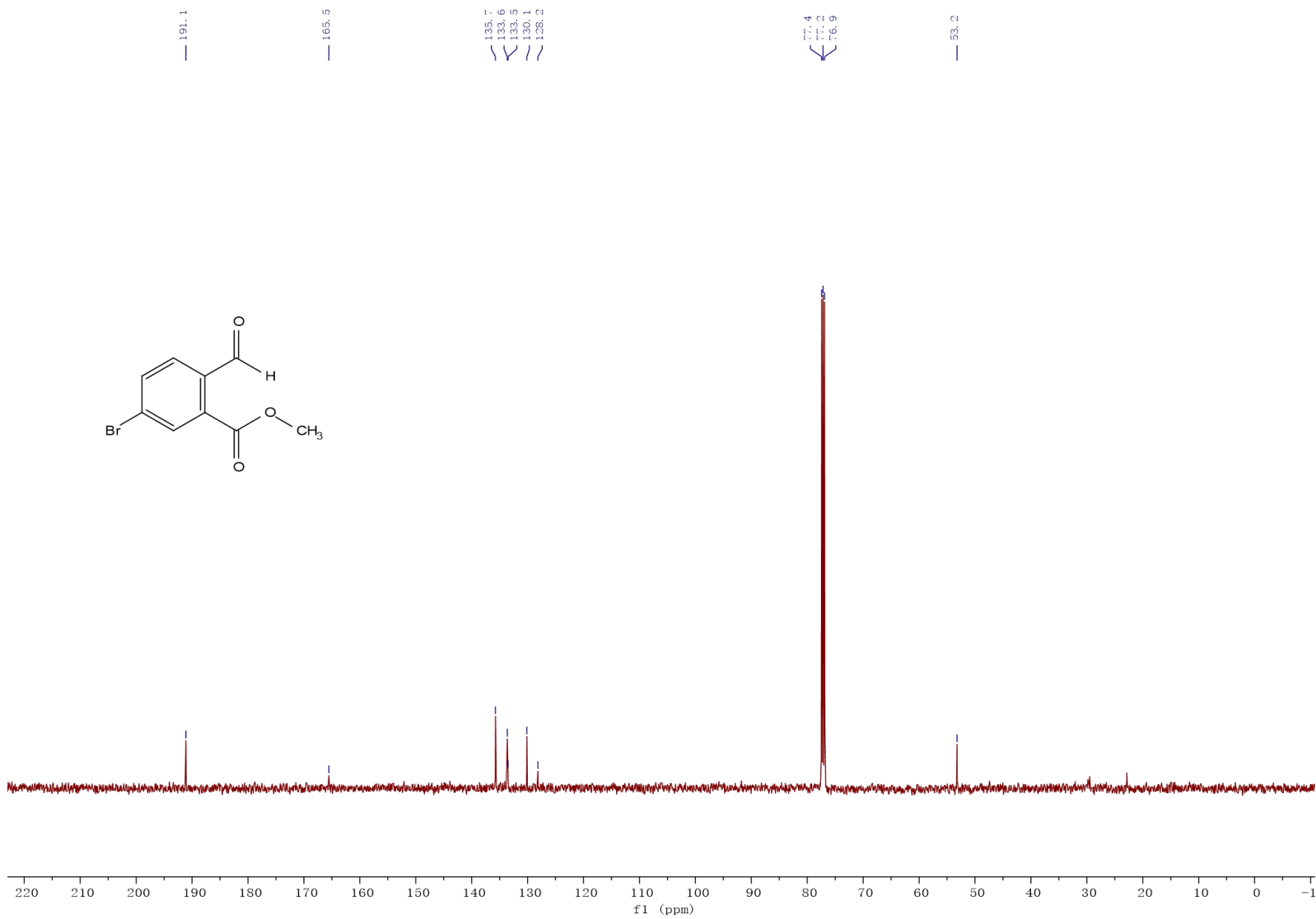
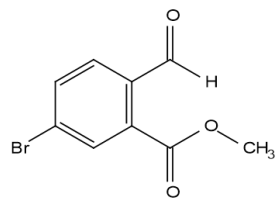


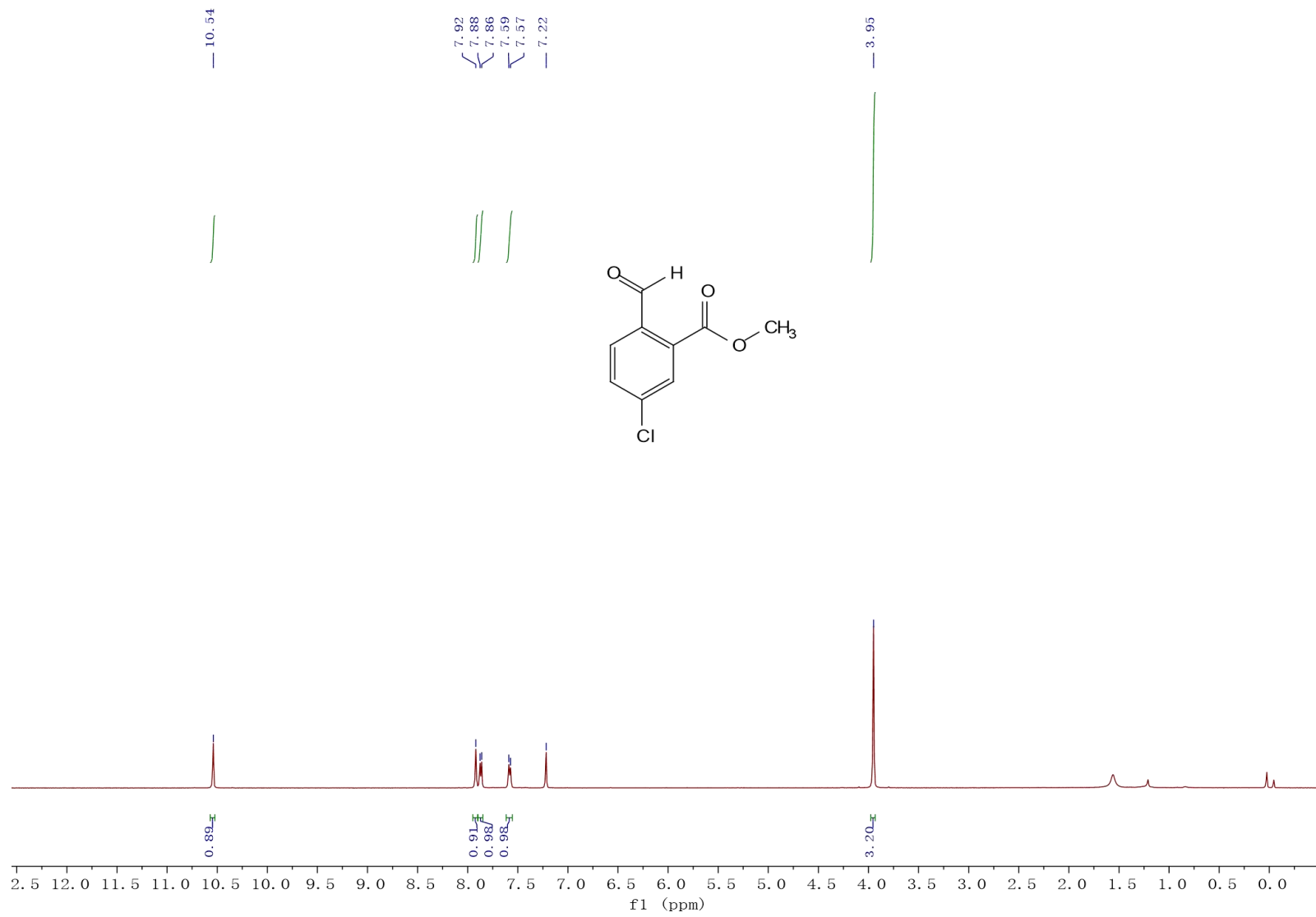


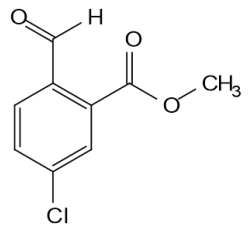
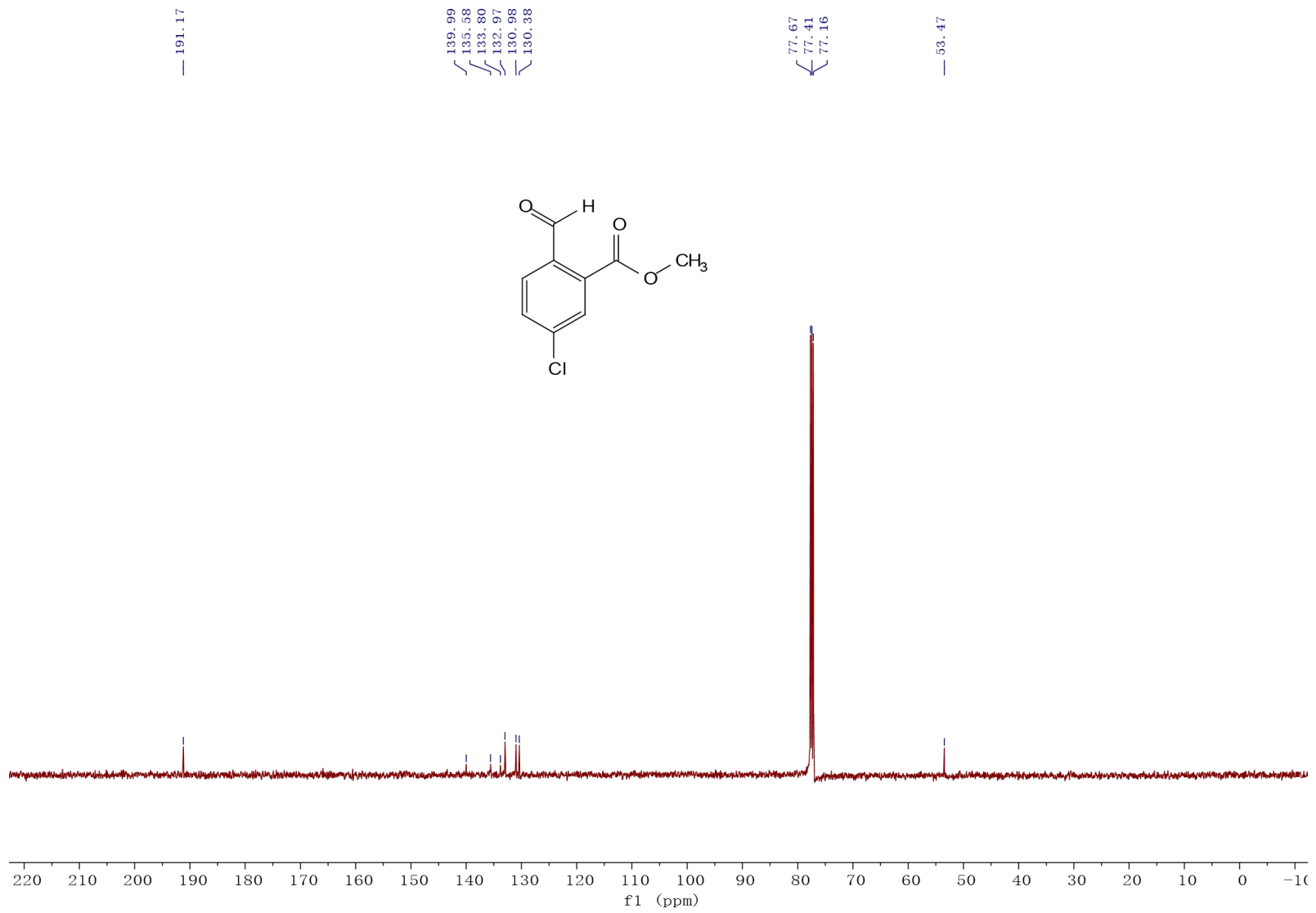


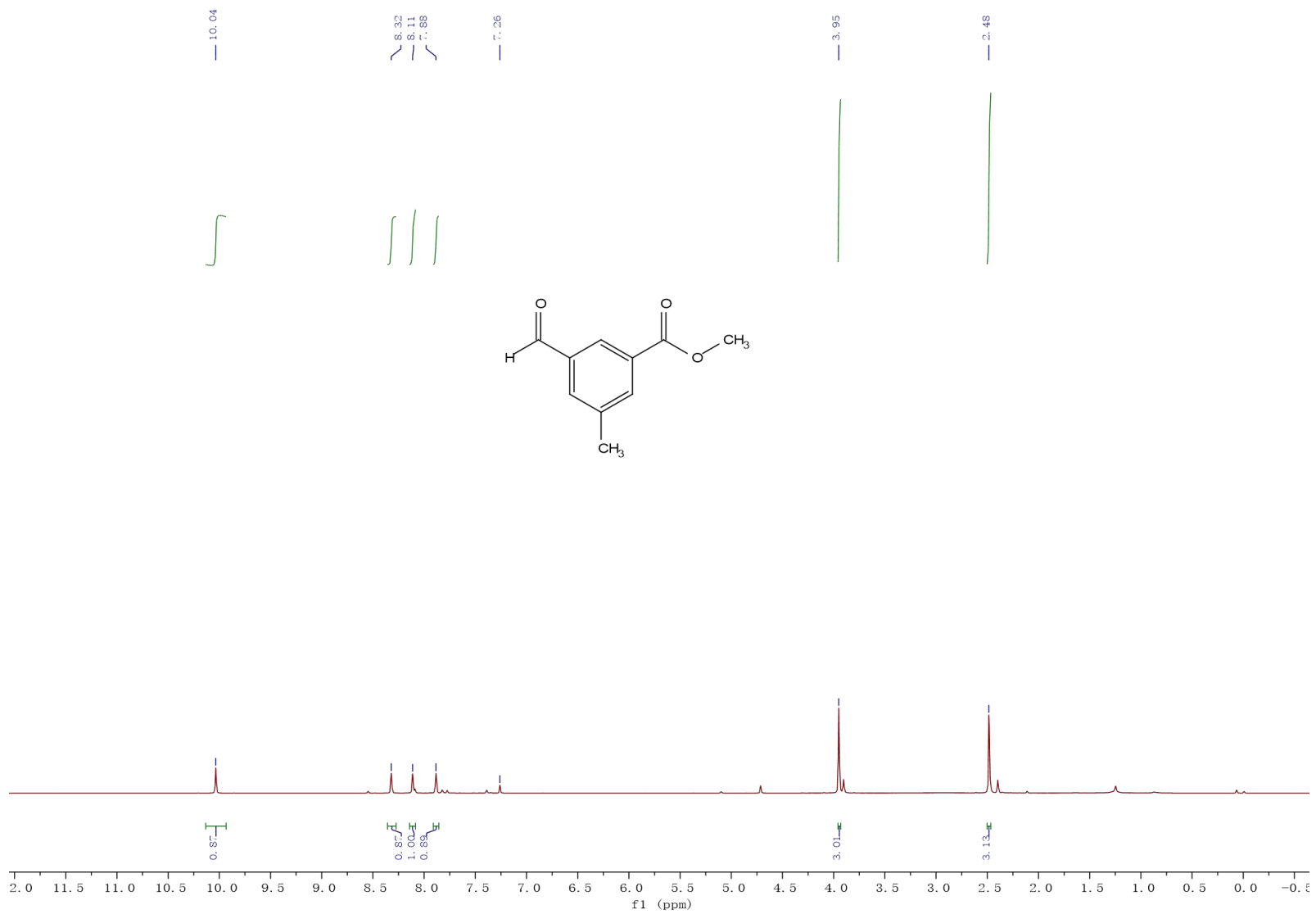


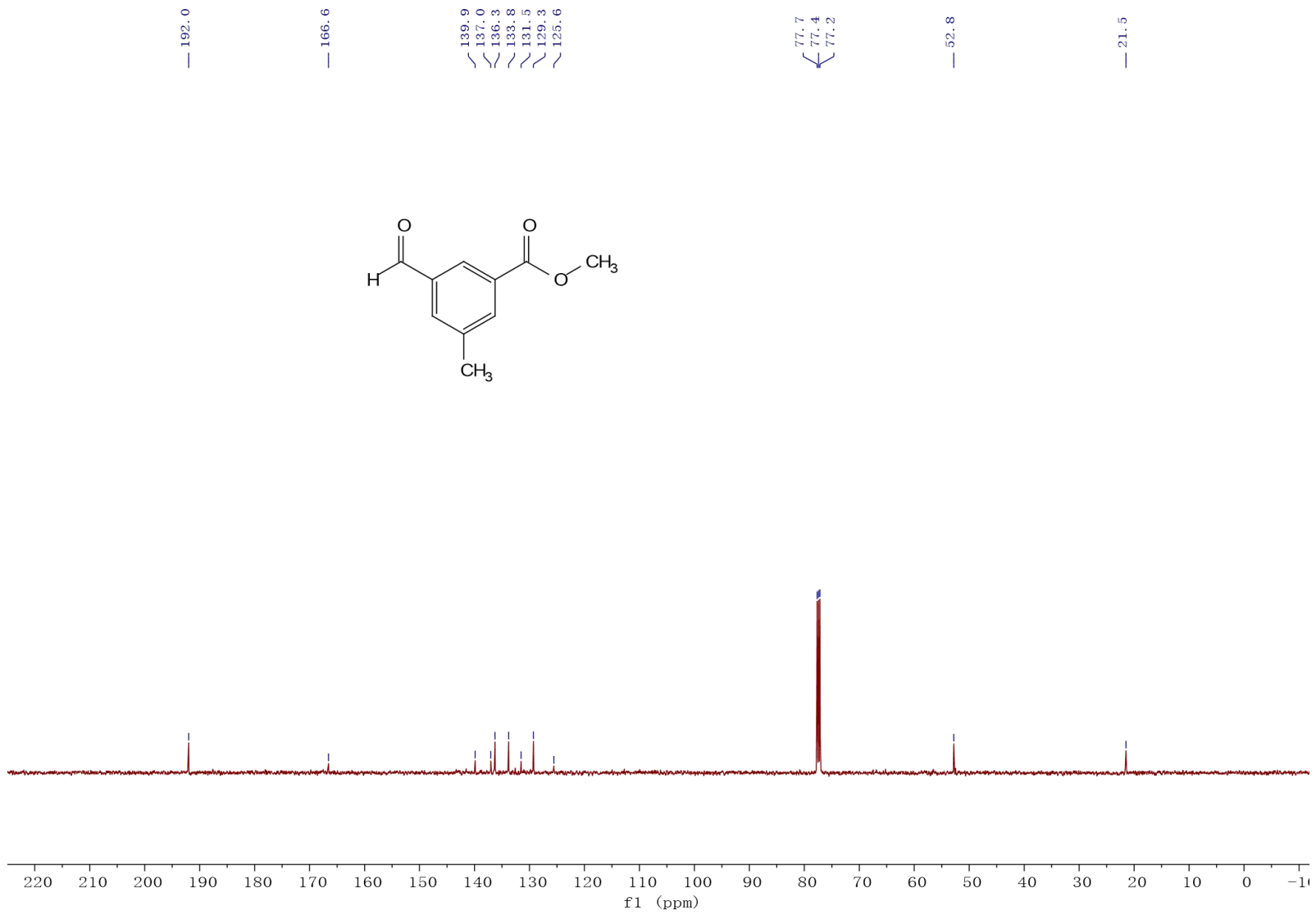


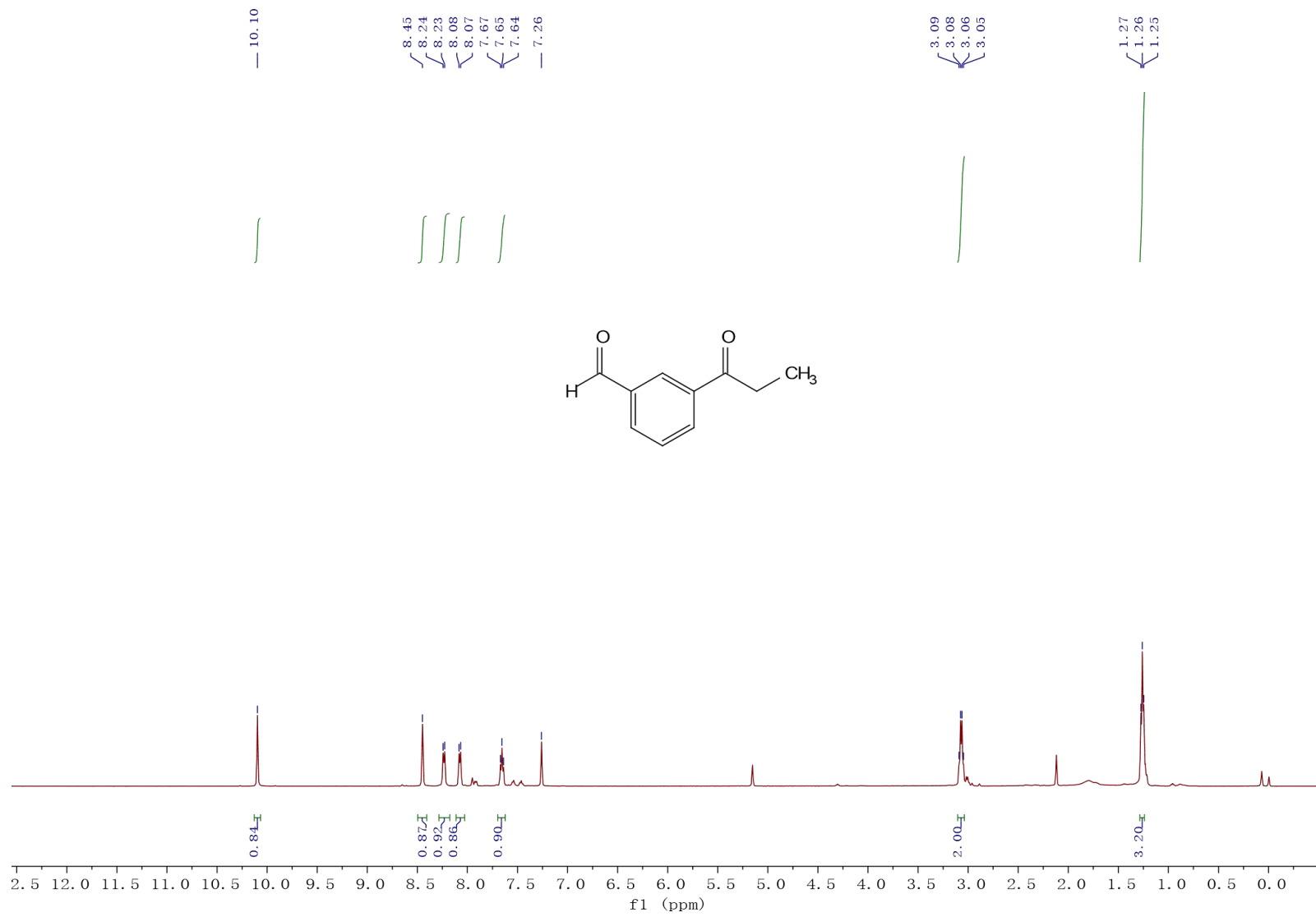


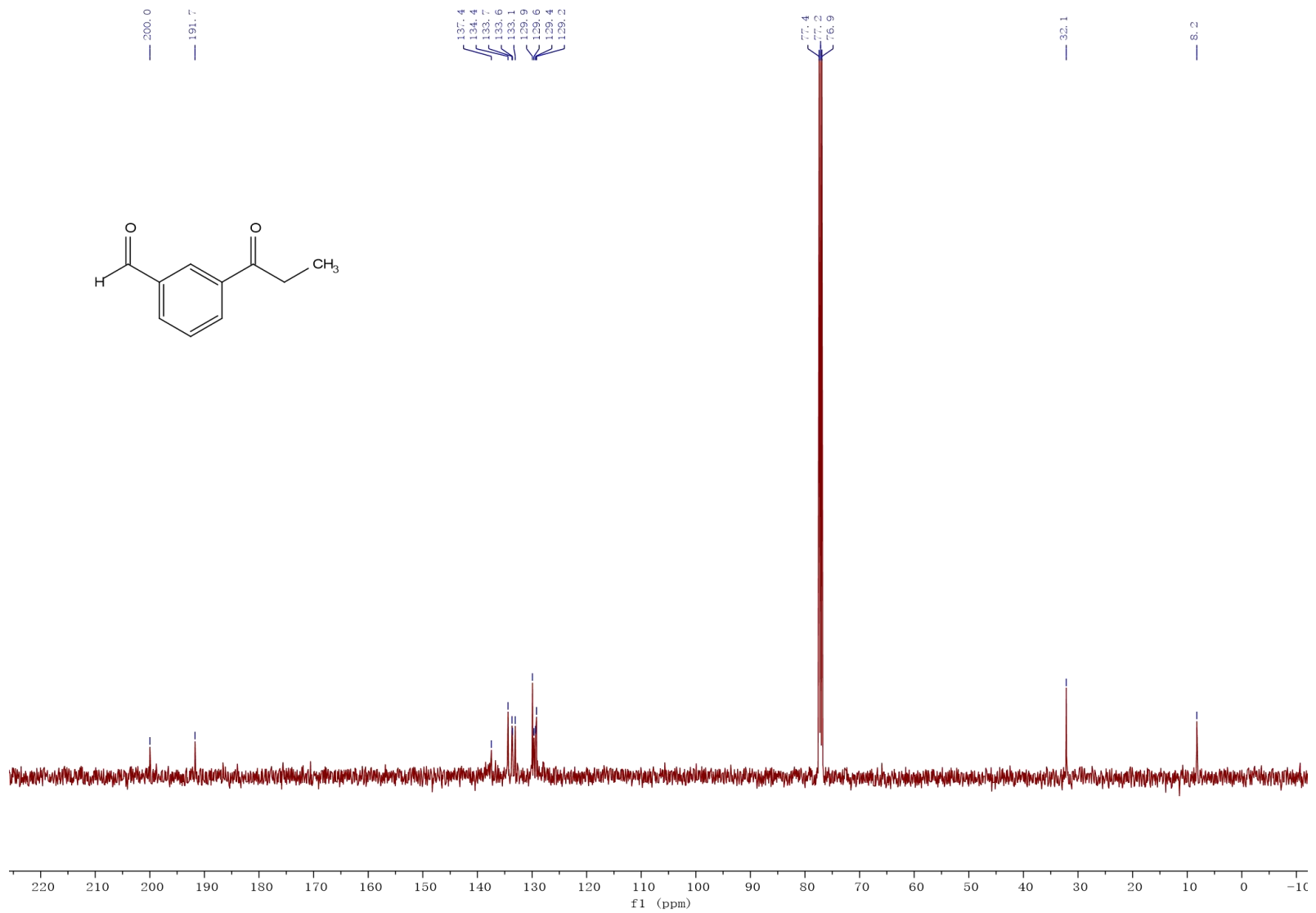




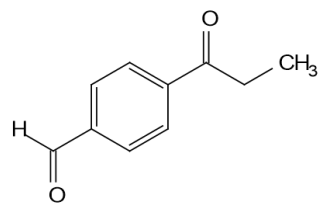


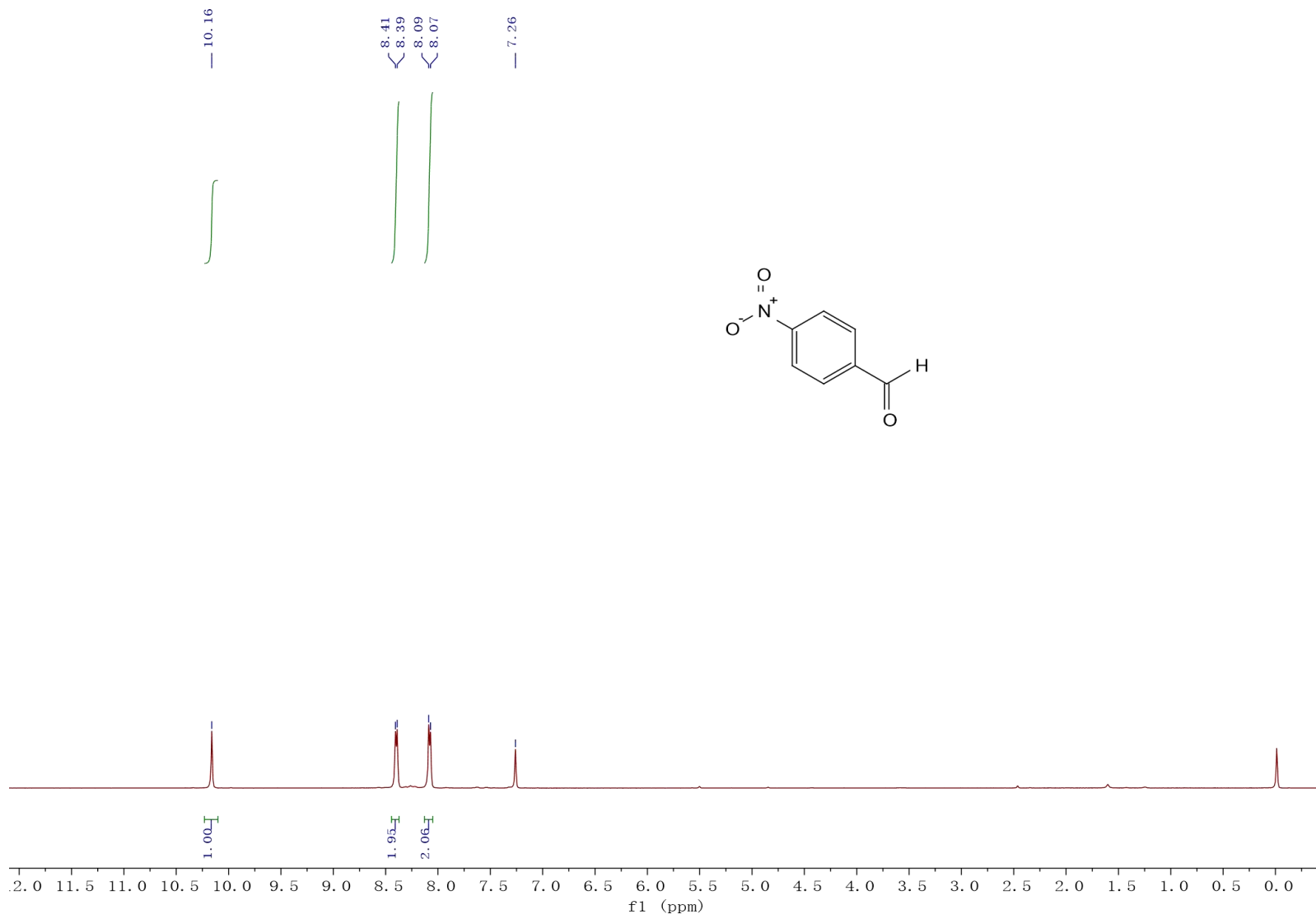


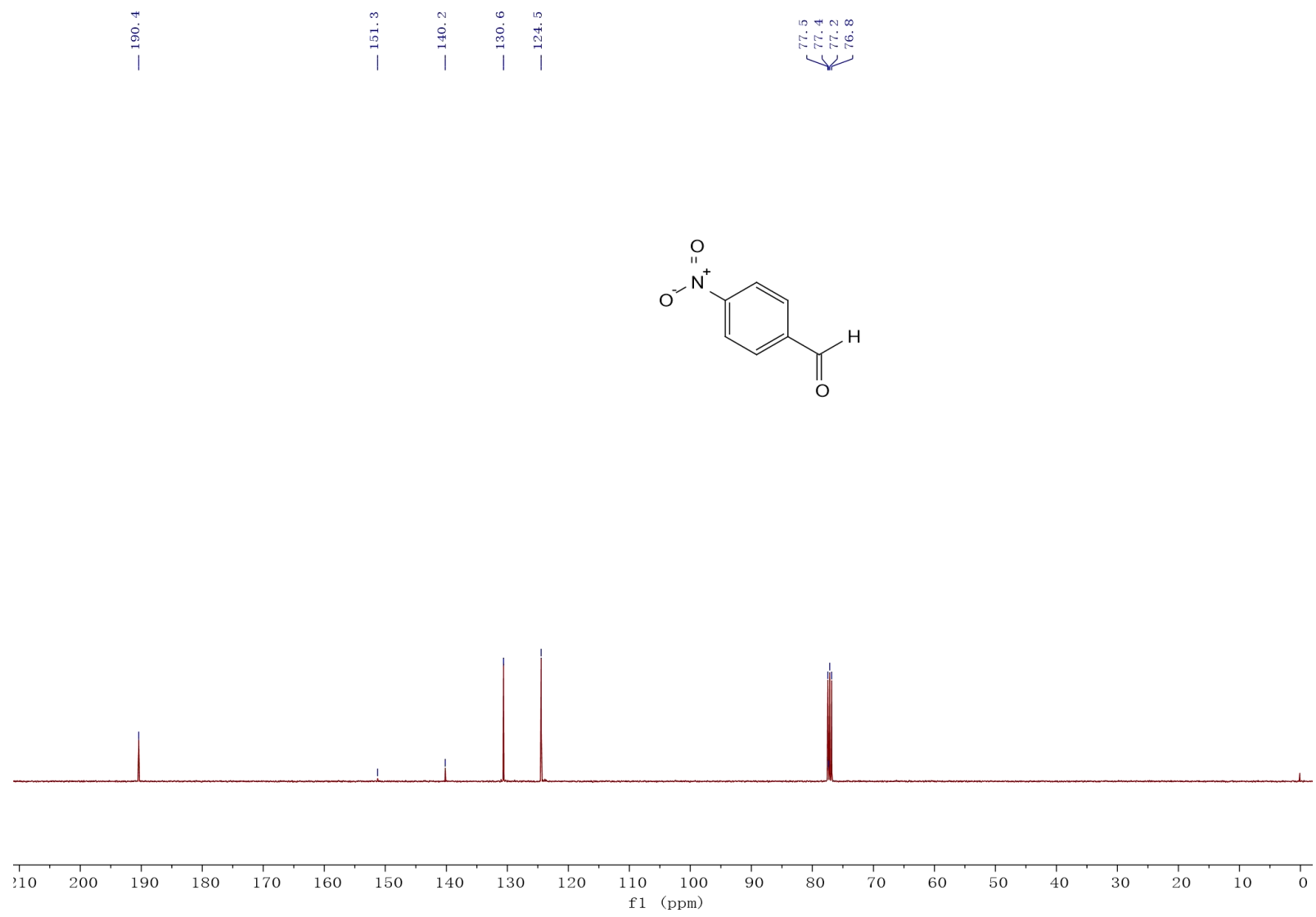


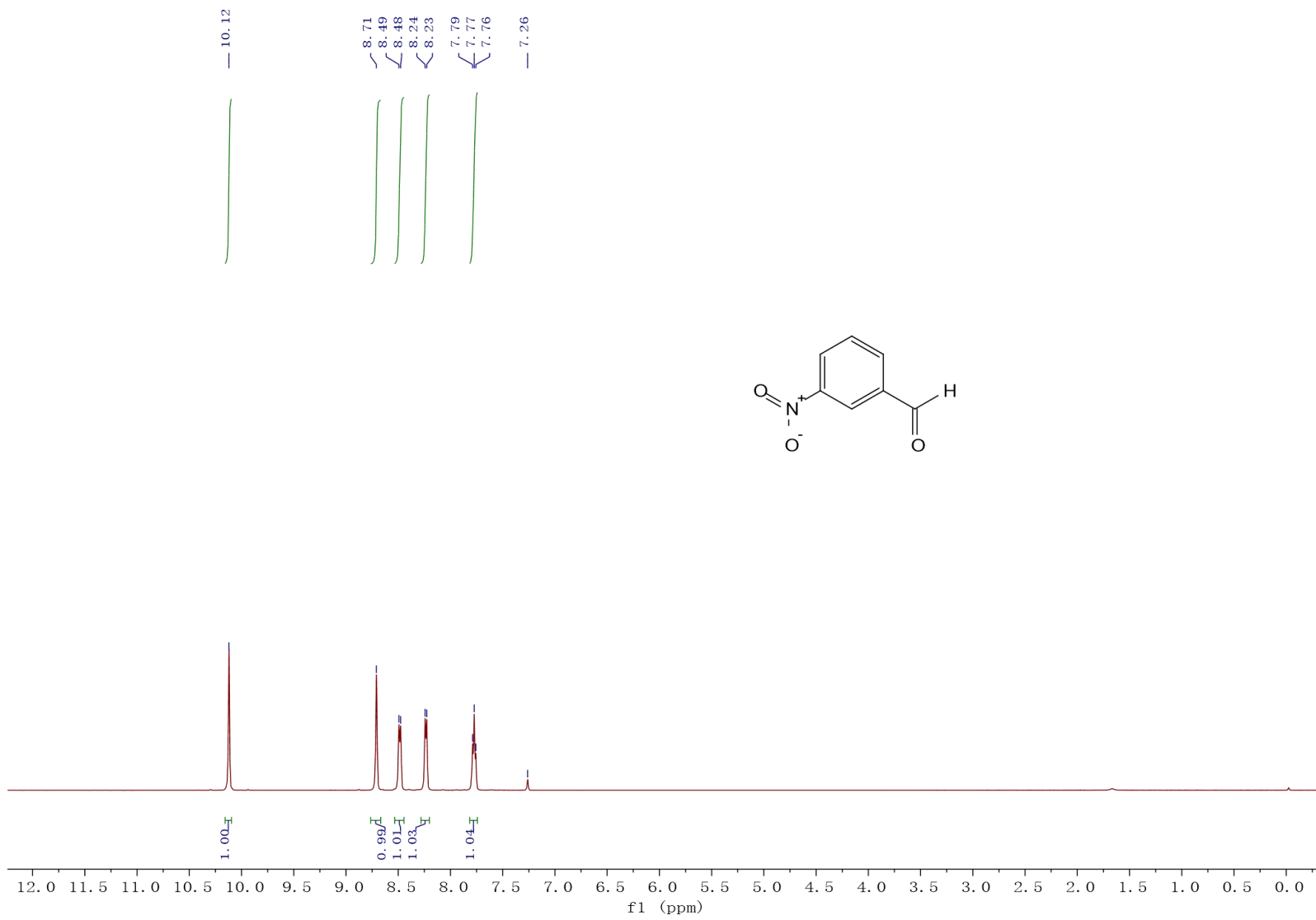


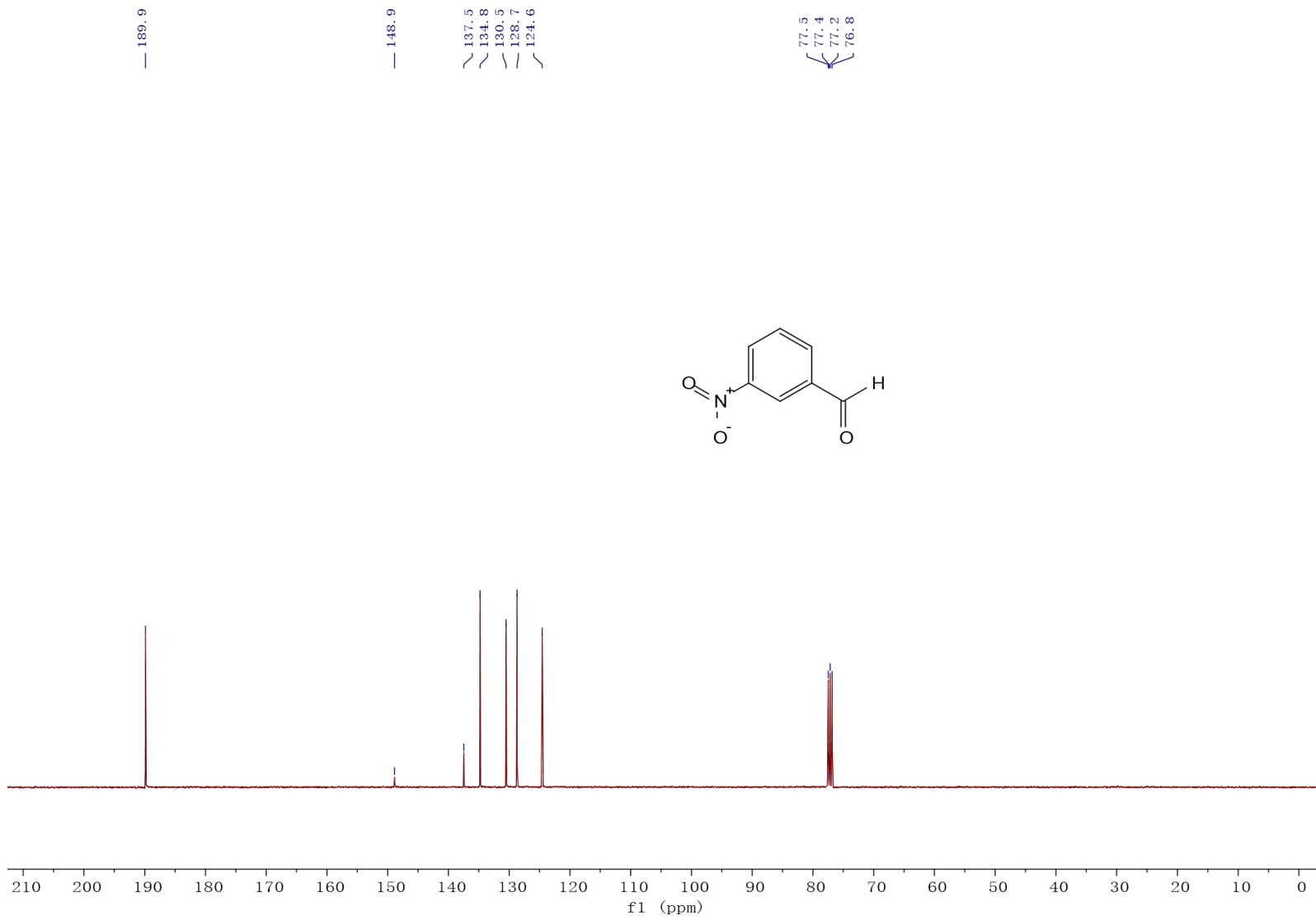


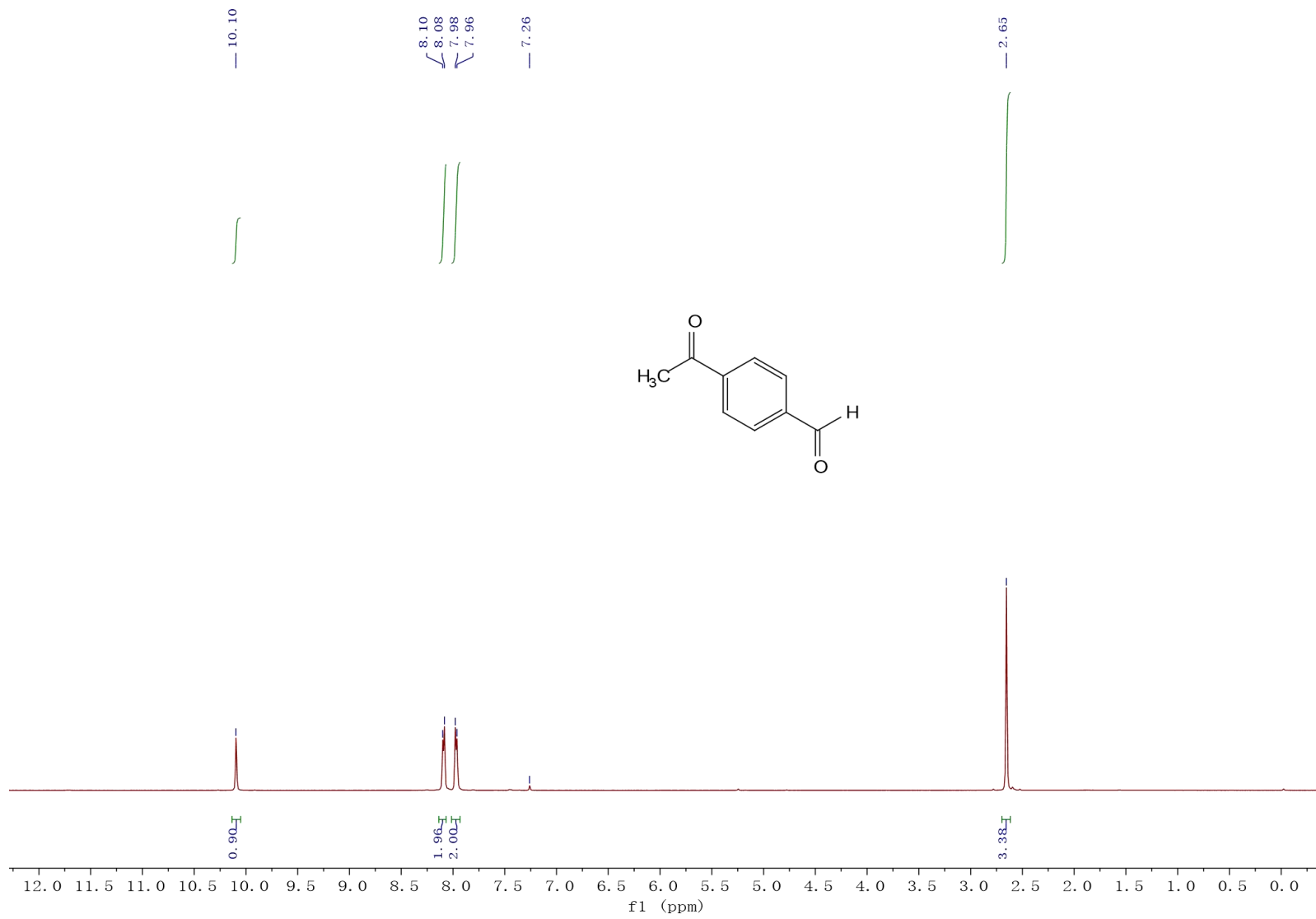


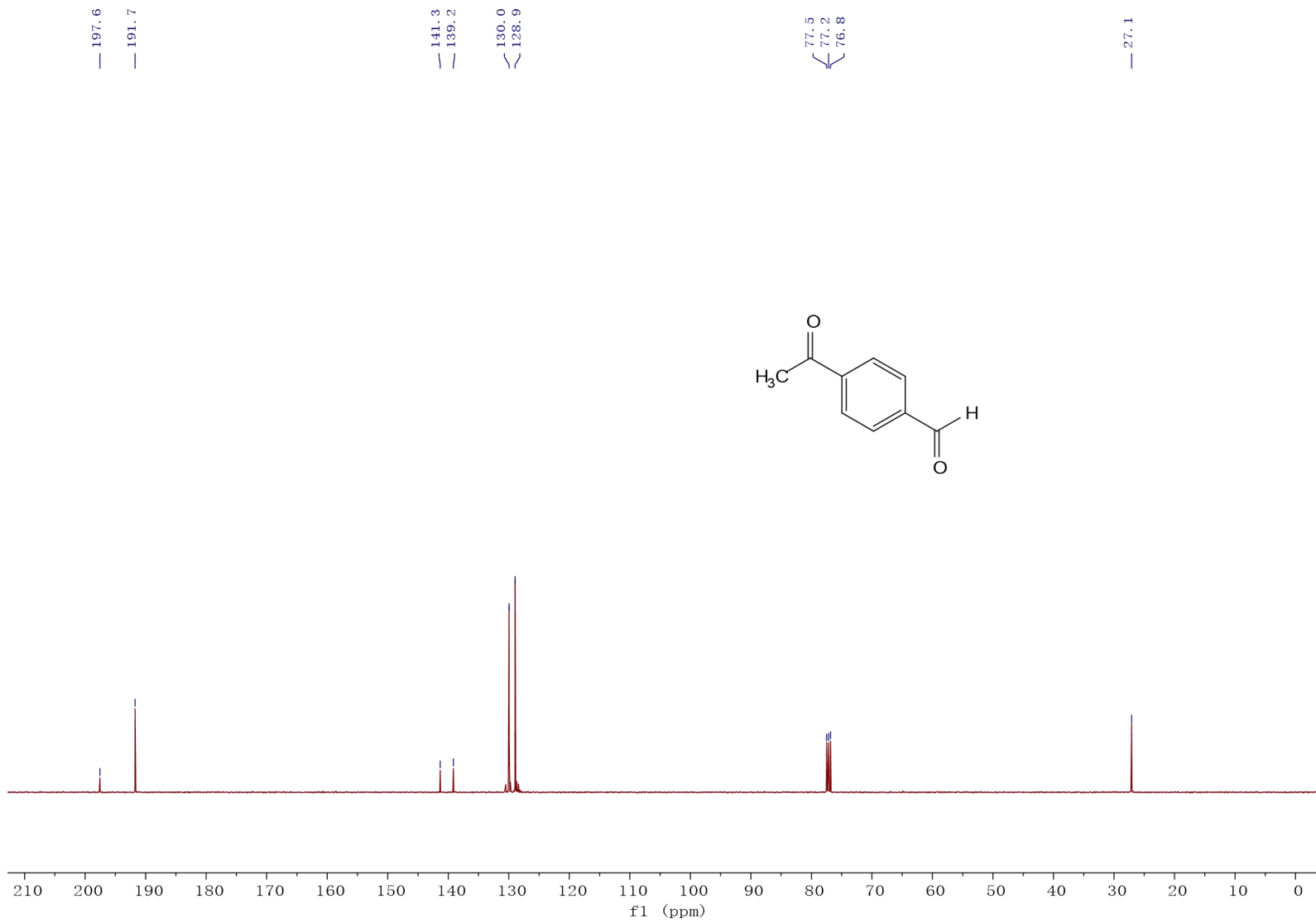








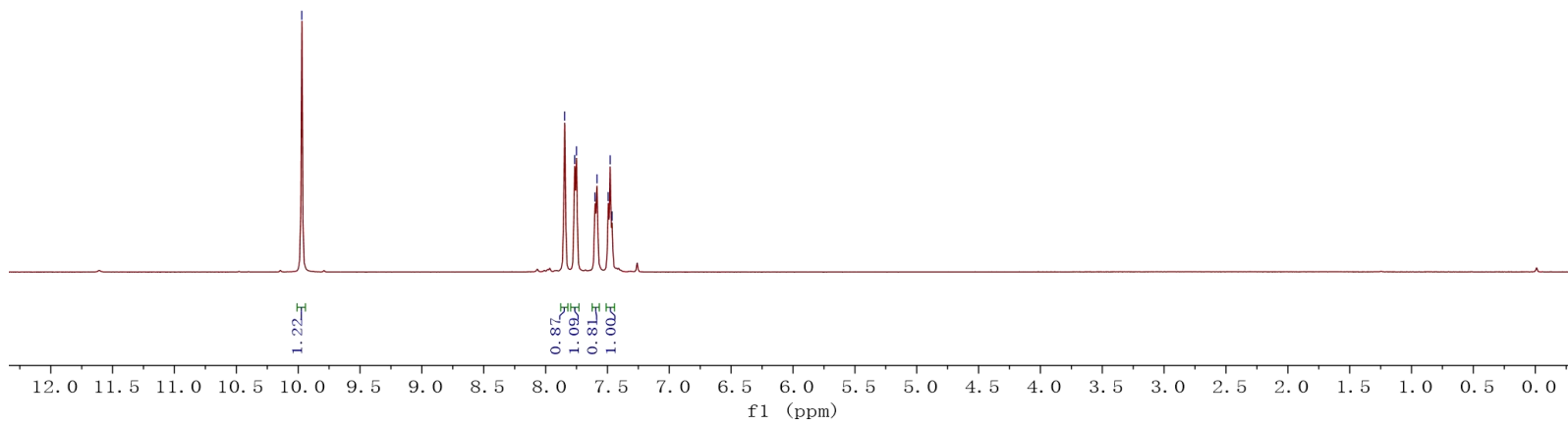
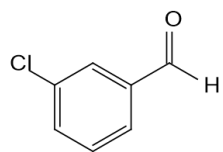




3-C1-20190614.1.1.1r

9.97

7.85
7.77
7.75
7.60
7.58
7.49
7.48
7.46

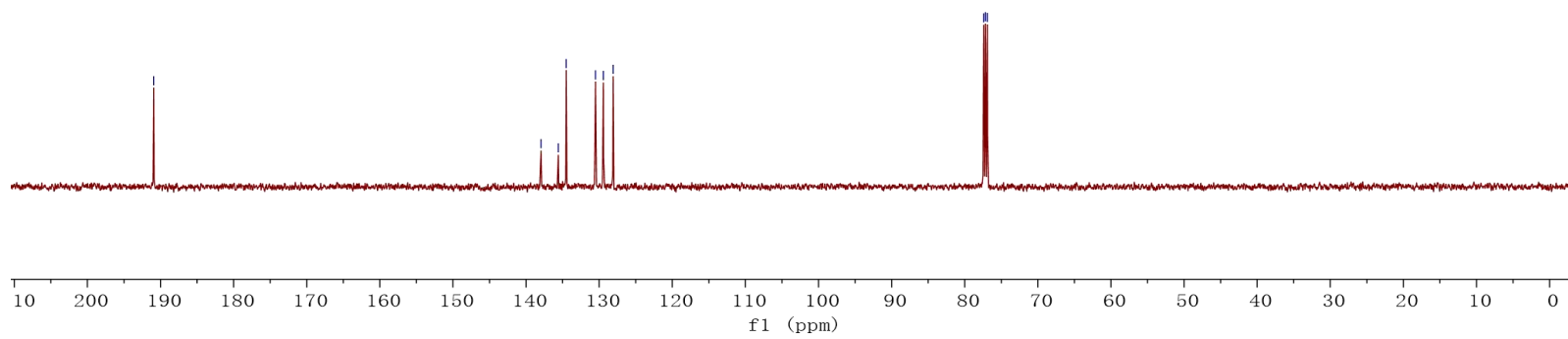
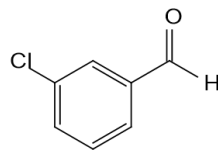


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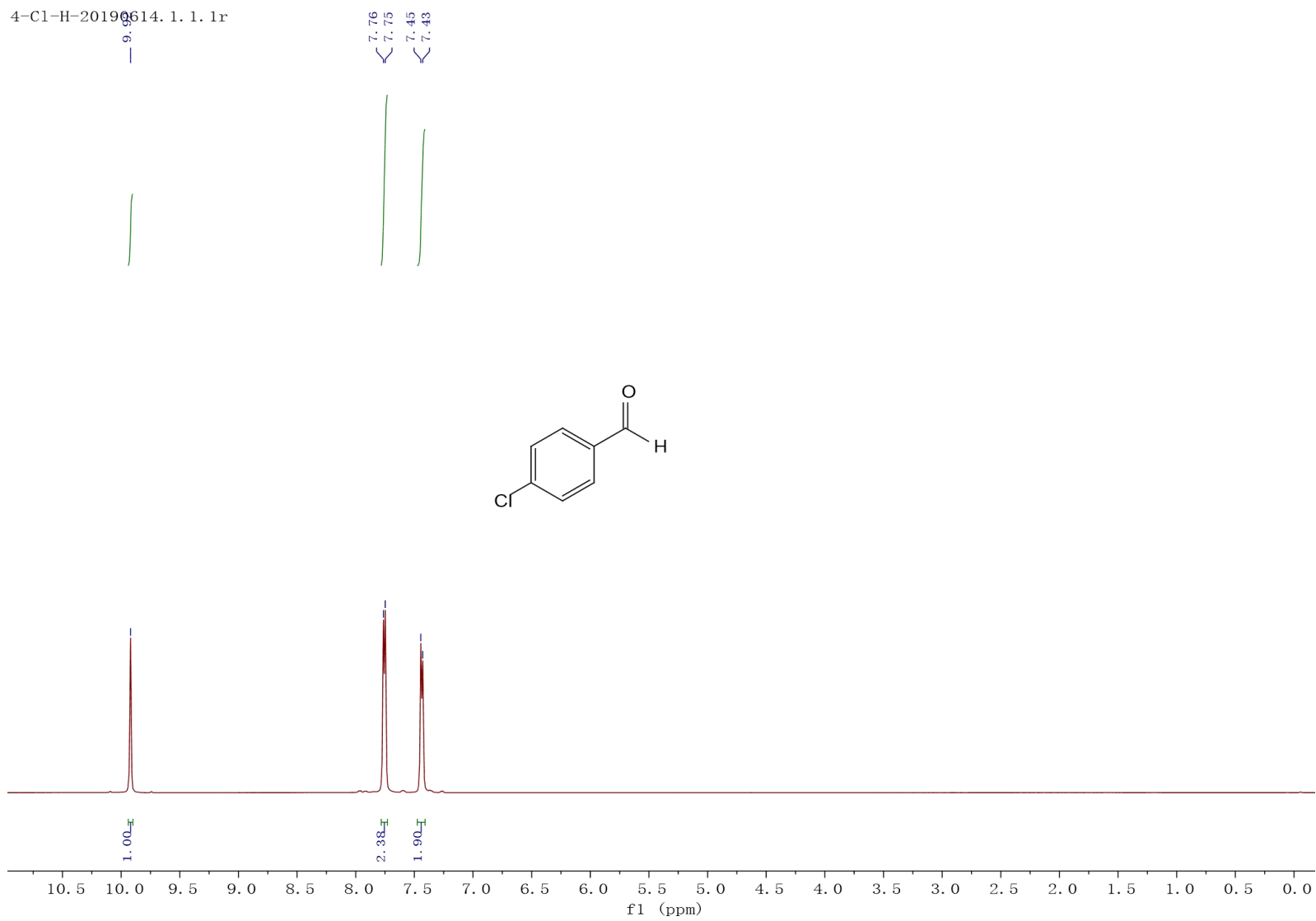
190.0

138.0
135.6
134.5
130.5
129.4
128.1

77.4
77.2
76.9



4-Cl-H-20190614. 1. 1. 1r



4-Cl-20190614.1.1r

190.3

140.8

134.7

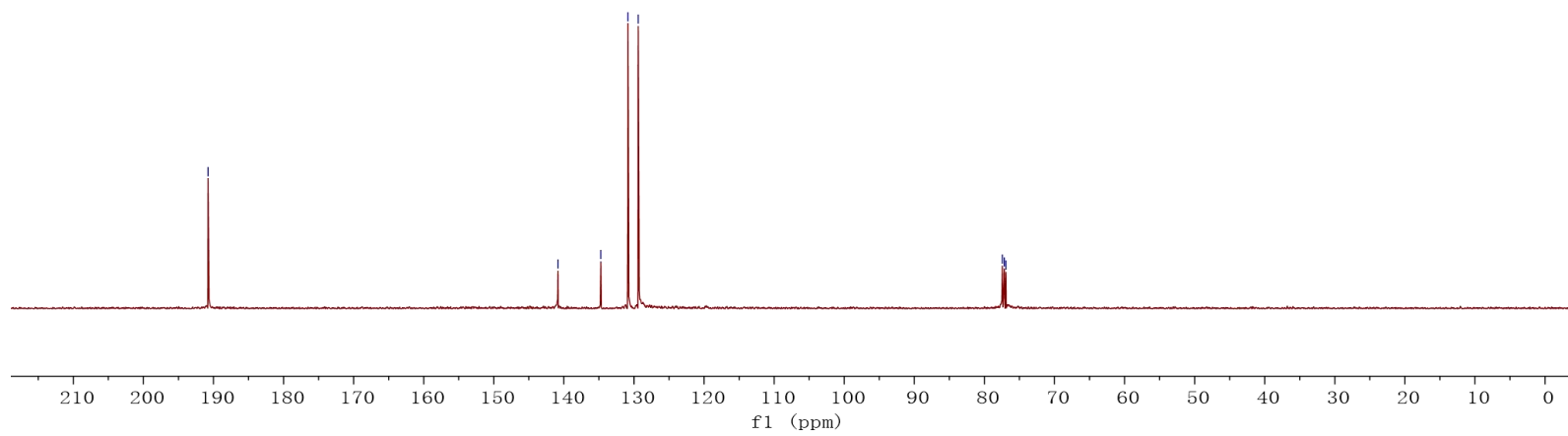
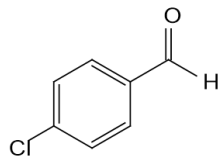
130.9

129.4

77.4

77.2

76.9



Br-c-20190614.1.1.1r

