

Supporting Information

Bioorganocatalyzed Green Friedländer : A versatile new Malic acid promoted solvent free approach to multisubstituted quinolines

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[#] *Equal Contribution*

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Experimental

General Remarks

All chemicals were reagent grade and purchased from Aldrich, Alfa Aesar, Merck, Spectrochem and Qualigens and were used without further purification. The reactions were monitored using pre-coated Aluminium TLC plates of silica gel G/UV-254 of 0.25 mm thickness (Merck 60 F-254). Column chromatography was performed using silica gel (60-120) and (100-200). NMR spectra were recorded on a Bruker Avance-II 400FT spectrometer at 400 MHz (^1H) and 100 MHz (^{13}C) in DMSO or CDCl_3 using TMS as an internal reference. Mass spectra (ESIMS) were obtained on a Waters UPLC-TQD mass spectrometer. IR spectra were recorded on a Thermo Scientific Nicolet iS5 FT-IR spectrometer. Elemental analyses were carried out in a Thermo Scientific (FLASH 2000) CHN Elemental Analyser. Melting points were determined by open glass capillary method and were uncorrected.

General Experimental Procedure^{abc}

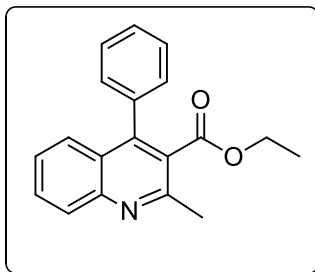
To a 50 mL round bottom flask were added *o*-acyl anilines (1 mmol), α -methylene ketone (1.1 mmol) and malic acid (0.5 mmol) and the resulting mixture was stirred at 55 °C under solvent free conditions. On completion of the reaction (TLC control), the reaction mixture was dissolved in EtOH (2mL) and cold water was added to it whence the solid product which separated out was filtered, washed with water and dried. The crude product was then recrystallized from a mixture of Et₂O/ hexane to obtain the pure quinolines.

^aIn those instances where required purity could not be achieved through recrystallization, column chromatography (100-200 mesh silica gel; EtOAc/Hexane) was performed to obtain the pure molecules.

^bIn case where quinolines were liquids, the reaction mixture was dissolved in EtOAc and washed with water. The EtOAc layer was separated and the aqueous fraction was extracted with EtOAc (3 x 3mL). The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo* to give the crude product which was subjected to column chromatography (100-200 mesh silica gel; EtOAc/Hexane) to afford the pure quinoline derivative.

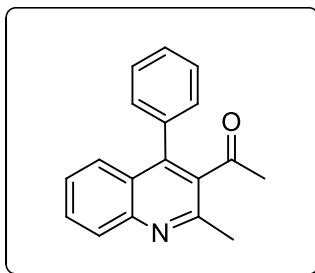
^cIn those cases where both the *o*-acyl aniline and α -methylene ketone were solids, a few drops of ethanol was added so as to obtain the reaction mixture in form of a paste.

Compound 3



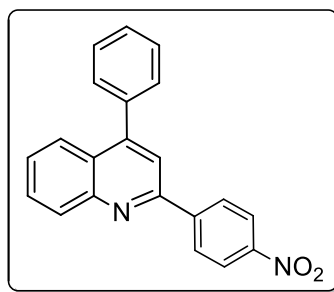
Yield: 96%, 279 mg; White solid; M.P.: 92-95 °C^{17b}; IR (KBr, cm⁻¹): 2913, 1753, 1682; ¹H NMR (400 MHz, CDCl₃) (δ, ppm): 8.09 (1H,d, J=8.4 Hz), 7.75-7.71 (1H, m), 7.59 (1H, d, J=8.3), 7.50-7.49 (3H,m), 7.46-7.42 (1H, m), 7.39-7.37 (2H,m), 4.08 (2H, q, J=7.1), 2.81 (3H, s), 0.97 (3H, t, J=7.1) ; ¹³C NMR (CDCl₃) (δ, ppm): 168.4, 154.6, 147.7, 146.2, 135.7, 130.2, 129.4, 128.8, 128.4, 128.2, 127.4, 126.5, 126.4, 125.1, 61.3, 23.8, 13.6; MS (ESI): *m/z* 291; found 292 [M+H]⁺; Anal calcd for C₁₉H₁₇NO₂: C 78.33; H 5.88; N 4.81; Found C 78.36, H 5.91, N 4.75%.

Compound 6b



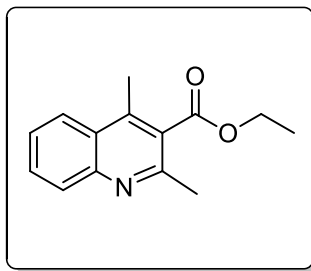
Yield: 90%, 235 mg; White solid; M.P.: 105-110 °C^{17a}; IR (KBr, cm⁻¹): 3021, 1721, 1590; ¹H NMR (300 MHz, CDCl₃) (δ, ppm): 8.08 (1H,d, J=8.4 Hz), 7.75-7.70 (1H, m), 7.62 (1H, d, J=8.4), 7.52-7.50 (3H,m), 7.47-7.42 (1H, m), 7.37-7.34(2H,m), 2.70 (3H, s), 2.00 (3H, s); ¹³C NMR (CDCl₃) (δ, ppm): 206.0, 153.7, 147.6, 144.1, 135.3, 134.9, 130.3, 130.2, 129.1, 129.0, 128.9, 126.7, 126.3, 125.2, 32.1, 24.0; MS (ESI): *m/z* 261; found 262 [M+H]⁺; Anal calcd for C₁₈H₁₅NO: C, 82.73; H, 5.79; N, 5.36; Found C 82.77, H, 5.74, N, 5.32%.

Compound 6d



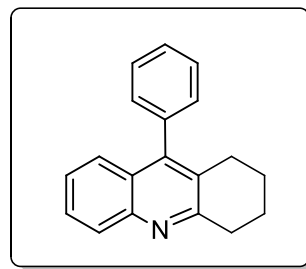
Yield: 72%, 234 mg; Pale yellow solid; M.P.: 160-165 °C^{20b}; IR (KBr, cm⁻¹): 3043, 3025, 1610, 1500; ¹H NMR (300 MHz, CDCl₃) (δ, ppm): 8.09 (1H,d, J=8.4 Hz), 7.99-7.90 (5H, m), 7.60 (1H, d, J=8.1), 7.49-7.44 (2H,m), 7.41 (6H, s); ¹³C NMR (CDCl₃) (δ, ppm): 154.0, 149.9, 148.8, 148.3, 145.4, 137.9, 130.4, 130.1, 129.6, 128.8, 128.3, 127.4, 126.2, 125.8, 124.0, 119.1 ; MS (ESI): *m/z* 326; found 327 [M+H]⁺; Anal calcd for C₂₁H₁₄N₂O₂: C, 77.29; H, 4.32; N, 8.58; Found C 77.25, H, 4.30, N, 8.61 %

Compound 6h



Yield: 94%, 215 mg; Yellow oil; IR (KBr, cm^{-1}): 3021, 1721, 1591, 1300; ^1H NMR (400 MHz, CDCl_3) (δ , ppm): 8.02-7.98 (2H,m), 7.71-7.67 (1H, m), 7.54-7.50 (1H, m), 4.48 (2H, q, $J=7.1$), 2.70 (3H, s), 2.64 (3H, s) ; ^{13}C NMR (CDCl_3) (δ , ppm): 169.1, 154.2, 147.0, 141.3, 129.9, 129.2, 127.9, 126.2, 125.7, 123.9, 61.6, 23.7, 15.6, 14.2; MS (ESI): m/z 229; found 230 $[\text{M}+\text{H}]^+$; Anal calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_2$: 73.34; H, 6.59; N, 6.11; Found : 73.30; H, 6.56; N, 6.15.

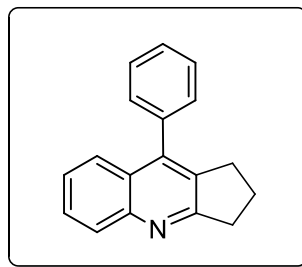
Compound 8a



Yield: 98%, 254 mg; White solid; M.P.: 138-142 $^{\circ}\text{C}^{17b}$; IR (KBr, cm^{-1}): 3084, 1561, 1476, 1371, 1195; ^1H NMR (300 MHz, CDCl_3) (δ , ppm): 8.01 (1H, d, $J=8.4$ Hz), 7.62-7.57 (1H, m), 7.54-7.52 (1H, m), 7.50-7.43 (2H, m), 7.32-7.31 (2H, m), 7.27-7.22 (2H, m), 3.20 (2H, t, $J=6.6$ Hz), 2.60 (2H, t, $J=6.6$ Hz), 2.01-1.92 (2H, m), 1.82-1.74 (2H, m) ; ^{13}C NMR (CDCl_3) (δ , ppm): 159.2, 146.7,

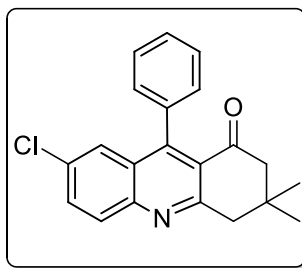
146.4,137.3, 129.2, 128.8, 128.5, 128.4, 127.9, 126.8, 125.9, 125.5,34.4, 28.2, 23.2, 23.1; MS (ESI): m/z 259; found 260 $[M+H]^+$;
Anal calcd for $C_{19}H_{17}N$: C, 87.99; H, 6.61; N, 5.40; Found C, 87.96; H, 6.59; N, 5.45.

Compound 8b



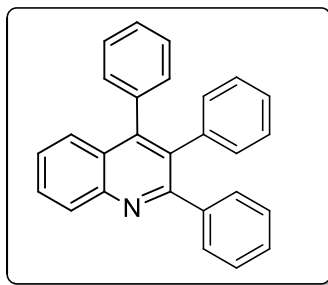
Yield: 96%, 235 mg; White solid; M.P.: 132-136 °C^{17b}; IR (KBr, cm^{-1}): 3070, 2911, 1565, 1204; ¹H NMR (400 MHz, $CDCl_3$) (δ , ppm): 8.08-8.05 (1H, m), 7.63-7.59 (2H, m), 7.53-7.43 (3H, m), 7.38-7.35 (3H, m), 3.23 (2H, t, $J=7.6$ Hz), 2.90 (2H, t, $J=7.4$ Hz), 2.15 (2H, p, $J=7.5$); ¹³C NMR ($CDCl_3$) (δ , ppm): 167.4, 147.9, 142.6, 136.7, 133.6, 129.3, 128.8, 128.5, 128.2, 127.9, 126.2, 125.6, 125.4, 35.2, 30.3, 23.5; MS (ESI): m/z 245; found 246 $[M+H]^+$; Anal calcd for $C_{18}H_{15}N$: C, 88.13; H, 6.16; N, 5.71; Found 88.17; H, 6.20; N, 5.74 %

Compound 8f



Yield: 78%, 261 mg; Yellow solid; M.P.: 213-217 °C^{20a}; IR (KBr, cm⁻¹): 3071, 2870, 1560; ¹H NMR (400 MHz, CDCl₃) (δ, ppm): 7.91 (1H, d, J= 8.9 Hz), 7.60 (1H, dd, J= 8.9, 2.2 Hz), 7.46-7.41 (3H, m), 7.34 (1H, d, J= 2.2 Hz), 7.09-7.06 (2H, m), 3.17 (2H, s), 2.48 (2H, s), 1.07 (6H, s); ¹³C NMR (CDCl₃) (δ, ppm): 197.7, 161.4, 150.1, 147.4, 136.8, 132.5, 132.4, 130.2, 128.3, 128.2, 128.0, 127.9, 126.7, 123.3, 54.1, 48.3, 32.2, 28.3; MS (ESI): *m/z* 335; found 336 [M+H]⁺; Anal calcd for C₂₁H₁₈ClNO: C, 75.11; H, 5.40; N, 4.17; Found C, 75.07; H, 5.38; N, 4.21

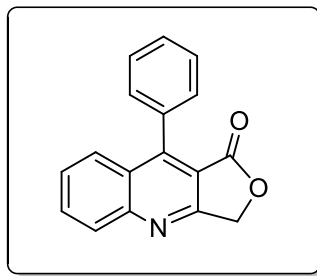
Compound 10



To a 50 mL round bottom flask was added 2-aminobenzophenone (1 mmol), 2-phenyl acetophenone (1.1 mmol) and malic acid (0.8 mmol) and the resulting mixture was stirred at 80 °C under solvent free conditions. On completion of the reaction (6.5h, TLC control),

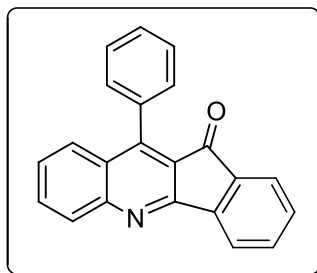
the reaction mixture was dissolved in EtOH (2mL) and cold water was added to it whence the solid product which separated out was filtered, washed with water and dried. The crude product was chromatographed (hexane/ethyl acetate, 19:1) to yield the pure 2, 3, 4-triphenyl quinoline (**10**) as a white solid. Yield: 76%, 271 mg; M.P.: 190-195°C^{5c}; IR (KBr, cm⁻¹):2923, 1549, 1480, 1433; ¹H NMR (400 MHz, CDCl₃) (δ, ppm): 8.27-8.24 (1H, m), 7.74-7.70 (1H, m), 7.59-7.57 (1H, m), 7.47-7.43 (1H, m), 7.39-7.36 (2H, m), 7.28-7.25 (3H, m), 7.22-7.19 (3H, m), 7.14-7.12 (2H, m), 7.00-6.99 (3H, m), 6.90-6.87 (2H, m); ¹³C NMR (CDCl₃) (δ, ppm): 159.0, 147.6, 147.3, 141.1, 138.3, 136.9, 132.9, 131.3, 130.3, 129.9, 129.7, 129.3, 127.8, 127.69, 127.61, 127.3, 127.2, 126.68, 126.64, 126.5,126.3; MS (ESI): *m/z* 357; found 358 [M+H]⁺; Anal calcd for C₂₇H₁₉N: C 90.72 , H 5.36, N 3.92 %; Found C 90.70, H 5.41, N 3.88%.

Compound 12



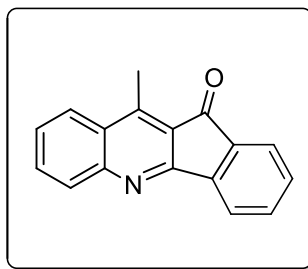
To a 50 mL round bottom flask were added 2-aminobenzophenone (1 mmol), tetronic acid (1.1 mmol) and malic acid (0.65 mmol) and the resulting mixture was stirred at 70 °C under solvent free conditions. On completion of the reaction (3.5h, TLC control), the crude product was then recrystallized from a mixture of Et₂O/hexane to obtain the pure furoquinoline derivative **12** as a white solid. Yield 81%, 211 mg ; M.P.: 193-197 °C²⁹ IR (KBr, cm⁻¹): 3266, 1788, 1646; ¹H NMR (300 MHz, CDCl₃) (δ, ppm): 8.2 (2H, d, J= 8.4), 7.92-7.87 (2H, m), 7.61-7.57 (4H, m), 7.47-7.44 (2H, m), 5.44 (2H, s); ¹³C NMR (CDCl₃) (δ, ppm): 168.0, 163.7, 151.6, 151.3, 132.7, 131.7, 129.9, 129.6, 129.4, 128.4, 128.2, 127.5, 127.1, 113.6, 69.7; MS (ESI): *m/z* 261; found 262 [M+H]⁺, Anal calcd for C₁₇H₁₁NO₂: C,78.15; H, 4.24; N, 5.36;Found C,78.19; H, 4.25; N, 5.38%.

Compound 14

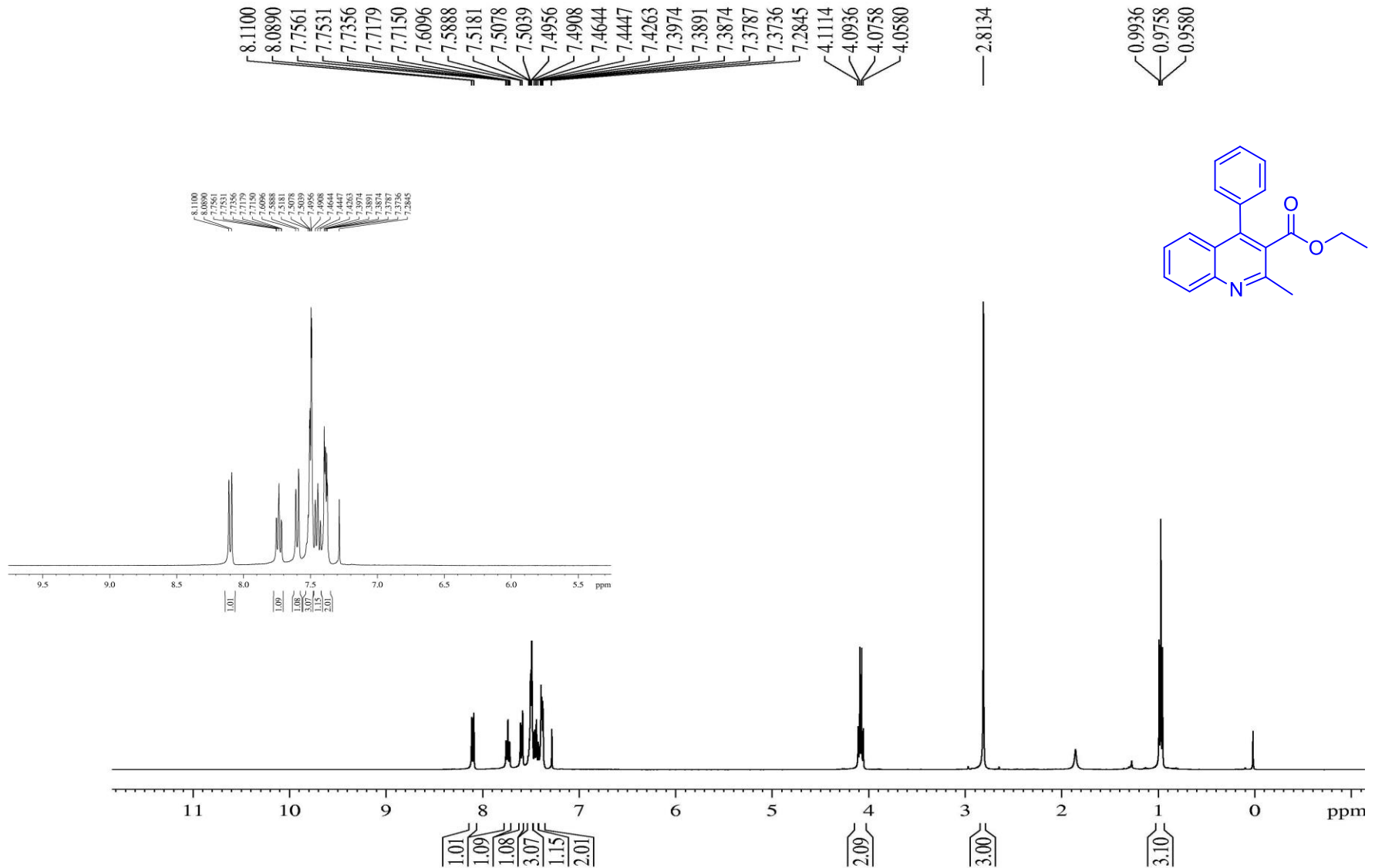


To a 50 mL round bottom flask were added 2-aminobenzophenone or 2- aminoacetophenone (1 mmol), 1, 3-Indanedione (1.1 mmol) and malic acid (0.65 mmol) and the resulting mixture was stirred at 70 °C under solvent free conditions. On completion of the reaction (2.5h in case of **14** and 2.4 h in case of **15** , TLC control). The crude product was then recrystallized from a mixture of Et₂O/ hexane to obtain the pure indeno[2,1*b*] quinoline **14** as a yellowish green solid and indeno[2,1*b*] quinoline **15** as an olive green solid respectively. Yield: 78%, 239 mg; M.P.: 182-187 °C^{18b}; IR (KBr, cm⁻¹): 3073, 3043, 1711, 1606; ¹H NMR (300 MHz, CDCl₃) (δ, ppm): 8.18-8.13 (2H, m), 7.81-7.63 (4H, m), 7.58-7.56 (3H, m), 7.52-7.49 (1H, m), 7.45-7.41 (3H, m); ¹³C NMR (CDCl₃) (δ, ppm): 190.4, 162.2, 150.5, 148.3, 143.4, 137.7, 135.5, 133.0, 131.9, 131.8, 130.0, 129.6, 129.1, 128.8, 128.3, 127.9, 127.3, 124.0, 123.0, 121.9; MS (ESI): *m/z* 307; found 308 [M+H]⁺, Anal calcd for C₂₂H₁₃NO: C 85.97; H , 4.26; N 4.56, Found C 86.01, H 4.30, N 4.53%.

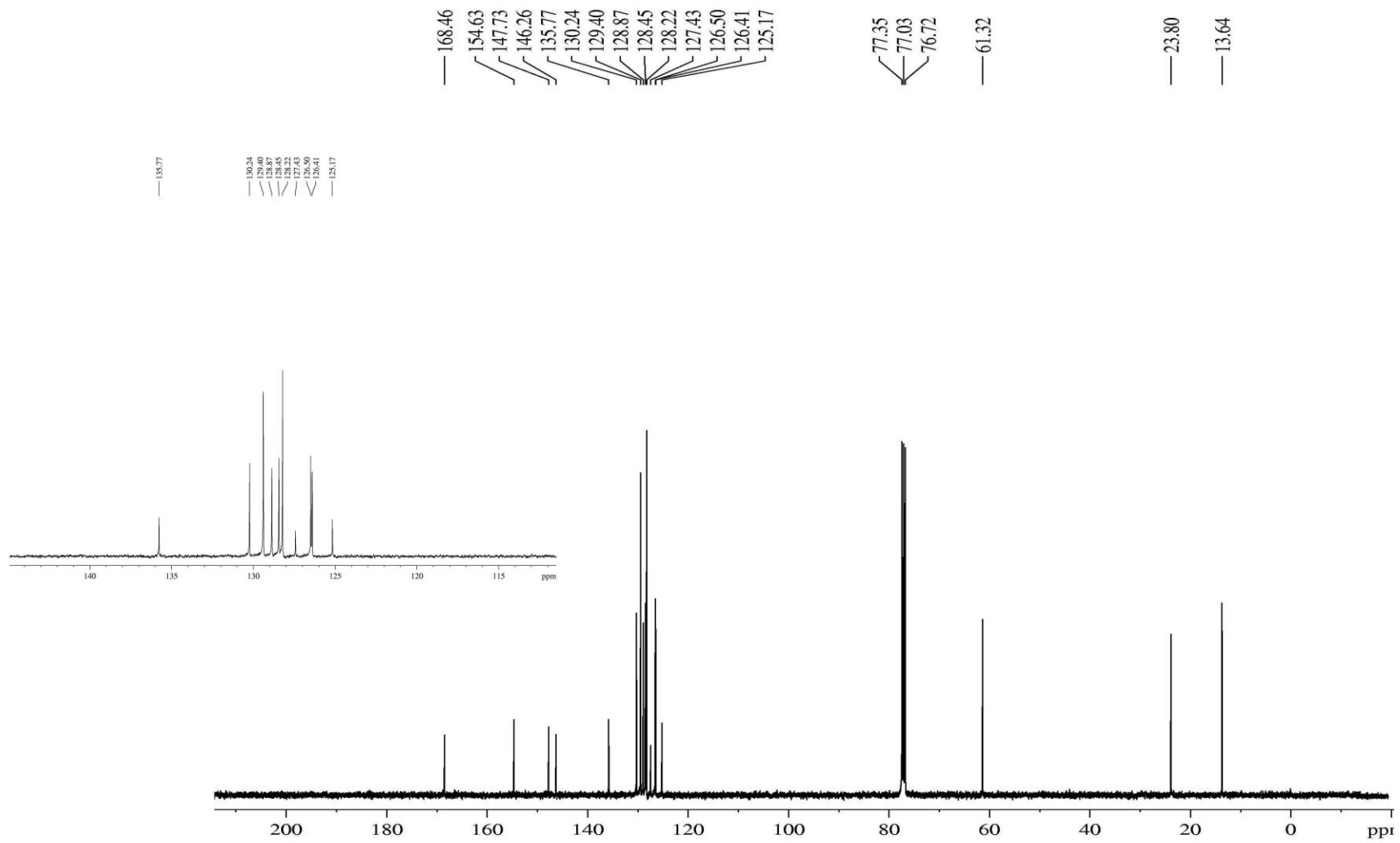
Compound 15



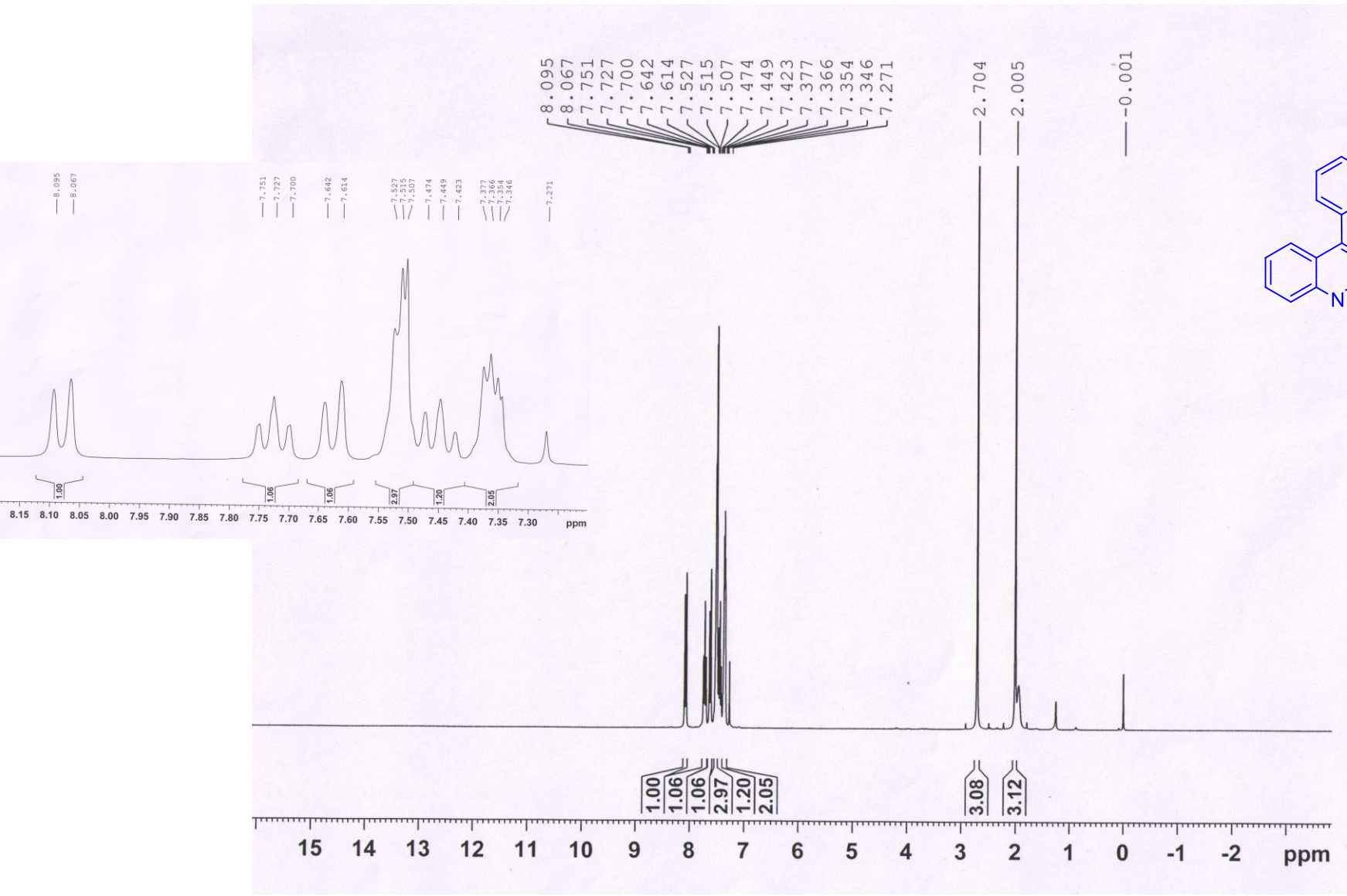
Yield: 81%, 199 mg; M.P.: 283-288°C; IR (KBr, cm^{-1}): 3069, 3015, 1710, 1648; ^1H NMR (300 MHz, CDCl_3) (δ , ppm): 8.06-8.02 (3H, m), 7.77-7.73 (1H, m), 7.71-7.66 (1H, m), 7.63-7.61 (1H, m), 7.53-7.45 (2H, m), 3.00 (1H, s); ^{13}C NMR (CDCl_3) (δ , ppm): 192.8, 162.0, 149.6, 146.8, 143.2, 137.7, 135.4, 131.7, 131.5, 130.3, 128.7, 127.0, 125.9, 123.9, 121.8, 12.6; MS (ESI): m/z 245; found 246 $[\text{M}+\text{H}]^+$, Anal calcd for $\text{C}_{17}\text{H}_{11}\text{NO}$: C, 83.25; H, 4.52; N, 5.71; Found C, 83.21; H, 4.57; N, 5.70%.



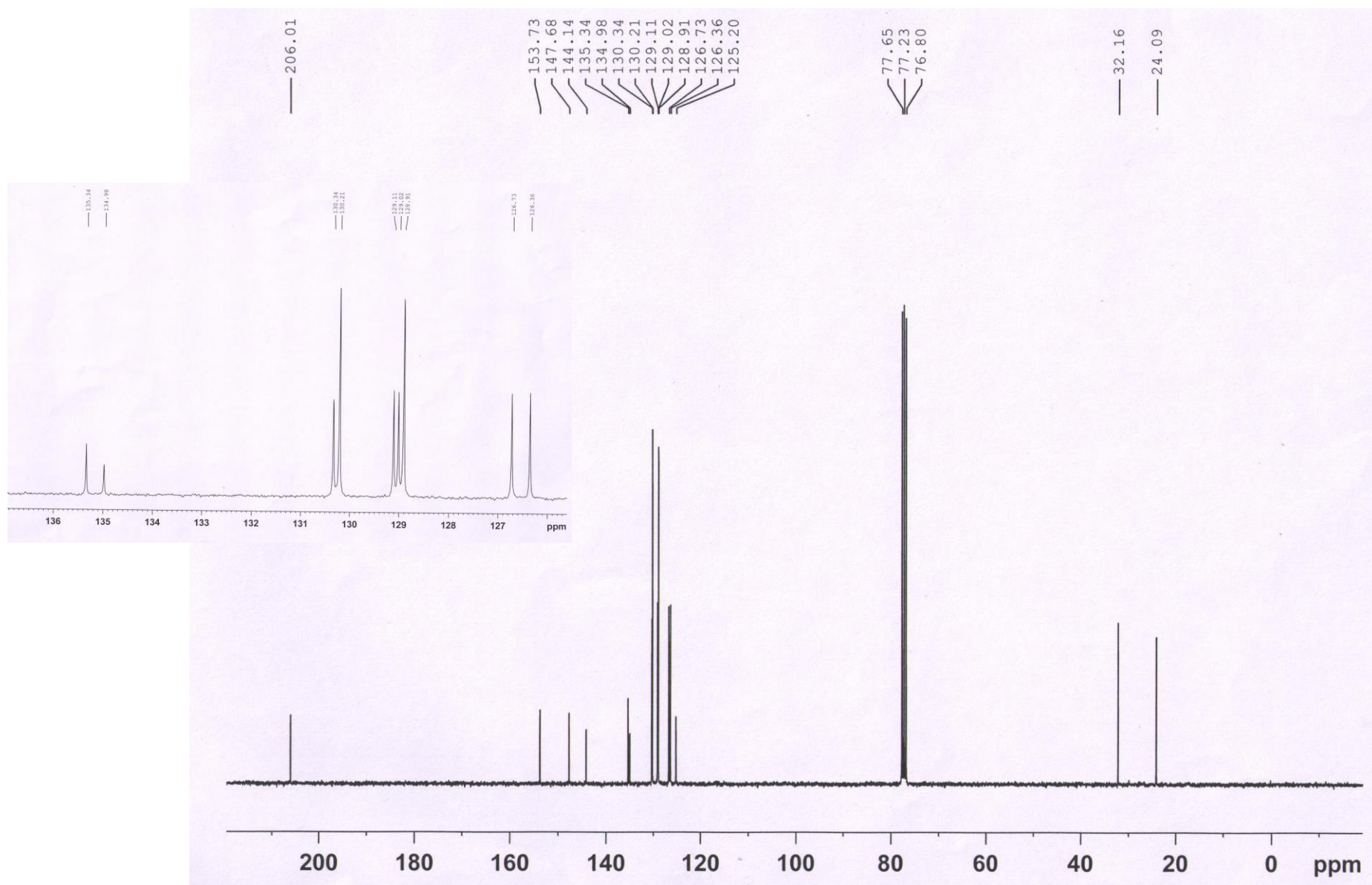
¹H NMR spectrum of compound **3** and its expansion



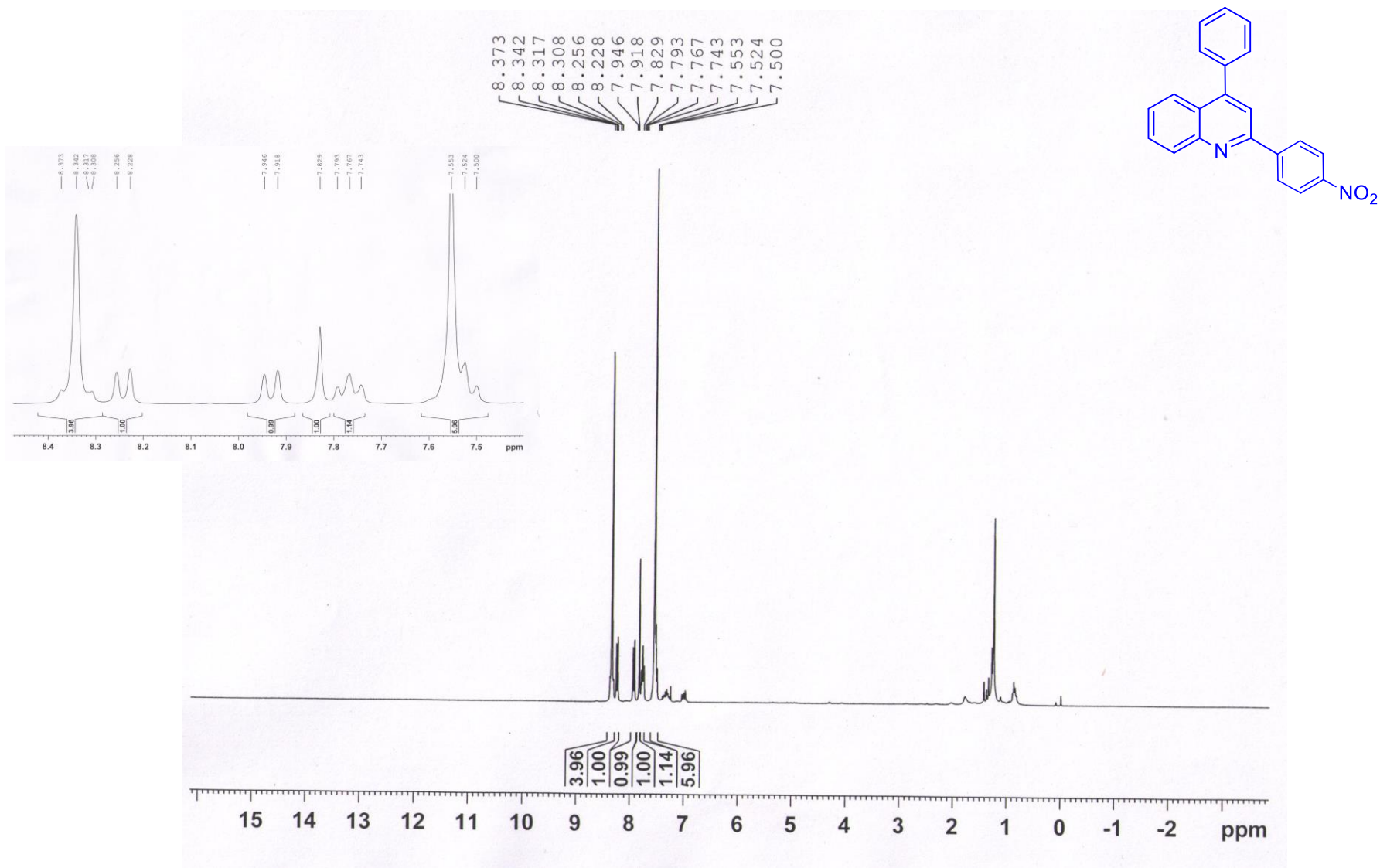
^{13}C NMR spectrum of compound **3** and its expansion



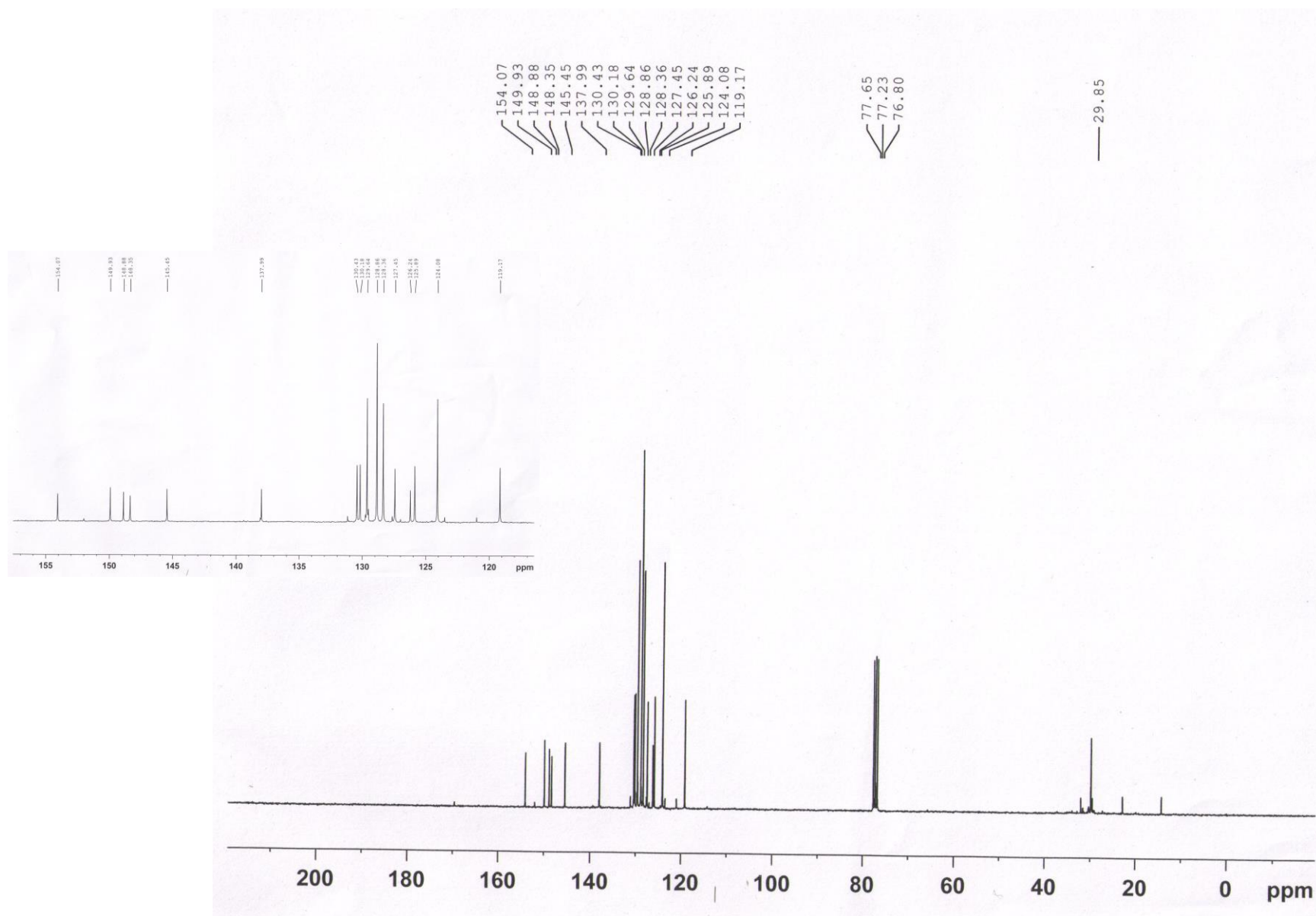
¹H NMR spectrum of compound **6b** and its expansion



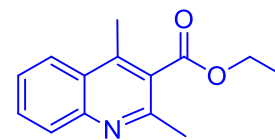
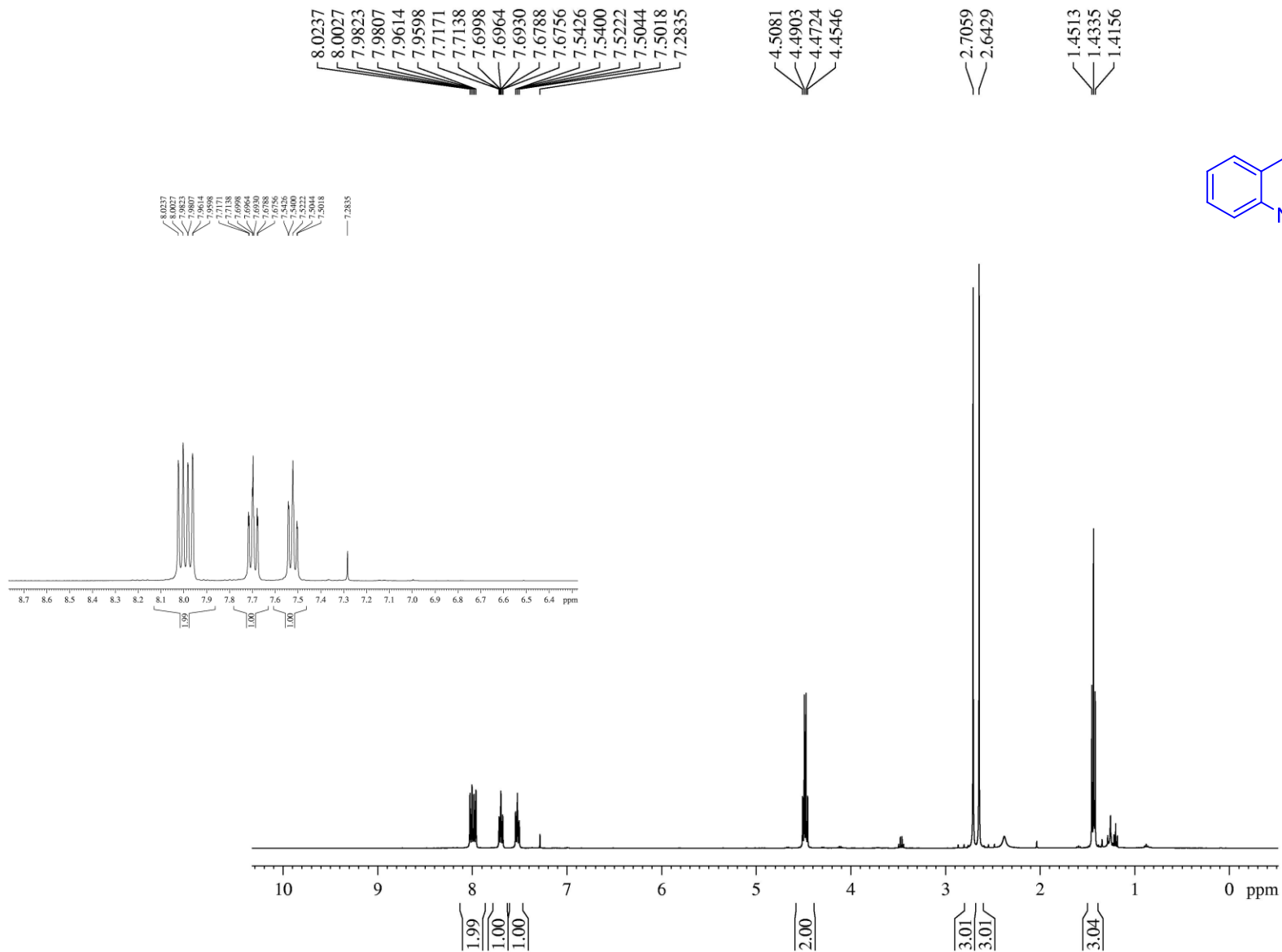
^{13}C NMR spectrum of compound **6b** and its expansion

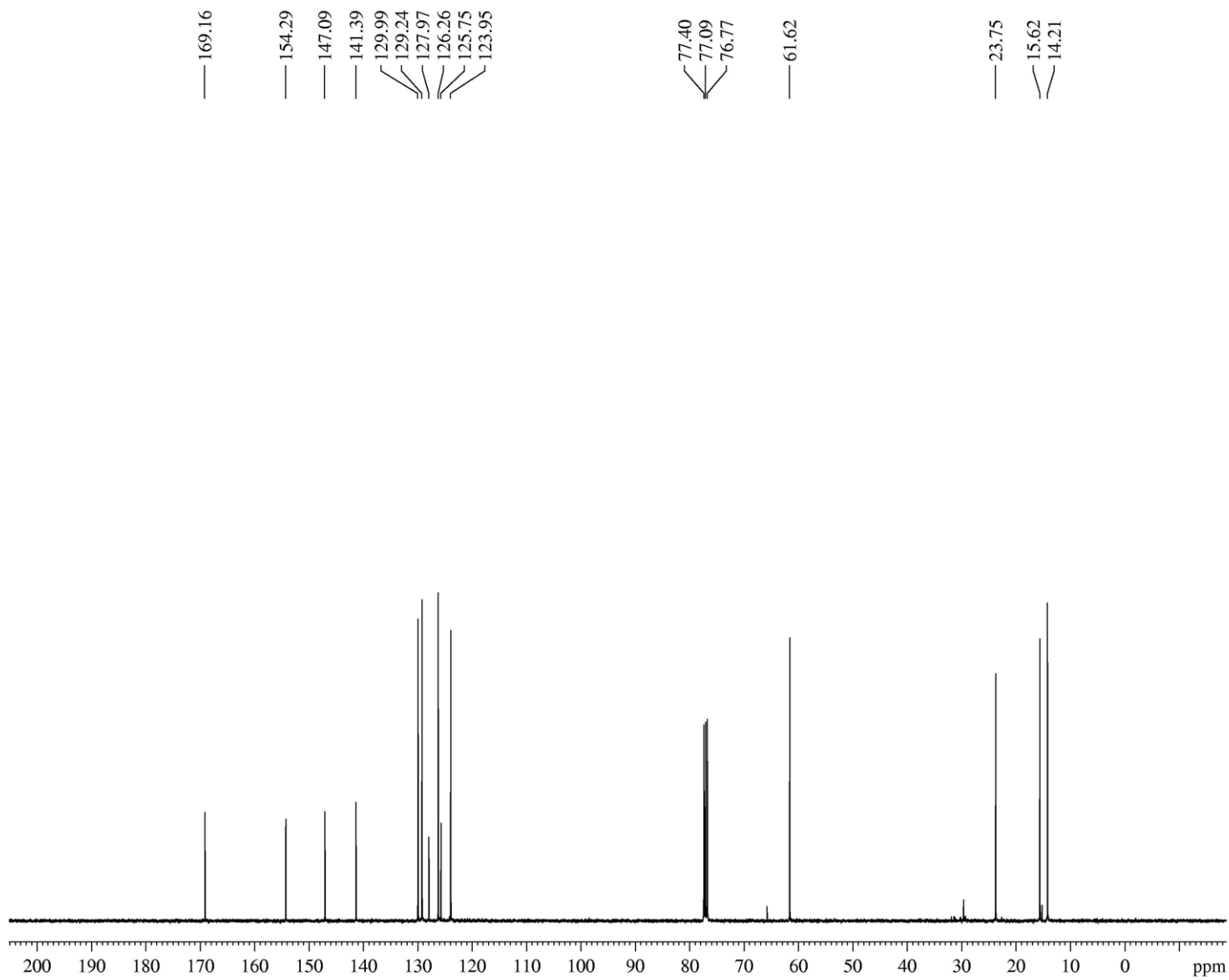


^1H NMR spectrum of compound **6d** and its expansion

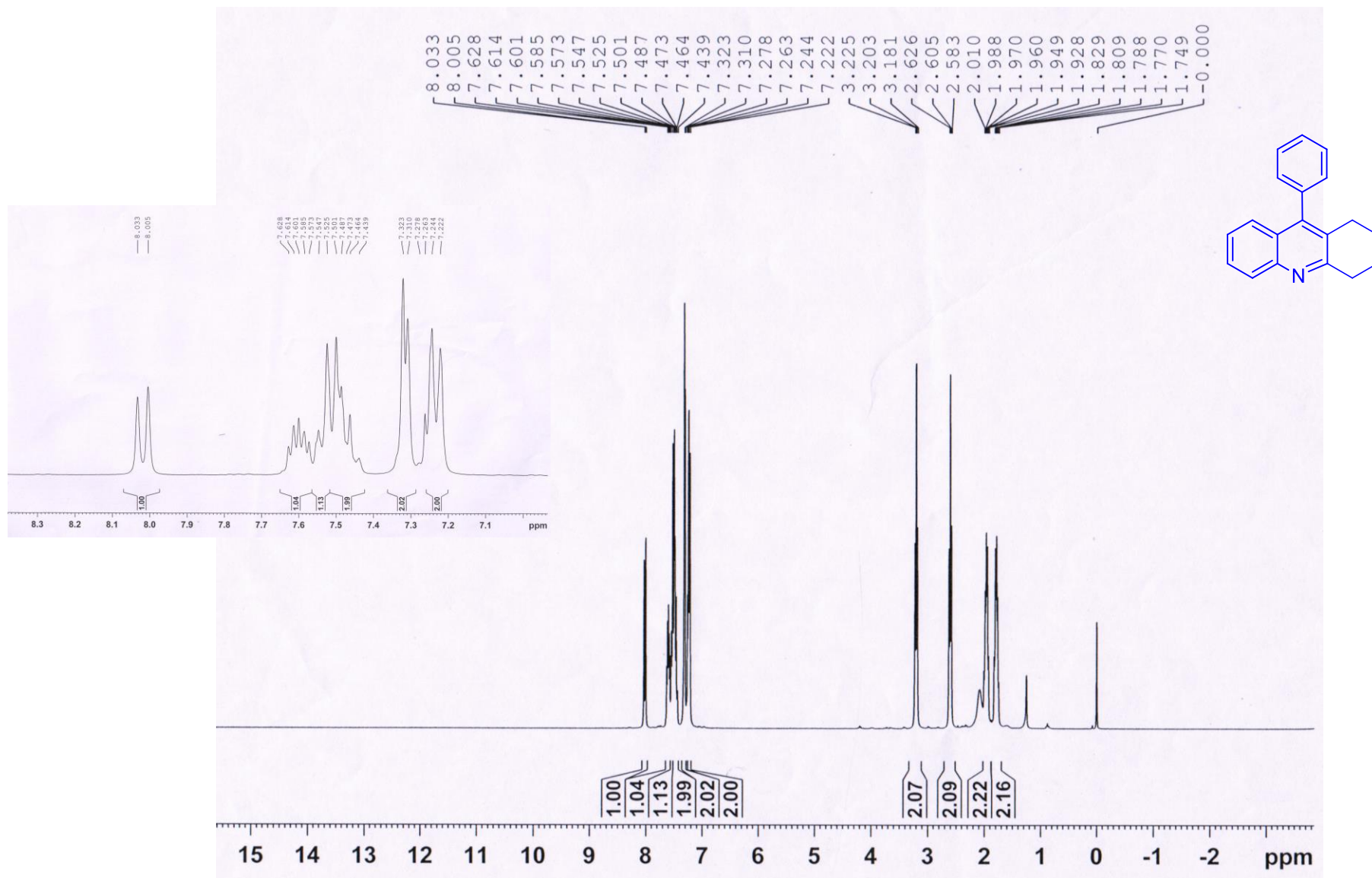


^{13}C NMR spectrum of compound **6d** and its expansion

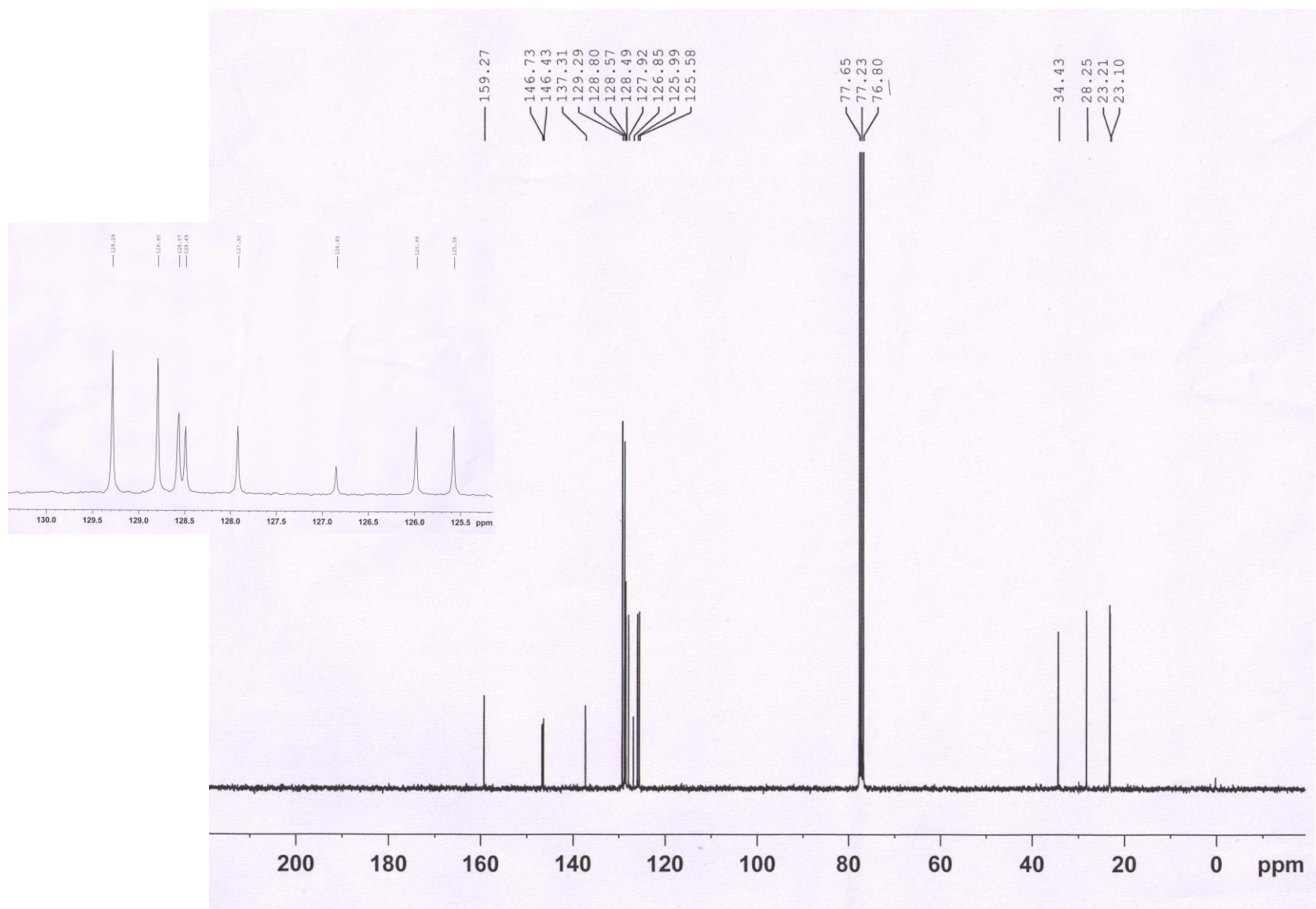




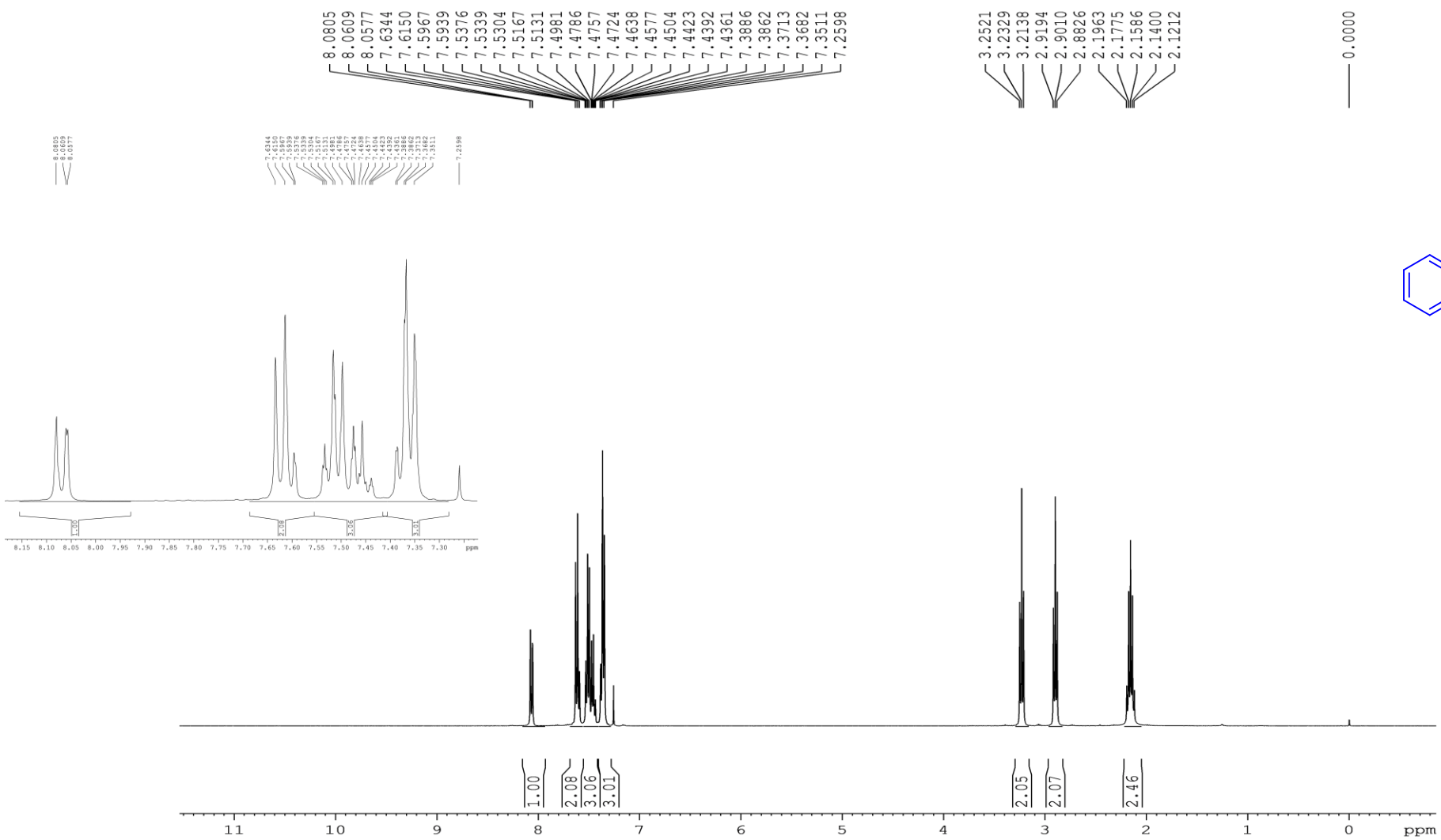
^{13}C NMR spectrum of compound **6h**



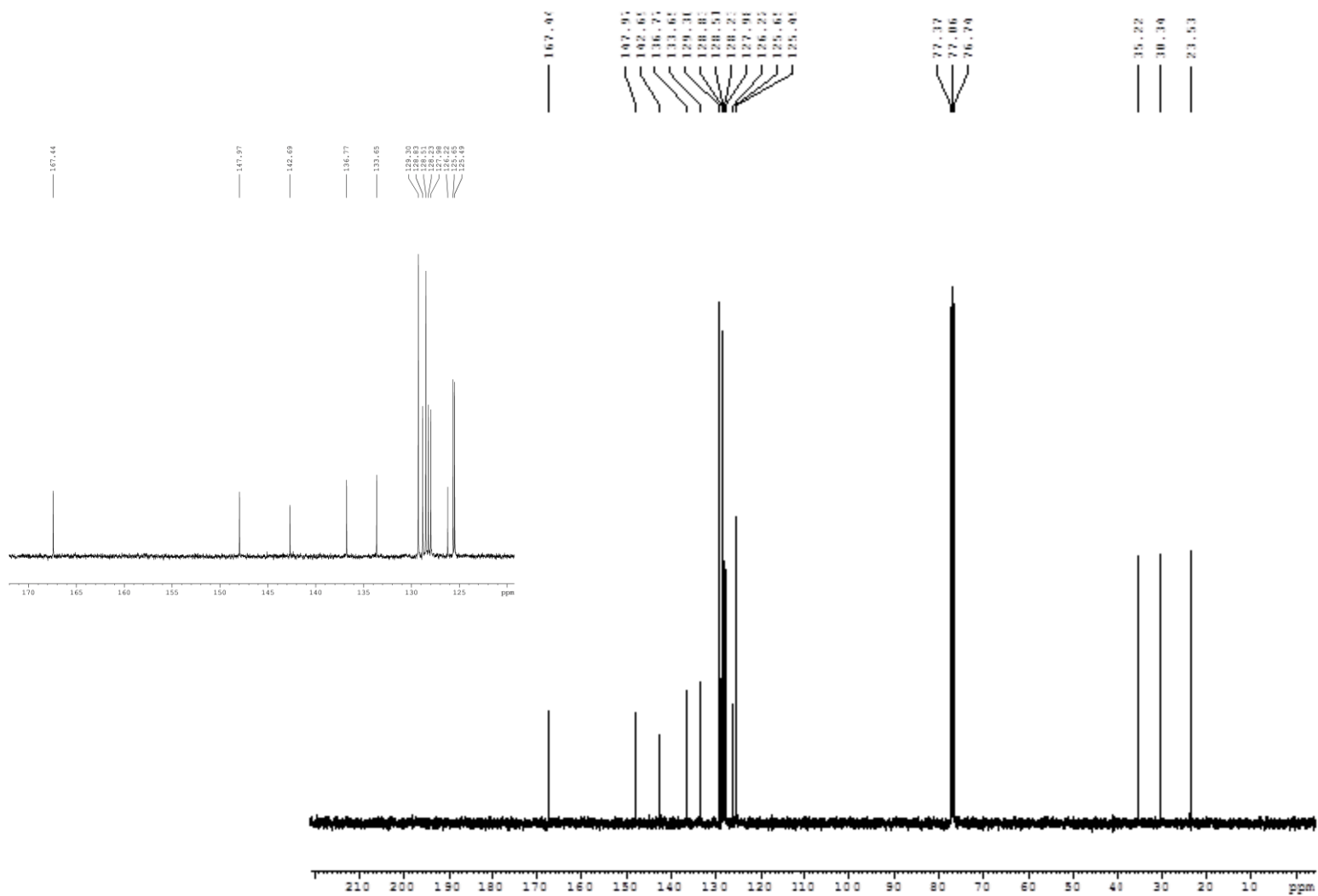
^1H NMR spectrum of compound **8a** and its expansion



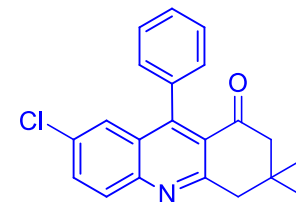
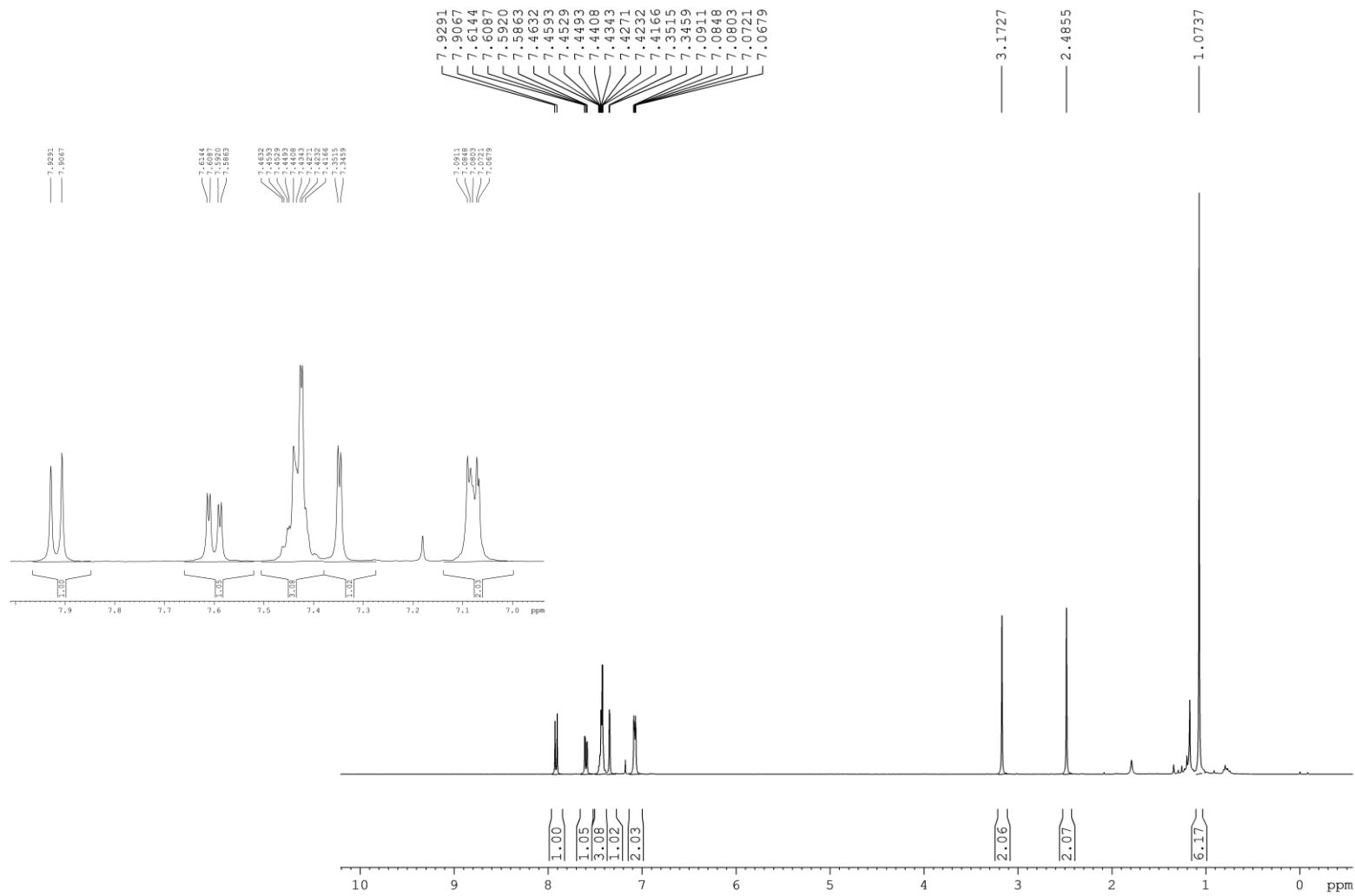
^{13}C NMR spectrum of compound **8a** and its expansion



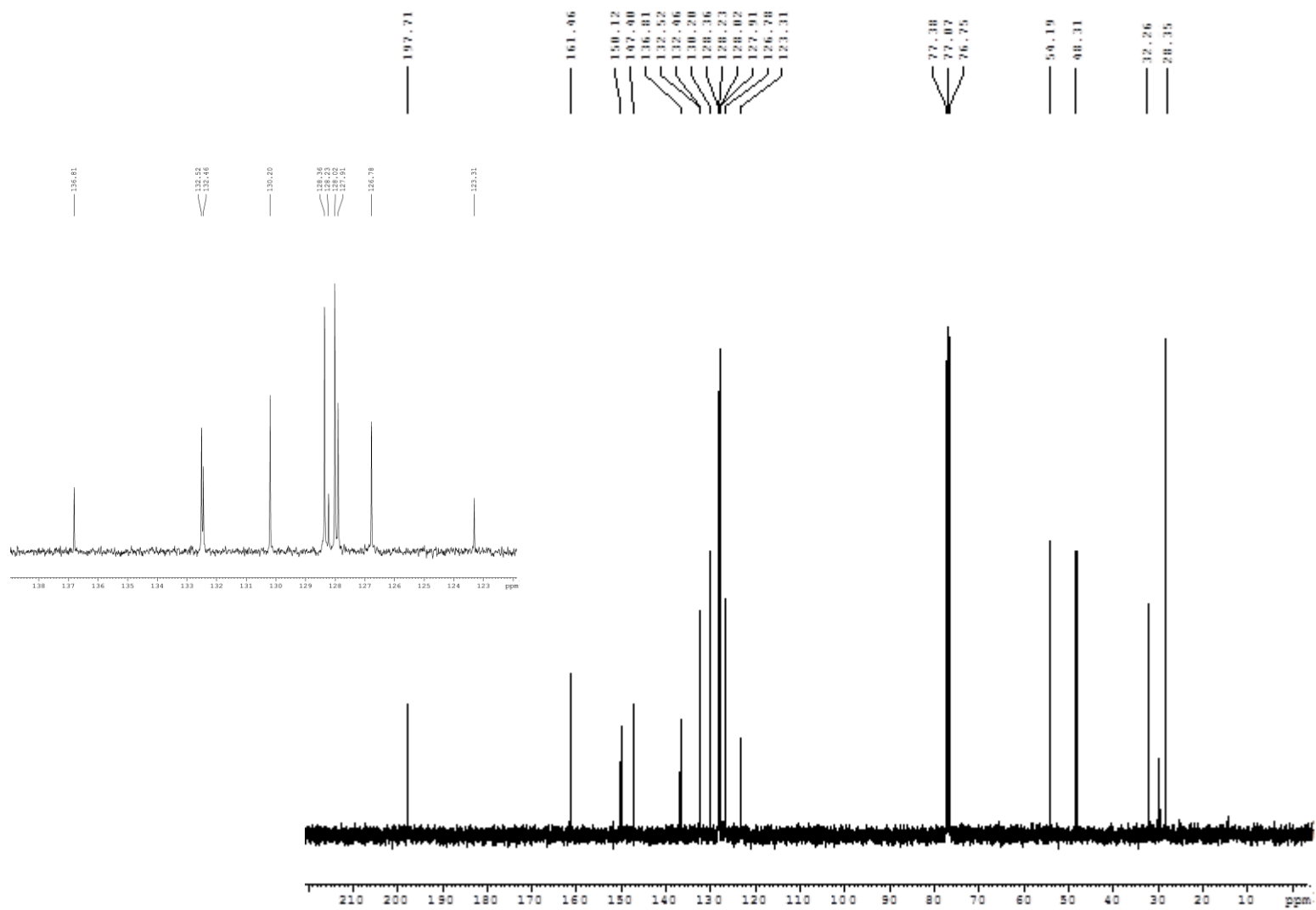
^1H NMR spectrum of compound **8b** and its expansion



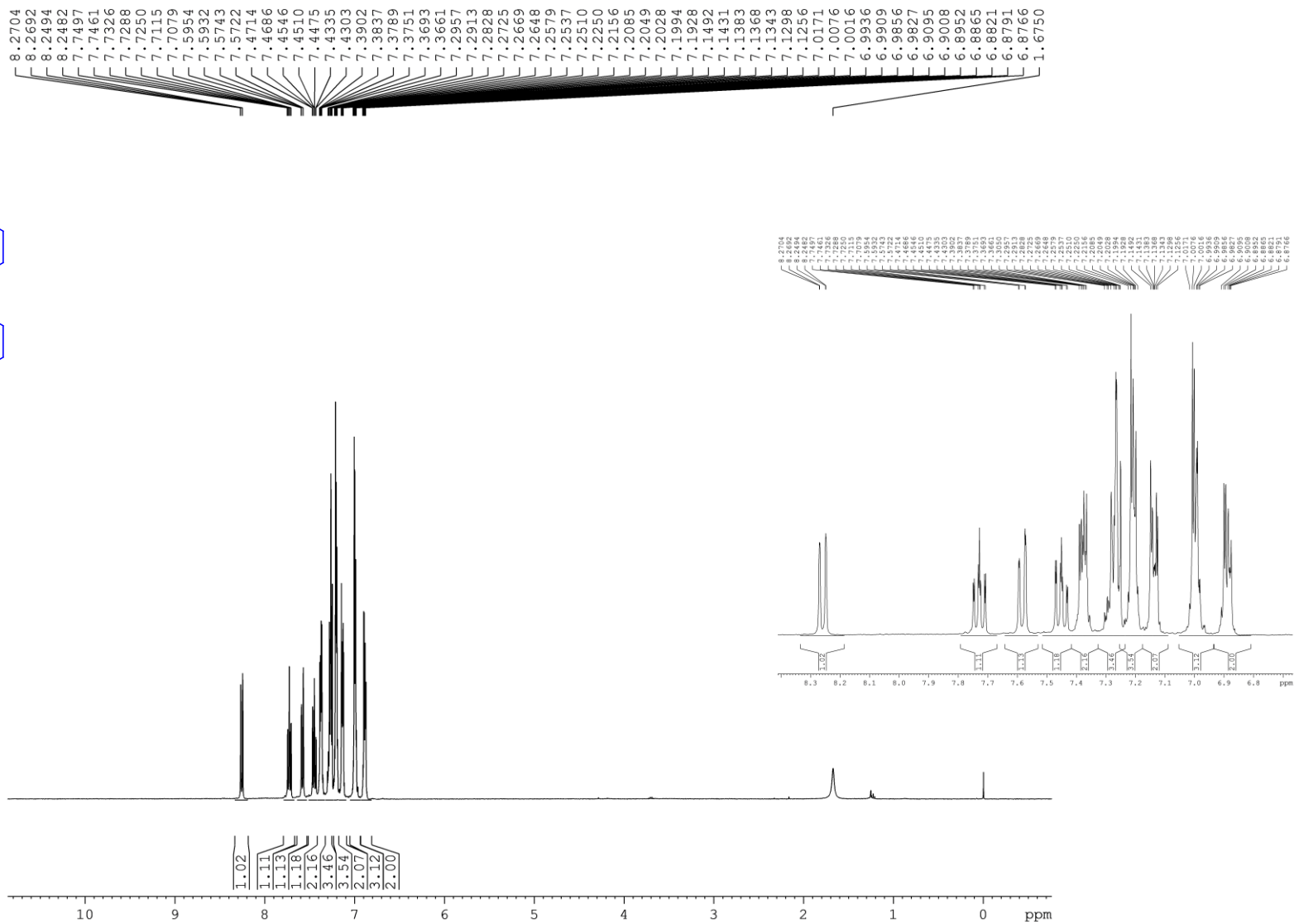
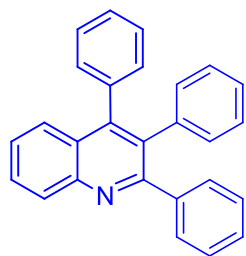
^{13}C NMR spectrum of compound **8b** and its expansion



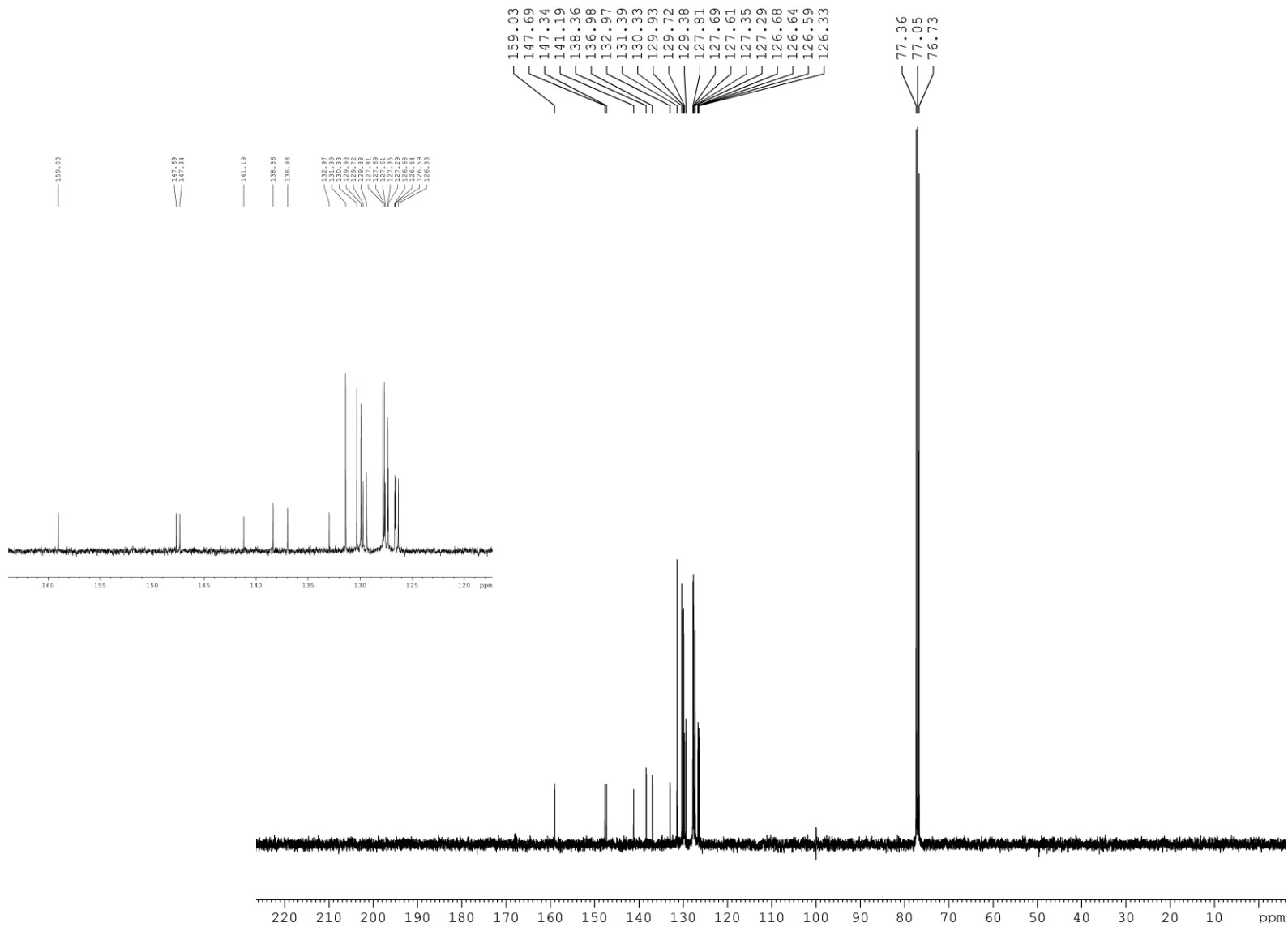
^1H NMR spectrum of compound **8f** and its expansion



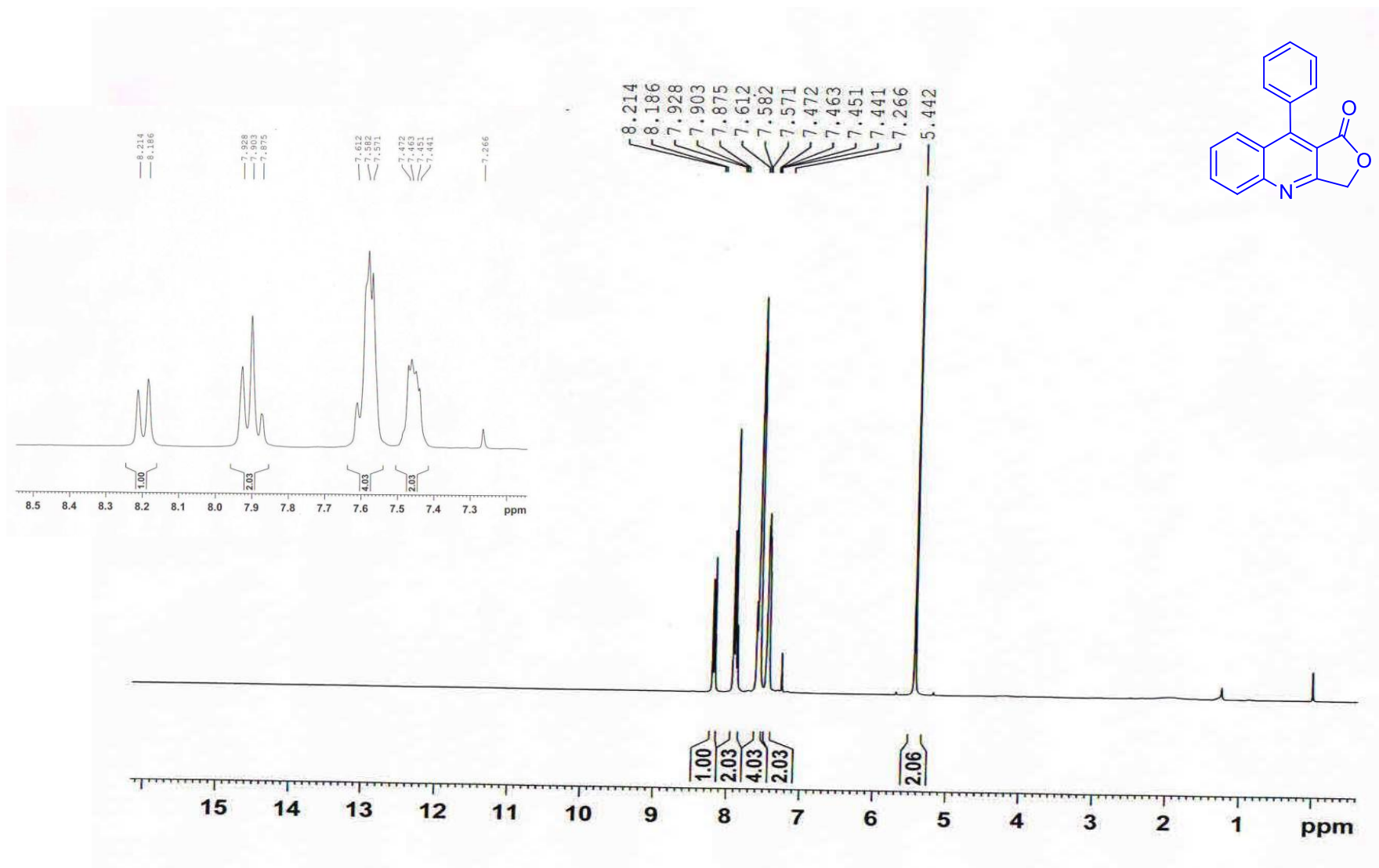
^{13}C NMR spectrum of compound **8f** and its expansion



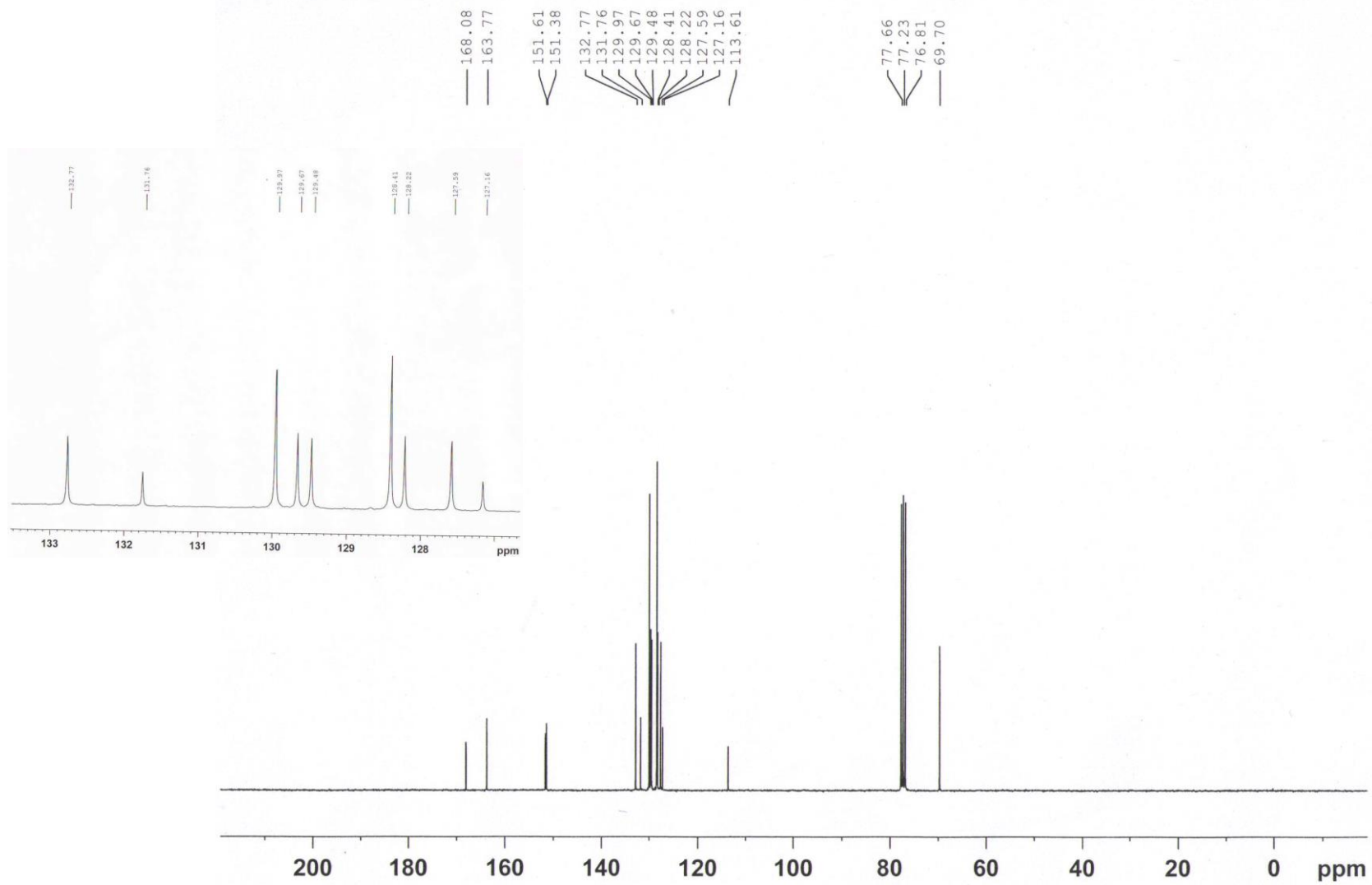
¹H NMR spectrum of compound **10** and its expansion



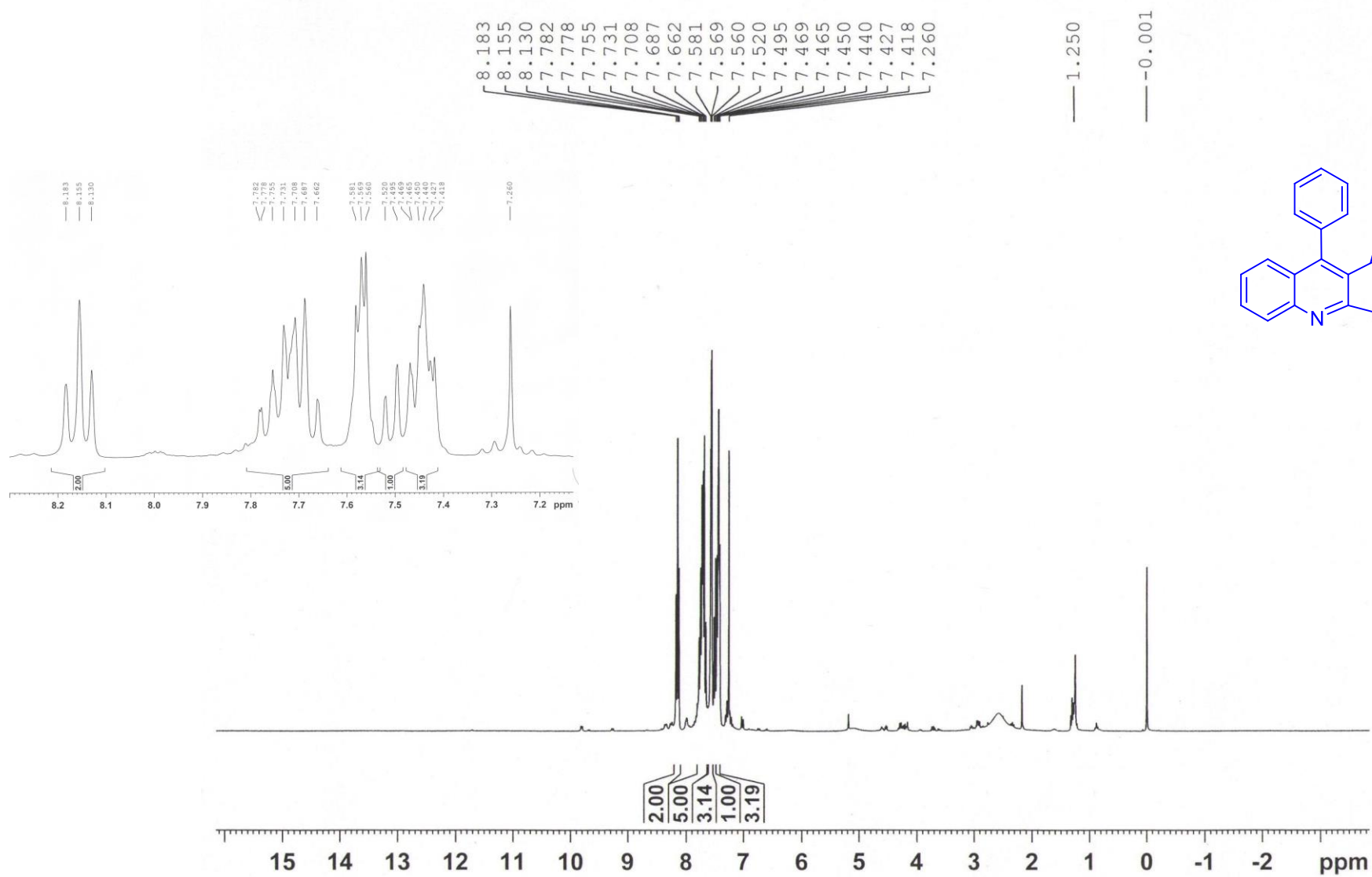
^{13}C NMR spectrum of compound **10** and its expansion



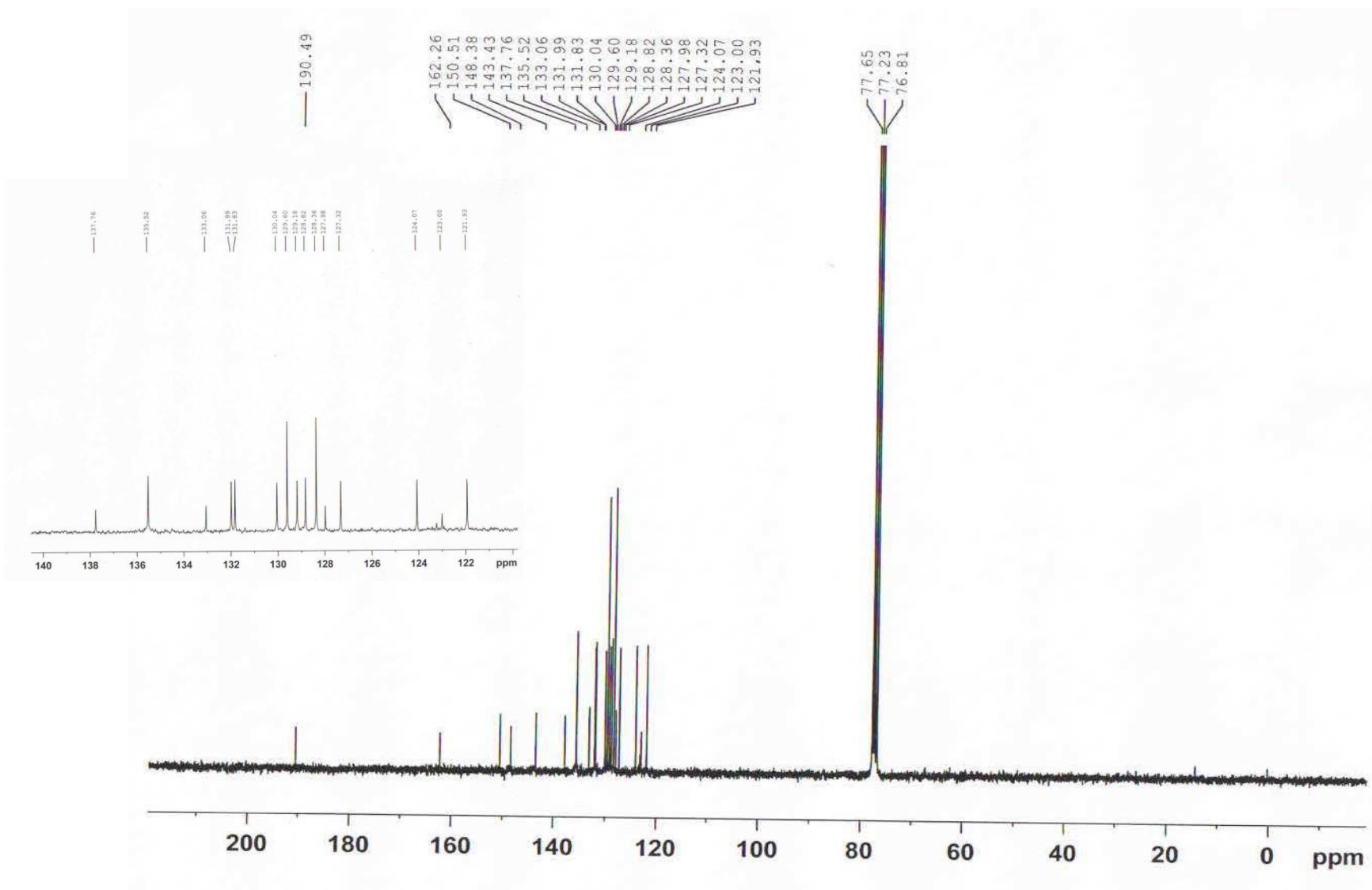
¹H NMR spectrum of compound **12** and its expansion



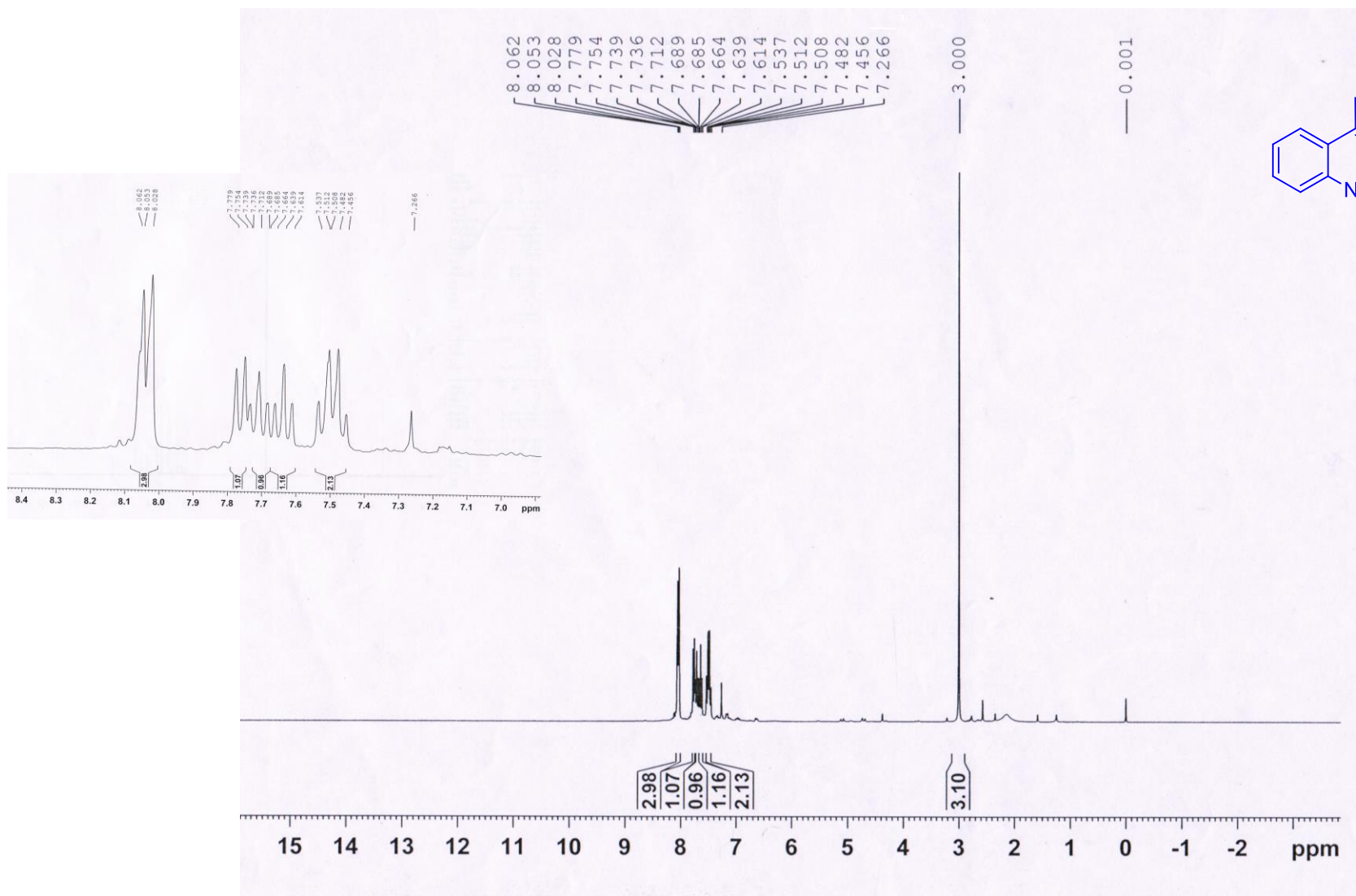
^{13}C NMR spectrum of compound **12** and its expansion



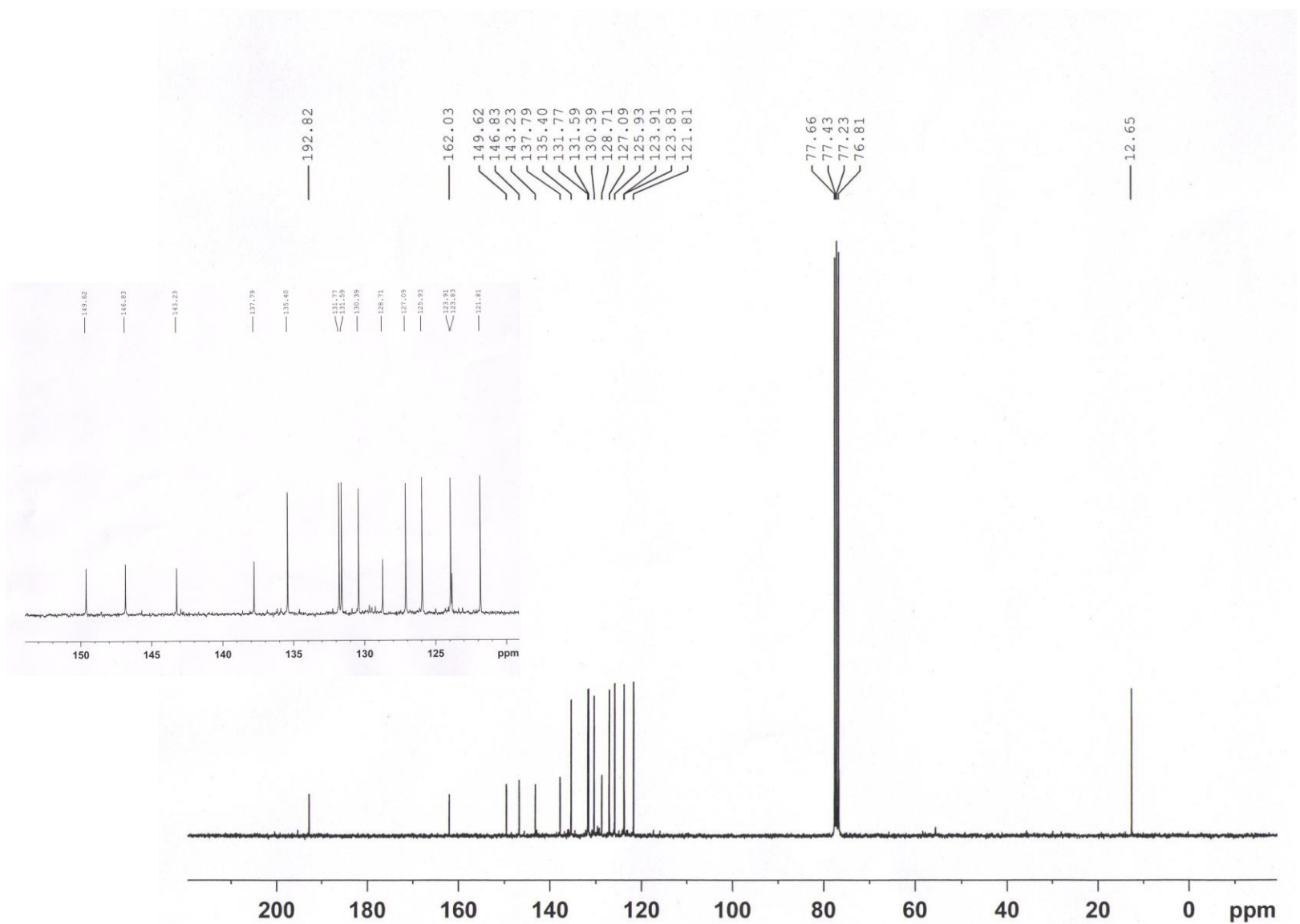
^1H NMR spectrum of compound **14** and its expansion



^{13}C NMR spectrum of compound **14** and its expansion

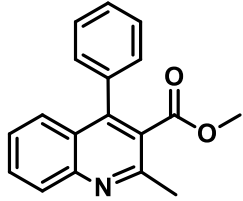
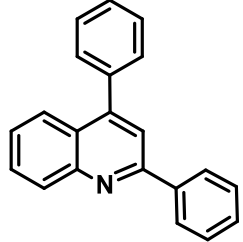
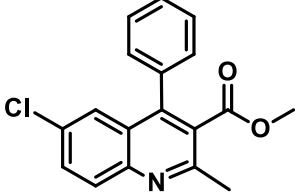


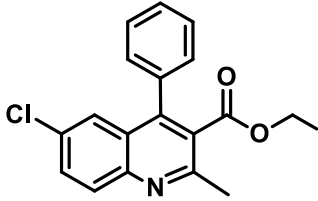
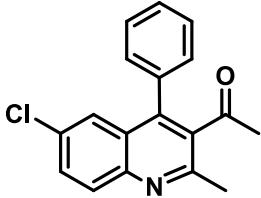
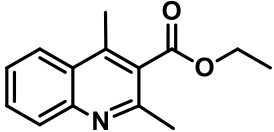
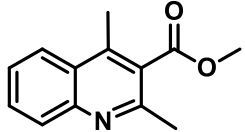
^1H NMR spectrum of compound **15** and its expansion

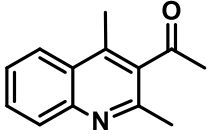
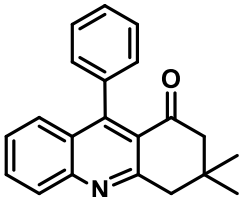
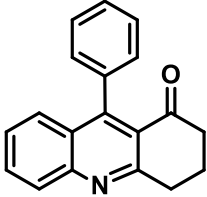
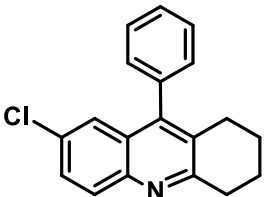


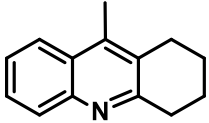
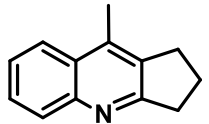
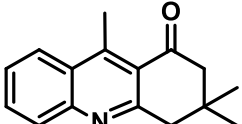
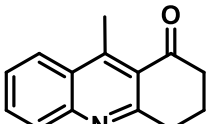
^{13}C NMR spectrum of compound **15** and its expansion

Table S1

| Entry | Quinolines | M.P. (Observed) | M.P. (Reported) | Reference |
|-------|---|-----------------|-----------------|-----------|
| 1 |  6a | 96-100 °C | 99 °C | 20b |
| 2 |  6c | 104-106 °C | 106 °C | 20b |
| 3 |  6e | 133-136 °C | 135 °C | 20b |

| | | | | |
|---|--|------------|------------|-----|
| 4 |  <p>6f</p> | 104-108 °C | 104-105 °C | 17a |
| 5 |  <p>6g</p> | 148-150 °C | 149-150 °C | 20b |
| 6 |  <p>6h</p> | oil | oil | 20b |
| 7 |  <p>6i</p> | oil | oil | 20b |

| | | | | |
|----|--|------------|--------|-----|
| 8 |  <p>6j</p> | oil | oil | 17c |
| 9 |  <p>8c</p> | 190-195 °C | 192 °C | 17a |
| 10 |  <p>8d</p> | 157-160 °C | 159 °C | 17a |
| 11 |  <p>8e</p> | 152-157 °C | 159 °C | 17b |

| | | | | |
|----|---|------------|------------|-----|
| 12 |  <p>8g</p> | 76-80 °C | 75-77 °C | 17c |
| 13 |  <p>8h</p> | 60-63 °C | 58-60 °C | 17c |
| 14 |  <p>8i</p> | 105-108 °C | 104-106 °C | 20a |
| 15 |  <p>8j</p> | 67-70 °C | 65-66 °C | 17c |

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