

# **Synthesis of 2-trifluoromethylquinolines *via* copper-mediated intramolecular oxidative cyclization of *N*-(2-alkenylaryl) enamines**

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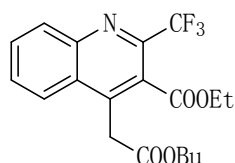
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## **Supporting Information**

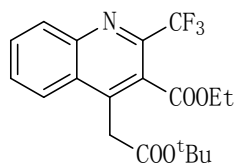
1. <sup>1</sup>H and <sup>13</sup>C NMR data of compounds **2-4**. (P2-9)
2. <sup>1</sup>H and <sup>13</sup>C NMR spectra of compounds **2-4**. (P10-47)

*General procedure for copper-catalyze intramolecular oxidative cyclization of N-(2-alkenylaryl)enamines (1a-r):* To a 25 mL tube containing a magnetic stir bar, was added *N*-(2-alkenylaryl) enamine **1** (0.2 mmol), CuCl<sub>2</sub> (10 mol%), and DMAc (2 mL). The resulting mixture was stirred at 60 °C in air for overnight (monitored by TLC). After being cooling to room temperature, evaporation of the solvent under reduced pressure followed purification by silica gel chromatography using petroleum ether/ethyl acetate (10:1) as eluent to provide the desired products **2** or **3a**.



Ethyl 4-(2-butoxy-2-oxoethyl)-2-(trifluoromethyl)quinoline-3-carboxylate (**2a**):

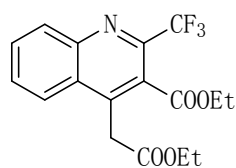
Isolated (R<sub>f</sub> = 0.5, EtOAc–petroleum ether = 1:10) as a yellow solid (61.0 mg, 80% yield), mp: 62-64 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.77 (t, *J* = 7.4 Hz, 3H), 1.13-1.22 (m, 2H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.43-1.50 (m, 2H), 4.02 (t, *J* = 6.6 Hz, 2H), 4.16 (s, 2H), 4.41 (q, *J* = 7.2 Hz, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.81 (t, *J* = 7.6 Hz, 1H), 8.03 (d, *J* = 8.2 Hz, 1H), 8.18 (d, *J* = 8.2 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 13.5, 13.8, 18.9, 30.4, 35.1, 62.6, 65.5, 121.2 (q, <sup>1</sup>*J*<sub>C-F</sub> = 275.1 Hz), 124.2, 125.2, 127.4, 129.7, 130.8, 131.4, 140.8 143.7 (q, <sup>2</sup>*J*<sub>C-F</sub> = 34.1 Hz), 146.3, 166.1, 168.8; HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>21</sub>F<sub>3</sub>NO<sub>4</sub>: 384.1417, Found: 384.1411



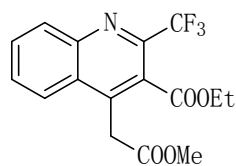
Ethyl 4-(2-(tert-butoxy)-2-oxoethyl)-2-(trifluoromethyl)quinoline-3-carboxylate (**2b**):

Isolated (R<sub>f</sub> = 0.5, EtOAc–petroleum ether = 1:10) as a yellow solid (66.0 mg, 86% yield), mp: 70-72 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.29 (s, 9H), 1.33 (t, *J* = 7.2 Hz, 3H), 4.05 (s, 2H), 4.39 (q, *J* = 7.2 Hz, 2H), 7.64 (t, *J* = 8.0 Hz, 1H), 7.74 (t, *J* = 7.6 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 13.9, 27.8, 36.4, 62.5, 82.3, 121.2 (q, <sup>1</sup>*J*<sub>C-F</sub> = 274.6 Hz), 124.3, 125.2, 127.6, 129.6, 130.8, 131.3, 141.3, 143.5 (q, <sup>2</sup>*J*<sub>C-F</sub> = 33.8 Hz), 146.4, 166.2, 167.8; HRMS

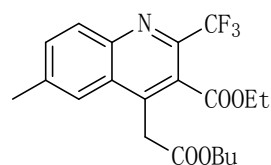
(ESI):  $m/z$   $[M + Na]^+$  calcd for  $C_{19}H_{20}F_3NNaO_4$ : 406.1237, Found: 406.1275.



Ethyl 4-(2-ethoxy-2-oxoethyl)-2-(trifluoromethyl)quinoline-3-carboxylate (**2c**): Isolated ( $R_f = 0.5$ , EtOAc–petroleum ether = 1:10) as a yellow solid (55.2 mg, 77% yield), mp: 62-64 °C;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  1.21 (t,  $J = 7.2$  Hz, 3H), 1.42 (t,  $J = 7.2$  Hz, 3H), 4.16 (q,  $J = 7.2$  Hz, 2H), 4.23 (s, 2H), 4.49 (q,  $J = 7.2$  Hz, 2H), 7.76 (t,  $J = 7.6$  Hz, 1H), 7.87 (t,  $J = 7.6$  Hz, 1H), 8.09 (d,  $J = 8.0$  Hz, 1H), 8.24 (d,  $J = 8.0$  Hz, 1H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  13.9, 14.0, 35.2, 61.7, 62.7, 121.2 (q,  $^1J_{C-F} = 275.0$  Hz), 124.2, 125.2, 127.5, 129.8, 130.9, 131.4, 140.74, 143.9 (q,  $^2J_{C-F} = 34.2$  Hz), 146.4, 166.1, 168.7; HRMS (ESI):  $m/z$   $[M + Na]^+$  calcd for  $C_{17}H_{16}F_3NNaO_4$ : 378.0924, Found: 378.0888.

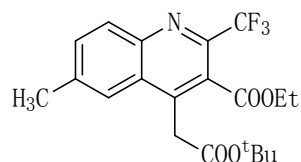


Ethyl 4-(2-methoxy-2-oxoethyl)-2-(trifluoromethyl)quinoline-3-carboxylate (**2d**): Isolated ( $R_f = 0.5$ , EtOAc–petroleum ether = 1:10) as a yellow solid (48.4 mg, 71% yield), mp: 82-84 °C;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  1.42 (t,  $J = 7.2$  Hz, 3H), 3.70 (s, 3H), 4.24 (s, 2H), 4.48 (q,  $J = 7.2$  Hz, 2H), 7.77 (t,  $J = 7.6$  Hz, 1H), 7.88 (t,  $J = 7.6$  Hz, 1H), 8.08 (d,  $J = 8.0$  Hz, 1H), 8.25 (d,  $J = 8.4$  Hz, 1H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  13.8, 34.9, 52.6, 62.7, 121.2 (q,  $^1J_{C-F} = 274.7$  Hz), 124.2, 125.3, 127.5, 129.9, 131.0, 131.5, 140.5, 143.9 (q,  $^2J_{C-F} = 34.1$  Hz), 146.5, 166.1, 169.2; HRMS (ESI):  $m/z$   $[M + Na]^+$  calcd for  $C_{16}H_{14}F_3NNaO_4$ : 364.0767, Found: 364.0730.

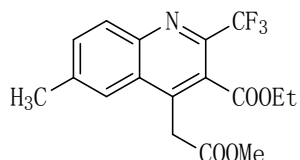


Ethyl 4-(2-butoxy-2-oxoethyl)-6-methyl-2-(trifluoromethyl)quinoline-3-carboxylate (**2e**): Isolated ( $R_f = 0.5$ , EtOAc–petroleum ether = 1:10) as a yellow solid (67.5 mg, 85% yield), mp: 74-76 °C;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  0.85 (t,  $J = 7.2$  Hz, 3H), 1.21-1.30 (m, 2H), 1.41 (t,  $J = 7.0$  Hz, 3H), 1.51-1.58 (m, 2H), 2.59 (s, 3H), 4.10 (t,  $J$

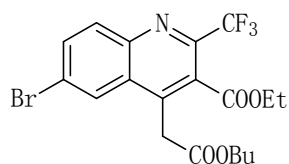
= 6.6 Hz, 2H), 4.19 (s, 2H), 4.47 (q,  $J = 7.2$  Hz, 2H), 7.68 (d,  $J = 8.4$  Hz, 1H), 7.82 (s, 1H), 8.11 (d,  $J = 8.8$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  13.5, 13.8, 18.9, 22.2, 30.4, 35.1, 62.6, 65.4, 121.3 (q,  $^1J_{\text{C-F}} = 274.3$  Hz), 123.0, 125.2, 127.5, 130.5, 133.7, 139.8, 140.3, 142.9 (q,  $^2J_{\text{C-F}} = 34.1$  Hz) 145.0, 166.3, 168.9; HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{20}\text{H}_{24}\text{F}_3\text{NO}_4$ : 398.1574, Found: 398.1577.



Ethyl 4-(2-(tert-butoxy)-2-oxoethyl)-6-methyl-2-(trifluoromethyl)quinoline-3-carboxylate (**2f**): Isolated ( $R_f = 0.5$ , EtOAc–petroleum ether = 1:10) as a yellow solid (64.3 mg, 81% yield), mp: 68-70 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.40 (s, 9H), 1.41 (t,  $J = 7.2$  Hz, 3H), 2.60 (s, 3H), 4.11 (s, 3H), 4.02 (s, 2H), 4.48 (q,  $J = 7.2$  Hz, 2H), 7.68 (d,  $J = 8.4$  Hz, 1H), 7.83 (s, 1H), 8.11 (d,  $J = 8.4$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  13.9, 22.2, 27.9, 36.4, 62.5, 82.2, 121.3 (q,  $^1J_{\text{C-F}} = 273.5$  Hz), 123.2, 125.2, 127.6, 130.5, 133.6, 140.1, 140.3, 142.9 (q,  $^2J_{\text{C-F}} = 34.3$  Hz), 145.0, 166.4, 168.0; HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{20}\text{H}_{23}\text{F}_3\text{NO}_4$ : 398.1574, Found: 398.1566.

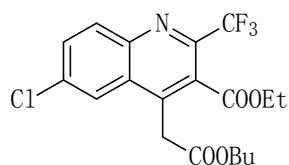


Ethyl 4-(2-methoxy-2-oxoethyl)-6-methyl-2-(trifluoromethyl)quinoline-3-carboxylate (**2g**): Isolated ( $R_f = 0.5$ , EtOAc–petroleum ether = 1:10) as a yellow solid (64.6 mg, 95% yield), mp: 127-129 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.41 (t,  $J = 7.0$  Hz, 3H), 2.60 (s, 3H), 3.70 (s, 3H), 4.20 (s, 2H), 4.41 (q,  $J = 7.2$  Hz, 2H), 7.68 (d,  $J = 8.2$  Hz, 1H), 7.80 (s, 1H), 8.11 (d,  $J = 8.2$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  13.8, 22.2, 34.8, 52.6, 62.6, 121.3 (q,  $^1J_{\text{C-F}} = 274.3$  Hz), 125.4, 127.5, 130.6, 133.8, 139.6, 140.4, 142.9 (q,  $^2J_{\text{C-F}} = 34.0$  Hz), 145.1, 166.3, 169.3; HRMS (ESI):  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{17}\text{H}_{16}\text{F}_3\text{NNaO}_4$ : 378.0929, Found: 378.0920.



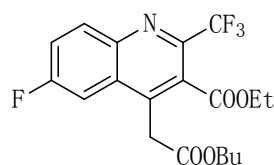
Ethyl 6-bromo-4-(2-butoxy-2-oxoethyl)-2-(trifluoromethyl)quinoline-3-carboxylate

**(2i)**: Isolated ( $R_f = 0.5$ , EtOAc–petroleum ether = 1:10) as a white solid (67.5 mg, 73% yield), mp: 84-86 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.87 (t,  $J = 8.0$  Hz, 3H), 1.23-1.31 (m, 2H), 1.42 (t,  $J = 7.2$ , 3H), 1.53-1.60 (m, 2H), 4.12 (t,  $J = 6.6$  Hz, 2H), 4.17 (s, 2H), 4.48 (q,  $J = 7.2$  Hz, 2H), 7.92 (d,  $J = 8.8$  Hz, 1H), 8.10 (d,  $J = 8.8$  Hz, 1H), 8.25 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  12.5, 12.8, 18.0, 29.4, 34.2, 61.8, 64.7, 120.0 (q,  $^1J_{\text{C-F}} = 274.2$  Hz), 123.5, 125.1, 125.8, 127.7, 131.4, 134.0, 138.9, 143.2 (q,  $^2J_{\text{C-F}} = 35.1$  Hz), 144.0, 166.7, 167.3; HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{20}\text{BrF}_3\text{NO}_4$ : 462.0522, Found: 462.0526.



Ethyl 4-(2-butoxy-2-oxoethyl)-6-chloro-2-(trifluoromethyl)quinoline-3-carboxylate

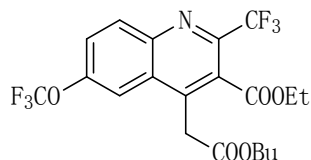
**(2j)**: Isolated ( $R_f = 0.5$ , EtOAc–petroleum ether = 1:10) as a yellow solid (66.7 mg, 80% yield), mp: 86-84 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.78 (t,  $J = 7.2$  Hz, 3H), 1.17-1.23 (m, 2H), 1.33 (t,  $J = 7.0$  Hz, 2H), 1.47-1.50 (m, 2H), 4.03 (t,  $J = 6.4$  Hz, 3H), 4.08 (s, 2H), 4.41 (q,  $J = 7.0$  Hz, 2H), 7.71 (d,  $J = 8.8$  Hz, 1H), 7.99 (s, 1H), 8.09 (d,  $J = 8.8$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  13.6, 13.9, 19.0, 30.4, 35.2, 62.9, 65.7, 121.0 (q,  $^1J_{\text{C-F}} = 274.2$  Hz), 123.4, 126.0, 128.3, 132.4, 132.5, 136.2, 140.0, 144.09 (q,  $^2J_{\text{C-F}} = 33.4$  Hz), 144.8, 165.8, 168.4; HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{20}\text{ClF}_3\text{NO}_4$ : 418.1027, Found: 418.1028.



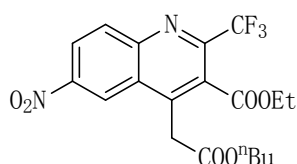
Ethyl 4-(2-butoxy-2-oxoethyl)-6-fluoro-2-(trifluoromethyl)quinoline-3-carboxylate

**(2k)**: Isolated ( $R_f = 0.5$ , EtOAc–petroleum ether = 1:10) as a white solid (58.5 mg, 73% yield), mp: 77-79 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.77 (t,  $J = 7.4$  Hz, 3H), 1.14-1.23 (m, 2H), 1.33 (t,  $J = 7.2$  Hz, 3H), 1.46-1.51 (m, 2H), 4.02 (t,  $J = 6.8$  Hz, 2H), 4.40 (q,  $J = 7.2$  Hz, 2H), 7.53-7.57 (m, 1H), 7.61 (d,  $J = 7.2$  Hz, 1H), 8.16 (dd,  $J = 5.6, 9.2$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  13.4, 13.8, 18.9, 30.4, 35.3, 62.8, 65.6, 108.2 (d,  $^2J_{\text{C-F}} = 23.0$  Hz), 121.1 (q,  $^1J_{\text{C-F}} = 274.7$  Hz), 121.9 (d,  $^2J_{\text{C-F}} = 25.8$  Hz),

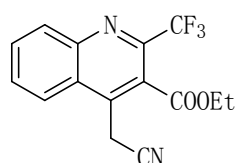
125.9, 128.8 (d,  $^3J_{C-F} = 10.1$  Hz), 133.7 (d,  $^3J_{C-F} = 9.5$  Hz), 140.2, 143.3 (q,  $^2J_{C-F} = 35.1$  Hz), 143.5, 162.5 (d,  $^1J_{C-F} = 252.0$  Hz), 165.8, 168.4; HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>20</sub>F<sub>4</sub>NO<sub>4</sub>: 402.1323, Found: 402.1334.



Ethyl 4-(2-butoxy-2-oxoethyl)-6-(trifluoromethoxy)-2-(trifluoromethyl)quinoline-3-carboxylate (**2l**): Isolated (Rf = 0.5, EtOAc–petroleum ether = 1:10) as a white solid (69 mg, 74% yield), mp: 74-76 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.86 (t,  $J = 7.4$  Hz, 3H), 1.21-1.31 (m, 2H), 1.42 (t,  $J = 8.0$  Hz, 3H), 1.52-1.59 (m, 2H), 4.11 (t,  $J = 8.0$  Hz, 2H), 4.19 (s, 2H), 4.49 (q,  $J = 7.2$  Hz, 2H), 7.73 (d,  $J = 9.2$  Hz, 1H), 7.91 (s, 1H), 8.31 (d,  $J = 9.2$  Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 13.3, 13.7, 18.8, 30.4, 35.3, 62.8, 65.7, 114.7, 120.4 (q,  $^1J_{C-F} = 258.0$  Hz), 120.9 (q,  $^1J_{C-F} = 274.7$  Hz), 125.2, 126.2, 128.2, 133.3, 140.8, 144.4 (q,  $^2J_{C-F} = 34.7$  Hz), 144.6, 149.4, 165.6, 168.2; HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>20</sub>F<sub>6</sub>NO<sub>5</sub>: 468.1240, Found: 468.1234.

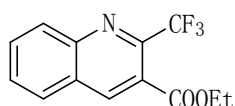


Ethyl 4-(2-butoxy-2-oxoethyl)-6-nitro-2-(trifluoromethyl)quinoline-3-carboxylate (**2m**): Isolated (Rf = 0.5, EtOAc–petroleum ether = 1:10) as a white solid (69.3 mg, 81% yield), mp: 80-82 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.88 (t,  $J = 7.2$  Hz, 3H), 1.26-1.33 (m, 2H), 1.44 (t,  $J = 7.0$  Hz, 3H), 1.58-1.63 (m, 2H), 4.14 (t,  $J = 6.4$  Hz, 2H), 4.30 (s, 2H), 4.51 (q,  $J = 7.2$  Hz, 2H), 8.42 (d,  $J = 8.8$  Hz, 1H), 8.63 (d,  $J = 7.2$  Hz, 1H), 9.07 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 13.5, 13.8, 19.0, 30.4, 35.3, 63.1, 66.0, 120.7 (q,  $^1J_{C-F} = 275.3$  Hz), 121.3, 124.7, 126.9, 127.1, 133.0, 143.4, 147.1 (q,  $^2J_{C-F} = 35.1$  Hz), 147.5, 148.3, 165.1, 168.0; HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>20</sub>F<sub>3</sub>N<sub>2</sub>O<sub>6</sub>: 429.1268, Found: 429.1278.



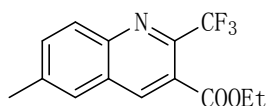
ethyl 4-(cyanomethyl)-2-(trifluoromethyl)quinoline-3-carboxylate (**2n**): Isolated (Rf =

0.5, EtOAc–petroleum ether = 1:10) as a yellow solid (46.8 mg, 76% yield), mp: 117–119 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.46 (t, *J* = 7.2 Hz, 3H), 4.24 (s, 2H), 4.53 (q, *J* = 7.2 Hz, 2H), 7.90 (t, *J* = 8.4 Hz, 1H), 7.97 (t, *J* = 8.0 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 8.31 (d, *J* = 8.2 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 13.8, 17.8, 63.4, 115.1, 120.9 (q, <sup>1</sup>*J*<sub>C-F</sub> = 274.4 Hz), 123.2, 125.1, 126.0, 130.8, 131.5, 132.2, 136.2, 144.07 (q, <sup>2</sup>*J*<sub>C-F</sub> = 34.6 Hz), 146.5, 165.5; HRMS (ESI): *m/z* [M + Na]<sup>+</sup> calcd for C<sub>15</sub>H<sub>11</sub>F<sub>3</sub>N<sub>2</sub>NaO<sub>2</sub>: 331.0665, Found: 331.0666.



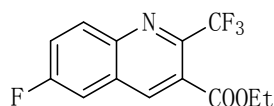
Ethyl 4-(1-methoxy-1-oxopropan-2-yl)-2-(trifluoromethyl)quinoline-3-carboxylate (**3a**): Isolated (R<sub>f</sub> = 0.5, EtOAc–petroleum ether = 1:10) as a white solid, mp: 64–66 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.45 (t, *J* = 7.2 Hz, 3H), 4.48 (q, *J* = 7.2 Hz, 2H), 7.74 (t, *J* = 7.2 Hz, 1H), 7.91 (t, *J* = 7.2 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 8.69 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 13.9, 62.5, 121.1 (q, <sup>1</sup>*J*<sub>C-F</sub> = 274.5 Hz), 124.1, 127.5, 128.2, 129.5, 130.1, 132.3, 140.1, 144.7 (q, <sup>2</sup>*J*<sub>C-F</sub> = 34.9 Hz), 146.9, 165.5; HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>11</sub>F<sub>3</sub>NO<sub>4</sub>: 270.0736, Found: 270.0755.

*General procedure for copper-catalyze intramolecular oxidative cyclization of N-(2-alkenylaryl) enamines (1s-v)*: To a 25 mL tube containing a magnetic stir bar, was added *N*-(2-alkenylaryl) enamine **1** (0.2 mmol), CuI (10 mol%), and DCE (2 mL). The resulting mixture was stirred at 60 °C in air for overnight (monitored by TLC). After being cooling to room temperature, evaporation of the solvent under reduced pressure followed purification by silica gel chromatography using petroleum ether/ethyl acetate (10:1) as eluent to provide the desired products **3b-e**.

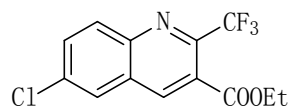


Ethyl 6-methyl-2-(trifluoromethyl)quinoline-3-carboxylate (**3b**): Isolated (R<sub>f</sub> = 0.5, EtOAc–petroleum ether = 1:10) as a white solid (38.5 mg, 68% yield), mp: 49–50 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.44 (t, *J* = 6.6 Hz, 3H), 2.59 (s, 3H), 4.47 (q, *J* = 6.8

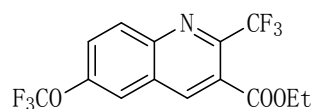
Hz, 2H), 7.70 (s, 1H), 7.72 (t,  $J = 8.4$  Hz, 1H), 8.11 (d,  $J = 8.4$  Hz, 1H), 8.57 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.0, 21.8, 62.4, 121.3 (q,  $^1J_{\text{C-F}} = 273.9$  Hz), 124.0, 126.9, 127.5, 129.7, 134.8, 139.3, 140.1, 143.8 (q,  $^2J_{\text{C-F}} = 34.5$  Hz), 145.5, 165.7; HRMS (ESI):  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{14}\text{H}_{12}\text{F}_3\text{NNaO}_2$ : 306.0712; found: 306.0719.



Ethyl 6-fluoro-2-(trifluoromethyl)quinoline-3-carboxylate (**3c**): Isolated ( $R_f = 0.5$ , EtOAc–petroleum ether = 1:10) as a white solid (29.8 mg, 52% yield), mp: 78-79 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.44 (t,  $J = 7.2$  Hz, 3H), 4.48 (q,  $J = 7.2$  Hz, 2H), 7.59 (d,  $J = 8.0$  Hz, 1H), 7.67 (t,  $J = 8.4$  Hz, 1H), 8.27 (dd,  $J = 5.2, 9.2$  Hz, 1H), 8.63 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  13.9, 62.7, 111.3 (d,  $^2J_{\text{C-F}} = 22.1$  Hz), 121.0 (q,  $^1J_{\text{C-F}} = 273.8$  Hz), 122.9 (d,  $^2J_{\text{C-F}} = 25.9$  Hz), 124.9, 128.5 (d,  $^3J_{\text{C-F}} = 10.7$  Hz), 132.9 (d,  $^3J_{\text{C-F}} = 9.4$  Hz), 139.3, 144.0, 144.1 (q,  $^2J_{\text{C-F}} = 35.9$  Hz), 162.1 (d,  $^1J_{\text{C-F}} = 252.3$  Hz), 165.3; HRMS (ESI):  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{13}\text{H}_9\text{F}_4\text{NNaO}_2$ : 310.0462; found: 310.0471.



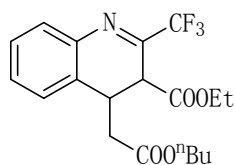
Ethyl 6-chloro-2-(trifluoromethyl)quinoline-3-carboxylate (**3d**): Isolated ( $R_f = 0.5$ , EtOAc–petroleum ether = 1:10) as a white solid (34.5 mg, 57% yield), mp: 81-82 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.45 (t,  $J = 7.0$  Hz, 3H), 4.48 (q,  $J = 7.2$  Hz, 2H), 7.84 (d,  $J = 9.2$  Hz, 2H), 7.95 (s, 1H), 8.19 (d,  $J = 9.2$  Hz, 1H), 8.60 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  13.9, 62.7, 121.0 (q,  $^1J_{\text{C-F}} = 272.9$  Hz), 125.0, 126.7, 128.1, 131.7, 133.4, 135.7, 139.0, 144.9 (q,  $^2J_{\text{C-F}} = 35.2$  Hz), 145.2, 165.2; HRMS (ESI):  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{13}\text{H}_9\text{ClF}_3\text{NNaO}_2$ : 326.0166; found: 326.0191.



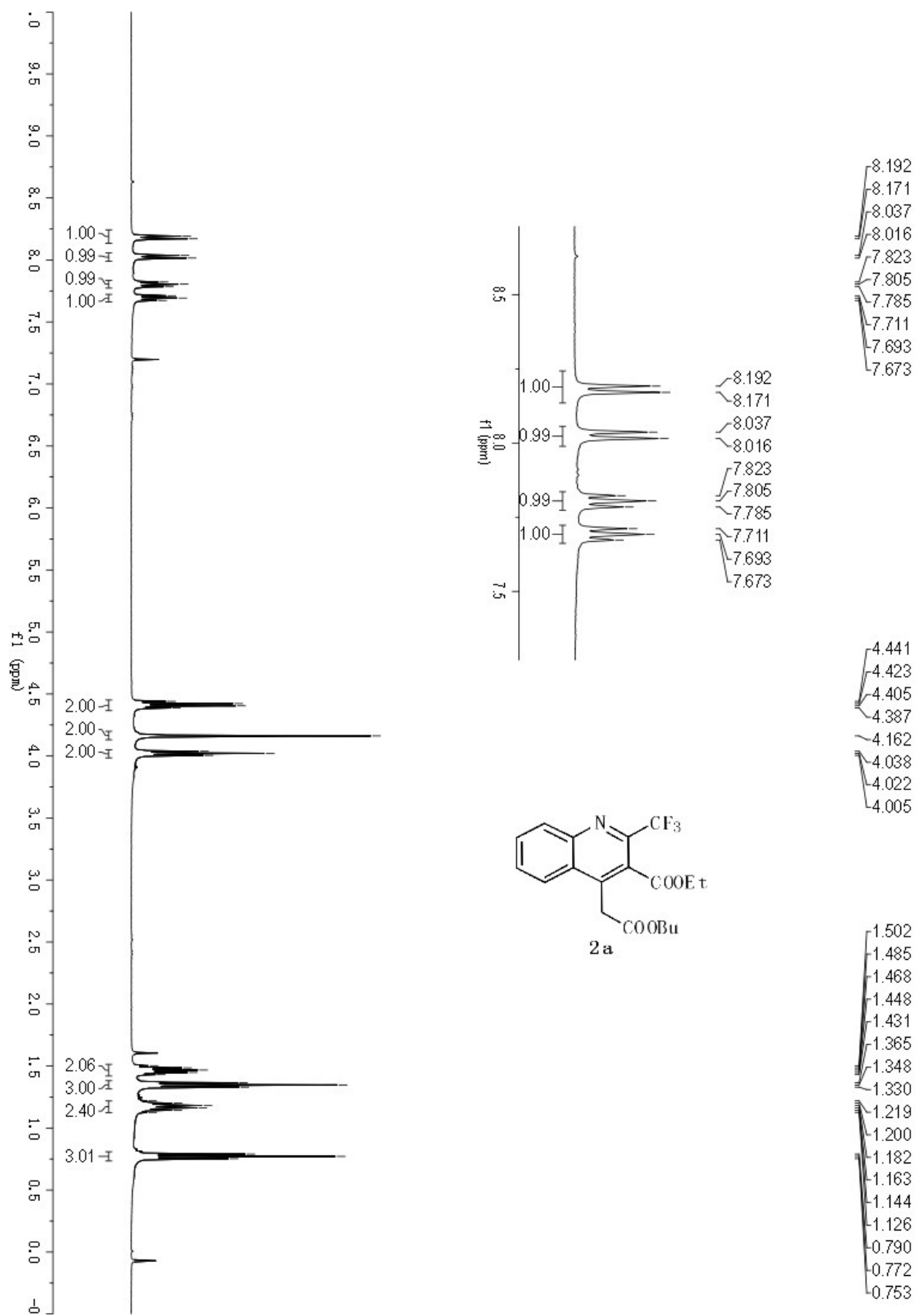
Ethyl 6-(trifluoromethoxy)-2-(trifluoromethyl)quinoline-3-carboxylate (**3e**): Isolated ( $R_f = 0.5$ , EtOAc–petroleum ether = 1:10) as a white solid (46.6 mg, 66% yield), mp: 76-77 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.45 (t,  $J = 7.0$  Hz, 3H), 4.49 (q,  $J = 7.2$  Hz, 2H), 7.75 (d,  $J = 8.8$  Hz, 1H), 7.79 (s, 1H), 8.31 (d,  $J = 9.2$  Hz, 1H), 8.70 (s, 1H);  $^{13}\text{C}$

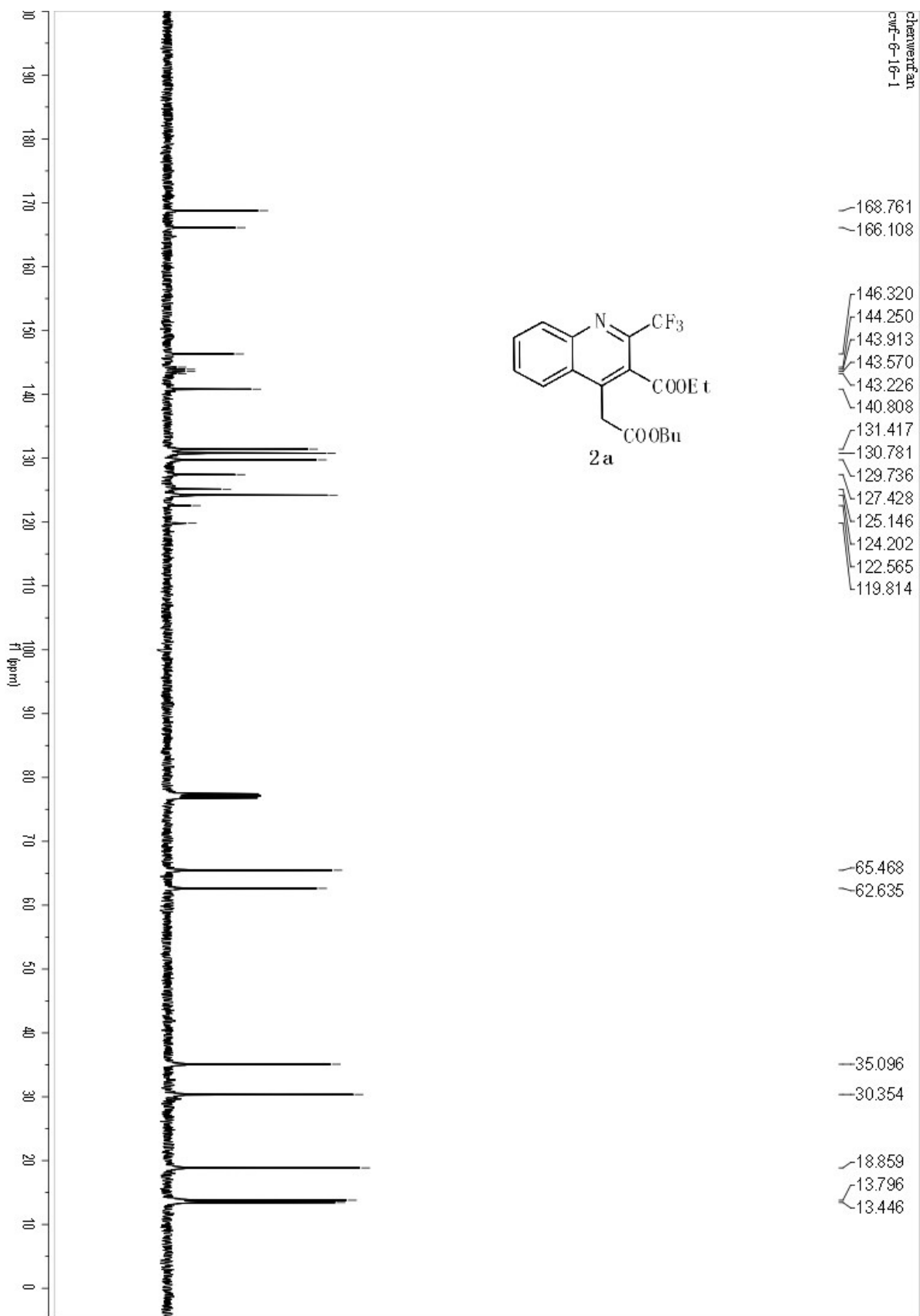


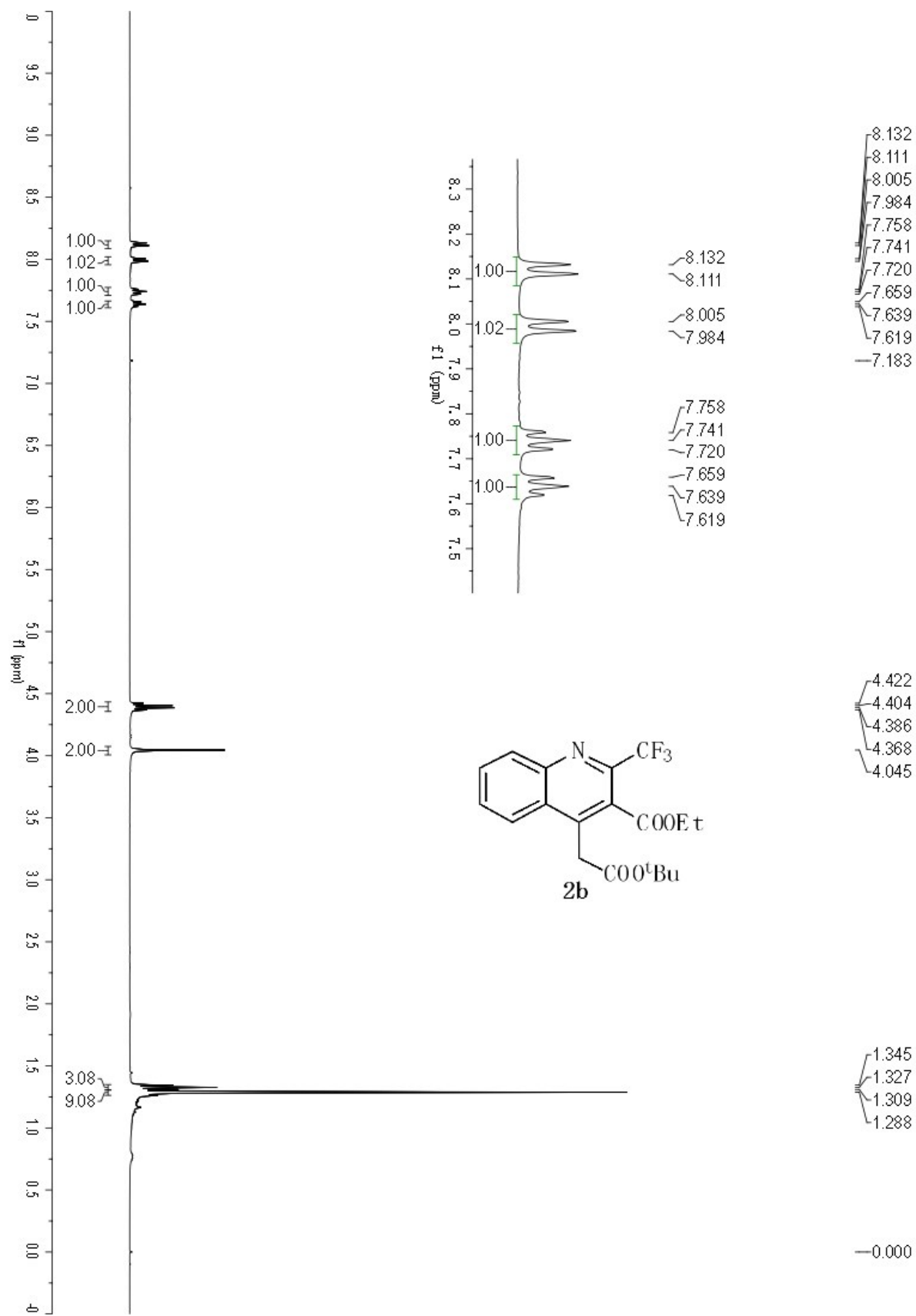
NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  13.9, 62.7, 117.4, 120.4 (q,  $^1J_{C-F}$  = 258.0 Hz), 120.9 (q,  $^1J_{C-F}$  = 274.2 Hz), 125.2, 126.3, 127.9, 132.6, 139.8, 145.0, 145.2 (q,  $^2J_{C-F}$  = 35.5 Hz), 149.1, 165.1; HRMS (ESI):  $m/z$  [M + Na]<sup>+</sup> calcd for C<sub>14</sub>H<sub>9</sub>F<sub>6</sub>NNaO<sub>3</sub>: 376.0739, Found: 376.0769.

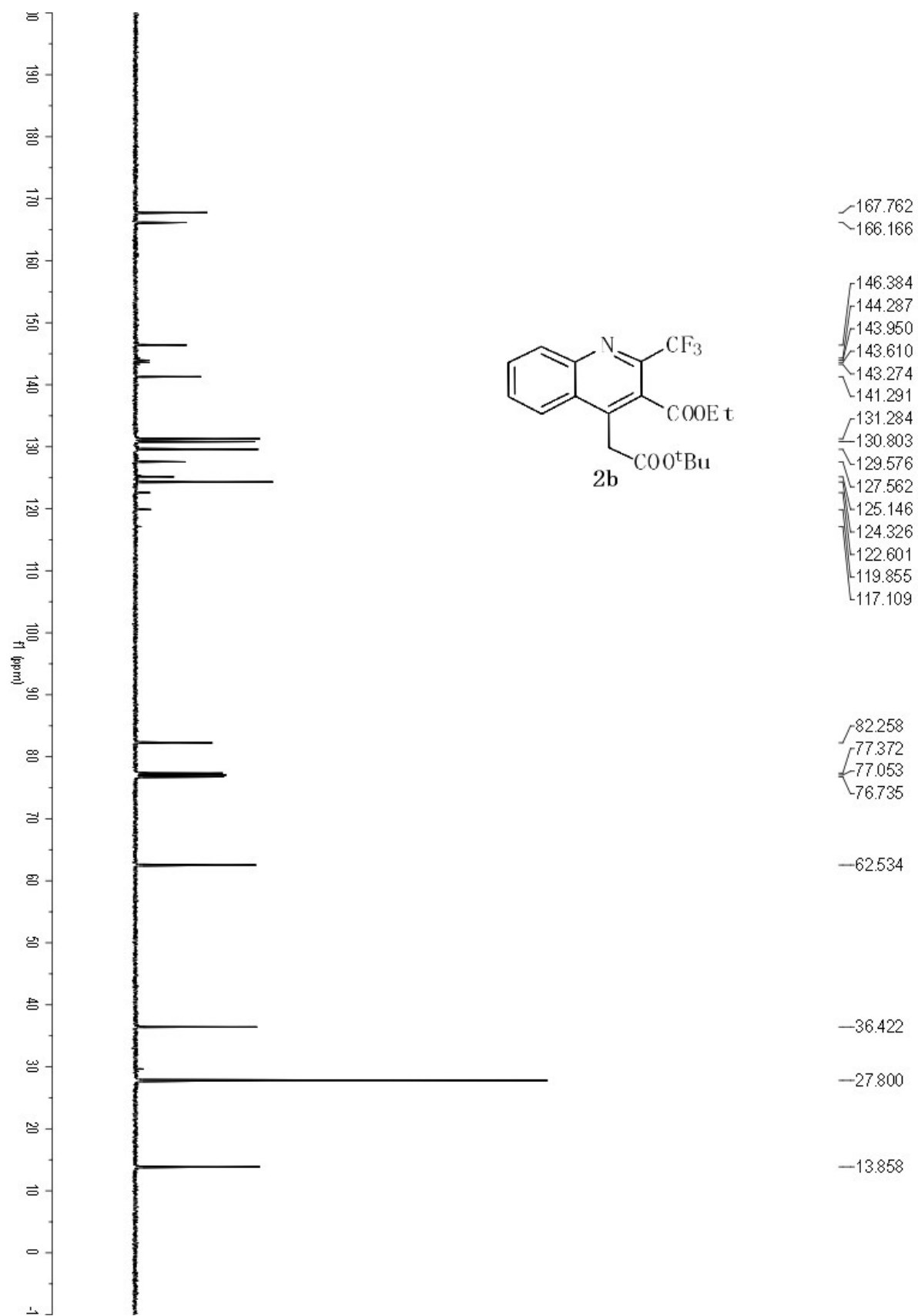


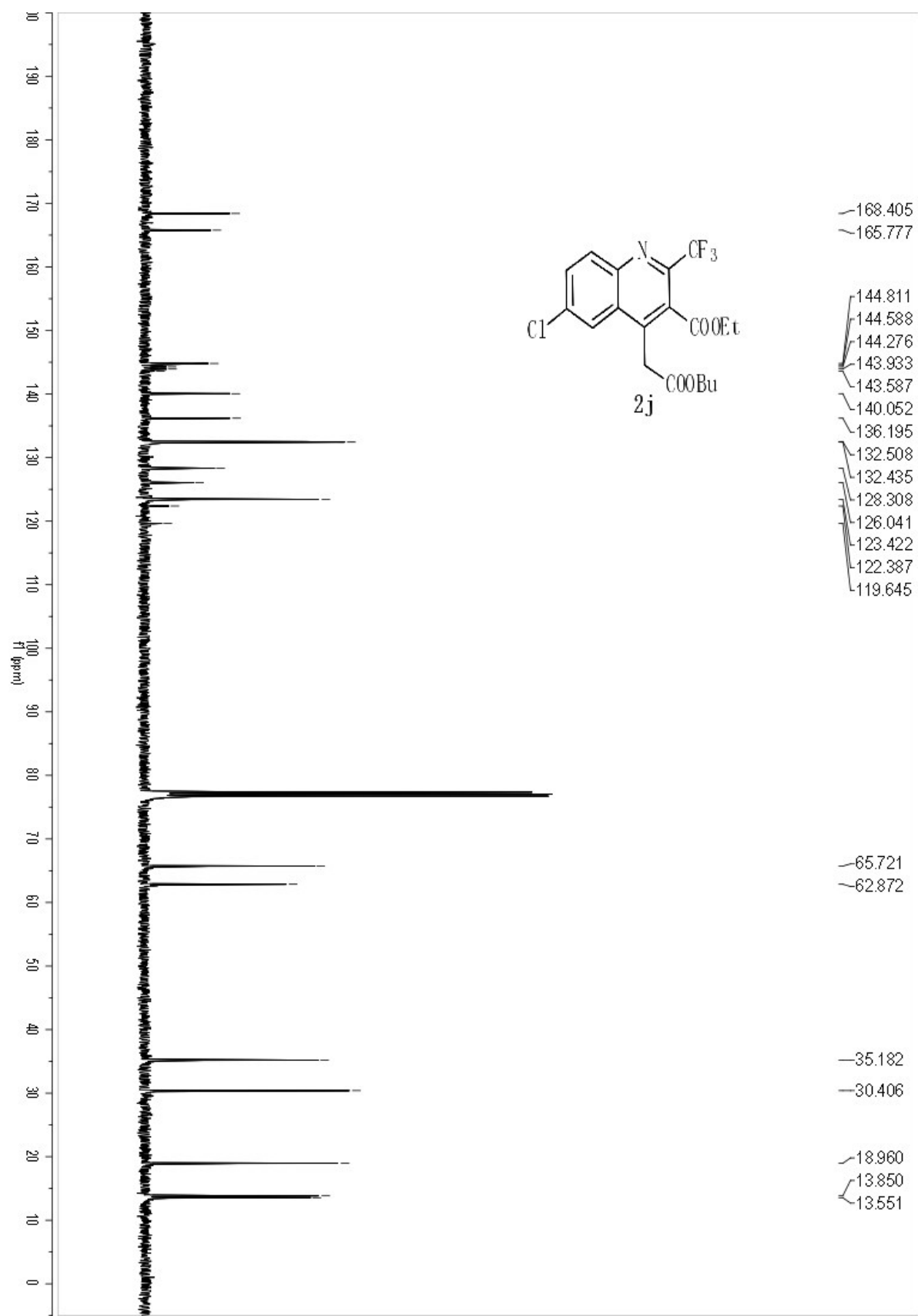
Ethyl 4-(2-butoxy-2-oxoethyl)-2-(trifluoromethyl)-3,4-dihydroquinoline-3-carboxylate (**4a**): Isolated ( $R_f$  = 0.5, EtOAc–petroleum ether = 1:10) as a yellow solid, mp: 68–70 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.88 (t,  $J$  = 7.2 Hz, 3H), 1.23–1.33 (m, 5H), 1.48–1.55 (m, 2H), 2.47 (dd,  $J$  = 8.8, 14.4 Hz, 2H), 2.61 (dd,  $J$  = 8.8, 14.4 Hz, 2H), 3.98 (t,  $J$  = 6.8 Hz, 3H), 4.25 (q,  $J$  = 7.2 Hz, 2H), 4.45–4.48 (m, 1H), 6.86 (d,  $J$  = 7.6 Hz, 1H), 7.04 (t,  $J$  = 7.6 Hz, 1H), 7.14–7.20 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  13.6, 13.9, 19.0, 30.5, 35.8, 41.8, 60.9, 64.4, 102.6, 115.2, 121.9 (q,  $^1J_{C-F}$  = 274.0 Hz), 122.9, 124.5, 127.7, 128.5, 135.4 (q,  $^2J_{C-F}$  = 33.7 Hz), 135.6, 164.8, 171.2; HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>23</sub>F<sub>3</sub>NO<sub>4</sub>: 386.1574, Found: 386.1579.

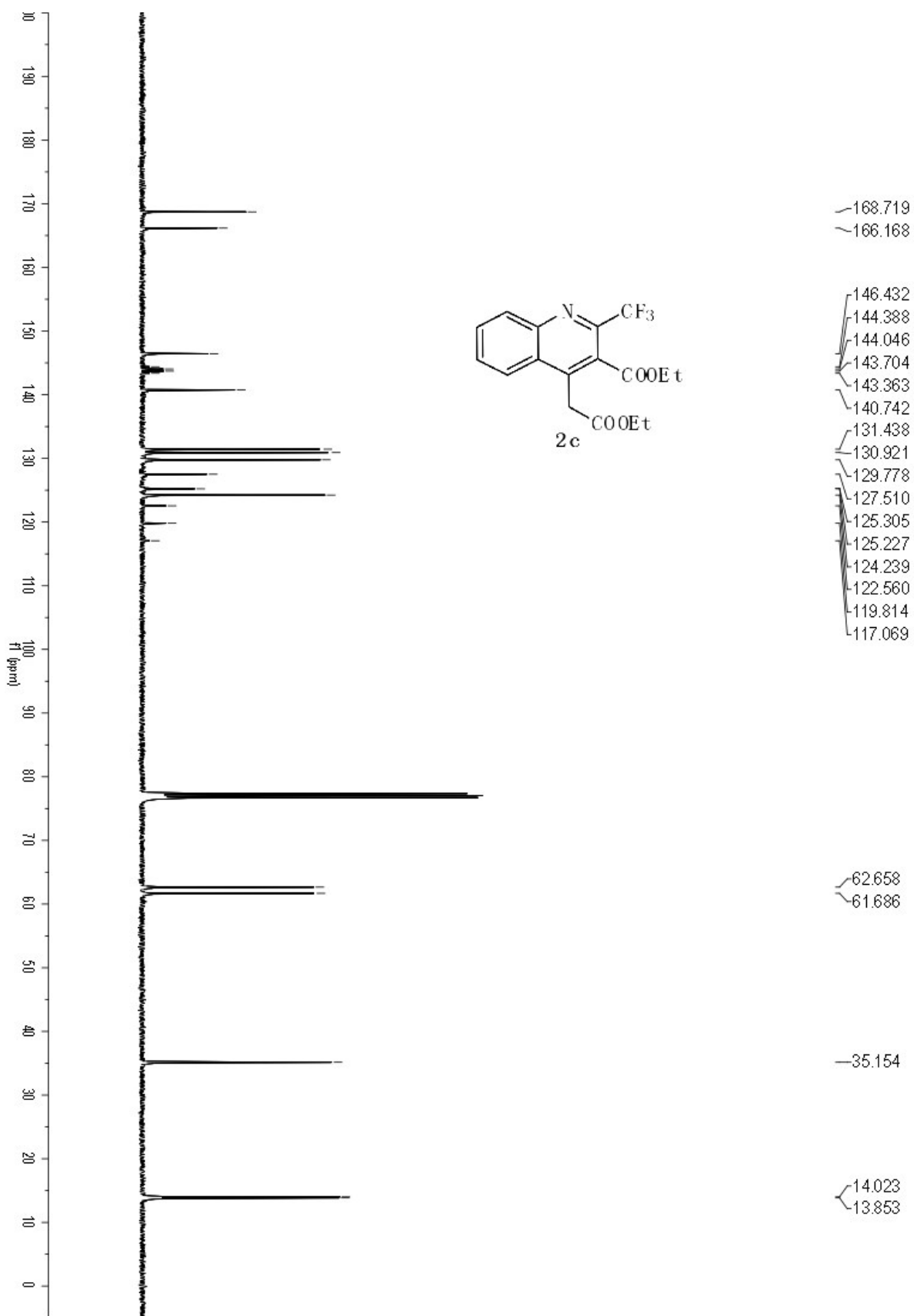


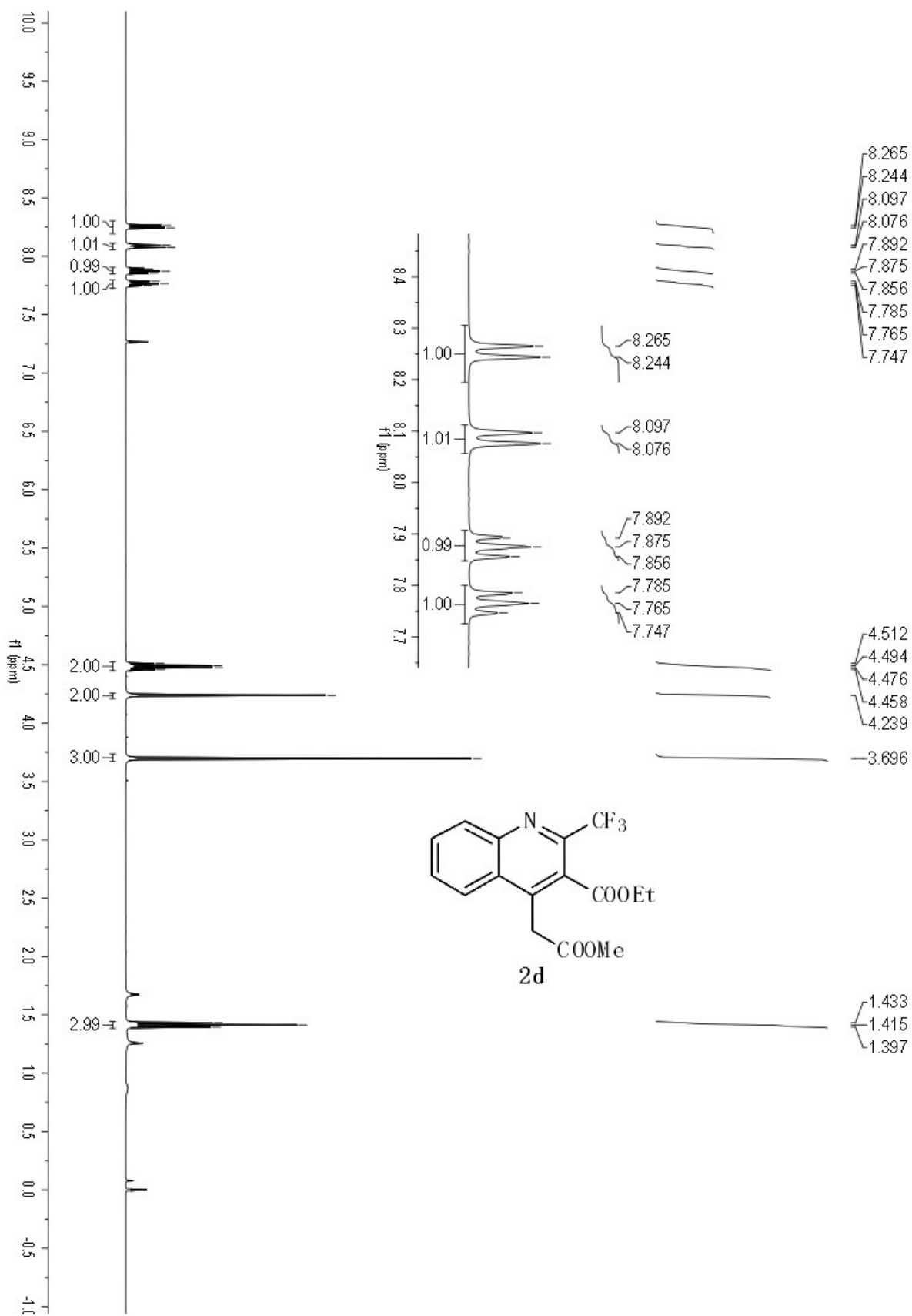




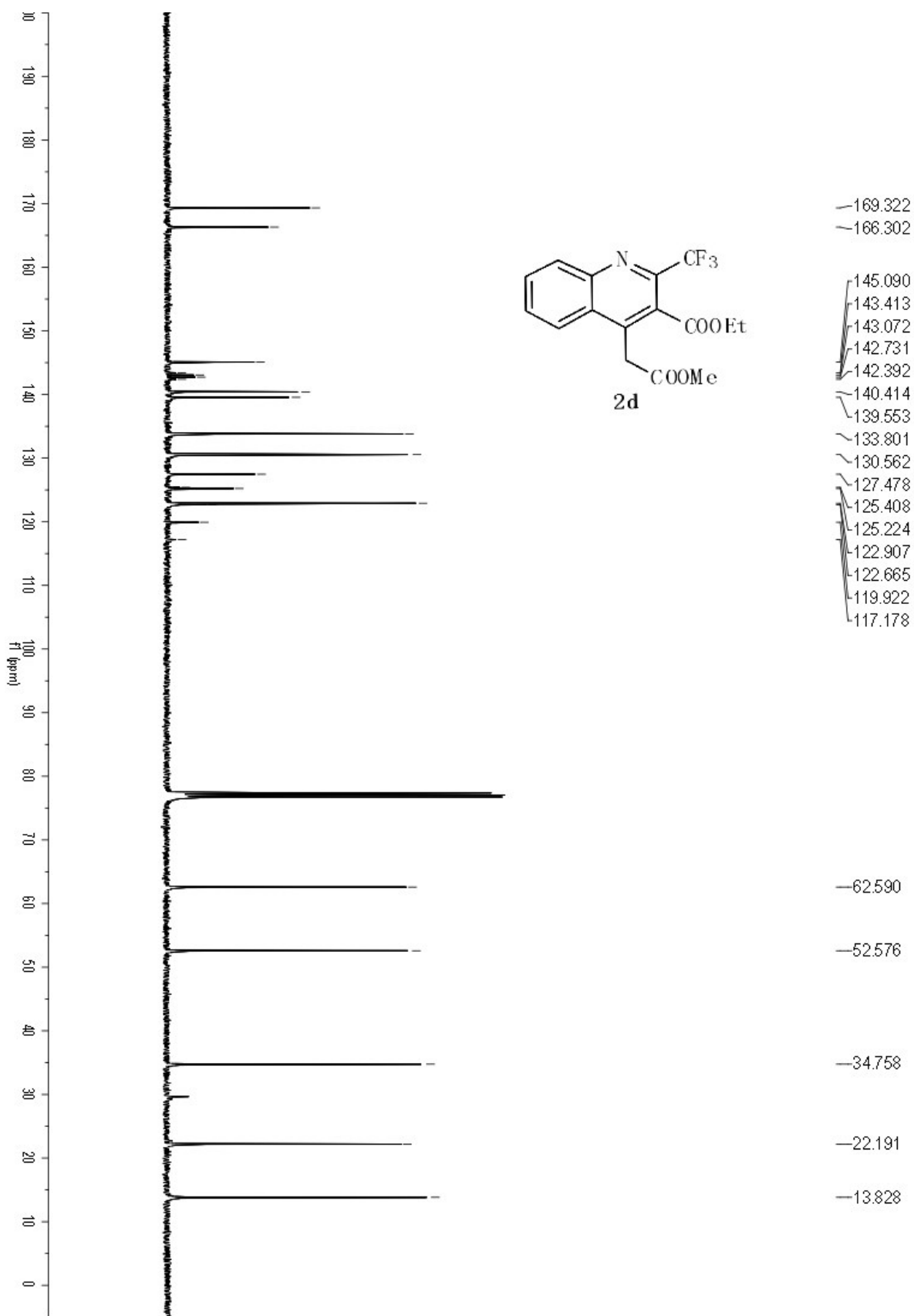


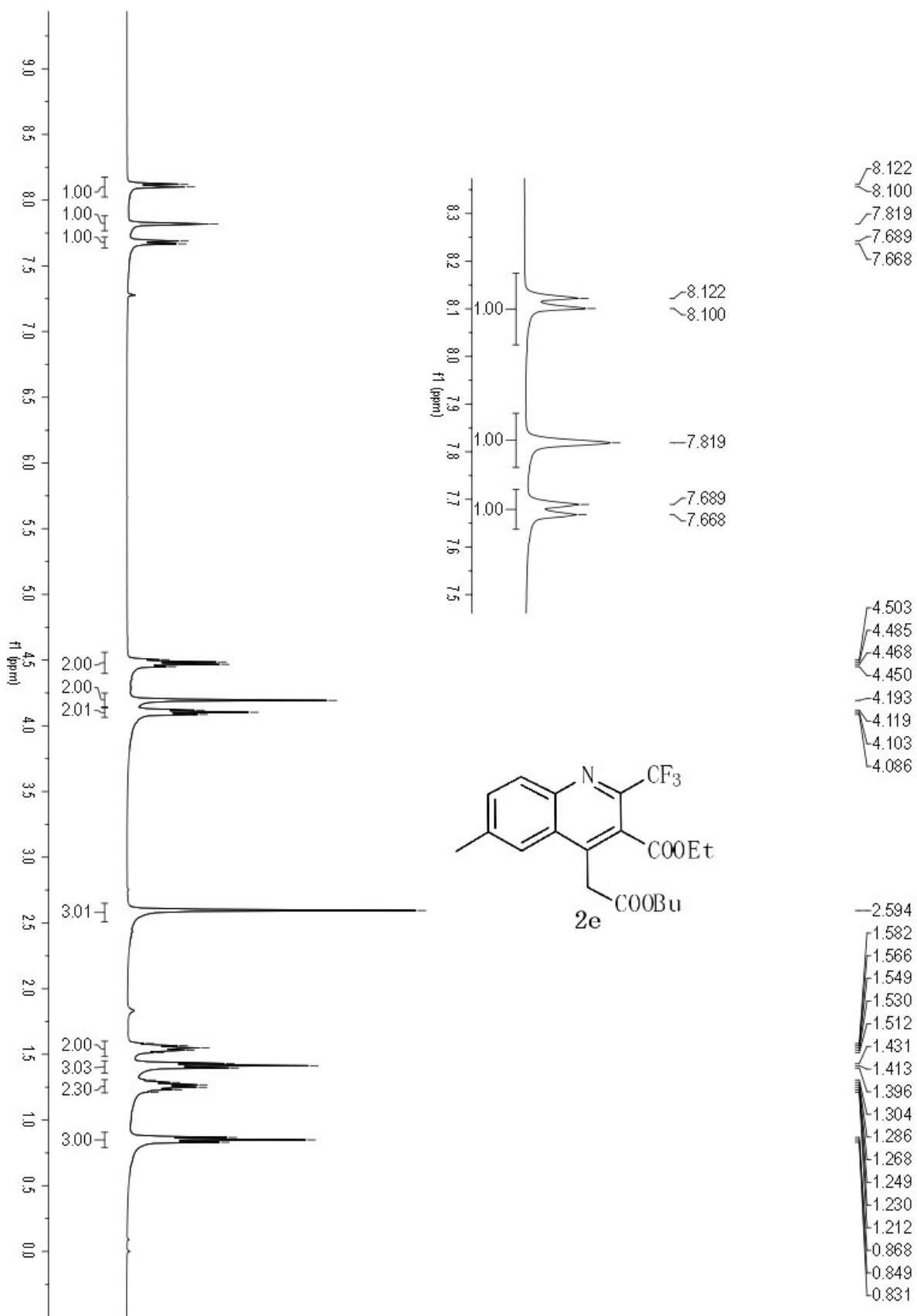




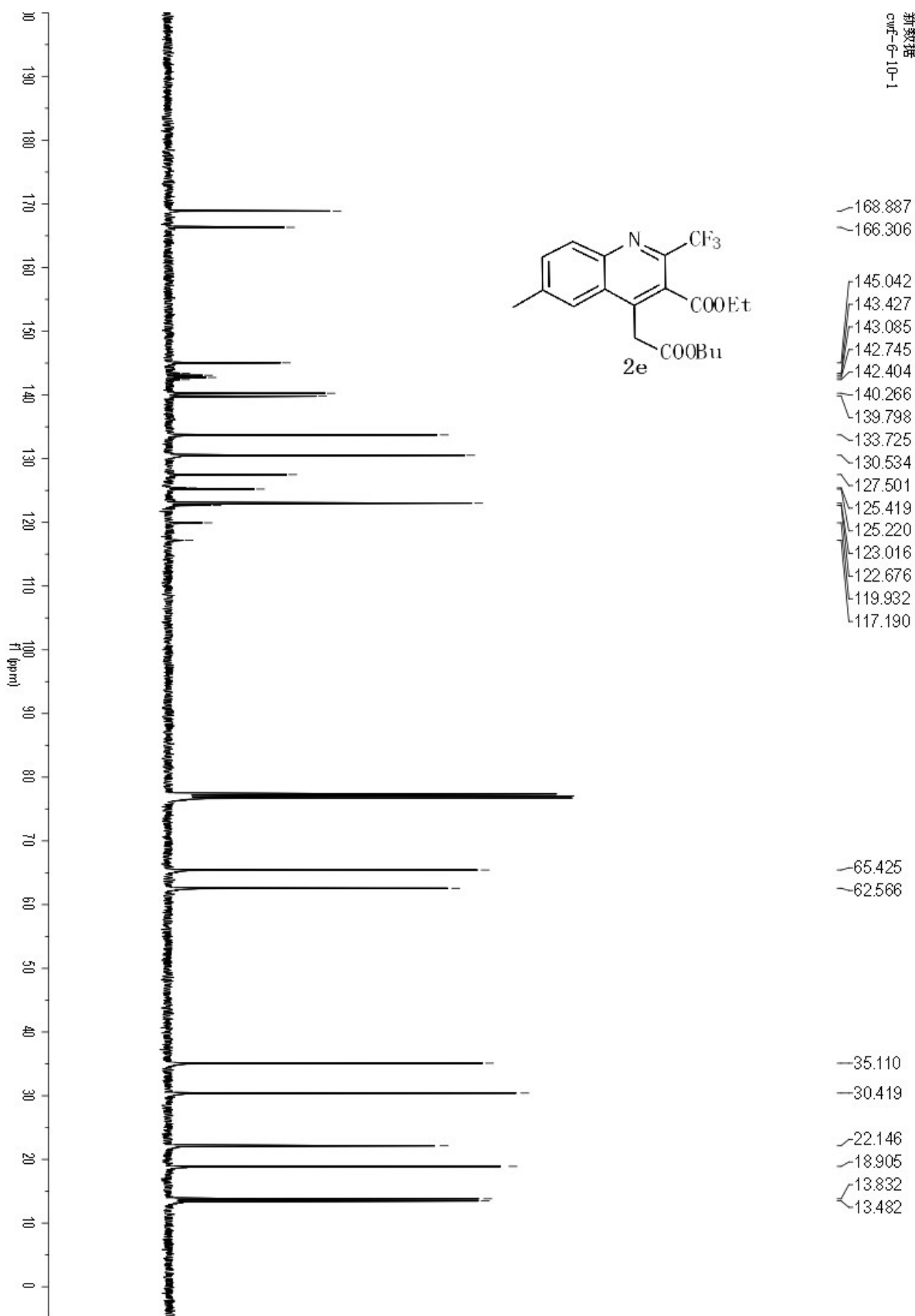
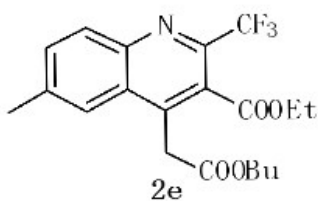


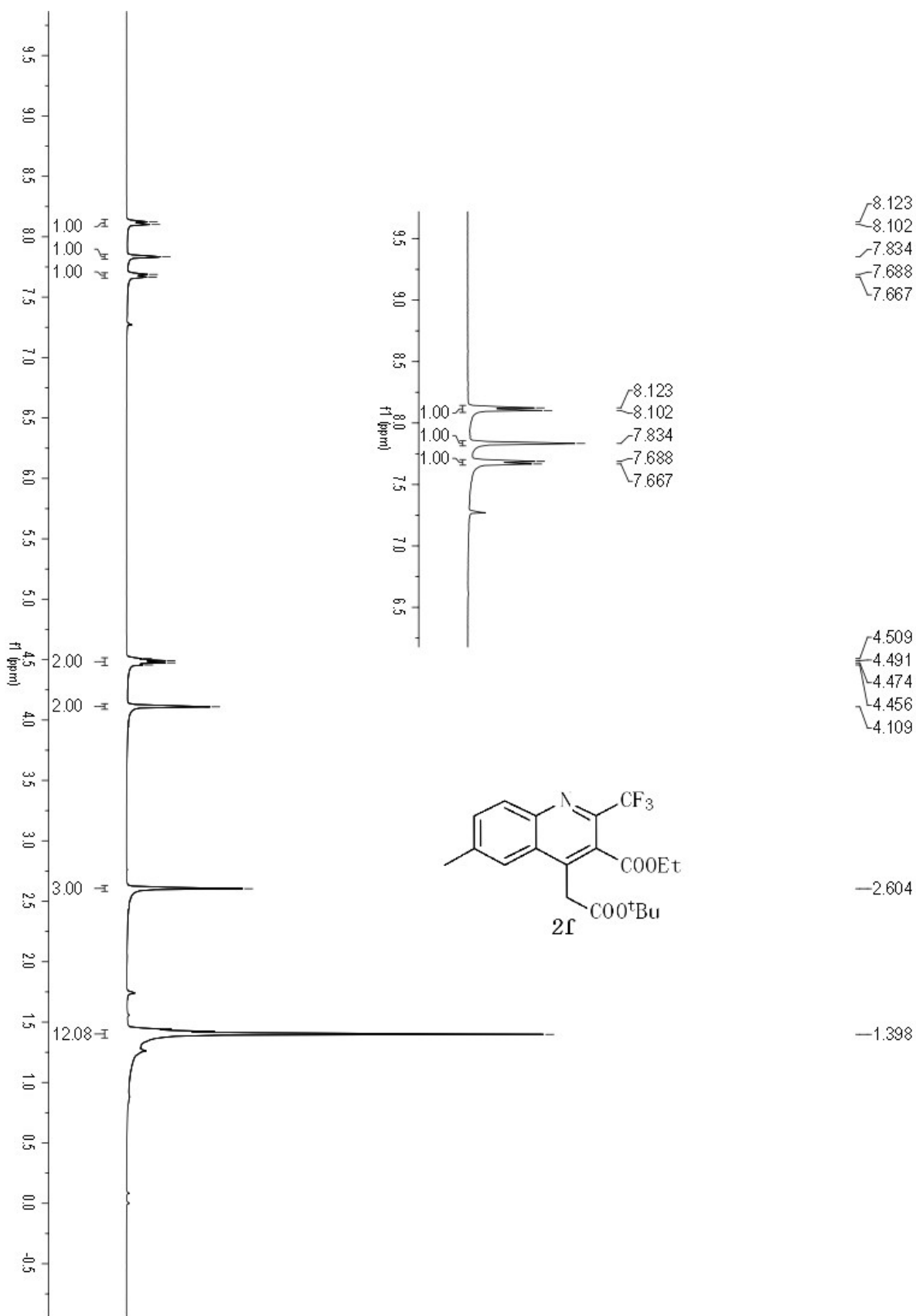


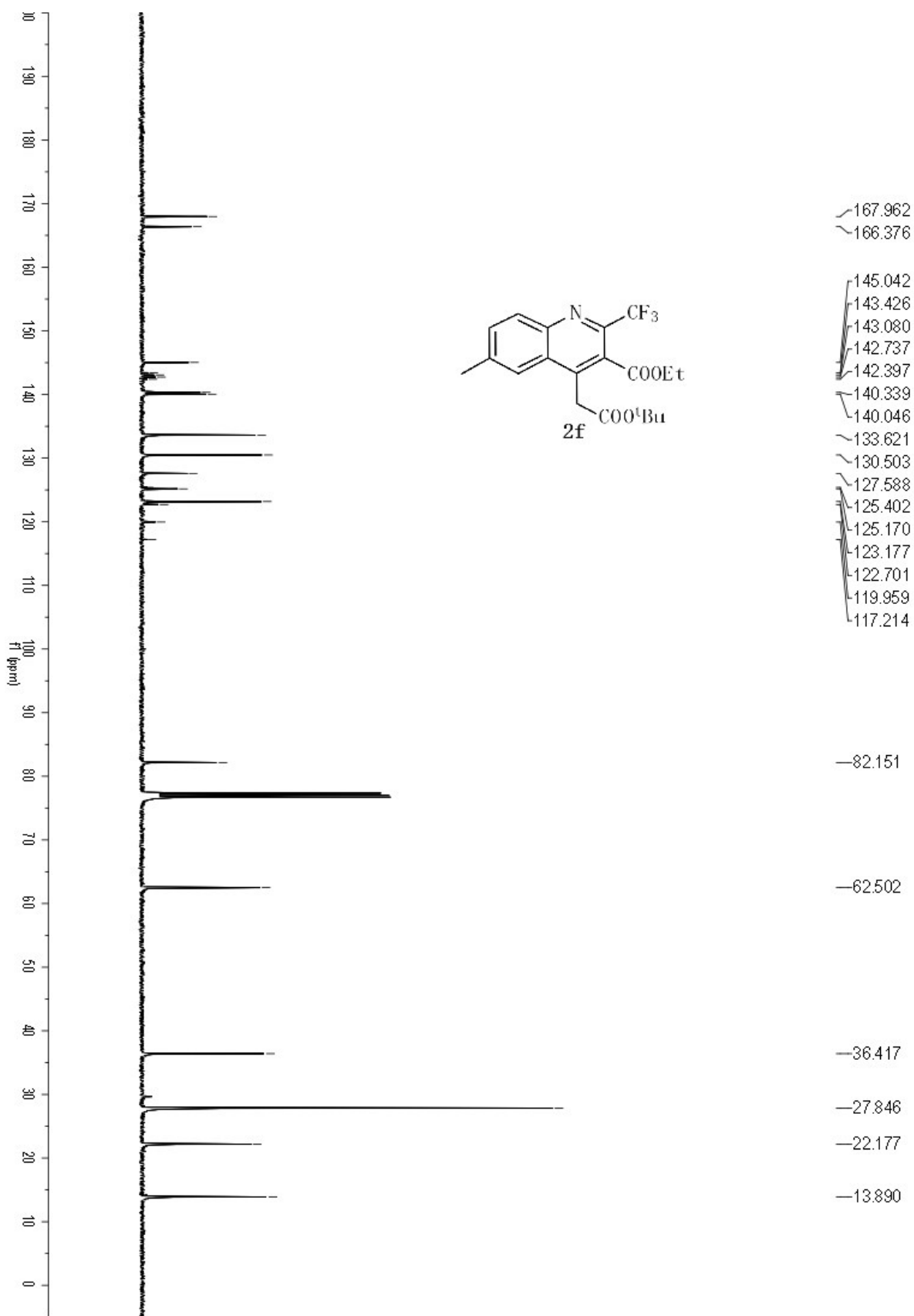


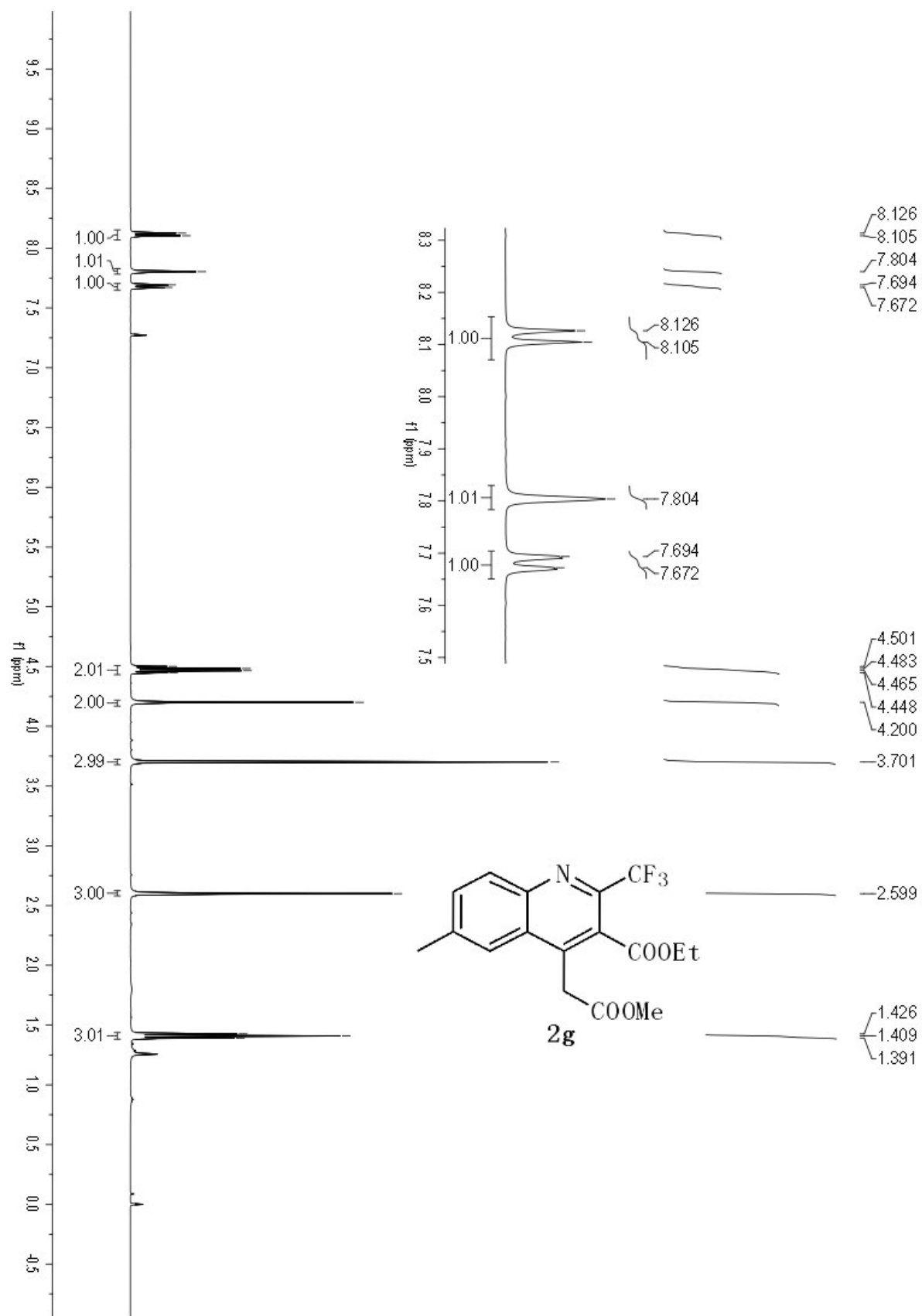


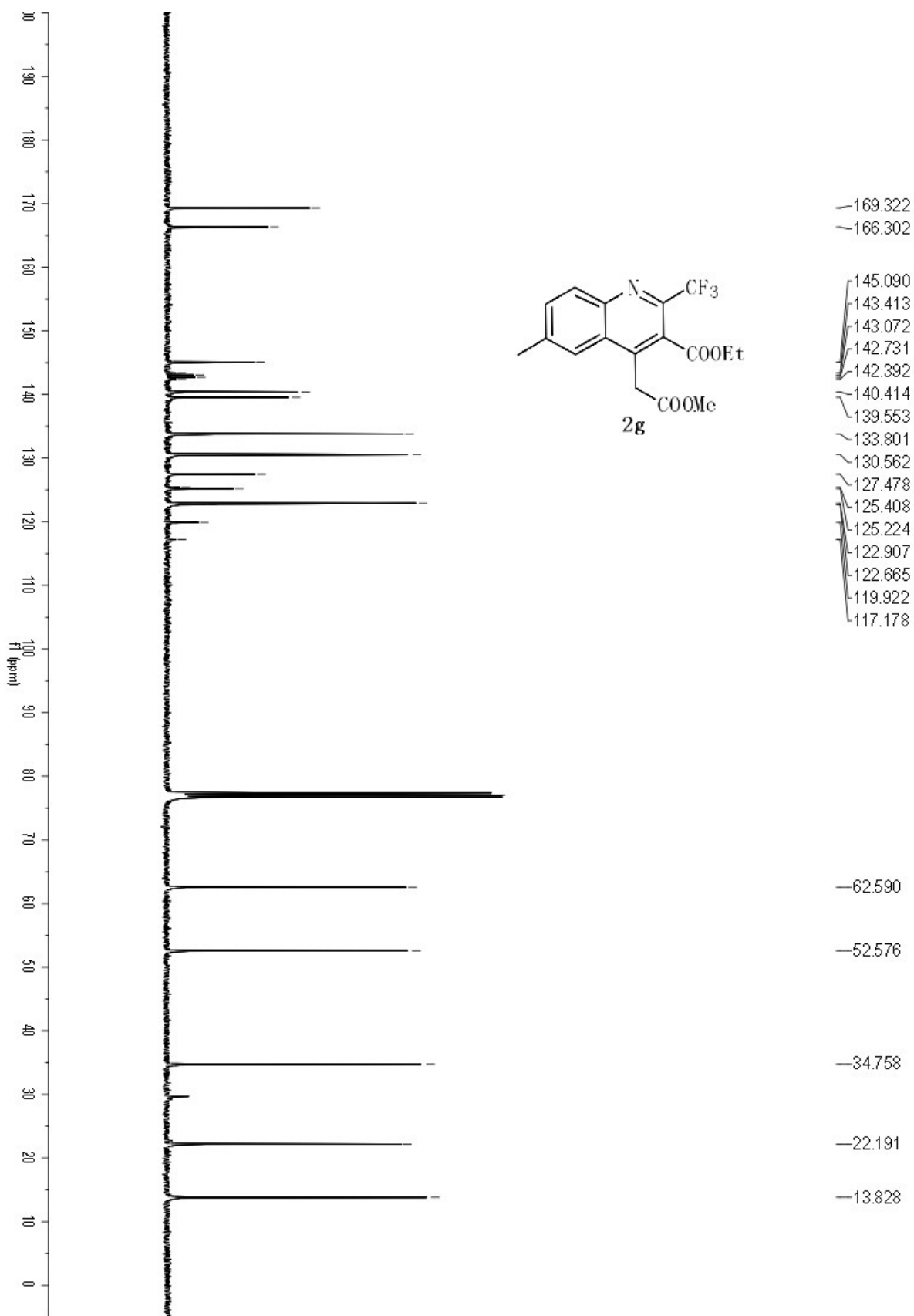
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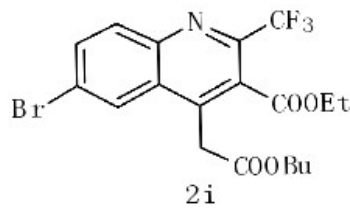
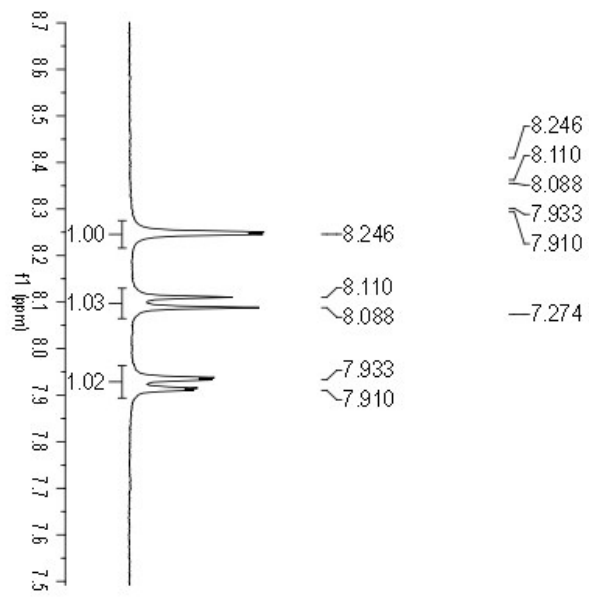
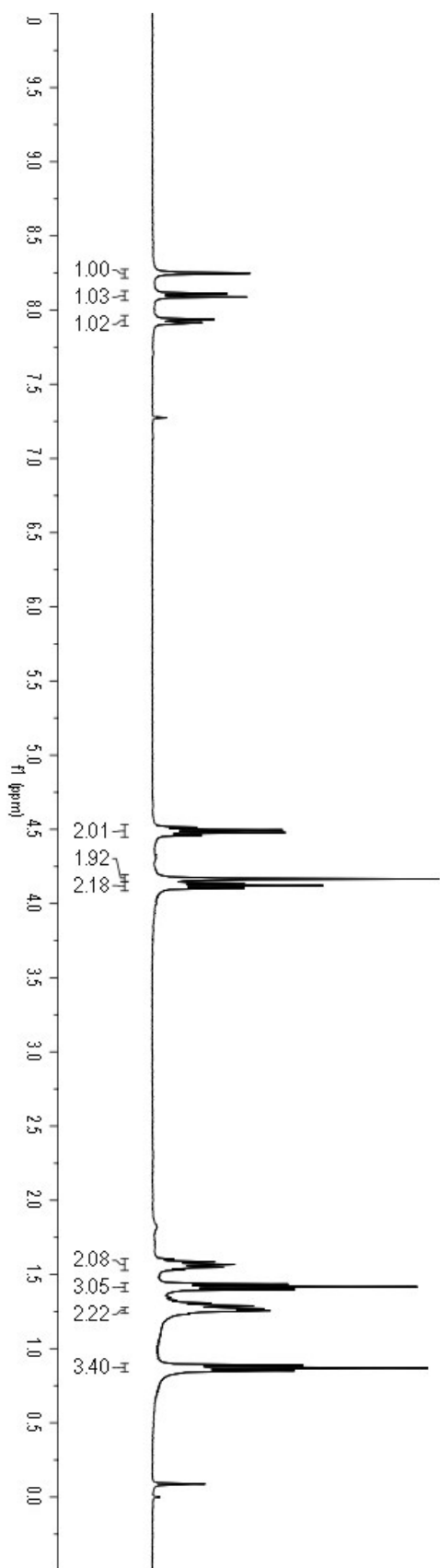












- 8.246
- 8.110
- 8.088
- 7.933
- 7.910
- 7.274
- 4.514
- 4.496
- 4.479
- 4.461
- 4.166
- 4.137
- 4.121
- 4.104
- 1.602
- 1.585
- 1.568
- 1.548
- 1.532
- 1.435
- 1.417
- 1.399
- 1.308
- 1.289
- 1.270
- 1.257
- 1.233
- 0.888
- 0.869
- 0.851



