

*Supporting Information*

tandem radical cyclization for the construction of 1-difluoroalkylated Isoquinolines via Cu

catalyzed and visible light-promoted two pathways

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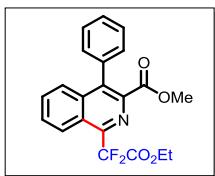
## 1. General Information

Procedure for the synthesis of **1a-1q** please see article.<sup>[1]</sup> Unless otherwise noted, otherwise noted, reagents were obtained from commercial suppliers and were used without further purification. <sup>1</sup>H NMR (400 MHz or 600 MHz) and <sup>13</sup>C NMR (150 MHz) spectra were obtained on Bruker 400 M or 600 M nuclear resonance spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet. Flash column chromatography was performed using 200-300 mesh silica gel.

General Procedure for the Synthesis of **3a-3q** using Cu/B<sub>2</sub>pin<sub>2</sub>: To a mixture of an appropriate **1a-1q** (0.2 mmol), CuBr (10 mol %) DTBDPy (10 mol %), B<sub>2</sub>pin<sub>2</sub> (1eq), NaOAc (2eq) in a standard Schlenk tube, The mixture was evacuated and backfilled with N<sub>2</sub> (3 times) the DCE (1.5 mL) was added via syringe. Then, ethyl bromodifluoroacetate (0.4mmol) was added, and the mixture was stirred at 100 °C for 8 h. The resulting reaction mixture was concentrated under reduced pressure and purified by column chromatography using petroleum ether/ethyl acetate to afford the corresponding products.

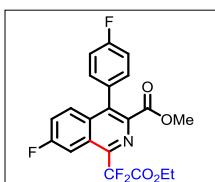
General Procedure for the Synthesis of **3a-3q** using photoredox catalysis: To a mixture of an appropriate **1a-1q** (0.2 mmol), *fac*-[Ir(ppy)<sub>3</sub>] (2 mol %), Na<sub>2</sub>CO<sub>3</sub> (2eq) in a standard Schlenk tube, The mixture was evacuated and backfilled with N<sub>2</sub> (3 times) the DMF (1.5 mL) was added via syringe. Then, ethyl bromodifluoroacetate (0.4mmol) was added, and the mixture was stirred in the blue LED at for 24 h. The resulting reaction mixture was concentrated under reduced pressure and purified by column chromatography using petroleum ether/ethyl acetate to afford the corresponding products.

## 2 Experimental Details

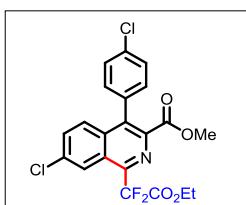


Methyl 1-(2-ethoxy-1,1-difluoro-2-oxoethyl)-4-phenylisoquinoline-3-carboxylate (**3a**)

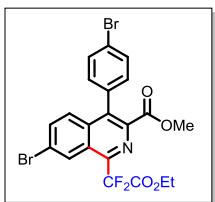
<sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 8.58 (d, *J* = 8.5 Hz, 1H), 7.86 – 7.75 (m, 1H), 7.71 (d, *J* = 5.1 Hz, 2H), 7.51 (d, *J* = 5.0 Hz, 3H), 7.37 – 7.29 (m, 2H), 4.54 (q, *J* = 7.0 Hz, 2H), 3.67 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 3H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 166.4, 163.5 (t, *J* = 30.2 Hz), 149.3 (t, *J* = 28.7 Hz), 139.5, 137.3, 137.2, 135.3, 131.4, 129.8, 129.5, 128.5, 128.5, 127.6, 125.7, 125.2 (t, *J* = 4.5 Hz), 115.5 (t, *J* = 253.5 Hz), 63.4, 52.4, 14.1. <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -98.26. HRMS (ESI) calcd for C<sub>21</sub>H<sub>17</sub>F<sub>2</sub>NO<sub>4</sub> (M+Na)<sup>+</sup>: 408.1018, found 408.1012.



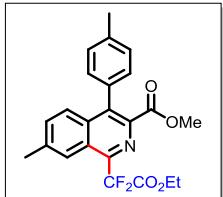
Methyl 1-(2-ethoxy-1,1-difluoro-2-oxoethyl)-7-fluoro-4-(4-fluorophenyl)isoquinoline-3-carboxylate (**3b**) <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 8.19 (dd, *J* = 9.5, 2.2 Hz, 1H), 7.70 (dd, *J* = 9.4, 5.4 Hz, 1H), 7.52 (m, 1H), 7.33 – 7.18 (m, 4H), 4.54 (q, *J* = 7.1 Hz, 2H), 3.70 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 3H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 166.0, 163.8, 163.1 (t, *J* = 30.2 Hz), 162.2, 161.5, 149.0, 139.3, 136.4, 134.5, 131.3 (d, *J* = 9.0 Hz), 130.8 (d, *J* = 3.0 Hz), 130.4 (d, *J* = 9.0 Hz), 126.8 (d, *J* = 10.6 Hz), 122.2 (d, *J* = 9.0 Hz), 115.9, 115.7, 115.2 (t, *J* = 253.7 Hz), 109.6 (d, *J* = 22.7 Hz), 63.5, 52.5, 14.1. <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -98.96, -105.62, -112.57. HRMS (ESI) calcd for C<sub>21</sub>H<sub>15</sub>F<sub>4</sub>NO<sub>4</sub> (M+Na)<sup>+</sup>: 444.0829, found 444.0830.



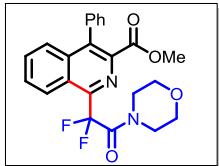
Methyl 7-chloro-4-(4-chlorophenyl)-1-(2-ethoxy-1,1-difluoro-2-oxoethyl)isoquinoline-3-carboxylate (**3c**) <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 8.55 (d, *J* = 2.0 Hz, 1H), 7.68 (dd, *J* = 9.1, 2.0 Hz, 1H), 7.60 (d, *J* = 9.1 Hz, 1H), 7.55 – 7.43 (m, 2H), 7.28 – 7.20 (m, 2H), 4.54 (q, *J* = 7.1 Hz, 2H), 3.71 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 3H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 165.8, 163.1 (t, *J* = 31.7 Hz), 148.8 (t, *J* = 30.2 Hz), 139.5, 136.6, 136.2, 135.6, 135.0, 133.2, 132.8, 130.8, 129.0, 129.0, 126.2, 124.4, 115.1 (t, *J* = 253.7 Hz), 63.5, 52.6, 14.1. <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -98.40. HRMS (ESI) calcd for C<sub>21</sub>H<sub>15</sub>Cl<sub>2</sub>F<sub>2</sub>NO<sub>4</sub> (M+Na)<sup>+</sup>: 476.0238, found 408.0240.



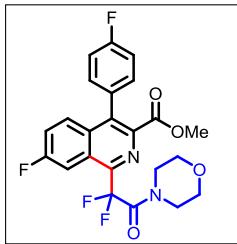
Methyl 7-bromo-4-(4-bromophenyl)-1-(2-ethoxy-1,1-difluoro-2-oxoethyl)isoquinoline-3-carboxylate (**3d**)  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.72 (d, *J* = 1.9 Hz, 1H), 7.81 (dd, *J* = 9.1, 1.9 Hz, 1H), 7.72 – 7.61 (m, 2H), 7.52 (d, *J* = 9.0 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 2H), 4.54 (q, *J* = 7.1 Hz, 2H), 3.71 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 3H).  $^{13}\text{C}$  NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$  165.7, 163.0 (t, *J* = 30.6 Hz), 148.8 (t, *J* = 30.2 Hz), 139.4, 136.3, 135.7, 135.3, 133.7, 131.9, 131.1, 128.9, 127.6, 126.5, 125.1, 123.2, 115.1 (t, *J* = 253.7 Hz), 63.6, 52.6, 14.1.  $^{19}\text{F}$  NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  -98.29. HRMS (ESI) calcd for C<sub>21</sub>H<sub>15</sub>Br<sub>2</sub>F<sub>2</sub>NO<sub>4</sub> (M+Na)<sup>+</sup> : 565.9208, found 565.9214.



Methyl 1-(2-ethoxy-1,1-difluoro-2-oxoethyl)-7-methyl-4-(p-tolyl) isoquinoline-3-carboxylate (**3e**)  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.31 (s, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.53 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.31 (d, *J* = 7.7 Hz, 2H), 7.18 (d, *J* = 7.8 Hz, 2H), 4.53 (q, *J* = 7.1 Hz, 2H), 3.69 (s, 3H), 2.60 (s, 3H), 2.46 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 3H).  $^{13}\text{C}$  NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$  166.5, 163.6 (t, *J* = 31.7 Hz), 148.3 (d, *J* = 28.7 Hz), 140.3, 138.6, 138.2, 137.6, 135.7, 133.5, 132.5, 129.4, 129.1, 127.5, 126.0, 123.9, 115.7 (t, *J* = 253.7 Hz), 63.3, 52.3, 22.3, 21.6, 14.1.  $^{19}\text{F}$  NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  -98.48. HRMS (ESI) calcd for C<sub>23</sub>H<sub>21</sub>F<sub>2</sub>NO<sub>4</sub> (M+Na)<sup>+</sup> : 436.1331, found 436.1339.

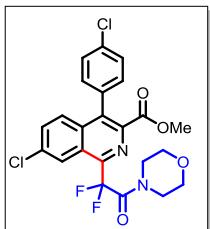


Methyl 1-(1,1-difluoro-2-morpholino-2-oxoethyl)-4-phenylisoquinoline-3-carboxylate (**3f**)  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.65 (d, *J* = 8.5 Hz, 1H), 7.89 – 7.69 (m, 3H), 7.52 (dd, *J* = 5.3, 1.8 Hz, 3H), 7.33 (dd, *J* = 6.3, 2.6 Hz, 2H), 3.82 (s, 4H), 3.67 (d, *J* = 3.8 Hz, 5H), 3.61 (d, *J* = 5.1 Hz, 2H).  $^{13}\text{C}$  NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$  166.4, 162.1 (t, *J* = 27.2 Hz), 149.6 (t, *J* = 30.2 Hz), 139.8, 137.3, 137.2, 135.2, 131.5, 129.8, 129.5, 128.6, 128.5, 127.6, 125.7, 125.6, 116.6 (t, *J* = 252.2 Hz), 66.7 (d, *J* = 71.0 Hz), 52.5, 47.4, 43.7.  $^{19}\text{F}$  NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  -92.02. HRMS (ESI) calcd for C<sub>23</sub>H<sub>20</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub> (M+Na)<sup>+</sup> : 449.1283, found 449.1281.

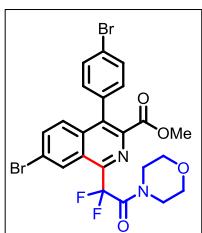


Methyl 1-(1,1-difluoro-2-morpholino-2-oxoethyl)-7-fluoro-4-(4-fluorophenyl)isoquinoline-3-carboxylate (**3g**)  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.25 (d, *J* = 9.7 Hz, 1H), 7.72 (dd, *J* = 9.5, 5.4 Hz, 1H), 7.53 (t, *J* = 8.3 Hz, 1H), 7.33 – 7.20 (m, 4H), 3.82 (s, 4H), 3.72 (d, *J* = 1.6 Hz, 3H), 3.67 (d, *J* = 5.0 Hz, 2H), 3.62 (d, *J* = 5.0 Hz, 2H).  $^{13}\text{C}$  NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$  166.1, 163.8, 163.2, 162.2, 161.9–161.5 (m), 149.4 (t, *J* = 30.2 Hz), 139.5, 136.3, 134.6, 131.3 (d, *J* = 10.6 Hz), 130.7 (t, *J* = 3.0

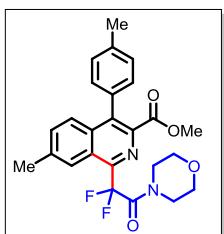
Hz), 130.4 (t,  $J$  = 21.1 Hz), 127.1 (t,  $J$  = 10.6 Hz), 122.3 (t,  $J$  = 24.2 Hz), 116.4 (t,  $J$  = 253.7 Hz), 115.9 (t,  $J$  = 21.1 Hz), 109.9 (t,  $J$  = 22.7 Hz), 66.7 (t,  $J$  = 68.0 Hz), 52.7, 47.4, 43.8.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -92.76, -92.78, -105.35, -112.40. HRMS (ESI) calcd for  $\text{C}_{23}\text{H}_{18}\text{F}_4\text{N}_2\text{O}_4$  ( $\text{M}+\text{Na}$ ) $^+$  : 485.1095, found 485.1101.



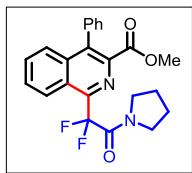
Methyl 7-chloro-4-(4-chlorophenyl)-1-(1,1-difluoro-2-morpholino-2-oxoethyl)isoquinoline-3-carboxylate (**3h**)  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.60 (d,  $J$  = 2.0 Hz, 1H), 7.69 (dd,  $J$  = 9.2, 2.0 Hz, 1H), 7.62 (d,  $J$  = 9.1 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.26 (s, 2H), 3.82 (s, 4H), 3.73 (s, 3H), 3.68 (t,  $J$  = 4.6 Hz, 2H), 3.64 – 3.55 (m, 2H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  165.8, 161.7 (t,  $J$  = 27.2 Hz), 139.8, 136.7, 136.2, 135.7, 135.1, 133.1, 132.9, 130.8, 129.0, 129.0, 126.4, 124.8, 116.3 (t,  $J$  = 252.2 Hz), 66.7 (d,  $J$  = 71.0 Hz), 52.8, 47.4, 43.8.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -92.16. HRMS (ESI) calcd for  $\text{C}_{23}\text{H}_{18}\text{Cl}_2\text{F}_2\text{N}_2\text{O}_4$  ( $\text{M}+\text{Na}$ ) $^+$  : 517.0504, found 517.0510.



Methyl 7-bromo-4-(4-bromophenyl)-1-(1,1-difluoro-2-morpholino-2-oxoethyl)isoquinoline-3-carboxylate (**3i**)  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.78 (s, 1H), 7.82 (d,  $J$  = 9.1 Hz, 1H), 7.67 (d,  $J$  = 7.8 Hz, 2H), 7.54 (d,  $J$  = 9.2 Hz, 1H), 7.18 (d,  $J$  = 7.7 Hz, 2H), 3.83 (s, 4H), 3.73 (d,  $J$  = 1.7 Hz, 3H), 3.67 (d,  $J$  = 4.7 Hz, 2H), 3.60 (d,  $J$  = 4.9 Hz, 2H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  165.8, 161.6 (t,  $J$  = 27.2 Hz), 149.1 (t,  $J$  = 30.2 Hz), 139.7, 136.2, 135.8, 135.4, 133.5, 131.9, 131.1, 128.9, 128.0, 126.6, 125.2, 123.3, 116.3 (t,  $J$  = 252.2 Hz), 66.7 (d,  $J$  = 72.5 Hz), 52.8, 47.4, 43.8.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -92.00. HRMS (ESI) calcd for  $\text{C}_{23}\text{H}_{18}\text{Br}_2\text{F}_2\text{N}_2\text{O}_4$  ( $\text{M}+\text{Na}$ ) $^+$  : 606.9473, found 606.9477.



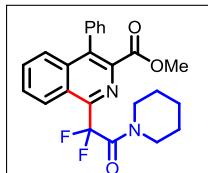
Methyl 1-(1,1-difluoro-2-morpholino-2-oxoethyl)-7-methyl-4-(p-tolyl)isoquinoline-3-carboxylate (**3j**)  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.38 (s, 1H), 7.65 (d,  $J$  = 8.8 Hz, 1H), 7.55 (d,  $J$  = 8.8 Hz, 1H), 7.32 (d,  $J$  = 7.6 Hz, 2H), 7.24 – 7.16 (m, 2H), 3.82 (s, 4H), 3.70 (d,  $J$  = 1.7 Hz, 3H), 3.65 (d,  $J$  = 4.6 Hz, 2H), 3.57 (d,  $J$  = 4.7 Hz, 2H), 2.61 (s, 3H), 2.47 (s, 3H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  166.6, 162.2 (t,  $J$  = 27.2 Hz), 148.6 (t,  $J$  = 30.2 Hz), 140.5, 138.9, 138.3, 137.5, 135.8, 133.7, 132.3, 129.4, 129.2, 127.4, 126.0, 124.3, 124.3, 116.8 (t,  $J$  = 252.2 Hz), 66.7 (d,  $J$  = 75.5 Hz), 52.4, 47.4, 43.7, 22.4, 21.6.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -92.10. HRMS (ESI) calcd for  $\text{C}_{25}\text{H}_{24}\text{F}_2\text{N}_2\text{O}_4$  ( $\text{M}+\text{Na}$ ) $^+$  : 477.1596, found 477.1605.



Methyl 1-(1,1-difluoro-2-oxo-2-(pyrrolidin-1-yl)ethyl)-4-phenylisoquinoline-3-carboxylate (**3k**)

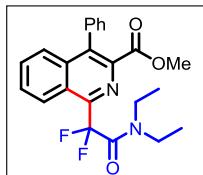
<sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 8.74 – 8.62 (m, 1H), 7.77 (m, 1H), 7.73 – 7.65 (m, 2H), 7.51 (dd, *J* = 5.2, 1.9 Hz, 3H), 7.38 – 7.29 (m, 2H), 3.75 – 3.56 (m, 7H), 1.91 (dq, *J* = 7.1, 4.1, 3.3 Hz, 4H).

<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 166.6, 162.0, 149.7, 139.8, 137.3, 136.9, 135.4, 131.3, 129.7, 129.6, 128.5, 128.4, 127.4, 126.1, 125.8, 116.3, 52.4, 47.7, 47.6, 26.5, 23.7. <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -95.59. HRMS (ESI) calcd for C<sub>23</sub>H<sub>20</sub>F<sub>2</sub>N<sub>2</sub>O<sub>3</sub> (M+Na)<sup>+</sup> : 433.1334, found 433.1329.



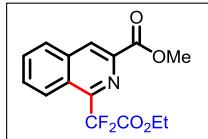
Methyl 1-(1,1-difluoro-2-oxo-2-(piperidin-1-yl)ethyl)-4-phenylisoquinoline-3-carboxylate (**3l**)

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 8.65 (d, *J* = 8.5 Hz, 1H), 7.77 (dq, *J* = 9.0, 4.6 Hz, 1H), 7.71 (d, *J* = 4.1 Hz, 2H), 7.51 (dd, *J* = 5.2, 1.7 Hz, 3H), 7.33 (dd, *J* = 6.5, 2.6 Hz, 2H), 3.71 (d, *J* = 5.6 Hz, 2H), 3.67 (s, 3H), 3.51 (t, *J* = 5.5 Hz, 2H), 1.65 (d, *J* = 2.7 Hz, 4H), 1.49 (t, *J* = 5.6 Hz, 2H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 166.6, 161.7 (t, *J* = 25.7 Hz), 150.0 (t, *J* = 28.7 Hz), 139.9, 137.2, 136.8, 135.4, 131.3, 129.7, 129.6, 128.5, 128.5, 127.4, 125.8 (t, *J* = 4.2 Hz), 116.5 (t, *J* = 252.2 Hz), 52.5, 47.7, 44.6, 25.8, 25.6, 24.6. <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -92.45. HRMS (ESI) calcd for C<sub>24</sub>H<sub>22</sub>F<sub>2</sub>N<sub>2</sub>O<sub>3</sub> (M+Na)<sup>+</sup> : 447.1491, found 447.1492.



Methyl 1-(2-(diethylamino)-1,1-difluoro-2-oxoethyl)-4-phenylisoquinoline-3-carboxylate (**3m**)

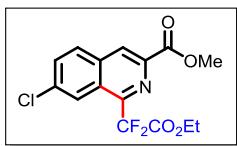
<sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 8.64 (d, *J* = 8.5 Hz, 1H), 7.94 – 7.64 (m, 3H), 7.51 (dd, *J* = 5.5, 1.7 Hz, 3H), 7.32 (dd, *J* = 6.7, 2.7 Hz, 2H), 3.66 (s, 3H), 3.53 (q, *J* = 7.1 Hz, 2H), 3.36 (q, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.12 (t, *J* = 7.0 Hz, 3H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 166.6, 162.6, 150.0, 139.8, 137.2, 136.9, 135.4, 131.3, 129.6, 129.6, 128.5, 128.5, 127.5, 125.9 (d, *J* = 25.7 Hz), 116.3 (t, *J* = 252.2 Hz), 52.4, 42.4, 41.3, 13.9, 11.9. <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -92.98. HRMS (ESI) calcd for C<sub>23</sub>H<sub>22</sub>F<sub>2</sub>N<sub>2</sub>O<sub>3</sub> (M+Na)<sup>+</sup> : 435.1491, found 435.1492.



Methyl 1-(2-ethoxy-1,1-difluoro-2-oxoethyl)isoquinoline-3-carboxylate (**3n**)

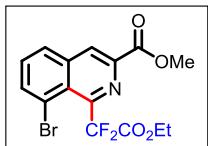
<sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 8.60 – 8.50 (m, 1H), 8.14 – 8.00 (m, 1H), 7.85 (qd, *J* = 7.2, 3.6 Hz, 2H), 4.55 (q, *J* = 7.1 Hz, 2H), 4.00 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 165.4, 163.5 (t, *J* = 31.7 Hz), 150.4 (t, *J* = 28.7 Hz), 139.6, 137.2, 131.6, 130.8, 129.2,

127.0, 126.6, 125.5 (t,  $J = 4.5$  Hz), 115.3 (t,  $J = 255.2$  Hz), 63.5, 52.8, 14.1.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -98.67. HRMS (ESI) calcd for  $\text{C}_{15}\text{H}_{13}\text{F}_2\text{NO}_4$  ( $\text{M}+\text{Na}^+$ ) : 332.0705, found 332.0706.



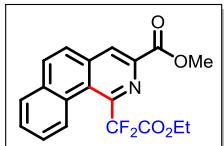
Methyl 7-chloro-1-(2-ethoxy-1,1-difluoro-2-oxoethyl)isoquinoline-3-carboxylate (**3o**)

$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.65 (s, 1H), 8.52 (s, 1H), 8.01 (d,  $J = 8.8$  Hz, 1H), 7.81 (dd,  $J = 8.8, 1.9$  Hz, 1H), 4.55 (q,  $J = 7.1$  Hz, 2H), 3.99 (s, 3H), 1.47 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  165.1, 163.2 (t,  $J = 31.7$  Hz), 149.9 (t,  $J = 24.2$  Hz), 139.9, 137.2, 135.5, 132.9, 130.6, 127.0, 126.6, 124.7 (t,  $J = 4.5$  Hz), 115.1, 63.6, 52.9, 14.1.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -98.72. HRMS (ESI) calcd for  $\text{C}_{15}\text{H}_{12}\text{ClF}_2\text{NO}_4$  ( $\text{M}+\text{Na}^+$ ) : 366.0315, found 366.0321.



Methyl 8-bromo-1-(2-ethoxy-1,1-difluoro-2-oxoethyl)isoquinoline-3-carboxylate (**3p**)

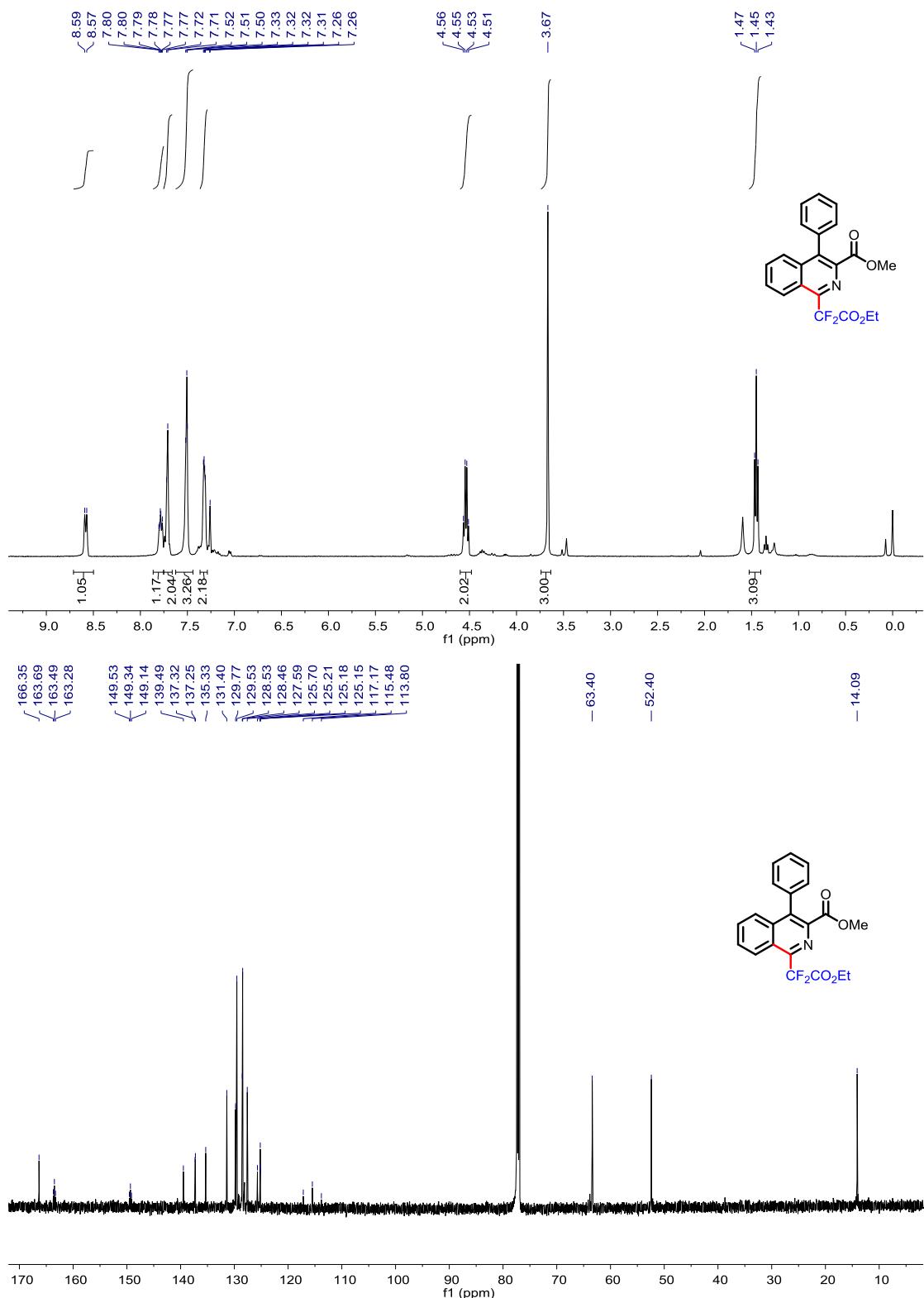
$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.63 (s, 1H), 8.21 (dd,  $J = 7.5, 1.2$  Hz, 1H), 8.04 (dd,  $J = 8.1, 1.2$  Hz, 1H), 7.63 (t,  $J = 7.8$  Hz, 1H), 4.49 (q,  $J = 7.2$  Hz, 2H), 4.02 (s, 3H), 1.41 (t,  $J = 7.2$  Hz, 3H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  164.8, 164.3 (t,  $J = 31.7$  Hz), 149.1 (t,  $J = 28.7$  Hz), 140.3, 138.9, 138.9, 131.4, 129.7, 127.5, 118.4, 114.6 (t,  $J = 258.2$  Hz), 63.3, 53.1, 14.0.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -92.68. HRMS (ESI) calcd for  $\text{C}_{15}\text{H}_{12}\text{BrF}_2\text{NO}_4$  ( $\text{M}+\text{Na}^+$ ) : 409.9810, found 409.9807.

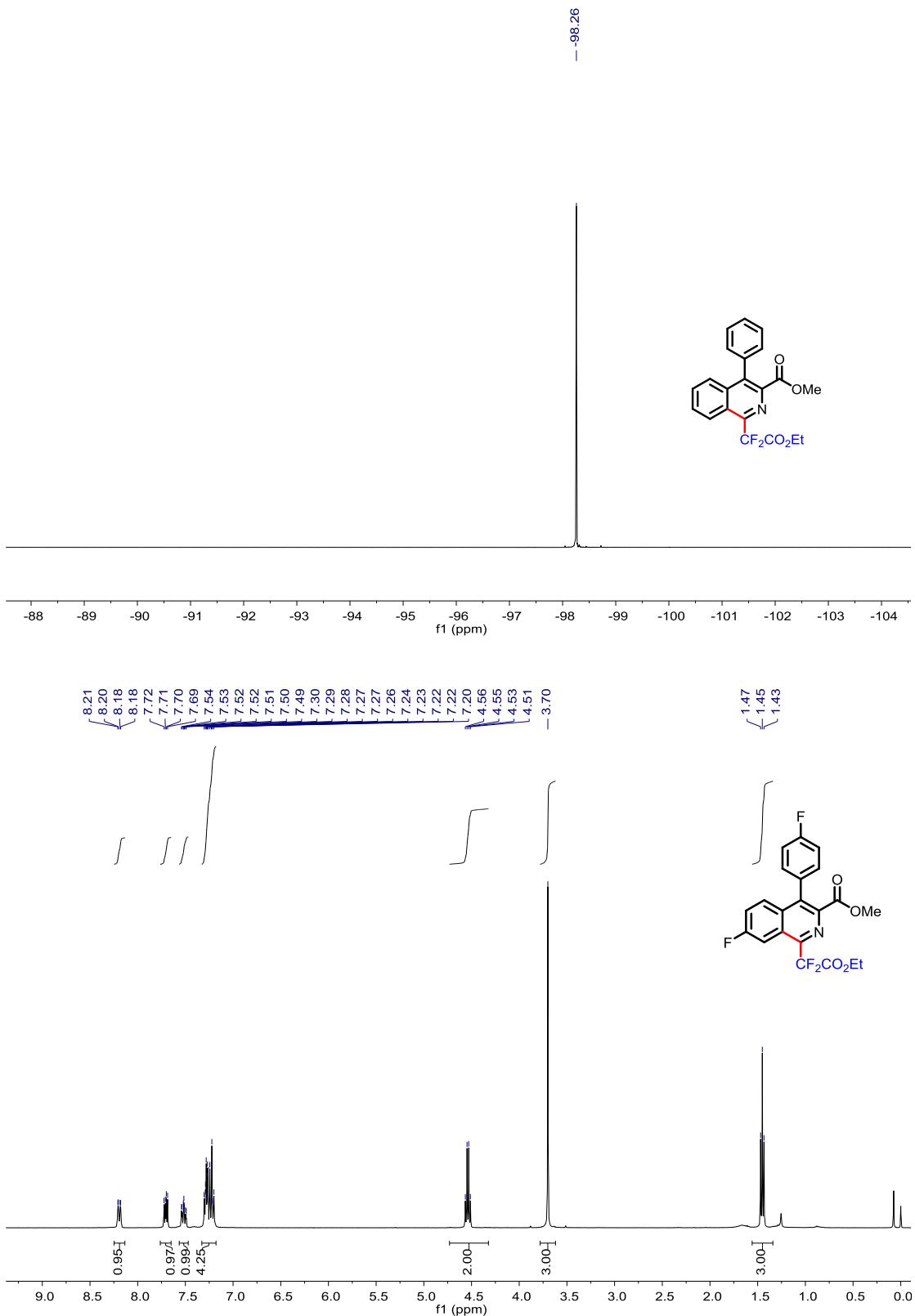


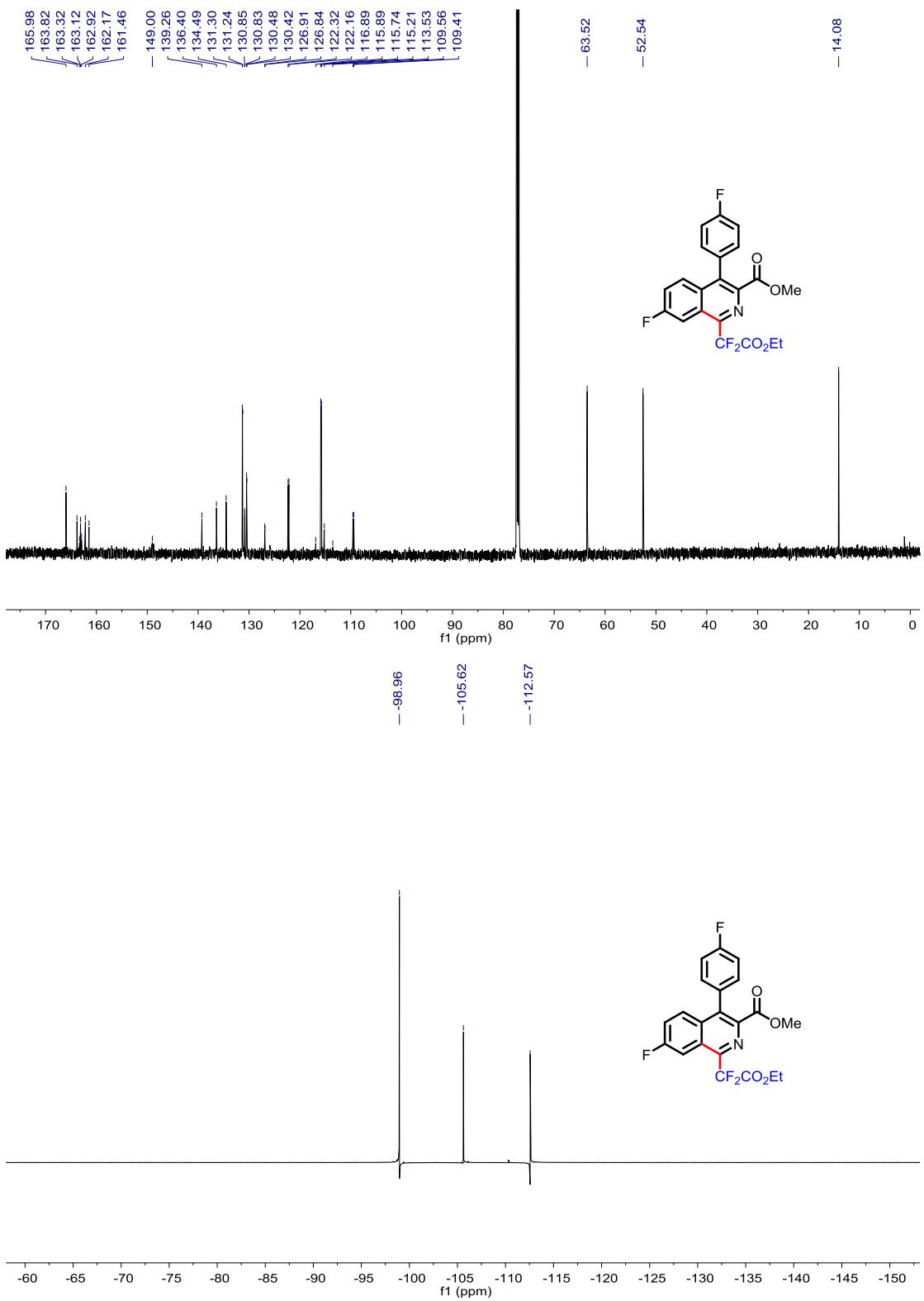
Methyl 1-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzo[h]isoquinoline-3-carboxylate (**3q**)

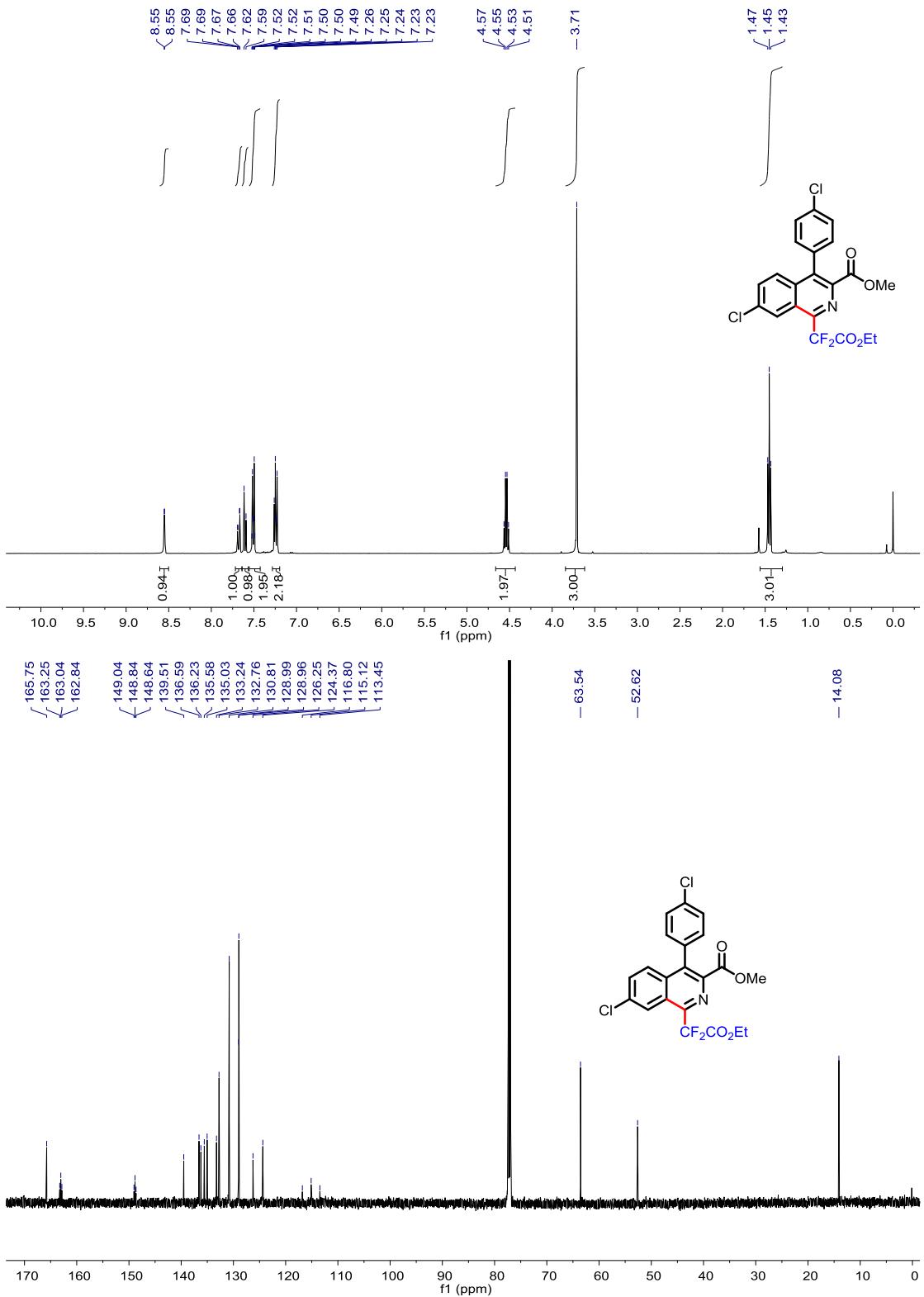
$^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  9.14 (d,  $J = 7.9$  Hz, 1H), 8.63 (s, 1H), 8.05 (d,  $J = 8.7$  Hz, 1H), 8.02 – 7.93 (m, 1H), 7.87 – 7.75 (m, 3H), 4.51 (q,  $J = 7.1$  Hz, 2H), 4.02 (s, 3H), 1.41 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  165.0, 164.2 (t,  $J = 31.7$  Hz), 148.2 (t,  $J = 31.7$  Hz), 140.3, 139.5, 134.5, 133.8, 129.2, 129.0 (t,  $J = 6.0$  Hz), 128.9, 128.0, 127.4, 127.1, 126.7, 125.9, 116.9 (t,  $J = 256.7$  Hz), 63.2, 52.9, 14.1.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -99.40. HRMS (ESI) calcd for  $\text{C}_{19}\text{H}_{15}\text{F}_2\text{NO}_4$  ( $\text{M}+\text{Na}^+$ ) : 382.0861, found 382.0863.

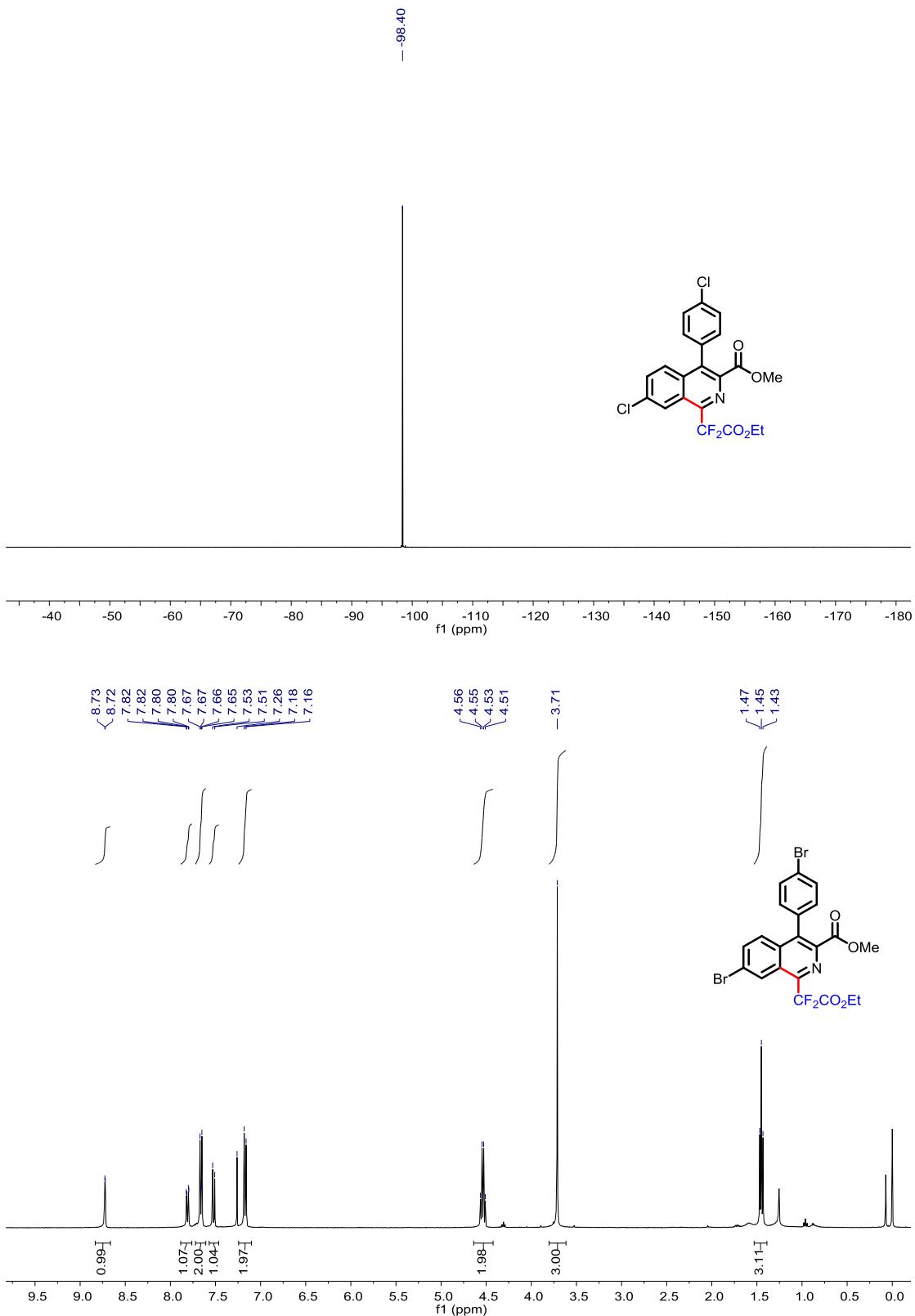
### 3 NMR Spectra

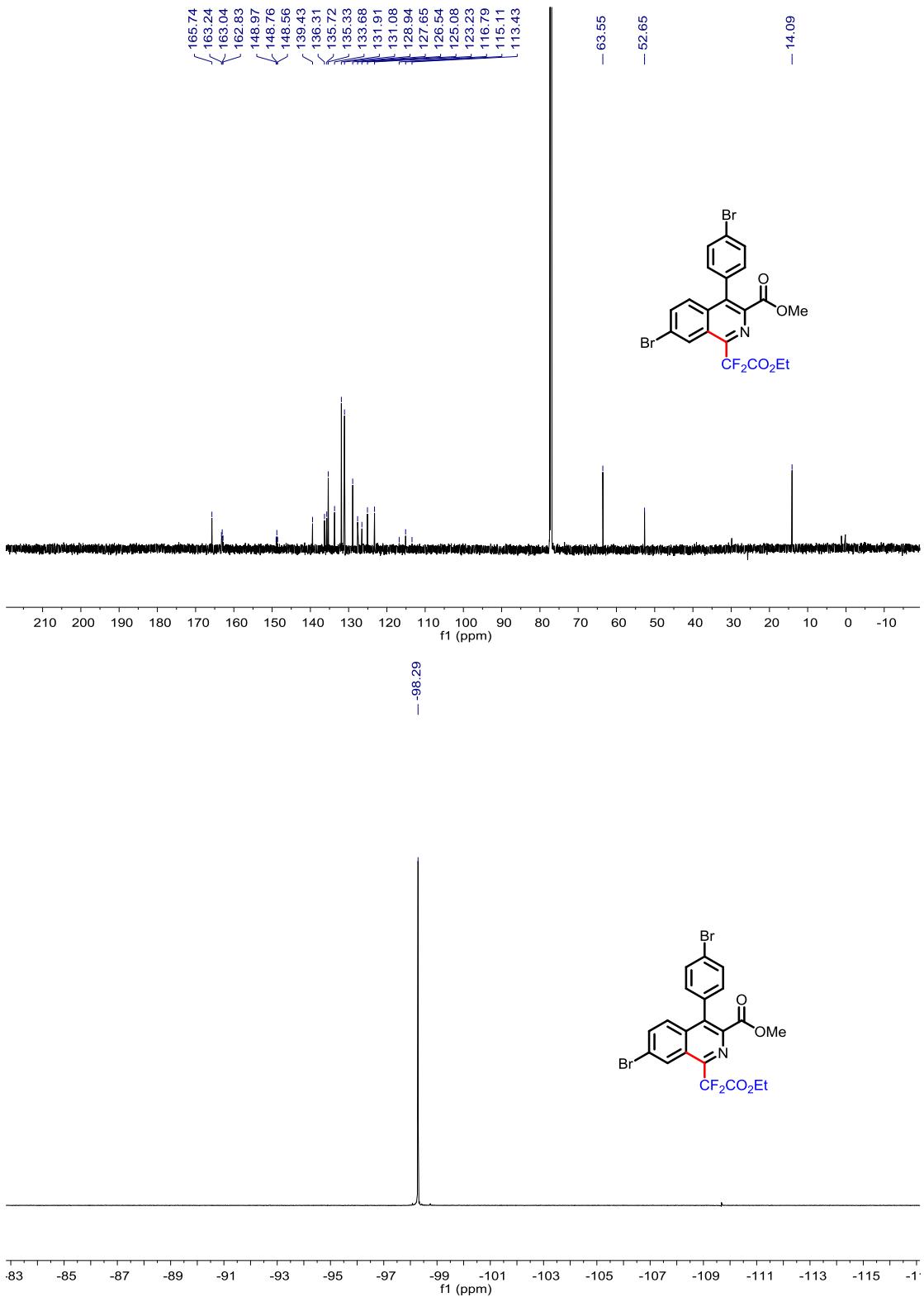


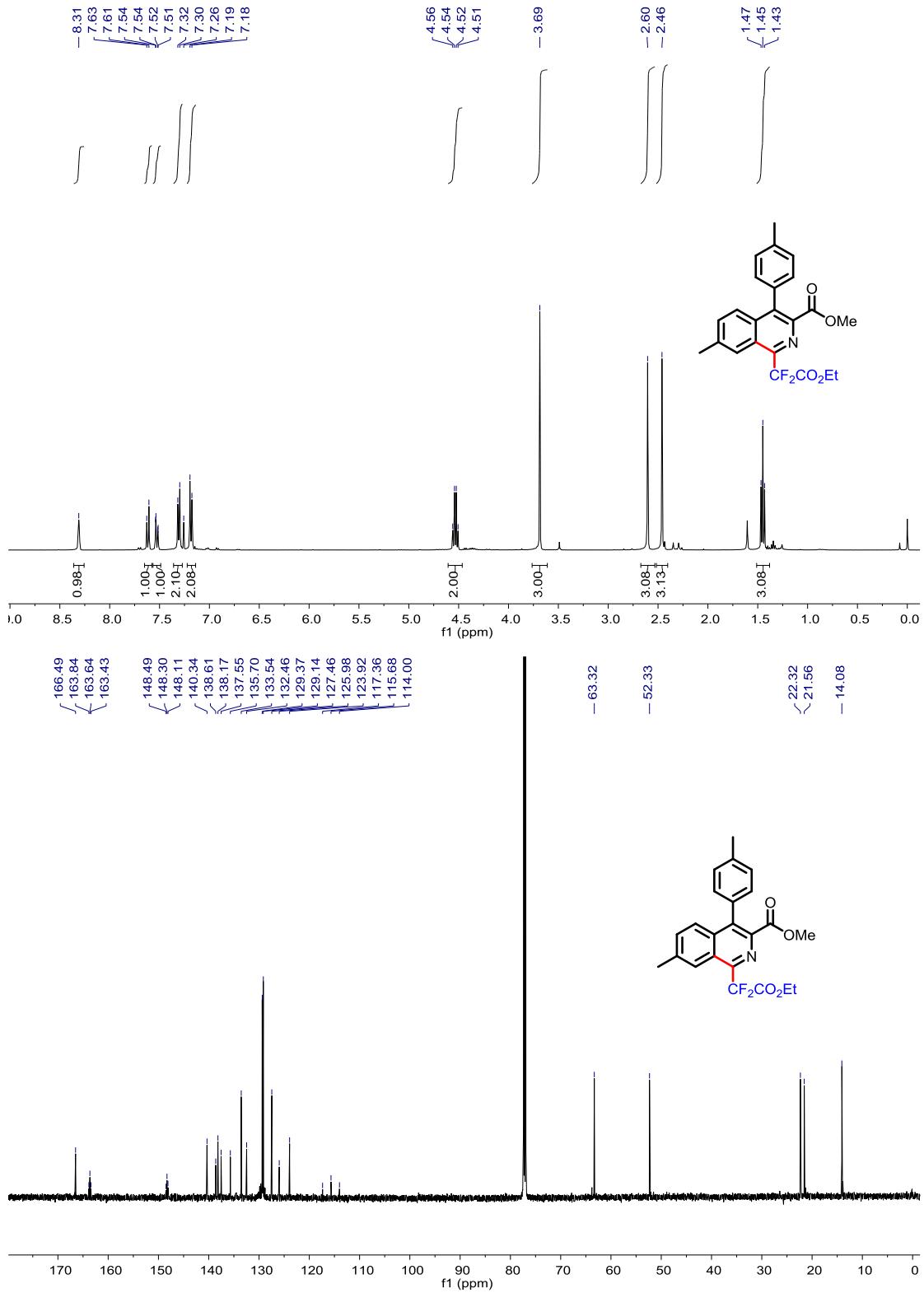


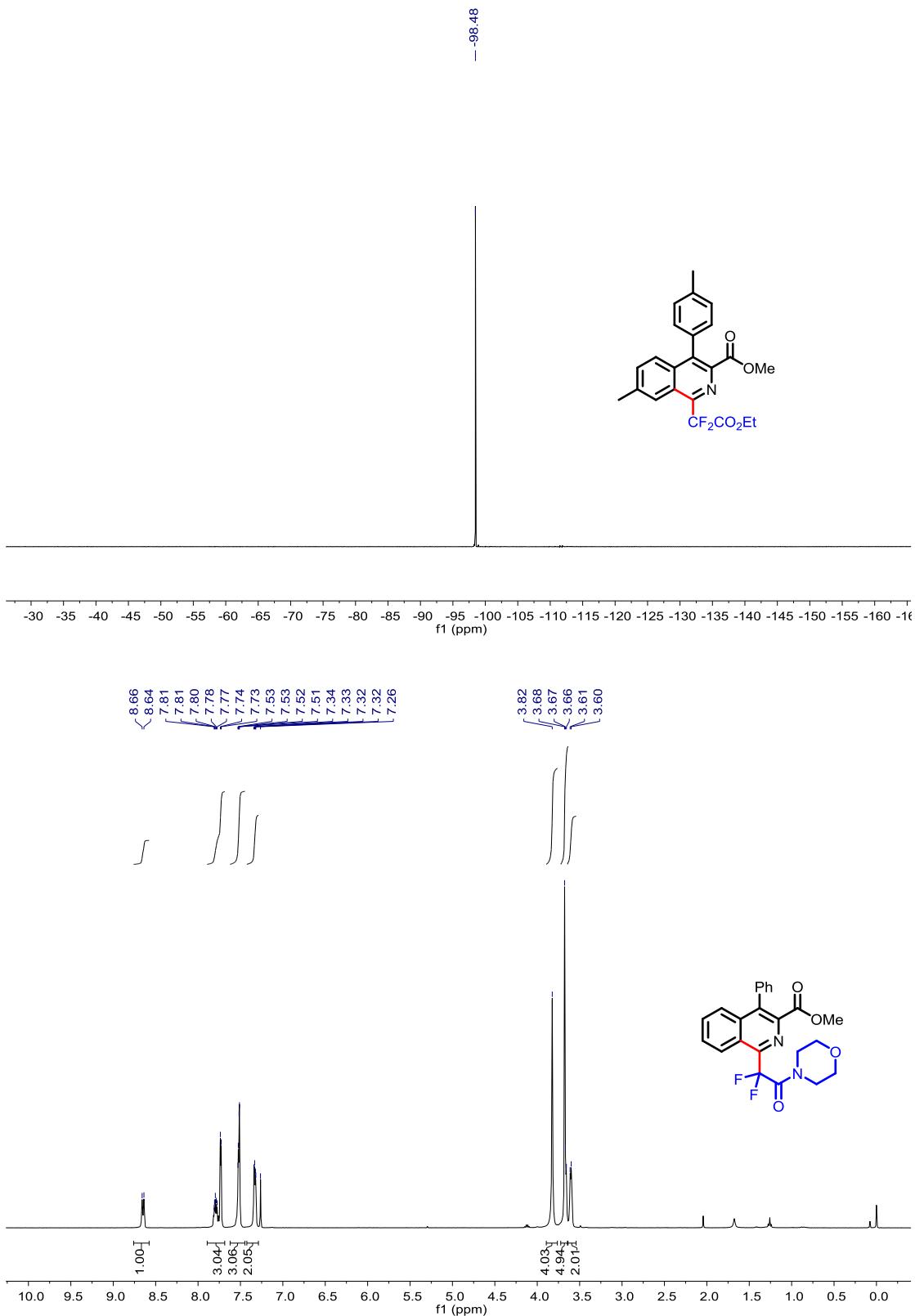


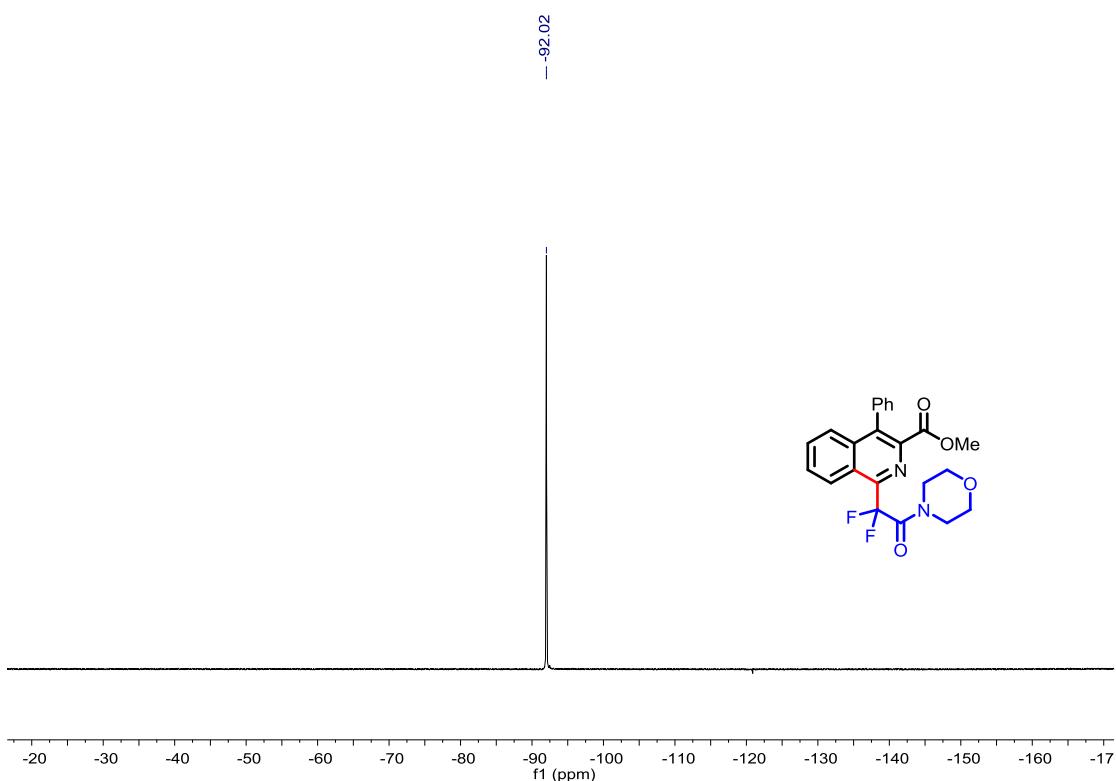
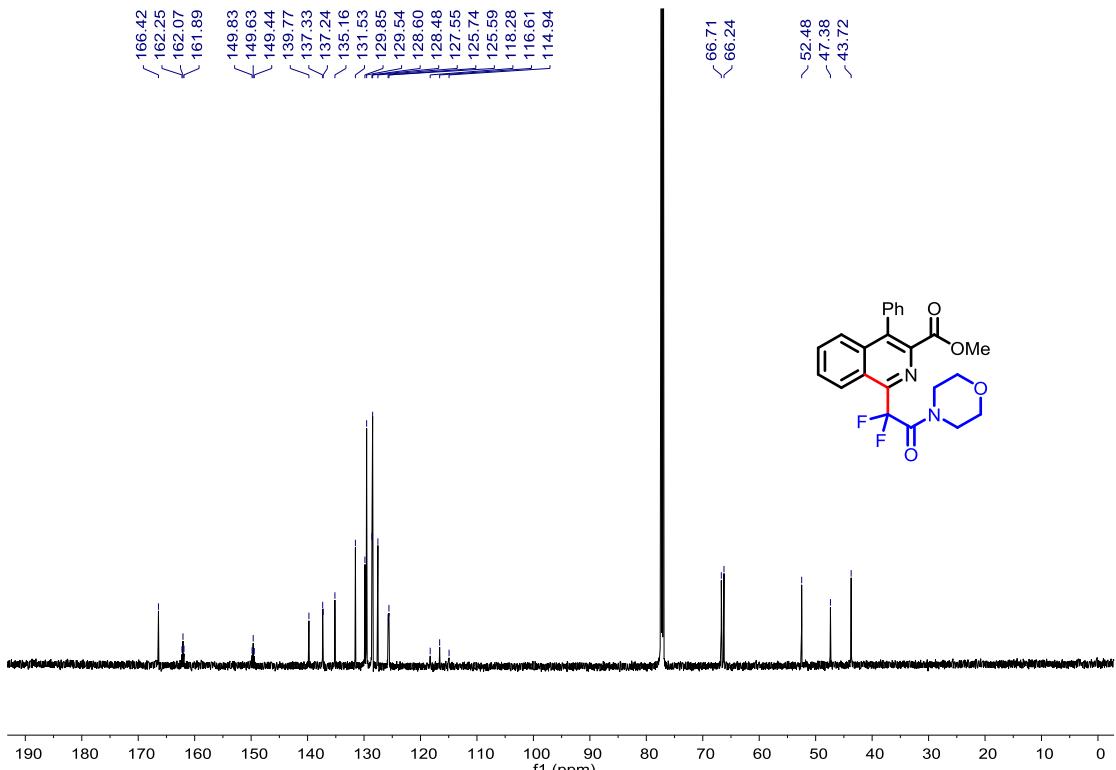


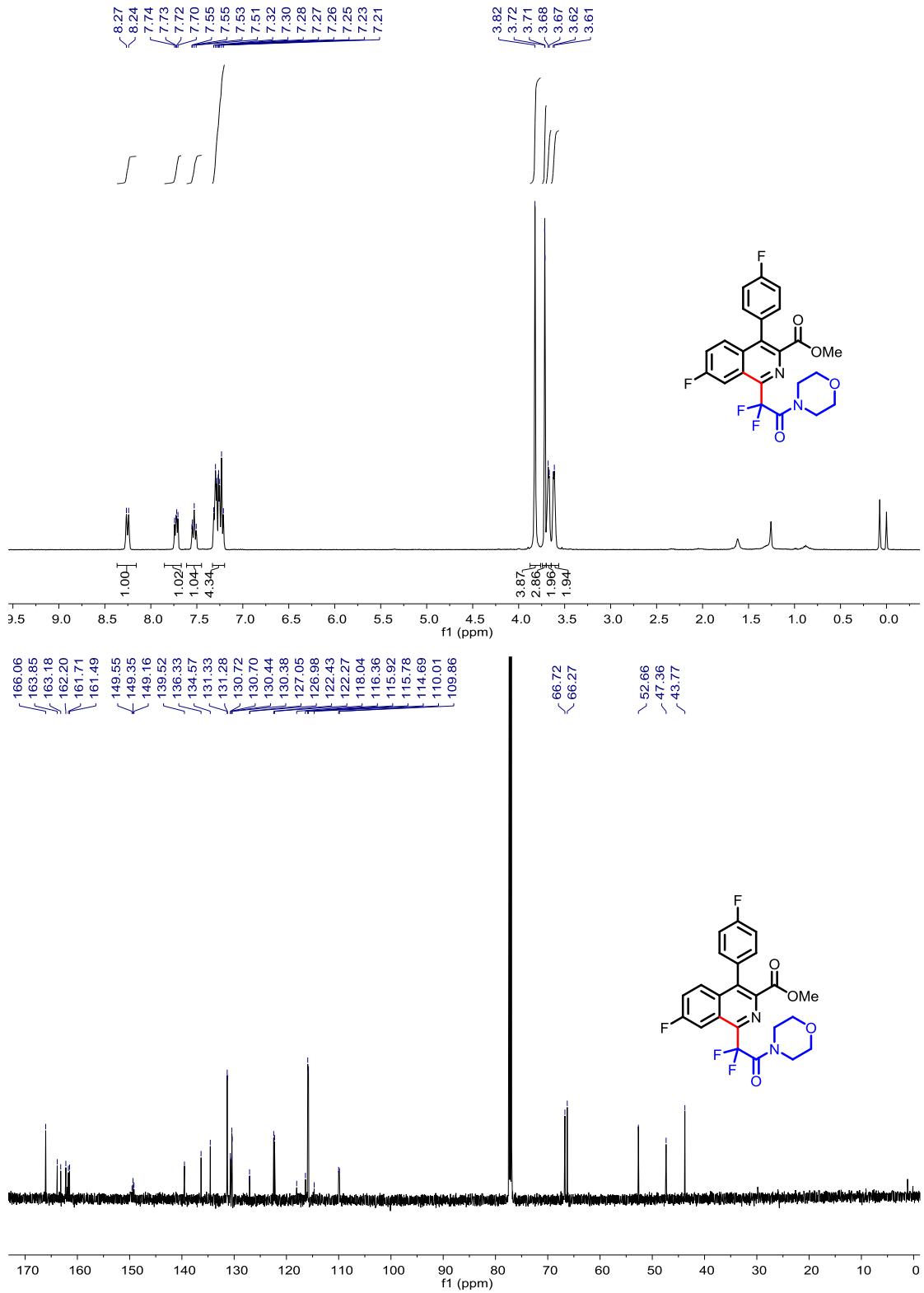


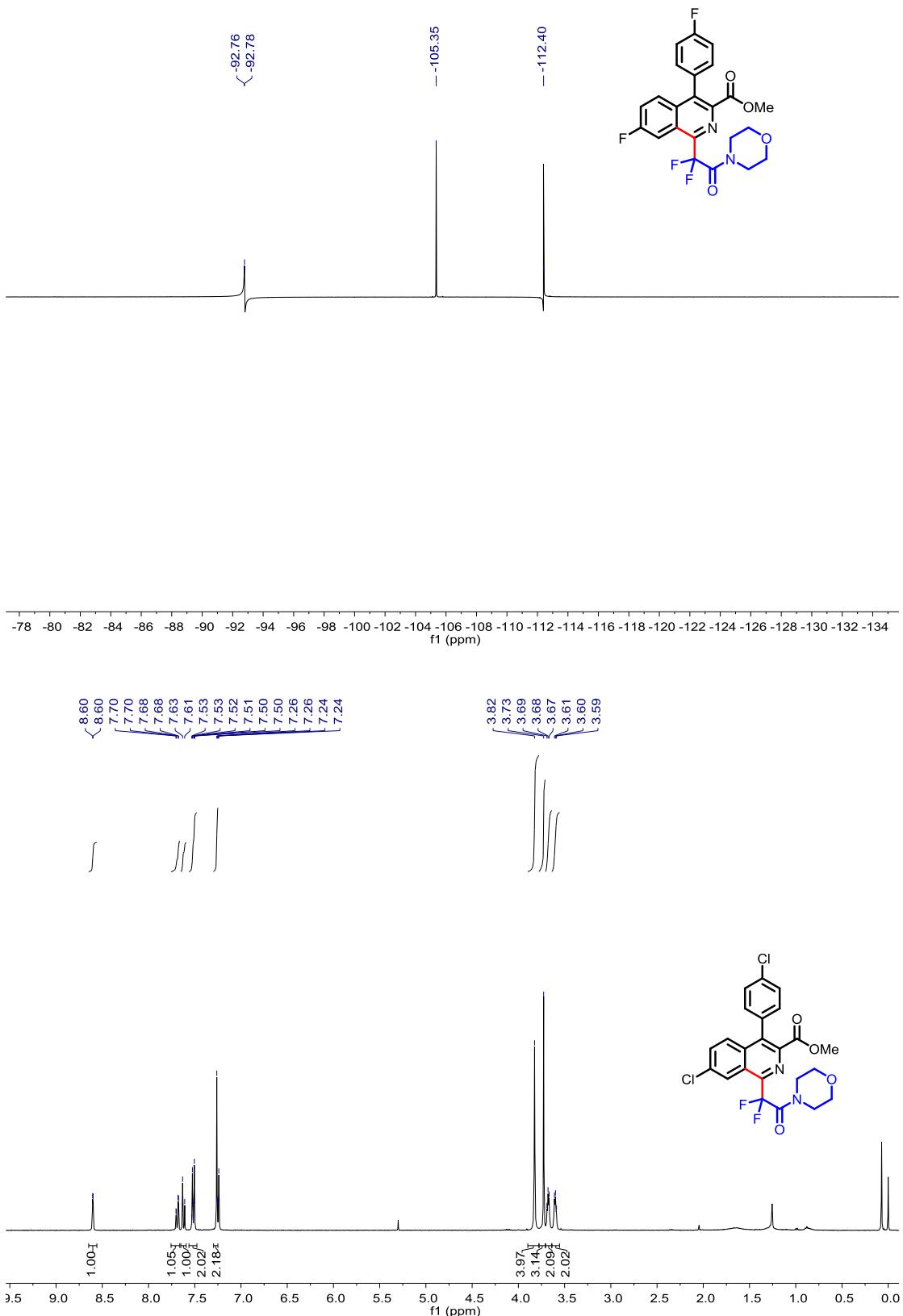


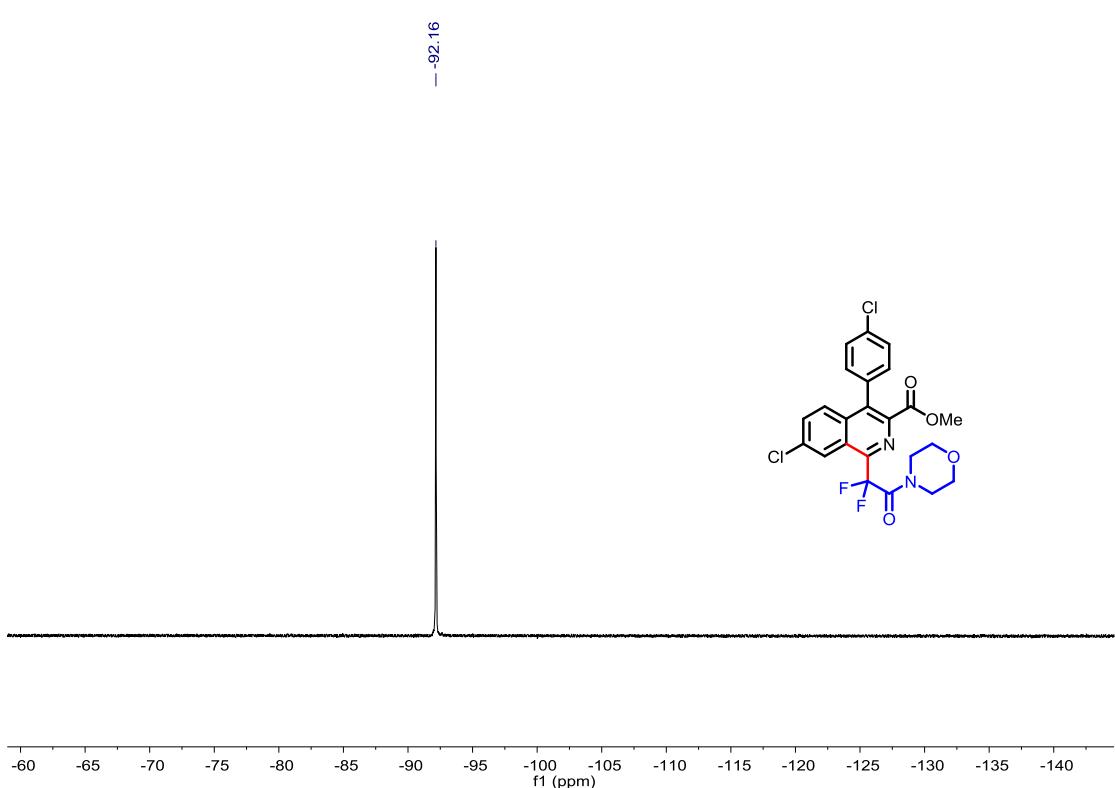
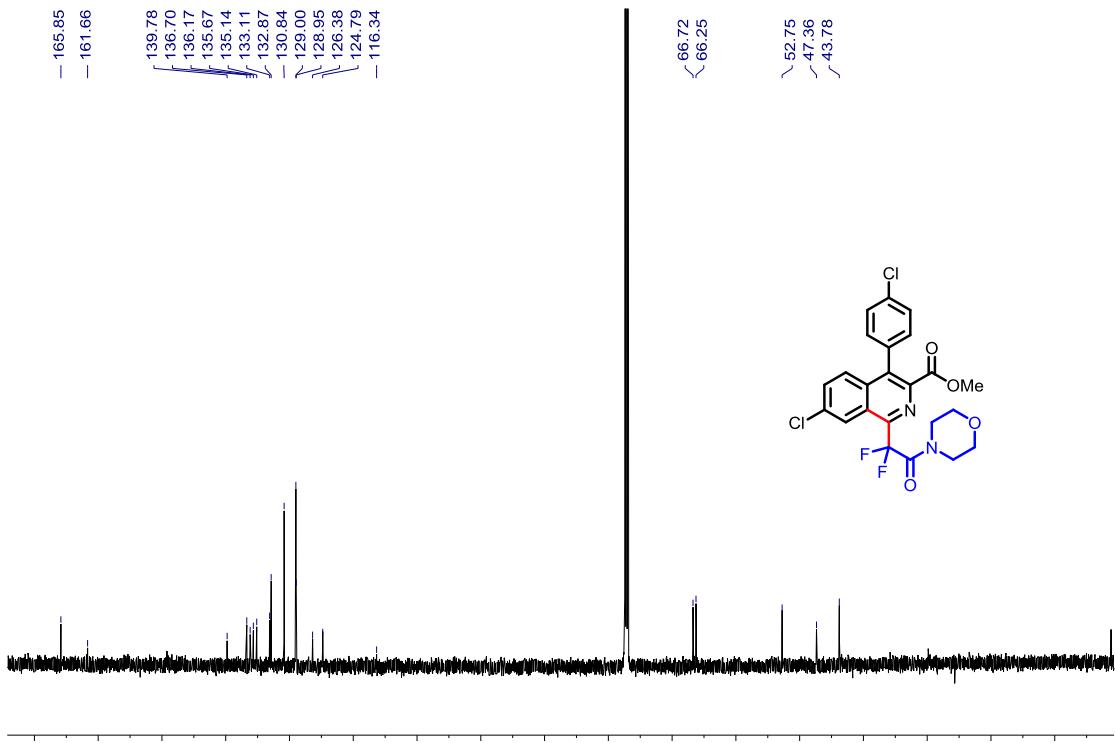


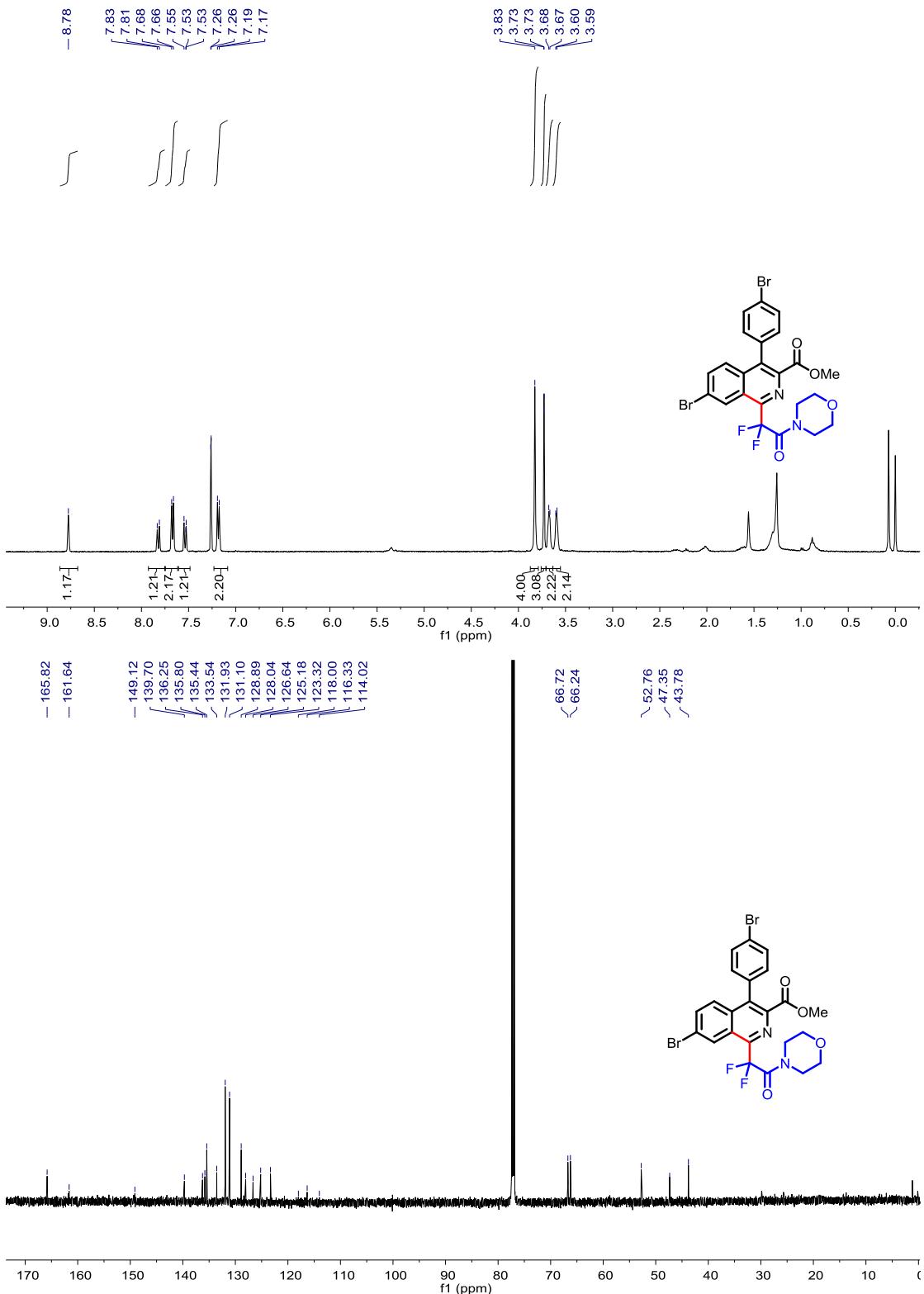


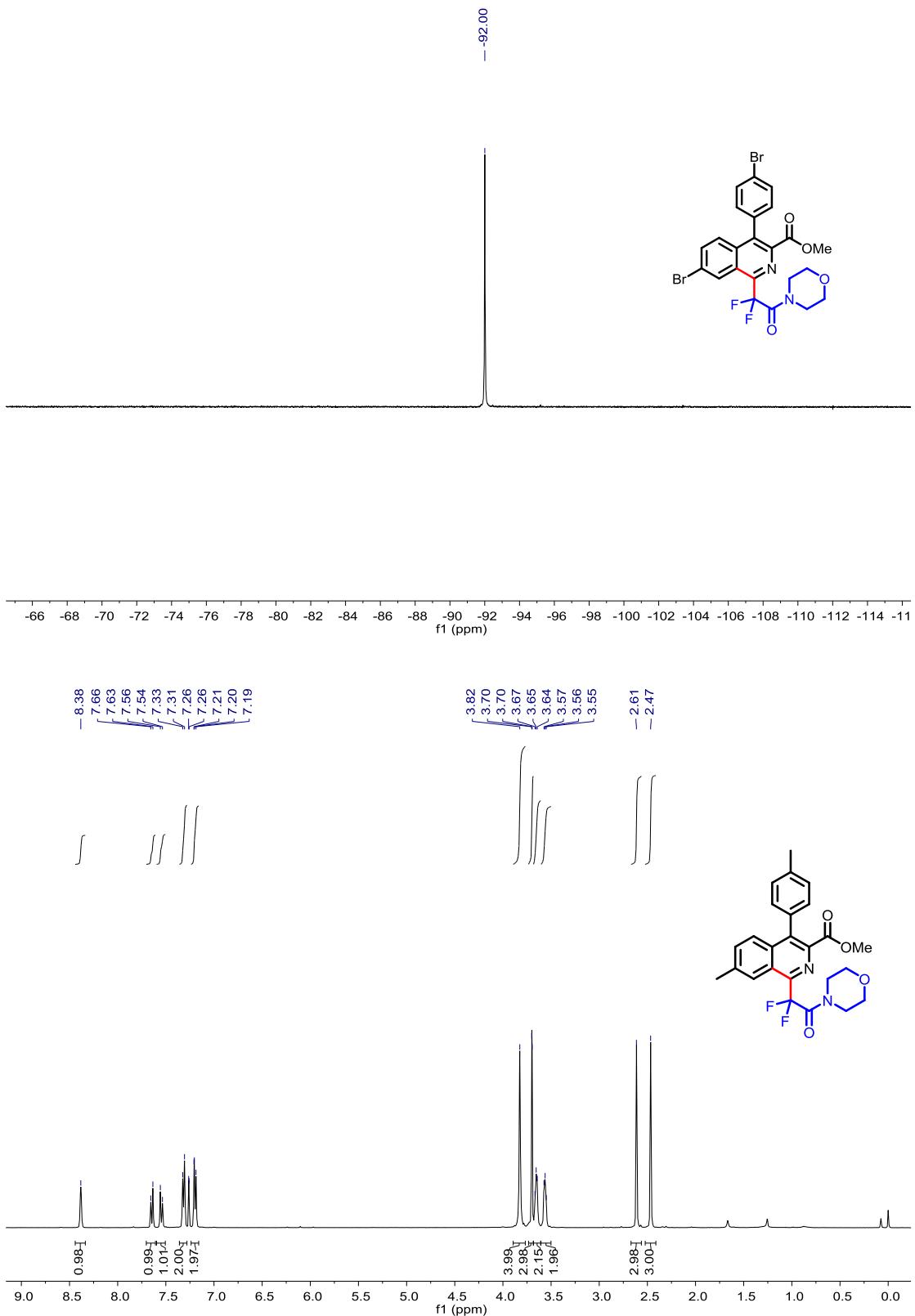


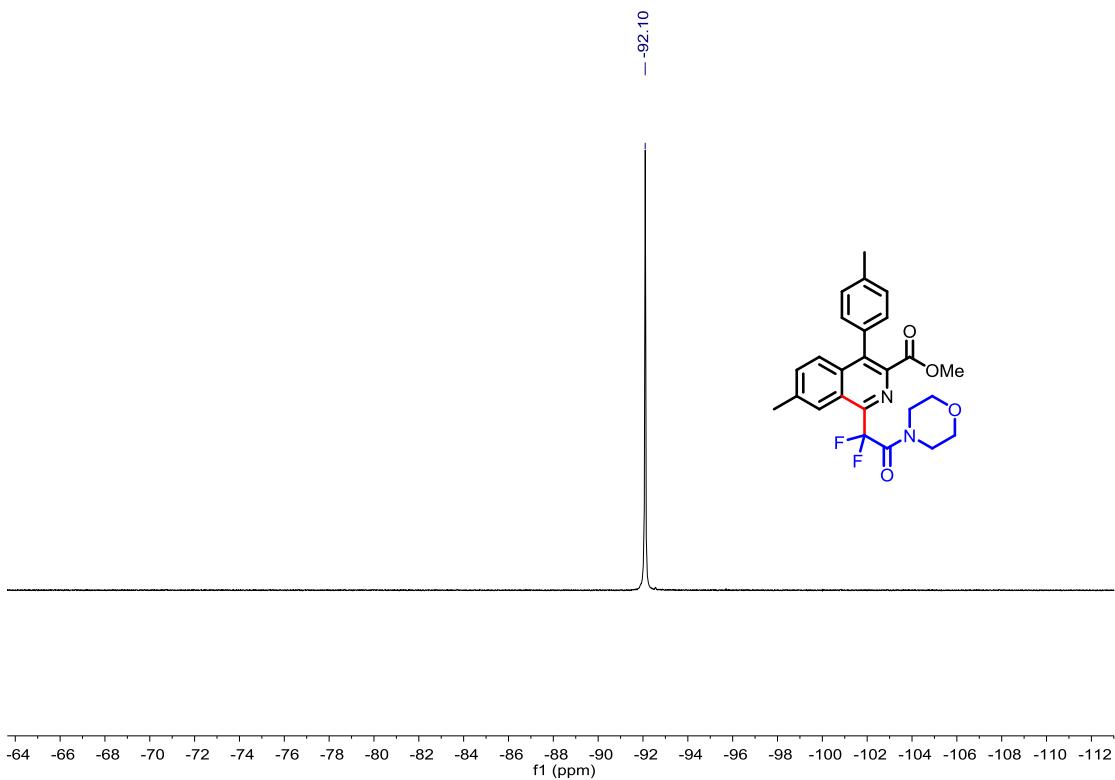
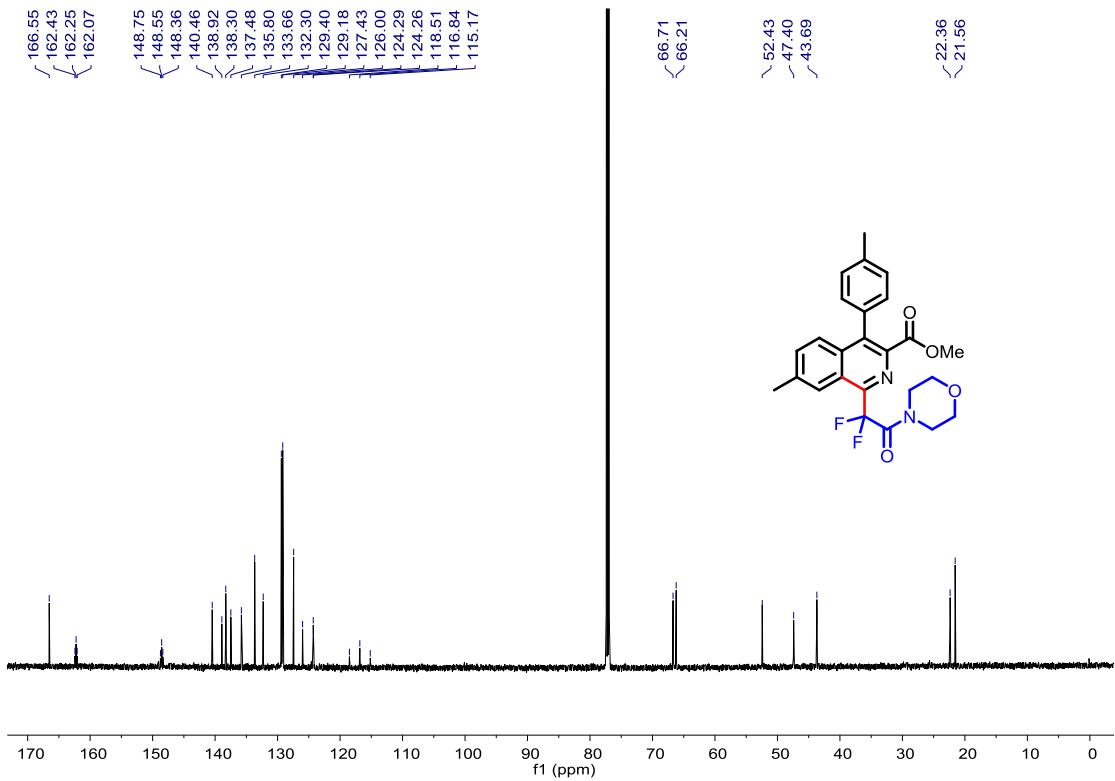


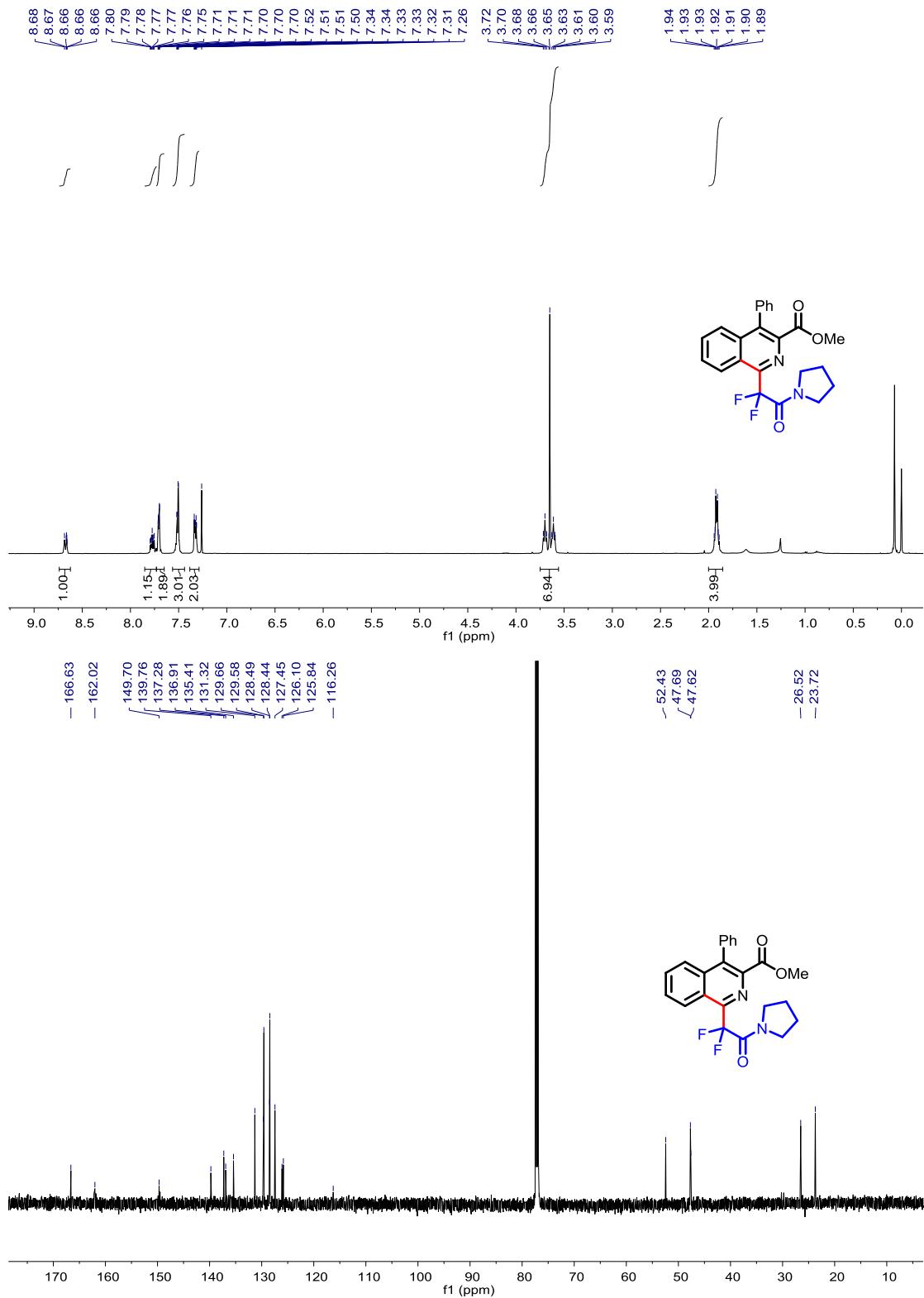


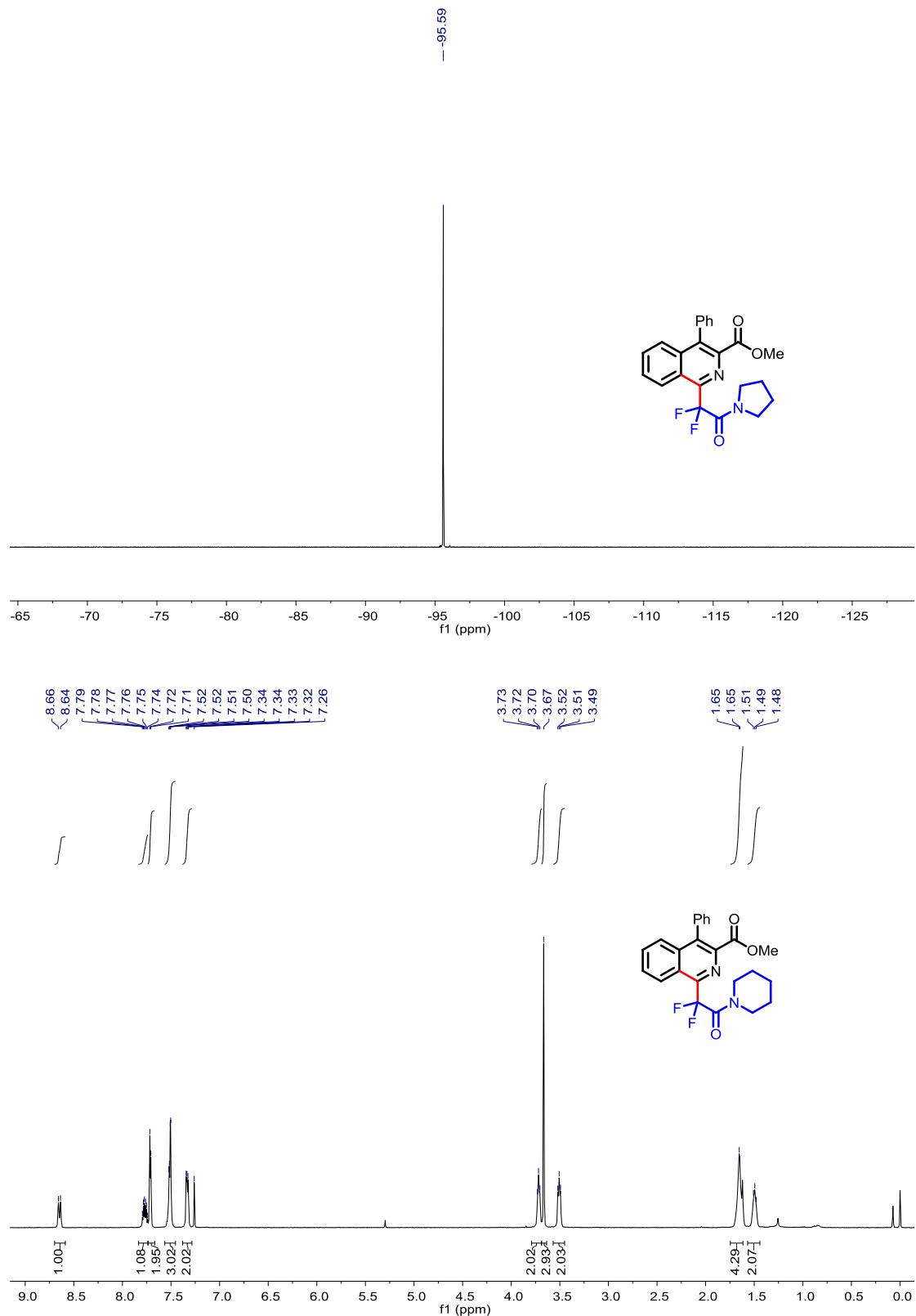


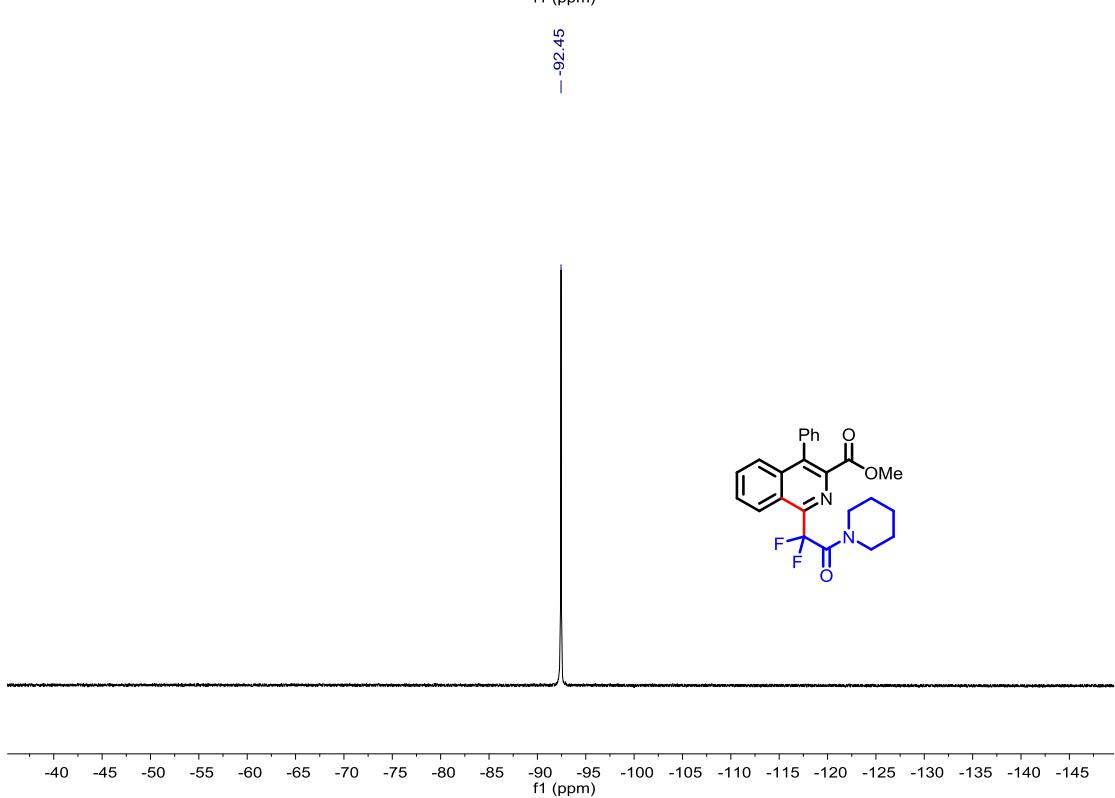
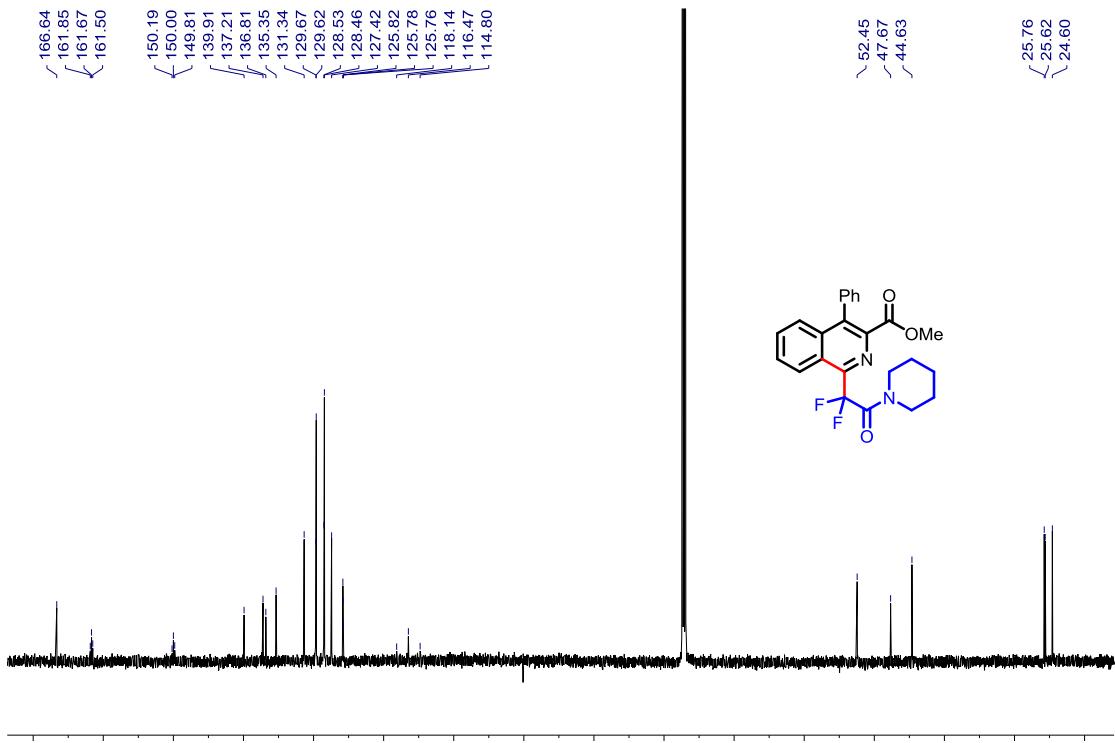


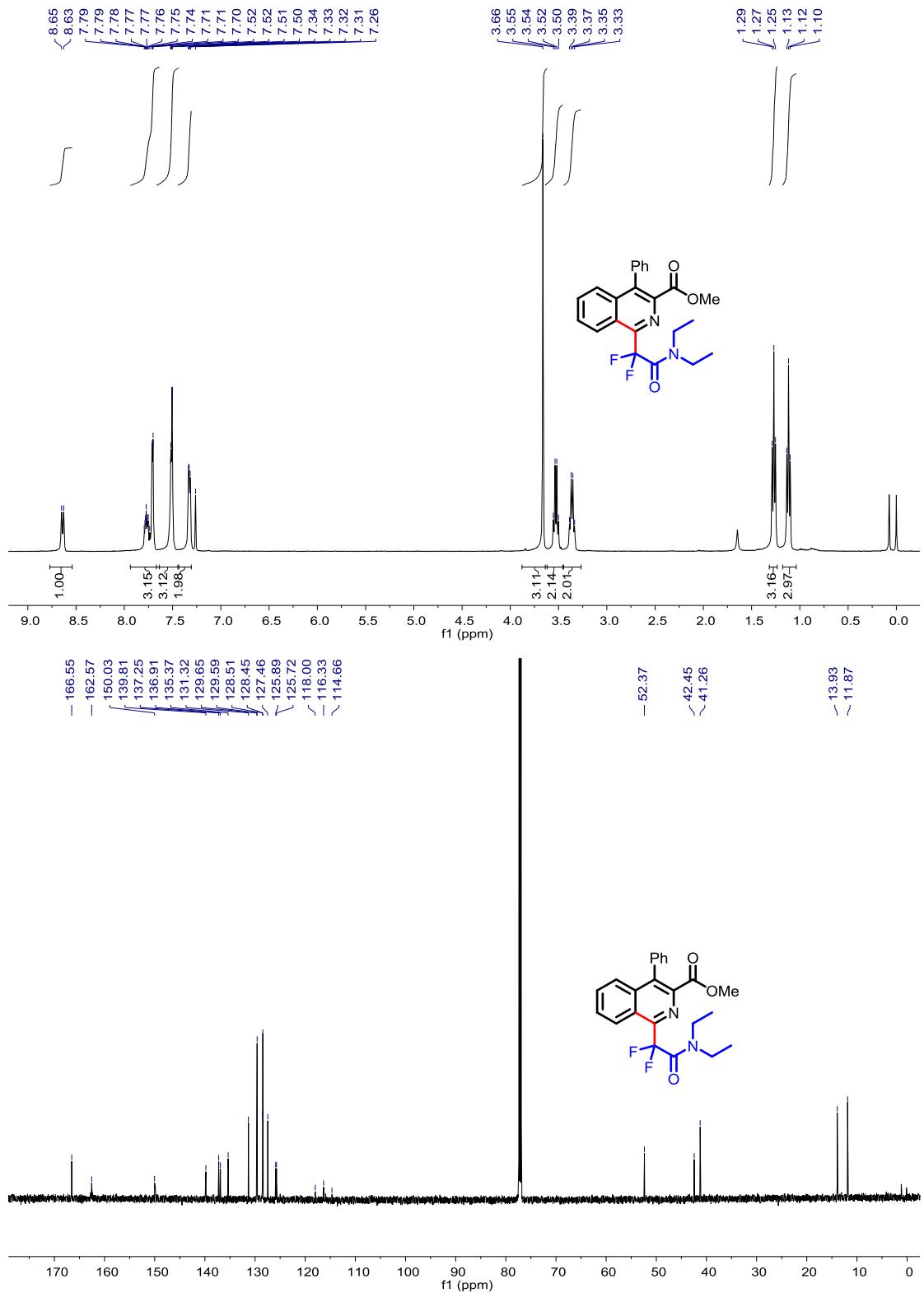


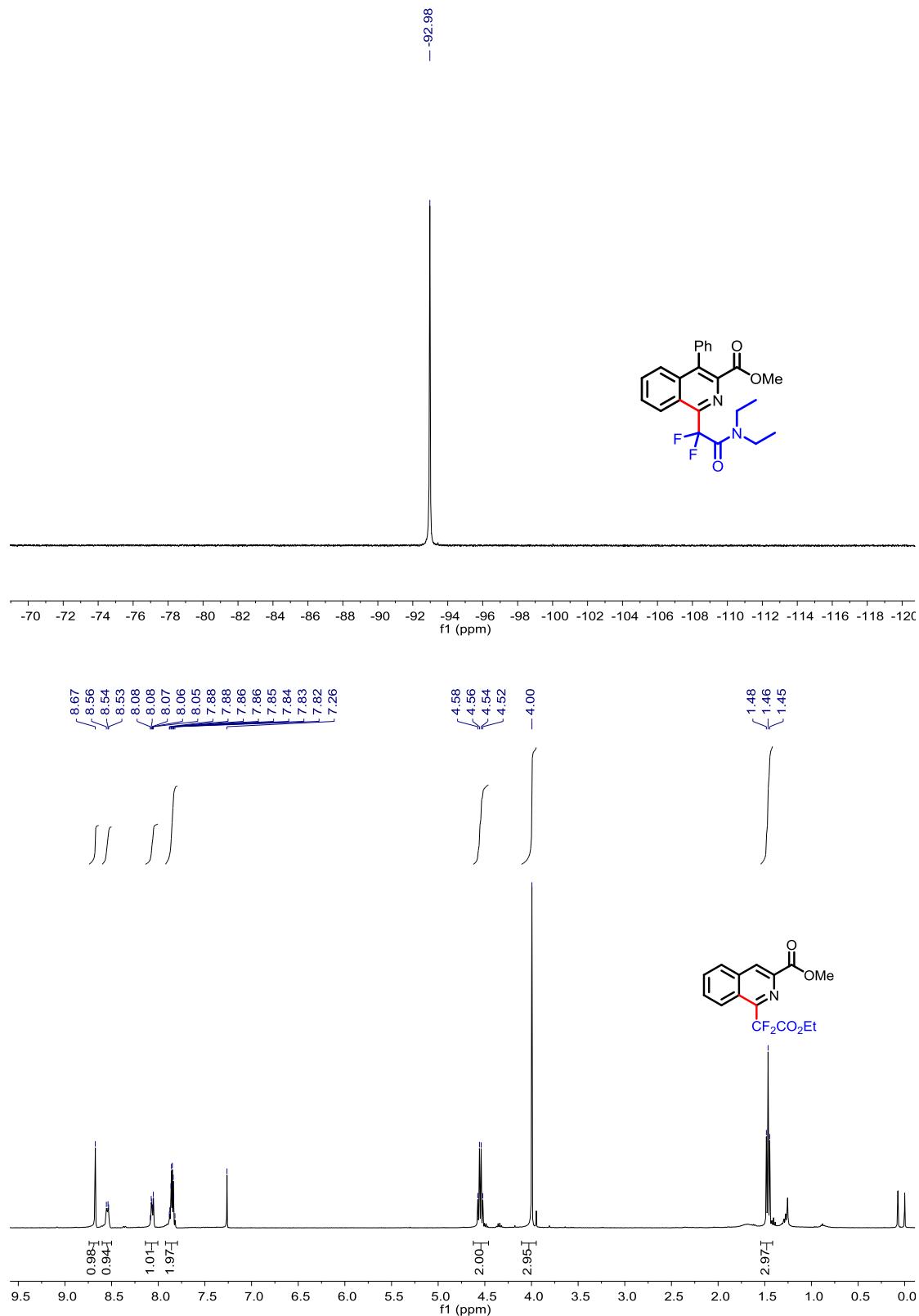


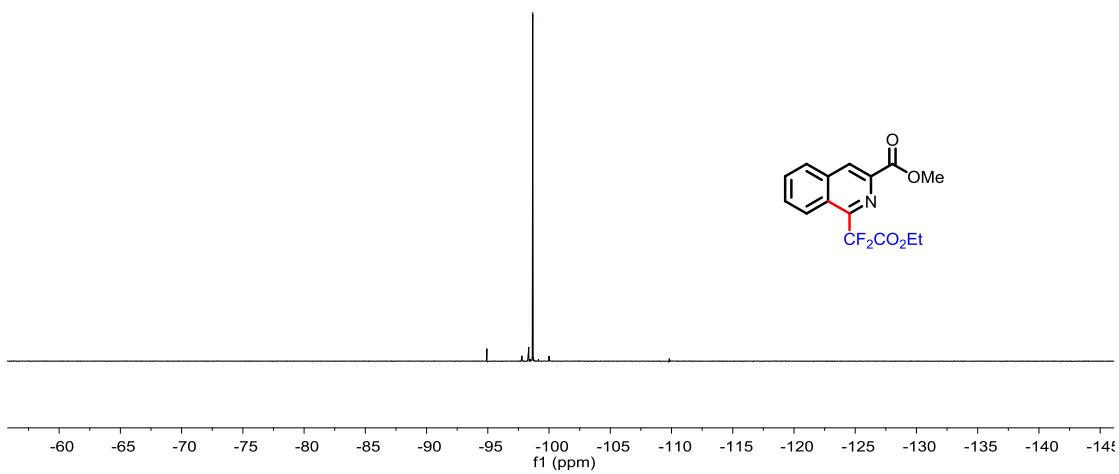
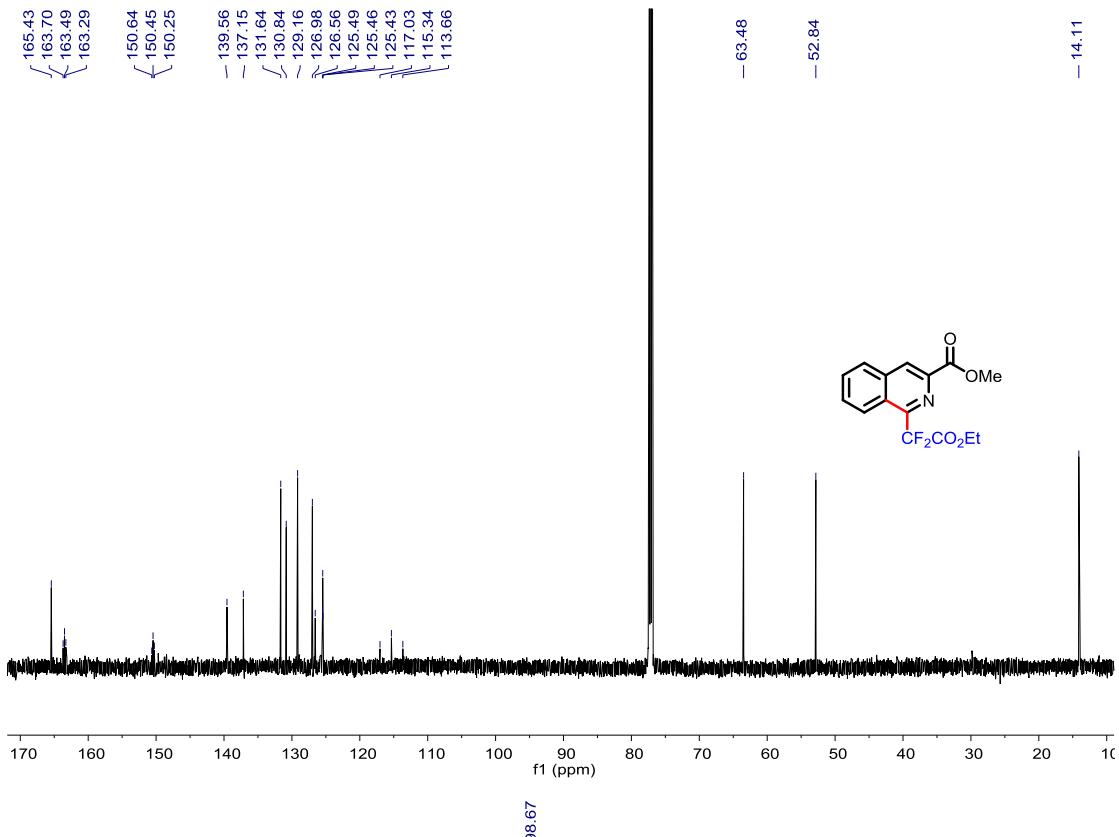


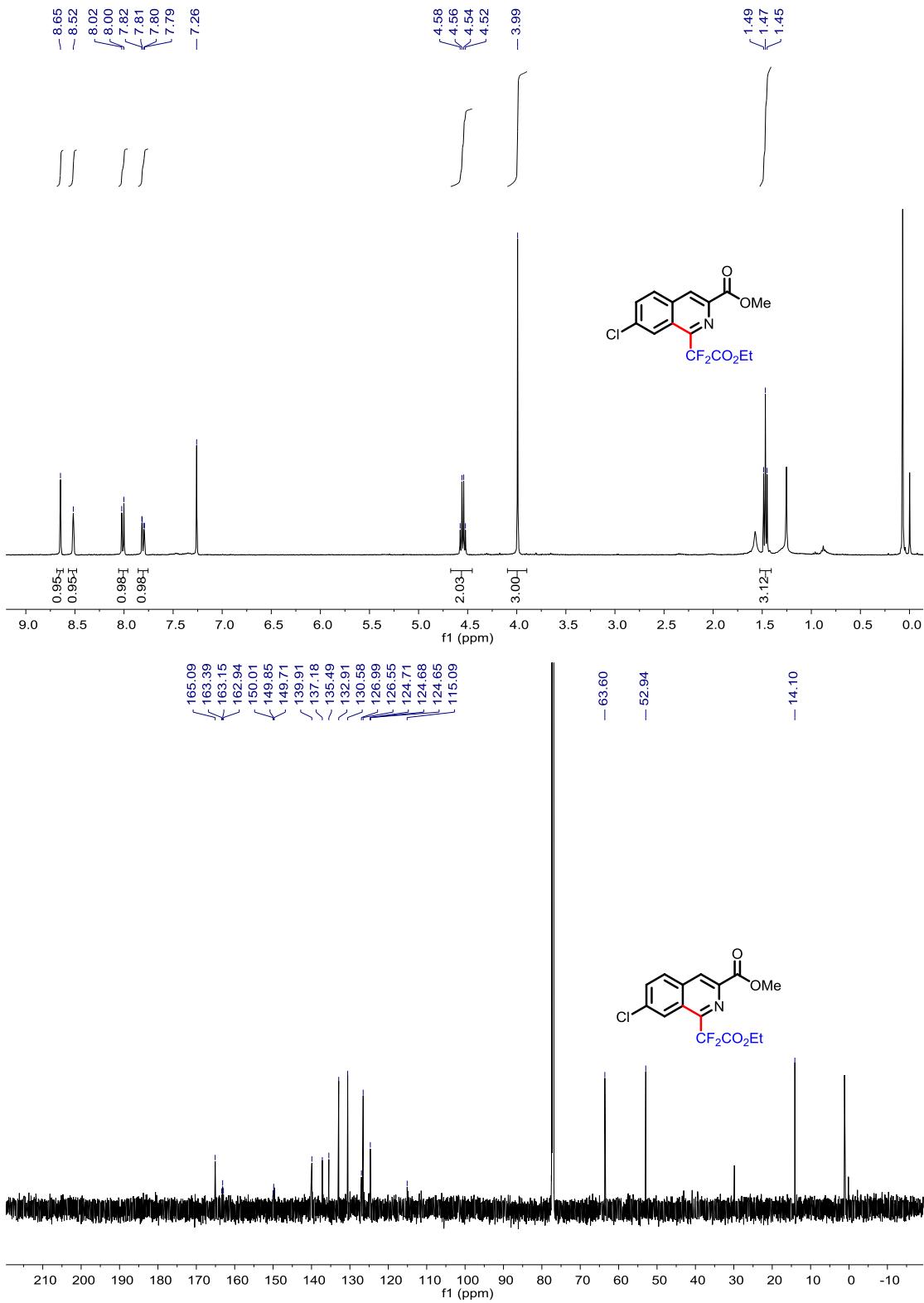


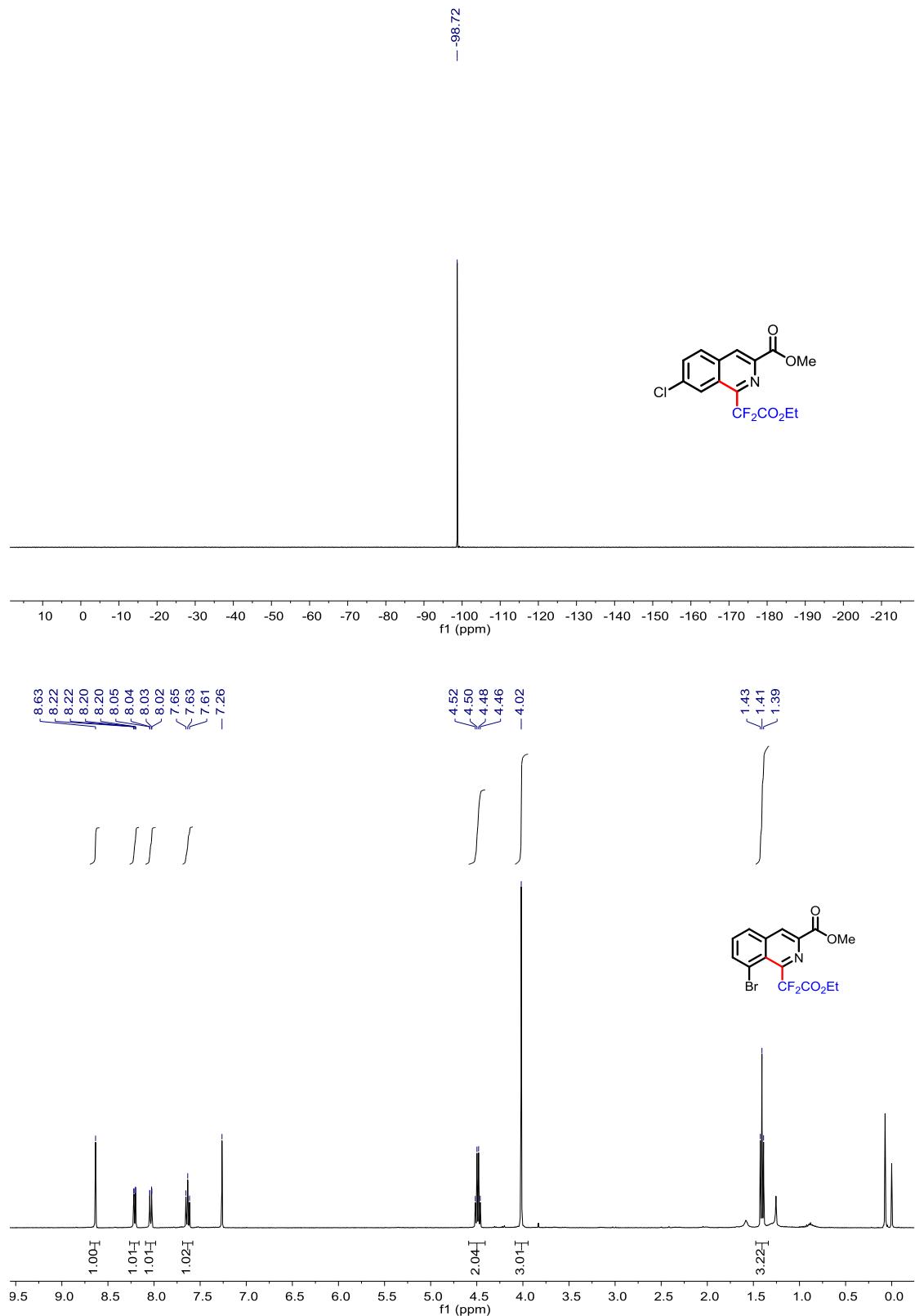


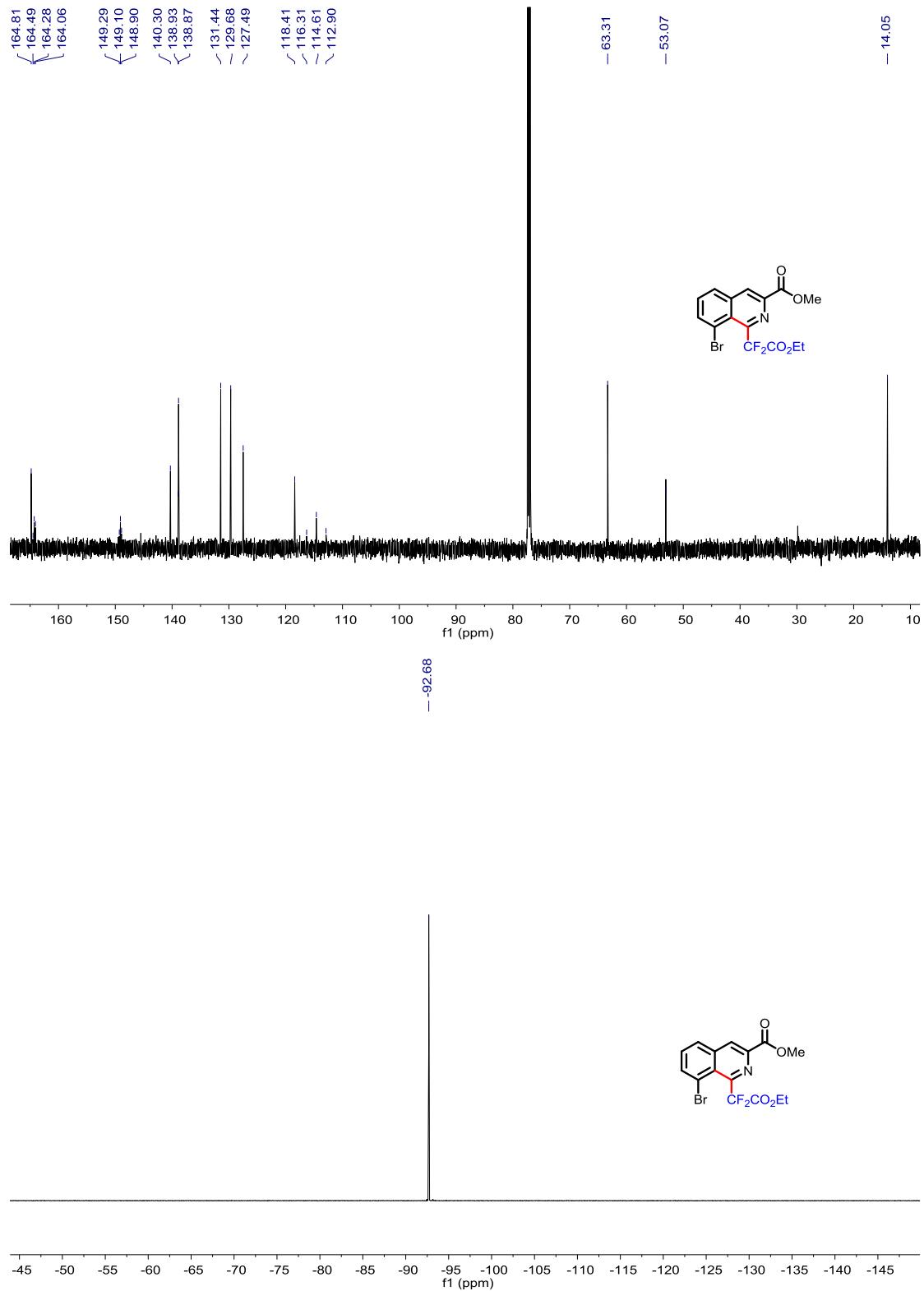


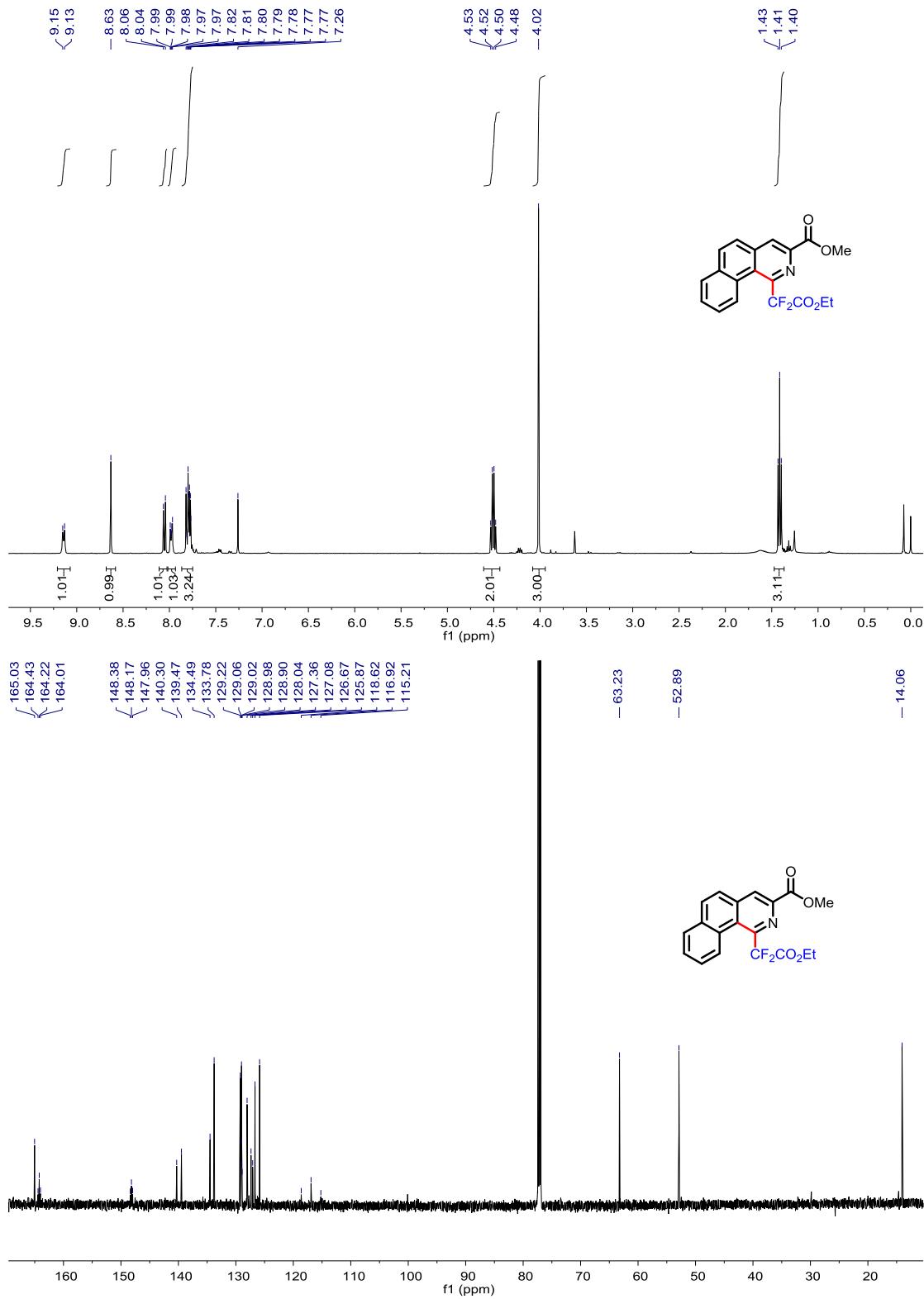


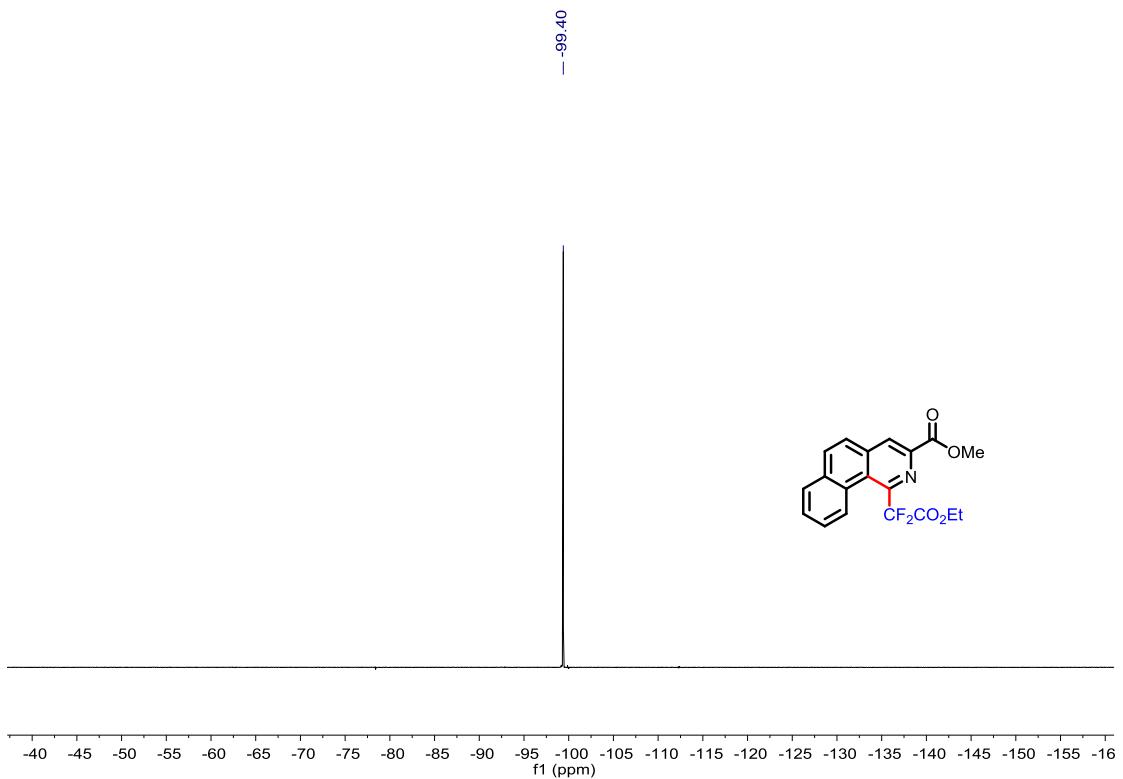












#### **4 References**

1. H. Jiang, Y. Cheng, R. Wang, Y. Zhang and S. Yu, *Chem. Commun.*, 2014, **50**, 6164-6167.