



## Supporting Information

for

### **Synthesis of 3,4,5-trisubstituted isoxazoles in water via a [3 + 2]-cycloaddition of nitrile oxides and 1,3-diketones, $\beta$ -ketoesters, or $\beta$ -ketoamides**

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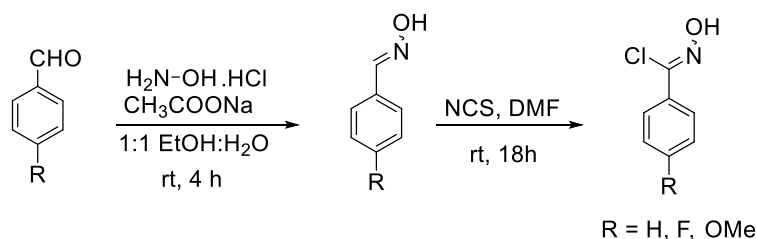
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### **Synthetic schemes for phenyl hydroximoyl chlorides and 1,3-diketones, characterization data, and copies of $^1\text{H}$ , $^{13}\text{C}$ , and $^{19}\text{F}$ NMR spectra**

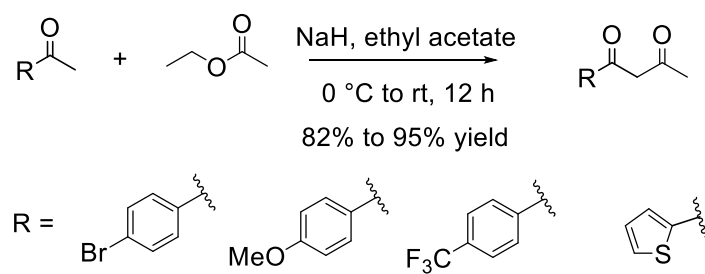
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**Figure S1:** Synthesis of phenyl hydroximoyl chlorides **1a–c**.



**Figure S2:** Synthesis of 1,3-diketones **2b–e**.

### Characterization of compounds **3a–aa** and **4**:

#### **(3-(4-Fluorophenyl)-5-methylisoxazol-4-yl)(phenyl)methanone (3a)**

Yield: 98%. Yellow sticky gel.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.69 – 7.62 (m, 2H), 7.49 – 7.39 (m, 3H), 7.32 (tt,  $J = 7.5, 1.4$  Hz, 2H), 6.99 – 6.85 (m, 2H), 2.46 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  189.96, 173.09, 163.57 (d,  $J = 250$  Hz), 161.05, 137.33, 133.62, 130.61 (d,  $J = 7.5$  Hz), 129.49, 128.61, 124.38 (d,  $J = 3.8$  Hz), 115.73, 115.57 (d,  $J = 3.8$  Hz), 12.87.  $^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ )  $\delta$  -110.63. HRMS  $m/z$  calcd. for  $\text{C}_{17}\text{H}_{13}\text{FNO}_2$   $[\text{M}+\text{H}]^+$  282.0930, found 282.0930.

#### **3,4-Bis(4-fluorophenyl)-1,2,5-oxadiazole 2-oxide (4)**

General synthetic procedure for the [3 + 2]-cycloaddition reaction was followed but with 5% water, 95% methanol as the solvent mixture and no DIPEA. Yield: 95%. Clear sticky gel.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  7.60–7.56 (m, 4H), 7.42–7.37 (m, 4H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}-d_6$ )  $\delta$  164.54 (d,  $J = 57$  Hz), 162.06 (d,  $J = 57$  Hz), 155.90, 131.65 (d,  $J = 9.1$  Hz), 130.86 (d,  $J = 9.1$

Hz), 122.73 (d,  $J = 3.2$  Hz), 119.04 (d,  $J = 3.2$  Hz), 116.44 (d,  $J = 7.7$  Hz), 116.22 (d,  $J = 7.7$  Hz), 114.18.  $^{19}\text{F}$  NMR (377 MHz, DMSO- $d_6$ )  $\delta$  -108.74 (ttd,  $J = 8.9, 5.4, 1.8$  Hz, 1F), -108.82 (ttd,  $J = 8.9, 5.4, 1.4$  Hz, 1F). HRMS  $m/z$  calcd. for  $\text{C}_{14}\text{H}_9\text{N}_2\text{O}_2\text{F}_2$   $[\text{M}+\text{H}]^+$  275.0632, found 275.0637.

**(4-Bromophenyl)(5-methyl-3-phenylisoxazol-4-yl)methanone (3b)**

Yield: 82%. White crystal. Mp 105–107 °C.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.55 (d,  $J = 8.4$  Hz, 2H), 7.49 – 7.38 (m, 4H), 7.35 (t,  $J = 7.3$  Hz, 1H), 7.29 (t,  $J = 7.4$  Hz, 2H), 2.55 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  189.01, 173.41, 161.83, 136.11, 131.86, 131.01, 130.01, 128.74, 128.66, 128.60, 128.04, 115.40, 12.91. HRMS  $m/z$  calcd. for  $\text{C}_{17}\text{H}_{13}\text{BrNO}_2$   $[\text{M}+\text{H}]^+$  342.0130, found 342.0134.

**(4-Bromophenyl)(3-(4-fluorophenyl)-5-methylisoxazol-4-yl)methanone (3c)**

Yield: 95%. White solid. Mp 84–86 °C.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.54 (d,  $J = 8.6$  Hz, 2H), 7.48 (d,  $J = 8.3$  Hz, 2H), 7.44 (t,  $J = 8.6$  Hz, 2H), 6.98 (t,  $J = 8.6$  Hz, 2H), 2.50 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  188.90, 173.39, 163.77 (d,  $J = 250$  Hz), 160.95, 136.08, 132.04, 131.01, 130.66 (d,  $J = 8.8$  Hz), 129.03, 124.23 (d,  $J = 3.8$  Hz), 115.92 (d,  $J = 21$  Hz), 115.33, 13.00.  $^{19}\text{F}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  -110.18. HRMS  $m/z$  calcd. for  $\text{C}_{17}\text{H}_{12}\text{BrFNO}_2$   $[\text{M}+\text{H}]^+$  360.0035, found 360.0049.

**(4-Bromophenyl)(3-(4-methoxyphenyl)-5-methylisoxazol-4-yl)methanone (3d)**

Yield: 70%. White solid. Mp 91–93 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.54 (d,  $J = 8.5$  Hz, 2H), 7.45 (d,  $J = 8.6$  Hz, 2H), 7.36 (d,  $J = 8.8$  Hz, 2H), 6.78 (d,  $J = 8.8$  Hz, 2H), 3.76 (s, 3H), 2.49 (s, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  189.23, 173.12, 160.96, 136.18, 131.91, 131.07, 130.05, 128.77, 120.31, 115.11, 114.44, 114.15, 55.41, 12.89. HRMS  $m/z$  calcd. for  $\text{C}_{18}\text{H}_{15}\text{BrNO}_3$   $[\text{M}+\text{H}]^+$  372.0235, found 372.0245.

**(4-Methoxyphenyl)(5-methyl-3-phenylisoxazol-4-yl)methanone (3e)**

Yield: 78%. White solid. Mp 88–90 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.73 (d,  $J = 8.9$  Hz, 2H), 7.56 – 7.48 (m, 2H), 7.38 – 7.26 (m, 3H), 6.83 (d,  $J = 8.9$  Hz, 2H), 3.82 (s, 3H), 2.50 (s, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  188.62, 171.89, 164.06, 161.78, 132.12, 130.26, 129.82, 128.60,

128.54, 128.36, 115.80, 113.88, 55.59, 12.69. HRMS  $m/z$  calcd. for  $C_{18}H_{16}NO_3$   $[M+H]^+$  294.1130, found 294.1143.

**(3-(4-Fluorophenyl)-5-methylisoxazol-4-yl)(4-methoxyphenyl)methanone (3f)**

Yield: 73%. White crystal. Mp 115–117 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.69 (d,  $J$  = 8.9 Hz, 2H), 7.49 (dd,  $J$  = 8.8, 5.3 Hz, 2H), 6.96 (t,  $J$  = 8.7 Hz, 2H), 6.81 (d,  $J$  = 8.9 Hz, 2H), 3.80 (s, 3H), 2.44 (s, 3H);  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  188.43, 171.97, 164.16, 163.60 (d,  $J$  = 250 Hz), 160.84, 132.07, 130.50 (d,  $J$  = 9.1 Hz), 130.14, 124.52 (d,  $J$  = 3.0 Hz), 115.82, 115.64 (d,  $J$  = 5.0 Hz), 113.94, 55.57, 12.69.  $^{19}F$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  -110.72. HRMS  $m/z$  calcd. for  $C_{18}H_{15}FNO_3$   $[M+H]^+$  312.1036, found 312.1046.

**(4-Methoxyphenyl)(3-(4-methoxyphenyl)-5-methylisoxazol-4-yl)methanone (3g)**

Yield: 70%. White solid. Mp 84–86 °C.  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.75 – 7.69 (m, 2H), 7.47 – 7.41 (m, 2H), 6.85 – 6.77 (m, 4H), 3.82 (s, 3H), 3.76 (s, 3H), 2.44 (s, 3H);  $^{13}C$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  188.89, 171.61, 164.10, 161.33, 160.82, 132.19, 130.33, 129.93, 120.70, 115.65, 114.10, 113.94, 55.63, 55.36, 12.70. HRMS  $m/z$  calcd. for  $C_{19}H_{18}NO_4$   $[M+H]^+$  324.1236, found 324.1246.

**(5-Methyl-3-phenylisoxazol-4-yl)(4-(trifluoromethyl)phenyl)methanone (3h)**

Yield: 87%. White solid. Mp 78–80 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.73 (d,  $J$  = 7.8 Hz, 2H), 7.60 – 7.47 (m, 2H), 7.37 (dt,  $J$  = 6.9, 1.5 Hz, 2H), 7.34 – 7.19 (m, 3H), 2.58 (s, 3H).  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  189.08, 174.32, 161.96, 140.29, 134.52 (d,  $J$  = 33 Hz), 130.03, 129.75, 128.71 (d,  $J$  = 12 Hz), 127.99, 125.48 (q,  $J$  = 3.7 Hz), 124.60, 122.14, 115.43, 13.06.  $^{19}F$  NMR (377 MHz,  $CDCl_3$ )  $\delta$  -63.29. HRMS  $m/z$  calcd. for  $C_{18}H_{13}F_3NO_2$   $[M+H]^+$  332.0898, found 332.0888.

**(3-(4-Fluorophenyl)-5-methylisoxazol-4-yl)(4-(trifluoromethyl)phenyl)methanone (3i)**

Yield: 85%. White solid. Mp 116–118 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.80 – 7.72 (m, 2H), 7.58 (d,  $J$  = 8.1 Hz, 2H), 7.46 – 7.34 (m, 2H), 7.00 – 6.89 (m, 10H), 2.53 (s, 3H).  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  188.93, 174.22, 163.79 (d,  $J$  = 200 Hz), 161.07, 140.24, 134.79 (q,  $J$  = 26 Hz), 130.75 (d,  $J$  = 8.5 Hz), 129.78, 125.67 (q,  $J$  = 3.7 Hz), 124.12 (d,  $J$  = 3.4 Hz), 122.37, 115.90 (d,  $J$  = 17 Hz), 115.34, 13.14.  $^{19}F$  NMR (377 MHz,  $CDCl_3$ )  $\delta$  -63.25, -110.12. HRMS  $m/z$  calcd. for  $C_{18}H_{12}F_4NO_2$   $[M+H]^+$  350.0804, found 350.0798.

**(3-(4-Methoxyphenyl)-5-methylisoxazol-4-yl)(4-(trifluoromethyl)phenyl)methanone (3j)**

Yield: 74%. Yellowish white solid. Mp 69–71 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.86 – 7.71 (m, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 3.76 (s, 3H), 2.56 (s, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 189.25, 174.06, 161.50, 161.00, 140.31, 134.47 (q, *J* = 33 Hz), 129.98 (d, *J* = 35 Hz), 125.50 (d, *J* = 4.0 Hz), 124.74, 121.97, 120.15, 115.27, 114.11, 55.36, 13.05; <sup>19</sup>F NMR (377 MHz, CDCl<sub>3</sub>) δ -63.21. HRMS *m/z* calcd. for C<sub>19</sub>H<sub>15</sub>F<sub>3</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 362.1004, found 362.1005.

**(5-Methyl-3-phenylisoxazol-4-yl)(thiophen-2-yl)methanone (3k)**

Yield: 86%. White solid. Mp 103–105 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.63 (dd, *J* = 4.9, 1.2 Hz, 1H), 7.54 (dd, *J* = 7.9, 1.8 Hz, 2H), 7.40 – 7.27 (m, 4H), 6.94 (dd, *J* = 4.9, 3.8 Hz, 1H), 2.54 (s, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 181.75, 172.00, 161.30, 144.02, 135.41, 135.21, 130.00, 128.75, 128.52, 128.26, 115.84, 12.67. HRMS *m/z* calcd. for C<sub>15</sub>H<sub>12</sub>NO<sub>2</sub>S [M+H]<sup>+</sup> 270.0589, found 270.0583.

**(3-(4-Fluorophenyl)-5-methylisoxazol-4-yl)(thiophen-2-yl)methanone (3l)**

Yield: 92%. White solid. Mp 56–58 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.66 (t, *J* = 3.5 Hz, 1H), 7.59 – 7.50 (m, 2H), 7.32 (d, *J* = 3.8 Hz, 1H), 7.07 – 6.94 (m, 3H), 2.52 (s, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 181.59, 172.03, 163.74 (d, *J* = 250 Hz), 160.39, 143.91, 135.66, 135.22, 130.51 (d, *J* = 8.8 Hz), 128.35, 124.41 (d, *J* = 3.7 Hz), 116.00, 115.78 (d, *J* = 12 Hz), 12.72; <sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>) δ -110.34. HRMS *m/z* calcd. for C<sub>15</sub>H<sub>11</sub>FNO<sub>2</sub>S [M+H]<sup>+</sup> 288.0495, found 288.0490.

**(3-(4-Methoxyphenyl)-5-methylisoxazol-4-yl)(thiophen-2-yl)methanone (3m)**

Yield: 80%. Sticky gel. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.65 (t, *J* = 3.5 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.32 (d, *J* = 3.5 Hz, 1H), 6.96 (d, *J* = 4.0 Hz, 1H), 6.88 – 6.80 (m, 2H), 3.78 (s, 3H), 2.52 (s, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 182.04, 171.76, 160.96, 160.87, 144.12, 135.44, 135.29, 129.93, 128.35, 120.57, 115.70, 114.22, 55.39, 12.68. HRMS *m/z* calcd. for C<sub>16</sub>H<sub>14</sub>NO<sub>3</sub>S [M+H]<sup>+</sup> 300.0694, found 300.0696.

### **5-Methyl-N,3-diphenylisoxazole-4-carboxamide (3n)**

Yield: 80%. White crystal. Mp 198–200 °C. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra matched with literature [1]. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.68 (m, 2H), 7.63 – 7.52 (m, 3H), 7.28 (m, 2H), 7.23 (m, 2H), 7.12 (brs, 1H), 7.10 (m, 1H), 2.80 (s, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 175.31, 159.83, 159.34, 137.19, 130.85, 129.44, 129.26, 129.04, 128.01, 124.64, 119.60, 111.24, 13.18. HRMS *m/z* calcd. for C<sub>17</sub>H<sub>15</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 279.1134, found 279.1139.

### **3-(4-Fluorophenyl)-5-methyl-N-phenylisoxazole-4-carboxamide (3o)**

Yield: 82%. White crystal. Mp 172–174 °C. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra matched with literature [1]. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.72 – 7.57 (m, 4H), 7.32 – 7.20 (m, 3H), 7.18 – 7.05 (m, 2H), 2.82 (s, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 175.14, 164.29 (d, *J* = 250 Hz), 159.44, 159.12, 137.16, 131.40 (d, *J* = 8.8 Hz), 129.28, 125.01, 124.09 (d, *J* = 3.7 Hz), 119.80, 116.77 (d, *J* = 22 Hz), 111.48, 13.21. <sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>) δ -108.64. HRMS *m/z* calcd. for C<sub>17</sub>H<sub>14</sub>FN<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 297.1039, found 297.1045.

### **3-(4-Methoxyphenyl)-5-methyl-N-phenylisoxazole-4-carboxamide (3p)**

Yield: 78%. White crystal. Mp 144–146 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.59 (d, *J* = 8.7 Hz, 2H), 7.36 – 7.19 (m, 4H), 7.15 – 7.04 (m, 3H), 3.89 (s, 3H), 2.77 (s, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 175.26, 161.68, 159.69, 137.37, 130.81, 129.18, 124.76, 119.94, 119.83, 114.99, 111.25, 55.64, 13.30. HRMS *m/z* calcd. for C<sub>18</sub>H<sub>17</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup> 309.1239, found 309.1243.

### **Benzyl 5-methyl-3-phenylisoxazole-4-carboxylate (3q)**

Yield: 85%. White solid. Mp 33–35 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.67 – 7.57 (m, 2H), 7.52 – 7.46 (m, 1H), 7.46 – 7.38 (m, 2H), 7.34 (m, 3H), 7.28 – 7.19 (m, 2H), 5.25 (s, 2H), 2.75 (s, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 176.21, 162.69, 161.89, 135.32, 129.79, 129.48, 128.65, 128.53, 128.44, 128.39, 128.16, 108.44, 66.61, 13.77. HRMS *m/z* calcd. for C<sub>18</sub>H<sub>16</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 294.1130, found 294.1143.

### **Benzyl 3-(4-fluorophenyl)-5-methylisoxazole-4-carboxylate (3r)**

Yield: 90%. White solid. Mp 49–51 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.59 (t, *J* = 8.7, 2H), 7.36 (m, 3H), 7.25 (m, 2H), 7.07 (t, *J* = 8.7 Hz, 2H), 5.24 (s, 2H), 2.74 (s, 3H); <sup>13</sup>C NMR (101 MHz,



CDCl<sub>3</sub>)  $\delta$  176.41, 163.84 (d,  $J$  = 250 Hz), 161.86, 161.80, 135.21, 131.54 (d,  $J$  = 8.0 Hz), 128.72, 128.62, 128.53, 124.55 (d,  $J$  = 4.0 Hz), 115.28 (d,  $J$  = 22 Hz), 108.37, 66.76, 13.84. <sup>19</sup>F NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  -111.14. HRMS  $m/z$  calcd. for C<sub>18</sub>H<sub>15</sub>FNO<sub>3</sub> [M+H]<sup>+</sup> 312.1036, found 312.1032.

**Benzyl 3-(4-methoxyphenyl)-5-methylisoxazole-4-carboxylate (3s)**

Yield: 75%. White solid. Mp 47–49 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.56 (d,  $J$  = 8.7 Hz, 2H), 7.35 (m, 3H), 7.29 – 7.24 (m, 2H), 6.92 (d,  $J$  = 8.7 Hz, 2H), 5.26 (s, 2H), 3.86 (s, 3H), 2.73 (d,  $J$  = 1.0 Hz, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  176.01, 162.23, 161.93, 160.81, 135.28, 130.79, 128.55, 128.38, 128.37, 120.58, 113.54, 108.19, 66.51, 55.30, 13.75. HRMS  $m/z$  calcd. for C<sub>19</sub>H<sub>18</sub>NO<sub>4</sub> [M+H]<sup>+</sup> 324.1236, found 324.1236.

**Ethyl 3-(4-fluorophenyl)-5-methylisoxazole-4-carboxylate (3t)**

Yield: 86%. White crystal. Mp 58–60 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.70 – 7.59 (m, 2H), 7.20 – 7.08 (m, 2H), 4.26 (q,  $J$  = 7.1 Hz, 2H), 2.73 (s, 3H), 1.26 (t,  $J$  = 7.1 Hz, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  175.96, 163.72 (d,  $J$  = 250 Hz), 161.85, 161.70, 131.43 (d,  $J$  = 8.6 Hz), 124.56 (d,  $J$  = 3.6 Hz), 115.07 (d,  $J$  = 21 Hz), 108.35, 60.78, 14.00, 13.61. <sup>19</sup>F NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  -111.22. HRMS  $m/z$  calcd. for C<sub>13</sub>H<sub>13</sub>FNO<sub>3</sub> [M+H]<sup>+</sup> 250.0879, found 250.0878.

**N-Benzyl-5-methyl-3-phenylisoxazole-4-carboxamide (3u)**

Yield: 92%. White crystal. Mp 135–137 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.54 – 7.48 (m, 2H), 7.44 (d,  $J$  = 7.5 Hz, 1H), 7.39 (dd,  $J$  = 7.2, 1.2 Hz, 2H), 7.32 – 7.24 (m, 3H), 7.09 (dd,  $J$  = 7.3, 2.3 Hz, 2H), 5.73 (s, 1H), 4.42 (d,  $J$  = 5.7 Hz, 2H), 2.73 (s, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  174.27, 161.47, 160.19, 137.48, 130.48, 129.19, 129.08, 128.79, 128.15, 127.82, 127.71, 111.12, 43.67, 13.05. HRMS  $m/z$  calcd. for C<sub>18</sub>H<sub>17</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 293.1290, found 293.1294.

**N-Benzyl-3-(4-fluorophenyl)-5-methylisoxazole-4-carboxamide (3v)**

Yield: 82%. White crystal. Mp 179–181 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.51 (dd,  $J$  = 8.8, 5.2 Hz, 2H), 7.35 – 7.27 (m, 2H), 7.13 (dd,  $J$  = 7.3, 2.3 Hz, 2H), 7.05 (t,  $J$  = 8.6 Hz, 2H), 5.62 (s, 1H), 4.44 (d,  $J$  = 5.7 Hz, 2H), 2.71 (s, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  174.04, 164.07 (d,  $J$  = 250 Hz), 161.38, 159.37, 137.47, 131.13 (d,  $J$  = 8.0 Hz), 128.92, 127.94 (d,  $J$  = 2.0 Hz), 124.18 (d,  $J$  =

3.0 Hz), 116.48, 116.26, 111.28, 43.82, 12.99.  $^{19}\text{F}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  -109.57. HRMS  $m/z$  calcd. for  $\text{C}_{18}\text{H}_{16}\text{FN}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  311.1196, found 311.1194.

***N*-Benzyl-3-(4-methoxyphenyl)-5-methylisoxazole-4-carboxamide (3w)**

Yield: 74%. White crystal. Mp 143–145 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.46 – 7.39 (m, 2H), 7.27 (dt,  $J$  = 6.3, 2.2 Hz, 3H), 7.15 – 7.08 (m, 2H), 6.85 (d,  $J$  = 8.8 Hz, 2H), 5.78 (s, 1H), 4.42 (d,  $J$  = 5.7 Hz, 2H), 3.80 (s, 3H), 2.70 (s, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  174.07, 161.62, 161.30, 159.90, 137.60, 130.48, 128.77, 127.91, 127.69, 120.05, 114.61, 111.04, 55.47, 43.63, 13.03. HRMS  $m/z$  calcd. for  $\text{C}_{19}\text{H}_{19}\text{N}_2\text{O}_3$   $[\text{M}+\text{H}]^+$  323.1396, found 323.1394.

**(3-(4-Fluorophenyl)-5-(trifluoromethyl)isoxazol-4-yl)(phenyl)methanone (3x)**

General synthetic procedure for the [3 + 2]-cycloaddition reaction was followed but with 5% water, 95% methanol as the solvent mixture. Yield: 40%. Sticky gel.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.86 – 7.78 (m, 2H), 7.69 – 7.60 (m, 1H), 7.60 – 7.53 (m, 2H), 7.47 (t,  $J$  = 7.9 Hz, 2H), 7.04 (t,  $J$  = 8.6 Hz, 2H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  187.00, 164.34 (d,  $J$  = 250 Hz), 160.85, 156.77 (q,  $J$  = 42 Hz), 136.12, 135.26, 130.37 (d,  $J$  = 8.8 Hz), 129.79, 129.26, 122.67 (d,  $J$  = 2.5 Hz), 118.73, 118.72 (d,  $J$  = 2.5 Hz), 116.50 (d,  $J$  = 21 Hz);  $^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.50, -108.50. HRMS  $m/z$  calcd. for  $\text{C}_{17}\text{H}_{10}\text{F}_4\text{NO}_2$   $[\text{M}+\text{H}]^+$  336.0648, found 336.0656.

**(3-(4-Methoxyphenyl)-5-(trifluoromethyl)isoxazol-4-yl)(phenyl)methanone (3y)**

General synthetic procedure for the [3 + 2]-cycloaddition reaction was followed but with 5% water, 95% methanol as the solvent mixture. Yield: 35%. Sticky gel.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.86 – 7.79 (m, 2H), 7.67 – 7.58 (m, 1H), 7.54 – 7.43 (m, 4H), 6.90 – 6.82 (m, 2H), 3.78 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  187.40, 161.70, 161.28, 156.39 (q,  $J$  = 42 Hz), 136.24, 135.09, 129.81 (d,  $J$  = 3.8 Hz), 129.70, 129.20, 118.77 (d,  $J$  = 5.0 Hz), 118.65, 116.63, 114.66, 55.46;  $^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.55. HRMS  $m/z$  calcd. for  $\text{C}_{18}\text{H}_{13}\text{F}_3\text{NO}_3$   $[\text{M}+\text{H}]^+$  348.0848, found 348.0826.

**(3-(4-Methoxyphenyl)-5-(trifluoromethyl)isoxazol-4-yl)(naphthalen-1-yl)methanone (3z)**

General synthetic procedure for the [3 + 2]-cycloaddition reaction was followed but with 5% water, 95% methanol as the solvent mixture. Yield: 40%. Yellow sticky gel.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

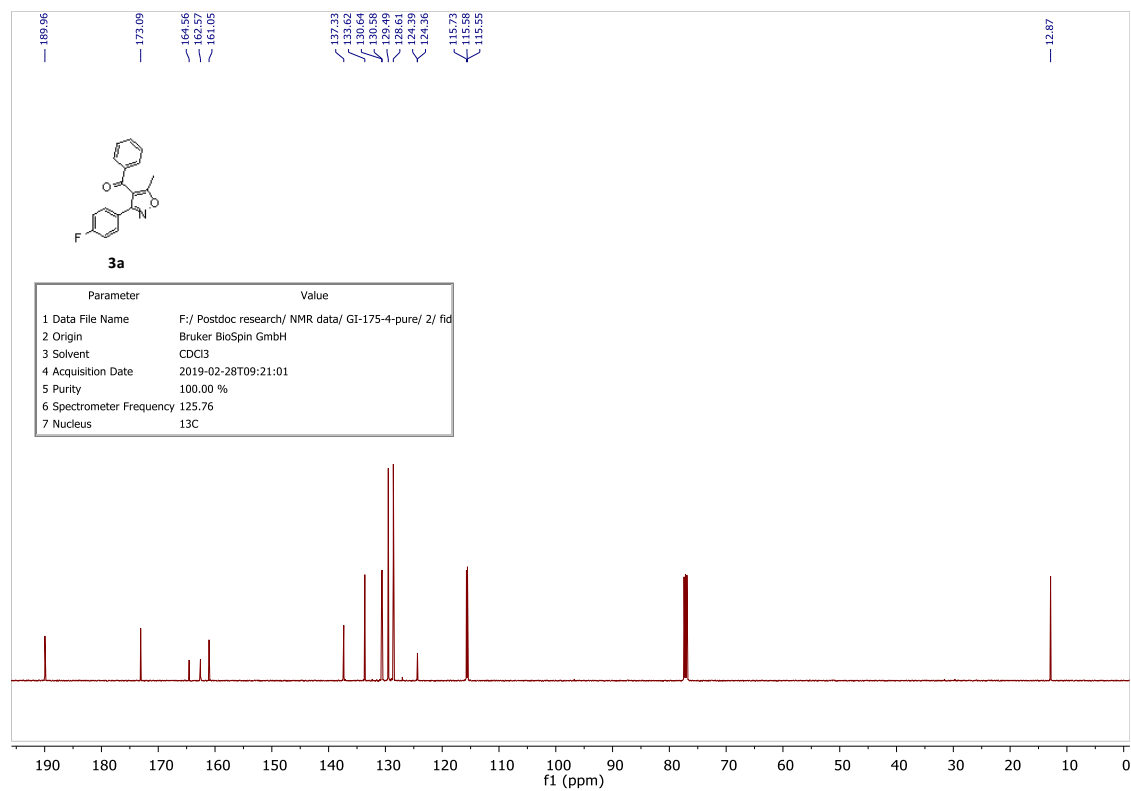
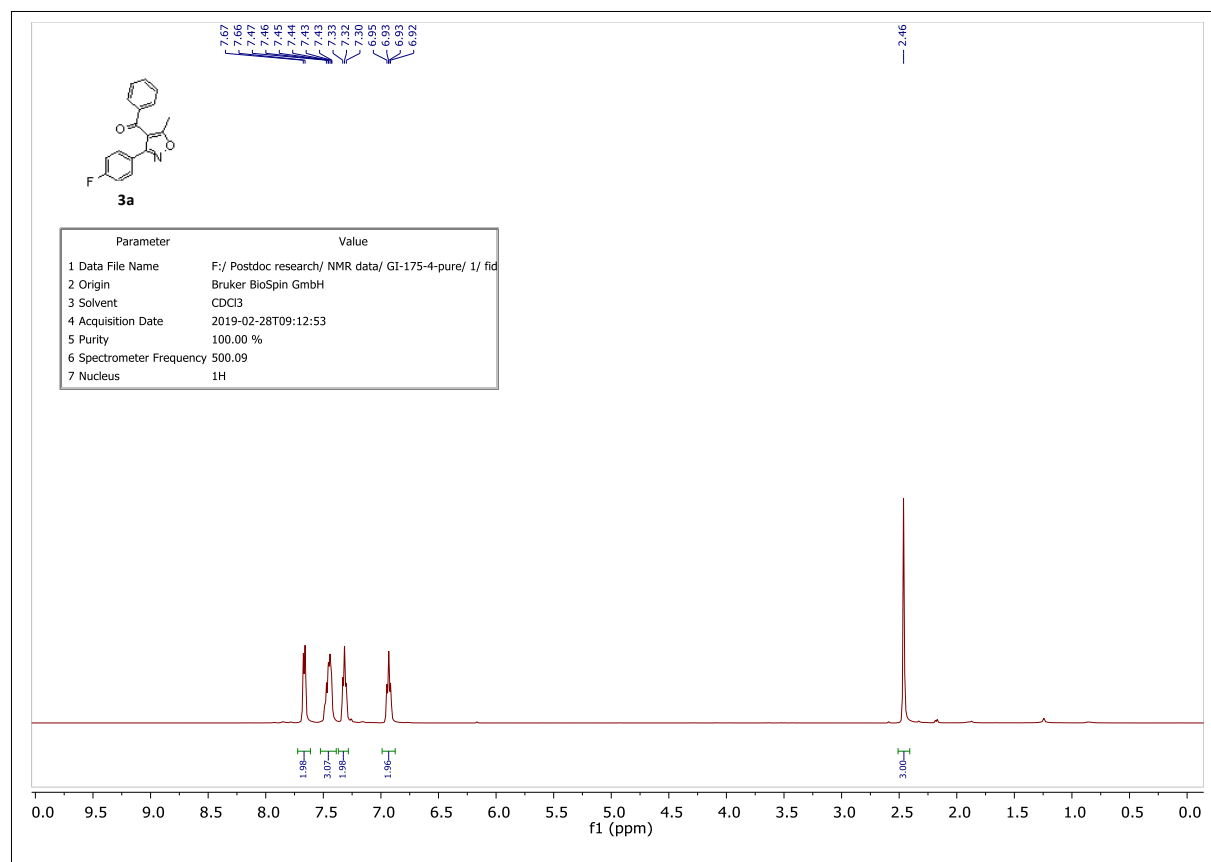
$\delta$  8.30 – 8.23 (m, 1H), 8.04 (dd,  $J$  = 8.7, 1.8 Hz, 1H), 8.01 – 7.85 (m, 3H), 7.72 – 7.51 (m, 4H), 6.90 – 6.80 (m, 2H), 3.76 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  187.24, 161.68, 161.38, 156.36 (q,  $J$  = 42 Hz), 136.49, 133.77, 133.21, 132.42, 130.04, 129.81, 129.65, 129.37, 128.04, 127.43, 123.83, 118.77, 118.75, 116.69, 114.68, 55.27.  $^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.48. HRMS  $m/z$  calcd. for  $\text{C}_{22}\text{H}_{15}\text{F}_3\text{NO}_3$   $[\text{M}+\text{H}]^+$  398.1004, found 398.1027.

**(3-(4-Fluorophenyl)-5-(trifluoromethyl)isoxazol-4-yl)(naphthalen-1-yl)methanone (3aa)**

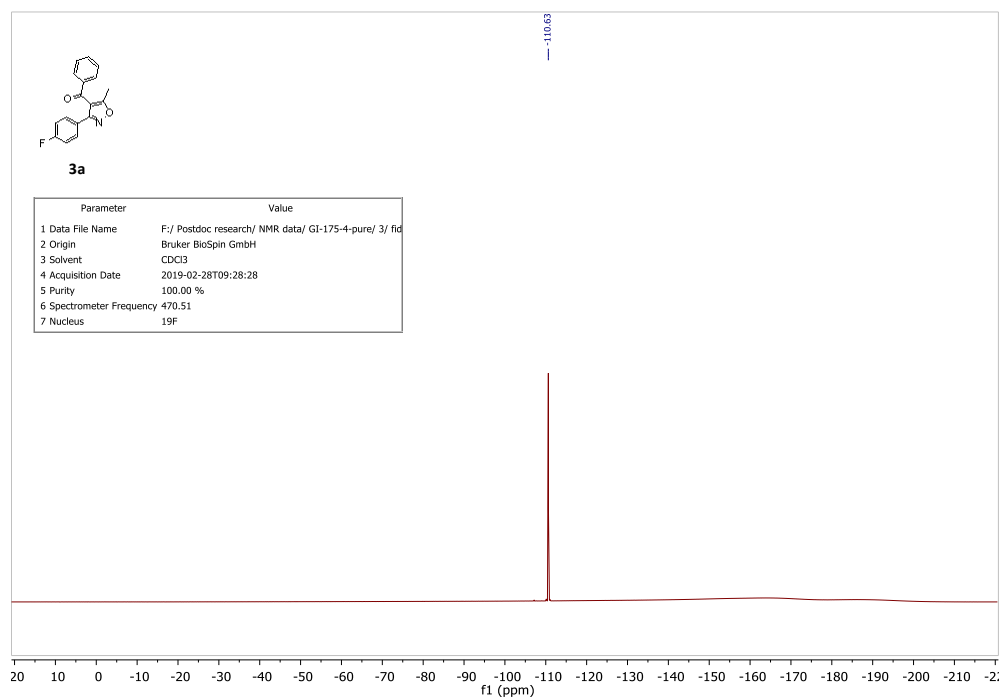
General synthetic procedure for the [3 + 2]-cycloaddition reaction was followed but with 5% water, 95% methanol as the solvent mixture. Yield: 40%. Yellow sticky gel.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.30 – 8.15 (m, 1H), 8.15 – 7.82 (m, 4H), 7.73 – 7.48 (m, 4H), 7.10 – 6.98 (m, 2H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  186.83, 164.31 (d,  $J$  = 250 Hz), 160.94, 156.73 (q,  $J$  = 42 Hz), 136.54, 133.66, 133.21, 132.38, 130.32 (d,  $J$  = 8.0 Hz), 129.96 (d,  $J$  = 6.0 Hz), 129.47, 128.07, 127.53, 123.74, 122.72 (d,  $J$  = 3.0 Hz), 119.04, 118.83 (d,  $J$  = 2.0 Hz), 116.60, 116.38.  $^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ )  $\delta$  -62.41, -108.43. HRMS  $m/z$  calcd. for  $\text{C}_{21}\text{H}_{12}\text{F}_4\text{NO}_2$   $[\text{M}+\text{H}]^+$  386.0804, found 386.0825.

**Reference**

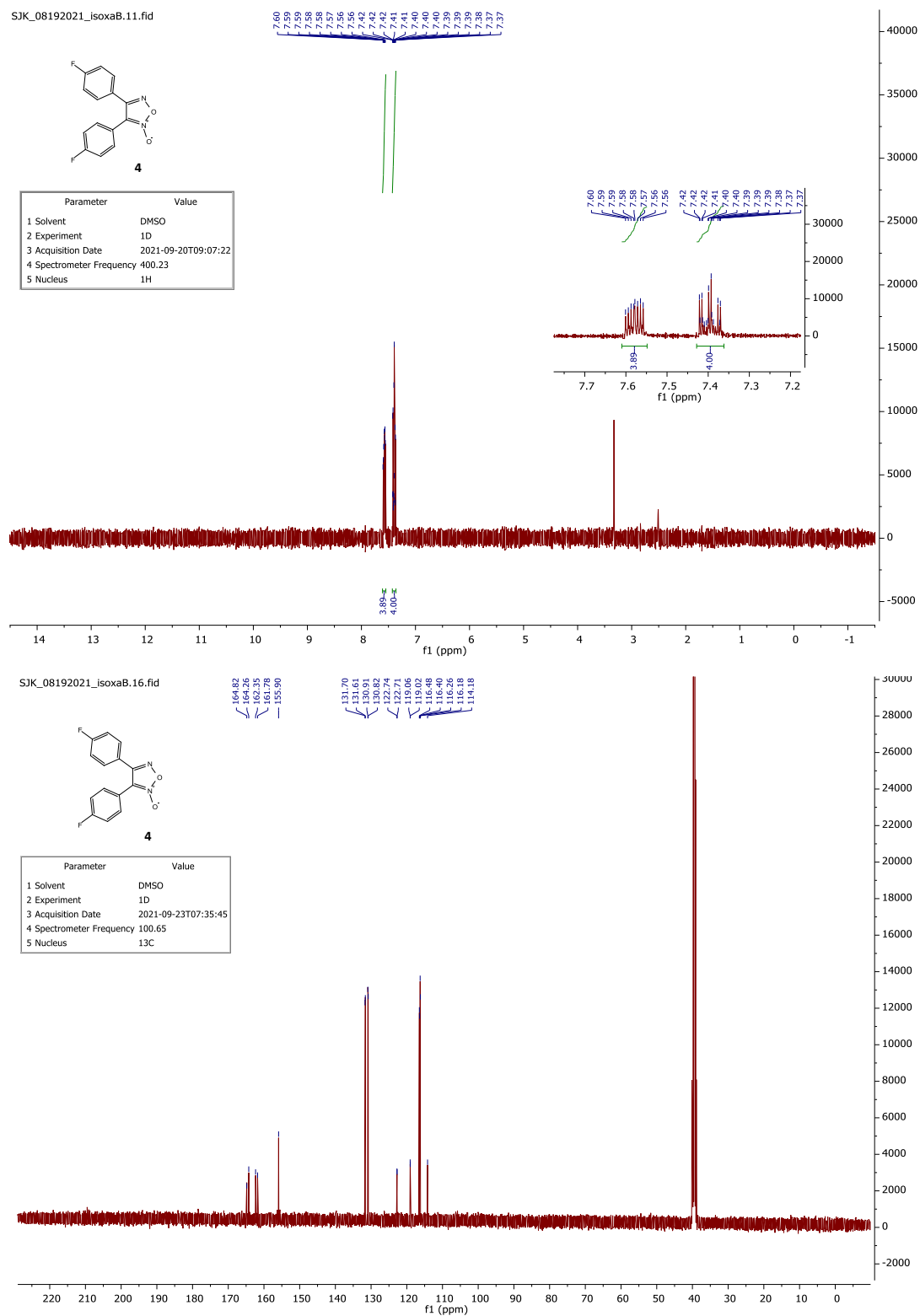
1. Zhou, X.; Xu, X.; Shi, Z.; Liu, K.; Gao, H.; Li, W. *Org. Biomol. Chem.* **2016**, *14*, 5246–5250.



**Figure S3:**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of compound **3a**.

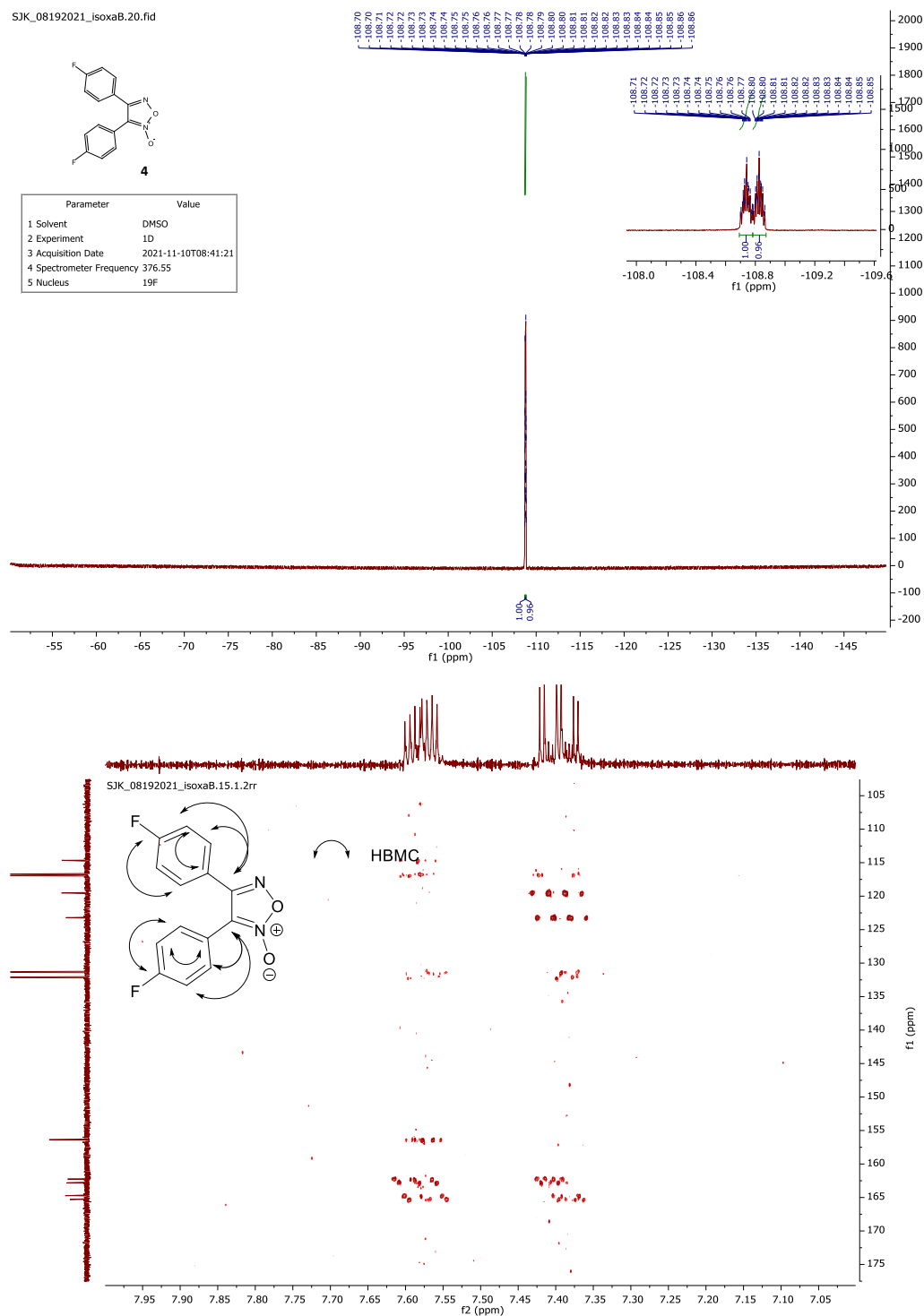


**Figure S4:**  $^{19}\text{F}$  NMR spectrum of compound **3a**.

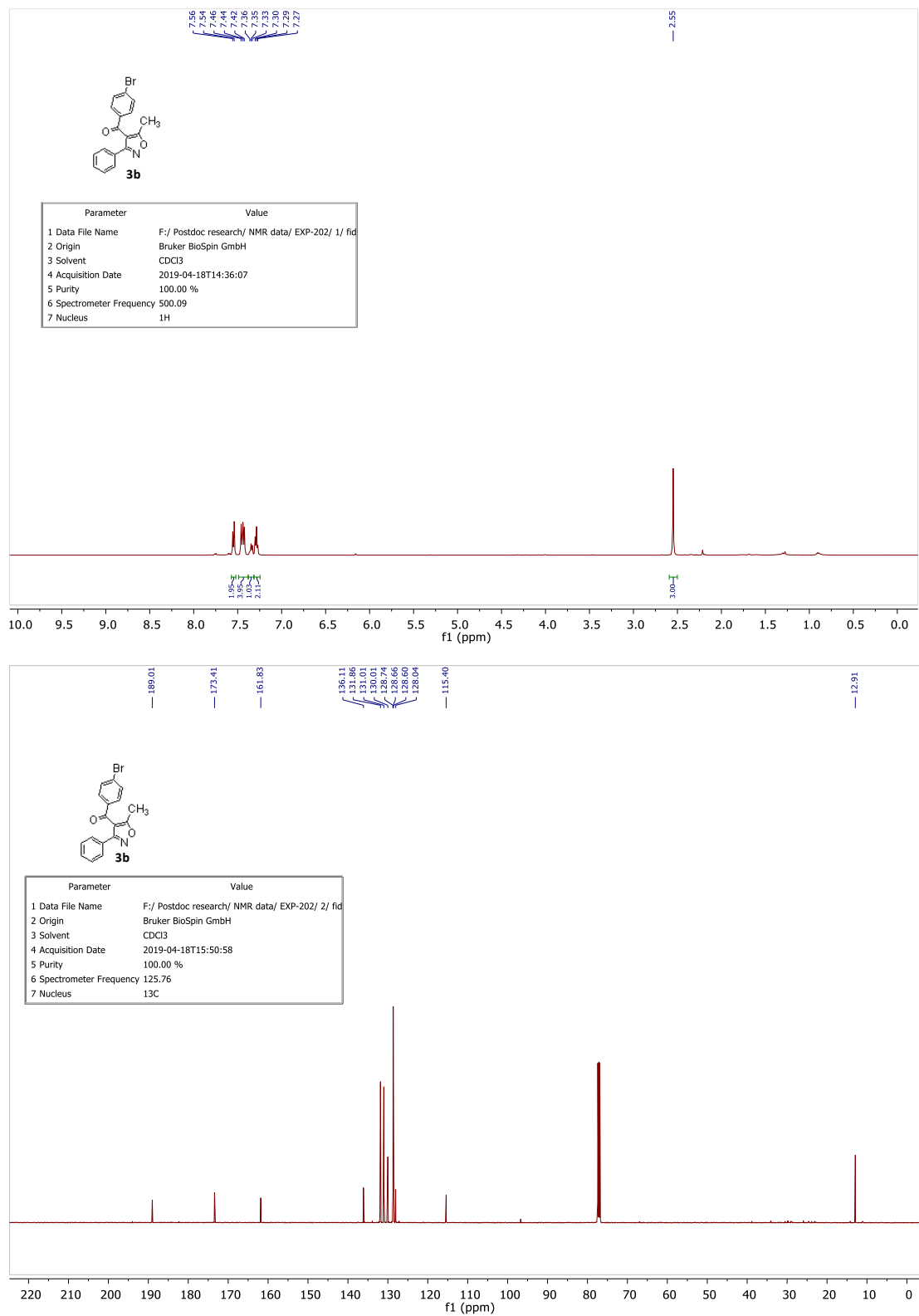


**Figure S5:** <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound 4.

SJK\_08192021\_isoxaB.20.fid

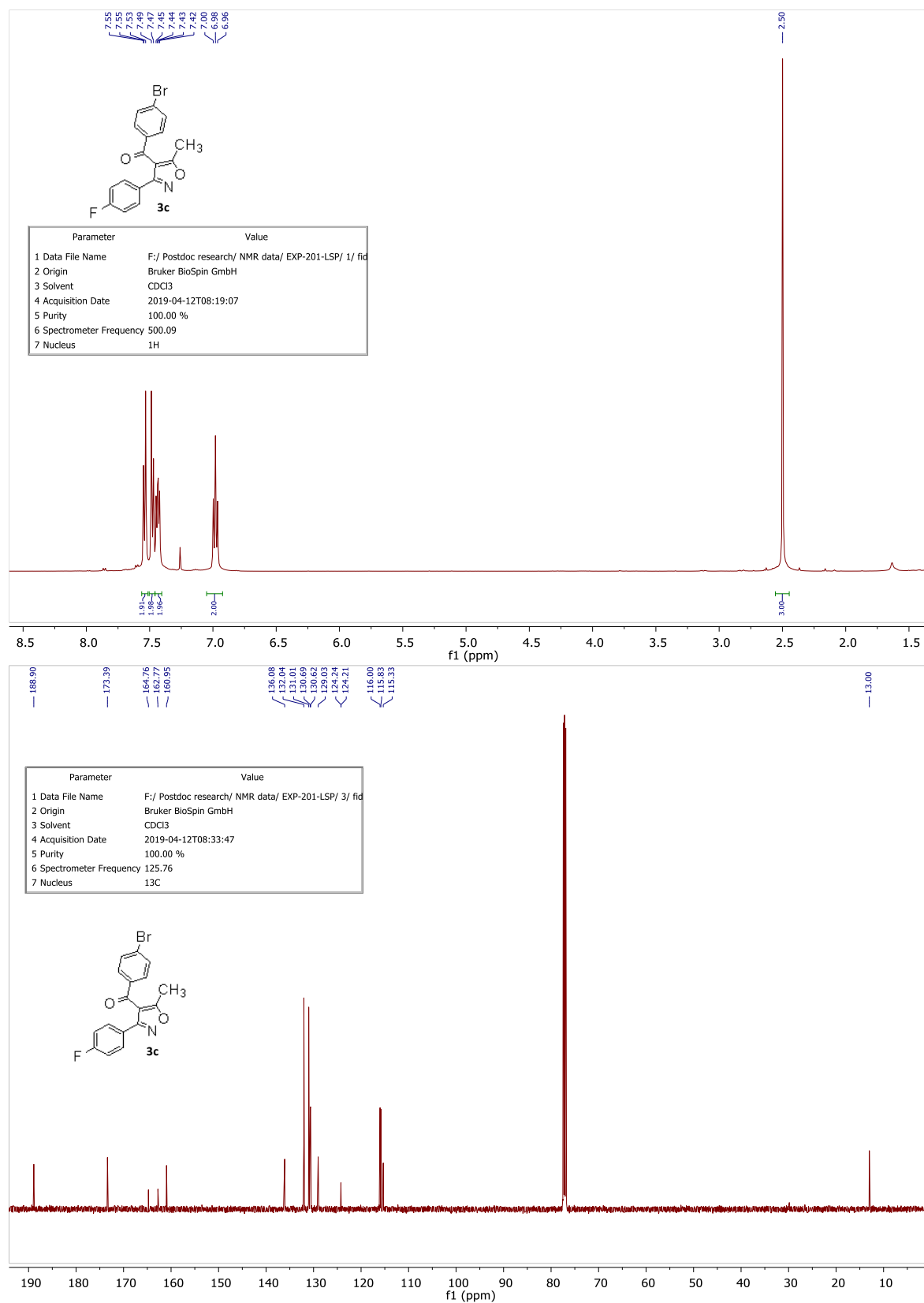


**Figure S6:**  $^{19}\text{F}$  NMR and HMBC spectra of compound **4**. Compound **4** has a molecular formula of  $\text{C}_{14}\text{H}_8\text{N}_2\text{O}_2\text{F}_2$ , as evidenced from DART-HRMS analysis ( $m/z$  calcd. for  $\text{C}_{14}\text{H}_9\text{N}_2\text{O}_2\text{F}_2$   $[\text{M}+\text{H}]^+$  275.0632, found 275.0637). The oxadiazole and fluorophenyl groups are revealed by  $^{19}\text{F}$  and HMBC spectral data, which identified **4** as 3,4-bis(4-fluorophenyl)-1,2,5-oxadiazole 2-oxide.

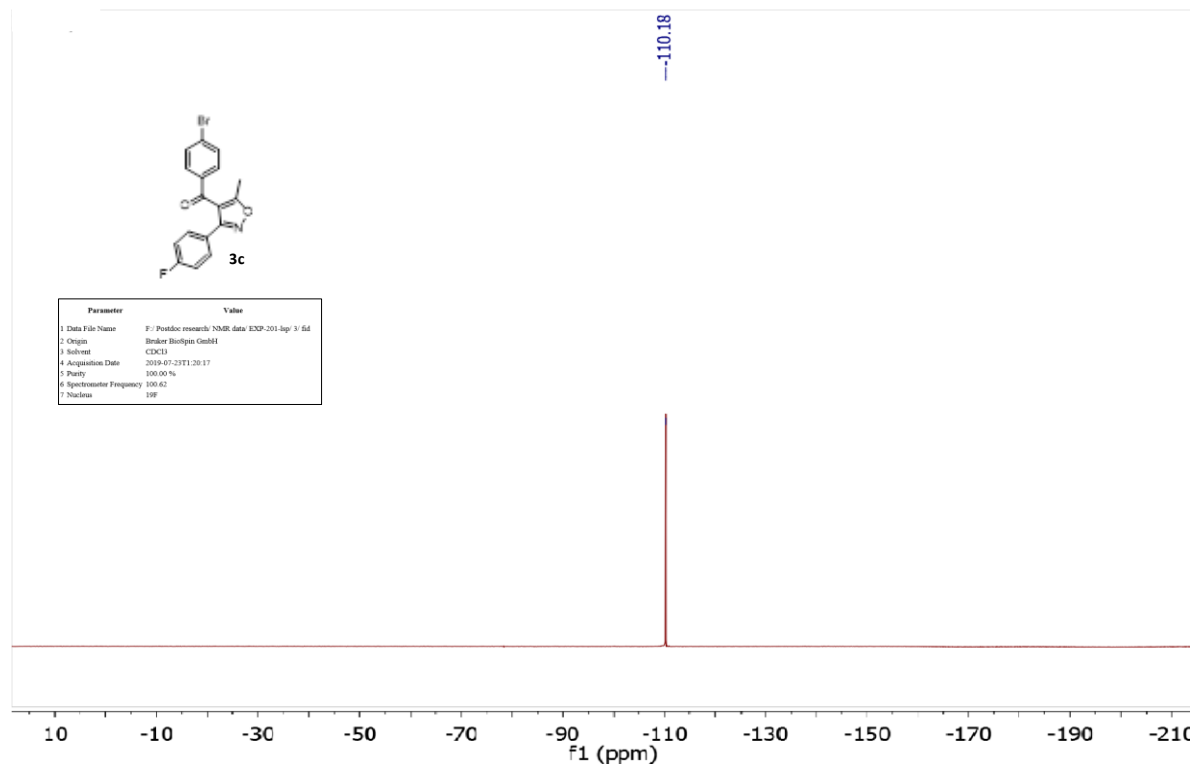


**Figure S7:** <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound **3b**.

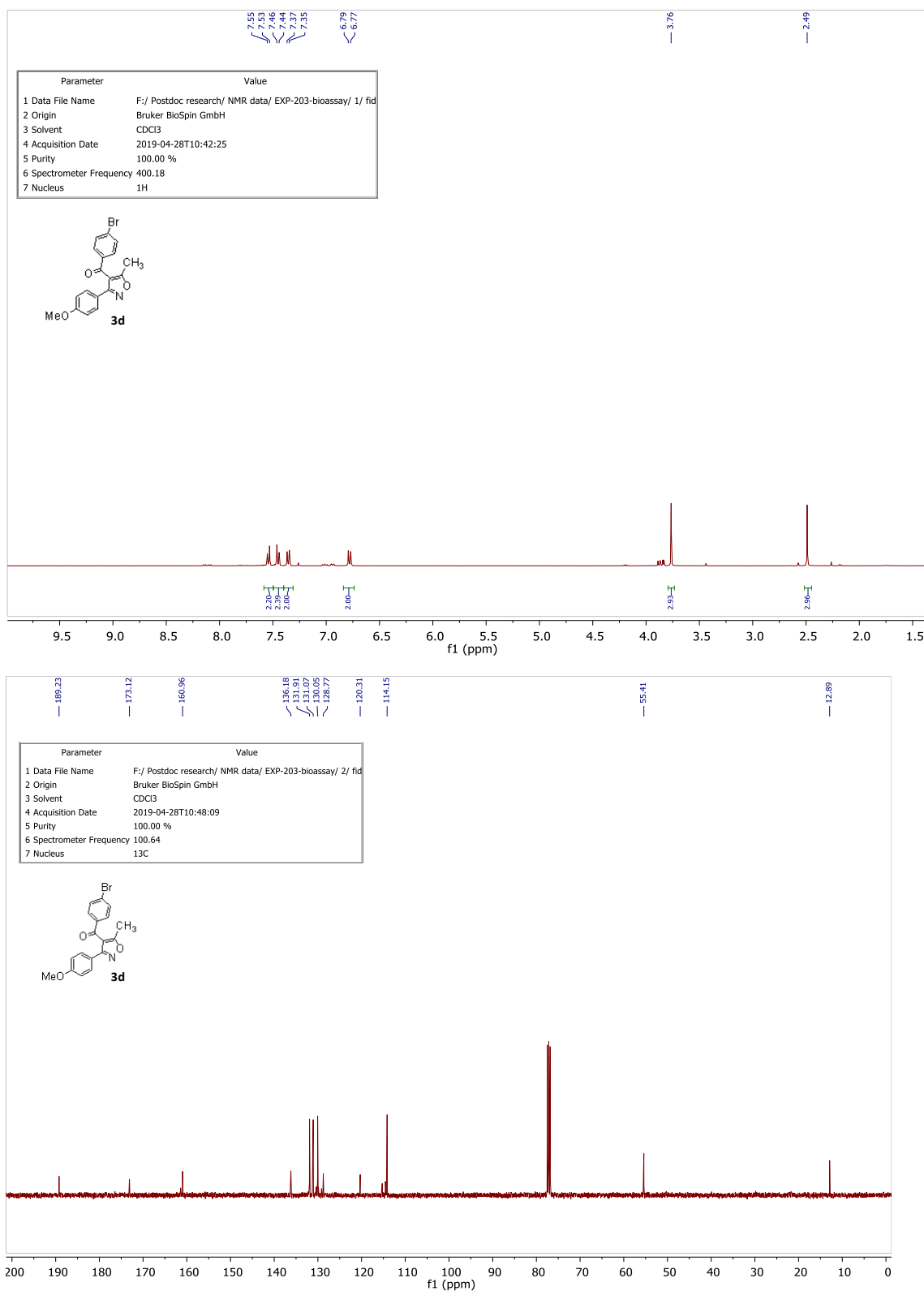




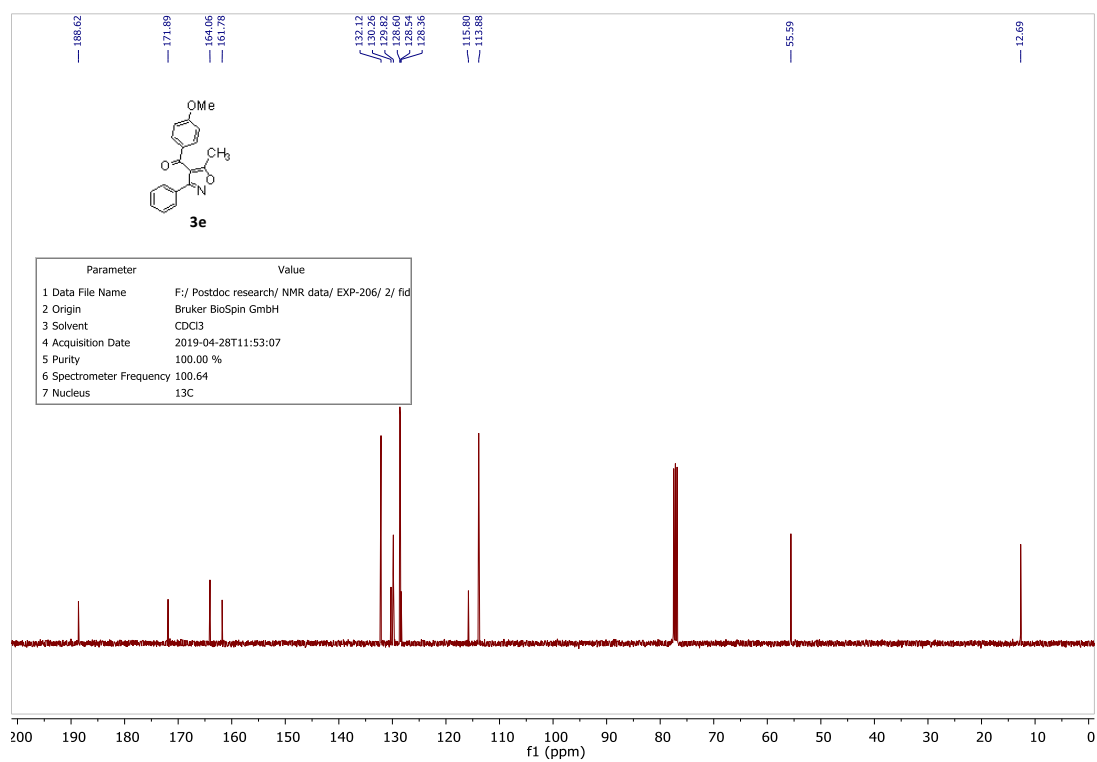
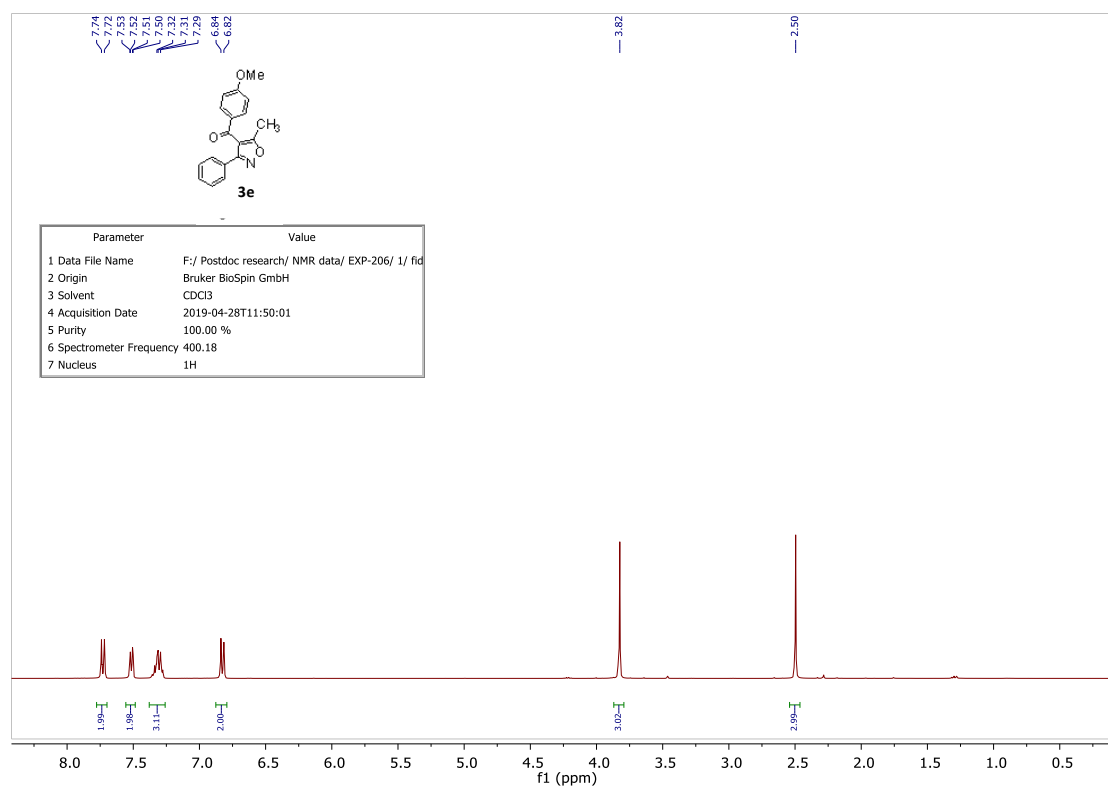
**Figure S8:** <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound 3c.



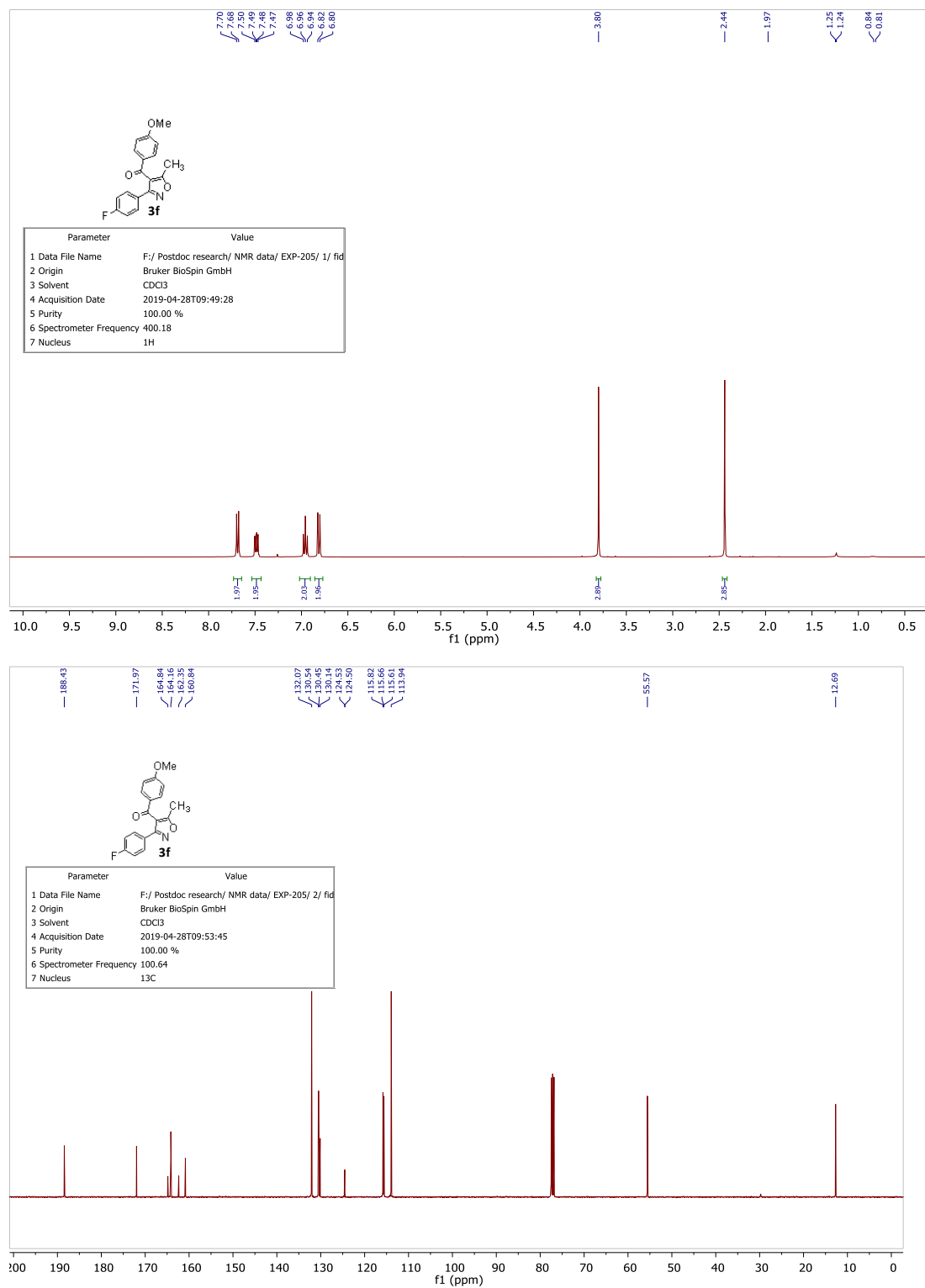
**Figure S9:**  $^{19}\text{F}$  NMR spectrum of compound **3c**.



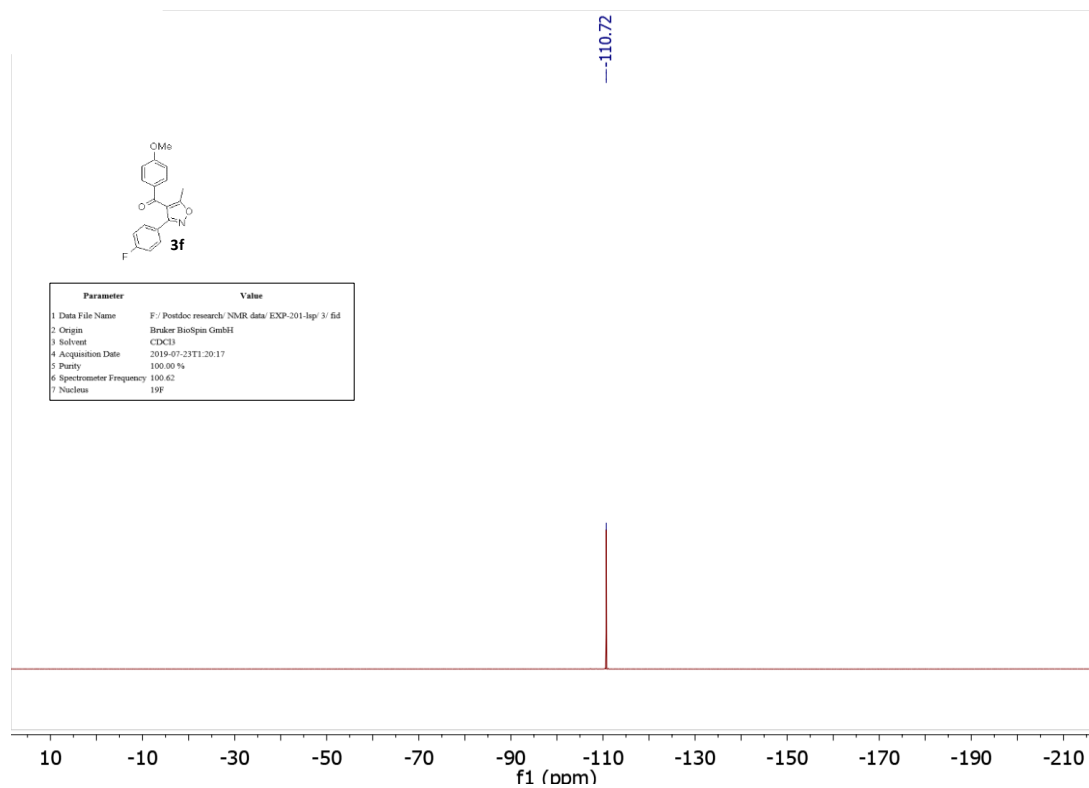
**Figure S10:** <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound **3d**.



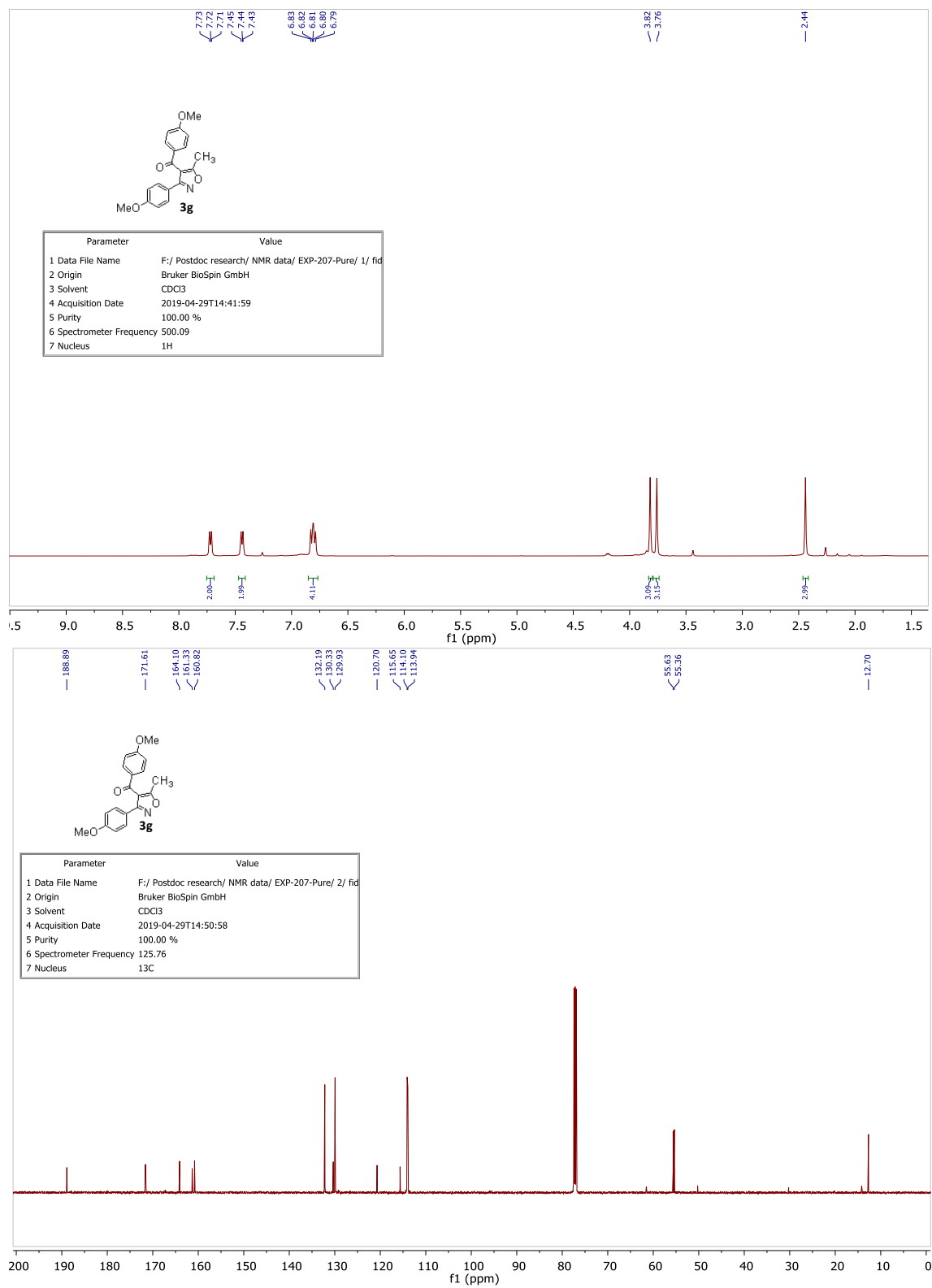
**Figure S11:** <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound **3e**.



**Figure S12:** <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound 3f.



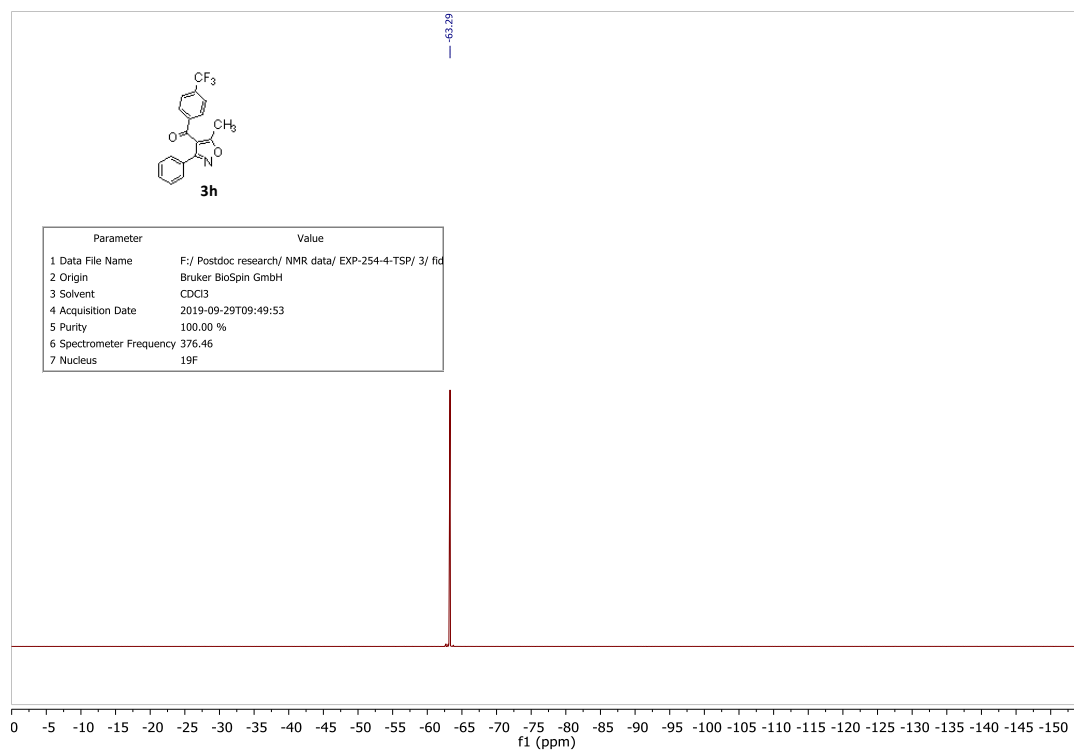
**Figure S13:** <sup>19</sup>F NMR spectrum of compound **3f**.



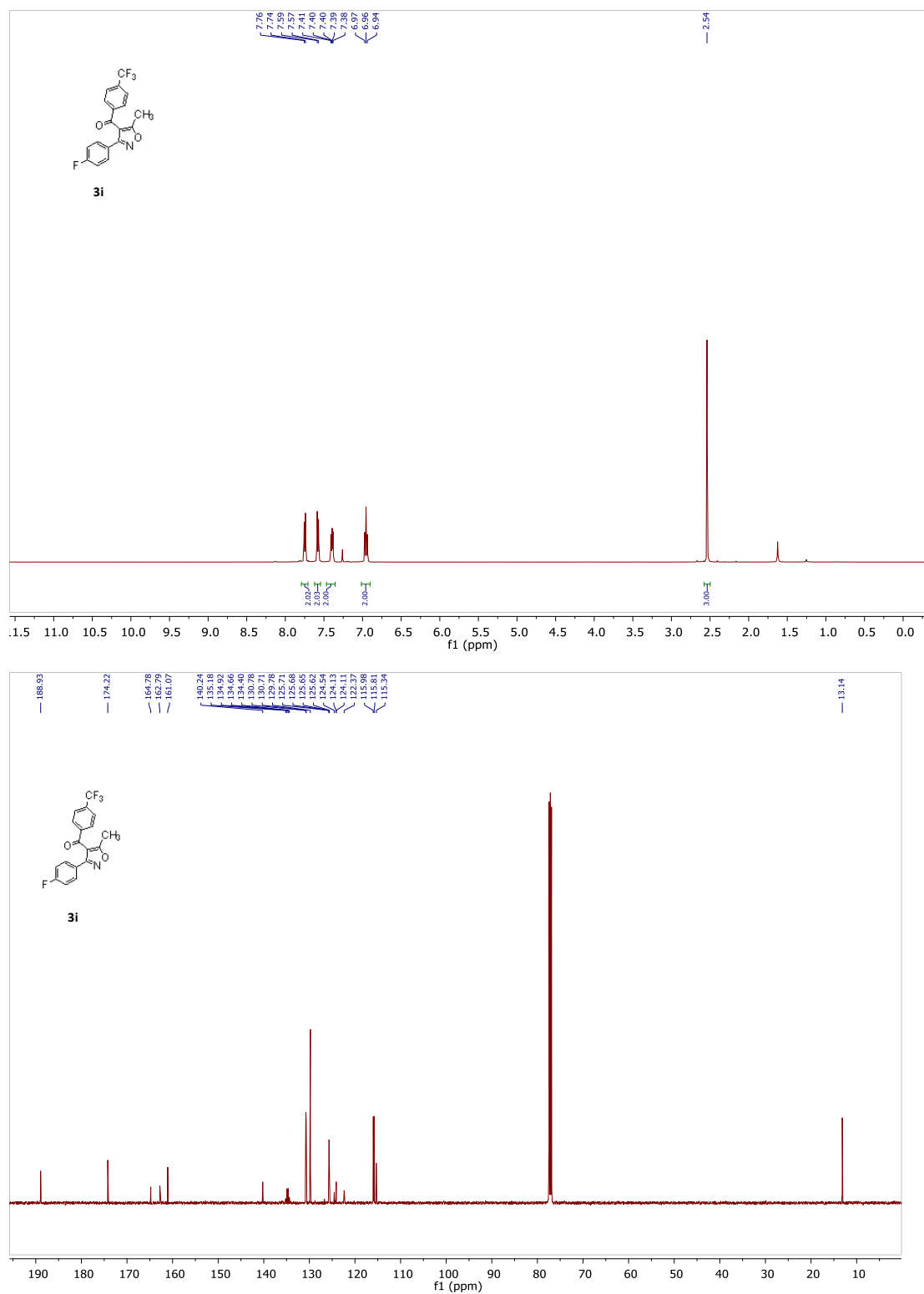
**Figure S14:** <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound **3g**.



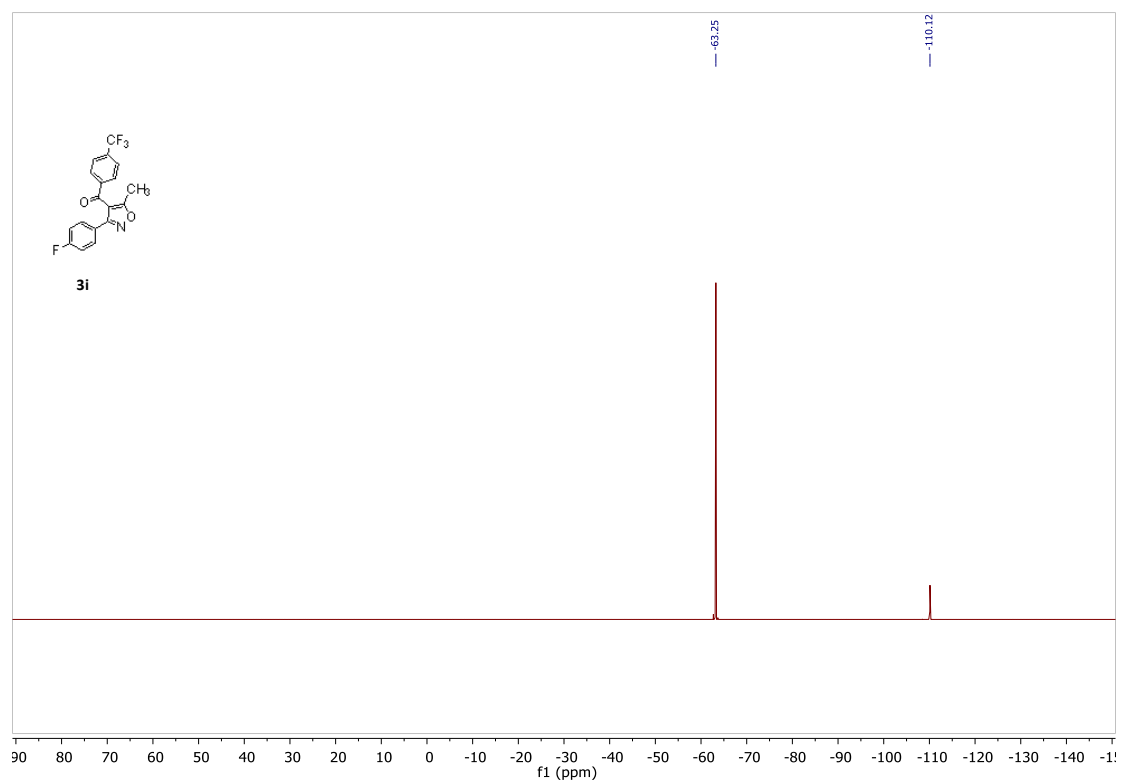




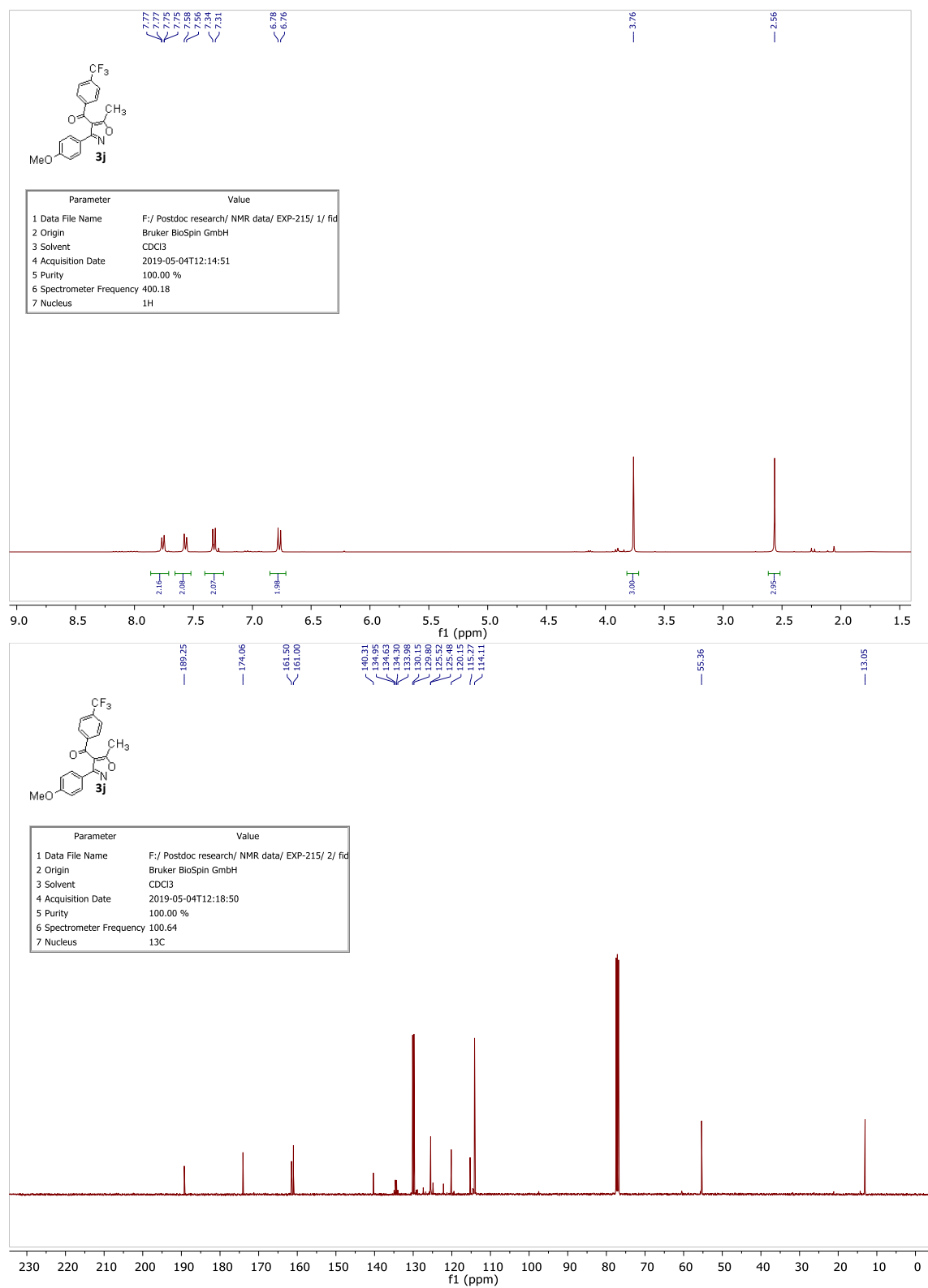
**Figure S16:**  $^{19}\text{F}$  NMR spectrum of compound **3h**.

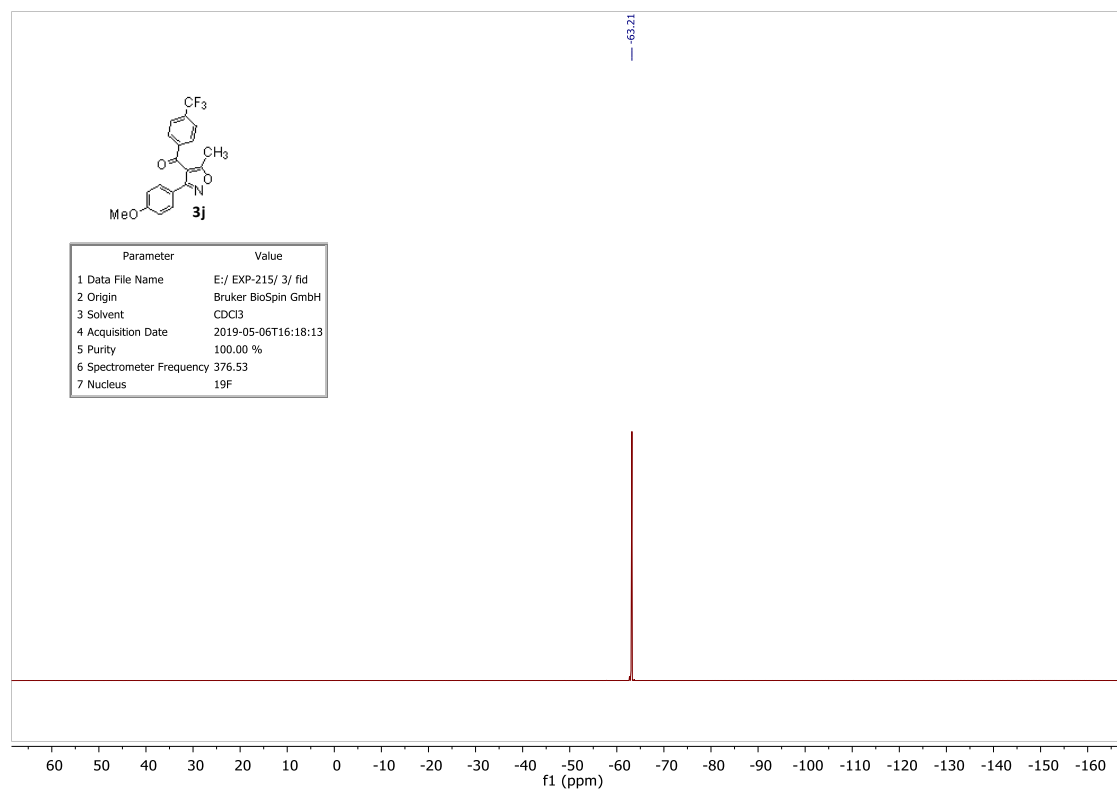


**Figure S17:**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of compound **3i**.

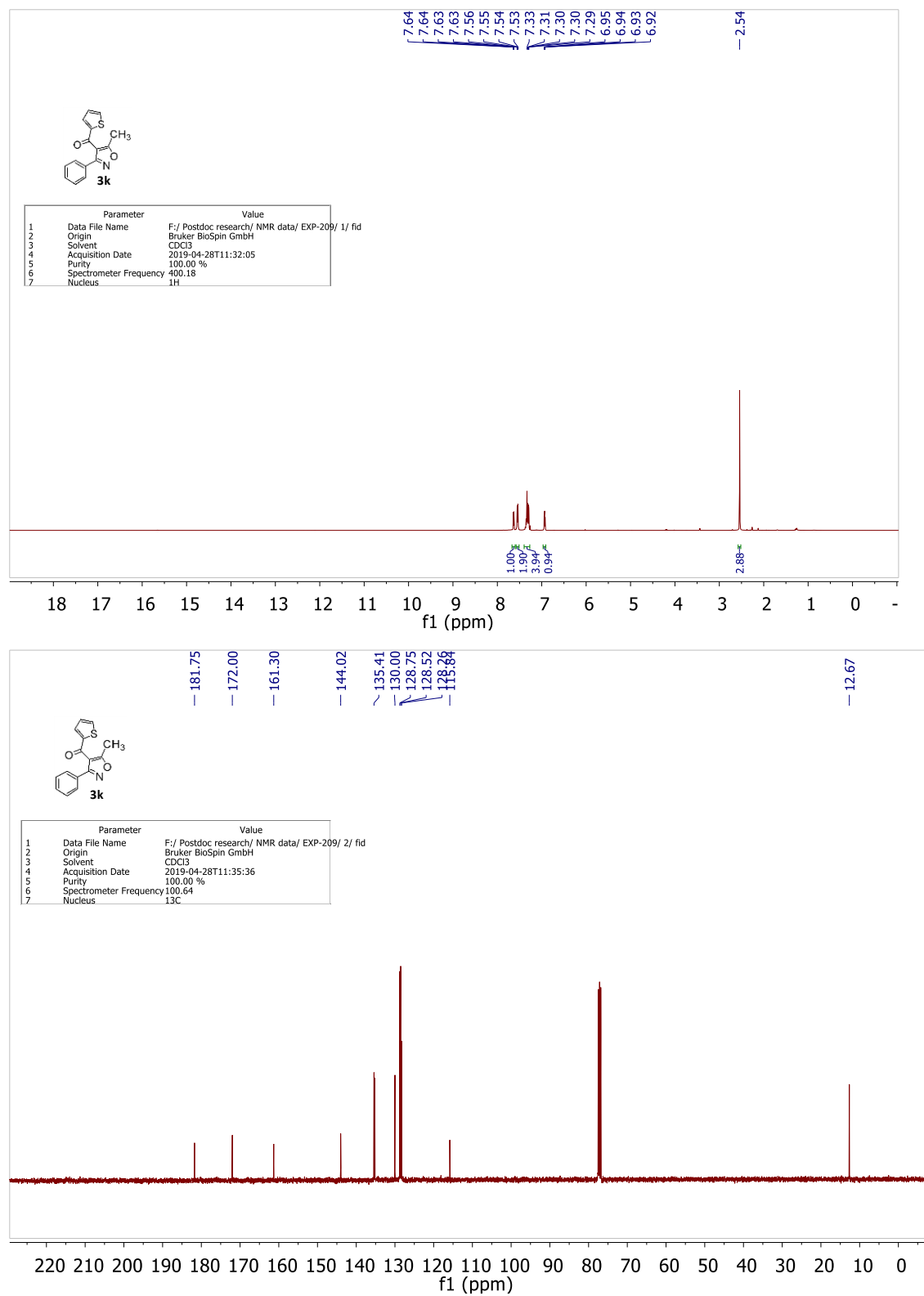


**Figure S18:**  $^{19}\text{F}$  NMR spectrum of compound **3i**.

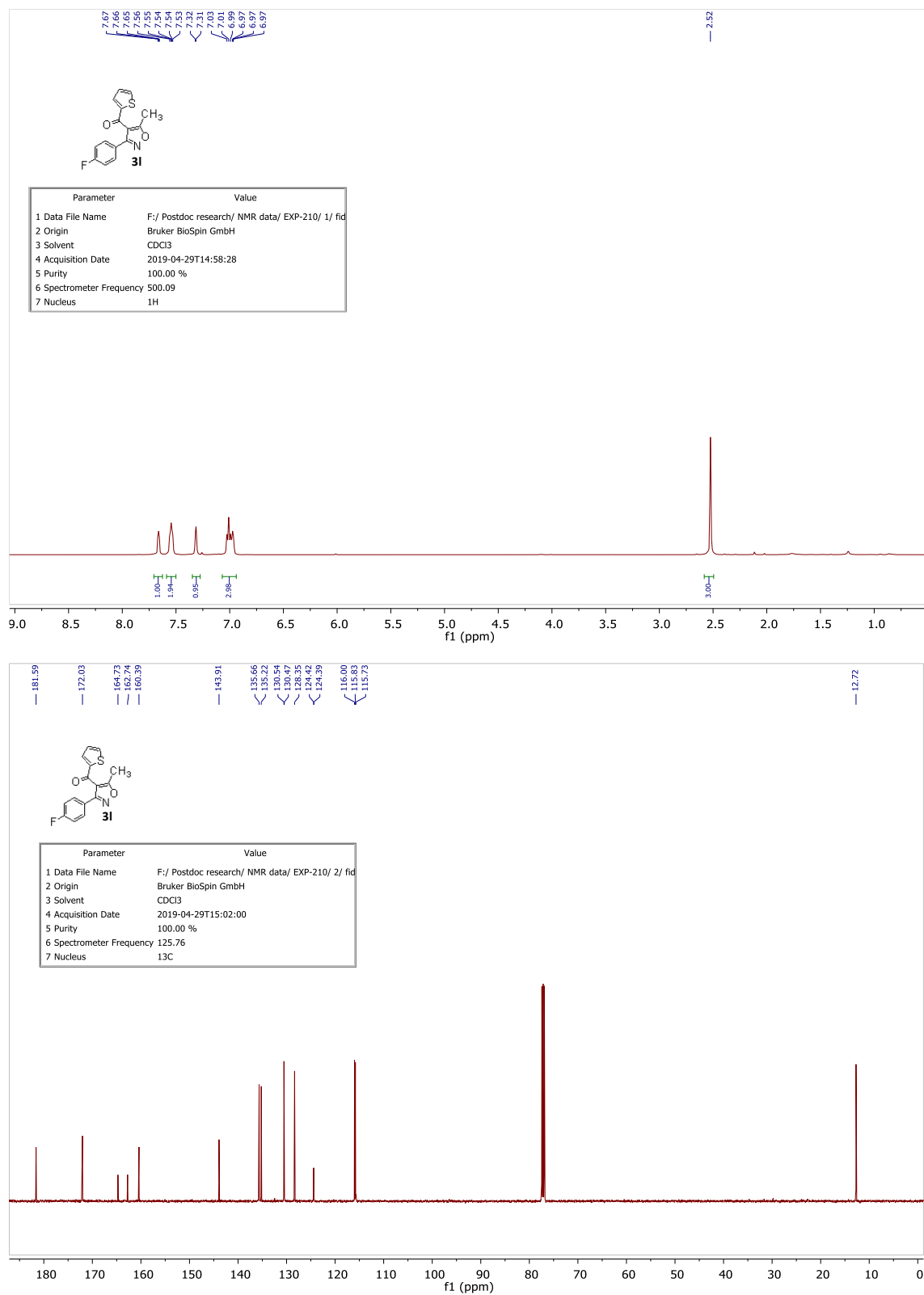




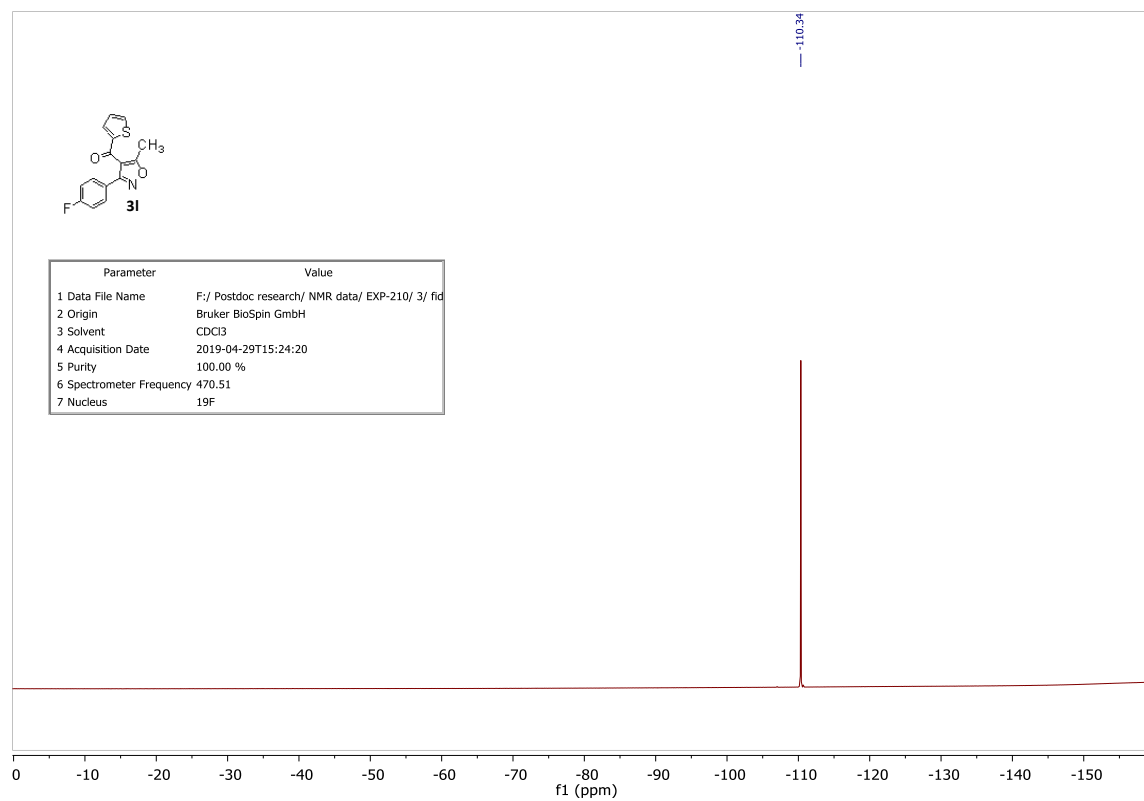
**Figure S20:**  $^{19}\text{F}$  NMR spectrum of compound **3j**.



**Figure S21:** <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound **3k**.

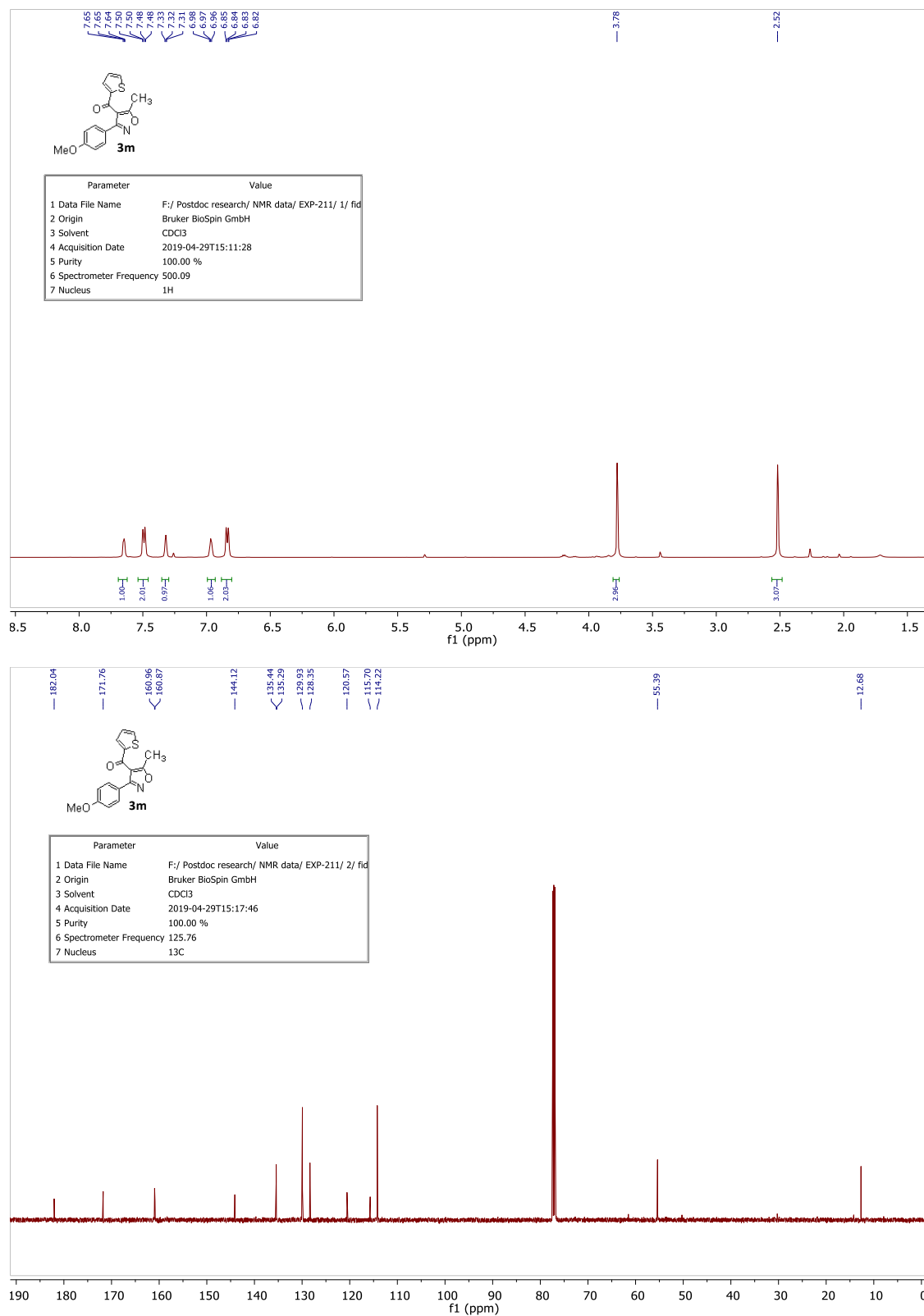


**Figure S22:** <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound 3I.

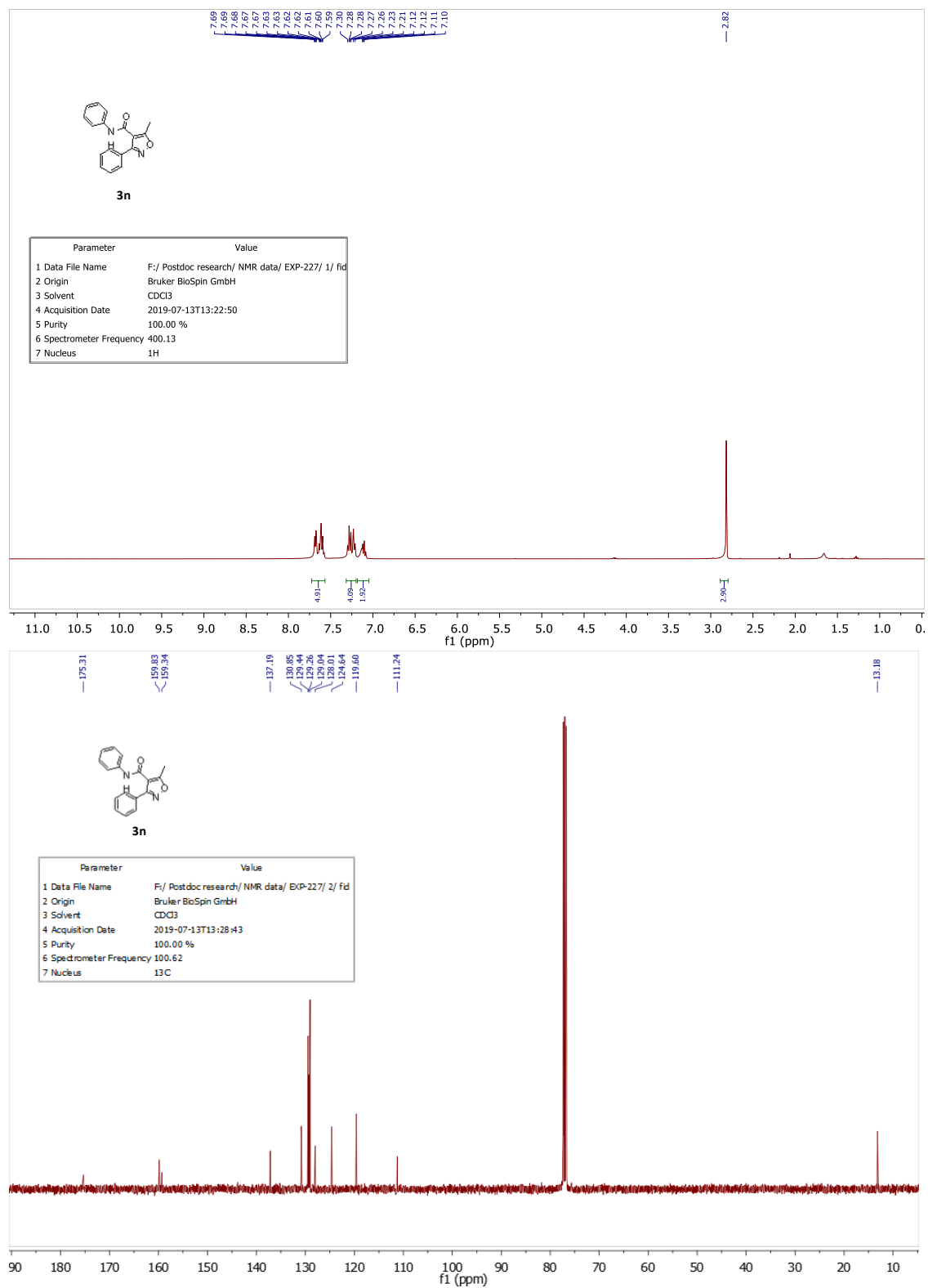


**Figure S23:** <sup>19</sup>F NMR spectrum of compound **3l**.

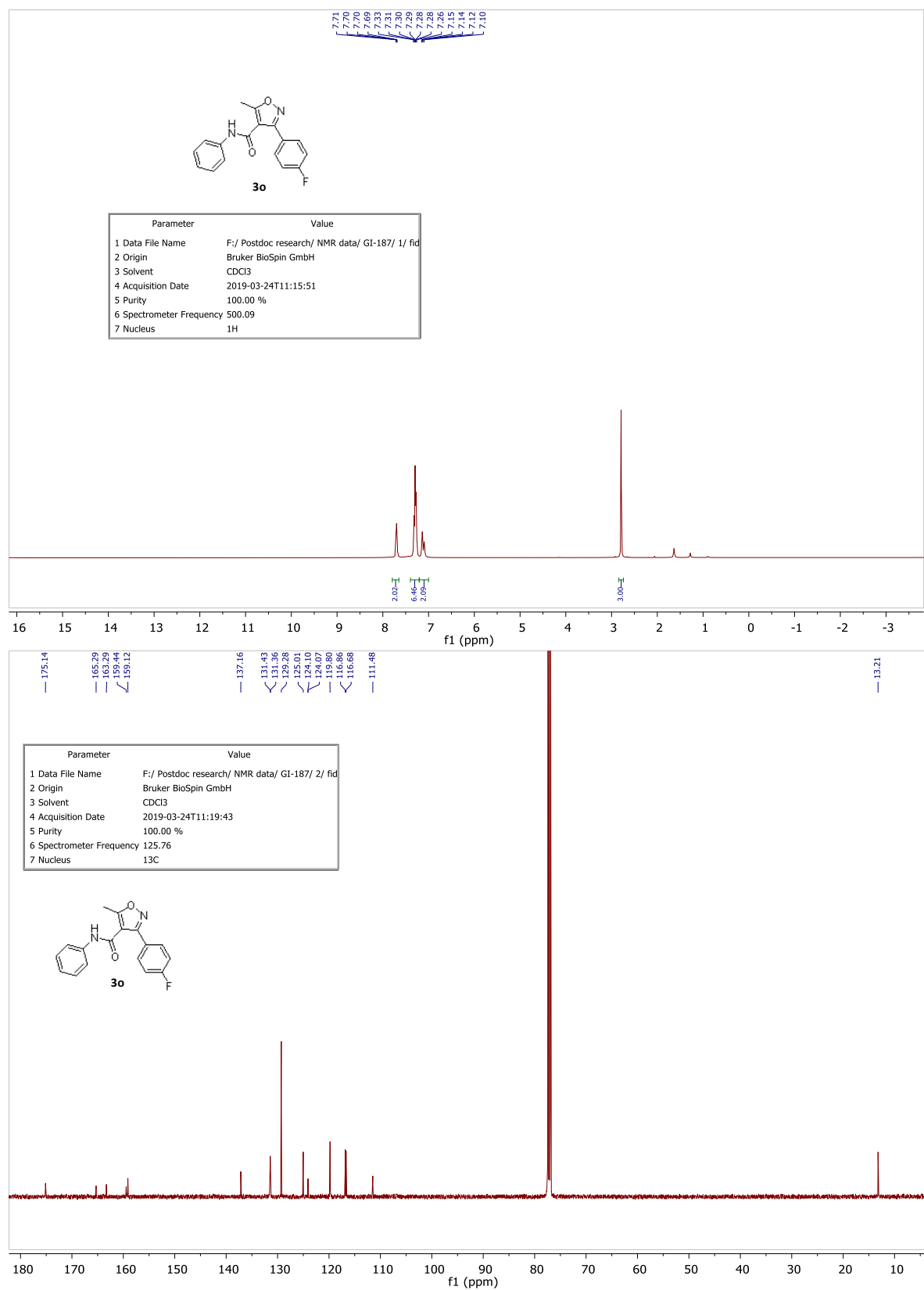




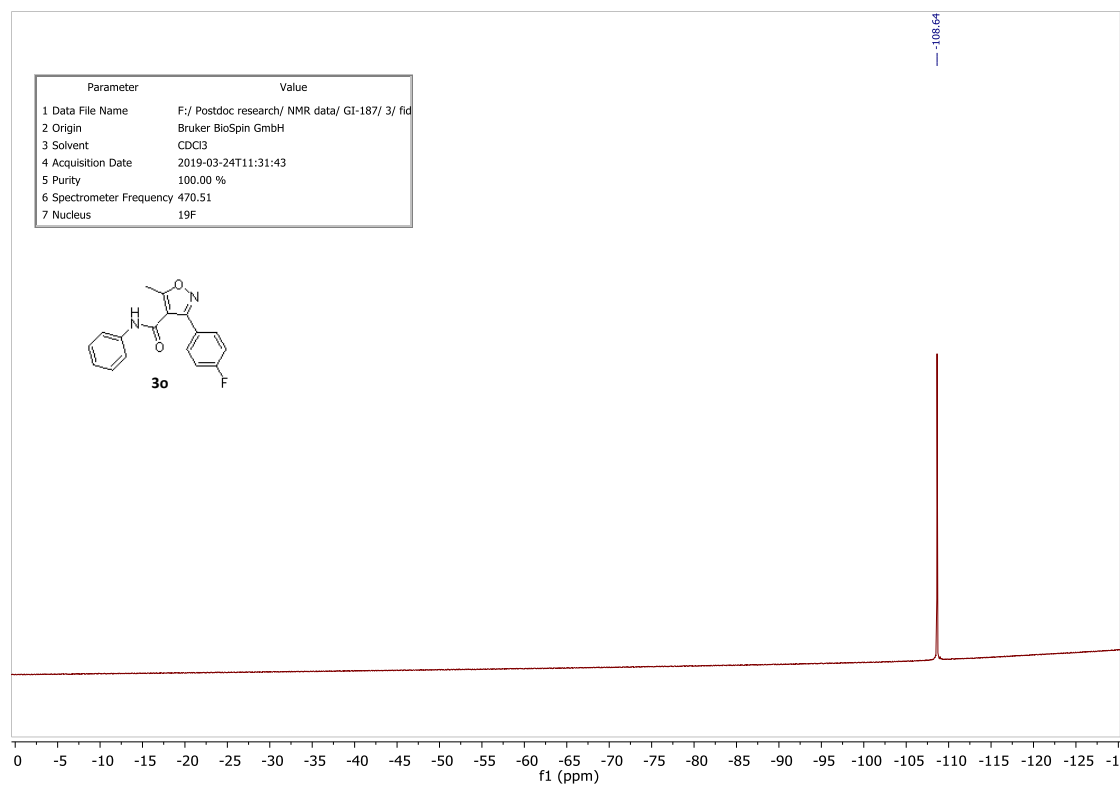
**Figure S24:** <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound **3m**.



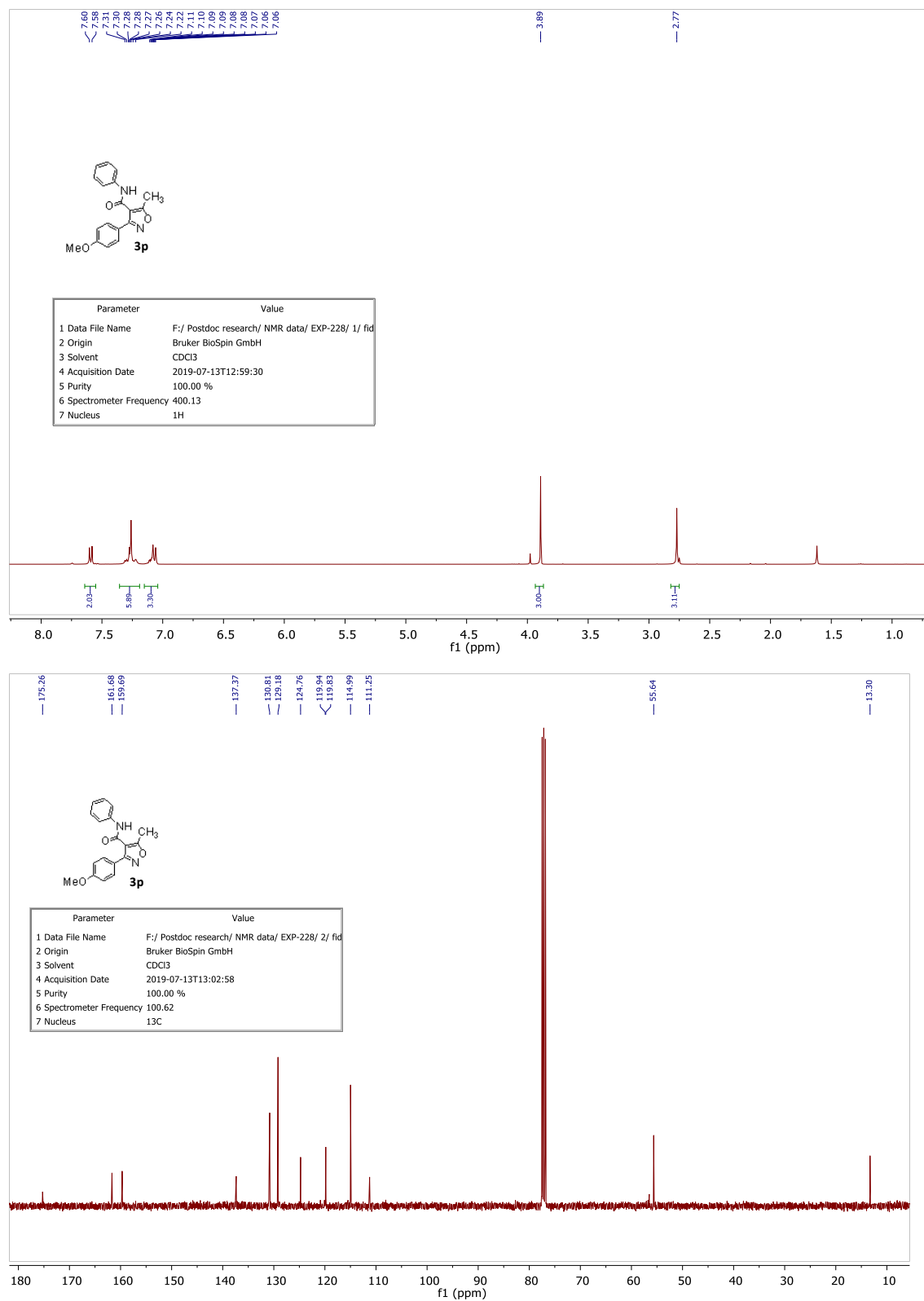
**Figure S25:** <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound **3n**.



**Figure S26:** <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound **3o**.

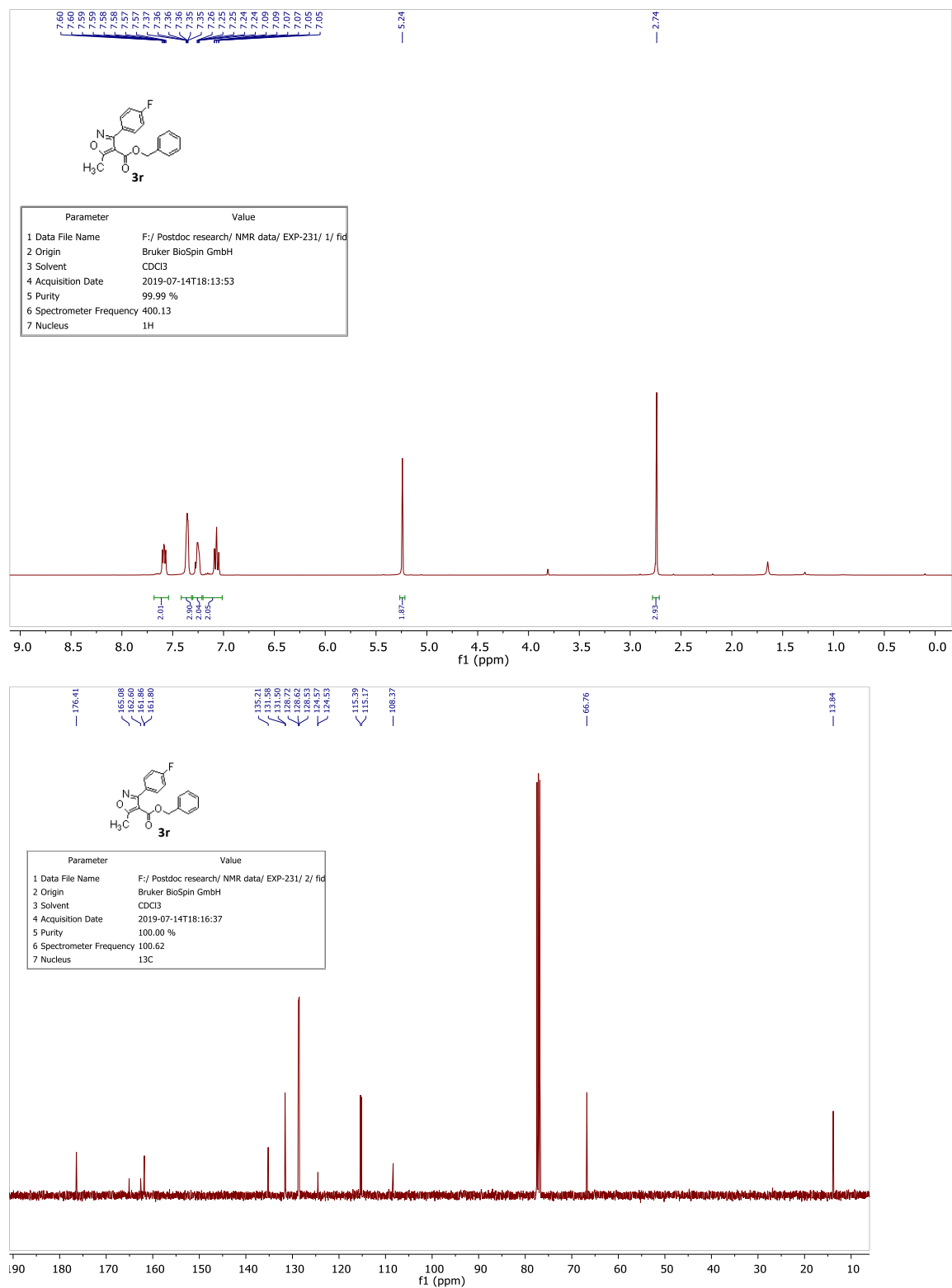


**Figure S27:** <sup>19</sup>F NMR spectrum of compound **3o**.

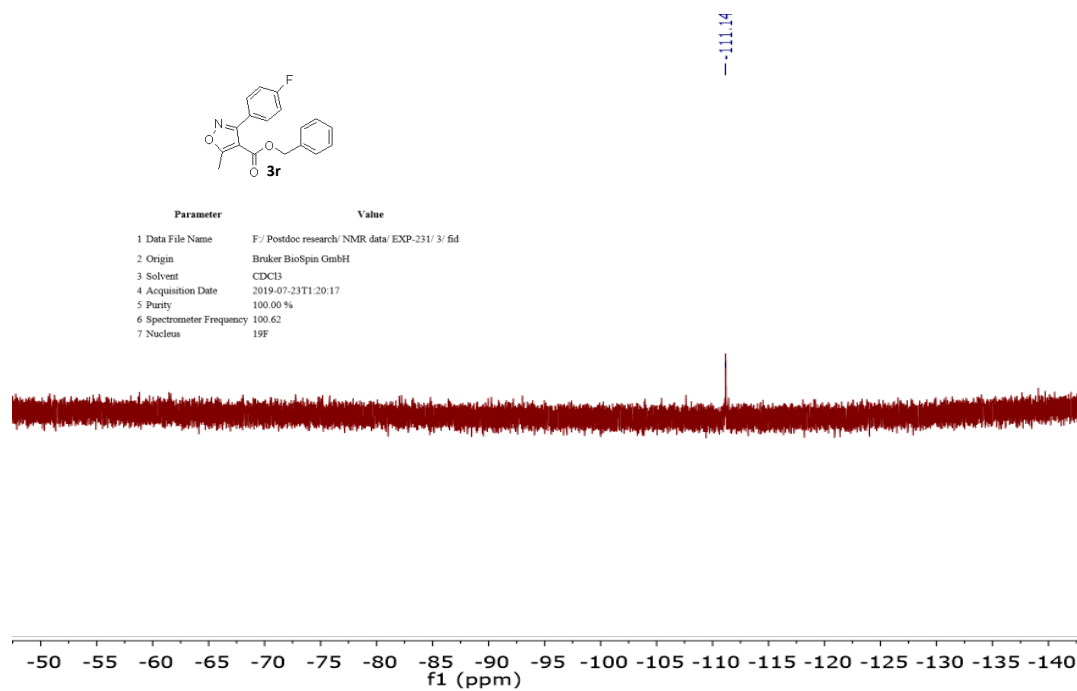


**Figure S28:** <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound 3p.



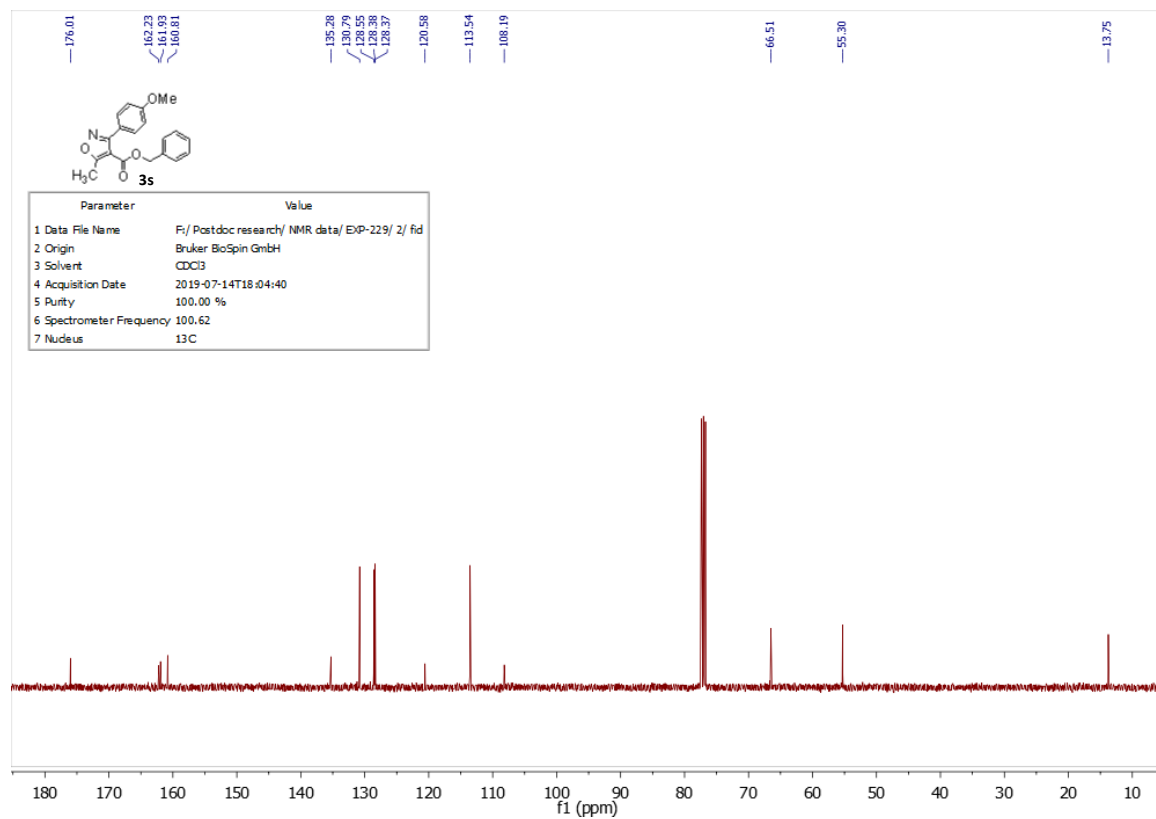
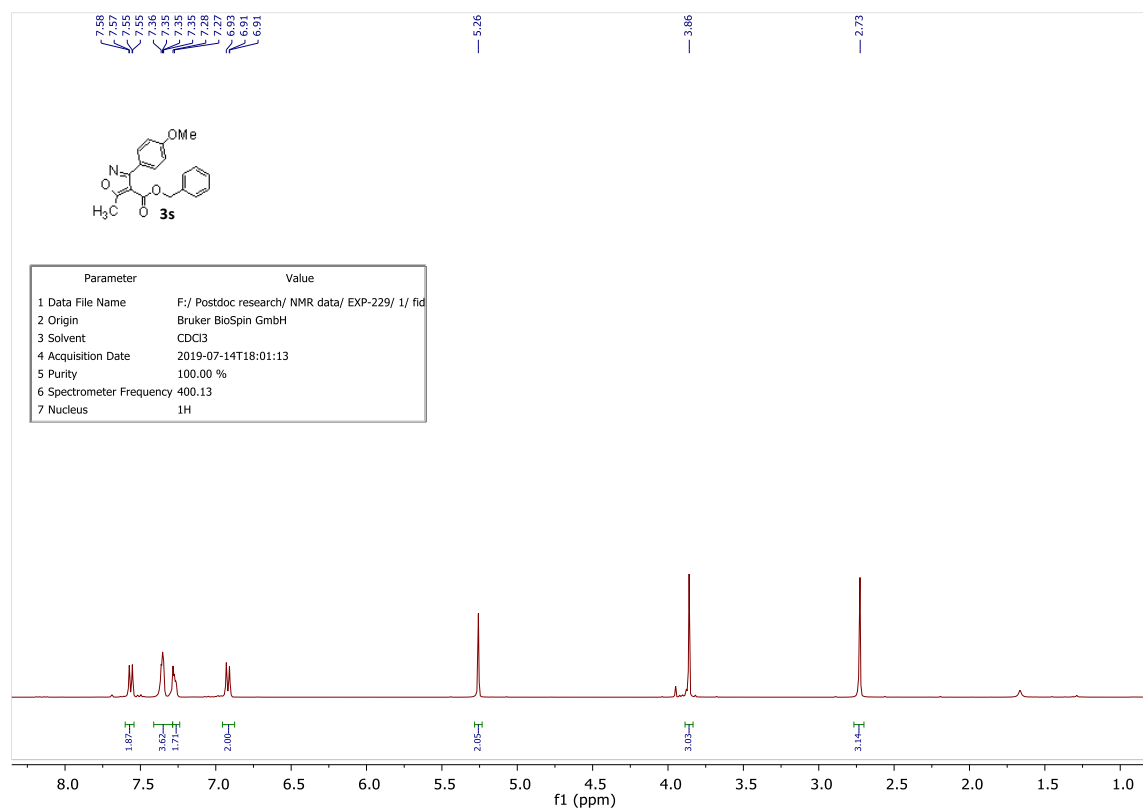


**Figure S30:** <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound 3r.

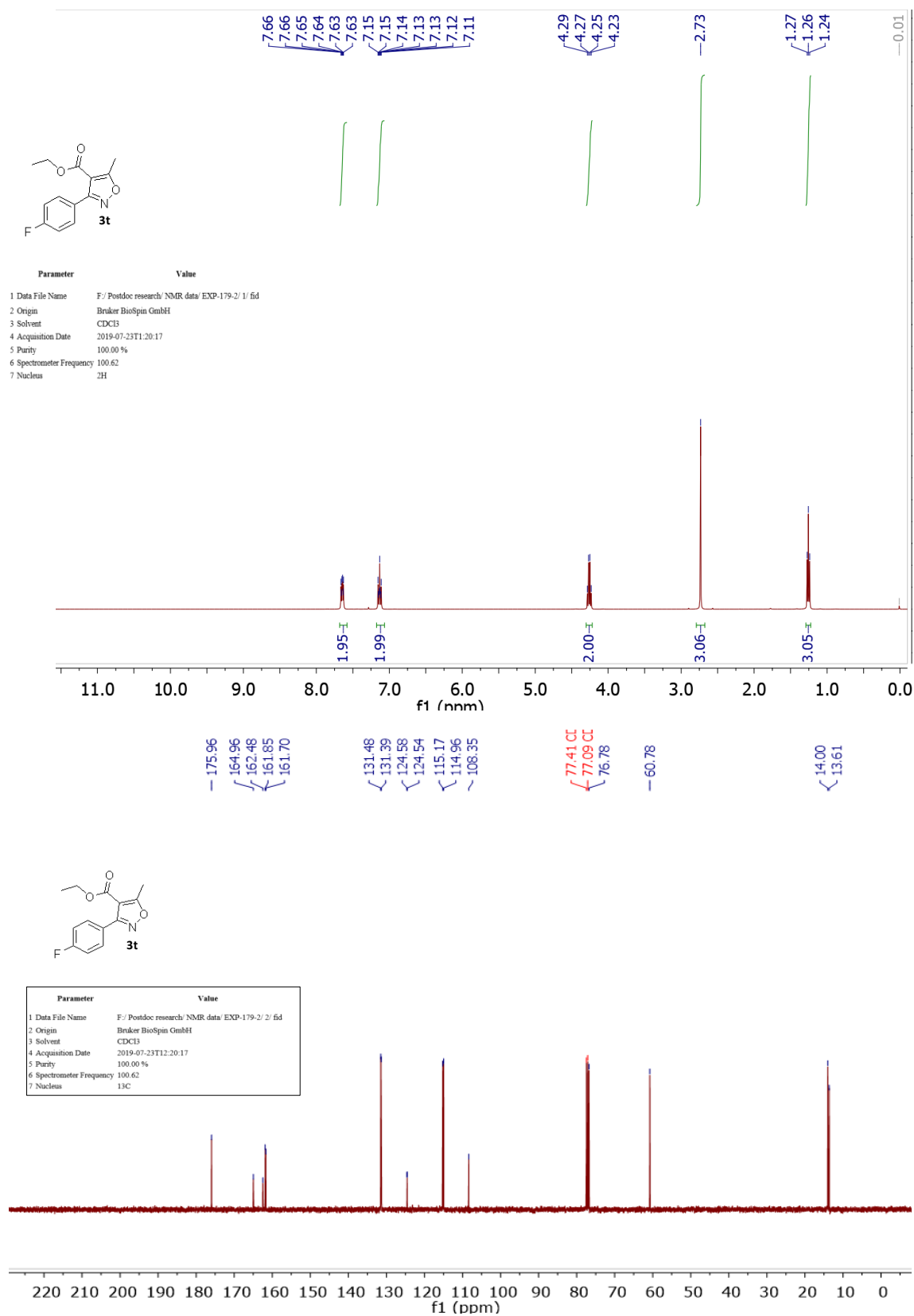


**Figure S31:** <sup>19</sup>F NMR spectrum of compound **3r**.

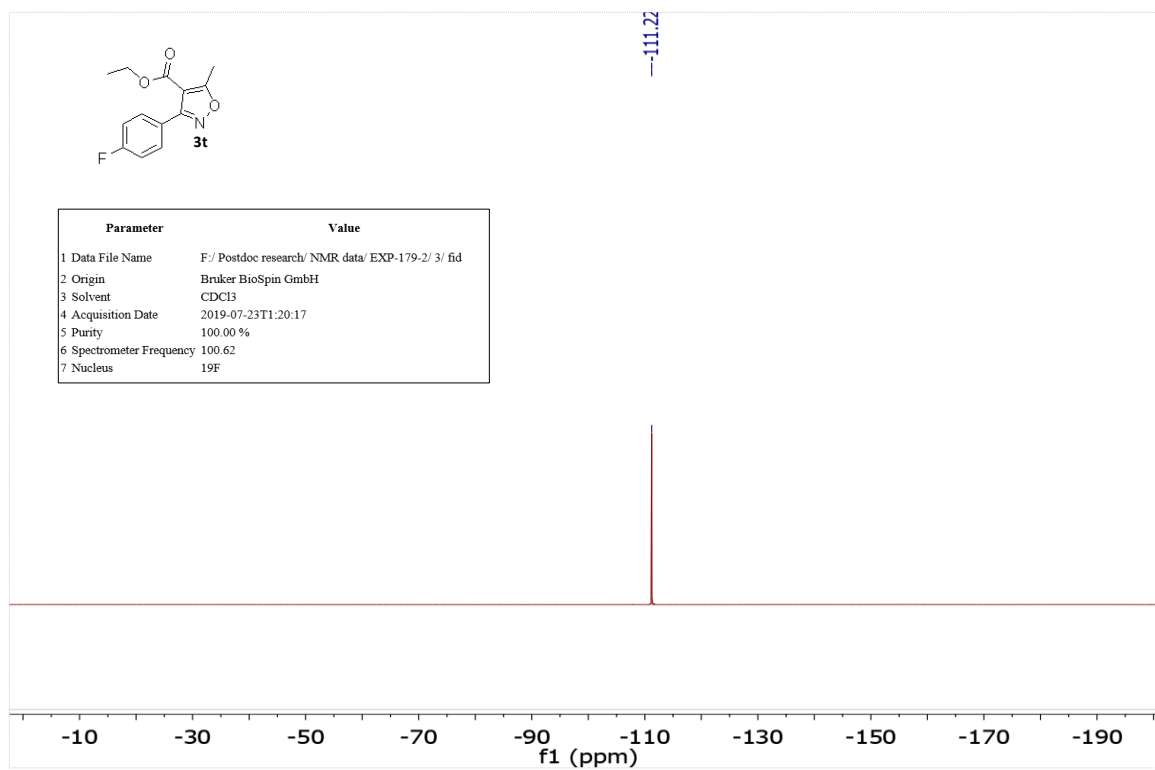




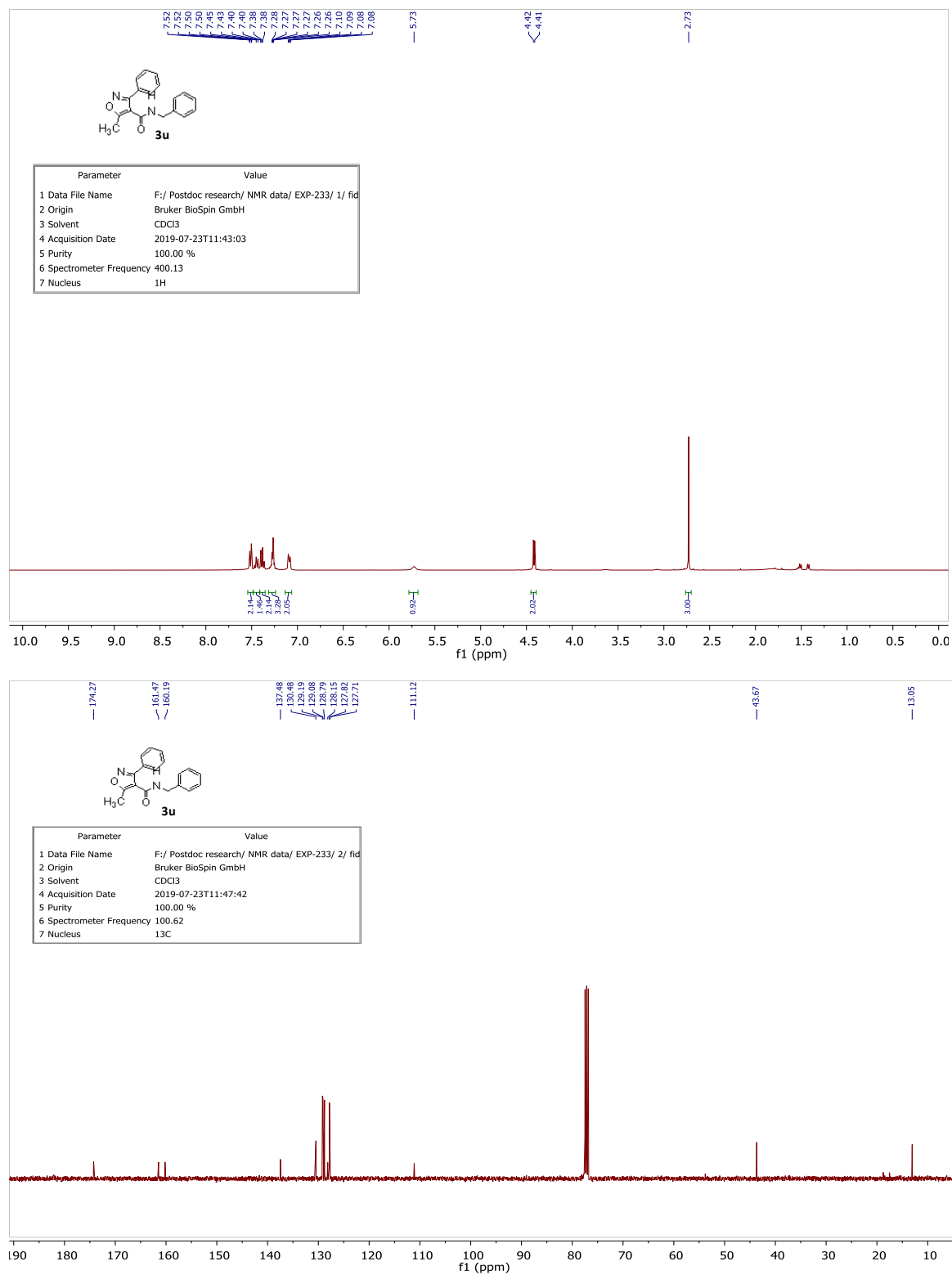
**Figure S32:** <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound **3s**.



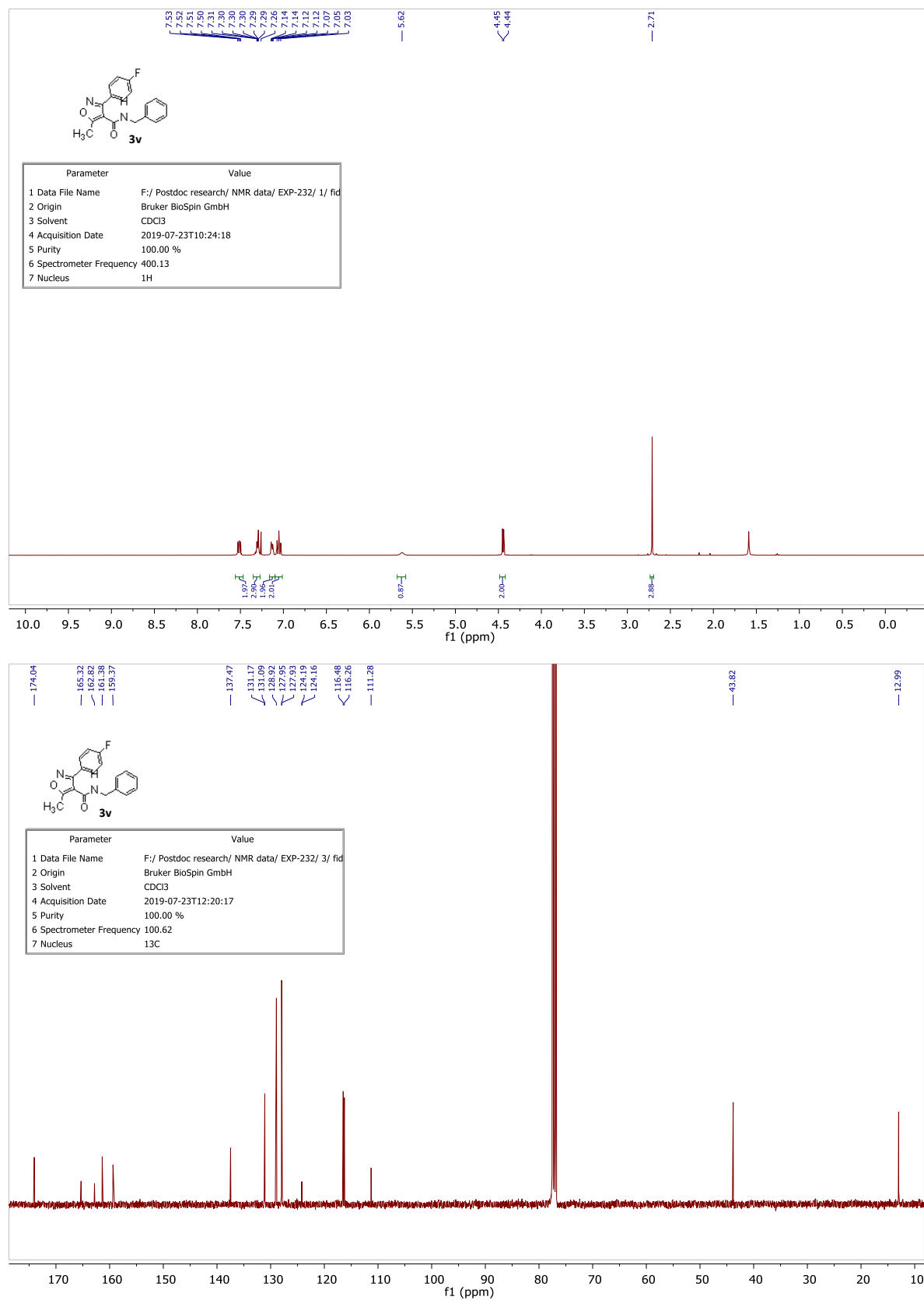
**Figure S33:** <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound **3t**.



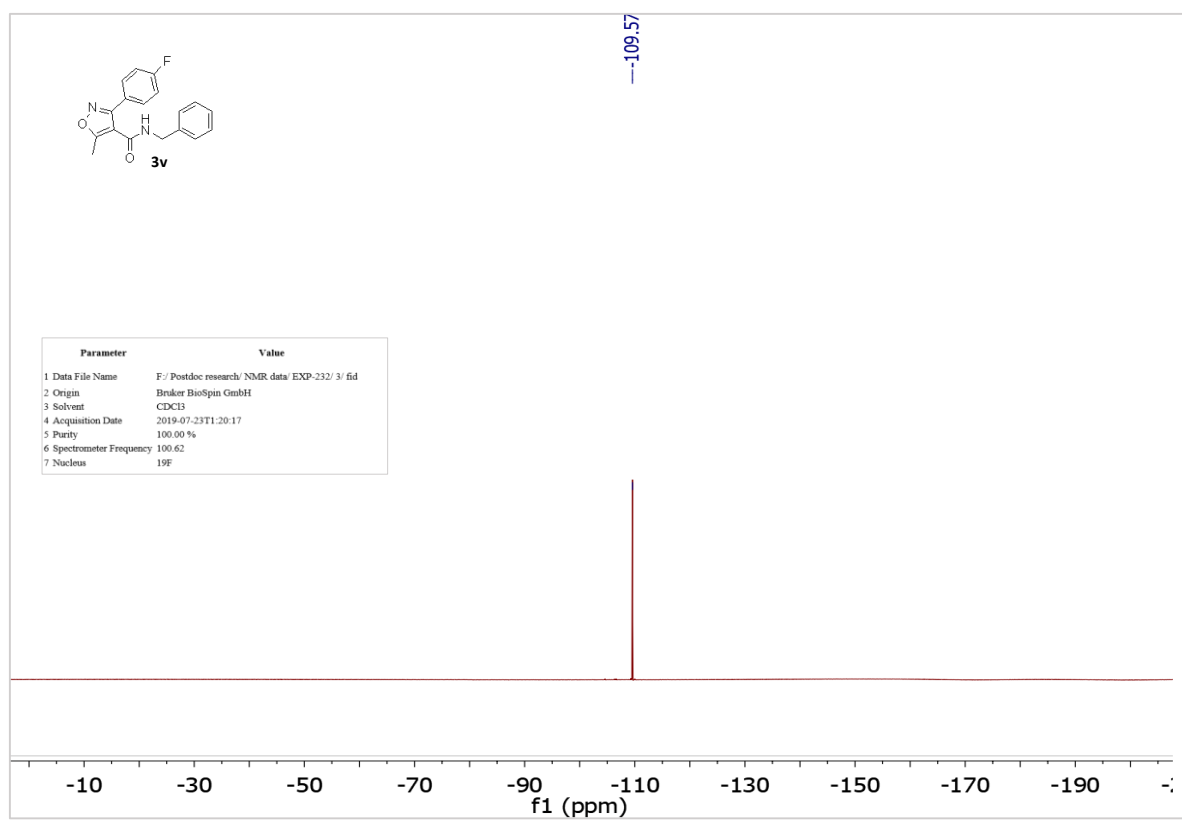
**Figure S34:** <sup>19</sup>F NMR spectrum of compound **3t**.



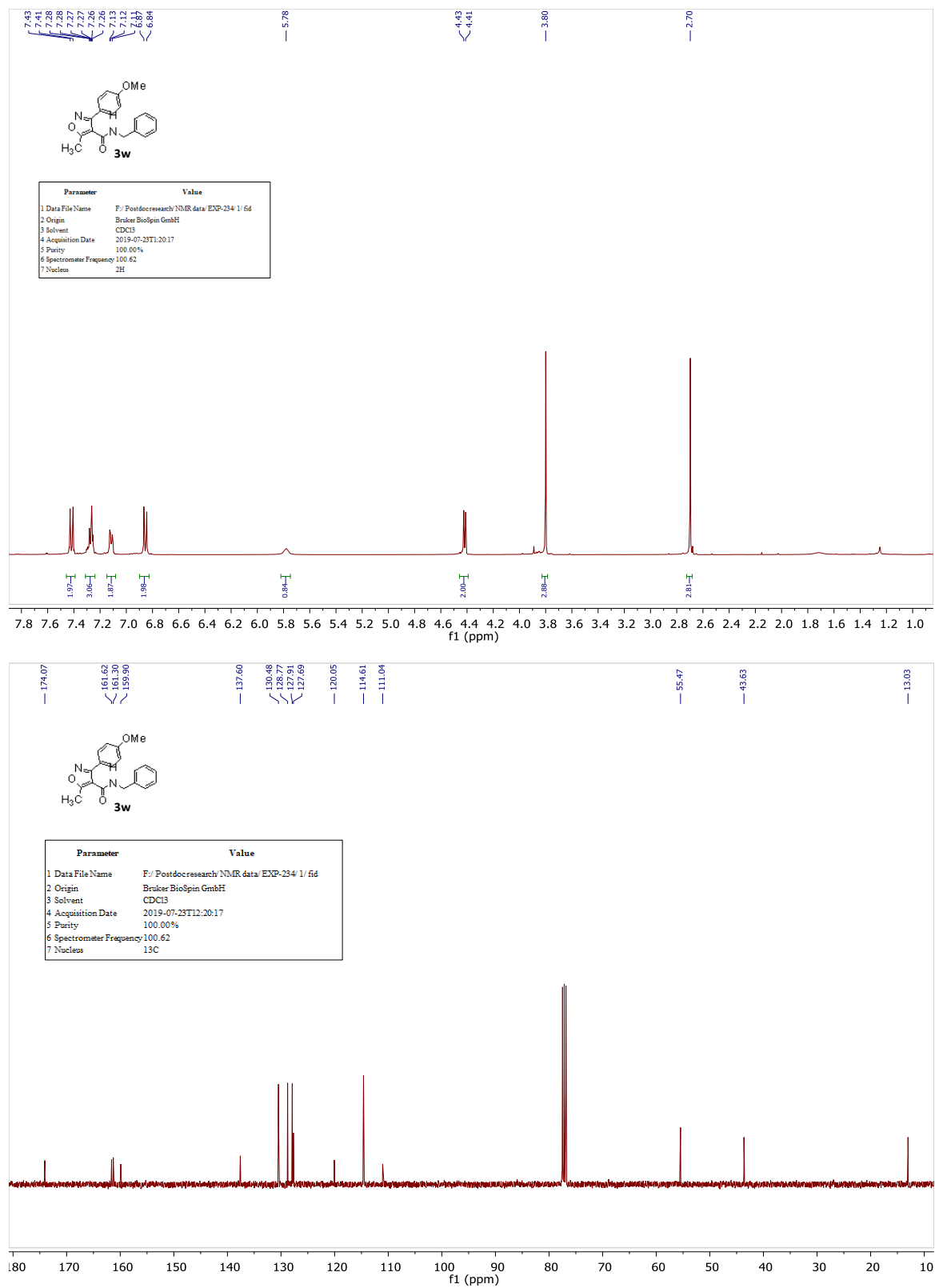
**Figure S35:** <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound 3u.



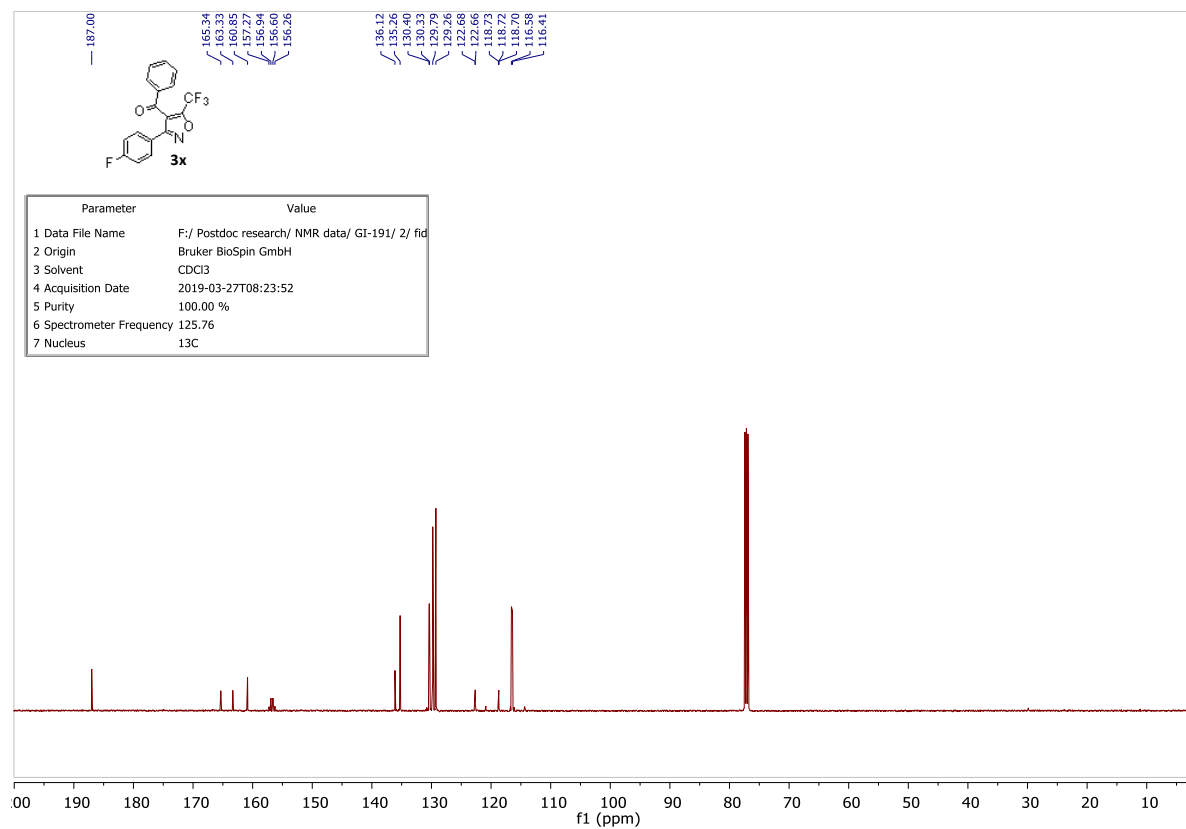
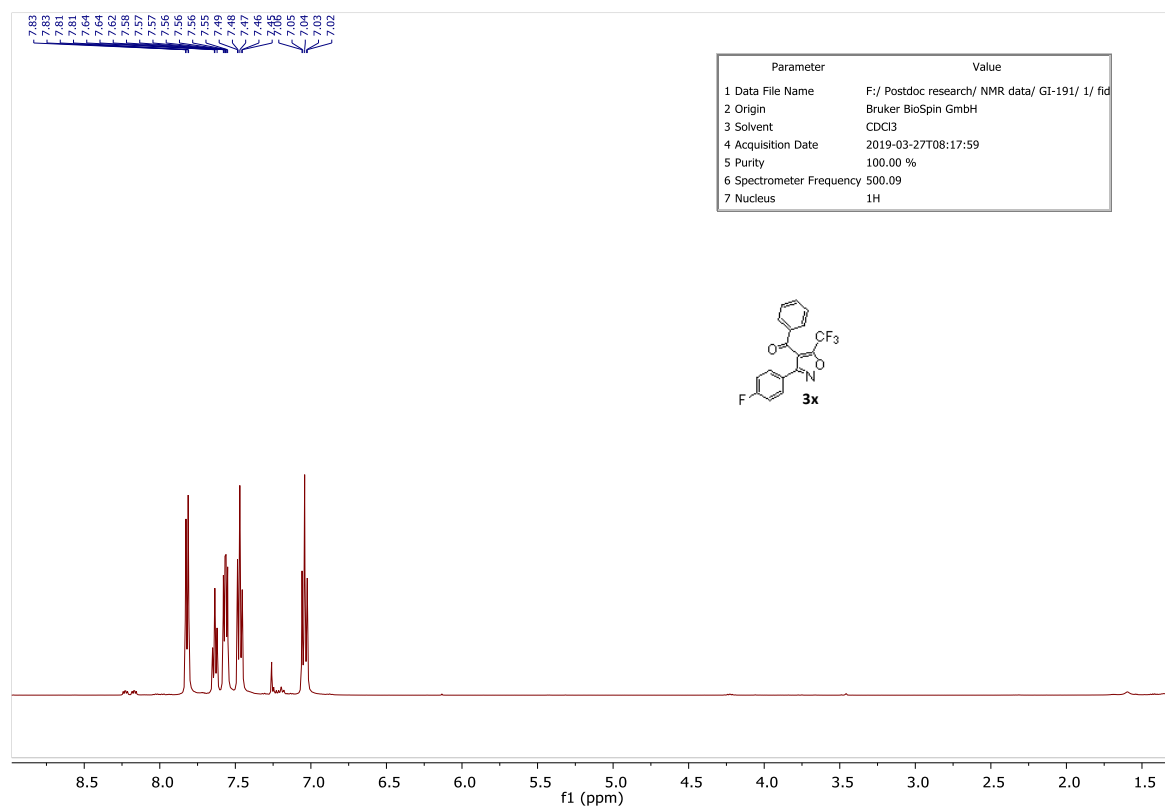
**Figure S36:** <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound 3v.



**Figure S37:** <sup>19</sup>F NMR spectrum of compound **3v**.

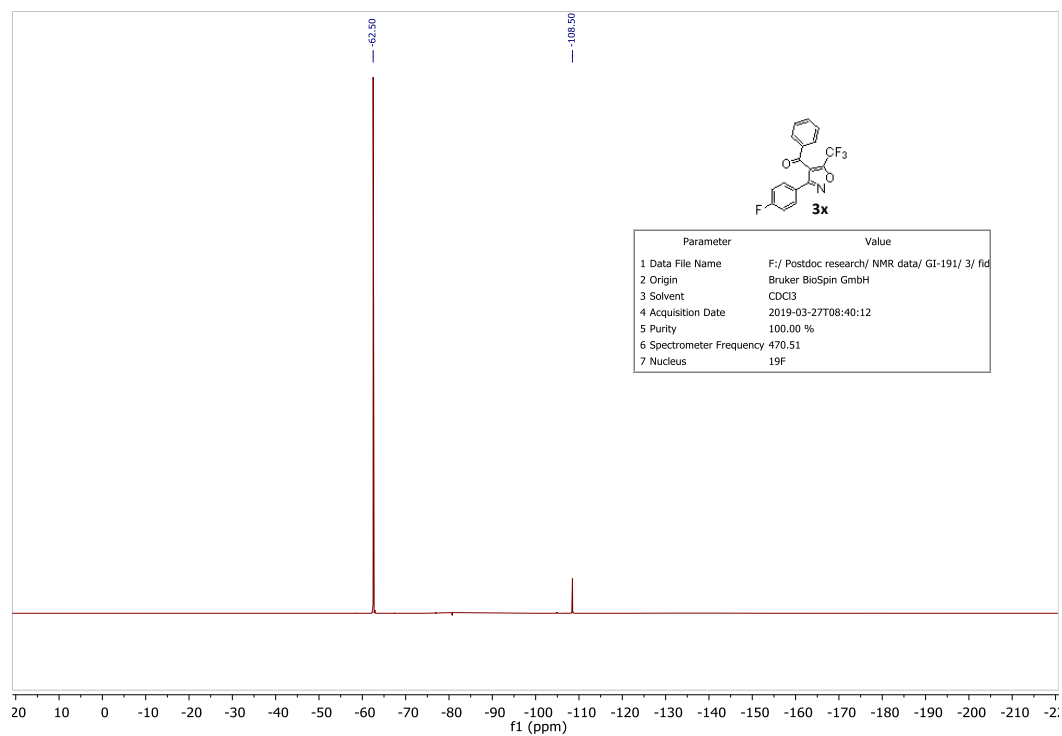


**Figure S38:** <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound 3w.

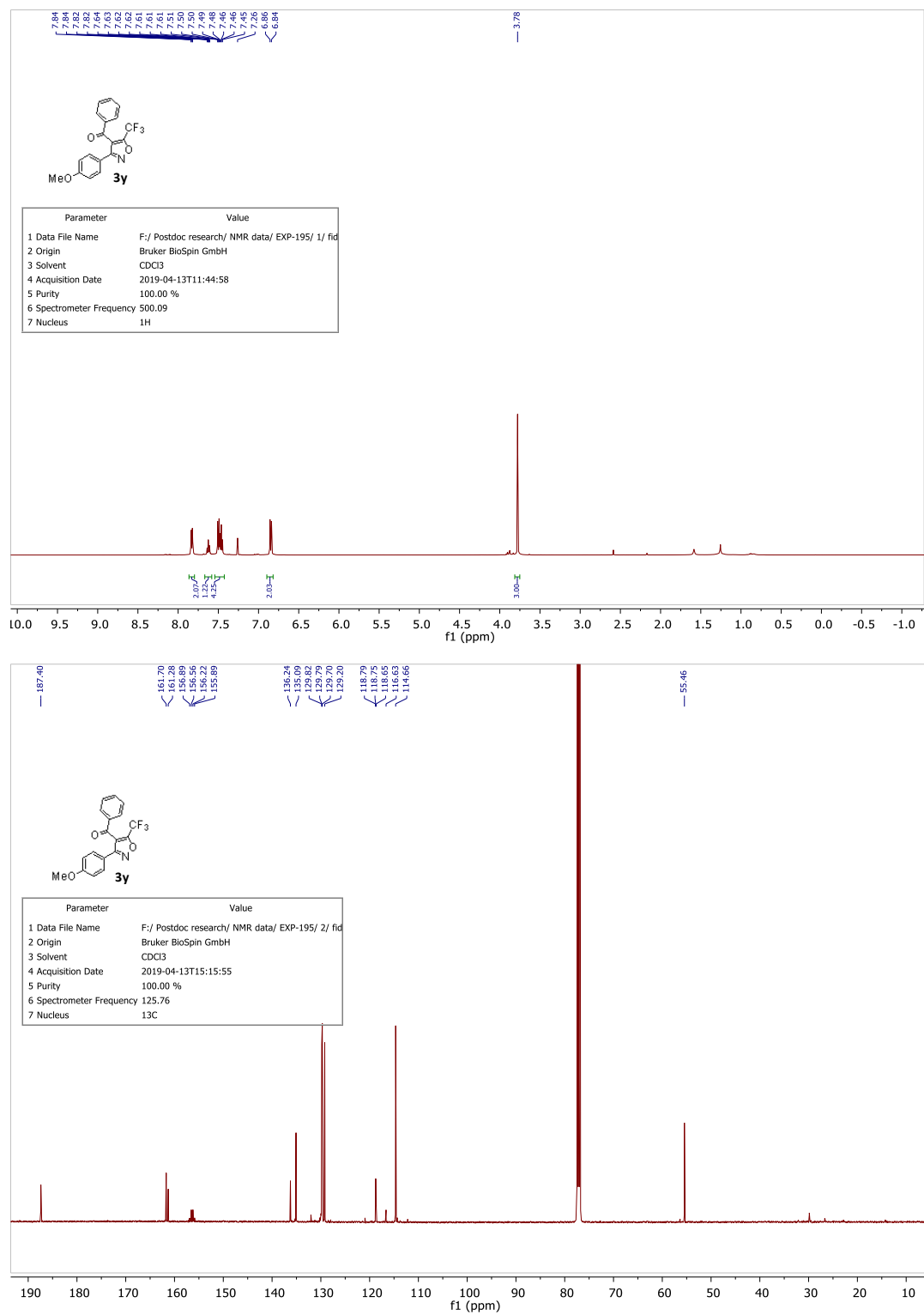


**Figure S39:**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of compound **3x**.

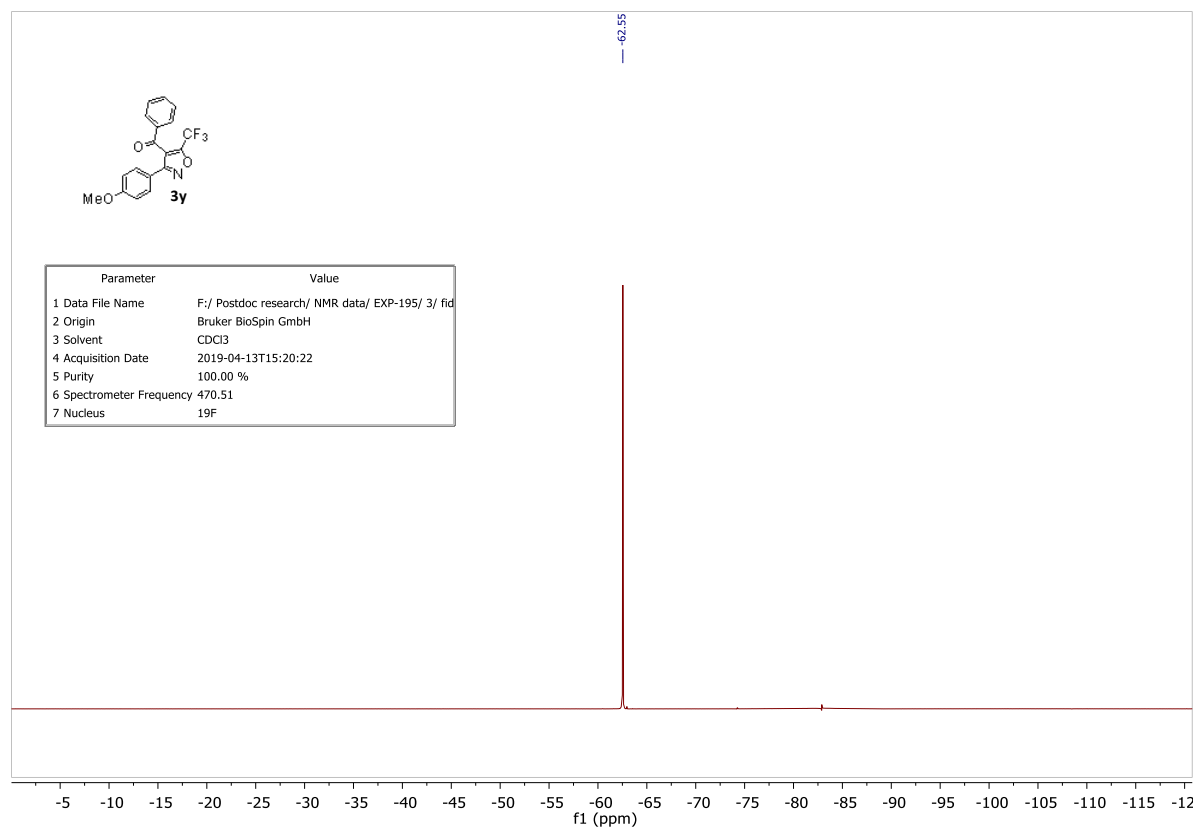




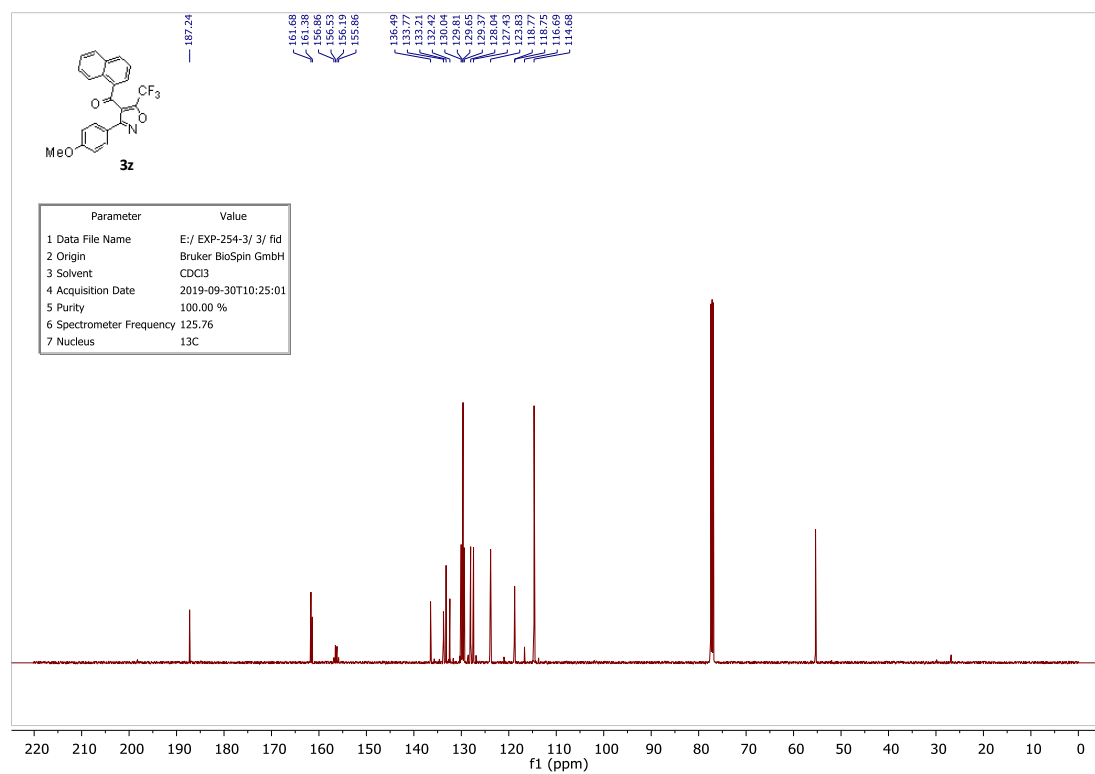
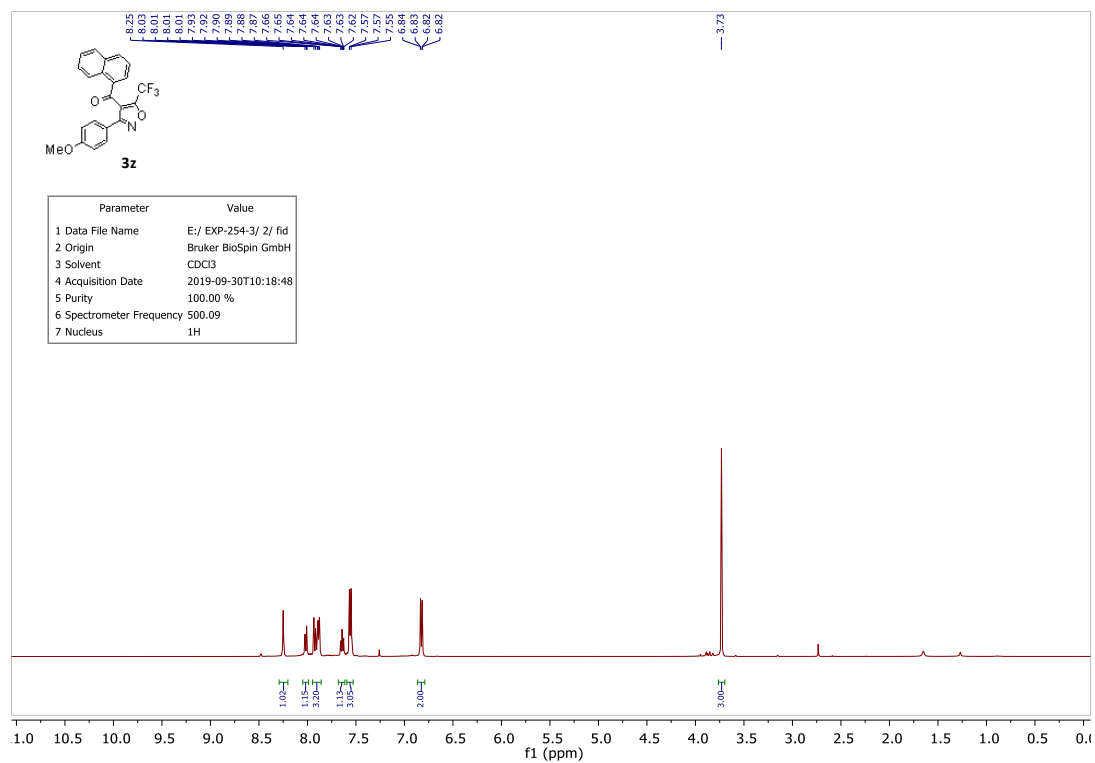
**Figure S40:**  $^{19}\text{F}$  NMR spectrum of compound **3x**.



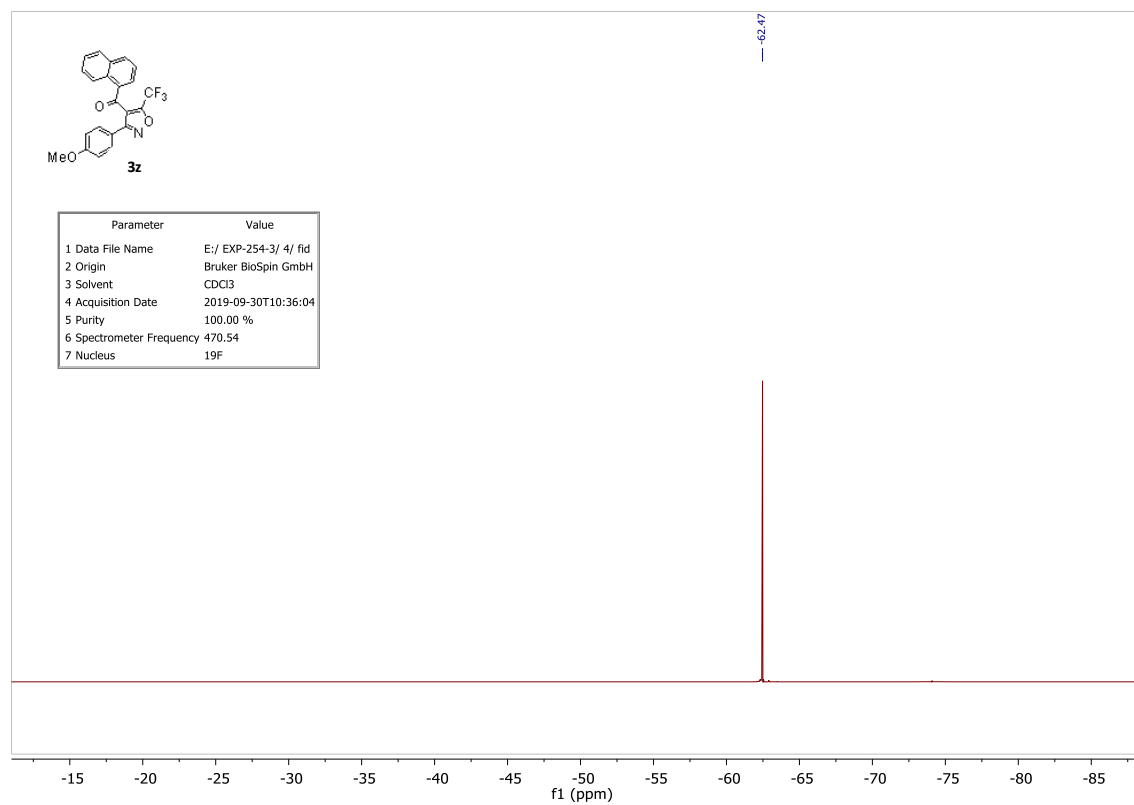
**Figure S41:** <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound **3y**.



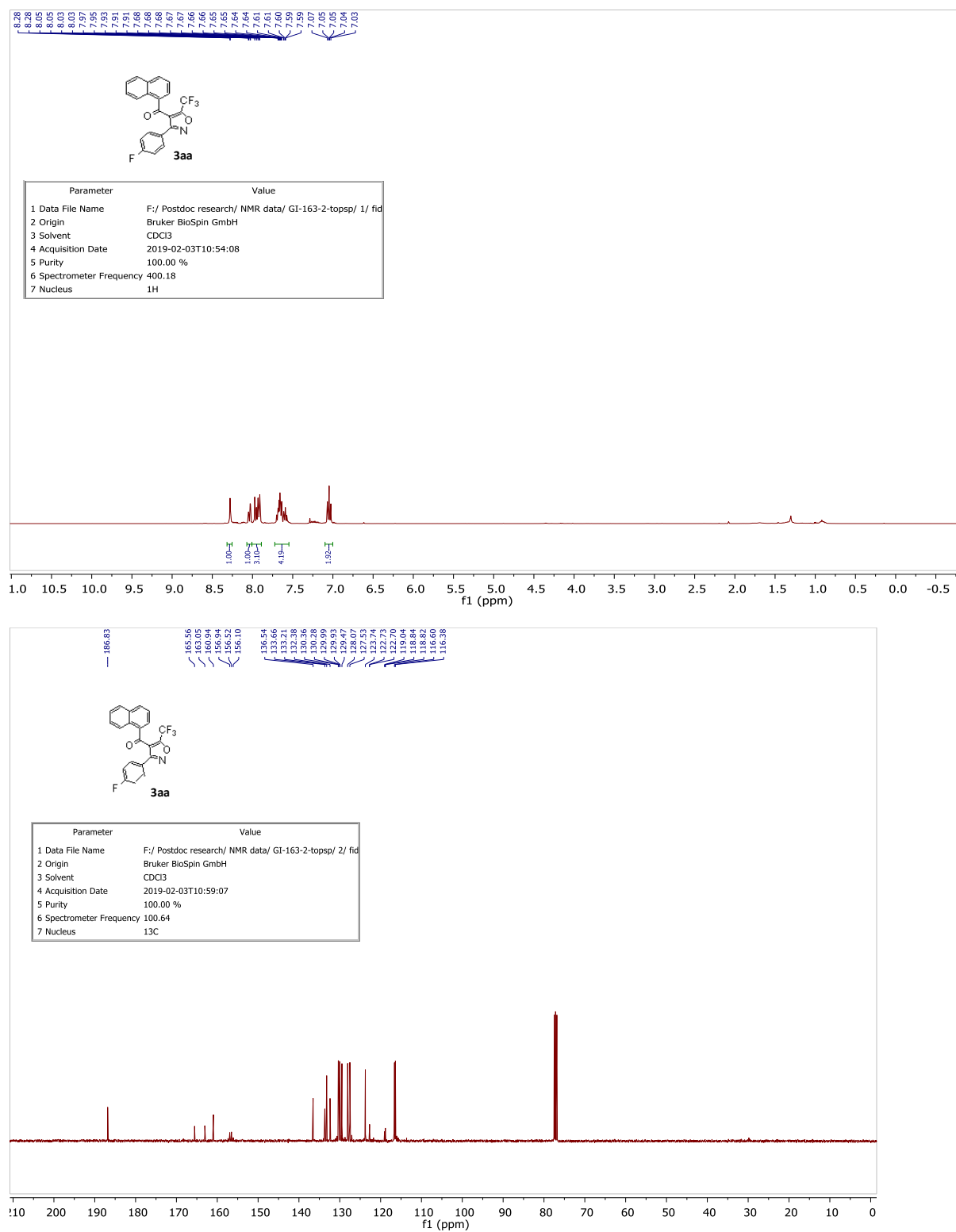
**Figure S42:** <sup>19</sup>F NMR spectrum of compound **3y**.



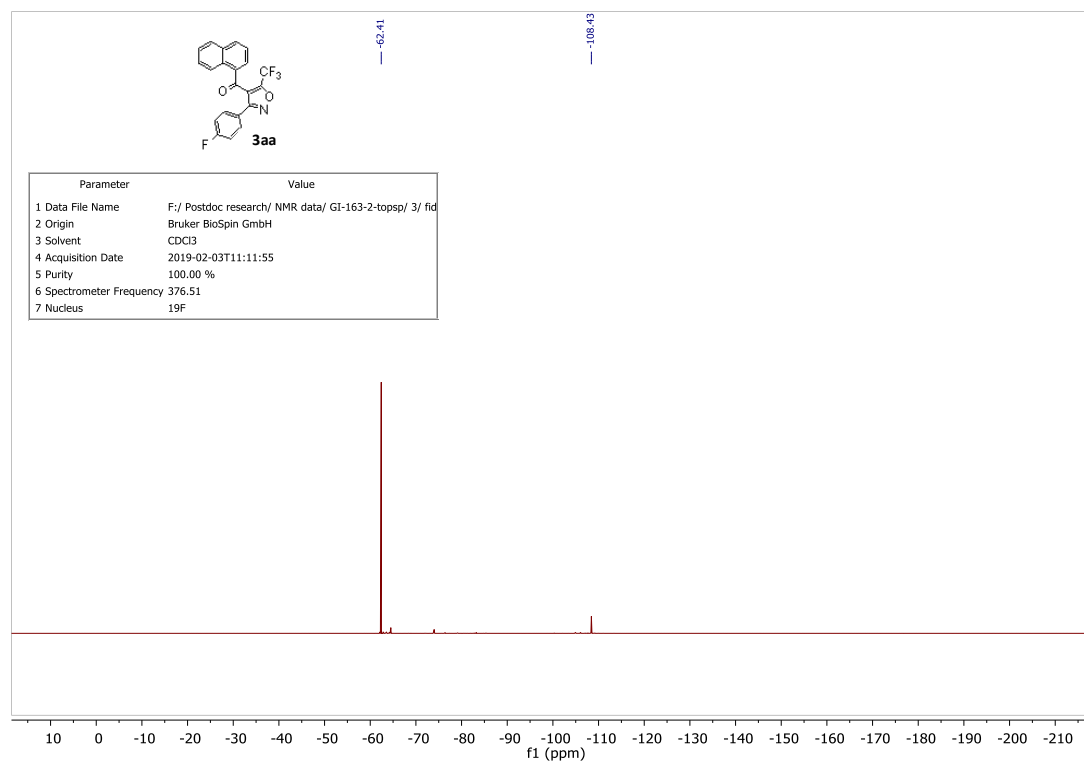
**Figure S43:** <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound **3z**.



**Figure S44:** <sup>19</sup>F NMR spectrum of compound **3z**.



**Figure S45:** <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound 3aa.



**Figure S46:**  $^{19}\text{F}$  NMR spectrum of compound **3aa**.