

## One-pot synthesis of 4-substituted 2-fluoroalkyloxazoles from NH-1,2,3-triazoles and fluoroalkylated acid anhydrides

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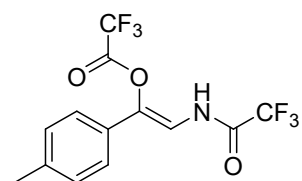
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### General

All solvents were dried by activated molecular sieves (3 and 4 Å) and stored under argon. All commercially available chemicals were used as received, unless stated otherwise. Triethylamine was dried with activated 3 Å molecular sieves before use. Starting NH-1,2,3-triazoles were prepared according to procedures published in literature.<sup>1-2</sup> Flash column chromatography was performed using silica gel 60 (0.040–0.063 mm). <sup>1</sup>H, <sup>13</sup>C and <sup>19</sup>F NMR spectra were measured at ambient temperature using 5 mm diameter NMR tubes. <sup>13</sup>C NMR spectra were proton decoupled. The chemical shift values ( $\delta$ ) are reported in ppm relative to internal Me<sub>4</sub>Si (0 ppm for <sup>1</sup>H, <sup>13</sup>C NMR) or residual solvents (CDCl<sub>3</sub>, 7.26 ppm) and internal CFCl<sub>3</sub> (0 ppm for <sup>19</sup>F NMR). Coupling constants (*J*) are reported in Hertz. For <sup>19</sup>F NMR yields, PhCF<sub>3</sub> was used as an internal standard which was added directly into the crude reaction mixture. High resolution MS spectra (HRMS) were recorded on a Waters Micromass AutoSpec Ultima or Agilent 7890A GC coupled with Waters GCT Premier orthogonal acceleration time-of-flight (TOF) detector using electron impact (EI) ionization or on an LTQ Orbitrap XL using electrospray ionization (ESI).

### Synthesis of (Z)-1-(*p*-tolyl)-2-(2,2,2-trifluoroacetamido)vinyl 2,2,2-trifluoroacetate (**2a**)

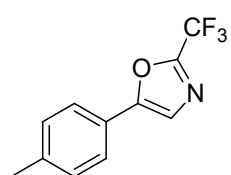


To the suspension of 4-(*p*-tolyl)-NH-1,2,3-triazole **1a** (0.1 mmol, 15.9 mg) in dry DCE (0.5 ml) in a 10 ml vial TFAA (0.25 mmol, 2.5 equiv., 35  $\mu$ l) was added. The mixture was heated at 50 °C for 4 h. Solvent was evaporated under reduced pressure to give (Z)-1-(*p*-tolyl)-2-(2,2,2-trifluoroacetamido)vinyl 2,2,2-

trifluoroacetate **2a** (35 mg, 99%) as a white solid. NMR matches previously reported data.<sup>7</sup> Double bond configuration was confirmed by <sup>1</sup>H-<sup>1</sup>H ROESY experiment.

### General procedure 1 for the synthesis of 2-fluoroalkyl oxazoles 3

To the suspension of 4,5-disubstituted NH-1,2,3-triazole **1** (0.2 mmol) in dry DCE (1 ml) in a 10 ml vial, fluoroalkylated acid anhydride (0.5 mmol, 2.5 equiv.) was added. The vial was sealed, and the mixture was stirred at the temperature mentioned below for each compound (rt to 80 °C) until complete conversion to the intermediate acyloxyenamide **2** (monitored by the disappearance of N-acyltriazole peak at ca. -70 ppm in <sup>19</sup>F NMR). Then Et<sub>3</sub>N (0.4 mmol, 2 equiv., 56 μl) was added and the resulting mixture was stirred at room temperature for 15 min. After addition of silica gel the mixture was evaporated under reduced pressure (250-500 Torr) and the crude product was purified by column chromatography using pentane/DCM as eluent to give the target oxazole **3**.

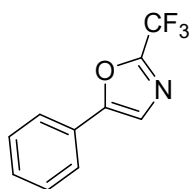


5-(*p*-Tolyl)-2-(trifluoromethyl)oxazole (**3a**)

Prepared according to the general procedure 1 from 31.8 mg (0.2 mmol) of NH-triazole, TFAA and Et<sub>3</sub>N. Reaction conditions for the first step: 8 h at 50 °C. Eluent: pentane/DCM 2:1 to 1:1. Yield: 42 mg (93%); a colorless oil; NMR matched the previously reported data.<sup>3</sup>

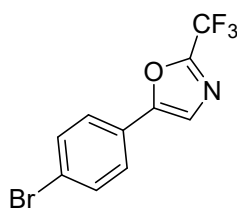
5-Phenyl-2-

Prepared according to the general procedure 1 from 29 mg (0.2 mmol) of NH-triazole, TFAA and Et<sub>3</sub>N. Reaction conditions for the first step: 12 h at 70°C. Eluent: pentane/DCM 2:1 to 1:1. Yield: 38 mg (90%); a colorless oil; NMR matched the previously reported data.<sup>3</sup>



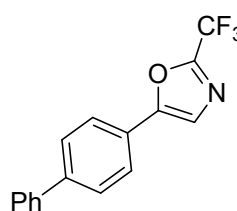
(trifluoromethyl)oxazole (**3b**)

to the general procedure 1 from 29 mg (0.2 mmol) of NH-triazole, TFAA and Et<sub>3</sub>N. Reaction conditions for the first step: 12 h at 70°C. Eluent: pentane/DCM 2:1 to 1:1. Yield: 38 mg (90%); a colorless oil; NMR matched the previously reported data.<sup>3</sup>



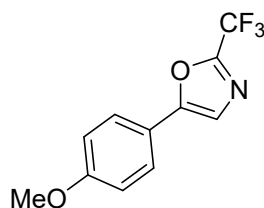
5-(4-Bromophenyl)-2-(trifluoromethyl)oxazole (**3c**)

Prepared according to the general procedure 1 from 44.8 mg (0.2 mmol) of NH-triazole, TFAA and Et<sub>3</sub>N. Reaction conditions for the first step: 24 h at 80°C. Eluent: pentane/DCM 2:1 to 1:1. Yield: 50 mg (86%); a colorless oil; NMR matched the previously reported data.<sup>4</sup>



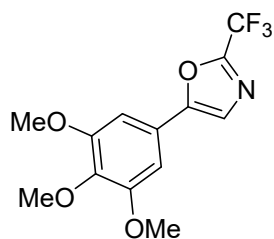
5-([1,1'-Biphenyl]-4-yl)-2-(trifluoromethyl)oxazole (**3d**)

Prepared according to the general procedure 1 from 33.1 mg (0.15 mmol) of NH-triazole, TFAA and Et<sub>3</sub>N. Reaction conditions for the first step: 14 h at 80°C. Eluent: pentane/DCM 2:1 to 1:1. Yield: 40.3 mg (70%); a white solid, mp 88-90°C (CHCl<sub>3</sub>); NMR matched the previously reported data.<sup>5</sup>



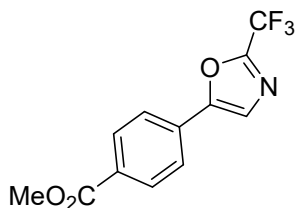
5-(4-Methoxyphenyl)-2-(trifluoromethyl)oxazole (**3e**)

Prepared according to the general procedure 1 from 17.5 mg (0.1 mmol) of NH-triazole, TFAA and Et<sub>3</sub>N. Reaction conditions for the first step: 4 h at 50°C. Eluent: pentane/DCM 1:1 to 1:2. Yield: 22.5 mg (93%); a pale-yellow oil; NMR matched the previously reported data.<sup>3</sup>



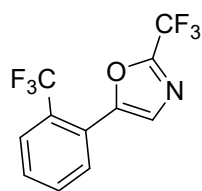
2-(Trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)oxazole (**3f**)

Prepared according to the general procedure 1 from 47 mg (0.2 mmol) of NH-triazole, TFAA and Et<sub>3</sub>N. Reaction conditions for the first step: 6 h at 50°C. Eluent: pentane/EtOAc 9:1 to 4:1. Yield: 51 mg (84%); a yellow solid, mp 74-76°C (CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.37 (s, 1H, H4), 6.87 (s, 2H), 3.92 (s, 6H, 2×OMe), 3.88 (s, 3H, OMe); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 153.9, 153.8, 149.5 (q, *J* = 44.4 Hz, C2), 139.6, 121.9, 121.6, 116.5 (q, *J* = 270.3 Hz, CF<sub>3</sub>), 102.3, 60.9, 56.3; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -66.1 (s, 3F); HRMS (EI<sup>+</sup>) *m/z* calcd for C<sub>13</sub>H<sub>12</sub>O<sub>4</sub>NF<sub>3</sub> [M]<sup>+</sup>: 303.0713, found 303.0719.



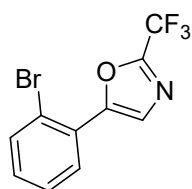
Methyl 4-(2-(trifluoromethyl)oxazol-5-yl)benzoate (**3g**)

Prepared according to the general procedure 1 from 40.6 mg (0.2 mmol) of NH-triazole, TFAA and Et<sub>3</sub>N. Reaction conditions for the first step: 48 h at 80°C. Eluent: pentane/EtOAc 9:1. Yield: 36.5 mg (67%); a pale-yellow solid; NMR matched the previously reported data.<sup>4</sup>



2-(Trifluoromethyl)-5-(2-(trifluoromethyl)phenyl)oxazole (**3h**)

Prepared according to the general procedure 1 from 42.4 mg (0.2 mmol) of NH-triazole, TFAA and Et<sub>3</sub>N. Reaction conditions for the first step: 19 h at 70°C. Eluent: pentane/DCM 3:1 to 1:1. Yield: 40 mg (71%); a colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.85-7.82 (m, 1H), 7.77-7.74 (m, 1H), 7.70-7.66 (m, 1H), 7.62-7.57 (m, 1H), 7.48 (s, 1H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 150.7 (q, *J* = 44.4 Hz, C2), 150.4, 132.2, 130.5, 130.2, 127.9 (q, *J* = 31.5 Hz), 126.9 (q, *J* = 5.8 Hz), 126.8 (q, *J* = 4.4 Hz), 124.6 (q, *J* = 1.8 Hz), 123.4 (q, *J* = 273.2 Hz, Ar-CF<sub>3</sub>), 116.4 (q, *J* = 270.7 Hz, oxazole-CF<sub>3</sub>); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -60.6 (s, 3F, Ar-CF<sub>3</sub>), -66.3 (s, 3F, oxazole-CF<sub>3</sub>); HRMS (EI<sup>+</sup>) *m/z* calcd for C<sub>11</sub>H<sub>5</sub>ONF<sub>6</sub> [M]<sup>+</sup>: 281.0270, found 281.0273.

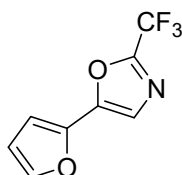


5-(2-Bromophenyl)-2-(trifluoromethyl)oxazole (**3i**)

Prepared according to the general procedure 1 from 44.8 mg (0.2 mmol) of NH-triazole, TFAA and Et<sub>3</sub>N. Reaction conditions for the first step: 16 h at 80°C. Eluent: pentane/DCM 2:1 to 1:1. Yield: 43 mg (74%); a colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.94 (s, 1H), 7.77 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.71 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.44 (td, *J* = 7.7, 1.3 Hz, 1H), 7.30-7.25 (m, 1H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 151.4, 149.8 (q, *J* = 44.2 Hz, C2), 134.3, 130.7, 129.2, 127.8, 127.1, 126.9, 120.6, 116.5 (q, *J* = 270.7 Hz, CF<sub>3</sub>); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -66.2 (s, 3F); HRMS (EI<sup>+</sup>) *m/z* calcd for C<sub>10</sub>H<sub>5</sub>BrONF<sub>3</sub> [M]<sup>+</sup>: 290.9501, found 290.9503.

5-(Furan-2-yl)-

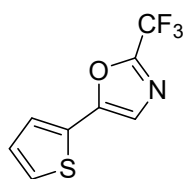
Prepared according to the general procedure 1 from 27.5 mg (0.2 mmol) of NH-triazole, TFAA and Et<sub>3</sub>N. Reaction conditions for the first step: 6 h at 50°C. **Attention:** the product is highly volatile, thus the reaction mixture was directly subjected to chromatography without evaporation. After separation a very gentle evaporation (300 Torr, 30°C) was necessary to avoid significant loss of the yield. Eluent: pentane/DCM 2:1 to 1:1. Yield: 31 mg (76%); a yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.53 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.35 (s, 1H), 6.80 (dd, *J* = 3.5, 0.8 Hz, 1H), 6.55 (dd, *J* = 3.5, 1.8 Hz, 1H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 149.4, 149.2



2-(trifluoromethyl)oxazole (**3j**)

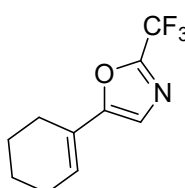
Prepared according to the general procedure 1 from 27.5 mg (0.2 mmol) of NH-triazole, TFAA and Et<sub>3</sub>N. Reaction conditions for the first step: 6 h at 50°C. **Attention:** highly volatile, thus the reaction mixture was directly subjected to chromatography without evaporation. After separation a very gentle evaporation (300 Torr, 30°C) was necessary to avoid significant loss of the yield. Eluent: pentane/DCM 2:1 to 1:1. Yield: 31 mg (76%); a yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.53 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.35 (s, 1H), 6.80 (dd, *J* = 3.5, 0.8 Hz, 1H), 6.55 (dd, *J* = 3.5, 1.8 Hz, 1H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 149.4, 149.2

(q,  $J = 44.3$  Hz, C2), 128.1, 127.7, 127.5, 126.4, 121.9, 116.4 (q,  $J = 270.4$  Hz, CF<sub>3</sub>); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -66.1 (s, 3F); HRMS (EI<sup>+</sup>)  $m/z$  calcd for C<sub>8</sub>H<sub>4</sub>O<sub>2</sub>NF<sub>3</sub> [M]<sup>+</sup>: 203.0189, found 203.0190.



5-(Thiophen-2-yl)-2-(trifluoromethyl)oxazole (**3k**)

Prepared according to the general procedure 1 from 30.2 mg (0.2 mmol) of NH-triazole, TFAA and Et<sub>3</sub>N. Reaction conditions for the first step: 3 h at 50°C. Eluent: pentane/DCM 2:1 to 1:1. Yield: 33 mg (75%); a yellow oil; NMR matched the previously reported data.<sup>3</sup>

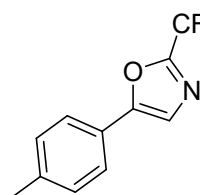


5-(Cyclohex-1-en-1-yl)-2-(trifluoromethyl)oxazole (**3l**)

Prepared according to the general procedure 1 from 29.8 mg (0.2 mmol) of NH-triazole, TFAA and Et<sub>3</sub>N. Reaction conditions for the first step: 3 h at 50°C. Eluent: pentane/DCM 2:1 to 1:1. Yield: 27.5 mg (63%); a colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.96 (s, 1H), 6.46 (tt,  $J = 3.9, 1.7$  Hz, 1H), 2.31-2.21 (m, 4H), 1.79-1.73 (m, 2H), 1.64-1.70 (m, 2H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 150.5, 149.0 (q,  $J = 43.6$  Hz, C2), 128.5, 123.9, 120.9, 116.6 (q,  $J = 270.3$  Hz, CF<sub>3</sub>), 25.2, 24.5, 21.8, 21.7; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -66.3 (s, 3F); HRMS (EI<sup>+</sup>)  $m/z$  calcd for C<sub>10</sub>H<sub>10</sub>ONF<sub>3</sub> [M]<sup>+</sup>: 217.0709, found 217.0708.

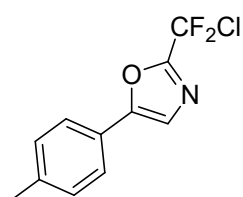
2-

Prepared of NH-triazole, for the first mg (99%); a



(Perfluoroethyl)-5-(*p*-tolyl)oxazole (**3m**)

Prepared according to the general procedure 1 from 31.8 mg (0.2 mmol) perfluoropropionic anhydride and Et<sub>3</sub>N. Reaction conditions step: 14 h at 50°C. Eluent: pentane/DCM 2:1 to 1:1. Yield: 55 mg (99%); a white solid, mp 76-78°C (CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.59-7.57 (m, 2H), 7.43 (s, 1H), 7.28-7.26 (m, 2H), 2.40 (s, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 154.9, 148.9 (t,  $J = 31.0$  Hz, C2), 140.3, 129.8, 124.9, 123.5, 122.2, 118.0 (qt,  $J = 286.1, 35.8$  Hz, CF<sub>2</sub>), 107.1 (tq,  $J = 254.9, 40.9$  Hz, CF<sub>3</sub>); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -83.9 (m, 2F), -115.4 (m, 3F); HRMS (EI<sup>+</sup>)  $m/z$  calcd for C<sub>12</sub>H<sub>8</sub>F<sub>5</sub>NO [M]<sup>+</sup>: 277.0521, found 277.0523.

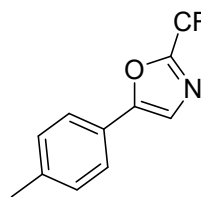


2-(Chlorodifluoromethyl)-5-(*p*-tolyl)oxazole (**3n**)

Prepared according to the general procedure 1 from 31.8 mg (0.2 mmol) of NH-triazole, chlorodifluoroacetic anhydride and Et<sub>3</sub>N. Reaction conditions for the first step: 14 h at 50°C. Eluent: pentane/DCM 2:1 to 1:1. Yield: 45 mg (92%); a pale-yellow solid, mp 52-54°C (CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.60-7.56 (m, 2H), 7.37 (s, 1H), 7.28-7.25 (m, 2H), 2.40 (s, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 154.0, 152.7 (t,  $J = 35.9$  Hz, C2), 140.1, 129.8, 124.8, 123.6, 121.8, 120.9, 118.1 (t,  $J = 286.9$  Hz, CF<sub>2</sub>Cl), 21.4; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -53.4 (s, 2F); HRMS (EI<sup>+</sup>)  $m/z$  calcd for C<sub>11</sub>H<sub>8</sub>ClF<sub>2</sub>NO [M]<sup>+</sup>: 243.0257, found 243.0258.

2-(Difluoromethyl)-

Prepared according triazole, the first step: 22 h at reaction (0.2 mmol

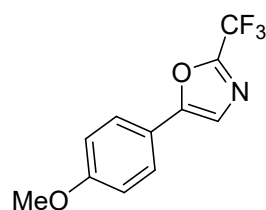


5-(*p*-tolyl)oxazole (**3o**)

to the general procedure 1 from 31.8 mg (0.2 mmol) of NH-difluoroacetic anhydride and Et<sub>3</sub>N. Reaction conditions for 75°C. **Attention:** 0.35 molar solution in DCE was used for this NH-triazole in 0.7 ml DCE). Eluent: pentane/EtOAc 9:1. Yield: 23.5 mg (56%); a colorless oil, which solidified upon storage; NMR matched the previously reported data.<sup>6</sup>

## General procedure 2 for the one step synthesis of oxazoles from NH-triazoles and anhydrides in MeCN

To the suspension of 4,5-disubstituted NH-1,2,3-triazole **1** (0.2 mmol) in dry MeCN (1 ml) in a 10 ml vial, fluoroalkylated acid anhydride (0.5 mmol, 2.5 equiv.) was added. The vial was sealed, and the mixture was stirred at room temperature for 2 hours. After addition of silica gel, solvent was removed under reduced pressure (250-500 Torr) and the product was purified by column chromatography to give the target oxazole **3**.



5-(4-Methoxyphenyl)-2-(trifluoromethyl)oxazole (**3e**)

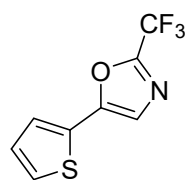
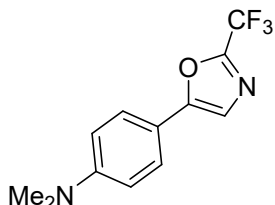
Prepared according to the general procedure 2 from 17.5 mg (0.1 mmol) of NH-triazole and TFAA. Eluent: pentane/DCM 1:1 to 1:2. Yield: 15.0 mg (67%); a pale-yellow oil; NMR matched the previously reported data.<sup>3</sup>

*N,N*-dimethyl-4-(2-

Prepared according to NH-triazole and TFAA.

dark (m, 2H), 7.22 (s, 1H),

yellow (m, 2H), 7.22 (s, 1H), *N,N*-dimethyl-4-(2-(trifluoromethyl)oxazol-5-yl)aniline (**3p**) the general procedure 2 from 8.8 mg (0.047 mmol) of Eluent: pentane/EtOAc 3:1 to 1:1. Yield: 9.0 mg (75%); a amorphous solid; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.55-7.53 6.75-6.72 (m, 2H), 3.03 (s, 6H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 155.0, 151.1, 148.4 (q, *J* = 43.1 Hz, C2), 126.2, 119.4, 114.0, 116.7 (q, *J* = 270.0 Hz, CF<sub>3</sub>), 112.0, 40.2; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -66.0 (s, 3F); HRMS (EI<sup>+</sup>) *m/z* calcd for C<sub>12</sub>H<sub>11</sub>F<sub>3</sub>N<sub>2</sub>O [M]<sup>+</sup>: 256.0818, found 256.0817.



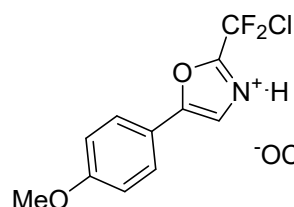
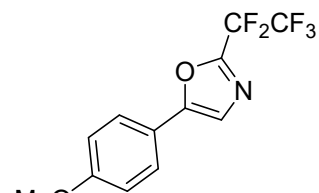
5-(Thiophen-2-yl)-2-(trifluoromethyl)oxazole (**3k**)

Prepared according to the general procedure 2 from 30.2 mg (0.2 mmol) of NH-triazole and TFAA. Eluent: pentane/DCM 2:1 to 1:1. Yield: 20.2 mg (46%); a yellow oil; NMR matched the previously reported data.<sup>3</sup>

5-(4-

Prepared mmol) of NH-pentane/DCM (CHCl<sub>3</sub>); <sup>1</sup>H

Methoxyphenyl)-2-(perfluoroethyl)oxazole (**3q**) according to the general procedure 2 from 35 mg (0.2 triazole and perfluoropropionic anhydride. Eluent: 1:1 to 1:2. Yield: 45 mg (77%); a yellow solid, mp 51-53°C NMR (400 MHz, CDCl<sub>3</sub>) δ 7.64-7.60 (m, 2H), 7.36 (s, 1H), 7.00-6.96 (m, 2H), 3.86 (s, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 160.9, 154.7, 148.6 (t, *J* = 31.0 Hz, C2), 126.6, 121.4, 119.1, 118.0 (qt, *J* = 286.4, 35.8 Hz, CF<sub>2</sub>), 114.6, 107.1 (tq, *J* = 254.9, 40.7 Hz, CF<sub>3</sub>); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -83.9 (t, *J* = 3.0 Hz), -115.3 (q, *J* = 3.0 Hz); HRMS (EI<sup>+</sup>) *m/z* calcd for C<sub>12</sub>H<sub>8</sub>F<sub>5</sub>NO<sub>2</sub> [M]<sup>+</sup>: 293.0470, found 293.0470.



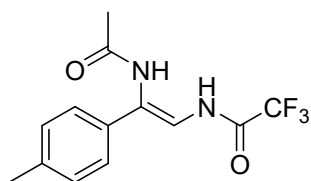
2-(Chlorodifluoromethyl)-5-(4-methoxyphenyl)oxazol-3-ium chlorodifluoroacetate (**3r**)

Prepared according to the general procedure 2 from 35 mg (0.2 mmol) of NH-triazole and chlorodifluoroacetic anhydride. Eluent: pentane/EtOAc 19:1. Yield: 56.5 mg (73%); a colorless oil; <sup>1</sup>H NMR (400

MHz, CDCl<sub>3</sub>) δ 9.53 (br s, 1H, NH), 7.65-7.62 (m, 2H), 7.42 (s, 1H), 7.00-6.98 (m, 2H), 3.87 (s, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 161.1, 160.8 (t, *J* = 34.1 Hz, C2), 154.6, 152.4 (t, *J* = 36.7 Hz), 126.7, 119.8, 118.4, 117.6 (t, *J* = 287.6 Hz, oxazole-CF<sub>2</sub>Cl), 117.0 (t, *J* = 300.4 Hz, CF<sub>2</sub>ClCO<sub>2</sub><sup>-</sup>), 114.7, 55.4; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -53.8 (s, 2F, oxazole-CF<sub>2</sub>Cl), -65.1 (s, 2F, CF<sub>2</sub>ClCO<sub>2</sub><sup>-</sup>); HRMS (ESI<sup>+</sup>) *m/z* calcd for C<sub>11</sub>H<sub>9</sub>ClF<sub>2</sub>NO<sub>2</sub> [M]<sup>+</sup>: 260.0284, found 260.0284.

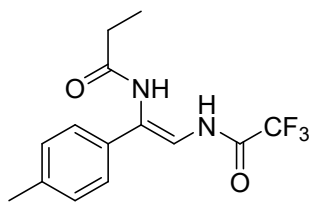
#### Synthesis of bis-enamides **4**

To the suspension of NH-triazole **1a** (0.1 mmol) in nitrile (1 ml) TFAA (0.25 mmol, 2.5 equiv., 35 μl) was added and the mixture was stirred at room temperature for 5 hours. After addition of silica gel the solvent was evaporated and the product was purified by column chromatography (cyclohexane/EtOAc).



(*Z*)-*N*-(2-Acetamido-2-(*p*-tolyl)vinyl)-2,2,2-trifluoroacetamide (**4a**)

Product **4a** was obtained from NH-triazole, acetonitrile and TFAA. Eluent: 9:1 to 5:1 cyclohexane/EtOAc. Yield: 13.5 mg (47%); a white amorphous solid; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.39 (br d, *J* = 8.9 Hz, 1H, NH), 7.29-7.27 (m, 2H), 7.21-7.18 (m, 2H), 7.03 (br s, 1H, NH), 6.62 (d, *J* = 8.9 Hz, 1H, =CH), 2.36 (s, 3H, Me), 2.28 (s, 3H, Me); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 170.2, 154.3 (q, *J* = 38.2 Hz, COCF<sub>3</sub>), 139.4, 132.7, 129.8, 126.5, 123.6, 115.8 (q, *J* = 286.9 Hz, CF<sub>3</sub>), 110.0, 23.9, 21.2; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -76.3 (s, 3F); HRMS (ESI<sup>+</sup>) *m/z* calcd for C<sub>13</sub>H<sub>14</sub>O<sub>2</sub>N<sub>2</sub>F<sub>3</sub> [M+H]<sup>+</sup>: 287.1002, found 287.1002.



(*Z*)-*N*-(1-(*p*-Tolyl)-2-(2,2,2-trifluoroacetamido)vinyl)propionamide (**4b**)

Product **4b** was obtained from NH-triazole, propionitrile and TFAA. Eluent: 9:1 to 5:1 cyclohexane/EtOAc. Yield: 10 mg (32%); a white solid, mp 155-157°C (CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.52 (br d, *J* = 8.9 Hz, 1H, NH), 7.30-7.28 (m, 2H), 7.21-7.18 (m, 2H), 6.63 (d, *J* = 8.8 Hz, 1H, =CH), 2.50 (q, *J* = 7.6 Hz, 2H), 2.37 (s, 3H), 1.30 (t, *J* = 7.6 Hz, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 173.6, 154.2 (q, *J* = 37.8 Hz, COCF<sub>3</sub>), 139.4, 133.0, 129.8, 126.4, 123.4, 115.9 (q, *J* = 286.8 Hz, CF<sub>3</sub>), 109.8, 30.4, 21.2, 9.9; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -76.4 (s, 3F); HRMS (ESI<sup>+</sup>) *m/z* calcd for C<sub>14</sub>H<sub>15</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub> [M]<sup>+</sup>: 300.1081, found 300.1083.

#### References

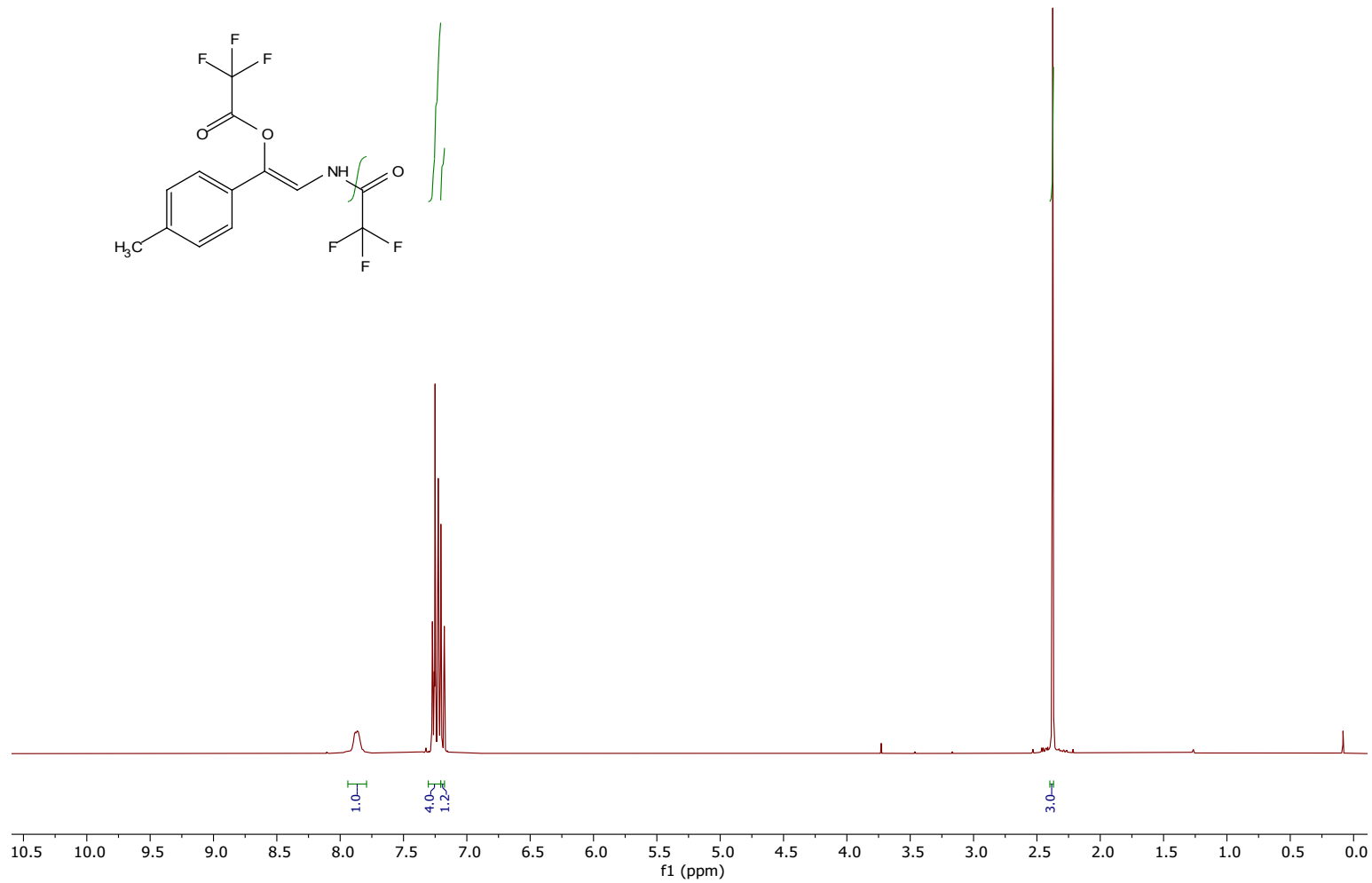
1. Hui, R.; Zhao, M.; Chen, M.; Ren, Z.; Guan, Z. *Chin. J. Chem.* **2017**, *35*, 1808.
2. Jin, T.; Kamijo, S.; Yamamoto, Y. *Eur. J. Org. Chem.* **2004**, 3789.
3. Motornov, V.; Košťál, A.; Markos, A.; Taffner, D.; Beier, P.; *Org. Chem. Front.*, **2019**, *6*, 3776.
4. Kobayashi, Y.; Masakado, S.; Murai, T.; Hamada, S.; Furuta, T.; Takemoto, Y. *Org. Biomol. Chem.*, **2021**, *19*, 6628.
5. Karuppusami, V.; Ilangovan, A. *Org. Lett.*, **2020**, *22*, 7147.
6. Tichý, D.; Košťál, V.; Motornov, V.; Klimánková, I.; Beier, P.; *J. Org. Chem.*, **2020**, *85*, 11482.
7. Motornov, V.; Beier, P., *Org. Lett.*, **2022**, *24*, 1958.



# Copies of $^1\text{H}$ , $^{13}\text{C}$ and $^{19}\text{F}$ NMR spectra

(Z)-1-(p-tolyl)-2-(2,2,2-trifluoroacetamido)vinyl 2,2,2-trifluoroacetate **2a**

$^1\text{H}$  NMR



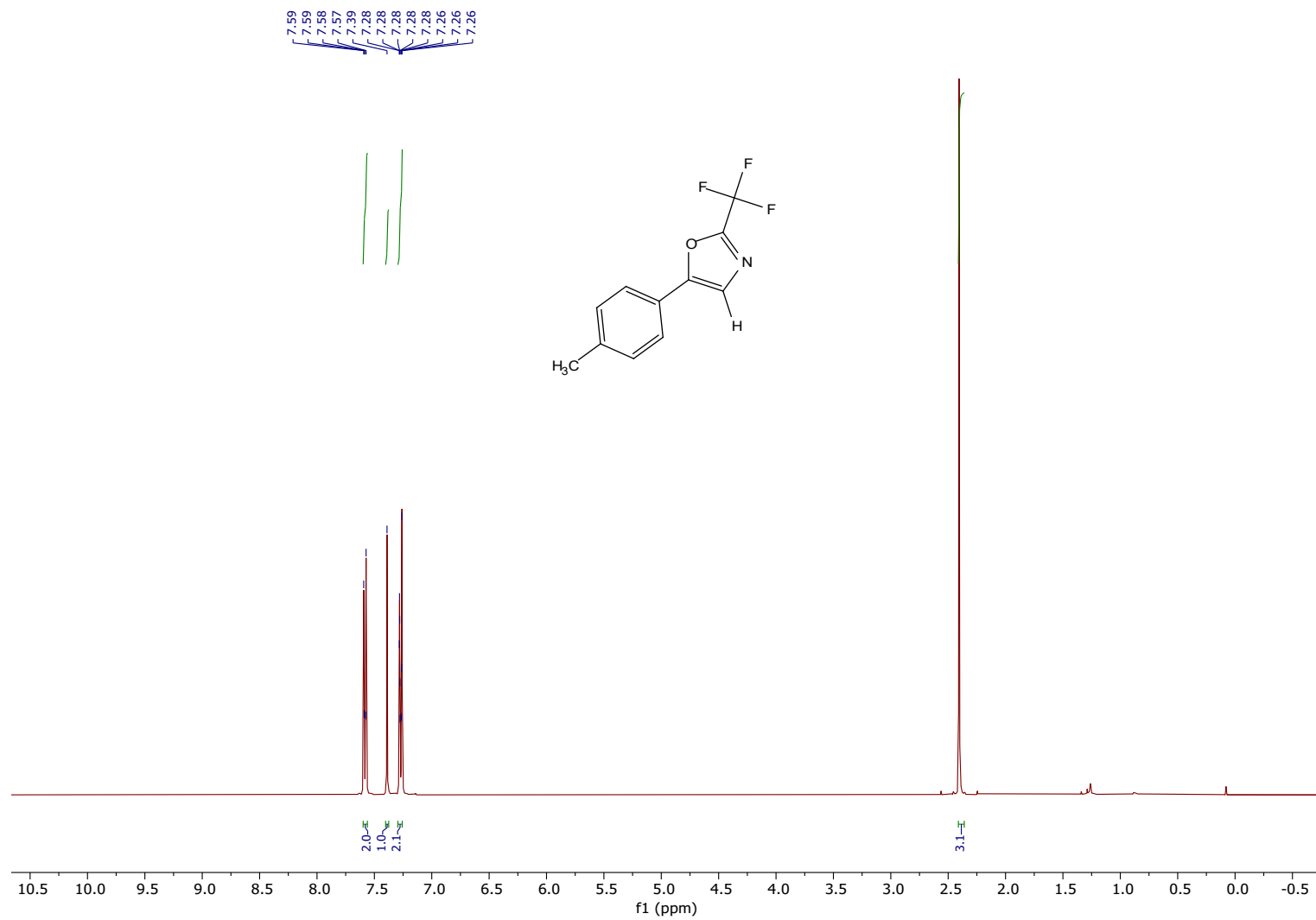




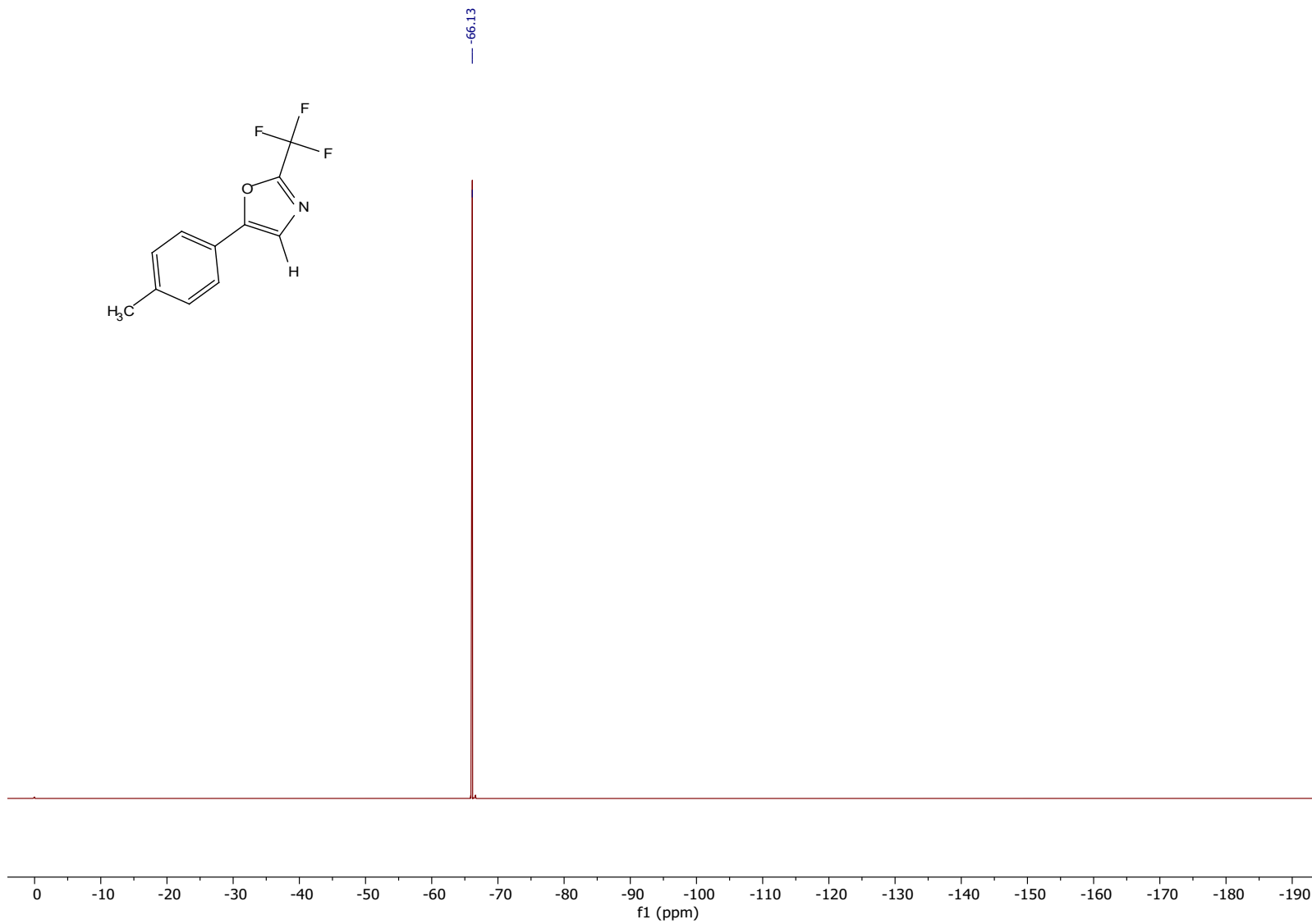
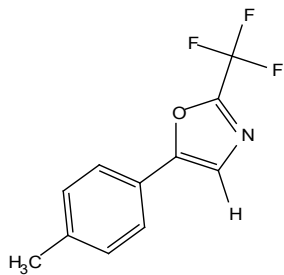


5-(*p*-Tolyl)-2-(trifluoromethyl)oxazole (**3a**)

<sup>1</sup>H NMR

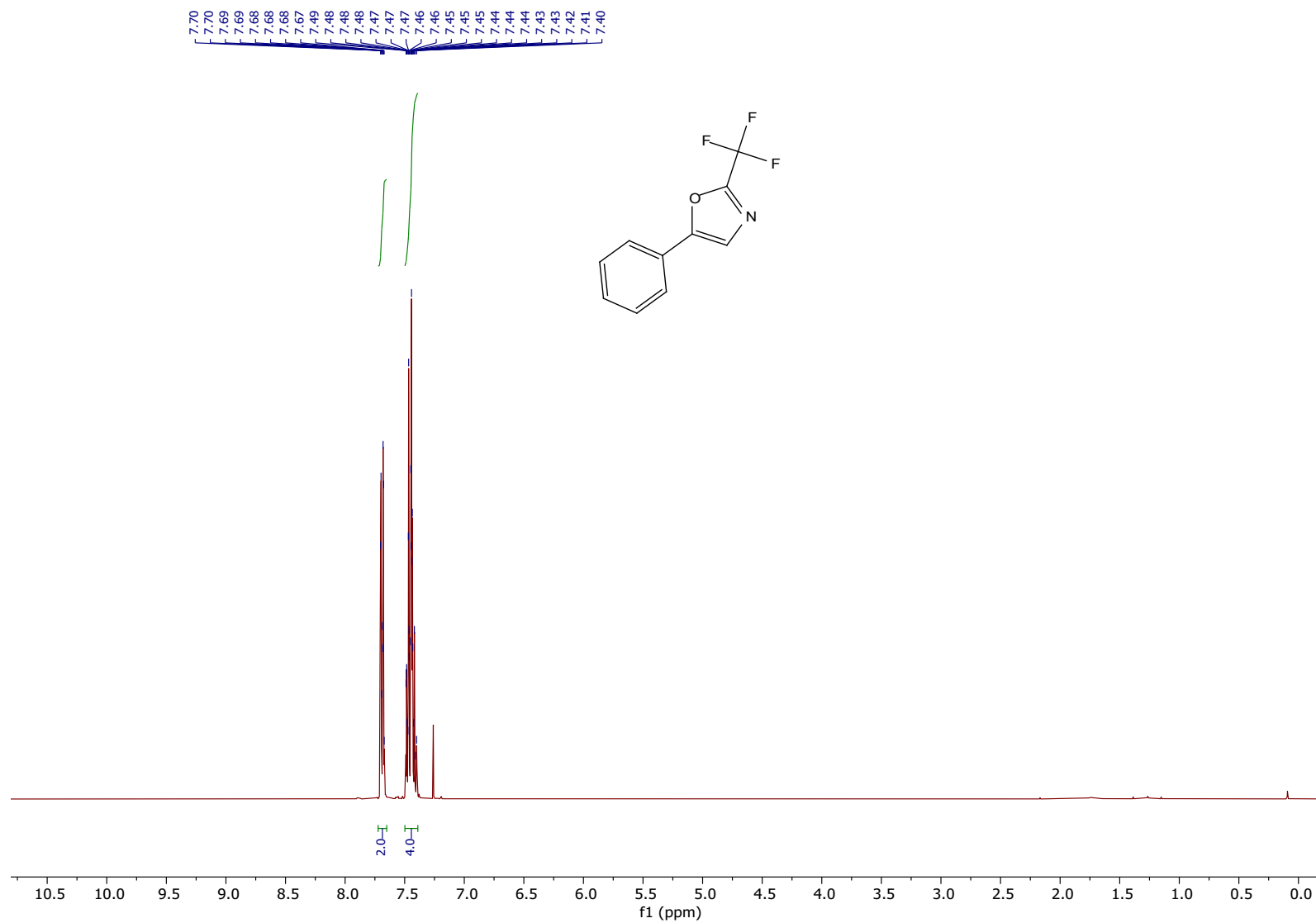


<sup>19</sup>F NMR

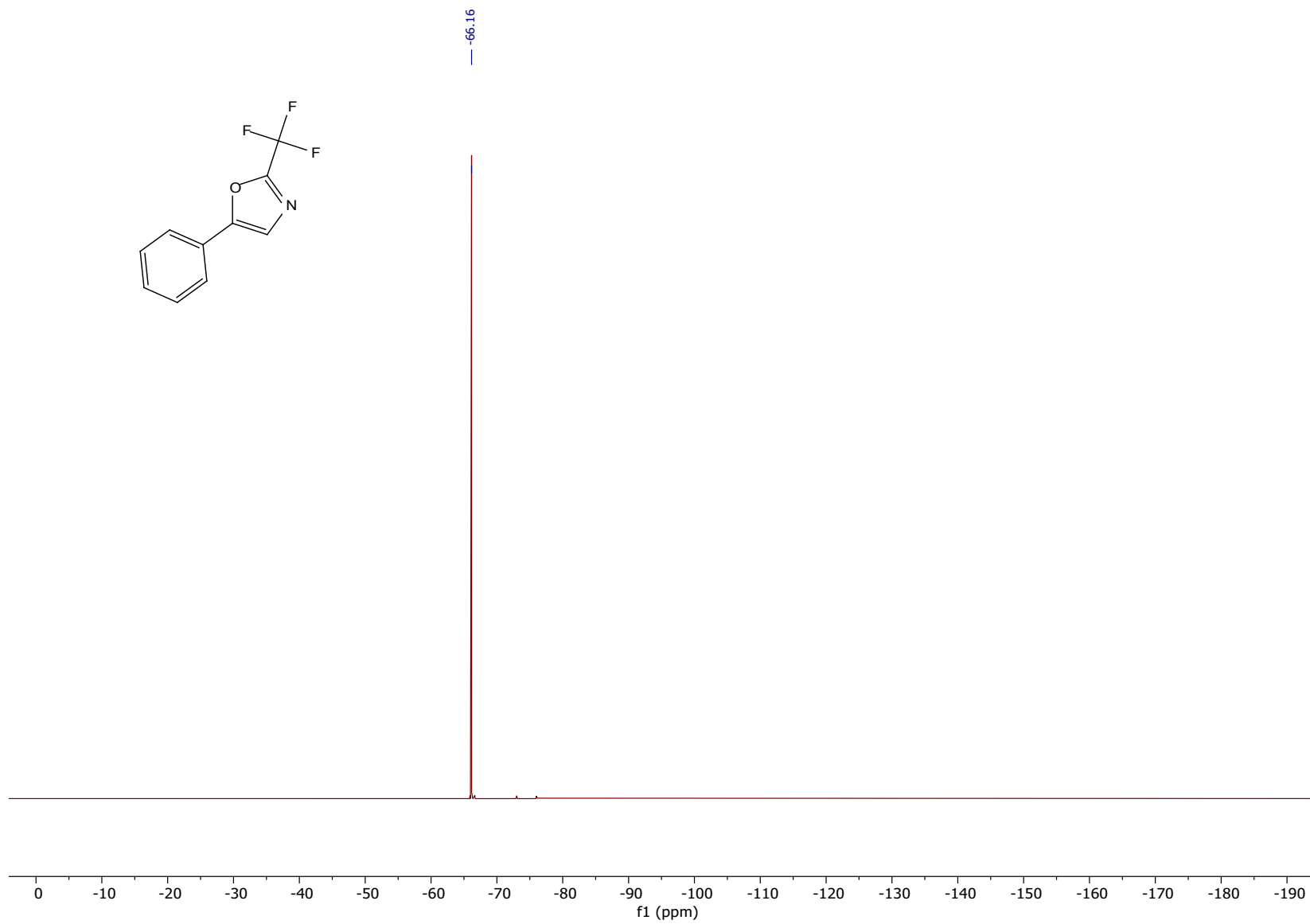
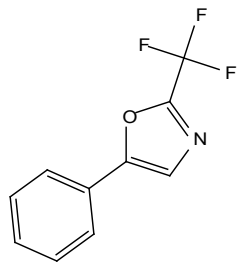


# 5-Phenyl-2-(trifluoromethyl)oxazole (**3b**)

$^1\text{H}$  NMR



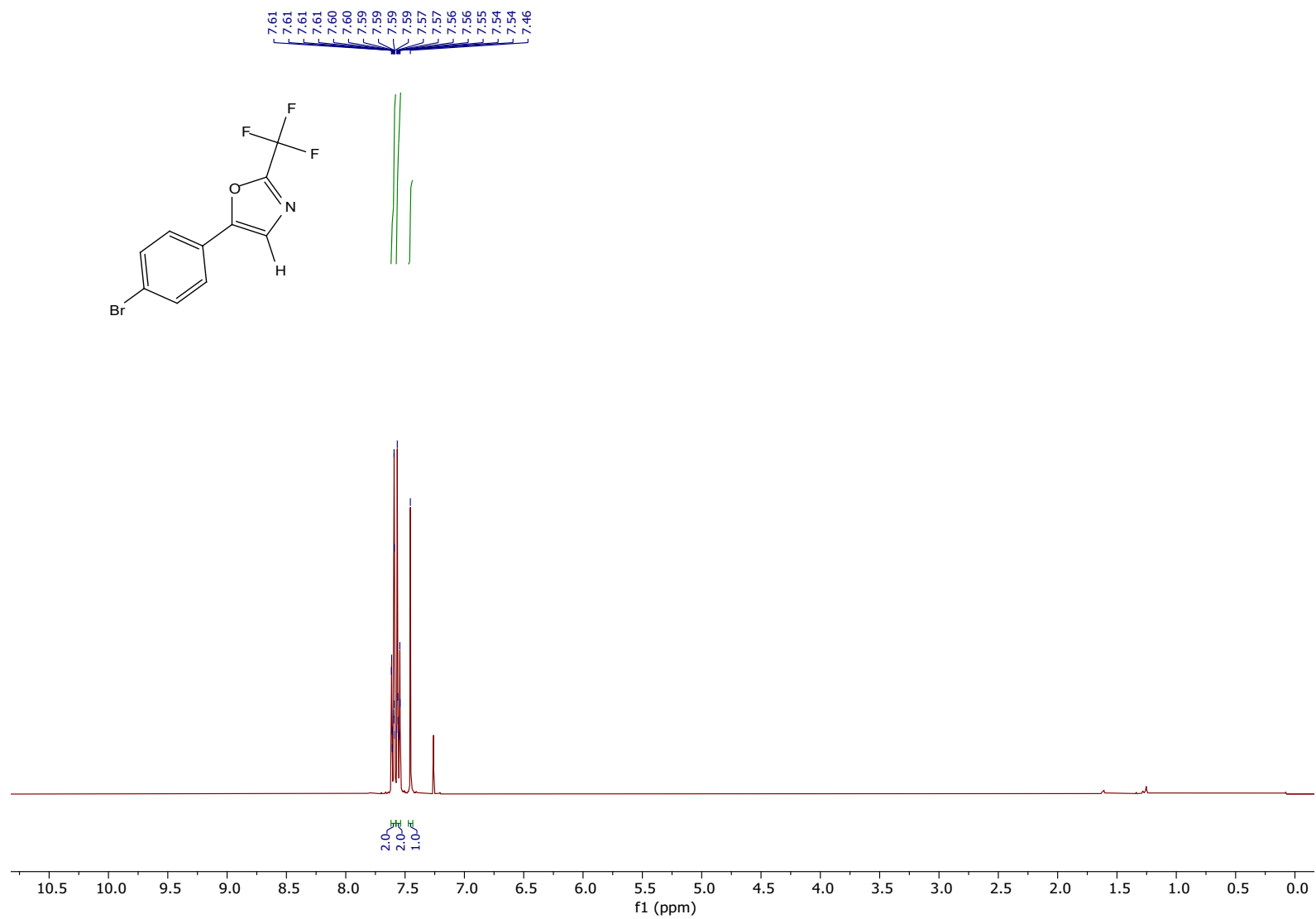
<sup>19</sup>F NMR



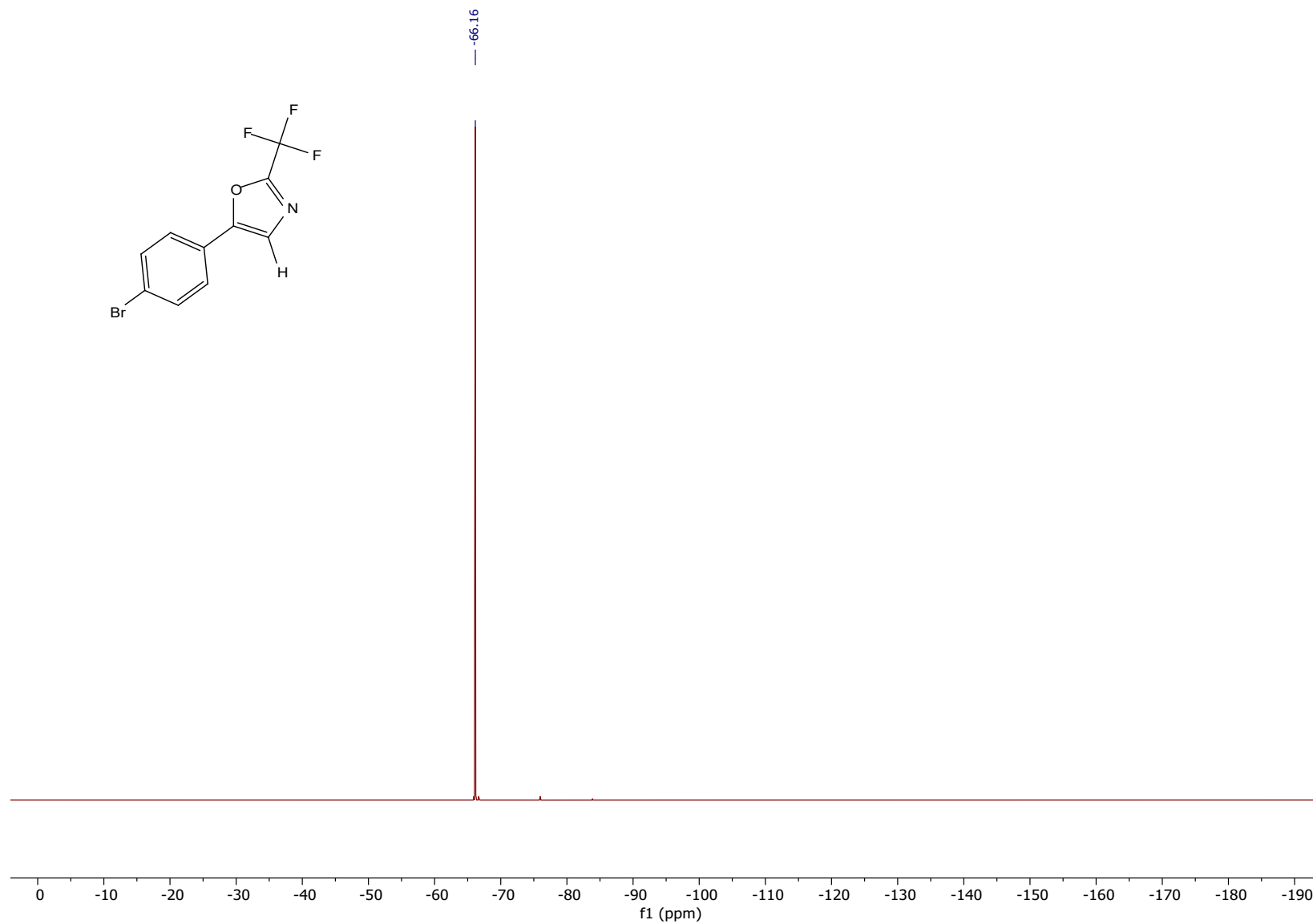
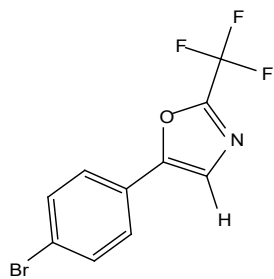
SI14

5-(4-Bromophenyl)-2-(trifluoromethyl)oxazole (**3c**)

$^1\text{H}$  NMR



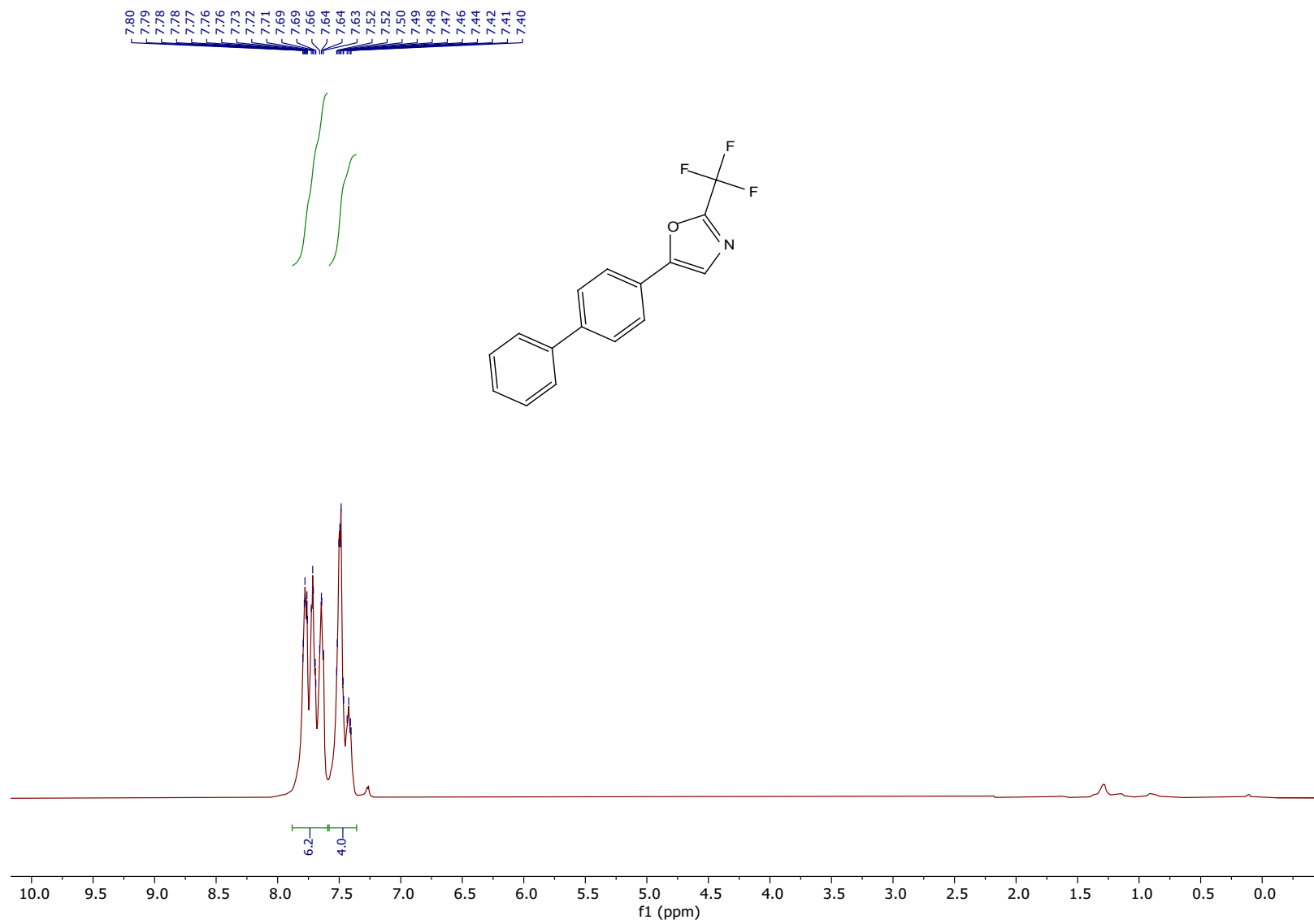
<sup>19</sup>F NMR





5-([1,1'-Biphenyl]-4-yl)-2-(trifluoromethyl)oxazole (**3d**)

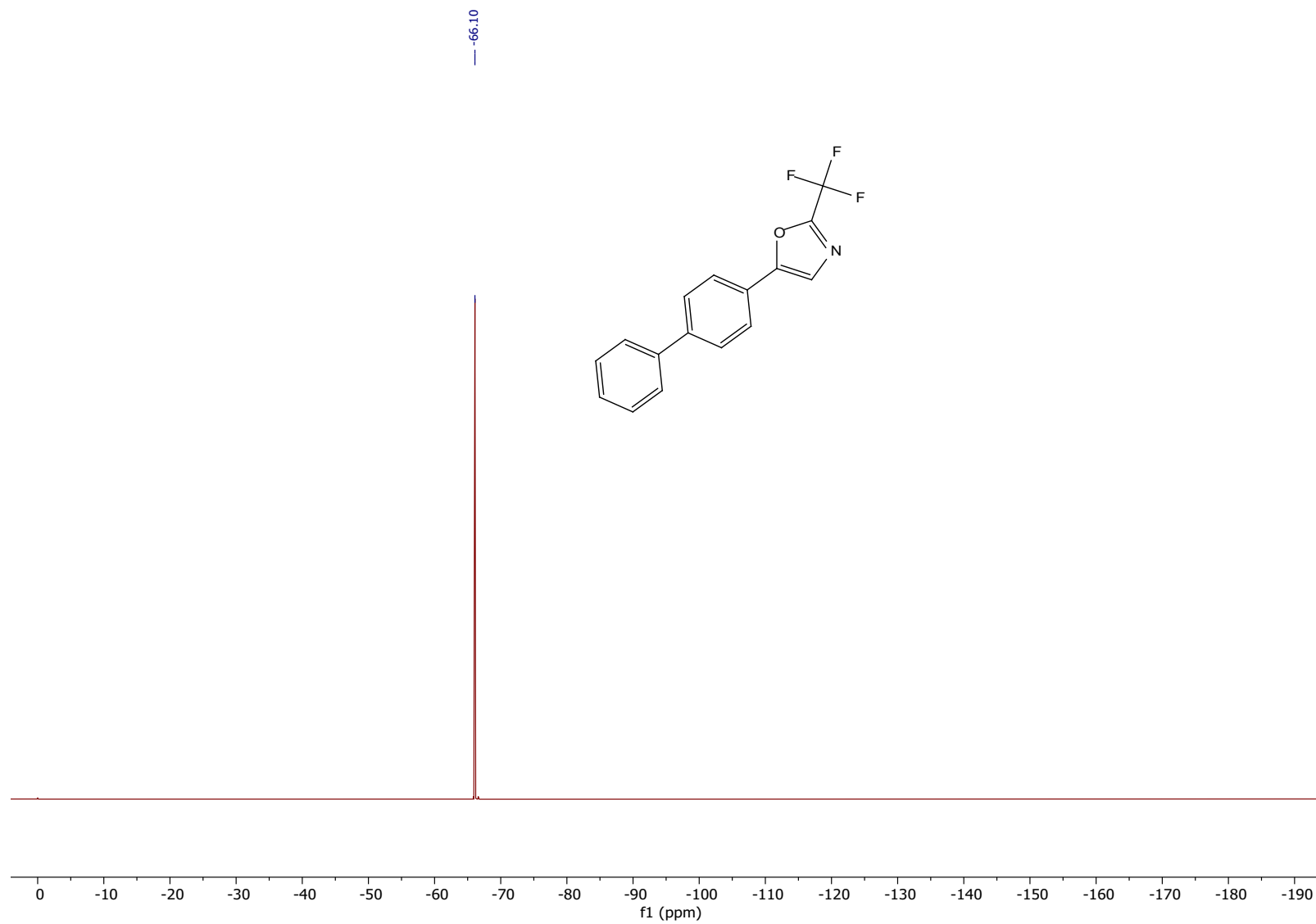
$^1\text{H}$  NMR



SI17

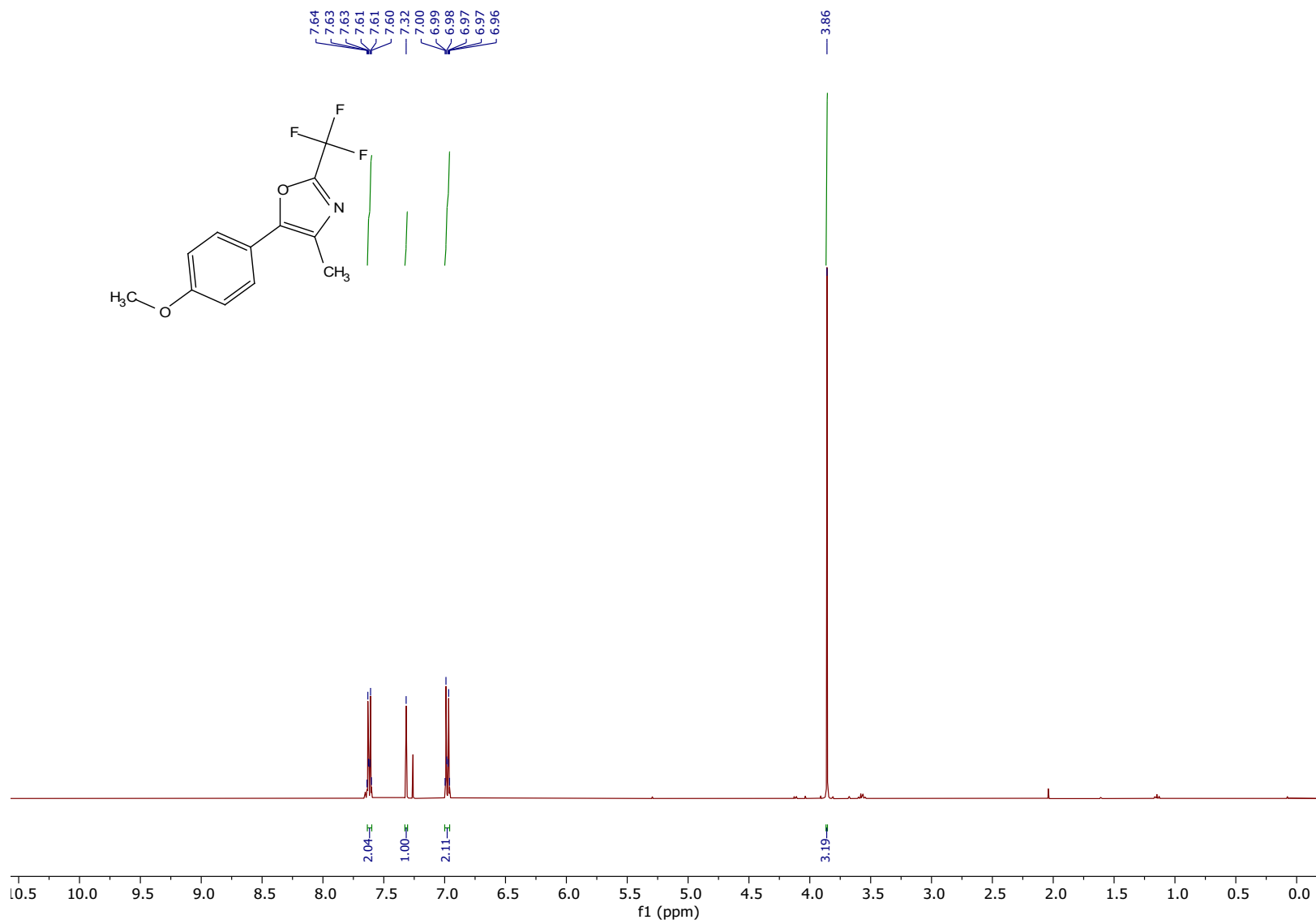


$^{19}\text{F}$  NMR



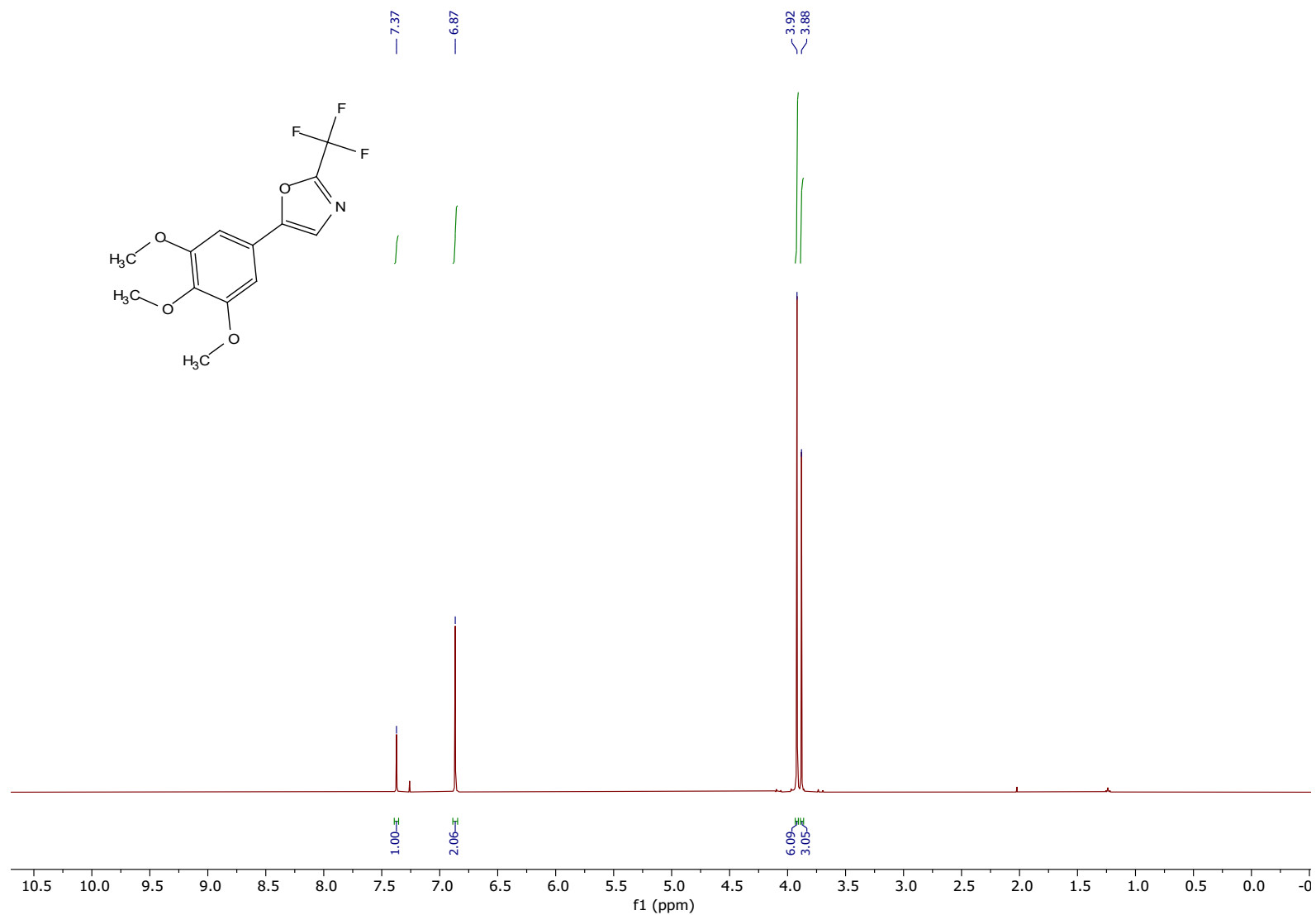
5-(4-Methoxyphenyl)-2-(trifluoromethyl)oxazole (**3e**)

$^1\text{H}$  NMR

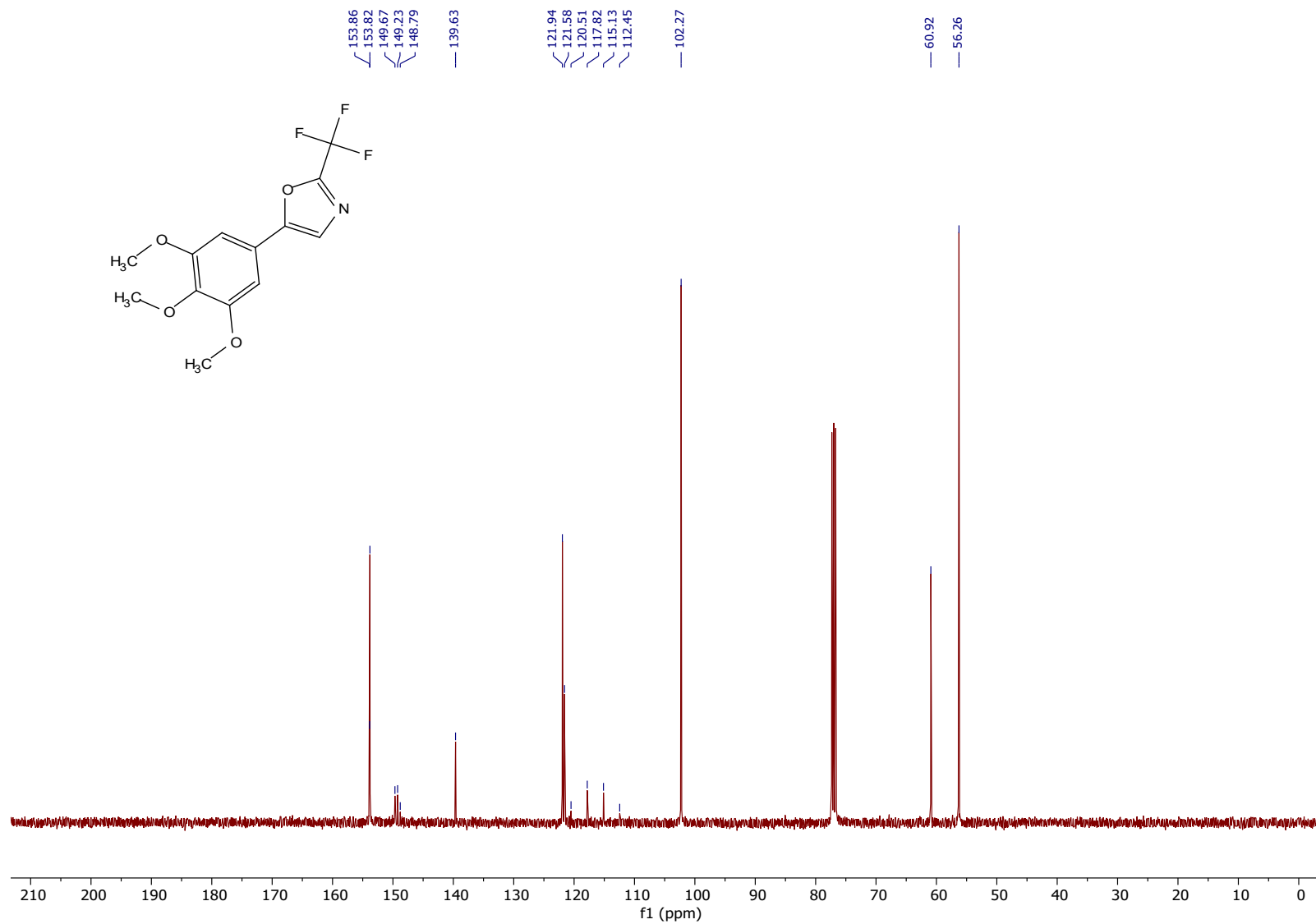


2-(Trifluoromethyl)-5-(3,4,5-trimethoxyphenyl)oxazole (**3f**)

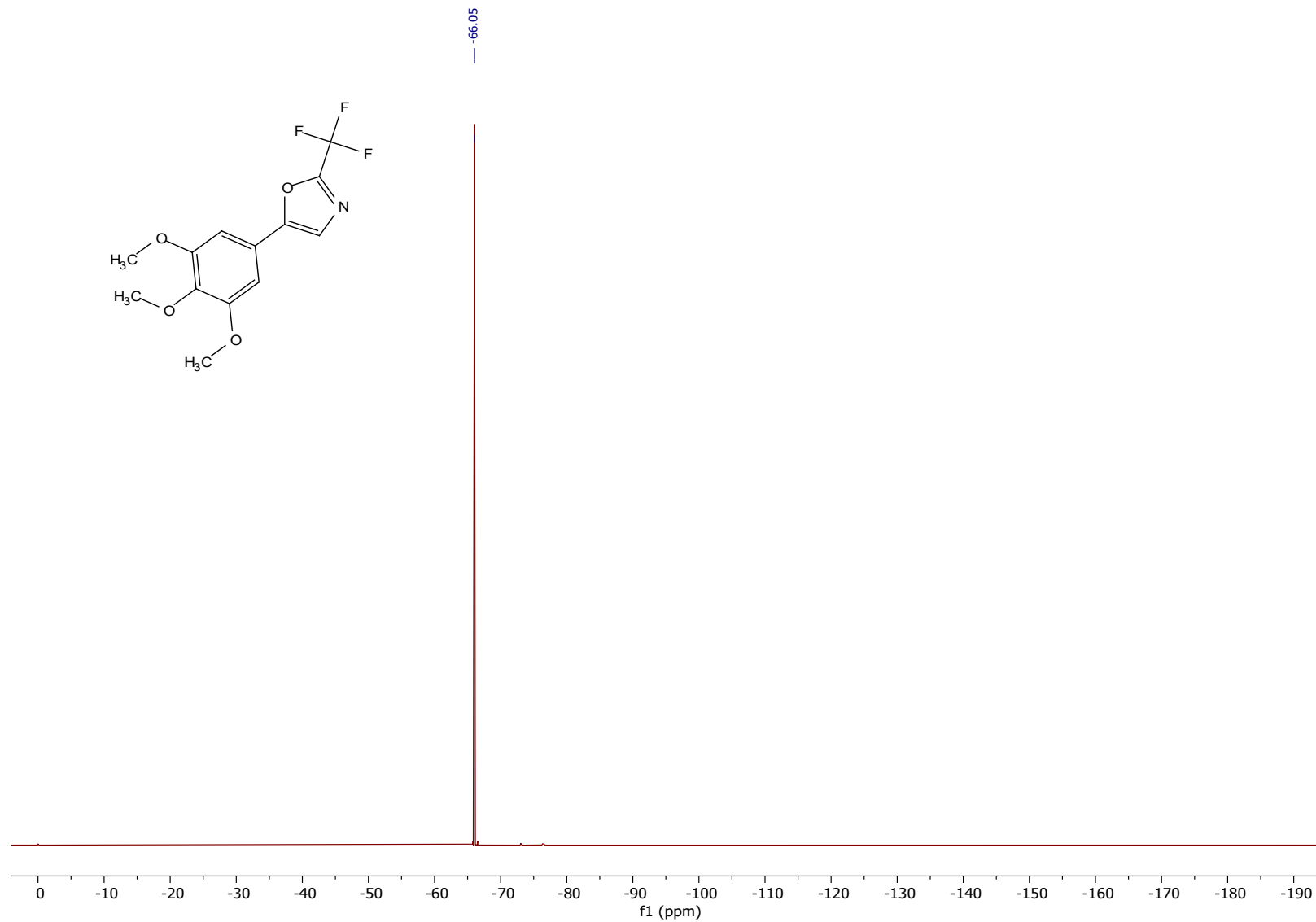
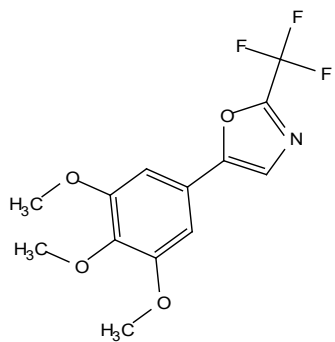
<sup>1</sup>H NMR



<sup>13</sup>C NMR

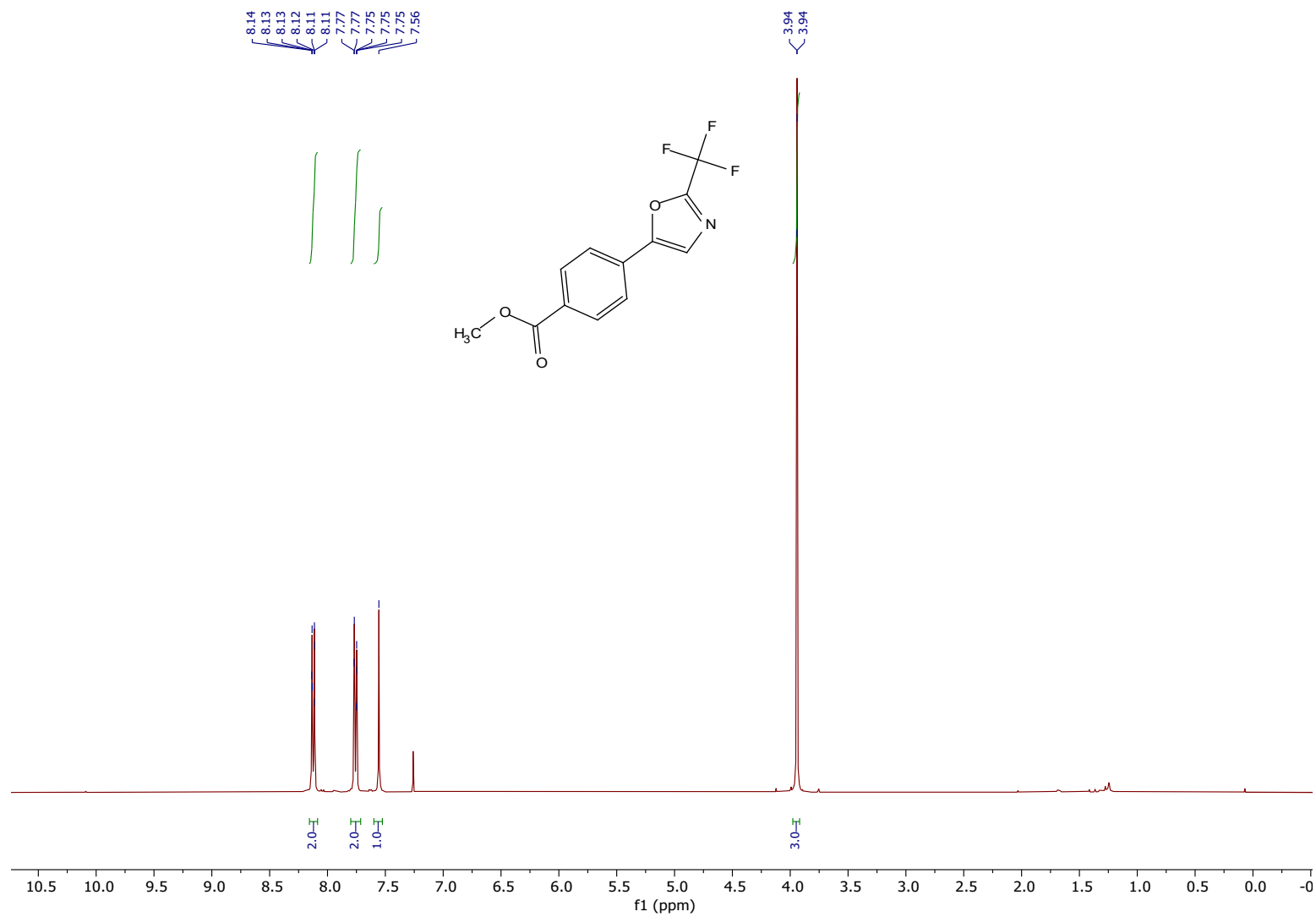


<sup>19</sup>F NMR



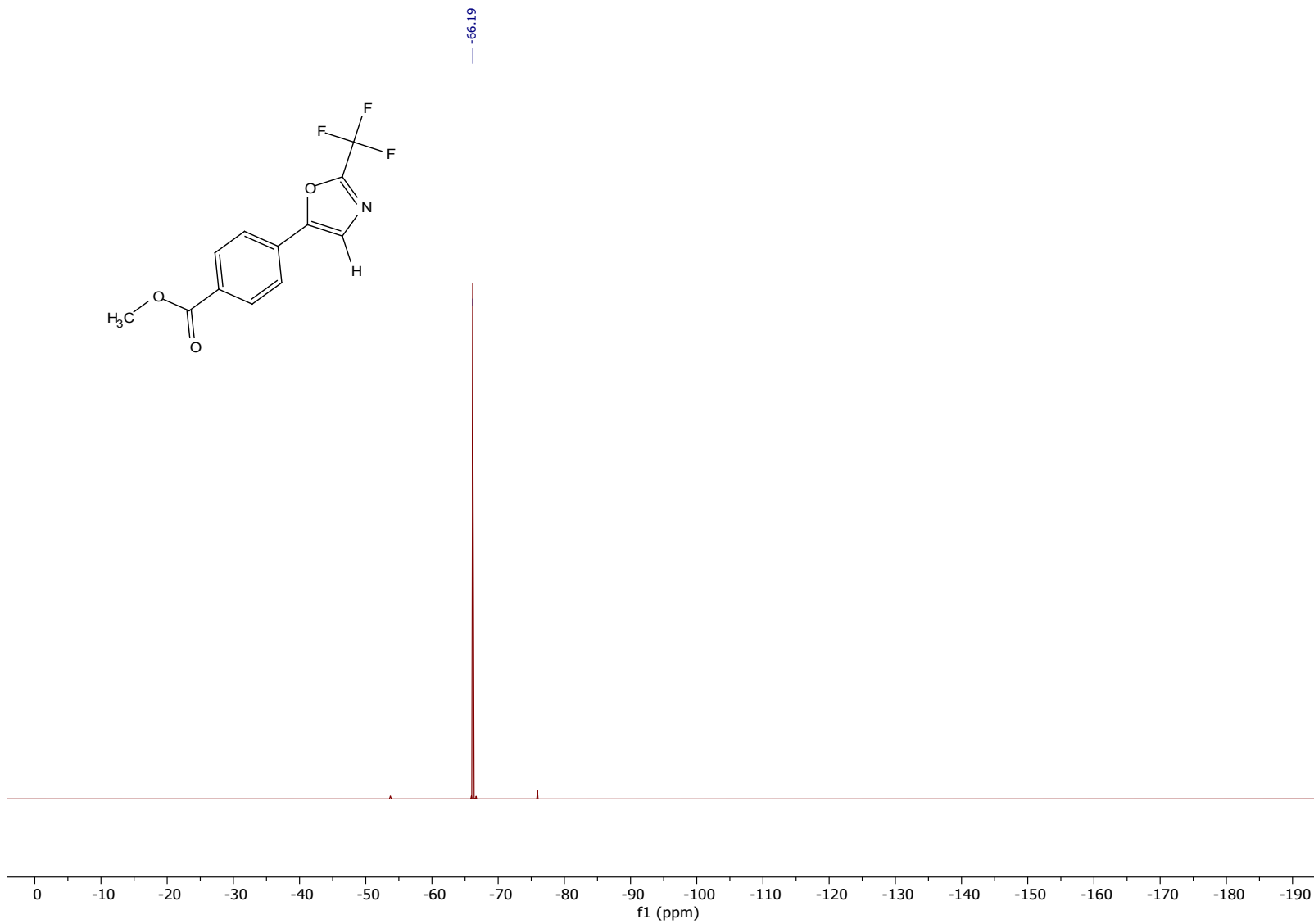
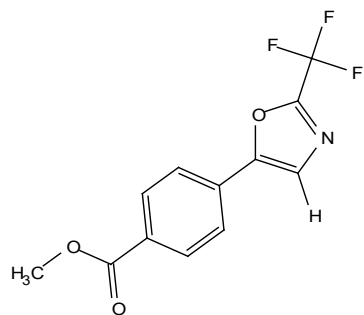
Methyl 4-(2-(trifluoromethyl)oxazol-5-yl)benzoate (**3g**)

$^1\text{H}$  NMR



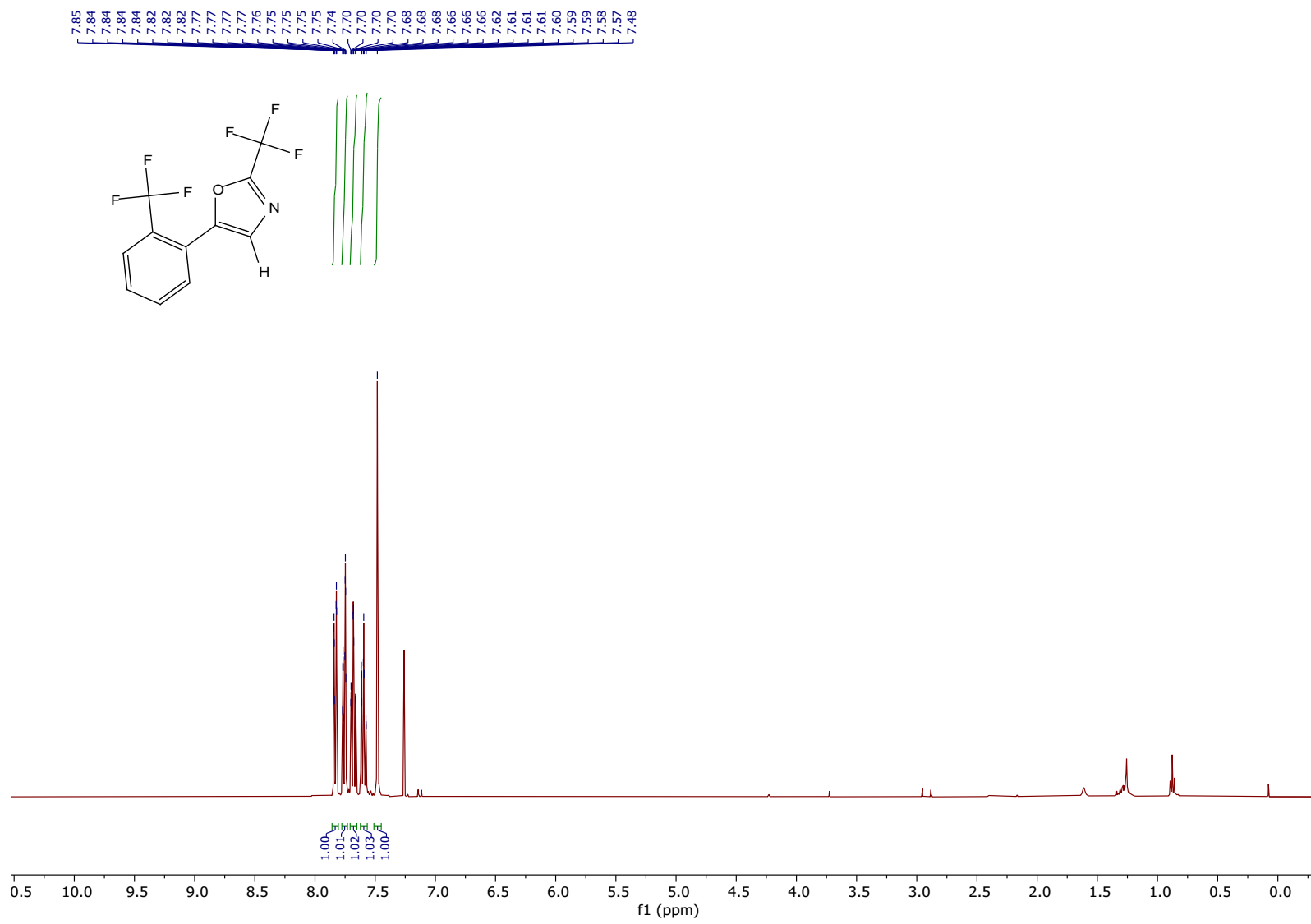


<sup>19</sup>F NMR

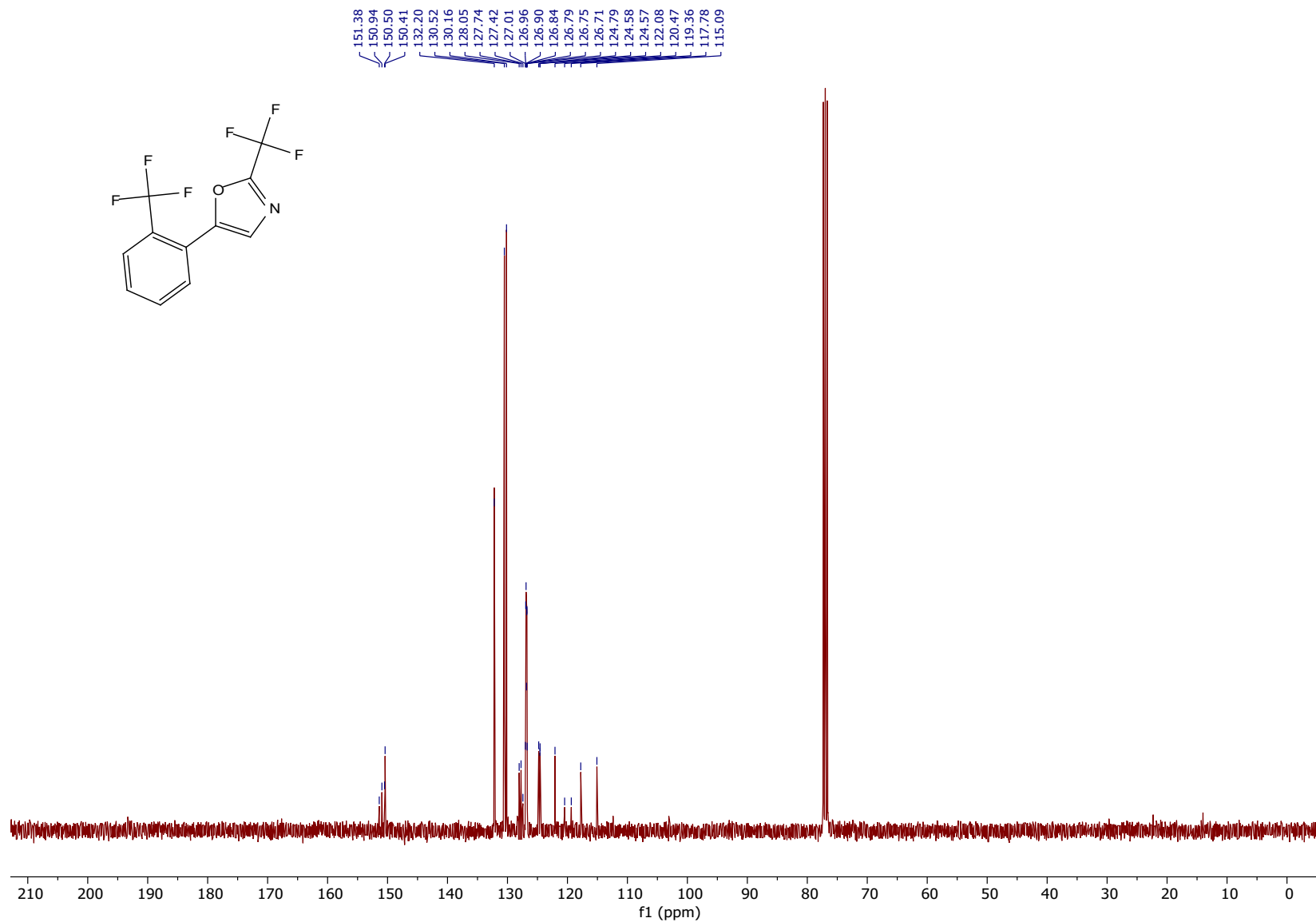
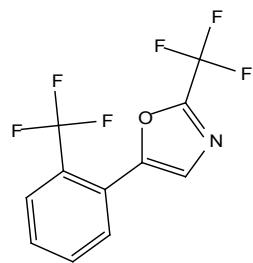


# 2-(Trifluoromethyl)-5-(2-(trifluoromethyl)phenyl)oxazole (**3h**)

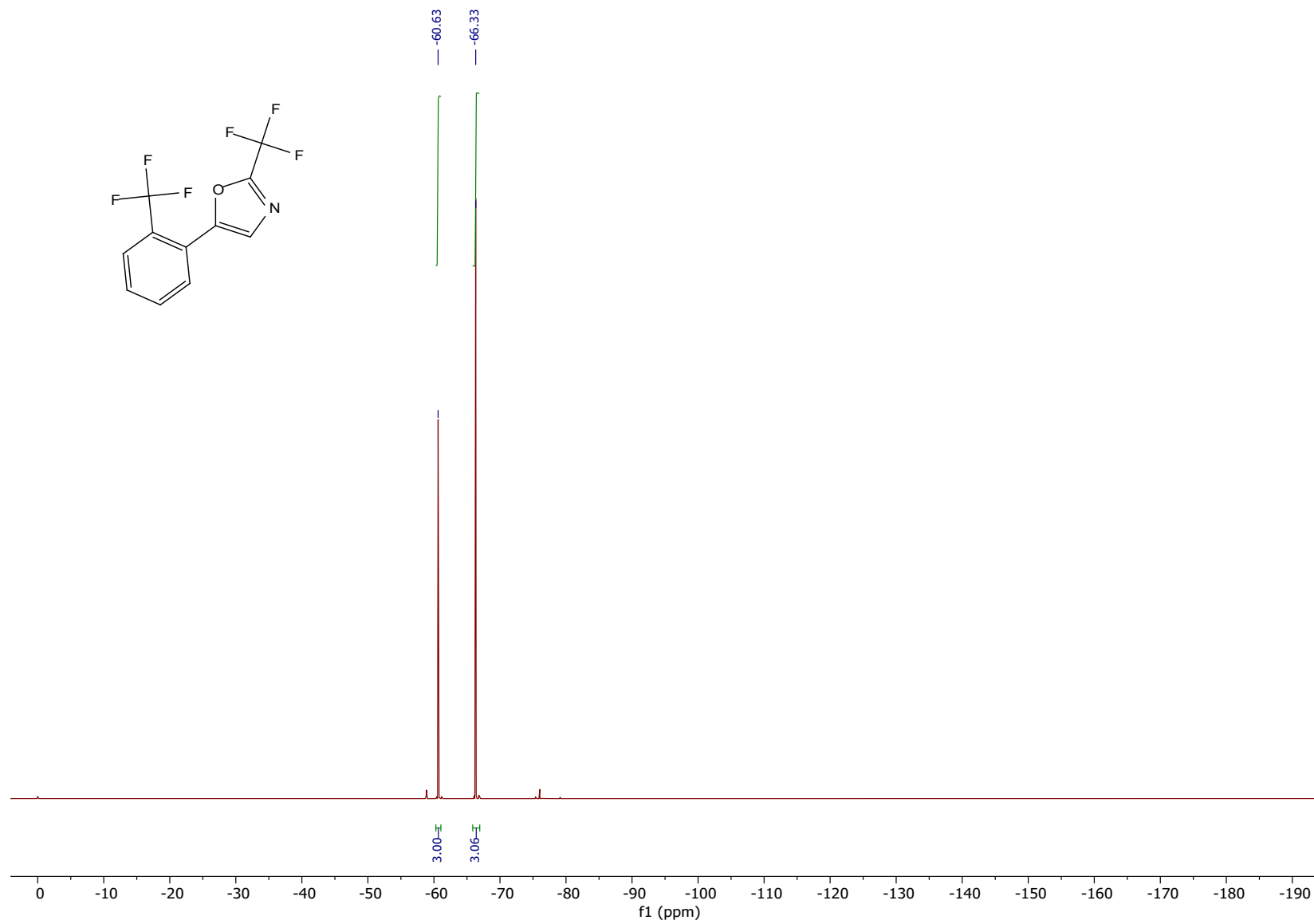
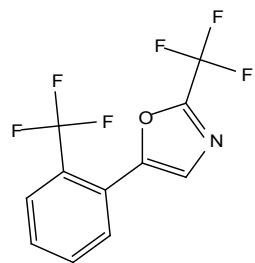
<sup>1</sup>H NMR



<sup>13</sup>C NMR

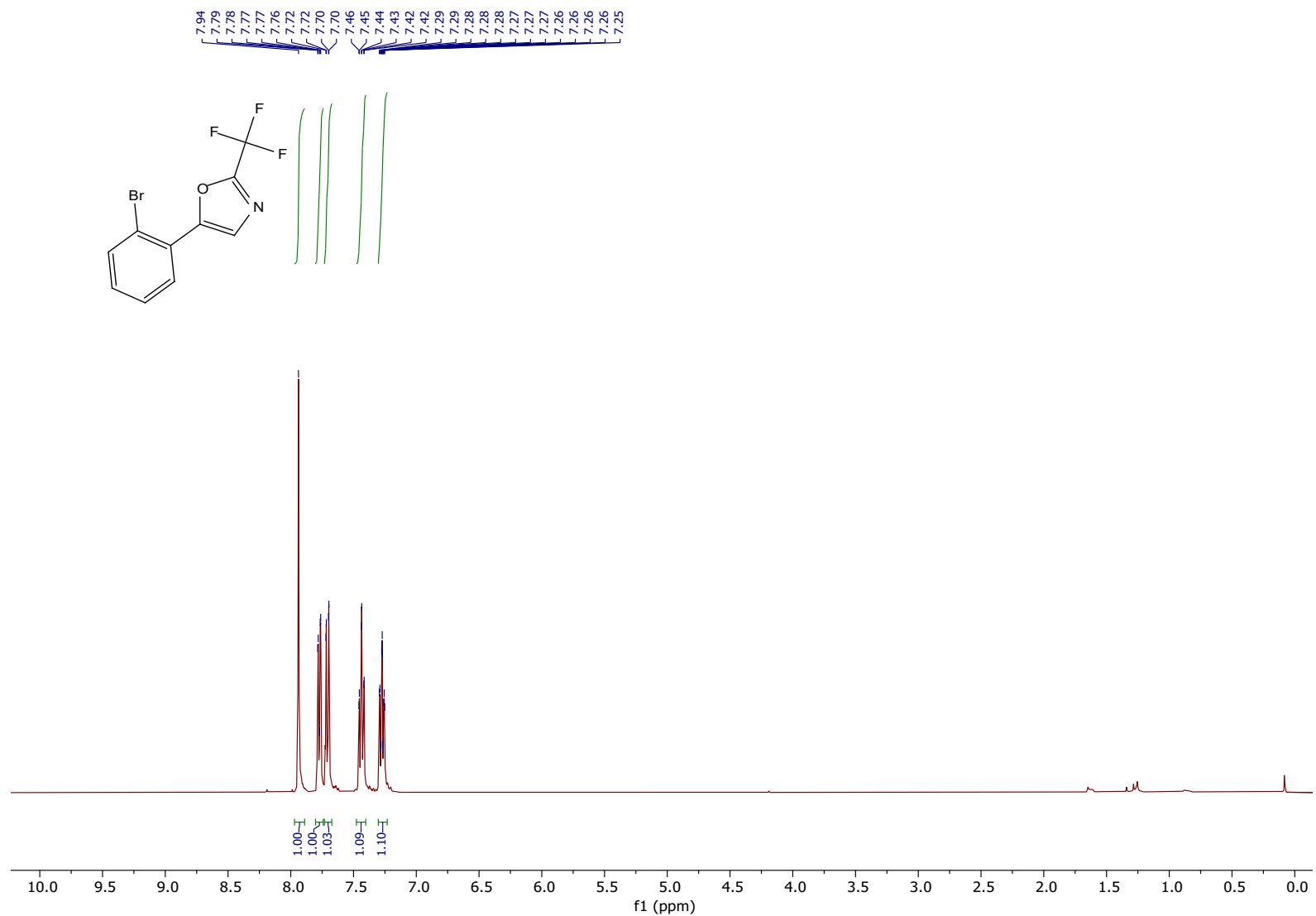


<sup>19</sup>F NMR

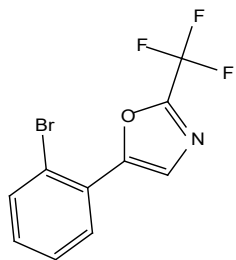


# 5-(2-Bromophenyl)-2-(trifluoromethyl)oxazole (3i)

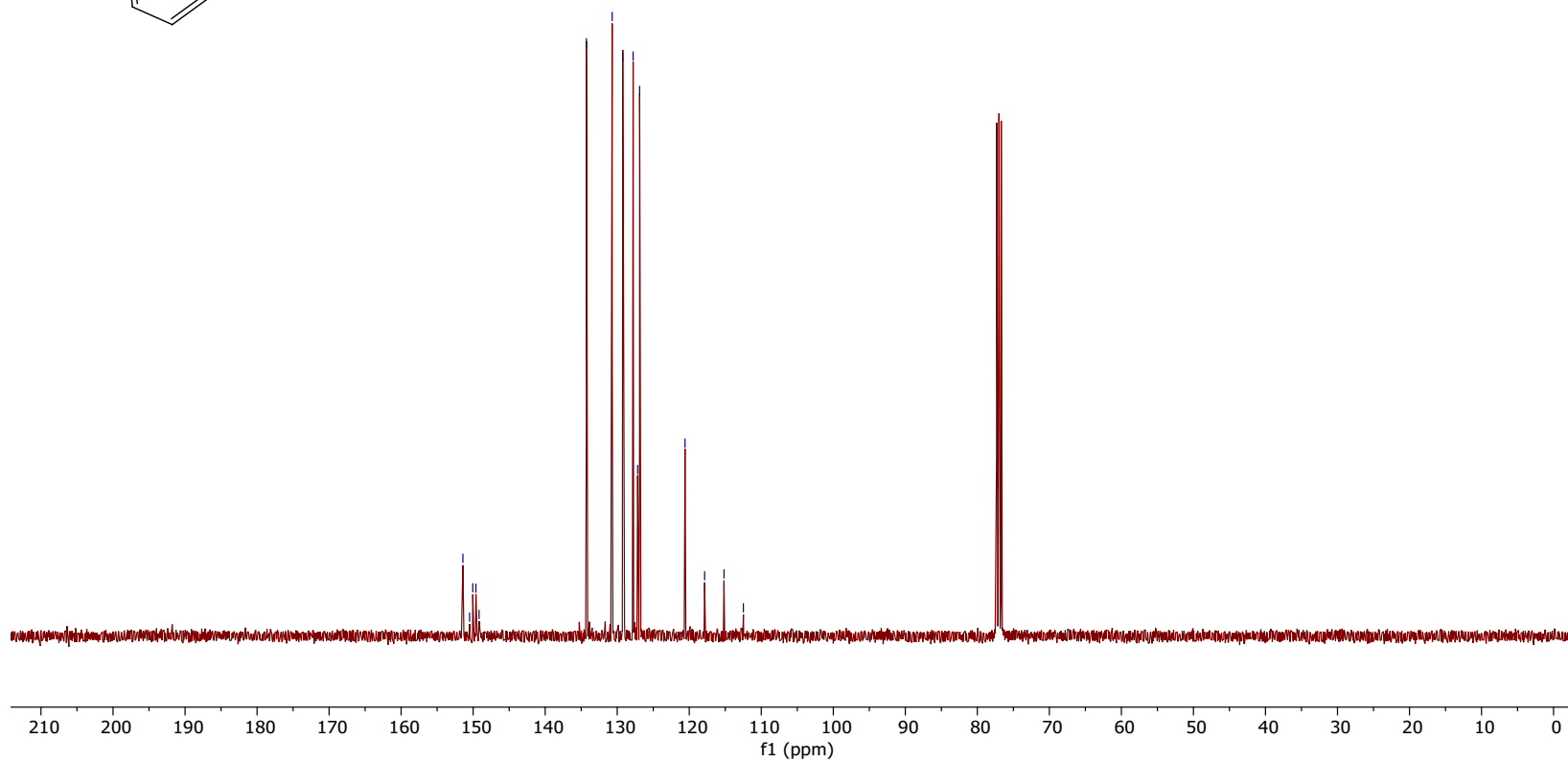
<sup>1</sup>H NMR



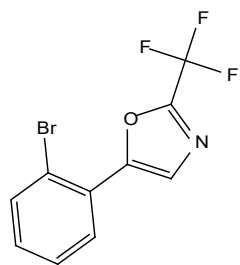
<sup>13</sup>C NMR



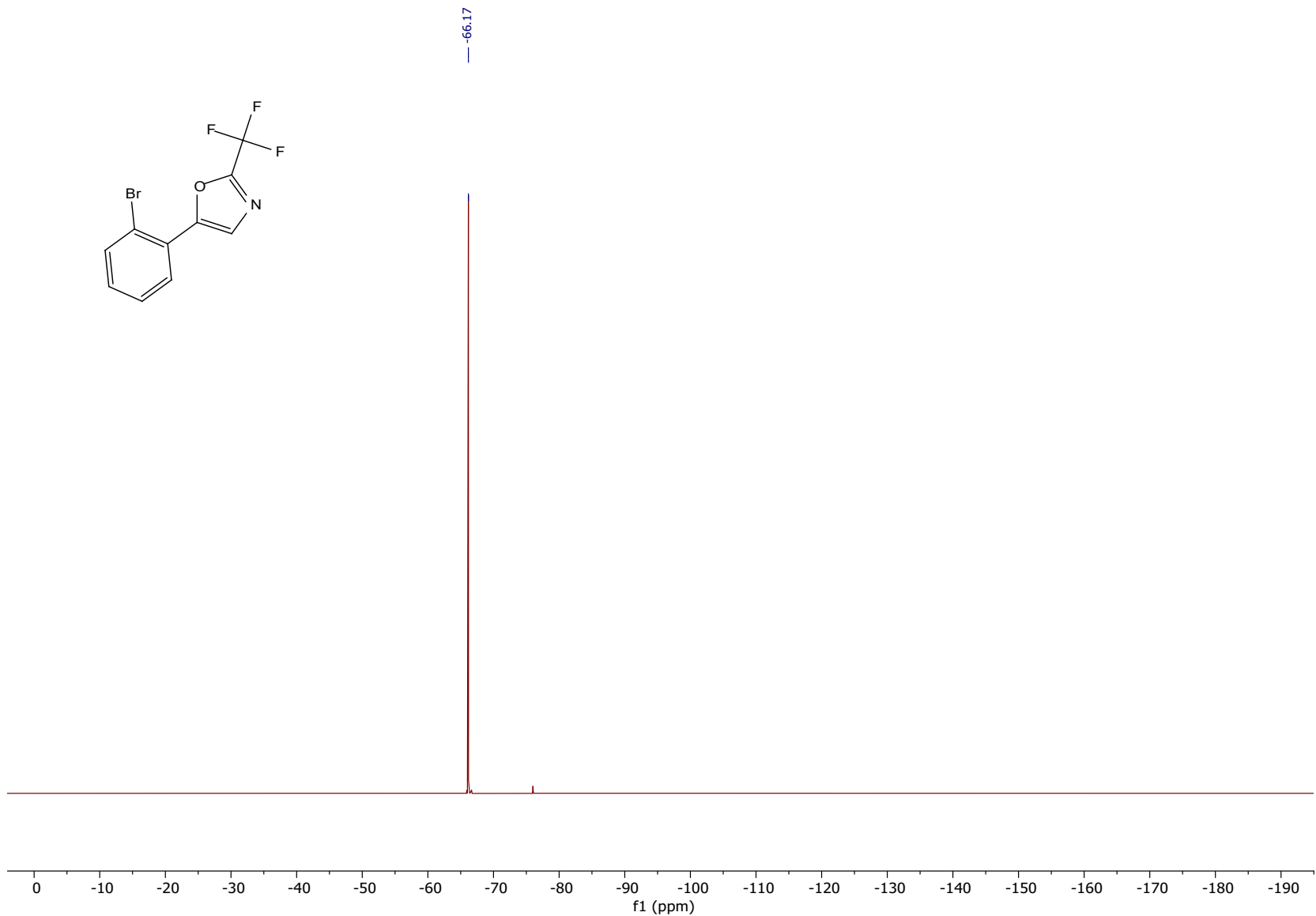
- 151.43
- 150.50
- 150.06
- 149.62
- 149.18
- 134.28
- 130.70
- 129.23
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- 127.17
- 126.89
- 120.58
- 117.86
- 115.17
- 112.48



<sup>19</sup>F NMR



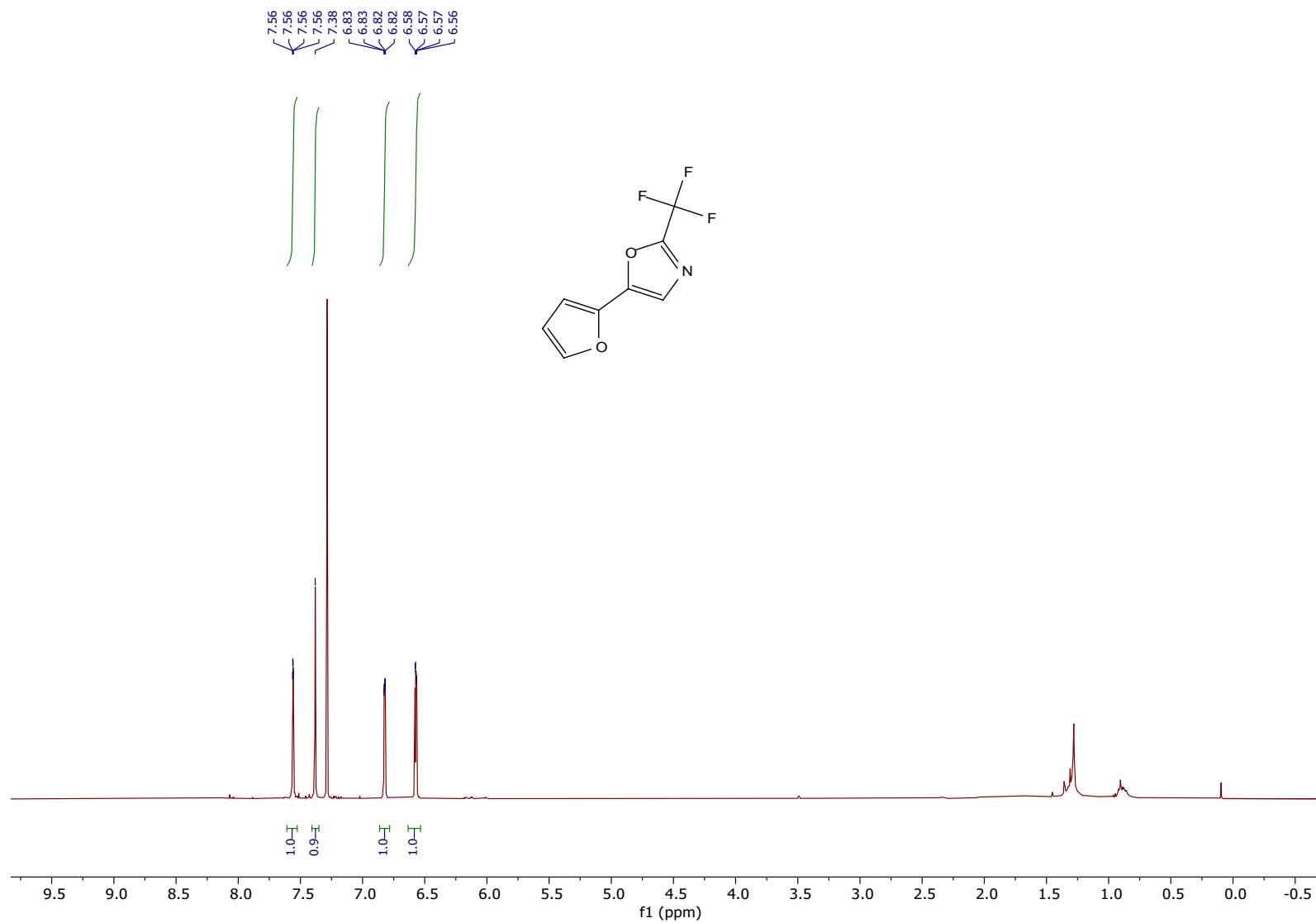
-66.17



SI31

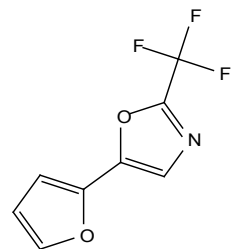
5-(Furan-2-yl)-2-(trifluoromethyl)oxazole (**3j**)

$^1\text{H}$  NMR



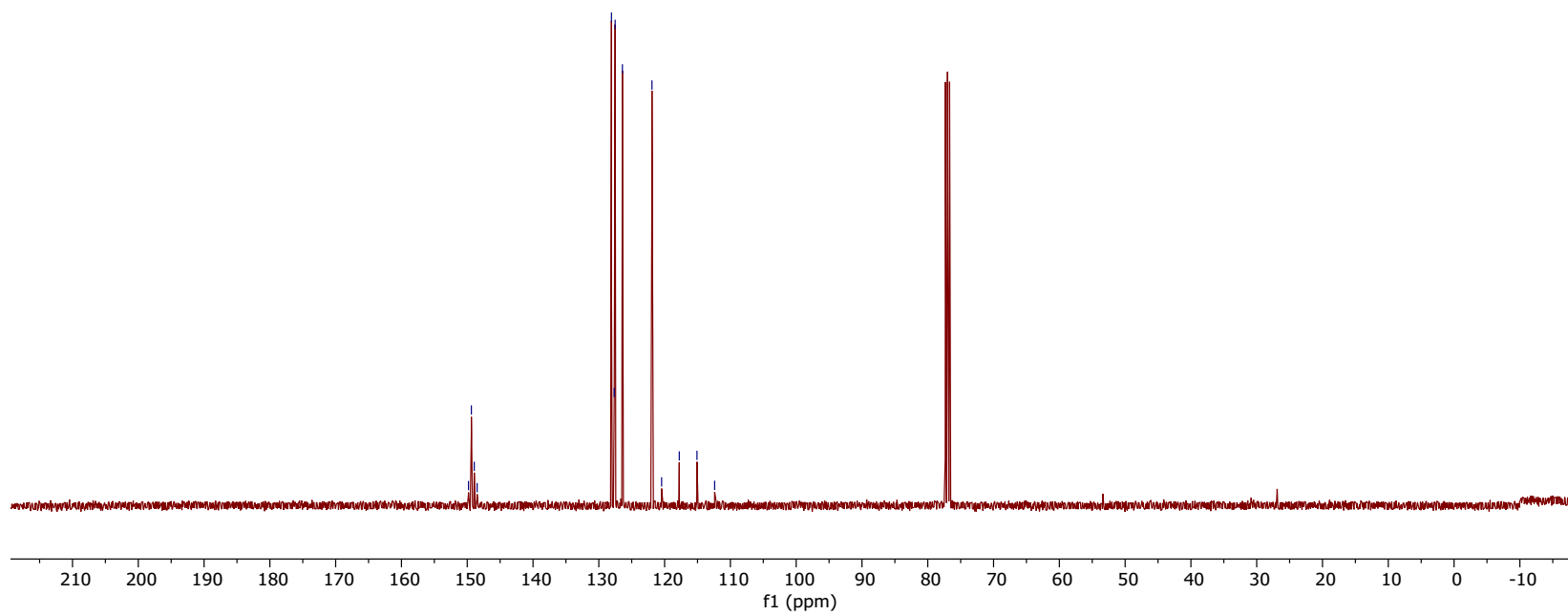


$^{13}\text{C}$  NMR

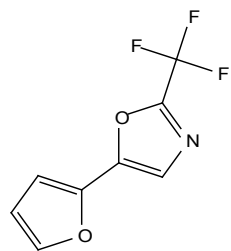


149.81  
149.37  
148.93  
148.49

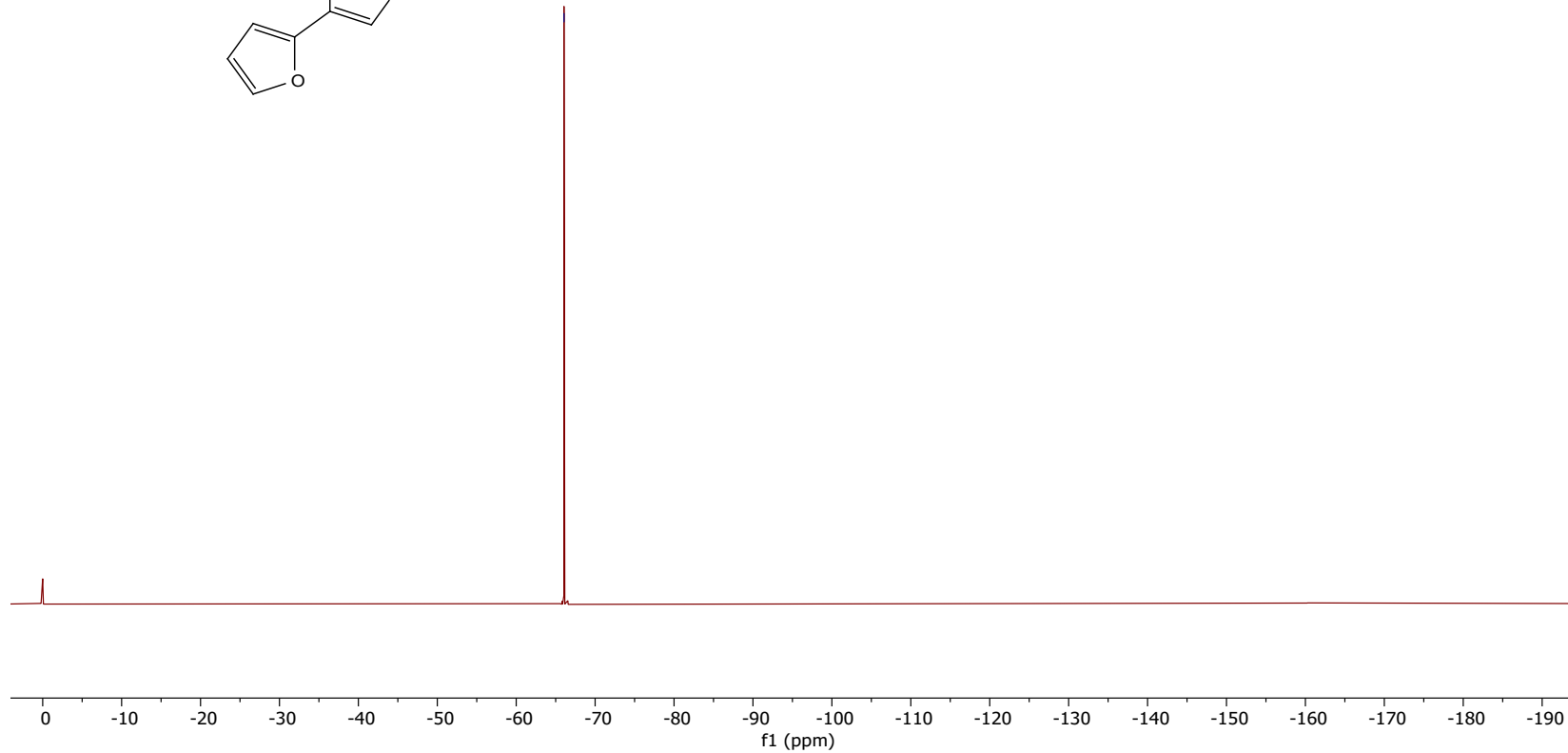
128.08  
127.66  
127.52  
126.41  
121.92  
120.45  
117.77  
115.08  
112.39



<sup>19</sup>F NMR

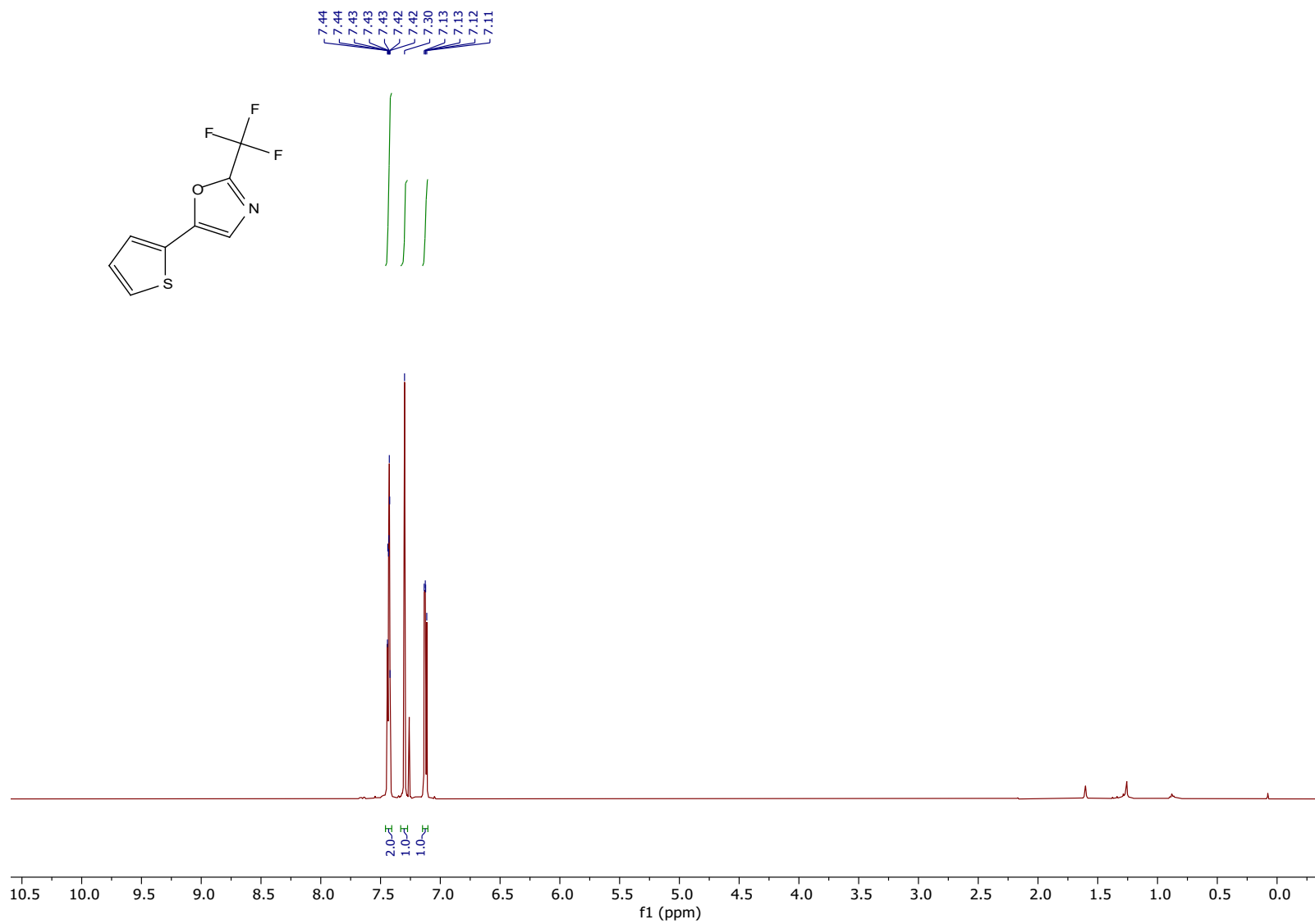


-66.05

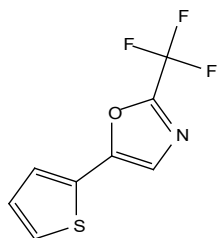


5-(Thiophen-2-yl)-2-(trifluoromethyl)oxazole (**3k**)

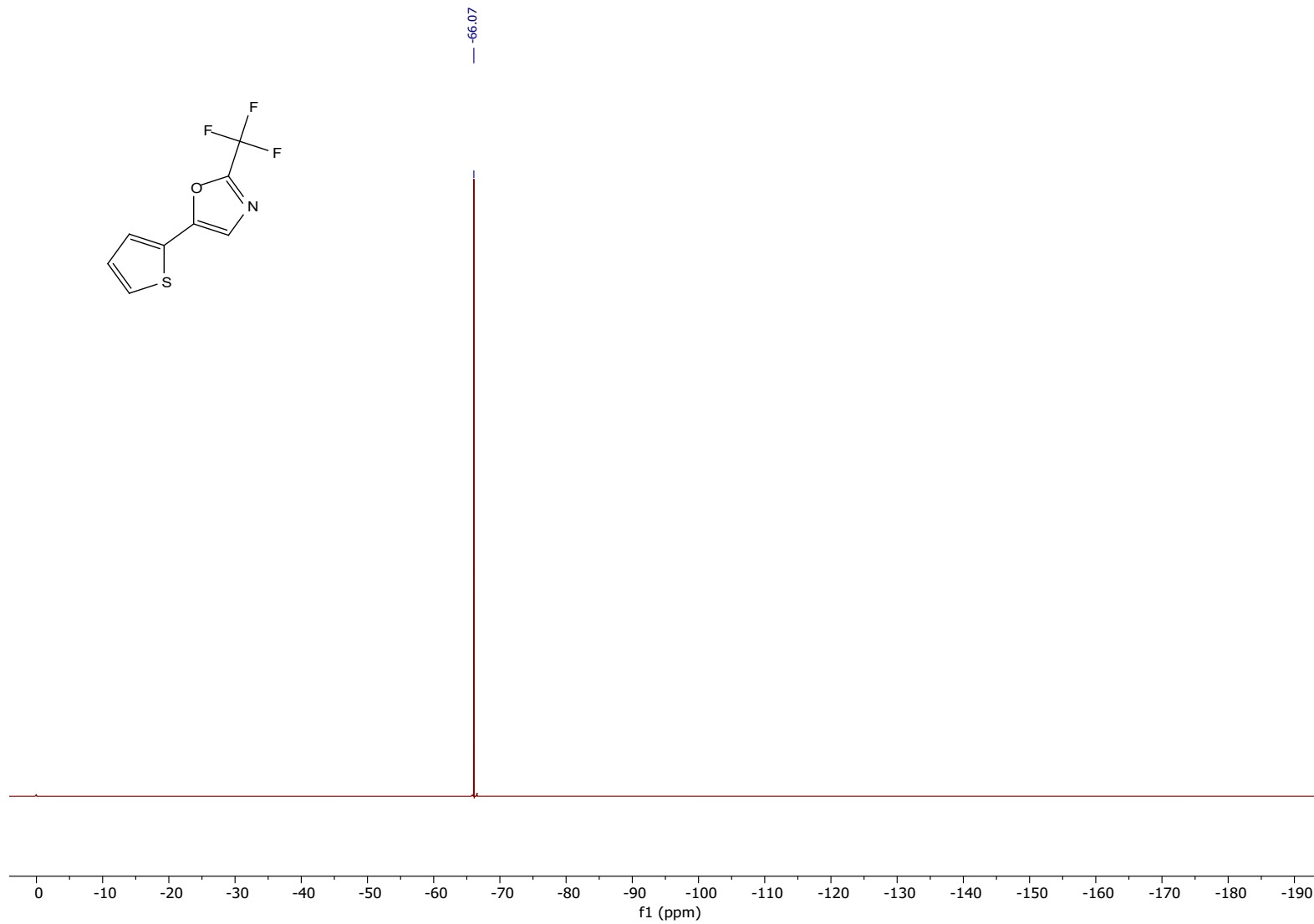
$^1\text{H}$  NMR



<sup>19</sup>F NMR

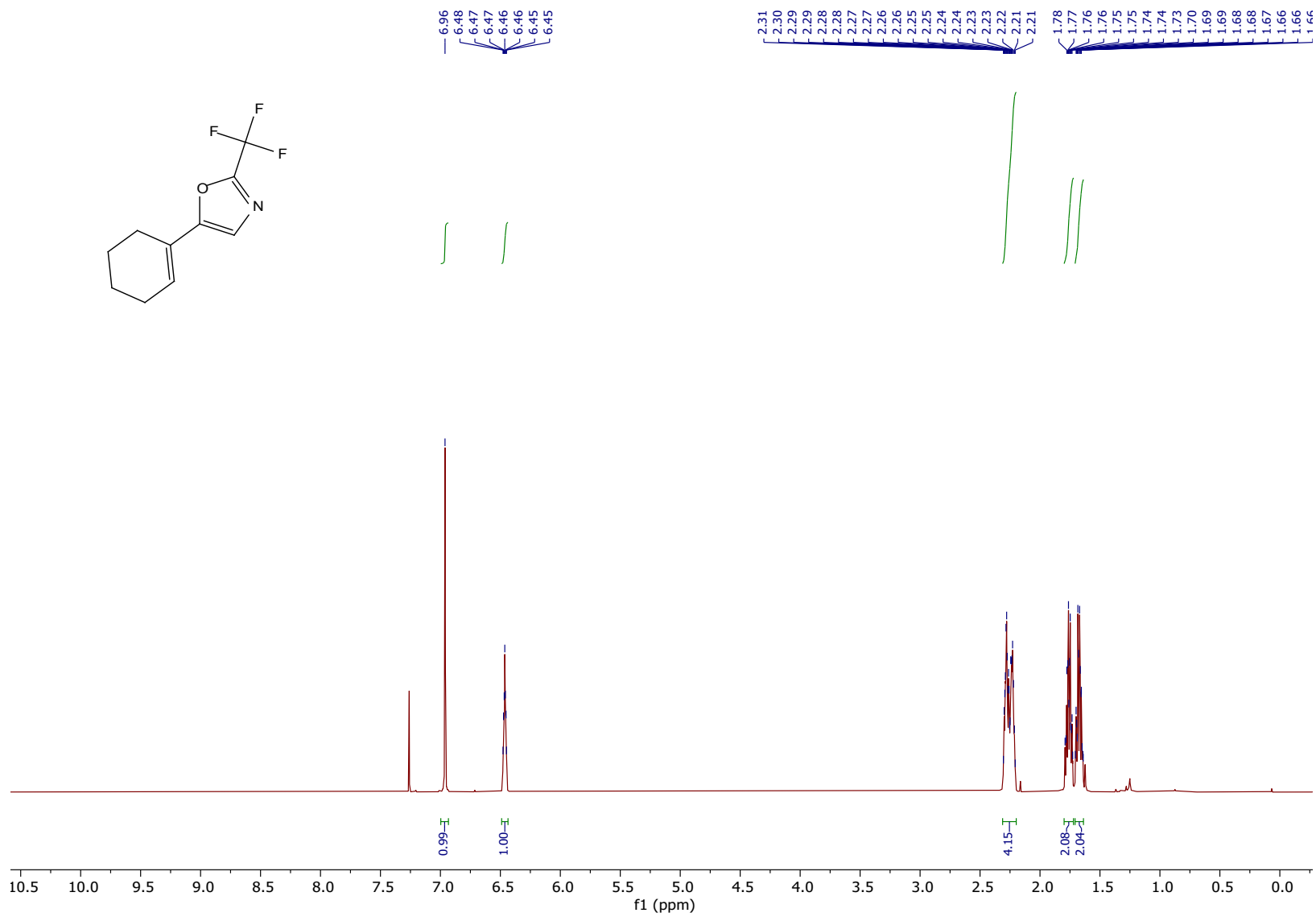


-66.07

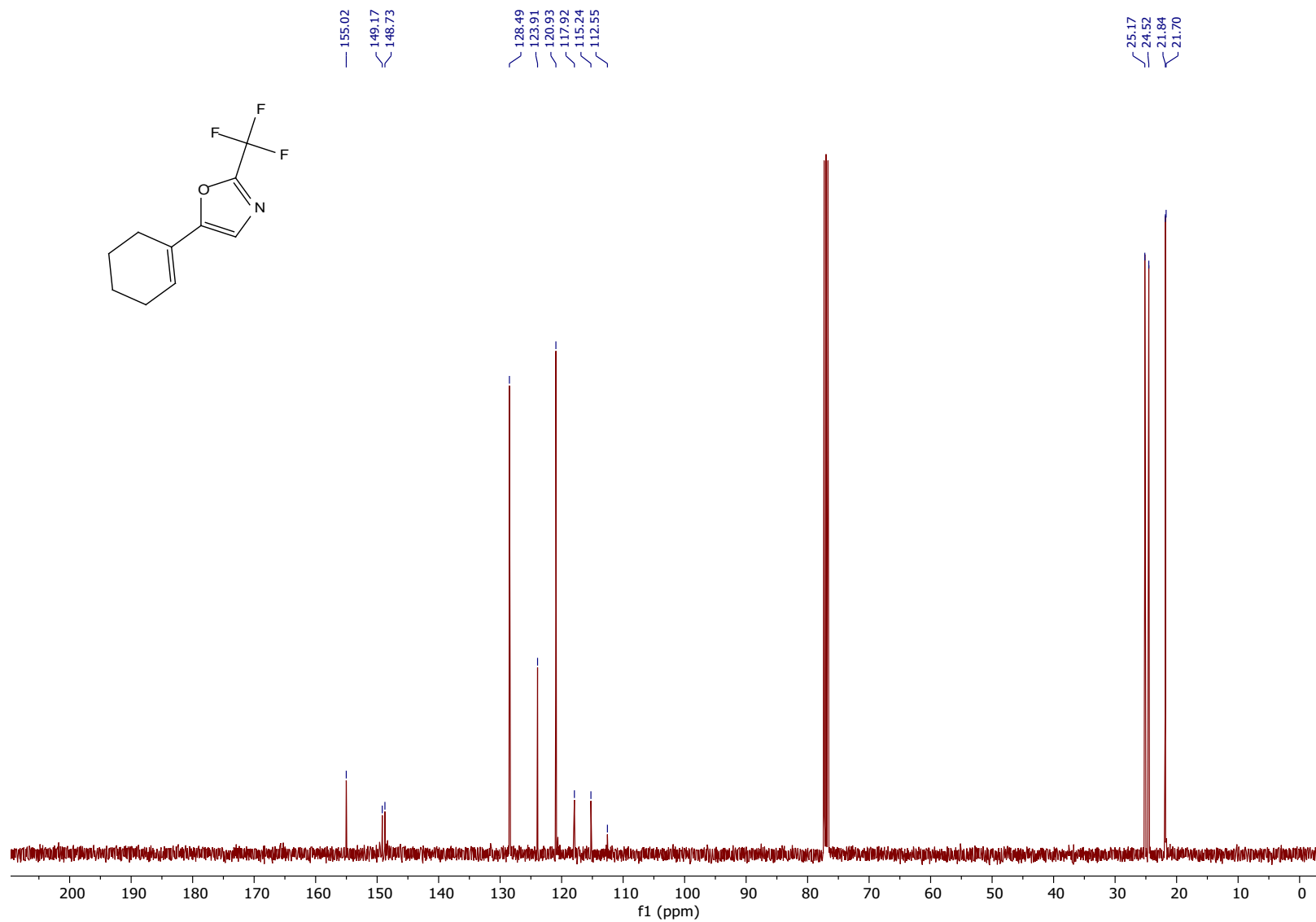


# 5-(Cyclohex-1-en-1-yl)-2-(trifluoromethyl)oxazole (**3**)

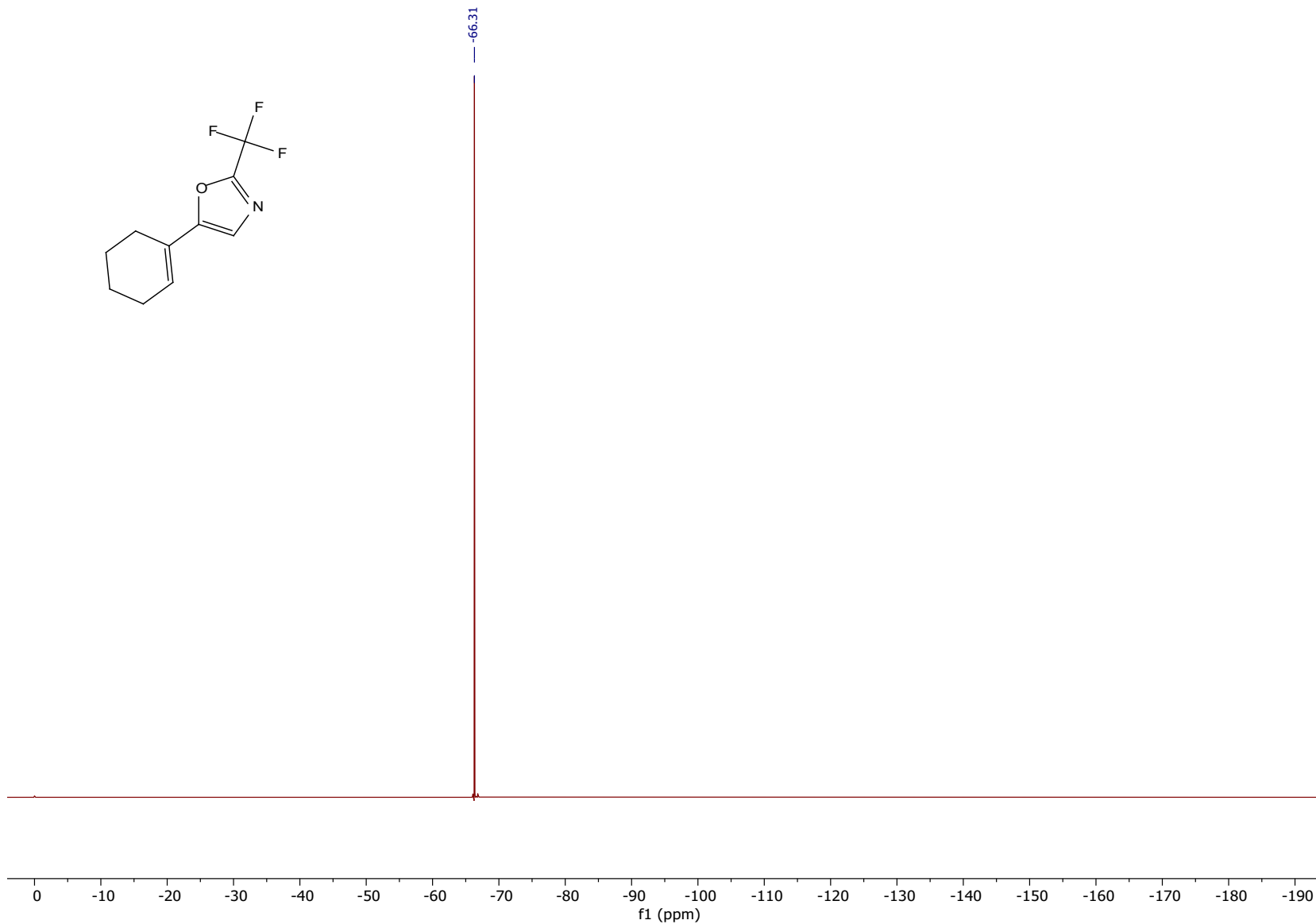
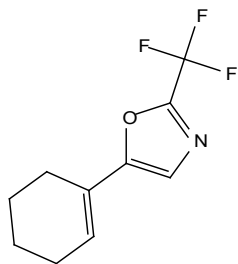
<sup>1</sup>H NMR



<sup>13</sup>C NMR



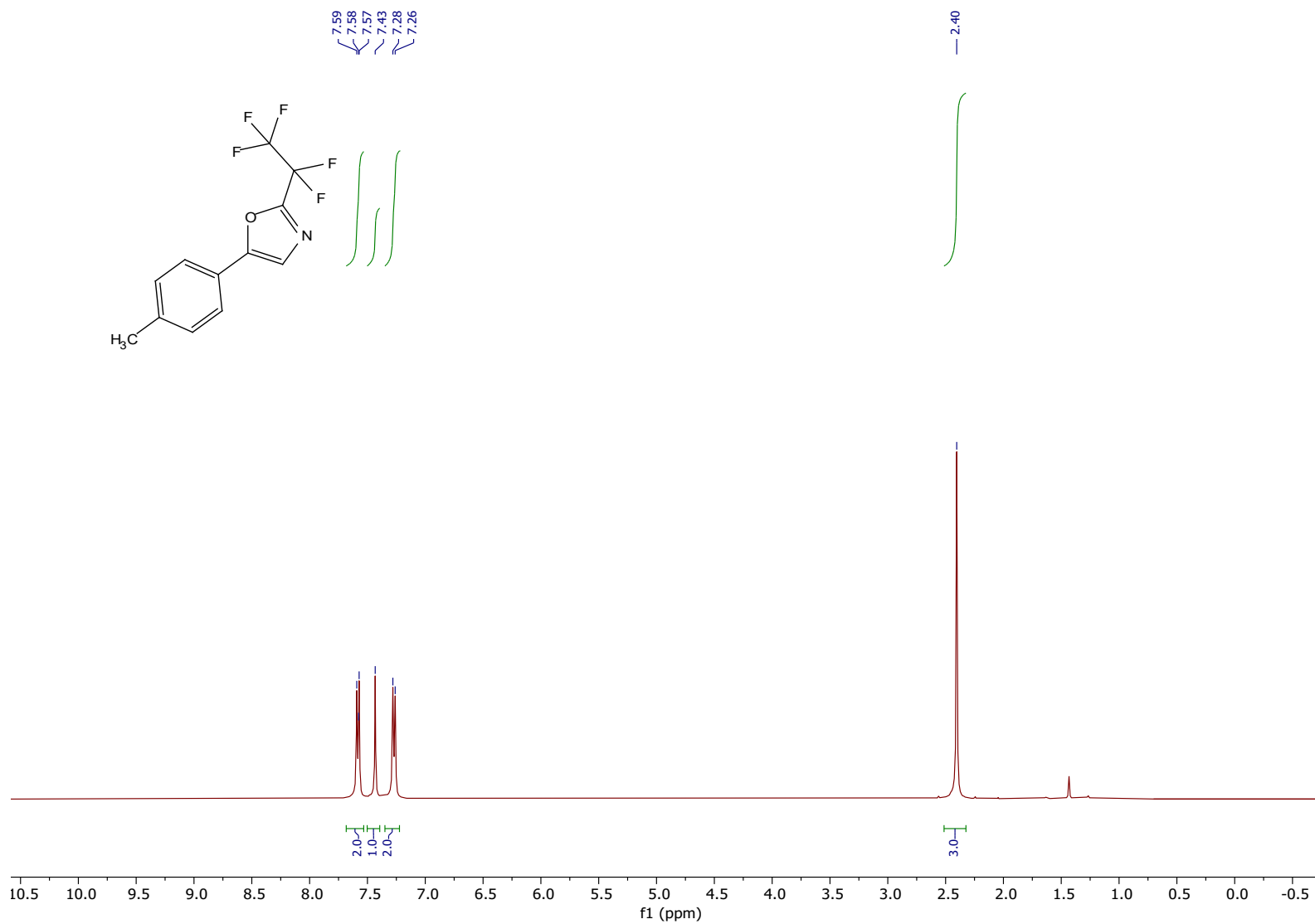
<sup>19</sup>F NMR



SI39

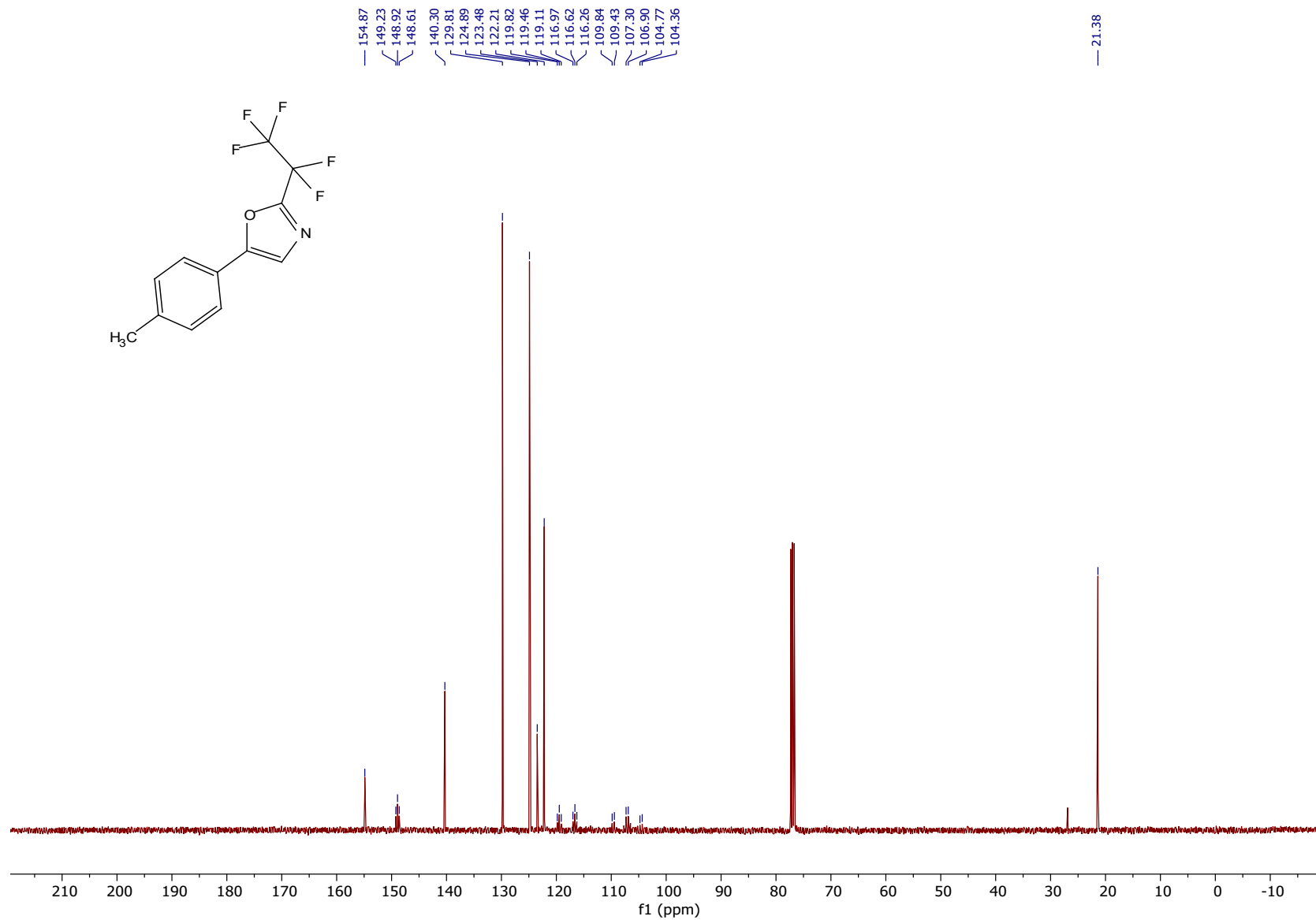
2-(Perfluoroethyl)-5-(p-tolyl)oxazole (**3m**)

$^1\text{H}$  NMR

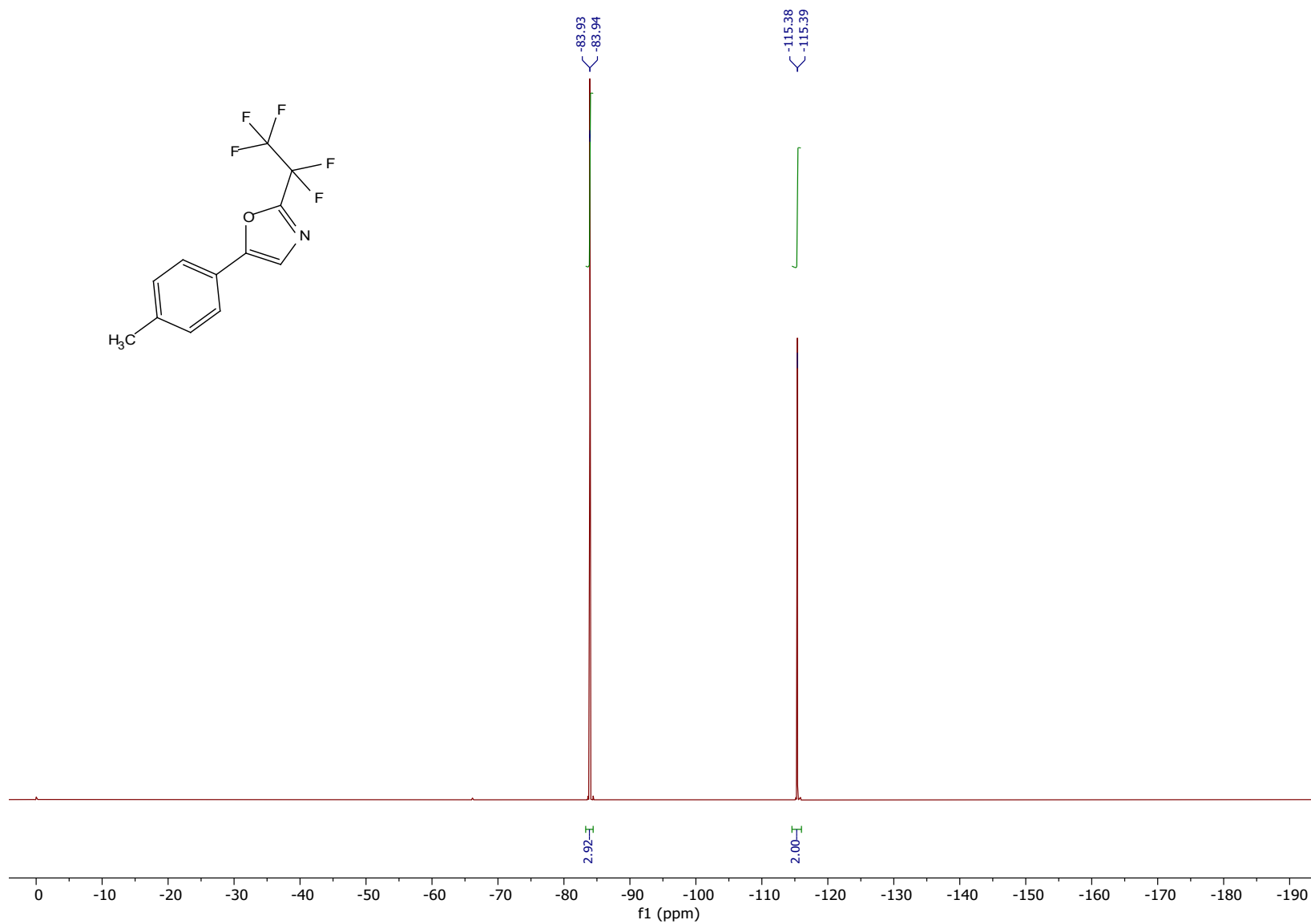
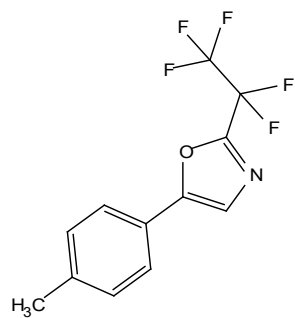




<sup>13</sup>C NMR

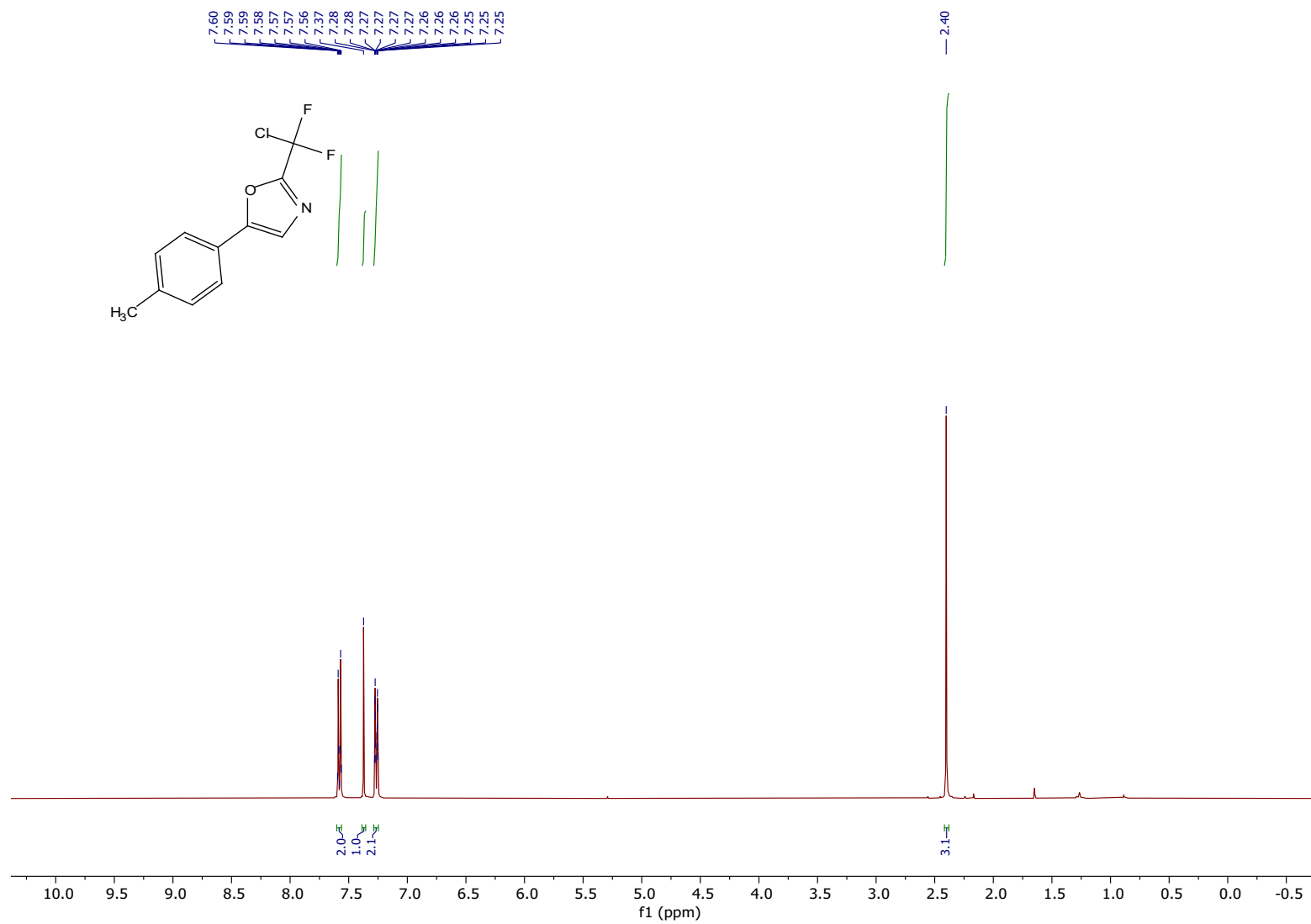


<sup>19</sup>F NMR

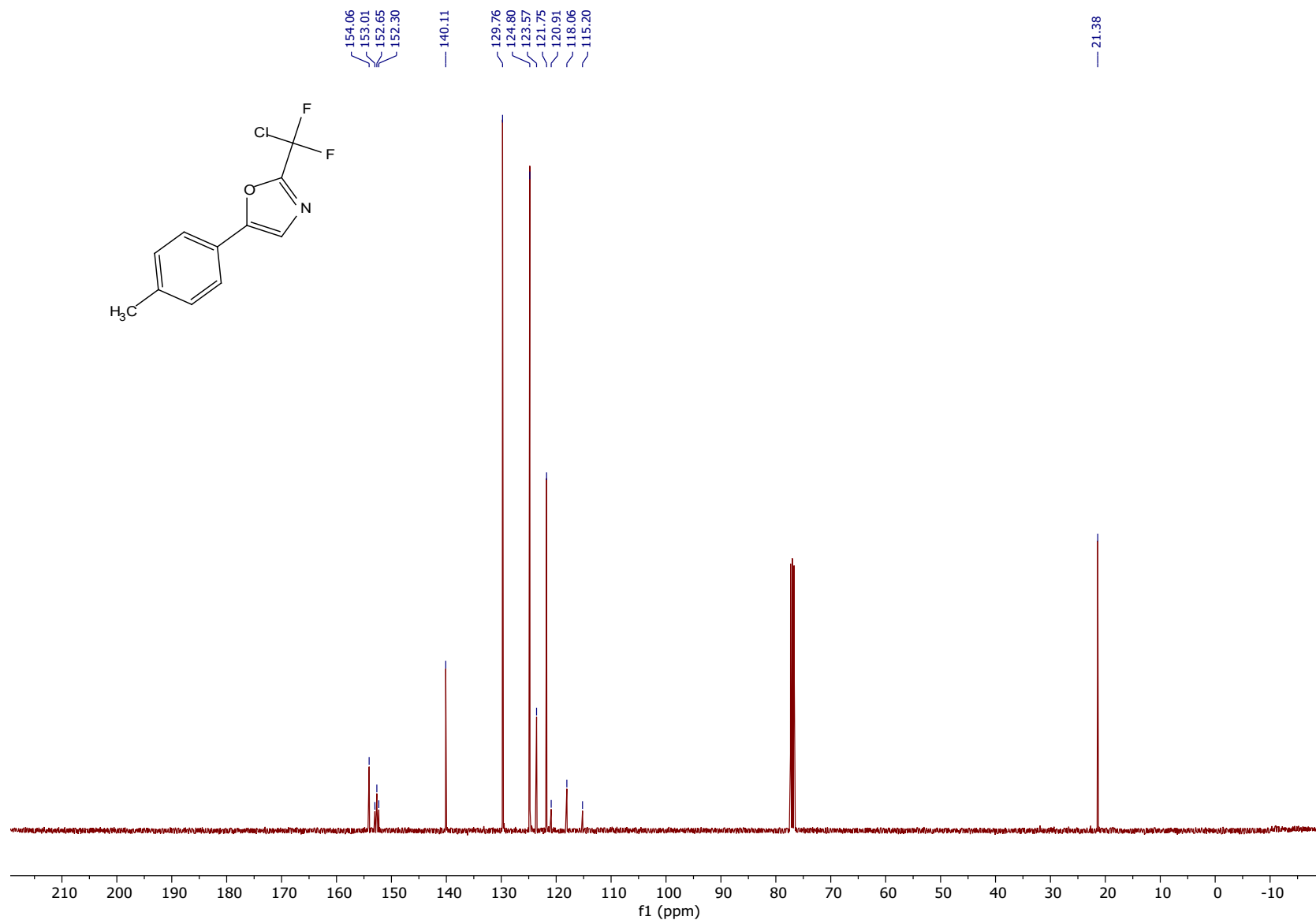
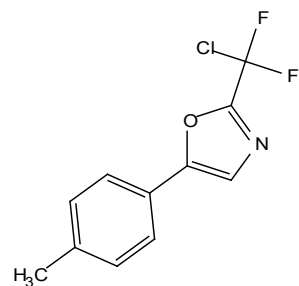


# 2-(Chlorodifluoromethyl)-5-(p-tolyl)oxazole (**3n**)

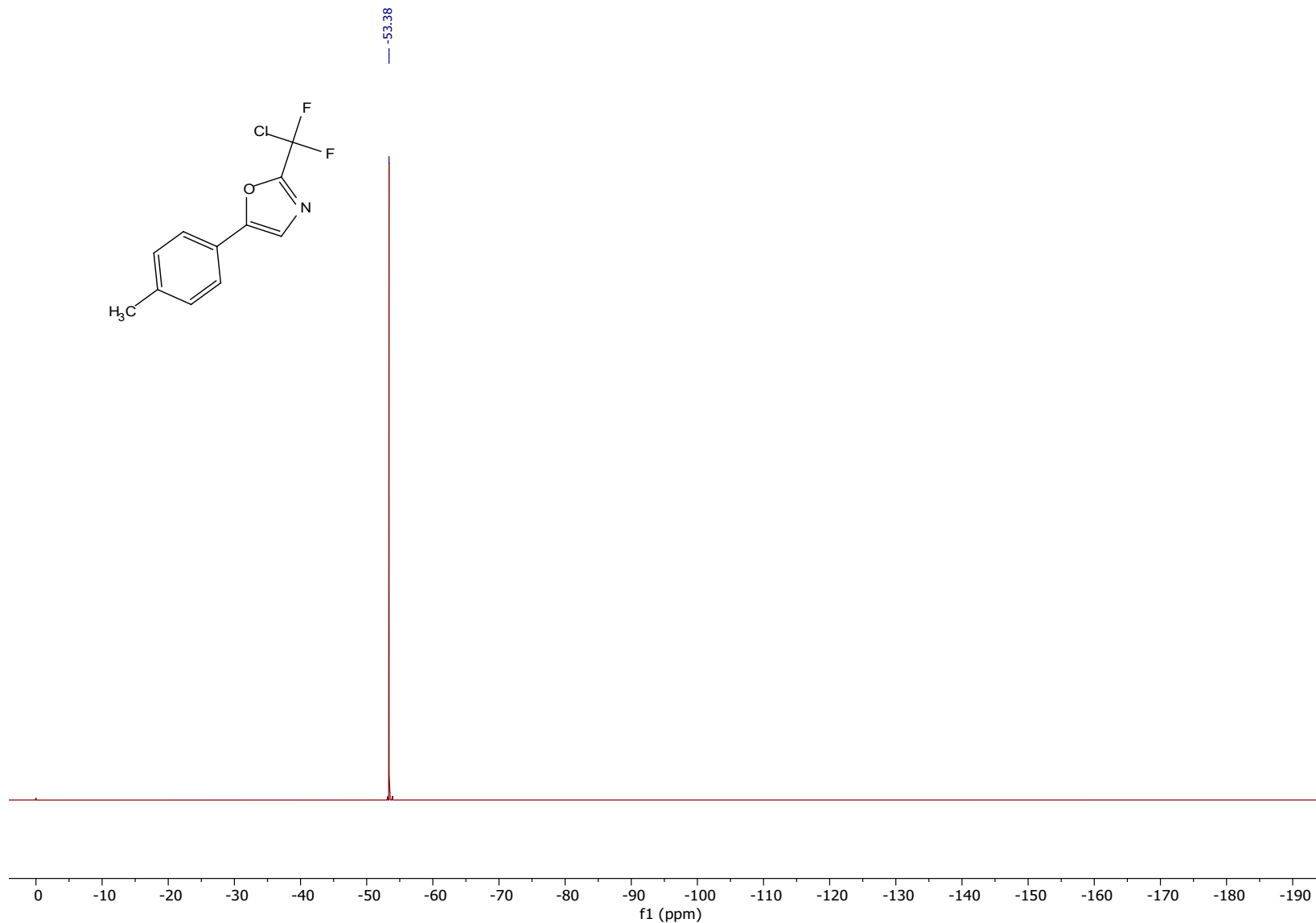
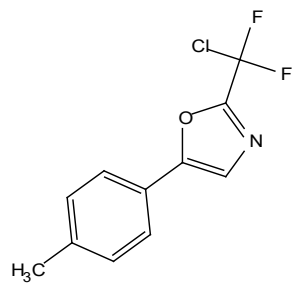
<sup>1</sup>H NMR



<sup>13</sup>C NMR



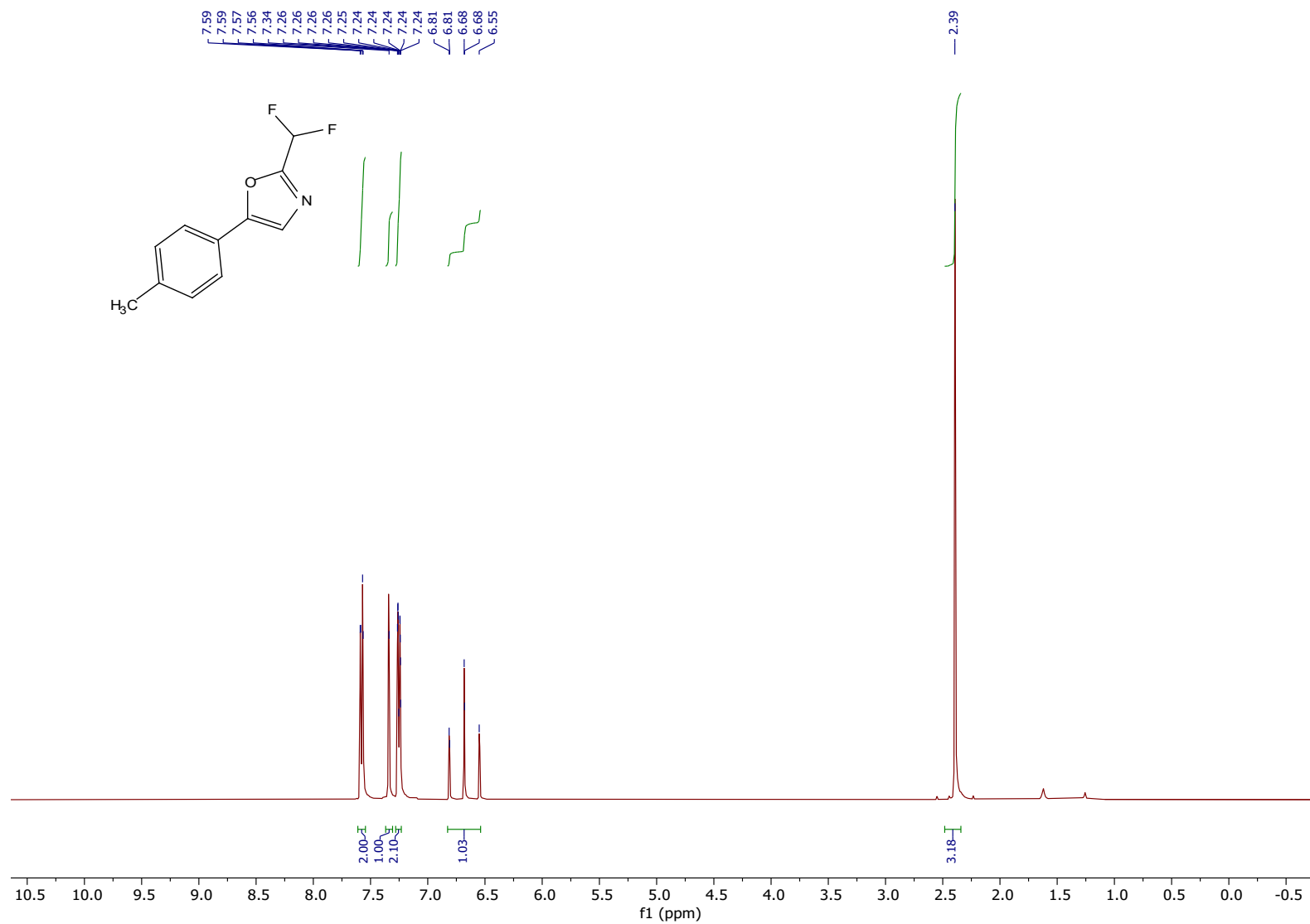
<sup>19</sup>F NMR



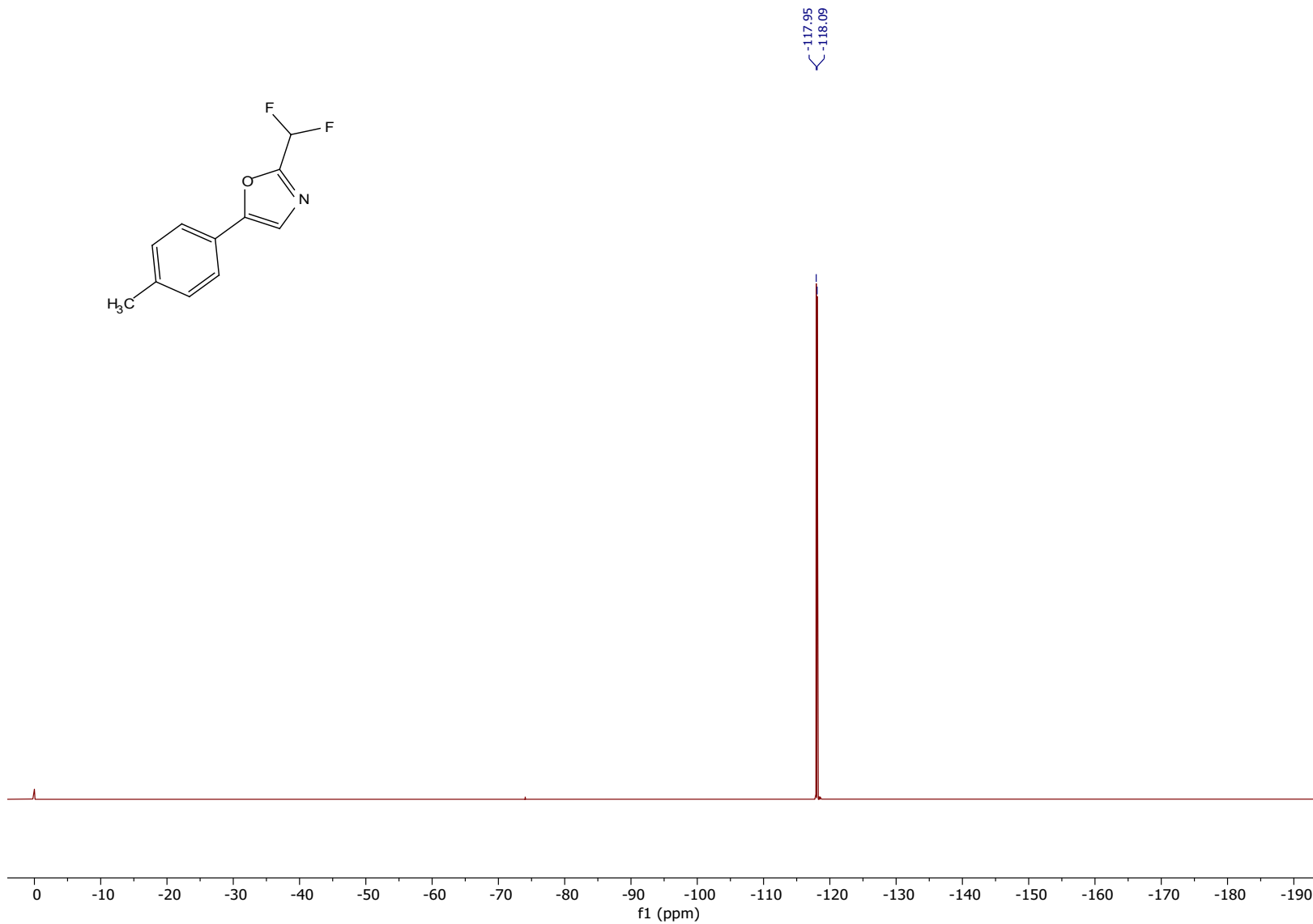
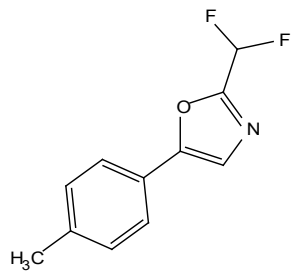
SI45

2-(Difluoromethyl)-5-(p-tolyl)oxazole (**3o**)

<sup>1</sup>H NMR

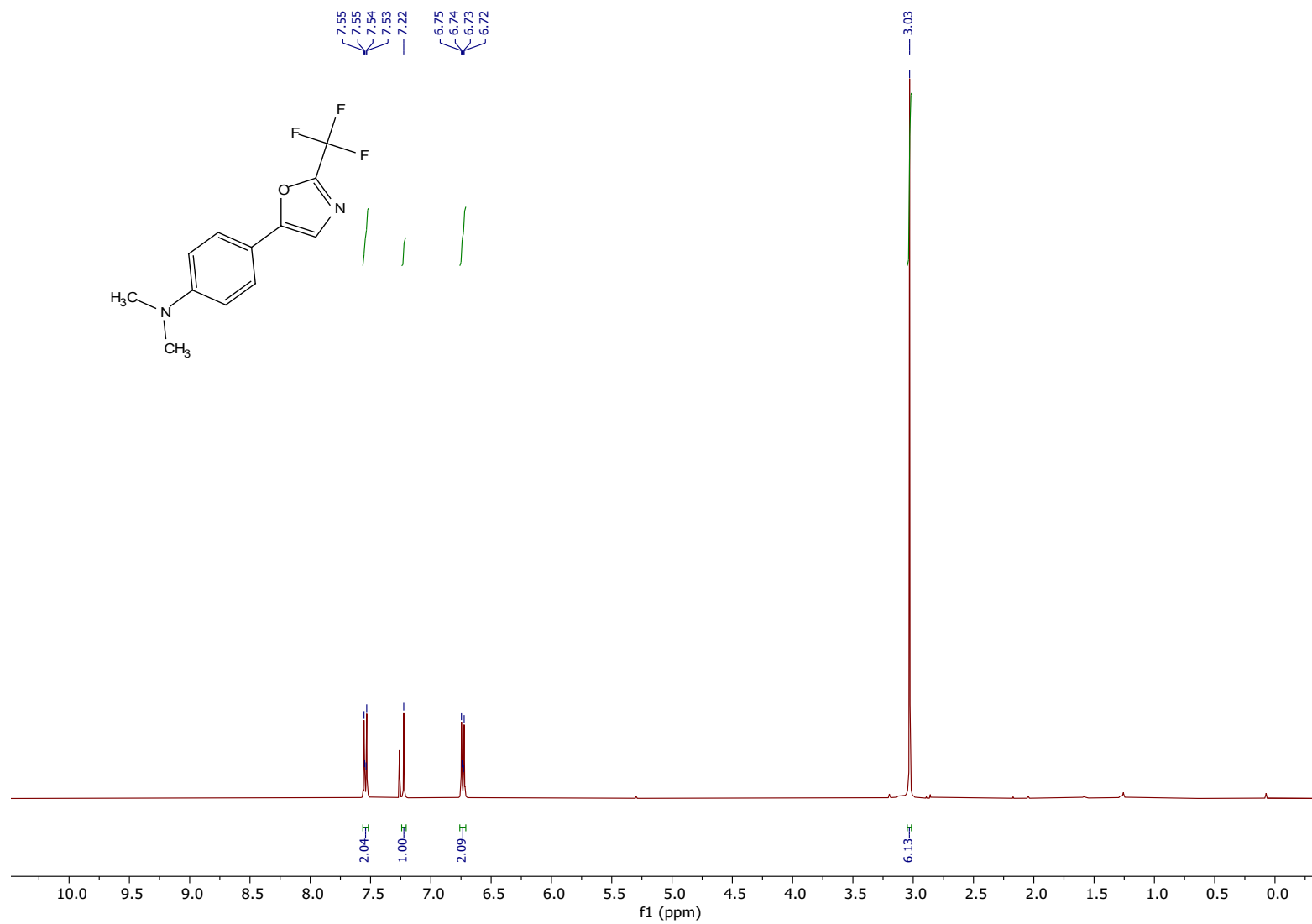


<sup>19</sup>F NMR



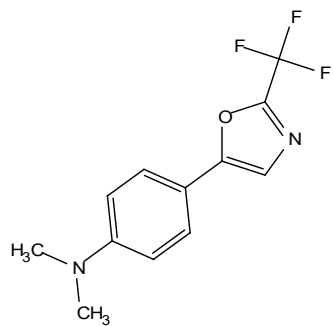
*N,N*-dimethyl-4-(2-(trifluoromethyl)oxazol-5-yl)aniline (**3p**)

$^1\text{H}$  NMR





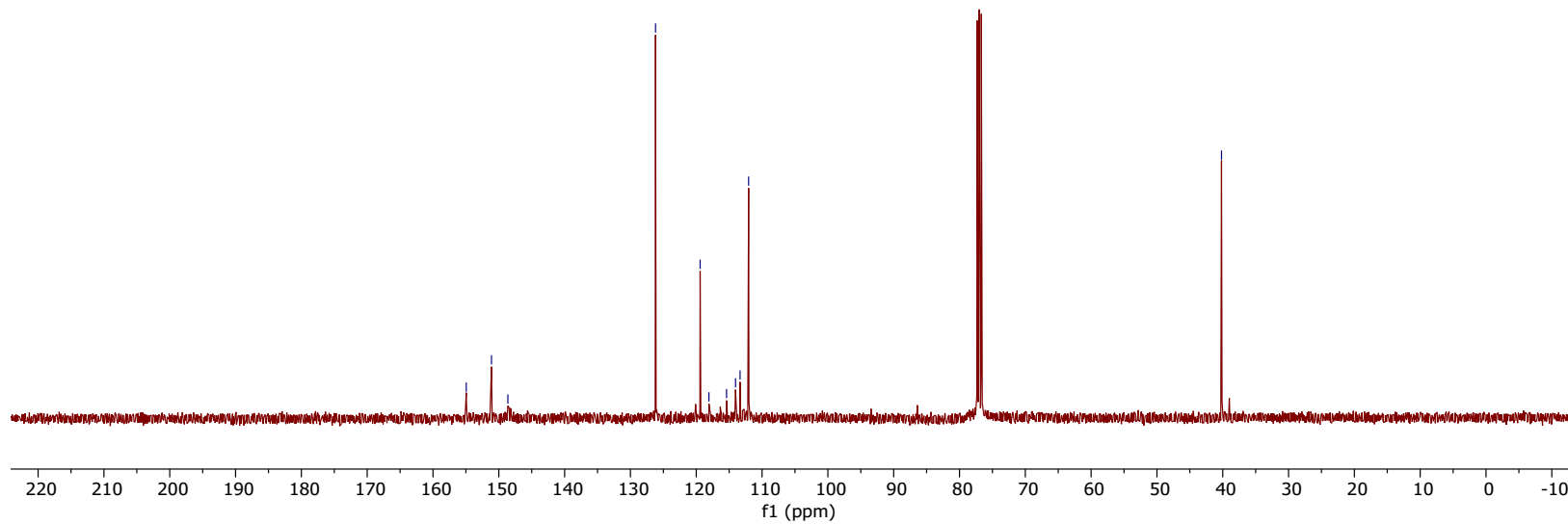
<sup>13</sup>C NMR



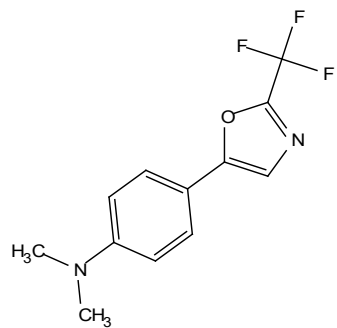
154.95  
151.12  
148.62

126.19  
119.41  
118.07  
115.40  
114.03  
113.34  
112.04

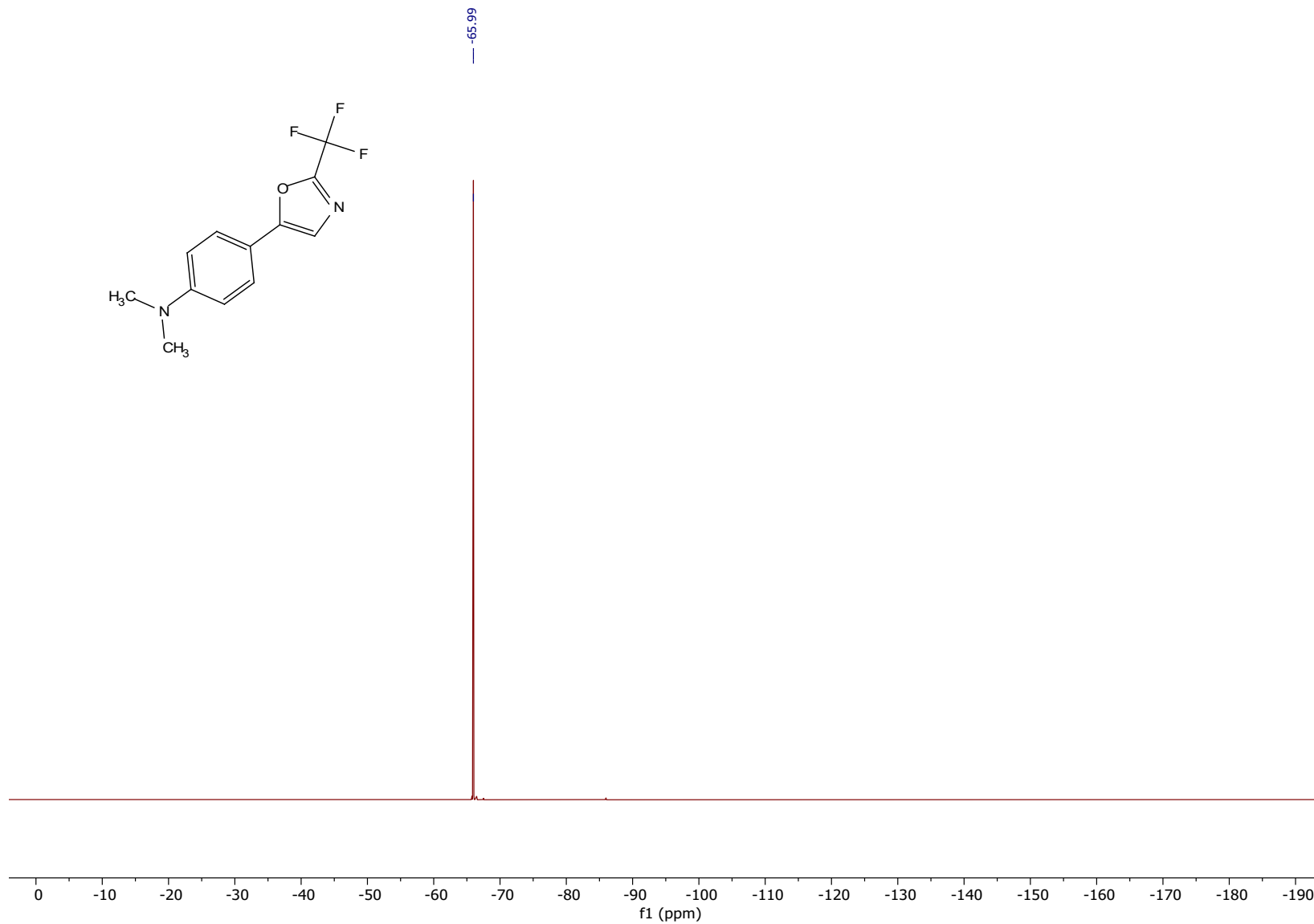
40.19



<sup>19</sup>F NMR



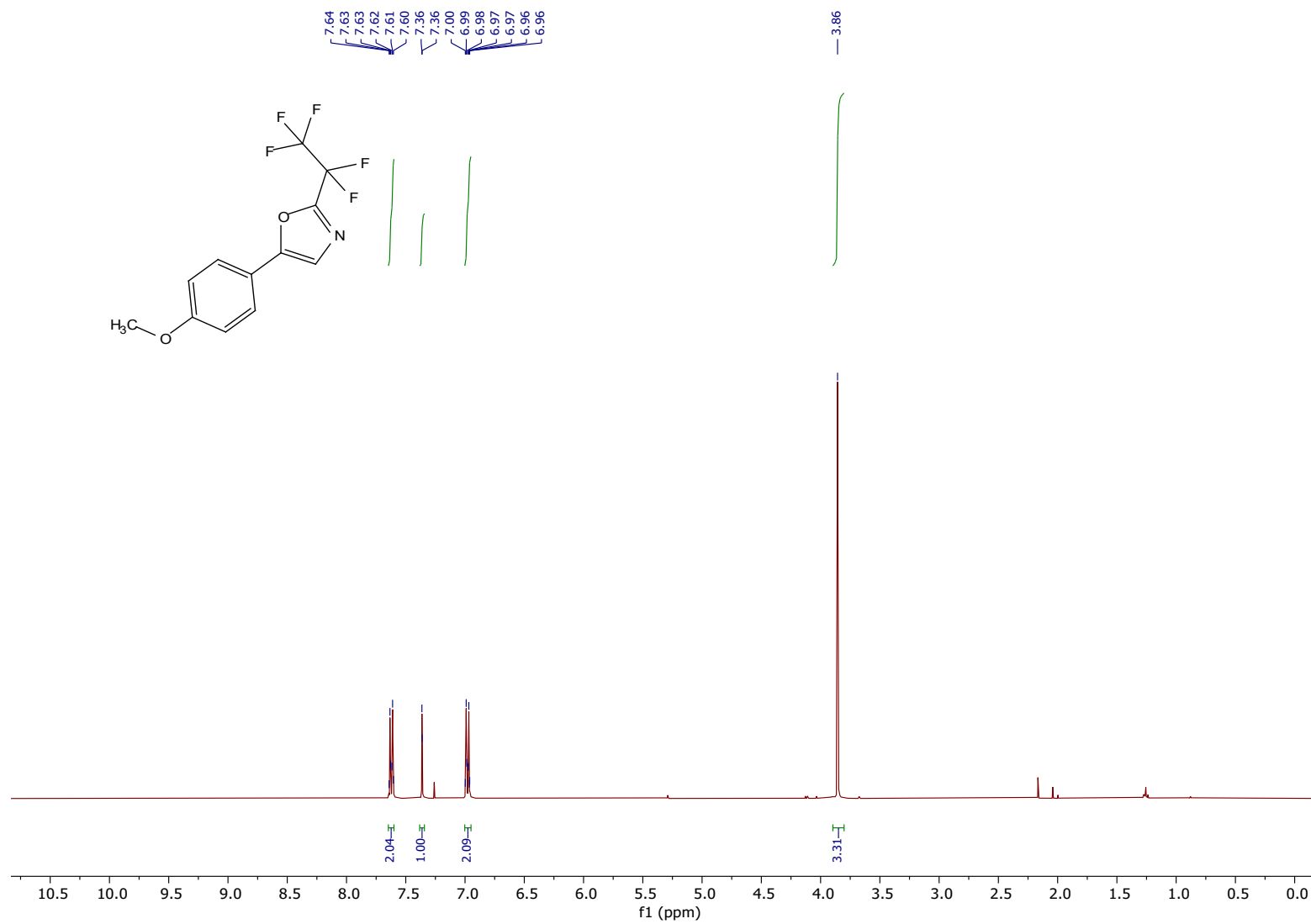
-65.99



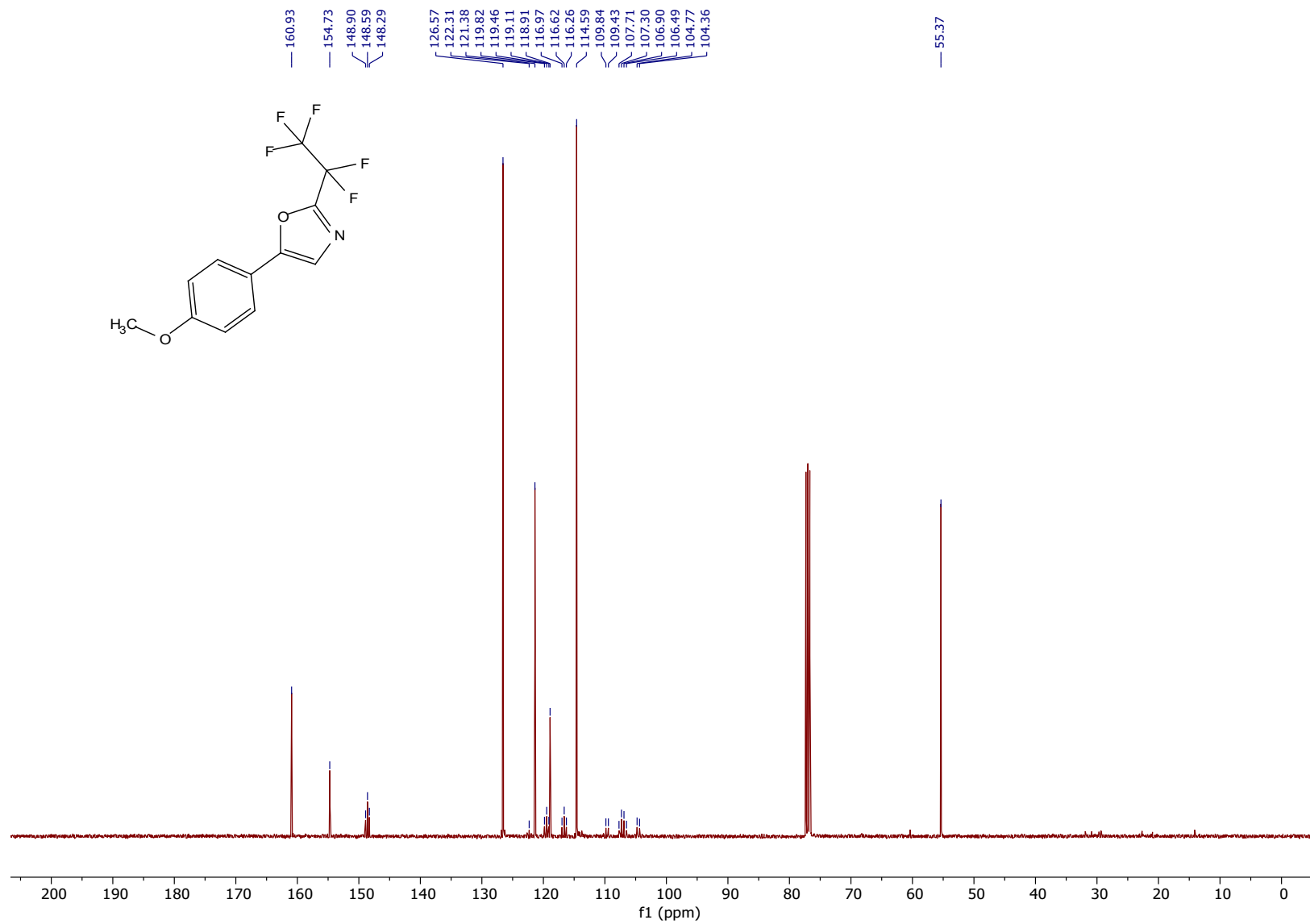
SI50

5-(4-Methoxyphenyl)-2-(perfluoroethyl)oxazole (**3q**)

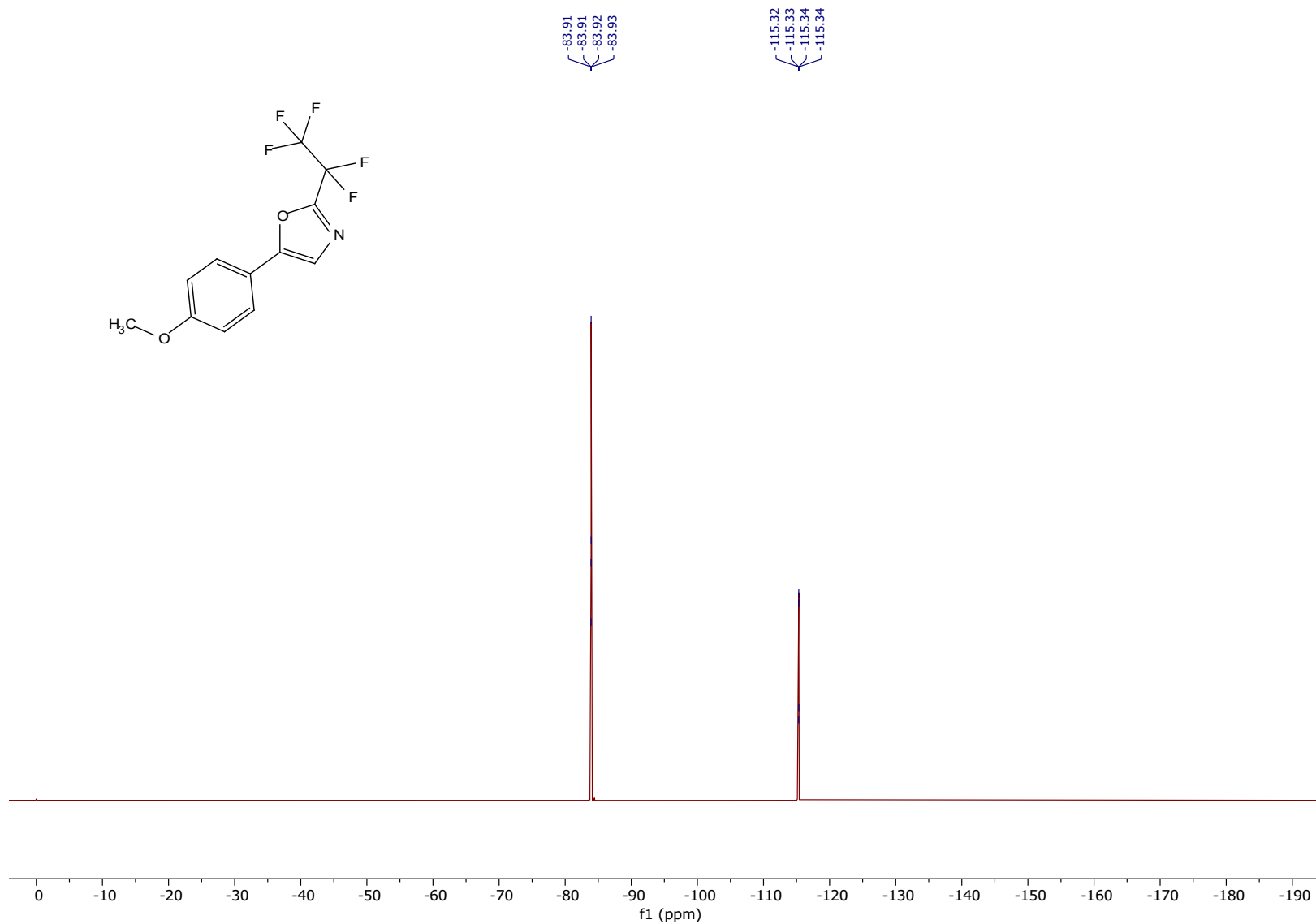
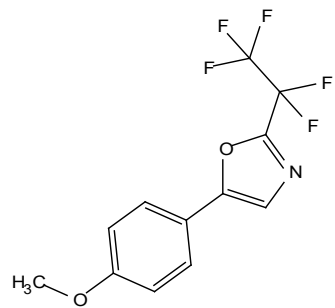
<sup>1</sup>H NMR



<sup>13</sup>C NMR

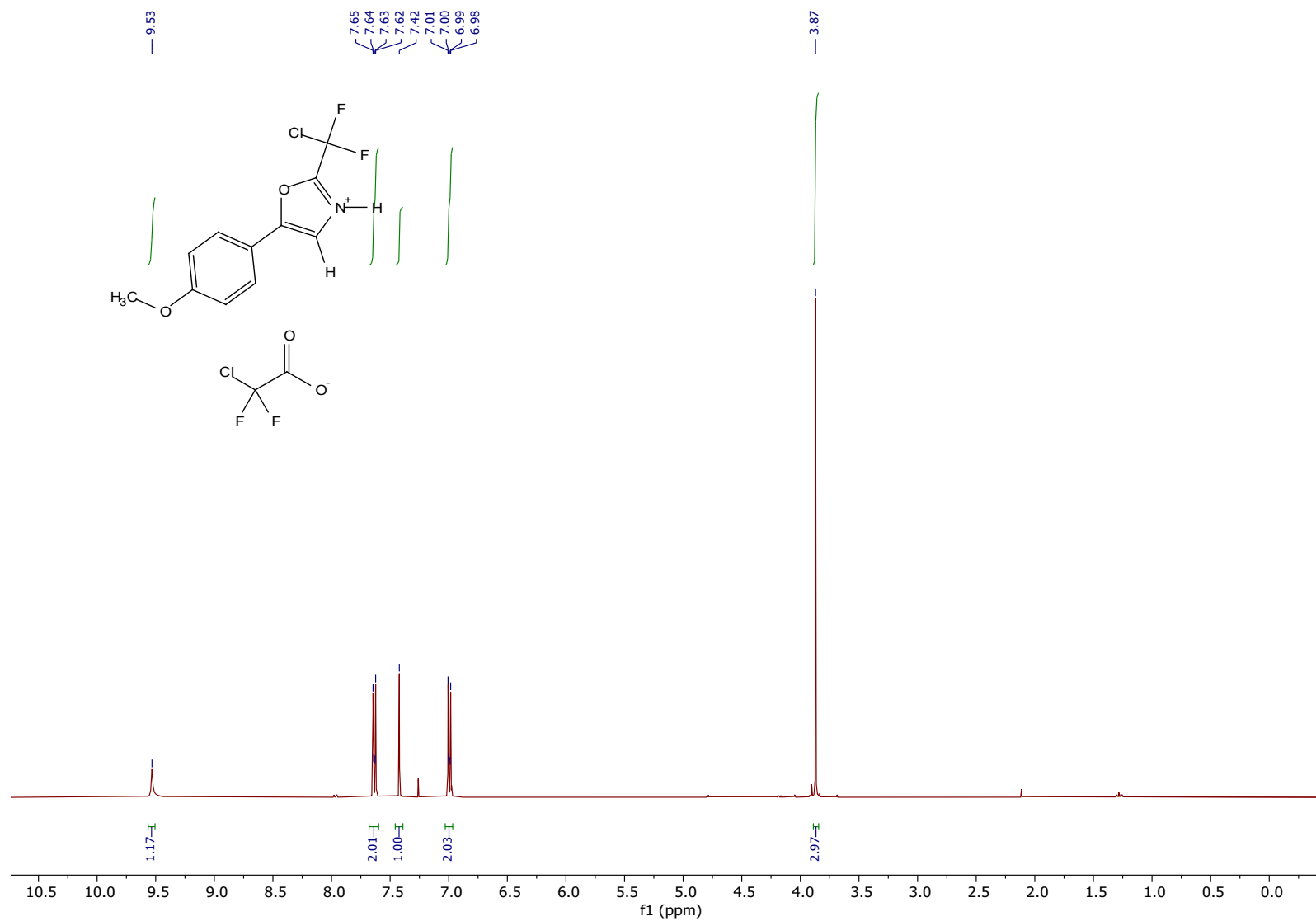


<sup>19</sup>F NMR

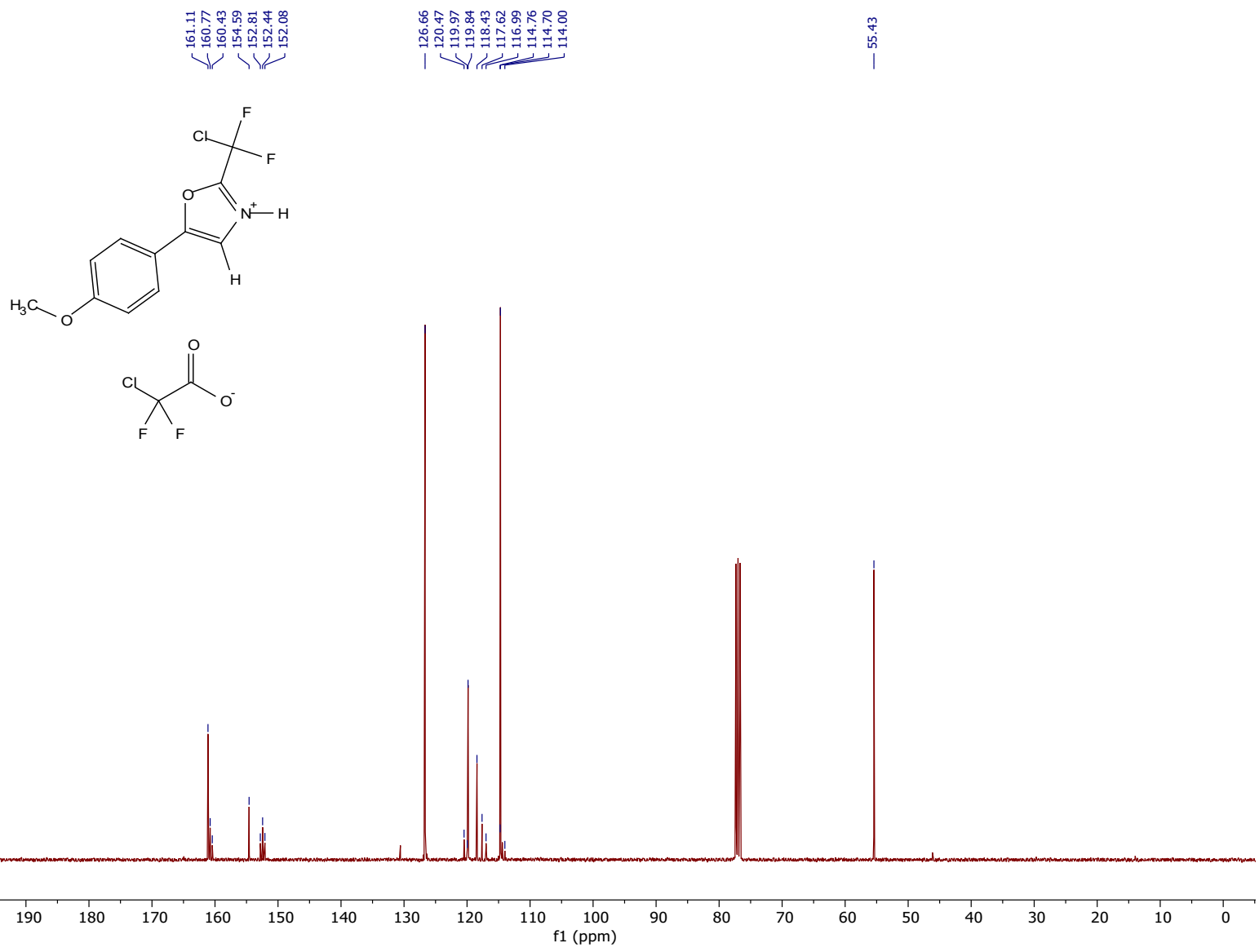


2-(Chlorodifluoromethyl)-5-(4-methoxyphenyl)oxazol-3-ium chlorodifluoroacetate (**3r**)

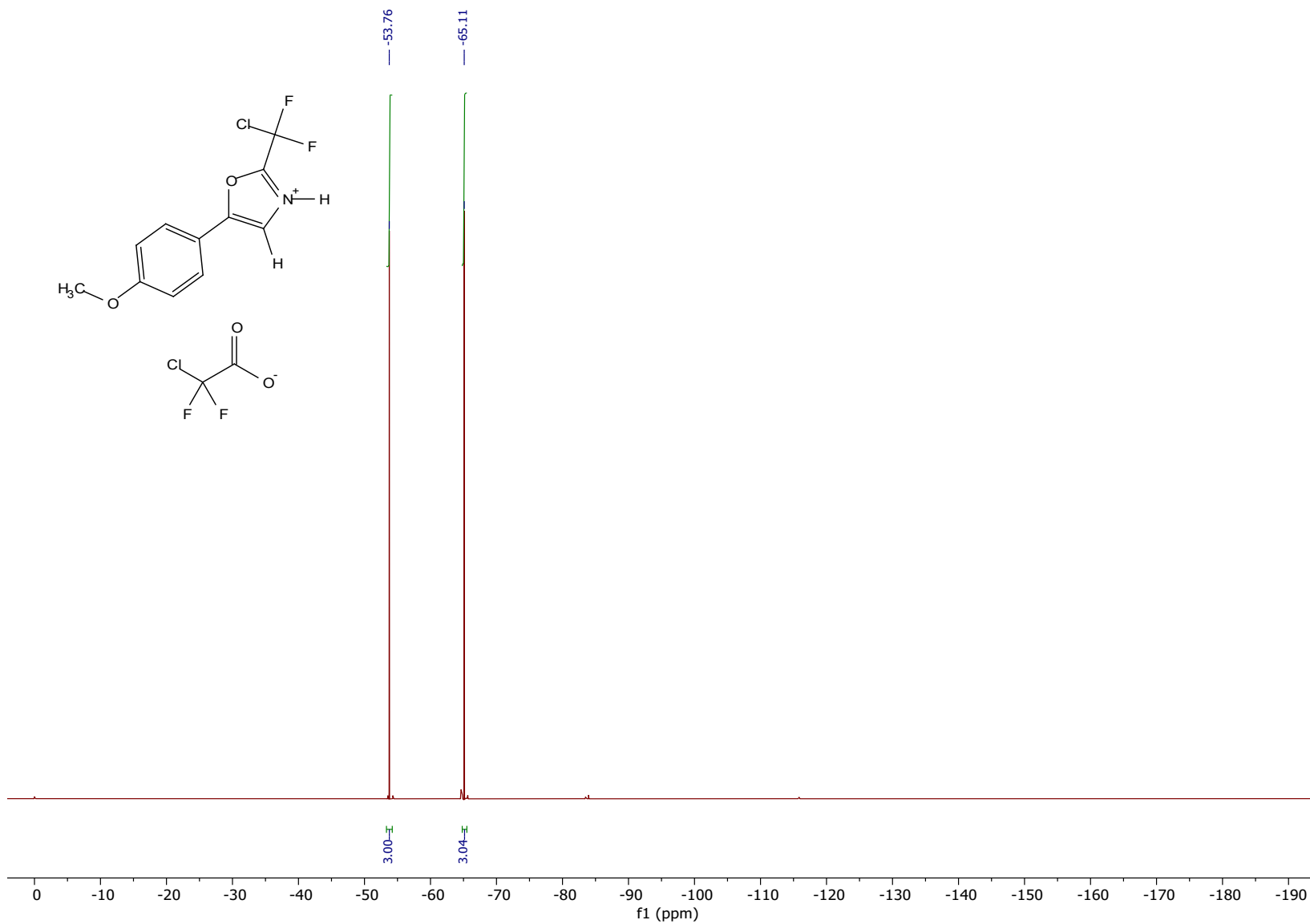
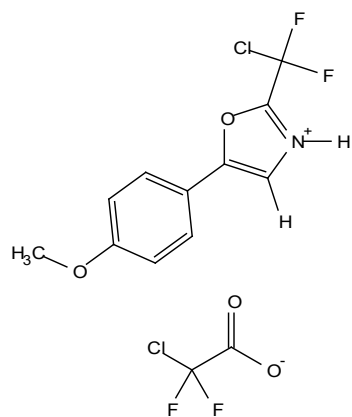
$^1\text{H}$  NMR



<sup>13</sup>C NMR



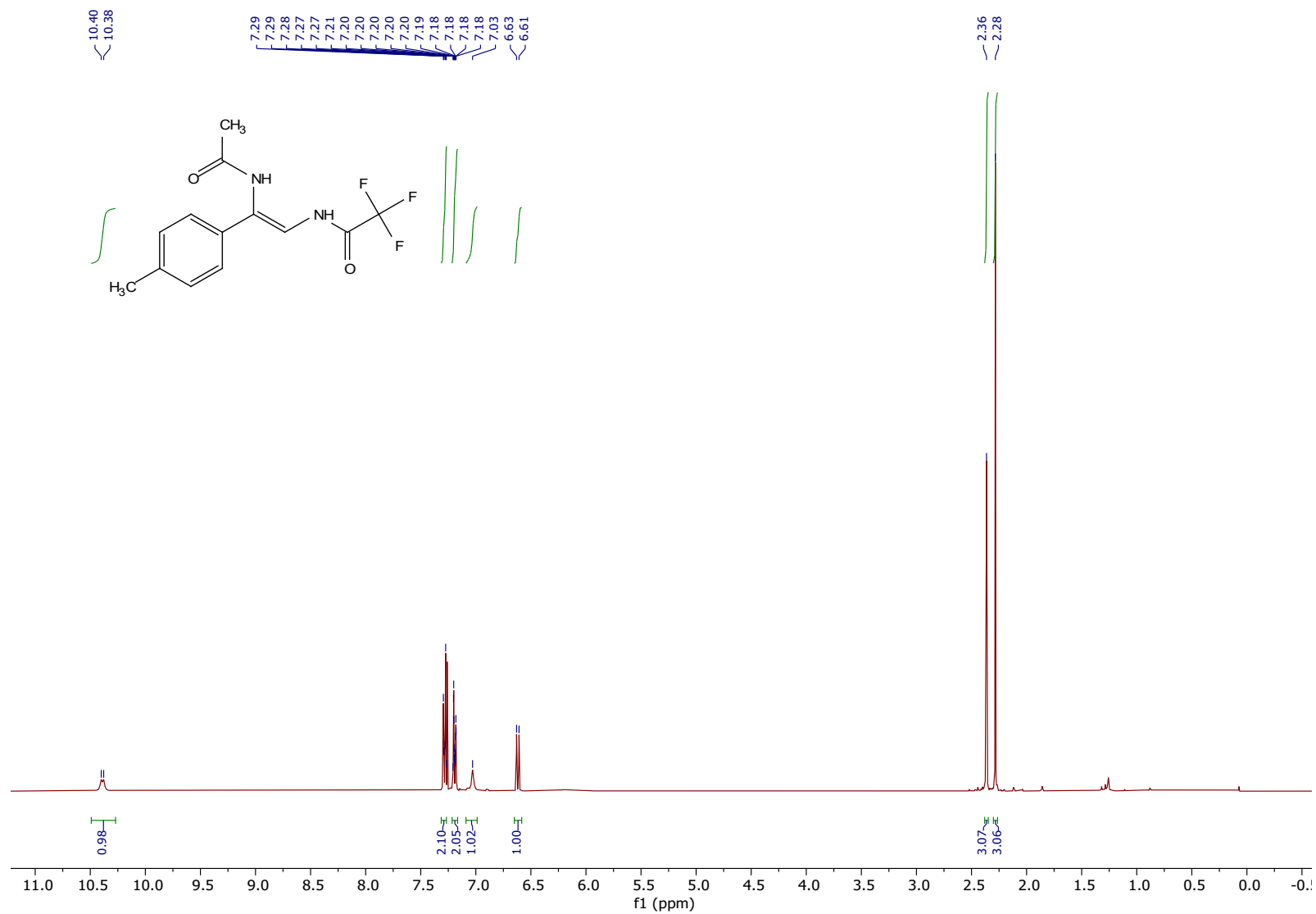
<sup>19</sup>F NMR



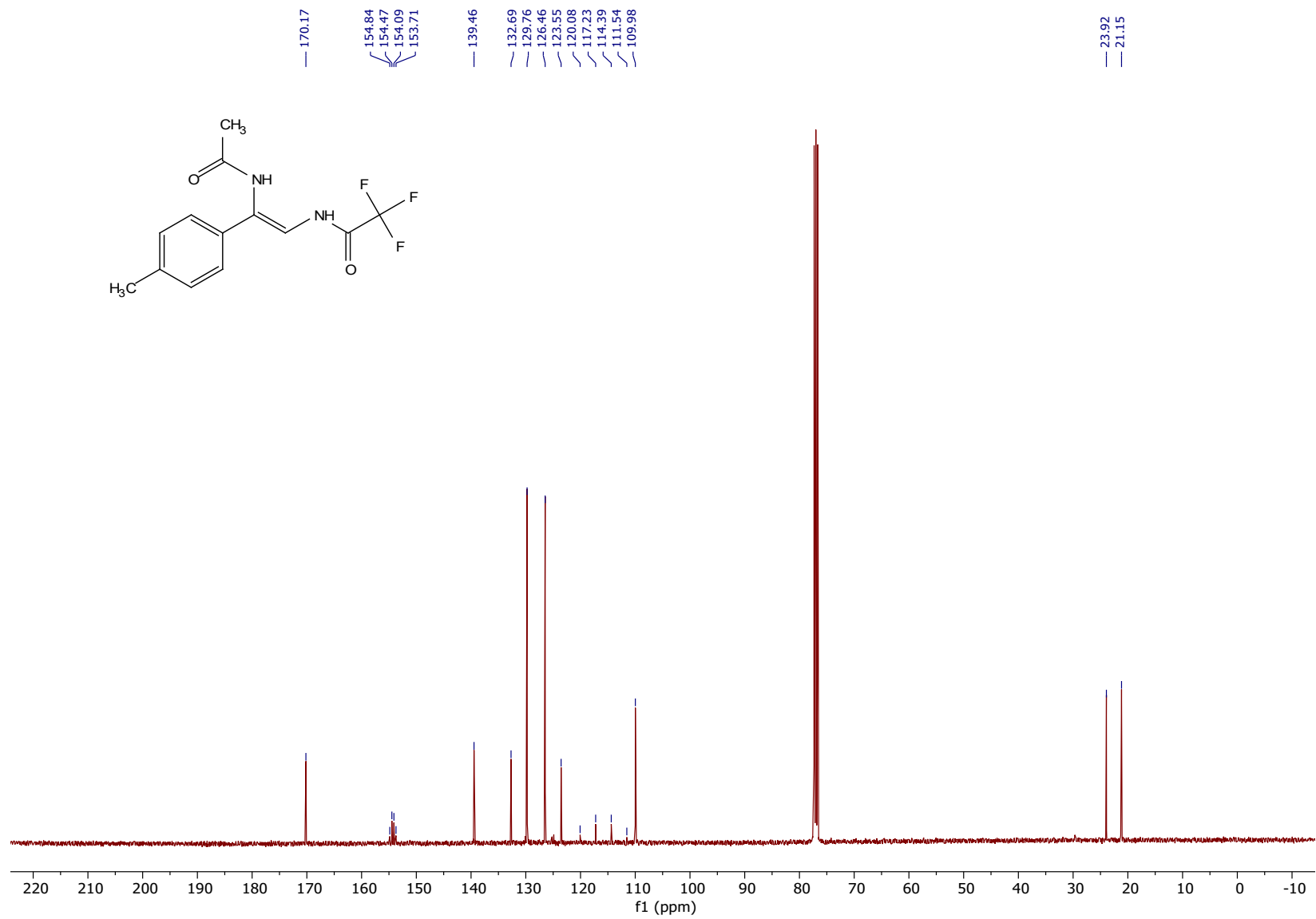


(Z)-N-(2-Acetamido-2-(p-tolyl)vinyl)-2,2,2-trifluoroacetamide (**4a**)

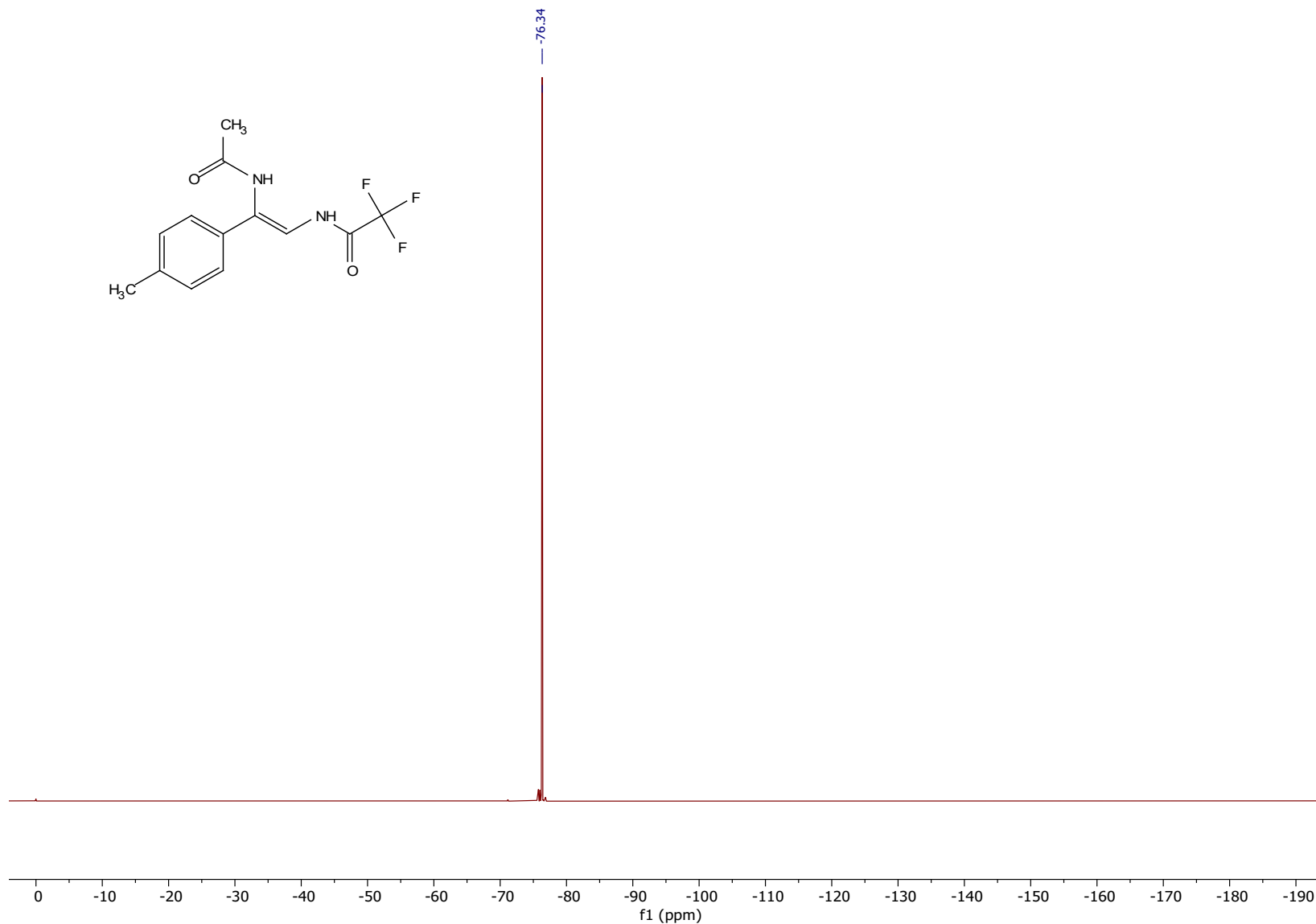
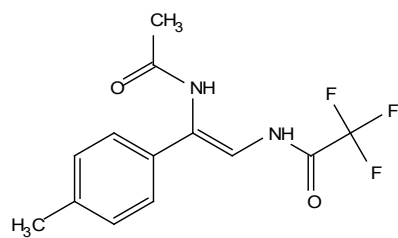
$^1\text{H}$  NMR



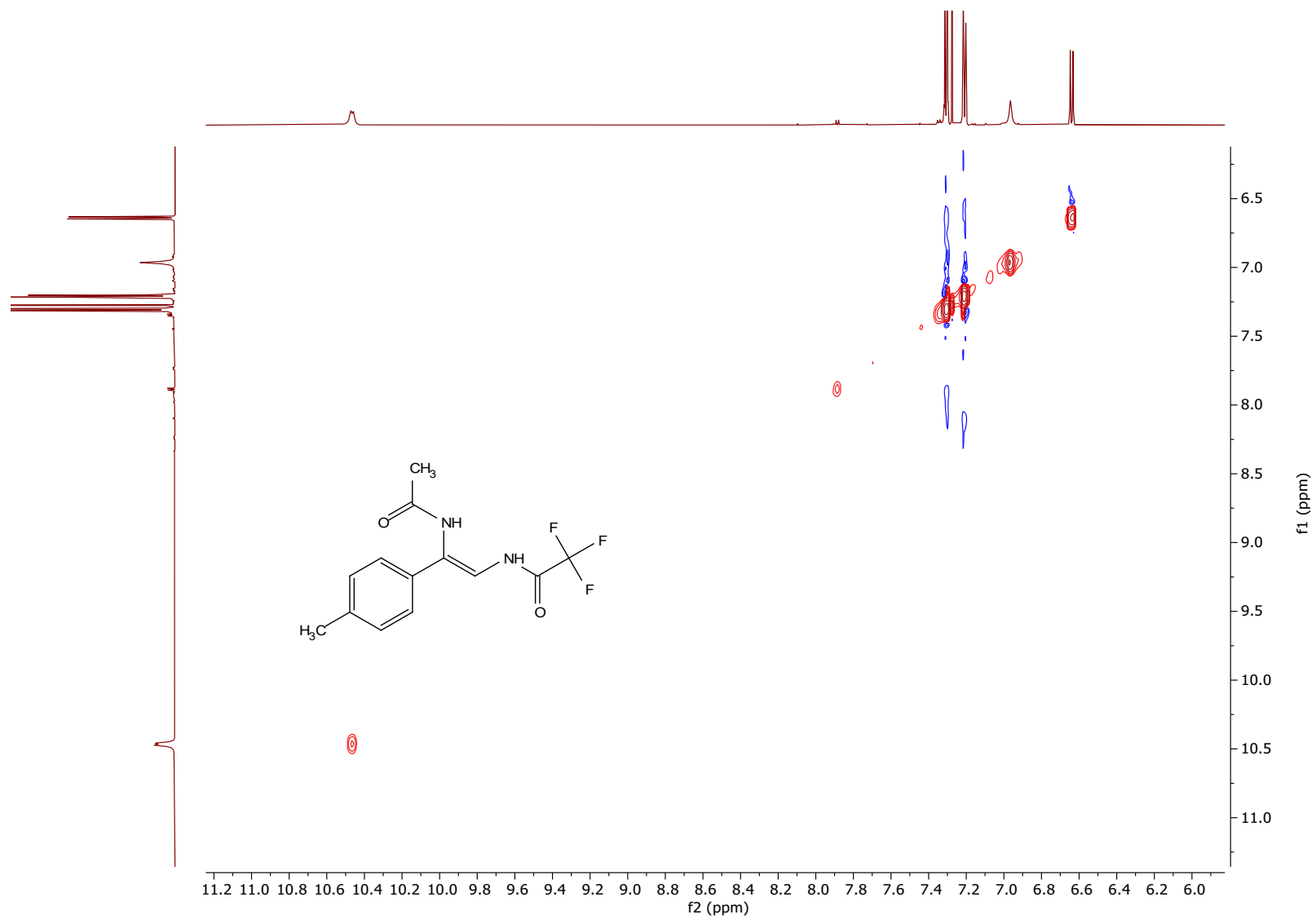
<sup>13</sup>C NMR



<sup>19</sup>F NMR

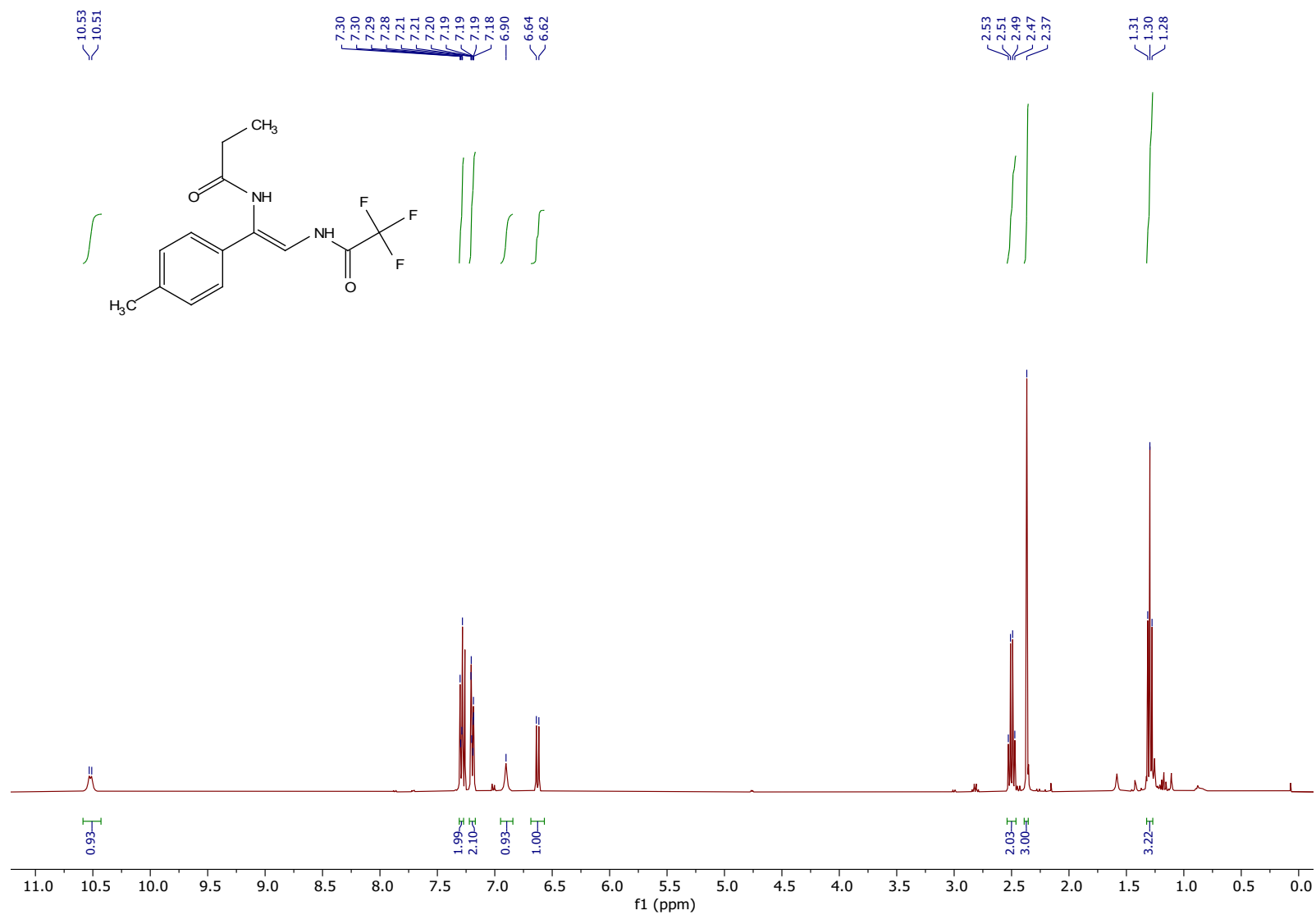


$^1\text{H}$ - $^1\text{H}$  NOESY NMR

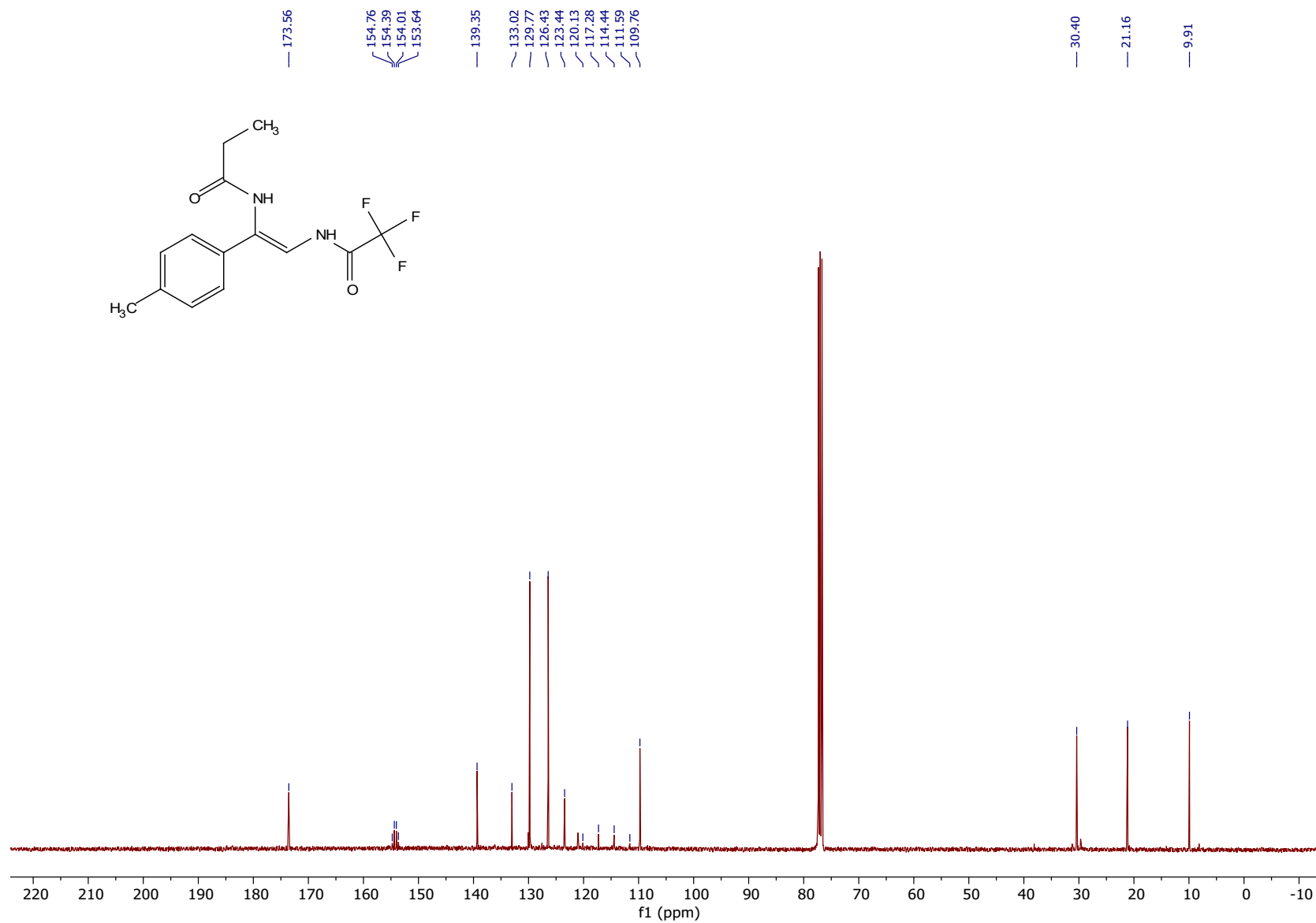


(Z)-N-(1-(p-Tolyl)-2-(2,2,2-trifluoroaceto)vinyl)propionamide (**4b**)

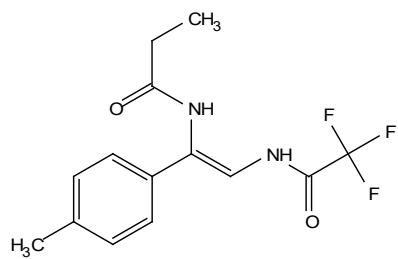
<sup>1</sup>H NMR



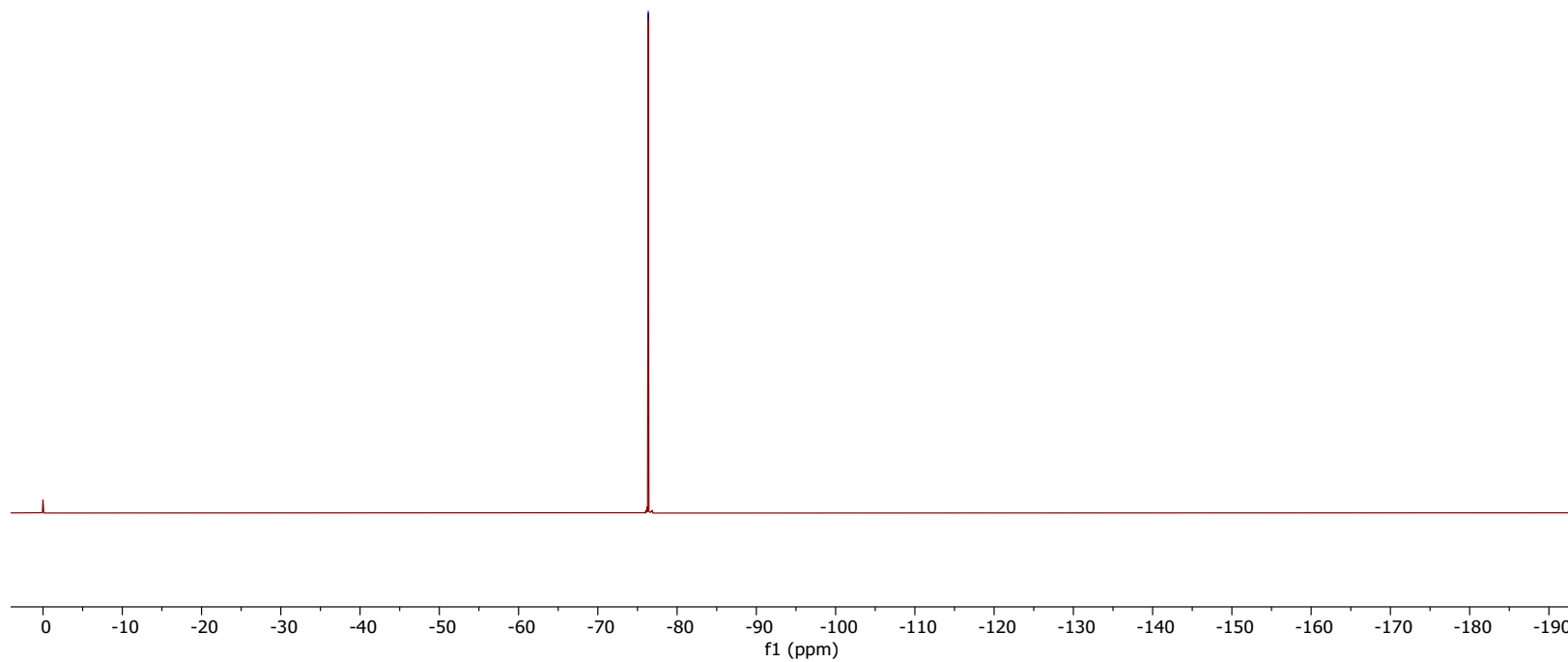
<sup>13</sup>C NMR



<sup>19</sup>F NMR



-76.36



SI63

$^1\text{H}$ - $^1\text{H}$  NOESY NMR

