

## Supporting Information

# Synthesis of trifluoromethylated isoxazoles and their elaboration including inter- and intramolecular C-H functionalisation

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## 1. General experimental details

All reactions were performed using oven-dried glassware (200 °C) under an atmosphere of argon unless otherwise stated. Solvents were freshly distilled over sodium benzophenone ketyl (THF, Et<sub>2</sub>O) or calcium hydride (CH<sub>2</sub>Cl<sub>2</sub>, toluene, hexane and EtOAc). Additional anhydrous solvents were obtained from commercial sources and used directly (DMF, DMA). DIPEA and Et<sub>3</sub>N were freshly distilled over calcium hydride and stored over 4 Å molecular sieves. All reagents were obtained from commercial sources and used without further purification. <sup>n</sup>BuLi was titrated prior to use with BHT and 1,10-phenanthroline as indicator.

Flash column chromatography was performed using high-purity grade silica gel (Merck grade 9385) with a pore size 60 Å and 230–400 mesh particle size under air pressure. Analytical thin layer chromatography (TLC) was performed using silica gel 60 F<sub>254</sub> pre-coated glass backed plates and visualized by ultraviolet radiation (254 nm) and/or potassium permanganate solution as appropriate.

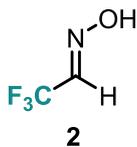
<sup>1</sup>H NMR spectra were recorded on either a 400 MHz DPX-400 Dual Spectrometer or a 500 MHz DCH Cryoprobe Spectrometer as indicated. Chemical shifts are reported in ppm with the resonance resulting from incomplete deuteration of the solvent as the internal standard (CDCl<sub>3</sub>: 7.26 ppm, s; CD<sub>3</sub>OD: 3.31 ppm, qn). <sup>13</sup>C NMR spectra were recorded on the same spectrometers with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (<sup>13</sup>CDCl<sub>3</sub>: 77.16 ppm, t; <sup>13</sup>CD<sub>3</sub>OD: 49.00, septet). <sup>19</sup>F NMR spectra were recorded on a 376 MHz Avance III HD Spectrometer. Chemical shifts are reported in ppm with CFCl<sub>3</sub> as the external standard (CFCl<sub>3</sub>: 0.00 ppm). Data are reported as follows: chemical shift δ/ppm, integration (<sup>1</sup>H and <sup>19</sup>F), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, br = broad, m = multiplet or combinations thereof; <sup>13</sup>C signals are singlets unless otherwise stated), coupling constants *J* in Hz. <sup>1</sup>H NMR signals are reported to 2 decimal places and <sup>13</sup>C signals to 1 decimal place unless rounding would produce a value identical to another signal. In this case, an additional decimal place is reported for both signals concerned.

Infrared spectra were recorded neat as thin films on a Perkin-Elmer Spectrum One FTIR spectrometer and selected peaks are reported (s = strong, m = medium, w = weak, br = broad).

High resolution mass spectrometry (HRMS) was performed using electrospray ionisation (ESI) or electron impact (EI) on either a Waters Micromass LCT Premier spectrometer or performed by the Mass Spectrometry Service for the Chemistry Department at the University of Cambridge. All *m/z* values are reported to 4 decimal places and are within ± 5 ppm of theoretical values.

Specific optical rotation was recorded on a Perkin-Elmer Model 343 digital polarimeter, using a Na/Hal lamp set at 589 nm and with a path length of 100 mm. [ $\alpha$ ]<sub>D</sub> values were measured using spectroscopy grade solvent at the specified concentration (in g cm<sup>-3</sup>) and temperature, with units of 10<sup>-1</sup> cm<sup>2</sup> g<sup>-1</sup>.

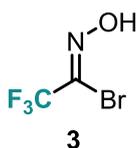
## 2. Synthetic procedures and characterisation



**Trifluoroacetaldehyde oxime (2):** Trifluoroacetaldehyde methyl hemiacetal (**1**) (10.00 g, 76.9 mmol, 1 eq.) and hydroxylamine hydrochloride (8.00 g, 115.1 mmol, 1.5 eq.) were dissolved in 30% aqueous MeOH (50 mL). An aqueous solution of 50% NaOH (16 mL, 195.1 mmol, 2.5 eq.) was added slowly dropwise *via* syringe pump over 45 min to the stirred reaction mixture at 0 °C. The reaction mixture was allowed to warm to r.t. and stirred overnight. Hexane (50 mL) was added, the layers were separated and the aqueous layer was acidified with 37% aqueous HCl to pH 6. The mixture was then extracted with Et<sub>2</sub>O (2 × 100 mL) and the combined organic extracts dried (MgSO<sub>4</sub>), affording the crude title product **2** in Et<sub>2</sub>O as a pale yellow liquid and used immediately without further purification.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 11.07 (br s, 1 H), 7.42 (q, *J* = 4.3 Hz, 1 H).

<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>): δ -67.7 (s, 3 F).



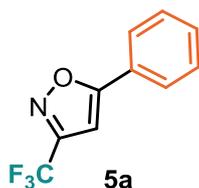
**Trifluoroacetoxyhydroximoyl bromide (3):** *N*-bromosuccinimide (15.03 g, 84.5 mmol) was dissolved in DMF (30 mL) and added slowly dropwise *via* syringe pump over 1 h to the stirred solution of trifluoroacetaldehyde oxime (**2**) at 0 °C, warmed to r.t. and stirred overnight. The reaction mixture was washed with water (2 × 100 mL), brine (100 mL) and dried (MgSO<sub>4</sub>), affording the crude title compound **3** in Et<sub>2</sub>O (113.76 g containing 12.40 g of **3**, 84% over 2 steps) as a red-brown liquid. The solution was stored in the freezer under argon as a precaution and used without further without purification.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 12.18 (br s, 1 H).

<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>): δ -69.9 (s, 3 F).

## 2.1. Aryl alkyne cycloadditions

**General procedure for aryl alkynes:** The Et<sub>2</sub>O solution of **3** (2.64 g containing 0.287 g of **3**, 1.5 mmol, 1 eq.) and the appropriate aryl alkyne (3.0 mmol, 2 eq.) were dissolved in toluene (4 mL). A solution of Et<sub>3</sub>N (0.42 mL, 0.303 g, 3.0 mmol, 2 eq.) in toluene (1.6 mL) was added slowly dropwise to the stirred reaction mixture *via* syringe pump over 2 h at r.t., forming a white precipitate. Hexane (25 mL) was added and the white precipitate filtered off. The white precipitate was washed further on the filter with EtOAc (5 mL). The filtrate was washed with water (25 mL), brine (25 mL), dried (MgSO<sub>4</sub>), evaporated under reduced pressure and purified by flash column chromatography.



**5-phenyl-3-(trifluoromethyl)isoxazole (5a):** The reaction of **3** (44.0 g containing 4.78 g of **3**, 25.0 mmol, 1 eq.) and phenylacetylene (5.11 g, 50.0 mmol, 2 eq.) using the general procedure for aryl alkynes, purified using silica gel column chromatography (hexane → 10% EtOAc/hexane), afforded the title compound **5a** (5.13 g, 96%) as a pale yellow solid, m.p. 44.5-45.5 °C (lit. m.p.<sup>1</sup> 44-45.5 °C). Data consistent with literature.<sup>1</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.78-7.74 (m, 2 H), 7.49-7.45 (m, 3 H), 6.72 (s, 1 H).

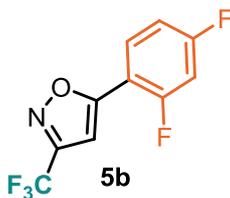
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 172.6, 156.1 (q, *J* = 38.2 Hz), 131.4, 129.3, 126.14, 126.07, 119.9 (q, *J* = 271.1 Hz), 96.8.

<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>): δ -63.7 (s, 3 F).

FTIR (ν<sub>max</sub>, cm<sup>-1</sup>): 1613 (w), 1474 (m), 1456 (m), 1245 (m), 1148 (s), 1123 (s), 972 (s), 951 (m), 804 (w).

HRMS (EI): *m/z* calculated for C<sub>10</sub>H<sub>6</sub>F<sub>3</sub>NO [M]<sup>+</sup> 213.0391, found 213.0396.

*R<sub>f</sub>* = 0.13 (hexane)



**5-(2,4-difluorophenyl)-3-(trifluoromethyl)isoxazole (5b):** The reaction of **3** (2.64 g containing 0.287 g of **3**, 1.5 mmol, 1 eq.) and 1-ethynyl-2,4-difluorobenzene (0.414 g, 3.0 mmol, 2 eq.) using the general procedure for aryl alkynes, purified using silica gel column chromatography (hexane → 10% EtOAc/hexane), afforded the title compound **5b** (0.274 g, 73%) as a white solid, m.p. 66.5-67.5 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.97 (td, *J* = 8.4, 6.5 Hz, 1 H), 7.13 – 7.02 (m, 1 H), 7.02 – 6.94 (m, 1 H), 6.86 (d, *J* = 3.3 Hz, 1 H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 165.6 (dd, *J* = 2.9, 1.3 Hz), 164.7 (dd, *J* = 255.9, 12.3 Hz), 159.9 (dd, *J* = 256.9, 12.2 Hz), 156.5 (q, *J* = 37.7 Hz), 129.1 (dd, *J* = 10.2, 3.3 Hz), 119.8 (q,

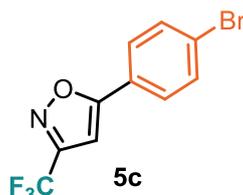
$J = 271.2$  Hz), 112.8 (dd,  $J = 22.0, 3.6$  Hz), 111.4 (dd,  $J = 12.3, 4.0$  Hz), 105.2 (dd,  $J = 25.9, 25.1$  Hz), 100.3 (dqn,  $J = 11.3, 1.3$  Hz).

$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ):  $\delta$  -63.9 (s, 3 F), -104.1 (d,  $J = 10.6$  Hz, 1 F), -107.5 (d,  $J = 10.6$  Hz, 1 F).

FTIR ( $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 1615 (m), 1603 (m), 1585 (w), 1514 (w), 1478 (m), 1469 (m), 1455 (m), 1421 (m), 1316 (w), 1281 (m), 1262 (m), 1220 (m), 1165 (s), 1146 (s), 1122 (m), 1099 (m), 1041 (m), 969 (m), 950 (m), 933 (m), 856 (s), 836 (m), 805 (s).

HRMS (EI): calculated for  $\text{C}_{10}\text{H}_4\text{F}_3\text{NO}$   $[\text{M}]^+$  249.0213, found 249.0208.

$R_f = 0.25$  (hexane).



**5-(4-bromophenyl)-3-(trifluoromethyl)isoxazole (5c):** The reaction of **3** (1.41 g containing 0.154 g of **3**, 0.8 mmol, 1 eq.) and 1-bromo-4-ethynylbenzene (0.290 g, 1.6 mmol, 2 eq.) using the general procedure for aryl alkynes, purified using silica gel column chromatography (hexane  $\rightarrow$  5% EtOAc/hexane), afforded the title compound **5c** (0.197 g, 84%) as a white solid, m.p. 107-108 °C.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.72 – 7.59 (m, 4 H), 6.75 (s, 1 H).

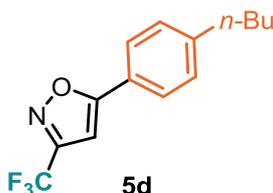
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.5, 156.3 (q,  $J = 38.4$  Hz), 132.7, 127.6, 126.0, 125.1, 119.7 (q,  $J = 271.2$  Hz), 97.3 (q,  $J = 1.3$  Hz).

$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ):  $\delta$  -63.7 (s, 3 F).

FTIR ( $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 1608 (w), 1505 (w), 1471 (m), 1456 (m), 1440 (m), 1402 (m), 1310 (w), 1286 (w), 1246 (m), 1189 (m), 1177 (s), 1129 (s), 1115 (s), 1104 (m), 1073 (m), 1050 (m), 1010 (m), 969 (m), 948 (m), 814 (s).

HRMS (ESI): calculated for  $\text{C}_{10}\text{H}_6\text{BrF}_3\text{NO}$   $[\text{M}+\text{H}]^+$  291.9579, found 291.9580.

$R_f = 0.23$  (hexane).



**5-(4-butylphenyl)-3-(trifluoromethyl)isoxazole (5d):** The reaction of **3** (2.64 g containing 0.287 g of **3**, 1.5 mmol, 1 eq.) and 1-butyl-4-ethynylbenzene (0.475 g, 3.0 mmol, 2 eq.) using the general procedure for aryl alkynes, purified using silica gel column chromatography (hexane  $\rightarrow$  10% EtOAc/hexane), afforded the title compound **5d** (0.402 g, 99%) as a yellow solid, m.p. close to r.t..

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.71 (d,  $J = 8.2$  Hz, 2 H), 7.31 (d,  $J = 8.2$  Hz, 2 H), 6.68 (s, 1 H), 2.68 (t,  $J = 7.7$  Hz, 2 H), 1.71 – 1.57 (m, 2 H), 1.46 – 1.32 (m, 2 H), 0.95 (t,  $J = 7.3$  Hz, 3 H).

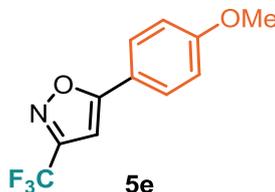
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.8, 156.1 (q,  $J = 38.1$  Hz), 146.9, 129.4, 126.1, 123.7, 119.9 (q,  $J = 271.1$  Hz), 96.3 (q,  $J = 1.3$  Hz), 35.7, 33.4, 22.4, 14.0.

$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ):  $\delta$  -63.7 (s, 3 F).

**FTIR** ( $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 2960 (w), 2933 (w), 2862 (w), 1617 (m), 1597 (w), 1475 (s), 1457 (m), 1418 (w), 1244 (s), 1183 (s), 1150 (s), 1128 (s), 1114 (s), 970 (s), 951 (m), 941 (w), 837 (m), 794 (m).

**HRMS (EI)**: calculated for  $\text{C}_{14}\text{H}_{14}\text{F}_3\text{NO}$   $[\text{M}]^+$  269.1013, found 269.1022.

$R_f$  = 0.15 (hexane).



**5-(4-methoxyphenyl)-3-(trifluoromethyl)isoxazole (5e)**: The reaction of **3** (1.76 g containing 0.192 g of **3**, 1.0 mmol, 1 eq.) and 1-ethynyl-4-methoxybenzene (0.264 g, 2.0 mmol, 2 eq.) using the general procedure for aryl alkynes, purified using silica gel column chromatography with ca. 1 cm layer of 10% w/w  $\text{AgNO}_3$  impregnated silica on top (5% EtOAc/hexane), afforded the title compound **5e** (0.205 g, 84%) as a white solid, m.p. 82-83 °C.

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.70 (d,  $J$  = 8.7 Hz, 2 H), 6.98 (d,  $J$  = 8.7 Hz, 2 H), 6.59 (s, 1 H), 3.85 (s, 3 H).

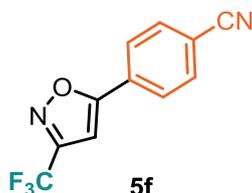
**$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.4, 161.9, 155.9 (q,  $J$  = 38.0 Hz), 127.6, 119.8 (q,  $J$  = 271.0 Hz), 118.7, 114.6, 95.3 (q,  $J$  = 1.3 Hz), 55.3.

**$^{19}\text{F}$  NMR** (376 MHz,  $\text{CDCl}_3$ ):  $\delta$  -63.8 (s, 3 F).

**FTIR** ( $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 1612 (m), 1598 (m), 1520 (w), 1467 (m), 1455 (m), 1437 (m), 1322 (w), 1309 (m), 1269 (w), 1242 (m), 1171 (s), 1125 (s), 1110 (s), 1027 (s), 968 (m), 943 (s), 834 (s), 806 (s).

**HRMS (ESI)**: calculated for  $\text{C}_{11}\text{H}_9\text{F}_3\text{NO}_2$   $[\text{M}+\text{H}]^+$  244.0580, found 244.0582.

$R_f$  = 0.22 (10% EtOAc/hexane).



**4-(3-(trifluoromethyl)isoxazol-5-yl)benzotrile (5f)**: The reaction of **3** (2.64 g containing 0.287 g of **3**, 1.5 mmol, 1 eq.) and 4-ethynylbenzotrile (0.381 g, 3.0 mmol, 2 eq.) using the general procedure for aryl alkynes, purified using silica gel column chromatography (5% EtOAc/hexane), afforded the title compound **5f** (0.211 g, 60%) as a white solid, m.p. 120-121 °C.

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.93 (d,  $J$  = 8.3 Hz, 2 H), 7.81 (d,  $J$  = 8.3 Hz, 2 H), 6.90 (s, 1 H).

**$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  170.3, 156.4 (q,  $J$  = 38.7 Hz), 133.2, 129.8, 126.7, 119.5 (q,  $J$  = 271.4 Hz), 117.9, 114.9, 99.0 (q,  $J$  = 1.3 Hz).

**$^{19}\text{F}$  NMR** (376 MHz,  $\text{CDCl}_3$ ):  $\delta$  -63.7 (s, 3 F).

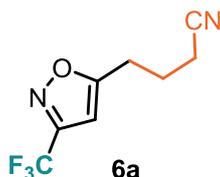
**FTIR** ( $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 2231 (w), 1592 (w), 1474 (m), 1454 (m), 1411 (w), 1313 (w), 1290 (w), 1241 (m), 1174 (m), 1143 (s), 1127 (s), 1108 (m), 1045 (w), 974 (s), 951 (m), 850 (s), 800 (s).

**HRMS (ESI)**: calculated for  $\text{C}_{11}\text{H}_6\text{F}_3\text{N}_2\text{O}$   $[\text{M}+\text{H}]^+$  239.0427, found 239.0431.

$R_f$  = 0.23 (10% EtOAc/hexane)

## 2.2. Alkyl alkyne cycloadditions

**General procedure for alkyl alkynes:** The Et<sub>2</sub>O solution of **3** (2.64 g containing 0.287 g of **3**, 1.5 mmol, 1 eq.) and the appropriate alkyl alkyne (3.0 mmol, 2 eq.) were dissolved in toluene (4 mL). A solution of Na<sub>2</sub>CO<sub>3</sub> (0.318 g, 3.0 mmol, 2 eq.) in water (5 mL) was added dropwise to the stirred reaction mixture *via* syringe pump over 16 h at r.t., then hexane (25 mL) was added. The reaction flask was washed with EtOAc (5 mL) and the organic layer washed with water (25 mL), brine (25 mL), dried (MgSO<sub>4</sub>), evaporated under reduced pressure and purified by flash column chromatography.



**4-(3-(trifluoromethyl)isoxazol-5-yl)butanenitrile (6a):** The reaction of **3** (2.64 g containing 0.287 g of **3**, 1.5 mmol, 1 eq.) and 5-hexynenitrile (0.279 g, 3.0 mmol, 2 eq.) using the general procedure for alkyl alkynes, purified using silica gel column chromatography (hexane → 20% EtOAc/hexane), afforded the title compound **6a** (0.224 g, 73%) as a colourless liquid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 6.34 (s, 1 H), 2.99 (t, *J* = 7.3 Hz, 2 H), 2.44 (t, *J* = 7.3 Hz, 2 H), 2.08 (p, *J* = 7.3 Hz, 2 H).

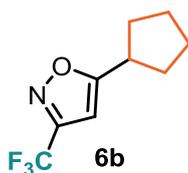
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 173.8, 155.5 (q, *J* = 38.2 Hz), 119.6 (q, *J* = 271.0 Hz), 118.5, 99.5 (q, *J* = 1.3 Hz), 25.4, 23.1, 16.5.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -63.9 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 2250 (w), 1600 (w), 1491 (m), 1459 (w), 1434 (w), 1301 (w), 1263 (w), 1241 (w), 1181 (s), 1143 (s), 1096 (m), 995 (w), 969 (s), 939 (m), 808 (m).

**HRMS (EI):** calculated for C<sub>8</sub>H<sub>7</sub>F<sub>3</sub>N<sub>2</sub>O [M]<sup>+</sup> 204.0506, found 204.0505.

*R<sub>f</sub>* = 0.16 (20% EtOAc/hexane).



**5-cyclopentyl-3-(trifluoromethyl)isoxazole (6b):** The reaction of **3** (2.64 g containing 0.287 g of **3**, 1.5 mmol, 1 eq.) and cyclopentylacetylene (0.282 g, 3.0 mmol, 2 eq.) using the general procedure for alkyl alkynes, purified using silica gel column chromatography (hexane → 5% EtOAc/hexane), afforded the title compound **6b** (0.168 g, 54%) as a colourless liquid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 6.20 (s, 1 H), 3.31 – 3.18 (m, 1 H), 2.20 – 2.03 (m, 2 H), 1.87 – 1.60 (m, 6 H).

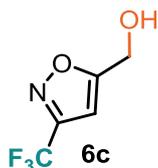
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 180.4, 155.3 (q, *J* = 37.9 Hz), 120.0 (q, *J* = 270.9 Hz), 97.2 (q, *J* = 1.3 Hz), 37.6, 31.9, 25.3.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -63.9 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 2965 (w), 2878 (w), 1594 (w), 1489 (m), 1456 (w), 1346 (w), 1305 (w), 1253 (m), 1181 (s), 1142 (s), 1101 (m), 998 (w), 968 (s), 935 (w), 911 (w), 801 (m).

**HRMS (ESI):** calculated for C<sub>9</sub>H<sub>11</sub>F<sub>3</sub>NO [M+H]<sup>+</sup> 206.0787, found 206.0793.

*R<sub>f</sub>* = 0.21 (hexane).



**(3-(trifluoromethyl)isoxazol-5-yl)methanol (6c):** The reaction of **3** (2.64 g containing 0.287 g of **3**, 1.5 mmol, 1 eq.) and propargyl alcohol (0.168 g, 3.0 mmol, 2 eq.) using the general procedure for alkyl alkynes without chromatography, afforded the title compound **6c** (0.185 g, 74%) as a colourless liquid. Data consistent with literature.<sup>1</sup>

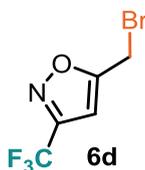
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 6.50 (s, 1 H), 4.78 (s, 2 H), 3.71 (br s, 1 H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 174.5, 155.6 (q, *J* = 38.5 Hz), 119.6 (q, *J* = 271.1 Hz), 99.8 (q, *J* = 1.3 Hz), 56.1.

<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>): δ -63.7 (s, 3 F).

FTIR (ν<sub>max</sub>, cm<sup>-1</sup>): 3370 (br w), 1602 (w), 1493 (m), 1453 (w), 1365 (w), 1302 (w), 1259 (w), 1143 (s), 1097 (m), 1041 (m), 995 (m), 969 (s), 931 (m), 812 (m), 756 (m).

HRMS (ESI): calculated for C<sub>5</sub>H<sub>5</sub>F<sub>3</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 168.0267, found 168.0262.



**5-(bromomethyl)-3-(trifluoromethyl)isoxazole (6d):** The reaction of **3** (26.4 g containing 2.87 g of **3**, 15.0 mmol, 1 eq.) and propargyl bromide (3.57 g, 30.0 mmol, 2 eq.) using the general procedure for alkyl alkynes with Et<sub>2</sub>O as solvent instead, purified using silica gel column chromatography (4% Et<sub>2</sub>O/pentane), afforded the title compound **6d** (2.66 g, 77%) as a pale yellow volatile liquid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 6.58 (s, 1 H), 4.50 (s, 2 H).

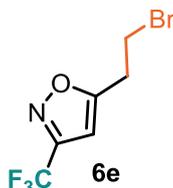
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 170.4, 155.9 (q, *J* = 38.7 Hz), 119.5 (q, *J* = 271.2 Hz), 101.5 (q, *J* = 1.2 Hz), 17.5.

<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>): δ -63.8 (s, 3 F).

FTIR (ν<sub>max</sub>, cm<sup>-1</sup>): 1659 (w), 1602 (w), 1491 (m), 1460 (w), 1428 (w), 1300 (m), 1222 (m), 1185 (s), 1144 (s), 947 (m), 813 (m), 756 (s).

HRMS (ESI): calculated for C<sub>5</sub>H<sub>4</sub>BrF<sub>3</sub>NO [M+H]<sup>+</sup> 229.9423, found 229.9419.

R<sub>f</sub> = 0.43 (4% EtOAc/hexane).



**5-(2-bromoethyl)-3-(trifluoromethyl)isoxazole (6e):** The reaction of **3** (26.4 g containing 2.87 g of **3**, 15.0 mmol, 1 eq.) and 4-bromo-1-butyne (3.99 g, 30.0 mmol, 2 eq.) using the general procedure for alkyl alkynes with Et<sub>2</sub>O as solvent instead, purified using silica gel column chromatography (4% EtOAc/hexane), afforded the title compound **6e** (2.75 g, 75%) as a pale yellow liquid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 6.44 (s, 1 H), 3.64 (t, *J* = 6.7 Hz, 2 H), 3.41 (t, *J* = 6.7 Hz, 2 H).

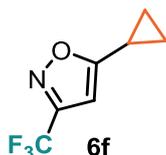
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 172.6, 155.6 (q, *J* = 38.3 Hz), 119.7 (q, *J* = 271.0 Hz), 100.2 (q, *J* = 1.3 Hz), 30.2, 27.2.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -63.7 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 1601 (w), 1491 (m), 1462 (w), 1443 (w), 1423 (w), 1334 (w), 1307 (w), 1260 (m), 1181 (s), 1143 (s), 1093 (m), 1021 (w), 998 (w), 969 (s), 946 (m), 875 (w), 805 (m).

**HRMS (ESI):** calculated for C<sub>6</sub>H<sub>6</sub>BrF<sub>3</sub>NO [M+H]<sup>+</sup> 243.9579, found 243.9568.

*R<sub>f</sub>* = 0.27 (10% EtOAc/hexane).



**5-cyclopropyl-3-(trifluoromethyl)isoxazole (6f):** The reaction of **3** (44.0 g containing 4.78 g of **3**, 25.0 mmol, 1 eq.) and cyclopropylacetylene (3.31 g, 50.0 mmol, 2 eq.) using the general procedure for alkyl alkynes, purified using silica gel column chromatography (hexane → 5% EtOAc/hexane), afforded the title compound **6f** (2.82 g, 64%) as a pale yellow volatile liquid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 6.13 (s, 1 H), 2.15 – 2.04 (m, 1 H), 1.21 – 1.10 (m, 2 H), 1.07 – 0.97 (m, 2 H).

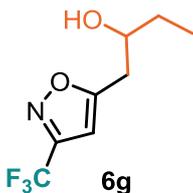
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 177.8, 155.6 (q, *J* = 37.9 Hz), 119.9 (q, *J* = 270.9 Hz), 96.5 (q, *J* = 1.3 Hz), 9.0, 8.3.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -64.0 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 1600 (m), 1494 (m), 1467 (w), 1457 (w), 1431 (w), 1339 (m), 1289 (w), 1259 (m), 1221 (m), 1180 (s), 1144 (s), 1117 (m), 1091 (m), 1060 (w), 1032 (w), 990 (m), 969 (s), 937 (m), 879 (m), 817 (w), 791 (m).

**HRMS (EI):** calculated for C<sub>7</sub>H<sub>6</sub>F<sub>3</sub>NO [M]<sup>+</sup> 177.0396, found 177.0396.

*R<sub>f</sub>* = 0.19 (hexane).



**1-(3-(trifluoromethyl)isoxazol-5-yl)butan-2-ol (6g):** The reaction of **3** (2.64 g containing 0.287 g of **3**, 1.5 mmol, 1 eq.) and 5-hexyn-3-ol (0.294 g, 3.0 mmol, 2 eq.) using the general procedure for alkyl alkynes, purified using silica gel column chromatography (20% EtOAc/hexane → EtOAc), afforded the title compound **6g** (0.193 g, 62%) as a colourless liquid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 6.37 (s, 1 H), 3.97 – 3.85 (m, 1 H), 2.98 (dd, *J* = 15.4, 4.1 Hz, 1 H), 2.90 (dd, *J* = 15.4, 8.0 Hz, 1 H), 2.39 (br s, 1 H), 1.64 – 1.45 (m, 2 H), 0.96 (t, *J* = 7.5 Hz, 3 H).

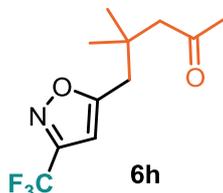
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 173.8, 155.6 (q, *J* = 38.1 Hz), 119.8 (q, *J* = 270.9 Hz), 100.2 (q, *J* = 1.3 Hz), 71.0, 34.3, 30.1, 9.7.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -63.8 (s, 3 F).

**FTIR** ( $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3423 (br w), 2971 (w), 2941 (w), 2885 (w), 1599 (w), 1489 (m), 1464 (w), 1296 (w), 1246 (w), 1207 (m), 1182 (s), 1153 (s), 1095 (m), 1057 (w), 1020 (w), 1000 (w), 969 (s), 942 (w), 902 (w), 853 (w), 804 (w), 759 (w).

**HRMS (ESI)**: calculated for  $\text{C}_8\text{H}_{10}\text{F}_3\text{NO}_2\text{Na}$   $[\text{M}+\text{Na}]^+$  232.0556, found 232.0551.

$R_f$  = 0.19 (20% EtOAc/hexane).



**4,4-dimethyl-5-(3-(trifluoromethyl)isoxazol-5-yl)pentan-2-one (6h)**: The reaction of **3** (2.64 g containing 0.287 g of **3**, 1.5 mmol, 1 eq.) and 4,4-dimethyl-6-heptyn-2-one (0.415 g, 3.0 mmol, 2 eq.) using the general procedure for alkyl alkynes, purified using silica gel column chromatography (hexane  $\rightarrow$  20% EtOAc/hexane), afforded the title compound **6h** (0.278 g, 74%) as a colourless liquid.

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )**:  $\delta$  6.25 (s, 1 H), 2.96 (s, 2 H), 2.34 (s, 2 H), 2.10 (s, 3 H), 1.04 (s, 6 H).

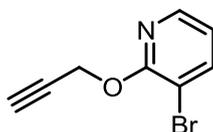
**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )**:  $\delta$  207.8, 174.4, 155.3 (q,  $J$  = 38.0 Hz), 119.9 (q,  $J$  = 270.8 Hz), 100.8 (q,  $J$  = 1.3 Hz), 52.4, 37.5, 34.1, 32.1, 27.7.

**$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )**:  $\delta$  -63.7 (s, 3 F).

**FTIR** ( $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 2964 (w), 1715 (m), 1669 (w), 1596 (w), 1488 (m), 1433 (w), 1363 (w), 1309 (w), 1245 (w), 1182 (s), 1145 (s), 1092 (m), 998 (w), 969 (s), 941 (w), 807 (w), 769 (w).

**HRMS (ESI)**: calculated for  $\text{C}_{11}\text{H}_{15}\text{F}_3\text{NO}_2$   $[\text{M}+\text{H}]^+$  250.1049, found 250.1038.

$R_f$  = 0.24 (10% EtOAc/hexane).



**3-bromo-2-(prop-2-yn-1-yloxy)pyridine**: To a suspension of NaH (60% dispersion in mineral oil, 93.6 mg, 2.34 mmol, 1.1 eq.) in anhydrous THF (3 mL) was added slowly dropwise propargyl alcohol (0.136 mL, 2.34 mmol, 1.1 eq.) at 0 °C. The mixture was warmed to r.t. and stirred further for 15 min. A solution of 3-bromo-2-chloropyridine (300 mg, 1.56 mmol, 1 eq.) in anhydrous THF (2 mL) was added dropwise and the mixture stirred at r.t. for 72 h. The reaction was then quenched with water (25 mL) and extracted with EtOAc (3  $\times$  25 mL). The combined organic extracts were dried ( $\text{MgSO}_4$ ) and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (4% EtOAc/hexane), which afforded the title compound as a white solid (77 mg, 23%), m.p. 44-45 °C.

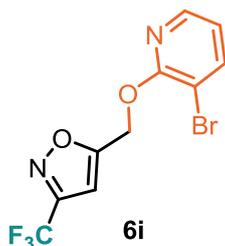
**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )**:  $\delta$  8.13 – 8.07 (m, 1 H), 7.85 – 7.78 (m, 1 H), 6.85 – 6.77 (m, 1 H), 5.05 – 5.01 (m, 2 H), 2.47 (t,  $J$  = 2.4 Hz, 1 H).

**$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )**:  $\delta$  158.5, 145.4, 142.1, 118.6, 107.0, 78.9, 74.6, 54.4.

**FTIR** ( $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3268 (m), 2948 (w), 2122 (w), 1584 (m), 1554 (w), 1455 (s), 1439 (s), 1420 (s), 1370 (m), 1304 (s), 1262 (w), 1243 (s), 1188 (w), 1122 (m), 1067 (m), 1030 (s), 1008 (s), 1001 (s), 972 (m), 934 (s), 880 (w), 817 (w), 790 (s).

**HRMS (ESI)**: calculated for  $\text{C}_8\text{H}_7\text{BrNO}$   $[\text{M}+\text{H}]^+$  211.9706, found 211.9699.

$R_f$  = 0.32 (5% EtOAc/hexane).



**5-(((3-bromopyridin-2-yl)oxy)methyl)-3-(trifluoromethyl)isoxazole (6i):** The reaction of **3** (1.25 g containing 0.135 g of **3**, 0.71 mmol, 2 eq.) and 3-bromo-2-(prop-2-yn-1-yloxy)pyridine (0.070 g, 0.35 mmol, 1 eq.) using the general procedure for alkyl alkynes with 2 eq. of hydroximoyl bromide and Et<sub>2</sub>O as solvent, purified using silica gel column chromatography (2% → 10% EtOAc/hexane), afforded the title compound **6i** (0.074 g, 65%) as a white solid, m.p. 37-39 °C.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 8.10 (dd, *J* = 4.8, 1.6 Hz, 1 H), 7.86 (dd, *J* = 7.6, 1.6 Hz, 1 H), 6.88 (dd, *J* = 7.6, 4.8 Hz, 1 H), 6.62 (s, 1 H), 5.60 (s, 2 H).

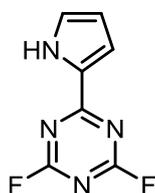
<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 171.0, 158.2, 155.6 (q, *J* = 38.5 Hz), 145.4, 142.5, 119.7 (q, *J* = 271.2 Hz), 119.3, 107.0, 101.3, 59.0.

<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>): δ -63.6 (s, 3 F).

FTIR (ν<sub>max</sub>, cm<sup>-1</sup>): 2927 (w), 2856 (w), 1582 (m), 1558 (w), 1488 (m), 1450 (m), 1435 (m), 1423 (m), 1380 (m), 1309 (m), 1287 (m), 1254 (m), 1236 (m), 1144 (s), 1099 (m), 1069 (m), 1036 (s), 1015 (m), 1001 (m), 969 (s), 936 (m), 819 (m), 794 (s), 760 (m).

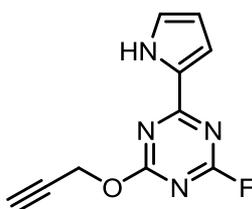
HRMS (ESI): calculated for C<sub>10</sub>H<sub>7</sub>BrF<sub>3</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 322.9638, found 322.9623.

*R*<sub>f</sub> = 0.19 (5% EtOAc/hexane).



**2,4-difluoro-6-(1H-pyrrol-2-yl)-1,3,5-triazine:** Prepared as reported in literature.<sup>2</sup> Pyrrole (0.95 g, 14.2 mmol, 1 eq.) and cyanuric fluoride (1.91 g, 14.2 mmol, 1 eq.) was refluxed in MeCN (10 mL) for 2 h. The reaction mixture was cooled to r.t. and water (60 mL) was added to precipitate the yellow solid product, which was filtered off, dried *in vacuo* and purified by vacuum sublimation (130 °C, 0.1 mmHg) to provide the title product as white crystals (3.50 g, 65%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 9.64 (br s, 1 H), 7.48 – 7.41 (m, 1 H), 7.21 – 7.15 (m, 1 H), 6.48 – 6.42 (m, 1 H).



**2-fluoro-4-(prop-2-yn-1-yloxy)-6-(1H-pyrrol-2-yl)-1,3,5-triazine:** To a solution of 2,4-difluoro-6-(1H-pyrrol-2-yl)-1,3,5-triazine (400 mg, 1.83 mmol, 1.1 eq.) in MeCN (5 mL) was added propargyl alcohol (93 mg, 1.66 mmol, 1 eq.) and DIPEA (0.32 mL, 1.83 mmol, 1.1 eq.). The reaction mixture was stirred at r.t. for 30 min then washed with saturated aqueous

NH<sub>4</sub>Cl (3 × 5 mL) and dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure and purified by silica gel column chromatography (15% Et<sub>2</sub>O/hexane), which afforded the title compound as a white powder (383 mg, 96%), m.p. 91-92 °C.

**<sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD):** δ 7.29 (dd, *J* = 3.9, 1.5 Hz, 1 H), 7.14 (dd, *J* = 2.4, 1.5 Hz, 1 H), 6.33 (dd, *J* = 3.9, 2.4 Hz, 1 H), 5.17 (d, *J* = 2.5 Hz, 2 H), 3.04 (t, *J* = 2.5 Hz, 1 H).

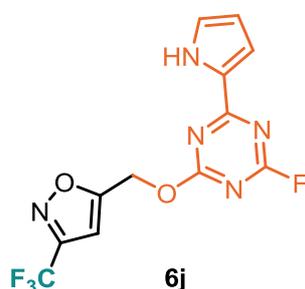
**<sup>13</sup>C NMR (125 MHz, CD<sub>3</sub>OD):** δ 173.9 (d, *J* = 16.8 Hz), 172.0 (d, *J* = 224.1 Hz), 170.8 (d, *J* = 14.3 Hz), 128.8, 127.6, 118.7, 112.5, 78.2, 77.3, 57.2.

**<sup>19</sup>F NMR (376 MHz, CD<sub>3</sub>OD):** δ -42.9 (s, 1 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 3398 (m), 3253 (m), 1614 (s), 1592 (m), 1580 (m), 1520 (s), 1476 (m), 1438 (s), 1416 (s), 1372 (m), 1341 (s), 1280 (m), 1256 (w), 1234 (w), 1107 (w), 1095 (s), 1077 (s), 1043 (m), 1015 (m), 990 (w), 963 (m), 923 (m), 884 (w), 831 (w), 807 (s).

**HRMS (ESI):** calculated for C<sub>10</sub>H<sub>8</sub>FN<sub>4</sub>O [M+H]<sup>+</sup> 219.0677, found 219.0672.

*R<sub>f</sub>* = 0.36 (40% Et<sub>2</sub>O/hexane).



**5-(((4-fluoro-6-(1H-pyrrol-2-yl)-1,3,5-triazin-2-yl)oxy)methyl)-3-(trifluoromethyl)isoxazole (6j):** The reaction of **3** (1.62 g containing 0.176 g of **3**, 0.92 mmol, 2 eq.) and 2-fluoro-4-(prop-2-yn-1-yloxy)-6-(1H-pyrrol-2-yl)-1,3,5-triazine (0.100 g, 0.46 mmol, 1 eq.) using the general procedure for alkyl alkynes with 2 eq. of hydroximoyl bromide and Et<sub>2</sub>O as solvent, purified using silica gel column chromatography (5% → 20% EtOAc/hexane), afforded the title compound **6j** (0.085 g, 56%) as a white solid, m.p. 53-54 °C.

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 9.64 (s, 1 H), 7.40 – 7.33 (m, 1 H), 7.16 – 7.11 (m, 1 H), 6.71 (s, 1 H), 6.44 – 6.39 (m, 1 H), 5.66 (s, 2 H).

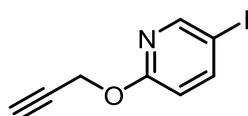
**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 172.5 (d, *J* = 16.4 Hz), 170.7 (d, *J* = 228.8 Hz), 169.5 (d, *J* = 14.0 Hz), 168.8, 155.8 (q, *J* = 38.8 Hz), 127.6, 126.0, 119.5 (q, *J* = 271.3 Hz), 118.2, 112.8, 102.2, 59.9.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -38.7 (br s, 1 F), -63.6 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 3399 (br w), 1596 (m), 1567 (s), 1523 (m), 1494 (m), 1476 (m), 1412 (s), 1378 (m), 1335 (s), 1302 (m), 1260 (m), 1185 (s), 1152 (s), 1105 (m), 1087 (s), 1035 (s), 970 (m), 950 (w), 931 (m), 884 (m), 861 (w), 846 (m), 812 (s), 753 (m).

**HRMS (ESI):** calculated for C<sub>12</sub>H<sub>8</sub>F<sub>4</sub>N<sub>5</sub>O<sub>2</sub> [M+H]<sup>+</sup> 330.0609, found 330.0598.

*R<sub>f</sub>* = 0.33 (20% EtOAc/hexane).



**5-iodo-2-(prop-2-yn-1-yloxy)pyridine:** To a suspension of NaH (60% dispersion in mineral oil, 80.7 mg, 2.02 mmol, 1.5 eq.) in anhydrous THF (3 mL) was added slowly dropwise propargyl alcohol (0.117 mL, 2.02 mmol, 1.5 eq.) at 0 °C. The mixture was warmed to r.t. and stirred further for 15 min. A solution of 2-fluoro-5-iodopyridine (300 mg, 1.35 mmol, 1 eq.) in anhydrous THF (2 mL) was added dropwise and the mixture stirred at r.t. for 2 h.

The reaction was then quenched with water (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (2% → 5% EtOAc/hexane), which afforded the title compound as a white solid (344 mg, 96%), m.p. 91-92 °C.

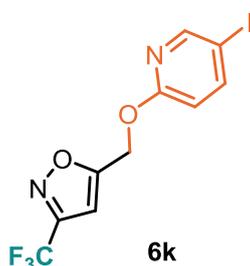
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 8.35 (dd, *J* = 2.3, 0.5 Hz, 1 H), 7.81 (dd, *J* = 8.7, 2.3 Hz, 1 H), 6.65 (dd, *J* = 8.7, 0.5 Hz, 1 H), 4.93 (d, *J* = 2.4 Hz, 2 H), 2.48 (t, *J* = 2.4 Hz, 1 H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 161.9, 152.7, 146.8, 113.7, 83.2, 78.9, 74.7, 53.7.

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 3275 (m), 2925 (w), 2853 (w), 1581 (m), 1557 (m), 1470 (s), 1445 (s), 1374 (m), 1349 (w), 1337 (s), 1277 (s), 1244 (s), 1220 (m), 1151 (w), 1127 (m), 1081 (m), 1039 (w), 1024 (m), 1011 (s), 996 (s), 960 (s), 937 (m), 856 (w), 830 (s).

**HRMS (ESI):** calculated for C<sub>8</sub>H<sub>7</sub>INO [M+H]<sup>+</sup> 259.9567, found 259.9568.

*R<sub>f</sub>* = 0.38 (4% EtOAc/hexane).



**5-(((5-iodopyridin-2-yl)oxy)methyl)-3-(trifluoromethyl)isoxazole (6k):** The reaction of **3** (2.04 g containing 0.222 g of **3**, 1.16 mmol, 2 eq.) and 5-(((5-iodopyridin-2-yl)oxy)methyl)-3-(trifluoromethyl)isoxazole (0.150 g, 0.58 mmol, 1 eq.) using the general procedure for alkyl alkynes with 2 eq. of hydroximoyl bromide and Et<sub>2</sub>O as solvent, purified using silica gel column chromatography (2% → 4% EtOAc/hexane), afforded the title compound **6k** (0.135 g, 63%) as a white solid, m.p. 60-61 °C.

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 8.34 (s, 1 H), 7.85 (d, *J* = 8.6 Hz, 1 H), 6.67 (d, *J* = 8.6 Hz, 1 H), 6.57 (s, 1 H), 5.50 (s, 2 H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 170.9, 161.5, 155.6 (q, *J* = 38.4 Hz), 152.7, 147.2, 119.7 (q, *J* = 271.2 Hz), 113.6, 101.4, 83.8, 58.0.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -63.6 (s, 3 F).

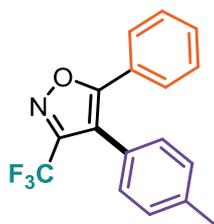
**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 2923 (w), 2852 (w), 1615 (w), 1604 (w), 1579 (m), 1557 (m), 1495 (m), 1467 (s), 1449 (s), 1387 (w), 1376 (w), 1357 (m), 1343 (s), 1292 (m), 1279 (s), 1260 (m), 1243 (m), 1217 (m), 1198 (s), 1186 (s), 1152 (s), 1131 (m), 1097 (m), 1079 (m), 1049 (m), 1037 (m), 996 (m), 968 (s), 936 (m), 920 (m), 864 (w), 836 (m), 824 (s), 765 (s).

**HRMS (ESI):** calculated for C<sub>10</sub>H<sub>7</sub>F<sub>3</sub>IN<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 370.9499, found 370.9494.

*R<sub>f</sub>* = 0.36 (4% EtOAc/hexane).

### 2.3. Intermolecular C-H cross-coupling

**General procedure for intermolecular C-H coupling reactions:** The isoxazole (2.0 mmol, 1 eq.), aryl bromide (4.0 mmol, 2 eq.), potassium acetate (0.393 g, 4.0 mmol, 2 eq.) and palladium(II) chloride (18 mg, 0.1 mmol, 0.05 eq.) in DMA (7 mL) were stirred at 130 °C for 72 h. The flask was then cooled to r.t. and Et<sub>2</sub>O (25 mL) was added. The mixture was filtered through a plug of Celite, eluting with EtOAc. The filtrate was then washed with water (3 × 25 mL), brine (25 mL), dried (MgSO<sub>4</sub>) and evaporated under reduced pressure, purified by flash column chromatography.



7a

**5-phenyl-4-(p-tolyl)-3-(trifluoromethyl)isoxazole (7a):** The cross-coupling of **5a** (0.490 g, 2.3 mmol, 1 eq.) and 4-bromotoluene (0.804 g, 4.7 mmol, 2 eq.) using the general procedure for intermolecular C-H coupling reactions, purified by silica gel column chromatography (hexane → 10% Et<sub>2</sub>O/hexane) afforded the title compound **7a** (0.591 g, 85%) as a yellow solid, m.p. 66-67 °C.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.60 – 7.54 (m, 2 H), 7.47 – 7.40 (m, 1 H), 7.40 – 7.33 (m, 2 H), 7.32 – 7.23 (m, 4 H), 2.46 (s, 3 H).

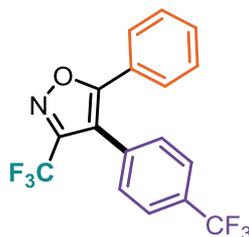
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 167.8, 155.0 (q, *J* = 35.8 Hz), 139.2, 130.7, 130.0 (q, *J* = 0.6 Hz), 129.9, 129.0, 127.1, 126.7, 124.5, 120.0 (q, *J* = 272.2 Hz), 114.4 (q, *J* = 0.7 Hz), 21.5.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -63.6 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 1626 (w), 1596 (w), 1519 (w), 1478 (m), 1446 (m), 1380 (w), 1339 (m), 1288 (w), 1245 (w), 1207 (m), 1174 (s), 1138 (s), 1087 (m), 1027 (w), 984 (m), 967 (m), 950 (m), 849 (w), 821 (m), 783 (m), 767 (w), 750 (m).

**HRMS (ESI):** calculated for C<sub>17</sub>H<sub>13</sub>F<sub>3</sub>NO [M+H]<sup>+</sup> 304.0944, found 304.0934.

**R<sub>f</sub>** = 0.15 (hexane).



7b

**5-phenyl-3-(trifluoromethyl)-4-(4-(trifluoromethyl)phenyl)isoxazole (7b):** The cross-coupling of **5a** (0.426 g, 2.0 mmol, 1 eq.) and 4-bromobenzotrifluoride (0.900 g, 4.0 mmol, 2 eq.) using the general procedure for intermolecular C-H coupling reactions, purified by silica gel column chromatography (hexane → 4% Et<sub>2</sub>O/hexane) afforded the title compound **7b** (0.619 g, 87%) as a pale yellow solid, m.p. 74-75 °C.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.75 (d, *J* = 7.8 Hz, 2 H), 7.55 – 7.42 (m, 5 H), 7.38 (t, *J* = 7.8 Hz, 2 H).

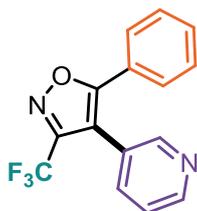
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 168.6, 154.7 (q, *J* = 36.3 Hz), 131.7 (q, *J* = 1.4 Hz), 131.5 (q, *J* = 32.8 Hz), 131.3, 130.7 (q, *J* = 0.6 Hz), 129.3, 127.3, 126.2 (q, *J* = 3.8 Hz), 126.1, 124.0 (q, *J* = 272.4 Hz), 119.9 (q, *J* = 272.2 Hz), 113.0.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -62.0 (s, 3 F), -63.3 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 1627 (m), 1613 (w), 1482 (m), 1444 (m), 1408 (w), 1323 (s), 1216 (m), 1170 (s), 1128 (s), 1088 (s), 1066 (s), 1023 (m), 985 (m), 974 (m), 847 (m), 780 (m).

**HRMS (ESI):** calculated for C<sub>17</sub>H<sub>10</sub>F<sub>6</sub>NO [M+H]<sup>+</sup> 358.0661, found 358.0649.

*R<sub>f</sub>* = 0.52 (5% Et<sub>2</sub>O/hexane).



**7c**

**5-phenyl-4-(pyridin-3-yl)-3-(trifluoromethyl)isoxazole (7c):** The cross-coupling of **5a** (0.426 g, 2.0 mmol, 1 eq.) and 3-bromopyridine (0.632 g, 4.0 mmol, 2 eq.) using the general procedure for intermolecular C-H coupling reactions, purified by silica gel column chromatography (20% EtOAc/hexane → 40% EtOAc/hexane) afforded the title compound **7c** (0.454 g, 78%) as a pale yellow viscous oil.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.71 (dd, *J* = 4.8, 1.3 Hz, 1 H), 8.59 (d, *J* = 1.3 Hz, 1 H), 7.69 (d, *J* = 7.9 Hz, 1 H), 7.51 – 7.43 (m, 2 H), 7.43 – 7.38 (m, 2 H), 7.35 (t, *J* = 7.4 Hz, 2 H).

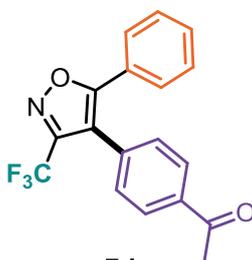
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 168.9, 154.8 (q, *J* = 36.3 Hz), 150.7 (q, *J* = 0.7 Hz), 150.4, 137.6, 131.3, 129.2, 127.2, 125.9, 124.1, 123.8, 119.8 (q, *J* = 272.3 Hz), 110.8.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -62.0 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 1623 (w), 1566 (w), 1497 (m), 1469 (m), 1447 (m), 1411 (m), 1342 (m), 1176 (s), 1141 (s), 1090 (m), 1046 (m), 1029 (m), 981 (m), 964 (m), 814 (m), 778 (m), 757 (m).

**HRMS (ESI):** calculated for C<sub>15</sub>H<sub>10</sub>F<sub>3</sub>N<sub>2</sub>O [M+H]<sup>+</sup> 291.0740, found 291.0728.

*R<sub>f</sub>* = 0.22 (20% EtOAc/hexane).



**7d**

**1-(4-(5-phenyl-3-(trifluoromethyl)isoxazol-4-yl)phenyl)ethanone (7d):** The cross-coupling of **5a** (0.426 g, 2.0 mmol, 1 eq.) and 4-bromoacetophenone (0.796 g, 4.0 mmol, 2 eq.) using the general procedure for intermolecular C-H coupling reactions, purified by silica gel column chromatography (10% EtOAc/hexane → 20% EtOAc/hexane) afforded the title compound **7d** (0.396 g, 60%) as a pale yellow solid, m.p. 118-119 °C.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.03 (d, *J* = 8.4 Hz, 2 H), 7.49 – 7.43 (m, 4 H), 7.43 – 7.37 (m, 1 H), 7.33 (t, *J* = 7.4 Hz, 2 H), 2.64 (s, 3 H).

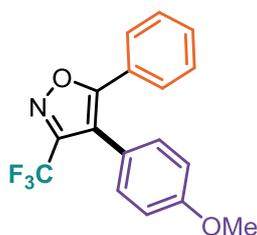
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 197.4, 168.3, 154.5 (q, *J* = 36.2 Hz), 137.5, 132.5, 131.1, 130.5 (q, *J* = 0.5 Hz), 129.1, 129.0, 127.1, 126.0, 119.8 (q, *J* = 272.3 Hz), 113.3 (q, *J* = 0.7 Hz), 26.6.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -62.0 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 1684 (s), 1623 (w), 1604 (w), 1480 (m), 1443 (m), 1403 (m), 1356 (w), 1338 (m), 1264 (m), 1210 (m), 1184 (s), 1144 (s), 1089 (m), 1017 (w), 985 (m), 972 (m), 959 (m), 855 (m), 839 (m), 782 (m), 762 (w).

**HRMS (ESI):** calculated for C<sub>18</sub>H<sub>13</sub>F<sub>3</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 332.0893, found 332.0878.

*R<sub>f</sub>* = 0.24 (10% EtOAc/hexane).



**7e**

**4-(4-methoxyphenyl)-5-phenyl-3-(trifluoromethyl)isoxazole (7e):** The cross-coupling of **5a** (0.426 g, 2.0 mmol, 1 eq.) and 4-bromoanisole (0.748 g, 4.0 mmol, 2 eq.) using the general procedure for intermolecular C-H coupling reactions, purified by silica gel column chromatography (4% EtOAc/hexane) afforded the title compound **7e** (0.331 g, 52%) as a yellow solid, m.p. 88-89 °C.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.58 – 7.51 (m, 2 H), 7.44 – 7.37 (m, 1 H), 7.38 – 7.31 (m, 2 H), 7.27 (d, *J* = 8.7 Hz, 2 H), 6.99 (d, *J* = 8.7 Hz, 2 H), 3.87 (s, 3 H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 167.8, 160.3, 155.0 (q, *J* = 35.7 Hz), 131.4, 130.7, 129.0, 127.0, 126.7, 120.0 (q, *J* = 272.3 Hz), 119.4, 114.7, 114.1 (q, *J* = 0.7 Hz), 55.3.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -62.2 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 3021 (w), 2937 (w), 2840 (w), 1622 (w), 1607 (w), 1595 (w), 1575 (w), 1518 (m), 1480 (m), 1469 (m), 1441 (m), 1341 (m), 1307 (w), 1287 (m), 1249 (m), 1213 (m), 1178 (s), 1138 (s), 1108 (m), 1089 (m), 1030 (m), 1015 (m), 977 (m), 950 (m), 836 (s), 798 (w), 785 (m).

**HRMS (ESI):** calculated for C<sub>18</sub>H<sub>13</sub>F<sub>3</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 320.0893, found 320.0879.

*R<sub>f</sub>* = 0.29 (4% EtOAc/hexane).



**7f**

**5-cyclopropyl-4-(pyridin-3-yl)-3-(trifluoromethyl)isoxazole (7f):** The cross-coupling of **6f** and 3-bromopyridine (0.632 g, 4.0 mmol, 2 eq.) using the general procedure for intermolecular C-H coupling reactions, purified by silica gel column chromatography (20% EtOAc/hexane → 50% EtOAc/hexane) afforded the title compound **7f** (0.241 g, 47%) as a yellow viscous oil.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.62 – 8.52 (m, 2 H), 7.65 (d, *J* = 7.9 Hz, 1 H), 7.31 (dd, *J* = 7.9, 4.9 Hz, 1 H), 1.97 – 1.83 (m, 1 H), 1.16 – 1.08 (m, 2 H), 1.08 – 0.98 (m, 2 H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 173.8, 153.5 (q, *J* = 36.3 Hz), 150.2 (q, *J* = 0.8 Hz), 149.7, 137.1 (q, *J* = 1.1 Hz), 123.7, 123.5, 119.8 (q, *J* = 272.0 Hz), 110.9 (q, *J* = 0.7 Hz), 8.9, 7.5.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -62.1 (s, 3 F).

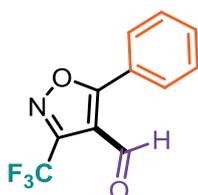
**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 1619 (w), 1587 (w), 1568 (w), 1497 (m), 1481 (m), 1412 (w), 1362 (w), 1310 (m), 1245 (m), 1185 (s), 1141 (s), 1063 (w), 1051 (w), 1030 (w), 998 (m), 978 (s), 947 (w), 879 (w), 813 (m), 757 (m).

**HRMS (ESI):** calculated for C<sub>12</sub>H<sub>10</sub>F<sub>3</sub>N<sub>2</sub>O [M+H]<sup>+</sup> 255.0740, found 255.0736.

**R<sub>f</sub>** = 0.30 (50% EtOAc/hexane).

## 2.4. Lithiation reactions

**General procedure for lithiation reactions:** To a solution of the isoxazole (0.6 mmol, 1 eq.) in anhydrous THF (3 mL) was added <sup>n</sup>BuLi dropwise at -78 °C and stirred for 30 min. The electrophile was added slowly dropwise and stirred for 10 min. The reaction mixture was then warmed to r.t. and quenched with aqueous NH<sub>4</sub>Cl (3 mL) and water (25 mL) was added. The mixture was extracted with Et<sub>2</sub>O (2 × 25 mL) and the combined organic extracts dried (MgSO<sub>4</sub>), evaporated under reduced pressure and purified by flash column chromatography.



**8a**

**5-phenyl-3-(trifluoromethyl)isoxazole-4-carbaldehyde (8a):** The reaction of **5a** (0.128 g, 0.6 mmol, 1 eq.) with <sup>n</sup>BuLi (1.25 M in hexanes, 0.72 mL, 0.9 mmol, 1.5 eq.) and DMF (0.75 mL, 0.70 g, 9.6 mmol, 16 eq.) using the general procedure for lithiation reactions, purified by silica gel column chromatography (hexane → 10% EtOAc/hexane) afforded the title product **8a** (0.136 g, 94%) as a white solid, m.p. 47-47.5 °C.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 10.05 (s, 1 H), 7.96 (d, *J* = 7.4 Hz, 2 H), 7.67 (t, *J* = 7.4 Hz, 1 H), 7.59 (t, *J* = 7.4 Hz, 2 H).

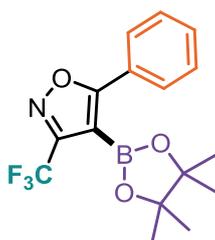
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 181.0, 176.6, 154.0 (q, *J* = 39.2 Hz), 133.3, 129.5, 129.1, 124.8, 119.3 (q, *J* = 272.4 Hz), 113.6.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -63.2 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 1699 (s), 1603 (w), 1587 (w), 1559 (m), 1510 (w), 1481 (m), 1460 (m), 1448 (m), 1398 (w), 1330 (m), 1312 (m), 1290 (w), 1230 (w), 1199 (m), 1180 (m), 1137 (s), 1075 (s), 1066 (s), 1001 (w), 962 (m), 926 (w), 800 (s), 773 (m), 754 (m).

**HRMS (ESI):** calculated for C<sub>11</sub>H<sub>7</sub>F<sub>3</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 242.0423, found 242.0425.

*R<sub>f</sub>* = 0.32 (10% EtOAc/hexane).



**8b**

**5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)isoxazole (8b):** The reaction of **5a** (0.128 g, 0.6 mmol, 1 eq.) with <sup>n</sup>BuLi (1.25 M in hexanes, 0.72 mL, 0.9 mmol, 1.5 eq.) and isopropyl pinacol borate (0.179 g, 0.96 mmol, 1.6 eq.) using the general procedure for lithiation reactions, without column chromatography, afforded the title product **8b** (0.195 g, 96%) as a pale yellow solid, m.p. 77-79 °C.

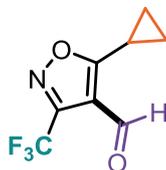
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.99 – 7.93 (m, 2 H), 7.53 – 7.44 (m, 3 H), 1.35 (s, 12 H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 177.4, 158.7 (q, *J* = 37.2 Hz), 131.3, 128.7, 128.1, 127.2, 120.1 (q, *J* = 271.7 Hz), 85.0, 24.6. Carbon signal next to boron not observed due to quadrupolar relaxation.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -62.9 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 2981 (w), 1608 (w), 1595 (w), 1570 (w), 1486 (m), 1439 (m), 1382 (m), 1367 (m), 1333 (m), 1228 (w), 1212 (w), 1168 (m), 1138 (s), 1106 (m), 1089 (m), 1037 (m), 1024 (m), 1003 (w), 973 (m), 953 (m), 855 (m), 829 (w), 795 (w), 778 (w), 757 (m).

**HRMS (EI):** calculated for C<sub>16</sub>H<sub>17</sub>BF<sub>3</sub>NO<sub>3</sub> [M]<sup>+</sup> 339.1256, found 339.1248.



**8c**

**5-cyclopropyl-3-(trifluoromethyl)isoxazole-4-carbaldehyde (8c):** The reaction of **6f** (0.106 g, 0.6 mmol, 1 eq.) with <sup>n</sup>BuLi (1.40 M in hexanes, 1.07 mL, 1.5 mmol, 2.5 eq.) and DMF (0.75 mL, 0.70 g, 9.6 mmol, 16 eq.) using the general procedure for lithiation reactions, purified by silica gel column chromatography (10% EtOAc/hexane) afforded the title product **8c** (0.042 g, 34%) as a pale yellow oil.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 9.98 (q, *J* = 0.8 Hz, 1 H), 2.90 – 2.82 (m, 1 H), 1.44 – 1.35 (m, 4 H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 182.7, 181.7 (q, *J* = 1.0 Hz), 153.7 (q, *J* = 38.9 Hz), 119.5 (q, *J* = 272.3 Hz), 113.9, 11.9, 9.4.

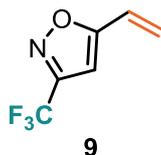
**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -62.1 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 1696 (s), 1574 (m), 1506 (m), 1475 (w), 1433 (w), 1410 (w), 1357 (w), 1322 (w), 1309 (m), 1246 (w), 1226 (m), 1187 (s), 1144 (s), 1117 (m), 1067 (w), 1036 (w), 989 (s), 917 (w), 876 (m), 802 (m), 754 (m).

**HRMS (ESI):** calculated for C<sub>8</sub>H<sub>7</sub>F<sub>3</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 206.0423, found 206.0425.

*R<sub>f</sub>* = 0.34 (10% EtOAc/hexane).

## 2.5. Isoxazoline scaffold formation



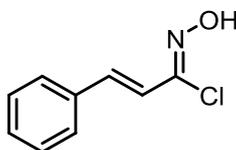
**3-(trifluoromethyl)-5-vinylisoxazole:** To a solution of **6e** (1.96 g, 8.06 mmol) in Et<sub>2</sub>O (50 mL) was added Ambersep<sup>®</sup> 900 (hydroxide form, 5.0 g) and the mixture stirred at r.t. for 6 h. The immobilised base was filtered off, affording the crude volatile title product **9** as a solution in Et<sub>2</sub>O (34.99 g containing 1.31 g of **9**, 99%) as a colourless liquid. The solution was used without further purification and stored in the freezer.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 6.63 (dd, *J* = 17.7, 11.4 Hz, 1 H), 6.42 (s, 1 H), 6.11 (d, *J* = 17.7 Hz, 1 H), 5.69 (d, *J* = 11.4 Hz, 1 H).

<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>): δ -63.6 (s, 3 F).

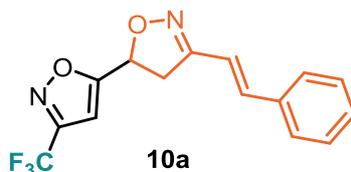
*R*<sub>f</sub> = 0.69 (20% EtOAc/hexane).

**General procedure for isoxazoline cycloadditions:** To a solution of **9** (1.60 g containing 60 mg of **9**, 0.33 mmol) and the nitrile oxide precursor (0.66 mmol) in Et<sub>2</sub>O (2 mL) was added slowly dropwise a solution of Et<sub>3</sub>N (0.09 mL, 0.66 mmol, 2 eq.) in toluene (1 mL) over 5 min. The reaction mixture was further stirred for 2 h. Hexane (5 mL) was added and the white precipitate filtered off. The white precipitate was washed further on the filter with EtOAc (5 mL). The filtrate was washed with water (5 mL), brine (5 mL), dried (MgSO<sub>4</sub>), evaporated under reduced pressure and purified by flash column chromatography.



**N-hydroxycinnamimidoyl chloride:** Cinnamaldehyde (4.81 mL, 37.8 mmol, 1.0 eq.) was dissolved in MeOH/H<sub>2</sub>O (3:1, 40 mL) and then hydroxylamine hydrochloride (2.63 g, 37.8 mmol, 1.0 eq.) and NaOH (3.78 g, 94.5 mmol, 2.5 eq.) added slowly portionwise at 0 °C. The reaction was then warmed to r.t. and stirred overnight. The aqueous layer was washed with Et<sub>2</sub>O (25 mL) and then acidified with 6 N aqueous HCl until ca. pH 6 at 0 °C. The aqueous layer was then extracted with Et<sub>2</sub>O (3 × 25 mL), the combined organic extracts dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to provide the crude aldoxime. The crude aldoxime (5.60 g, ca. 37.8 mmol) was then redissolved in DMF (45 mL) and cooled to 0 °C. Approximately one-third of *N*-chlorosuccinimide (5.05 g, 37.8 mmol, 1 eq.) was added slowly portionwise, then one drop of 1 N aqueous HCl was added to initiate the reaction. The remainder of the NCS was added slowly portionwise and the reaction mixture stirred further at r.t. for 5 h. Water (100 mL) was added and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with water (5 × 50 mL), brine (50 mL), dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (20% EtOAc/hexane) to provide the title compound (3.46 g, 50% over 2 steps) as a pale yellow solid. Data consistent with literature.<sup>3</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.75 (s, 1 H), 7.49 (d, *J* = 7.0 Hz, 2 H), 7.42 – 7.28 (m, 4 H), 6.86 (d, *J* = 15.7 Hz, 1 H).



**(E)-3-styryl-3'-(trifluoromethyl)-4,5-dihydro-5,5'-biisoxazole (10a):** The reaction of **9** (1.60 g containing 60 mg of **9**, 0.33 mmol, 1 eq.), *N*-hydroxycinnamimidoyl chloride (107.7 mg, 0.66 mmol, 2 eq.) and Et<sub>3</sub>N (0.09 mL, 0.66 mmol, 2 eq.) in Et<sub>2</sub>O (2 mL), using the general procedure for isoxazoline cycloadditions, purified by silica gel column chromatography (20% EtOAc/hexane) afforded the title compound **10a** as a pale yellow solid (101 mg, 99%), m.p. 109-111 °C.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.47 (d, *J* = 6.9 Hz, 2 H), 7.42 – 7.33 (m, 3 H), 7.08 (d, *J* = 16.5 Hz, 1 H), 6.82 (d, *J* = 16.5 Hz, 1 H), 6.61 (s, 1 H), 5.83 (dd, *J* = 11.1, 6.4 Hz, 1 H), 3.69 (dd, *J* = 16.5, 11.1 Hz, 1 H), 3.50 (dd, *J* = 16.5, 6.4 Hz, 1 H).

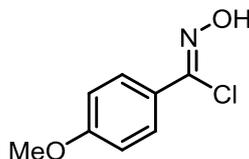
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 173.1, 157.2, 155.7 (q, *J* = 38.7 Hz), 138.4, 135.3, 129.6, 129.1, 127.3, 119.5 (q, *J* = 271.3 Hz), 116.5, 100.1 (q, *J* = 1.3 Hz), 73.8, 39.1.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -63.6 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 3157 (w), 2921 (w), 2851 (w), 1631 (w), 1605 (w), 1578 (w), 1567 (w), 1490 (m), 1451 (m), 1368 (m), 1343 (m), 1259 (w), 1234 (w), 1204 (m), 1190 (m), 1180 (s), 1139 (s), 1091 (m), 1074 (w), 1032 (w), 971 (m), 956 (m), 940 (m), 917 (m), 899 (s), 863 (m), 841 (m), 825 (m).

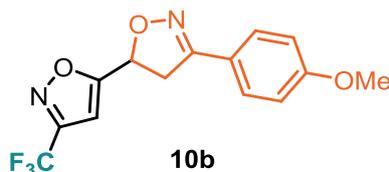
**HRMS (ESI):** calculated for C<sub>15</sub>H<sub>12</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 309.0845, found 309.0833.

*R<sub>f</sub>* = 0.44 (20% EtOAc/hexane).



***N*-hydroxy-4-methoxybenzimidoyl chloride:** *p*-anisaldehyde (4.65 mL, 36.7 mmol, 1.0 eq.) was dissolved in MeOH/H<sub>2</sub>O (3:1, 40 mL) and then hydroxylamine hydrochloride (2.55 g, 36.7 mmol, 1.0 eq.) and NaOH (3.67 g, 91.8 mmol, 2.5 eq.) added slowly portionwise at 0 °C. The reaction was then warmed to r.t. and stirred overnight. The aqueous layer was washed with Et<sub>2</sub>O (25 mL) and then acidified with 6 N aqueous HCl until ca. pH 6 at 0 °C. The aqueous layer was then extracted with Et<sub>2</sub>O (3 × 25 mL), the combined organic extracts dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to provide the crude aldoxime. The crude aldoxime (3.60 g, ca. 23.8 mmol) was then redissolved in DMF (30 mL) and cooled to 0 °C. Approximately one-third of *N*-chlorosuccinimide (3.24 g, 23.8 mmol, 1 eq.) was added slowly portionwise, then one drop of 1 N aqueous HCl was added to initiate the reaction. The remainder of the NCS was added slowly portionwise and the reaction mixture stirred further at r.t. for 5 h. Water (100 mL) was added and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with water (5 × 50 mL), brine (50 mL), dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (20% EtOAc/hexane) to provide the title compound (2.66 g, 60% over 2 steps) as a yellow solid. Data consistent with literature.<sup>4</sup>

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.78 (d, *J* = 8.9 Hz, 2 H), 7.74 (s, 1 H), 6.92 (d, *J* = 8.9 Hz, 2 H), 3.85 (s, 3 H).



**3-(4-methoxyphenyl)-3'-(trifluoromethyl)-4,5-dihydro-5,5'-biisoxazole (10b):** The reaction of **9** (1.07 g containing 40 mg of **9**, 0.216 mmol, 1 eq.), *N*-hydroxy-4-methoxybenzimidoyl chloride (70.5 mg, 0.432 mmol, 2 eq.) and Et<sub>3</sub>N (0.06 mL, 0.432 mmol, 2 eq.) in Et<sub>2</sub>O (2 mL), using the general procedure for isoxazoline cycloadditions, purified by silica gel column chromatography (25% EtOAc/hexane), afforded the title compound **10b** as a white solid (62.0 mg, 92%), m.p. 82-83 °C.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.62 (d, *J* = 8.9 Hz, 2 H), 6.94 (d, *J* = 8.9 Hz, 2 H), 6.62 (s, 1 H), 5.86 (ddd, *J* = 11.1, 6.2, 0.5 Hz, 1 H), 3.85 (s, 3 H), 3.82 (dd, *J* = 16.6, 11.1 Hz, 1 H), 3.61 (dd, *J* = 16.6, 6.2 Hz, 1 H).

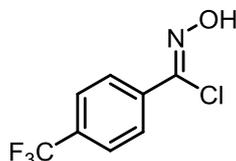
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 173.5, 161.8, 155.9, 155.8 (q, *J* = 38.7 Hz), 128.7, 120.7, 119.6 (q, *J* = 271.4 Hz), 114.5, 100.1 (q, *J* = 1.1 Hz), 73.7, 55.6, 40.8.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -63.4 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 3129 (w), 3001 (w), 2970 (w), 2942 (w), 2843 (w), 1608 (m), 1569 (w), 1515 (m), 1490 (m), 1457 (w), 1442 (w), 1421 (w), 1358 (m), 1335 (m), 1304 (m), 1254 (m), 1188 (s), 1176 (s), 1150 (s), 1117 (m), 1092 (m), 1044 (m), 1024 (m), 969 (m), 944 (m), 934 (w), 916 (m), 871 (s), 846 (s), 831 (s), 816 (s).

**HRMS (ESI):** calculated for C<sub>14</sub>H<sub>12</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup> 313.0795, found 313.0781.

*R<sub>f</sub>* = 0.39 (25% EtOAc/hexane).



***N*-hydroxy-4-(trifluoromethyl)benzimidoyl chloride:** 4-(trifluoromethyl)benzaldehyde (3.0 g, 17.2 mmol, 1 eq.) and hydroxylamine hydrochloride (1.8 g, 25.8 mmol, 1.5 eq.) were dissolved in MeOH /H<sub>2</sub>O (3:1, 10 mL). An aqueous solution of 50% NaOH (3.5 mL, 43.1 mmol, 2.5 eq.) was added slowly dropwise *via* syringe pump over 45 min to the stirred reaction mixture at 0 °C. The reaction mixture was allowed to warm to r.t. and stirred overnight. Hexane (15 mL) was added, the layers were separated and the aqueous layer was acidified with 37% aqueous HCl to pH 6 at 0 °C. The mixture was then extracted with Et<sub>2</sub>O (2 × 20 mL) and the combined organic extracts dried (MgSO<sub>4</sub>). The solvent was evaporated under reduced pressure to provide the crude aldoxime. The crude aldoxime (2.56 g, ca. 13.6 mmol) was then redissolved in DMF (15 mL) and cooled to 0 °C. Approximately one-third of *N*-chlorosuccinimide (2.17 g, 16.3 mmol, 1.2 eq.) was added slowly portionwise, then one drop of 1 N aqueous HCl was added to initiate the reaction. The remainder of the NCS was added slowly portionwise and the reaction mixture stirred further at r.t. for 5 h. Water (100 mL) was added and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with water (5 × 100 mL), brine (100 mL), dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (20% EtOAc/hexane) to provide the title compound (2.91 g, 76% over 2 steps) as a white solid, m.p. 87-89 °C.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.50 (s, 1 H), 7.96 (d, *J* = 8.2 Hz, 2 H), 7.67 (d, *J* = 8.2 Hz, 2 H).

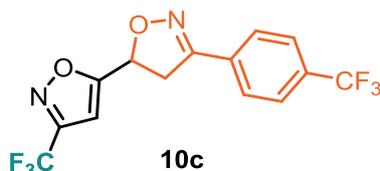
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 139.4, 135.8 (q, *J* = 1.1 Hz), 132.7 (q, *J* = 32.8 Hz), 127.7, 125.7 (q, *J* = 3.8 Hz), 123.8 (q, *J* = 272.4 Hz).

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -63.2 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 3288 (br w), 1712 (m), 1614 (w), 1439 (w), 1409 (m), 1323 (s), 1235 (m), 1158 (s), 1115 (s), 1068 (s), 999 (s), 939 (s), 845 (s), 773 (m).

**HRMS (ESI):** calculated for C<sub>8</sub>H<sub>4</sub>ClF<sub>3</sub>NO [M-H]<sup>-</sup> 221.9939, found 221.9939.

*R<sub>f</sub>* = 0.74 (20% EtOAc/hexane).



**3'-(trifluoromethyl)-3-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5,5'-biisoxazole (10c):**

The reaction of **9** (2.67 g containing 100 mg of **9**, 0.448 mmol, 1 eq.), *N*-hydroxy-4-(trifluoromethyl)benzimidoyl chloride (109.5 mg, 0.672 mmol, 1.5 eq.) and Et<sub>3</sub>N (0.12 mL, 0.672 mmol, 2 eq.) in Et<sub>2</sub>O (4 mL), using the general procedure for isoxazoline cycloadditions, purified by silica gel column chromatography (20% EtOAc/hexane), afforded the title compound **10c** as a white solid (127.3 mg, 82%), m.p. 84-85 °C.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.80 (d, *J* = 8.2 Hz, 2 H), 7.69 (d, *J* = 8.2 Hz, 2 H), 6.64 (s, 1 H), 5.95 (dd, *J* = 11.3, 6.6 Hz, 1 H), 3.87 (dd, *J* = 16.9, 11.3 Hz, 1 H), 3.67 (dd, *J* = 16.9, 6.6 Hz, 1 H).

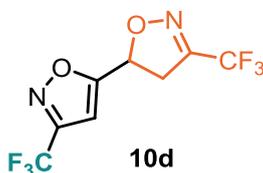
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 172.6, 155.8 (q, *J* = 38.8 Hz), 155.4, 132.6 (q, *J* = 32.9 Hz), 131.7 (q, *J* = 1.2 Hz), 127.4, 126.1 (q, *J* = 3.7 Hz), 123.8 (q, *J* = 272.4 Hz), 119.5 (q, *J* = 271.4 Hz), 100.4 (q, *J* = 1.0 Hz), 74.3, 40.1.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -63.3 (s, 3 F), -63.4 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 3137 (w), 1619 (w), 1601 (w), 1491 (m), 1446 (w), 1414 (w), 1327 (m), 1269 (w), 1255 (w), 1229 (w), 1193 (m), 1180 (m), 1149 (s), 1125 (s), 1112 (m), 1101 (m), 1073 (m), 1033 (w), 1015 (w), 1008 (w), 973 (m), 942 (w), 928 (w), 888 (m), 870 (w), 839 (s), 753 (w).

**HRMS (ESI):** calculated for C<sub>14</sub>H<sub>9</sub>F<sub>6</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 351.0563, found 351.0552.

*R<sub>f</sub>* = 0.29 (20% EtOAc/hexane).



**3,3'-bis(trifluoromethyl)-4,5-dihydro-5,5'-biisoxazole (10d):** The reaction of **9** (2.67 g containing 100 mg of **9**, 0.52 mmol, 1 eq.), **3** (0.64 g containing 70 mg of **3**, 0.78 mmol, 1.5 eq.) and Et<sub>3</sub>N (0.14 mL, 1.04 mmol, 2 eq.) in Et<sub>2</sub>O (4 mL), using the general procedure for isoxazoline cycloadditions, purified by silica gel column chromatography (10% Et<sub>2</sub>O/pentane), afforded the title compound **10d** as a yellow oil (66.7 mg, 47%).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 6.65 (s, 1 H), 6.00 (dd, *J* = 11.7, 7.2 Hz, 1 H), 3.69 (dd, *J* = 17.6, 11.7 Hz, 1 H), 3.49 (dd, *J* = 17.6, 7.2 Hz, 1 H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 170.6, 156.0 (q, *J* = 38.9 Hz), 148.9 (q, *J* = 38.2 Hz), 119.4 (q, *J* = 271.4 Hz), 119.2 (q, *J* = 271.8 Hz), 101.0 (q, *J* = 1.3 Hz), 75.6, 37.5.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -63.8 (s, 3 F), -66.6 (s, 3 F).

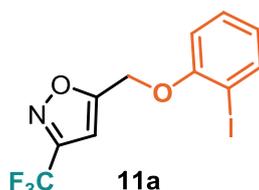
**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 1635 (w), 1607 (w), 1493 (m), 1440 (w), 1393 (m), 1345 (w), 1258 (m), 1185 (s), 1136 (s), 1084 (s), 998 (w), 971 (m), 911 (m), 869 (w), 848 (m), 818 (m), 751 (m).

**HRMS (ESI):** calculated for C<sub>8</sub>H<sub>4</sub>F<sub>6</sub>N<sub>2</sub>O<sub>2</sub>Na [M+Na]<sup>+</sup> 297.0069, found 297.0057.

**R<sub>f</sub>** = 0.37 (20% EtOAc/hexane).

## 2.6. Preparation of 5,6,6-fused precursors

**General procedure for phenol alkylation reactions:** To a solution of **6d** (0.200 g, 0.87 mmol, 1 eq.) in anhydrous DMF (15 mL) was added the appropriate phenol (0.96 mmol, 1.1 eq.) and potassium carbonate (0.132 g, 0.96 mmol, 1.1 eq.). The mixture was heated at 60 °C for 3 h. The flask was then cooled to r.t. and diluted with EtOAc (25 mL). The organic layer was washed with water (3 × 25 mL), brine (25 mL), dried (MgSO<sub>4</sub>) and evaporated under reduced pressure, purified by flash column chromatography.



**5-((2-iodophenoxy)methyl)-3-(trifluoromethyl)isoxazole (11a):** The reaction of **6d** (0.500 g, 2.17 mmol, 1 eq.), 2-iodophenol (0.526 g, 2.39 mmol, 1.1 eq.) and potassium carbonate (0.330 g, 2.39 mmol, 1.1 eq.) in anhydrous DMF (40 mL) using the general procedure for phenol alkylation reactions, purified by silica gel column chromatography (15% Et<sub>2</sub>O/hexane) afforded the title compound **11a** (0.618 g, 77%) as a white solid, m.p. 66-67 °C.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.82 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.39 – 7.30 (m, 1 H), 6.87 (d, *J* = 8.1 Hz, 1 H), 6.82 (t, *J* = 7.8 Hz, 1 H), 6.74 (s, 1 H), 5.26 (s, 2 H).

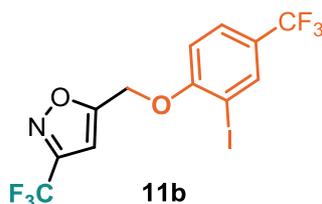
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 170.5, 156.3, 155.7 (q, *J* = 38.5 Hz), 140.1, 129.9, 124.4, 119.7 (q, *J* = 271.2 Hz), 112.8, 101.3 (q, *J* = 1.3 Hz), 86.7, 62.7.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -63.5 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 1607 (w), 1582 (w), 1573 (w), 1493 (m), 1475 (m), 1453 (m), 1440 (m), 1391 (w), 1279 (m), 1260 (m), 1247 (s), 1193 (m), 1178 (s), 1143 (s), 1089 (m), 1063 (s), 1039 (m), 1018 (s), 1002 (m), 968 (s), 937 (m), 929 (m), 837 (m), 813 (s).

**HRMS (ESI):** calculated for C<sub>11</sub>H<sub>8</sub>F<sub>3</sub>INO<sub>2</sub> [M+H]<sup>+</sup> 368.9462, found 368.9464.

*R<sub>f</sub>* = 0.45 (30% Et<sub>2</sub>O/hexane).



**5-((2-iodo-4-(trifluoromethyl)phenoxy)methyl)-3-(trifluoromethyl)isoxazole (11b):** The reaction of **6d** (0.150 g, 0.65 mmol, 1 eq.), 2-iodo-4-(trifluoromethyl)phenol (0.11 mL, 0.72 mmol, 1.1 eq.) and potassium carbonate (0.100 g, 0.72 mmol, 1.1 eq.) in anhydrous DMF (15 mL) using the general procedure for phenol alkylation reactions, purified by silica gel column chromatography (15% Et<sub>2</sub>O/hexane) afforded the title compound **11b** (0.190 g, 67%) as a white solid, m.p. 58-59 °C.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.07 (s, 1 H), 7.62 (d, *J* = 8.6 Hz, 1 H), 6.93 (d, *J* = 8.6 Hz, 1 H), 6.75 (s, 1 H), 5.33 (s, 2 H).

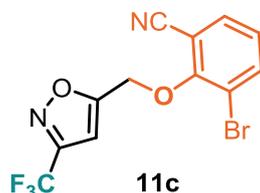
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 169.5, 158.7 (q, *J* = 0.9 Hz), 155.9 (q, *J* = 38.8 Hz), 137.3 (q, *J* = 3.7 Hz), 127.3 (q, *J* = 3.7 Hz), 126.4 (q, *J* = 33.4 Hz), 123.1 (q, *J* = 272.1 Hz), 119.6 (q, *J* = 271.4 Hz), 111.7, 101.5 (q, *J* = 1.1 Hz), 86.3, 62.6.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -62.4 (s, 3 F), -63.5 (s, 3 F).

**FTIR** ( $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 1603 (w), 1577 (w), 1497 (w), 1456 (w), 1401 (w), 1323 (s), 1299 (w), 1275 (m), 1256 (m), 1183 (m), 1141 (s), 1118 (s), 1082 (m), 1058 (m), 1004 (w), 967 (m), 935 (m), 902 (m), 850 (w), 817 (m), 785 (m), 756 (w).

**HRMS (ESI)**: calculated for  $\text{C}_{12}\text{H}_6\text{O}_2\text{NF}_6\text{INa}$   $[\text{M}+\text{Na}]^+$  459.9240, found 459.9227.

$R_f = 0.45$  (40%  $\text{Et}_2\text{O}$ /hexane).



**3-bromo-2-((3-(trifluoromethyl)isoxazol-5-yl)methoxy)benzonitrile (11c)**: The reaction of **6d** (0.200 g, 0.87 mmol, 1 eq.), 3-bromo-2-hydroxybenzonitrile (0.195 g, 0.96 mmol, 1.1 eq.) and potassium carbonate (0.132 g, 0.96 mmol, 1.1 eq.) in anhydrous DMF (15 mL) using the general procedure for phenol alkylation reactions, purified by silica gel column chromatography (50%  $\text{Et}_2\text{O}$ /hexane) afforded the title compound **11c** (0.216 g, 72%) as a pale yellow solid, m.p. 73-74 °C.

**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )**:  $\delta$  7.84 (dd,  $J = 8.1, 1.6$  Hz, 1 H), 7.61 (dd,  $J = 7.7, 1.6$  Hz, 1 H), 7.22 – 7.14 (m, 1 H), 6.82 (s, 1 H), 5.38 (d,  $J = 0.6$  Hz, 2 H).

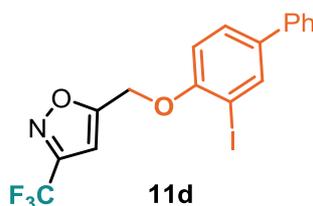
**$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )**:  $\delta$  169.1, 156.8, 155.8 (q,  $J = 38.7$  Hz), 138.8, 133.1, 126.8, 119.6 (q,  $J = 271.2$  Hz), 118.0, 115.0, 109.0, 102.5, 66.0.

**$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )**:  $\delta$  -63.5 (s, 3 F).

**FTIR** ( $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 2232 (w), 1643 (w), 1490 (m), 1443 (m), 1373 (m), 1307 (m), 1253 (m), 1219 (m), 1186 (s), 1141 (s), 1105 (m), 1071 (m), 1007 (w), 983 (m), 969 (s), 930 (m), 838 (m), 787 (s), 768 (m).

**HRMS (ESI)**: calculated for  $\text{C}_{12}\text{H}_7\text{BrF}_3\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  346.9638, found 346.9637.

$R_f = 0.28$  (40%  $\text{Et}_2\text{O}$ /hexane).



**5-(((3-iodo-[1,1'-biphenyl]-4-yl)oxy)methyl)-3-(trifluoromethyl)isoxazole (11d)**: The reaction of **6d** (0.120 g, 0.52 mmol, 1 eq.), 4-hydroxy-3-iodobiphenyl (0.170 g, 0.57 mmol, 1.1 eq.) and potassium carbonate (0.080 g, 0.57 mmol, 1.1 eq.) in anhydrous DMF (15 mL) using following the general procedure for phenol alkylation reactions, purified by silica gel column chromatography (15%  $\text{Et}_2\text{O}$ /hexane) afforded the title compound **11d** (0.095 g, 41%) as a pale yellow solid, m.p. 69-70 °C.

**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )**:  $\delta$  8.06 (d,  $J = 2.2$  Hz, 1 H), 7.55 (dd,  $J = 8.5, 2.2$  Hz, 1 H), 7.54 – 7.51 (m, 2 H), 7.47 – 7.40 (m, 2 H), 7.39 – 7.33 (m, 1 H), 6.93 (d,  $J = 8.5$  Hz, 1 H), 6.76 (s, 1 H), 5.30 (d,  $J = 0.6$  Hz, 2 H).

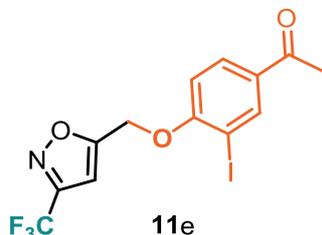
**$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )**:  $\delta$  170.4, 155.8 (q,  $J = 38.6$  Hz), 155.7, 139.0, 138.6, 137.7, 129.0, 128.4, 127.7, 127.0, 119.7 (q,  $J = 271.3$  Hz), 112.9, 101.3, 87.2, 62.8.

**$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )**:  $\delta$  -63.5 (s, 3 F).

**FTIR** ( $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 1595 (w), 1558 (w), 1474 (m), 1452 (m), 1385 (w), 1272 (m), 1247 (m), 1224 (m), 1182 (s), 1148 (s), 1094 (m), 1065 (m), 1042 (m), 1030 (m), 1016 (m), 1004 (m), 969 (s), 933 (m), 886 (m), 849 (w), 812 (m), 760 (s).

**HRMS (ESI)**: calculated for  $\text{C}_{17}\text{H}_{12}\text{F}_3\text{INO}_2\text{Na}$   $[\text{M}+\text{Na}]^+$  467.9679, found 467.9663.

$R_f = 0.45$  (40%  $\text{Et}_2\text{O}$ /hexane).



**1-(3-iodo-4-((3-(trifluoromethyl)isoxazol-5-yl)methoxy)phenyl)ethan-1-one (11e)**: The reaction of **6d** (0.200 g, 0.87 mmol, 1 eq.), 4-hydroxy-3-iodoacetophenone (0.253 g, 0.96 mmol, 1.1 eq.) and potassium carbonate (0.132 g, 0.96 mmol, 1.1 eq.) in anhydrous DMF (15 mL) using the general procedure for phenol alkylation reactions, purified by silica gel column chromatography (50%  $\text{Et}_2\text{O}$ /hexane) afforded the title compound **11e** (0.240 g, 67%) as a pale yellow solid, m.p. 106-107 °C.

**$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )**:  $\delta$  8.41 (d,  $J = 2.1$  Hz, 1 H), 7.96 (dd,  $J = 8.6, 2.1$  Hz, 1 H), 6.90 (d,  $J = 8.6$  Hz, 1 H), 6.75 (s, 1 H), 5.34 (s, 2 H), 2.55 (s, 3 H).

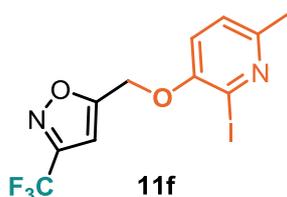
**$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )**:  $\delta$  195.4, 169.6, 159.6, 155.8 (q,  $J = 38.7$  Hz), 140.6, 133.2, 130.6, 119.6 (q,  $J = 271.3$  Hz), 111.3, 101.5, 86.4, 62.5, 26.5.

**$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )**:  $\delta$  -63.5 (s, 3 F).

**FTIR** ( $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 1666 (s), 1589 (m), 1567 (m), 1498 (m), 1483 (m), 1463 (w), 1453 (w), 1425 (w), 1400 (m), 1357 (w), 1305 (m), 1285 (w), 1256 (s), 1240 (m), 1192 (m), 1154 (s), 1093 (w), 1083 (w), 1054 (m), 1020 (w), 1005 (w), 971 (m), 937 (m), 909 (m), 849 (w), 813 (s), 778 (m).

**HRMS (ESI)**: calculated for  $\text{C}_{13}\text{H}_{10}\text{F}_3\text{INO}_3$   $[\text{M}+\text{H}]^+$  411.9652, found 411.9642.

$R_f = 0.41$  (80%  $\text{Et}_2\text{O}$ /hexane).



**5-(((2-iodo-6-methylpyridin-3-yl)oxy)methyl)-3-(trifluoromethyl)isoxazole (11f)**: The reaction of **6d** (0.150 g, 0.65 mmol, 1 eq.), 3-hydroxy-2-iodo-6-methylpyridine (0.170 g, 0.72 mmol, 1.1 eq.) and potassium carbonate (0.100 g, 0.72 mmol, 1.1 eq.) in anhydrous DMF (15 mL) using the general procedure for phenol alkylation reactions, purified by silica gel column chromatography (15%  $\text{Et}_2\text{O}$ /hexane) afforded the title compound **11f** (0.204 g, 82%) as a white solid, m.p. 60-62 °C.

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )**:  $\delta$  7.05 (d,  $J = 8.2$  Hz, 1 H), 6.99 (d,  $J = 8.2$  Hz, 1 H), 6.73 (s, 1 H), 5.24 (s, 2 H), 2.49 (s, 3 H).

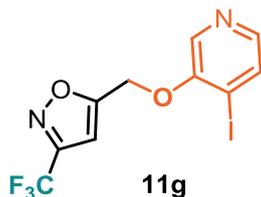
**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )**:  $\delta$  169.8, 155.8 (q,  $J = 38.7$  Hz), 154.3, 151.5, 123.1, 120.1, 119.6 (q,  $J = 271.3$  Hz), 111.4, 101.6 (q,  $J = 1.1$  Hz), 62.8, 23.4.

**$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )**:  $\delta$  -63.5 (s, 3 F).

**FTIR** ( $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 1609 (w), 1581 (w), 1557 (m), 1517 (w), 1494 (m), 1458 (w), 1438 (m), 1389 (m), 1372 (w), 1360 (m), 1285 (s), 1264 (m), 1255 (m), 1178 (s), 1159 (s), 1146 (s), 1093 (m), 1077 (s), 1056 (m), 1035 (m), 1004 (m), 969 (s), 933 (m), 862 (w), 821 (s), 799 (s), 756 (m).

**HRMS (ESI)**: calculated for  $\text{C}_{11}\text{H}_9\text{F}_3\text{IN}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  384.9655, found 384.9642.

$R_f$  = 0.20 (40%  $\text{Et}_2\text{O}$ /hexane).



**5-(((4-iodopyridin-3-yl)oxy)methyl)-3-(trifluoromethyl)isoxazole (11g)**: The reaction of **6d** (0.100 g, 0.43 mmol, 1 eq.), 4-iodo-3-hydroxypyridine (0.106 g, 0.47 mmol, 1.1 eq.) and potassium carbonate (0.066 g, 0.47 mmol, 1.1 eq.) in anhydrous DMF (15 mL) using the general procedure for phenol alkylation reactions, purified by silica gel column chromatography (50%  $\rightarrow$  90%  $\text{Et}_2\text{O}$ /hexane) afforded the title compound **11g** (0.080 g, 50%) as a yellow oil.

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )**:  $\delta$  8.18 (s, 1 H), 7.97 (d,  $J$  = 4.9 Hz, 1 H), 7.78 (d,  $J$  = 4.9 Hz, 1 H), 6.73 (s, 1 H), 5.36 (s, 2 H).

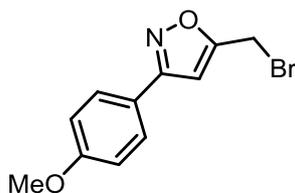
**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )**:  $\delta$  169.5, 155.8 (q,  $J$  = 38.7 Hz), 153.7, 144.9, 134.8, 134.7, 119.5 (q,  $J$  = 271.4 Hz), 101.6 (q,  $J$  = 1.1 Hz), 98.1, 63.0.

**$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )**:  $\delta$  -63.5 (s, 3 F).

**FTIR** ( $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3042 (w), 2920 (w), 1604 (w), 1559 (m), 1494 (m), 1477 (m), 1452 (w), 1412 (m), 1385 (w), 1302 (m), 1260 (m), 1232 (m), 1182 (s), 1134 (s), 1092 (m), 1076 (m), 1054 (m), 1041 (m), 1005 (w), 968 (m), 930 (m), 837 (s), 803 (s), 763 (m).

**HRMS (ESI)**: calculated for  $\text{C}_{10}\text{H}_7\text{F}_3\text{IN}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  370.9499, found 370.9492.

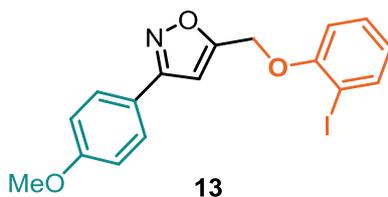
$R_f$  = 0.11 (40%  $\text{Et}_2\text{O}$ /hexane).



**5-(bromomethyl)-3-(4-methoxyphenyl)isoxazole**: To a solution of *N*-hydroxy-4-methoxybenzimidoyl chloride (1.23 g, 6.6 mmol, 1 eq.) in toluene (15 mL) was added propargyl bromide (1.57 g, 13.2 mmol, 2 eq.). A solution of  $\text{Na}_2\text{CO}_3$  (1.40 g, 13.2 mmol, 2 eq.) in water (25 mL) was added dropwise to the stirred reaction mixture *via* syringe pump over 16 h at r.t., then hexane (100 mL) was added. The reaction flask was washed with  $\text{EtOAc}$  (25 mL) and the organic layer washed with water (50 mL), brine (50 mL), dried ( $\text{MgSO}_4$ ), evaporated under reduced pressure and purified by silica gel column chromatography (15%  $\text{EtOAc}$ /hexane), which afforded the title compound as a pale yellow solid (1.44 g, 81%). Data consistent with literature.<sup>5</sup>

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )**:  $\delta$  7.70 (d,  $J$  = 8.7 Hz, 2 H), 6.95 (d,  $J$  = 8.7 Hz, 2 H), 6.55 (s, 1 H), 4.47 (s, 2 H), 3.82 (s, 3 H).

$R_f$  = 0.61 (40%  $\text{EtOAc}$ /hexane).



**5-((2-iodophenoxy)methyl)-3-(4-methoxyphenyl)isoxazole (13):** The reaction of 5-(bromomethyl)-3-(4-methoxyphenyl)isoxazole (0.400 g, 1.5 mmol, 1.0 eq.), 2-iodophenol (0.370 g, 1.6 mmol, 1.1 eq.) and potassium carbonate (0.230 g, 1.6 mmol, 1.1 eq.) in anhydrous DMF (15 mL) using the general procedure for phenol alkylation reactions, purified by trituration with hexane afforded the title compound **13** (0.521 g, 86%) as a white solid, m.p. 102-104 °C.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.82 (dd, *J* = 7.9, 0.8 Hz, 1 H), 7.76 (d, *J* = 8.7 Hz, 2 H), 7.35 – 7.29 (m, 1 H), 6.98 (d, *J* = 8.7 Hz, 2 H), 6.91 (d, *J* = 7.9 Hz, 1 H), 6.79 (t, *J* = 7.5 Hz, 1 H), 6.69 (s, 1 H), 5.25 (s, 2 H), 3.86 (s, 3 H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 167.9, 162.3, 161.3, 156.7, 140.0, 129.8, 128.4, 124.0, 121.4, 114.5, 112.9, 101.4, 86.8, 63.0, 55.5.

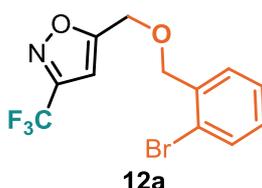
**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 1616 (m), 1582 (w), 1571 (w), 1528 (w), 1477 (m), 1455 (m), 1440 (m), 1408 (m), 1374 (m), 1358 (m), 1297 (m), 1277 (m), 1247 (s), 1177 (m), 1125 (w), 1064 (m), 1020 (s), 947 (w), 907 (m), 893 (w), 834 (s), 819 (m), 800 (s).

**HRMS (ESI):** calculated for C<sub>17</sub>H<sub>15</sub>INO<sub>3</sub> [M+H]<sup>+</sup> 408.0091, found 408.0089.

**R<sub>f</sub>** = 0.32 (20% EtOAc/hexane).

## 2.7. Preparation of 5,7,6-fused precursors

**General procedure for alcohol alkylation reactions:** To a suspension of NaH (0.040 g, 60% dispersion in mineral oil, 0.96 mmol, 1.1 eq.) in anhydrous THF (5 mL) was added slowly the appropriate alcohol (0.96 mmol, 1.1 eq.) at 0 °C and stirred for 30 min. A solution of **6d** (0.200 g, 0.87 mmol, 1 eq.) in anhydrous THF (5 mL) was added slowly dropwise to the reaction mixture, then heated to 60 °C for 3 h. The flask was then cooled to r.t. and diluted with Et<sub>2</sub>O (25 mL) and quenched with water (25 mL). The organic layer separated and the aqueous layer extracted further with Et<sub>2</sub>O (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried (MgSO<sub>4</sub>) and evaporated under reduced pressure, purified by flash column chromatography.



**5-(((2-bromobenzyl)oxy)methyl)-3-(trifluoromethyl)isoxazole (12a):** The reaction of **6d** (0.916 g, 4.0 mmol, 1 eq.), 2-bromobenzyl alcohol (0.823 g, 4.4 mmol, 1.1 eq.) and NaH (0.176 g, 60% dispersion in mineral oil, 4.4 mmol, 1.1 eq.) in anhydrous THF (20 + 20 mL) using the general procedure for alcohol alkylation reactions, purified by silica gel column chromatography (4% EtOAc/hexane) afforded the title compound **12a** (1.24 g, 92%) as a colourless oil.

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.57 (dd, *J* = 8.0, 1.1 Hz, 1 H), 7.50 – 7.44 (m, 1 H), 7.34 (td, *J* = 7.6, 1.1 Hz, 1 H), 7.19 (td, *J* = 7.6, 1.7 Hz, 1 H), 6.57 (s, 1 H), 4.76 (d, *J* = 0.7 Hz, 2 H), 4.72 (s, 2 H).

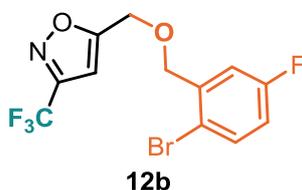
**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 172.0, 155.6 (q, *J* = 38.4 Hz), 136.2, 132.9, 129.8, 129.6, 127.7, 123.2, 119.7 (q, *J* = 271.1 Hz), 100.8, 72.8, 63.2.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -63.6 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 1571 (w), 1492 (m), 1472 (w), 1441 (w), 1359 (w), 1304 (w), 1243 (w), 1181 (s), 1147 (s), 1084 (s), 1045 (w), 1027 (m), 998 (w), 969 (s), 930 (m), 813 (m), 750 (s).

**HRMS (ESI):** calculated for C<sub>12</sub>H<sub>10</sub>BrF<sub>3</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 335.9842, found 335.9837.

*R<sub>f</sub>* = 0.31 (4% EtOAc/hexane).



**5-(((2-bromo-5-fluorobenzyl)oxy)methyl)-3-(trifluoromethyl)isoxazole (12b):** The reaction of **6d** (0.200 g, 0.87 mmol, 1 eq.), 2-bromo-5-fluorobenzyl alcohol (0.196 g, 0.96 mmol, 1.1 eq.) and NaH (0.040 g, 60% dispersion in mineral oil, 0.96 mmol, 1.1 eq.) in anhydrous THF (5 + 5 mL) using the general procedure for alcohol alkylation reactions, purified by silica gel column chromatography (15% Et<sub>2</sub>O/hexane) afforded the title compound **12b** (0.200 g, 62%) as a colourless oil.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.50 (dd, *J* = 8.5, 5.1 Hz, 1 H), 7.22 (dd, *J* = 9.2, 3.0 Hz, 1 H), 6.91 (td, *J* = 8.5, 3.0 Hz, 1 H), 6.59 (s, 1 H), 4.79 (s, 2 H), 4.66 (s, 2 H).

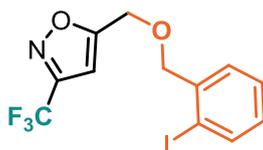
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 171.6, 163.5, 161.1, 155.6 (q, *J* = 38.5 Hz), 138.6 (d, *J* = 7.5 Hz), 134.0 (d, *J* = 7.9 Hz), 119.7 (q, *J* = 271.2 Hz), 116.6 (d, *J* = 22.6 Hz), 116.3 (d, *J* = 3.3 Hz), 116.1 (d, *J* = 24.1 Hz), 100.9 (q, *J* = 1.0 Hz), 72.3 (d, *J* = 0.9 Hz), 63.5.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -63.6 (s, 3 F), -114.4 (s, 1 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 1607 (w), 1583 (w), 1492 (m), 1470 (m), 1414 (w), 1359 (w), 1305 (w), 1269 (m), 1243 (m), 1222 (w), 1183 (s), 1148 (s), 1102 (m), 1086 (s), 1032 (m), 999 (w), 970 (s), 931 (m), 873 (m), 811 (m), 756 (w).

**HRMS (ESI):** calculated for C<sub>12</sub>H<sub>9</sub>BrF<sub>4</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 353.9747, found 353.9741.

*R<sub>f</sub>* = 0.80 (40% Et<sub>2</sub>O/hexane)



**12c**

**5-(((2-iodobenzyl)oxy)methyl)-3-(trifluoromethyl)isoxazole (12c):** The reaction of **6d** (0.200 g, 0.87 mmol, 1 eq.), 2-iodobenzyl alcohol (0.196 g, 0.96 mmol, 1.1 eq.) and NaH (0.040 g, 60% dispersion in mineral oil, 0.96 mmol, 1.1 eq.) in anhydrous THF (5 + 5 mL) using the general procedure for alcohol alkylation reactions, purified by silica gel column chromatography (15% Et<sub>2</sub>O/hexane) afforded the title compound **12c** (0.065 g, 20%) as a colourless oil.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.85 (d, *J* = 7.9 Hz, 1 H), 7.45 – 7.40 (m, 1 H), 7.37 (t, *J* = 7.4 Hz, 1 H), 7.03 (td, *J* = 7.9, 1.4 Hz, 1 H), 6.58 (s, 1 H), 4.77 (s, 2 H), 4.64 (s, 2 H).

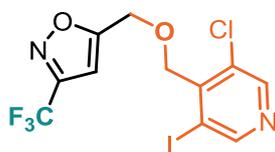
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 172.0, 155.6 (q, *J* = 38.4 Hz), 139.6, 139.1, 130.0, 129.3, 128.6, 119.7 (q, *J* = 271.2 Hz), 100.9 (q, *J* = 1.0 Hz), 98.3, 77.2 (superimposed on CDCl<sub>3</sub> peak), 63.2.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -63.6 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 1606 (w), 1588 (w), 1567 (w), 1491 (m), 1465 (w), 1438 (w), 1359 (w), 1303 (w), 1256 (m), 1242 (m), 1225 (m), 1181 (s), 1147 (s), 1084 (s), 1045 (m), 1013 (m), 969 (s), 930 (m), 867 (w), 812 (m).

**HRMS (ESI):** calculated for C<sub>12</sub>H<sub>10</sub>F<sub>3</sub>INO<sub>2</sub> [M+H]<sup>+</sup> 383.9703, found 383.9684.

*R<sub>f</sub>* = 0.63 (40% Et<sub>2</sub>O/hexane).



**12d**

**5-(((3-chloro-5-iodopyridin-4-yl)methoxy)methyl)-3-(trifluoromethyl)isoxazole (12d):** The reaction of **6d** (0.150 g, 0.65 mmol, 1 eq.), 2-chloro-4-iodo-3-pyridinemethanol (0.195 g, 0.72 mmol, 1.1 eq.) and NaH (0.030 g, 60% dispersion in mineral oil, 0.72 mmol, 1.1 eq.) in anhydrous THF (5 + 5 mL) using the general procedure for alcohol alkylation reactions, purified by silica gel column chromatography (30% Et<sub>2</sub>O/hexane) afforded the title compound **12d** (0.192 g, 70%) as a pale yellow solid, m.p. 58-59 °C.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.93 (d, *J* = 5.1 Hz, 1 H), 7.75 (d, *J* = 5.1 Hz, 1 H), 6.59 (s, 1 H), 4.90 (s, 2 H), 4.79 (s, 2 H).

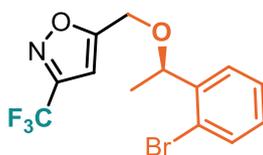
<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 171.6, 155.6 (q, *J* = 38.5 Hz), 151.7, 149.7, 134.6, 133.8, 119.7 (q, *J* = 271.2 Hz), 114.4, 101.0 (q, *J* = 0.9 Hz), 74.2, 63.6.

<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>): δ -63.6 (s, 3 F).

FTIR (ν<sub>max</sub>, cm<sup>-1</sup>): 1606 (w), 1553 (m), 1534 (m), 1491 (m), 1436 (w), 1360 (m), 1305 (w), 1261 (w), 1243 (w), 1223 (w), 1180 (s), 1147 (s), 1104 (m), 1088 (m), 1071 (m), 995 (w), 969 (s), 930 (m), 826 (m), 759 (m).

HRMS (ESI): calculated for C<sub>11</sub>H<sub>8</sub>ClF<sub>3</sub>IN<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 418.9266, found 418.9251.

*R<sub>f</sub>* = 0.19 (40% Et<sub>2</sub>O/hexane).



**12e**

**(*R*)-5-((1-(2-bromophenyl)ethoxy)methyl)-3-(trifluoromethyl)isoxazole (12e):** The reaction of **6d** (0.200 g, 0.87 mmol, 1 eq.), (*R*)-(+)-2-bromo- $\alpha$ -methylbenzyl alcohol (0.192 g, 0.96 mmol, 1.1 eq.) and NaH (0.040 g, 60% dispersion in mineral oil, 0.96 mmol, 1.1 eq.) in anhydrous THF (5 + 5 mL) using the general procedure for alcohol alkylation reactions, purified by silica gel column chromatography (15% Et<sub>2</sub>O/hexane) afforded the title compound **12e** (0.151 g, 50%) as a colourless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.55 (d, *J* = 7.9 Hz, 1 H), 7.51 (dd, *J* = 7.9, 1.4 Hz, 1 H), 7.42 – 7.33 (m, 1 H), 7.17 (td, *J* = 7.9, 1.4 Hz, 1 H), 6.50 (s, 1 H), 5.00 (q, *J* = 6.4 Hz, 1 H), 4.59 – 4.48 (m, 2 H), 1.48 (d, *J* = 6.4 Hz, 3 H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 172.2, 155.5 (q, *J* = 38.4 Hz), 141.4, 133.0, 129.5, 128.3, 127.1, 122.8, 119.8 (q, *J* = 271.1 Hz), 100.6, 77.6, 61.6, 22.7.

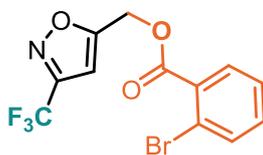
<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>): δ -63.6 (s, 3 F).

FTIR (ν<sub>max</sub>, cm<sup>-1</sup>): 2928 (w), 2855 (w), 1606 (w), 1570 (w), 1492 (m), 1471 (w), 1439 (w), 1373 (w), 1348 (w), 1304 (w), 1262 (m), 1247 (m), 1226 (w), 1184 (s), 1150 (s), 1110 (m), 1086 (s), 1062 (w), 1046 (w), 1025 (m), 1001 (w), 969 (s), 933 (m), 898 (w), 860 (w), 810 (m), 755 (s).

HRMS (ESI): calculated for C<sub>13</sub>H<sub>12</sub>BrF<sub>3</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 349.9998, found 349.9987.

*R<sub>f</sub>* = 0.76 (40% Et<sub>2</sub>O/hexane).

[ $\alpha$ ]<sub>D</sub><sup>30.5</sup> = +28.4° (CHCl<sub>3</sub>, *c* = 1.0).



**12f**

**(3-(trifluoromethyl)isoxazol-5-yl)methyl 2-bromobenzoate (12f):** To a suspension of NaH (0.073 g, 60% dispersion in mineral oil, 0.96 mmol, 1.4 eq.) in anhydrous THF (3 mL) was added slowly 2-bromobenzoic acid (0.367 g, 1.83 mmol, 1.4 eq.) portionwise at 0 °C and stirred for 20 min. A small spatula of tetrabutylammonium iodide was added, followed by a solution of **6d** (0.300 g, 1.30 mmol, 1 eq.) in anhydrous THF (3 mL) slowly dropwise, the mixture warmed to r.t. and stirred for 3 h. The mixture was quenched with water (10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 25 mL). The combined organic extracts were then dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by silica gel column

chromatography (10% → 30% Et<sub>2</sub>O/hexane), which afforded the title compound **12f** (0.393 g, 86%) as a pale yellow oil.

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.88 – 7.83 (m, 1 H), 7.73 – 7.67 (m, 1 H), 7.42 – 7.36 (m, 2 H), 6.69 (s, 1 H), 5.50 (d, *J* = 0.6 Hz, 2 H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 169.2, 165.1, 155.8 (q, *J* = 38.7 Hz), 134.9, 133.6, 131.9, 130.5, 127.5, 122.4, 119.6 (q, *J* = 271.2 Hz), 102.2, 56.9.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -63.6 (s, 3 F).

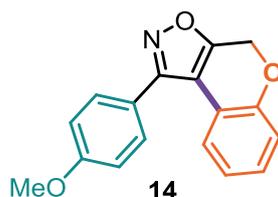
**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 3145 (w), 1739 (s), 1609 (w), 1591 (w), 1568 (w), 1493 (m), 1471 (w), 1435 (m), 1369 (w), 1286 (m), 1243 (s), 1184 (s), 1147 (s), 1109 (s), 1091 (s), 1045 (m), 1030 (s), 1010 (w), 969 (s), 934 (m), 878 (w), 816 (w), 790 (w), 759 (m).

**HRMS (ESI):** calculated for C<sub>12</sub>H<sub>8</sub>BrF<sub>3</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 349.9634, found 349.9630.

**R<sub>f</sub>** = 0.37 (10% EtOAc/hexane).

## 2.8. Intramolecular C-H cross-coupling

**General procedure for intramolecular C-H coupling reactions:** To a screw-capped vial equipped with a magnetic stir-bar under air was added palladium(II) acetate (2.2 mg, 0.01 mmol, 0.05 eq.), tris(4-fluorophenyl)phosphine (3.2 mg, 0.01 mmol, 0.05 eq.), pivalic acid (6.1 mg, 0.06 mmol, 0.3 eq.) and potassium carbonate (83 mg, 0.6 mmol, 3.0 eq.). The vial sealed then evacuated and backfilled with argon three times, then a solution of the cyclisation precursor (0.2 mmol, 1 eq.) in anhydrous DMA (3 mL) was added. The mixture was stirred at 65 °C for 6 h. The reaction mixture was then cooled to r.t. and purified directly by flash column chromatography.



**1-(4-methoxyphenyl)-4H-chromeno[4,3-d]isoxazole (14):** The reaction of **13** (100 mg, 0.25 mmol, 1 eq.), palladium(II) acetate (2.8 mg, 0.013 mmol, 0.05 eq.), tris(4-fluorophenyl)phosphine (4.0 mg, 0.013 mmol, 0.05 eq.), pivalic acid (7.6 mg, 0.075 mmol, 0.3 eq.) and potassium carbonate (104 mg, 0.750 mmol, 3 eq.) using the general procedure for intramolecular C-H coupling reactions, purified by silica gel column chromatography (15% Et<sub>2</sub>O/hexane), afforded the title compound **14** (42.0 mg, 60%) as a white solid, m.p. 115-117 °C.

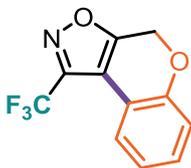
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.63 (d, *J* = 8.5 Hz, 2 H), 7.26 – 7.23 (m, 1 H), 7.15 (t, *J* = 7.6 Hz, 1 H), 7.07 – 6.99 (m, 3 H), 6.88 (t, *J* = 7.6 Hz, 1 H), 5.40 (s, 2 H), 3.89 (s, 3 H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 163.6, 161.2, 158.8, 151.7, 130.3, 128.6, 123.1, 122.4, 120.8, 117.7, 117.2, 114.5, 109.3, 63.4, 55.5.

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 3060 (w), 3017 (w), 2982 (w), 2918 (w), 2875 (w), 1631 (w), 1609 (s), 1528 (m), 1497 (s), 1455 (s), 1431 (s), 1372 (m), 1319 (m), 1306 (m), 1253 (s), 1234 (s), 1202 (m), 1193 (m), 1181 (m), 1154 (w), 1133 (m), 1111 (w), 1093 (m), 1070 (w), 1047 (w), 1033 (s), 1024 (s), 1016 (s), 1008 (s), 970 (w), 929 (w), 879 (m), 843 (m), 833 (s), 814 (s), 796 (m), 760 (w).

**HRMS (ESI):** calculated for C<sub>17</sub>H<sub>14</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 280.0974, found 280.0985.

*R<sub>f</sub>* = 0.70 (60% Et<sub>2</sub>O/hexane).



**1-(trifluoromethyl)-4H-chromeno[4,3-d]isoxazole (15a):** The reaction of **11a** (80 mg, 0.217 mmol, 1 eq.), palladium(II) acetate (2.4 mg, 0.011 mmol, 0.05 eq.), tris(4-fluorophenyl)phosphine (3.4 mg, 0.011 mmol, 0.05 eq.), pivalic acid (6.6 mg, 0.065 mmol, 0.3 eq.) and potassium carbonate (90 mg, 0.650 mmol, 3 eq.) using the general procedure for intramolecular C-H coupling reactions, purified by silica gel column chromatography (15% Et<sub>2</sub>O/hexane), afforded the title compound **15a** (47.0 mg, 90%) as a white solid, m.p. 74-76 °C.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.46 (d, *J* = 7.7 Hz, 1 H), 7.29 – 7.22 (m, 1 H), 7.11 – 7.00 (m, 2 H), 5.44 (s, 2 H).

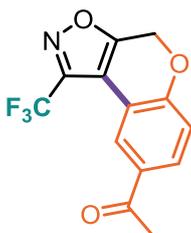
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 165.2, 151.6, 149.9 (q, *J* = 38.6 Hz), 130.1, 124.6 (q, *J* = 3.0 Hz), 123.2, 120.2 (q, *J* = 271.5 Hz), 117.4, 114.6, 109.3, 62.7.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -63.2 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 1518 (w), 1456 (m), 1335 (m), 1141 (s), 1105 (m), 1050 (m), 984 (m), 918 (m), 823 (m), 756 (s).

**HRMS (ESI):** calculated for C<sub>11</sub>H<sub>7</sub>F<sub>3</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 242.0423, found 242.0425.

*R<sub>f</sub>* = 0.56 (40% Et<sub>2</sub>O/hexane).



**15b**

**1-(1-(trifluoromethyl)-4*H*-chromeno[4,3-*d*]isoxazol-8-yl)ethan-1-one (15b):** The reaction of **11e** (100 mg, 0.243 mmol, 1 eq.), palladium(II) acetate (2.7 mg, 0.012 mmol, 0.05 eq.), tris(4-fluorophenyl)phosphine (3.8 mg, 0.012 mmol, 0.05 eq.), pivalic acid (7.4 mg, 0.073 mmol, 0.3 eq.) and potassium carbonate (101 mg, 0.729 mmol, 3 eq.) using the general procedure for intramolecular C-H coupling reactions, purified by silica gel column chromatography (20% → 40% Et<sub>2</sub>O/hexane), afforded the title compound **15b** (60.2 mg, 87%) as a white solid, m.p. 125-127 °C.

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 8.05 (d, *J* = 2.0 Hz, 1 H), 7.87 (dd, *J* = 8.6, 2.0 Hz, 1 H), 7.07 (d, *J* = 8.6 Hz, 1 H), 5.54 (s, 2 H), 2.57 (s, 3 H).

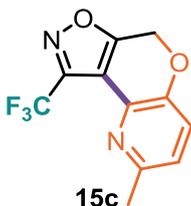
**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 196.1, 164.8, 155.4, 149.9 (q, *J* = 38.8 Hz), 132.4, 130.6, 125.0 (q, *J* = 2.8 Hz), 120.0 (q, *J* = 271.6 Hz), 117.4, 114.2, 108.7, 63.2, 26.4.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -63.1 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 2921 (w), 2854 (w), 1675 (m), 1601 (m), 1574 (w), 1512 (m), 1460 (m), 1428 (m), 1390 (w), 1359 (m), 1322 (w), 1283 (m), 1269 (w), 1249 (m), 1212 (m), 1184 (m), 1152 (s), 1124 (m), 1077 (m), 1045 (m), 1015 (m), 994 (m), 963 (m), 918 (m), 905 (m), 846 (m), 836 (m), 800 (m).

**HRMS (ESI):** calculated for C<sub>13</sub>H<sub>9</sub>F<sub>3</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 284.0529, found 284.0517.

*R<sub>f</sub>* = 0.36 (40% Et<sub>2</sub>O/hexane).



**15c**

**2-methyl-9-(trifluoromethyl)-6*H*-isoxazolo[4',5':4,5]pyrano[3,2-*b*]pyridine (15c):** The reaction of **11f** (80 mg, 0.208 mmol, 1 eq.), palladium(II) acetate (2.3 mg, 0.010 mmol, 0.05 eq.), tris(4-fluorophenyl)phosphine (3.3 mg, 0.010 mmol, 0.05 eq.), pivalic acid (6.3 mg, 0.062 mmol, 0.3 eq.) and potassium carbonate (86.2 mg, 0.624 mmol, 3 eq.) using the general procedure for intramolecular C-H coupling reactions, purified by silica gel column

chromatography (15% Et<sub>2</sub>O/hexane), afforded the title compound **15c** (30.5 mg, 57%) as a white solid, m.p. 149-150 °C.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.14 (d, *J* = 8.3 Hz, 1 H), 6.98 (d, *J* = 8.3 Hz, 1 H), 5.49 (s, 2 H), 2.49 (s, 3 H).

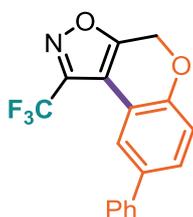
<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 166.9, 152.7, 150.6 (q, *J* = 39.8 Hz), 146.4, 134.4, 123.9, 123.6, 119.7 (q, *J* = 271.8 Hz), 111.0, 63.2, 23.8.

<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>): δ -63.3 (s, 3 F).

FTIR (ν<sub>max</sub>, cm<sup>-1</sup>): 2924 (w), 2852 (w), 1634 (w), 1584 (w), 1517 (m), 1476 (m), 1458 (m), 1437 (m), 1373 (w), 1323 (m), 1283 (w), 1247 (m), 1206 (m), 1181 (m), 1144 (s), 1077 (m), 1021 (m), 998 (m), 906 (m), 869 (w), 829 (m), 811 (m), 763 (m).

HRMS (ESI): calculated for C<sub>11</sub>H<sub>8</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 257.0532, found 257.0520.

R<sub>f</sub> = 0.54 (40% Et<sub>2</sub>O/hexane).



**15d**

**8-phenyl-1-(trifluoromethyl)-4H-chromeno[4,3-d]isoxazole (15d):** The reaction of **11d** (100 mg, 0.225 mmol, 1 eq.), palladium(II) acetate (2.5 mg, 0.011 mmol, 0.05 eq.), tris(4-fluorophenyl)phosphine (3.6 mg, 0.011 mmol, 0.05 eq.), pivalic acid (6.9 mg, 0.067 mmol, 0.3 eq.) and potassium carbonate (93.3 mg, 0.675 mmol, 3 eq.) using the general procedure for intramolecular C-H coupling reactions, purified by silica gel column chromatography (15% Et<sub>2</sub>O/hexane), afforded the title compound **15d** (41.6 mg, 57%) as a white solid, m.p. 90-91 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.68 (s, 1 H), 7.55 (d, *J* = 7.4 Hz, 2 H), 7.52 – 7.43 (m, 3 H), 7.37 (t, *J* = 7.4 Hz, 1 H), 7.11 (d, *J* = 8.5 Hz, 1 H), 5.48 (s, 2 H).

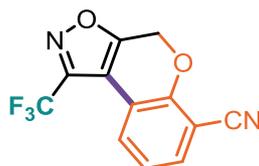
<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 165.4, 151.1, 149.9 (q, *J* = 38.6 Hz), 140.1, 136.4, 129.1, 128.7, 127.5, 126.9, 123.1 (q, *J* = 2.6 Hz), 120.2 (q, *J* = 271.6 Hz), 117.7, 114.9, 109.4, 62.8.

<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>): δ -63.0 (s, 3 F).

FTIR (ν<sub>max</sub>, cm<sup>-1</sup>): 3061 (w), 3036 (w), 2920 (w), 2852 (w), 1610 (w), 1520 (m), 1497 (w), 1482 (m), 1459 (m), 1414 (m), 1332 (m), 1297 (m), 1266 (w), 1226 (m), 1190 (s), 1141 (s), 1121 (s), 1080 (m), 1055 (m), 1041 (w), 1025 (w), 1010 (m), 1000 (m), 989 (m), 913 (m), 889 (m), 840 (m), 829 (m), 799 (m), 759 (s).

HRMS (ESI): calculated for C<sub>17</sub>H<sub>11</sub>F<sub>3</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 318.0736, found 318.0735.

R<sub>f</sub> = 0.73 (40% Et<sub>2</sub>O/hexane).



**15e**

**1-(trifluoromethyl)-4H-chromeno[4,3-d]isoxazole-6-carbonitrile (15e):** The reaction of **11c** (100 mg, 0.288 mmol, 1 eq.), palladium(II) acetate (3.2 mg, 0.014 mmol, 0.05 eq.), tris(4-fluorophenyl)phosphine (4.6 mg, 0.014 mmol, 0.05 eq.), pivalic acid (8.8 mg, 0.086

mmol, 0.3 eq.) and potassium carbonate (119.4 mg, 0.864 mmol, 3 eq.) using the general procedure for intramolecular C-H coupling reactions, purified by silica gel column chromatography (15% Et<sub>2</sub>O/hexane), afforded the title compound **15e** (30.1 mg, 39%) as a white solid, m.p. 160-161 °C.

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.64 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.51 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.14 (t, *J* = 7.8 Hz, 1 H), 5.67 (s, 2 H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 164.8, 153.6, 149.9 (q, *J* = 39.0 Hz), 133.2, 128.6 (q, *J* = 2.8 Hz), 123.3, 119.9 (q, *J* = 271.7 Hz), 115.6, 115.3, 108.0, 102.4, 63.8.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -63.6 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 2230 (w), 1635 (w), 1598 (w), 1582 (w), 1508 (m), 1471 (m), 1458 (m), 1435 (m), 1340 (m), 1298 (m), 1279 (w), 1252 (m), 1232 (m), 1209 (m), 1191 (m), 1170 (s), 1139 (s), 1090 (m), 1062 (m), 1028 (m), 1001 (m), 923 (w), 906 (m), 853 (m), 814 (m), 796 (s), 768 (m).

**HRMS (ESI):** calculated for C<sub>12</sub>H<sub>6</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 267.0376, found 267.0370.

*R<sub>f</sub>* = 0.46 (40% Et<sub>2</sub>O/hexane).



**15f**

**1-(trifluoromethyl)-4H-isoxazolo[4',5':4,5]pyrano[2,3-c]pyridine (15f):** The reaction of **11g** (60 mg, 0.162 mmol, 1 eq.), palladium(II) acetate (1.8 mg, 0.008 mmol, 0.05 eq.), tris(4-fluorophenyl)phosphine (2.6 mg, 0.008 mmol, 0.05 eq.), pivalic acid (5.0 mg, 0.049 mmol, 0.3 eq.) and potassium carbonate (67.2 mg, 0.486 mmol, 3 eq.) using the general procedure for intramolecular C-H coupling reactions, purified by silica gel column chromatography (50% Et<sub>2</sub>O/hexane), afforded the title compound **15f** (20.2 mg, 51%) as a yellow solid, m.p. 125-127 °C.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.39 (s, 1 H), 8.32 (d, *J* = 4.9 Hz, 1 H), 7.33 (d, *J* = 4.9 Hz, 1 H), 5.55 (s, 2 H).

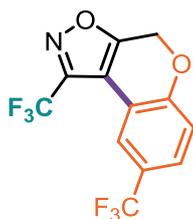
**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 166.9, 150.2 (q, *J* = 39.2 Hz), 147.4, 144.7, 139.5, 121.5, 119.8 (q, *J* = 271.7 Hz), 117.8 (q, *J* = 2.4 Hz), 107.5, 63.1.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -63.1 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 2929 (w), 2850 (w), 1632 (w), 1597 (w), 1547 (w), 1517 (w), 1479 (w), 1462 (m), 1412 (m), 1384 (w), 1366 (w), 1336 (m), 1294 (w), 1247 (m), 1221 (w), 1189 (s), 1147 (s), 1133 (s), 1063 (m), 1012 (m), 1001 (m), 992 (s), 918 (w), 899 (m), 841 (s), 829 (s), 777 (m), 760 (w).

**HRMS (ESI):** calculated for C<sub>10</sub>H<sub>6</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 243.0376, found 243.0368.

*R<sub>f</sub>* = 0.61 (40% Et<sub>2</sub>O/hexane).



**15g**

**1,8-bis(trifluoromethyl)-4H-chromeno[4,3-d]isoxazole (15g):** The reaction of **11b** (80 mg, 0.183 mmol, 1 eq.), palladium(II) acetate (2.0 mg, 0.009 mmol, 0.05 eq.), tris(4-fluorophenyl)phosphine (2.9 mg, 0.009 mmol, 0.05 eq.), pivalic acid (5.6 mg, 0.055 mmol, 0.3 eq.) and potassium carbonate (75.9 mg, 0.549 mmol, 3 eq.) using the general procedure for intramolecular C-H coupling reactions, purified by silica gel column chromatography (15% Et<sub>2</sub>O/hexane), afforded the title compound **15g** (36.8 mg, 65%) as a white solid, m.p. 118-119 °C.

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.68 (d, *J* = 1.5 Hz, 1 H), 7.51 (dd, *J* = 8.6, 1.5 Hz, 1 H), 7.12 (d, *J* = 8.6 Hz, 1 H), 5.54 (s, 2 H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 165.2, 154.1, 150.0 (q, *J* = 38.9 Hz), 127.2 (q, *J* = 3.4 Hz), 125.6 (q, *J* = 33.2 Hz), 123.9 (q, *J* = 271.6 Hz), 121.7, 120.0 (q, *J* = 271.6 Hz), 117.8, 114.9, 108.5, 63.1.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -62.8 (s, 3 F), -63.1 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 2924 (w), 2850 (w), 1617 (w), 1585 (w), 1520 (w), 1486 (w), 1469 (w), 1458 (w), 1436 (w), 1385 (w), 1338 (m), 1297 (m), 1281 (m), 1228 (m), 1206 (m), 1188 (m), 1151 (s), 1109 (s), 1075 (s), 1044 (m), 1013 (m), 994 (m), 909 (m), 896 (m), 849 (m), 840 (m), 803 (m).

**HRMS (ESI):** calculated for C<sub>12</sub>H<sub>6</sub>F<sub>6</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 310.0297, found 310.0286.

*R<sub>f</sub>* = 0.73 (40% Et<sub>2</sub>O/hexane).



**15h**

**1-(trifluoromethyl)-4,6-dihydrobenzo[5,6]oxepino[4,3-d]isoxazole (15h):** The reaction of **12c** (90 mg, 0.235 mmol, 1 eq.), palladium(II) acetate (2.6 mg, 0.012 mmol, 0.05 eq.), tris(4-fluorophenyl)phosphine (3.7 mg, 0.012 mmol, 0.05 eq.), pivalic acid (7.2 mg, 0.071 mmol, 0.3 eq.) and potassium carbonate (97.4 mg, 0.705 mmol, 3 eq.) using the general procedure for intramolecular C-H coupling reactions, purified by silica gel column chromatography (15% Et<sub>2</sub>O/hexane), afforded the title compound **15h** (36.3 mg, 60%) as a white solid, m.p. 75-77 °C.

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.71 (d, *J* = 7.5 Hz, 1 H), 7.44 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.35 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.30 (dd, *J* = 7.5, 1.2 Hz, 1 H), 5.17 (s, 2 H), 4.66 (s, 2 H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 170.1, 152.7 (q, *J* = 36.5 Hz), 138.6, 129.4, 129.1, 128.5, 128.1 (q, *J* = 3.8 Hz), 125.8, 120.3 (q, *J* = 272.1 Hz), 114.5, 72.8, 67.7.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -61.3 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 2919 (w), 2848 (w), 1615 (w), 1598 (w), 1505 (w), 1478 (m), 1448 (m), 1439 (m), 1373 (w), 1316 (m), 1282 (w), 1236 (m), 1196 (m), 1180 (m), 1171 (m), 1139 (s),

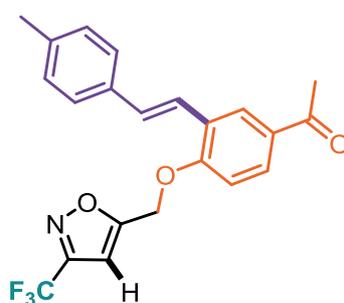
1125 (s), 1109 (s), 1061 (m), 1039 (w), 1011 (w), 974 (m), 962 (m), 926 (m), 878 (w), 829 (w), 786 (m), 769 (s).

**HRMS (ESI):** calculated for  $C_{12}H_9F_3NO_2$   $[M+H]^+$  256.0580, found 256.0570.

**$R_f$**  = 0.61 (40%  $Et_2O$ /hexane).

## 2.9. Intermolecular Suzuki cross-coupling

**General procedure for intermolecular Suzuki cross-couplings:** To a screw-capped vial equipped with a magnetic stir-bar was added the appropriate isoxazole (0.150 mmol, 1 eq.), the appropriate boronic acid (0.225 mmol, 1.5 eq.),  $K_3PO_4$  (95.5 mg, 0.450 mmol, 3 eq.),  $PdCl_2(PPh_3)_2$  (5.3 mg, 0.0075 mmol, 0.05 eq.) and dimethoxyethane/water (1:1, 2 mL). The vial was sealed and stirred at 65 °C for 2 h. The reaction mixture was then cooled to r.t. and purified directly by flash column chromatography.



**16a**

**(E)-1-(3-(4-methylstyryl)-4-((3-(trifluoromethyl)isoxazol-5-yl)methoxy)phenyl)ethan-1-one (16a):** The reaction of **11e** (50.0 mg, 0.122 mmol, 1 eq.), *trans*-2-(4-methylphenyl)vinylboronic acid (29.6 mg, 0.183 mmol, 1.5 eq.),  $K_3PO_4$  (77.7 mg, 0.366 mmol, 3 eq.) and  $PdCl_2(PPh_3)_2$  (4.3 mg, 0.0061 mmol, 0.05 eq.) using the general procedure for intermolecular Suzuki cross-couplings, purified by silica gel column chromatography (20% EtOAc/hexane), afforded the title compound **16a** (29.3 mg, 60%) as a pale orange solid, m.p. 104–106 °C.

**$^1H$  NMR (500 MHz,  $CDCl_3$ ):**  $\delta$  8.25 (d,  $J = 2.2$  Hz, 1 H), 7.86 (dd,  $J = 8.6, 2.2$  Hz, 1 H), 7.43 (d,  $J = 8.1$  Hz, 2 H), 7.35 (d,  $J = 16.5$  Hz, 1 H), 7.23 – 7.17 (m, 3 H), 6.95 (d,  $J = 8.6$  Hz, 1 H), 6.64 (s, 1 H), 5.36 (s, 2 H), 2.62 (s, 3 H), 2.37 (s, 3 H).

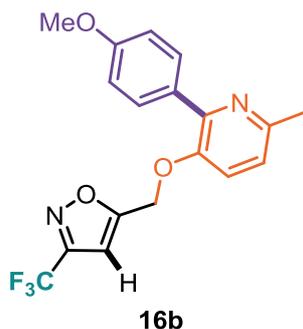
**$^{13}C$  NMR (125 MHz,  $CDCl_3$ ):**  $\delta$  197.0, 170.0, 158.0, 155.8 (q,  $J = 38.7$  Hz), 138.3, 134.4, 131.8, 131.5, 129.6, 129.3, 127.7, 127.3, 126.8, 120.6, 119.6 (q,  $J = 271.3$  Hz), 111.6, 101.4, 61.5, 26.6, 21.4.

**$^{19}F$  NMR (376 MHz,  $CDCl_3$ ):**  $\delta$  -63.5 (s, 3 F).

**FTIR ( $\nu_{max}$ ,  $cm^{-1}$ ):** 3022 (w), 2921 (w), 1676 (s), 1590 (s), 1514 (w), 1499 (m), 1461 (w), 1447 (m), 1419 (w), 1407 (w), 1396 (w), 1356 (m), 1261 (s), 1238 (m), 1216 (m), 1183 (s), 1153 (s), 1095 (m), 1087 (m), 1050 (m), 1021 (w), 991 (m), 977 (w), 967 (s), 947 (w), 924 (m), 868 (w), 806 (s), 756 (m).

**HRMS (ESI):** calculated for  $C_{22}H_{19}F_3NO_3$   $[M+H]^+$  402.1312, found 402.1304.

$R_f = 0.21$  (20% EtOAc/hexane).



**5-(((2-(4-methoxyphenyl)-6-methylpyridin-3-yl)oxy)methyl)-3-(trifluoromethyl)isoxazole (16b):** The reaction of **11f** (50.0 mg, 0.130 mmol, 1 eq.), 4-methoxyphenylboronic acid (29.6 mg, 0.195 mmol, 1.5 eq.),  $K_3PO_4$  (82.8 mg, 0.390 mmol, 3 eq.) and  $PdCl_2(PPh_3)_2$  (4.6 mg, 0.0065 mmol, 0.05 eq.) using the general procedure for intermolecular Suzuki cross-couplings, purified by silica gel column chromatography (20% EtOAc/hexane), afforded the title compound **16b** (33.8 mg, 71%) as an orange solid, m.p. 57-58 °C.

$^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  7.84 (d,  $J = 8.9$  Hz, 2 H), 7.21 (d,  $J = 8.3$  Hz, 1 H), 7.04 (d,  $J = 8.3$  Hz, 1 H), 6.97 (d,  $J = 8.9$  Hz, 2 H), 6.44 (s, 1 H), 5.11 (d,  $J = 0.5$  Hz, 2 H), 3.85 (s, 3 H), 2.56 (s, 3 H).

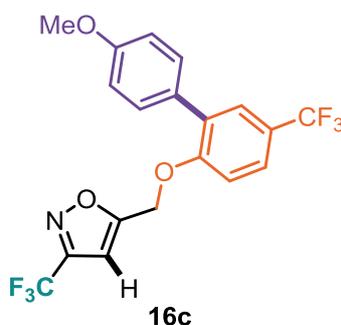
$^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  170.5, 160.1, 155.6 (q,  $J = 38.6$  Hz), 152.4, 149.4, 148.2, 130.8, 129.9, 122.7, 121.9, 119.6 (q,  $J = 271.2$  Hz), 113.7, 101.1, 62.6, 55.4, 23.9.

$^{19}F$  NMR (376 MHz,  $CDCl_3$ ):  $\delta$  -63.6 (s, 3 F).

FTIR ( $\nu_{max}$ ,  $cm^{-1}$ ): 2966 (w), 2927 (w), 2842 (w), 1609 (m), 1579 (m), 1513 (m), 1496 (m), 1461 (m), 1449 (m), 1418 (w), 1392 (m), 1298 (m), 1246 (s), 1177 (s), 1139 (s), 1112 (m), 1094 (m), 1075 (m), 1043 (m), 1025 (m), 1005 (w), 967 (s), 890 (w), 840 (m), 812 (s), 767 (m), 757 (m).

HRMS (ESI): calculated for  $C_{18}H_{16}F_3N_2O_3$   $[M+H]^+$  365.1108, found 365.1110.

$R_f = 0.46$  (30% EtOAc/hexane).



**5-(((4'-methoxy-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)oxy)methyl)-3-(trifluoromethyl)isoxazole (16c):** The reaction of **11b** (50.0 mg, 0.114 mmol, 1 eq.), 4-methoxyphenylboronic acid (26.1 mg, 0.171 mmol, 1.5 eq.),  $K_3PO_4$  (72.9 mg, 0.343 mmol, 3 eq.) and  $PdCl_2(PPh_3)_2$  (4.0 mg, 0.0057 mmol, 0.05 eq.) using the general procedure for intermolecular Suzuki cross-couplings, purified by silica gel column chromatography (15% EtOAc/hexane), afforded the title compound **16c** (47.0 mg, 99%) as a yellow solid, m.p. 62-64 °C.

$^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  7.62 (d,  $J = 2.2$  Hz, 1 H), 7.59 – 7.56 (m, 1 H), 7.46 (d,  $J = 8.9$  Hz, 2 H), 7.07 (d,  $J = 8.5$  Hz, 1 H), 6.99 (d,  $J = 8.9$  Hz, 2 H), 6.43 (s, 1 H), 5.23 (s, 2 H), 3.87 (s, 3 H).

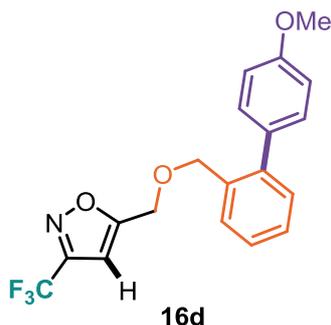
**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 170.2, 159.6, 156.7, 155.7 (q, *J* = 38.6 Hz), 132.1, 130.7, 128.8, 128.4 (q, *J* = 3.2 Hz), 125.6 (q, *J* = 3.5 Hz), 125.2 (q, *J* = 33.4 Hz), 124.2 (q, *J* = 271.6 Hz), 119.6 (q, *J* = 271.3 Hz), 113.9, 113.2, 101.1, 62.2, 55.5.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -62.3 (s, 3 F), -63.6 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 1611 (m), 1576 (w), 1520 (m), 1499 (m), 1457 (w), 1429 (w), 1407 (w), 1335 (s), 1298 (m), 1264 (m), 1248 (s), 1220 (m), 1178 (s), 1140 (s), 1115 (s), 1085 (m), 1040 (s), 1008 (m), 969 (s), 934 (w), 907 (w), 833 (m), 810 (s), 755 (m).

**HRMS (ESI):** calculated for C<sub>19</sub>H<sub>14</sub>F<sub>6</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 418.0872, found 418.0870.

*R<sub>f</sub>* = 0.38 (15% EtOAc/hexane).



**5-(((4'-methoxy-[1,1'-biphenyl]-2-yl)methoxy)methyl)-3-(trifluoromethyl)isoxazole (16d):**

The reaction of **12a** (50.0 mg, 0.150 mmol, 1 eq.), 4-methoxyphenylboronic acid (34.2 mg, 0.225 mmol, 1.5 eq.), K<sub>3</sub>PO<sub>4</sub> (95.5 mg, 0.343 mmol, 3 eq.) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (5.3 mg, 0.0075 mmol, 0.05 eq.) using the general procedure for intermolecular Suzuki cross-couplings, purified by silica gel column chromatography (5% EtOAc/hexane), afforded the title compound **16d** (51.4 mg, 95%) as a pale yellow oil.

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 7.53 – 7.49 (m, 1 H), 7.41 – 7.35 (m, 2 H), 7.32 – 7.29 (m, 1 H), 7.27 (d, *J* = 8.8 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 6.37 (s, 1 H), 4.60 (d, *J* = 0.6 Hz, 2 H), 4.54 (s, 2 H), 3.86 (s, 3 H).

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 172.2, 159.1, 155.5 (q, *J* = 38.4 Hz), 142.2, 134.1, 132.9, 130.5, 130.4, 129.8, 128.5, 127.5, 119.7 (q, *J* = 271.2 Hz), 113.7, 100.6, 71.4, 62.8, 55.4.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ -63.6 (s, 3 F).

**FTIR (ν<sub>max</sub>, cm<sup>-1</sup>):** 2922 (w), 2850 (w), 1611 (m), 1580 (w), 1516 (m), 1485 (m), 1465 (m), 1443 (m), 1360 (w), 1297 (m), 1244 (s), 1177 (s), 1148 (s), 1106 (m), 1080 (m), 1051 (m), 1037 (s), 1018 (m), 1002 (m), 969 (s), 932 (m), 875 (w), 834 (m), 812 (m), 800 (m), 763 (s).

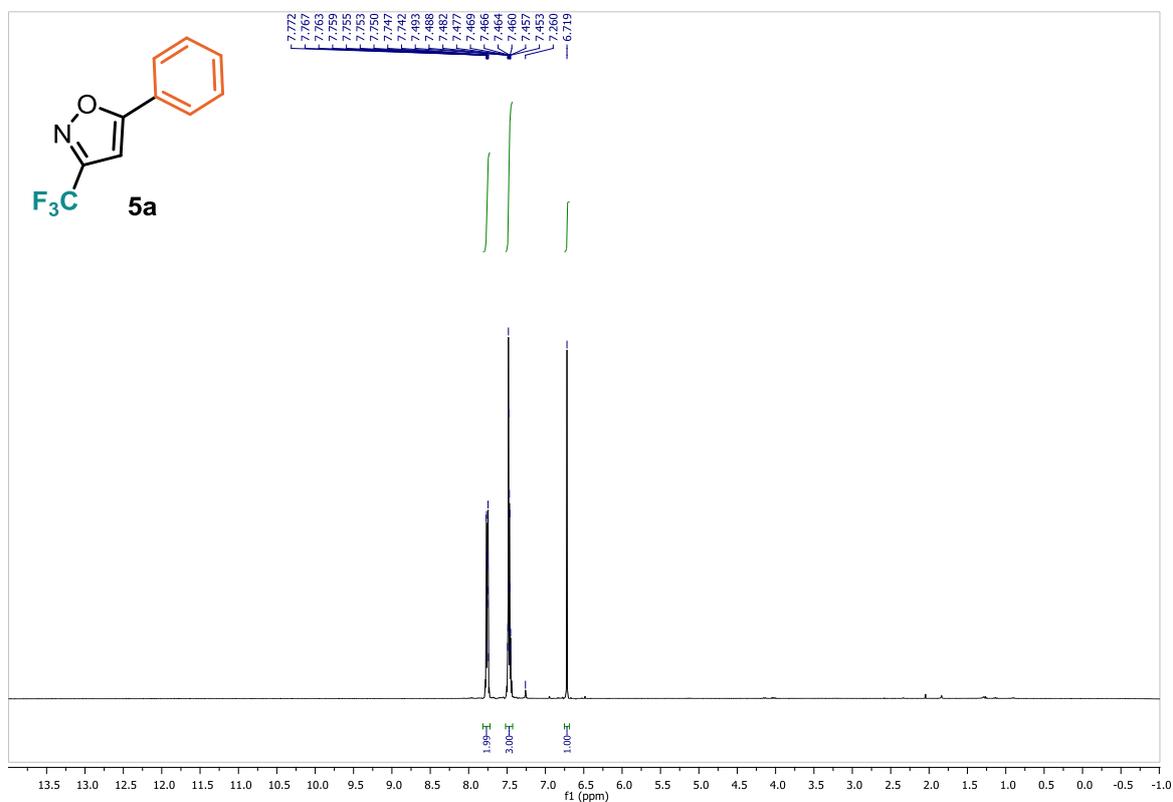
**HRMS (ESI):** calculated for C<sub>19</sub>H<sub>17</sub>F<sub>3</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 364.1155, found 364.1150.

*R<sub>f</sub>* = 0.24 (5% EtOAc/hexane).

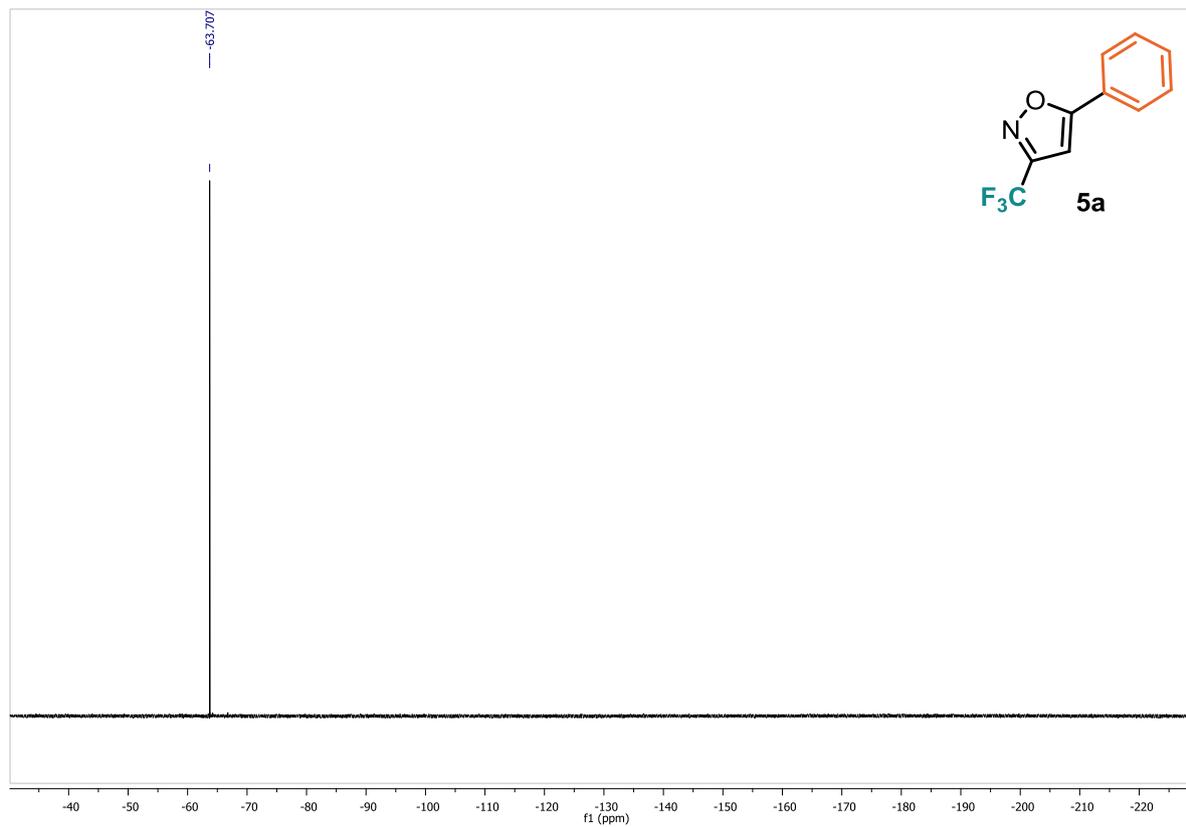
### 3. NMR spectra

#### 5-phenyl-3-(trifluoromethyl)isoxazole (5a):

$^1\text{H}$  NMR, 400 MHz,  $\text{CDCl}_3$ :

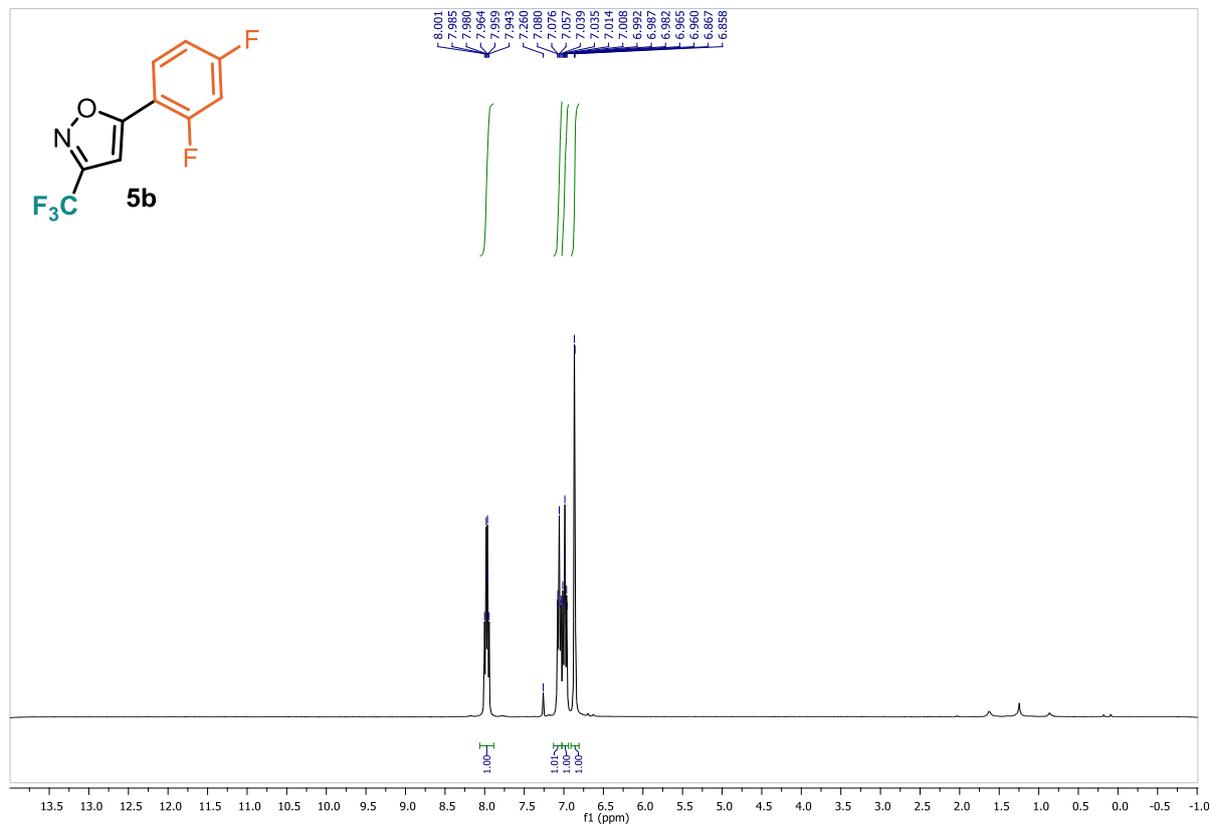


<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:

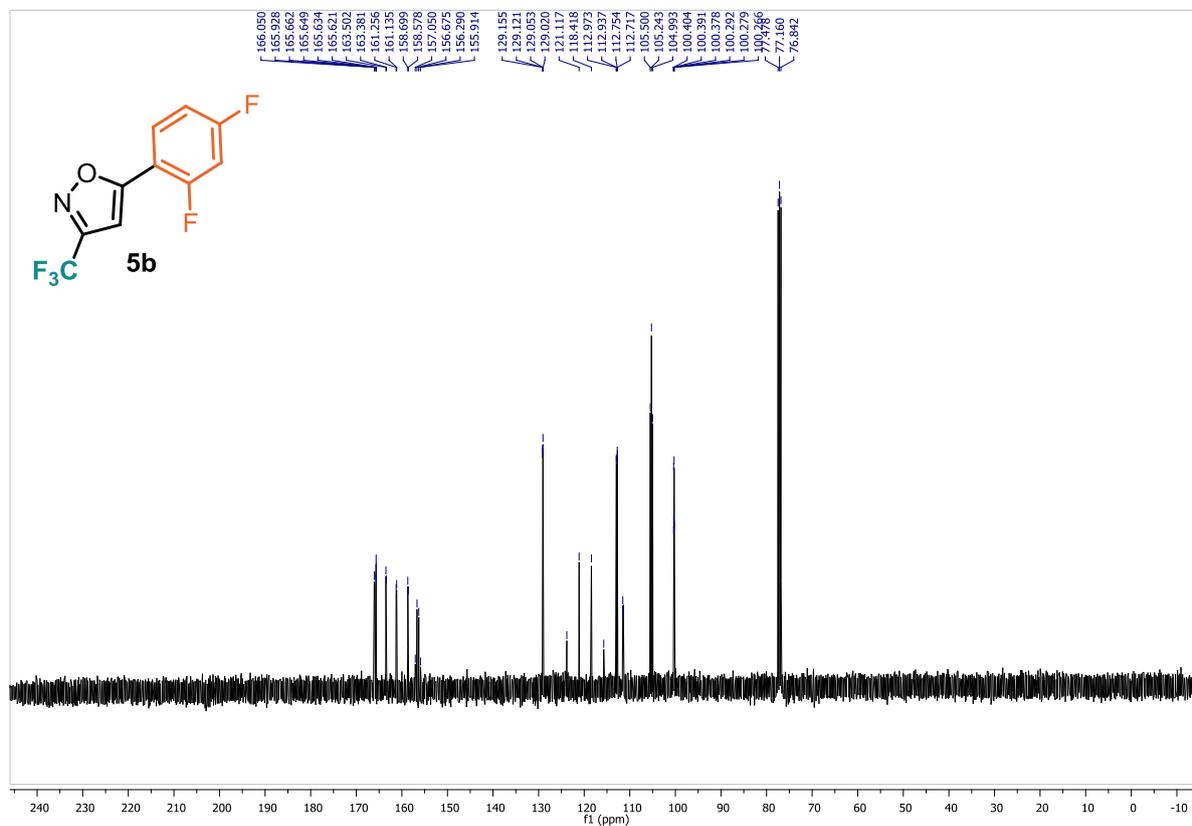


### 5-(2,4-difluorophenyl)-3-(trifluoromethyl)isoxazole (5b):

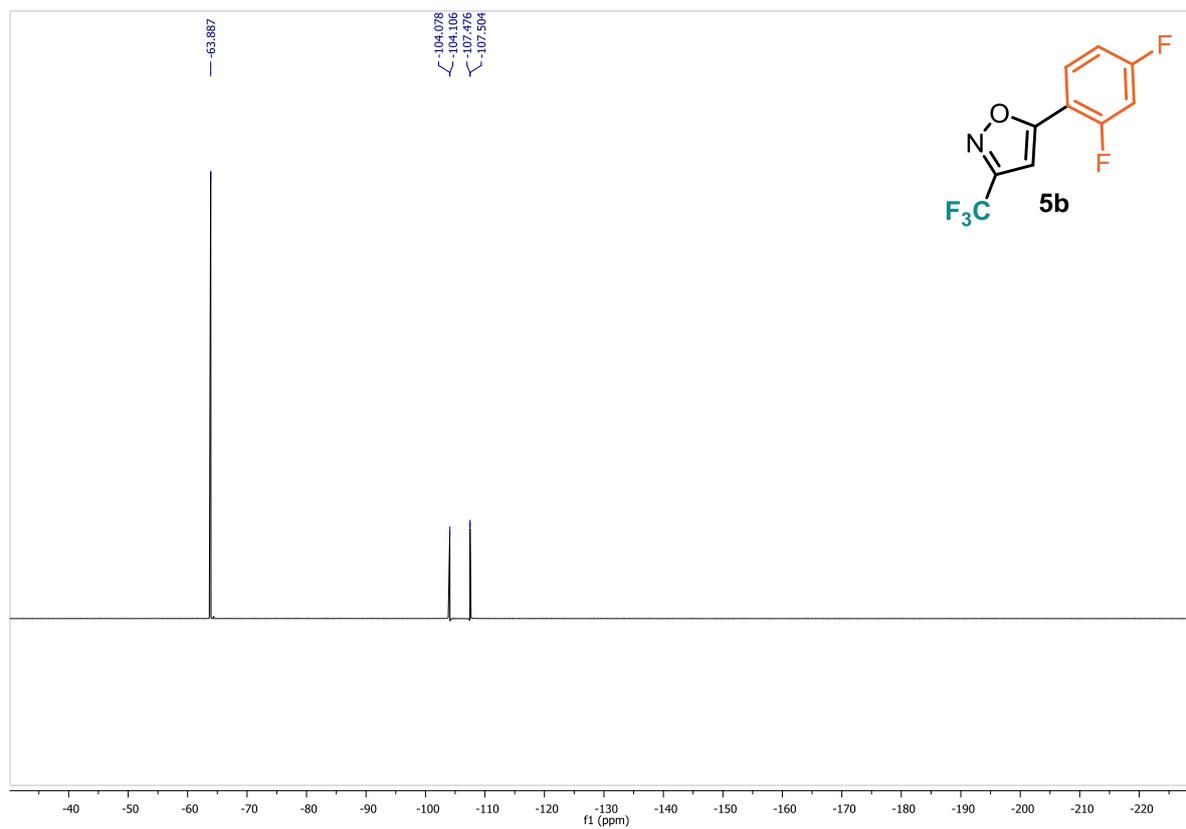
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:

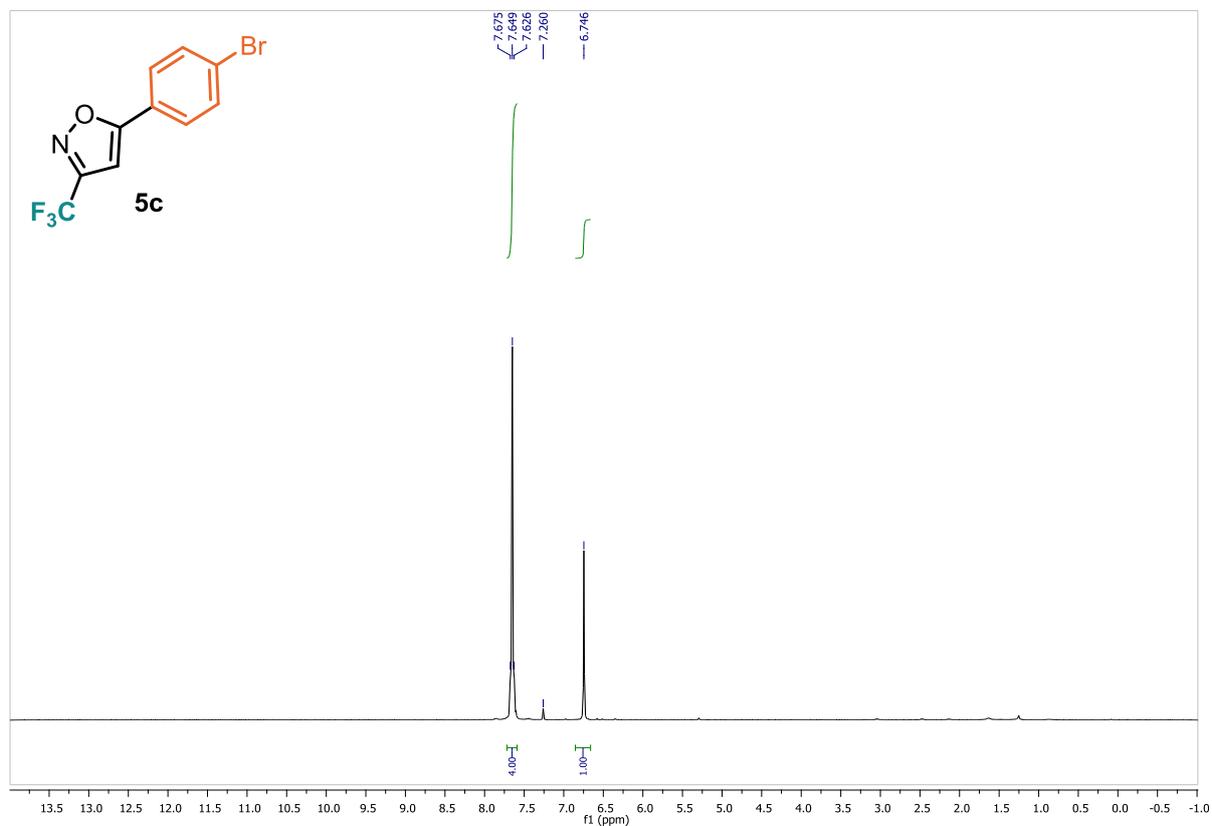


**<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:**

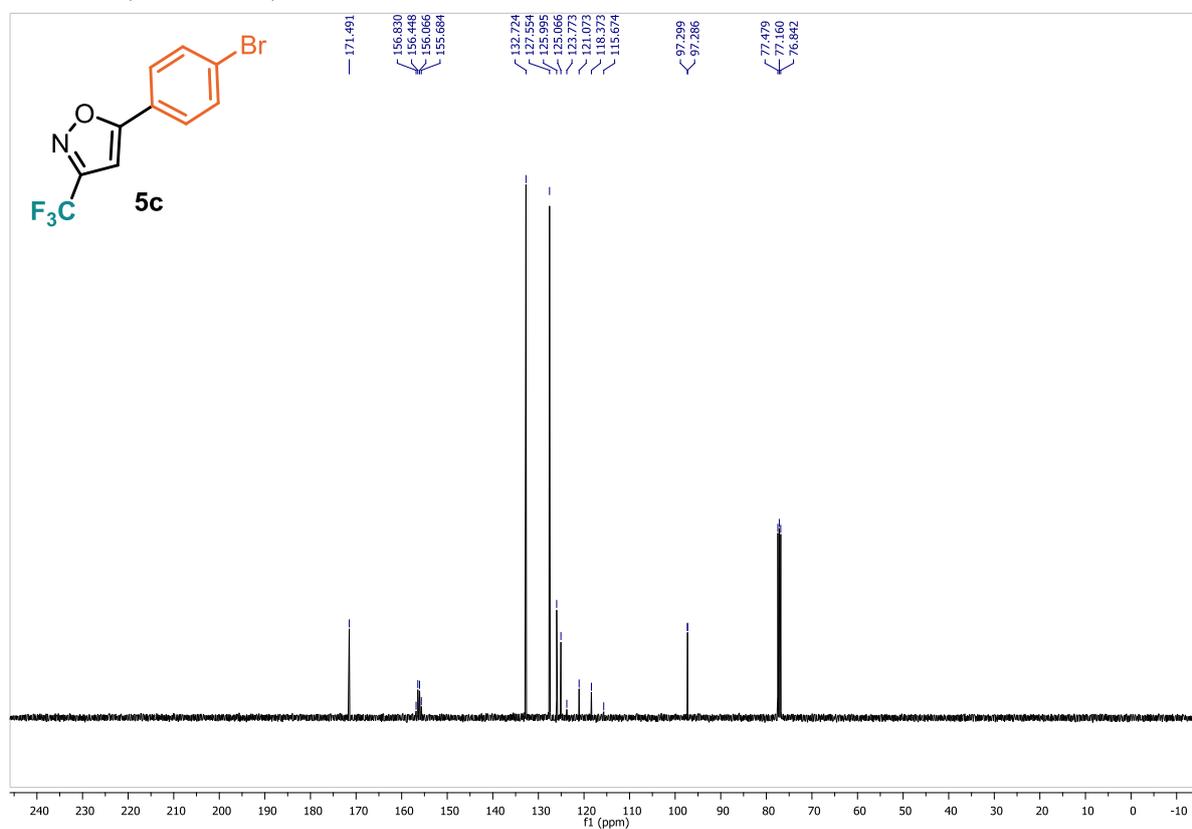


### 5-(4-bromophenyl)-3-(trifluoromethyl)isoxazole (5c):

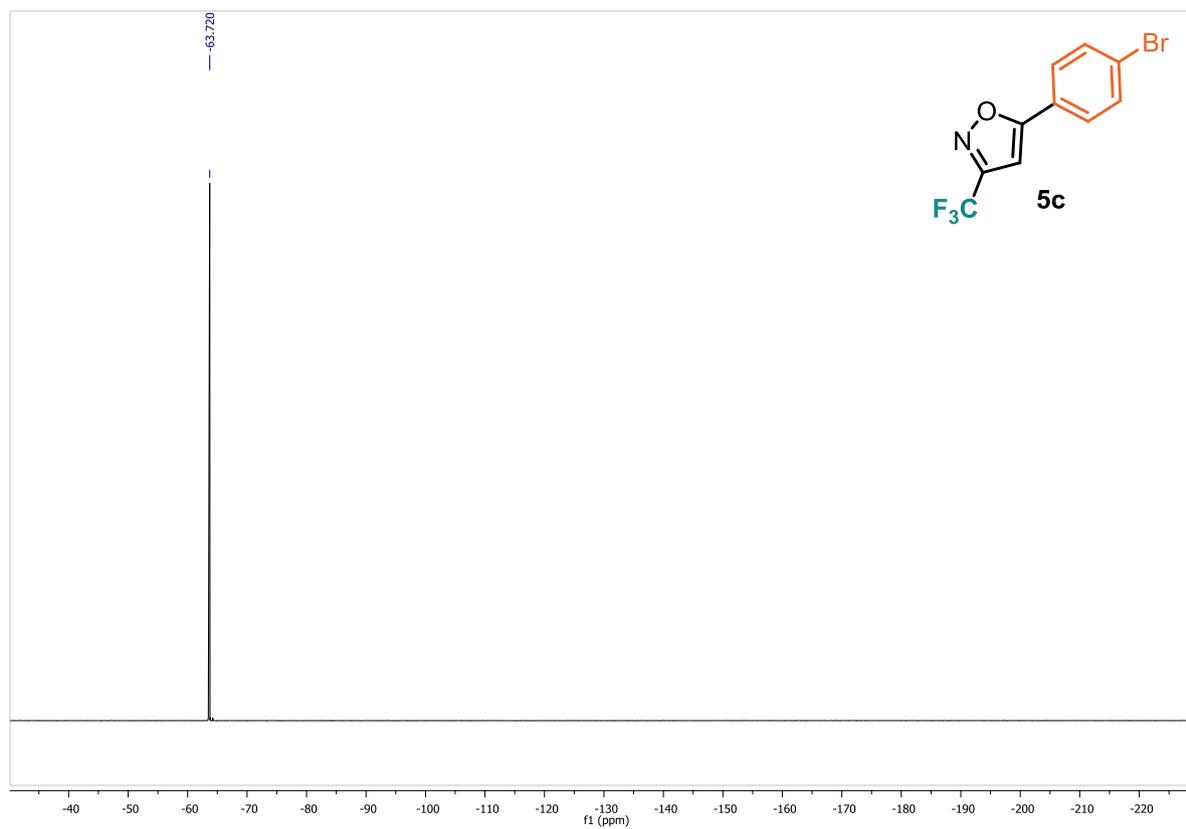
$^1\text{H}$  NMR, 400 MHz,  $\text{CDCl}_3$ :



$^{13}\text{C}$  NMR, 100 MHz,  $\text{CDCl}_3$ :

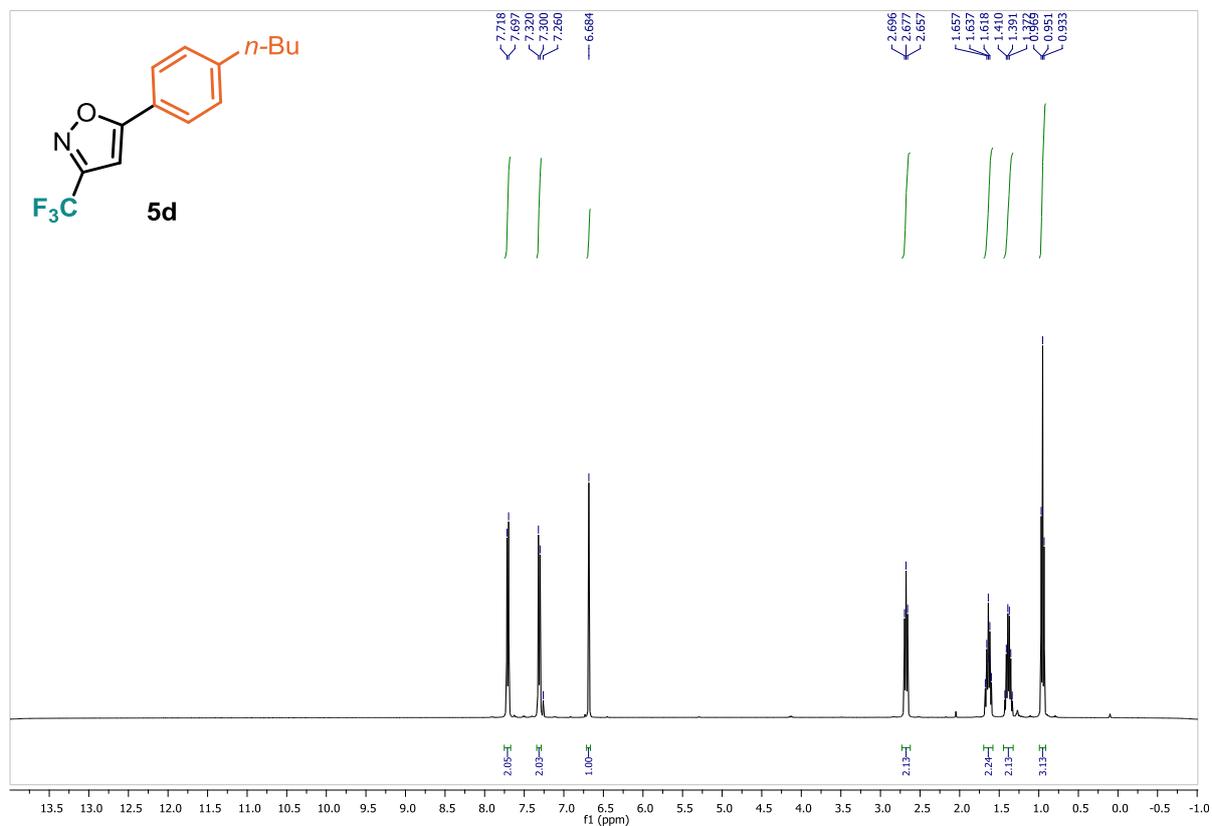


**<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:**

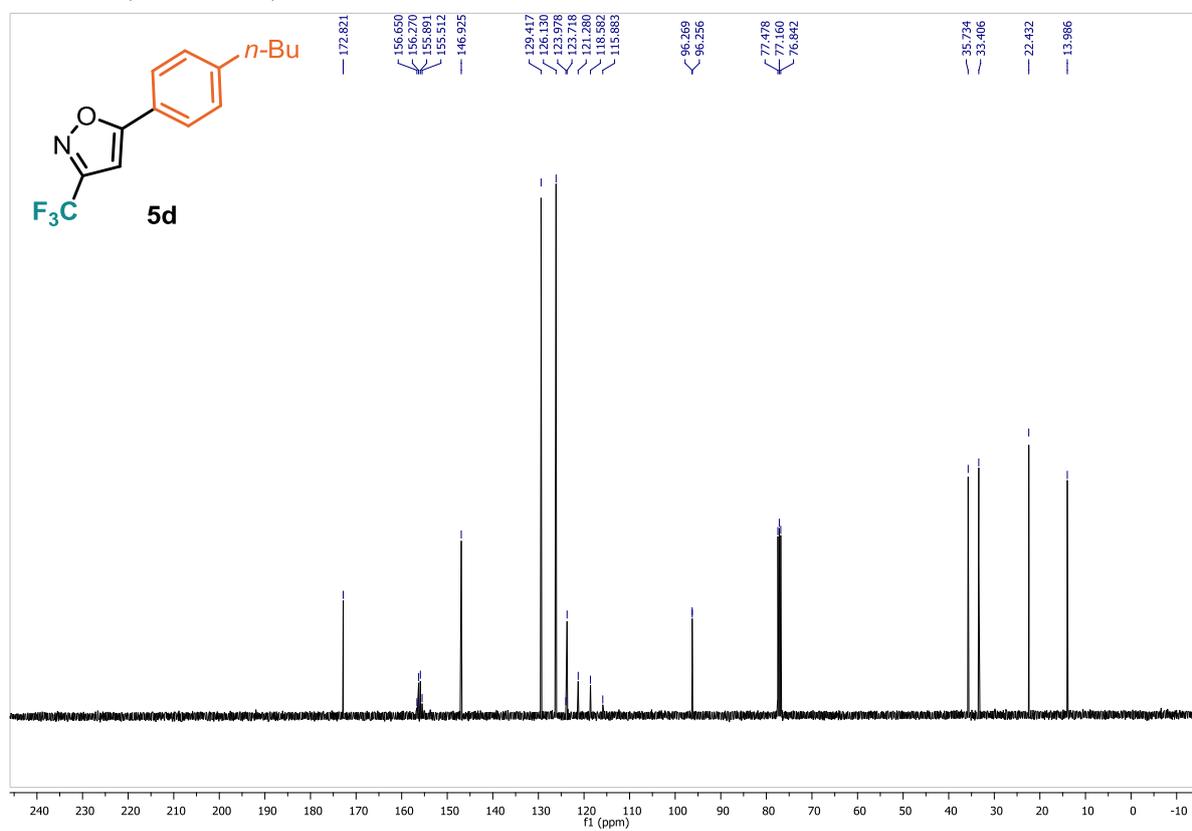


### 5-(4-butylphenyl)-3-(trifluoromethyl)isoxazole (5d):

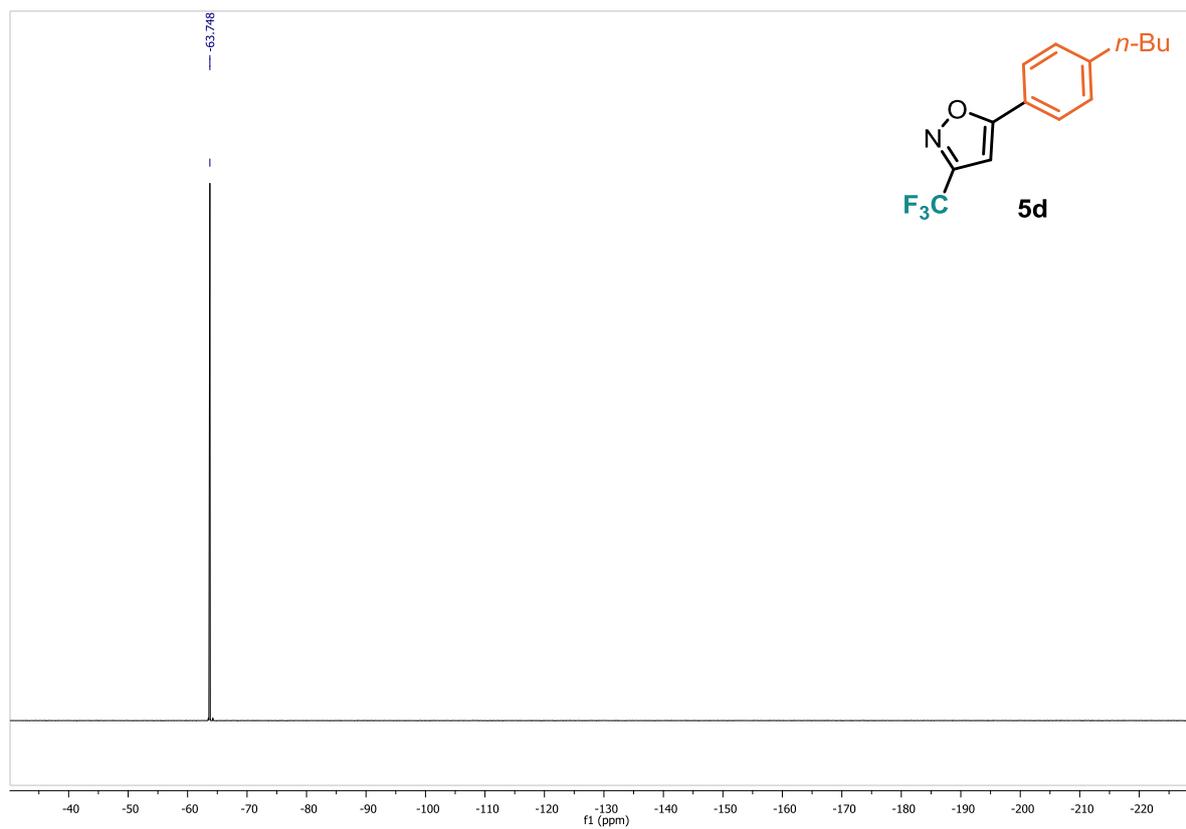
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:

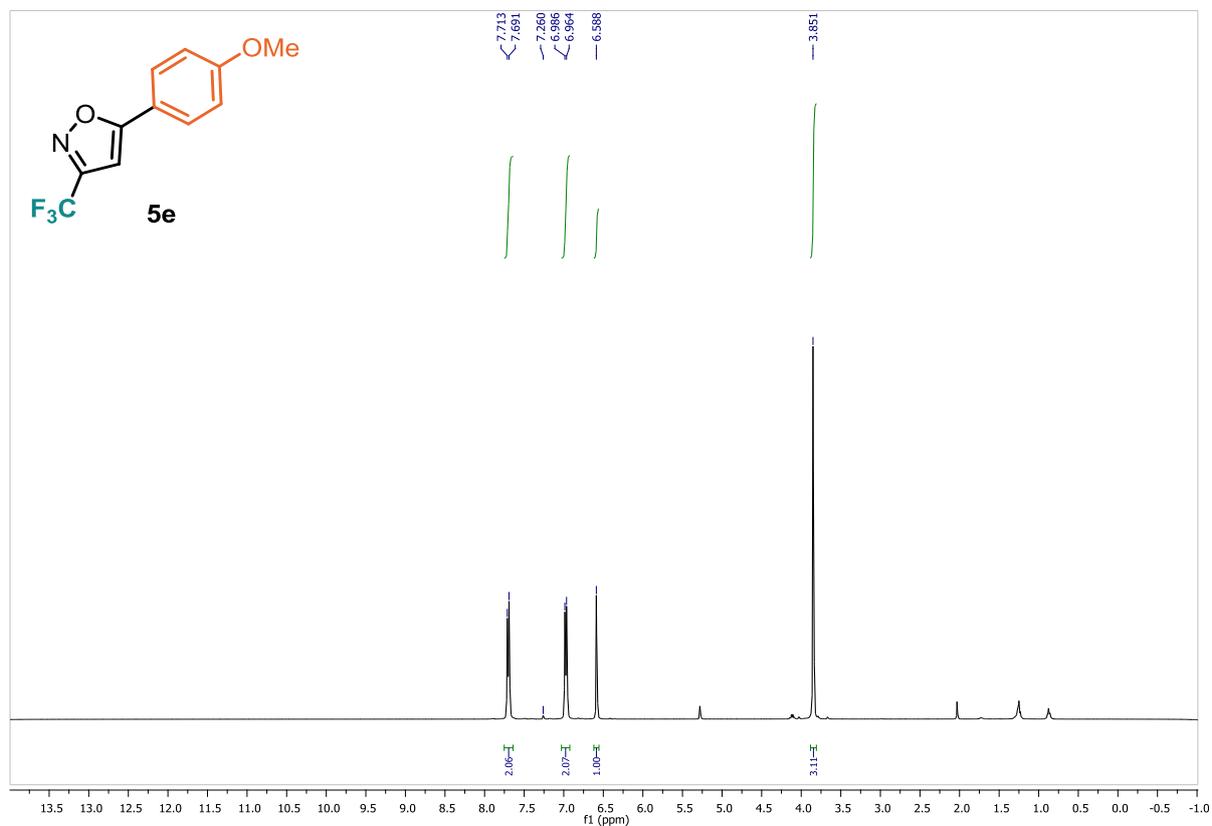


<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:

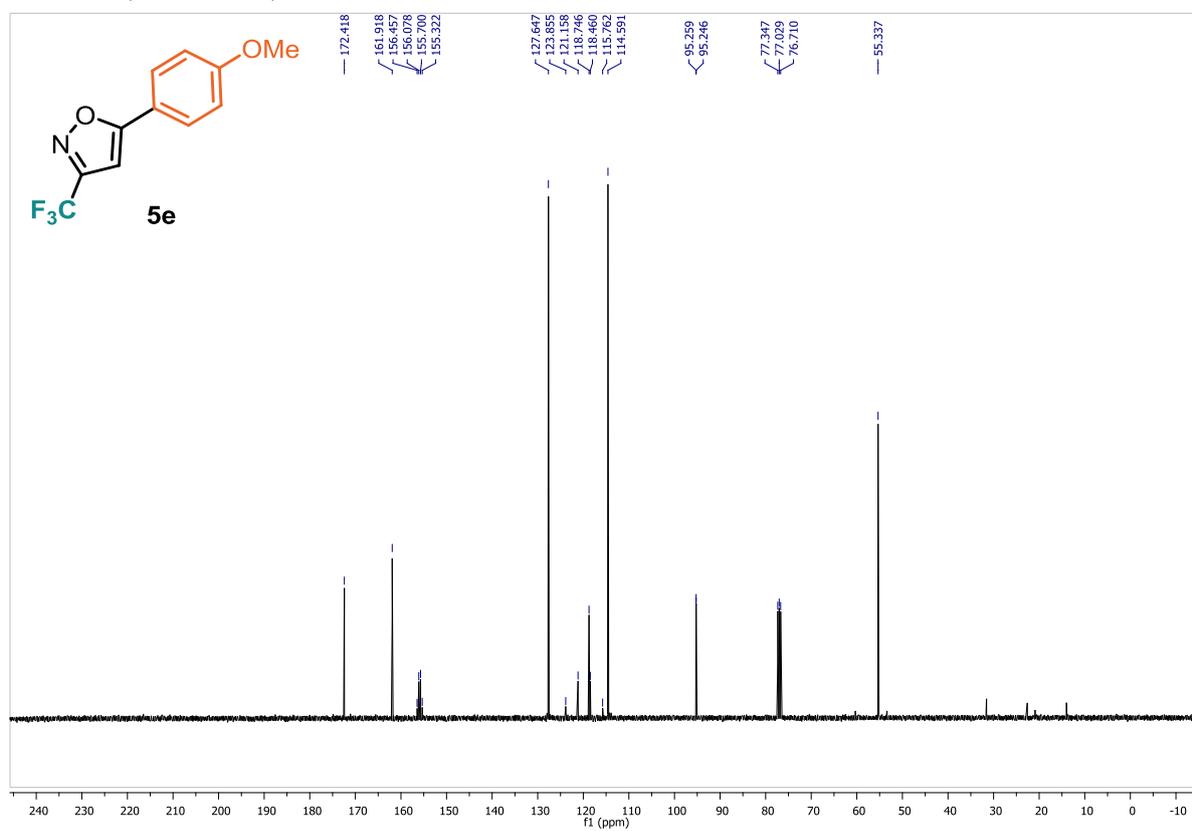


### 5-(4-methoxyphenyl)-3-(trifluoromethyl)isoxazole (5e):

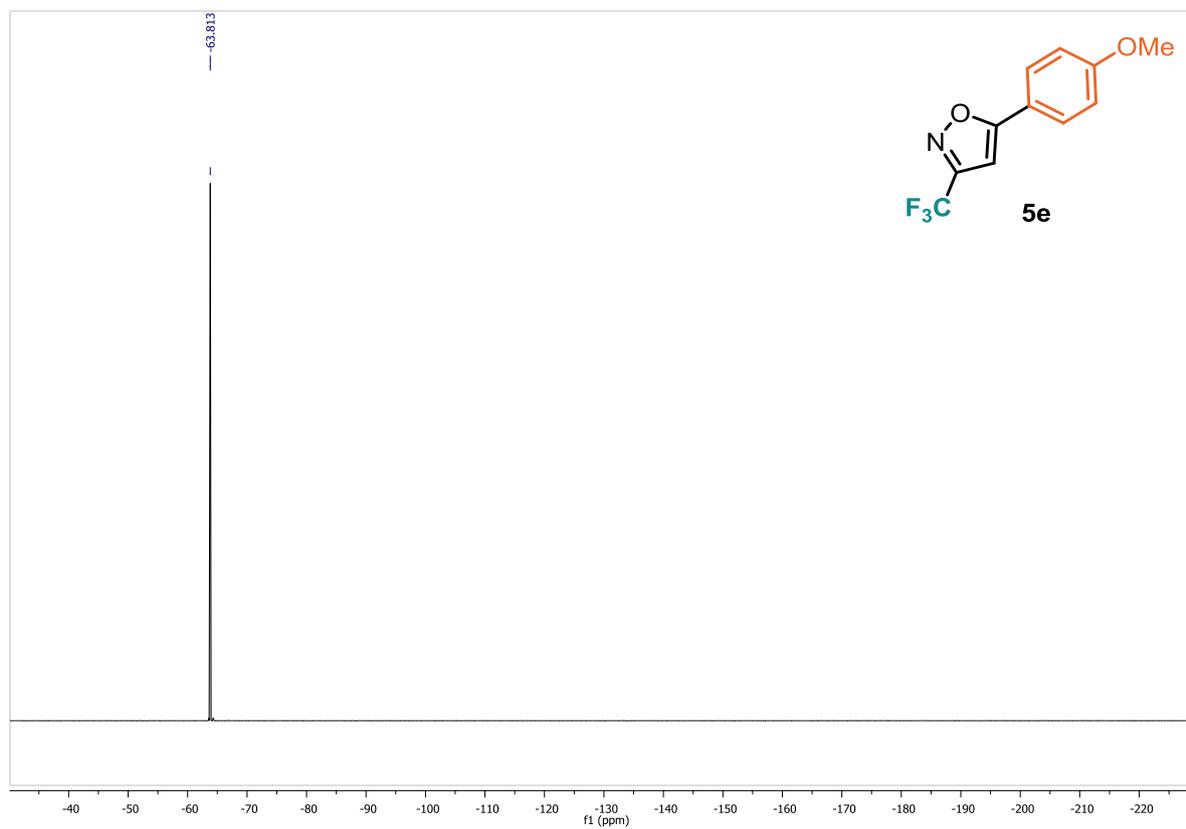
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:

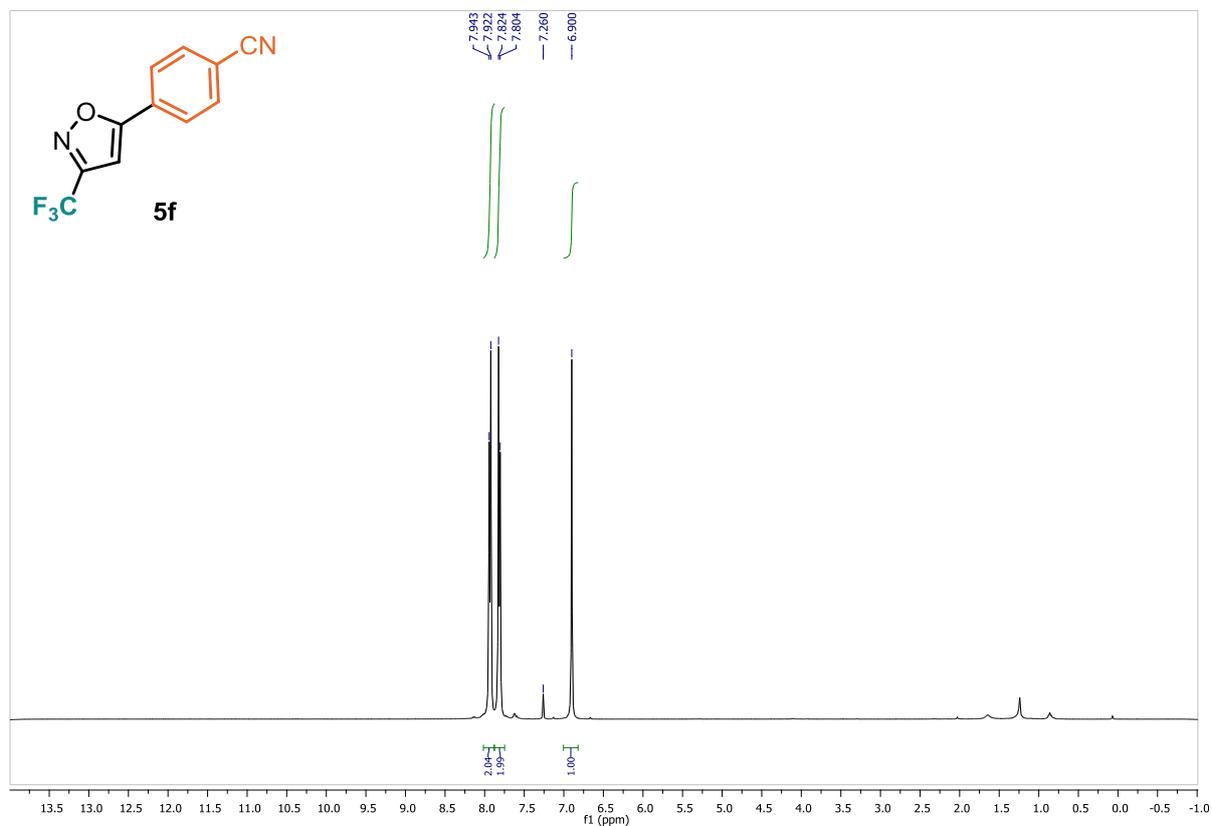


<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:

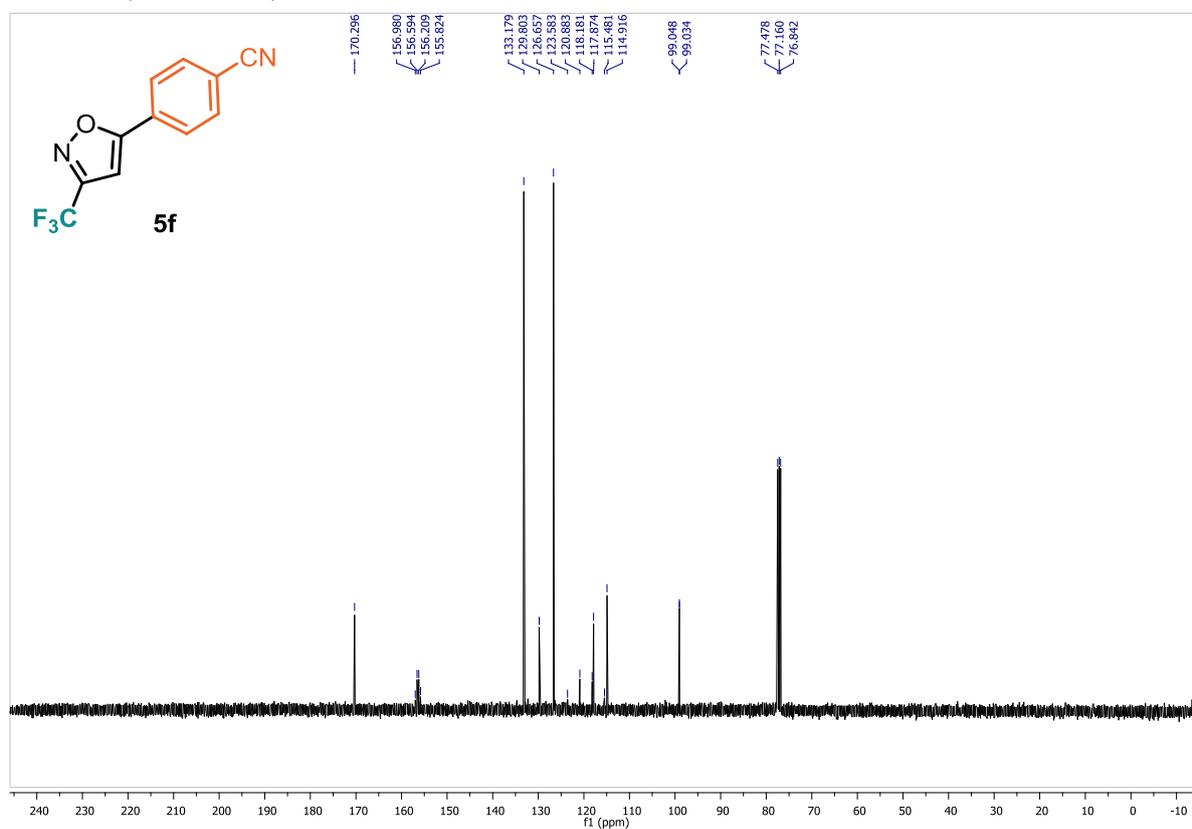


### 4-(3-(trifluoromethyl)isoxazol-5-yl)benzonitrile (**5f**):

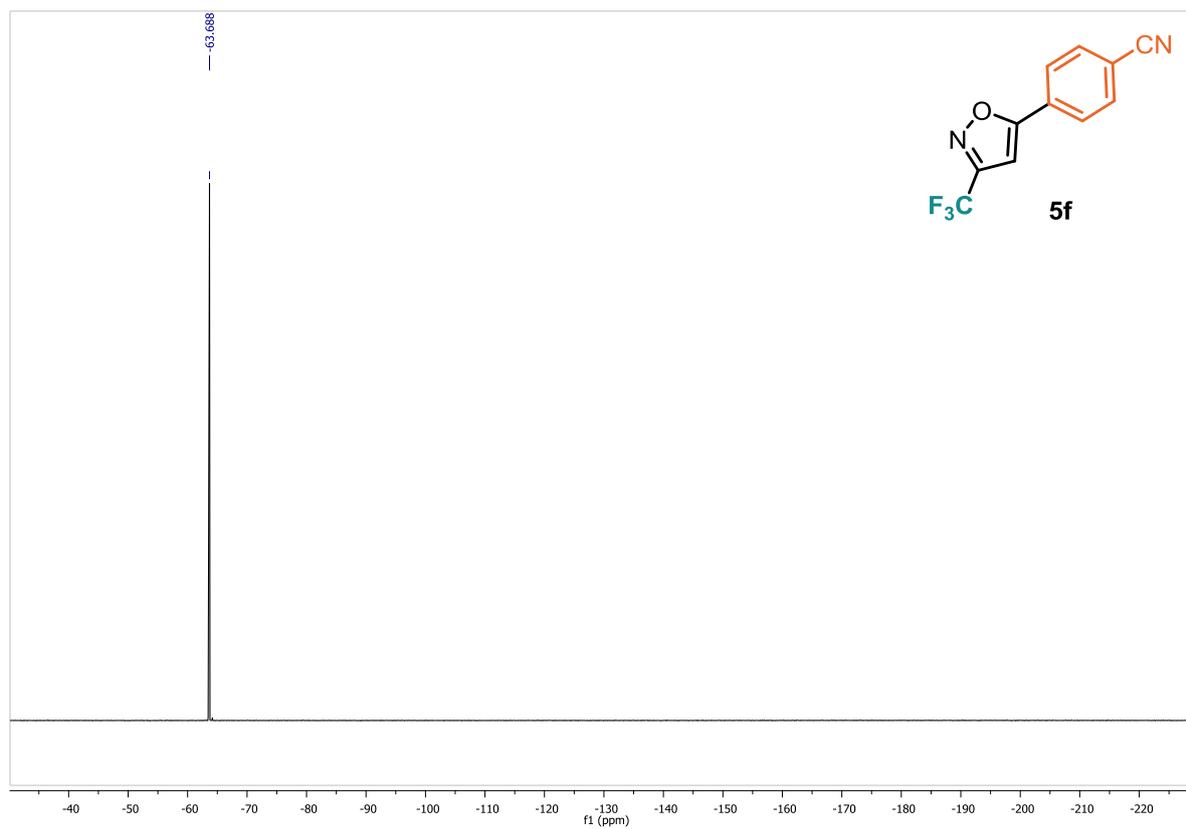
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:

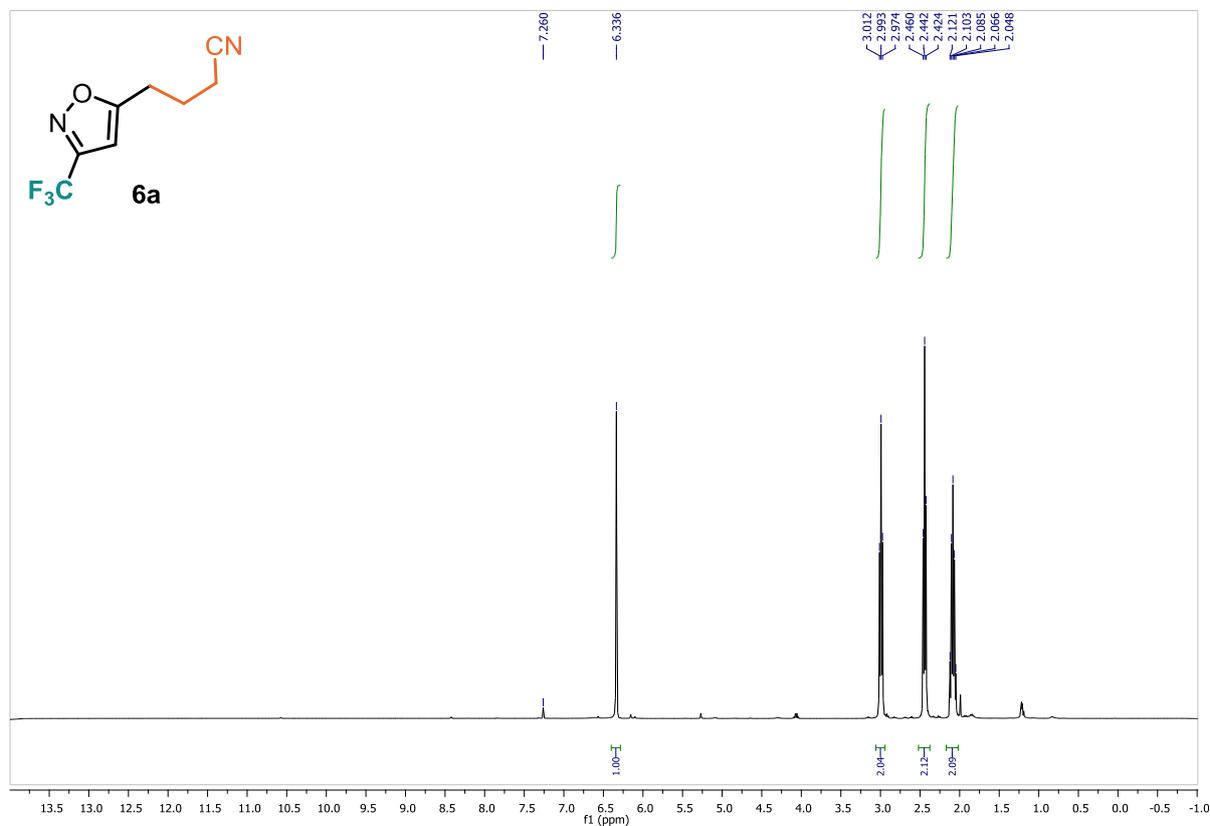


**$^{19}\text{F}$  NMR, 376 MHz,  $\text{CDCl}_3$ :**

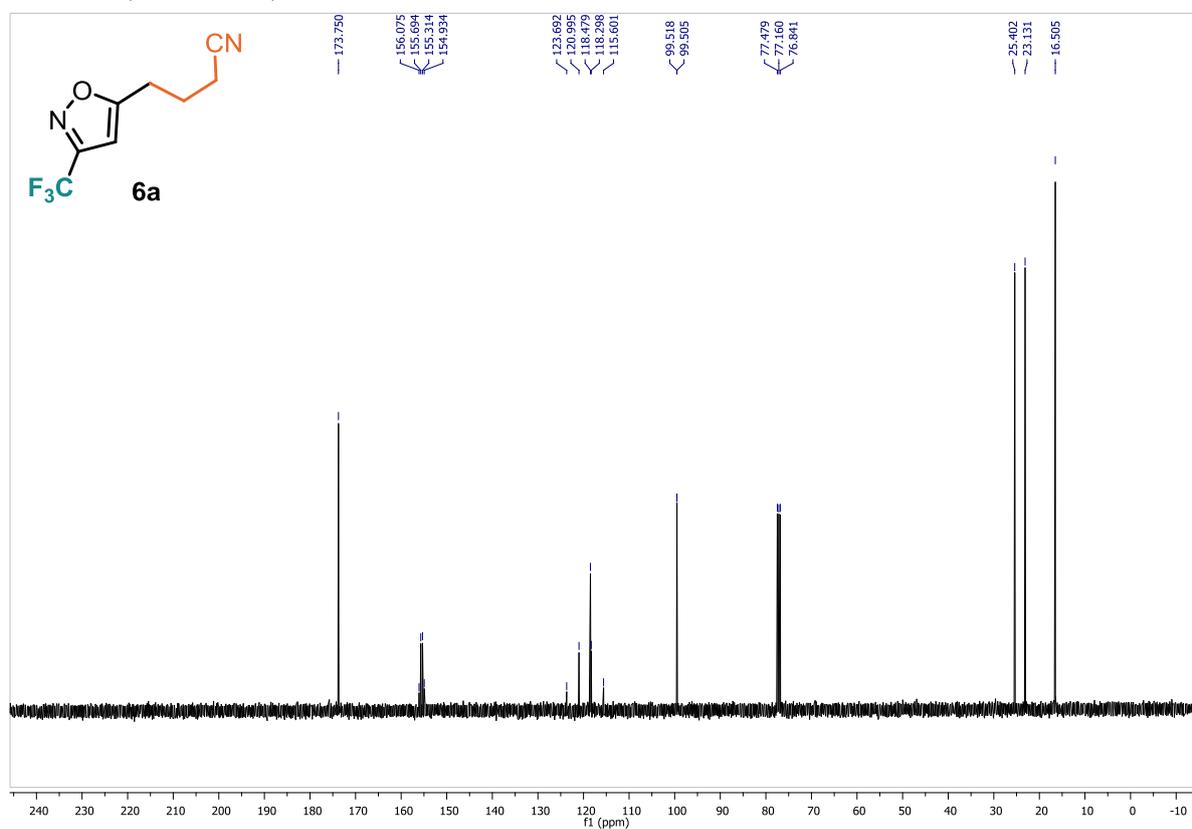


### 4-(3-(trifluoromethyl)isoxazol-5-yl)butanenitrile (6a):

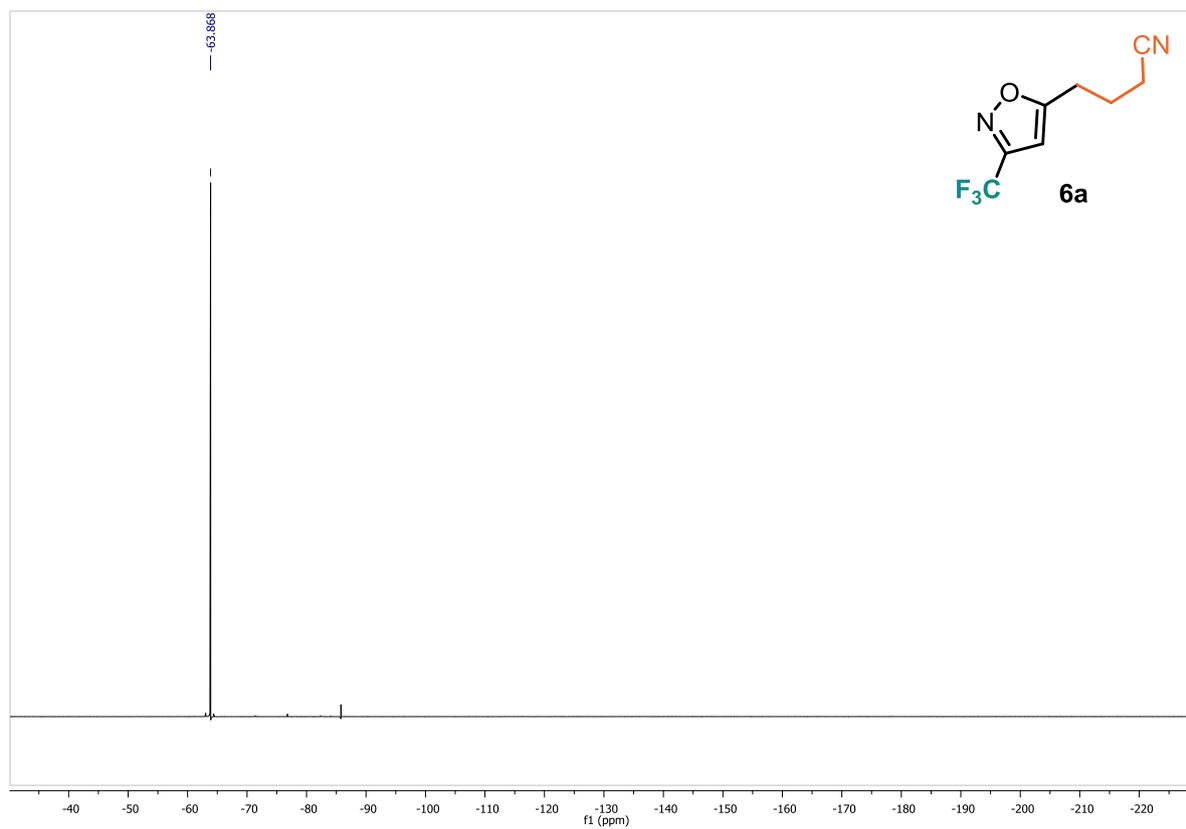
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:

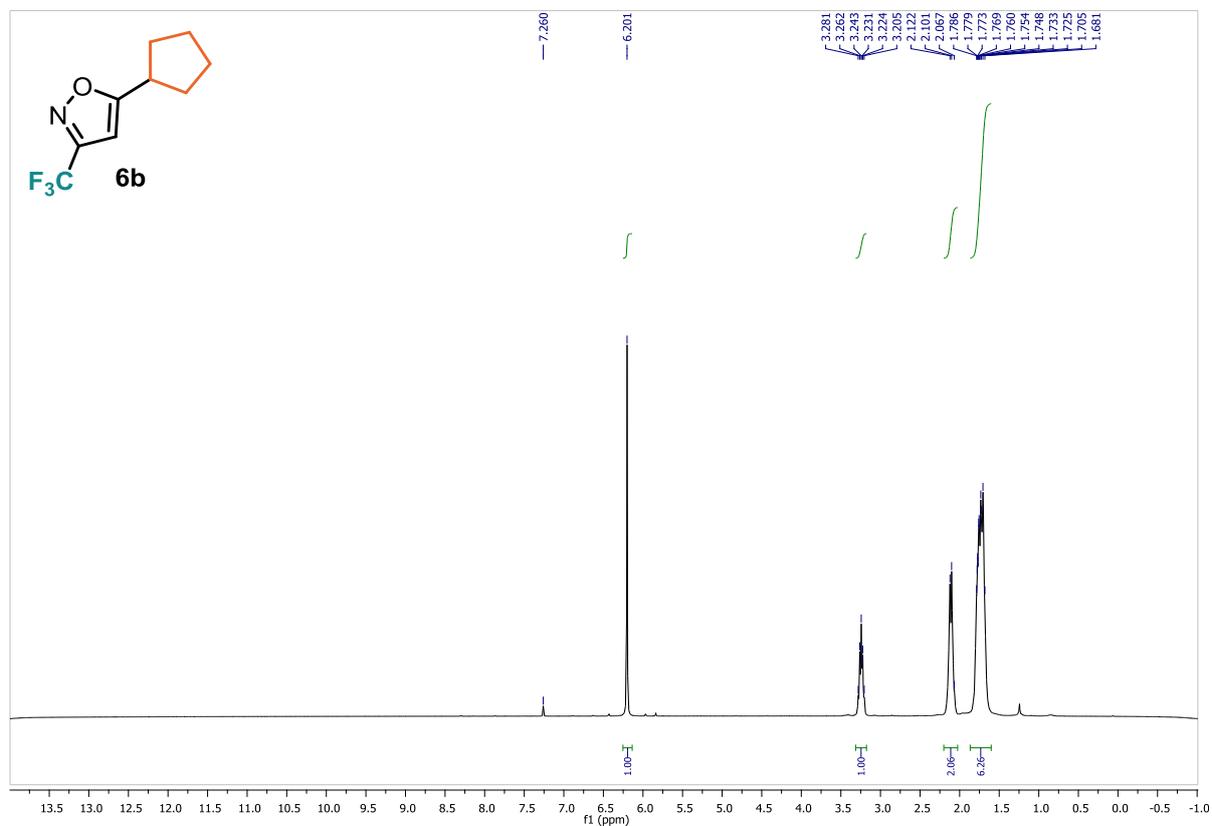


**<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:**

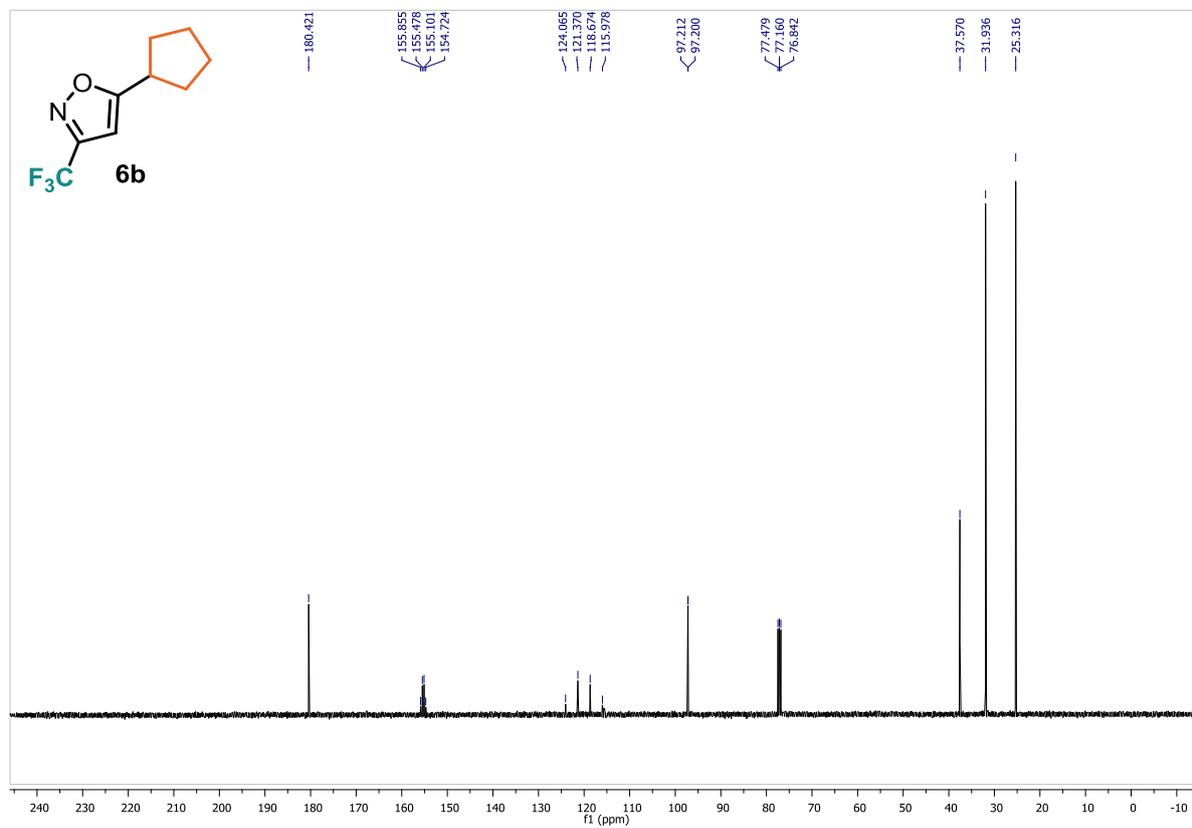


### 5-cyclopentyl-3-(trifluoromethyl)isoxazole (6b):

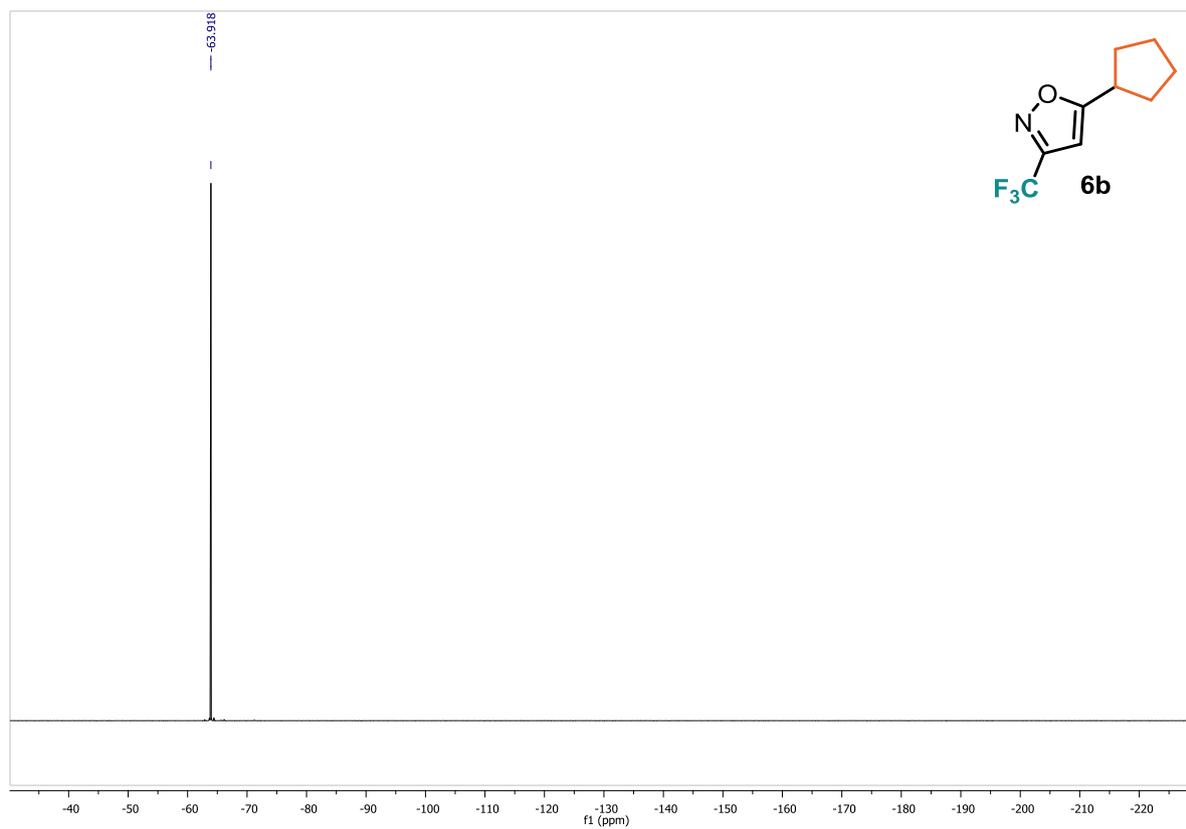
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:

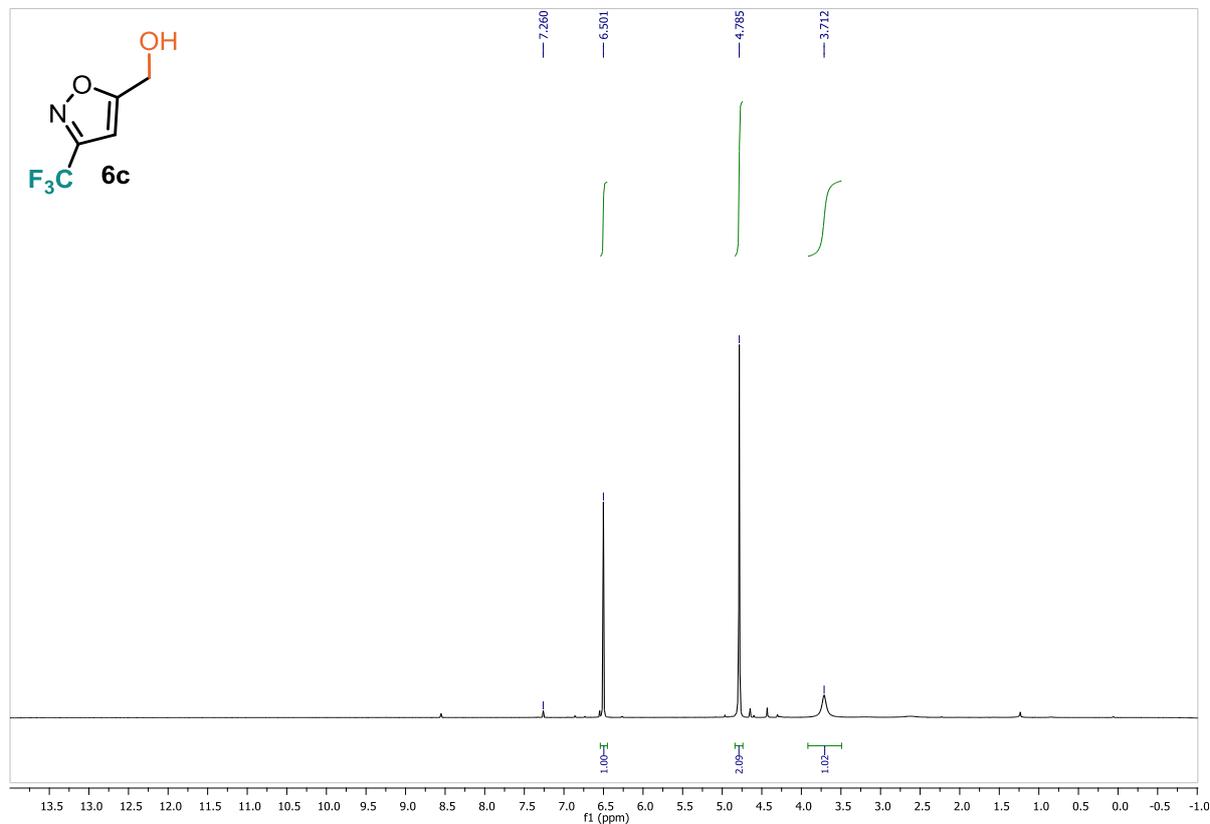


<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:

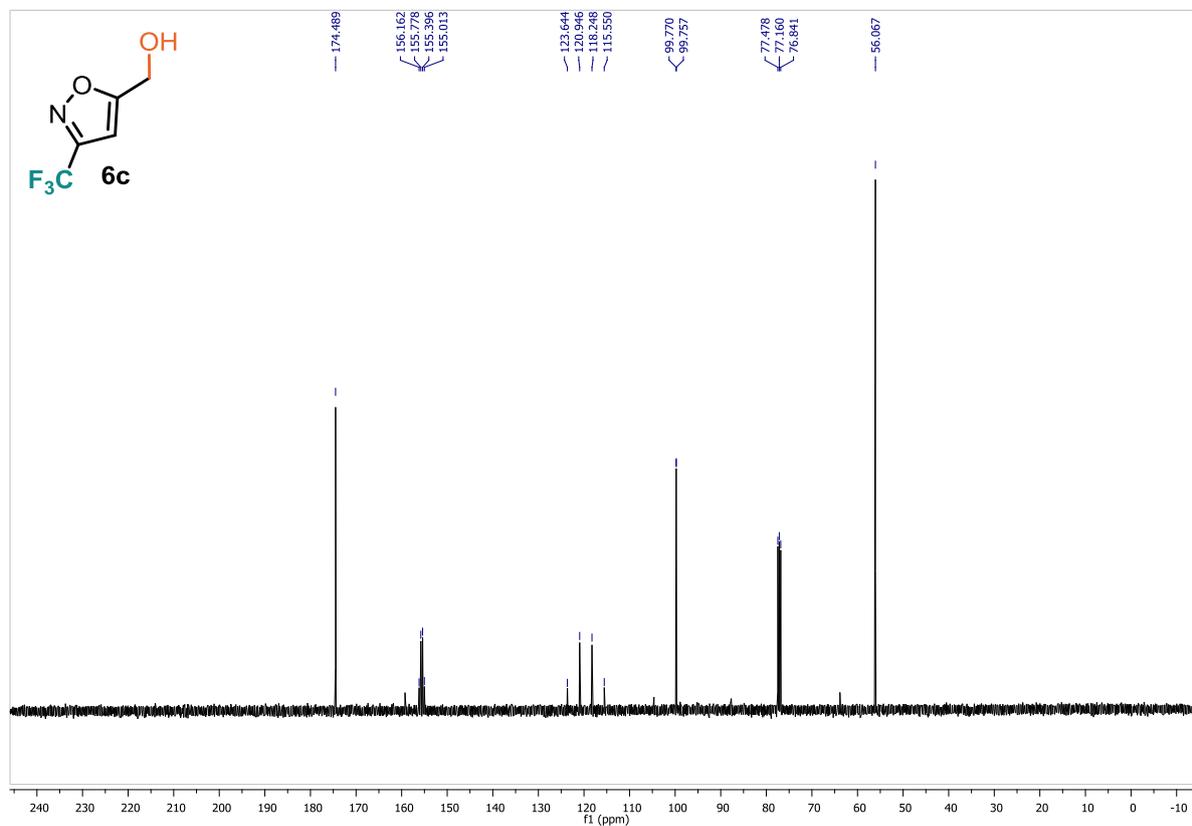


**(3-(trifluoromethyl)isoxazol-5-yl)methanol (6c):**

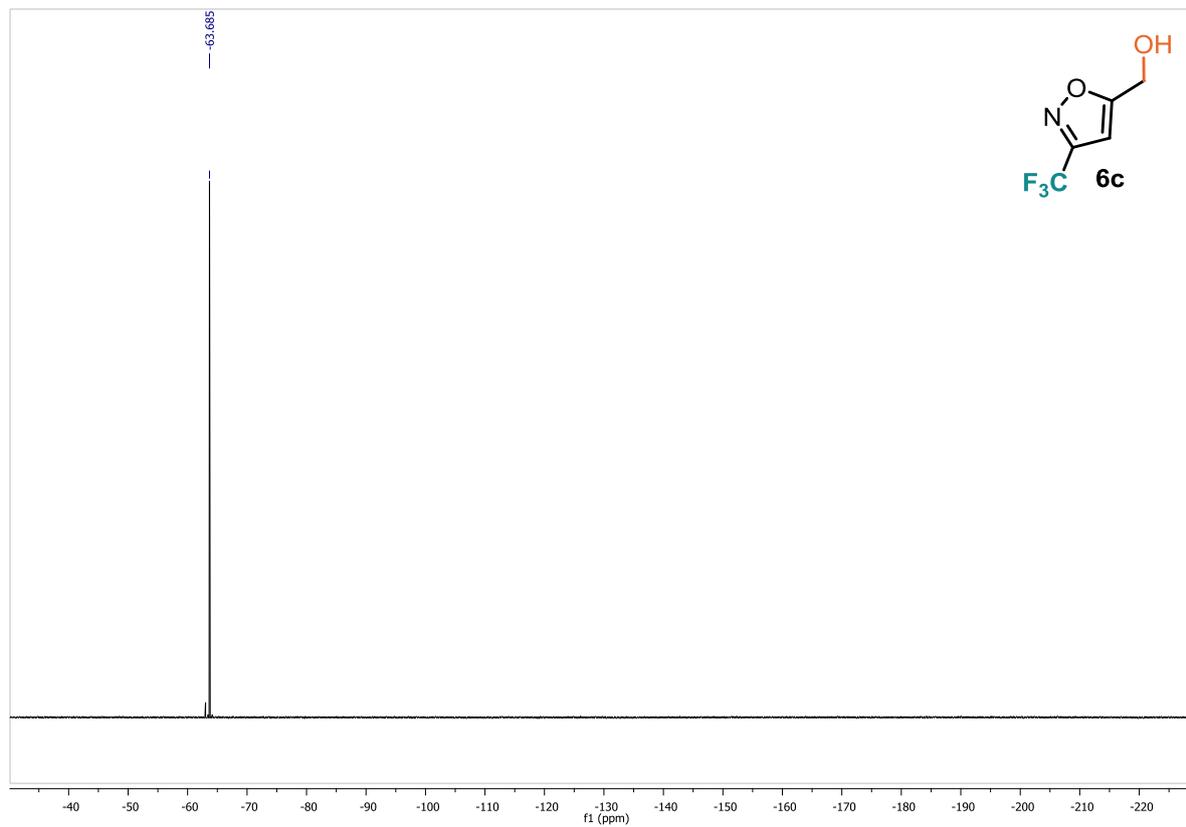
**<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:**



**<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:**

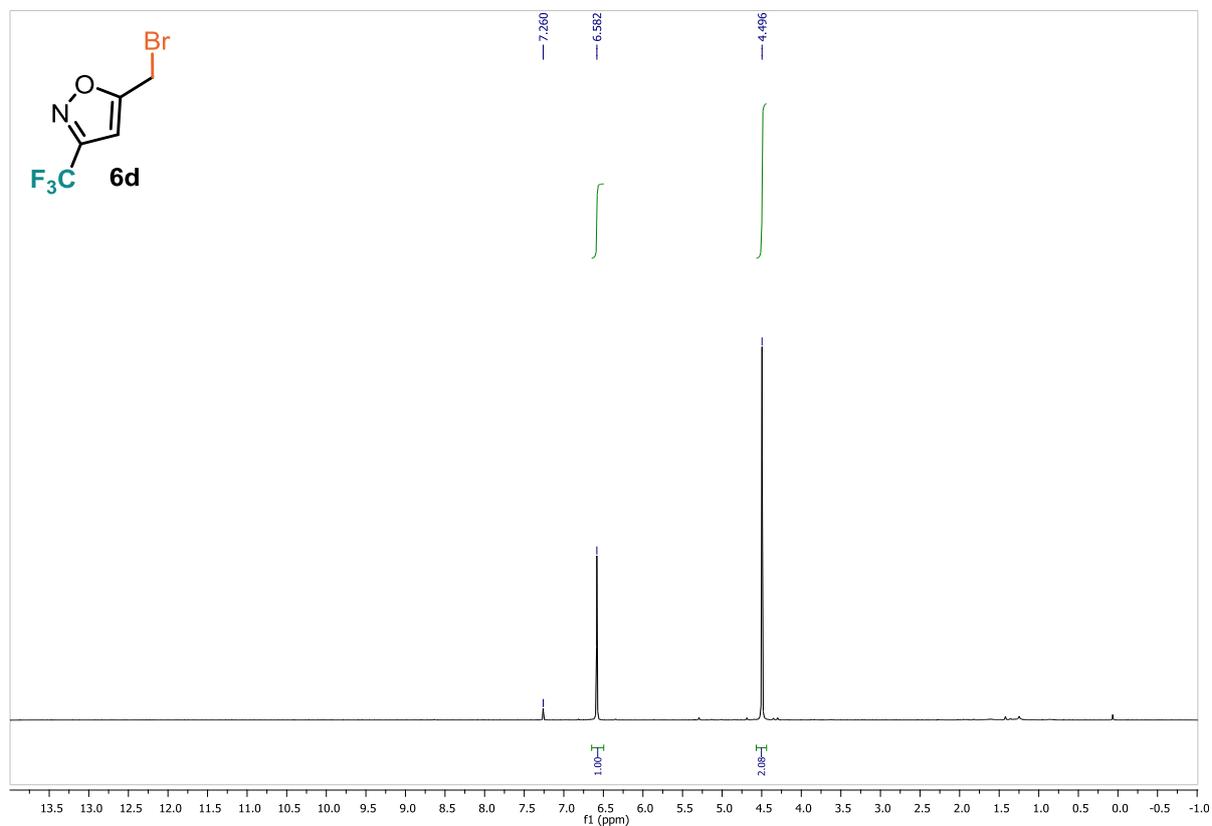


<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:

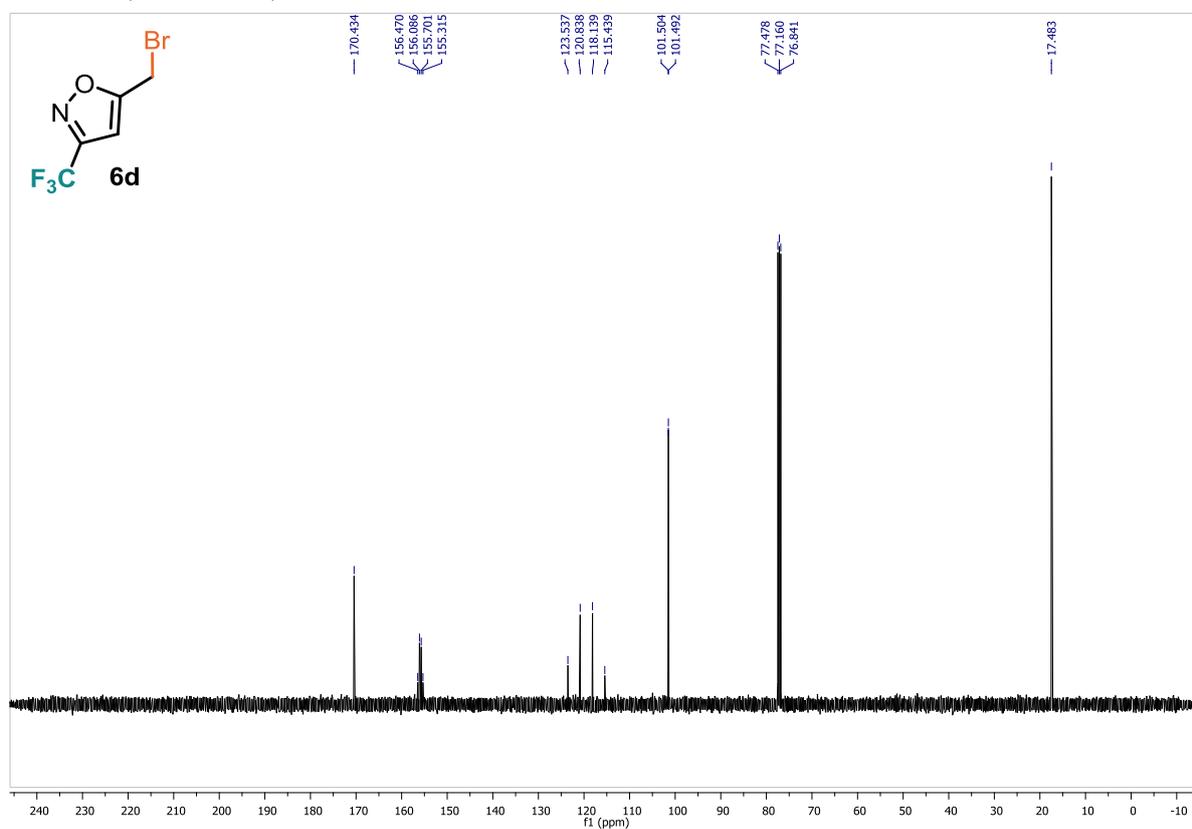


### 5-(bromomethyl)-3-(trifluoromethyl)isoxazole (6d):

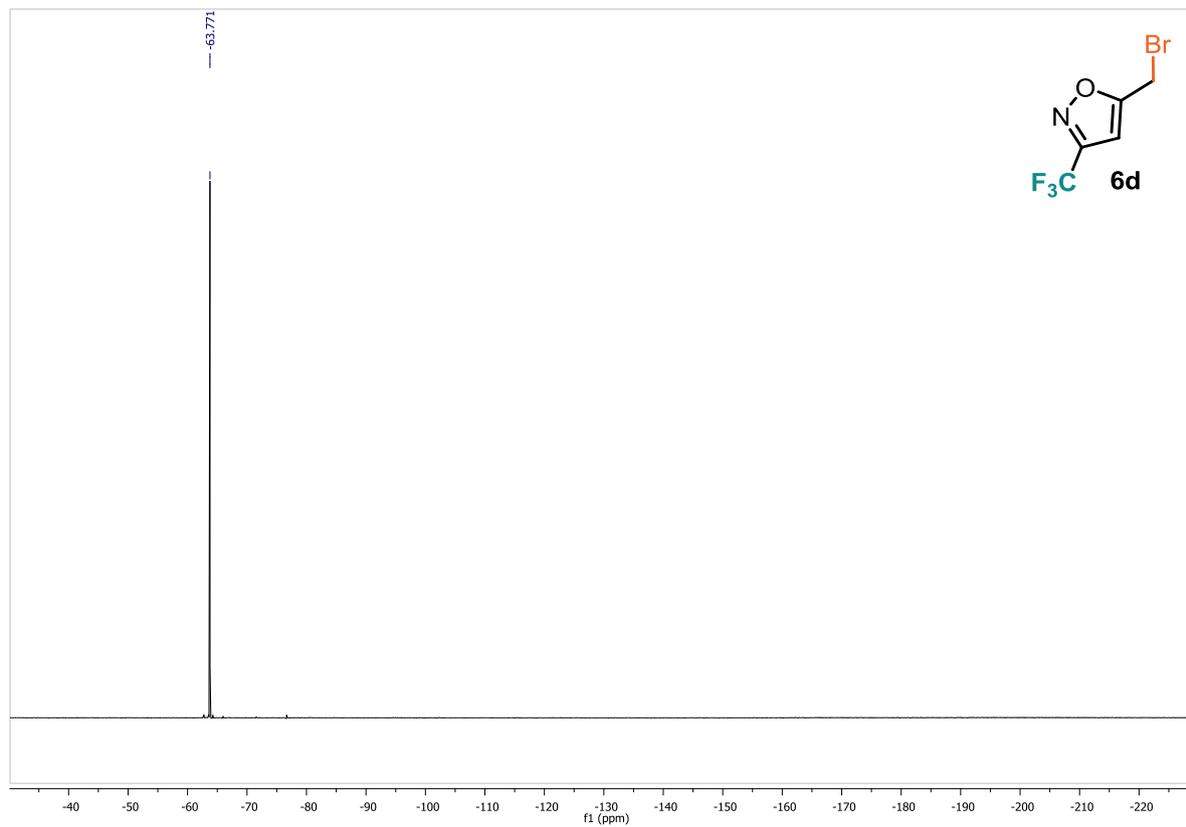
$^1\text{H}$  NMR, 400 MHz,  $\text{CDCl}_3$ :



$^{13}\text{C}$  NMR, 100 MHz,  $\text{CDCl}_3$ :

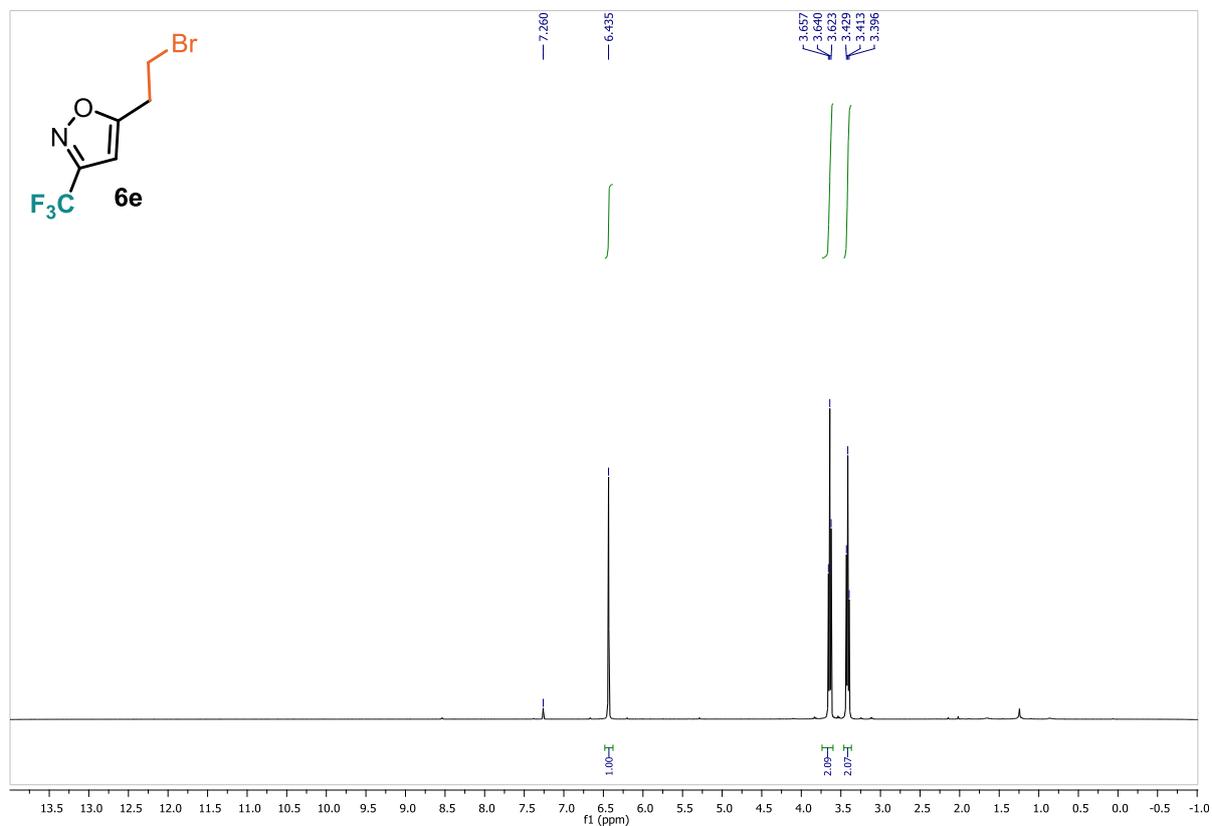


<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:

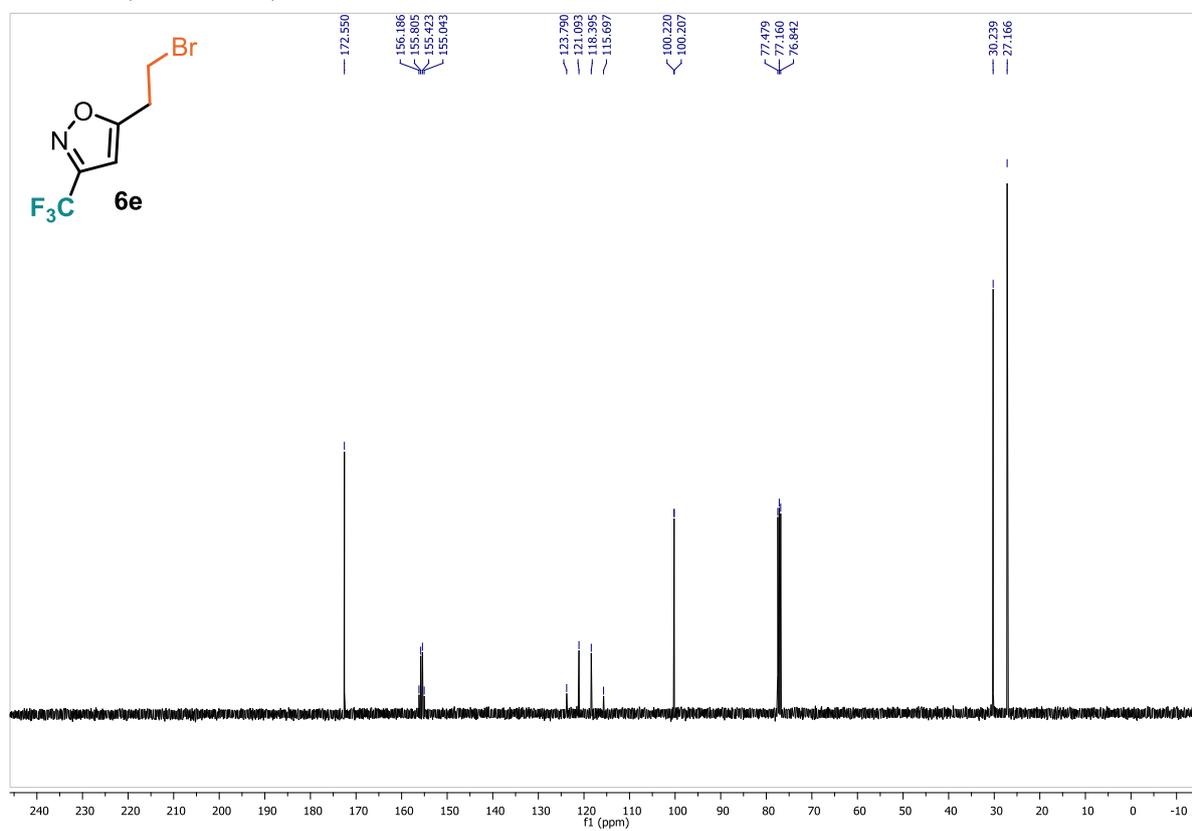


### 5-(2-bromoethyl)-3-(trifluoromethyl)isoxazole (6e):

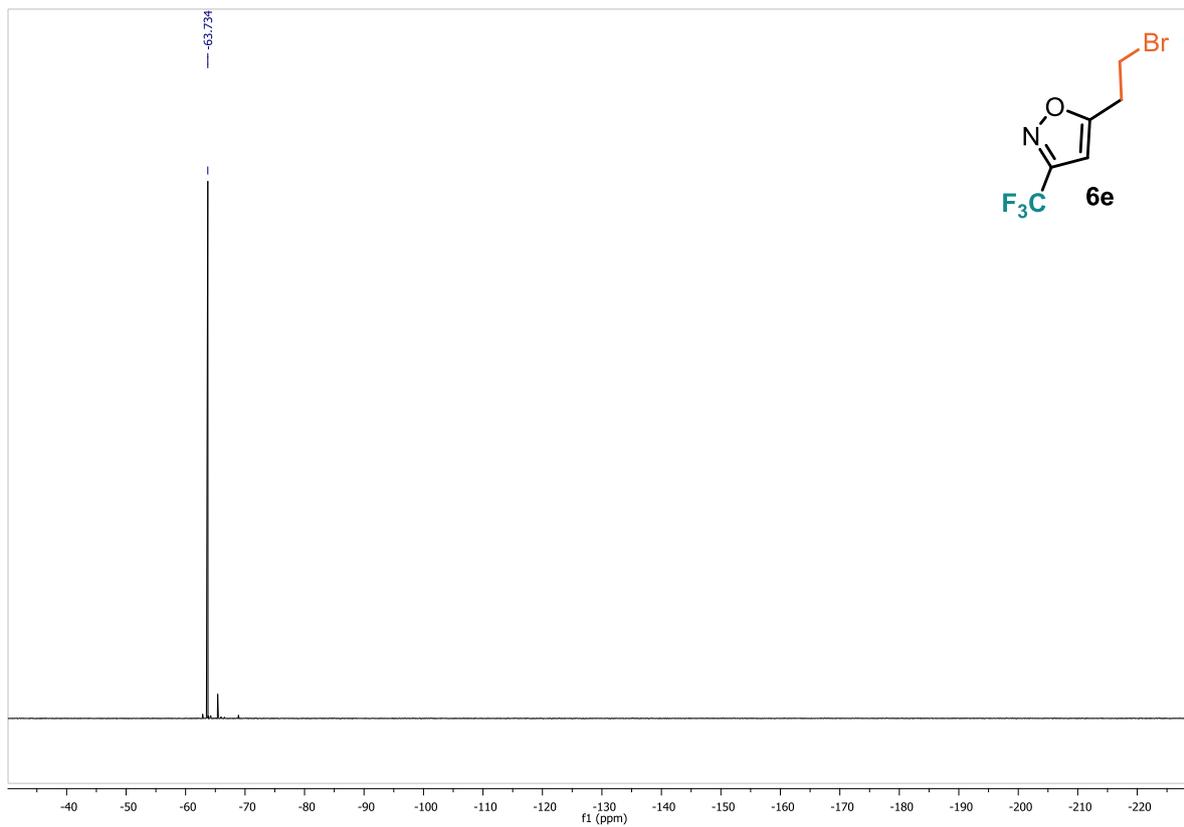
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:

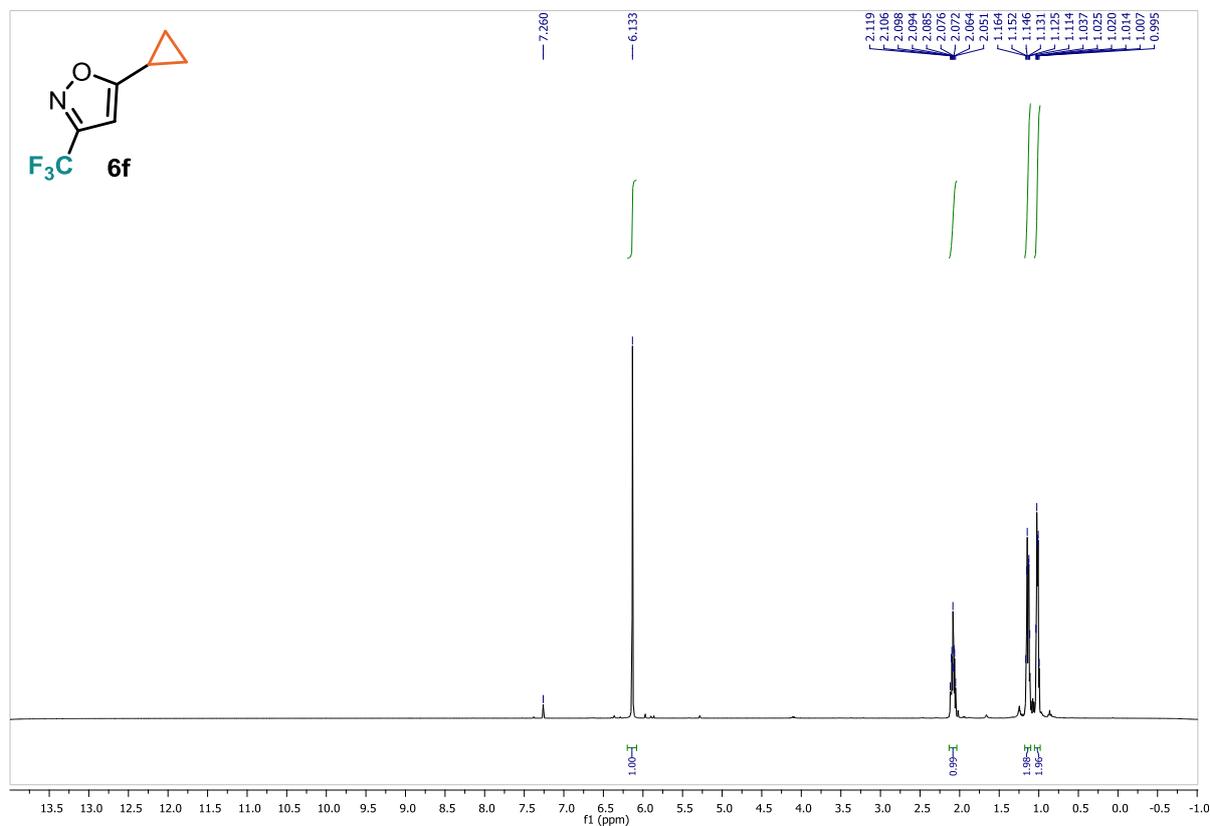


<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:

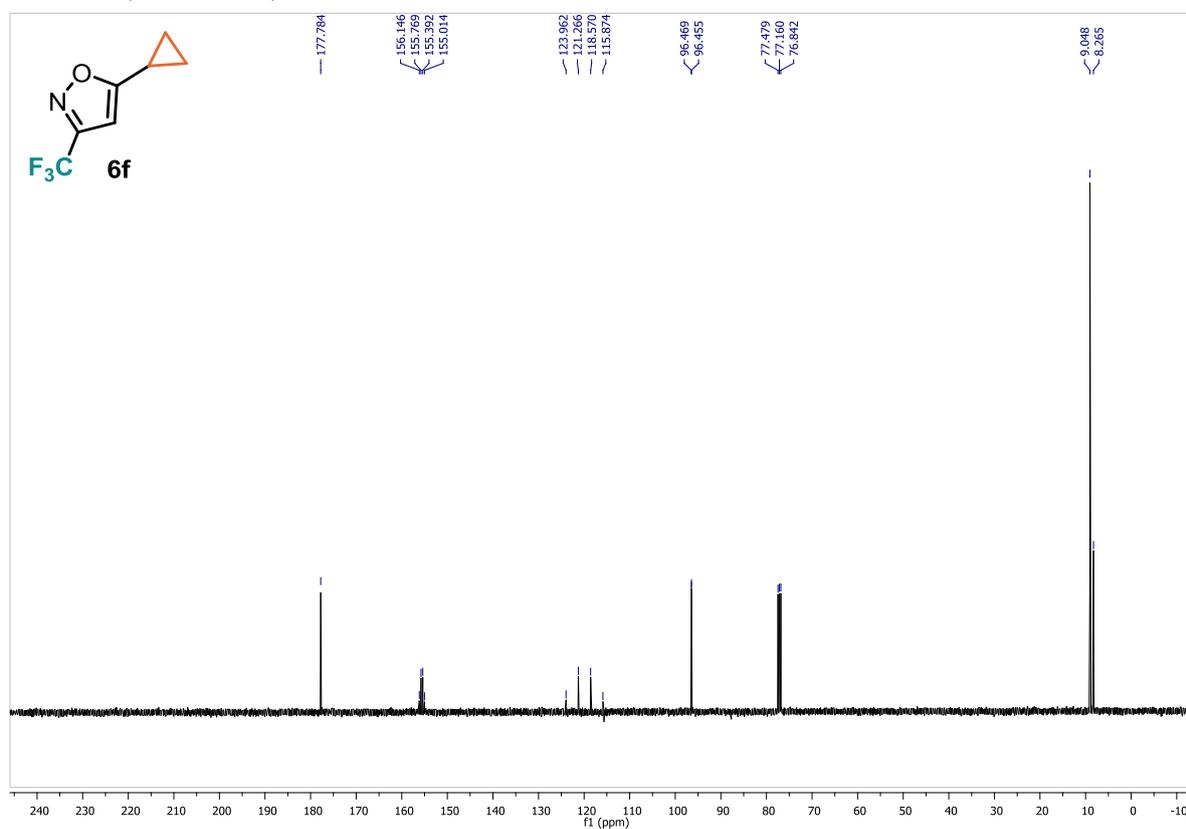


### 5-cyclopropyl-3-(trifluoromethyl)isoxazole (6f):

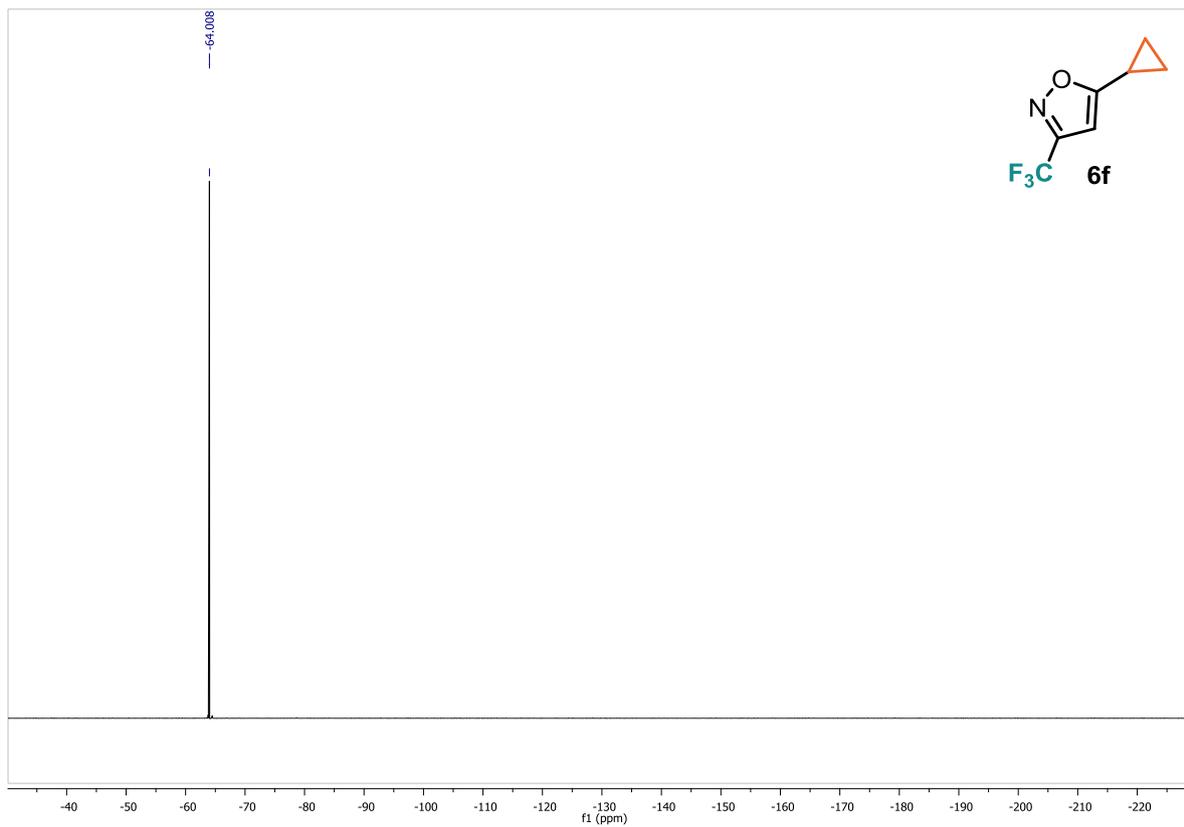
$^1\text{H}$  NMR, 400 MHz,  $\text{CDCl}_3$ :



$^{13}\text{C}$  NMR, 100 MHz,  $\text{CDCl}_3$ :

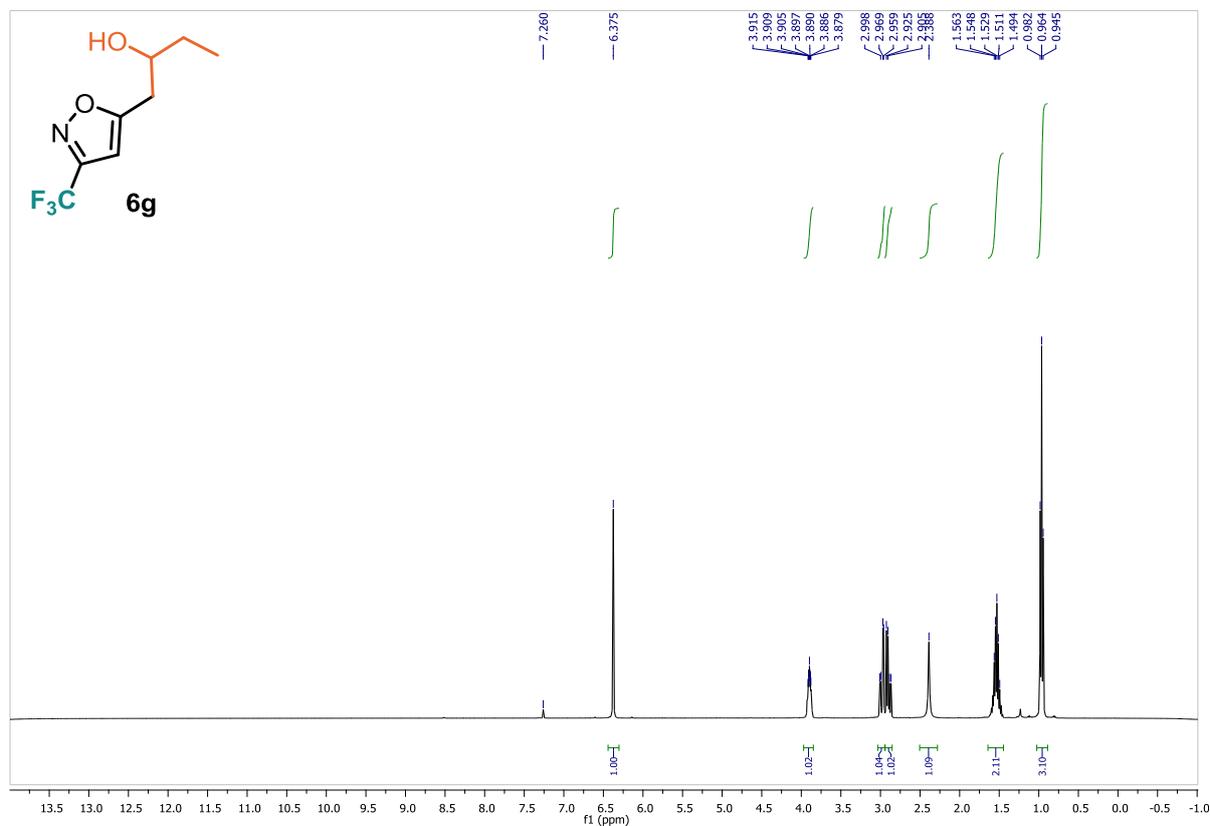


**$^{19}\text{F}$  NMR, 376 MHz,  $\text{CDCl}_3$ :**

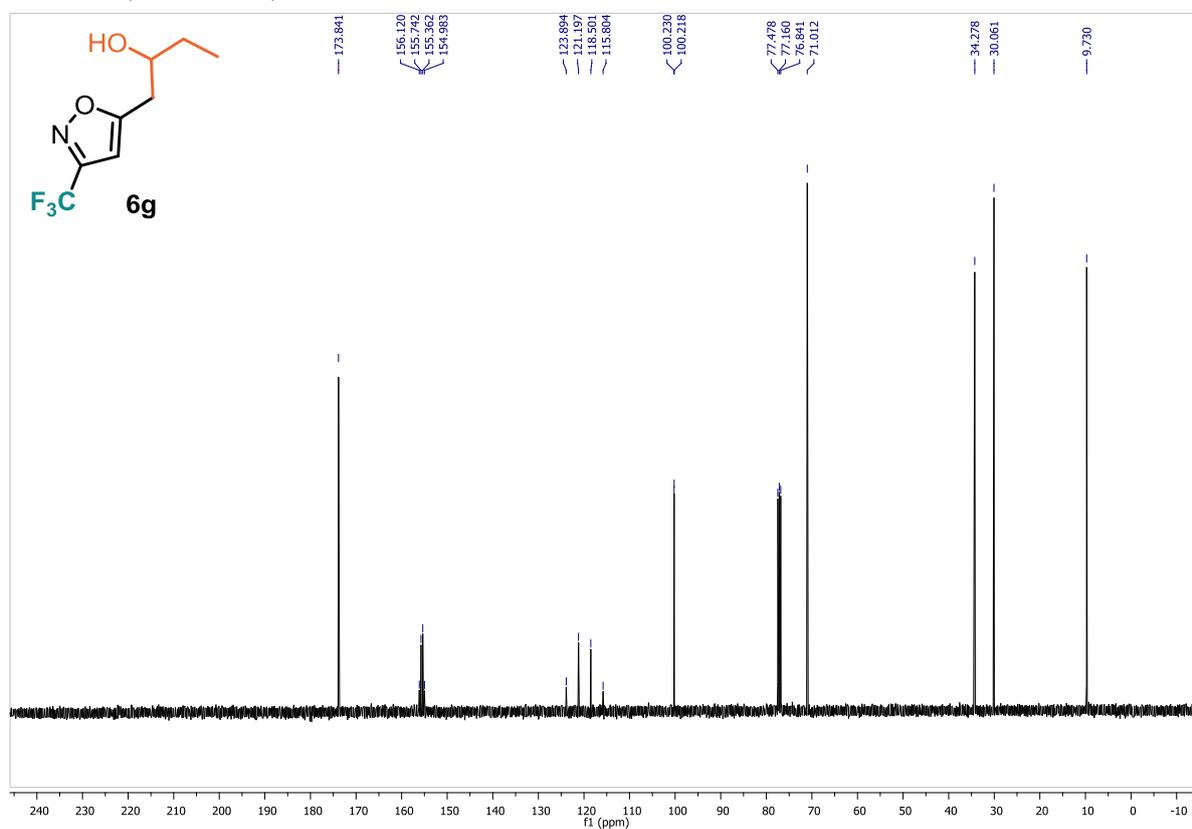


# 1-(3-(trifluoromethyl)isoxazol-5-yl)butan-2-ol (6g):

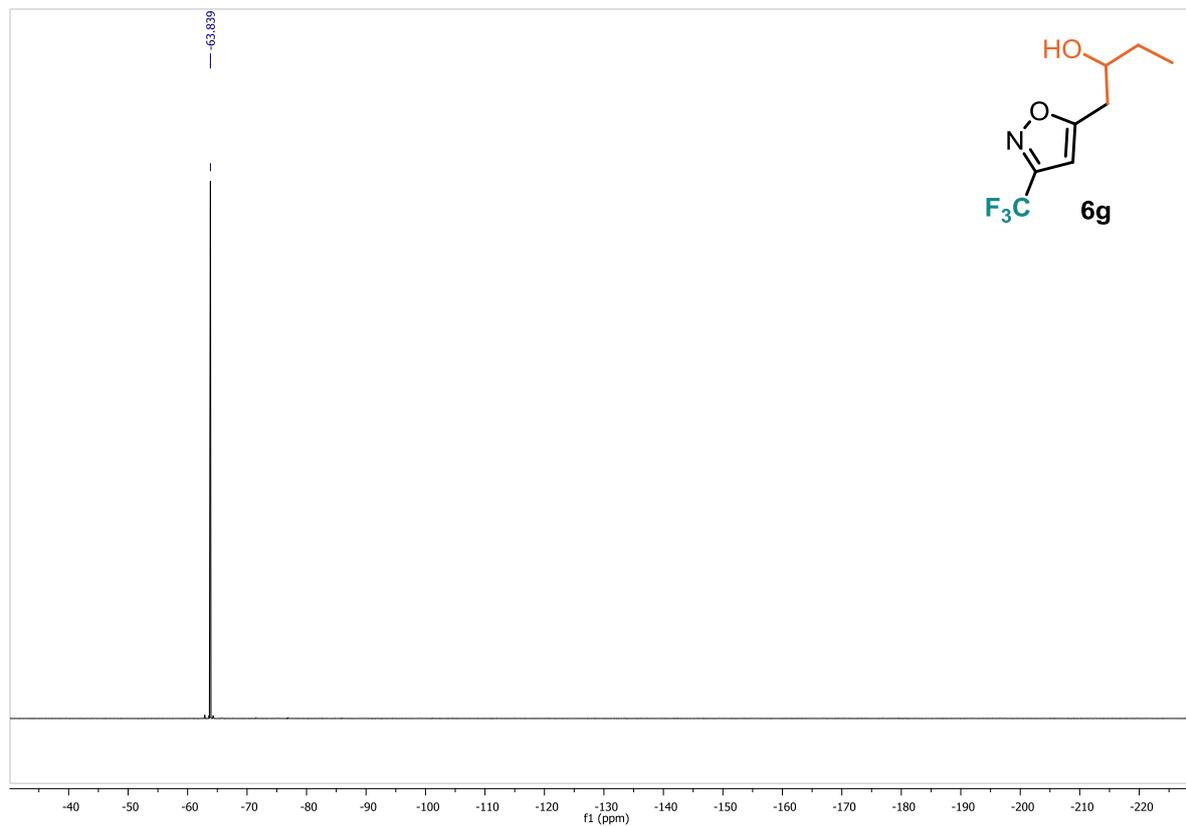
$^1\text{H}$  NMR, 400 MHz,  $\text{CDCl}_3$ :



$^{13}\text{C}$  NMR, 100 MHz,  $\text{CDCl}_3$ :

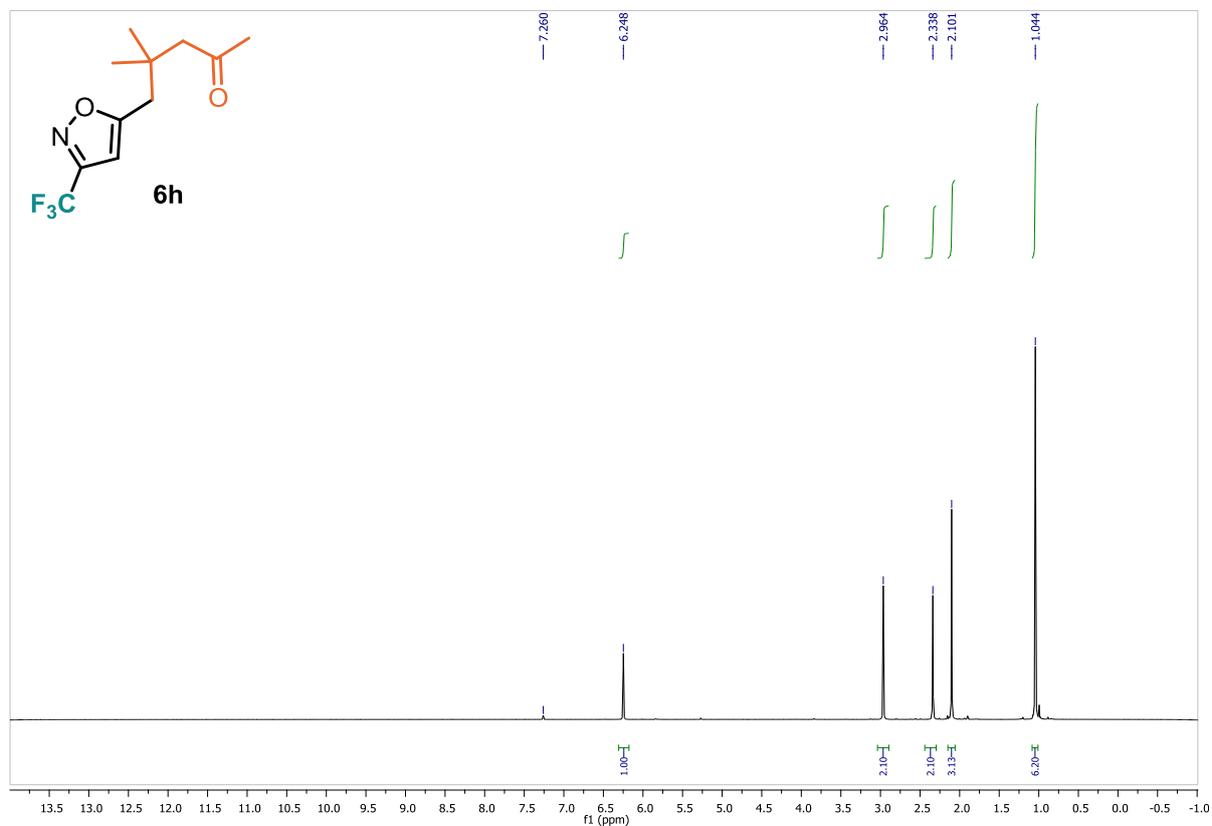


**<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:**

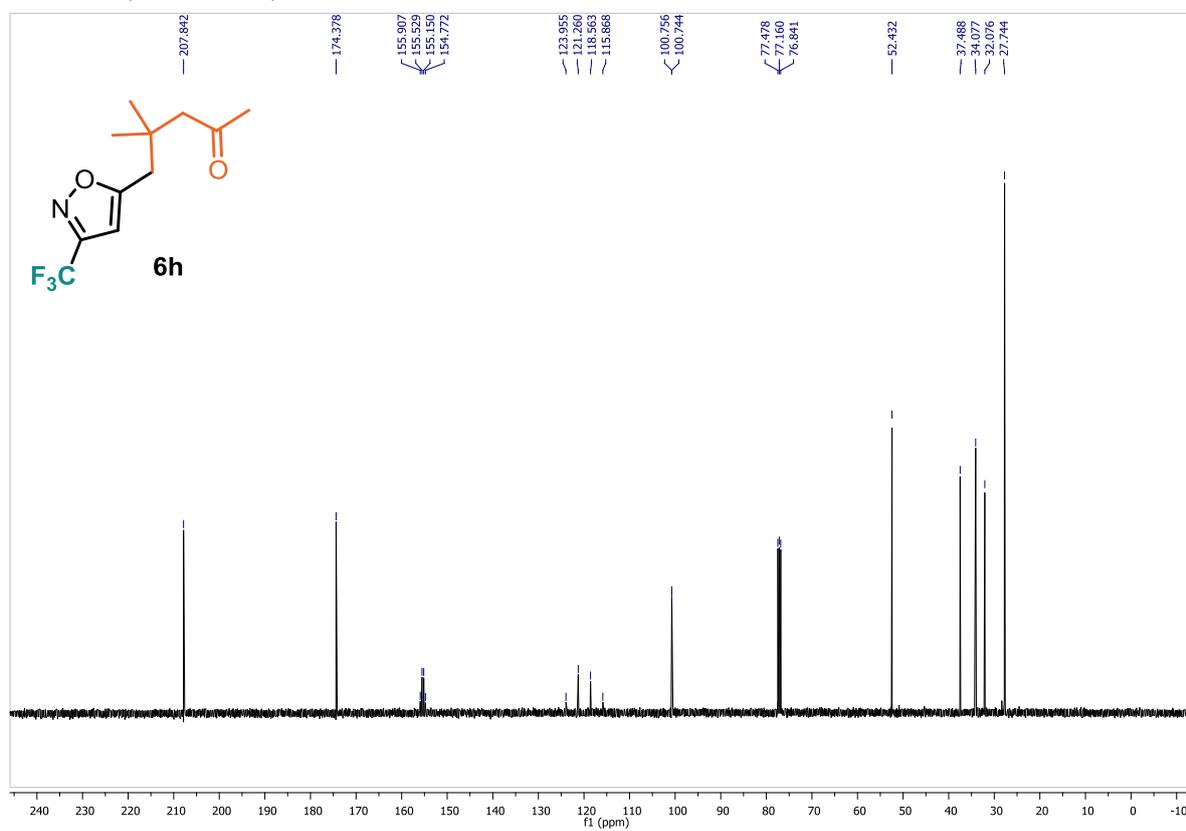


**4,4-dimethyl-5-(3-(trifluoromethyl)isoxazol-5-yl)pentan-2-one (6h):**

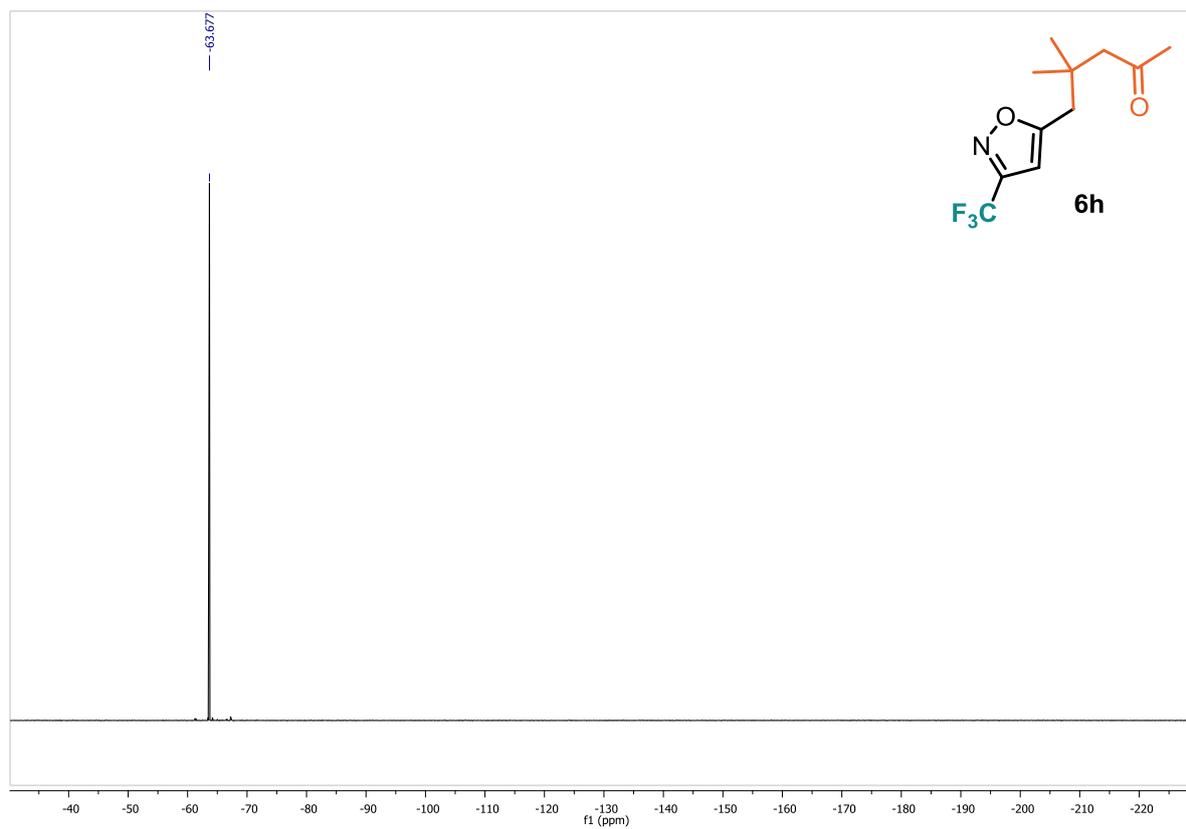
**<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:**



**<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:**

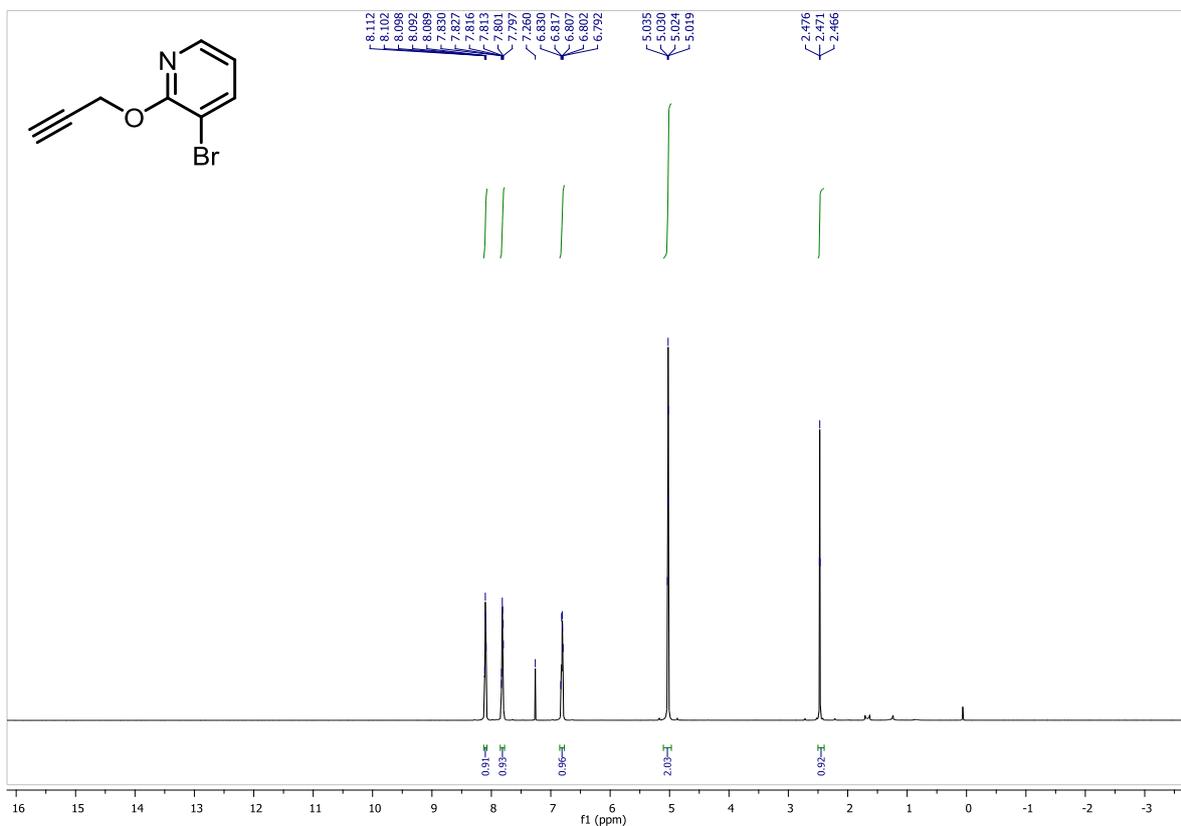


**<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:**

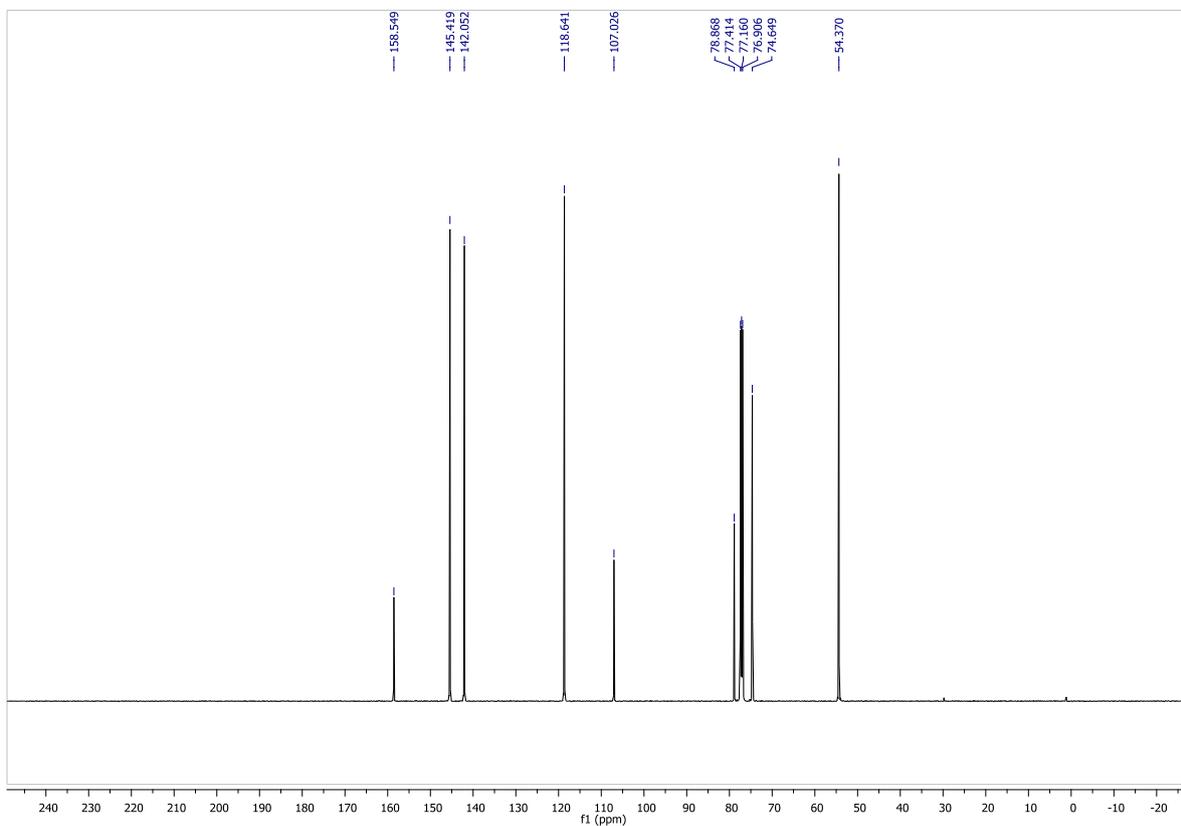


### 3-bromo-2-(prop-2-yn-1-yloxy)pyridine:

<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>:

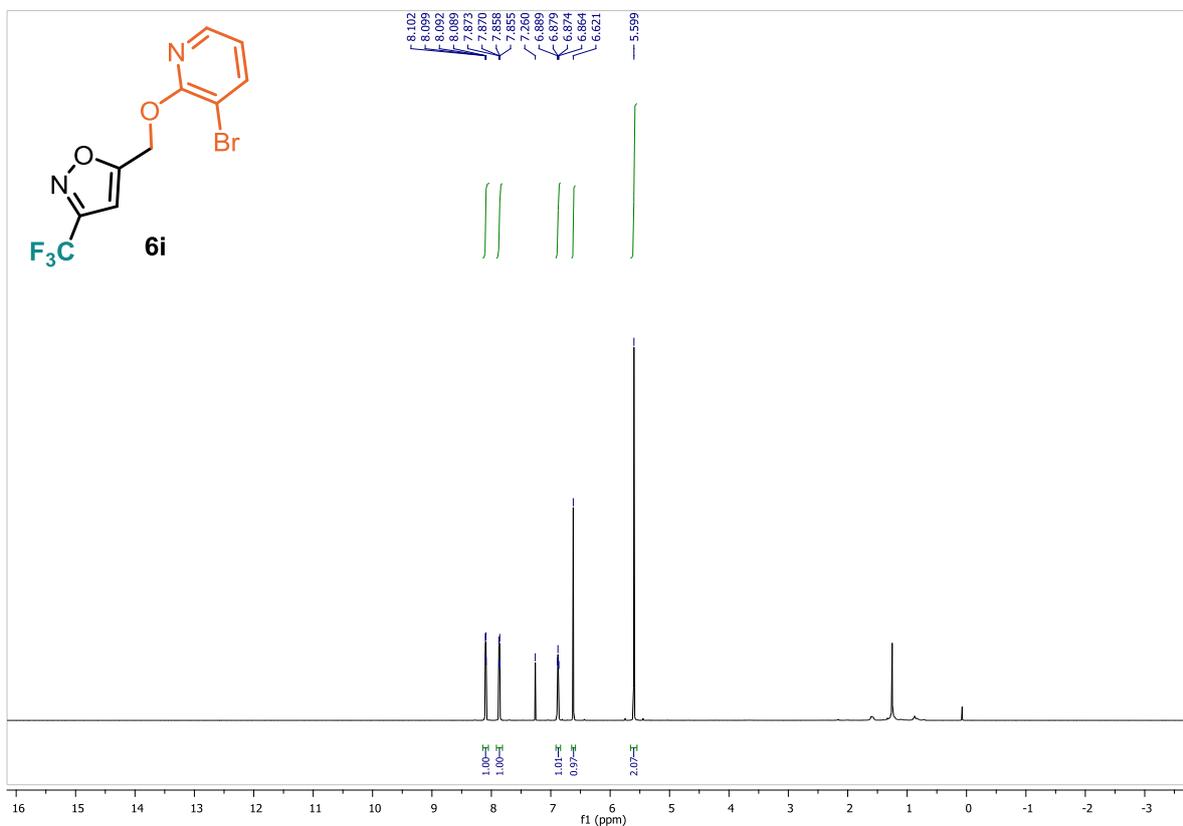


<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>:

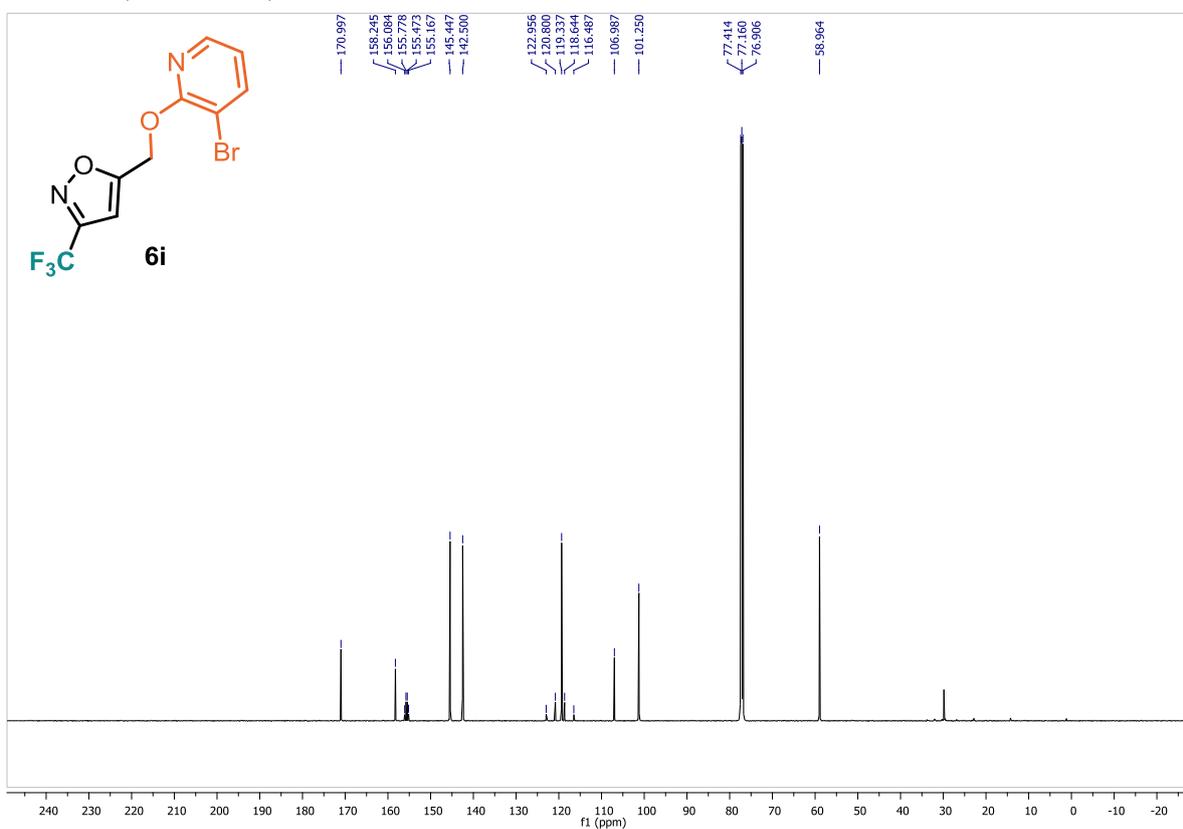


### 5-(((3-bromopyridin-2-yl)oxy)methyl)-3-(trifluoromethyl)isoxazole (**6i**):

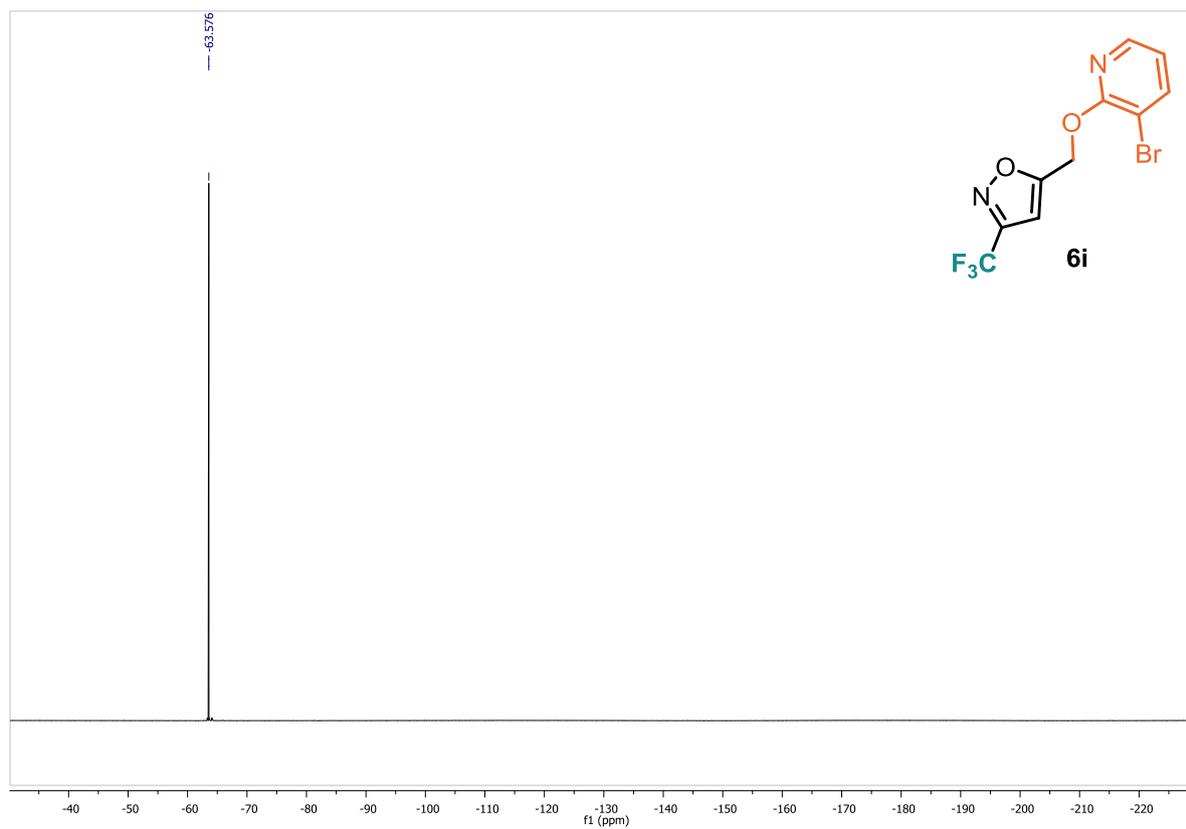
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>:

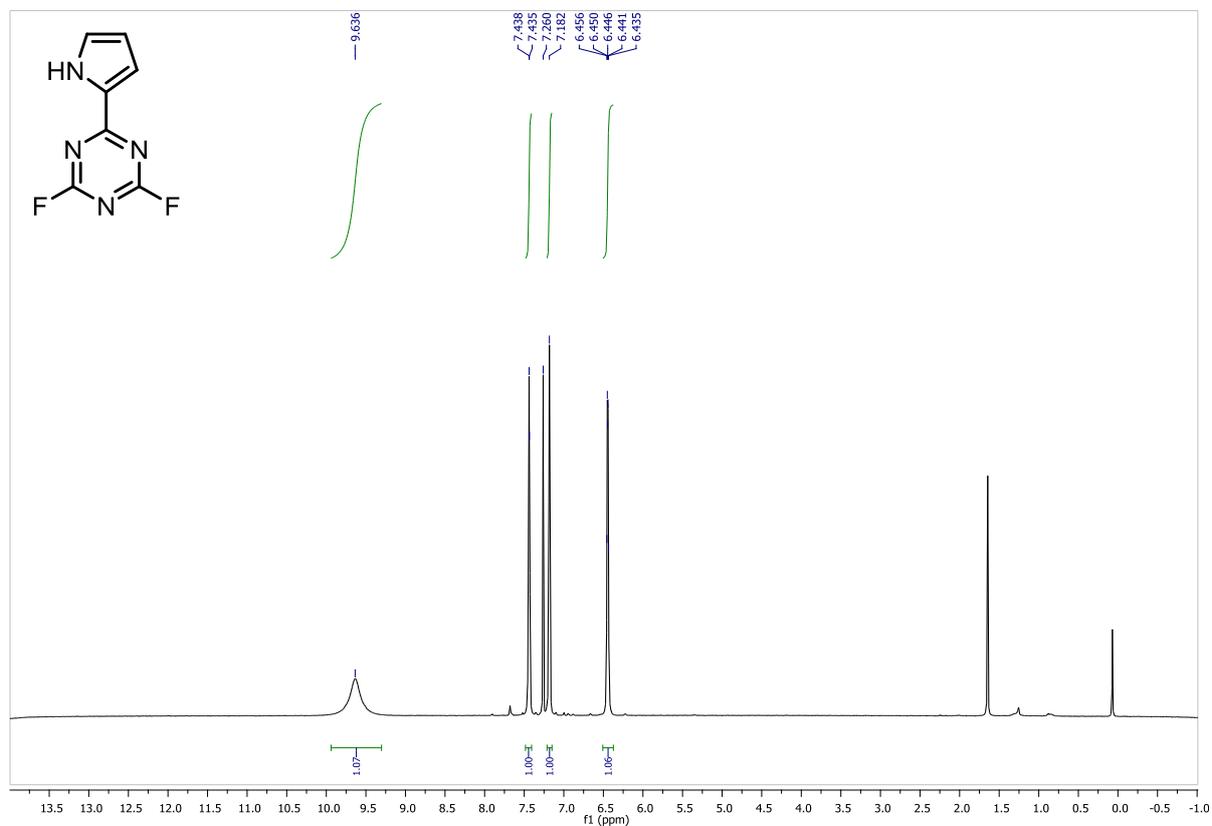


<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:



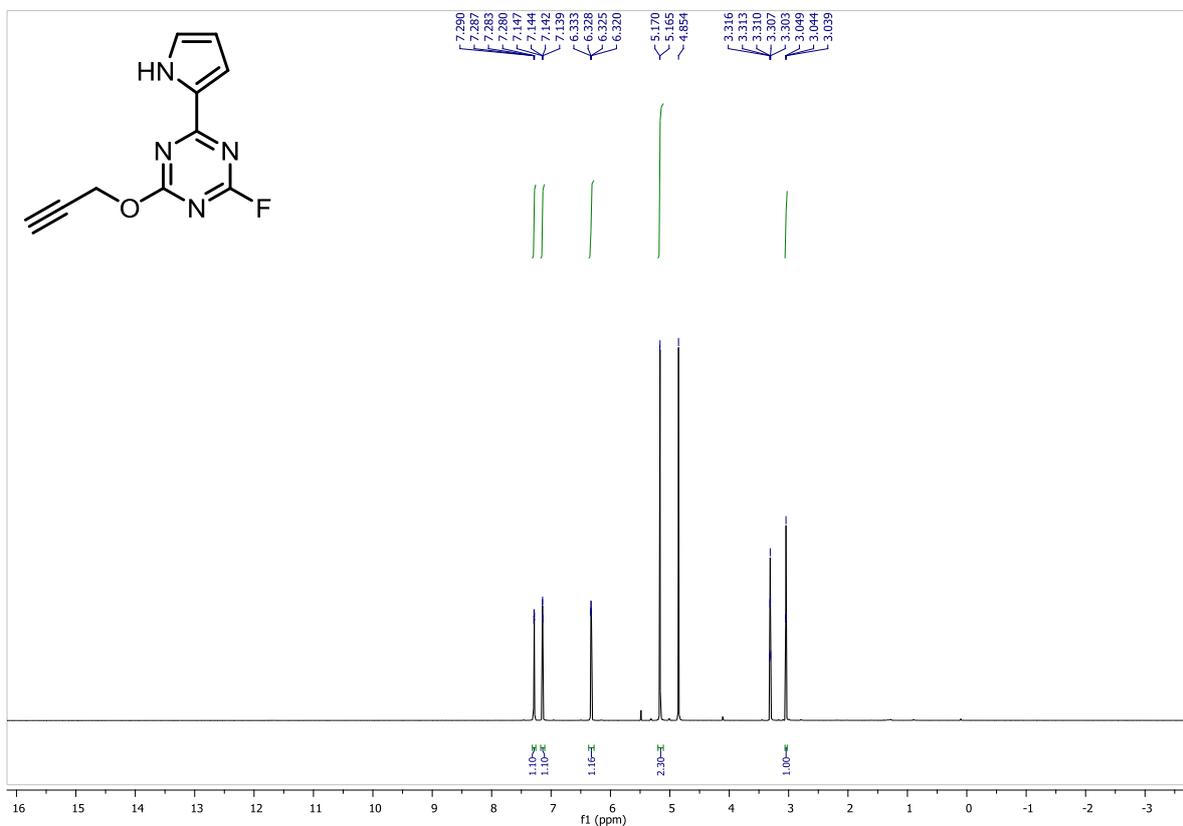
**2,4-difluoro-6-(1*H*-pyrrol-2-yl)-1,3,5-triazine:**

**<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:**

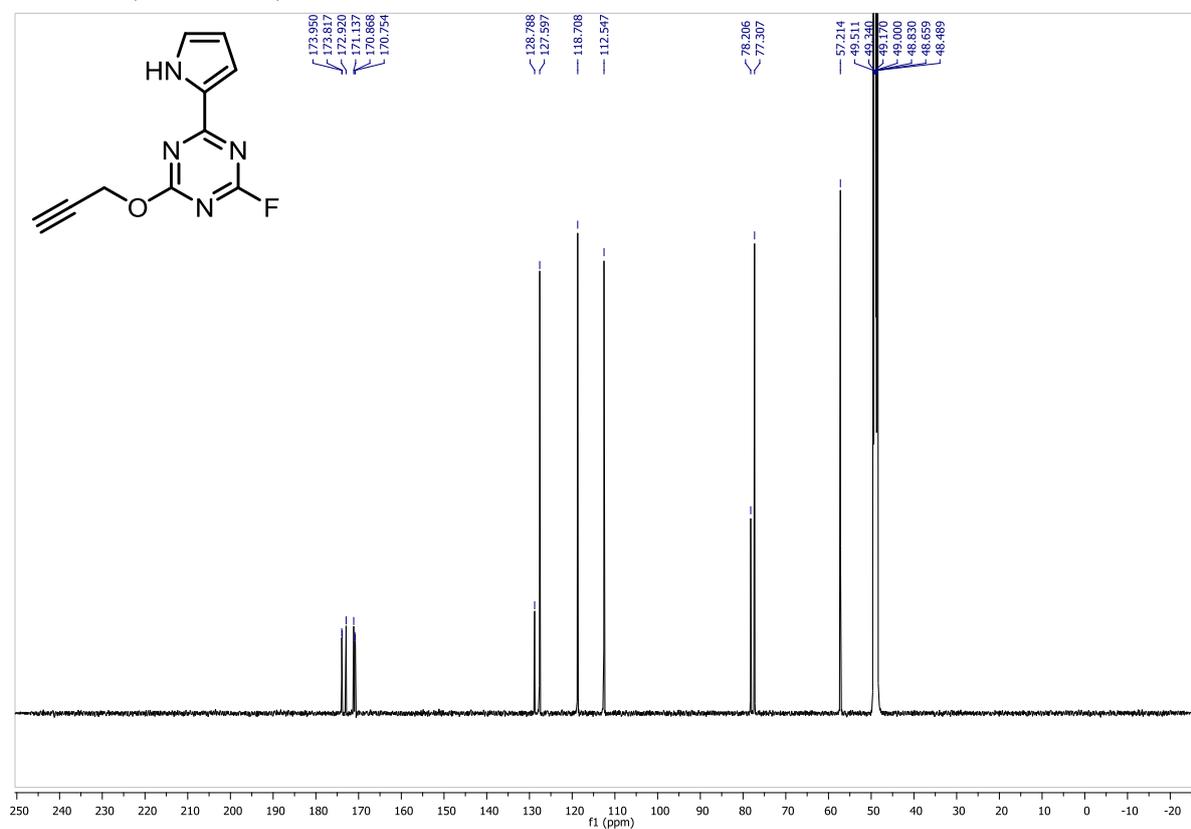


## 2-fluoro-4-(prop-2-yn-1-yloxy)-6-(1H-pyrrol-2-yl)-1,3,5-triazine:

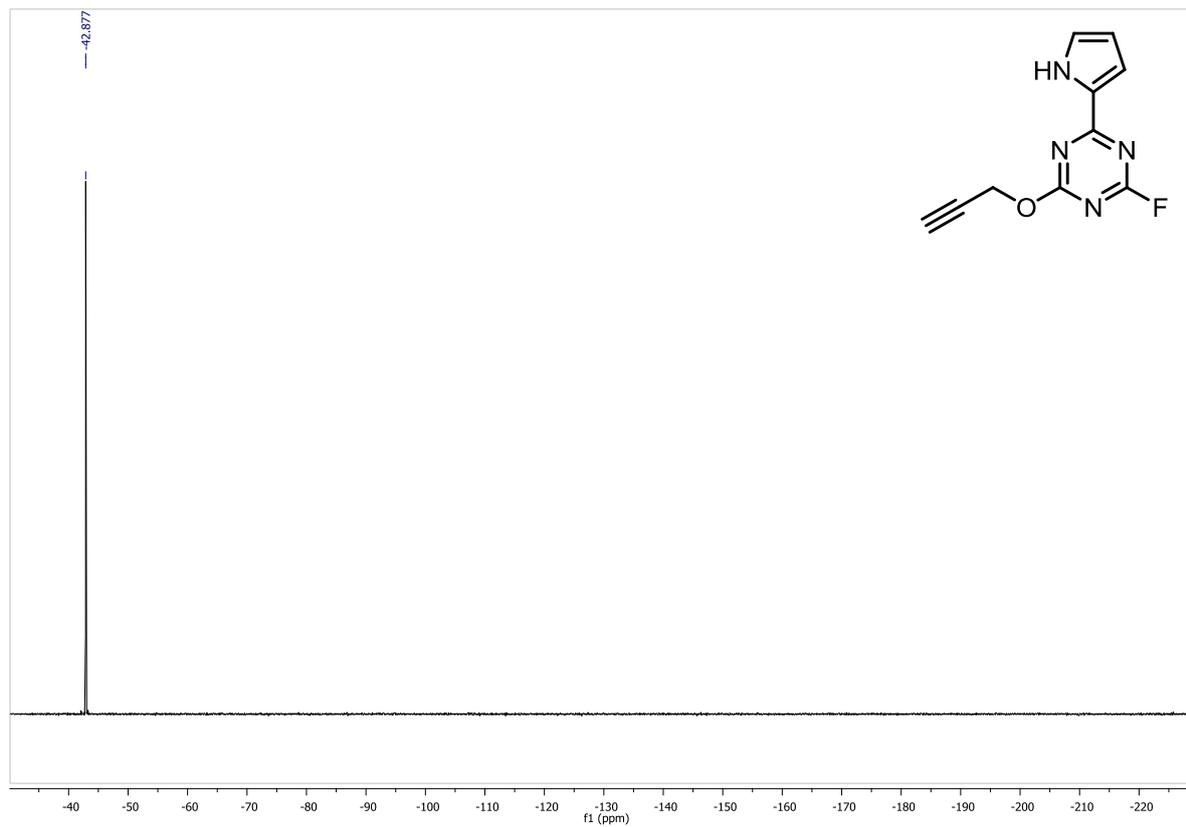
<sup>1</sup>H NMR, 500 MHz, CD<sub>3</sub>OD:



<sup>13</sup>C NMR, 125 MHz, CD<sub>3</sub>OD:

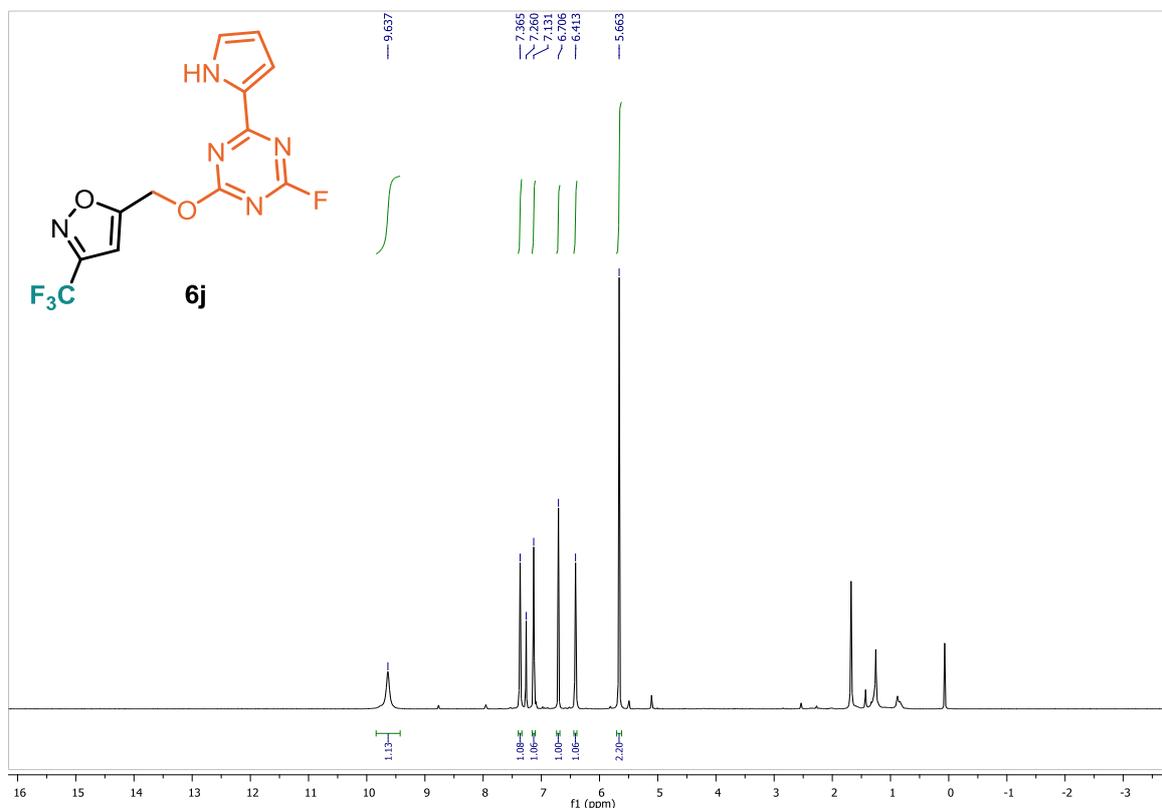


**<sup>19</sup>F NMR, 376 MHz, CD<sub>3</sub>OD:**

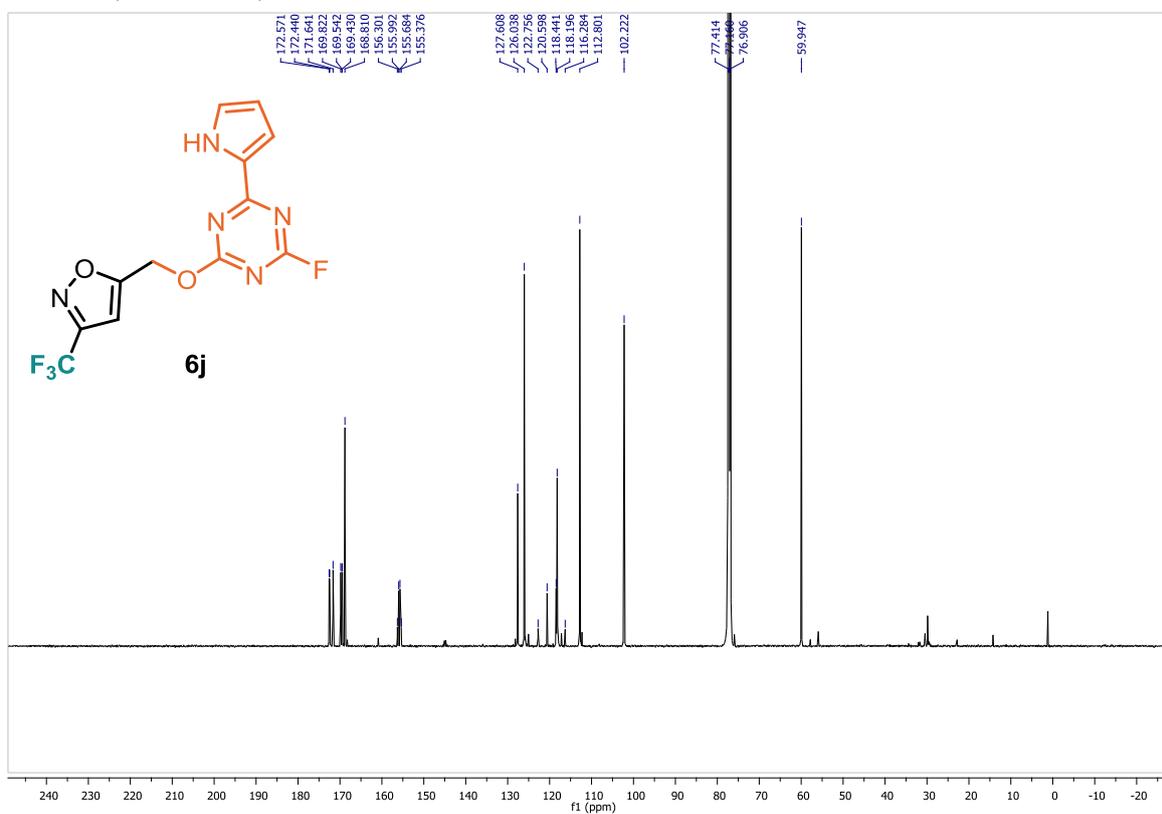


**5-(((4-fluoro-6-(1H-pyrrol-2-yl)-1,3,5-triazin-2-yl)oxy)methyl)-3-(trifluoromethyl)-isoxazole (6j):**

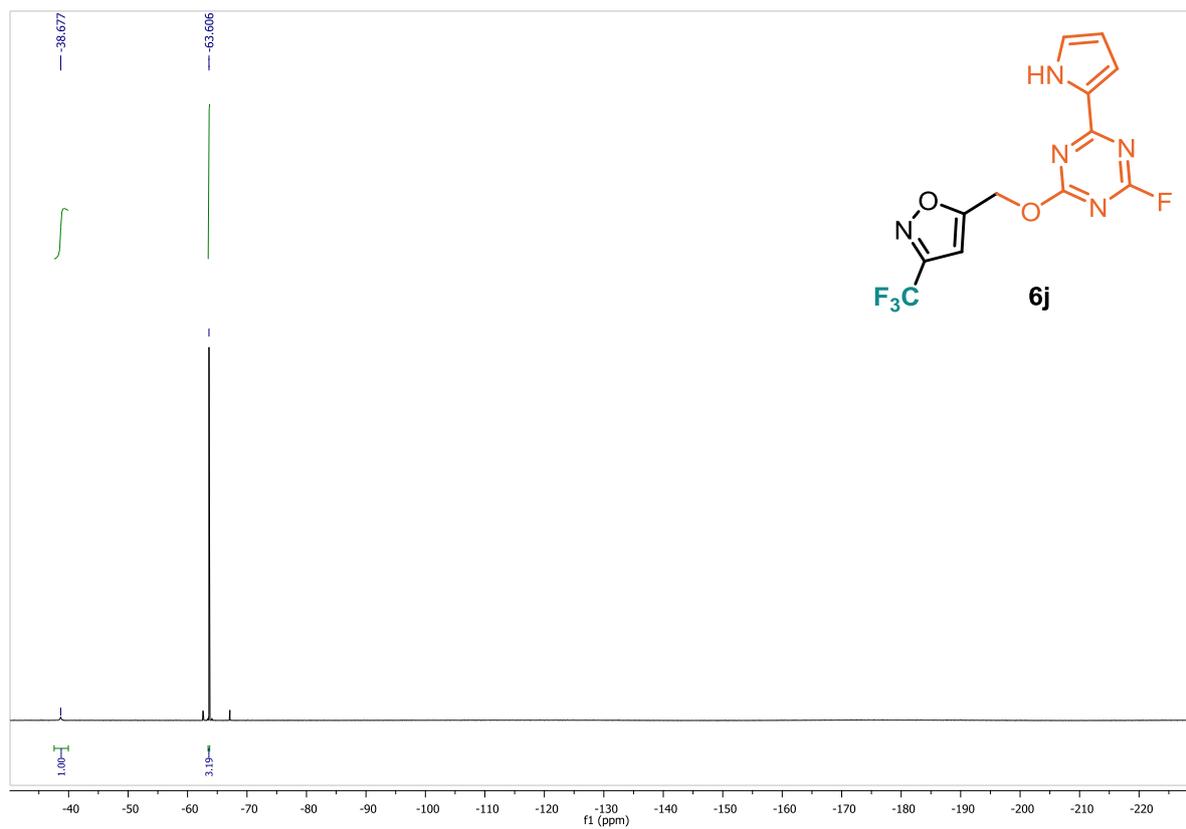
**<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>:**



**<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>:**

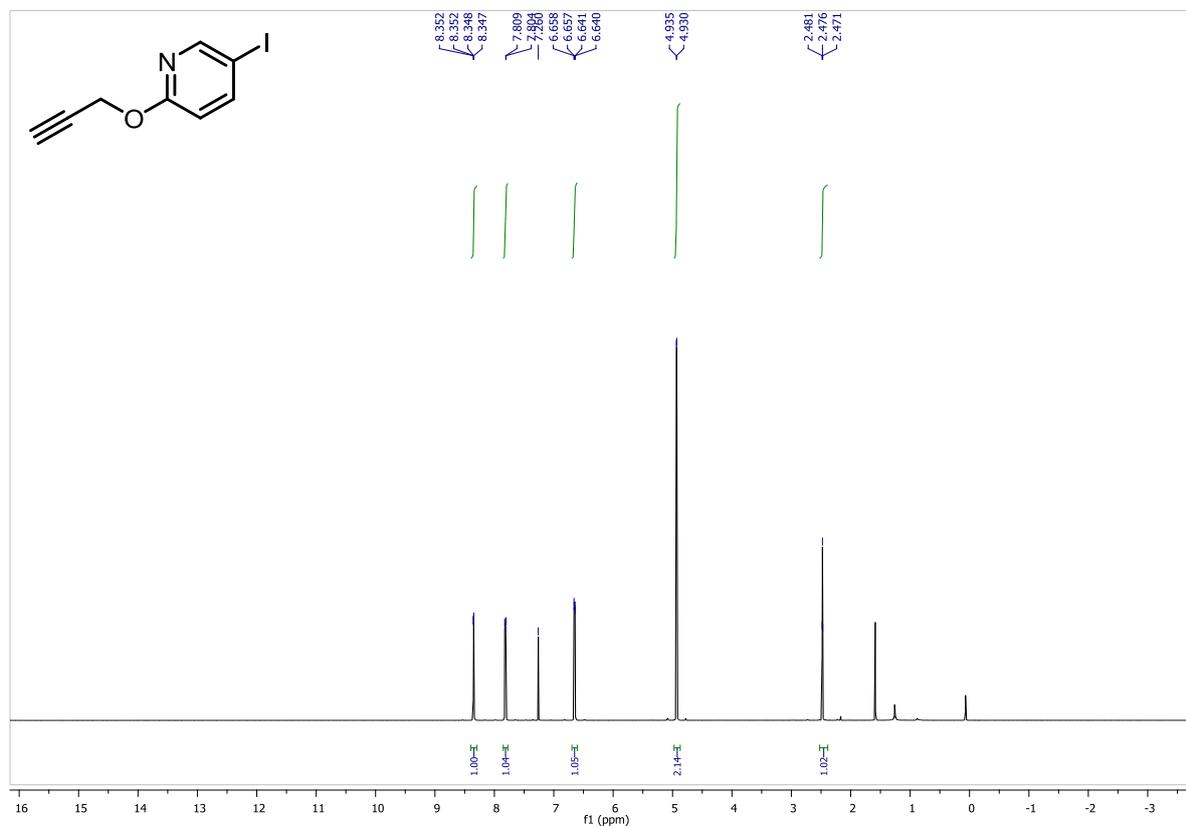


<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:

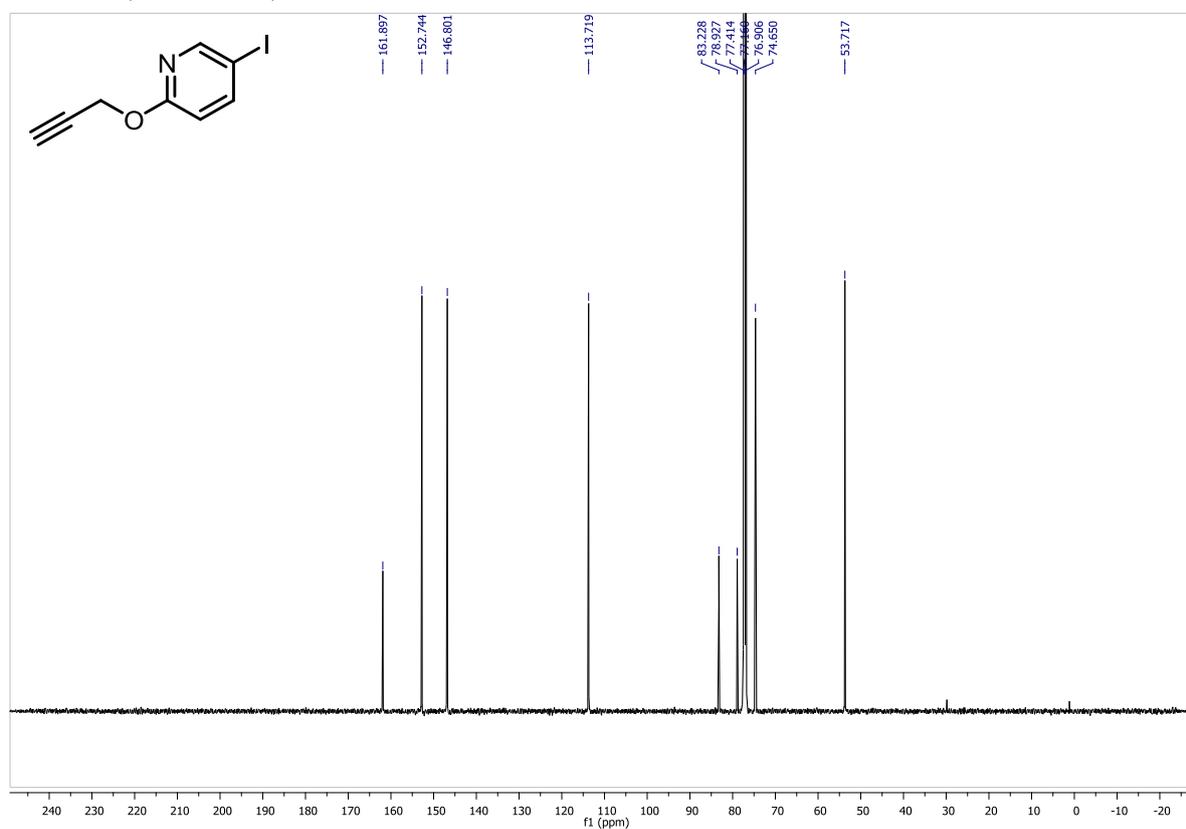


### 5-iodo-2-(prop-2-yn-1-yloxy)pyridine:

$^1\text{H}$  NMR, 500 MHz,  $\text{CDCl}_3$ :

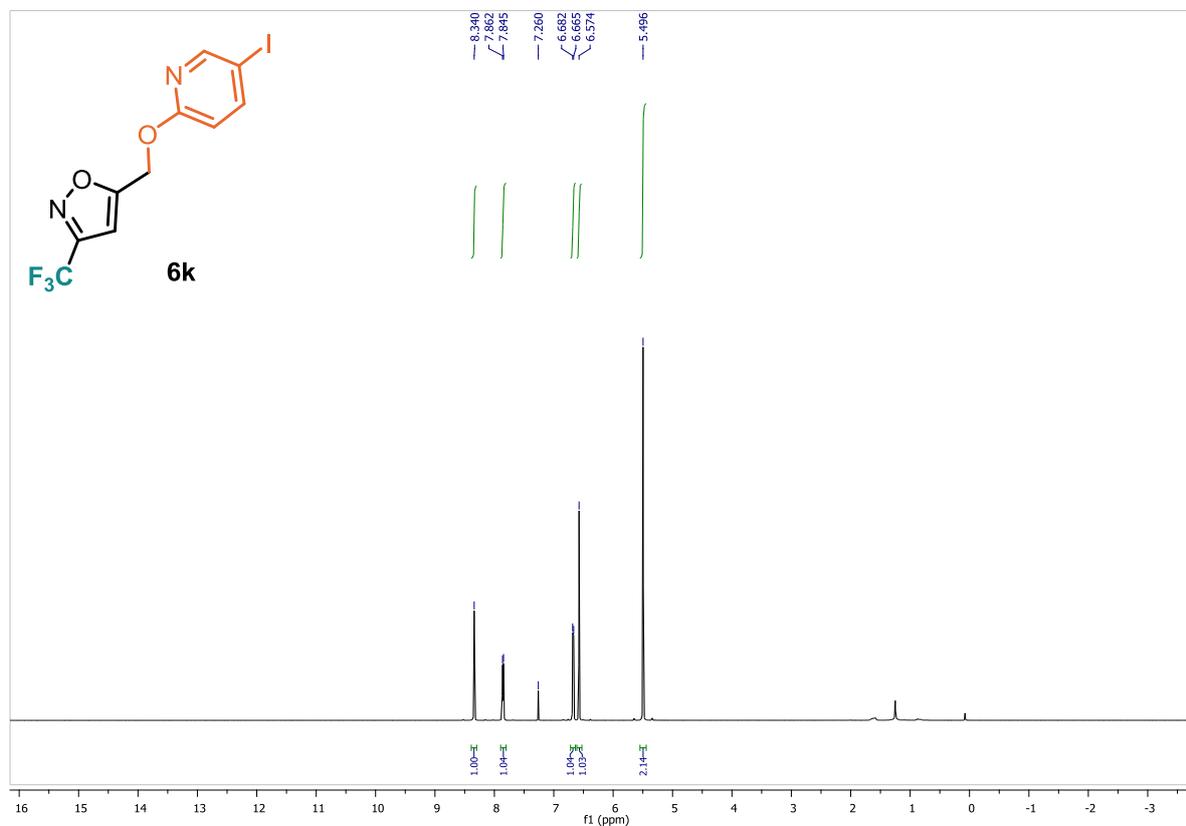


$^{13}\text{C}$  NMR, 125 MHz,  $\text{CDCl}_3$ :

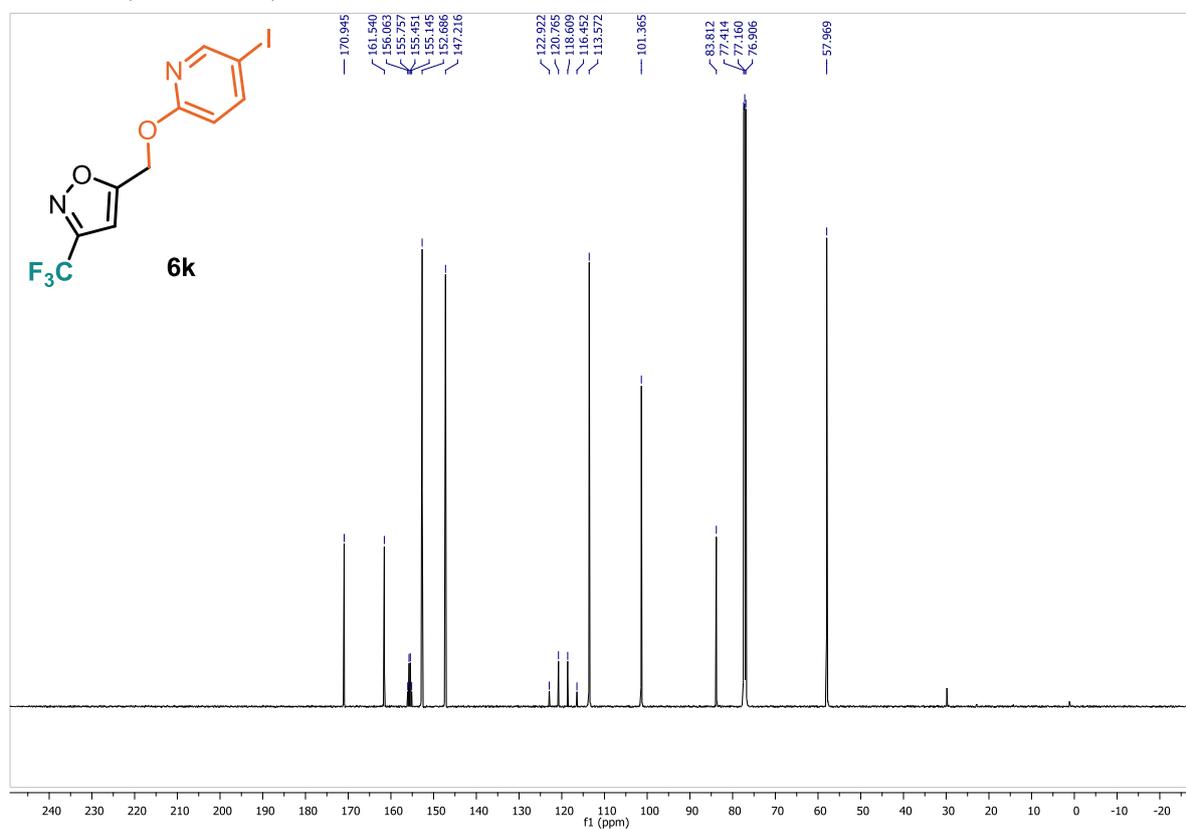


**5-(((5-iodopyridin-2-yl)oxy)methyl)-3-(trifluoromethyl)isoxazole (6k):**

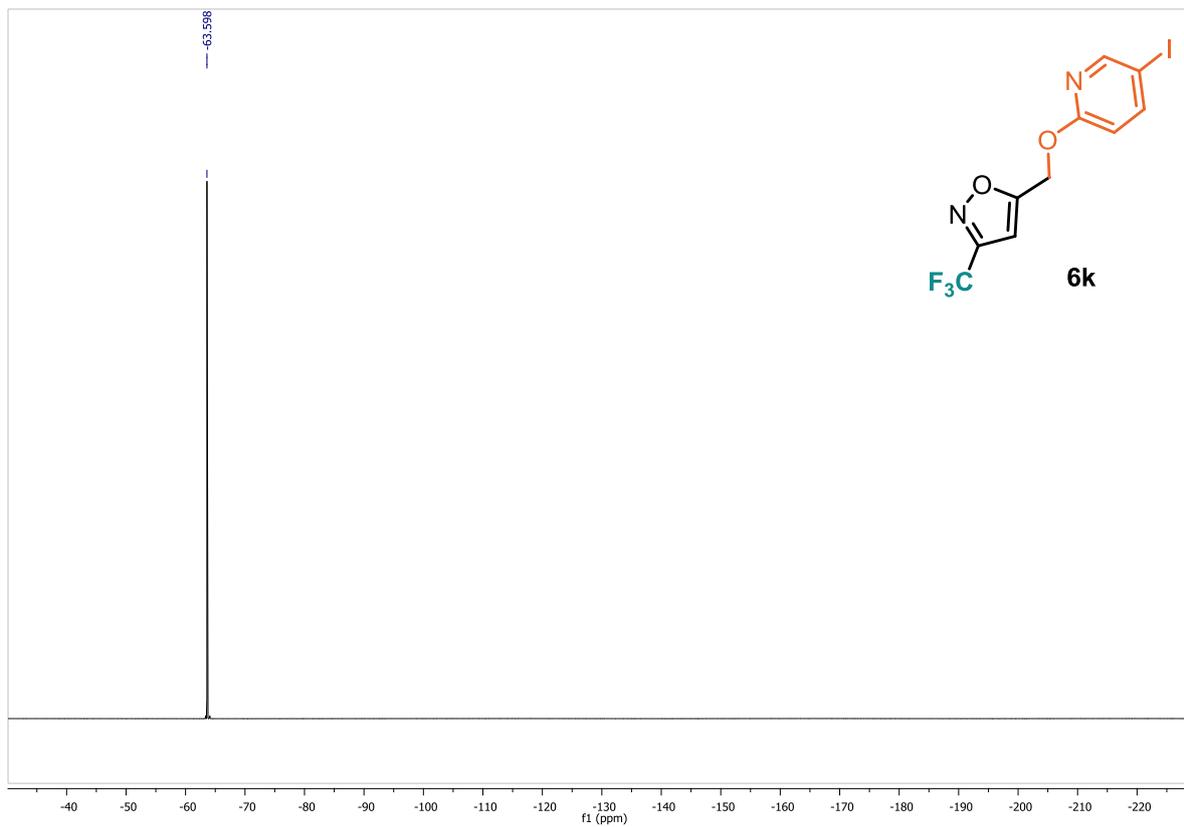
**<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>:**



**<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>:**

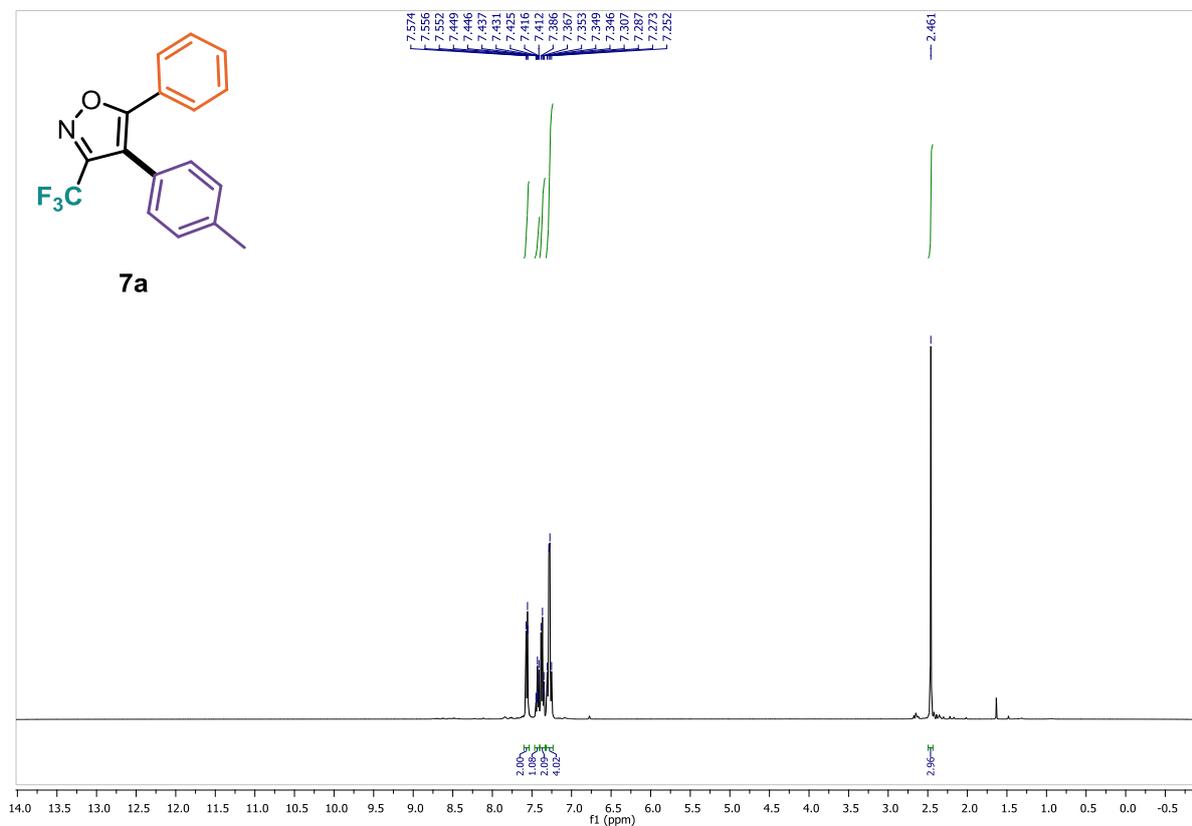


**<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:**

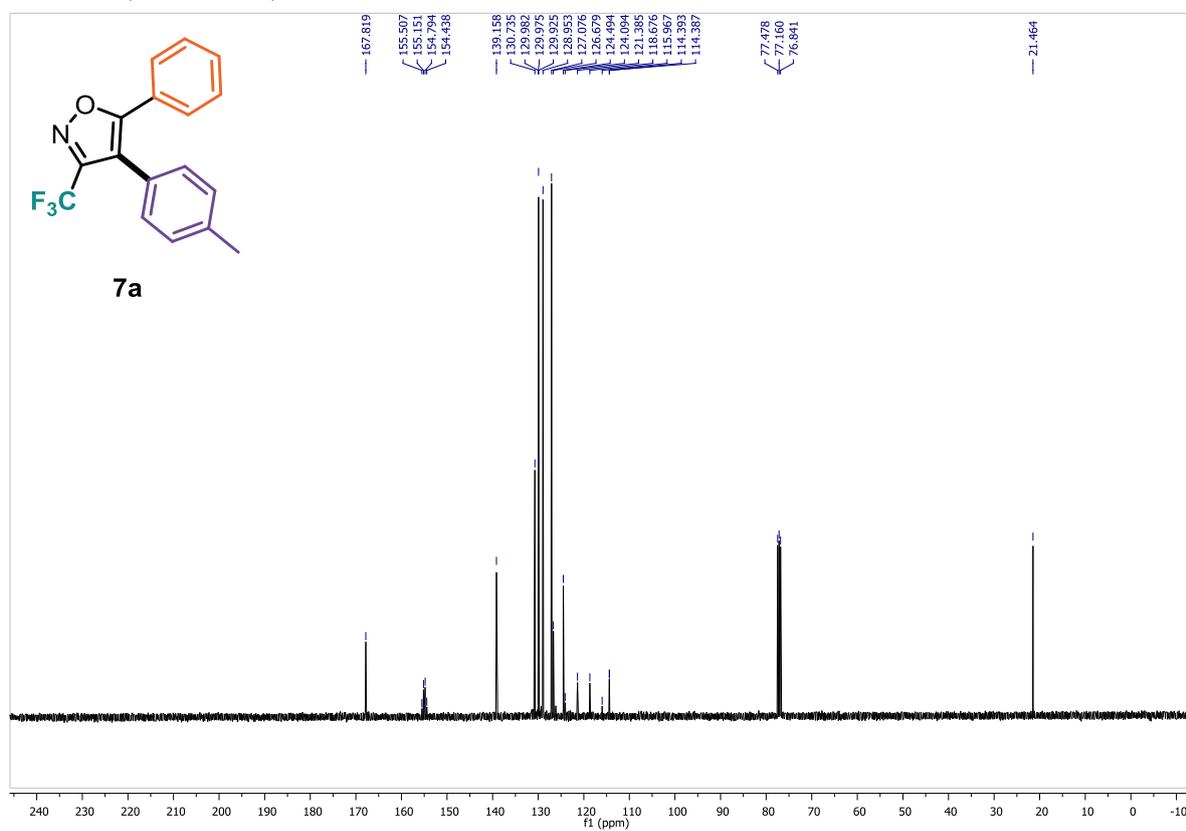


### 5-phenyl-4-(*p*-tolyl)-3-(trifluoromethyl)isoxazole (7a):

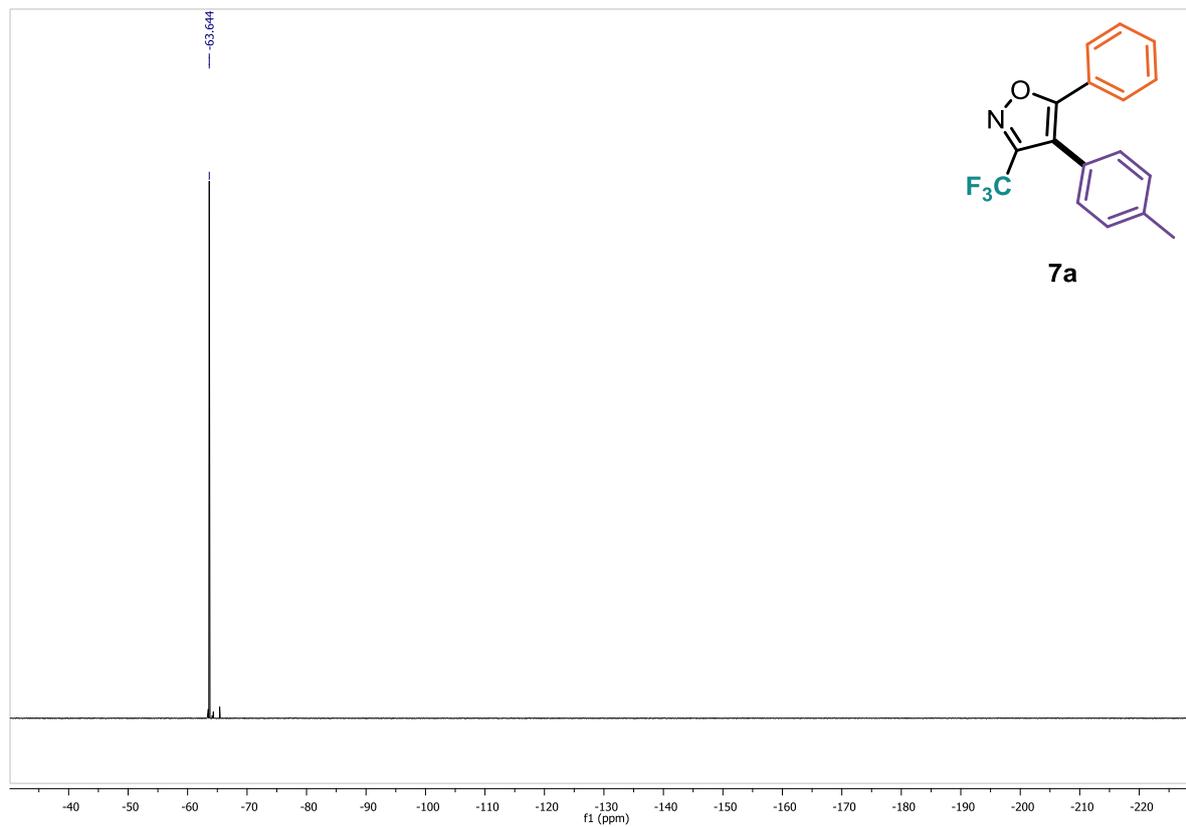
$^1\text{H}$  NMR, 400 MHz,  $\text{CDCl}_3$ :



$^{13}\text{C}$  NMR, 100 MHz,  $\text{CDCl}_3$ :

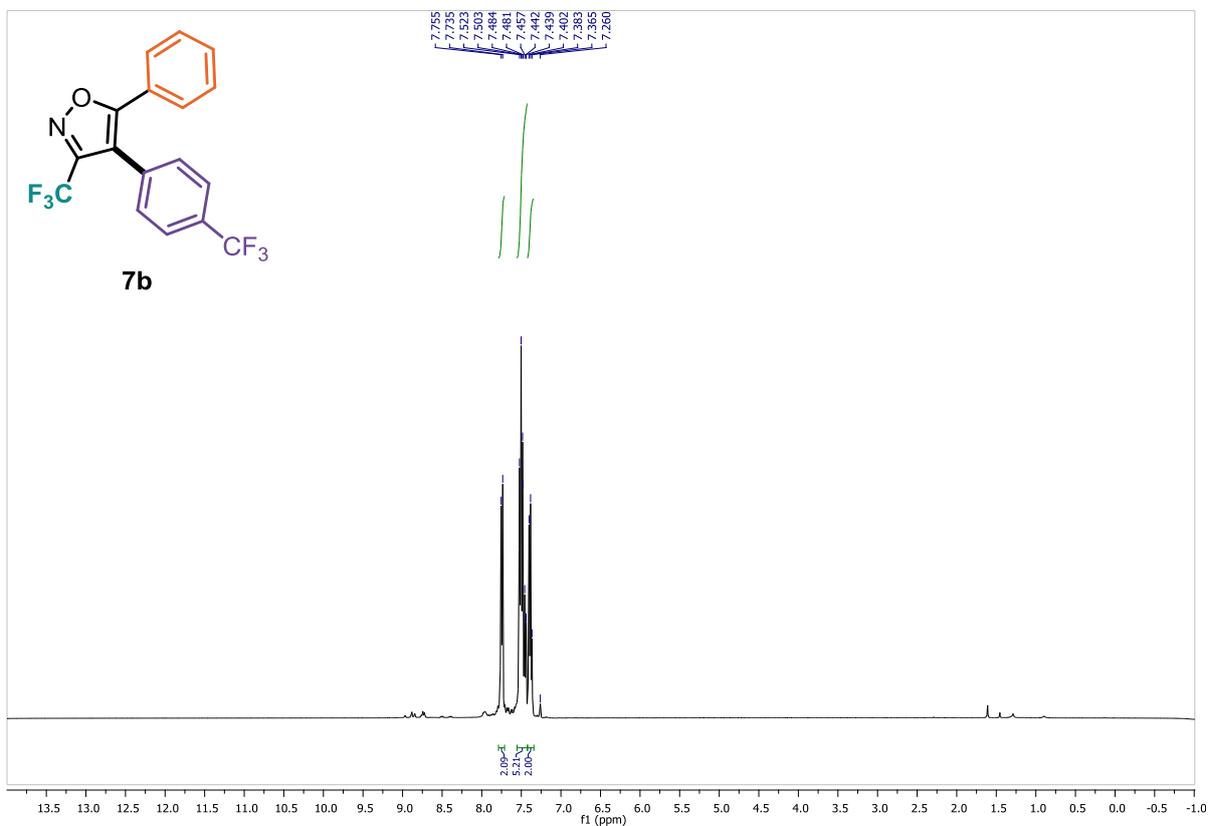


**<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:**

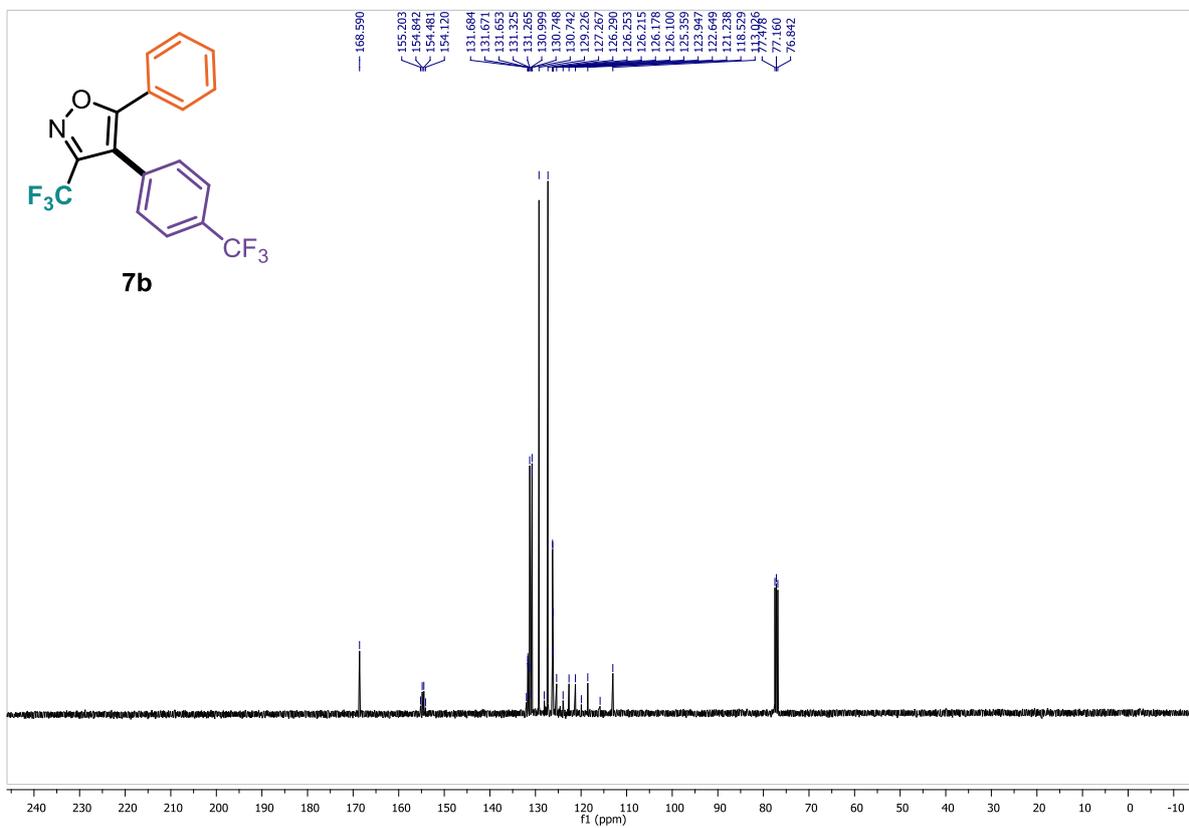


### 5-phenyl-3-(trifluoromethyl)-4-(4-(trifluoromethyl)phenyl)isoxazole (7b):

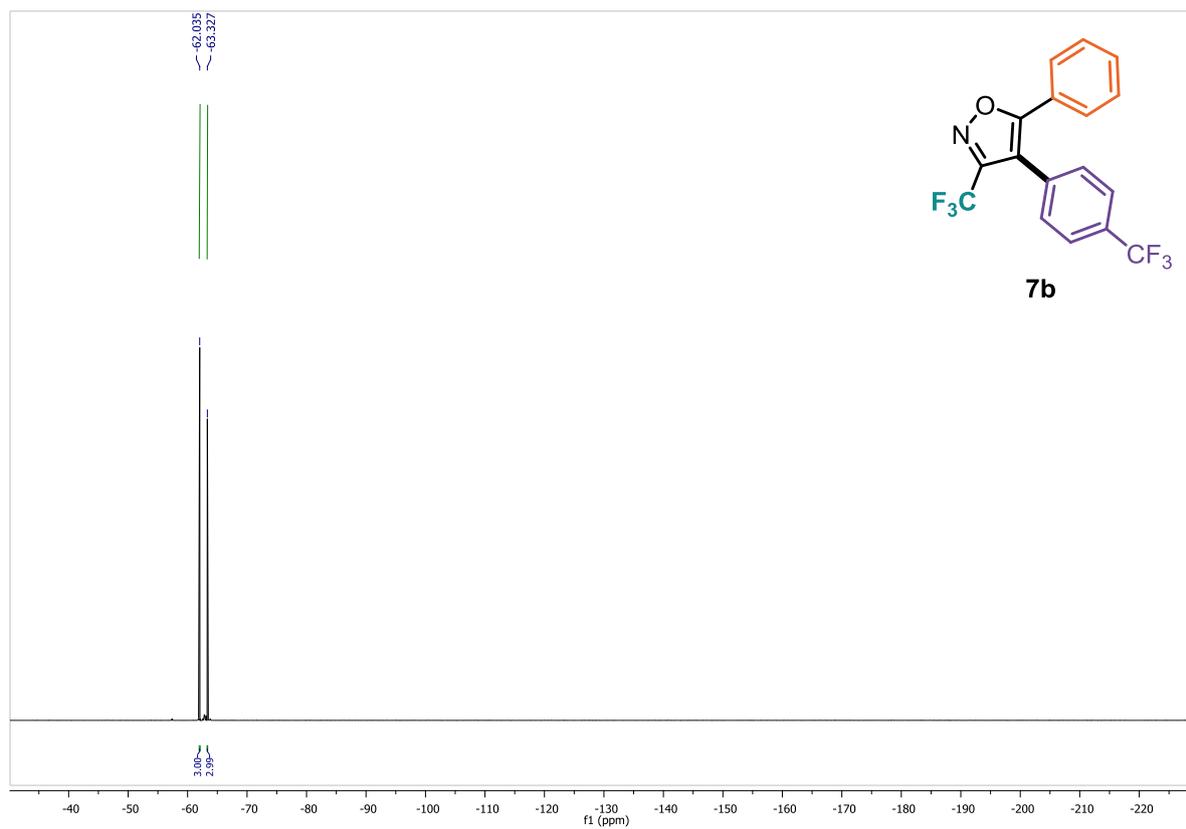
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:

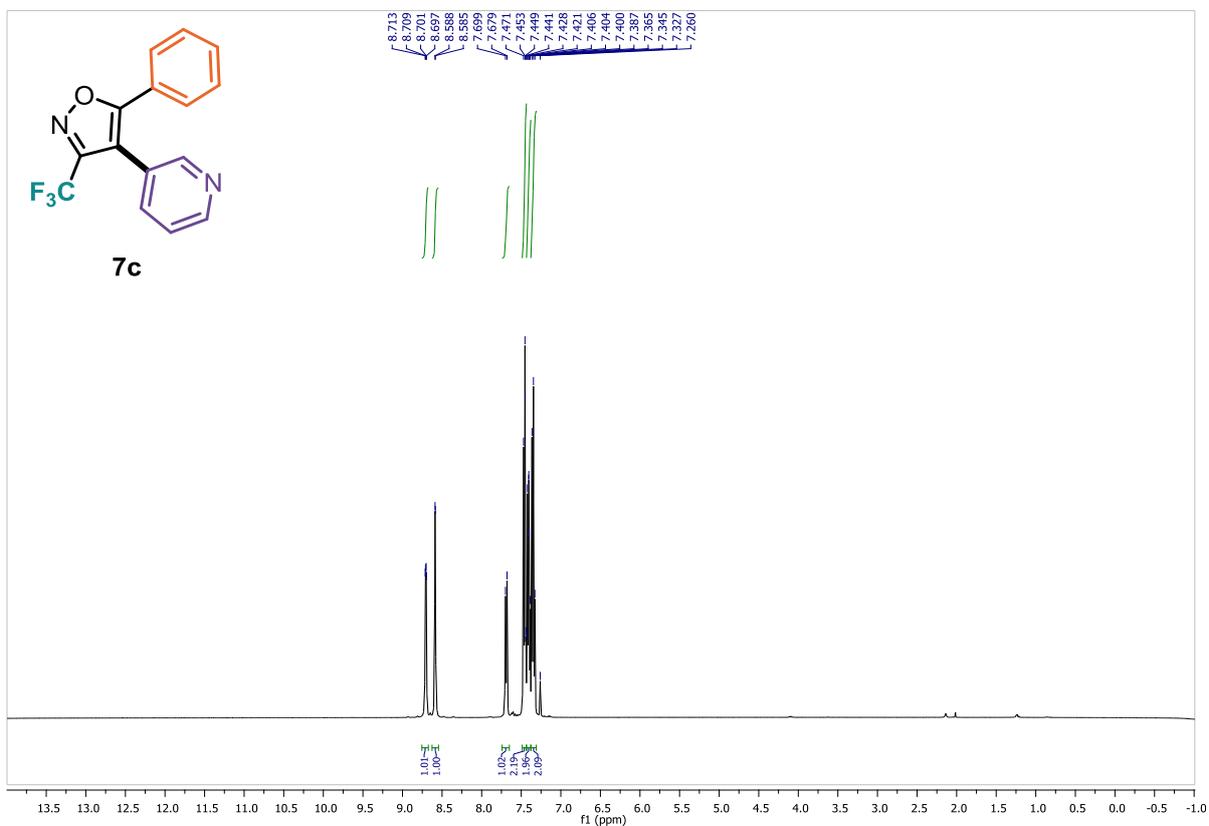


**$^{19}\text{F}$  NMR, 376 MHz,  $\text{CDCl}_3$ :**

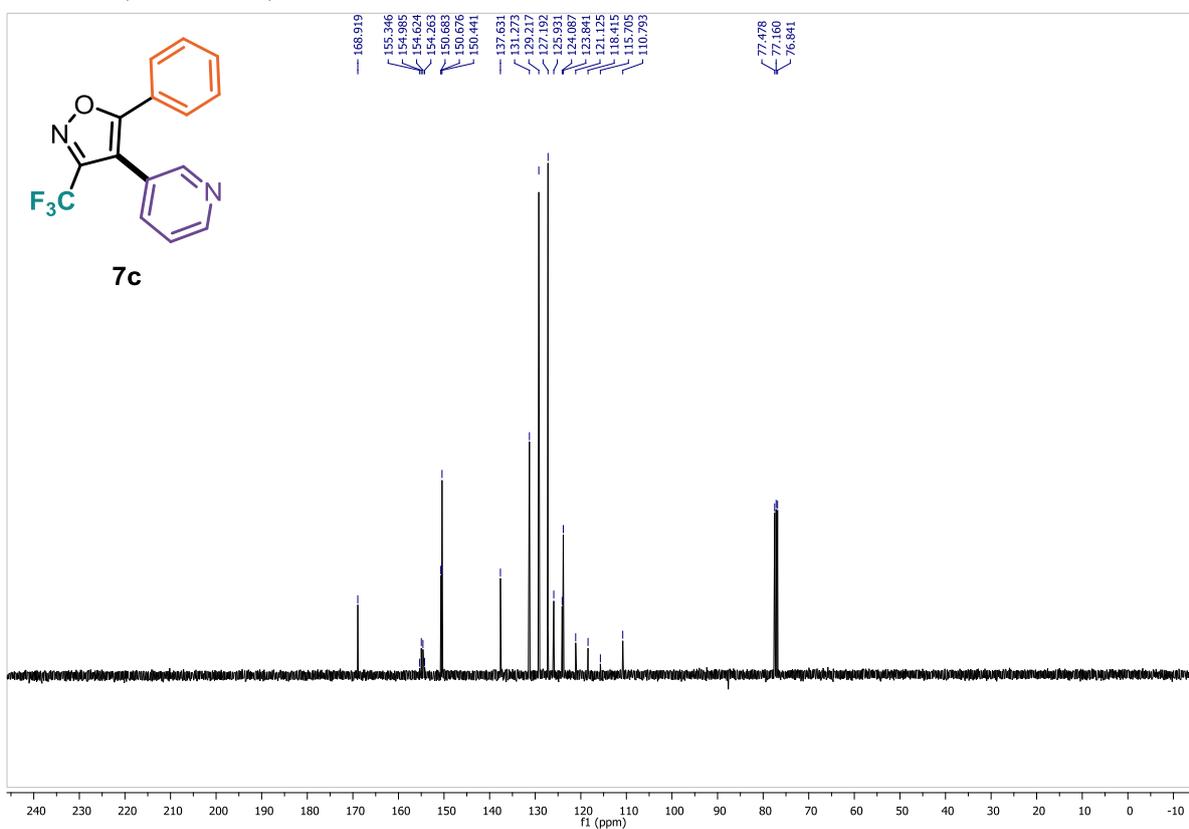


### 5-phenyl-4-(pyridin-3-yl)-3-(trifluoromethyl)isoxazole (7c):

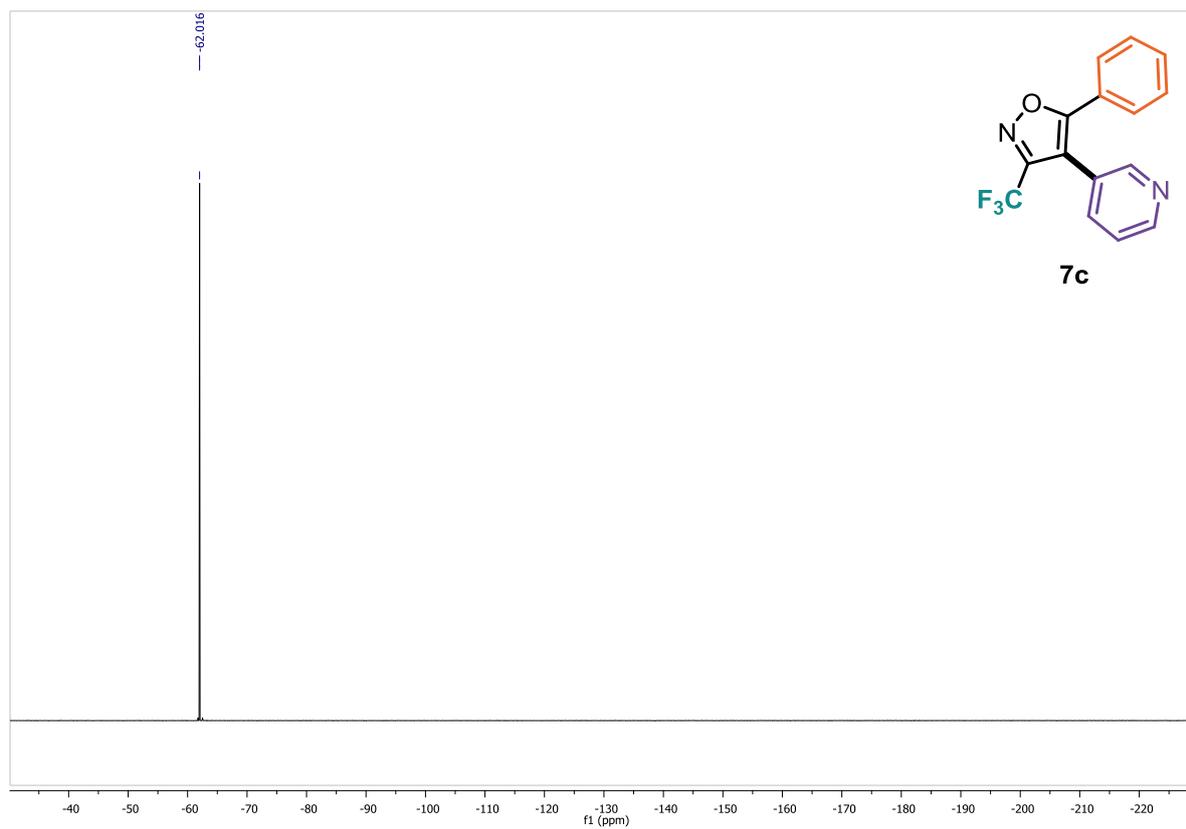
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:

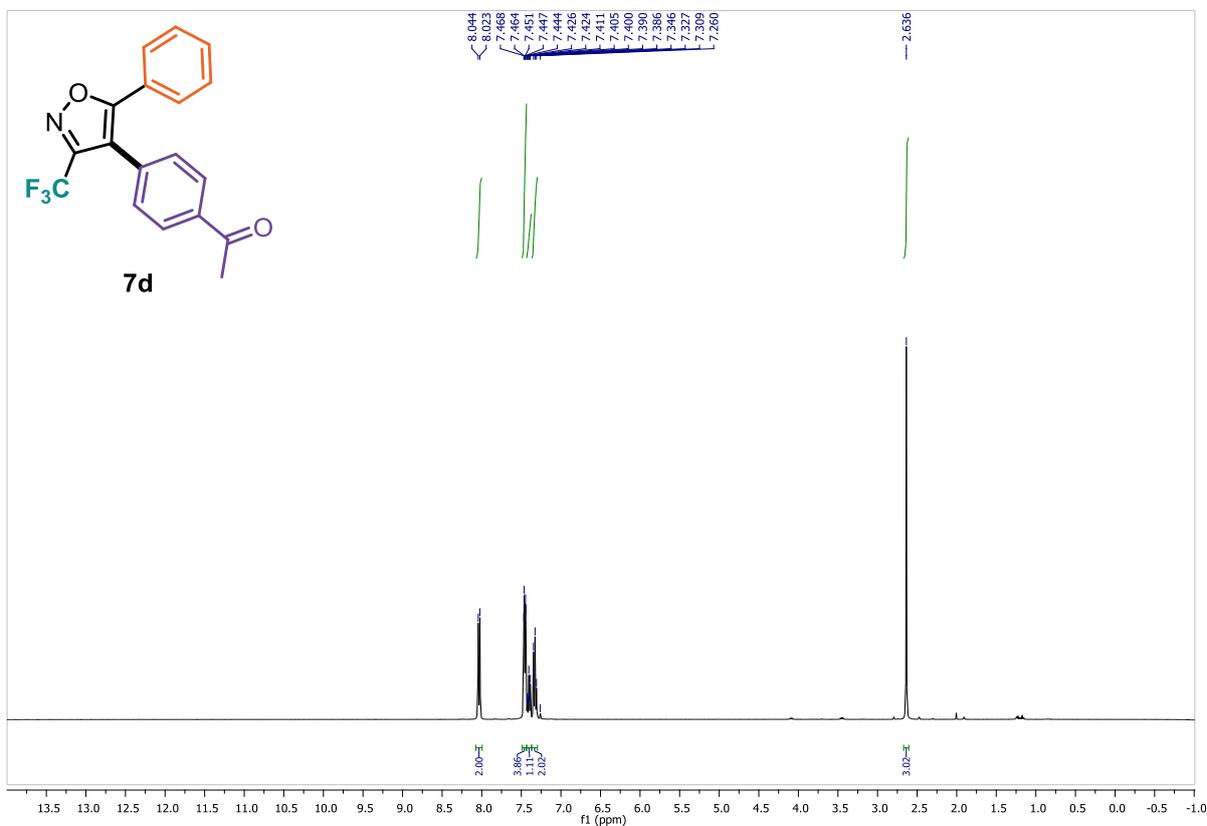


**<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:**

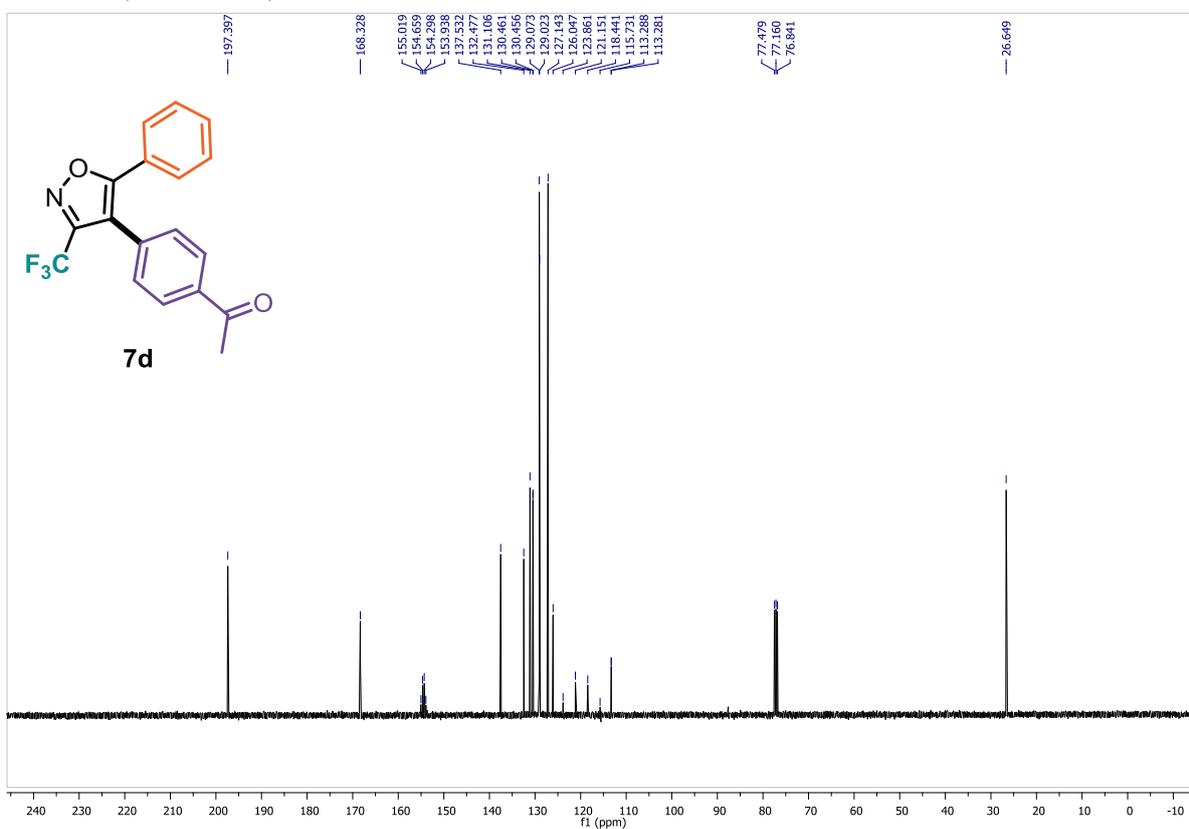


# 1-(4-(5-phenyl-3-(trifluoromethyl)isoxazol-4-yl)phenyl)ethanone (7d):

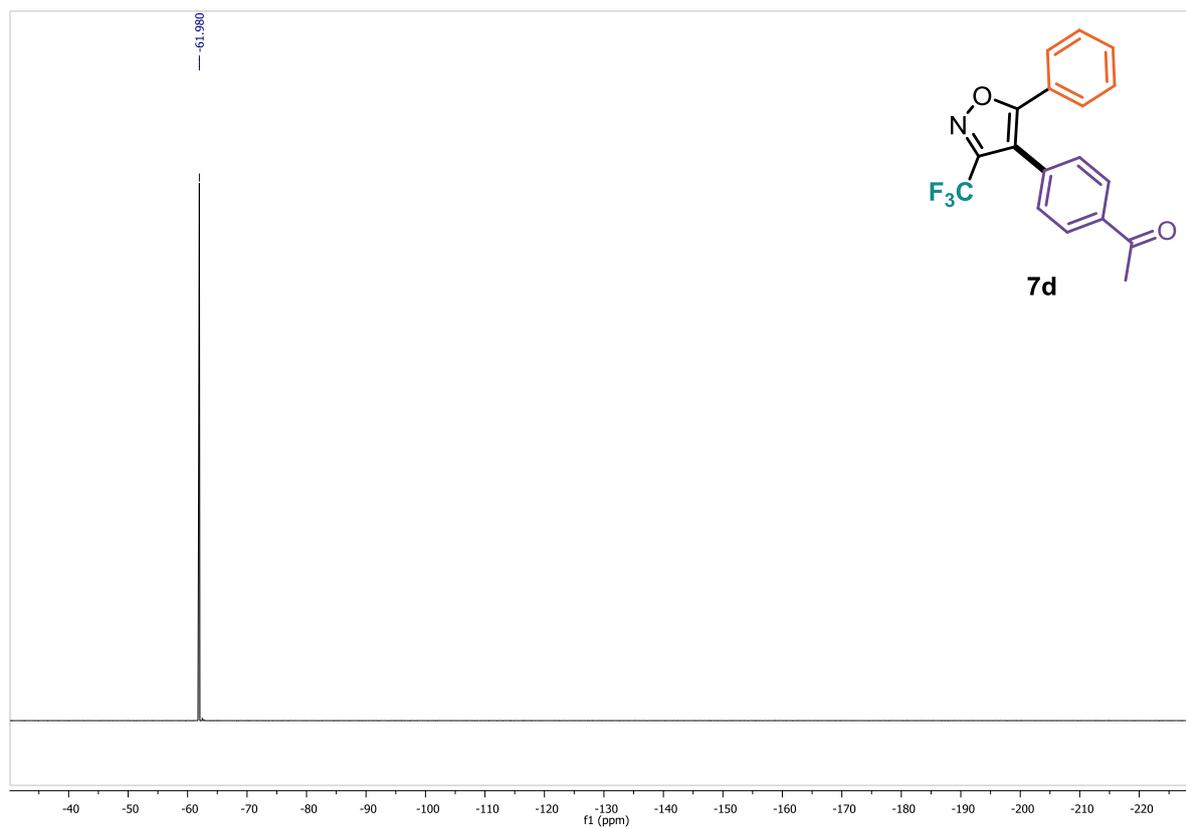
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:

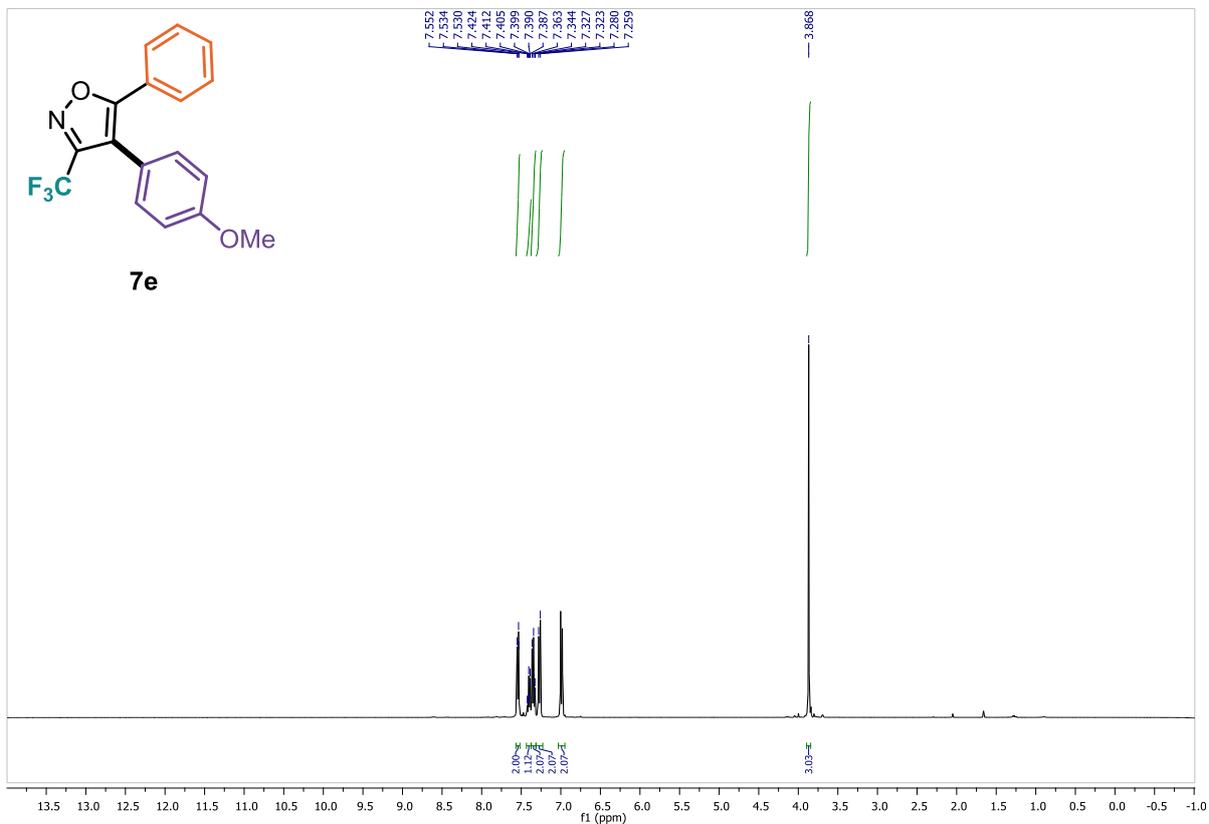


**$^{19}\text{F}$  NMR, 376 MHz,  $\text{CDCl}_3$ :**

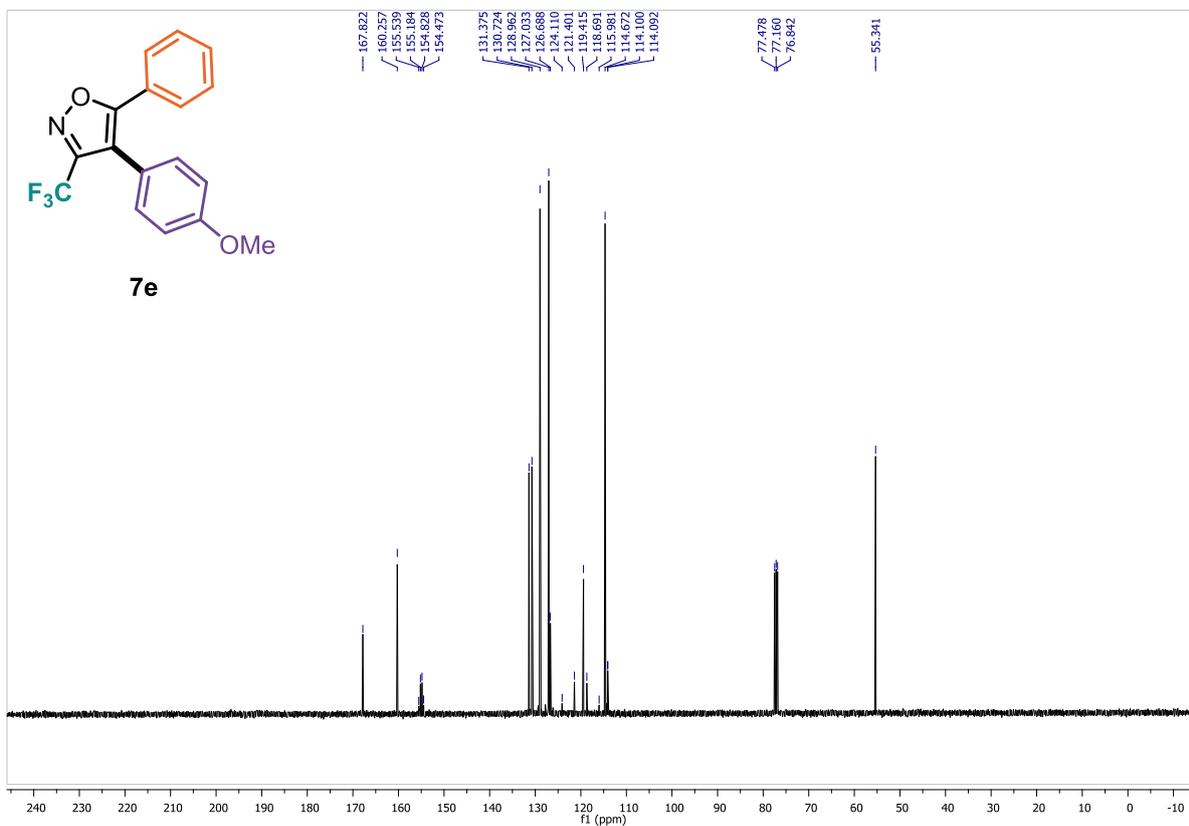


### 4-(4-methoxyphenyl)-5-phenyl-3-(trifluoromethyl)isoxazole (7e):

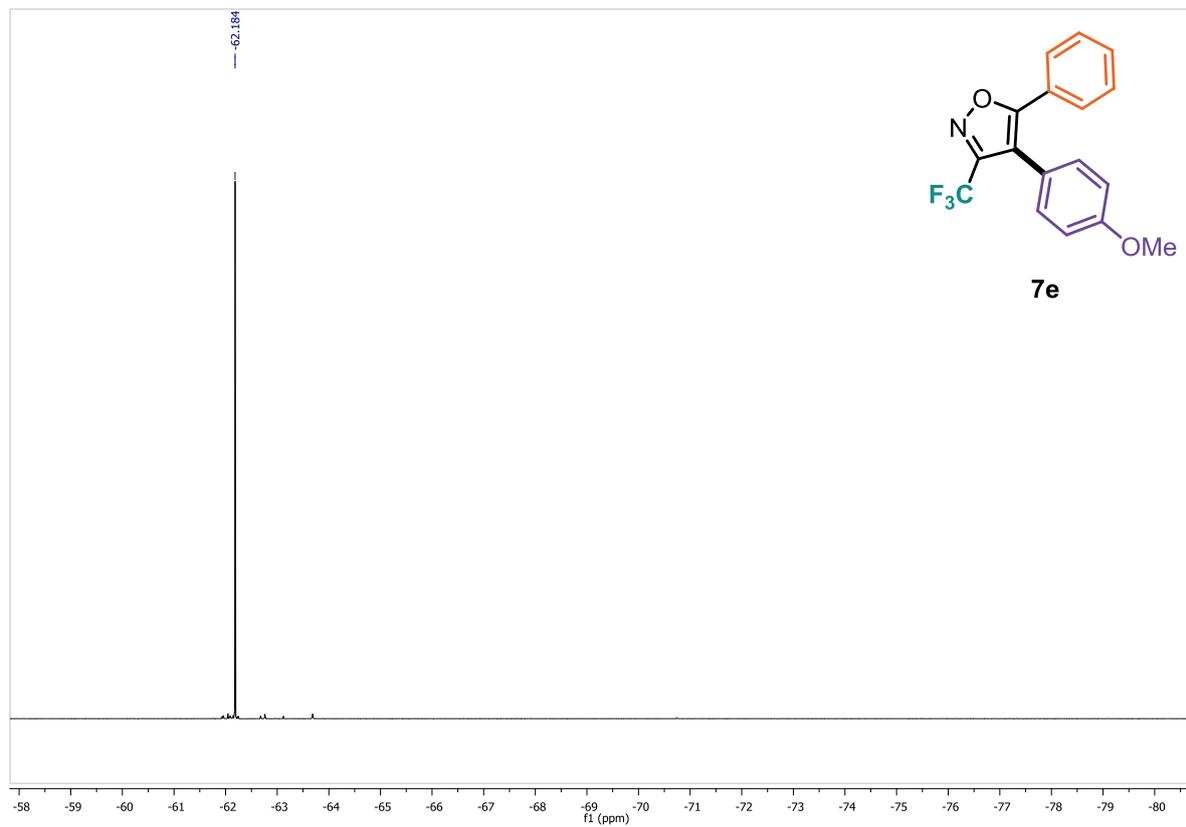
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:

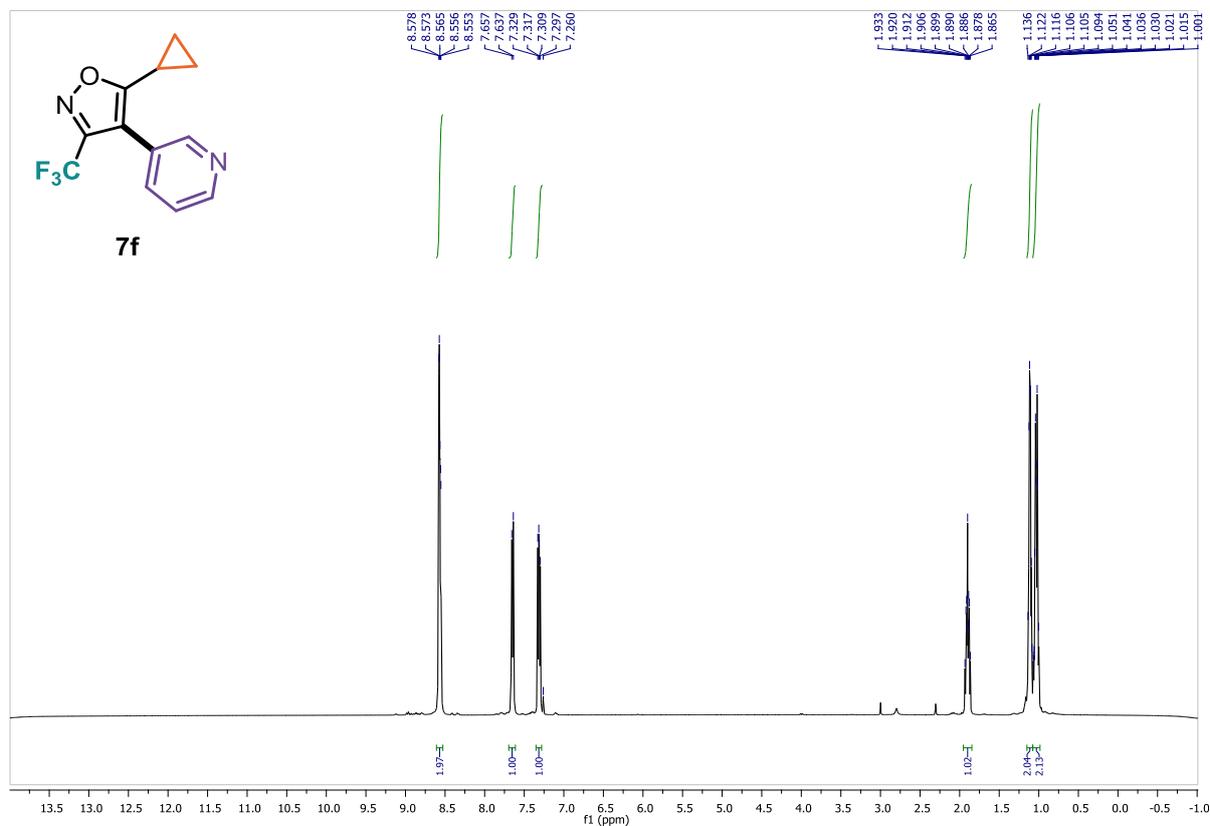


**$^{19}\text{F}$  NMR, 376 MHz,  $\text{CDCl}_3$ :**

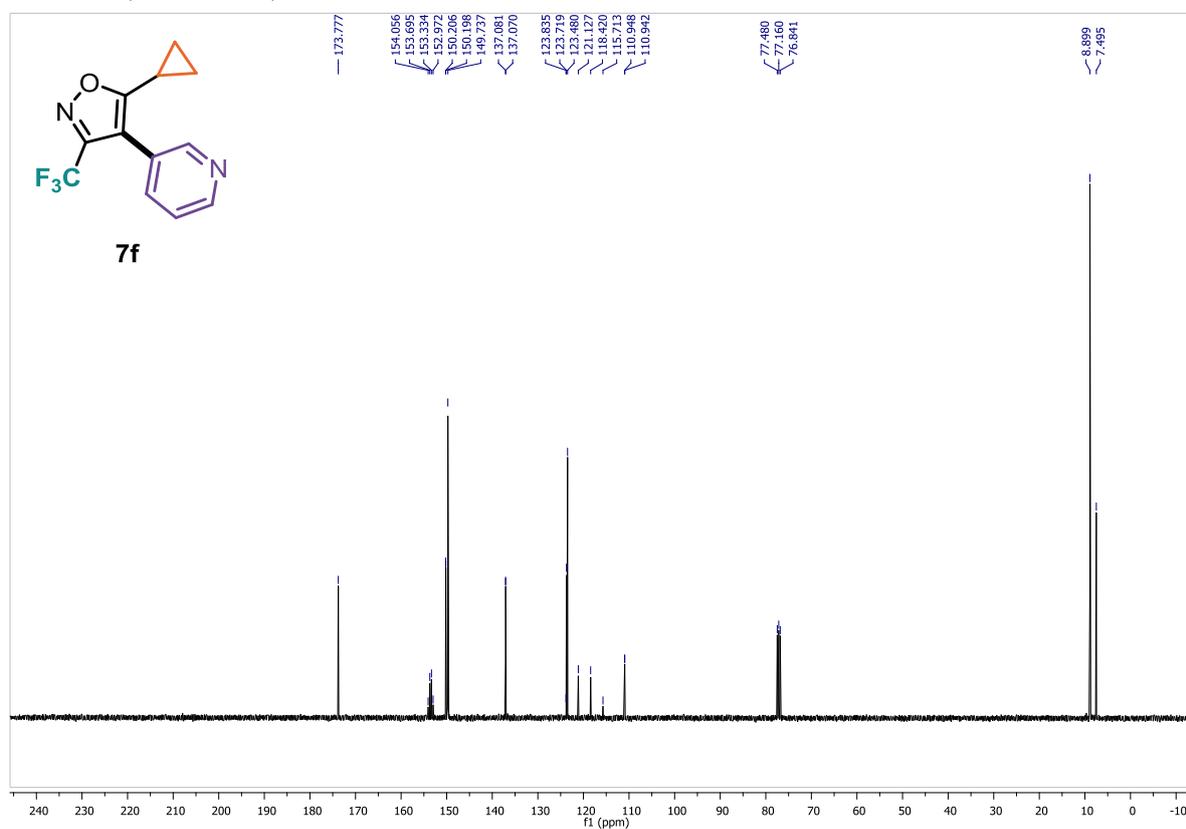


### 5-cyclopropyl-4-(pyridin-3-yl)-3-(trifluoromethyl)isoxazole (7f):

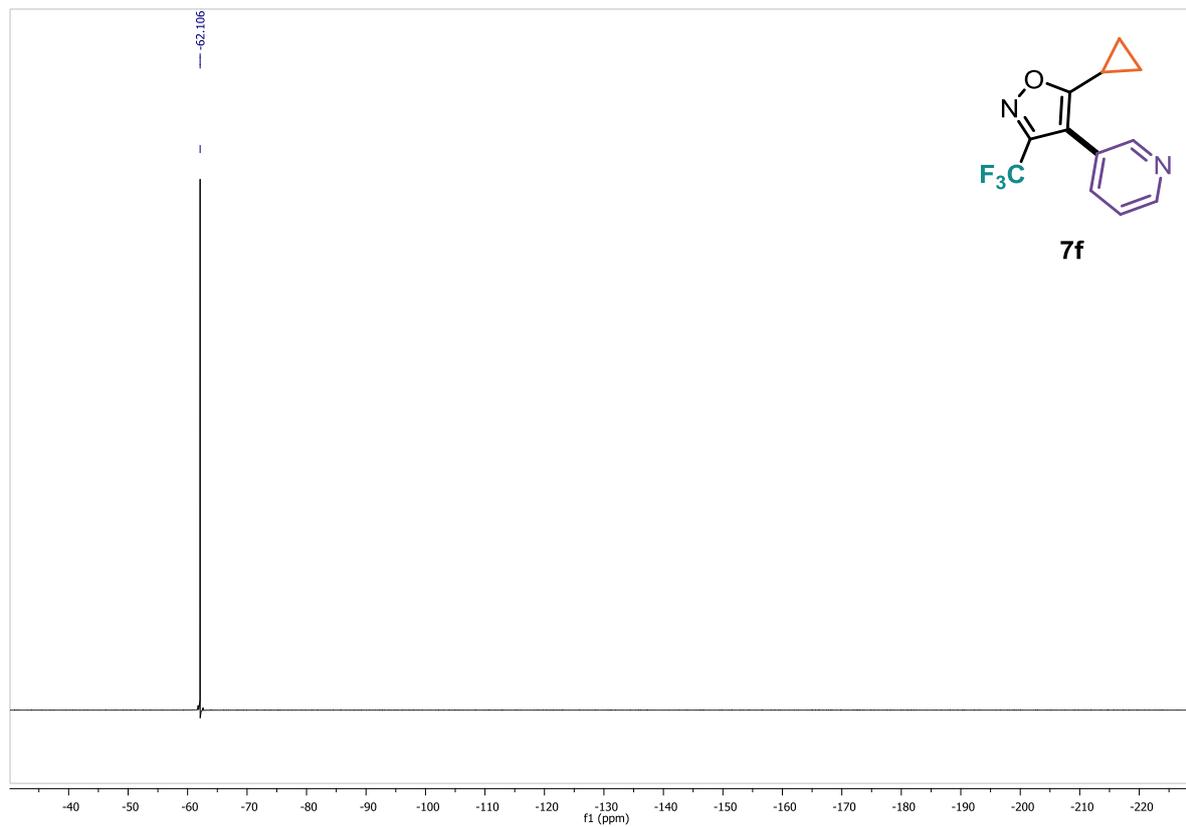
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:

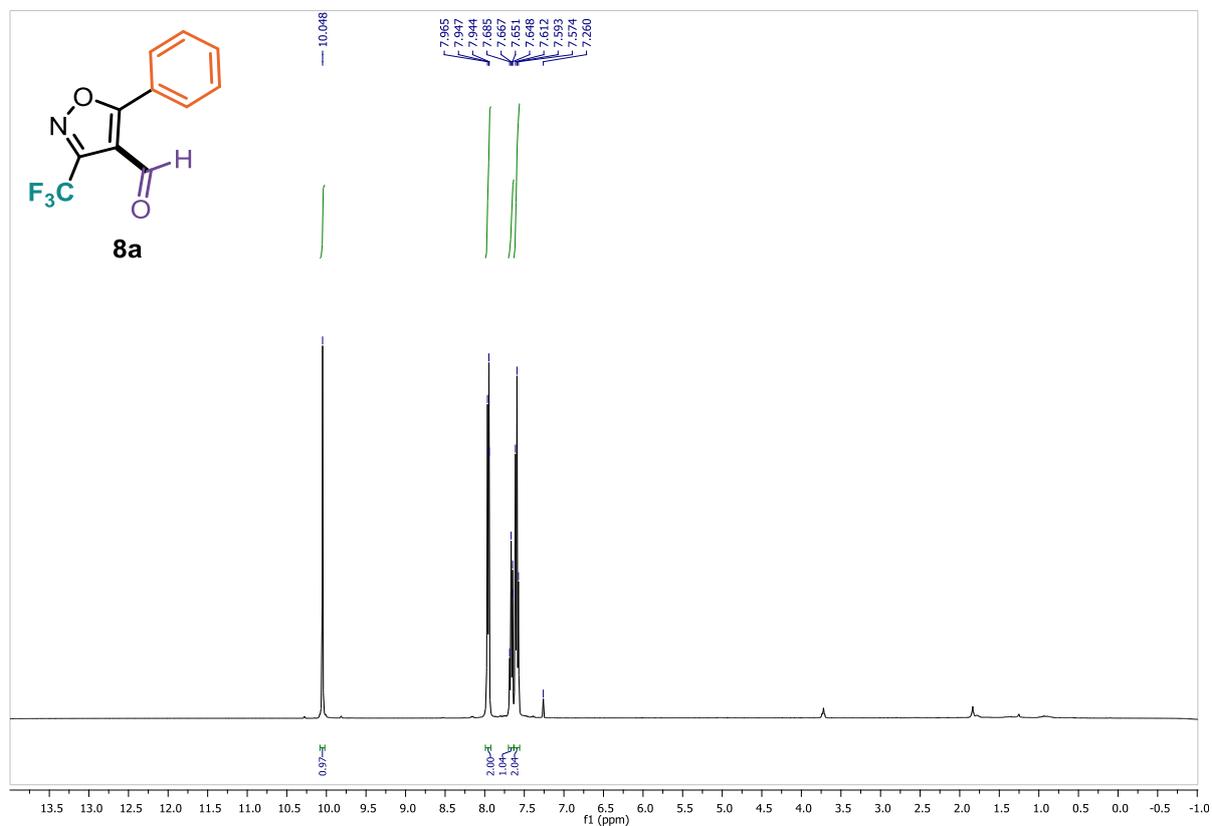


**<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:**

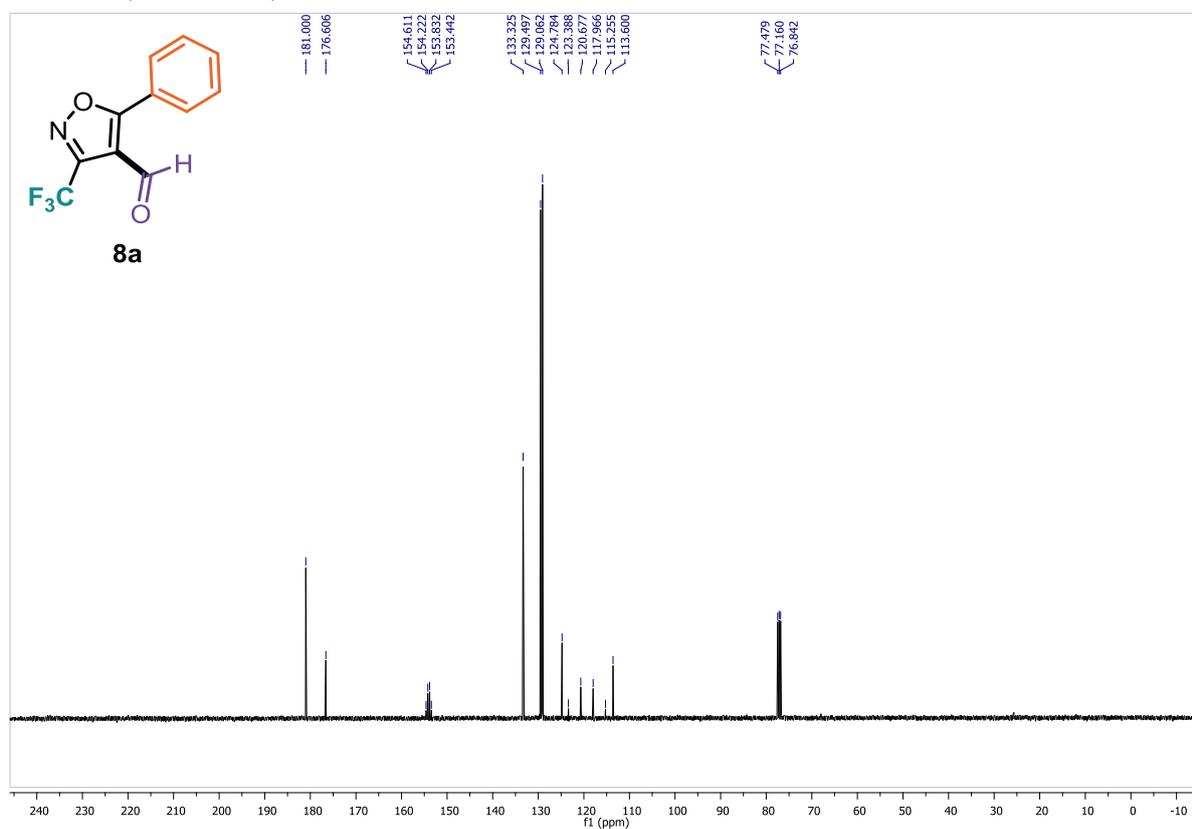


### 5-phenyl-3-(trifluoromethyl)isoxazole-4-carbaldehyde (8a):

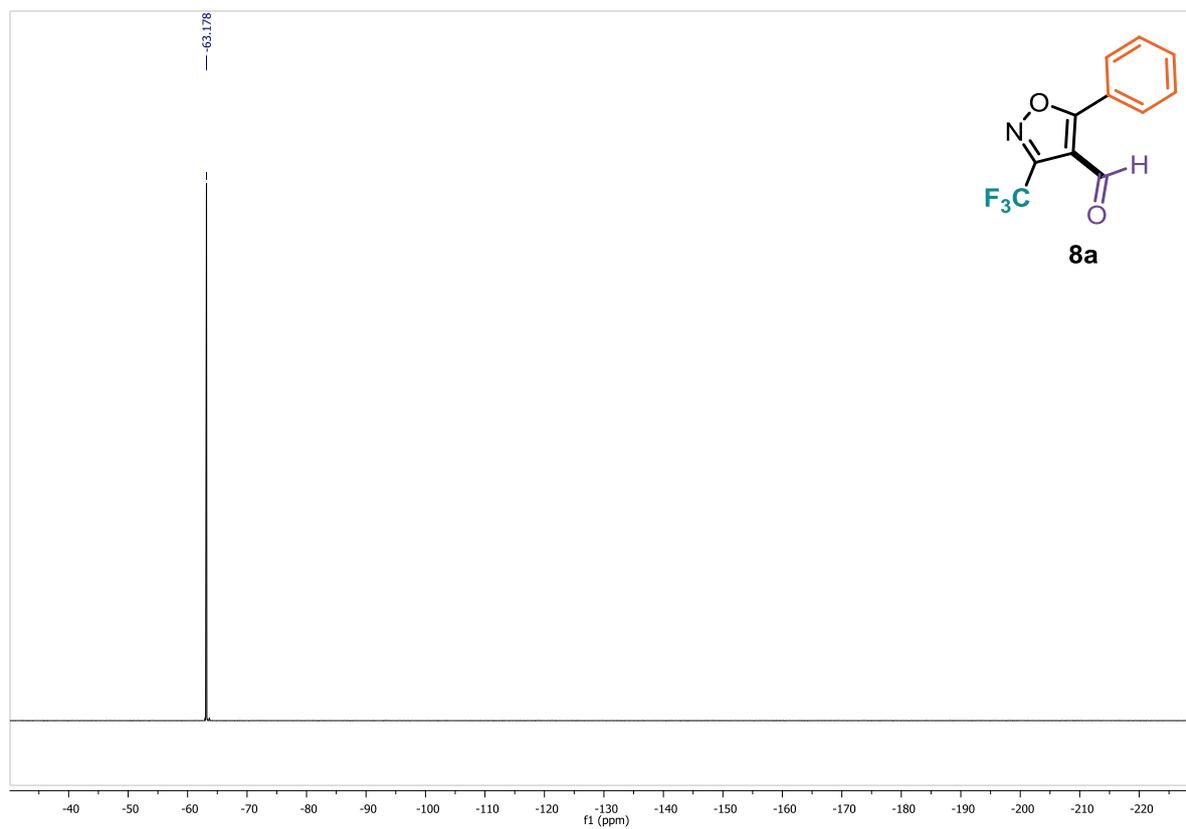
$^1\text{H}$  NMR, 400 MHz,  $\text{CDCl}_3$ :



$^{13}\text{C}$  NMR, 100 MHz,  $\text{CDCl}_3$ :

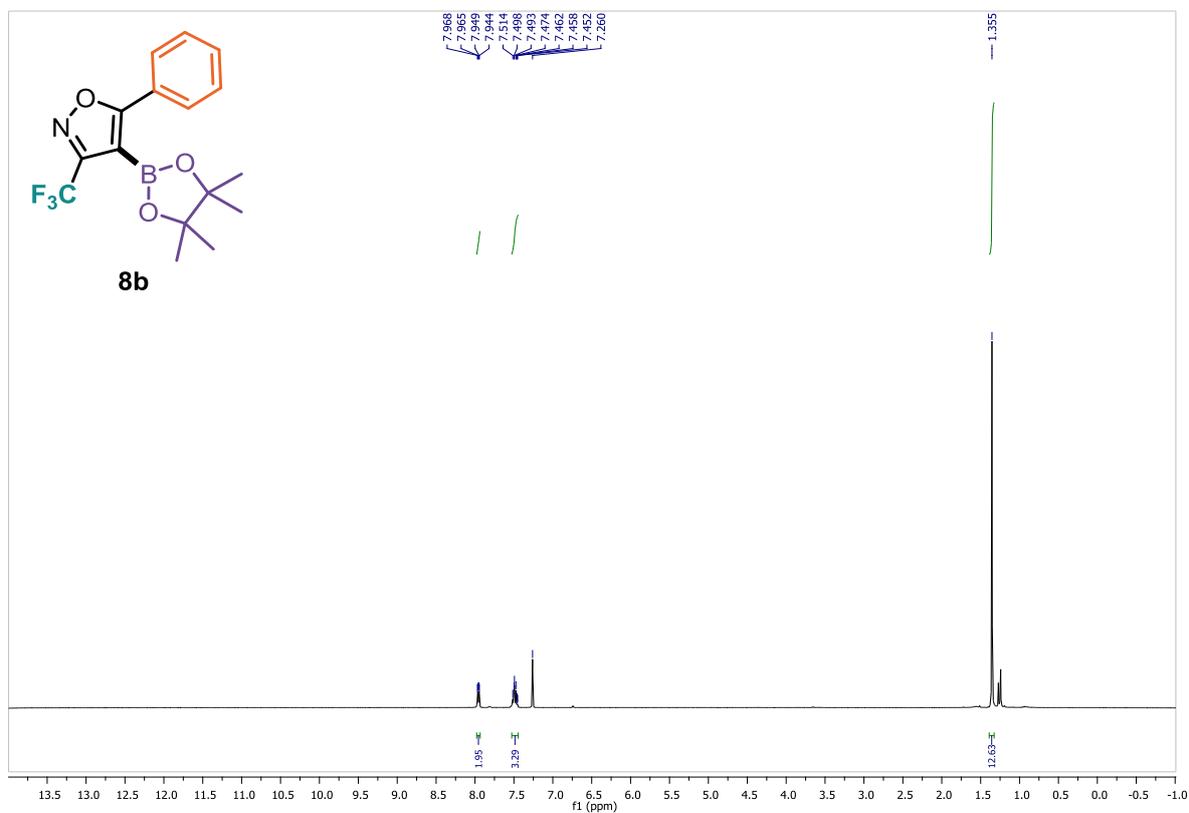


<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:

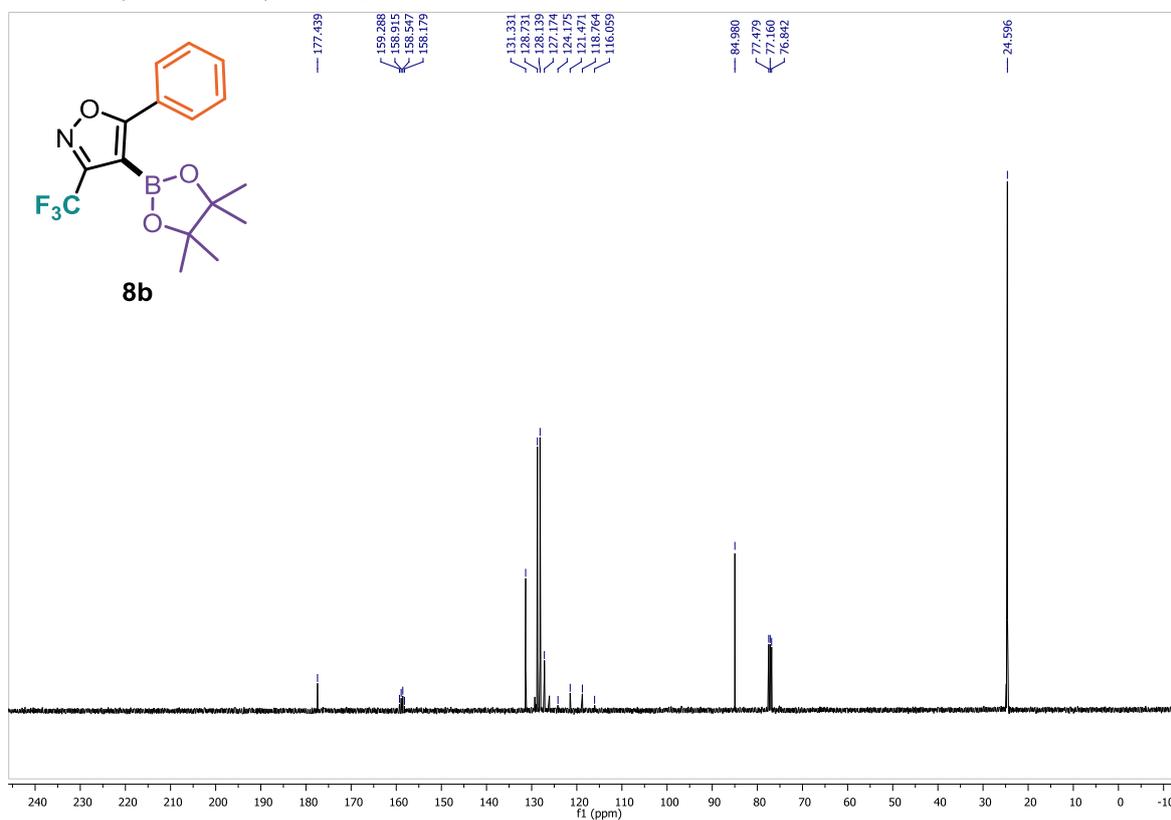


**5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)isoxazole (8b):**

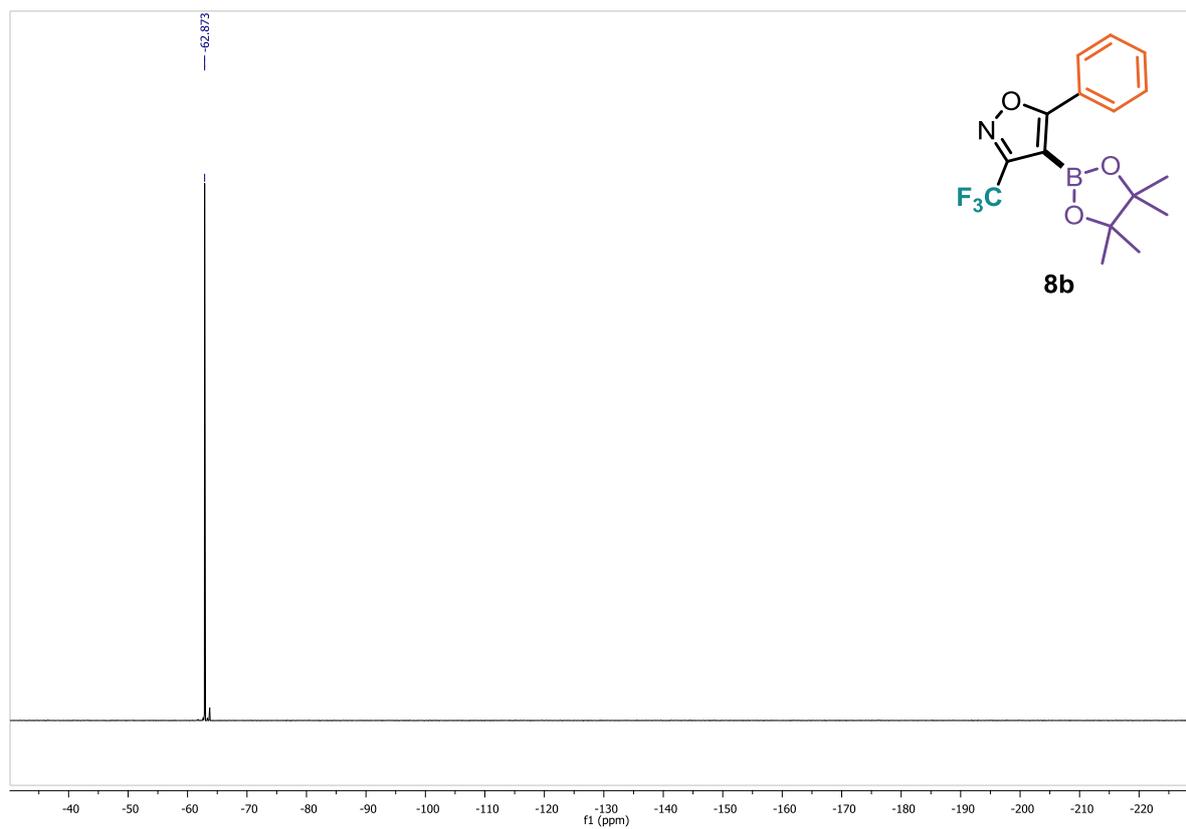
**<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:**



**<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:**

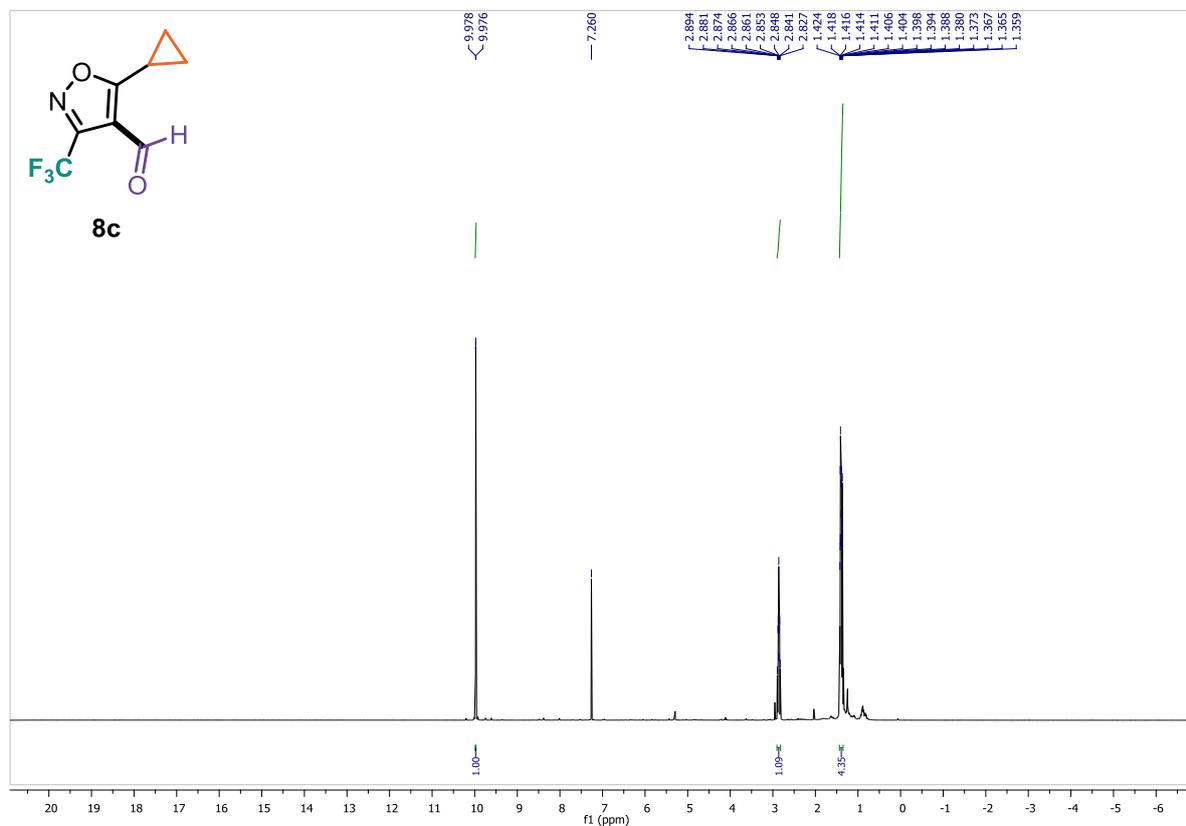


$^{19}\text{F}$  NMR, 376 MHz,  $\text{CDCl}_3$ :

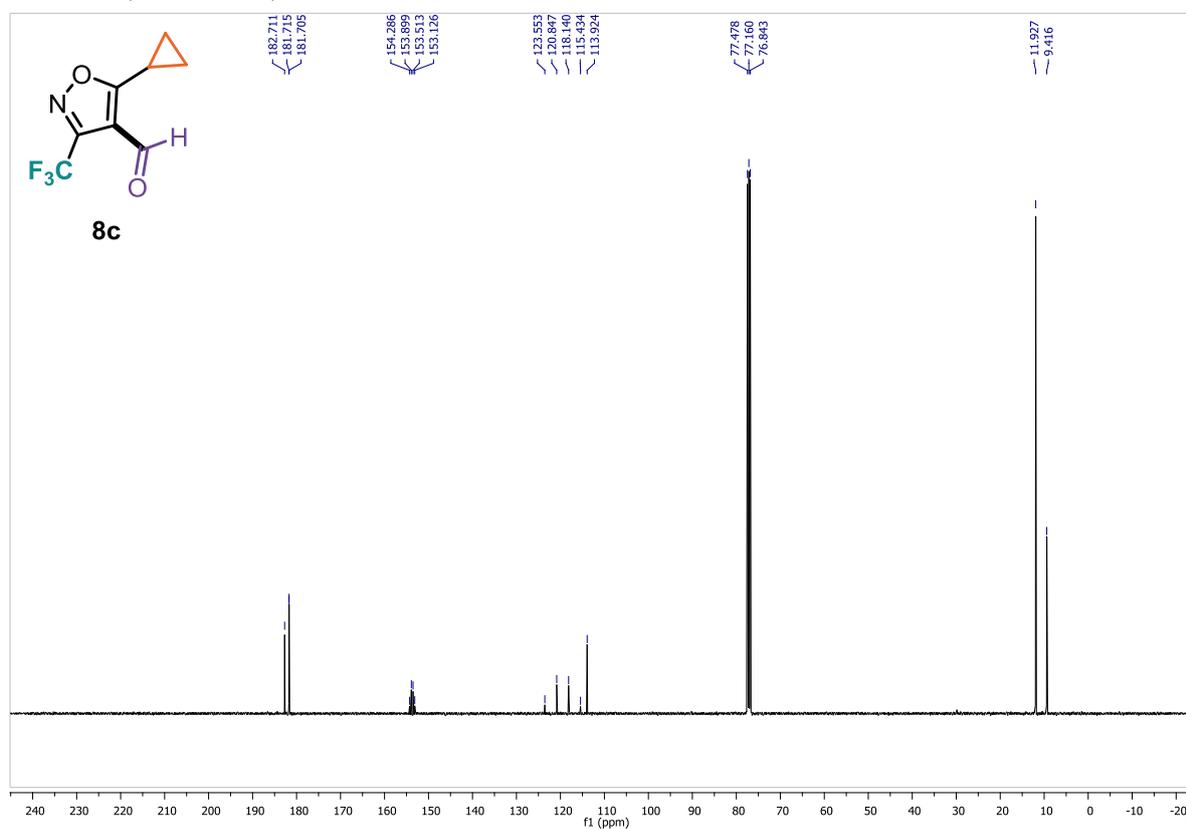


### 5-cyclopropyl-3-(trifluoromethyl)isoxazole-4-carbaldehyde (8c):

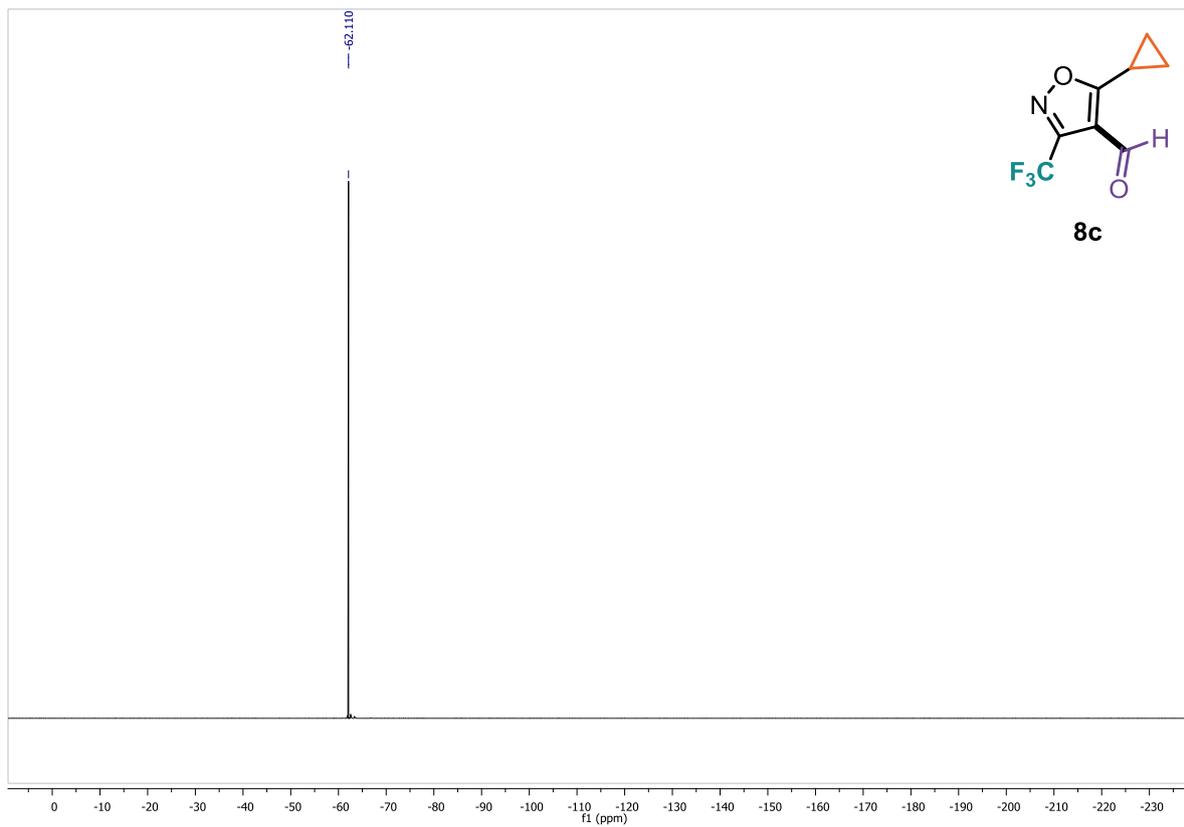
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:

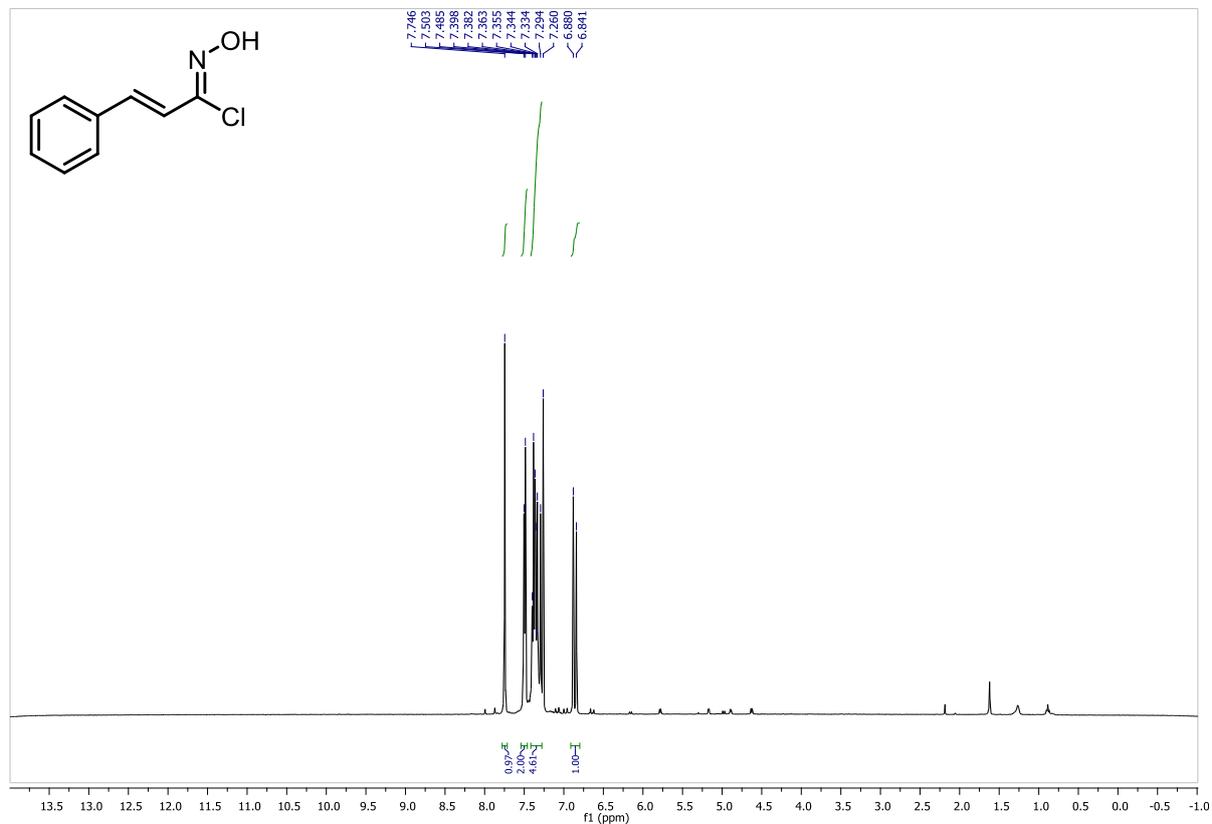


**$^{19}\text{F}$  NMR, 376 MHz,  $\text{CDCl}_3$ :**



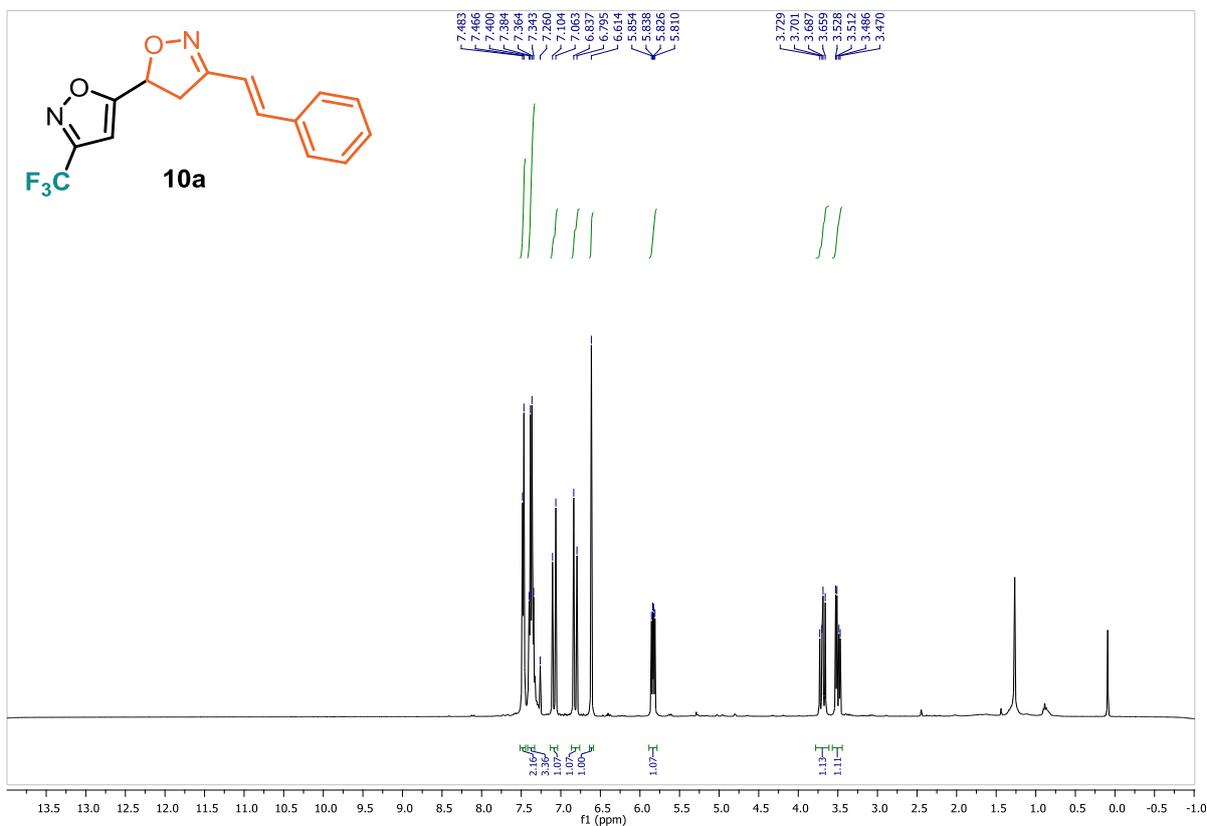
***N*-hydroxycinnamimidoyl chloride:**

<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:

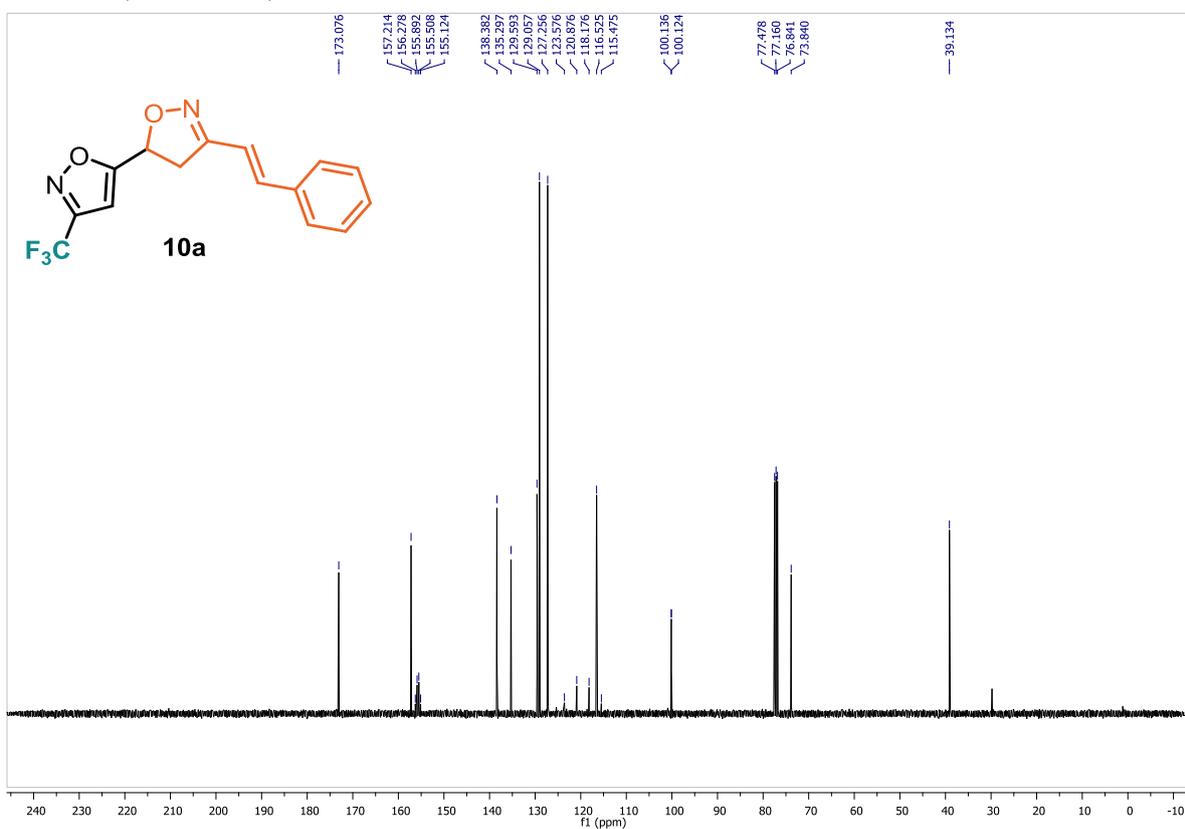


**(E)-3-styryl-3'-(trifluoromethyl)-4,5-dihydro-5,5'-biisoxazole (10a):**

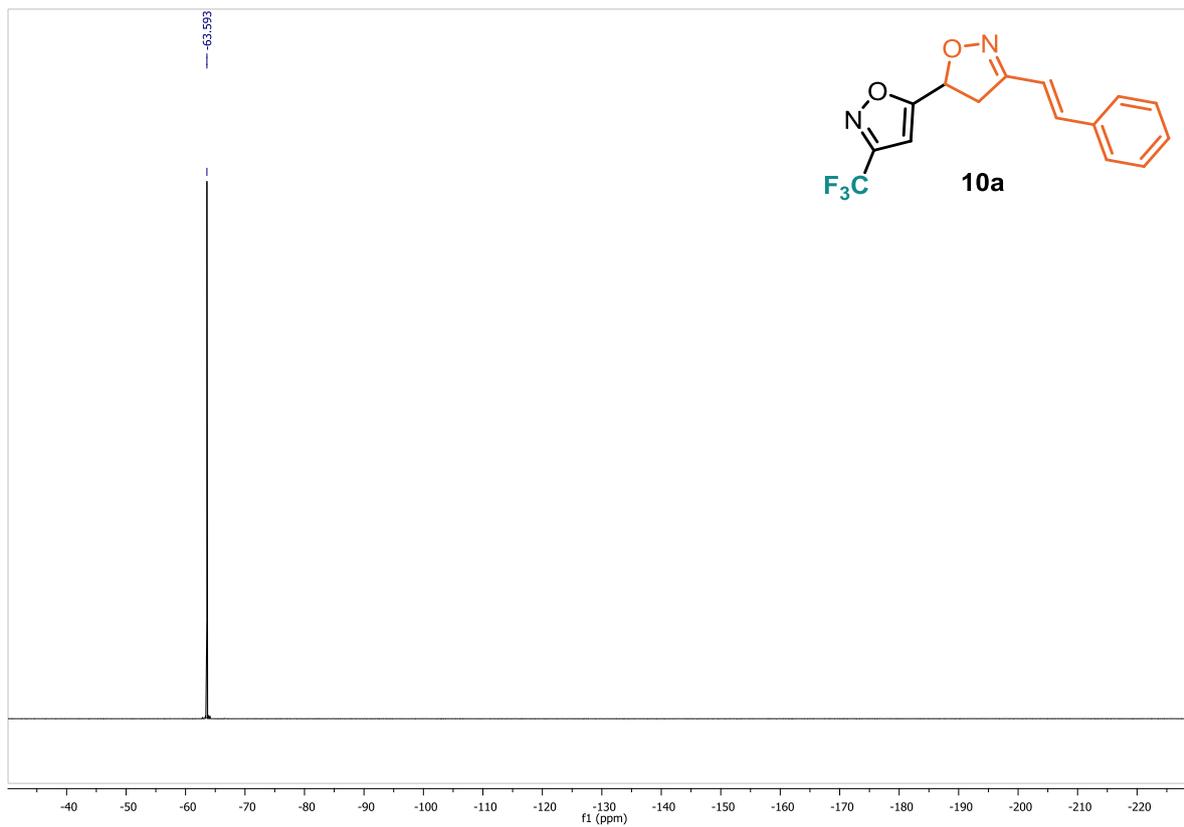
**<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:**



**<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:**

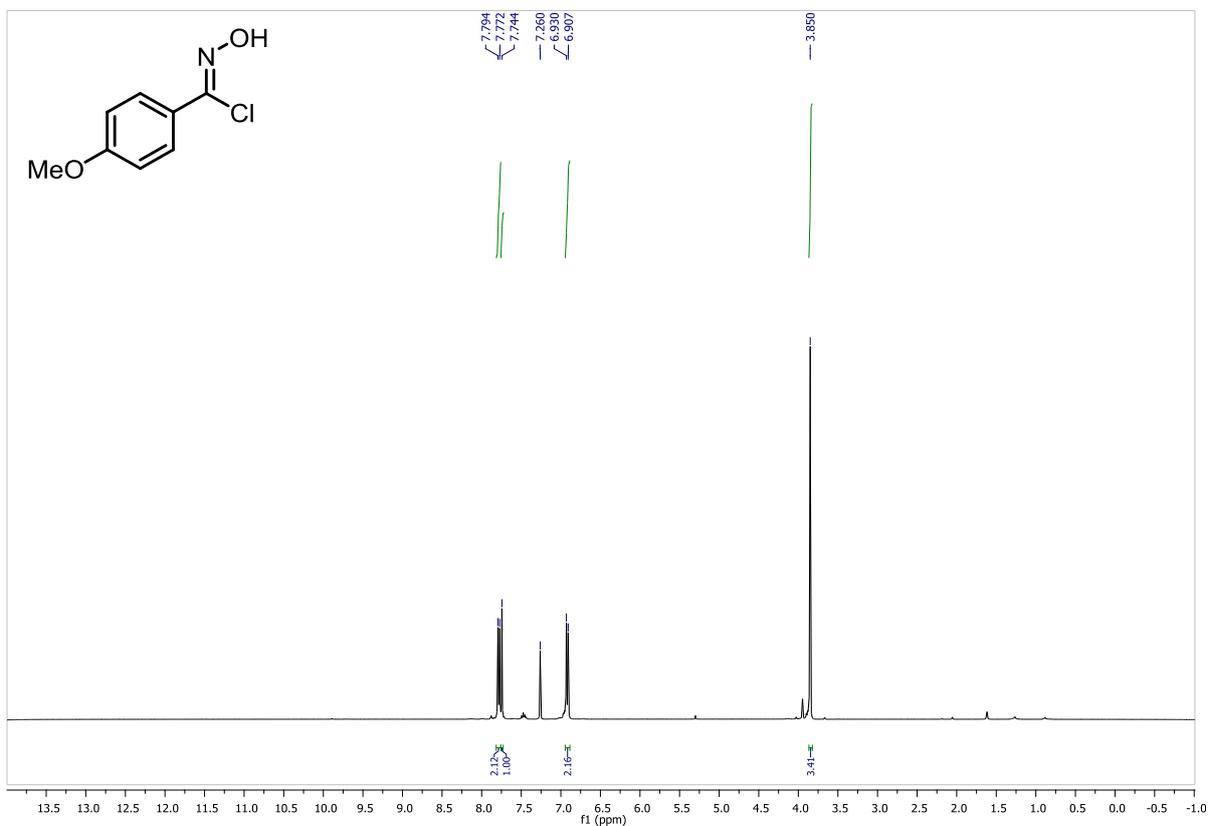


<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:



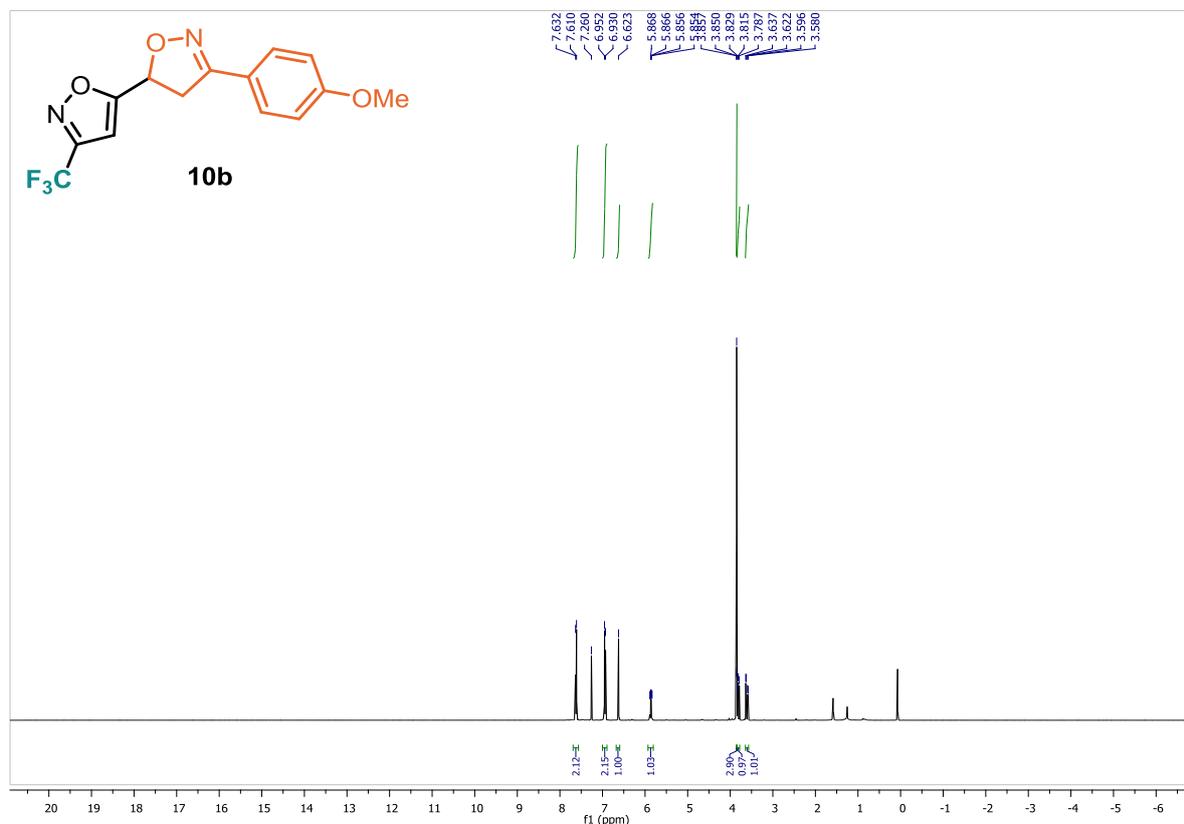
***N*-hydroxy-4-methoxybenzimidoyl chloride:**

**<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:**

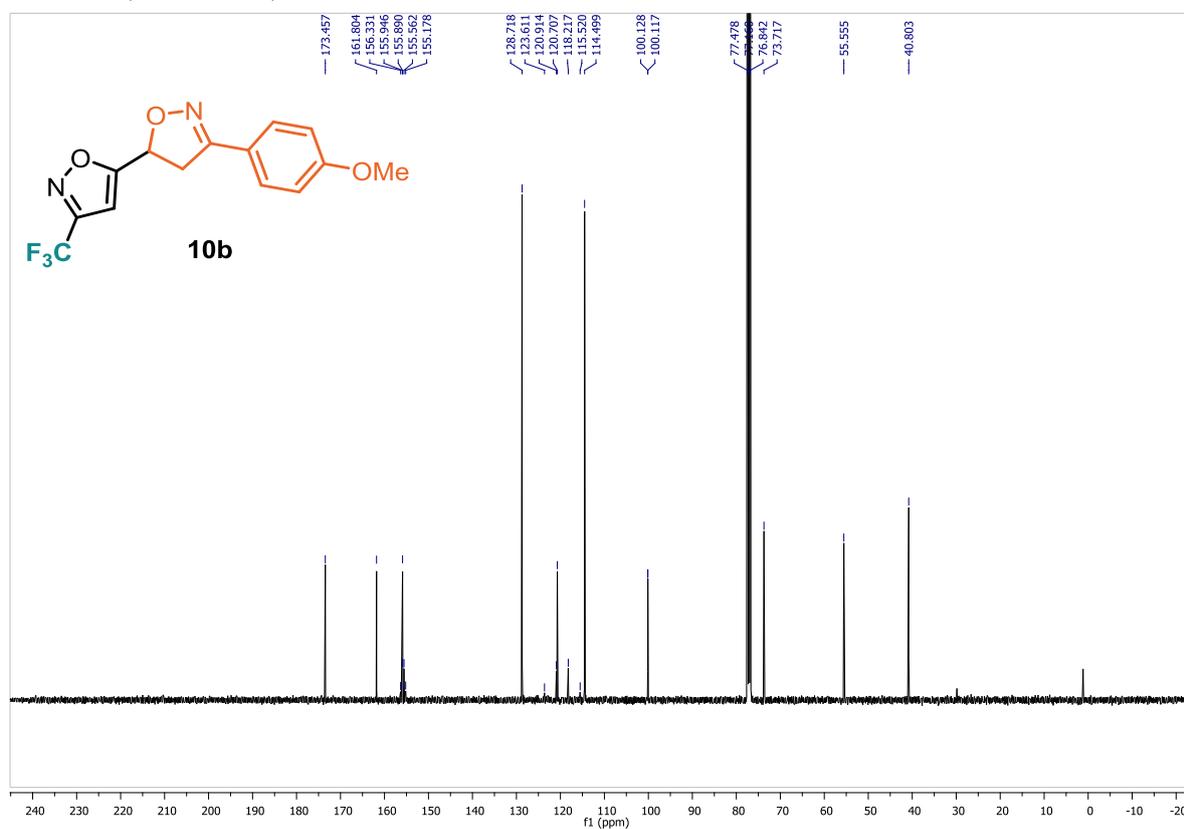


### 3-(4-methoxyphenyl)-3'-(trifluoromethyl)-4,5-dihydro-5,5'-biisoxazole (10b):

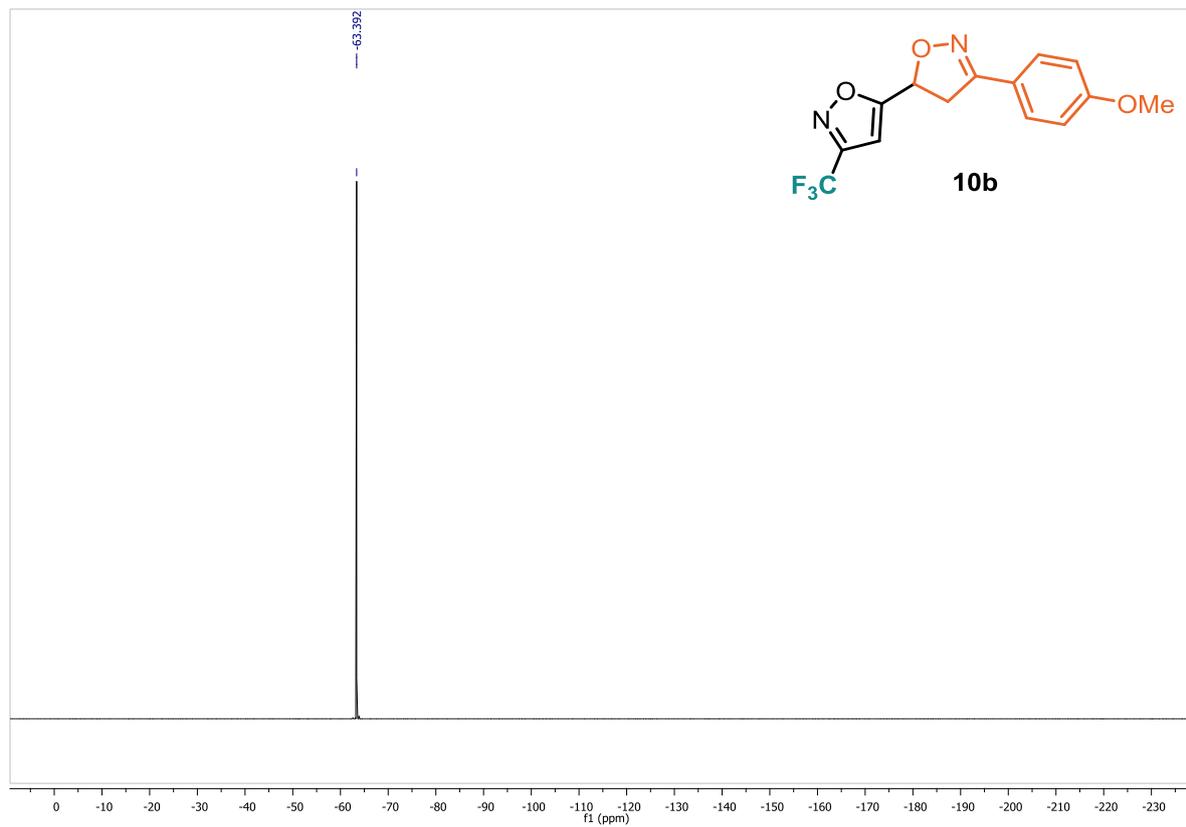
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:

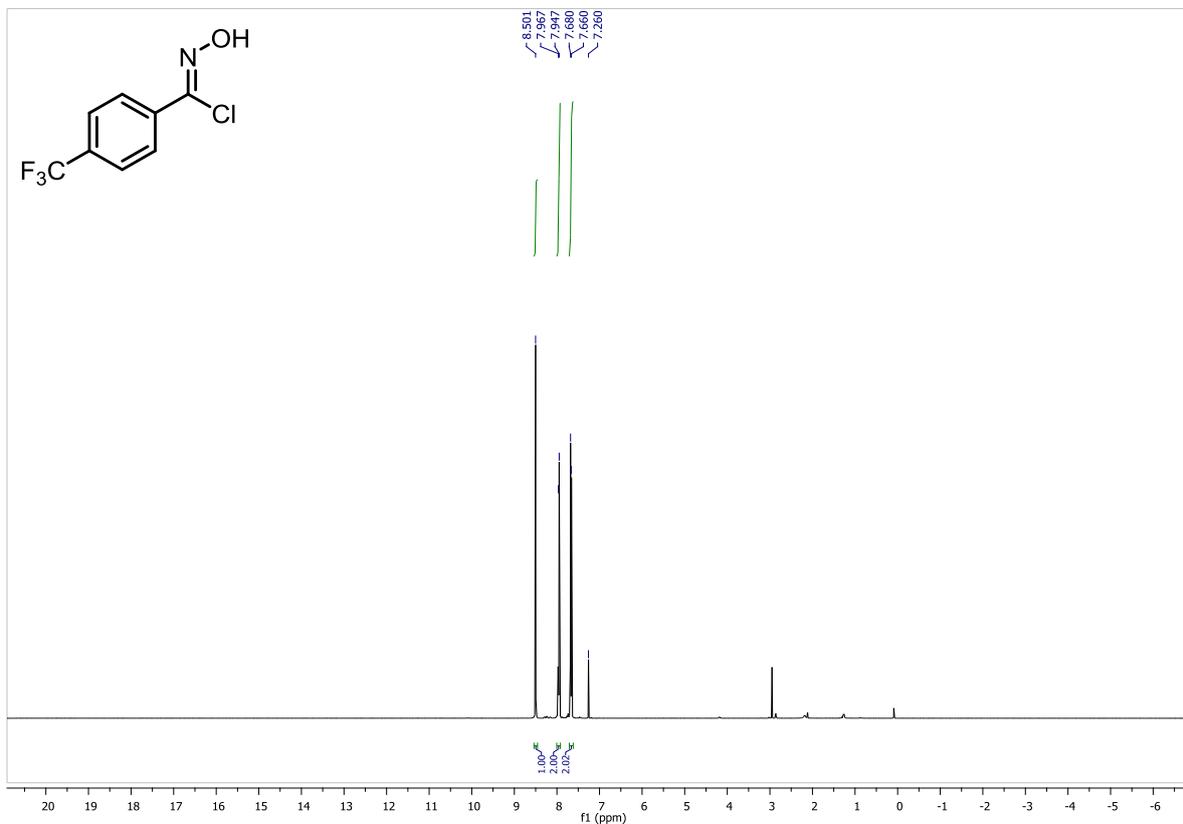


<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:

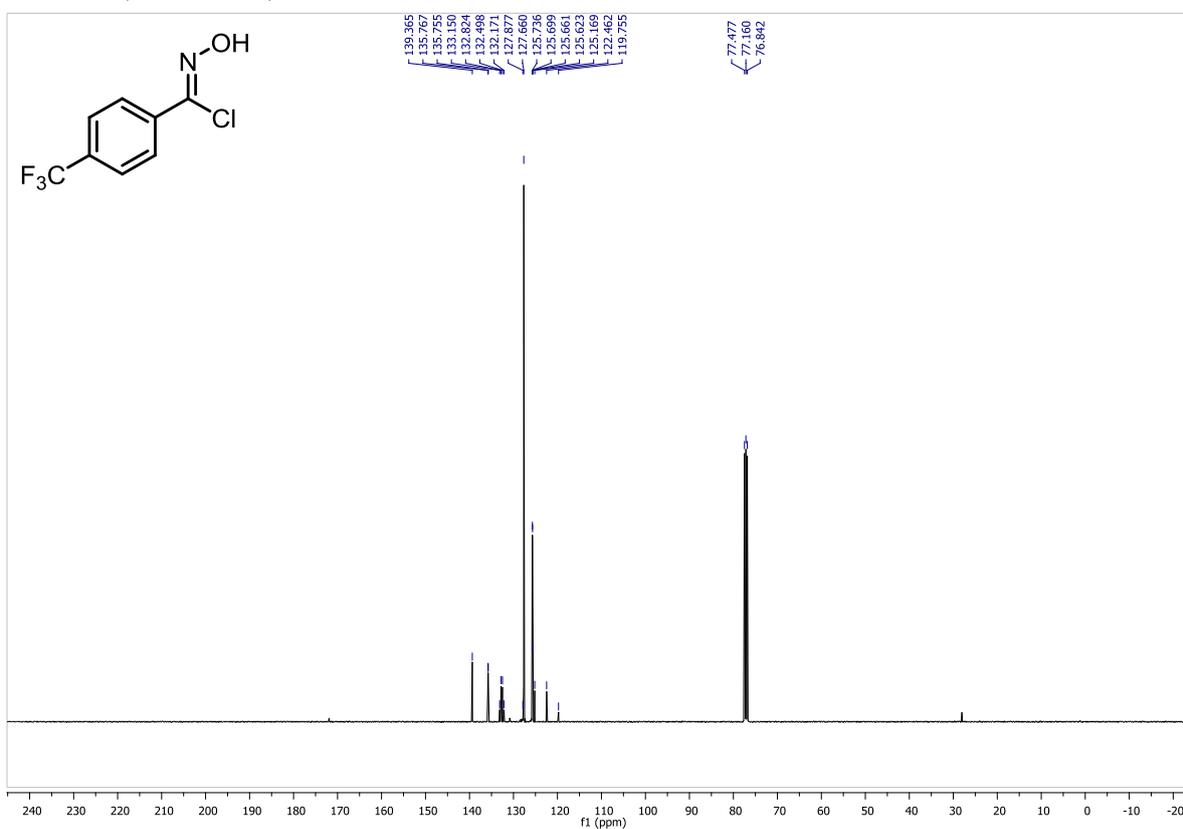


**N-hydroxy-4-(trifluoromethyl)benzimidoyl chloride:**

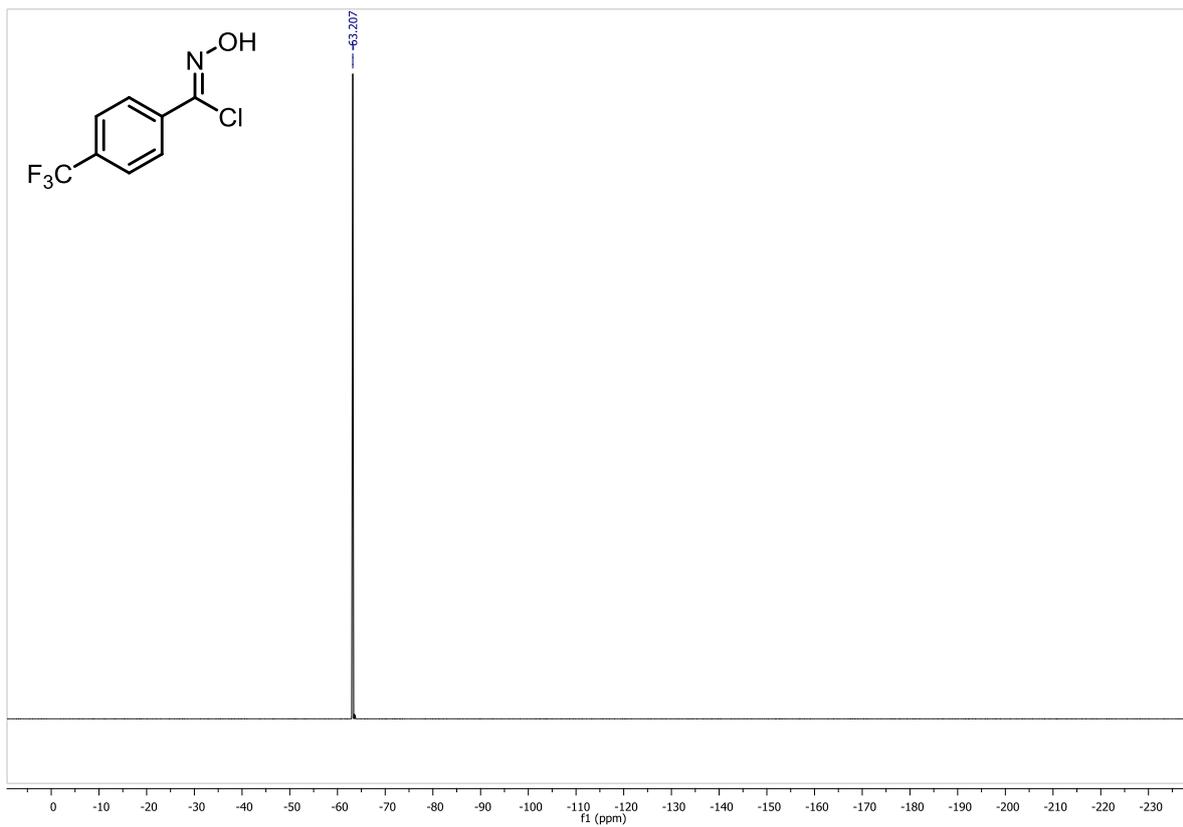
**<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:**



**<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:**

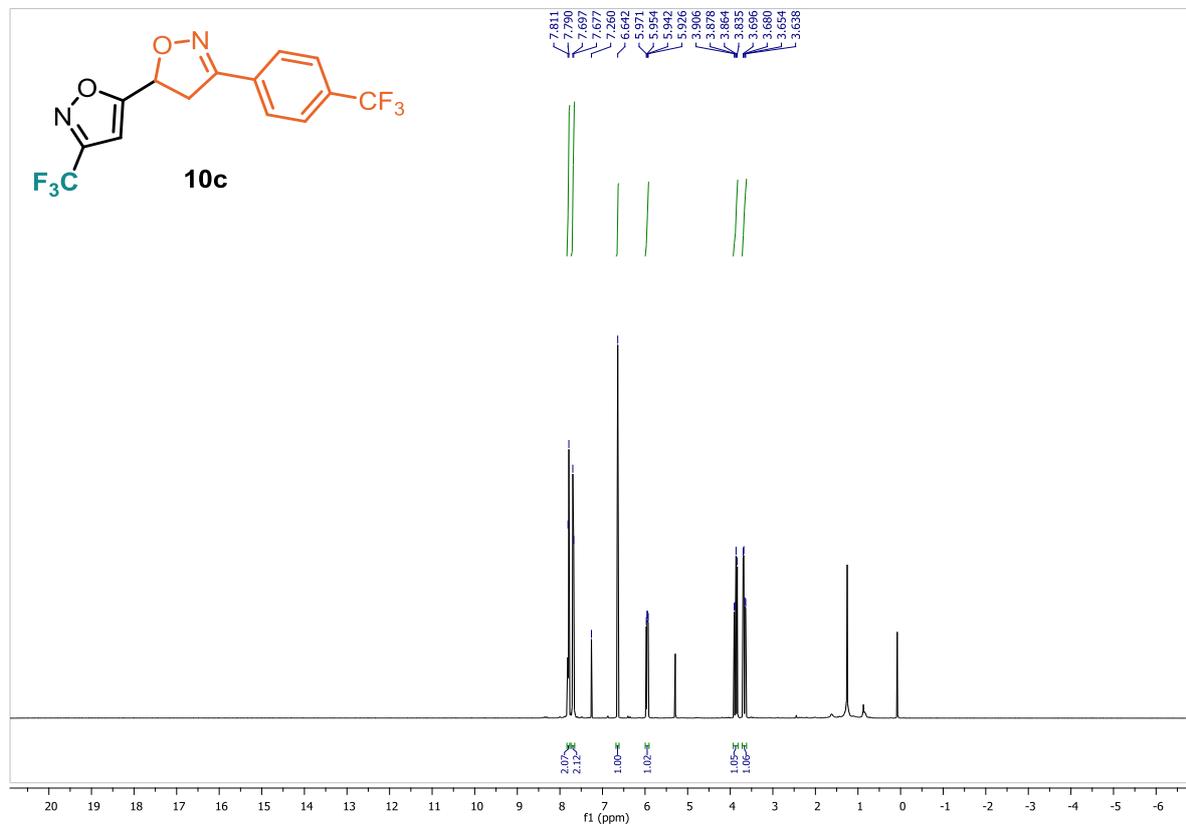


**$^{19}\text{F}$  NMR, 376 MHz,  $\text{CDCl}_3$ :**

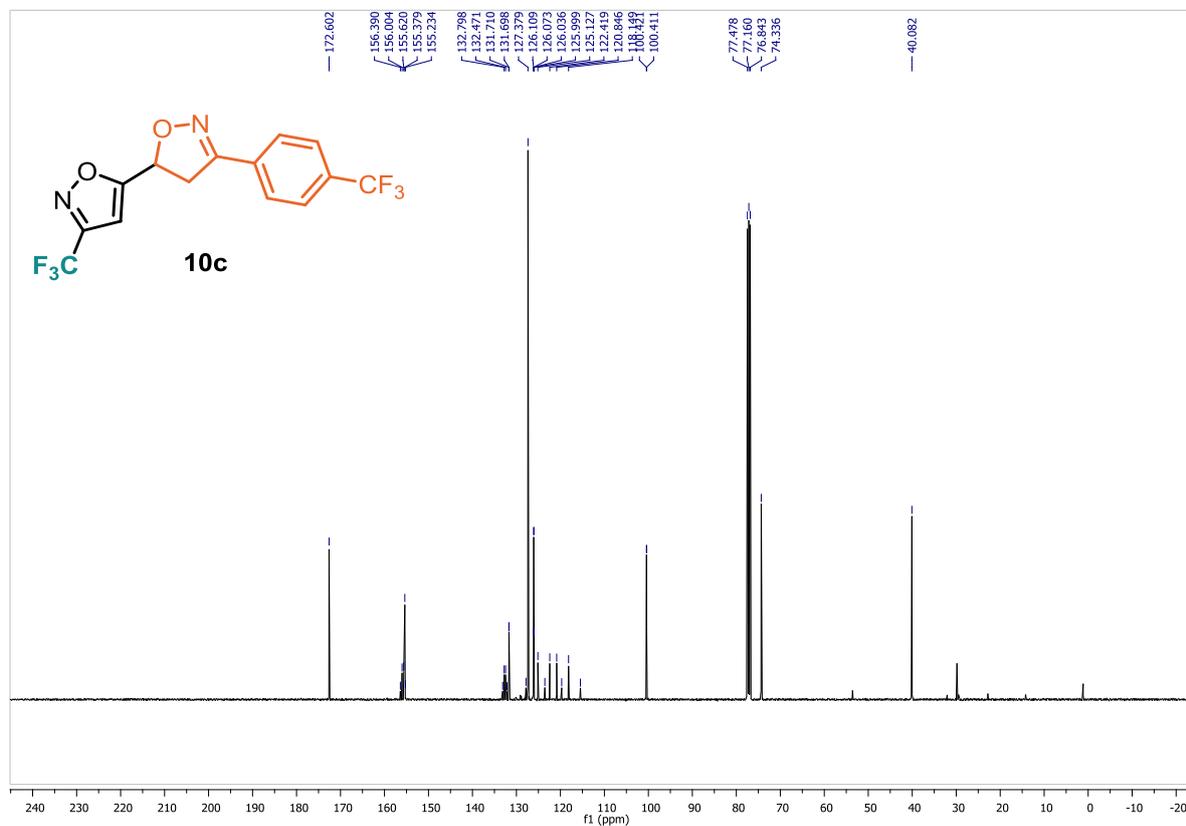


**3'-(trifluoromethyl)-3-(4-(trifluoromethyl)phenyl)-4,5-dihydro-5,5'-biisoxazole (10c):**

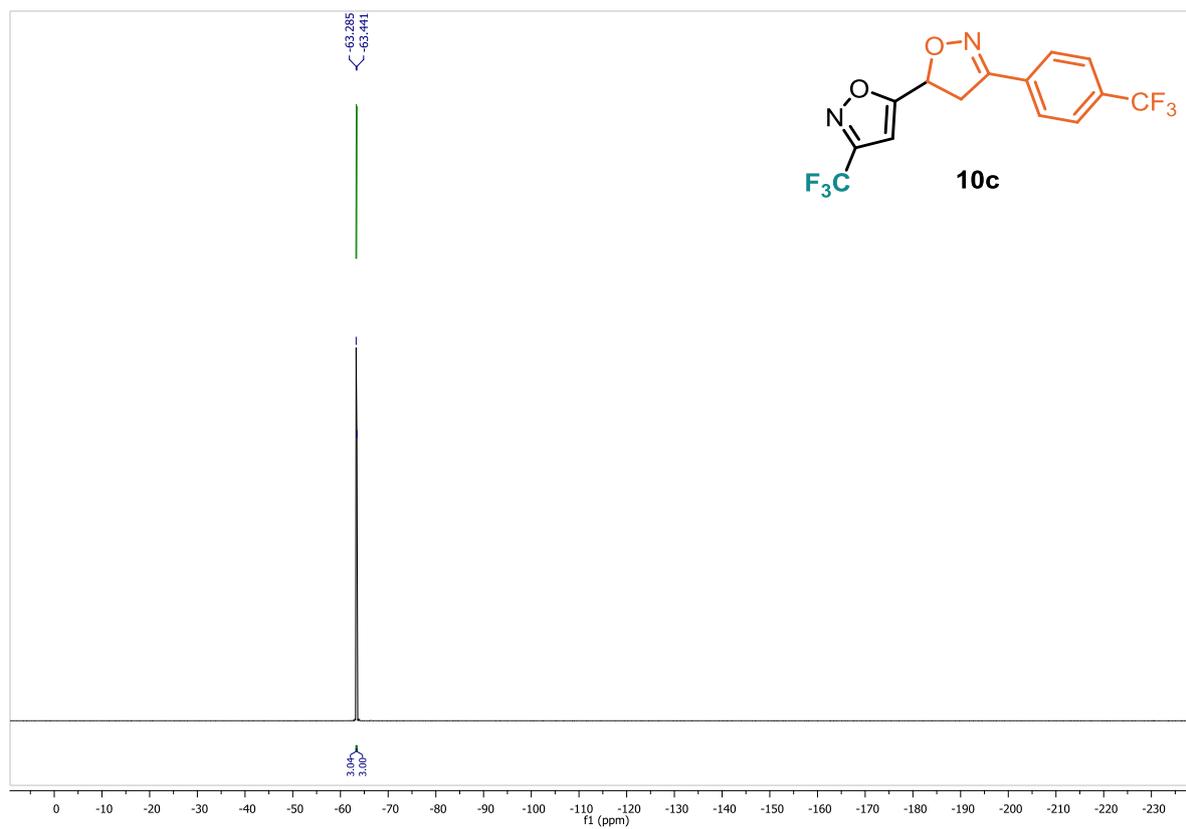
**<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:**



**<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:**

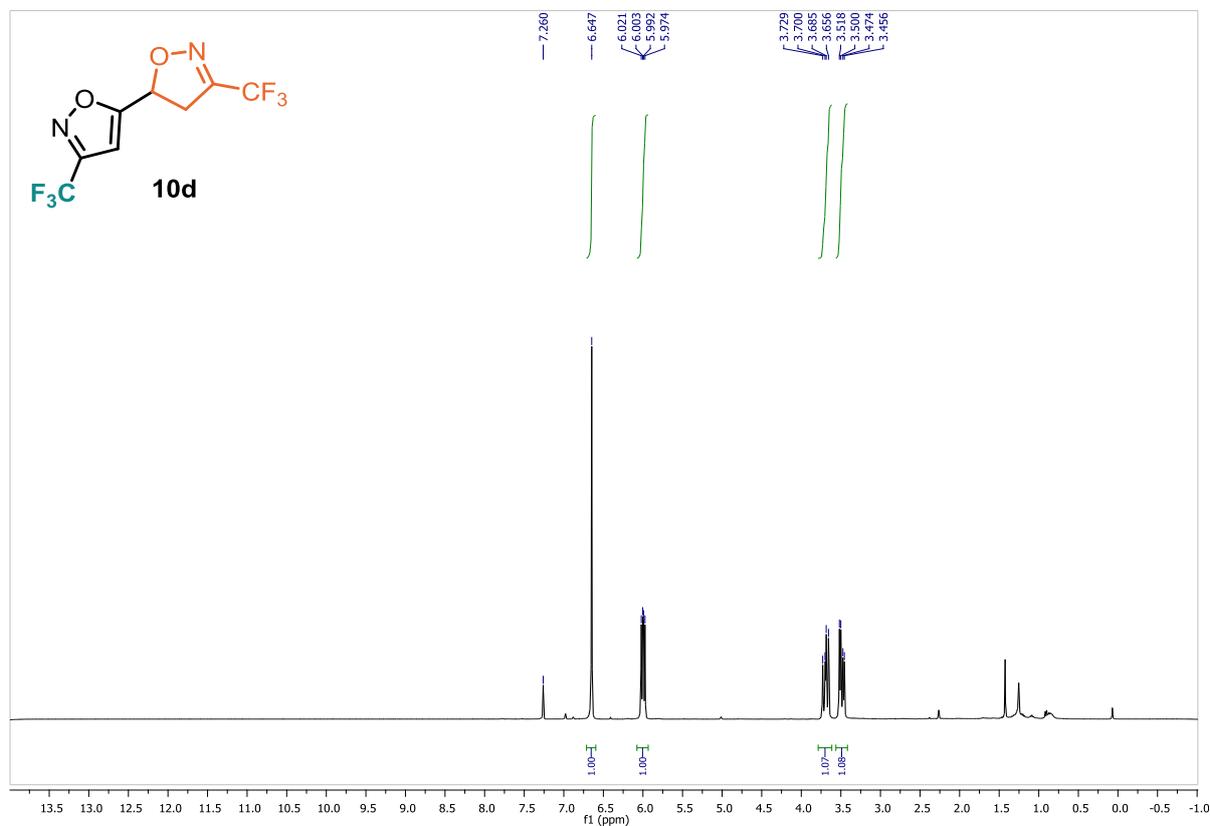


<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:

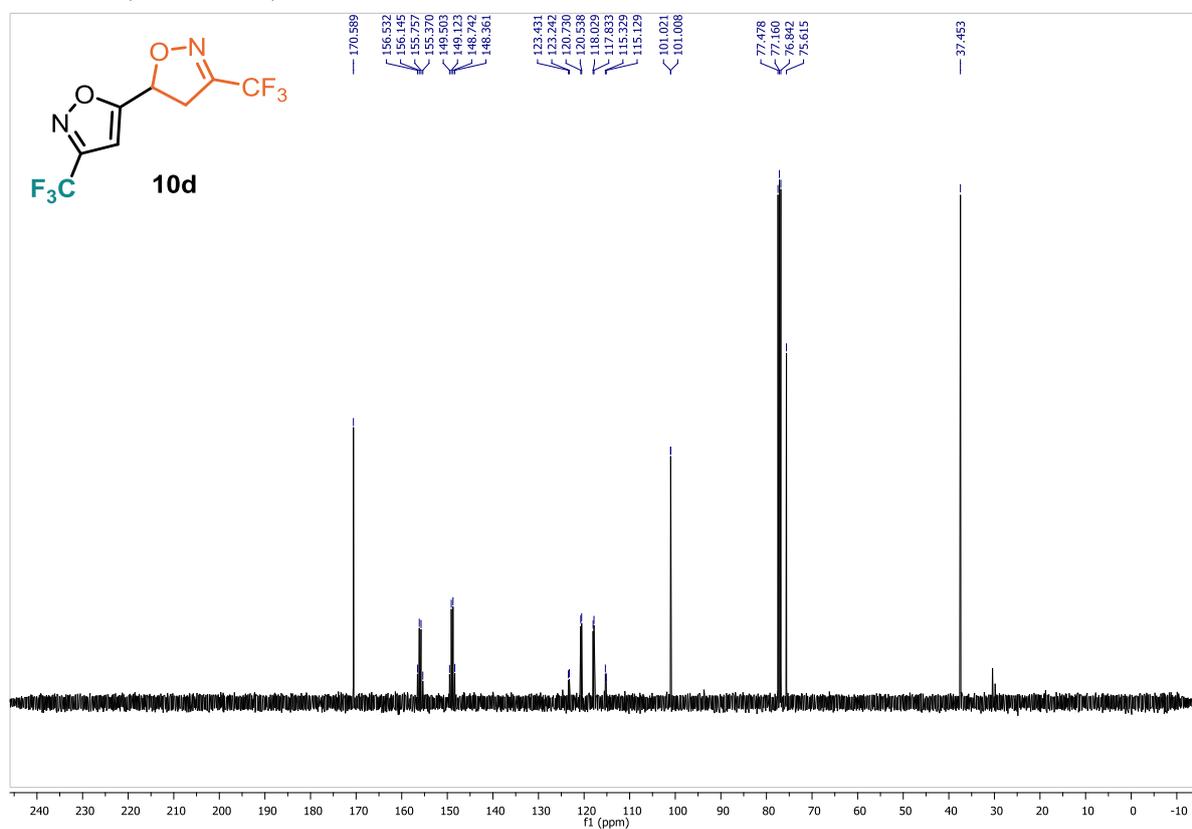


### 3,3'-bis(trifluoromethyl)-4,5-dihydro-5,5'-biisoxazole (10d):

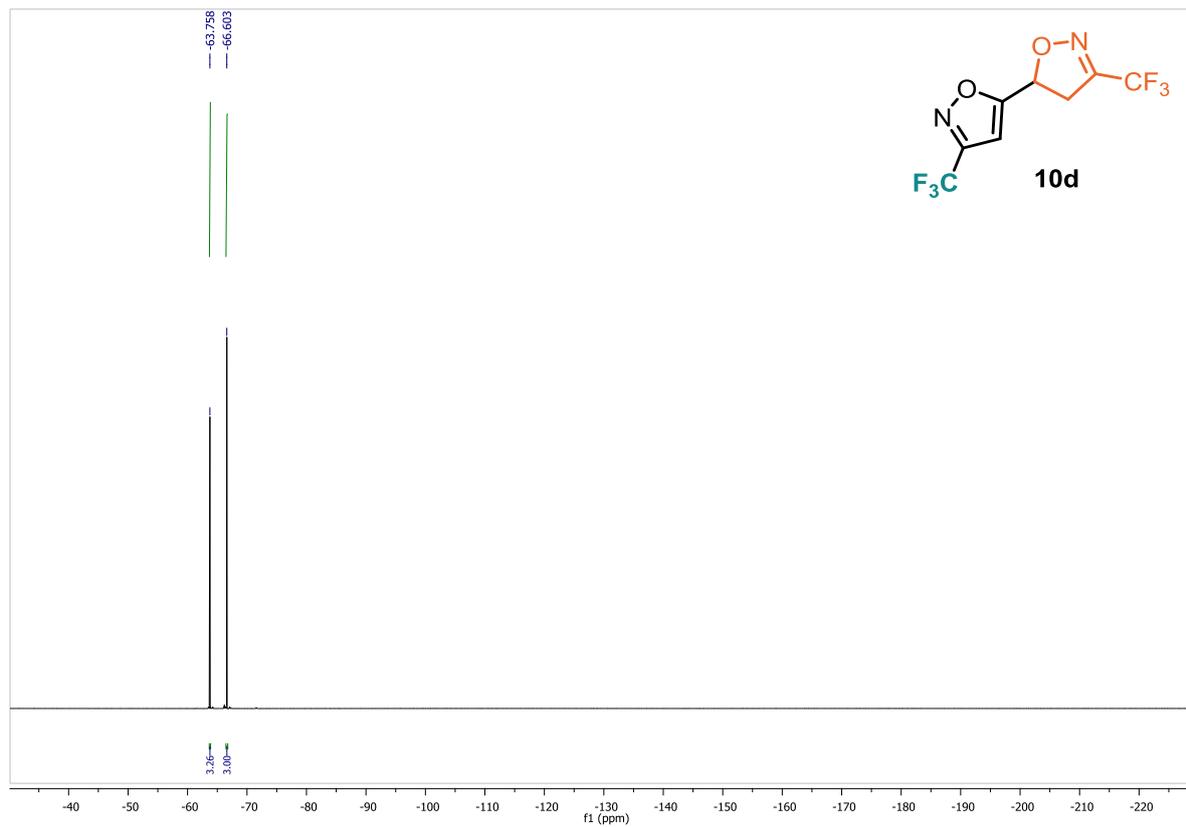
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:

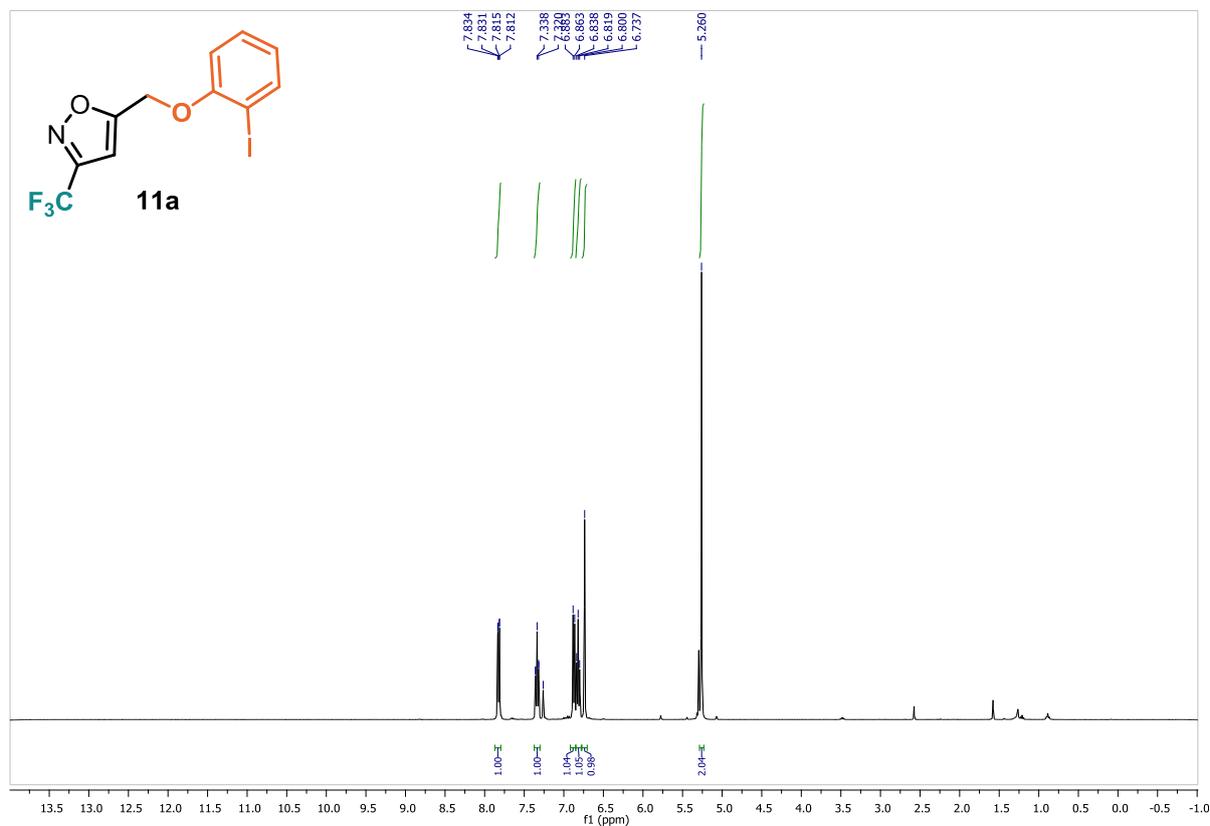


**<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:**

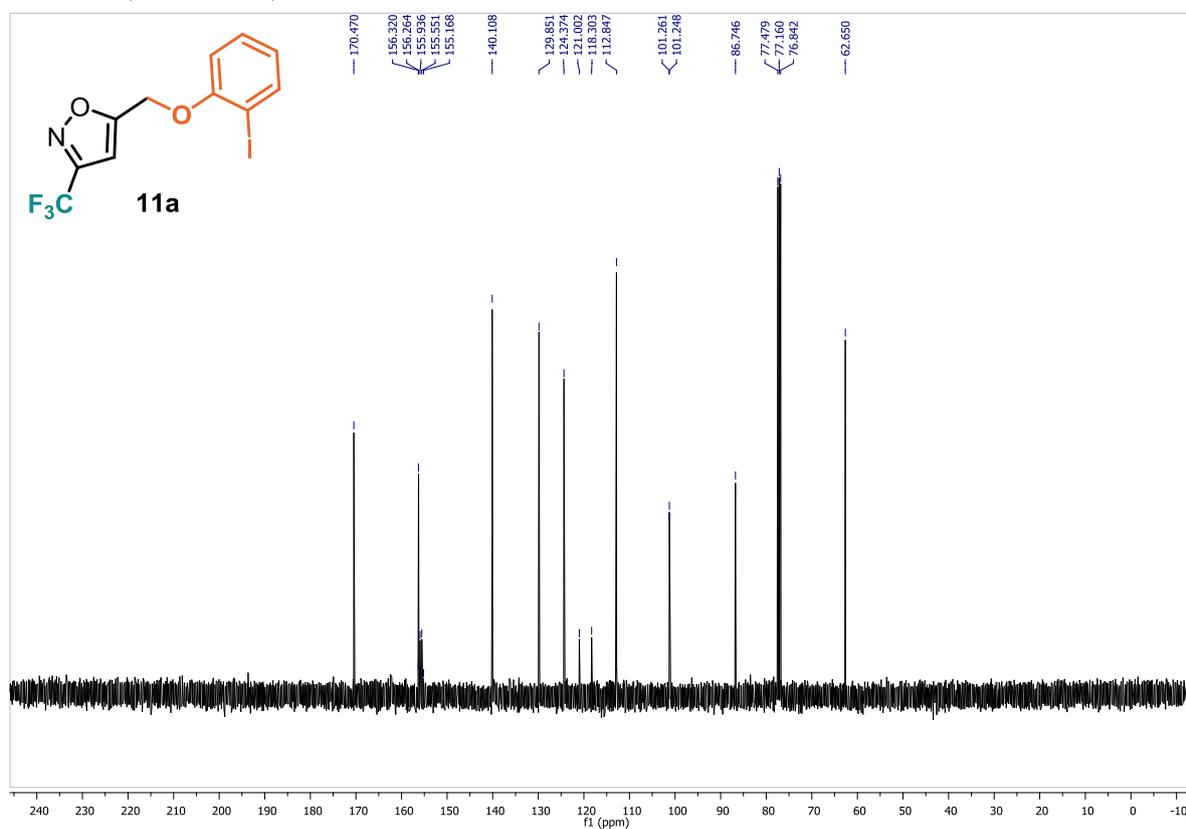


### 5-((2-iodophenoxy)methyl)-3-(trifluoromethyl)isoxazole (11a):

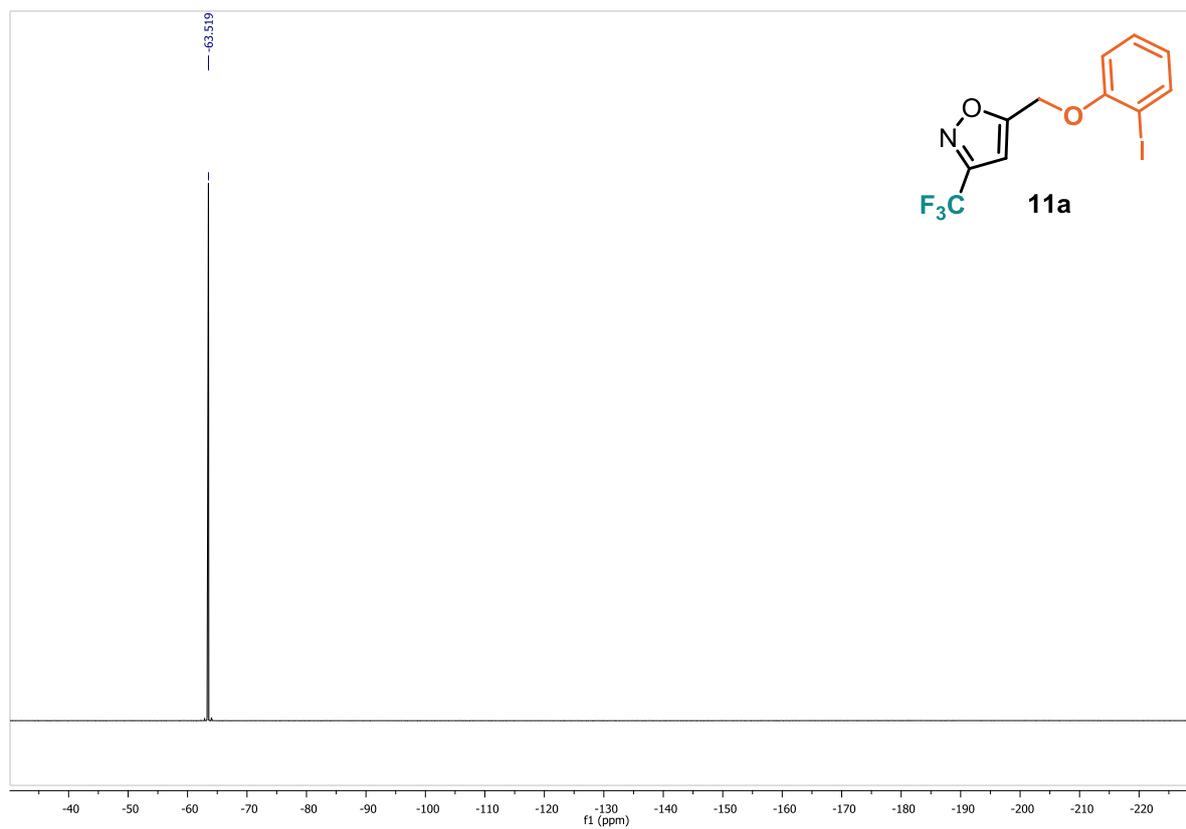
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:

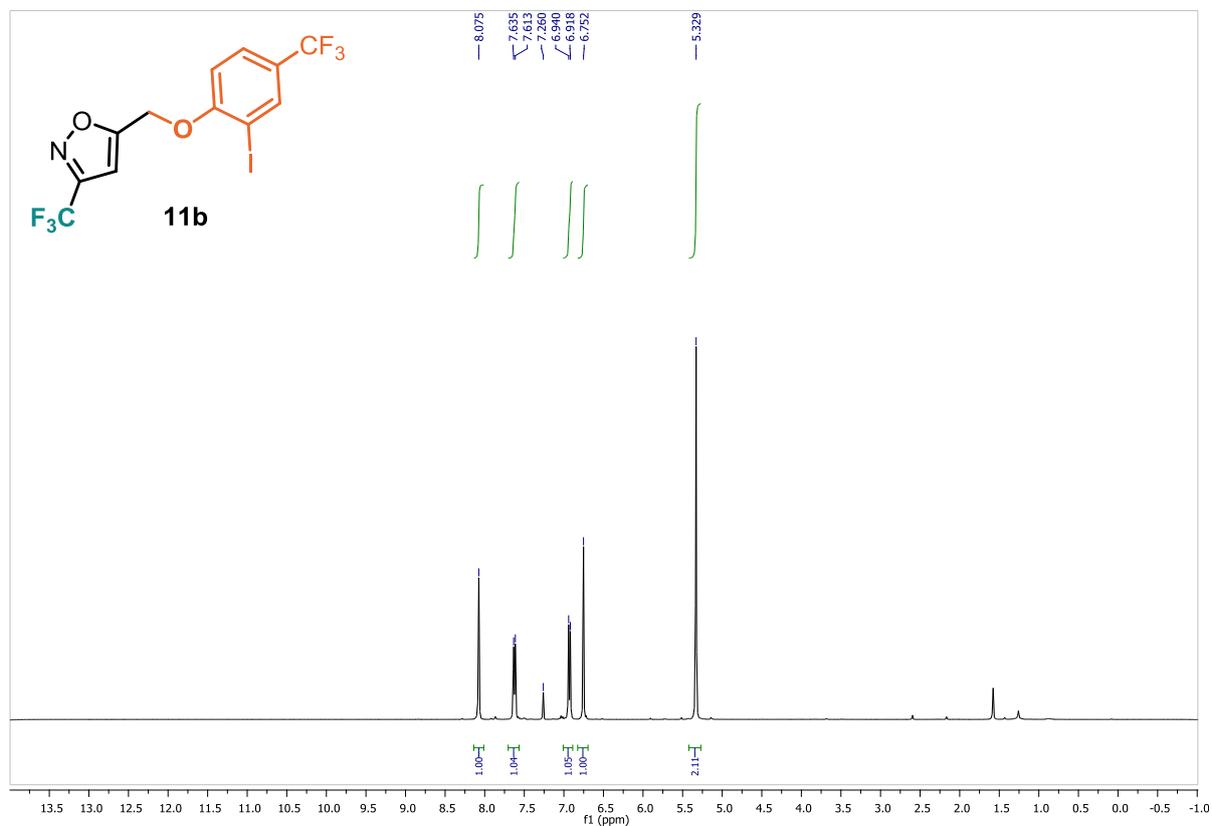


<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:

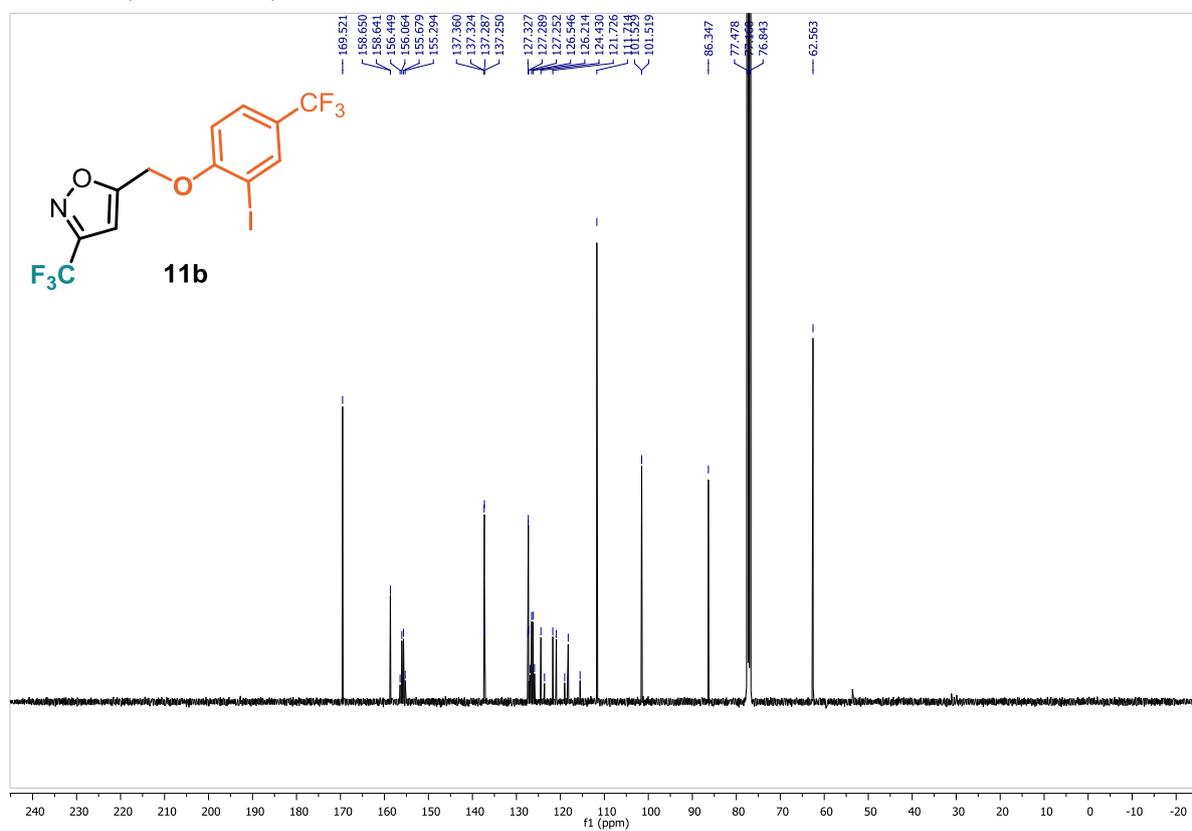


### 5-((2-iodo-4-(trifluoromethyl)phenoxy)methyl)-3-(trifluoromethyl)isoxazole (11b):

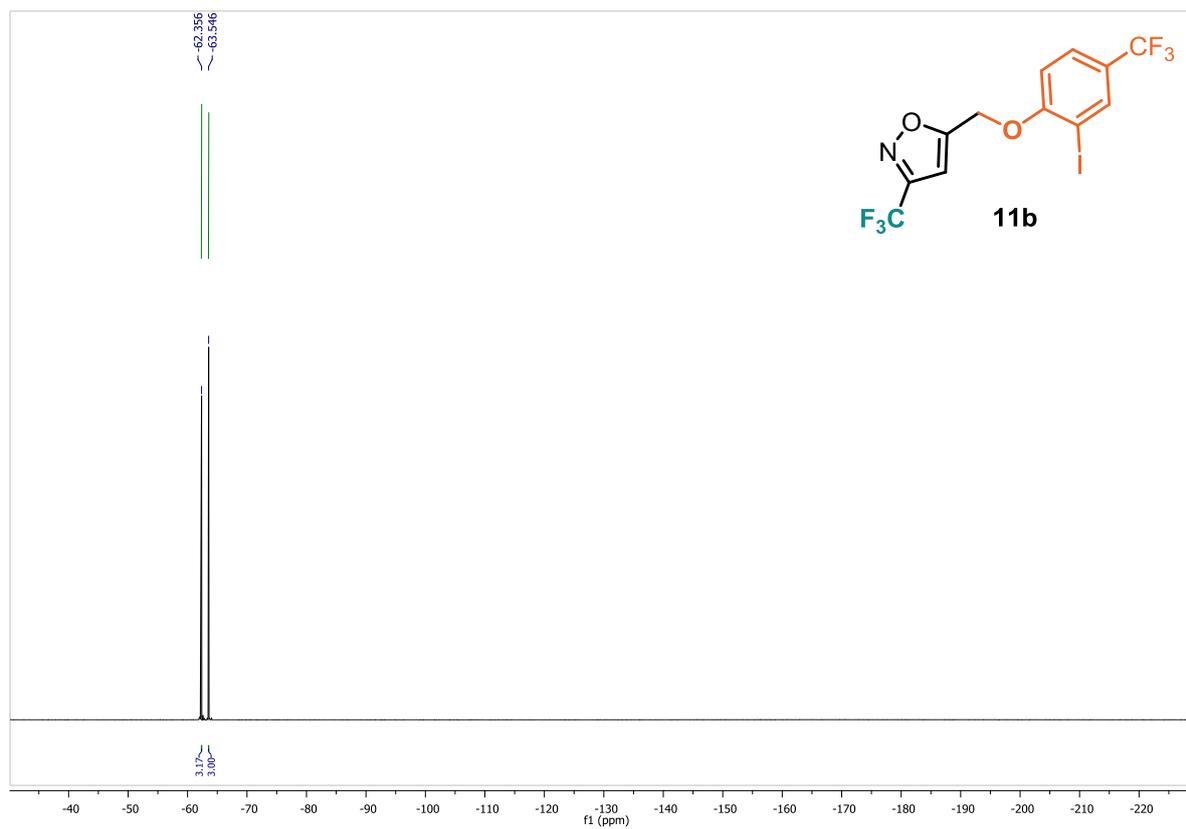
$^1\text{H}$  NMR, 400 MHz,  $\text{CDCl}_3$ :



$^{13}\text{C}$  NMR, 100 MHz,  $\text{CDCl}_3$ :

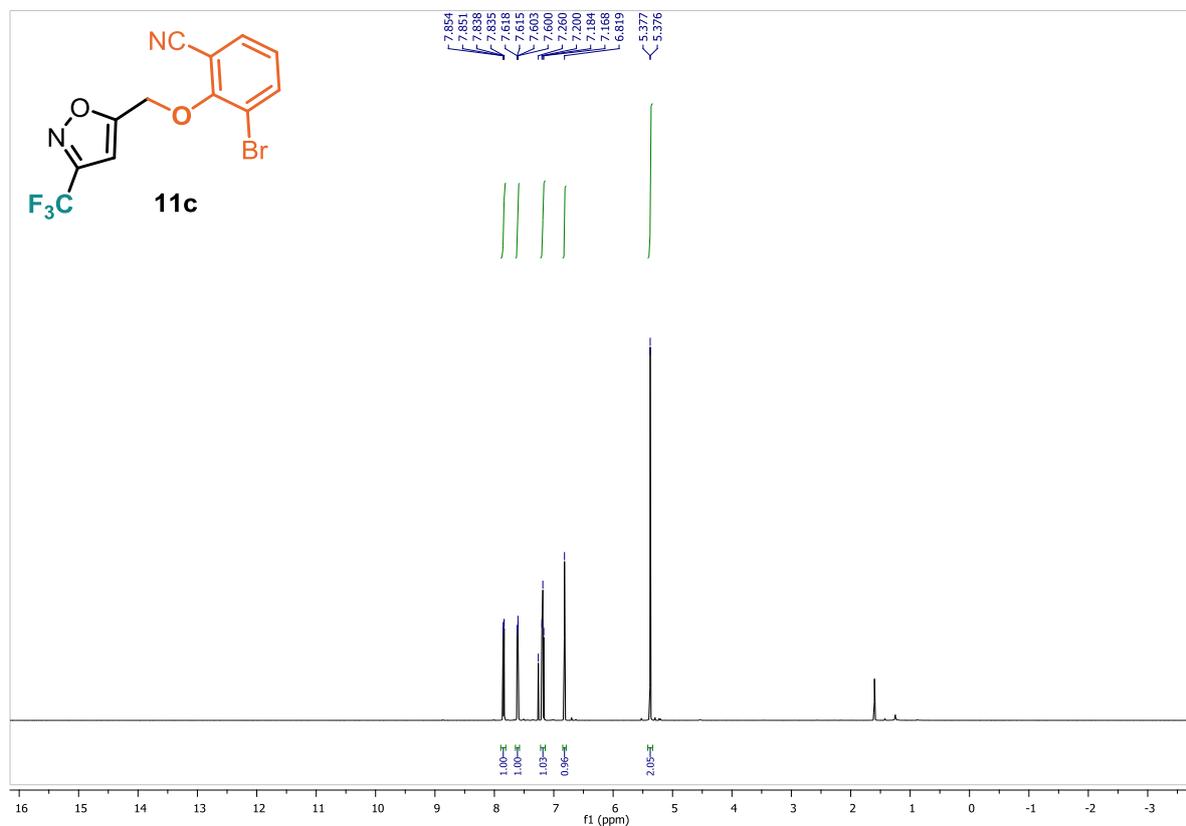


<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:

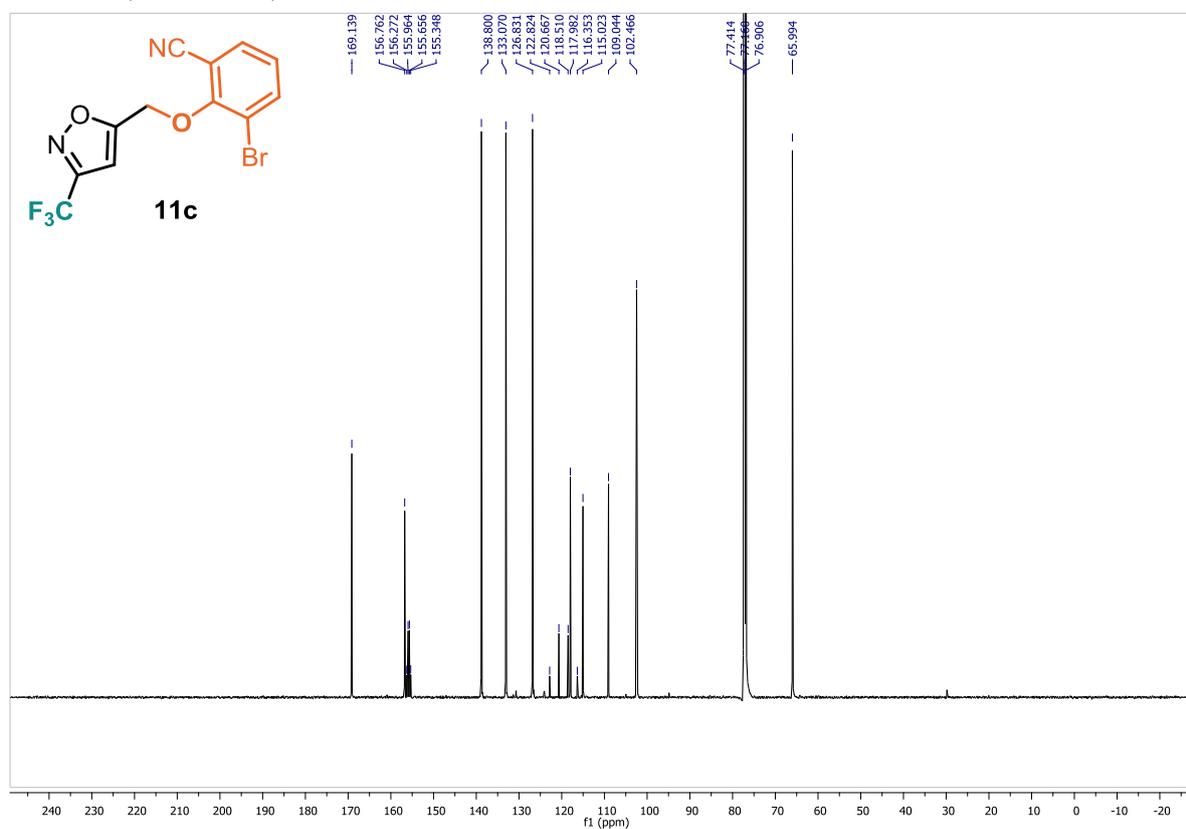


### 3-bromo-2-((3-(trifluoromethyl)isoxazol-5-yl)methoxy)benzonitrile (11c):

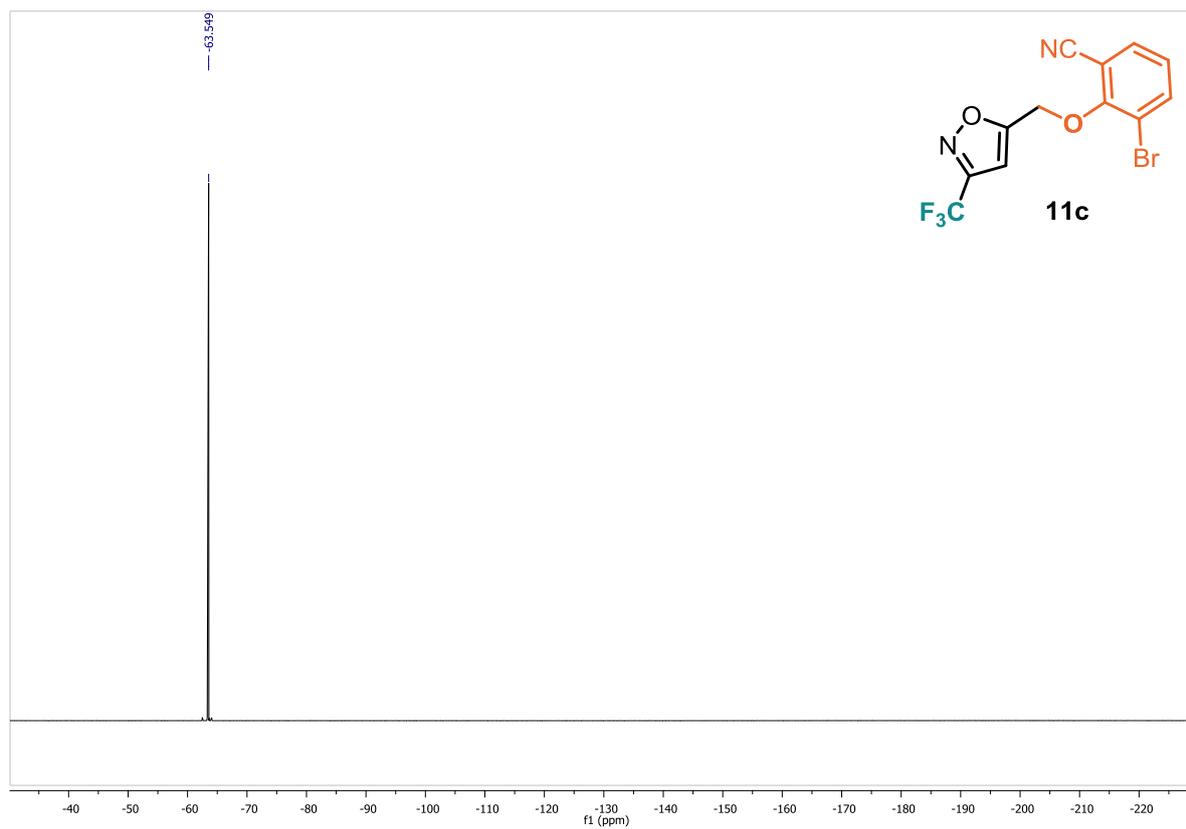
$^1\text{H}$  NMR, 500 MHz,  $\text{CDCl}_3$ :



$^{13}\text{C}$  NMR, 125 MHz,  $\text{CDCl}_3$ :

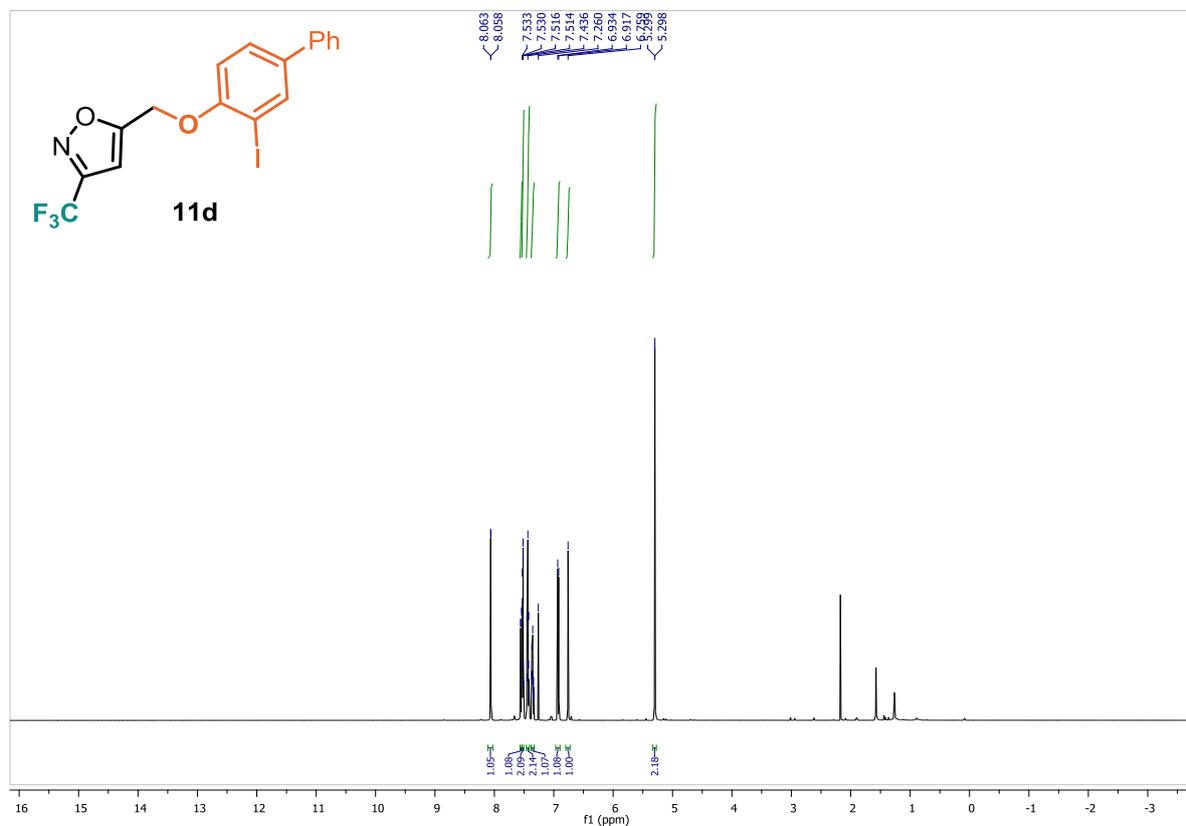


<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:

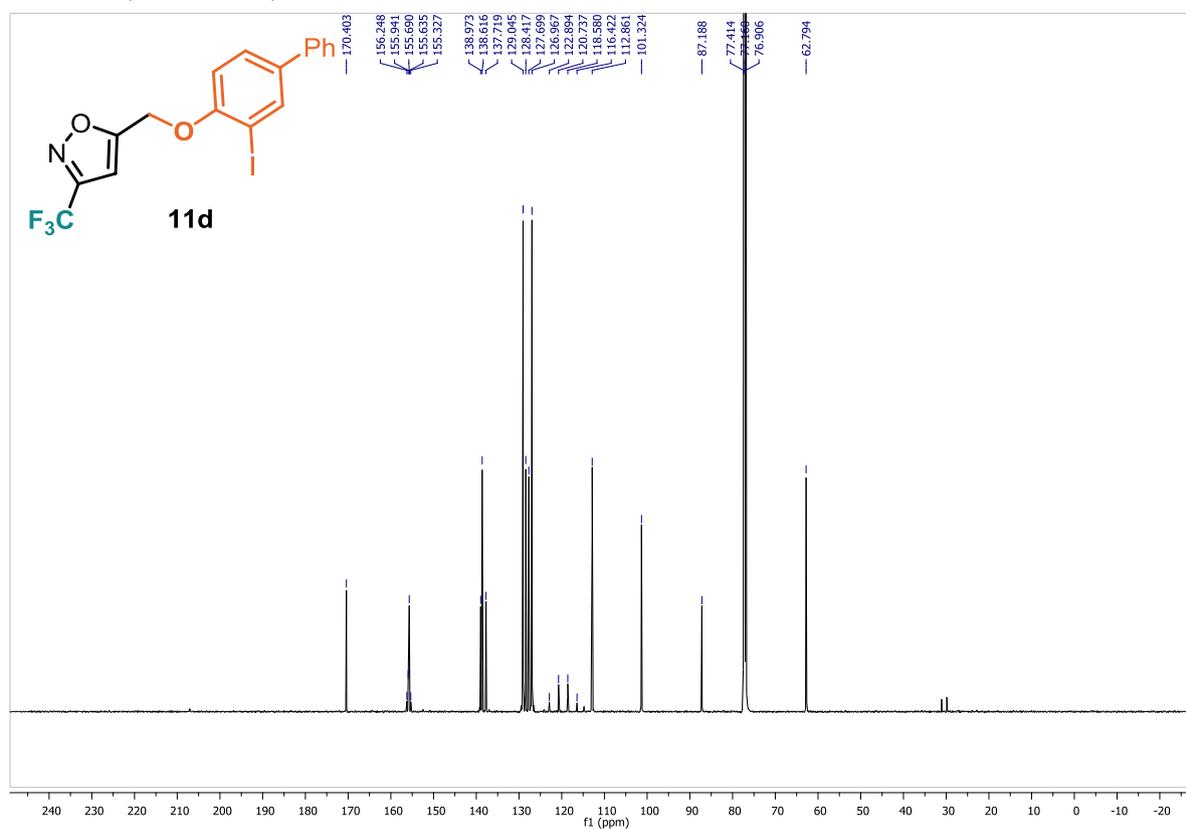


**5-(((3-iodo-[1,1'-biphenyl]-4-yl)oxy)methyl)-3-(trifluoromethyl)isoxazole (11d):**

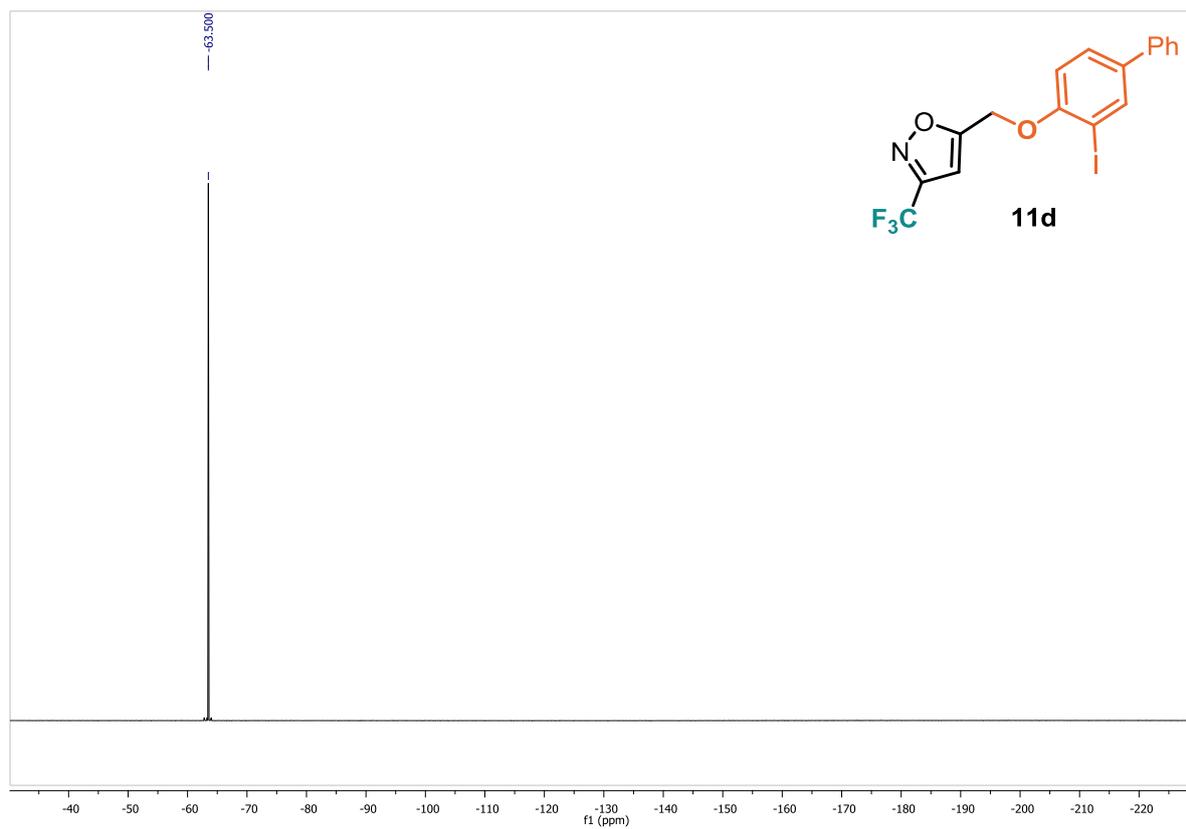
**<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>:**



**<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>:**

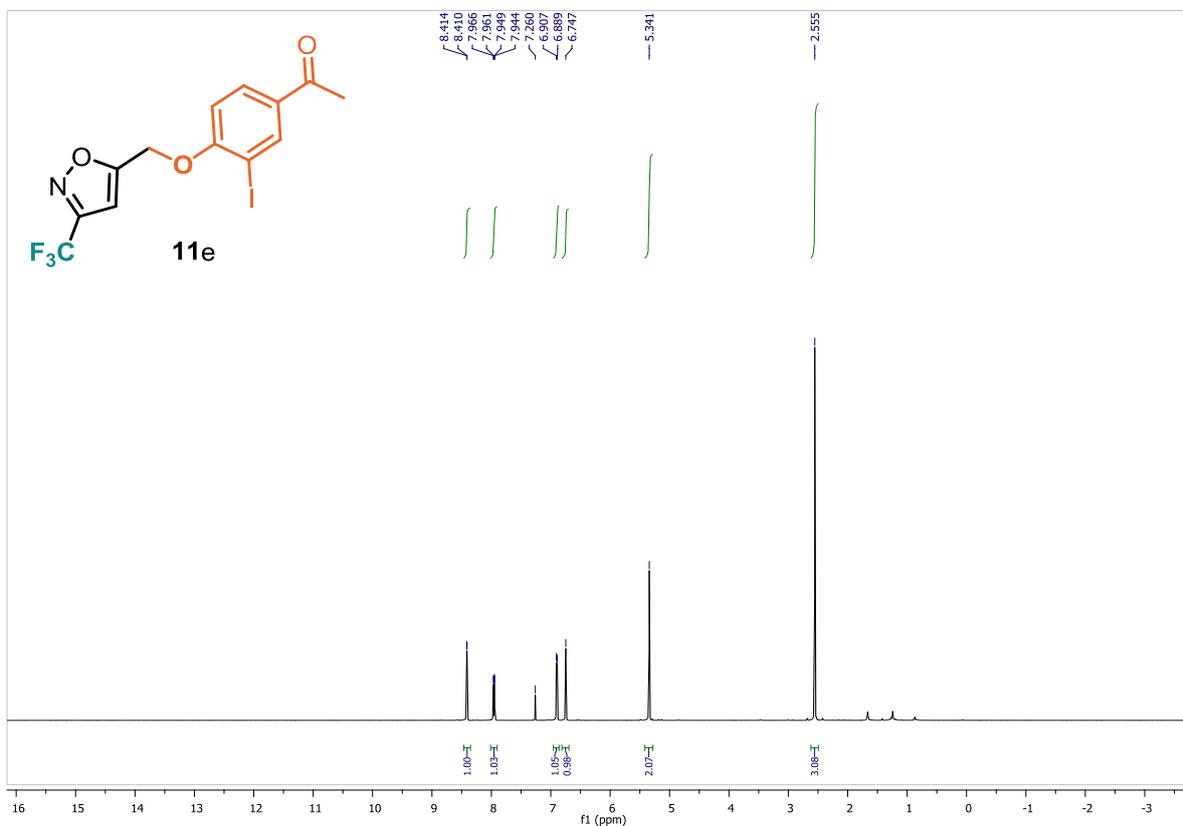


<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:

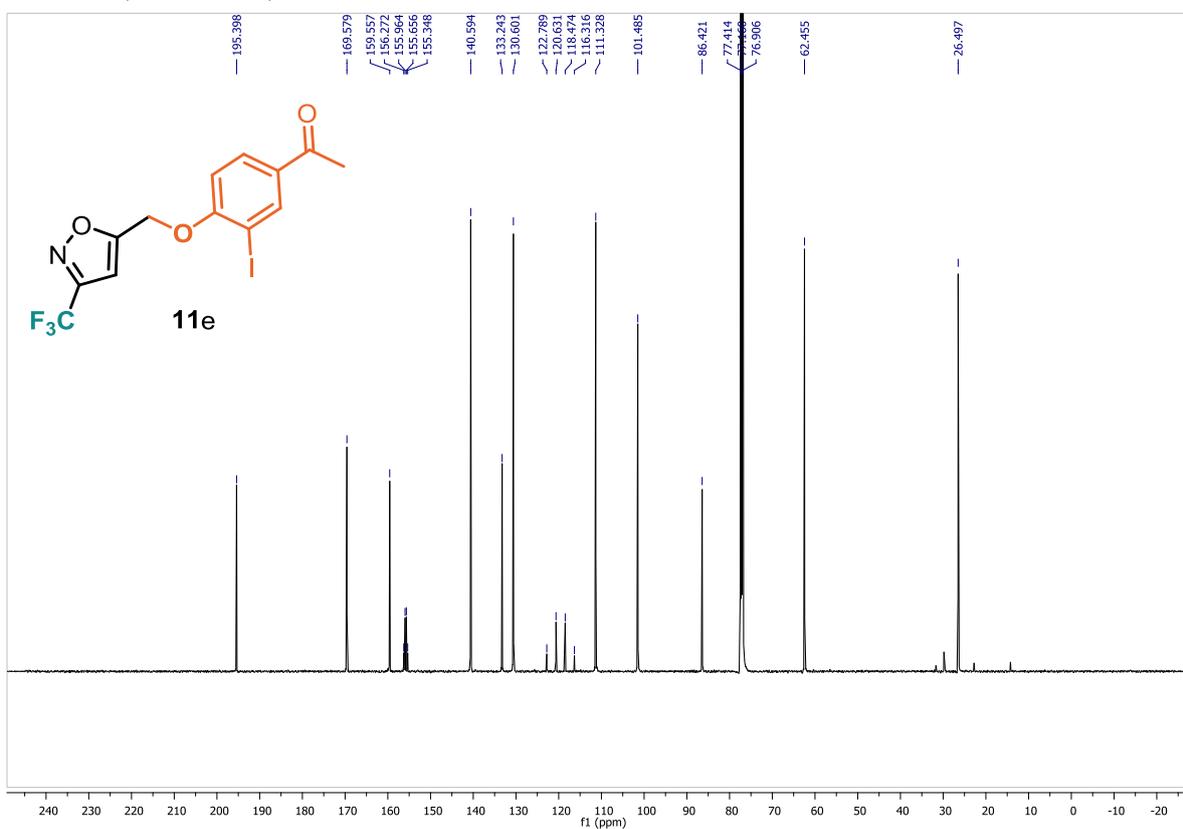


# 1-(3-iodo-4-((3-(trifluoromethyl)isoxazol-5-yl)methoxy)phenyl)ethan-1-one (11e):

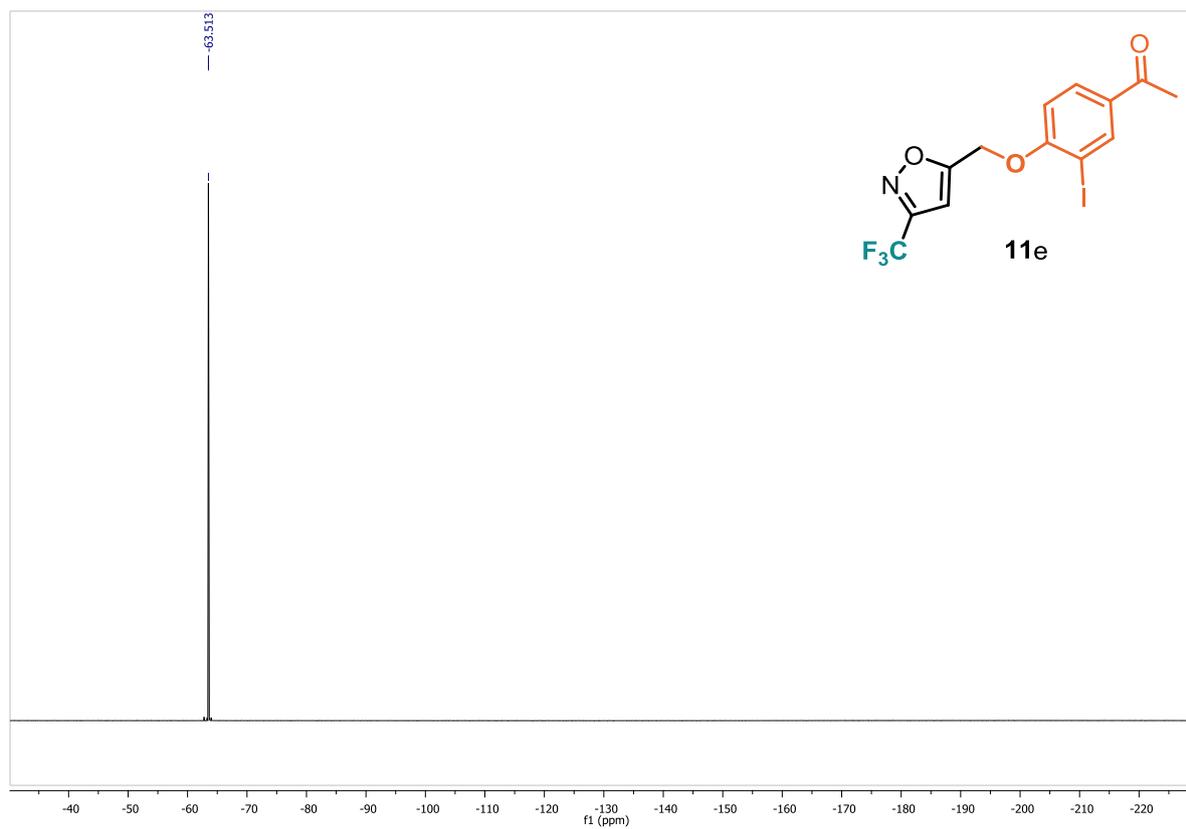
$^1\text{H}$  NMR, 500 MHz,  $\text{CDCl}_3$ :



$^{13}\text{C}$  NMR, 125 MHz,  $\text{CDCl}_3$ :

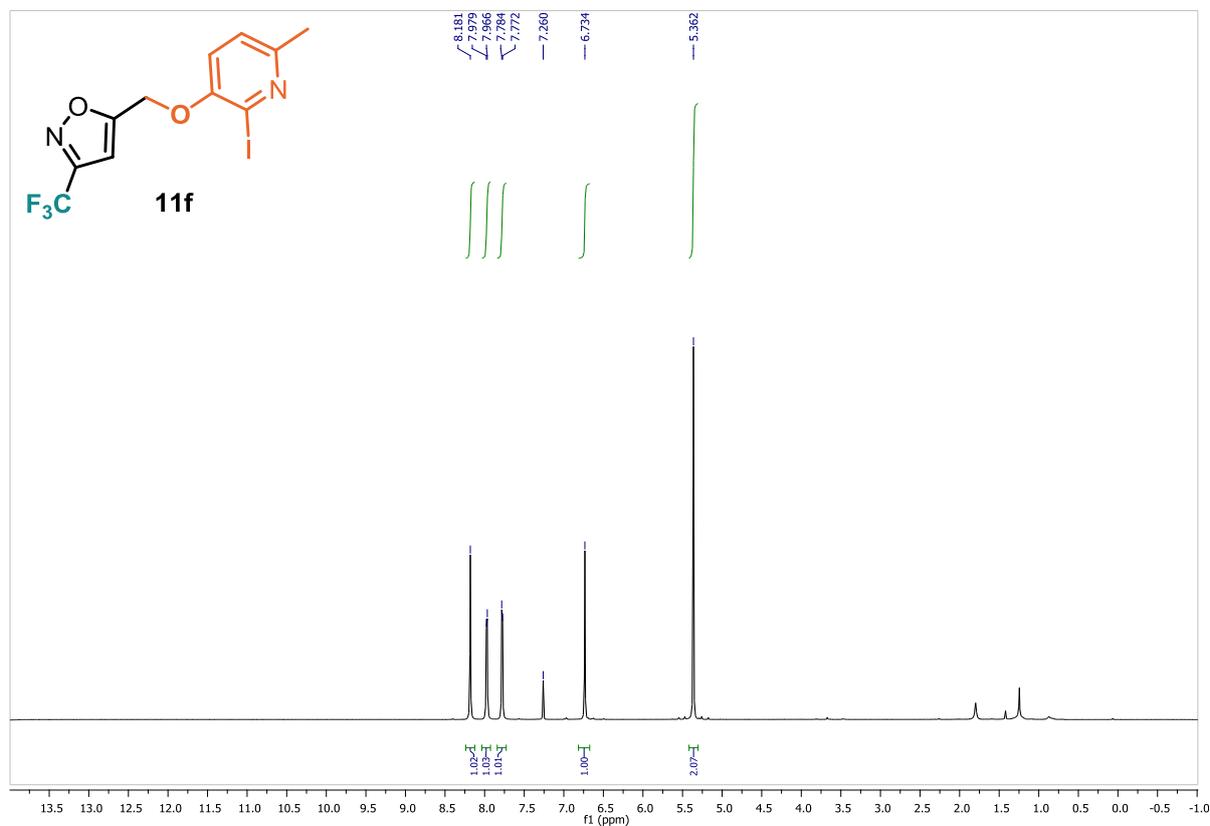


<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:

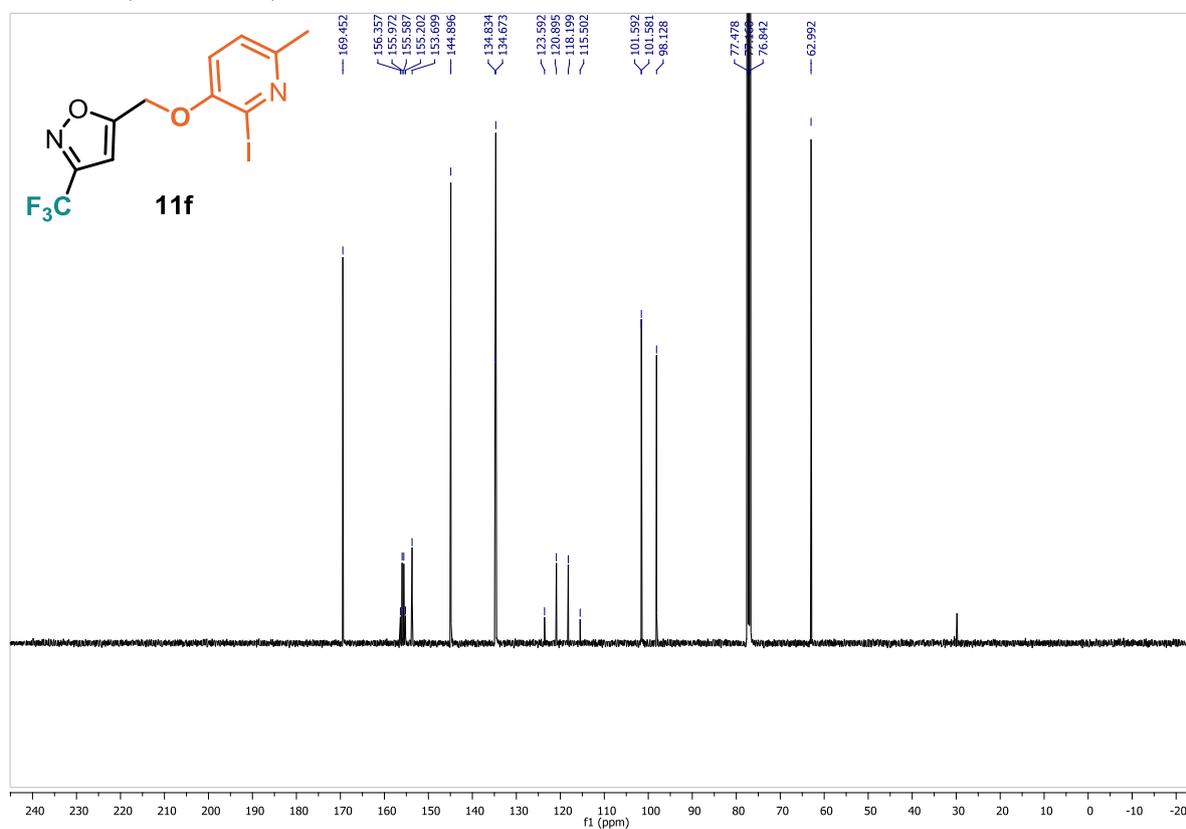


### 5-(((2-iodo-6-methylpyridin-3-yl)oxy)methyl)-3-(trifluoromethyl)isoxazole (11f):

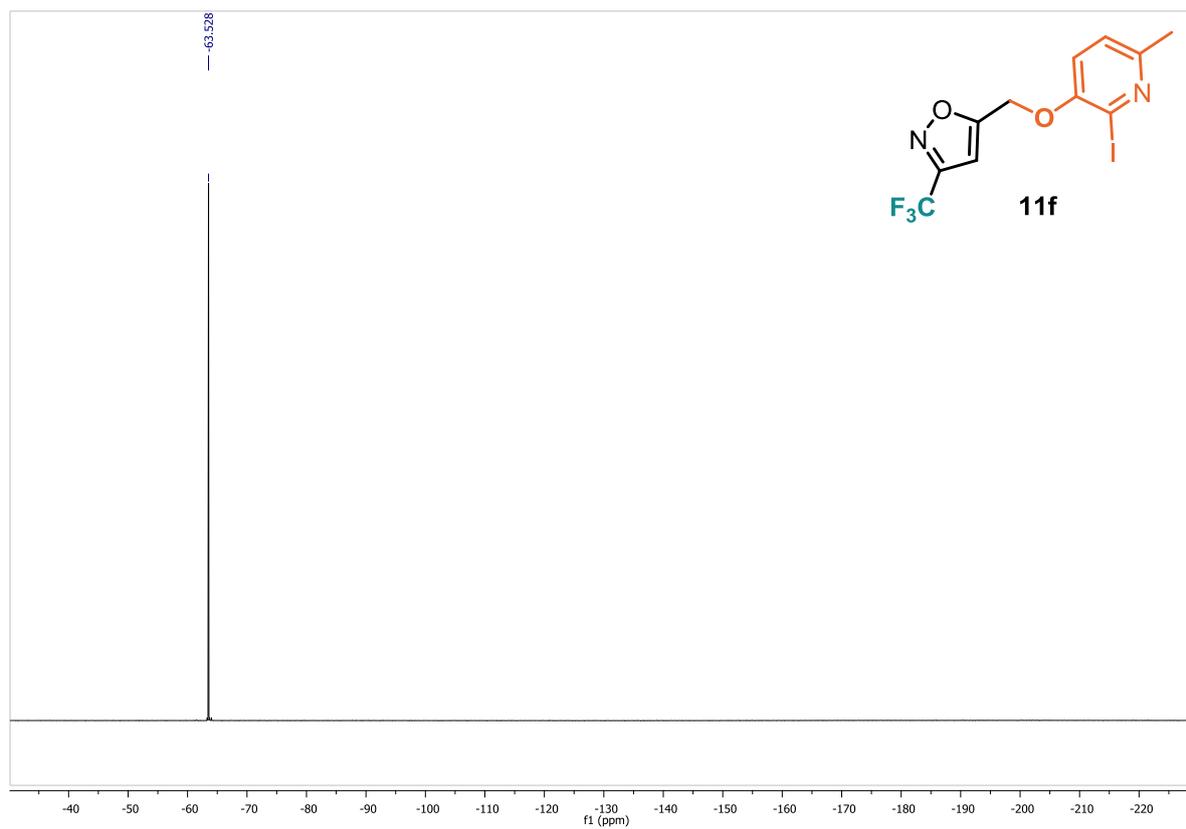
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:

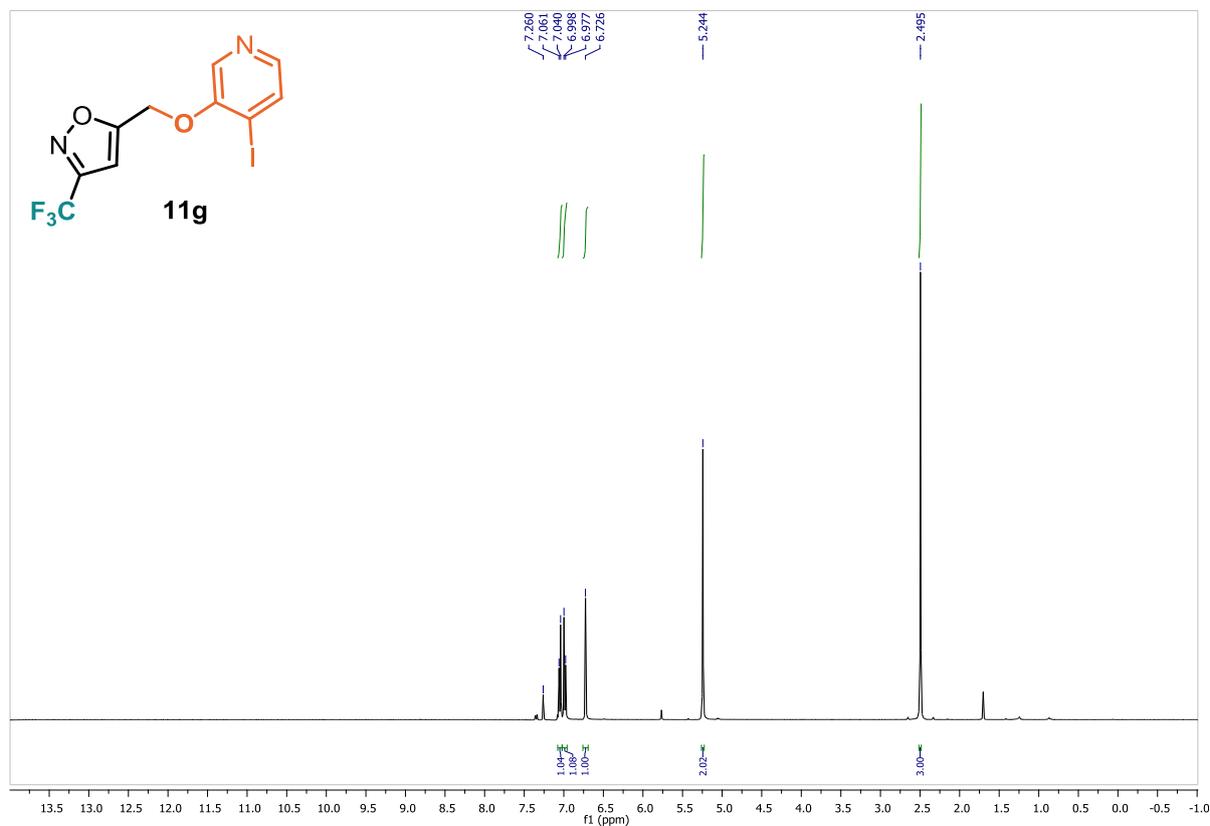


**<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:**

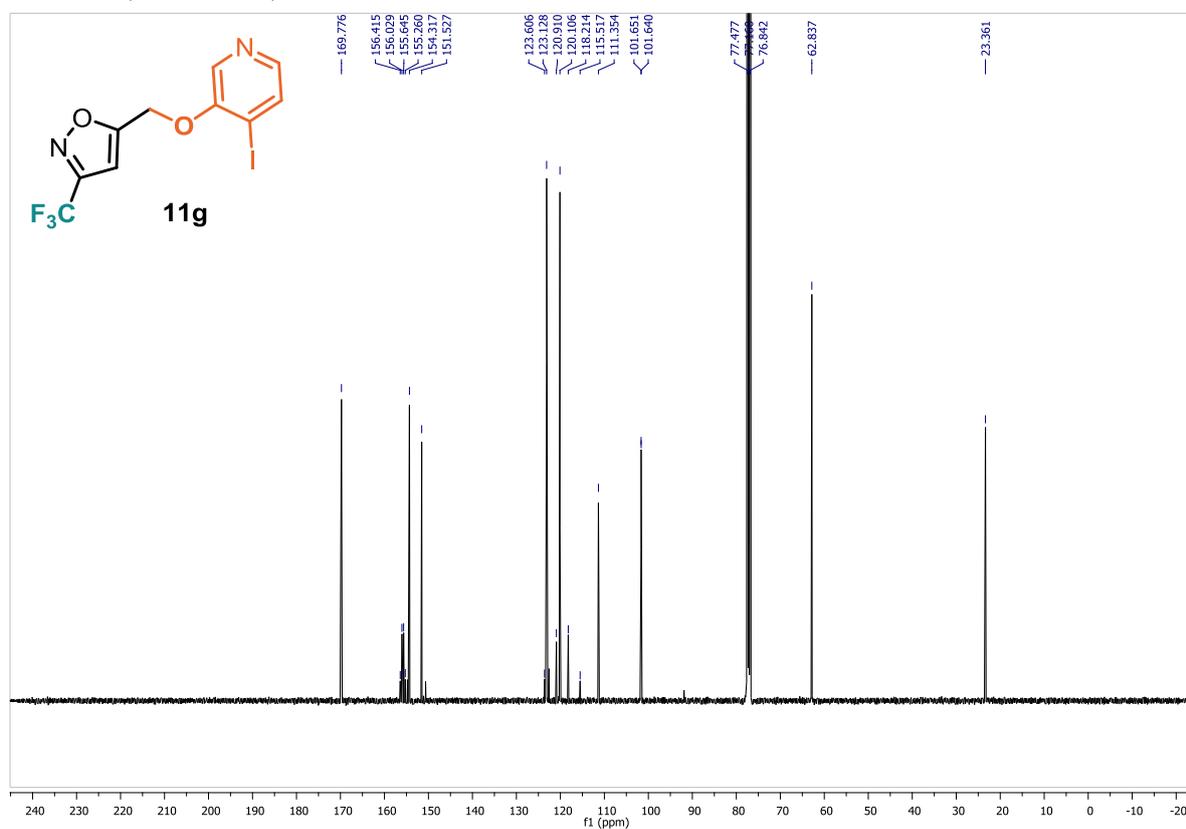


5-(((4-iodopyridin-3-yl)oxy)methyl)-3-(trifluoromethyl)isoxazole (**11g**):

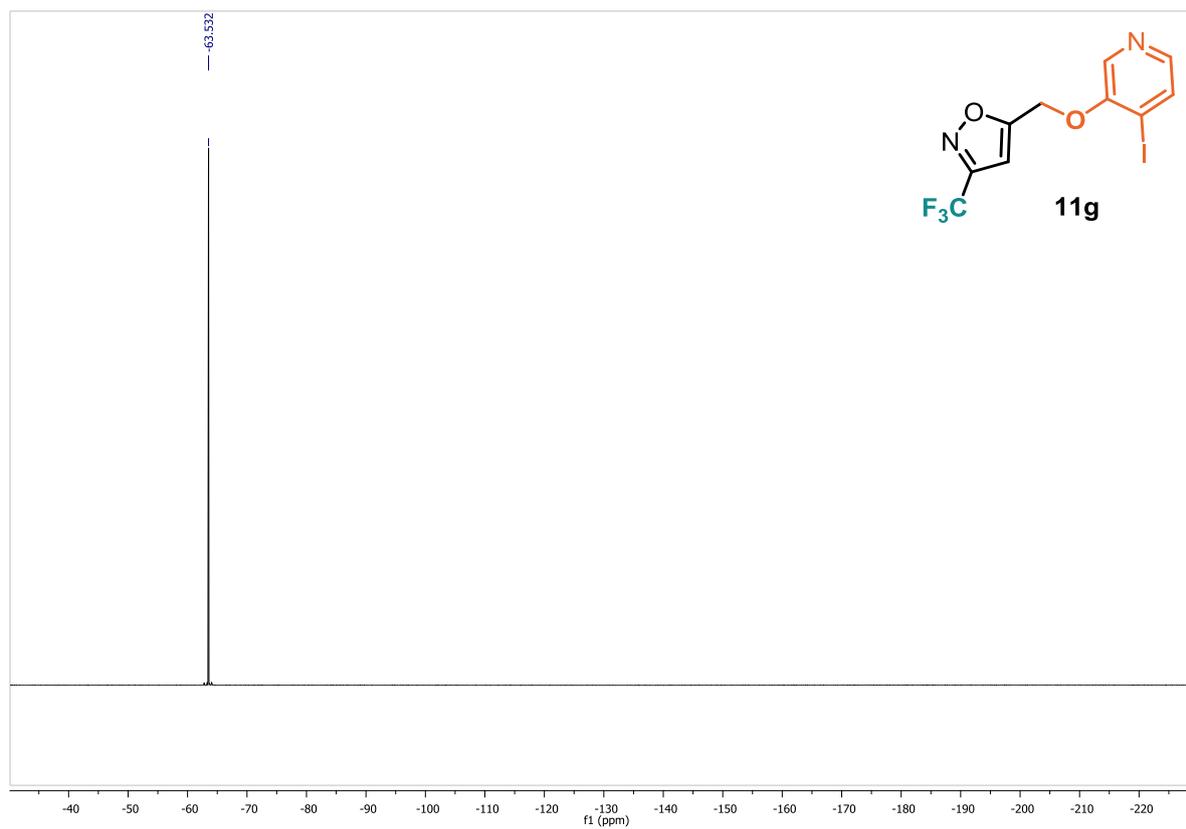
$^1\text{H}$  NMR, 400 MHz,  $\text{CDCl}_3$ :



$^{13}\text{C}$  NMR, 100 MHz,  $\text{CDCl}_3$ :

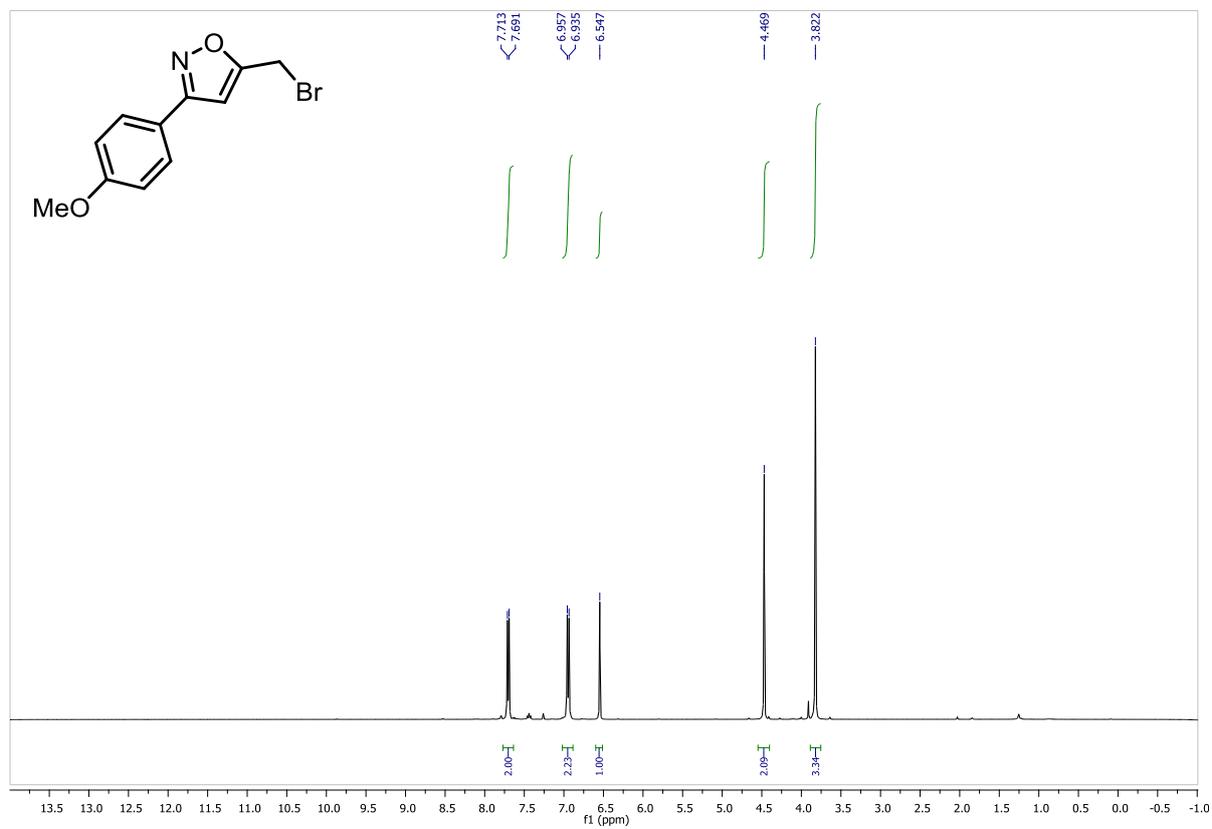


**$^{19}\text{F}$  NMR, 376 MHz,  $\text{CDCl}_3$ :**



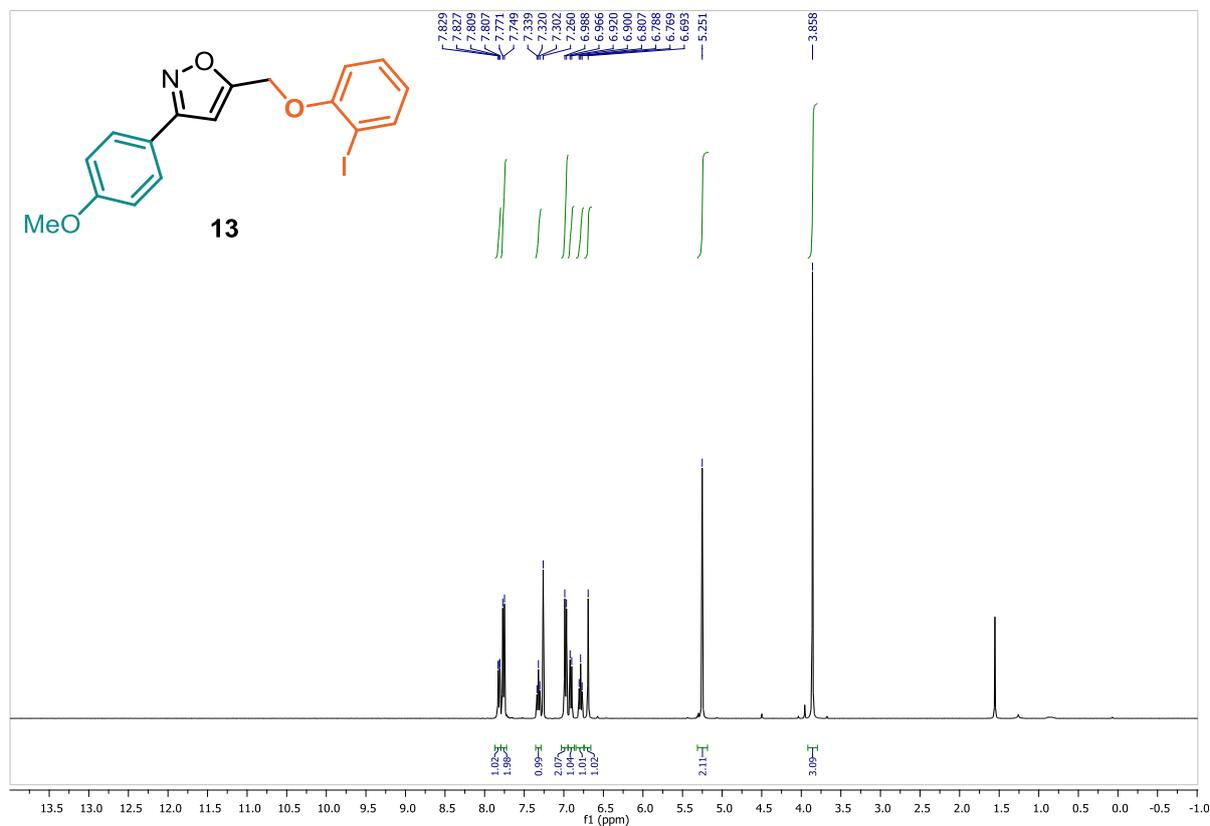
### 5-(bromomethyl)-3-(4-methoxyphenyl)isoxazole:

<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:

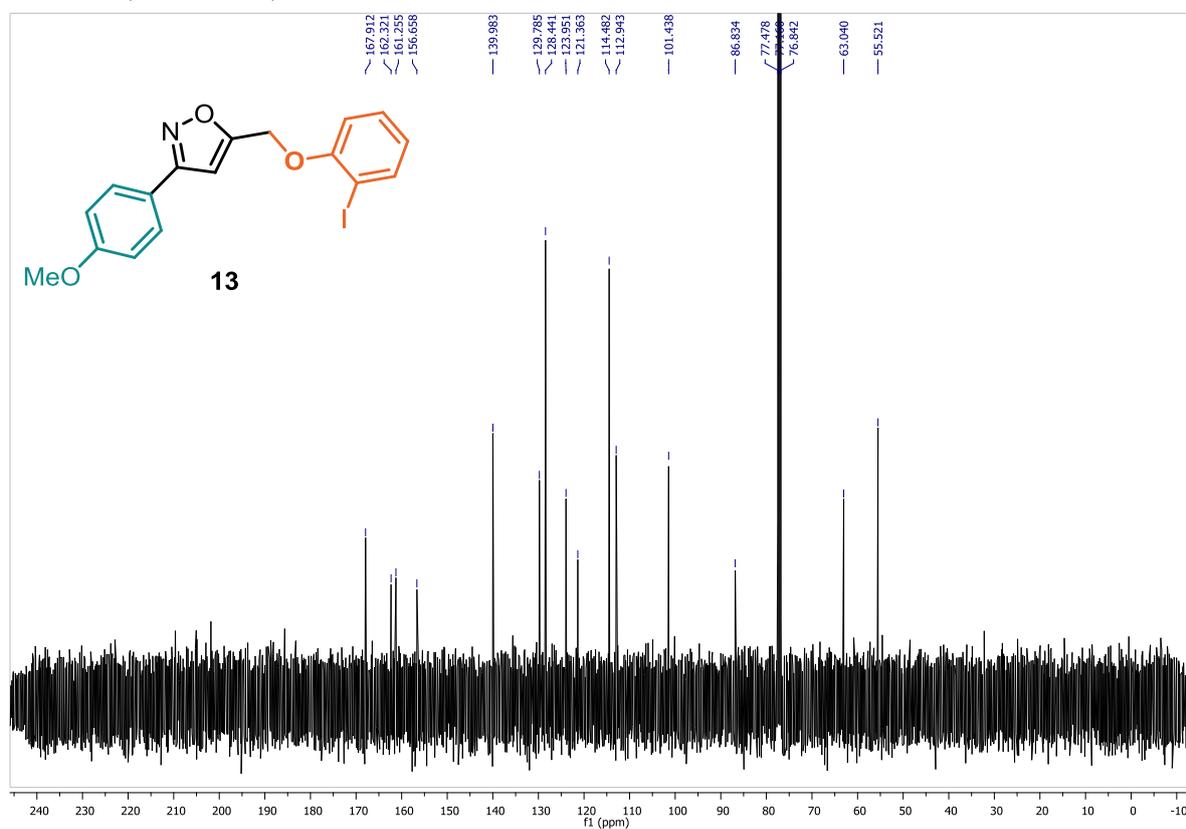


### 5-((2-iodophenoxy)methyl)-3-(4-methoxyphenyl)isoxazole (13):

<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:

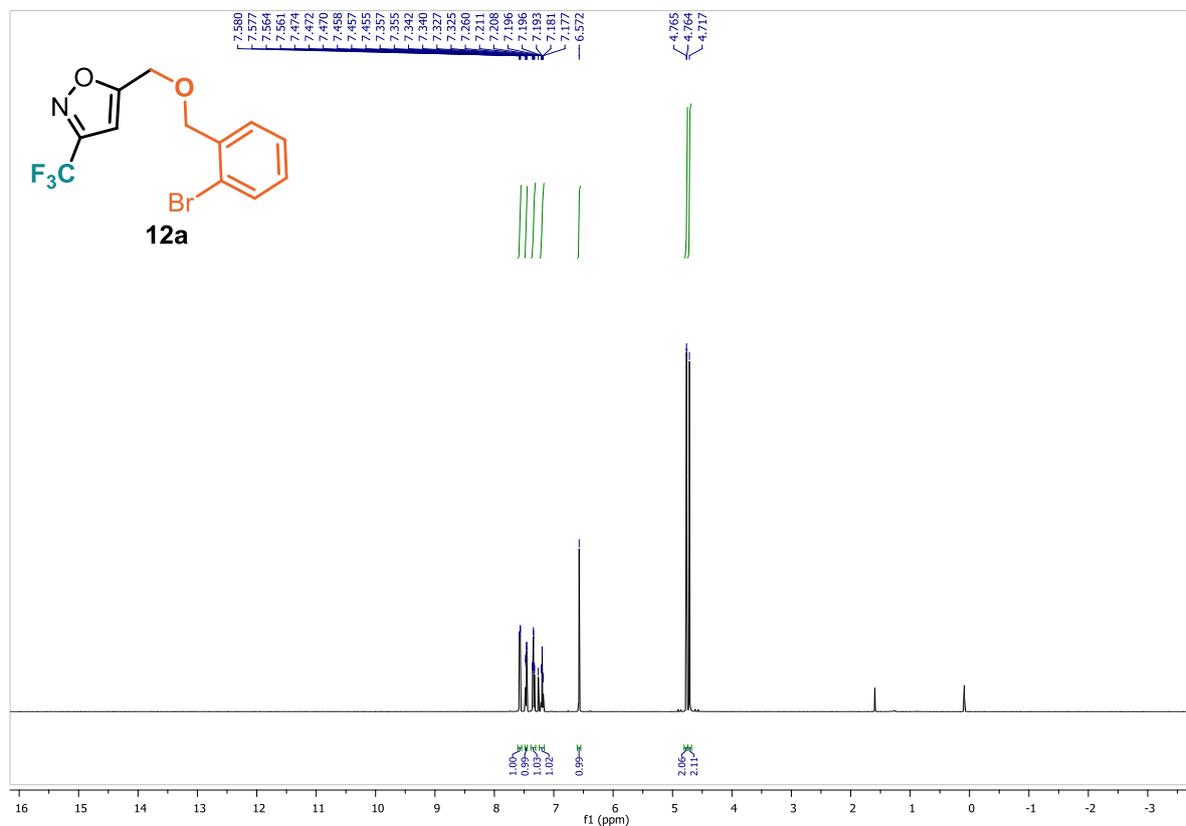


<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:

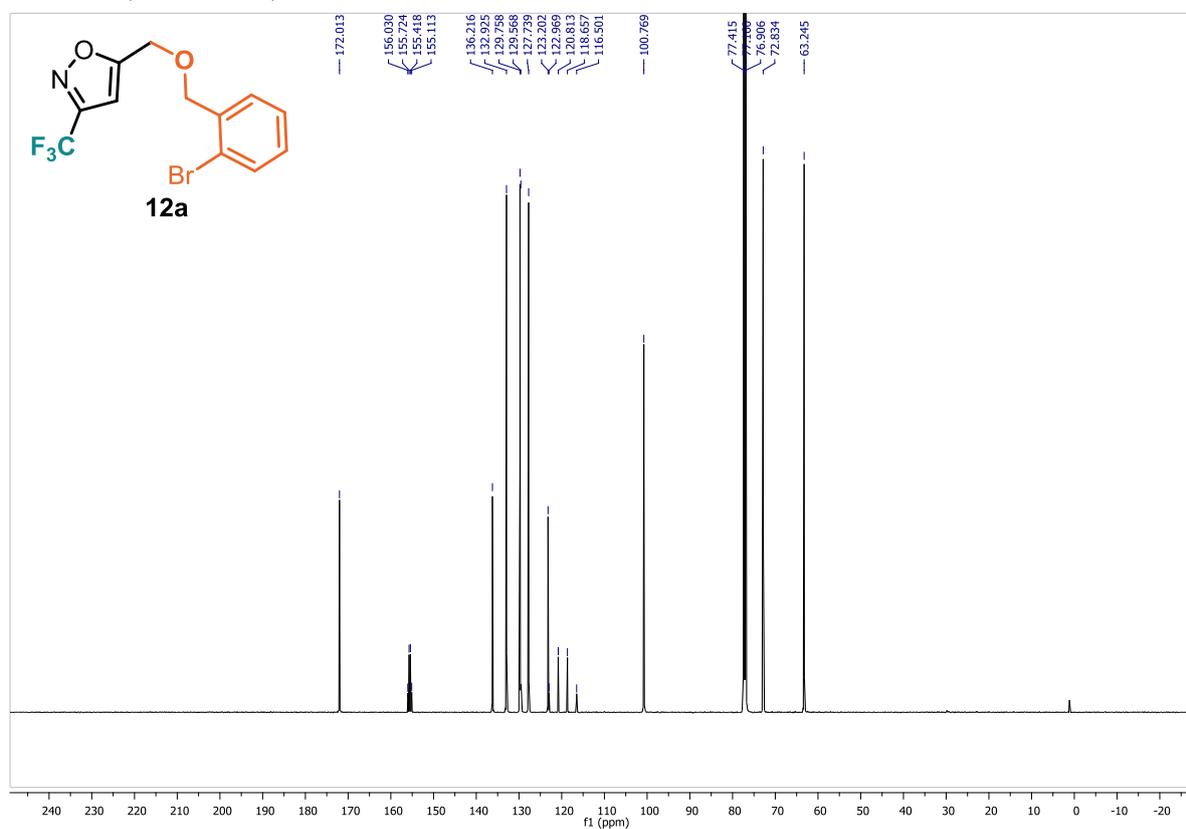


### 5-(((2-bromobenzyl)oxy)methyl)-3-(trifluoromethyl)isoxazole (12a):

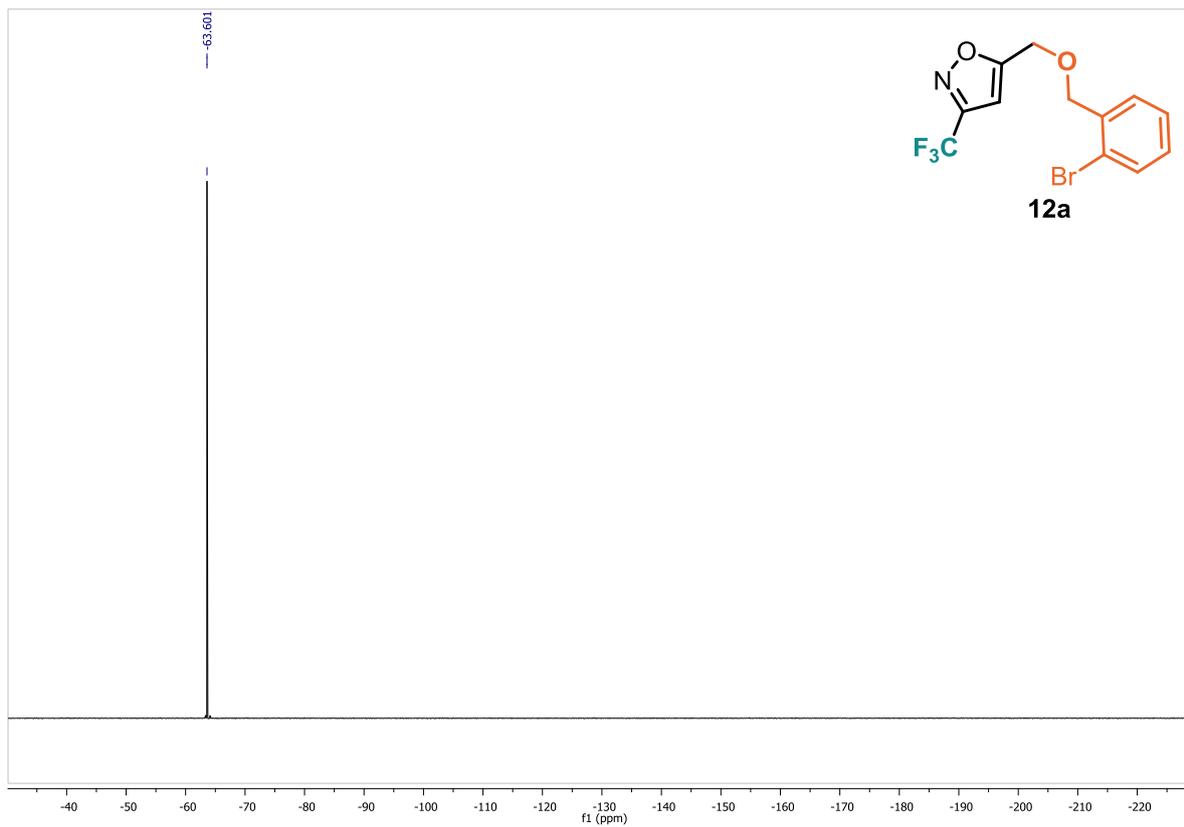
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>:

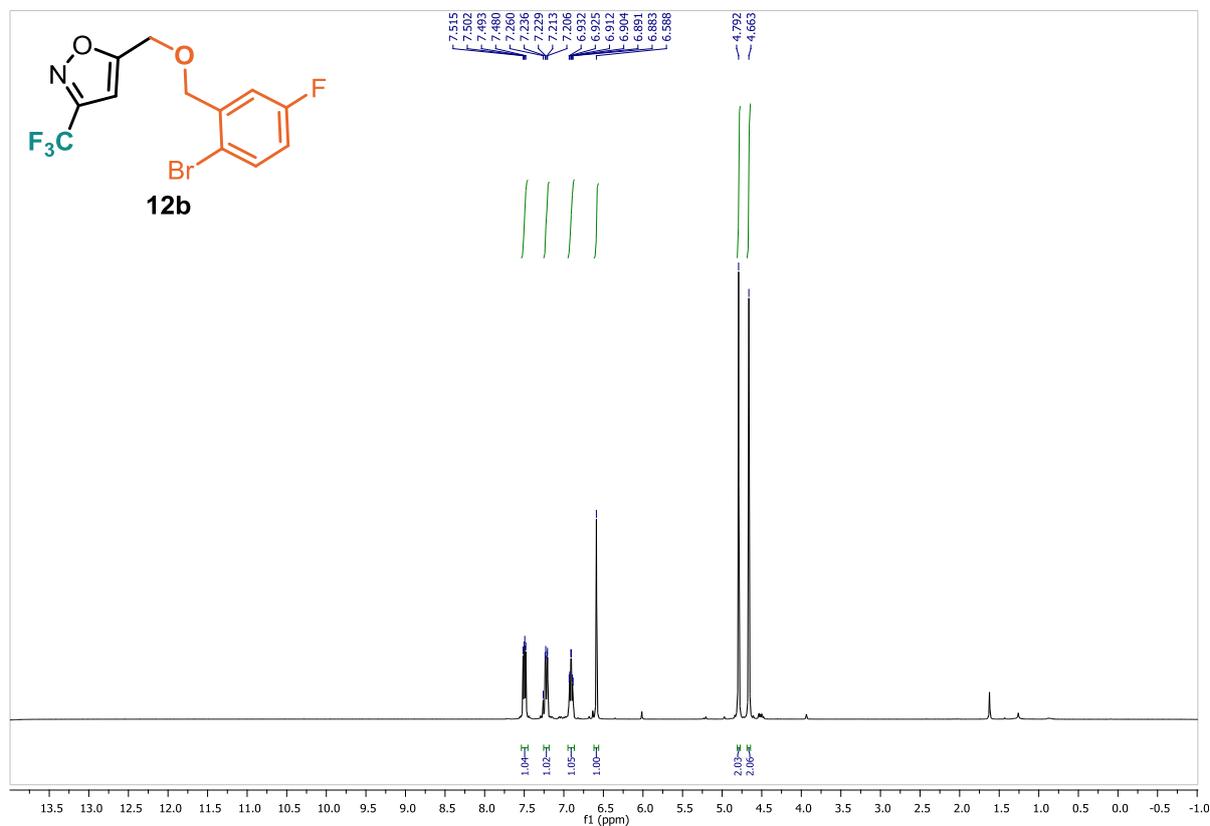


<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:

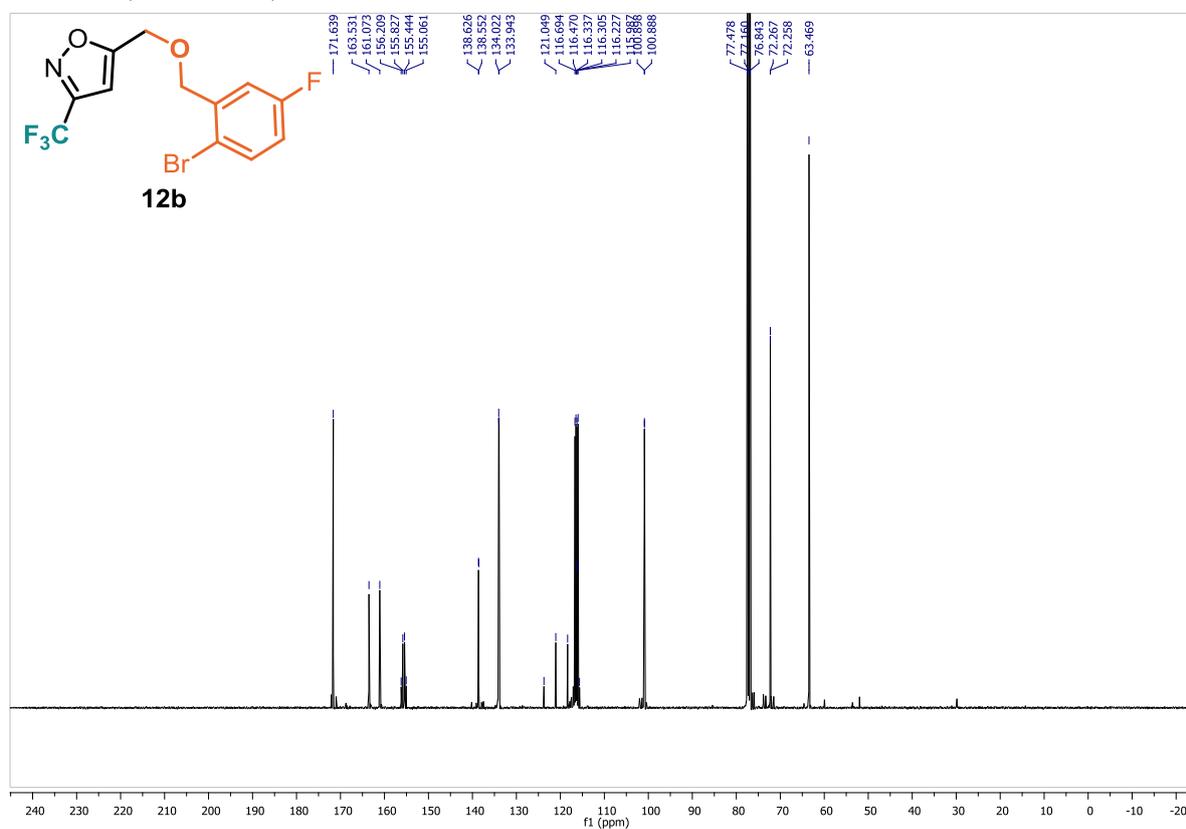


### 5-(((2-bromo-5-fluorobenzyl)oxy)methyl)-3-(trifluoromethyl)isoxazole (12b):

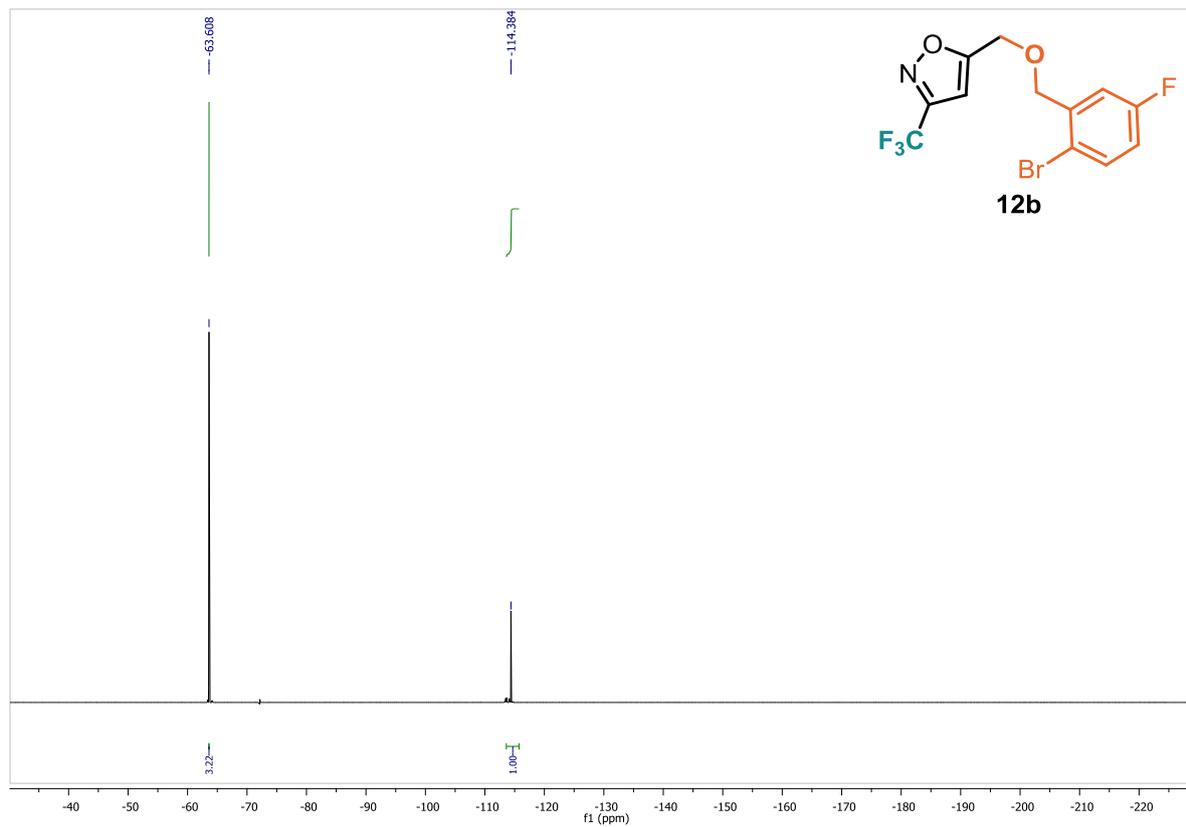
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:

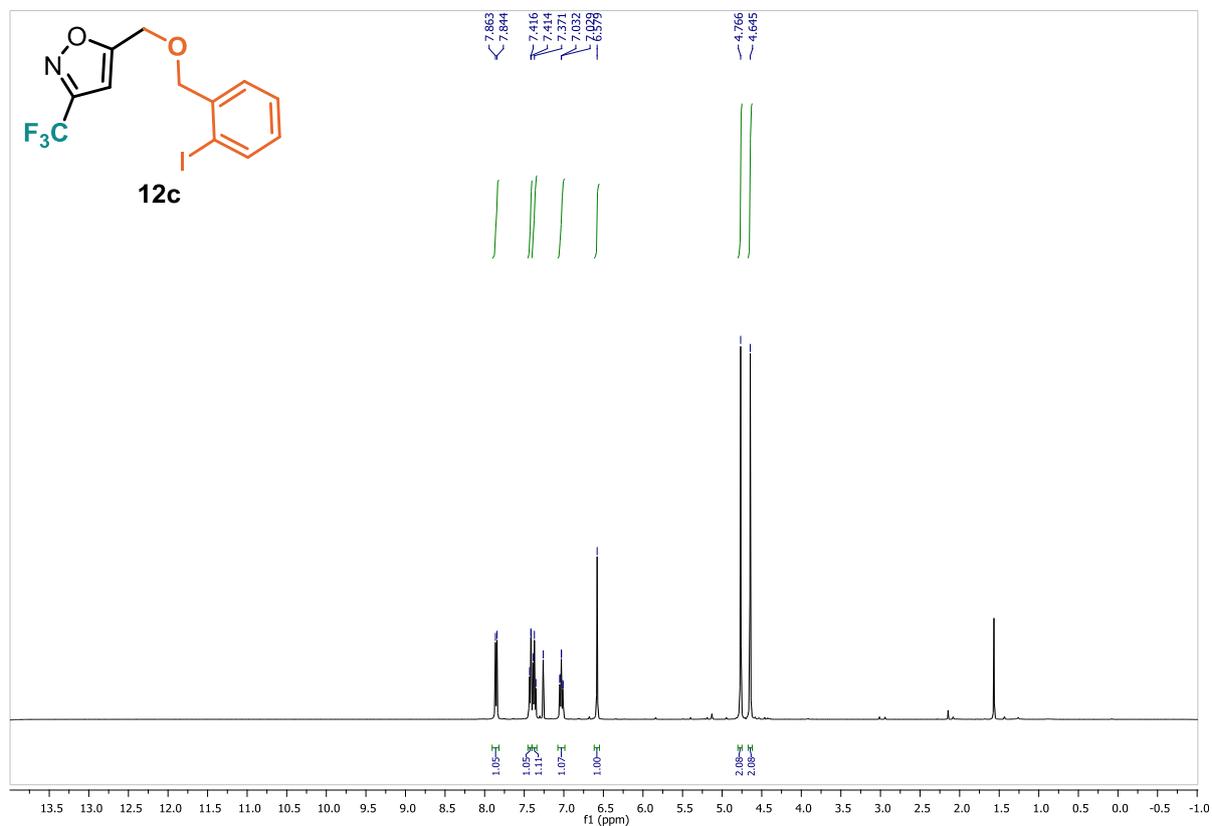


<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:

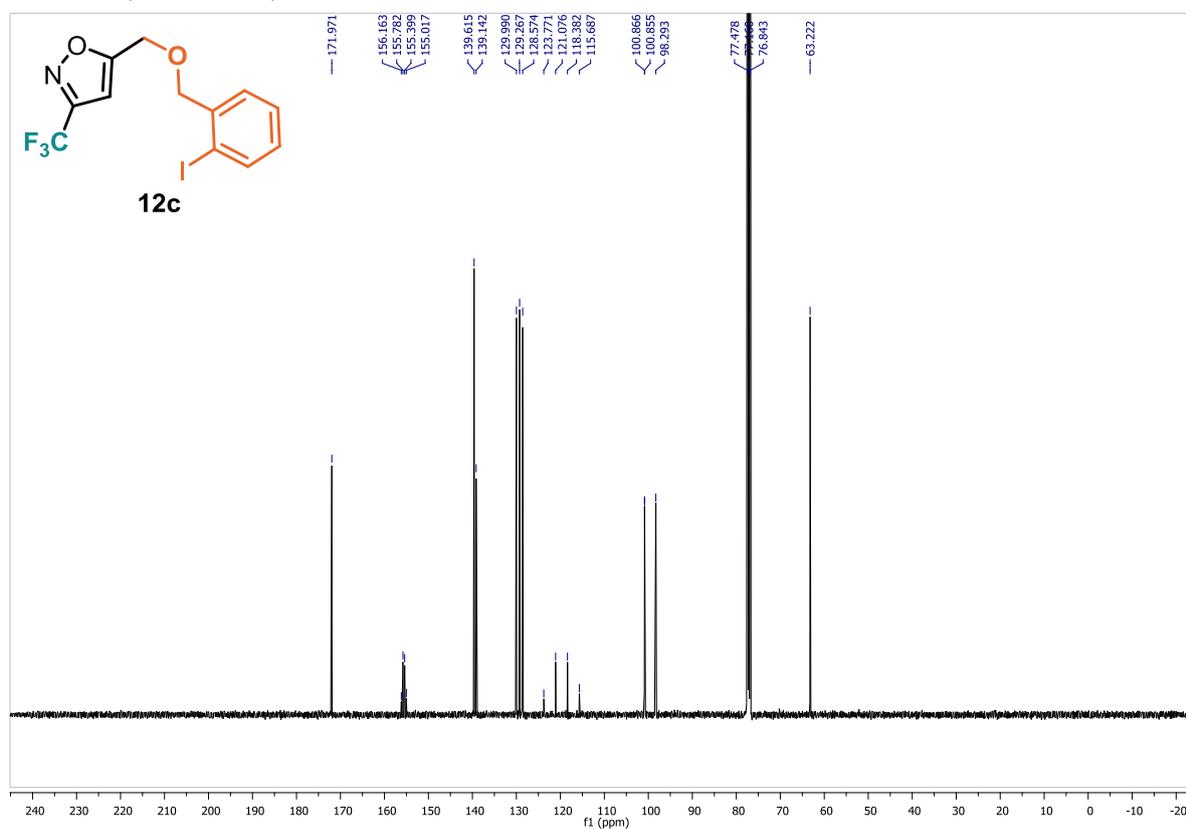


### 5-(((2-iodobenzyl)oxy)methyl)-3-(trifluoromethyl)isoxazole (12c):

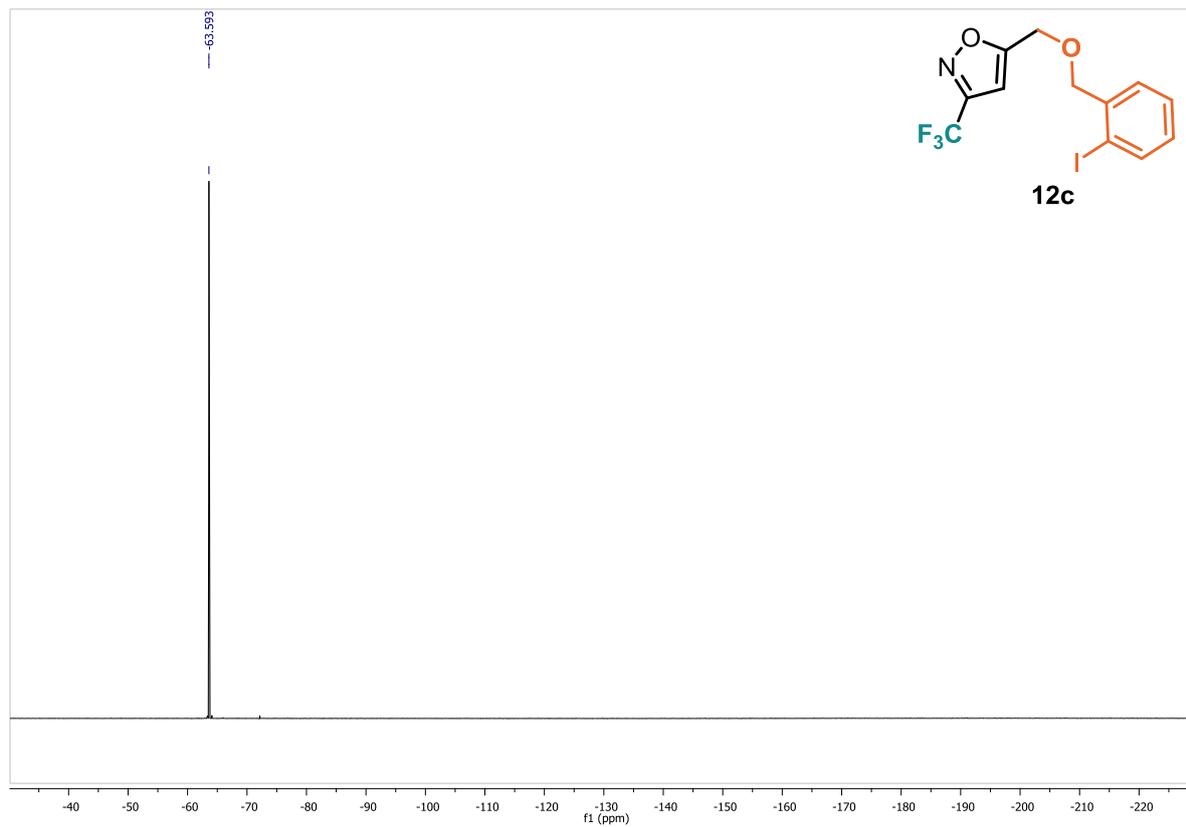
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:

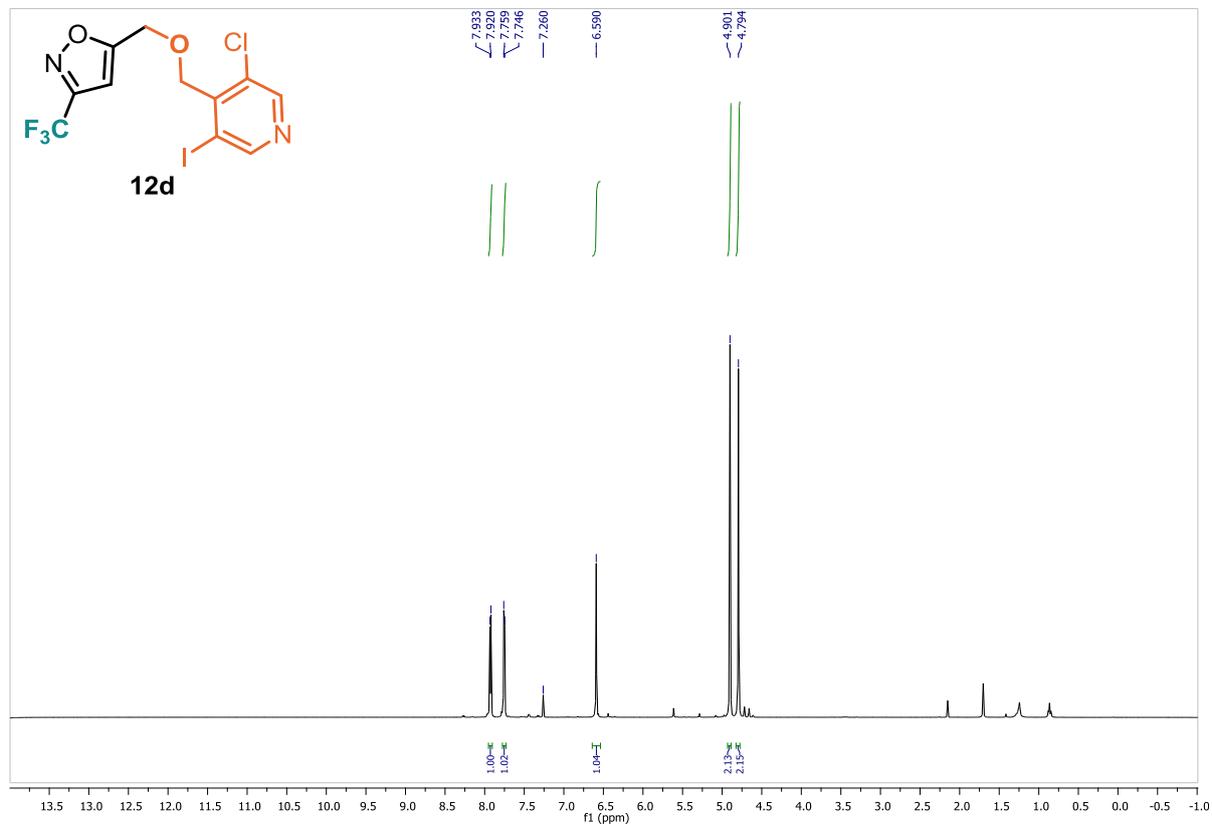


**$^{19}\text{F}$  NMR, 376 MHz,  $\text{CDCl}_3$ :**

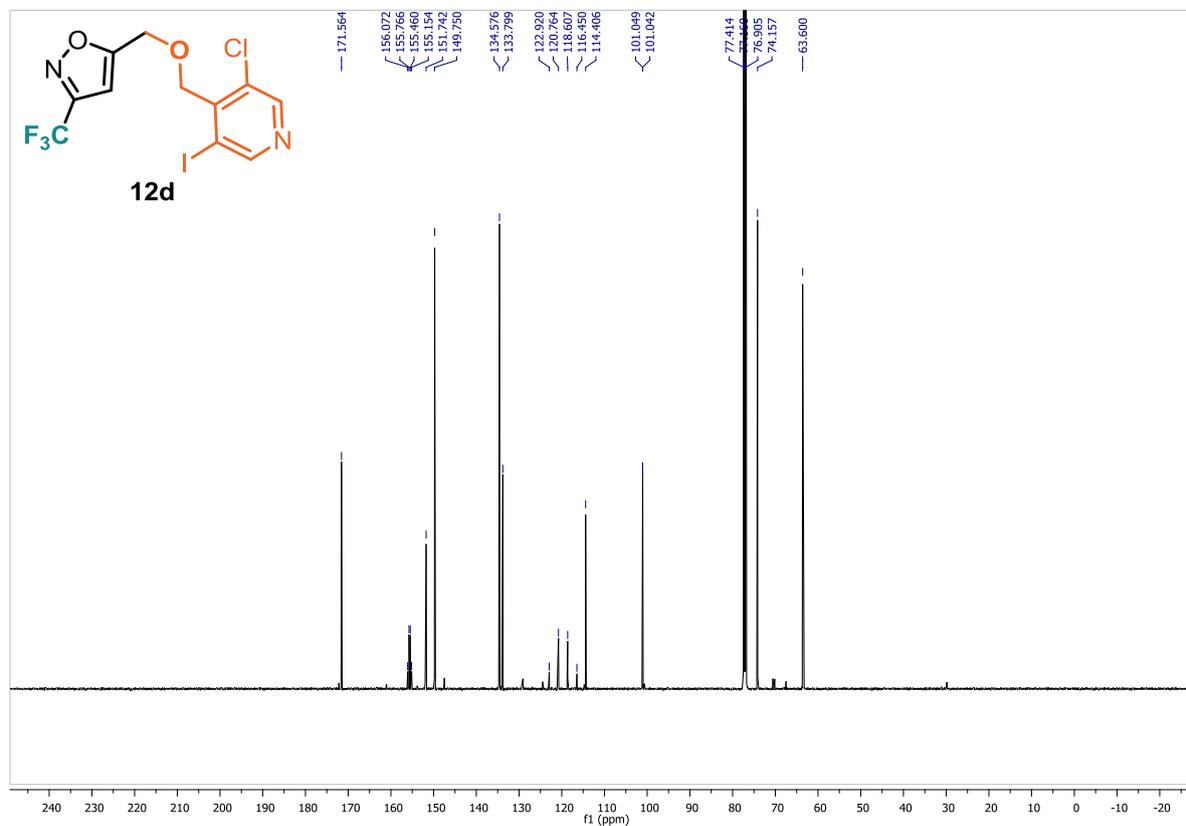


5-(((3-chloro-5-iodopyridin-4-yl)methoxy)methyl)-3-(trifluoromethyl)isoxazole (12d):

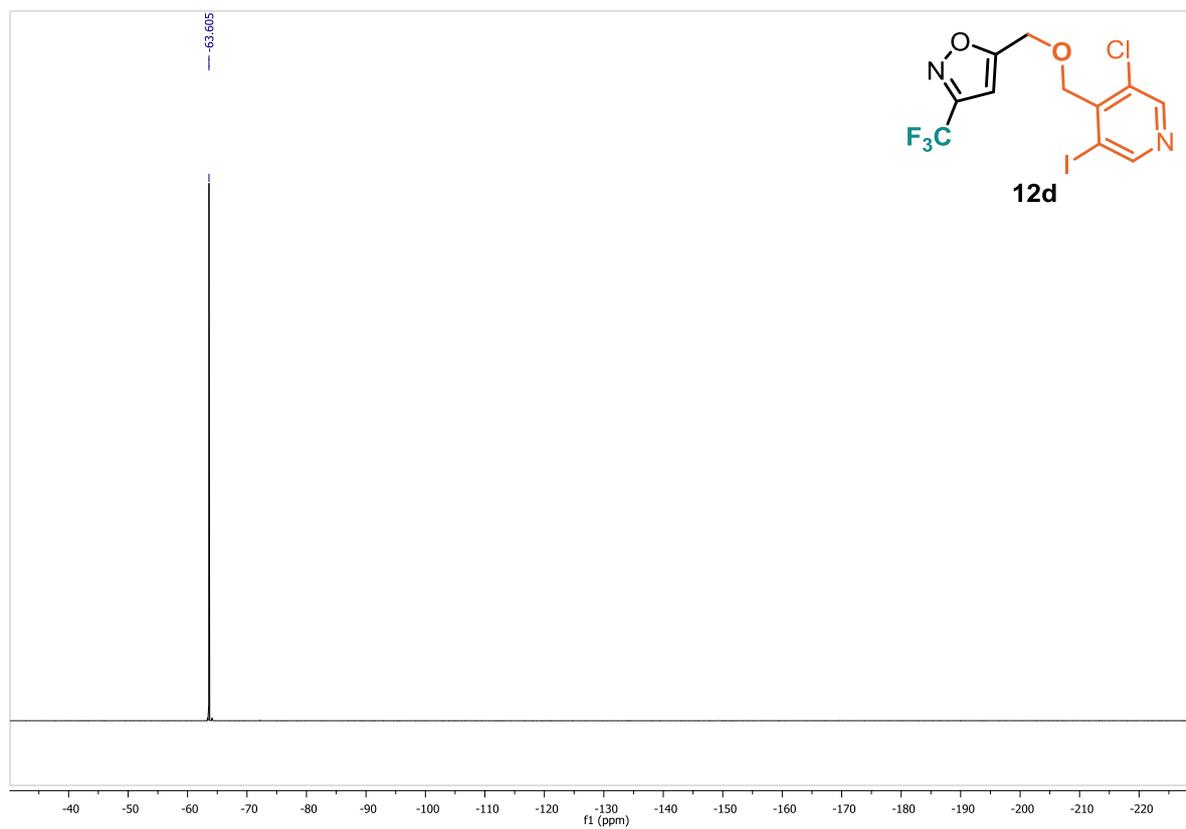
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>:

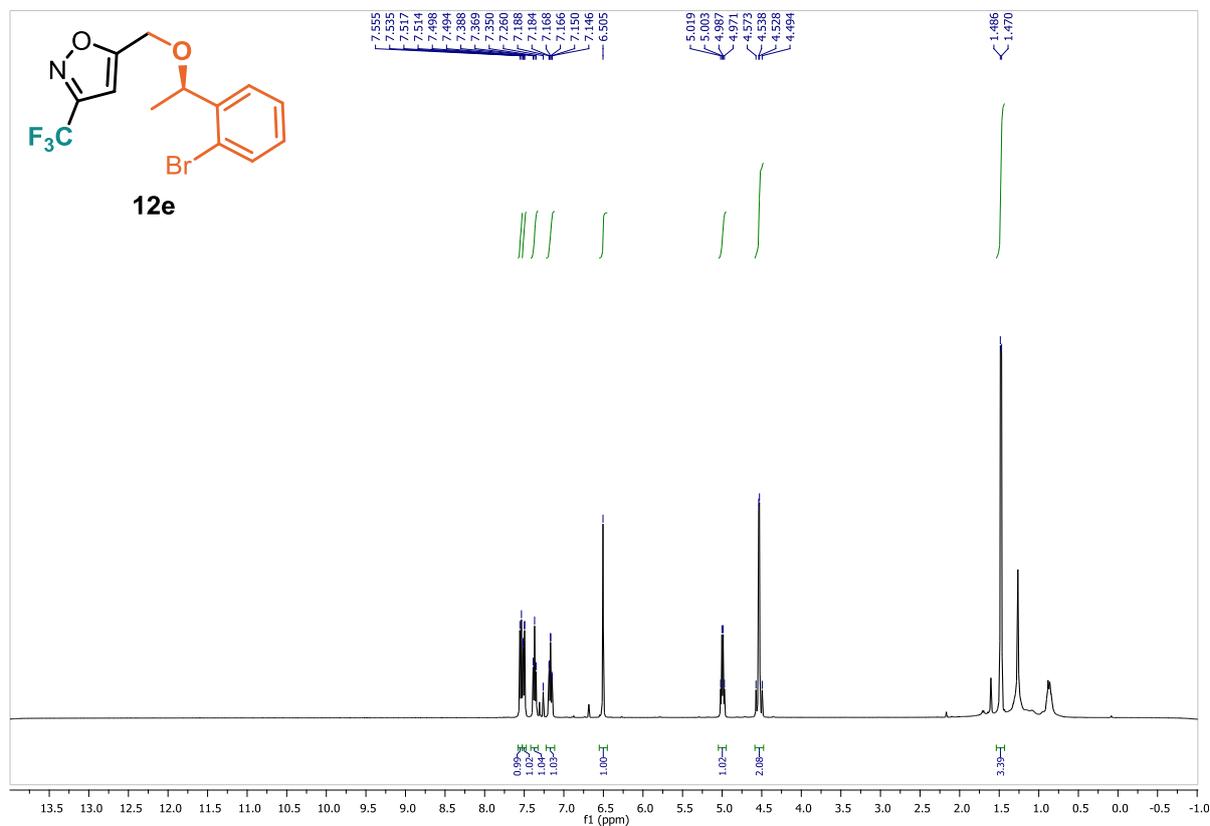


**<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:**

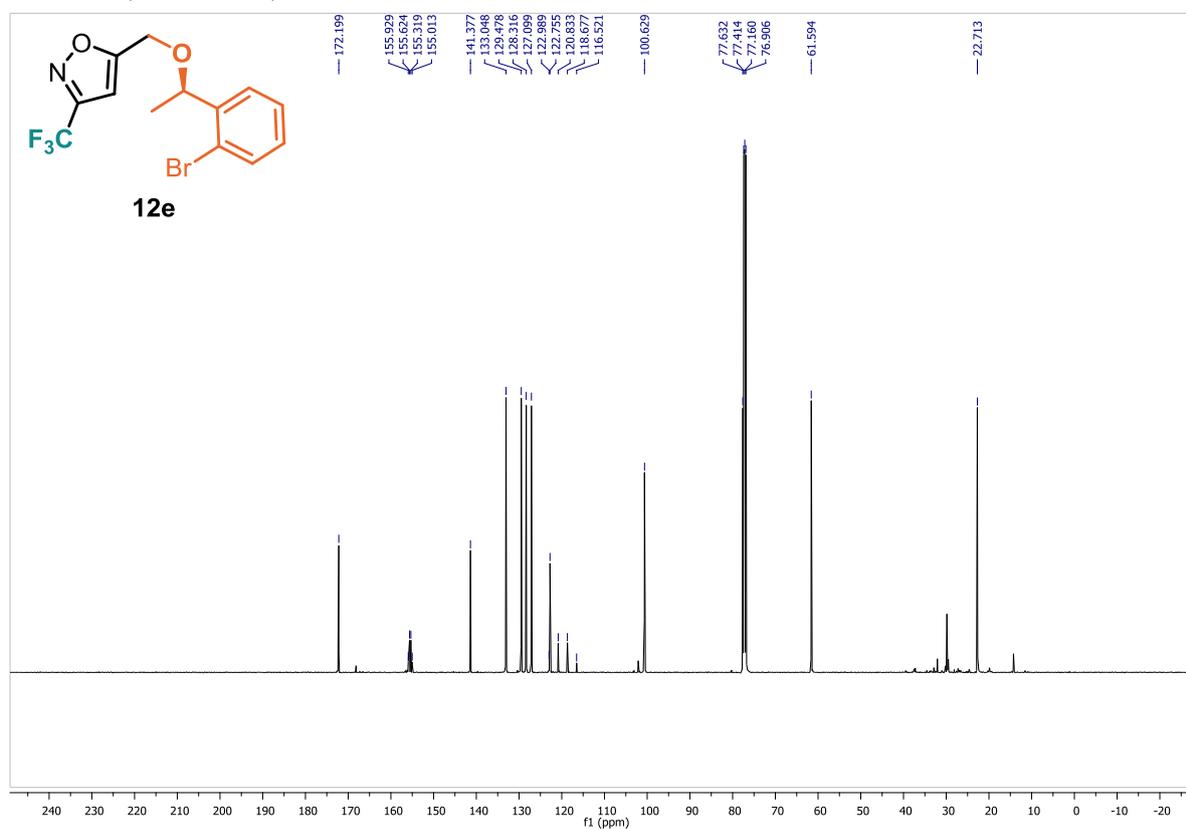


**(R)-5-((1-(2-bromophenyl)ethoxy)methyl)-3-(trifluoromethyl)isoxazole (12e):**

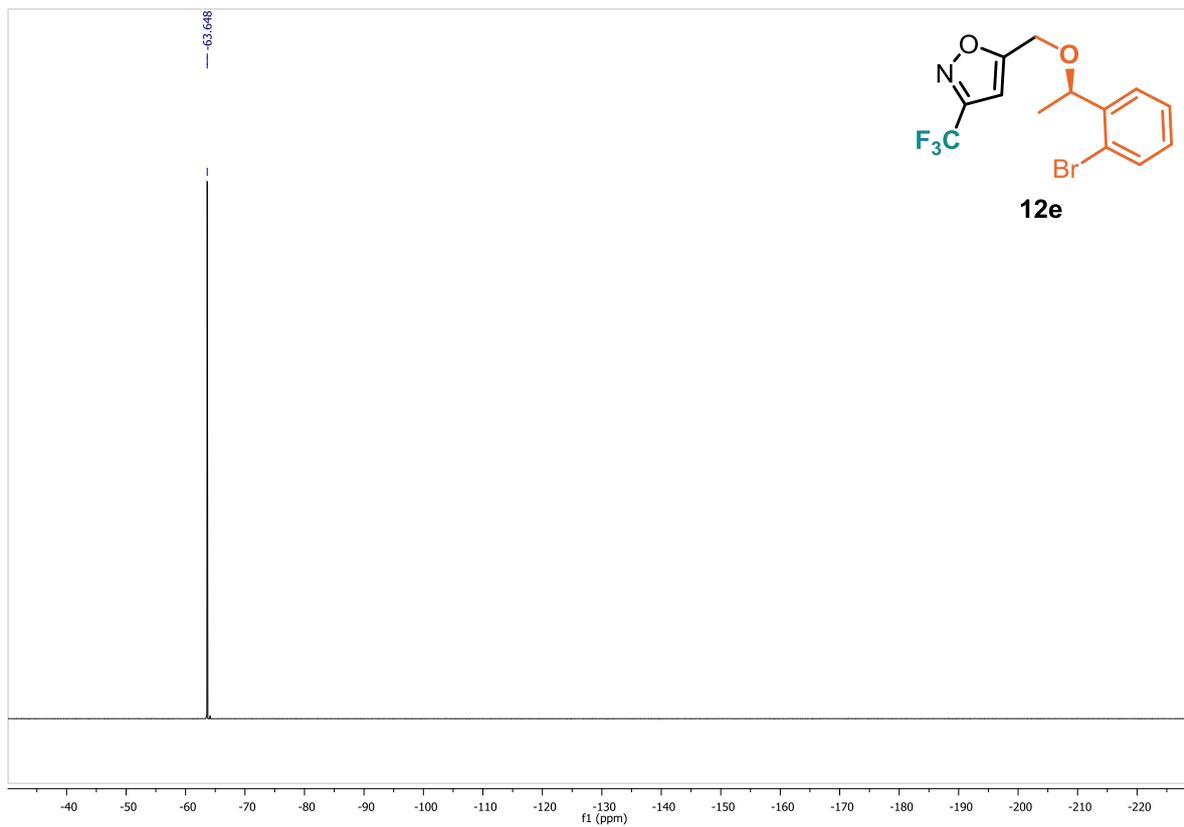
**<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:**



**<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>:**

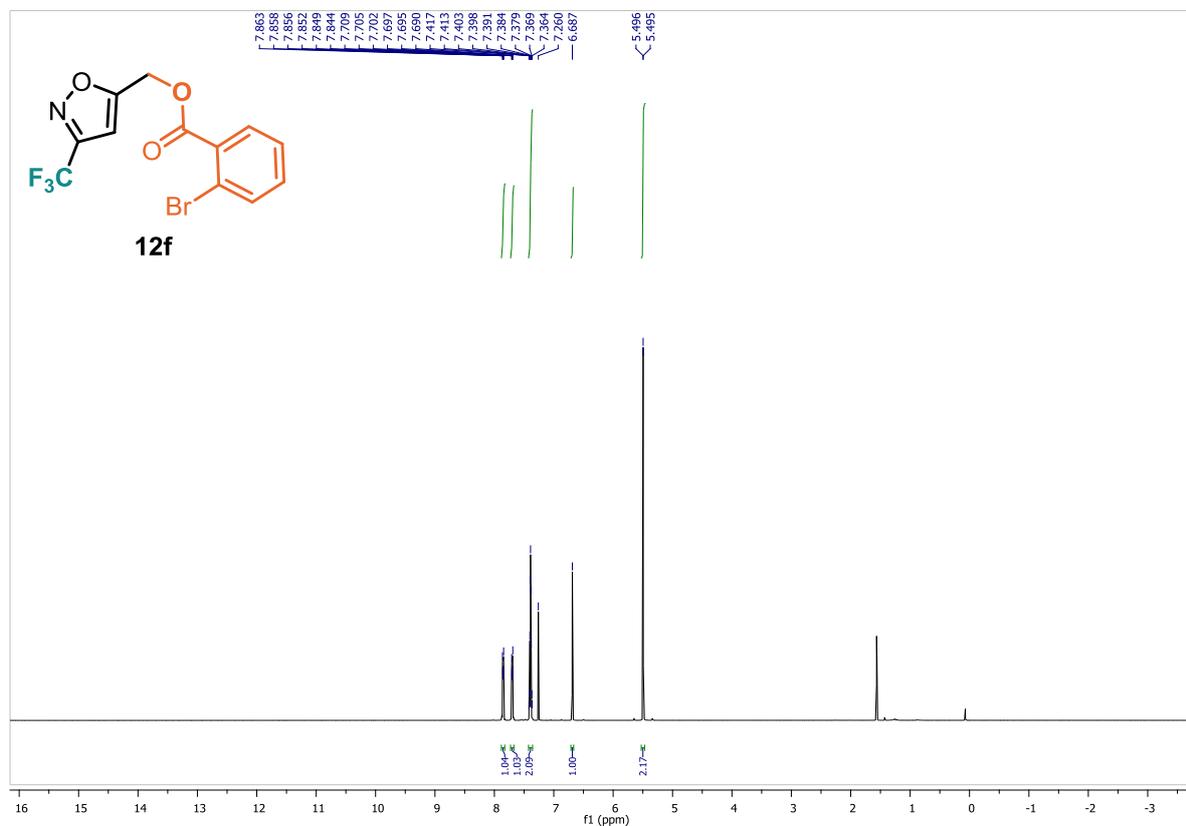


**<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:**

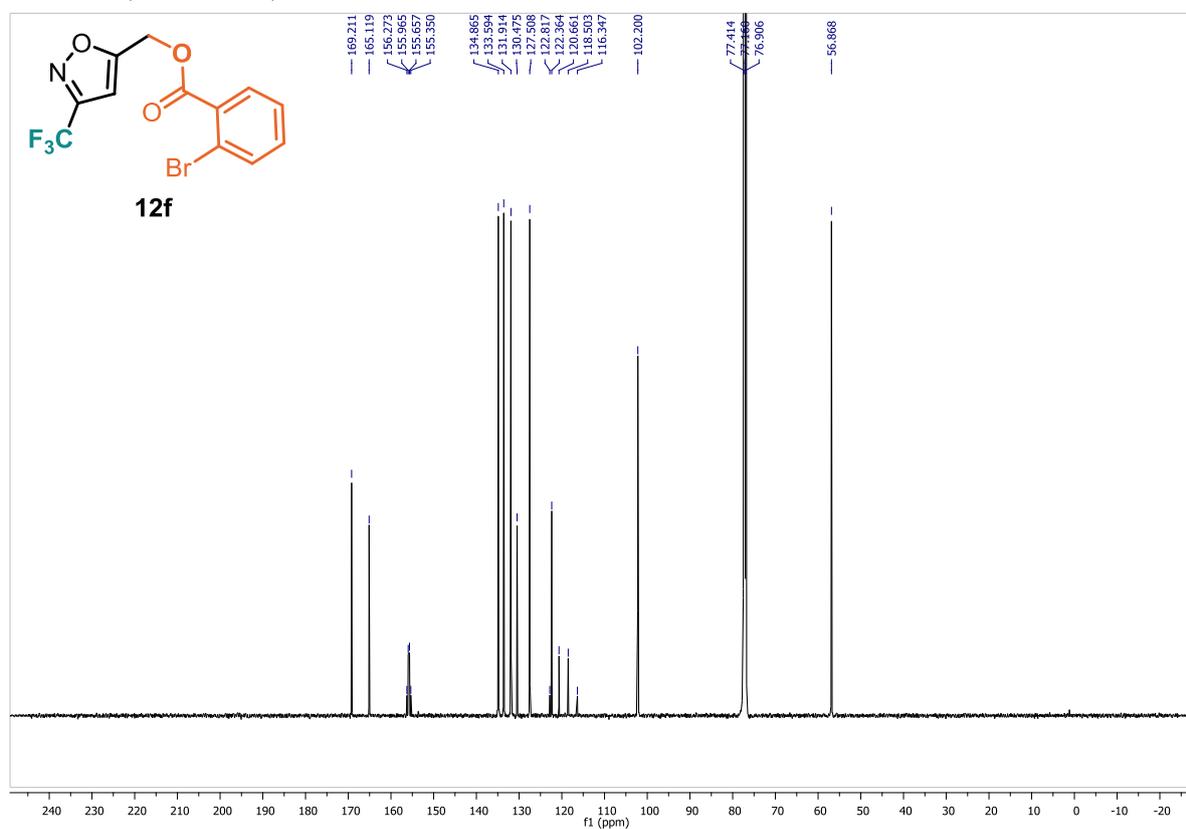


**(3-(trifluoromethyl)isoxazol-5-yl)methyl 2-bromobenzoate (12f):**

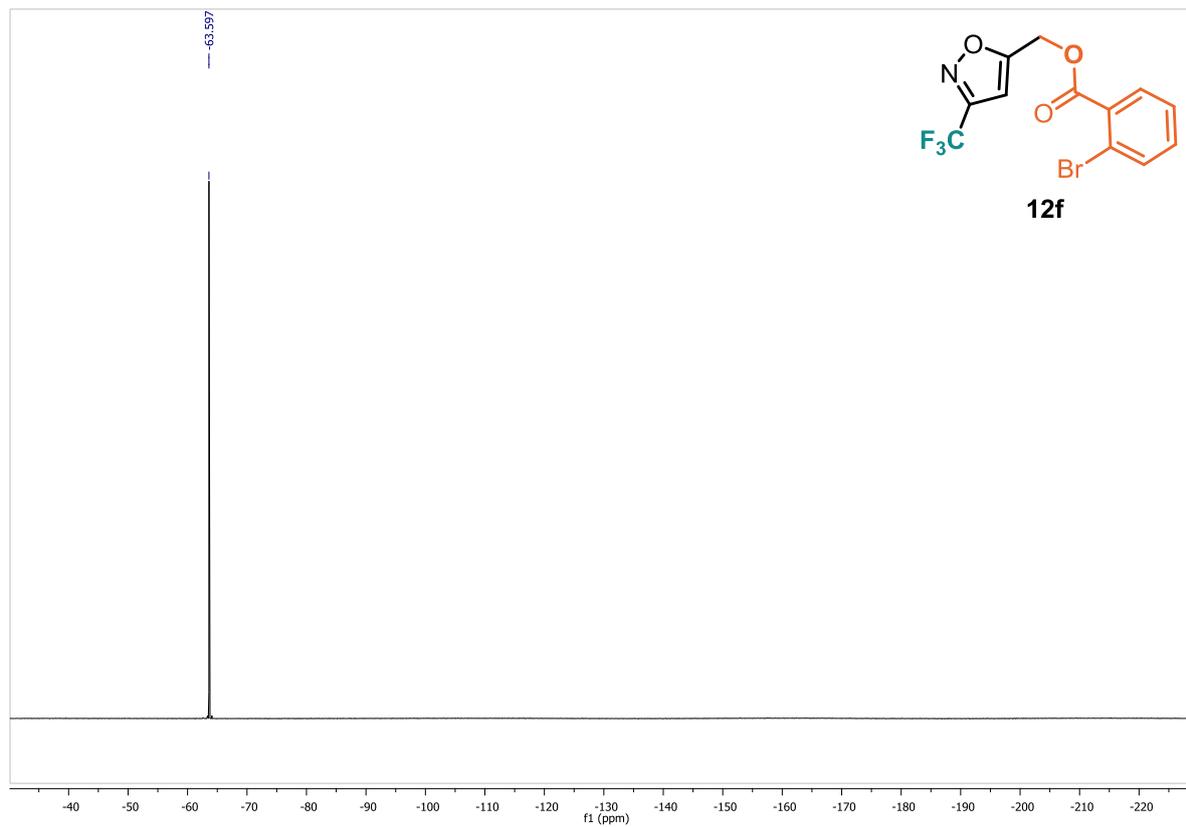
**<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>:**



**<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>:**

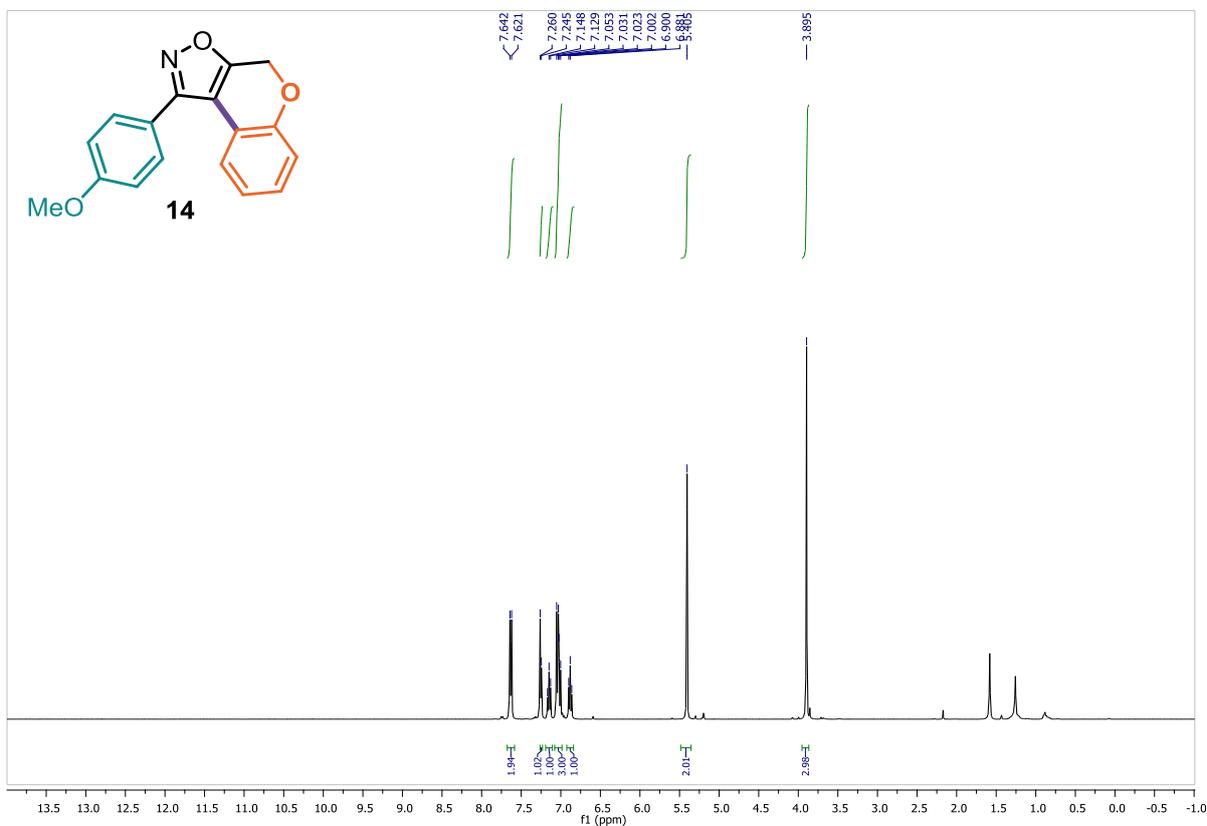


**<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:**

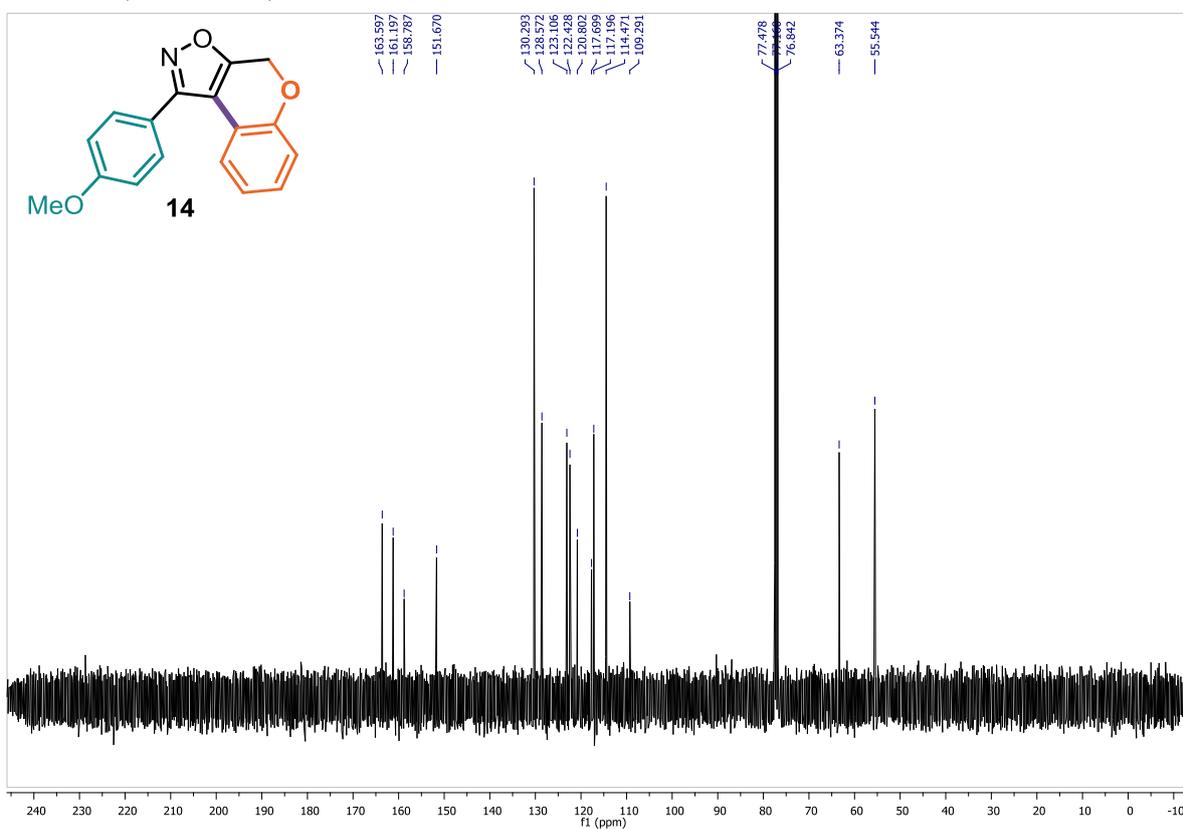


# 1-(4-methoxyphenyl)-4*H*-chromeno[4,3-*d*]isoxazole (14):

<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:

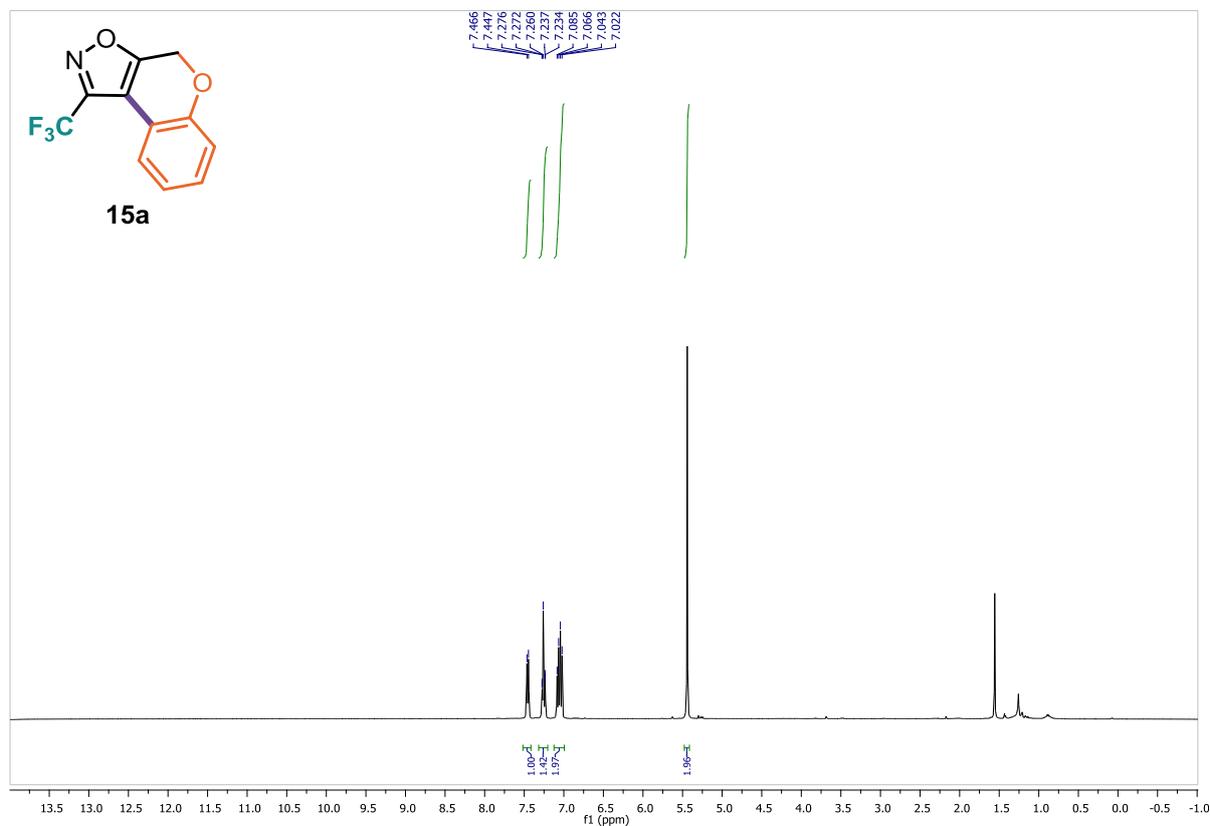


<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:

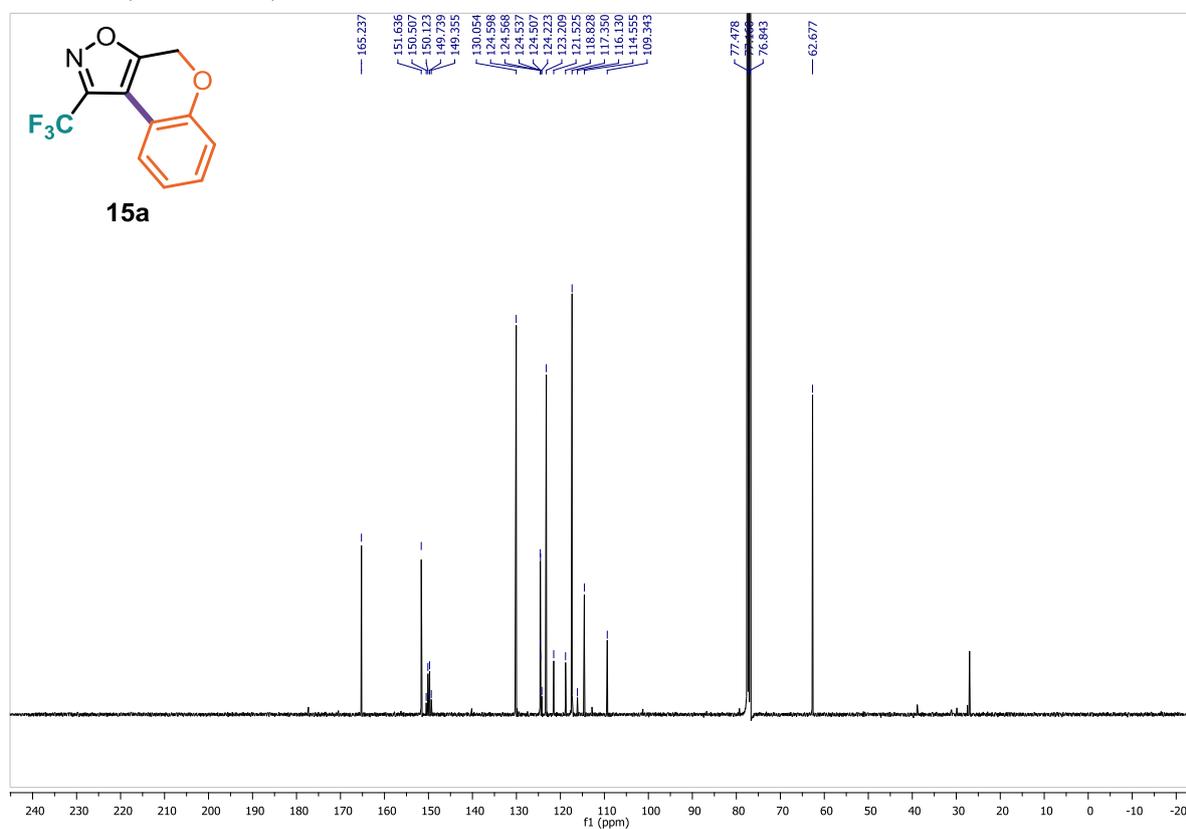


# 1-(trifluoromethyl)-4*H*-chromeno[4,3-*d*]isoxazole (15a):

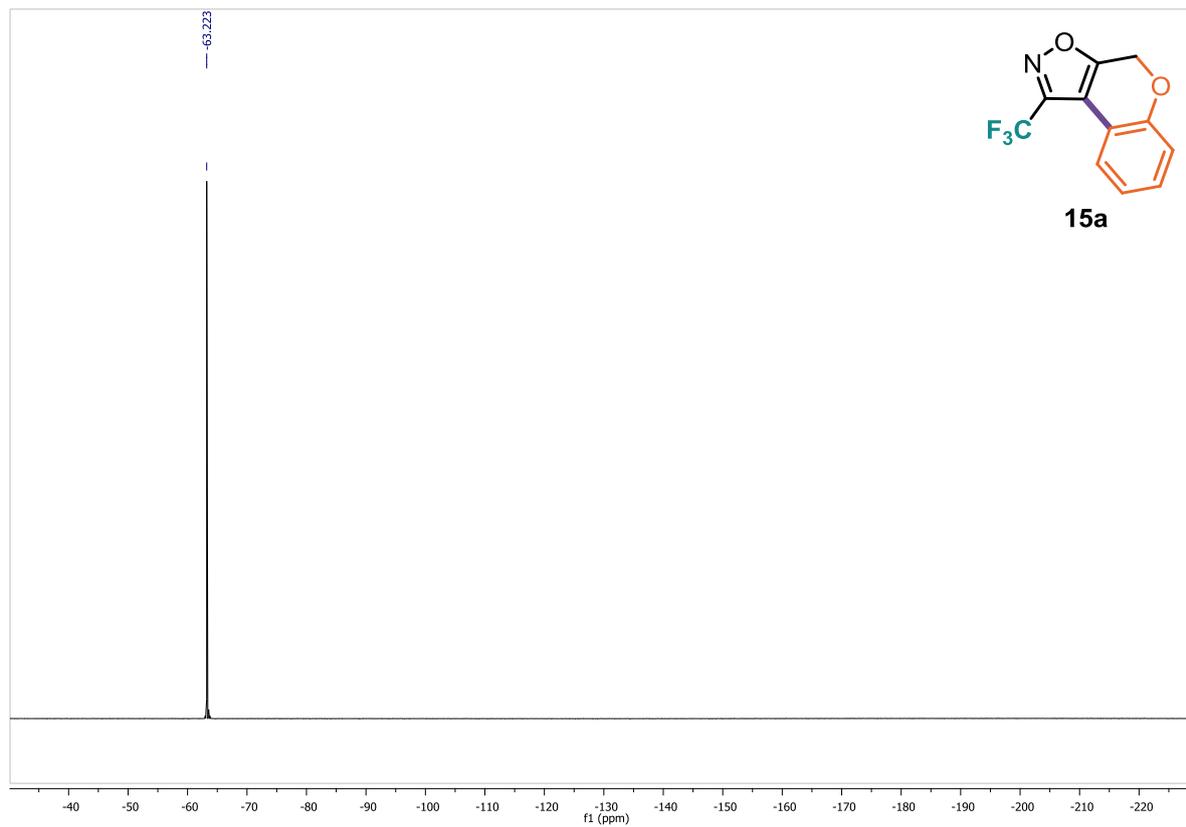
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 100 MHz, CDCl<sub>3</sub>:

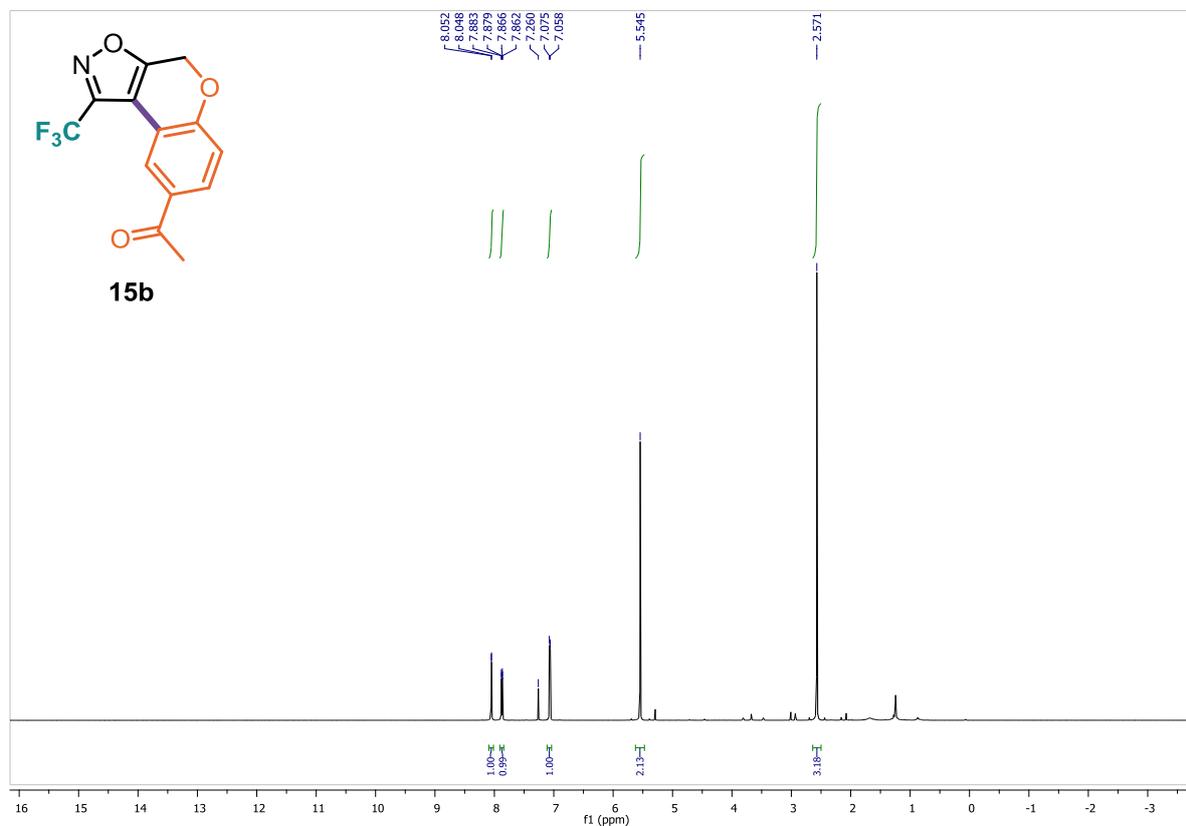


**<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:**

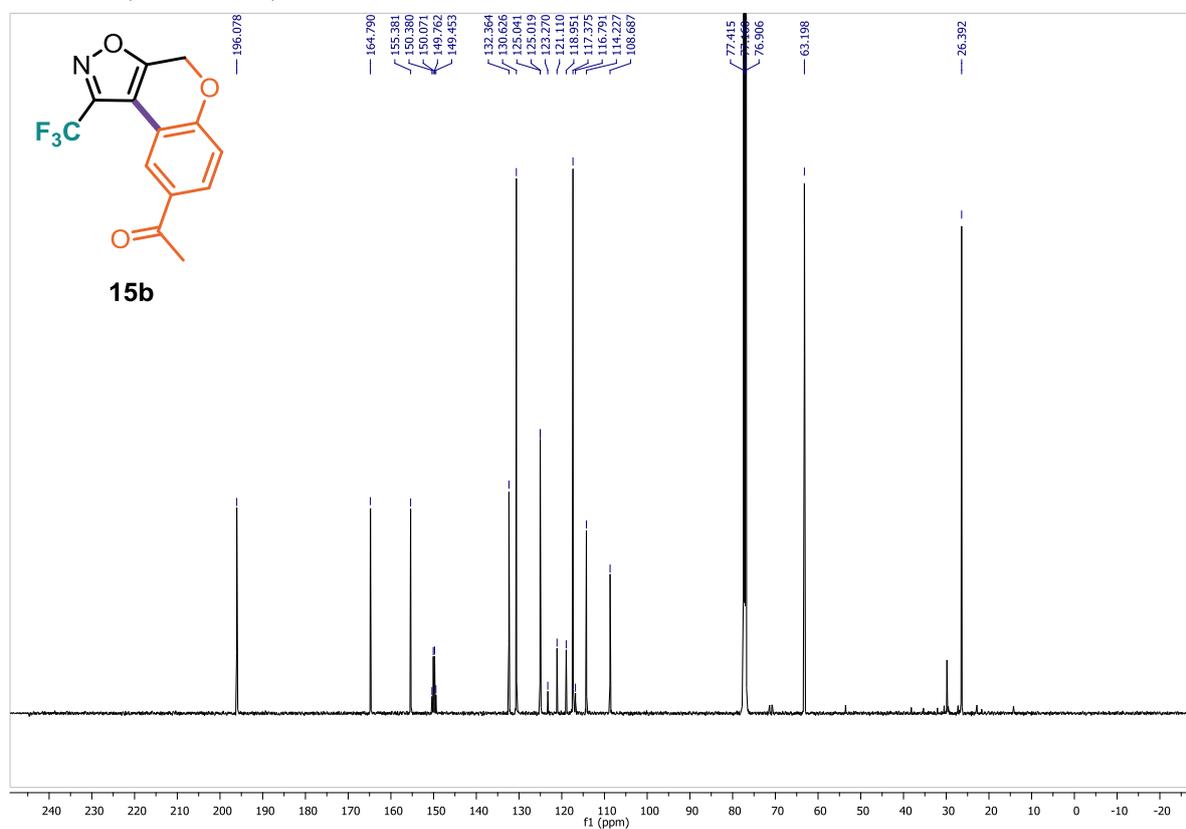


**1-(1-(trifluoromethyl)-4*H*-chromeno[4,3-*d*]isoxazol-8-yl)ethan-1-one (15b):**

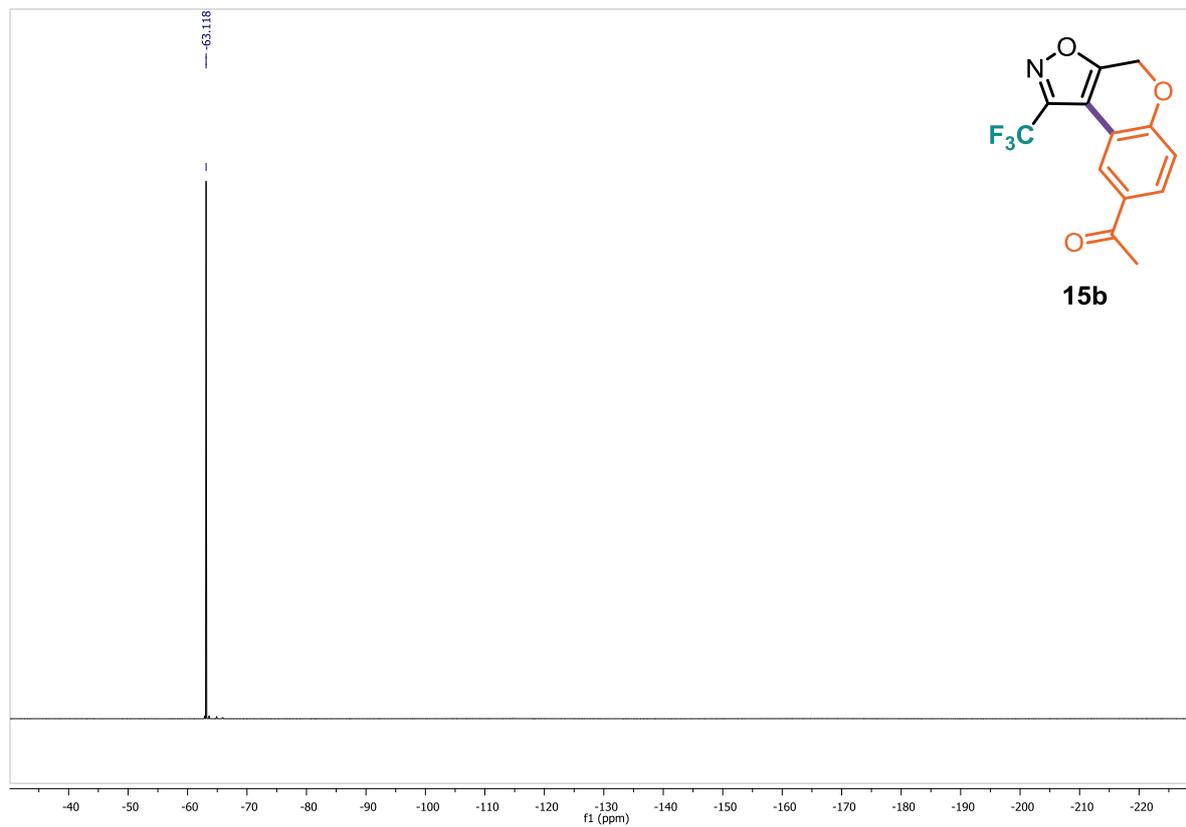
**<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>:**



**<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>:**

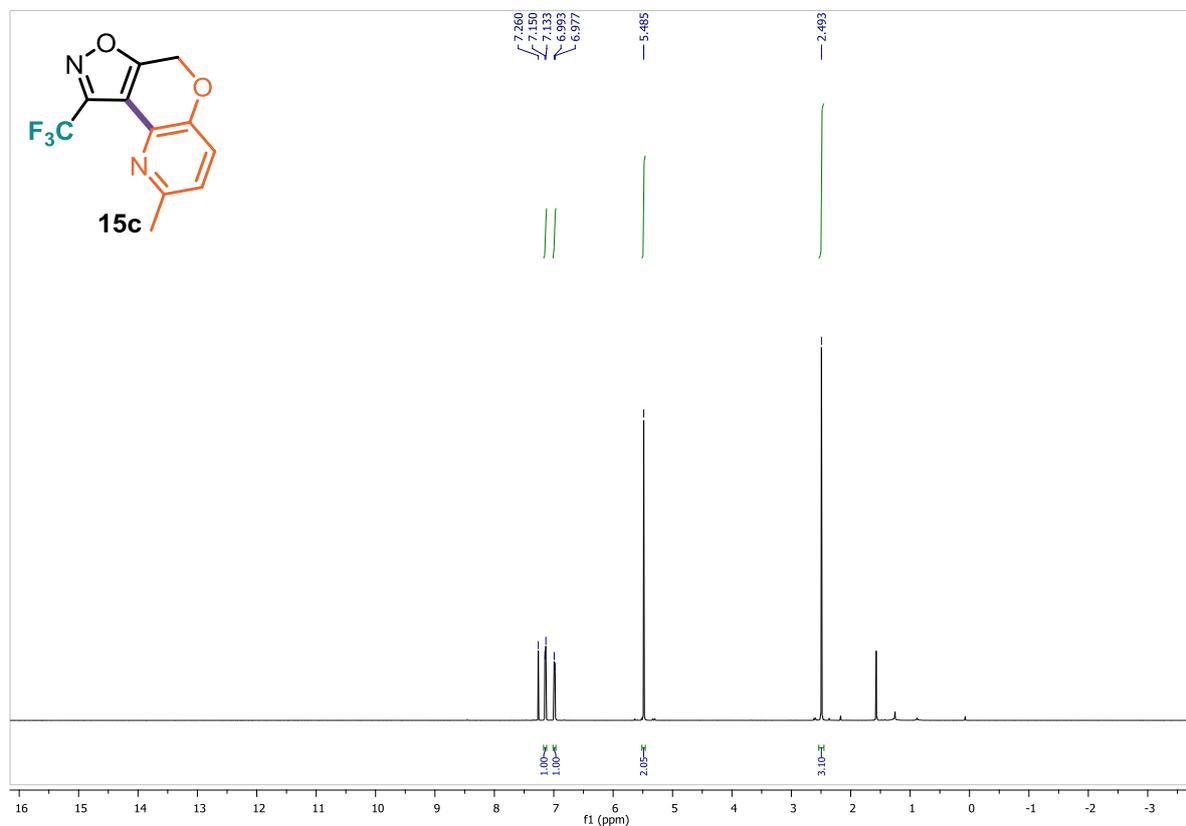


**$^{19}\text{F}$  NMR, 376 MHz,  $\text{CDCl}_3$ :**

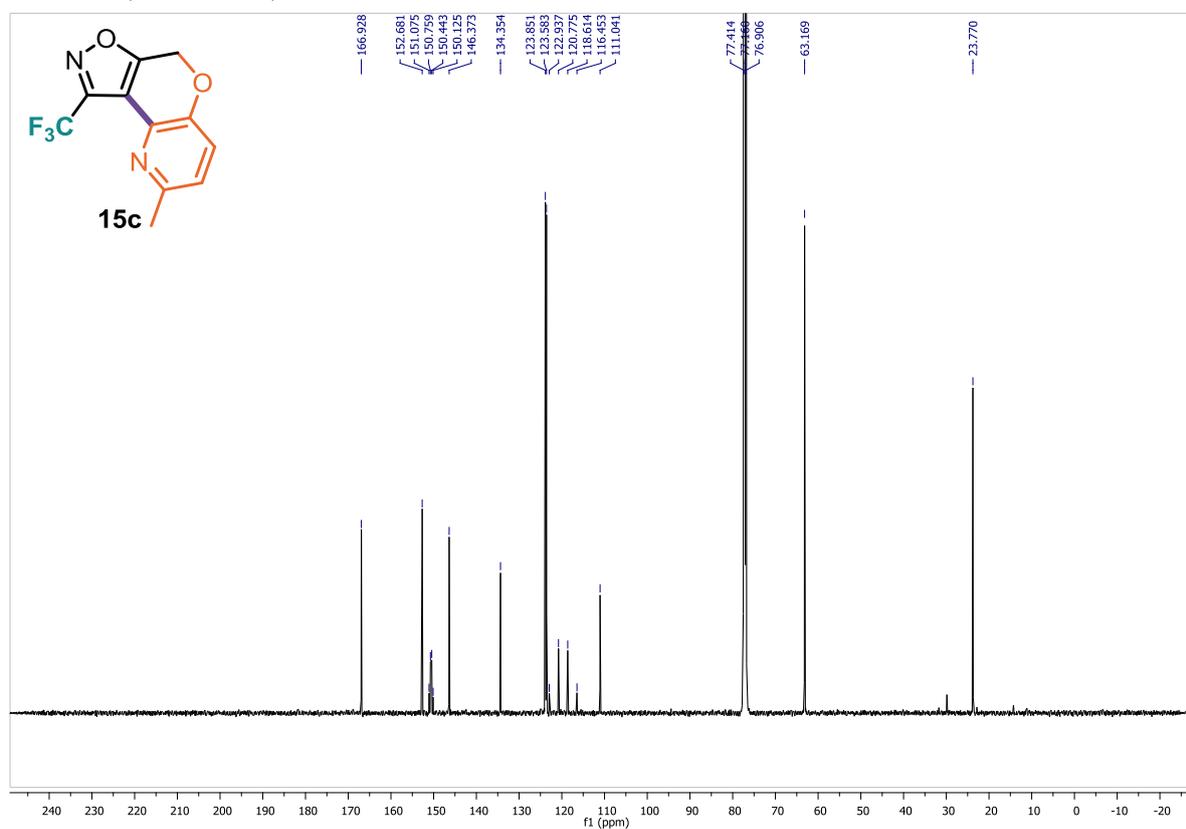


**2-methyl-9-(trifluoromethyl)-6*H*-isoxazolo[4',5':4,5]pyrano[3,2-*b*]pyridine (15c):**

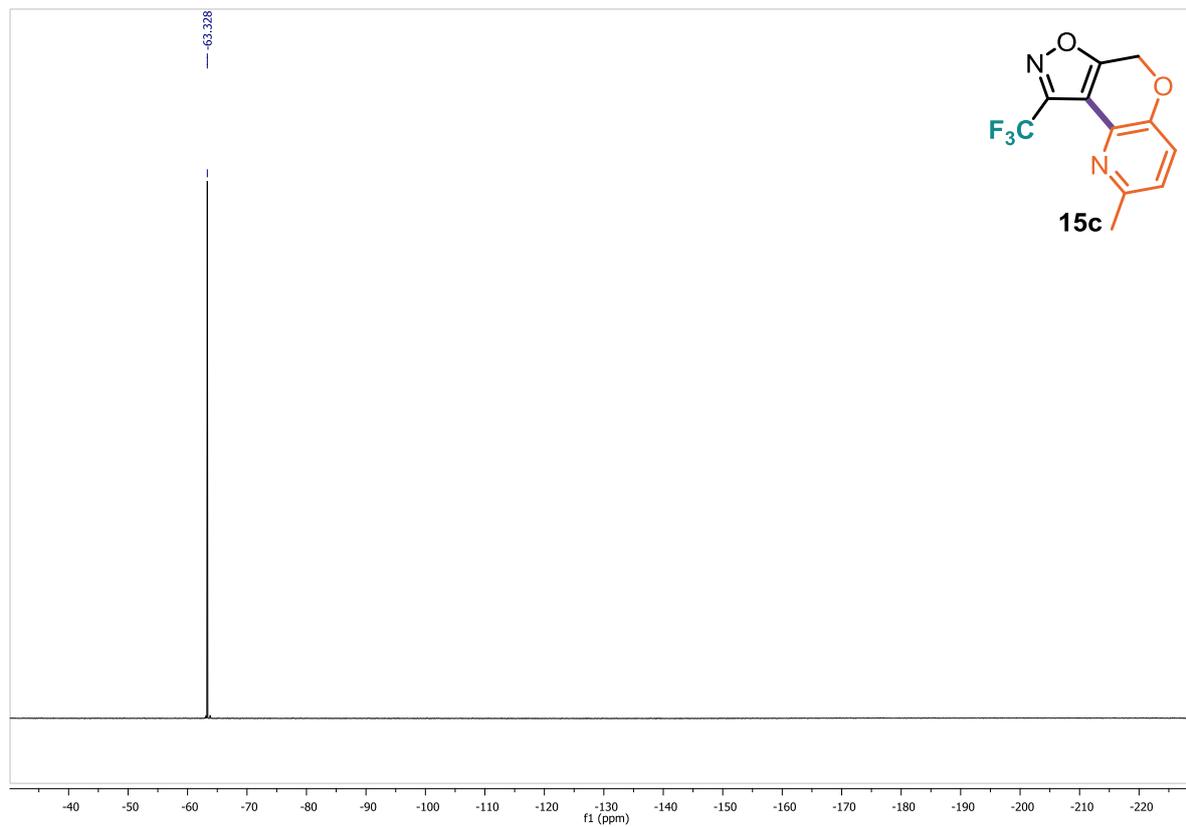
**<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>:**



**<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>:**

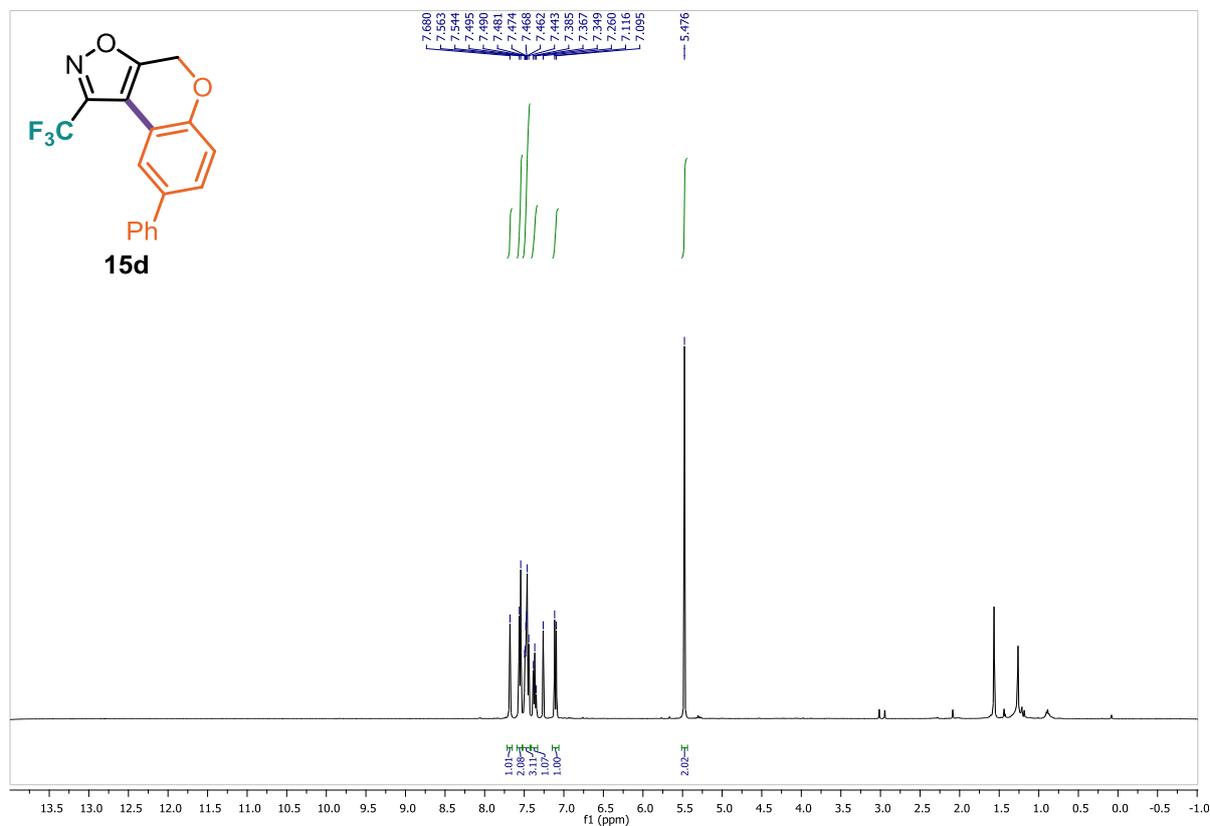


**<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:**

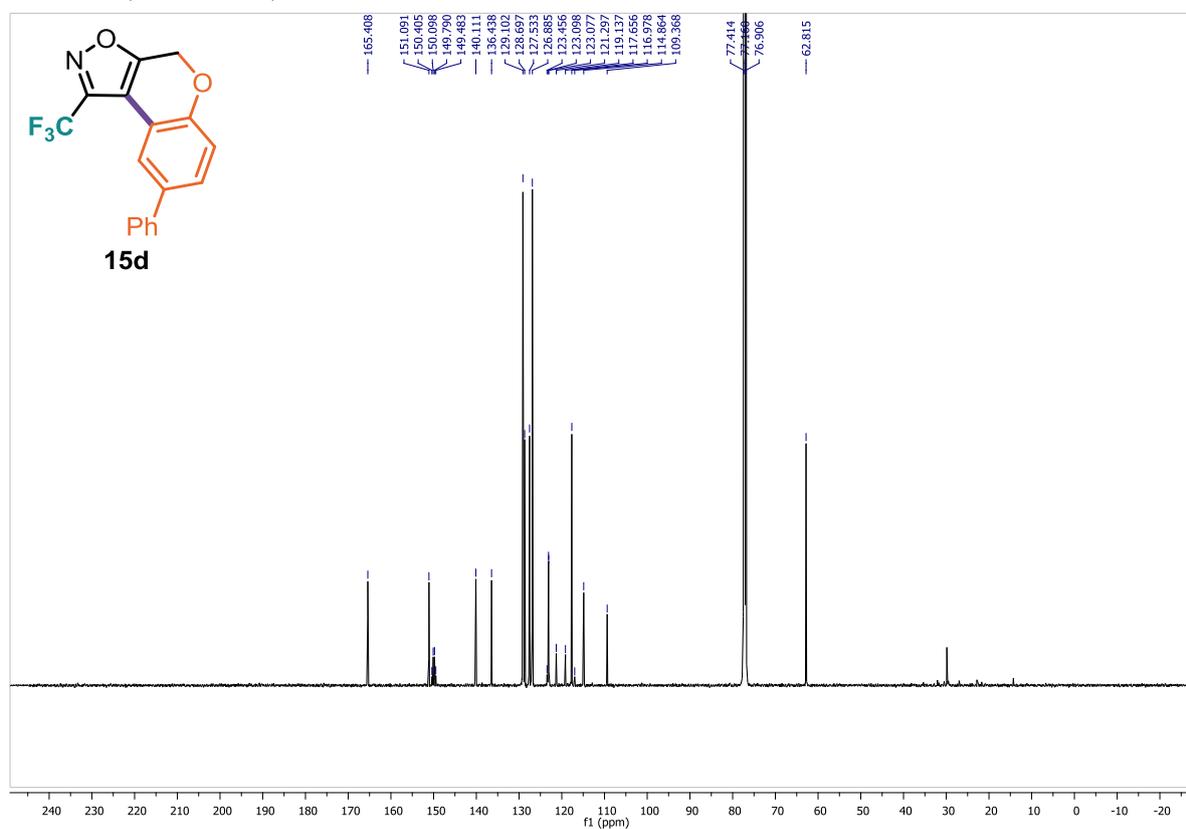


### 8-phenyl-1-(trifluoromethyl)-4*H*-chromeno[4,3-*d*]isoxazole (15d):

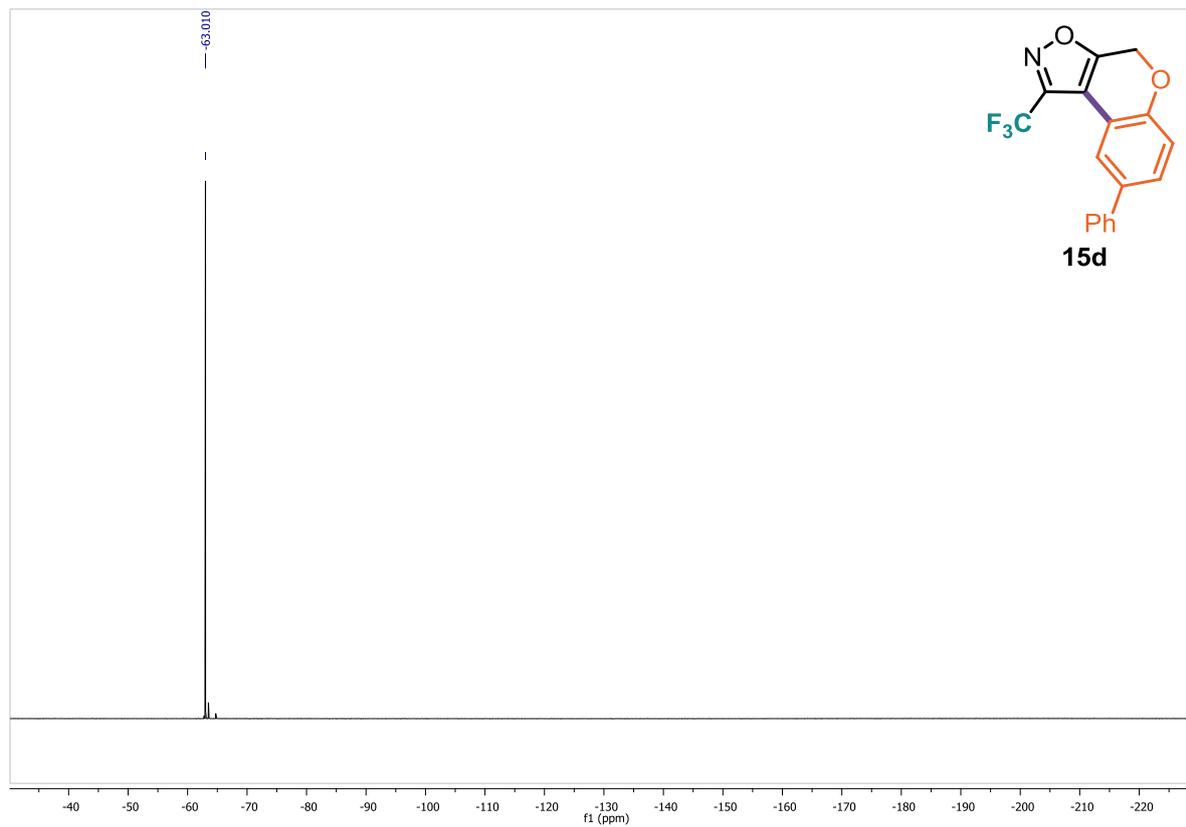
<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>:

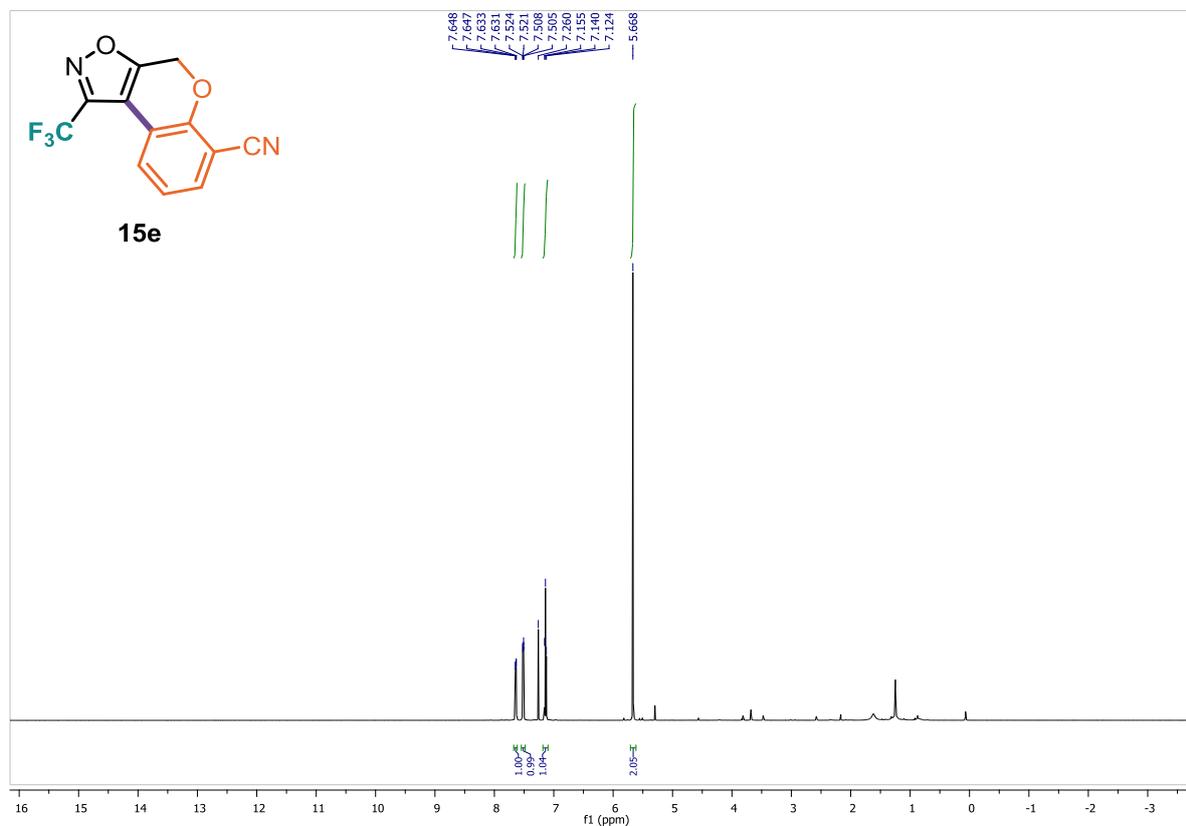


**<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:**

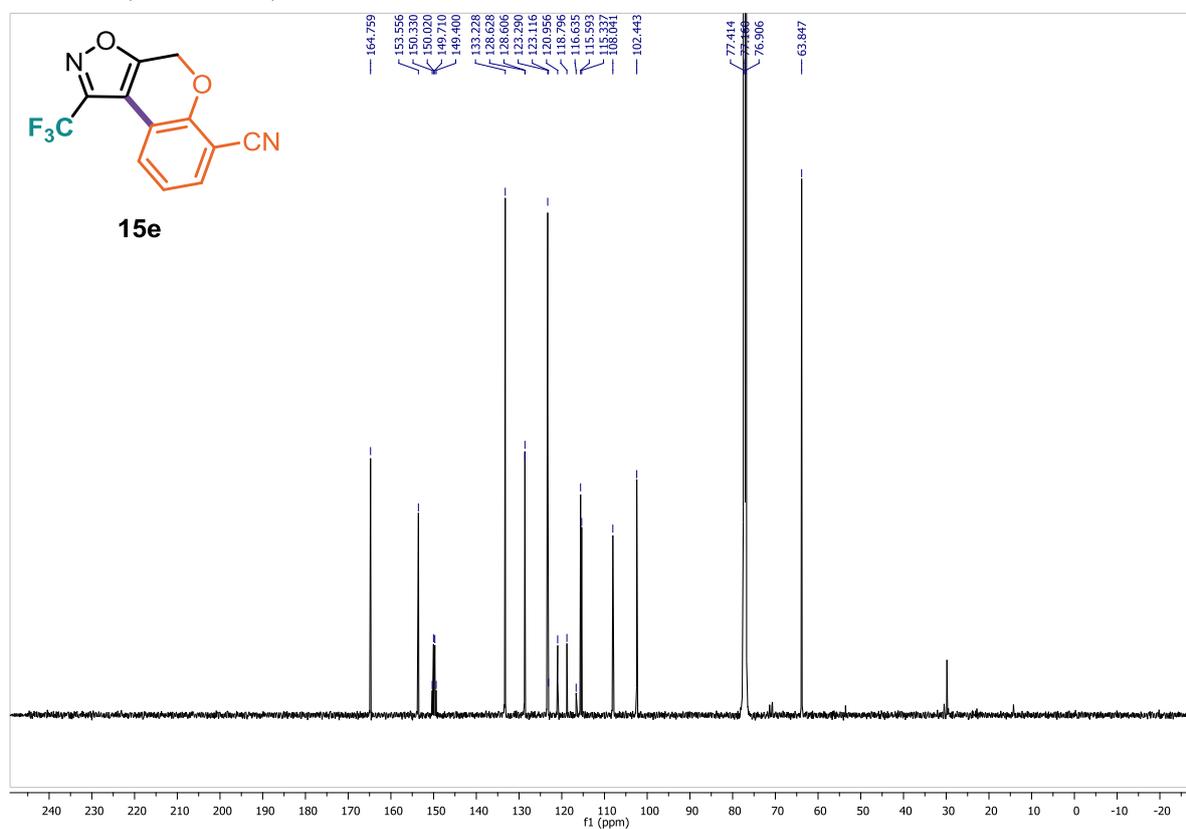


**1-(trifluoromethyl)-4*H*-chromeno[4,3-*d*]isoxazole-6-carbonitrile (15e):**

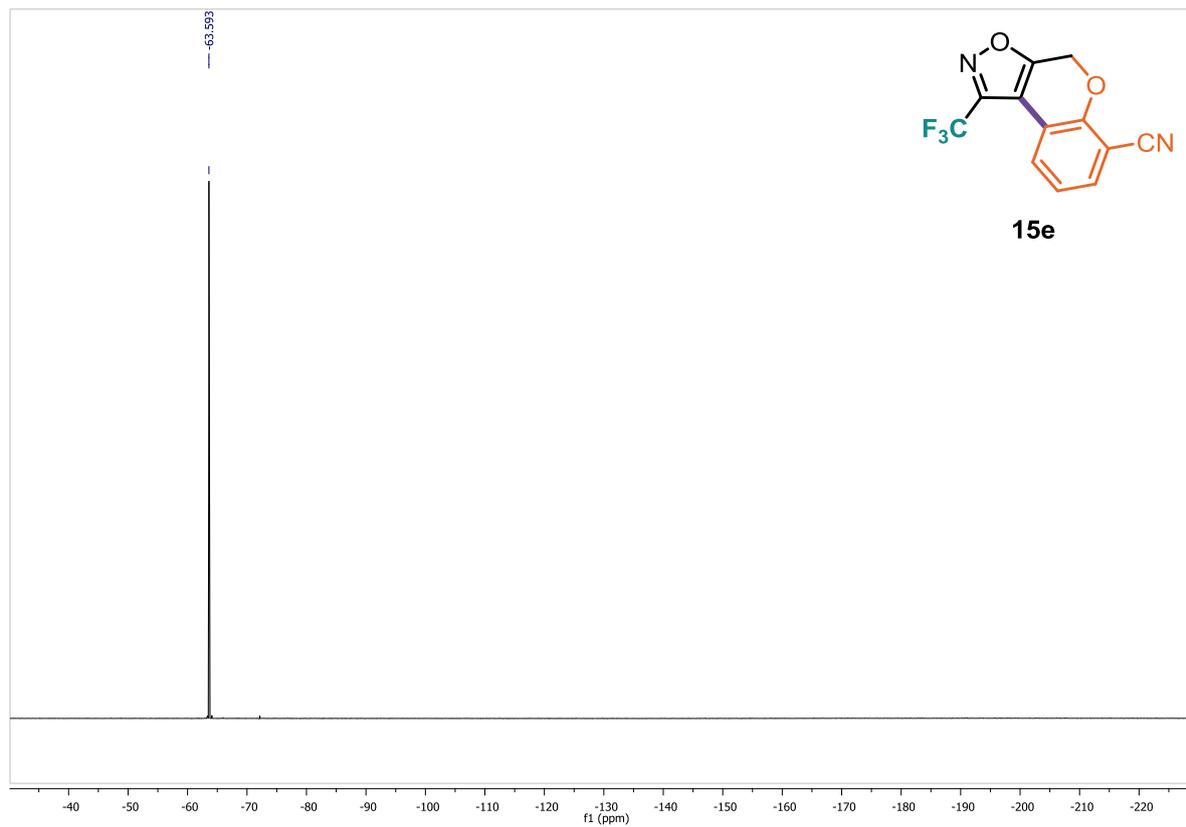
**<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>:**



**<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>:**

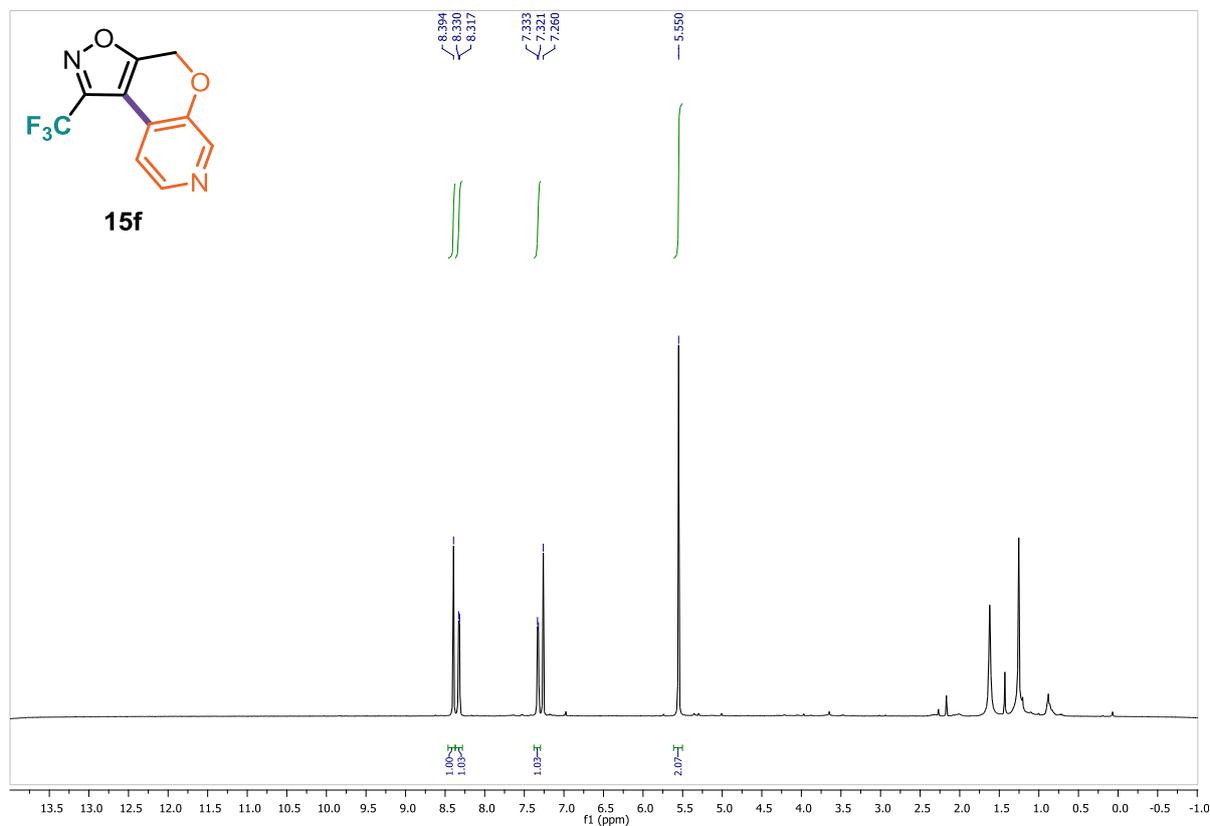


**<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:**

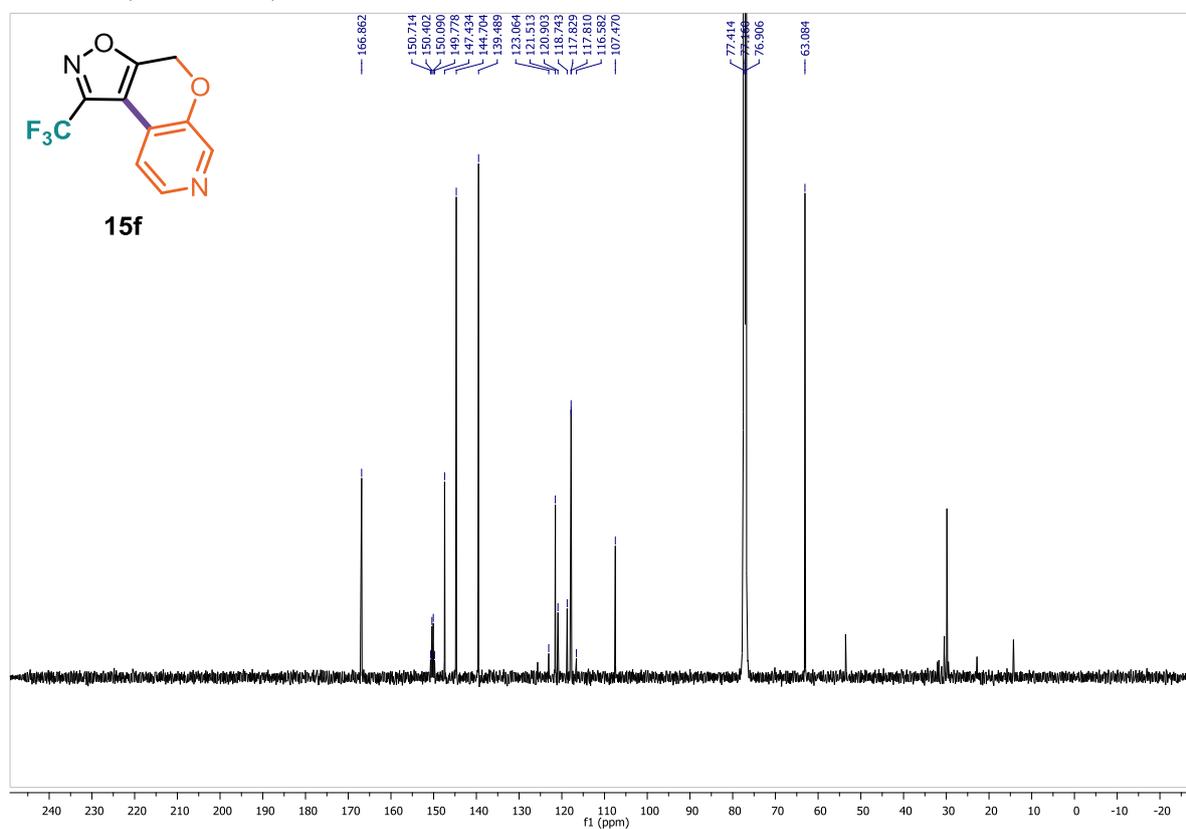


**1-(trifluoromethyl)-4*H*-isoxazolo[4',5':4,5]pyrano[2,3-*c*]pyridine (15f):**

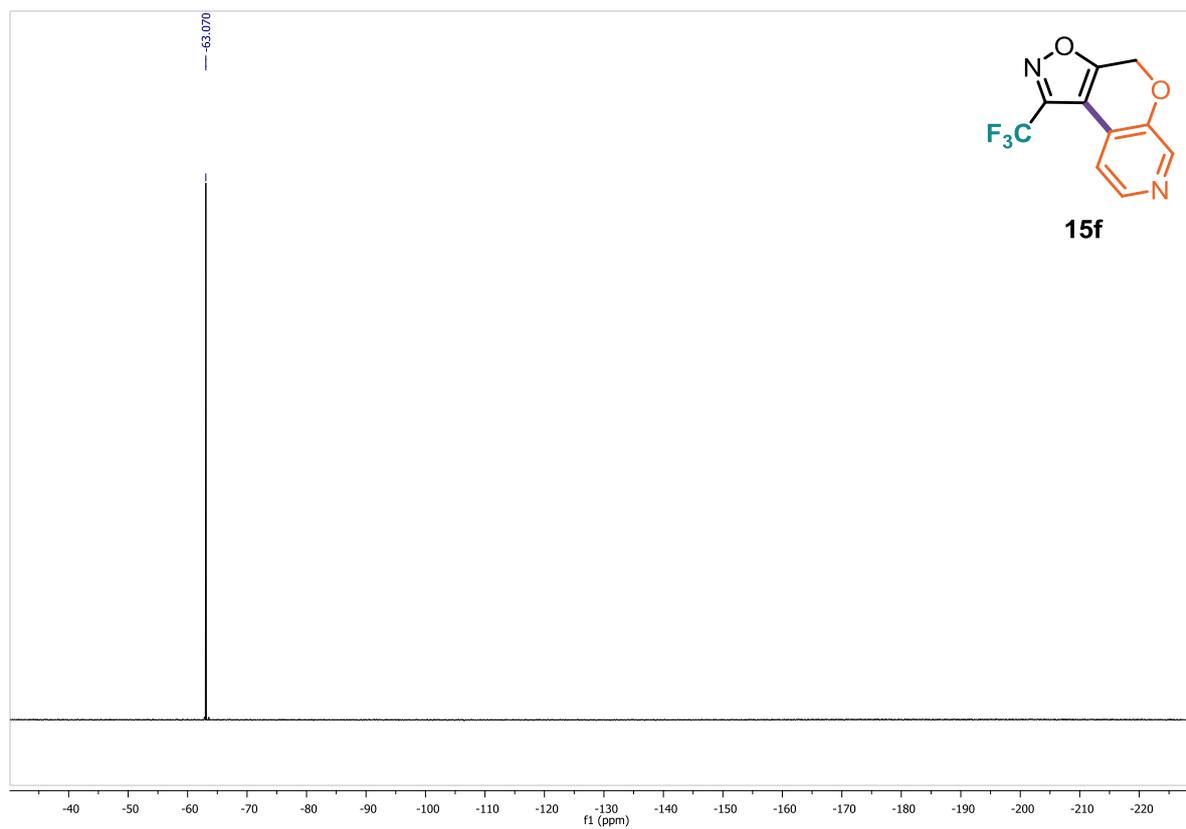
**<sup>1</sup>H NMR, 400 MHz, CDCl<sub>3</sub>:**



**<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>:**

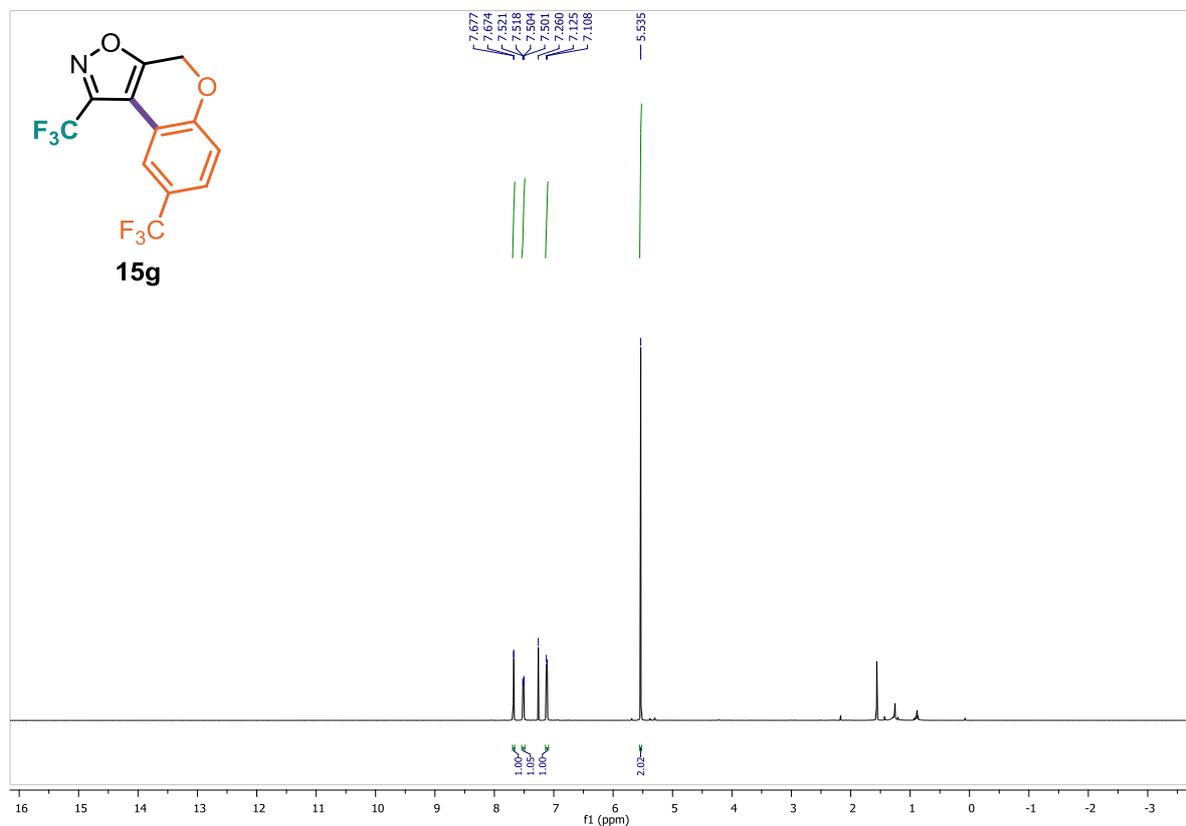


**$^{19}\text{F}$  NMR, 376 MHz,  $\text{CDCl}_3$ :**

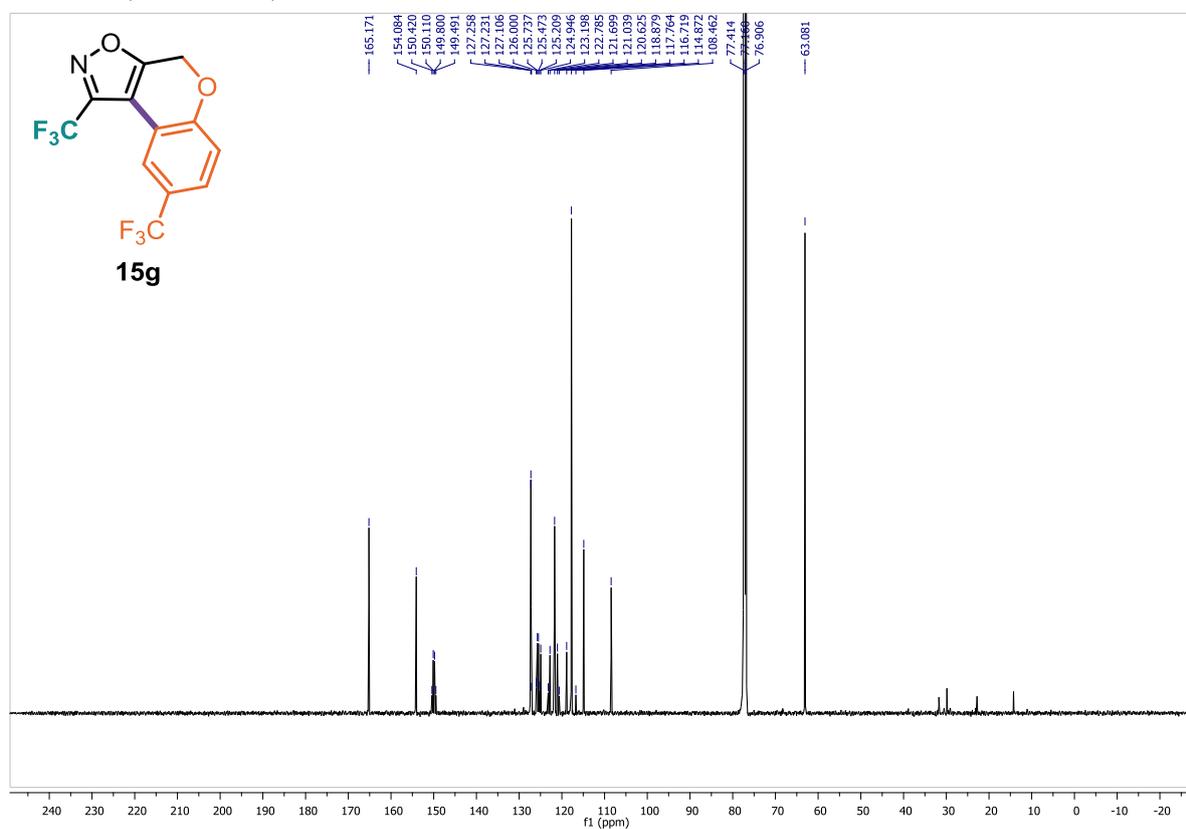


**1,8-bis(trifluoromethyl)-4*H*-chromeno[4,3-*d*]isoxazole (15g):**

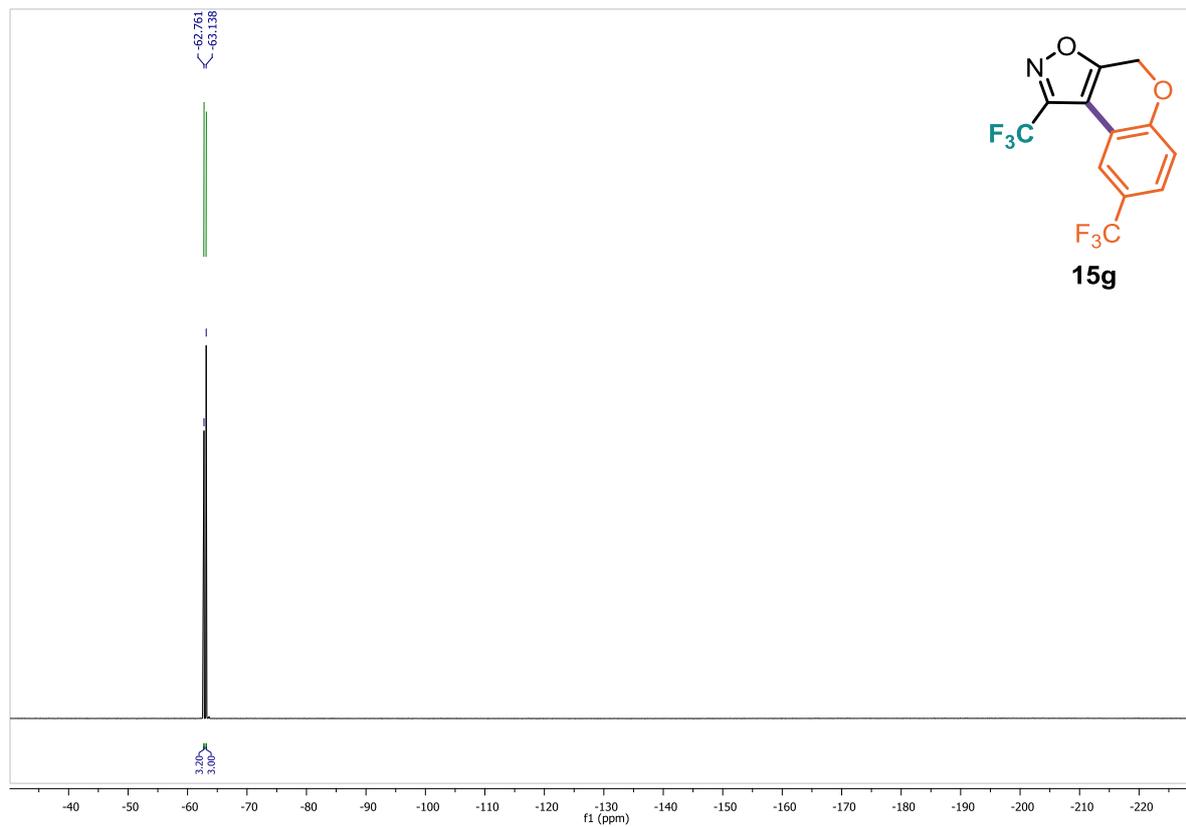
**<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>:**



**<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>:**

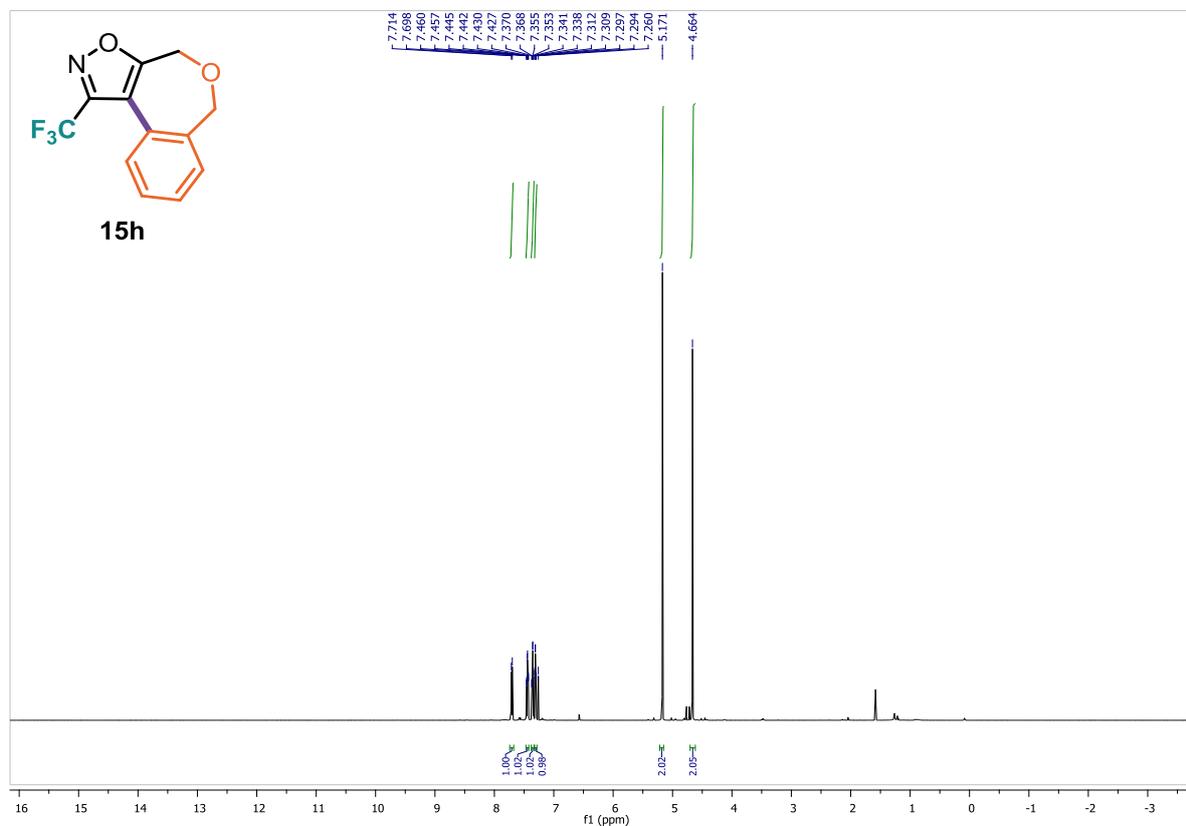


**<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:**

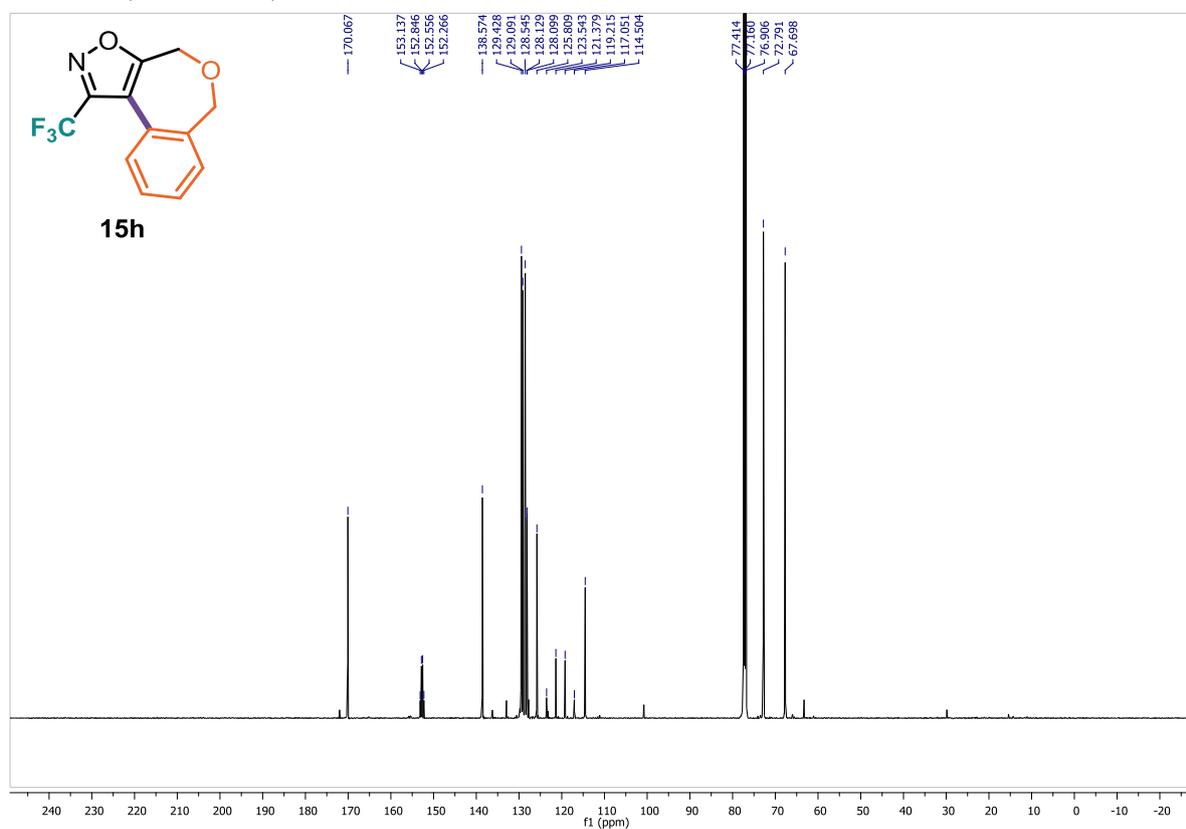


**1-(trifluoromethyl)-4,6-dihydrobenzo[5,6]oxepino[4,3-d]isoxazole (15h):**

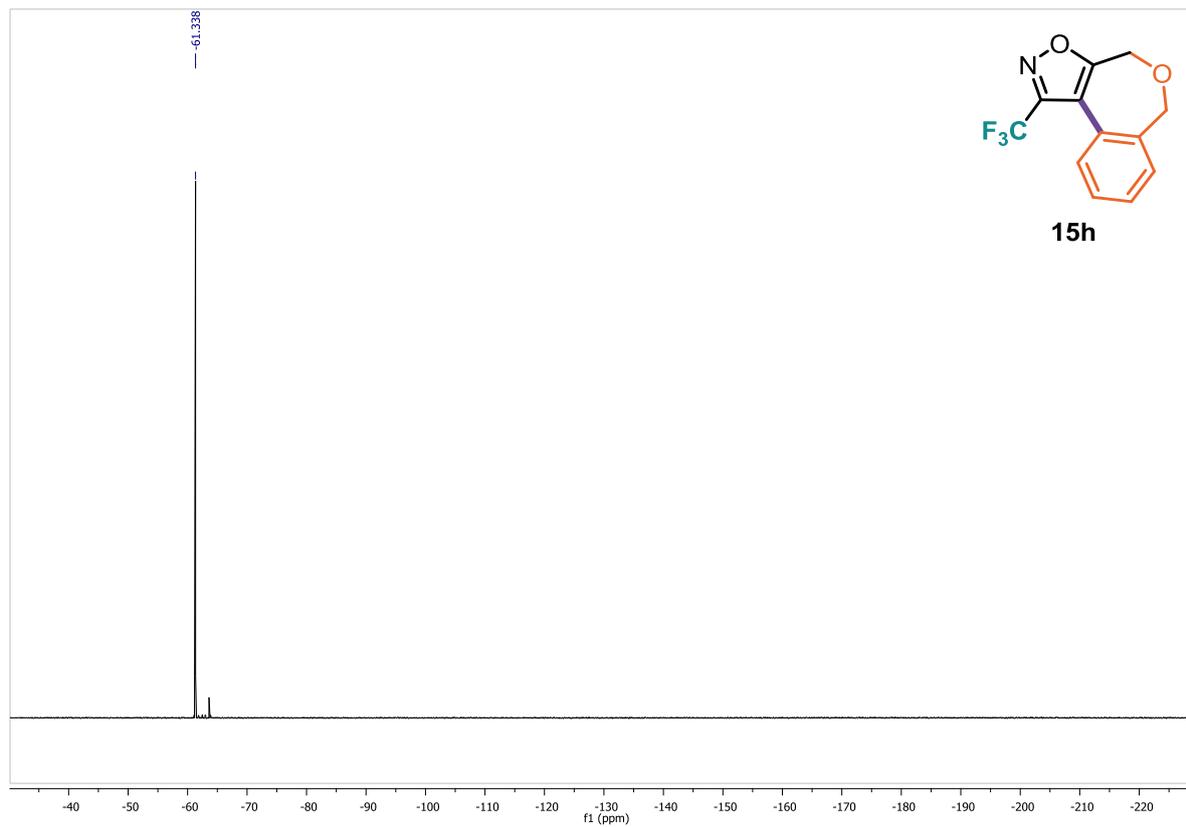
**<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>:**



**<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>:**

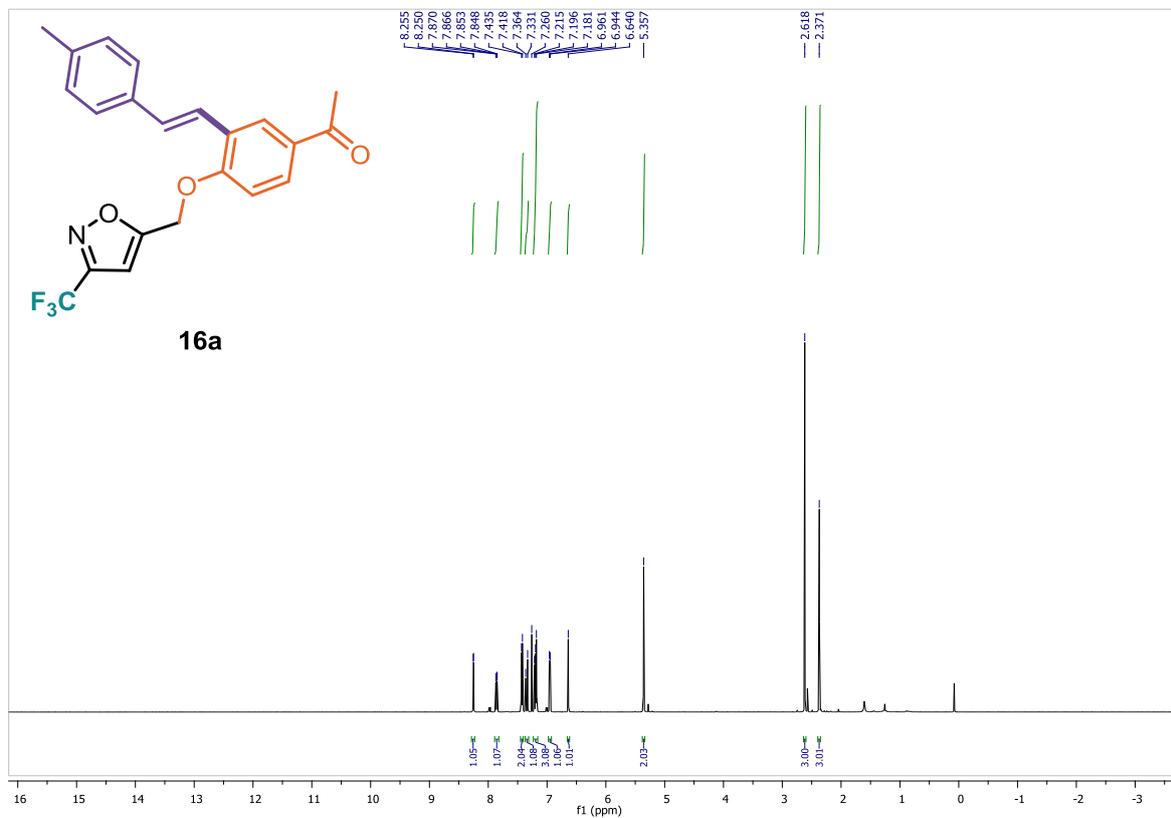


**<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:**

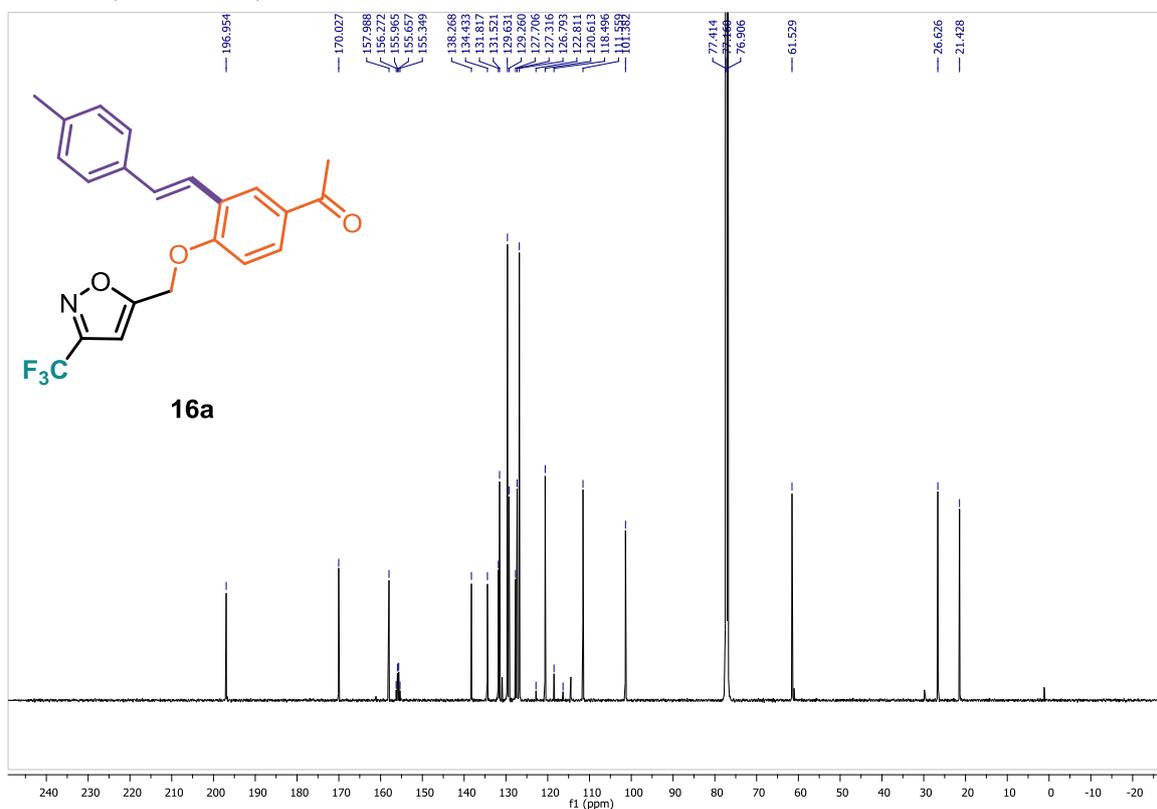


**(E)-1-(3-(4-methylstyryl)-4-((3-(trifluoromethyl)isoxazol-5-yl)methoxy)phenyl)ethan-1-one (16a):**

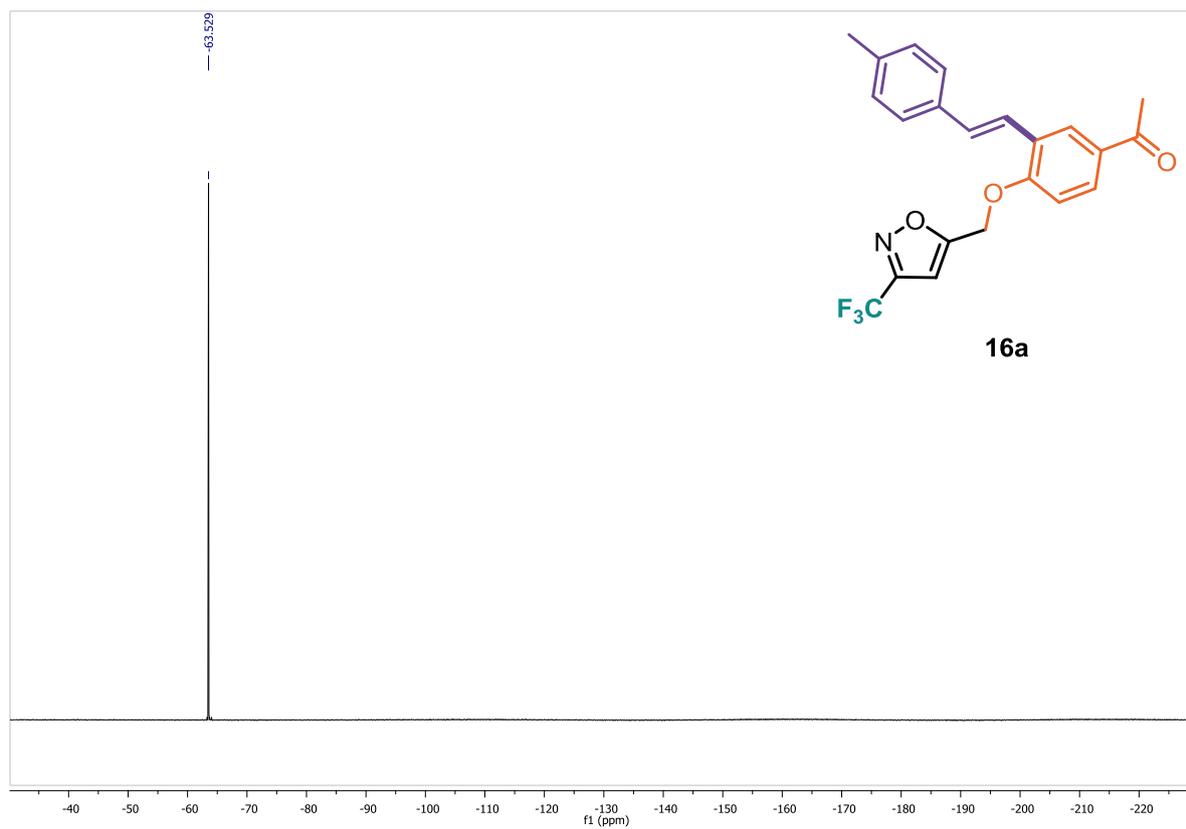
**<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>:**



**<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>:**

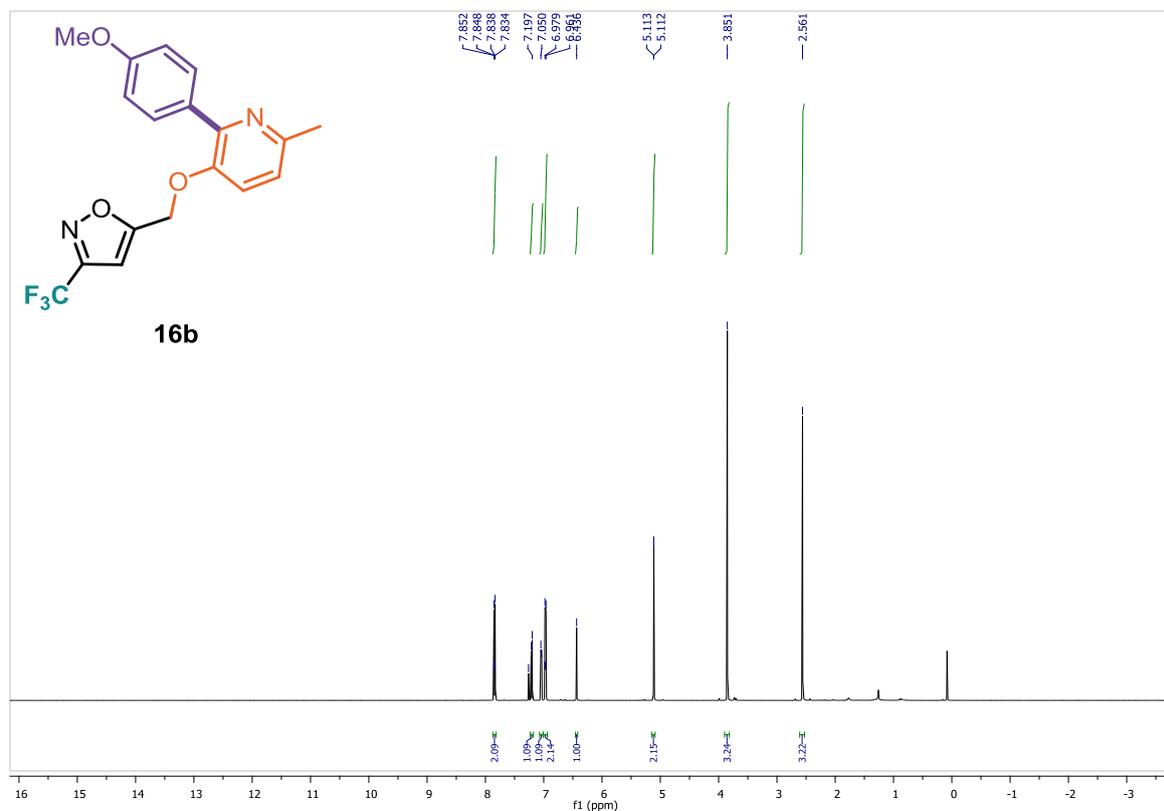


<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:

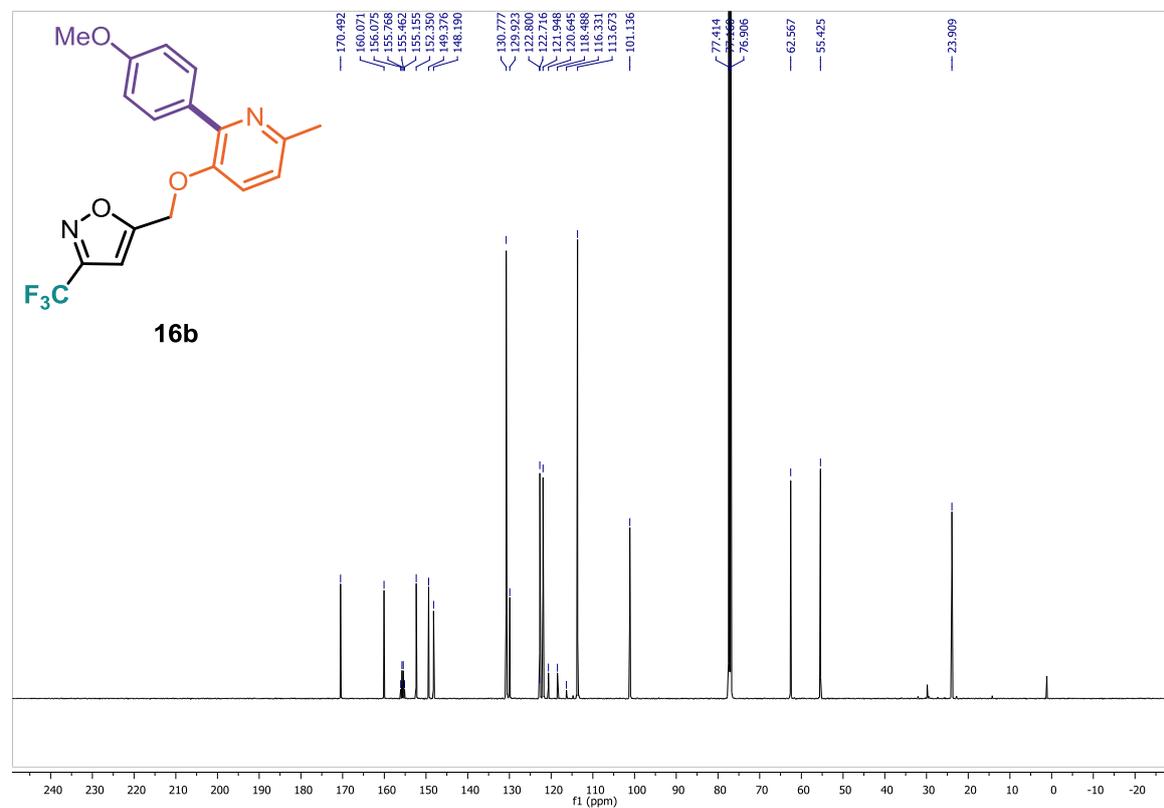


**5-(((2-(4-methoxyphenyl)-6-methylpyridin-3-yl)oxy)methyl)-3-(trifluoromethyl)-isoxazole (16b):**

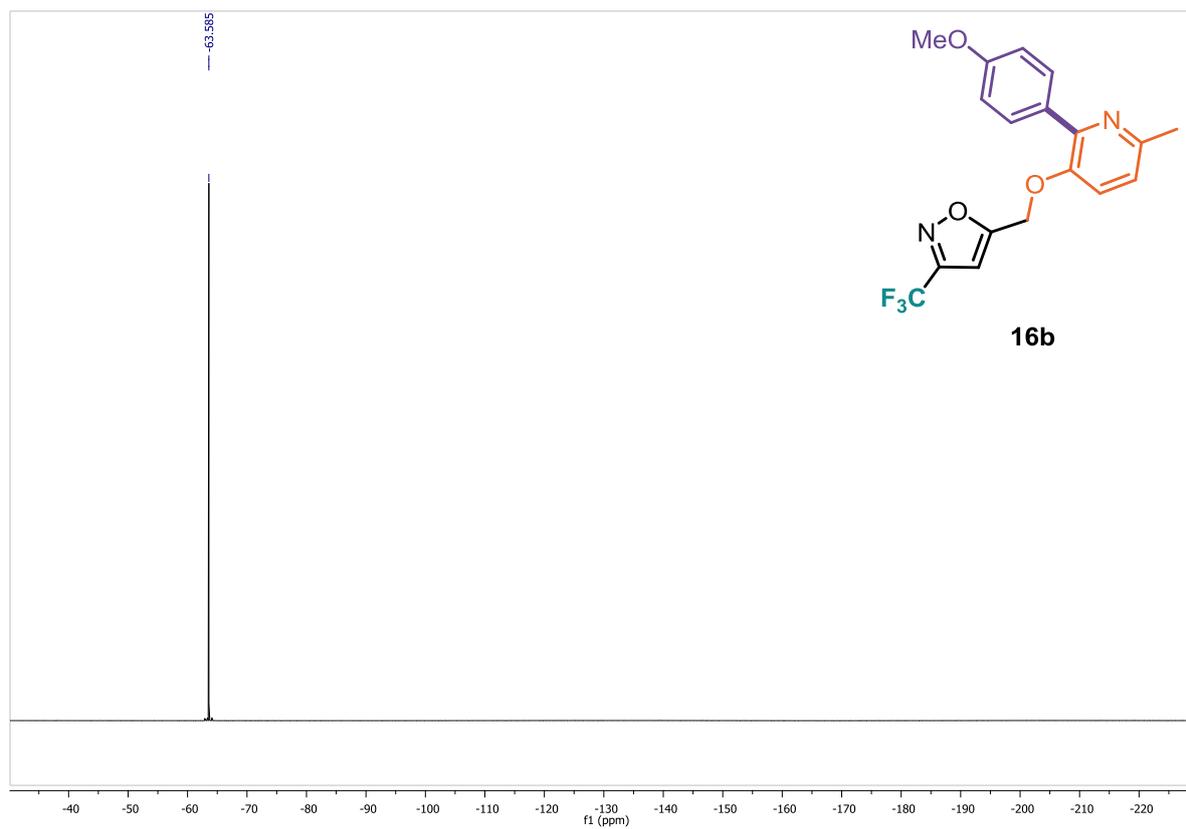
**<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>:**



**<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>:**

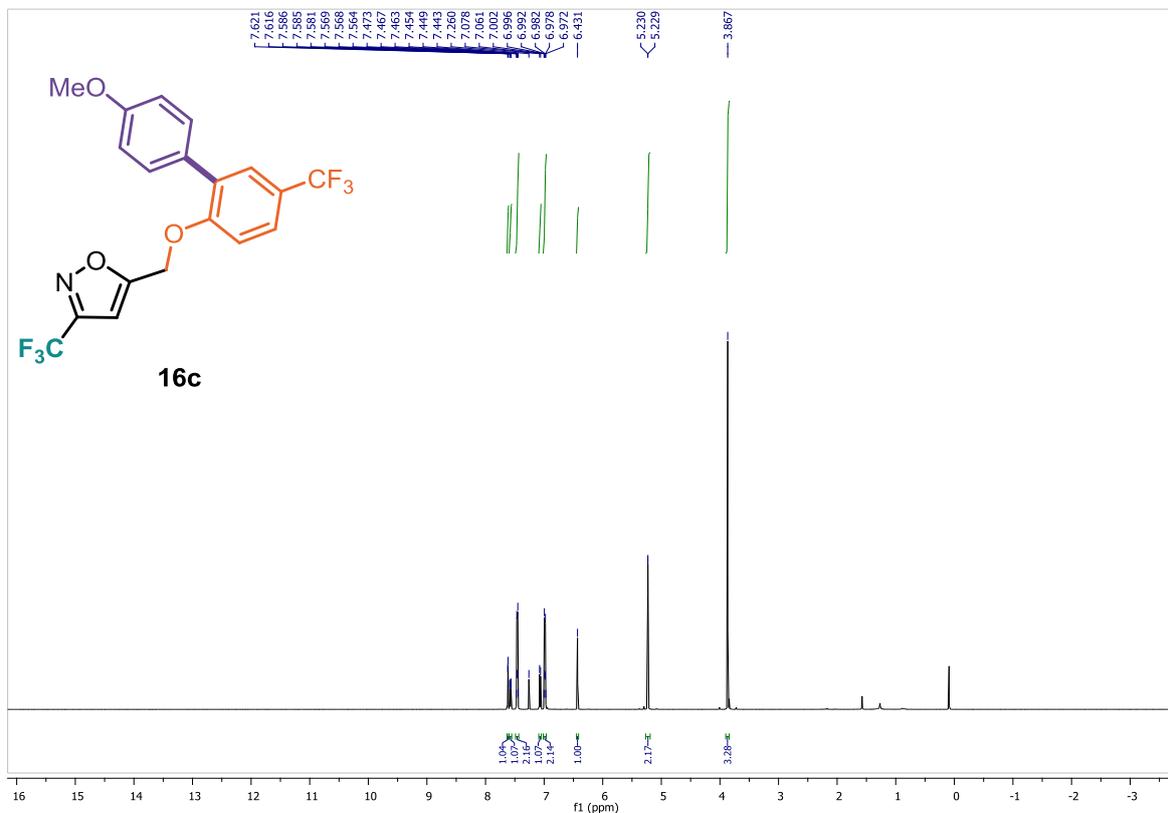


**<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:**

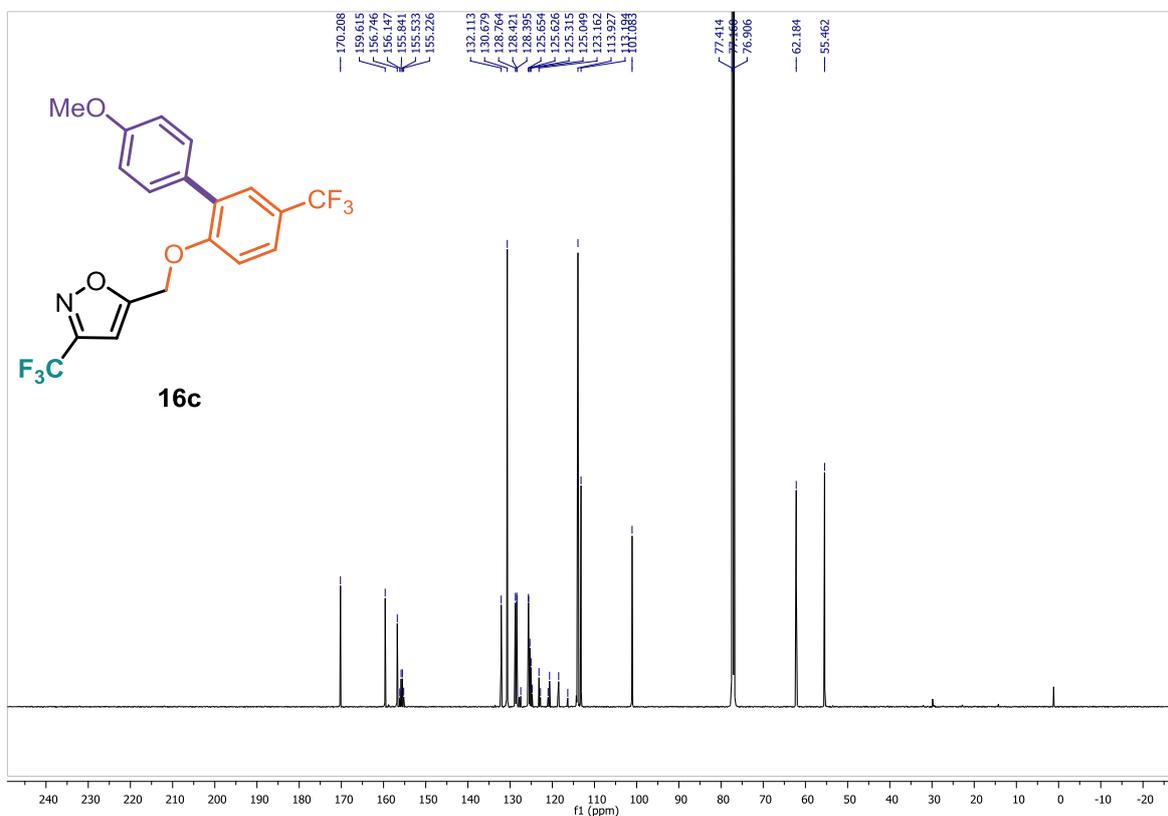


**5-(((4'-methoxy-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)oxy)methyl)-3-(trifluoromethyl)isoxazole (16c):**

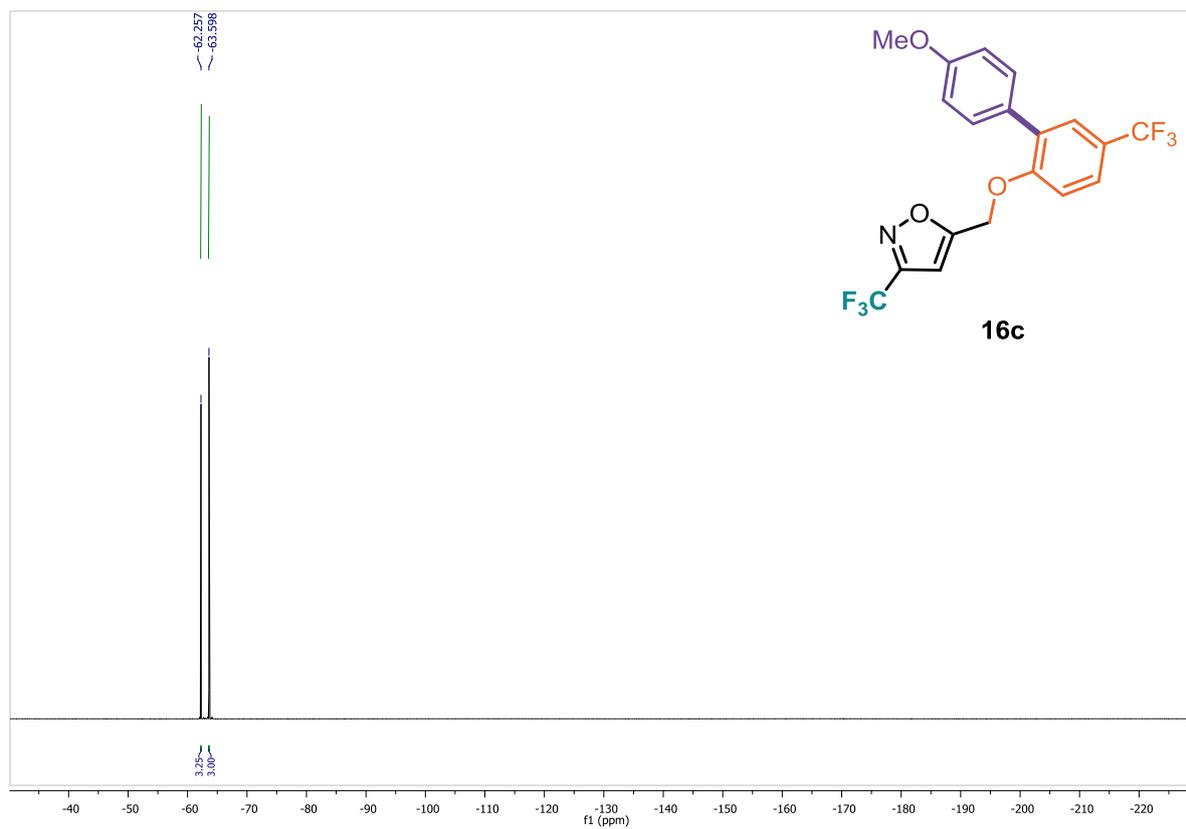
**<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>:**



**<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>:**

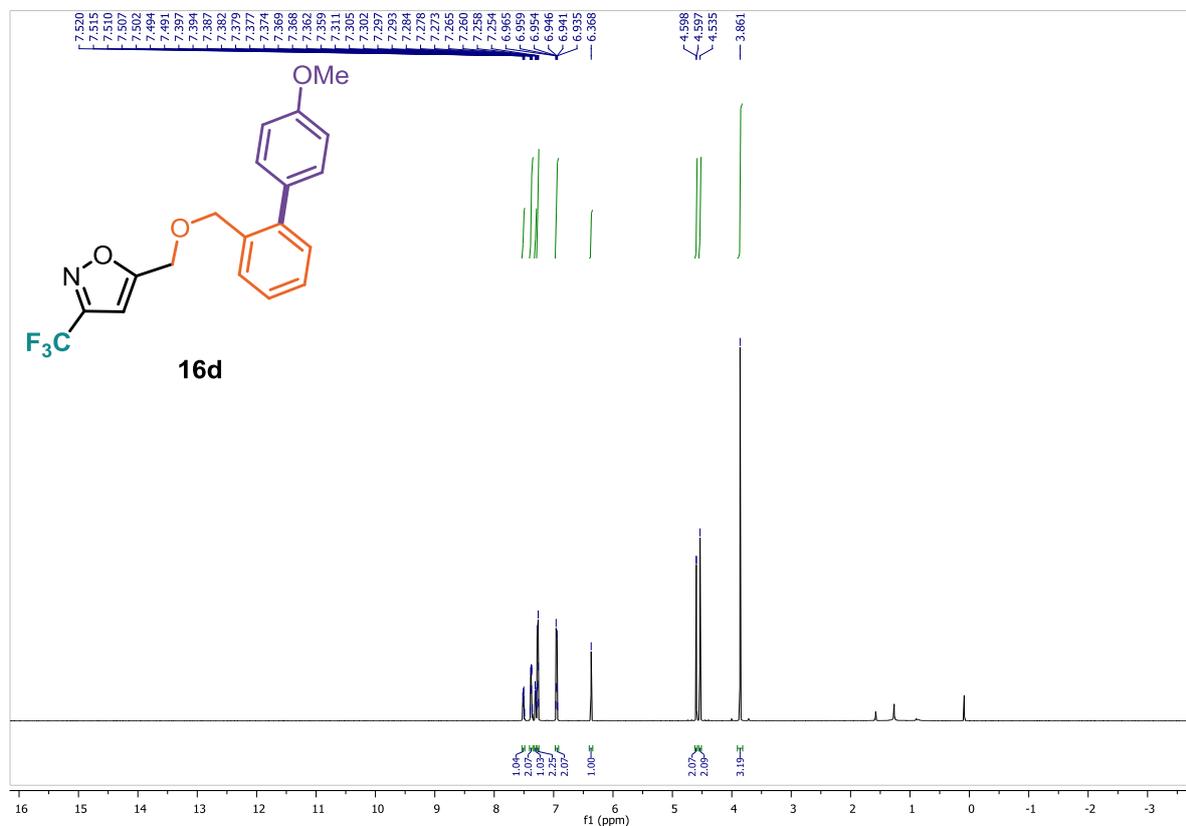


**<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:**

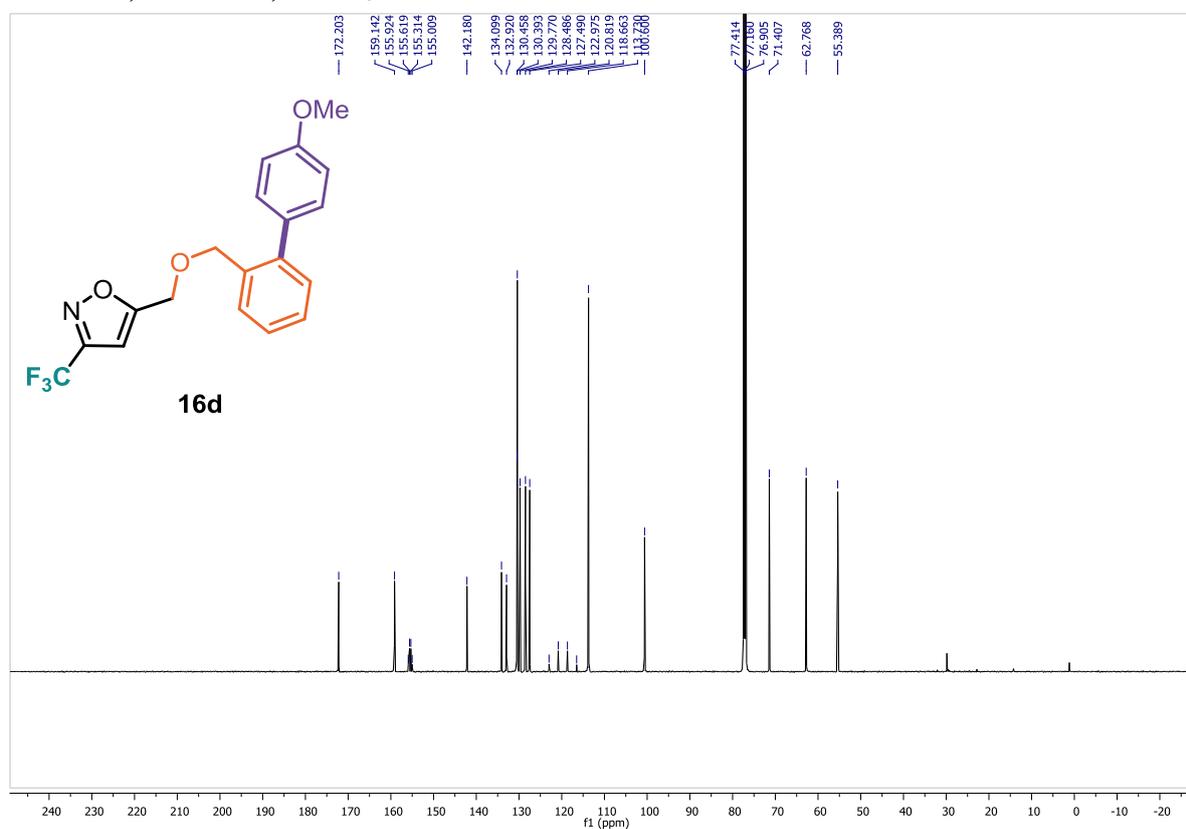


# 5-(((4'-methoxy-[1,1'-biphenyl]-2-yl)methoxy)methyl)-3-(trifluoromethyl)isoxazole (16d):

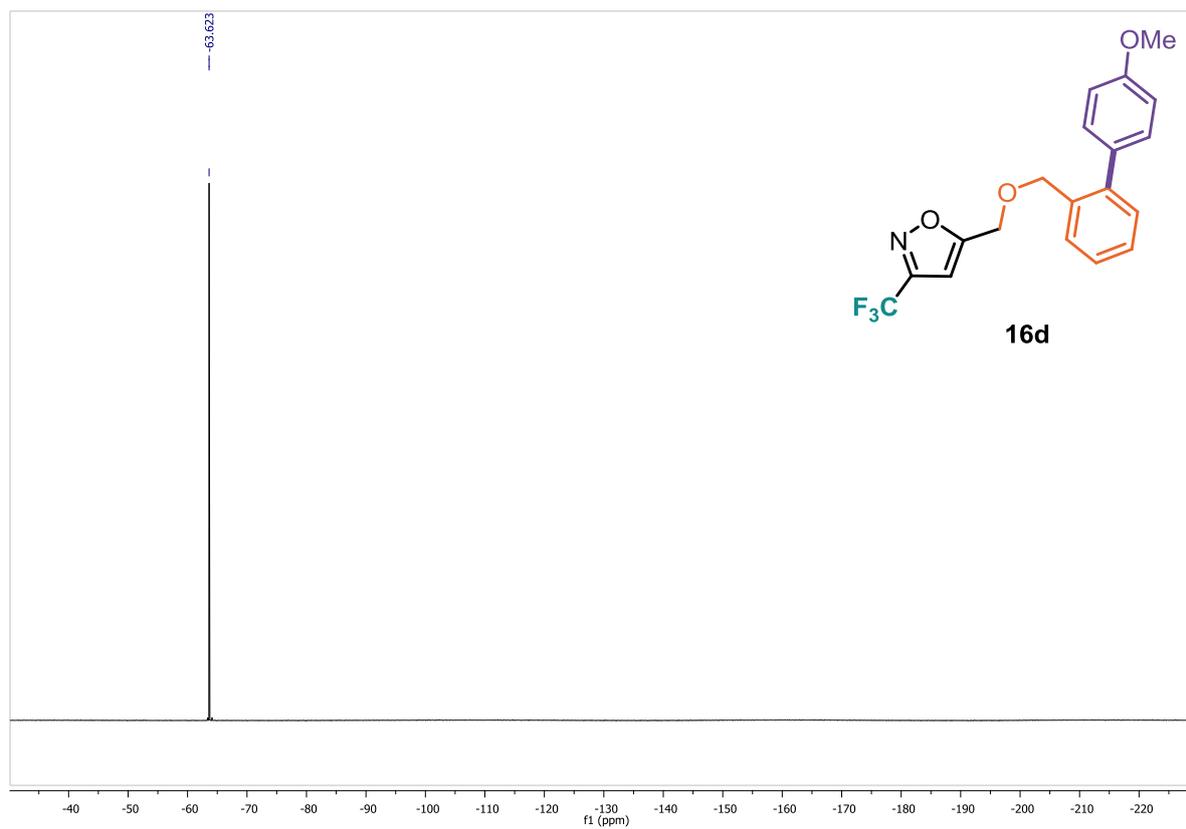
<sup>1</sup>H NMR, 500 MHz, CDCl<sub>3</sub>:



<sup>13</sup>C NMR, 125 MHz, CDCl<sub>3</sub>:



**<sup>19</sup>F NMR, 376 MHz, CDCl<sub>3</sub>:**



## References

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