

## Supporting Information

### **One-Pot Synthesis of Substituted Trifluoromethylated 2,3-Dihydro-1*H*-imidazoles**

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## 1. Materials and methods

All reactions were carried out under argon atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon prior to use. Dry THF was freshly distilled from sodium and benzophenone under argon. Commercially available reagents and solvents were used without further purification. Grignard reagents were purchased from *Aldrich* or synthesized with the described procedure. Reactions were monitored by TLC with pre-coated silica gel 60 F<sub>254</sub> aluminium plates (*Merck KGaA*, Darmstadt) using UV light as the visualizing agent. The *N,O*-acetals and trifluoroethylamines used in the described protocols below were synthesized according to literature procedures.<sup>1</sup> The crude products were purified by standard flash chromatography using silica gel (35–70  $\mu$ m) from *Acros Organics*. Analytical RP-HPLC was measured on a *JASCO* system with a *Phenomenex Luna* C18 column (5  $\mu$ m, 250  $\times$  4.6 mm). ESI- and HR-ESI-mass spectra were recorded on a *Thermo Finnigan LTQ FT* or on a *Bruker maxis* equipped with a *Waters Acquity UPLC* using a *Kinetex* C18 column (2.6  $\mu$ m, 100 Å) at 40 °C. In all cases, mixtures of water (eluent A) and acetonitrile (eluent B) were used as solvents; if required, 0.05 % formic acid or 0.1 % TFA were added. <sup>1</sup>H, <sup>13</sup>C, and <sup>19</sup>F NMR spectra were recorded on a *Varian* 300 MHz and 600 MHz spectrometer or on a *Bruker Avance II* 400 MHz spectrometer in DMSO-d<sub>6</sub> or CDCl<sub>3</sub>. The chemical shifts are reported in ppm relative to the signal of the deuterated solvent. Multiplicities are given as: s (singlet), br s (broad singlet), d (doublet), t (triplet), and m (multiplet). Melting points were measured on a Melting Point *B-540 Büchi*.

## 2. Experimental procedures and analytic data

### 2.1 Typical Procedures

#### Typical procedure for the synthesis of CF<sub>3</sub>-imidazole derivatives 2, Typical Procedure TPI:

The hemiaminal ether **1** (1 equiv) was solved in freshly distilled THF in a dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum and cooled to –15 °C. The *Grignard* reagent (3 equiv) was added dropwise with a syringe and the solution was stirred until TLC-analysis showed complete conversion. Subsequently, sat. NH<sub>4</sub>Cl solution was added and the mixture was extracted three times with Et<sub>2</sub>O. The organic solvent was dried with MgSO<sub>4</sub>, filtrated and evaporated and the crude product was purified by flash chromatography (SiO<sub>2</sub>).

#### Typical Procedure for the magnesium insertion, Typical procedure TPII:

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with *i*PrMgCl·LiCl (1.25 M in THF, 1.1 equiv). The neat aryl bromide (1 equiv) was added at the appropriate temperature. The reaction mixture was stirred at the stated temperature, while the completion of the Br/Mg exchange was monitored by GC-analysis.

#### Typical procedure for the synthesis of CF<sub>3</sub>-imidazole derivatives 2 with *n*BuLi, Typical Procedure TPIII:

The hemiaminal ether **1** (1 equiv) and trifluoroethylamine **3** (1 equiv) were solved in freshly distilled THF in a dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum and cooled to –60 °C. *n*BuLi (3 equiv) was added dropwise with a syringe, the solution was stirred at –60 °C for 30 min, warmed up to –30 °C and stirred until no further conversion was observed. Subsequently, sat. NH<sub>4</sub>Cl solution was added and the mixture was extracted three times with Et<sub>2</sub>O. The organic solvent was dried with MgSO<sub>4</sub>, filtrated and evaporated and the crude product was purified by flash chromatography (SiO<sub>2</sub>).

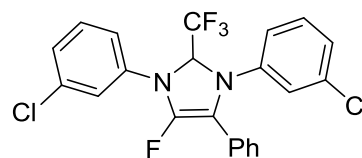
### 2.2 Synthesis of CF<sub>3</sub>-imidazole derivatives

#### 1,3-bis(3-Chlorophenyl)-4-fluoro-5-phenyl-2-(trifluoromethyl)-2,3-dihydro-1*H*-imidazole **2a** and 3-chloro-*N*-(2,2,2-trifluoro-1-phenylethyl)aniline **3a**

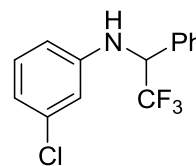
According to the **TPI**, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** (200 mg, 0.79 mmol) was reacted with PhMgCl (1.0 M in MeTHF, 2.37 mL, 2.37 mmol) in dry THF (12 mL) for 3 h at 0 °C. The crude product was purified by flash chromatography (SiO<sub>2</sub>, cyclohexane → cyclohexane/DCM 20:1) to give the desired imidazole derivative **2a** (125 mg, 70%) as a yellow solid and 3-chloro-*N*-(2,2,2-trifluoro-1-phenylethyl)aniline **3a** (36.0 mg, 16%) as a light yellow liquid.

**1,3-bis(3-Chlorophenyl)-4-fluoro-5-phenyl-2-(trifluoromethyl)-2,3-dihydro-1H-imidazole 2a**

**R<sub>f</sub>** (cyclohexane/ethyl acetate 10:1) = 0.60. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.51 – 7.46 (m, 2 H, H2'', H6''), 7.38 – 7.33 (m, 2 H, H3'', H5''), 7.31 – 7.24 (m, 2 H, H4'', H5'), 7.15 (tdd,  $J_{H2',H4'} = J_{H2',H6'} = 1.9$  Hz,  $J_{H2',H5'} = J_{H2',CH} = 0.4$  Hz, 1 H, H2'), 7.12 (ddd,  $J_{H4',H5'} = 8.0$  Hz,  $J_{H4',H2'} = 1.9$  Hz,  $J_{H4',H6'} = 0.9$  Hz, 1 H, H4'), 7.12 (ddd,  $J_{H5,H6} = 8.1$  Hz,  $J_{H5,H4} = 7.7$  Hz,  $J_{H5,H2} = 0.7$  Hz, 1 H, H5), 7.05 (dtd,  $J_{H6',H5'} = 8.1$  Hz,  $J_{H6',H2'} = 2.3$  Hz,  $J_{H6',H4'} = 0.9$  Hz, 1 H, H6'), 7.03 – 6.99 (m, 2 H, H2, H4), 6.88 (ddd,  $J_{H6,H5} = 8.1$  Hz,  $J_{H6,H2} = 2.2$  Hz,  $J_{H6,H4} = 1.1$  Hz, 1 H, H6), 5.11 – 5.03 (m, 1 H, CH) ppm. **<sup>19</sup>F NMR** (282 MHz, CDCl<sub>3</sub>):  $\delta$  = -83.32 (d,  $J_{CF_3,CH} = 4.9$  Hz, CF<sub>3</sub>), -135.19 (dt,  $J_{CF,CH} = 4.5$  Hz,  $J = 2.2$  Hz, CF) ppm. **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 149.11 (d,  $J_{C,F} = 1.5$  Hz, C1), 147.25 (d,  $J_{C,F} = 277.5$  Hz, CF), 145.46 (d,  $J_{C,F} = 6.0$  Hz, C1'), 135.81 (C3'), 135.46 (C3), 131.11 (C5'), 130.71 (C5), 129.16 (d,  $J_{C,F} = 0.9$  Hz, C3'', C5''), 128.67 (d,  $J_{C,F} = 7.0$  Hz, C1''), 128.12 (d,  $J_{C,F} = 2.0$  Hz, C4''), 126.51 (d,  $J_{C,F} = 5.1$  Hz, C2'', C6''), 125.37 (C4'), 124.91 (C4), 122.69 (q,  $J_{C,F} = 282.9$  Hz, CF<sub>3</sub>), 121.46 (C2), 120.08 (d,  $J_{C,F} = 2.4$  Hz, C2'), 119.30 (C6), 117.87 (d,  $J_{C,F} = 1.9$  Hz, C6'), 110.52 (d,  $J_{C,F} = 21.8$  Hz, FCCN), 85.10 (qd,  $J_{C,F} = 34.7$  Hz,  $J_{C,F} = 5.4$  Hz, CH) ppm. **HRMS** (EI):  $m/z$  calcd. for C<sub>22</sub>H<sub>14</sub>Cl<sub>2</sub>F<sub>4</sub>N<sub>2</sub> [M] 452.0470, found 452.0467. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min):  $t_R$  = 17.20 min,  $\lambda$  = 214 nm. **mp** 93 °C.

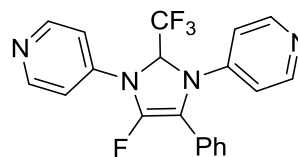
**3-Chloro-N-(2,2,2-trifluoro-1-phenylethyl)aniline 3a**

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.48 – 7.36 (m, 5 H, 5 × H<sub>phenyl</sub>), 7.07 (t,  $J_{H5,H4} = J_{H5,H6} = 8.1$  Hz, 1 H, H5), 6.75 (ddd,  $J_{H4,H5} = 7.9$  Hz,  $J_{H4,H2} = 1.9$  Hz,  $J_{H4,H6} = 0.9$  Hz, 1 H, H4), 6.65 (t,  $J_{H2,H4} = J_{H2,H6} = 2.1$  Hz, 1 H, H2), 6.51 (ddd,  $J_{H6,H5} = 8.2$  Hz,  $J_{H6,H2} = 2.3$  Hz,  $J_{H6,H4} = 0.8$  Hz, 1 H, H6), 4.89 (q,  $J_{CH,CF_3} = 7.2$  Hz, 1 H, CH), 4.40 (s, 1 H, NH) ppm. **<sup>19</sup>F NMR** (280 MHz, CDCl<sub>3</sub>):  $\delta$  = -74.02 (d,  $J_{CF_3,CH} = 7.2$  Hz, CF<sub>3</sub>) ppm. **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 146.62 (C1), 135.08 (C3), 133.48 (C1<sub>phenyl</sub>), 130.32 (C5), 129.31 (C4<sub>phenyl</sub>), 129.01 (C3<sub>phenyl</sub>, C5<sub>phenyl</sub>), 127.80 (C2<sub>phenyl</sub>, C6<sub>phenyl</sub>), 124.84 (q,  $J_{C,F} = 282.1$  Hz, CF<sub>3</sub>), 119.24 (C4), 113.81 (C2), 112.05 (C6), 60.34 (q,  $J_{C,F} = 30.1$  Hz, CCF<sub>3</sub>) ppm. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd. for C<sub>14</sub>H<sub>13</sub>ClF<sub>3</sub>N<sup>+</sup> [M+H]<sup>+</sup> 286.0605, found 286.0608. **HPLC-MS** (0.1% TFA, 0 min: 4% B → 2.8 min: 100% B, flow: 2.4 mL/min):  $t_R$  = 2.52 min,  $\lambda$  = 220 nm.

**N,N'-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-phenyl-2,3-dihydro-1H-imidazole 2b**

According to the **TPI**, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyridine **1b** (200 mg, 0.91 mmol) was reacted with PhMgCl (1.0 M in MeTHF, 2.72 mL, 2.72 mmol) in dry THF (12 mL) for 1.5 h at -15 °C. The crude product was purified by flash chromatography (SiO<sub>2</sub>, DCM → DCM/MeOH 20:1) to give the desired imidazole derivative **2b** (163 mg, 93%) as a light yellow solid.

**R<sub>f</sub>** (ethyl acetate/MeOH 10:1) = 0.19. **<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 8.50 (d,  $J_{H2,H3} = J_{H6,H5} = 6.5$  Hz, 2 H, H2, H6), 8.34 (d,  $J_{H2',H3'} = J_{H6',H5'} = 6.5$  Hz, 2 H, H2', H6'), 7.50 – 7.42 (m, 4 H, H2'', H3'', H5'', H6''), 7.37 (tt,  $J_{H4'',H3''} = J_{H4'',H5''} = 6.7$  Hz,  $J_{H4'',H2''} = J_{H4'',H6''} = 2.1$  Hz, 1 H, H4''), 7.25 (d,  $J_{H3,H2} = J_{H5,H6} = 4.7$  Hz, 2 H, H3, H5), 6.87 (d,  $J_{H3',H2'} = J_{H5',H6'} = 6.4$  Hz, 2 H, H3', H5'), 6.68 (q,  $J_{CH,CF_3} = 4.9$  Hz, 1 H, CH) ppm. **<sup>19</sup>F NMR** (380 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = -82.32 (d,  $J_{CF_3,CH} = 4.9$  Hz, CF<sub>3</sub>), -133.83 (s, CF) ppm. **<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>):



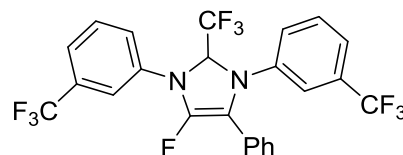
$\delta$  = 152.42 (C4'), 150.79 (C2, C6), 150.22 (C2', C6'), 148.85 (d,  $J_{C,F}$  = 6.2 Hz, C4), 146.59 (d,  $J_{C,F}$  = 279.7 Hz, CF), 129.27 (C3'', C5''), 128.48 (C4''), 127.57 (d,  $J_{C,F}$  = 6.7 Hz, C1''), 125.71 (C2'', C6''), 122.74 (q,  $J_{C,F}$  = 284.6 Hz, CF<sub>3</sub>), 114.06 (C3', C5'), 111.85 (C3, C5), 110.08 (d,  $J_{C,F}$  = 24.0 Hz, FCCN), 79.20 (q,  $J_{C,F}$  = 35.1 Hz, CHCF<sub>3</sub>) ppm. **HRMS** (ESI+):  $m/z$  calcd. for C<sub>20</sub>H<sub>15</sub>F<sub>4</sub>N<sub>4</sub><sup>+</sup> [M+H]<sup>+</sup> 387.1233, found 387.1233. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min):  $t_R$  = 9.16 min,  $\lambda$  = 214 nm. **mp** 159 °C.

### *N,N'*-1,3-(3-Trifluoromethylphenyl)-2-(trifluoromethyl)-4-fluoro-5-phenyl-2,3-dihydro-1*H*-imidazole **2c**

According to the **TPI**, *N*-(1-ethoxy-2,2,2-trifluoroethyl)-3-(trifluoromethyl)aniline **1c** (200 mg, 0.69 mmol) was reacted with PhMgBr (3.0 M in THF, 0.69 mL, 2.06 mmol) in dry THF (10 mL) for 4 h at −15 °C. The crude product was purified by flash chromatography (SiO<sub>2</sub>, cyclohexane/ethyl acetate 100:1) to give the desired imidazole derivative **2c** (100 mg, 56%) as a colorless oil.

**R<sub>f</sub>** (ethyl acetate/MeOH 10:1) = 0.48. **<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>):

$\delta$  = 8.77 (d,  $J_{H3,H2} = J_{H5,H6} = 6.4$  Hz, 2 H, H<sub>3</sub>, H<sub>5</sub>), 8.62 (d,  $J_{H3',H2'} = J_{H5',H6'} = 6.5$  Hz, 2 H, H<sub>3'</sub>, H<sub>5'</sub>), 7.65 (m, 2 H, H<sub>2</sub>, H<sub>6</sub>), 7.58 – 7.55 (m, 3 H, H<sub>4</sub>', H<sub>5</sub>'', H<sub>6</sub>''), 7.38 – 7.33 (m, 2 H, CHCF<sub>3</sub>, H<sub>2</sub>''), 7.18 (d,



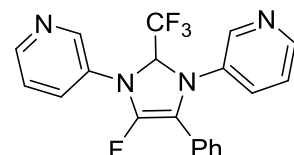
$J_{H2',H3'} = J_{H6',H5'} = 7.2$  Hz, 2 H, H<sub>2'</sub>, H<sub>6'</sub>) ppm. **<sup>19</sup>F NMR** (380 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = −81.14 (d,  $J_{CF_3,CH} = 4.2$  Hz, CF<sub>3</sub>), −130.91 (s, CF) ppm. **<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 156.66 (C1'), 152.09 (d,  $J_{C,F} = 5.9$  Hz, C1), 147.28 (d,  $J_{C,F} = 284.4$  Hz, CF), 144.33 (C3, C5), 142.93 (C3', C5'), 134.30 (C3''), 131.60 (C5''), 129.24 (C4''), 128.20 (d,  $J_{C,F} = 6.4$  Hz, C1''), 125.41 (C6''), 124.42 (C2''), 114.01 (C2', C6'), 112.43 (C2, C6), 109.17 (d,  $J_{C,F} = 26.0$  Hz, FCCN), 77.16 (q,  $J_{C,F} = 35.1$  Hz, CHCF<sub>3</sub>) ppm. **HRMS** (ESI-):  $m/z$  calcd. for C<sub>25</sub>H<sub>14</sub>F<sub>10</sub>N<sub>2</sub>O<sub>2</sub><sup>−</sup> [M+HCOO]<sup>−</sup> 564.0901, found 565.0980. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min):  $t_R$  = 19.25 min,  $\lambda$  = 214 nm.

### *N,N'*-1,3-(Pyridin-3-yl)-2-(trifluoromethyl)-4-fluoro-5-phenyl-2,3-dihydro-1*H*-imidazole **2d**

According to the **TPI**, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridine-3-amine **1d** (200 mg, 0.91 mmol) was reacted with PhMgBr (3.0 M in THF, 0.76 mL, 2.28 mmol) in dry THF (10 mL) for 3 h at −15 °C. The crude product was purified by flash chromatography (SiO<sub>2</sub>, cyclohexane/ethyl acetate 1:2 → ethyl acetate/MeOH 100:1) to give the desired imidazole derivative **2d** (158 mg, 90%) as a light yellow solid.

**R<sub>f</sub>** (ethyl acetate/MeOH 10:1) = 0.32. **<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 8.56 (t,

$J_{H2,H4} = J_{H2,H6} = 2.2$  Hz, 1 H, H<sub>2</sub>), 8.39 (dd,  $J_{H4,H5} = 4.7$  Hz,  $J_{H4,H6} = 1.4$  Hz, 1 H, H<sub>4</sub>), 8.35 (dd,  $J_{H2',H6'} = 2.8$  Hz,  $J_{H2',H4'} = 0.7$  Hz, 1 H, H<sub>2'</sub>), 8.26 (dd,  $J_{H4',H5'} = 4.7$  Hz,  $J_{H4',H6'} = 1.4$  Hz, 1 H, H<sub>4'</sub>), 7.71 (ddd,  $J_{H6,H5} = 8.3$  Hz,  $J_{H6,H2} = 2.5$  Hz,  $J_{H6,H4} = 1.4$  Hz, 1 H, H<sub>6</sub>), 7.50 – 7.40 (m, 5 H, H<sub>6'</sub>, H<sub>5</sub>, H<sub>2</sub>'', H<sub>4</sub>'', H<sub>6</sub>''), 7.34 – 7.25



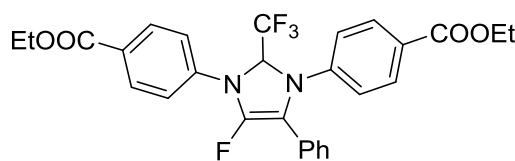
(m, 2 H, H<sub>3</sub>'', H<sub>5</sub>''), 7.28 (m, 3 H, H<sub>5'</sub>, H<sub>3</sub>'', H<sub>5</sub>''), 6.40 (q,  $J_{CH,CF_3} = 5.3$  Hz, 1 H, CHCF<sub>3</sub>) ppm. **<sup>19</sup>F NMR** (380 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = −82.81 (d,  $J_{CF_3,CH} = 5.4$  Hz, CF<sub>3</sub>), −136.81 (s, CF) ppm. **<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 146.66 (d,  $J_{C,F} = 280.2$  Hz, CF), 145.88 (C4), 145.32 (C4'), 143.29 (C2'), 142.60 (C1'), 141.60 (C2), 139.60 (d,  $J_{C,F} = 5.9$  Hz, C1), 129.04 (C4''), 128.69 (C6'), 128.04 (C3'', C5''), 127.75 (d,  $J_{C,F} = 6.8$  Hz, C1''), 127.30

(C6), 126.05 (C2'', C6''), 124.25 (C5), 123.80 (C5'), 122.78 (q,  $J_{C,F}$  = 283.1 Hz, CF<sub>3</sub>), 109.68 (d,  $J_{C,F}$  = 22.5 Hz, FCCN), 81.28 (q,  $J_{C,F}$  = 33.9 Hz,  $J_{C,F}$  = 5.1 Hz, CHCF<sub>3</sub>) ppm. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd. for C<sub>20</sub>H<sub>15</sub>F<sub>4</sub>N<sub>4</sub><sup>+</sup> [M+H]<sup>+</sup> 387.1233, found 387.1233. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min):  $t_R$  = 10.33 min,  $\lambda$  = 214 nm. **mp** 160 °C.

#### ***N,N'*-1,3-(4-(Ethoxycarbonyl)phenyl)-2-(trifluoromethyl)-4-fluoro-5-phenyl-2,3-dihydro-1*H*-imidazole 2e**

According to the **TPI**, ethyl-*N*-(1-ethoxy-2,2,2-trifluoroethyl)-4-aminobenzoate **1e** (200 mg, 0.69 mmol) was reacted with PhMgBr (3.0 M in THF, 0.69 mL, 2.06 mmol) in dry THF (10 mL) for 4 h at −15 °C. The crude product was purified by flash chromatography (SiO<sub>2</sub>, cyclohexane/ethyl acetate 100:1 → 30:1) to give the desired imidazole derivative **2e** (115 mg, 63%) as a yellow solid.

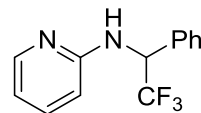
**R<sub>f</sub>** (cyclohexane/ethyl acetate 7:3) = 0.42. **<sup>1</sup>H NMR** (600 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 7.96 (d,  $J_{H3,H4}$  =  $J_{H5,H6}$  = 8.9 Hz, 2 H, H3, H5), 7.80 (d,  $J_{H3',H4'}$  =  $J_{H5',H6'}$  = 8.9 Hz, 2 H, H3', H5'), 7.47 – 7.41 (m, 4 H, H2'', H3'', H5'', H6''), 7.36 (d,  $J_{H2,H3}$  =  $J_{H6,H5}$  = 8.9 Hz, 2 H, H2, H6), 7.35 – 7.31 (m, 1 H, H4'') 7.08 (d,  $J_{H2',H3'}$  =  $J_{H6',H5'}$  = 8.8 Hz, 2 H, H2', H6'), 6.43 (q,  $J_{CH,CF_3}$  = 5.1 Hz, 1 H, CHCF<sub>3</sub>), 4.28 (q,  $J_{CH_2,CH_3}$  = 7.1 Hz, 2 H, CH<sub>2</sub>), 4.22 (q,  $J_{CH_2,CH_3}$  = 7.0 Hz, 2 H, CH<sub>2</sub>), 1.28 (t,  $J_{CH_3,CH_2}$  = 7.1 Hz, 3 H, CH<sub>3</sub>), 1.23 (t,  $J_{CH_3,CH_2}$  = 7.1 Hz, 3 H, CH<sub>3</sub>) ppm. **<sup>19</sup>F NMR** (280 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = −82.40 (d,  $J_{CF_3,CH}$  = 5.1 Hz, CF<sub>3</sub>), −134.39 (s, CF) ppm. **<sup>13</sup>C NMR** (150 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 165.01 (2×COOEt), 150.27 (C1'), 146.89 (d,  $J_{C,F}$  = 5.6 Hz, C1), 146.87 (d,  $J_{C,F}$  = 277.6 Hz, CF), 130.80 (C3, C5), 130.31 (C3', C5'), 129.11 (C3'', C5''), 128.15 (C4''), 127.90 (d,  $J_{C,F}$  = 6.7 Hz, C1''), 125.78 (C2'', C6''), 125.45 (C4), 125.20 (C4'), 122.82 (q,  $J_{C,F}$  = 283.5 Hz, CF<sub>3</sub>), 120.27 (C2', C6'), 118.26 (C2, C6), 110.41 (d,  $J_{C,F}$  = 22.9 Hz, FCCN), 81.32 (q,  $J_{C,F}$  = 34.3 Hz, CHCF<sub>3</sub>), 60.67 (CH<sub>2</sub>), 60.51 (CH<sub>2</sub>), 14.16 (CH<sub>3</sub>), 14.13 (CH<sub>3</sub>) ppm. **HRMS** (EI):  $m/z$  calcd. for C<sub>28</sub>H<sub>24</sub>F<sub>4</sub>N<sub>2</sub>O<sub>4</sub><sup>+</sup> [M]<sup>+</sup> 528.1672, found 528.1676. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min):  $t_R$  = 20.30 min,  $\lambda$  = 214 nm. **mp** 67 – 74 °C.



#### ***N*-(2,2,2-Trifluoro-1-phenylethyl)pyridin-2-amine 3f**

According to **TPI**, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridine-2-amine **1f** (100 mg, 0.45 mmol) was reacted with PhMgBr (3.0 M in Et<sub>2</sub>O, 0.45 mL, 1.36 mmol) in dry THF (6 mL). The crude product was purified by flash chromatography (SiO<sub>2</sub>, cyclohexane/ethyl acetate 10:1) to give the amine **3f** (115 mg, quant.) as yellow oil.

**R<sub>f</sub>** (cyclohexane/ethyl acetate 19:1) = 0.14. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.12 (ddd,  $J_{H6,H5}$  = 5.1 Hz,  $J_{H6,H4}$  = 1.9 Hz,  $J_{H6,H3}$  = 0.9 Hz, 1 H, H6), 7.52 – 7.34 (m, 6 H, H4, H2', H3', H4', H5', H6'), 6.66 (dd,  $J_{H5,H4}$  = 7.2 Hz,  $J_{H5,H6}$  = 5.1 Hz, 1 H, H5), 6.47 (dt,  $J_{H3,H4}$  = 8.3 Hz,  $J_{H3,H4}$  = 0.9 Hz, 1 H, H3), 5.86 (p,  $J_{CH,NH}$  =  $J_{CH,CF_3}$  = 8.1 Hz, 1 H, CHCF<sub>3</sub>), 5.04 (d,  $J_{NH,CH}$  = 9.1 Hz, 1 H, NH) ppm. **<sup>19</sup>F NMR** (280 MHz, CDCl<sub>3</sub>):  $\delta$  = −73.88 (d,  $J_{CF_3,CH}$  = 7.9 Hz, CF<sub>3</sub>) ppm. **<sup>13</sup>C NMR** (150 MHz, CDCl<sub>3</sub>):  $\delta$  = 156.42 (C2), 148.08 (C6), 137.77 (C4), 134.49 (q,  $J(C,F)$  = 1.0 Hz, C1'), 129.06 (C3', C5'), 128.96 (C4'), 128.07 (C2', C6'), 125.35 (q,  $J(C,F)$  = 281.9 Hz, CF<sub>3</sub>), 114.79 (C5), 108.62 (C3), 56.52 (q,  $J(C,F)$  = 30.5 Hz, CHCF<sub>3</sub>) ppm. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd. for C<sub>13</sub>H<sub>12</sub>F<sub>3</sub>N<sub>2</sub><sup>+</sup> [M+H]<sup>+</sup> 253.0953, found 253.0945. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B. Flow: 1 mL/min):  $t_R$  = 6.28 min,  $\lambda$  = 214 nm.



***N,N'*-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(3-chlorophenyl)-2,3-dihydro-1*H*-imidazole 2g**

The magnesium reagent was prepared from 3-bromo-1-chlorobenzene (0.16 mL, 1.36 mmol) and *i*PrMgCl·LiCl (1.2 M in THF, 1.14 mL, 1.40 mmol) according to **TPII** within 3.5 h at 0 °C.

According to the **TPI**, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyridine **1b** (100 mg, 0.45 mmol) was reacted with the *Grignard* reagent in dry THF (5 mL) for 3 h at −15 °C. The crude product was purified by flash chromatography (SiO<sub>2</sub>, ethyl acetate/MeOH 50:1 → 25:1) to give the desired imidazole derivative **2g** (102 mg, quant.) as a yellow solid.

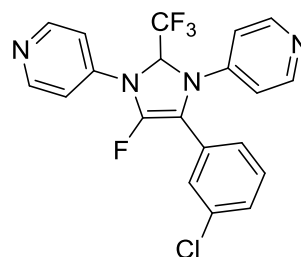
**R<sub>f</sub>** (ethyl acetate/MeOH 10:1) = 0.19. **<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>): δ = 8.77

(d,  $J_{H2,H3} = J_{H6,H5} = 6.4$  Hz, 2 H, H2, H6), 8.62 (d,  $J_{H2',H3'} = J_{H6',H5'} = 6.5$  Hz, 2 H, H2', H6'), 7.65 (d,  $J_{H3,H2} = J_{H5,H6} = 5.8$  Hz, 2 H, H3, H5), 7.58 – 7.55 (m, 3 H, H4", H5", H6"), 7.38 – 7.33 (m, 2 H, CHCF<sub>3</sub>, H2"), 7.18 (d,  $J_{H3',H2'} = J_{H5',H6'} = 7.2$  Hz,

2 H, H3', H5') ppm. **<sup>19</sup>F NMR** (380 MHz, DMSO-*d*<sub>6</sub>): δ = −81.14 (d,  $J_{CF3,CH} = 4.2$  Hz, CF<sub>3</sub>), −130.91 (s, CF) ppm. **<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>): δ = 156.66 (C4'), 152.09 (d,  $J_{C,F} = 5.9$  Hz, C4), 147.28 (d,  $J_{C,F} = 284.4$  Hz, CF),

144.33 (C2, C6), 142.93 (C2', C6'), 134.30 (C3"), 131.60 (C5"), 129.24 (C4"), 128.20 (d,  $J_{C,F} = 6.4$  Hz, C1"), 125.41 (C6"), 124.42 (C2"), 114.01 (C3', C5'), 112.43 (C3, C5), 109.17 (d,  $J_{C,F} = 26.0$  Hz, FCCN), 77.16 (q,  $J_{C,F} = 35.1$  Hz, CHCF<sub>3</sub>) ppm. **HRMS** (ESI+): *m/z* calcd. for C<sub>20</sub>H<sub>14</sub>ClF<sub>4</sub>N<sub>4</sub><sup>+</sup> [M+H]<sup>+</sup> 421.0843, found 421.0836.

**HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): *t<sub>R</sub>* = 9.49 min, λ = 214 nm. **mp** 179 °C.



***N,N'*-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(4-cyanophenyl)-2,3-dihydro-1*H*-imidazole 2h**

The magnesium reagent was prepared from 4-bromobenzonitrile (373 mg, 2.05 mmol) and *i*PrMgCl·LiCl (1.20 M in THF, 1.90 mL, 2.25 mmol) according to **TPII** within 1.5 h at 0 °C.

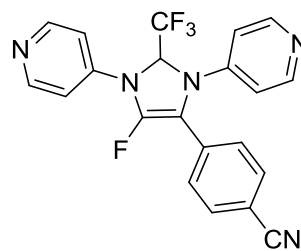
According to the **TPI**, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyridine **1b** (135 mg, 0.61 mmol) was reacted with the *Grignard* reagent in dry THF (7 mL) for 2 h at −15 °C. The crude product was purified by flash chromatography (SiO<sub>2</sub>, ethyl acetate/MeOH 100:1 → 10:1) to give the desired imidazole derivative **2h** (95 mg, 76%) as a yellow oil.

**R<sub>f</sub>** (ethyl acetate/MeOH 10:1) = 0.17 **<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>): δ = 8.77 (d,

$J_{H2,H3} = J_{H6,H5} = 6.5$  Hz, 2 H, H2, H6), 8.63 (d,  $J_{H2',H3'} = J_{H6',H5'} = 6.0$  Hz, 2 H, H2', H6'), 8.00 (d,  $J_{H3',H2'} = J_{H5',H6'} = 8.4$  Hz, 1 H, H3", H5"), 7.75 – 7.63 (m, 2 H, H3, H5), 7.61 (d,  $J_{H6',H5'} = J_{H2'',H3''} = 8.4$  Hz, 2 H, H2", H6"), 7.46 – 7.31 (m, 1 H, CHCF<sub>3</sub>), 7.21 – 7.12 (m, 2 H, H3', H5') ppm. **<sup>19</sup>F NMR** (380 MHz, DMSO-*d*<sub>6</sub>):

δ = −81.13 (m, CF<sub>3</sub>), −128.03 (s, CF) ppm. **<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>):

δ = 156.53 (C4'), 151.56 (C4), 148.43 (d,  $J_{C,F} = 287.0$  Hz, CF), 144.72 (C2, C6), 143.20 (C2', C6'), 133.47 (C3", C5"), 130.73 (C1"), 126.39 (C4", C6"), 122.46 (q,  $J_{C,F} = 286.4$  Hz, CF<sub>3</sub>), 118.37 (CN), 112.56 (C3', C5'), 111.18 (C3, C5), 108.79 (d,  $J_{C,F} = 25.4$  Hz, FCCN), 77.19 (qd,  $J_{C,F} = 36.1$  Hz, CHCF<sub>3</sub>) ppm. **HRMS** (ESI+): *m/z* calcd.





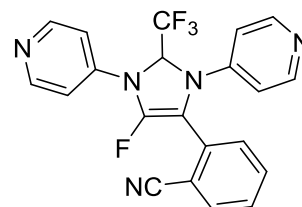
for  $C_{21}H_{14}F_4N_5^+$   $[M+H]^+$  412.1185, found 412.1181. **HPLC** (0.1% TFA, 0 min: 4% B  $\rightarrow$  15 min: 100% B, flow: 1 mL/min):  $t_R$  = 9.02 min,  $\lambda$  = 214 nm.

***N,N'*-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(2-cyanophenyl)-2,3-dihydro-1*H*-imidazole 2i**

The magnesium reagent was prepared from 2-bromobenzonitrile (491 mg, 2.70 mmol) and *i*PrMgCl·LiCl (1.20 M in THF, 2.50 mL, 3.00 mmol) according to **TPII** within 3 h at 0 °C.

According to the **TPI**, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyridine **1b** (200 mg, 0.91 mmol) was reacted with the *Grignard* reagent in dry THF (7 mL) for 3 h at −15 °C. The crude product was purified by flash chromatography (SiO<sub>2</sub>, ethyl acetate/MeOH 100:1  $\rightarrow$  10:1) to give the desired imidazole derivative **2i** (151 mg, 81%) as a yellow solid.

**R<sub>f</sub>** (ethyl acetate/MeOH 10:1) = 0.18. **<sup>1</sup>H NMR** (600 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 8.56 (d,  $J_{H2,H3} = J_{H6,H5} = 6.6$  Hz, 2 H, H2, H6), 8.38 (d,  $J_{H2',H3'} = J_{H6',H5'} = 6.5$  Hz, 2 H, H2', H6'), 7.84 (d,  $J_{H3'',H4''} = 7.8$  Hz, 1 H, H3''), 7.62 (td,  $J_{H5'',H4''} = J_{H5'',H6''} = 7.7$  Hz,  $J_{H5'',H3''} = 1.4$  Hz, 1 H, H5''), 7.55 (d,  $J_{H6'',H5''} = 7.8$  Hz, 1 H, H6''), 7.50 (t,  $J_{H4'',H3''} = 7.6$ ,  $J_{H4'',H5''} = 7.6$  Hz, 1 H, H4''), 7.11 – 7.06 (m, 2 H, H3, H5), 6.74 (d,  $J_{H3',H2'} = J_{H5',H6'} = 6.5$  Hz, 2 H, H3', H5'), 5.45 (q,  $J_{CH,CF_3} = 4.6$  Hz, 1 H, CHCF<sub>3</sub>) ppm. **<sup>19</sup>F NMR** (380 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = −82.57 (d,  $J_{CF_3,CH} = 4.6$  Hz, CF<sub>3</sub>), −125.75 (s, CF) ppm. **<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 152.95 (C4'), 151.41 (C2, C6), 151.06 (C2', C6'), 149.52 (d,  $J_{C,F} = 5.9$  Hz, C4), 147.72 (d,  $J_{C,F} = 282.6$  Hz, CF), 134.30 (C3''), 133.57 (C5''), 131.27 (d,  $J_{C,F} = 6.2$  Hz, C1''), 129.61 (C4''), 128.40 (C6''), 122.27 (q,  $J_{C,F} = 283.9$  Hz, CF<sub>3</sub>), 117.39 (CN), 113.57 (C3', C5'), 112.33 (C3, C5), 111.31 (C2''), 107.63 (d,  $J_{C,F} = 25.2$  Hz, FCCN), 82.34 (qd,  $J_{C,F} = 36.3$  Hz,  $J_{C,F} = 3.8$  Hz, CHCF<sub>3</sub>) ppm. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd. for  $C_{21}H_{14}F_4N_5^+$   $[M+H]^+$  412.1185, found 412.1177. **HPLC** (0.1% TFA, 0 min: 4% B  $\rightarrow$  15 min: 100% B, flow: 1 mL/min):  $t_R$  = 8.82 min,  $\lambda$  = 214 nm. **mp** 94 °C.

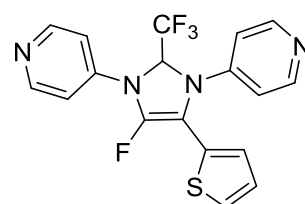


***N,N'*-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(thiophen-2-yl)-2,3-dihydro-1*H*-imidazole 2j**

The magnesium reagent was prepared from 2-bromothiophene (259 mg, 1.59 mmol) and *i*PrMgCl·LiCl (1.25 M in THF, 1.40 mL, 1.70 mmol) according to **TPII** within 3.5 h at 0 °C.

According to the **TPI**, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyridine **1b** (100 mg, 0.45 mmol) was reacted with the *Grignard* reagent in dry THF (5 mL) for 3 h at −15 °C. The crude product was purified by flash chromatography (SiO<sub>2</sub>, ethyl acetate/MeOH 25:1) to give the desired imidazole derivative **2j** (95 mg, quant.) as a yellow oil.

**R<sub>f</sub>** (ethyl acetate/MeOH 10:1) = 0.17. **<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 8.51 – 8.47 (m, 2 H, H2, H6), 8.41 – 8.36 (m, 2 H, H2', H6'), 7.67 (dd,  $J_{H3'',H4''} = 5.1$  Hz,  $J_{H3'',H5''} = 1.2$  Hz, 1 H, H3''), 7.24 – 7.20 (m, 2 H, H3, H5), 7.19 (dd,  $J_{H5'',H4''} = 3.7$  Hz,  $J_{H5'',H3''} = 1.2$  Hz, 1 H, H5''), 7.15 (dd,  $J_{H4'',H3''} = 5.0$  Hz,  $J_{H4'',H5''} = 3.7$  Hz, 1 H, H4''), 6.99 – 6.93 (m, 2 H, H3', H5'), 6.65 (q,



$J_{\text{CH},\text{CF}_3} = 4.9$  Hz, 1 H,  $\text{CHCF}_3$ ) ppm.  **$^{19}\text{F}$  NMR** (280 MHz,  $\text{DMSO}-d_6$ ):  $\delta = -82.32$  (d,  $J_{\text{CF}_3,\text{CH}} = 4.8$  Hz,  $\text{CF}_3$ ),  $-132.78$  (s, CF) ppm.  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 152.47$  ( $\text{C4}'$ ), 150.82 ( $\text{C2}$ ,  $\text{C6}$ ), 150.31 ( $\text{C2}'$ ,  $\text{C6}'$ ), 148.79 (d,  $J_{\text{C},\text{F}} = 6.4$  Hz,  $\text{C4}$ ), 145.38 (d,  $J_{\text{C},\text{F}} = 279.5$  Hz, CF), 129.18 (d,  $J_{\text{C},\text{F}} = 8.5$  Hz,  $\text{C1}''$ ), 128.20 ( $\text{C4}''$ ), 127.49 ( $\text{C3}''$ ), 126.04 ( $\text{C5}''$ ), 122.60 (q,  $J_{\text{C},\text{F}} = 284.2$  Hz,  $\text{CF}_3$ ), 114.39 ( $\text{C3}'$ ,  $\text{C5}'$ ), 111.83 ( $\text{C3}$ ,  $\text{C5}$ ), 106.21 (d,  $J_{\text{C},\text{F}} = 26.4$  Hz, FCCN), 79.53 (q,  $J_{\text{C},\text{F}} = 34.4$  Hz,  $\text{CHCF}_3$ ) ppm. **HRMS** (ESI+):  $m/z$  calcd. for  $\text{C}_{18}\text{H}_{13}\text{F}_4\text{N}_4\text{S}^+$   $[\text{M}+\text{H}]^+$  393.0797, found 393.0786. **HPLC** (0.1% TFA, 0 min: 4% B  $\rightarrow$  15 min: 100% B, flow: 1 mL/min):  $t_R = 9.02$  min,  $\lambda = 214$  nm.

### ***N,N'*-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(pyridin-2-yl)-2,3-dihydro-1*H*-imidazole 2k**

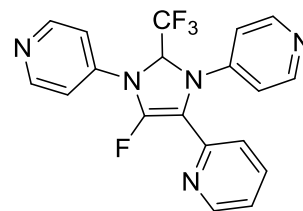
The magnesium reagent was prepared from 2-bromopyridine (130  $\mu\text{L}$ , 1.36 mmol) and  $i\text{PrMgCl}\cdot\text{LiCl}$  (1.25 M in THF, 1.14 mL, 1.40 mmol) according to **TPII** within 3 h at 0 °C.

According to the **TPI**, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyridine **1b** (100 mg, 0.45 mmol) was reacted with the *Grignard* reagent in dry THF (5 mL) for 2 h at  $-15$  °C. The crude product was purified by flash chromatography ( $\text{SiO}_2$ , ethyl acetate/MeOH 50:1  $\rightarrow$  10:1) to give the desired imidazole derivative **2k** (37 mg, 42%) as a yellow oil and *N*-(2,2,2-trifluoro-1-(pyridin-2-yl)ethyl)pyridin-4-amine **3k** (44 mg, 39%) as a yellow oil.

### ***N,N'*-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(pyridin-2-yl)-2,3-dihydro-1*H*-imidazole 2k**

**R<sub>f</sub>** (ethyl acetate/MeOH 10:1) = 0.18.  **$^1\text{H}$  NMR** (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 8.62$

(dd,  $J_{\text{H3}'',\text{H4}''} = 4.7$  Hz,  $J = 2.7$  Hz, 1 H,  $\text{H3}''$ ), 8.52 - 8.48 (m, 2 H,  $\text{H2}$ ,  $\text{H6}$ ), 8.36 - 8.33 (m, 2 H,  $\text{H2}'$ ,  $\text{H6}'$ ), 7.86 (td,  $J_{\text{H5}'',\text{H4}''} = J_{\text{H5}'',\text{H6}''} = 7.8$  Hz,  $J = 1.9$  Hz, 1 H,  $\text{H5}''$ ), 7.40 (d,  $J_{\text{H6}'',\text{H5}''} = 7.9$  Hz, 1 H,  $\text{H6}''$ ), 7.33 (ddd,  $J_{\text{H4}'',\text{H5}''} = 7.6$  Hz,  $J_{\text{H4}'',\text{H3}''} = 4.8$  Hz,  $J = 1.1$  Hz, 1 H,  $\text{H4}''$ ), 7.28 - 7.22 (m, 2 H,  $\text{H3}$ ,  $\text{H5}$ ), 6.86 - 6.82 (m, 2 H,  $\text{H3}'$ ,  $\text{H5}'$ ), 6.72 (q,  $J_{\text{CH},\text{CF}_3} = 4.6$  Hz, 1 H,  $\text{CHCF}_3$ ) ppm.  **$^{19}\text{F}$  NMR** (380 MHz,  $\text{DMSO}-d_6$ ):

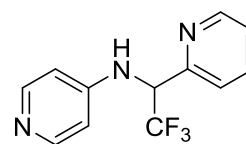


$\delta = -82.05$  (d,  $J_{\text{CF}_3,\text{CH}} = 4.8$  Hz,  $\text{CF}_3$ ),  $-128.03$  (s, CF) ppm.  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 152.65$  ( $\text{C4}'$ ), 150.85 ( $\text{C2}$ ,  $\text{C6}$ ), 150.10 ( $\text{C2}'$ ,  $\text{C6}'$ ), 149.95 ( $\text{C3}''$ ), 148.10 (d,  $J_{\text{C},\text{F}} = 6.0$  Hz,  $\text{C4}$ ), 147.27 (d,  $J_{\text{C},\text{F}} = 7.8$  Hz,  $\text{C2}''$ ), 146.03 (d,  $J_{\text{C},\text{F}} = 272.5$  Hz, CF), 137.26 ( $\text{C5}''$ ), 122.74 ( $\text{C4}''$ ), 122.73 (q,  $J_{\text{C},\text{F}} = 285.2$  Hz,  $\text{CF}_3$ ), 121.25 ( $\text{C6}''$ ), 113.98 ( $\text{C3}'$ ,  $\text{C5}'$ ), 111.89 ( $\text{C3}$ ,  $\text{C5}$ ), 109.56 (d,  $J_{\text{C},\text{F}} = 20.3$  Hz, FCCN), 78.97 (q,  $J_{\text{C},\text{F}} = 35.1$  Hz,  $\text{CHCF}_3$ ) ppm. **HRMS** (ESI+):  $m/z$  calcd. for  $\text{C}_{19}\text{H}_{14}\text{F}_4\text{N}_5^+$   $[\text{M}+\text{H}]^+$  388.1185, found 388.1175. **HPLC** (0.1% TFA, 0 min: 4% B  $\rightarrow$  15 min: 100% B, flow: 1 mL/min):  $t_R = 7.77$  min,  $\lambda = 214$  nm.

### ***N*-(2,2,2-Trifluor-1-(pyridin-2-yl)ethyl)pyridin-4-amine 3k**

**R<sub>f</sub>** (ethyl acetate/MeOH 10:1) = 0.10.  **$^1\text{H}$  NMR** (600 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 8.65$  (ddd,

$J_{\text{H3}',\text{H4}'} = 4.8$  Hz,  $J_{\text{H3}',\text{H5}'} = 1.8$  Hz,  $J_{\text{H3}',\text{H6}'} = 0.9$  Hz, 1 H,  $\text{H3}'$ ), 8.09 (d,  $J_{\text{H2},\text{H3}} = J_{\text{H6},\text{H5}} = 6.6$  Hz, 2 H,  $\text{H2}/\text{H6}$ ), 7.90 (td,  $J_{\text{H5}',\text{H4}'} = J_{\text{H5}',\text{H6}'} = 7.7$  Hz,  $J_{\text{H5}',\text{H3}'} = 1.8$  Hz, 1 H,  $\text{H5}'$ ), 7.67 (d,  $J_{\text{H6}',\text{H5}'} = 7.9$  Hz, 1 H,  $\text{H6}'$ ), 7.47 - 7.43 (m, 2 H,  $\text{H4}'$ ,



NH), 6.88 (d,  $J_{\text{H3},\text{H2}} = J_{\text{H5},\text{H6}} = 6.5$  Hz, 2 H,  $\text{H3}$ ,  $\text{H5}$ ), 5.83 (dq,  $J_{\text{CH},\text{NH}} = 9.6$  Hz,  $J_{\text{CH},\text{CF}_3} = 7.6$  Hz, 1 H,  $\text{CHCF}_3$ ) ppm.  **$^{19}\text{F}$  NMR** (380 MHz,  $\text{DMSO}-d_6$ ):  $\delta = -71.76$  (d,  $J_{\text{CF}_3,\text{CH}} = 7.6$  Hz,  $\text{CF}_3$ ) ppm.  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 152.47 - 152.46$  (m,  $\text{C1}'$ ), 152.33 ( $\text{C4}$ ), 149.51 ( $\text{C2}$ ,  $\text{C6}$ ), 149.37 ( $\text{C3}'$ ), 137.38 ( $\text{C5}'$ ), 125.12 (q,  $J_{\text{C},\text{F}} = 283.9$  Hz,

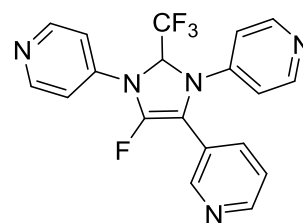
CF<sub>3</sub>), 124.28 (C4'), 123.79 (C6'), 108.33 (C3, C5), 57.18 (q,  $J_{C,F}$  = 29.4 Hz, CHCF<sub>3</sub>) ppm. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd. for C<sub>12</sub>H<sub>11</sub>F<sub>3</sub>N<sub>3</sub><sup>+</sup> [M+H]<sup>+</sup> 254.0905, found 254.0897. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min):  $t_R$  = 8.78 min,  $\lambda$  = 214 nm.

***N,N'*-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(pyridin-3-yl)-2,3-dihydro-1*H*-imidazole 2i**

The magnesium reagent was prepared from 3-bromopyridine (0.26 mL, 2.70 mmol) and *i*PrMgCl·LiCl (1.20 M in THF, 2.50 mL, 3.00 mmol) according to **TPII** within 2 h at 0 °C.

According to the **TPI**, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyridine **1b** (200 mg, 0.91 mmol) was reacted with the *Grignard* reagent in dry THF (7 mL) for 2 h at −15 °C. The crude product was purified by flash chromatography (SiO<sub>2</sub>, ethyl acetate/MeOH 100:1 → 10:1) to give the desired imidazole derivative **2i** (171 mg, 97%) as a yellow solid.

**R<sub>f</sub>** (ethyl acetate/MeOH 10:1) = 0.10. **<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 8.70 – 8.66 (m, 1 H, H2''), 8.55 (dd,  $J_{H6'',H5''}$  = 4.8 Hz,  $J_{H6'',H4''}$  = 1.6 Hz, 1 H, H6''), 8.54 – 8.50 (m, 2 H, H2, H6), 8.40 – 8.33 (m, 2 H, H2', H6'), 7.76 (ddd,  $J_{H4'',H5''}$  = 8.0 Hz,  $J_{H4'',H2''}$  = 2.5 Hz,  $J_{H4'',H6''}$  = 1.7 Hz, 1 H, H4''), 7.47 (ddd,  $J_{H5'',H4''}$  = 8.0 Hz,  $J_{H5'',H6''}$  = 4.8 Hz,  $J_{H5'',H2''}$  = 0.9 Hz, 1 H, H5''), 7.30 – 7.24 (m, 2 H, H3, H5), 6.92 – 6.88 (m, 2 H, H3', H5'), 6.73 (q,  $J_{CH,CF_3}$  = 4.9 Hz, 1 H, CHCF<sub>3</sub>) ppm. **<sup>19</sup>F NMR**



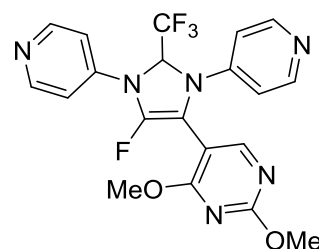
(380 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = −82.40 (d,  $J_{CF_3,CH}$  = 4.9 Hz, CF<sub>3</sub>), −131.84 (s, CF) ppm. **<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 152.43 (C4'), 150.41 (C2, C6), 149.71 (C2', C6'), 149.34 (C6''), 148.59 (d,  $J_{C,F}$  = 6.1 Hz, C4), 147.62 (d,  $J_{C,F}$  = 281.2 Hz, CF), 146.47 (d,  $J_{C,F}$  = 5.4 Hz, C2''), 132.91 (C4''), 124.22 (C5''), 123.91 – 123.84 (m, C3''), 122.64 (q,  $J_{C,F}$  = 284.4 Hz, CF<sub>3</sub>), 114.24 (C3', C5'), 112.06 (C3, C5), 107.18 (d,  $J_{C,F}$  = 25.0 Hz, FCCN), 79.11 (q,  $J_{C,F}$  = 35.3 Hz, CHCF<sub>3</sub>) ppm. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd. for C<sub>19</sub>H<sub>14</sub>F<sub>4</sub>N<sub>5</sub><sup>+</sup> [M+H]<sup>+</sup> 388.1185, found 388.1180. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min):  $t_R$  = 7.31 min,  $\lambda$  = 214 nm. **mp** 95 – 98 °C.

***N,N'*-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(2,4-dimethoxypyrimidin-5-yl)-2,3-dihydro-1*H*-imidazole 2m**

The magnesium reagent was prepared from 5-bromo-2,4-dimethoxypyrimidine (449 mg, 2.05 mmol) and *i*PrMgCl·LiCl (1.20 M in THF, 1.90 mL, 2.25 mmol) according to **TPH** within 1 h at 0 °C.

According to the **TPI**, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyridine **1b** (150 mg, 0.68 mmol) was reacted with the *Grignard* reagent in dry THF (7 mL) for 2 h at –15 °C. The crude product was purified by flash chromatography (SiO<sub>2</sub>, ethyl acetate/MeOH 100:1 → 10:1) to give the desired imidazole derivative **2m** (120 mg, 79%) as a yellow solid.

**R<sub>f</sub>** (ethyl acetate/MeOH 10:1) = 0.17. **<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>): δ = 8.50 (d, *J*<sub>H2,H3</sub> = *J*<sub>H6,H5</sub> = 4.4 Hz, 2 H, H2, H6), 8.32 (d, *J*<sub>H2',H3'</sub> = *J*<sub>H6',H5'</sub> = 4.5 Hz, 2 H, H2', H6'), 8.31 (s, 1 H, H6''), 7.18 (d, *J*<sub>H3,H2</sub> = *J*<sub>H5,H6</sub> = 4.5 Hz, 2 H, H3, H5), 6.83 (d, *J*<sub>H3',H2'</sub> = *J*<sub>H5',H6'</sub> = 4.3 Hz, 2 H, H3', H5'), 6.68 (q, *J*<sub>CH,CF<sub>3</sub></sub> = 4.8 Hz, 1 H, CHCF<sub>3</sub>), 4.02 (s, 3 H, OCH<sub>3</sub>), 3.93 (s, 3 H, OCH<sub>3</sub>) ppm. **<sup>19</sup>F NMR** (280 MHz, DMSO-*d*<sub>6</sub>): δ = –82.11 (d, *J*<sub>CF<sub>3</sub>,CH</sub> = 4.9 Hz, CF<sub>3</sub>), –130.90 (s, CF) ppm. **<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>): δ = 167.51 (COCH<sub>3</sub>), 165.40 (COCH<sub>3</sub>), 157.97 (C6''), 152.30 (C4'), 151.26 (C2, C6), 150.82 (C2', C6'), 149.39 (d, *J*<sub>C,F</sub> = 6.0 Hz, C4), 146.48 (d, *J*<sub>C,F</sub> = 277.2 Hz, CF), 123.11 (d, *J*<sub>C,F</sub> = 277.2 Hz, CF<sub>3</sub>), 113.72 (C3', C5'), 112.18 (C3, C5), 103.69 (d, *J*<sub>C,F</sub> = 27.3 Hz, FCCN), 103.64 (d, *J*<sub>C,F</sub> = 6.0 Hz, C1''), 79.13 (q, *J*<sub>C,F</sub> = 30.4 Hz, CHCF<sub>3</sub>), 55.37 (OCH<sub>3</sub>), 55.11 (OCH<sub>3</sub>) ppm. **HRMS** (ESI+): *m/z* calcd. for C<sub>20</sub>H<sub>17</sub>F<sub>4</sub>N<sub>6</sub>O<sub>2</sub><sup>+</sup> [M+H]<sup>+</sup> 449.1349, found 449.1338. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): *t<sub>R</sub>* = 8.28 min, λ = 214 nm. **mp** 154 °C.

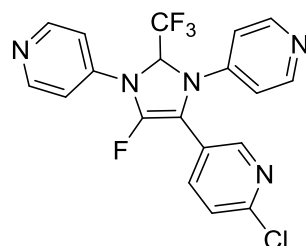


***N,N'*-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(6-chloropyridin-3-yl)-2,3-dihydro-1*H*-imidazole 2n**

The magnesium reagent was prepared from 3-bromo-2-chloropyridine (520 mg, 2.70 mmol) and *i*PrMgCl·LiCl (1.20 M in THF, 2.50 mL, 3.00 mmol) according to **TPH** within 1 h at 0 °C.

According to the **TPI**, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyridine **1b** (200 mg, 0.91 mmol) was reacted with the *Grignard* reagent in dry THF (7 mL) for 4 h at –15 °C. The crude product was purified by flash chromatography (SiO<sub>2</sub>, ethyl acetate/MeOH 100:1 → 10:1) to give the desired imidazole derivative **2n** (130 mg, 69%) as a yellow solid.

**R<sub>f</sub>** (ethyl acetate/MeOH 10:1) = 0.25. **<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>): δ = 8.53 – 8.50 (m, 2 H, H2, H6), 8.50 – 8.49 (m, 1 H, H2''), 8.42 – 8.36 (m, 2 H, H2', H6'), 7.79 (dd, *J*<sub>H4'',H5''</sub> = 8.4 Hz, *J*<sub>H4'',H2''</sub> = 2.5 Hz, 1 H, H4''), 7.62 (dd, *J*<sub>H5'',H4''</sub> = 8.4 Hz, *J*<sub>H5'',H3''</sub> = 0.7 Hz, 1 H, H5''), 7.32 – 7.22 (m, 2 H, H3, H5), 6.95 – 6.88 (m, 2 H, H3', H5'), 6.74 (q, *J*<sub>CH,CF<sub>3</sub></sub> = 4.9 Hz, 1 H, CHCF<sub>3</sub>) ppm. **<sup>19</sup>F NMR** (380 MHz, DMSO-*d*<sub>6</sub>): δ = –82.39 (d, *J*<sub>CF<sub>3</sub>,CH</sub> = 4.9 Hz, CF<sub>3</sub>), –130.50 (s, CF) ppm. **<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>): δ = 151.87 (C4'), 150.83 (C2, C6), 150.45 (C2', C6'), 149.34 (C6''), 148.24 (d, *J*<sub>C,F</sub> = 6.1 Hz, C4), 146.58 (d, *J*<sub>C,F</sub> = 5.8 Hz, C3'', C2''), 136.19 (C4''), 122.52 (d, *J*<sub>C,F</sub> = 7.2 Hz, C5''), 122.62 (q, *J*<sub>C,F</sub> = 284.5 Hz, CF<sub>3</sub>), 114.33 (C3', C5'), 112.11 (C3, C5), 106.12 (d, *J*<sub>C,F</sub> = 24.6 Hz, FCCN), 79.27 (q,



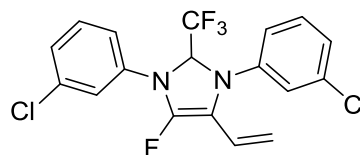
$J_{C,F} = 34.8$  Hz,  $\text{CHCF}_3$ ) ppm. **HRMS** (ESI+):  $m/z$  calcd. for  $\text{C}_{19}\text{H}_{13}\text{ClF}_4\text{N}_5^+$   $[\text{M}+\text{H}]^+$  422.0790, found 422.0790. **HPLC** (0.1% TFA, 0 min: 4% B  $\rightarrow$  15 min: 100% B, flow: 1 mL/min):  $t_R = 7.76$  min,  $\lambda = 214$  nm. **mp** 63 – 73 °C

***N,N'*-1,3-(3-Chlorophenyl)-2-(trifluoromethyl)-4-fluoro-5-vinyl-2,3-dihydro-1*H*-imidazole 2o and 3-Chloro-*N*-(2,2,2-trifluoro-1-vinylethyl)aniline 3o**

According to the **TPI**, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** (230 mg, 0.90 mmol) was reacted with vinyl magnesium chloride (1 M in THF, 1.81 mL, 1.81 mmol) in dry THF (12 mL) for 1 h at –15 °C. The crude product was purified by flash chromatography ( $\text{SiO}_2$ , cyclohexane  $\rightarrow$  cyclohexane/DCM 20:1) to give the desired imidazole derivative **2o** (30 mg, 17%) as a blue liquid and 3-chloro-*N*-(1,1,1-trifluorobut-3-en-2-yl)aniline **3o** (131 mg, 62%) as a colorless liquid.

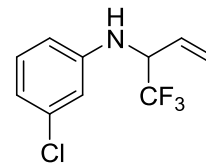
***N,N'*-1,3-(3-Chlorophenyl)-2-(trifluoromethyl)-4-fluoro-5-vinyl-2,3-dihydro-1*H*-imidazole 2o**

**<sup>1</sup>H NMR** (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 7.40$  (t,  $J_{\text{H}_5,\text{H}_4} = J_{\text{H}_5,\text{H}_6} = 8.1$  Hz, 1 H, H5), 7.34 (t,  $J_{\text{H}_5,\text{H}_4} = J_{\text{H}_5,\text{H}_6} = 8.1$  Hz, 1 H, H5), 7.21 (ddd,  $J_{\text{H}_6,\text{H}_5} = 8.0$  Hz,  $J_{\text{H}_6,\text{H}_5} = 2.0$  Hz,  $J = 0.9$  Hz, 1 H, H6), 7.18 – 7.10 (m, 3 H, H4, 2  $\times$  H2), 7.08 (t,  $J_{\text{H}_2,\text{H}_4} = J_{\text{H}_2,\text{H}_6} = 2.1$  Hz, 1 H, H4), 7.04 (ddd,  $J_{\text{H}_6,\text{H}_5} = 8.1$  Hz,  $J_{\text{H}_6,\text{H}_5} = 2.3$  Hz,  $J = 0.9$  Hz, 1 H, H6), 6.63 – 6.46 (m, 1 H,  $\text{CH}_2=\text{CH}$ ), 6.22 (q,  $J_{\text{CH},\text{CF}_3} = 5.2$  Hz, 1 H, CH), 5.20 (dt,  $J_{\text{CH}=\text{CH}_{\text{cis}},\text{CH}=\text{CH}_2} = 11.2$  Hz,  $J = 1.6$  Hz, 1 H,  $\text{HCH}_{\text{cis}}=\text{CH}$ ), 4.89 (dt,  $J_{\text{CH}=\text{CH}_{\text{trans}},\text{CH}=\text{CH}_2} = 17.4$  Hz,  $J = 1.4$  Hz, 1 H,  $\text{HCH}_{\text{trans}}=\text{CH}$ ) ppm. **<sup>19</sup>F NMR** (380 MHz,  $\text{DMSO}-d_6$ ):  $\delta = -82.55$  (d,  $J_{\text{CF}_3,\text{CH}} = 5.9$  Hz,  $\text{CF}_3$ ), -136.94 (s, CF) ppm. **<sup>13</sup>C NMR** (101 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 147.64$ , 143.85, 133.98, 133.40, 131.22, 130.61, 124.86, 124.52, 124.20, 121.50, 121.43, 121.00, 119.64, 119.22, 117.66, 117.63, 115.52, 115.47, 112.15, 109.86 (d,  $J_{C,F} = 24.5$  Hz) ppm. **HRMS** (ESI+):  $m/z$  calcd. for  $\text{C}_{18}\text{H}_{13}\text{Cl}_2\text{F}_4\text{N}_2^+$   $[\text{M}+\text{H}]^+$  403.0386, found 403.0389. **HPLC-MS** (0.05% formic acid, 0 min: 4% B  $\rightarrow$  2.8 min: 100% B, flow: 2.4 mL/min):  $t_R = 3.19$  min,  $\lambda = 220$  nm.



**3-Chloro-*N*-(2,2,2-trifluoro-1-vinylethyl)aniline 3o**

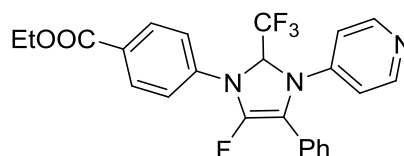
**<sup>1</sup>H NMR** (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 7.11$  (t,  $J_{\text{H}_5,\text{H}_4} = J_{\text{H}_5,\text{H}_6} = 8.1$  Hz, 1 H, H5), 6.87 (t,  $J_{\text{H}_2,\text{H}_4} = J_{\text{H}_2,\text{H}_6} = 2.1$  Hz, 1 H, H2), 6.77 (dd,  $J_{\text{H}_6,\text{H}_5} = 8.0$  Hz,  $J_{\text{H}_6,\text{H}_2} = 2.0$  Hz, 1 H, H6), 6.64 (ddd,  $J_{\text{H}_4,\text{H}_5} = 7.8$  Hz,  $J_{\text{H}_4,\text{H}_2} = 2.0$  Hz,  $J_{\text{H}_4,\text{H}_6} = 0.8$  Hz, 1 H, H4), 6.48 (d,  $J_{\text{NH},\text{CH}} = 9.7$  Hz, 1 H, NH), 5.86 (ddd,  $J_{\text{CH}=\text{CH}_2,\text{CH}=\text{CH}_{\text{trans}}} = 16.8$  Hz,  $J_{\text{CH}=\text{CH}_2,\text{CH}=\text{CH}_{\text{cis}}} = 10.4$  Hz,  $J_{\text{CH}=\text{CH}_2,\text{CH}} = 6.2$  Hz, 1 H,  $\text{CH}_2=\text{CH}$ ), 5.56 (d,  $J_{\text{CH}=\text{CH}_{\text{trans}},\text{CH}=\text{CH}_2} = 17.1$  Hz, 1 H,  $\text{HCH}_{\text{trans}}=\text{CH}$ ), 5.43 (d,  $J_{\text{CH}=\text{CH}_{\text{cis}},\text{CH}=\text{CH}_2} = 10.4$  Hz, 1 H,  $\text{HCH}_{\text{cis}}=\text{CH}$ ), 5.10 – 4.97 (m, 1 H, CH) ppm. **<sup>19</sup>F NMR** (377 MHz,  $\text{DMSO}-d_6$ ):  $\delta = -73.77$  (d,  $J_{\text{CF}_3,\text{CH}} = 7.7$  Hz,  $\text{CF}_3$ ) ppm. **<sup>13</sup>C NMR** (101 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 148.36$  (C1), 133.62 (C3), 130.36 (C5), 129.80 ( $\text{CH}_2=\text{CH}$ ), 125.52 (q,  $J_{C,F} = 283.4$  Hz,  $\text{CF}_3$ ), 120.83 ( $\text{CH}_2=\text{CH}$ ), 116.70 (C4), 112.31 (C2), 111.71 (C6), 55.83 (q,  $J_{C,F} = 29.4$  Hz,  $\text{CCF}_3$ ) ppm. **HRMS** (ESI+):  $m/z$  calcd. for  $\text{C}_{10}\text{H}_{10}\text{ClF}_3\text{N}^+$   $[\text{M}+\text{H}]^+$  236.0448, found 236.0452. **HPLC-MS** (0.05% formic acid, 0 min: 4% B  $\rightarrow$  2.8 min: 100% B, flow: 2.4 mL/min):  $t_R = 2.53$  min,  $\lambda = 220$  nm.



#### Ethyl 4-(5-fluoro-4-phenyl-3-(pyridin-4-yl)-2-(trifluoromethyl)-2,3-dihydro-1H-imidazol-1-yl)benzoate **2p**

According to the **TPIII**, ethyl 4-((1-ethoxy-2,2,2-trifluoroethyl)amino)benzoate **1e** (60 mg, 0.20 mmol) and *N*-(2,2,2-trifluoro-1-phenylethyl)pyridin-4-amine **3b** (52 mg, 0.20 mmol) were reacted with *n*BuLi (1.6 M in hexane, 0.38 mL, 0.60 mmol) in dry THF (6 mL) for 4 h at  $-30^{\circ}\text{C}$ . The crude product was purified by flash chromatography ( $\text{SiO}_2$ , cyclohexane/ethyl acetate 2:1  $\rightarrow$  ethyl acetate) to give desired imidazole derivative **2p** (57 mg, 62%) as a yellow oil, ethyl 4-((1-ethoxy-2,2,2-trifluoroethyl)amino)benzoate **1e** (25 mg, 37%) and *N*-(2,2,2-trifluoro-1-phenylethyl)pyridin-4-amine **3b** (17 mg, 34%).

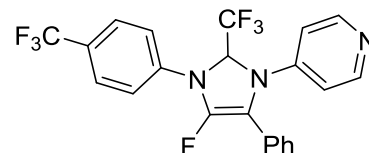
**R<sub>f</sub>** (cyclohexane/ethyl acetate = 3:1) = 0.50. **<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.33 (d,  $J_{\text{H}2',\text{H}3'} = J_{\text{H}6',\text{H}5'} = 5.5$  Hz, 2 H, H2', H6'), 8.06 – 8.00 (m, 2 H, H3, H5), 7.48 (d,  $J_{\text{H}2'',\text{H}3''} = J_{\text{H}6'',\text{H}5''} = 7.3$  Hz, 2 H, H2'', H6''), 7.40 (t,  $J_{\text{H}3'',\text{H}4''} = J_{\text{H}5'',\text{H}4''} = J_{\text{H}3'',\text{H}2''} = J_{\text{H}5'',\text{H}6''} = 7.6$  Hz, 2 H, H3'', H5''), 7.33 (d,  $J = 7.3$  Hz, 1 H, H4''), 7.17 (dd,  $J_{\text{H}2,\text{H}3} = J_{\text{H}6,\text{H}5} = 8.8$  Hz,  $J = 2.4$  Hz, 2 H, H2, H6), 6.77 (d,  $J_{\text{H}3',\text{H}2'} = J_{\text{H}5',\text{H}6'} = 6.0$  Hz, 2 H, H3', H5'), 5.34 (dq,  $J_{\text{CH},\text{CF}_3} = 4.8$  Hz, 1 H, CH), 4.35 (q,  $J_{\text{CH}_2,\text{CH}_3} = 7.1$  Hz, 2 H, CH<sub>2</sub>), 1.36 (t,  $J_{\text{CH}_3,\text{CH}_2} = 7.1$  Hz, 3 H, CH<sub>3</sub>) ppm. **<sup>19</sup>F NMR** (380 MHz,  $\text{CDCl}_3$ ):  $\delta$  =  $-82.76$  (d,  $J_{\text{CF}_3,\text{CH}} = 4.9$  Hz, CF<sub>3</sub>),  $-131.73$  (s, CF) ppm. **<sup>13</sup>C NMR** (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 165.79 (COOEt), 154.01 (C4'), 150.69 (C2', C6'), 147.42 (d,  $J_{\text{C},\text{F}} = 277.8$  Hz, CF), 147.19 (d,  $J_{\text{C},\text{F}} = 6.0$  Hz, C1), 131.57 (C3, C5), 129.18 (C3'', C5''), 128.35 (C4''), 128.09 (d,  $J_{\text{C},\text{F}} = 6.8$  Hz, C1''), 126.93, 126.13 (d,  $J_{\text{C},\text{F}} = 4.8$  Hz, C2'', C6''), 122.45 (q,  $J_{\text{C},\text{F}} = 283.6$  Hz, CF<sub>3</sub>), 118.24 (C2, C6), 113.84 (C3', C5'), 109.91 (d,  $J_{\text{C},\text{F}} = 23.9$  Hz, FCCN), 83.65 (qd,  $J_{\text{C},\text{F}} = 35.7$  Hz,  $J_{\text{C},\text{F}} = 4.6$  Hz, CHCF<sub>3</sub>), 61.18 (CH<sub>2</sub>), 14.44 (CH<sub>3</sub>) ppm. **HRMS** (EI):  $m/z$  calcd. for  $\text{C}_{24}\text{H}_{20}\text{F}_4\text{N}_3\text{O}_2^+$  [M+H]<sup>+</sup> 458.1486, found 458.14895.



#### 4-(4-Fluoro-5-phenyl-2-(trifluoromethyl)-3-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1H-imidazol-1-yl)pyridine **2q**

According to the **TPIII**, *N*-(1-ethoxy-2,2,2-trifluoroethyl)-4-(trifluoromethyl)aniline **1q** (57 mg, 0.20 mmol) and *N*-(2,2,2-trifluoro-1-phenylethyl)pyridin-4-amine **3b** (50 mg, 0.20 mmol) were reacted with *n*BuLi (2.5 M in hexane, 0.18 mL, 0.44 mmol) in dry THF (6 mL) for 4 h at  $-30^{\circ}\text{C}$ . The crude product was purified by flash chromatography ( $\text{SiO}_2$ , cyclohexane/ethyl acetate 5:1  $\rightarrow$  ethyl acetate) to give desired imidazole derivative **2q** (59 mg, 65%) as a yellow oil, *N*-(1-ethoxy-2,2,2-trifluoroethyl)-4-(trifluoromethyl)aniline **1q** (14 mg, 25%) and *N*-(2,2,2-trifluoro-1-phenylethyl)pyridin-4-amine **3b** (17 mg, 34%).

**R<sub>f</sub>** (cyclohexane/ethyl acetate = 5:1) = 0.27. **<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.34 (dd,  $J_{\text{H}2,\text{H}3} = J_{\text{H}6,\text{H}5} = 4.9$  Hz,  $J = 1.4$  Hz, 2 H, H2, H6), 7.62 (d,  $J_{\text{H}3',\text{H}2'} = J_{\text{H}5',\text{H}6'} = 8.5$  Hz, 2 H, H3', H5'), 7.50 – 7.46 (m, 2 H, H2'', H6''), 7.41 (t,  $J_{\text{H}3'',\text{H}4'',\text{H}5''} = J_{\text{H}5'',\text{H}4'',\text{H}3''} = 7.4$  Hz, 2 H, H3'', H5''), 7.36 – 7.30 (m, 1 H, H4''), 7.24 (dd,  $J_{\text{H}2',\text{H}3'} = J_{\text{H}6',\text{H}5'} = 8.6$  Hz,  $J = 2.0$  Hz, 2 H, H2', H6'), 6.78 (dd,  $J_{\text{H}3,\text{H}2} = J_{\text{H}5,\text{H}6} = 4.7$  Hz,  $J = 1.6$  Hz, 2 H, H3, H5), 5.29 (dq,  $J_{\text{CH},\text{CF}_3} = 4.8$  Hz, 1 H, CH) ppm. **<sup>19</sup>F NMR** (380 MHz,  $\text{CDCl}_3$ ):  $\delta$  =  $-62.36$  (CF<sub>3</sub>),  $-82.91$  (d,  $J_{\text{CF}_3,\text{CH}} = 4.8$  Hz, CF<sub>3</sub>),  $-134.36$  (s, CF) ppm. **<sup>13</sup>C NMR** (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 153.99 (d,  $J_{\text{C},\text{F}} = 1.4$  Hz, C4), 150.80 (C2, C6), 147.28 (d,  $J_{\text{C},\text{F}} = 277.7$  Hz, CF), 146.39 (d,  $J_{\text{C},\text{F}} = 6.2$  Hz, C1'), 129.22 (d,  $J_{\text{C},\text{F}} = 0.8$  Hz, C3'', C5''), 128.44 (d,  $J_{\text{C},\text{F}} = 1.8$  Hz, C4''), 128.04 (d,  $J_{\text{C},\text{F}} = 6.8$  Hz, C1''), 127.29 (q,  $J_{\text{C},\text{F}} = 3.8$  Hz, C4'), 127.04 (C3', C5'), 126.17 (d,  $J_{\text{C},\text{F}} = 4.8$  Hz, C2'', C6''), 123.94 (d,  $J_{\text{C},\text{F}} = 271.8$  Hz, CF<sub>3</sub>), 122.43 (q,  $J_{\text{C},\text{F}} = 283.2$  Hz, CF<sub>3</sub>), 119.20 – 118.90 (m, C2', C6'), 113.86 (C3, C5), 110.02 (d,  $J_{\text{C},\text{F}} = 23.7$  Hz, FCCN), 83.80 (qd,  $J_{\text{C},\text{F}} = 35.8$  Hz,  $J_{\text{C},\text{F}} = 4.8$  Hz,

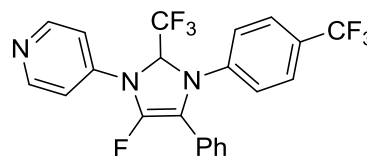


CHCl<sub>3</sub>) ppm. **HRMS** (ESI<sup>+</sup>): *m/z* calcd. for C<sub>22</sub>H<sub>15</sub>F<sub>4</sub>N<sub>3</sub><sup>+</sup> [M+H]<sup>+</sup> 454.1149, found 454.1146. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): *t<sub>R</sub>* = 16.43 min, λ = 214 nm.

#### 4-(5-Fluoro-4-phenyl-2-(trifluoromethyl)-3-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-imidazol-1-yl)pyridine **2r**

According to the **TPIII**, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-4-amine **1b** (59 mg, 0.26 mmol) and *N*-(2,2,2-trifluoro-1-phenylethyl)-4-(trifluoromethyl)aniline **3r** (127 mg, 0.4 mmol) were reacted with *n*BuLi (2.5 M in hexane, 0.31 mL, 0.78 mmol) in dry THF (6 mL) for 4 h at −30 °C. The crude product was purified by flash chromatography (SiO<sub>2</sub>, cyclohexane/ethyl acetate 5:1 → ethyl acetate) to give desired imidazole derivative **2r** (31 mg, 26%) as a yellow oil, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-4-amine **1b** (43 mg, 61%) and *N*-(2,2,2-trifluoro-1-phenylethyl)-4-(trifluoromethyl)aniline **3r** (30 mg, 63%).

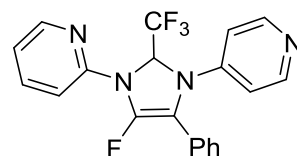
**R<sub>f</sub>** (ethyl acetate) = 0.44. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ = 8.50 (d, *J*<sub>H2,H3</sub> = *J*<sub>H6,H5</sub> = 5.6 Hz, 2 H, H<sub>2</sub>, H<sub>6</sub>), 7.47 (m, 4 H, H<sub>3'</sub>, H<sub>5'</sub>, H<sub>2''</sub>, H<sub>6''</sub>), 7.43 – 7.35 (m, 2 H, H<sub>3''</sub>, H<sub>5''</sub>), 7.35 – 7.28 (m, 1 H, H<sub>4''</sub>), 7.06 (d, *J*<sub>H2',H3'</sub> = *J*<sub>H6',H5'</sub> = 8.5 Hz, 2 H, H<sub>2'</sub>, H<sub>6'</sub>), 7.00 (dt, *J*<sub>H3,H2</sub> = *J*<sub>H5,H6</sub> = 4.5 Hz, *J* = 2.1 Hz, 2 H, H<sub>3</sub>, H<sub>5</sub>), 5.30 (dq, *J*<sub>CH,CF<sub>3</sub></sub> = 4.8 Hz, 1 H, CH) ppm. **<sup>19</sup>F NMR** (380 MHz, CDCl<sub>3</sub>): δ = −62.25 (CF<sub>3</sub>), −82.76 (d, *J*<sub>CF<sub>3</sub>,CH</sub> = 4.9 Hz, CF<sub>3</sub>), −134.24 (s, CF) ppm. **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ = 151.24 (C<sub>2</sub>, C<sub>6</sub>), 150.15 (C<sub>1'</sub>), 149.93 (C<sub>4</sub>), 146.28 (d, *J*<sub>C,F</sub> = 280.5 Hz, CF), 129.15 (C<sub>3''</sub>, C<sub>5''</sub>), 128.77 (C<sub>4''</sub>), 128.46 (d, *J*<sub>C,F</sub> = 2.0 Hz, C<sub>1''</sub>), 127.91 (d, *J*<sub>C,F</sub> = 6.9 Hz, C<sub>3'</sub>, C<sub>5'</sub>), 126.92 (q, *J*<sub>C,F</sub> = 3.8 Hz, CCF<sub>3</sub>), 126.36 (d, *J*<sub>C,F</sub> = 5.0 Hz, C<sub>2''</sub>, C<sub>6''</sub>), 120.56 (C<sub>2'</sub>, C<sub>6'</sub>), 111.67 (C<sub>3</sub>, C<sub>5</sub>), 111.14 (d, *J*<sub>C,F</sub> = 21.6 Hz, FCCN), 83.15 (qd, *J*<sub>C,F</sub> = 35.9 Hz, *J*<sub>C,F</sub> = 4.3 Hz, CHCl<sub>3</sub>) ppm. **HRMS** (ESI<sup>+</sup>): *m/z* calcd. for C<sub>22</sub>H<sub>15</sub>F<sub>4</sub>N<sub>3</sub><sup>+</sup> [M+H]<sup>+</sup> 454.1149, found 454.1148. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): *t<sub>R</sub>* = 15.84 min, λ = 214 nm.



#### 2-(5-Fluoro-4-phenyl-3-(pyridin-4-yl)-2-(trifluoromethyl)-2,3-dihydro-1*H*-imidazol-1-yl)pyridine **2s**

According to the **TPIII**, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyridine **1b** (50 mg, 0.23 mmol) and *N*-(2,2,2-trifluoro-1-phenylethyl)pyridin-4-amine **3b** (87 mg, 0.35 mmol) were reacted with *n*BuLi (1.6 M in hexane, 0.43 mL, 0.69 mmol) in dry THF (8 mL) for 4 h at −30 °C. The crude product was purified by flash chromatography (SiO<sub>2</sub>, cyclohexane/ethyl acetate 1:1 → ethyl acetate) to give desired imidazole derivative **2s** (75 mg, 85%) as a colorless oil.

**R<sub>f</sub>** (ethyl acetate) = 0.50. **<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>): δ = 8.40 – 8.30 (m, 2 H, H<sub>2</sub><sub>pyrid-4-yl</sub>, H<sub>6</sub><sub>pyrid-4-yl</sub>), 8.25 (ddd, *J*<sub>H6,H5</sub> = 4.9 Hz, *J*<sub>H6,H4</sub> = 1.9 Hz, *J* = 0.9 Hz, 1 H, H<sub>6</sub><sub>pyrid-2-yl</sub>), 7.70 – 7.63 (m, 1 H, H<sub>4</sub><sub>pyrid-2-yl</sub>), 7.49 – 7.44 (m, 2 H, H<sub>2''</sub>, H<sub>6''</sub>), 7.43 – 7.36 (m, 2 H, H<sub>3''</sub>, H<sub>5''</sub>), 7.36 – 7.29 (m, 1 H, H<sub>4''</sub>), 7.19 (ddt, *J*<sub>H3,H4</sub> = 8.4 Hz, *J*<sub>H3,H5</sub> = 3.2 Hz, *J* = 0.9 Hz, 1H, H<sub>3</sub><sub>pyrid-2-yl</sub>), 6.98 (ddd, *J*<sub>H5,H4</sub> = 7.3 Hz, *J*<sub>H5,H6</sub> = 4.9 Hz, *J* = 0.8 Hz, 1 H, H<sub>5</sub><sub>pyrid-2-yl</sub>), 6.86 – 6.76 (m, 2 H, H<sub>3</sub><sub>pyrid-4-yl</sub>, H<sub>5</sub><sub>pyrid-4-yl</sub>), 6.61 (dq, *J*<sub>CH,CF<sub>3</sub></sub> = 5.0 Hz, 1 H, CH) ppm. **<sup>19</sup>F NMR** (380 MHz, CDCl<sub>3</sub>): δ = −82.69 (d, *J*<sub>CF<sub>3</sub>,CH</sub> = 5.1 Hz, CF<sub>3</sub>), −131.29 (t, *J* = 3.9 Hz, CF) ppm. **<sup>13</sup>C NMR** (150 MHz, CDCl<sub>3</sub>): δ = 154.25 (d, *J*<sub>C,F</sub> = 7.0 Hz, H<sub>2</sub><sub>pyrid-2-yl</sub>), 154.14 (H<sub>4</sub><sub>pyrid-4-yl</sub>), 150.25 (C<sub>2</sub><sub>pyrid-4-yl</sub>, C<sub>6</sub><sub>pyrid-4-yl</sub>), 148.22 (C<sub>6</sub><sub>pyrid-2-yl</sub>), 147.65

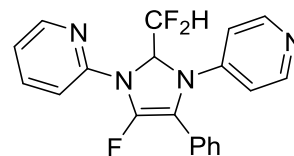


(d,  $J_{C,F} = 279.1$  Hz, CF), 138.75 ( $C4_{\text{pyrid-2-yl}}$ ), 129.13 ( $C3''$ ,  $C5''$ ), 128.43 (d,  $J_{C,F} = 6.8$  Hz,  $C1''$ ), 128.16 ( $C4''$ ), 126.10 ( $C2''$ ,  $C6''$ ), 122.85 (q,  $J_{C,F} = 284.0$  Hz,  $CF_3$ ), 119.06 ( $C5_{\text{pyrid-2-yl}}$ ), 113.68, ( $C3_{\text{pyrid-4-yl}}$ ,  $C5_{\text{pyrid-4-yl}}$ ), 110.81 (d,  $J = 9.2$  Hz,  $C3_{\text{pyrid-2-yl}}$ ), 109.33 (d,  $J_{C,F} = 25.4$  Hz, FCCN), 78.03 (q,  $J_{C,F} = 35.9$  Hz,  $CHCF_3$ ). **HRMS** (ESI+):  $m/z$  calcd. for  $C_{20}H_{15}F_4N_4^+$   $[M+H]^+$  387.1227, found 387.1225.

## 2-(2-(Difluoromethyl)-5-fluoro-4-phenyl-3-(pyridin-4-yl)-2,3-dihydro-1H-imidazol-1-yl)pyridine 2t

According to the **TPIII**, *N*-(1-ethoxy-2,2-difluoroethyl)pyridin-2-amine **1t** (36 mg, 0.18 mmol) and *N*-(2,2,2-trifluoro-1-phenylethyl)pyridin-4-amine **3b** (68 mg, 0.27 mmol) were reacted with *n*BuLi (2.5 M in hexane, 0.24 mL, 0.60 mmol) in dry THF (6 mL) for 4 h at  $-30$  °C. The crude product was purified by flash chromatography ( $SiO_2$ , cyclohexane/ethyl acetate 1:1  $\rightarrow$  ethyl acetate) to give desired imidazole derivative **2t** (50 mg, 75%) as a colorless oil.

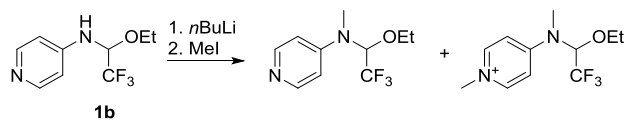
**R<sub>f</sub>** (ethyl acetate) = 0.45. **<sup>1</sup>H NMR** (400 MHz,  $CDCl_3$ ):  $\delta$  = 8.31 (d,  $J_{H3,H2} = J_{H5,H6} = 5.4$  Hz, 2 H,  $H2_{\text{pyrid-4-yl}}$ ,  $H6_{\text{pyrid-4-yl}}$ ), 8.24 (ddd,  $J_{H6,H5} = 5.0$  Hz,  $J_{H6,H4} = 1.9$  Hz,  $J = 0.9$  Hz, 1 H,  $H6_{\text{pyrid-2-yl}}$ ), 7.64 (ddd,  $J_{H4,H3} = 8.4$ ,  $J_{H4,H5} = 7.3$  Hz,  $J = 1.9$  Hz, 1 H,  $H4_{\text{pyrid-2-yl}}$ ), 7.47 (d,  $J_{H2'',H3''} = J_{H6'',H5''} = 7.2$  Hz, 2 H,  $H2''$ ,  $H6''$ ), 7.38 (dd,  $J_{H3'',H2''} = J_{H5'',H6''} = 8.5$  Hz,  $J_{H3'',H4''} = J_{H5'',H4''} = 6.9$  Hz, 2 H,  $H3''$ ,  $H5''$ ), 7.33 – 7.27 (m, 1 H,  $H4''$ ), 7.13 (ddt,  $J_{H3,H4} = 8.4$  Hz,  $J_{H3,H5} = 3.4$  Hz,  $J = 1.0$  Hz, 1 H,  $H3_{\text{pyrid-2-yl}}$ ), 6.94 (ddd,  $J_{H5,H4} = 7.3$  Hz,  $J_{H5,H6} = 4.9$  Hz,  $J = 0.9$  Hz, 1 H,  $H5_{\text{pyrid-2-yl}}$ ), 6.84 – 6.73 (m, 2 H,  $H3_{\text{pyrid-4-yl}}$ ,  $H5_{\text{pyrid-4-yl}}$ ), 6.18 (m, 1 H, CH), 6.10 (td,  $J_{CHF_2,CHF_2} = 55.3$  Hz,  $J_{CHF_2,CH} = 3.3$  Hz, 1 H,  $CF_2H$ ) ppm. **<sup>19</sup>F NMR** (380 MHz,  $CDCl_3$ ):  $\delta$  =  $-129.27$  (ddd,  $J_{CHF_2,CHF_2} = 287.6$ ,  $J_{CHF_2,CHF_2} = 55.0$ ,  $J_{CHF_2,CH} = 3.0$  Hz),  $-132.99$  (t,  $J = 4.1$  Hz, CF),  $-137.21$  (ddd,  $J_{CHF_2,CHF_2} = 287.6$ ,  $J_{CHF_2,CHF_2} = 55.6$ ,  $J_{CHF_2,CH} = 13.9$  Hz) ppm. **<sup>13</sup>C NMR** (100 MHz,  $CDCl_3$ ):  $\delta$  = 154.55 ( $H4_{\text{pyrid-4-yl}}$ ), 154.13 (d,  $J_{C,F} = 6.7$  Hz,  $H2_{\text{pyrid-2-yl}}$ ), 150.34 ( $C2_{\text{pyrid-4-yl}}$ ,  $C6_{\text{pyrid-4-yl}}$ ), 148.37 ( $C6_{\text{pyrid-2-yl}}$ ), 147.44 (d,  $J_{C,F} = 279.4$  Hz, CF), 138.59 ( $C4_{\text{pyrid-2-yl}}$ ), 129.06 ( $C3''$ ,  $C5''$ ), 128.82 (d,  $J_{C,F} = 7.0$  Hz,  $C1''$ ), 127.80 ( $C4''$ ), 125.93 (d,  $J_{C,F} = 4.9$  Hz,  $C2''$ ,  $C6''$ ), 118.38 ( $C5_{\text{pyrid-2-yl}}$ ), 115.04 – 109.77 (m,  $CF_2H$ ), 113.80 ( $C3_{\text{pyrid-4-yl}}$ ,  $C5_{\text{pyrid-4-yl}}$ ), 110.31 (d,  $J_{C,F} = 9.3$  Hz,  $C3_{\text{pyrid-2-yl}}$ ), 108.74 (d,  $J_{C,F} = 24.2$  Hz, FCCN), 81.11 – 79.62 (m,  $CHCF_2H$ ) ppm. **HRMS** (ESI+):  $m/z$  calcd. for  $C_{20}H_{15}F_3N_4^+$   $[M+H]^+$  369.1322, found 369.1322.





### 3. Mechanistic experiments and NMR-studies

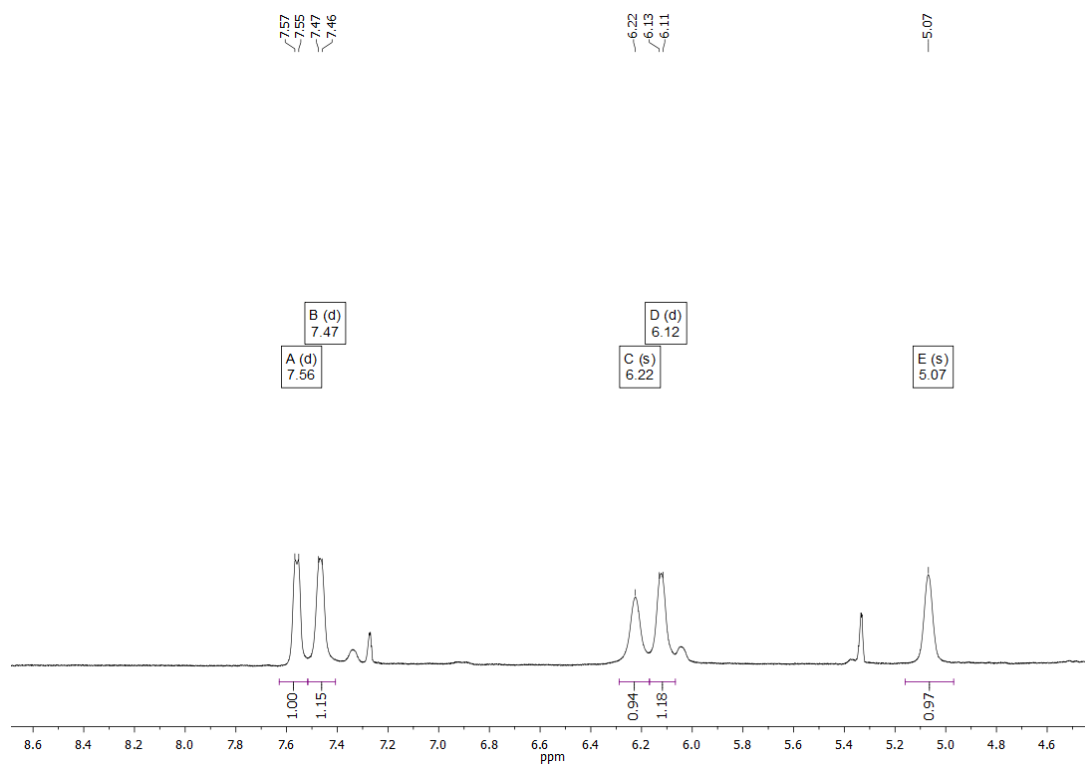
#### Deprotonation of *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-4-amine **1b** with *n*BuLi



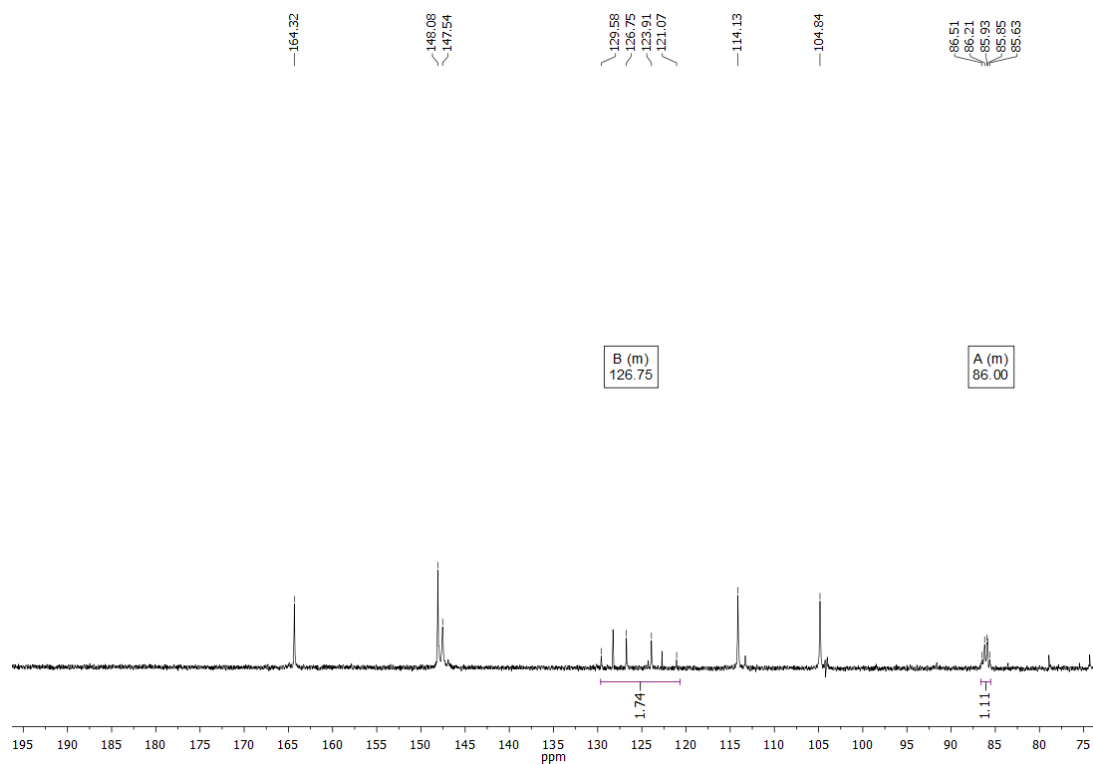
In a dry and argon flushed NMR tube containing a thin, fused capillary tube with CD<sub>3</sub>OD, *N,O*-acetal **1b** (25 mg, 0.11 mmol) was solved in freshly distilled THF (0.7 mL) and cooled to  $-78^{\circ}\text{C}$ . *n*BuLi (2.5 M in hexane, 0.05 mL, 0.11 mmol) was added at once. The NMR tube was well shaken to ensure a homogeneuos distribution of the base.

<sup>1</sup>H, and <sup>13</sup>C NMR were measured at  $-30^{\circ}\text{C}$ .

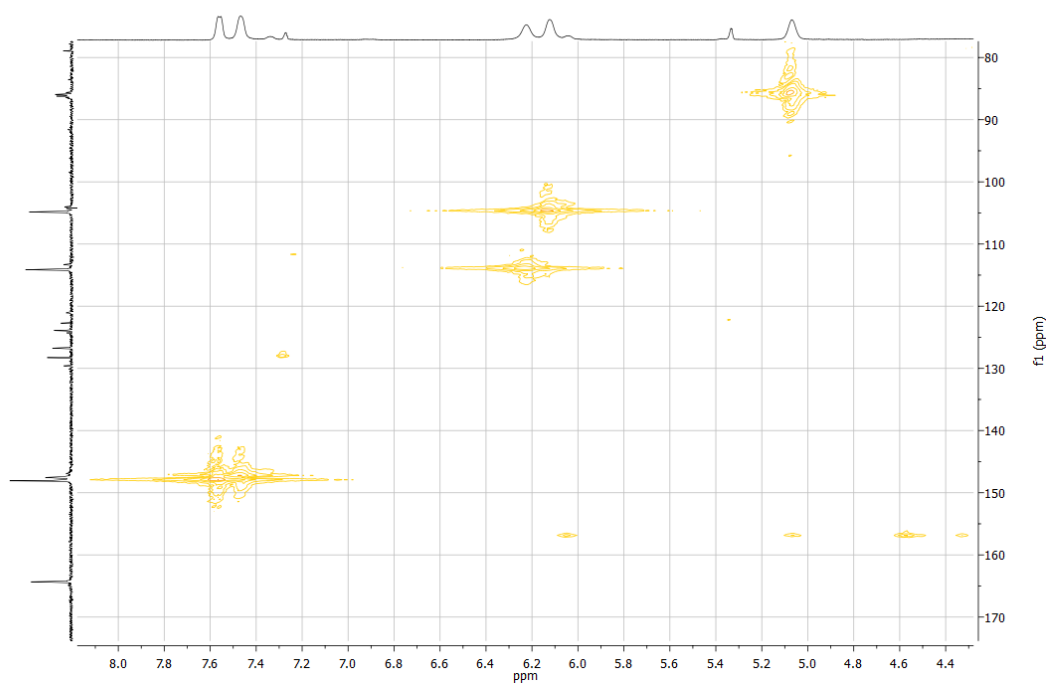
#### <sup>1</sup>H NMR:



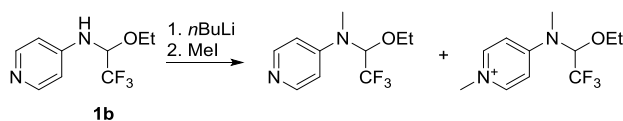
**$^{13}\text{C}$  NMR:**



**HSQC:**



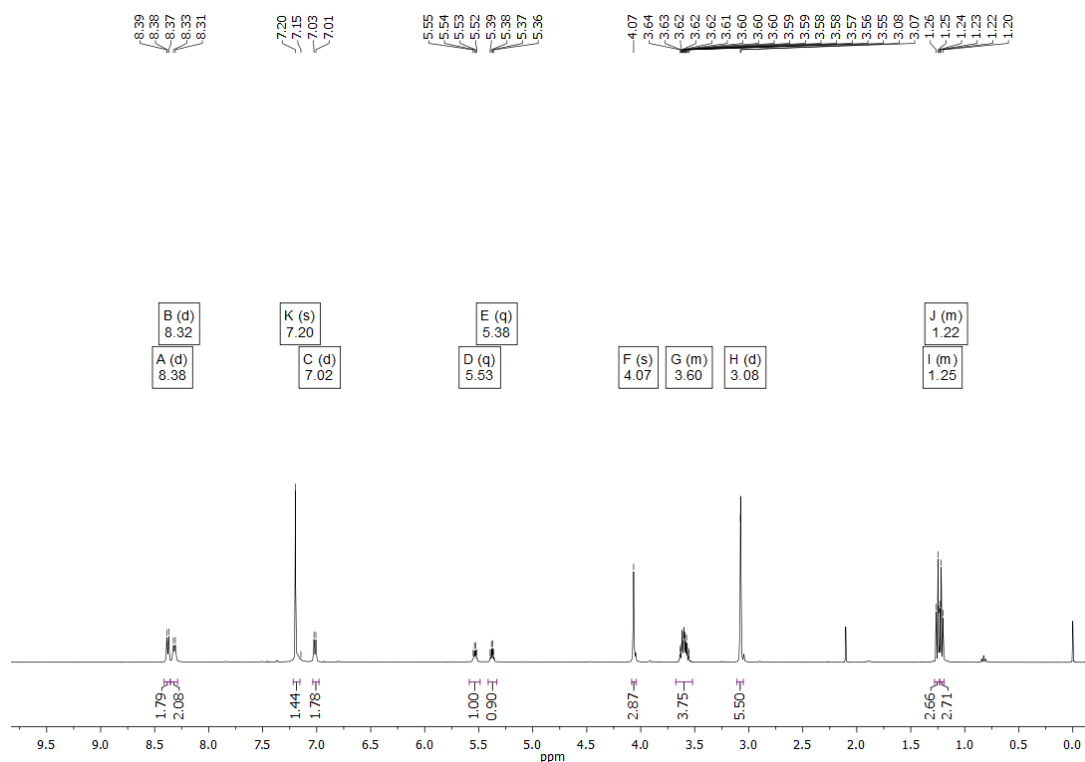
## Deprotonation of *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-4-amine **1b** with *n*BuLi



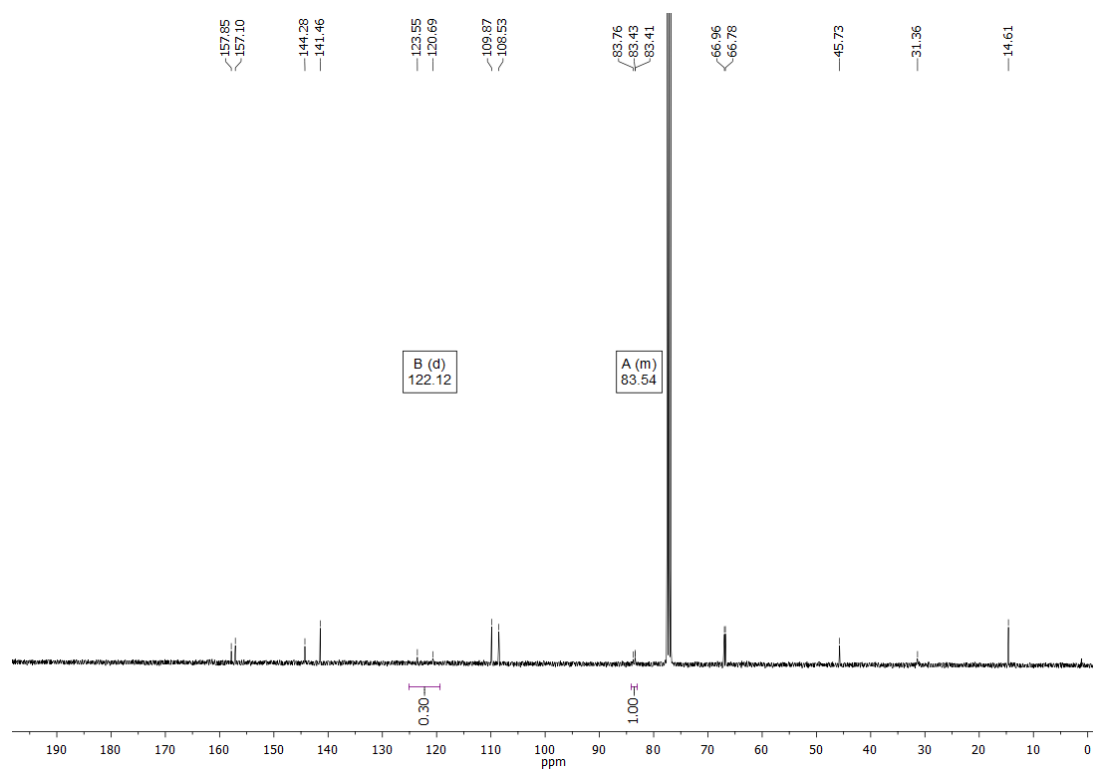
In a dry and argon flushed *Schlenk*-flask the *N,O*-acetal **1b** (50 mg, 0.23 mmol) was solved in freshly distilled THF (3 mL) and cooled to  $-78\text{ }^{\circ}\text{C}$ . *n*BuLi (2.5 M in hexane, 0.11 mL, 0.27 mmol) was added dropwise to the reaction mixture, which was stirred for 30 min at  $-78\text{ }^{\circ}\text{C}$ . Subsequently iodomethane (35 mg, 0.25 mmol) was added to the solution. After 2 h the reaction mixture was quenched with methanol (2 mL) and the solvent was removed *in vacuo*.

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.38 (d,  $J$  = 7.3 Hz, 2 H, H2, H6), 8.32 (d,  $J$  = 7.2 Hz, 2 H, H2', H6'), 7.20 (m, 2 H, H3', H5'), 7.02 (d,  $J$  = 6.8 Hz, 2 H, H3, H5), 5.53 (q,  $J$  = 4.7 Hz, 1 H, CH), 5.38 (q,  $J$  = 4.7 Hz, 1 H, CH'), 4.07 (s, 3 H,  $\text{CH}_3$ '), 3.68 – 3.52 (m, 4 H,  $2 \times \text{CH}_2$ ), 3.08 (d,  $J$  = 1.3 Hz, 6 H,  $2 \times \text{CH}_3$ ), 1.28 – 1.23 (m, 3 H,  $\text{CH}_3$ ), 1.23 – 1.19 (m, 3 H,  $\text{CH}_3$ ) ppm.  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 157.85 (C1), 157.10 (C1'), 144.28 (C2', C6'), 141.46 (C2, C6), 122.12 (q,  $J_{\text{C,F}}$  = 287.5 Hz,  $\text{CF}_3$ ), 109.87 (C3', C5'), 108.53 (C3, C5), 84.14 – 83.02 (m,  $\text{CHCF}_3$ ), 66.96 ( $\text{CH}_2$ ), 66.78 ( $\text{CH}_2$ ), 45.73 ( $\text{CH}_3$ ), 31.36 ( $\text{CH}_3$ ), 14.61 ( $\text{CH}_2\text{CH}_3$ ) ppm. **HRMS** (ESI+):  $m/z$  calcd. for  $\text{C}_{10}\text{H}_{14}\text{F}_3\text{N}_2\text{O}^+$   $[\text{M}+\text{H}]^+$  235.1053, found 253.10508. **HRMS** (ESI+):  $m/z$  calcd. for  $\text{C}_{11}\text{H}_{16}\text{F}_3\text{N}_2\text{O}^+$   $[\text{M}+\text{H}]^+$  249.1209, found 249.1209.

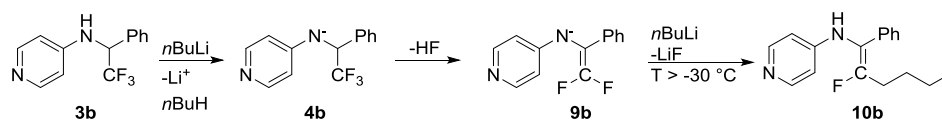
### $^1\text{H}$ NMR:



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



## Reaction of *N*-(2,2,2-trifluoro-1-phenylethyl)pyridin-4-amine **3b** with two equivalents of *n*BuLi

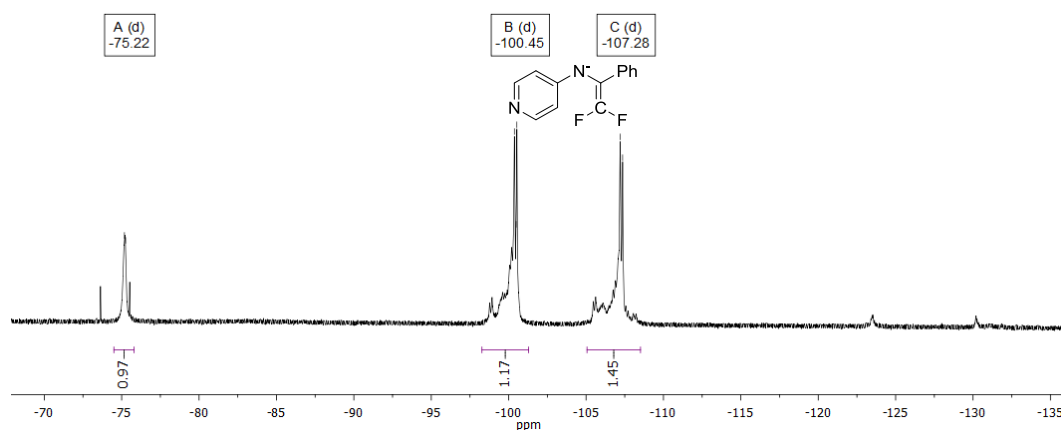


In a dry and argon flushed NMR tube, containing a thin, fused capillary tube with CD<sub>3</sub>OD, the CF<sub>3</sub>-amine **3b** (25 mg, 0.10 mmol) was solved in freshly distilled THF (0.7 mL) and cooled to  $-78\text{ }^\circ\text{C}$ . Two equivalents of *n*BuLi (2.5 M in hexane, 0.08 mL, 0.20 mmol) were added at once. The NMR tube was well shaken to ensure a homogeneous distribution of the base.

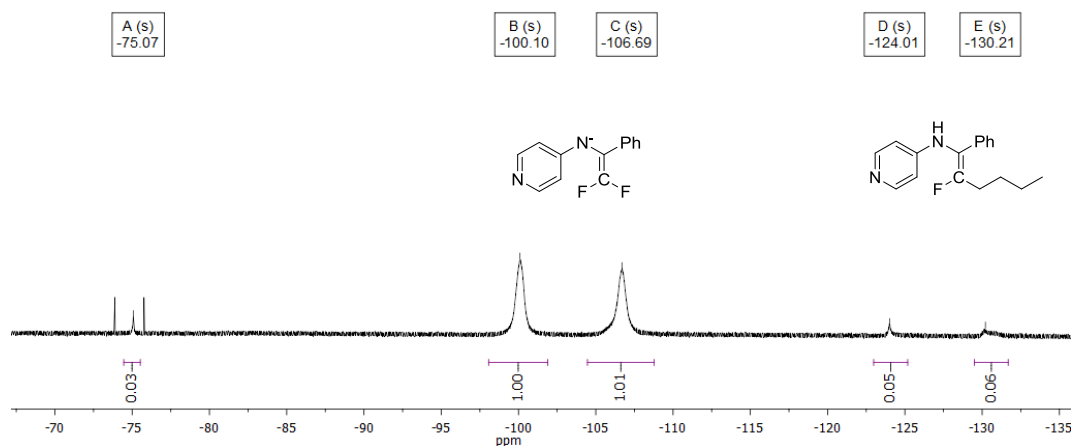
<sup>19</sup>F NMR measured at the stated temperatures below.

After the measurement were completed, the mixture was quenched with water and extracted with Et<sub>2</sub>O (3 x 20 mL). The solvent was dried with MgSO<sub>4</sub>, filtered and evaporated to give a mixture of (*E*)- and (*Z*)-*N*-(2-fluoro-1-phenylhex-1-en-1-yl)pyridin-4-amine **10b** as a yellow oil.

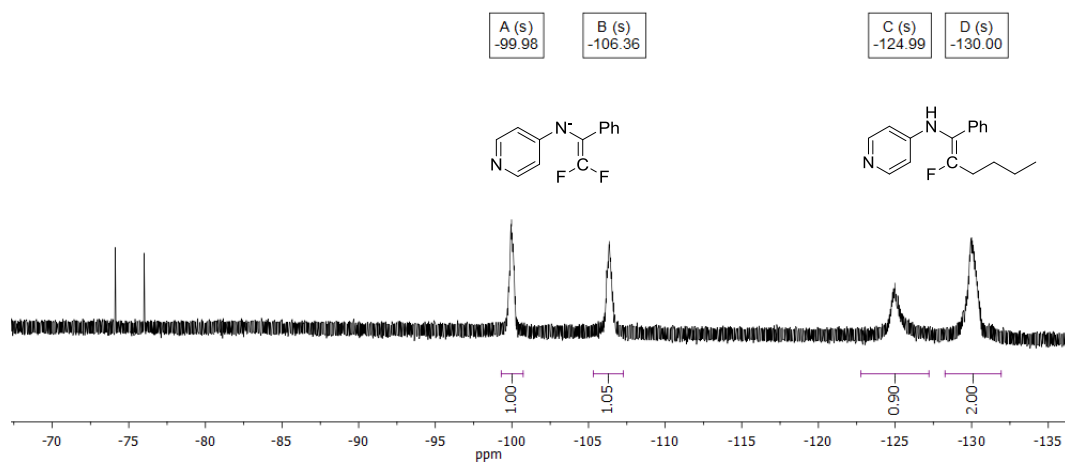
$-60\text{ }^\circ\text{C}$ :



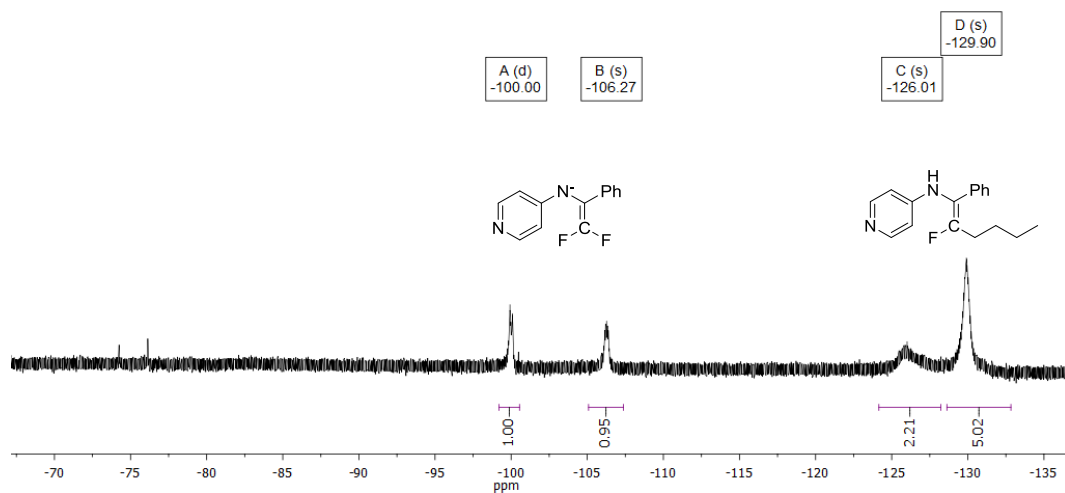
$-40\text{ }^\circ\text{C}$ :



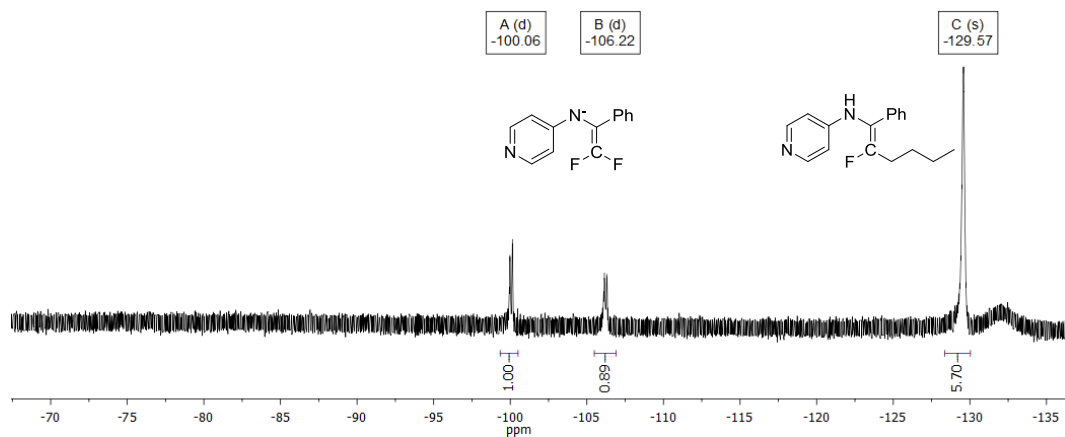
**-20 °C:**



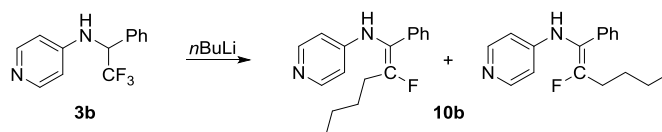
**-10 °C:**



**20 °C:**



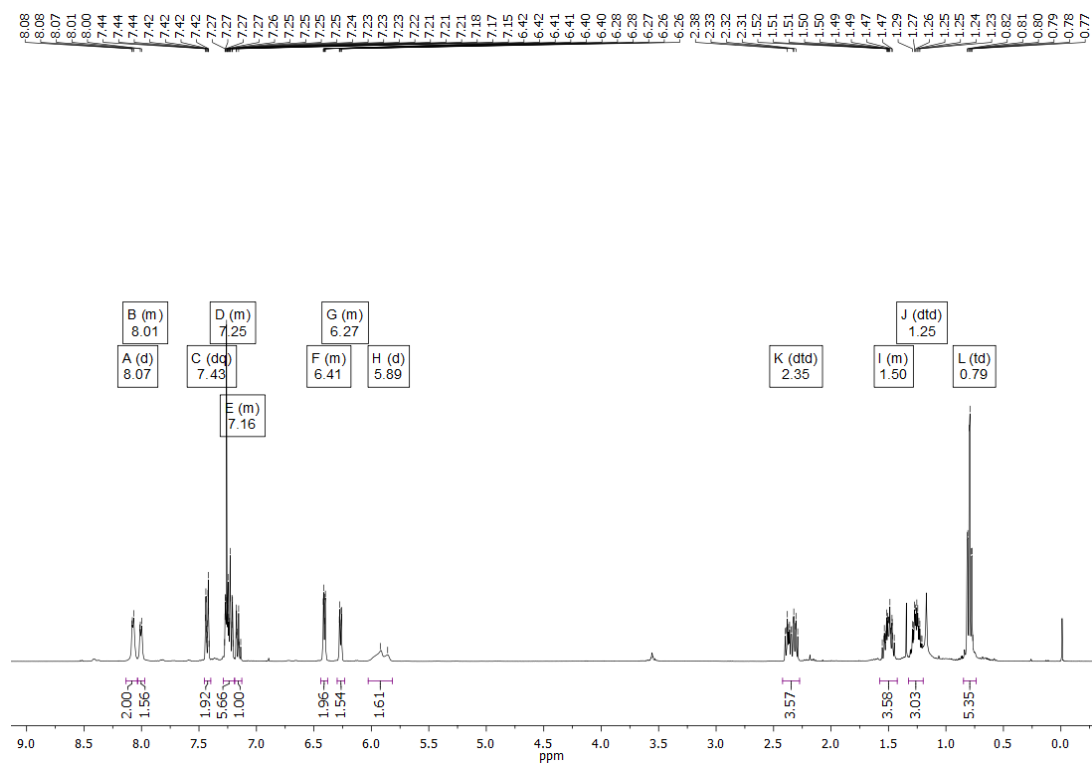
**Reaction of *N*-(2,2,2-trifluoro-1-phenylethyl)pyridin-4-amine **3b** with two equivalents of *n*BuLi**



*N*-(2,2,2-trifluoro-1-phenylethyl)pyridin-4-amine **3b** (30 mg, 0.12 mmol) was solved in freshly distilled THF (2 mL) in a dry and argon flushed flask, equipped with a magnetic stirrer and a septum and cooled to  $-40\text{ }^{\circ}\text{C}$ . *n*BuLi (2.5 M in hexane, 0.11 mL, 0.26 mmol) was added dropwise with a syringe and the solution was warmed up to  $-20\text{ }^{\circ}\text{C}$  and stirred for 1.5 h at  $-20\text{ }^{\circ}\text{C}$ . After the reaction was completed, sat.  $\text{NH}_4\text{Cl}$  solution (5 mL) was added and the mixture was extracted three times with  $\text{Et}_2\text{O}$  (3 x 20 mL). The solvent was dried with  $\text{MgSO}_4$ , filtered and evaporated to give a mixture of *(E)*- and *(Z)*-*N*-(2-fluoro-1-phenylhex-1-en-1-yl)pyridin-4-amine **10b** as a yellow oil.

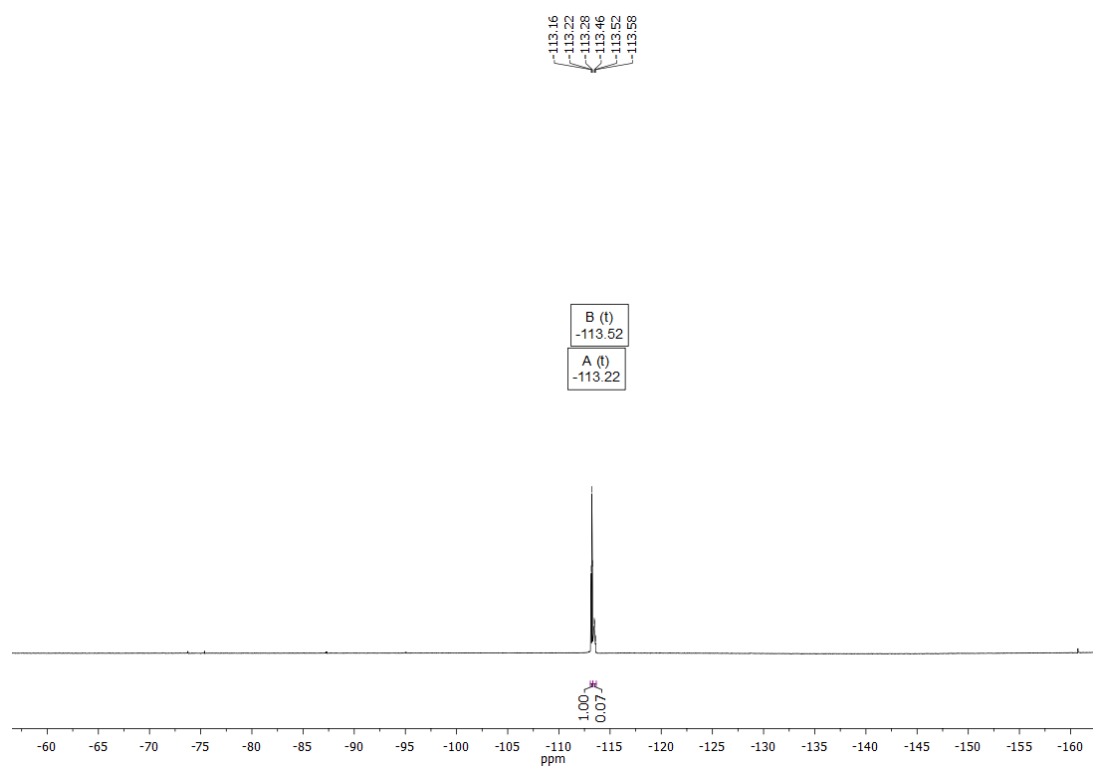
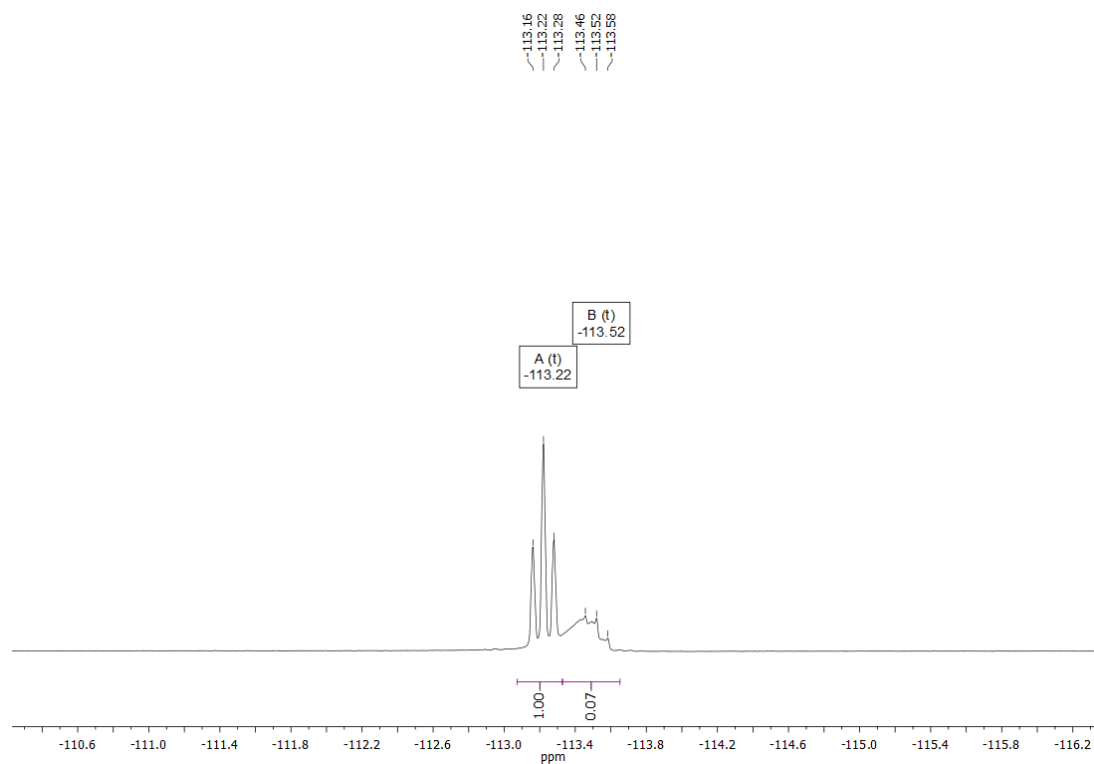
**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.07 (d,  $J_{\text{H}_2,\text{H}_3} = J_{\text{H}_6,\text{H}_5} = 4.8\text{ Hz}$ , 2 H,  $\text{H}_{2\text{Pyridyl}}$ ,  $\text{H}_{6\text{Pyridyl}}$ ), 8.03 – 7.97 (m, 2 H,  $\text{H}_{2\text{Pyridyl}}$ ,  $\text{H}_{6\text{Pyridyl}}$ ), 7.43 (d,  $J_{\text{H}_2',\text{H}_3'} = J_{\text{H}_6',\text{H}_5'} = 7.4\text{ Hz}$ , 4 H,  $\text{H}_{2\text{Phenyl}}$ ,  $\text{H}_{6\text{Phenyl}}$ ), 7.29 – 7.19 (m, 4 H,  $\text{H}_{3\text{Phenyl}}$ ,  $\text{H}_{5\text{Phenyl}}$ ), 7.19 – 7.13 (m, 2 H,  $\text{H}_{4\text{Phenyl}}$ ), 6.44 – 6.38 (m, 2 H,  $\text{H}_{3\text{Pyridyl}}$ ,  $\text{H}_{5\text{Pyridyl}}$ ), 6.30 – 6.23 (m, 2 H,  $\text{H}_{3\text{Pyridyl}}$ ,  $\text{H}_{5\text{Pyridyl}}$ ), 5.89 (m, 2 H, NH), 2.35 (dtd,  $J_{\text{CH}_2,\text{CF}} = 23.9\text{ Hz}$ ,  $J_{\text{CH}_2,\text{CH}_2} = 7.7\text{ Hz}$ ,  $J = 5.2\text{ Hz}$ , 4 H,  $\text{CH}_2$ ), 1.58 – 1.42 (m, 4 H,  $\text{CH}_2$ ), 1.25 (dtd,  $J_{\text{CH}_2,\text{CH}_2} = 14.6\text{ Hz}$ ,  $J_{\text{CH}_2,\text{CH}_3} = 7.4\text{ Hz}$ ,  $J = 3.4\text{ Hz}$ , 4 H,  $\text{CH}_2$ ), 0.79 (td,  $J_{\text{CH}_3,\text{CH}_2} = 7.3\text{ Hz}$ ,  $J = 2.5\text{ Hz}$ , 6 H,  $\text{CH}_3$ ) ppm;  **$^{19}\text{F}$  NMR** (380 MHz,  $\text{CDCl}_3$ ):  $\delta$  =  $-113.22$  (t,  $J_{\text{CF},\text{CH}_2} = 22.1\text{ Hz}$ , CF),  $-113.52$  (t,  $J_{\text{CF},\text{CH}_2} = 23.7\text{ Hz}$ , CF) ppm;  **$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 161.40 (d,  $J_{\text{C},\text{F}} = 264.3\text{ Hz}$ , CF), 153.90 (d,  $J_{\text{C},\text{F}} = 253.7\text{ Hz}$ , CF), 152.79 ( $\text{C}_{4\text{Pyridyl}}$ ), 150.91 ( $\text{C}_{4\text{Pyridyl}}$ ), 150.12 ( $\text{C}_{2\text{Pyridyl}}$ ,  $\text{C}_{6\text{Pyridyl}}$ ), 149.74 ( $\text{C}_{2\text{Pyridyl}}$ ,  $\text{C}_{6\text{Pyridyl}}$ ), 134.21 (d,  $J_{\text{C},\text{F}} = 4.3\text{ Hz}$ ,  $\text{C}_{1\text{Phenyl}}$ ), 133.98 (d,  $J_{\text{C},\text{F}} = 5.0\text{ Hz}$ ,  $\text{C}_{1\text{Phenyl}}$ ), 128.81 ( $\text{C}_{\text{Phenyl}}$ ), 128.78 ( $\text{C}_{\text{Phenyl}}$ ), 128.53 ( $\text{C}_{\text{Phenyl}}$ ), 128.46 ( $\text{C}_{\text{Phenyl}}$ ), 127.92 ( $\text{C}_{\text{Phenyl}}$ ), 127.90 ( $\text{C}_{\text{Phenyl}}$ ), 127.75 ( $\text{C}_{\text{Phenyl}}$ ), 127.68 ( $\text{C}_{\text{Phenyl}}$ ), 119.53 (d,  $J_{\text{C},\text{F}} = 15.4\text{ Hz}$ , CNH), 117.61 (d,  $J_{\text{C},\text{F}} = 29.5\text{ Hz}$ , CNH), 109.99 ( $\text{C}_{3\text{Pyridyl}}$ ,  $\text{C}_{5\text{Pyridyl}}$ ), 108.67 ( $\text{C}_{3\text{Pyridyl}}$ ,  $\text{C}_{5\text{Pyridyl}}$ ), 29.14 ( $\text{CH}_2$ ), 29.12 (d,  $J_{\text{C},\text{F}} = 25.3\text{ Hz}$ ,  $\text{CH}_2$ ), 28.66 (d,  $J_{\text{C},\text{F}} = 25.3\text{ Hz}$ ,  $\text{CH}_2$ ), 28.21 ( $\text{CH}_2$ ), 22.37 ( $\text{CH}_2$ ), 22.33 ( $\text{CH}_2$ ), 13.89 ( $\text{CH}_3$ ), 13.85 ( $\text{CH}_3$ ) ppm; **HRMS** (ESI $^{+}$ ):  $m/z$  calcd. for  $\text{C}_{17}\text{H}_{20}\text{FN}_2^{+}$  [ $\text{M}+\text{H}$ ] $^{+}$  271.1605; found 271.1605.

**<sup>1</sup>H NMR:**

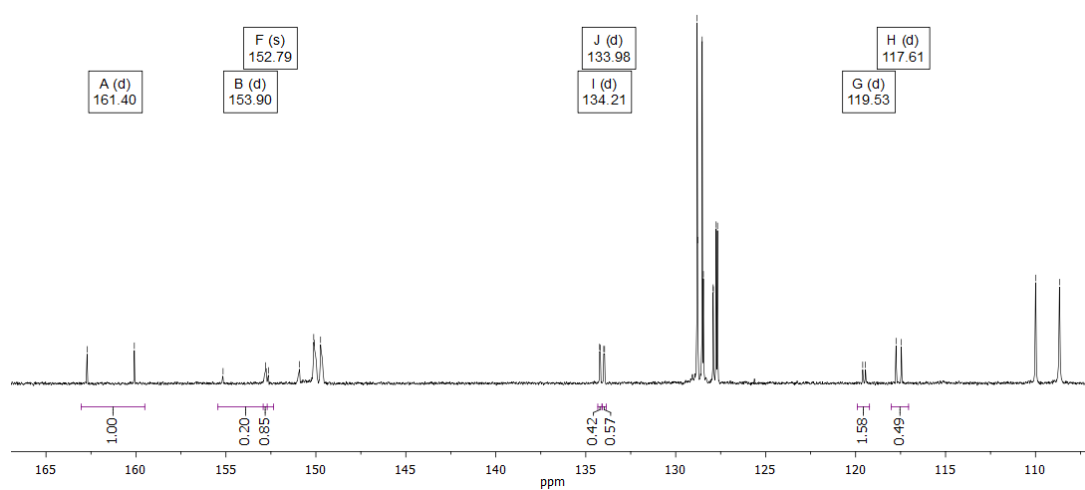
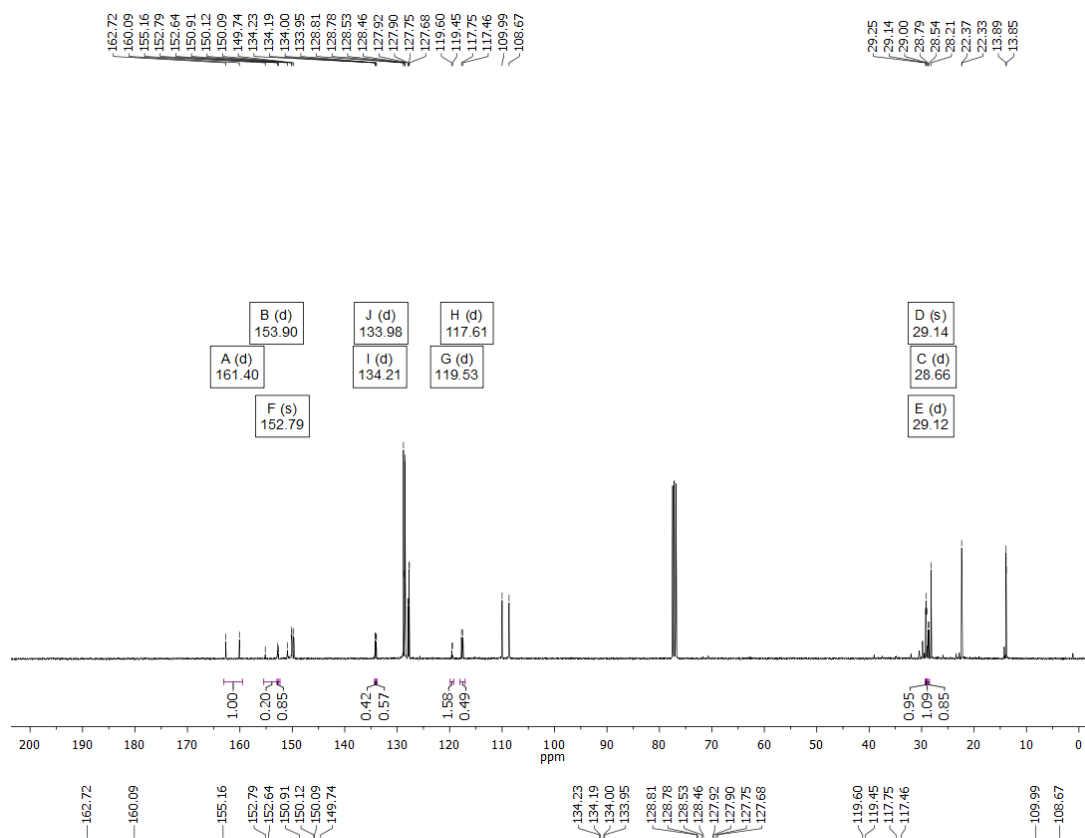




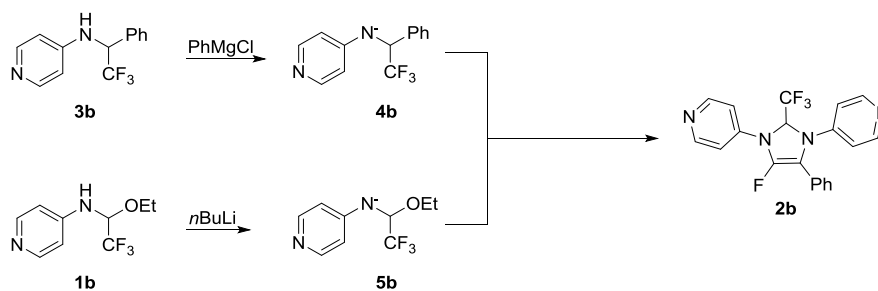
**$^{19}\text{F}$  NMR:**



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



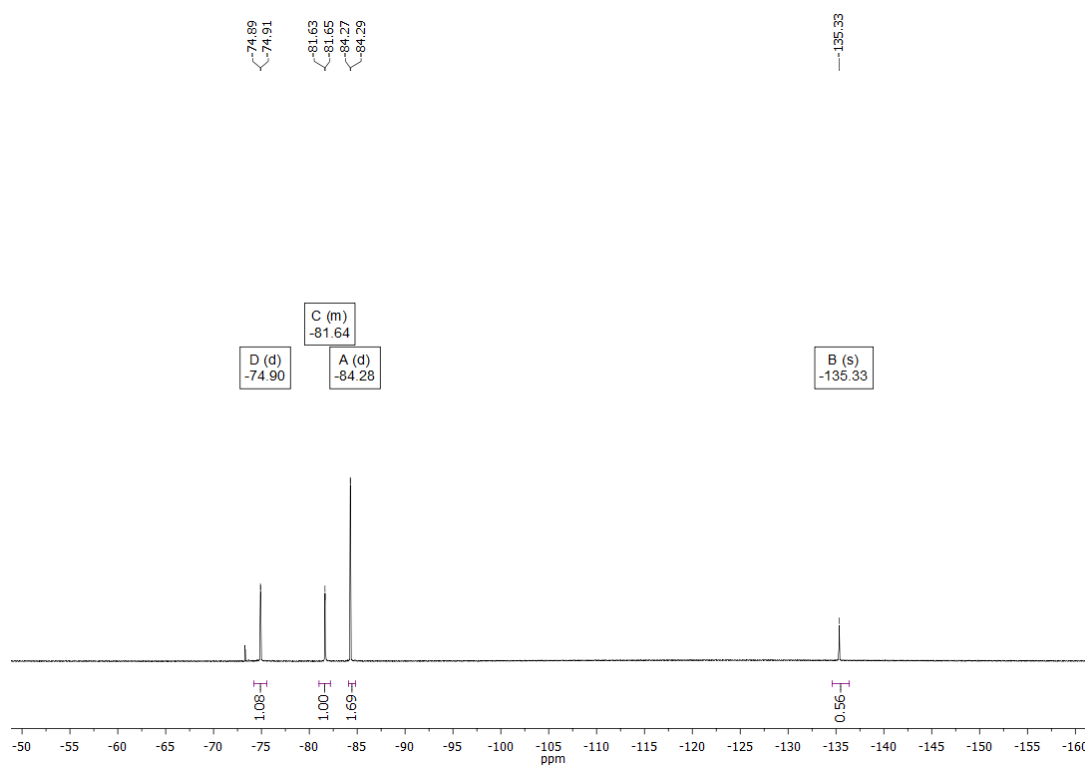
**Reaction of *N*-(2,2,2-trifluoro-1-phenylethyl)pyridin-4-amine **3b** and *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-4-amine **1b****



*N*-(2,2,2-trifluoro-1-phenylethyl)pyridin-4-amine **3b** (57 mg, 0.23 mmol) was solved in freshly distilled THF (3 mL) in a dry and argon flushed flask, equipped with a magnetic stirrer and a septum and cooled to  $-20\text{ }^{\circ}\text{C}$ . After dropwise addition of  $\text{PhMgCl}$  (2.8 M in hexane, 0.10 mL, 0.23 mmol), the solution was stirred for 30 min. In a second *Schlenk*-flask *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-4-amine **1b** was solved in freshly distilled THF (3 mL) and cooled to  $-60\text{ }^{\circ}\text{C}$ .  $n\text{BuLi}$  (1.6 M in hexane, 0.14 mL, 0.23 mmol) was added dropwise with a syringe and the solution was stirred at  $-60\text{ }^{\circ}\text{C}$  for 30 min. Subsequently, the solution containing the deprotonated amine **4b** was added to the second flask. After stirring the reaction mixture for 3 h, sat.  $\text{NH}_4\text{Cl}$  solution (5 mL) was added and the mixture was extracted with  $\text{Et}_2\text{O}$  (3 x 20 mL). The solvent was dried with  $\text{MgSO}_4$ , filtered and evaporated to give a mixture of imidazole derivative **2b** and both starting materials **3b** and **1b** in a 1.7:1:1 ratio.

The crude product mixture was analyzed *via*  $^{19}\text{F}$  NMR in  $\text{CDCl}_3$ .

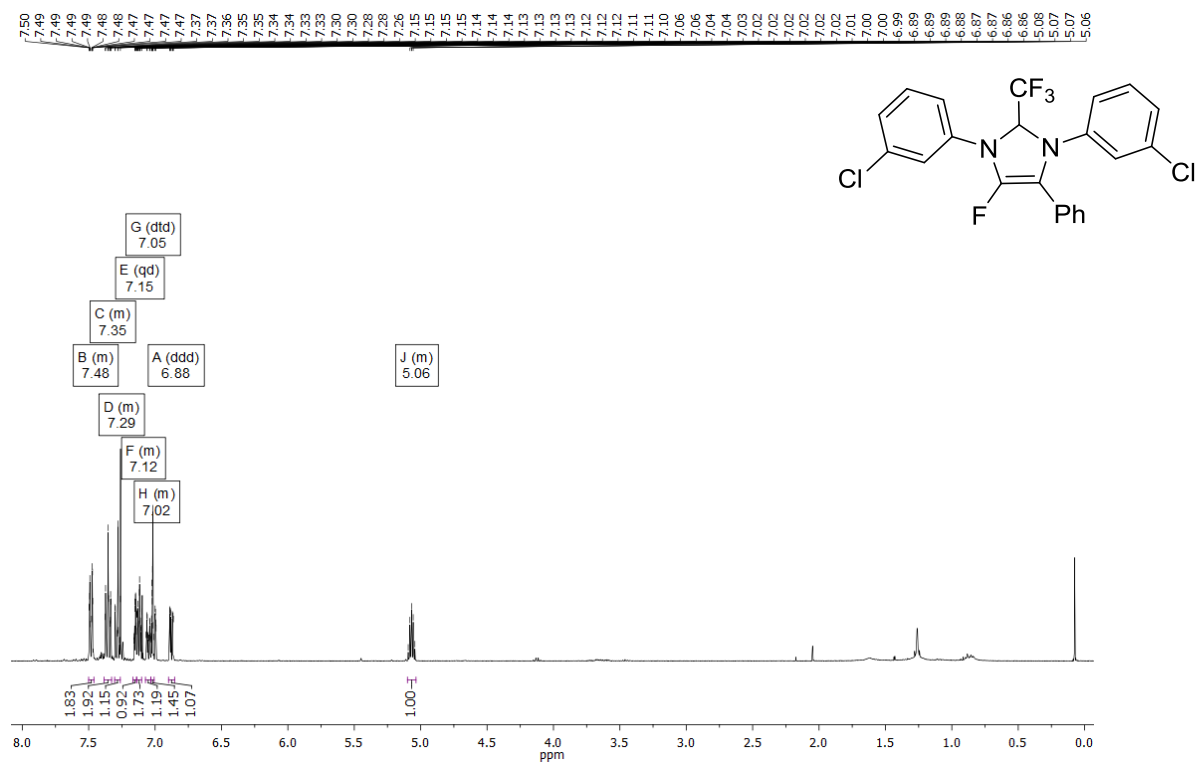
**$^{19}\text{F}$  NMR:**



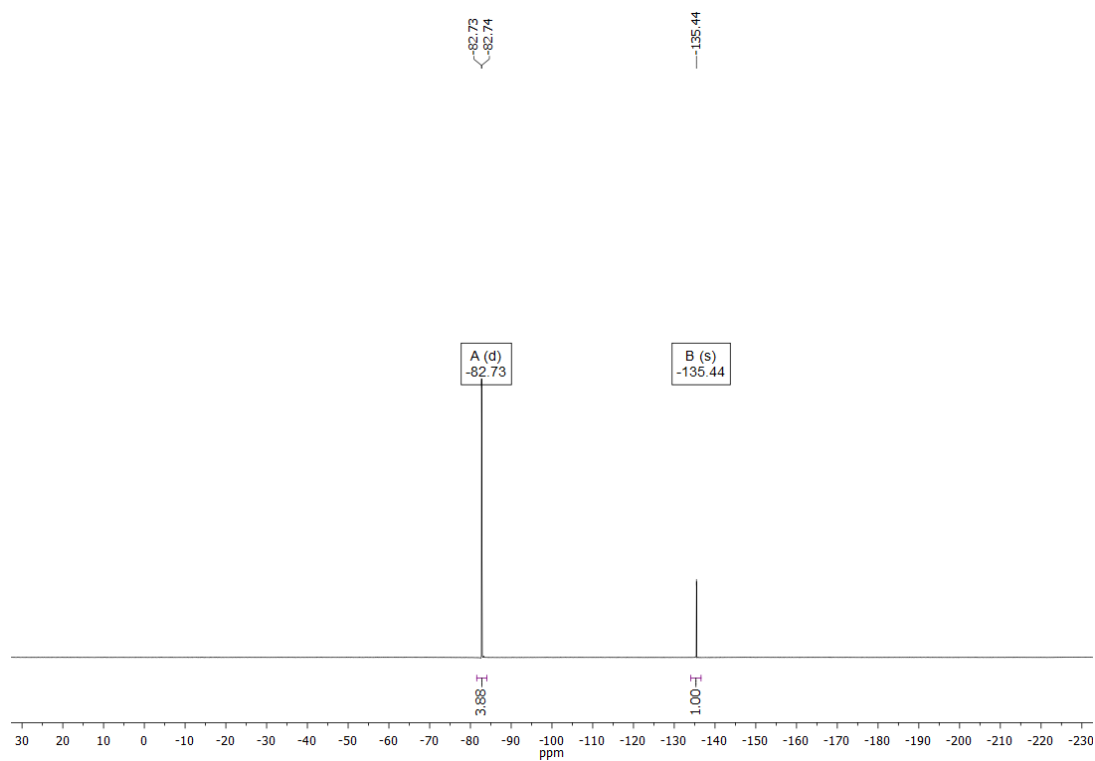
#### 4. $^1\text{H}$ NMR, $^{19}\text{F}$ NMR and $^{13}\text{C}$ NMR spectra

##### 1,3-bis(3-Chlorophenyl)-4-fluoro-5-phenyl-2-(trifluoromethyl)-2,3-dihydro-1H-imidazole 2a

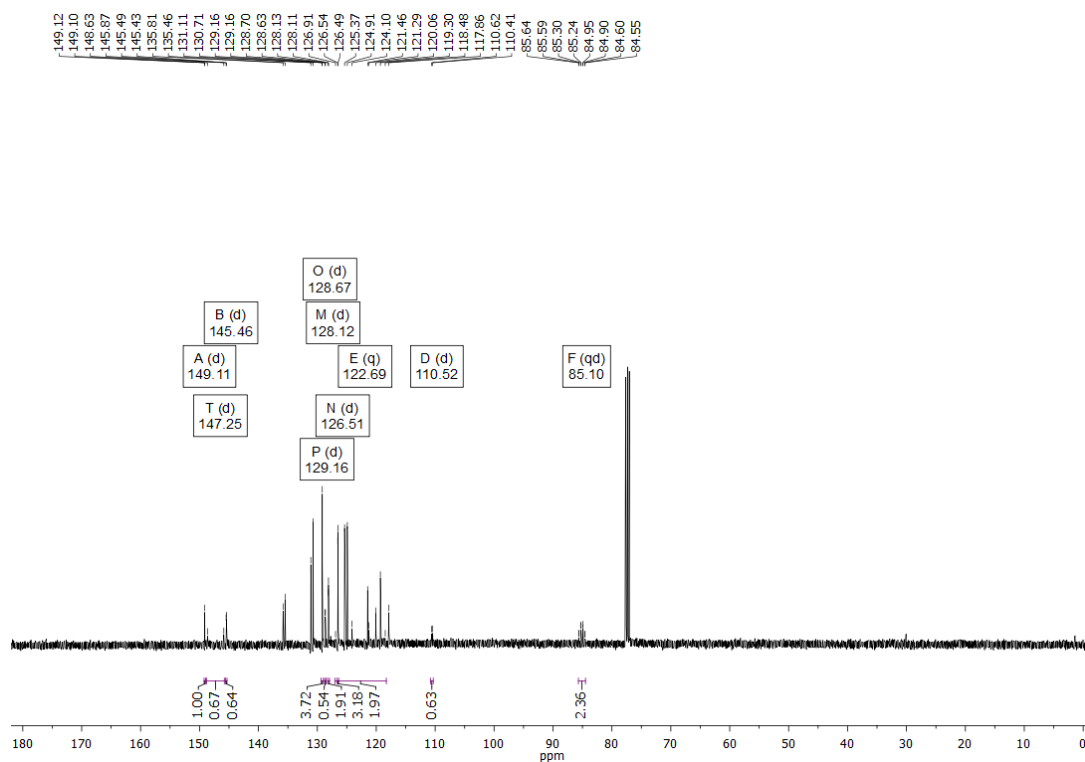
##### $^1\text{H}$ NMR



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

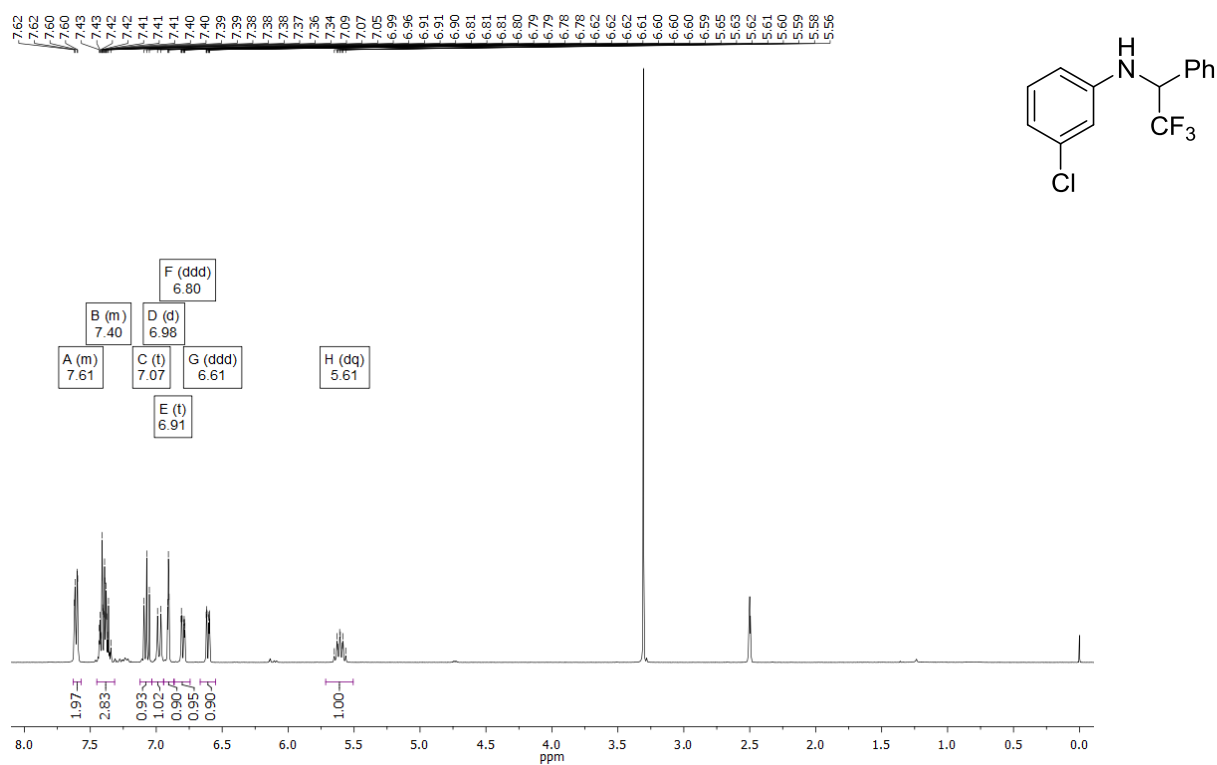


### <sup>13</sup>C NMR

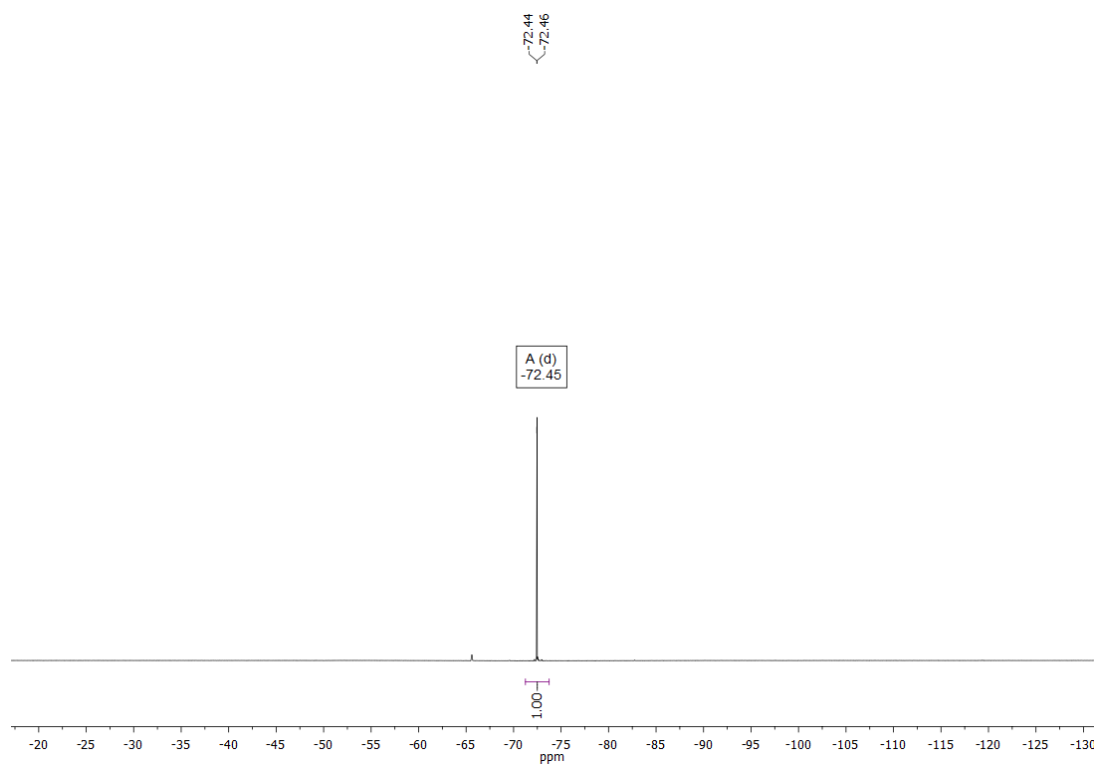


### 3-Chloro-N-(2,2,2-trifluoro-1-phenylethyl)aniline 3a

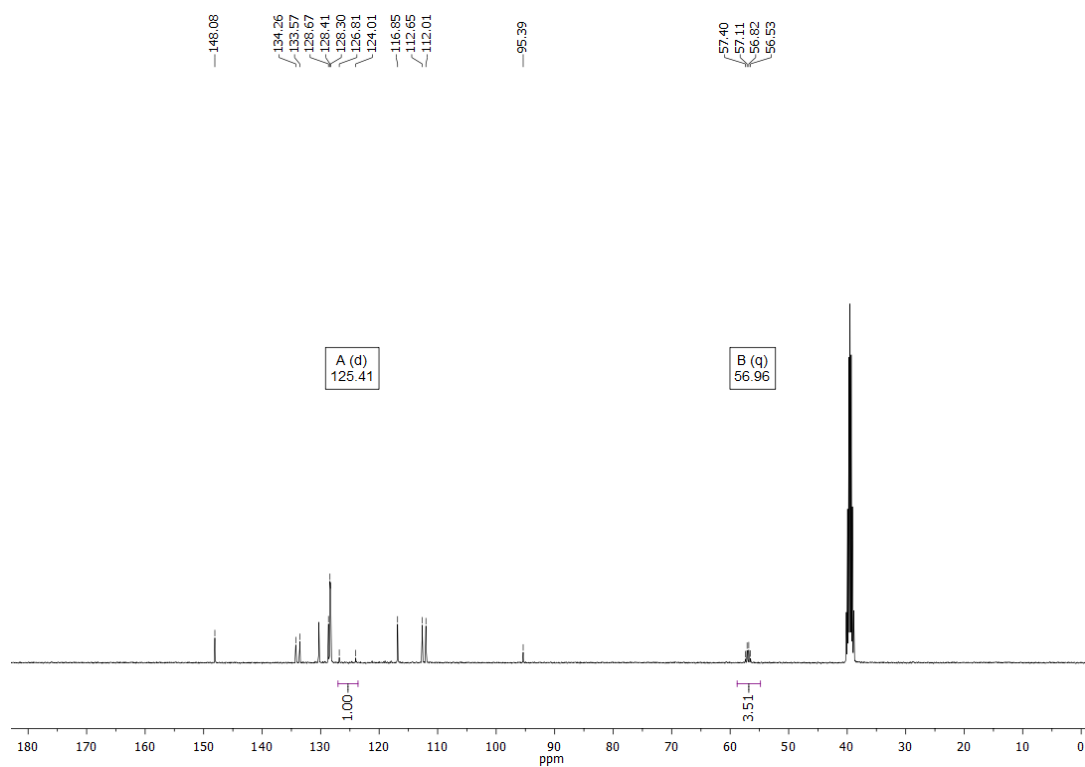
#### <sup>1</sup>H NMR



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

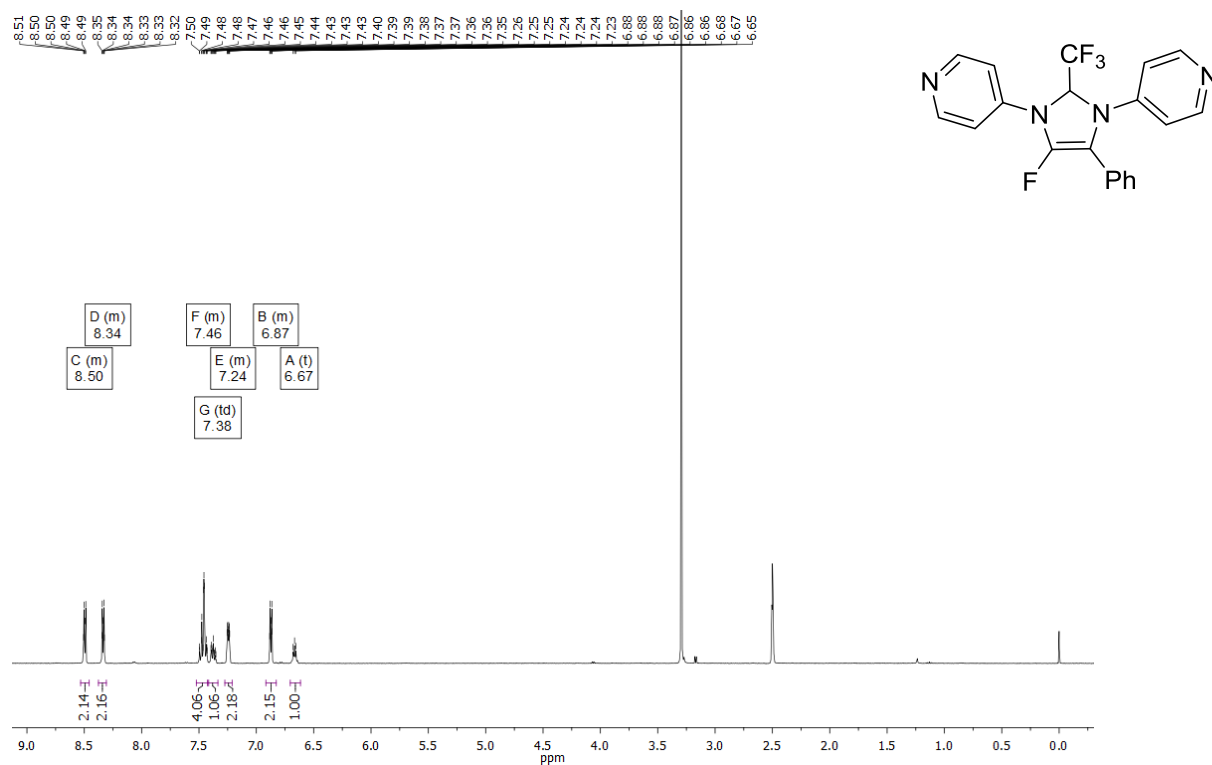


**$^{13}\text{C}$  NMR**

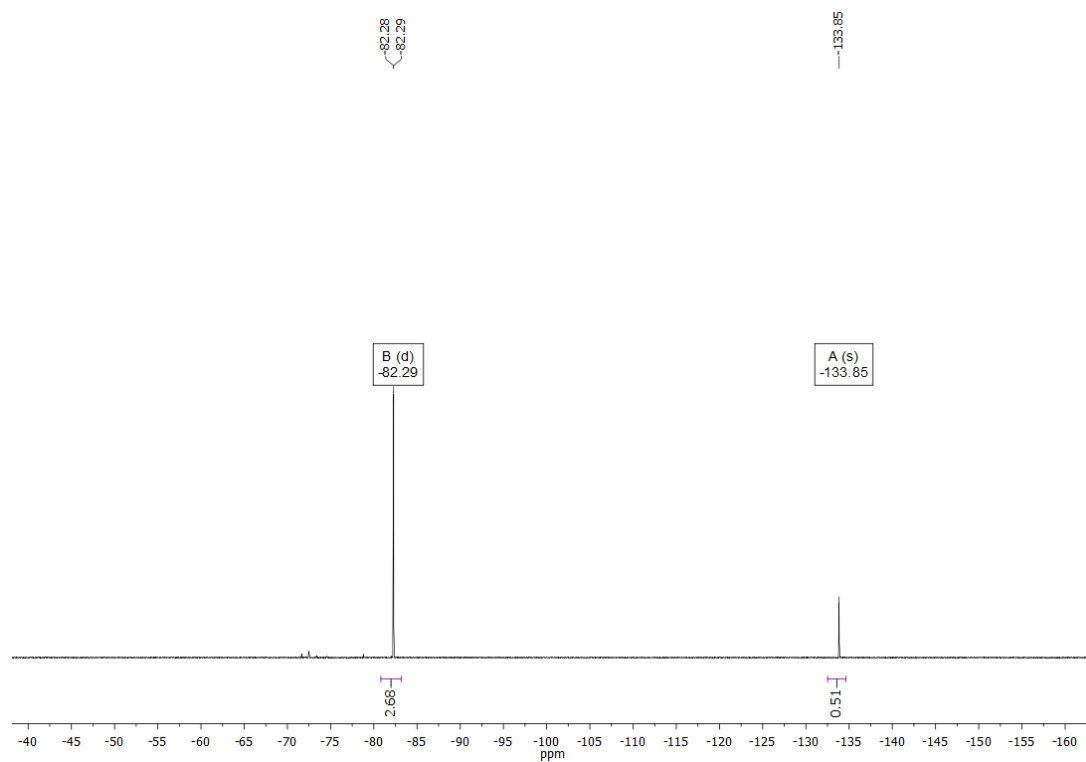


***N,N'*-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-phenyl-2,3-dihydro-1*H*-imidazole 2b**

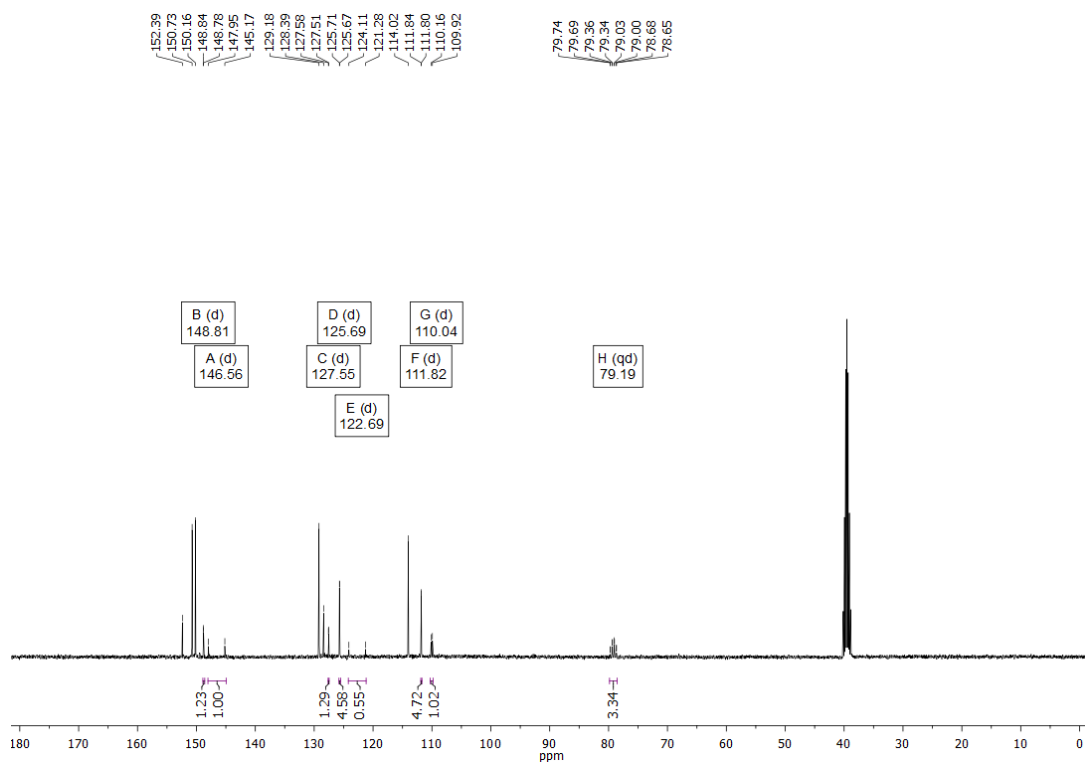
**<sup>1</sup>H NMR**



**<sup>19</sup>F NMR**

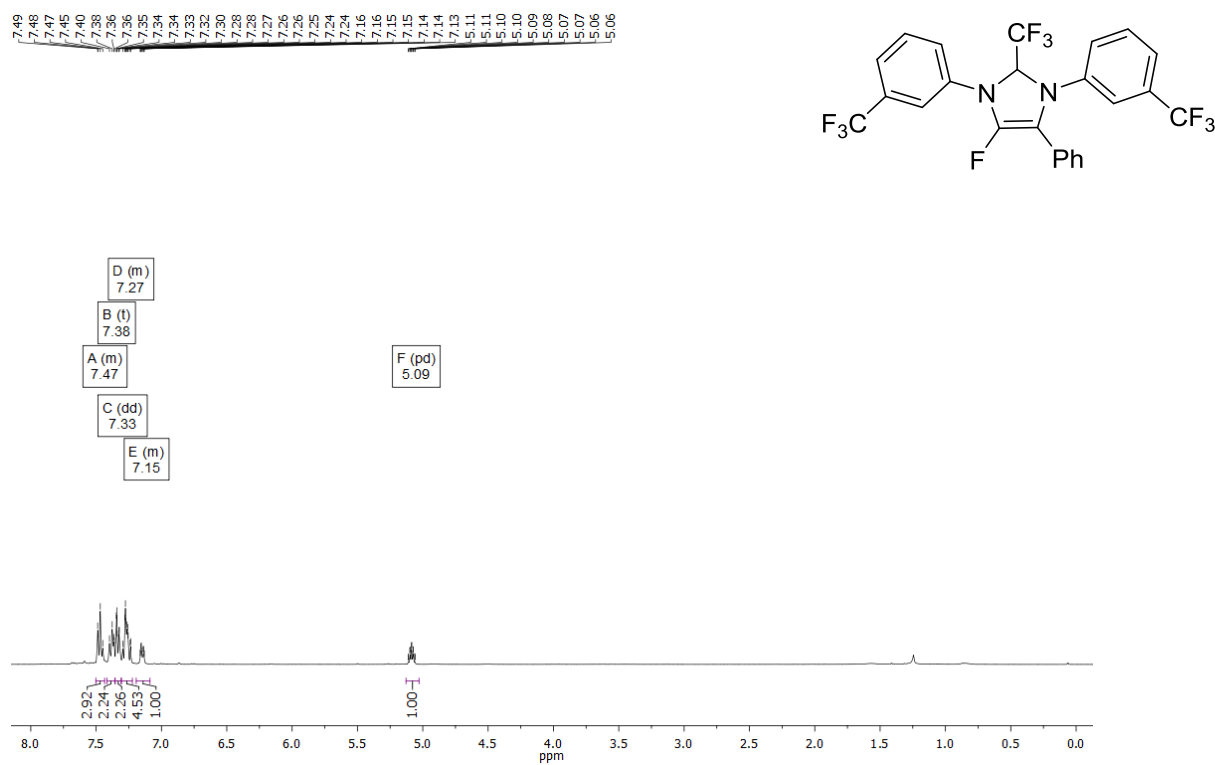


### <sup>13</sup>C NMR



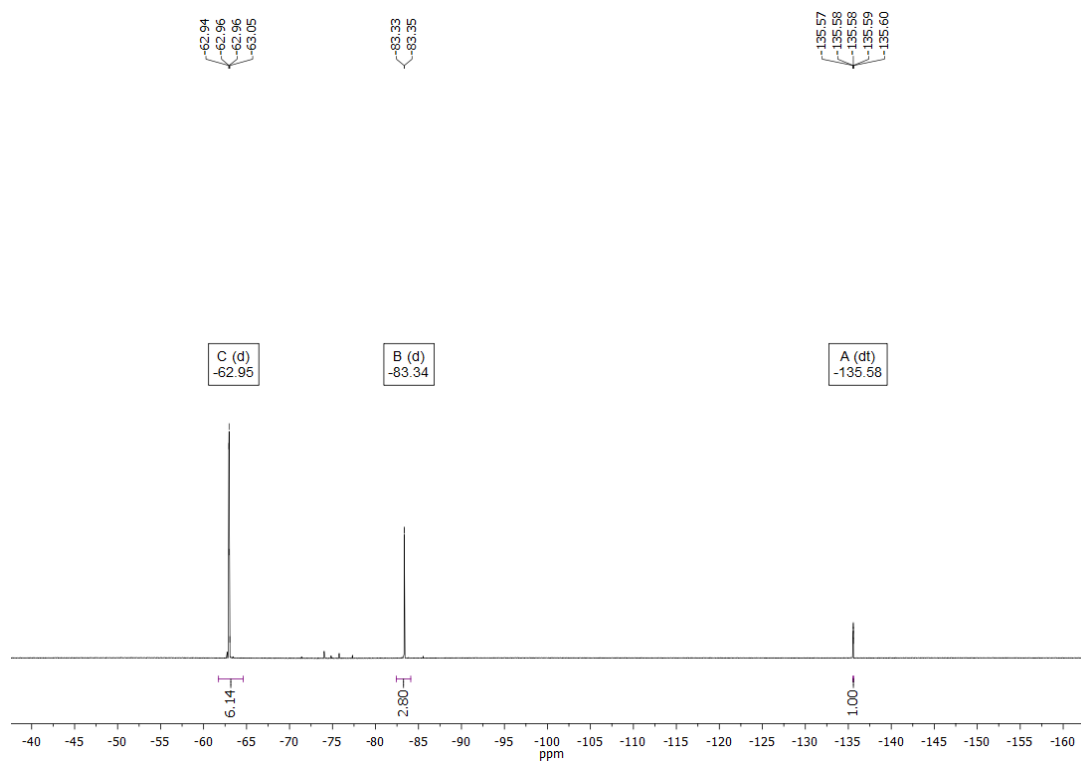
### *N,N'*-1,3-bis(3-(trifluoromethyl)phenyl)-2-(trifluoromethyl)-4-fluoro-5-phenyl-2,3-dihydro-1*H*-imidazole 2c

### <sup>1</sup>H NMR

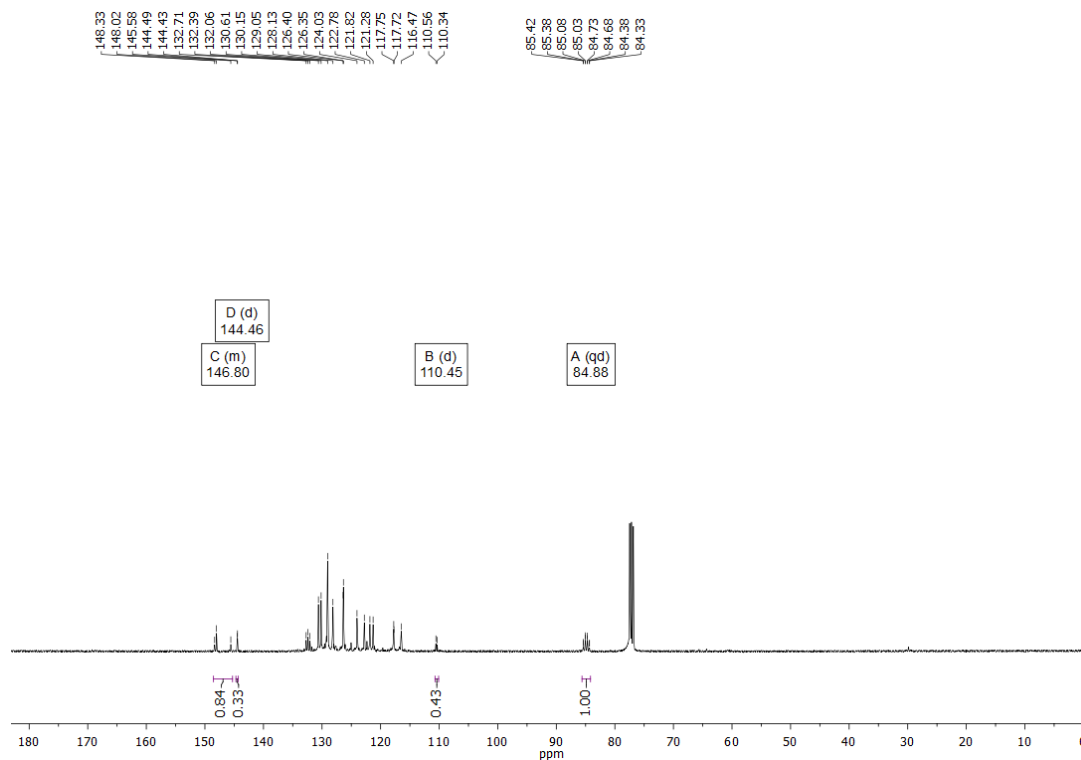




# <sup>19</sup>F NMR

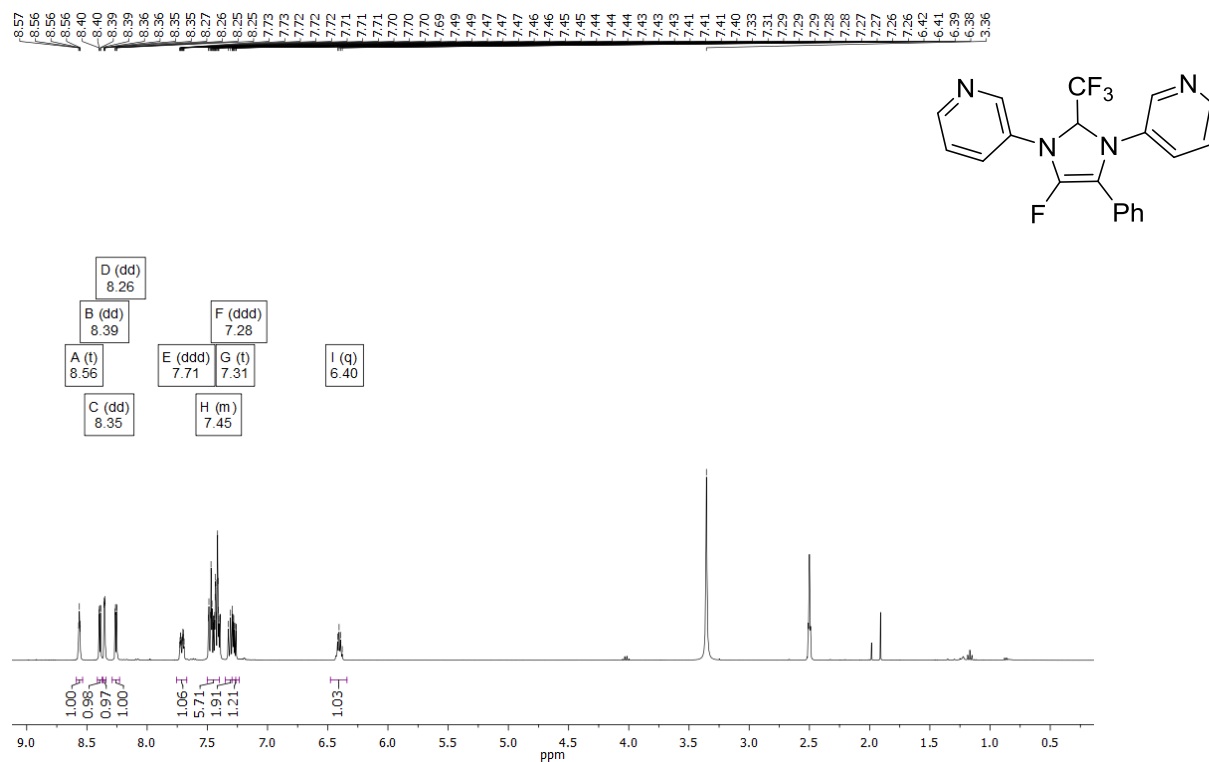


# <sup>13</sup>C NMR

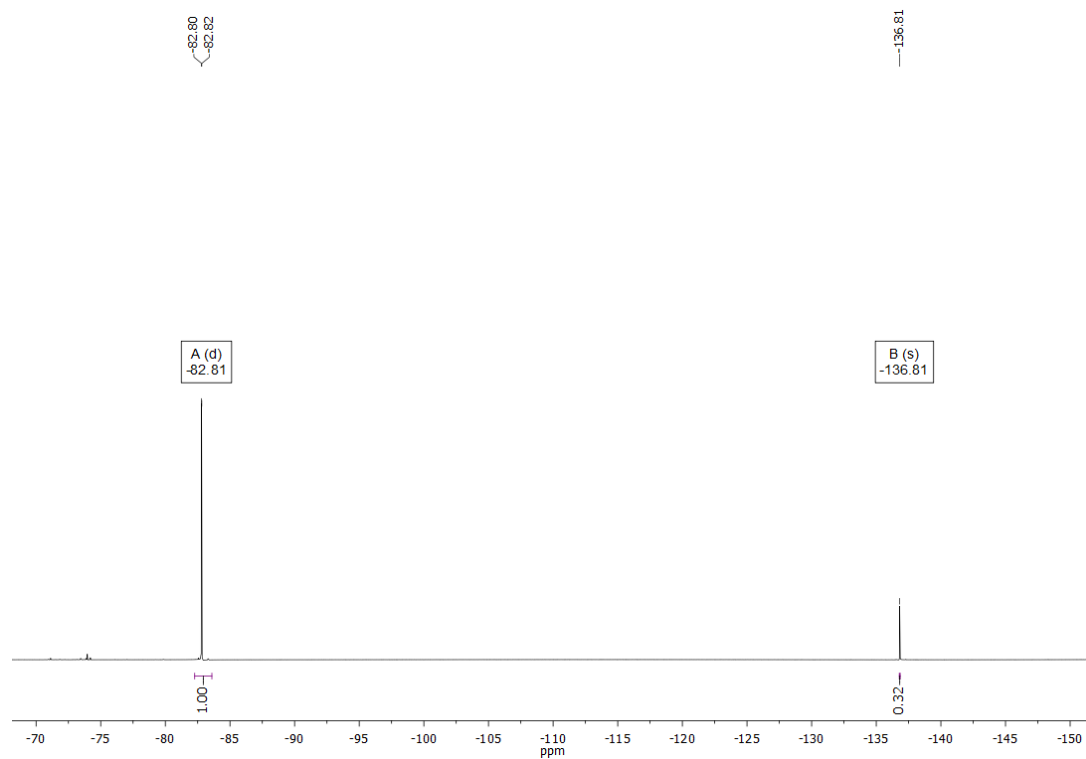


***N,N'*-1,3-(Pyridin-3-yl)-2-(trifluoromethyl)-4-fluoro-5-phenyl-2,3-dihydro-1*H*-imidazole 2d**

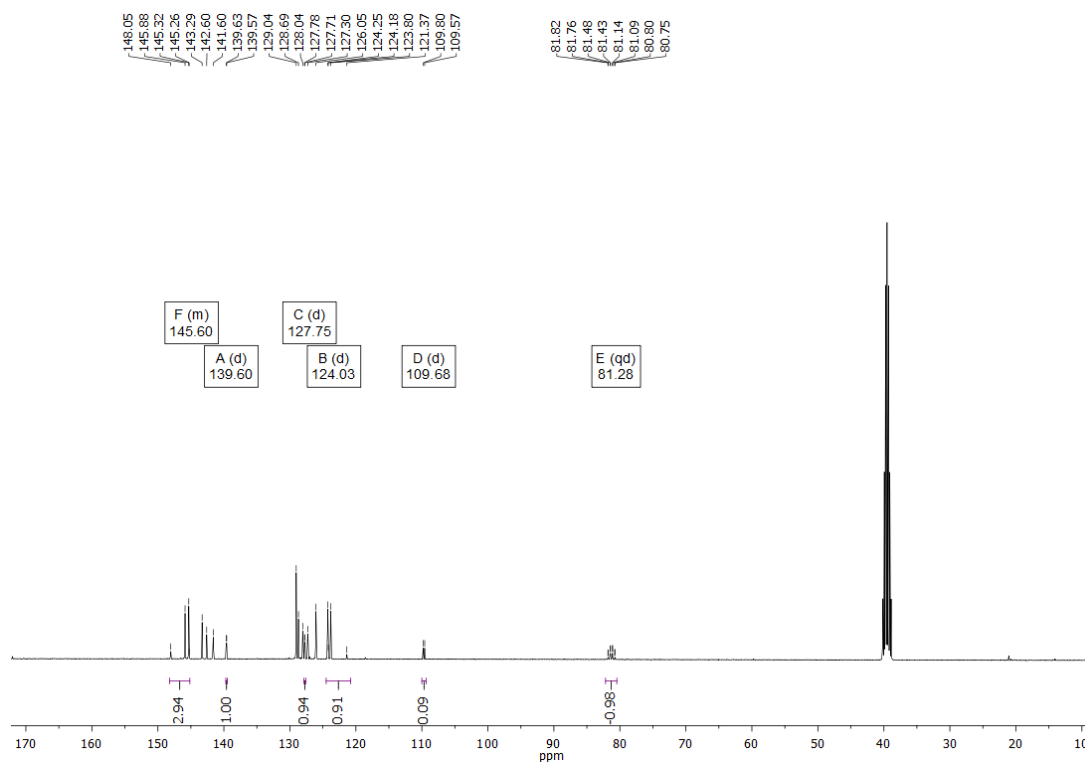
**<sup>1</sup>H NMR**



**<sup>19</sup>F NMR**

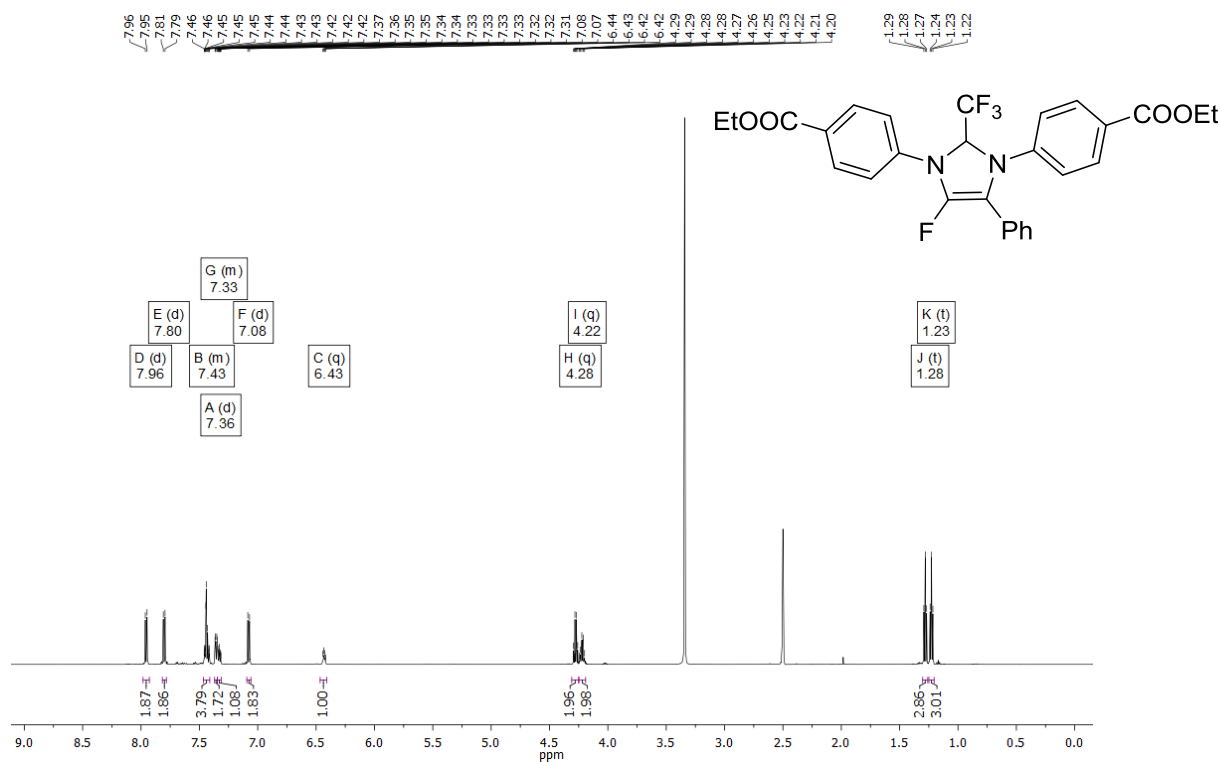


### <sup>13</sup>C NMR

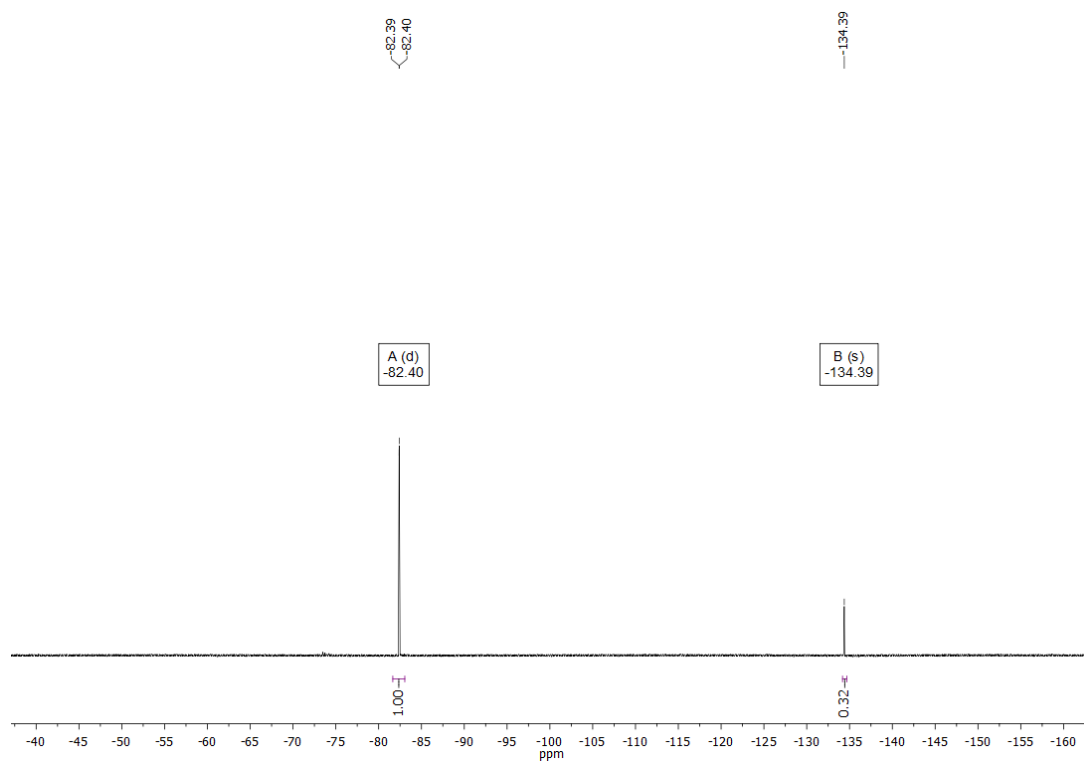


### *N,N'*-1,3-(4-(Ethoxycarbonyl)phenyl)-2-(trifluoromethyl)-4-fluoro-5-phenyl-2,3-dihydro-1*H*-imidazole 2e

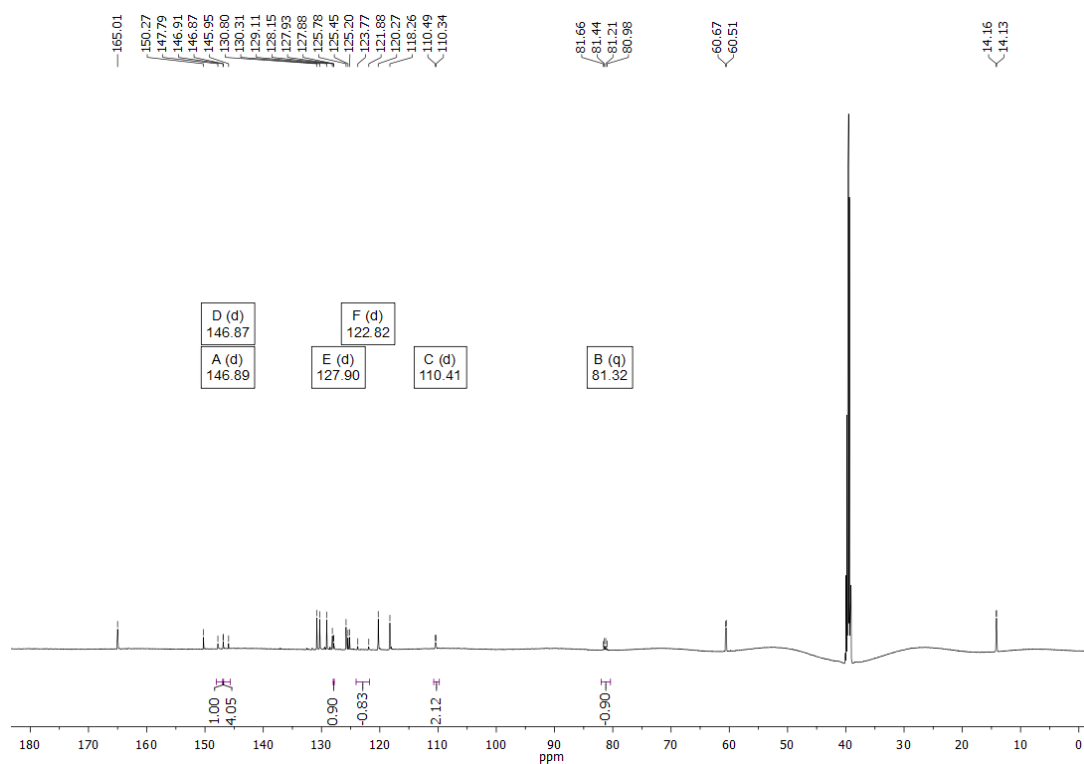
### <sup>1</sup>H NMR



# <sup>19</sup>F NMR

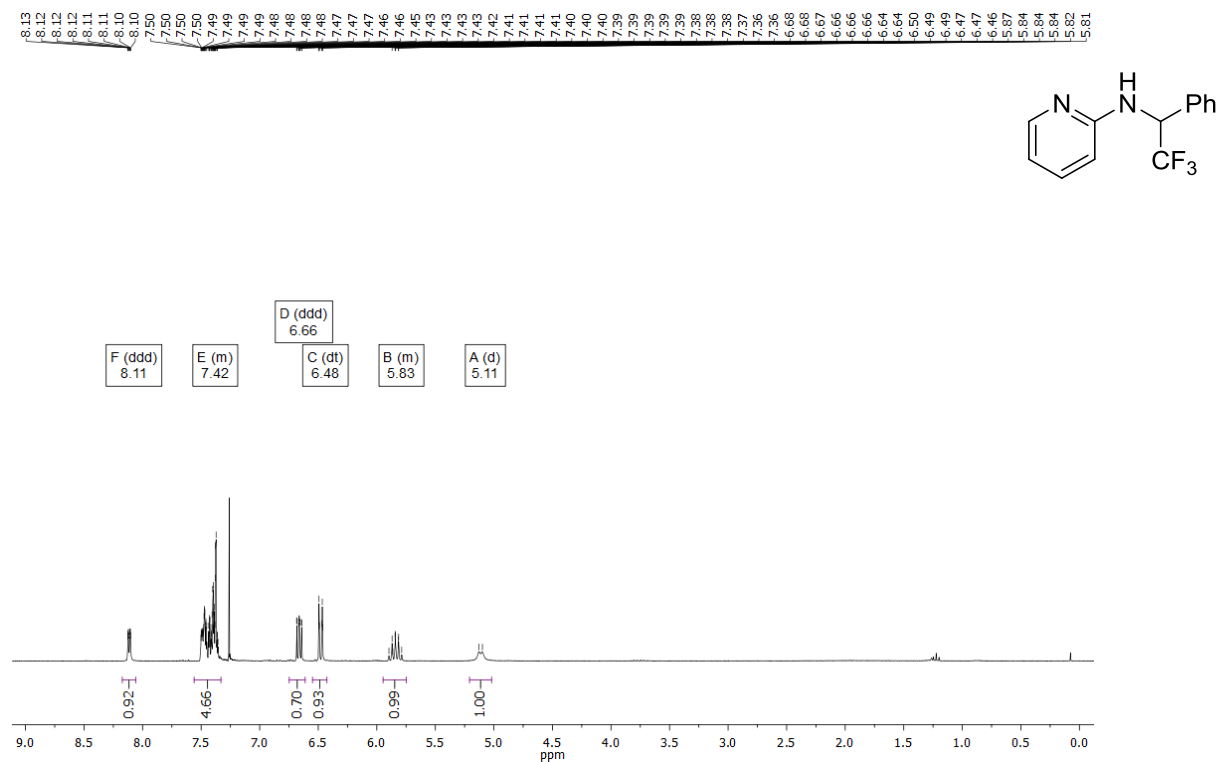


# <sup>13</sup>C NMR

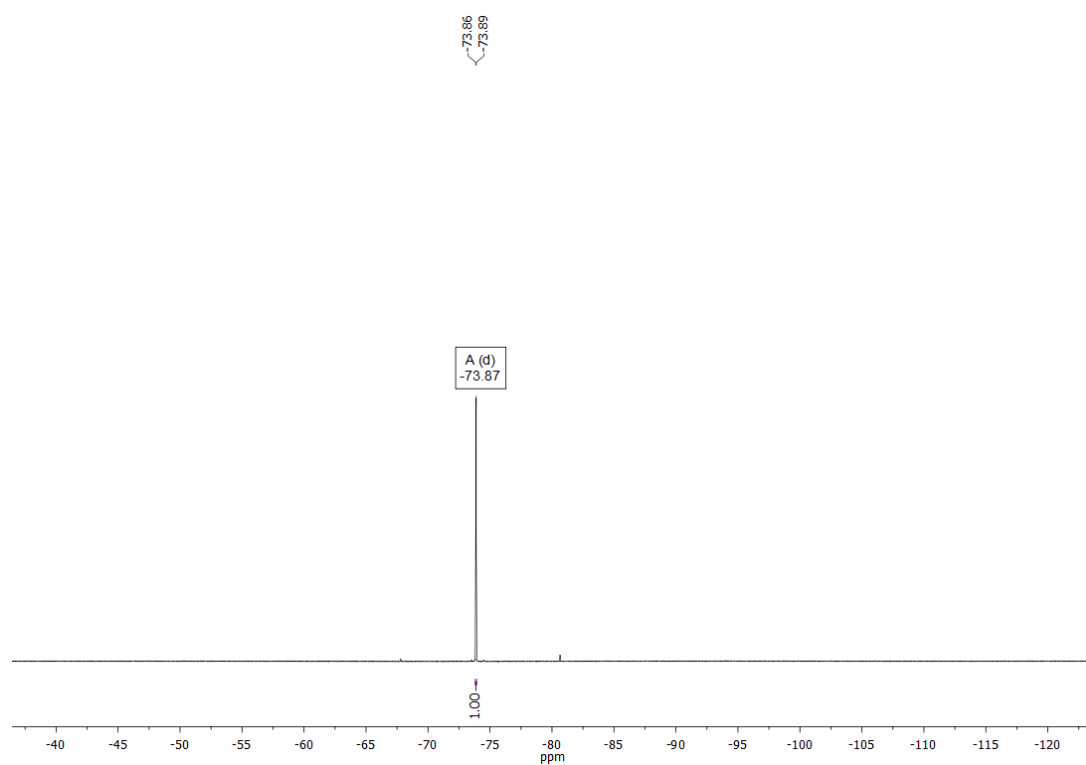


***N*-(2,2,2-Trifluoro-1-phenylethyl)pyridin-2-amine 3f**

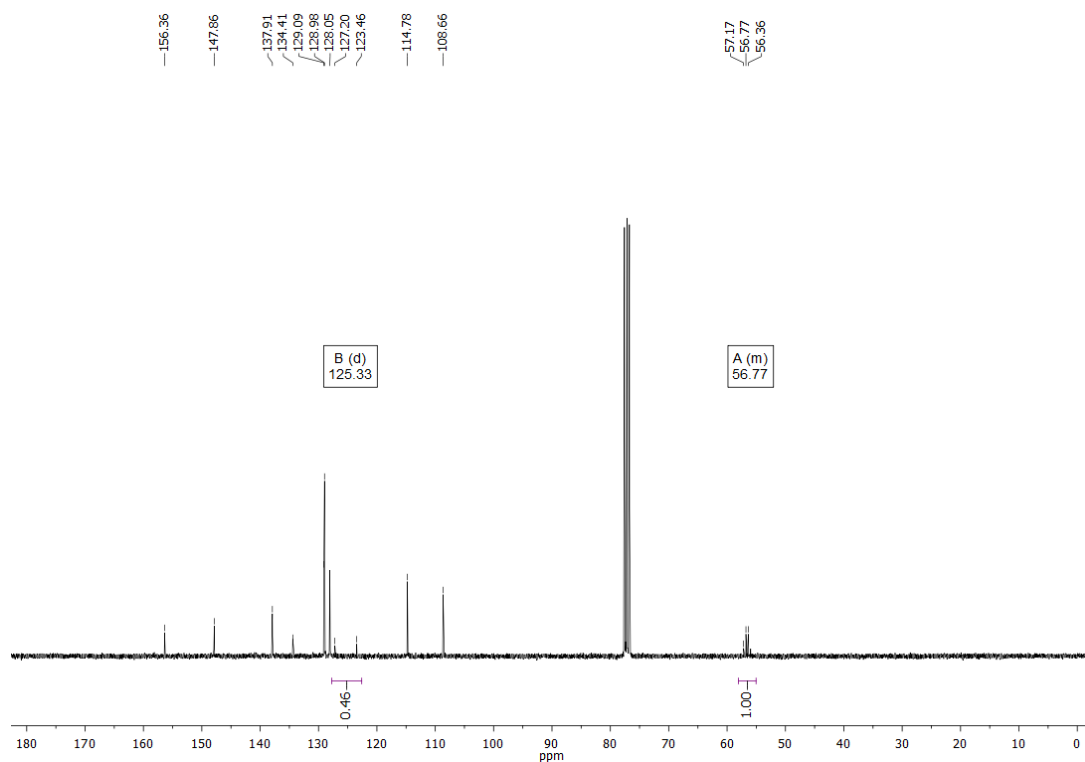
**<sup>1</sup>H NMR**



**<sup>19</sup>F NMR**

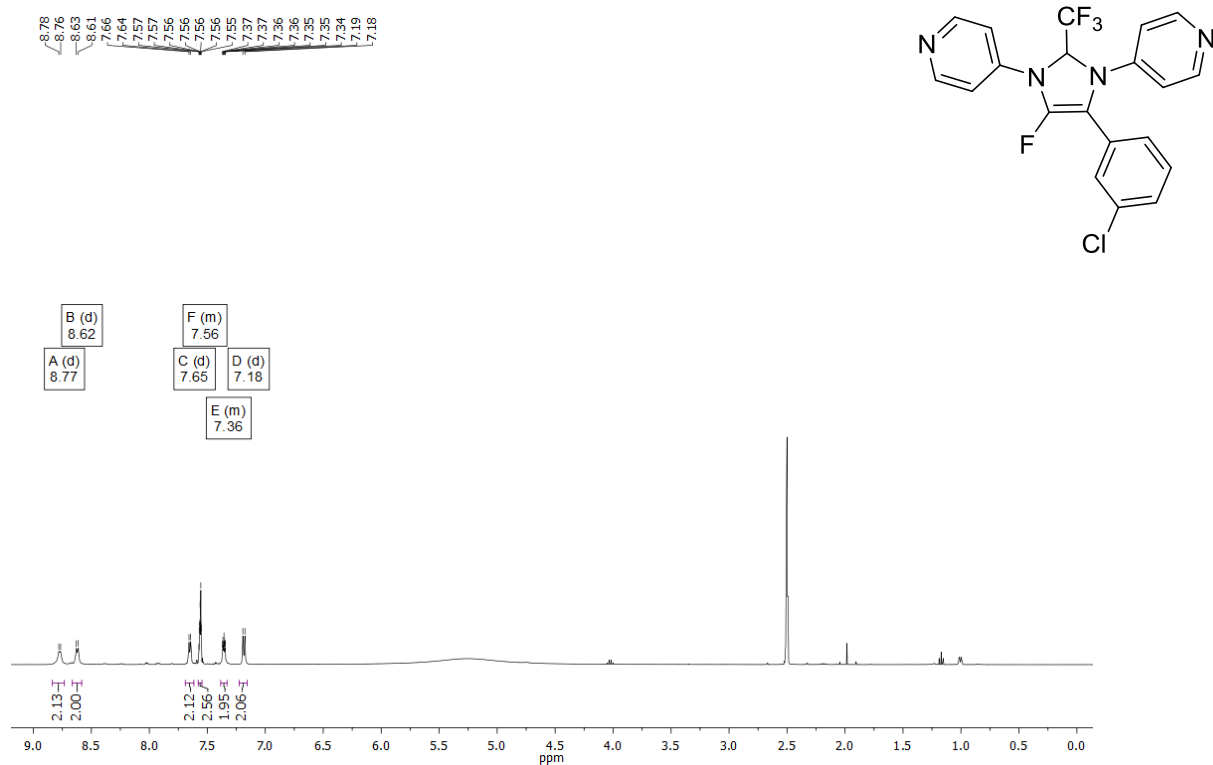


### <sup>13</sup>C NMR

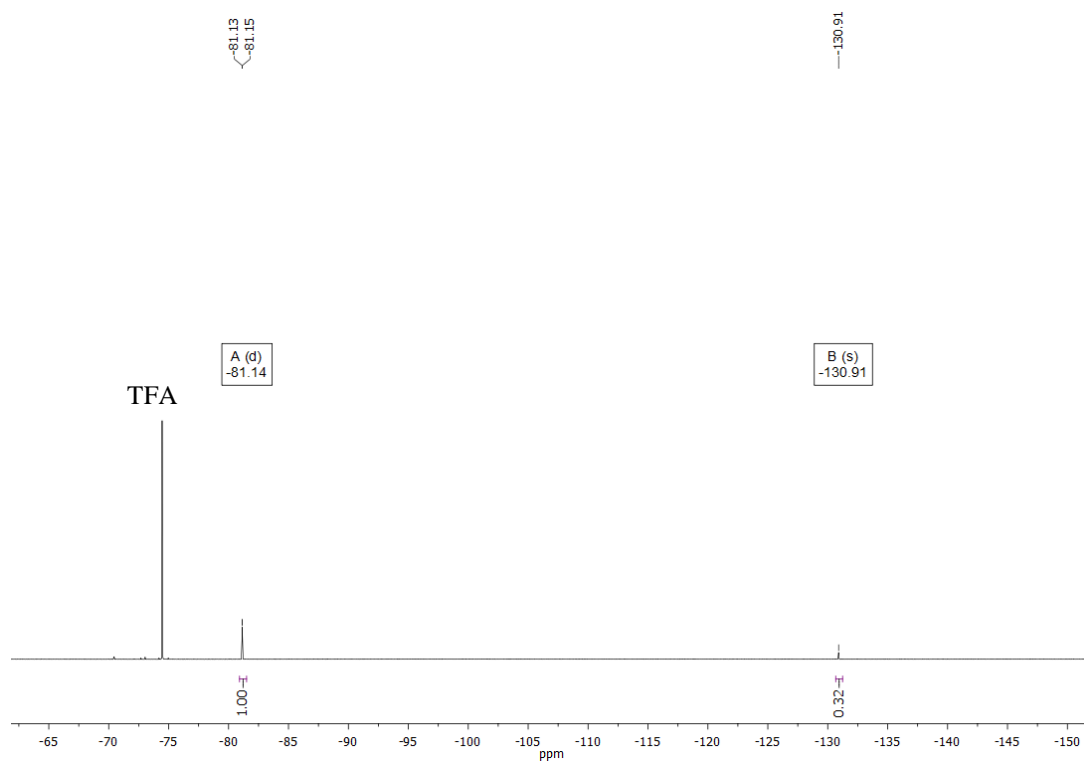


### *N,N'*-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(3-chlorophenyl)-2,3-dihydro-1*H*-imidazole 2g

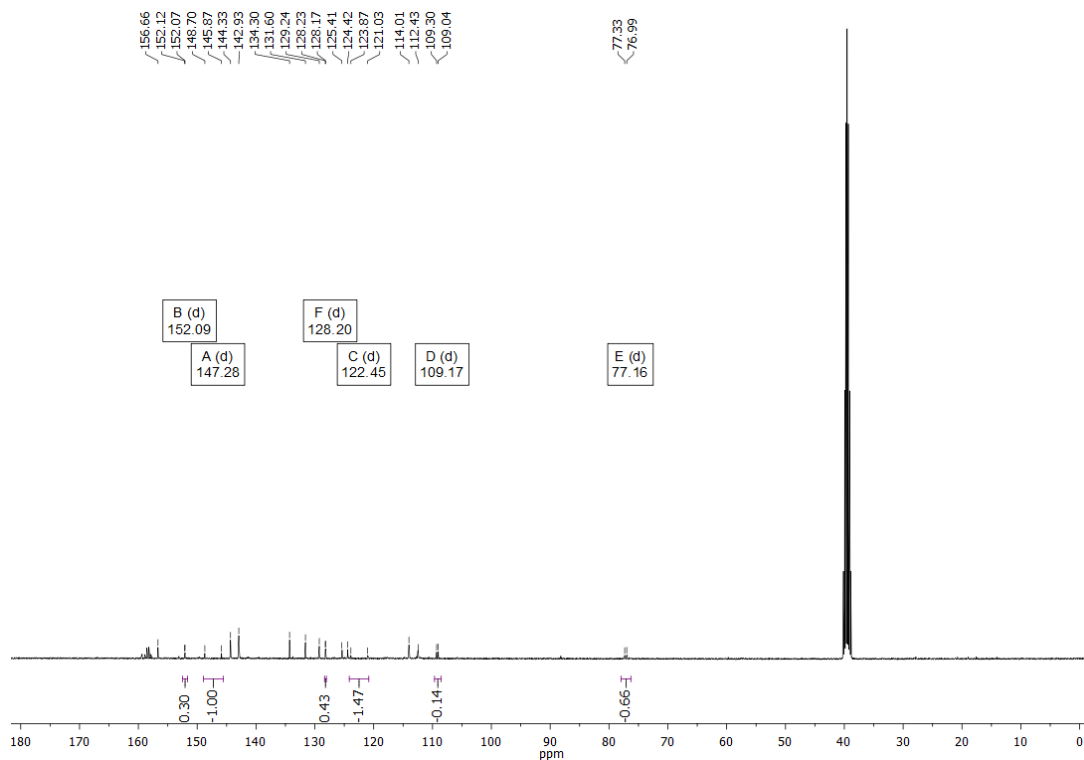
### <sup>1</sup>H NMR



# <sup>19</sup>F NMR

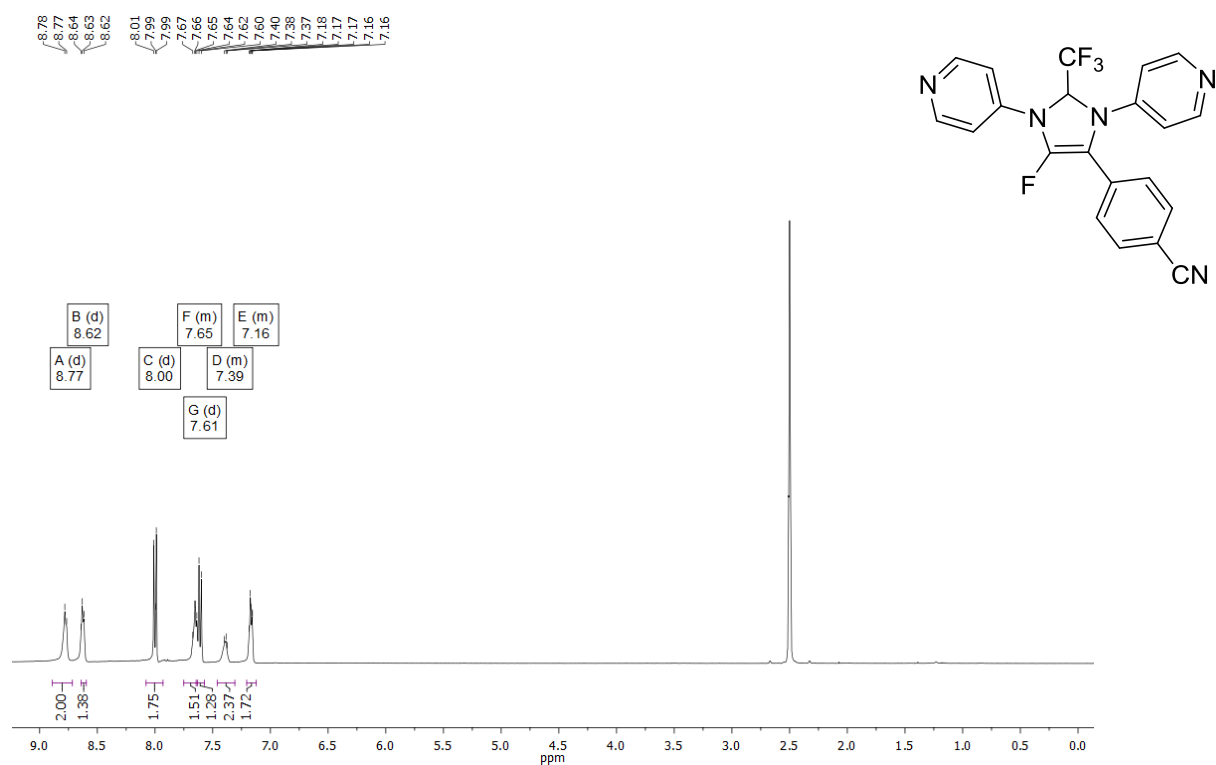


# <sup>13</sup>C NMR

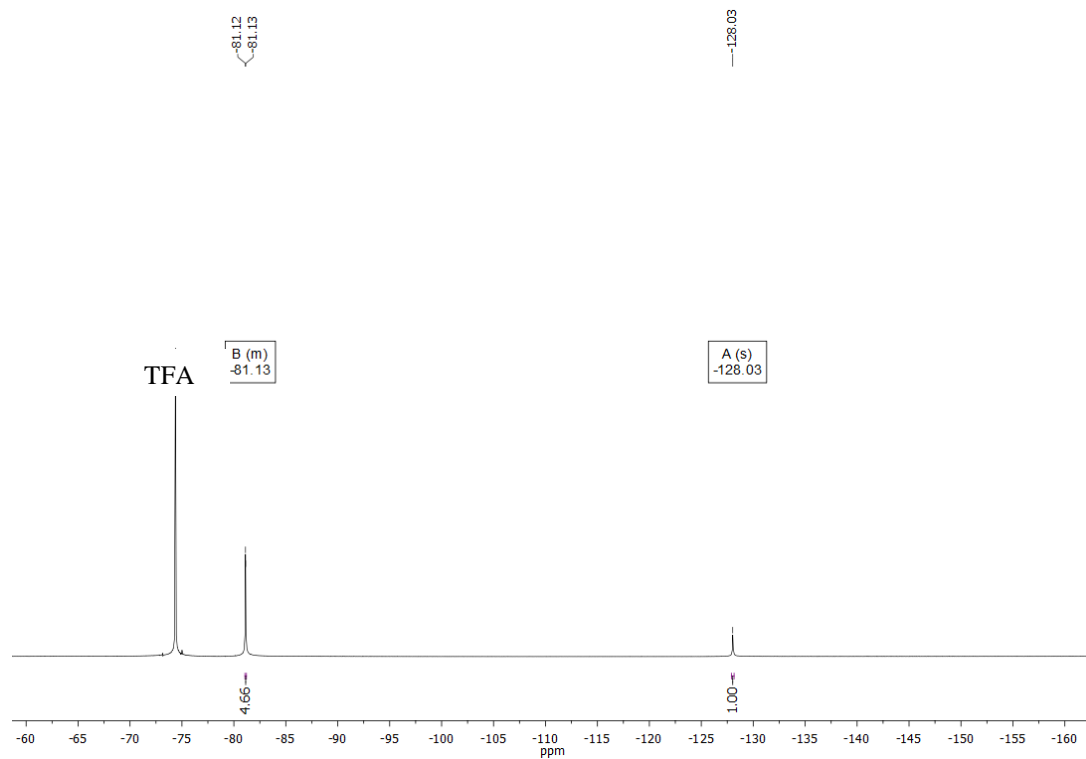


***N,N'*-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(4-cyanophenyl)-2,3-dihydro-1*H*-imidazole 2h**

**<sup>1</sup>H NMR**

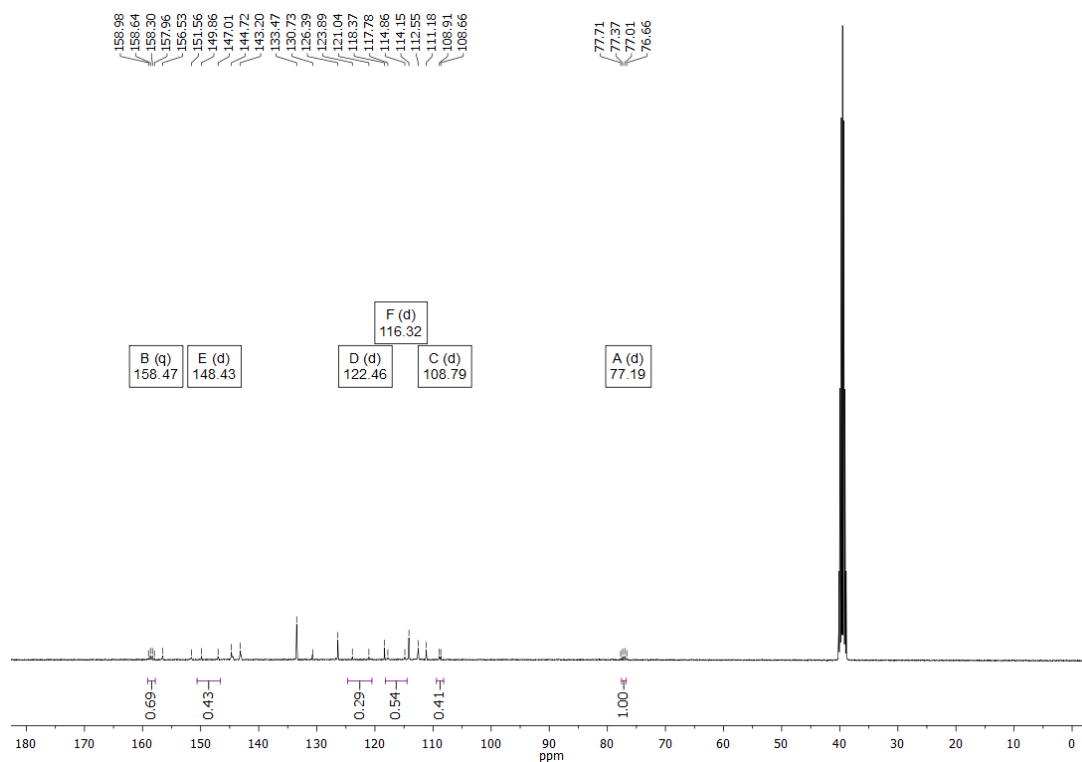


**<sup>19</sup>F NMR**



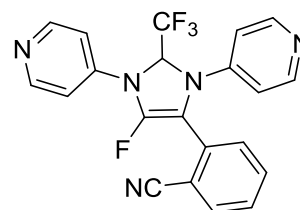
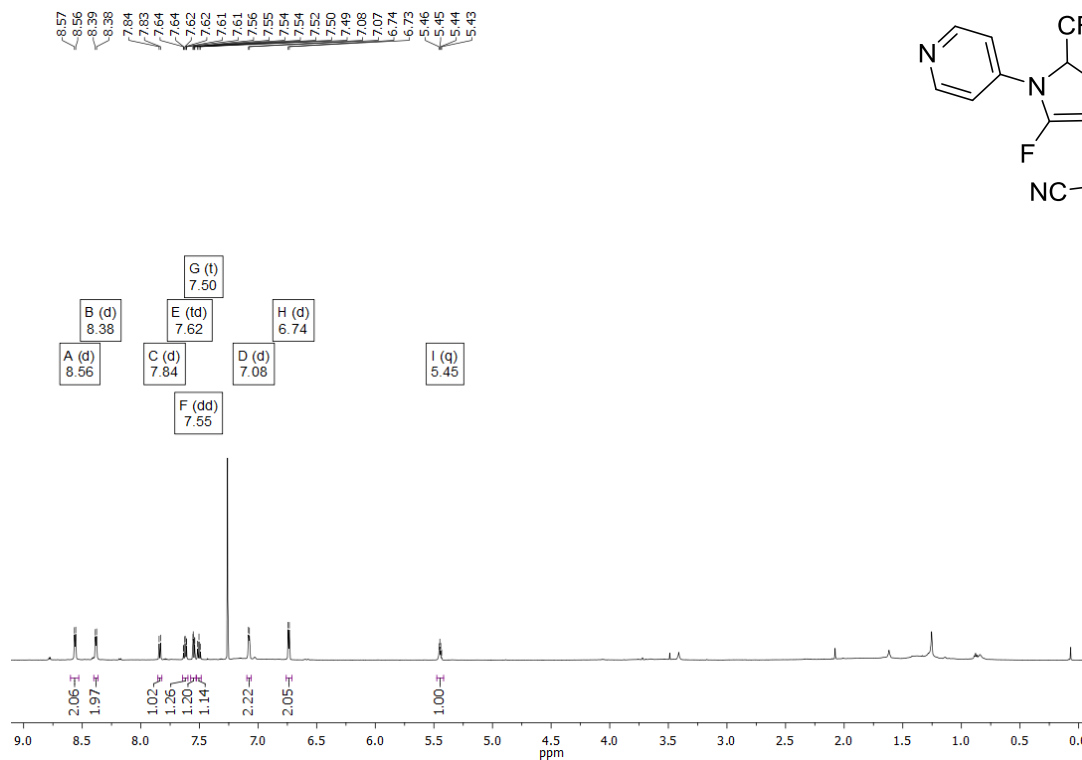


### <sup>13</sup>C NMR

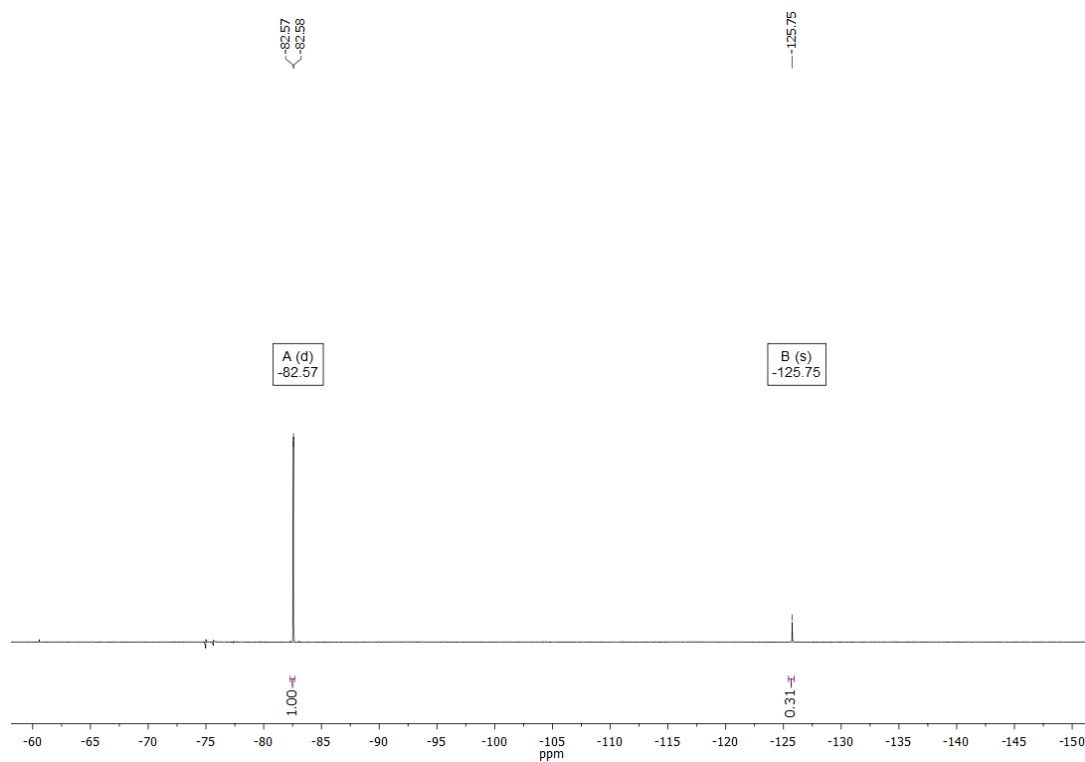


### *N,N'*-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(2-cyanophenyl)-2,3-dihydro-1*H*-imidazole **2i**

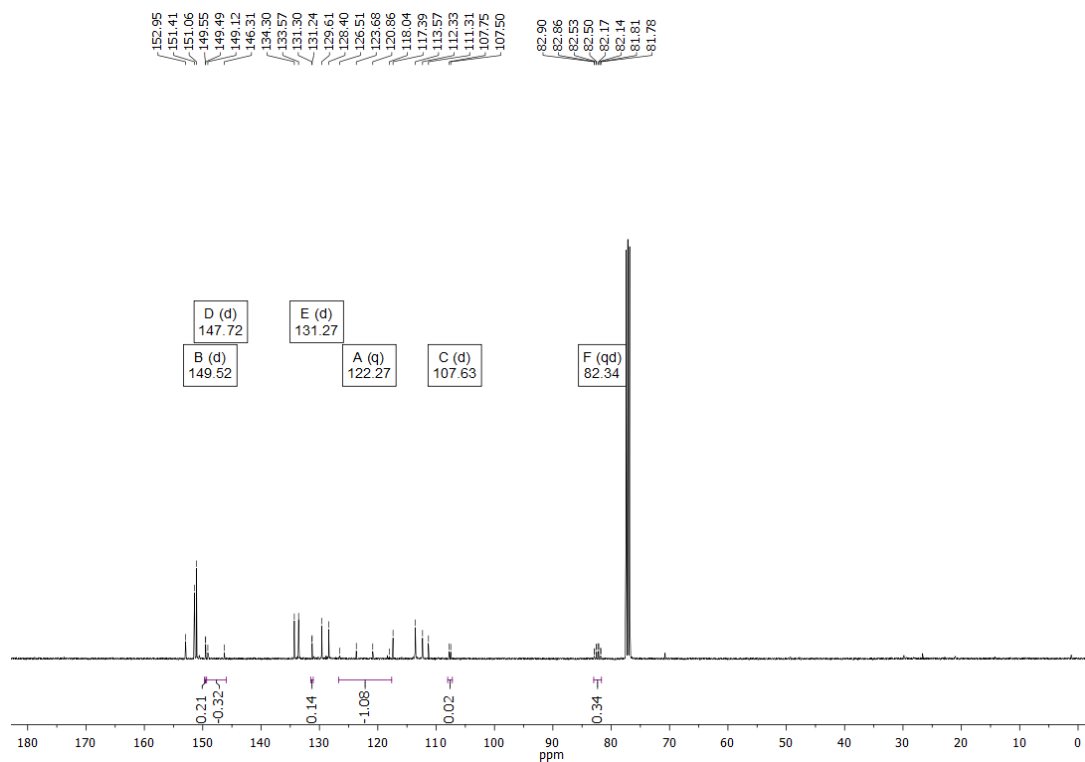
### <sup>1</sup>H NMR



# <sup>19</sup>F NMR

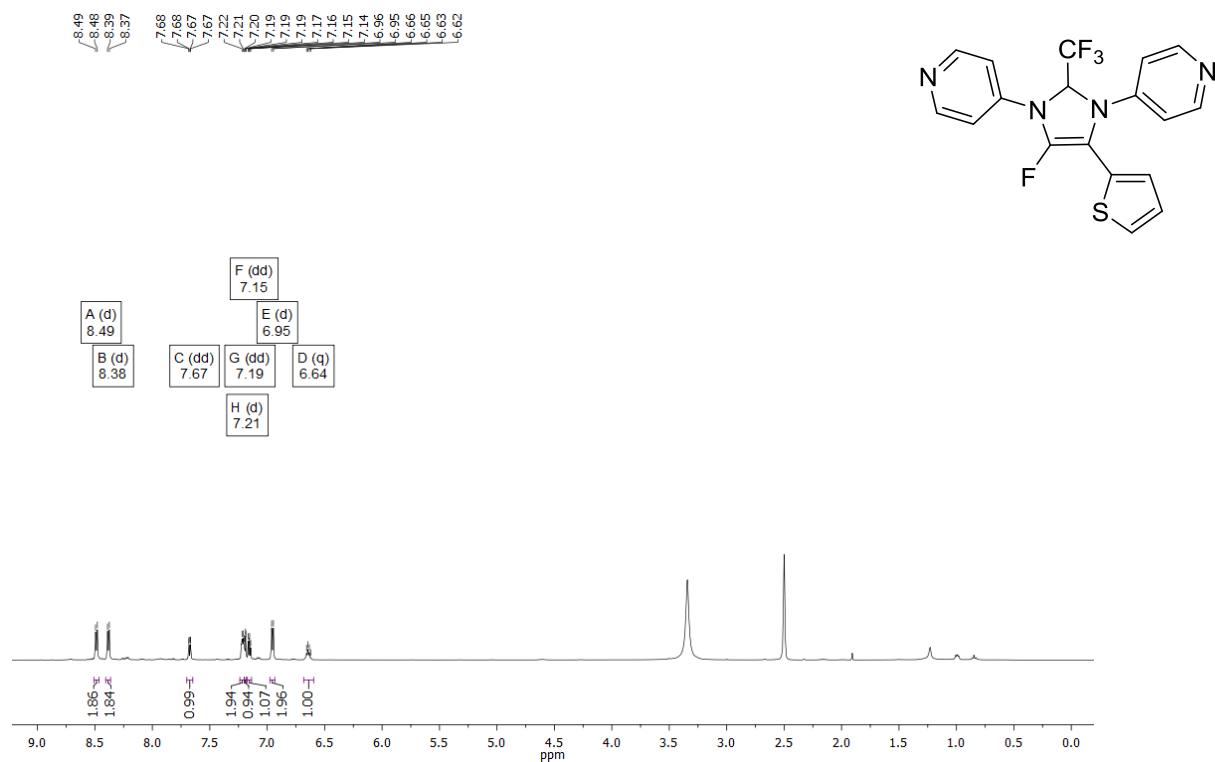


# <sup>13</sup>C NMR

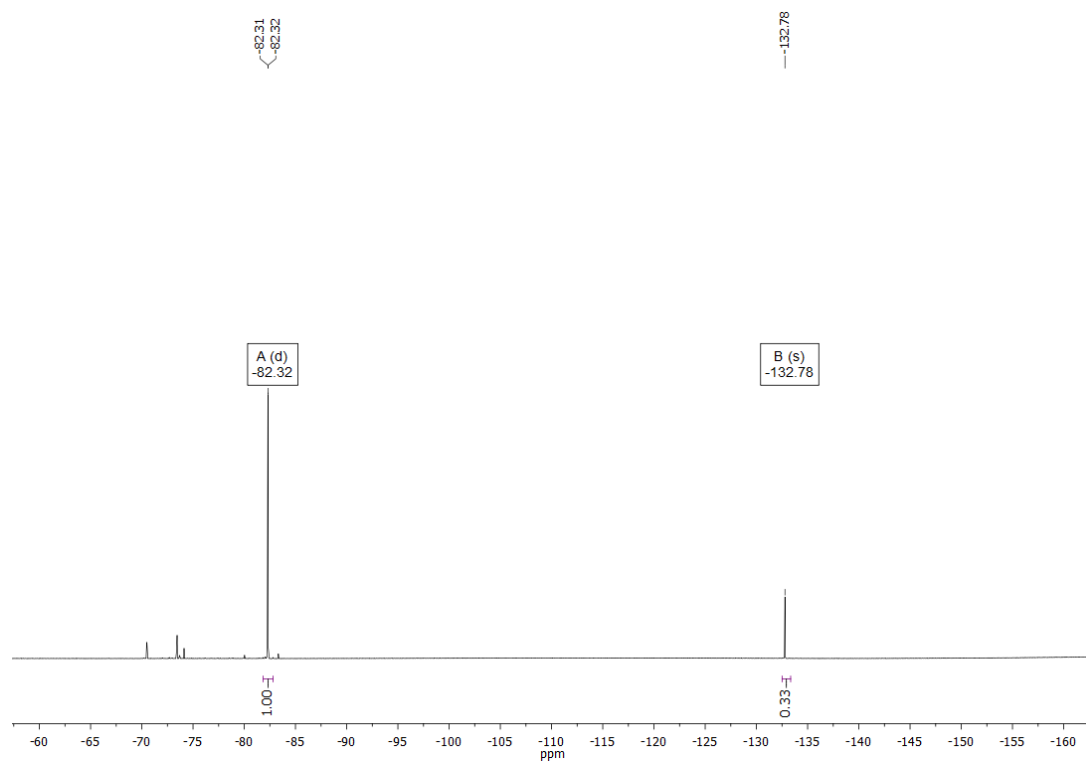


***N,N'*-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(thiophen-2-yl)-2,3-dihydro-1*H*-imidazole 2j**

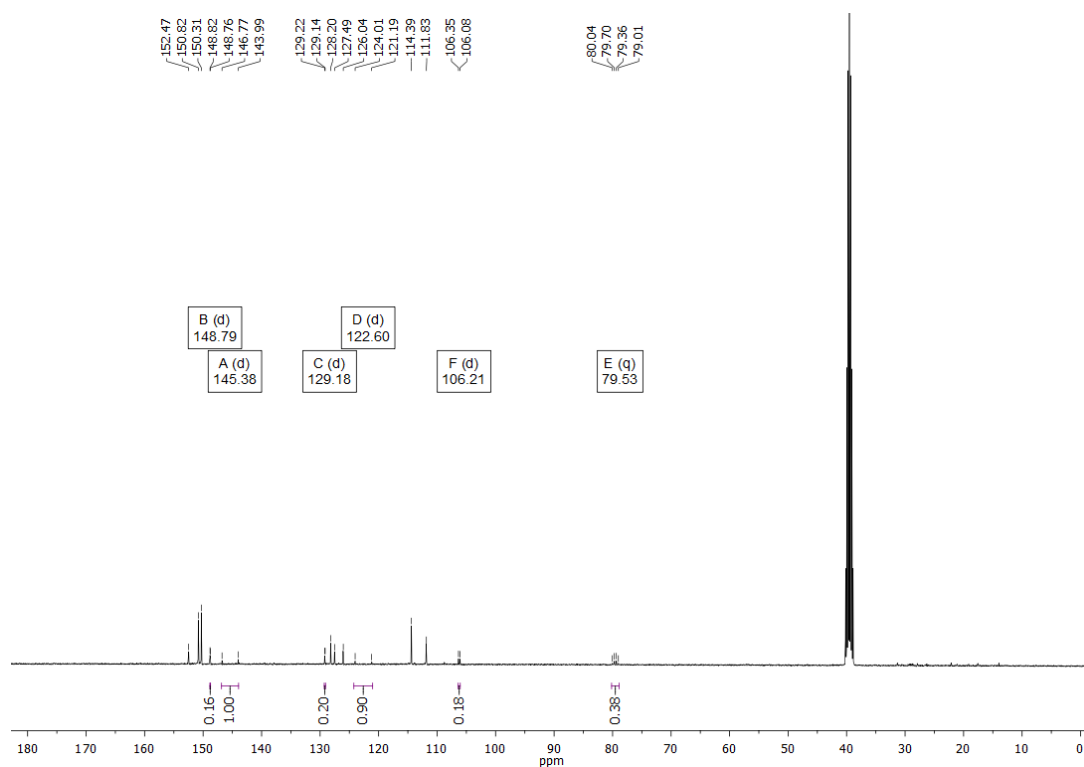
**<sup>1</sup>H NMR**



**<sup>19</sup>F NMR**

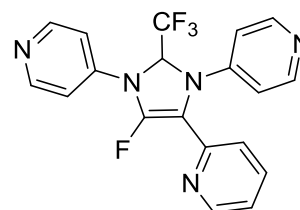


### <sup>13</sup>C NMR

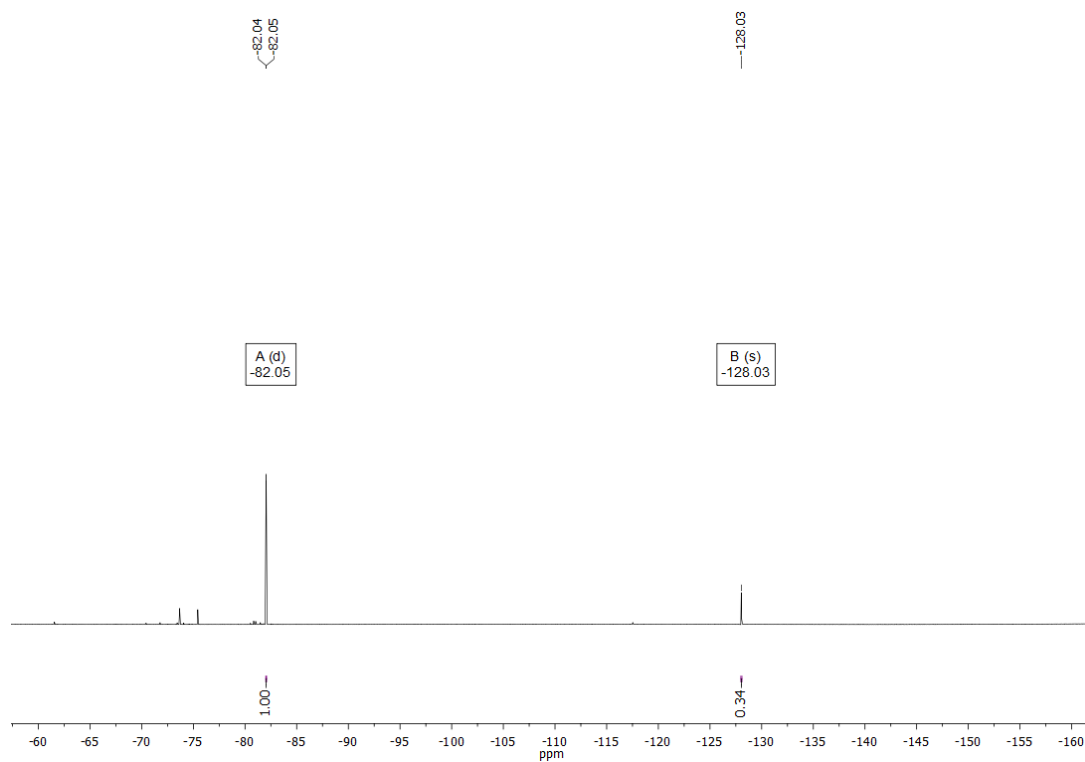


### *N,N'*-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(pyridin-2-yl)-2,3-dihydro-1*H*-imidazole 2k

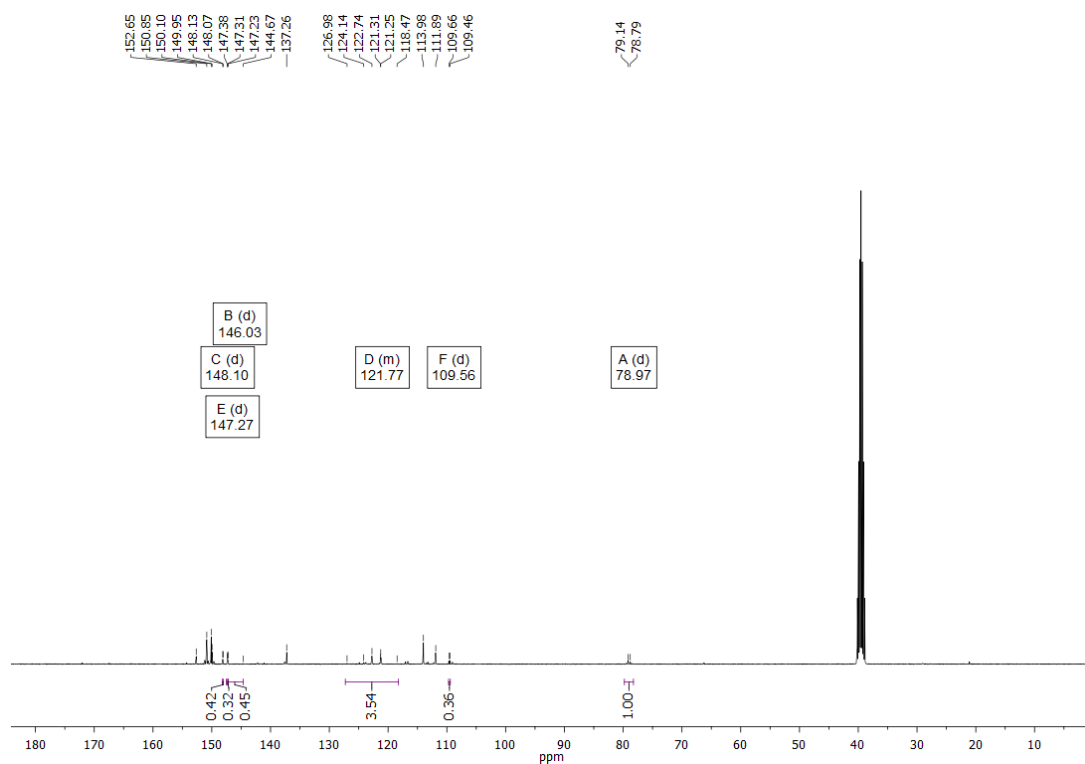
### <sup>1</sup>H NMR



# <sup>19</sup>F NMR



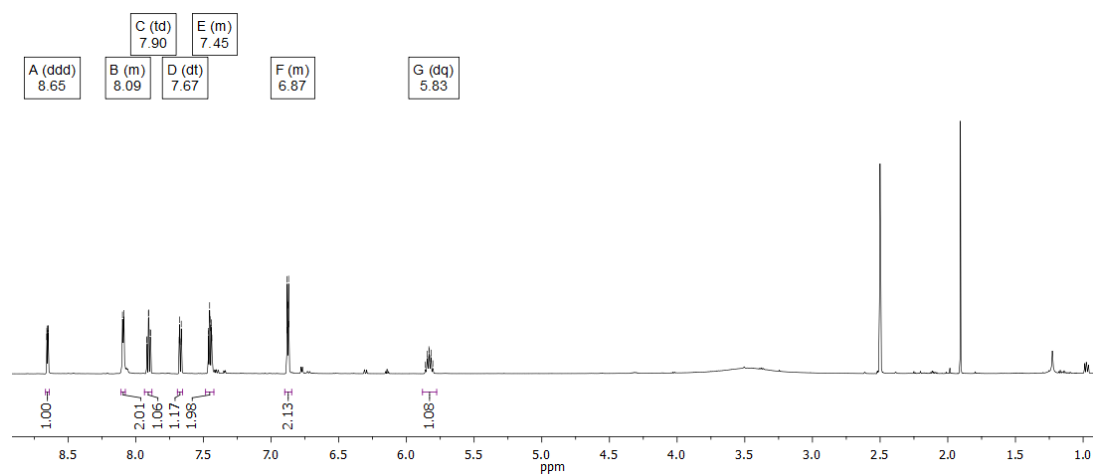
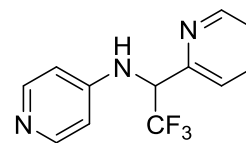
# <sup>13</sup>C NMR



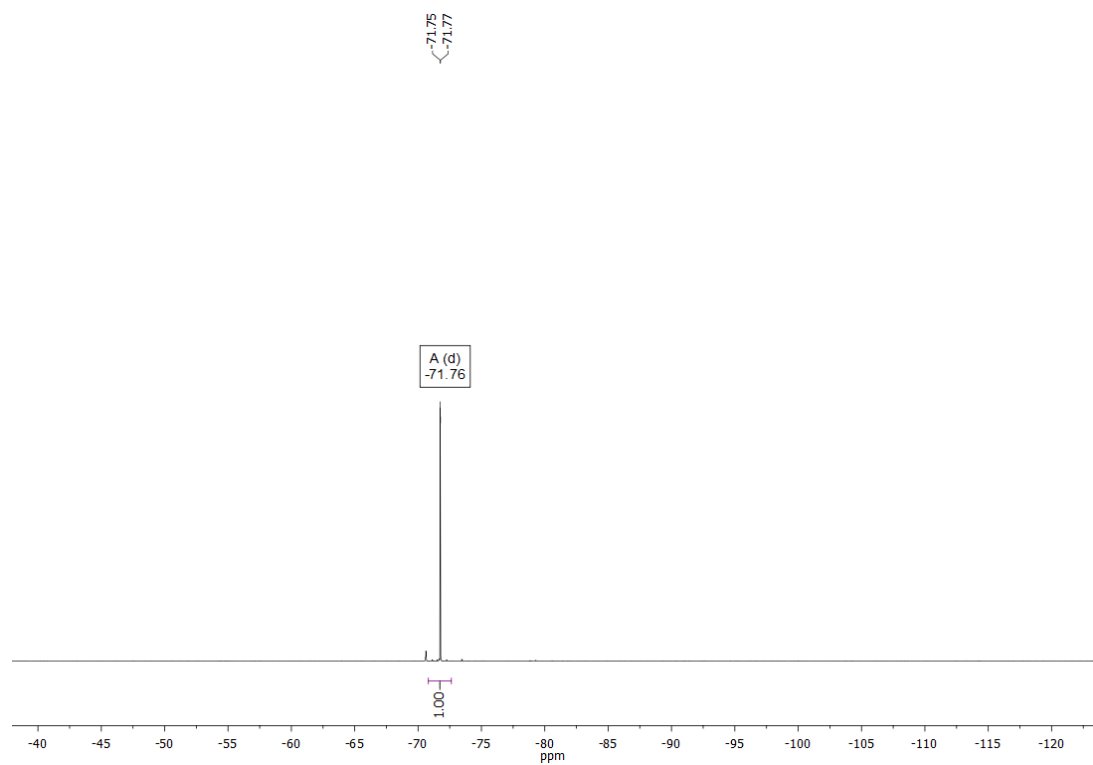
***N*-(2,2,2-Trifluor-1-(pyridin-2-yl)ethyl)pyridin-4-amine 3k**

**<sup>1</sup>H NMR**

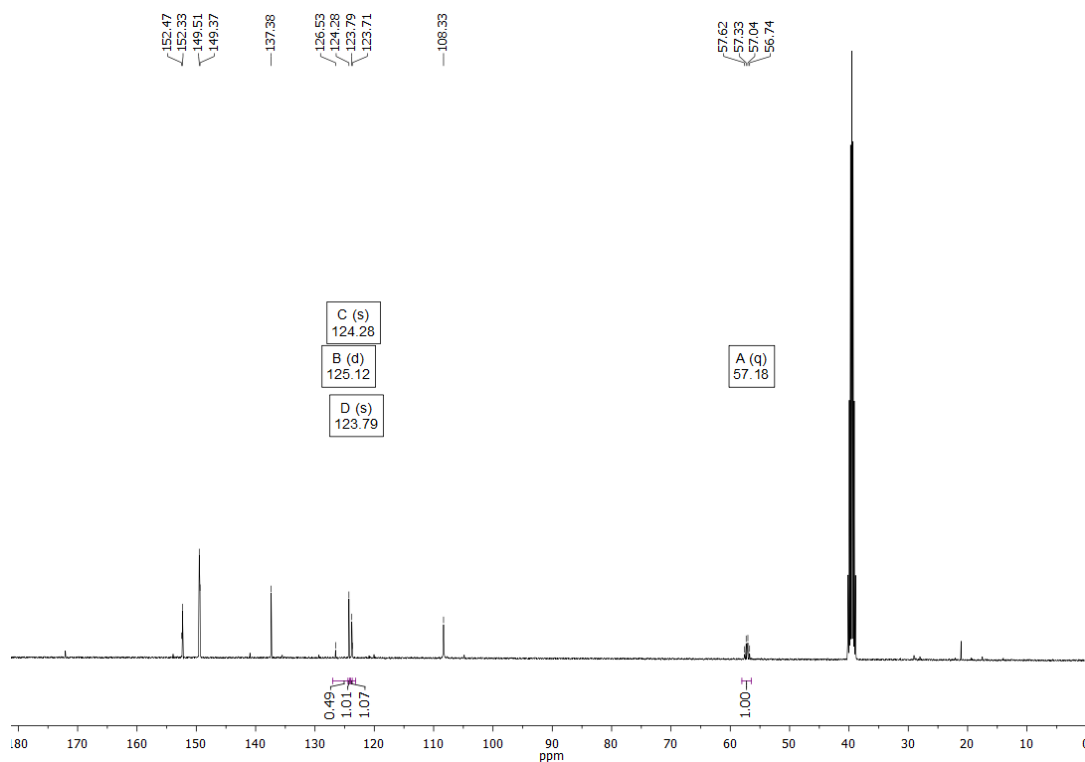
8.66  
8.66  
8.65  
8.65  
8.65  
8.65  
8.10  
8.10  
8.09  
8.09  
7.92  
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7.89  
7.68  
7.68  
7.67  
7.66  
7.46  
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6.88  
6.88  
6.87  
6.87  
5.86  
5.85  
5.84  
5.83  
5.82  
5.81



**<sup>19</sup>F NMR**

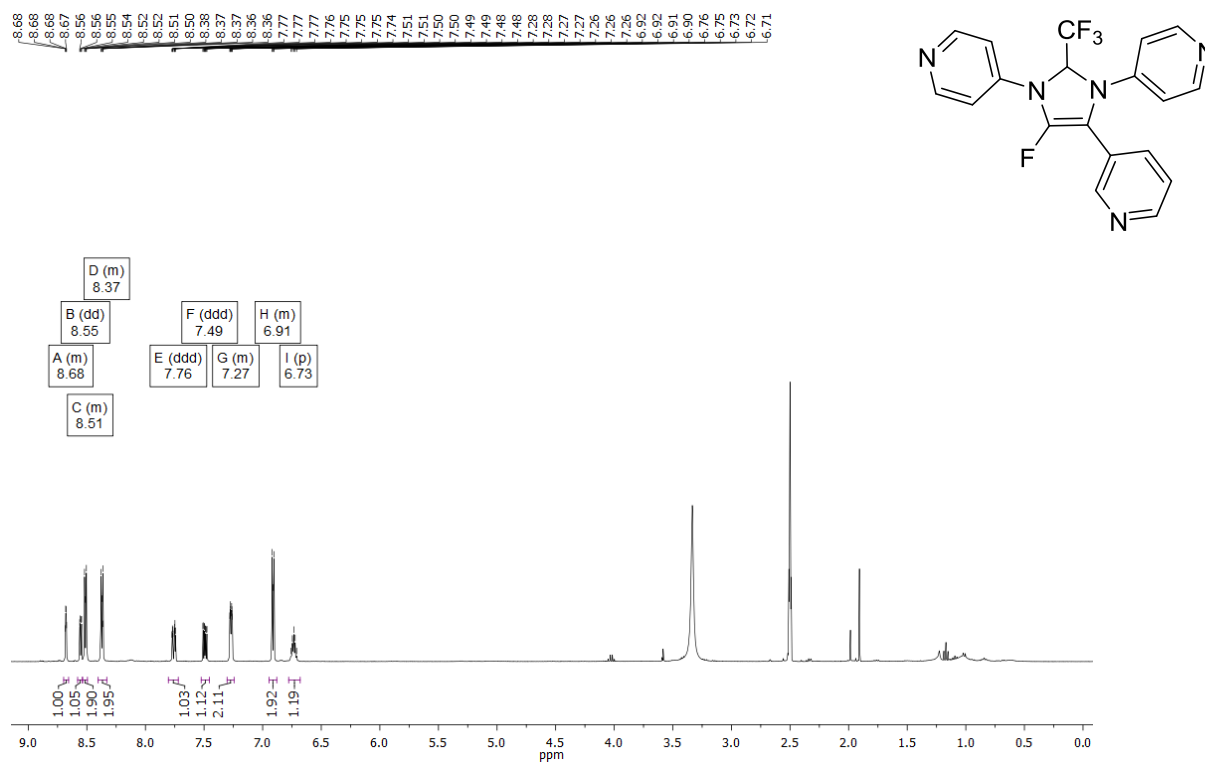


### <sup>13</sup>C NMR

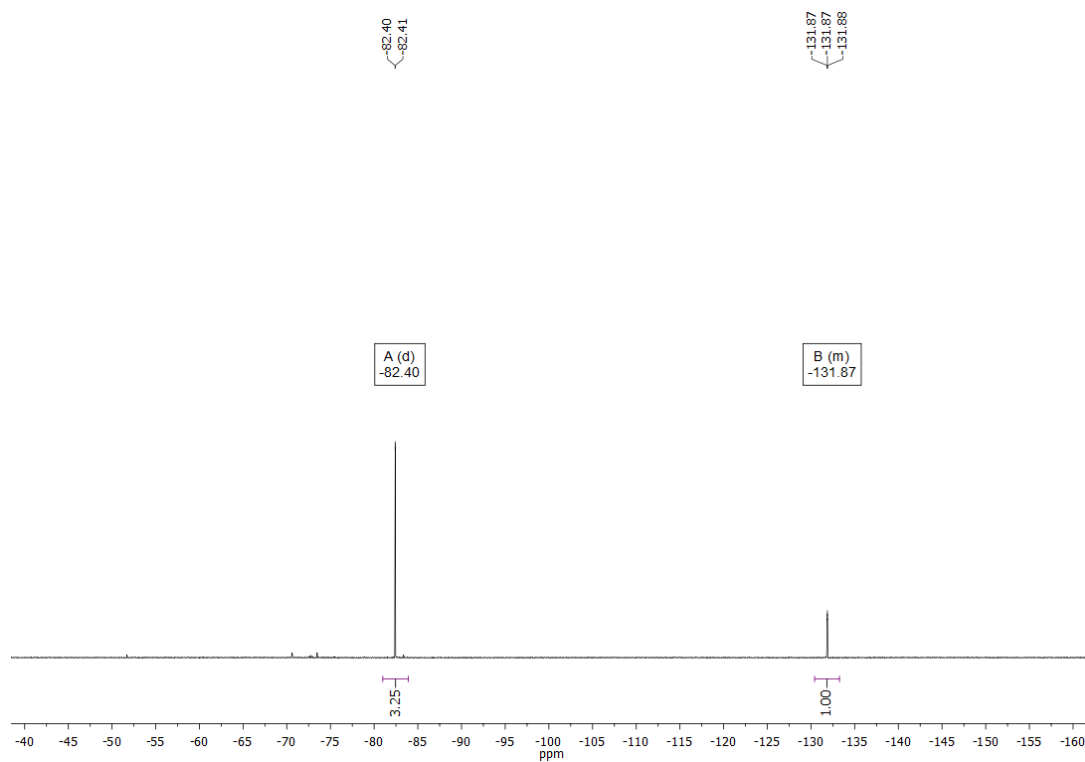


### *N,N'*-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(pyridin-3-yl)-2,3-dihydro-1*H*-imidazole 2l

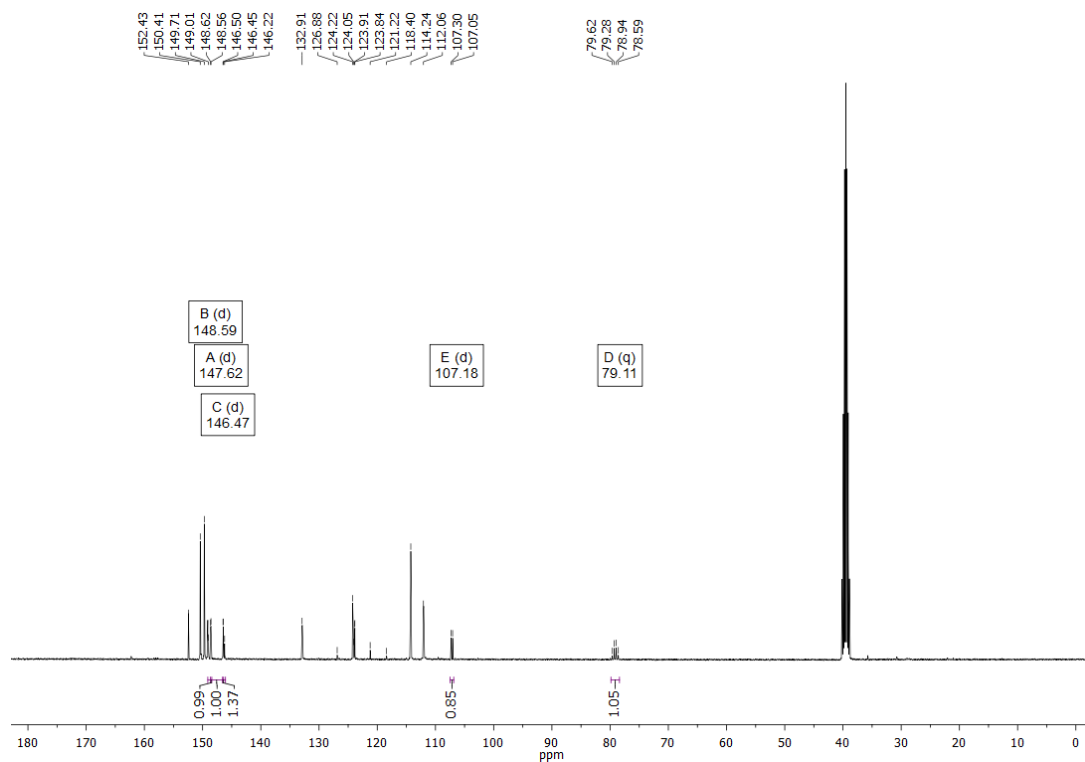
### <sup>1</sup>H NMR



# <sup>19</sup>F NMR



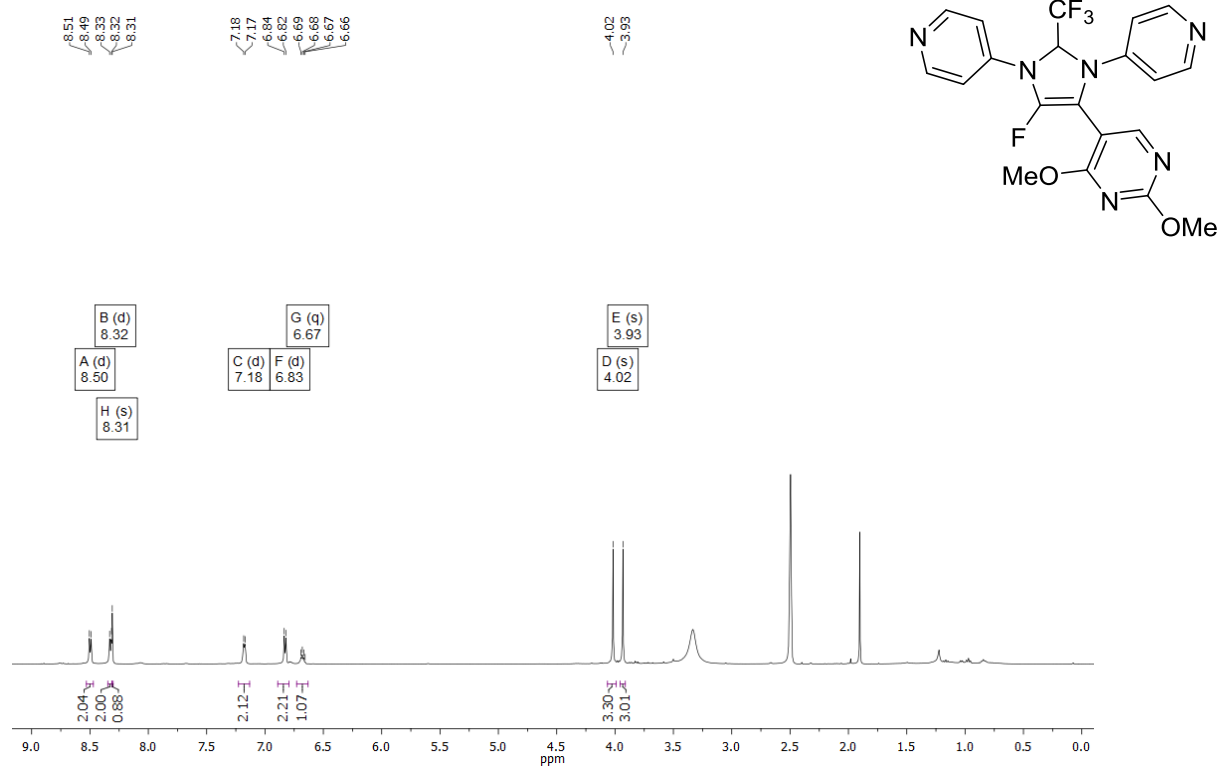
# <sup>13</sup>C NMR



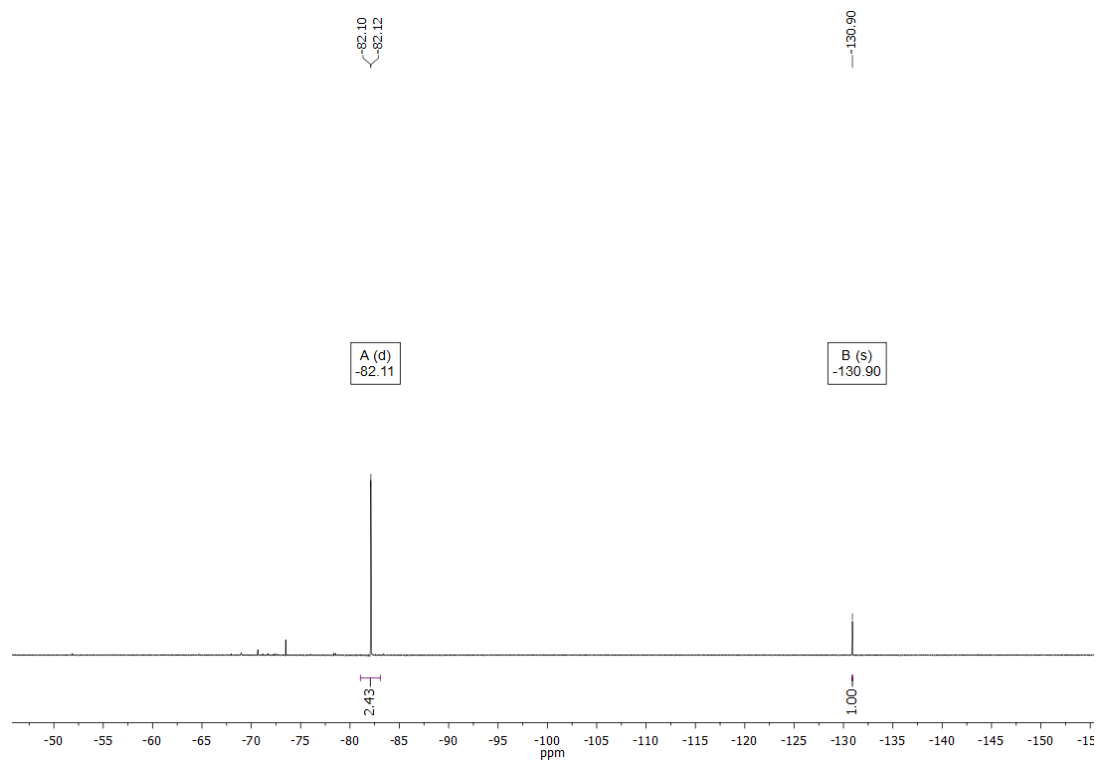


***N,N'*-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(2,4-dimethoxypyrimidin-5-yl)-2,3-dihydro-1*H*-imidazole 2m**

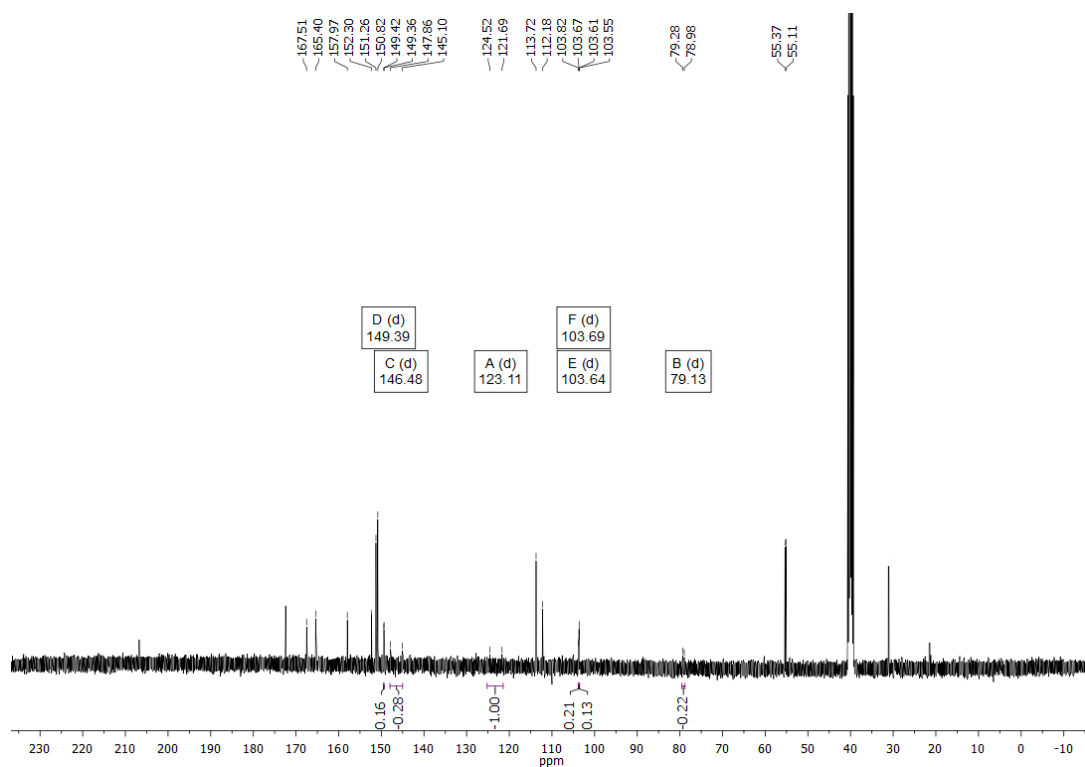
**<sup>1</sup>H NMR**



**<sup>19</sup>F NMR**

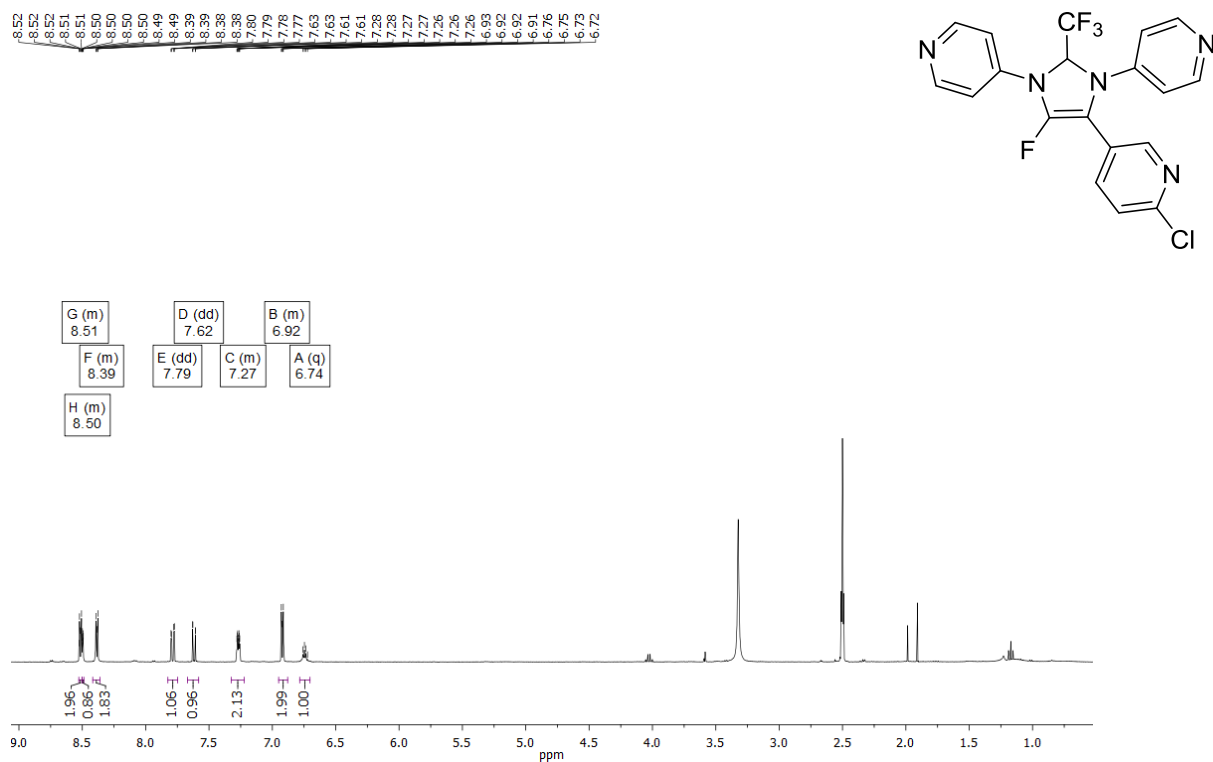


# <sup>13</sup>C NMR

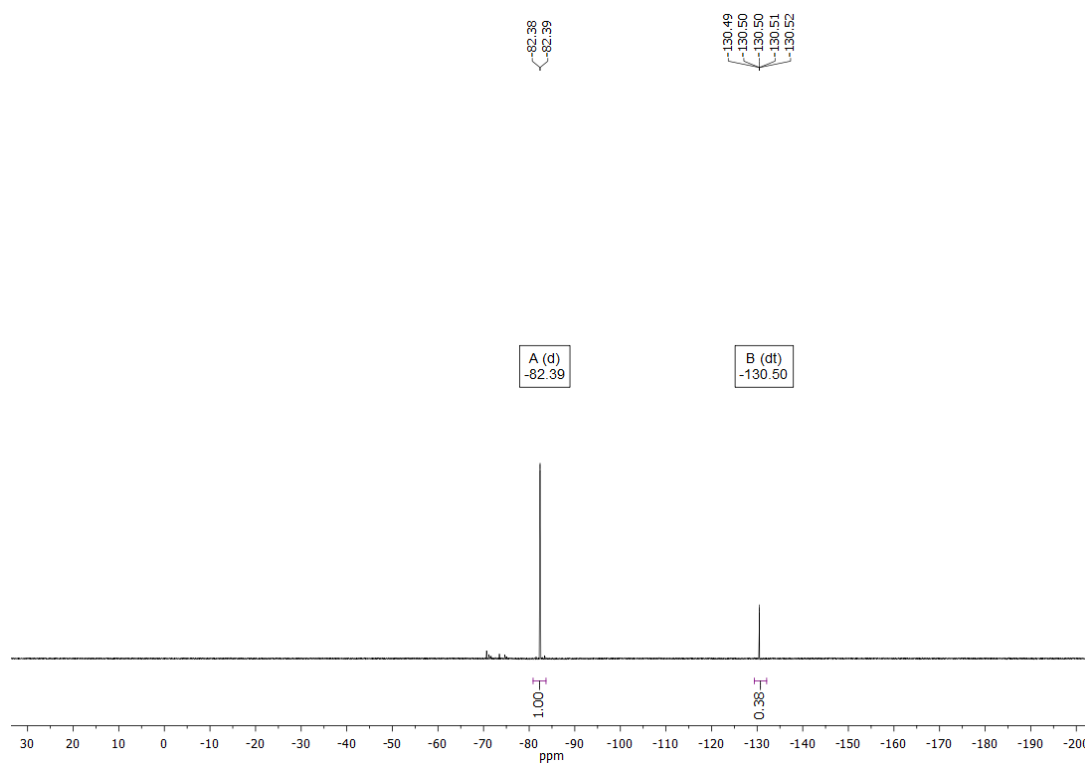


## *N,N'*-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(6-chloropyridin-3-yl)-2,3-dihydro-1*H*-imidazole **2n**

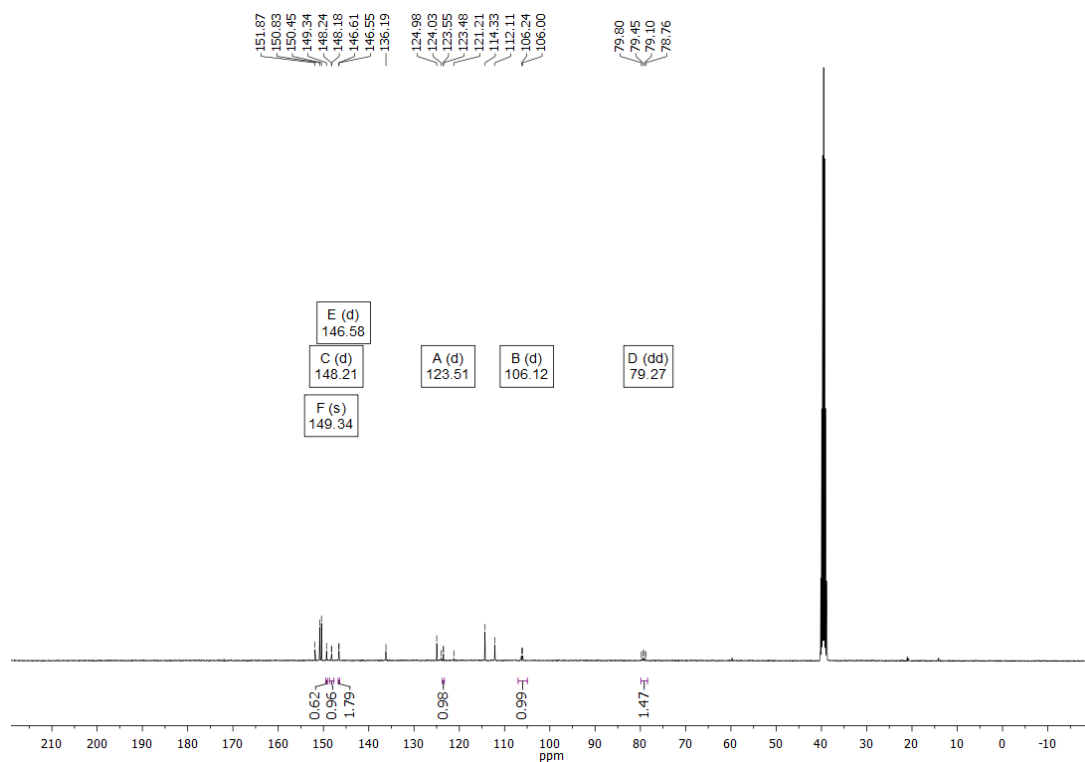
# <sup>1</sup>H NMR



# <sup>19</sup>F NMR

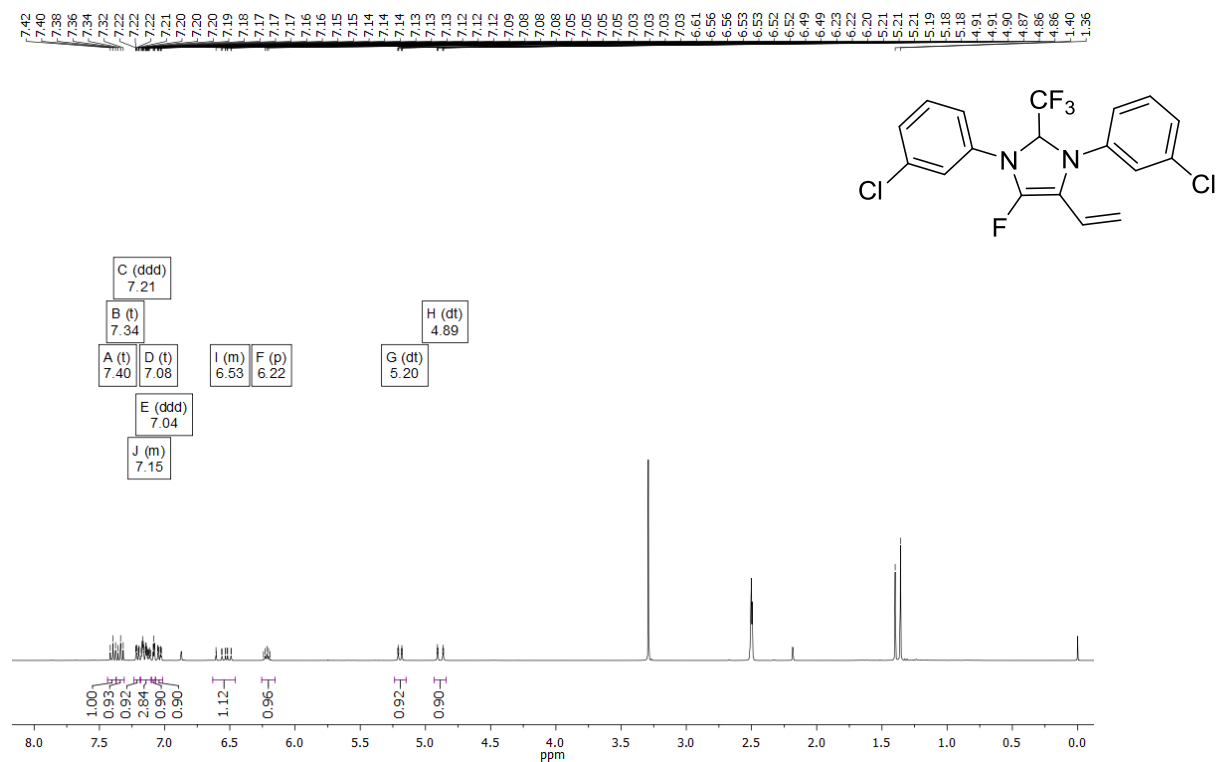


# <sup>13</sup>C NMR

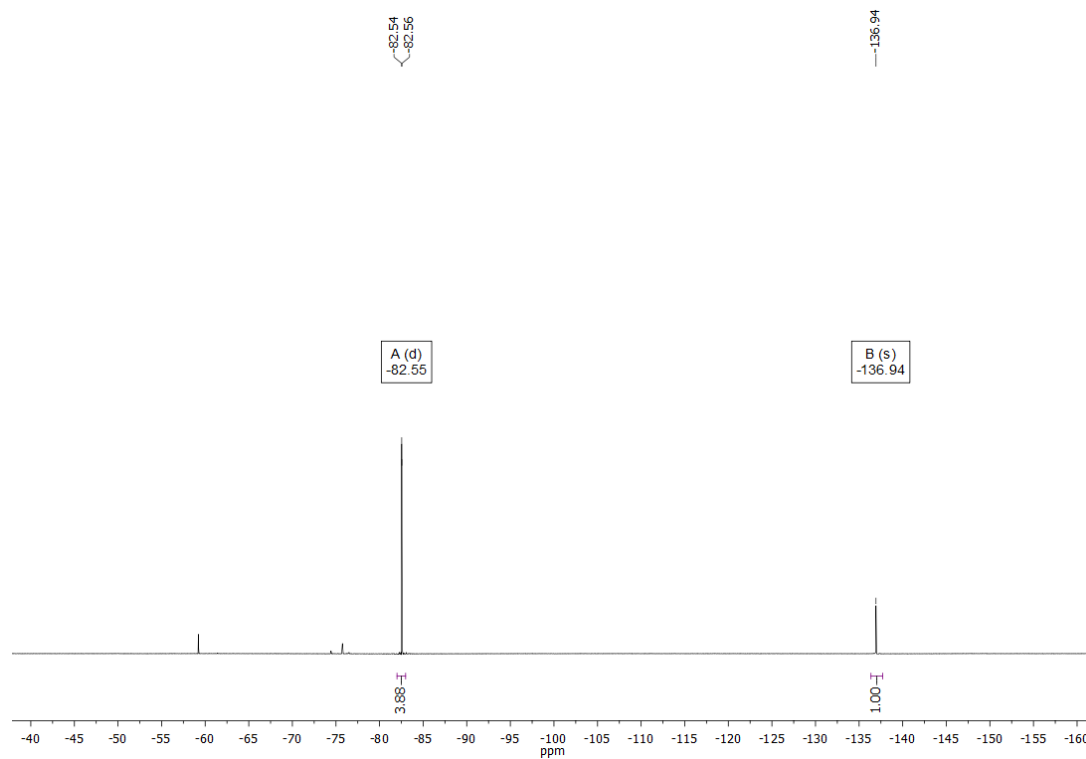


***N,N'*-1,3-(3-Chlorophenyl)-2-(trifluoromethyl)-4-fluoro-5-vinyl-2,3-dihydro-1*H*-imidazole 2o**

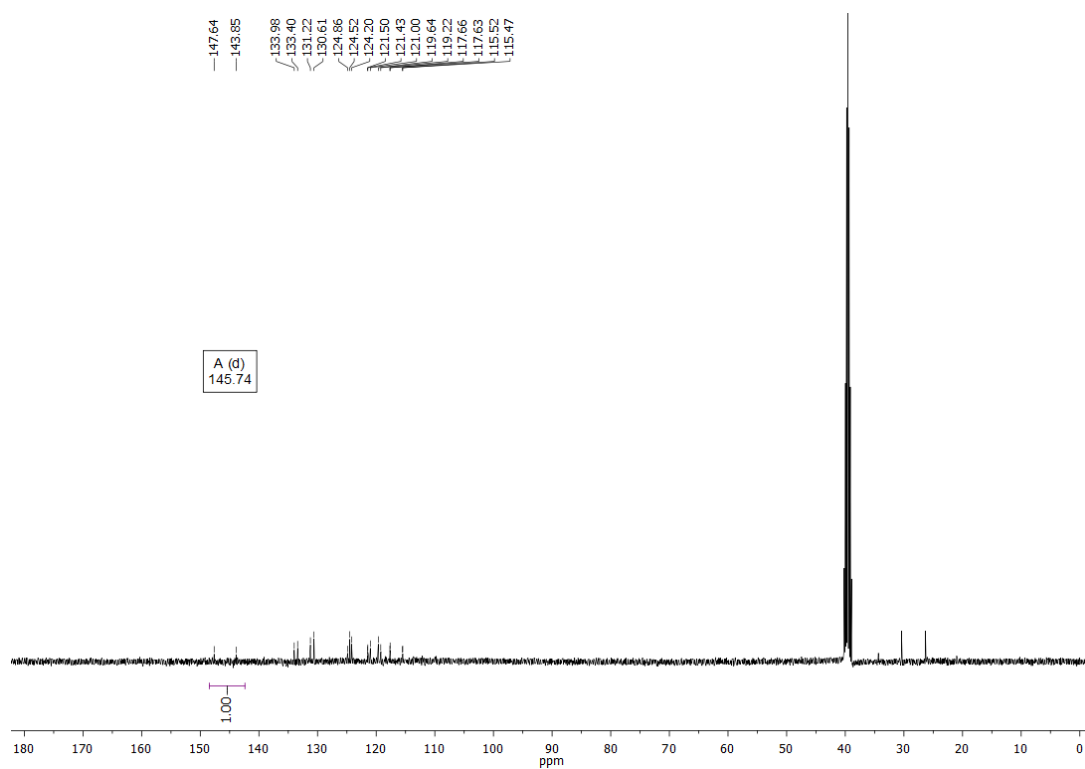
**<sup>1</sup>H NMR**



**<sup>19</sup>F NMR**

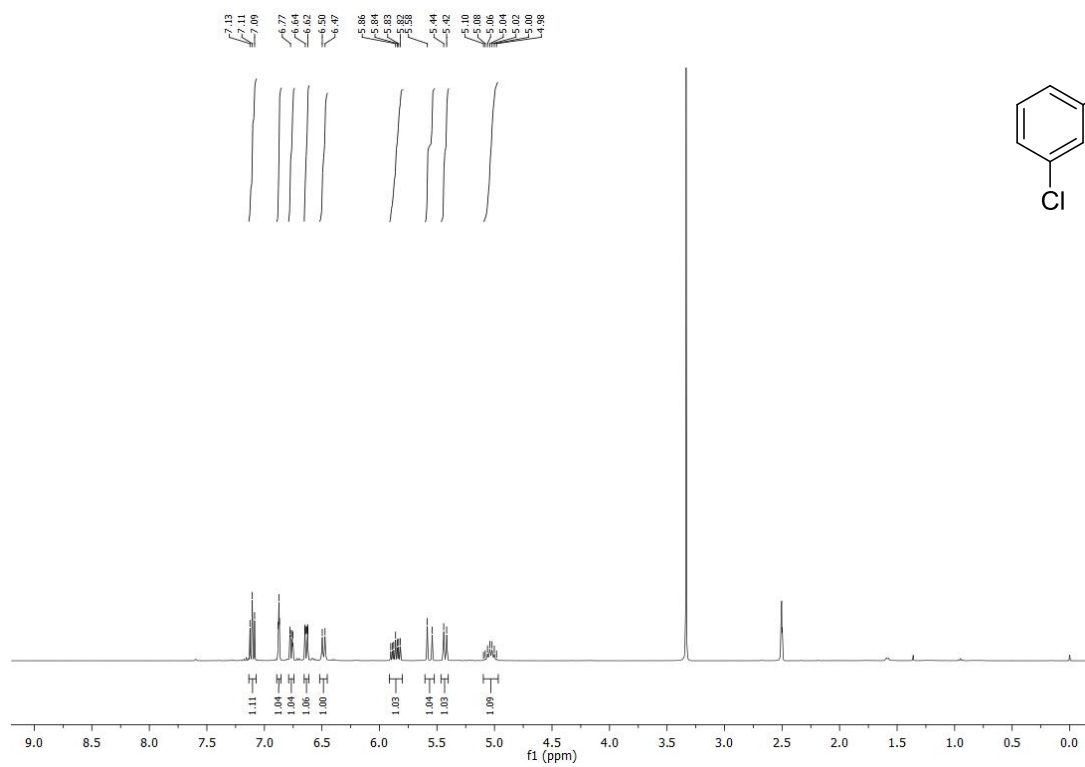


### <sup>13</sup>C NMR

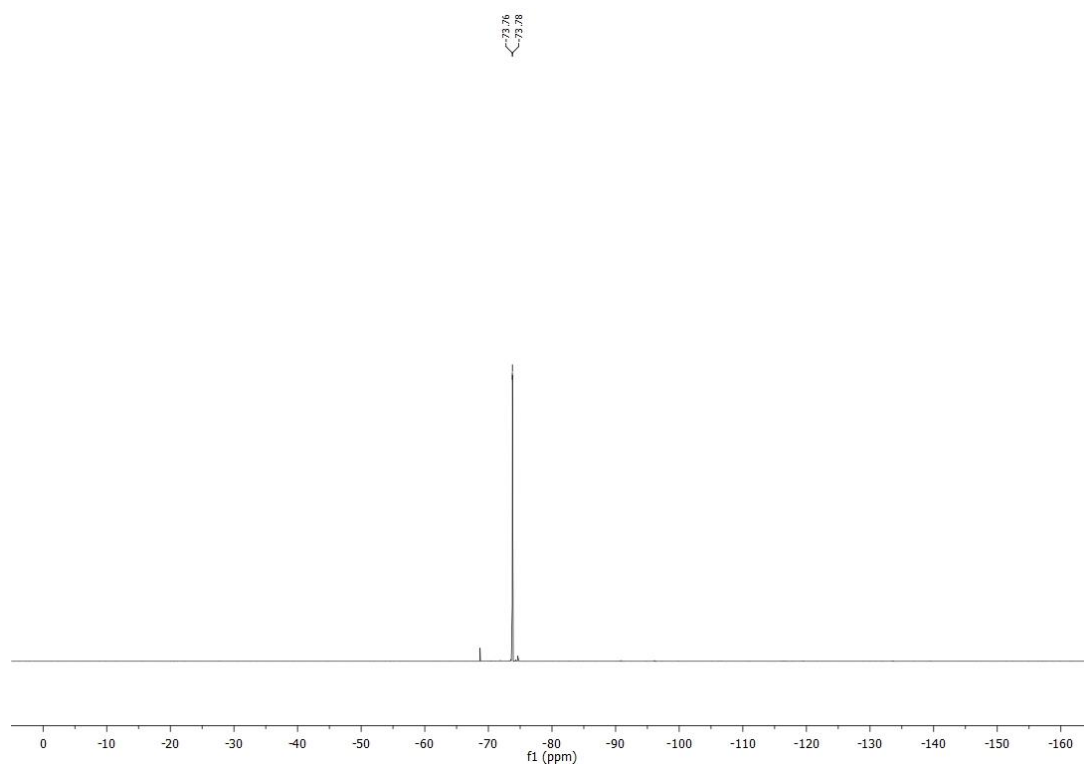


### 3-Chloro-*N*-(2,2,2-trifluoro-1-vinylethyl)aniline 3o

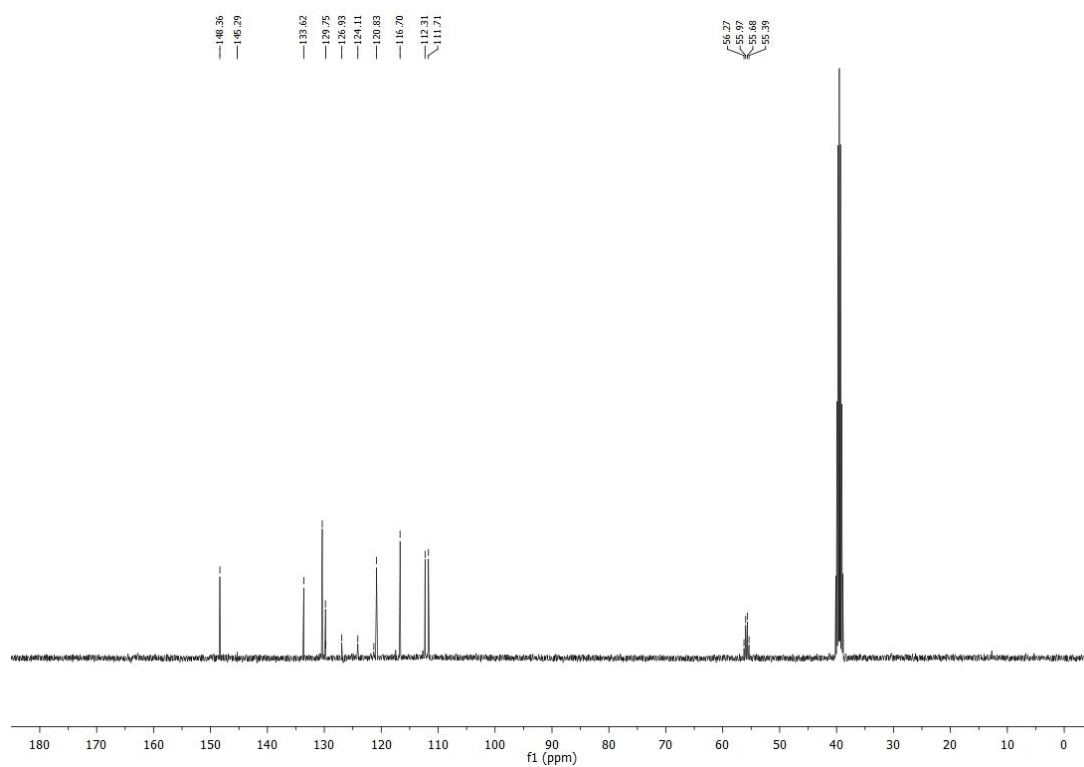
#### <sup>1</sup>H NMR



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

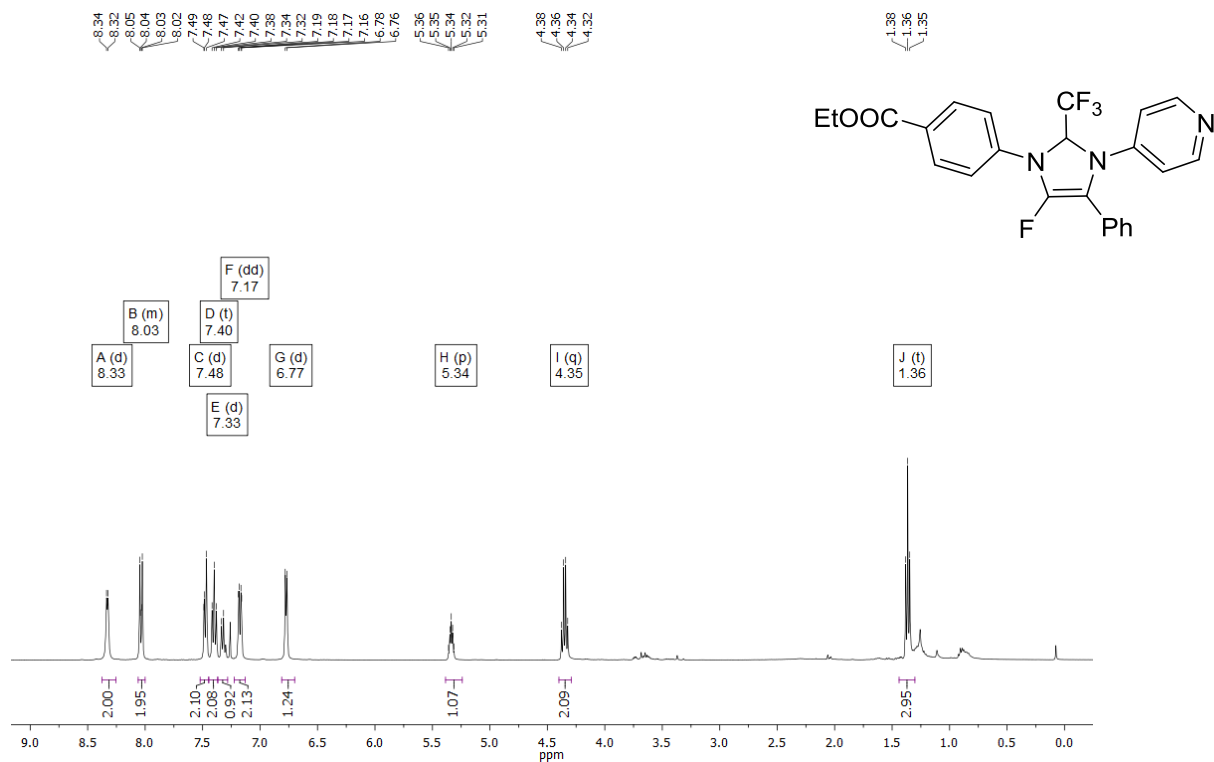


**$^{13}\text{C}$  NMR**

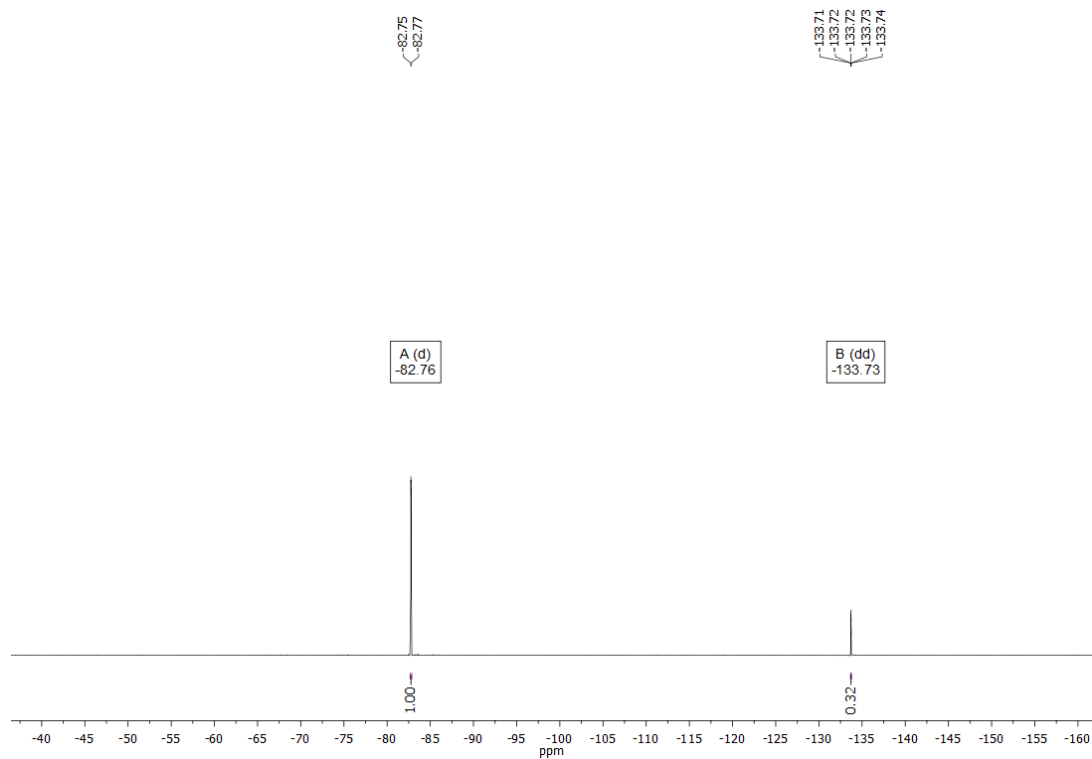


**Ethyl 4-(5-fluoro-4-phenyl-3-(pyridin-4-yl)-2-(trifluoromethyl)-2,3-dihydro-1H-imidazol-1-yl)benzoate 2p**

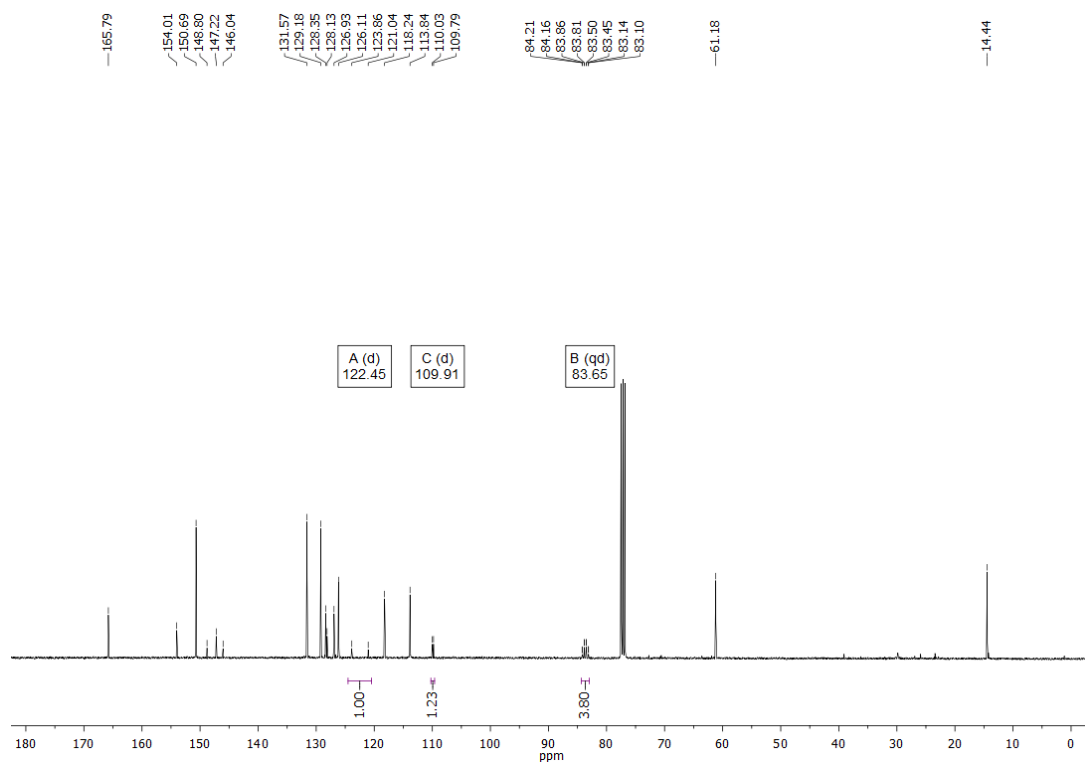
**<sup>1</sup>H NMR**



**<sup>19</sup>F NMR**

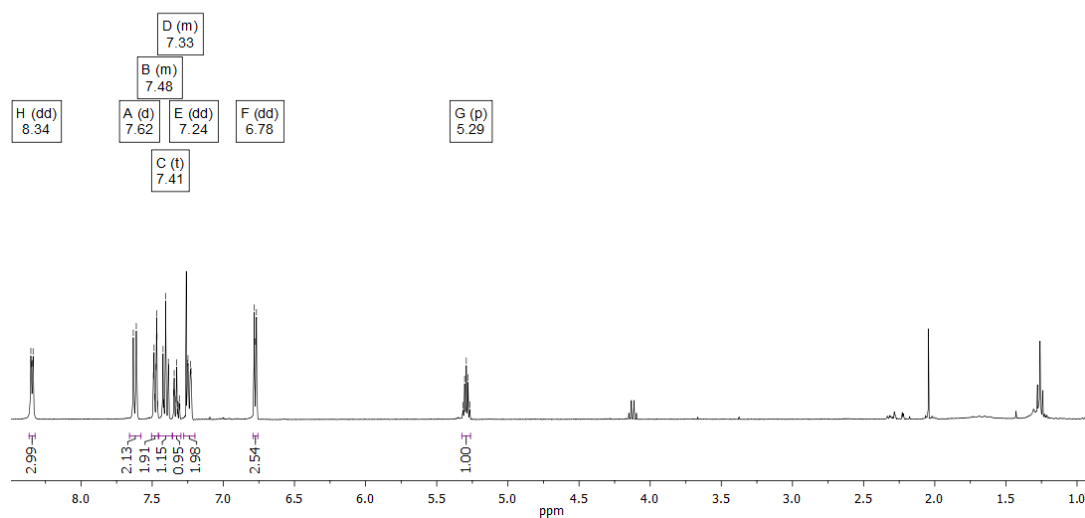
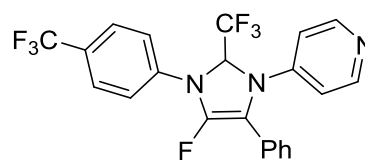
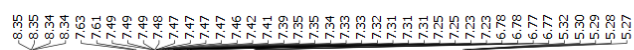


### <sup>13</sup>C NMR



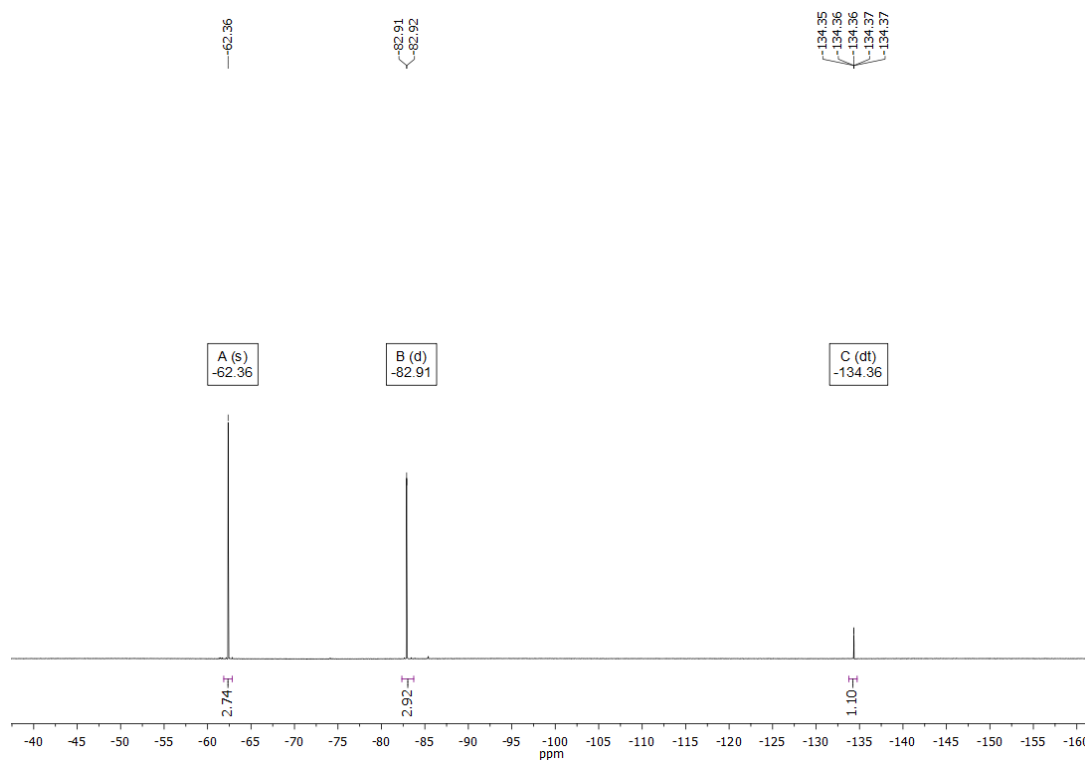
### 4-(4-Fluoro-5-phenyl-2-(trifluoromethyl)-3-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1H-imidazol-1-yl)pyridine 2q

#### <sup>1</sup>H NMR

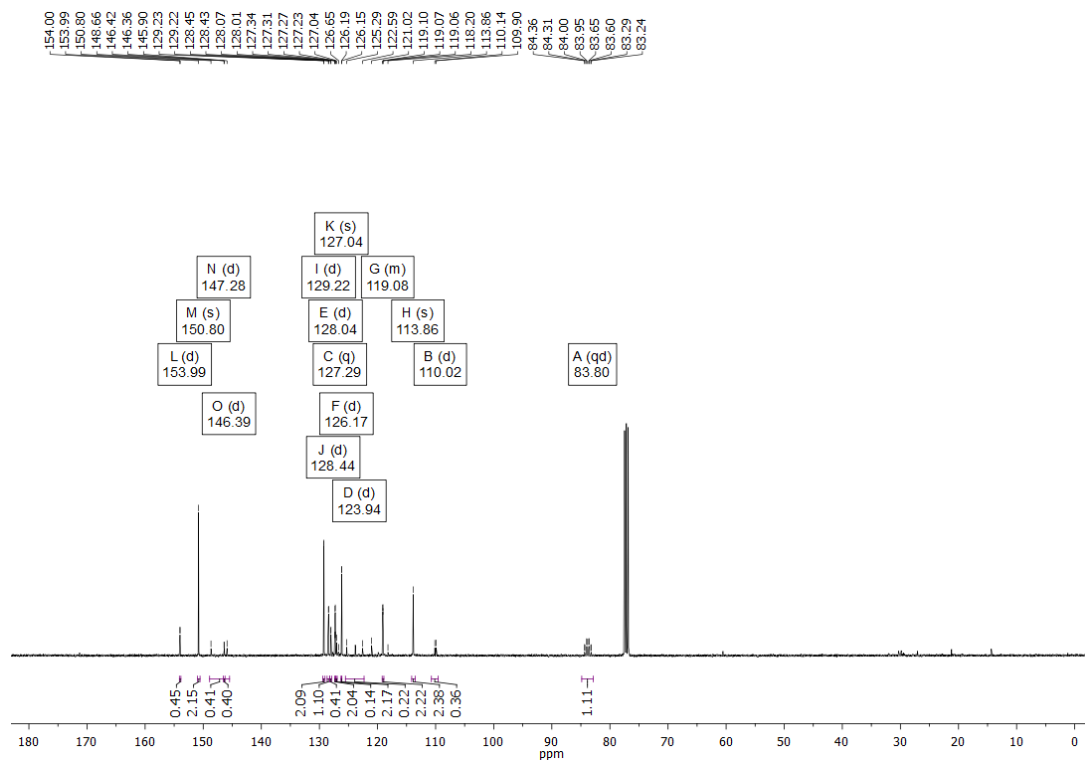




# <sup>19</sup>F NMR

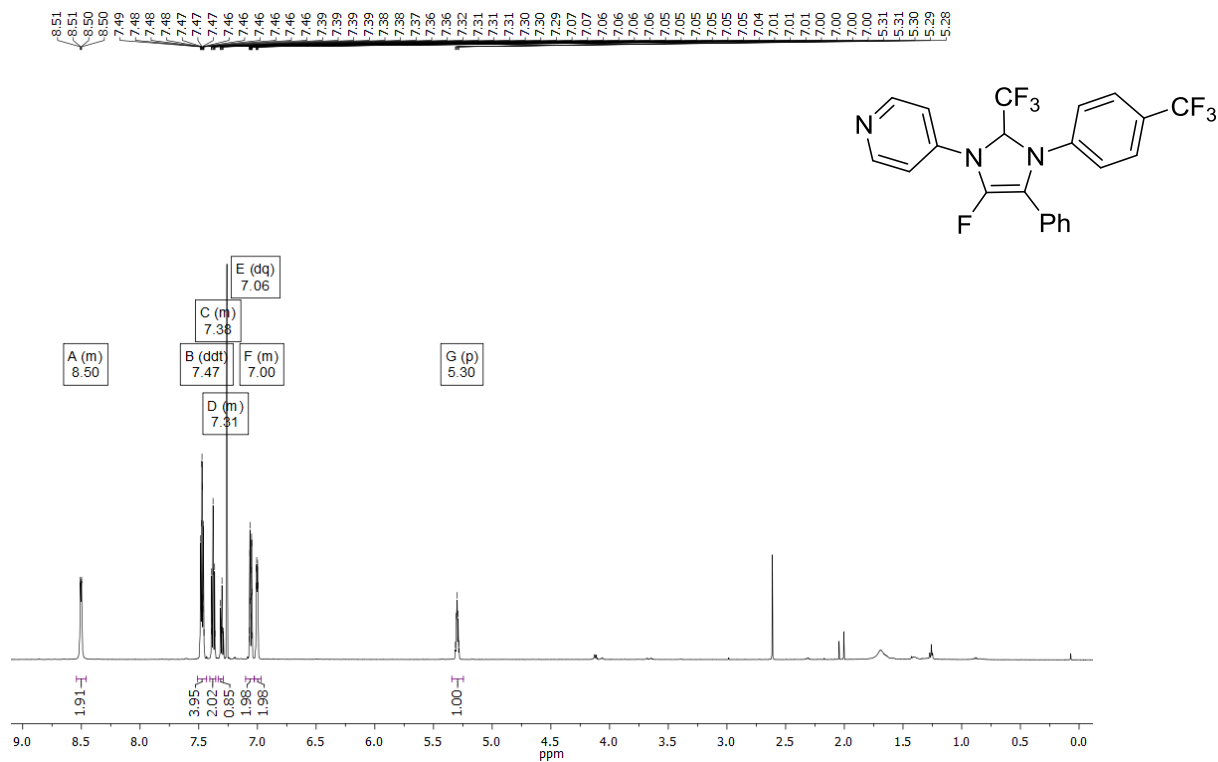


# <sup>13</sup>C NMR

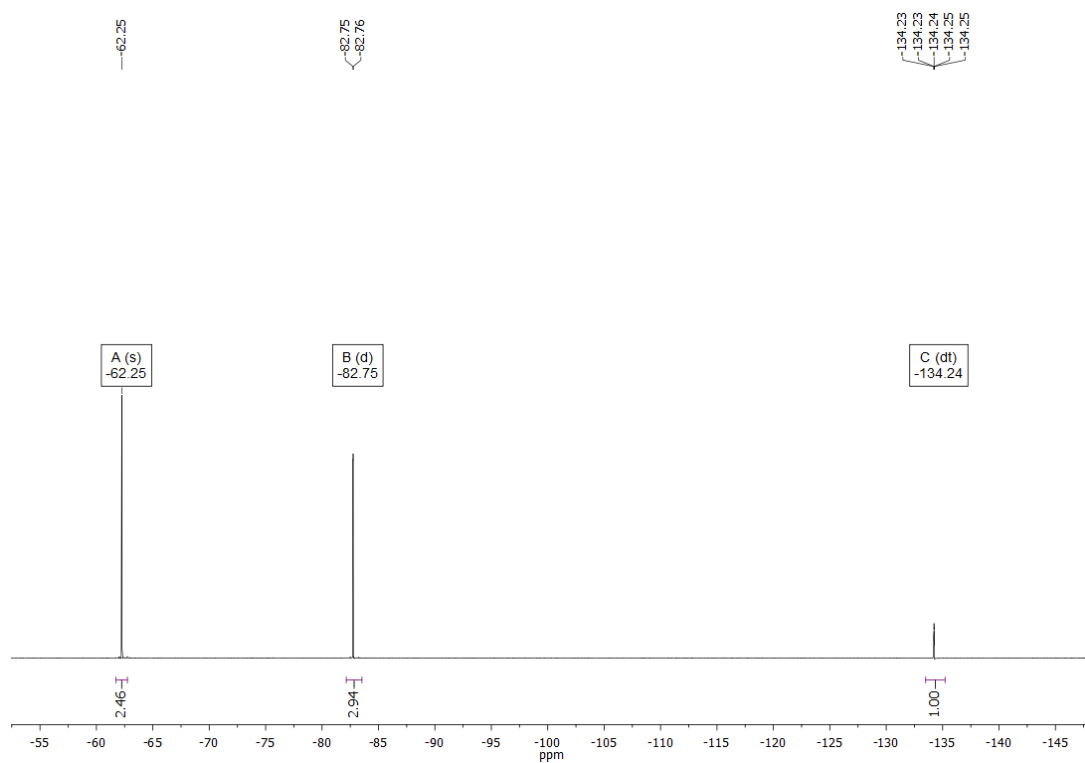


**4-(5-Fluoro-4-phenyl-2-(trifluoromethyl)-3-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1H-imidazol-1-yl)pyridine 2r**

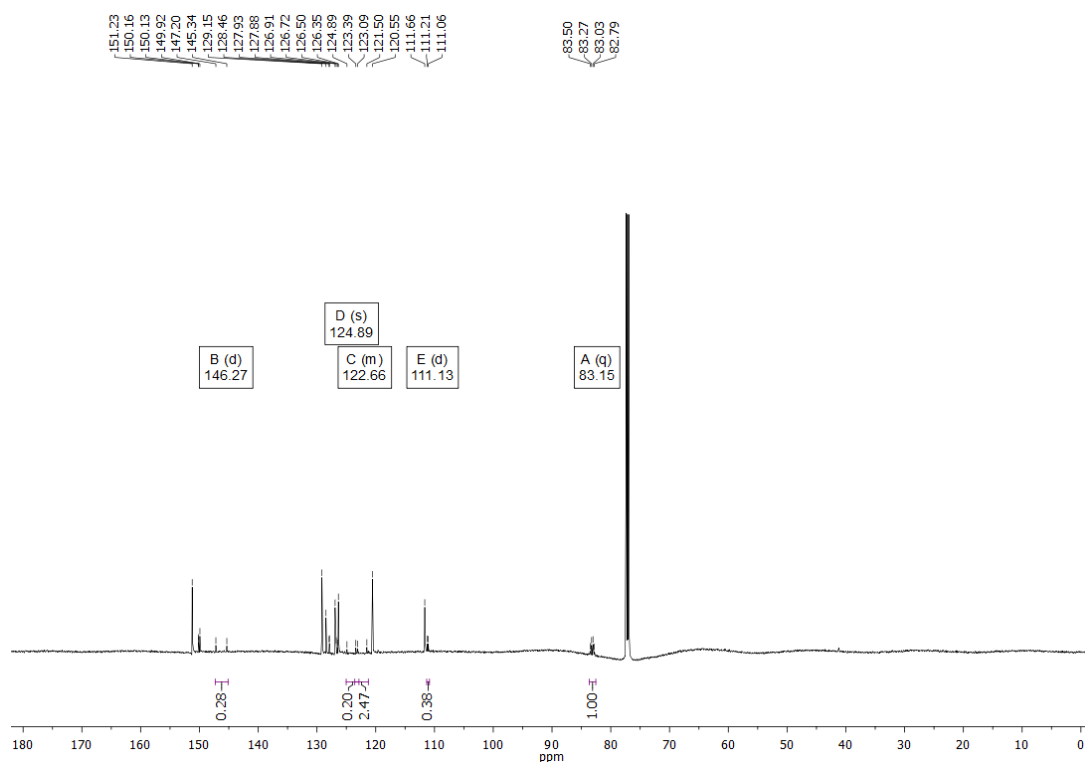
**<sup>1</sup>H NMR**



**<sup>19</sup>F NMR**

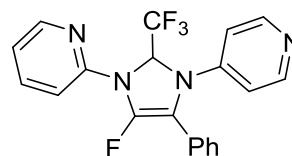
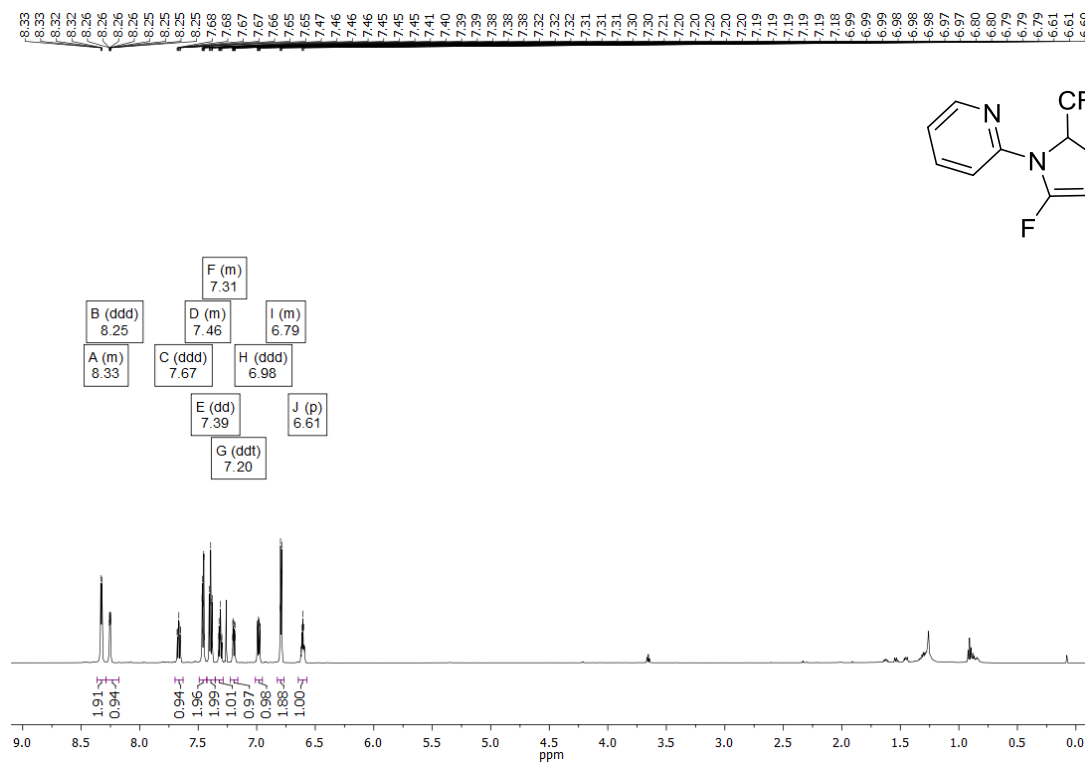


# <sup>13</sup>C NMR

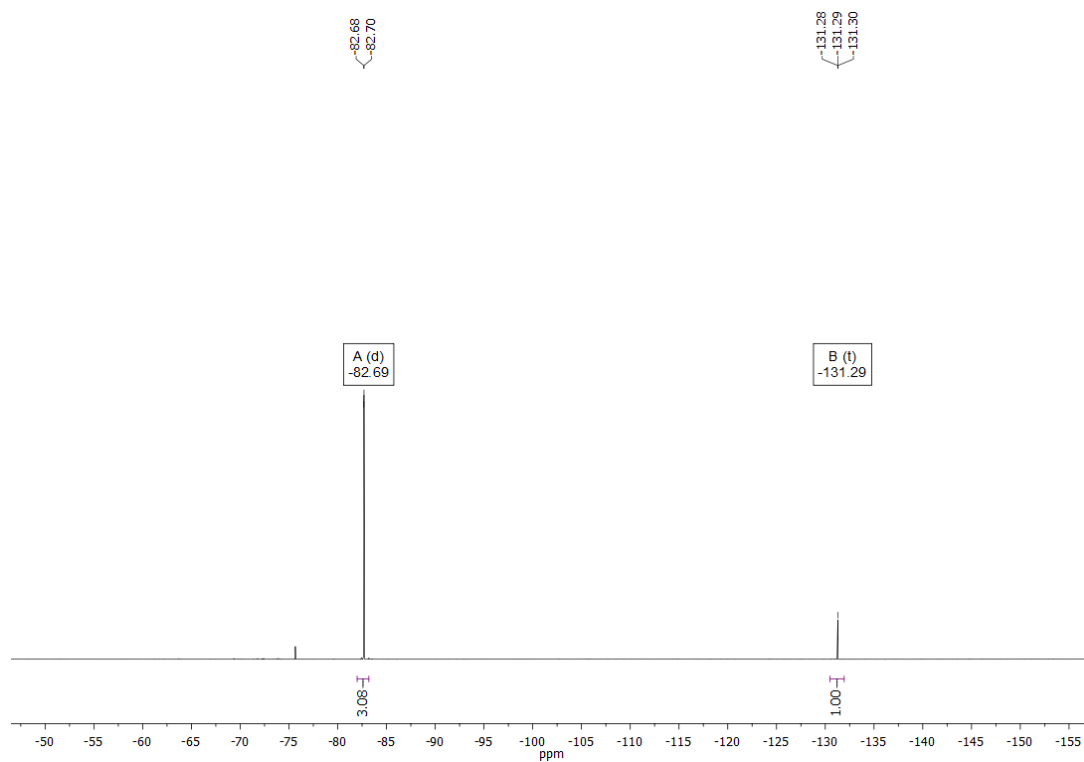


## 2-(5-Fluoro-4-phenyl-3-(pyridin-4-yl)-2-(trifluoromethyl)-2,3-dihydro-1H-imidazol-1-yl)pyridine 2s

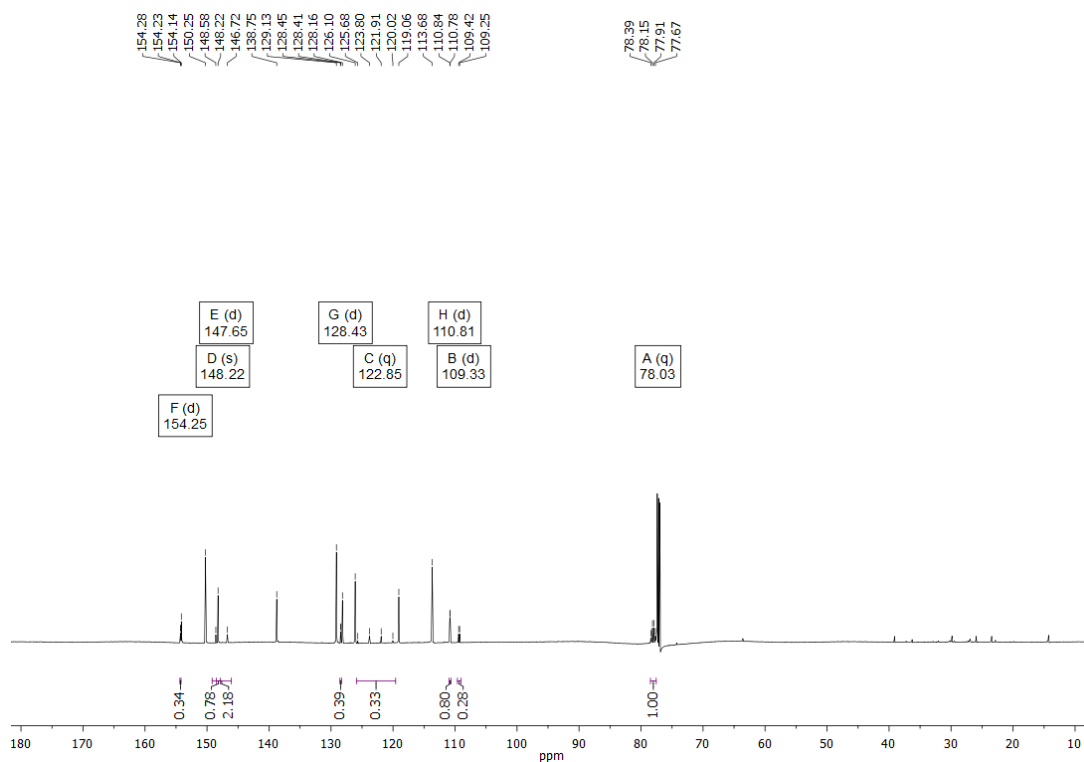
# <sup>1</sup>H NMR



# <sup>19</sup>F NMR

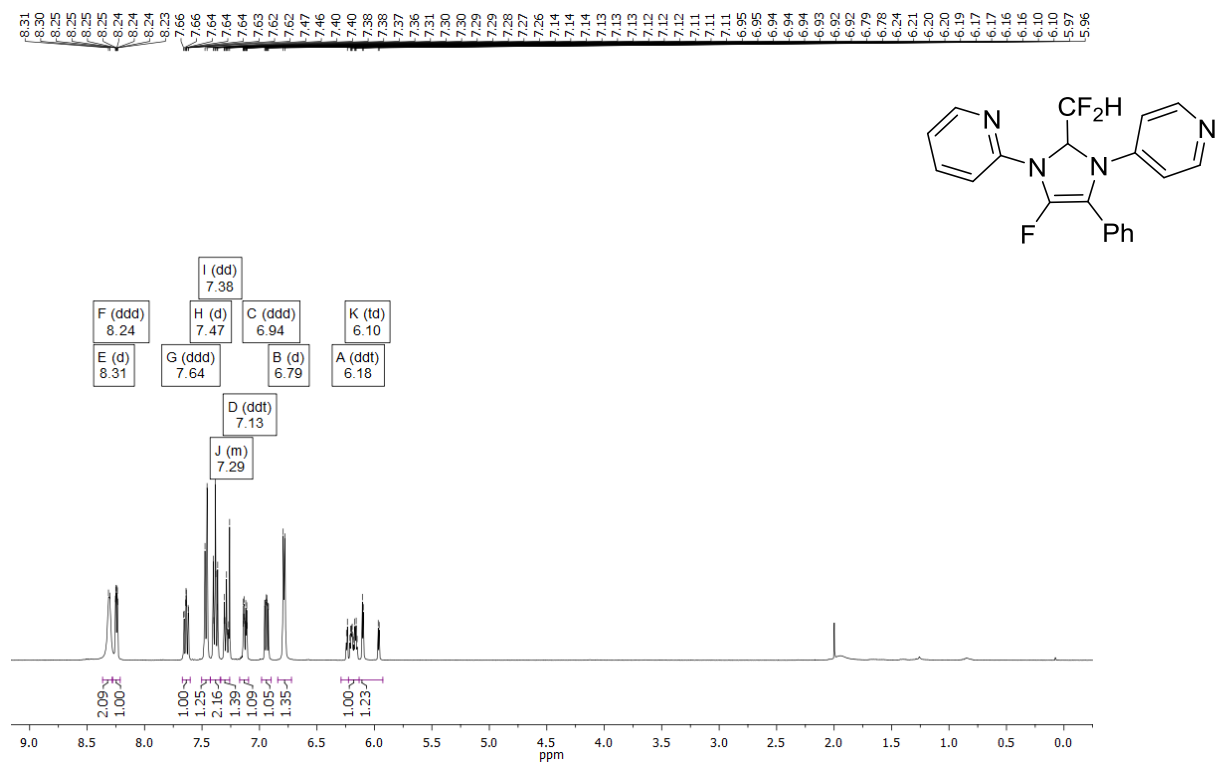


# <sup>13</sup>C NMR

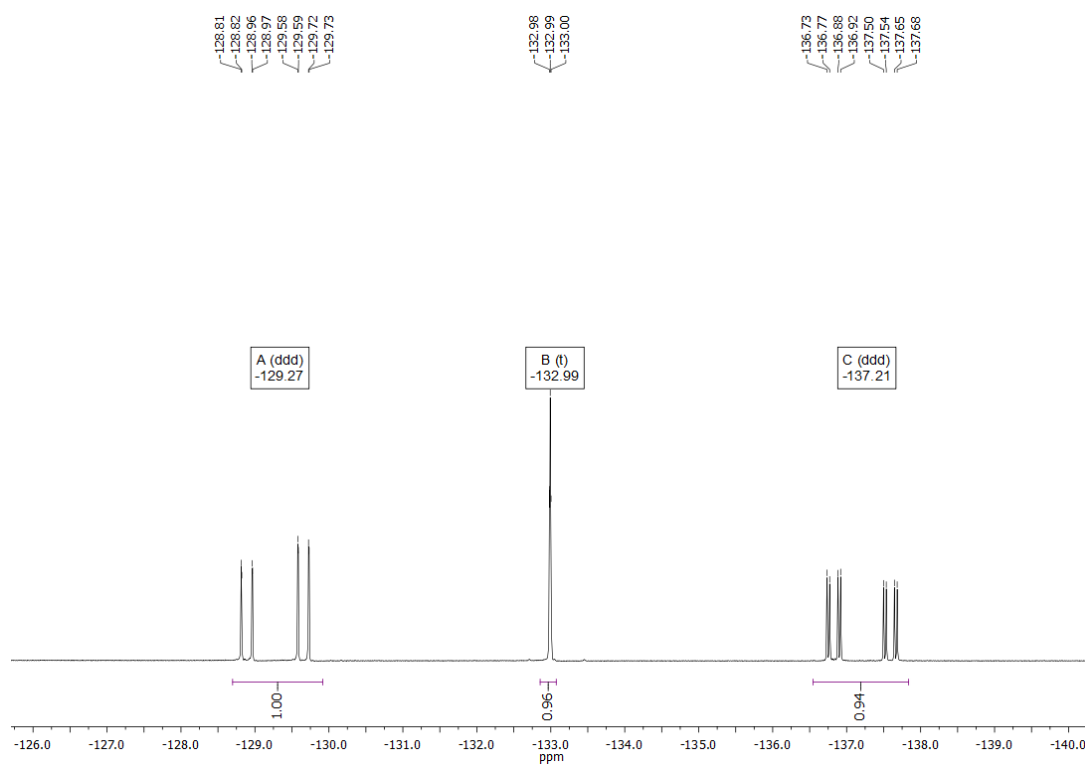


**2-(2-(Difluoromethyl)-5-fluoro-4-phenyl-3-(pyridin-4-yl)-2,3-dihydro-1H-imidazol-1-yl)pyridine 2t**

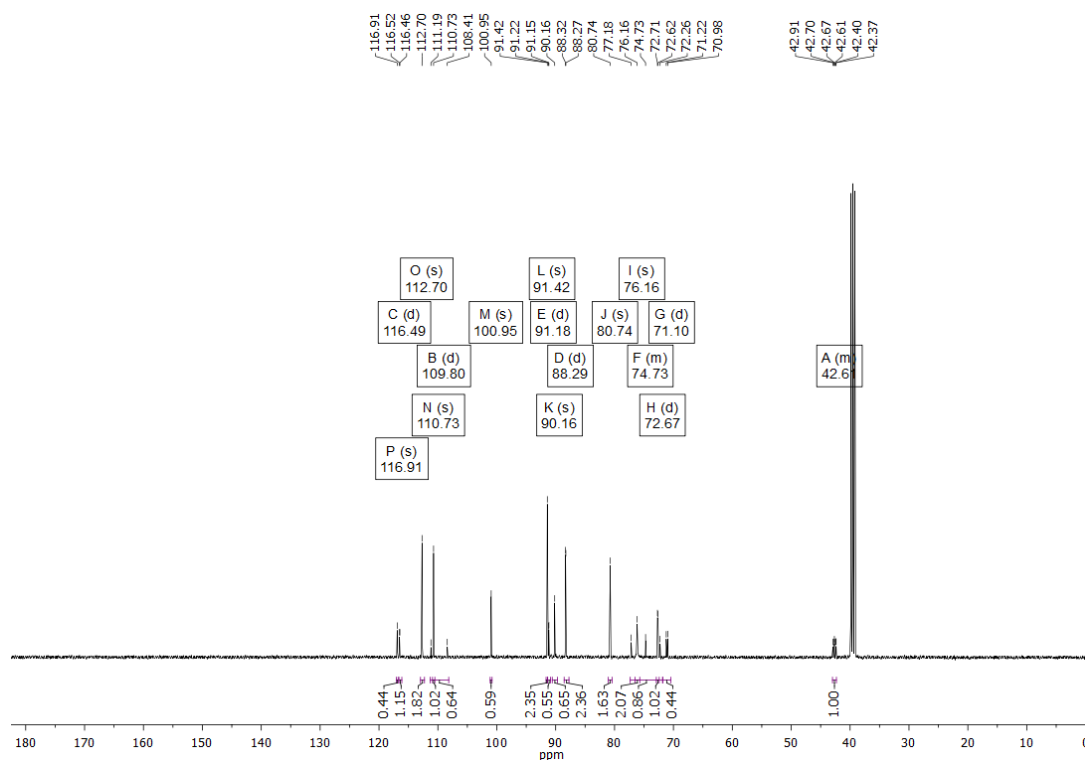
**<sup>1</sup>H NMR**



**<sup>19</sup>F NMR**



# <sup>13</sup>C NMR



## References:

- (1) For the synthesis of *N,O*-acetals, see: (a) Deutsch, A.; Wagner, C.; Deutsch, C.; Hoffmann-Röder, A. *Eur. J. Org. Chem.* **2016**, 2016, 930–945. (b) Gong, Y.; Kato, K. *J. Fluorine Chem.* **2004**, 125, 767–773. For the synthesis of trifluoroethylamines, see: (c) Prakash, G. K. S.; Mogi, R.; Olah, G. A. *Org. Lett.* **2006**, 8, 3589–3592.