

## Supporting Information

### Synthesis of functionalized $\alpha$ -trifluoroethyl amine scaffolds via Grignard addition to *N*-aryl hemiaminal ethers

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## 1. Materials and methods

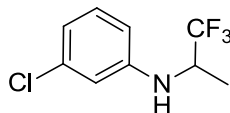
All reactions were carried out under an argon atmosphere using flame-dried glassware. Commercially available reagents and solvents were used without further purification. Grignard reagents were purchased from *Aldrich*. Dry THF was purchased from *Aldrich* and/or distilled from sodium and benzophenone. Hemiaminal substrates were synthesized from the 1-ethoxy-2,2,2-trifluoroethanol and the corresponding amines using *p*TSA in EtOH according to standard procedures.<sup>[1]</sup> They were purified by flash chromatography, and dried under reduced pressure prior to use. 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 crude trifluoroethyl amine derivatives were purified by MPLC with a *CombiFlash Rf Teledyne ISCO* or by standard flash chromatography using silica gel (35–70 μm) from *Acros Organics*. Analytical RP-HPLC was measured on a *JASCO* system with a *Phenomenex Luna* C18 column (5 μm, 250 × 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 μ, 100 Å) at 40 °C and HPLC-MS was performed on *Agilent 1100* and *Agilent 1200* systems using *Chromolith Speed ROD* RP-18e columns. 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 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. IR spectra were measured on a Perkin-Elmer *FT-IR Spektrum BXII* spectrometer with a Smiths *Dura SampIR II* ATR.

## 2. General procedure for the addition of Grignard reagents to *N*-hemiaminal ethers

A dry Schlenk flask was flushed with argon, equipped with a magnetic stirrer and a septum and charged with *N*-aryl hemiaminal ether in dry THF (ca. 0.05 M). The solution was cooled to -15 °C, the Grignard reagent (2 eq) was added dropwise, and the solution was stirred at -15 °C until complete consumption of the starting material (ca. 1 h, TLC and LC-MS control). Then, the solution was quenched with 1:1 THF/H<sub>2</sub>O (12 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, and the solvent was evaporated in *vacuo*. Purification by flash chromatography furnished the desired amines **2a-j**, **3a-h**, **5** and **6**.

## 3. Experimental data

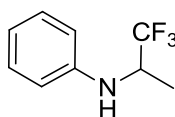
### 3-Chloro-*N*-(2,2,2-trifluoro-1-methylethyl)aniline **2a**



According to the general procedure, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** (152 mg, 0.60 mmol) was reacted with MeMgBr (1.4 M in toluene/THF 3:1, 0.86 mL, 1.20 mmol) in dry THF (12 mL). The crude product was purified by flash chromatography (cyclohexane → cyclohexane/CH<sub>2</sub>Cl<sub>2</sub> 80/20) to give the desired amine **2a** (116 mg, 87 %) as a light yellow oil.

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>): δ = 7.09 (t, *J* = 8.1 Hz, 1H, H5), 6.78 (t, *J* = 2.1 Hz, 1H, H2), 6.68 (dd, *J* = 8.2, 2.0 Hz, 1H, H6), 6.60 (ddd, *J* = 7.8, 1.9, 0.7 Hz, 1H, H4), 6.26 (d, *J* = 9.0 Hz, 1H, NH), 4.45 – 4.30 (m, 1H, CH), 1.28 (d, *J* = 6.8 Hz, 3H, CH<sub>3</sub>) ppm. **<sup>19</sup>F NMR** (377 MHz, DMSO-*d*<sub>6</sub>): δ = -75.76 (d, *J* = 7.0 Hz, CF<sub>3</sub>) ppm. **<sup>13</sup>C NMR** (101 MHz, DMSO-*d*<sub>6</sub>): δ = 148.64 (C1), 133.59 (C3), 130.33 (C5), 126.77 (q, <sup>1</sup>*J* (C,F) = 284.0 Hz, CF<sub>3</sub>), 116.29 (C4), 111.94 (C2), 111.32 (C6), 49.07 (q, <sup>2</sup>*J*(C,F) = 29.5 Hz, CCF<sub>3</sub>), 14.28 (CH<sub>3</sub>) ppm. **FT-IR** (ATR):  $\tilde{\nu}$  = 3420 (br, vw), 1598 (s), 1510 (m), 1482 (m), 1252 (m), 1133 (vs), 1022 (s), 990 (m), 841 (w), 764 (m), 680 (m) cm<sup>-1</sup>. **HPLC-MS** (0.1 % TFA; 0 min: 4 % B → 2.8 min: 100 % B, flow: 2.4 mL/min): *t*<sub>R</sub> = 2.52 min, λ = 220 nm. **HR-ESI-MS** (positive, *m/z*) calc. for C<sub>9</sub>H<sub>10</sub>ClF<sub>3</sub>N<sup>+</sup> [MH]<sup>+</sup> 224.0448; found 224.0448.

### *N*-(2,2,2-Trifluoro-1-methylethyl)aniline **2b**<sup>[2]</sup>

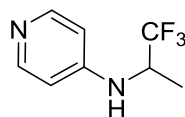


According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1b**<sup>[2]</sup> (200 mg, 0.91 mmol) was reacted with MeMgBr (1.4 M in toluene/THF 3:1, 1.30 mL, 1.82 mmol) in dry THF

(12 mL). The crude product was purified by flash chromatography (cyclohexane → cyclohexane/CH<sub>2</sub>Cl<sub>2</sub> 80/20) to give the desired amine **2b** (109 mg, 63 %) as a light yellow liquid.

**<sup>1</sup>H NMR** (400 MHz, DMSO-d<sub>6</sub>): δ = 7.15 – 7.01 (m, 2H, H3; H5), 6.71 (d, *J* = 7.8 Hz, 2H, H2, H6), 6.59 (tt, *J* = 7.4 Hz, 1.0, 1H, H4), 5.88 (d, *J* = 8.9 Hz, 1H, NH), 4.38 – 4.20 (m, 1H, CH), 1.29 (d, *J* = 6.8 Hz, 3H, CH<sub>3</sub>) ppm. **<sup>19</sup>F NMR** (377 MHz, DMSO-d<sub>6</sub>): δ = -75.70 (d, *J* = 7.2 Hz, CF<sub>3</sub>) ppm. **<sup>13</sup>C NMR** (101 MHz, DMSO-d<sub>6</sub>): δ = 147.00 (C<sub>q</sub>), 128.84 (CH<sub>ar</sub>), 126.90 (q, <sup>1</sup>*J* (C,F) = 284.2 Hz, CF<sub>3</sub>), 116.85 (CH<sub>ar</sub>), 112.58 (CH<sub>ar</sub>), 49.31 (q, <sup>2</sup>*J*(C,F) = 29.4 Hz, CCF<sub>3</sub>), 14.35 (CH<sub>3</sub>) ppm. **FT-IR** (ATR):  $\tilde{\nu}$  = 3406 (br, vw), 3026 (vw), 1603 (m), 1511 (m), 1497 (m), 1387 (w), 1250 (s), 1166 (m) 1127 (vs), 1018 (s), 946 (w), 747 (s), 691 (s) cm<sup>-1</sup>. **HPLC-MS** (0.1 % TFA; 0 min: 4 % B → 2.8 min: 100 % B, flow: 2.4 mL/min): *t<sub>R</sub>* = 2.19 min, λ = 220 nm. **HR-ESI-MS** (positive, *m/z*) calc. for C<sub>9</sub>H<sub>11</sub>ClF<sub>3</sub>N<sup>+</sup> [MH]<sup>+</sup> 190.0838; found 190.0838.

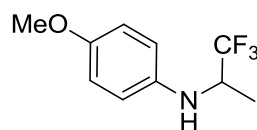
#### ***N*-(1,1,1-trifluoropropan-2-yl)pyridin-4-amine 2c**



Following the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyridine **1c** (196 mg, 0.89 mmol) was reacted with MeMgBr (1.4 M in toluene/THF 3:1, 1.27 mL, 1.78 mmol) in dry THF (12 mL). The crude product was purified by flash chromatography (cyclohexane → cyclohexane/CH<sub>2</sub>Cl<sub>2</sub> 80/20) to give the desired amine **2c** (137 mg, 81 %) as a white solid.

**<sup>1</sup>H NMR** (400 MHz, DMSO-d<sub>6</sub>): δ = 8.07 (dd, *J* = 4.8, 1.5 Hz, 2H, H3; H5), 6.81 (d, *J* = 9.0 Hz, 1H, NH), 6.66 (dd, *J* = 4.9, 1.5 Hz, 2H, H2; H6), 4.56 – 4.41 (m, 1H, CH), 1.30 (d, *J* = 6.8 Hz, 3H, CH<sub>3</sub>) ppm. **<sup>19</sup>F NMR** (376 MHz, DMSO-d<sub>6</sub>): δ = -75.82 (d, *J* = 7.2 Hz, CF<sub>3</sub>) ppm. **<sup>13</sup>C NMR** (101 MHz, DMSO-d<sub>6</sub>): δ = 152.50 (C4), 149.54 (CH<sub>ar</sub>), 126.56 (q, <sup>1</sup>*J* (C,F) = 284.0 Hz, CF<sub>3</sub>), 107.71 (CH<sub>ar</sub>), 48.13 (q, <sup>2</sup>*J*(C,F) = 29.9 Hz, CCF<sub>3</sub>), 14.06 (CH<sub>3</sub>) ppm. **FT-IR** (ATR):  $\tilde{\nu}$  = 3234 (w), 2994 (br, w), 1602 (s), 1533 (m), 1325 (w), 1267 (m), 1220 (s), 1162 (s), 1138 (vs), 1020 (s), 992 (s), 812 (s), 673 (m) cm<sup>-1</sup>. **HPLC-MS** (0.1 % TFA; 0 min: 4 % B → 2.8 min: 100 % B, flow: 2.4 mL/min): *t<sub>R</sub>* = 1.07 min, λ = 220 nm. **m.p.** 148 °C. **HR-ESI-MS** (positive, *m/z*) calc. for C<sub>8</sub>H<sub>10</sub>F<sub>3</sub>N<sub>2</sub><sup>+</sup> [MH]<sup>+</sup> 191.0791; found 191.0798.

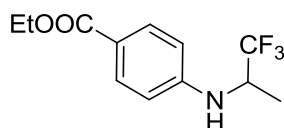
#### 4-Methoxy-*N*-(2,2,2-trifluoro-1-methylethyl)aniline **2d**<sup>[3]</sup>



According to the general procedure, 4-methoxy-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1d**<sup>[4]</sup> (190 mg, 0.76 mmol) was reacted with MeMgBr (1.4 M in toluene/THF 3:1, 1.09 mL, 1.52 mmol) in dry THF (12 mL). The crude product was purified by flash chromatography (cyclohexane → cyclohexane/CH<sub>2</sub>Cl<sub>2</sub> 60/40) to give the desired amine **2d** (67 mg, 40 %) as a light yellow liquid.

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 6.75 – 6.65 (m, 4H, 4 × H<sub>ar</sub>), 5.46 (d,  $J$  = 9.0 Hz, 1H, NH), 4.24 – 4.09 (m, 1H, CH), 3.64 (s, 3H, OCH<sub>3</sub>), 1.26 (d,  $J$  = 6.8 Hz, 3H, CH<sub>3</sub>) ppm. **<sup>19</sup>F NMR** (376 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = -75.65 (d,  $J$  = 7.3 Hz, CF<sub>3</sub>) ppm. **<sup>13</sup>C NMR** (101 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 151.34 (C<sub>q</sub>), 141.07 (C<sub>q</sub>), 127.01 (q,  $^1J$ (C,F) = 284.3 Hz, CF<sub>3</sub>), 114.44 (CH<sub>ar</sub>), 113.91 (CH<sub>ar</sub>), 55.25 (OCH<sub>3</sub>), 50.36 (q,  $^2J$ (C,F) = 29.0 Hz, CCF<sub>3</sub>), 14.44(CH<sub>3</sub>) ppm. **FT-IR** (ATR):  $\tilde{\nu}$  = 3386 (br, vw), 2942 (br, vw), 1511 (vs), 1457 (w), 1273 (w), 1232 (s), 1130 (vs), 1018 (s), 946 (w), 819 (s), 666 (m) cm<sup>-1</sup>. **HPLC-MS** (0.05 % formic acid; 0 min, 4 % B → 2.8 min, 100 % B, flow: 2.4 mL/min):  $t_R$  = 2.25 min,  $\lambda$  = 220 nm. **HR-ESI-MS** (positive, *m/z* calc. for C<sub>10</sub>H<sub>13</sub>F<sub>3</sub>NO<sup>+</sup> [MH]<sup>+</sup> 220.0944; found 220.0941.

#### Ethyl-*N*-(2,2,2-trifluoro-1-methylethyl)4-aminobenzoate **2e**

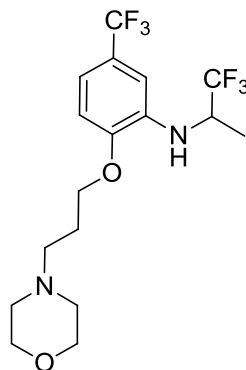


Following the general procedure, ethyl-*N*-(1-ethoxy-2,2,2-trifluoroethyl)-4-aminobenzoate **1e** (220 mg, 0.76 mmol) was reacted with MeMgBr (1.4 M in toluene/THF 3:1, 1.08 mL, 1.51 mmol) in dry THF (12 mL). The desired amine **2e** (186 mg, 94 %) was isolated after workup as a yellow solid without further purification.

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 7.72 (d,  $J$  = 8.8 Hz, 2H, 2 × H<sub>ar</sub>), 6.79 (m, 3H, NH ; 2 × H<sub>ar</sub>), 4.58 – 4.40 (m, 1H, CH), 4.22 (q,  $J$  = 7.1 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 1.32 (d,  $J$  = 6.7 Hz, 3H, CHCH<sub>3</sub>), 1.27 (t,  $J$  = 7.1 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>) ppm. **<sup>19</sup>F NMR** (376 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = -75.76 (d,  $^3J$ (F,H) = 7.1 Hz, CF<sub>3</sub>) ppm. **<sup>13</sup>C NMR** (101 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 165.63 (COOEt), 151.29 (C1), 130.75 (C3; C5), 124.07 (q,  $^1J$ (C,F) = 284.8 Hz, CF<sub>3</sub>), 117.68 (C4), 111.74 (C2; C6), 59.65 (CH<sub>2</sub>), 48.78 (q,  $^2J$ (C,F) = 29.7 Hz, CCF<sub>3</sub>), 14.25 (CH<sub>3</sub>), 14.17 (CH<sub>3</sub>) ppm. **FT-IR** (ATR):  $\tilde{\nu}$  = 2251 (m), 2976 (br, vw), 1684 (s), 1601 (s), 1265 (w), 1286 (s), 1251 (vs), 1148 (vs), 1124 (s), 1097 (s), 1015 (s), 847 (m), 769 (vs), 700 (s) cm<sup>-1</sup>. **HPLC-MS** (0.05 % formic acid; 0 min: 4 % B → 2.8 min: 100 % B, flow: 2.4 mL/min):

$t_R = 2.35$  min,  $\lambda = 220$  nm. **m.p.** 86 °C. **HR-ESI-MS** (positive, m/z) calc. for  $C_{12}H_{15}F_3NO_2^+$   $[MH]^+$  262.1049; found 262.1049.

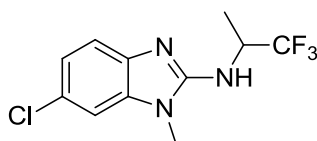
### 2-(3-Morpholinopropoxy)-5-(trifluoromethyl)-*N*-(2,2,2-trifluoro-1-methylethyl)aniline **2f**



According to the general procedure, 2-(3-morpholinopropoxy)-5-(trifluoromethyl)-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1f** (184 mg, 0.43 mmol) was reacted with MeMgBr (1.4 M in toluene/THF 3:1, 1.08 mL, 0.86 mmol) in dry THF (12 mL). The crude product was purified by flash chromatography ( $CH_2Cl_2 \rightarrow CH_2Cl_2/MeOH$  85/15) to give the desired amine **2f** (97 mg, 57 %) as a yellow liquid.

**$^1H$  NMR** (400 MHz, DMSO- $d_6$ ):  $\delta = 7.08$  (s, 1H, H<sub>6</sub>), 7.04 – 6.95 (m, 2H, H<sub>3</sub>; H<sub>4</sub>), 5.05 (d,  $J = 9.5$  Hz, 1H, NH), 4.66 – 4.53 (m, 1H, CH), 4.15 – 4.10 (m, 2H, CH<sub>2</sub>), 3.58 – 3.55 (m, 4H, 2 × CH<sub>2</sub>), 2.42 (t,  $J = 7.1$  Hz, 2H, CH<sub>2</sub>), 2.39 – 2.32 (m, 4H, 2 × CH<sub>2</sub>), 1.97 – 1.87 (m, 2H, CH<sub>2</sub>), 1.36 (d,  $J = 6.7$  Hz, 3H, CH<sub>3</sub>) ppm.  **$^{19}F$  NMR** (377 MHz, DMSO- $d_6$ ):  $\delta = -59.89$  (CF<sub>3</sub>), -75.75 (d,  $J = 7.3$  Hz, CHCF<sub>3</sub>) ppm.  **$^{13}C$  NMR** (101 MHz, DMSO- $d_6$ ):  $\delta = 148.25$  (C<sub>q</sub>), 136.56 (C<sub>q</sub>), 126.73 (CF<sub>3</sub>), 124.68 (CF<sub>3</sub>), 121.48 (CH<sub>ar</sub>), 114.44 (CCF<sub>3</sub>), 111.03 (CH<sub>ar</sub>), 107.02 (CH<sub>ar</sub>), 66.77 (CH<sub>2</sub>), 66.13 (CH<sub>2</sub>), 54.71 (CH<sub>2</sub>), 53.31 (CH<sub>2</sub>), 49.24 (CHCF<sub>3</sub>), 25.47 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 14.44 (CH<sub>3</sub>) ppm. **FT-IR** (ATR):  $\tilde{\nu} = 3420$  (br, vw), 2956 (br, vw), 1606 (w), 1532 (w), 1447 (m), 1328 (w), 1256 (m), 1109 (vs), 960 (w), 861 (m), 874 (w)  $cm^{-1}$ . **HPLC-MS** (0.05 % formic acid; 0 min: 4 % B  $\rightarrow$  2.8 min: 100 % B, flow: 2.4 mL/min):  $t_R = 1.73$  min,  $\lambda = 220$  nm. **HR-ESI-MS** (positive, m/z) calc. for  $C_{17}H_{23}F_6N_2O_2^+$   $[MH]^+$  401.1658; found 401.1657.

### (6-Chloro-1-methyl-1H-benzimidazol-2-yl)-(2,2,2-trifluoro-1-methylethyl)amine **2g**

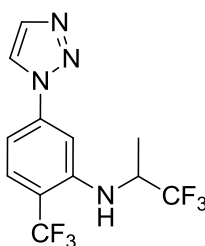


According to the general procedure, (6-chloro-1-methyl-1H-benzimidazol-2-yl)-(1-ethoxy-2,2,2-trifluoroethyl)amine **1g** (32 mg, 0.07 mmol) was reacted with MeMgBr (1.4 M in toluene/THF 3:1,

0.10 mL, 0.15 mmol) in dry THF (5 mL). The crude product was purified by flash chromatography (cyclohexane → cyclohexane/CH<sub>2</sub>Cl<sub>2</sub> 70/30) to give the desired amine **2g** (14 mg, 69 %) as a light yellow liquid.

**<sup>1</sup>H NMR** (400 MHz, DMSO-d<sub>6</sub>): δ = 7.32 (d, *J* = 2.0 Hz, 1H, H<sub>ar</sub>), 7.20 (dd, *J* = 8.4, 2.6 Hz, 2H, NH; H<sub>ar</sub>), 6.99 (dd, *J* = 8.3, 2.1 Hz, 1H, H<sub>ar</sub>), 4.86 (dp, *J* = 15.1, 7.5 Hz, 1H, CH), 3.55 (s, 3H, NCH<sub>3</sub>), 1.41 (d, *J* = 7.0 Hz, 3H, CH<sub>3</sub>) ppm. **<sup>19</sup>F NMR** (376 MHz, DMSO-d<sub>6</sub>): δ = -75.96 (d, *J* = 7.9 Hz, 1H, CF<sub>3</sub>) ppm. **<sup>13</sup>C NMR** (101 MHz, DMSO-d<sub>6</sub>): δ = 154.61 (C<sub>q</sub>), 140.54 (C<sub>q</sub>), 136.22 (C<sub>q</sub>), 126.16 (q, <sup>1</sup>*J* (C,F) = 282.4 Hz, CF<sub>3</sub>), 124.75 (C<sub>q</sub>), 120.44 (CH<sub>ar</sub>), 116.19 (CH<sub>ar</sub>), 107.99 (CH<sub>ar</sub>), 49.66 (q, <sup>2</sup>*J* (C,F) = 30.8, CCF<sub>3</sub>), 28.63 (NCH<sub>3</sub>), 13.88 (CH<sub>3</sub>) ppm. **FT-IR** (ATR):  $\tilde{\nu}$  = 3064 (br, w), 1707 (w), 1597 (m), 1563 (m), 1453 (m), 1265 (s), 1135 (vs), 1058 (m), 916 (w), 807 (m), 670 (w) cm<sup>-1</sup>. **HPLC-MS** (0.05 % formic acid; 0 min: 4 % B → 2.8 min: 100 % B, flow: 2.4 mL/min): *t*<sub>R</sub> = 1.47 min, λ = 220 nm. **HR-ESI-MS** (positive, *m/z*) calc. for C<sub>11</sub>H<sub>12</sub>ClF<sub>3</sub>N<sub>3</sub> [MH]<sup>+</sup> 278.0666; found 278.0668.

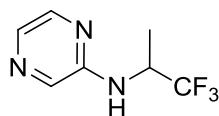
### 5-(1,2,3-Triazol-1-yl)-2-(trifluoromethyl)-*N*-(2,2,2-trifluoro-1-methylethyl)aniline **2h**



According to the general procedure, 2-(1,2,3-triazol-1-yl)-5-(trifluoromethyl)-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1h** (175 mg, 0.49 mmol) was reacted with MeMgBr (1.4 M in toluene/THF 3:1, 0.71 mL, 0.99 mmol) in dry THF (12 mL). The desired amine **2h** (154 mg, 96 %) was isolated after workup as a yellow solid without further purification.

**<sup>1</sup>H NMR** (400 MHz, DMSO-d<sub>6</sub>): δ = 8.61 (d, *J* = 1.1 Hz, 1H, H<sub>triazole</sub>), 8.05 (d, *J* = 1.1 Hz, 1H, H<sub>triazole</sub>), 7.62 – 7.56 (m, 1H, H<sub>3</sub>), 7.52 (s, 1H, H<sub>6</sub>), 7.18 (dd, *J* = 8.3, 1.3 Hz, 1H, H<sub>4</sub>), 6.24 (d, *J* = 9.3 Hz, 1H, NH), 4.85 – 4.74 (m, 1H, CH), 1.32 (d, *J* = 6.7 Hz, 3H, CH<sub>3</sub>). **<sup>19</sup>F NMR** (376 MHz, DMSO-d<sub>6</sub>): δ = -61.41 (CF<sub>3</sub>), -75.85 (d, *J* = 7.0 Hz, CHCF<sub>3</sub>) ppm. **<sup>13</sup>C NMR** (101 MHz, DMSO-d<sub>6</sub>): δ = 140.77 (C<sub>q</sub>), 133.97 (CH<sub>ar</sub>), 130.59 (q, <sup>2</sup>*J*(C,F) = 32.0 Hz, CCF<sub>3</sub>), 126.45 (CH<sub>ar</sub>), 126.41 (q, <sup>1</sup>*J* (C,F) = 283.6 Hz, HCCF<sub>3</sub>), 126.27 (CH<sub>ar</sub>), 125.41 (C<sub>q</sub>), 123.78 (q, <sup>1</sup>*J* (C,F) = 272.6 Hz, CF<sub>3</sub>), 113.96 (CH<sub>ar</sub>), 110.63 (CH<sub>ar</sub>), 49.21 (q, <sup>2</sup>*J*(C,F) = 29.7 Hz, HCCF<sub>3</sub>), 14.15 (CH<sub>3</sub>) ppm. **FT-IR** (ATR):  $\tilde{\nu}$  = 3282 (br, vw), 3155 (vw), 1620 (w), 1597 (w), 1448 (m), 1345 (m), 1285 (m), 1166 (m), 1125 (vs), 1092 (vs), 979 (s), 858 (m), 815 (s), 781 (m), 668 (m) cm<sup>-1</sup>. **HPLC-MS** (0.05 % formic acid; 0 min: 4 % B → 2.8 min: 100 % B, flow: 2.4 mL/min): *t*<sub>R</sub> = 2.40 min, λ = 220 nm. **m.p.** 83 °C. **HR-ESI-MS** (positive, *m/z*) calc. for C<sub>12</sub>H<sub>11</sub>F<sub>6</sub>N<sub>4</sub><sup>+</sup> [MH]<sup>+</sup> 325.0882; found 325.0886.

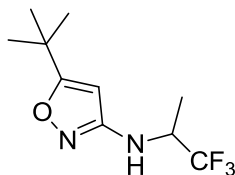
### ***N*-(2,2,2-Trifluoro-1-methylethyl)aminopyrazine 2i**



Following the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyrazine **1i** (50 mg, 0.23 mmol) was reacted with MeMgBr (1.4 M in toluene/THF 3:1, 0.32 mL, 0.45 mmol) in dry THF (5 mL). The crude product was purified by flash chromatography (cyclohexane/EtOAc 4/1) to give the desired amine **2i** (35 mg, 80 %) as a white solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.02 (dd,  $J$  = 2.7, 1.5 Hz, 1H, H<sub>6</sub>), 7.96 (d,  $J$  = 1.4 Hz, 1H, H<sub>3</sub>), 7.90 (d,  $J$  = 2.7 Hz, 1H, H<sub>5</sub>), 4.88 (m, 1H, CH), 4.57 (d,  $J$  = 8.9 Hz, 1H, NH), 1.42 (dd,  $J$  = 6.9, 0.6 Hz, 3H, CH<sub>3</sub>) ppm. **<sup>19</sup>F NMR** (282 MHz, CDCl<sub>3</sub>):  $\delta$  = -77.67 (d,  $J$  = 7.3 Hz, CHCF<sub>3</sub>) ppm. **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 152.86 (C1), 141.60 (C6), 134.27 (C5), 132.72 (C3), 125.80 (q,  $^1J$  (C,F) = 281.9 Hz, CF<sub>3</sub>), 47.46 (q,  $^2J$  (C,F) = 31.2 Hz, CCF<sub>3</sub>), 14.76 (CH<sub>3</sub>) ppm. **FT-IR** (ATR):  $\tilde{\nu}$  = 3256 (w), 3057 (w), 1601 (m), 1521 (s), 1457 (m), 1398 (m), 1268 (s), 1163 (s), 1135 (vs), 1096 (s), 1023 (s), 1000 (m), 825 (s) cm<sup>-1</sup>. **HPLC** (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B. flow: 1 mL/min):  $t_R$  = 10.95 min,  $\lambda$  = 214 nm. **m.p.** 81 °C. **HR-ESI-MS** (positive,  $m/z$ ) calc. for C<sub>7</sub>H<sub>9</sub>F<sub>3</sub>N<sub>3</sub><sup>+</sup> [MH]<sup>+</sup> 192.0743; found 192.0742.

### **5-(*tert*-Butyl)-*N*-(2,2,2-trifluoro-1-methylethyl)isoxazol-3-amine 2j**



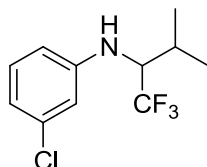
According to the general procedure, 5-(*tert*-butyl)-*N*-(1-ethoxy-2,2,2-trifluoroethyl)isoxazol-3-amine **1j** (100 mg, 0.38 mmol) was reacted with MeMgBr (1.4 M in toluene/THF 3:1, 0.54 mL, 0.76 mmol) in dry THF (6 mL). The crude product was purified by flash chromatography (cyclohexane/EtOAc 4/1) to give the desired amine **2j** (66 mg, 74 %) as a white solid.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 5.48 (s, 1H, H<sub>ar</sub>), 4.19 (m, 1H, CHCH<sub>3</sub>), 3.90 (s, 1H, NH), 1.40 (d,  $J$  = 6.9 Hz, 3H, CHCH<sub>3</sub>), 1.30 (s, 9H, 3 × CH<sub>3</sub>) ppm. **<sup>19</sup>F NMR** (282 MHz, CDCl<sub>3</sub>):  $\delta$  = -78.10 (d,  $J$  = 6.9 Hz, CF<sub>3</sub>) ppm. **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 181.24 (-HCCO-), 162.87 (-HCCN-), 125.67 (d,  $^1J$  (C,F) = 280.7 Hz, CF<sub>3</sub>), 89.75 (-CCHC-), 51.34 (q,  $^2J$  (C,F) = 31.1 Hz, CCF<sub>3</sub>), 32.77 ((CH<sub>3</sub>)<sub>3</sub>C), 28.60 (3 × CH<sub>3</sub>), 14.92 (CH<sub>3</sub>) ppm. **FT-IR** (ATR):  $\tilde{\nu}$  = 3297 (br, w), 2970 (w), 1612 (m), 1551 (m), 1459 (m), 1265 (m), 1183 (m), 1135 (vs), 1016 (m), 981 (m), 781 (m) cm<sup>-1</sup>. **HPLC** (0.1 % TFA,



0 min: 4 % B → 15 min: 100 % B. flow: 1 mL/min):  $t_R = 14.633$  min,  $\lambda = 214$  nm. **m.p.** 98 °C. **HR-ESI-MS** (positive, m/z) calc. for  $C_{10}H_{16}F_3N_2O^+$   $[MH]^+$  237.1209; found 237.1208.

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



#### Reaction with *i*PrMgCl:

Following the general procedure, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** (200 mg, 0.79 mmol) was reacted with *i*PrMgBr (1.0 M in THF, 1.58 mL, 1.58 mmol) in dry THF (12 mL). The crude product was purified by flash chromatography (cyclohexane → cyclohexane/CH<sub>2</sub>Cl<sub>2</sub> 20/1) to give the desired amine **3a** (139 mg, 70 %) as a light yellow liquid together with the side product 3-chloro-*N*-2,2,2-trifluoroethyl)aniline **4** (26 mg, 16 %, light yellow liquid).

#### Reaction with *i*PrMgCl·LiCl:

According to the general procedure, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** (165 mg, 0.65 mmol) was reacted with *i*PrMgBr·LiCl (1.1 M in THF, 1.18 mL, 1.30 mmol) in dry THF (8 mL). The crude product was purified by flash chromatography (cyclohexane → cyclohexane/EtOAc 40/1) to give the desired amine **3a** (112 mg, 68 %) as a light yellow liquid together with the side product 3-chloro-*N*-2,2,2-trifluoroethyl)aniline **4** (40 mg, 30 %, light yellow liquid).

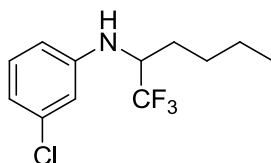
**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta = 7.07$  (t,  $J = 8.1$  Hz, 1H, H5), 6.88 (t,  $J = 2.1$  Hz, 1H, H2), 6.76 (dd,  $J = 8.1, 2.0$  Hz, 1H, H6), 6.58 (ddd,  $J = 7.8, 1.9, 0.7$  Hz, 1H, H4), 6.08 (d,  $J = 10.1$  Hz, 1H, NH), 4.29 – 4.09 (m, 1H, NHCH), 2.16 – 2.00 (m, 1H, CH), 0.98 (t,  $J = 6.1$  Hz, 6H, 2 × CH<sub>3</sub>) ppm. **<sup>19</sup>F NMR** (377 MHz, DMSO-*d*<sub>6</sub>):  $\delta = -70.57$  (d,  $J = 8.4$  Hz, CF<sub>3</sub>) ppm. **<sup>13</sup>C NMR** (101 MHz, DMSO-*d*<sub>6</sub>):  $\delta = 149.82$  (C1), 133.60 (C3), 130.29 (C5), 126.59 (q,  $^1J$  (C,F) = 285.6 Hz, CF<sub>3</sub>), 116.05 (C4), 111.92 (C2), 111.12 (C6), 57.63 (q,  $^2J$ (C,F) = 26.9 Hz, CCF<sub>3</sub>), 28.15 (CH), 19.40 (CH<sub>3</sub>), 17.48 (CH<sub>3</sub>) ppm. **FT-IR** (ATR):  $\tilde{\nu} = 3429$  (br, vw), 2969 (w), 1597 (s), 1509 (m), 1483 (m), 1261 (m), 1135 (vs), 1079 (s), 990 (m), 842 (br,m), 763 (m), 679 (s) cm<sup>-1</sup>. **HPLC-MS** (0.05 % formic acid; 0 min: 4 % B → 2.8 min: 100 % B, flow: 2.4 mL/min):  $t_R = 2.70$  min,  $\lambda = 220$  nm. **HR-ESI-MS** (positive, m/z) calc. for  $C_{11}H_{14}ClF_3N^+$   $[MH]^+$  252.0761; found 252.0761.

### 3-Chloro-*N*-(2,2,2-trifluoroethyl)aniline **4**

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta = 7.10$  (t,  $J = 8.1$  Hz, 1H, H5), 6.78 (t,  $J = 2.1$  Hz, 1H, H2), 6.68 (dd,  $J = 8.1, 2.0$  Hz, 1H, H6), 6.62 (ddd,  $J = 7.8, 2.0, 0.8$  Hz, 1H, H4), 6.49 (t,  $J = 6.9$  Hz, 1H, NH),

3.95 (qd,  $J = 9.7, 7.0$  Hz, 2H, CH<sub>2</sub>) ppm. **<sup>19</sup>F NMR** (377 MHz, DMSO-d<sub>6</sub>):  $\delta = -70.61$  (t,  $J = 9.5$  Hz, CF<sub>3</sub>) ppm. **<sup>13</sup>C NMR** (101 MHz, DMSO-d<sub>6</sub>):  $\delta = 149.06$  (C1), 133.62 (C3), 130.37 (C5), 125.71 (q,  $^1J$  (C,F) = 281.1 Hz, CF<sub>3</sub>), 116.46 (C4), 111.69 (C2), 111.13 (C6), 43.65 (q,  $^2J$ (C,F) = 32.3, CCF<sub>3</sub>) ppm. **HPLC-MS** (0.05 % formic acid; 0 min: 4 % B → 2.8 min: 100 % B, flow: 2.4 mL/min):  $t_R = 2.24$  min,  $\lambda = 220$  nm. **HR-ESI-MS** (positive, m/z) calc. for C<sub>8</sub>H<sub>8</sub>ClF<sub>3</sub>N<sup>+</sup> [MH]<sup>+</sup> 210.0292; found 210.0291.

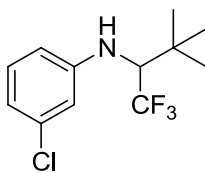
### 3-Chloro-*N*-(2,2,2-trifluoro-1-butylethyl)aniline **3b**



According to the general procedure, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** (200 mg, 0.79 mmol) was reacted with *n*BuMgBr (2.0 M in Et<sub>2</sub>O, 0.79 mL, 1.58 mmol) in dry THF (12 mL). The desired amine **3b** (197 mg, 94 %) was isolated after workup without further purification as a light yellow liquid.

**<sup>1</sup>H NMR** (400 MHz, DMSO-d<sub>6</sub>):  $\delta = 7.08$  (t,  $J = 8.1$  Hz, 1H, H5), 6.80 (t,  $J = 2.1$  Hz, 1H, H2), 6.70 (dd,  $J = 8.3, 1.8$  Hz, 1H, H6), 6.59 (ddd,  $J = 7.8, 1.9, 0.7$  Hz, 1H, H4), 6.20 (d,  $J = 9.1$  Hz, 1H, NH), 4.26 – 4.12 (m, 1H, CH), 1.76 – 1.64 (m, 1H, CH<sub>2</sub>), 1.62 – 1.49 (m, 1H, CH<sub>2</sub>), 1.47 – 1.21 (m, 4H, 2 × CH<sub>2</sub>), 0.85 (t,  $J = 7.1$  Hz, 3H, CH<sub>3</sub>) ppm. **<sup>19</sup>F NMR** (377 MHz, DMSO-d<sub>6</sub>):  $\delta = -74.78$  (d,  $J = 7.4$  Hz, CF<sub>3</sub>) ppm. **<sup>13</sup>C NMR** (101 MHz, DMSO-d<sub>6</sub>):  $\delta = 149.48$  (C1), 133.61 (C3), 130.35 (C5), 126.63 (q,  $^1J$  (C,F) = 284.4 Hz, CF<sub>3</sub>), 116.08 (C4), 111.67 (C2), 111.04 (C6), 53.40 (q,  $^2J$ (C,F) = 28.4 Hz, CCF<sub>3</sub>), 27.80 (CH<sub>2</sub>), 26.99 (CH<sub>2</sub>), 21.70 (CH<sub>2</sub>), 13.70 (CH<sub>3</sub>) ppm. **FT-IR** (ATR):  $\tilde{\nu} = 3420$  (br, vw), 2959 (w), 2932 (w), 1598 (s), 1509 (m), 1483 (m), 1250 (m), 1167 (m), 1130 (vs), 1088 (s), 990 (m), 764 (m), 679 (s) cm<sup>-1</sup>. **HPLC-MS** (0.05 % formic acid; 0 min: 4 % B → 2.8 min: 100 % B, flow: 2.4 mL/min):  $t_R = 2.87$  min,  $\lambda = 220$  nm. **HR-ESI-MS** (positive, m/z) calc. for C<sub>12</sub>H<sub>16</sub>ClF<sub>3</sub>N<sup>+</sup> [MH]<sup>+</sup> 266.0918; found 266.0918.

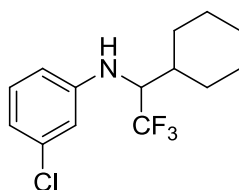
### 3-Chloro-*N*-(2,2,2-trifluoro-1-*tert*-butylethyl)aniline **3c**



Following the general procedure, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** (200 mg, 0.79 mmol) was reacted with *tert*-BuMgBr (2.0 M in Et<sub>2</sub>O, 0.79 mL, 1.58 mmol) in dry THF (12 mL). The reaction time was 3 h. The crude product was purified by flash chromatography (cyclohexane → cyclohexane/CH<sub>2</sub>Cl<sub>2</sub> 20/1) to give the desired amine **3c** (120 mg, 57 %) as a light yellow liquid.

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 7.07 (t,  $J$  = 8.1 Hz, 1H, H5), 6.94 (t,  $J$  = 2.1 Hz, 1H, H2), 6.82 (dd,  $J$  = 8.3, 1.8 Hz, 1H, H6), 6.57 (ddd,  $J$  = 7.8, 1.9, 0.7 Hz, 1H, H4), 6.07 (d,  $J$  = 10.7 Hz, 1H, NH), 4.22 – 4.04 (m, 1H, CH), 1.05 (s, 9H, 3 × CH<sub>3</sub>) ppm. **<sup>19</sup>F NMR** (377 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = -66.68 (d,  $J$  = 8.6 Hz, CF<sub>3</sub>) ppm. **<sup>13</sup>C NMR** (101 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 150.02 (C1), 133.60 (C3), 130.28 (C5), 126.94 (q,  $^1J$ (C,F) = 286.8 Hz, CF<sub>3</sub>), 115.98 (C4), 111.94 (C2), 111.18 (C6), 60.37 (q,  $^2J$ (C,F) = 25.7 Hz, CCF<sub>3</sub>), 34.41 (C<sub>q</sub>), 26.74 (3 × CH<sub>3</sub>) ppm. **FT-IR** (ATR):  $\tilde{\nu}$  = 3433 (br, vw), 2967 (w), 1698 (br, w), 1599 (s), 1510 (m), 1481 (m), 1251 (m), 1156 (s), 1106 (vs), 990 (m), 762 (m), 679 (s) cm<sup>-1</sup>. **HPLC-MS** (0.05 % formic acid; 0 min: 4 % B → 2.8 min: 100 % B, flow: 2.4 mL/min):  $t_R$  = 2.63 min,  $\lambda$  = 220 nm. **HR-ESI-MS** (positive, *m/z*) calc. for C<sub>12</sub>H<sub>16</sub>ClF<sub>3</sub>N<sup>+</sup> [MH]<sup>+</sup> 266.0918; found 266.0912.

### 3-Chloro-*N*-(2,2,2-trifluoro-1-cyclohexylethyl)aniline **3d**

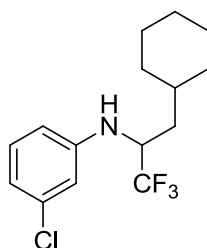


Following the general procedure, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** (177 mg, 0.70 mmol) was reacted with cyclohexylmagnesium bromide (1.0 M in THF, 1.40 mL, 1.40 mmol) in dry THF (12 mL). The crude product was purified by flash chromatography (cyclohexane → cyclohexane/CH<sub>2</sub>Cl<sub>2</sub> 20/1) to give the desired amine **3d** (159 mg, 78 %) as a light yellow oil.

**<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 7.06 (t,  $J$  = 8.1 Hz, 1H, H5), 6.84 (t,  $J$  = 2.1 Hz, 1H, H2), 6.73 (dd,  $J$  = 8.3, 1.8 Hz, 1H, H6), 6.57 (ddd,  $J$  = 7.9, 1.9, 0.7 Hz, 1H, H4), 6.08 (d,  $J$  = 10.1 Hz, 1H, NH), 4.19 – 4.05 (m, 1H, CH), 1.81 – 1.55 (m, 6H, CH<sub>2</sub>), 1.25 – 1.04 (m, 5H, CH; CH<sub>2</sub>) ppm. **<sup>19</sup>F NMR** (376 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = -70.05 (d,  $J$  = 8.4 Hz, CF<sub>3</sub>) ppm. **<sup>13</sup>C NMR** (101 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 149.79 (C1), 133.60 (C3), 130.33 (C5), 126.54 (q,  $^1J$ (C,F) = 285.6 Hz, CF<sub>3</sub>), 116.03 (C4), 111.84

(C2), 111.03 (C6), 57.45 (q,  $^2J(\text{C},\text{F}) = 27.0$  Hz,  $\text{CCF}_3$ ), 37.89 (CH), 28.96 ( $\text{CH}_2$ ), 27.19 ( $\text{CH}_2$ ), 25.50 ( $\text{CH}_2$ ), 25.45 ( $\text{CH}_2$ ), 25.36 ( $\text{CH}_2$ ) ppm. **FT-IR** (ATR):  $\tilde{\nu} = 3425$  (br, w), 2923 (m), 2855 (w), 1597 (vs), 1510 (m), 1264 (m), 1238 (s), 1146 (vs), 1119 (vs), 1093 (m), 990 (m), 835 (m), 761 (s), 679 (vs)  $\text{cm}^{-1}$ . **HPLC-MS** (0.05 % formic acid; 0 min: 4 % B  $\rightarrow$  2.8 min: 100 % B, flow: 2.4 mL/min):  $t_R = 2.96$  min,  $\lambda = 220$  nm. **HR-ESI-MS** (positive, m/z) calc. for  $\text{C}_{14}\text{H}_{18}\text{ClF}_3\text{N}^+$   $[\text{MH}]^+$  292.1074; found 292.1071.

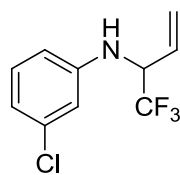
### 3-Chloro-*N*-(2,2,2-trifluoro-1-methylcyclohexylethyl)aniline **3e**



Following the general procedure, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** (200 mg, 0.79 mmol) was reacted with cyclohexylmethylmagnesium bromide (0.5 M in  $\text{Et}_2\text{O}$ , 3.16 mL, 1.58 mmol) in dry THF (12 mL). The crude product was purified by flash chromatography (cyclohexane  $\rightarrow$  cyclohexane/ $\text{CH}_2\text{Cl}_2$  3/2) to give the desired amine **3e** (62 mg, 26 %) as a colorless oil together with the side product 3-chloro-*N*-2,2,2-trifluoroethyl)aniline **4** (32 mg, 19 %, light yellow liquid).

**$^1\text{H}$  NMR** (400 MHz,  $\text{DMSO-d}_6$ ):  $\delta = 7.08$  (t,  $J = 8.1$  Hz, 1H, H5), 6.81 (t,  $J = 2.1$  Hz, 1H, H2), 6.71 (dd,  $J = 8.2, 1.8$  Hz, 1H, H6), 6.58 (ddd,  $J = 7.8, 1.9, 0.7$  Hz, 1H, H4), 6.21 (d,  $J = 9.0$  Hz, 1H, NH), 4.33 – 4.19 (m, 1H, NHCH), 1.74 – 1.34 (m, 8H,  $4 \times \text{CH}_2$ ), 1.26 – 0.93 (m, 4H,  $2 \times \text{CH}_2$ ), 0.92 – 0.78 (m, 1H, CH) ppm.  **$^{19}\text{F}$  NMR** (377 MHz,  $\text{DMSO-d}_6$ ):  $\delta = -74.91$  (d,  $J = 9.0$  Hz,  $\text{CF}_3$ ) ppm.  **$^{13}\text{C}$  NMR** (101 MHz,  $\text{DMSO-d}_6$ ):  $\delta = 149.26$  (C1), 133.62 (C3), 130.40 (C5), 126.84 (q,  $^1J(\text{C},\text{F}) = 284.6$  Hz,  $\text{CF}_3$ ), 116.08 (C4), 111.61 (C2), 110.90 (C6), 51.12 (q,  $^2J(\text{C},\text{F}) = 28.4$  Hz,  $\text{CCF}_3$ ), 35.29 ( $\text{CH}_2$ ), 33.32 ( $\text{CH}_2$ ), 32.95 (CH), 31.35 ( $\text{CH}_2$ ), 25.87 ( $\text{CH}_2$ ), 25.70 ( $\text{CH}_2$ ), 25.39 ( $\text{CH}_2$ ) ppm. **FT-IR** (ATR):  $\tilde{\nu} = 3421$  (br, vw), 2922 (m), 2852 (w), 1598 (vs), 1509 (m), 1449 (m), 1254 (s), 1150 (s), 1122 (vs), 1091 (s), 990 (m), 844 (br,m), 763 (m), 679 (s)  $\text{cm}^{-1}$ . **HPLC-MS** (0.05 % formic acid; 0 min: 4 % B  $\rightarrow$  2.8 min: 100 % B, flow: 2.4 mL/min):  $t_R = 2.83$  min,  $\lambda = 220$  nm. **HR-ESI-MS** (positive, m/z) calc. for  $\text{C}_{15}\text{H}_{20}\text{ClF}_3\text{N}^+$   $[\text{MH}]^+$  306.1231; found 306.1228.

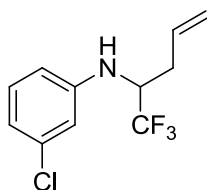
### 3-Chloro-*N*-(2,2,2-trifluoro-1-vinylethyl)aniline **3f**



Following the general procedure, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** (229 mg, 0.90 mmol) was reacted with vinylmagnesium bromide (1.0 M in THF, 1.81 mL, 1.81 mmol) in dry THF (12 mL). The crude product was purified by flash chromatography (cyclohexane → cyclohexane/CH<sub>2</sub>Cl<sub>2</sub> 4/1) to give the desired amine **3f** (131 mg, 62 %) as a colorless oil.

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ = 7.11 (t, *J* = 8.1 Hz, 1H, H5), 6.87 (t, *J* = 2.1 Hz, 1H, H2), 6.77 (dd, *J* = 8.0, 2.0 Hz, 1H, H6), 6.64 (ddd, *J* = 7.8, 2.0, 0.8 Hz, 1H, H4), 6.48 (d, *J* = 9.7 Hz, 1H, NH), 5.86 (ddd, *J* = 16.8, 10.4, 6.2 Hz, 1H, CH<sub>2</sub>=CH), 5.56 (d, *J* = 17.1 Hz, 1H, HCH<sub>trans</sub>=CH), 5.43 (d, *J* = 10.4 Hz, 1H, HCH<sub>cis</sub>=CH), 5.10 – 4.97 (m, 1H, CH) ppm. <sup>19</sup>F NMR (377 MHz, DMSO-d<sub>6</sub>): δ = -73.77 (d, *J* = 7.7 Hz, CF<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-d<sub>6</sub>): δ = 148.36 (C1), 133.62 (C3), 130.36 (C5), 129.80 (CH<sub>2</sub>=CH), 125.52 (q, <sup>1</sup>*J*(C,F) = 283.4 Hz, CF<sub>3</sub>), 120.83 (CH<sub>2</sub>=CH), 116.70 (C4), 112.31 (C2), 111.71 (C6), 55.83 (q, <sup>2</sup>*J*(C,F) = 29.4 Hz, CCF<sub>3</sub>) ppm. FT-IR (ATR):  $\tilde{\nu}$  = 3417 (br, vw), 3029 (br, vw), 1597 (s), 1482 (m), 1250 (m), 1156 (s), 1114 (vs), 991 (m), 941 (m), 847 (m), 764 (s), 679 (s) cm<sup>-1</sup>. HPLC-MS (0.05 % formic acid; 0 min: 4 % B → 2.8 min: 100 % B, flow: 2.4 mL/min): *t*<sub>R</sub> = 2.53 min, λ = 220 nm. HR-ESI-MS (positive, *m/z*) calc. for C<sub>10</sub>H<sub>10</sub>ClF<sub>3</sub>N<sup>+</sup> [MH]<sup>+</sup> 236.0448; found 236.0452.

### 3-Chloro-*N*-(2,2,2-trifluoro-1-allylethyl)aniline **3g**

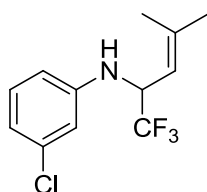


According to the general procedure, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** (230 mg, 0.91 mmol) was reacted with allylmagnesium bromide (1.0 M in MeTHF, 1.81 mL, 1.81 mmol) in dry THF (12 mL). The crude product was purified by flash chromatography (cyclohexane → cyclohexane/CH<sub>2</sub>Cl<sub>2</sub> 4/1) to give the desired amine **3g** (191 mg, 84 %) as a colorless oil.

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ = 7.07 (t, *J* = 8.1 Hz, 1H, H5), 6.79 (t, *J* = 2.1 Hz, 1H, H2), 6.69 (dd, *J* = 8.2, 1.8 Hz, 1H, H6), 6.61 – 6.57 (d, *J* = 8.0 Hz, 1, H4), 6.26 (d, *J* = 9.3 Hz, 1H, NH), 5.77 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H, H<sub>2</sub>C=CHCH<sub>2</sub>), 5.17 (dd, *J* = 17.2, 1.7 Hz, 1H, HCH<sub>trans</sub>=CH), 5.09 – 5.04 (dd, *J* = 10.2, 1.7 Hz, 1H, HCH<sub>cis</sub>=CH), 4.35 (tqd, *J* = 11.0, 7.4, 3.9 Hz, 1H, CH), 2.55 – 2.45 (m,

1H, CH<sub>2</sub>) 2.40 – 2.28 (m, 1H, CH<sub>2</sub>) ppm. <sup>19</sup>F NMR (376 MHz, DMSO-d<sub>6</sub>): δ = -74.47 (d, *J* = 7.3 Hz, CF<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-d<sub>6</sub>): δ = 149.14 (C1), 133.60 (H<sub>2</sub>C=CH), 132.95 (C3), 130.35 (C5), 126.33 (q, <sup>1</sup>*J*(C,F) = 284.7 Hz, CF<sub>3</sub>), 118.24 (H<sub>2</sub>C=CH), 116.26 (C4), 111.81 (C2), 111.19 (C6), 53.17 (q, <sup>2</sup>*J*(C,F) = 28.4 Hz, CCF<sub>3</sub>), 32.53 (CH<sub>2</sub>) ppm. FT-IR (ATR):  $\tilde{\nu}$  = 3417 (br, vw), 1597 (vs), 1509 (m), 1482 (m), 1322 (w), 1275 (m), 1246 (s), 1122 (vs), 1093 (s), 991 (m), 844 (m), 764 (s), 679 (s) cm<sup>-1</sup>. HPLC-MS (0.05 % formic acid; 0 min: 4 % B → 2.8 min: 100 % B, flow: 2.4 mL/min): *t*<sub>R</sub> = 2.65 min, λ = 220 nm. HR-ESI-MS (positive, *m/z*) calc. for C<sub>12</sub>H<sub>14</sub>ClF<sub>3</sub>N<sup>+</sup> [MH]<sup>+</sup> 250.0605; found 250.0604.

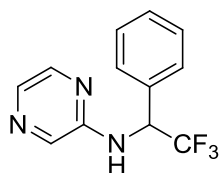
### 3-Chloro-*N*-(2,2,2-trifluoro-1-dimethylvinylethyl)aniline **3h**



According to the general procedure, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** (180 mg, 0.71 mmol) was reacted with 2-methyl-1-propenylmagnesium bromide (0.5 M in THF, 2.84 mL, 1.42 mmol) in dry THF (12 mL). The crude product was purified by flash chromatography (cyclohexane → cyclohexane/CH<sub>2</sub>Cl<sub>2</sub> 4/1) to give the desired amine **3h** (159 mg, 85 %) as a light yellow liquid.

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ = 7.09 (t, *J* = 8.05 Hz, 1H, H5), 6.87 (t, *J* = 2.1 Hz, 1H, C2), 6.75 (dd, *J* = 8.2, 1.9 Hz, 1H, H6), 6.61 (ddd, *J* = 5.6, 2.8, 2.2 Hz, 1H, H4), 6.31 (d, *J* = 8.6 Hz, 1H, NH), 5.16 (d, *J* = 8.6 Hz, 1H, HC=C(CH<sub>3</sub>)<sub>2</sub>), 4.98 – 4.87 (m, 1H, CH), 1.75 (d, *J* = 0.8 Hz, 3H, CH<sub>3</sub>), 1.73 (d, *J* = 0.7 Hz, 3H, CH<sub>3</sub>). <sup>19</sup>F NMR (376 MHz, DMSO-d<sub>6</sub>): δ = -74.16 (d, *J* = 7.2 Hz, CF<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-d<sub>6</sub>): δ = 148.46 (C1), 139.75 ((CH<sub>3</sub>)<sub>2</sub>C=CH), 133.59 (C3), 130.30 (C5), 126.22 (q, <sup>1</sup>*J*(C,F) = 284.8 Hz, CF<sub>3</sub>), 116.91 (C4 / (CH<sub>3</sub>)<sub>2</sub>C=CH), 116.42 (C4 / (CH<sub>3</sub>)<sub>2</sub>C=CH), 112.13 (C2), 111.43 (C6), 52.37 (q, <sup>2</sup>*J*(C,F) = 29.8 Hz, CCF<sub>3</sub>), 25.39 (CH<sub>3</sub>), 18.57 (CH<sub>3</sub>) ppm. FT-IR (ATR):  $\tilde{\nu}$  = 3417 (br, vw), 3029 (br, w), 1598 (m), 1482 (m), 1379 (w), 1164 (s), 1114 (vs), 990 (m), 866 (w), 764 (w), 680 (s) cm<sup>-1</sup>. HPLC-MS (0.05 % formic acid; 0 min: 4 % B → 2.8 min: 100 % B, flow: 2.4 mL/min): *t*<sub>R</sub> = 2.74 min, λ = 220 nm. HR-ESI-MS (positive, *m/z*) calc. for C<sub>12</sub>H<sub>14</sub>ClF<sub>3</sub>N<sup>+</sup> [MH]<sup>+</sup> 264.0761; found 264.0763.

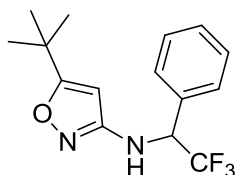
### *N*-(2,2,2-Trifluoro-1-phenylethyl)aminopyrazine **5**



According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyrazine **1i** (200 mg, 0.90 mmol) was reacted with PhMgBr (1.5 M in THF, 1.18 mL, 1.81 mmol) in dry THF (12 mL). The crude product was purified by flash chromatography (cyclohexane/EtOAc 10/1) to give the desired amine **5** (174 mg, 76 %) as yellow oil.

**<sup>1</sup>H NMR** (599 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.04 – 8.02 (m, 1H, H<sub>6</sub>), 8.01 (s, 1H, H<sub>3</sub>), 7.91 (d,  $J$  = 2.6 Hz, 1H, H<sub>5</sub>), 7.49 – 7.45 (m, 2H, 2 × H<sub>phenyl</sub>), 7.43 – 7.38 (m, 3H, 3 × H<sub>phenyl</sub>), 5.89 (p,  $J$  = 7.9 Hz, 1H, CH), 5.26 (d,  $J$  = 9.0 Hz, 1H, NH) ppm. **<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>):  $\delta$  = -73.81 (d,  $J$  = 7.8 Hz, CF<sub>3</sub>) ppm. **<sup>13</sup>C NMR** (151 MHz, CDCl<sub>3</sub>):  $\delta$  = 152.48 (C<sub>2</sub>), 141.61 (C<sub>6</sub>), 134.65 (C<sub>5</sub>), 133.53 (C<sub>1phenyl</sub>), 132.95 (C<sub>3</sub>), 129.20 (CH<sub>phenyl</sub>), 128.94 (CH<sub>phenyl</sub>), 127.86 (CH<sub>phenyl</sub>), 127.85 (CH<sub>phenyl</sub>), 124.91 (q,  $^1J$  (C,F) = 282.0 Hz, CF<sub>3</sub>), 55.64 (q,  $^2J$ (C,F) = 30.9 Hz, CCF<sub>3</sub>) ppm. **FT-IR** (ATR):  $\tilde{\nu}$  = 3258 (br, w), 3036 (w), 1594 (m), 1515 (s), 1396 (m), 1250 (s), 1168 (s), 1147 (s), 1114 (vs), 1003 (s), 825 (m), 696 (s) cm<sup>-1</sup>. **HPLC** (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B. flow: 1 mL/min):  $t_R$  = 13.48 min,  $\lambda$  = 214 nm. **HR-ESI-MS** (positive,  $m/z$ ) calc. for C<sub>12</sub>H<sub>11</sub>F<sub>3</sub>N<sub>3</sub><sup>+</sup> [MH]<sup>+</sup> 254.0900; found 254.0899.

### 5-(*tert*-Butyl)-*N*-(2,2,2-trifluoro-1-phenylethyl)isoxazol-3-amine **6**



Following the general procedure, 5-(*tert*-butyl)-*N*-(1-ethoxy-2,2,2-trifluoroethyl)isoxazol-3-amine **1j** (200 mg, 0.88 mmol) was reacted with PhMgBr (1.5 M in THF, 1.15 mL, 1.77 mmol) in dry THF (12 mL). The crude product was purified by flash chromatography (cyclohexane/EtOAc 10/1) to give the desired amine **6** (189 mg, 72 %) as a white solid.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.50 – 7.33 (m, 5H, 5 × H<sub>phenyl</sub>), 5.49 (s, 1H, H<sub>isoxazole</sub>), 5.25 – 5.09 (m, 1H, CH), 4.52 (d,  $J$  = 6.3 Hz, 1H, NH), 1.27 (d,  $J$  = 0.4 Hz, 9H, 3 × CH<sub>3</sub>) ppm. **<sup>19</sup>F NMR** (282 MHz, CDCl<sub>3</sub>):  $\delta$  = -74.37 (d,  $J$  = 7.6 Hz, CF<sub>3</sub>) ppm. **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 181.34 (-HCCO-), 162.55 (-HCCN-), 133.62 (C<sub>1phenyl</sub>), 129.19 (CH<sub>phenyl</sub>), 128.87 (CH<sub>phenyl</sub>), 127.78 (CH<sub>phenyl</sub>), 127.77 (CH<sub>phenyl</sub>), 124.71 (d,  $^1J$  (C,F) = 281.8 Hz, CF<sub>3</sub>), 89.95 (-CCHC-), 59.44 (q,  $^2J$ (C,F) = 31.0 Hz, CCF<sub>3</sub>), 32.77 ((CH<sub>3</sub>)<sub>3</sub>C), 28.63 (CH<sub>3</sub>), 28.58 (2 × CH<sub>3</sub>) ppm. **FT-IR** (ATR):  $\tilde{\nu}$  = 3261 (br, w), 2971

(w), 1611 (m), 1549 (m), 1402 (w), 1254 (m), 1170 (s), 1119 (vs), 977 (w), 910 (w), 695 (s)  $\text{cm}^{-1}$ .  
**HPLC** (0.1 % TFA, 0 min: 4 % B  $\rightarrow$  15 min: 100 % B. flow: 1 mL/min):  $t_R = 15.83$  min,  $\lambda = 214$  nm.  
**m.p.** 78°C. **HR-ESI-MS** (positive, m/z) calc. for  $\text{C}_{15}\text{H}_{18}\text{F}_3\text{N}_2\text{O}^+$   $[\text{MH}]^+$  299.1366; found 299.1365.

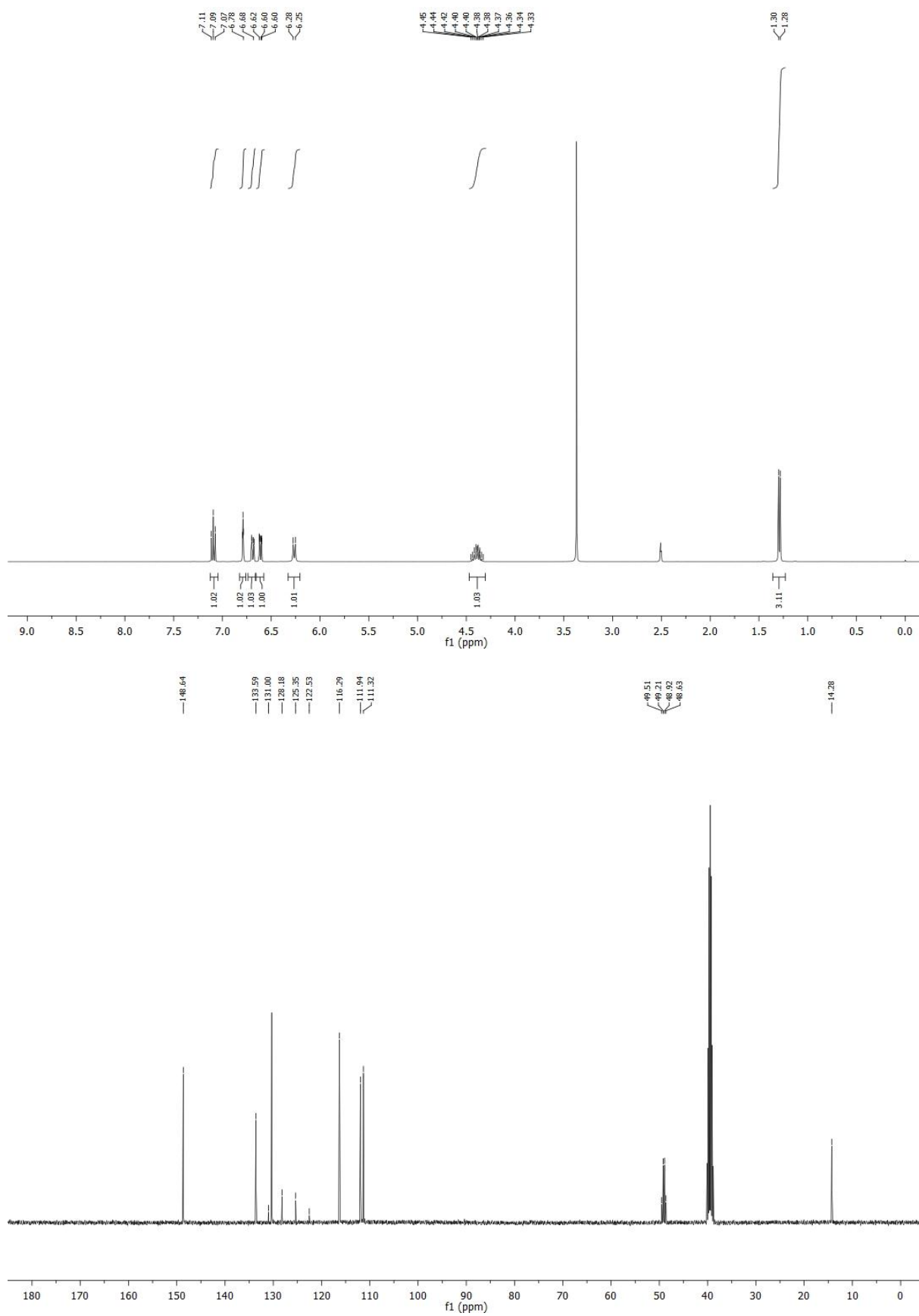
#### 4. References

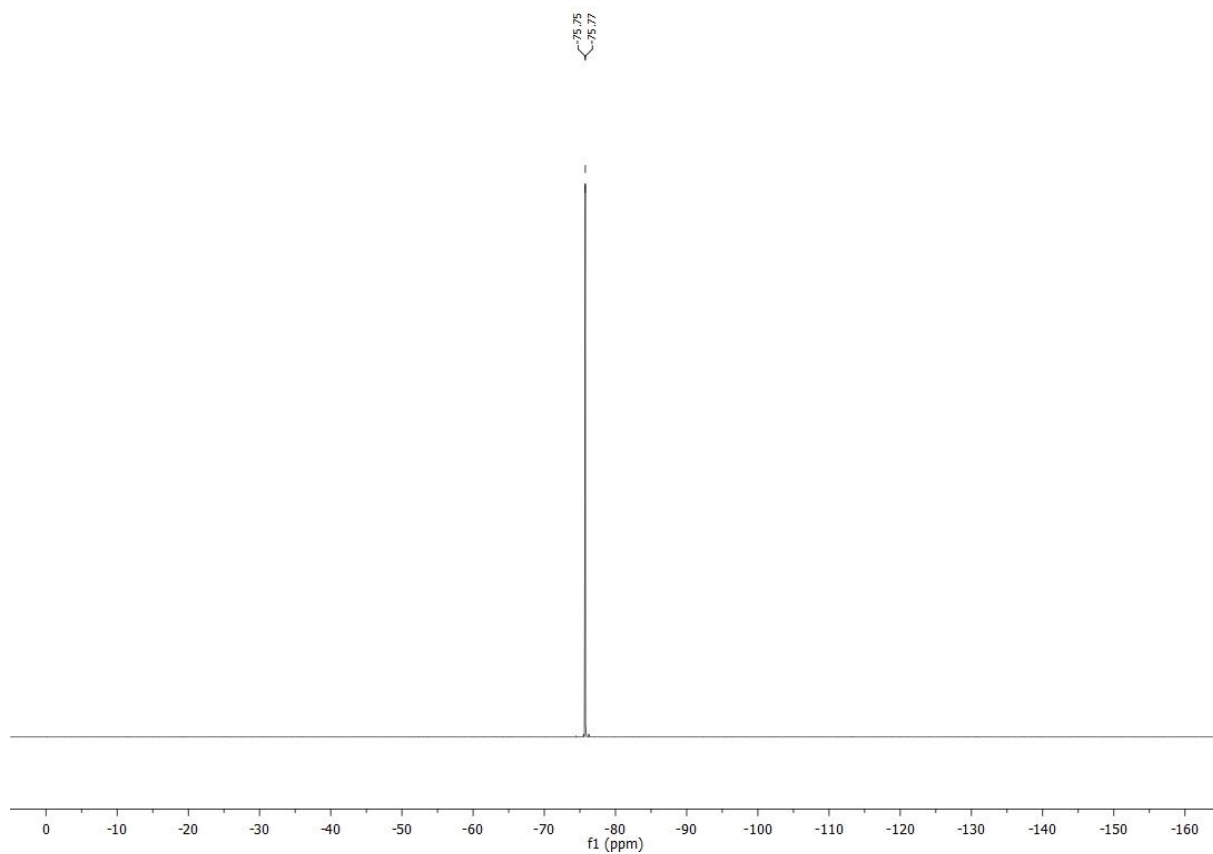
- 1 Y. Gong and K. Kato, *J. Fluorine Chem.*, 2004, **125**, 767.
- 2 Y. Gong and K. Kato, *J. Fluorine Chem.*, 2001, **111**, 77.
- 3 S. R. Stauffer, J. Sun, B. S. Katzenellenbogen and J. A. Katzenellenbogen, *Biorg. Med. Chem.*, 2000, **8**, 1293.
- 4 G. Guanti, L. Banfi, E. Narisano, C. Scolastico and E. Bosone, *Synthesis*, 1985, **6/7**, 609.



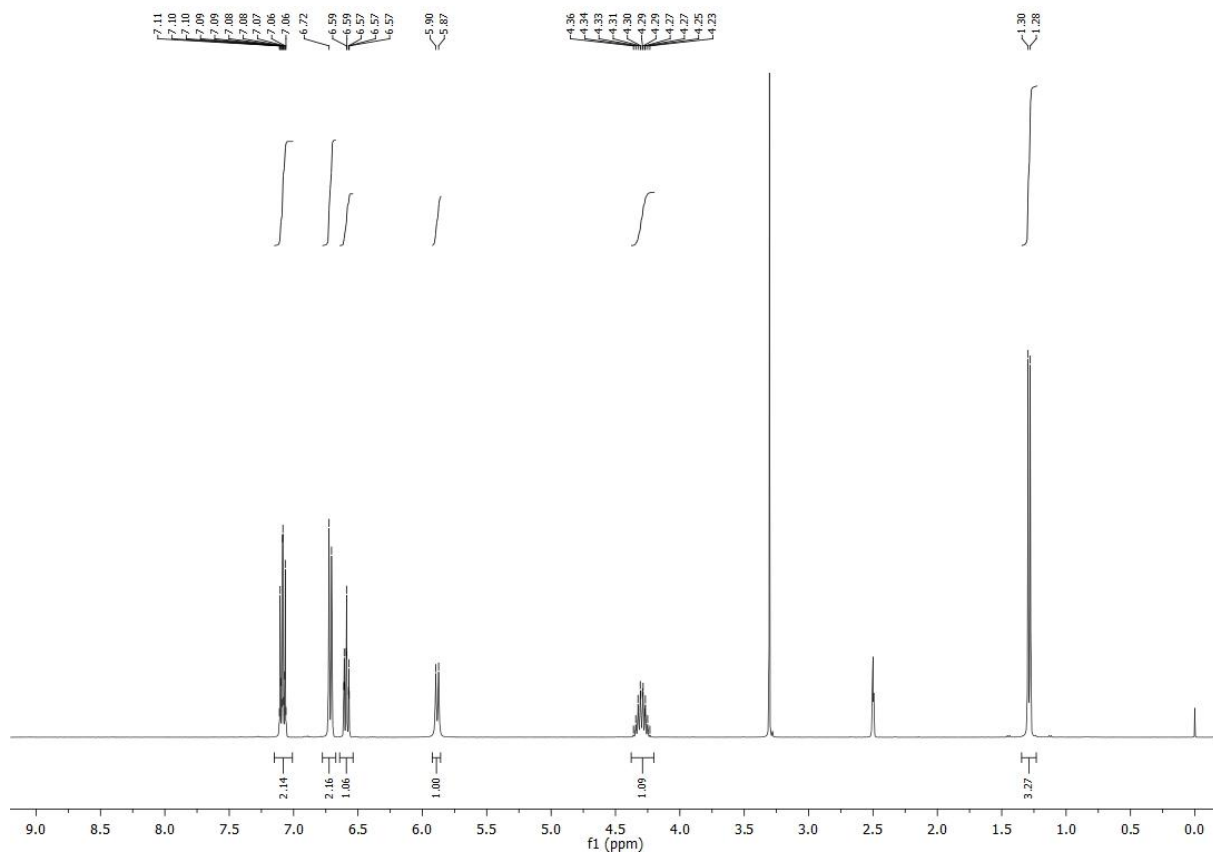
## 5. $^1\text{H}$ NMR, $^{13}\text{C}$ NMR and $^{19}\text{F}$ NMR spectra

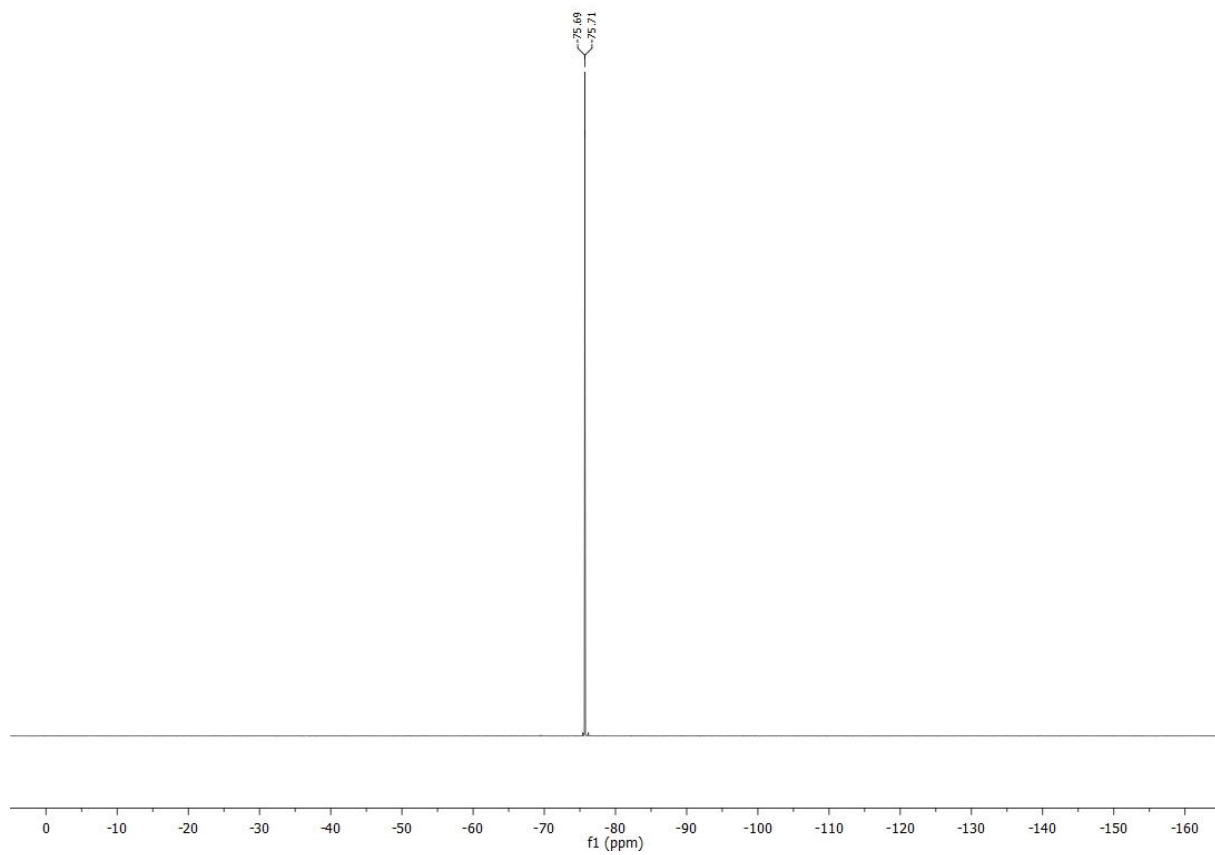
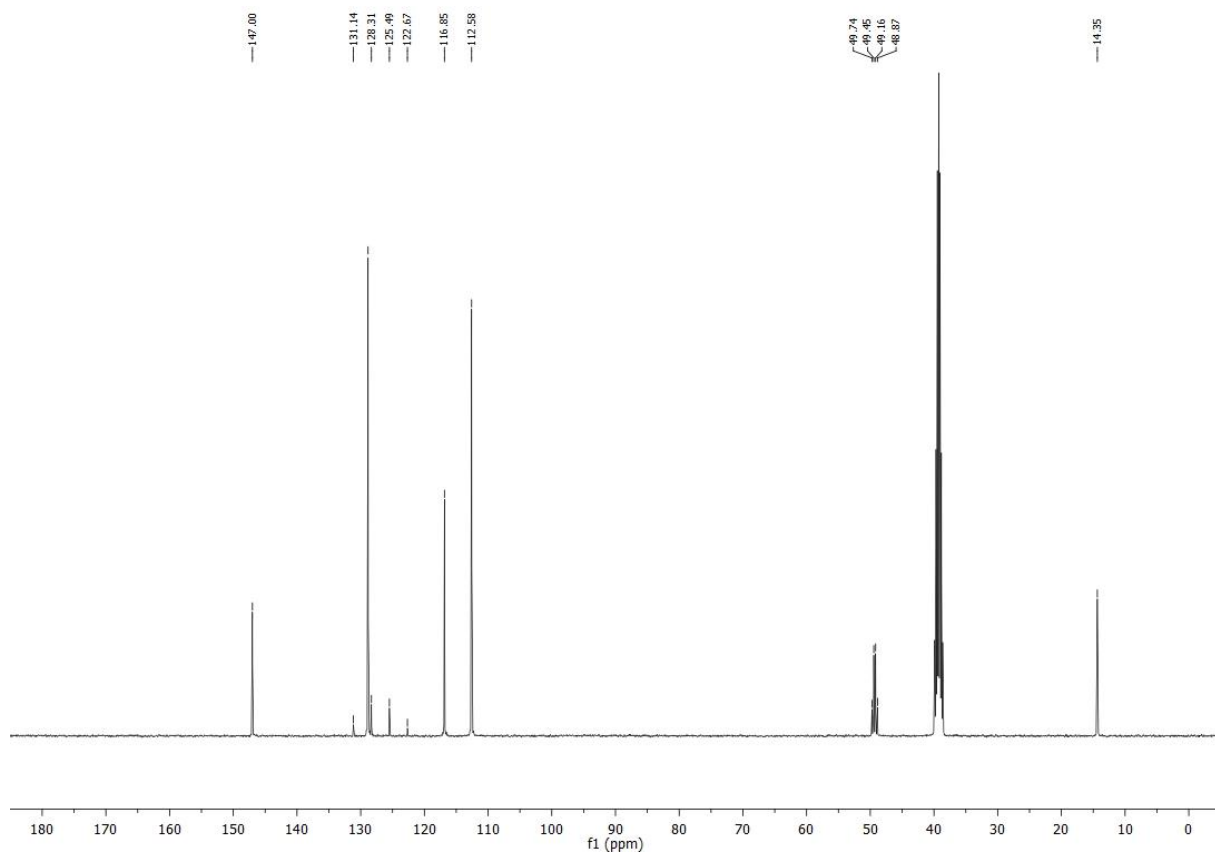
### 3-Chloro-*N*-(2,2,2-trifluoro-1-methylethyl)aniline **2a**



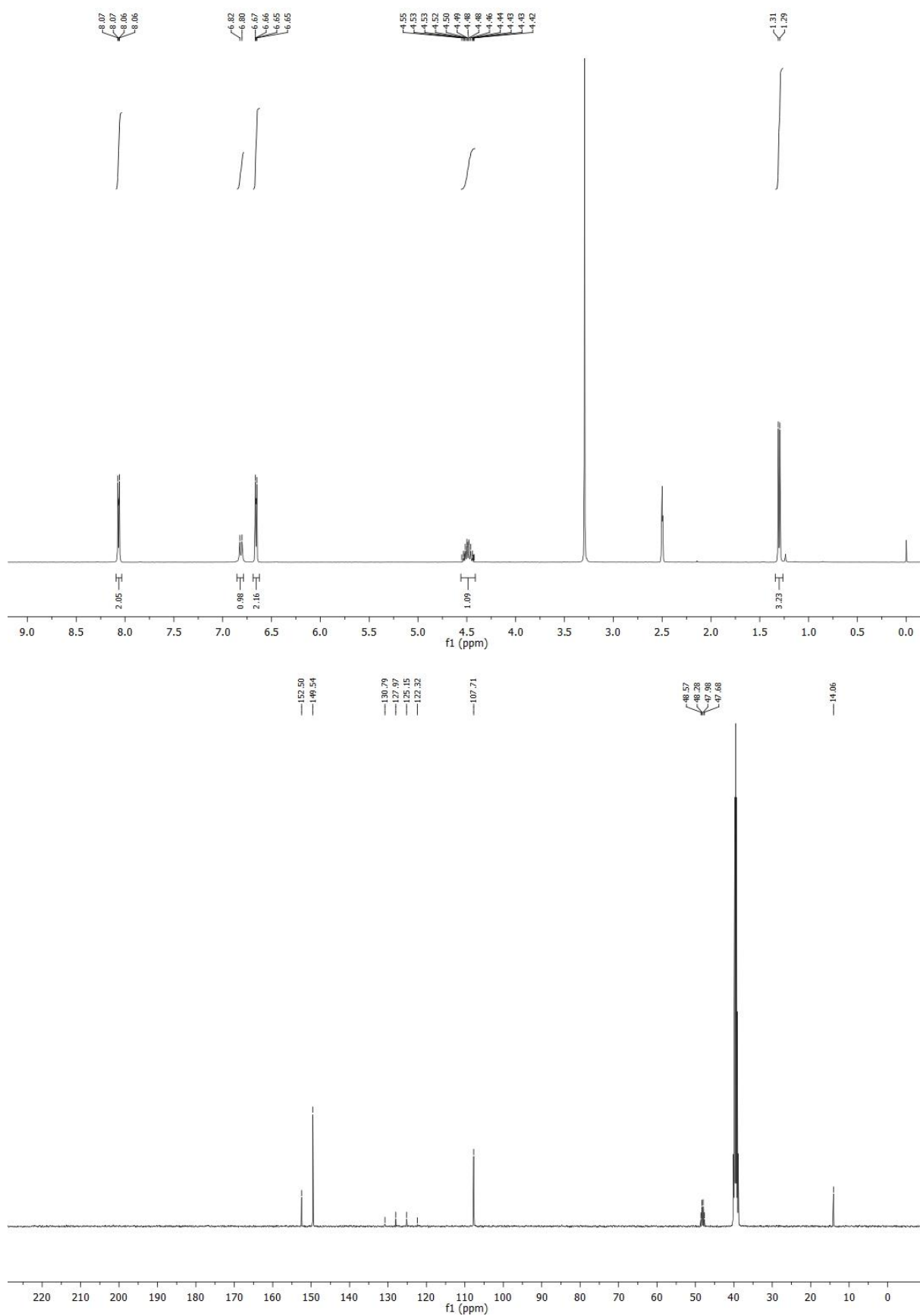


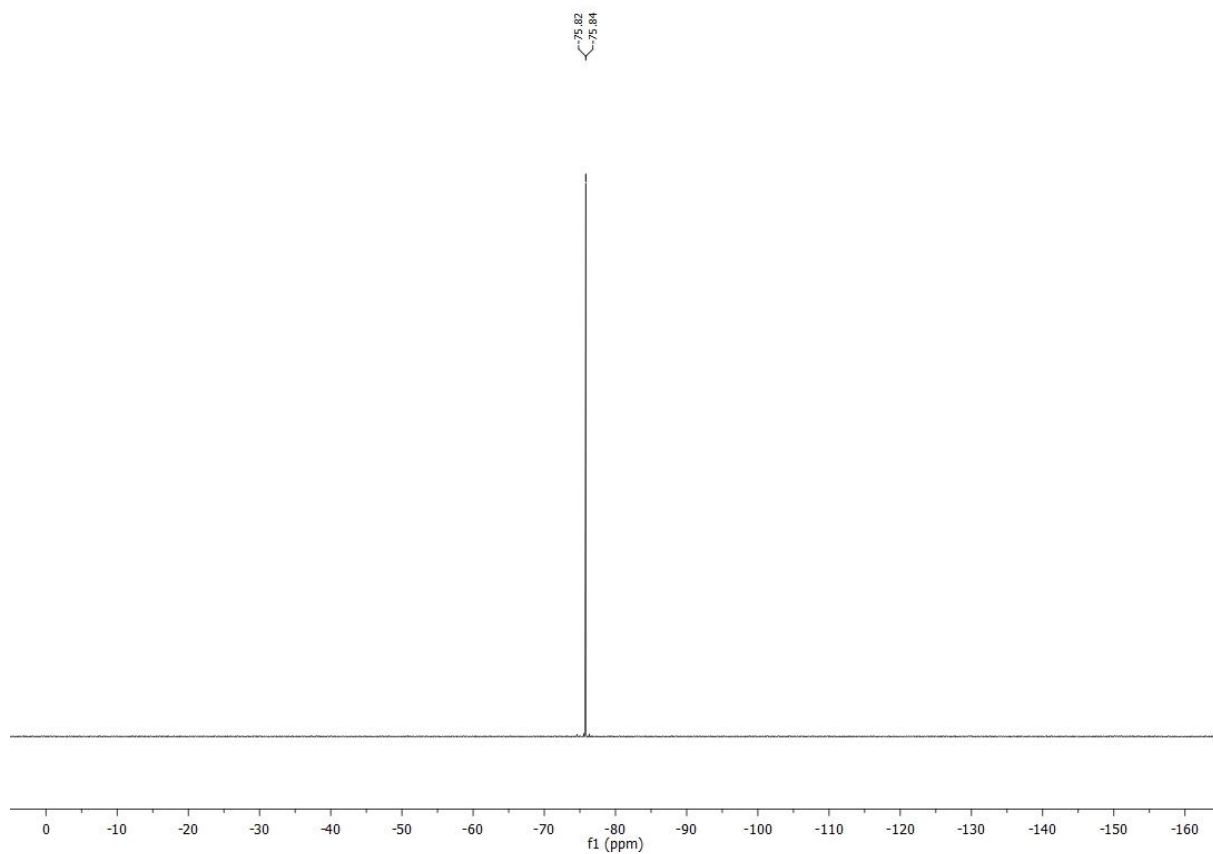
***N*-(2,2,2-Trifluoro-1-methylethyl)aniline 2b**



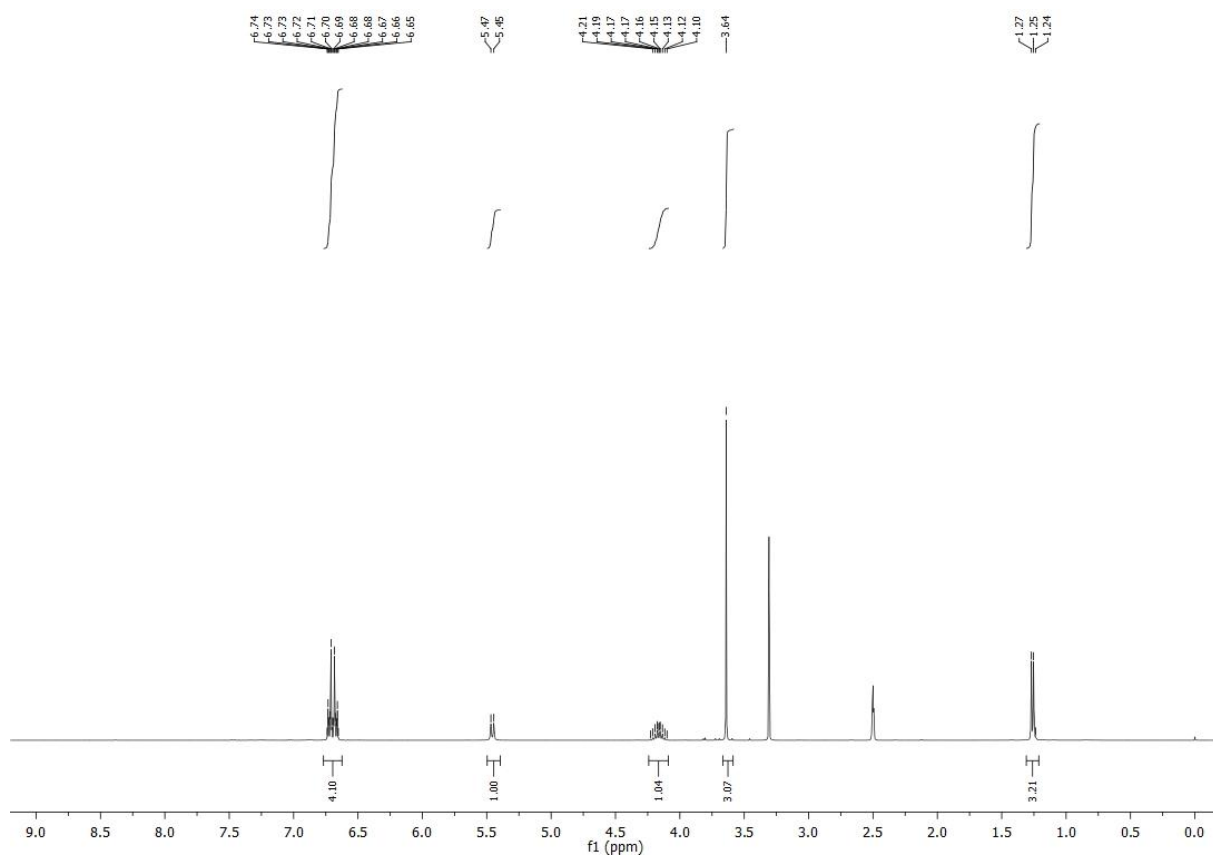


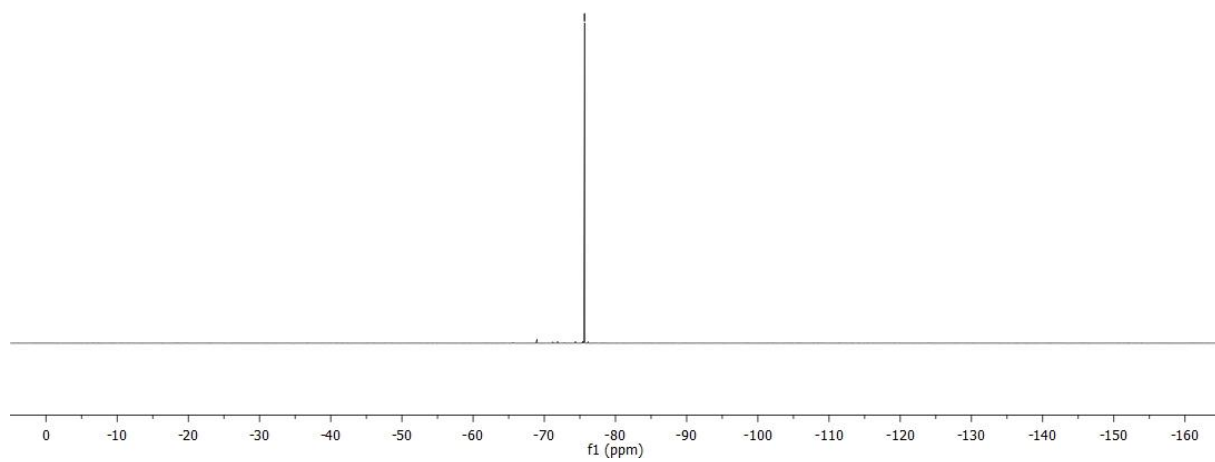
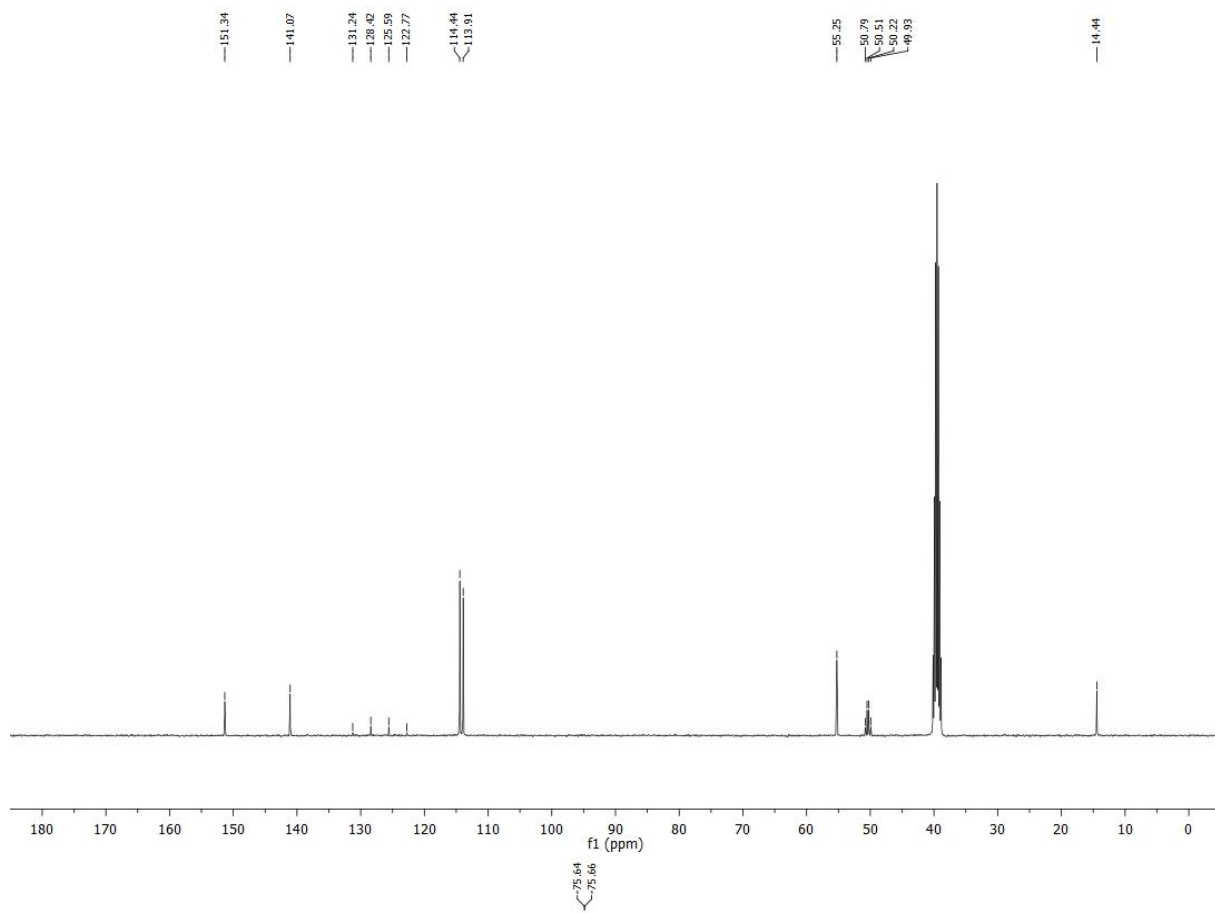
### *N*-(2,2,2-Trifluoro-1-methylethyl)aminopyridine 2c



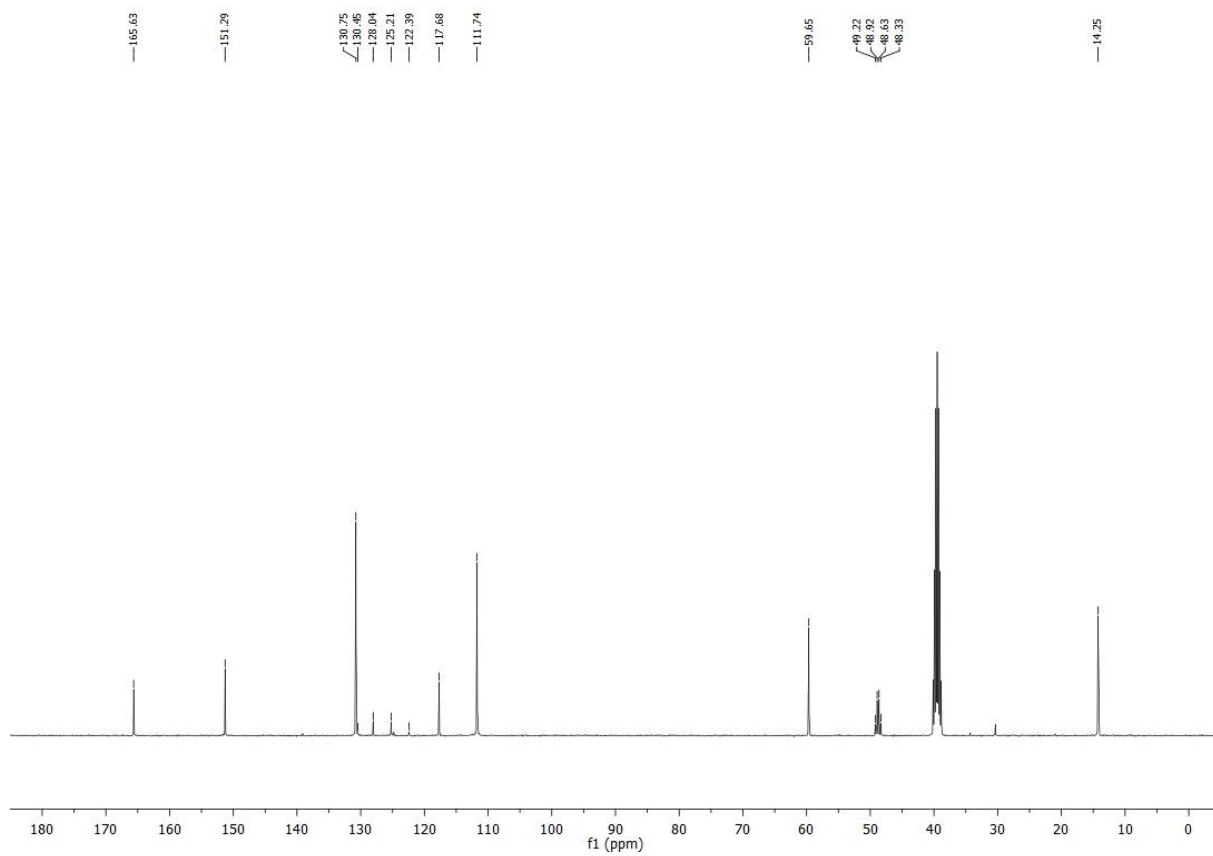
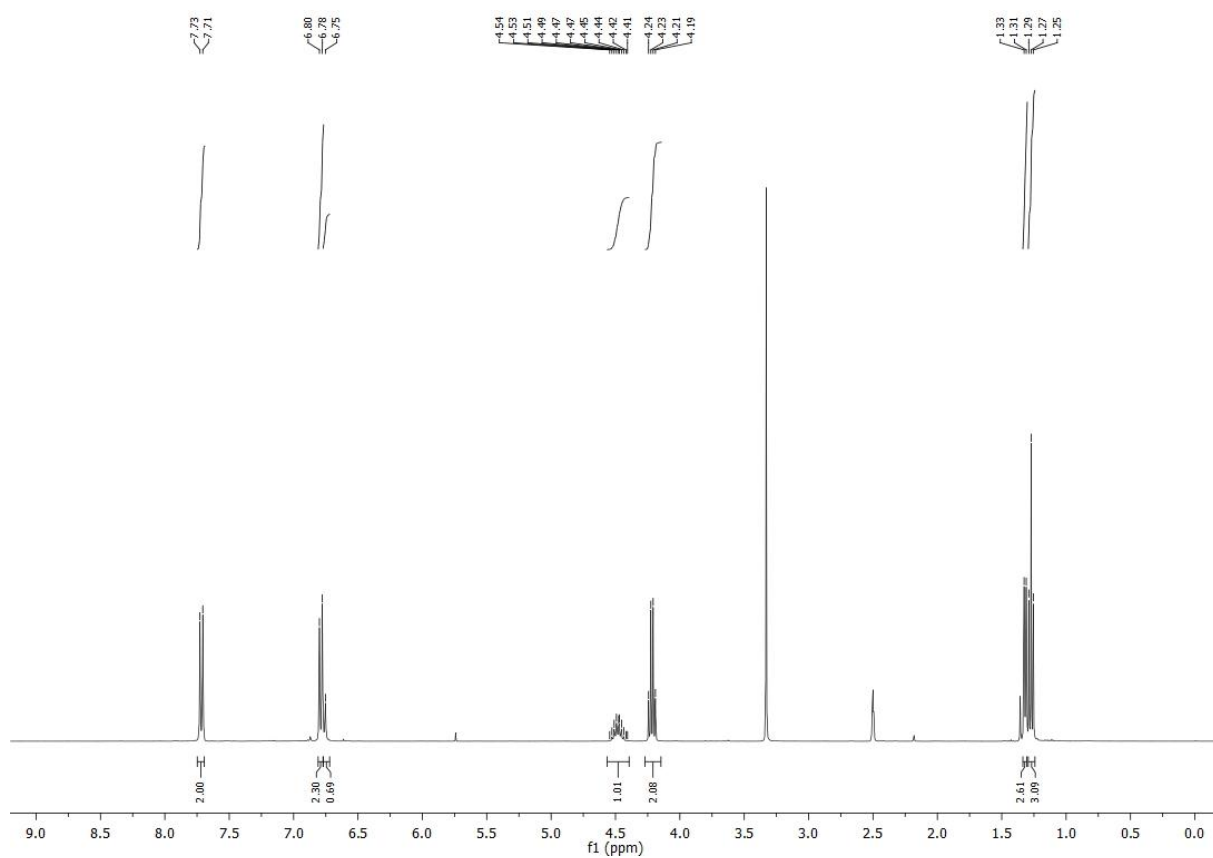


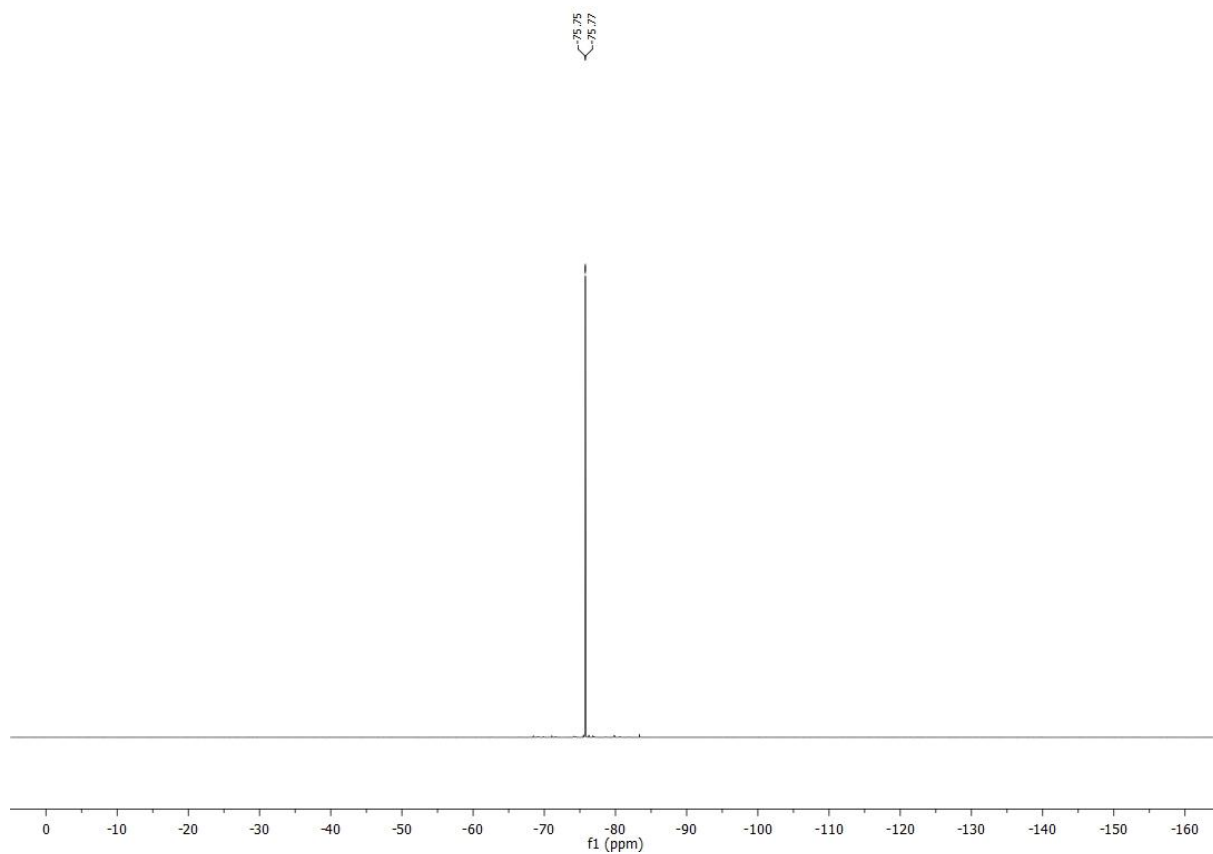
#### 4-Methoxy-N-(2,2,2-trifluoro-1-methylethyl)aniline 2d



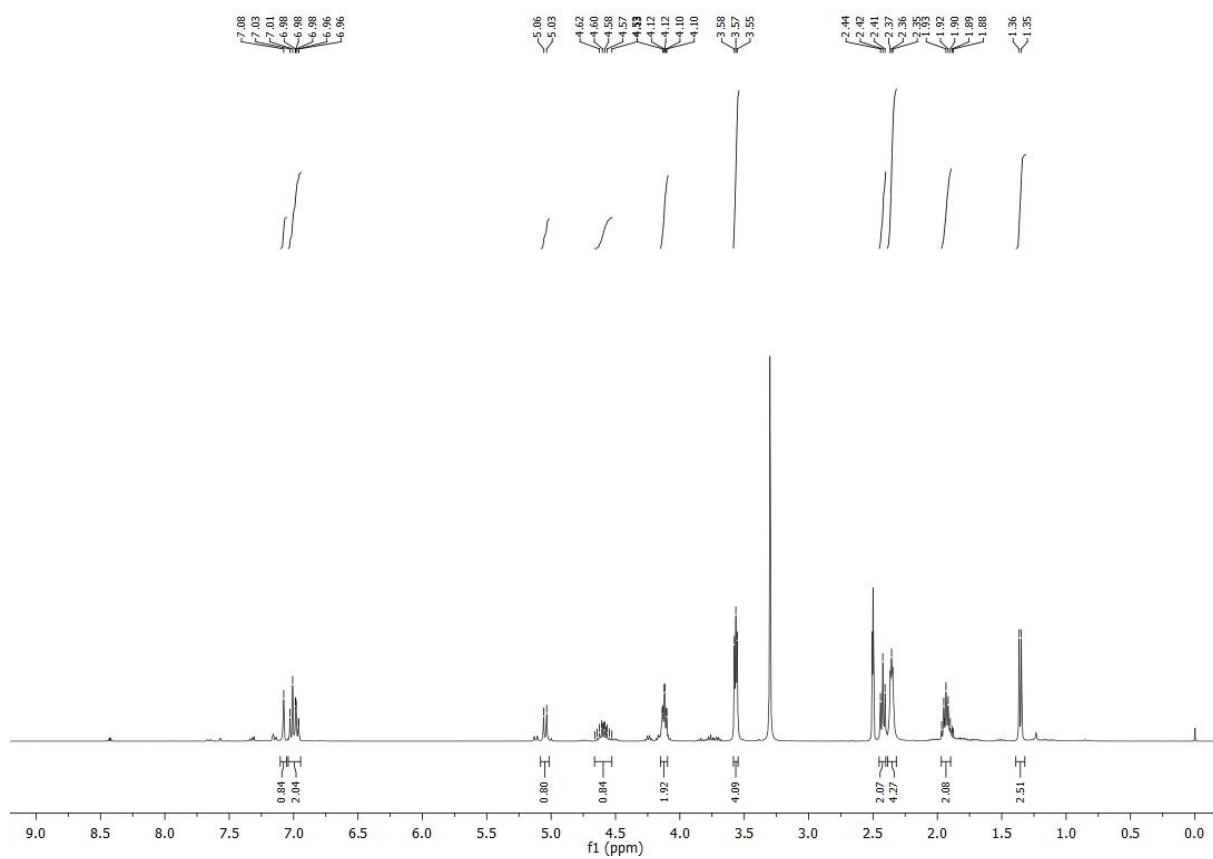


### Ethyl-N-(2,2,2-trifluoro-1-methylethyl)4-aminobenzoate 2e

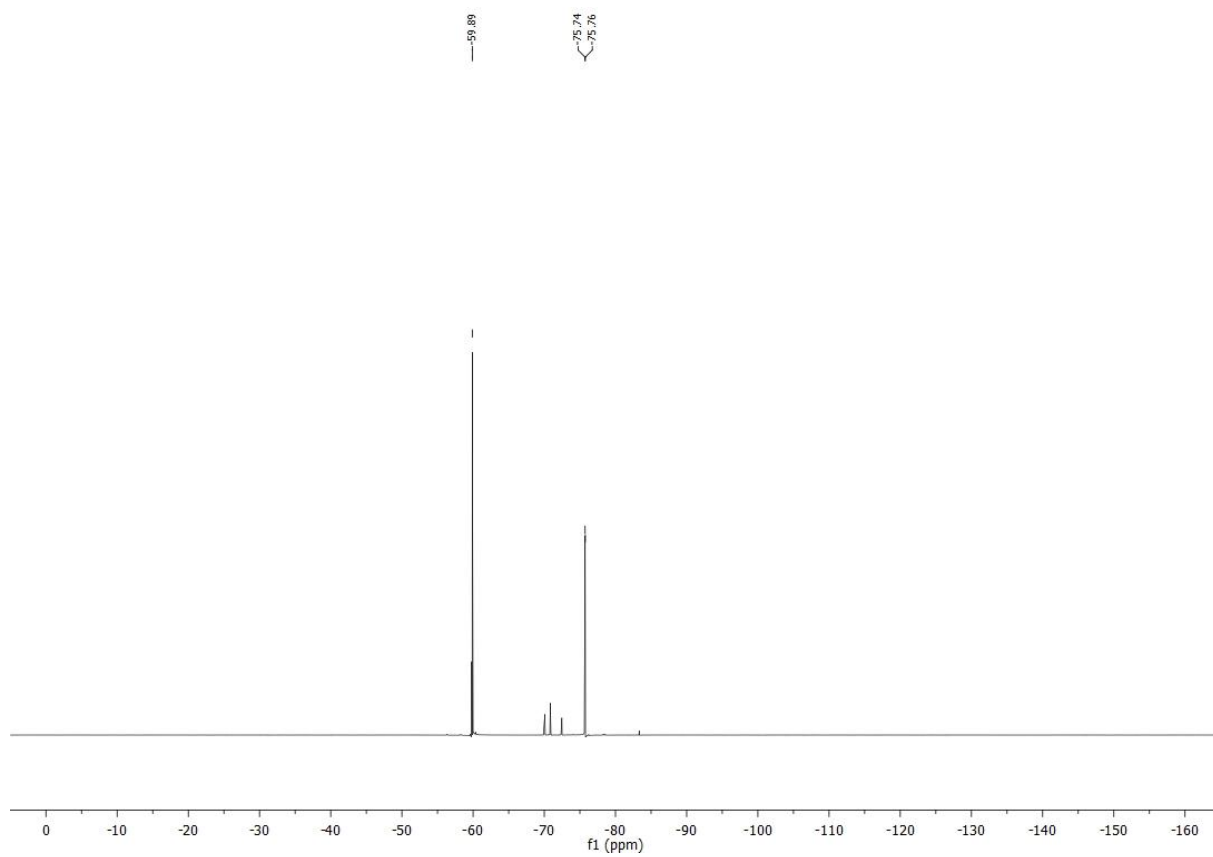
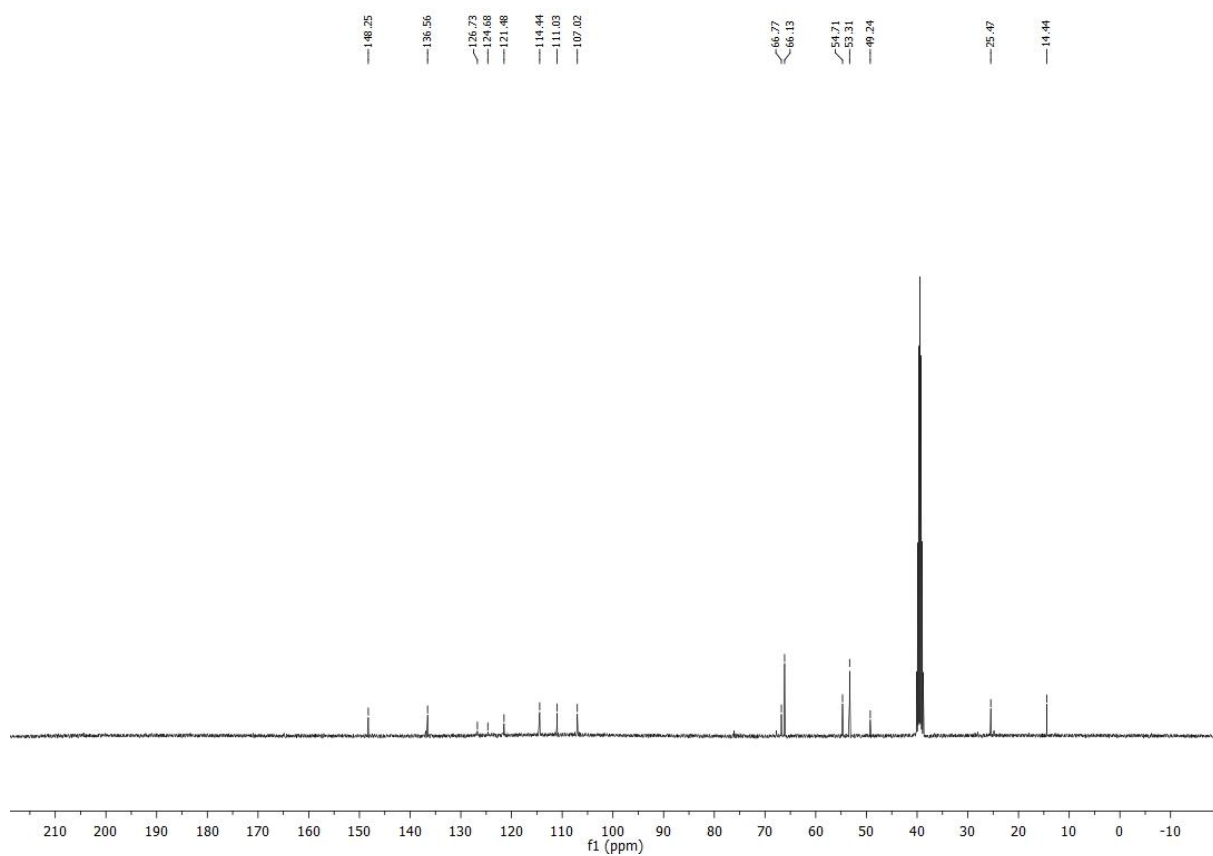




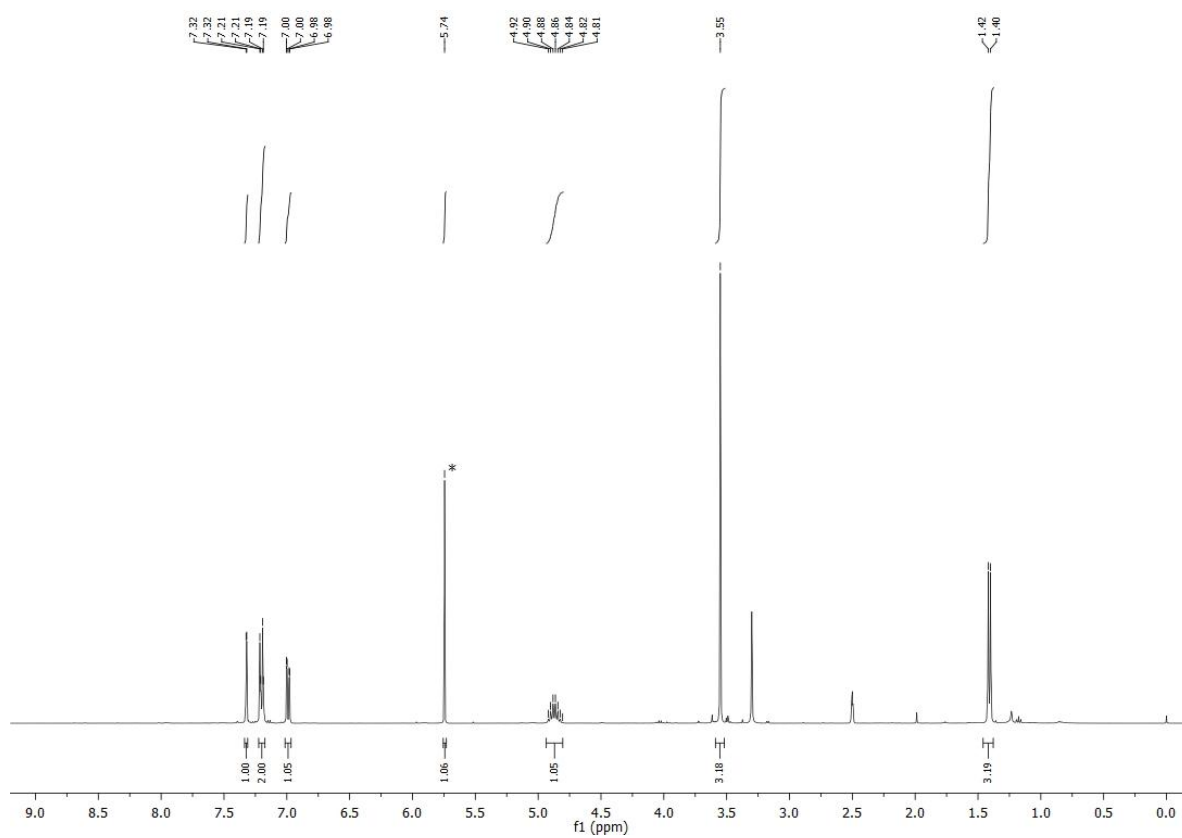
**2-(3-Morpholinopropoxy)-5-(trifluoromethyl)-N-(2,2,2-trifluoro-1-methylethyl)aniline 2f**



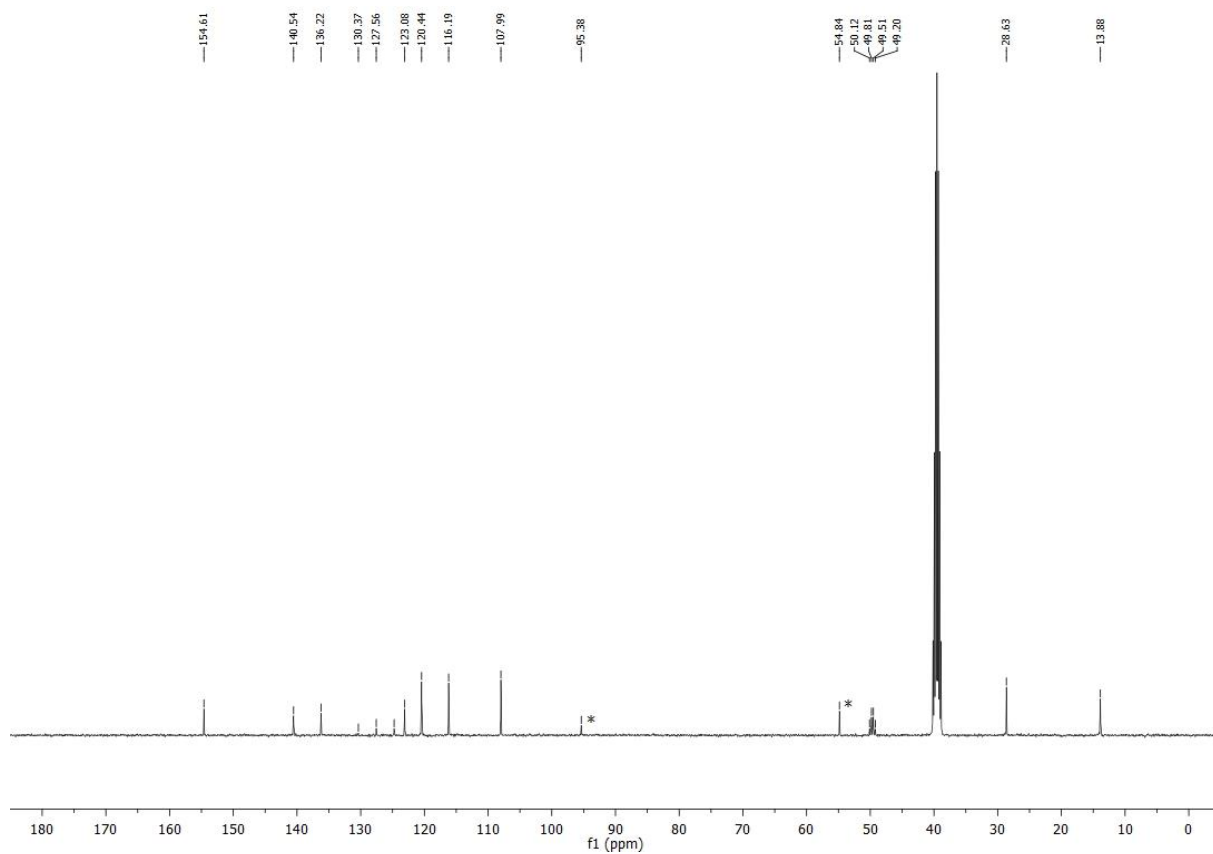




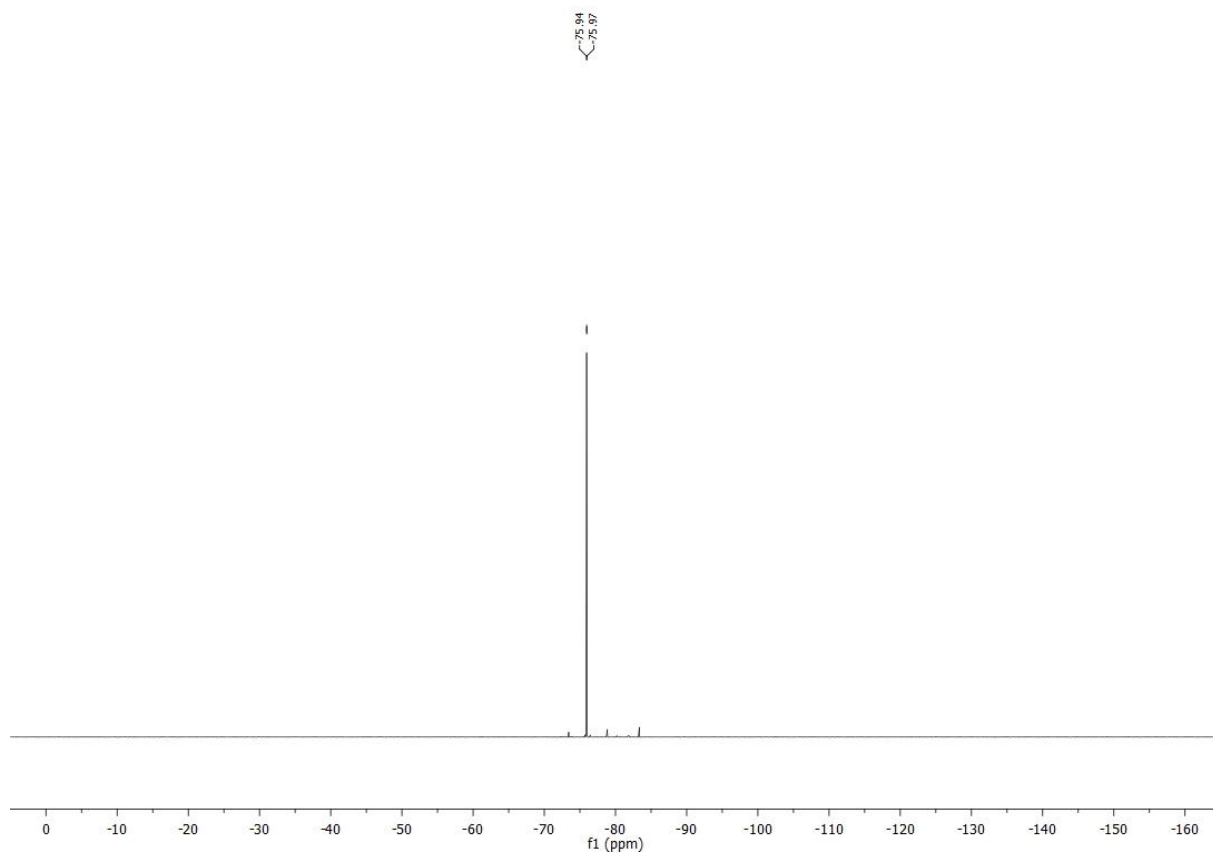
**(6-Chloro-1-methyl-1H-benzimidazol-2-yl)-(2,2,2-trifluoro-1-methylethyl)amine 2g**



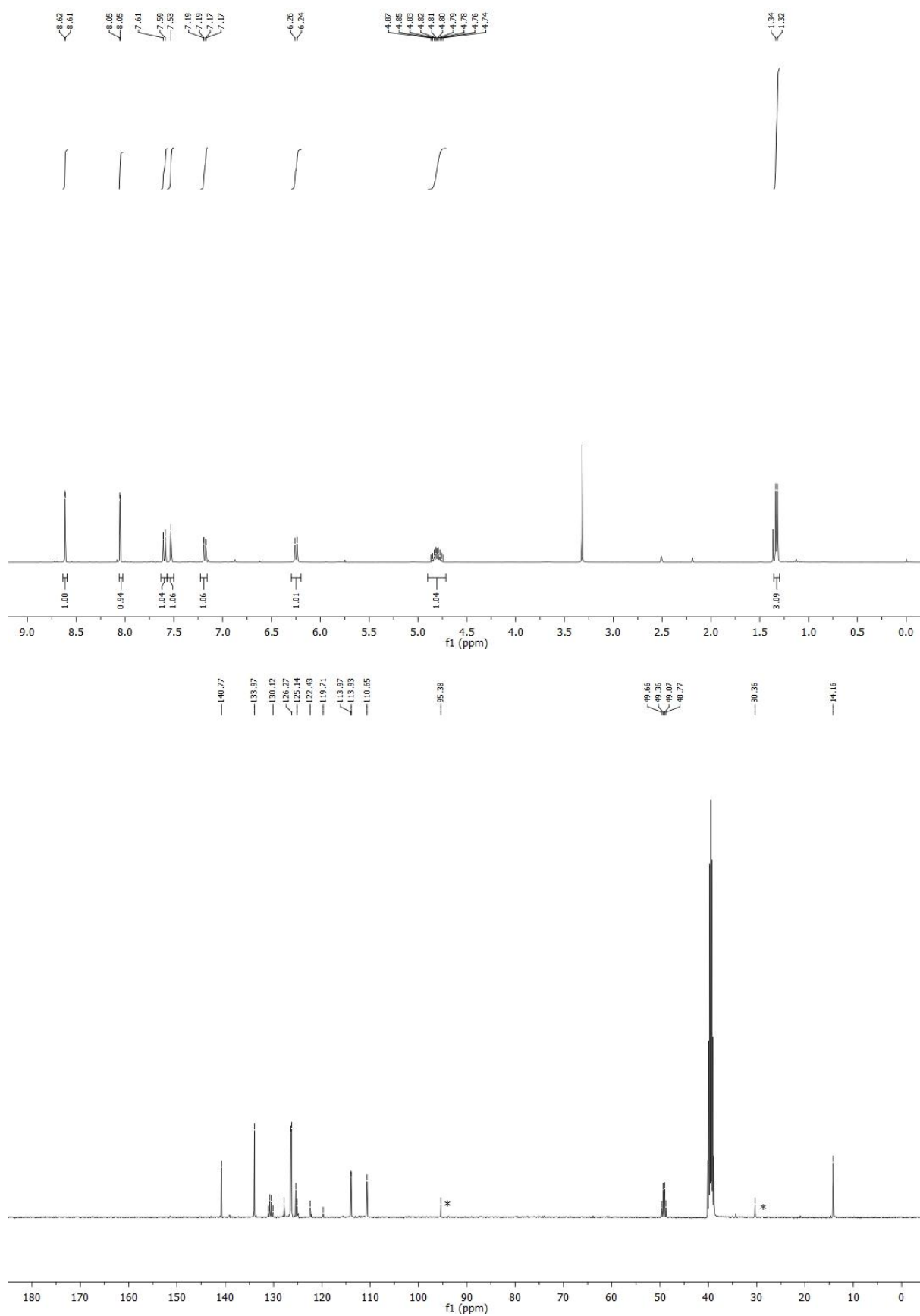
\* Impurities of solvents



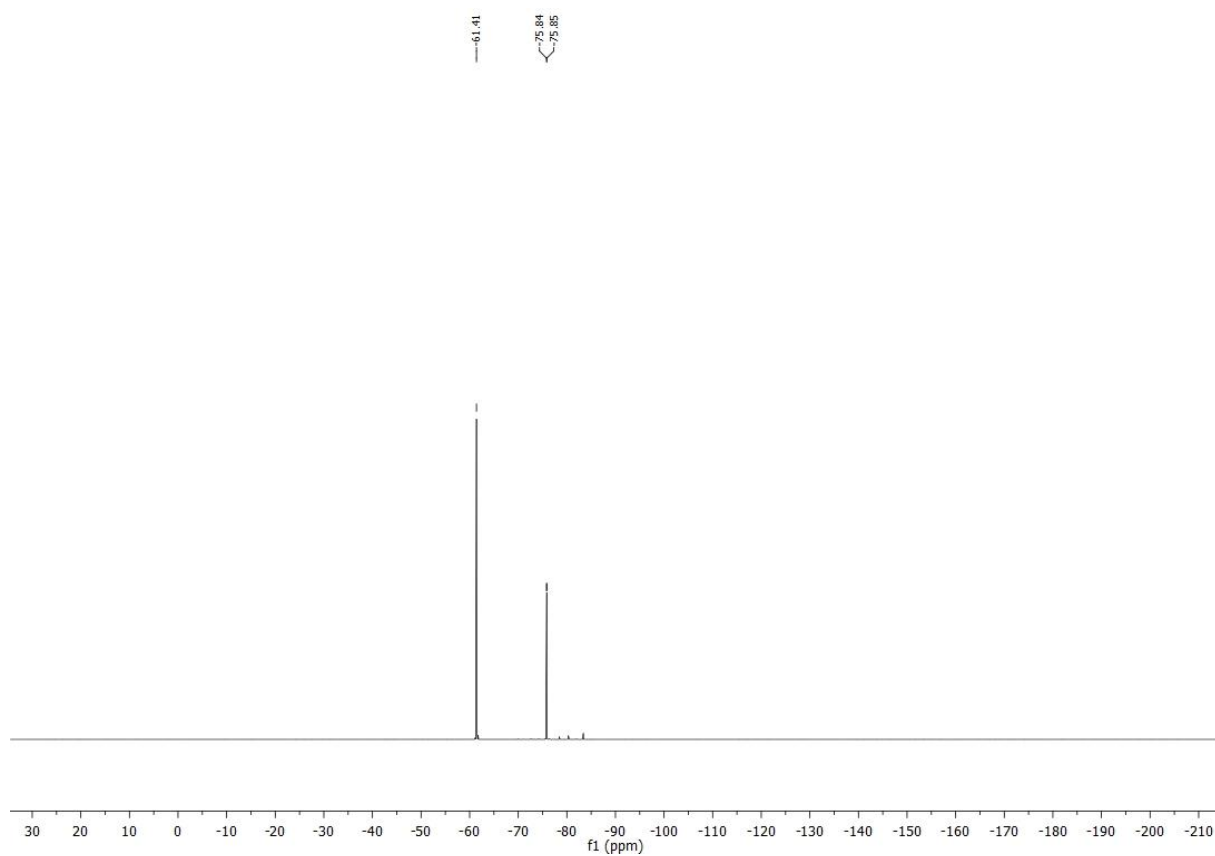
\* Impurities of solvents



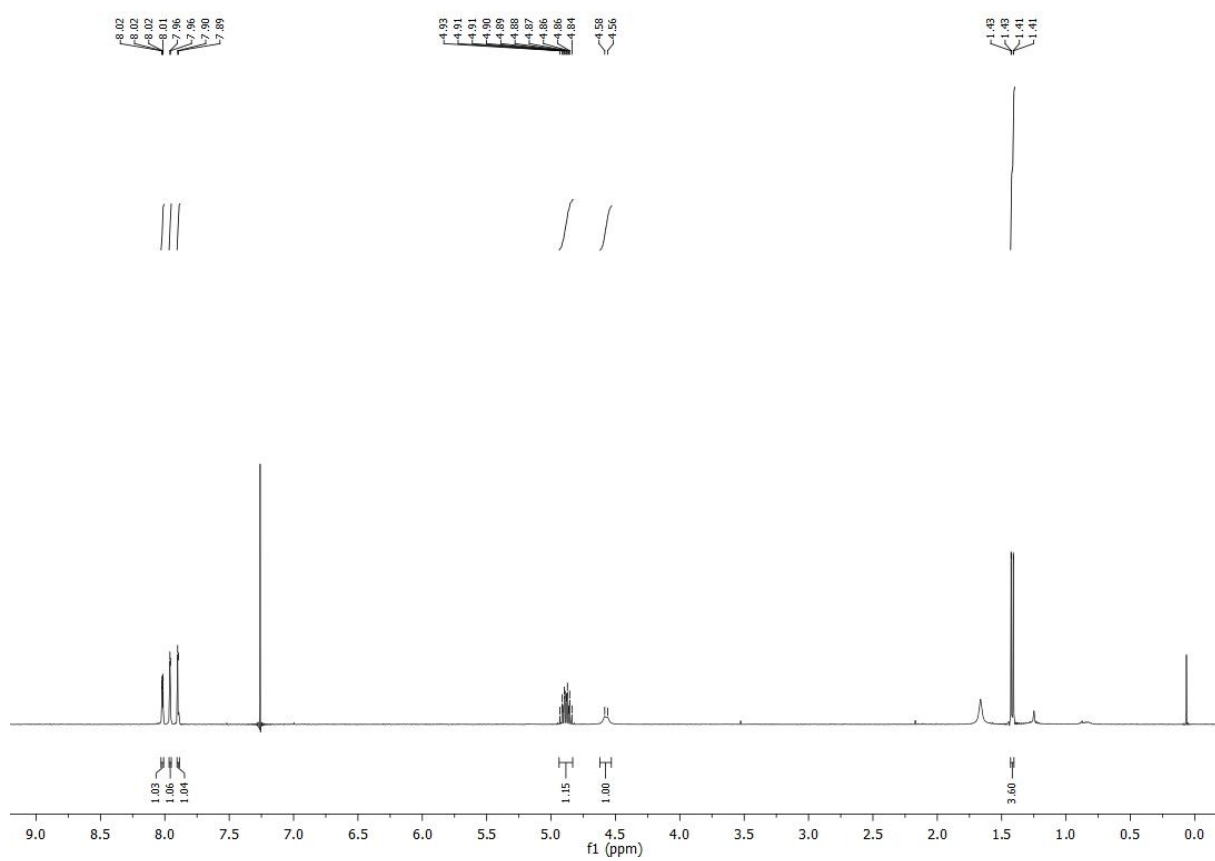
**2-(1,2,3-Triazol-1-yl)-5-(trifluoromethyl)-N-(2,2,2-trifluoro-1-methylethyl)aniline 2h**

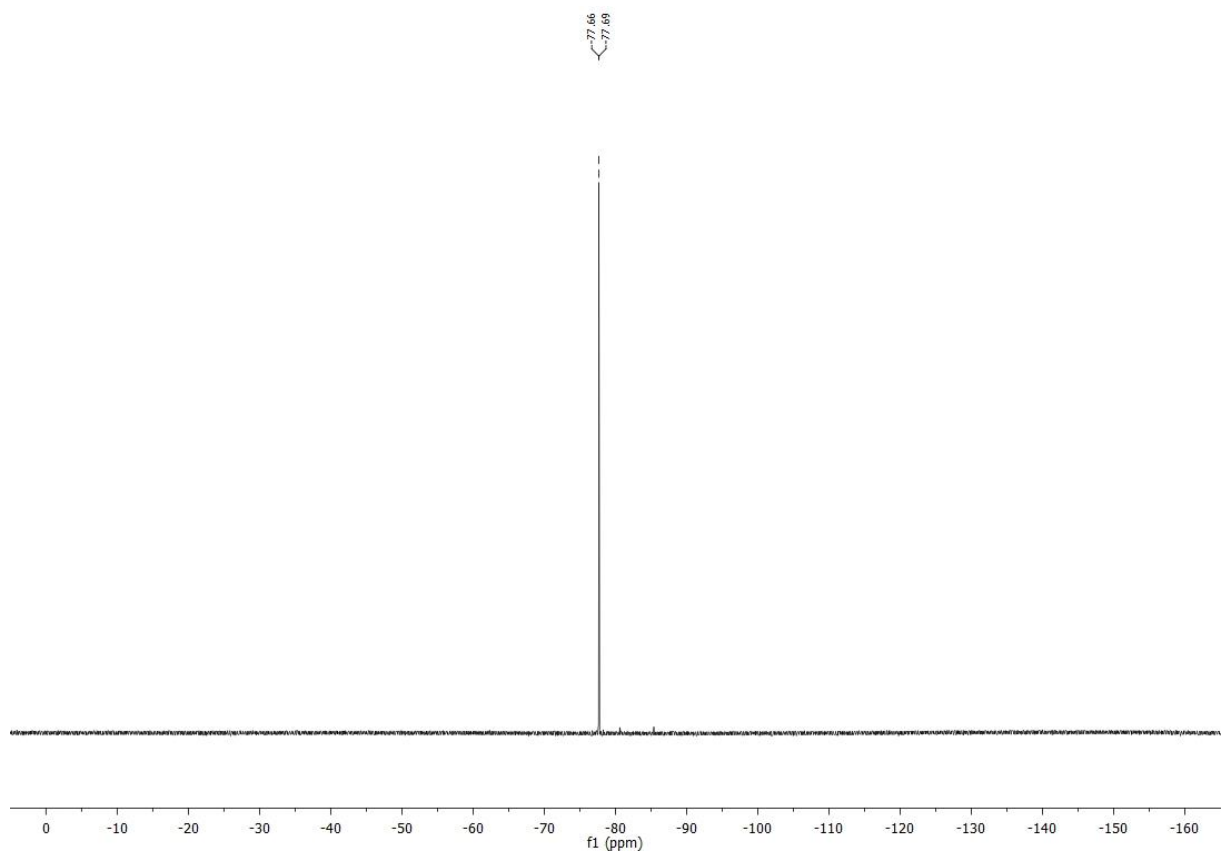
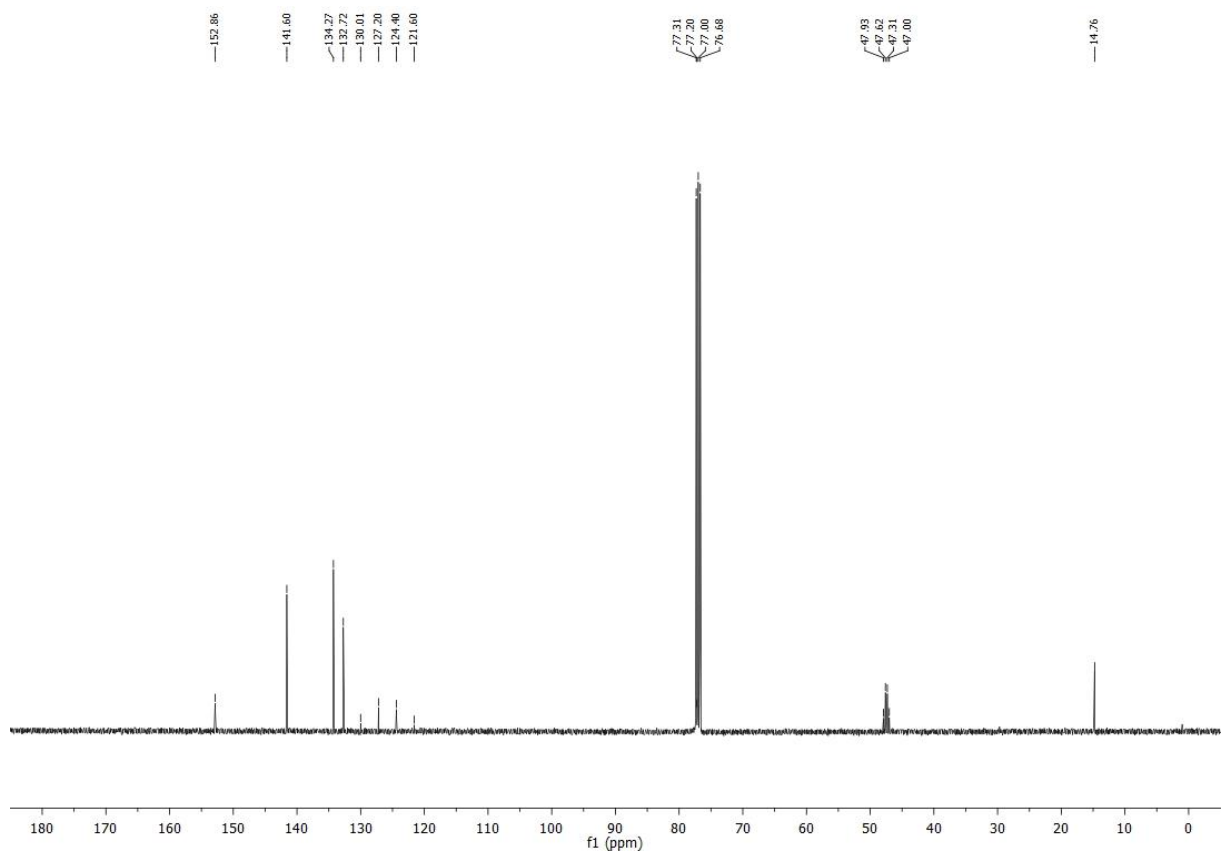


\* Impurities of solvents

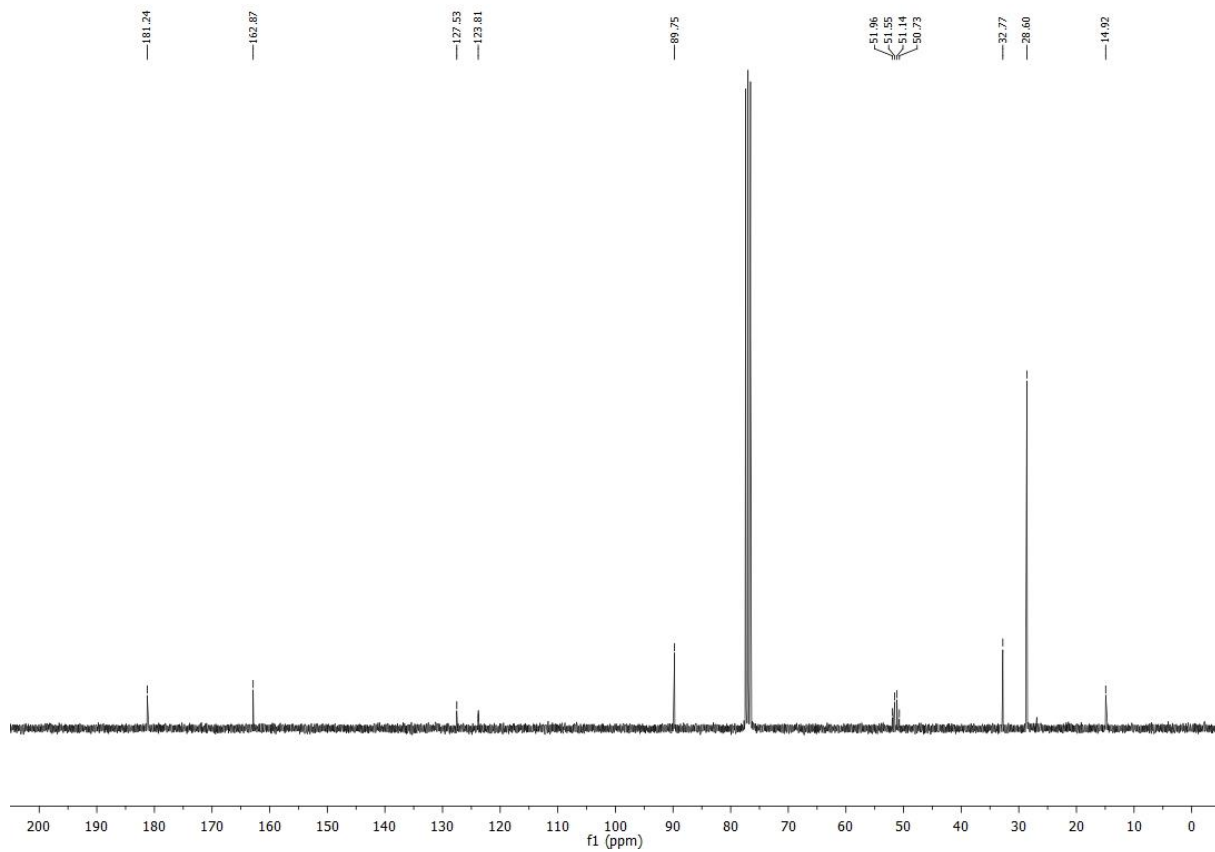
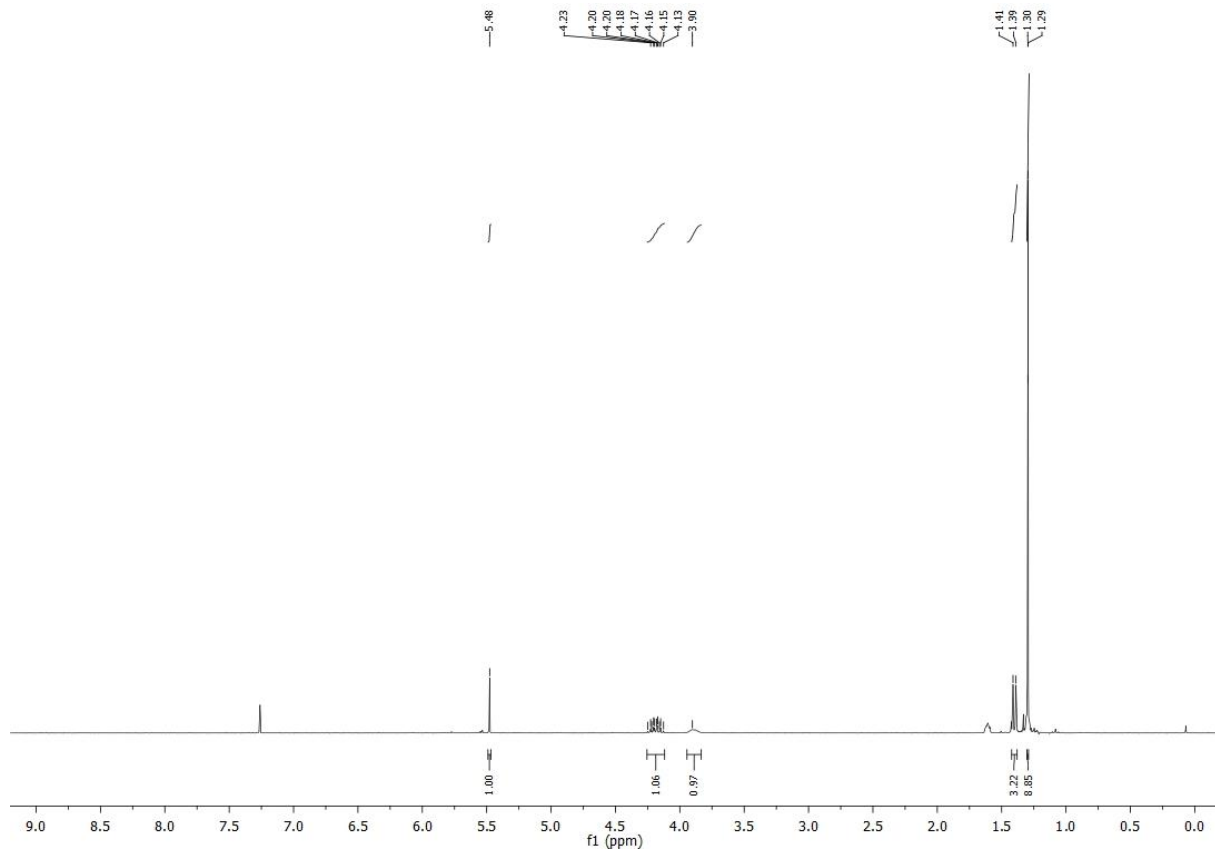


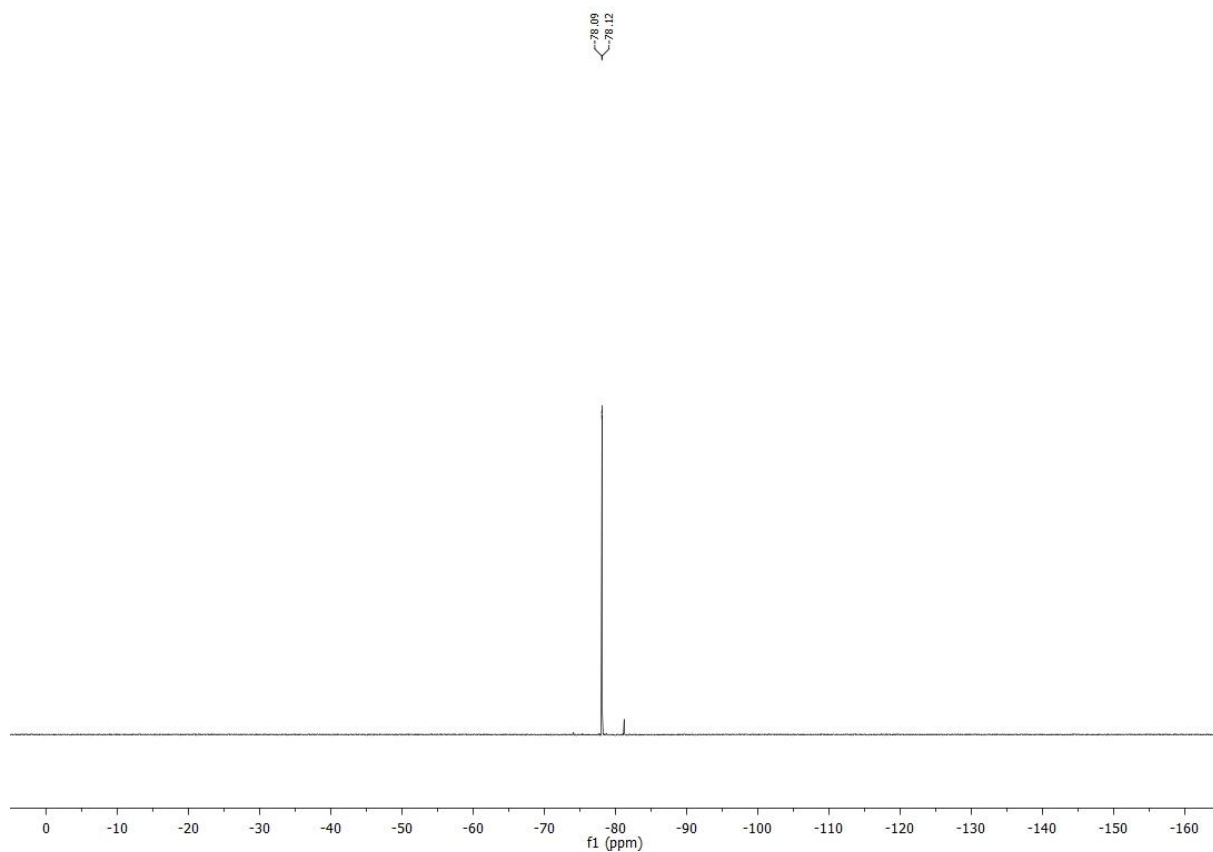
***N*-(2,2,2-Trifluoro-1-methylethyl)aminopyrazine 2i**



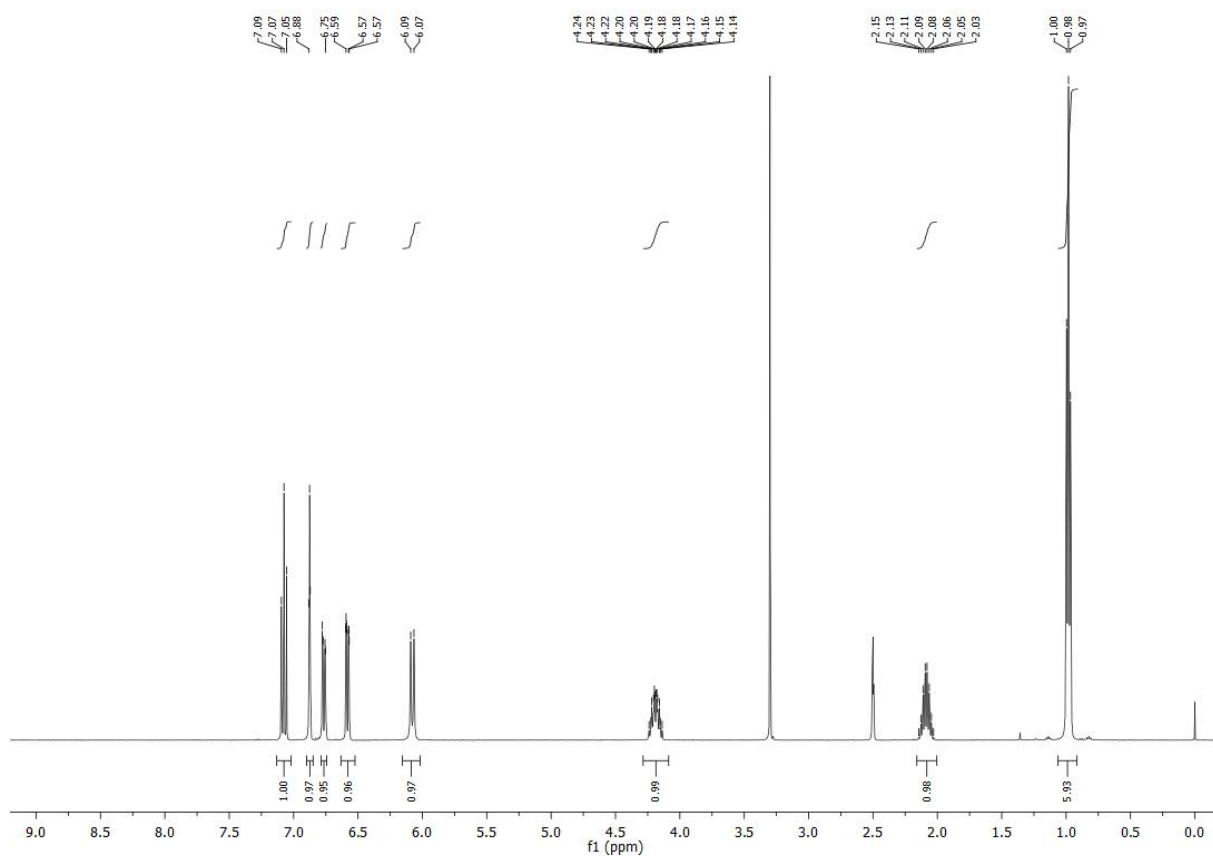


**5-(*tert*-Butyl)-*N*-(2,2,2-trifluoro-1-methylethyl)isoxazol-3-amine 2j**

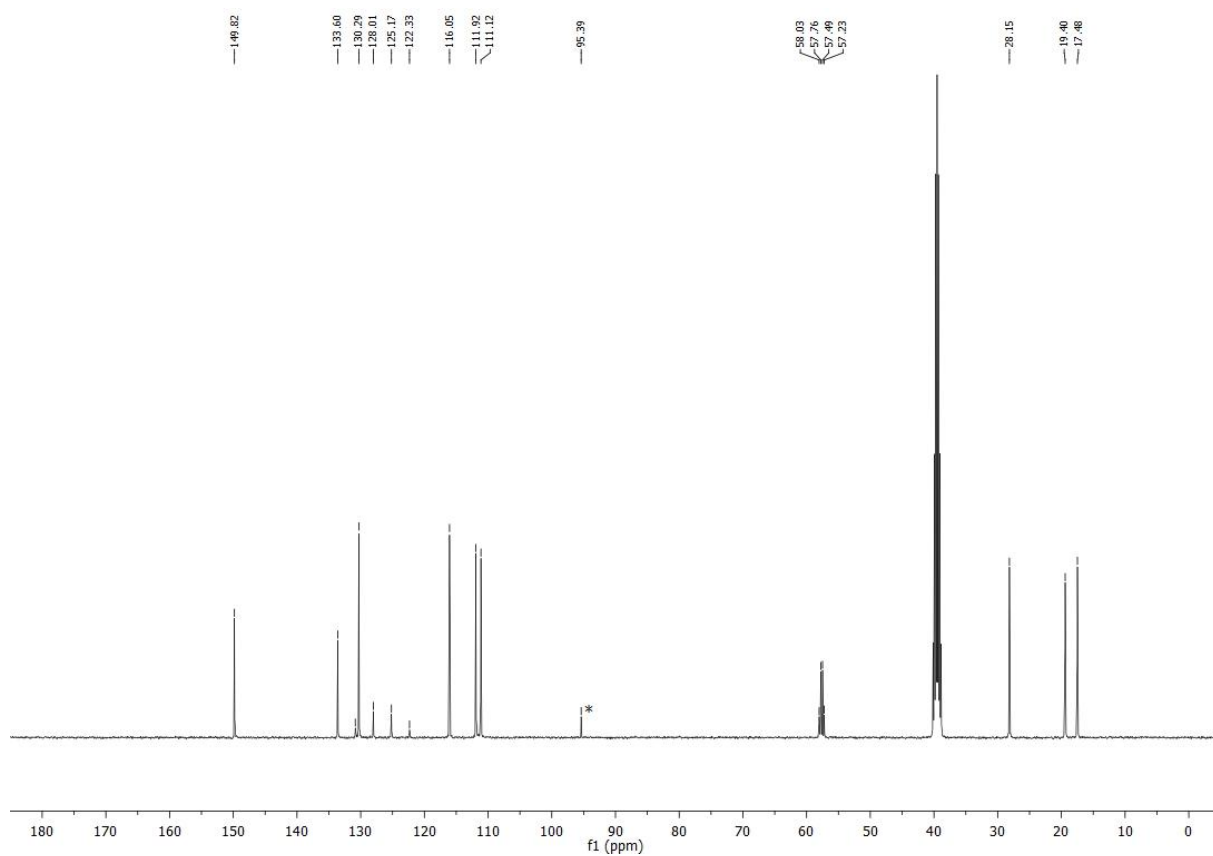




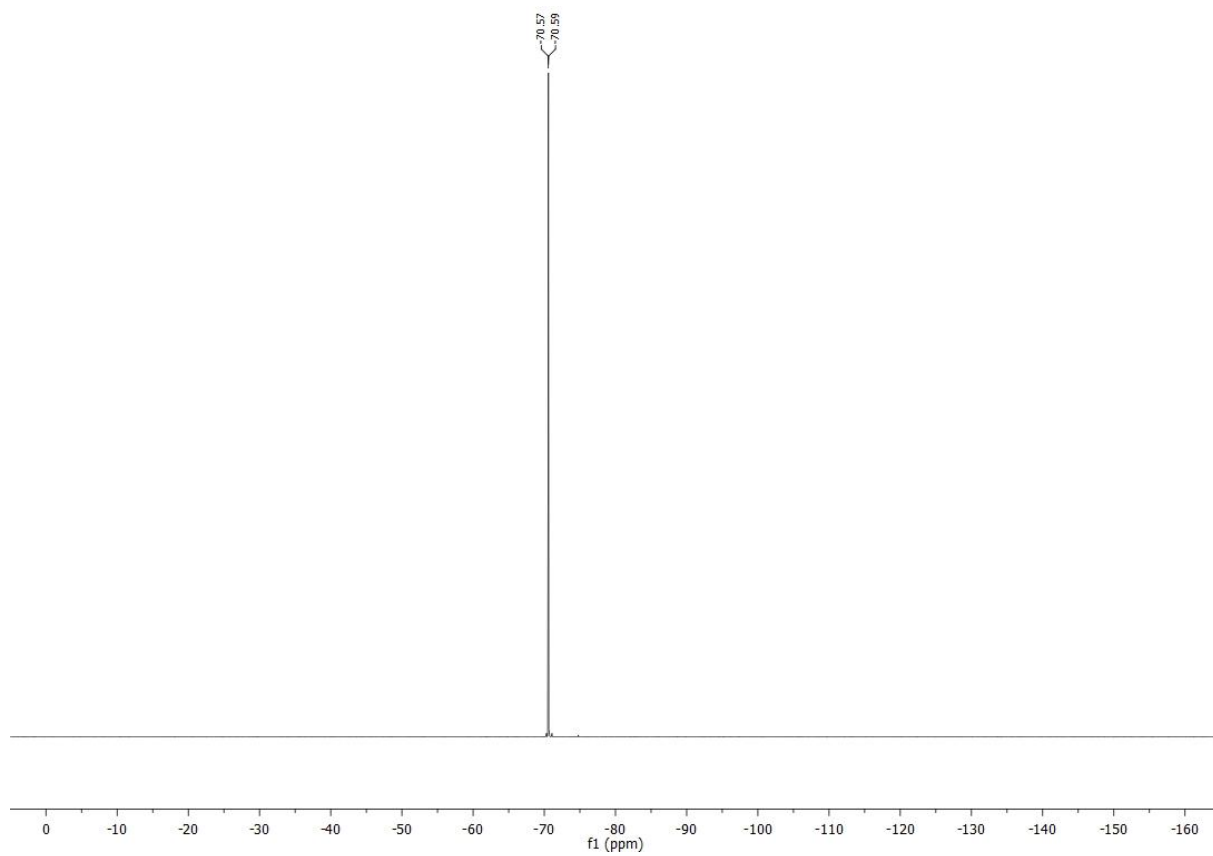
### 3-Chloro-*N*-(2,2,2-trifluoro-1-isopropylethyl)aniline 3a



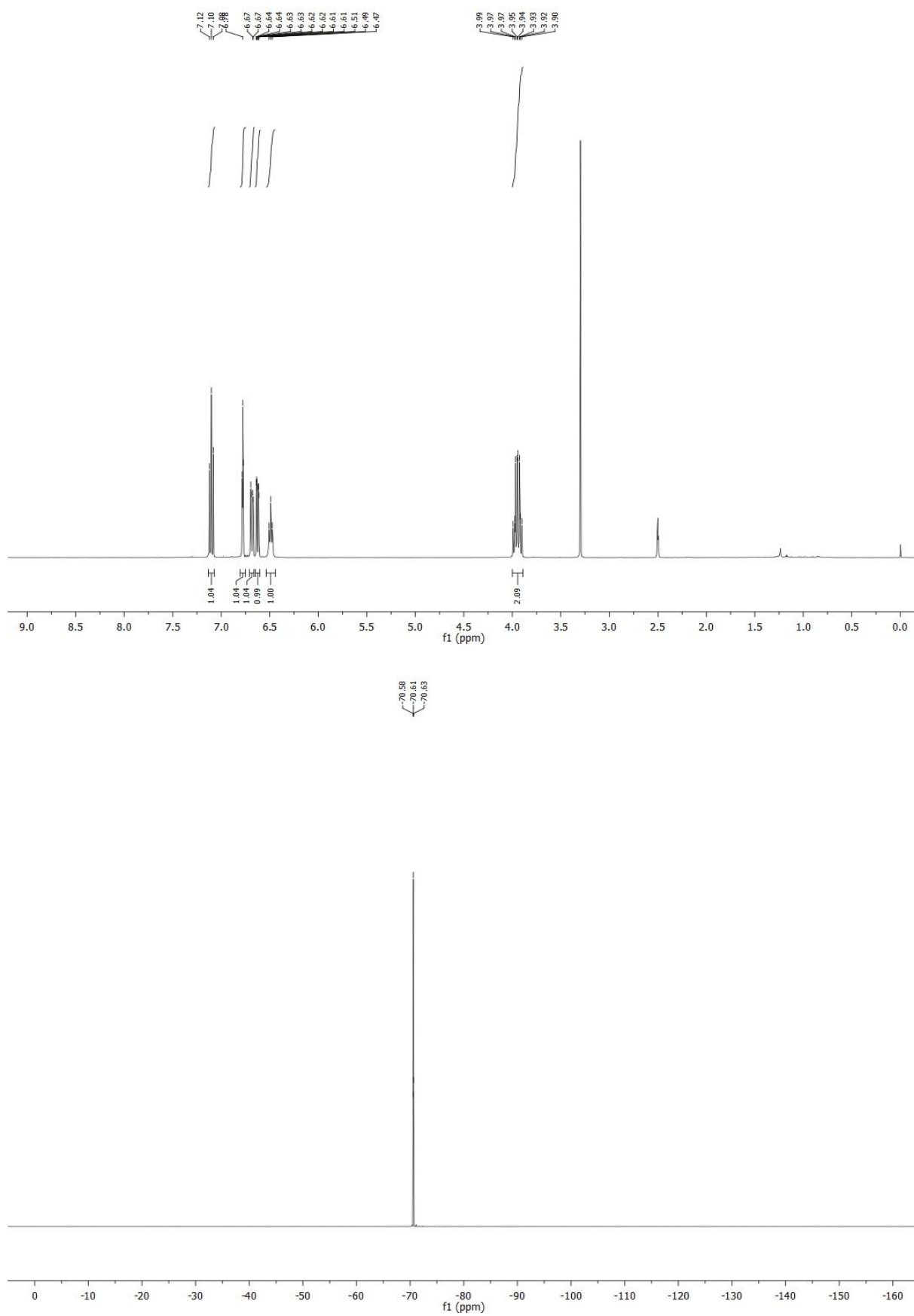




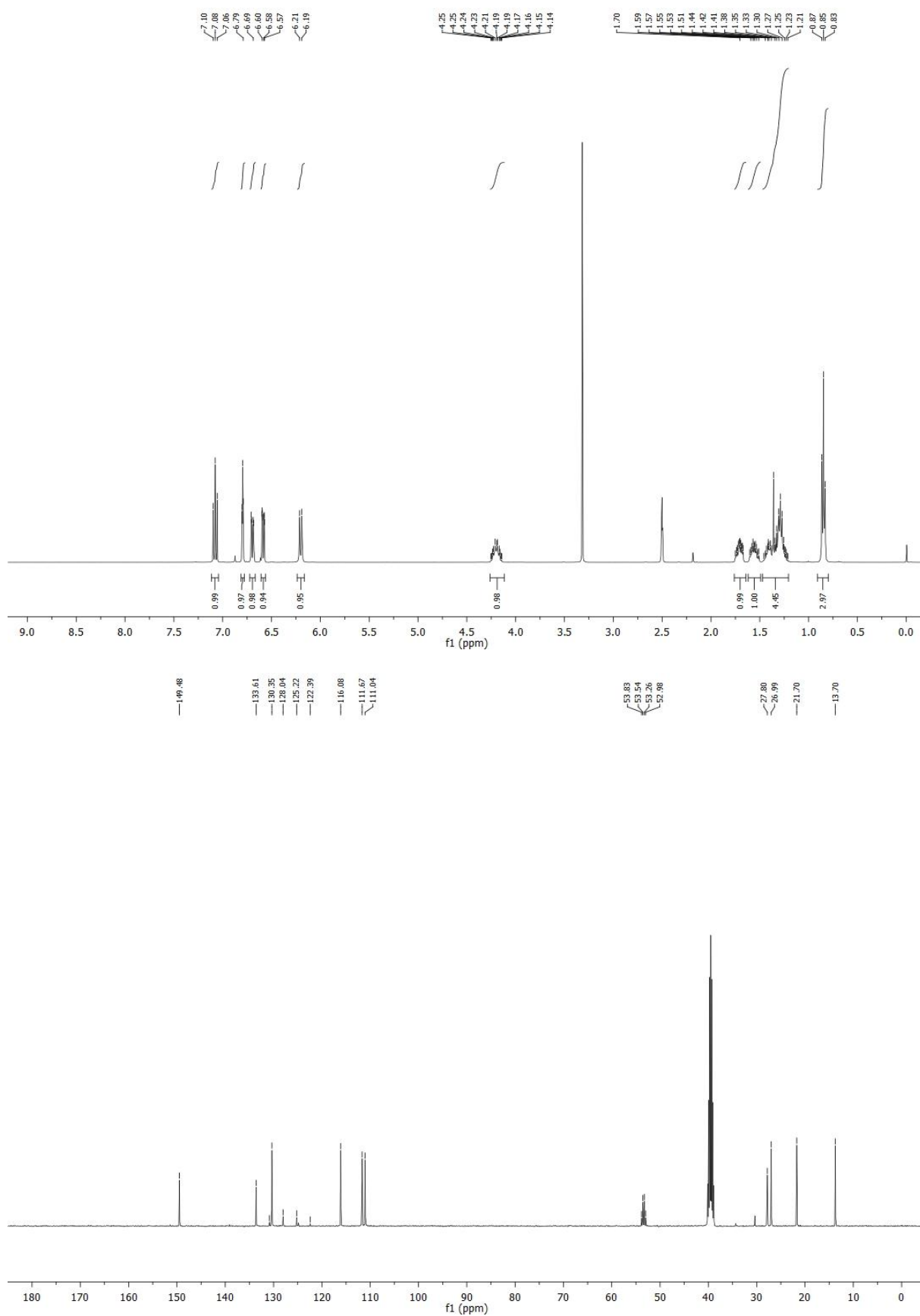
\* Impurities of solvents

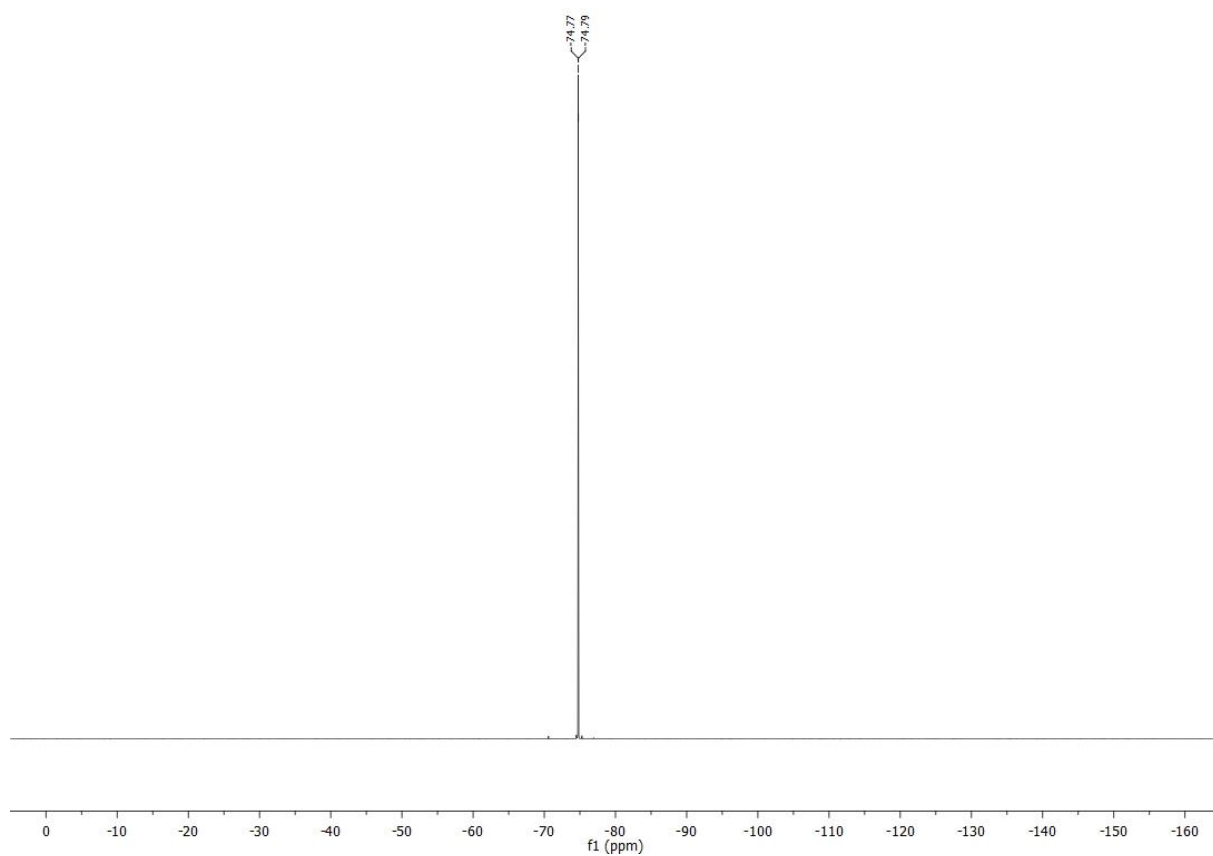


### 3-Chloro-*N*-(2,2,2-trifluoroethyl)aniline 4

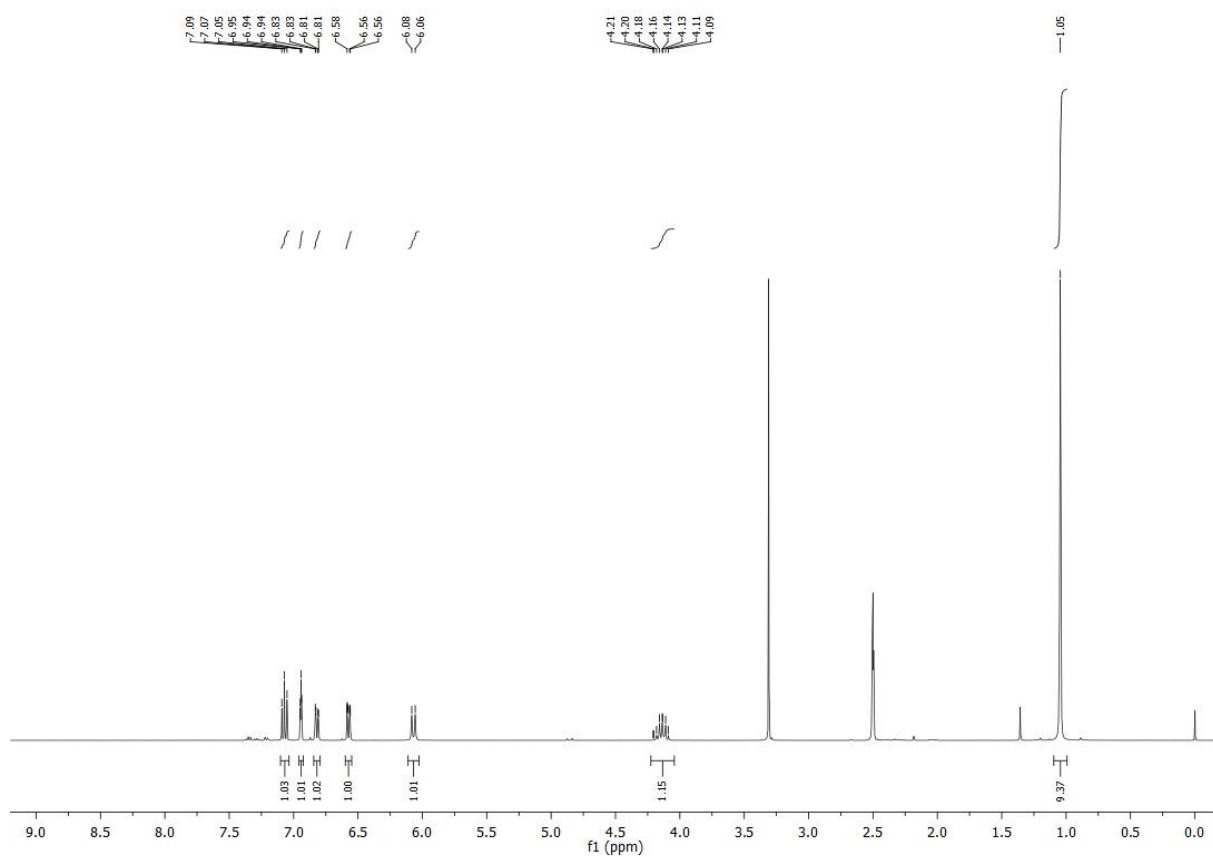


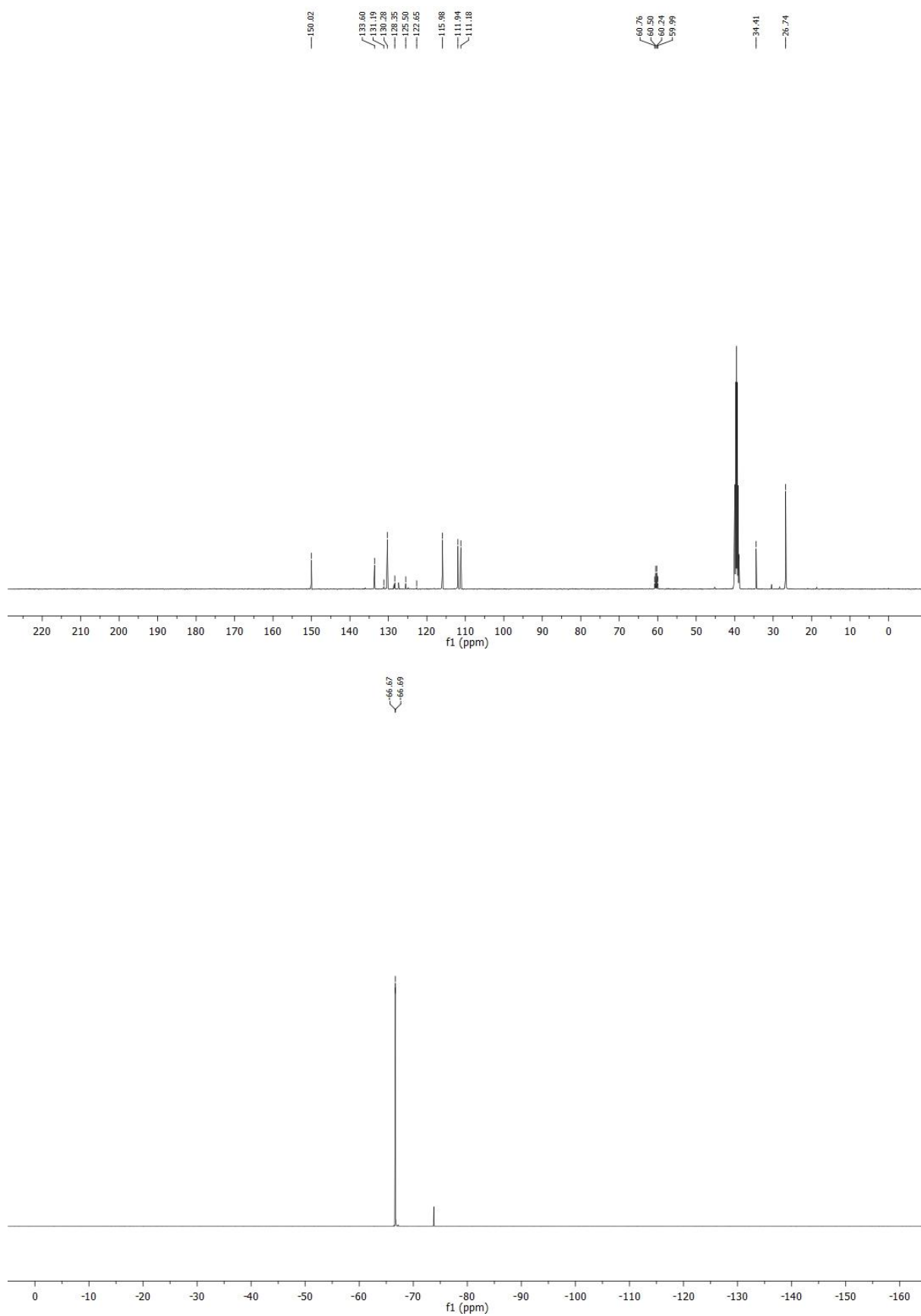
### 3-Chloro-*N*-(2,2,2-trifluoro-1-butylethyl)aniline 3b



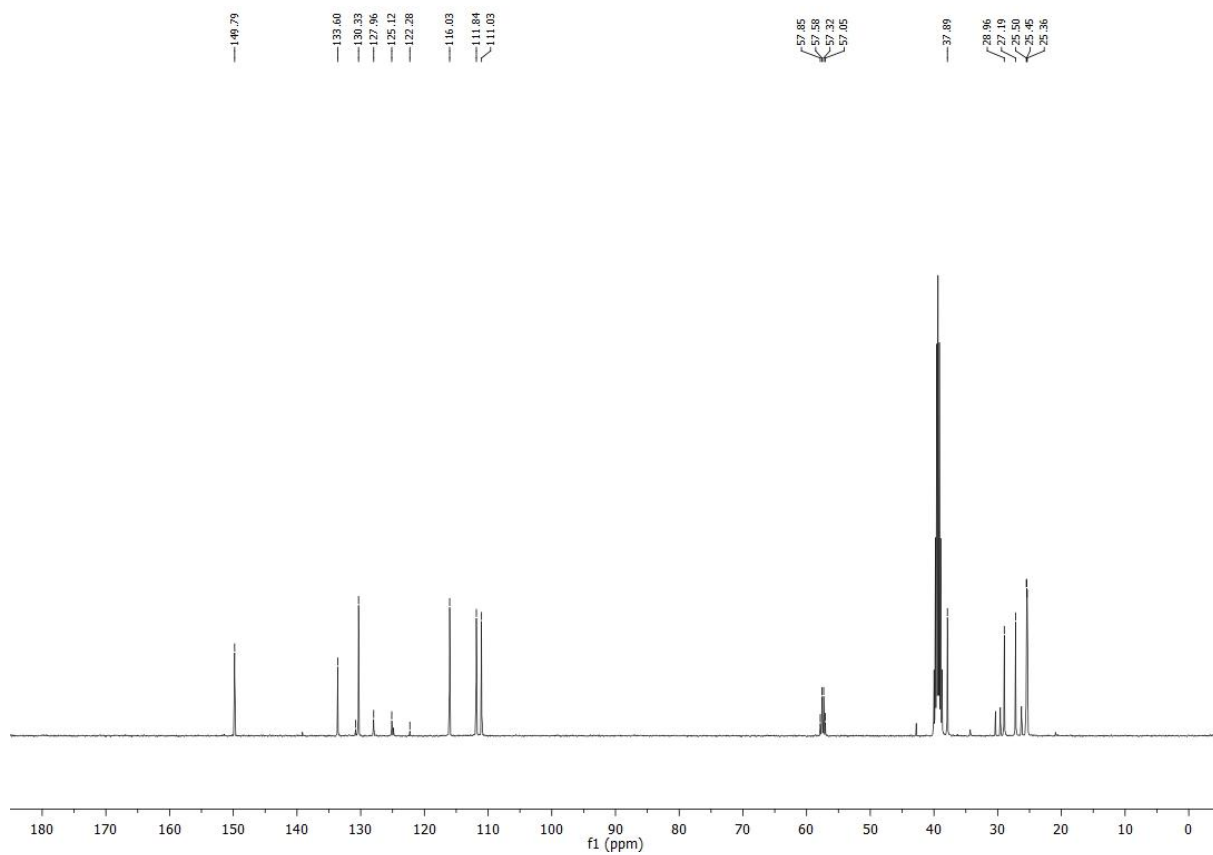
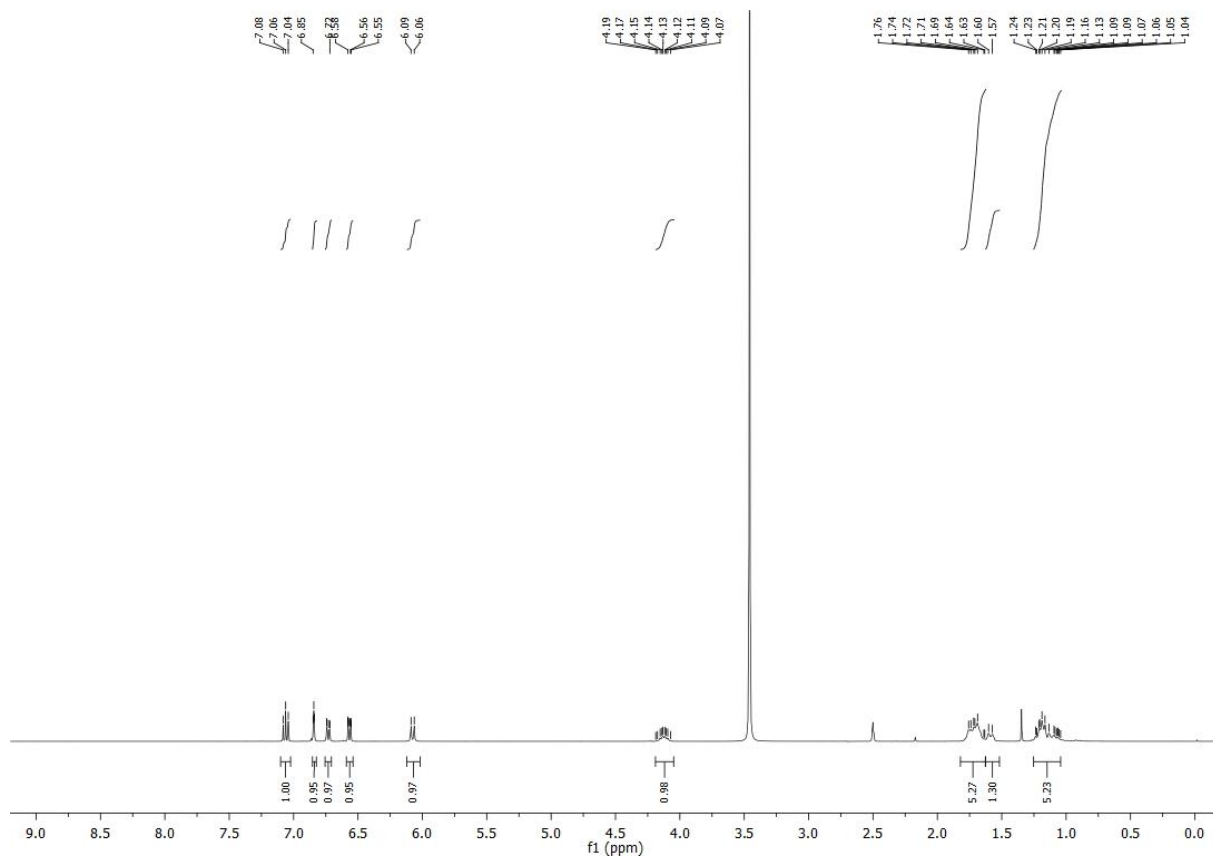


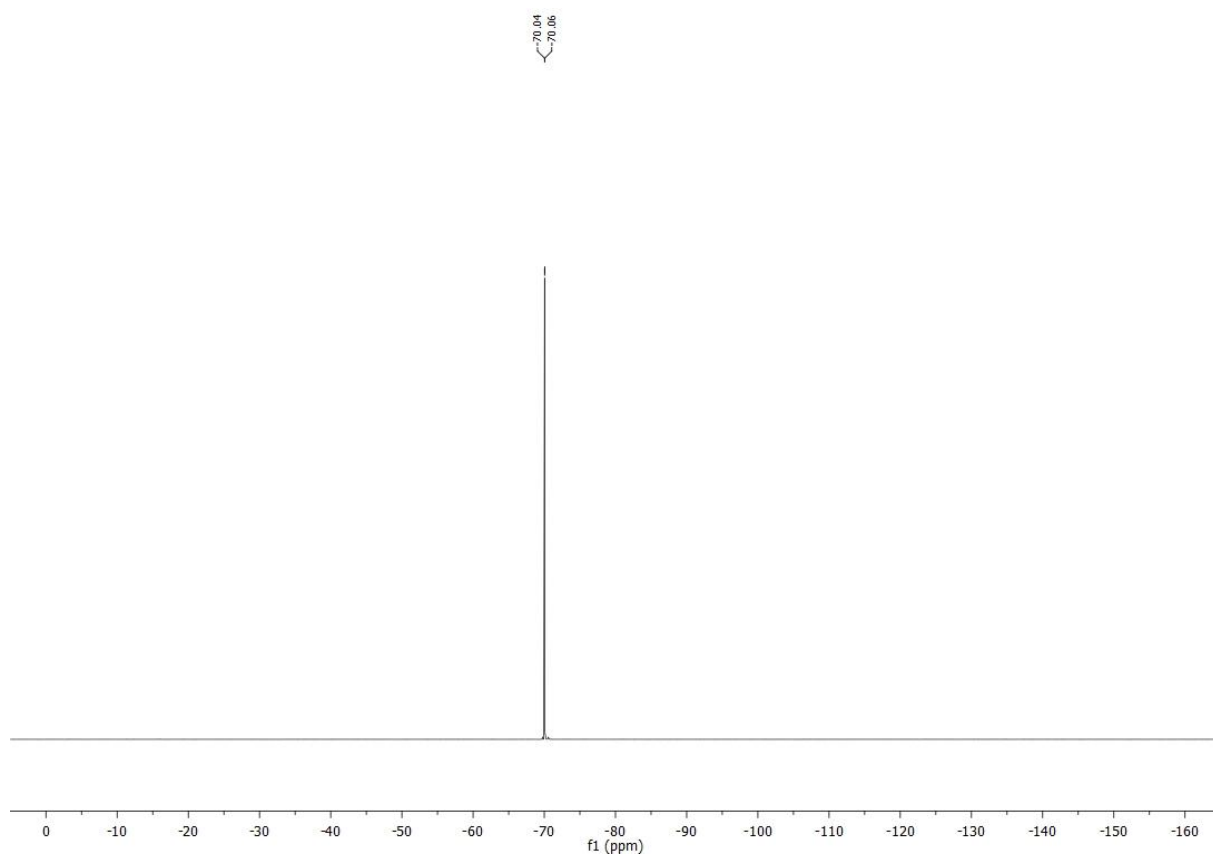
**3-Chloro-N-(2,2,2-trifluoro-1-tert-butylethyl)aniline 3c**



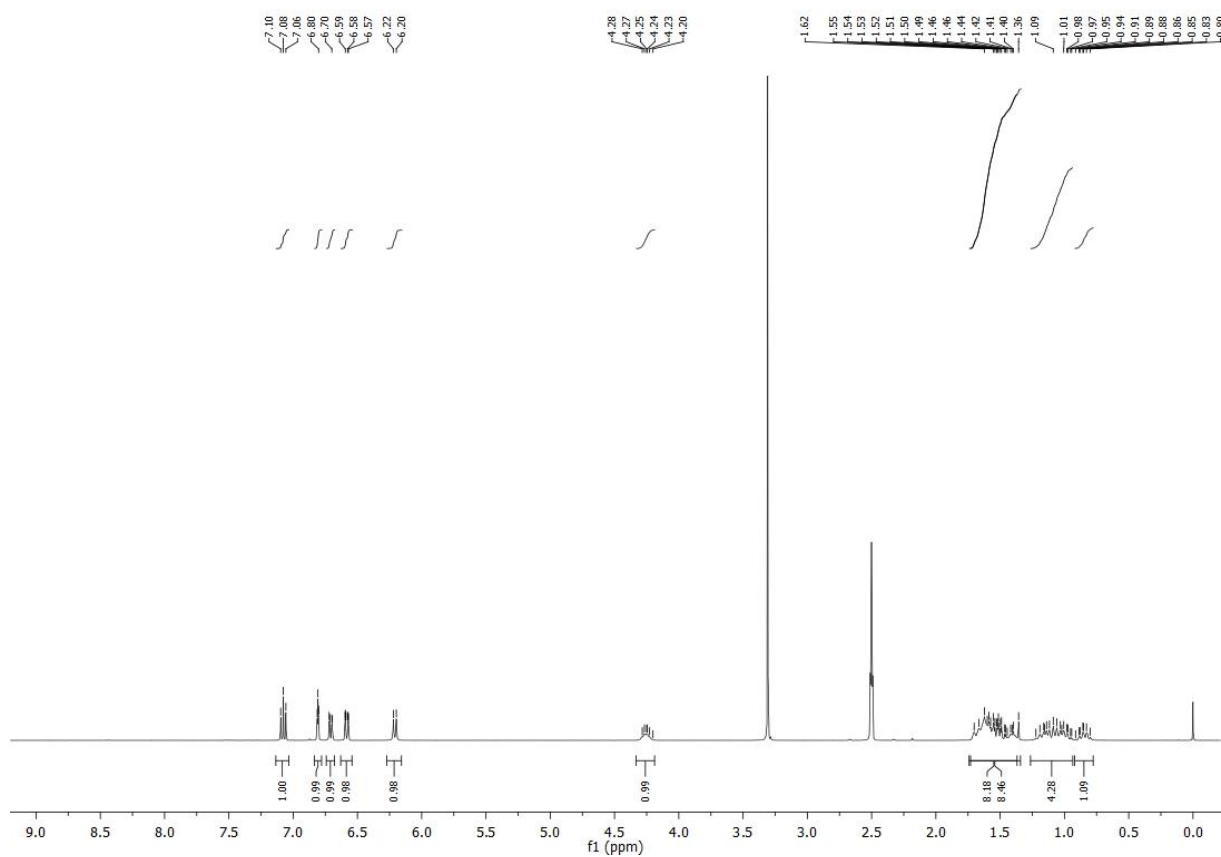


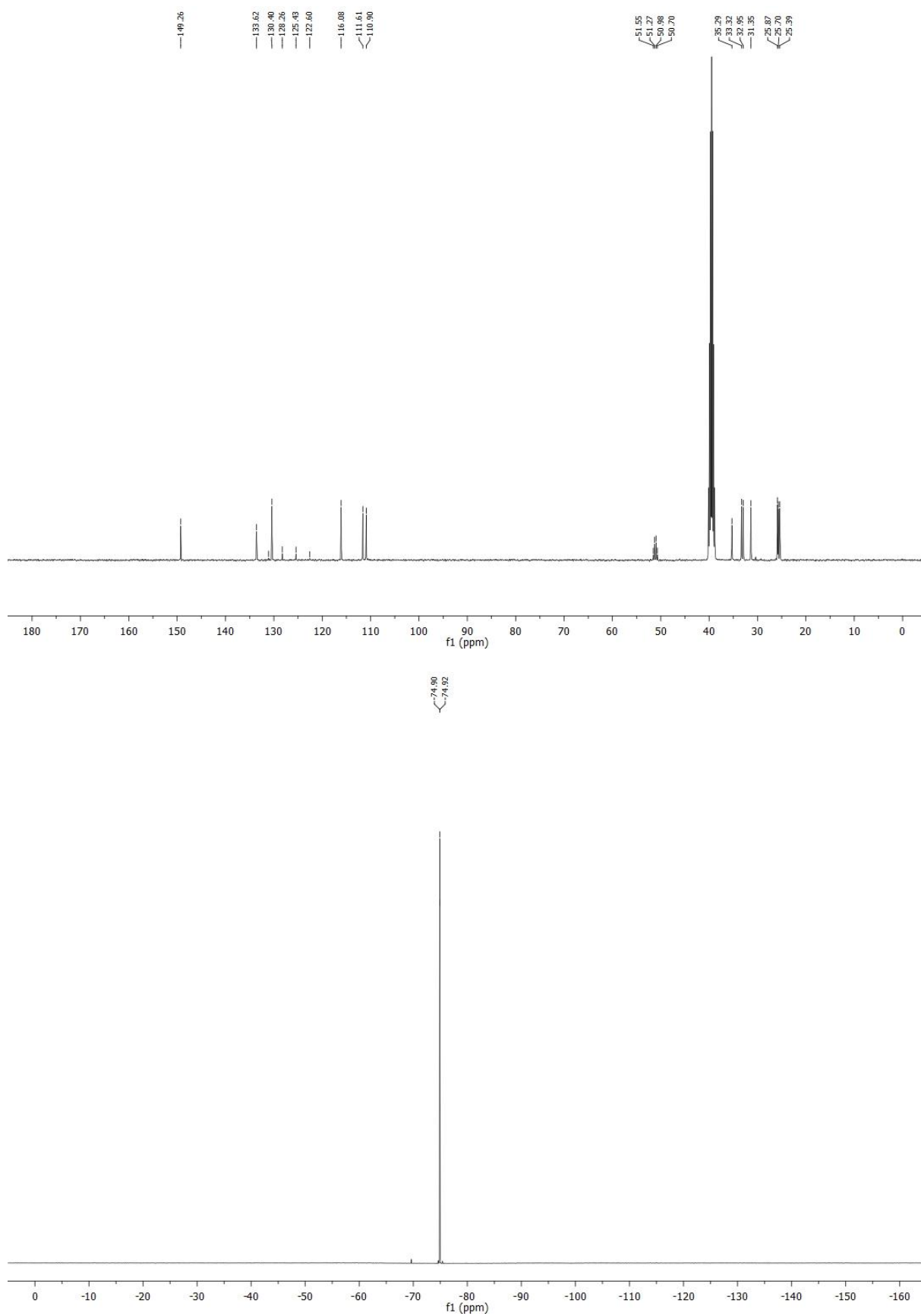
**3-Chloro-*N*-(2,2,2-trifluoro-1-cyclohexylethyl)aniline 3d**





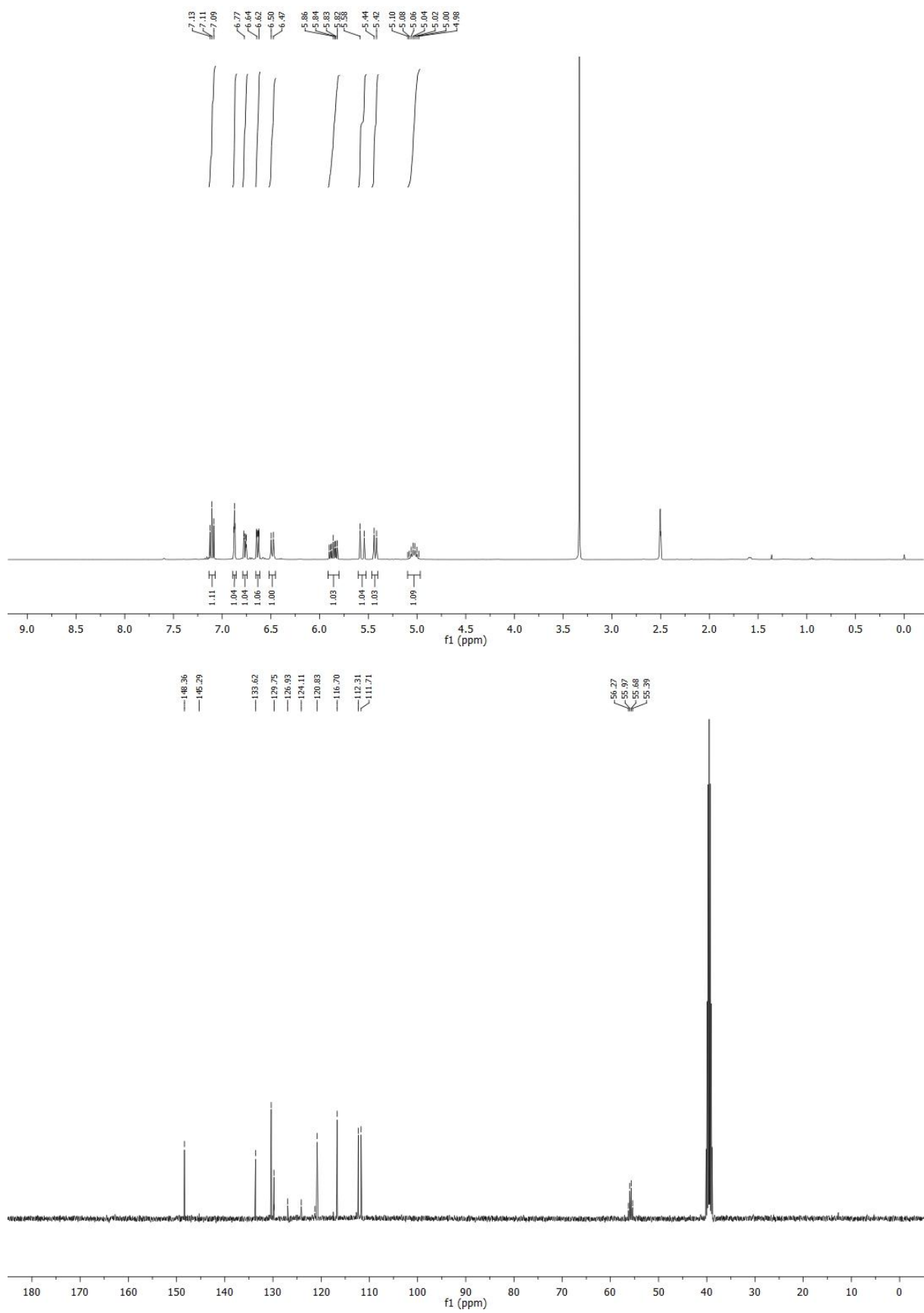
### 3-Chloro-*N*-(2,2,2-trifluoro-1-methylcyclohexylethyl)aniline 3e

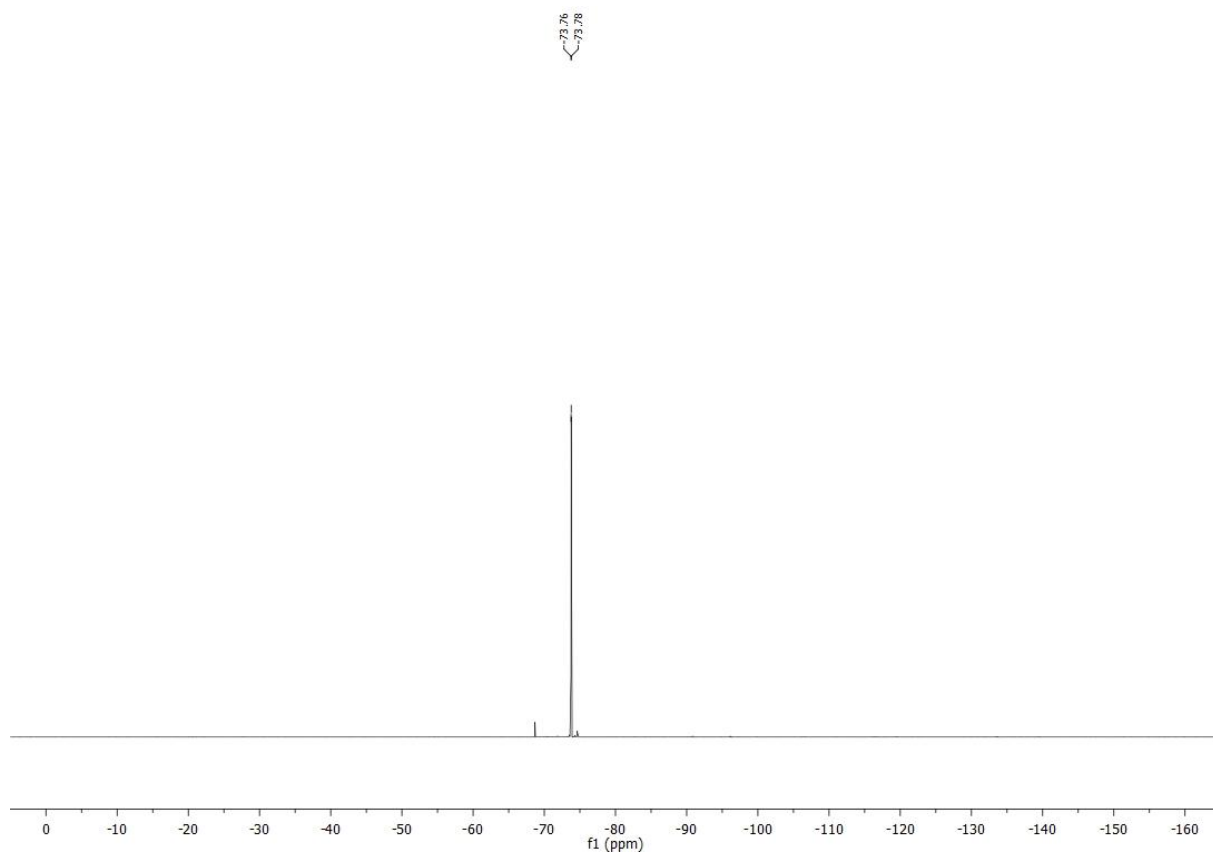




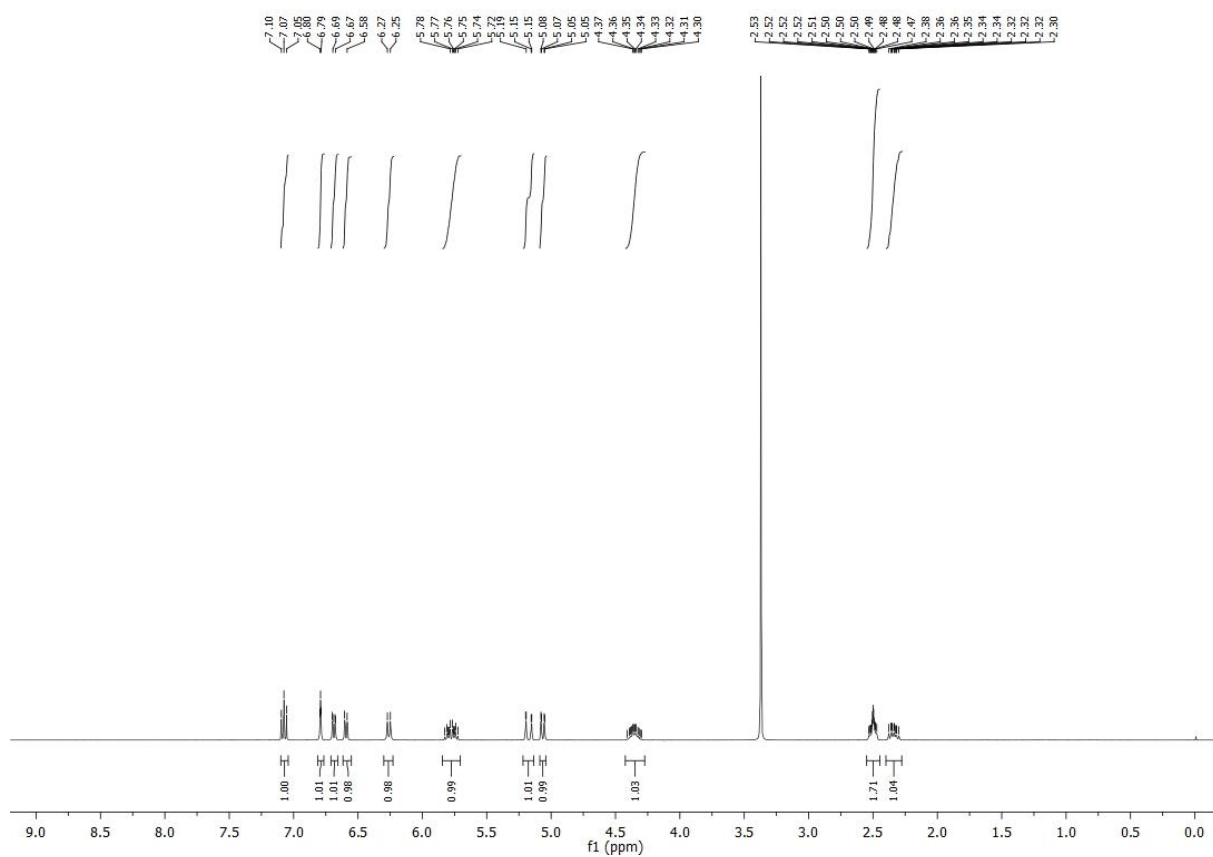
**3-Chloro-*N*-(2,2,2-trifluoro-1-vinylethyl)aniline 3f**

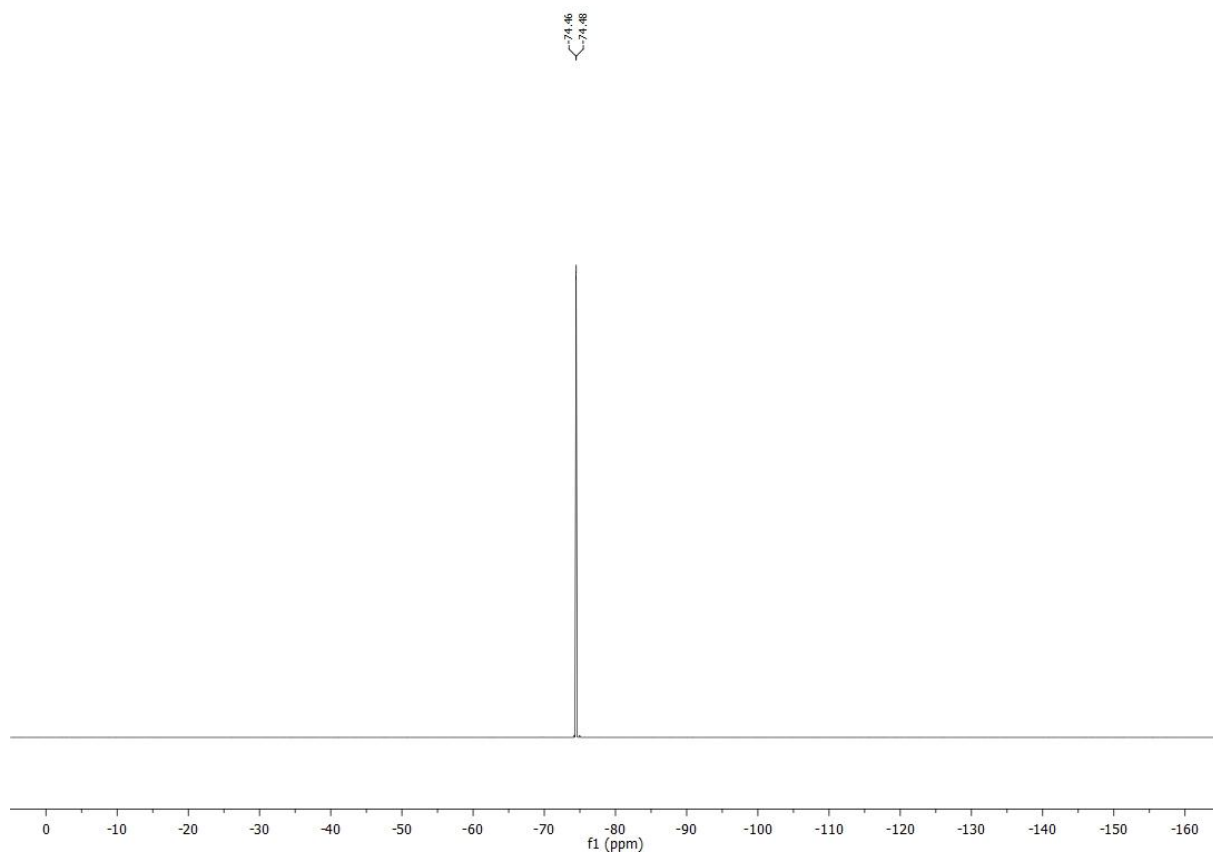
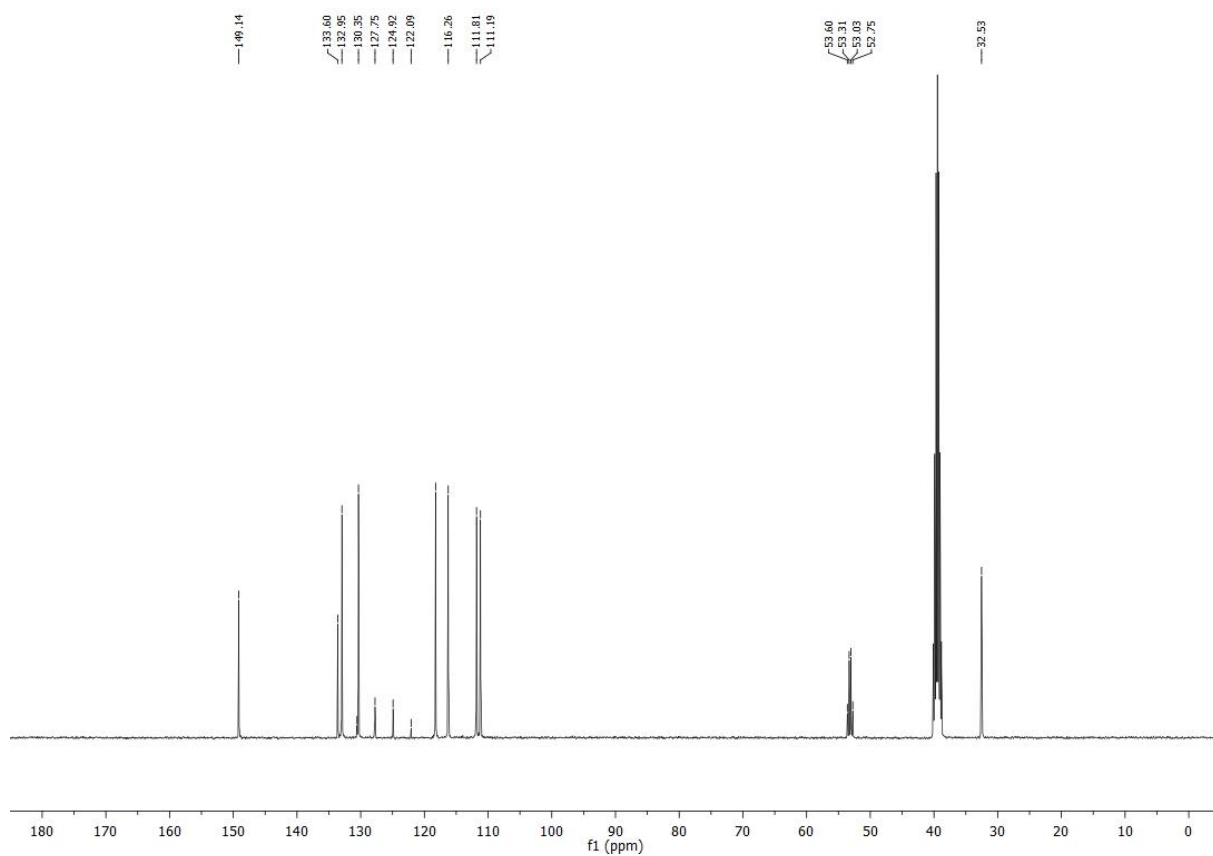




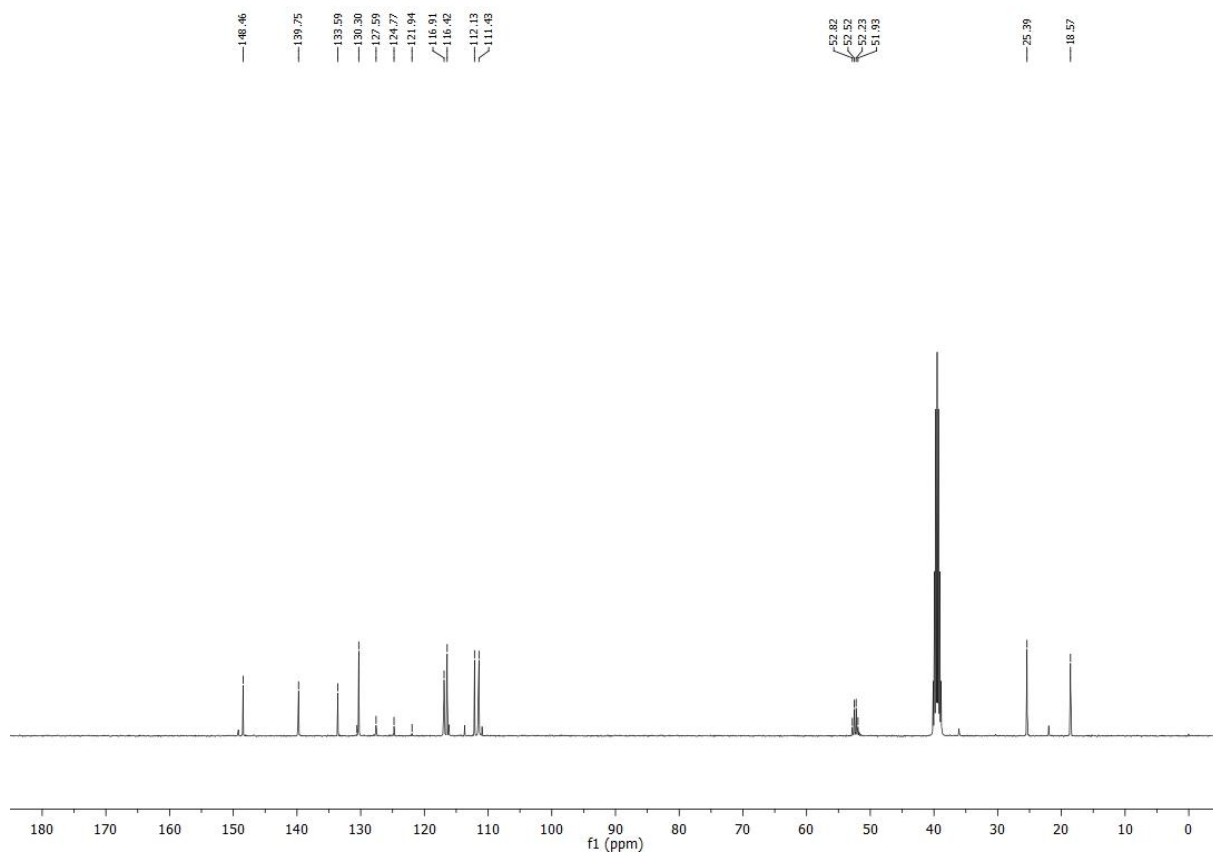
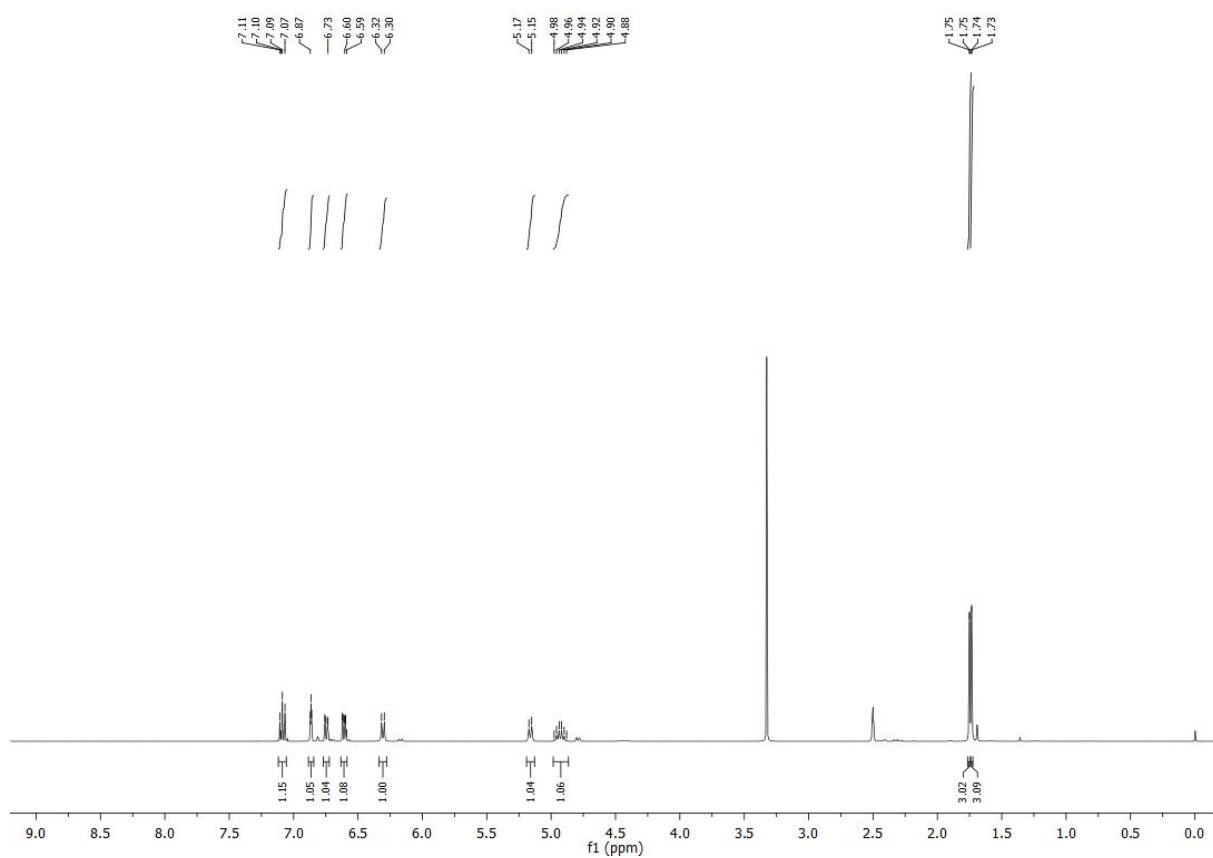


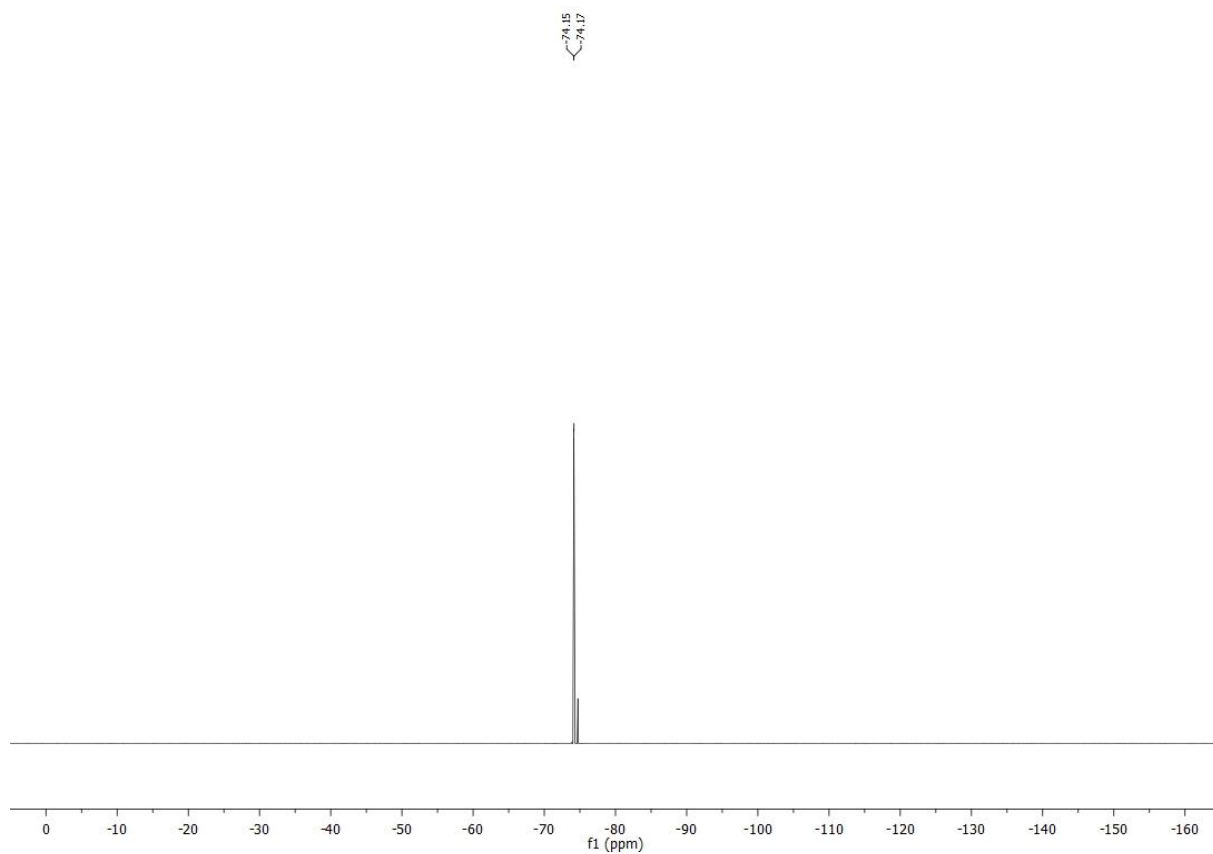
### 3-Chloro-N-(2,2,2-trifluoro-1-allylethyl)aniline 3g



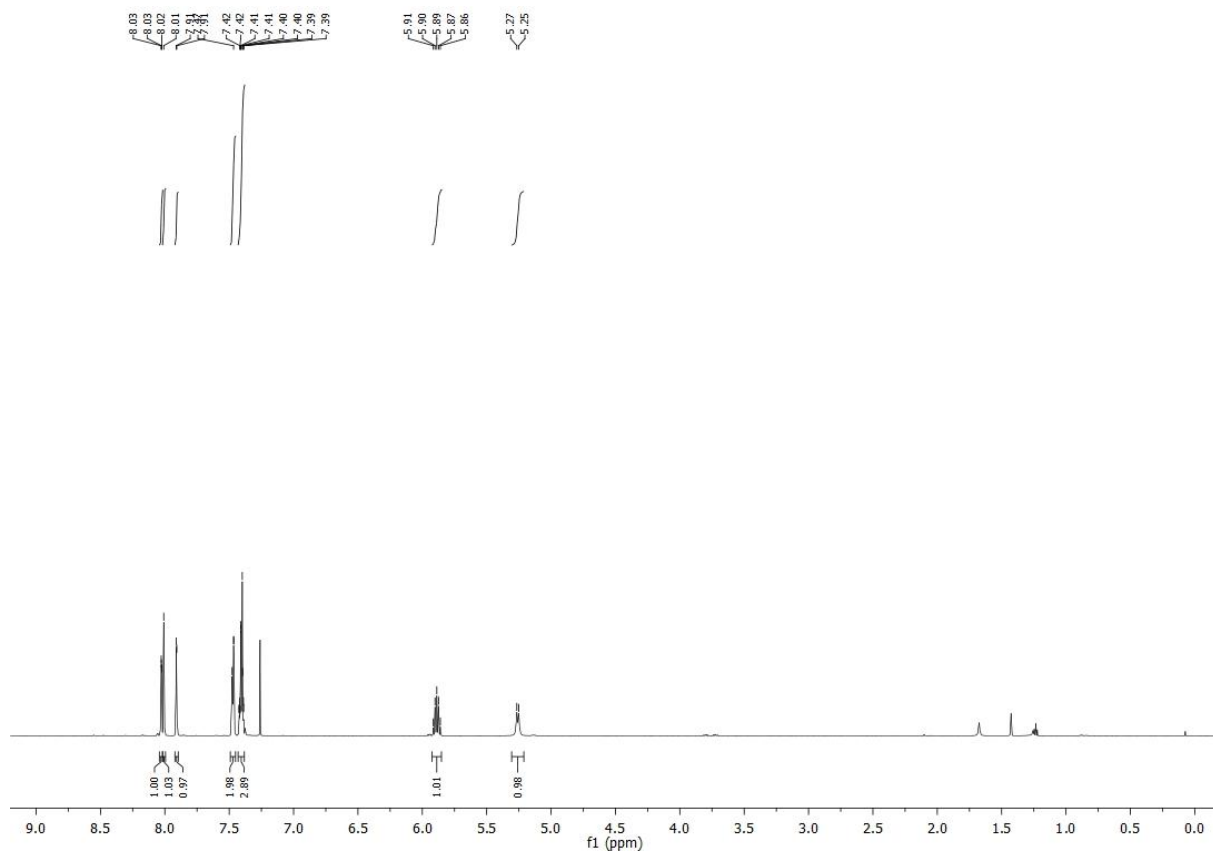


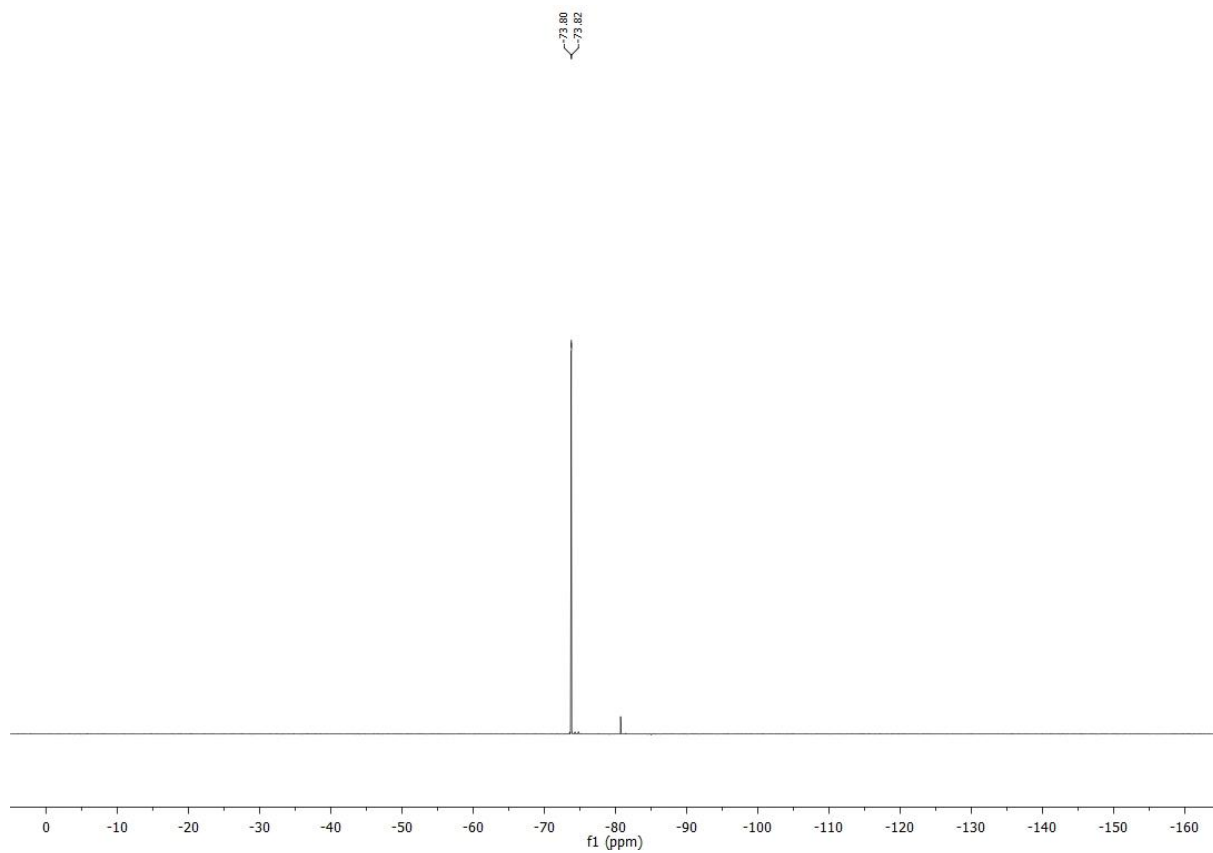
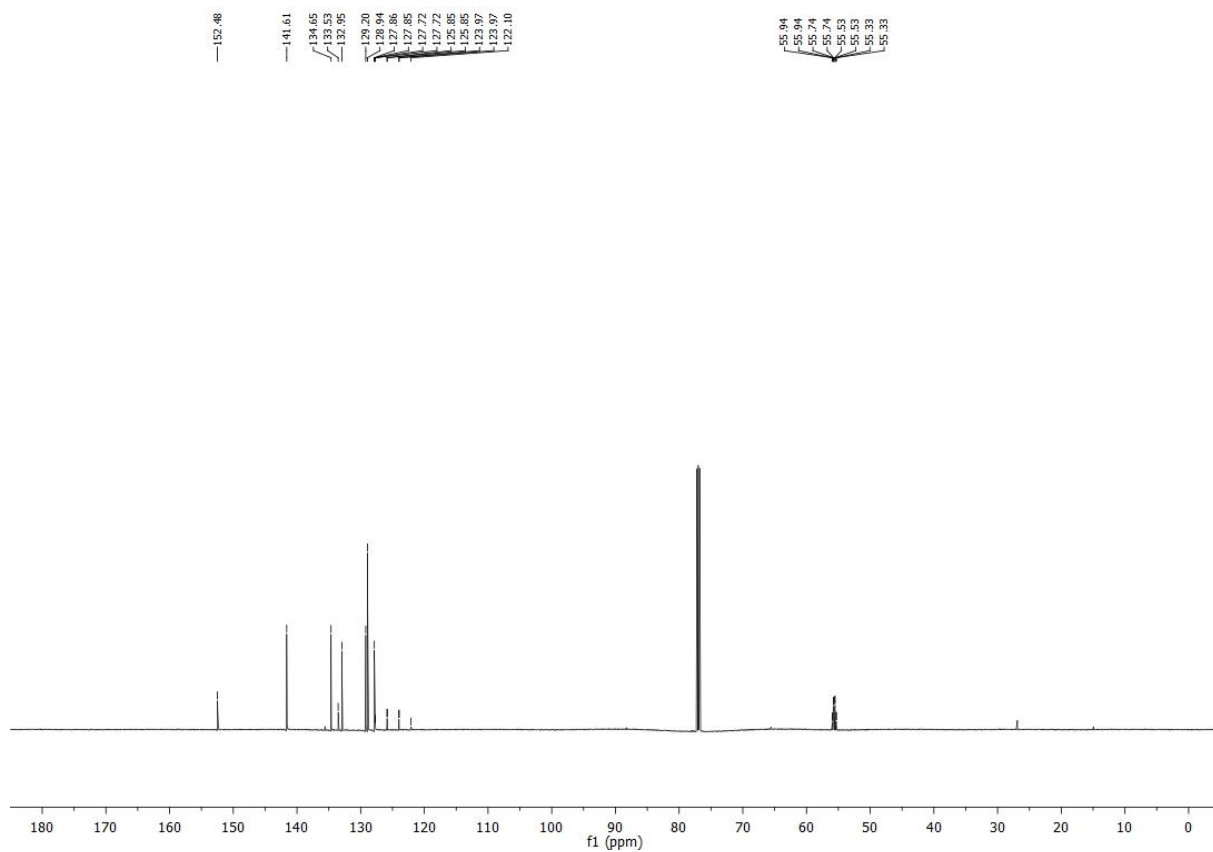
### 3-Chloro-N-(2,2,2-trifluoro-1-dimethylethyl)aniline 3h





***N*-(2,2,2-Trifluoro-1-phenylethyl)aminopyrazine 5**





**5-(*tert*-Butyl)-*N*-(2,2,2-trifluoro-1-phenylethyl)isoxazol-3-amine 6**

