

*Supporting Information*

**Superelectrophilic Csp<sup>3</sup>-H bond fluorination of aliphatic amines in superacid: The striking role of ammonium-carbenium dications**

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## A. General method

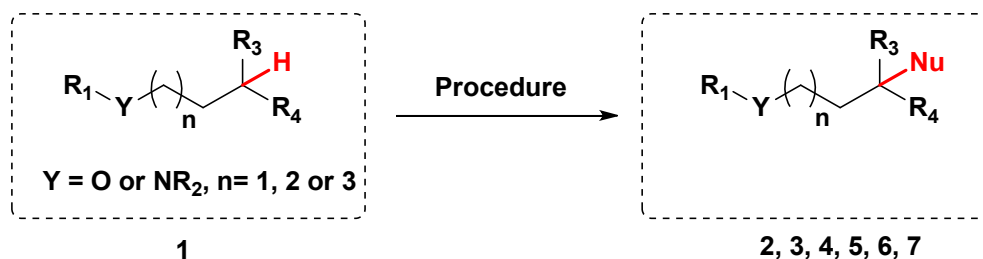
The authors draw the reader's attention to the dangerous features of superacidic chemistry. Handling of hydrogen fluoride and antimony pentafluoride must be done by experienced chemists with all the necessary safety arrangements in place.

Reactions performed in superacid were carried out in a sealed Teflon<sup>®</sup> flask with a magnetic stirrer. No further precautions have to be taken to prevent mixture from moisture (test reaction worked out in anhydrous conditions leads to the same results as expected).

The separation of the reaction crudes is carried out by manual flash chromatography or using a Combiflash Rf200 device equipped with UV (254 nm) and ELSD detectors. TLC was carried out on aluminium sheets precoated with silica gel (Merk); the spots were visualized under UV light ( $\lambda=254$  nm). Yields refer to isolated pure products.

All <sup>1</sup>H NMR, <sup>13</sup>C NMR, and <sup>19</sup>F NMR spectra were respectively recorded at 400 (or 500) MHz, 100 (or 125) MHz and 376 (or 471) MHz on Avance Nandbay 400 MHz and Avance Neo Avance III 1BAY spectrometers, using a convenient deuterated solvent (reported in the characterization charts) and the residual peak of CDCl<sub>3</sub> for <sup>1</sup>H NMR as reference and C<sub>6</sub>F<sub>6</sub> as external standard for <sup>19</sup>F NMR. Data are presented as follows: chemical shift, integration, multiplicity (bs = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintuplet, sex = sextuplet, m = multiplet), and coupling constant (*J*/Hz). All melting points were determined in a capillary tube with a device Büchi melting point B-545 and high-resolution mass-spectra were obtained on a Waters Xevo Qtof spectrometer.

## General Pathway



Substrates **1** were synthesized according to literature procedure or are commercially available. Products **2** refer to fluorinated compounds. Products **3** refer to hydroxylated compounds. Products **4, 5, 6** and **7** refer to the addition of other nucleophiles.

## General procedures for synthesis of substrates **1**

### Procedure 1:<sup>1</sup>

The corresponding amine (1.0 equiv.) was dissolved in THF or DMF at 0 °C and sodium hydride (1.2 equiv., 60% in oil) was added. After 15 min at 0 °C, the corresponding alkyl bromide (1.0 or 2.0 equiv.) was added *via* syringe during 15 min at 0 °C, then the mixture was stirred at room temperature until completion by TLC. The mixture reaction was concentrated, then water and dichloromethane or ethyl acetate were added. The aqueous phase was separated and extracted with additional portions of solvent. The combined organic phases were dried with  $MgSO_4$ , filtered, and concentrated to give the corresponding product after purification by flash chromatography.

### Procedure 2:<sup>2</sup>

The corresponding acyl chloride (1.0 equiv.) was dissolved in DCM under nitrogen atmosphere at 0 °C and then corresponding amine (1.5 equiv.) was added *via* syringe. After 10 min at 0 °C,  $Et_3N$  (3.0 equiv.) was added *via* syringe. The mixture was stirred for 12 hours at room temperature. The crude reaction was quenched by aqueous  $NH_4Cl$  and washed with HCl aq.

<sup>1</sup> Y. Yu, Q. Tang, Z. Xu, S. Li, M. Jin, Z. Zhao, C. Dong, S. Wu, H.B. Zhou, *Eur. J. Med. Chem.* **2018**, *159*, 206-216.

<sup>2</sup> I. Buslov, X. Hu, *Adv. Synth. Catal.* **2014**, *356*, 3325–3330.

(2M). Then, after extraction with DCM, the organic phase was washed with brine and dried over  $\text{MgSO}_4$ , filtered and concentrated to give the corresponding product after purification by flash chromatography.

## General procedures for synthesis of products

### Procedure A:

To a mixture of  $\text{HF/SbF}_5$  (22 mol%  $\text{SbF}_5$ ) maintained at  $-40\text{ }^\circ\text{C}$  in a Teflon<sup>®</sup> flask, was successively added the substrate and the carbon tetrachloride ( $\text{CCl}_4$ , 1.2 equiv.). The reaction mixture was magnetically stirred at the same temperature for 30 min. A mixture of hydrofluoric acid and pyridine (70/30 w/w) was then added. The mixture was magnetically stirred at the same temperature for 1 hour. The reaction mixture was then neutralized with water/ice and sodium carbonate and then extracted with dichloromethane (X3). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered and concentrated in vacuo. The products were isolated by column chromatography over silica gel.

### Procedure A':

To a mixture of  $\text{HF/SbF}_5$  (22 mol%  $\text{SbF}_5$ ) maintained at the required temperature in a Teflon<sup>®</sup> flask, was successively added the substrate and the carbon tetrachloride ( $\text{CCl}_4$ , 2.4 equiv.). The reaction mixture was magnetically stirred at the same temperature for 30 min. A mixture of hydrofluoric acid and pyridine (70/30 w/w) was then added. The mixture was magnetically stirred at the same temperature for 1 hour. The reaction mixture was then neutralized with water/ice and sodium carbonate and then extracted with dichloromethane (X3). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered and concentrated in vacuo. The products were isolated by column chromatography over silica gel.

### Procedure B:

To a mixture of  $\text{HF/SbF}_5$  (22 mol%  $\text{SbF}_5$ ) maintained at  $-20\text{ }^\circ\text{C}$  in a Teflon<sup>®</sup> flask, was successively added the substrate and the carbon tetrachloride ( $\text{CCl}_4$ , 1.2 equiv.). The reaction mixture was magnetically stirred at the same temperature for 10 min, then the nucleophilic partner was added and the reaction mixture was magnetically stirred at  $0\text{ }^\circ\text{C}$  during 15 min.

The reaction mixture was then neutralized with water/ice and sodium carbonate and then extracted with dichloromethane (X3). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered and concentrated in vacuo. The products were isolated by column chromatography over silica gel.

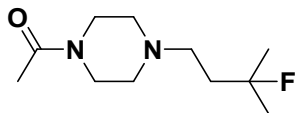
**Procedure C:**

To a mixture of HF/ $\text{SbF}_5$  (22 mol%  $\text{SbF}_5$ ) maintained at  $-20\text{ }^\circ\text{C}$  in a Teflon<sup>®</sup> flask, was successively added the substrate and the carbon tetrachloride ( $\text{CCl}_4$ , 1.2 equiv.). The reaction mixture was magnetically stirred at the same temperature for 30 min, then at room temperature for 24 hours. The reaction mixture was then neutralized with water/ice and sodium carbonate and then extracted with dichloromethane (X3). The combined organic phases were dried ( $\text{MgSO}_4$ ), filtered and concentrated in vacuo. The products were isolated by column chromatography over silica gel.

## B. Experimental procedures and characterization data

**Compound 2a:** 1-(4-(3-fluoro-3-methylbutyl)piperazin-1-yl)ethan-1-one

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This compound was obtained after reaction of substrate **1a** (160 mg, 0.8 mmol), following the general procedure **A** with 6 mL of HF/SbF<sub>5</sub> and 2 mL of HF/Pyr. The crude reaction mixture was purified over silica gel with dichloromethane/methanol (98/2) as the eluent, thereby obtaining compound **2a** (121 mg, 69 %) as an orange oil.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm) δ:** 3.61 (t, *J* = 4.9 Hz, 2H), 3.45 (t, *J* = 5.1 Hz, 2H), 2.47 (m, 2H), 2.43 (m, 4H), 2.08 (s, 3H), 1.81 (dm, *J* = 19.2 Hz, 2H), 1.36 (d, *J* = 21.5 Hz, 6H).

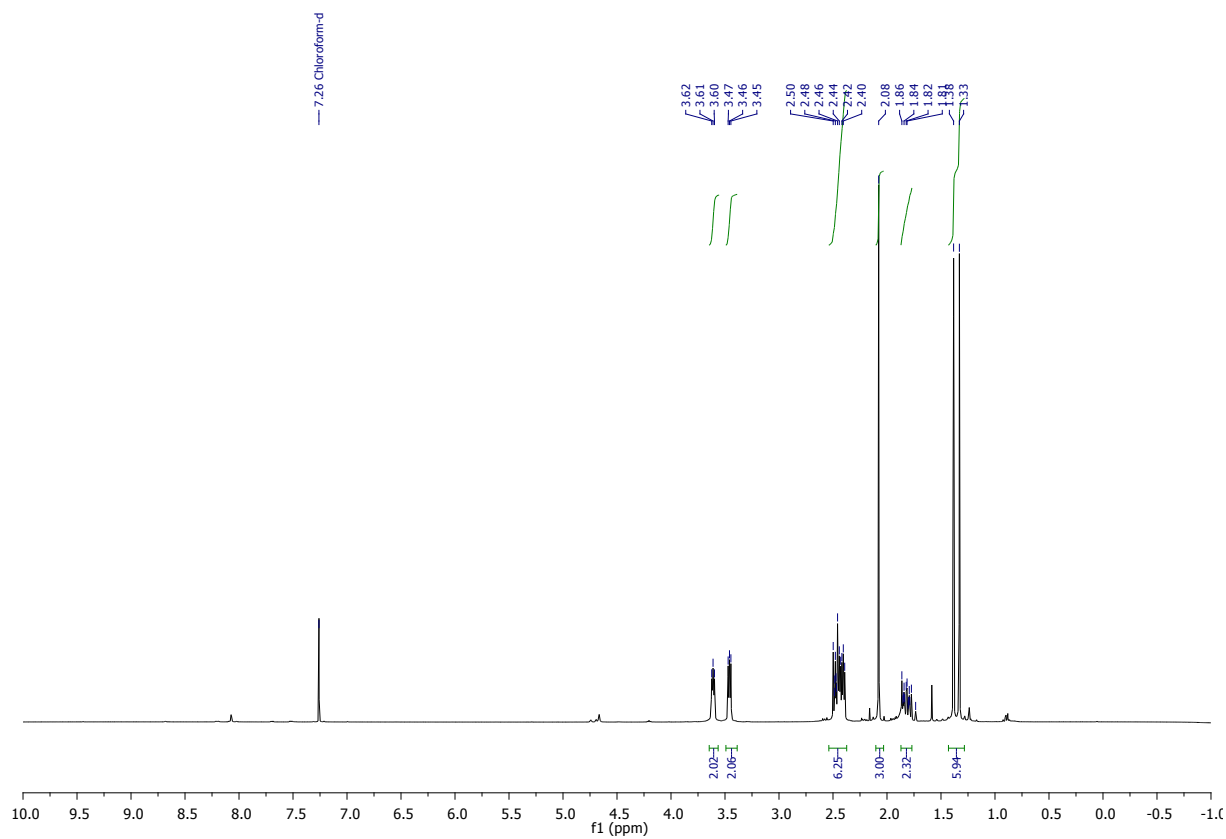
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm) δ:** 169.0 (C), 94.9 (d, *J* = 164 Hz, C), 53.5 (CH<sub>2</sub>), 53.2 (d, *J* = 6 Hz, CH<sub>2</sub>), 52.9 (CH<sub>2</sub>), 46.4 (CH<sub>2</sub>), 41.5 (CH<sub>2</sub>), 38.3 (d, *J* = 22 Hz, CH<sub>2</sub>), 27.0 (d, *J* = 23 Hz, 2 CH<sub>3</sub>), 21.5 (CH<sub>3</sub>).

**<sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>, ppm) δ:** -138.3.

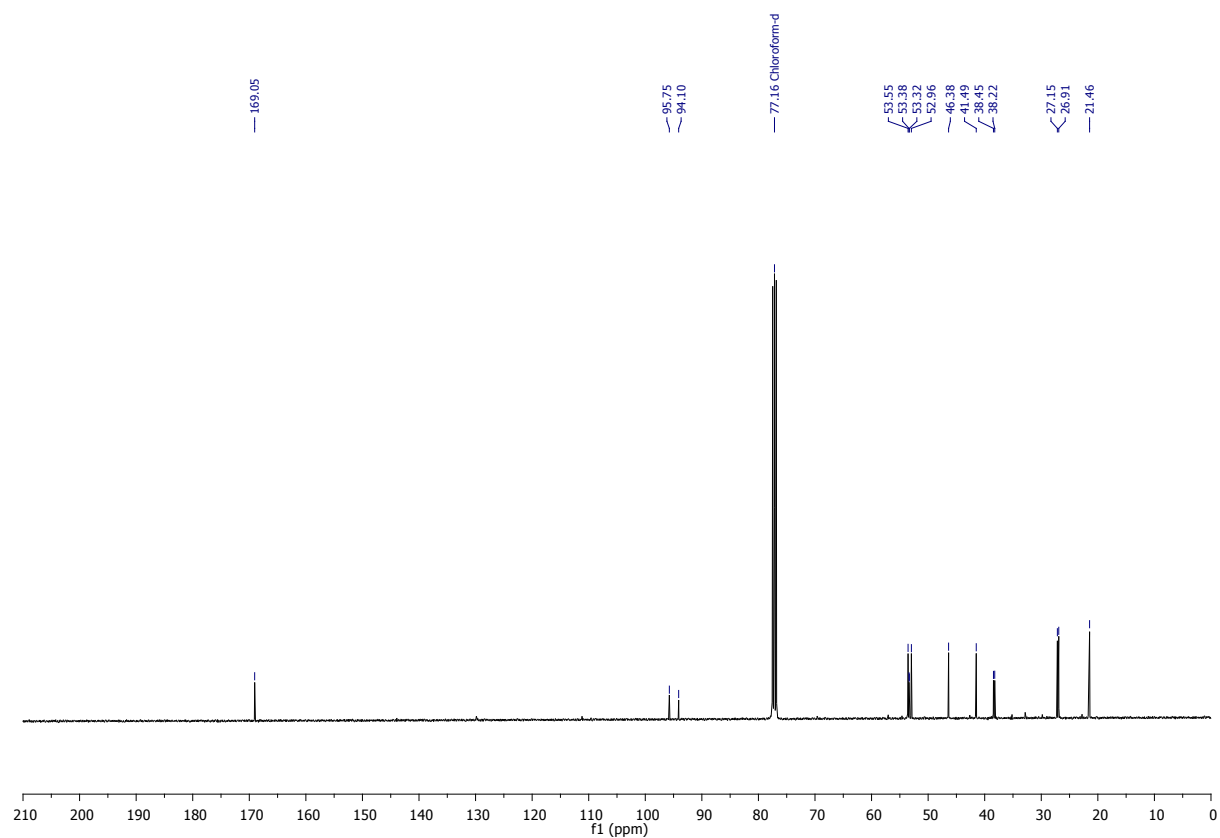
**HRMS (ESI):** *m/z* [M+H]<sup>+</sup> calc for C<sub>11</sub>H<sub>22</sub>FN<sub>2</sub>O : 217.171068, found 217.171585.



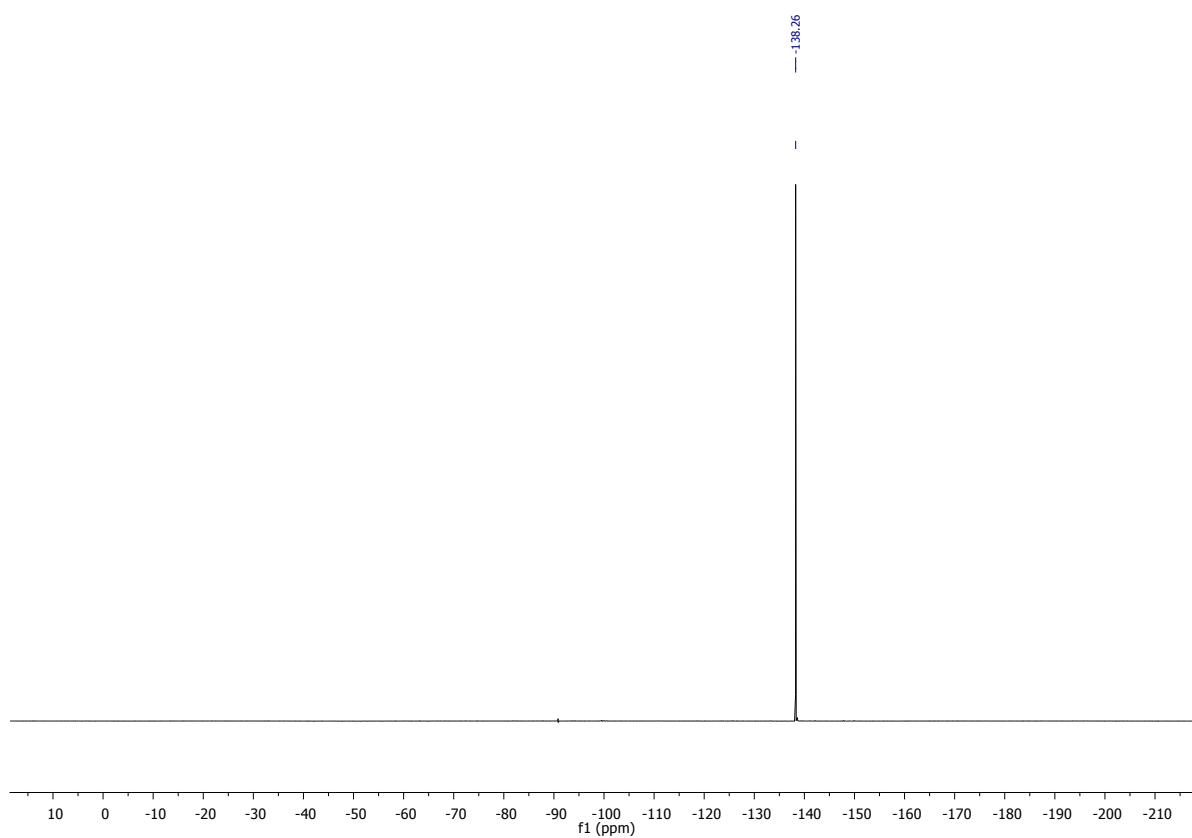
# <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



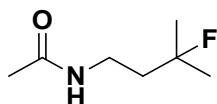
# <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)



**$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{CDCl}_3$ )**



## Compound 2b: N-(3-fluoro-3-methylbutyl)acetamide



This compound was obtained after reaction of 3-fluoro-3-methylbutan-1-amine **1b** (150 mg, 1.7 mmol), following the general procedure **A** with 6 mL of HF/SbF<sub>5</sub> and 2 mL of HF/Pyr. The crude reaction mixture was acetylated in water with an excess of acetyl chloride overnight at RT and purified over silica gel with dichloromethane/methanol (98/2) as the eluent, thereby obtaining compound **2b** (155 mg, 62 %) as a yellow oil.

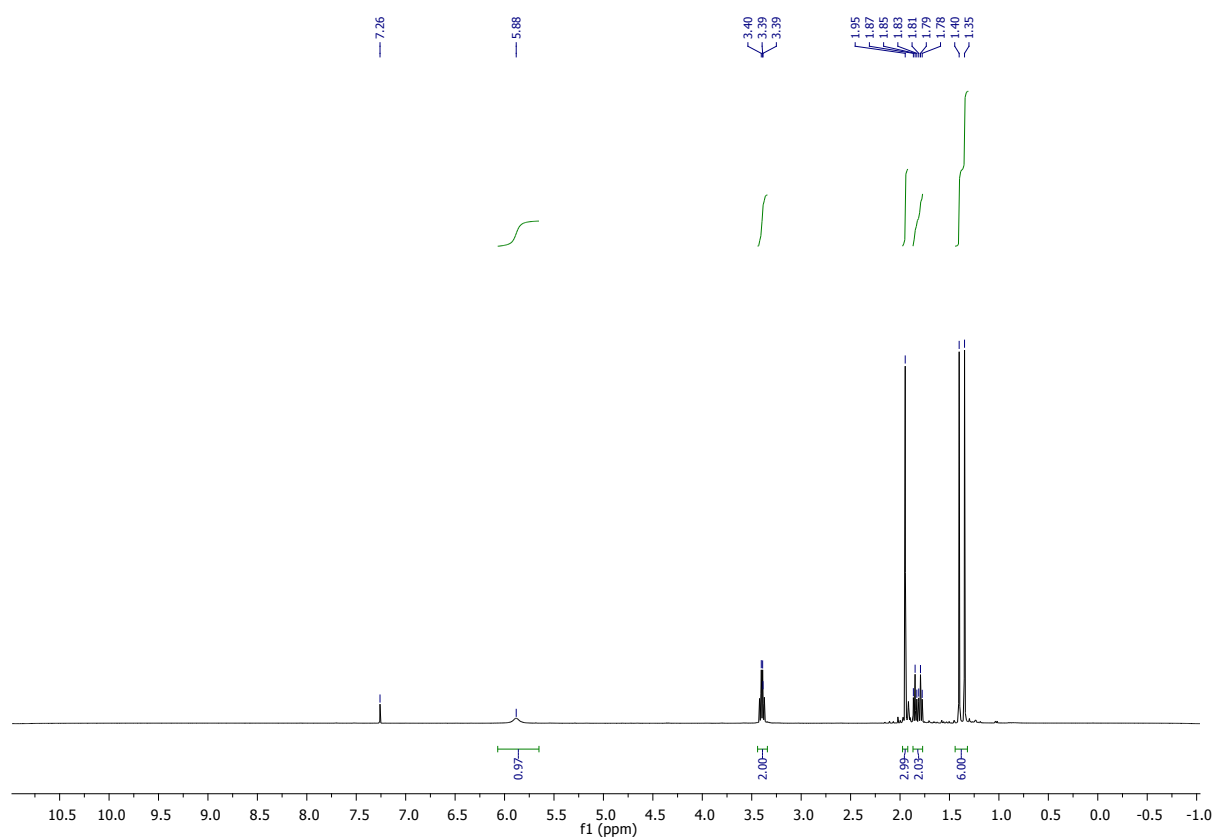
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm) δ:** 5.88 (s, NH), 3.39 (m, 2H), 1.95 (s, 3H), 1.80 (dt, *J* = 21.7 Hz, *J* = 6.9 Hz, 2H), 1.37 (d, *J* = 21.7 Hz, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm) δ:** 170.0 (C), 96.0 (d, *J* = 162 Hz, C), 40.0 (d, *J* = 21 Hz, CH<sub>2</sub>), 35.4 (d, *J* = 3 Hz, CH<sub>2</sub>), 26.8 (d, *J* = 24 Hz, 2 CH<sub>3</sub>), 23.4 (CH<sub>3</sub>).

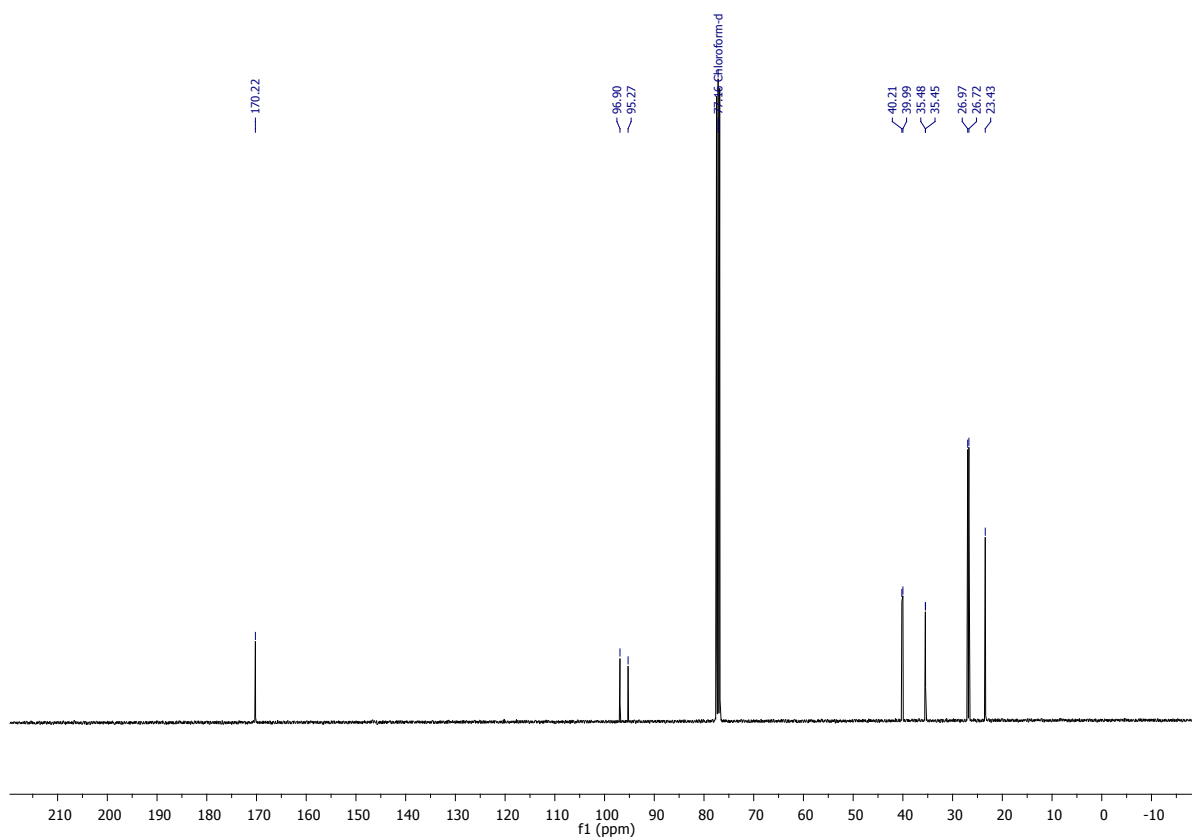
**<sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>, ppm) δ:** -138.0.

**HRMS (ESI):** *m/z* [M+Na]<sup>+</sup> calc for C<sub>7</sub>H<sub>14</sub>FNNaO : 170.0952, found 170.0955.

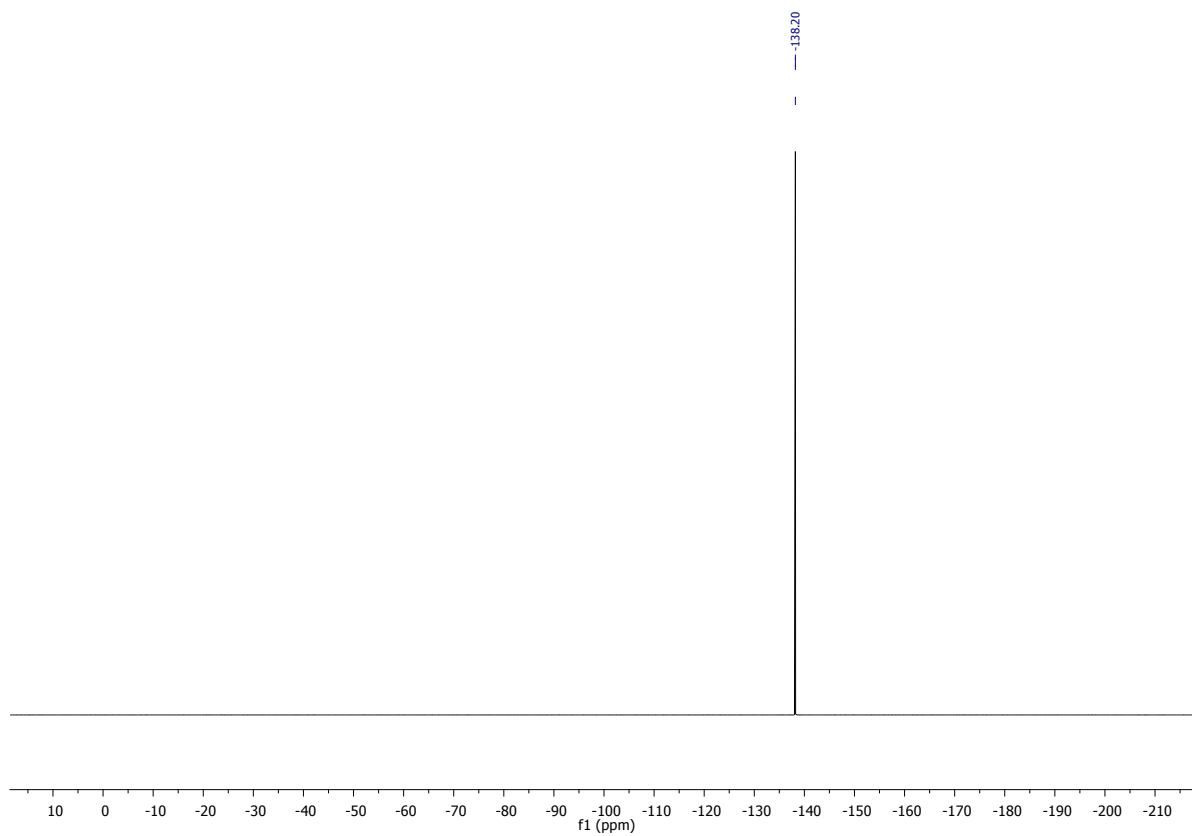
### <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )**

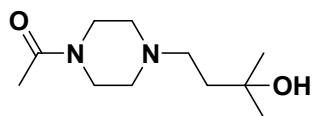


**$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{CDCl}_3$ )**



**Compound 3a:** 1-(4-(3-hydroxy-3-methylbutyl)piperazin-1-yl)ethan-1-one

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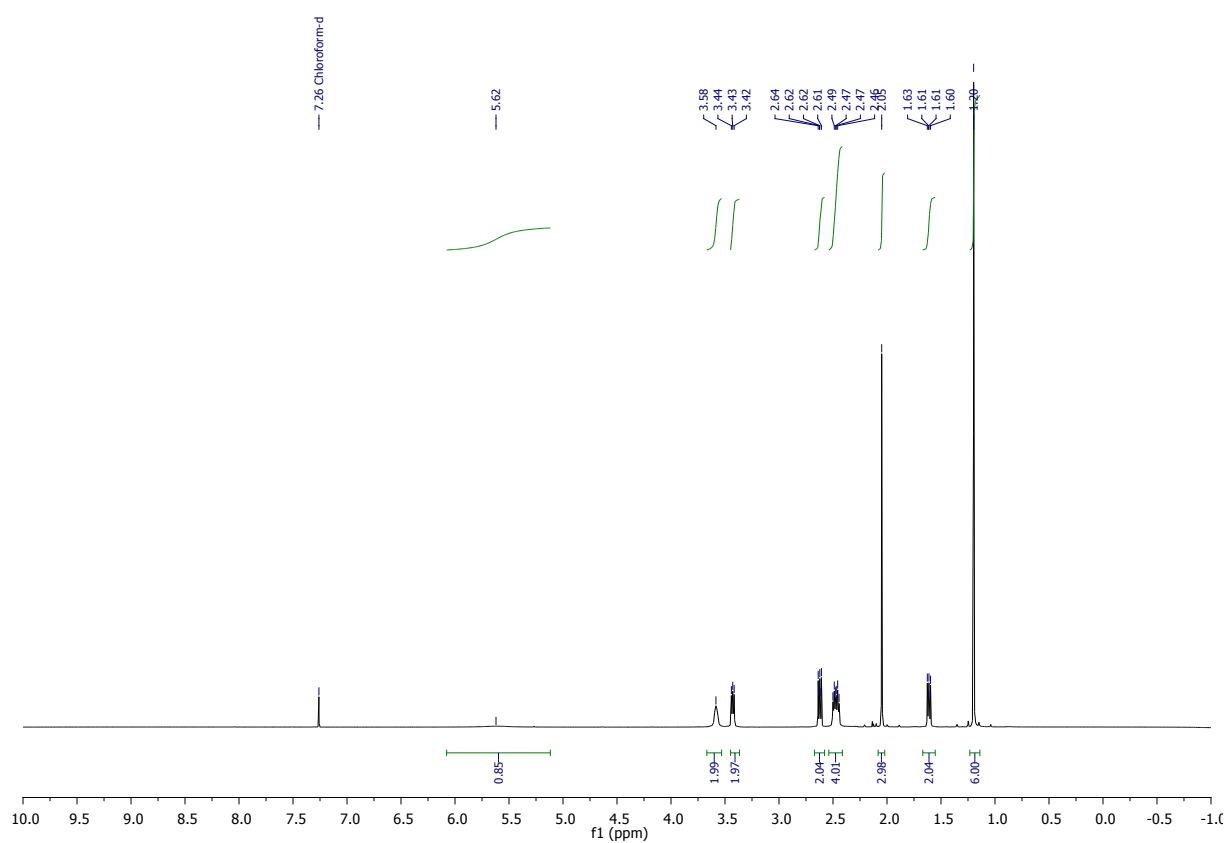
This compound was obtained after reaction of substrate **1a** (160 mg, 0.81 mmol), following the general procedure **C** with 6 mL of HF/SbF<sub>5</sub>, the mixture being stirred at -40 °C for 30 min without addition of HF/Pyridine. The crude reaction mixture was purified over silica gel with dichloromethane/methanol (98/2) as the eluent, thereby obtaining compound **2a** (96 mg, 55%) followed by compound **3a** (31 mg, 18%) as an orange oil.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm) δ:** 5.62 (bs, OH, 1H), 3.58 (m, 2H), 3.43 (t, *J* = 4.9 Hz, 2H), 2.62 (m, 2H), 2.47 (dt, *J* = 12.5 Hz, *J* = 5.0 Hz, 4H), 2.05 (s, 3H), 1.61 (m, 2H), 1.20 (s, 6H).

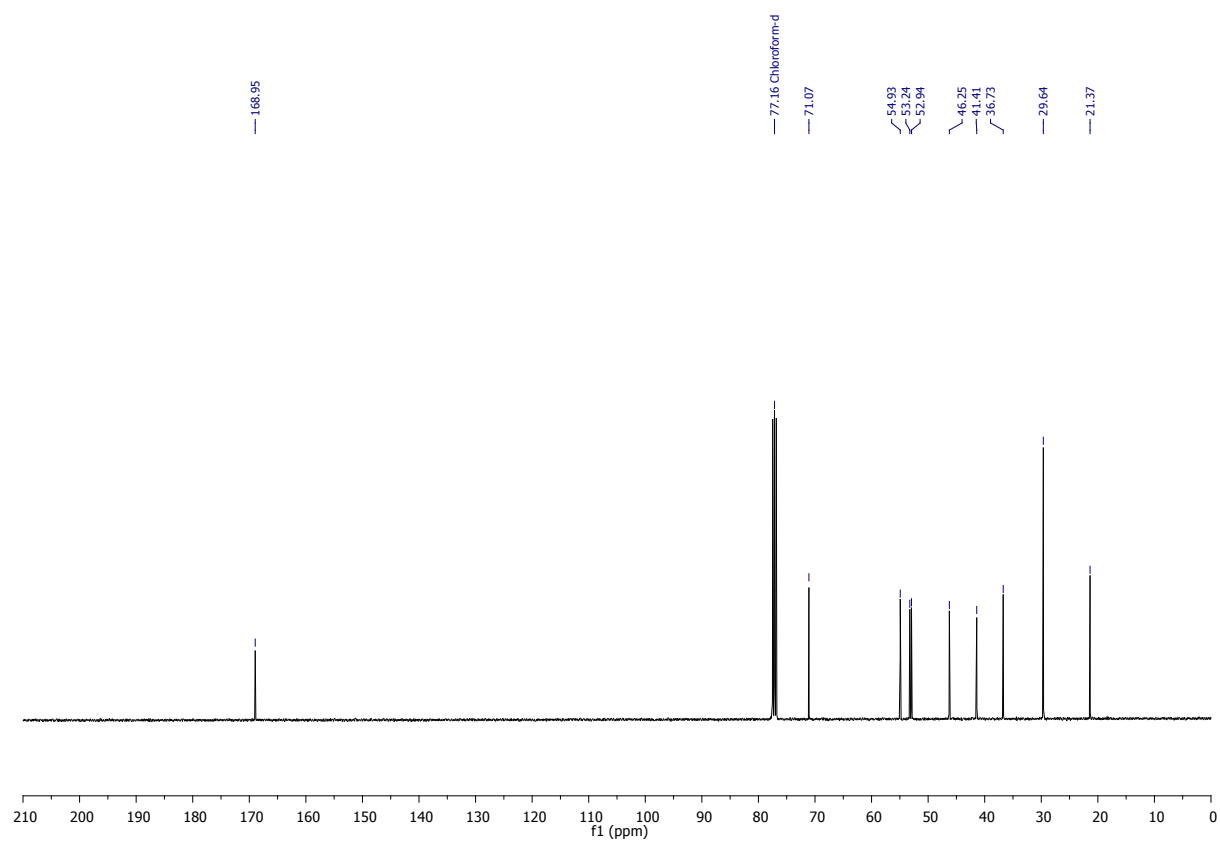
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm) δ:** 168.9 (C), 71.1 (C), 54.9 (CH<sub>2</sub>), 53.2 (CH<sub>2</sub>), 52.9 (CH<sub>2</sub>), 46.2 (CH<sub>2</sub>), 41.4 (CH<sub>2</sub>), 36.7 (CH<sub>2</sub>), 29.6 (2CH<sub>3</sub>), 21.4 (CH<sub>3</sub>).

**HRMS (ESI):** *m/z* [M+H]<sup>+</sup> calc for C<sub>11</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub>: 215.175404, found 215.175853.

### $^1\text{H}$ NMR (400 MHz, $\text{CDCl}_3$ )

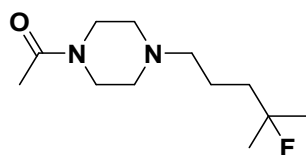


### $^{13}\text{C}$ NMR (100 MHz, $\text{CDCl}_3$ )



**Compound 2e:** 1-(4-(4-fluoro-4-methylpentyl)piperazin-1-yl)ethan-1-one

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This compound was obtained after reaction of substrate **1e** (65 mg, 0.3 mmol), following the general procedure **A'** with 3 mL of HF/SbF<sub>5</sub> and 1 mL of HF/Pyr. The crude reaction mixture was purified over silica gel with dichloromethane/methanol (98/2) as the eluent, thereby obtaining compound **2e** (70 mg, 82%) as an orange oil.

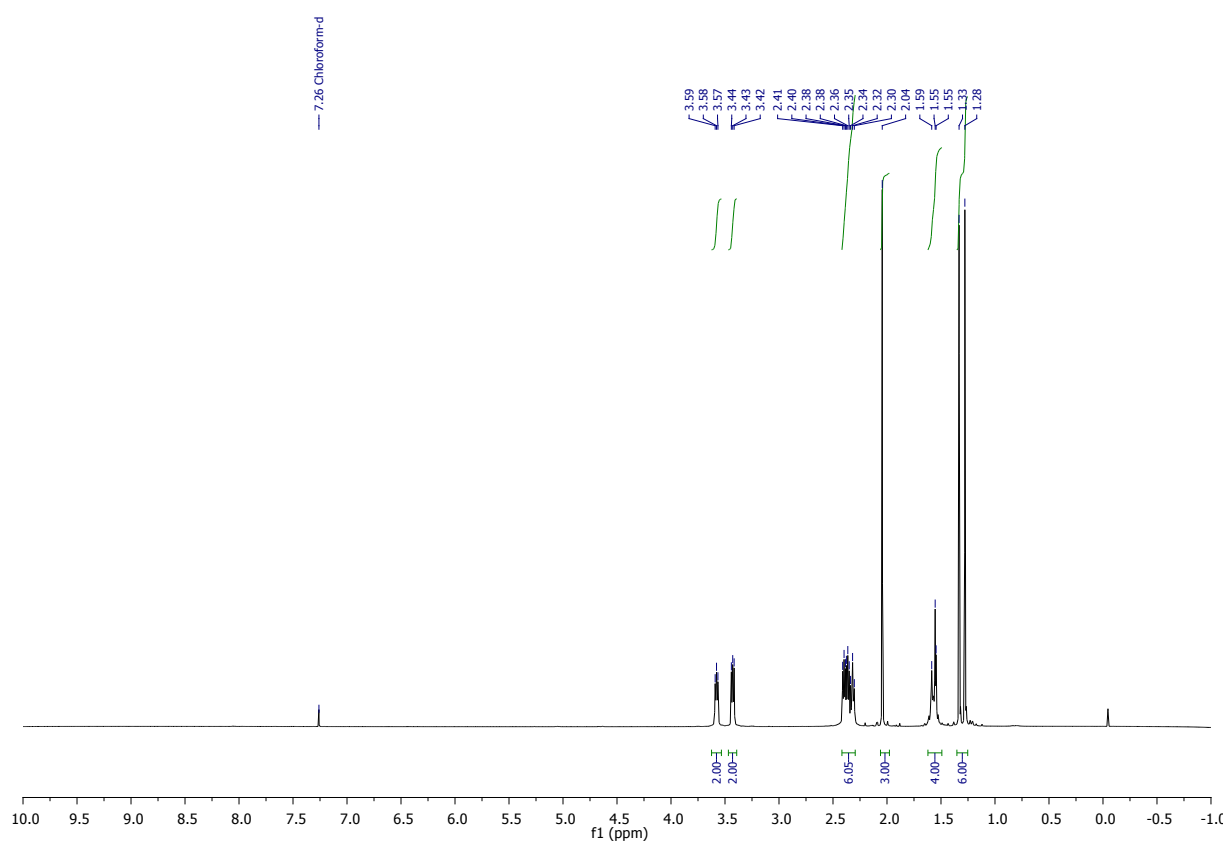
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm) δ:** 3.58 (t, *J* = 4.5 Hz, 2H) 3.43 (t, *J* = 5.0 Hz, 2H), 2.35 (m, 6H), 2.04 (s, 3H), 1.69-1.55 (m, 4H), 1.31 (d, *J* = 21.4 Hz, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm) δ:** 168.9 (C), 95.4 (d, *J* = 173 Hz, C), 58.5 (CH<sub>2</sub>), 53.3 (CH<sub>2</sub>), 52.8 (CH<sub>2</sub>), 46.3 (CH<sub>2</sub>), 41.4 (CH<sub>2</sub>), 39.0 (d, *J* = 23 Hz, CH), 26.7 (d, *J* = 25 Hz, 2 CH<sub>3</sub>), 21.3 (CH<sub>3</sub>), 21.3 (d, *J* = 4 Hz, CH<sub>2</sub>).

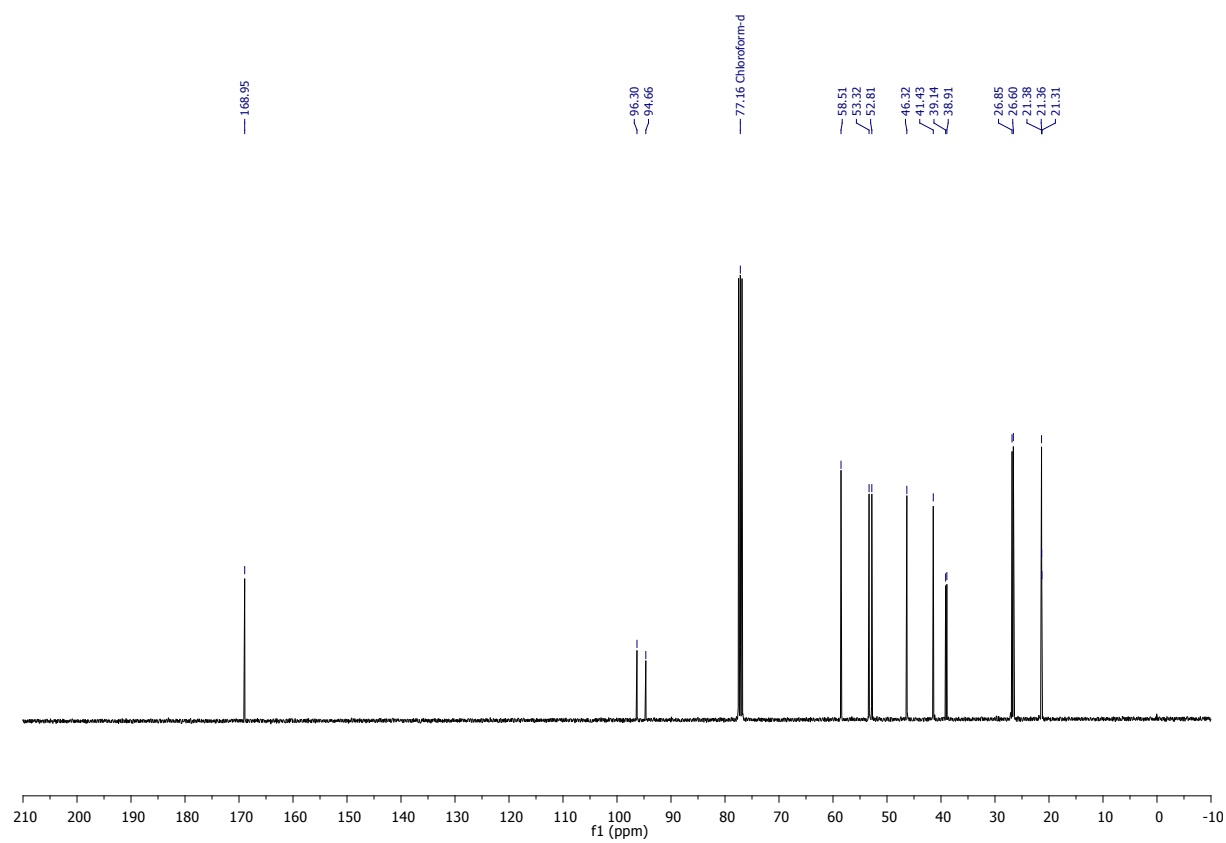
**<sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>, ppm) δ:** -138.5.

**HRMS (ESI):** *m/z* [M+H]<sup>+</sup> calc for C<sub>12</sub>H<sub>24</sub>FN<sub>2</sub>O : 231.1867, found 231.1869.

# <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

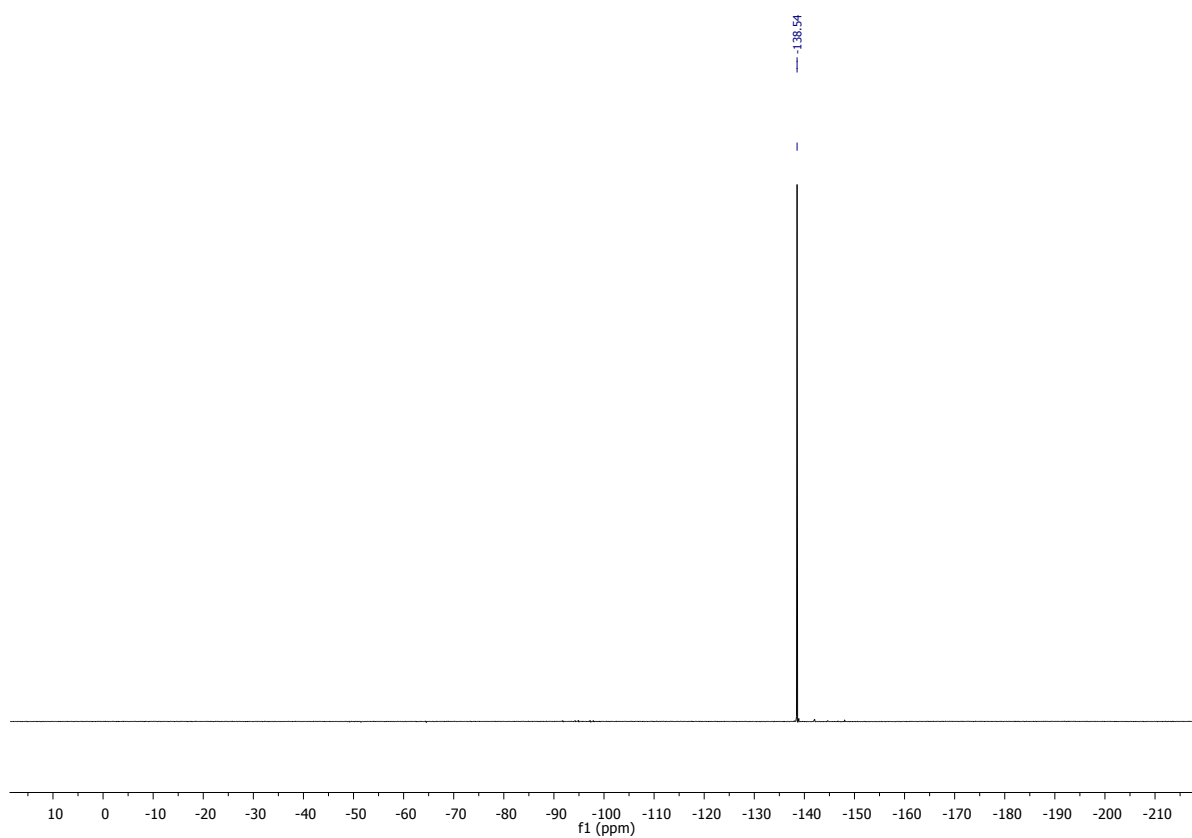


# <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)



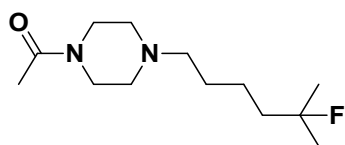


**$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{CDCl}_3$ )**



**Compound 2f:** 1-(4-(5-fluoro-5-methylhexyl)piperazin-1-yl)ethan-1-one

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This compound was obtained after reaction of substrate **1f** (120 mg, 0.5 mmol), following the general procedure **A'** with 3 mL of HF/SbF<sub>5</sub> and 2 mL of HF/Pyr. The crude reaction mixture was purified over silica gel with dichloromethane/methanol (98/2) as the eluent, thereby obtaining compound **2f** (101 mg, 63%) as an orange oil.

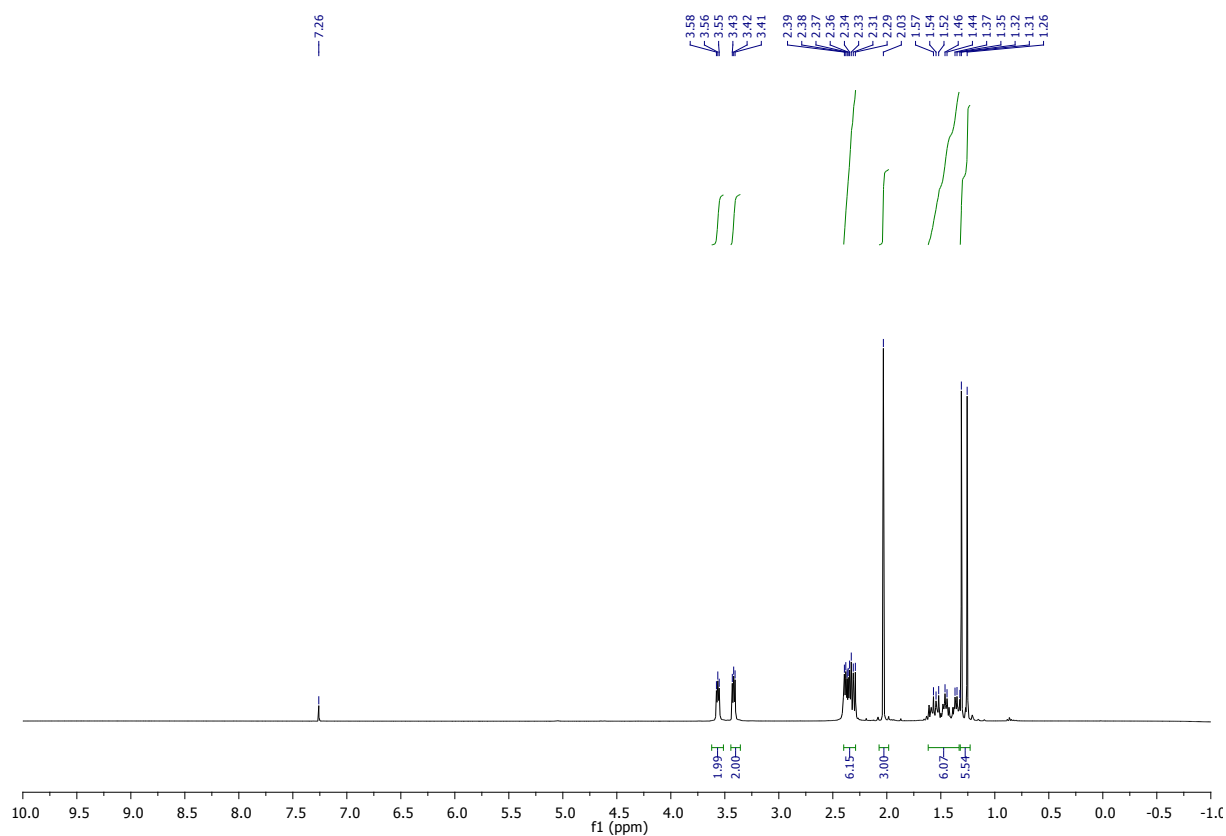
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm) δ:** 3.56 (t, *J* = 5.1 Hz, 2H), 3.42 (t, *J* = 5.1 Hz, 2H), 2.39-2.29 (m, 6H), 2.03 (s, 3H), 1.66-1.33 (m, 6H), 1.28 (d, *J* = 21.5 Hz, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm) δ:** 169.0 (C), 95.6 (d, *J* = 165 Hz, C), 58.4 (CH<sub>2</sub>), 53.4 (CH<sub>2</sub>), 52.8 (CH<sub>2</sub>), 46.3 (CH<sub>2</sub>), 41.4 (CH<sub>2</sub>), 41.2 (d, *J* = 21 Hz, CH<sub>2</sub>), 27.1 (CH<sub>2</sub>), 26.6 (d, *J* = 24 Hz, 2 CH<sub>3</sub>), 21.8 (d, *J* = 5 Hz, CH<sub>2</sub>), 21.3 (CH<sub>3</sub>).

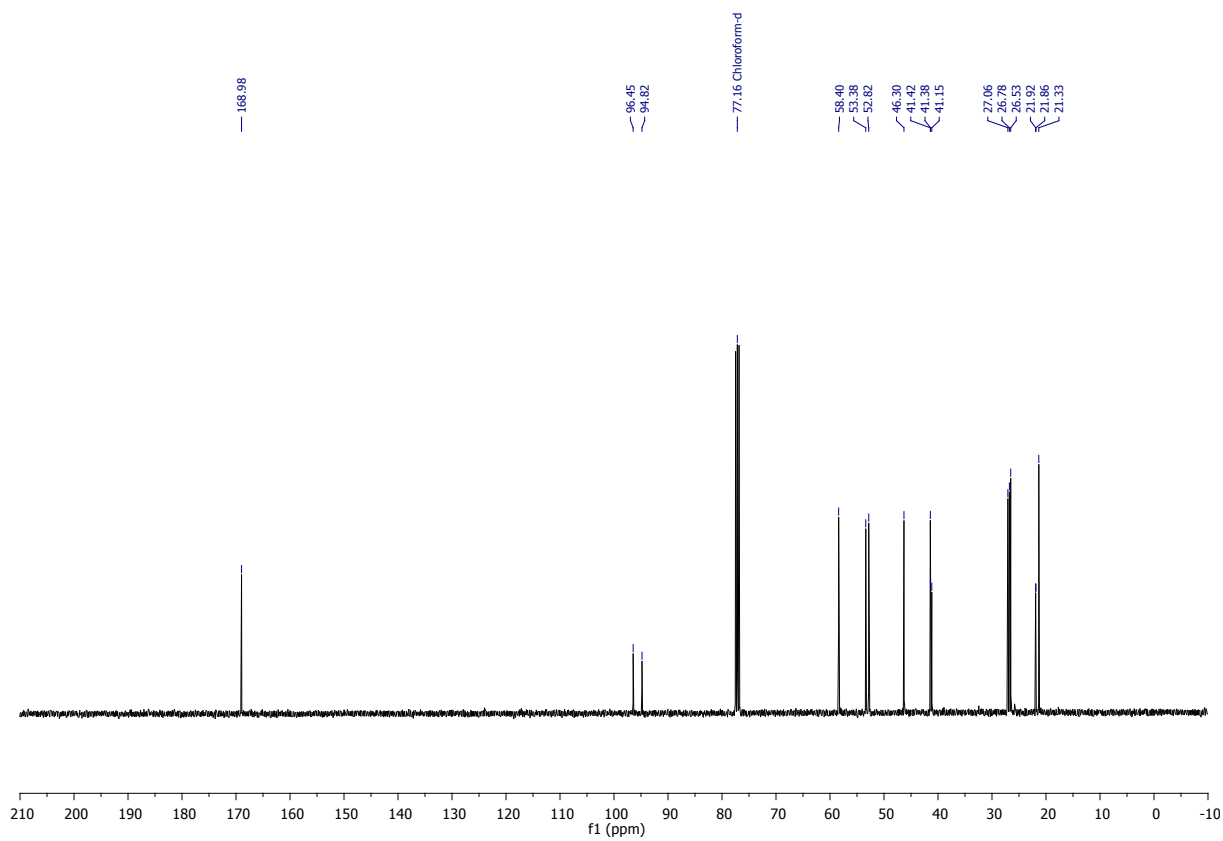
**<sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>, ppm) δ:** -137.7.

**HRMS (ESI):** *m/z* [M+H]<sup>+</sup> calc for C<sub>13</sub>H<sub>26</sub>FN<sub>2</sub>O : 245.2024, found 245.2025.

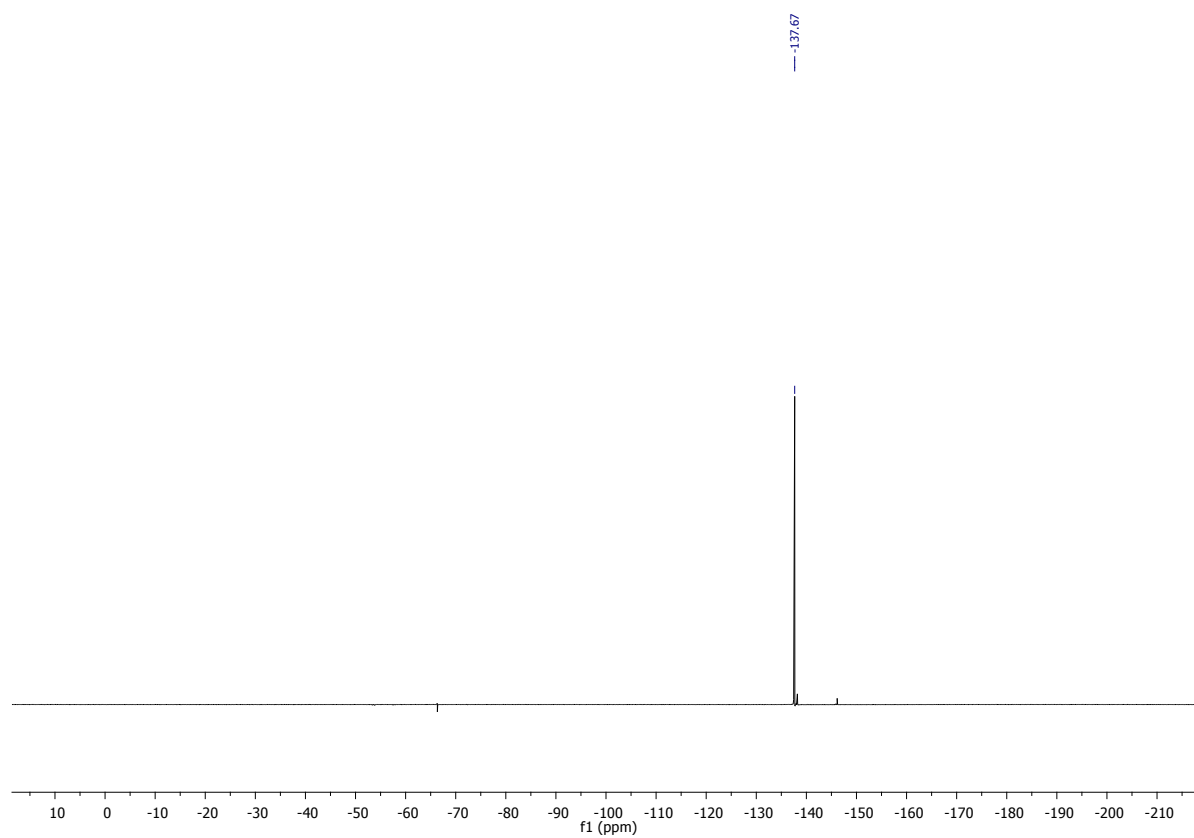
### $^1\text{H}$ NMR (400 MHz, $\text{CDCl}_3$ )



### $^{13}\text{C}$ NMR (100 MHz, $\text{CDCl}_3$ )

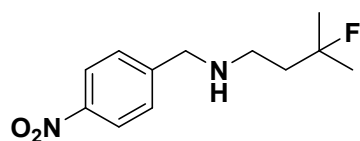


**$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{CDCl}_3$ )**



**Compound 2g:** 3-fluoro-3-methyl-*N*-(4-nitrobenzyl)butan-1-amine

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This compound was obtained after reaction of substrate **1e** (224 mg, 1.0 mmol), following the general procedure **A'** at -40 °C with 6 mL of HF/SbF<sub>5</sub> and 2 mL of HF/Pyr. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate (9/1) as the eluent, thereby obtaining compound **2e** (220 mg, 92%) as a brown oil.

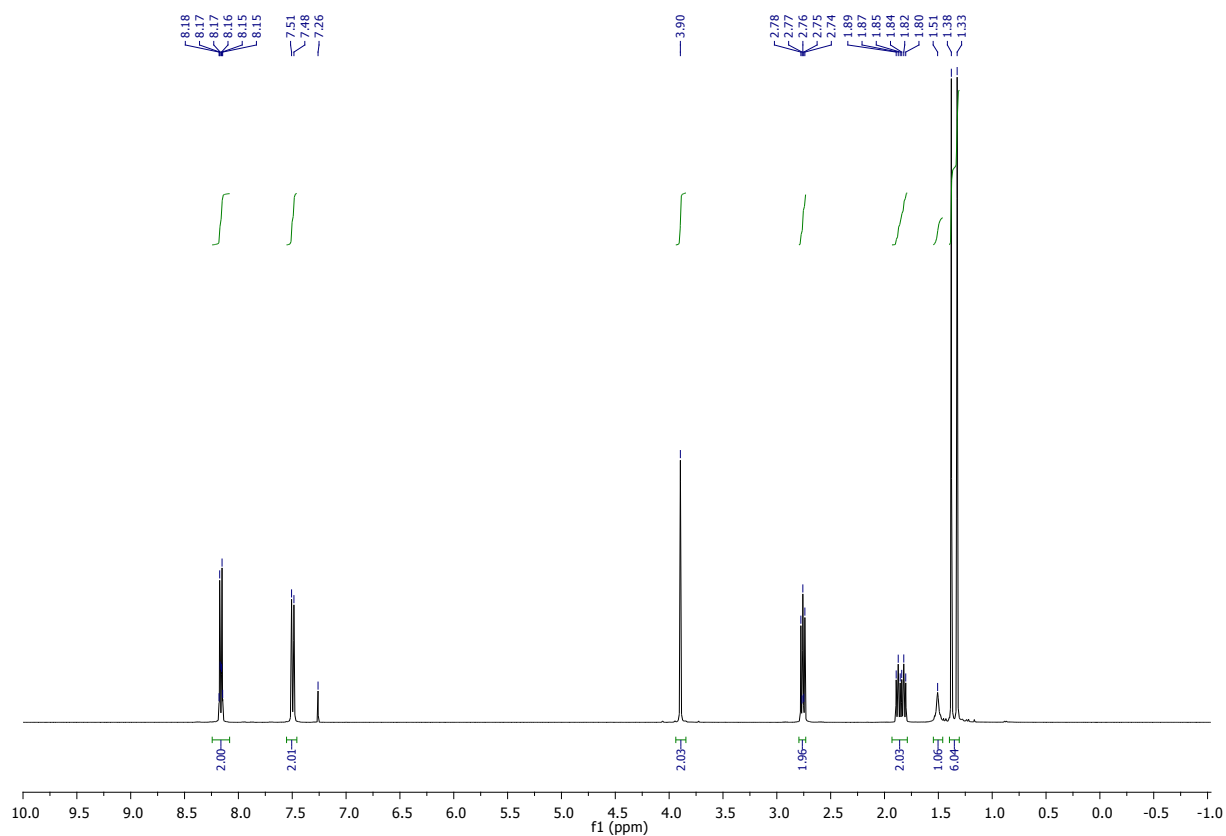
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm) δ:** 8.16 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 3.90 (s, 2H), 2.76 (app t, *J* = 7.0 Hz, 2H), 1.85 (dt, *J* = 22.0, 7.0 Hz, 2H), 1.51 (s, 1H), 1.35 (d, *J* = 21.5 Hz, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm) δ:** 148.3 (C), 147.1 (C), 128.7 (2 CH), 123.7 (2 CH), 95.6 (d, *J* = 164 Hz, CH), 53.4 (CH<sub>2</sub>), 44.8 (d, *J* = 4 Hz, CH<sub>2</sub>), 41.2 (d, *J* = 22 Hz, CH<sub>2</sub>), 27.0 (d, *J* = 24 Hz, 2 CH<sub>3</sub>).

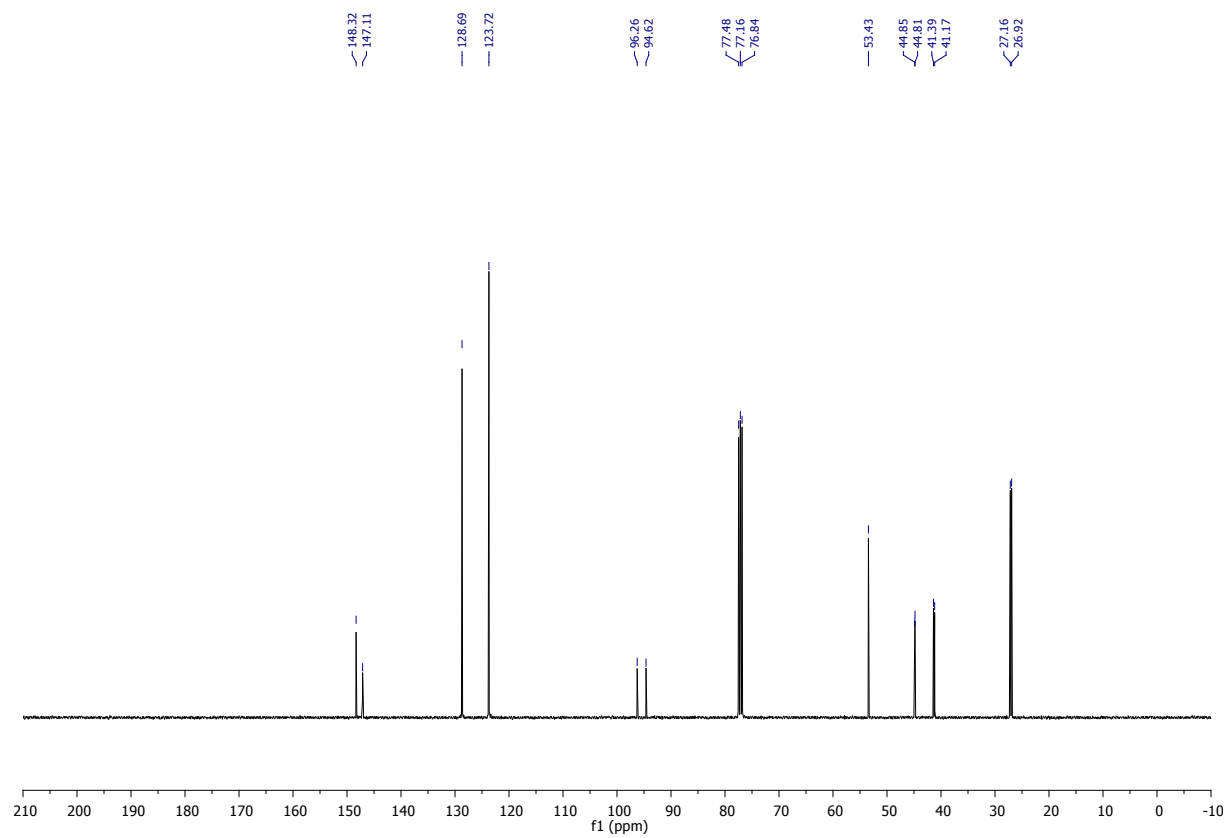
**<sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>, ppm) δ:** -137.9.

**HRMS (ESI):** *m/z* [M+H]<sup>+</sup> calc for C<sub>12</sub>H<sub>18</sub>FN<sub>2</sub>O<sub>2</sub>: 241.1347, found 241.1353.

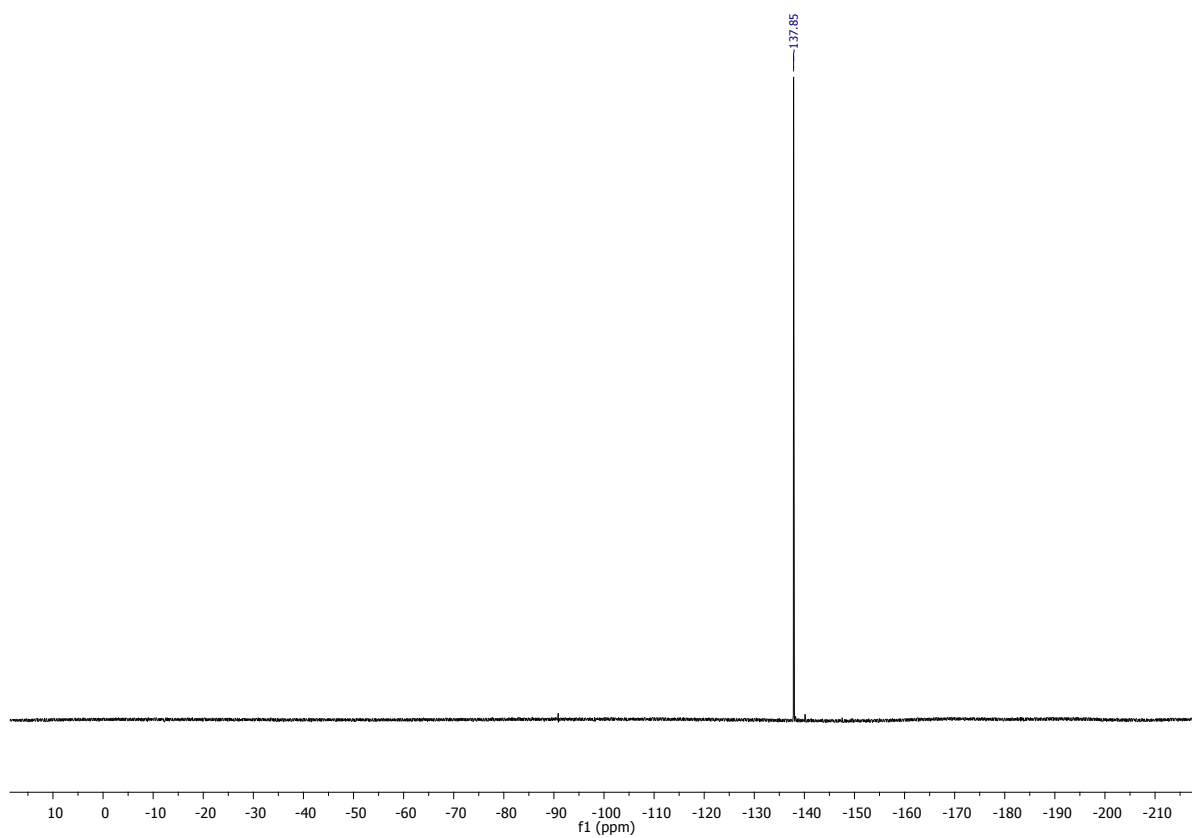
### $^1\text{H}$ NMR (400 MHz, $\text{CDCl}_3$ )



### $^{13}\text{C}$ NMR (100 MHz, $\text{CDCl}_3$ )

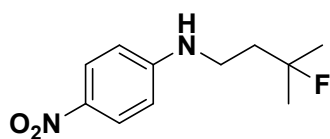


**$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{CDCl}_3$ )**



**Compound 2h:** *N*-(3-fluoro-3-methylbutyl)-4-nitroaniline

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This compound was obtained after reaction of substrate **1d** (202 mg, 1.0 mmol), following the general procedure **A'** at -40 °C with 6 mL of HF/SbF<sub>5</sub> and 2 mL of HF/Pyr. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate (9/1) as the eluent, thereby obtaining compound **2d** (168 mg, 77%) as an orange oil.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm) δ:** 8.07 (d, *J* = 9.1 Hz, 2H), 6.52 (d, *J* = 9.1 Hz, 2H), 4.85 (s, 1H), 3.38 (dd, *J* = 12.2, 7.0 Hz, 2H), 1.98 (dt, *J* = 22.0, 7.0 Hz, 2H), 1.43 (d, *J* = 22.0 Hz, 6H).

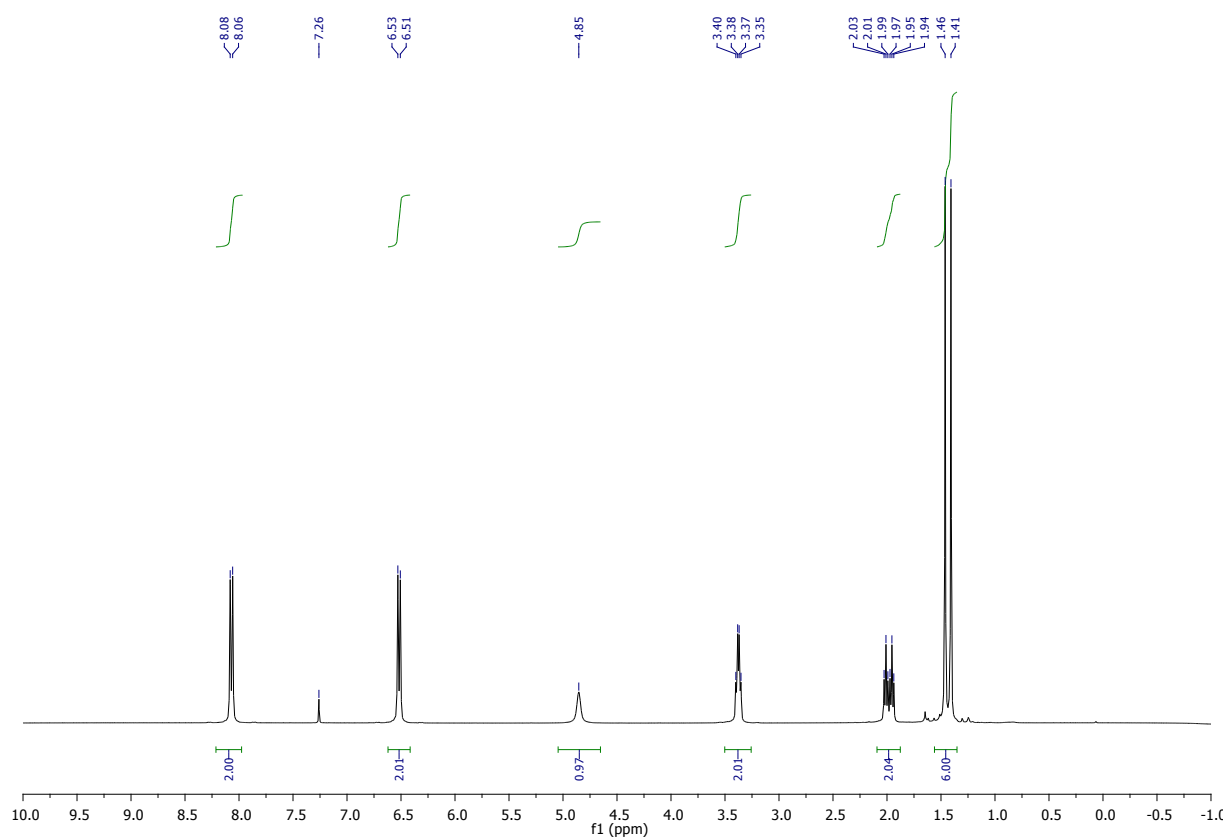
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm) δ:** : 153.3 (C), 138.1 (C), 126.6 (2 CH), 111.1 (2 CH), 95.6 (d, *J* = 164 Hz, C), 39.6 (d, *J* = 21 Hz, CH<sub>2</sub>), 39.2 (d, *J* = 3 Hz, CH<sub>2</sub>), 26.9 (d, *J* = 25 Hz, 2 CH<sub>3</sub>).

**<sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>, ppm) δ:** -138.0.

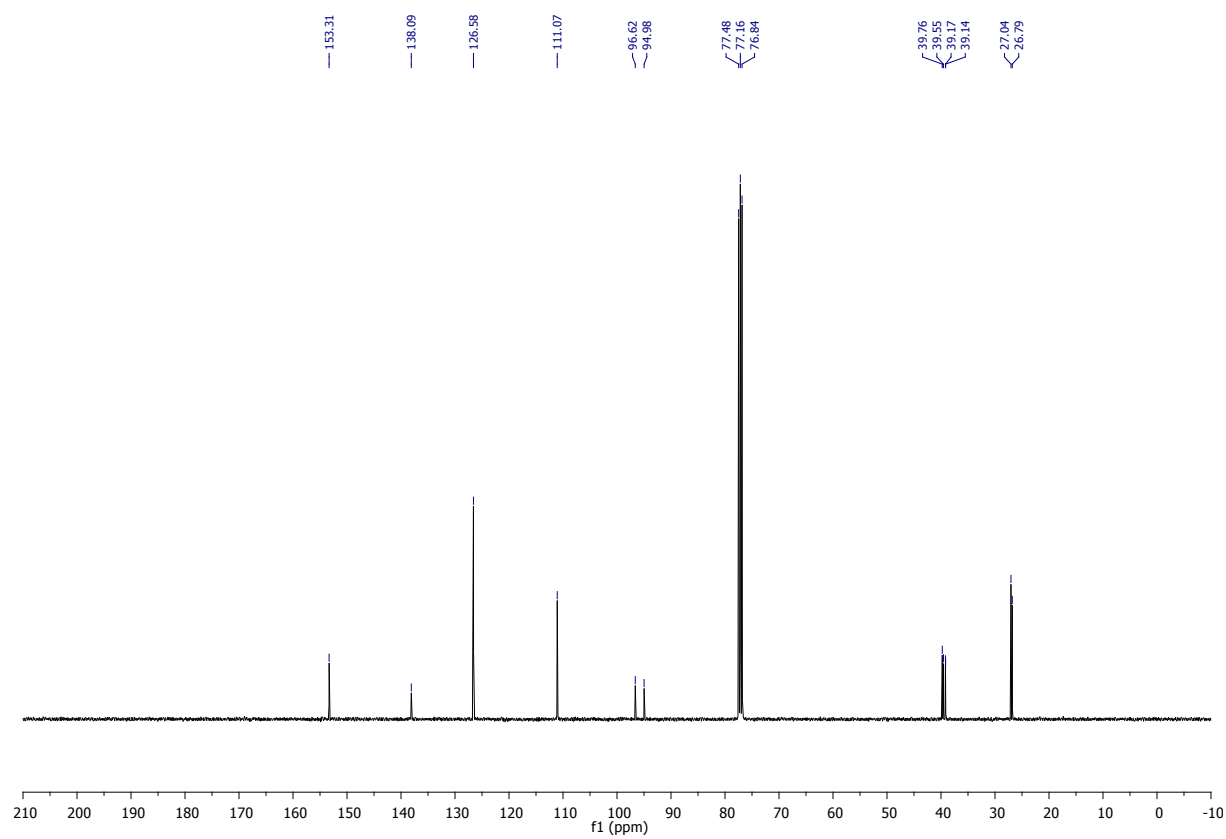
**HRMS (ESI):** *m/z* [M+ Na]<sup>+</sup> calc for C<sub>11</sub>H<sub>15</sub>FN<sub>2</sub>O<sub>2</sub>Na : 249.1010, found 249.1011.



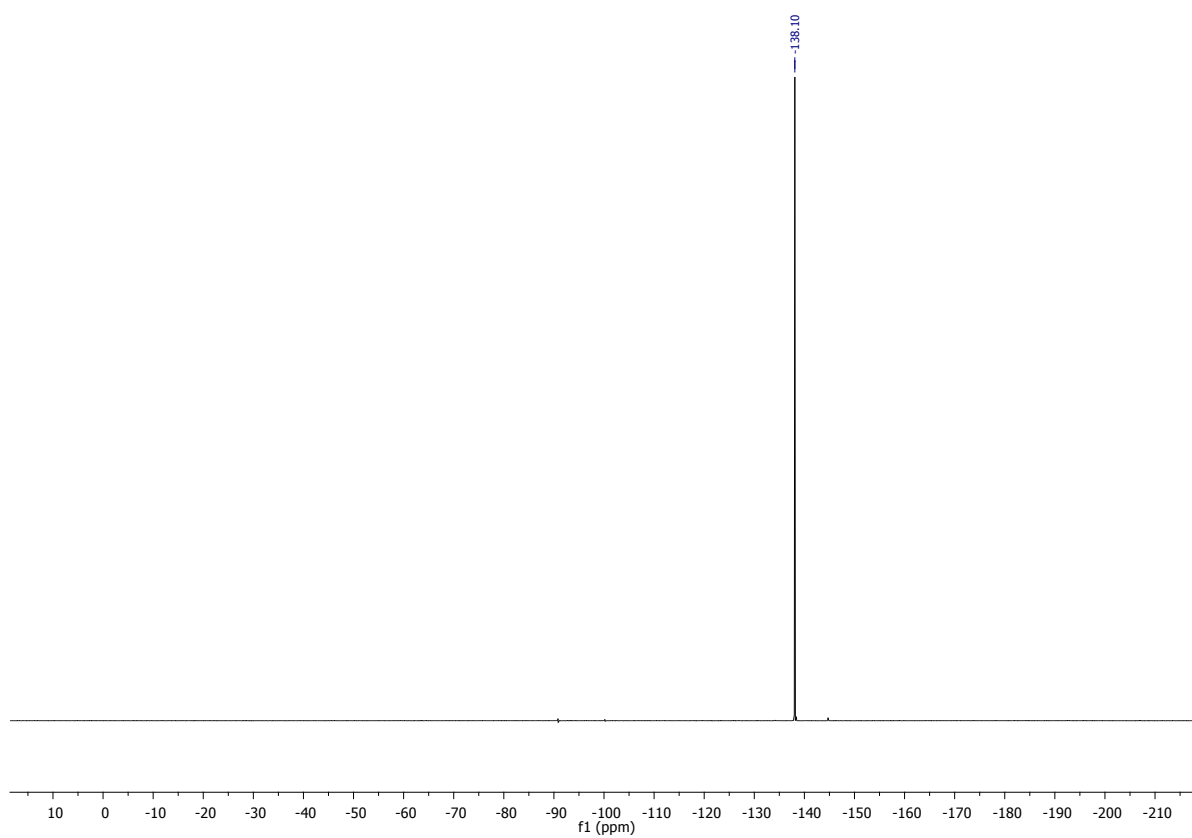
### <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



### <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)

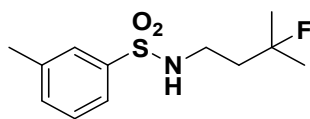


**$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{CDCl}_3$ )**



**Compound 2i:** 3-(2-fluoro-2-methylpropyl)pyridine

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This compound was obtained after reaction of substrate **1i** (220 mg, 0.91 mmol), following the general procedure **A'** at -40 °C with 6 mL of HF/SbF<sub>5</sub> and 2 mL of HF/Pyridine. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate (4/6) as the eluent, thereby obtaining compound **2i** (89 mg, 38%) as a yellow oil.

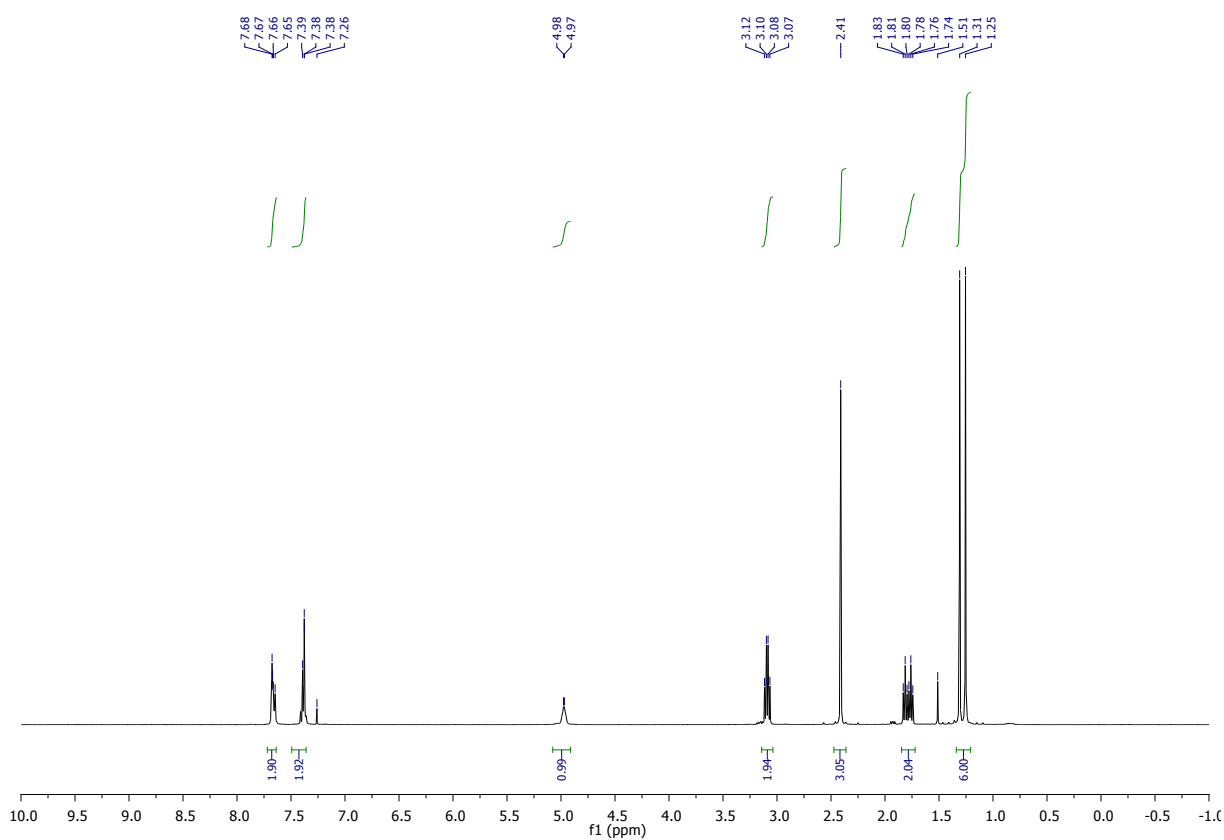
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm) δ:** 7.68-7.65 (m, 2H), 7.49-7.36 (m, 2H), 4.97 (bs, 1H), 3.09 (dd, *J* = 13.1, 7.1 Hz, 2H), 2.41 (s, 3H), 1.79 (dt, *J* = 21.0, 7.1 Hz, 2H), 1.28 (d, *J* = 21.7 Hz, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm) δ:** 139.6 (C), 139.4 (C), 133.5 (CH), 129.1 (CH), 127.5 (CH), 124.3 (CH), 95.5 (d, *J* = 167 Hz, C), 40.2 (d, *J* = 22 Hz, CH<sub>2</sub>), 39.0 (d, *J* = 4 Hz, CH<sub>2</sub>), 26.8 (d, *J* = 24 Hz, 2 CH<sub>3</sub>), 21.42 (CH<sub>3</sub>).

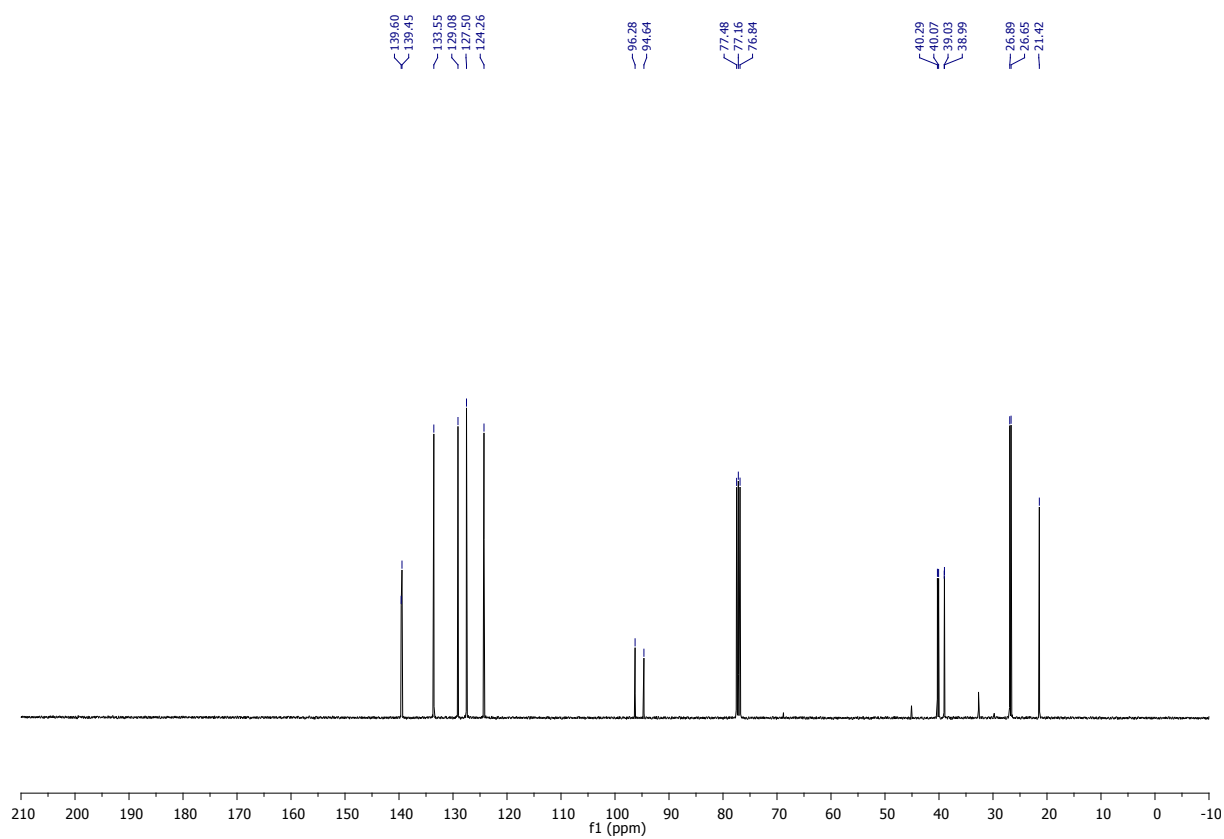
**<sup>19</sup>F {<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>, ppm) δ:** -138.6.

**HRMS (ESI):** *m/z* [M+H]<sup>+</sup> calc for C<sub>12</sub>H<sub>18</sub>FNO<sub>2</sub>S: 260.1115, found 260.1116.

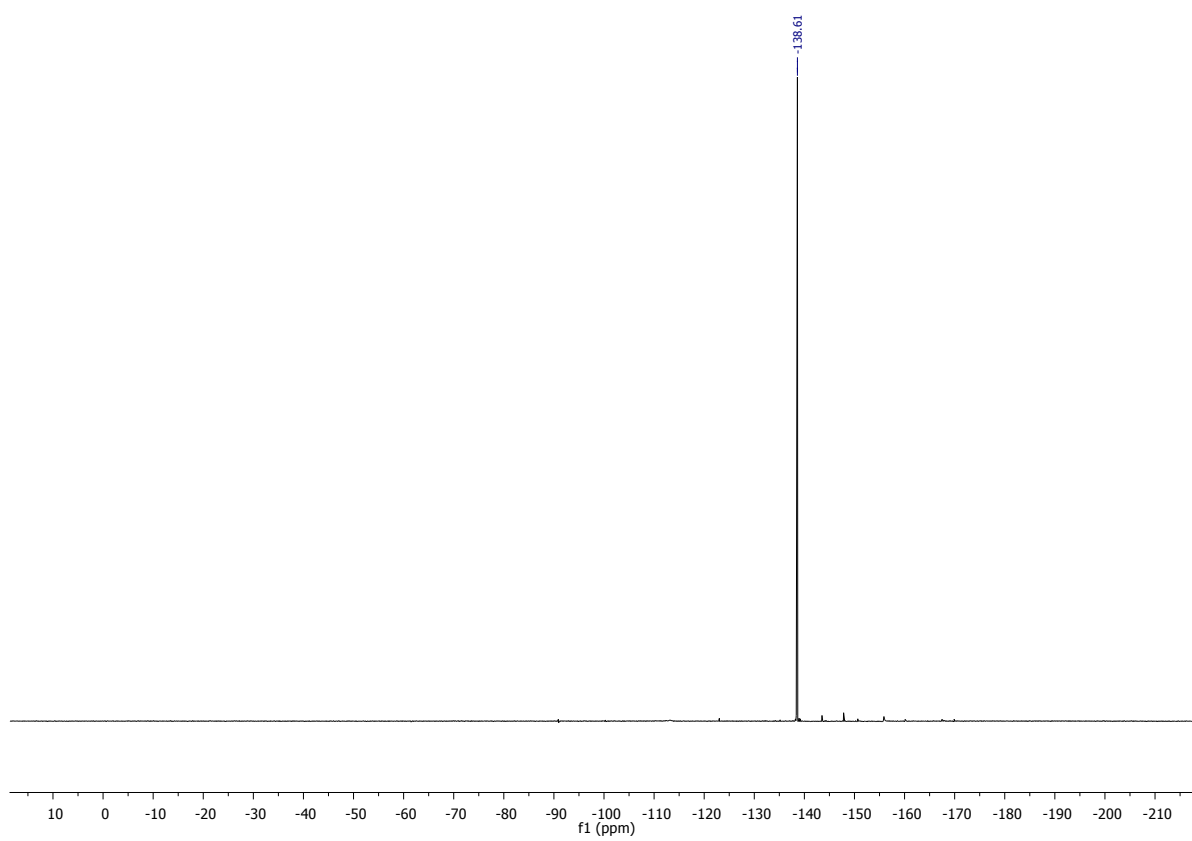
### <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



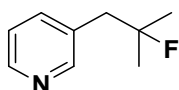
### <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)



**$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{CDCl}_3$ )**



## Compound 2j: 3-(2-fluoro-2-methylpropyl)pyridine



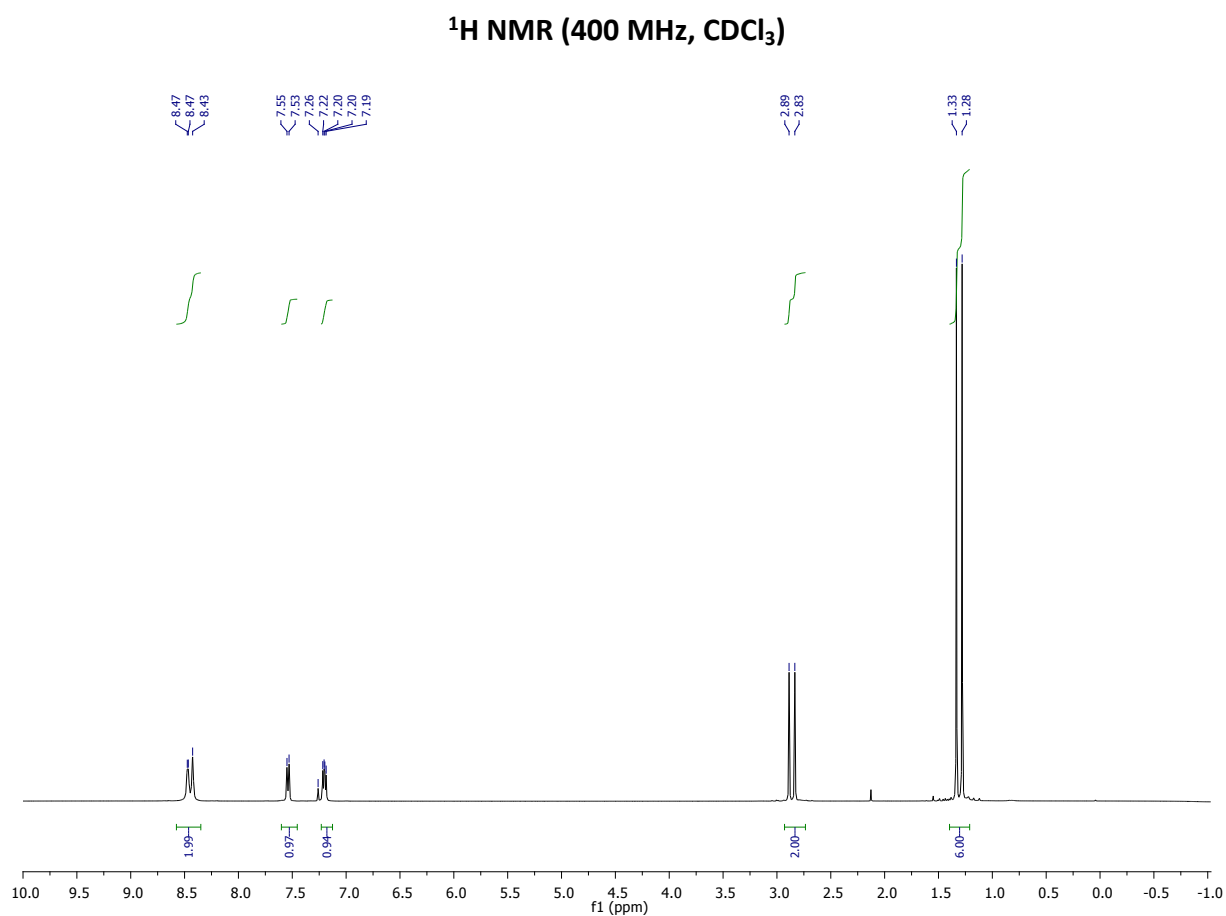
This compound was obtained after reaction of substrate **1j** (140 mg, 1.0 mmol), following the general procedure **A'** at -40 °C with 6 mL of HF/SbF<sub>5</sub> and 2 mL of HF/Pyr. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate (4/6) as the eluent, thereby obtaining compound **2j** (115 mg, 73%) as a yellow oil.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm) δ:** 8.58 -8.35 (m, 2H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.20 (dd, *J* = 7.7, 4.8 Hz, 1H), 2.86 (d, *J* = 21.4 Hz, 2H), 1.31 (d, *J* = 21.2 Hz, 6H).

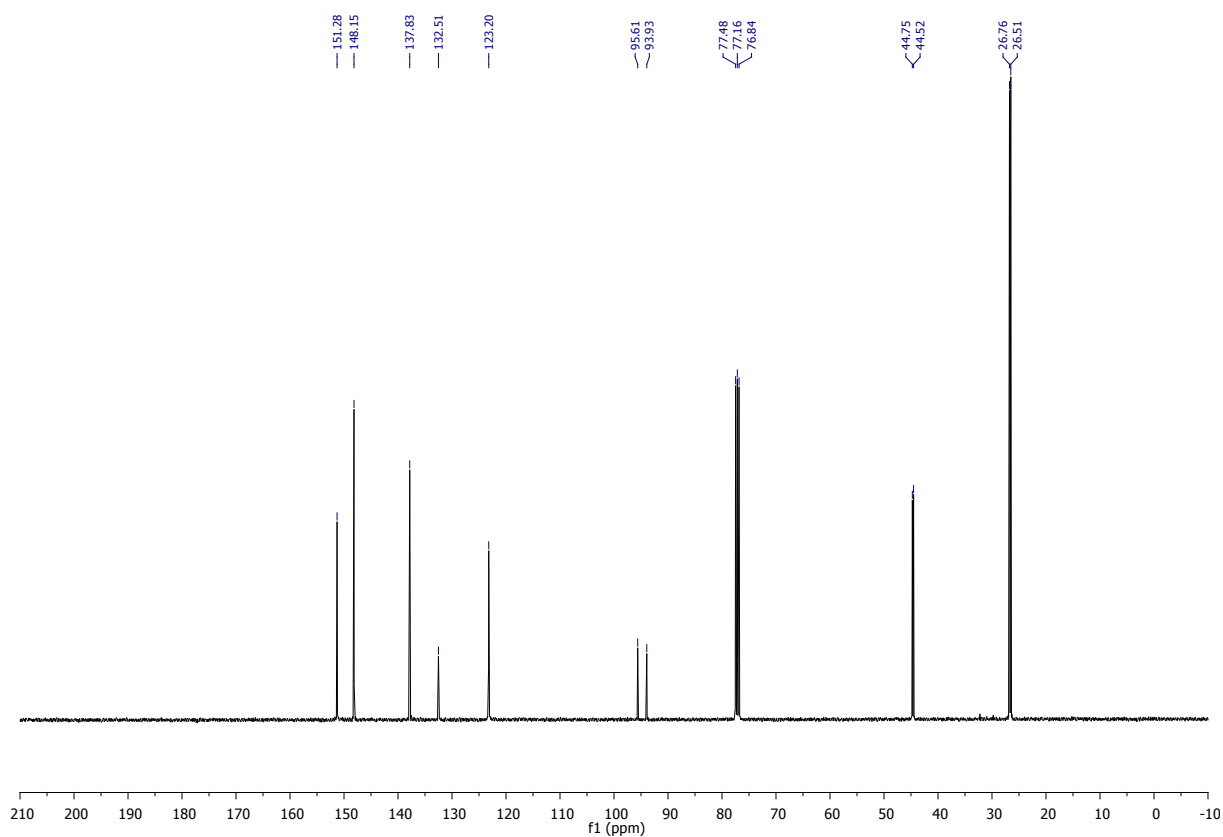
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm) δ:** 151.3 (CH), 148.1 (CH), 137.8 (CH), 132.5 (CH), 123.2 (CH), 94.8 (d, *J* = 169 Hz, C) 44.6 (d, *J* = 23 Hz, CH<sub>2</sub>), 26.6 (d, *J* = 24 Hz, 2 CH<sub>3</sub>).

**<sup>19</sup>F {<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>, ppm) δ:** -139.6.

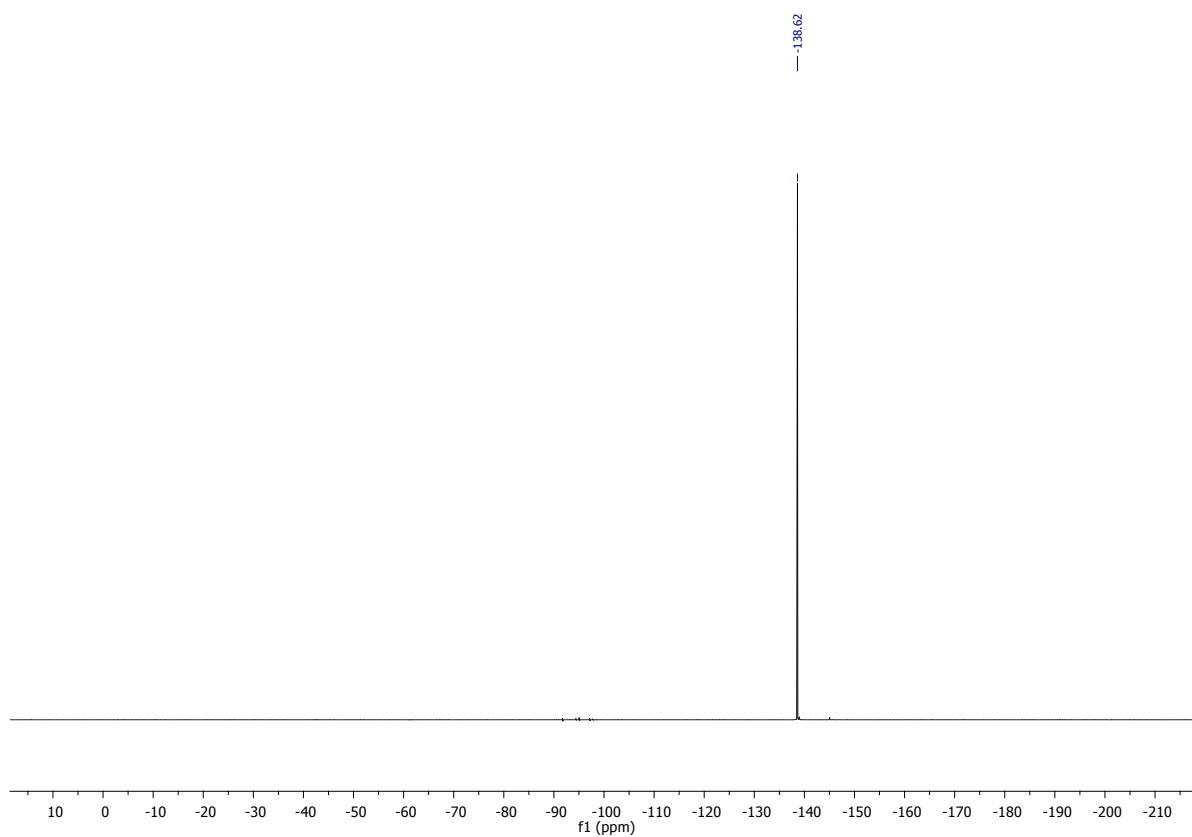
**HRMS (ESI):** *m/z* [M+H]<sup>+</sup> calc for C<sub>9</sub>H<sub>13</sub>FN: 154.1031, found 154.1026.



**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )**

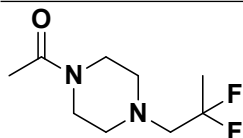


**$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{CDCl}_3$ )**



**Compound 2h:** 1-(4-(2,2-difluoropropyl)piperazin-1-yl)ethanone

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This compound was obtained after reaction of substrate **1h** (60 mg, 0.38 mmol), following the general procedure **C** with 2 mL of HF/SbF<sub>5</sub>. The crude reaction mixture was purified over silica gel with dichloromethane/NH<sub>3</sub> in MeOH (98/2) as the eluent, thereby obtaining compound **2h** (38 mg, 63%) as a yellow oil. The spectroscopic data correspond to those previously described in the literature.<sup>3</sup>

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm) δ:** 3.62 – 3.56 (m, 2H), 3.45 – 3.40 (m, 2H), 2.66 (t, *J* = 13.4 Hz, 2H), 2.60 – 2.51 (m, 4H), 2.05 (s, 3H), 1.62 (t, *J* = 18.7 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm) δ:** 169.1 (C), 124.0 (t, *J* = 239 Hz, C), 62.5 (t, *J* = 28.5 Hz, CH<sub>2</sub>), 54.1 (CH<sub>2</sub>), 53.9 (CH<sub>2</sub>), 46.4 (CH<sub>2</sub>), 41.6 (CH<sub>2</sub>), 21.9 (t, *J* = 26.5 Hz, CH<sub>3</sub>), 21.3 (CH<sub>3</sub>).

**<sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>, ppm) δ:** -92.2.

**HRMS (ESI):** *m/z* [M+H]<sup>+</sup> calc for C<sub>9</sub>H<sub>15</sub>FN<sub>2</sub>O: 186.117, found 186.118

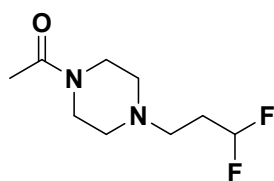
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<sup>3</sup> F. Liu, A. Martin-Mingot, M.-P. Jouannetaud, C. Bachmann, G. Frapper, F. Zunino and S. Thibaudeau, *J. Org. Chem.* **2011**, *76*, 1460.



**Compound 2l:** 1-(4-(3,3-difluoropropyl)piperazin-1-yl)ethanone

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This compound was obtained after reaction of substrate **1l** (334.5 mg, 1.6 mmol), following the general procedure **C** with 6 mL of HF/SbF<sub>5</sub>. The crude reaction mixture was purified over silica gel with dichloromethane/NH<sub>3</sub> in MeOH (7.5 % M) (98/2) as the eluent, thereby obtaining compound **2l** (254 mg, 77%) as a brown oil. The spectroscopic data correspond to those previously described in the literature.<sup>3</sup>

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm) δ:** 5.87 (tt, *J* = 56.7 Hz, *J* = 4.5 Hz, 1H), 3.55 (app t, *J* = 4.9 Hz, 2H), 3.41 (app t, *J* = 5.0 Hz, 2H), 2.47 (t, *J* = 7.1 Hz, 2H), 2.40 (app t, *J* = 5.1 Hz, 2H), 2.36 (app t, *J* = 5.1 Hz, 2H), 2.03 (s, 3H), 2.01-1.93 (m, 2H).

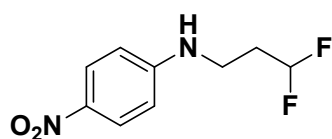
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm) δ:** 169.1 (C), 116.4 (t, *J* = 239 Hz, CH), 53.3 (CH<sub>2</sub>), 52.6 (CH<sub>2</sub>), 51.3 (t, *J* = 6 Hz, CH<sub>2</sub>), 46.2 (CH<sub>2</sub>), 41.3 (CH<sub>2</sub>), 31.6 (t, *J* = 21 Hz, CH<sub>2</sub>), 21.3 (CH<sub>3</sub>).

**<sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>, ppm) δ:** -117.0.

**HRMS (ESI):** *m/z* [M+H]<sup>+</sup> calc for C<sub>9</sub>H<sub>16</sub>F<sub>2</sub>N<sub>2</sub>O: 206.123, found 206.123

**Compound 2m:** *N*-(3,3-difluoropropyl)-4-nitroaniline

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This compound was obtained after reaction of substrate **1m** (50 mg, 0.23 mmol), following the general procedure **C** with 2 mL of HF/SbF<sub>5</sub>. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate (8/2) as the eluent, thereby obtaining compound **2m** (42 mg, 84%) as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm)  $\delta$ :** 8.10 (m, 2H), 6.56 (d,  $J$  = 9.2 Hz, 2H), 5.99 (tt,  $J$  = 56.0, 4.0 Hz, 1H), 4.62 (s, 1H), 3.48 (m, 2H), 2.22 (ttd,  $J$  = 17.6, 6.7, 4.0 Hz, 2H).

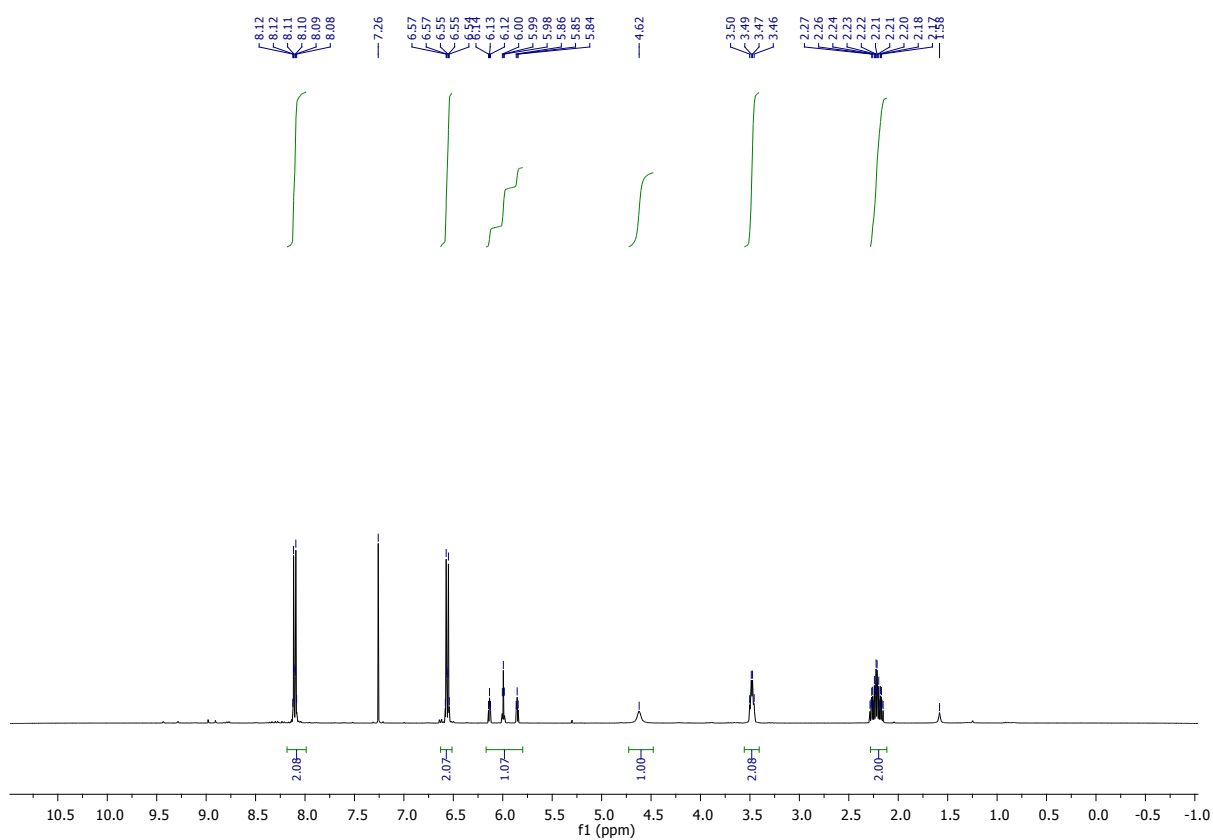
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm)  $\delta$ :** 152.8 (C), 138.7 (C), 126.6 (CH), 116.0 (CH, t,  $J$  = 240 Hz), 111.3 (CH), 36.9 (t,  $J$  = 6 Hz, CH<sub>2</sub>), 33.5 (t,  $J$  = 21 Hz, CH<sub>2</sub>).

**<sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>, ppm)  $\delta$ :** -116.6.

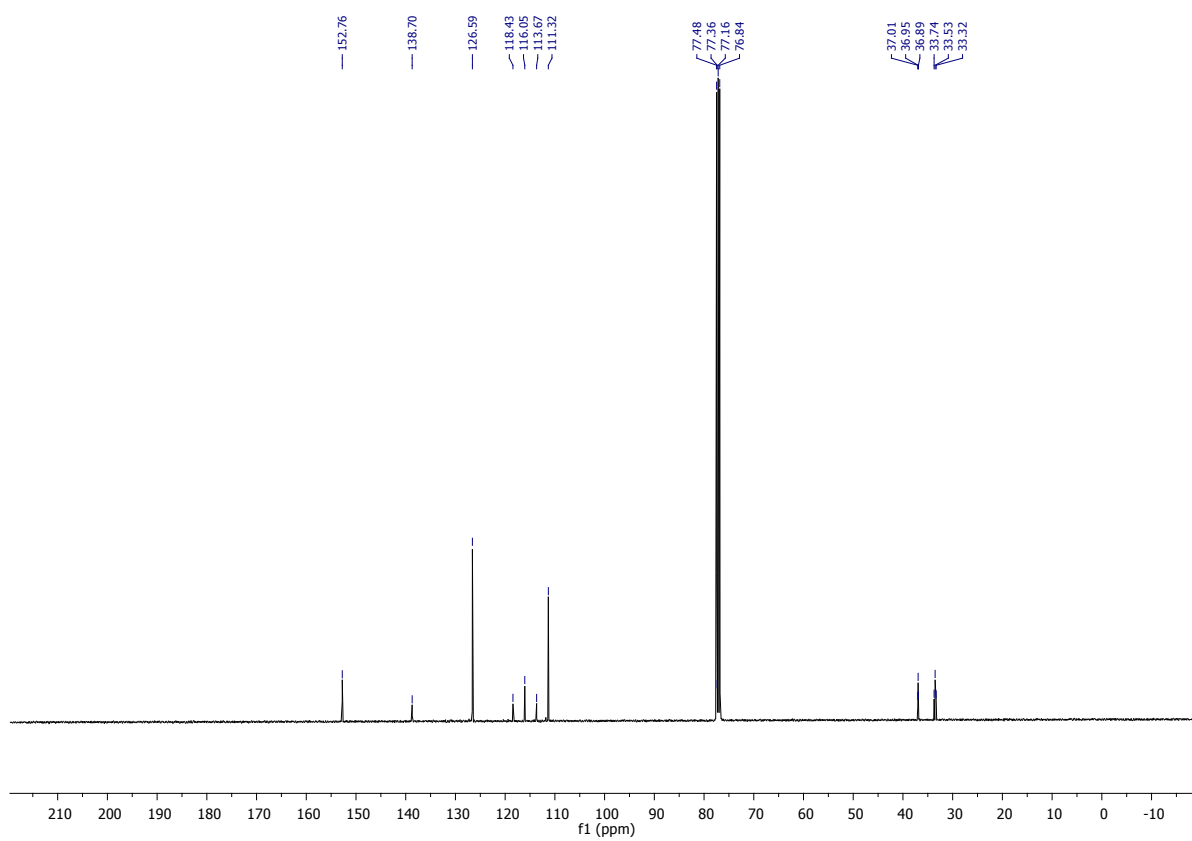
**Mp:** 46.6-47.9 °C.

**HRMS (ESI):**  $m/z$  [M+H]<sup>+</sup> calc for C<sub>9</sub>H<sub>11</sub>F<sub>2</sub>N<sub>2</sub>O<sub>2</sub>: 217.0783, found 217.0788.

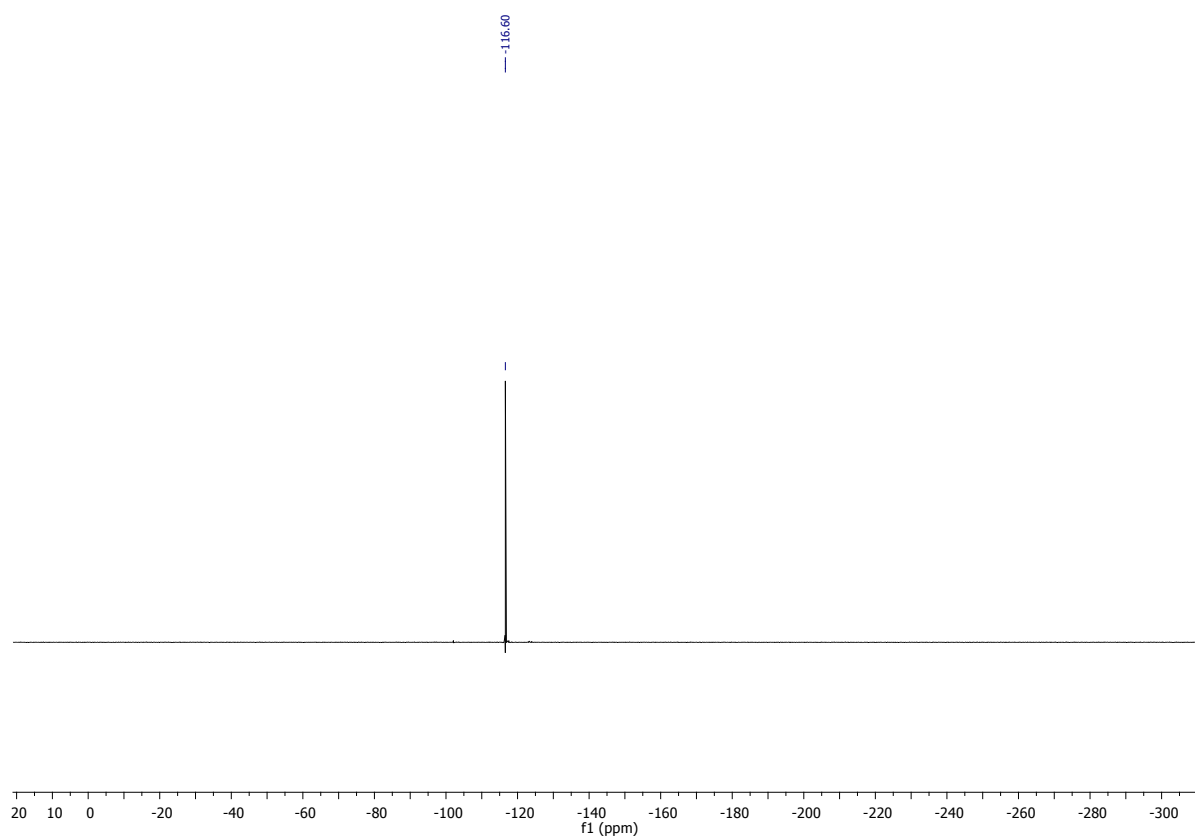
### <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



### <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)

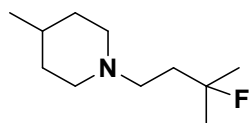


**$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{CDCl}_3$ )**



**Compound 2n:** 1-(3-fluoro-3-methylbutyl)-4-methylpiperidine

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This compound was obtained after reaction of substrate **1n** (178 mg, 1.0 mmol), following the general procedure **A** at -40 °C with 6 mL of HF/SbF<sub>5</sub> and 2 mL of HF/Pyr. The crude reaction mixture was purified over silica gel with dichloromethane/methanol (98/2) as the eluent, thereby obtaining compound **2n** (80 mg, 43%) as a yellow oil.

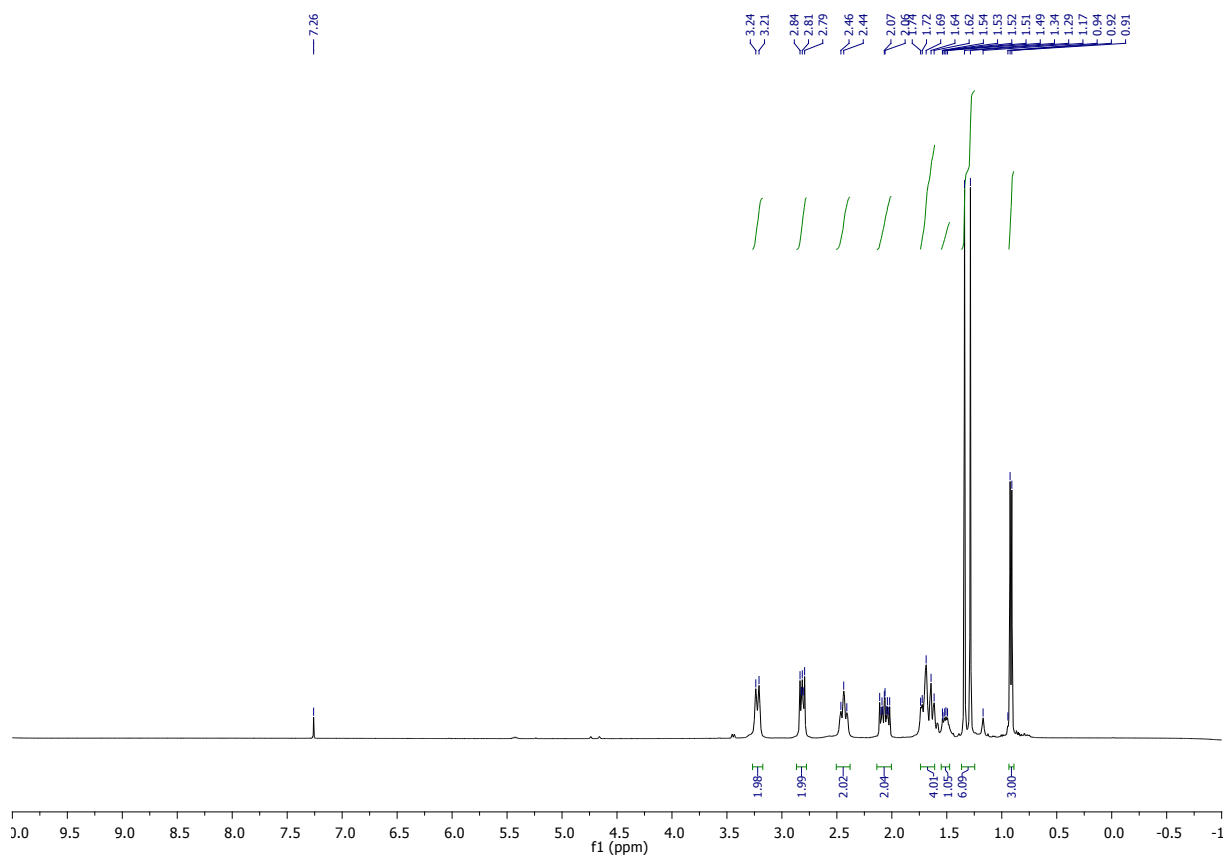
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm) δ:** 3.22 (d, *J* = 11.7 Hz, 2H), 2.87-2.78 (m, 2H), 2.44 (t, *J* = 10.8 Hz, 2H), 2.14-2.00 (m, 2H), 1.74-1.61 (m, 4H), 1.55-1.47 (m, 1H), 1.31 (d, *J* = 21.4 Hz, 6H), 0.92 (d, *J* = 6.4 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm) δ:** 93.9 (d, *J* = 167 Hz, C), 53.5 (2 CH<sub>2</sub>), 54.2 (d, *J* = 5 Hz, CH<sub>2</sub>), 37.7 (d, *J* = 22 Hz, CH<sub>2</sub>), 30.9 (2 CH<sub>2</sub>), 29.5 (CH), 26.5 (d, *J* = 24 Hz, 2 CH<sub>3</sub>), 21.0 (CH<sub>3</sub>).

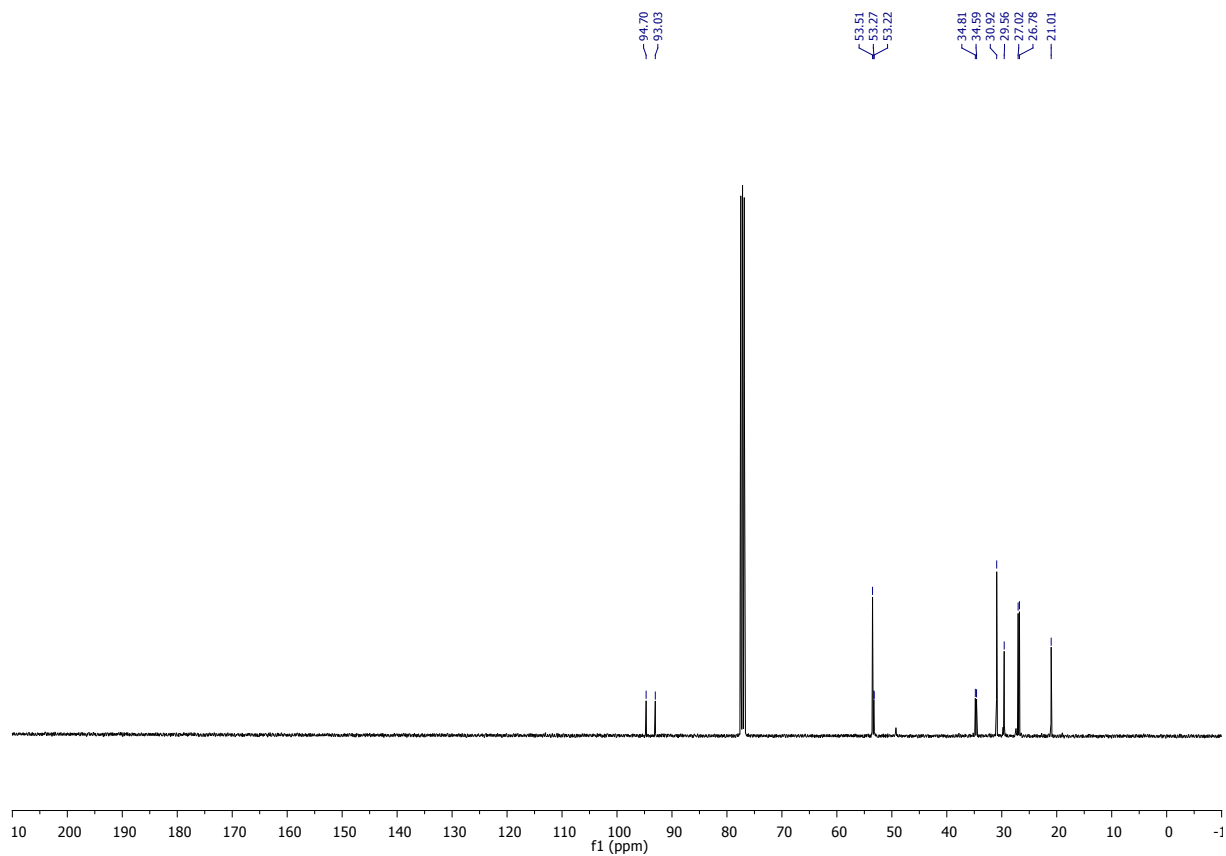
**<sup>19</sup>F {<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>, ppm) δ:** -141.5.

**HRMS (ESI):** *m/z* [M+H]<sup>+</sup> calc for C<sub>11</sub>H<sub>23</sub>FN: 188.1809, found 188.1813.

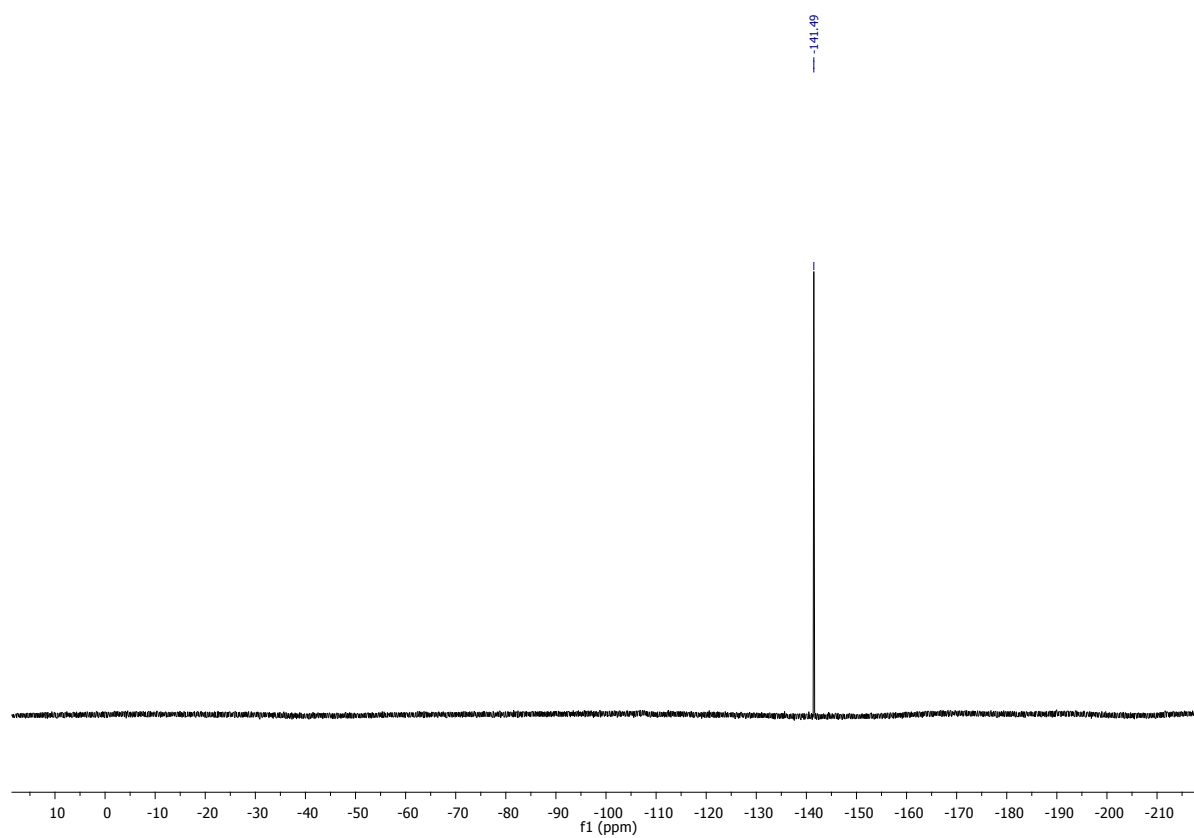
# $^1\text{H}$ NMR (400 MHz, $\text{CDCl}_3$ )



# $^{13}\text{C}$ NMR (100 MHz, $\text{CDCl}_3$ )

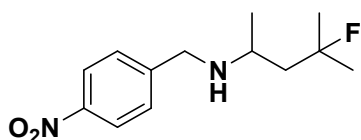


**$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{CDCl}_3$ )**



**Compound 2o:** 3-fluoro-3-methyl-*N*-(1-(4-nitrophenyl)ethyl)butan-1-amine

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This compound was obtained after reaction of substrate **1o** (100 mg, 0.42 mmol), following the general procedure **A** at -40 °C with 6 mL of HF/SbF<sub>5</sub> and 2 mL of HF/Pyr. The crude reaction mixture was purified over silica gel with dichloromethane/methanol (98/2) as the eluent, thereby obtaining compound **2o** (74 mg, 68%) as a yellow oil.

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, ppm) δ:** 8.18 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), , 3.96 (d, *J* = 14.2 Hz, 1H), 3.84 (d, *J* = 14.2 Hz, 1H), 2.99 (m, 1H), 2.48 (bs, 1H), 1.90 (td, *J* = 15.8, 7.7 Hz, 1H), 1.60 (ddd, *J* = 29.6, 15.01, 4.2 Hz, 1H), 1.38 (d, *J* = 21.6, 17.7 Hz, 3H), 1.33 (d, *J* = 17.4 Hz, 3H), 1.15 (d, *J* = 6.2 Hz, 3H).

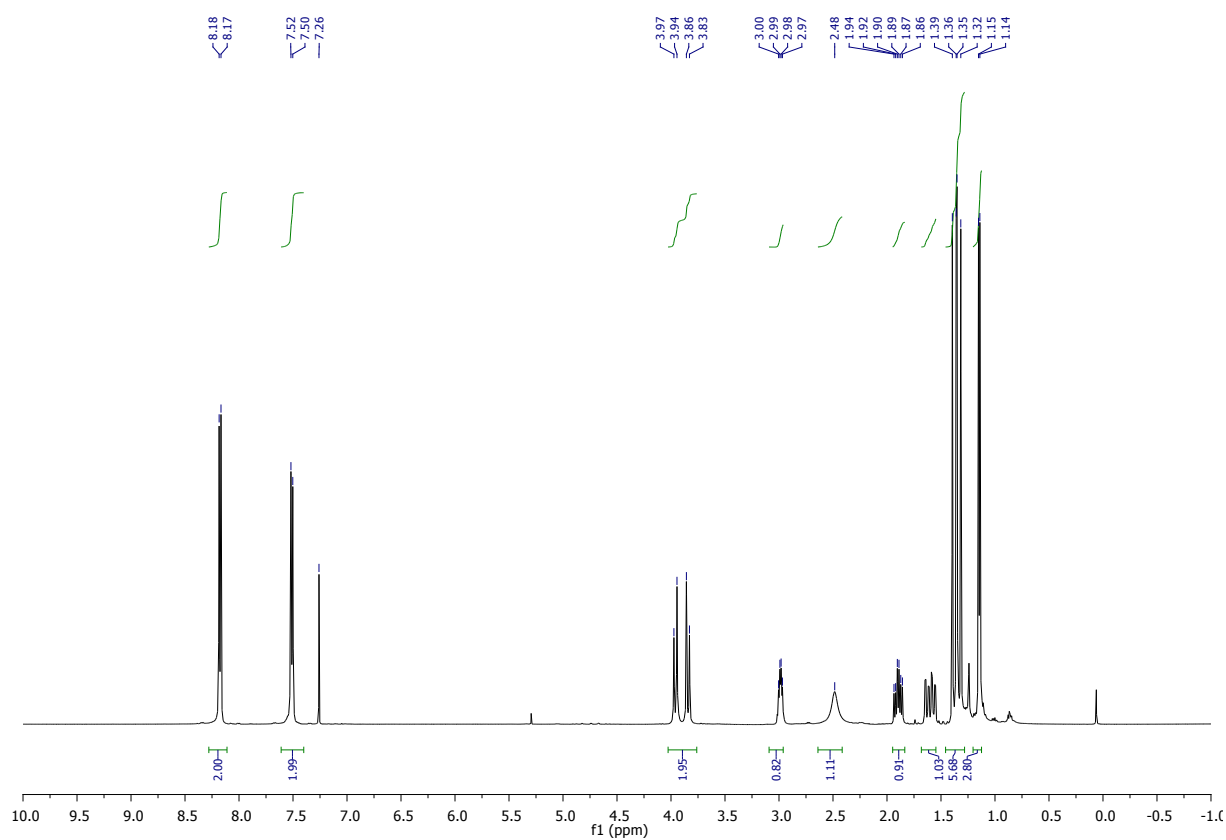
**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, ppm) δ:** 148.9 (C), 147.2 (C), 129.0 (2 CH), 123.8 (2 CH), 96.4 (d, *J* = 164 Hz, C), 50.4 (CH<sub>2</sub>), 49.6 (CH), 47.7 (d, *J* = 21 Hz, CH<sub>2</sub>), 41.2 (d, *J* = 22 Hz, CH<sub>2</sub>), 28.2 (d, *J* = 25 Hz, CH<sub>3</sub>), 26.6 (d, *J* = 25 Hz, CH<sub>3</sub>), 21.5 (CH<sub>3</sub>).

**<sup>19</sup>F{<sup>1</sup>H} NMR (471 MHz, CDCl<sub>3</sub>, ppm):** -137.3.

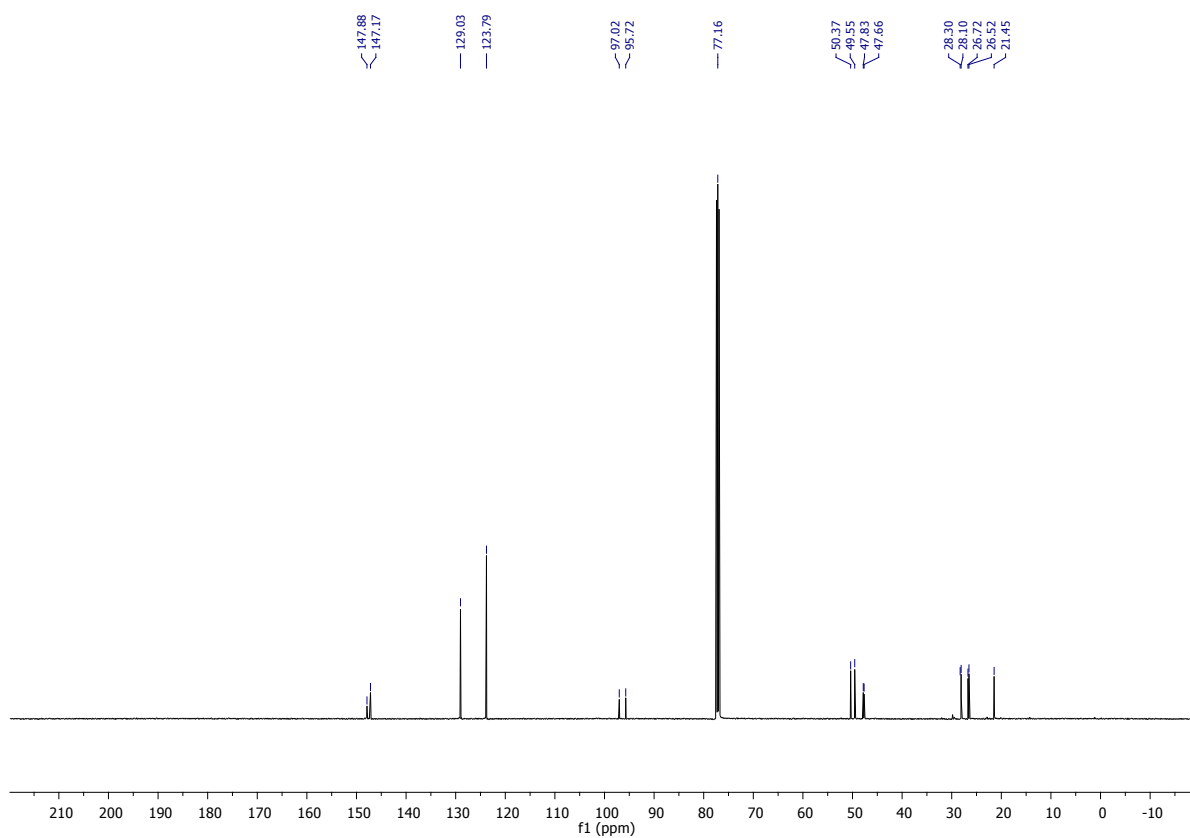
**HRMS (ESI):** *m/z* [M+H]<sup>+</sup> calc for C<sub>13</sub>H<sub>20</sub>FN<sub>2</sub>O<sub>2</sub>: 255.1503, found 255.1511.



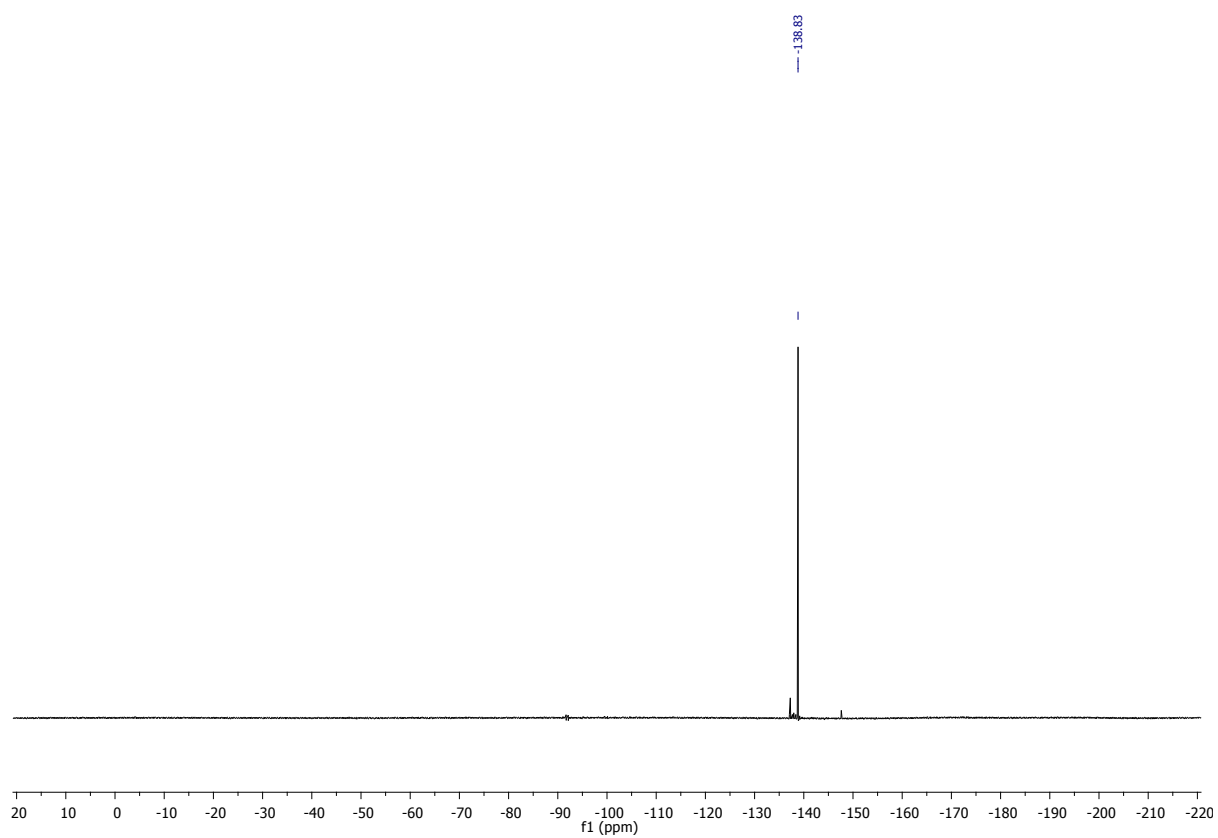
### <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)



### <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)

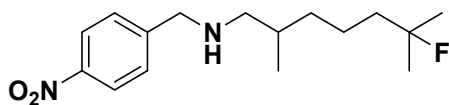


**$^{19}\text{F}\{^1\text{H}\}$  NMR (471 MHz,  $\text{CDCl}_3$ )**



**Compound 2p:** 6-fluoro-2,6-dimethyl-*N*-(4-nitrobenzyl)heptan-1-amine

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This compound was obtained after reaction of substrate **1p** (90 mg, 0.3 mmol), following the general procedure **A** at -40 °C with 6 mL of HF/SbF<sub>5</sub> and 2 mL of HF/Pyr. The crude reaction mixture was purified over silica gel with dichloromethane/methanol (98/2) as the eluent, thereby obtaining compound **2p** (60 mg, 62%) as a brown oil.

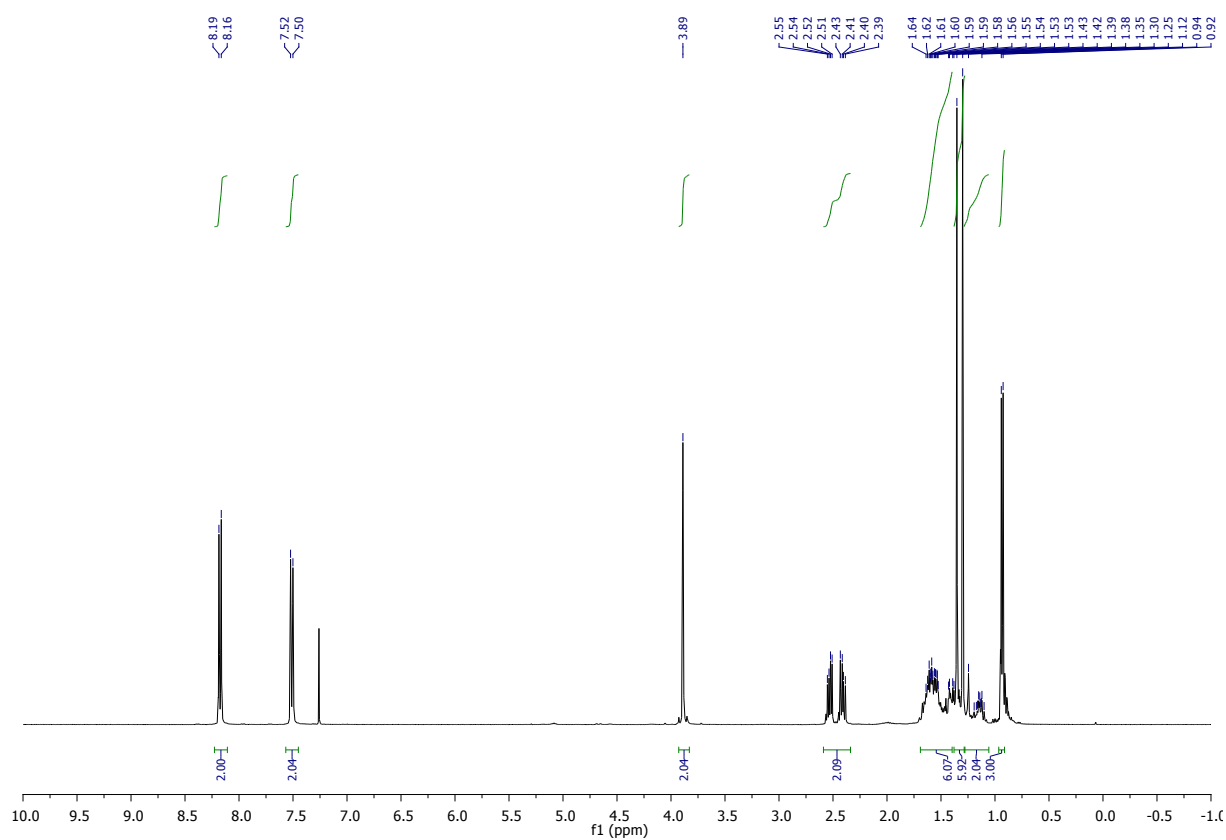
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm) δ:** 8.18 (d, *J* = 8.7 Hz, 2H), 7.51 (d, *J* = 8.7 Hz, 2H), 3.89 (s, 2H), 2.53 (dd, *J* = 11.5, 5.9 Hz, 2H), 2.41 (dd, *J* = 11.9, 5.7 Hz, 2H), 1.72-1.38 (m, 6H), 1.33 (d, *J* = 21.5 Hz, 6H), 1.27-1.07 (m, 2H), 0.93 (d, *J* = 6.7 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm) δ:** 148.6 (C), 147.2 (C), 128.7 (2 CH), 123.7 (2 CH), 95.8 (d, *J* = 164 Hz, C), 56.0 (CH<sub>2</sub>), 53.5 (CH<sub>2</sub>), 41.8 (d, *J* = 23 Hz, CH<sub>2</sub>), 35.2 (CH<sub>2</sub>), 33.5 (CH), 26.7 (d, *J* = 25 Hz, CH<sub>3</sub>), 26.6 (d, *J* = 25 Hz, CH<sub>3</sub>), 21.4 (d, *J* = 5 Hz, CH<sub>2</sub>), 18.2 (CH<sub>3</sub>).

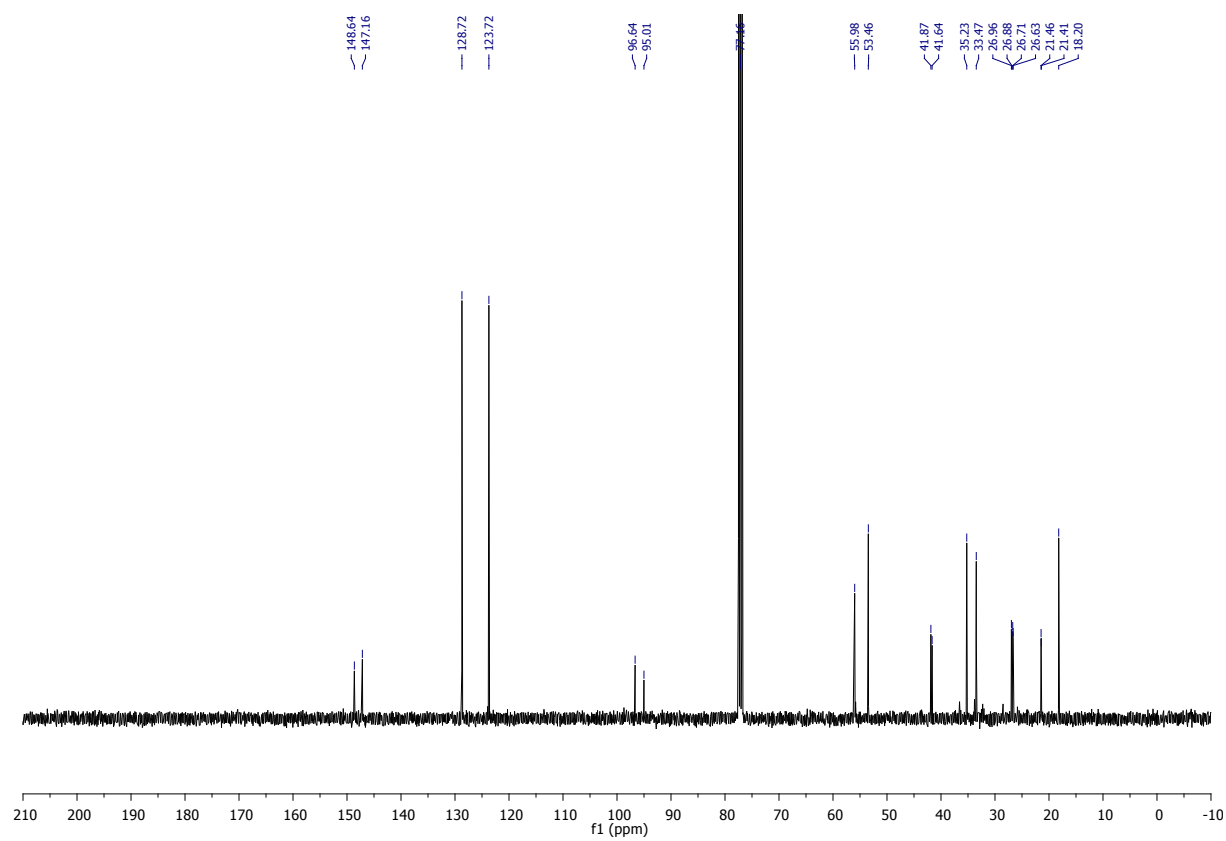
**<sup>19</sup>F {<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>, ppm) δ:** -138.0.

**HRMS (ESI):** *m/z* [M+H]<sup>+</sup>: calc for C<sub>16</sub>H<sub>25</sub>FN<sub>2</sub>O<sub>2</sub> : 297.1972, found 297.1987.

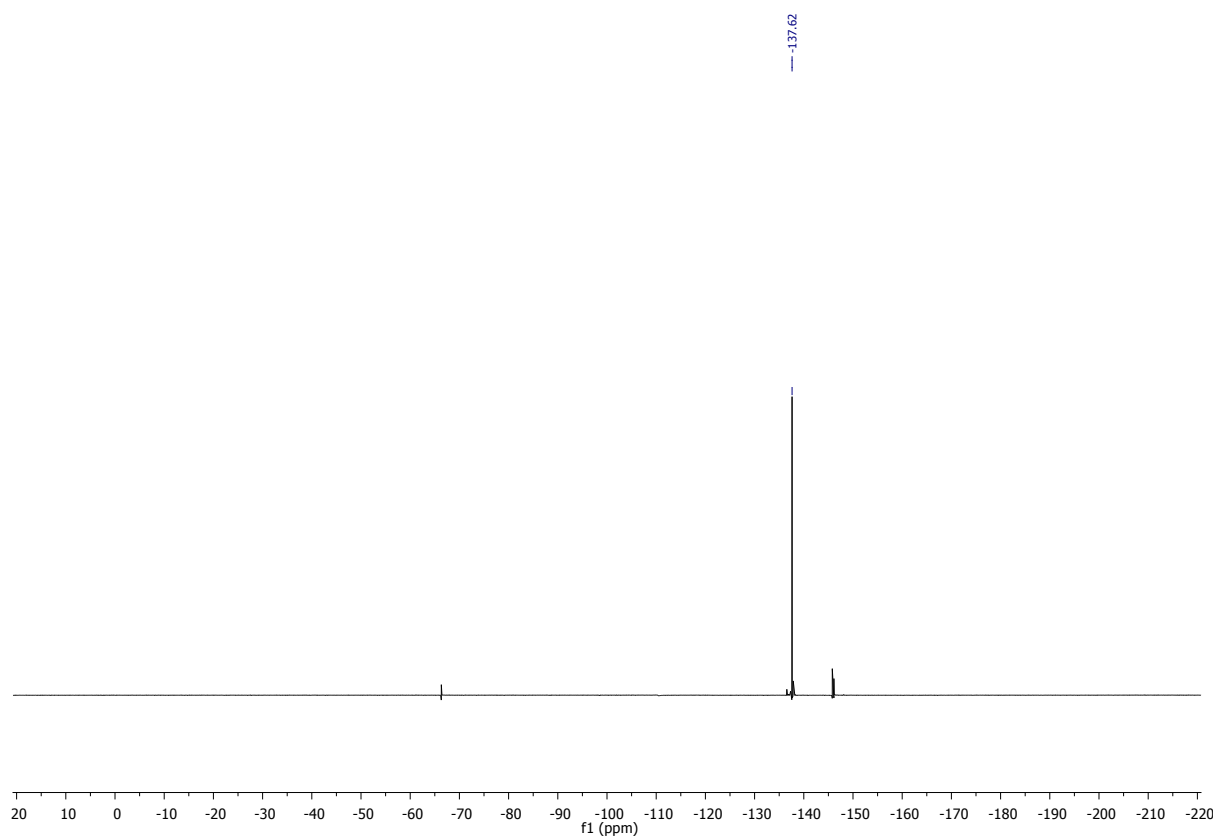
### <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



### <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)

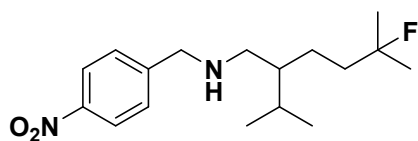


**$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{CDCl}_3$ )**



**Compound 2q:** 5-fluoro-2-isopropyl-5-methyl-*N*-(4-nitrobenzyl)hexan-1-amine

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This compound was obtained after reaction of substrate **1q** (48 mg, 0.2 mmol), following the general procedure **A** at -40 °C with 6 mL of HF/SbF<sub>5</sub> and 2 mL of HF/Pyr. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate (7/3) as the eluent, thereby obtaining compound **2q** (38 mg, 75%) as a brown oil.

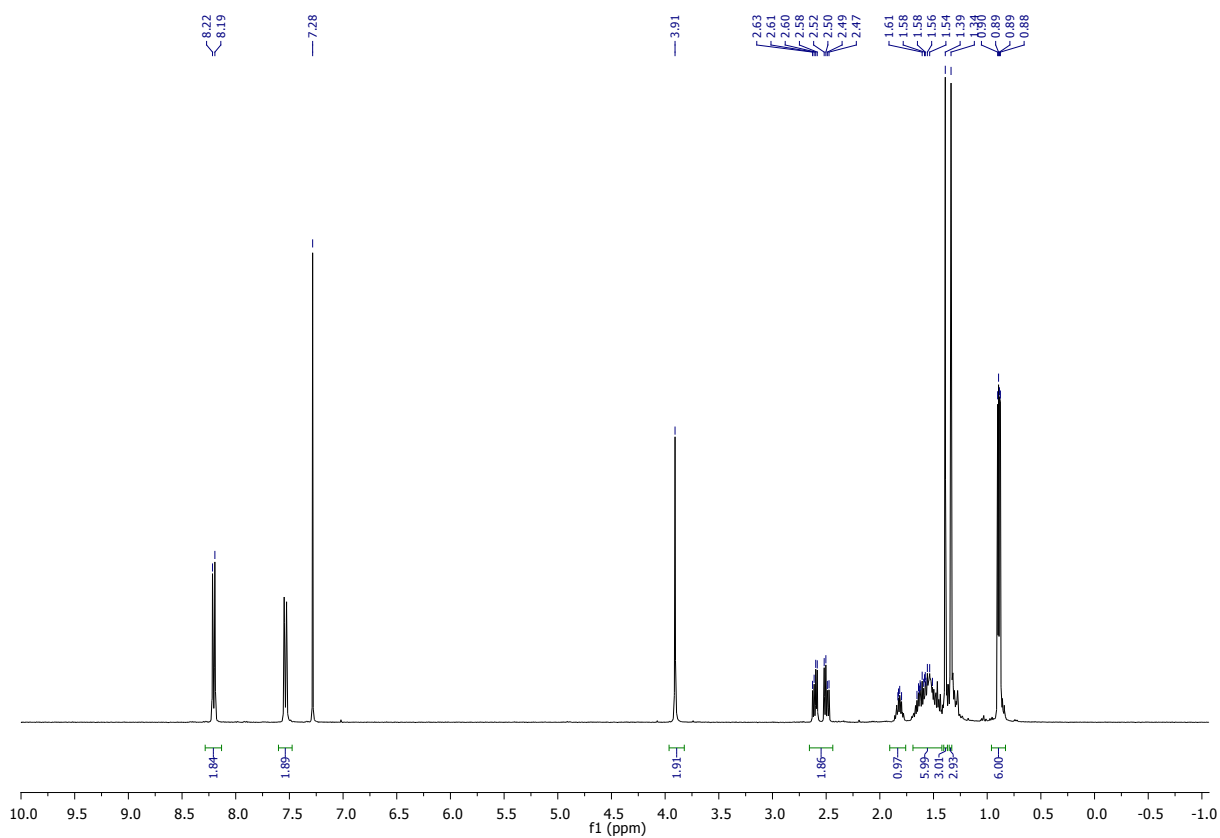
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm) δ:** 8.21 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 3.91 (s, 2H), 2.60 (dd, *J* = 11.7, 5.8 Hz, 1H), 2.50 (dd, *J* = 11.7, 6.3 Hz, 1H), 1.88-1.74 (m, 1H), 1.67-1.40 (m, 6H), 1.34 (d, *J* = 21.5 Hz, 6H), 0.87 (dd, *J* = 6.9, 3.5 Hz, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm) δ:** 148.6 (C), 147.01 (C), 128.6 (2 CH), 123.6 (2 CH), 95.9 (d, *J* = 164 Hz, C), 53.5 (CH<sub>2</sub>), 50.5 (CH<sub>2</sub>), 44.5 (CH), 39.4 (d, *J* = 23 Hz, CH<sub>2</sub>), 28.5 (CH<sub>3</sub>), 26.6 (d, *J* = 26 Hz, 2 CH<sub>3</sub>), 23.0 (d, *J* = 5 Hz, CH<sub>2</sub>), 19.7 (CH<sub>3</sub>), 19.3 (CH<sub>3</sub>).

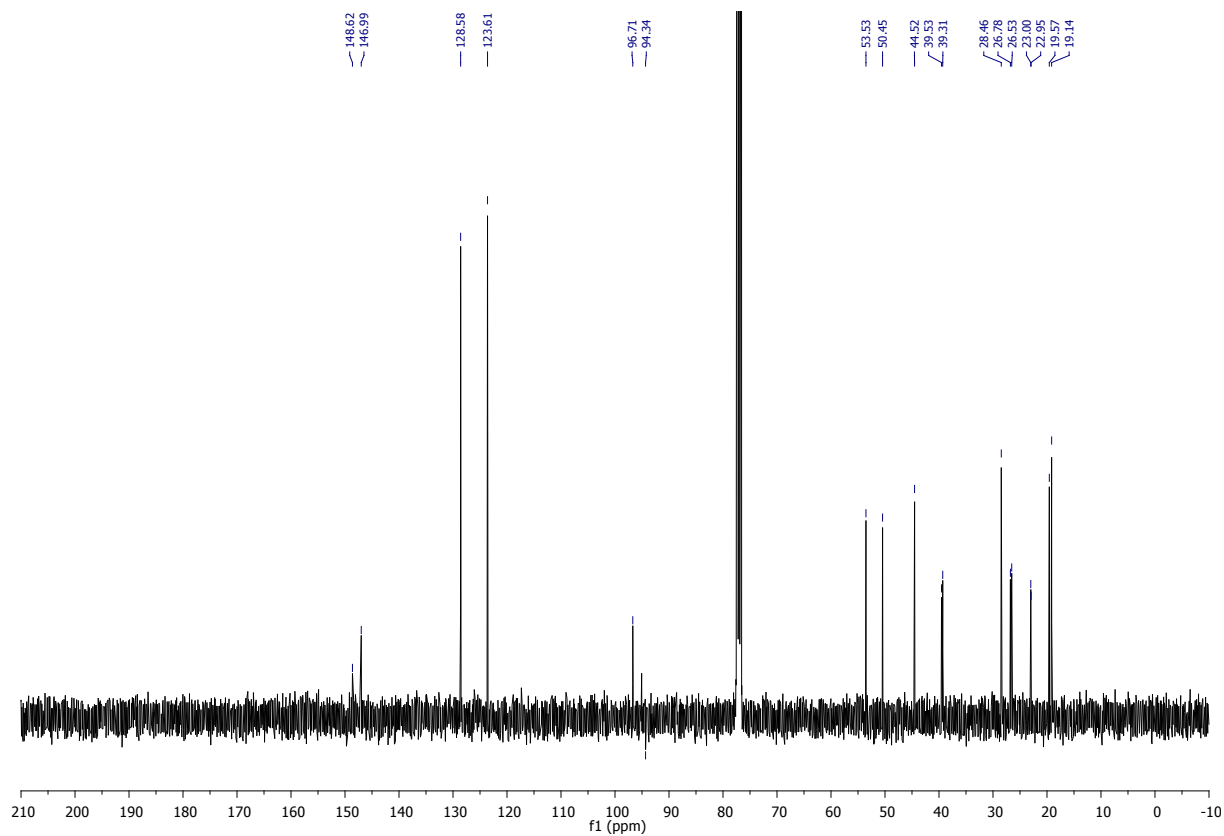
**<sup>19</sup>F {<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>, ppm) δ:** -138.0.

**HRMS (ESI):** *m/z* [M+H]<sup>+</sup>: calc for: 311.2129, found 311.2143.

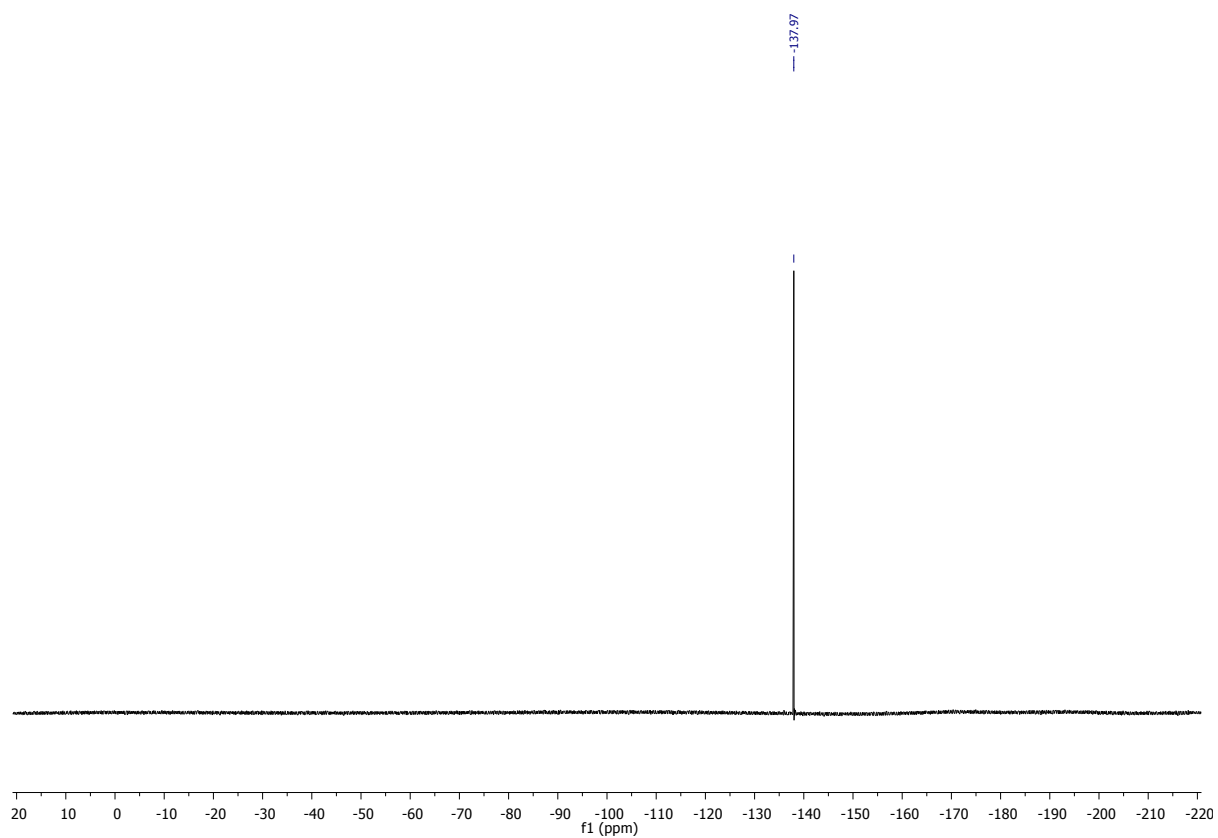
### <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



### <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)



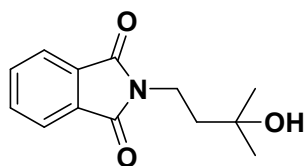
**$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{CDCl}_3$ )**





**Compound 3r:** 2-(3-hydroxy-3-methylbutyl)isoindoline-1,3-dione

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This compound was obtained after reaction of substrate **1r** (180 mg, 0.82 mmol), following the general procedure **C** with 6 mL of HF/SbF<sub>5</sub>, the mixture being stirred at -40 °C for 30 min without addition of HF/Pyridine. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate (9/1) as the eluent, thereby obtaining compound **3r** (180 mg, 93%) as a white solid. The spectroscopic data correspond to those previously described in the literature.<sup>4</sup>

**Mp:** 68 °C.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm) δ:** 7.82 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.69 (dd, *J* = 5.5, 3.0 Hz, 2H), 3.86-3.80 (m, 2H), 1.88-1.82 (m, 3H), 1.30 (s, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm) δ:** 168.6 (C), 134.0 (2 CH), 132.3 (C), 123.3 (2 CH), 70.0 (C), 41.5 (CH<sub>2</sub>), 34.1 (CH<sub>2</sub>), 29.5 (2 CH<sub>3</sub>).

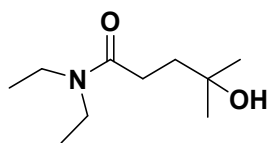
**HRMS (ESI):** *m/z* [M+Na]<sup>+</sup>: calc for C<sub>13</sub>H<sub>15</sub>NO<sub>3</sub>Na: 256.0944, found 256.0950.

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<sup>4</sup> H. Chen, Z. Liu, Y. Lv, X. Tan, H. Shen, H.-Z. Yu and C. Li, *Angew. Chem., Int. Ed.* **2017**, *56*, 15411.

**Compound 3s:** *N,N*-diethyl-4-hydroxy-4-methylpentanamide

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This compound was obtained after reaction of substrate **1s** (176 mg, 1.06 mmol), following the general procedure **C** with 6 mL of HF/SbF<sub>5</sub>, the mixture being stirred at -40 °C for 30 min without addition of HF/Pyridine. The crude reaction mixture was purified over silica gel with dichloromethane/methanol (90/10) as the eluent, thereby obtaining compound **3s** (183 mg, 98%) as a white solid.

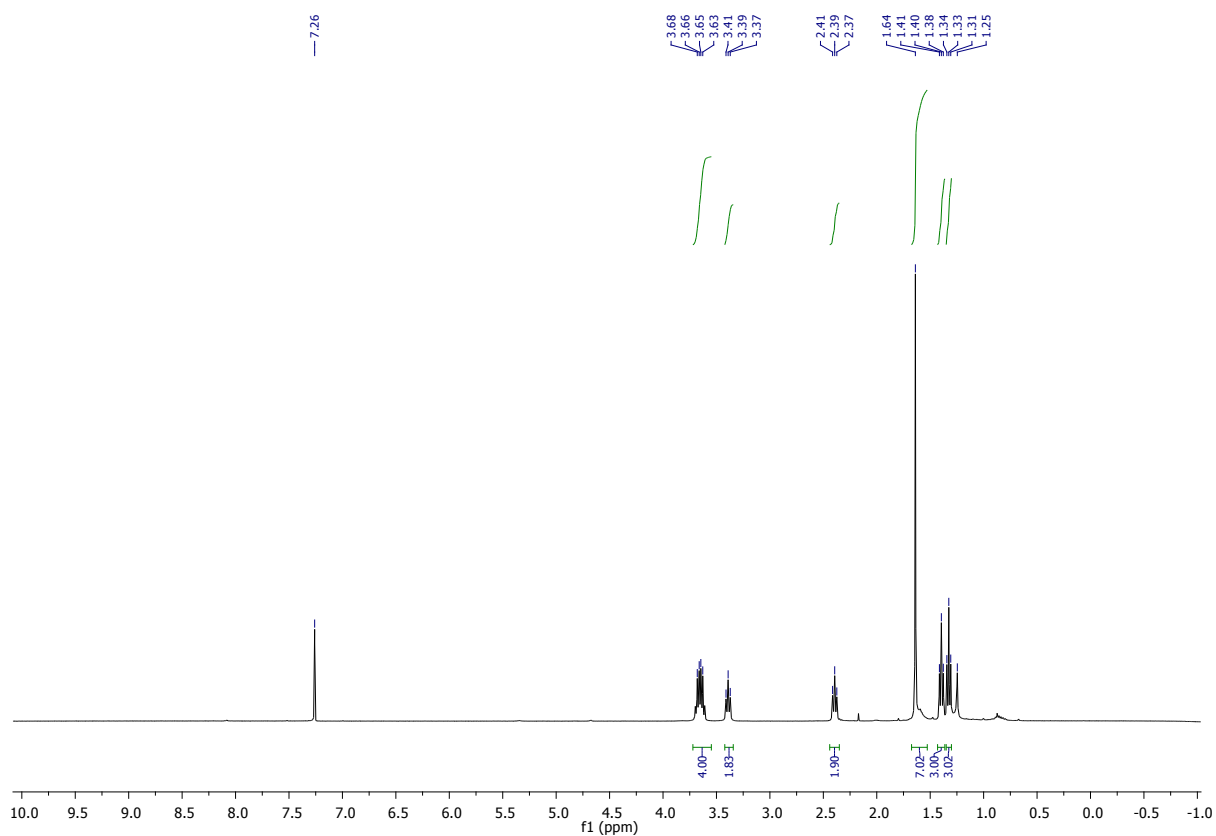
**Mp:** 85 °C.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm) δ:** 3.65 (m, 4H), 3.39 (t, *J* = 8.0 Hz, 1H), 2.39 (t, *J* = 8.0 Hz, 1H), 1.64 (s, 6H), 1.59-1.45 (bs, OH), 1.40 (t, *J* = 8.0 Hz, 3H), 1.33 (t, *J* = 8.0 Hz, 3H).

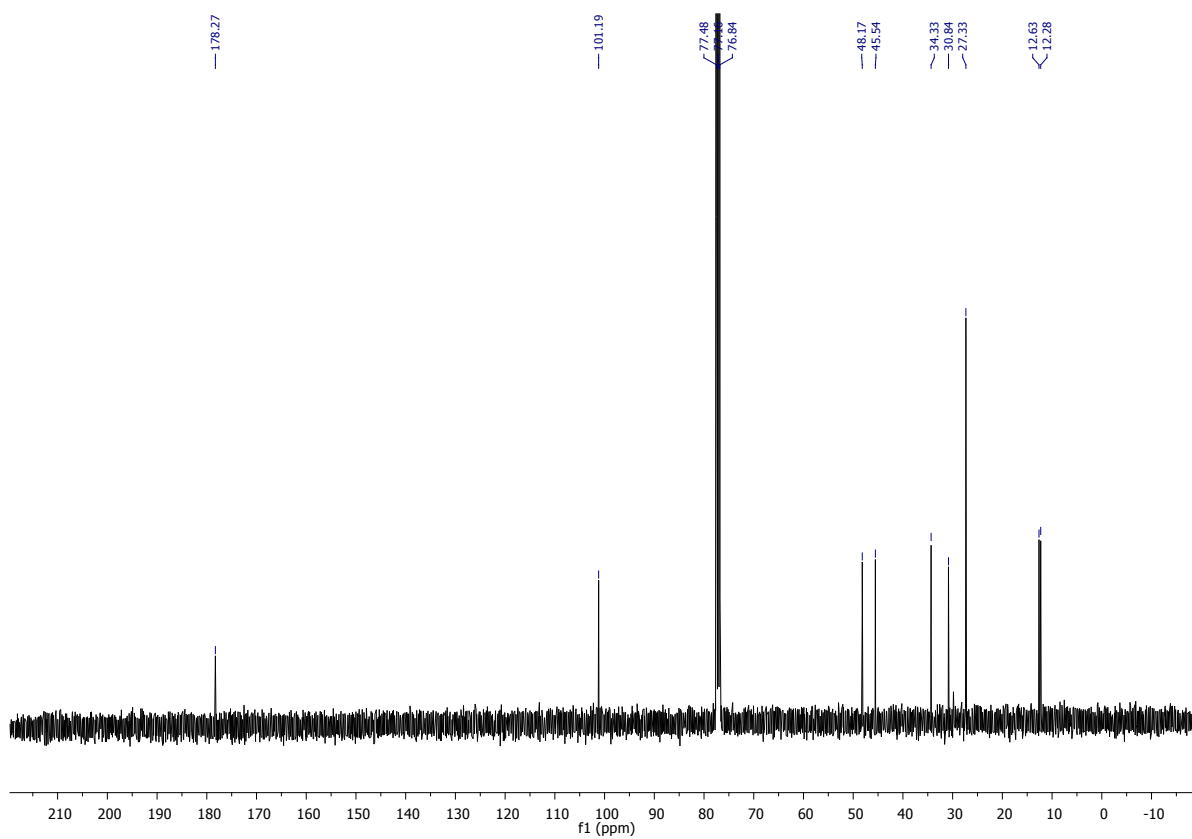
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm) δ:** 178.2 (C), 101.1 (C), 48.1 (CH<sub>2</sub>), 45.4 (CH<sub>2</sub>), 34.2 (CH<sub>2</sub>), 30.8 (CH<sub>2</sub>), 27.3 (2CH<sub>3</sub>), 12.6 (CH<sub>3</sub>), 12.3 (CH<sub>3</sub>).

**HRMS (ESI):** *m/z* [M-OH]<sup>+</sup>: calc C<sub>10</sub>H<sub>20</sub>NO: 170.15394, found 170.15396.

### $^1\text{H}$ NMR (400 MHz, $\text{CDCl}_3$ )

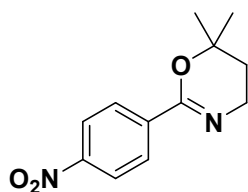


### $^{13}\text{C}$ NMR (100 MHz, $\text{CDCl}_3$ )



**Compound 3t:** 6,6-dimethyl-2-(4-nitrophenyl)-5,6-dihydro-4H-1,3-oxazine

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This compound was obtained after reaction of substrate **1t** (160 mg, 0.66 mmol), following the general procedure **C** with 6 mL of HF/SbF<sub>5</sub>, the mixture being stirred at -40 °C for 30 min without addition of HF/Pyridine. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate (8/2) as the eluent, thereby obtaining compound **3t** (148 mg, 95%) as a yellow solid.

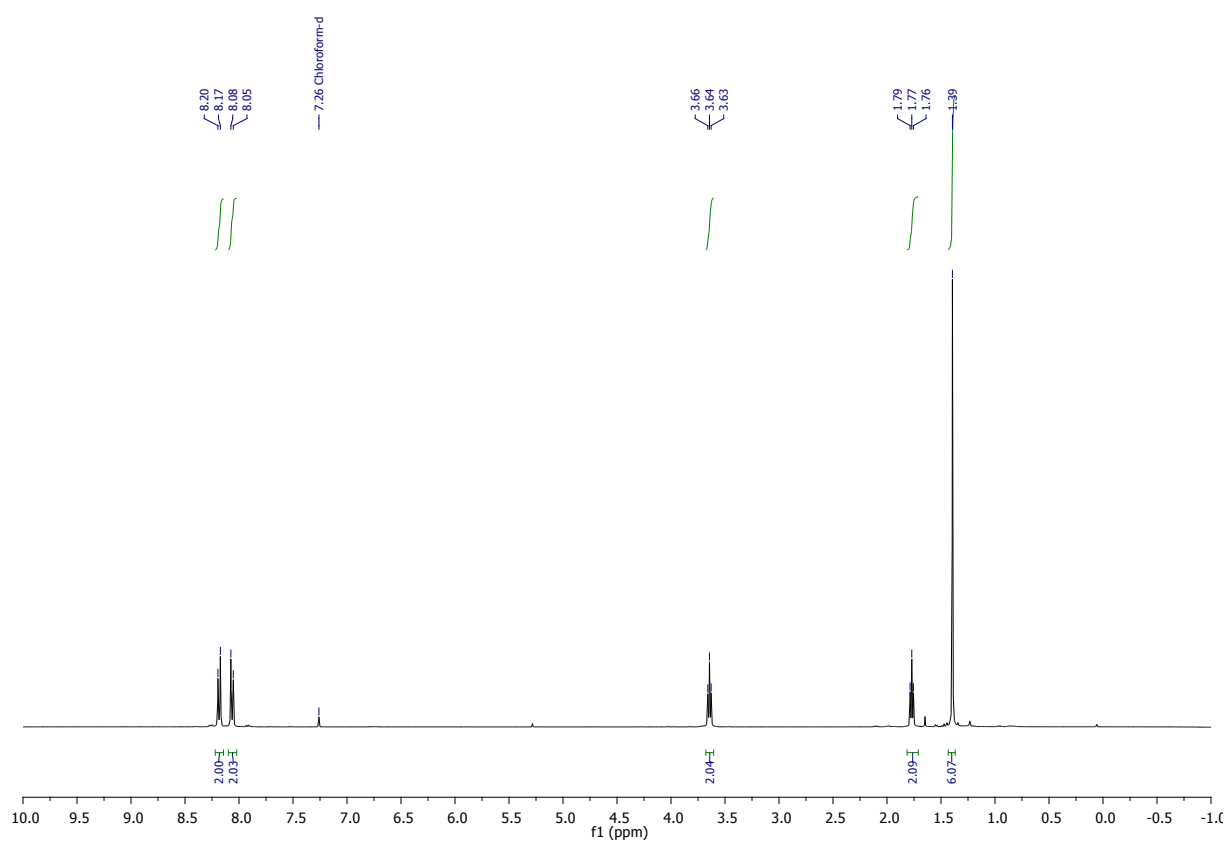
**Mp:** 122 °C.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm) δ:** 8.18 (d, *J* = 9.0 Hz, 2H), 8.06 (d, *J* = 8.9 Hz, 2H), 3.64 (t, *J* = 6.2 Hz, 2H), 1.77 (t, *J* = 6.2 Hz, 2H), 1.39 (s, 6H).

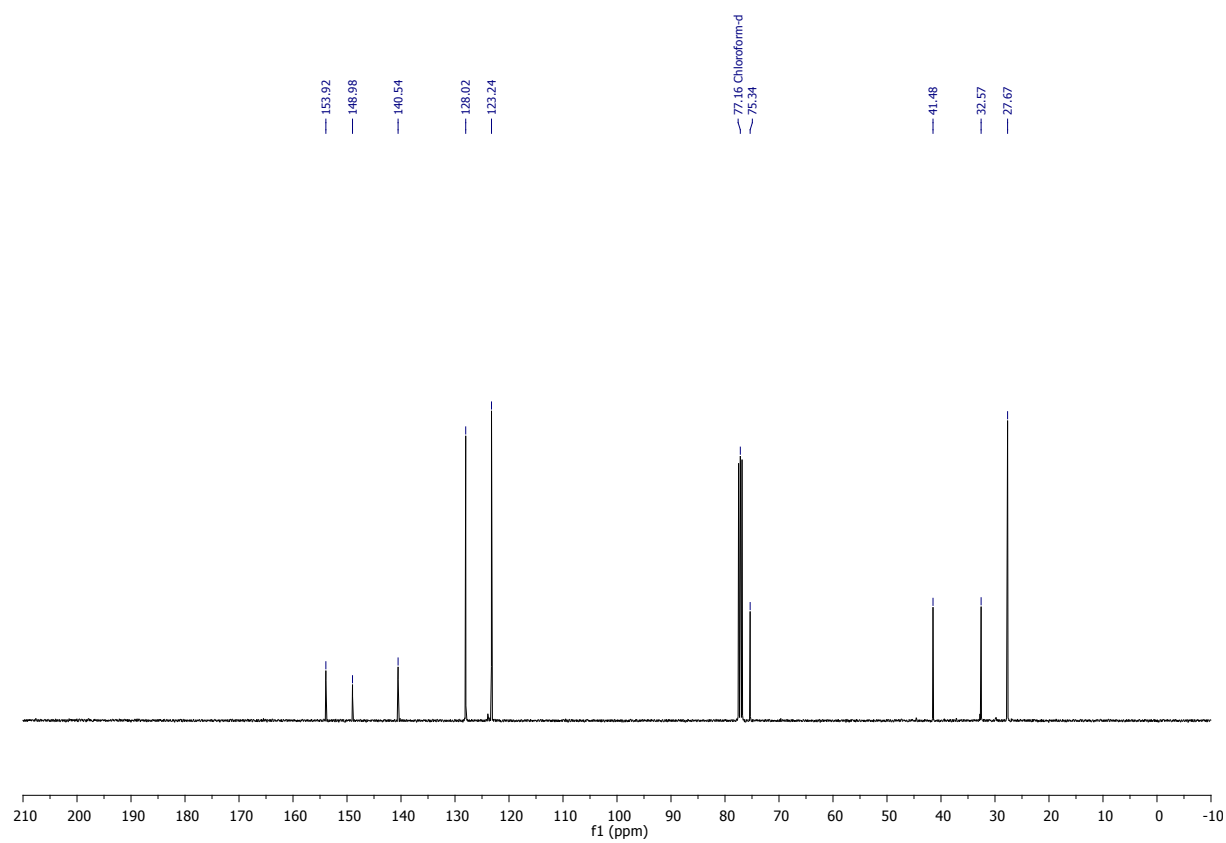
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm) δ:** 153.9 (C), 149.0 (C), 140.5 (C), 128.0 (2 CH), 123.2 (2 CH), 75.3 (C), 41.5 (CH<sub>2</sub>), 32.6 (CH<sub>2</sub>), 27.7 (2 CH<sub>3</sub>).

**HRMS (ESI):** *m/z* [M+H]<sup>+</sup>: calc for C<sub>12</sub>H<sub>15</sub>N<sub>2</sub>O<sub>3</sub>: 235.1077, found 235.1077.

### $^1\text{H}$ NMR (400 MHz, $\text{CDCl}_3$ )

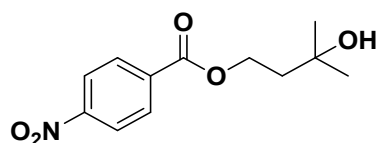


### $^{13}\text{C}$ NMR (100 MHz, $\text{CDCl}_3$ )



**Compound 3u:** 3-hydroxy-3-methylbutyl-4-nitrobenzoate

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This compound was obtained after reaction of substrate **1u** (219 mg, 0.9 mmol), following the general procedure **C** with 6 mL of HF/SbF<sub>5</sub> the mixture being stirred at -40 °C for 30 min without addition of HF/Pyridine. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate (8/2) as the eluent, thereby obtaining the compound **3u** (190 mg, 81%) as a white solid.

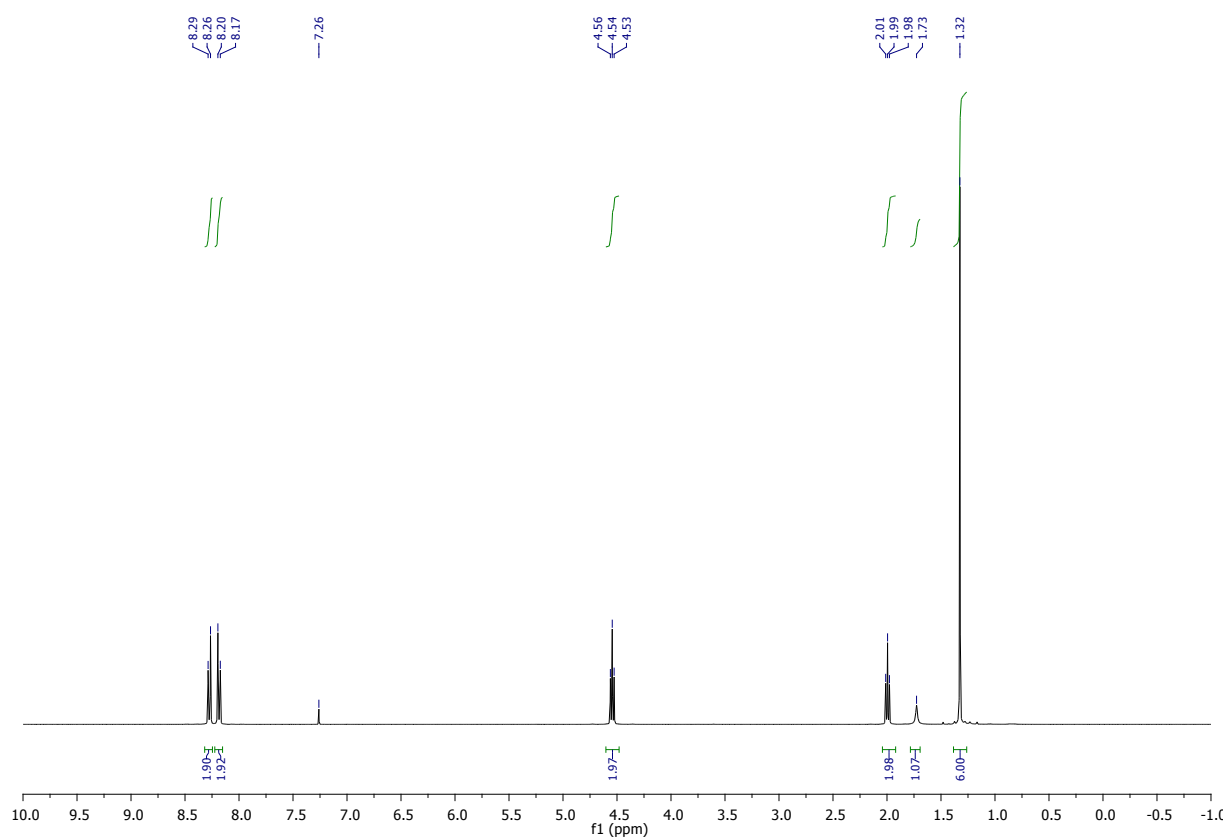
**Mp:** 66 °C.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm) δ:** 8.28 (d, *J* = 8.9 Hz, 2H), 8.18 (d, *J* = 9.0 Hz, 2H), 4.54 (t, *J* = 6.9 Hz, 2H), 1.99 (t, *J* = 6.9 Hz, 2H), 1.73 (bs, 1H), 1.32 (s, 6H).

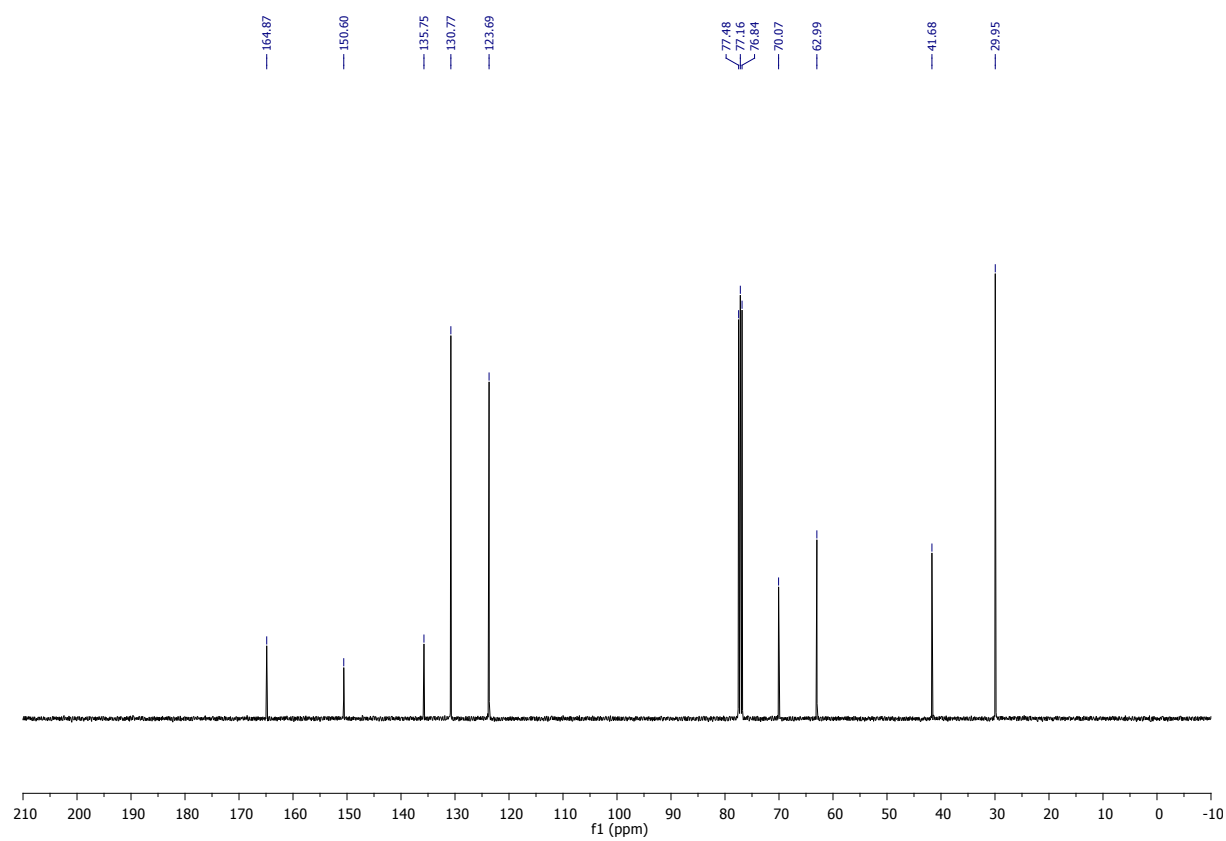
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm) δ:** 164.9 (C), 150.6 (C), 135.7 (C), 130.8 (2 CH), 123.7 (2 CH), 70.1 (C), 63.0 (CH<sub>2</sub>), 41.7 (CH<sub>2</sub>), 29.9 (2 CH<sub>3</sub>).

**HRMS (ESI):** *m/z* [M+Na]<sup>+</sup>: calc for C<sub>12</sub>H<sub>15</sub>NO<sub>5</sub>Na: 276.0842, found 276.0847.

### $^1\text{H}$ NMR (400 MHz, $\text{CDCl}_3$ )

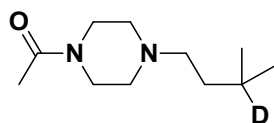


### $^{13}\text{C}$ NMR (100 MHz, $\text{CDCl}_3$ )



**Compound 4a:** 1-(4-(3-methylbutyl-3-*d*)piperazin-1-yl)ethan-1-one

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This compound was obtained after reaction of substrate **1a** (161 mg, 0.8 mmol), following the general procedure **B** with 6 mL of HF/SbF<sub>5</sub> with 183 μL (1.6 mmol, 2.0 equiv.) of cyclohexane-*d*<sub>12</sub> as nucleophile. The crude reaction mixture was purified over silica gel with dichloromethane/methanol (98/2) as the eluent, thereby obtaining an inseparable mixture of **4a/1a** (9/1) (152 mg, 92%) as an orange oil.

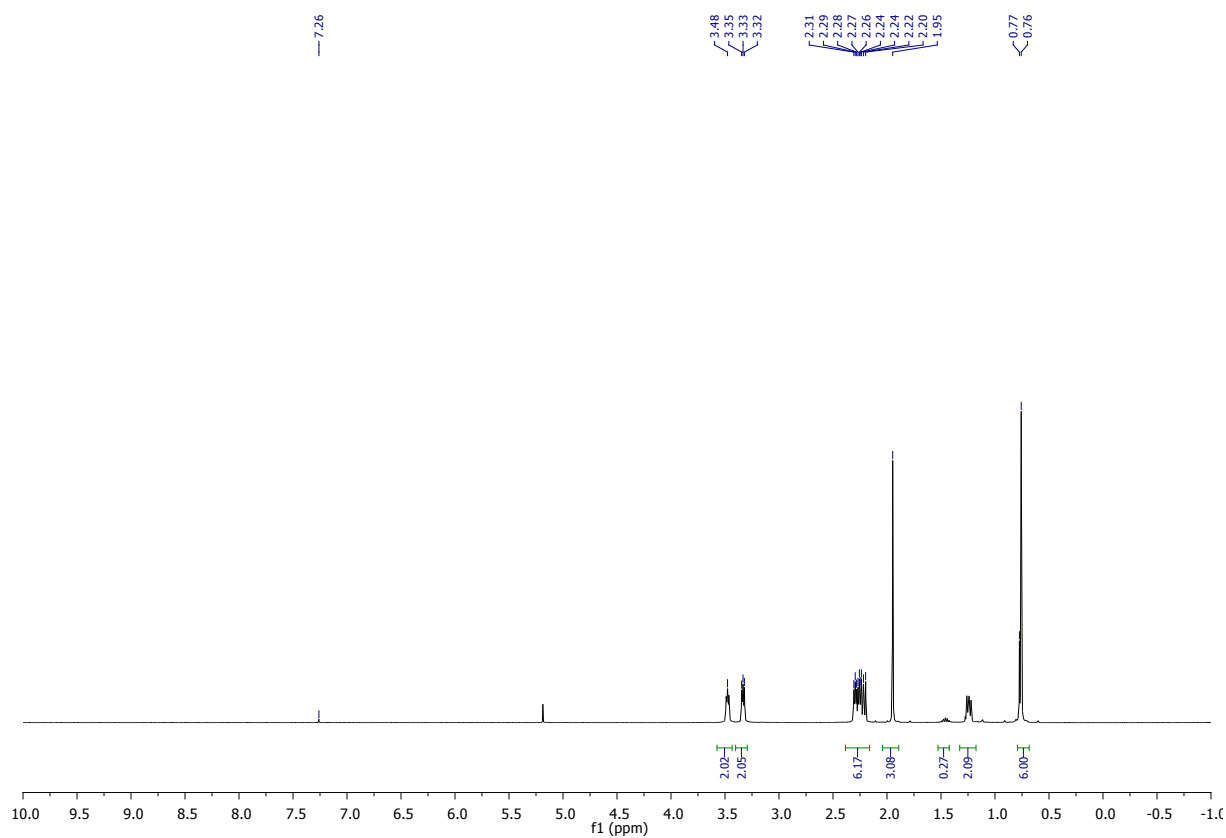
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm) δ:** 3.54-3.44 (m, 2H), 3.36-3.30 (m, 2H), 2.34- 2.18 (m, 6H), 1.95 (s, 3H), 1.28-1.21 (m, 2H), 0.76 (s, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm):** 168.7 (C), 56.3 (CH<sub>2</sub>), 53.3 (CH<sub>2</sub>), 52.7 (CH<sub>2</sub>), 46.1 (CH<sub>2</sub>), 41.2 (CH<sub>2</sub>), 35.6 (CH<sub>2</sub>), 25.9 (t (1: 1: 1), *J* = 19 Hz, C), 22.4 (2 CH<sub>3</sub>), 21.4 (CH<sub>3</sub>).

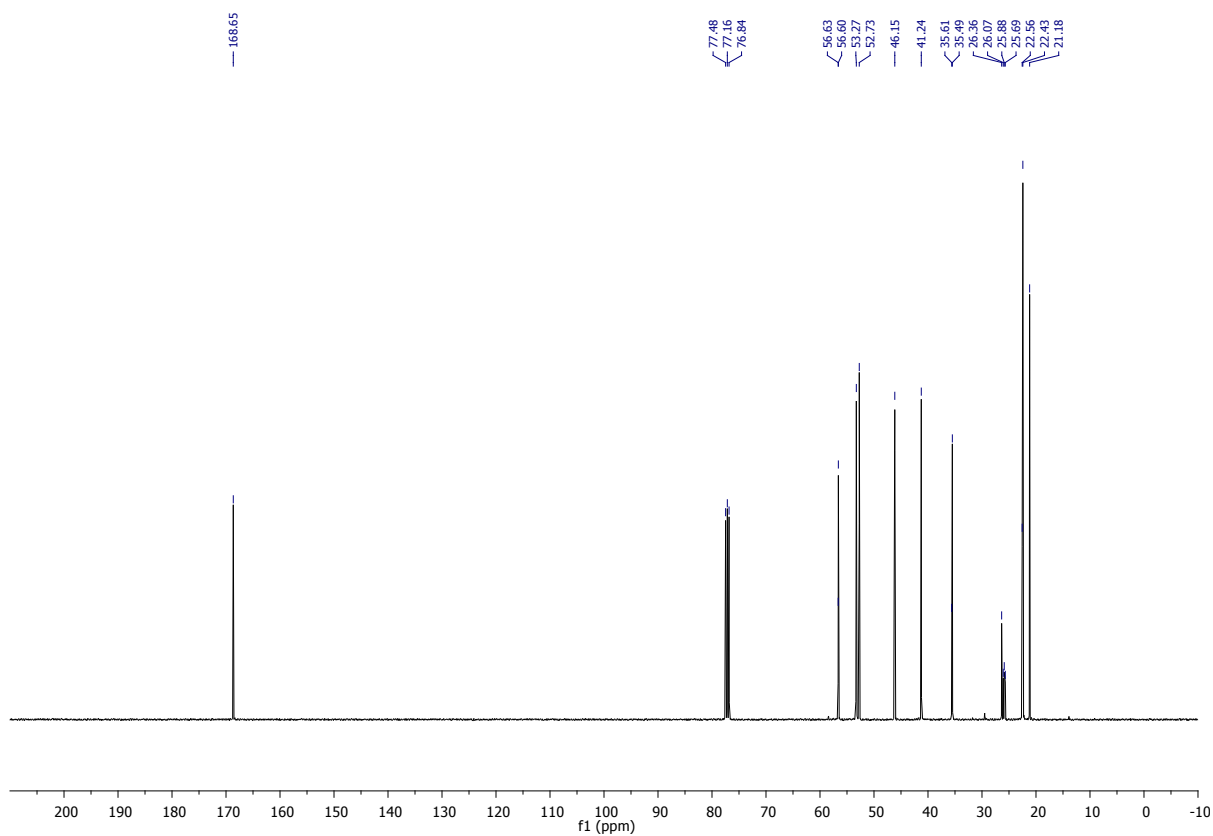
**HRMS (ESI):** *m/z* [M+H]<sup>+</sup> calc for C<sub>11</sub>H<sub>22</sub>DN<sub>2</sub>O: 200.1868, found 200.1873.



### $^1\text{H}$ NMR (400 MHz, $\text{CDCl}_3$ )

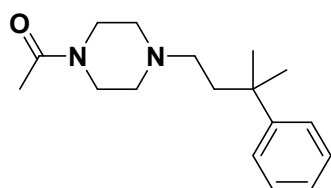


### $^{13}\text{C}$ NMR (100 MHz, $\text{CDCl}_3$ )



**Compound 5a:** 1-(4-(3-methyl-3-phenylbutyl)piperazin-1-yl)ethanone

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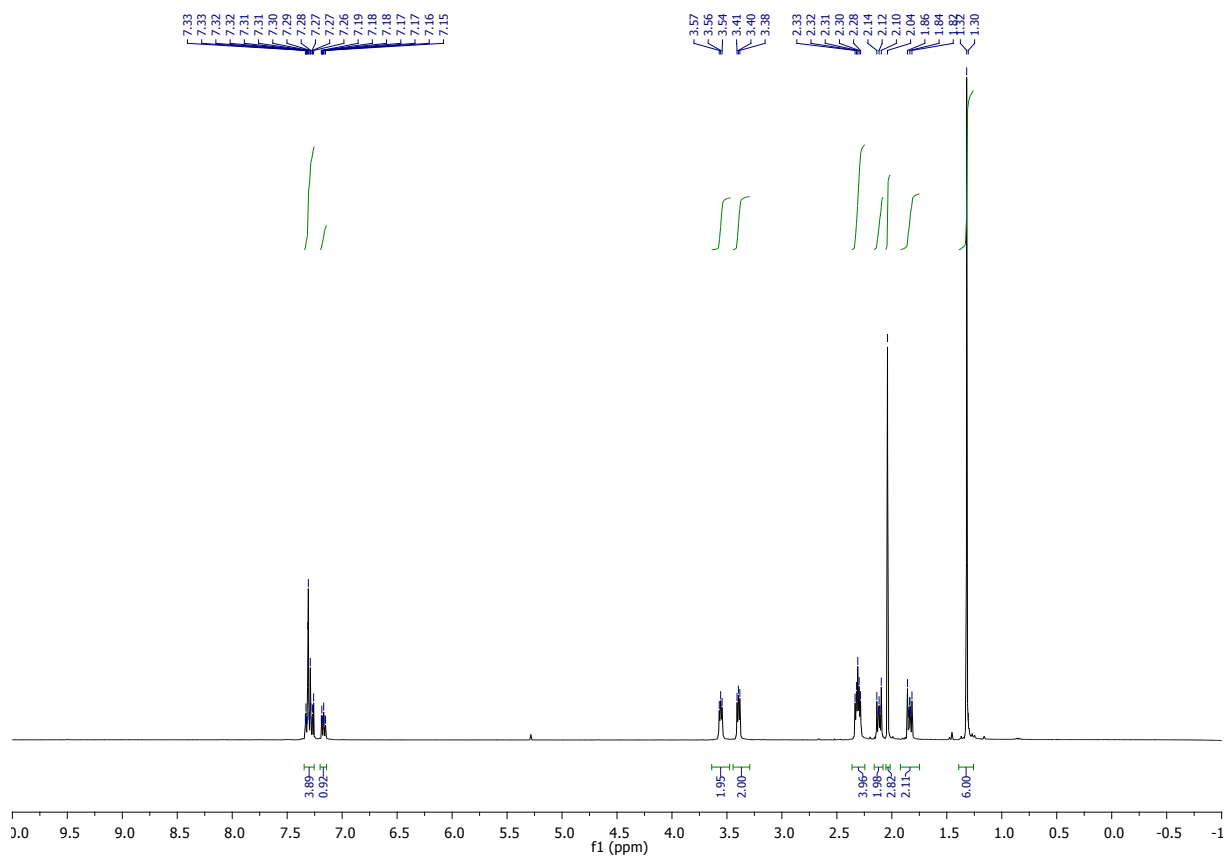
This compound was obtained after reaction of substrate **1a** (150 mg, 0.76 mmol), following the general procedure **B** with 6 mL of HF/SbF<sub>5</sub> and 3 mL of benzene as nucleophile. The crude reaction mixture was purified over silica gel with dichloromethane/methanol (98/2) as the eluent, thereby obtaining compound **5a** (153 mg, 73%) as an orange oil.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm) δ:** 7.35-7.25 (m, 4H), 7.19-7.14 (m, 1H), 3.56 (app t, *J* = 5.0 Hz, 2H) 3.40 (app t, *J* = 5.0 Hz, 2H), 2.31 (m, 4H), 2.12 (m, 2H), 2.04 (s, 3H), 1.84 (m, 2H), 1.32 (s, 6H).

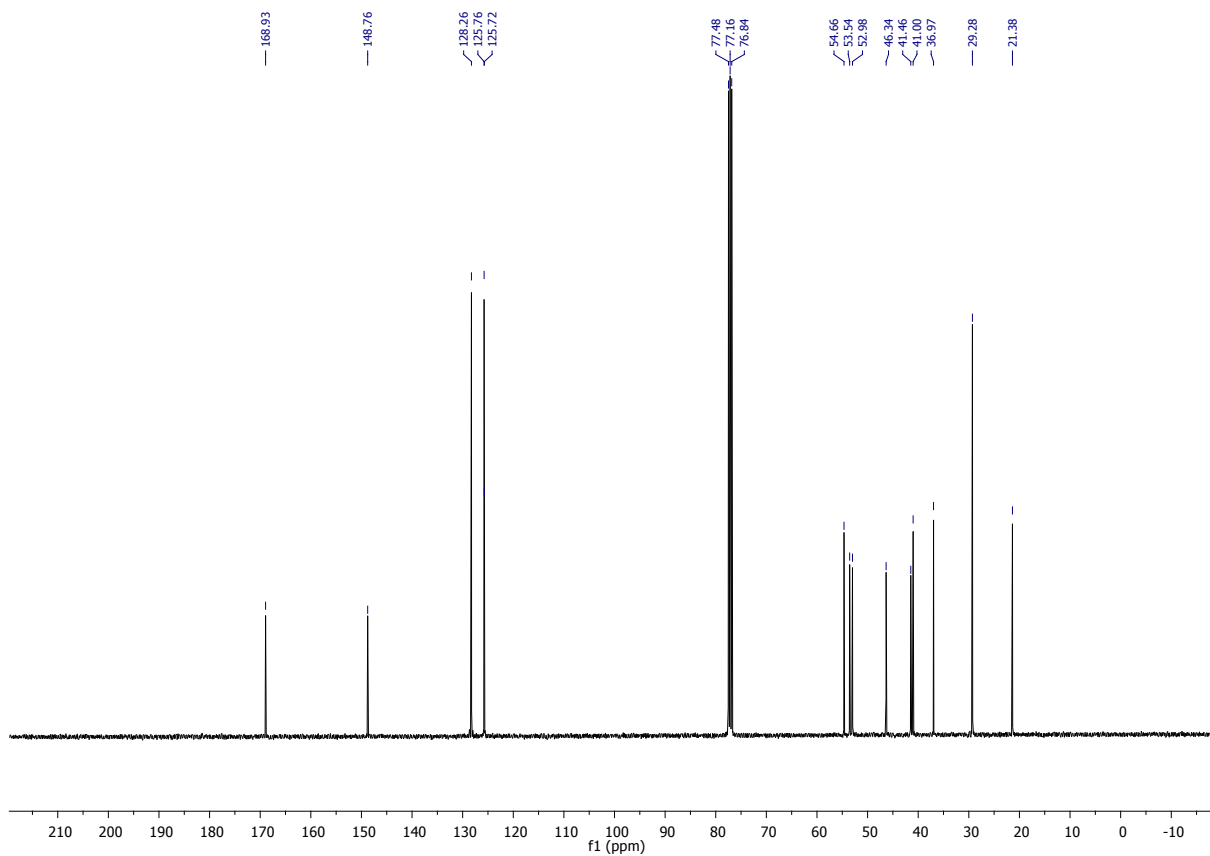
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm) δ:** 168.9 (C), 148.8 (C), 128.3 (CH), 125.8 (CH), 125.7 (CH), 54.7 (CH<sub>2</sub>), 53.5 (CH<sub>2</sub>), 53.0 (CH<sub>2</sub>), 46.3 (CH<sub>2</sub>), 41.5 (CH<sub>2</sub>), 41.0 (CH<sub>2</sub>), 37.0 (C), 29.3 (CH<sub>3</sub>), 21.4 (CH<sub>3</sub>).

**HRMS (ESI):** *m/z* [M+Na]<sup>+</sup> calc for C<sub>17</sub>H<sub>26</sub>N<sub>2</sub>NaO: 297.1937, found 297.1937

### <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

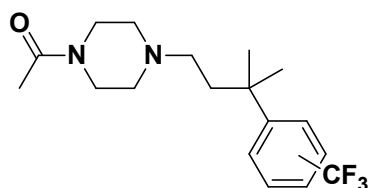


### <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)



**Compound 6a:** 1-(4-(3-methyl-3-(trifluoromethyl)phenyl)butyl)piperazin-1-yl)ethanone

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This compound was obtained after reaction of substrate **1a** (200 mg, 1.01 mmol), following the general procedure **B** with 6 mL of HF/SbF<sub>5</sub> and 3 mL of trifluoromethylbenzene as nucleophile. The crude reaction mixture was purified over silica gel with dichloromethane/methanol (98/2) as the eluent, thereby obtaining compound **6a** as a mixture of ortho/meta/para isomers (279 mg, 81%) as an orange oil.

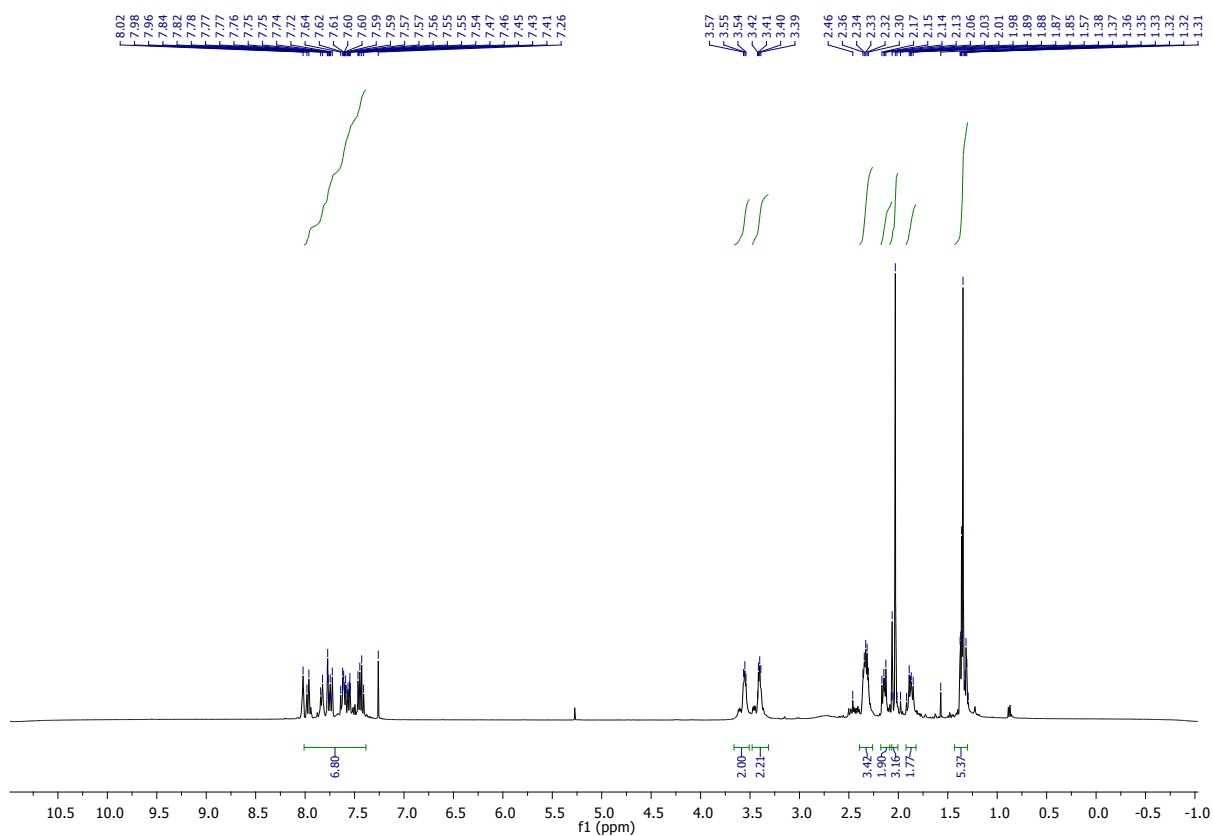
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm) δ:** 8.02-7.40 (m, 4H), 3.55 (m, 2H), 3.40 (m, 2H), 2.35-2.30 (m, 4H), 2.16-2.12 (m, 2H), 2.03 (s, 3H), 1.84-1.89 (m, 2H), 1.34 (s, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm) δ:** 168.9 (C), 149.5-134.3 (C), 130.8 (q, *J* = 33 Hz, C), 133.1-126.0 (CH), 123.8 (q, *J* = 272 Hz, CF<sub>3</sub>), 54.5 (CH<sub>2</sub>), 53.4 (CH<sub>2</sub>), 52.8 (CH<sub>2</sub>), 46.1 (CH<sub>2</sub>), 41.2 (CH<sub>2</sub>), 40.6 (CH<sub>2</sub>), 37.2 (C), 29.0 (CH<sub>3</sub>), 21.3 (CH<sub>3</sub>, C-2).

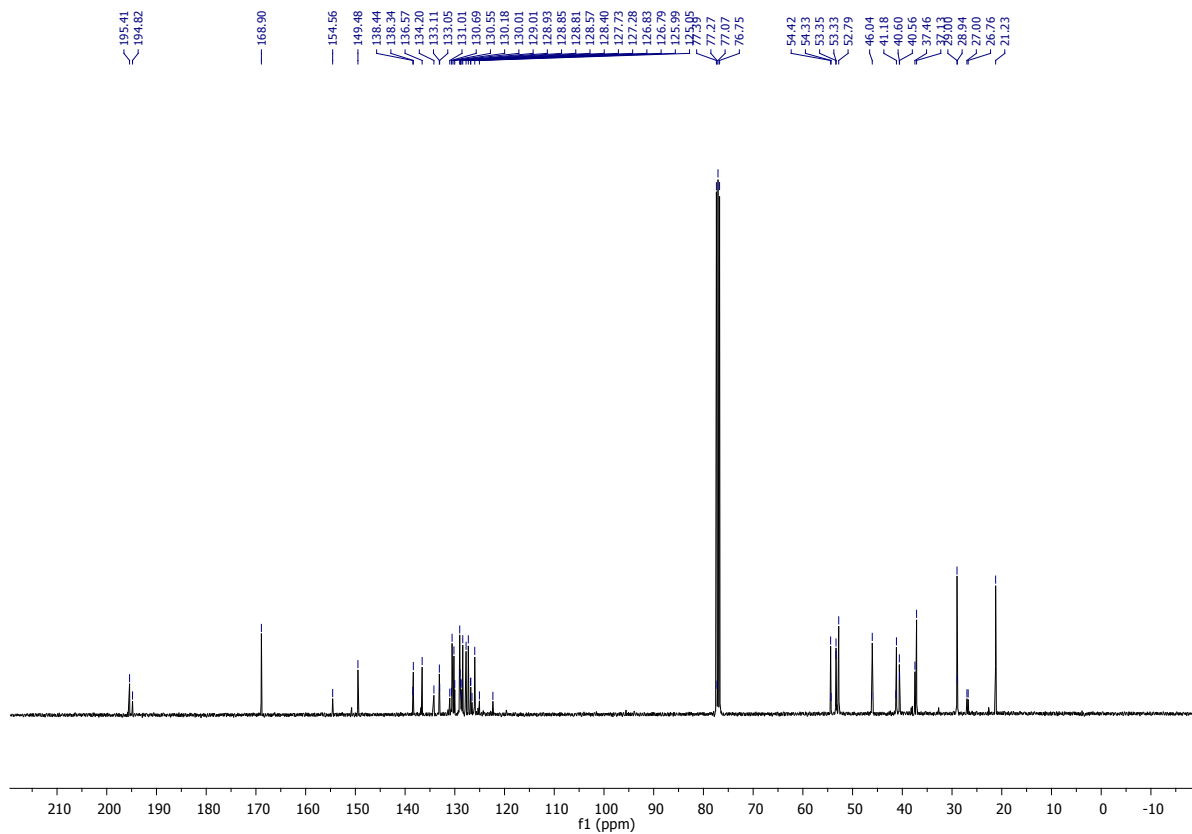
**<sup>19</sup>F{<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>, ppm) δ:** -62.4, -62.6 and -62.7.

**HRMS (ESI):** *m/z* [M+H]<sup>+</sup> calc for C<sub>18</sub>H<sub>26</sub>F<sub>3</sub>N<sub>2</sub>O: 343.1992, found 343.1992.

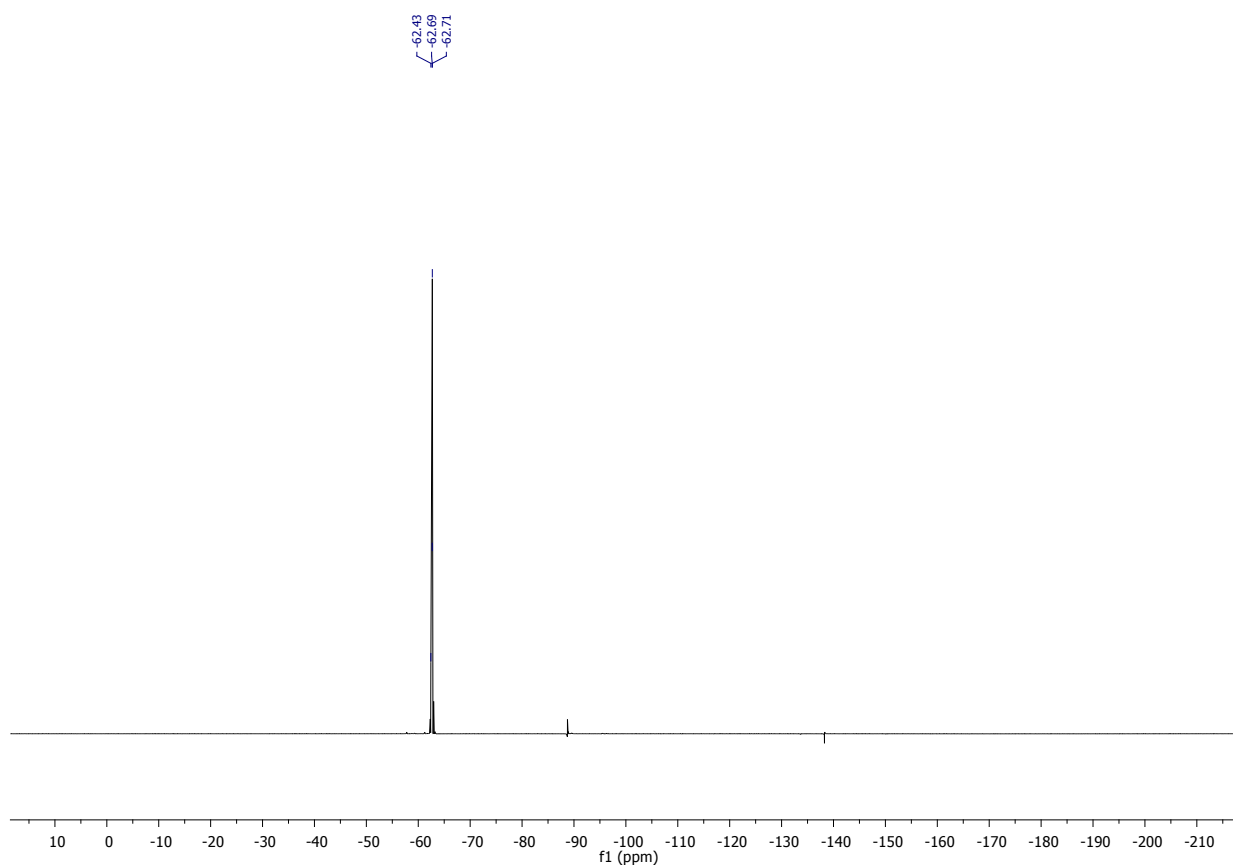
### <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



### <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)

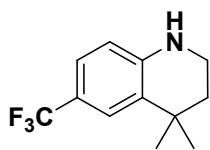


**$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{CDCl}_3$ )**



**Compound 4v:** 4,4-dimethyl-6-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline

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This compound was obtained after reaction of substrate **1v** (215 mg, 0.93 mmol), following the general procedure **C** with 6 mL, the mixture being stirred at -40 °C for 30 min without addition of HF/Pyridine. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate (9/1) as the eluent, thereby obtaining compound **4v** (169 mg, 80%) as a brown oil.

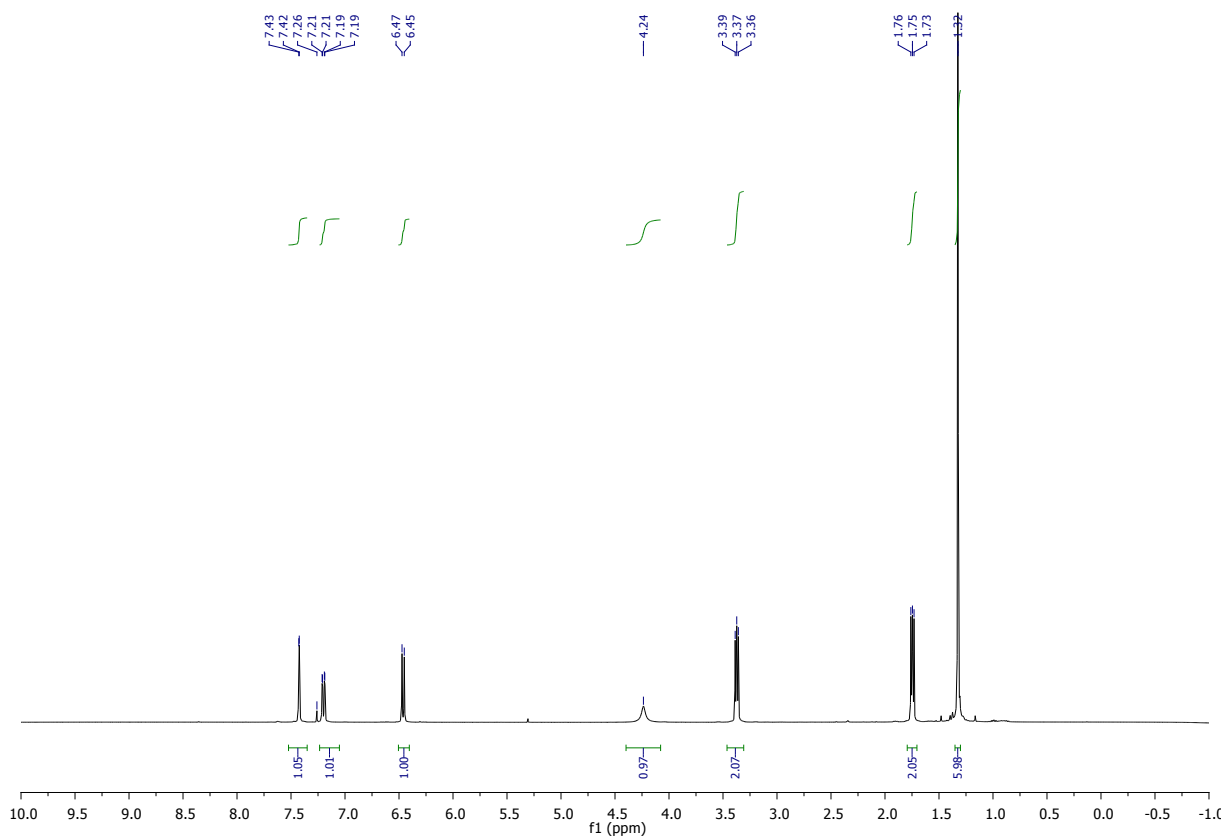
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm) δ:** 7.43 (d, *J* = 1.6 Hz, 1H), 7.20 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 6.46 (d, *J* = 8.4 Hz, 1H), 4.24 (bs, 1H), 3.46-3.31 (m, 2H), 1.79-1.70 (m, 2H), 1.32 (s, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm) δ:** 146.3 (C), 129.5 (C), 125.5 (q, *J* = 269 Hz, CF<sub>3</sub>), 123.9 (q, *J* = 3.8 Hz, CH), 123.4 (q, *J* = 3.8 Hz, CH), 118.1 (q, *J* = 32 Hz, C), 113.4 (CH), 38.2 (CH<sub>2</sub>), 36.3 (CH<sub>2</sub>), 31.9 (C), 30.50 (CH<sub>3</sub>).

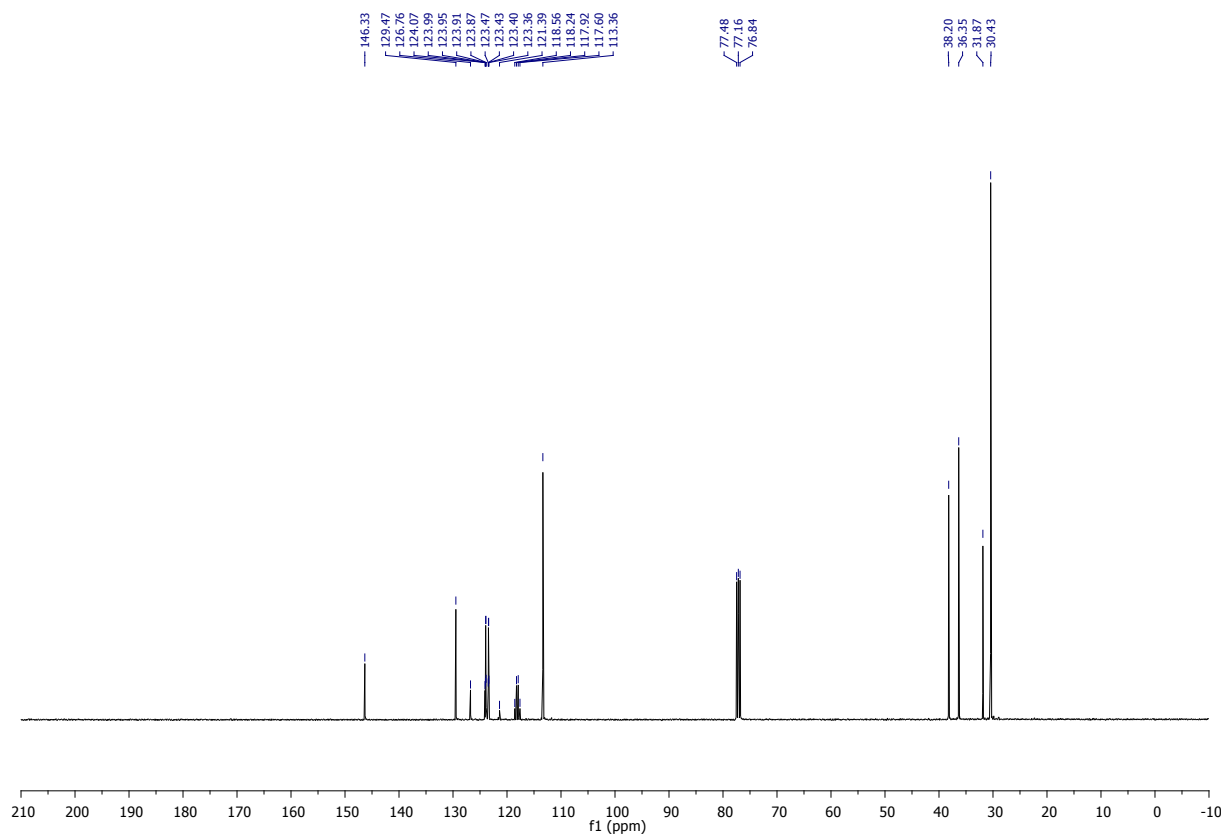
**<sup>19</sup>F {<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>, ppm) δ:** -60.6.

**HRMS (ESI):** *m/z* [M+H]<sup>+</sup>: calc for C<sub>12</sub>H<sub>15</sub>F<sub>3</sub>N: 230.1151, found 230.1157.

### <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

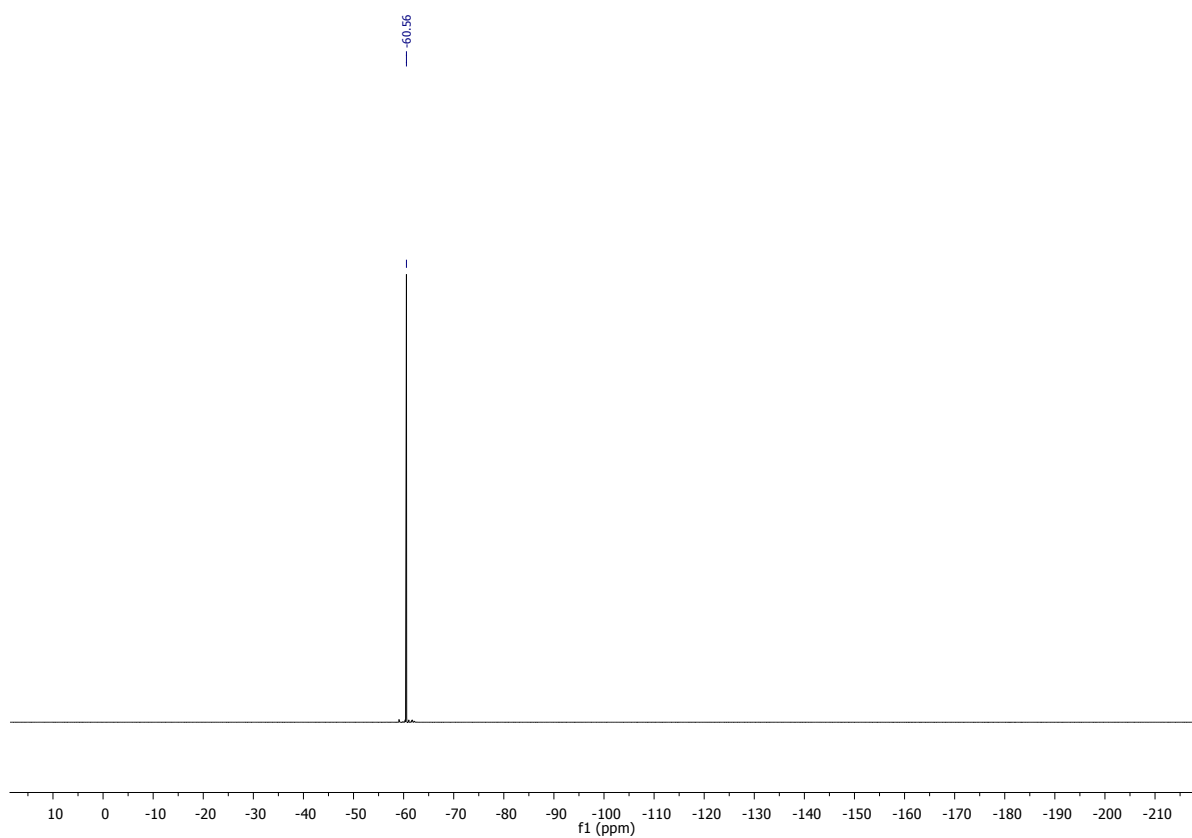


### <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)



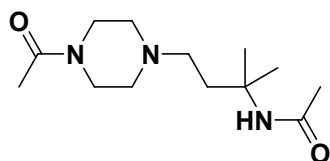


**$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{CDCl}_3$ )**



**Compound 7a:** *N*-(4-(4-acetylpiperazin-1-yl)-2-methylbutan-2-yl)acetamide

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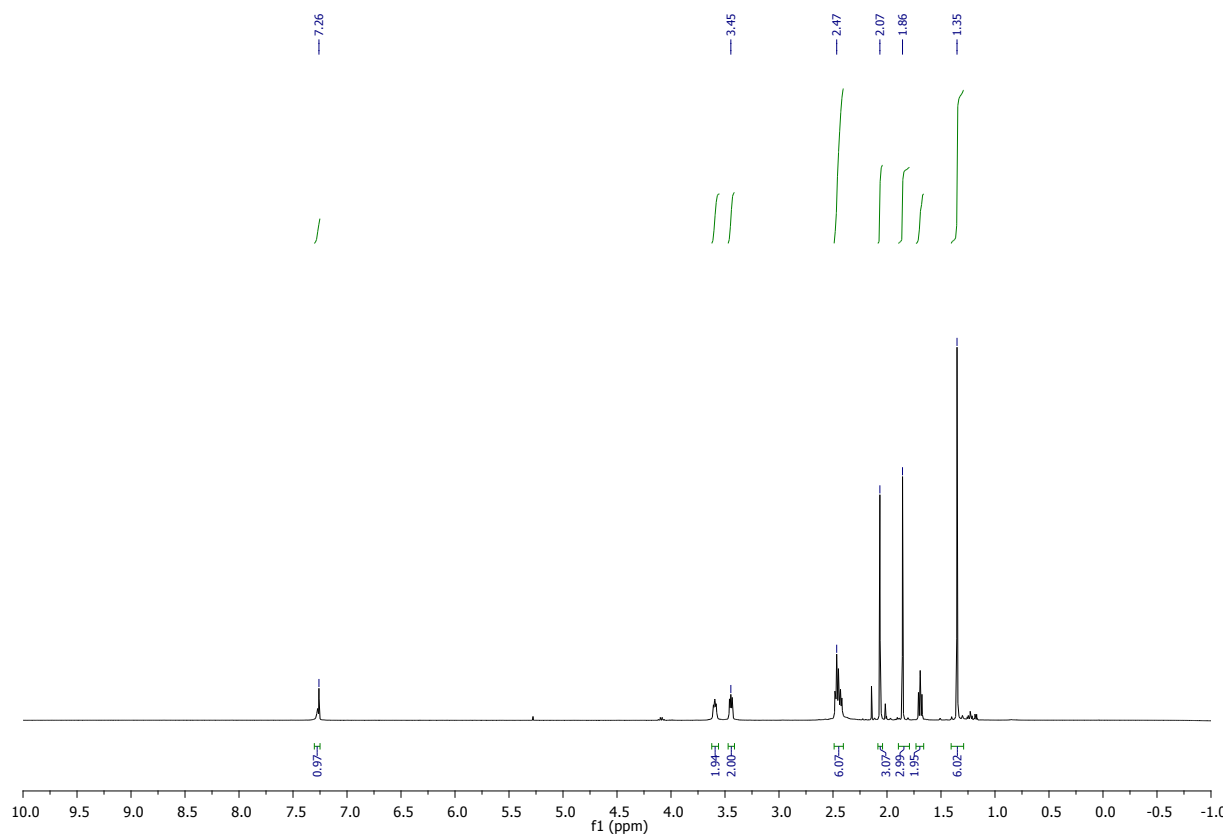
This compound was obtained after reaction of substrate **1a** (200 mg, 1.0 mmol), following the general procedure **B** with 6 mL of HF/SbF<sub>5</sub> and 106  $\mu$ L of acetonitrile (2.0 mmol, 2.0 equiv.) as nucleophile. The crude reaction mixture was purified over silica gel with dichloromethane/methanol (98/2) as the eluent, thereby obtaining compound **7a** (210 mg, 81%) as an orange oil.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm)  $\delta$ :** 7.26 (bs, NH), 3.62-3.56 (m, 2H), 3.45 (m, 2H), 2.45-2.40 (m, 6H), 2.07 (s, 3H), 1.86 (s, 3H), 1.69 (t, *J* = 6.4 Hz, 2H), 1.35 (s, 6H).

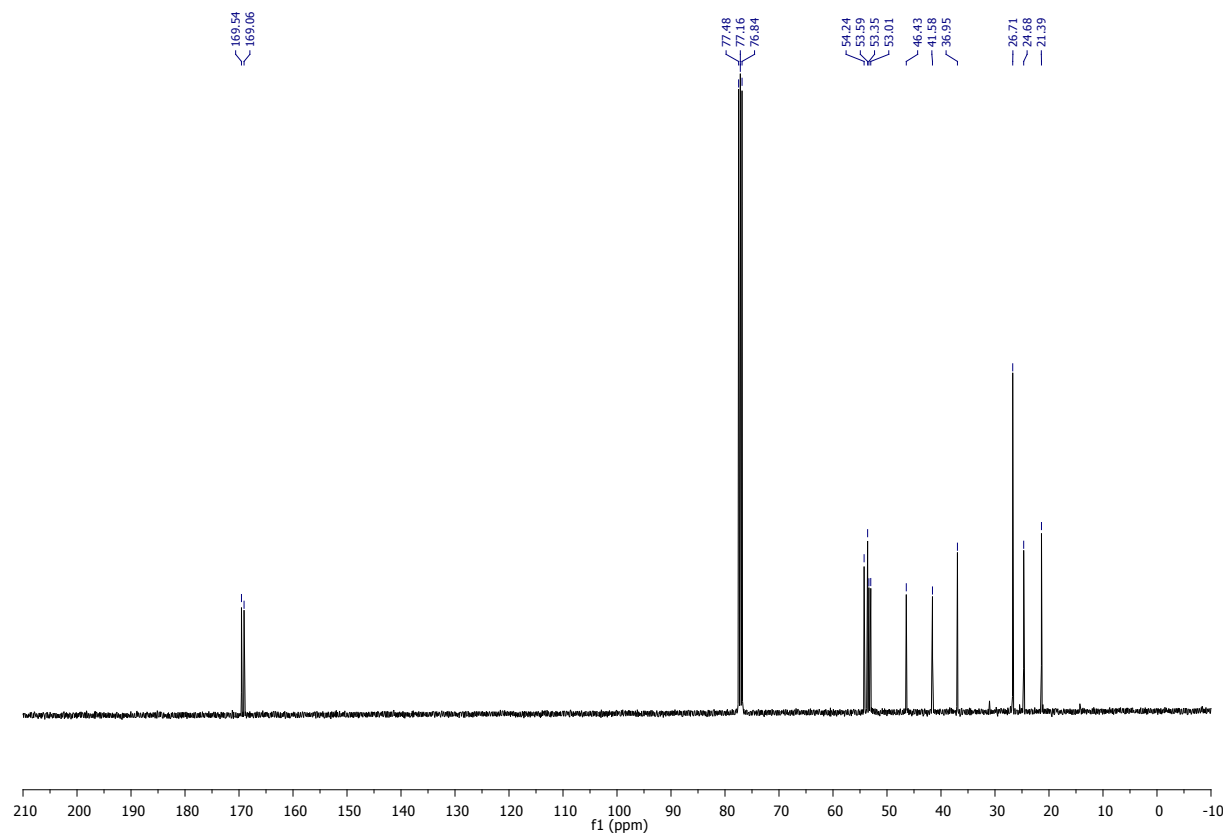
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm)  $\delta$ :** 169.5 (C), 169.1 (C), 54.2 (CH<sub>2</sub>), 53.6 (C), 53.3 (CH<sub>2</sub>), 53.0 (CH<sub>2</sub>), 46.4 (CH<sub>2</sub>), 41.6 (CH<sub>2</sub>), 37.0 (CH<sub>2</sub>), 26.7 (2 CH<sub>3</sub>), 24.7 (CH<sub>3</sub>), 21.4 (CH<sub>3</sub>).

**HRMS (ESI):** *m/z* [M+H]<sup>+</sup> calc for C<sub>13</sub>H<sub>26</sub>N<sub>3</sub>O<sub>2</sub>: 256,2020 found 256.2020.

### <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)

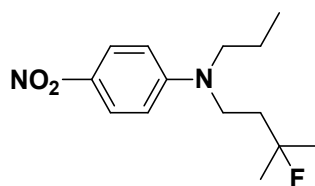


### <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)



**Compound 2w:** *N*-(3-fluoro-3-methylbutyl)-4-nitro-*N*-propylaniline

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This compound was obtained after reaction of substrate **1w** (30 mg, 0.12 mmol), following the general procedure **C** with 2 mL of HF/SbF<sub>5</sub> at 0 °C during 15 min. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate (9/1) as the eluent, thereby obtaining compound **2w** (13 mg, 40%) as an orange oil.

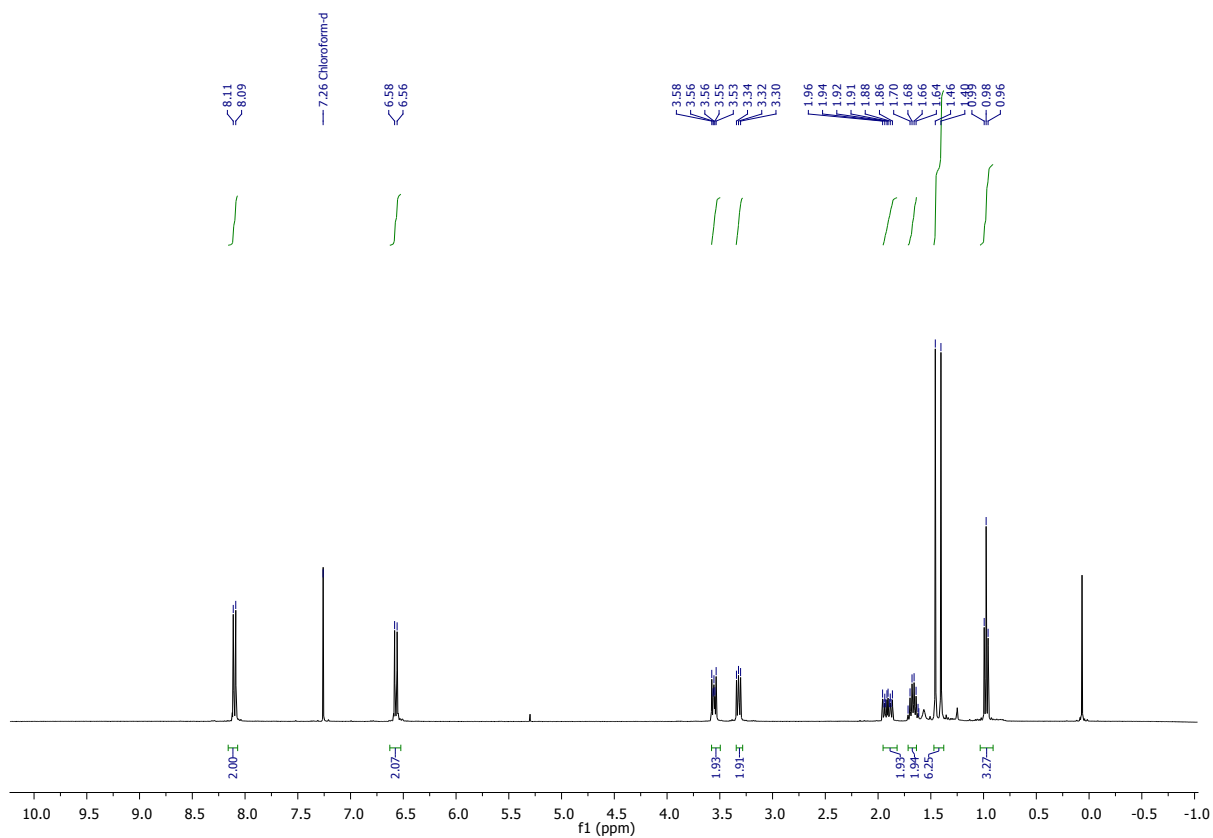
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm) δ:** 8.10 (d, *J* = 9.5 Hz, 2H), 6.57 (d, *J* = 9.5 Hz, 2H), 3.58 – 3.50 (m, 2H), 3.34 – 3.28 (m, 2H), 1.95 – 1.82 (m, 2H), 1.67 (dd, *J* = 15.4, 7.6 Hz, 2H), 1.43 (d, *J* = 21.3 Hz, 6H), 0.98 (t, *J* = 7.4 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm) δ:** 152.5 (C), 136.7 (C), 126.6 (2 CH), 110.1 (2 CH), 94.6 (C, d, *J* = 166.1 Hz), 53.0 (CH<sub>2</sub>), 46.4 (d, *J* = 5 Hz CH<sub>2</sub>), 37.8 (d, *J* = 24 Hz, CH<sub>3</sub>), 26.9 (d, *J* = 24 Hz, CH<sub>3</sub>), 20.6 (CH<sub>2</sub>), 11.4 (CH<sub>3</sub>).

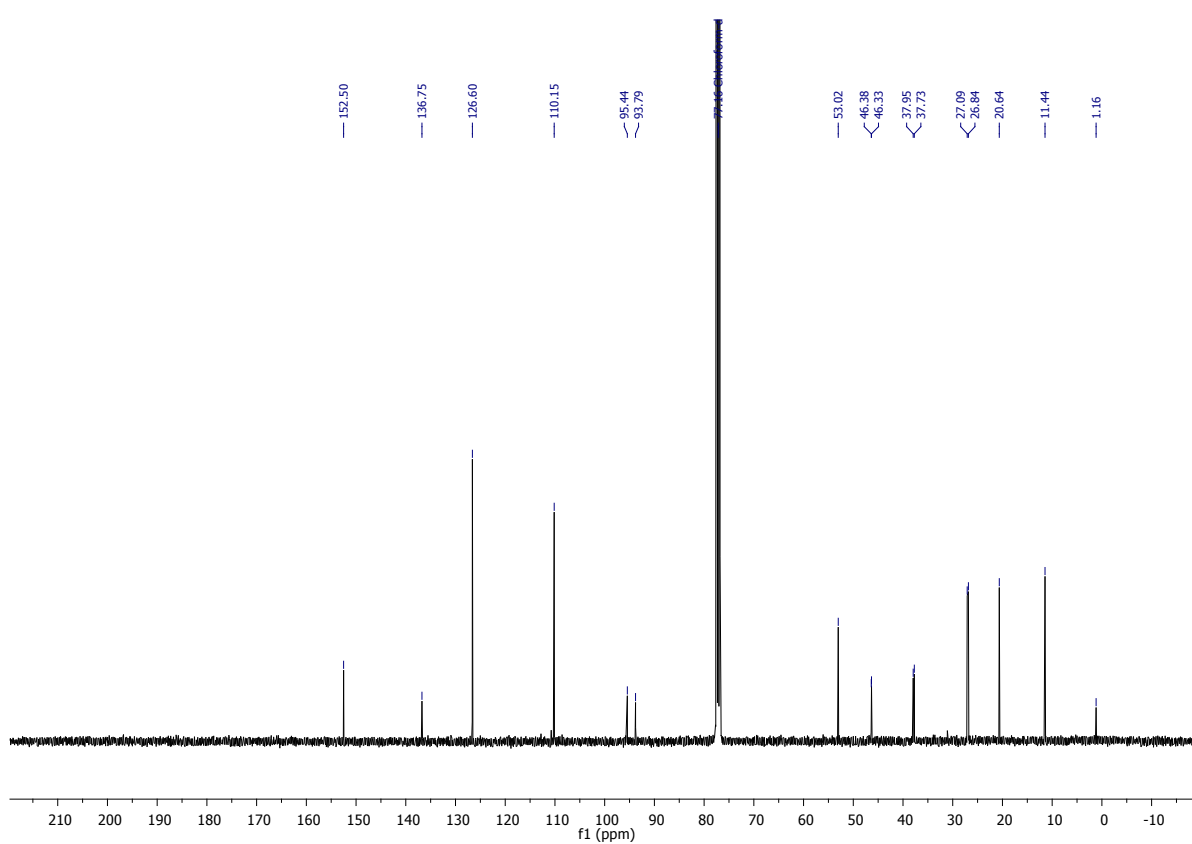
**<sup>19</sup>F {<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>, ppm) δ:** -141.9.

**HRMS (ESI):** *m/z* [M+H]<sup>+</sup> calc for C<sub>14</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>2</sub>: 269,1610 found 269.1610.

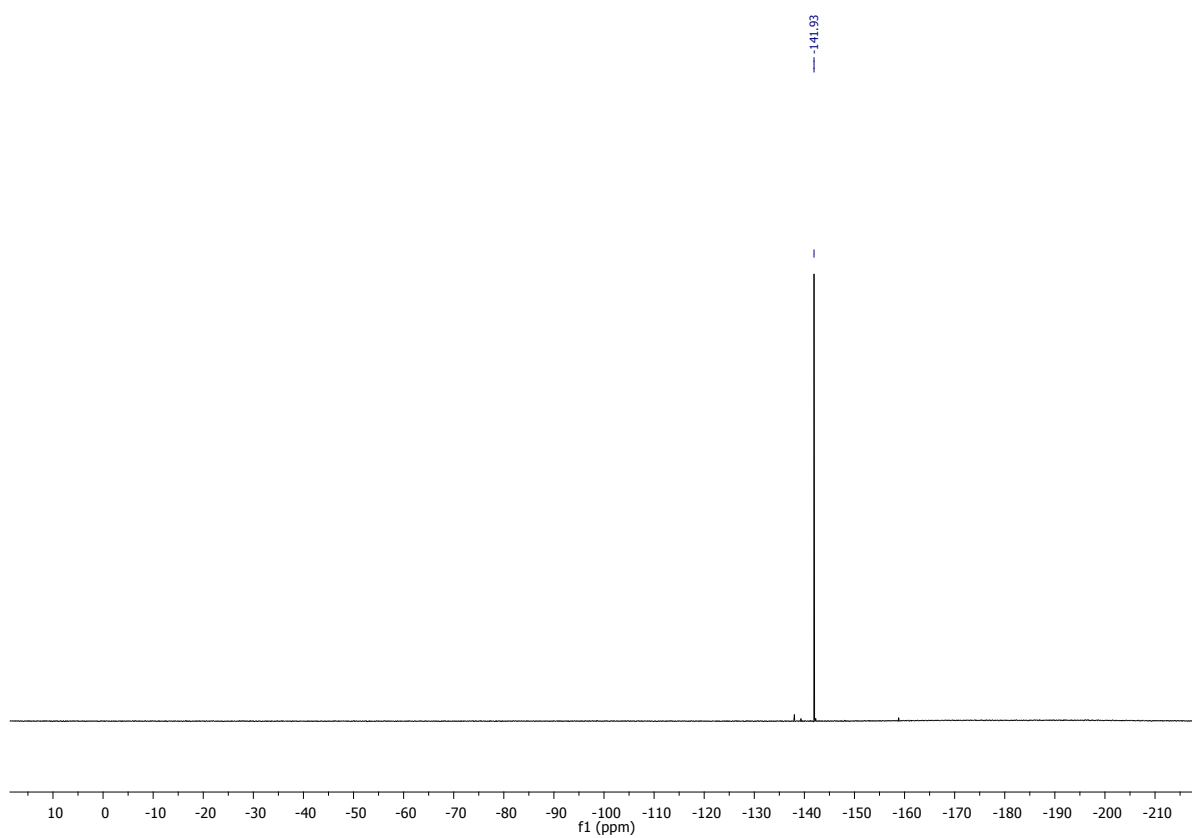
# <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)



# <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)

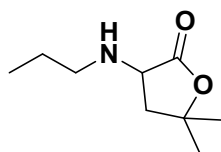


**$^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{CDCl}_3$ )**



**Compound 2y:** 5,5-dimethyl-3-(propylamino)dihydrofuran-2(3H)-one

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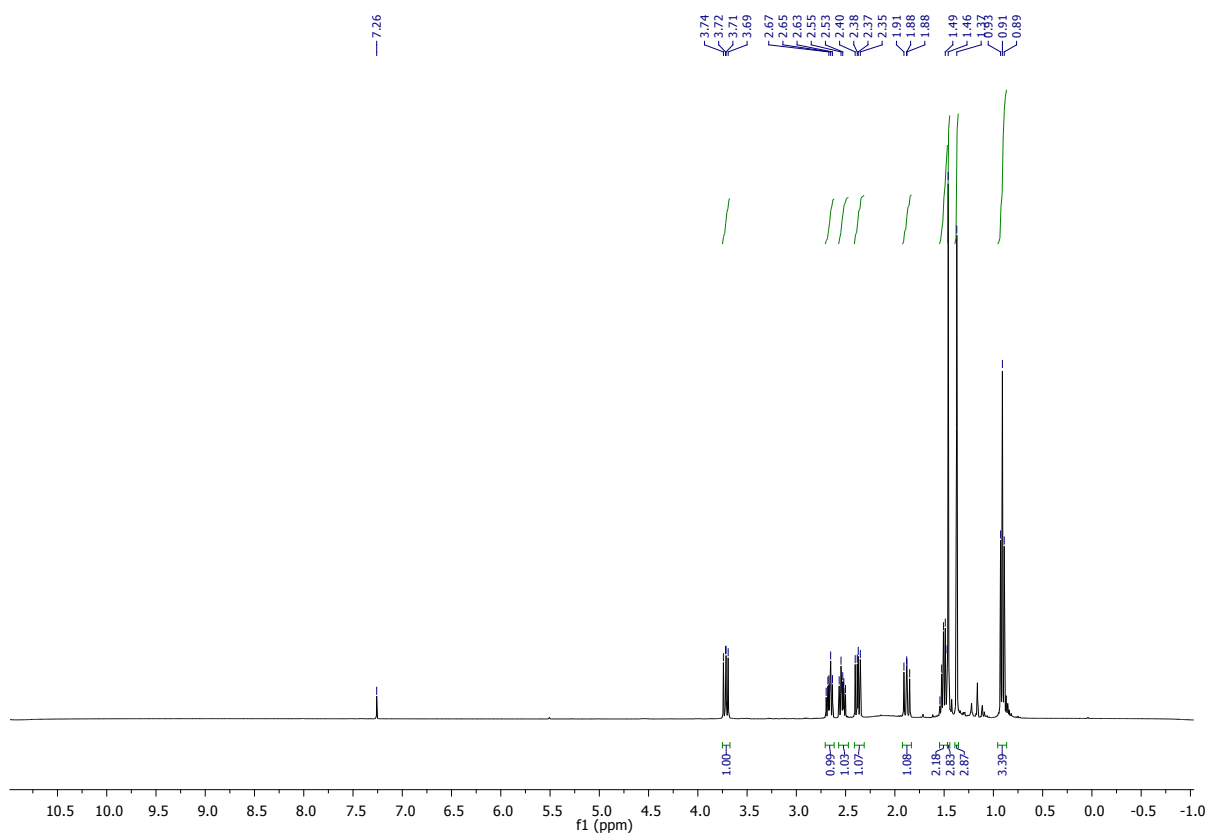
This compound was obtained after reaction of substrate **1y** (40 mg, 0.12 mmol). following the general procedure **C** with 2 mL of HF/SbF<sub>5</sub> at 0 °C for 2 h without CCl<sub>4</sub>. The crude reaction mixture was purified over silica gel with petroleum ether/ethyl acetate (9/1) as the eluent, thereby obtaining compound **2y** (24 mg, 60%) as an orange oil.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm) δ:** 3.72 (dd, *J* = 10.8, 8.5 Hz, 1H), 2.67 (m, 1H), 2.53 (m, 1H), 2.38 (dd, *J* = 12.5, 8.5 Hz, 1H), 1.88 (dd, *J* = 12.2, 11.1 Hz, 1H), 1.55 – 1.46 (m, 2H), 1.46 (s, 3H), 1.37 (s, 3H), 0.91 (t, *J* = 7.4 Hz, 3H).

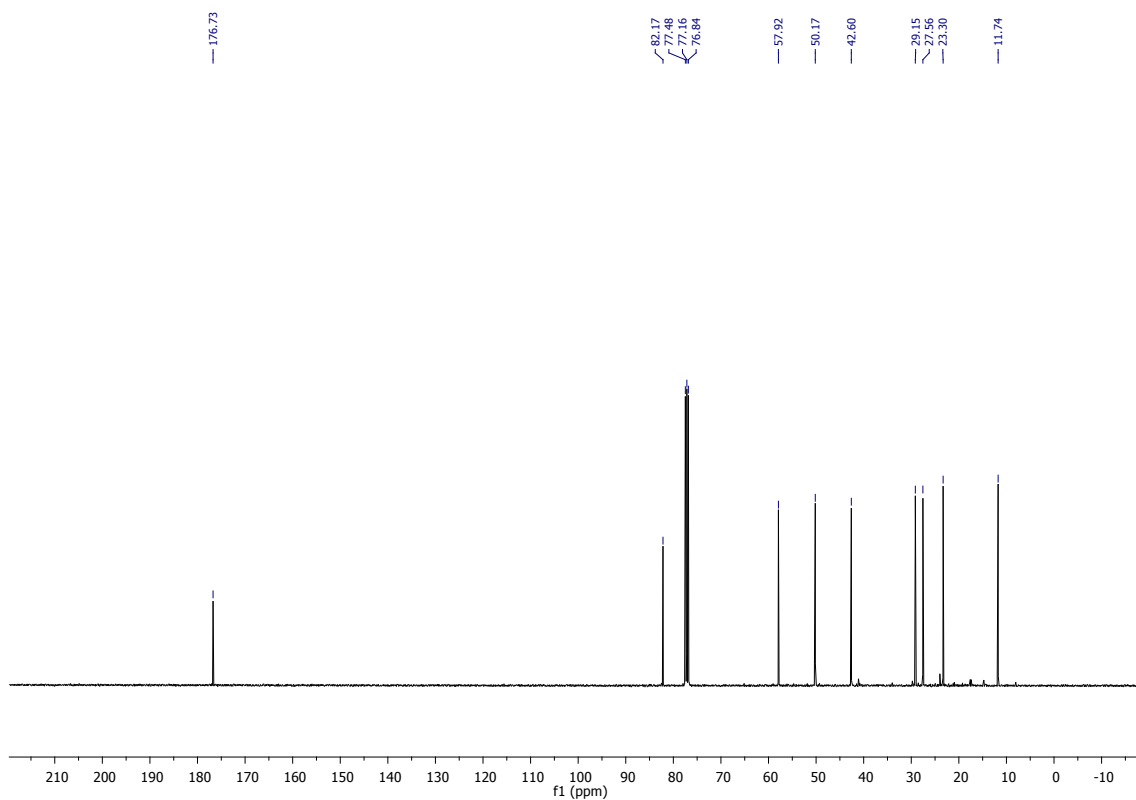
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm) δ:** 176.7 (C), 82.2 (C), 57.9 (CH), 50.2 (CH<sub>2</sub>), 42.6 (CH<sub>2</sub>), 29.1 (CH<sub>3</sub>), 27.6 (CH<sub>3</sub>), 23.3 (CH<sub>2</sub>), 11.7 (CH<sub>3</sub>).

**HRMS (ESI):** *m/z* [M+H]<sup>+</sup> calc for C<sub>9</sub>H<sub>18</sub>NO<sub>2</sub>: 172.1332 found 172.1333.

### $^1\text{H}$ NMR (400 MHz, $\text{CDCl}_3$ )



### $^{13}\text{C}$ NMR (100 MHz, $\text{CDCl}_3$ )



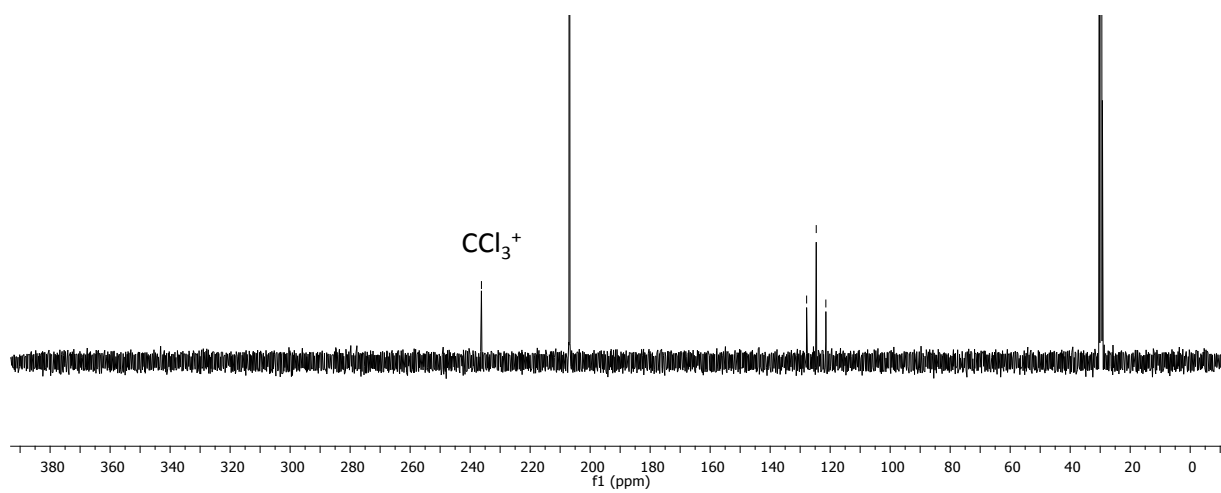


## C. $^1\text{H}$ and $^{13}\text{C}$ in *situ* NMR spectra

### $\text{CCl}_4$ in solution of $\text{HF}/\text{SbF}_5$

$^{13}\text{C}$  NMR spectra of  $\text{CCl}_4$  (0.12 mL) in solution of  $\text{HF}/\text{SbF}_5$  (1 mL, 22 mol%  $\text{SbF}_5$ ) at  $-40\text{ }^\circ\text{C}$  with acetone- $d_6$  as external reference

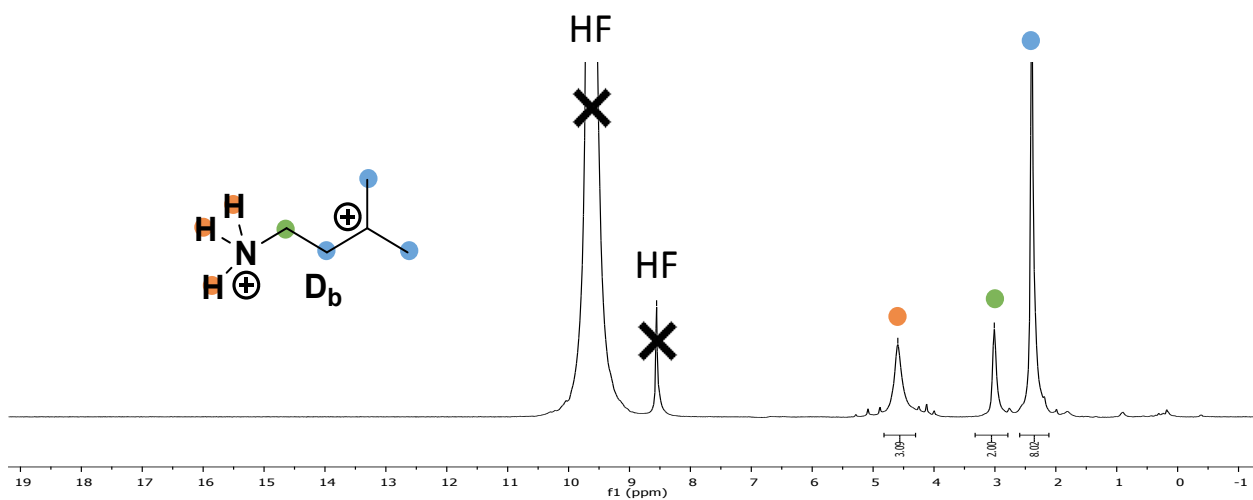
$^{13}\text{C}$  NMR (100 MHz)



## Isopentylamine in solution of HF/SbF<sub>5</sub> with CCl<sub>4</sub>

<sup>1</sup>H and <sup>13</sup>C NMR spectra of isopentylamine **1b** (87 mg, 1.0 mmol) with CCl<sub>4</sub> (1.2 equiv.) in solution of HF/SbF<sub>5</sub> (1 mL, 22 mol %) at -20 °C with acetone-*d*<sub>6</sub> as external reference

<sup>1</sup>H NMR (400 MHz)



<sup>13</sup>C NMR (100 MHz)

