



## Supporting Information

for

### **Synthesis of extended fluorinated tripeptides based on the tetrahydropyridazine scaffold**

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### **Experimental procedures, product characterization, X-ray analysis and copies of NMR spectra**

## Experimental section

### 1) General experimental methods

All experiments dealing with air- and moisture-sensitive compounds were conducted under an atmosphere of dry argon. The solvents, dry solvents and reagents were purchased from commercial sources and used without further purification. TLC was performed on silica gel, 60F-250 (0.26 mm thickness) plates. The plates were visualized with UV light (254 nm) or with a 3.5% solution of phosphomolybdic acid in ethanol or with a solution of  $\text{KMnO}_4$  in water. Flash chromatography (FC) was performed on Merck 60 silica gel (230–400 mesh). Melting points were determined on a Büchi melting point apparatus. NMR spectra were measured on an Ultrafield Avance 300 ( $^1\text{H}$ , 300 MHz;  $^{13}\text{C}$ , 75 MHz) and Bruker AMX 200 ( $^1\text{H}$ , 200 MHz;  $^{19}\text{F}$ , 188 MHz) spectrometer. Unless otherwise stated, NMR data were obtained under ambient temperature conditions and  $\text{CDCl}_3$ ,  $\text{CD}_3\text{OD}$ , or  $\text{DMSO}-d_6$  were used as solvent. Chemical shifts  $\delta$  are in ppm, and the following abbreviations are used: singlet (s), doublet (d), doublet doublet (dd), triplet (t), q (quartet), quintuplet (quint), sextuplet (sx), septuplet (sp), multiplet (m) and broad singlet (brs). High-resolution mass spectra were recorded on a MicrotofQ Bruker Daltonics.

### 2) General procedure:

#### General procedure [A]: synthesis of fluorinated hydrazones

The carbazate (1 equiv), and *p*-toluenesulfonic acid (0.05 equiv) are added to a solution of the fluorinated acetaldehyde ethyl hemiacetal (1.1 equiv) in toluene (0.1 M) in a round-bottomed flask. The reaction mixture is refluxed with a Dean–Stark apparatus to remove the water and the reaction is followed by  $^{19}\text{F}$  NMR until disappearance of the starting material. Then, the solvent is removed under reduced pressure. The crude product is used directly in the next steps without further purification.

#### General procedure [B]: allylation reaction

The methyl or ethyl 2-(bromomethyl)acrylate (1.2 equiv) is added to a solution of hydrazone **3** (1 equiv) in tetrahydrofuran (5 mL/2 mmol). Then, an aqueous solution of saturated  $\text{NH}_4\text{Cl}$  (5 mL/2 mmol), and lastly zinc (1.2 equiv) are added to the reaction mixture. The mixture is stirred at room temperature until completion ( $^{19}\text{F}$  NMR or TLC), then diluted with water (5 mL) and extracted with diethyl ether (3 × 5 mL). The organic layer is washed with an aqueous solution of saturated  $\text{NH}_4\text{Cl}$  (5 mL), dried with  $\text{MgSO}_4$ , filtered and concentrated under vacuum. The residue is purified by flash chromatography (eluent: cyclohexane/ethyl acetate, ratio: 9:1–7:3).

#### General procedure [C]: oxidation of hydrazides

To a solution of the allylated compound **5** (1 equiv) in  $\text{CH}_2\text{Cl}_2$  (5 mL) at 0 °C,  $\text{I}_2$  or NBS (1.1 equiv) is added and lastly  $\text{K}_2\text{CO}_3$  (1.1 equiv). The mixture is stirred at room temperature until completion. Then, the reaction mixture is diluted with 5 mL of  $\text{CH}_2\text{Cl}_2$ , washed with 5 mL of an aqueous saturated solution of  $\text{Na}_2\text{S}_2\text{O}_3$  (only for the reaction with  $\text{I}_2$ ), an aqueous saturated solution of  $\text{NH}_4\text{Cl}$  (2 × 5 mL), dried over  $\text{Na}_2\text{SO}_4$ , then filtered and concentrated under vacuum. If necessary, the residue is purified by flash chromatography (eluent: cyclohexane/ethyl acetate, ratio : 9:1–7:3).

#### General procedure [D]: cyclization procedure

Hydrazone **6** (1 equiv) is added to anhydrous DMF (6 mL/1 mmol) followed by  $\text{K}_2\text{CO}_3$  (0.1 equiv). The reaction mixture is stirred overnight at room temperature. Once finished, it is diluted with water (5 mL) and extracted with diethyl ether (3 × 15 mL) for **7a–d** and ethyl acetate (3 × 15 mL) for **7e,f**. The organic layer is washed with an aqueous solution of saturated  $\text{NH}_4\text{Cl}$  (10 mL), dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under vacuum.

#### General procedure [E]: saponification and amino acid coupling procedure

To a solution of the ester **7** (1 equiv) in THF (1 mL/0.2 mmol of ester), is added an aqueous solution of  $\text{LiOH}\cdot\text{H}_2\text{O}$  (2.5 equiv in 1 mL/0.2 mmol of ester) at 0 °C. The reaction mixture is stirred at 0 °C until completion (0.5–2 h, followed by TLC), then diluted with  $\text{AcOEt}$  (5 mL) and carefully acidified at 0 °C by an aqueous solution of  $\text{HCl}$  0.1 N at 0 °C. The two layers are separated and the aqueous layer is extracted again with  $\text{AcOEt}$  (3 × 5 mL). The organic phases are combined, washed with an aqueous solution of saturated  $\text{NaCl}$  (5 mL), dried over  $\text{MgSO}_4$ , filtered, and then evaporated to dryness. The corresponding acid is directly used without further purification in the next step. To a solution of the acid (1 equiv), EDC  $\text{HCl}$  (1.2 equiv), HOBt (1.2 equiv) and L-Val-OMe· $\text{HCl}$  (1.2 equiv) in dry DMF (1 mL/0.2 mmol), was added DIPEA (2.2 equiv) at 0 °C. The reaction mixture is stirred at room temperature overnight, then diluted with  $\text{AcOEt}$  (10 mL), washed

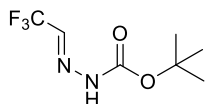
with water (2 × 3 mL), 10% NaHCO<sub>3</sub> aqueous solution (3 mL), 10% citric acid aqueous solution (3 mL) and saturated aqueous solution of NH<sub>4</sub>Cl (3 mL). The organic phase is dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under vacuum. Purification of the residue by silica gel column chromatography using cyclohexane/ethyl acetate ratio 7:3–5:5) as the eluent furnishes the tripeptide products.

### 3) Compounds characterization:

#### a) Hydrazones 3a–f:

##### *tert*-Butyl (*E*)-2-(2,2,2-trifluoroethylidene)hydrazine-1-carboxylate (**3a**)

The product **3a** is obtained following the general procedure (A) as a white powder (2.17 g, 93%).



Chemical Formula: C<sub>7</sub>H<sub>11</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>  
Exact Mass: 212,0773

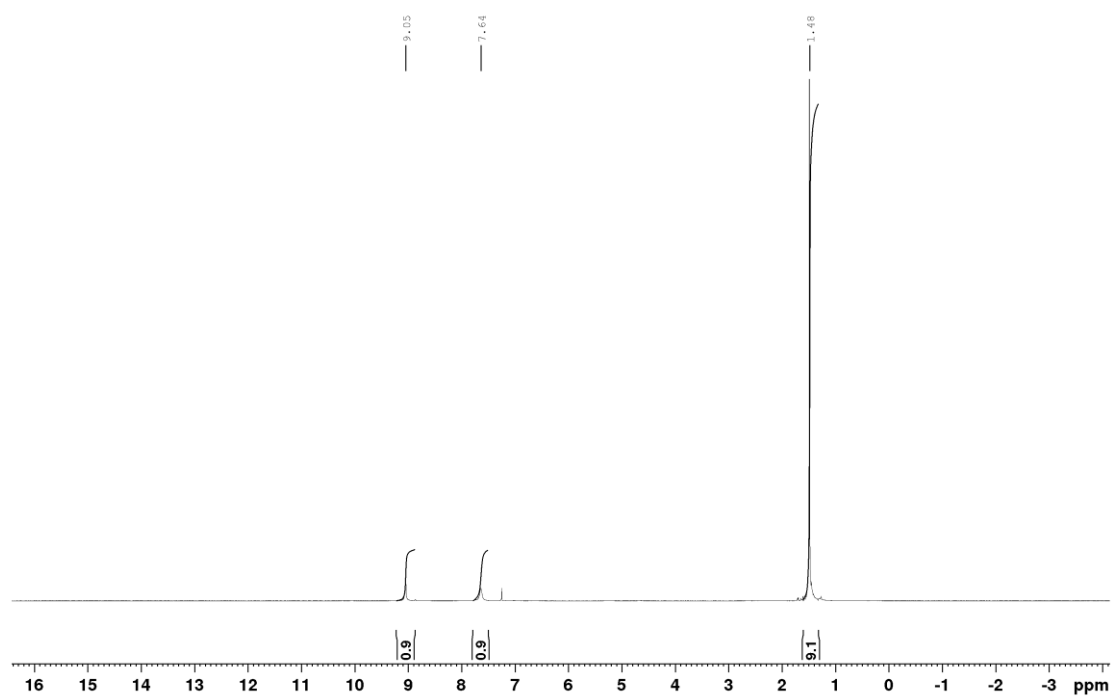
**<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>): δ = 9.05 (brs, 1H, NH), 7.64 (m, 1H, CH), 1.48 (s, 9H, (CH<sub>3</sub>)<sub>3</sub>)

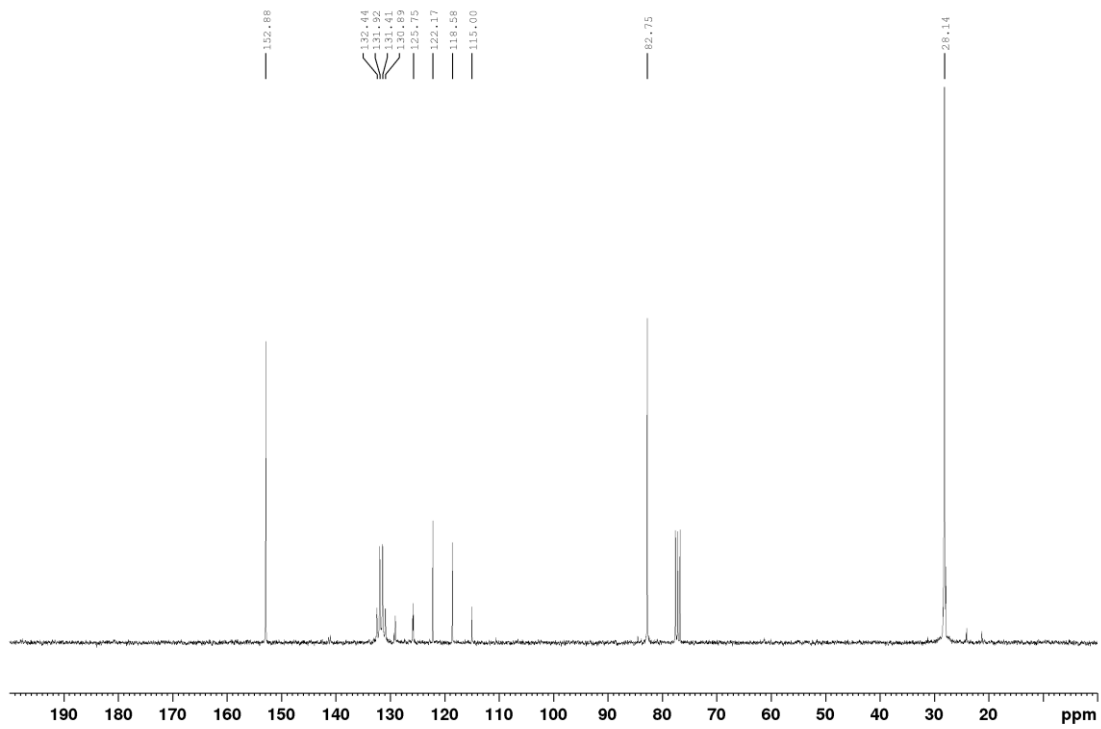
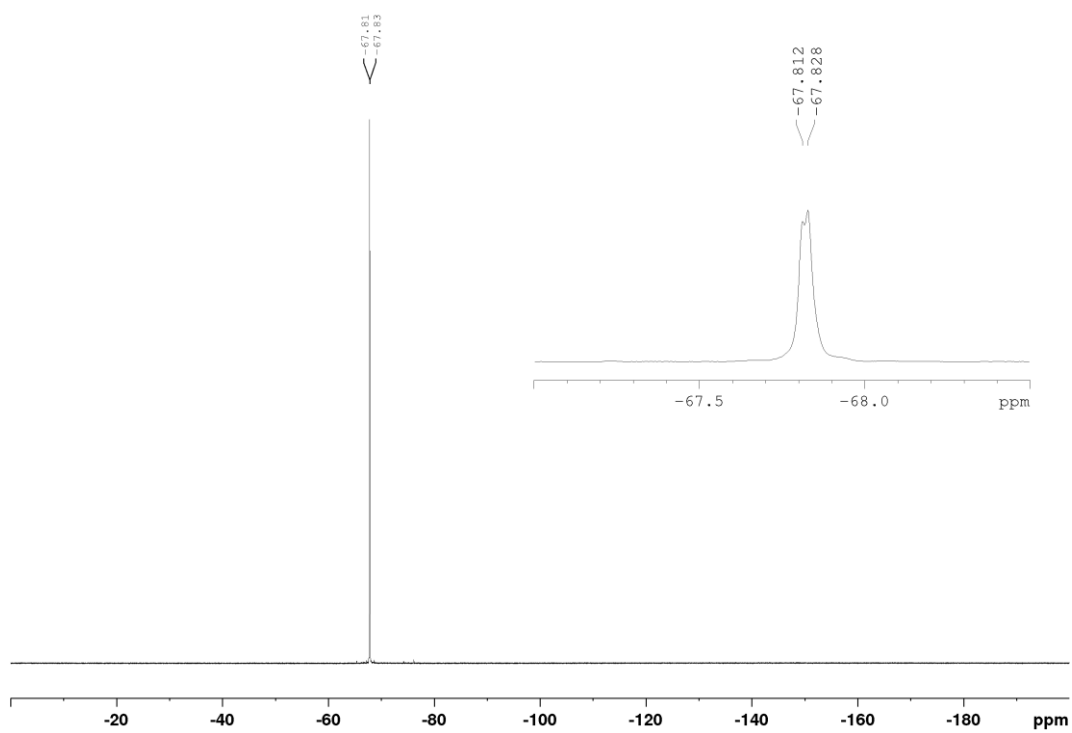
**<sup>19</sup>F NMR** (188 MHz, CDCl<sub>3</sub>): δ = - 67.8 (d, <sup>3</sup>J<sub>H,F</sub> = 3.0 Hz, 3F)

**<sup>13</sup>C NMR** (75MHz, CDCl<sub>3</sub>): δ = 152.9 (CO), 131.7 (q, <sup>2</sup>J<sub>C,F</sub> = 39 Hz, CH), 120.4 (q, <sup>1</sup>J<sub>C,F</sub> = 271 Hz, CF<sub>3</sub>), 82.8 (Cq), 28.1(CH<sub>3</sub>)

**HRMS (ESI+TOF)** m/z C<sub>7</sub>H<sub>11</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub> [M+Na]<sup>+</sup> calc. 235,0665, found 235.0672

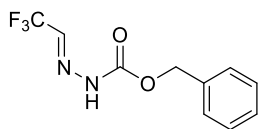
**Melting point:** 117°C





**Benzyl (E)-2-(2,2,2-trifluoroethylidene)hydrazine-1-carboxylate (3b)**

The product **3b** is obtained following the general procedure (A) as a white lightly yellow powder (2.91 g, 98%).



Chemical Formula: C<sub>10</sub>H<sub>9</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>  
Exact Mass: 246,0616

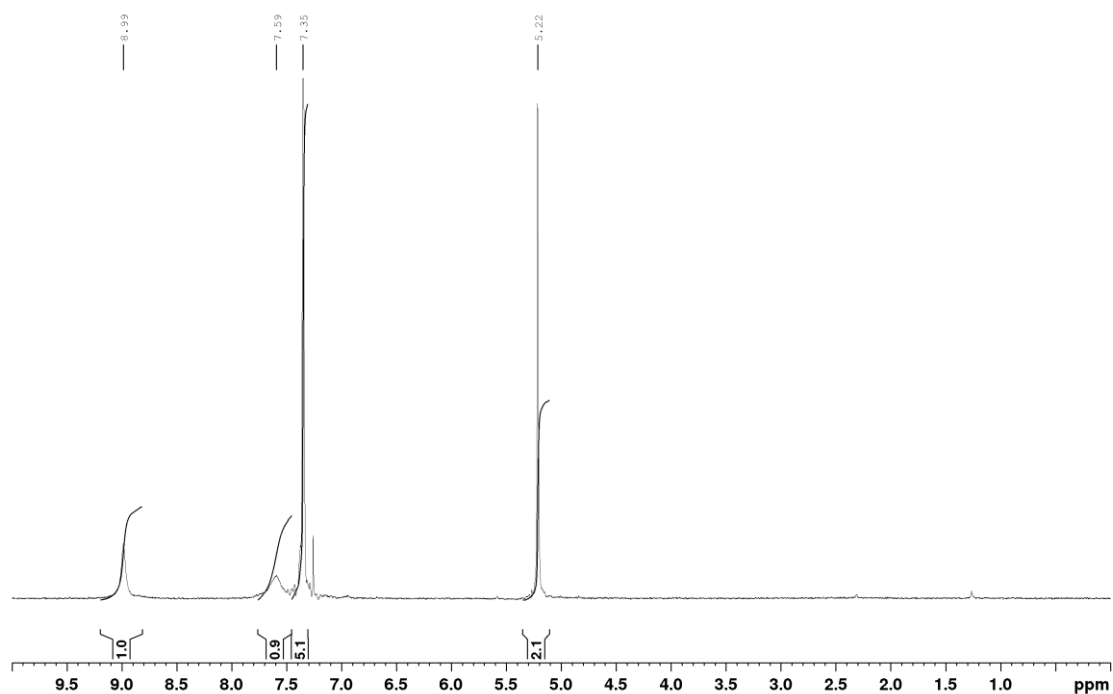
**<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>): δ = 8.99 (brs, 1H, NH), 7.59 (m, 1H, CH), 7.35 (m, 5H, Haro), 5.22 (s, 2H, CH<sub>2</sub>).

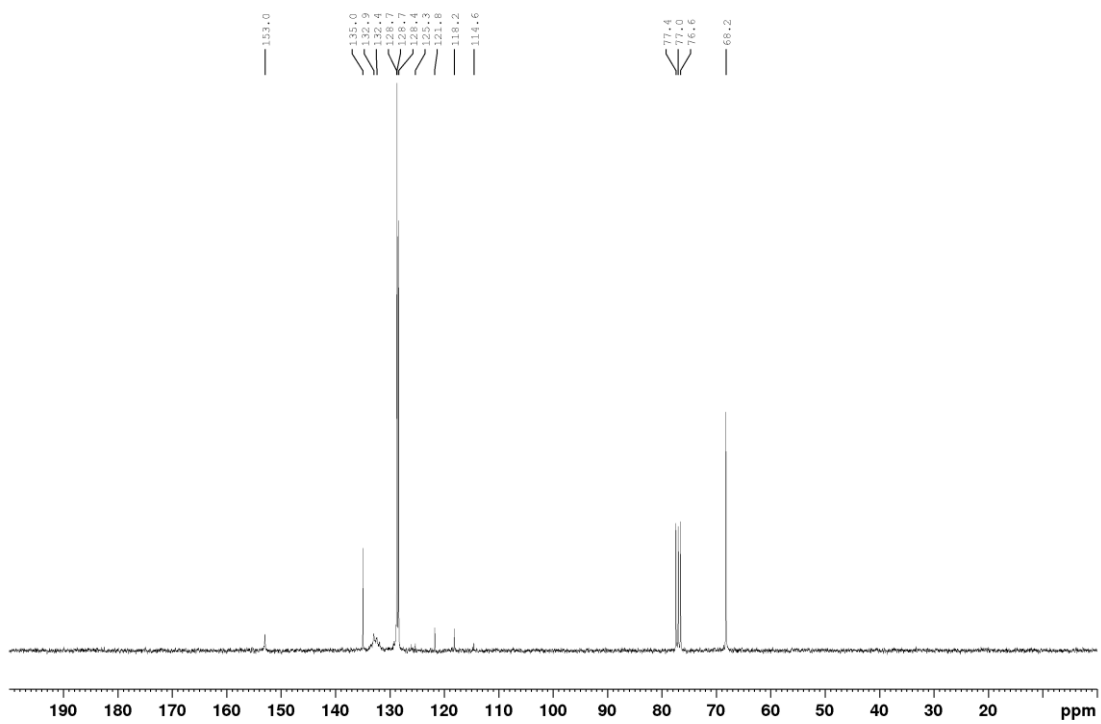
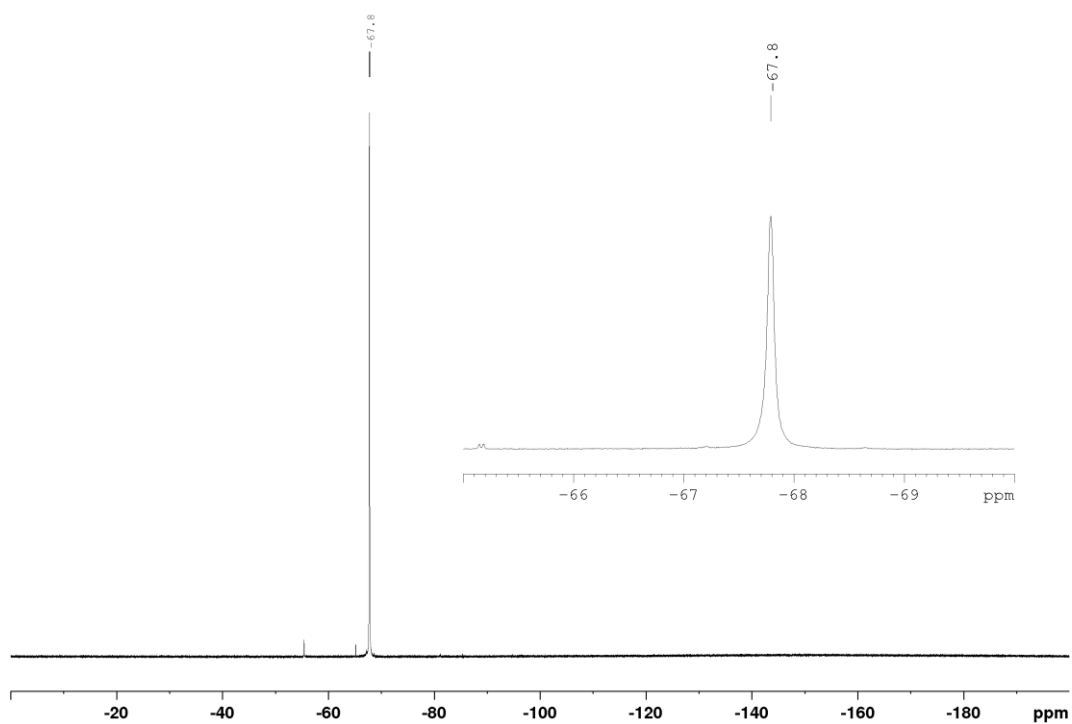
**<sup>19</sup>F NMR** (188 MHz, CDCl<sub>3</sub>): δ = - 67.8 (brs, 3F).

**<sup>13</sup>C NMR** (75MHz, CDCl<sub>3</sub>): δ= 153.0 (CO), 135.0 (Caro), 132.7 (q, <sup>2</sup>J<sub>C,F</sub> = 41 Hz, CH), 128.8, 128.7, 128.4 (CHaro), 119.0 (q, <sup>1</sup>J<sub>C,F</sub> = 270 Hz, CF<sub>3</sub>), 68.2 (CH<sub>2</sub>).

**HRMS (ESI+TOF)** m/z C<sub>10</sub>H<sub>9</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub> [M+Na]<sup>+</sup> calc. 269,0508, found 269,0533

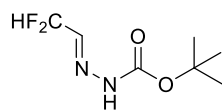
**Melting point:** 125°C





**tert-Butyl (E)-2-(2,2-difluoroethylidene)hydrazine-1-carboxylate (3c)**

The product **3c** is obtained following the general procedure (A) as a white powder (1.67g, 92%).



Chemical Formula: C<sub>7</sub>H<sub>12</sub>F<sub>2</sub>N<sub>2</sub>O<sub>2</sub>  
Exact Mass: 194,0867

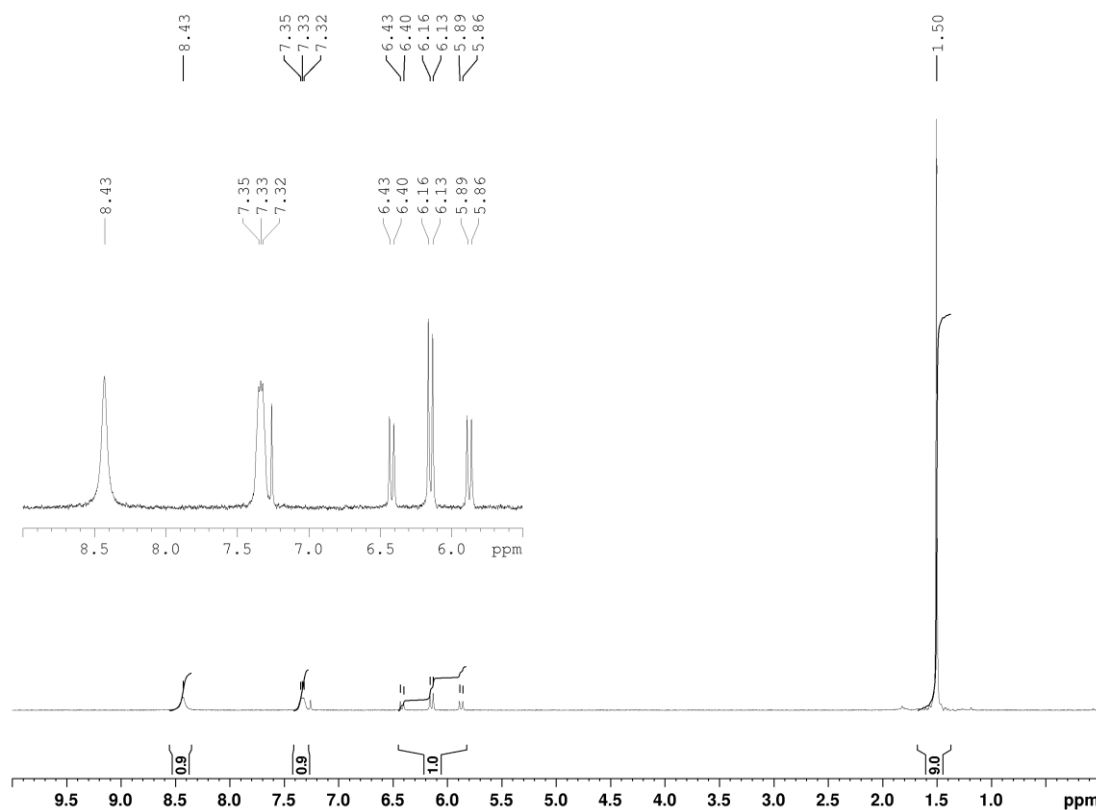
**<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>): δ = 8.43 (s, 1H, NH), 7.35-7.32 (m, 1H, CH), 6.14 (dt, 1H, <sup>2</sup>J<sub>H,F</sub> = 54 Hz, <sup>3</sup>J<sub>H,H</sub> = 6 Hz, CF<sub>2</sub>H), 1.50 (s, 9H, (CH<sub>3</sub>)<sub>3</sub>).

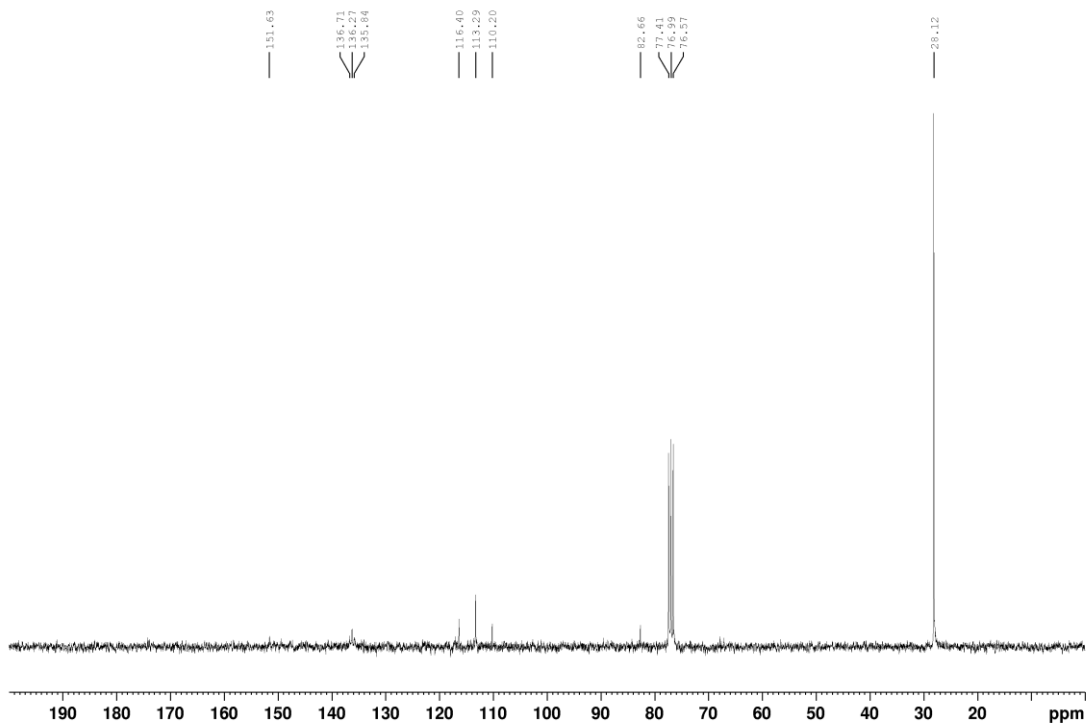
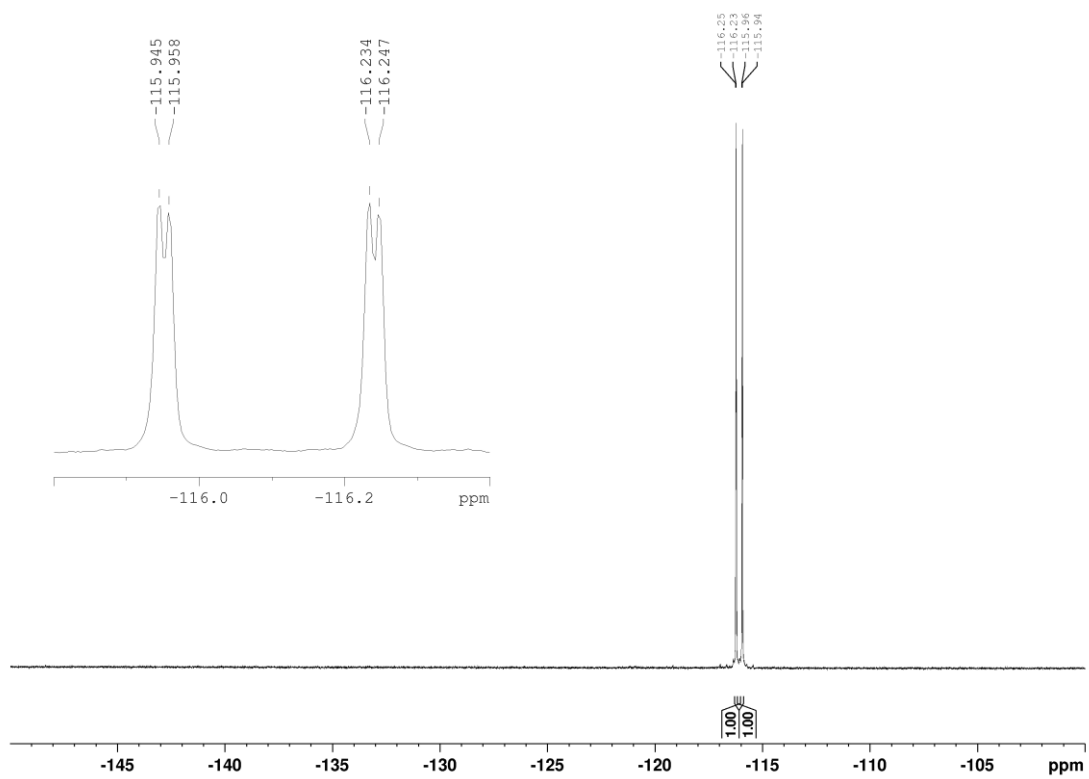
**<sup>19</sup>F NMR** (188 MHz, CDCl<sub>3</sub>): δ = - 116.1 (dd, 2F, <sup>2</sup>J<sub>H,F</sub> = 54 Hz, <sup>3</sup>J<sub>H,F</sub> = 2.5 Hz)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 153.6 (CO), 136.3 (t, <sup>2</sup>J<sub>C,F</sub> = 34 Hz, CH), 113.3 (t, <sup>1</sup>J<sub>C,F</sub> = 233 Hz, CF<sub>2</sub>H), 82.7 (Cq), 28.1 (CH<sub>3</sub>).

**HRMS (ESI+TOF)** m/z C<sub>7</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>F<sub>2</sub> [M+Na]<sup>+</sup> calc. 217.0667, found 217.0765.

**Melting point:** 138°C

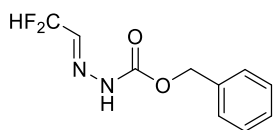






**Benzyl (E)-2-(2,2-difluoroethylidene)hydrazine-1-carboxylate (3d)**

The product **3d** is obtained following the general procedure (A) as a white powder (2.68 g, 99%).



Chemical Formula: C<sub>10</sub>H<sub>10</sub>F<sub>2</sub>N<sub>2</sub>O<sub>2</sub>  
Exact Mass: 228.0710

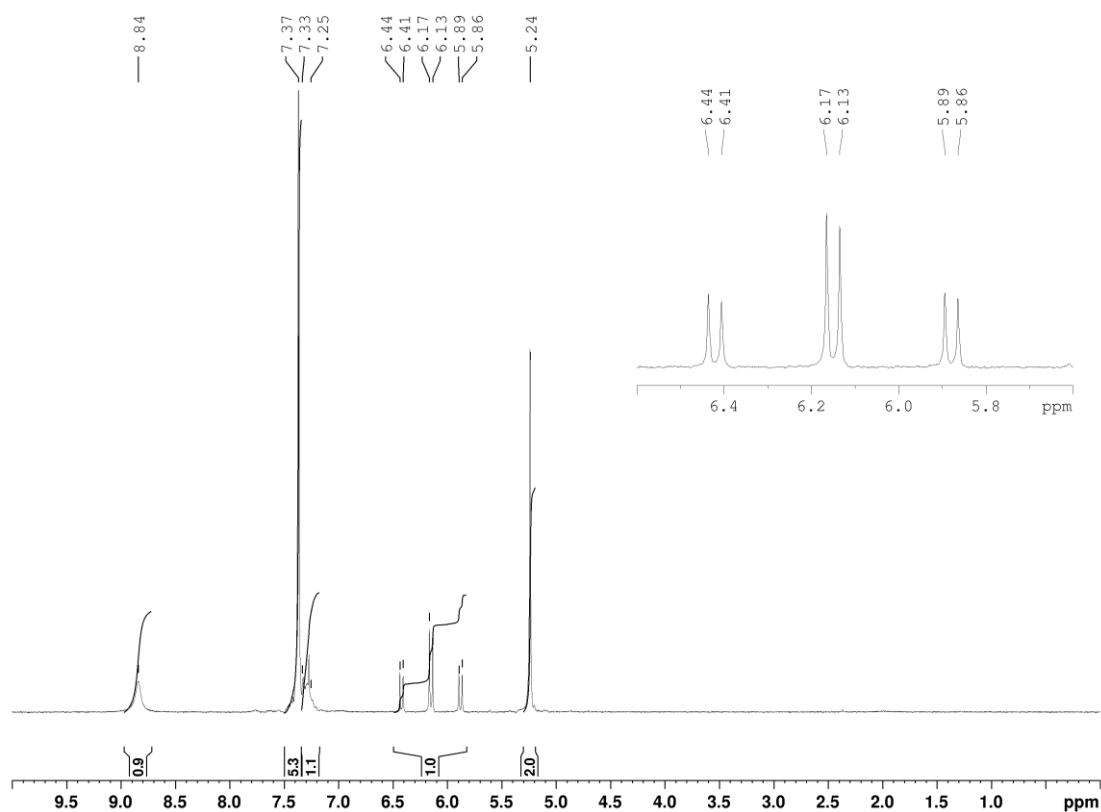
**<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>): δ = 8.84 (s, 1H, NH), 7.37 (m, 5H, Haro), 7.33-7.25 (m, 1H, CH), 6.15 (dt, 1H, <sup>2</sup>J<sub>H,F</sub> = 54 Hz, <sup>3</sup>J<sub>H,H</sub> = 6 Hz, CF<sub>2</sub>H), 5.24 (s, 2H, CH<sub>2</sub>).

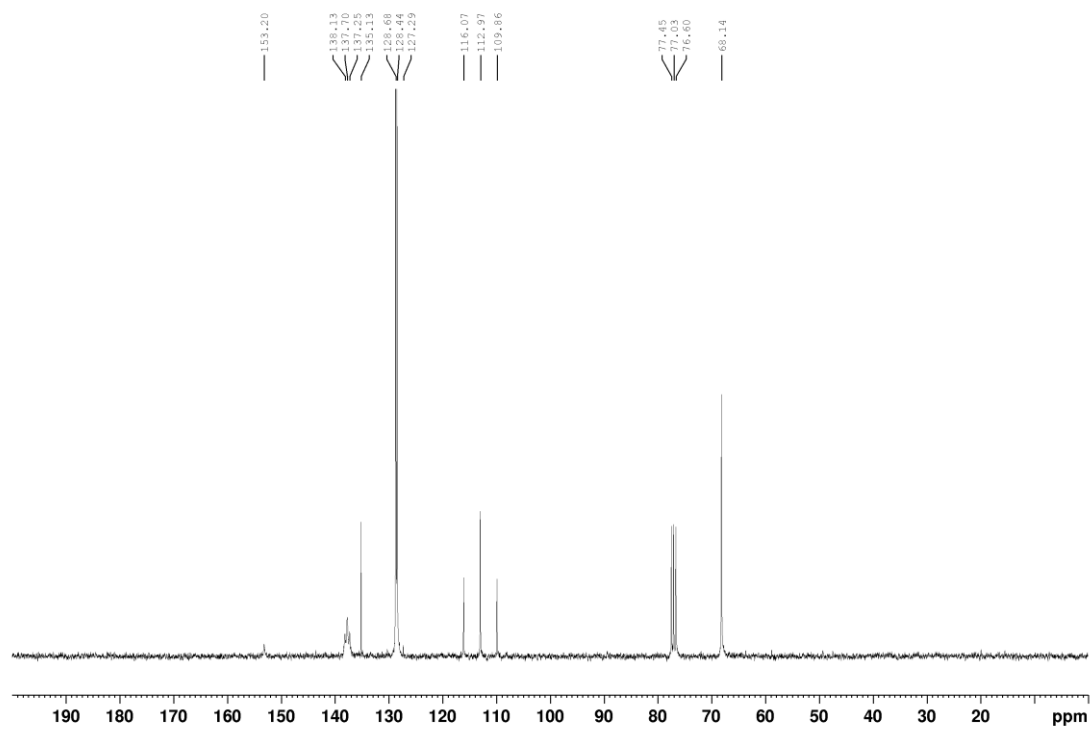
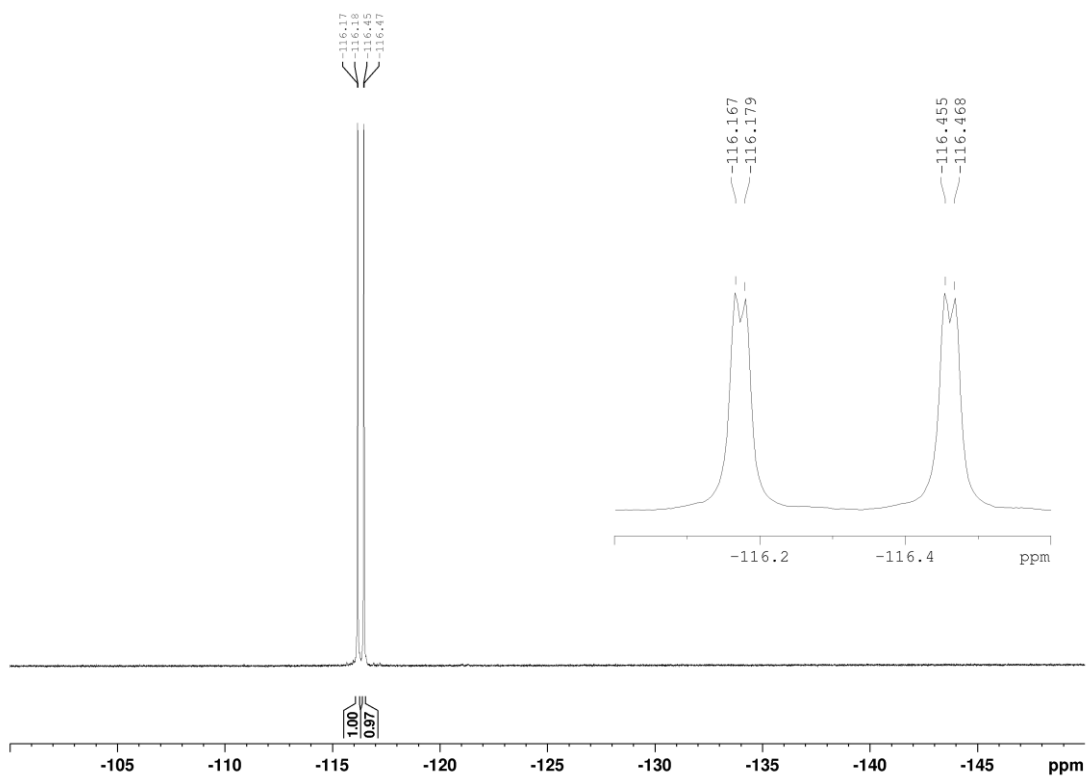
**<sup>19</sup>F NMR** (188 MHz, CDCl<sub>3</sub>): δ = - 116.3 (dd, <sup>2</sup>J<sub>H,F</sub> = 54 Hz, <sup>3</sup>J<sub>H,F</sub> = 1.9 Hz, 2F)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 153.2 (CO), 137.7 (t, <sup>2</sup>J<sub>C,F</sub> = 33 Hz, CH), 135.1 (Caro), 128.7, 128.4, 127.2 (CHaro), 112.9 (t, <sup>1</sup>J<sub>C,F</sub> = 234 Hz, CF<sub>2</sub>H), 68.1 (CH<sub>2</sub>).

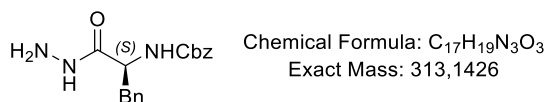
**HRMS (ESI+TOF)** m/z C<sub>10</sub>H<sub>10</sub>F<sub>2</sub>N<sub>2</sub>O<sub>2</sub> [M+Na]<sup>+</sup> calc. 251.0501, found 251.0578.

**Melting point:** 152°C





### Benzyl (S)-(1-hydrazineyl-1-oxo-3-phenylpropan-2-yl)carbamate



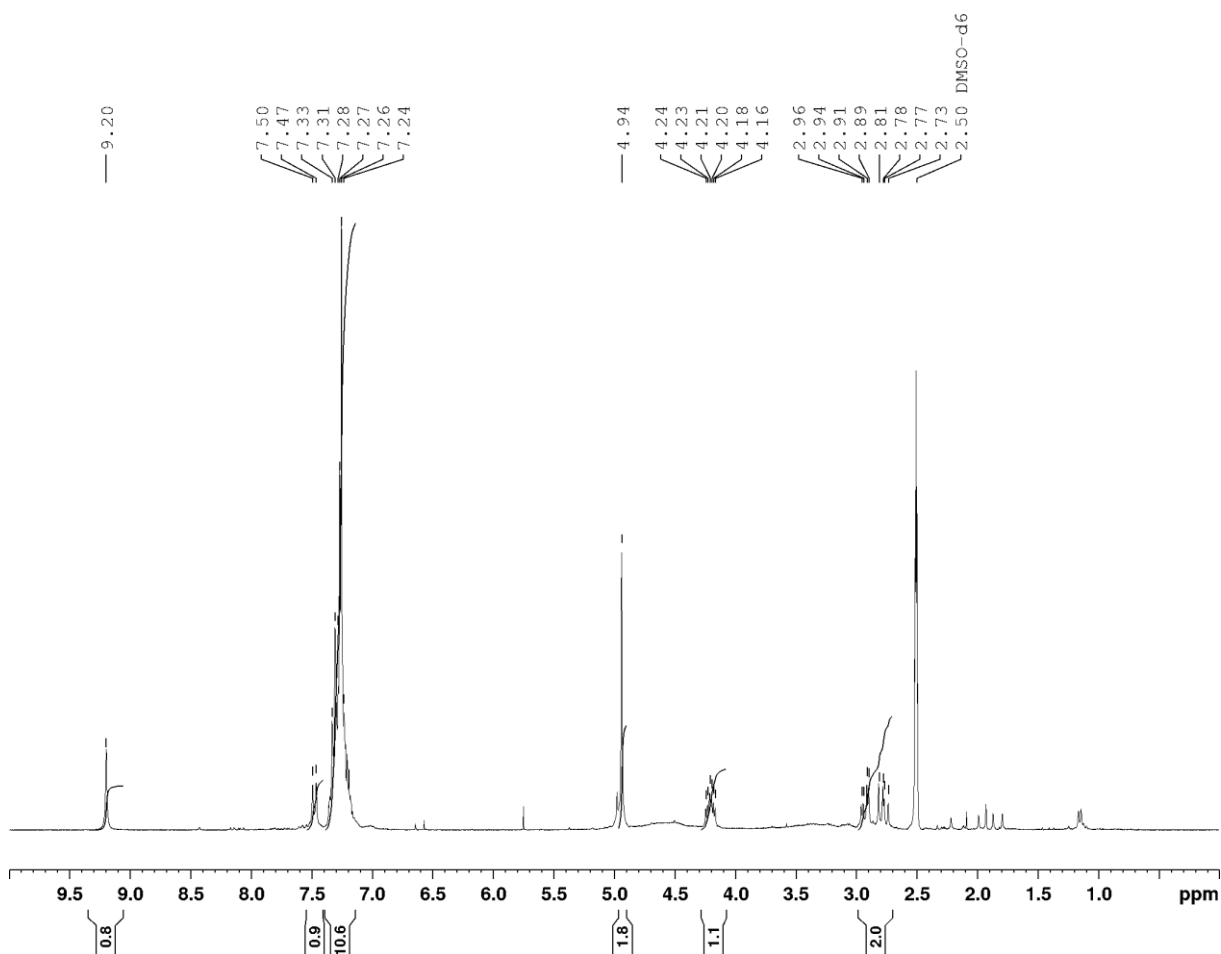
To a solution of L-Z-PheOH (2 g, 1 equiv), BocNHNH<sub>2</sub> (0.87 g, 1 equiv), EDC·HCl (1.39 g, 1.1 equiv), HOBt (1.11 g, 1.1 equiv) in dry CH<sub>2</sub>Cl<sub>2</sub> (15 mL), is added diisopropylethylamine (1.70 g, 2 equiv) at 0 °C. The reaction mixture is stirred overnight at room temperature, then diluted with 15 mL of CH<sub>2</sub>Cl<sub>2</sub> and washed with NaHCO<sub>3</sub> 10% aqueous solution, citric acid 10% aqueous solution and NaCl saturated aqueous solution. The organic layer is dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. Then, the residue (2.90 g, 1 equiv) is diluted in the minimum of CH<sub>2</sub>Cl<sub>2</sub> and a solution of HCl 4 N in dioxane (11 mL, 5.5 equiv) is added at 0 °C and stirred at room temperature until disappearance of the starting material (followed by TLC). After evaporation of the solvent, the residue is suspended in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and basified with an aqueous saturated solution of Na<sub>2</sub>CO<sub>3</sub>. After separation of the organic layer, the aqueous layer is extracted again with CH<sub>2</sub>Cl<sub>2</sub> (2 × 15 mL). The three organic layers are combined and dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The Z-L-phenylalanine hydrazide is obtained as a white powder (2.35 g, 85% overall yield).

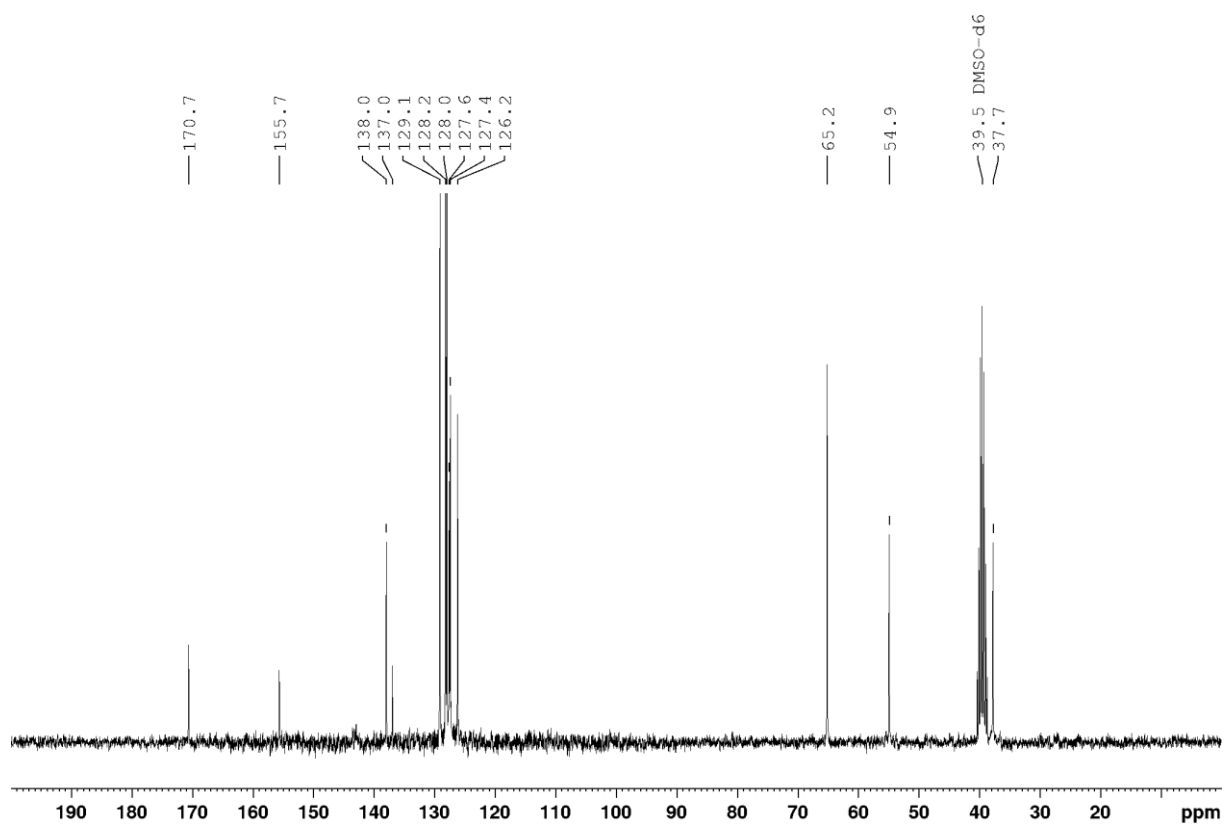
**<sup>1</sup>H NMR** (300 MHz, DMSO-d<sub>6</sub>): δ = 9.20 (s, 1H, NH), 7.48 (d, <sup>3</sup>J<sub>H,H</sub> = 8.7 Hz, 1H, NHCbz), 7.33-7.24 (m, 10H, Haro), 4.94 (s, 2H, CH<sub>2</sub>Cbz), 4.19 (ddd, <sup>3</sup>J<sub>H,H</sub> = 8.7 Hz, <sup>3</sup>J<sub>H,H</sub> = 4.6 Hz, <sup>3</sup>J<sub>H,H</sub> = 10.2 Hz, 1H, CH), 2.93 (dd, <sup>3</sup>J<sub>H,H</sub> = 4.6 Hz, <sup>2</sup>J<sub>H,H</sub> = 13.7 Hz, 1H, CH<sub>2</sub>Ph), 2.77 (dd, <sup>3</sup>J<sub>H,H</sub> = 10.3 Hz, <sup>2</sup>J<sub>H,H</sub> = 13.7 Hz, 1H, CH<sub>2</sub>Ph).

**<sup>13</sup>C NMR** (75 MHz, DMSO-d<sub>6</sub>): δ = 170.6 (CO), 155.7 (COBn), 138.0, 137.0 (Caro), 129.1, 128.2, 128.0, 127.6, 127.4, 126.2 (CHaro), 65.2 (CH<sub>2</sub>Cbz), 54.9 (CH), 37.7 (CH<sub>2</sub>Ph).

**HRMS (ESI+TOF)** m/z C<sub>17</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub> [M+H]<sup>+</sup> calc. 314.1499, found 314.1503.

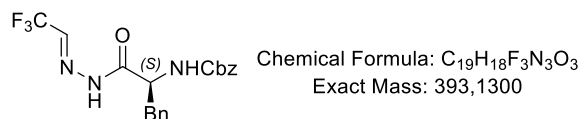
**Melting point:** 155°C





**Benzyl (S,E)-(1-oxo-3-phenyl-1-(2-(2,2,2-trifluoroethylidene)hydrazineyl)propan-2-yl)carbamate (3e)**

The product **3e** is obtained following the general procedure (A) as a mixture of two conformers (ratio: 51/49), (0.745 g, 91%).



Conformer 1:

**<sup>1</sup>H NMR** (300 MHz, DMSO-d<sub>6</sub>): δ = 12.19 (s, 1H, NH), 7.97 (d, <sup>3</sup>J<sub>H,H</sub>=3.45, 1H, NHCbz), 7.87 (d, <sup>3</sup>J<sub>H,H</sub>=7.89 Hz, 1H, CH), 7.39-7.28 (m, 10H, Haro), 5.02 (s, 2H, CH<sub>2</sub>Cbz), 4.35 (m, 1H, CH), 3.10-2.75 (m, 2H, CH<sub>2</sub>Ph).

**<sup>19</sup>F NMR** (188 MHz, DMSO-d<sub>6</sub>): δ = -66.2 (d, <sup>3</sup>J<sub>H,F</sub> = 2.55 Hz, 3F).

**<sup>13</sup>C NMR** (75 MHz, DMSO-d<sub>6</sub>): δ = 169.5 (CO), 156.0 (COCbz), 137.8, 136.8 (Caro), 134.1 (q, <sup>2</sup>J<sub>C,F</sub> = 38 Hz, CH-CF<sub>3</sub>), 129.2, 128.9, 128.3, 128.1, 127.6, 126.5, 125.5 (CHaro), 120.3 (q, <sup>1</sup>J<sub>C,F</sub> = 266 Hz, CF<sub>3</sub>), 65.4 (CH<sub>2</sub>Cbz), 55.6 (CH), 36.7, (CH<sub>2</sub>Ph).

Conformer 2:

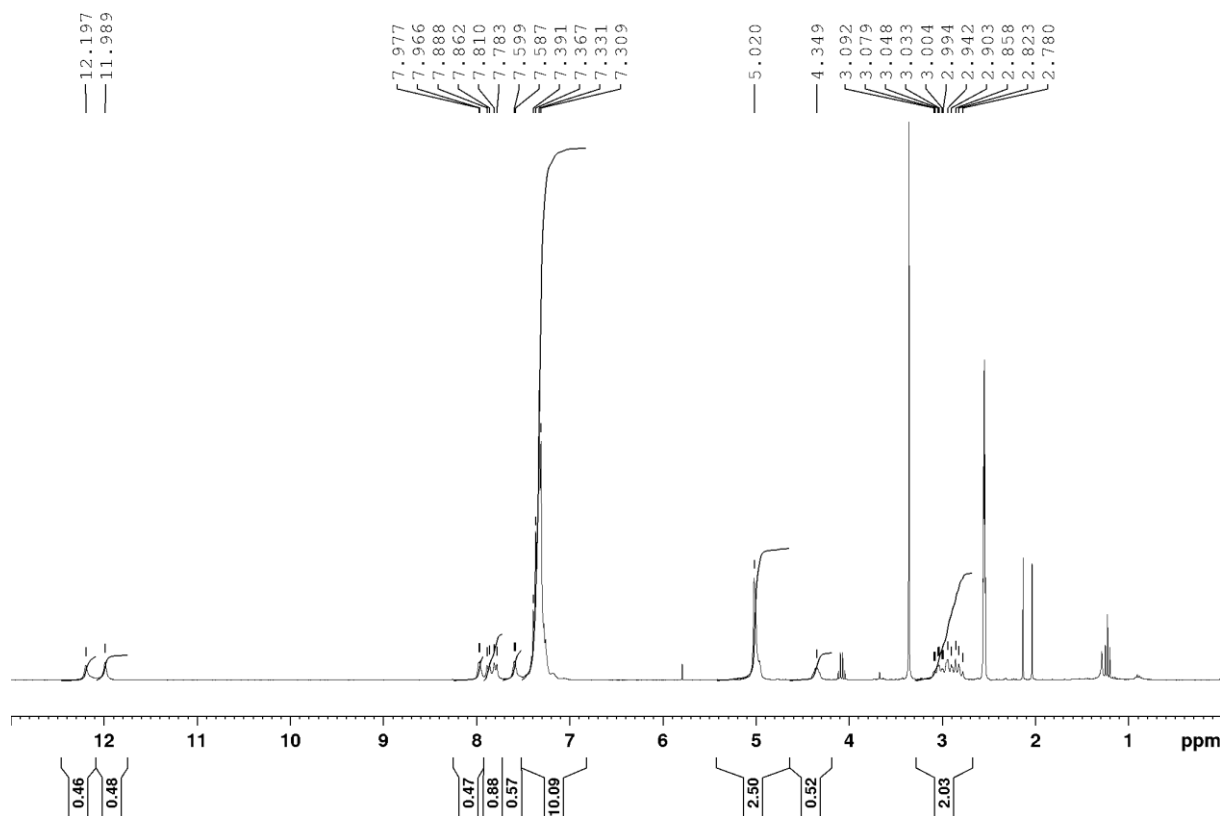
**<sup>1</sup>H NMR** (300 MHz, DMSO-d<sub>6</sub>): δ = 11.99 (s, 1H, NH), 7.79 (d, <sup>3</sup>J<sub>H,H</sub>=8.19 Hz, 1H, NHCbz), 7.59 (d, <sup>3</sup>J<sub>H,H</sub> = 3.57 Hz, 1H, CH), 7.39-7.28 (m, 10H, Haro), 5.02 (s, 2H, CH<sub>2</sub>Cbz), 4.96 (m, 1H, CH), 3.10-2.75 (m, 2H, CH<sub>2</sub>Ph).

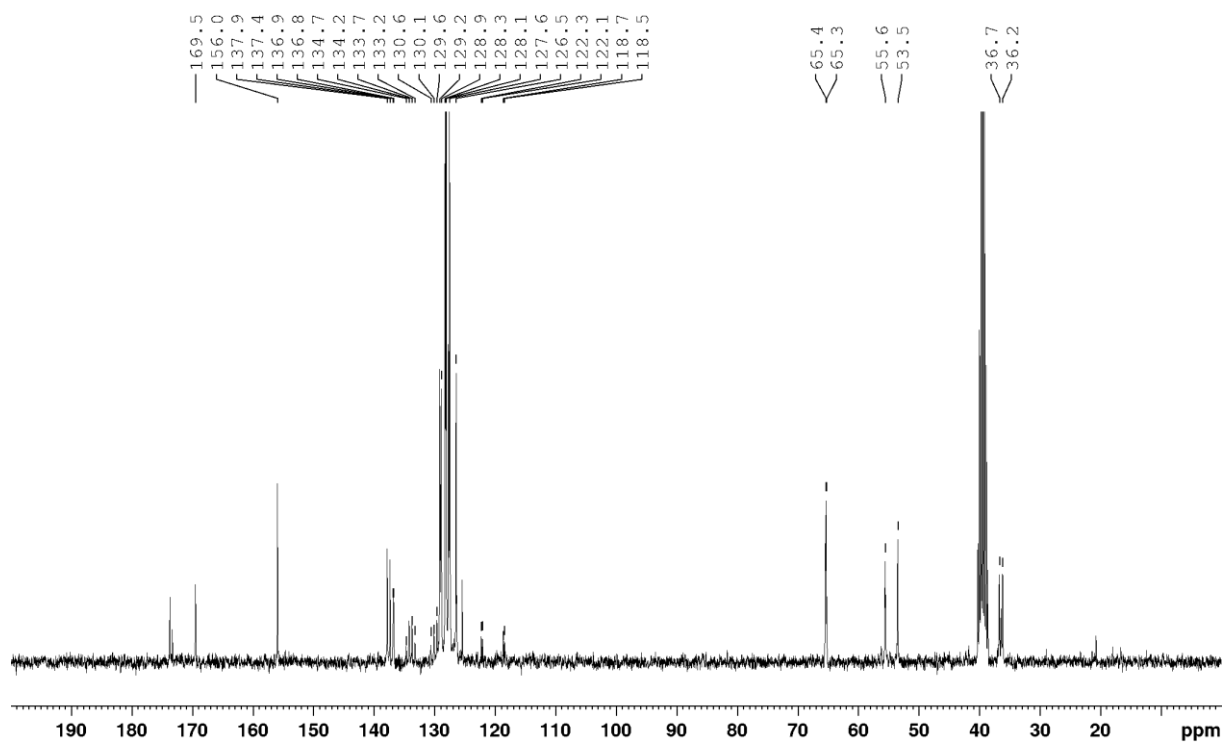
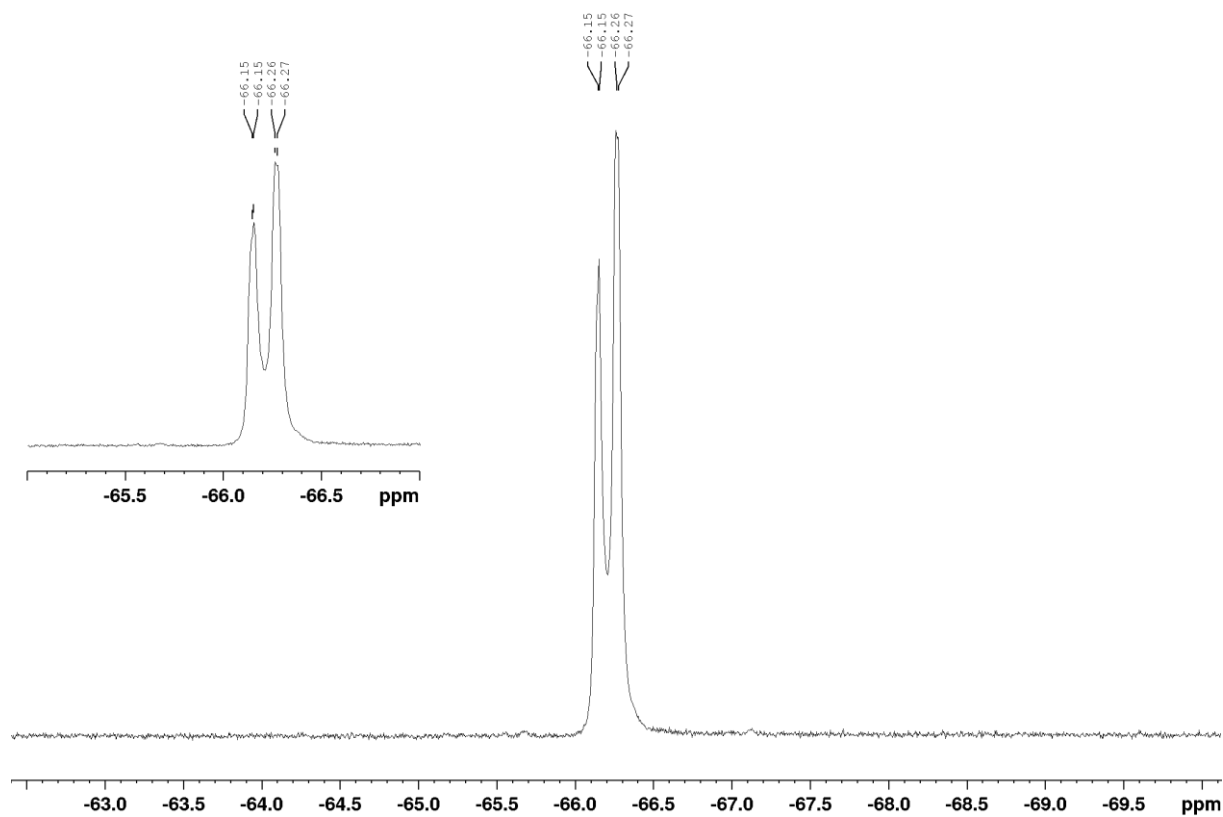
**<sup>19</sup>F NMR** (188 MHz, DMSO-d<sub>6</sub>): δ = -66.3 (d, 3F, <sup>3</sup>J<sub>H,F</sub> = 2.60 Hz, 3F).

**<sup>13</sup>C NMR** (75 MHz, DMSO-d<sub>6</sub>): δ = 169.5 (CO), 156.0 (COCbz), 137.4, 136.8 (Caro), 129.9 (q, <sup>2</sup>J<sub>C,F</sub> = 38 Hz, CH-CF<sub>3</sub>), 129.2, 128.9, 128.3, 128.1, 127.6, 126.5, 125.5 (CHaro), 120.1 (q, <sup>1</sup>J<sub>C,F</sub> = 266 Hz, CF<sub>3</sub>), 65.3 (CH<sub>2</sub>Cbz), 53.5 (CH), 36.2 (CH<sub>2</sub>Ph).

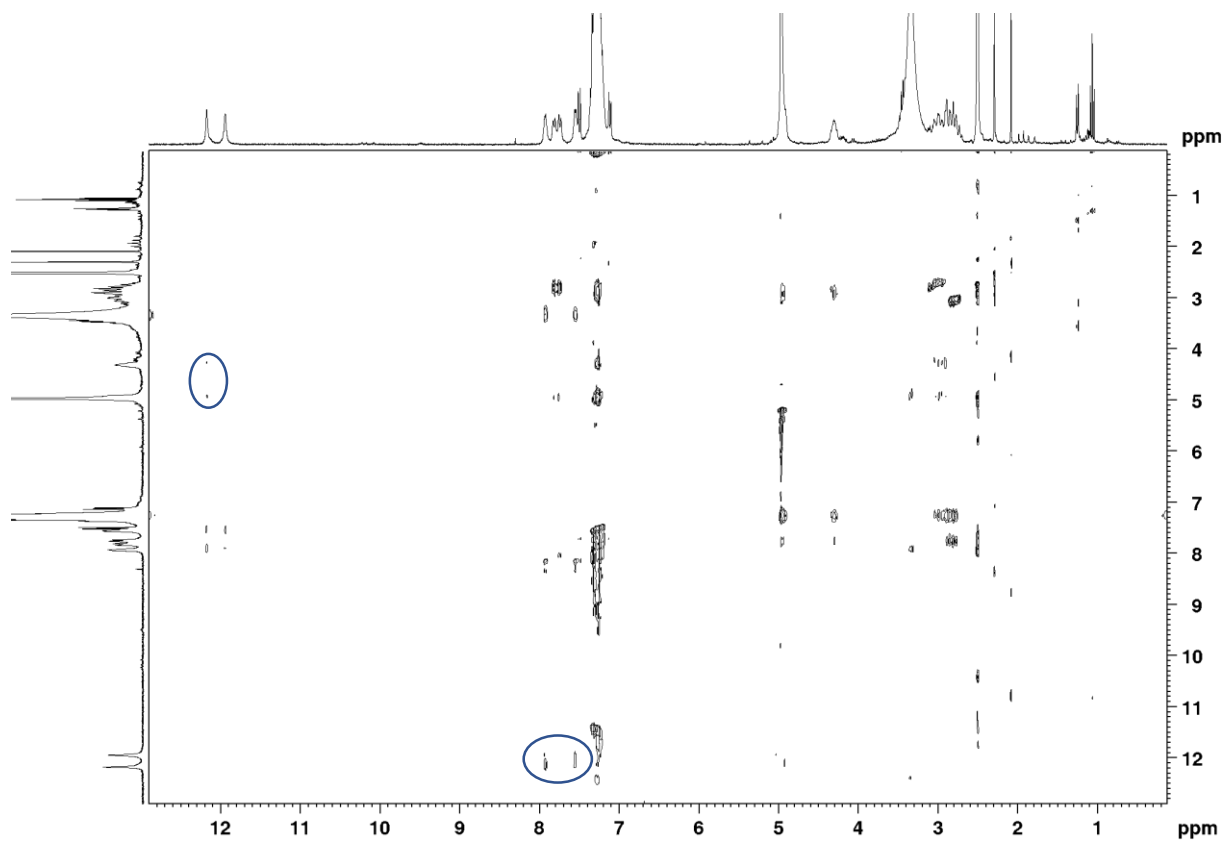
**HRMS (ESI+TOF)** m/z C<sub>19</sub>H<sub>18</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub> [M+Na]<sup>+</sup> calc. 416.1192, found 416.1187.

**Melting point:** 176°C



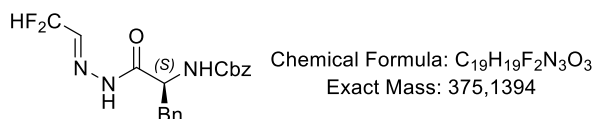


2D 1H-1H NOESY experiments of 3e



**Benzyl (S,E)-(1-oxo-3-phenyl-1-(2-(2,2-difluoroethylidene)hydrazineyl)propan-2-yl)carbamate (3f)**

The product **3f** is obtained following the general procedure (A) as a mixture of two conformers (ratio: 51/49) (1.15 g, 96%).



**Conformer 1:**

**<sup>1</sup>H NMR** (200 MHz, DMSO-d<sub>6</sub>): δ = 11.91 (s, 1H, NH), 7.80 (d, <sup>3</sup>J<sub>H,H</sub> = 7.9 Hz, 1H, NHCbz), 7.72 (d, <sup>3</sup>J<sub>H,H</sub> = 4.7 Hz, 1H, CH), 7.38-7.26 (m, 10H, Haro), 6.44 (td, <sup>2</sup>J<sub>H,F</sub> = 81 Hz, <sup>3</sup>J<sub>H,H</sub> = 4.9 Hz, 1H, CF<sub>2</sub>H), 4.99 (s, 2H, CH<sub>2</sub>Cbz), 4.29 (m, 1H, CH), 3.05-2.74 (m, 2H, CH<sub>2</sub>Ph).

**<sup>19</sup>F NMR** (188 MHz, DMSO-d<sub>6</sub>): δ = -116.59 (dd, <sup>2</sup>J<sub>H,F</sub> = 54 Hz, <sup>3</sup>J<sub>H,F</sub> = 2.7 Hz, 2F)

**<sup>13</sup>C NMR** (75 MHz, DMSO-d<sub>6</sub>): δ = 169.0 (CO), 155.9 (COCbz), 140.1 (t, <sup>2</sup>J<sub>C,F</sub> = 31 Hz, CH-CF<sub>2</sub>H), 137.8, 136.9 (Caro), 129.1, 128.2, 128.1, 127.7, 127.5, 126.4 (CHaro), 113.3 (t, <sup>1</sup>J<sub>C,F</sub> = 233 Hz, CF<sub>2</sub>H), 65.4 (CH<sub>2</sub>Cbz), 55.5 (CH), 36.9, 36.3 (CH<sub>2</sub>Ph).

**Conformer 2:**

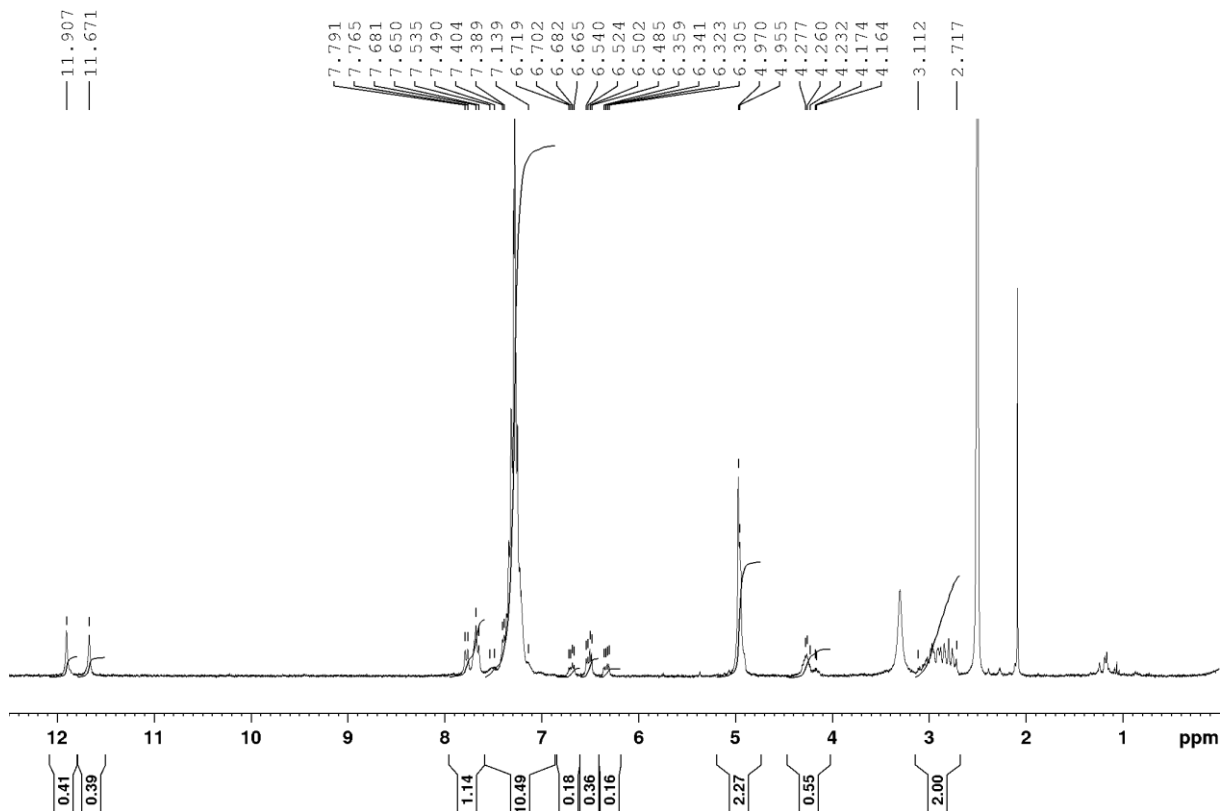
**<sup>1</sup>H NMR** (200 MHz, DMSO-d<sub>6</sub>): δ = 11.67 (s, 1H, NH), 7.68 (d, <sup>3</sup>J<sub>H,H</sub> = 9.1 Hz, 1H, NHCbz), 7.42 (d, <sup>3</sup>J<sub>H,H</sub> = 4.4 Hz, 1H, CH), 7.38-7.26 (m, 10H, Haro), 6.51 (td, <sup>2</sup>J<sub>H,F</sub> = 54 Hz, <sup>3</sup>J<sub>H,H</sub> = 5 Hz, 1H, CF<sub>2</sub>H), 4.99 (s, 2H, CH<sub>2</sub>Cbz), 4.93 (m, 1H, CH), 3.05-2.74 (m, 2H, CH<sub>2</sub>Ph)

**<sup>19</sup>F NMR** (188 MHz, DMSO-d<sub>6</sub>): δ = -116.61 (dd, <sup>2</sup>J<sub>H,F</sub> = 81 Hz, <sup>3</sup>J<sub>H,F</sub> = 3.6 Hz, 2F)

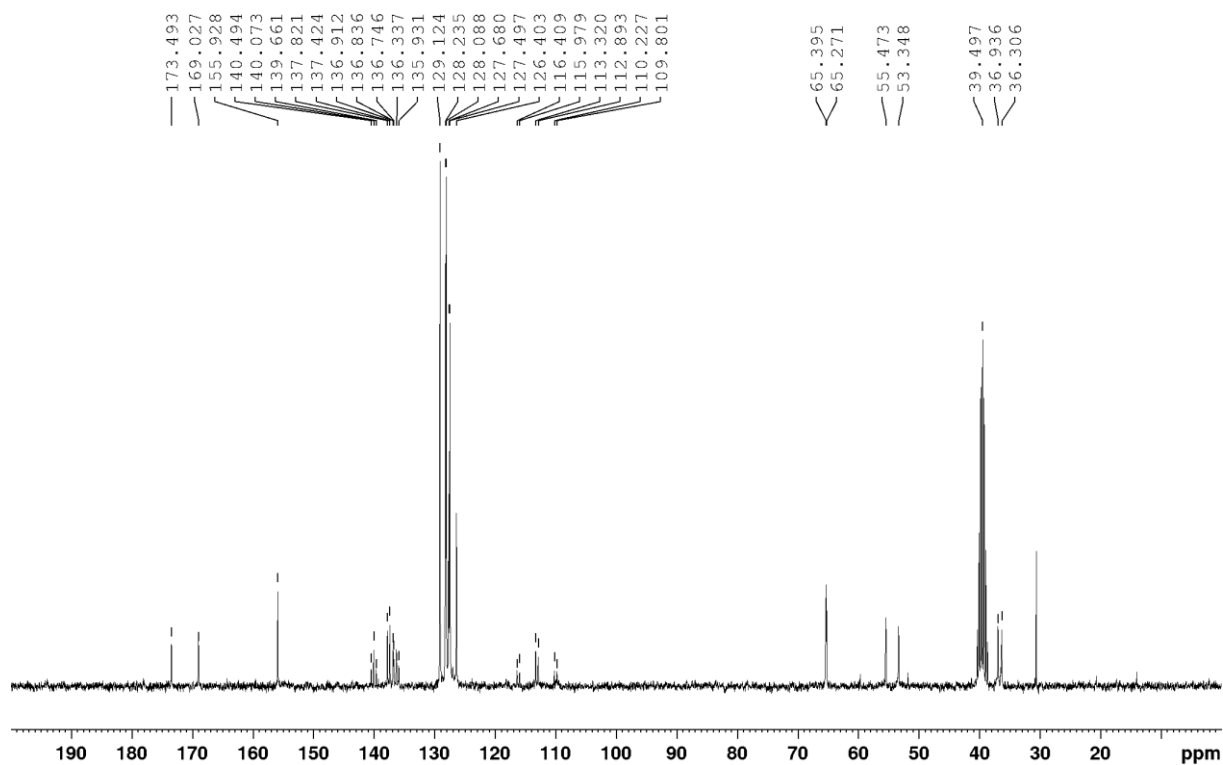
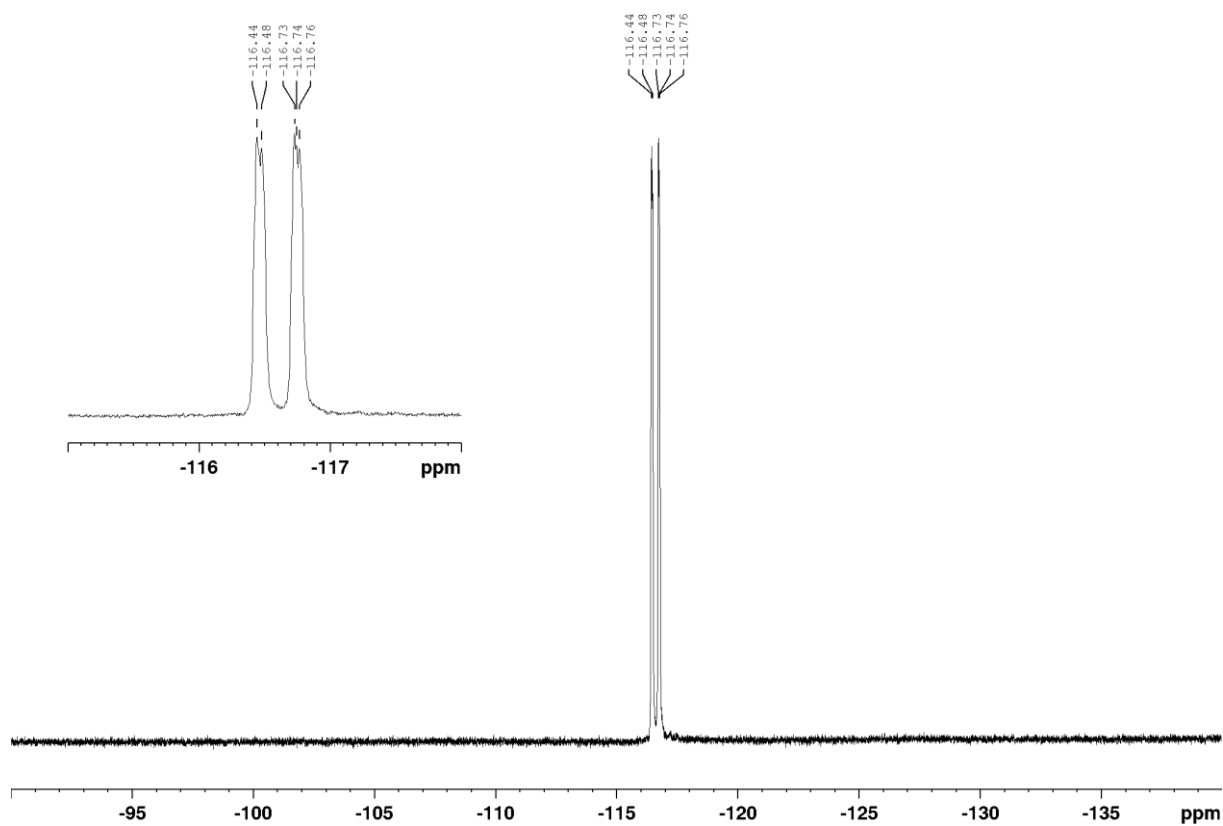
**<sup>13</sup>C NMR** (75 MHz, DMSO-d<sub>6</sub>): δ = 169.0 (CO), 155.9 (COCbz), 137.4, 136.8 (Caro), 136.3 (t, <sup>2</sup>J<sub>C,F</sub> = 31 Hz, CHCF<sub>2</sub>H), 129.1, 128.2, 128.1, 127.7, 127.5, 126.4 (CHaro), 112.9 (t, <sup>1</sup>J<sub>C,F</sub> = 233 Hz, CF<sub>2</sub>H), 65.3 (CH<sub>2</sub>Cbz), 53.3 (CH), 36.3 (CH<sub>2</sub>Ph).

**HRMS (ESI+TOF)** m/z C<sub>19</sub>H<sub>19</sub>F<sub>2</sub>N<sub>3</sub>O<sub>3</sub> [M+Na]<sup>+</sup> calc. 398.1286, found 398.1281.

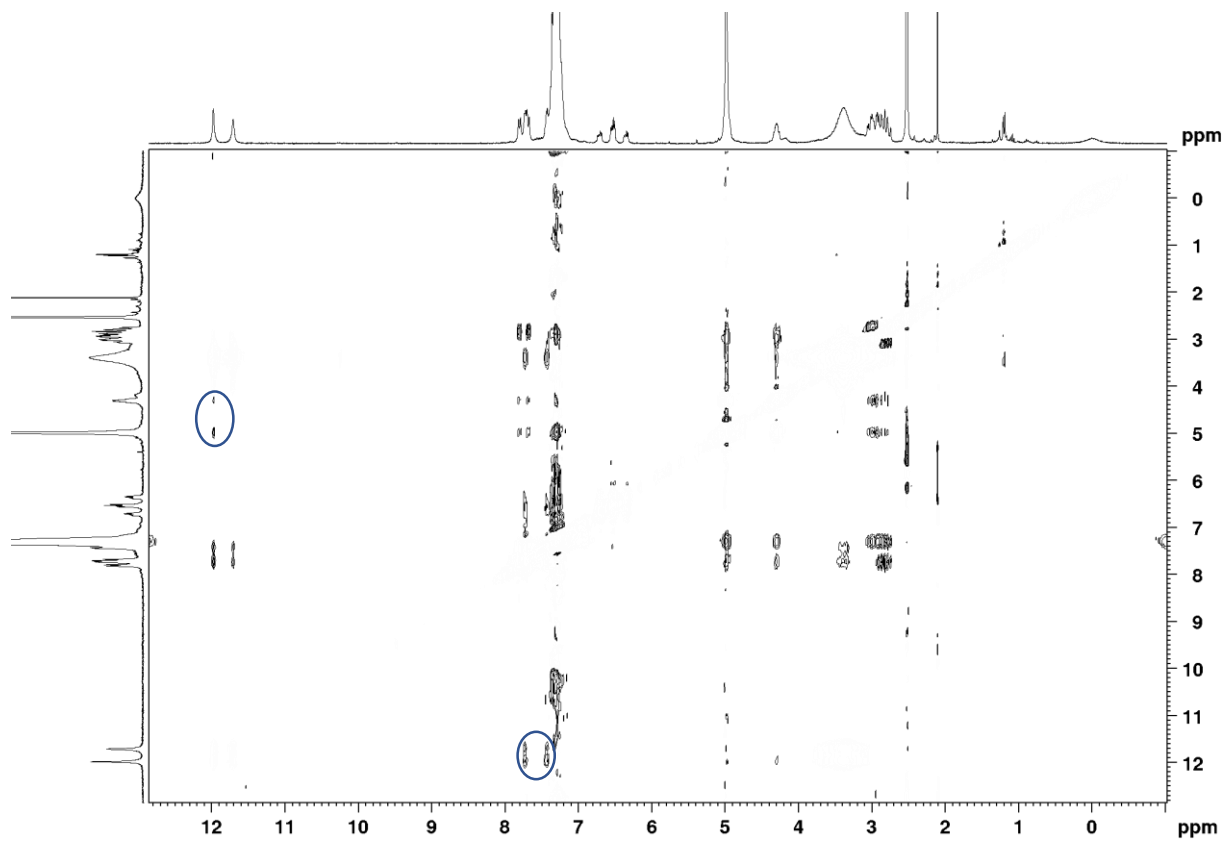
**Melting point:** 193°C







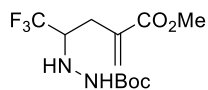
2D  $^1\text{H}$ - $^1\text{H}$  NOESY experiment of 3f



b) **Allylated compounds 5a-f:**

**tert-Butyl 2-(1,1,1-trifluoro-4-(methoxycarbonyl)pent-4-en-2-yl)hydrazine-1-carboxylate (5a)**

The product **5a** is obtained following the general procedure (**B**) as a yellow oil (0.531g, 73%).



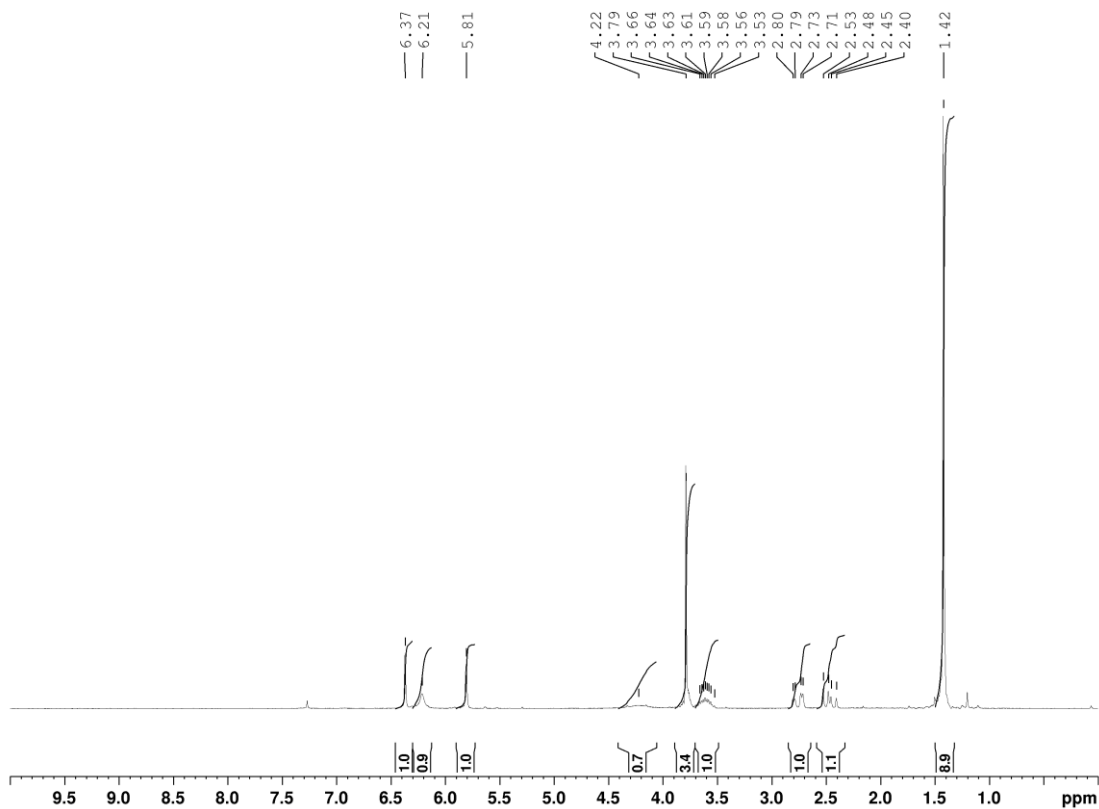
Chemical Formula: C<sub>12</sub>H<sub>19</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>  
Exact Mass: 312,1297

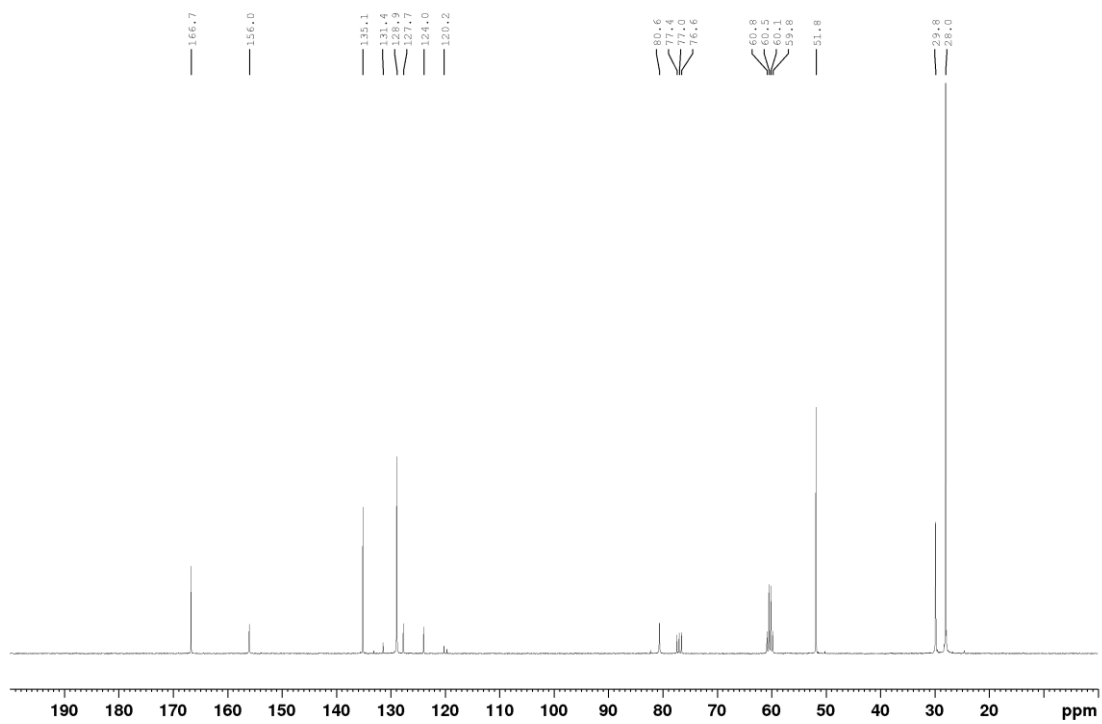
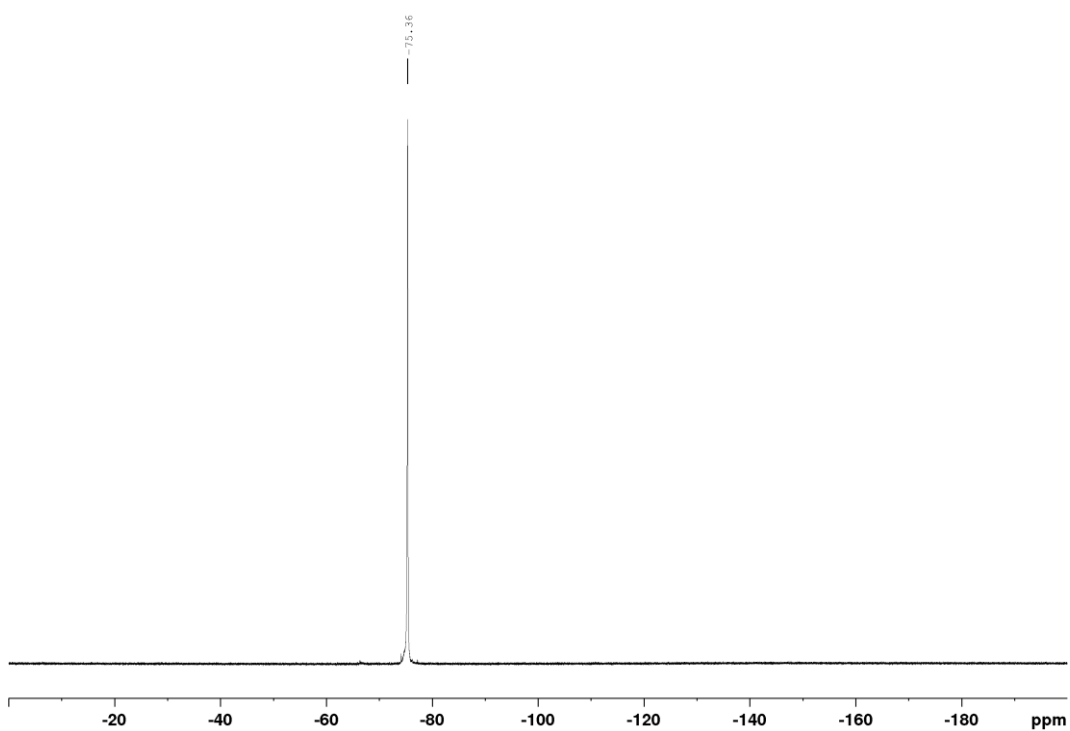
**<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>): δ = 6.37 (s, 1H, =CH<sub>2</sub>), 6.21 (brs, 1H, NHBoc), 5.81 (s, 1H, =CH<sub>2</sub>), 4.22 (brs, 1H, NH), 3.79 (s, 3H, OCH<sub>3</sub>), 3.55-3.79 (m, 1H, CH), 2.76 (dd, <sup>3</sup>J<sub>H,H</sub> = 3.5 Hz, <sup>1</sup>J<sub>H,H</sub> = 14.6 Hz, 1H, CH<sub>2</sub>), 2.46 (dd, <sup>3</sup>J<sub>H,H</sub> = 9.0 Hz, <sup>1</sup>J<sub>H,H</sub> = 14.6 Hz, 1H, CH<sub>2</sub>), 1.42 (s, 9H, (CH<sub>3</sub>)<sub>3</sub>).

**<sup>19</sup>F NMR** (188 MHz, CDCl<sub>3</sub>): δ = - 75.4 (brs, 3F)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 166.7 (CO), 156.0 (COCbz), 135.1 (=Cq), 128.9 (=CH<sub>2</sub>), 125.8 (q, <sup>1</sup>J<sub>H,H</sub> = 282 Hz, CF<sub>3</sub>), 80.6 (Cq), 60.3 (q, <sup>2</sup>J<sub>H,H</sub> = 27 Hz, CH-CF<sub>3</sub>), 51.8 (OCH<sub>3</sub>), 29.8 (CH<sub>2</sub>), 28.0 (CH<sub>3</sub>).

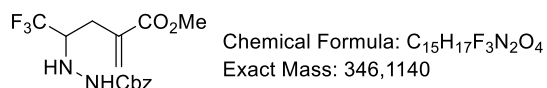
**HRMS (ESI+TOF)** m/z C<sub>12</sub>H<sub>19</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub> [M+Na]<sup>+</sup> calc. 335.1189, found. 335.1156





**Benzyl 2-(1,1,1-trifluoro-4-(methoxycarbonyl)pent-4-en-2-yl)hydrazine-1-carboxylate (5b)**

The product **5b** is obtained following the general procedure (B) as a yellow oil (0.633 g, 81%).

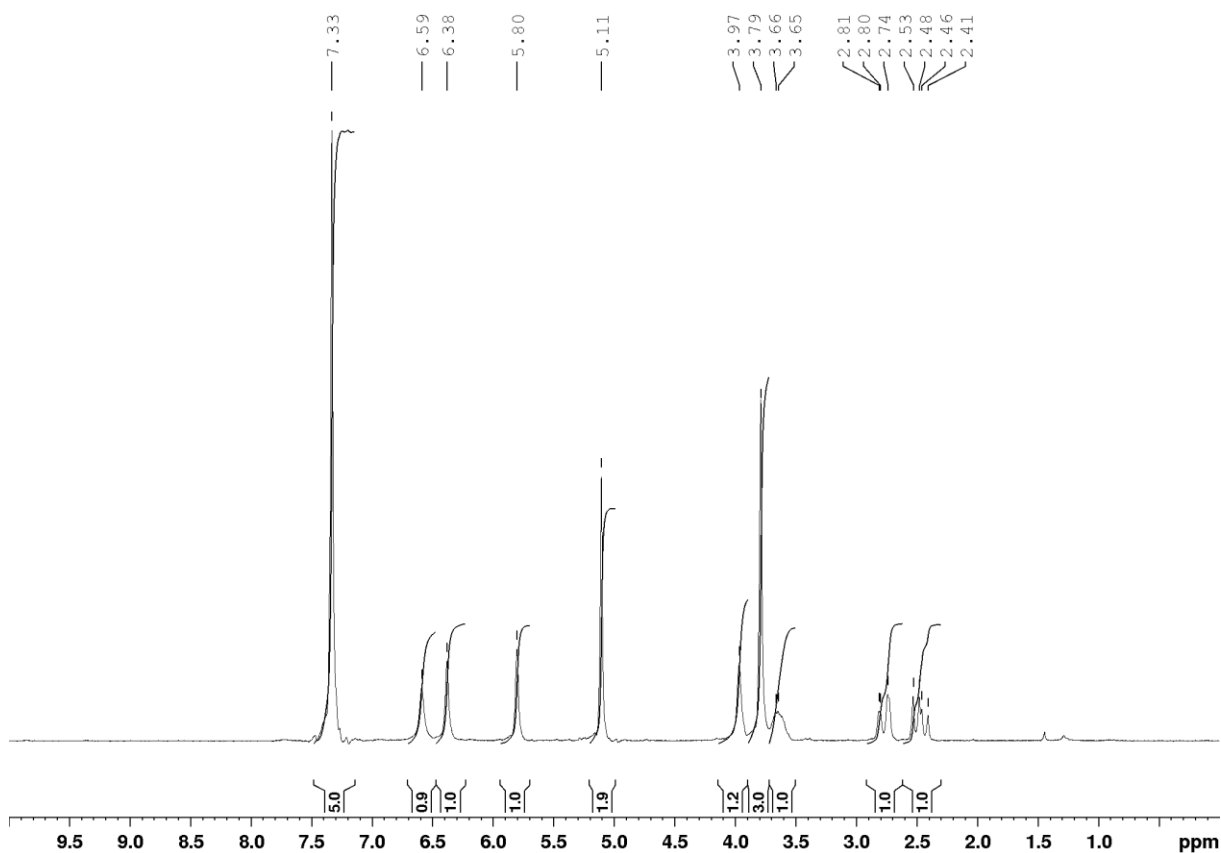


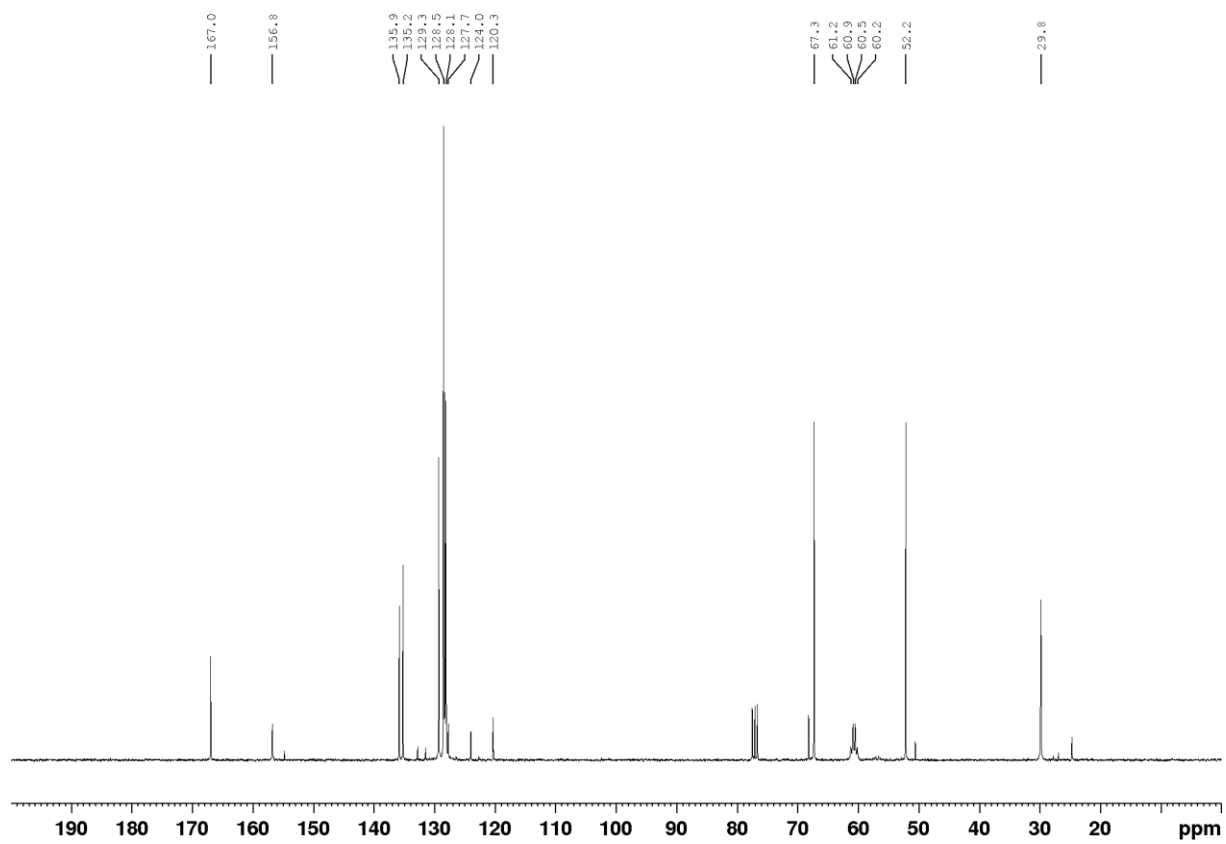
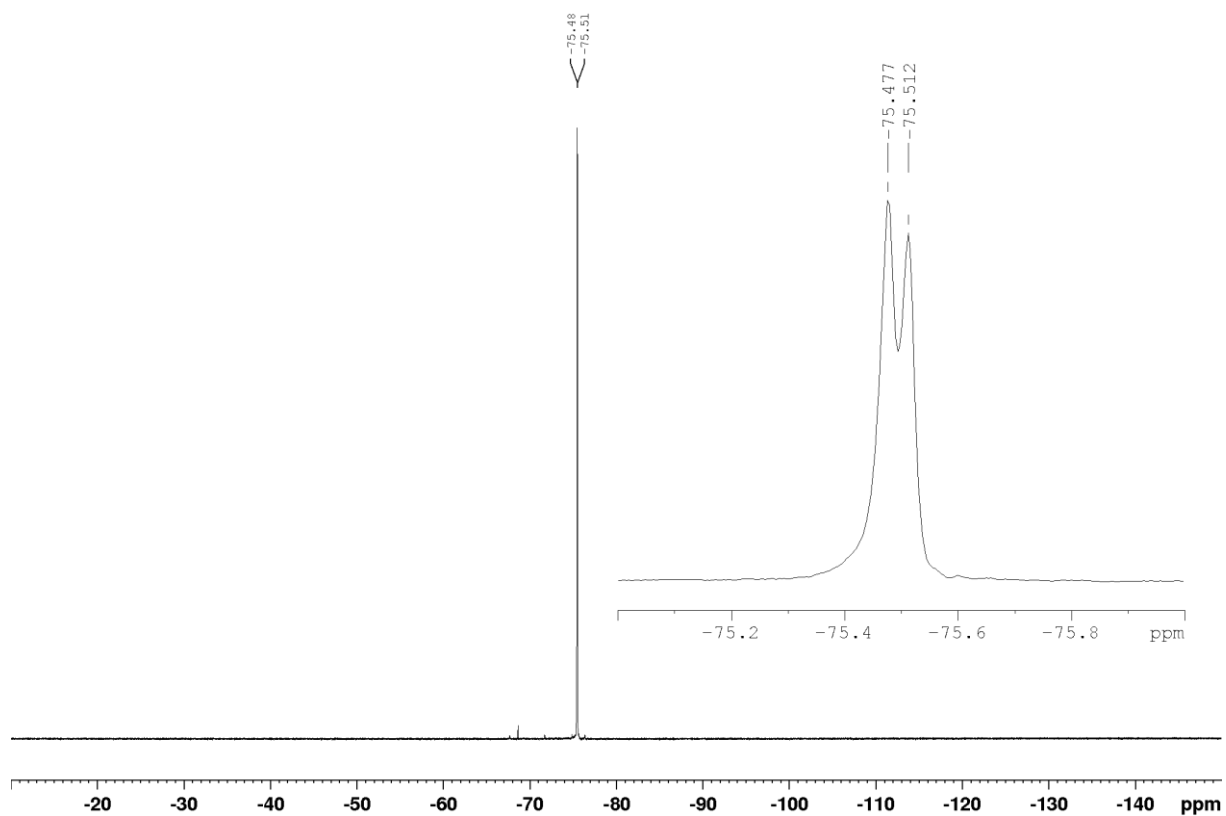
**<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>): δ = 7.33 (m, 5H, Haro), 6.59 (brs, 1H, NH), 6.38 (s, 1H, =CH<sub>2</sub>), 5.80 (s, 1H, =CH<sub>2</sub>), 5.11 (s, 2H, CH<sub>2</sub>Cbz), 3.97 (m, 1H, NH), 3.79 (s, 3H, OCH<sub>3</sub>), 3.66 (m, 1H, CHCF<sub>3</sub>), 2.77 (dd, <sup>3</sup>J<sub>H,H</sub> = 3.0 Hz, <sup>3</sup>J<sub>H,H</sub> = 14.4 Hz, 1H, CH<sub>2</sub>), 2.49 (dd, <sup>3</sup>J<sub>H,H</sub> = 4.2 Hz, <sup>3</sup>J<sub>H,H</sub> = 14.5 Hz, 1H, CH<sub>2</sub>).

**<sup>19</sup>F NMR** (188 MHz, CDCl<sub>3</sub>): δ = - 75.49 (d, <sup>3</sup>J<sub>H,H</sub> = 6.6 Hz, 3F)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 167.0 (CO), 156.8 (COCbz), 135.9 (=Cq), 135.2 (Caro), 129.3, 128.5, 128.1 (CHaro), 125.9 (q, <sup>1</sup>J<sub>H,H</sub> = 279 Hz, CF<sub>3</sub>), 120.3 (=CH<sub>2</sub>), 67.3 (CH<sub>2</sub>Cbz), 60.7 (q, <sup>2</sup>J<sub>H,H</sub> = 26.9 Hz, CHCF<sub>3</sub>), 52.2 (CH<sub>3</sub>), 29.8 (CH<sub>2</sub>).

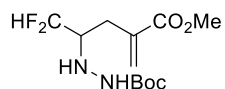
**HRMS (ESI+TOF)** m/z C<sub>15</sub>H<sub>17</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub> [M+Na]<sup>+</sup> calc. 369.1033, found. 369.1123





***tert*-Butyl -2-(1,1-difluoro-4-(methoxycarbonyl)pent-4-en-2-yl)hydrazine-1-carboxylate (5c)**

The product **5c** is obtained following the general procedure (**B**) as a yellow oil (0.669g, 88%).



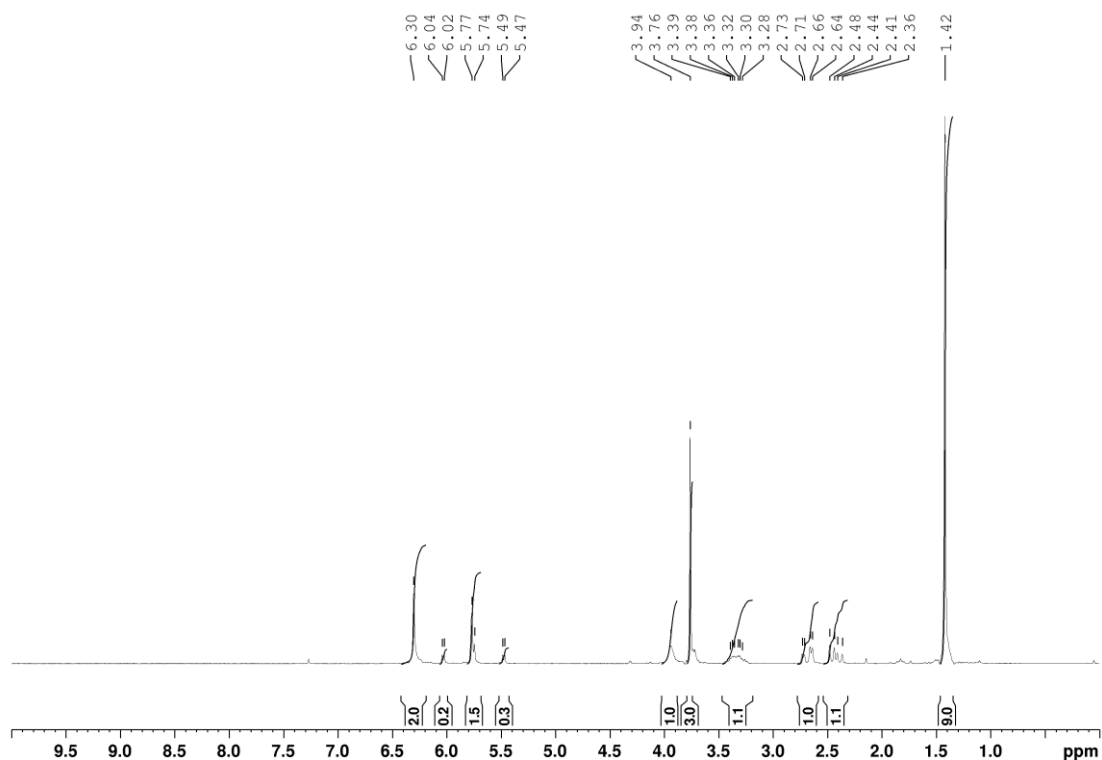
Chemical Formula: C<sub>12</sub>H<sub>20</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>  
Exact Mass: 294,1391

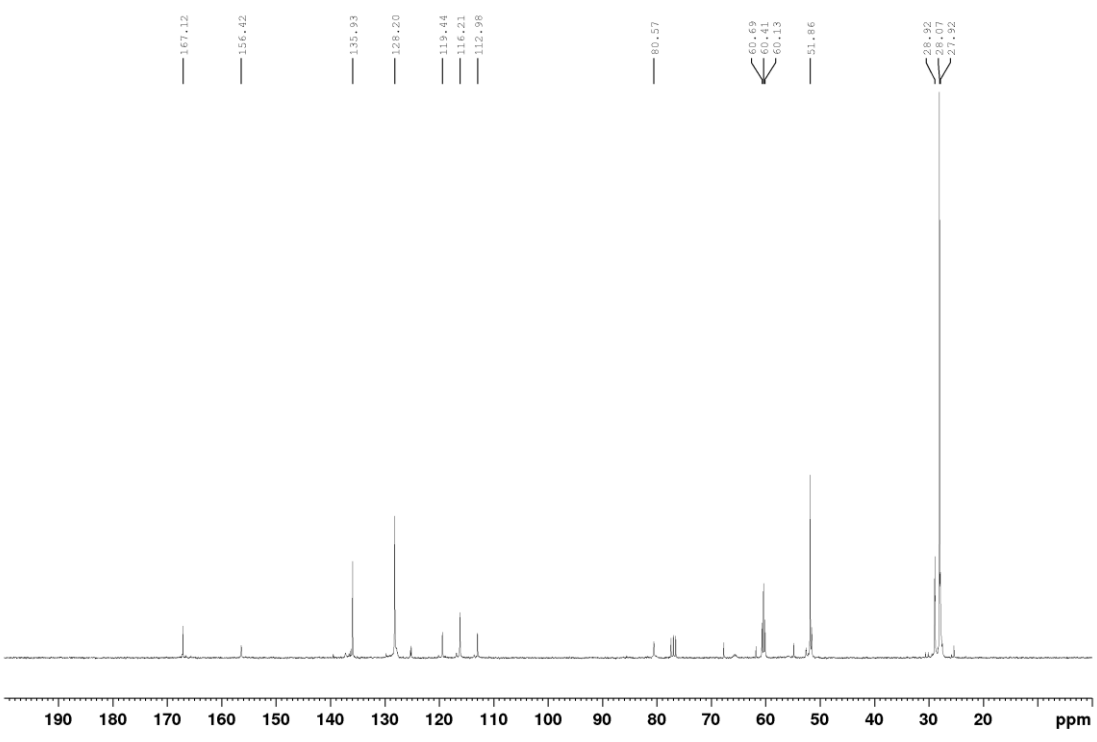
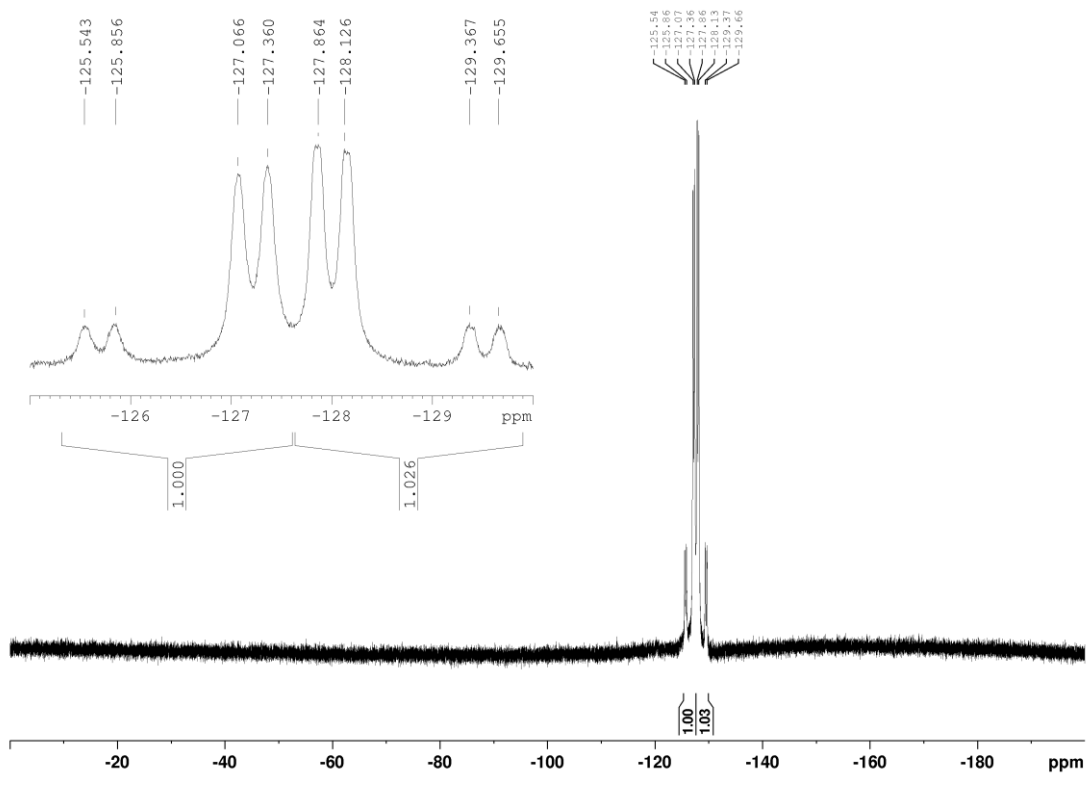
**<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>): δ = 6.30 (s, 1H, =CH<sub>2</sub>), 6.29 (s, 1H, NHBoc), 5.77 (s, 1H, =CH<sub>2</sub>), 5.76 (td, <sup>3</sup>J<sub>H,H</sub> = 3.9 Hz, <sup>2</sup>J<sub>H,F</sub> = 55.7 Hz, 1H, CF<sub>2</sub>H), 3.94 (brs, 1H, NH), 3.76 (s, 3H, OCH<sub>3</sub>), 3.35 (m, 1H, CHCF<sub>2</sub>H), 2.69 (dd, <sup>3</sup>J<sub>H,H</sub> = 8.7 Hz, <sup>2</sup>J<sub>H,H</sub> = 14.5 Hz, 1H, CH<sub>2</sub>), 2.42 (dd, <sup>3</sup>J<sub>H,H</sub> = 4.1 Hz, <sup>2</sup>J<sub>H,H</sub> = 14.5 Hz, 1H, CH<sub>2</sub>), 1.42 (m, 9H, (CH<sub>3</sub>)<sub>3</sub>).

**<sup>19</sup>F NMR** (188 MHz, CDCl<sub>3</sub>): δ = -126.4 (dd, <sup>2</sup>J<sub>F,F</sub> = 288 Hz, <sup>2</sup>J<sub>H,F</sub> = 54 Hz, 1F), -128.7 (dd, <sup>2</sup>J<sub>F,F</sub> = 288 Hz, <sup>2</sup>J<sub>H,F</sub> = 54 Hz, 1F).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 167.1 (CO), 156.4 (COBoc), 135.9 (=Cq), 128.2 (=CH<sub>2</sub>), 116.2 (t, <sup>1</sup>J<sub>C,F</sub> = 243 Hz, CHF<sub>2</sub>), 80.6 (Cq), 60.4 (t, <sup>2</sup>J<sub>C,F</sub> = 21 Hz, CH-CHF<sub>2</sub>), 51.9 (OCH<sub>3</sub>), 28.9 (CH<sub>2</sub>), 28.1 ((CH<sub>3</sub>)<sub>3</sub>).

**HRMS (ESI+TOF)** m/z C<sub>12</sub>H<sub>20</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub> [M+Na]<sup>+</sup> calc. 317.1283, found. 317.1266

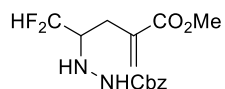






**Benzyl -2-(1,1-difluoro-4-(methoxycarbonyl)pent-4-en-2-yl)hydrazine-1-carboxylate (5d)**

The product **5d** is obtained following the general procedure (B) as a yellow oil (0.566 g, 79%).



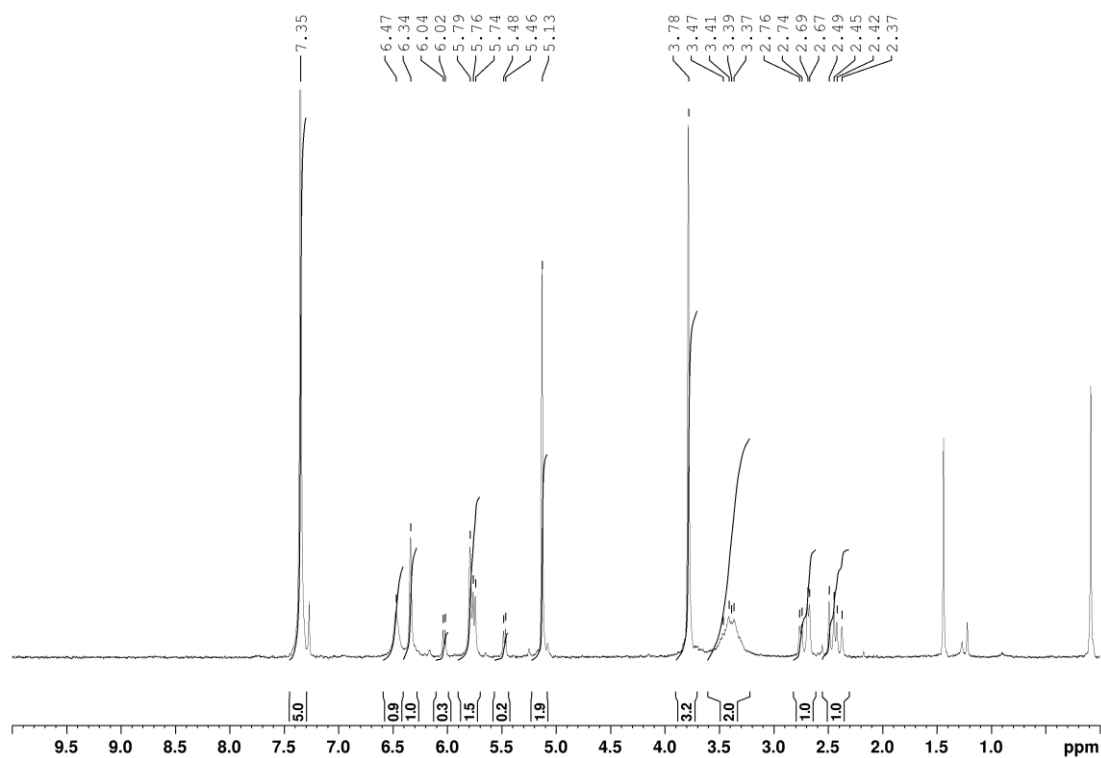
Chemical Formula: C<sub>15</sub>H<sub>18</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>  
Exact Mass: 328,1235

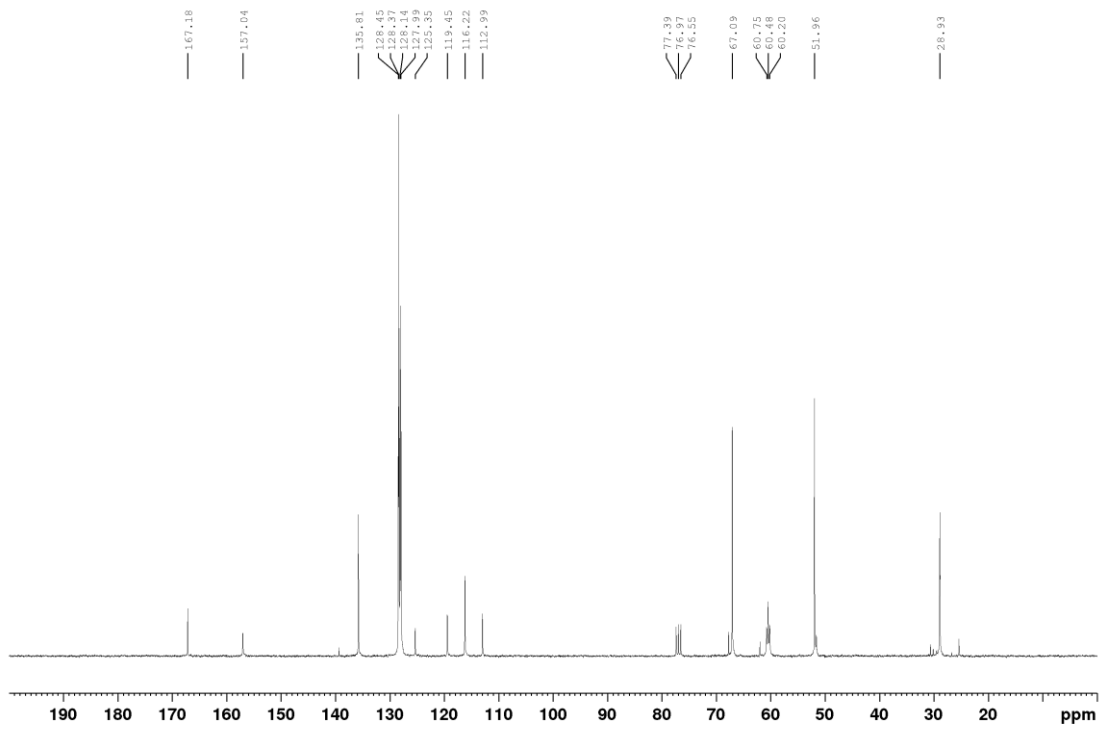
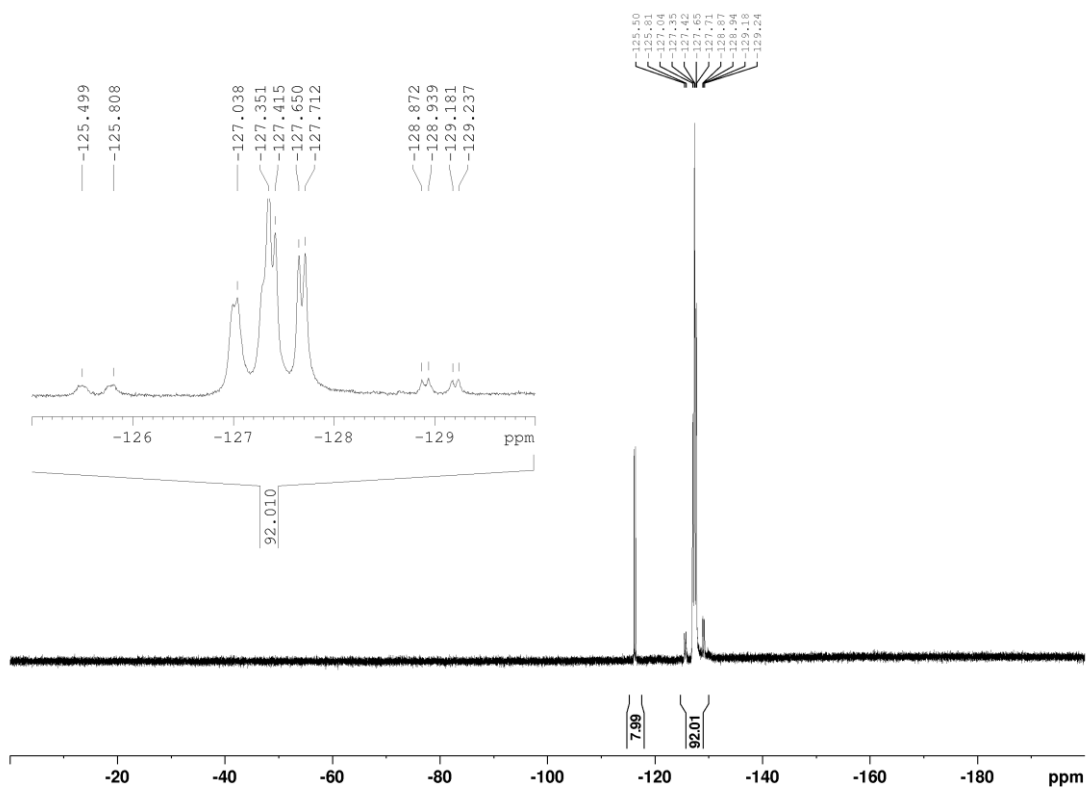
**<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>): δ = 7.35 (m, 5H, Haro), 6.47 (s, 1H, NHCbz), 6.34 (s, 1H, =CH<sub>2</sub>), 5.79 (s, 1H, =CH<sub>2</sub>), 5.75 (dt, <sup>3</sup>J<sub>H,H</sub> = 3.9 Hz, <sup>2</sup>J<sub>H,F</sub> = 55.7 Hz, 1H, CF<sub>2</sub>H), 5.13 (s, 2H, CH<sub>2</sub>Ph), 3.78 (s, 3H, OCH<sub>3</sub>), 3.39 (m, 2H, NH and CH), 2.71 (dd, <sup>3</sup>J<sub>H,H</sub> = 3.9 Hz, <sup>2</sup>J<sub>H,H</sub> = 14.7 Hz, 1H, CH<sub>2</sub>), 2.43 (dd, <sup>3</sup>J<sub>H,H</sub> = 9.0 Hz, <sup>2</sup>J<sub>H,H</sub> = 14.5 Hz, 1H, CH<sub>2</sub>).

**<sup>19</sup>F NMR** (188 MHz, CDCl<sub>3</sub>): δ = -126.4 (ddd, <sup>2</sup>J<sub>F,F</sub> = 290 Hz, <sup>2</sup>J<sub>H,F</sub> = 58 Hz, <sup>3</sup>J<sub>H,F</sub> = 7 Hz, 1F), -128.3 (ddd, <sup>2</sup>J<sub>F,F</sub> = 288 Hz, <sup>2</sup>J<sub>H,F</sub> = 56 Hz, <sup>3</sup>J<sub>H,F</sub> = 12 Hz, 1F).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 167.2 (CO), 157.0 (CO<sub>Cbz</sub>), 135.8 (=C), 128.5 (Caro), 128.4, 128.1, 128.0 (CHaro), 125.4 (=CH<sub>2</sub>), 116.2 (t, <sup>1</sup>J<sub>C,F</sub> = 242 Hz, CF<sub>2</sub>H), 67.1 (CH<sub>2</sub>Cbz), 60.5 (t, <sup>2</sup>J<sub>C,F</sub> = 20 Hz, CHCF<sub>2</sub>H), 52.0 (OCH<sub>3</sub>), 29.0 (CH<sub>2</sub>).

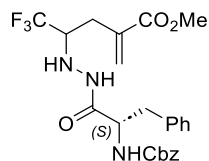
**HRMS (ESI+TOF)** m/z C<sub>15</sub>H<sub>18</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub> [M+Na]<sup>+</sup> calc. 351.1127, found. 351.1114





**Methyl 4-(2-(((benzyloxy)carbonyl)-L-phenylalanyl)hydrazineyl)-5,5,5-trifluoro-2-methylenepentanoate (5e)**

The product **5e** is obtained following the general procedure (**B**) as a yellow oil (0.580 g, 66%) as a mixture of two diastereoisomers (ratio: 52/48).



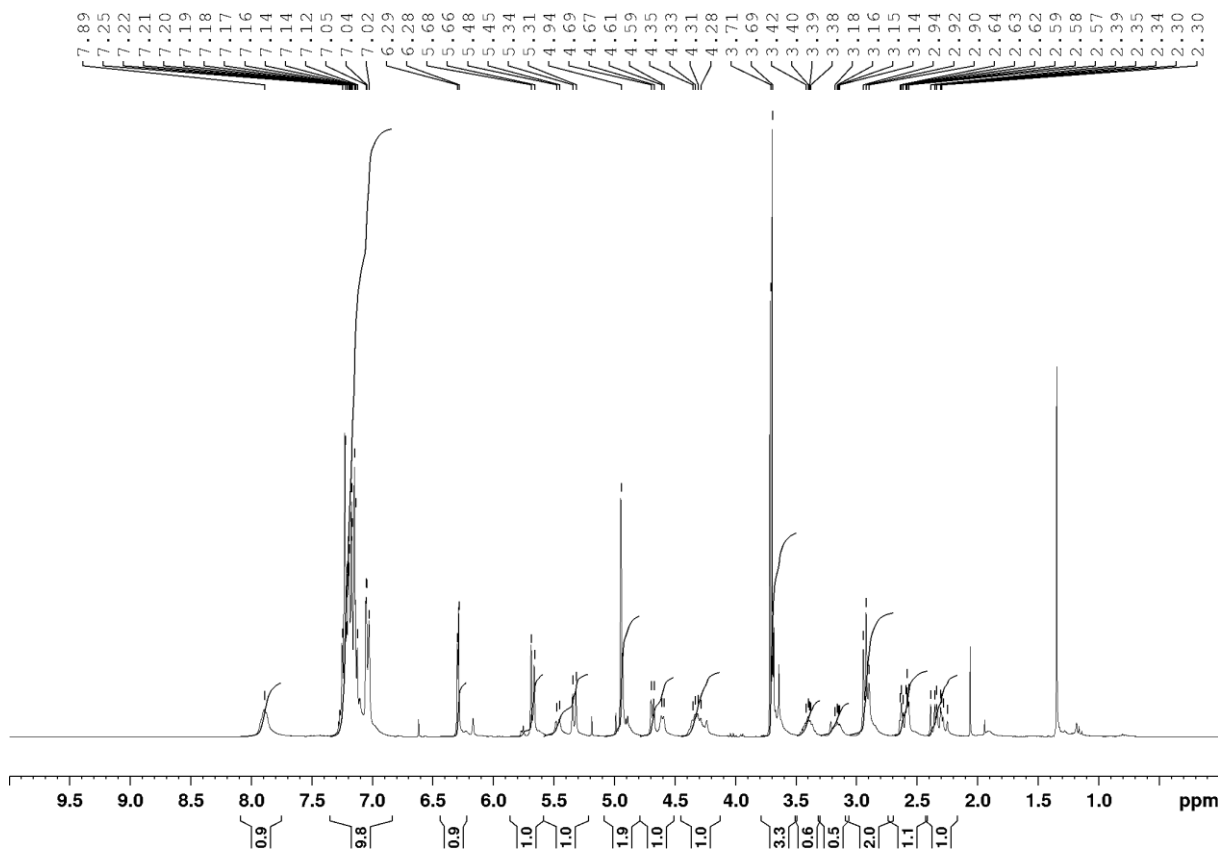
Chemical Formula:  $C_{24}H_{26}F_3N_3O_5$   
Exact Mass: 493,1825

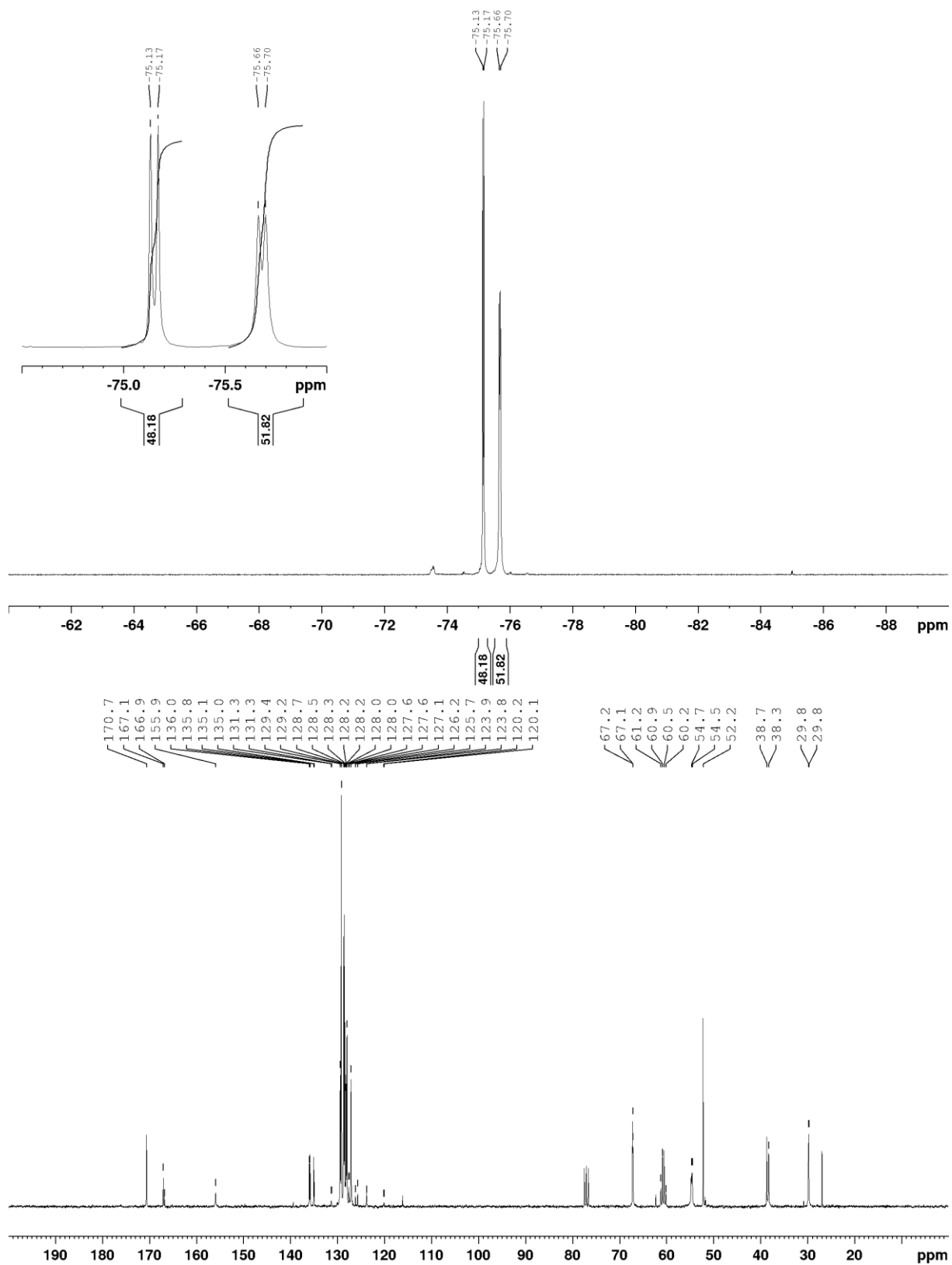
**$^1H$  NMR** (200 MHz,  $CDCl_3$ ):  $\delta$  = 7.89 (brs, 1H, NHCO), 7.25-7.02 (m, 10H, Haro), 6.29 and 6.28 (brs, 1H, =CH<sub>2</sub>), 5.68 and 5.66 (brs, 1H, =CH<sub>2</sub>), 5.46 (d,  $^3J_{H,H}$  = 8.1 Hz, 0.5H, NHCbz), 5.33 (d,  $^3J_{H,H}$  = 8.36 Hz, 0.5 H, NHCbz), 4.94 (s, 2H, CH<sub>2</sub>Cbz), 4.68 (d,  $^3J_{H,H}$  = 6.16 Hz, 0.5 H, NHN), 4.60 (d,  $^3J_{H,H}$  = 6.16 Hz, 0.5 H, NHN), 4.32 (q,  $^3J_{H,H}$  = 5.2 Hz, 1 H, CH $\alpha$ ), 3.71 and 3.69 (2s, 3H, OCH<sub>3</sub>), 3.42-3.38 (m, 0.5H, CH), 3.18-3.14 (m, 0.5H, CH), 2.92 (m, 2H, CH<sub>2</sub>Ph), 2.60 (td,  $^2J_{H,H}$  = 14.4 Hz,  $^3J_{H,H}$  = 3.7 Hz, 1H, CH<sub>2</sub>), 2.32 (dd,  $^2J_{H,H}$  = 14.8 Hz,  $^3J_{H,H}$  = 10.6 Hz, 1H, CH<sub>2</sub>).

**$^{19}F$  NMR** (188 MHz,  $CDCl_3$ ):  $\delta$  = -75.2 (d,  $^3J_{H,F}$  = 6.96 Hz, 3F), -75.7 (d,  $^3J_{H,F}$  = 6.63 Hz, 3F).

**$^{13}C$  NMR** (75 MHz,  $CDCl_3$ ):  $\delta$  = 170.7 (CONH), 167.1 and 166.9 (COCbz), 155.9 (CO), 136.0 and 135.8 (=C), 135.1 and 134.9 (Caro), 129.4, 129.2, 128.7, 128.5, 128.3, 128.2, 128.2, 128.0, 127.9, 127.1 (CHaro), 126.2 and 125.7 (=CH<sub>2</sub>), 125.8 (q,  $^1J_{C,F}$  = 281Hz, CF<sub>3</sub>), 125.7 (q,  $^1J_{C,F}$  = 280 Hz, CF<sub>3</sub>), 67.2 and 67.1 (CH<sub>2</sub>Cbz), 60.7 (q,  $^2J_{H,F}$  = 27 Hz, CHCF<sub>3</sub>), 54.7 and 54.5 (CH $\alpha$ ), 52.2 (OCH<sub>3</sub>), 38.7 and 38.3 (CH<sub>2</sub>Ph), 29.8 and 29.8 (CH<sub>2</sub>).

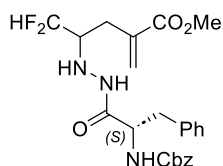
**HRMS (ESI+TOF)** m/z  $C_{24}H_{26}F_3N_3O_5$  [M+H]<sup>+</sup> calc. 494.1898, found. 494.1905





**Methyl 4-(2-(((benzyloxy)carbonyl)-L-phenylalanyl)hydrazineyl)-5,5-difluoro-2-methylenepentanoate (5f)**

The product **5f** is obtained following the general procedure (B) as a yellow oil (1.07 g, 75%) as a mixture of two diastereoisomers (ratio: 51/49).



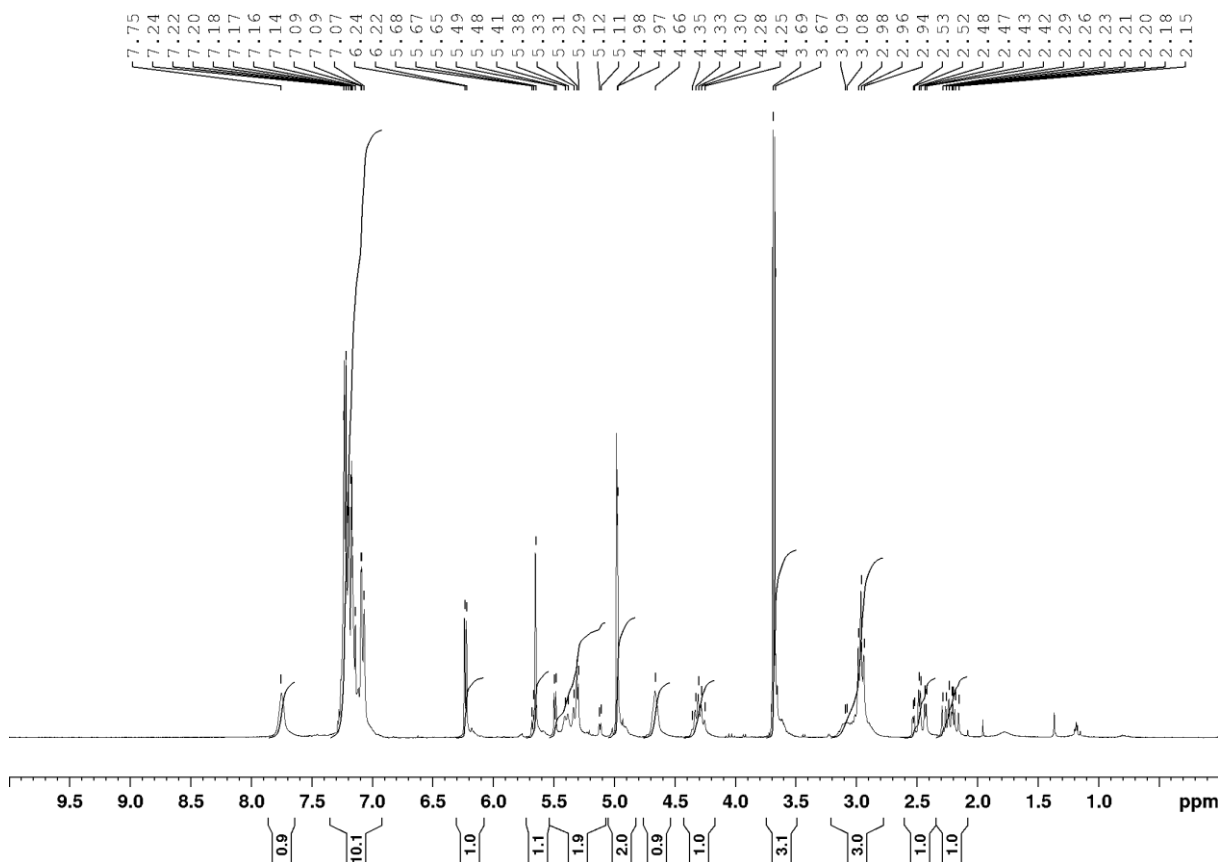
Chemical Formula: C<sub>24</sub>H<sub>27</sub>F<sub>2</sub>N<sub>3</sub>O<sub>5</sub>  
Exact Mass: 475,1919

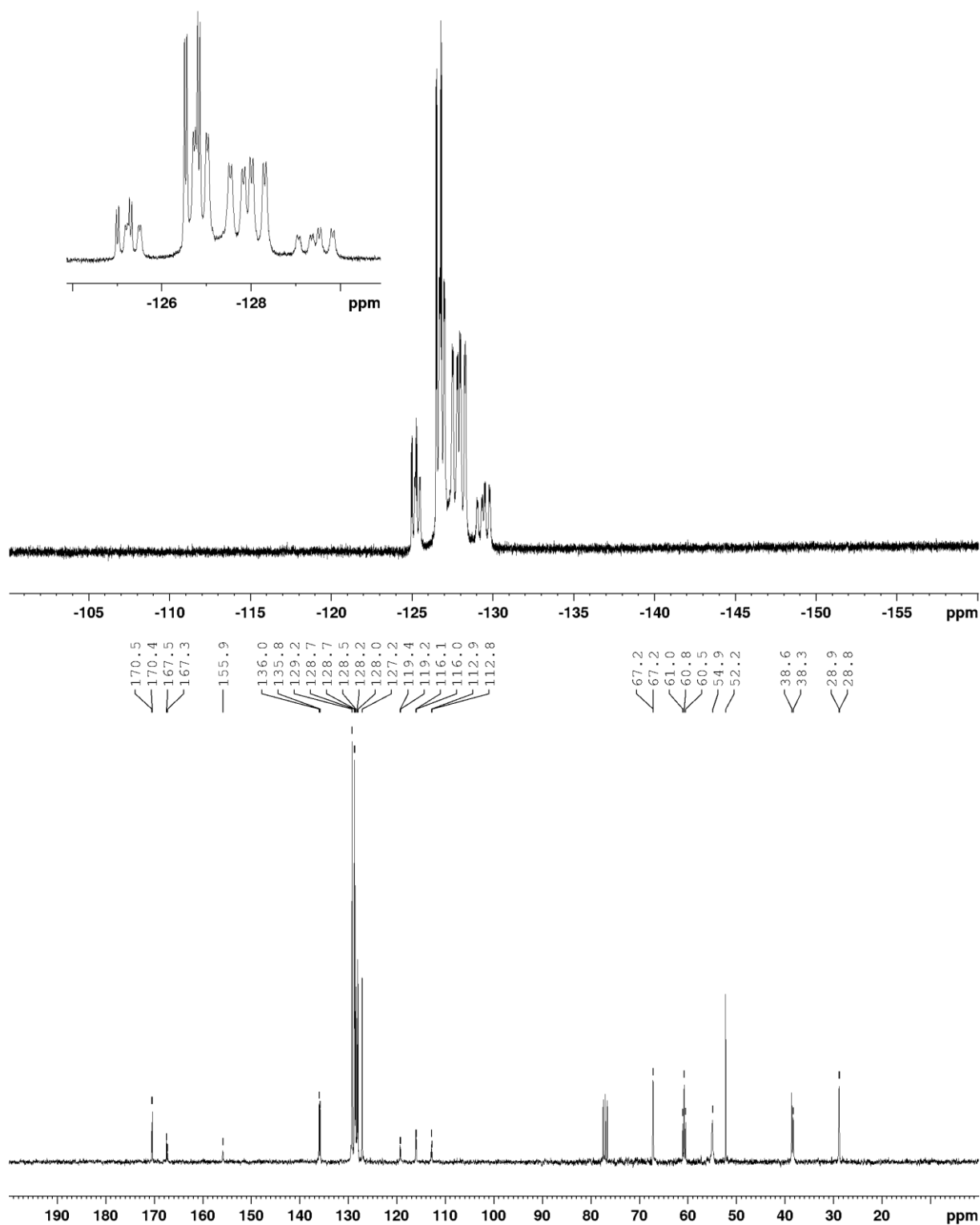
**<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>): δ = 7.76 (brs, 1H, NHCO), 7.28-7.07 (m, 10H, Haro), 6.23 (d, <sup>3</sup>J<sub>H,H</sub> = 4.5 Hz, 1H, =CH<sub>2</sub>), 5.65 (brs, 1H, =CH<sub>2</sub>), 5.48 (td, <sup>2</sup>J<sub>H,F</sub> = 55.7 Hz, <sup>3</sup>J<sub>H,H</sub> = 4.3 Hz, 0.5H, CF<sub>2</sub>H), 5.39 (d, <sup>3</sup>J<sub>H,H</sub> = 7.6 Hz, 1H, NHCbz), 5.34 (d, <sup>3</sup>J<sub>H,H</sub> = 7.7 Hz, 1H, NHCbz), 5.21 (td, <sup>2</sup>J<sub>H,F</sub> = 56.0 Hz, <sup>3</sup>J<sub>H,H</sub> = 4.1 Hz, 0.5H, CF<sub>2</sub>H), 4.97 (s, 2H, CH<sub>2</sub>Cbz), 4.66 (sl, 1H, NHN), 4.30 (q, <sup>3</sup>J<sub>H,H</sub> = 7.7 Hz, 1H, CHα), 3.68 and 3.67 (2s, 3H, OCH<sub>3</sub>), 3.09 (m, 1H, CH), 2.97 and 2.95 (2d, <sup>3</sup>J<sub>H,H</sub> = 6.6 Hz and <sup>3</sup>J<sub>H,H</sub> = 7.2 Hz, 2H, CH<sub>2</sub>Ph), 2.48 (dd, <sup>2</sup>J<sub>H,H</sub> = 14.9 Hz, <sup>3</sup>J<sub>H,H</sub> = 3.9 Hz, 1H, CH<sub>2</sub>), 2.22 (dd, <sup>2</sup>J<sub>H,H</sub> = 14.7 Hz, <sup>3</sup>J<sub>H,H</sub> = 9.5 Hz, 1H, CH<sub>2</sub>)

**<sup>19</sup>F NMR** (188 MHz, CDCl<sub>3</sub>): δ = -125.9 (ddd, <sup>2</sup>J<sub>F,F</sub> = 287 Hz, <sup>2</sup>J<sub>H,F</sub> = 55 Hz, <sup>3</sup>J<sub>H,F</sub> = 10.1 Hz, 1F), -126.1 (ddd, <sup>2</sup>J<sub>F,F</sub> = 286 Hz, <sup>2</sup>J<sub>H,F</sub> = 55 Hz, <sup>3</sup>J<sub>H,F</sub> = 8.4 Hz, 1F), -128.5 (ddd, <sup>2</sup>J<sub>F,F</sub> = 287 Hz, <sup>2</sup>J<sub>H,F</sub> = 55 Hz, <sup>3</sup>J<sub>H,F</sub> = 11.5 Hz, 1F), -128.9 (ddd, <sup>2</sup>J<sub>F,F</sub> = 286 Hz, <sup>2</sup>J<sub>H,F</sub> = 55 Hz, <sup>3</sup>J<sub>H,F</sub> = 12.4 Hz, 1F).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 170.5 and 170.4 (CONH), 167.5 and 167.3 (COCbz), 155.9 (CO), 136.0 and 135.8 (=C), 129.2, 128.8, 128.7, 128.2, 128.0 (CHaro), 127.2 (=CH<sub>2</sub>), 116.1 (t, <sup>1</sup>J<sub>C,F</sub> = 244 Hz, CF<sub>2</sub>H), 116.0 (t, <sup>1</sup>J<sub>C,F</sub> = 244 Hz, CF<sub>2</sub>H), 67.2 and 67.1 (CH<sub>2</sub>Cbz), 60.8 (t, <sup>2</sup>J<sub>C,F</sub> = 21 Hz, CHCF<sub>2</sub>H), 54.9 (CHα), 52.2 (OCH<sub>3</sub>), 38.6 and 38.3 (CH<sub>2</sub>Ph), 28.9 and 28.8 (CH<sub>2</sub>).

**HRMS (ESI+TOF)** m/z C<sub>24</sub>H<sub>28</sub>F<sub>2</sub>N<sub>3</sub>O<sub>5</sub> [M+H]<sup>+</sup> calc. 476.1997, found. 476.2000

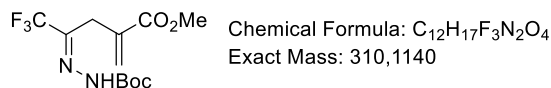




c) Hydrazones 6a-f

***tert*-Butyl (E)-2-(1,1,1-trifluoro-4-(methoxycarbonyl)pent-4-en-2-ylidene)hydrazine-1-carboxylate (6a)**

The product **6a** is obtained following the general procedure (C) as a slightly yellow oil (0.347 g, 80% (l<sub>2</sub>) / 77%(NBS))

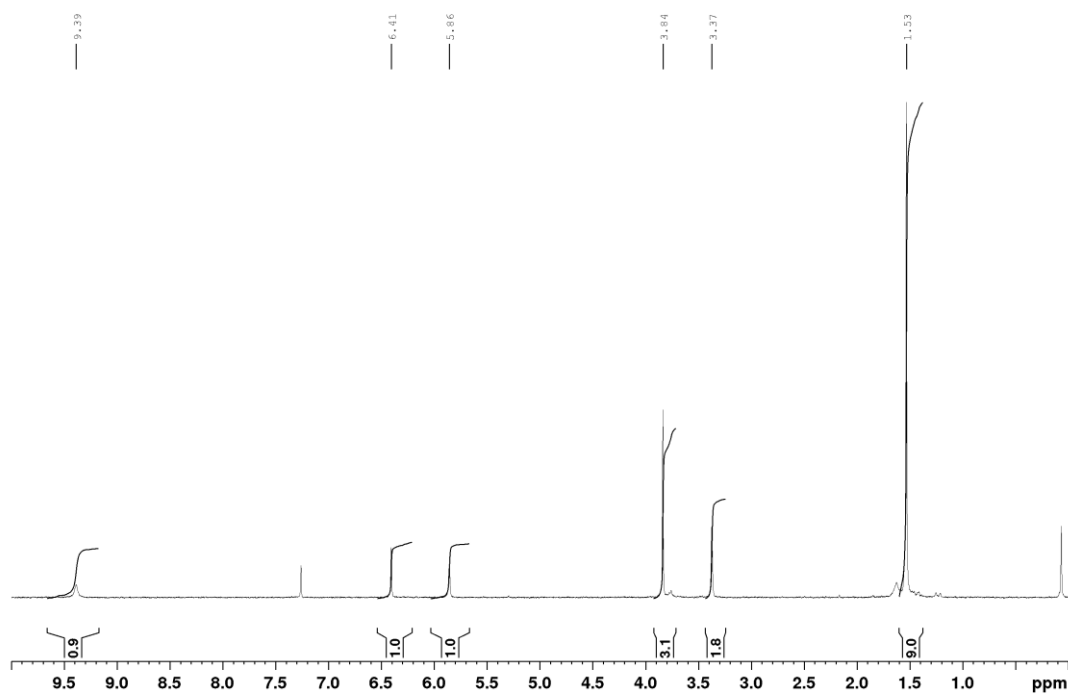


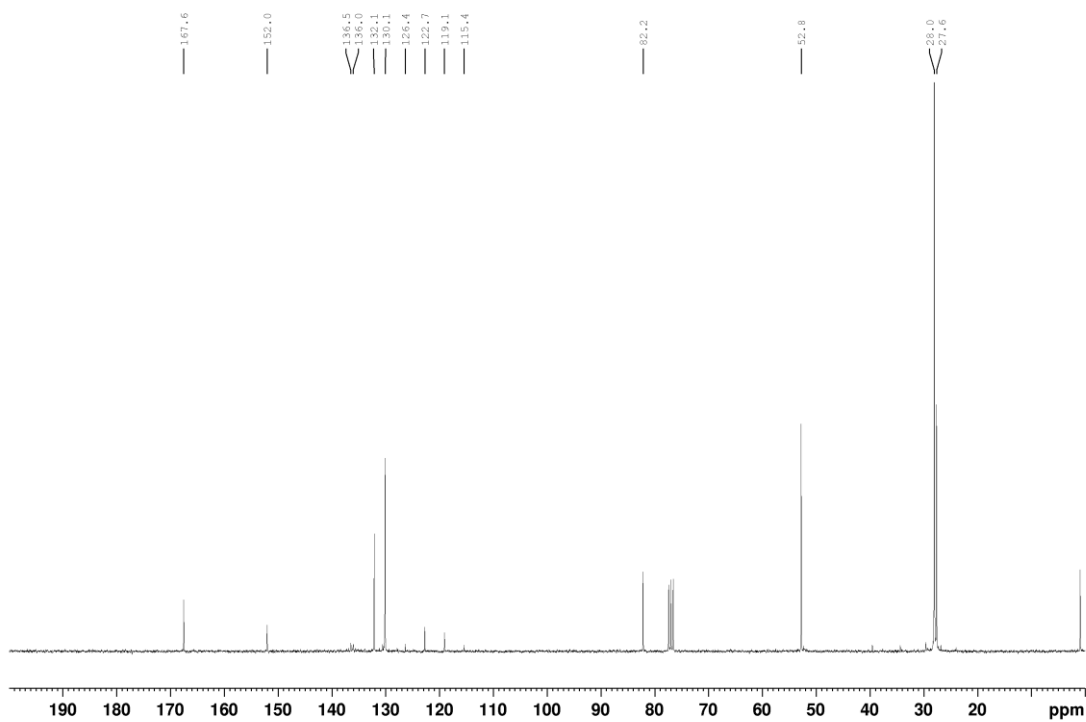
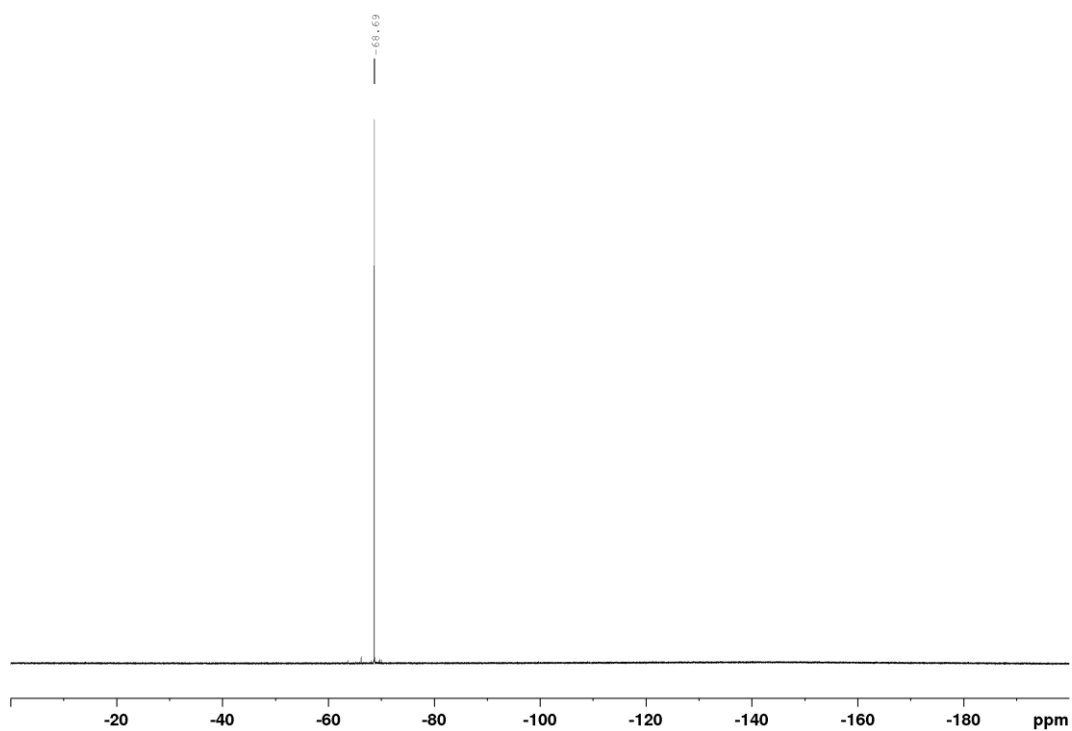
**<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>): δ = 9.39 (s, 1H, NHBoc), 6.41 (s, 1H, =CH<sub>2</sub>), 5.86 (s, 1H, =CH<sub>2</sub>), 3.84 (s, 3H, OCH<sub>3</sub>), 3.37 (s, 2H, CH<sub>2</sub>), 1.53 (s, 9H, (CH<sub>3</sub>)<sub>3</sub>).

**<sup>19</sup>F NMR** (188 MHz, CDCl<sub>3</sub>): δ = - 68.69 (s, 3F)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 167.6 (COBoc), 152.0 (CO), 136.3 (q, <sup>2</sup>J<sub>C,F</sub> = 34 Hz, C=N), 132.1 (=C), 130.1 (=CH<sub>2</sub>), 120.9 (q, <sup>1</sup>J<sub>C,F</sub> = 274 Hz, CF<sub>3</sub>), 82.2 (Cq), 52.8 (OCH<sub>3</sub>), 28.0 (CH<sub>2</sub>), 27.6 (CH<sub>3</sub>).

**HRMS (ESI+TOF)** m/z C<sub>12</sub>H<sub>17</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub> [M+Na]<sup>+</sup> calc. 333.1038, found. 333.1152

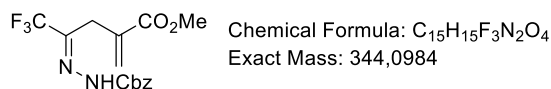






**Benzyl (E)-2-(1,1,1-trifluoro-4-(methoxycarbonyl)pent-4-en-2-ylidene)hydrazine-1-carboxylate (6b)**

The product **6b** is obtained following the general procedure (C) as a slightly yellow oil (0.470 g, 80% (I<sub>2</sub>)/82% (NBS))

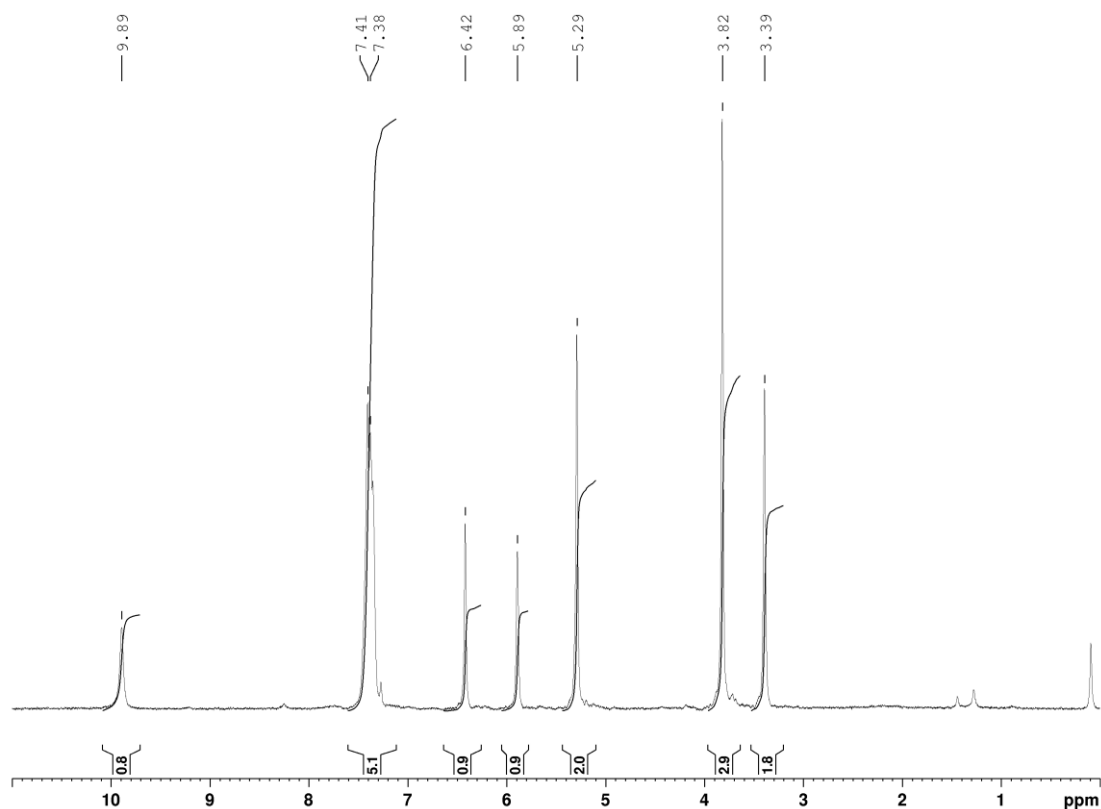


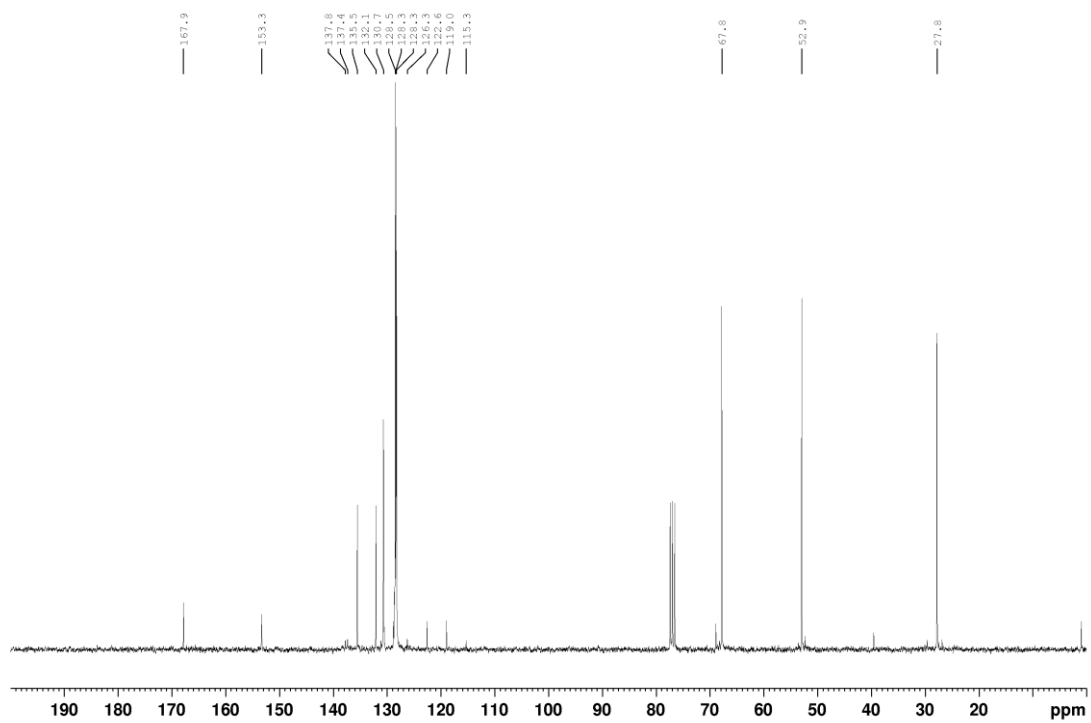
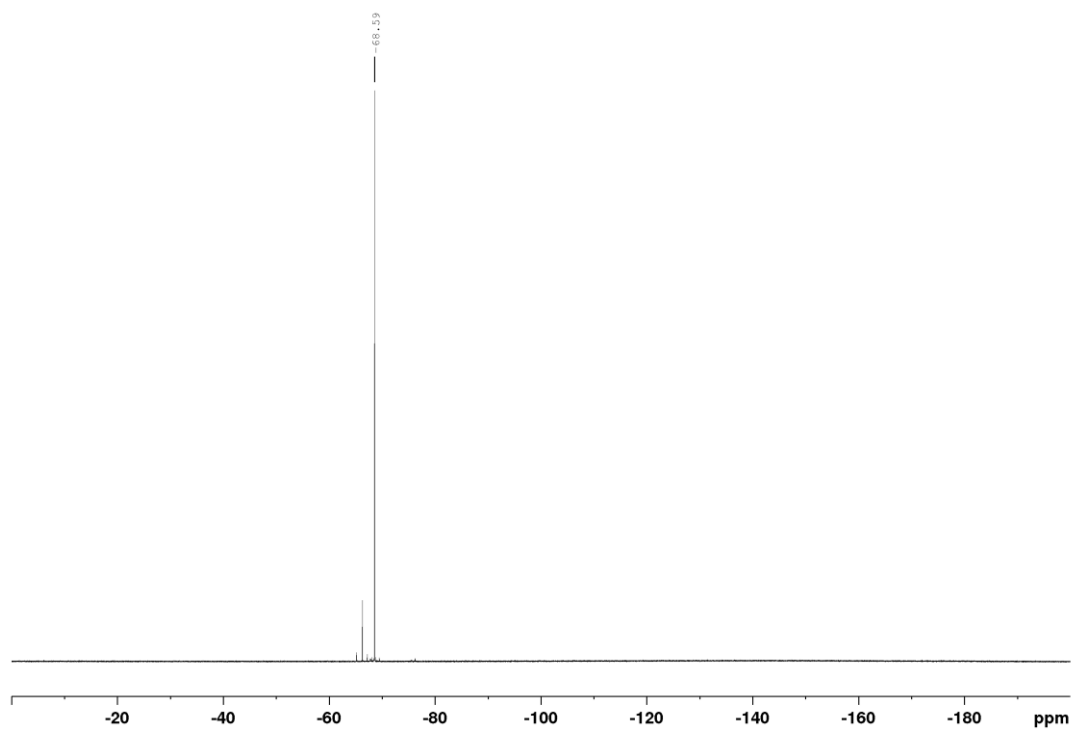
**<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>): δ 9.89 (brs, 1H, NH), 7.41-7.38 (m, 5H, Haro), 6.42 (s, 1H, =CH<sub>2</sub>), 5.89 (s, 1H, =CH<sub>2</sub>), 5.29 (s, 2H, CH<sub>2</sub>Cbz), 3.82 (s, 3H, OCH<sub>3</sub>), 3.39 (s, 2H, CH<sub>2</sub>).

**<sup>19</sup>F NMR** (188 MHz, CDCl<sub>3</sub>): δ = -68.59 (s, 3F)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 167.9 (COCbz), 153.3 (CO), 137.6 (q, <sup>2</sup>J<sub>C,F</sub> = 34 Hz, C=N), 135.5 (=C), 132.1 (=CH<sub>2</sub>), 130.7 (Caro), 128.5, 128.3, 128.2 (CHaro), 120.8 (q, <sup>1</sup>J<sub>C,F</sub> = 274 Hz, CF<sub>3</sub>), 67.8 (CH<sub>2</sub>Cbz), 52.9 (OCH<sub>3</sub>), 27.8 (CH<sub>2</sub>).

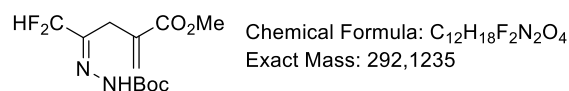
**HRMS (ESI+TOF)** m/z C<sub>15</sub>H<sub>15</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub> [M+Na]<sup>+</sup> calc. 367.0882, found. 367.0841





***tert*-Butyl (E)-2-(1,1-difluoro-4-(methoxycarbonyl)pent-4-en-2-ylidene)hydrazine-1-carboxylate (6c)**

The product **6c** is obtained following the general procedure (C) as a yellow solid (0.346 g, 69% (I<sub>2</sub>)/73% (NBS))

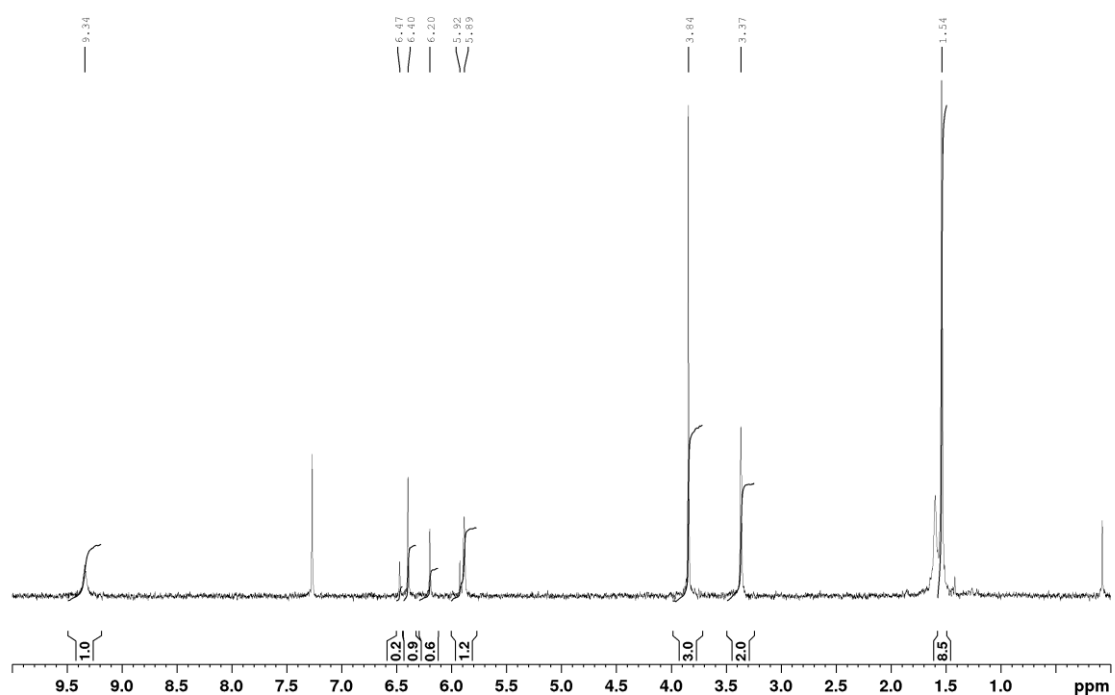


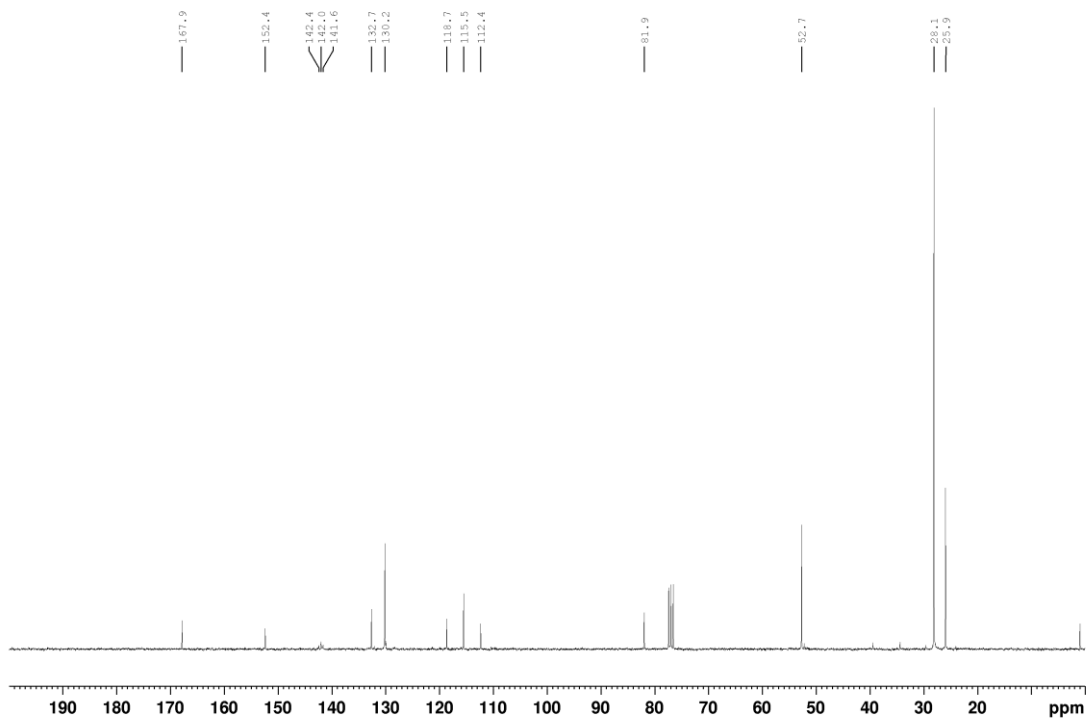
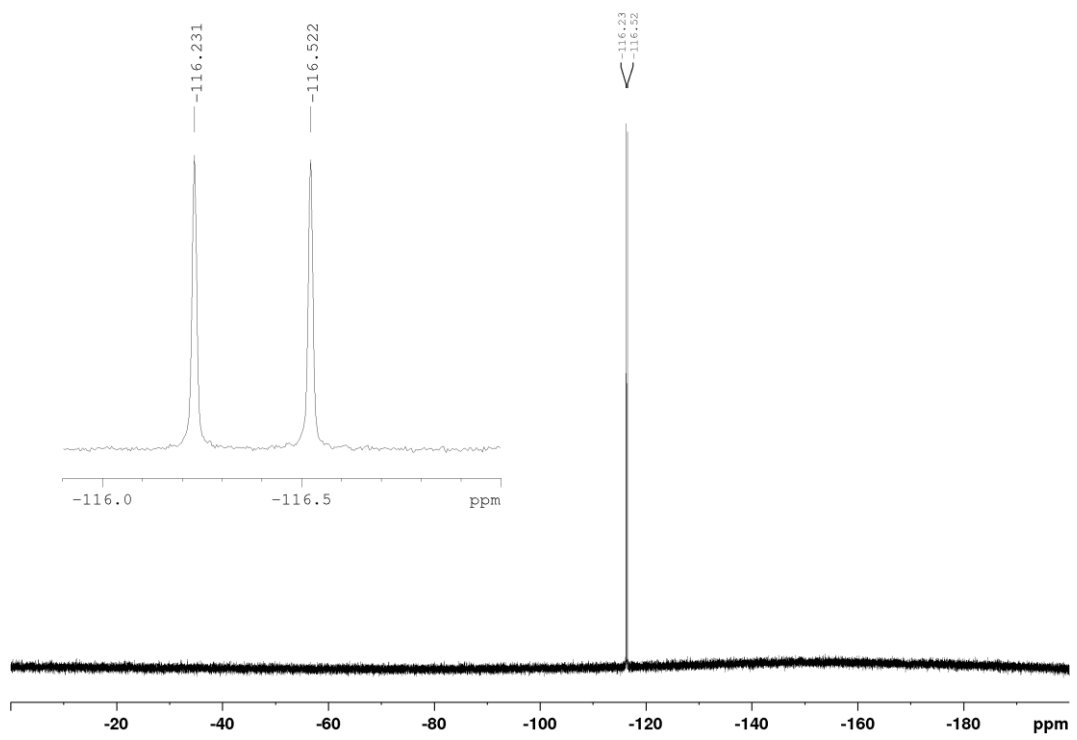
**<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>): δ = 9.34 (s, 1H, NHBoc), 6.40 (s, 1H, =CH<sub>2</sub>), 6.20 (t, <sup>2</sup>J<sub>H,F</sub> = 54 Hz, 1H, CF<sub>2</sub>H), 5.88 (s, 1H, =CH<sub>2</sub>), 3.84 (s, 3H, OCH<sub>3</sub>), 3.37 (s, 2H, CH<sub>2</sub>), 1.54 (m, 9H, (CH<sub>3</sub>)<sub>3</sub>).

**<sup>19</sup>F NMR** (188 MHz, CDCl<sub>3</sub>): δ = -116.4 (d, <sup>2</sup>J<sub>H,F</sub> = 54 Hz, 2F)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 167.9 (COBoc), 152.4 (CO), 142.0 (t, <sup>2</sup>J<sub>C,F</sub> = 29 Hz, C=N), 132.7 (=C), 130.2 (=CH<sub>2</sub>), 115.5 (t, <sup>1</sup>J<sub>C,F</sub> = 238 Hz, CF<sub>2</sub>H), 81.9 (Cq), 52.7 (OCH<sub>3</sub>), 28.1 (CH<sub>2</sub>), 25.9 (CH<sub>3</sub>).

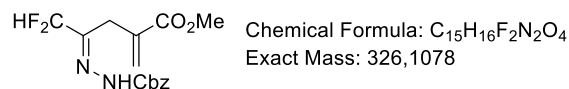
**HRMS (ESI+TOF)** m/z C<sub>12</sub>H<sub>18</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub> [M+Na]<sup>+</sup> calc. 315.1132, found. 315.1154





**Benzyl (E)-2-(1,1-difluoro-4-(methoxycarbonyl)pent-4-en-2-ylidene)hydrazine-1-carboxylate (6d)**

The product **6d** is obtained following the general procedure (C) as a yellow oil (0.222 g, 78% (I<sub>2</sub>)/76% (NBS))

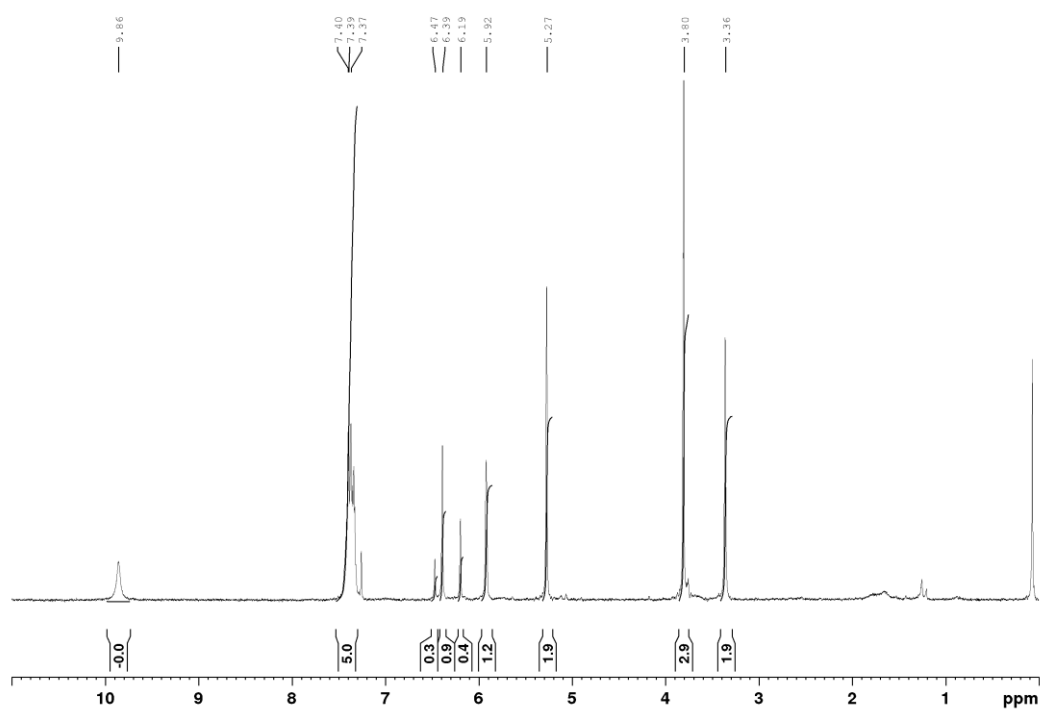


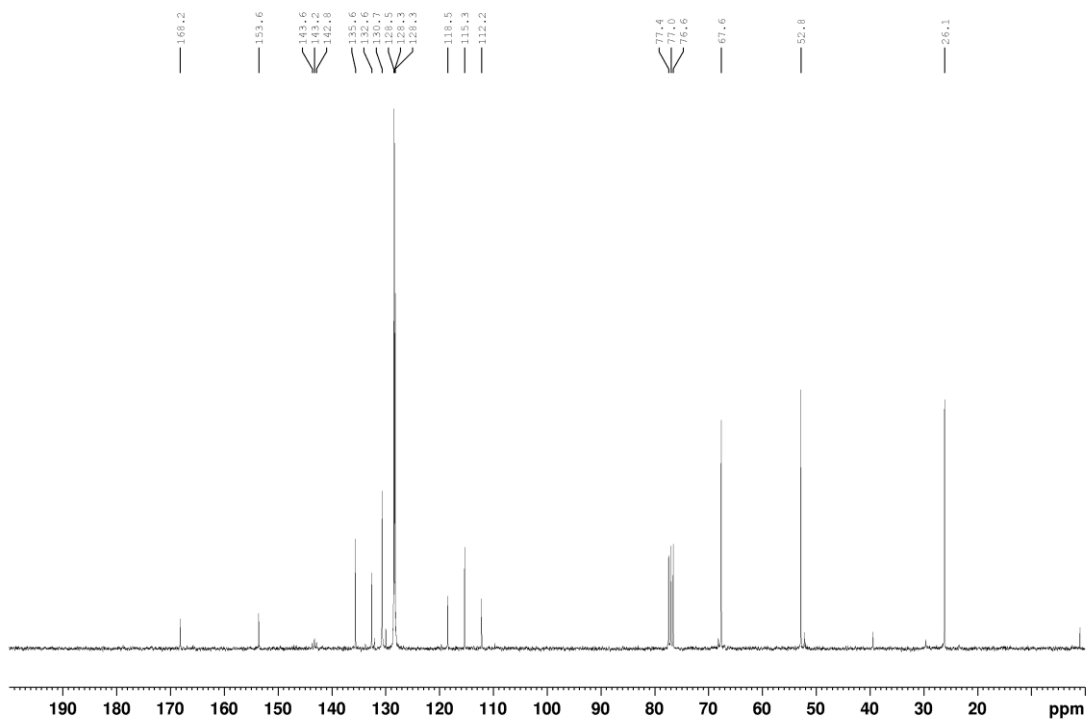
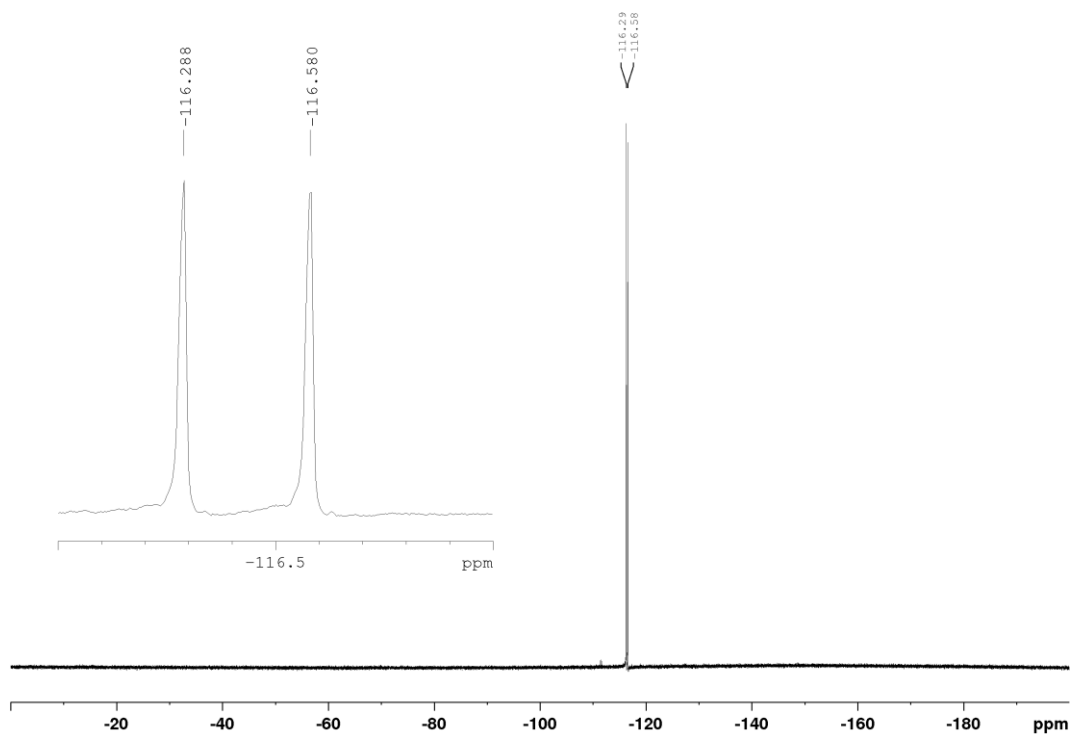
**<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>): δ = 9.86 (s, 1H, NHCbz), 7.40-7.37 (m, 5H, Haro), 6.39 (s, 1H, =CH<sub>2</sub>), 6.19 (t, <sup>2</sup>J<sub>H,F</sub> = 54 Hz, 1H, CF<sub>2</sub>H), 5.92 (s, 1H, =CH<sub>2</sub>), 5.27 (s, 2H, CH<sub>2</sub>Cbz), 3.80 (s, 3H, OCH<sub>3</sub>), 3.36 (s, 2H, CH<sub>2</sub>).

**<sup>19</sup>F NMR** (188 MHz, CDCl<sub>3</sub>): δ = -116.4 (d, <sup>2</sup>J<sub>H,F</sub> = 54 Hz, 2F)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 168.2 (COCbz), 153.6 (CO), 143.2 (t, <sup>2</sup>J<sub>C,F</sub> = 30 Hz, C=N), 135.6 (=C), 132.6 (=CH<sub>2</sub>), 130.7 (Caro), 128.5, 128.3, 128.2 (CHaro), 115.3 (t, <sup>1</sup>J<sub>C,F</sub> = 238 Hz, CF<sub>2</sub>H), 67.6 (CH<sub>2</sub>Cbz), 52.8 (OCH<sub>3</sub>), 26.1 (CH<sub>2</sub>).

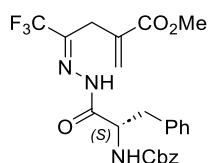
**HRMS (ESI+TOF)** m/z C<sub>15</sub>H<sub>16</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub> [M+Na]<sup>+</sup> calc. 349.0976, found. 349.0957





**Methyl (E)-4-(2-(((benzyloxy)carbonyl)-L-phenylalanyl)hydrazineylidene)-5,5,5-trifluoro-2-methylenepentanoate (6e)**

The product **6e** is obtained following the general procedure (C) as a mixture of two conformers (ratio 77/23) as a yellow oil (0.667 g, 75%).



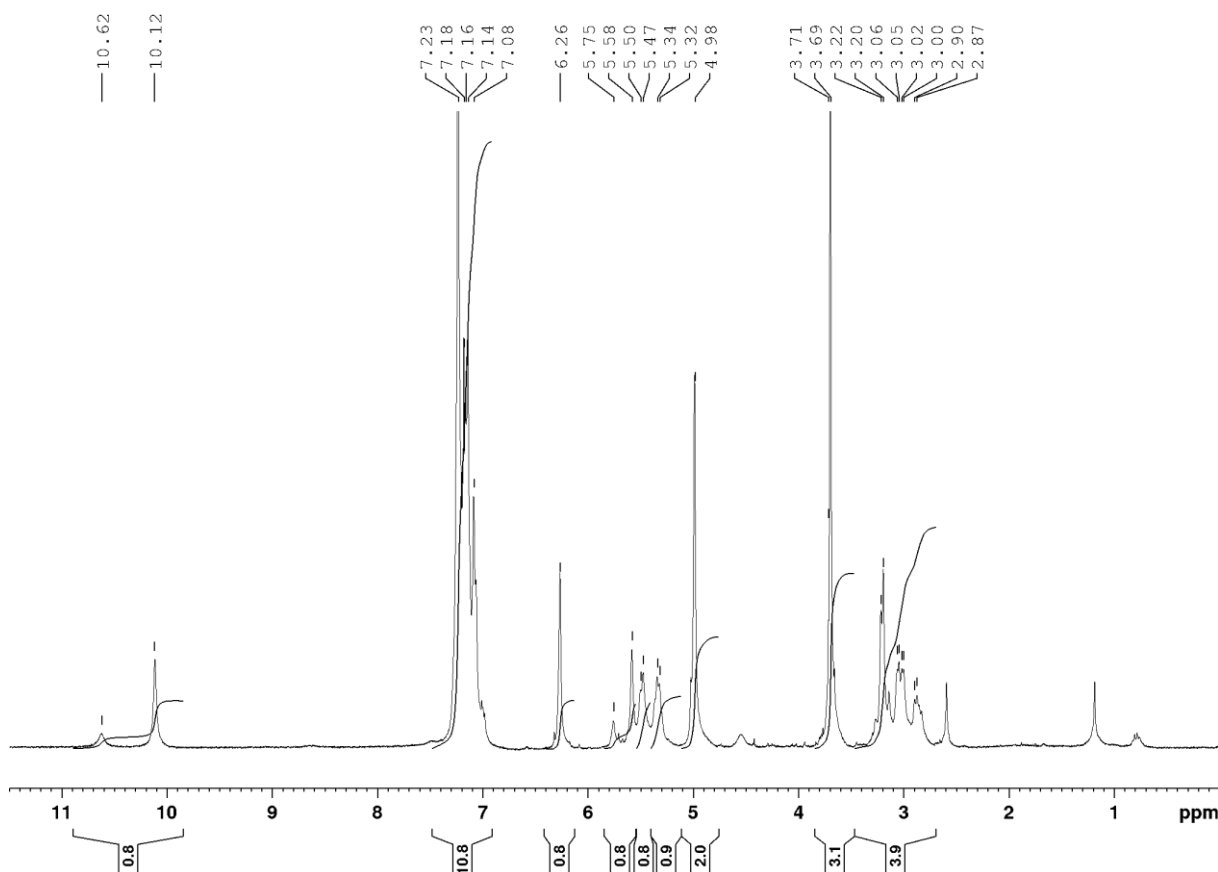
Chemical Formula:  $C_{24}H_{24}F_3N_3O_5$   
Exact Mass: 491,1668

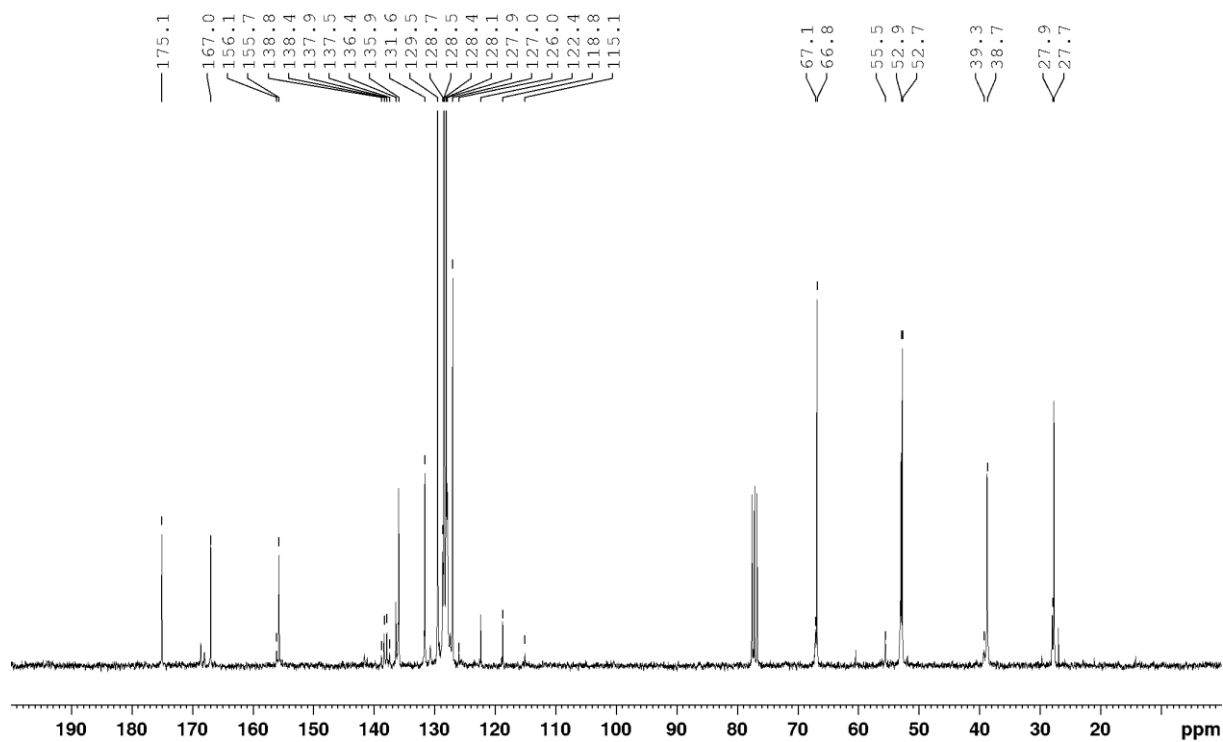
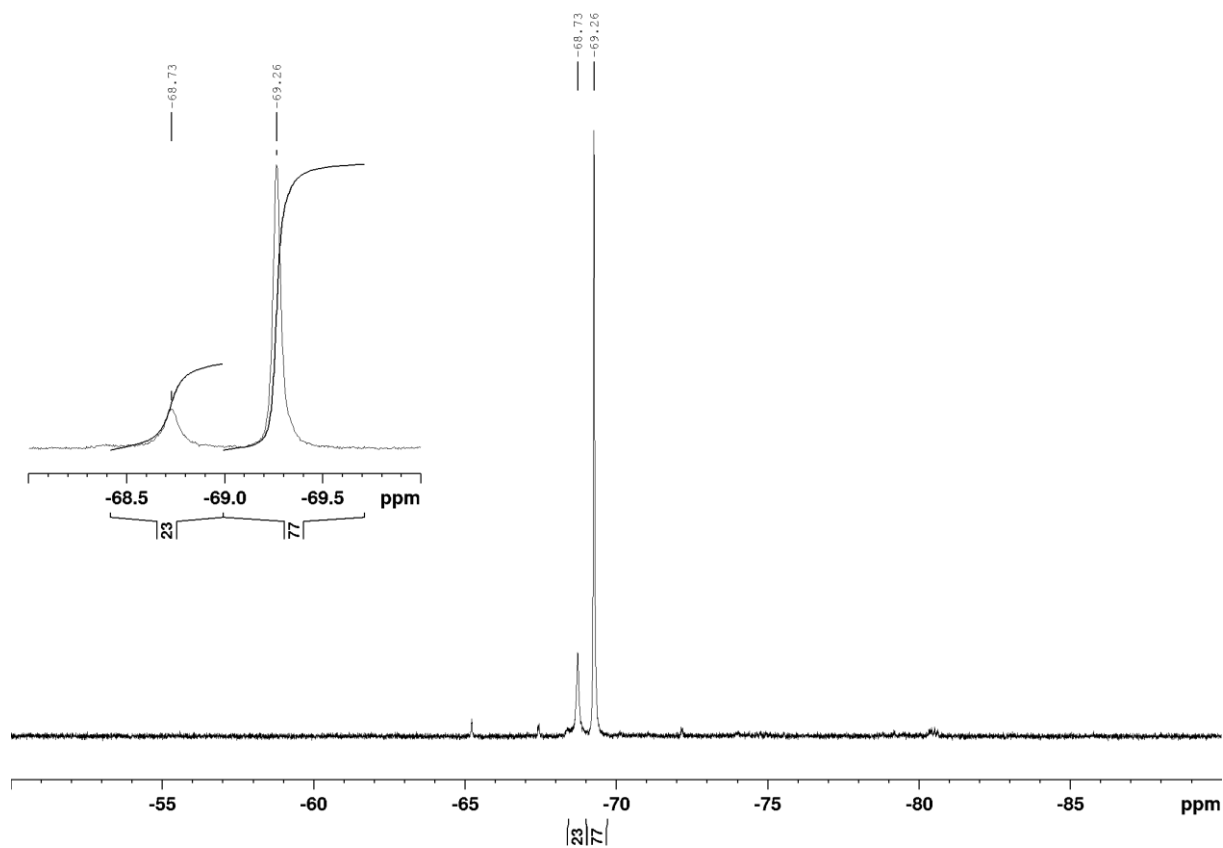
**<sup>1</sup>H NMR** (200 MHz,  $CDCl_3$ ):  $\delta$  = 10.62 and 10.12 (2brs, 0.2 and 0.8H, NHN), 7.23-7.08 (m, 10H, Haro), 6.26 (s, 1H, =CH<sub>2</sub>), 5.75 and 5.48 (2s, 0.2 and 0.8H, NHCbz), 5.58 (d, <sup>3</sup>J<sub>H,H</sub> = 7.6 Hz, 1H, =CH<sub>2</sub>), 5.33 (d, <sup>3</sup>J<sub>H,H</sub> = 6.6 Hz, 1H, CH $\alpha$ ), 4.98 (s, 2H, CH<sub>2</sub>Cbz), 3.71 and 3.69 (s, 3H, OCH<sub>3</sub>), 3.21 (d, <sup>3</sup>J<sub>H,H</sub> = 6.6 Hz, 2H, CH<sub>2</sub>), 3.03 (dd, <sup>1</sup>J<sub>H,H</sub> = 13.7 Hz, <sup>3</sup>J<sub>H,H</sub> = 5.15 Hz, 1H, CH<sub>2</sub>Ph), 2.87 (dd, <sup>1</sup>J<sub>H,H</sub> = 13.2 Hz, <sup>3</sup>J<sub>H,H</sub> = 7.96 Hz, 1H, CH<sub>2</sub>Ph).

**<sup>19</sup>F NMR** (188 MHz,  $CDCl_3$ ):  $\delta$  = -68.7(s, 3F), -69.3(s, 3F).

**<sup>13</sup>C NMR** (75 MHz,  $CDCl_3$ ):  $\delta$  = 175.1 (CONH), 167.0 (COCbz), 156.15 and 155.7 (CO), 138.2 (q, <sup>2</sup>J<sub>C,F</sub> = 36 Hz, C=N), 136.4 and 135.9 (=C), 131.6 (=CH<sub>2</sub>), 129.5 (Caro), 129.1, 128.7, 128.5, 128.4, 128.1, 127.9, 127.0 (CHaro), 120.6 (q, <sup>1</sup>J<sub>C,F</sub> = 278 Hz, CF<sub>3</sub>), 67.1 and 66.8 (CH<sub>2</sub>Cbz), 55.6 (CH $\alpha$ ), 52.9 and 52.7 (OCH<sub>3</sub>), 39.3 and 38.7 (CH<sub>2</sub>Ph), 28.0 and 27.6 (CH<sub>2</sub>).

**HRMS (ESI+TOF)** m/z  $C_{24}H_{24}F_3N_3O_5$  [M+H]<sup>+</sup> calc. 492.1741, found. 492.1748

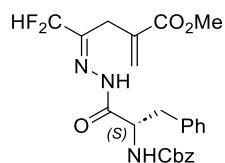






**Methyl (E)-4-(2-(((benzyloxy)carbonyl)-L-phenylalanyl)hydrazineylidene)-5,5-difluoro-2-methylenepentanoate (6f)**

The product **6f** is obtained following the general procedure (C) as a mixture of two conformers (ratio 52/48) a yellow oil (0.566 g, 69%).



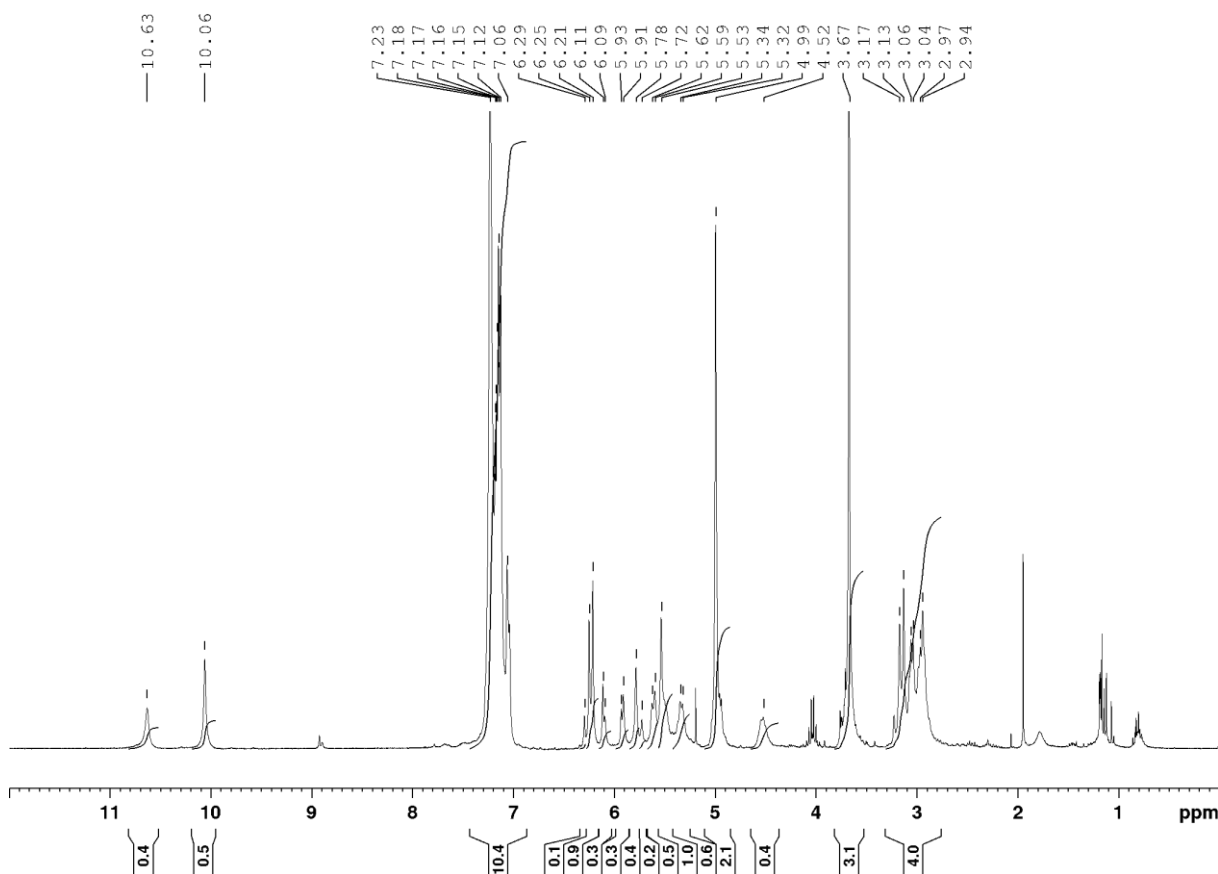
Chemical Formula: C<sub>24</sub>H<sub>25</sub>F<sub>2</sub>N<sub>3</sub>O<sub>5</sub>  
Exact Mass: 473,1762

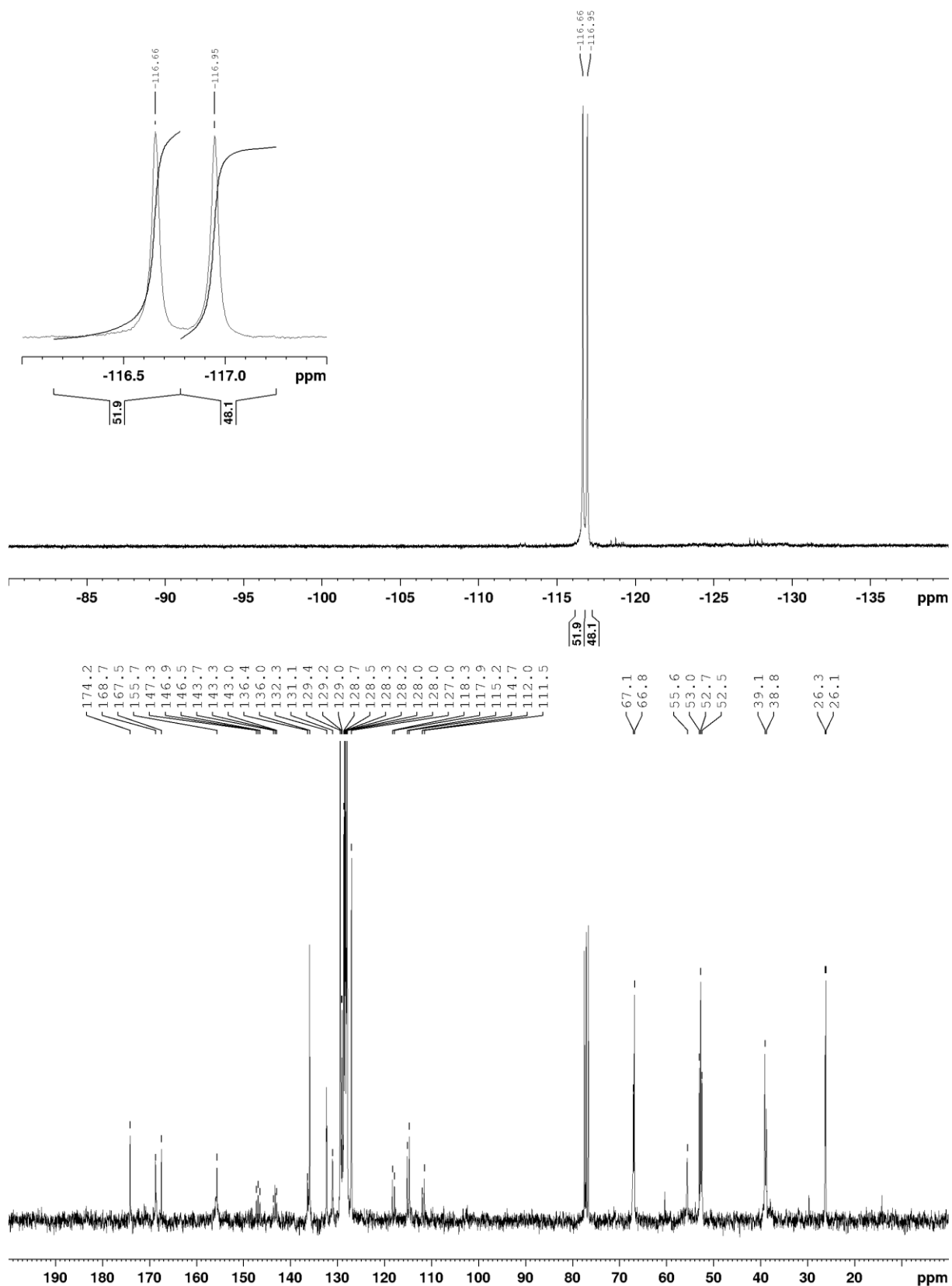
**<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>): δ = 10.63 and 10.06 (2s, 0.4 and 0.5H, NHN), 7.23-7.06 (m, 10H, Haro), 6.23 (d, <sup>3</sup>J<sub>H,H</sub> = 11.28 Hz, 1H, =CH<sub>2</sub>), 6.11 (t, <sup>2</sup>J<sub>H,F</sub> = 54 Hz, 0.5H, CF<sub>2</sub>H), 5.91 (t, <sup>2</sup>J<sub>H,F</sub> = 54 Hz, 0.5H, CF<sub>2</sub>H), 5.78 (s, 0.5H, NHCbz), 5.61 (d, <sup>3</sup>J<sub>H,H</sub> = 8.52 Hz, 0.5H, NHCbz), 5.53 (s, 1H, =CH<sub>2</sub>), 5.33 (m, 0.6H, CHα), 4.99 (s, 2H), 4.52 (m, 0.4H, CHα), 3.67 (s, 3H, OCH<sub>3</sub>), 3.15 (d, <sup>2</sup>J<sub>H,H</sub> = 12.2 Hz, 2H, CH<sub>2</sub>), 3.05 (d, <sup>3</sup>J<sub>H,H</sub> = 6.81 Hz, 1H, CH<sub>2</sub>Ph), 2.96 (d, <sup>3</sup>J<sub>H,H</sub> = 7.11 Hz, 1H, CH<sub>2</sub>Ph).

**<sup>19</sup>F NMR** (188 MHz, CDCl<sub>3</sub>): δ = -116.63 (d, <sup>2</sup>J<sub>H,F</sub> = 54 Hz, 2F), -116.59 (d, <sup>2</sup>J<sub>H,F</sub> = 54 Hz, 2F).

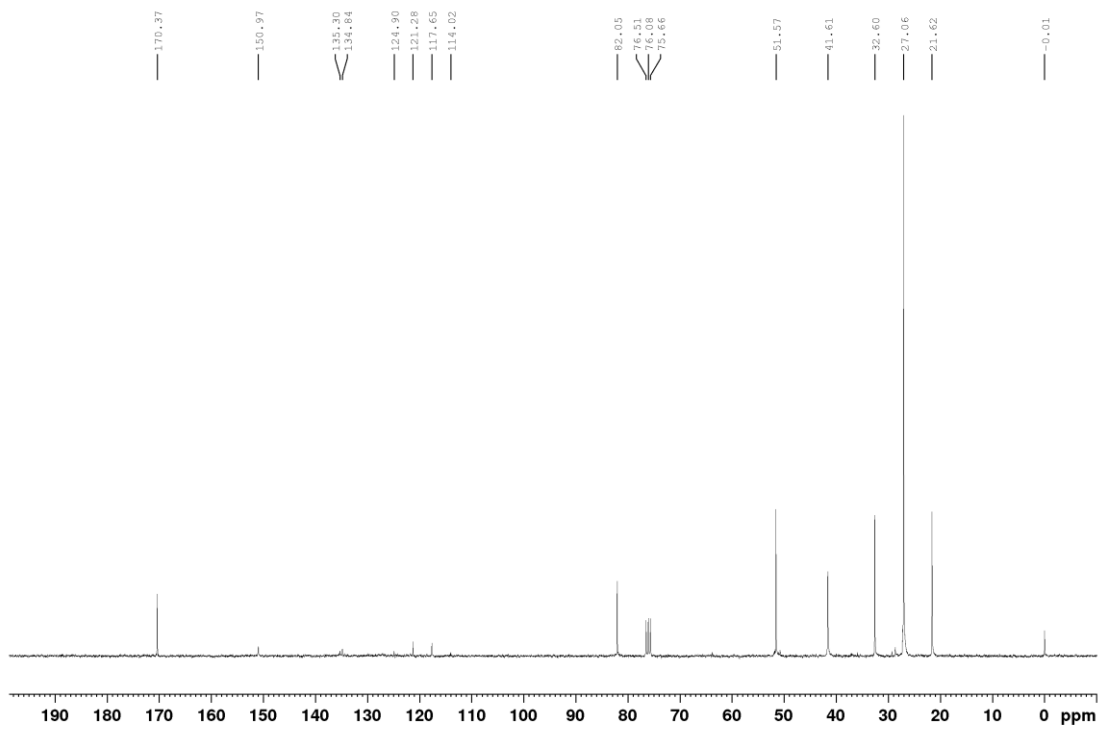
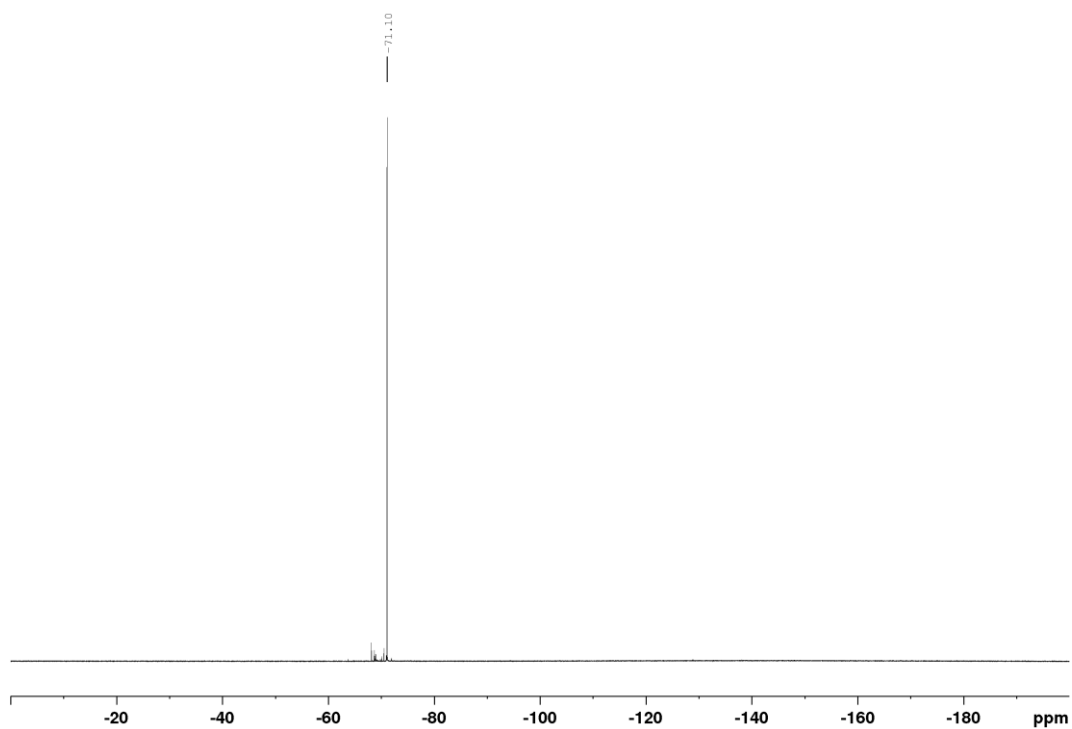
**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 174.2 (CONH), 168.7 and 167.5 (COcbz), 155.7 (CO), 146.9 (t, <sup>2</sup>J<sub>C,F</sub> = 29.6 Hz, C=N), 143.3 (t, <sup>2</sup>J<sub>C,F</sub> = 29.1 Hz, C=N), 136.4 and 136.0 (=C), 131.1 and 129.4 (=CH<sub>2</sub>), 129.2 and 129.0 (Caro), 128.7, 128.5, 128.3, 128.2, 128.1, 128.0, 127.0 (CHaro), 115.2 (t, <sup>1</sup>J<sub>C,F</sub> = 239.4 Hz, CF<sub>2</sub>H), 114.7 (t, <sup>1</sup>J<sub>C,F</sub> = 239.4 Hz, CF<sub>2</sub>H), 67.1 and 66.8 (CH<sub>2</sub>Cbz), 55.6 (CHα), 53.0 and 52.7 (OCH<sub>3</sub>), 39.1 and 38.8 (CH<sub>2</sub>Ph), 26.3 and 26.1 (CH<sub>2</sub>).

**HRMS (ESI+TOF)** m/z C<sub>24</sub>H<sub>25</sub>F<sub>2</sub>N<sub>3</sub>O<sub>5</sub> [M+Na]<sup>+</sup> calc. 496.1654, found. 496.1662



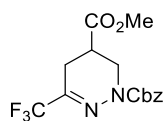






**1-Benzyl 5-methyl 3-(trifluoromethyl)-5,6-dihydropyridazine-1,5(4H)-dicarboxylate (7b)**

The product **7b** is obtained following the general procedure **D** as a yellow oil (0.396 g, 94%)



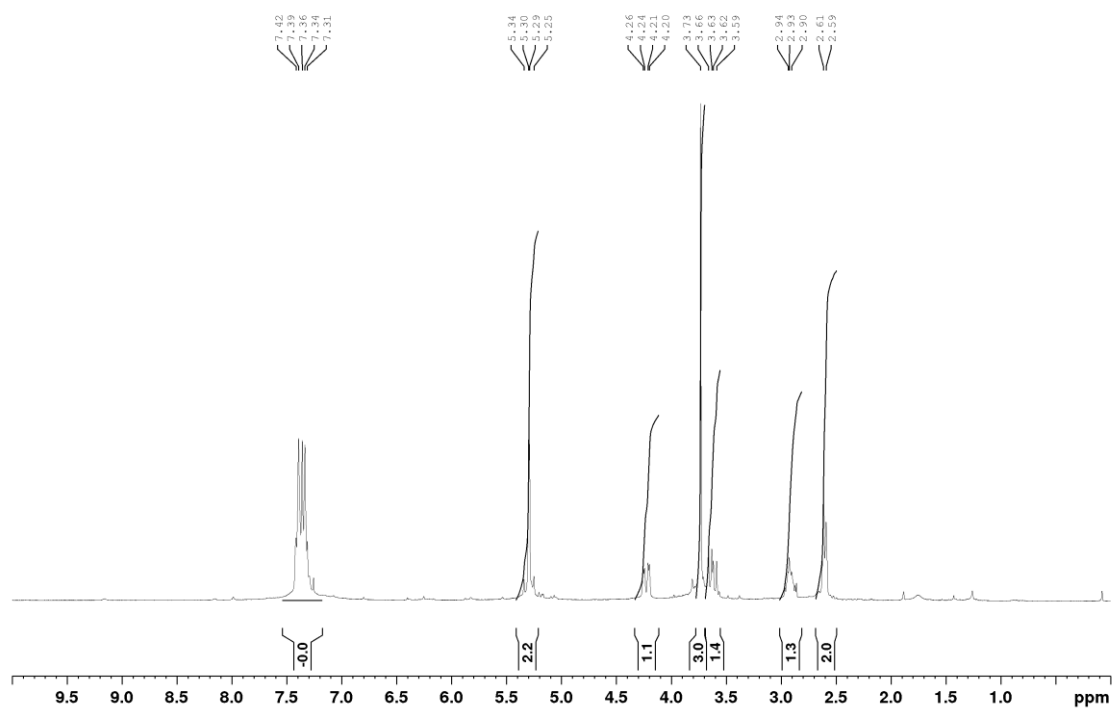
Chemical Formula: C<sub>15</sub>H<sub>15</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>  
Exact Mass: 344,0984

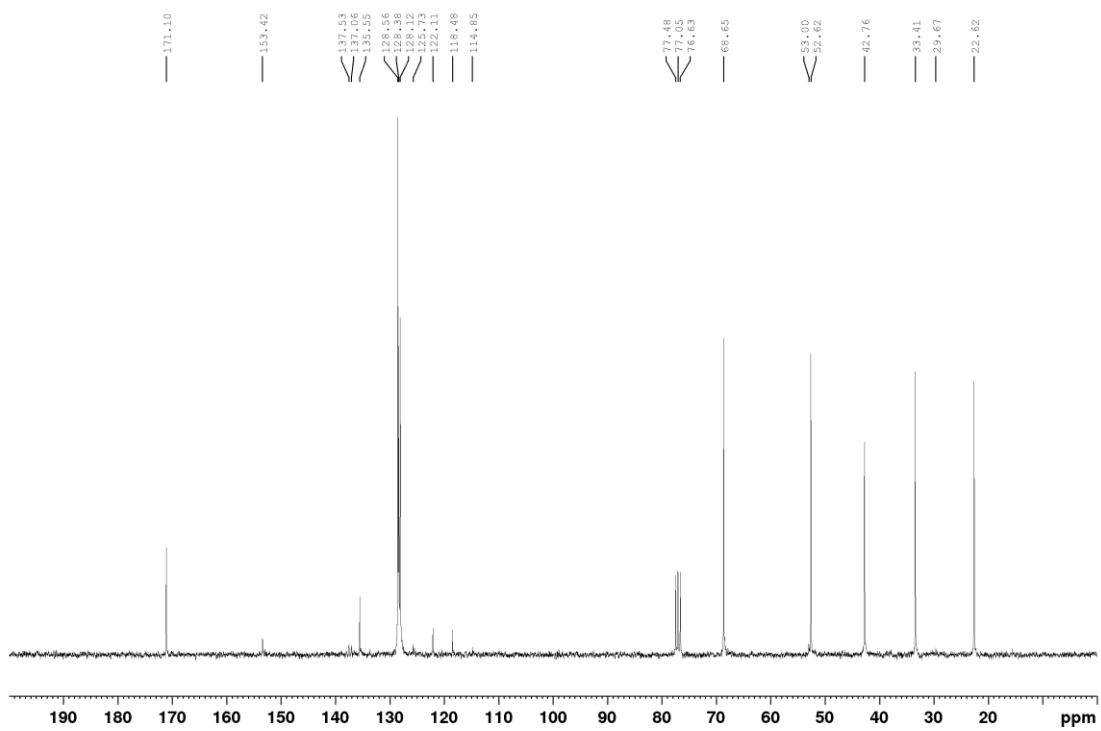
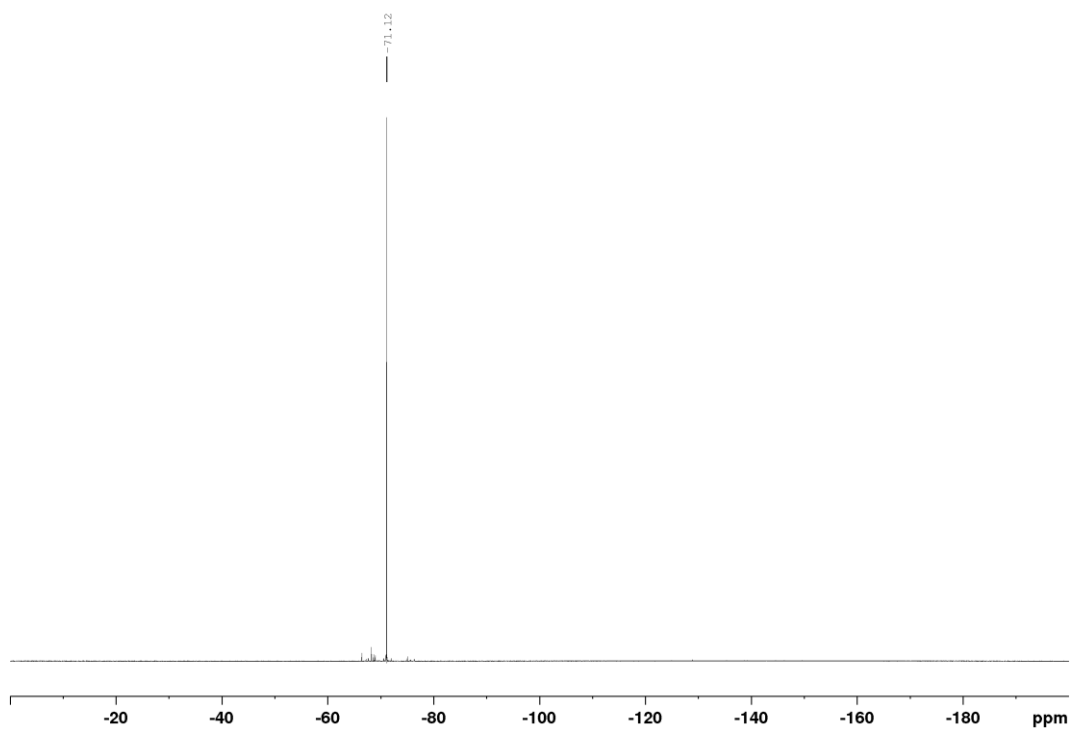
**<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>): δ = 7.42-7.31 (m, 5H, Haro), 5.32 (d, <sup>2</sup>J<sub>H,H</sub> = 12 Hz, 1H, CH<sub>2</sub>Cbz), 5.27 (d, <sup>2</sup>J<sub>H,H</sub> = 12 Hz, 1H, CH<sub>2</sub>Cbz), 4.22 (dd, <sup>2</sup>J<sub>H,H</sub> = 13 Hz, <sup>3</sup>J<sub>H,H</sub> = 4.0 Hz, 1H, CH<sub>2</sub>NCbz), 3.73 (s, 3H, OCH<sub>3</sub>), 3.62 (dd, <sup>2</sup>J<sub>H,H</sub> = 13 Hz, <sup>3</sup>J<sub>H,H</sub> = 9 Hz, 1H, CH<sub>2</sub>NCbz), 2.95 (m, 1H, CH), 2.62 (d, <sup>3</sup>J<sub>H,H</sub> = 7.3 Hz, 2H, CH<sub>2</sub>).

**<sup>19</sup>F NMR** (188 MHz, CDCl<sub>3</sub>): δ = - 71.12 (s, 3F)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 171.1 (COCbz), 153.4 (CO), 137.3 (q, <sup>2</sup>J<sub>C,F</sub> = 35 Hz, C=N), 135.6 (Caro), 128.6, 128.4, 128.1 (CHaro), 118 (q, <sup>1</sup>J<sub>C,F</sub> = 271 Hz, CF<sub>3</sub>), 68.7 (CH<sub>2</sub>Cbz), 52.6 (OCH<sub>3</sub>), 42.8 (CH<sub>2</sub>NCbz), 33.4 (CH), 22.6 (CH<sub>2</sub>).

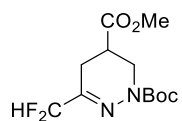
**HRMS (ESI+TOF)** m/z C<sub>15</sub>H<sub>15</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub> [M+Na]<sup>+</sup> calc. 367.0882, found. 367.0841





**1-(tert-Butyl) 5-methyl 3-(difluoromethyl)-3,4-dihydropyridazine-1,5(2H)-dicarboxylate (7c)**

The product **7c** is obtained following the general procedure **D** as an orange oil (0.286 g, 83%)



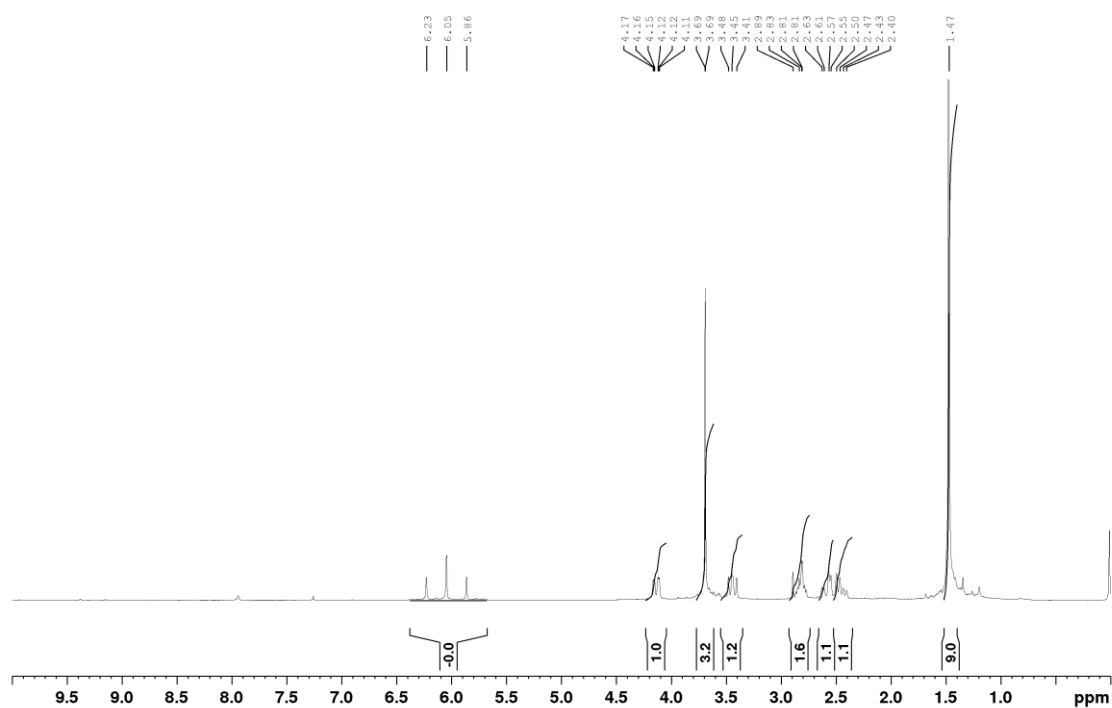
Chemical Formula: C<sub>12</sub>H<sub>18</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>  
Exact Mass: 292,1235

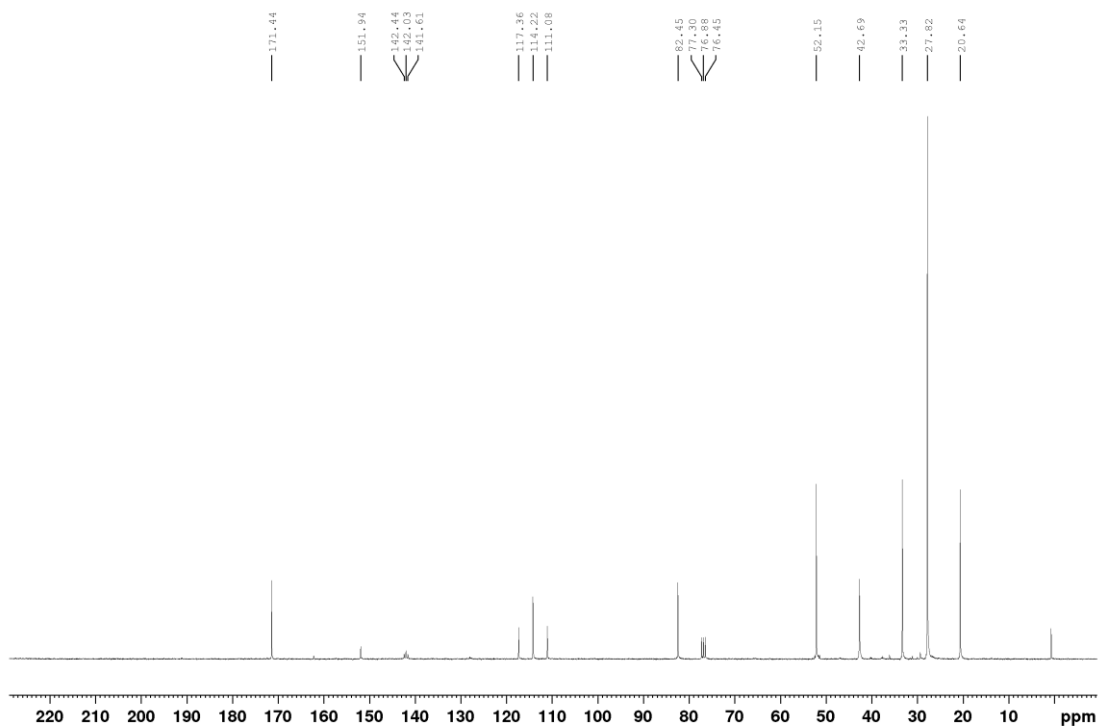
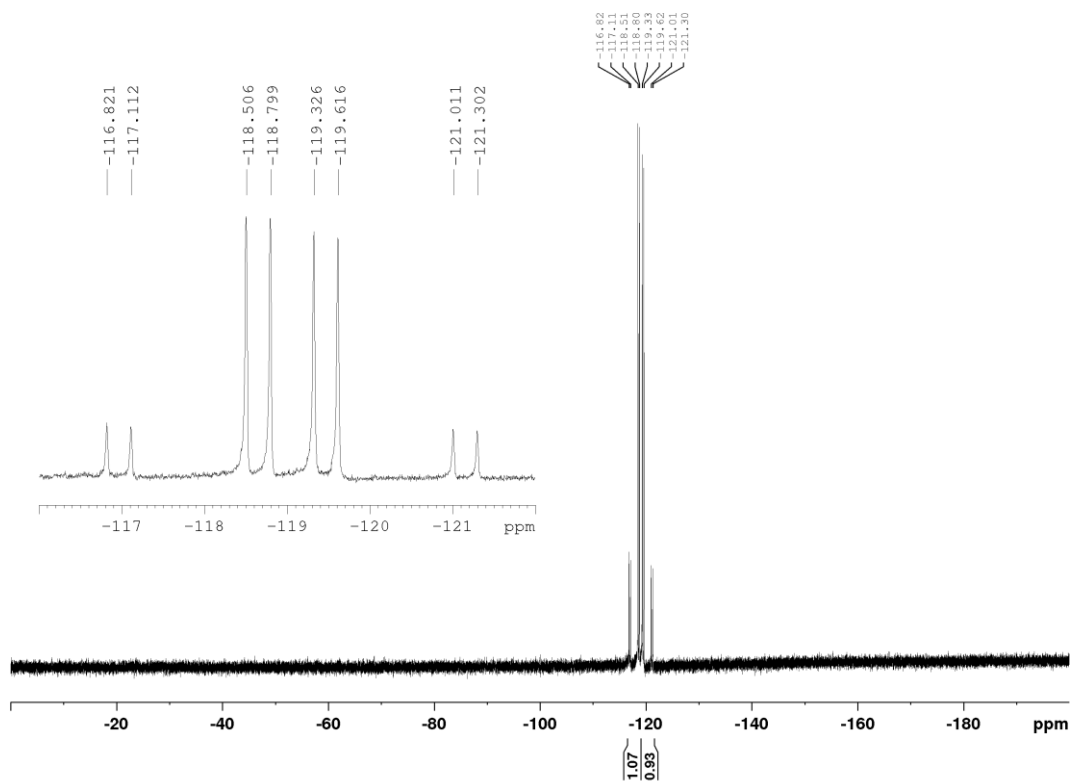
**<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>): δ = 6.04 (t, <sup>2</sup>J<sub>H,F</sub> = 54 Hz, 1H, CF<sub>2</sub>H), 4.13 (ddd, <sup>2</sup>J<sub>H,H</sub> = 13 Hz, <sup>2</sup>J<sub>H,H</sub> = 2 Hz, <sup>3</sup>J<sub>H,H</sub> = 7 Hz, 1H, CH<sub>2</sub>NBoc), 3.69 (s, 3H, OCH<sub>3</sub>), 3.44 (dd, <sup>2</sup>J<sub>H,H</sub> = 12 Hz, <sup>3</sup>J<sub>H,H</sub> = 7 Hz, 1H, CH<sub>2</sub>NBoc), 2.81 (m, 1H, CH), 2.58 (dd, <sup>2</sup>J<sub>H,H</sub> = 18 Hz, <sup>3</sup>J<sub>H,H</sub> = 6 Hz, 1H, CH<sub>2</sub>), 2.45 (dd, <sup>2</sup>J<sub>H,H</sub> = 18 Hz, <sup>3</sup>J<sub>H,H</sub> = 9 Hz, 1H, CH<sub>2</sub>), 1.47 (m, 9H, (CH<sub>3</sub>)<sub>3</sub>).

**<sup>19</sup>F NMR** (188 MHz, CDCl<sub>3</sub>): δ = -117.5 (dd, <sup>2</sup>J<sub>F,F</sub> = 317 Hz, <sup>2</sup>J<sub>H,F</sub> = 54 Hz, 1F), -120.3 (dd, <sup>2</sup>J<sub>F,F</sub> = 317 Hz, <sup>2</sup>J<sub>H,F</sub> = 54 Hz, 1F)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 171.4 (COBoc), 151.9 (CO), 142.0 (t, <sup>2</sup>J<sub>C,F</sub> = 31 Hz, C=N), 114.2 (t, <sup>1</sup>J<sub>C,F</sub> = 236 Hz, CF<sub>2</sub>H), 82.5 (Cq), 52.2 (OCH<sub>3</sub>), 42.7 (CH<sub>2</sub>NBoc), 33.3 (CH), 27.8 (CH<sub>3</sub>), 20.6 (CH<sub>2</sub>).

**HRMS (ESI+TOF)** m/z C<sub>12</sub>H<sub>18</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub> [M+Na]<sup>+</sup> calc. 315.1132, found. 315.1165

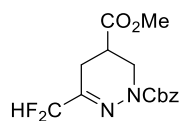






**1-Benzyl 5-methyl 3-(difluoromethyl)-5,6-dihydropyridazine-1,5(4H)-dicarboxylate (7d)**

The product **7d** is obtained following the general procedure **D** an orange oil (0.135 g, 79%)



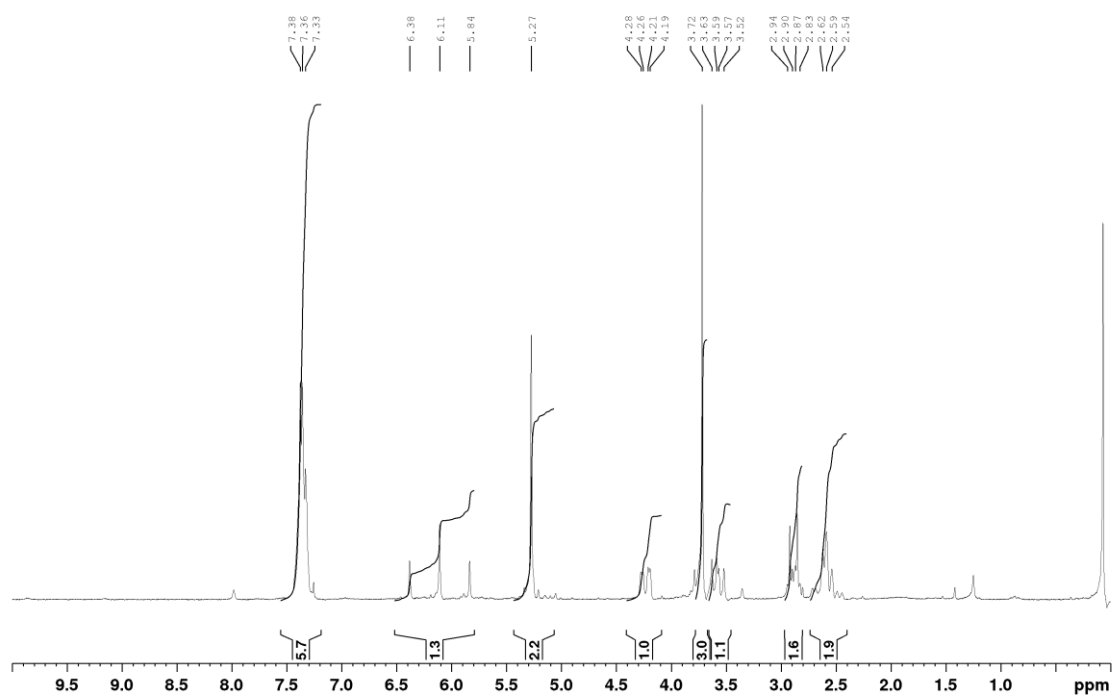
Chemical Formula: C<sub>15</sub>H<sub>16</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>  
Exact Mass: 326,1078

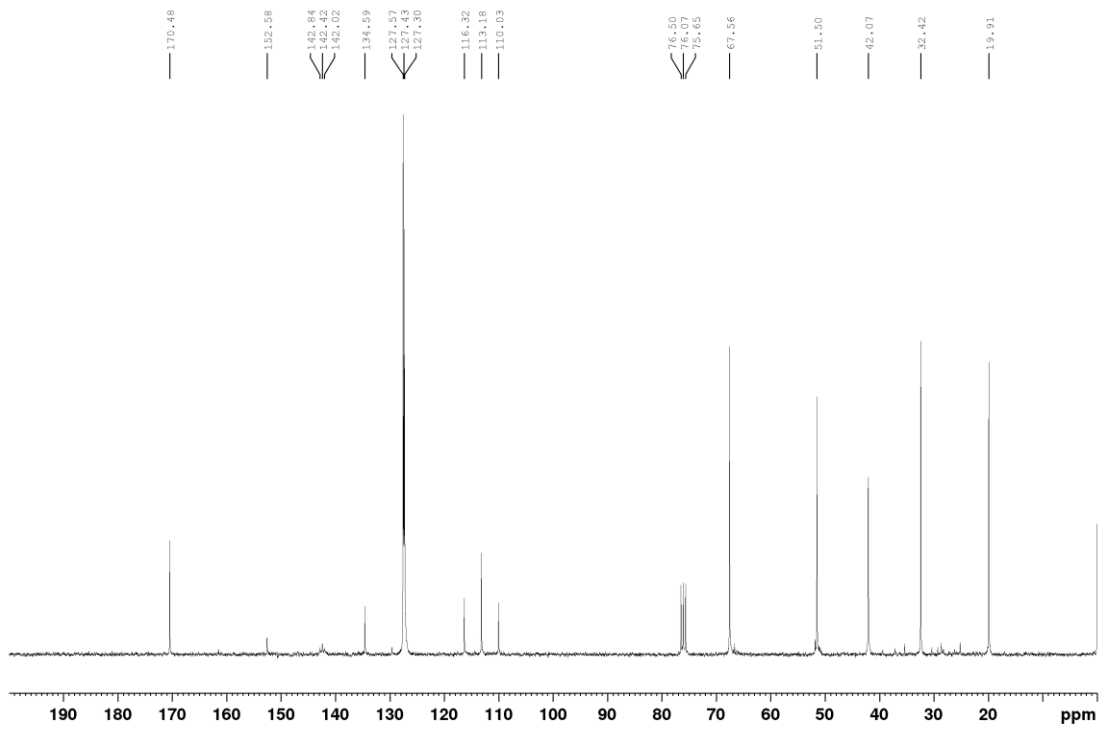
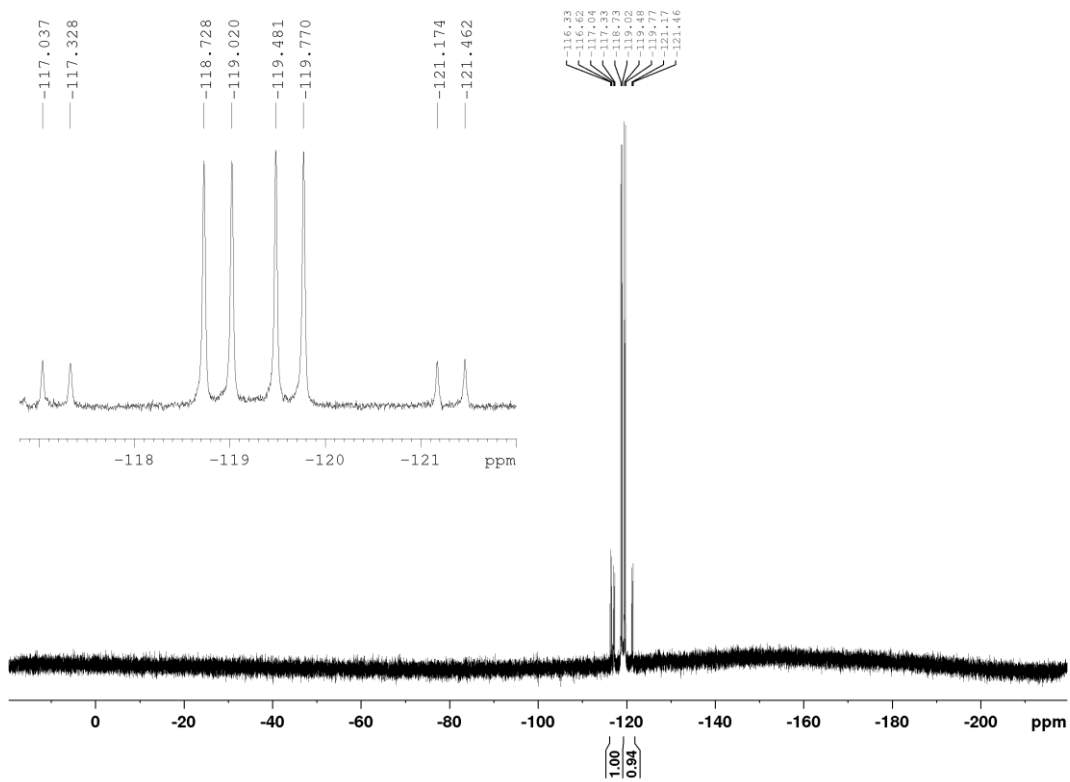
**<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>): δ = 7.38-7.33 (m, 5H, Haro), 6.11 (t, <sup>2</sup>J<sub>H,F</sub> = 54 Hz, 1H, CF<sub>2</sub>H), 5.27 (s, 2H, CH<sub>2</sub>Cbz), 4.23 (dd, <sup>2</sup>J<sub>H,H</sub> = 12 Hz, <sup>3</sup>J<sub>H,H</sub> = 4 Hz, 1H, CH<sub>2</sub>NCbz), 3.72 (s, 3H, OCH<sub>3</sub>), 3.60 (dd, <sup>2</sup>J<sub>H,H</sub> = 12 Hz, <sup>3</sup>J<sub>H,H</sub> = 9 Hz, 1H, CH<sub>2</sub>NCbz), 2.60 (m, 1H, CH), 2.87 (m, 2H, CH<sub>2</sub>),

**<sup>19</sup>F NMR** (188 MHz, CDCl<sub>3</sub>): δ = -118.0 (dd, <sup>2</sup>J<sub>H,F</sub> = 54 Hz, <sup>2</sup>J<sub>F,F</sub> = 318 Hz, 1F), -120.5 (dd, <sup>2</sup>J<sub>H,F</sub> = 54 Hz, <sup>2</sup>J<sub>F,F</sub> = 318 Hz, 1F).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 170.5 (COCbz), 152.6 (CO), 142.4 (t, <sup>2</sup>J<sub>C,F</sub> = 30 Hz, C=N), 134.6 (Caro), 127.6, 124.4, 127.3 (CHaro), 113.2 (t, <sup>1</sup>J<sub>C,F</sub> = 237 Hz, CF<sub>2</sub>H), 67.6 (CH<sub>2</sub>Cbz), 51.5 (OCH<sub>3</sub>), 42.1 (CH<sub>2</sub>NCbz), 32.4 (CH), 20.0 (CH<sub>2</sub>).

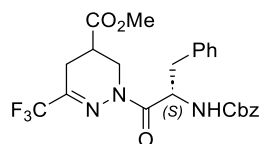
**HRMS (ESI+TOF)** m/z C<sub>15</sub>H<sub>16</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub> [M+Na]<sup>+</sup> calc. 349.0976, found. 349.0942





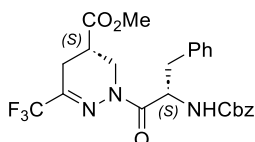
**Methyl 2-(((benzyloxy)carbonyl)-L-phenylalanyl)-6-(trifluoromethyl)-2,3,4,5-tetrahydropyridazine-4-carboxylate (7e)**

The product **7e** is obtained following the general procedure **D** as a yellow oil (0.480g, 78%).



Chemical Formula:  $C_{24}H_{24}F_3N_3O_5$   
Exact Mass: 491,1668

**Methyl (S)-2-(((benzyloxy)carbonyl)-L-phenylalanyl)-6-(trifluoromethyl)-2,3,4,5-tetrahydropyridazine-4-carboxylate (7e)**

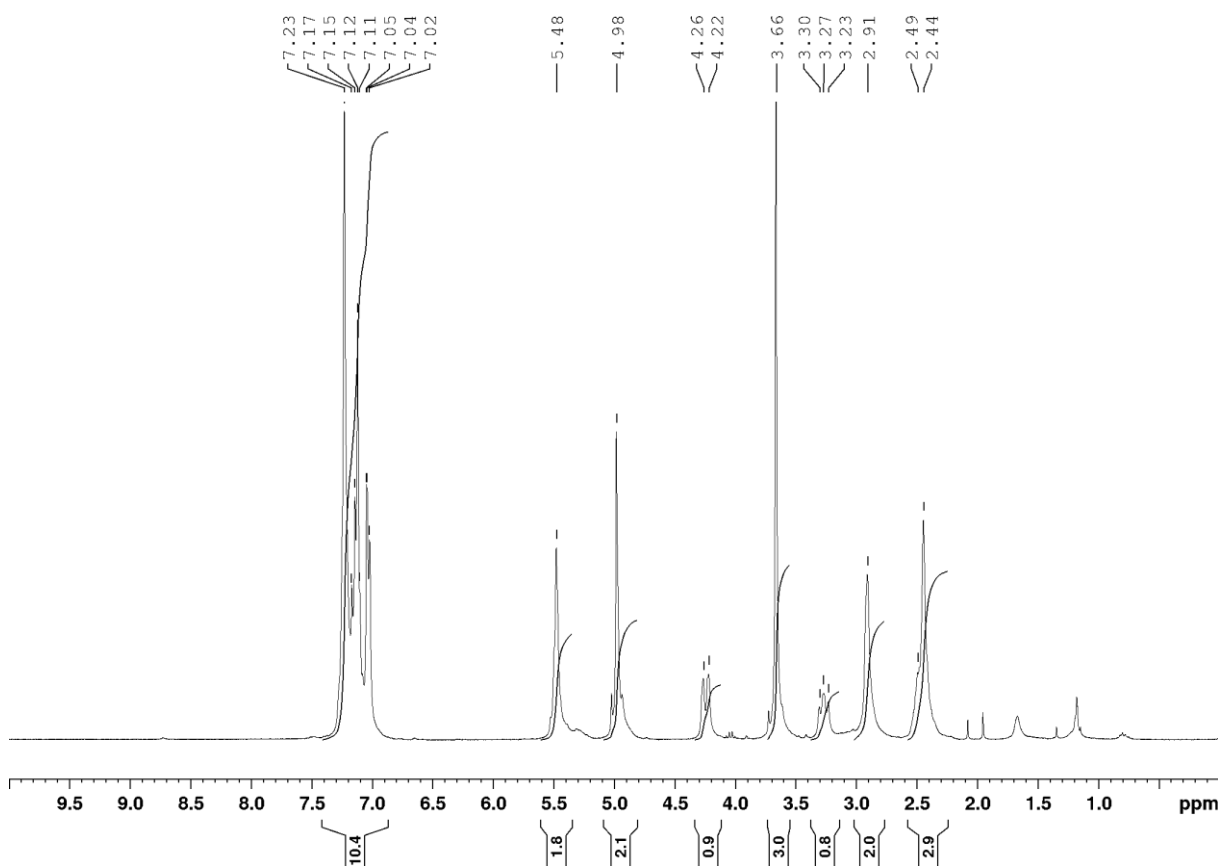


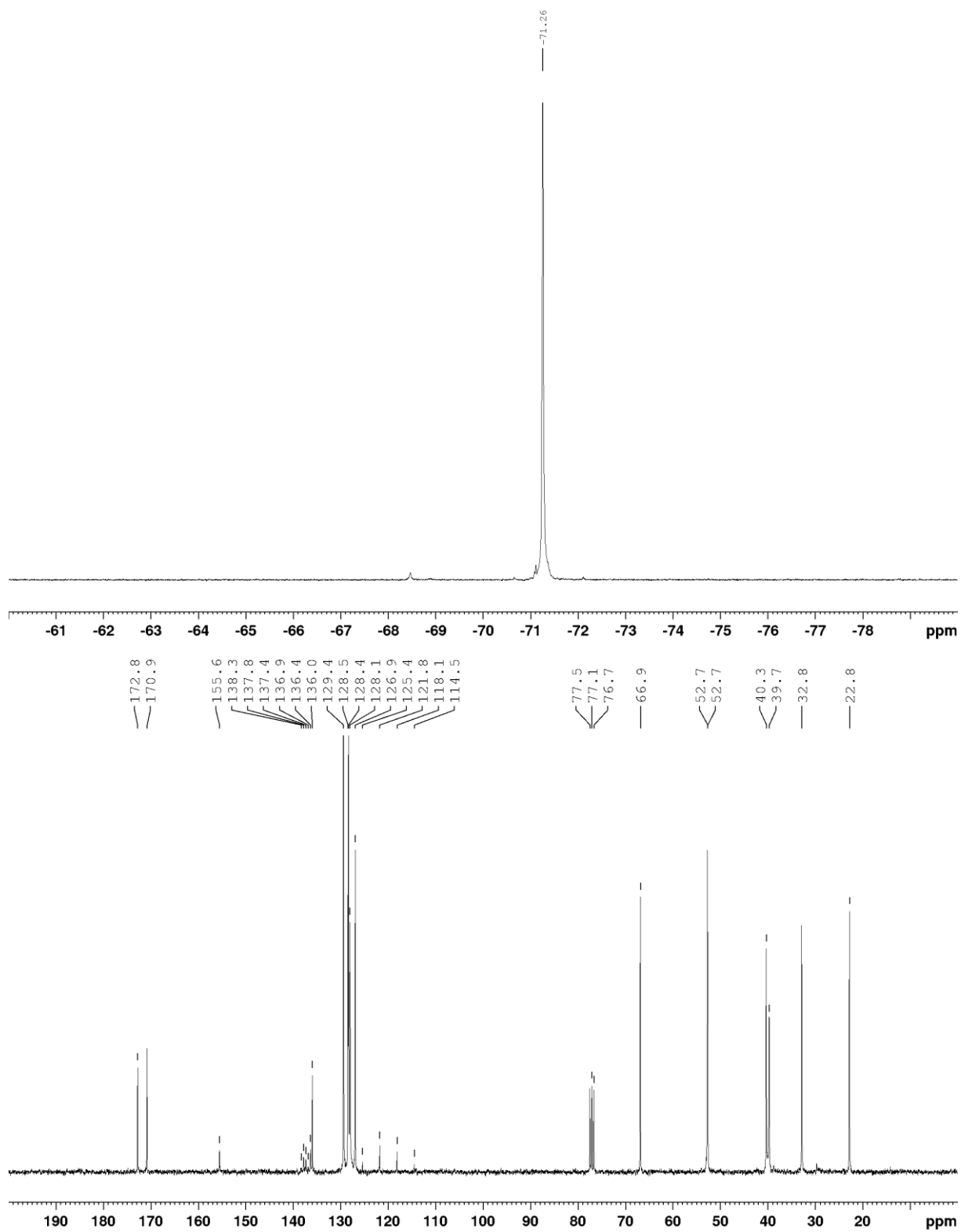
**$^1H$  NMR** (200 MHz,  $CDCl_3$ ):  $\delta$  = 7.23-7.02 (m, 10H,  $H_{arO}$ ), 5.48 (m, 2H, NHCbz and  $CH\alpha$ ), 4.98 (s, 2H,  $CH_2$ Cbz), 4.24 (d,  $^3J_{H,H}$  = 8.2 Hz, 1H,  $CH_2N$ ), 3.66 (s, 3H,  $OCH_3$ ), 3.27 (t,  $^3J_{H,H}$  = 6.4 Hz, 1H,  $CH_2N$ ), 2.91 (s, 2H,  $CH_2Ph$ ), 2.49 (m, 1H, CH), 2.44 (m, 2H,  $CH_2$ ).

**$^{19}F$  NMR** (188 MHz,  $CDCl_3$ ):  $\delta$  = - 71.26 (s, 3F).

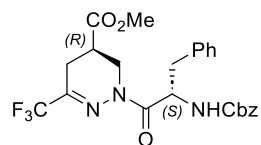
**$^{13}C$  NMR** (75 MHz,  $CDCl_3$ ):  $\delta$  = 172.8 (CON), 170.9 (COCbz), 155.6 (CO), 137.6 (q,  $^2J_{C,F}$  = 36.7 Hz, C=N), 136.4 and 136.0 (Caro), 129.4, 128.5, 128.4, 128.1, 126.9 ( $CH_{arO}$ ), 119.9 (q,  $^1J_{C,F}$  = 274 Hz,  $CF_3$ ), 66.9 ( $CH_2$ Cbz), 52.8 ( $OCH_3$ ), 52.7 ( $CH\alpha$ ), 40.3 ( $CH_2N$ ), 39.7 (CH), 32.8 ( $CH_2Ph$ ), 22.8 ( $CH_2$ ).

**HRMS (ESI+TOF)** m/z  $C_{24}H_{24}F_3N_3O_5$  [M+H]<sup>+</sup> calc.492.1740, found 492.1753.





**Methyl (R)-2-(((benzyloxy)carbonyl)-L-phenylalanyl)-6-(trifluoromethyl)-2,3,4,5-tetrahydropyridazine-4-carboxylate (7e')**

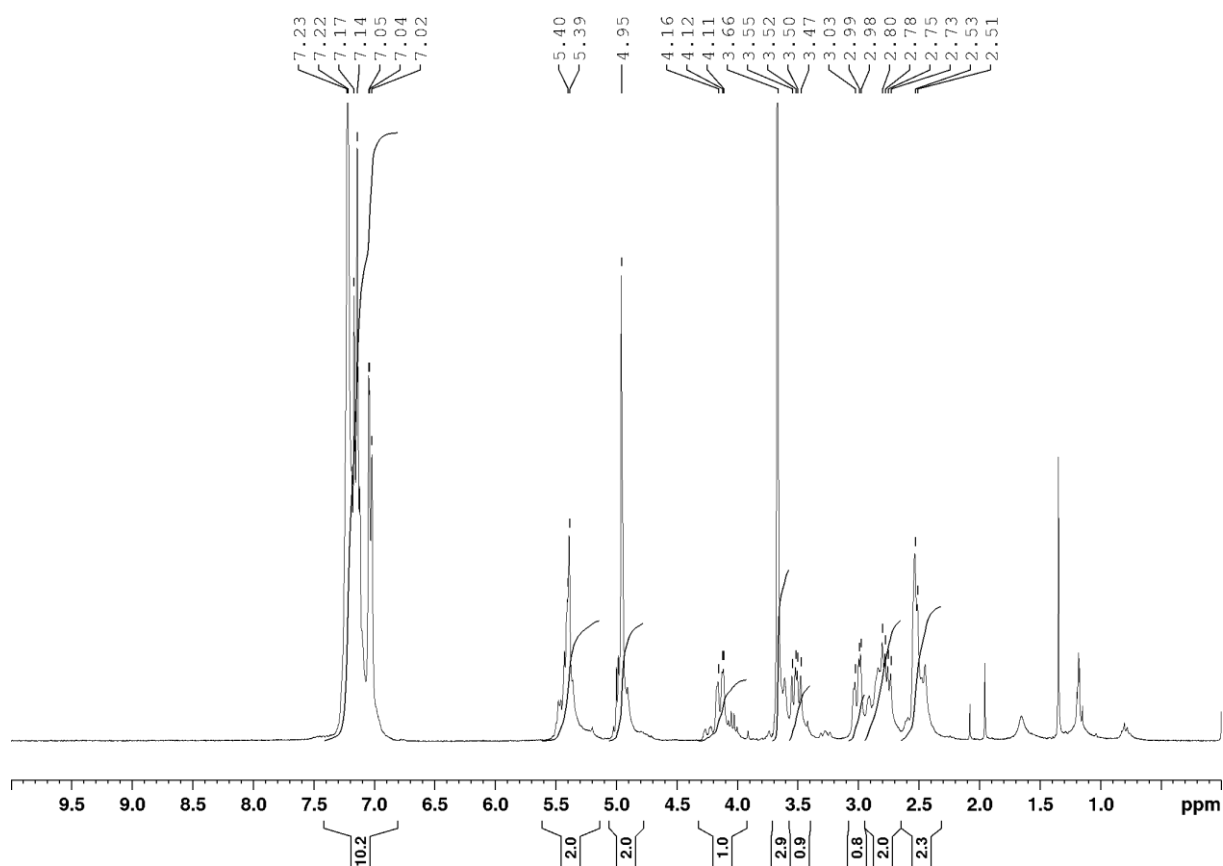


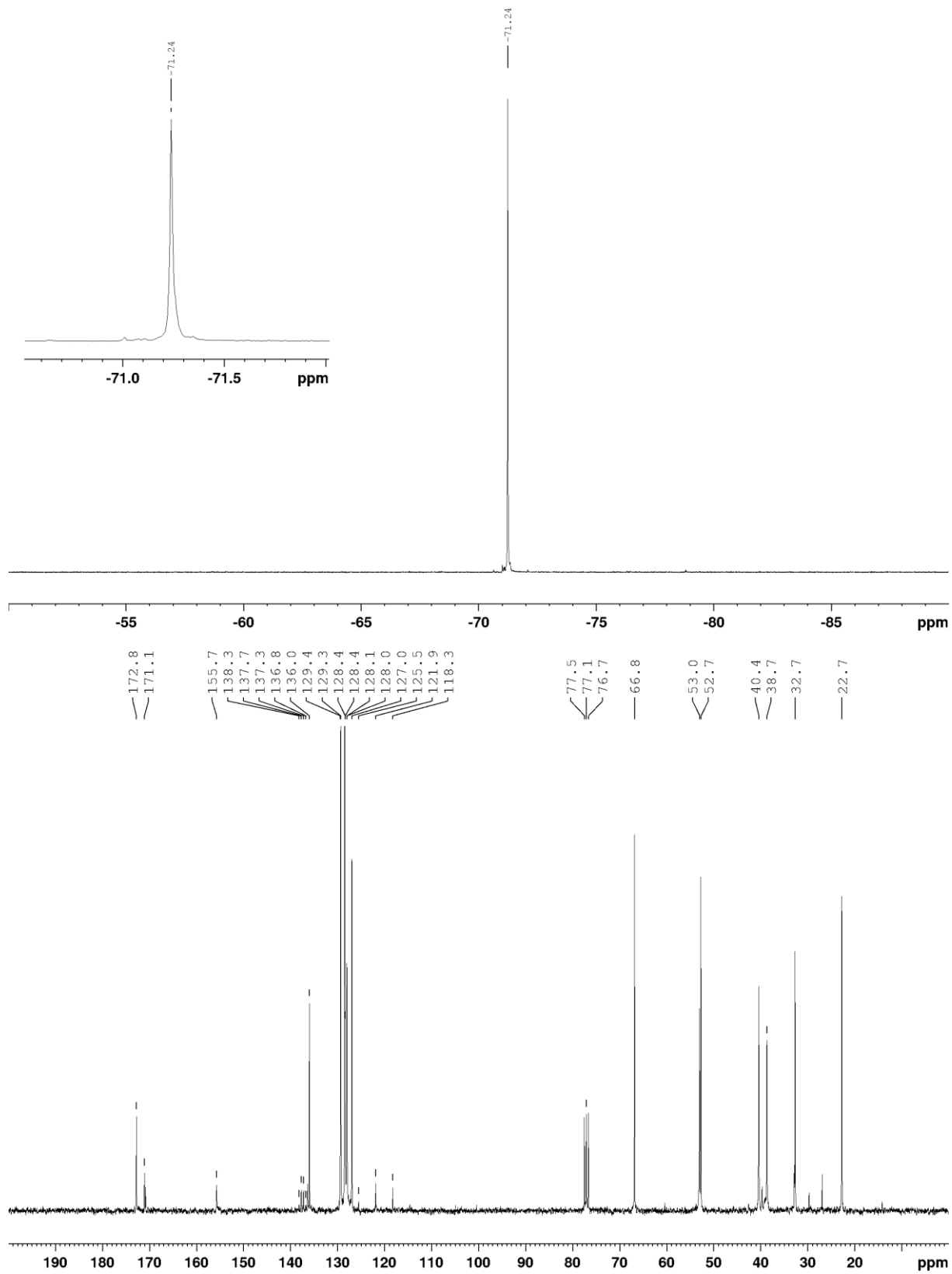
**<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>): δ = 7.23-7.02 (m, 10H, Haro), 5.40-5.39 (m, 2H, NHCbz and CH<sub>α</sub>), 4.95 (s, 2H, CH<sub>2</sub>Cbz), 4.12 (dd, <sup>2</sup>J<sub>H,H</sub> = 13.6 Hz, <sup>3</sup>J<sub>H,H</sub> = 3.1 Hz 1H, CH<sub>2</sub>N), 3.66 (s, 3H, OCH<sub>3</sub>), 3.51 (dd, <sup>2</sup>J<sub>H,H</sub> = 13.4 Hz, <sup>3</sup>J<sub>H,H</sub> = 8.6 Hz, 1H, CH<sub>2</sub>N), 3.01 (dd, <sup>2</sup>J<sub>H,H</sub> = 13.6 Hz, <sup>3</sup>J<sub>H,H</sub> = 4.0 Hz, 1H, CH<sub>2</sub>Ph), 2.87 (m, 1H, CH), 2.76 (dd, <sup>2</sup>J<sub>H,H</sub> = 13.7 Hz, <sup>3</sup>J<sub>H,H</sub> = 7.1 Hz, 1H, CH<sub>2</sub>Ph), 2.53 (m, 2H, CH<sub>2</sub>).

**<sup>19</sup>F NMR** (188 MHz, CDCl<sub>3</sub>): δ = - 71.24 (s, 3F).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 172.8 (CON), 171.1 (COCbz), 155.7 (CO), 137.5 (q, <sup>2</sup>J<sub>C,F</sub> = 35.8 Hz, C=N), 129.4 (Caro), 129.3 (Caro), 128.5, 128.4, 128.1, 128.0, 127.0 (CH<sub>ar</sub>), 120.1 (q, <sup>1</sup>J<sub>C,F</sub> = 274 Hz, CF<sub>3</sub>), 66.8 (CH<sub>2</sub>Cbz), 53.0 (OCH<sub>3</sub>), 52.7 (CH<sub>α</sub>), 40.4 (CH<sub>2</sub>N), 38.7 (CH), 32.7 (CH<sub>2</sub>Ph), 22.7 (CH<sub>2</sub>).

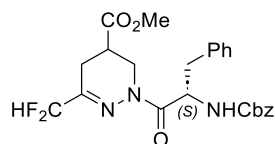
**HRMS (ESI+TOF)** m/z C<sub>24</sub>H<sub>24</sub>F<sub>3</sub>N<sub>3</sub>O<sub>5</sub> [M+H]<sup>+</sup> calc.492.1740, found 492.1732.





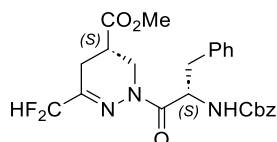
**Methyl 2-(((benzyloxy)carbonyl)-L-phenylalanyl)-6-(difluoromethyl)-2,3,4,5-tetrahydropyridazine-4-carboxylate (7f)**

The product **7f** is obtained following the general procedure **D** as a yellow oil (0.646 g, 65%).



Chemical Formula: C<sub>24</sub>H<sub>25</sub>F<sub>2</sub>N<sub>3</sub>O<sub>5</sub>  
Exact Mass: 473,1762

**Methyl (S)-2-(((benzyloxy)carbonyl)-L-phenylalanyl)-6-(difluoromethyl)-2,3,4,5-tetrahydropyridazine-4-carboxylate (7f)**

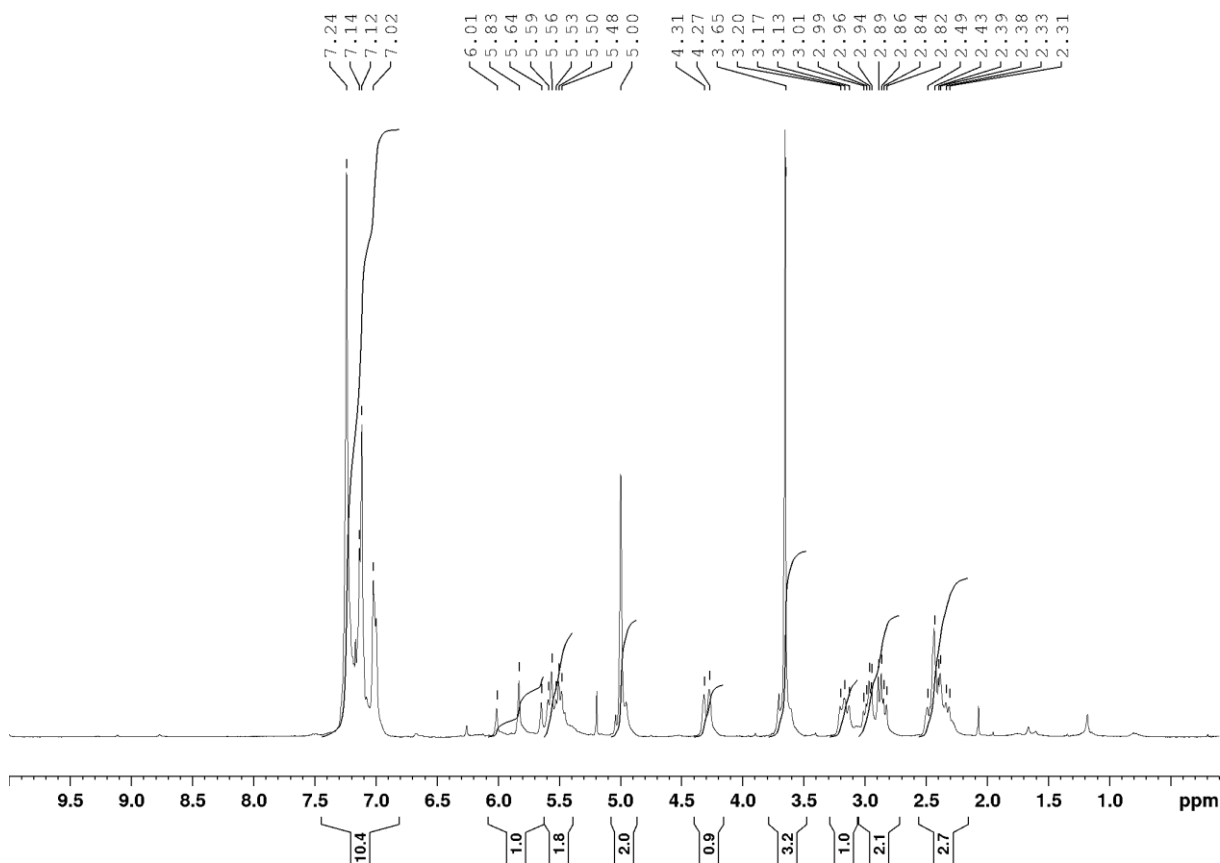


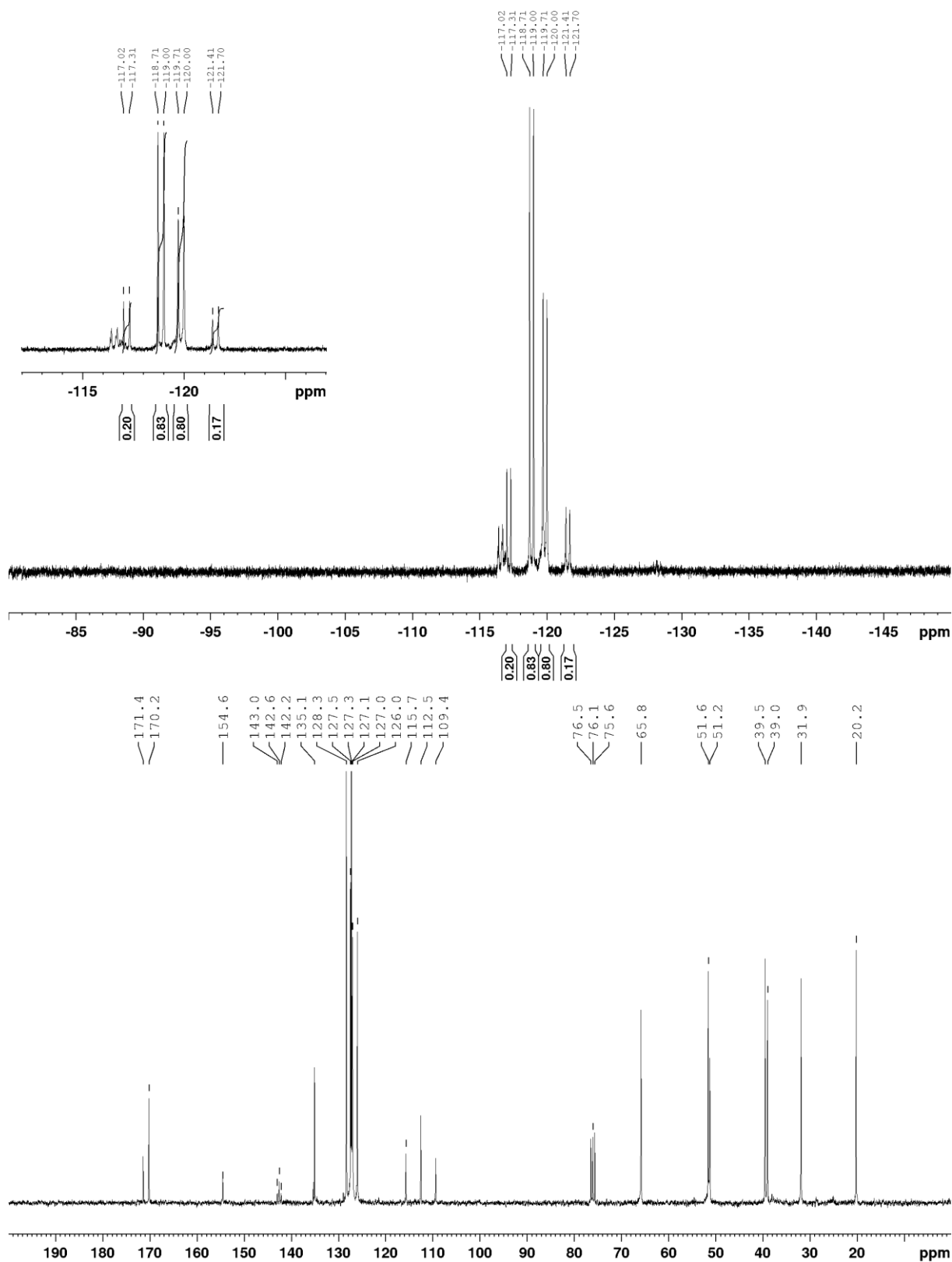
**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ = 7.24-7.02 (m, 10H, Haro), 5.83 (t, <sup>2</sup>J<sub>H,F</sub> = 54.8 Hz, 1H, CF<sub>2</sub>H), 5.57 (d, <sup>3</sup>J<sub>H,H</sub> = 8.5 Hz, 1H, NHCbz), 5.49 (q, <sup>3</sup>J<sub>H,H</sub> = 7.3 Hz, 1H, CHα), 5.00 (s, 2H, CH<sub>2</sub>Cbz), 4.29 (d, <sup>2</sup>J<sub>H,H</sub> = 14.3 Hz, 1H, CHN), 3.65 (s, 3H, OCH<sub>3</sub>), 3.16 (d, <sup>2</sup>J<sub>H,H</sub> = 11.1 Hz, 1H, CHN), 2.98 (dd, <sup>2</sup>J<sub>H,H</sub> = 13.3 Hz, <sup>3</sup>J<sub>H,H</sub> = 5.9 Hz, 1H, CH<sub>2</sub>Ph), 2.85 (dd, <sup>2</sup>J<sub>H,H</sub> = 12.9 Hz, <sup>3</sup>J<sub>H,H</sub> = 7.4 Hz, 1H, CH<sub>2</sub>Ph), 2.49-2.31 (m, 3H, CH and CH<sub>2</sub>).

**<sup>19</sup>F NMR** (188 MHz, CDCl<sub>3</sub>): δ = -118.0 (dd, <sup>2</sup>J<sub>F,F</sub> = 319 Hz, <sup>2</sup>J<sub>H,F</sub> = 54.6 Hz 1F), -120.7 (dd, <sup>2</sup>J<sub>F,F</sub> = 319 Hz, <sup>2</sup>J<sub>H,F</sub> = 55.2 Hz 1F).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 171.4 (CON), 170.2 (COCbz), 154.6 (CO), 142.6 (t, <sup>2</sup>J<sub>C,F</sub> = 31.1 Hz, C=N), 135.1, 128.4 (Caro), 127.5, 127.3, 127.1, 127.0, 125.6 (CHaro), 112.6 (t, <sup>1</sup>J<sub>C,F</sub> = 238 Hz, CF<sub>2</sub>H), 65.8 (CH<sub>2</sub>Cbz), 51.6 (CHα), 51.2 (OCH<sub>3</sub>), 39.5 (CH<sub>2</sub>N), 39.0 (CH), 31.9 (CH<sub>2</sub>Ph), 20.2 (CH<sub>2</sub>).

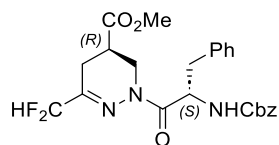
**HRMS (ESI+TOF)** m/z C<sub>24</sub>H<sub>24</sub>F<sub>3</sub>N<sub>3</sub>O<sub>5</sub> [M+H]<sup>+</sup> calc. 474.1834, found 474.1854.







**Methyl (R)-2-(((benzyloxy)carbonyl)-L-phenylalanyl)-6-(difluoromethyl)-2,3,4,5-tetrahydropyridazine-4-carboxylate (7f')**

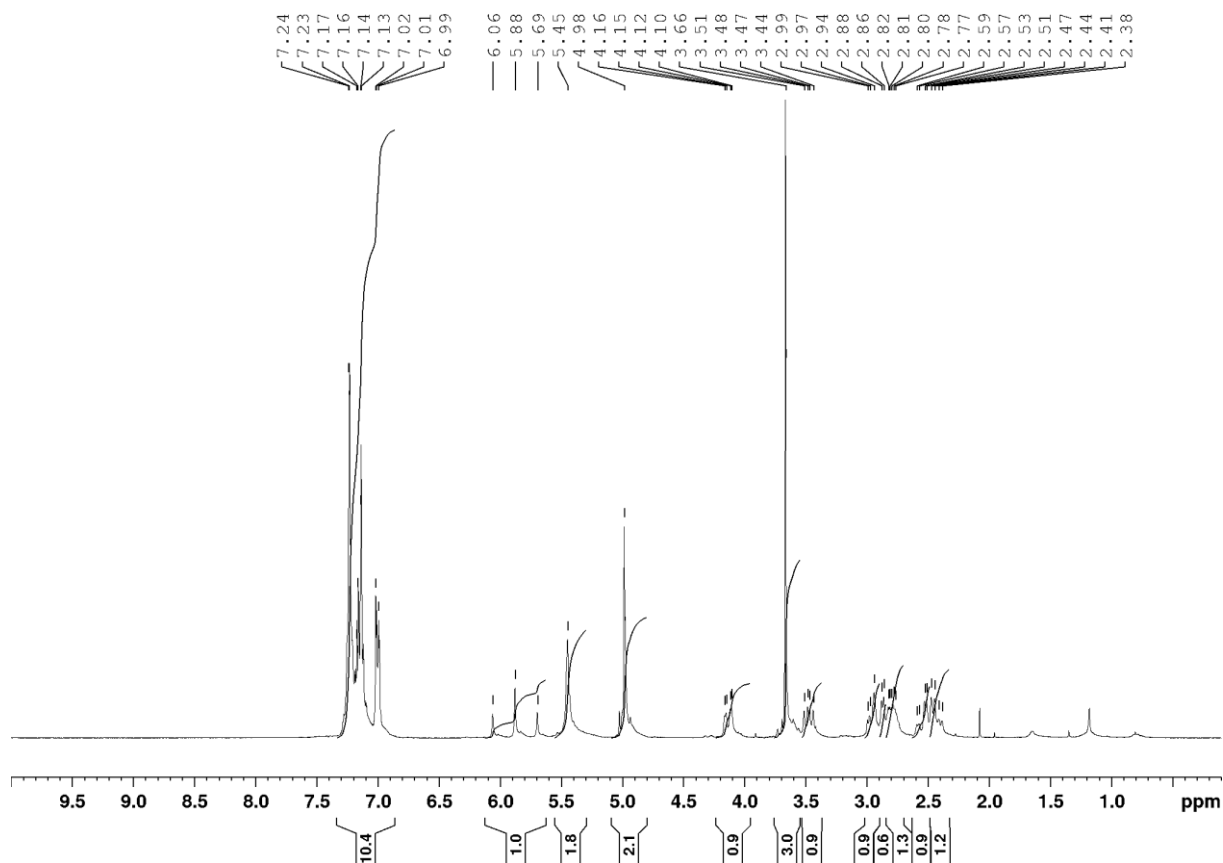


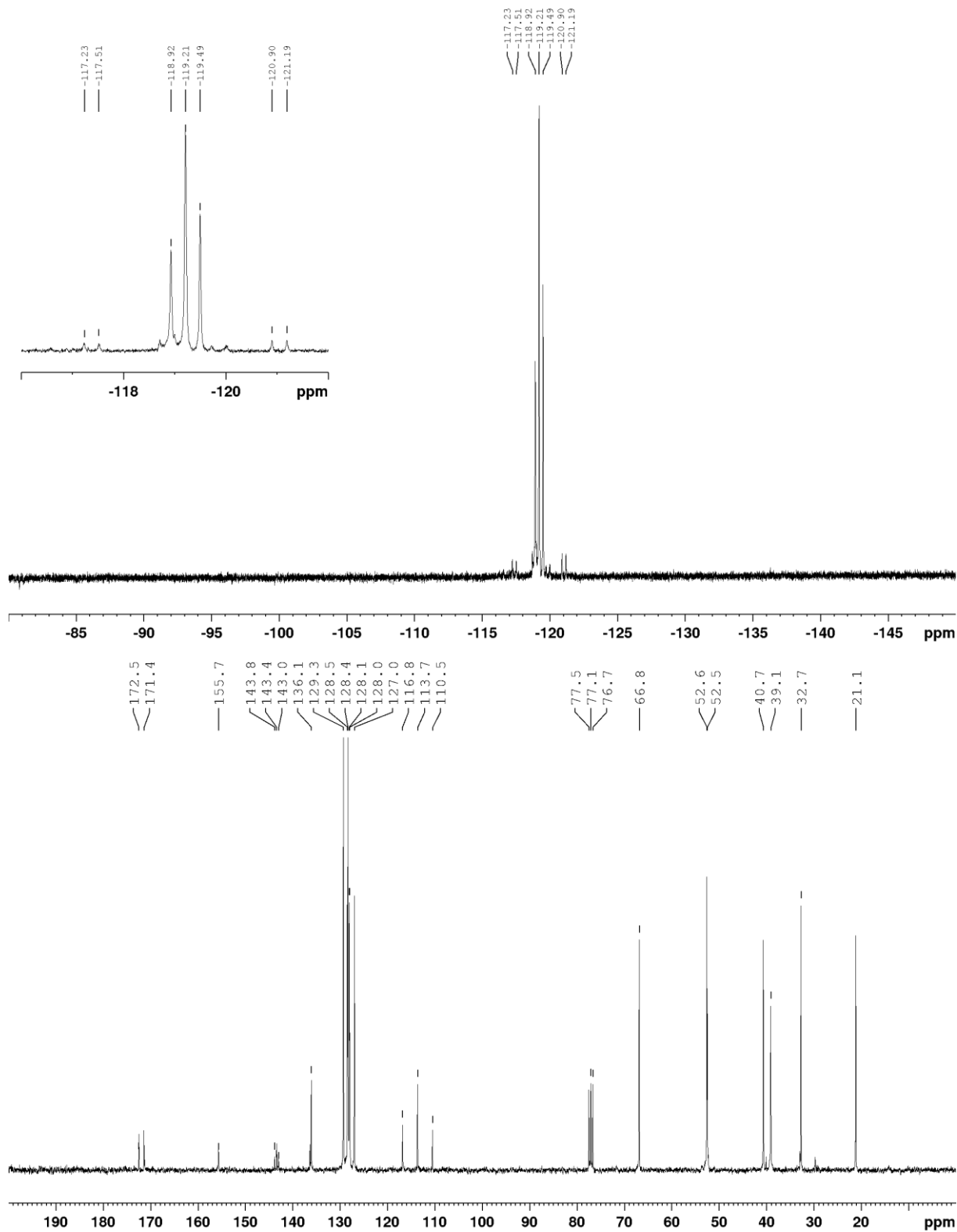
**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ = 7.24-6.99 (m, 10H, Haro), 5.88 (t, <sup>2</sup>J<sub>H,F</sub> = 54.8 Hz, 1H, CF<sub>2</sub>H), 5.45 (brs, 2H, NHCbz and CHα), 4.98 (s, 2H, CH<sub>2</sub>Cbz), 4.13 (dd, <sup>2</sup>J<sub>H,H</sub> = 13.4 Hz, <sup>3</sup>J<sub>H,H</sub> = 3.3 Hz, 1H, CH<sub>2</sub>N), 3.66 (s, 3H, OCH<sub>3</sub>), 3.47 (dd, <sup>2</sup>J<sub>H,H</sub> = 13.4 Hz, <sup>3</sup>J<sub>H,H</sub> = 8.8 Hz, 1H, CH<sub>2</sub>N), 2.95 (m, 1H, CH<sub>2</sub>Ph), 2.86 (d, <sup>3</sup>J<sub>H,H</sub> = 5.9 Hz, 1H, CH<sub>2</sub>Ph), 2.79 (m, 1H, CH), 2.55 (dd, <sup>2</sup>J<sub>H,H</sub> = 18.6 Hz, <sup>3</sup>J<sub>H,H</sub> = 5.3 Hz, 1H, CH<sub>2</sub>), 2.43 (dd, <sup>2</sup>J<sub>H,H</sub> = 18.4 Hz, <sup>3</sup>J<sub>H,H</sub> = 8.1 Hz, 1H, CH<sub>2</sub>).

**<sup>19</sup>F NMR** (188 MHz, CDCl<sub>3</sub>): δ = -118.2 (dd, <sup>2</sup>J<sub>F,F</sub> = 319 Hz, <sup>2</sup>J<sub>H,F</sub> = 54.1 Hz 1F), -120.2 (dd, <sup>2</sup>J<sub>F,F</sub> = 319 Hz, <sup>2</sup>J<sub>H,F</sub> = 54.3 Hz 1F).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 172.5 (CON), 171.4 (COCbz), 155.7 (CO), 143.4 (t, <sup>2</sup>J<sub>C,F</sub> = 31.2 Hz, C=N), 136.1, 129.3 (Caro), 128.5, 128.4, 128.1, 128.0, 127.0 (CHaro), 113.7 (t, <sup>1</sup>J<sub>C,F</sub> = 238 Hz, CF<sub>2</sub>H), 66.9 (CH<sub>2</sub>Cbz), 52.6 (CHα), 52.5 (OCH<sub>3</sub>), 40.7 (CH<sub>2</sub>N), 39.1 (CH), 32.7 (CH<sub>2</sub>Ph), 21.1 (CH<sub>2</sub>).

**HRMS (ESI+TOF)** m/z C<sub>24</sub>H<sub>25</sub>F<sub>5</sub>N<sub>3</sub>O<sub>5</sub> [M+H]<sup>+</sup> calc. 474.1834, found 474.1838.

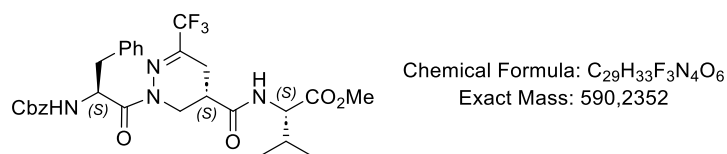




e) **Tripeptides 8e, 8e', 8f and 8f':**

**Methyl ((S)-2-(((benzyloxy)carbonyl)-L-phenylalanyl)-6-(trifluoromethyl)-2,3,4,5-tetrahydropyridazine-4-carbonyl)-L-valinate (8e)**

The product **8e** is obtained following the general procedure **E** as a white foam (160 mg, 65%).

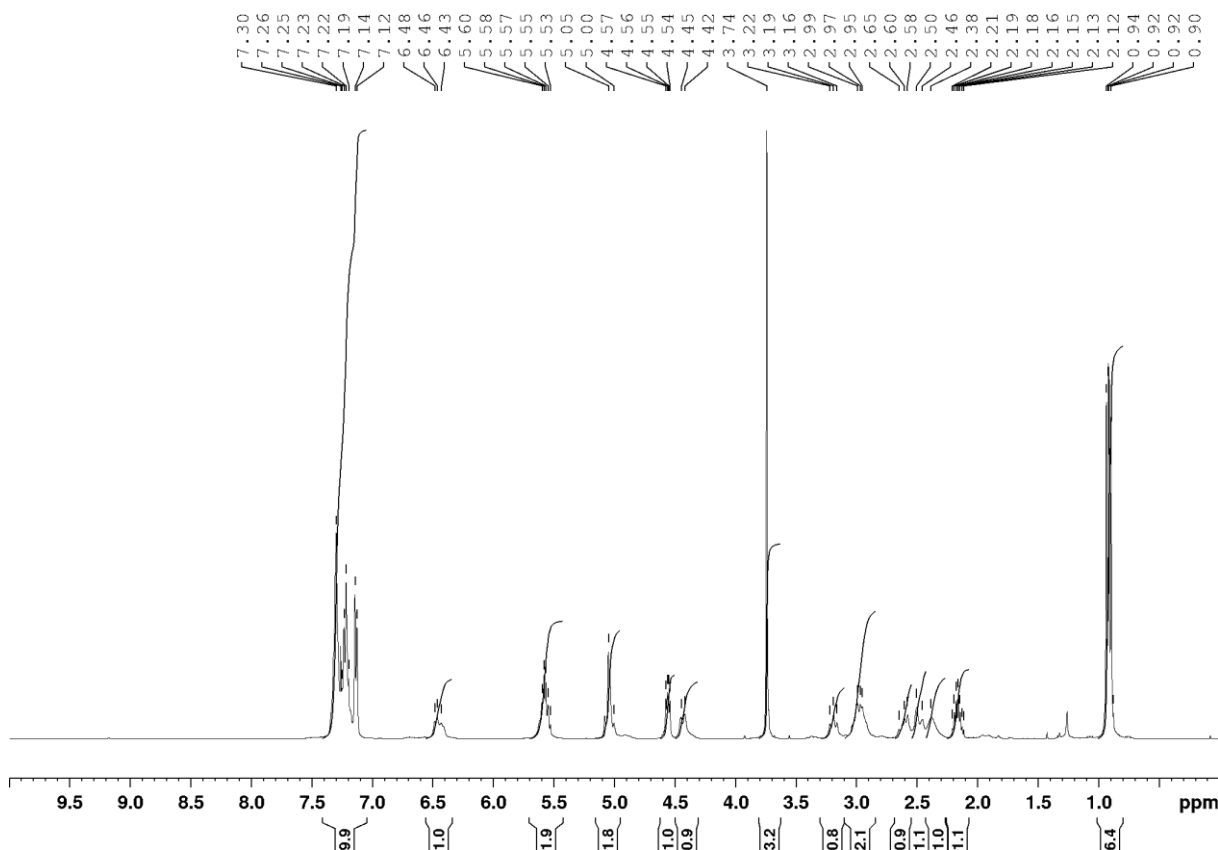


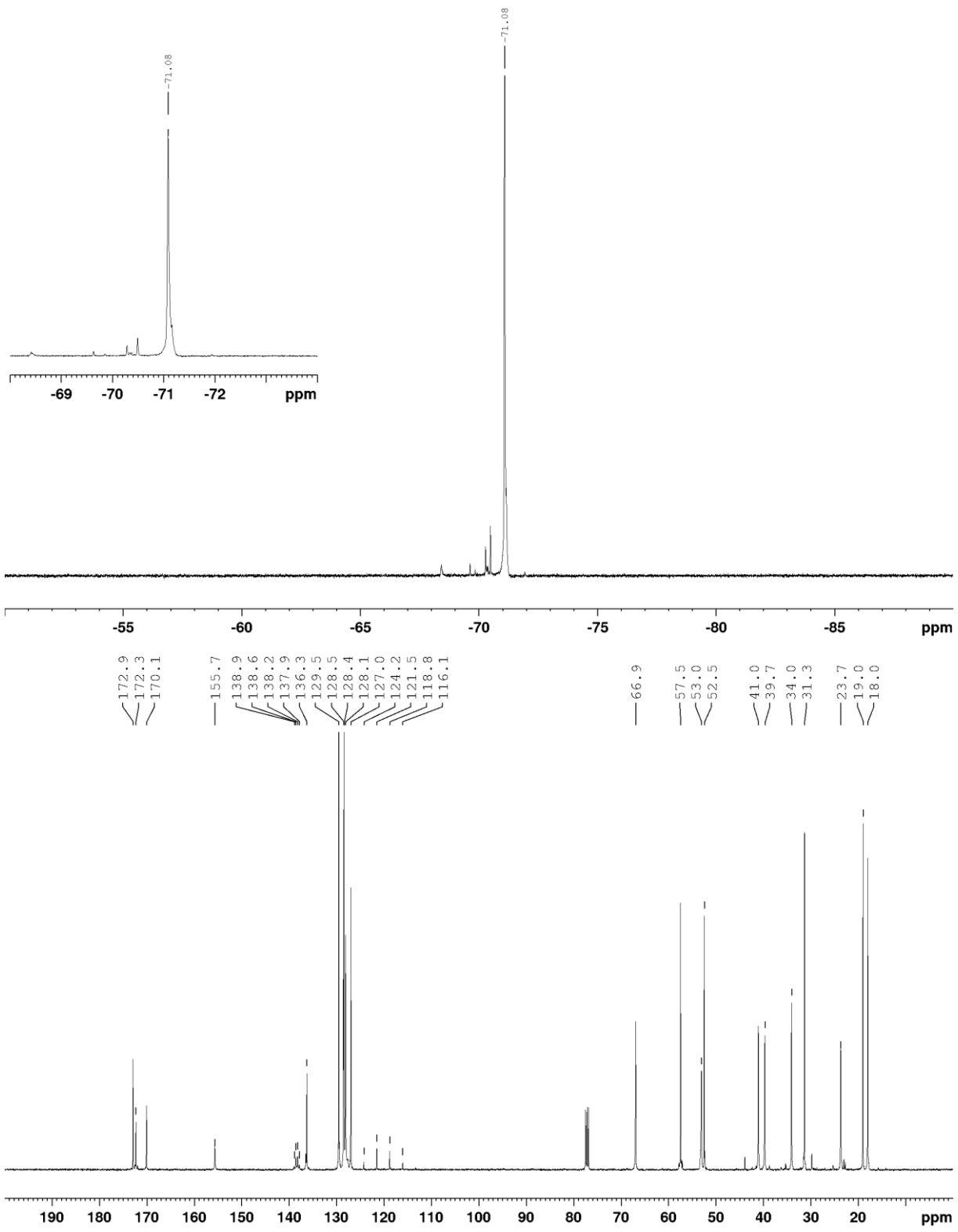
**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ = 7.30-7.12 (m, 10H, Haro), 6.46 (m, 1H, NHVal), 5.60-5.53 (m, 2H, NHPhe and CHαPhe), 5.0 (m, 2H, CH<sub>2</sub>Cbz), 4.56 (dd, <sup>3</sup>J<sub>H,H</sub> = 8.4 Hz, <sup>3</sup>J<sub>H,H</sub> = 4.9 Hz, 1H, CHαVal), 4.43 (d, <sup>2</sup>J<sub>H,H</sub> = 12.7 Hz, 1H, CH<sub>2</sub>N), 3.74 (s, 3H, OCH<sub>3</sub>), 3.19 (t, <sup>2</sup>J<sub>H,H</sub> = 11.9 Hz, 1H, CH<sub>2</sub>N), 3.06 - 2.85 (m, 2H, CH<sub>2</sub>Ph), 2.60 (m, 1H, CH<sub>2</sub>), 2.48 (m, 1H, CH<sub>2</sub>), 2.38 (m, 1H, CH), 2.16 (s, <sup>3</sup>J<sub>H,H</sub> = 6.8 Hz, 1H, CHiPr), 0.93 (d, <sup>3</sup>J<sub>H,H</sub> = 6.8 Hz, 3H, CH<sub>3</sub>), 0.91 (d, <sup>3</sup>J<sub>H,H</sub> = 6.8 Hz, 3H, CH<sub>3</sub>).

**<sup>19</sup>F NMR** (188 MHz, CDCl<sub>3</sub>): δ = - 71.1 (s, 3F).

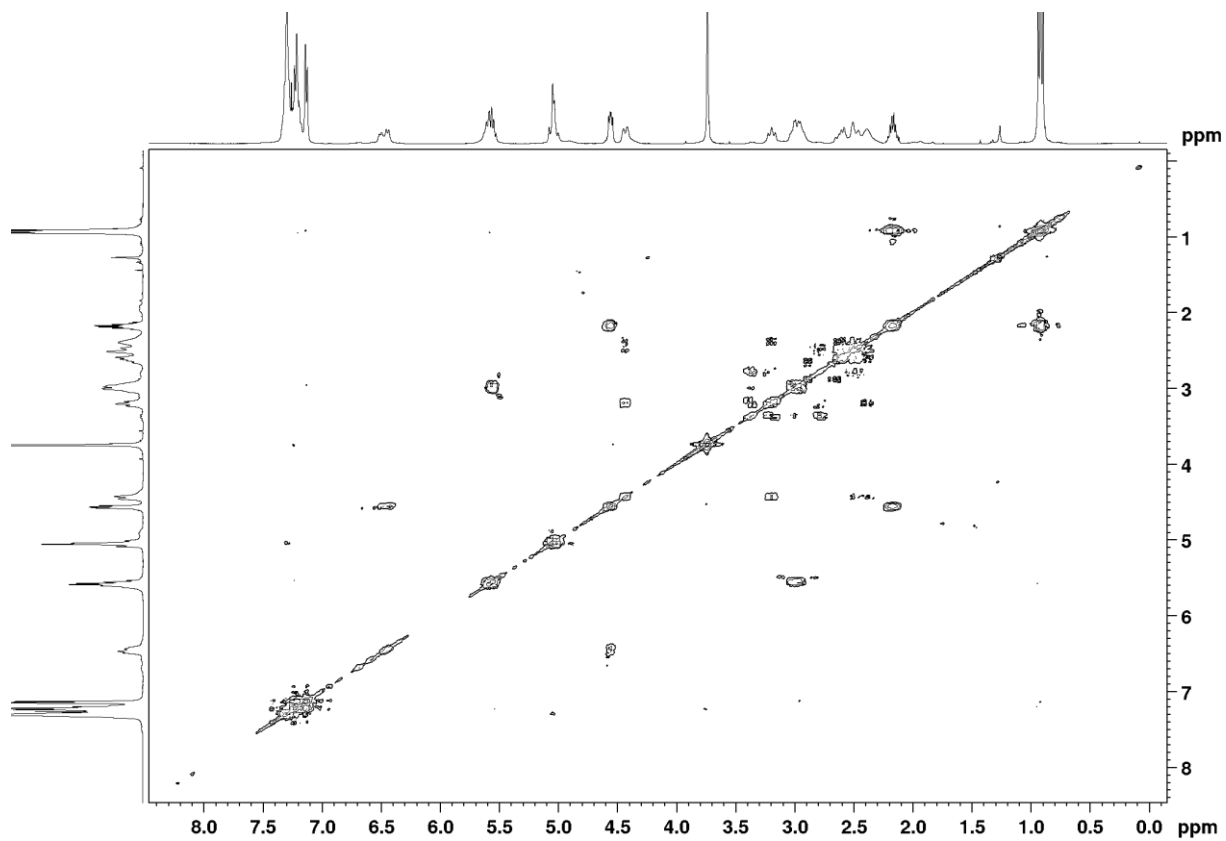
**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 172.9 (CON), 172.3 (CONH), 170.1 (COCbz), 155.7 (CO), 138.4 (q, <sup>2</sup>J<sub>C,F</sub> = 35 Hz, C=N), 136.3, 129.5 (Caro), 128.5, 128.4, 128.1, 126.9 (CHaro), 120.1 (q, <sup>1</sup>J<sub>C,F</sub> = 274 Hz, CF<sub>3</sub>), 67.0 (CH<sub>2</sub>Cbz), 57.5 (CHαVal), 53.0 (CHαPhe), 52.5 (OCH<sub>3</sub>), 41.0 (CH<sub>2</sub>N), 39.7 (CH<sub>2</sub>Ph), 34.0 (CH), 31.3 (CHiPr), 23.7 (CH<sub>2</sub>), 19.0, 18.0 (CH<sub>3</sub>iPr).

**HRMS (ESI+TOF)** m/z C<sub>29</sub>H<sub>33</sub>F<sub>3</sub>N<sub>4</sub>O<sub>6</sub> [M+H]<sup>+</sup> calc.591.2425, found 591.2430.

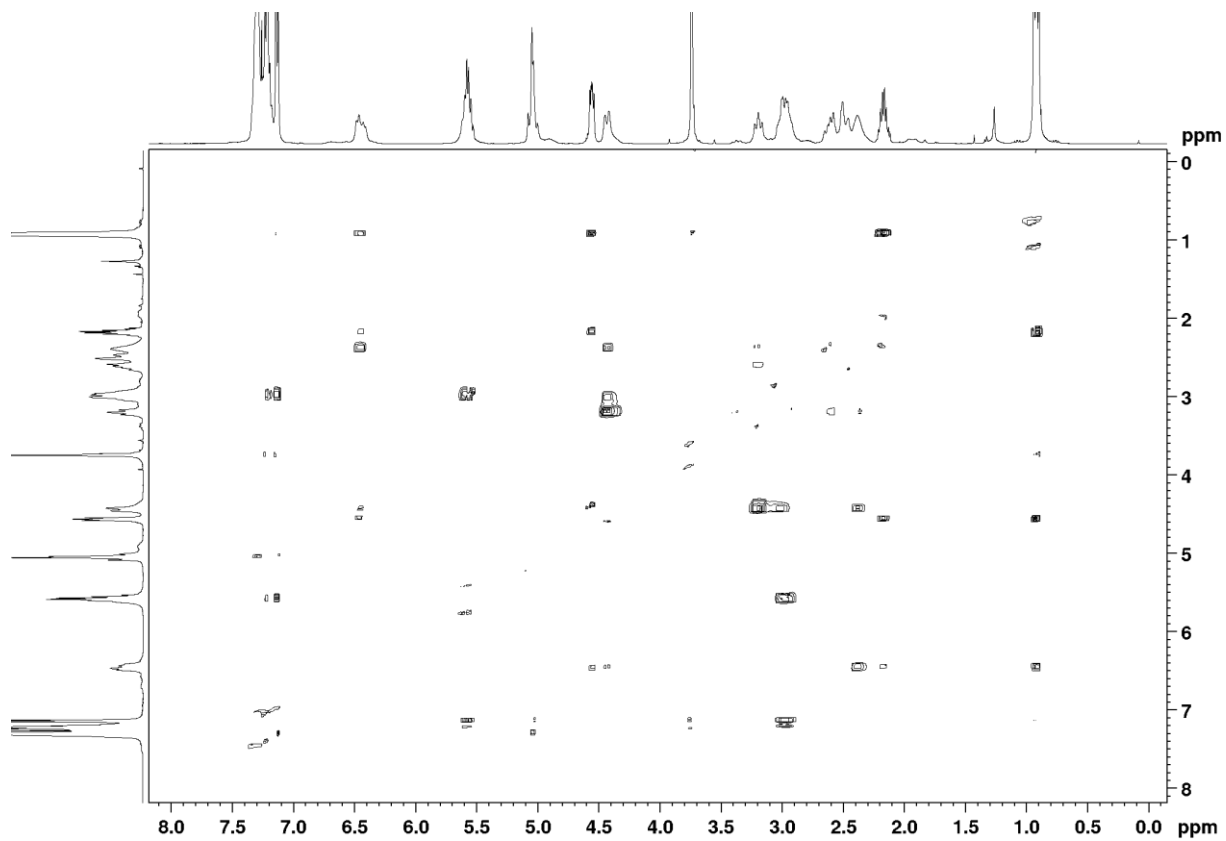




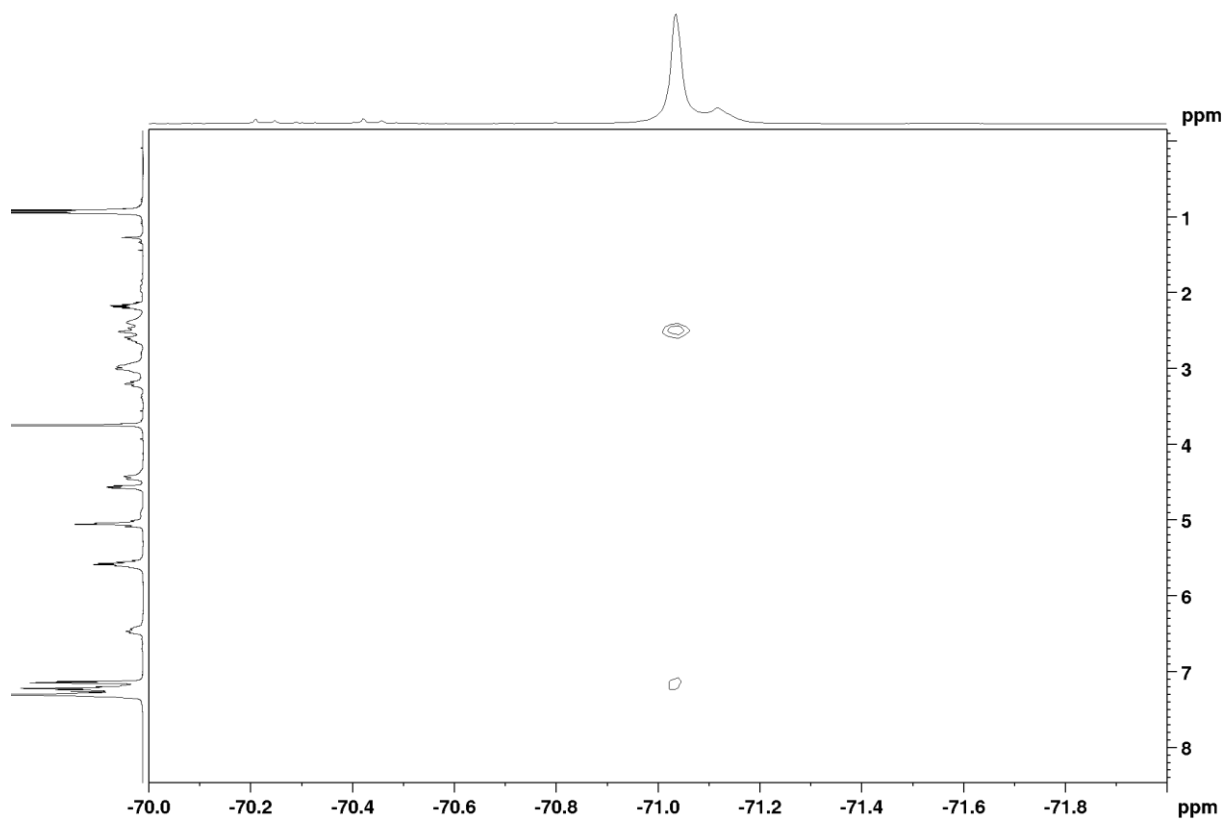
2D  $^1\text{H}$ - $^1\text{H}$  COSY experiments of compound 8e:



2D  $^1\text{H}$ - $^1\text{H}$  NOESY experiments of compound 8e

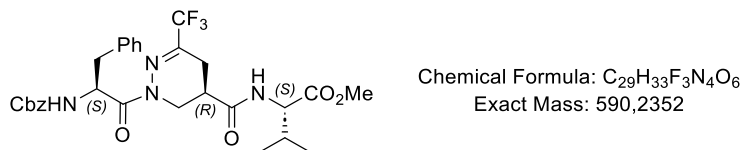


2D  $^{19}\text{F}$ - $^1\text{H}$  NOESY experiments of compound 8e



**Methyl ((R)-2-(((benzyloxy)carbonyl)-L-phenylalanyl)-6-(trifluoromethyl)-2,3,4,5-tetrahydropyridazine-4-carbonyl)-L-valinate (8e')**

The product **8e'** is obtained following the general procedure **E** as a white foam (115 mg, 61%).

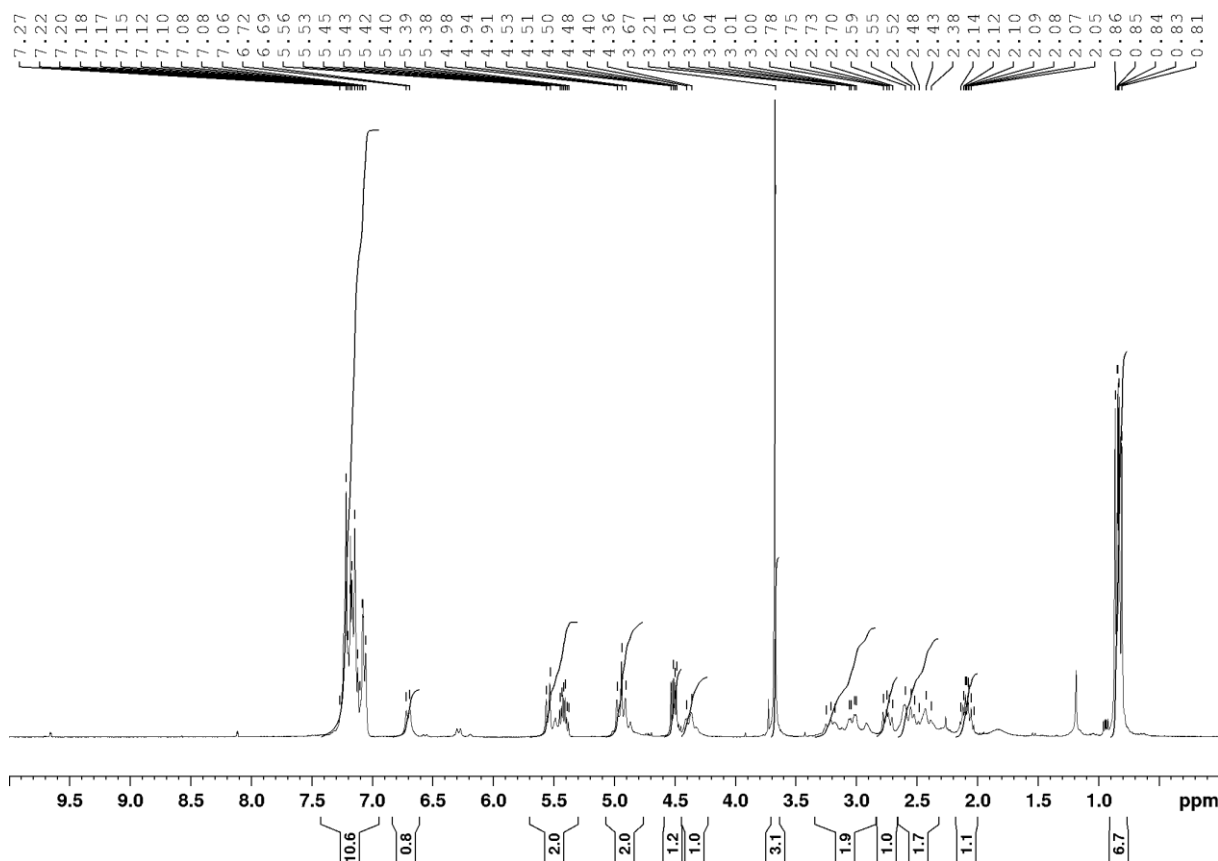


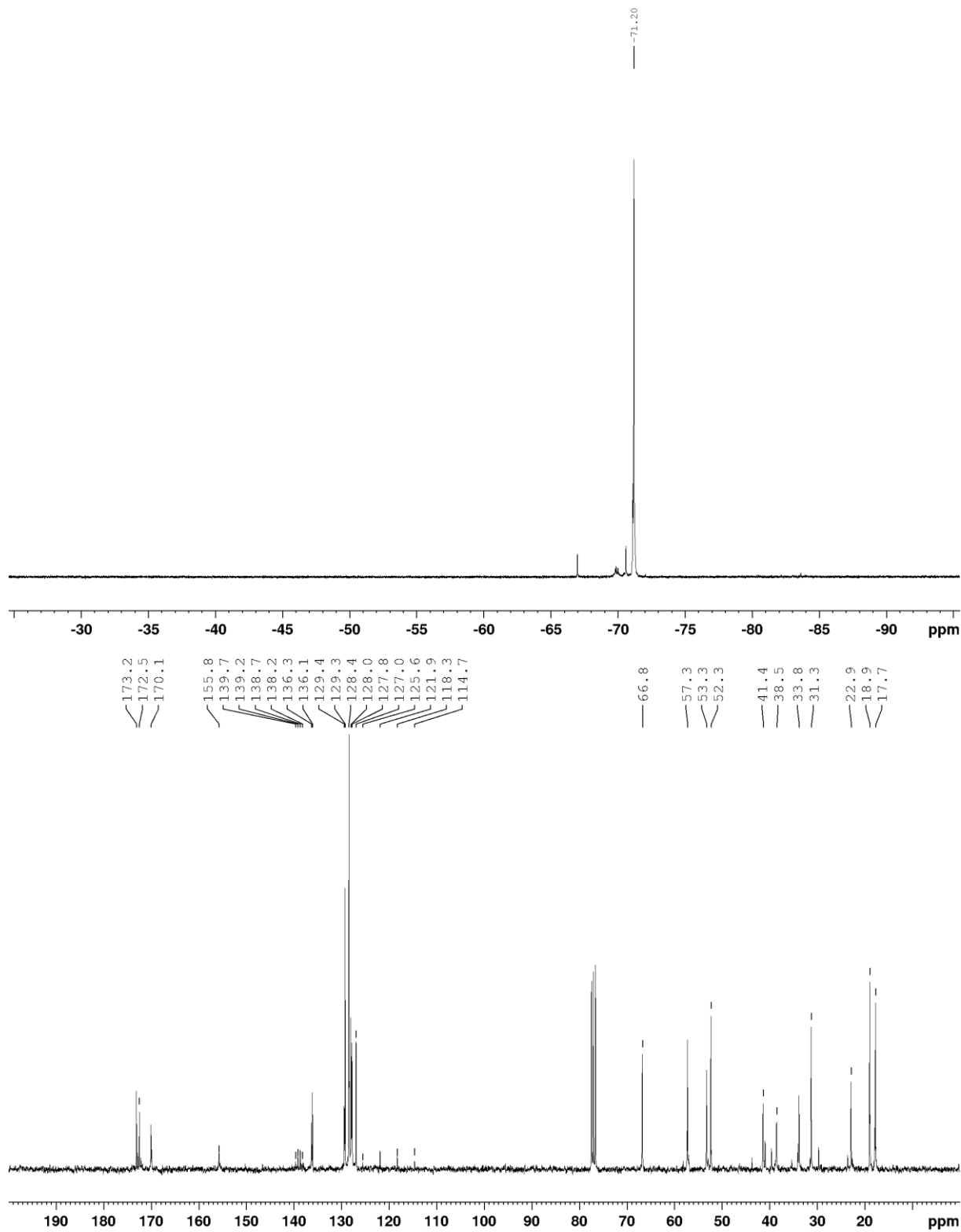
**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ = 7.27-7.06 (m, 10H, Haro), 6.71 (d, <sup>2</sup>J<sub>H,H</sub> = 8.7 Hz, 1H, NHVal), 5.54 (d, <sup>2</sup>J<sub>H,H</sub> = 8.5 Hz, 1H, NHCbz), 5.41 (td, <sup>3</sup>J<sub>H,H</sub> = 8.6 Hz, <sup>3</sup>J<sub>H,H</sub> = 5.0 Hz, 1H, CHαPhe), 4.96 (d, <sup>2</sup>J<sub>H,H</sub> = 11.6 Hz, 1H, CH<sub>2</sub>Cbz), 4.92 (d, <sup>2</sup>J<sub>H,H</sub> = 11.9 Hz, 1H, CH<sub>2</sub>Cbz), 4.51 (dd, <sup>3</sup>J<sub>H,H</sub> = 8.8 Hz, <sup>3</sup>J<sub>H,H</sub> = 5.0 Hz, 1H, CHαVal), 4.38 (d, <sup>2</sup>J<sub>H,H</sub> = 13.2 Hz, 1H, CH<sub>2</sub>N), 3.67 (s, 3H, OCH<sub>3</sub>), 3.20 (m, 1H, CH<sub>2</sub>N), 3.03 (dd, <sup>2</sup>J<sub>H,H</sub> = 13.3 Hz, <sup>3</sup>J<sub>H,H</sub> = 3.8 Hz, 1H, CH<sub>2</sub>Ph), 2.73 (dd, <sup>2</sup>J<sub>H,H</sub> = 13.3 Hz, <sup>3</sup>J<sub>H,H</sub> = 8.5 Hz, 1H, CH<sub>2</sub>Ph), 2.66-2.29 (m, 3H, CH and CH<sub>2</sub>), 2.08 (st, <sup>3</sup>J<sub>H,H</sub> = 6.5 Hz, 1H, CHiPr), 0.85 (d, <sup>3</sup>J<sub>H,H</sub> = 6.5 Hz, 3H, CH<sub>3</sub>iPr), 0.81 (d, <sup>3</sup>J<sub>H,H</sub> = 6.5 Hz, 3H, CH<sub>3</sub>iPr).

**<sup>19</sup>F NMR** (188 MHz, CDCl<sub>3</sub>): δ = - 71.2 (s, 3F).

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 173.2 (CON), 172.5 (CONH), 170.1 (COCbz), 155.8 (CO), 138.9 (q, <sup>2</sup>J<sub>C,F</sub> = 36 Hz, C=N), 136.3, 136.1 (Caro), 129.4, 129.3, 128.5, 128.0, 127.8, 127.0 (CHaro), 120.1 (q, <sup>1</sup>J<sub>C,F</sub> = 274 Hz, CF<sub>3</sub>), 66.8 (CH<sub>2</sub>Cbz), 57.3 (CHαVal), 53.23 (CHαPhe), 52.4 (OCH<sub>3</sub>), 41.4 (CH<sub>2</sub>N), 38.5 (CH<sub>2</sub>Ph), 33.8 (CH), 31.3 (CHiPr), 22.9 (CH<sub>2</sub>), 19.0 (CH<sub>3</sub>iPr), 17.8 (CH<sub>3</sub>iPr).

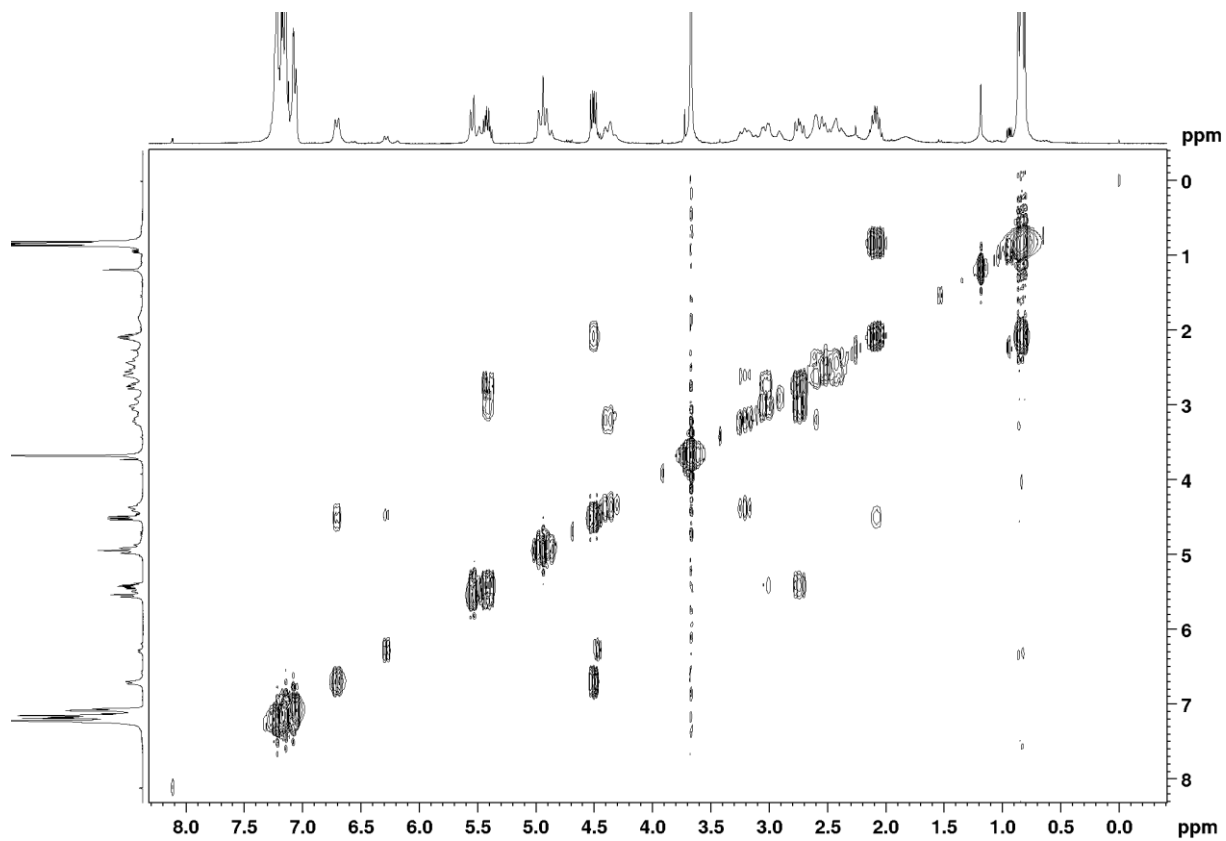
**HRMS (ESI+TOF)** m/z C<sub>29</sub>H<sub>33</sub>F<sub>3</sub>N<sub>4</sub>O<sub>6</sub> [M+H]<sup>+</sup> calc.591.2425, found 591.2429.



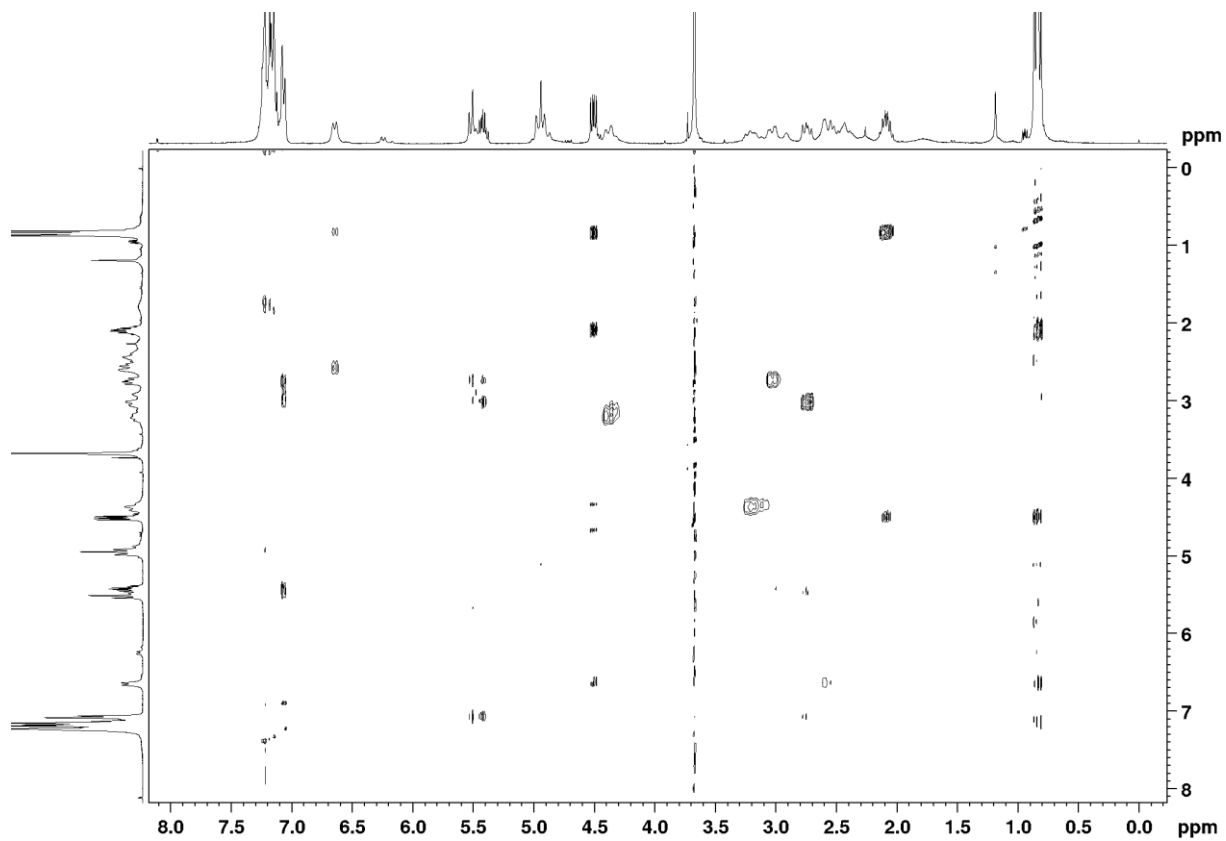




2D  $^1\text{H}$ - $^1\text{H}$  COSY experiments of  $8e'$

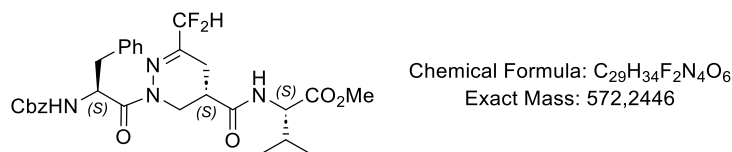


2D  $^1\text{H}$ - $^1\text{H}$  NOESY experiments of  $8e'$



**Methyl ((S)-2-(((benzyloxy)carbonyl)-L-phenylalanyl)-6-(difluoromethyl)-2,3,4,5-tetrahydropyridazine-4-carbonyl)-L-valinate (8f)**

The product **8f** is obtained following the general procedure **E** as a white foam (69 mg, 52%).

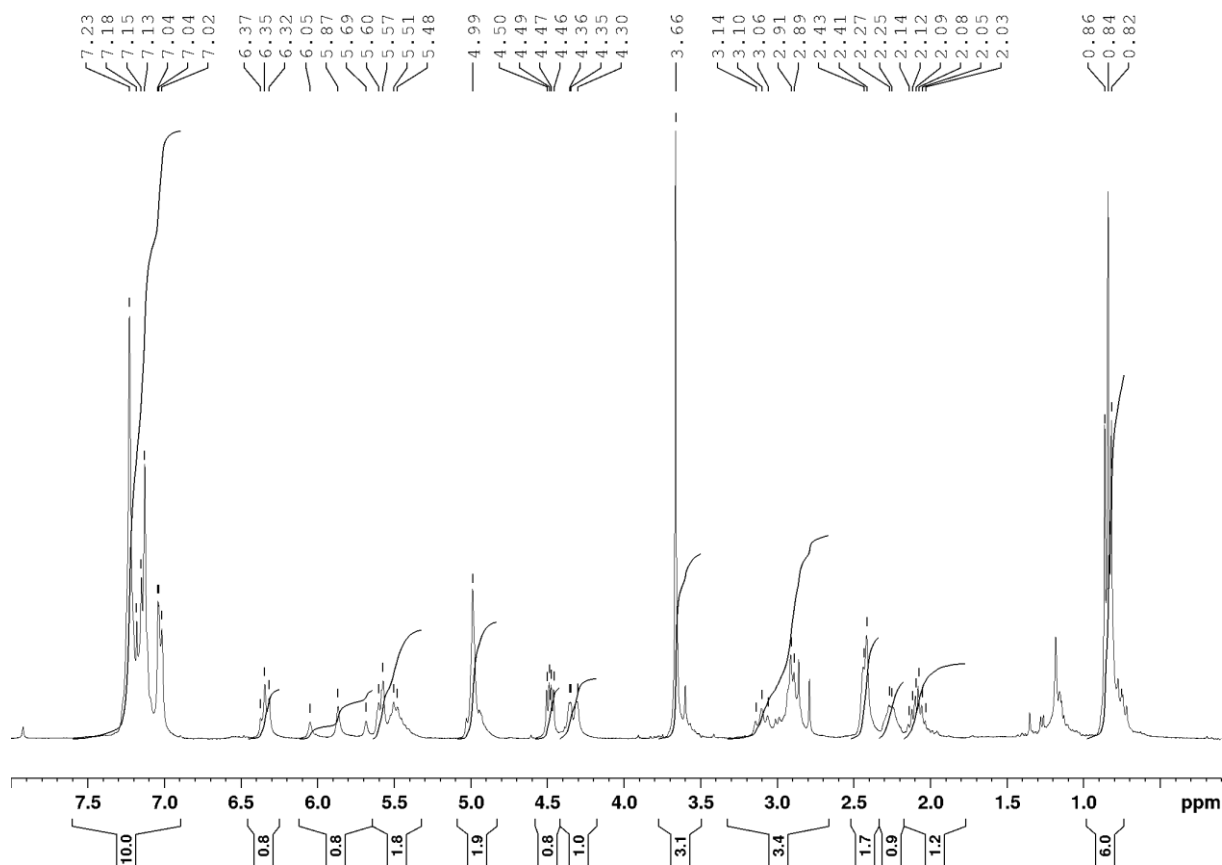


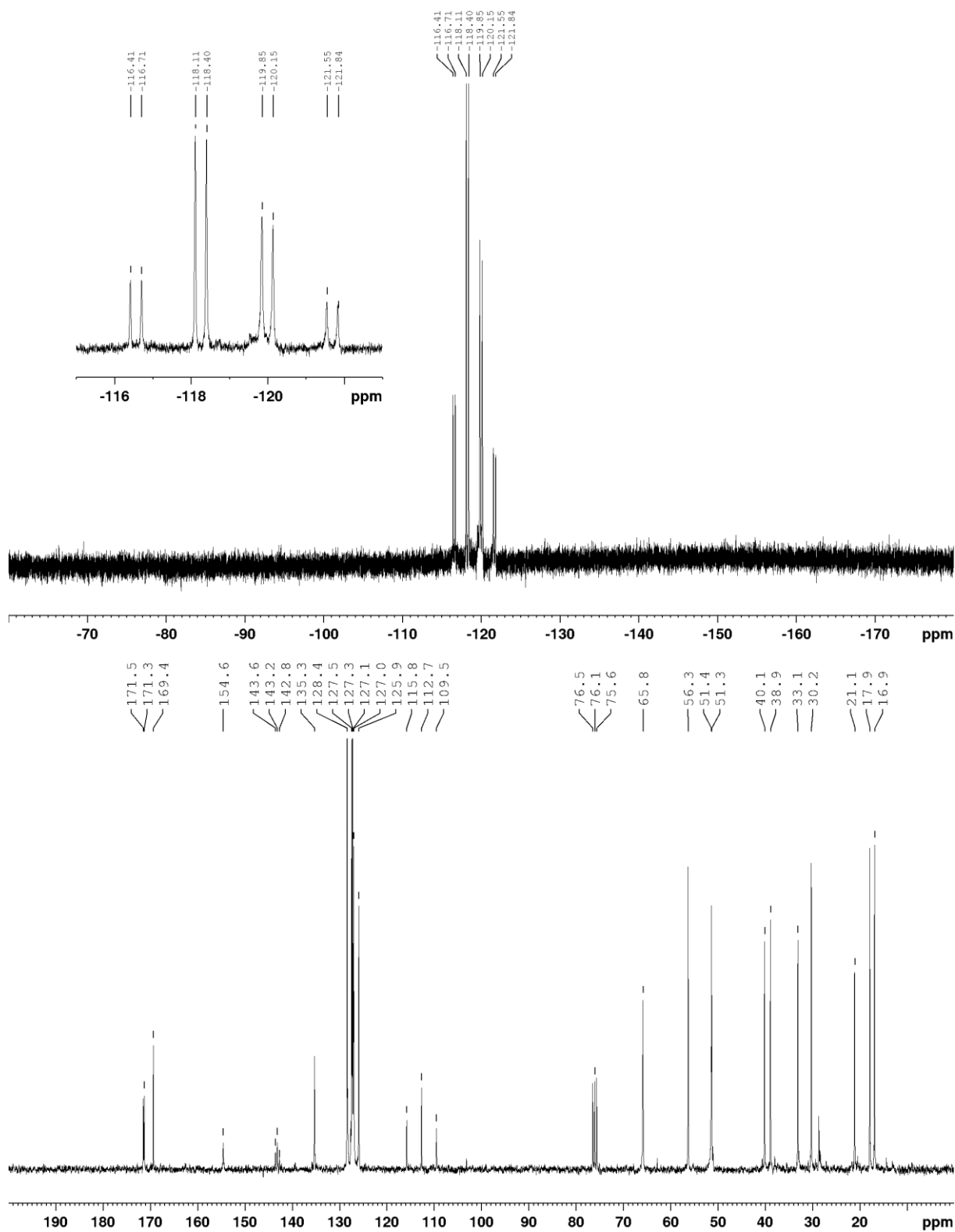
**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ = 7.23-7.02 (m, 10H, Haro), 6.33 (d, <sup>3</sup>J<sub>H,H</sub> = 8.4 Hz, 1H, NHVal), 5.87 (t, <sup>2</sup>J<sub>H,F</sub> = 54.8 Hz, 1H, CF<sub>2</sub>H), 5.59 (d, <sup>3</sup>J<sub>H,H</sub> = 9.9 Hz, 1H, NHCbz), 5.49 (q, <sup>3</sup>J<sub>H,H</sub> = 6.9 Hz, 1H, CHαPhe), 4.99 (s, 2H, CH<sub>2</sub>Cbz), 4.48 (dd, <sup>3</sup>J<sub>H,H</sub> = 4.9 Hz, <sup>3</sup>J<sub>H,H</sub> = 8.6 Hz, 1H, CHαVal), 4.33 (dd, <sup>2</sup>J<sub>H,H</sub> = 13.2 Hz, <sup>3</sup>J<sub>H,H</sub> = 2.8 Hz, 1H, CH<sub>2</sub>N), 3.66 (s, 3H, OCH<sub>3</sub>), 3.10 (t, <sup>2</sup>J<sub>H,H</sub> = 11.7 Hz, 1H, CH<sub>2</sub>N), 3.02 - 2.80 (m, 2H, CH<sub>2</sub>Ph), 2.42 (brs, 2H, CH<sub>2</sub>), 2.26 (m, 1H, CH), 2.10 (st, <sup>3</sup>J<sub>H,H</sub> = 6.5 Hz, 1H, CHiPr), 0.85 (d, <sup>3</sup>J<sub>H,H</sub> = 6.5 Hz, 3H, CH<sub>3</sub>iPr), 0.83 (d, <sup>3</sup>J<sub>H,H</sub> = 6.5 Hz, 3H, CH<sub>3</sub>iPr).

**<sup>19</sup>F NMR** (188 MHz, CDCl<sub>3</sub>): δ = -117.4 (dd, <sup>2</sup>J<sub>H,F</sub> = 55.1 Hz, <sup>2</sup>J<sub>F,F</sub> = 319.7 Hz, 1F), -120.9 (dd, <sup>2</sup>J<sub>H,F</sub> = 54.9 Hz, <sup>2</sup>J<sub>F,F</sub> = 319.8 Hz, 1F).

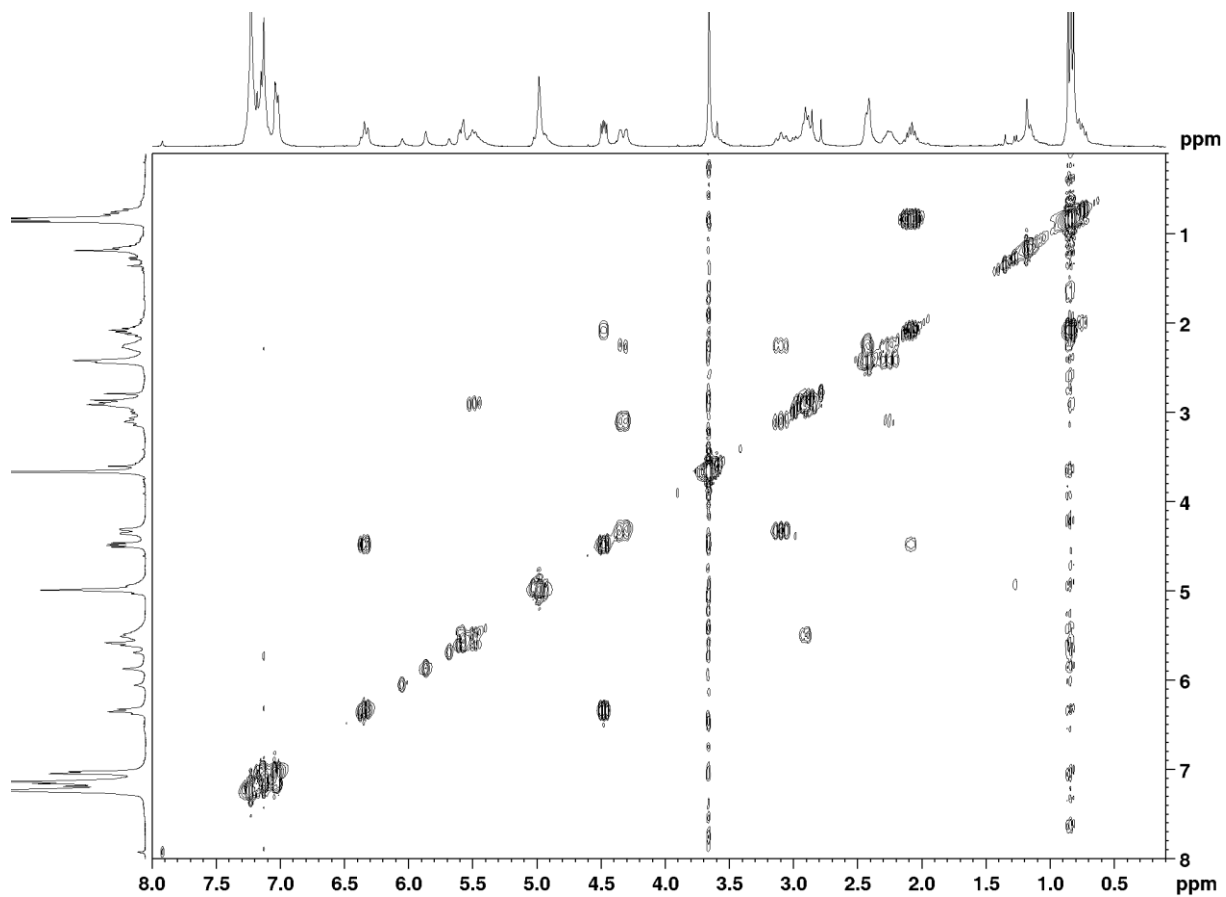
**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ = 171.5 (CON), 171.3 (COCbz), 169.4 (CONH), 154.6 (CO), 143.2 (q, <sup>2</sup>J<sub>C,F</sub> = 30.7 Hz, C=N), 135.3 (Caro), 128.4, 127.5, 127.3, 127.1, 127.0, 126.0 (CHaro), 112.7 (q, <sup>1</sup>J<sub>C,F</sub> = 238 Hz, CF<sub>2</sub>H), 65.8 (CH<sub>2</sub>Cbz), 56.3 (CHαVal), 51.4 (CHαPhe), 51.3 (OCH<sub>3</sub>), 40.1 (CH<sub>2</sub>N), 38.9 (CH<sub>2</sub>Ph), 33.1 (CH), 30.2 (CHiPr), 21.1 (CH<sub>2</sub>), 17.9 (CH<sub>3</sub>iPr), 16.9 (CH<sub>3</sub>iPr).

**HRMS (ESI+TOF)** m/z C<sub>29</sub>H<sub>33</sub>F<sub>3</sub>N<sub>4</sub>O<sub>6</sub> [M+Na]<sup>+</sup> calc. 595.2338, found 595.2350.

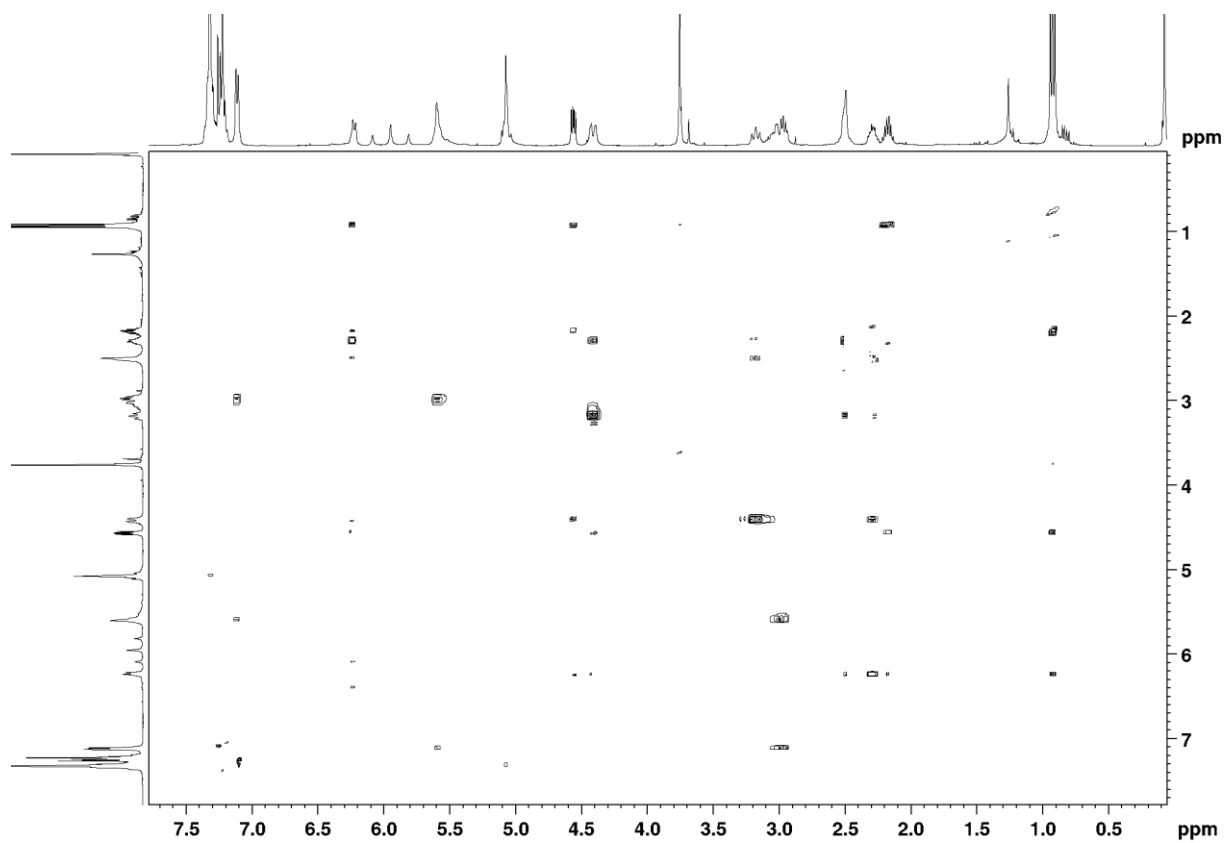




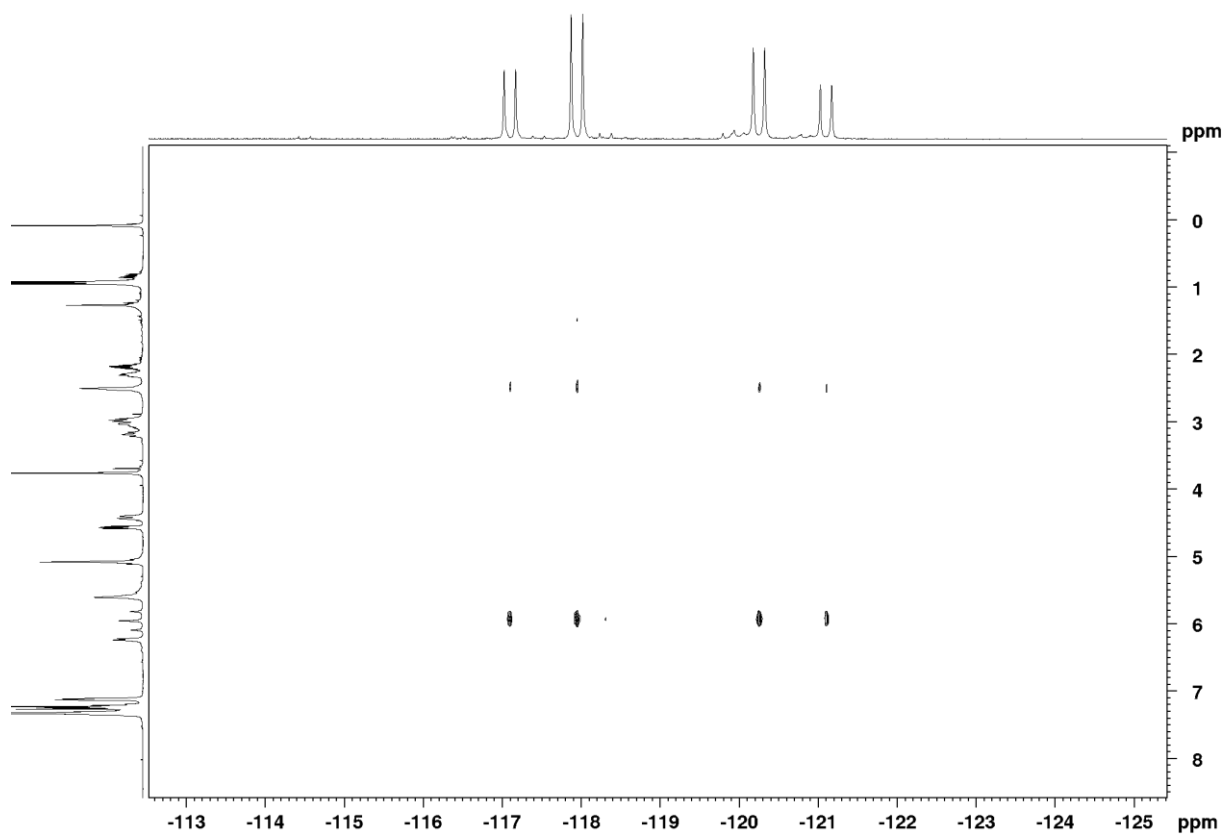
2D  $^1\text{H}$ - $^1\text{H}$  COSY Experiments of compound 8f:



2D  $^1\text{H}$ - $^1\text{H}$  NOESY experiments of compound 8f

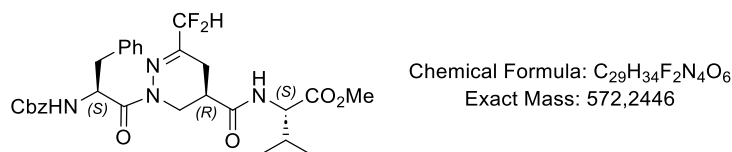


2D  $^{19}\text{F}$ - $^1\text{H}$  NOESY experiments of compound 8f



**Methyl ((R)-2-(((benzyloxy)carbonyl)-L-phenylalanyl)-6-(difluoromethyl)-2,3,4,5-tetrahydropyridazine-4-carbonyl)-L-valinate (8f')**

The product **8f'** is obtained following the general procedure **E** as a white foam (53 mg, 44%).

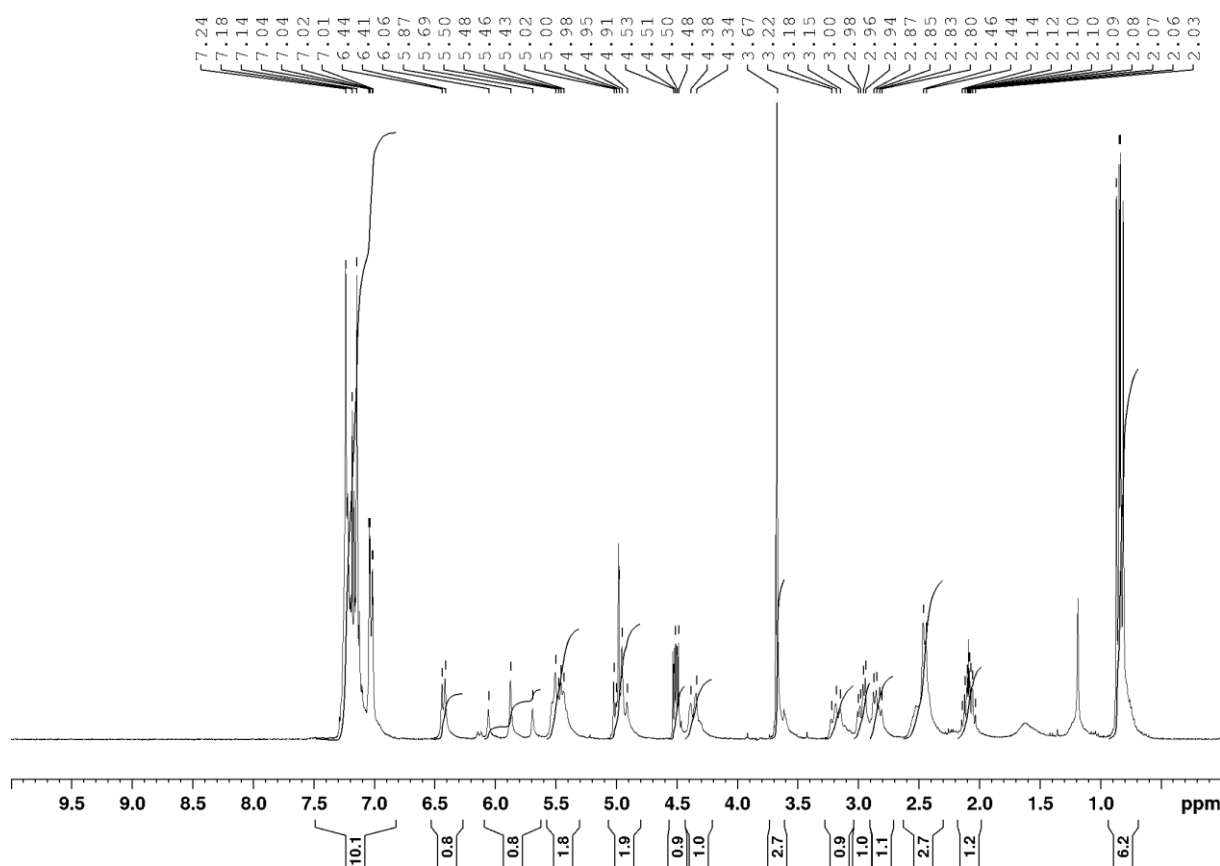


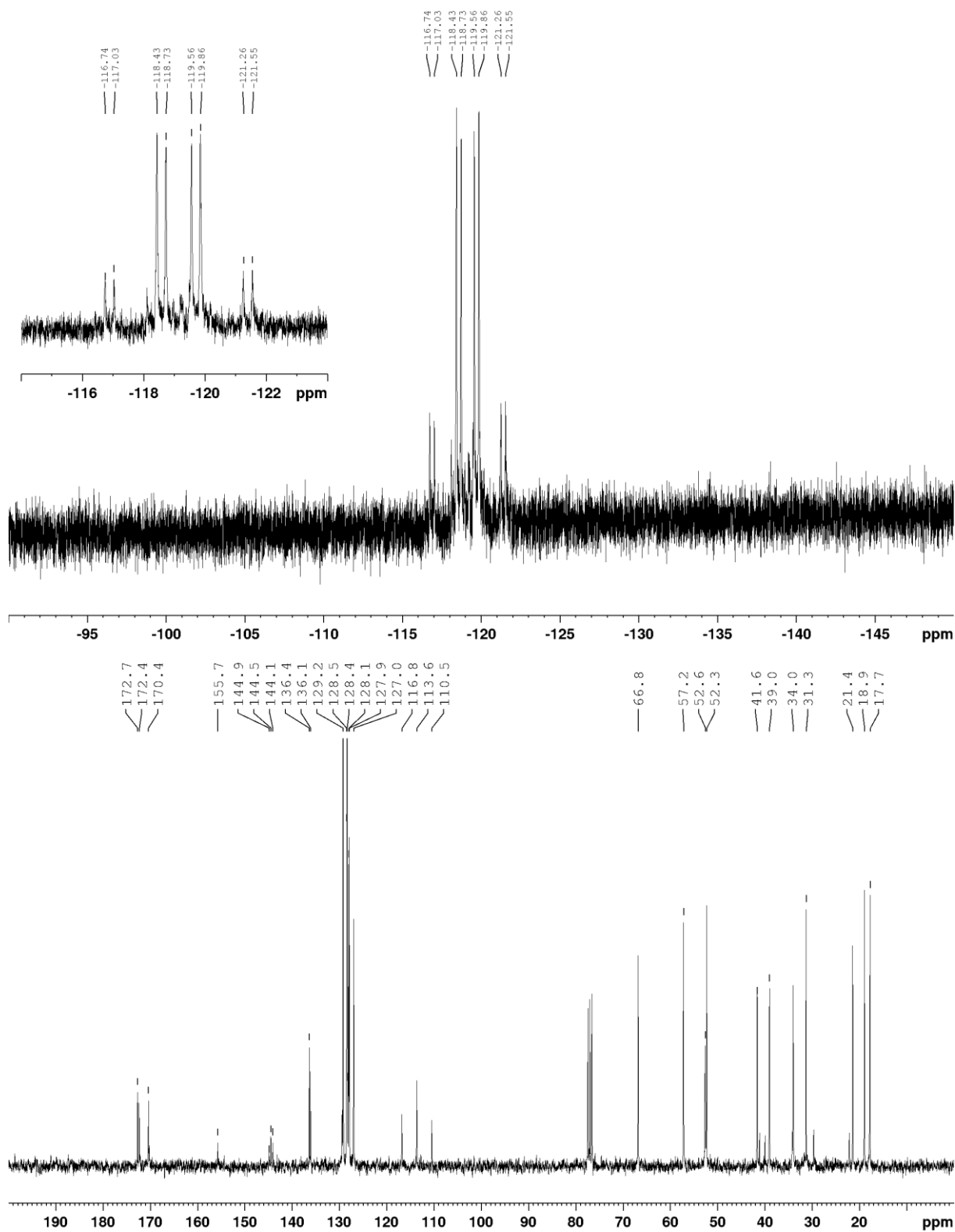
**<sup>1</sup>H NMR** (300 MHz,  $CDCl_3$ ):  $\delta$  = 7.24-7.01 (m, 10H, Haro), 6.43 (d,  $^3J_{H,H}$  = 8.6 Hz, 1H, NHVal), 5.87 (t,  $^2J_{H,F}$  = 54.8 Hz, 1H,  $CF_2H$ ), 5.50 (t,  $^3J_{H,H}$  = 7.8 Hz, 1H, NHPhe), 5.44 (d,  $^3J_{H,H}$  = 6.8 Hz, 1H, CH $\alpha$ Phe), 4.99 (d,  $^2J_{H,H}$  = 12.2 Hz, 1H,  $CH_2$ Cbz), 4.93 (d,  $^2J_{H,H}$  = 12.3 Hz, 1H,  $CH_2$ Cbz), 4.51 (dd,  $^3J_{H,H}$  = 4.96 Hz,  $^3J_{H,H}$  = 8.8 Hz, 1H, CH $\alpha$ Val), 4.36 (d,  $^2J_{H,H}$  = 13.2 Hz, 1H,  $CH_2N$ ), 3.67 (s, 3H,  $OCH_3$ ), 3.18 (t,  $^2J_{H,H}$  = 11.2 Hz, 1H,  $CH_2N$ ), 2.97 (dd,  $^2J_{H,H}$  = 13.5 Hz,  $^3J_{H,H}$  = 5.6 Hz, 1H,  $CH_2Ph$ ), 2.83 (dd,  $^2J_{H,H}$  = 13.4 Hz,  $^3J_{H,H}$  = 6.7 Hz, 1H,  $CH_2Ph$ ), 2.53 (m, 1H, CH), 2.45 (d,  $^3J_{H,H}$  = 6.0 Hz, 2H,  $CH_2$ ), 2.06 (dst,  $^3J_{H,H}$  = 8.2 Hz,  $^3J_{H,H}$  = 6.8 Hz, 1H,  $CHiPr$ ), 0.86 (d,  $^3J_{H,H}$  = 6.8 Hz, 3H,  $CH_3iPr$ ), 0.82 (d,  $^3J_{H,H}$  = 6.9 Hz, 3H,  $CH_3iPr$ ).

**<sup>19</sup>F NMR** (188 MHz,  $CDCl_3$ ):  $\delta$  = -117.7 (dd,  $^2J_{H,F}$  = 56.4 Hz,  $^2J_{F,F}$  = 318.9 Hz, 1F), -120.6 (dd,  $^2J_{H,F}$  = 54.6 Hz,  $^2J_{F,F}$  = 318.6 Hz, 1F).

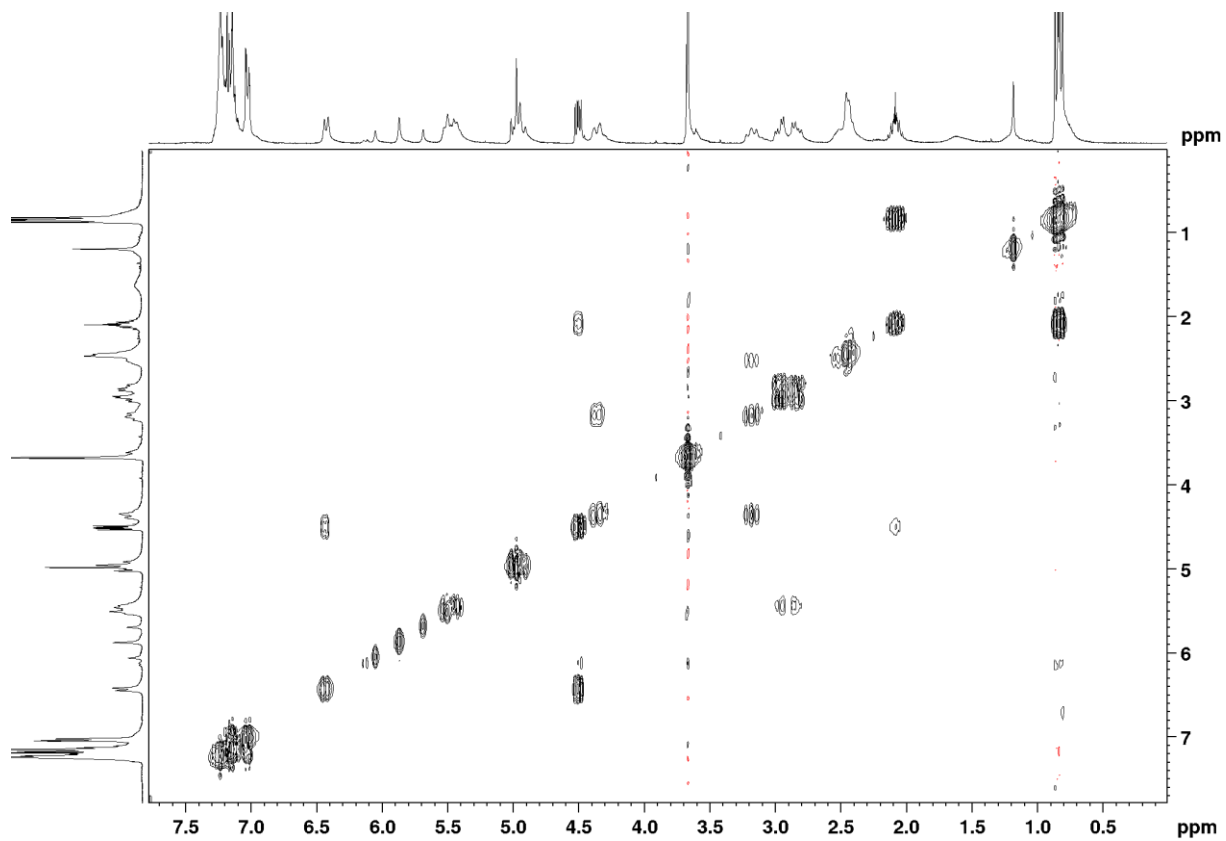
**<sup>13</sup>C NMR** (75 MHz,  $CDCl_3$ ):  $\delta$  = 172.7 (CON), 172.4 (COCbz), 170.4 (CONH), 155.7 (CO), 144.5 (q,  $^2J_{C,F}$  = 30.8 Hz, C=N), 136.9, 136.15 (Caro), 129.4, 128.5, 128.4, 128.1, 127.9, 127.0 (CHaro), 113.6 (q,  $^1J_{C,F}$  = 238.2 Hz,  $CF_2H$ ), 66.8 ( $CH_2$ Cbz), 57.2 (CH $\alpha$ Val), 52.6 (CH $\alpha$ Phe), 52.3 ( $OCH_3$ ), 41.6 ( $CH_2N$ ), 39.0 ( $CH_2Ph$ ), 34.0 ( $CHiPr$ ), 31.3 (CH), 21.4 ( $CH_2$ ), 18.9 ( $CH_3iPr$ ), 17.8 ( $CH_3iPr$ ).

**HRMS (ESI+TOF)**  $m/z$   $C_{29}H_{33}F_2N_4O_6Na$   $[M+Na]^+$  calc. 595.2338, found 595.2350.

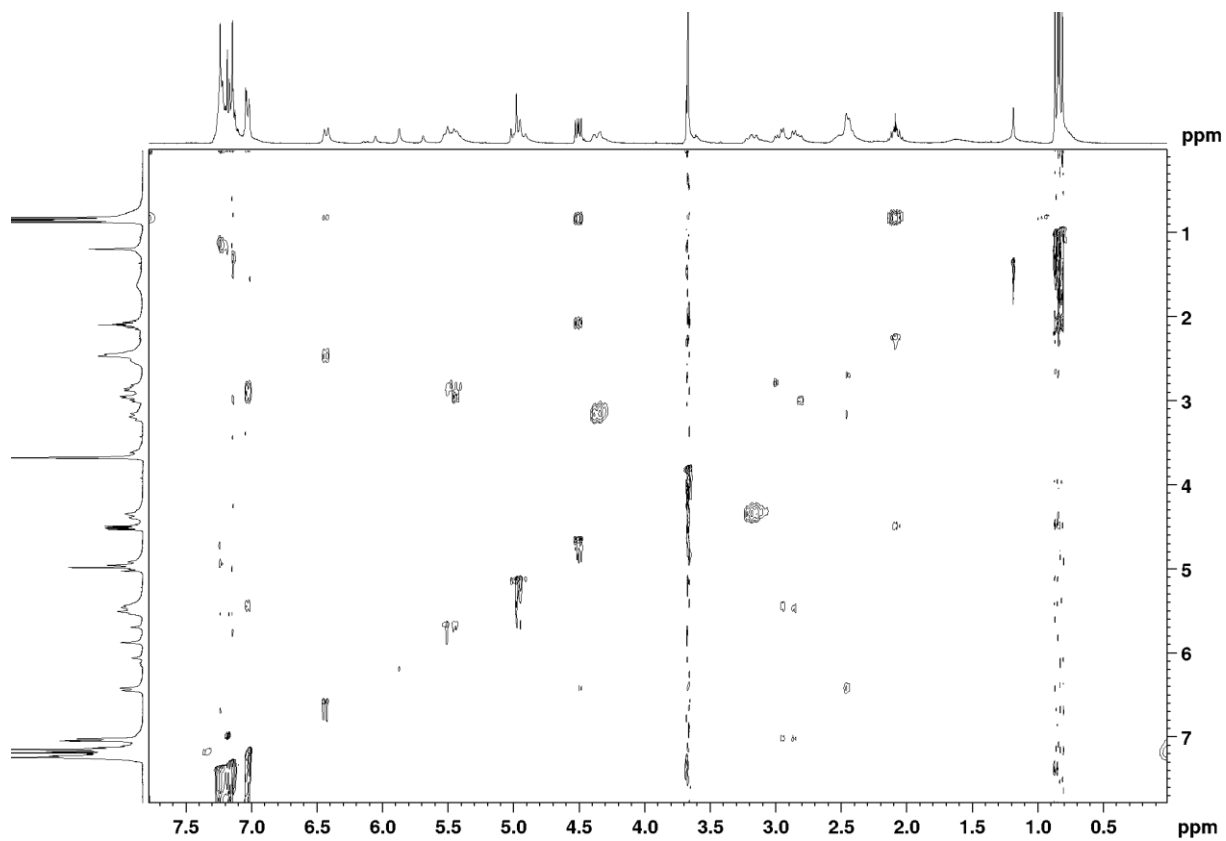




2D  $^1\text{H}$ - $^1\text{H}$  COSY experiments of compound 8f'

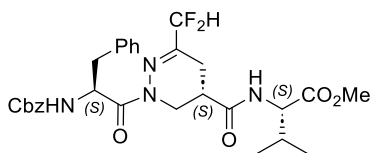
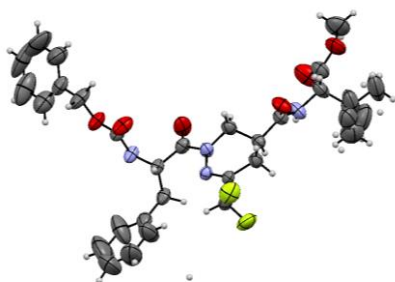


2D  $^1\text{H}$ - $^1\text{H}$  NOESY experiments of compound 8f'





f) X-ray analysis of 8f:



Chemical Formula: C<sub>29</sub>H<sub>34</sub>F<sub>2</sub>N<sub>4</sub>O<sub>6</sub>  
Exact Mass: 572,2446

Bond precision: C-C = 0.0035 Å

Wavelength=0.71073

Cell: a=15.8351 (12) b=5.0455 (4) c=17.8221 (13)

alpha=90

beta=94.756 (7)

gamma=90

Temperature: 173 K

	Calculated	Reported
Volume	1419.01 (19)	1419.01 (19)
Space group	P 21	P 21
Hall group	P 2yb	P 2yb
Moiety formula	C <sub>29</sub> H <sub>34</sub> F <sub>2</sub> N <sub>4</sub> O <sub>6</sub>	C <sub>29</sub> H <sub>34</sub> F <sub>2</sub> N <sub>4</sub> O <sub>6</sub>
Sum formula	C <sub>29</sub> H <sub>34</sub> F <sub>2</sub> N <sub>4</sub> O <sub>6</sub>	C <sub>29</sub> H <sub>34</sub> F <sub>2</sub> N <sub>4</sub> O <sub>6</sub>
Mr	572.60	572.60
Dx, g cm <sup>-3</sup>	1.340	1.340
Z	2	2
Mu (mm <sup>-1</sup> )	0.103	0.103
F000	604.0	604.0
F000'	604.33	
h, k, lmax	21, 6, 24	21, 6, 24
Nref	7645 [ 4238]	6500
Tmin, Tmax	0.996, 0.998	0.756, 1.000
Tmin'	0.977	

Correction method= # Reported T Limits: Tmin=0.756 Tmax=1.000

AbsCorr = GAUSSIAN

Data completeness= 1.53/0.85

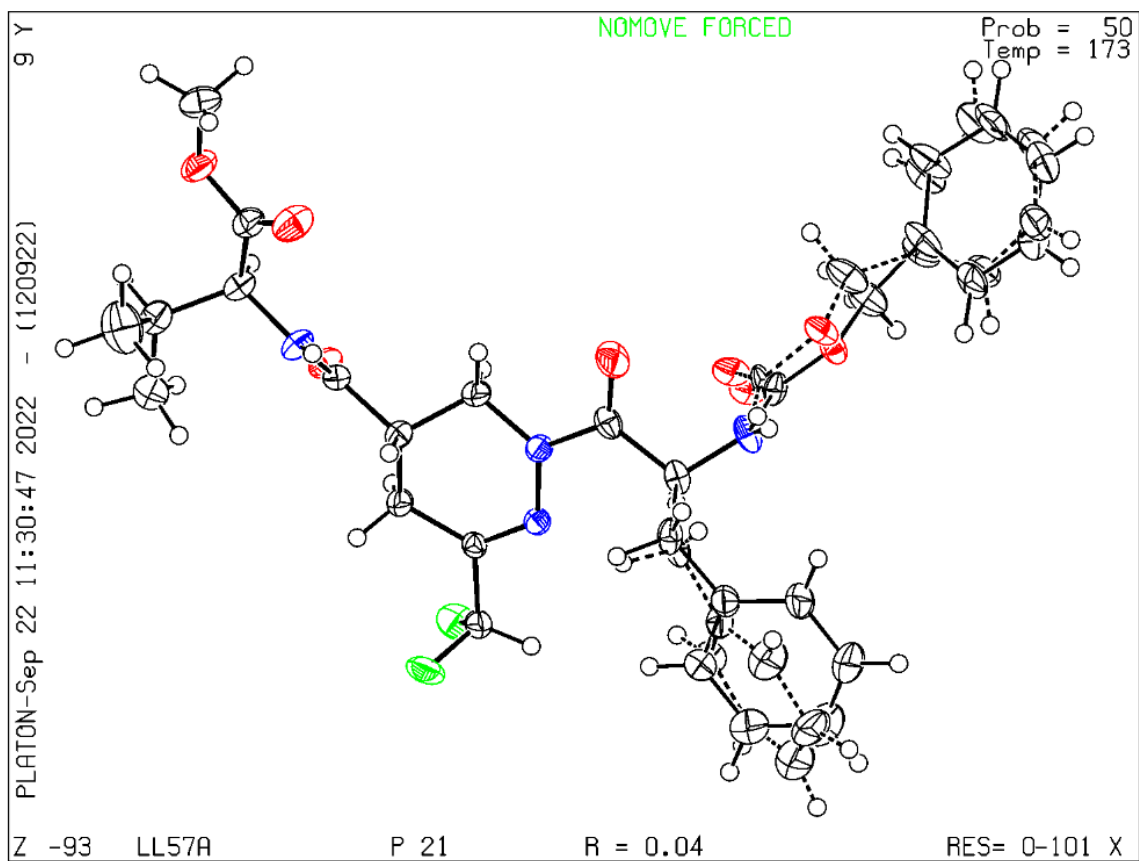
Theta(max)= 29.183

R(reflections)= 0.0435 ( 5145)

wR2(reflections)=  
0.1079 ( 6500)

S = 1.069

Npar= 541



**g) <sup>1</sup>H NMR spectra comparison of 7f,f' and 7e,e' for configuration assignment.**

