

# Access to Novel Functionalized Trifluoromethyl $\beta$ -Lactams by Ring Expansion of Aziridines

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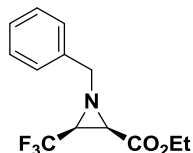
## Supporting Information

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**General informations.** All experiments dealing with air and moisture-sensitive compounds were conducted under an atmosphere of dry argon. The usual solvents were purchased from commercial sources. Tetrahydrofuran (THF) was distilled on sodium/benzophenone. Reagents were used without further purification as received from commercial. TLC was performed on silica gel, 60F-250 (0.26mm 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 Kofler melting point apparatus. NMR spectra were measured on an Ultrafield AVANCE300 (1H, 300 MHz; 13C, 75 MHz) and BRUKER AMX 200 (1H, 200 MHz; 19F, 188 MHz) spectrometer. Unless otherwise stated, NMR data were obtained under ambient temperature conditions and  $\text{CDCl}_3$  was used as solvent. Chemical shifts  $\delta$  are in ppm, and the following abbreviations are used: singlet (s), doublet (d), doublet doublet (dd), triplet (t), quintuplet (quint), multiplet (m) and broad singlet (brs). High resolution mass spectra were recorded on a MicrotofQ Bruker Daltonics.

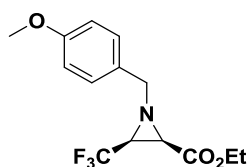
## General procedure for preparation of 3-trifluoromethyl-aziridine-2-ethyl ester derivatives

To a solution of the corresponding imine (1 eq) in anhydrous Et<sub>2</sub>O (0.25 M) at -78°C were added BF<sub>3</sub>·Et<sub>2</sub>O (0.1 eq) and Ethyl Diazoacetate (1.2 eq). The reaction was stirred at -78 °C for 4h and monitored by NMR <sup>19</sup>F. When the reaction was completed, a solution of saturated NaHCO<sub>3</sub> was added and the aqueous layer was extracted by Et<sub>2</sub>O (3x50 ml). The organic layers were washed with water and brine, then dried over MgSO<sub>4</sub> and concentrated under vacuum. Crude product was purified on silica gel chromatography (Cyclohexane / AcOEt : 9/1).



### *Cis- 1-benzyl-3-trifluoromethyl-aziridine-2-ethyl ester*<sup>1</sup>

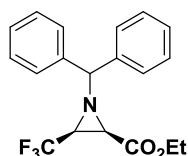
Aziridine was prepared from the corresponding aldimine (2.86 g, 15.3 mmol) following general procedure. Colorless oil (2.73 g, 65 % yield). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) :  $\delta$  7.36 (m, 5H), 4.24 (q,  $J$  = 6 Hz, 2H), 3.77 (s, 2H), 2.56 (d,  $J$  = 6 Hz, 2H), 2.44 (quint,  $J$  = 6 Hz, 1H), 1.28 (t,  $J$  = 6 Hz, 3H); <sup>19</sup>F NMR (188 MHz, CDCl<sub>3</sub>) :  $\delta$  -67.47 (d,  $J$  = 5.64 Hz).



### *Cis- 1-(4-methoxybenzyl)-3-trifluoromethyl-aziridine-2-ethyl ester*

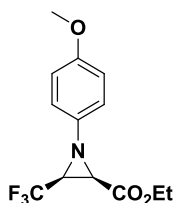
Aziridine was prepared from the corresponding aldimine (2.0 g, 9.2 mmol) following general procedure. Colorless oil (1.8 g, 65% yield).

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) :  $\delta$  7.27 (d,  $J$  = 9 Hz, 2H) , 6.90 (d,  $J$  = 9 Hz, 2H), 4.20 (m,  $J$  = 6 Hz,  $J$  = 9 Hz, 1H), 3.82 (s, 3H), 3.76 (d,  $J$  = 12 Hz, 1H), 3.70 (d,  $J$  = 12 Hz, 1H), 2.55 (d,  $J$  = 6 Hz, 1H), 2.42 (quint,  $J$  = 6 Hz, 1H), 1.28 (t,  $J$  = 6 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) :  $\delta$  166.3, 159.4, 129.8, 127.5, 123.4 (q,  $J$  = 273 Hz), 114.1, 61.8, 61.5, 55.4, 42.1 (q,  $J$  = 39 Hz), 41.0, 14.0; <sup>19</sup>F NMR (188 MHz, CDCl<sub>3</sub>) :  $\delta$  -67.44 (d,  $J$  = 5.6 Hz). Anal Calcd for C<sub>14</sub>H<sub>16</sub>F<sub>3</sub>NO<sub>3</sub> : C, 55.44 ; H, 5.32 ; N, 4.62. Found : C, 55.31 ; H, 5.11 ; N, 4.47.



### *Cis- 1-dibenzyl-3-trifluoromethyl-aziridine-2-ethyl ester*<sup>2</sup>

Aziridine was prepared from the corresponding aldimine (1.0 g, 3.8 mmol) following general procedure. Colorless oil (0.5 g, 38% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) :  $\delta$  7.49-7.46 (m, 2H), 7.35-7.32 (m, 2H), 7.24-7.13 (m, 6H), 4.10 (m, 2H), 3.77 (s, 1H), 2.55 (d,  $J$  = 6 Hz, 1H), 2.45 (quint,  $J$  = 6 Hz, 1H), 1.15 (t,  $J$  = 6 Hz, 3H); <sup>19</sup>F NMR (188 MHz, CDCl<sub>3</sub>) :  $\delta$  -67.42 (d,  $J$  = 5.6 Hz).

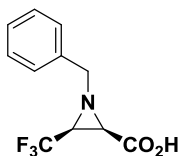


***Cis-1-(4-methoxyphenyl)-3-trifluoromethyl-aziridine-2-ethyl ester*<sup>1</sup>**

Aziridine was prepared from the corresponding aldimine (0.511 g, 2.51 mmol) following general procedure. Colorless oil (0.53 g, 73 % yield). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) :  $\delta$  6.96 (d,  $J$  = 10 Hz, 2H), 6.82 (d,  $J$  = 10 Hz, 2H), 4.32 (q,  $J$  = 6 Hz, 2H), 3.77 (s, 3H), 3.08 (d,  $J$  = 6 Hz, 2H), 2.89 (quint,  $J$  = 6 Hz, 1H), 1.32 (t,  $J$  = 6 Hz, 3H); <sup>19</sup>F NMR (188 MHz, CDCl<sub>3</sub>) :  $\delta$  -67.43 (d,  $J$  = 5.64 Hz).

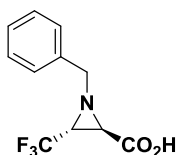
**General procedure for the preparation of 3-trifluoromethyl-aziridine-2-carboxylic acid derivatives**

To a solution of aziridine ester (1 eq) in ethanol was added a solution of NaOH 2N (10 eq). The reaction was stirred at room temperature overnight. When the reaction was completed, a solution of HCl 1N was added until pH = 1-2 and the aqueous layer was extracted by AcOEt (3x50 ml). The organic layers were washed with water, brine, then concentrated to give the product without any further purification.



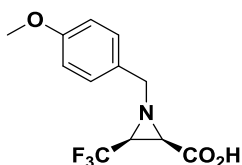
***Cis-1-benzyl-3-trifluoromethyl-aziridine-2-carboxylic acid (cis-1a)***

Aziridine acid was obtained from the corresponding aziridine ester (2.2 g, 8.0 mmol) following general saponification procedure. White solid (1.7 g, 87% yield). m. p. : 166°C. <sup>1</sup>H NMR (300 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) :  $\delta$  7.47-7.28 (m, 5H), 3.85 (d,  $J$  = 15 Hz, 1H), 3.73 (d,  $J$  = 15 Hz, 1H), 2.96 (m, 2H); <sup>13</sup>C NMR (75 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) :  $\delta$  167.4, 138.4, 129.2, 129.0, 128.2, 124.7 (q,  $J$  = 271.5), 62.51, 43.22 (q,  $J$  = 39 Hz), 42.35; <sup>19</sup>F NMR (188 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) :  $\delta$  -66.045 (brs). HRMS (ESI-QTOF)  $m/z$  C<sub>11</sub>H<sub>10</sub>F<sub>3</sub>NO<sub>2</sub> [M+Na]<sup>+</sup> cal. 268.0556, found 268.0557.



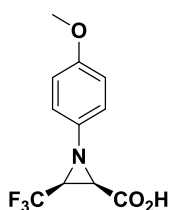
***Trans-1-benzyl-3-trifluoromethyl-aziridine-2-carboxylic acid (trans-1a)***

Aziridine acid was obtained from the corresponding aziridine ester (0.3 g, 1.09 mmol) following general saponification procedure. White solid (0.251 g, 94% yield). m. p. : 158°C. <sup>1</sup>H NMR (200 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) :  $\delta$  7.26-7.14 (m, 5H), 3.96 (d,  $J$  = 15 Hz, 1H), 3.90 (d,  $J$  = 15 Hz, 1H), 3.05 (qd,  $J$  = 2.4 Hz,  $J$  = 5.1 Hz, 1H), 2.90 (d,  $J$  = 2.4 Hz, 1H); <sup>13</sup>C NMR (75 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) :  $\delta$  168.0, 139.0, 130.3, 130.2, 128.1, 124.5 (q,  $J$  = 270.75), 54.8, 43.8 (q,  $J$  = 39.75 Hz), 38.0; <sup>19</sup>F NMR (188 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) :  $\delta$  -70.10 (brs). HRMS (ESI-QTOF)  $m/z$  C<sub>11</sub>H<sub>10</sub>F<sub>3</sub>NO<sub>2</sub> [M+H]<sup>+</sup> cal. 246.0736, found 246.0741.



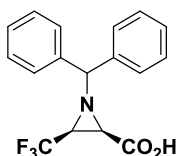
***Cis-1-(4-methoxybenzyl)-3-trifluoromethyl-aziridine-2-carboxylic acid (cis-1b)***

Aziridine acid was obtained from the corresponding aziridine ester (0.5 g, 1.65 mmol) following general saponification procedure. White solid (0.41 g, 90% yield). m. p. : 163°C.  $^1\text{H}$  NMR (200 MHz,  $(\text{CD}_3)_2\text{CO}$ ) :  $\delta$  7.35 (d,  $J$  = 9 Hz, 2H), 6.90 (d,  $J$  = 9 Hz, 2H), 3.79 (s, 3H), 3.78 (d,  $J$  = 12 Hz, 1H), 3.63 (d,  $J$  = 12 Hz, 1H), 2.9 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $(\text{CD}_3)_2\text{CO}$ ) :  $\delta$  167.5, 160.2, 130.4, 130.1, 124.9 (q,  $J$  = 275.25), 114.6, 62.0, 55.5, 43.1 (q,  $J$  = 39 Hz), 42.2;  $^{19}\text{F}$  NMR (188 MHz,  $(\text{CD}_3)_2\text{CO}$ ) :  $\delta$  -66.02 (d,  $J$  = 5.6 Hz). Anal. Calcd for  $\text{C}_{12}\text{H}_{12}\text{F}_3\text{NO}_3$  : C, 52.37 ; H, 4.39 ; N, 5.09. Found : C, 52.19 ; H, 4.16 ; N, 4.99.



***Cis-1-(4-methoxyphenyl)-3-trifluoromethyl-aziridine-2-carboxylic acid (cis-1c)***

Aziridine acid was obtained from the corresponding aziridine ester (0.53 g, 1.83 mmol) following general saponification procedure. White solid (0.47 g, 97% yield). m. p. : 124°C.  $^1\text{H}$  NMR (200 MHz,  $(\text{CD}_3)_2\text{CO}$ ) :  $\delta$  7.05 (d,  $J$  = 9 Hz, 2H), 6.89 (d,  $J$  = 9 Hz, 2H), 3.76 (s, 3H), 3.35-3.31 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $(\text{CD}_3)_2\text{CO}$ ) :  $\delta$  167.2, 157.5, 144.4, 124.8 (q,  $J$  = 271.5 Hz), 121.5, 115.3, 55.8, 43.2 (q,  $J$  = 39.75 Hz), 42.2;  $^{19}\text{F}$  NMR (188 MHz,  $(\text{CD}_3)_2\text{CO}$ ) :  $\delta$  -67.11 (brs). Anal Calcd for  $\text{C}_{11}\text{H}_9\text{F}_3\text{NO}_3$  : C, 50.58 ; H, 3.8 ; N, 5.36. Found : C, 50.30 ; H, 3.55 ; N, 5.20.



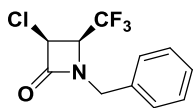
***Cis-1-dibenzyl-3-trifluoromethyl-aziridine-2-carboxylic acid (cis-1d)***

Aziridine acid was obtained from the corresponding aziridine ester (0.5 g, 1.43 mmol) following general saponification procedure. White solid (0.382 g, 83% yield). m. p. : 130°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42-7.13 (m, 10H), 3.81 (s, 1H), 2.62 (d,  $J$  = 6 Hz, 1H), 2.53 (quint,  $J$  = 6 Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  169.5, 140.8, 128.8, 128.8, 128.0, 127.9, 127.4, 127.2, 123.0 (q,  $J$  = 273.75 Hz), 76.9, 44.0 (q,  $J$  = 40.5 Hz), 41.8;  $^{19}\text{F}$  NMR (188 MHz,  $\text{CDCl}_3$ )  $\delta$  -68.45 (d,  $J$  = 5.6 Hz). HRMS (ESI-QTOF)  $m/z$   $\text{C}_{17}\text{H}_{14}\text{F}_3\text{NO}_2$   $[\text{M}+\text{Na}]^+$  cal. 344.0869, found 344.0869.

**General procedure for the preparation of Chloro- $\beta$ -lactam**

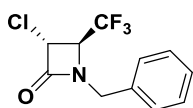
To a solution of aziridine (1 eq) in anhydrous toluene under argon was added NaH (1.1 eq). The solution was cooled to 0°C then chlorinating reagent ( $\text{SOCl}_2$  or  $\text{POCl}_3$ ) (1.5 eq) was added dropwise. The reaction mixture was stirred at 80°C for 1h and then cooled to room temperature. The solvent was concentrated and ethyl acetate was added

followed by a solution of saturated NaHCO<sub>3</sub>. The aqueous layer was extracted with AcOEt (2x20 mL) and the organic phases were washed with water and brine, then concentrated under vacuum. Crude product was purified on silica gel chromatography (Cyclohexane / AcOEt : 9/1).



***Cis-1-benzyl-3-chloro-4-trifluoromethyl-azetidin-2-one (cis-2a)***

$\beta$ -lactam was obtained from the corresponding *cis* aziridine acid **cis-1a** (0.4 g, 1.62 mmol) with POCl<sub>3</sub> (0.275 g, 1.8 mmol) following general procedure. White solid (0.33g, 76% yield). m. p. : 94°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  7.29-7.14 (m, 5H), 4.87 (d, *J* = 5.7 Hz, 1H), 4.78 (d, *J* = 15 Hz, 1H), 3.99 (quint, *J* = 6 Hz, 1H), 3.96 (d, *J* = 15 Hz, 1H) ; <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) :  $\delta$  162.6, 133.6, 129.2, 128.6, 123.1 (q, *J* = 278.25 Hz), 56.0 (q, *J* = 33.75 Hz), 55.3, 46.1 ; <sup>19</sup>F NMR (188 MHz, CDCl<sub>3</sub>)  $\delta$  -69.52 (d, *J* = 7.5 Hz). HRMS (ESI-QTOF) *m/z* C<sub>11</sub>H<sub>9</sub>ClF<sub>3</sub>NO [M+H]<sup>+</sup> cal. 264.0398, found 264.0399.



***Trans-1-benzyl-3-chloro-4-trifluoromethyl-azetidin-2-one (trans-2a)***

$\beta$ -lactam was obtained from the corresponding *trans* aziridine acid **trans-1a** (0.1 g, 0.41 mmol) with SOCl<sub>2</sub> (0.053 g, 0.45 mmol) and NaH (0.01 g, 0.45 mmol) following general procedure. Colorless oil (0.06 g, 55% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  7.32-7.18 (m, 5H), 4.84 (d, *J* = 15 Hz, 1H), 4.74 (d, *J* = 1.4 Hz, 1H), 3.95 (d, *J* = 15 Hz, 1H), 3.75 (qd, *J* = 2 Hz, *J* = 5.8 Hz, 1H); <sup>19</sup>F NMR (188 MHz, CDCl<sub>3</sub>)  $\delta$  -74.12 (d, *J* = 5.7 Hz).

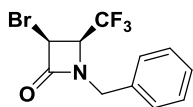
**General procedure for the preparation bromo- $\beta$ -lactam**

**Method A:**

To a solution of aziridine (1 eq) in anhydrous toluene under argon was added NaH (1.1 eq). The solution was cooled to 0°C then SOBr<sub>2</sub> (1.1 eq) was added dropwise. The reaction mixture was stirred at 80°C for 1h and then cooled to room temperature. The solvent was concentrated and ethyl acetate was added followed by a solution of saturated NaHCO<sub>3</sub>. The aqueous layer was extracted with AcOEt (2x20 mL). The organic phases were washed with water (x2), brine (x1), dried over MgSO<sub>4</sub> and then concentrated under vacuum. Crude product was purified on silica gel chromatography (Cyclohexane / AcOEt : 8/2).

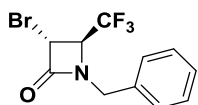
**Method B**

To a solution aziridine (1 eq) in anhydrous dichloromethane was added a solution of triphenylphosphine dibromide (1 eq) in anhydrous dichloromethane. The reaction was stirred at room temperature for 30 min. A solution of saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> was added and aqueous layer was extracted with DCM (2x15 mL). The organic phases were then washed with water, brine, dried over MgSO<sub>4</sub>, and then concentrated under vacuum. Crude product was purified on silica gel chromatography (Cyclohexane / AcOEt : 8/2).



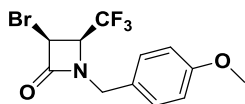
***Cis-1-benzyl-3-bromo-4-trifluoromethyl-azetidin-2-one (cis-3a)***

$\beta$ -lactam was obtained from the corresponding *cis* aziridine acid **cis-1a** (0.6 g, 2.44 mmol) with  $\text{PPh}_3\text{Br}_2$  (1.0 g, 2.44 mmol) following general procedure. White solid (0.56 g, 75% yield). m. p. : 105°C.  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40-7.26 (m, 5H), 4.99 (d,  $J$  = 6.0 Hz, 1H), 4.89 (d,  $J$  = 15.0 Hz, 1H), 4.10 (quint,  $J$  = 6.0 Hz, 1H), 4.05 (d,  $J$  = 15.0 Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) :  $\delta$  162.4, 133.6, 128.2, 129.2, 128.6, 123.2 (q,  $J$  = 279 Hz), 55.0 (q,  $J$  = 33.75 Hz), 46.4, 41.0;  $^{19}\text{F}$  NMR (188 MHz,  $\text{CDCl}_3$ )  $\delta$  -69.48 (d,  $J$  = 5.64 Hz). Anal Calcd for  $\text{C}_{11}\text{H}_9\text{BrF}_3\text{NO}$ : C, 42.88; H, 2.94, N, 4.55. Found: C, 42.7; H, 2.93, N, 4.24.



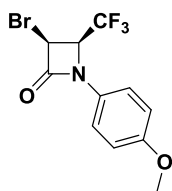
***Trans-1-benzyl-3-bromo-4-trifluoromethyl-azetidin-2-one (trans-3a)***

$\beta$ -lactam was obtained from the corresponding *trans* aziridine acid **trans-1a** (0.26 g, 1.06 mmol) with  $\text{PPh}_3\text{Br}_2$  (0.417 g, 1.60 mmol) following general procedure. Colorless oil (0.16 g, 50% yield).  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30-7.16 (m, 5H), 4.80 (d,  $J$  = 15 Hz, 1H), 4.72 (brs, 1H), 3.97 (d,  $J$  = 15 Hz, 1H), 3.80 (qd,  $J$  = 1.8 Hz,  $J$  = 5.7 Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) :  $\delta$  160.0, 133.4, 129.3, 128.6, 128.4, 123.3 (q,  $J$  = 279 Hz), 60.3 (q,  $J$  = 34.5 Hz), 42.3, 41.6;  $^{19}\text{F}$  NMR (188 MHz,  $\text{CDCl}_3$ )  $\delta$  -74.37 (d,  $J$  = 5.64 Hz). HRMS (ESI-QTOF)  $m/z$   $\text{C}_{11}\text{H}_9\text{BrF}_3\text{NO}$   $[\text{M}+\text{H}]^+$  cal. 307.9892, found 307.9891.



***Cis-3-bromo-1-(4'-methoxybenzyl)-4-trifluoromethyl-azetidin-2-one (cis-3b)***

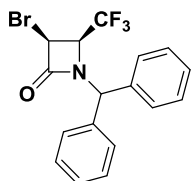
$\beta$ -lactam was obtained from the corresponding *cis* aziridine acid **cis-1b** (2.2 g, 7.99 mmol) with  $\text{PPh}_3\text{Br}_2$  (3.37 g, 7.99 mmol) following general procedure. White solid (2.2 g, 81% yield). m. p. : 95°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) :  $\delta$  7.18 (d,  $J$  = 6 Hz, 2H), 6.89 (d,  $J$  = 6 Hz, 2H), 4.94 (d,  $J$  = 6 Hz, 1H), 4.84 (d,  $J$  = 15 Hz, 1H), 4.05 (quint,  $J$  = 6 Hz, 1H), 3.95 (d,  $J$  = 15 Hz, 1H), 3.81 (s, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) :  $\delta$  162.4, 159.9, 130.1, 125.6, 123.2 (1C, q,  $J$  = 278 Hz), 114.6, 55.4, 54.6 (q,  $J$  = 33 Hz), 45.9, 41.0;  $^{19}\text{F}$  NMR (188 MHz,  $\text{CDCl}_3$ )  $\delta$  -69.45 (d,  $J$  = 6 Hz). HRMS (ESI-Q-TOF)  $m/z$   $\text{C}_{12}\text{H}_{11}\text{BrF}_3\text{NO}$   $[\text{M}+\text{Na}]^+$  cal. 359.9817, found 359.9819.



***Cis-3-bromo-1-(4'-methoxyphenyl)-4-trifluoromethyl-azetidin-2-one (cis-3c)***

$\beta$ -lactam was obtained from the corresponding *cis* aziridine acid **cis-1c** (1.0 g, 3.82 mmol) with  $\text{PPh}_3\text{Br}_2$  (1.61 g, 3.82 mmol) following general procedure. White solid (1.0 g, 81% yield). m. p. : 133°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) :  $\delta$  7.36

(d,  $J = 9$  Hz, 2H), 6.90 (d,  $J = 9$  Hz, 2H), 5.21 (d,  $J = 6$  Hz, 1H), 4.80 (quint,  $J = 6$  Hz, 1H), 3.79 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) :  $\delta$  160.1, 157.8, 128.9, 123.0 (q,  $J = 279.75$  Hz), 120.1, 114.7, 56.3 (q,  $J = 33$  Hz), 55.6, 41.0;  $^{19}\text{F}$  NMR (188 MHz,  $\text{CDCl}_3$ ) :  $\delta$  -68.44 (d,  $J = 5.55$  Hz). Anal Calcd for  $\text{C}_{11}\text{H}_9\text{BrF}_3\text{NO}_2$  : C, 40.77 ; H, 2.8 ; N, 4.36. Found : C, 40.93 ; H, 2.45 ; N, 4.23.

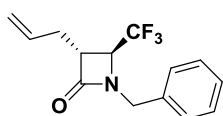


***Cis-1-benzhydryl-3-bromo-4-(trifluoromethyl)azetidin-2-one (cis-3d)***

$\beta$ -lactam was obtained from the corresponding *cis* aziridine acid **cis-1d** (0.382 g, 1.19 mmol) with  $\text{PPh}_3\text{Br}_2$  (0.5 g, 1.19 mmol) following general procedure. White solid (0.17 g, 38% yield). m. p. :  $123^\circ\text{C}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) :  $\delta$  7.30-7.15 (m, 10H), 5.70 (s, 1H), 4.86 (d,  $J = 5.4$  Hz, 1H), 4.08 (quint,  $J = 6$  Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) :  $\delta$  162.6, 137.4, 136.4, 129.9, 128.8, 128.7, 128.5, 128.3, 127.8, 123.1 (q,  $J = 279$  Hz), 63.8, 55.9 (q,  $J = 33.75$ ), 40.4;  $^{19}\text{F}$  NMR (188 MHz,  $\text{CDCl}_3$ ) :  $\delta$  -68.87 (d,  $J = 5.64$  Hz); HRMS (ESI-QTOF)  $m/z$   $\text{C}_{17}\text{H}_{13}\text{BrF}_3\text{NO}$   $[\text{M}+\text{Na}]^+$  cal. 406.0025, found 406.0021.

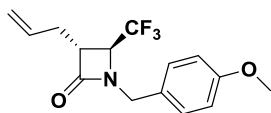
**General procedure for the preparation of *trans*-3-Allyl- 4-trifluoromethyl-azetidin-2-one derivatives**

To a solution of  $\beta$ -lactam (1 eq) in anhydrous toluene under inert atmosphere was added allyltributyltin (2 eq), and AIBN (1 eq). The mixture was immediately warmed at  $80^\circ\text{C}$ . After completion of the reaction (monitored by NMR  $^{19}\text{F}$ ), solvent was removed under vacuum crude product was purified on silica gel chromatography (Cyclohexane /  $\text{AcOEt}$  : 9/1).



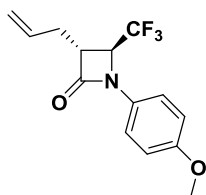
***Trans-3-Allyl-1-benzyl-4-trifluoromethyl-azetidin-2-one (4a)***

Product was obtained from the corresponding  $\beta$ -lactam **cis-3a** (0.145 g, 0.48 mmol) following general procedure. Colorless oil (0.08 g, 62% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29-7.17 (m, 5H), 5.62 (ddt,  $J = 7$  Hz,  $J = 10$  Hz,  $J = 17$  Hz, 1H), 5.03 (dd,  $J = 1.2$  Hz,  $J = 17$  Hz, 1H), 4.98 (dd,  $J = 1.2$  Hz,  $J = 10$  Hz, 1H), 4.78 ( $J = 15$  Hz, 1H), 3.86 ( $J = 15$  Hz, 1H), 3.42 (qd,  $J = 2$  Hz,  $J = 6$  Hz, 1H), 3.28 (td,  $J = 1$  Hz,  $J = 6.6$  Hz, 1H), 2.34 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) :  $\delta$  168.0, 134.8, 132.7, 129.0, 128.7, 128.3, 124.5 (q,  $J = 277.5$  Hz), 118.8, 54.8 (q,  $J = 67.5$  Hz), 51.5, 45.6, 31.5;  $^{19}\text{F}$  NMR (188 MHz,  $\text{CDCl}_3$ )  $\delta$  -74.10 (d,  $J = 5.82$  Hz). HRMS (ESI-QTOF)  $m/z$   $\text{C}_{14}\text{H}_{14}\text{F}_3\text{NO}$   $[\text{M}+\text{H}]^+$  cal. 270.1100, found 270.1099.



***Trans-3-Allyl-1-(4'-methoxybenzyl)-4-trifluoromethyl-azetidin-2-one (4b)***

Product was obtained from the corresponding  $\beta$ -lactam **cis-3b** (0.425 g, 1.25 mmol) following general procedure. Colorless oil (0.215 g, 57% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.15 (d,  $J$  = 6 Hz, 1H), 6.85 (d,  $J$  = 6 Hz, 1H), 5.67 (m, 1H), 5.08 (d,  $J$  = 12 Hz, 1H), 5.03 (d,  $J$  = 6 Hz, 1H), 4.77 (d,  $J$  = 12 Hz, 1H), 3.85 (d,  $J$  = 12 Hz, 1H), 3.77 (s, 3H), 3.46 (qd,  $J$  = 6 Hz,  $J$  = 3 Hz, 1H), 3.31 (m, 1H), 2.33 (m, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) :  $\delta$  167.7, 159.5, 132.7, 129.9, 126.8, 124.5 (q,  $J$  = 277 Hz), 118.6, 114.3, 55.2, 54.6 (q,  $J$  = 33.75 Hz), 51.3, 44.9, 31.4;  $^{19}\text{F}$  NMR (188 MHz,  $\text{CDCl}_3$ ) :  $\delta$  -74.08 (d,  $J$  = 6 Hz). HRMS (ESI-Q-TOF)  $m/z$   $\text{C}_{15}\text{H}_{16}\text{F}_3\text{NO}_2$   $[\text{M}+\text{Na}]^+$  cal. 322.1025, found 322.1029.



***Trans-3-Allyl-1-(4'-methoxyphenyl)-4-trifluoromethyl-azetidin-2-one (4c)***

Product was obtained from the corresponding  $\beta$ -lactam **cis-3c** (0.69 g, 2.12 mmol) following general procedure. White solid (0.480 g, 79% yield). m. p. : 56°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33 (d,  $J$  = 6 Hz, 1H), 6.86 (d,  $J$  = 6 Hz, 1H), 5.80 (m, 1H), 5.22 (d,  $J$  = 12 Hz, 1H), 5.17 (d,  $J$  = 6 Hz, 1H), 4.2 (qd,  $J$  = 6 Hz,  $J$  = 3 Hz, 1H), 3.77 (s, 3H), 3.45 (m, 1H), 2.57 (m, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) :  $\delta$  165.1, 157.0, 132.6, 129.8, 124.3 (q,  $J$  = 278.25 Hz), 119.4, 118.9, 114.4, 56.0 (q,  $J$  = 34.5 Hz), 55.4, 51.2, 31.8;  $^{19}\text{F}$  NMR (188 MHz,  $\text{CDCl}_3$ ) :  $\delta$  -72.84 (d,  $J$  = 4.88 Hz). HRMS (ESI-TOF)  $m/z$   $\text{C}_{14}\text{H}_{14}\text{F}_3\text{NO}_2$   $[\text{M}+\text{H}]^+$  cal. 286.1055, found 286.1051.

**General procedure for the preparation of *trans*-3-(hydroxy(alkyl/aryl)methyl)-4-trifluoromethyl-azetidin-2-one derivatives**

**Method A**

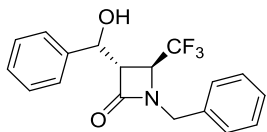
A mixture of corresponding  $\beta$ -lactam (1 eq), freshly distilled aldehyde (1.5 eq) and zinc (2 eq) were dissolved in dry THF and few drop of TMSCl were added. The reaction was stirred at room temperature and completion was monitored by  $^{19}\text{F}$  NMR. A solution of saturated  $\text{NH}_4\text{Cl}$  was added to the reaction mixture and aqueous layer was extracted with  $\text{Et}_2\text{O}$  (2x10 ml). The organic phases were then washed with water (x2), brine (x1) and dried over  $\text{MgSO}_4$ .

**Method B**

A solution of  $n\text{-BuLi}$  (1.5 eq, 1.6M in THF) was added to a solution of **cis-3-bromo-1-(4'-methoxyphenyl)-4-trifluoromethyl-azetidin-2-one** (1 eq) in dry THF under inert atmosphere at -100°C. After 15 minutes stirring, a solution of desired electrophile (2 eq) in dry THF was added dropwise and the reaction was stirred at -100 °C for 1h.

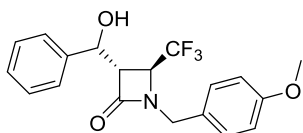


A solution of saturated  $\text{NH}_4\text{Cl}$  was added to the reaction mixture and aqueous layer was extracted with  $\text{Et}_2\text{O}$ . The organics were washed with water, brine, dried over  $\text{MgSO}_4$  and then removed under vacuum. The crude product was purified by chromatography on silica gel (Cyclohexane /  $\text{AcOEt}$  : 9/1).



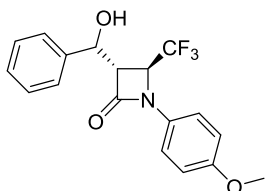
***Trans-1-benzyl-3-(hydroxy(phenyl)methyl)-4-(trifluoromethyl)azetidin-2-one (5a)***

Product was obtained from the  $\beta$ -lactam **cis-3a** (0.15 g, 0.49 mmol) and corresponding aldehyde (0.077 g, 0.73 mmol) following Method A. White solid (0.09 g, 65% yield). m. p. : 76-79°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38-6.85 (m, 10H), 5.17 and 4.99 (brs, 1H), 4.76 (d,  $J$  = 15.3 Hz, 1H), 3.94 and 3.68 (qd,  $J$  = 2.4 Hz,  $J$  = 6 Hz, 1H), 3.91 and 3.79 (d,  $J$  = 15.3 Hz, 1H), 3.63 and 3.50 (br m, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) :  $\delta$  166.9, 166.1, 165.9, 140.4, 139.5, 134.3, 134.0, 128.8, 128.7, 128.3, 128.1, 128.0, 126.6, 125.2, 124.2 (q,  $J$  = 277.5 Hz), 70.9, 68.8, 59.3, 58.3, 52.4 (q,  $J$  = 34.5 Hz), 51.3 (q,  $J$  = 33.75 Hz), 45.6, 45.3;  $^{19}\text{F}$  NMR (188 MHz,  $\text{CDCl}_3$ ) :  $\delta$  -73.85 (d,  $J$  = 5.64), -73.95 (d,  $J$  = 5.64 Hz). HRMS (ESI-TOF)  $m/z$   $\text{C}_{18}\text{H}_{16}\text{F}_3\text{NO}_2$   $[\text{M}+\text{Na}]^+$  cal. 358.1031, found 358.1029.



***Trans-1-(4'-methoxybenzyl)-3-(hydroxy(phenyl)methyl)-4-trifluoromethyl-azetidin-2-one (5b)***

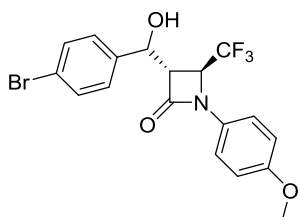
Product was obtained from the  $\beta$ -lactam **cis-3b** (0.6 g, 1.77 mmol) and corresponding aldehyde (0.282 g, 2.66 mmol) following Method A. White solid (0.382 g, 60% yield). m. p. : 98-102°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34-7.17 (m, 5H), 7.08 (d,  $J$  = 9 Hz, 2H), 6.75 and 6.65 (d,  $J$  = 9 Hz, 2H), 5.15 and 4.95 (brs, 1H), 4.02 and 3.91 (qd,  $J$  = 1.8 Hz,  $J$  = 6 Hz, 1H), 3.83 (d,  $J$  = 15 Hz, 1H), 3.71 (s, 3H), 3.62 and 3.47 (brs, 1H), 3.11 and 2.87 (brs, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) :  $\delta$  167.0, 166.0, 159.3, 140.5, 139.6, 129.7, 129.5, 128.8, 128.6, 128.0, 126.7, 126.2, 125.2, 124.2 (q,  $J$  = 278 Hz), 114.2, 70.8, 68.8, 59.1, 58.1, 55.2, 51.1 (q,  $J$  = 33.75 Hz), 45.0, 44.7;  $^{19}\text{F}$  NMR (188 MHz,  $\text{CDCl}_3$ ) :  $\delta$  -73.84 and -73.94 (d,  $J$  = 5.64 Hz). HRMS (ESI-TOF)  $m/z$   $\text{C}_{19}\text{H}_{18}\text{F}_3\text{NO}_3$   $[\text{M}+\text{Na}]^+$  cal. 388.1136, found 388.1139.



***Trans-1-(4'-methoxyphenyl)-3-(hydroxy(phenyl)methyl)-4-trifluoromethyl-azetidin-2-one (5c)***

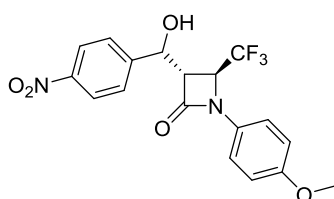
Product was obtained from the  $\beta$ -lactam **cis-3c** (0.7 g, 2.16 mmol) and corresponding aldehyde (0.343 g, 3.24 mmol) following Method A. Mixture of 2 diastereoisomers as a white solid (0.45 g, 60% yield). m. p. : 113-115°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38 (m, 7H), 6.86 (d,  $J$  = 9 Hz, 2H), 5.29 and 5.10 (t,  $J$  = 3 Hz, 1H), 4.68 and 4.42 (qd,  $J$  = 6 Hz,  $J$  = 3 Hz, 1H), 3.78 (s, 3H), 3.75 (dd,  $J$  = 2.4 Hz, 0.2H), 3.65 (t,  $J$  = 1.5 Hz, 0.8H), 2.87 and 2.67 (d,  $J$  = 4 Hz, 1H);  $^{13}\text{C}$  NMR (75

MHz, CDCl<sub>3</sub>) :  $\delta$  164.7, 163.6, 157.1, 140.5, 139.7, 129.4, 128.6, 128.0, 126.6, 125.1, 124.1 (q,  $J$  = 279 Hz), 120.0, 114.4, 71.4, 68.3, 59.2, 58.0, 55.4, 54.3 (q,  $J$  = 33.75 Hz), 52.5 (q,  $J$  = 34.5 Hz); <sup>19</sup>F NMR (188 MHz, CDCl<sub>3</sub>) :  $\delta$  -72.81 (d,  $J$  = 5.64 Hz) and -72.90 (d,  $J$  = 5.64 Hz). HRMS (ESI-TOF)  $m/z$  C<sub>18</sub>H<sub>16</sub>F<sub>3</sub>NO<sub>3</sub> [M+H]<sup>+</sup> cal. 352.1161, found 352.1165.



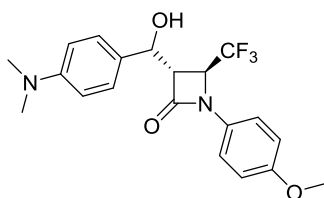
***Trans-3-(4-bromophenyl)(hydroxymethyl)-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one (7)***

Product was obtained from the  $\beta$ -lactam **cis-3c** (0.100 g, 0.295 mmol) and corresponding aldehyde (0.110 g, 0.59 mmol) following Method B. 2 diastereoisomers as a colorless oil (0.053 g, 40% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) :  $\delta$  7.42 (d,  $J$  = 9 Hz, 2H), 7.23 (m, 5H), 6.77 (d,  $J$  = 9 Hz, 2H), 5.18 (brs, 0.5H), 5.00 (d,  $J$  = 4.5 Hz, 0.5H), 4.52 and 4.33 (qd,  $J$  = 2.4 Hz,  $J$  = 5.4 Hz, 1H), 3.71 (s, 3H), 4.62 (dd,  $J$  = 2.4 Hz,  $J$  = 4.5 Hz, 0.5H), 3.52 (t,  $J$  = 2.7 Hz, 0.5H), 3.09 and 2.73 (brs, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) :  $\delta$  164.1, 163.1, 157.3, 139.4, 138.6, 131.9, 131.8, 129.3, 128.36, 126.8, 122.8, 122.0, 119.9, 114.4, 70.9, 67.9, 58.9, 57.7, 55.5, 54.3 (q,  $J$  = 35 Hz), 51.9 (q,  $J$  = 35 Hz); <sup>19</sup>F NMR (188 MHz, CDCl<sub>3</sub>) :  $\delta$  -72.76 (d,  $J$  = 5.45 Hz) and -72.88 (d,  $J$  = 5.65 Hz); HRMS (ESI-TOF)  $m/z$  C<sub>18</sub>H<sub>15</sub>BrF<sub>3</sub>NO<sub>3</sub> [M+Na]<sup>+</sup> cal. 452.0082, found 452.0086.



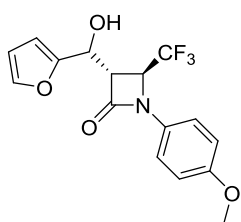
***3-(hydroxy(4-nitrophenyl)methyl)-1-(4'-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one (8)***

Product was obtained from the  $\beta$ -lactam **cis-3c** (0.200 g, 0.610 mmol) and corresponding aldehyde (0.185 g, 1.23 mmol) following Method B. 2 diastereoisomers as a white solid (0.130 g, 54% yield). *Major Isomer*: m.p. 188°C <sup>1</sup>H NMR (300 MHz, Acetone) :  $\delta$  8.27 (d,  $J$  = 8.9 Hz, 2H), 7.90 (d,  $J$  = 8.9 Hz, 2H), 7.46 (d,  $J$  = 9.0 Hz, 2H), 6.98 (d,  $J$  = 9.0 Hz, 2H), 5.61 (d,  $J$  = 4.6 Hz, 1H), 5.54 (dd,  $J$  = 4.0 Hz,  $J$  = 3.6 Hz, 1H), 5.09 (qd,  $J$  = 5.7 Hz,  $J$  = 2.4 Hz, 1H), 3.89 (t,  $J$  = 2.8 Hz, 1H), 3.80 (s, 3H). <sup>13</sup>C NMR (75 MHz, Acetone) :  $\delta$  164.0, 157.9, 150.6, 148.3, 130.9, 127.8, 125.7 (q,  $J$  = 279.5 Hz), 124.2, 120.3, 115.1, 68.3, 60.0, 55.7, 52.6 (q,  $J$  = 34.2 Hz). <sup>19</sup>F NMR (188 MHz, Acetone) :  $\delta$  -71.38 (d,  $J$  = 5.9 Hz). *Minor Isomer* m.p. 166°C <sup>1</sup>H NMR (300 MHz, Acetone) :  $\delta$  8.24 (d,  $J$  = 8.9 Hz, 2H), 7.87 (d,  $J$  = 8.8 Hz, 2H), 7.40 (d,  $J$  = 9.0 Hz, 2H), 6.95 (d,  $J$  = 9.0 Hz, 2H), 5.52 (d,  $J$  = 3.7 Hz, 1H), 5.48 (t,  $J$  = 3.9 Hz, 1H), 5.02 (qd,  $J$  = 5.7 Hz,  $J$  = 2.3 Hz, 1H), 3.97-3.89 (m, 1H), 3.79 (s, 3H); <sup>13</sup>C NMR (75 MHz, Acetone) :  $\delta$  162.2, 154.2, 152.7, 151.3, 135.2, 133.1, 128.3, 124.6, 119.4, 74.3, 63.2, 60.1, 58.8 (d,  $J$  = 34.6 Hz). <sup>19</sup>F NMR (188 MHz, Acetone) :  $\delta$  -71.37 (d,  $J$  = 5.9 Hz). HRMS (ESI-TOF)  $m/z$  C<sub>18</sub>H<sub>15</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> [M+Na]<sup>+</sup> cal. 419.0831, found 419.0833.



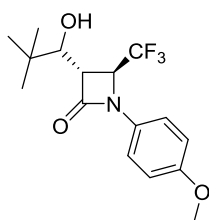
***trans-3-((4-(dimethylamino)phenyl)(hydroxy)methyl)-1-(4'-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one (9)***

Product was obtained from the  $\beta$ -lactam **cis-3c** (0.200 g, 0.610 mmol) and corresponding aldehyde (0.184 g, 1.23 mmol) following Method B. 2 diastereoisomers as a yellow oil (0.168 g, 70% yield). *Major Isomer*  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) :  $\delta$  7.35 (d,  $J$  = 8.9 Hz, 2H), 7.23 (d,  $J$  = 8.7 Hz, 2H), 6.87 (d,  $J$  = 8.9 Hz, 2H), 6.73 (d,  $J$  = 8.7 Hz, 2H), 5.20 (d,  $J$  = 3.4 Hz, 1H), 4.69 (qd,  $J$  = 5.5 Hz,  $J$  = 2.1 Hz, 1H), 3.78 (s, 3H), 3.63 (dd,  $J$  = 2.8 Hz, 1H), 2.95 (s, 6H), 2.51 (s, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) :  $\delta$  164.6, 157.1, 150.5, 130.0, 129.9, 126.4, 126.1, 122.4, 119.9, 118.9, 114.5, 112.7, 69.2, 59.2, 55.6, 53.7, 53.2, 52.8, 52.3, 40.7;  $^{19}\text{F}$ -NMR (188 MHz,  $\text{CDCl}_3$ ) :  $\delta$  -72.55 (brs). *Minor Isomer*  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) :  $\delta$  7.38 (d,  $J$  = 8.7 Hz, 2H), 7.31 (d,  $J$  = 9.0 Hz, 2H), 6.87 (d,  $J$  = 9.0 Hz, 2H), 6.72 (d,  $J$  = 8.7 Hz, 2H), 5.00 (d,  $J$  = 4.7 Hz, 1H), 4.39 (qd,  $J$  = 5.5 Hz,  $J$  = 2.3 Hz, 1H), 3.78 (s, 3H), 3.74 (dd,  $J$  = 4.7 Hz,  $J$  = 2.3 Hz, 1H), 2.95 (s, 6H), 2.36 (s, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) :  $\delta$  163.9, 157.1, 150.8, 130.0, 129.8, 127.9, 126.3, 124.3 (q,  $J$  = 279.0 Hz), 122.6, 119.9, 118.9, 114.5, 112.7, 71.7, 58.2, 55.6, 54.6 (q,  $J$  = 34.5 Hz), 40.7;  $^{19}\text{F}$ -NMR (188 MHz,  $\text{CDCl}_3$ ) :  $\delta$  -72.83 (brs). HRMS (ESI-TOF)  $m/z$   $\text{C}_{20}\text{H}_{21}\text{F}_3\text{N}_2\text{O}_3$   $[\text{M}+\text{H}]^+$  cal. 395.1583, found 395.1588.



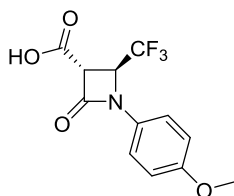
***Trans-3-(furan-2-yl(hydroxy)methyl)-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one (10)***

Product was obtained from the  $\beta$ -lactam **cis-3c** (0.10 g, 0.30 mmol) and corresponding aldehyde (0.058 g, 0.6 mmol) following Method B. 2 diastereoisomers as a yellow oil (0.067 g, 65% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) :  $\delta$  7.32-7.18 (m, 3H), 6.79 (d,  $J$  = 9 Hz, 2H), 6.48-6.27 (m, 2H), 5.20 and 5.06 (brs, 1H), 4.7 and 4.45 (qd,  $J$  = 2.1 Hz,  $J$  = 5.7 Hz, 1H), 3.76 (dd,  $J$  = 2.4 Hz,  $J$  = 5.1 Hz, 0.5H), 3.71 (s, 3H), 3.66 (t,  $J$  = 3 Hz, 0.5H), 3.03 and 2.79 (brs, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) :  $\delta$  163.7, 162.9, 157.2, 152.7, 152.3, 142.8, 142.7, 129.5, 120.0, 119.8, 114.4, 110.7, 110.3, 108.5, 107.1, 65.0, 63.2, 56.3, 55.9, 55.5, 54.2 (q,  $J$  = 34.5 Hz), 52.9 (q,  $J$  = 34.5 Hz);  $^{19}\text{F}$  NMR (188 MHz,  $\text{CDCl}_3$ ) :  $\delta$  -73.73 (d,  $J$  = 5.45 Hz), -72.03 (d,  $J$  = 5.45 Hz); HRMS (ESI-TOF)  $m/z$   $\text{C}_{16}\text{H}_{14}\text{F}_3\text{NO}_4$   $[\text{M}+\text{Na}]^+$  cal. 364.0773, found 364.0771.



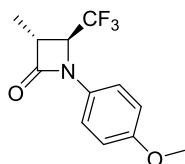
***Trans-3-(1-hydroxy-2,2-dimethylpropyl)-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one (11)***

Product was obtained from the  $\beta$ -lactam **cis-3c** (0.110 g, 0.34 mmol) and corresponding aldehyde (0.089 g, 0.68 mmol) following Method B. One diastereoisomer as a white solid (0.056 g, 50% yield). m. p. : 122°C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) :  $\delta$  7.36 (d,  $J$  = 9 Hz, 2H), 6.88 (d,  $J$  = 9 Hz, 2H), 4.44 (qd,  $J$  = 2.4 Hz,  $J$  = 5.4 Hz, 1H), 3.79 (s, 3H), 3.67 (m, 1H), 3.61 (m, 1H), 2.15 (d,  $J$  = 6.6 Hz, 1H), 1.05 (s, 9H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) :  $\delta$  163.8, 157.2, 129.8, 124.7 (q,  $J$  = 278.55), 119.8, 114.5, 78.2, 55.6, 55.5 (q,  $J$  = 33.6 Hz), 54.1, 35.2, 26.1.;  $^{19}\text{F}$  NMR (188 MHz,  $\text{CDCl}_3$ ) :  $\delta$  -72.63 (d,  $J$  = 5.6 Hz). HRMS (ESI-TOF)  $m/z$   $\text{C}_{16}\text{H}_{20}\text{F}_3\text{NO}_3$   $[\text{M}+\text{H}]^+$  cal. 332.1474, found 332.1473.



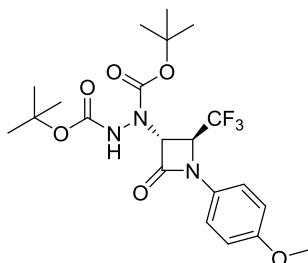
***Trans-1-(4-methoxyphenyl)-3-carboxy-4-(trifluoromethyl)azetidin-2-one (12).***

Product was obtained from the  $\beta$ -lactam **cis-3c** (0.333 g, 1.03 mmol) and carbon dioxide following Method B. 2 diastereoisomers as a brown oil. (0.139 g, 47% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) :  $\delta$  8.86 (s, 1H), 7.33 (d,  $J$  = 8.9 Hz, 2H), 6.88 (d,  $J$  = 8.9 Hz, 2H), 4.86 (qd,  $J$  = 5.3 Hz,  $J$  = 2.4 Hz, 1H), 4.25 (d,  $J$  = 2.3 Hz, 1H), 3.77 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz, Acetone) :  $\delta$  166.1, 158.9, 158.4, 130.5, 125.2 (q,  $J$  = 279.7 Hz), 120.8, 115.3, 56.4, 55.8, 54.7 (q,  $J$  = 34.9 Hz);  $^{19}\text{F}$  NMR (188 MHz,  $\text{CDCl}_3$ ) :  $\delta$  -73.15 (d,  $J$  = 5.2 Hz). HRMS (ESI-TOF)  $m/z$   $\text{C}_{12}\text{H}_{10}\text{F}_3\text{NO}_4$   $[\text{M}+\text{Na}]^+$  cal. 312.0460, found. 312.0466.



***Trans-1-(4-methoxyphenyl)-3-methyl-4-(trifluoromethyl)azetidin-2-one (13)***

Product was obtained from the  $\beta$ -lactam **cis-3c** (0.100 g, 0.30 mmol) and iodomethane (0.085 g, 0.6 mmol) following Method B. Colorless oil (0.054 g, 66 % yield).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) :  $\delta$  7.28 (d,  $J$  = 9 Hz, 2H), 6.80 (d,  $J$  = 9 Hz, 2H), 4.02 (qd,  $J$  = 2.1 Hz,  $J$  = 5.4 Hz, 1H), 3.71 (s, 3H), 3.34 (qd,  $J$  = 2.1 Hz,  $J$  = 7.5 Hz, 1H), 1.39 (d,  $J$  = 7.2 Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) :  $\delta$  166.3, 157.0, 130.0, 124.3 (q,  $J$  = 278.25 Hz), 119.3, 114.4, 58.5 (q,  $J$  = 33.75 Hz), 55.0, 46.8, 12.7;  $^{19}\text{F}$  NMR (188 MHz,  $\text{CDCl}_3$ ) :  $\delta$  -73.3 (d,  $J$  = 5.64 Hz); HRMS (ESI-TOF)  $m/z$   $\text{C}_{12}\text{H}_{12}\text{F}_3\text{NO}_2$   $[\text{M}+\text{H}]^+$  cal. 260.0898, found 260.0897.

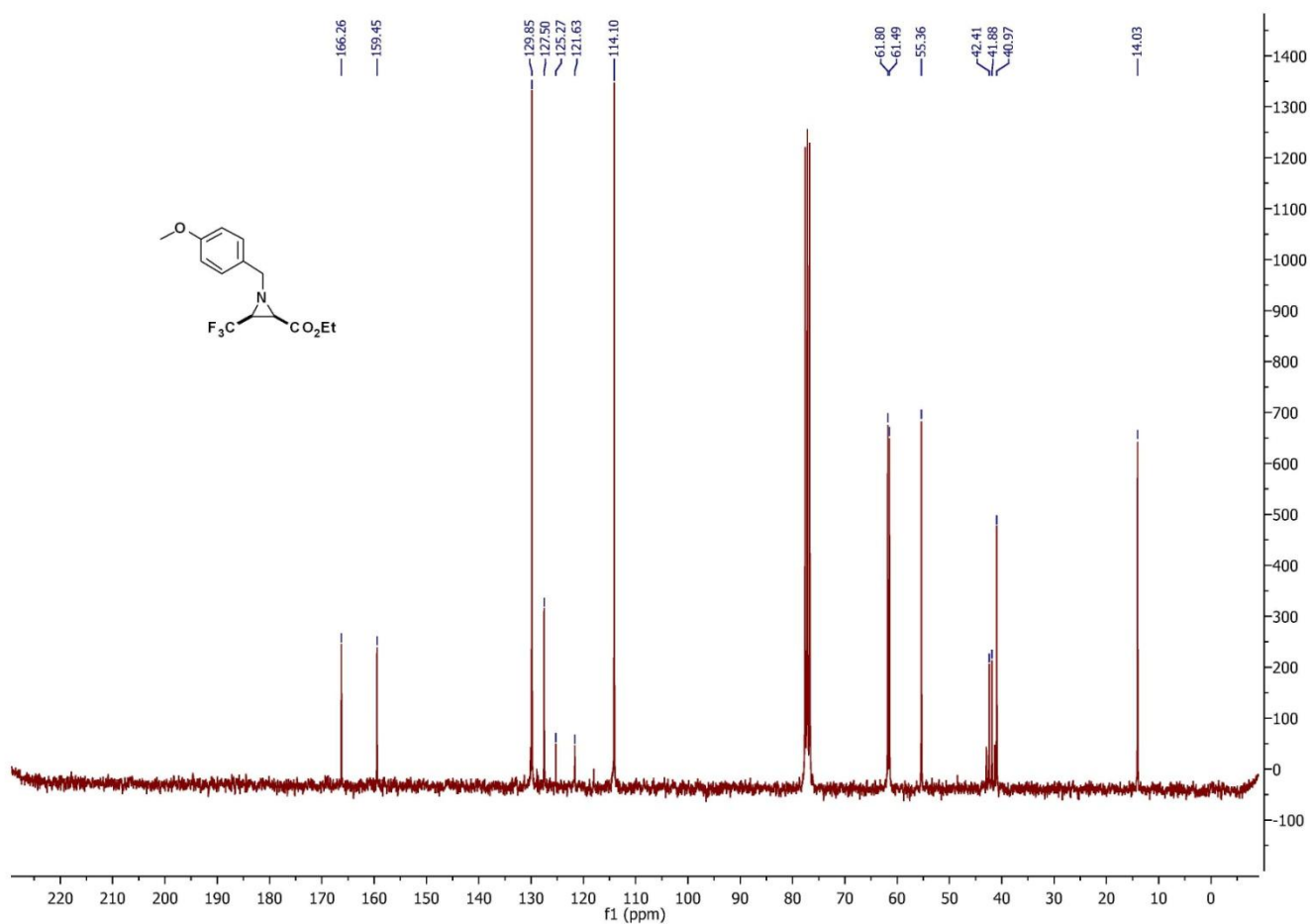
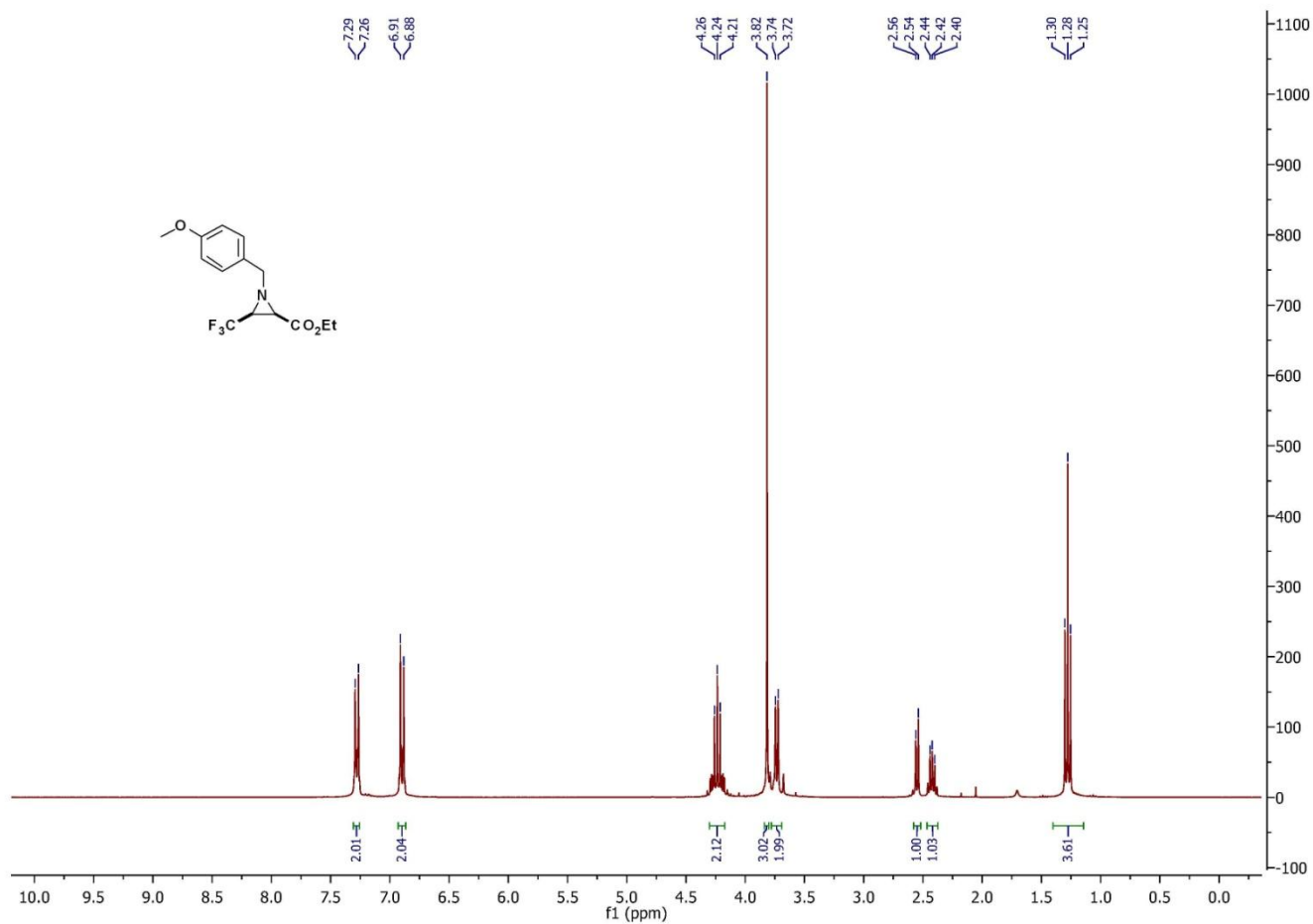


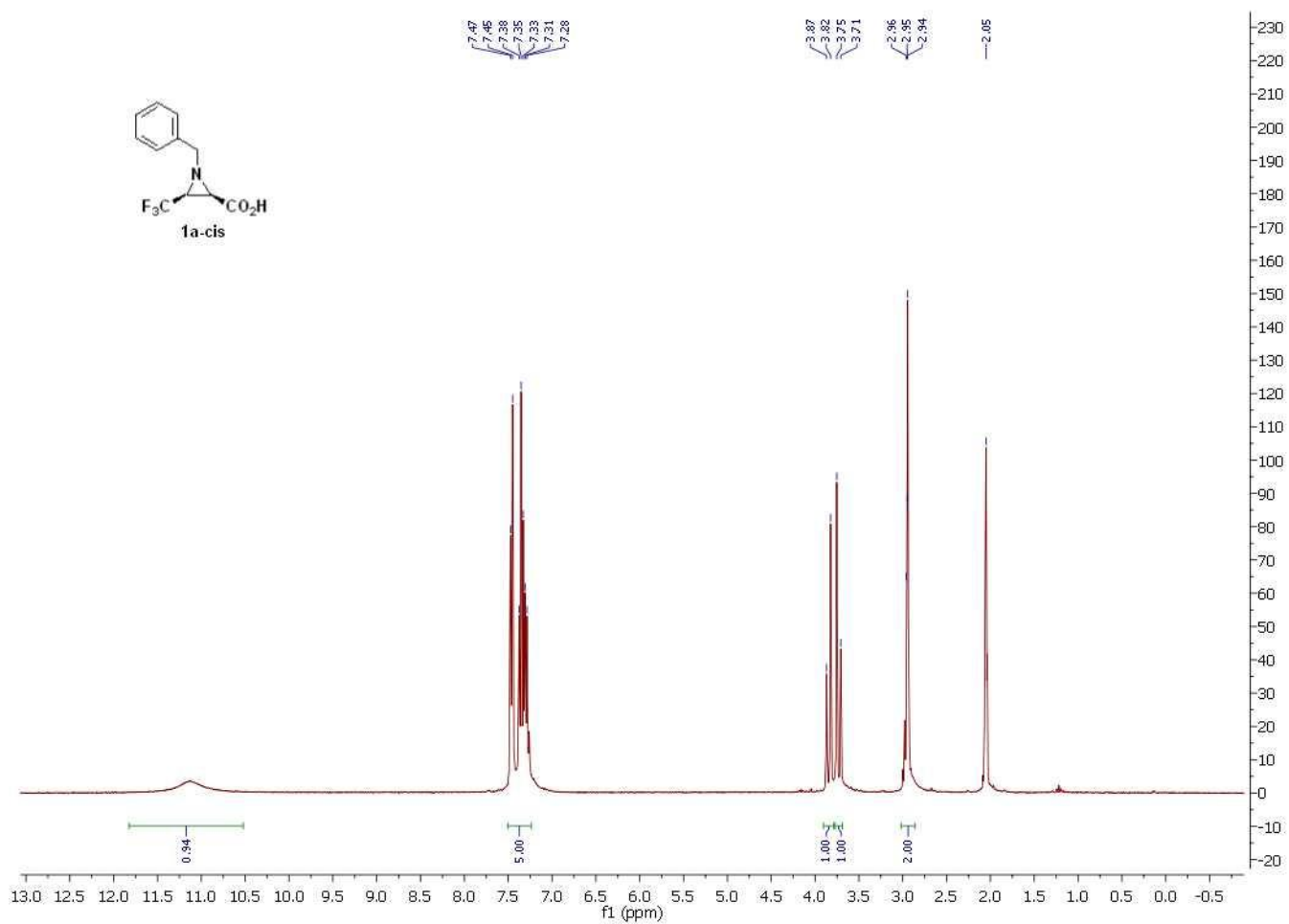
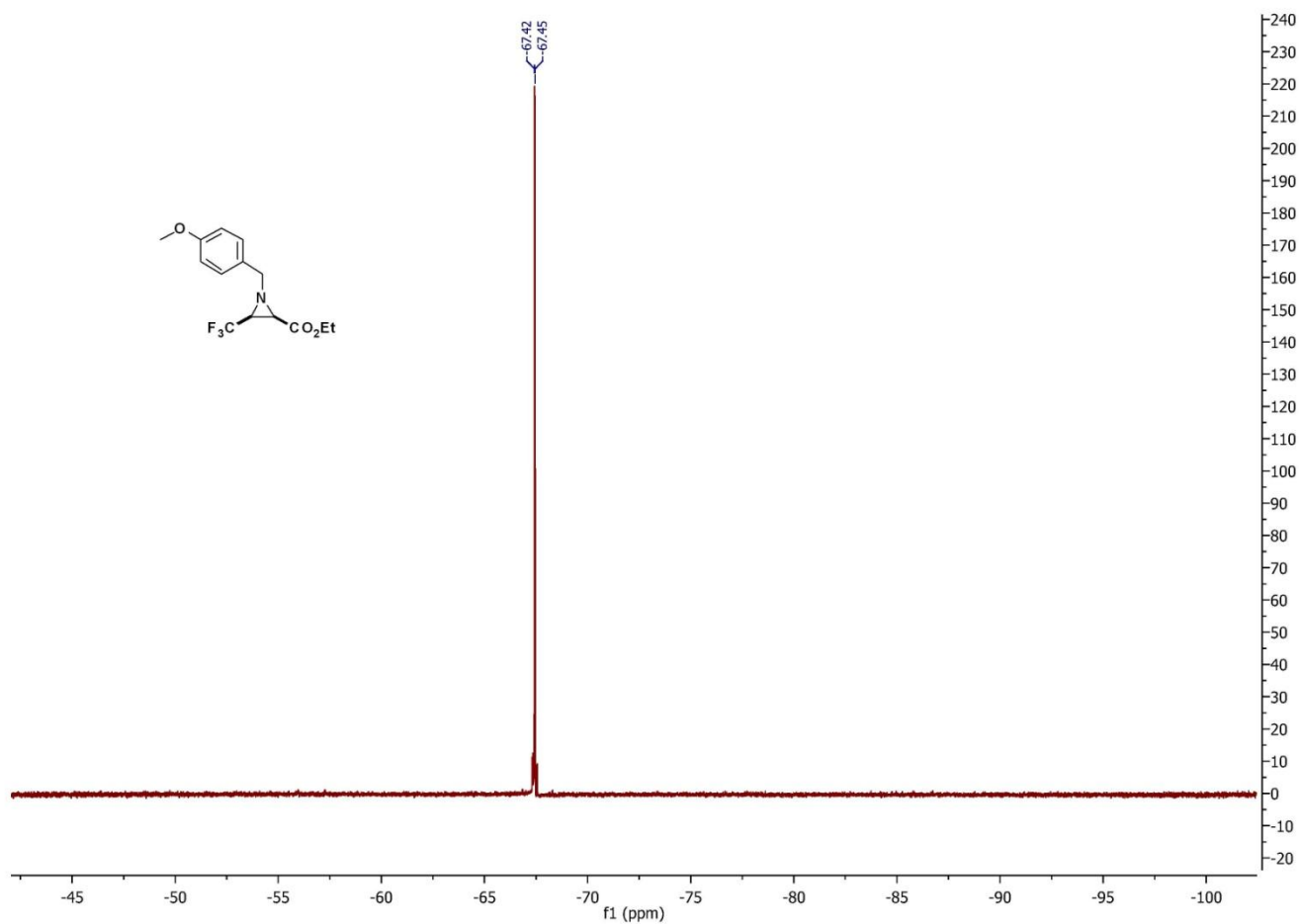
***Di-tert-butyl-1-(1-(4-methoxyphenyl)-2-oxo-4-(trifluoromethyl)azetidin-3-yl)hydrazine-1,2-dicarboxylate (14).***

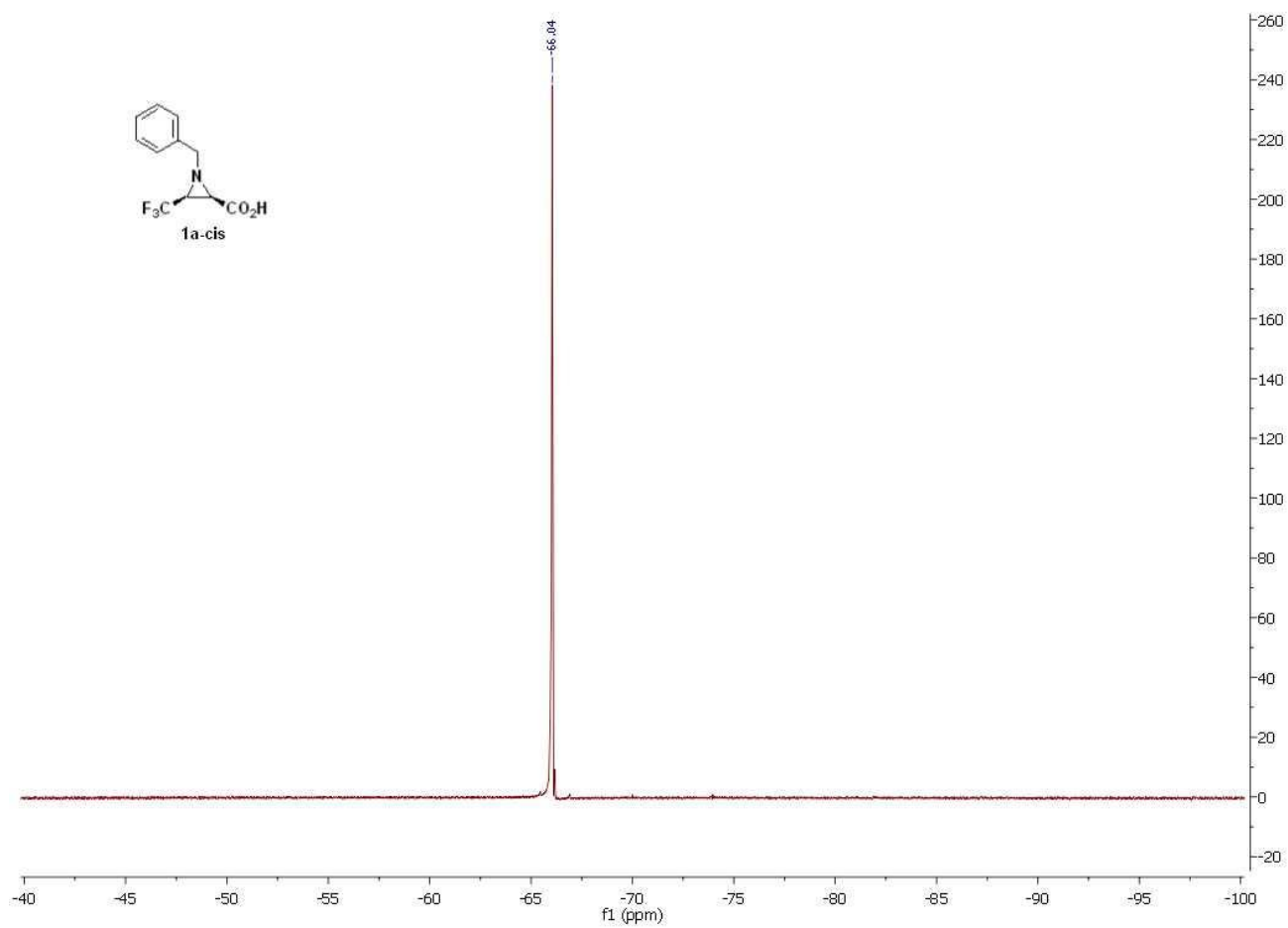
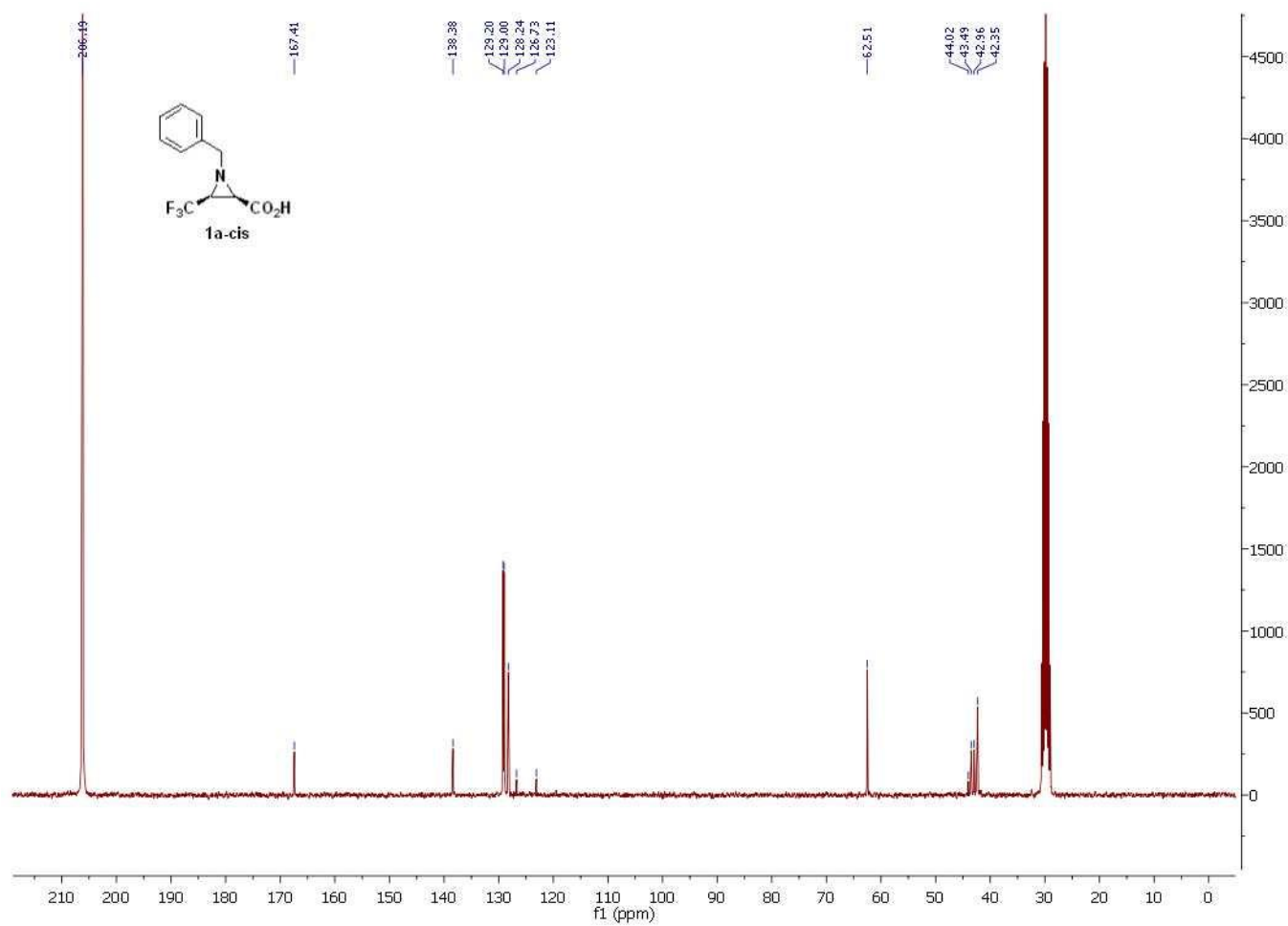
Product was obtained from the  $\beta$ -lactam **cis-3c** (0.150 g, 0.46 mmol) and di-tert-butyl-azodicarboxylate (0.211 g, 0.92 mmol) following Method B. Colorless oil (0.109 g, 50% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) :  $\delta$  7.32 (d,  $J$  = 9 Hz, 2H), 6.88 (d,  $J$  = 9 Hz, 2H), 6.60 (brs, 1H), 5.24 (brs, 1H), 4.89 (brs, 1H), 3.79 (s, 3H), 1.46 (s);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) : 161.6, 161.2, 157.4, 155.7, 152.9, 129.2, 123.9 (q,  $J$  = 279.75 Hz, 18H), 120.5, 119.9, 114.5, 84.1, 83.2, 82.3, 67.9, 57.7 (q,  $J$  = 33.75 Hz), 55.5;  $^{19}\text{F}$  NMR (188 MHz,  $\text{CDCl}_3$ ) :  $\delta$  -72.10 and -72.32 (brs) HRMS (ESI-TOF)  $m/z$   $\text{C}_{21}\text{H}_{28}\text{F}_3\text{N}_3\text{O}_6$   $[\text{M}+\text{Na}]^+$  cal. 498.1828, found 498.1826.

## References

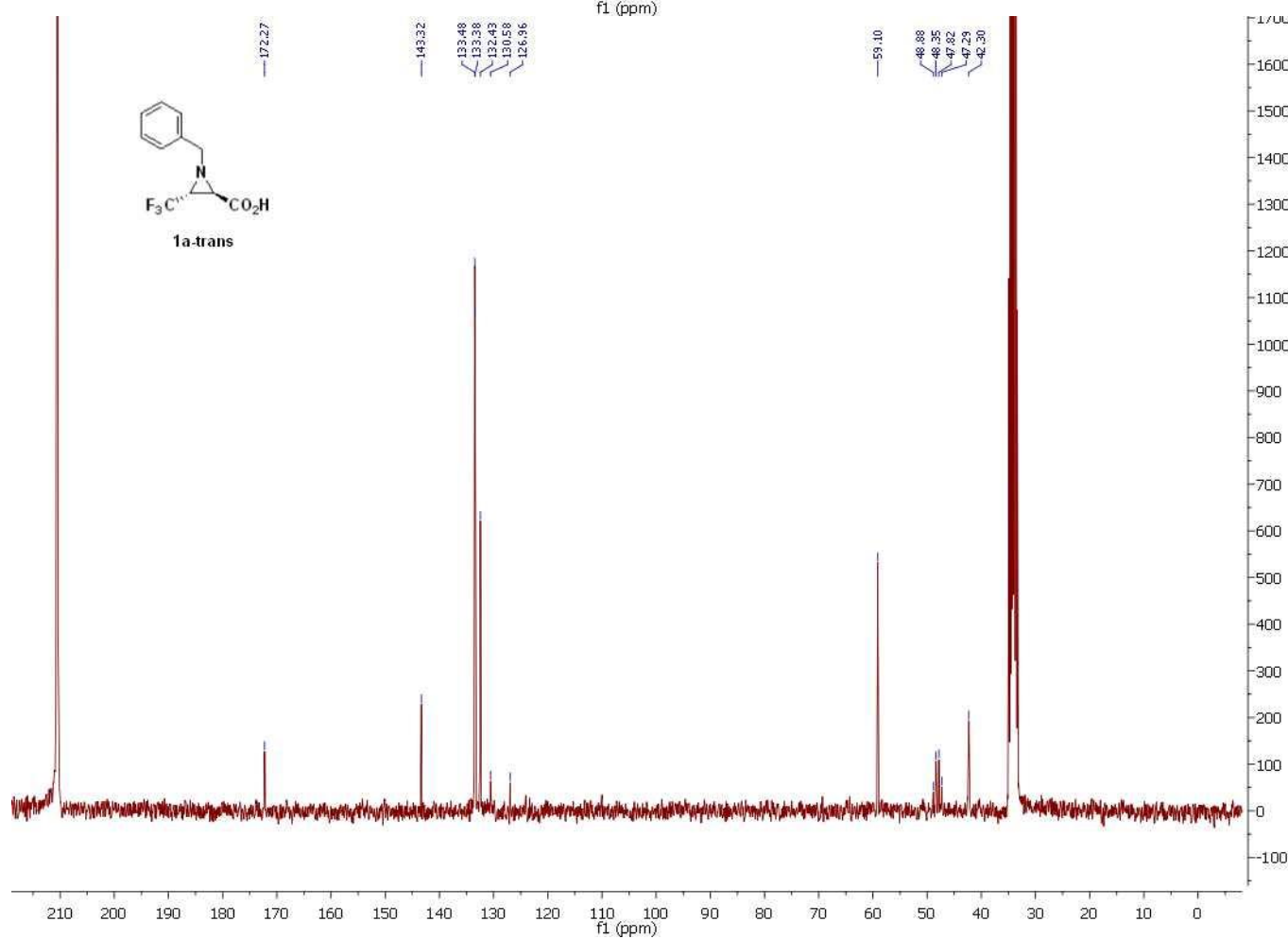
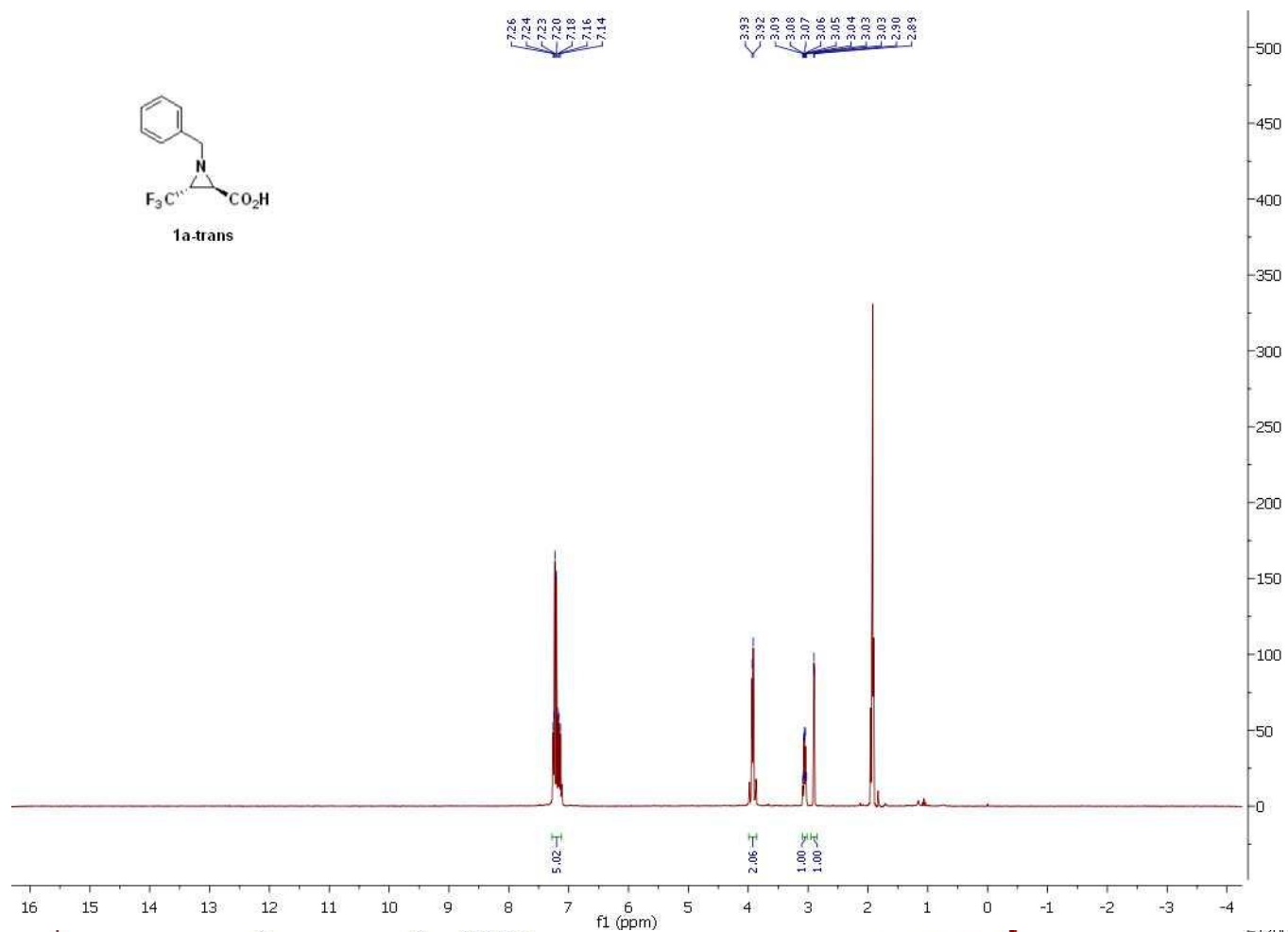
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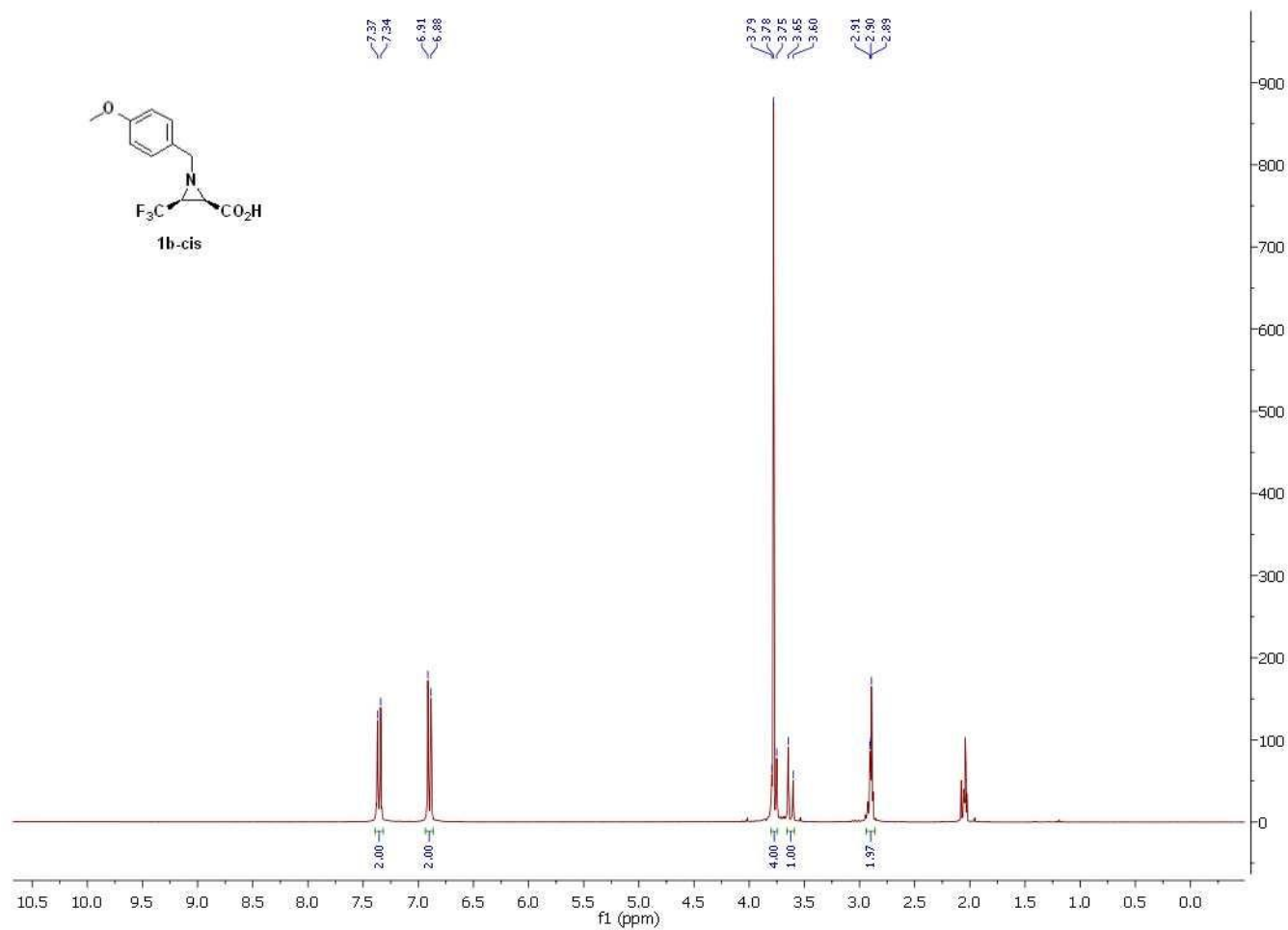
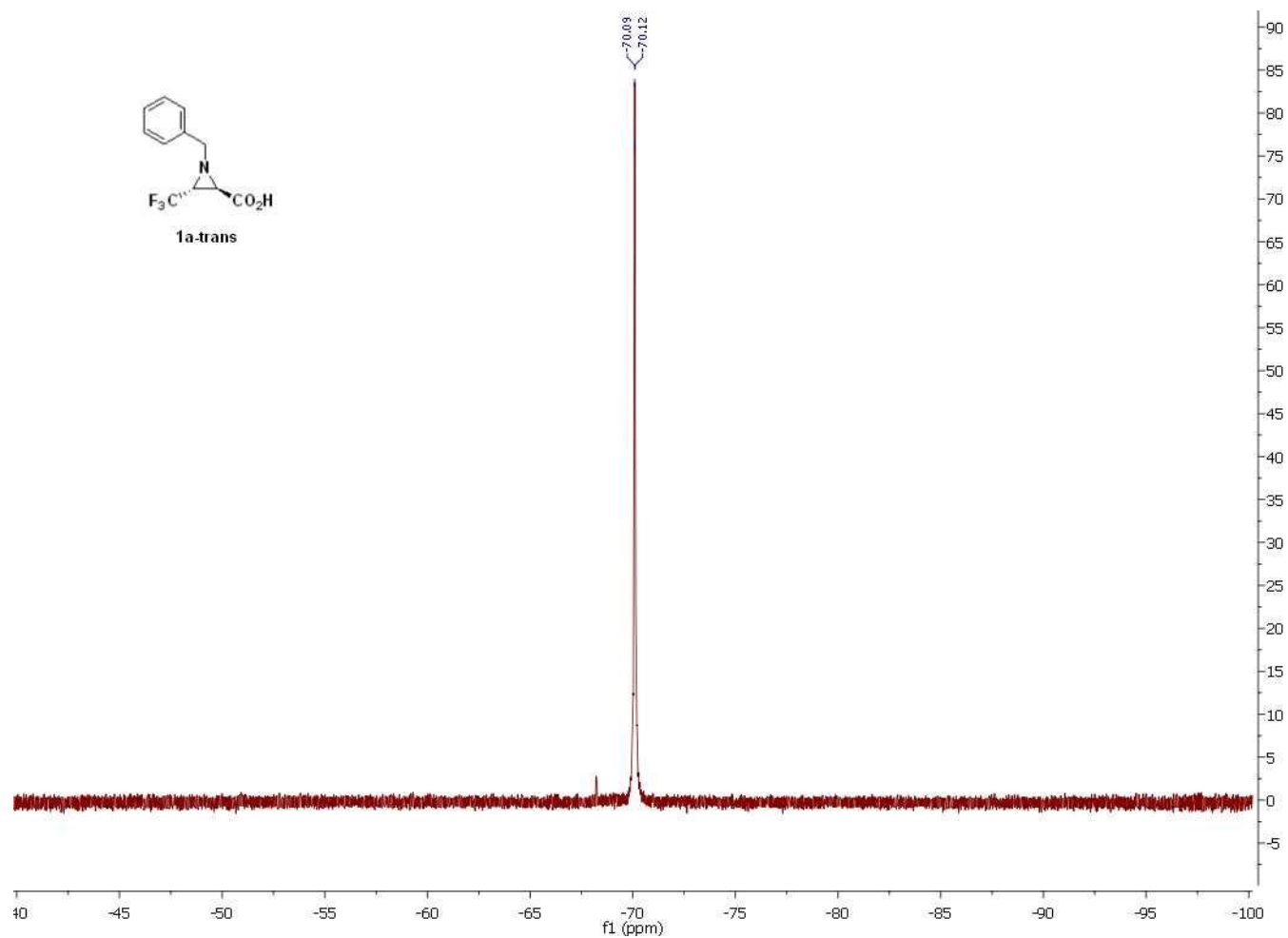


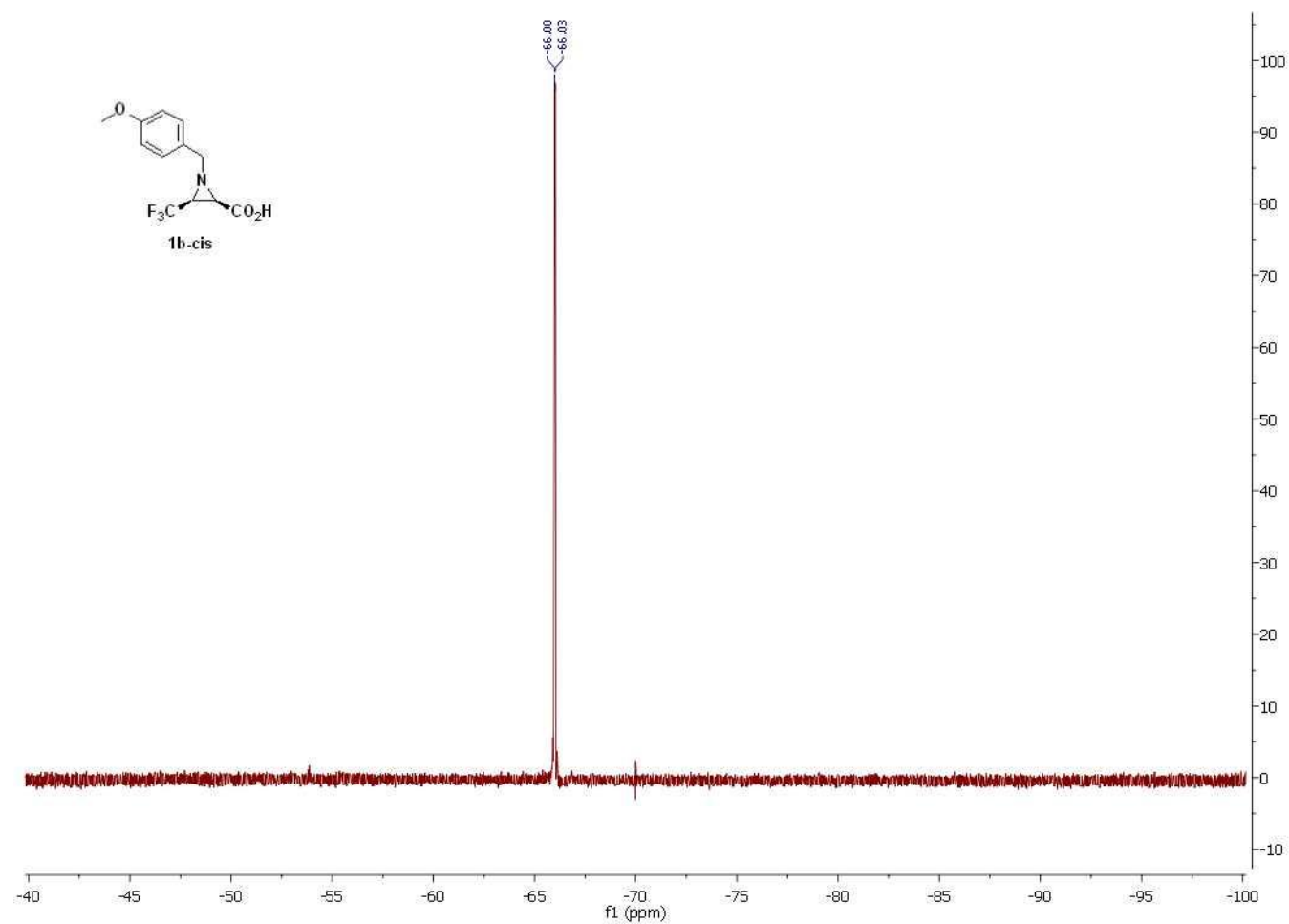
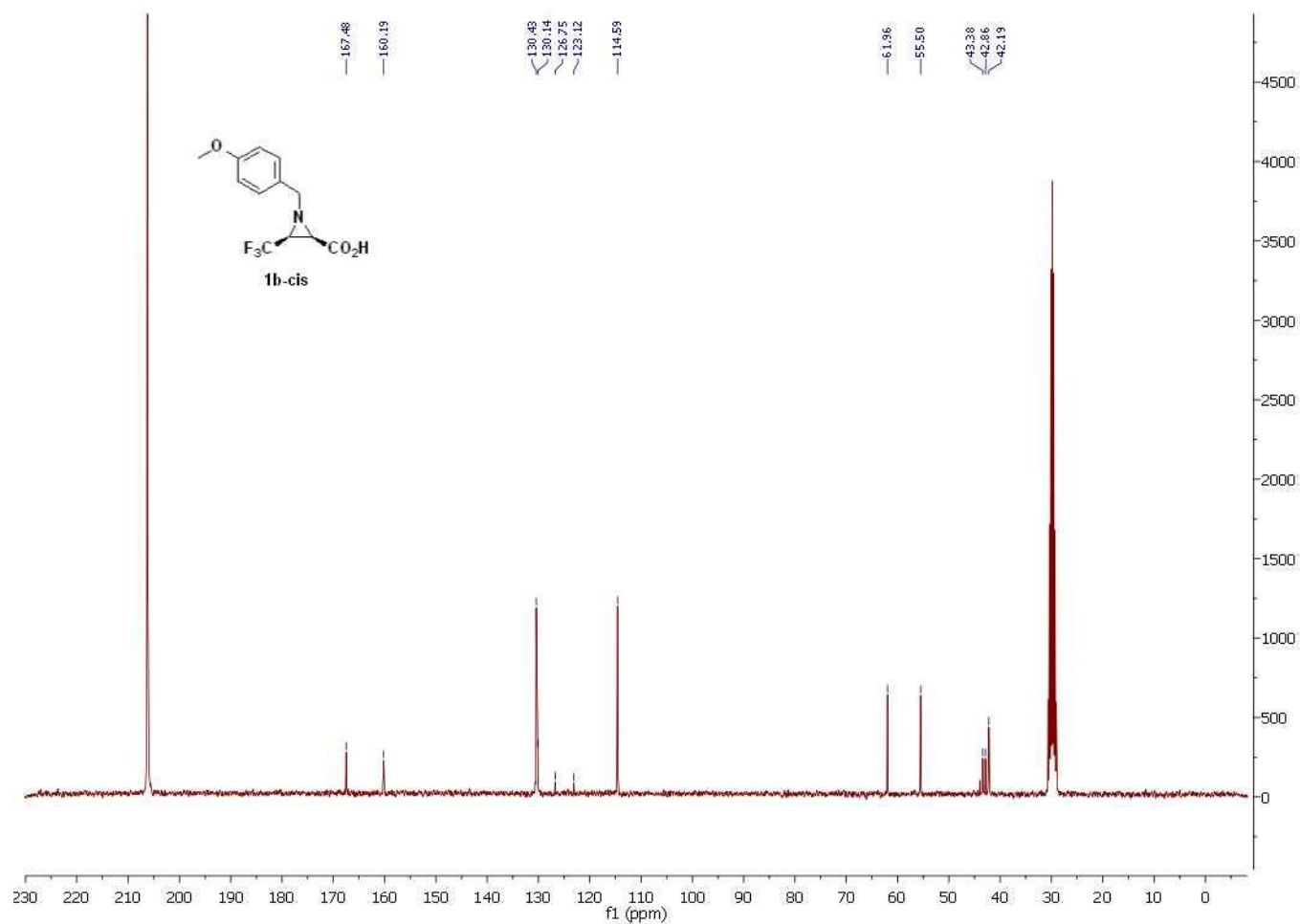


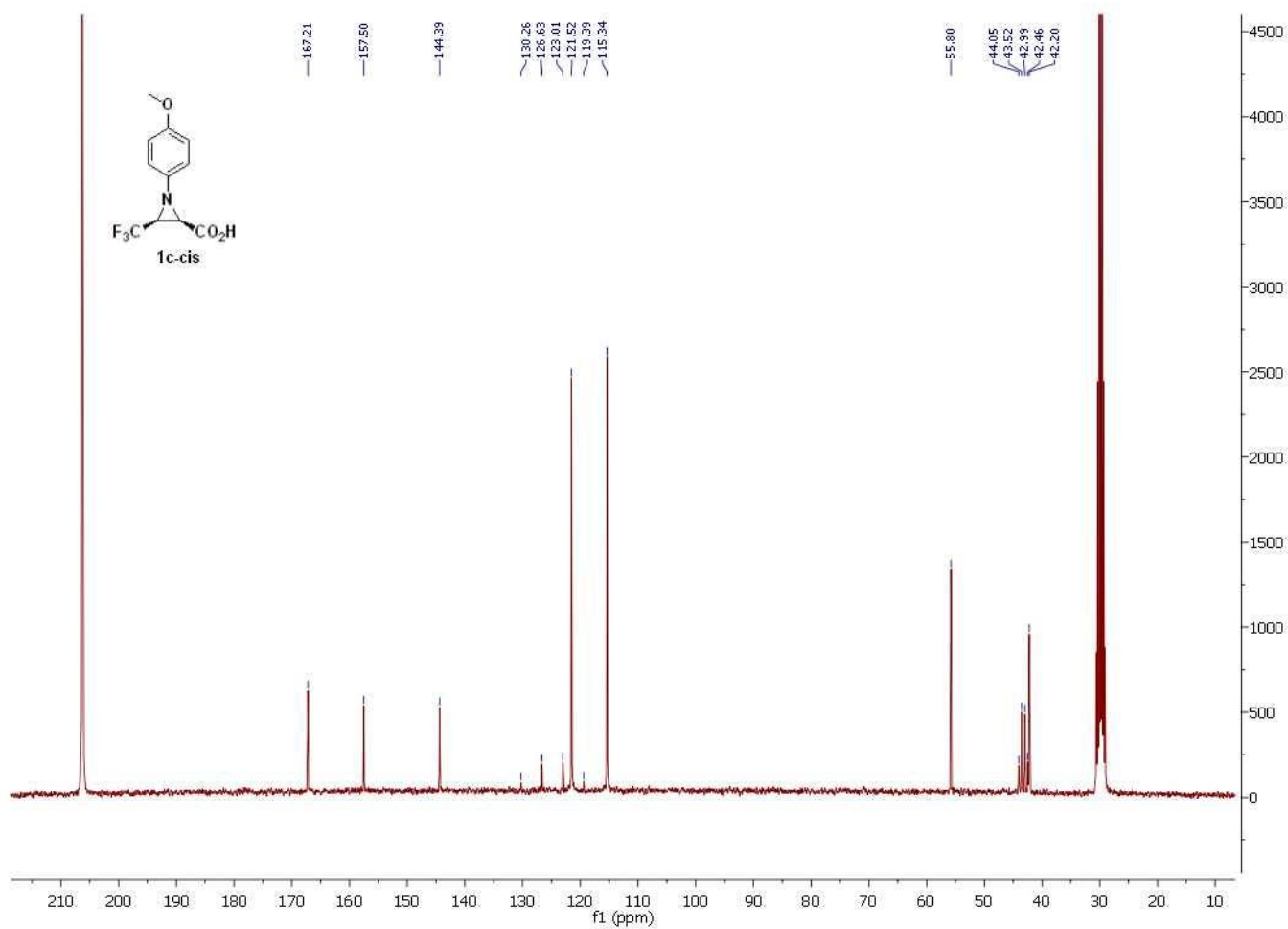
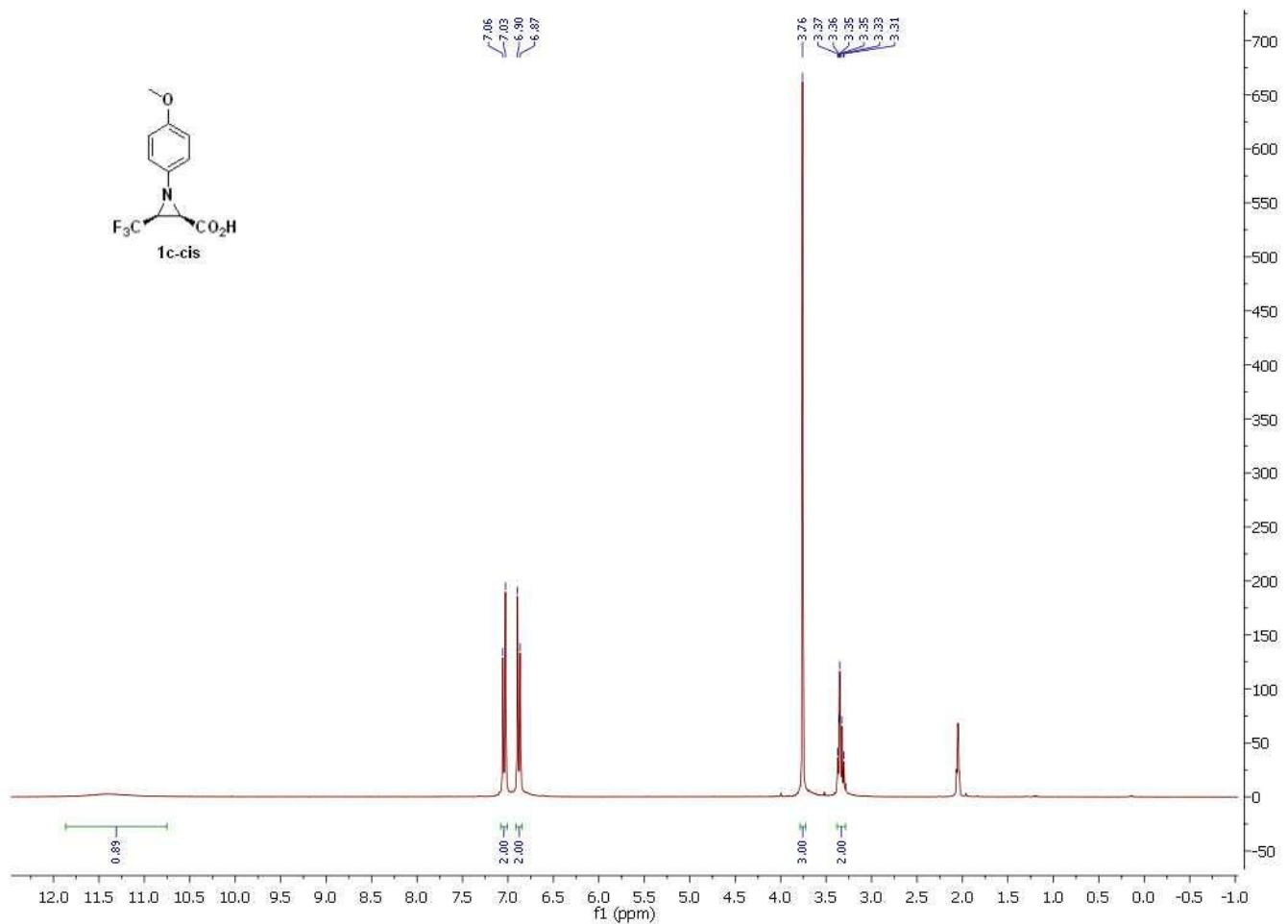


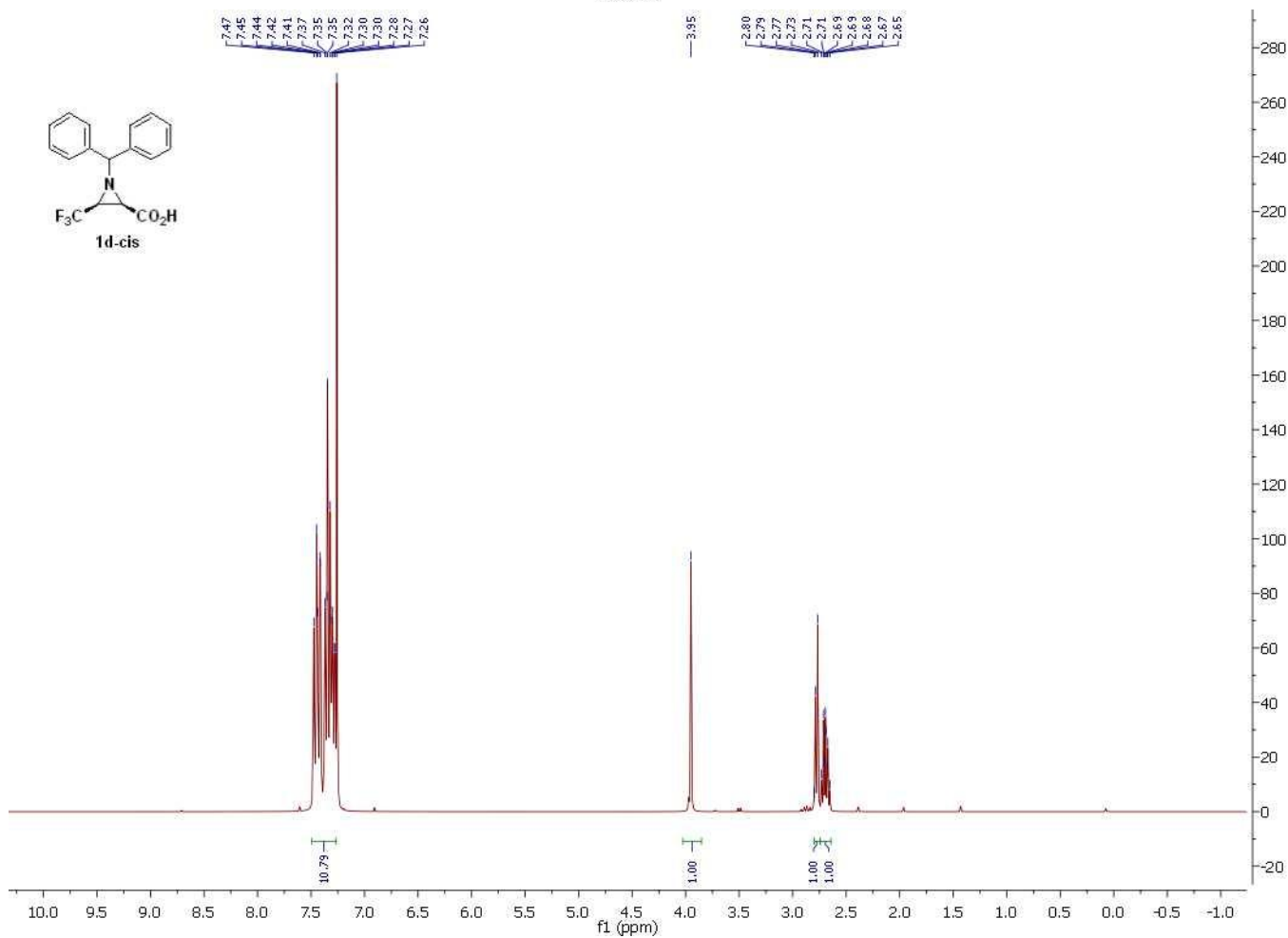
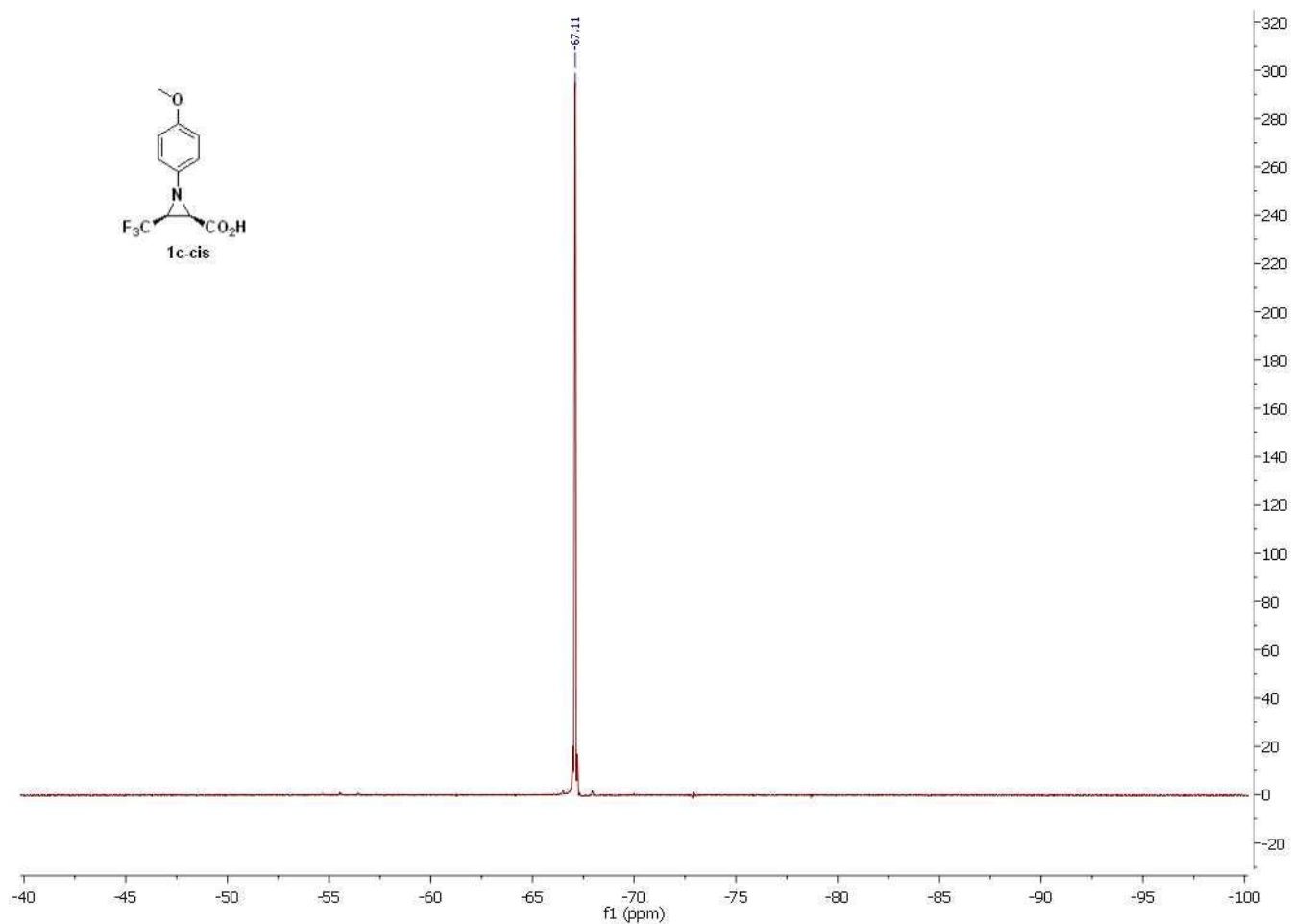


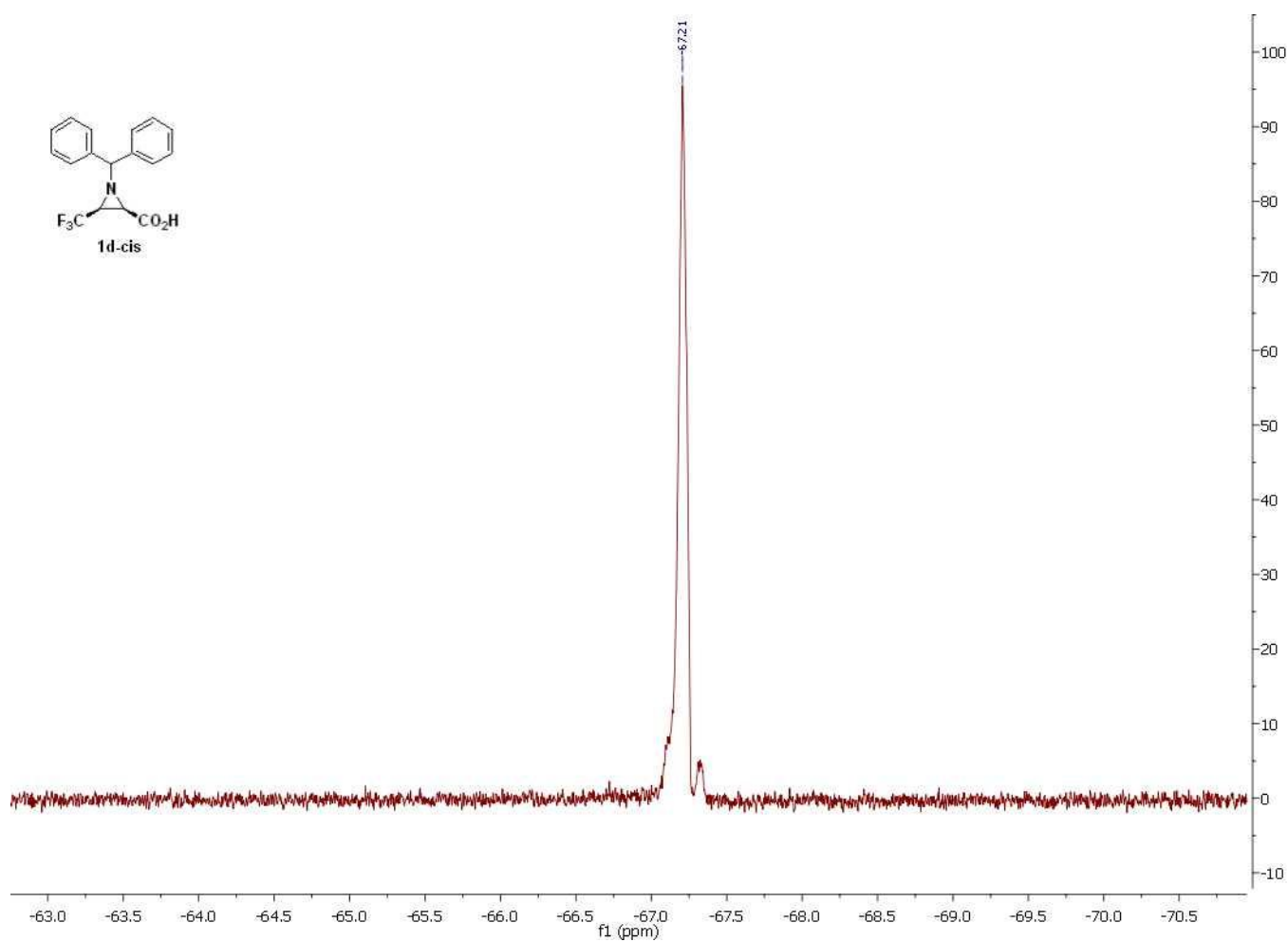
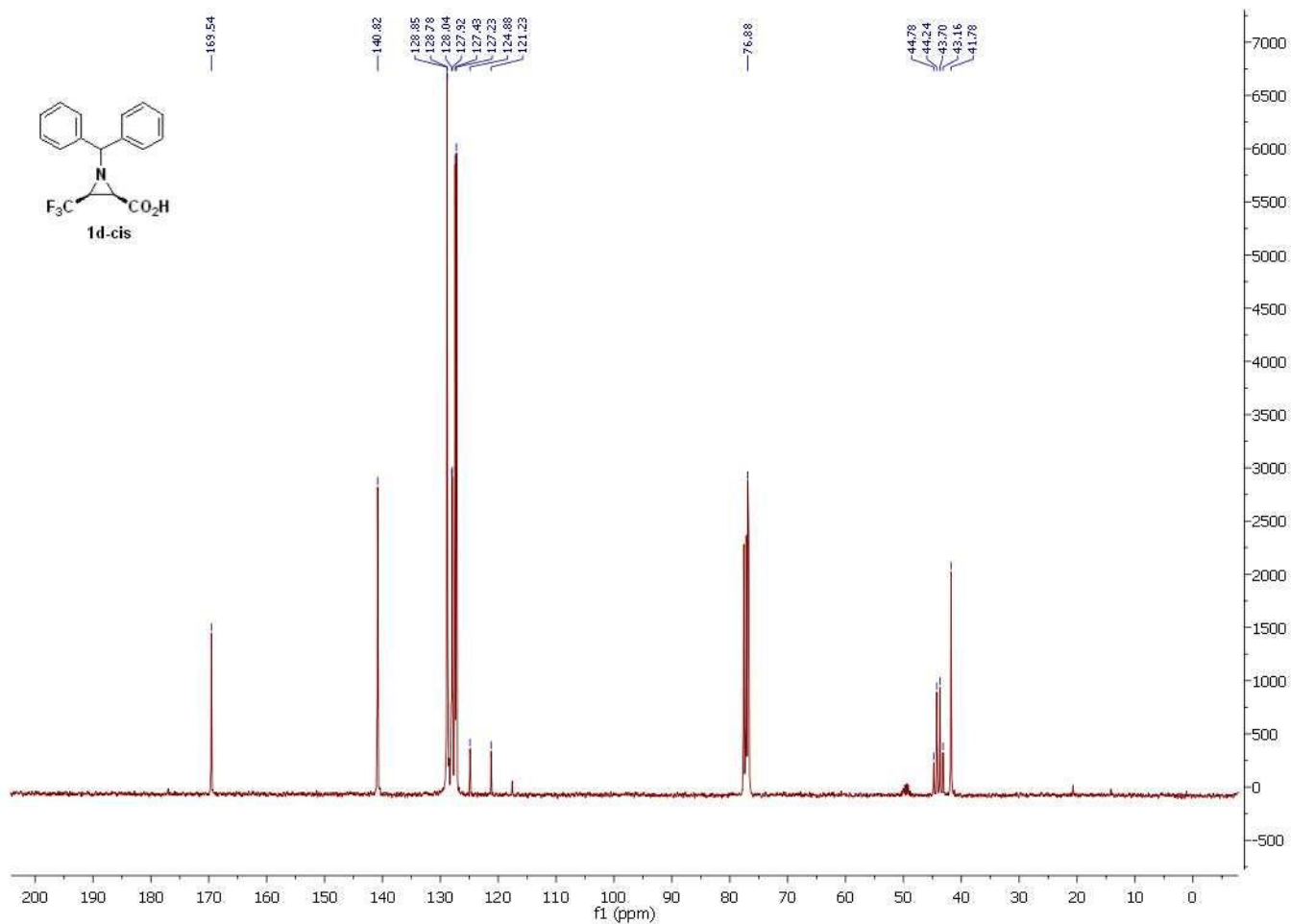


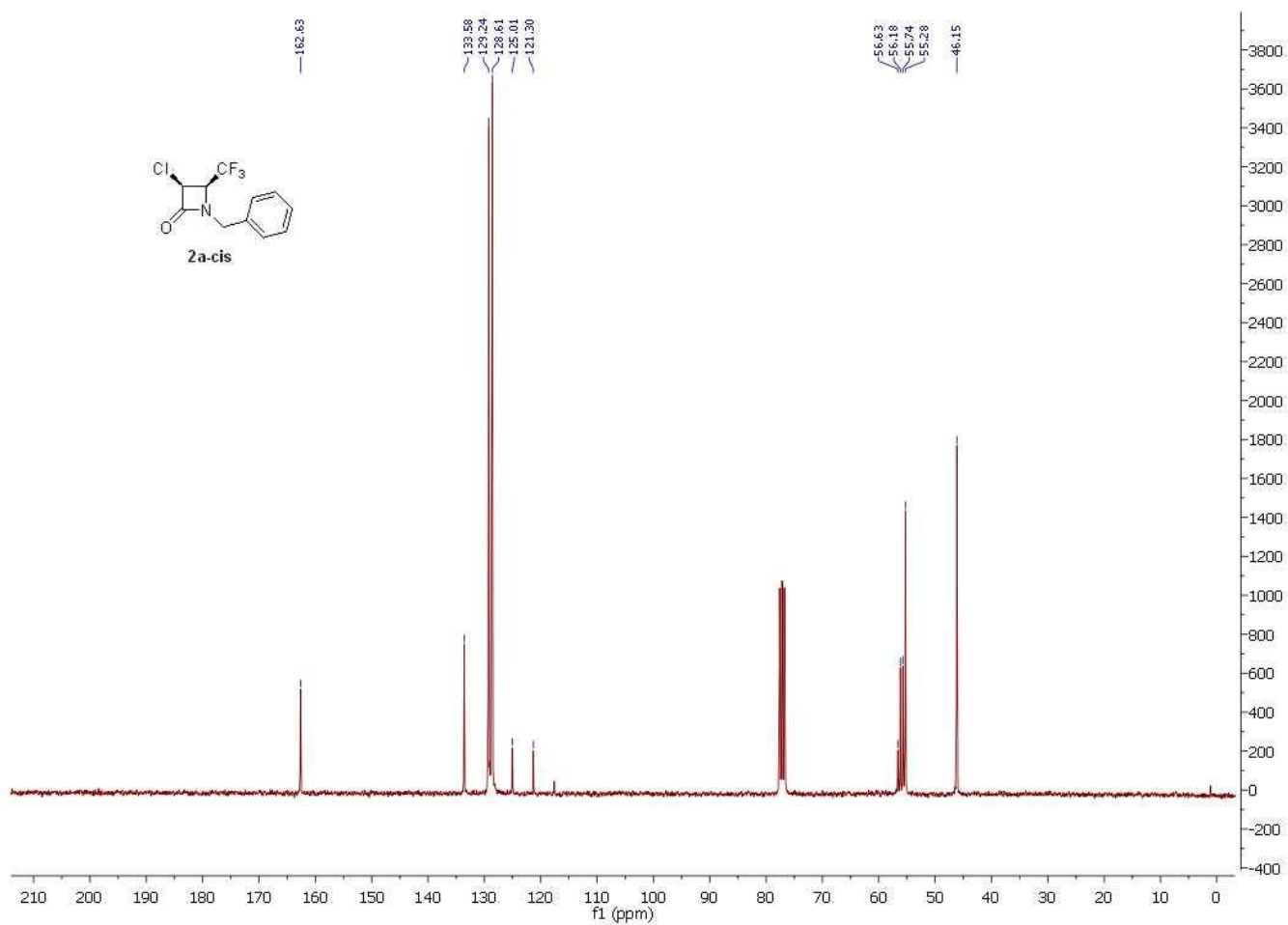
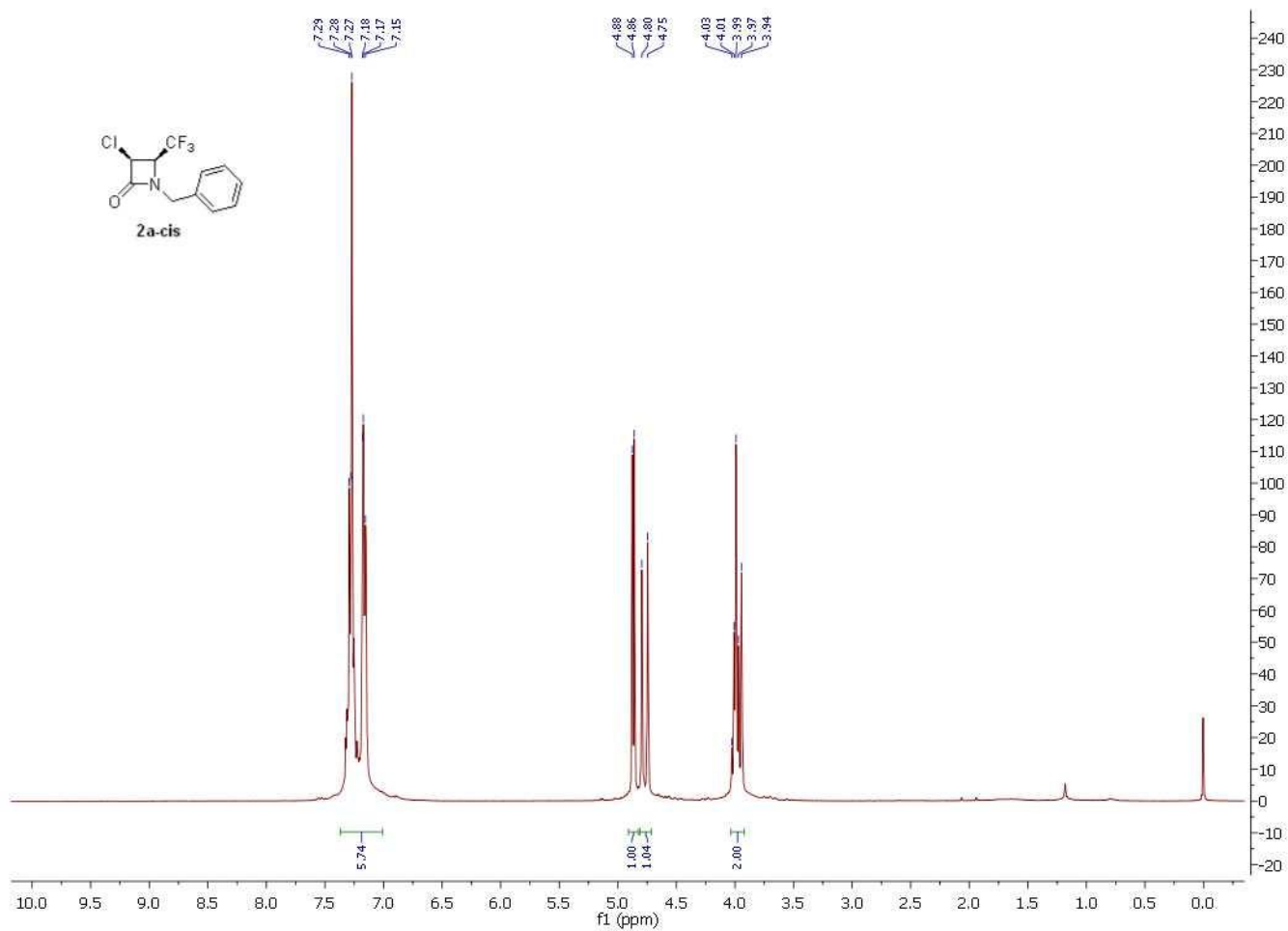


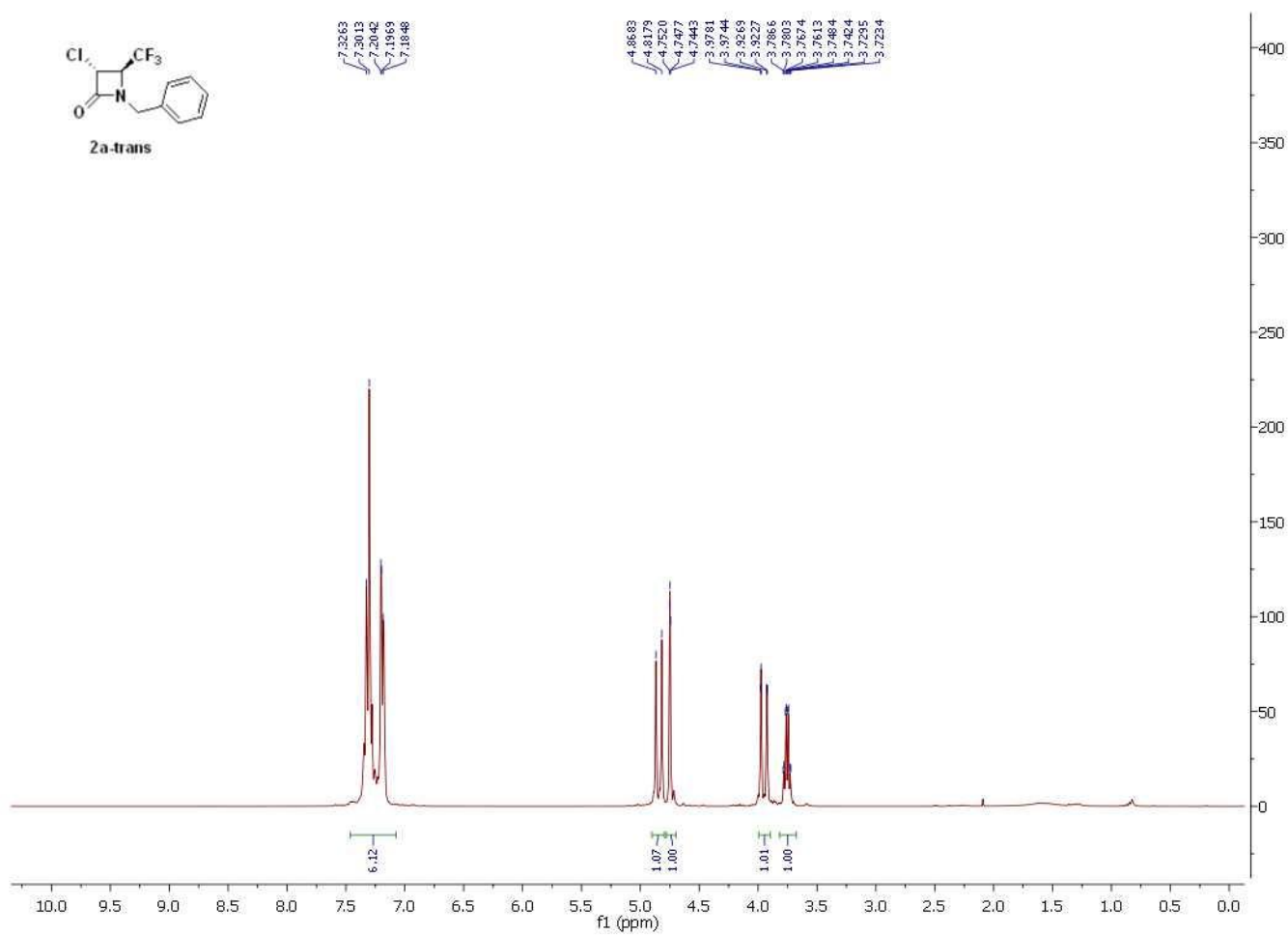
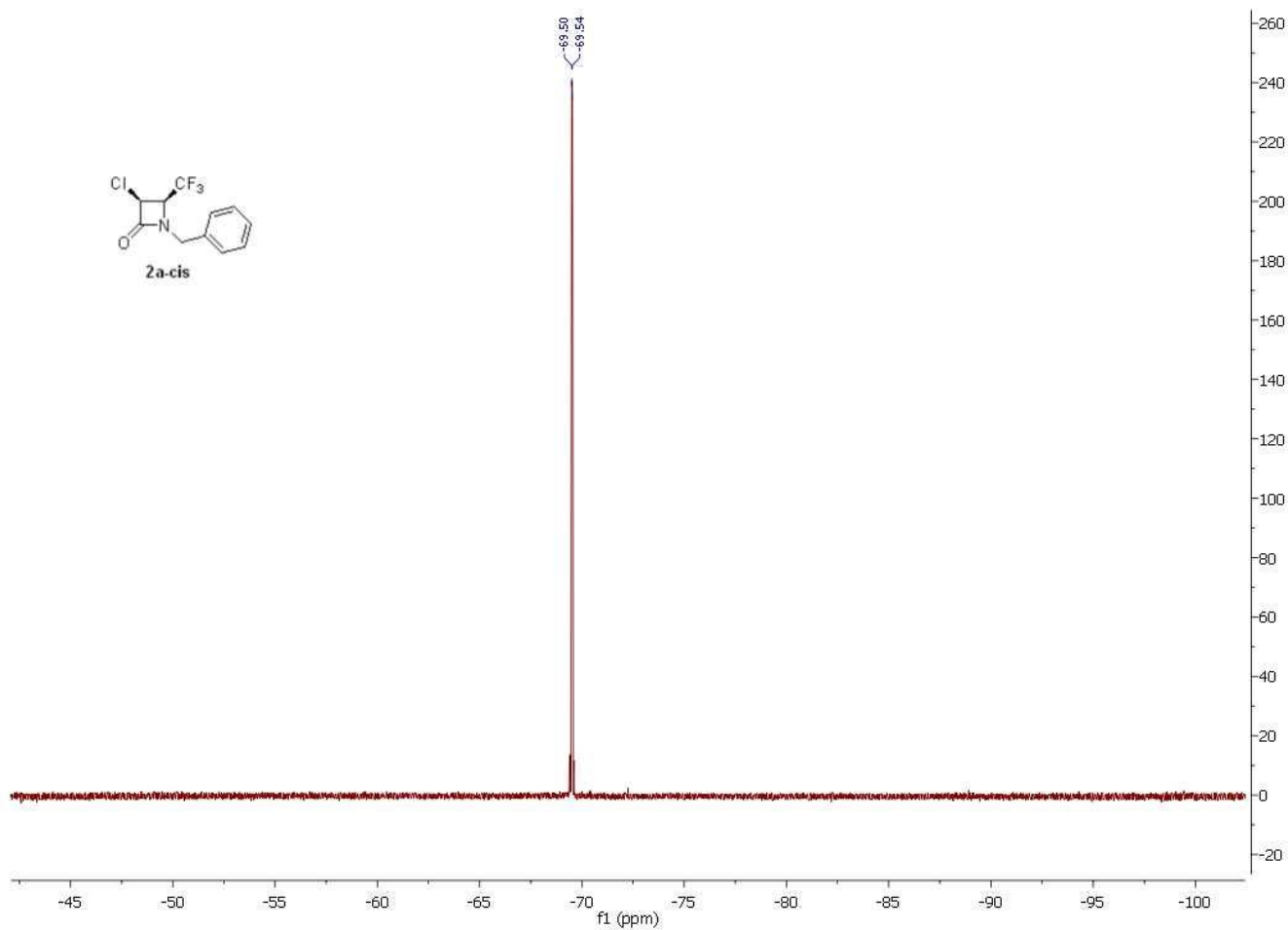




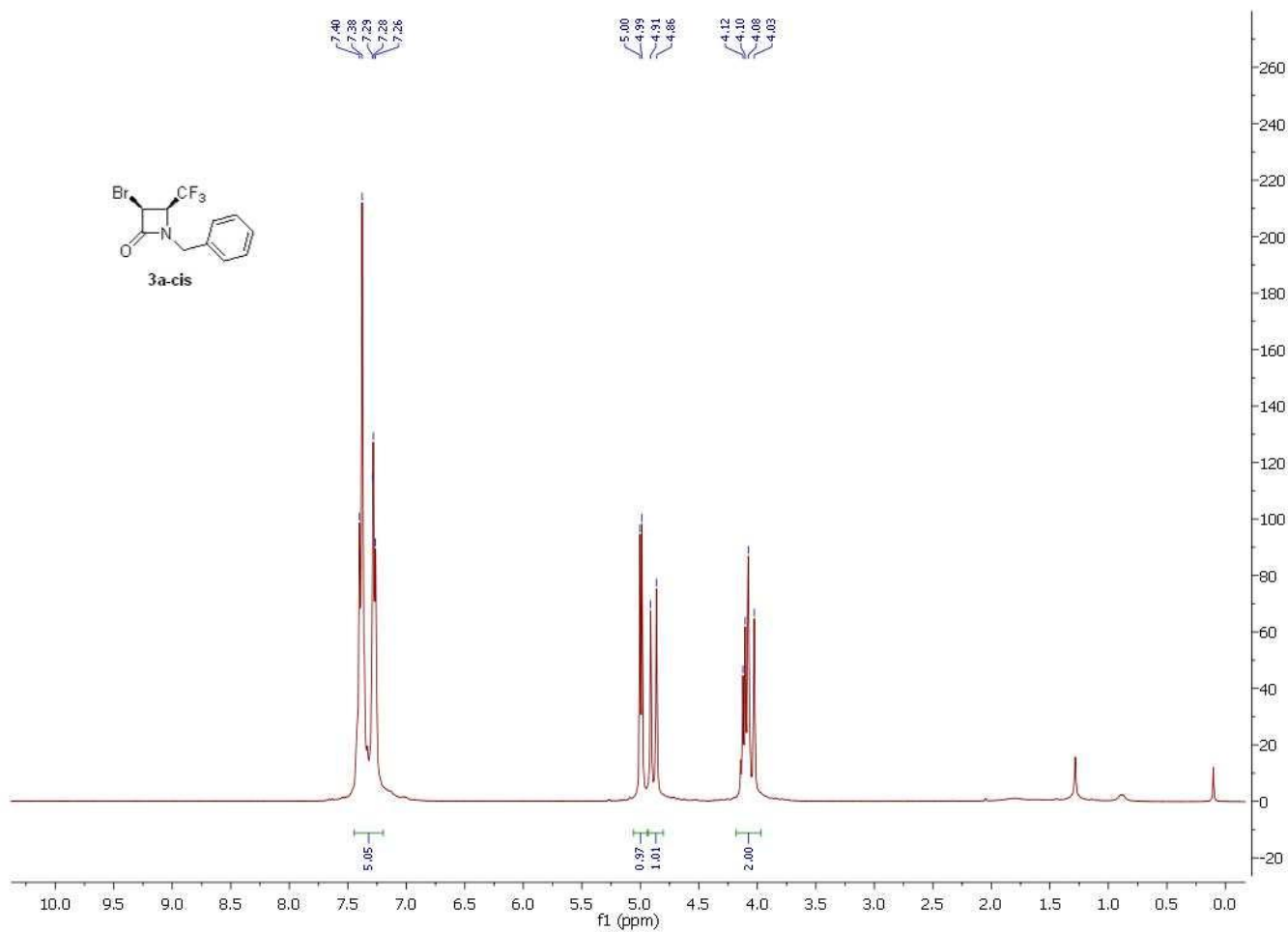
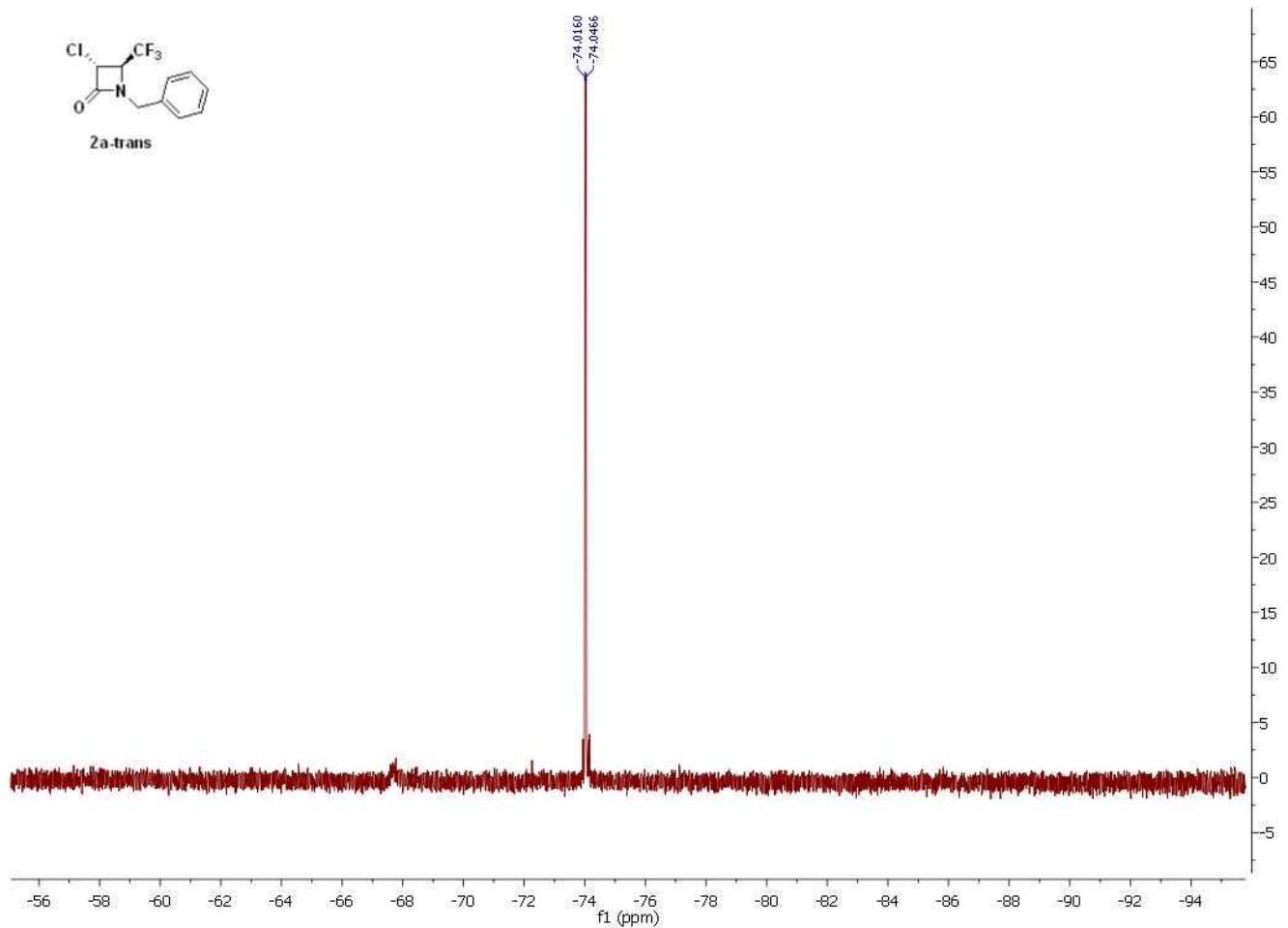


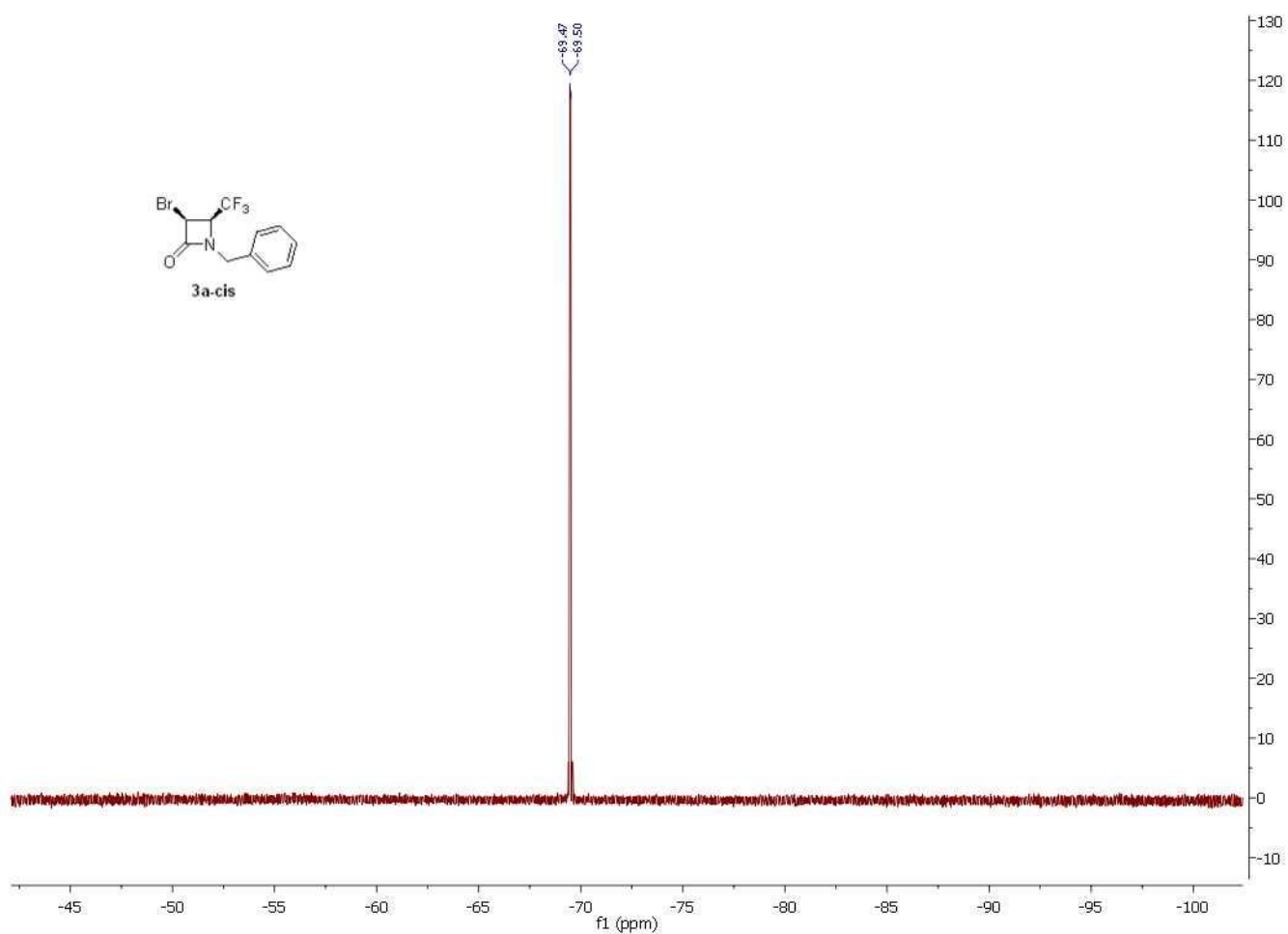
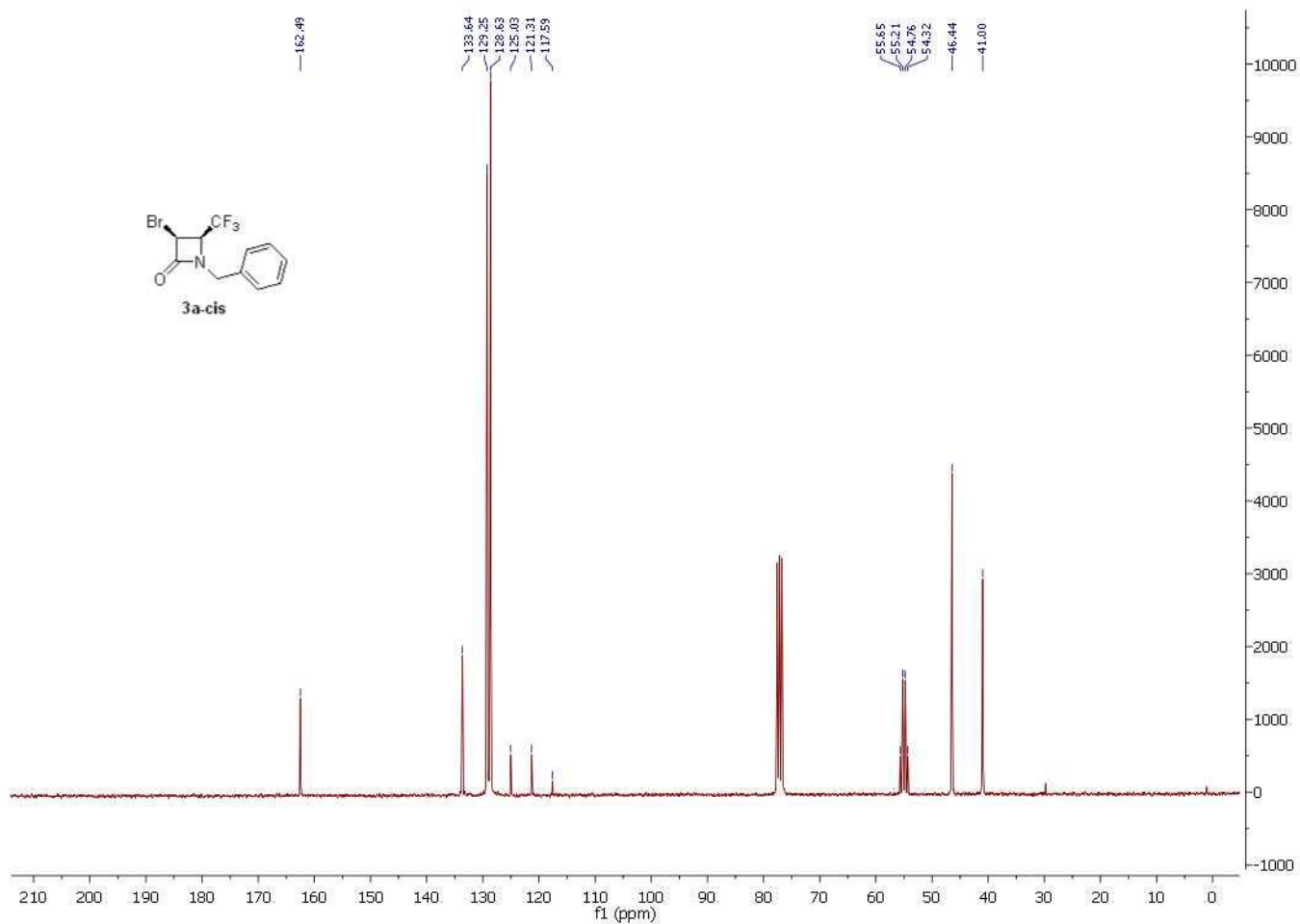


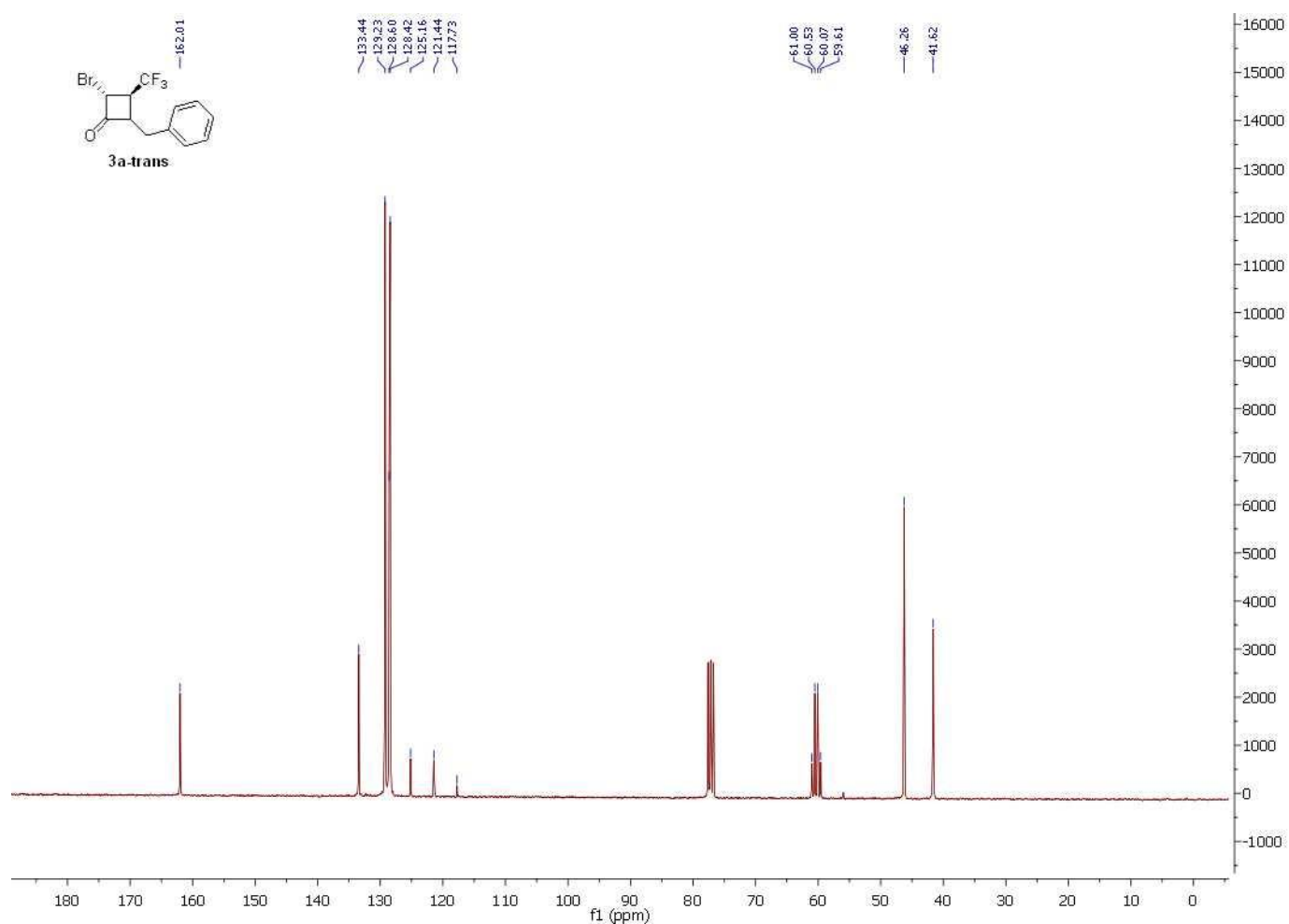
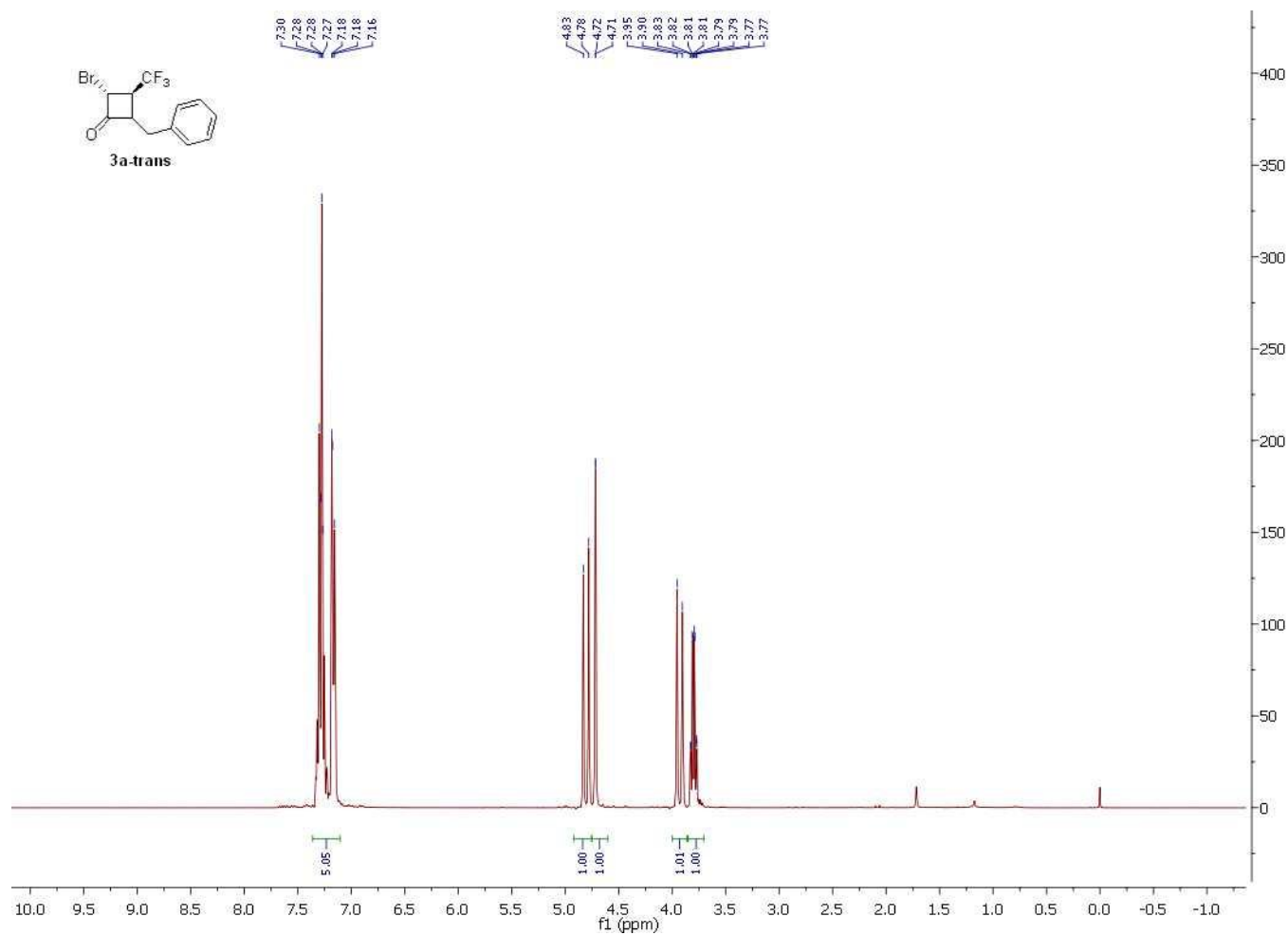


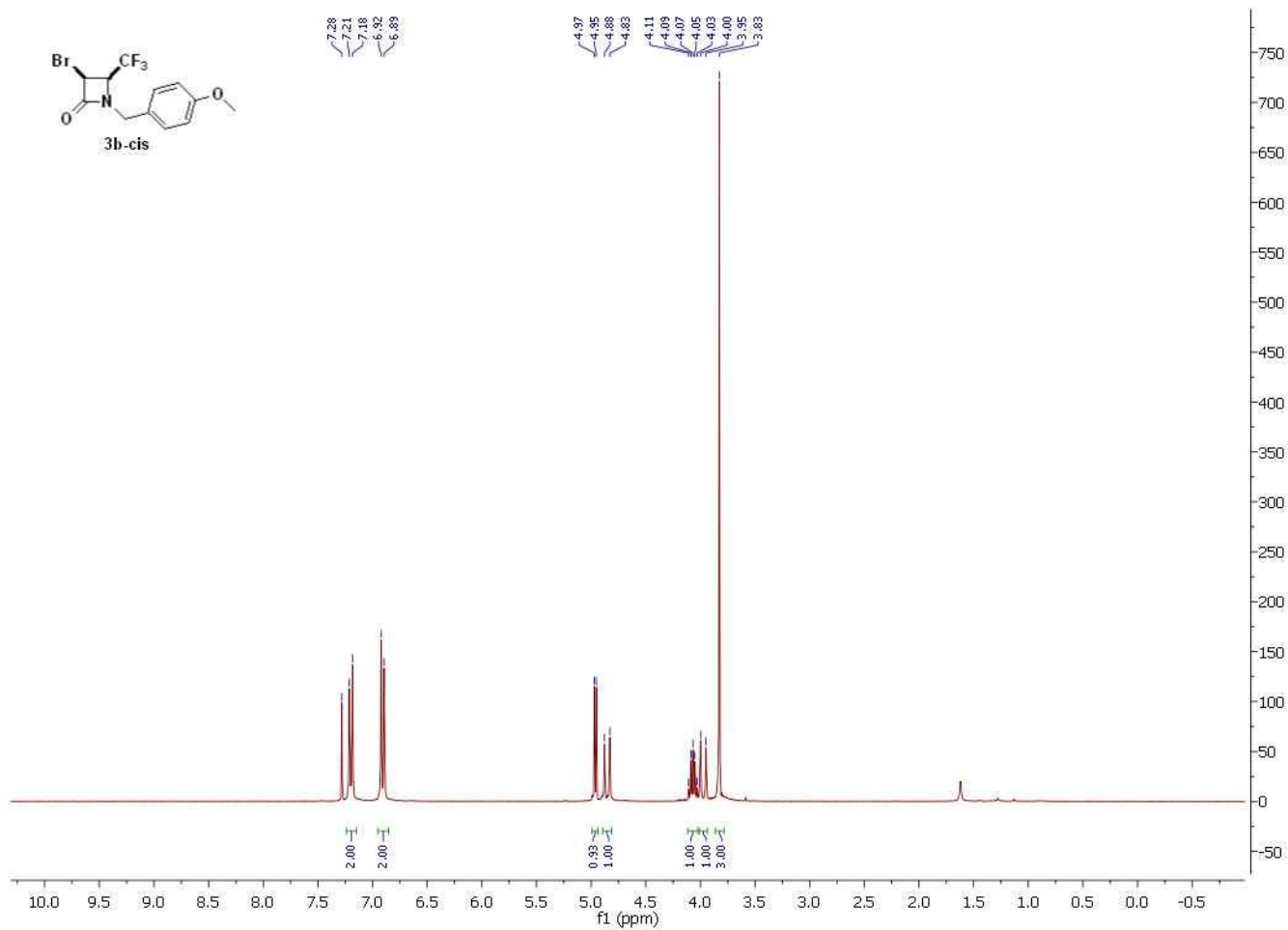
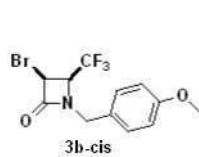
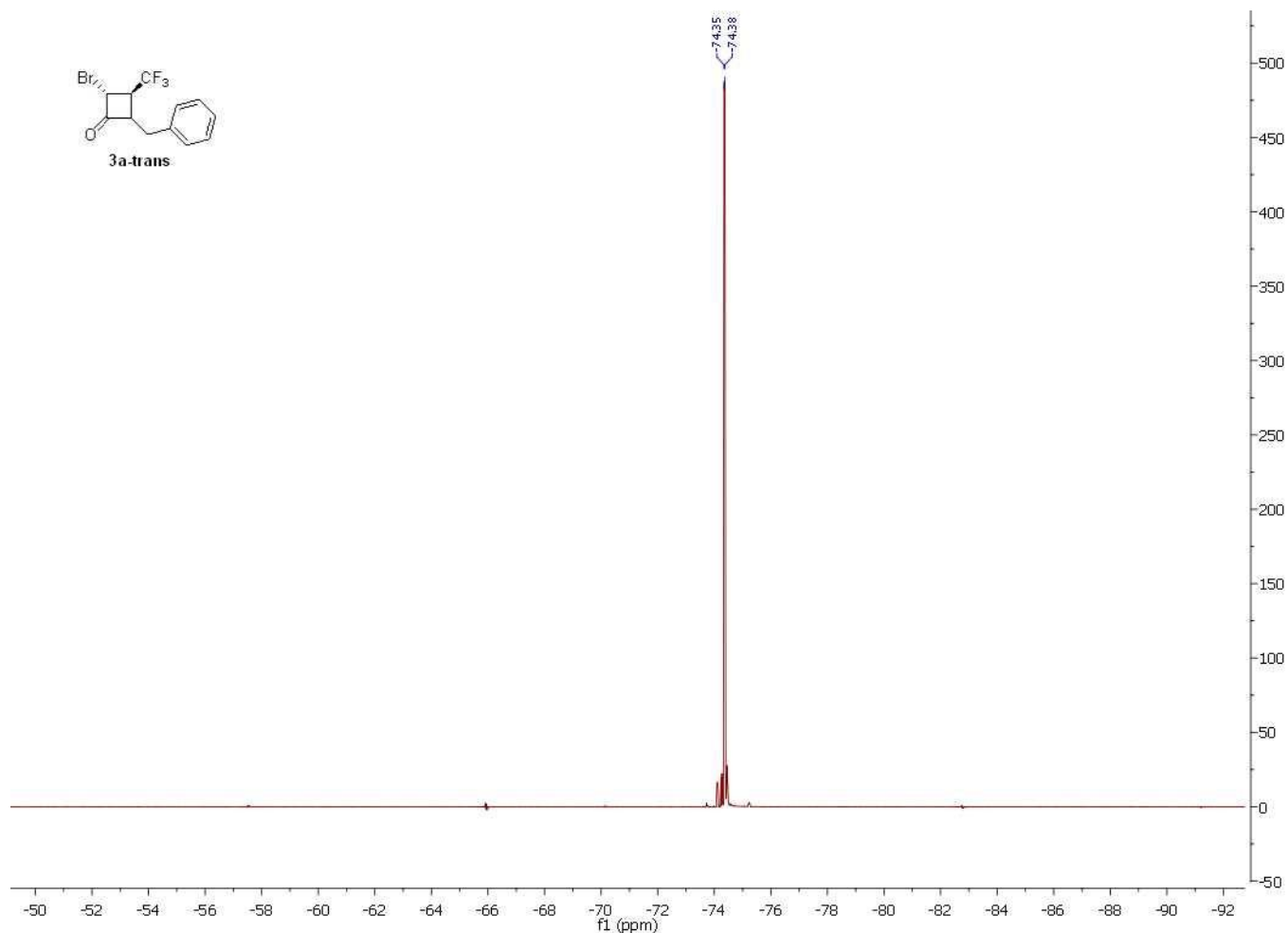
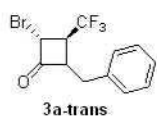


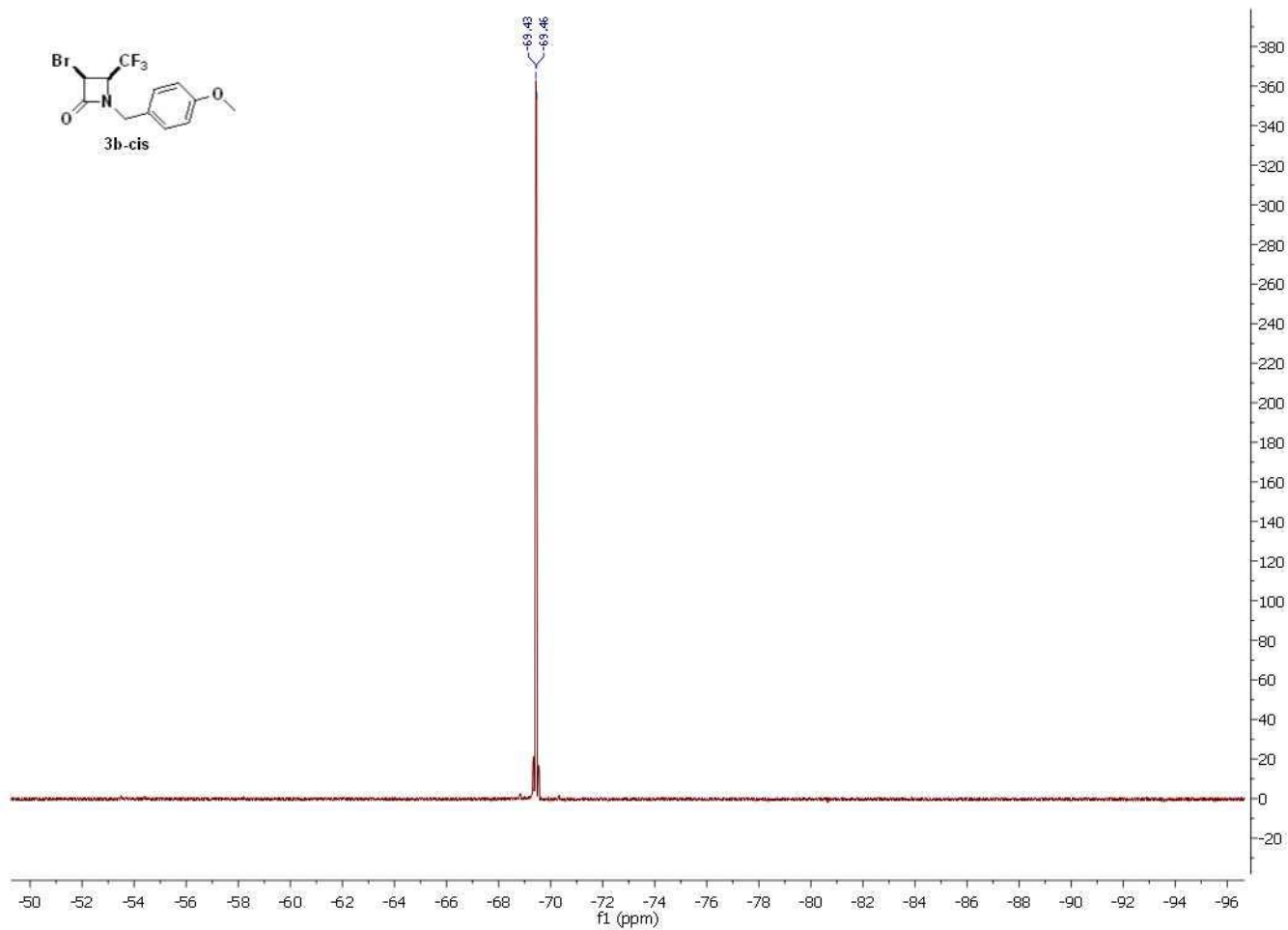
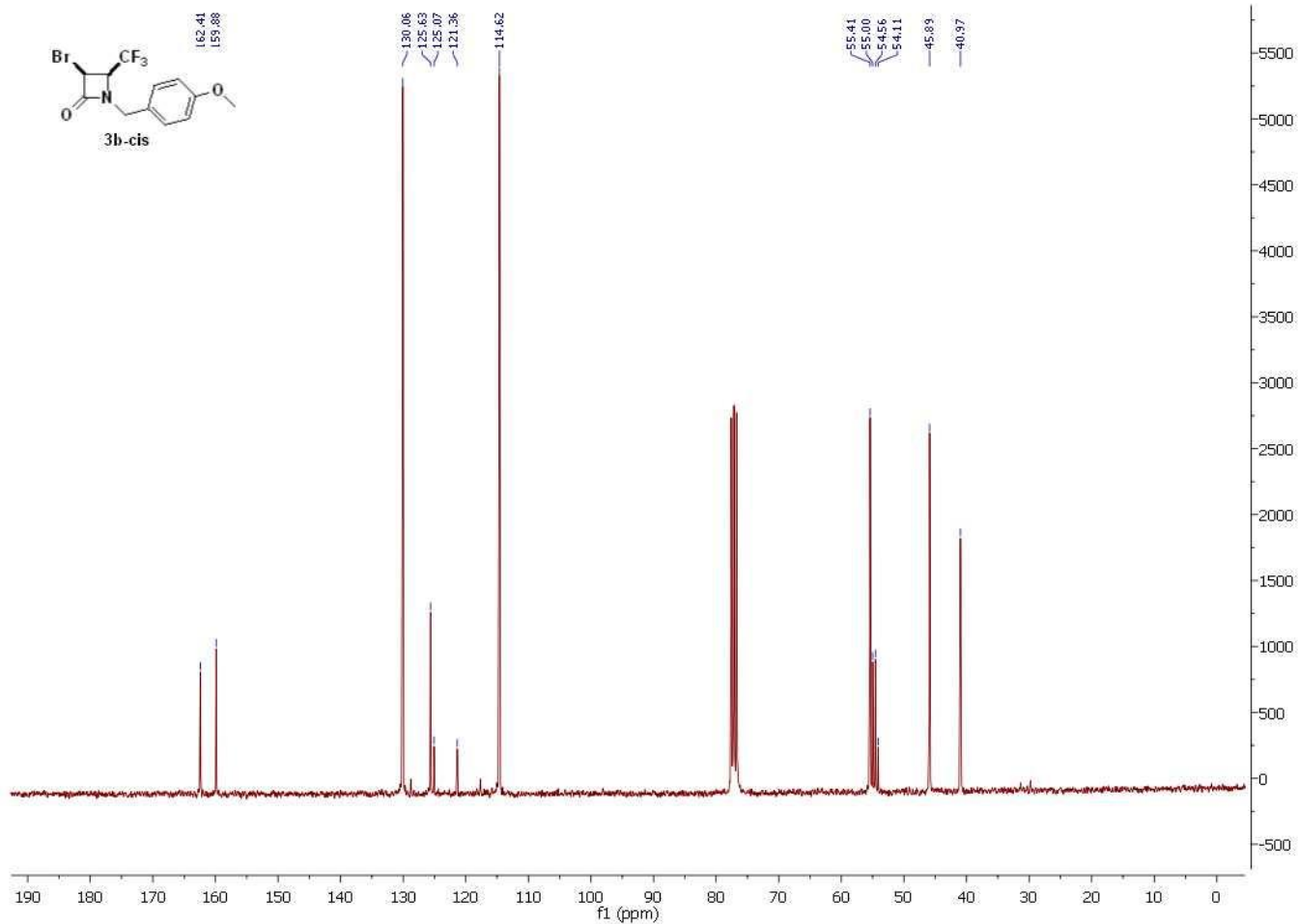


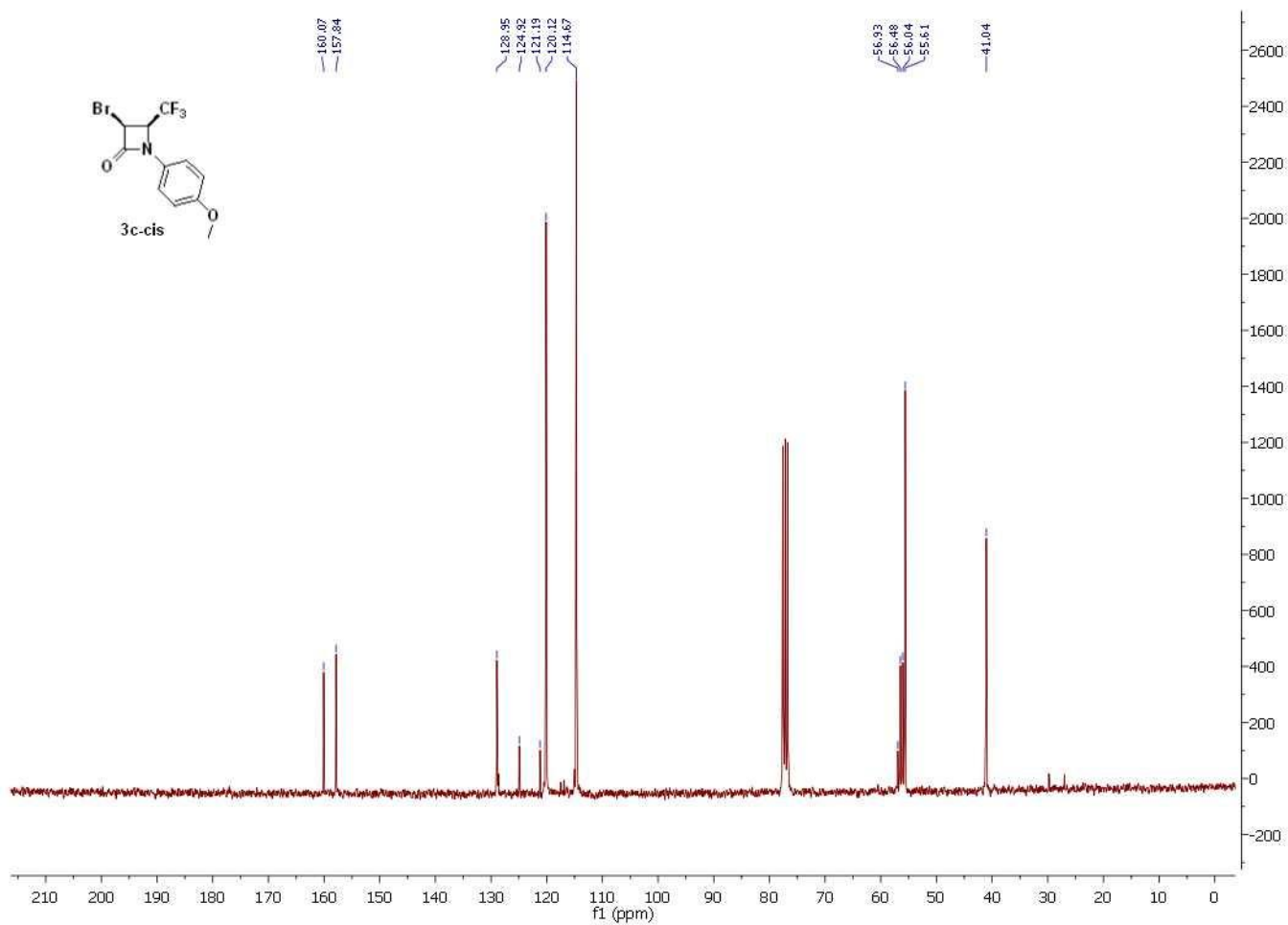
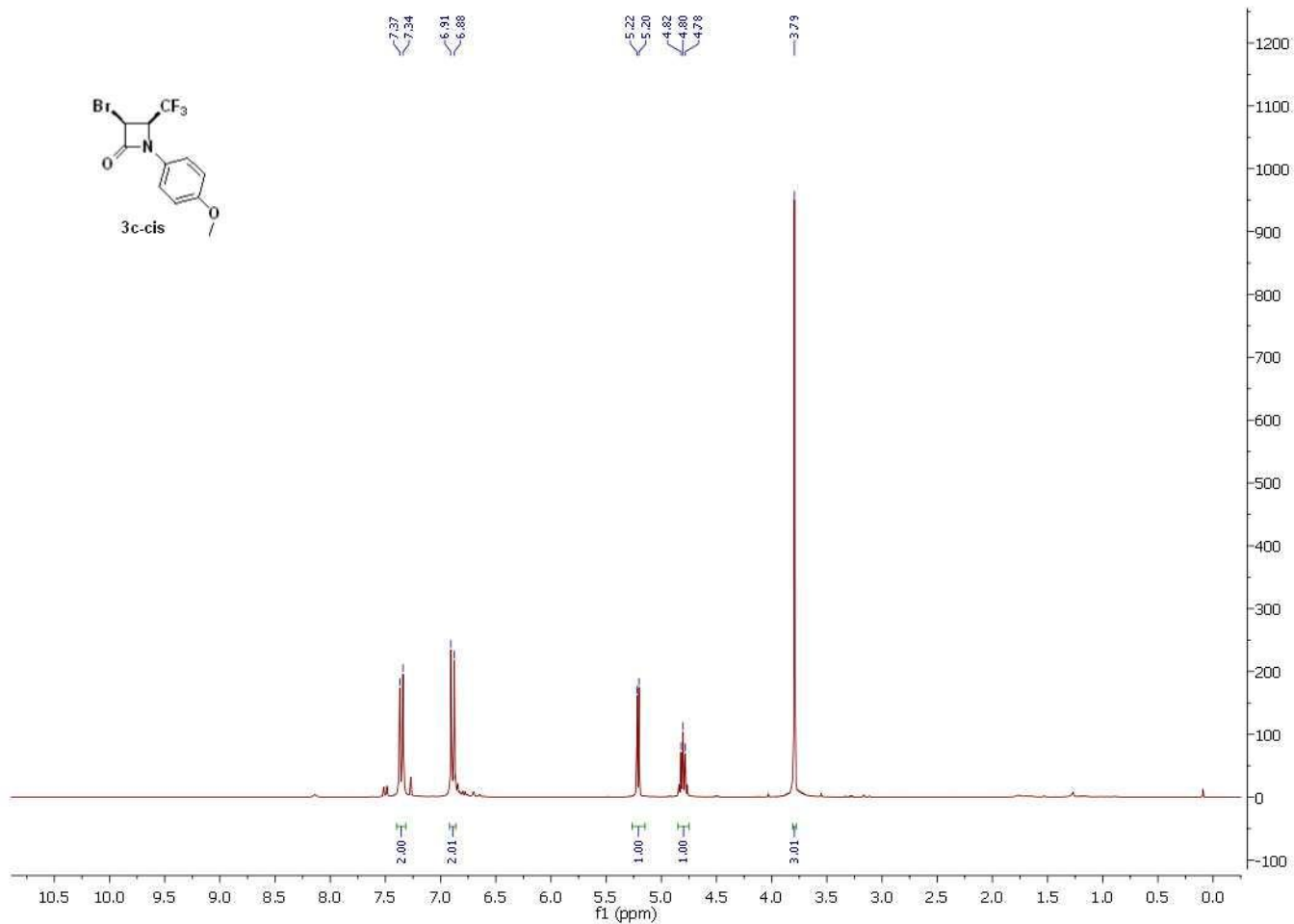


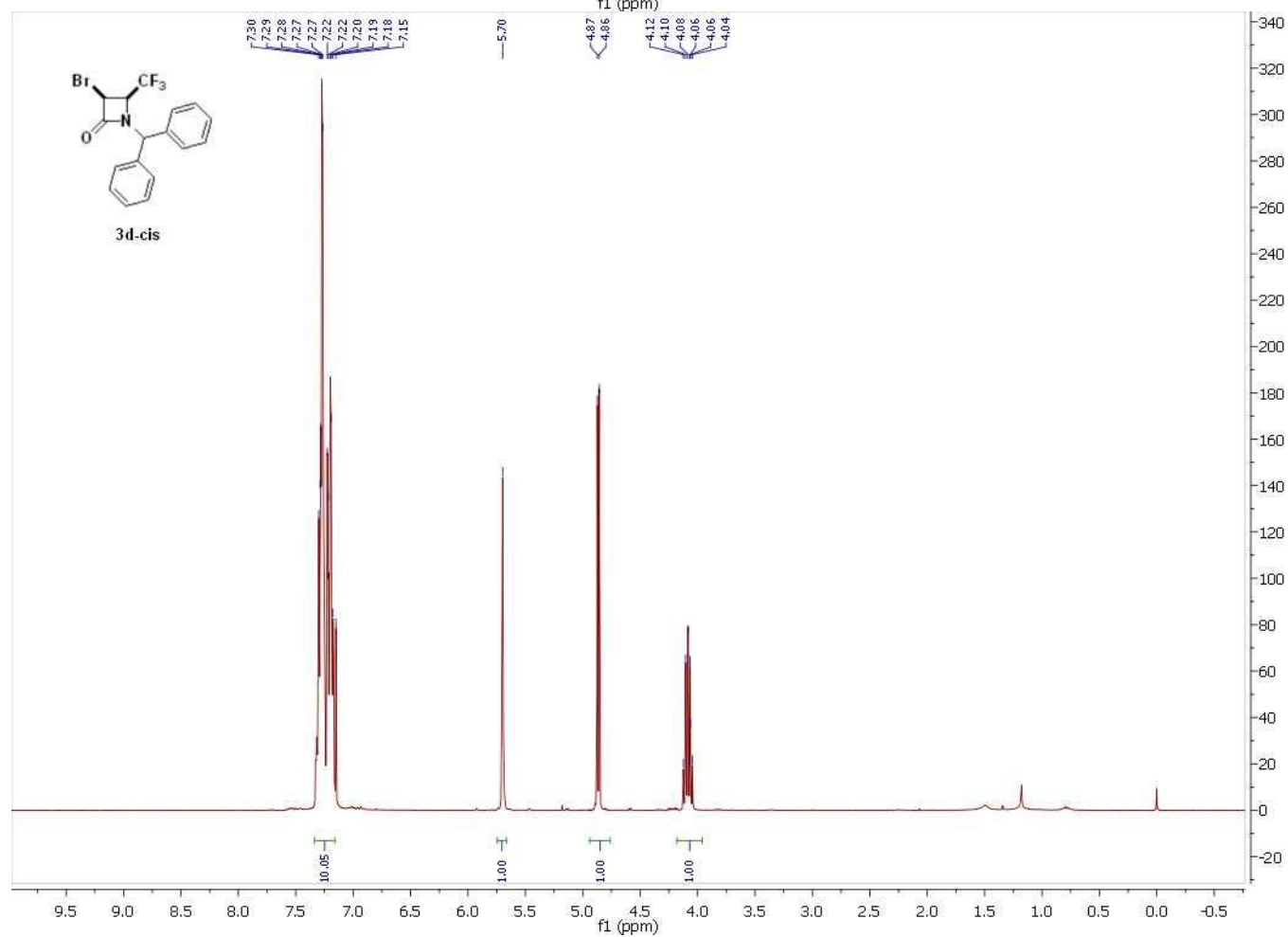
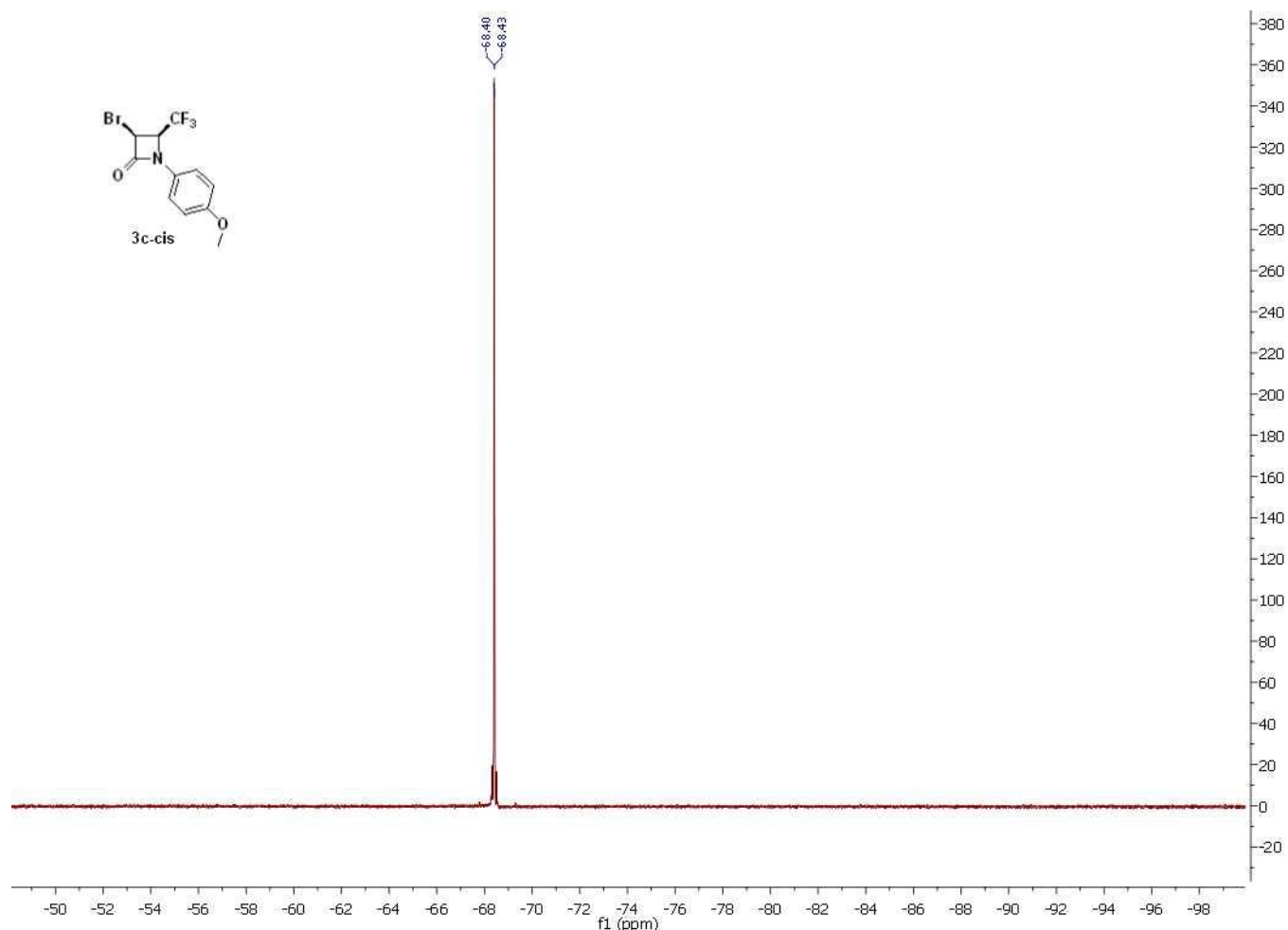


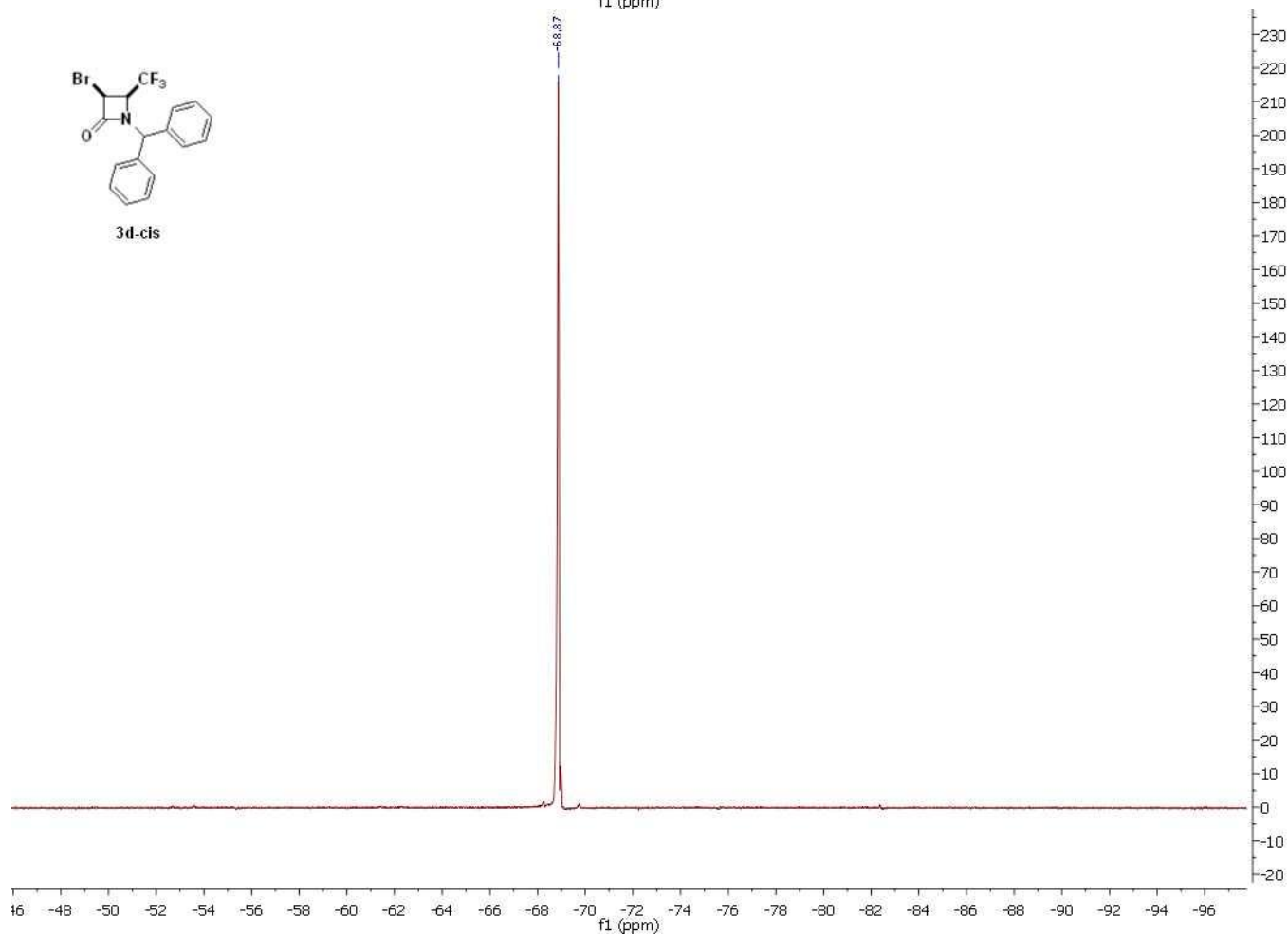
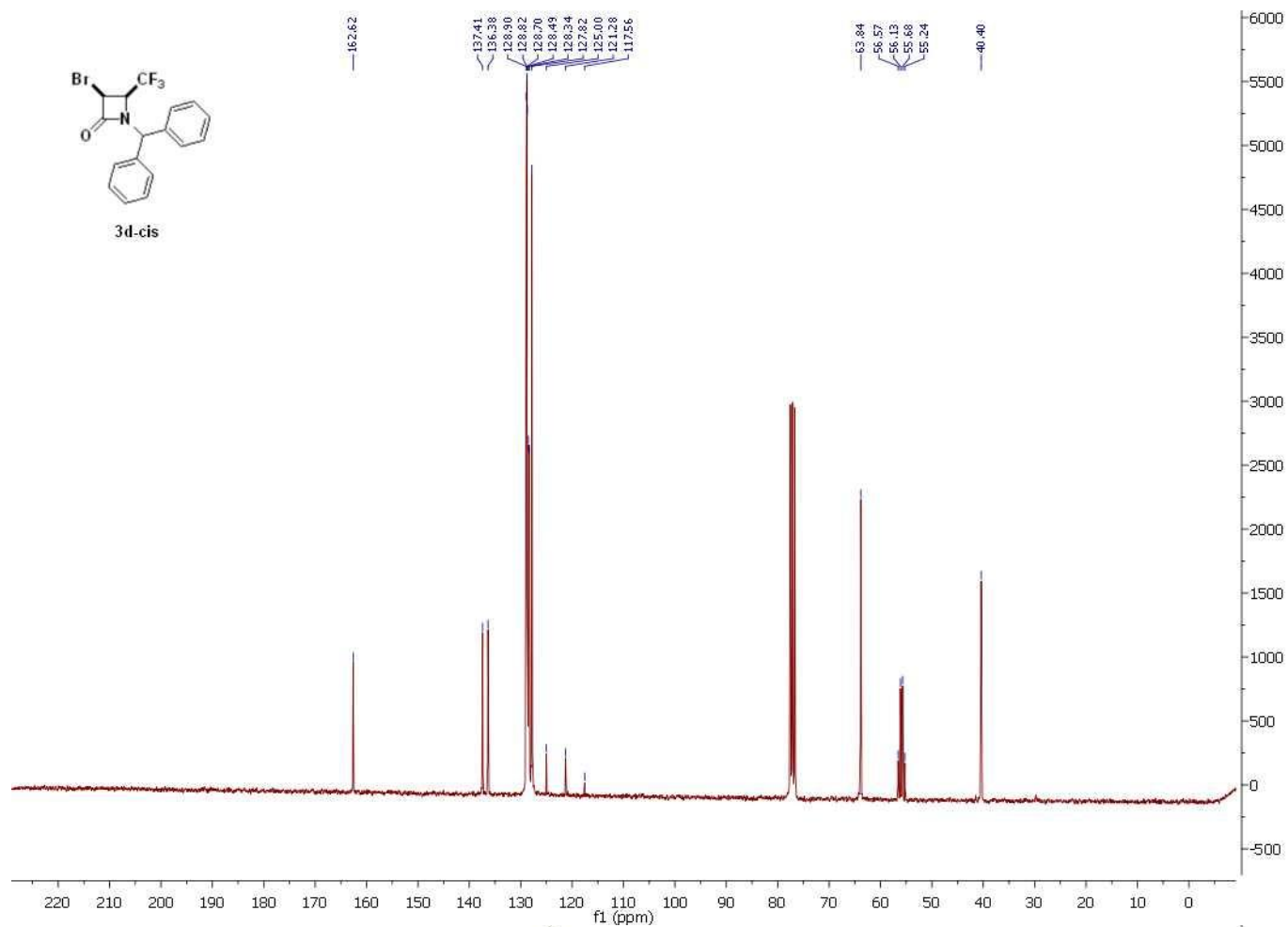




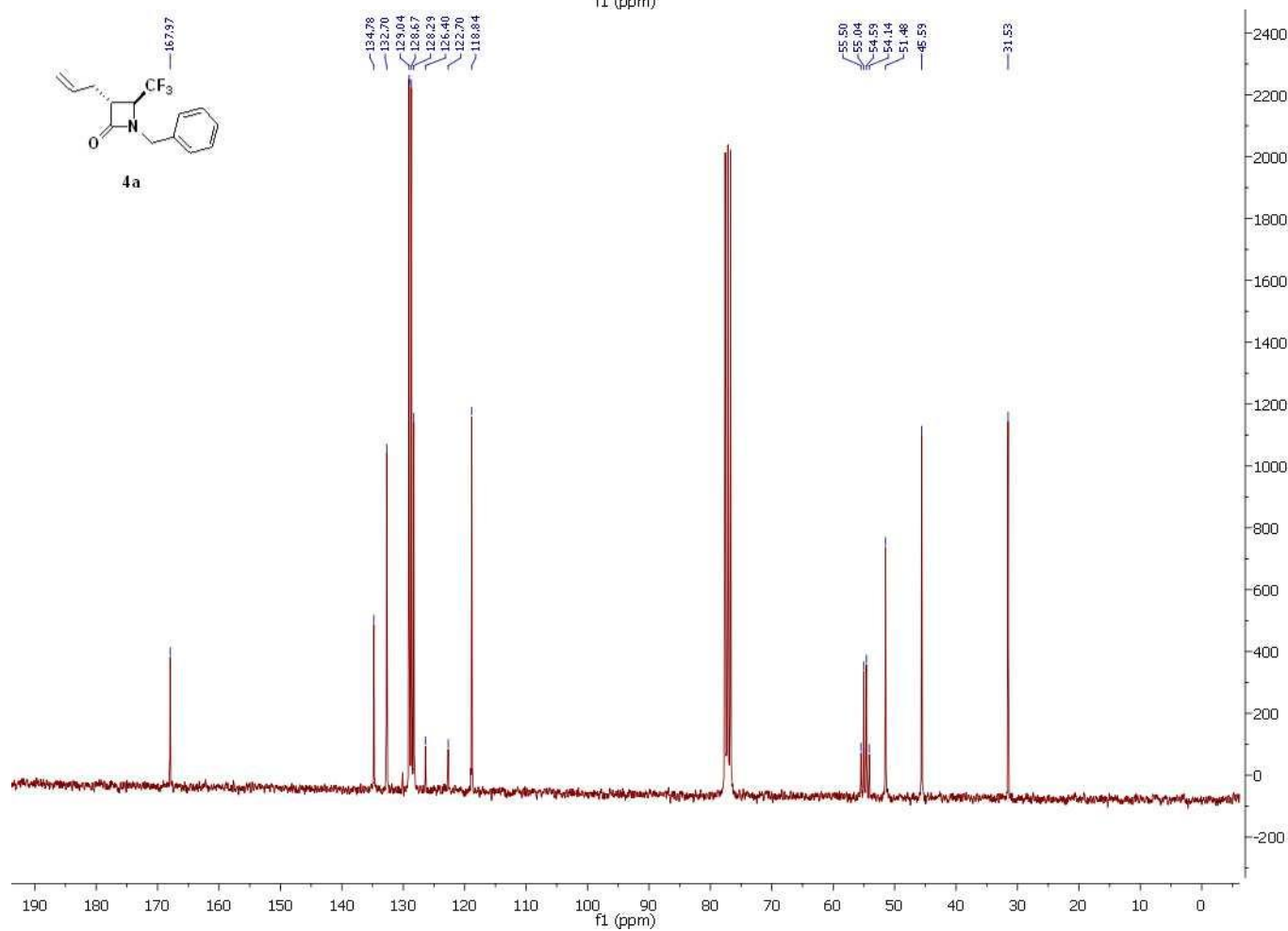
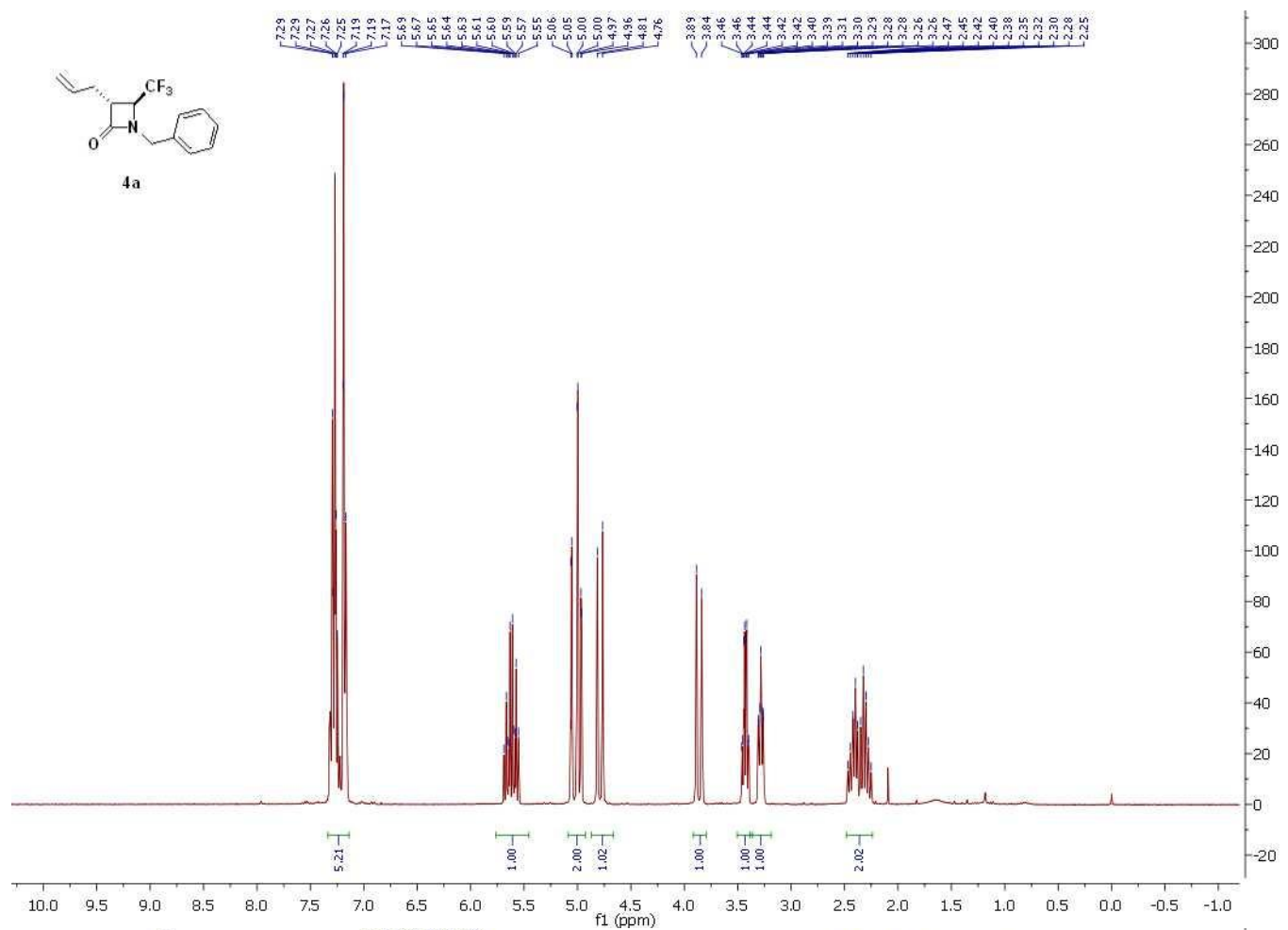


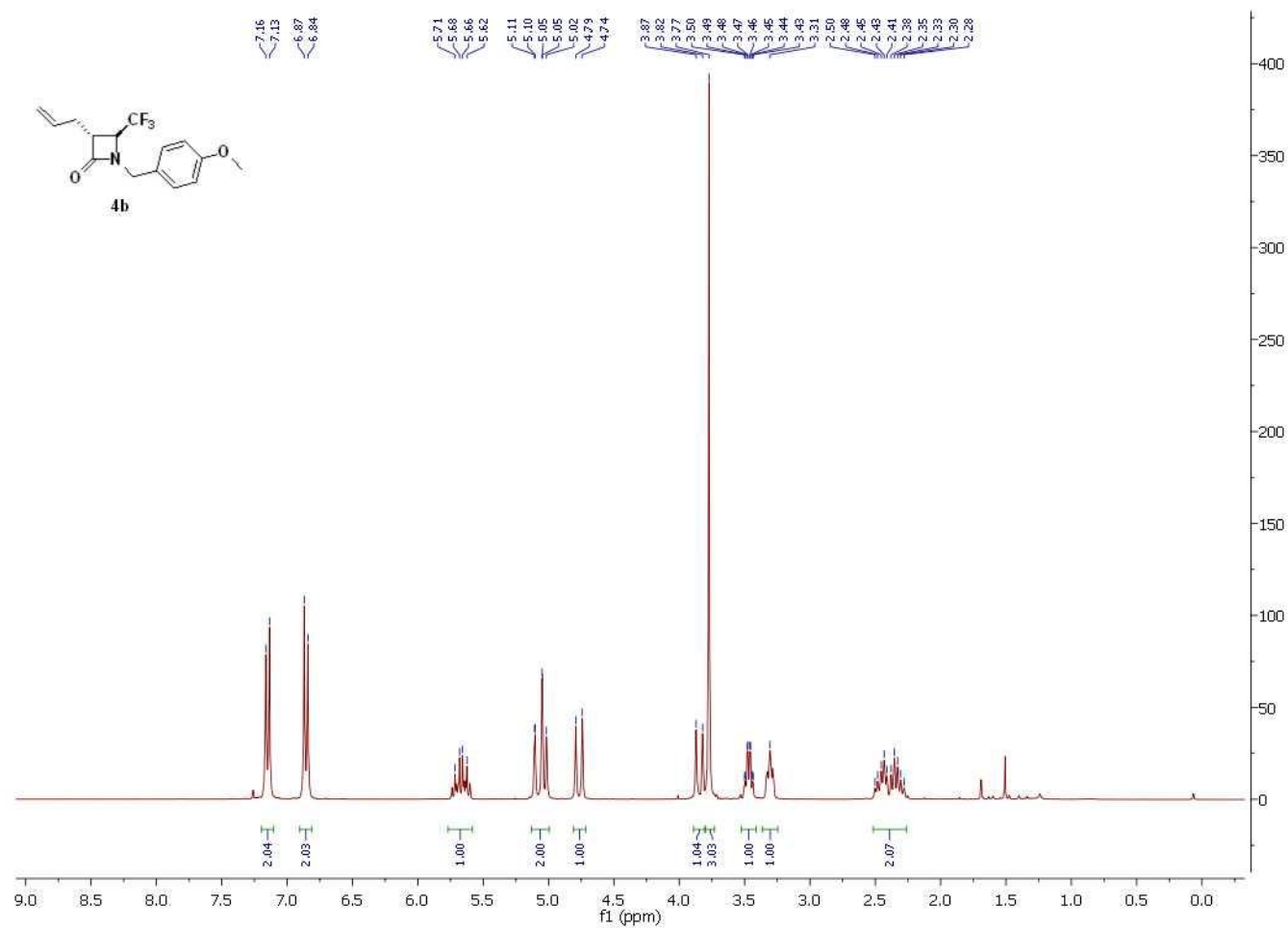
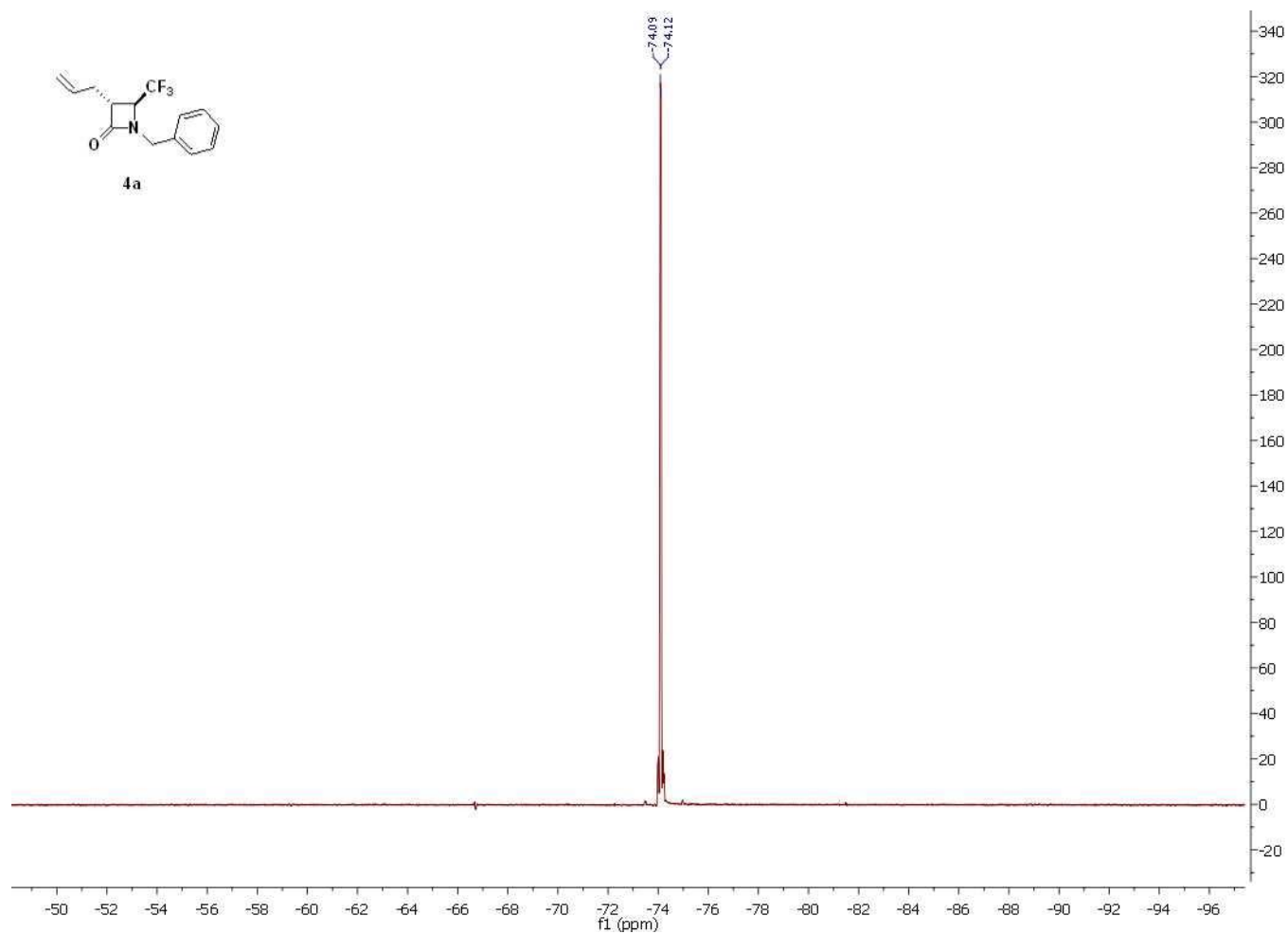


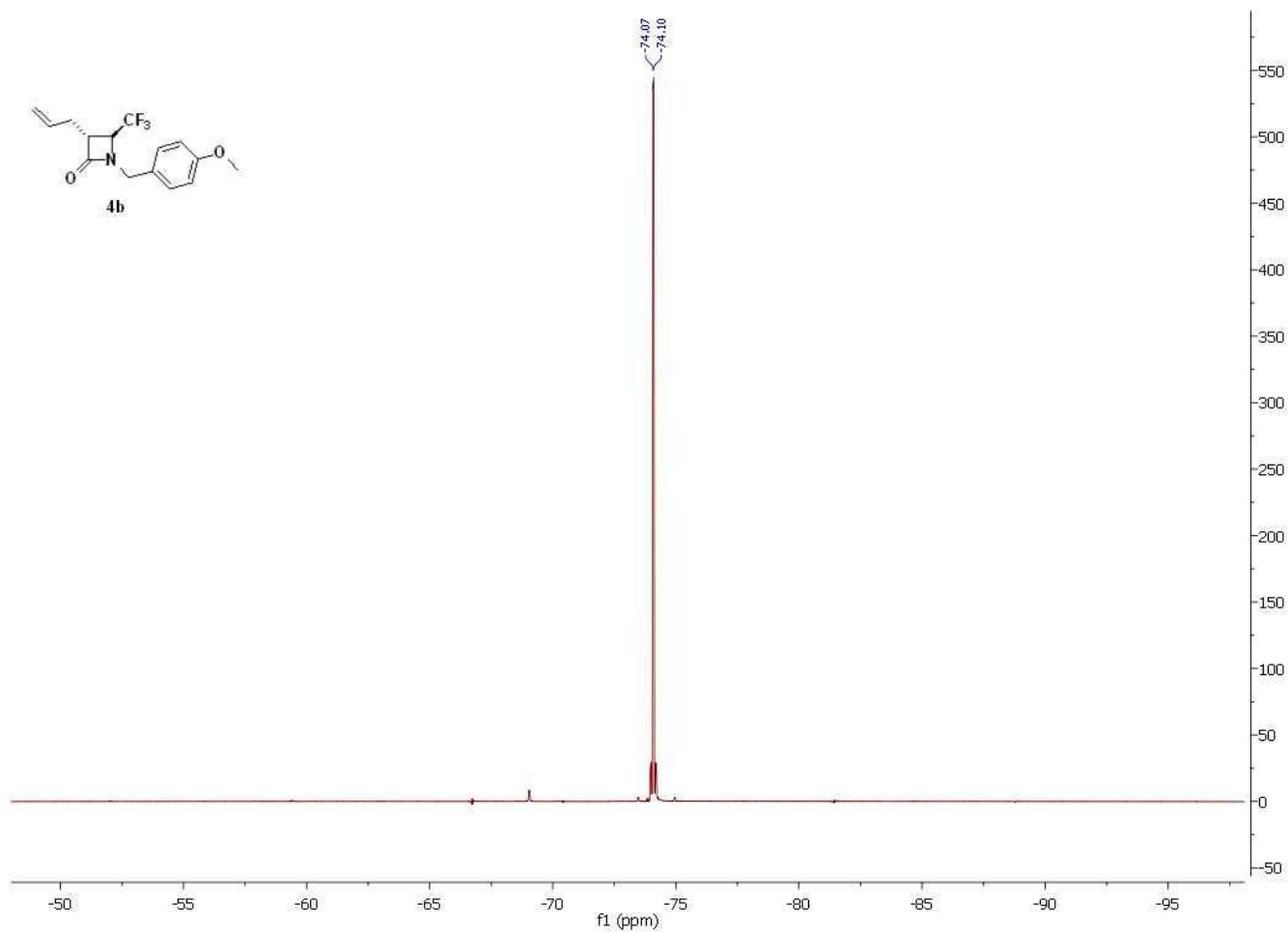
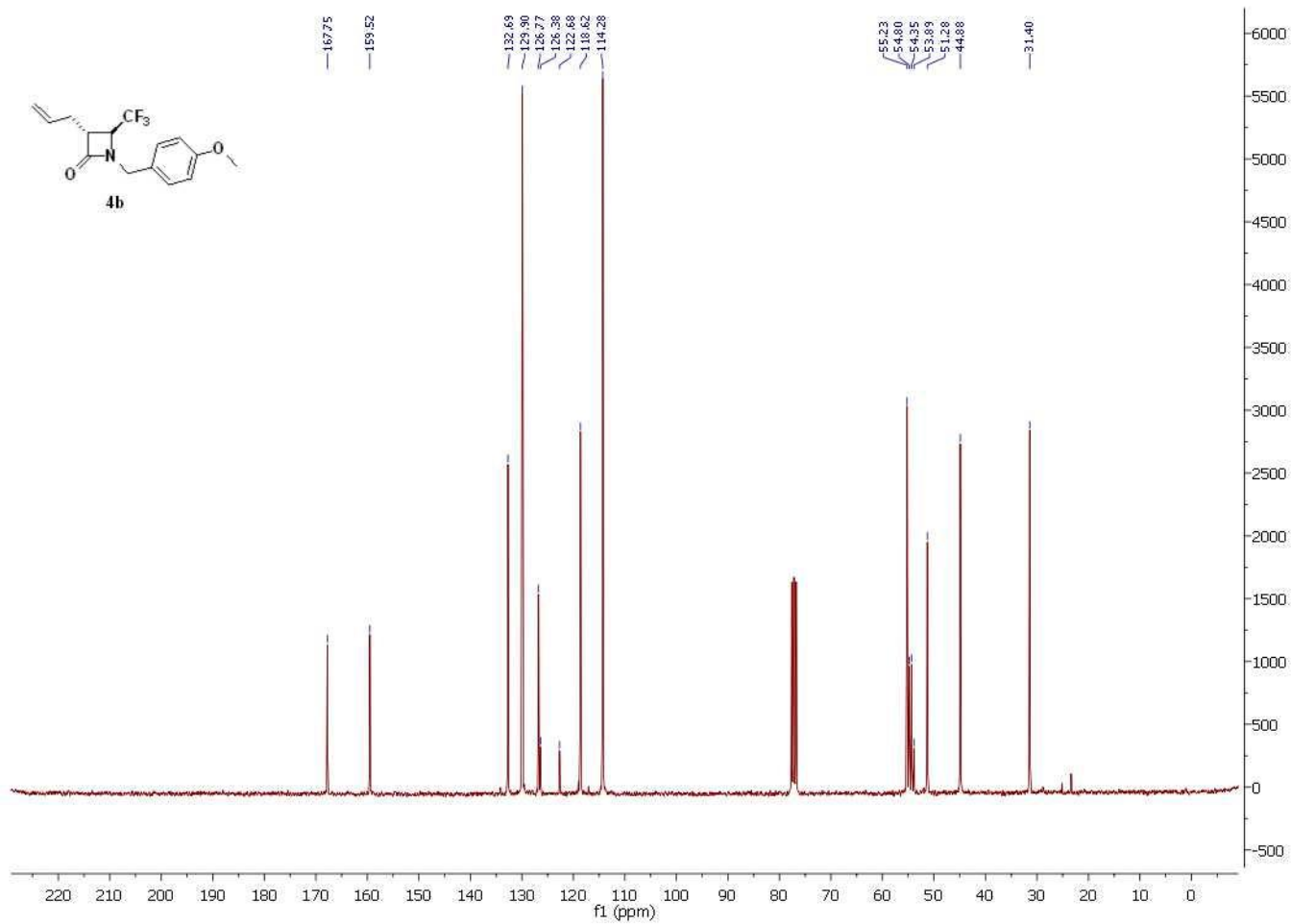


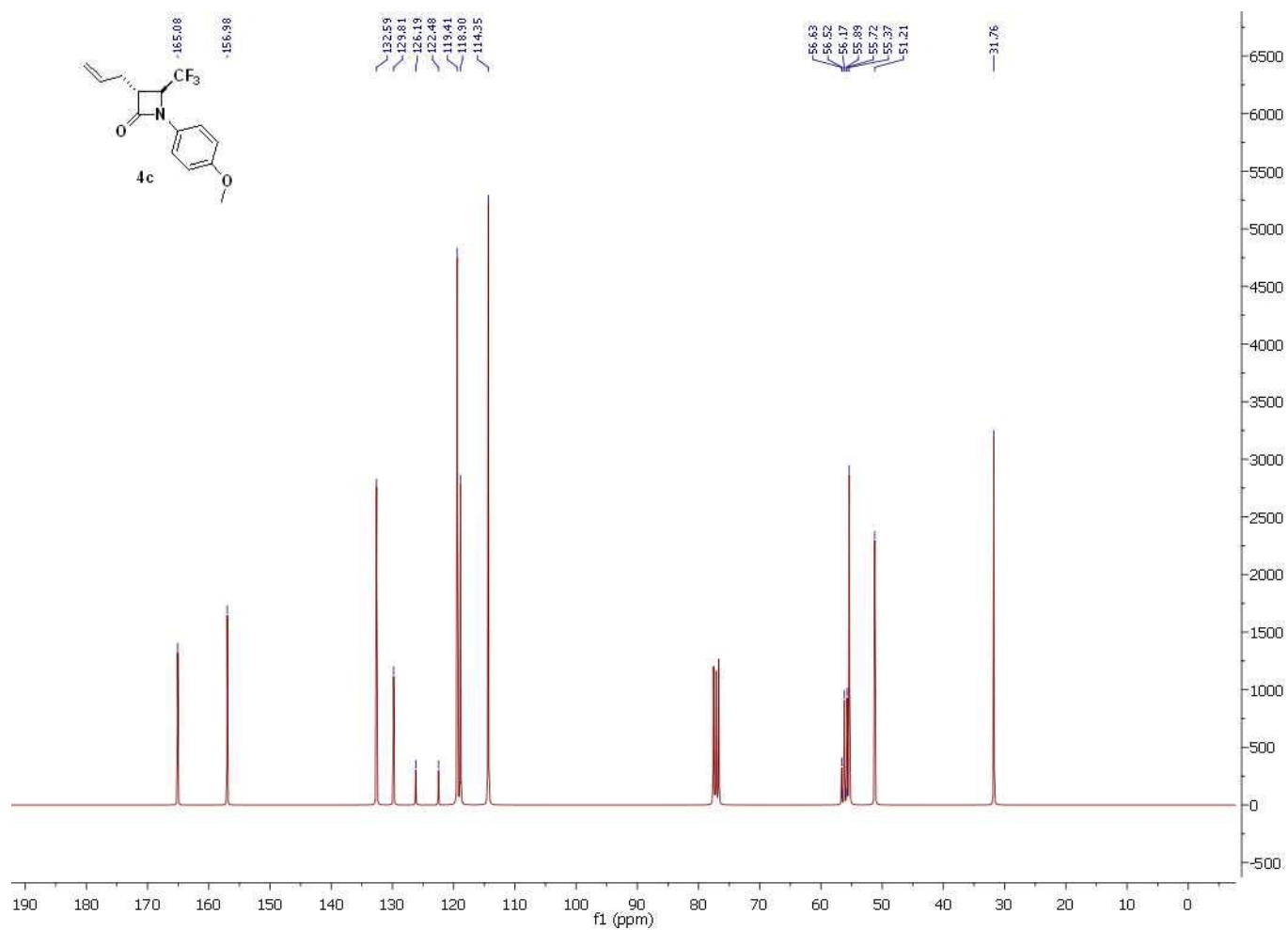
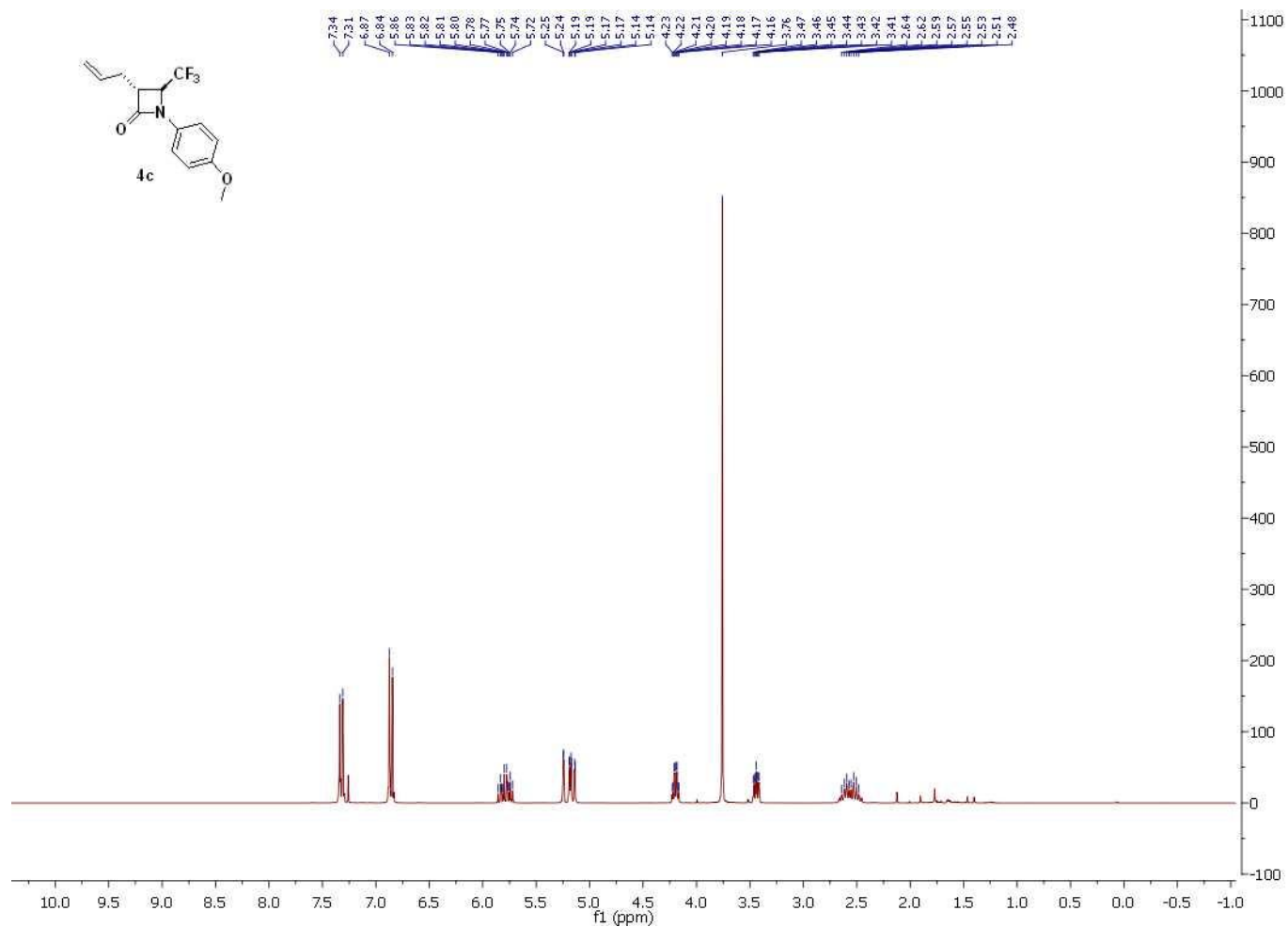


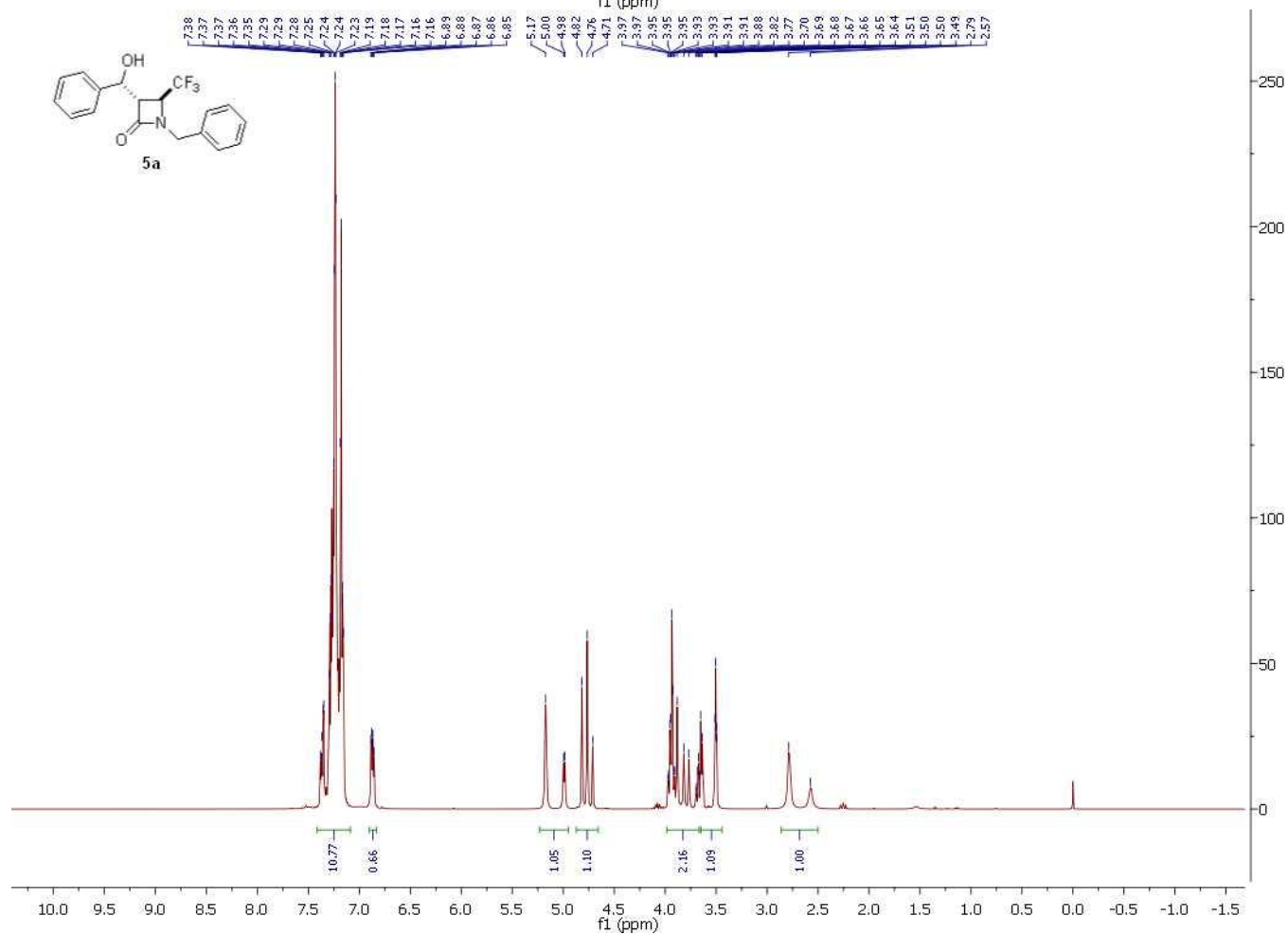
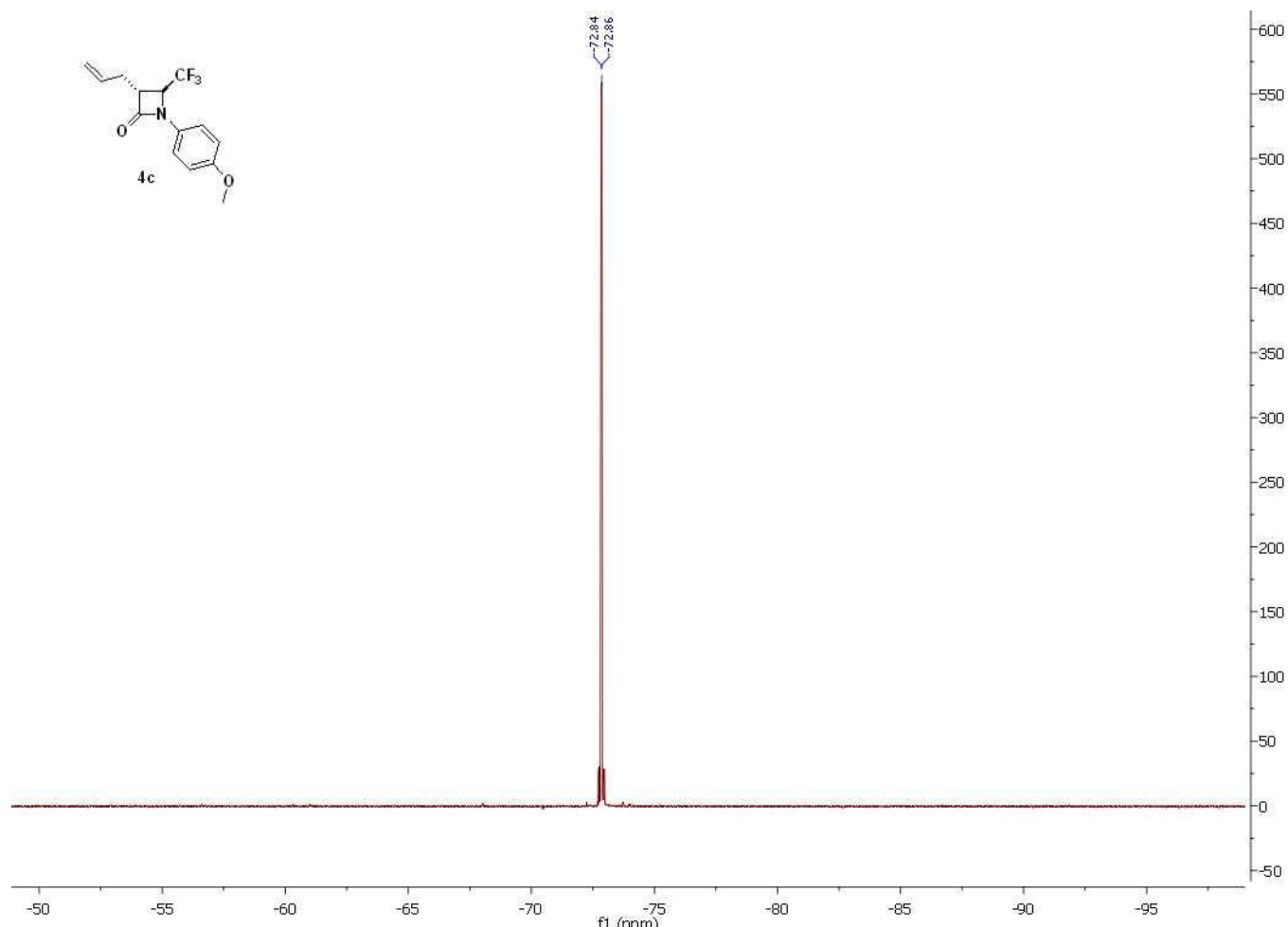


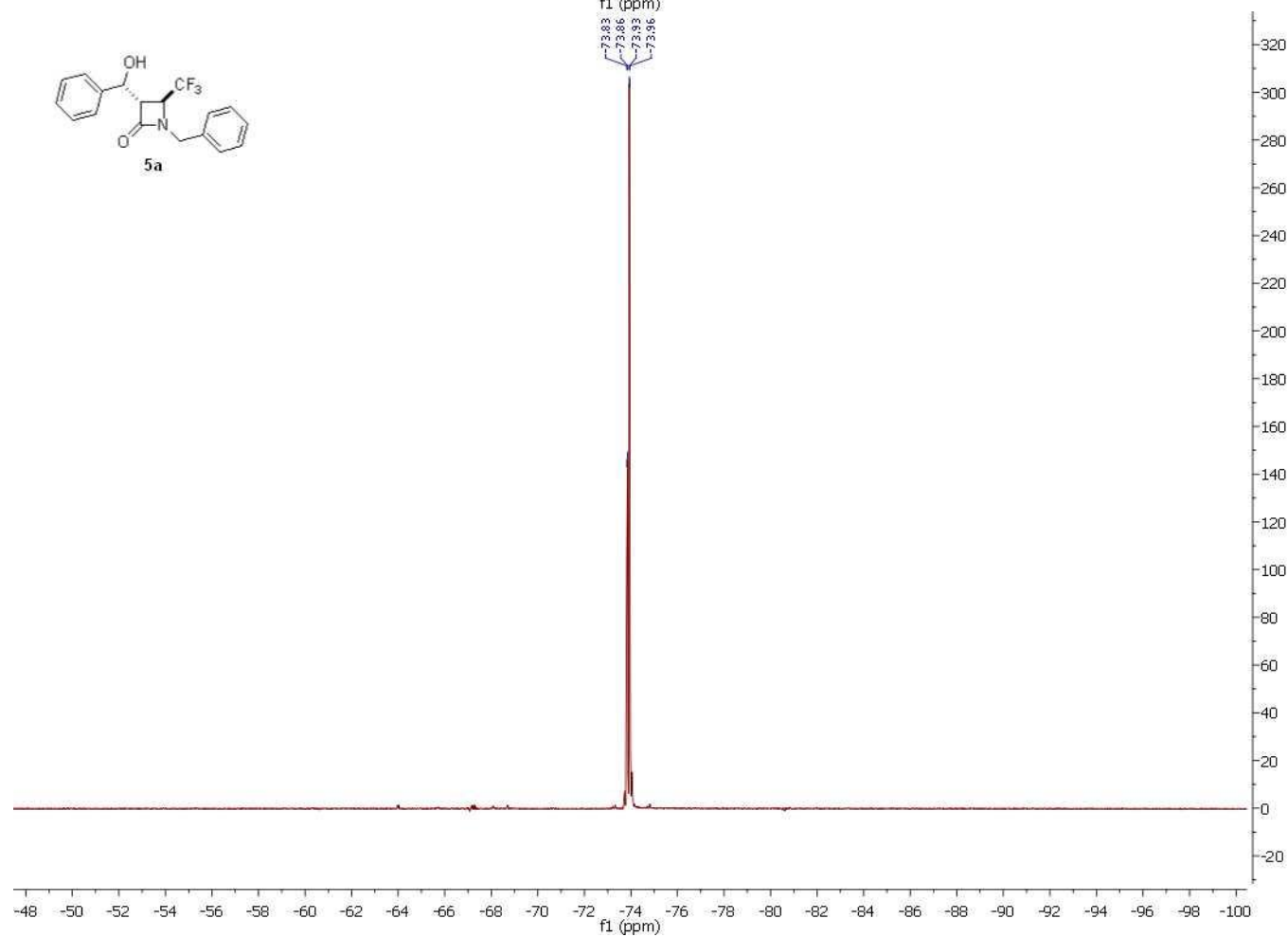
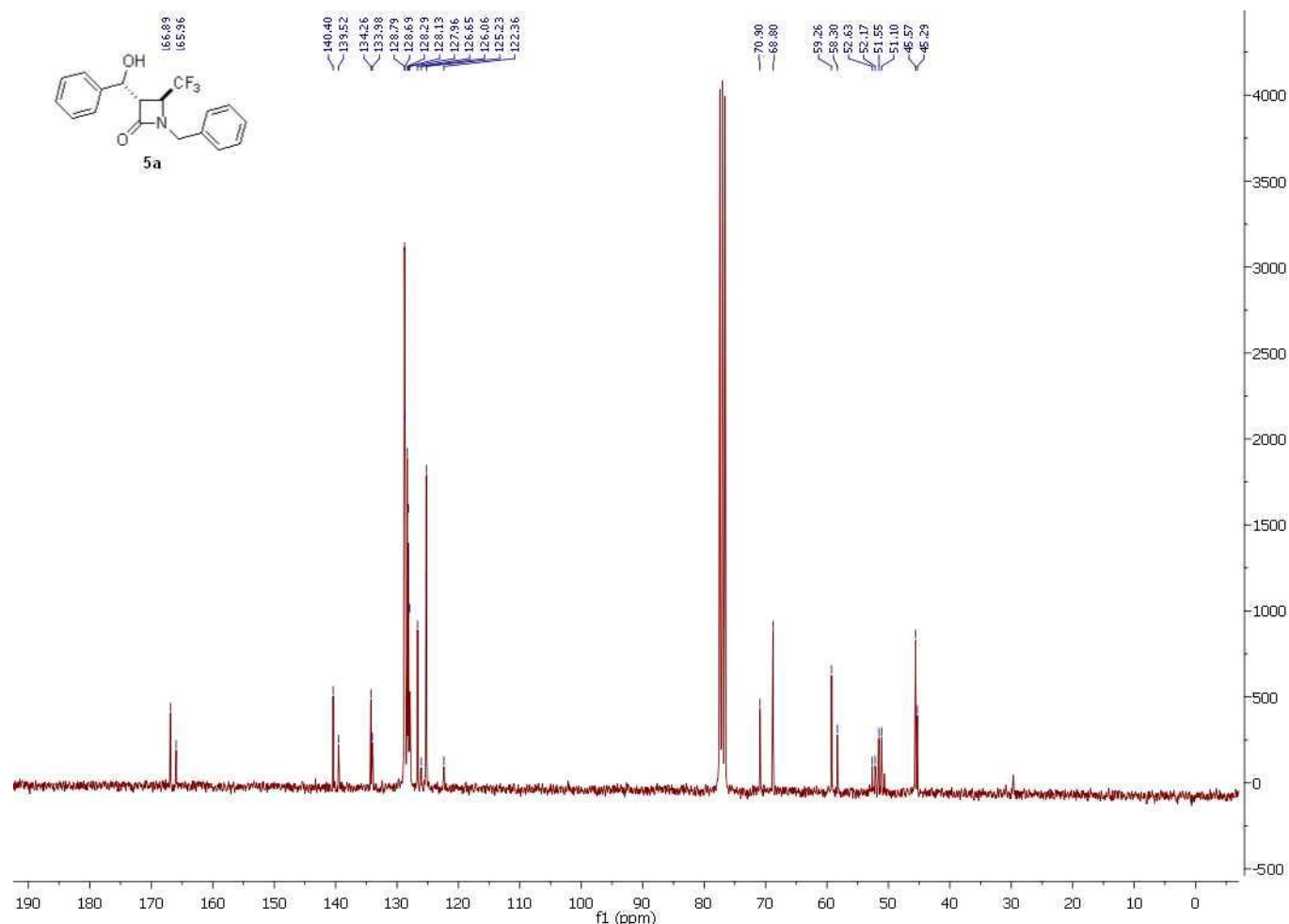


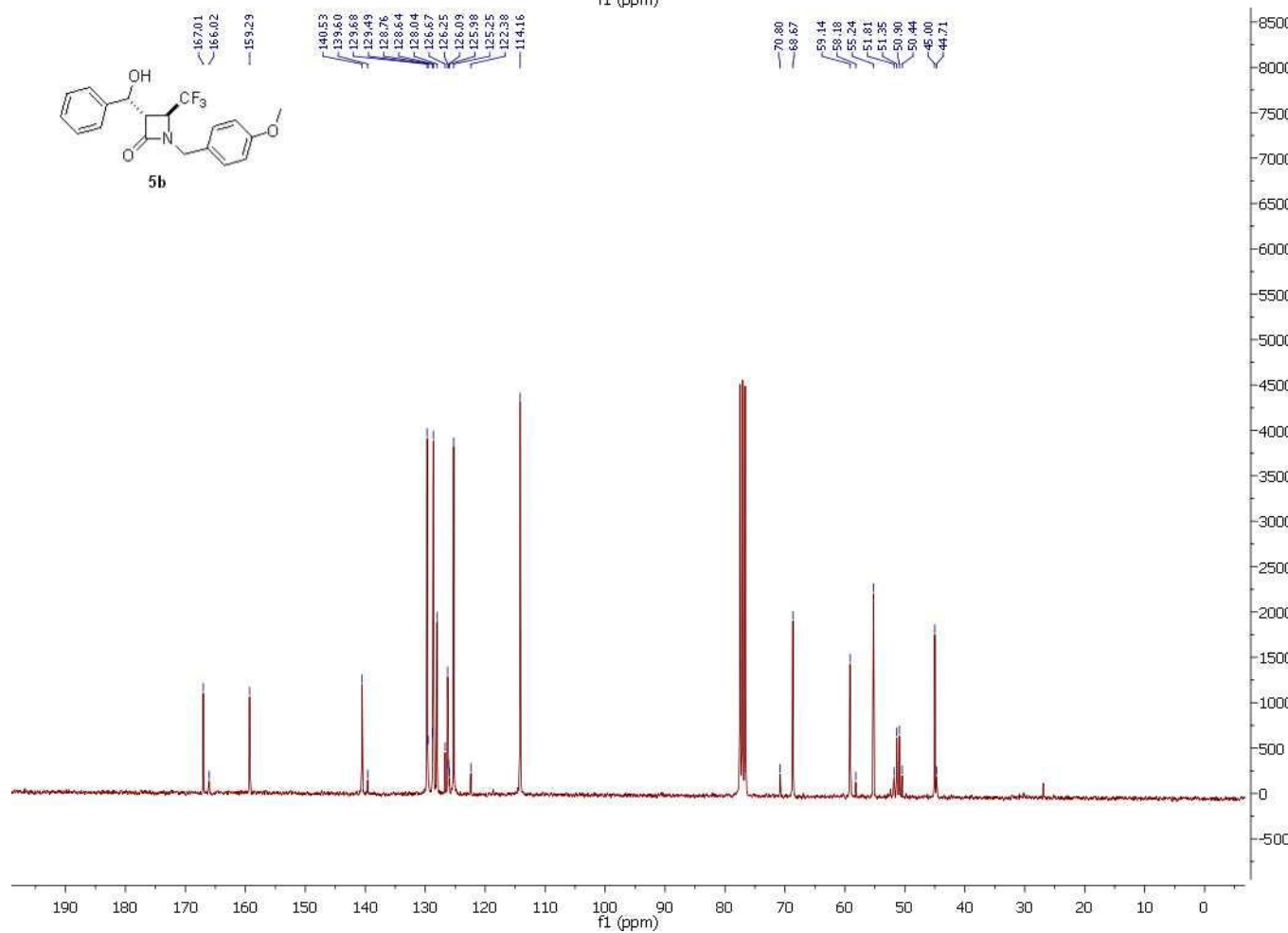
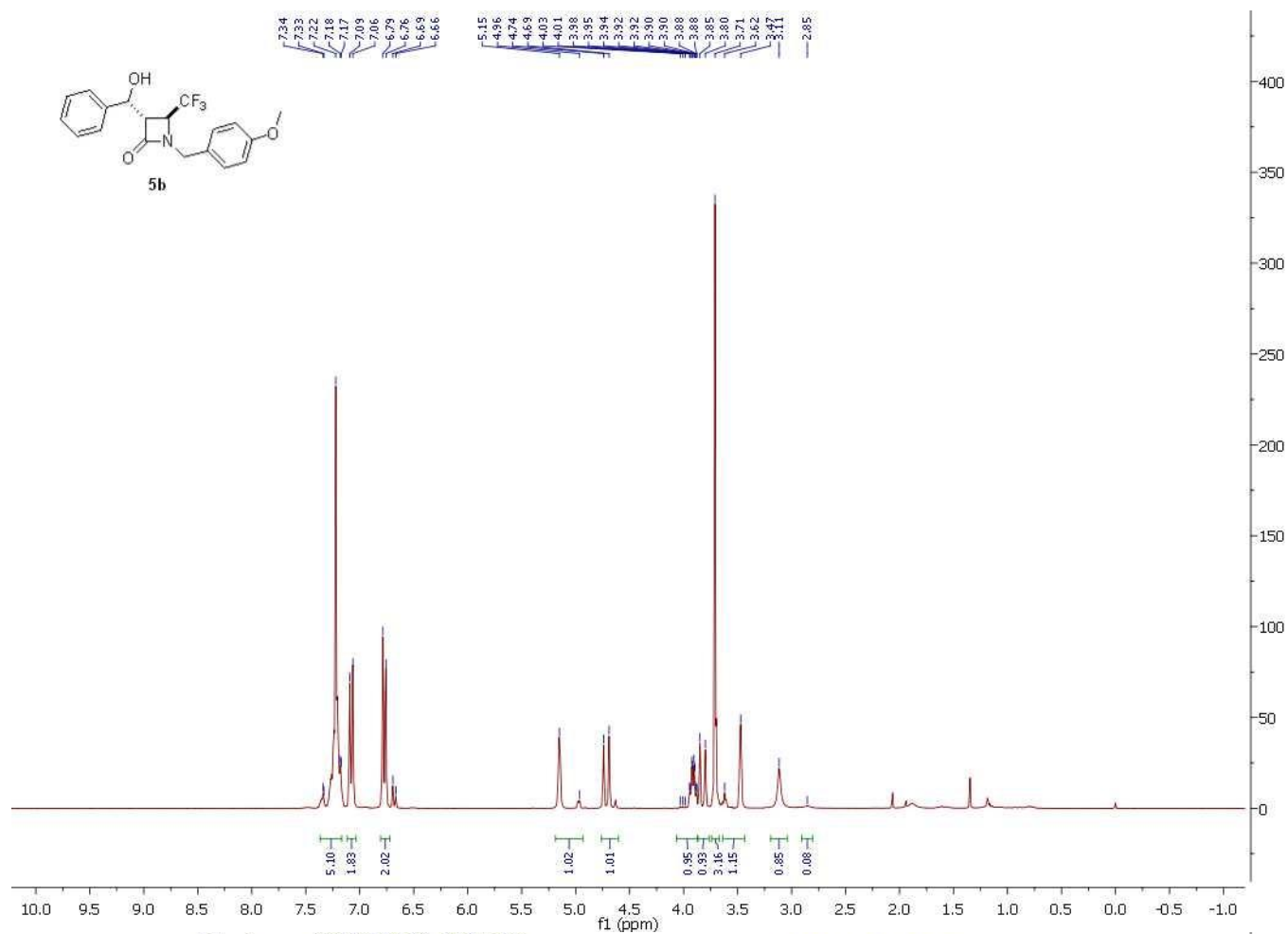


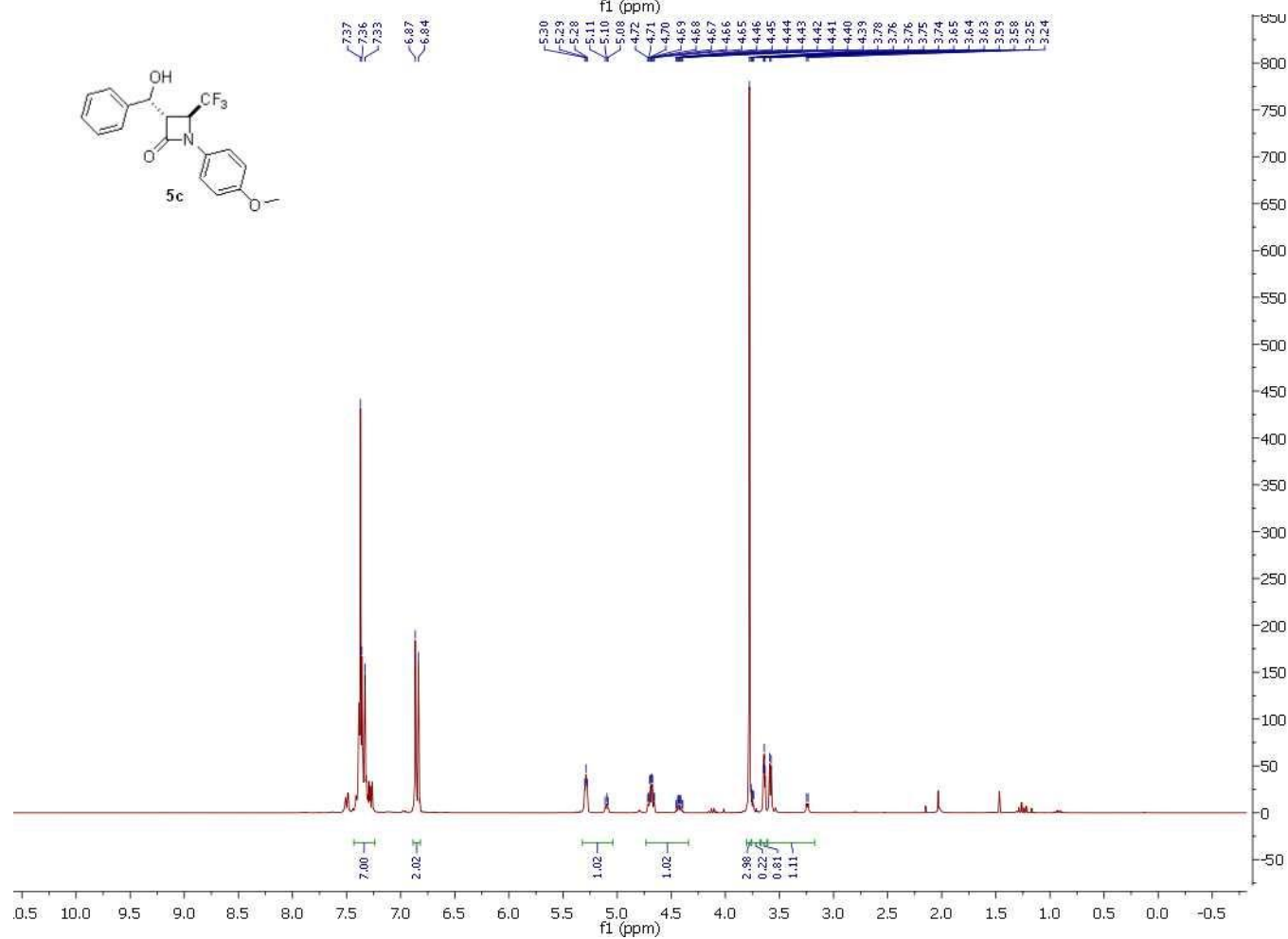
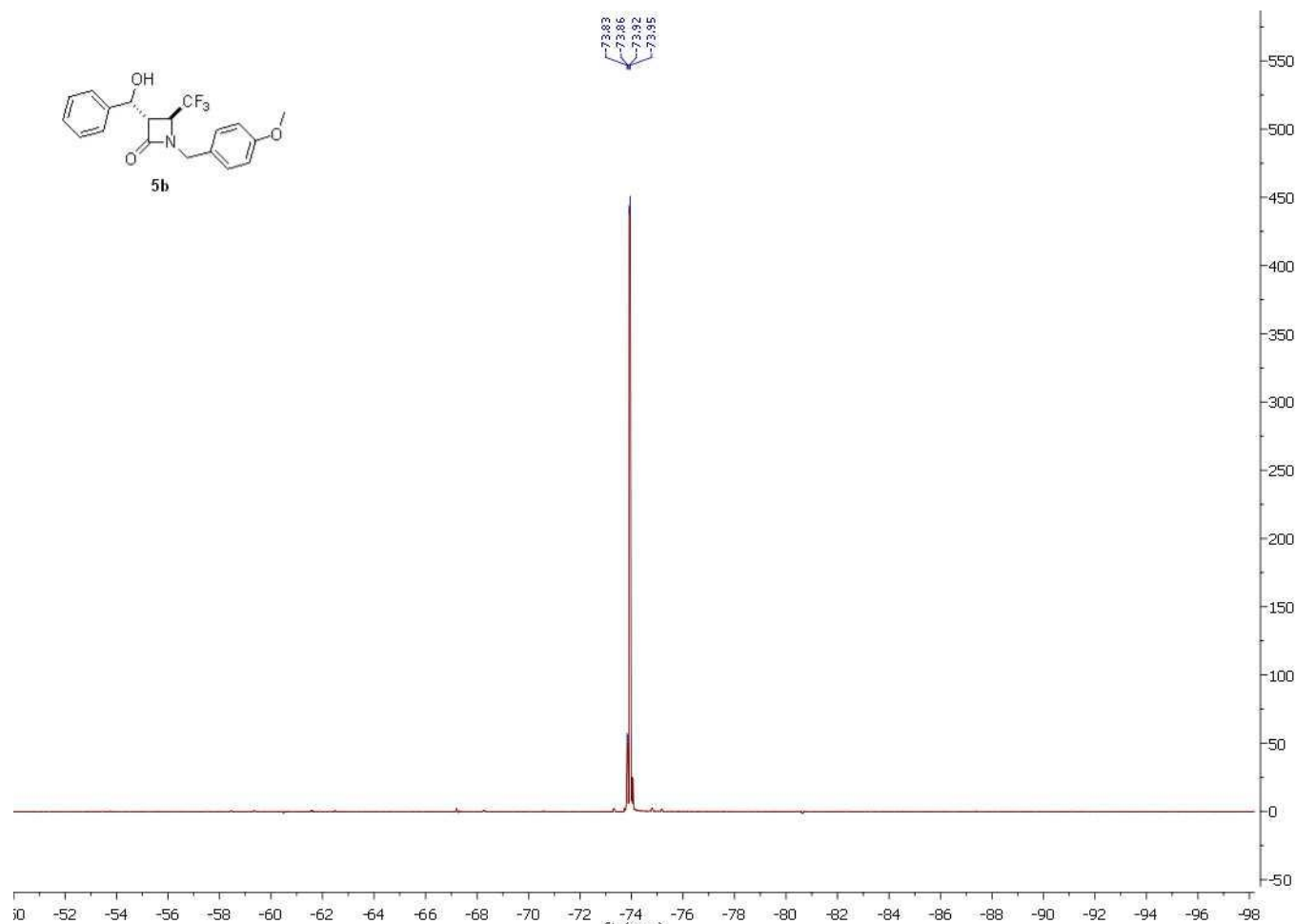




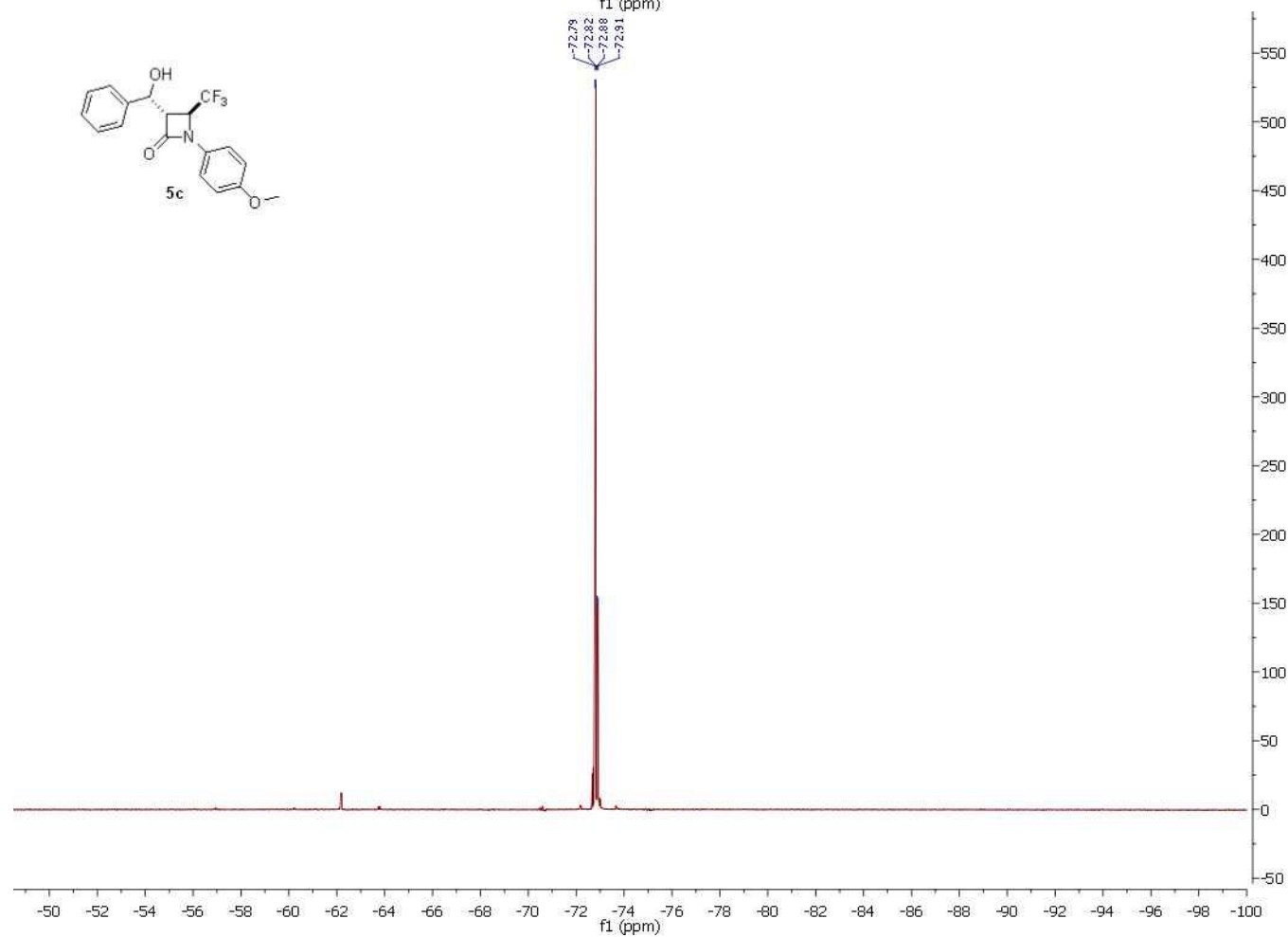
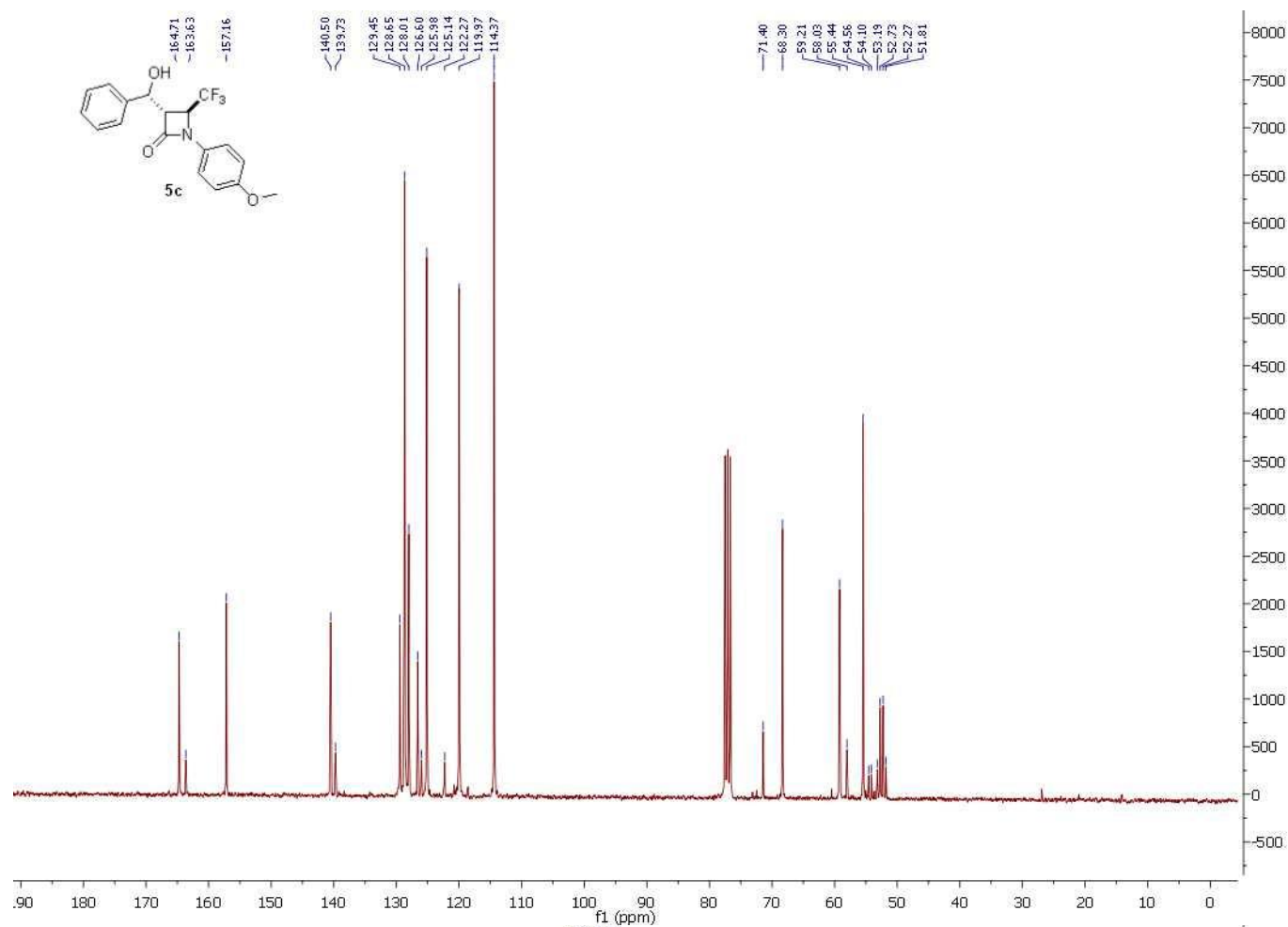


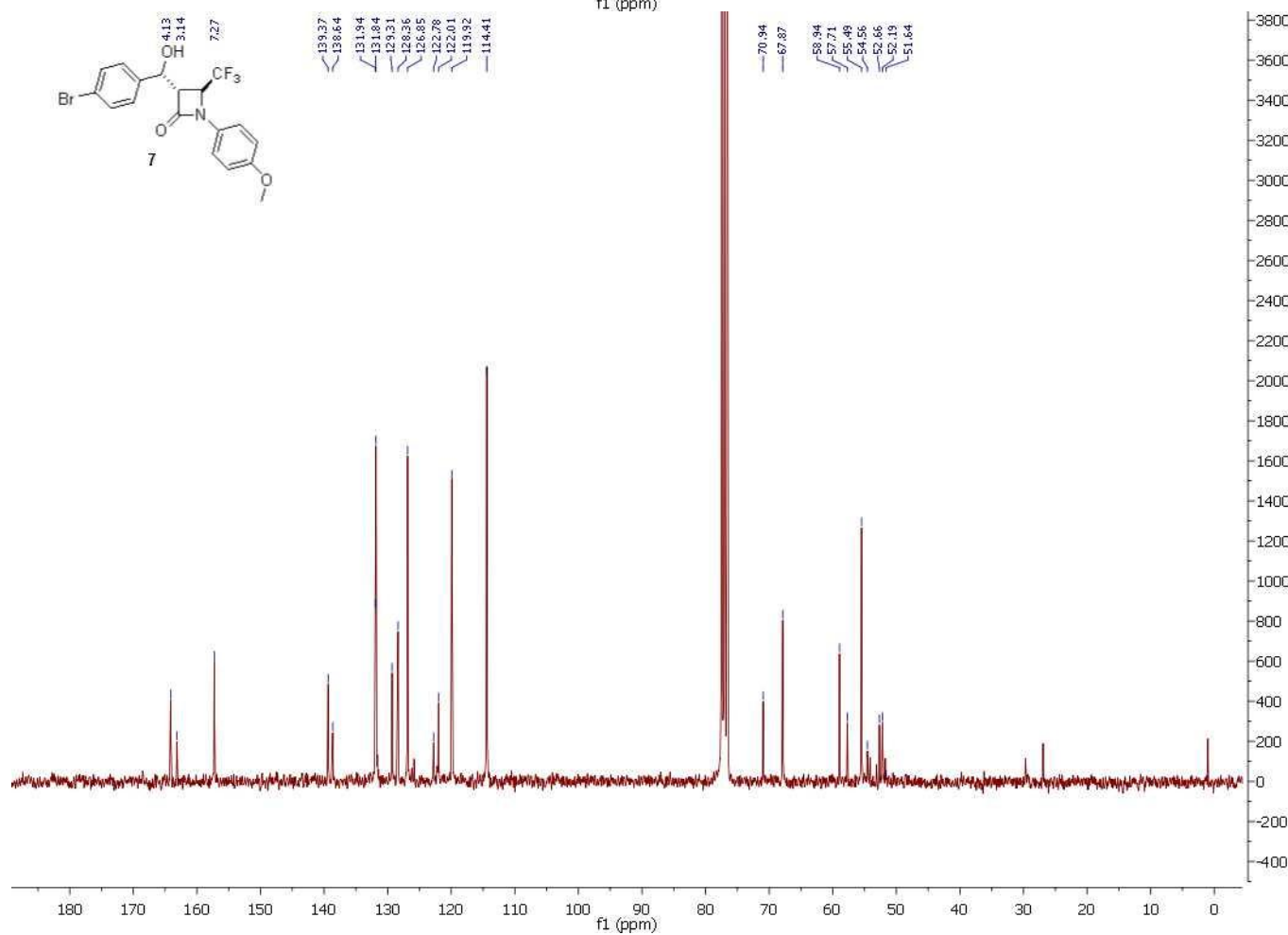
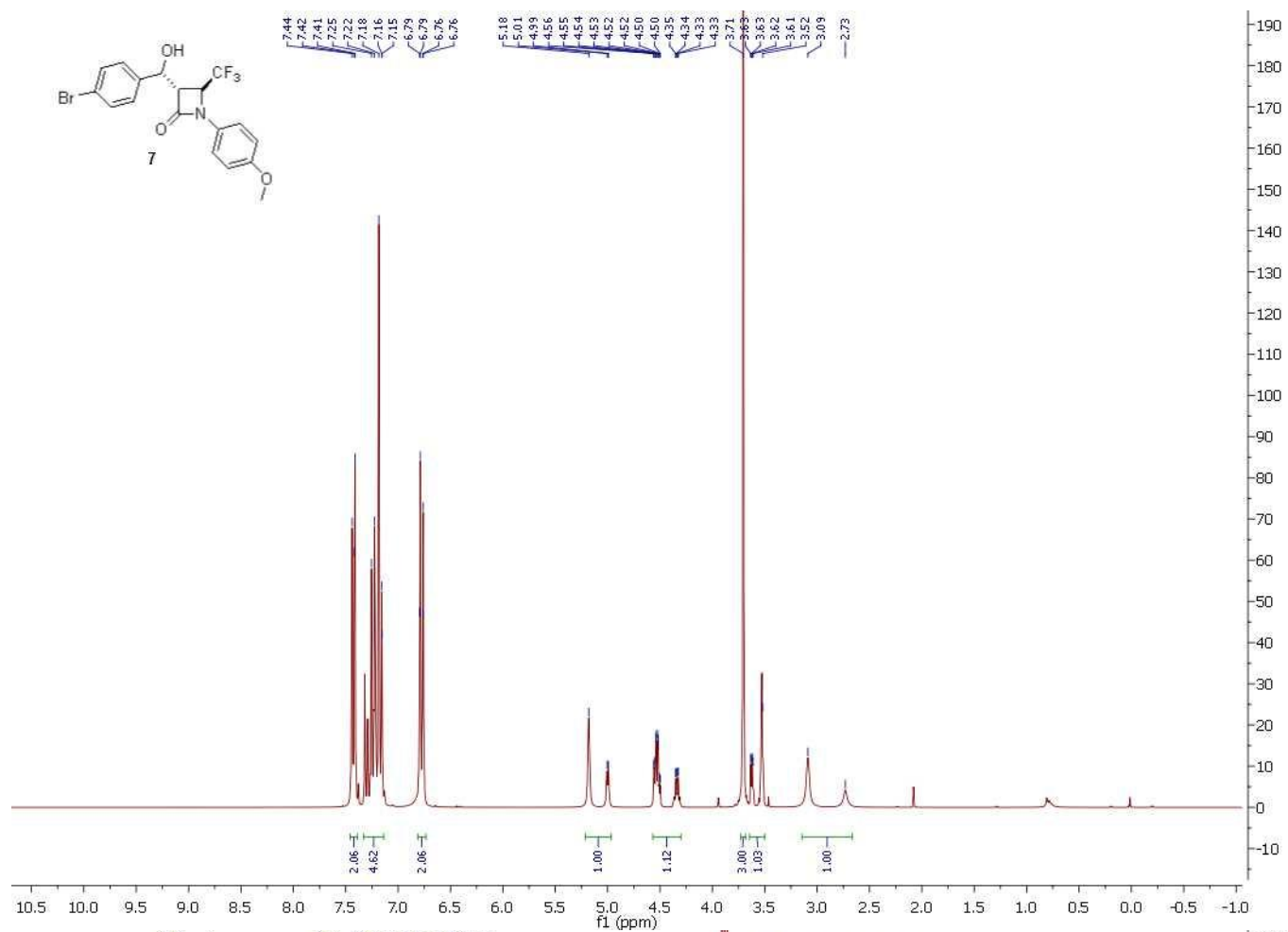


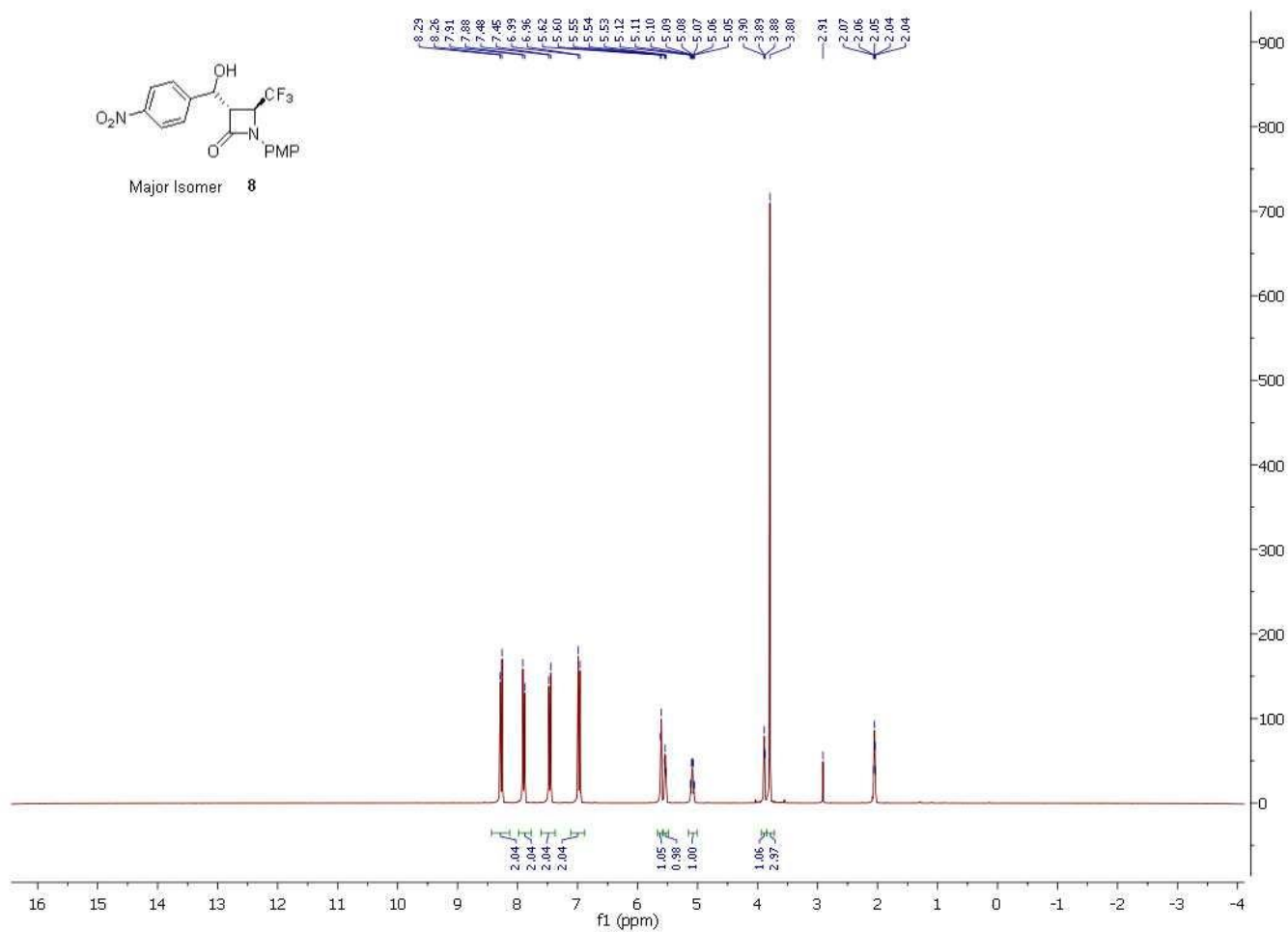
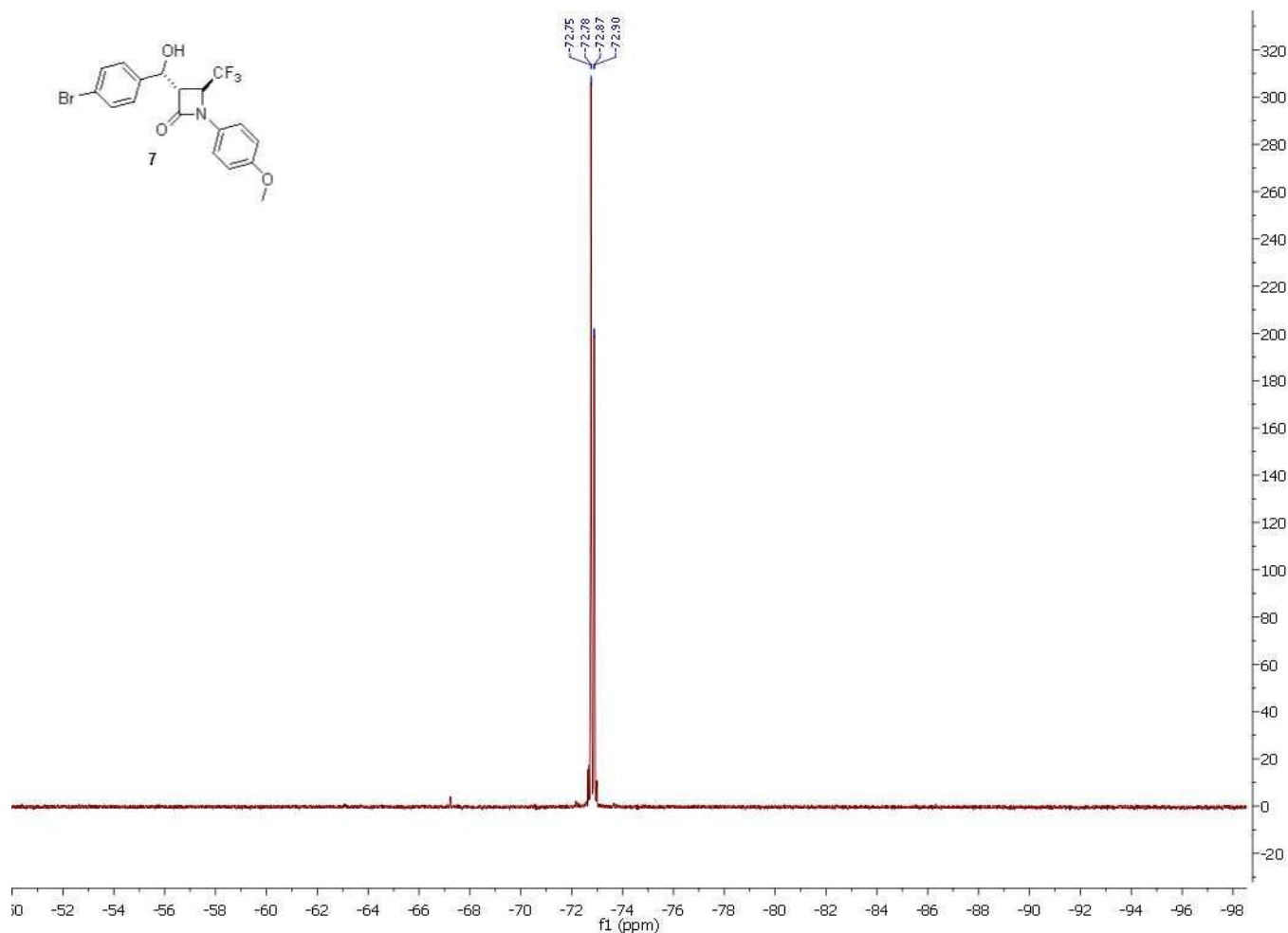


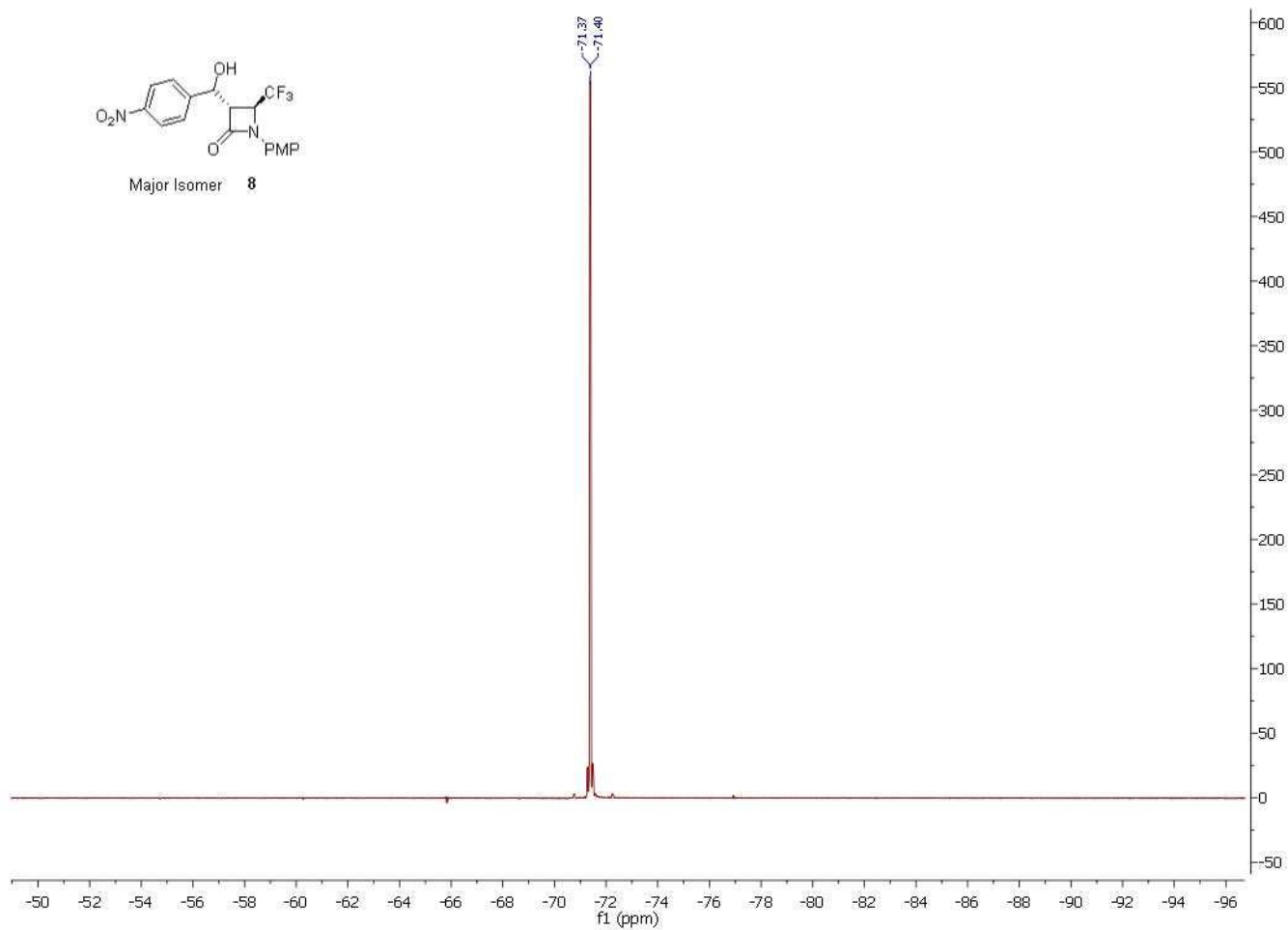
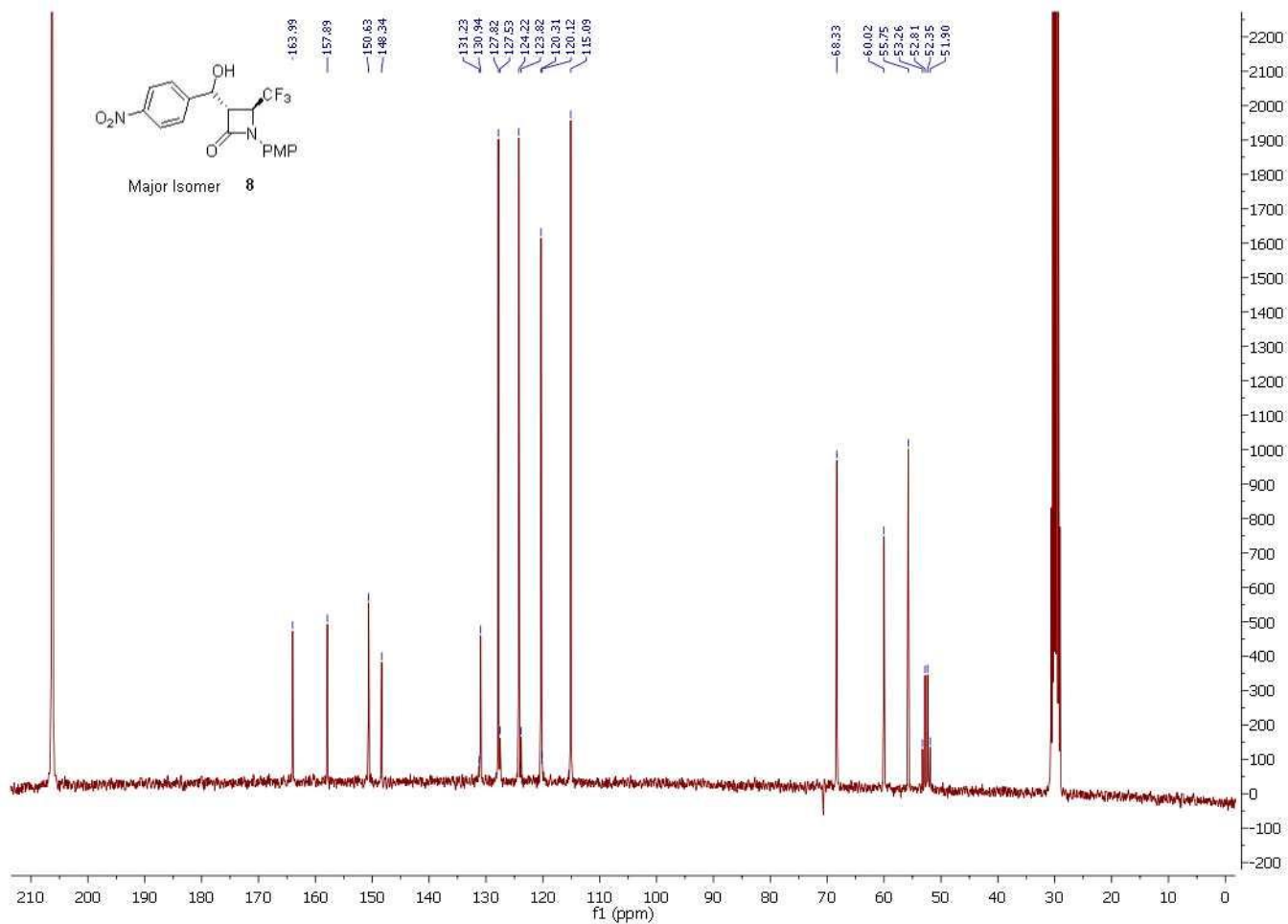


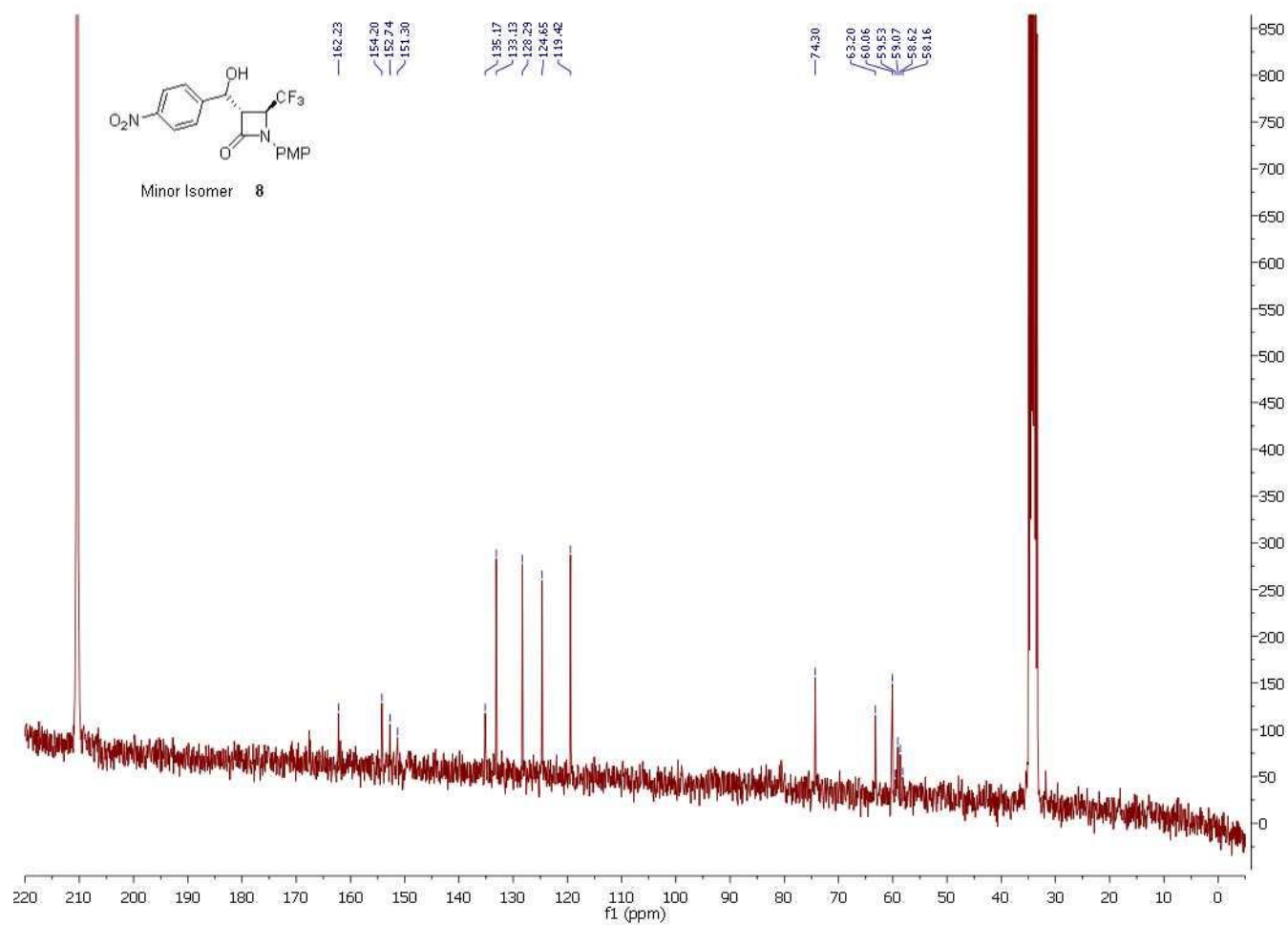
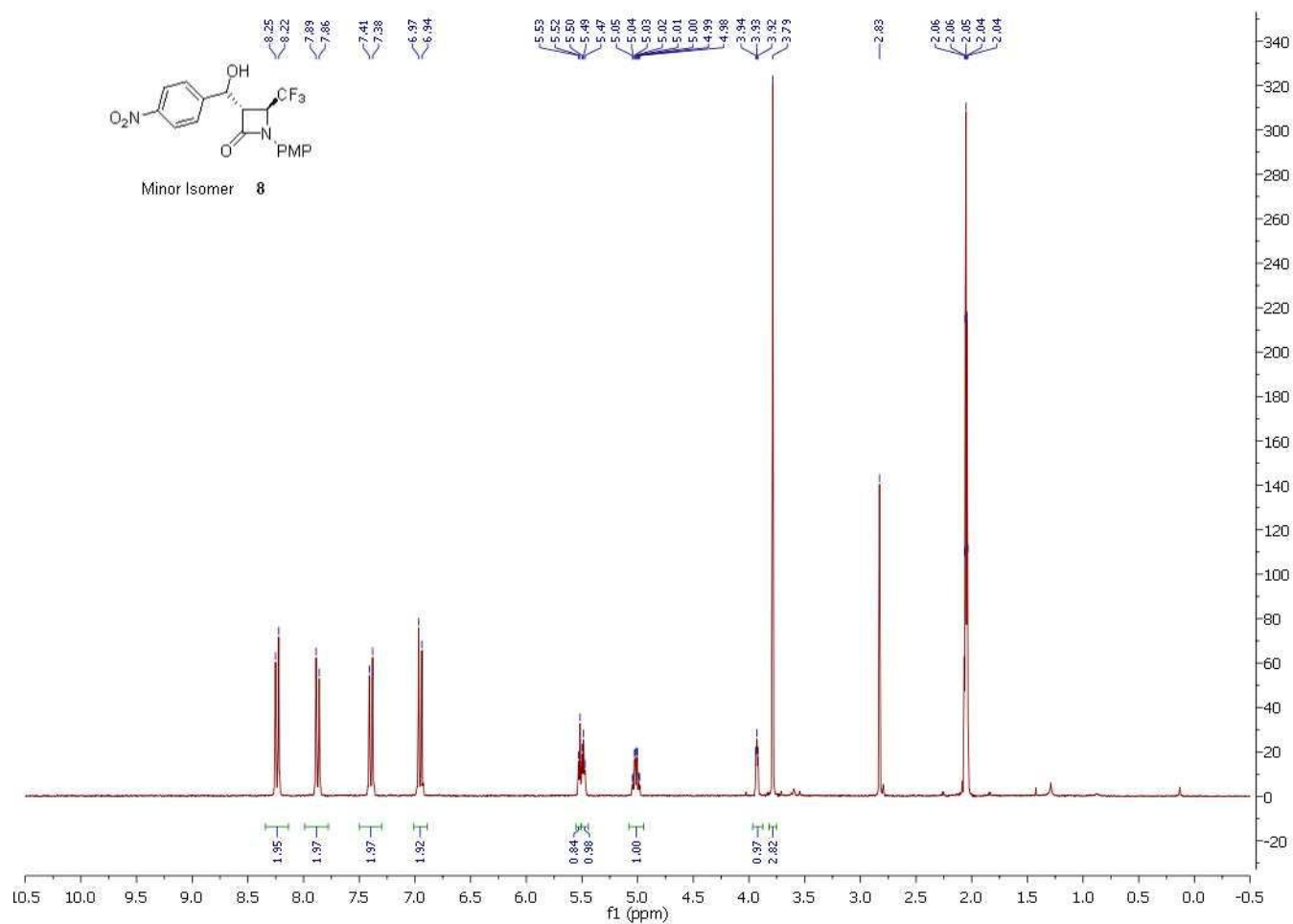


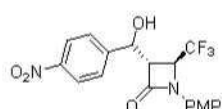




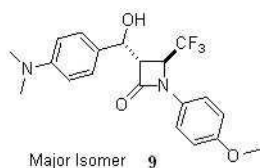
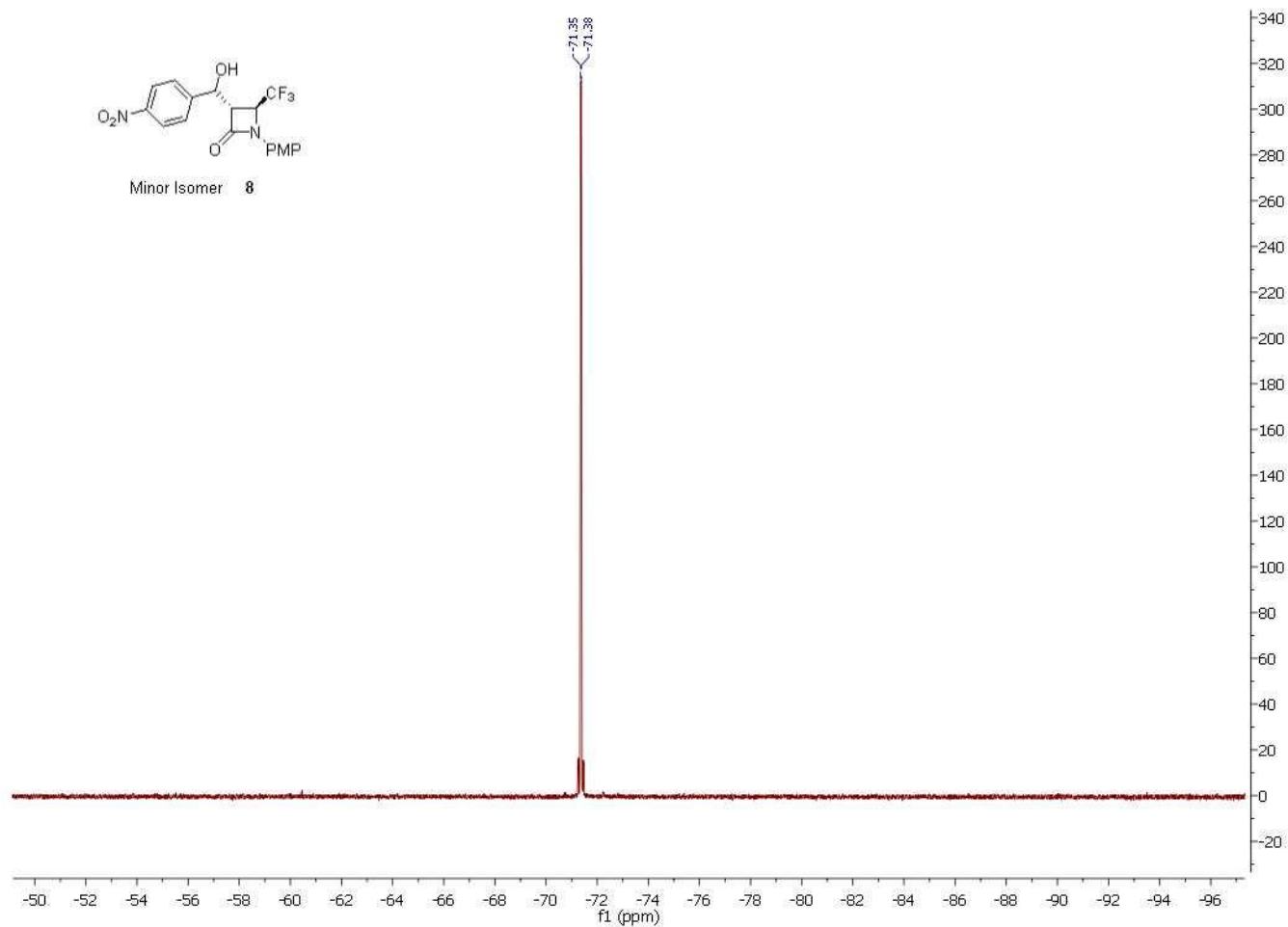








Minor Isomer 8



Major Isomer 9

