

# SUPPORTING INFORMATION

## 3-Benzyl-3-azabicyclo[3.1.1]heptan-6-one: a Promising Building Block for Medicinal Chemistry

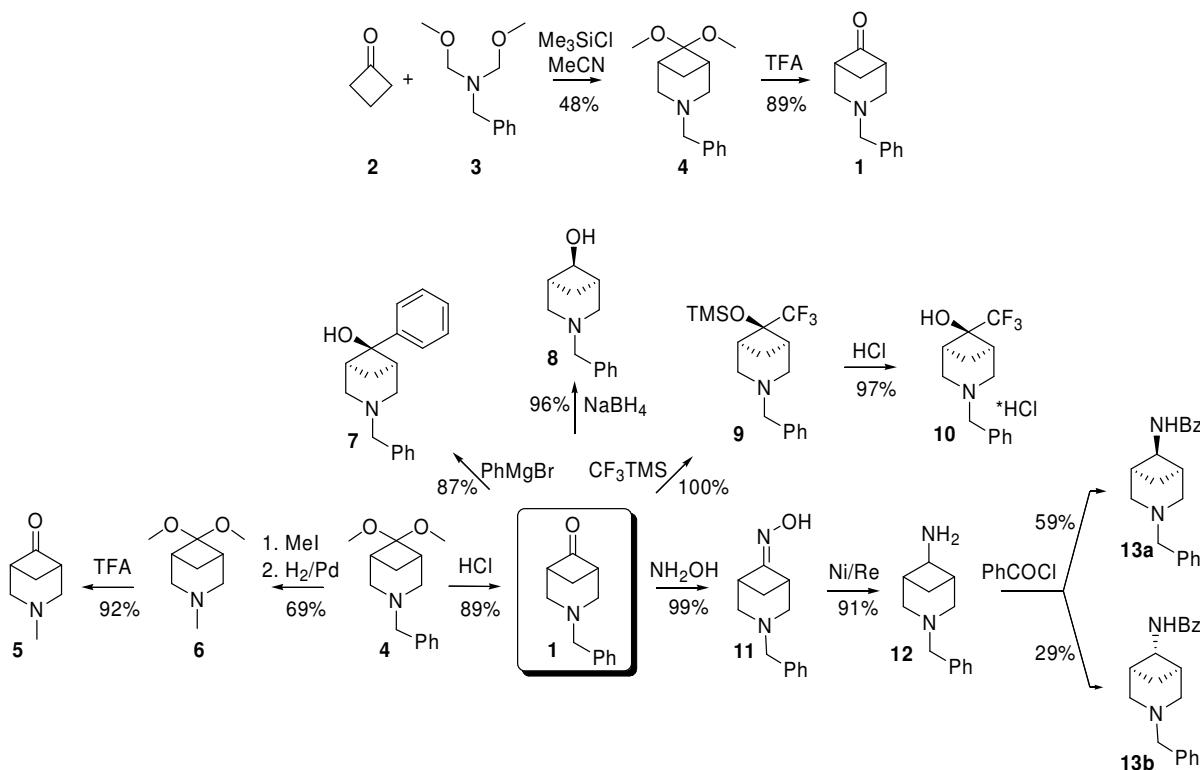
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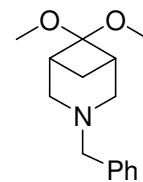
### 1) Synthesis of the compounds



Solvents were purified according to standard procedures. Starting materials were purchased from Aldrich and Enamine. Column chromatography was performed using Kieselgel Merck 60 (230-400 mesh) as the stationary phase.  $^1\text{H}$ -,  $^{19}\text{F}$ -,  $^{13}\text{C}$ -NMR spectra were recorded on Bruker Avance 500 spectrometer (at 499.9 MHz, 470.3 MHz and 124.9 MHz). DEBT-experiments were performed to assign the signals in  $^{13}\text{C}$ -NMR spectra. Chemical shifts are reported in ppm downfield from TMS ( $^1\text{H}$ ,  $^{13}\text{C}$ ) or  $\text{CFCl}_3$  ( $^{19}\text{F}$ ) as internal standards. Mass spectra were recorded on Agilent 1100 LCMSD SL instrument by chemical ionization (CI).

### 3-Benzyl-6,6-dimethoxy-3-azabicyclo[3.1.1]heptane (4)

A mixture of cyclobutanone (35.0 g, 0.50 mol), N,N-bis(methoxymethyl)benzylamine (97.5 g, 0.50 mol) (dropping funnel 1) and chlorotrimethylsilane (120.0 g, 1.10 mol) (dropping funnel 2) were added dropwise to acetonitrile (2500 mL) upon stirring at 40 °C during 3 h. The reaction mixture was additionally stirred for 16 h at room temperature. Thereafter, pH value of the reaction mixture was adjusted to pH 8 with saturated aq. solution of NaHCO<sub>3</sub>. The aqueous layer was extracted with EtOAc (3\*250 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated in vacuum. Distillation of the crude product under reduced pressure afforded pure **4** (69.2 g, 0.28 mol, 48% yield) as a colorless liquid. B.p. 90-95 °C (0.5 mm).



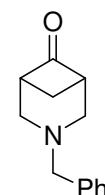
<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si), δ: 1.74 (1H, m, CHH of cyclobutane), 2.07 (1H, d, <sup>2</sup>J<sub>H-H</sub> = 8.3 Hz, CHH of cyclobutane), 2.54 (2H, m, CH of cyclobutane), 2.73 (2H, d, J = 9.7 Hz, NCHH), 3.077 (2H, m, NCHH), 3.24 (6H, 2 s, OCH<sub>3</sub>), 3.70 (2H, s, NCH<sub>2</sub>Ph), 7.25-7.38 (5H, m, Ph).

<sup>13</sup>C NMR (125 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si), δ: 21.40 (s, CH<sub>2</sub> of cyclobutane), 39.98 (s, CH of cyclobutane), 48.44 (s, OCH<sub>3</sub>), 49.09 (s, OCH<sub>3</sub>), 51.77 (s, PhCH<sub>2</sub>NCH<sub>2</sub>), 60.11 (s, NCH<sub>2</sub>Ph), 103.70 (s, quat-C, C-OCH<sub>3</sub>), 126.61 (s, CH, Ph), 128.03 (s, CH, Ph), 128.59 (s, CH, Ph), 139.54 (s, quat-C, Ph).

MS (m/z): 247.

### 3-Benzyl-3-azabicyclo[3.1.1]heptan-6-one (1)

Compound **4** (69.2 g, 0.28 mol) was dissolved in TFA (400 ml) and the formed solution was stirred overnight at 50 °C. An excess of trifluoroacetyl acid was evaporated in vacuum, and a saturated aq. solution of NaHCO<sub>3</sub> was added to adjust pH value of the solution to 8. The reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3\*100 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated in vacuum. The residue was purified by flash column chromatography with dichloromethane as an eluent to give ketone **1** as a yellow solid (50.1 g, 0.25 mol, 89% yield). M.p. 74 °C.



Crystals suitable for an X-ray analysis were obtained by a slow evaporation of a diluted solution of **1** in hexane.

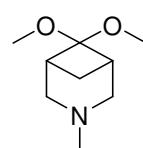
<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si), δ: 1.78 (1H, d, <sup>2</sup>J<sub>H-H</sub> = 5.0 Hz, CHH of cyclobutane), 1.95 (1H, m, CHH of cyclobutane), 3.02 (2H, m, CH of cyclobutane), 3.10 (2H, d, J = 10.0 Hz, NCHH), 3.33 (2H, d, J = 10.0 Hz, NCHH), 3.62 (2H, s, NCH<sub>2</sub>Ph), 7.23-7.31 (5H, m, Ph).

<sup>13</sup>C NMR (125 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si), δ: 25.18 (s, CH<sub>2</sub> of cyclobutane), 55.93 (s, CH of cyclobutane), 58.79 (s, PhCH<sub>2</sub>NCH<sub>2</sub>), 59.75 (s, NCH<sub>2</sub>Ph), 126.77 (s, CH, Ph), 127.92 (s, CH, Ph), 128.26 (s, CH, Ph), 137.70 (s, quat-C, Ph), 206.08 (s, C=O).

MS (m/z): 201.

### 3-Methyl-6,6-dimethoxy-3-azabicyclo[3.1.1]heptane (6)

A mixture of ketone **1** (2.0 g, 8.1 mmol) and CH<sub>3</sub>I (4.6 g, 32.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was heated at reflux for 2 h. The solvent was evaporated in vacuum. The residue was dissolved in MeOH (20 mL) and hydrogenated using Pd(OH)<sub>2</sub>/C as a



catalyst at 50 atm., 100 °C for 48 h. The solution was filtered and the filtrate was evaporated in vacuum to give product **6**\*HI as a solid. The product was dissolved in water (20 mL) and a saturated solution of K<sub>2</sub>CO<sub>3</sub> in water was added. The water phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3\*10mL). Organic phase was separated, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated in vacuum to give pure **6** (0.95 g, 5.6 mmol, 69% yield) as a yellowish oil.

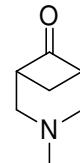
<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si), δ: 1.70 (1H, m, CHH of cyclobutane), 1.88 (1H, d, <sup>2</sup>J<sub>H-H</sub> = 8.0 Hz, CHH of cyclobutane), 2.32 (3H, s, NCH<sub>3</sub>), 2.59 (2H, m, CH of cyclobutane), 2.60 (2H, d, J = 10.0 Hz, NCHH), 3.077 (2H, d, J = 10.0 Hz, NCHH), 3.24 (6H, 2 s, OCH<sub>3</sub>).

<sup>13</sup>C NMR (125 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si), δ: 21.30 (s, CH<sub>2</sub> of cyclobutane), 39.88 (s, CH of cyclobutane), 43.12 (s, NCH<sub>3</sub>), 48.51 (s, OCH<sub>3</sub>), 49.15 (s, OCH<sub>3</sub>), 53.92 (s, CH<sub>3</sub>NCH<sub>2</sub>).

MS (m/z): 171.

### 3-Methyl-3-azabicyclo[3.1.1]heptan-6-one (5)

Compound **6** (200 mg, 1.2 mmol) was dissolved in TFA (5 ml) and the formed solution was stirred overnight at 50 °C. An excess of trifluoroacetyl acid was evaporated in vacuum, and a saturated aq. solution of NaHCO<sub>3</sub> was added to adjust pH value of the reaction mixture to 8. The reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3\*3 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated in vacuum to give ketone **5** as a yellowish oil (135 mg, 1.1 mol, 92% yield).



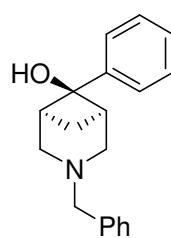
<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si), δ: 1.73 (1H, d, <sup>2</sup>J<sub>H-H</sub> = 9.0 Hz, CHH of cyclobutane), 1.95 (1H, m, CHH of cyclobutane), 2.31 (3H, s, NCH<sub>3</sub>), 3.05 (2H, m, CH of cyclobutane), 3.07 (2H, d, J = 10.5 Hz, NCHH), 3.36 (2H, d, J = 10.5 Hz, NCHH).

<sup>13</sup>C NMR (125 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si), δ: 25.65 (s, CH<sub>2</sub> of cyclobutane), 43.17 (s, NCH<sub>3</sub>), 56.27 (s, CH of cyclobutane), 61.63 (s, CH<sub>3</sub>NCH<sub>2</sub>), 206.98 (s, C=O).

MS (m/z): 125.

### 3-Benzyl-6-*endo*-hydroxy-6-*exo*-phenyl-3-azabicyclo[3.1.1]heptane (7)

To a cooled (-50 °C) solution of phenylmagnesium chloride (20.0 mmol) in THF (60 mL) a solution of ketone **1** (2.0 g, 9.9 mmol) in THF (10 mL) was added dropwise. After the addition had been completed, the reaction mixture was stirred under argon at -50 °C for 30 min followed by a gradual warming to 0 °C. Thereafter, a saturated aq. solution of NH<sub>4</sub>Cl (80.0 mL) was added. The formed organic layer was separated, and the aqueous layer was extracted with Et<sub>2</sub>O (50 mL). The combined organic extract was washed with brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent in vacuum provided the crude product. Recrystallization from hexane gave pure alcohol **7** as a yellow solid (2.4 g, 8.6 mmol, 87% yield). M.p. 74-75 °C.



Crystals suitable for an X-ray analysis were obtained by a slow evaporation of a diluted solution of **7** in hexane.

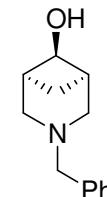
<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si), δ: 1.03 (1H, d, <sup>2</sup>J<sub>H-H</sub> = 9.8 Hz, CHH of cyclobutane), 1.72 (1H, m, CHH of cyclobutane), 2.88 (2H, m, CH of cyclobutane), 2.94 (2H, d, J = 10.3 Hz, NCHH), 3.57 (2H, d, J = 10.3 Hz, NCHH), 3.73 (2H, s, NCH<sub>2</sub>Ph), 7.29 - 7.42 (8H, m, Ph+Ph), 7.58 (2H, m, Ph).

<sup>13</sup>C NMR (125 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si), δ: 29.82 (s, CH<sub>2</sub> of cyclobutane), 42.67 (s, CH of cyclobutane), 56.00 (s, PhCH<sub>2</sub>NCH<sub>2</sub>), 61.21 (s, NCH<sub>2</sub>Ph), 77.89 (s, quat-C, C(Ph)OH), 126.56 (s, CH, Ph), 127.27 (s, CH, Ph), 127.36 (s, CH, Ph), 128.17 (s, CH, Ph), 128.49 (s, CH, Ph), 128.69 (s, CH, Ph), 137.69 (s, quat-C, Ph), 142.79 (s, quat-C, Ph).

MS (m/z): 279.

### 3-Benzyl-6-*endo*-hydroxy-3-azabicyclo[3.1.1]heptane (8)

To a cooled (-78 °C) solution of ketone **1** (2.0 g, 9.9 mmol) in absolute methanol (30 mL) a cooled (-40 °C) suspension of NaBH<sub>4</sub> (0.4 g, 10.6 mmol) in absolute methanol (20 mL) was added. The reaction mixture was stirred at -60 °C for 1 h followed by a gradual warming to a room temperature. The solvent was evaporated in vacuum. Water (10 mL) and CH<sub>2</sub>Cl<sub>2</sub> (30 mL) were added to the residue, and the obtained suspension was stirred at room temperature for 1 h. Organic phase was separated, and the aqueous layer was extracted once again with CH<sub>2</sub>Cl<sub>2</sub> (30 mL). The combined organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated in vacuum to yield pure alcohol **8** (1.93 g, 9.5 mmol, 96% yield) as a yellow oil.



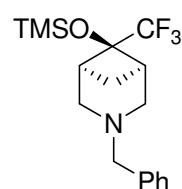
<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si), δ: 1.01 (1H, d, <sup>2</sup>J<sub>H-H</sub> = 9.5 Hz, CHH of cyclobutane), 1.53 (1H, m, CHH of cyclobutane), 2.56 (2H, m, CH of cyclobutane), 2.73 (2H, d, J = 10.5 Hz, NCHH), 3.31 (2H, d, J = 8.8 Hz, NCHH), 3.58 (2H, s, NCH<sub>2</sub>Ph), 4.02 (1H, t, J = 5.1 Hz, CHOH), 7.26 - 7.35 (5H, m, Ph).

<sup>13</sup>C NMR (125 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si), δ: 28.89 (s, CH<sub>2</sub> of cyclobutane), 39.45 (s, CH of cyclobutane), 54.97 (s, PhCH<sub>2</sub>NCH<sub>2</sub>), 61.41 (s, NCH<sub>2</sub>Ph), 69.12 (s, CHOH), 127.15 (s, CH, Ph), 128.30 (s, CH, Ph), 128.58 (s, CH, Ph), 137.76 (s, quat-C, Ph).

MS (m/z): 203.

### 3-Benzyl-6-*endo*-(trimethylsilyl)oxy-6-*exo*-trifluoromethyl-3-azabicyclo[3.1.1]heptane (9)

Dry CsF (0.6 g, 4.0 mmol) was added to the solution of ketone **1** (2.0 g, 9.9 mmol) in dry THF (50 mL), and the formed suspension was cooled to -5 °C. CF<sub>3</sub>TMS (2.0 g, 14.1 mmol) was slowly added, and the reaction mixture was stirred at room temperature for 16 h. Evaporation of the solvent in vacuum provided a residue, which was treated with hot hexane. Insoluble material was filtered off, and the organic phase was evaporated in vacuum to give product **9** (3.4 g, 9.9 mmol, 100% yield) as pale yellow liquid. It was used in the next step without additional purification.



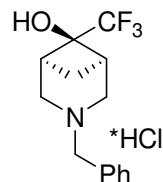
<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si), δ: 0.27 (9H, s, Si(CH<sub>3</sub>)<sub>3</sub>), 1.98 (1H, m, CHH of cyclobutane), 2.16 (1H, d, <sup>2</sup>J<sub>H-H</sub> = 10.5 Hz, CHH of cyclobutane), 2.65 (2H, broad s, CH of cyclobutane), 2.85 (2H, d, J = 9.8 Hz, NCHH), 3.15 (2H, d, J = 8.6 Hz, NCHH), 3.75 (2H, s, NCH<sub>2</sub>Ph), 7.28-7.40 (5H, m, Ph).

<sup>13</sup>C NMR (125 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si),  $\delta$ : 1.59 (s, Si(CH<sub>3</sub>)<sub>3</sub>), 20.20 (q, <sup>4</sup>J<sub>C-F</sub> = 4.5 Hz, CH<sub>2</sub> of cyclobutane), 39.56 (s, CH of cyclobutane), 50.88 (s, PhCH<sub>2</sub>NCH<sub>2</sub>), 59.69 (s, NCH<sub>2</sub>Ph), 77.54 (q, <sup>2</sup>J<sub>C-F</sub> = 28.0 Hz, C-CF<sub>3</sub>), 126.77 (q, <sup>1</sup>J<sub>C-F</sub> = 284.7 Hz, CF<sub>3</sub>), 126.83 (s, CH, Ph), 128.21 (s, CH, Ph), 128.54 (s, CH, Ph), 139.43 (s, quat-C, Ph).

MS (*m/z*): 343.

### 3-Benzyl-6-*endo*-hydroxy-6-*exo*-trifluoromethyl-3-azabicyclo[3.1.1]heptane hydrochloride (10)

Compound **9** (3 g, 8.7 mmol) was dissolved in 3N solution of HCl in MeOH (50 mL) and the reaction mixture stirred at 50 °C for 1 h. The solvent was removed on a rotary evaporator to give alcohol **10** (2.3 g, 8.4 mmol, 97% yield) as a white solid. M.p. >220 °C, decomposition.



Crystals suitable for an X-ray analysis were obtained by a slow evaporation of a diluted solution of **10** in MeOH-water.

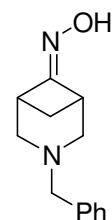
<sup>1</sup>H NMR (500 MHz; DMSO-d6; Me<sub>4</sub>Si),  $\delta$ : 2.05 (1H, m, CHH of cyclobutane), 2.26 (1H, d, <sup>2</sup>J<sub>H-H</sub> = 10.6 Hz, CHH of cyclobutane), 2.74 (2H, d, <sup>3</sup>J<sub>H-H</sub> = 6.4 Hz, CH of cyclobutane), 3.54 (2H, m, NCHH), 3.60 (2H, m, NCHH), 4.36 (2H, d, <sup>3</sup>J<sub>H-H</sub> = 5.0 Hz, NCH<sub>2</sub>Ph), 7.46 (3H, s, Ph), 7.80 (2H, s, Ph), 11.61 (1H, s, NH).

<sup>13</sup>C NMR (125 MHz; DMSO-d6; Me<sub>4</sub>Si),  $\delta$ : 20.29 (s, CH<sub>2</sub> of cyclobutane), 36.46 (s, CH of cyclobutane), 52.61 (s, PhCH<sub>2</sub>NCH<sub>2</sub>), 59.68 (s, NCH<sub>2</sub>Ph), 72.95 (q, <sup>2</sup>J<sub>C-F</sub> = 28.8 Hz, C-CF<sub>3</sub>), 126.87 (q, <sup>1</sup>J<sub>C-F</sub> = 281.2 Hz, CF<sub>3</sub>), 120.06 (s, CH, Ph), 129.85 (s, CH, Ph), 130.67 (s, quat-C, Ph), 131.88 (s, CH, Ph).

<sup>19</sup>F NMR (471 MHz; DMSO-d6; CFCl<sub>3</sub>),  $\delta$ : -76.81 (s, CF<sub>3</sub>).

### 3-Benzyl-3-azabicyclo[3.1.1]heptan-6-one-, oxime (11)

Ketone **1** (2.0 g, 9.9 mmol) was added to a solution of hydroxylamine hydrochloride (1.39 g, 20 mmol) in water (20 mL). The obtained suspension was stirred for 2 h at 50 °C and for 18 h at room temperature. An aq. solution of K<sub>2</sub>CO<sub>3</sub> was added to adjust pH value of the reaction mixture to 9. The formed precipitate was filtered off and dried on air to give pure oxime **11** (2.13 g, 9.8 mmol, 99% yield) as a white solid. M.p. 86-88 °C.



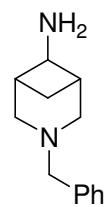
<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si),  $\delta$ : 1.91 (1H, d, *J* = 7.5 Hz, cyclobutane), 2.00 (1H, broad s, cyclobutane), 3.01 (4H, broad s, NCH<sub>2</sub>), 3.21 (1H, d, *J* = 8.0 Hz, cyclobutane), 3.52 (1H, broad s, cyclobutane), 3.72 (2H, s, NCH<sub>2</sub>Ph), 7.35 (5H, s, Ph), 8.90 (1H, s, OH).

<sup>13</sup>C NMR (125 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si),  $\delta$ : 28.14 (s, CH<sub>2</sub> of cyclobutane), 42.87 (s, CH of cyclobutane), 43.68 (s, CH of cyclobutane), 56.50 (s, PhCH<sub>2</sub>NCH<sub>2</sub>), 57.66 (s, PhCH<sub>2</sub>NCH<sub>2</sub>), 59.98 (s, NCH<sub>2</sub>Ph), 126.93 (s, CH, Ph), 128.15 (s, CH, Ph), 128.75 (s, CH, Ph), 138.23 (s, quat-C, Ph), 163.23 (s, C=NOH).

MS (*m/z*): 216.

### 3-Benzyl-3-azabicyclo[3.1.1]heptan-6-amine (12)

Oxime **11** (6.1 g, 28.2 mmol) was dissolved in 10% solution of ammonia in methanol (100 mL) followed by an addition of Ni-Re allow (1 g). The reaction mixture was hydrogenated upon stirring at room temperature at 50 bar for 16 h. The insoluble material was filtered off and discarded. The filtrate was evaporated in vacuum. The residue was purified by distillation at a reduced pressure to give pure amine **12** (5.2 g, 25.7 mmol, 91% yield) as a colorless liquid. B.p. 108 – 111 °C (1 mm).



<sup>1</sup>H NMR (500 MHz; DMSO-d6; Me<sub>4</sub>Si), δ 1.15 (0.7H, d, *J* = 9.0 Hz), 1.65 (0.8H, m), 1.83 (0.5H, m), 2.05 (0.5H, broad s), 2.05 (1.5H, broad s), 2.22 (2H, broad s, NH<sub>2</sub>), 2.78 (2H, m), 3.05-3.19 (3H, m), 2.62-2.67 (2H, 2 s, NCH<sub>2</sub>Ph), 7.31 (5H, m, Ph).

<sup>13</sup>C NMR (125 MHz; DMSO-d6; Me<sub>4</sub>Si), δ: 27.87, 29.74 (2 s, CH<sub>2</sub> of cyclobutane), 39.18, 40.60 (2 s, CH of cyclobutane), 51.48, 61.08 (2 s, CHNH<sub>2</sub>), 52.78, 57.08 (2 s, PhCH<sub>2</sub>NCH<sub>2</sub>), 61.08, 61.51 (2 s, NCH<sub>2</sub>Ph), 126.74, 126.87 (2 s, CH, Ph), 128.12, 128.24 (2 s, CH, Ph), 128.63, 128.67 (2 s, CH, Ph), 139.11, 139.37 (2 s, quat-C, Ph).

MS (*m/z*): 202.

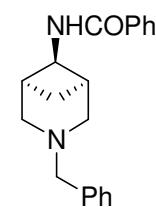
### 3-Benzyl-6-*endo*-benzoylamino-3-azabicyclo[3.1.1]heptane (13a)

### 3-Benzyl-6-*exo*-benzoylamino-3-azabicyclo[3.1.1]heptane (13b)

A solution of benzoyl chloride (0.8 g, 5.7 mmol) in diethyl ether (5 mL) was added dropwise to a stirred suspension of amine **12** (1.0 g, 5.0 mmol) in diethyl ether (20 mL) and 10% aq. NaOH (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for a 1 h. The organic layer was separated, and water phase was extracted with diethyl ether (2\*20 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated in vacuum. The formed mixture of **13a**/**13b** was separated by flash column chromatography using EtOAc/hexane = 1/2 mixture as an eluent. Elution gave isomer **13a** first (0.90 g, 3.0 mmol, 59% yield) as a yellowish solid. R<sub>f</sub> = 0.5. M.p. 93 °C.

Crystals suitable for an X-ray analysis were obtained by a slow evaporation of a diluted solution of **13a** in hexane.

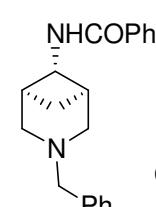
<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si), δ: 1.97 (1H, m, CHH of cyclobutane), 2.35 (1H, m, CHH of cyclobutane), 2.46 (2H, m, CH of cyclobutane), 2.98 (2H, d, *J* = 10.0 Hz, NCHH), 3.14 (2H, m, NCHH), 3.77 (2H, s, NCH<sub>2</sub>Ph), 3.94 (1H, td, *J* = 10.0, 1.0 Hz, CHNHCO), 6.52 (1H, broad s, NH), 7.35-7.82 (10H, m, Ph+Ph).



<sup>13</sup>C NMR (125 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si), δ: 1.02 (s, CH<sub>2</sub> of cyclobutane), 38.83 (s, CH of cyclobutane), 56.30 (s, CHNH), 59.67 (s, PhCH<sub>2</sub>NCH<sub>2</sub>), 60.57 (s, NCH<sub>2</sub>Ph), 126.87 (s, CH, Ph), 128.23 (s, CH, Ph), 128.58 (s, CH, Ph), 128.83 (s, quat-C, Ph), 131.42 (s, CH, Ph), 2 signals (s, CH, Ph and quat-C, Ph) are not seen, 134.81 (s, quat-C, Ph), 167.84 (s, C=O).

MS (*m/z*): 306.

Further elution gave isomer **13b** (0.44 g, 1.5 mmol, 29% yield) as a yellowish solid. R<sub>f</sub> = 0.3. M.p. 162 °C.

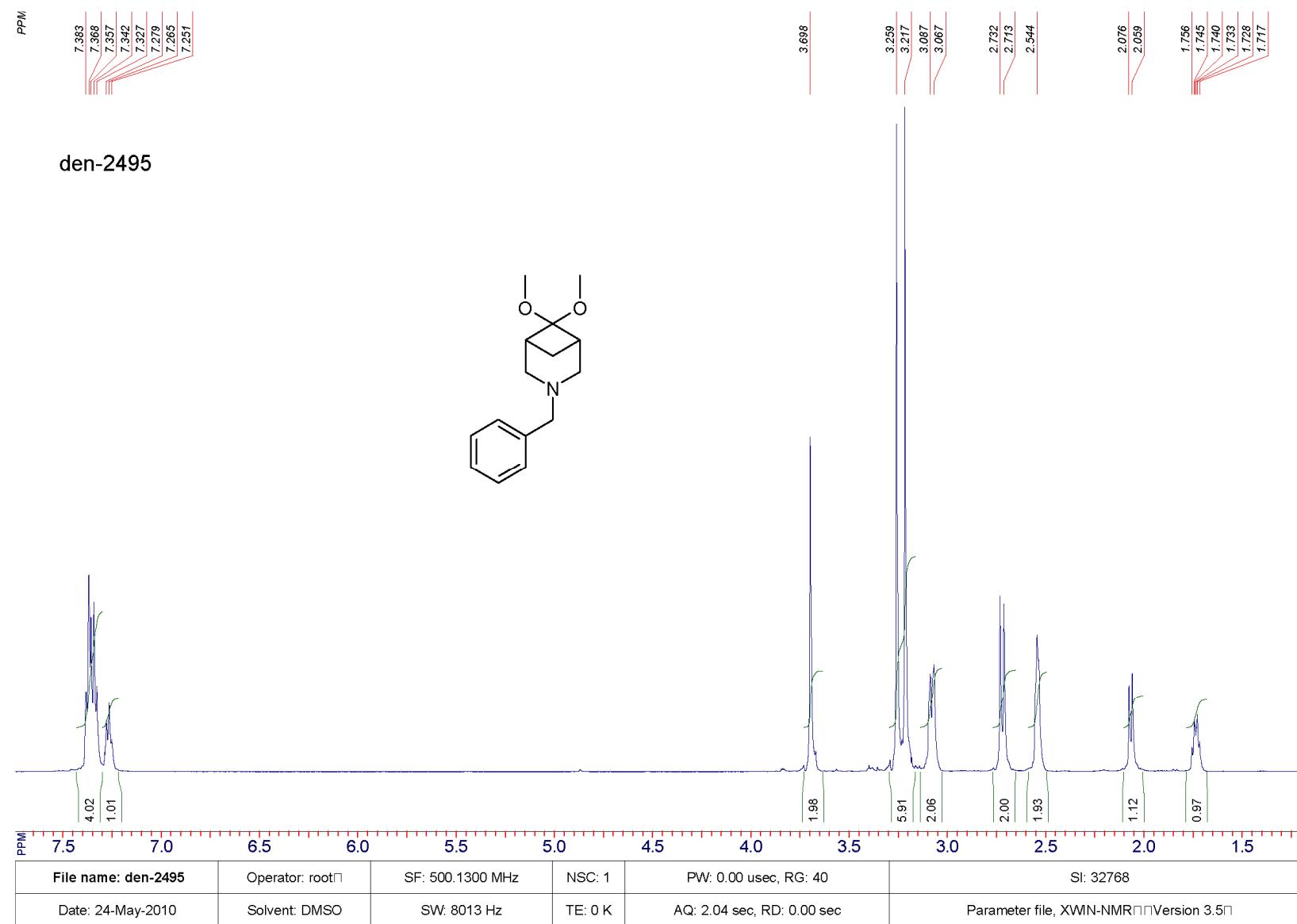


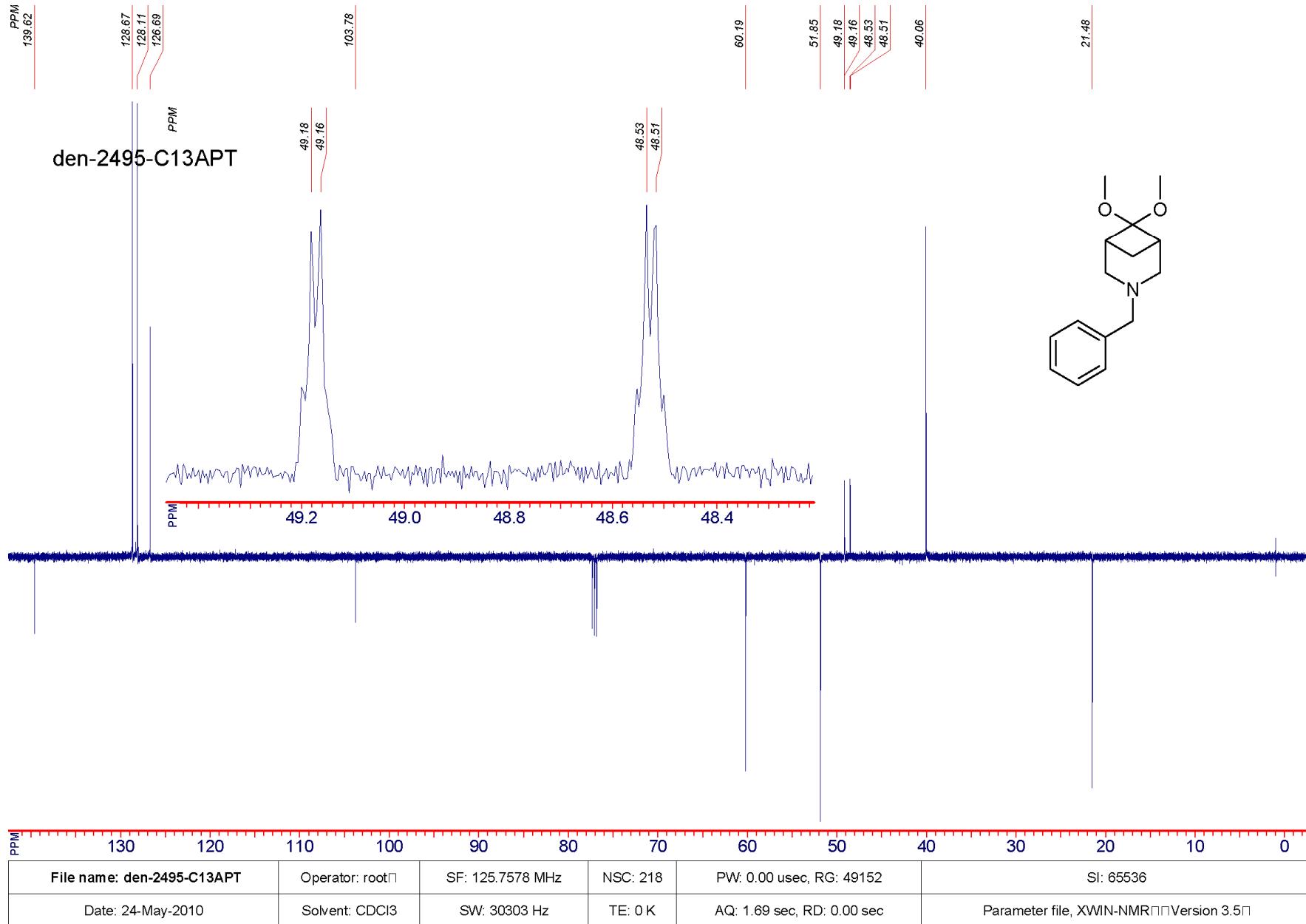
<sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si),  $\delta$ : 1.02 (1H, d,  $J$  = 8.5 Hz, CHH of cyclobutane), 1.90 (1H, m, CHH of cyclobutane), 2.64 (2H, m, CH of cyclobutane), 2.80 (2H, d,  $J$  = 10.0 Hz, NCHH), 3.29 (2H, d,  $J$  = 10.0 Hz, NCHH), 3.67 (2H, s, NCH<sub>2</sub>Ph), 4.72 (1H, m, CHNHCO), 7.35 - 7.75 (10H, m, Ph+Ph), 8.55 (1H, broad s, NH).

<sup>13</sup>C NMR (125 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si),  $\delta$ : 31.92 (s, CH<sub>2</sub> of cyclobutane), 38.56 (s, CH of cyclobutane), 46.49 (s, CHNH), 54.66 (s, PhCH<sub>2</sub>NCH<sub>2</sub>), 61.72 (s, NCH<sub>2</sub>Ph), 127.08 (s, CH, Ph), 127.41 (s, CH, Ph), 128.42 (s, CH, Ph), 128.43 (s, quat-C, Ph), 129.00 (s, CH, Ph), 131.24 (s, CH, Ph), 135.25 (s, quat-C, Ph), 138.53 (s, quat-C, Ph), 167.02 (s, C=O).

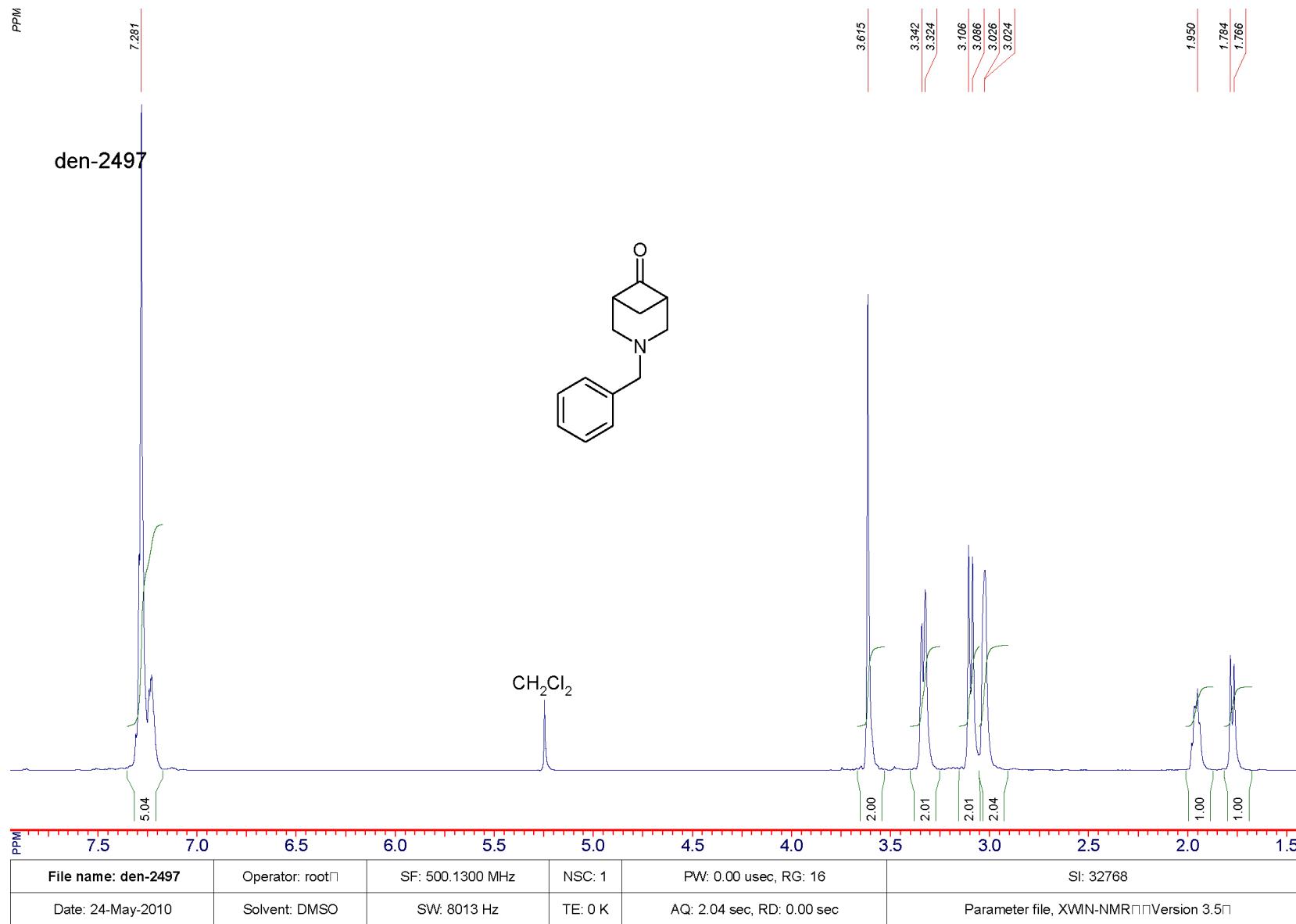
MS (*m/z*): 306.

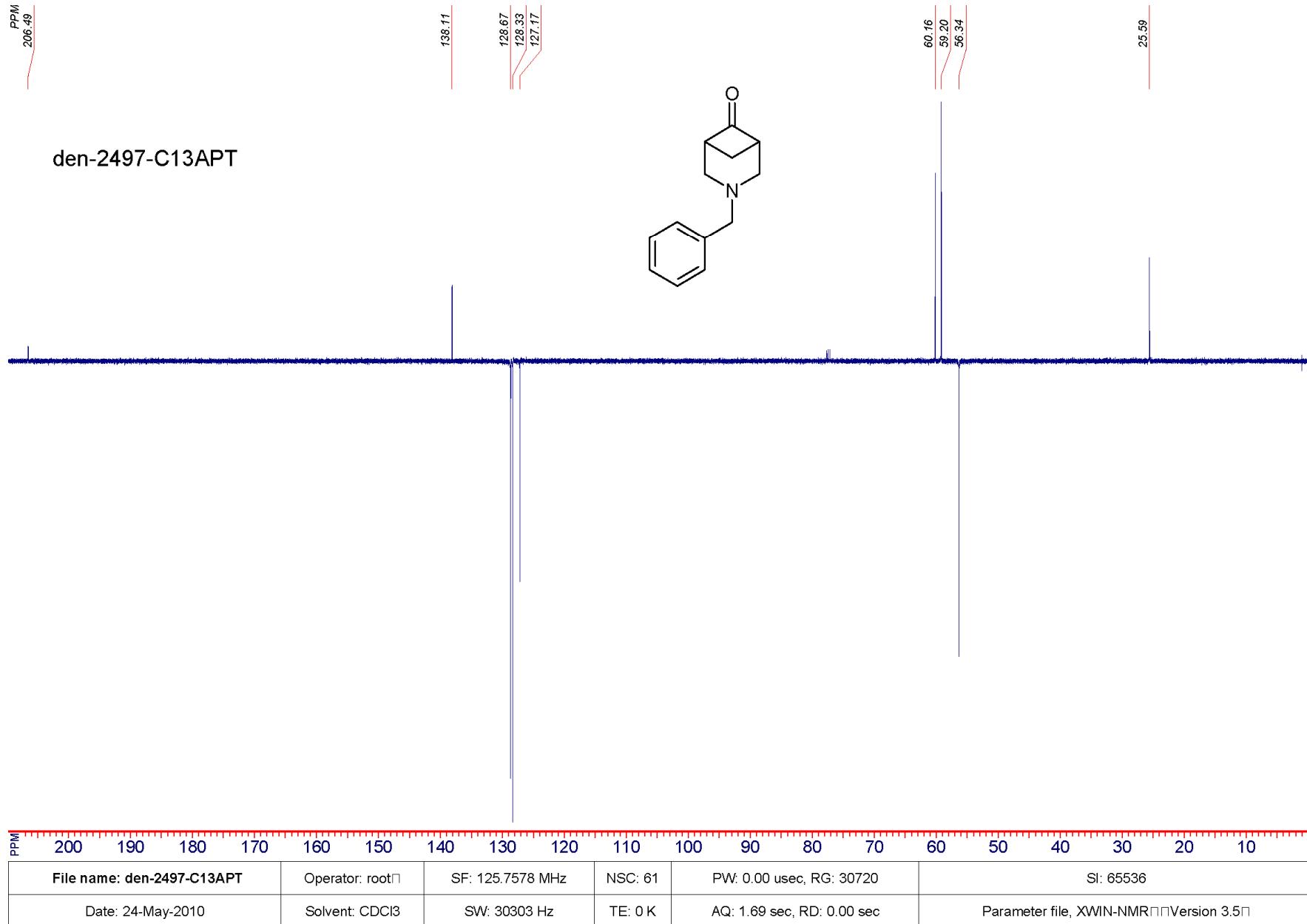
## Compound 4



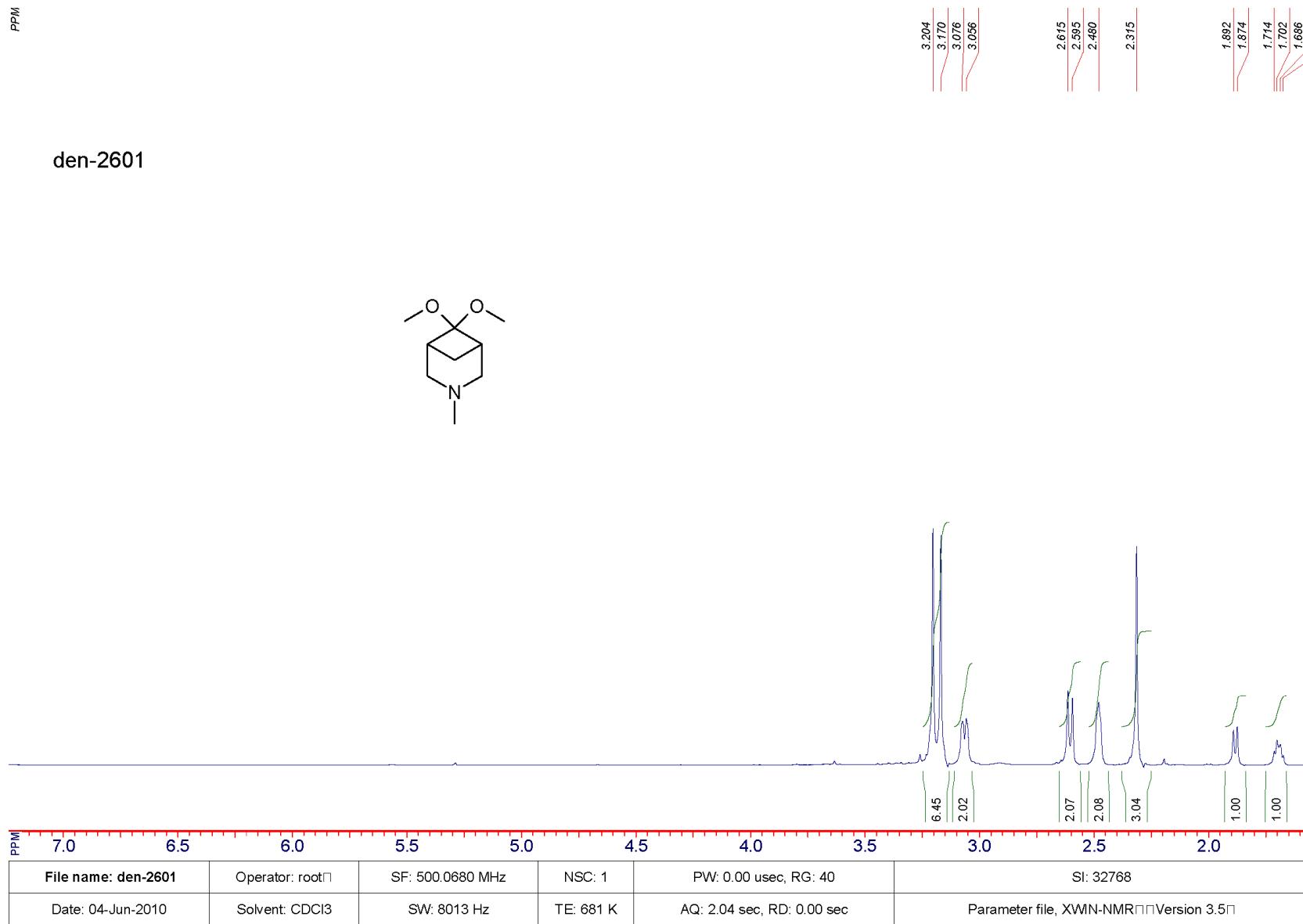


## Compound 1



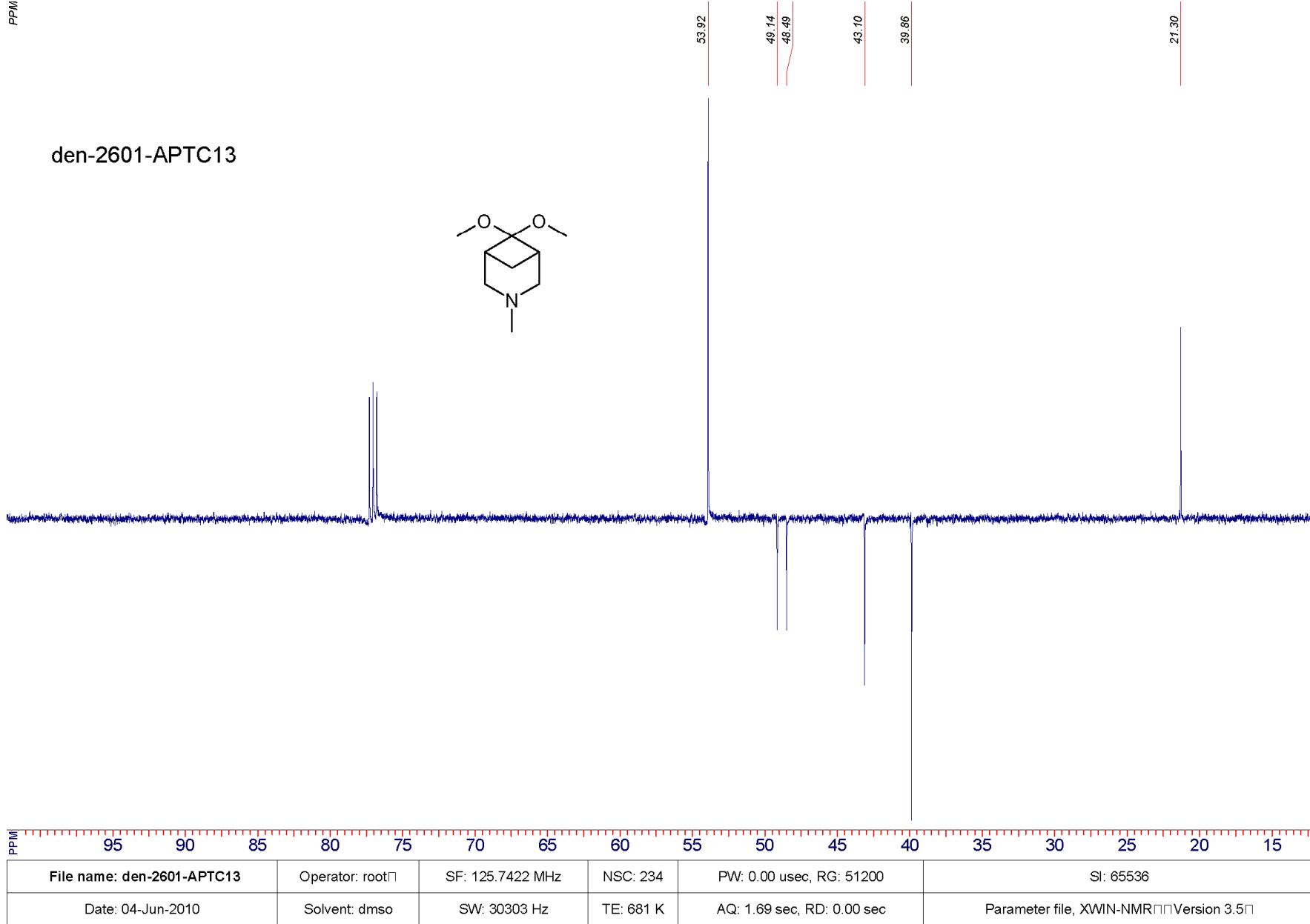
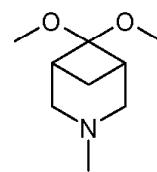


## Compound 6



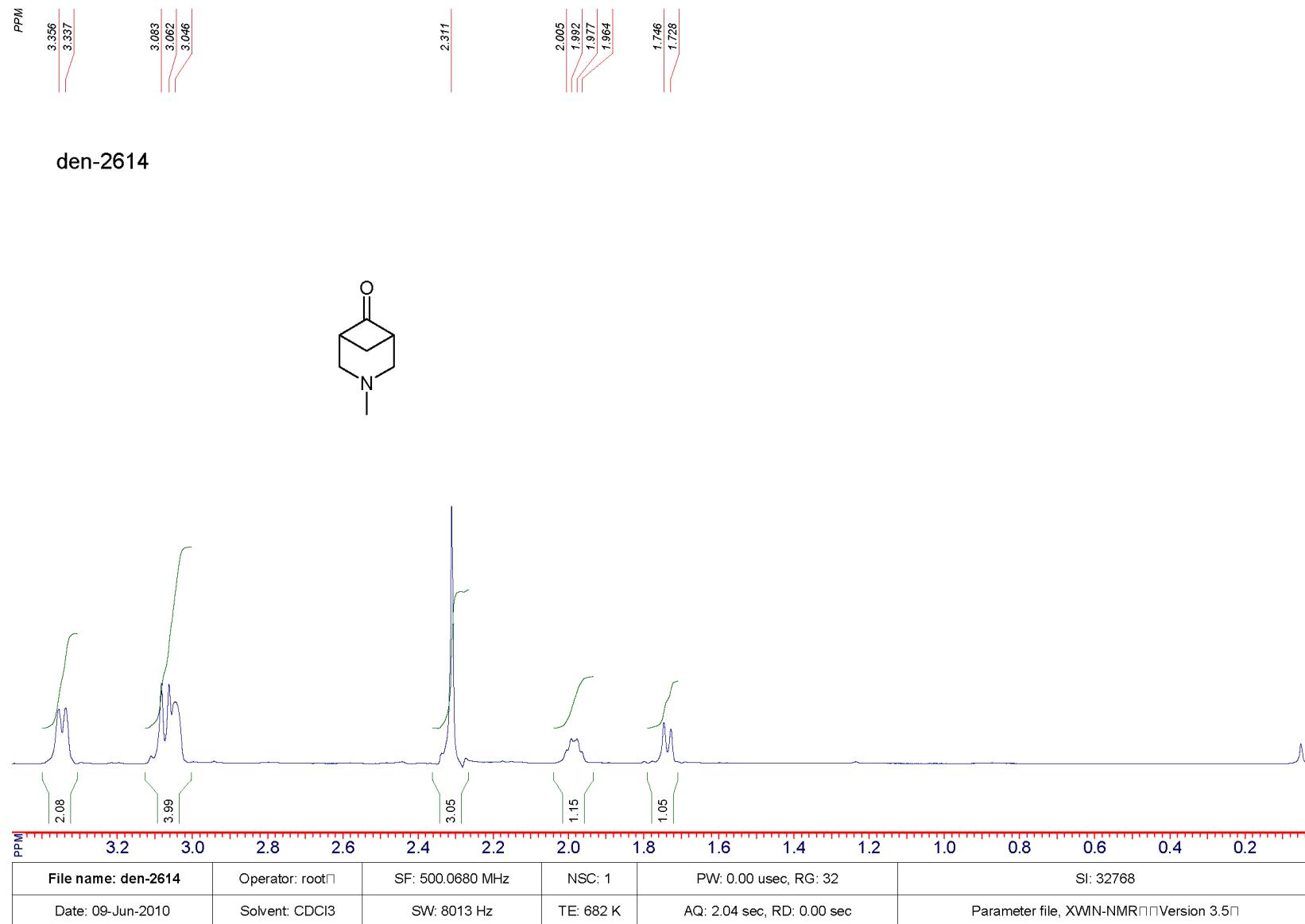
PPM

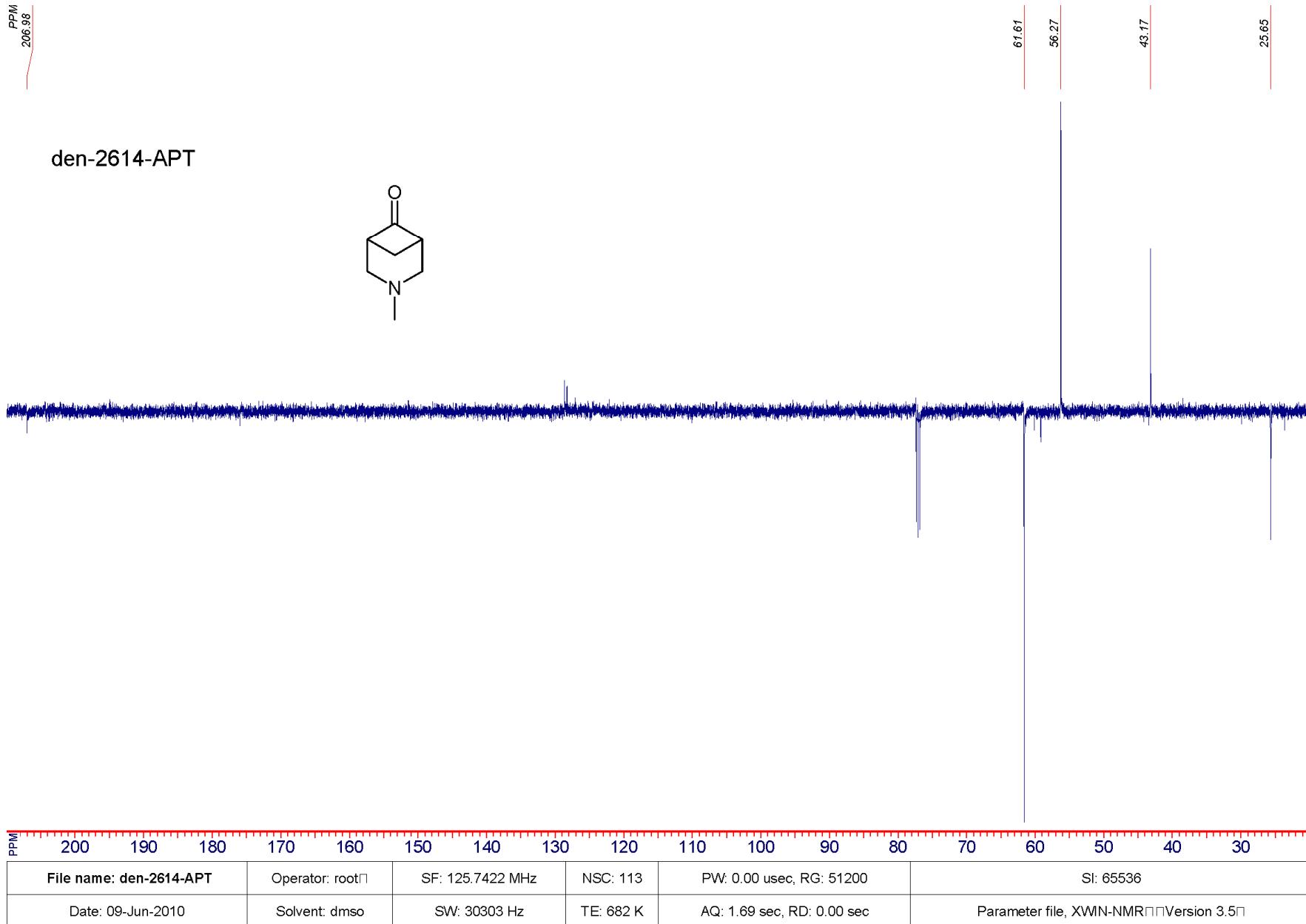
den-2601-APTC13



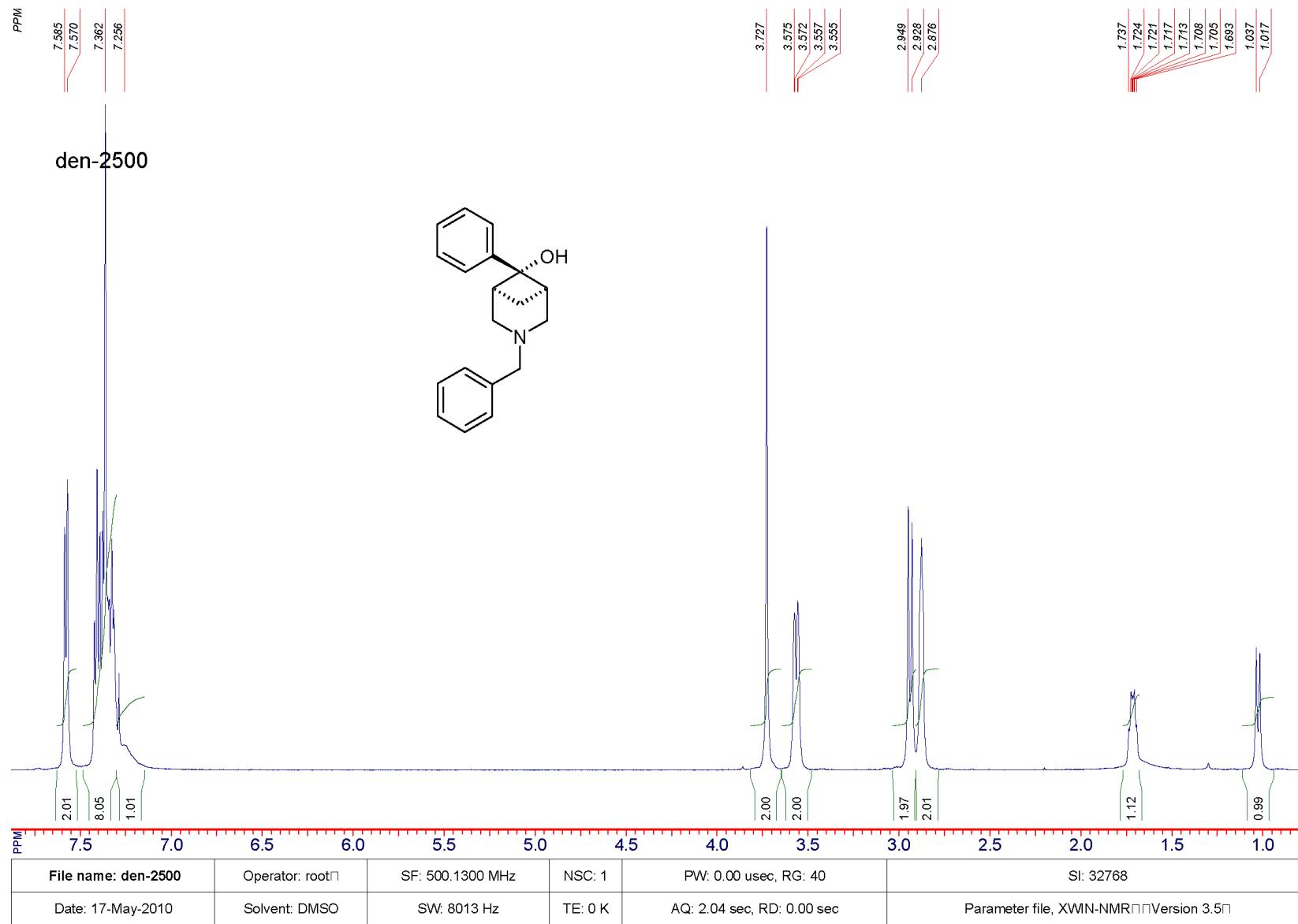
File name: den-2601-APTC13	Operator: root	SF: 125.7422 MHz	NSC: 234	PW: 0.00 usec, RG: 51200	SI: 65536
Date: 04-Jun-2010	Solvent: dmso	SW: 30303 Hz	TE: 681 K	AQ: 1.69 sec, RD: 0.00 sec	Parameter file, XWIN-NMR Version 3.5

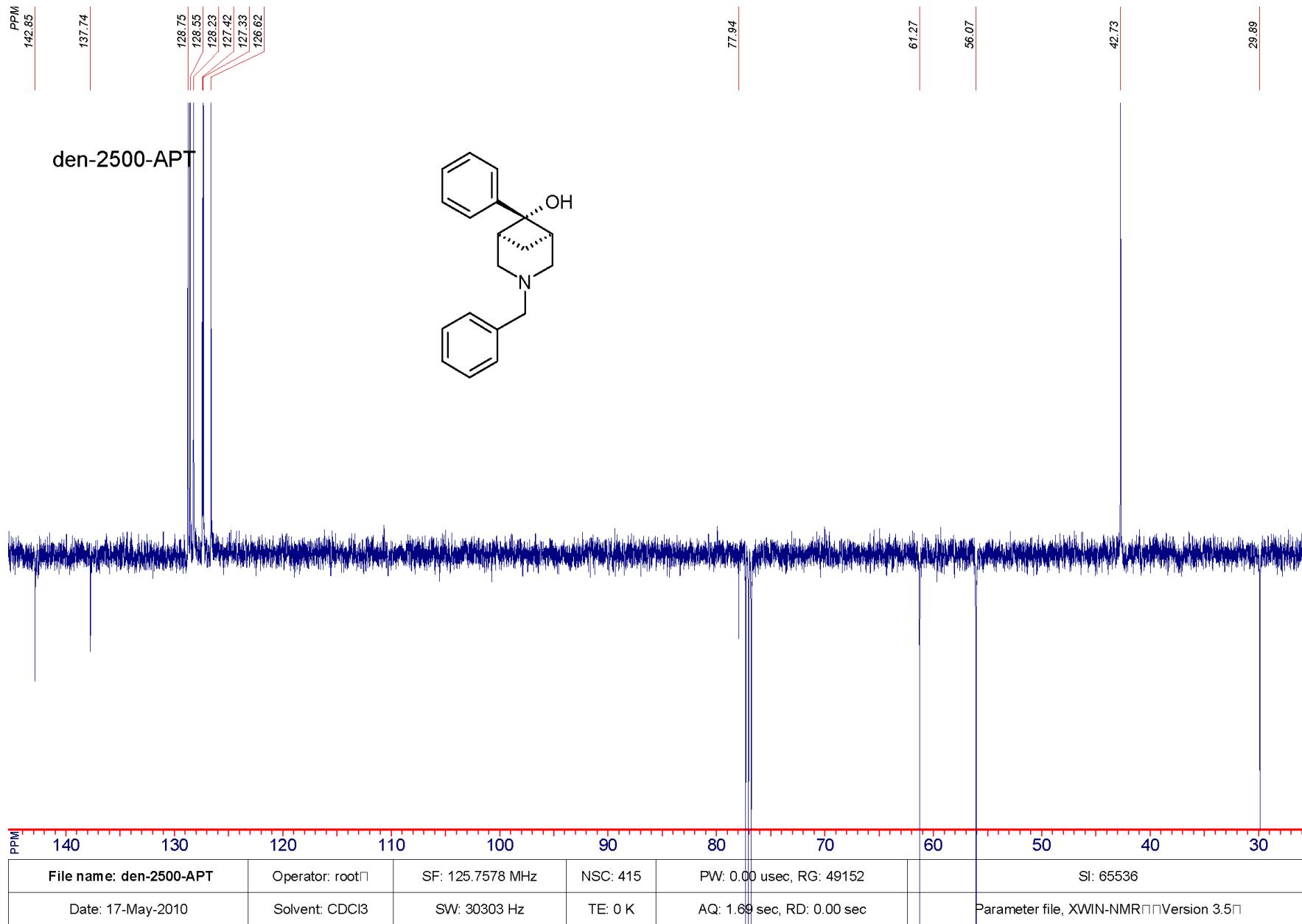
## Compound 5



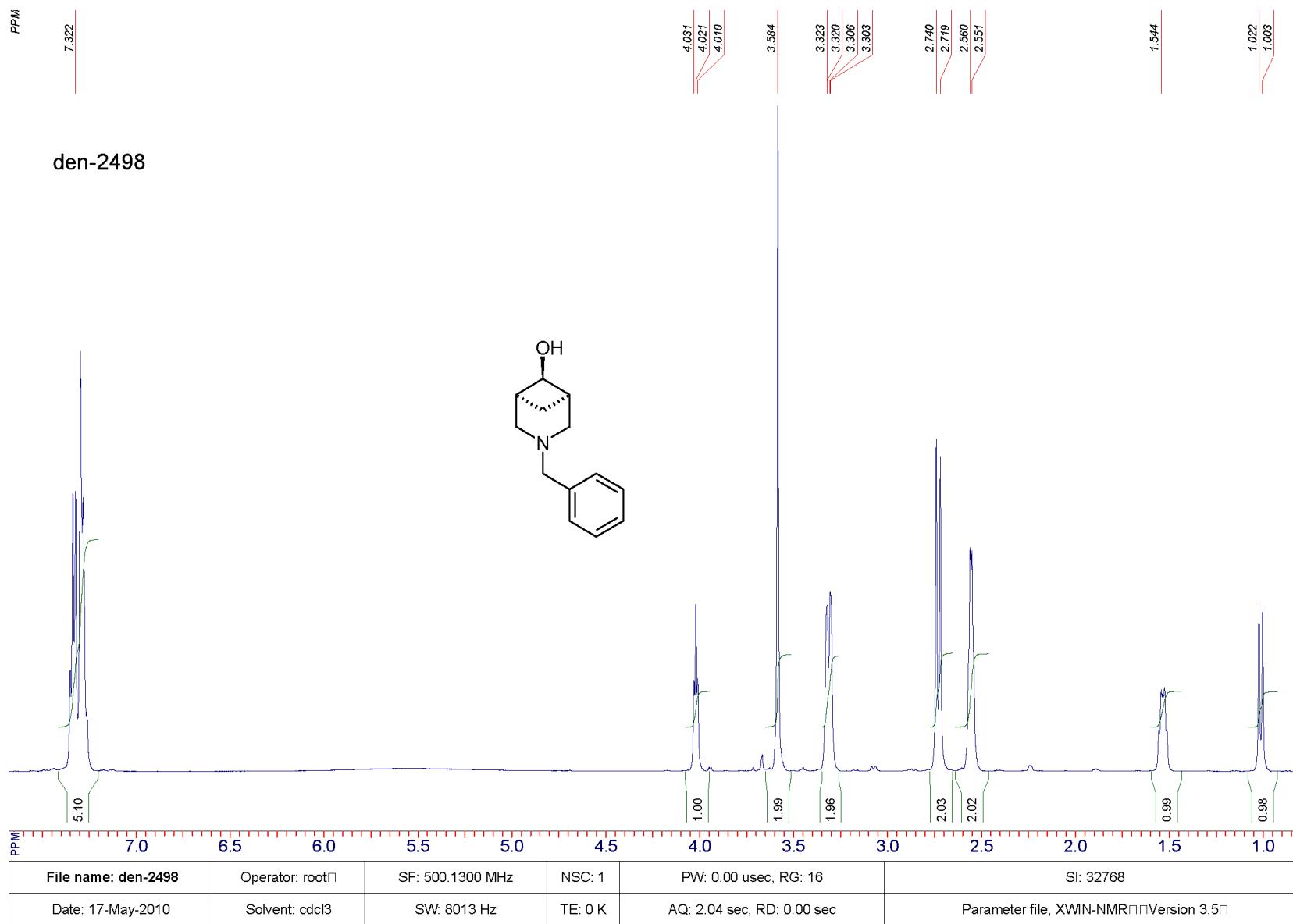


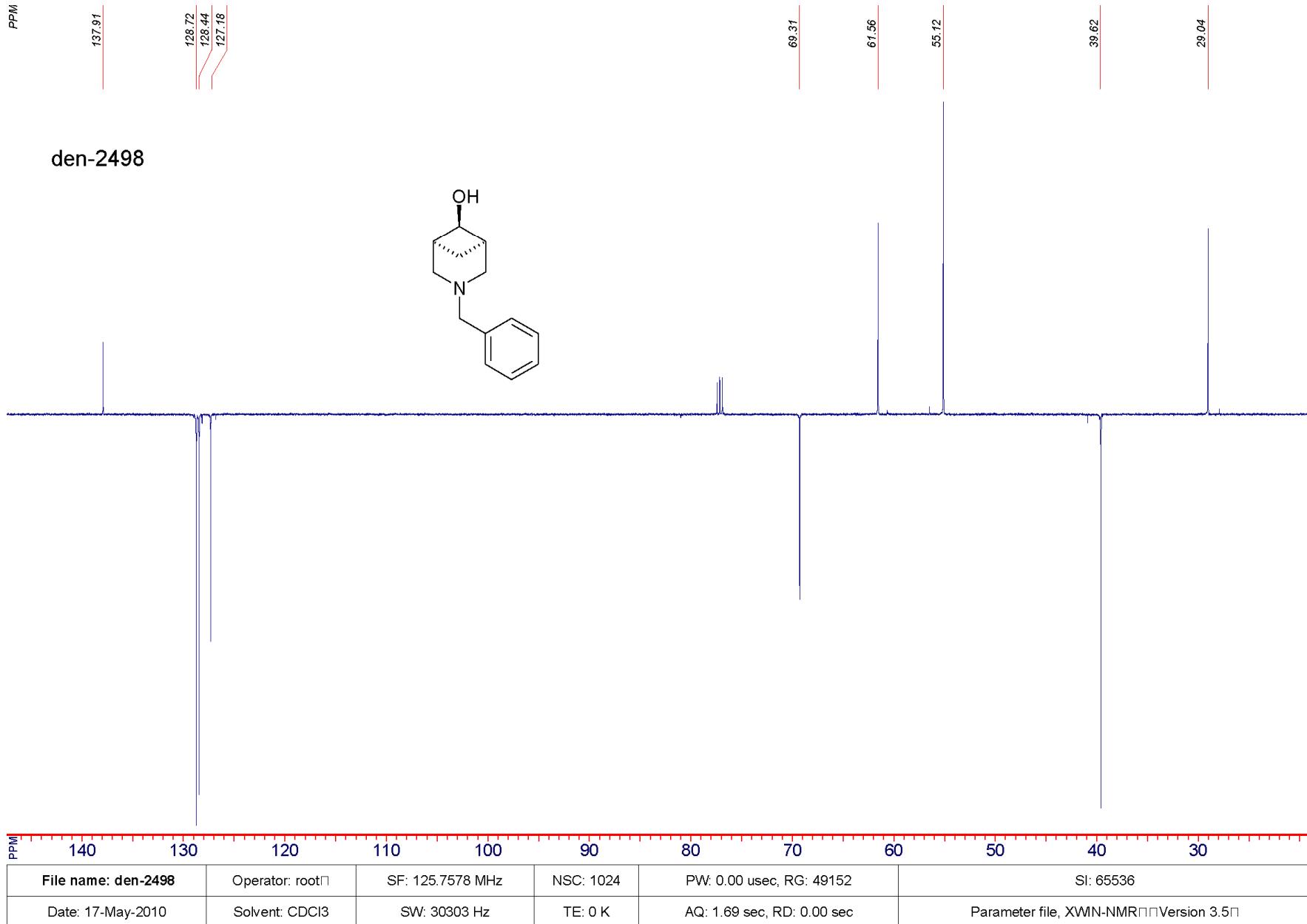
## Compound 7



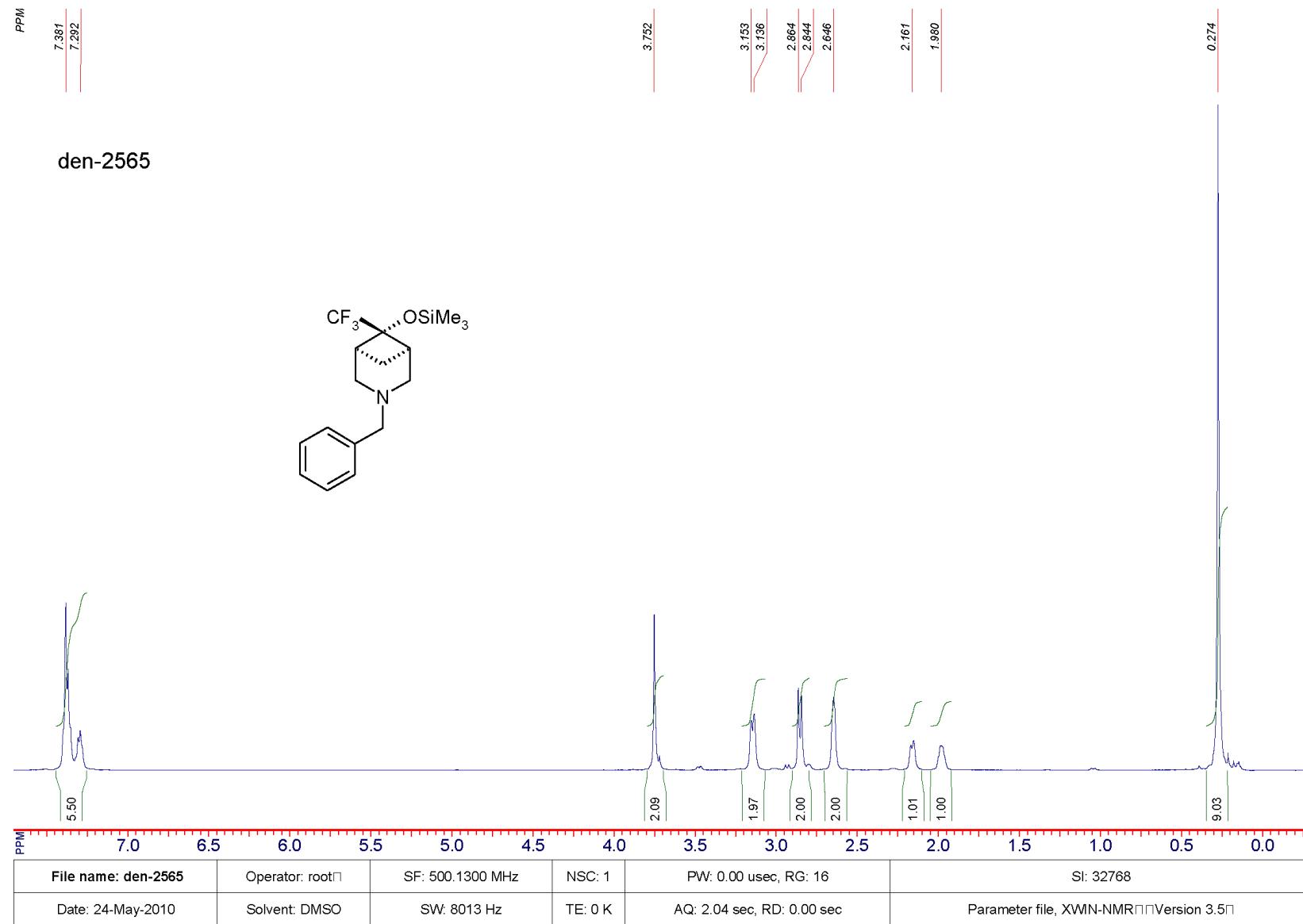


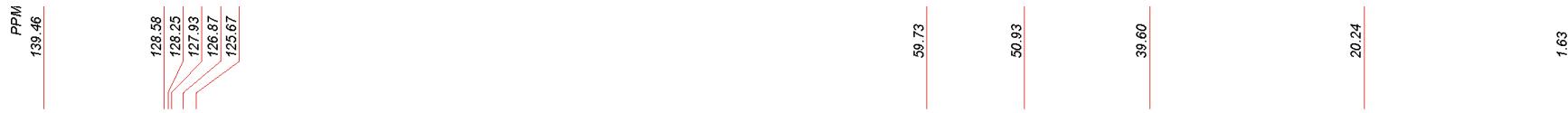
## Compound 8



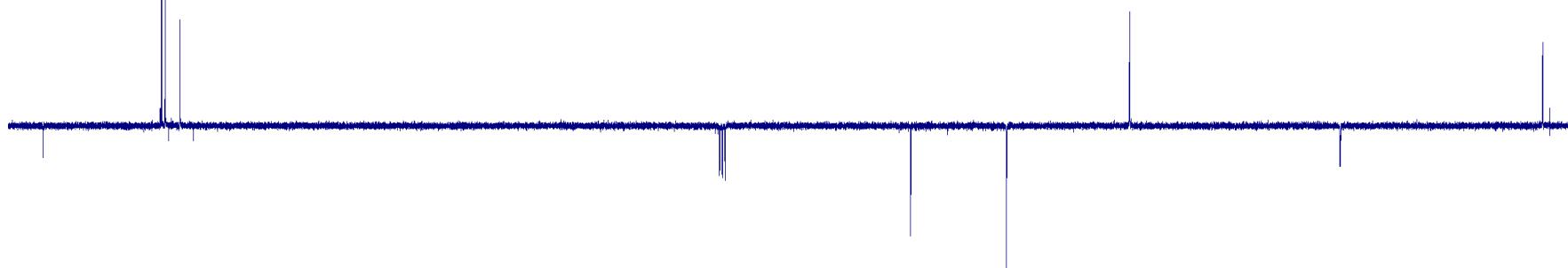
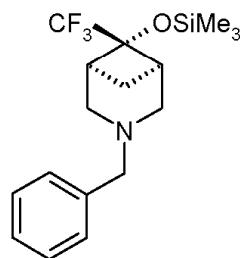


## Compound 9



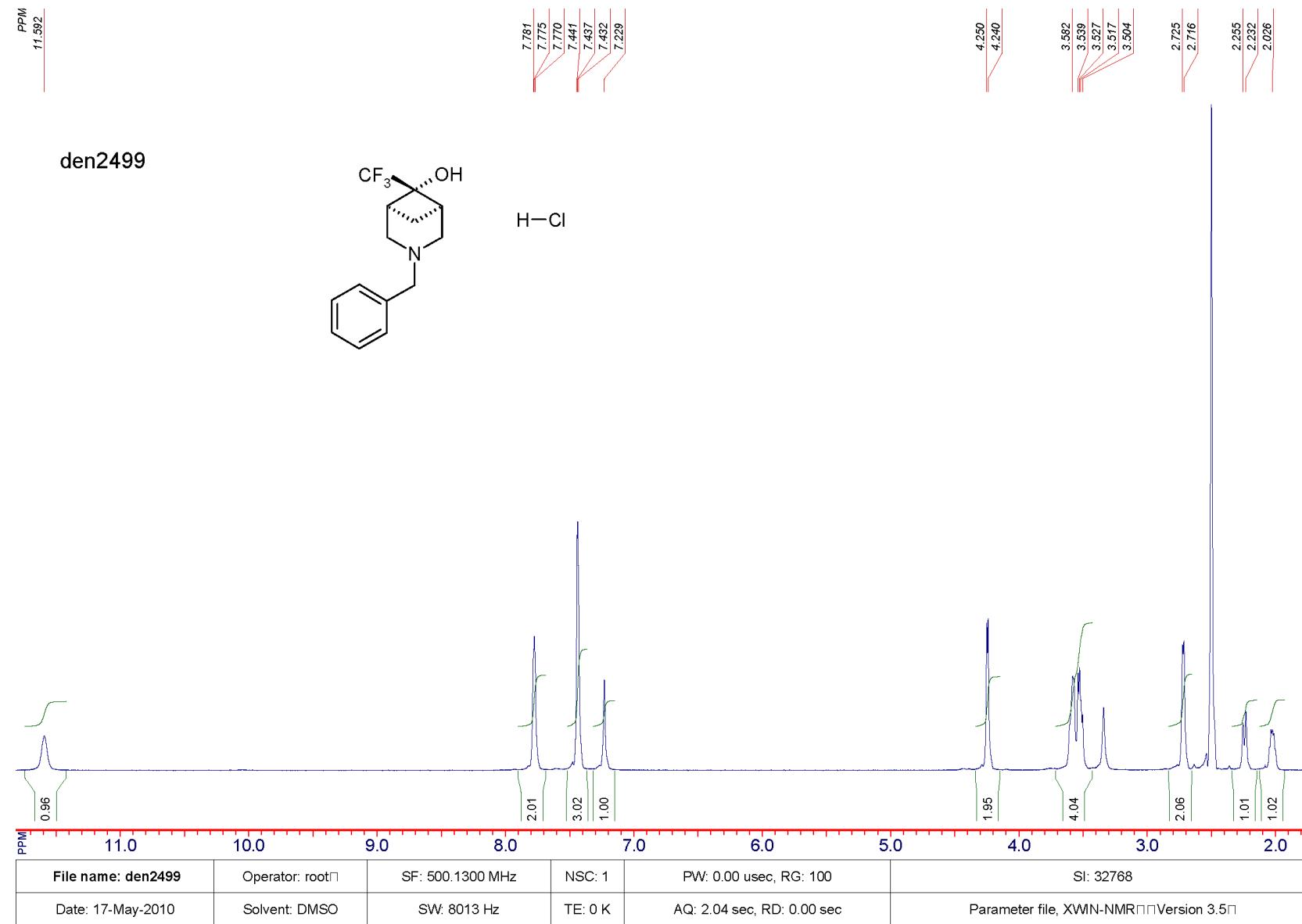


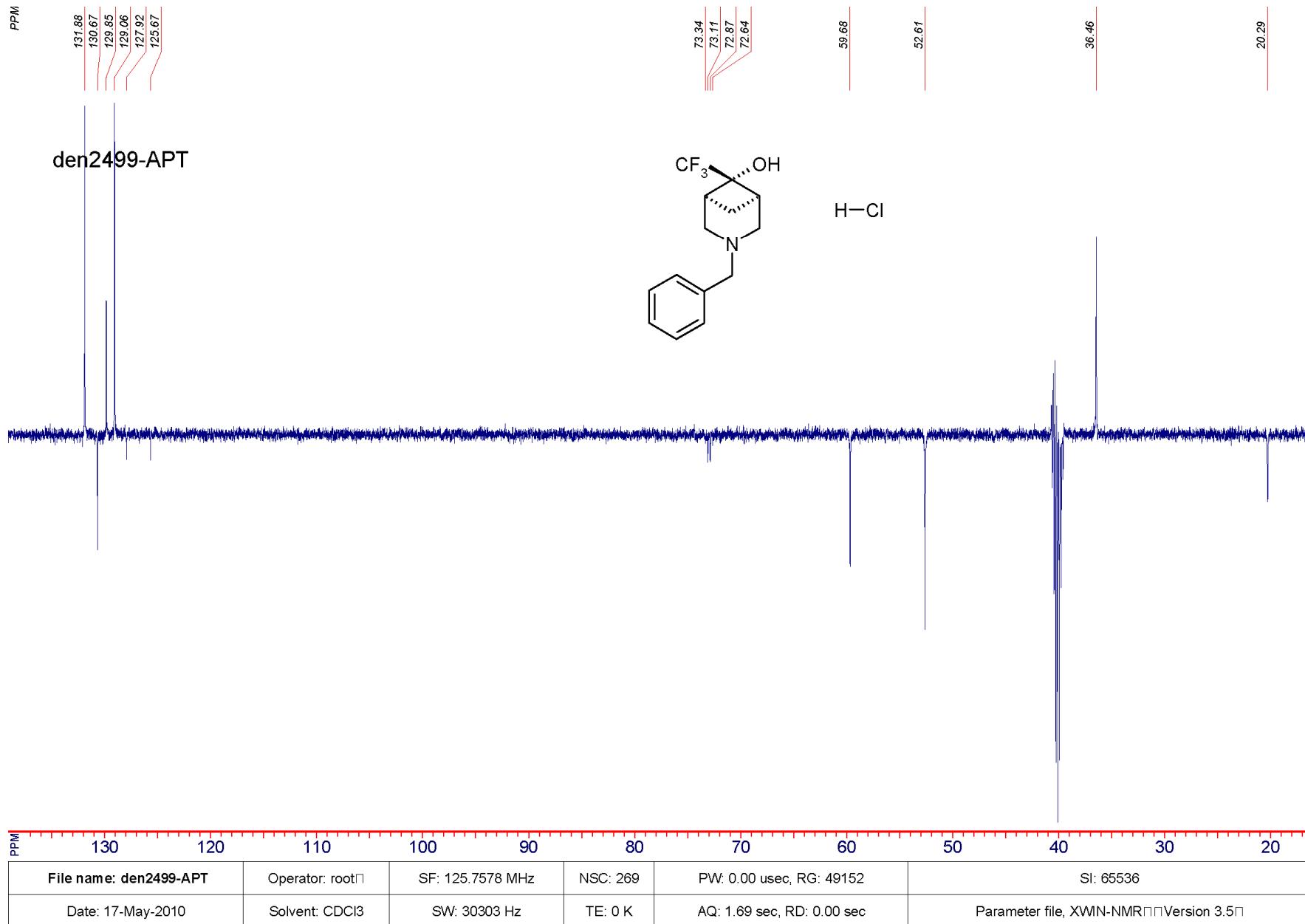
den-2565-C13APT



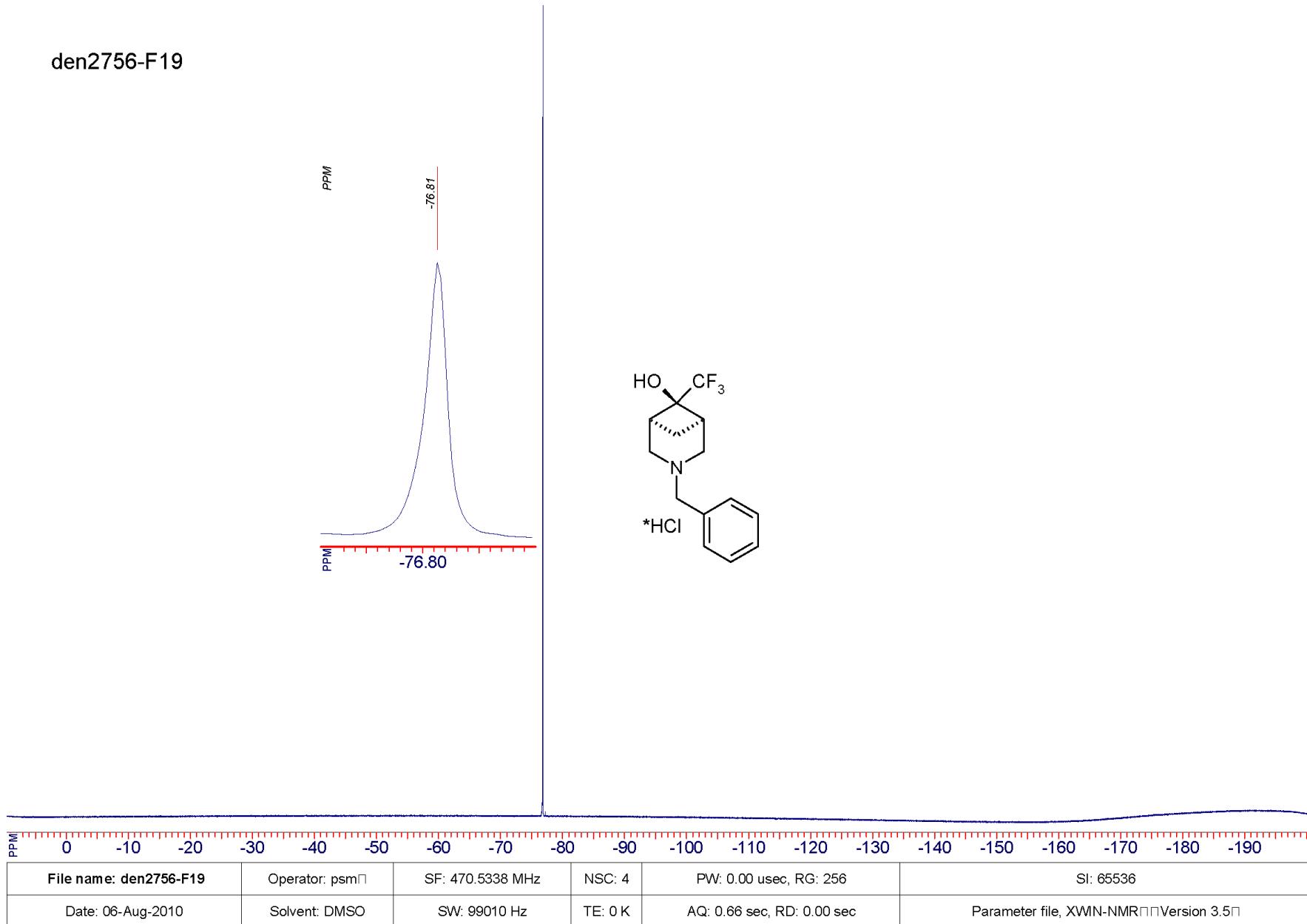
File name: den-2565-C13APT	Operator: root	SF: 125.7578 MHz	NSC: 173	PW: 0.00 usec, RG: 30720	SI: 65536
Date: 24-May-2010	Solvent: CDCl3	SW: 30303 Hz	TE: 0 K	AQ: 1.69 sec, RD: 0.00 sec	Parameter file, XWIN-NMR Version 3.5

## Compound 10

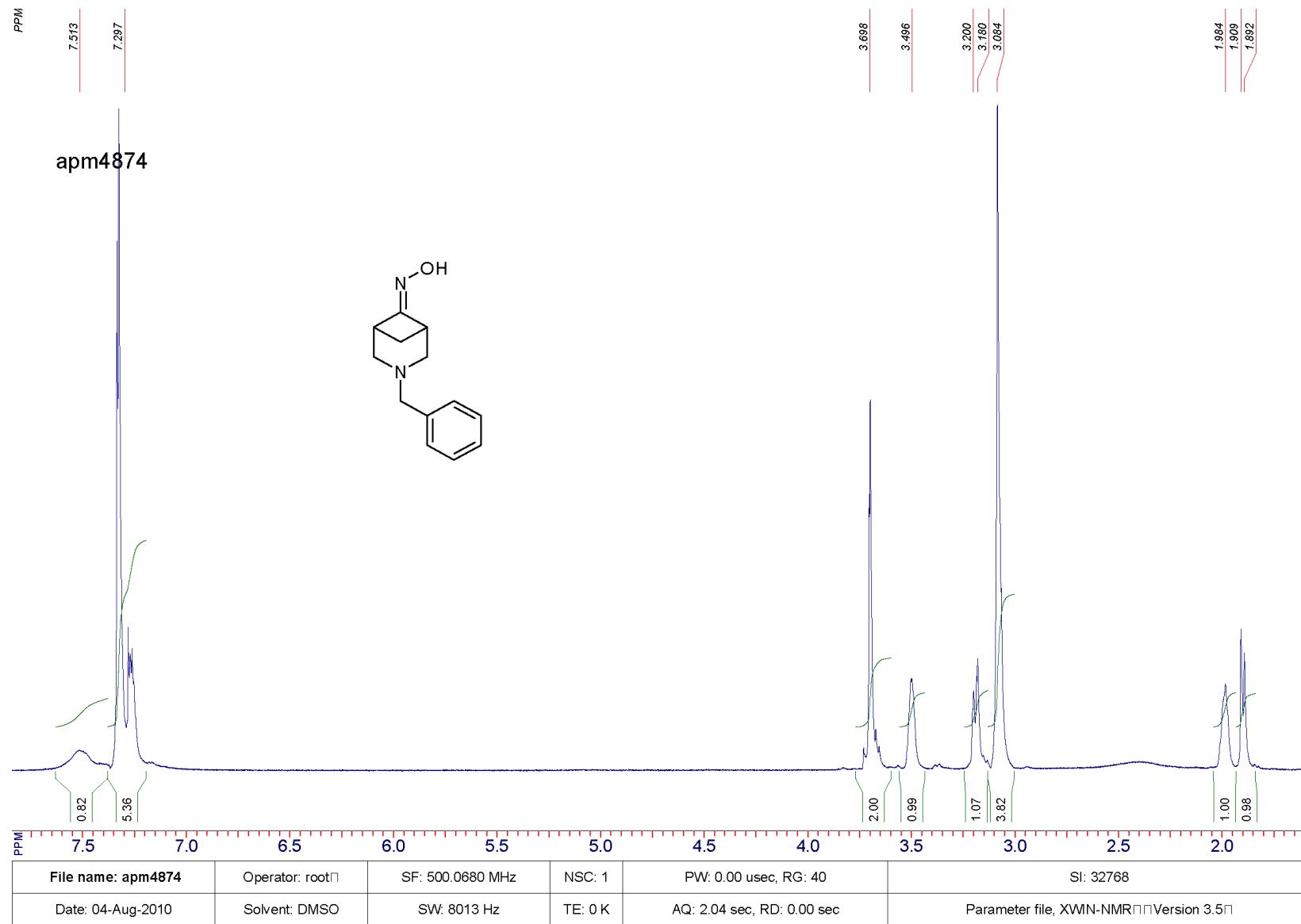


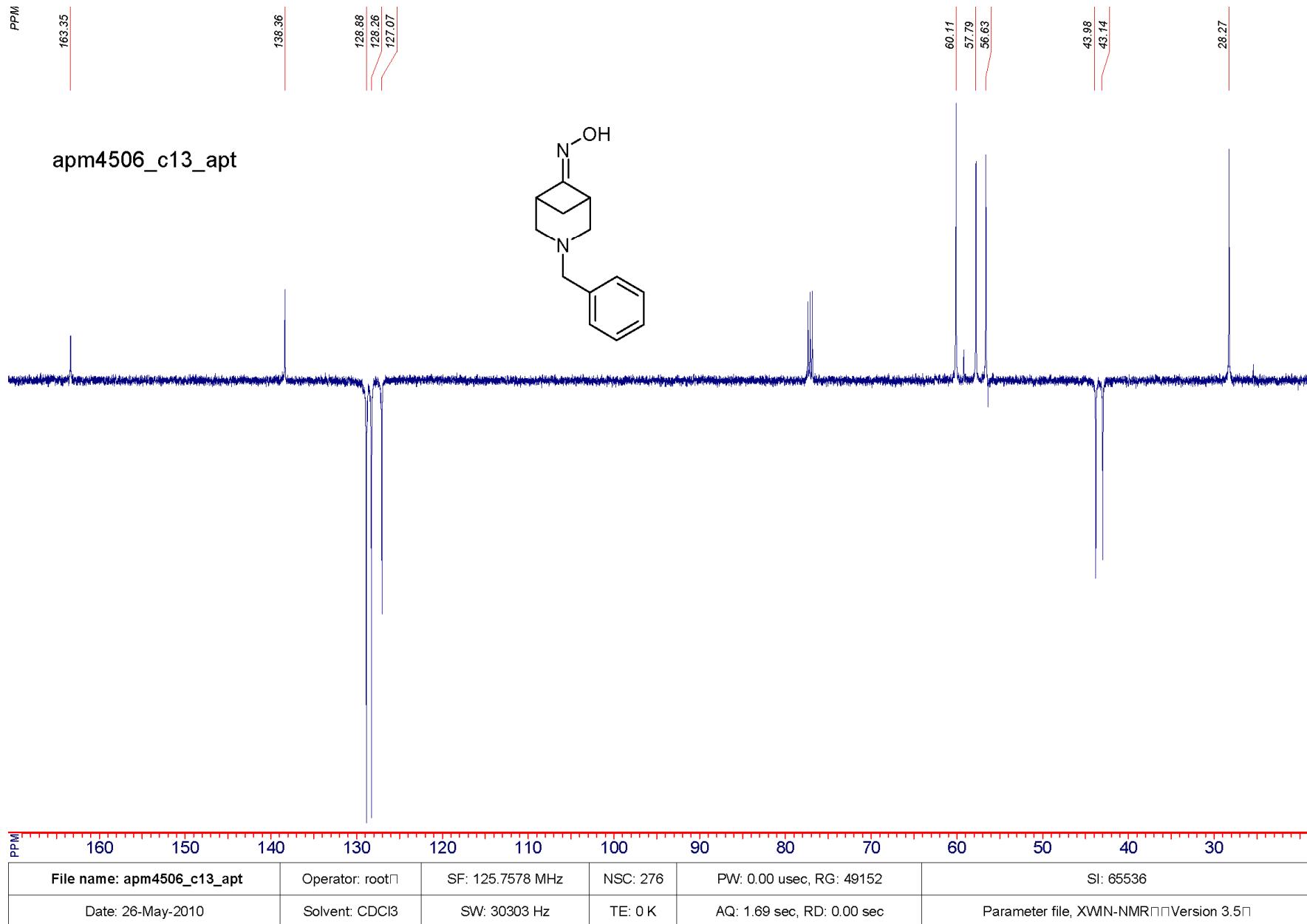


den2756-F19

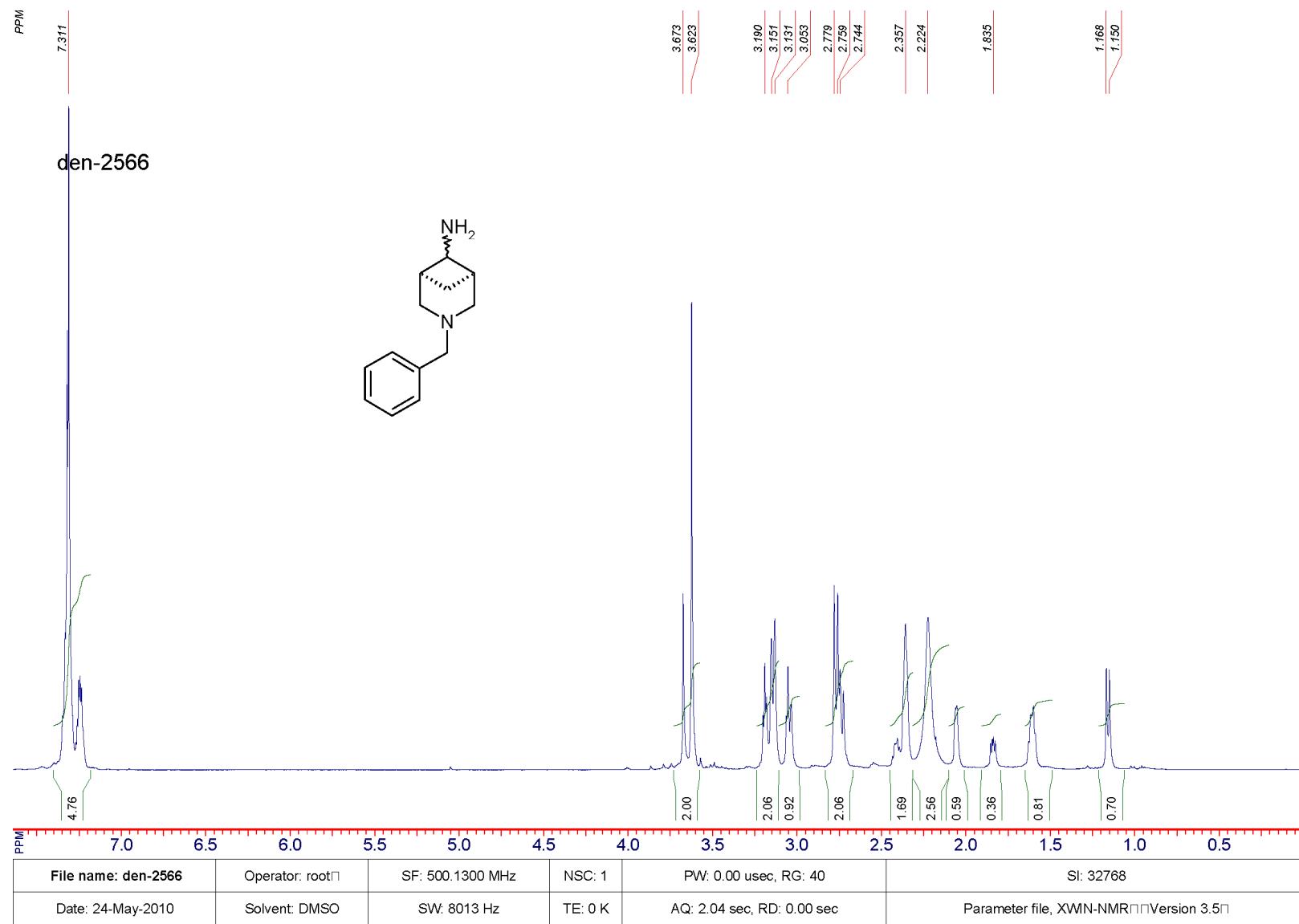


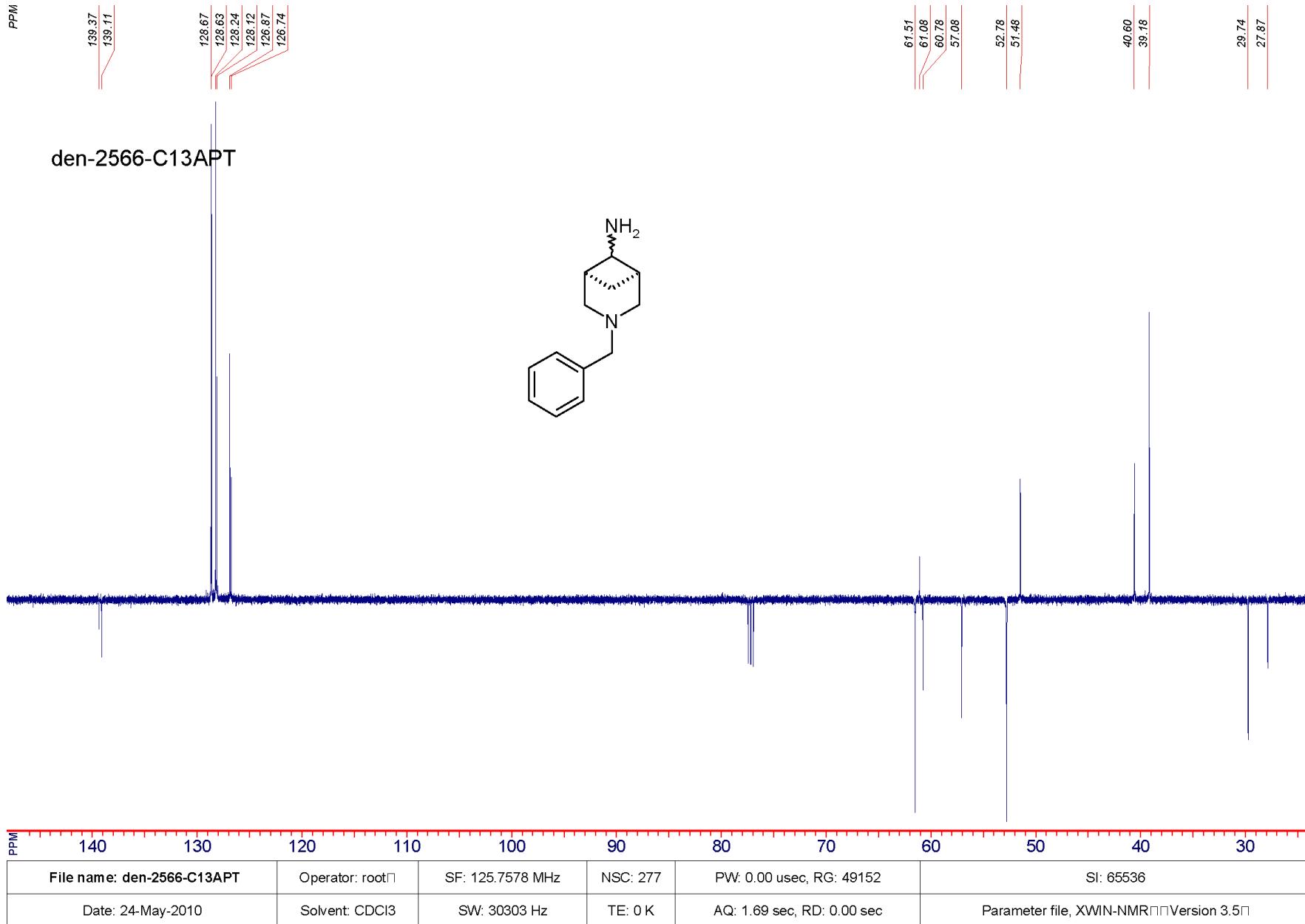
## Compound 11



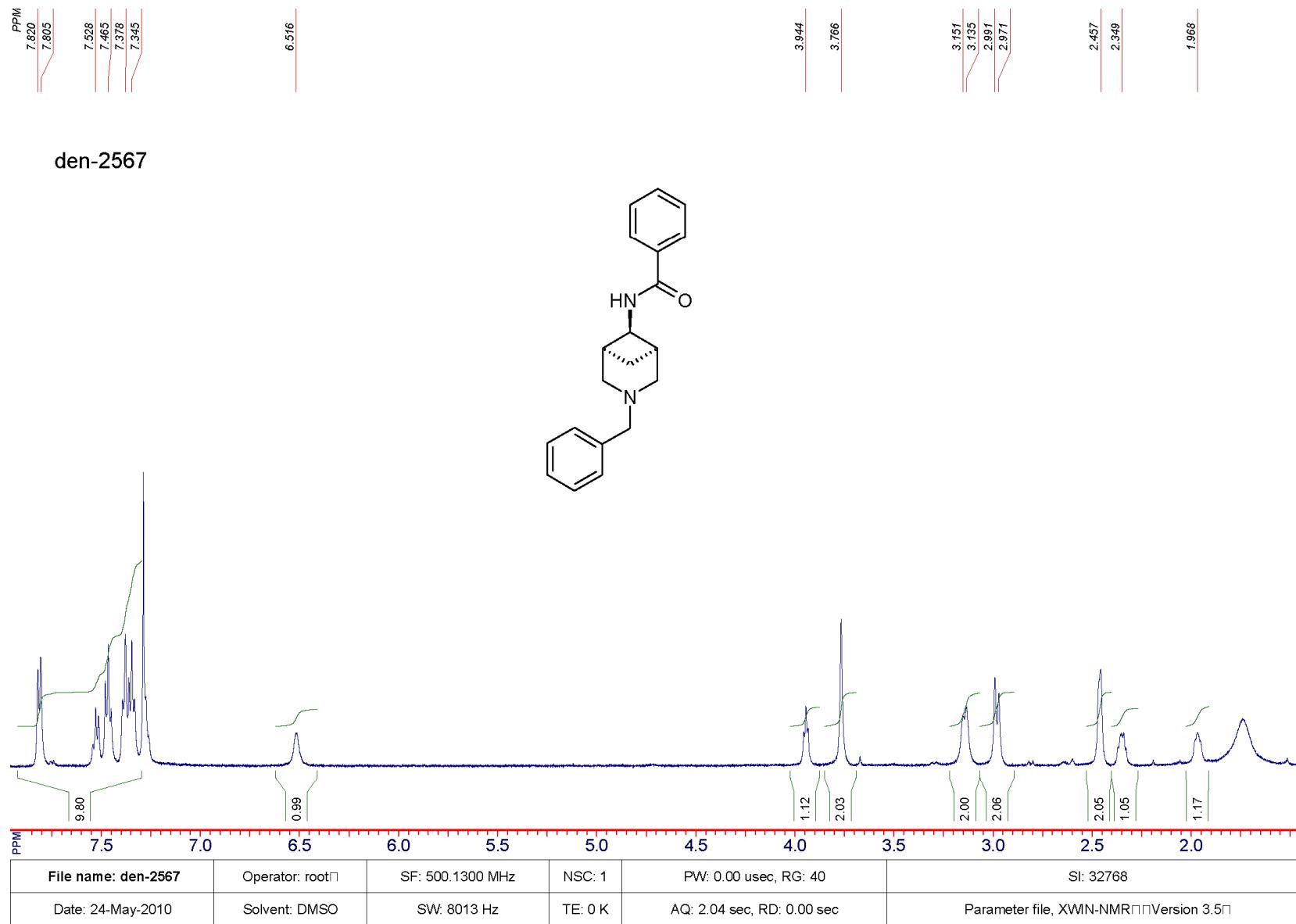


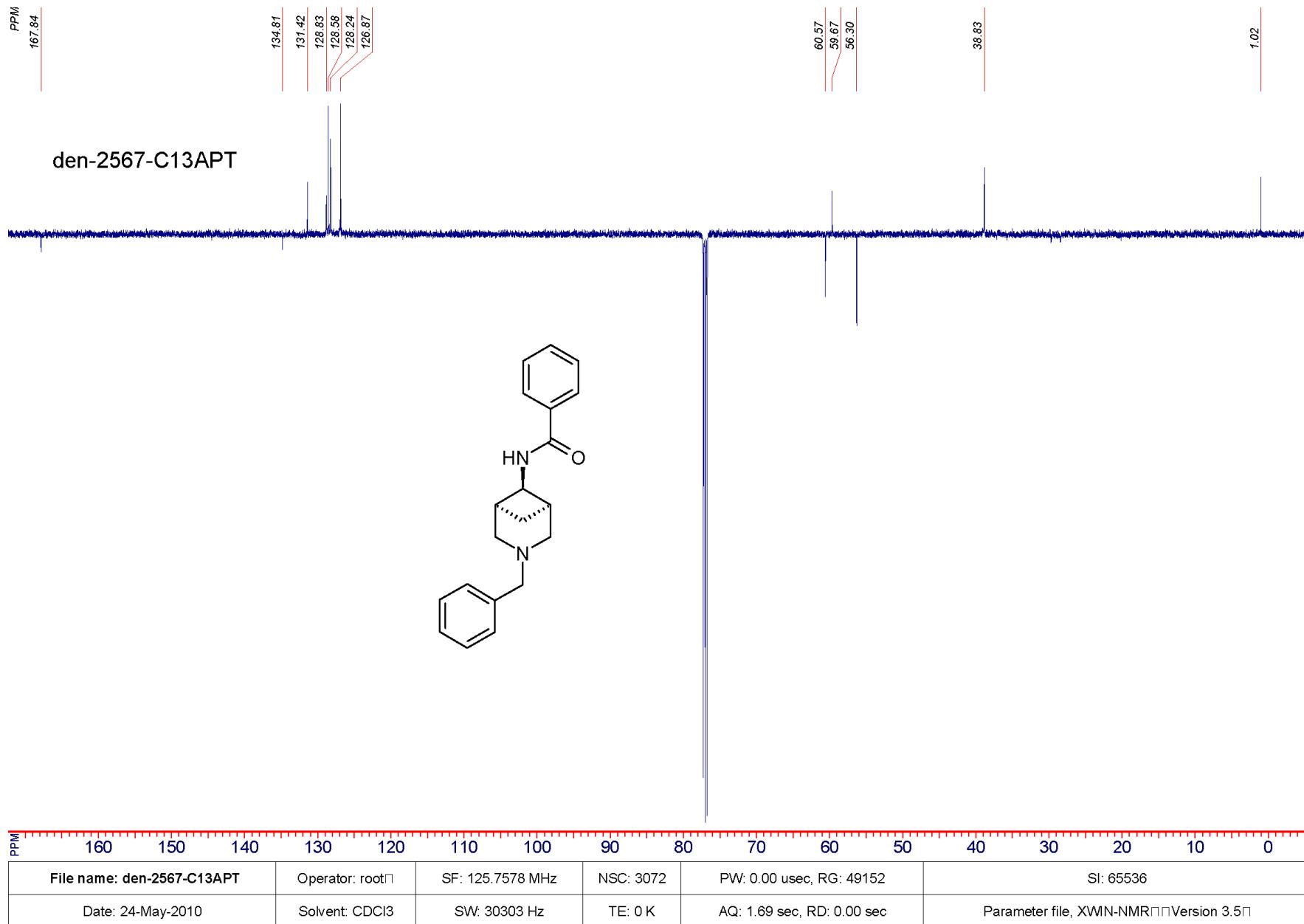
## Compound 12



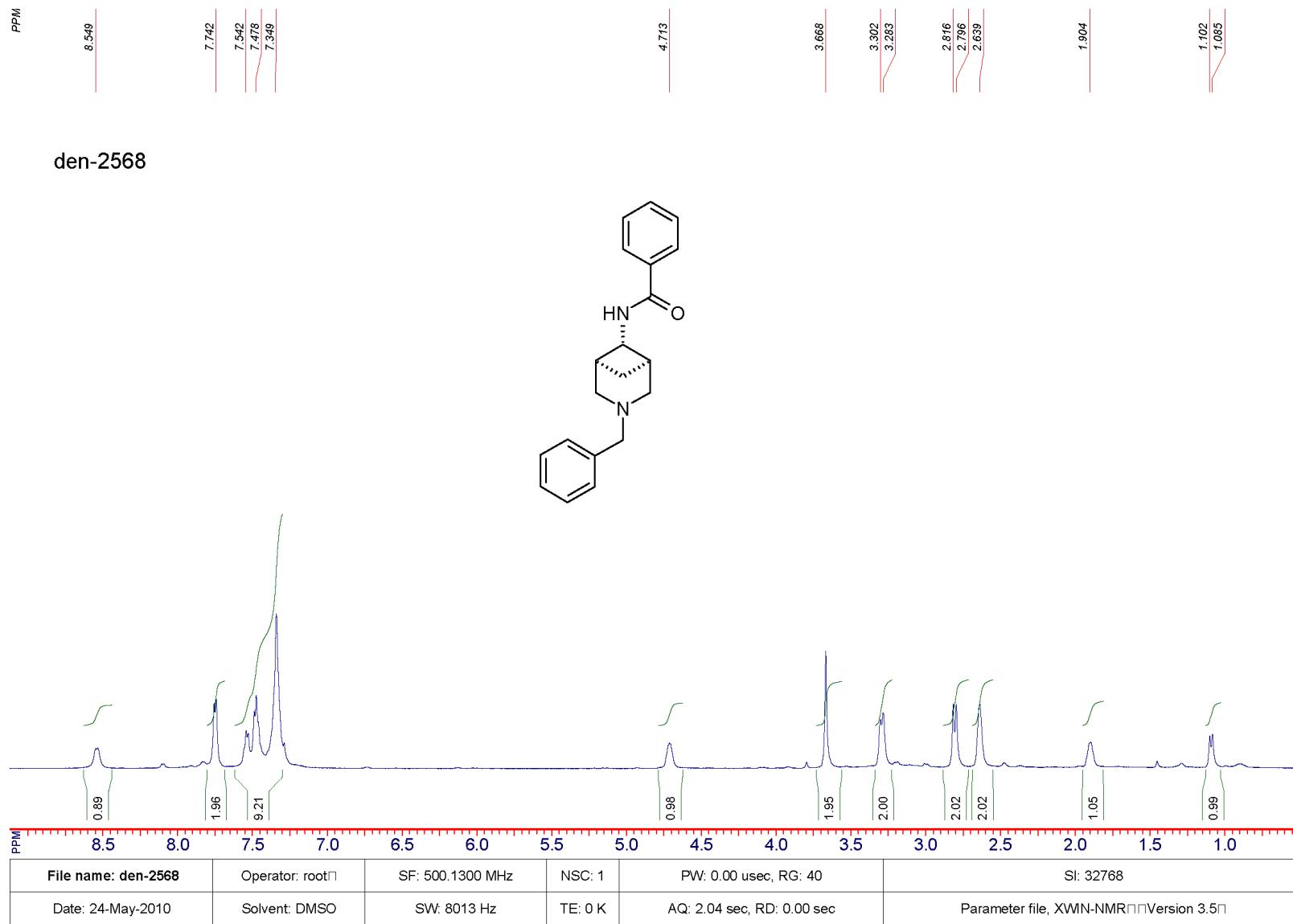


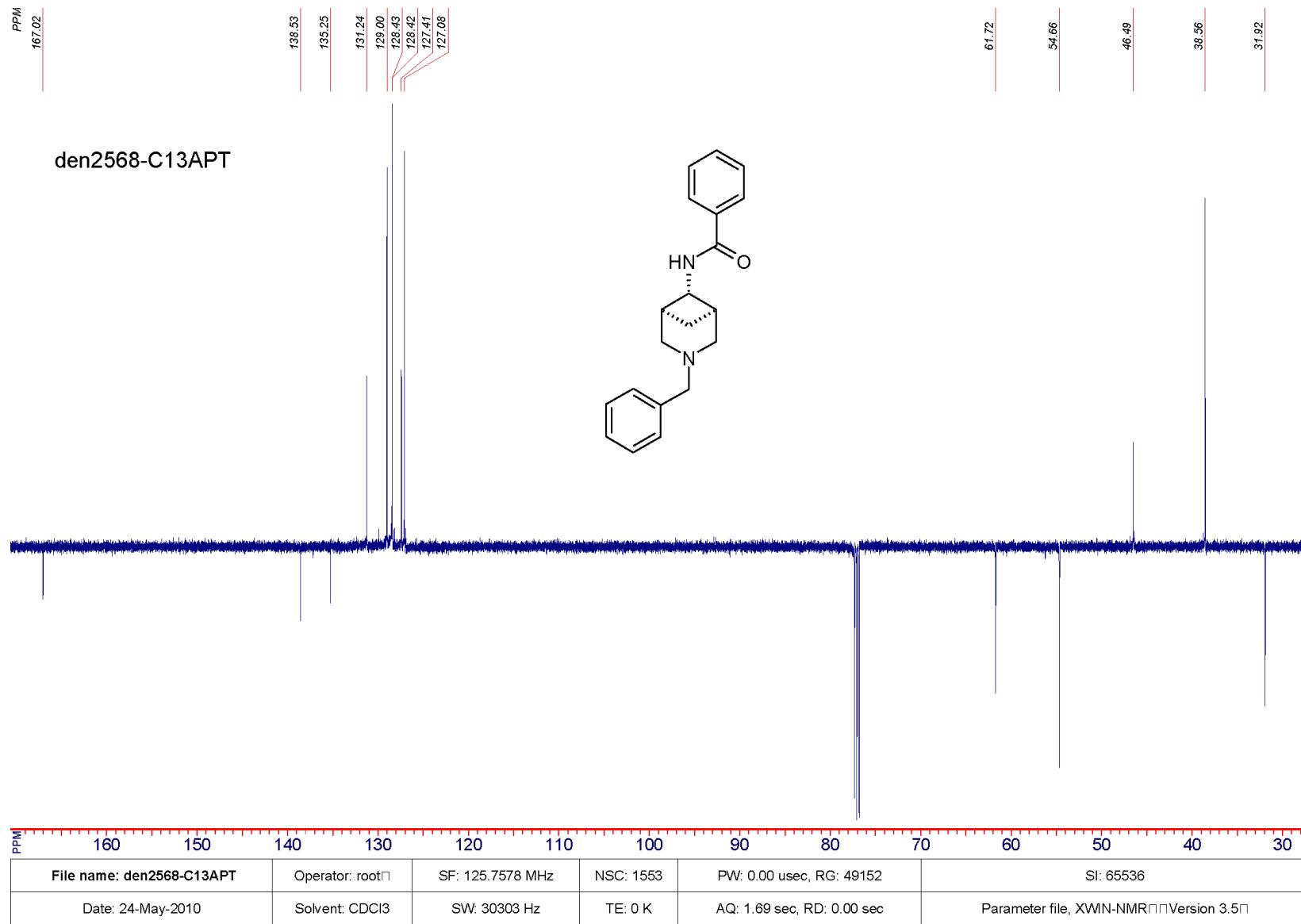
## Compound 13a



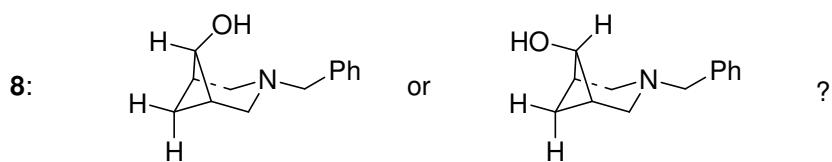


**Compound 13b**





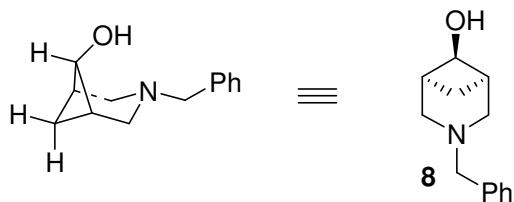
## 2) Determination of the stereoconfiguration of alcohol **8**



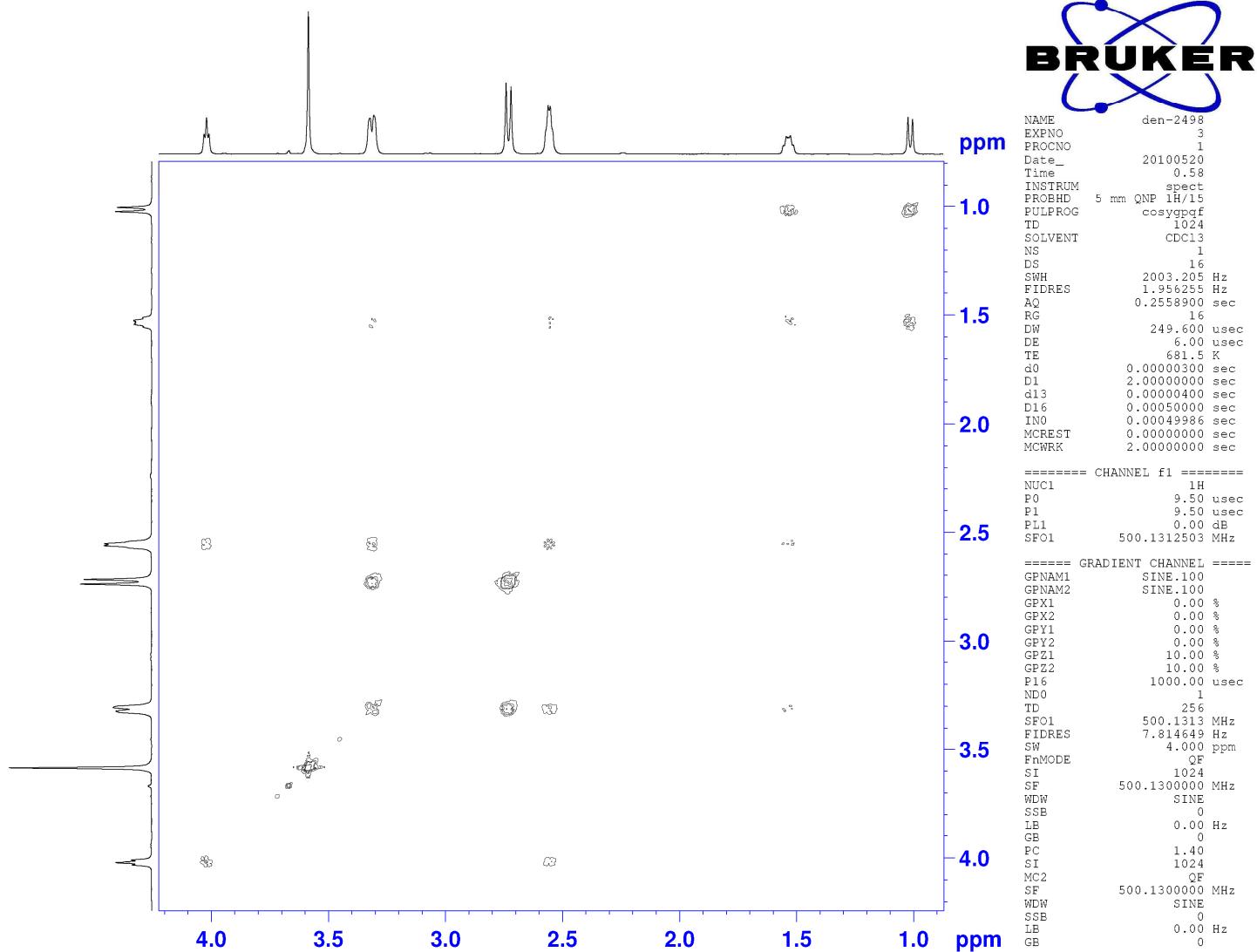
The stereoconfiguration of alcohol **8** was determined by NOESY-experiments:



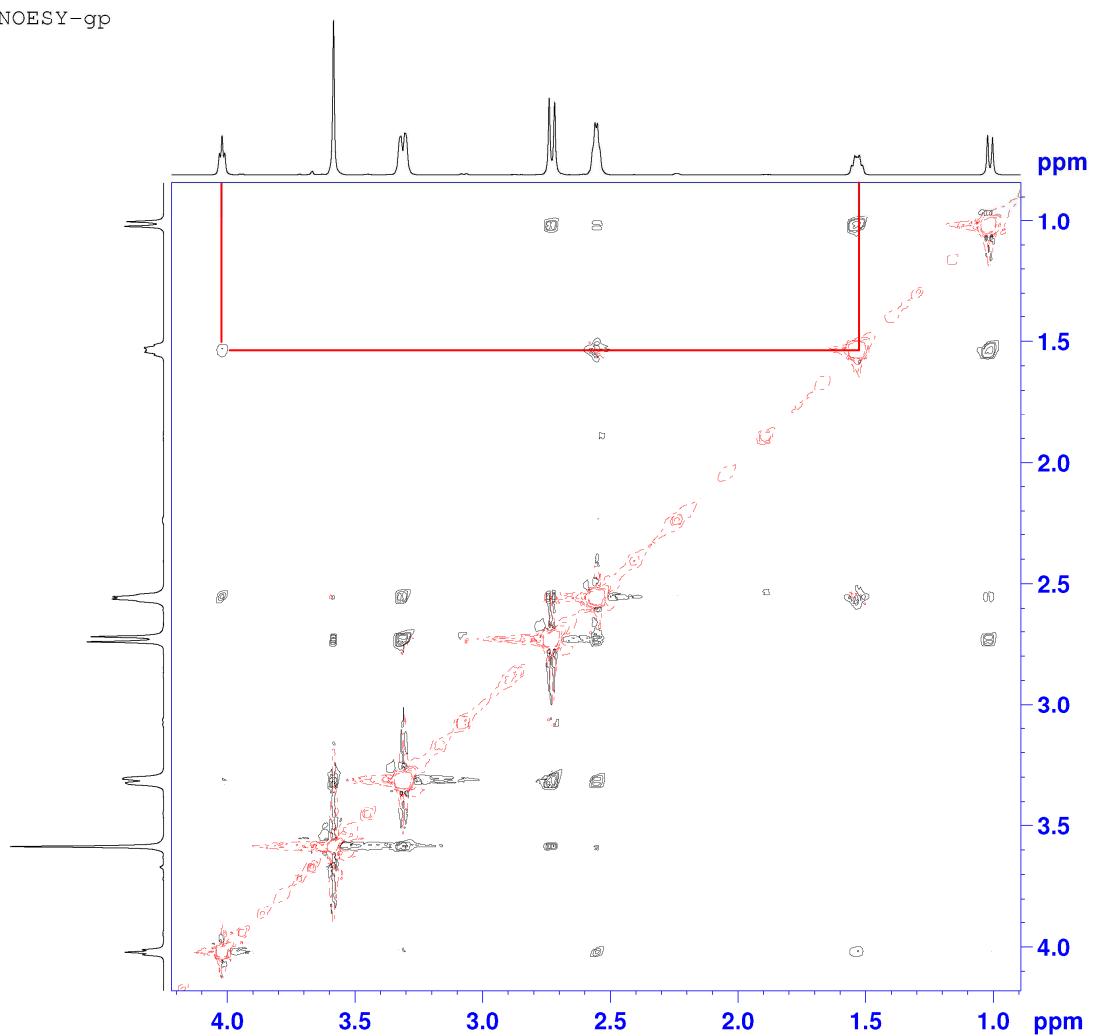
Conclusion:



Below the both COSY- and NOESY- spectra of the compound **8** are given. The key correlation in the NOESY spectrum of **8** (between *CHOH* and *CHH* of cyclobutane) is highlighted by a red bold line.



### NOESY-gp



**BRUKER**

```

NAME      den-2498
EXPNO         4
PROCNO        1
Date_ 20100520
Time_      1.10
INSTRUM spect
PROBHD 5 mm QNP 1H/15
PULPROG noesygpph
TD        2048
SOLVENT cdc13
NS         16
DS         16
SWH      3753.754 Hz
FIDRES 1.832888 Hz
AQ      0.2729768 sec
RG        20
DW      133.200 usec
DE        6.00 usec
TE        0.0 K
d0      0.00012120 sec
d1      2.5000000 sec
D8      0.5000000 sec
D16     0.00020000 sec
INO      0.00026660 sec
MCREST  0.00000000 sec
MCWRK   1.25000000 sec
STICNT      0
TAU      0.24879999 sec

```

```
===== CHANNEL f1 =====
NUC1           1H
P1            9.50 usec
P2            19.00 usec
PL1           0.00 dB
SFO1        500.1321256 MHZ
```

```

===== GRADIENT CHANNEL =====
GPNAME1      SINE.100
GPNAME2      SINE.100
GPX1         0.00 %
GPX2         0.00 %
GPY1         0.00 %
GPY2         0.00 %
GPZ1         40.00 %
GPZ2        -40.00 %
P16          1000.00 usec
NDO          -
TD           256
SP01         500.1321 MHz
FIDRES      14.652101 Hz
SW           7.500 Ppm
FnMODE       States-TPI
SI           2048
SF           500.1300000 MHz
WDN          QSINE
SSB          2
LR           0.00 Hz
GB           0
PC           1.40
SI           2048
MC2          States-TPI
SF           500.1300000 MHz
WDN          QSINE
SSB          2
LB           0.00 Hz
GB           0

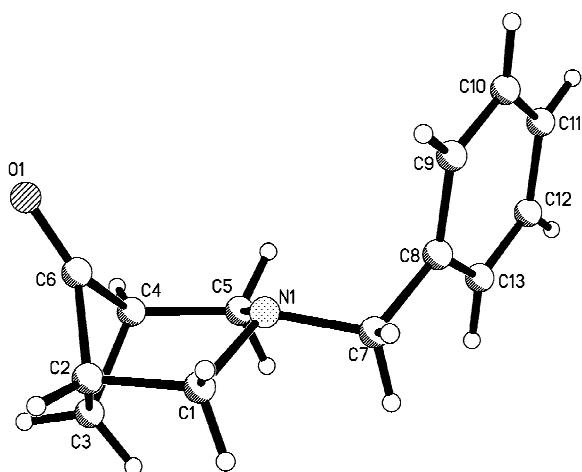
```

### 3) X-Ray diffraction study of the compounds 1, 7, 10 and 13a

#### 3.1 General

All investigated molecules have two chiral centers with different configuration (R, S or S, R) at the C2 and C4 atoms (Fig. S1-S5). It is noted only compound **13a** is crystallized in non-centrosymmetric space group what points to the existence in the crystal phase only one enantiomer. The absence of the heavy atoms in the molecule **13a** does not allow to determine unambiguously the configuration of the chiral centers from the X-ray diffraction data. All other investigated in this paper compounds exist in the crystal phase as racemates.

#### 3.2 The molecular structure of the compound 1

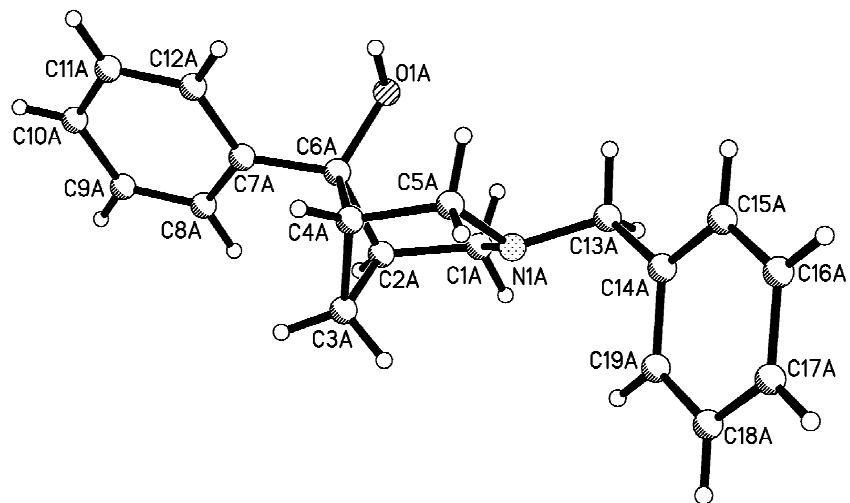


**Figure S1.** X-ray crystal structure of ketone **1**.

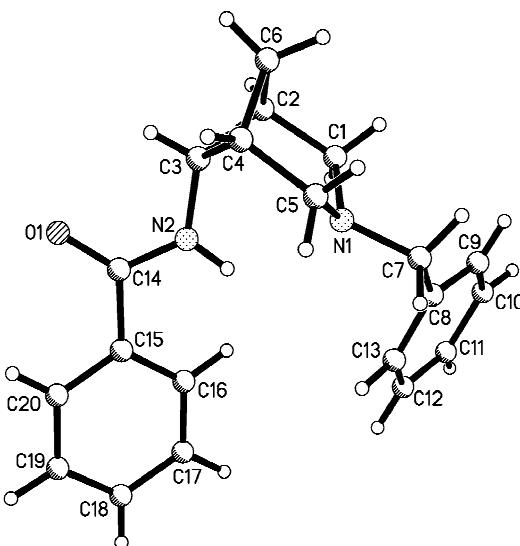
The piperidinone ring (N1-C1-C2-C6-C4-C5) of the framed fragment of the compound **1** adopts a boat conformation (the puckering parameters [1] are  $S = 1.07$ ,  $\Theta = 68.6^\circ$ ,  $\Psi = 0.6^\circ$ ). Deviations of the N1 and C6 atoms from the mean plane of the remaining atoms of the ring are  $-0.51$  Å and  $-1.01$  Å, respectively. The piperidine ring (N1-C1-C2-C3-C4-C5) adopts a chair conformation (the puckering parameters are  $S = 1.30$ ,  $\Theta = 12.6^\circ$ ,  $\Psi = 1.7^\circ$ ). The N1 and C3 atoms are deviated from the mean plane of the remaining atoms of the ring by  $-0.51$  Å and  $1.04$  Å, respectively. Butanone ring adopts a puckered conformation where puckering angle is  $40.9^\circ$ . The nitrogen atom has pyramidal configuration, the sum of the bond angles centered at this atom is  $336.4^\circ$ .

The phenyl ring of the substituent at the nitrogen atom has  $+sc$ -conformation relatively the C5-N1 bond and is turned with respect to the N1-C7 bond (the C5-N1-C7-C8 and N1-C7-C8-C9 torsion angles are  $59.4(1)^\circ$  and  $74.4(2)^\circ$ , respectively). At this rate the H5b...C8 shortened intramolecular contact appears ( $2.67$  Å as compared with van der Waals radii sum [2]  $2.87$  Å).

### 3.3 The molecular structure of the compounds 7 and 13a



**Figure S2.** Molecular structure of compound 7 according to X-ray diffraction data.



**Figure S3.** Molecular structure of compound 13a according to X-ray diffraction data.

Three molecules (**7-A**, **7-B** and **7-C**) are found in asymmetric part of the unit cell for the compound **7**. These molecules differ by some geometric parameters and configuration of the chiral centers (**7-A** and **7-C** have the same and **7-B** has the opposite configuration).

The N1-C1-C2-C3-C4-C5 piperidine ring of the framed fragment of the compounds **7** and **13a** adopts a boat conformation except for **7-C** molecule where the conformation of this ring is a chair (the puckering parameters are  $S = 1.06$ ,  $\Theta = 60.9^\circ$ ,  $\Psi = 0.2^\circ$  for **7-A**,  $S = 1.06$ ,  $\Theta = 62.8^\circ$ ,  $\Psi = 0.4^\circ$  for **7-B**,  $S = 1.27$ ,  $\Theta = 15.1^\circ$ ,  $\Psi = 1.1^\circ$  for **7-C** and  $S = 1.07$ ,  $\Theta = 65.2^\circ$ ,  $\Psi = 0.5^\circ$  for **13a**). On the contrary the N1-C1-C2-C6-C4-C5 piperidine ring adopt a chair conformation with exception of the **7-C** molecule where the conformation of this ring is a boat (the puckering parameters are  $S = 1.24$ ,  $\Theta = 17.5^\circ$ ,  $\Psi = 0.7^\circ$  for **7-A**,  $S = 1.25$ ,  $\Theta = 16.1^\circ$ ,  $\Psi = 0.5^\circ$  for **7-B**,  $S = 1.07$ ,  $\Theta = 64.2^\circ$ ,  $\Psi = 0.0^\circ$  for **7-C** and  $S = 1.28$ ,  $\Theta = 14.6^\circ$ ,  $\Psi = 1.4^\circ$  for **13a**). The deviations of the N1, C3 and C6 atoms from the mean plane of the remaining atoms of the framed fragment are  $-0.39 \text{ \AA}$ ,  $-1.06 \text{ \AA}$  and  $1.07 \text{ \AA}$ , respectively, for **7-A**,  $0.42 \text{ \AA}$ ,  $1.05 \text{ \AA}$  and  $-1.06 \text{ \AA}$ , respectively, for **7-B**,  $0.45 \text{ \AA}$ ,  $-1.05 \text{ \AA}$  and  $1.07 \text{ \AA}$  for **7-C**,  $0.46 \text{ \AA}$ ,  $1.05 \text{ \AA}$  and  $-1.04 \text{ \AA}$ , respectively, for **13a**. The boat conformation of the piperidine ring having the

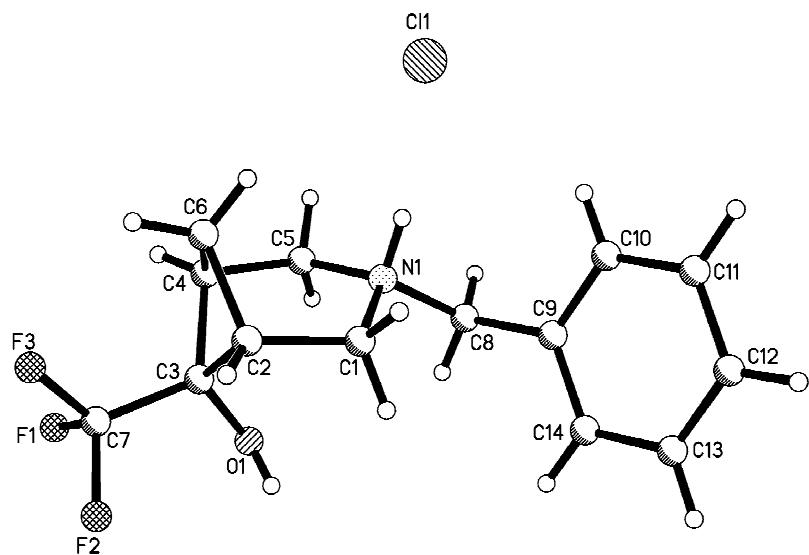
geminal substituent at the C6 atom creates favorable conditions for the formation of the O1-H1O...N1 intramolecular hydrogen bond (H...N 1.88 Å O-H...N 132°). Cyclobutane ring adopts a puckered conformation with the puckering angle 40.7° for **7-A**, 42.1° for **7-B**, 41.9° for **7-C** and 41.7° for **13a**. The nitrogen atom has a pyramidal configuration, the sum of the bond angles centered on this atom is 342.9° **7-A**, 341.7° **7-B**, 343.0° **7-C** and 339.1° **13a**.

The phenyl ring of the benzyl substituent at the nitrogen atom has *+ac-* (**7-A**), *-sc-* (**7-B**), *+sc-* (**7-C**) or *-sc-* (**13a**) conformation relatively the C1-N1 bond and is turned to a variable degree relatively the N1-C13 bond in **7** or the N1-C7 bond in **13a** (the corresponding torsion angles are: C1-N1-C13-C14 147.3(2)° **7-A**, -73.9(2)° **7-B**, 67.1(2)° **7-C**, C1-N1-C7-C8 -63.3(2)° **13a** and N1-C13-C14-C19 -49.7(2)° **7-A**, -67.7(2)° **7-B**, -90.2(2)° **7-C**, N1-C7-C8-C9 105.3(2)° **13a**).

The geminal substituents at the C6 atom in compound **7** are situated in such way that the hydroxy group has endo-orientation relatively framed fragment (the C1-C2-C6-O1 torsion angle is -35.4(2)° **7-A**, 33.5(2)° **7-B**, -38.7(2)° **7-C**) and phenyl ring has exo-orientation and it is turned relatively the C2-C6 bond (the C1-C2-C6-C7 and C2-C6-C7-C8 torsion angles are -163.7(2)° **7-A**, 163.0(1)° **7-B**, -163.8(2)° **7-C** and 8.8(3)° **7-A**, -52.2(2)° **7-B**, 65.4(2)° **7-C**, respectively). The positions of the hydroxy group in the molecules **7-A** and **7-B** are stabilized additionally by the attractive interactions C1-H1b...O1 2.39 Å (**7-A**) and C5-H5b...O1 2.40 Å (**7-B**).

Benzamide substituent at the C3 atom of the framed fragment in molecule **13a** has exo-orientation and it is turned relatively the C3-C4 bond (the N2-C3-C4-C5 and C14-N2-C3-C4 torsion angles are 43.0(2)° and 122.4(1)°, respectively). Such orientation of substituents probably is caused by the formation of the N2-H...N1 intramolecular hydrogen bond (H...N 2.21 Å N-H...N 119°). The phenyl ring of this substituent has *ap*- conformation relatively the C3-N2 bond and slightly non-coplanar to amide group (the C30N20C14-C15 and N2-C14-C15-C16 torsion angles are -178.4(1)° and -27.1(2)°, respectively).

### 3.4 The molecular structure of the compound 10



**Figure S4.** Molecular structure of compound **10** according to X-ray diffraction data.

The compounds **10** exists in the crystal phase as chlorides of the organic cations. The positive charge of the cation is located on the nitrogen atom due to its protonation (the hydrogen atom at the N1 is located from electron density difference maps and the N1-C7, N1-C5 and N1-C1 bonds (1.506(2) Å, 1.527(2) Å, 1.518(1) Å) are elongated as compared with mean value [3] for  $Csp^3-N$  bond 1.469 Å indicating protonation of the N1 atom).

The N1-C5-C4-C3-C2-C1 and N1-C5-C4-C6-C2-C1 piperidine rings adopt a boat and a chair conformations, respectively (the puckering parameters are  $S = 1.21$ ,  $\Theta = 24.8^\circ$ ,  $\Psi = 0.3^\circ$ ,  $S = 1.07$ ,  $\Theta = 51.9^\circ$ ,  $\Psi = 0.1^\circ$ ). The deviations of the N1, C3 and C6 atoms from the mean plane of the remaining atoms of the rings are 0.26 Å, -1.09 Å and -1.07 Å.

The aromatic ring of the benzyl substituent has-*sc*- (molecule **10**) conformation relatively the C1-N1 bond and the C1-N1-C8-C9 torsion angle in **10** is -50.9(2)° and it is turned relatively the N-Csp<sup>3</sup> exocyclic bond (the N1-C8-C9-C10 torsion angle in **10** is -68.2(2)°).

The geminal substituents at the C3 atom in the molecule **10** are situated in such way that the hydroxy group has endo-orientation relatively the framed fragment (the C1-C2-C3-O1 torsion angle is 28.2(2)°). The trifluoromethyl group, correspondingly, has exo-orientation and it is turned in such way that the C7-F1 bond has almost antiperiplanar conformation relatively the C2-C3 bond (the C1-C2-C3-C7 and C2-C3-C7-F1 torsion angles are 157.0(1)° and 164.3(1)°, respectively).

In the crystal phase the organic cations are bonded to each other through bridged chloride-anion by intermolecular hydrogen bonds: O1-H...Cl1' (x-1, 1.5-y, z-0.5) H...Cl 2.24 Å O-H...Cl 158° and N1-H...Cl1' (x, y, z) H...Cl 2.17 Å N-H...Cl 161° in **10**.

### 3.5 X-Ray diffraction studies of **1**, **7**, **10** and **13a**

X-Ray diffraction studies were performed using an automatic «Xcalibur 3» diffractometer (graphite monochromated MoK $\alpha$  radiation, CCD-detector,  $\omega$ -scanning). The structures were solved by direct method using SHELXTL package [4]. Positions of hydrogen atoms were located from electron density difference maps and refined using riding model with  $U_{\text{iso}} = 1.2U_{\text{eq}}$  of the carrier atom, except the H-atoms of the hydroxy groups which were refined within isotropic approximation, for the molecule **7**. The hydrogen atoms of all other molecules (**1**, **7**, **10** and **13a**) were refined in isotropic approximation. The crystallographic data and experimental parameters are listed in Table 2. Final atomic coordinates, geometrical parameters and crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, 11 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033; e-mail: [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk)). The deposition numbers are given in Table S1.

Table S1. The crystallographic data and experimental parameters for compounds **1**, **7**, **10** and **13a**.

Parameter	<b>1</b>	<b>7</b>	<b>10</b>	<b>13a</b>
Unit cell dimensions				
<i>a</i> , Å	10.8760(6)	13.744(1)	5.7056(4)	9.5004(6)
<i>b</i> , Å	10.2752(6)	18.415(3)	20.577(1)	10.8881(9)
<i>c</i> , Å	19.446(1)	17.850(2)	12.4401(8)	16.423(1)
$\alpha$ , deg.	90	90	90	90
$\beta$ , deg.	90	99.47(1)	101.509(7)	90
$\gamma$ , deg.	90	90	90	90
<i>V</i> , Å <sup>3</sup>	2173.1(2)	4456.2(8)	1431.2(2)	1698.8(2)
<i>F</i> (000)	864	1800	640	656
Crystal system	Orthorhombic	Monoclinic	Monoclinic	Orthorhombic
Space group	Pbca	P2 <sub>1</sub> /n	P2 <sub>1</sub> /c	Pna2 <sub>1</sub>
<i>Z</i>	8	12	4	4
<i>T</i> , K	293	100	100	293
$\mu$ , mm <sup>-1</sup>	0.078	0.076	0.295	0.074
<i>D</i> <sub>calc</sub> , g/cm <sup>3</sup>	1.230	1.249	1.428	1.198
2 $\Theta$ <sub>max</sub> , grad	60	55	60	60
Measured reflections	12614	37403	8230	18914
Independent reflections	3169	10208	4160	4927
<i>R</i> <sub>int</sub>	0.046	0.151	0.040	0.028
Reflections with <i>F</i> >4 $\sigma$ ( <i>F</i> )	1463	3246	2434	2877
Parameters	196	580	249	296
<i>R</i> <sub>1</sub>	0.041	0.041	0.038	0.034
w <i>R</i> <sub>2</sub>	0.079	0.054	0.061	0.070
<i>S</i>	0.799	0.484	0.799	0.820
CCDC number	778489	778492	778493	778490