

SUPPORTING INFORMATION

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

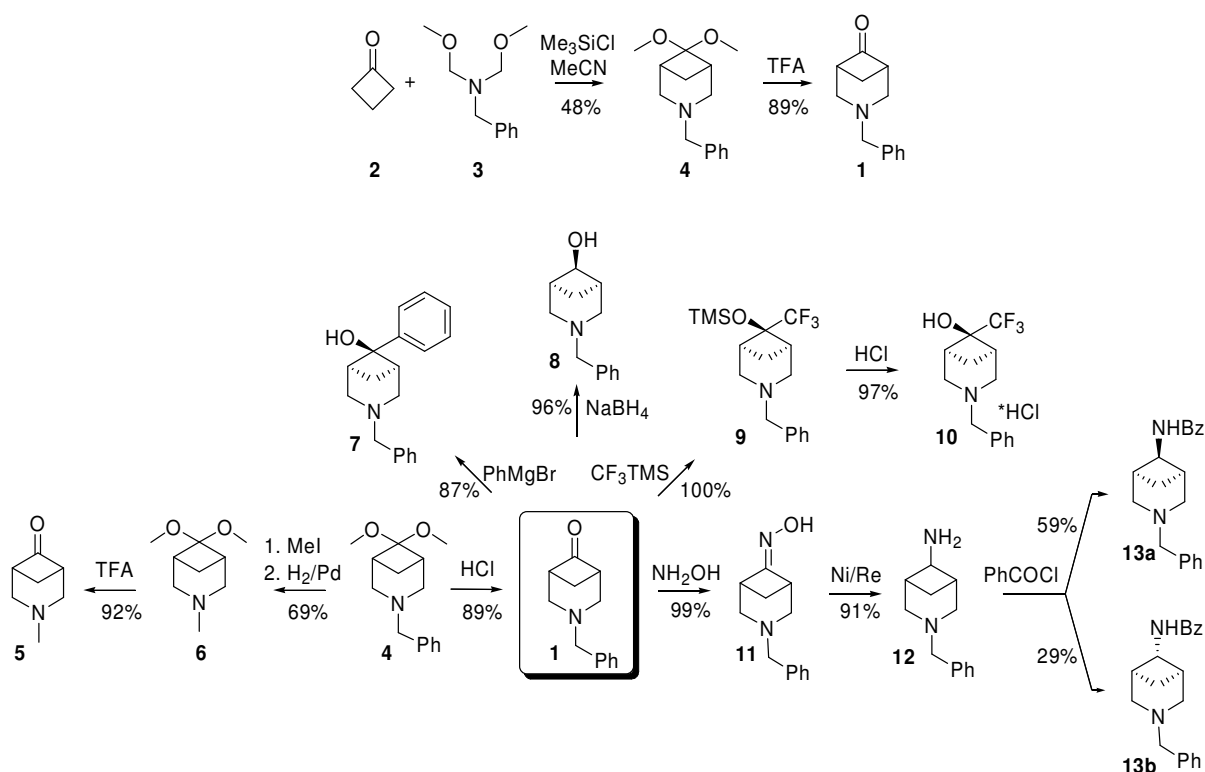
Aleksandr V. Denisenko,^a Andrey P. Mityuk,^a Oleksandr O. Grygorenko,^a Dmytro M. Volochnyuk,^a Oleg V. Shishkin,^b Andrey A. Tolmachev^a and Pavel K. Mykhailiuk^{*a}

^a Enamine Ltd., Vul. Oleksandra Matrosova 23, 01103 Kyiv, Ukraine and Department of Chemistry, Kyiv National Taras Shevchenko University, Vul. Volodymyrska 64, 01033 Kyiv, Ukraine

^b STC, 'Institute for Single Crystals,' National Academy of Science of Ukraine, 60 Lenina ave., Kharkiv 61001, Ukraine

Pavel.Mykhailiuk@gmail.com

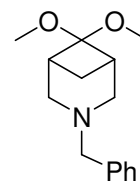
1) Synthesis of the compounds



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. ¹H-, ¹⁹F-, ¹³C-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 ¹³C-NMR spectra. Chemical shifts are reported in ppm downfield from TMS (¹H, ¹³C) or CFCl₃ (¹⁹F) 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 NaHCO₃. The aqueous layer was extracted with EtOAc (3*250 mL). The combined organic phase was dried over Na₂SO₄ 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).



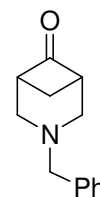
¹H NMR (500 MHz; CDCl₃; Me₄Si), δ: 1.74 (1H, m, CHH of cyclobutane), 2.07 (1H, d, ²J_{H-H} = 8.3 Hz, CHH of cyclobutane), 2.54 (2H, m, CH of cyclobutane), 2.73 (2H, d, J = 9.7 Hz, NCHH), 3.077 (2H, m, NCHH), 3.24 (6H, 2 s, OCH₃), 3.70 (2H, s, NCH₂Ph), 7.25-7.38 (5H, m, Ph).

¹³C NMR (125 MHz; CDCl₃; Me₄Si), δ: 21.40 (s, CH₂ of cyclobutane), 39.98 (s, CH of cyclobutane), 48.44 (s, OCH₃), 49.09 (s, OCH₃), 51.77 (s, PhCH₂NCH₂), 60.11 (s, NCH₂Ph), 103.70 (s, quat-C, C-OCH₃), 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 trifluoroacetic acid was evaporated in vacuum, and a saturated aq. solution of NaHCO₃ was added to adjust pH value of the solution to 8. The reaction mixture was extracted with CH₂Cl₂ (3*100 mL). The combined organic phase was dried over Na₂SO₄ 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.

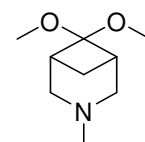
¹H NMR (500 MHz; CDCl₃; Me₄Si), δ: 1.78 (1H, d, ²J_{H-H} = 5.0 Hz, CHH of cyclobutane), 1.95 (1H, m, CHH of cyclobutane), 3.02 (2H, m, CH of cyclobutane), 3.10 (2H, d, J = 10.0 Hz, NCHH), 3.33 (2H, d, J = 10.0 Hz, NCHH), 3.62 (2H, s, NCH₂Ph), 7.23-7.31 (5H, m, Ph).

¹³C NMR (125 MHz; CDCl₃; Me₄Si), δ: 25.18 (s, CH₂ of cyclobutane), 55.93 (s, CH of cyclobutane), 58.79 (s, PhCH₂NCH₂), 59.75 (s, NCH₂Ph), 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 CH₃I (4.6 g, 32.4 mmol) in CH₂Cl₂ (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)₂/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 K₂CO₃ in water was added. The water phase was extracted with CH₂Cl₂ (3*10mL). Organic phase was separated, dried over Na₂SO₄ and evaporated in vacuum to give pure **6** (0.95 g, 5.6 mmol, 69% yield) as a yellowish oil.

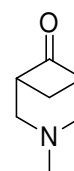
¹H NMR (500 MHz; CDCl₃; Me₄Si), δ: 1.70 (1H, m, CHH of cyclobutane), 1.88 (1H, d, ²J_{H-H} = 8.0 Hz, CHH of cyclobutane), 2.32 (3H, s, NCH₃), 2.59 (2H, m, CH of cyclobutane), 2.60 (2H, d, J = 10.0 Hz, NCHH), 3.077 (2H, d, J = 10.0 Hz, NCHH), 3.24 (6H, 2 s, OCH₃).

¹³C NMR (125 MHz; CDCl₃; Me₄Si), δ: 21.30 (s, CH₂ of cyclobutane), 39.88 (s, CH of cyclobutane), 43.12 (s, NCH₃), 48.51 (s, OCH₃), 49.15 (s, OCH₃), 53.92 (s, CH₃NCH₂).

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 trifluoroacetic acid was evaporated in vacuum, and a saturated aq. solution of NaHCO₃ was added to adjust pH value of the reaction mixture to 8. The reaction mixture was extracted with CH₂Cl₂ (3*3 mL). The combined organic phase was dried over Na₂SO₄ and evaporated in vacuum to give ketone **5** as a yellowish oil (135 mg, 1.1 mol, 92% yield).



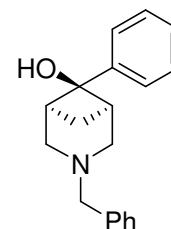
¹H NMR (500 MHz; CDCl₃; Me₄Si), δ: 1.73 (1H, d, ²J_{H-H} = 9.0 Hz, CHH of cyclobutane), 1.95 (1H, m, CHH of cyclobutane), 2.31 (3H, s, NCH₃), 3.05 (2H, m, CH of cyclobutane), 3.07 (2H, d, J = 10.5 Hz, NCHH), 3.36 (2H, d, J = 10.5 Hz, NCHH).

¹³C NMR (125 MHz; CDCl₃; Me₄Si), δ: 25.65 (s, CH₂ of cyclobutane), 43.17 (s, NCH₃), 56.27 (s, CH of cyclobutane), 61.63 (s, CH₃NCH₂), 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 NH₄Cl (80.0 mL) was added. The formed organic layer was separated, and the aqueous layer was extracted with Et₂O (50 mL). The combined organic extract was washed with brine, and dried over Na₂SO₄. 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.

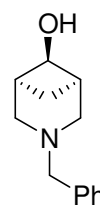
^1H NMR (500 MHz; CDCl_3 ; Me_4Si), δ : 1.03 (1H, d, $^2J_{\text{H-H}} = 9.8$ Hz, CHH of cyclobutane), 1.72 (1H, m, CHH of cyclobutane), 2.88 (2H, m, CH of cyclobutane), 2.94 (2H, d, $J = 10.3$ Hz, NCHH), 3.57 (2H, d, $J = 10.3$ Hz, NCHH), 3.73 (2H, s, NCH_2Ph), 7.29 - 7.42 (8H, m, Ph+Ph), 7.58 (2H, m, Ph).

^{13}C NMR (125 MHz; CDCl_3 ; Me_4Si), δ : 29.82 (s, CH_2 of cyclobutane), 42.67 (s, CH of cyclobutane), 56.00 (s, $\text{PhCH}_2\text{NCH}_2$), 61.21 (s, NCH_2Ph), 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_4 (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_2Cl_2 (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_2Cl_2 (30 mL). The combined organic phase was washed with brine, dried over Na_2SO_4 , and evaporated in vacuum to yield pure alcohol **8** (1.93 g, 9.5 mmol, 96% yield) as a yellow oil.



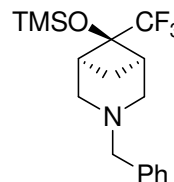
^1H NMR (500 MHz; CDCl_3 ; Me_4Si), δ : 1.01 (1H, d, $^2J_{\text{H-H}} = 9.5$ Hz, CHH of cyclobutane), 1.53 (1H, m, CHH of cyclobutane), 2.56 (2H, m, CH of cyclobutane), 2.73 (2H, d, $J = 10.5$ Hz, NCHH), 3.31 (2H, d, $J = 8.8$ Hz, NCHH), 3.58 (2H, s, NCH_2Ph), 4.02 (1 H, t, $J = 5.1$ Hz, CHOH), 7.26 - 7.35 (5 H, m, Ph).

^{13}C NMR (125 MHz; CDCl_3 ; Me_4Si), δ : 28.89 (s, CH_2 of cyclobutane), 39.45 (s, CH of cyclobutane), 54.97 (s, $\text{PhCH}_2\text{NCH}_2$), 61.41 (s, NCH_2Ph), 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-(trimethylsilyloxy)-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_3TMS (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.



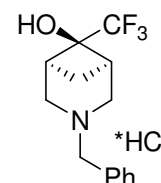
^1H NMR (500 MHz; CDCl_3 ; Me_4Si), δ : 0.27 (9H, s, $\text{Si(CH}_3)_3$), 1.98 (1H, m, CHH of cyclobutane), 2.16 (1H, d, $^2J_{\text{H-H}} = 10.5$ Hz, CHH of cyclobutane), 2.65 (2H, broad s, CH of cyclobutane), 2.85 (2H, d, $J = 9.8$ Hz, NCHH), 3.15 (2H, d, $J = 8.6$ Hz, NCHH), 3.75 (2H, s, NCH_2Ph), 7.28-7.40 (5H, m, Ph).

^{13}C NMR (125 MHz; CDCl_3 ; Me_4Si), δ : 1.59 (s, $\text{Si}(\text{CH}_3)_3$), 20.20 (q, $^4J_{\text{C-F}} = 4.5$ Hz, CH_2 of cyclobutane), 39.56 (s, CH of cyclobutane), 50.88 (s, $\text{PhCH}_2\text{NCH}_2$), 59.69 (s, NCH_2Ph), 77.54 (q, $^2J_{\text{C-F}} = 28.0$ Hz, C-CF_3), 126.77 (q, $^1J_{\text{C-F}} = 284.7$ Hz, CF_3), 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.

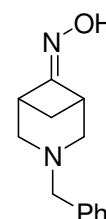
^1H NMR (500 MHz; DMSO-d_6 ; Me_4Si), δ : 2.05 (1H, m, CHH of cyclobutane), 2.26 (1H, d, $^2J_{\text{H-H}} = 10.6$ Hz, CHH of cyclobutane), 2.74 (2H, d, $^3J_{\text{H-H}} = 6.4$ Hz, CH of cyclobutane), 3.54 (2H, m, NCHH), 3.60 (2H, m, NCHH), 4.36 (2H, d, $^3J_{\text{H-H}} = 5.0$ Hz, NCH_2Ph), 7.46 (3H, s, Ph), 7.80 (2H, s, Ph), 11.61 (1H, s, NH).

^{13}C NMR (125 MHz; DMSO-d_6 ; Me_4Si), δ : 20.29 (s, CH_2 of cyclobutane), 36.46 (s, CH of cyclobutane), 52.61 (s, $\text{PhCH}_2\text{NCH}_2$), 59.68 (s, NCH_2Ph), 72.95 (q, $^2J_{\text{C-F}} = 28.8$ Hz, C-CF_3), 126.87 (q, $^1J_{\text{C-F}} = 281.2$ Hz, CF_3), 120.06 (s, CH, Ph), 129.85 (s, CH, Ph), 130.67 (s, quat-C, Ph), 131.88 (s, CH, Ph).

^{19}F NMR (471 MHz; DMSO-d_6 ; CFCl_3), δ : -76.81 (s, CF_3).

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_2CO_3 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.



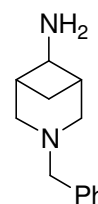
^1H NMR (500 MHz; CDCl_3 ; Me_4Si), δ : 1.91 (1H, d, $J = 7.5$ Hz, cyclobutane), 2.00 (1H, broad s, cyclobutane), 3.01 (4H, broad s, NCH_2), 3.21 (1H, d, $J = 8.0$ Hz, cyclobutane), 3.52 (1H, broad s, cyclobutane), 3.72 (2H, s, NCH_2Ph), 7.35 (5H, s, Ph), 8.90 (1H, s, OH).

^{13}C NMR (125 MHz; CDCl_3 ; Me_4Si), δ : 28.14 (s, CH_2 of cyclobutane), 42.87 (s, CH of cyclobutane), 43.68 (s, CH of cyclobutane), 56.50 (s, $\text{PhCH}_2\text{NCH}_2$), 57.66 (s, $\text{PhCH}_2\text{NCH}_2$), 59.98 (s, NCH_2Ph), 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 alloy (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).



¹H NMR (500 MHz; DMSO-d₆; Me₄Si), 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, NH₂), 2.78 (2H, m), 3.05-3.19 (3H, m), 2.62-2.67 (2H, 2 s, NCH₂Ph), 7.31 (5H, m, Ph).

¹³C NMR (125 MHz; DMSO-d₆; Me₄Si), δ: 27.87, 29.74 (2 s, CH₂ of cyclobutane), 39.18, 40.60 (2 s, CH of cyclobutane), 51.48, 61.08 (2 s, CHNH₂), 52.78, 57.08 (2 s, PhCH₂NCH₂), 61.08, 61.51 (2 s, NCH₂Ph), 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.

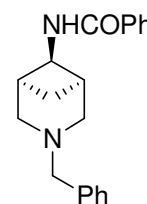
3-Benzyl-6-endo-benzoylamino-3-azabicyclo[3.1.1]heptane (13a)

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 Na₂SO₄ 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_f* = 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.

¹H NMR (500 MHz; CDCl₃; Me₄Si), 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, NCH₂Ph), 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).

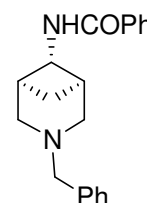


¹³C NMR (125 MHz; CDCl₃; Me₄Si), δ: 1.02 (s, CH₂ of cyclobutane), 38.83 (s, CH of cyclobutane), 56.30 (s, CHNH), 59.67 (s, PhCH₂NCH₂), 60.57 (s, NCH₂Ph), 126.87 (s, CH, Ph), 128.23 (s, CH, Ph), 128.58 (s, CH, Ph), 128.83 (s, quat-C, Ph), 131.42 (s, CH, Ph), 2 signals (s, CH, Ph and quat-C, Ph) are not seen, 134.81 (s, quat-C, Ph), 167.84 (s, C=O).

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MS (*m/z*): 306.

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

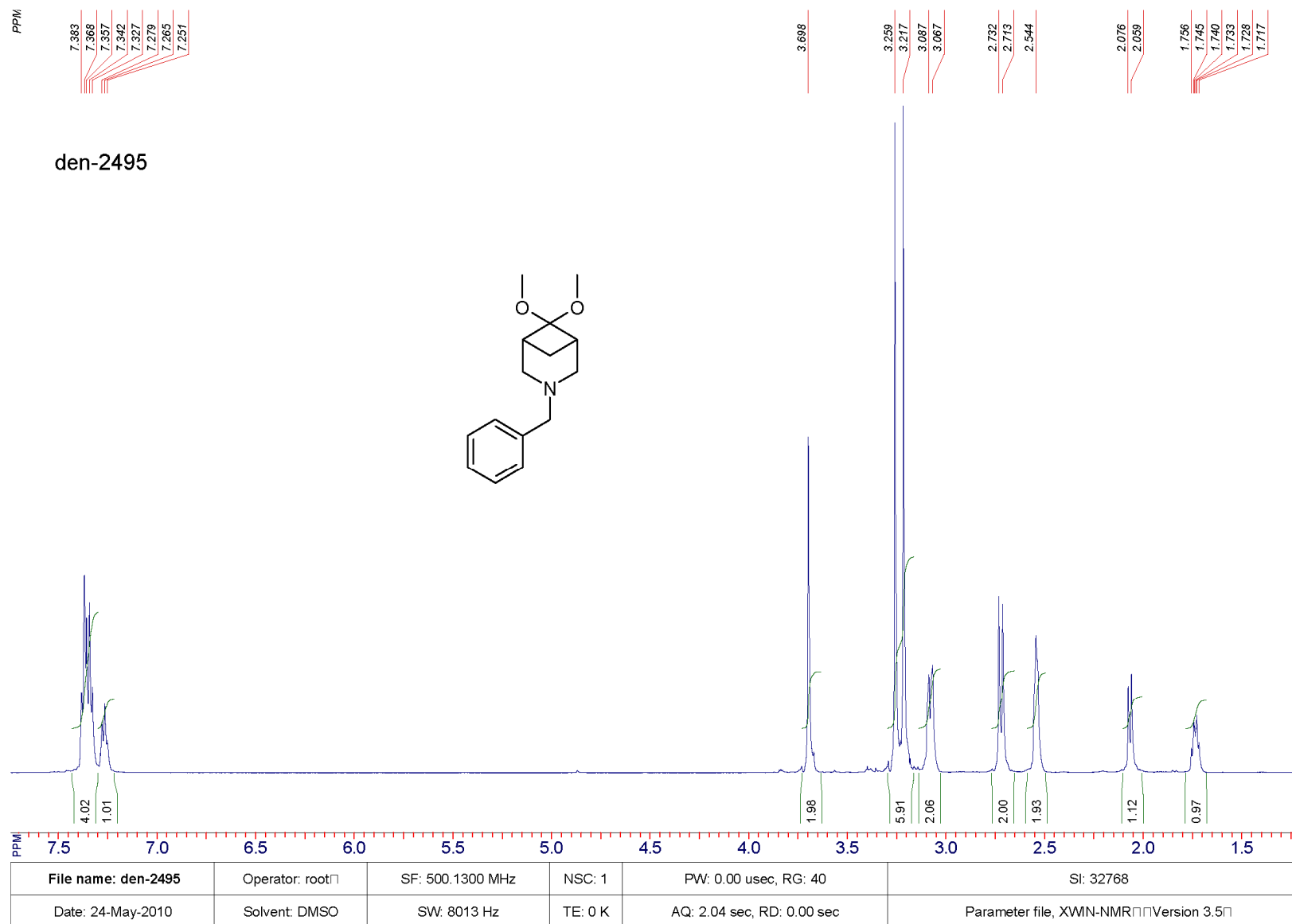


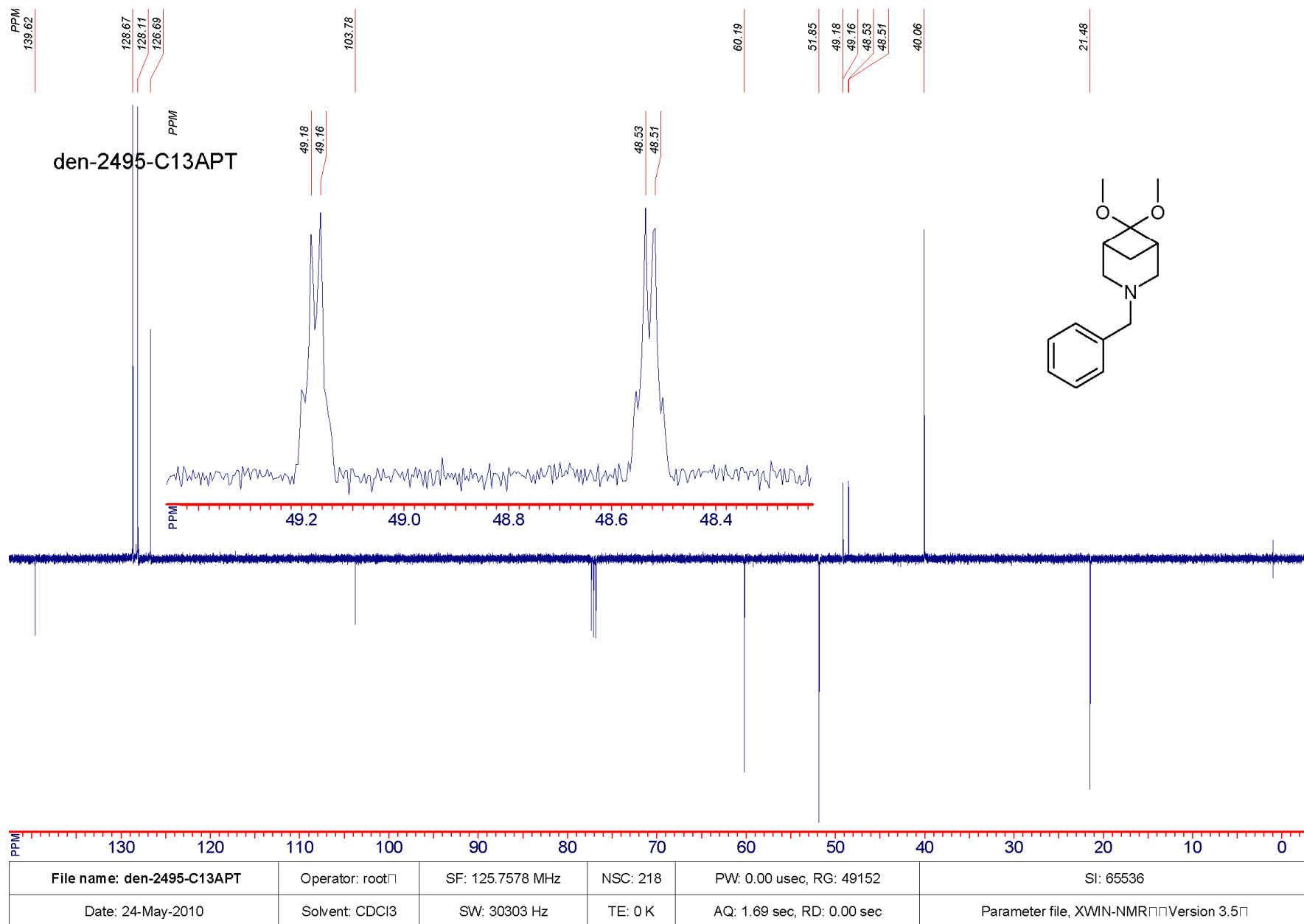
^1H NMR (500 MHz; CDCl_3 ; Me_4Si), δ : 1.02 (1H, d, $J = 8.5$ Hz, CHH of cyclobutane), 1.90 (1H, m, CHH of cyclobutane), 2.64 (2H, m, CH of cyclobutane), 2.80 (2H, d, $J = 10.0$ Hz, NCHH), 3.29 (2H, d, $J = 10.0$ Hz, NCHH), 3.67 (2H, s, NCH_2Ph), 4.72 (1H, m, CHNHCO), 7.35 - 7.75 (10H, m, $\text{Ph}+\text{Ph}$), 8.55 (1H, broad s, NH).

^{13}C NMR (125 MHz; CDCl_3 ; Me_4Si), δ : 31.92 (s, CH_2 of cyclobutane), 38.56 (s, CH of cyclobutane), 46.49 (s, CHNH), 54.66 (s, $\text{PhCH}_2\text{NCH}_2$), 61.72 (s, NCH_2Ph), 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).

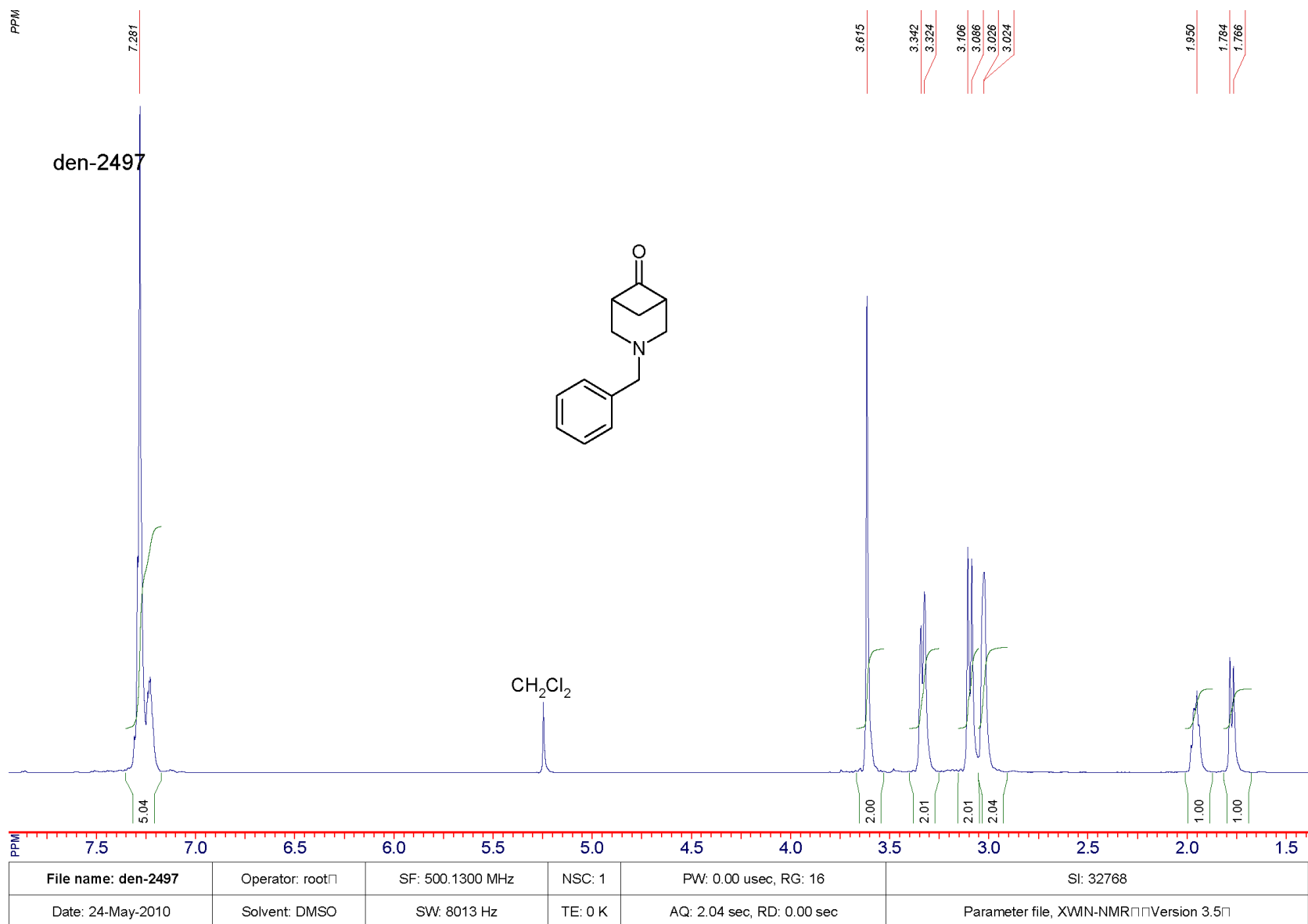
MS (m/z): 306.

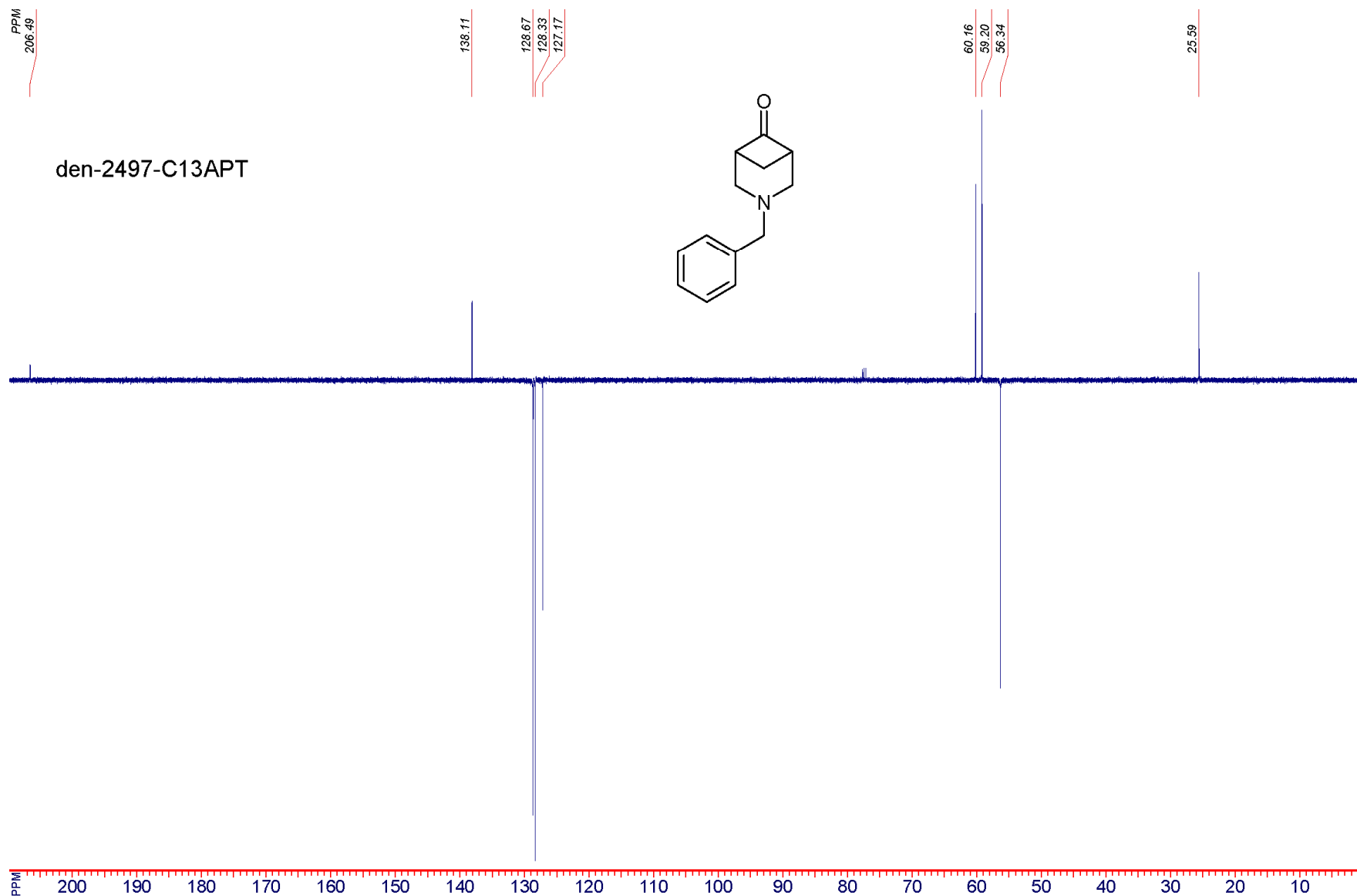
Compound 4





Compound 1



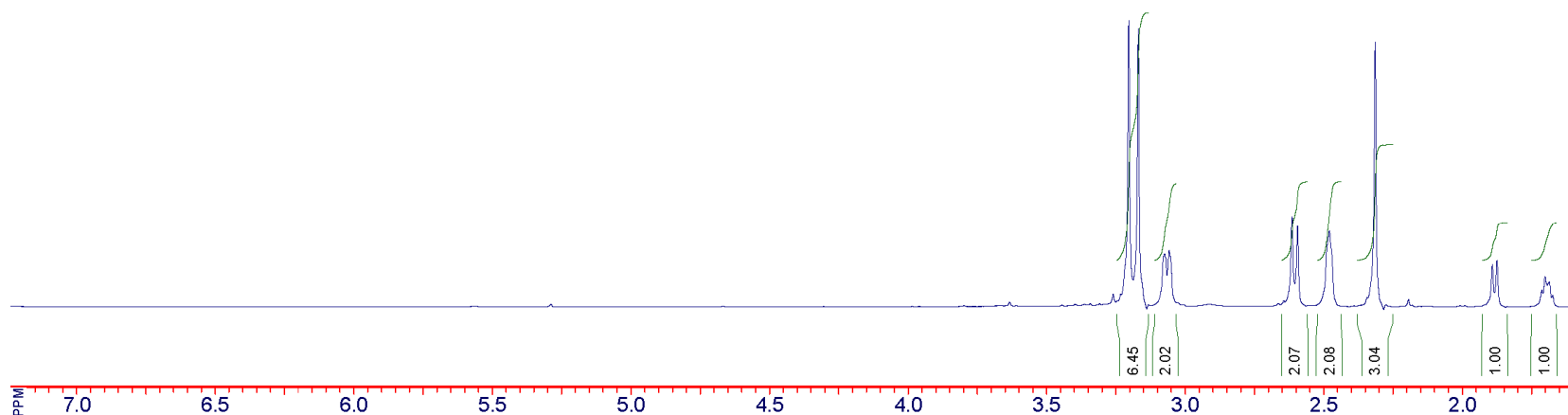
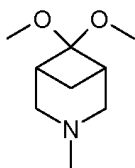


File name: den-2497-C13APT	Operator: root	SF: 125.7578 MHz	NSC: 61	PW: 0.00 usec, RG: 30720	SI: 65536
Date: 24-May-2010	Solvent: CDCl3	SW: 30303 Hz	TE: 0 K	AQ: 1.69 sec, RD: 0.00 sec	Parameter file, XWIN-NMRVersion 3.5

Compound 6

PPM

den-2601

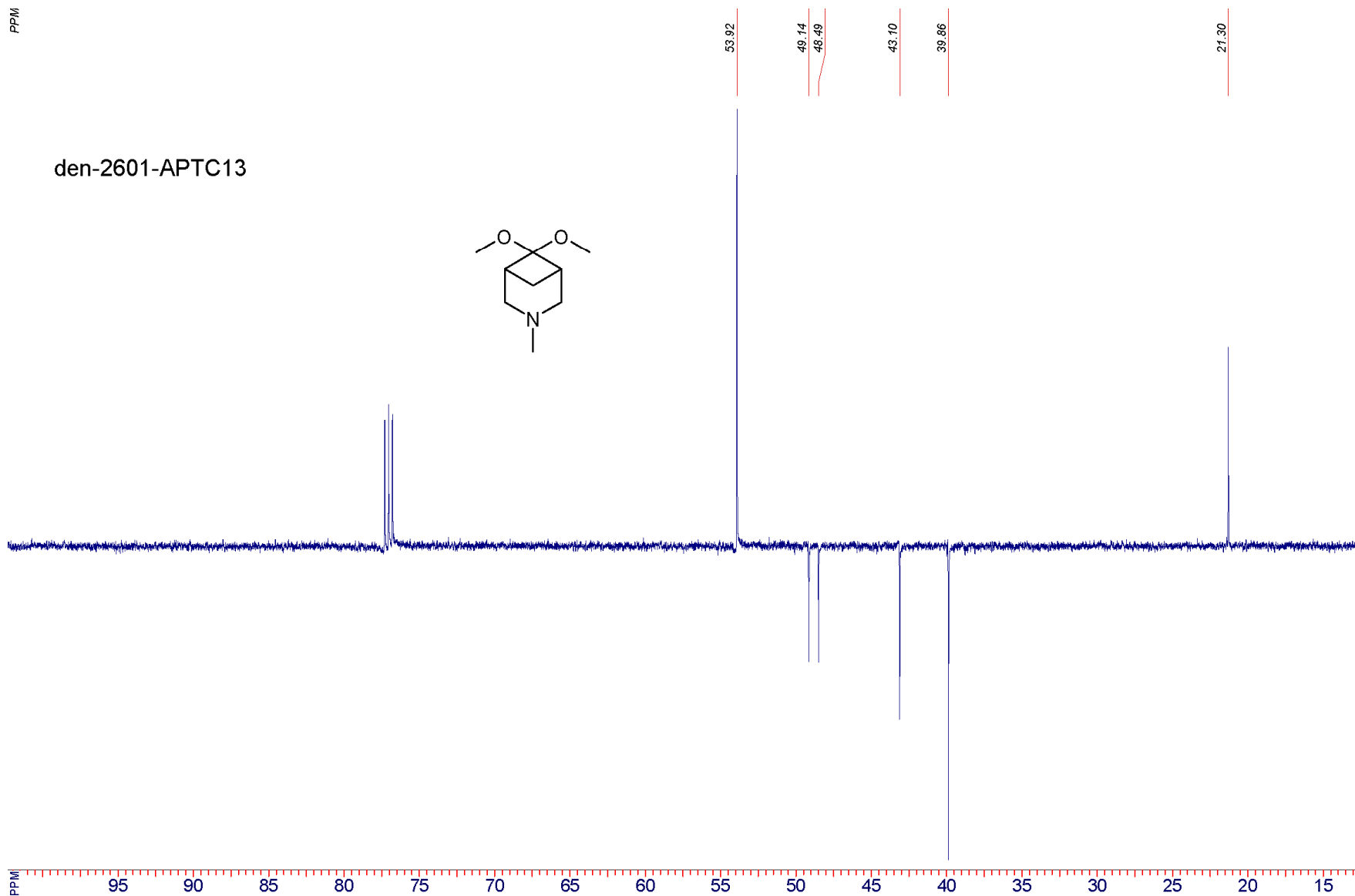
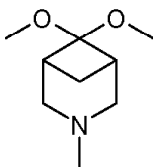


3.204	2.615	1.892
3.170	2.595	1.874
3.076	2.480	1.714
3.056	2.315	1.702
		1.686

File name: den-2601	Operator: root	SF: 500.0680 MHz	NSC: 1	PW: 0.00 usec, RG: 40	SI: 32768
Date: 04-Jun-2010	Solvent: CDCl3	SW: 8013 Hz	TE: 681 K	AQ: 2.04 sec, RD: 0.00 sec	Parameter file, XWIN-NMR Version 3.5

PPM

den-2601-APTC13

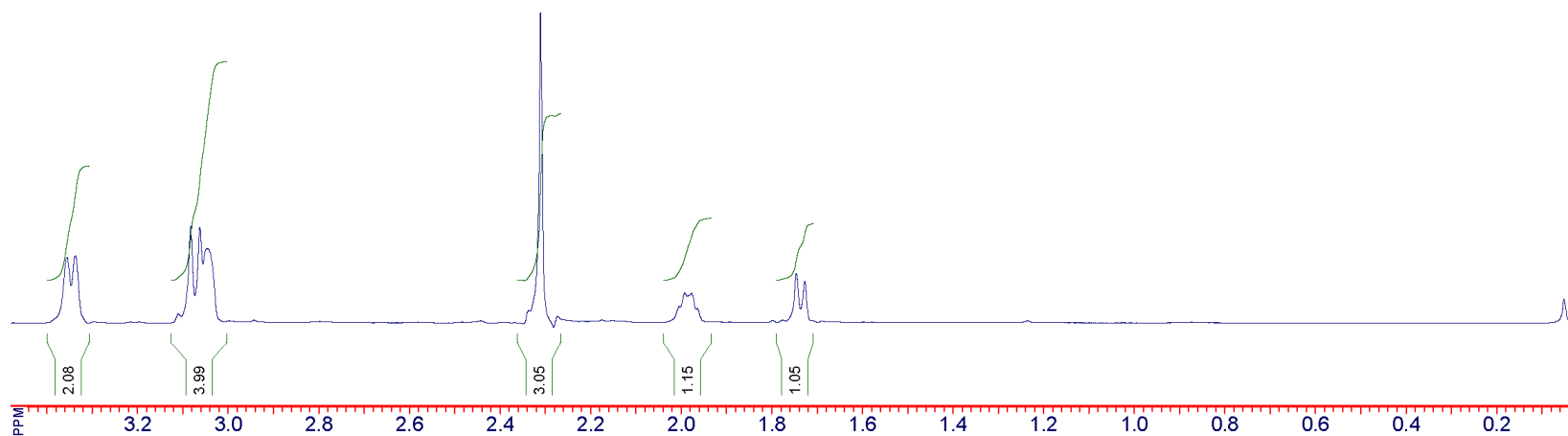
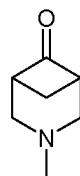


File name: den-2601-APTC13	Operator: root	SF: 125.7422 MHz	NSC: 234	PW: 0.00 usec, RG: 51200	SI: 65536
Date: 04-Jun-2010	Solvent: dmso	SW: 30303 Hz	TE: 681 K	AQ: 1.69 sec, RD: 0.00 sec	Parameter file, XWIN-NMR Version 3.5

Compound 5



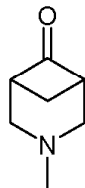
den-2614



File name: den-2614	Operator: root	SF: 500.0680 MHz	NSC: 1	PW: 0.00 usec, RG: 32	SI: 32768
Date: 09-Jun-2010	Solvent: CDCl3	SW: 8013 Hz	TE: 682 K	AQ: 2.04 sec, RD: 0.00 sec	Parameter file, XWIN-NMR Version 3.5

PPM
206.98

den-2614-APT

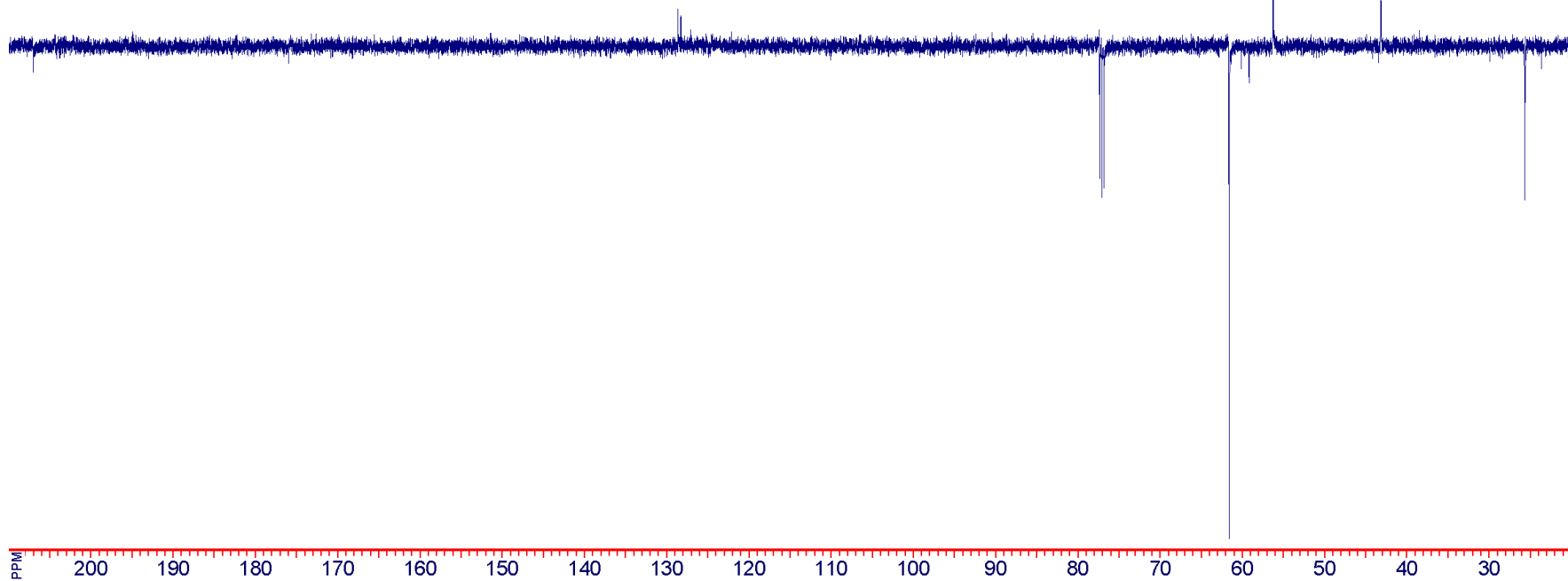


61.61

56.27

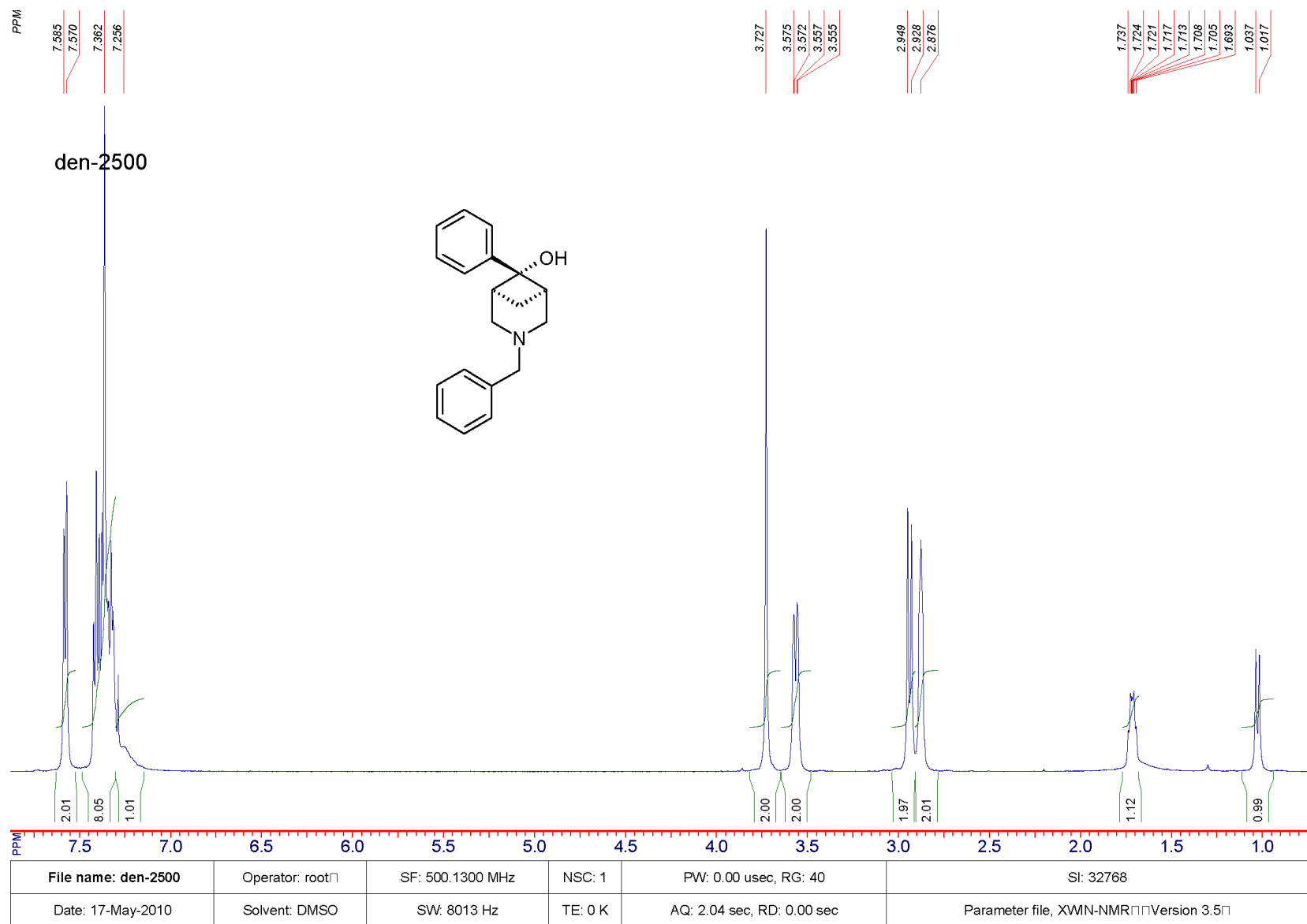
43.17

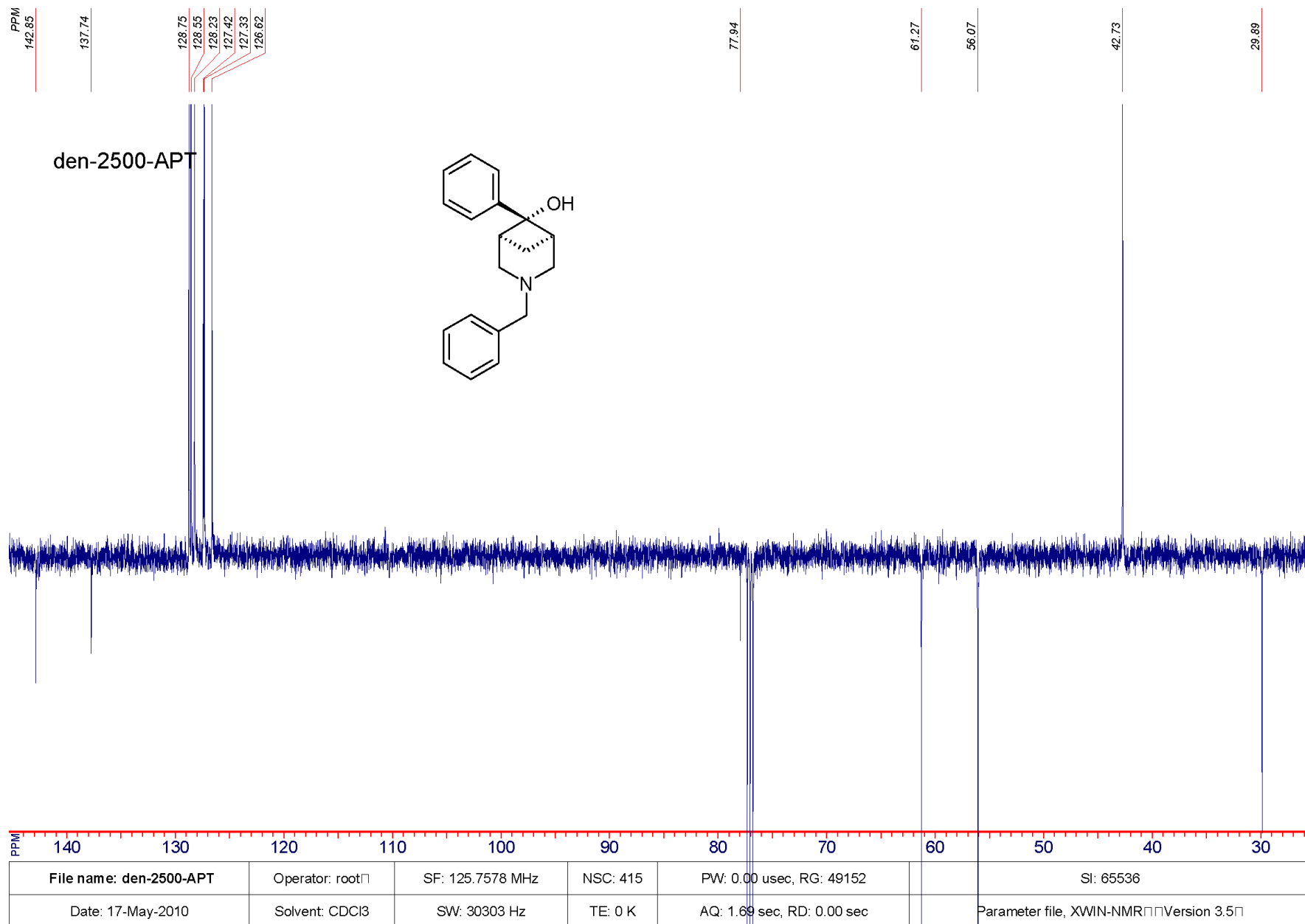
25.65



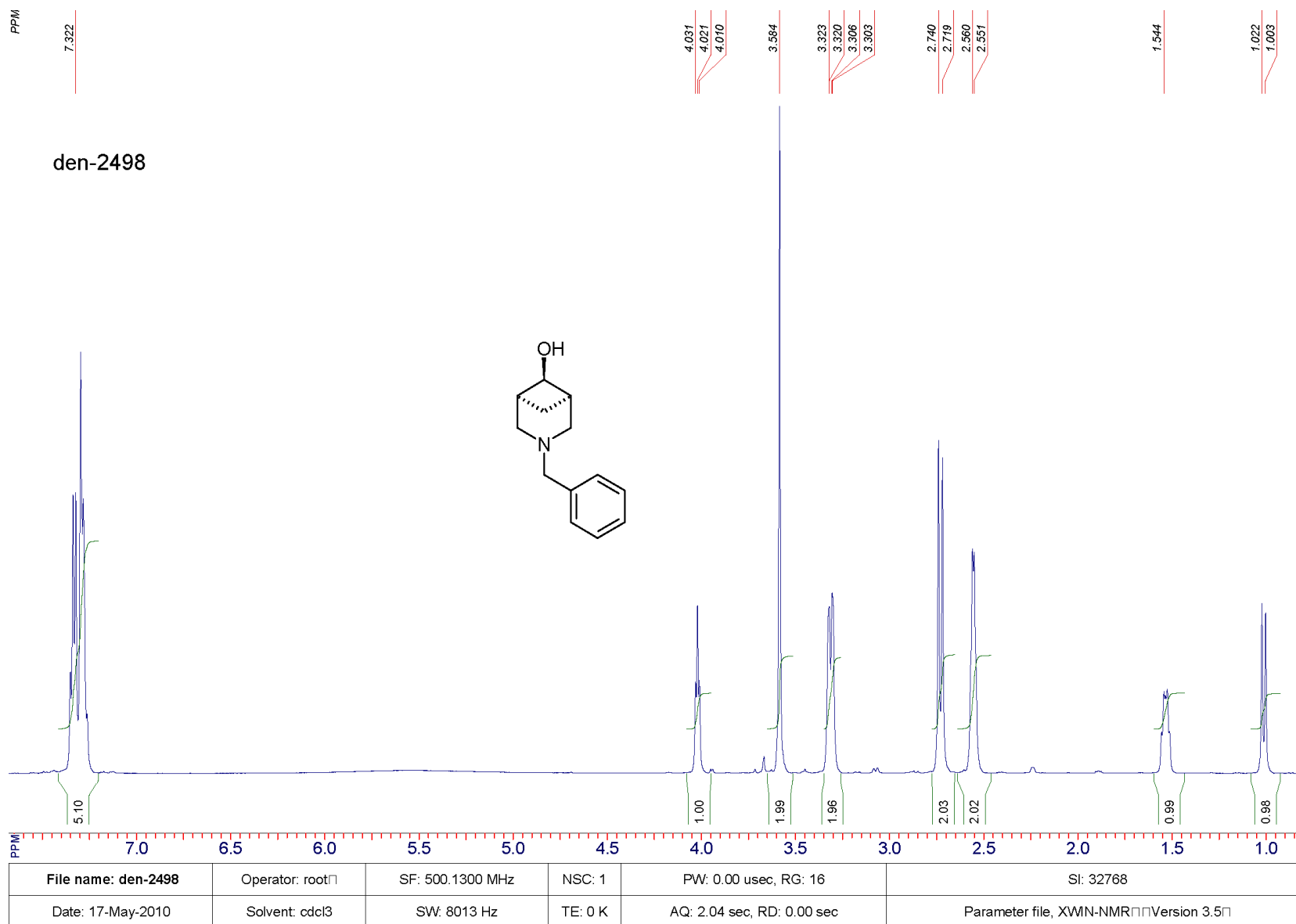
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Date: 09-Jun-2010	Solvent: dmso	SW: 30303 Hz	TE: 682 K	AQ: 1.69 sec, RD: 0.00 sec	Parameter file, XWIN-NMRVersion 3.5

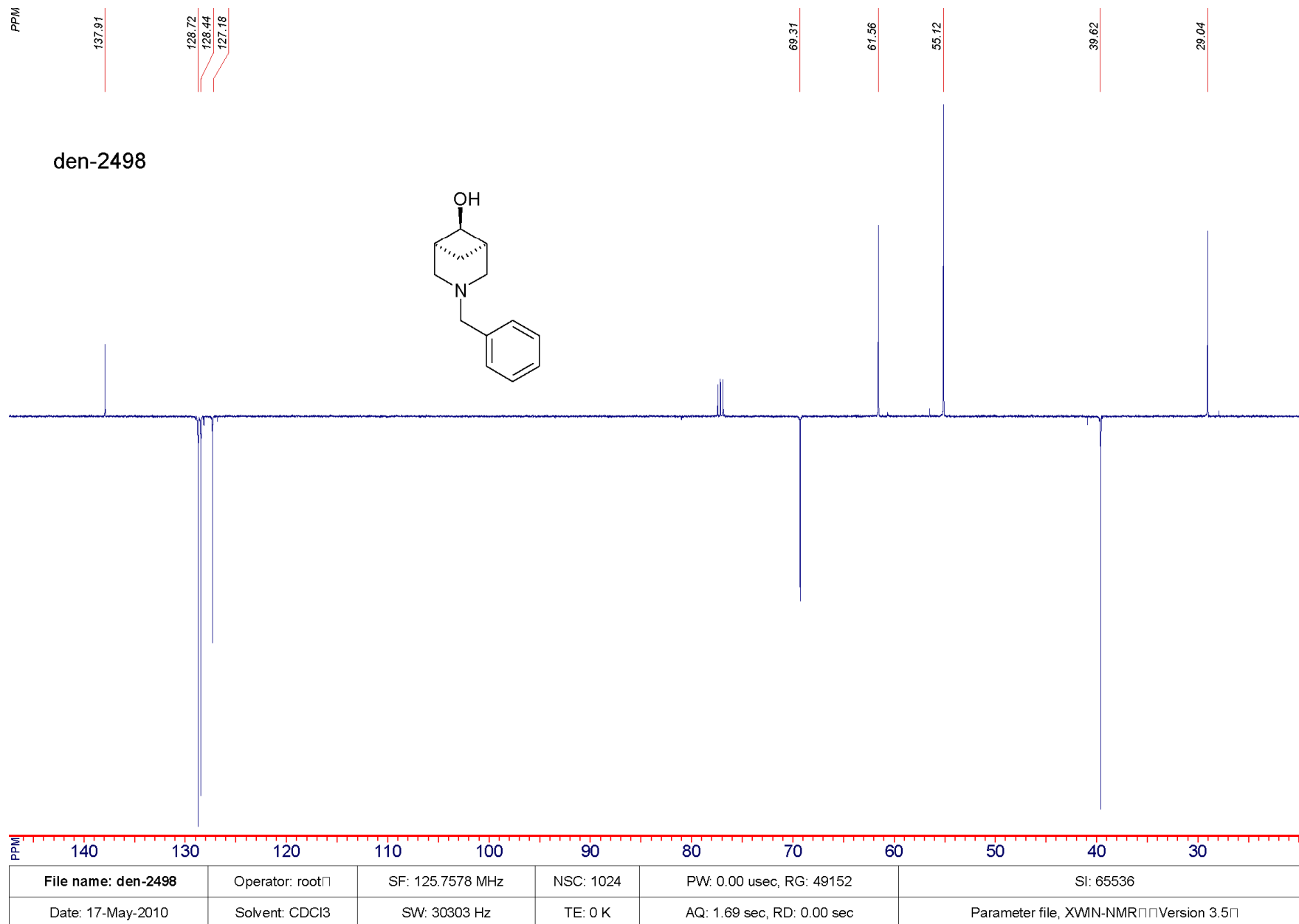
Compound 7



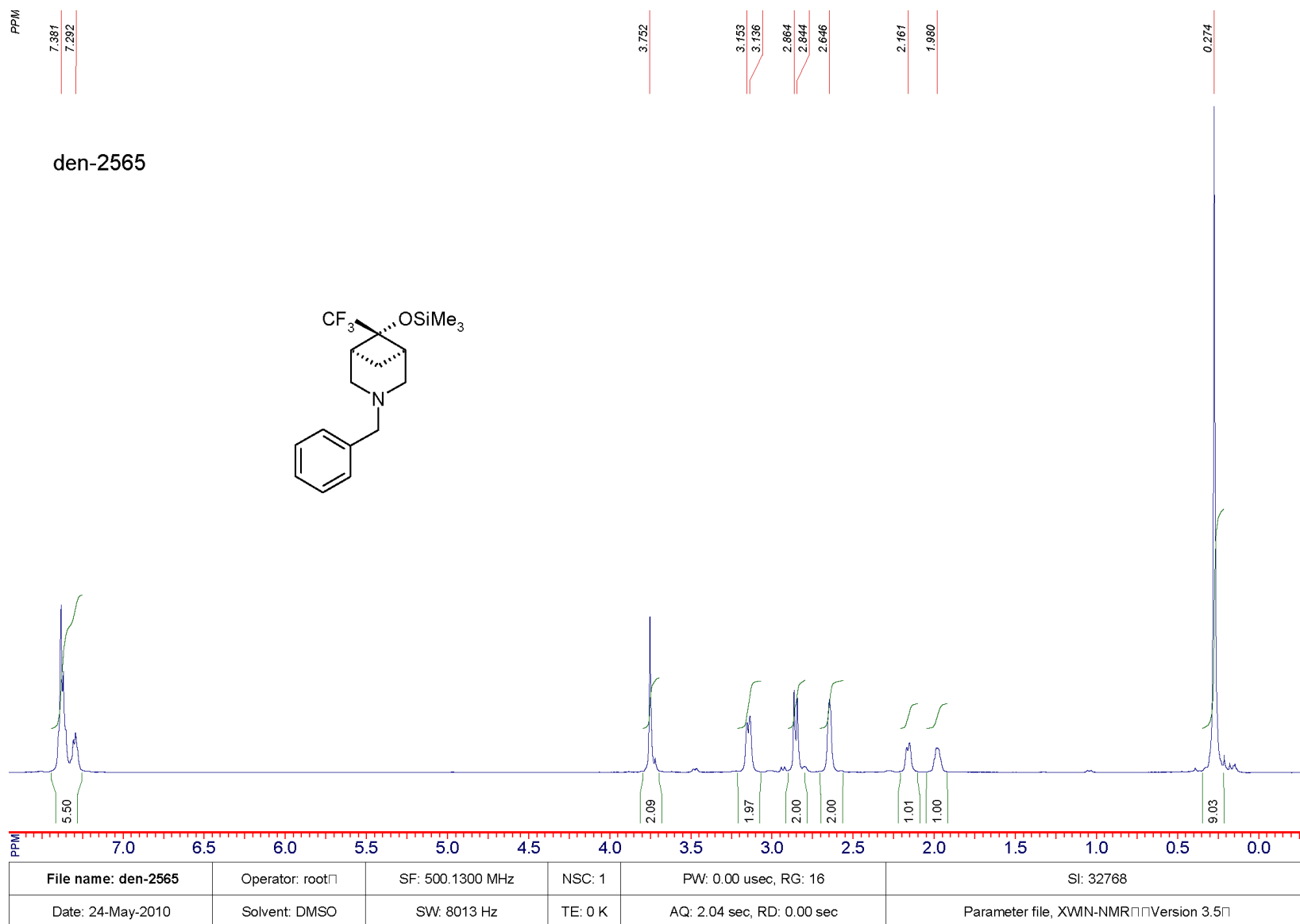


Compound 8



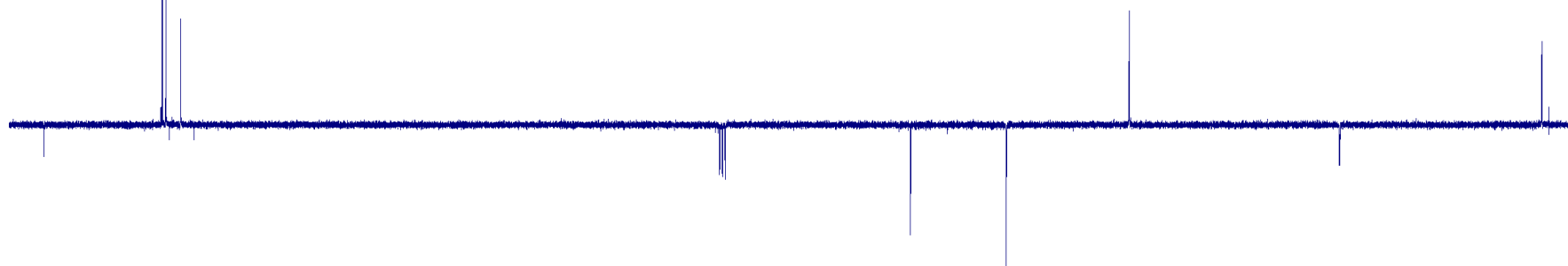
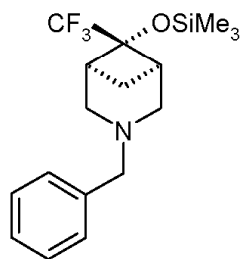


Compound 9





den-2565-C13APT



PPM	130	120	110	100	90	80	70	60	50	40	30	20	10
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

PPM
11.592

7.781
7.775
7.770
7.441
7.437
7.432
7.229

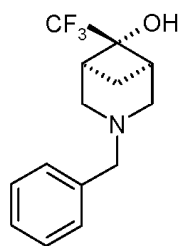
4.250
4.240

3.582
3.539
3.527
3.517
3.504

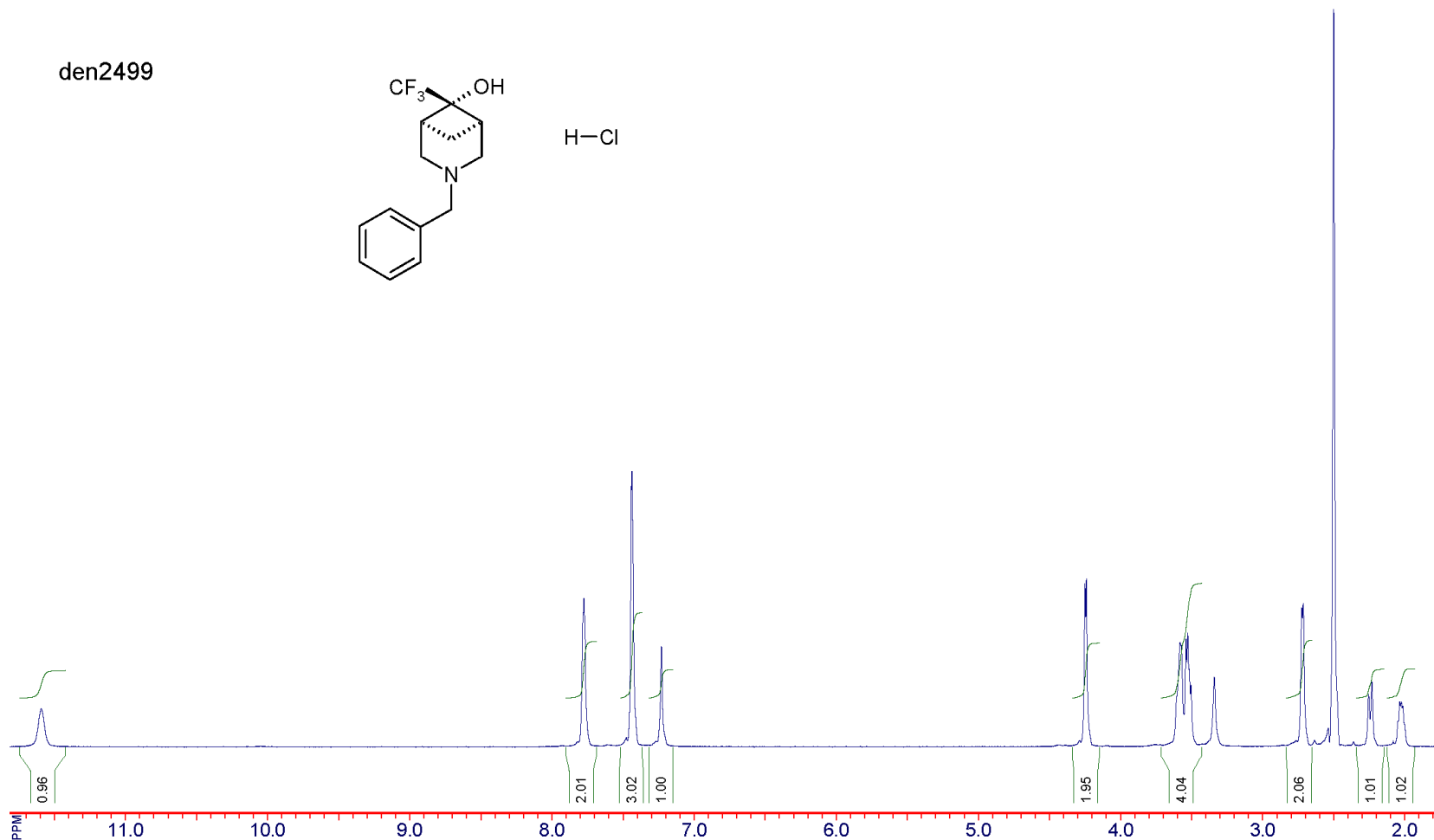
2.725
2.716

2.255
2.232
2.026

den2499

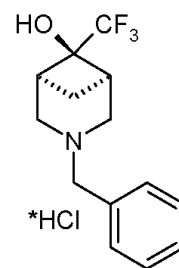
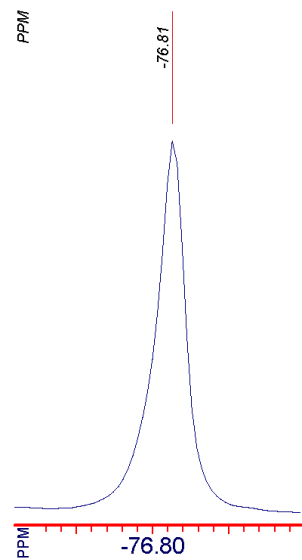


H—Cl



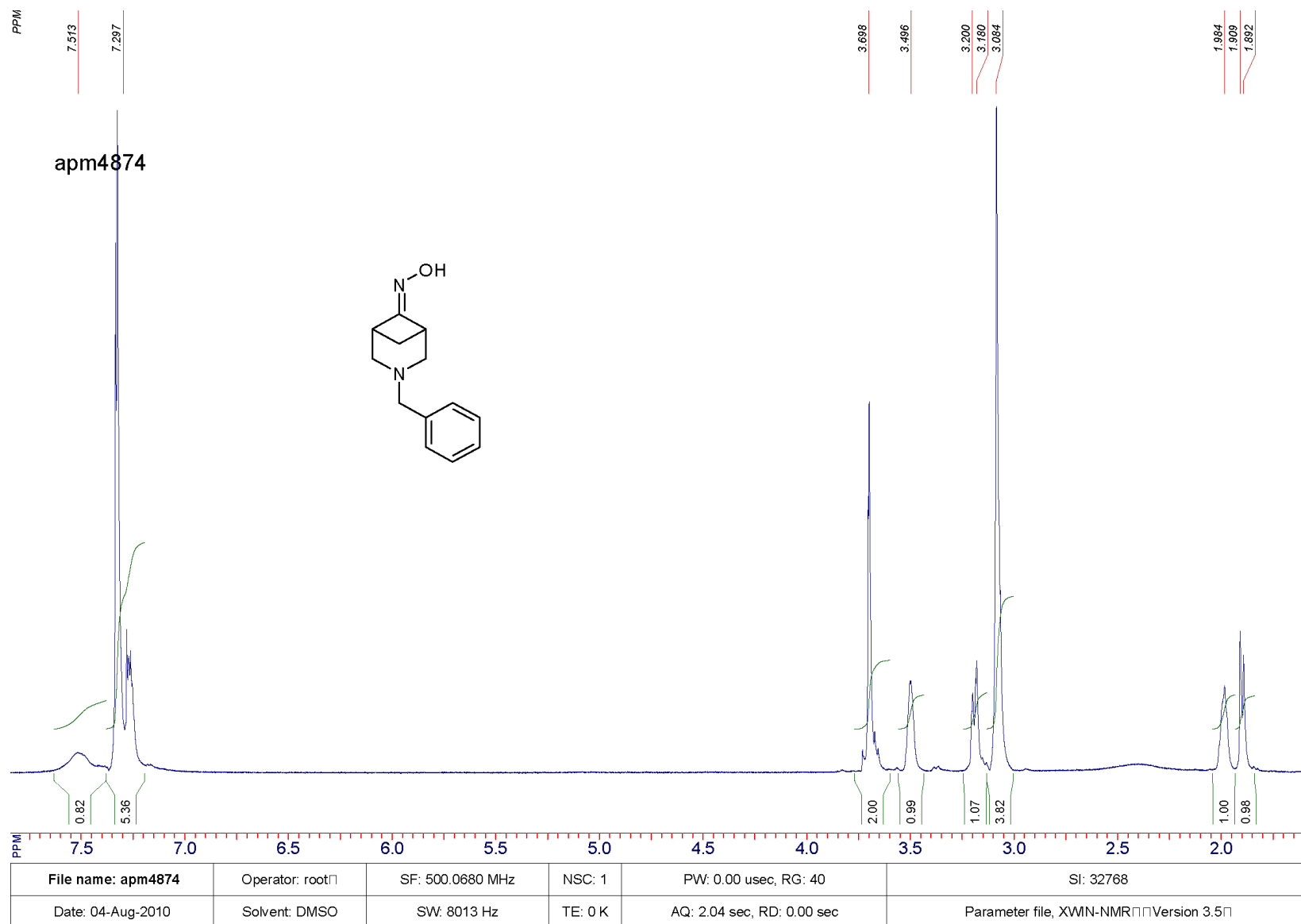
File name: den2499	Operator: root	SF: 500.1300 MHz	NSC: 1	PW: 0.00 usec, RG: 100	SI: 32768
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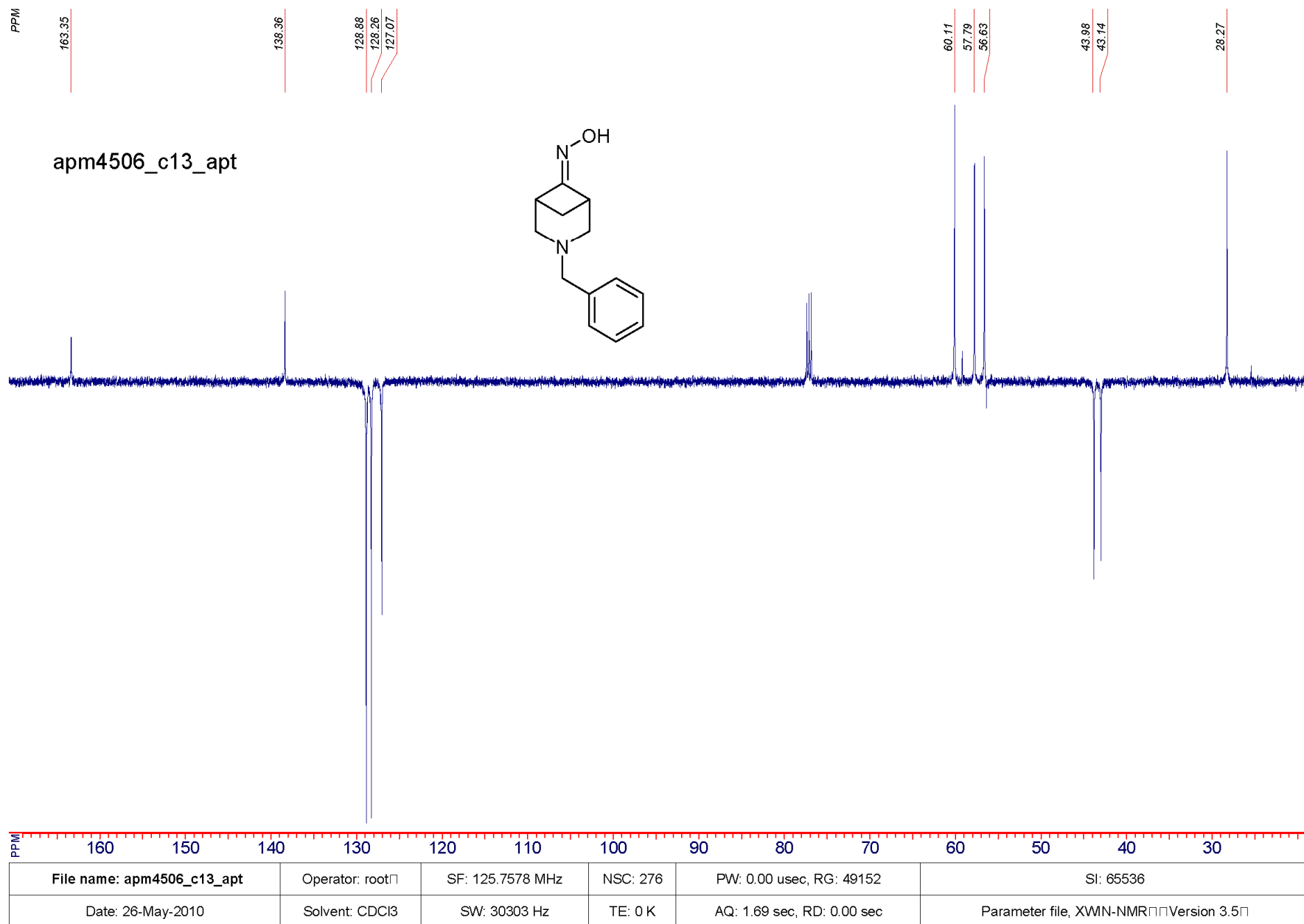
den2756-F19



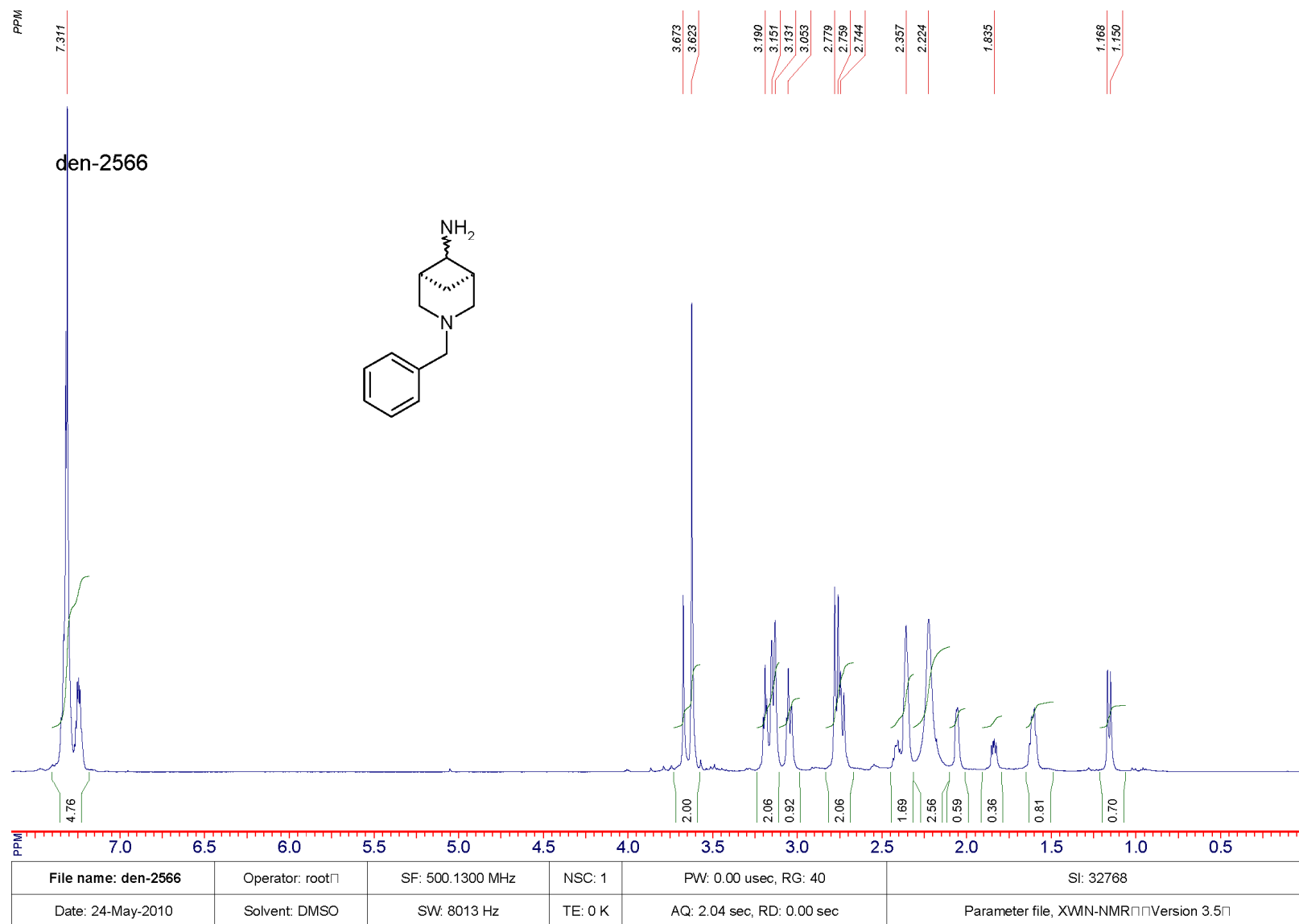
File name: den2756-F19	Operator: psm	SF: 470.5338 MHz	NSC: 4	PW: 0.00 usec, RG: 256	SI: 65536
Date: 06-Aug-2010	Solvent: DMSO	SW: 99010 Hz	TE: 0 K	AQ: 0.66 sec, RD: 0.00 sec	Parameter file, XWIN-NMR Version 3.5

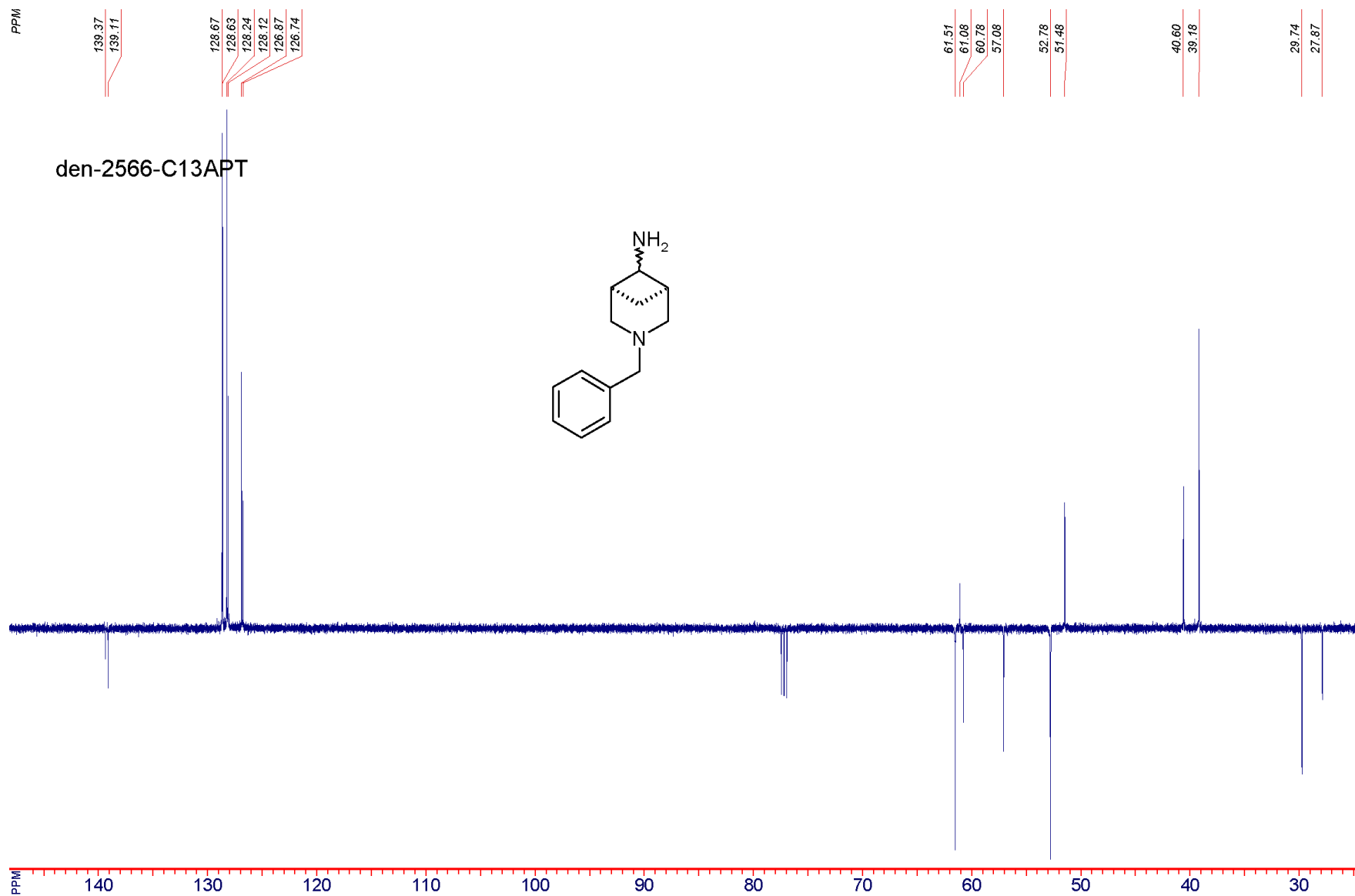
Compound 11





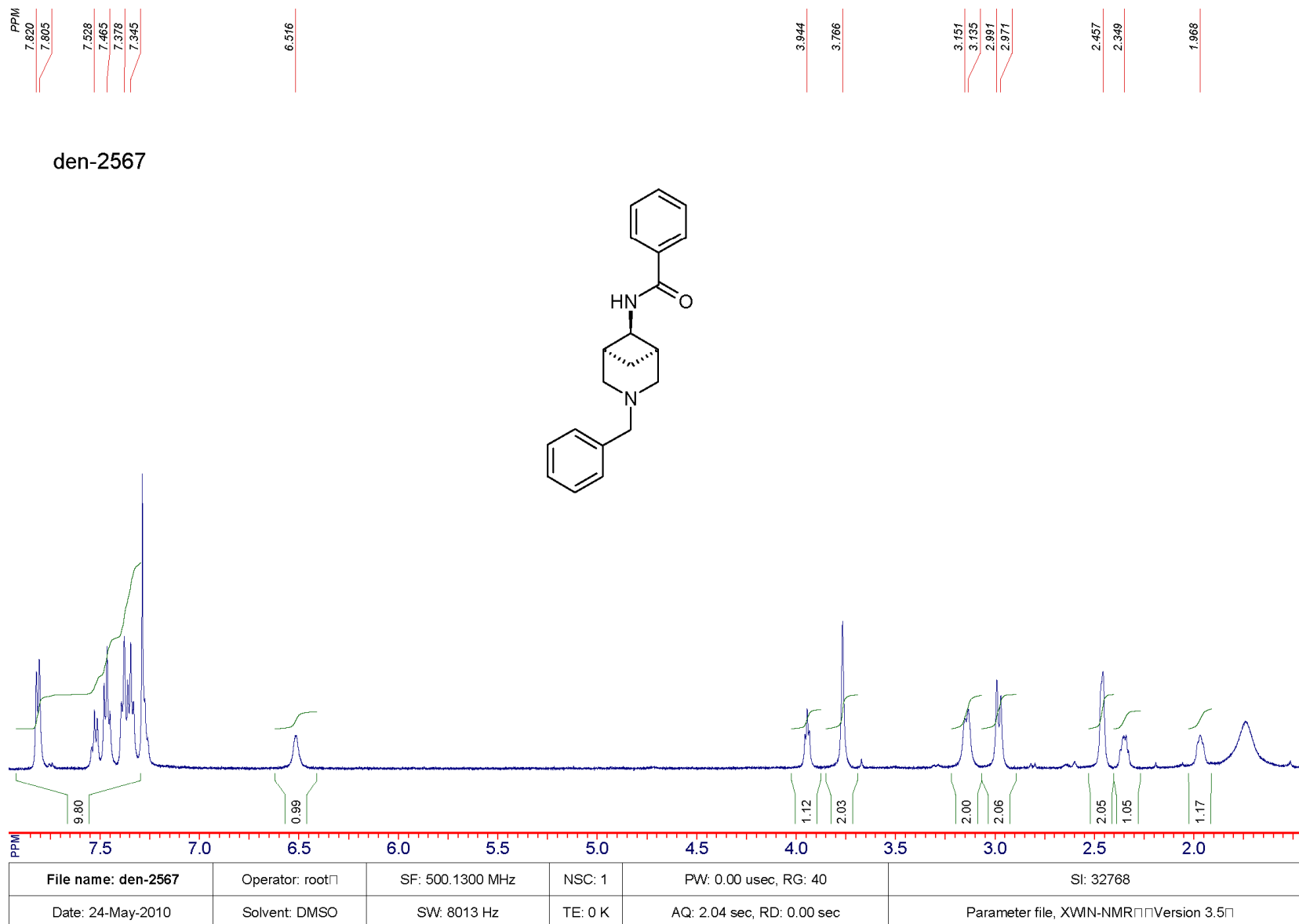
Compound 12

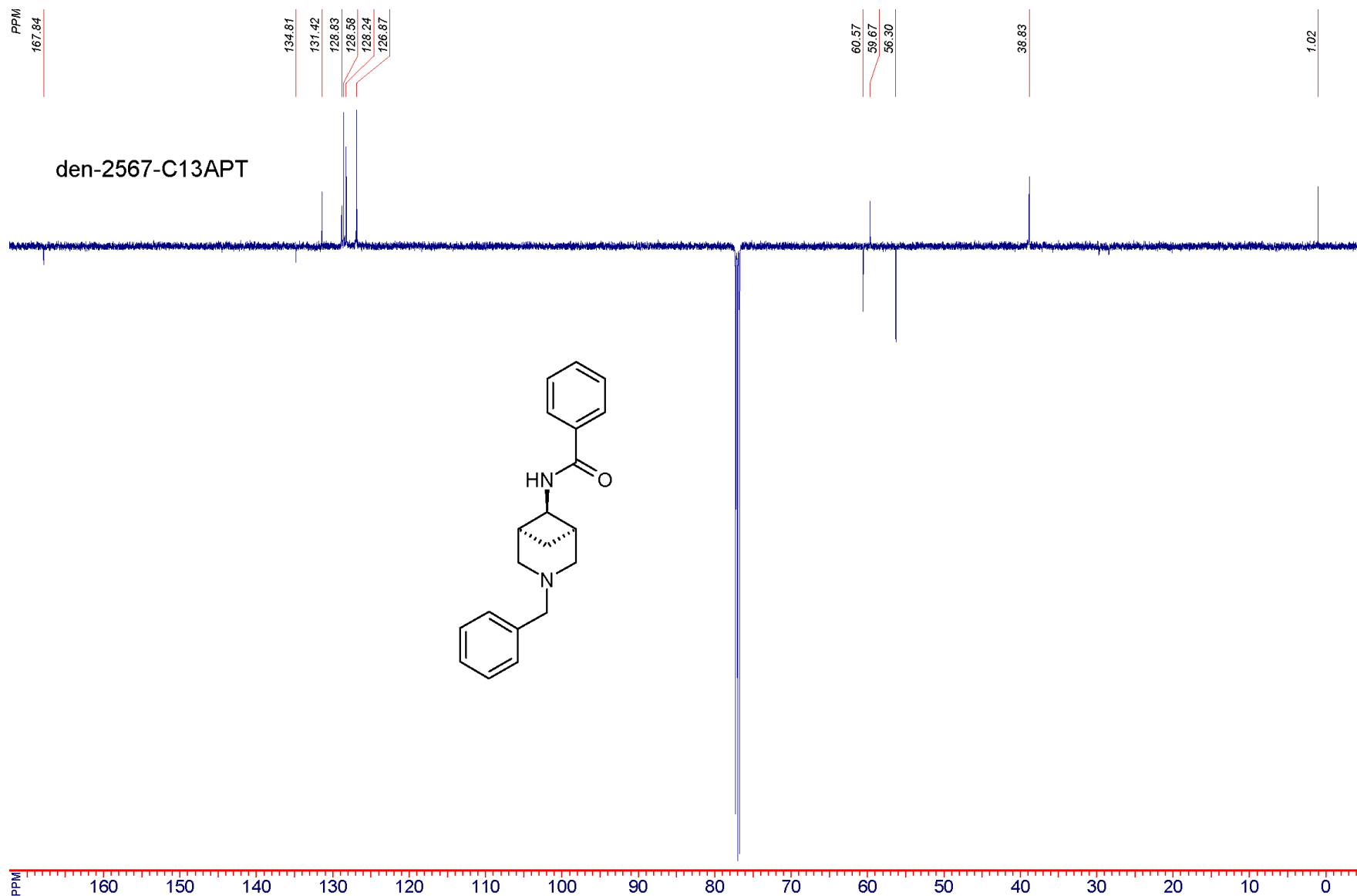




File name: den-2566-C13APT	Operator: root	SF: 125.7578 MHz	NSC: 277	PW: 0.00 usec, RG: 49152	SI: 65536
Date: 24-May-2010	Solvent: CDCl3	SW: 30303 Hz	TE: 0 K	AQ: 1.69 sec, RD: 0.00 sec	Parameter file, XWIN-NMR Version 3.5

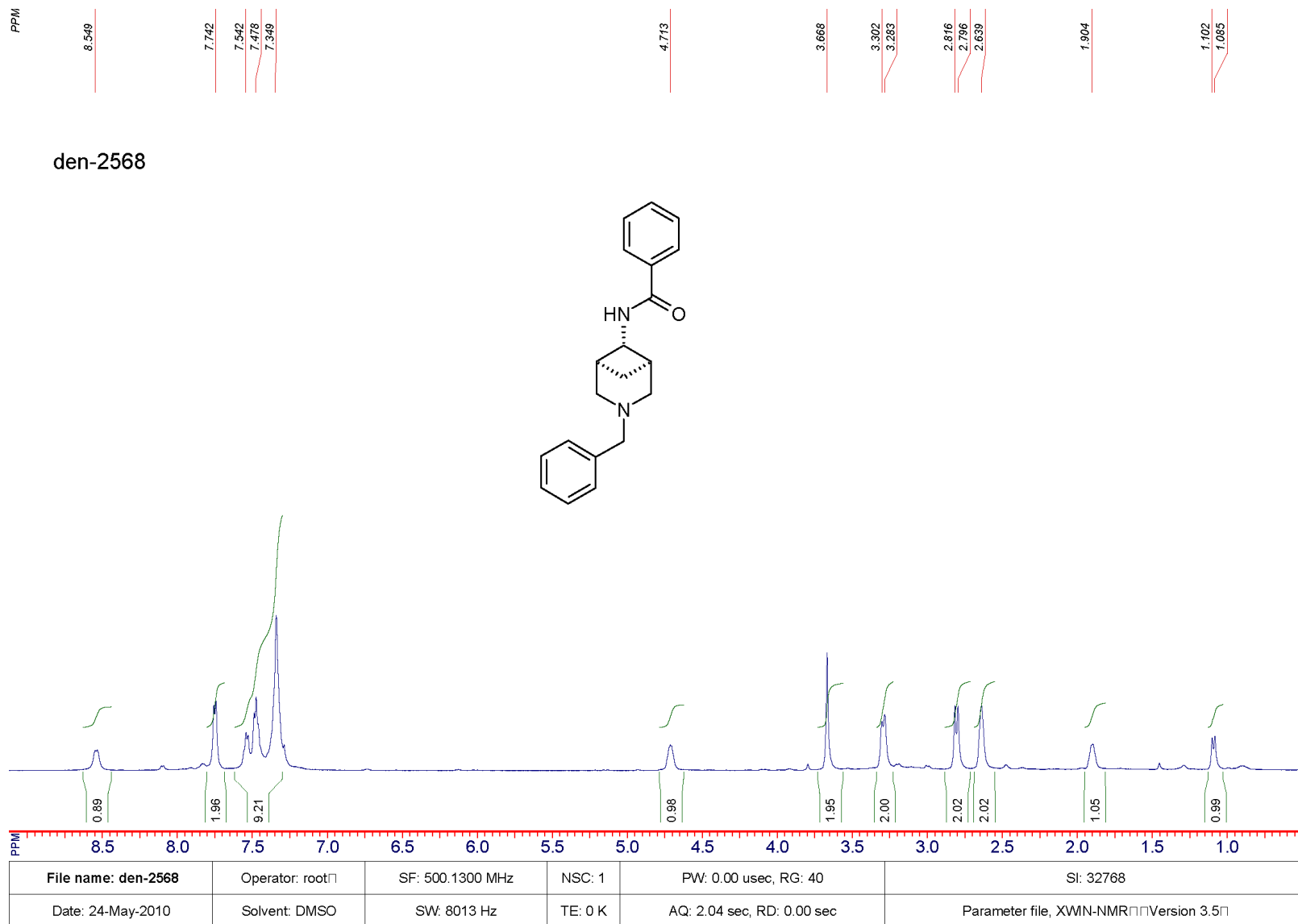
Compound 13a

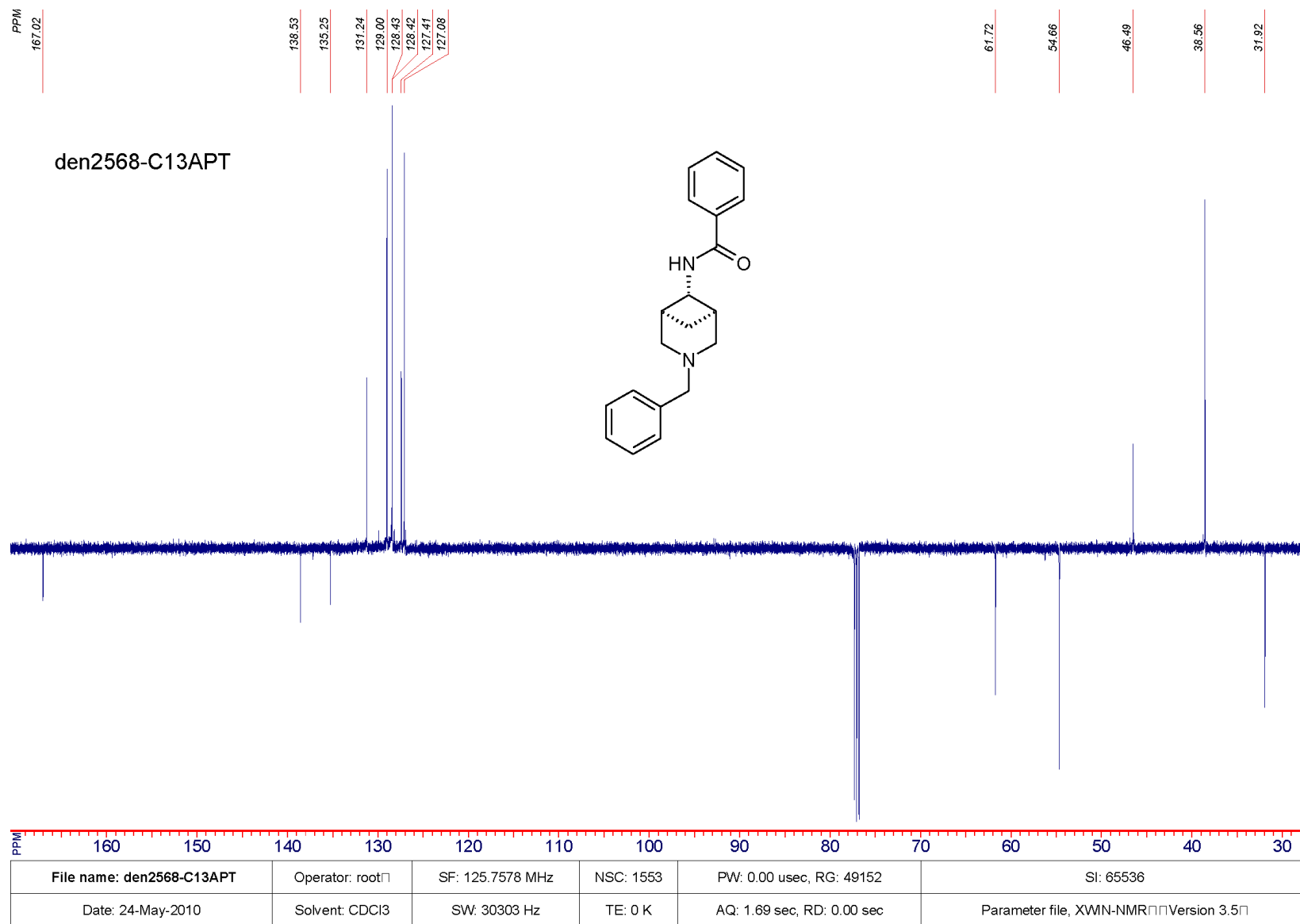




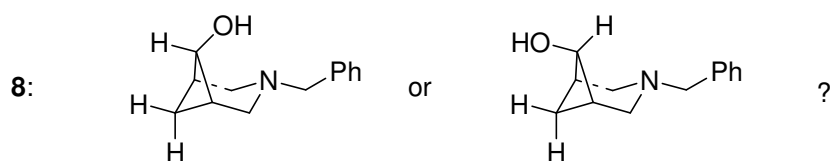
File name: den-2567-C13APT	Operator: root	SF: 125.7578 MHz	NSC: 3072	PW: 0.00 usec, RG: 49152	SI: 65536
Date: 24-May-2010	Solvent: CDCl3	SW: 30303 Hz	TE: 0 K	AQ: 1.69 sec, RD: 0.00 sec	Parameter file, XWIN-NMR Version 3.5

Compound 13b





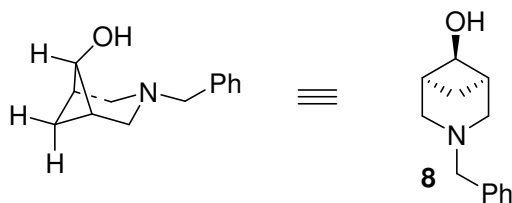
2) Determination of the stereoconfiguration of alcohol **8**



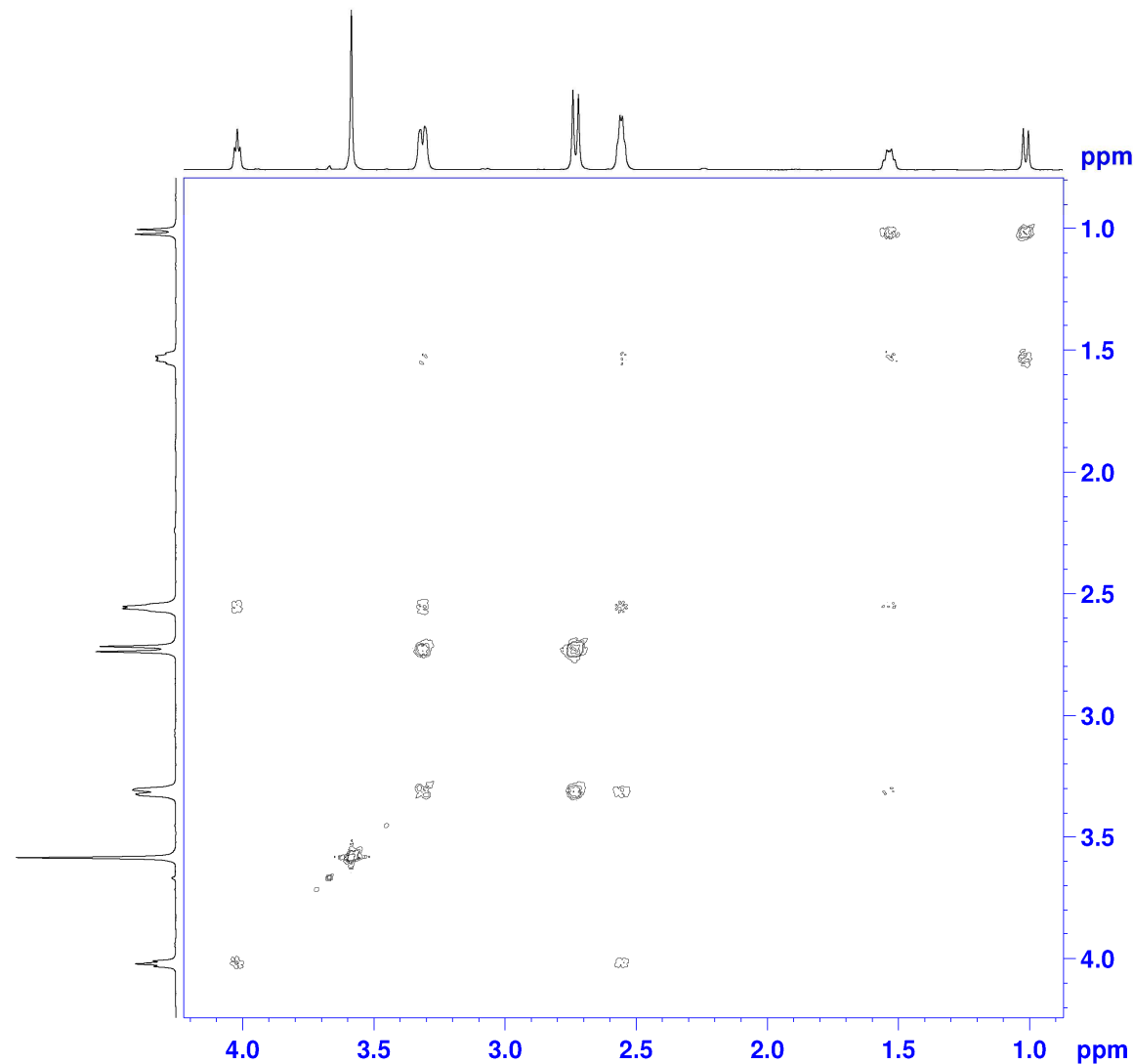
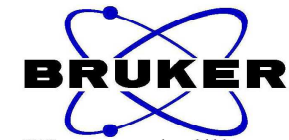
The stereoconfiguration of alcohol **8** was determined by NOESY-experiments:



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.



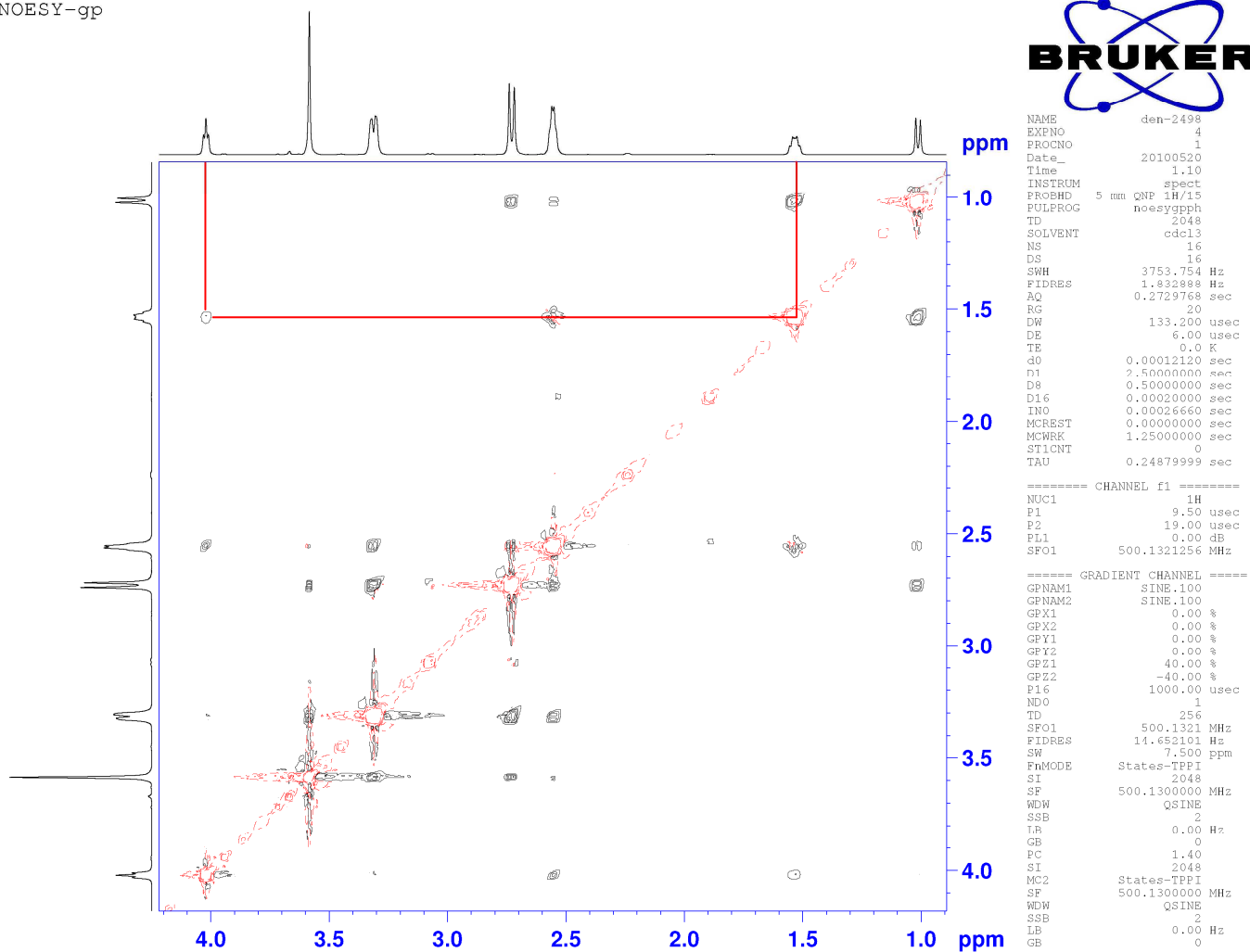
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EXPNO          3
PROCNO         1
Date_         20100520
Time          0.58
INSTRUM       spect
PROBHD        5 mm QNP 1H/15
PULPROG       cosygpgpf
TD            1024
SOLVENT       CDCl3
NS             1
DS            16
SMH           2003.205 Hz
FIDRES        1.956255 Hz
AQ            0.2558900 sec
RG             16
DW            249.600 usec
DE             6.00 usec
TE            681.5 K
d0            0.00000300 sec
D1            2.00000000 sec
d13           0.00000400 sec
D16           0.00050000 sec
IN0           0.00049986 sec
MCREST        0.00000000 sec
MCWRK         2.00000000 sec

===== CHANNEL f1 =====
NUC1           1H
P0             9.50 usec
P1             9.50 usec
PL1            0.00 dB
SF01          500.1312503 MHz

===== GRADIENT CHANNEL =====
GPNAM1        SINE.100
GPNAM2        SINE.100
GPX1           0.00 %
GPX2           0.00 %
GPY1           0.00 %
GPY2           0.00 %
GPZ1           10.00 %
GPZ2           10.00 %
P16            1000.00 usec
ND0             1
TD             256
SF01          500.1313 MHz
FIDRES        7.814649 Hz
SW             4.000 ppm
FnMODE        QF
SI             1024
SF           500.1300000 MHz
WDW            SINE
SSB             0
LB             0.00 Hz
GB             0
PC             1.40
SI             1024
MC2            QF
SF           500.1300000 MHz
WDW            SINE
SSB             0
LB             0.00 Hz
GB             0
  
```

NOESY-gp



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

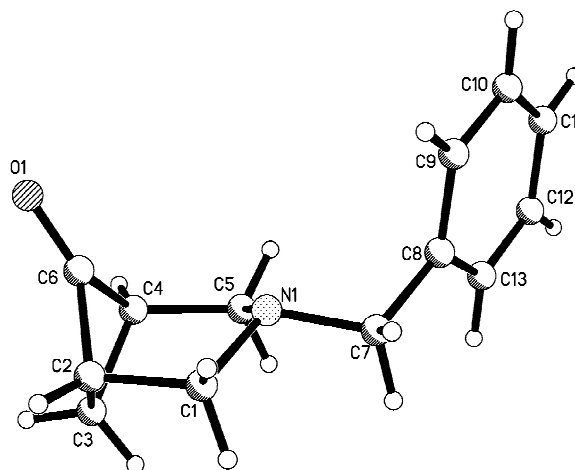


Figure S1. X-ray crystal structure of ketone **1**.

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° . The nitrogen atom has pyramidal configuration, the sum of the bond angles centered at this atom is 336.4° .

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**

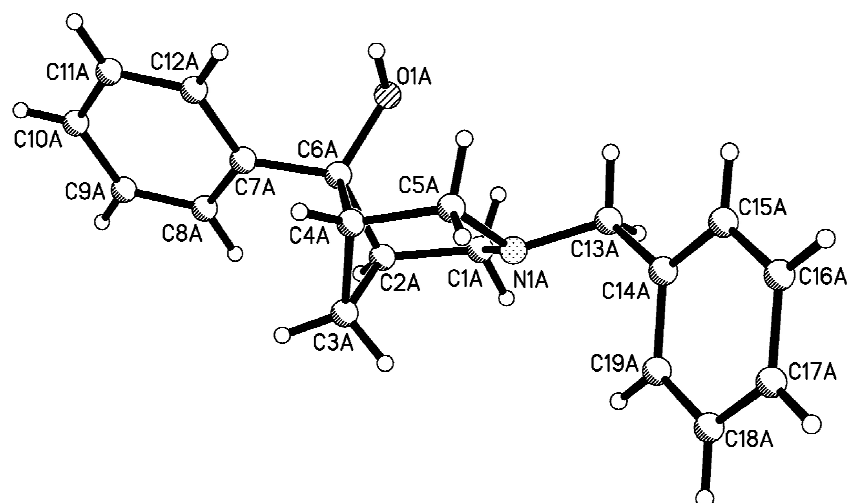


Figure S2. Molecular structure of compound **7** according to X-ray diffraction data.

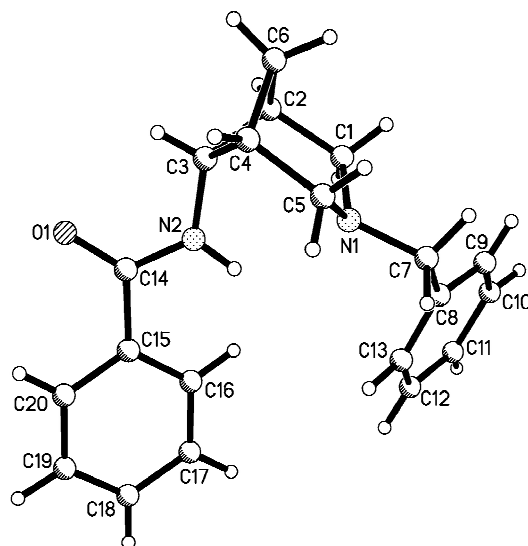


Figure S3. Molecular structure of compound **13a** according to X-ray diffraction data.

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 Å, -1.06 Å and 1.07 Å, respectively, for **7-A**, 0.42 Å, 1.05 Å and -1.06 Å, respectively, for **7-B**, 0.45 Å, -1.05 Å and 1.07 Å for **7-C**, 0.46 Å, 1.05 Å and -1.04 Å, 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**

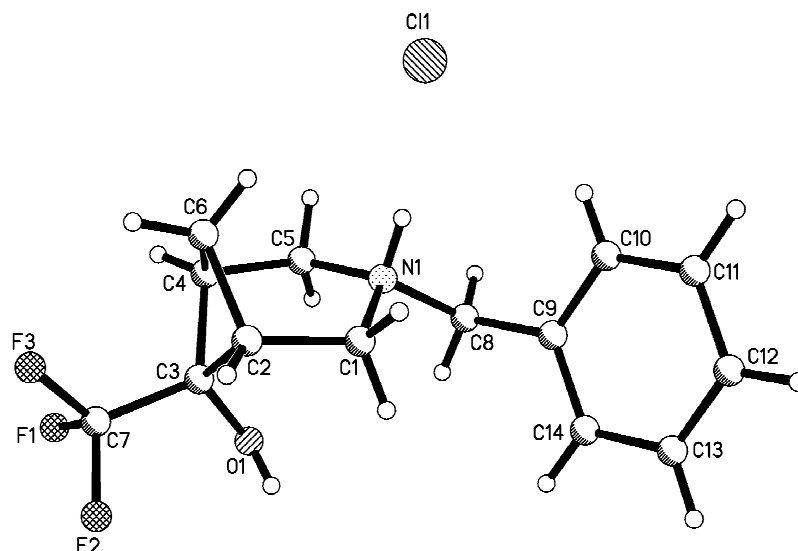


Figure S4. Molecular structure of compound **10** according to X-ray diffraction data.

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 Csp³-N bond 1.469 Å indicating prtonation 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 $-50.9(2)^\circ$ and it is turned relatively the N-Csp³ exocyclic bond (the N1-C8-C9-C10 torsion angle in **10** is $-68.2(2)^\circ$).

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 $28.2(2)^\circ$). 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 $157.0(1)^\circ$ and $164.3(1)^\circ$, 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 α radiation, CCD-detector, ω -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). The deposition numbers are given in Table S1.

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

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