

## Complementary Chemoenzymatic Routes to Both Enantiomers of Febrifugine

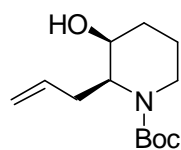
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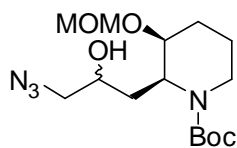
**General information:** Solvents were distilled from appropriate drying agents prior to use and stored under nitrogen. Chemicals were purchased from Sigma-Aldrich and used as received, unless stated otherwise. Reactions were carried out under an inert atmosphere of dry nitrogen or argon. Standard syringe techniques were applied for the transfer of dry solvents and air- or moisture-sensitive reagents. Reactions were followed using thin layer chromatography (TLC) on silica gel-coated plates (Merck 60 F254) with the indicated solvent mixture. Detection was performed with UV-light, and/or by charring at ~150 °C after dipping into a solution of either 2% anisaldehyde in ethanol/H<sub>2</sub>SO<sub>4</sub> or (NH<sub>4</sub>)<sub>6</sub>Mo<sub>7</sub>O<sub>24</sub>·4H<sub>2</sub>O (25 g/L) and (NH<sub>4</sub>)<sub>4</sub>Ce(SO<sub>4</sub>)<sub>4</sub>·2H<sub>2</sub>O (10 g/L) in 10% H<sub>2</sub>SO<sub>4</sub>. Melting points were analyzed with a Büchi melting point B-545. IR spectra were recorded on an ATI Mattson Genesis Series FTIR spectrometer, or a Bruker Tensor 27 FTIR spectrometer. Gas chromatography (GC) was performed on a Hewlett Packard 5890, containing a HP1 column (25 m x 0.32 mm x 0.17 µm), FID detection, and equipped with a HP3393A integrator. NMR spectra were recorded on a Bruker DMX 300 (300 MHz), and a Varian 400 (400 MHz) spectrometer in CDCl<sub>3</sub> solutions (unless otherwise reported). Chemical shifts are given in ppm with respect to tetramethylsilane (TMS) as internal standard. Coupling constants are reported as *J*-values in Hz. Column or flash chromatography was carried out using ACROS silica gel (0.035–0.070 mm, and ca 6 nm pore diameter). Optical rotations were determined with a Perkin Elmer 241 polarimeter. High resolution mass spectra were recorded on a JEOL AccuTOF (ESI), or a MAT900 (EI, CI, and ESI).

### (2*S*,3*S*)-2-Allyl-3-hydroxypiperidine-1-carboxylic acid *tert*-butyl ester (**14**)



To a solution of **3** (906 mg, 3.36 mmol) in THF (30 mL) was added LiAlH<sub>4</sub> (319 mg, 8.4 mmol) and the reaction was stirred overnight at 70 °C. The reaction was carefully quenched by addition of H<sub>2</sub>O (597 mg, 1.3 mg/mg LiAlH<sub>4</sub>), aqueous NaOH (15% in H<sub>2</sub>O, 597 mg, 1.3 mg/mg LiAlH<sub>4</sub>) and again H<sub>2</sub>O (1492 mg, 3.25 mg/mg LiAlH<sub>4</sub>). The resulting suspension was stirred vigorously for 10 min, filtrated and the filtrate was concentrated *in vacuo*. The residue was dissolved in aqueous 0.5 M NaOH (50 mL) and (Boc)<sub>2</sub>O (1.47 g, 6.74 mmol) was added. After stirring overnight the reaction was quenched by addition of aqueous 0.1 M HCl (400 mL) followed by extraction with EtOAc (4 x 200 mL). The combined organic layers were washed with saturated aqueous NaHCO<sub>3</sub> (300 mL) and brine (300 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtrated and concentrated *in vacuo*. Flash chromatography (1:9-1:2 EtOAc:heptane) afforded product **14** as a colorless oil (595 mg, 2.46 mmol, 73%). [α]<sub>D</sub><sup>20</sup> +48 (c 0.28, CH<sub>2</sub>Cl<sub>2</sub>). IR (film) 3386, 2929, 1688, 1661, 1418, 1364, 1248, 1176, 1150 cm<sup>-1</sup>. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>, rotamers) δ 5.81-5.71 (m, 1H), 5.09-4.98 (m, 2H), 4.43 (m, 1H), 3.91-3.89 (m, 1H), 3.81-3.80 (m, 1H), 2.70-2.64 (m, 1H), 2.47-2.43 (m, 1H), 2.37-2.28 (m, 1H), 1.80-1.51 (m, 3H), 1.48 (s, 9H), 0.89-0.95 (m, 2H). <sup>13</sup>C-NMR (75 MHz, CHCl<sub>3</sub>) δ 155.1, 135.3, 116.6, 79.6, 54.9, 37.2, 28.3, 28.2, 27.6, 24.2. HRMS (ESI<sup>+</sup>): calcd for C<sub>13</sub>H<sub>23</sub>NNaO<sub>3</sub> (*M*+Na<sup>+</sup>): 264.15756, found: 264.15674.

**(2S,3S)-2-(3-Azido-2-hydroxypropyl)-3-methoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (16)**

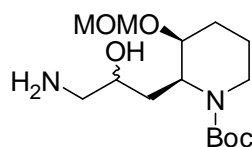


Epoxide **15** (20 mg, 0.066 mmol) was dissolved in a mixture of methanol (4 mL) and H<sub>2</sub>O (0.5 mL) and sodium azide (22 mg, 0.33 mmol) and ammonium chloride (11 mg, 0.2 mmol) were added. The reaction mixture was stirred overnight at 70 °C and then quenched with saturated aqueous NaHCO<sub>3</sub> (5 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layers were washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtrated and concentrated *in vacuo*. Flash chromatography (1:5 EtOAc:heptane) afforded the two pure diastereoisomers **16**<sub>major</sub> (11 mg, 0.032 mmol, 50%) and **16**<sub>minor</sub> (4 mg, 0.012 mmol, 20%) as colorless oils.

Major-**16**: [α]<sub>D</sub><sup>20</sup> -15.7 (c 0.31, CH<sub>2</sub>Cl<sub>2</sub>). IR (film) 3434, 2967, 2933, 2881, 2094, 1679, 1649, 1419, 1161, 1031 cm<sup>-1</sup>. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>, rotamers) δ 4.69-4.690 (m, 3H), 4.35-4.34 (m, 1H), 3.90-3.86 (m, 1H), 3.73 (m, 1H), 3.57-3.56 (m, 1H), 3.38-3.35 (m, 3H), 3.23-3.19 (m, 2H), 2.65-2.59 (m, 2H), 1.87-1.86 (m, 2H), 1.71 (m, 3H), 1.69 (m, 9H). <sup>13</sup>C-NMR (75 MHz, CHCl<sub>3</sub>) δ 156.5, 95.0, 80.9, 73.4, 66.8, 56.1, 55.6, 49.4, 38.6, 28.6, 28.3, 25.7, 24.0. HRMS (ESI<sup>+</sup>): calcd for C<sub>15</sub>H<sub>28</sub>N<sub>4</sub>NaO<sub>5</sub> (M+Na<sup>+</sup>): 367.1957, found: 367.1944.

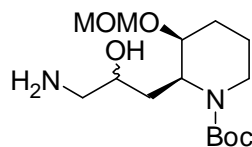
Minor-**16**: [α]<sub>D</sub><sup>20</sup> +25.3 (c 0.20, CH<sub>2</sub>Cl<sub>2</sub>). IR (film) 3438, 2933, 2872, 2107, 1684, 1666, 1416, 1148, 1040 cm<sup>-1</sup>. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>, rotamers) δ 4.67 (m, 2H), 4.44-4.39 (m, 1H), 3.89 (m, 2H), 3.62 (m, 2H), 3.37-3.32 (m, 5H), 2.77-2.70 (m, 1H), 1.94-1.91 (m, 3H), 1.62 (m, 2H), 1.46 (m, 10H). <sup>13</sup>C-NMR (75 MHz, CHCl<sub>3</sub>) δ 155.9, 95.2, 80.6, 74.5, 70.4, 56.3, 55.6, 51.7, 38.8, 29.8, 28.4, 25.7, 24.0. HRMS (ESI<sup>+</sup>): calcd for C<sub>15</sub>H<sub>28</sub>N<sub>4</sub>NaO<sub>5</sub> (M+Na<sup>+</sup>): 367.1957, found: 367.1932.

**(2S,3S)-2-(3-Amino-2-hydroxypropyl)-3-methoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (17)**



To a solution of **16**<sub>major</sub> (26 mg, 0.077 mmol) in a mixture of THF (6 mL) and aqueous 0.25 M NaOH (2 mL) was added trimethylphosphine (1 M solution in THF, 380 μl, 0.38 mmol). After stirring overnight the solvent was removed under reduced pressure. Purification with an Isolute<sup>®</sup> Flash SCX-2 ion exchange column gave product **17**<sub>major</sub> (19 mg, 0.06 mmol, 80%) as a white solid. mp = 85 °C. [α]<sub>D</sub><sup>20</sup> +5.9 (c 0.19, CH<sub>2</sub>Cl<sub>2</sub>). IR (film) 3377, 2945, 2885, 1679, 1671, 1411, 1372, 1152, 1040 cm<sup>-1</sup>. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>, rotamers) δ 4.74-4.61 (m, 4H), 3.89-3.72 (m, 1H), 3.51 (m, 2H), 3.38 (m, 4H), 2.71-2.64 (m, 4H), 1.84 (m, 2H), 1.70-1.64 (m, 3H), 1.55 (m, 10H). <sup>13</sup>C-NMR (75 MHz, CHCl<sub>3</sub>) δ 155.8, 94.5, 80.0, 73.0, 68.3, 55.0, 49.1, 47.4, 38.0, 28.1, 27.8, 25.2, 23.6. HRMS (ESI<sup>+</sup>): calcd for C<sub>15</sub>H<sub>30</sub>N<sub>2</sub>NaO<sub>5</sub> (M+Na<sup>+</sup>): 341.2052, found: 341.2053

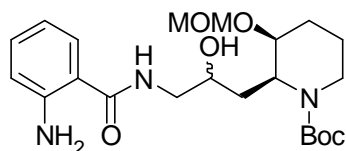
**(2S,3S)-2-(3-Amino-2-hydroxypropyl)-3-methoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (17)**



Compound **16**<sub>minor</sub> (134 mg, 0.39 mmol) was reacted with trimethylphosphine, following the same procedure as for **16**<sub>major</sub>. Purification with an Isolute<sup>®</sup> Flash SCX-2 ion exchange column gave the product **17**<sub>minor</sub> (114 mg, 0.36 mmol, 92%) as a colorless oil. [α]<sub>D</sub><sup>20</sup> +17.8 (c 0.30, CH<sub>2</sub>Cl<sub>2</sub>). IR (film) 3360, 2971, 2932, 2876, 1684, 1148, 1031 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, rotamers) δ 4.66 (m, 2H), 4.46 (m, 1H), 3.88 (m, 1H), 3.62-3.60 (m, 2H), 3.42-3.37 (m, 3H), 2.87-2.77 (m, 2H), 2.63-2.47 (m, 4H), 1.83 (m, 2H), 1.69-1.56 (m, 2H), 1.51 (m, 11H). No clear <sup>13</sup>C NMR could be

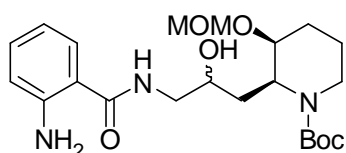
obtained due to rotamers. HRMS (ESI<sup>+</sup>): calcd for C<sub>15</sub>H<sub>30</sub>N<sub>2</sub>NaO<sub>5</sub> (M+Na<sup>+</sup>): 341.2052, found: 341.2053.

**(2S,3S)-2-[3-(2-Aminobenzoylamine)-2-hydroxypropyl]-3-methoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (18)**



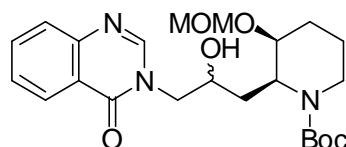
To a solution of **17**<sub>major</sub> (239 mg, 0.75 mmol) in dry EtOAc (70 mL) were added isatoic anhydride (429 mg, 2.63 mmol) and triethyl amine (151  $\mu$ l, 1.125 mmol) and the mixture was stirred overnight at 40 °C. The reaction was quenched by the addition of saturated aqueous NaHCO<sub>3</sub> (50 mL) and extracted with EtOAc (4  $\times$  75 mL). The combined organic layers were washed with brine (150 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtrated and concentrated *in vacuo*. The crude product was dissolved in a mixture of THF (20 mL), methanol (20 mL) and aqueous 1 M NaOH (20 mL). After stirring for 2 h, the reaction was quenched by adding saturated aqueous NaHCO<sub>3</sub> (70 mL) and extracted with EtOAc (4  $\times$  100 mL). The combined organic layers were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtrated and concentrated *in vacuo*. Flash chromatography (1:2-3:1 EtOAc:heptane) afforded product **18**<sub>major</sub> (222 mg, 0.51 mmol, 67%) as a colorless oil.  $[\alpha]_D^{20}$  +8.8 (c 0.19, CH<sub>2</sub>Cl<sub>2</sub>). IR (film) 3443, 3339, 2971, 2928, 2889, 1649, 1416, 1152, 1031 cm<sup>-1</sup>. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>, rotamers)  $\delta$  7.35-7.50 (m, 1H), 7.33 (m, 1H), 6.71-6.63 (m, 3H), 5.50 (m, 2H), 4.67-4.66 (m, 2H), 4.65-4.59 (m, 1H), 3.88-3.81 (m, 2H), 3.76-3.70 (m, 1H), 3.55-3.54 (m, 1H), 3.38 (m, 3H), 3.20-3.14 (m, 1H), 1.88-1.68 (m, 5H), 1.60-1.45 (m, 12H). <sup>13</sup>C-NMR (75 MHz, CHCl<sub>3</sub>)  $\delta$  169.2, 156.6, 148.6, 132.1, 127.3, 117.1, 116.6, 116.3, 95.0, 80.8, 73.6, 66.4, 55.6, 49.6, 44.6, 38.7, 28.7, 28.3, 25.7, 24.0. HRMS (ESI<sup>+</sup>): calcd for C<sub>22</sub>H<sub>35</sub>N<sub>3</sub>NaO<sub>6</sub> (M+Na<sup>+</sup>): 460.2424, found: 460.2381.

**(2S,3S)-2-[3-(2-Aminobenzoylamine)-2-hydroxypropyl]-3-methoxymethoxy-piperidine-1-carboxylic acid *tert*-butyl ester (18)**



Substrate **17**<sub>minor</sub> (107 mg, 0.34 mmol) was reacted with isatoic anhydride, following the same procedure as for **17**<sub>major</sub>. Flash chromatography (1:2-3:1 EtOAc:heptane) afforded product **18**<sub>minor</sub> (117 mg, 0.27 mmol, 80%).  $[\alpha]_D^{20}$  -3.7 (c 0.20, CH<sub>2</sub>Cl<sub>2</sub>). IR (film) 3447, 3343, 2937, 2885, 1649, 1528, 1416, 1364, 1260, 1156, 1035 cm<sup>-1</sup>. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>, rotamers)  $\delta$  7.37-7.35 (m, 1H), 7.19 (m, 1H), 6.73-6.66 (m, 3H), 5.52 (bs, 2H), 4.67 (m, 2H), 4.45 (m, 1H), 4.34 (m, 1H), 3.88 (m, 1H), 3.75-3.70 (m, 1H), 3.64-3.60 (m, 1H), 3.35-3.31 (m, 4H), 2.81-2.76 (m, 1H), 2.00-1.77 (m, 5H), 1.54 (m, 11H). <sup>13</sup>C-NMR (75 MHz, CHCl<sub>3</sub>)  $\delta$  170.0, 156.0, 148.7, 132.2, 127.4, 117.2, 116.5, 116.0, 95.3, 80.6, 74.8, 70.6, 60.4, 55.6, 51.8, 45.0, 38.8, 30.1, 28.4, 25.7, 24.0, 14.2. HRMS (ESI<sup>+</sup>): calcd for C<sub>22</sub>H<sub>35</sub>N<sub>3</sub>NaO<sub>6</sub> (M+Na<sup>+</sup>): 460.2423, found: 460.2381.

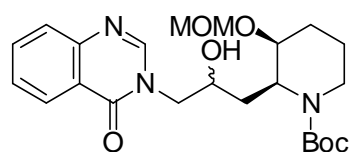
**(2S,3S)-2-[2-Hydroxy-3-(4-oxo-4H-quinazolin-3-yl)propyl]-3-methoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (19)**



To a solution of **18**<sub>major</sub> (232 mg, 0.52 mmol) in toluene (10 mL) were added *p*-TsOH (20 mg, 0.11 mmol) and triethyl orthoformate (260 mg, 1.56 mmol) and the mixture was stirred overnight at 40 °C. The reaction was quenched with saturated aqueous NaHCO<sub>3</sub> (10 mL) and extracted with EtOAc (4  $\times$  15 mL). The combined organic layers were washed with brine (40 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtrated and concentrated *in vacuo*. Flash chromatography (1:2-2:1 EtOAc:heptane) afforded product **19**<sub>major</sub> (197 mg, 0.44 mmol, 85%) as a

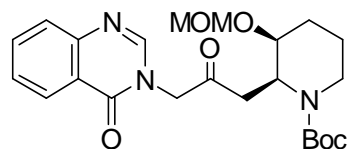
colorless oil.  $[\alpha]_D^{20} +59.8$  (c 0.28,  $\text{CH}_2\text{Cl}_2$ ). IR (film) 2971, 2941, 2876, 2353, 2340, 1684, 1645, 1558, 1152, 1035  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ , rotamers)  $\delta$  8.29-8.22 (m, 2H), 7.73 (m, 2H), 7.48 (m, 1H), 4.68 (m, 3H), 4.48-4.38 (m, 2H), 3.86 (m, 1H), 3.73 (m, 2H), 3.60-3.57 (m, 1H), 3.37 (m, 3H), 2.70 (m, 1H), 1.88 (m, 2H), 1.70 (m, 2H), 1.53-1.41 (m, 2H), 1.37 (m, 9H).  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CHCl}_3$ )  $\delta$  161.3, 156.5, 148.3, 148.0, 134.1, 127.5, 126.8, 126.5, 122.0, 95.0, 80.9, 73.4, 65.3, 55.6, 51.8, 49.5, 38.7, 28.7, 28.2, 25.7, 24.0. HRMS (ESI<sup>+</sup>): calcd for  $\text{C}_{23}\text{H}_{33}\text{N}_3\text{NaO}_6$  ( $M+\text{Na}^+$ ): 470.2267, found: 470.2267.

**(2S,3S)-2-[2-Hydroxy-3-(4-oxo-4H-quinazolin-3-yl)propyl]-3-methoxymethoxypiperidine-1-carboxylic acid tert-butyl ester (19)**



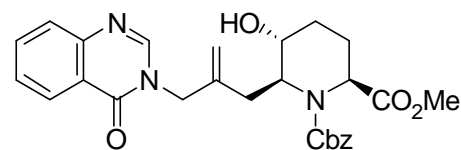
Substrate **18**<sub>minor</sub> (95 mg, 0.21 mmol) was reacted with triethyl orthoformate, following the same procedure as for **18**<sub>major</sub>. Flash chromatography (1:2-2:1 EtOAc: heptane) afforded product **19**<sub>minor</sub> (77 mg, 0.17 mmol, 82%).  $[\alpha]_D^{20} -19.4$  (c 0.27,  $\text{CH}_2\text{Cl}_2$ ). IR (film) 2971, 2941, 2876, 2353, 2340, 1684, 1645, 1558, 1152, 1035  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ , rotamers)  $\delta$  8.25-8.20 (m, 2H), 7.73-7.69 (m, 2H), 7.29 (m, 1H), 4.68 (m, 2H), 4.54 (m, 1H), 4.40-4.37 (m, 1H), 4.19-4.05 (m, 2H), 3.85-3.84 (m, 2H), 3.64-3.61 (m, 1H), 3.38 (m, 3H), 2.80 (m, 1H), 2.05 (m, 2H), 1.86 (m, 1H), 1.70 (m, 2H), 1.45 (m, 10H).  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CHCl}_3$ )  $\delta$  161.3, 156.5, 148.3, 148.0, 134.1, 127.5, 126.8, 126.5, 122.0, 95.0, 80.9, 73.4, 65.3, 55.6, 51.8, 49.5, 38.7, 28.7, 28.2, 25.7, 24.0. HRMS (ESI<sup>+</sup>): calcd for  $\text{C}_{23}\text{H}_{33}\text{N}_3\text{NaO}_6$  ( $M+\text{Na}^+$ ): 470.2267, found: 470.2268.

**(2S,3S)-2-[2-Oxo-3-(4-oxo-4H-quinazolin-3-yl)propyl]-3-methoxymethoxypiperidine-1-carboxylic acid tert-butyl ester (20)**



Both diastereoisomers of **19** (14 mg, 0.035 mmol) were dissolved in  $\text{CH}_2\text{Cl}_2$  (5 mL) and Dess-Martin periodinane (39 mg, 0.091 mmol) was added. After stirring overnight, the reaction was quenched with saturated aqueous  $\text{NaHCO}_3$  (5 mL) and extracted with dichloromethane (4 x 5 mL). The combined organic layers were washed with brine (15 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtrated and the solvent was removed under reduced pressure. Flash chromatography (1:2-2:1 EtOAc:heptane) afforded product **20** (10 mg, 0.022 mmol, 83%).  $[\alpha]_D^{20} +41.3$  (c 0.20,  $\text{CH}_2\text{Cl}_2$ ). IR (film) 2976, 2937, 2885, 1675, 1606, 1351, 1148, 1031  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ , rotamers)  $\delta$  8.29-8.27 (m, 1H), 8.04 (m, 1H), 7.76-7.71 (m, 2H), 7.51-7.47 (m, 1H), 5.24-5.20 (m, 1H), 5.00-4.98 (m, 2H), 4.69 (m, 2H), 3.86-3.84 (m, 1H), 3.75-3.73 (m, 1H), 3.40 (m, 3H), 3.07-04 (m, 1H), 2.85-2.65 (m, 2H), 2.07-2.04 (m, 1H), 1.90 (m, 1H), 1.72 (m, 1H), 1.44 (m, 10H).  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CHCl}_3$ )  $\delta$  201.1, 160.9, 155.3, 148.2, 146.9, 134.2, 127.5, 127.1, 126.6, 121.8, 95.5, 80.5, 74.1, 55.7, 53.4, 51.2, 38.4, 36.5, 28.3, 25.4, 23.7. HRMS (ESI<sup>+</sup>): calcd for  $\text{C}_{23}\text{H}_{31}\text{N}_3\text{NaO}_6$  ( $M+\text{Na}^+$ ): 468.2111, found: 468.2148.

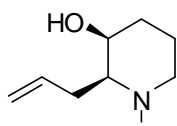
**(2S,5R,6S)-5-Hydroxy-6-[2-(4-oxo-4H-quinazolin-3-ylmethyl)-allyl]piperidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (22)**



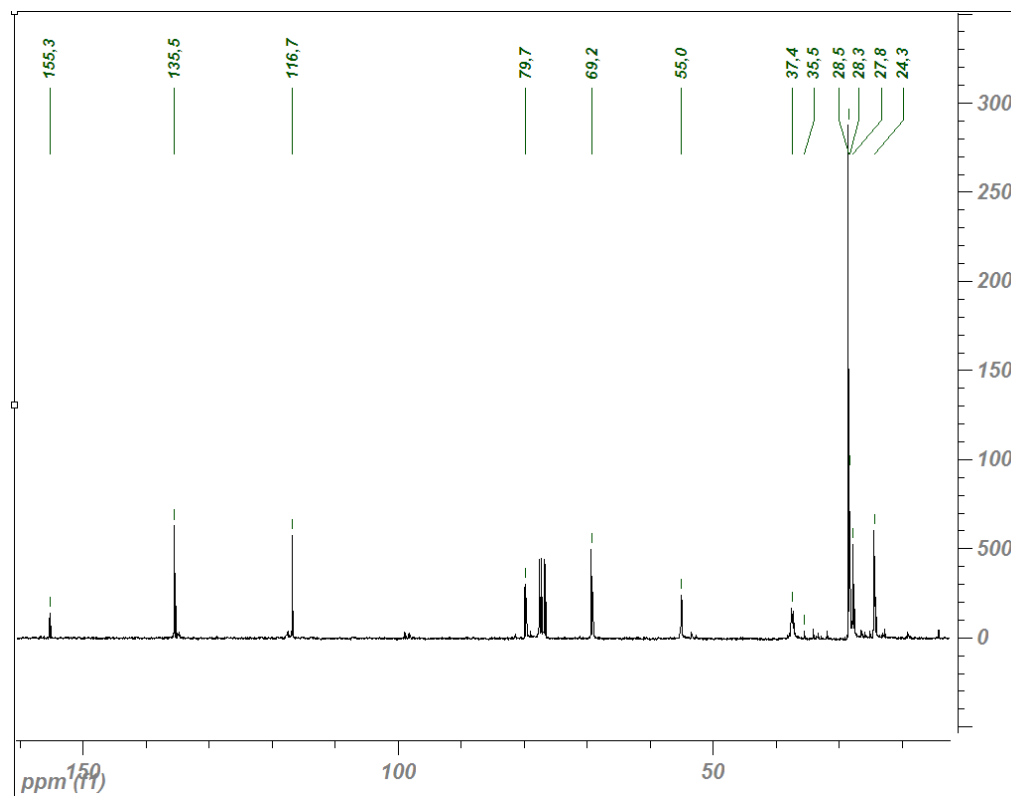
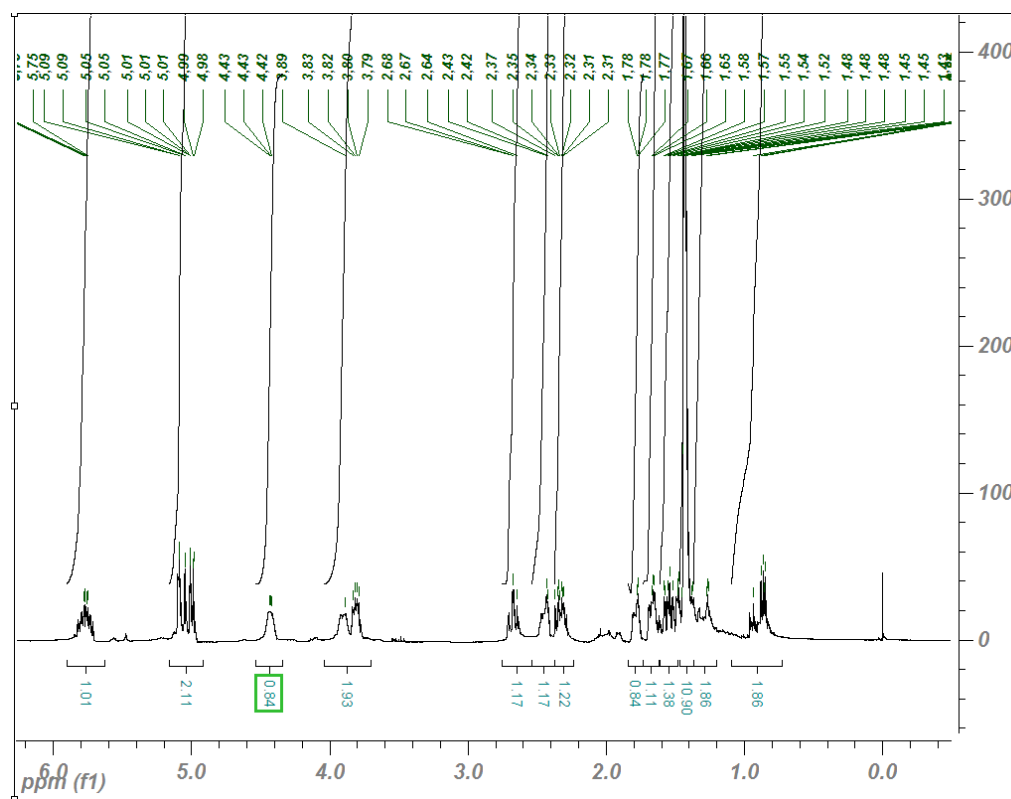
To a suspension of NaH (42 mg, 1.11 mmol) in DMF (5 mL) was added 4-hydroxyquinazoline (147 mg, 1.01 mmol) at 0 °C. After stirring for 30 min **21** (385 mg, 1.01 mmol) was added and the mixture was stirred overnight at rt. The reaction mixture was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (10 mL), extracted with EtOAc (3 x 30 mL), and the combined organic phases were washed

with brine (3 × 10 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. Flash chromatography (2:1-7:1 EtOAc:heptane) afforded product **22** as a colorless oil (395 mg, 0.80 mmol, 80%). [α]<sub>D</sub><sup>20</sup> + 3.4 (c 0.26, CH<sub>2</sub>Cl<sub>2</sub>). IR (film) 3447, 2946, 17.39, 1679, 1601, 1312, 772, 737, 690 cm<sup>-1</sup>. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>, rotamers) δ 8.28-8.21 (m, 1H), 8.09 (m, 1H), 7.72-7.67 (m, 2H), 7.48-7.43 (m, 1H), 7.32 (m, 5H), 5.21-5.18 (m, 1H), 5.09-4.82 (m, 3H), 4.71-4.47 (m, 3H), 4.02-3.82 (m, 2H), 3.70-3.62 (m, 3H), 2.56-2.52 (m, 1H), 2.34-2.20 (m, 3H), 1.81-1.71 (m, 2H). No clear <sup>13</sup>C-NMR due to rotamers. HRMS (ESI<sup>+</sup>): calcd for C<sub>27</sub>H<sub>29</sub>N<sub>3</sub>NaO<sub>6</sub> (M+Na<sup>+</sup>): 514.1970, found: 514.1954.

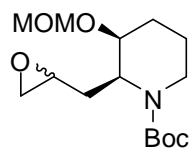
**(2S,3S)-2-Allyl-3-hydroxypiperidine-1-carboxylic acid *tert*-butyl ester (14)**



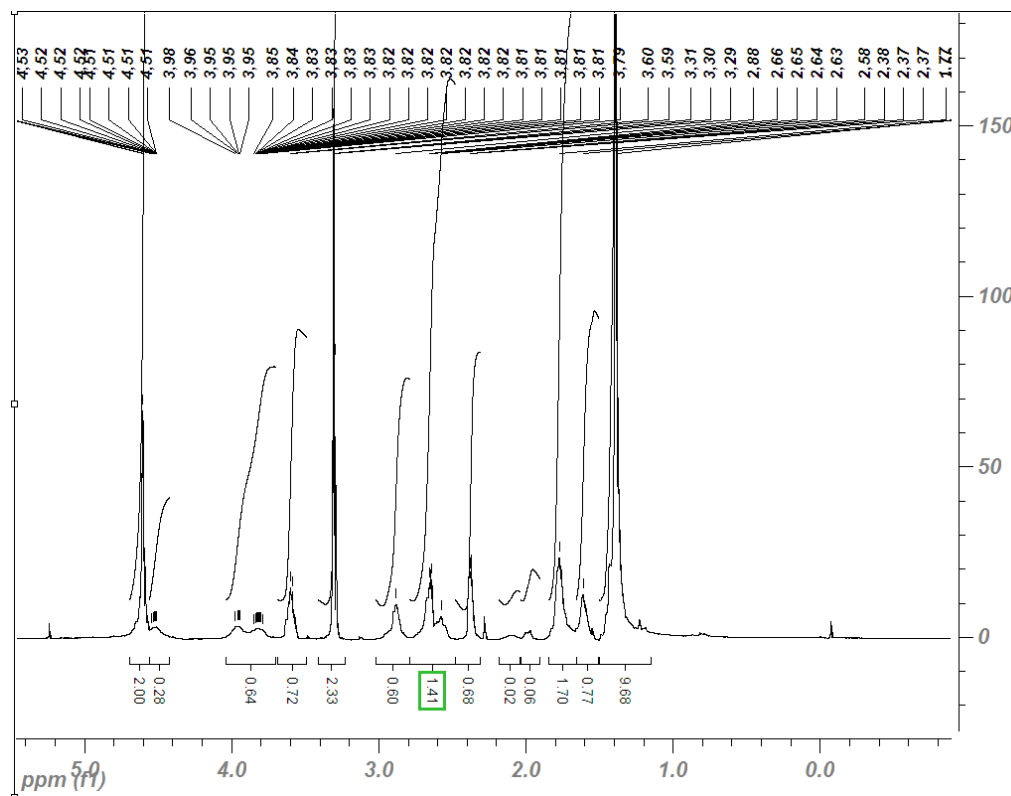
Boc  $^1\text{H}$  NMR 400 MHz  $\text{CDCl}_3$ ,  $^{13}\text{C}$  NMR 75 MHz  $\text{CDCl}_3$



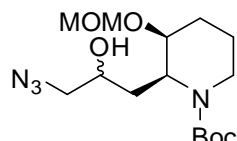
**(2S,3S)-3-Methoxymethoxy-2-oxiranylmethylpiperidine-1-carboxylic acid *tert*-butyl ester (15)**



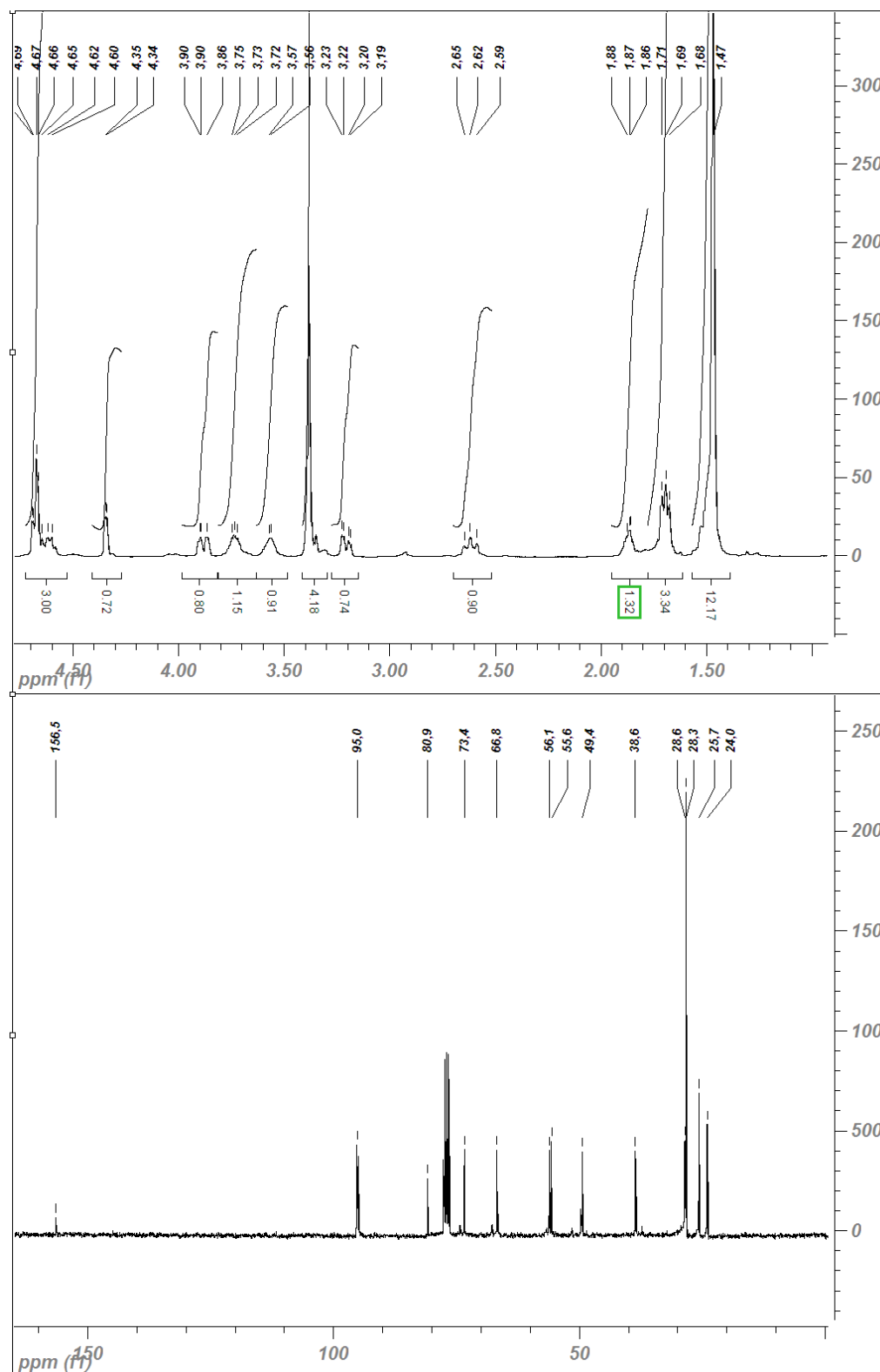
$^1\text{H NMR CDCl}_3$  400 MHz



**(2S,3S)-2-(3-Azido-2-hydroxypropyl)-3-methoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (major-16)**

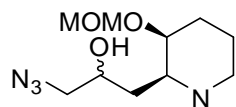


Boc  $^1\text{H}$  NMR  $\text{CDCl}_3$  400 MHz,  $^{13}\text{C}$  NMR  $\text{CDCl}_3$  75 MHz

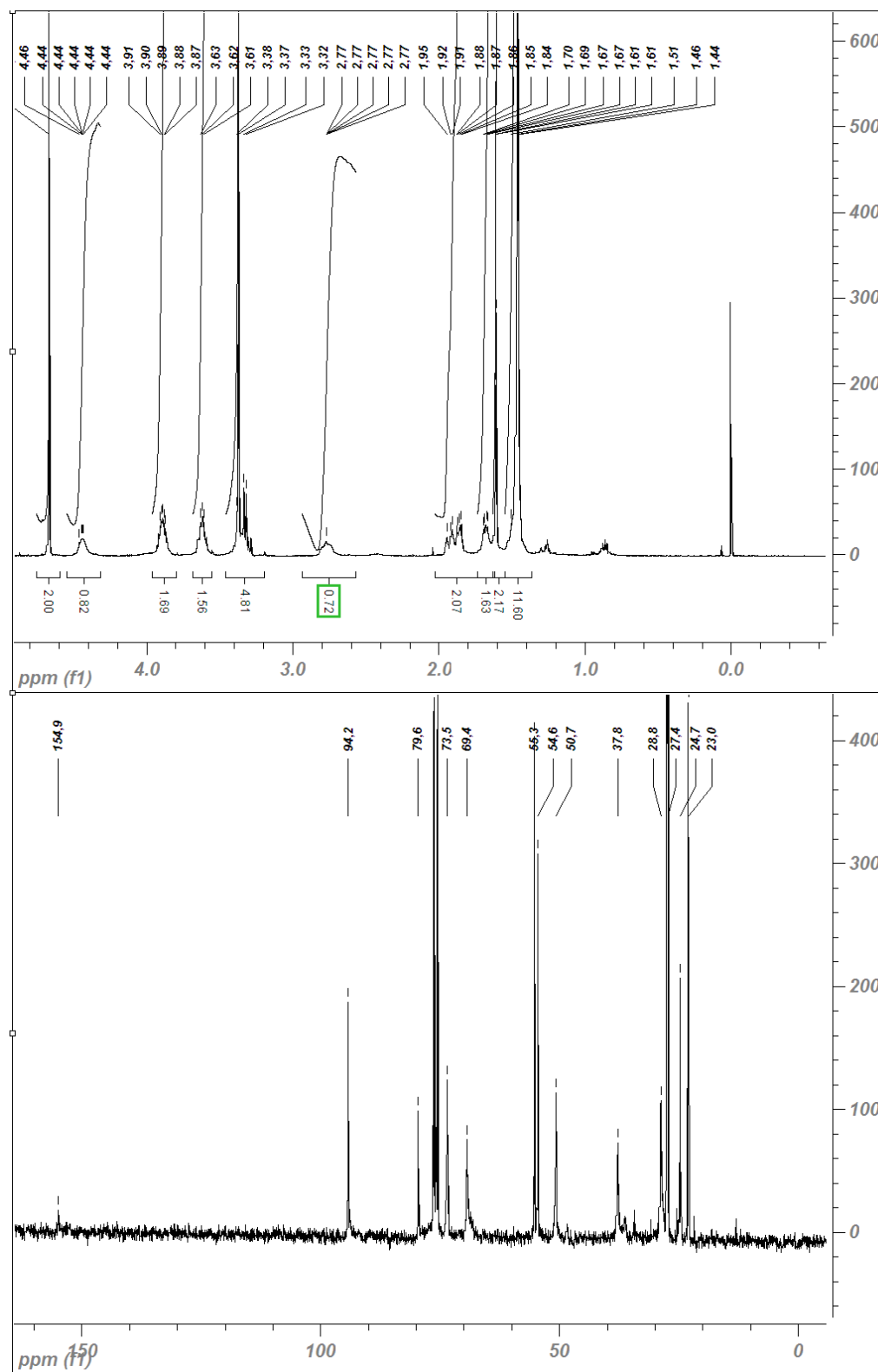




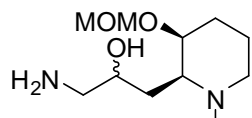
**(2S,3S)-2-(3-Azido-2-hydroxypropyl)-3-methoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (minor-16)**



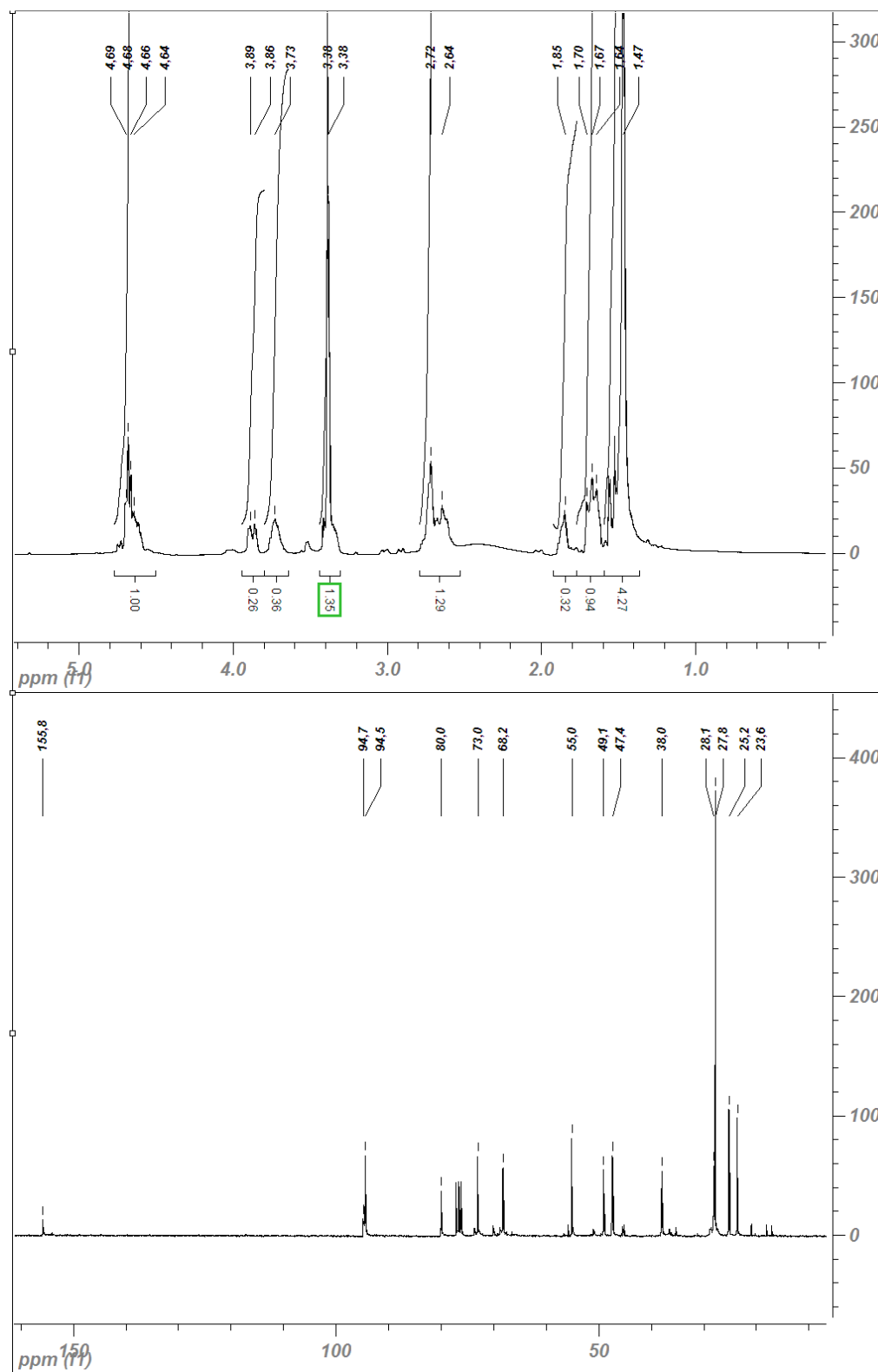
Boc  $^1\text{H}$  NMR  $\text{CDCl}_3$  400 MHz,  $^{13}\text{C}$  NMR  $\text{CDCl}_3$  75 MHz



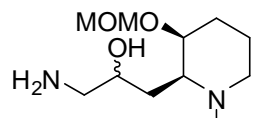
**(2S,3S)-2-(3-Amino-2-hydroxypropyl)-3-methoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (major-17)**



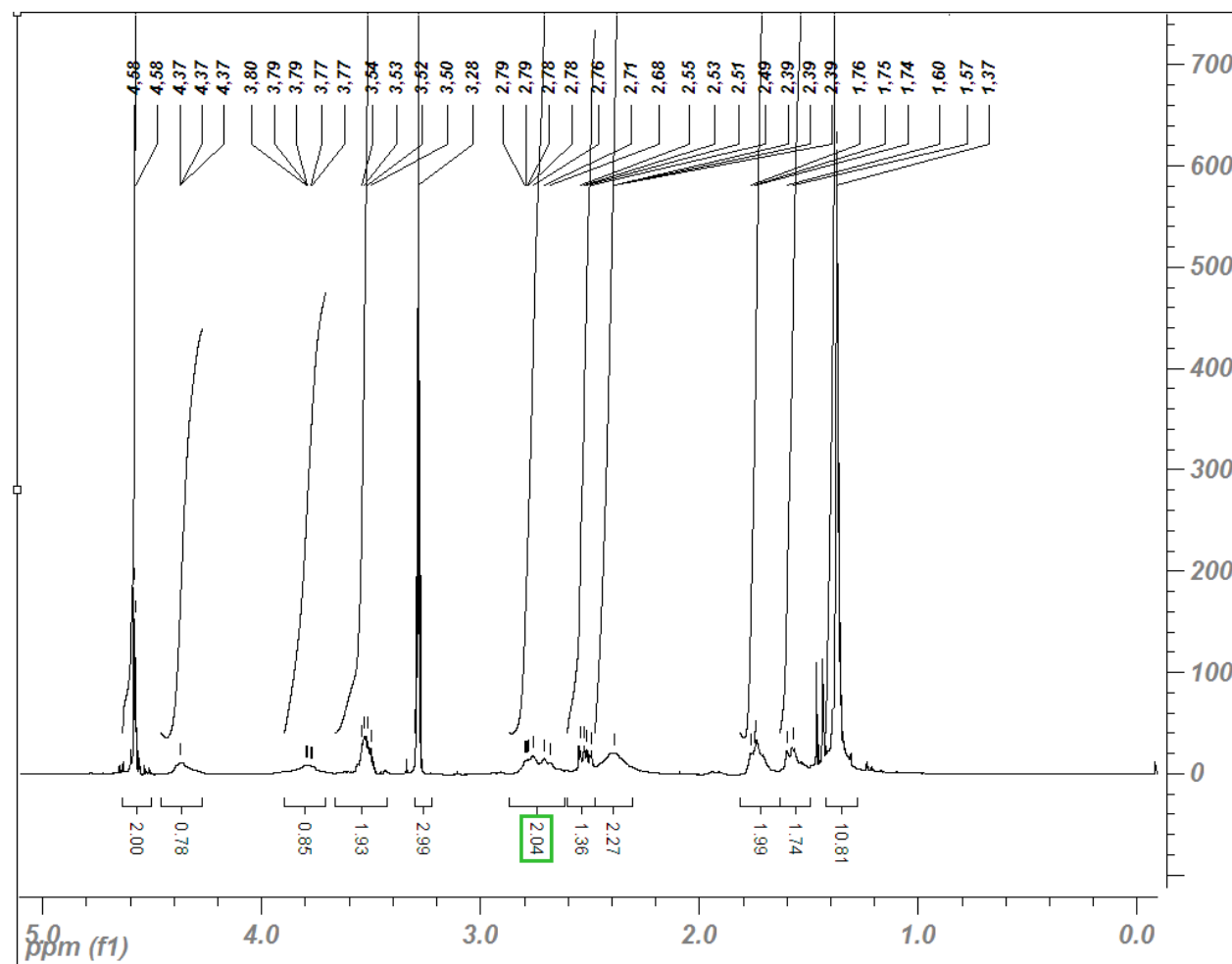
Boc  $^1\text{H}$  NMR  $\text{CDCl}_3$  400 MHz,  $^{13}\text{C}$  NMR  $\text{CDCl}_3$  75 MHz



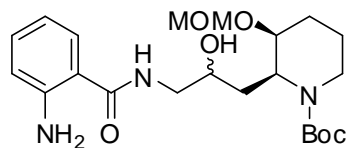
**(2S,3S)-2-(3-Amino-2-hydroxypropyl)-3-methoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (minor-17)**



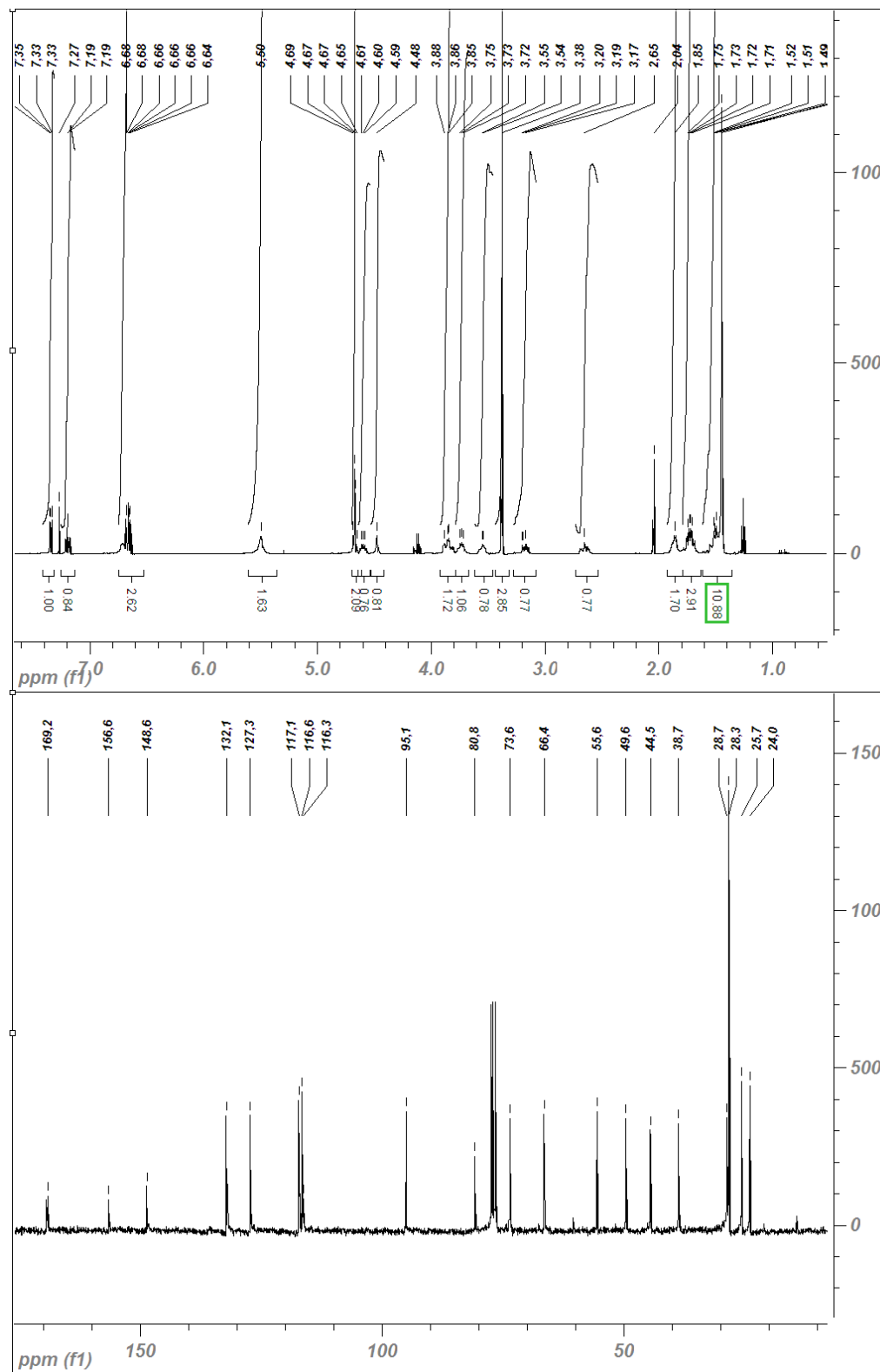
Boc  $^1\text{H}$  NMR  $\text{CDCl}_3$  400 MHz,



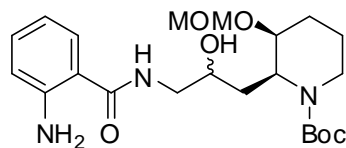
**(2S,3S)-2-[3-(2-Aminobenzoylamine)-2-hydroxypropyl]-3-methoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (major-18)**



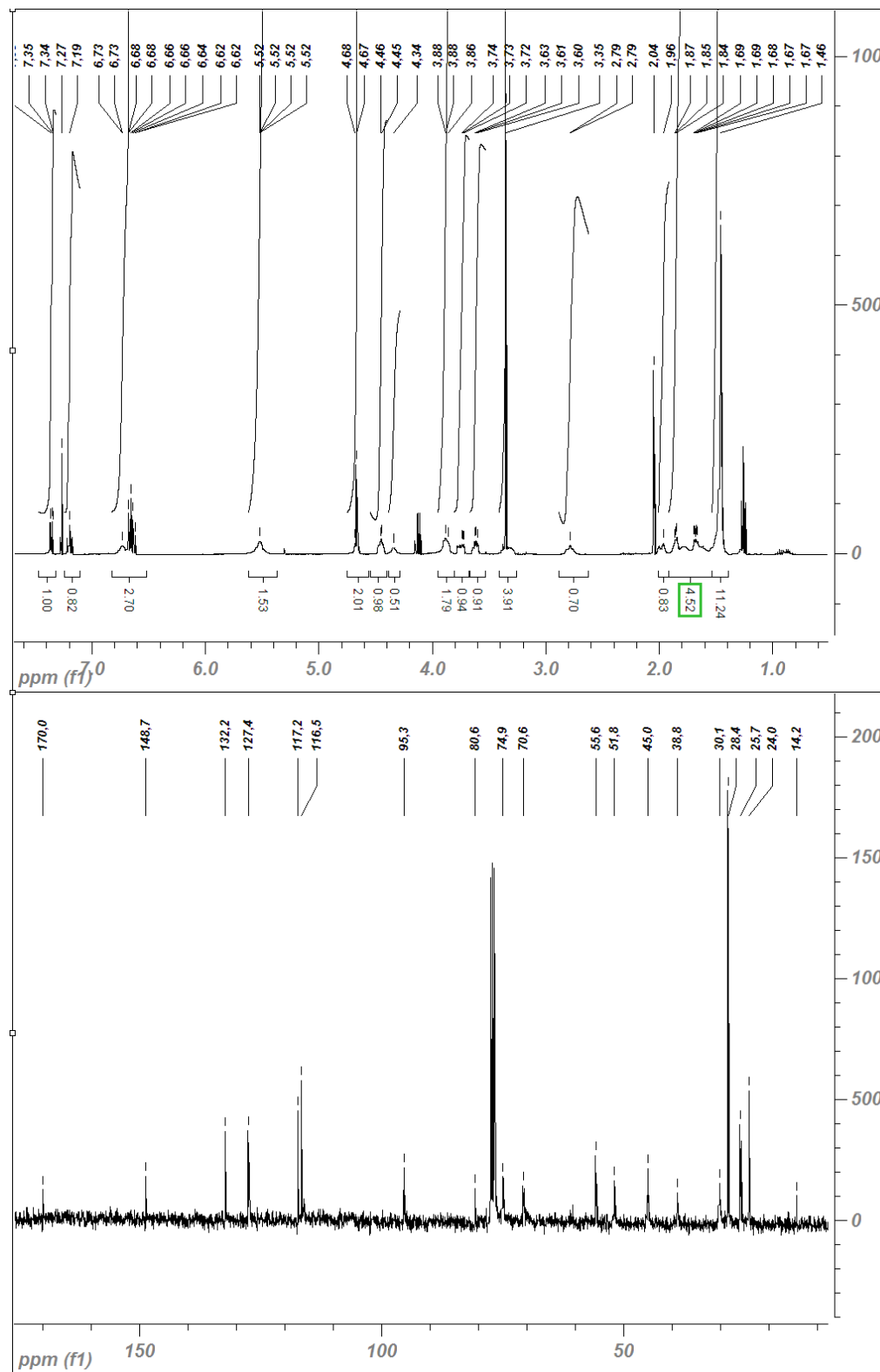
$^1\text{H NMR CDCl}_3$  400 MHz,  $^{13}\text{C NMR CDCl}_3$  75 MHz



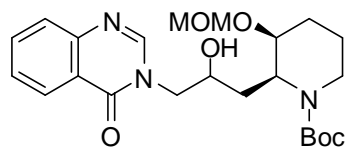
**(2S,3S)-2-[3-(2-Aminobenzoylamine)-2-hydroxypropyl]-3-methoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (minor-18)**



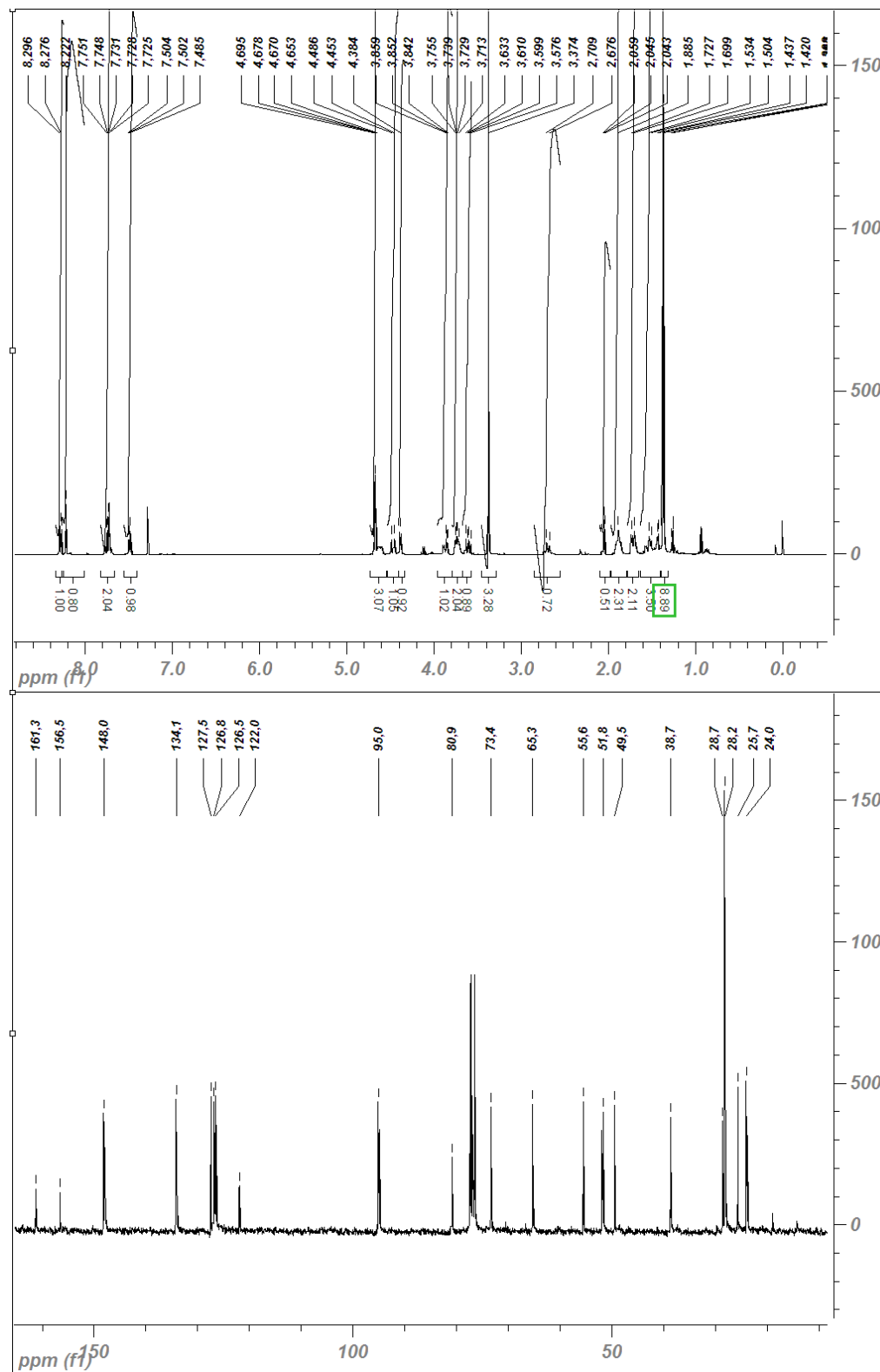
Boc  $^1\text{H}$  NMR  $\text{CDCl}_3$  400 MHz,  $^{13}\text{C}$  NMR  $\text{CDCl}_3$  75 MHz



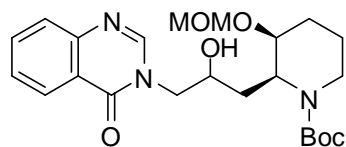
**(2S,3S)-2-[2-Hydroxy-3-(4-oxo-4H-quinazolin-3-yl)propyl]-3-methoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (major-19)**



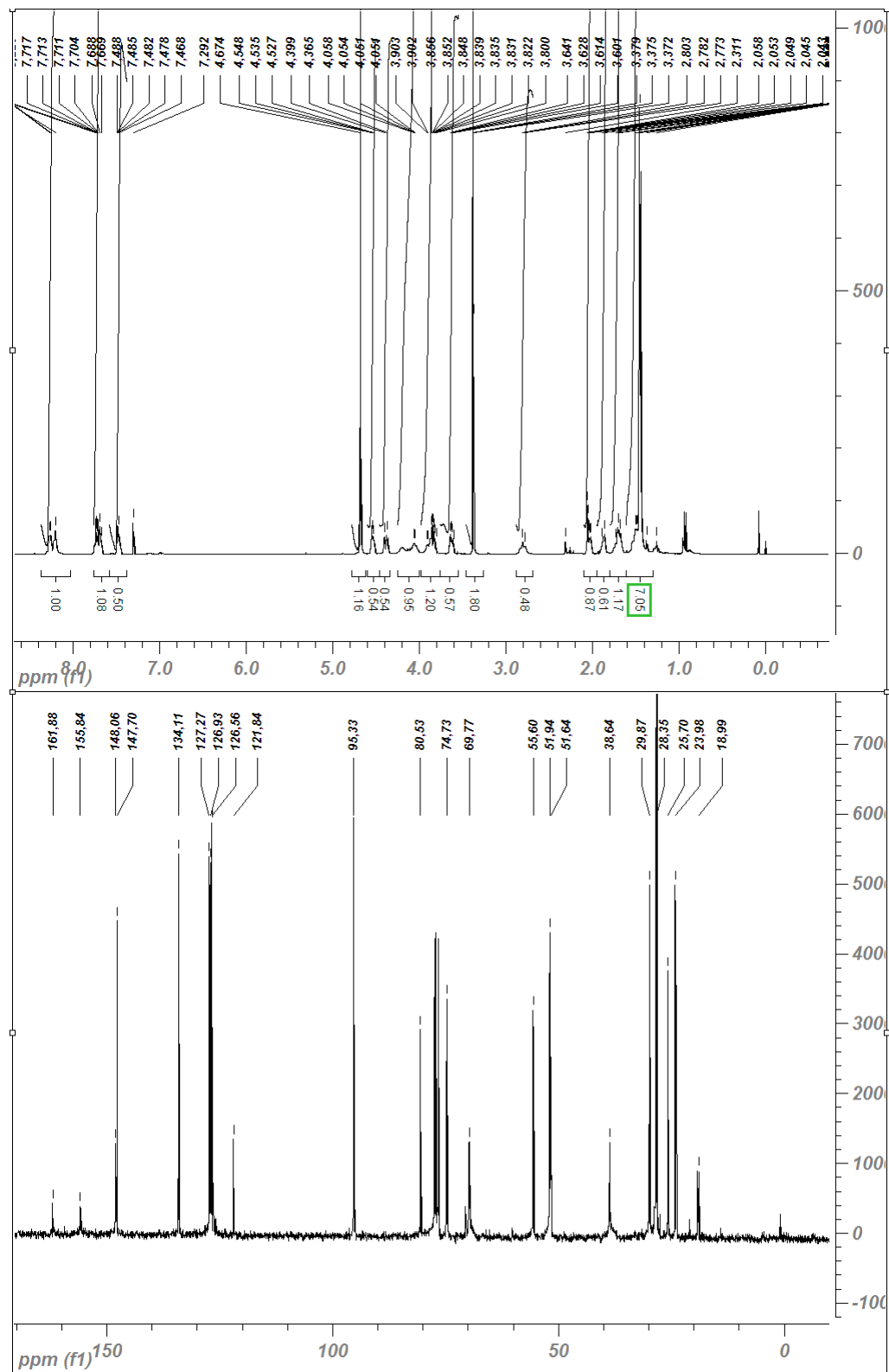
Boc  $^1\text{H}$  NMR  $\text{CDCl}_3$  400 MHz,  $^{13}\text{C}$  NMR  $\text{CDCl}_3$  75 MHz



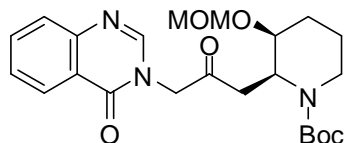
**(2S,3S)-2-[2-Hydroxy-3-(4-oxo-4H-quinazolin-3-yl)propyl]-3-methoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (minor-19)**



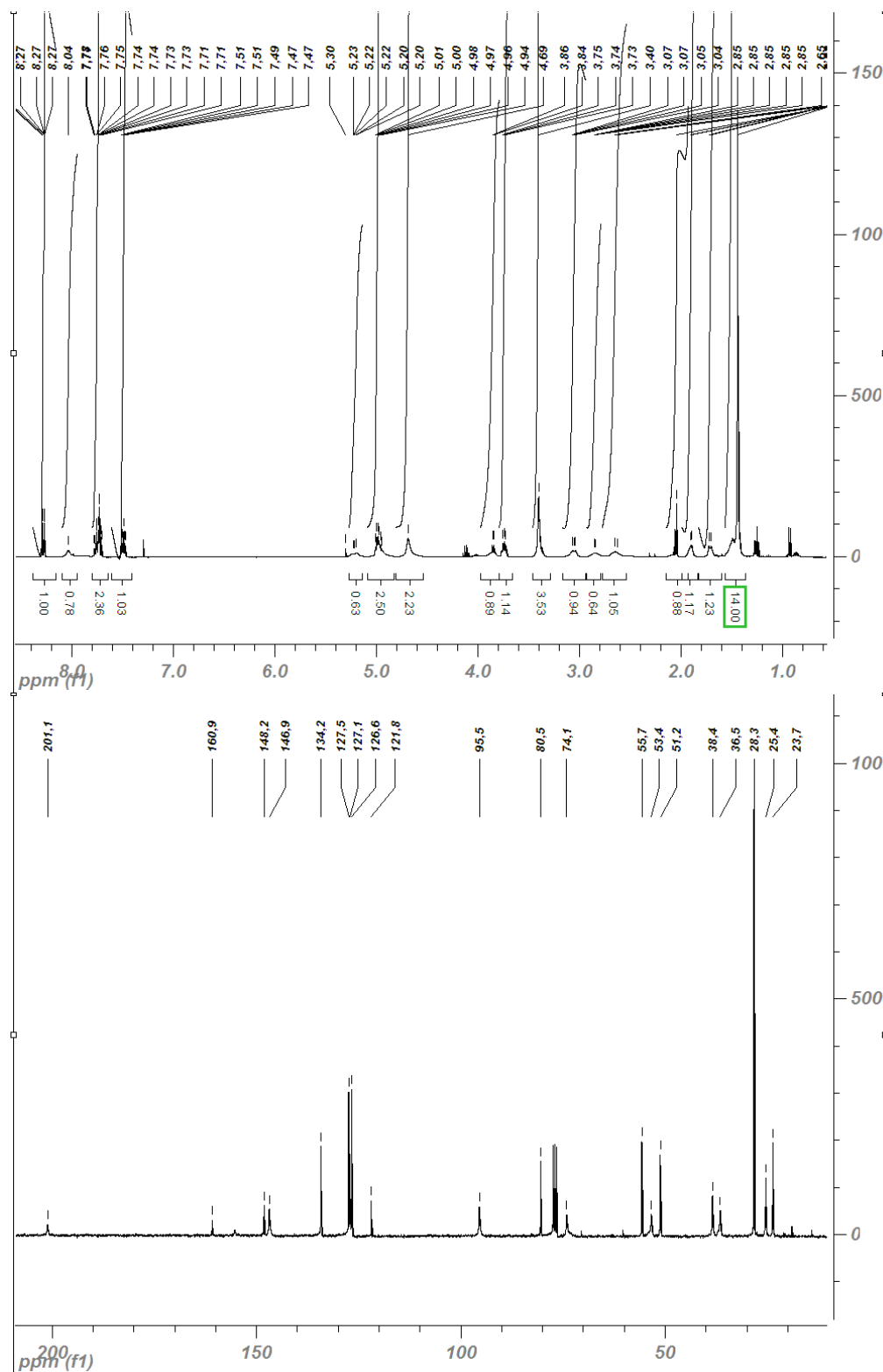
Boc  $^1\text{H}$  NMR  $\text{CDCl}_3$  400 MHz,  $^{13}\text{C}$  NMR  $\text{CDCl}_3$  75 MHz



**(2S,3S)-2-[2-Oxo-3-(4-oxo-4H-quinazolin-3-yl)propyl]-3-methoxymethoxypiperidine-1-carboxylic acid *tert*-butyl ester (20)**

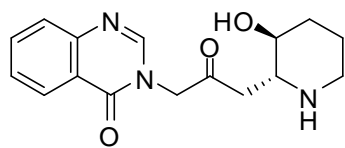


Boc  $^1\text{H}$  NMR  $\text{CDCl}_3$  400 MHz,  $^{13}\text{C}$  NMR  $\text{CDCl}_3$  75 MHz

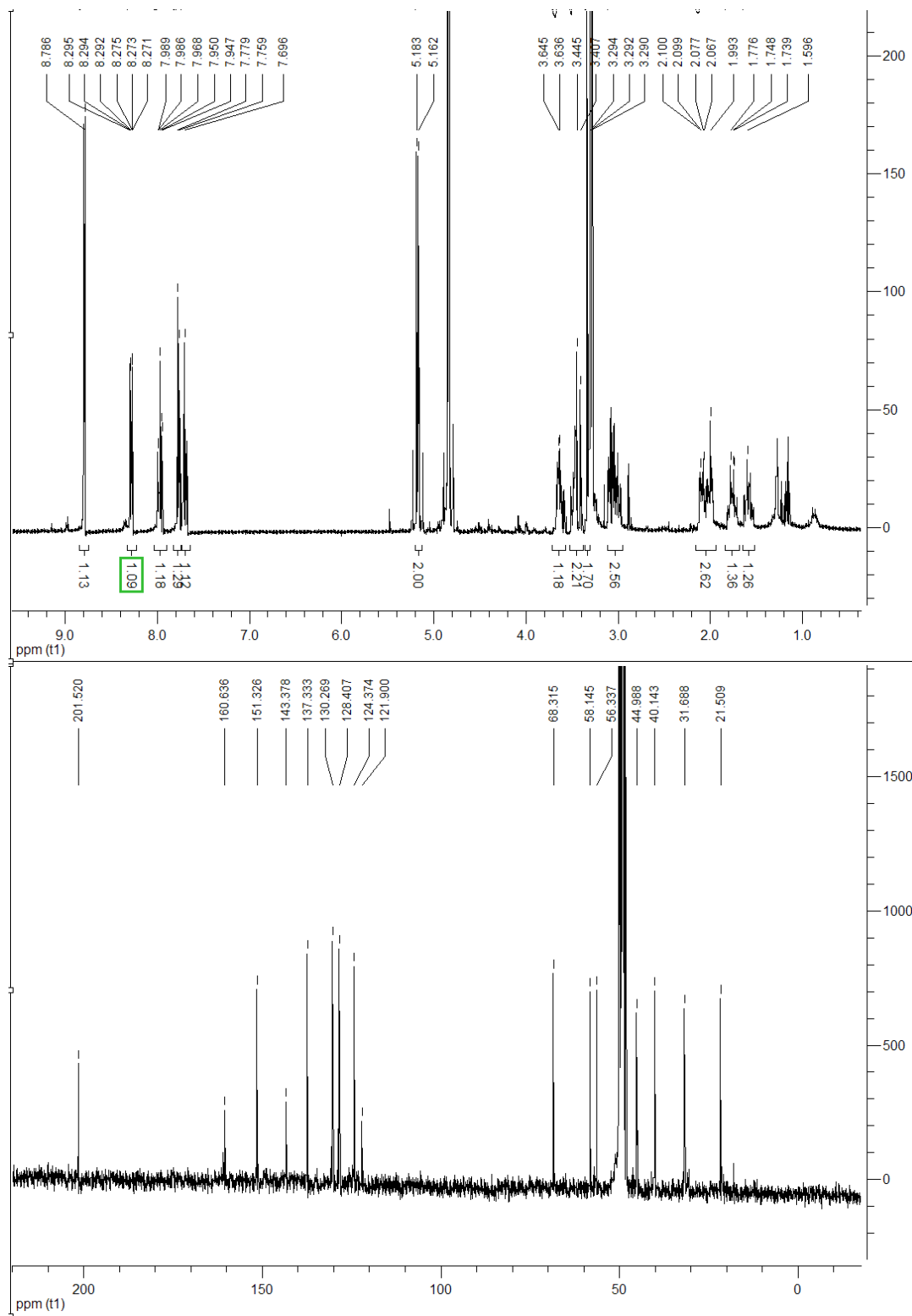




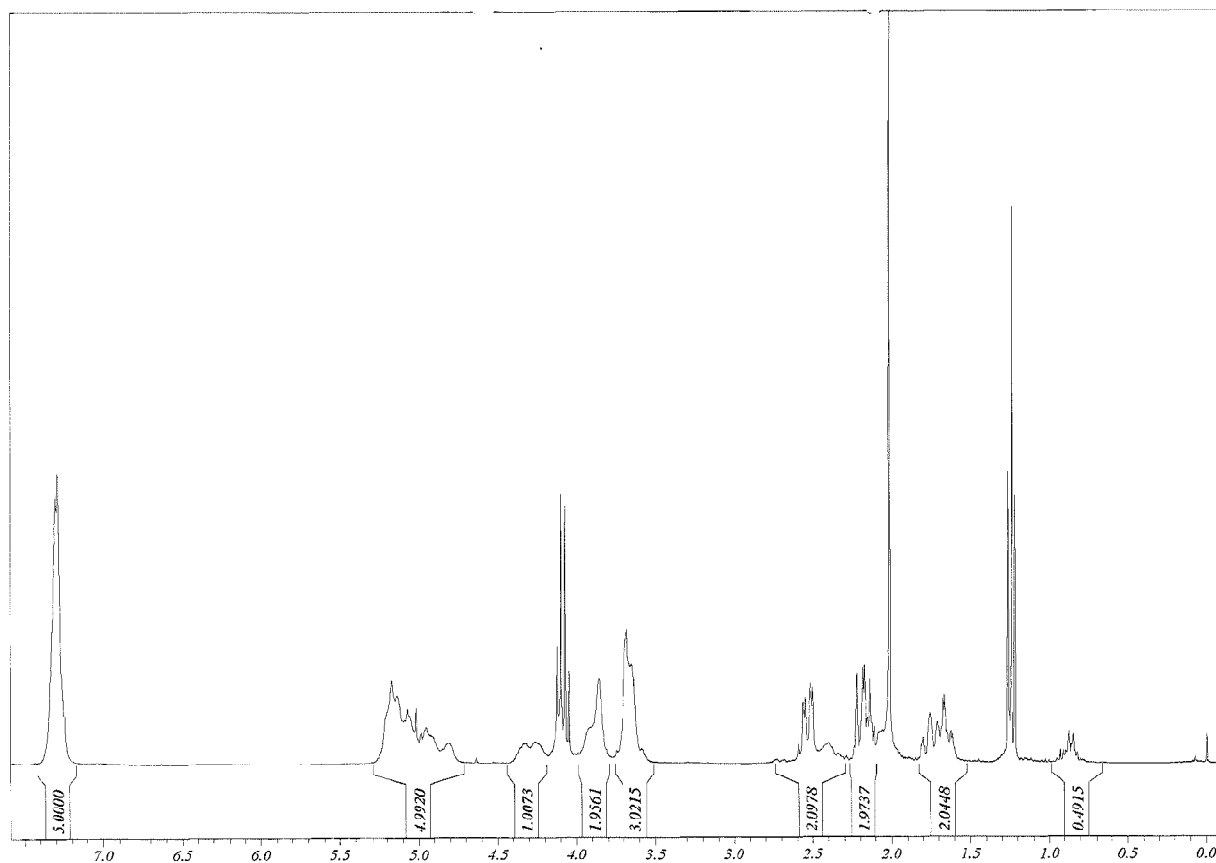
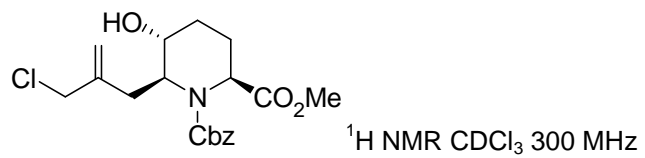
### Febrifugine-2HCl (1)



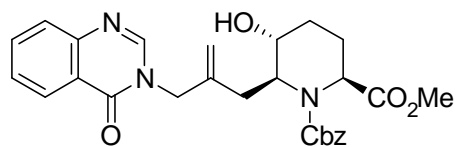
$^1\text{H}$  NMR  $\text{CD}_3\text{OD}$  400 MHz,  $^{13}\text{C}$  NMR MeOD 75 MHz



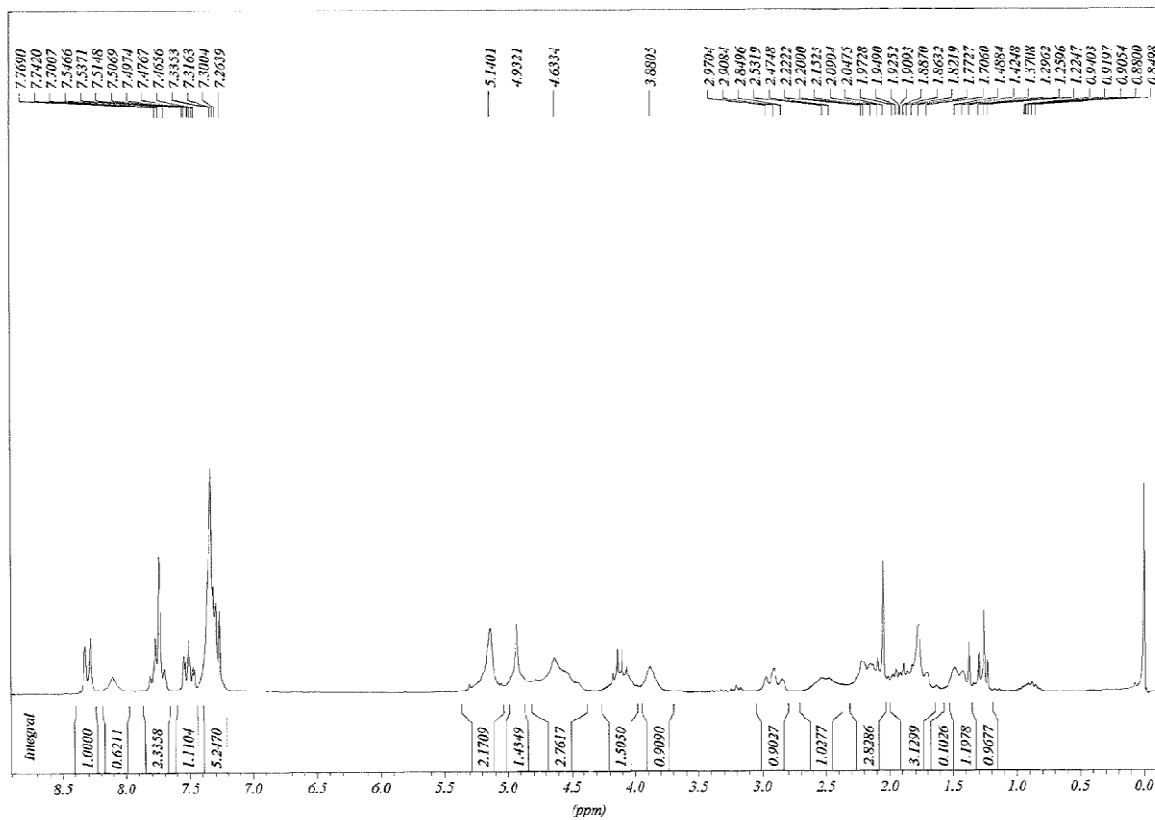
**(2*S*,5*R*,6*S*)-6-(2-Chloromethylallyl)-5-hydroxypiperidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (21).**



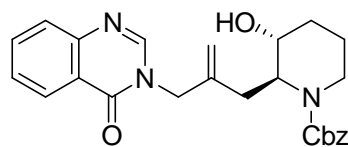
**(2*S*,5*R*,6*S*)-5-Hydroxy-6-[2-(4-oxo-4*H*-quinazolin-3-ylmethyl)-allyl]piperidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (22).**



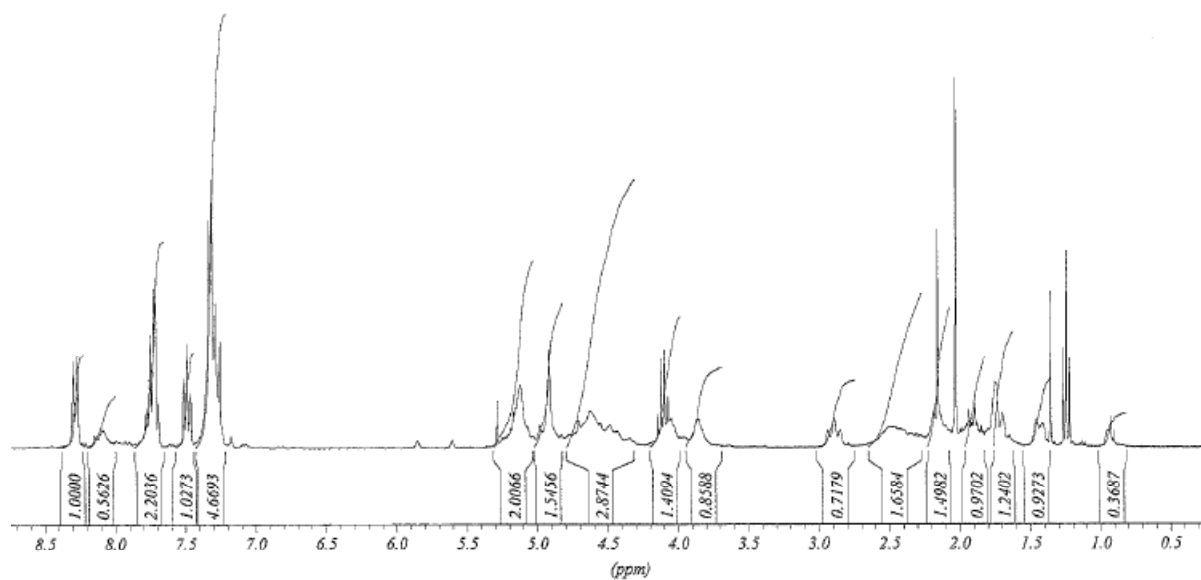
<sup>1</sup>H NMR CDCl<sub>3</sub> 300 MHz



**(2*S*,5*R*,6*S*)-5-Hydroxy-6-[2-(4-oxo-4*H*-quinazolin-3-ylmethyl)-allyl]piperidine-1-carboxylic acid benzyl ester (24).**

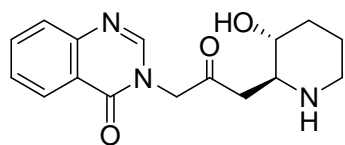


Cbz <sup>1</sup>H NMR CDCl<sub>3</sub> 300 MHz



**(5R,6S)-3-[3-(3-Hydroxy-piperidin-2-yl)-2-oxo-propyl]-3H-quinolizin-4-one-2HCl  
febrifugine-2HCl ((-)-1).**

**(ent-**



$^1\text{H}$  NMR  $\text{CD}_3\text{OD}$  400 MHz,  $^{13}\text{C}$  NMR  $\text{D}_2\text{O}$  75 MHz

