

## Supporting Information

### Direct Imine Acylation; Rapid Access to Diverse Heterocyclic Scaffolds

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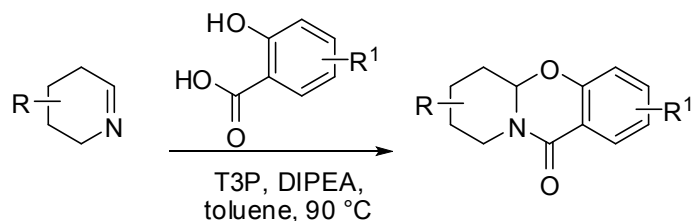
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#### General Information

Except where stated, all reagents were purchased from commercial sources and used without further purification. Except where stated, all experimental procedures were carried out under an atmosphere of argon. Anhydrous  $\text{CH}_2\text{Cl}_2$  and toluene were obtained from an Innovative Technology Inc. PureSolv<sup>®</sup> solvent purification system. Anhydrous THF was obtained by distillation over sodium benzophenone ketyl immediately before use.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on a JEOL ECX400 or JEOL ECS400 spectrometer, operating at 400 MHz and 100 MHz, respectively, or a Bruker DRX500 spectrometer, operating at 500 MHz and 125 MHz, respectively. All spectral data was acquired at 295 K. Chemical shifts ( $\delta$ ) are quoted in parts per million (ppm). The residual solvent peak,  $\delta_{\text{H}}$  7.26 and  $\delta_{\text{C}}$  77.0 for  $\text{CDCl}_3$  and  $\delta_{\text{H}}$  3.31 and  $\delta_{\text{C}}$  49.0 for  $\text{CD}_3\text{OD}$  was used as a reference. Coupling constants ( $J$ ) are reported in Hertz (Hz) to the nearest 0.1 Hz. The multiplicity abbreviations used are: s singlet, d doublet, t triplet, q quartet, m multiplet. Signal assignment was achieved by analysis of DEPT, COSY, NOESY, HMBC and HSQC experiments where required. Infrared (IR) spectra were recorded on a ThermoNicolet IR-100 spectrometer with NaCl plates as a thin film dispersed from either  $\text{CH}_2\text{Cl}_2$  or  $\text{CDCl}_3$ . Mass-spectra (low and high-resolution) were obtained by the University of York Mass Spectrometry Service, using electrospray ionisation (ESI) on a Bruker Daltonics, Micro-tof spectrometer. Melting points were determined using Gallenkamp apparatus and are uncorrected. Thin layer chromatography was carried out

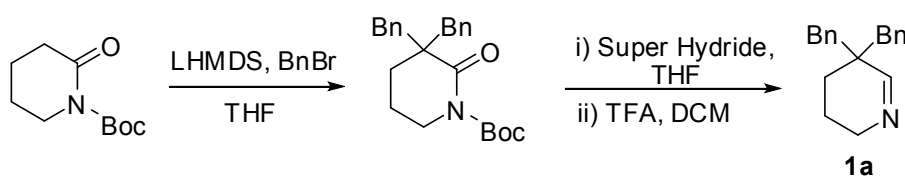
on Merck silica gel 60F<sub>254</sub> pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with either basic aqueous potassium permanganate or ethanolic *p*-anisaldehyde as appropriate. Flash column chromatography was carried out using slurry packed Fluka silica gel (SiO<sub>2</sub>), 35-70 µm, 60 Å, under a light positive pressure, eluting with the specified solvent system. Petrol refers to petroleum ether 40 – 60 °C. Compounds **1d–e**, **2b–h**, **6**, **9**, **11** and **13** were all purchased from Sigma-Aldrich and used as supplied. Compounds **1b**,<sup>1</sup> **2a**,<sup>2</sup> **1f**<sup>3</sup> and **1h**<sup>4</sup> were prepared according to literature procedures.

### General CAM procedure A



To a solution of imine (1 mmol) and acid (1.2 mmol) in dry toluene (10 mL) was added sequentially DIPEA (1.85 mmol) and then T3P (1.5 mmol, 50% solution in THF). The resulting solution was heated at either 50 °C, 90 °C or 120 °C in a sealable tube for the specified time, before cooling to RT and pouring into sat. aq. NaHCO<sub>3</sub> (20 mL). The aqueous layer was extracted with DCM (3 × 30 mL), concentrated *in vacuo* and purified by column chromatography.

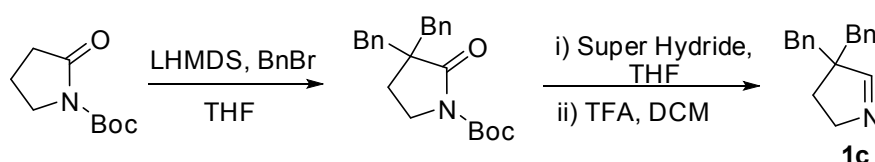
### 5,5-Dibenzyl-2,3,4,5-tetrahydropyridine (**1a**)



To a solution of *N*-Boc-piperidin-2-one (1.85 g, 9.30 mmol) in THF (40 mL) at −78 °C was added LHMDS (22.3 mL, 22.3 mmol, 1 M solution in THF) and the resulting solution was stirred at −78 °C for 1 h. Benzyl bromide (2.65 mL, 22.3 mmol) was then added and the mixture warmed to RT and stirred at this temperature for 2 h, before the reaction was quenched by the addition of sat. aq. NH<sub>4</sub>Cl (100 mL), extracted with ethyl acetate (3 × 100 mL), dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude benzylated piperidinone was next dissolved in THF (93 mL) and cooled to −78 °C. Super-Hydride<sup>TM</sup> (27.9 mL, 27.9 mmol, 1M solution in THF) was added dropwise over 5 minutes and stirring continued at −78 °C for a further 30 minutes. The excess reducing agent was quenched by the addition of ethanol:conc. aq. HCl (10:1, 93 mL) and the resulting mixture diluted with DCM (1 L), washed with water (500 mL), dried over MgSO<sub>4</sub> and concentrated *in vacuo*. A 1:1 mixture of DCM:TFA (40 mL), that had been pre-

cooled to 0 °C, was then added immediately to the crude product and the resulting solution was stirred at 0 °C for 15 minutes. The majority of the volatile organics were then quickly removed *in vacuo*, before the crude residue was dissolved in DCM (500 mL), washed with sat. aq. NaHCO<sub>3</sub> (200 mL), dried over MgSO<sub>4</sub> and concentrated *in vacuo*. Purification by column chromatography (SiO<sub>2</sub>, 1:1 → 1:2 petrol:ethyl acetate) afforded the title compound **1a** as a colourless solid (1.47 g, 60%); *R<sub>f</sub>* 0.15 (1:1 petrol:ethyl acetate); M.p. 63–65 °C;  $\nu_{\text{max}}$  (thin film)/cm<sup>-1</sup> 1645, 1602, 1493, 1453, 1265, 1194, 1059, 939;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 7.73 (1H, s), 7.31–7.20 (6H, m), 7.17–7.12 (4H, m), 3.22–3.16 (2H, m), 2.86 (2H, d, *J* = 13.4 Hz), 2.65 (2H, d, *J* = 13.4 Hz), 1.58–1.54 (2H, m), 1.30–1.24 (2H, m);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 168.8, 137.1, 130.4, 128.1, 126.4, 48.9, 45.0, 42.4, 27.2, 18.7; HRMS (ESI<sup>+</sup>): Found: 264.1742; C<sub>19</sub>H<sub>22</sub>N (MH<sup>+</sup>) Requires: 264.1747 (1.9 ppm error).

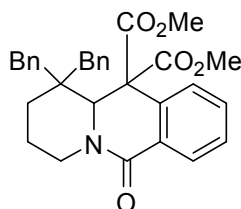
#### 4,4-Dibenzyl-3,4-dihydro-2H-pyrrole (**1c**)



To a solution of *N*-Boc-pyrrolidin-2-one (482 mg, 2.60 mmol) in THF (15 mL) at –78 °C was added LHMDS (6.24 mL, 6.24 mmol, 1 M solution in THF) and the resulting solution was stirred at –78 °C for 1 h. Benzyl bromide (0.742 mL, 6.24 mmol) was then added and the mixture warmed to RT and stirred at this temperature for 2 h, before the reaction was quenched by the addition of sat. aq. NH<sub>4</sub>Cl (50 mL), extracted with ethyl acetate (3 × 50 mL), dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude benzylated pyrrolidinone was next dissolved in THF (26 mL) and cooled to –78 °C. Super-Hydride<sup>TM</sup> (7.80 mL, 7.80 mmol, 1M solution in THF) was added dropwise over 5 minutes and stirring continued at –78 °C for a further 30 minutes after the addition was complete. The excess reducing agent was quenched by the addition of 10:1 ethanol:conc. aq. HCl (26 mL) and the resulting mixture diluted with DCM (500 mL), washed with water (250 mL), dried over MgSO<sub>4</sub> and concentrated *in vacuo*. A 1:1 mixture of DCM:TFA (12 mL), that had been pre-cooled to 0 °C, was then added immediately to the crude product and the resulting solution was stirred at 0 °C for 15 minutes. The majority of the volatile organics were then quickly removed *in vacuo*, before the crude residue was dissolved in DCM (250 mL), washed with sat. aq. NaHCO<sub>3</sub> (100 mL), dried over MgSO<sub>4</sub> and concentrated *in vacuo*. Purification by column chromatography (SiO<sub>2</sub>, 1:1 petrol:ethyl acetate) afforded the title compound **1c** as a colourless oil (433 mg, 67%); *R<sub>f</sub>* 0.22 (1:1 petrol:ethyl acetate);  $\nu_{\text{max}}$  (thin film)/cm<sup>-1</sup> 1600, 1578, 1472, 1432, 1081, 691;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 7.48 (1H, br s), 7.31–7.21 (6H, m), 7.16–7.12 (4H, m), 3.30–3.25 (2H, m), 2.95 (2H, d, *J* = 13.4 Hz), 2.87 (2H, d, *J* = 13.4 Hz), 1.77 (2H, t, *J* = 7.1 Hz);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 172.3,

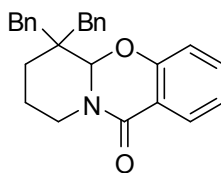
137.5, 130.2, 128.2, 126.4, 60.9, 58.7, 43.8, 31.0; HRMS (ESI<sup>+</sup>): Found: 250.1586; C<sub>18</sub>H<sub>20</sub>N (MH<sup>+</sup>) Requires: 250.1590 (0.4 ppm error).

**Dimethyl 1,1-dibenzyl-6-oxo-1,3,4,11a-tetrahydro-2H-pyrido[1,2-b]isoquinoline-11,11(6H)-dicarboxylate (4a)**



Synthesised using general CAM procedure A from imine **1a** (38.0 mg, 0.144 mmol), acid **2a** (46.3 mg, 0.173 mmol), DIPEA (46.4  $\mu$ L, 0.266 mmol) and T3P (137 mg, 0.216 mmol) in toluene (1.4 mL) at 90 °C for 20 h. Purification by column chromatography (4:1 petrol:ethyl acetate) afforded **4a** as a yellow solid (62.0 mg, 84%). *R<sub>f</sub>* 0.72 (ethyl acetate); M.p. 160–163 °C;  $\nu_{\text{max}}$  (thin film)/cm<sup>-1</sup> 1711, 1624, 1577, 1448, 1412, 1235, 1210, 1163, 731, 692;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 8.16 (1H, dd, *J* = 7.7, 1.1 Hz), 7.65 (1H, dd, *J* = 8.1, 0.7 Hz), 7.57–7.52 (1H, m), 7.45–7.41 (1H, m), 7.25–7.12 (6H, m), 7.04–7.00 (2H, m), 6.95–6.92 (2H, m), 5.17 (1H, s), 4.64 (1H, dt, *J* = 12.6, 6.6 Hz), 3.98 (3H, s), 3.69 (3H, s), 2.85 (1H, dt, *J* = 12.6, 5.9 Hz), 2.75 (1H, d, *J* = 13.2 Hz), 2.58 (1H, d, *J* = 14.6 Hz), 2.46 (1H, d, *J* = 14.6 Hz), 2.43 (1H, d, *J* = 13.2 Hz), 1.69–1.58 (1H, m), 1.55–1.46 (1H, m), 1.41–1.36 (1H, m), 0.99–0.89 (1H, m);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 169.6, 169.0, 162.3, 137.9, 137.7, 133.4, 131.9, 131.3, 130.7, 129.8, 128.6, 128.4, 128.0, 127.7, 126.4, 126.4, 63.2, 60.0, 53.9, 53.2, 44.8, 44.5, 40.5, 39.9, 33.5, 20.0; HRMS (ESI<sup>+</sup>): Found: 498.2278; C<sub>31</sub>H<sub>32</sub>NO<sub>5</sub> (MH<sup>+</sup>) Requires: 498.2275 (1.3 ppm error).

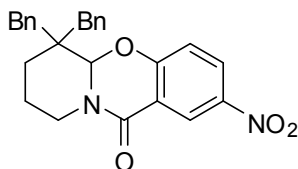
**6,6-Dibenzyl-6,7,8,9-tetrahydrobenzo[e]pyrido[2,1-b][1,3]oxazin-11(5aH)-one (4b)**



Synthesised using general CAM procedure A from imine **1a** (45.0 mg, 0.171 mmol), acid **2b** (28.3 mg, 0.205 mmol), DIPEA (55.0  $\mu$ L, 0.316 mmol) and T3P (163 mg, 0.256 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography (5:1 petrol:ethyl acetate) afforded **4b** as a colourless oil (54.5 mg, 83%); *R<sub>f</sub>* 0.22 (5:1 petrol:ethyl acetate);  $\nu_{\text{max}}$  (thin film)/cm<sup>-1</sup> 1640, 1588, 1448, 1310, 1212, 1053, 896, 742;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 7.94 (1H, dd, *J* = 7.7, 1.2 Hz), 7.49 (1H, td, *J* = 7.9, 1.2 Hz), 7.35–7.05 (12H, m), 5.09 (1H, s), 4.71–4.64 (1H, m), 3.23 (1H, d, *J* = 13.4 Hz), 3.22 (1H, d, *J* = 13.7 Hz), 2.91 (1H, d, *J* = 13.7 Hz), 2.48–2.40 (2H, m), 2.19–2.05 (1H, m), 1.64–1.56 (2H, m), 1.42–1.32 (1H, m);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 162.6, 156.1, 137.2, 136.4, 134.3, 131.1, 131.1, 128.1, 126.5, 122.0, 116.1, 115.7,

89.2, 42.4, 41.8, 41.4, 35.8, 27.6, 19.6; HRMS (ESI<sup>+</sup>): Found: 406.1763; C<sub>26</sub>H<sub>25</sub>NNaO<sub>2</sub> (MNa<sup>+</sup>) Requires: 406.1778, Found: 384.1940; C<sub>26</sub>H<sub>26</sub>NO<sub>2</sub> (MH<sup>+</sup>) Requires: 384.1958 (4.6 ppm error).

**6,6-Dibenzyl-2-nitro-6,7,8,9-tetrahydrobenzo[e]pyrido[2,1-b][1,3]oxazin-11(5a*H*)-one (4c)**



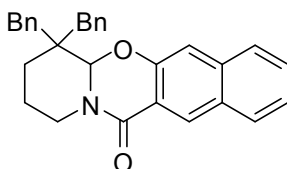
**Syntheses from acid 2c:**

Synthesised using general CAM procedure A from imine **1a** (37.0 mg, 0.141 mmol), acid **2c** (30.9 mg, 0.169 mmol), DIPEA (45.5  $\mu$ L, 0.261 mmol) and T3P (135 mg, 0.212 mmol) in toluene (1.4 mL) at 90 °C for 20 h. Purification by column chromatography (4:1 petrol:ethyl acetate) afforded **4c** as a colourless oil (55.0 mg, 91%).

Also synthesised using general CAM procedure A from imine **1a** (33.0 mg, 0.125 mmol), acid **2c** (27.6 mg, 0.150 mmol), DIPEA (40.3  $\mu$ L, 0.231 mmol) and T3P (119 mg, 0.188 mmol) in toluene (1.3 mL) at 50 °C for 2 h. Purification by column chromatography (4:1 petrol:ethyl acetate) afforded **4c** as a colourless oil (51.0 mg, 95%).

R<sub>f</sub> 0.80 (ethyl acetate);  $\nu_{\max}$  (thin film)/cm<sup>-1</sup> 1646, 1597, 1571, 1503, 1459, 1426, 1321, 1268, 693;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 8.83 (1H, d, *J* = 2.8 Hz), 8.36 (1H, dd, *J* = 9.2, 2.8 Hz), 7.35–7.19 (9H, m), 7.14–7.10 (2H, m), 5.26 (1H, s), 4.76–4.70 (1H, m), 3.18 (1H, d, *J* = 13.5 Hz), 3.17 (1H, d, *J* = 13.5 Hz, overlapping), 2.78 (1H, d, *J* = 13.5 Hz), 2.52–2.43 (2H, m), 2.17–2.04 (1H, m), 1.68–1.58 (2H, m), 1.47–1.35 (1H, m);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 160.4, 159.5, 142.5, 136.3, 135.9, 130.9, 129.5, 128.2, 126.7, 124.6, 116.7, 115.8, 90.4, 43.0, 42.2, 41.3, 35.6, 27.8, 19.6; HRMS (ESI<sup>+</sup>): Found: 429.1817; C<sub>26</sub>H<sub>25</sub>N<sub>2</sub>O<sub>4</sub> (MH<sup>+</sup>) Requires: 429.1809 (1.8 ppm error).

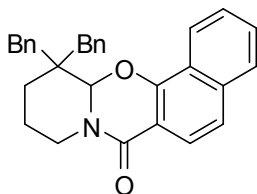
**4,4-Dibenzyl-2,3,4,4a-tetrahydronaphtho[2,3-e]pyrido[2,1-b][1,3]oxazin-12(1*H*)-one (4d)**



Synthesised using general CAM procedure A from imine **1a** (56.2 mg, 0.214 mmol), acid **2d** (48.2 mg, 0.256 mmol), DIPEA (69.0  $\mu$ L, 0.396 mmol) and T3P (204 mg, 0.321 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography (7:1→5:1 petrol:ethyl acetate) afforded **4d** as a white solid (88.4 mg, 95%); M.p. 204–205 °C; R<sub>f</sub> 0.29 (5:1 petrol:ethyl acetate);  $\nu_{\max}$  (thin film)/cm<sup>-1</sup> 1640,

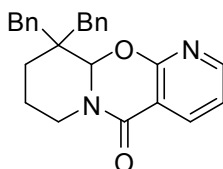
1608, 1580, 1491, 1438, 1388, 1338, 1264, 1233, 869;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 8.53 (1H, s), 7.89 (1H, d,  $J = 8.2$ ), 7.80 (1H, d,  $J = 8.2$ ), 7.56–7.48 (1H, m), 7.48 (1H, s), 7.42–7.37 (1H, m), 7.34–7.16 (10H, m), 5.16 (1H, s), 4.80–4.74 (1H, m), 3.29 (1H, d,  $J = 13.4$  Hz), 3.21 (1H, d,  $J = 13.7$  Hz), 2.91 (1H, d,  $J = 13.7$  Hz), 2.57–2.48 (1H, m), 2.45 (1H, d,  $J = 13.4$  Hz), 2.22–2.08 (1H, m), 1.66–1.56 (2H, m), 1.45–1.35 (1H, m);  $\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 162.3, 152.6, 137.3, 136.9, 136.6, 131.3, 131.1, 129.9, 129.6, 129.2, 128.7, 128.3, 128.2, 126.7, 126.6, 126.5, 124.8, 117.1, 110.8, 89.2, 43.0, 42.3, 41.7, 35.8, 27.9, 19.9; HRMS ( $\text{ESI}^+$ ): Found: 434.2126;  $\text{C}_{30}\text{H}_{28}\text{NO}_2$  ( $\text{MH}^+$ ) Requires: 434.2115 (2.6 ppm error).

**12,12-Dibenzyl-10,11,12,12a-tetrahydronaphtho[2,1-e]pyrido[2,1-b][1,3]oxazin-7(9H)-one (4e)**



Synthesised using general CAM procedure A from imine **1a** (50.6 mg, 0.192 mmol), acid **2e** (43.5 mg, 0.231 mmol), DIPEA (62.0  $\mu\text{L}$ , 0.356 mmol) and T3P (183 mg, 0.288 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography (7:1 petrol:ethyl acetate) afforded **4e** as colourless oil (76.7 mg, 92%);  $R_f$  0.29 (5:1 petrol:ethyl acetate);  $\nu_{\text{max}}$  (thin film)/ $\text{cm}^{-1}$  1626, 1574, 1491, 1442, 1418, 1380, 1264, 1237;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 9.58 (1H, d,  $J = 8.6$ ), 7.98 (1H, d,  $J = 9.0$ ), 7.79 (1H, d,  $J = 7.9$ ), 7.62–7.58 (1H, m), 7.45–7.40 (1H, m), 7.35–7.15 (9H, m), 7.12–7.07 (2H, m), 5.12 (1H, s), 4.74–4.66 (1H, m), 3.32 (1H, d,  $J = 13.7$  Hz), 3.26 (1H, d,  $J = 13.4$  Hz), 3.00 (1H, d,  $J = 13.7$  Hz), 2.59–2.47 (2H, m), 2.25–2.10 (1H, m), 1.70–1.60 (2H, m), 1.42–1.32 (1H, m);  $\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 165.0, 157.3, 137.5, 136.7, 136.0, 132.1, 131.2, 130.1, 129.0, 128.5, 128.3, 126.6, 126.5, 126.3, 124.7, 117.0, 107.9, 88.8, 41.9, 41.7, 41.7, 36.3, 27.6, 19.6; HRMS ( $\text{ESI}^+$ ): Found: 434.2131;  $\text{C}_{30}\text{H}_{28}\text{NO}_2$  ( $\text{MH}^+$ ) Requires: 434.2115 (3.8 ppm error).

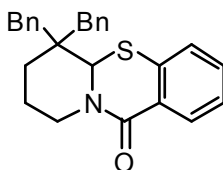
**10,10-Dibenzyl-8,9,10,10a-tetrahydrodipyrido[2,1-b:3',2'-e][1,3]oxazin-5(7H)-one (4f)**



Synthesised using general CAM procedure A from imine **1a** (43.5 mg, 0.165 mmol), acid **2f** (27.6 mg, 0.198 mmol), DIPEA (53.3  $\mu\text{L}$ , 0.306 mmol) and T3P (158 mg, 0.248 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography (5:1→3:1 petrol:ethyl acetate) afforded **4f** as a colourless oil (61.7 mg, 97%);  $R_f$  0.29 (3:1 petrol:ethyl acetate);  $\nu_{\text{max}}$  (thin film)/ $\text{cm}^{-1}$  1642, 1575, 1471, 1450, 1415, 1394, 1318, 1231;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 8.41 (1H, dd,  $J = 4.9, 1.8$  Hz), 8.28 (1H, dd,  $J =$

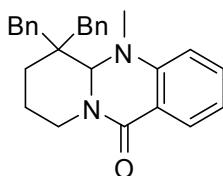
7.5, 1.8 Hz), 7.33–7.17 (10H, m), 7.10 (1H, dd,  $J = 7.5, 4.9$  Hz), 5.29 (1H, s), 4.73–4.65 (1H, m), 3.34 (1H, d,  $J = 13.5$  Hz), 3.16 (1H, d,  $J = 13.5$  Hz), 2.87 (1H, d,  $J = 13.5$  Hz), 2.50–2.38 (2H, m), 2.17–2.03 (1H, m), 1.67–1.55 (2H, m), 1.46–1.36 (1H, m);  $\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 161.4, 160.9, 152.8, 137.8, 136.7, 136.2, 131.2, 130.9, 128.2, 126.5, 119.0, 110.7, 89.5, 42.9, 42.2, 41.1, 35.3, 27.6, 19.7; HRMS ( $\text{ESI}^+$ ): Found: 407.1734;  $\text{C}_{25}\text{H}_{24}\text{N}_2\text{NaO}_2$  ( $\text{MNa}^+$ ) Requires: 407.1730 (0.9 ppm error), Found: 385.1907;  $\text{C}_{25}\text{H}_{25}\text{N}_2\text{O}_2$  ( $\text{MH}^+$ ) Requires: 385.1911 (1.0 ppm error).

#### 6,6-Dibenzyl-6,7,8,9-tetrahydrobenzo[e]pyrido[2,1-b][1,3]thiazin-11(5aH)-one (4g)



Synthesised using general CAM procedure A from imine **1a** (50.1 mg, 0.190 mmol), acid **2g** (35.2 mg, 0.228 mmol), DIPEA (61.3  $\mu\text{L}$ , 0.352 mmol) and T3P (182 mg, 0.286 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography (5:1 petrol:ethyl acetate) afforded **4g** as a white solid (72.5 mg, 96%); M.p. 182–184 °C;  $R_f$  0.44 (5:1 petrol:ethyl acetate);  $\nu_{\text{max}}$  (thin film)/ $\text{cm}^{-1}$  1616, 1433, 1266, 896;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 8.18 (1H, dd,  $J = 7.9, 0.9$  Hz), 7.38–7.16 (9H, m), 7.13–7.07 (4H, m), 5.00–4.93 (1H, m), 4.63 (1H, s), 3.19 (1H, d,  $J = 13.7$  Hz), 2.90 (1H, d,  $J = 13.1$  Hz), 2.67 (1H, d,  $J = 13.1$  Hz), 2.56–2.47 (1H, m), 2.26 (1H, d,  $J = 13.7$  Hz), 2.20–2.07 (1H, m), 1.77–1.70 (1H, m), 1.64–1.50 (2H, m);  $\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 162.6, 137.0, 136.5, 134.1, 132.3, 131.2, 131.1, 130.5, 128.4, 128.2, 126.7, 126.6, 125.8, 65.5, 48.0, 47.2, 40.9, 36.5, 30.5, 21.6; HRMS ( $\text{ESI}^+$ ): Found: 400.1739;  $\text{C}_{26}\text{H}_{26}\text{NOS}$  ( $\text{MH}^+$ ) Requires: 400.1730 (2.3 ppm error).

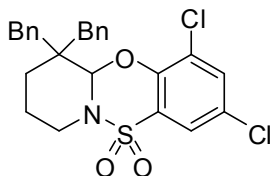
#### 6,6-Dibenzyl-5-methyl-6,7,8,9-tetrahydro-5H-pyrido[2,1-b]quinazolin-11(5aH)-one (4h)



Synthesised using general CAM procedure A from imine **1a** (39.0 mg, 0.148 mmol), acid **2h** (26.9 mg, 0.178 mmol), DIPEA (47.7  $\mu\text{L}$ , 0.273 mmol) and T3P (141 mg, 0.222 mmol) in toluene (1.5 mL) at 90 °C for 20 h. Purification by column chromatography (4:1 petrol:ethyl acetate) afforded **4h** as a colourless oil (72.0 mg, 97%).  $R_f$  0.55 (ethyl acetate);  $\nu_{\text{max}}$  (thin film)/ $\text{cm}^{-1}$  1623, 1580, 1471, 1452, 1432, 1397, 1280, 1253;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.97 (1H, dd,  $J = 7.7, 1.3$  Hz), 7.45–7.40 (1H, m), 7.30–7.14 (8H, m), 7.07–6.98 (4H, m), 4.91–4.84 (1H, m), 4.33 (1H, s), 3.16 (3H, s), 3.05 (1H, d,  $J = 13.5$  Hz), 2.81 (1H, d,  $J = 13.2$  Hz), 2.54–2.43 (2H, m), 2.23 (1H, d,  $J = 13.2$  Hz), 2.15–2.01 (1H, m), 1.68–1.62 (1H, m), 1.56–1.45 (2H, m);  $\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 162.1, 150.3, 137.7, 137.6, 133.4, 131.5, 131.1, 128.1, 126.5,

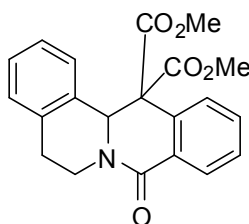
126.3, 122.0, 121.4, 120.7, 82.1, 48.2, 48.0, 44.8, 40.9, 37.1, 31.1, 21.7; HRMS (ESI<sup>+</sup>): Found: 397.2286; C<sub>27</sub>H<sub>29</sub>N<sub>2</sub>O (MH<sup>+</sup>) Requires: 397.2274 (2.9 ppm error).

**1,3-Dichloro-10,10-dibenzyl-8,9,10a-tetrahydro-7H-pyrido[1,2-*b*][4,1,2]benzoxathiazine 5,5-dioxide (7)**



To a solution of imine **1a** (35.0 mg, 0.133 mmol) and sulfonyl chloride **6** (41.7 mg, 0.160 mmol) in dry toluene (10 mL) was added DIPEA (42.9  $\mu$ L, 0.246 mmol). The resulting solution was heated at 90 °C in a sealable tube for 20 h, before cooling to RT and pouring into sat. aq. NaHCO<sub>3</sub> (20 mL). The aqueous layer was extracted with DCM (3  $\times$  30 mL), and the organic extracts combined, concentrated *in vacuo* and purified by column chromatography (2:1 petrol:ethyl acetate) affording **7** as white solid (60.0 mg, 92%); M.p. 188–191 °C; R<sub>f</sub> 0.65 (ethyl acetate);  $\nu_{\text{max}}$  (thin film)/cm<sup>-1</sup> 1432, 1337, 1217, 1161, 944, 690;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 7.63 (1H, d, *J* = 2.6 Hz), 7.57 (1H, d, *J* = 2.6 Hz), 7.45–7.23 (10H, m), 5.49 (1H, s), 3.65–3.57 (1H, m), 3.10 (1H, d, *J* = 14.3 Hz), 3.00 (1H, d, *J* = 14.3 Hz), 2.97 (1H, d, *J* = 14.6 Hz), 2.87 (1H, d, *J* = 14.6 Hz), 2.78–2.71 (1H, m), 2.13–2.00 (1H, m), 1.82–1.63 (2H, m), 1.55–1.49 (1H, m);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 147.0, 136.5, 136.4, 136.4, 131.1, 131.1, 128.5, 127.3, 126.9, 124.5, 124.2, 124.0, 90.0, 42.3, 42.1, 39.7, 35.5, 27.8; HRMS (ESI<sup>+</sup>): Found: 488.0828; C<sub>25</sub>H<sub>24</sub><sup>35</sup>Cl<sub>2</sub>NO<sub>2</sub>S (MH<sup>+</sup>) Requires: 488.0848 (4.1 ppm error).

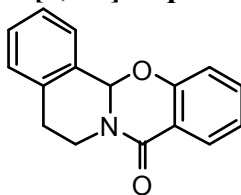
**Dimethyl 1,1-dibenzyl-6-oxo-3,4,6,11a-tetrahydro-1H-pyrido[1,2-*b*]isoquinoline-11,11(2*H*)-dicarboxylate (4i)**



Synthesised using general CAM procedure A from imine **1b** (25.0 mg, 0.191 mmol), acid **2a** (57.4 mg, 0.229 mmol), DIPEA (61.6  $\mu$ L, 0.353 mmol) and T3P (182 mg, 0.287 mmol) in toluene (1.9 mL) at 90 °C for 20 h. Purification by column chromatography (4:1 petrol:ethyl acetate) afforded **4i** as a colourless oil (48.0 mg, 69%). R<sub>f</sub> 0.49 (ethyl acetate);  $\nu_{\text{max}}$  (thin film)/cm<sup>-1</sup> 1710, 1627, 1437, 1384, 1234, 716;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 8.19 (1H, dd, *J* = 7.7, 1.8 Hz), 7.56–7.46 (2H, m), 7.30–7.14 (5H, m), 5.71 (1H, s), 4.93–4.86 (1H, m), 3.90 (3H, s), 3.49 (3H, s), 3.15–2.93 (2H, m), 2.81–2.74 (1H, m);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 170.2, 166.8, 164.3, 139.0, 137.2, 132.3, 132.0, 128.9, 128.9, 128.7, 128.3, 127.9, 127.7,

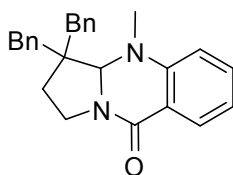
126.6, 126.5, 66.1, 61.2, 53.1, 53.0, 39.9, 29.6; HRMS (ESI<sup>+</sup>): Found: 366.1342; C<sub>21</sub>H<sub>20</sub>NO<sub>5</sub> (MH<sup>+</sup>) Requires: 366.1336 (1.8 ppm error).

**Dimethyl 8-oxo-5,13a-dihydro-6H-isoquino[3,2-a]isoquinoline-13,13(8H)-dicarboxylate (4j)**



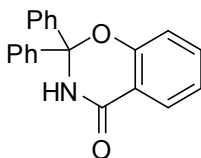
Synthesised using general CAM procedure A from imine **1b** (30.0 mg, 0.229 mmol), acid **2b** (37.9 mg, 0.275 mmol), DIPEA (73.8  $\mu$ L, 0.424 mmol) and T3P (219 mg, 0.344 mmol) in toluene (2.3 mL) at 90 °C for 20 h. Purification by column chromatography (3:1 petrol:ethyl acetate) afforded **4j** as a colourless oil (51.0 mg, 89%).  $R_f$  0.20 (2:1 petrol:ethyl acetate);  $\nu_{\max}$  (thin film)/cm<sup>-1</sup> 1643, 1588, 1446, 1395, 1211, 1014, 746;  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 8.03 (1H, dd,  $J$  = 7.7, 1.5 Hz), 7.62–7.58 (1H, m), 7.51–7.45 (1H, m), 7.41–7.35 (2H, m), 7.28–7.24 (1H, m), 7.15 (1H, t,  $J$  = 7.7 Hz), 7.07 (1H, d,  $J$  = 8.2 Hz), 6.28 (1H, s), 4.52 (1H, dt  $J$  = 12.8, 4.4 Hz), 3.46–3.38 (1H, m), 3.14–3.05 (1H, m), 2.90–2.83 (1H, m);  $\delta_C$  (100 MHz, CDCl<sub>3</sub>) 163.1, 157.6, 136.2, 134.3, 130.8, 129.5, 128.7, 128.6, 128.2, 127.3, 122.8, 118.8, 116.6, 84.1, 38.3, 28.6; HRMS (ESI<sup>+</sup>): Found: 252.1021; C<sub>16</sub>H<sub>14</sub>NO<sub>2</sub> (MH<sup>+</sup>) Requires: 252.1019 (0.9 ppm error).

**3,3-Dibenzyl-4-methyl-2,3,3a,4-tetrahydropyrrolo[2,1-b]quinazolin-9(1H)-one (4k)**



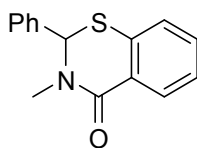
Synthesised using general CAM procedure A from imine **1c** (34.0 mg, 0.136 mmol), acid **2h** (24.8 mg, 0.164 mmol), DIPEA (43.8  $\mu$ L, 0.252 mmol) and T3P (130 mg, 0.204 mmol) in toluene (1.4 mL) at 90 °C for 20 h. Purification by column chromatography (4:1 petrol:ethyl acetate) afforded **4k** as a colourless oil (52.0 mg, 87%).  $R_f$  0.68 (ethyl acetate);  $\nu_{\max}$  (thin film)/cm<sup>-1</sup> 1677, 1626, 1464, 1381, 1292, 1244;  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 7.92 (1H, dd,  $J$  = 7.5, 1.5 Hz), 7.44–7.39 (1H, m), 7.35–7.20 (8H, m), 7.10–7.06 (2H, m), 6.90 (1H, t,  $J$  = 7.5 Hz), 6.85 (1H, d,  $J$  = 8.4 Hz), 4.70 (1H, s), 3.54–3.46 (2H, m), 3.24 (3H, s), 3.19 (1H, d,  $J$  = 14.3 Hz), 3.17 (1H, d,  $J$  = 14.1 Hz), 2.97 (1H, d,  $J$  = 14.1 Hz), 2.90 (1H, d,  $J$  = 14.3 Hz), 1.84–1.65 (2H, m);  $\delta_C$  (100 MHz, CDCl<sub>3</sub>) 162.5, 149.9, 137.5, 136.2, 133.6, 131.4, 131.0, 128.4, 128.1, 126.9, 126.8, 119.1, 117.7, 112.7, 77.9, 50.0, 42.4, 41.1, 37.7, 35.3, 28.1; HRMS (ESI<sup>+</sup>): Found: 405.1934; C<sub>26</sub>H<sub>26</sub>N<sub>2</sub>NaO (MH<sup>+</sup>) Requires: 405.1937 (1.9 ppm error).

### 2,2-Diphenyl-2*H*-benzo[*e*][1,3]oxazin-4(3*H*)-one (4l)



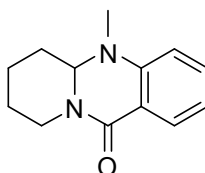
Synthesised using general CAM procedure A from imine **1d** (35.6  $\mu$ L, 0.200 mmol), acid **2b** (33.1 mg, 0.240 mmol), DIPEA (64.5  $\mu$ L, 0.370 mmol) and T3P (191 mg, 0.300 mmol) in toluene (2.0 mL) at 90 °C for 20 h. Purification by column chromatography (4:1 petrol:ethyl acetate) afforded **4l** as a white solid (36.0 mg, 60%). M.p. 220–223 °C;  $R_f$  0.60 (ethyl acetate);  $\nu_{\max}$  (thin film)/ $\text{cm}^{-1}$  1647, 1627, 1589, 1448, 1354, 1219;  $\delta_H$  (400 MHz,  $\text{CDCl}_3$ ) 7.85 (1H, dd,  $J = 7.9, 1.5$  Hz), 7.52–7.48 (4H, m), 7.44–7.34 (7H, m), 7.05–6.98 (2H, m), 6.72 (1H, br s);  $\delta_C$  (100 MHz,  $\text{CDCl}_3$ ) 162.6, 156.0, 141.3, 134.8, 129.1, 128.5, 127.8, 127.1, 122.3, 118.0, 117.5, 92.0; HRMS ( $\text{ESI}^+$ ): Found: 302.1174;  $\text{C}_{20}\text{H}_{16}\text{NO}_2$  ( $\text{MH}^+$ ) Requires: 302.1176 (0.6 ppm error).

### 3-Methyl-2-phenyl-2*H*-benzo[*e*][1,3]thiazin-4(3*H*)-one (4m)<sup>5</sup>



Synthesised using general CAM procedure A from imine **1e** (51.8 mg, 0.435 mmol), acid **2g** (80.4 mg, 0.522 mmol), DIPEA (140  $\mu$ L, 0.804 mmol) and T3P (415 mg, 0.652 mmol) in toluene (2.0 mL) at 90 °C for 20 h. Purification by column chromatography (2:1 petrol:ethyl acetate) afforded **23** as an orange solid (11.5 mg, 99%); M.p. 77–79 °C [Lit M.p. 79–81 °C]<sup>4</sup>;  $R_f$  0.29 (2:1 petrol:ethyl acetate);  $\delta_H$  (400 MHz,  $\text{CDCl}_3$ ) 8.16 (1H, dd,  $J = 7.7, 1.3$  Hz), 7.33–7.19 (7H, m), 7.09 (1H, d,  $J = 7.3$ ), 5.64 (1H, s), 3.25 (3H, s); HRMS ( $\text{ESI}^+$ ): Found: 256.0794;  $\text{C}_{15}\text{H}_{14}\text{NOS}$  ( $\text{MH}^+$ ) Requires: 256.0791. Data is consistent with those in the literature.<sup>5</sup>

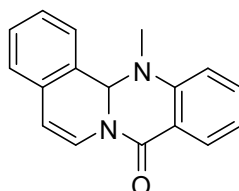
### 5-Methyl-6,7,8,9-tetrahydro-5*H*-pyrido[2,1-*b*]quinazolin-11(5*aH*)-one (4n)



Synthesised using general CAM procedure A from dodecahydo-4a,8a,12a-triazatriphenylene **1g**<sup>3</sup> (26.1 mg, 0.173 mmol), acid **14a** (43.0 mg, 0.173 mmol), DIPEA (55.7  $\mu$ L, 0.320 mmol) and T3P (165 mg, 0.260 mmol) in toluene (1.7 mL) at 90 °C for 20 h. Purification by column chromatography (4:1 petrol:ethyl acetate) afforded **18** as a colourless oil (15.0 mg, 40%);  $R_f$  0.39 (ethyl acetate);  $\nu_{\max}$  (thin

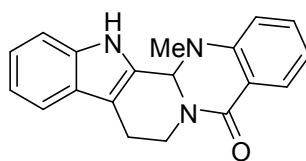
film)/cm<sup>-1</sup> 1624, 1581, 1463, 1449, 1290, 1156;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 7.92 (1H, dd,  $J$  = 8.0, 1.7 Hz), 7.32 (1H, td,  $J$  = 8.0, 1.7 Hz), 6.76 (1H, t,  $J$  = 8.0 Hz), 6.51 (1H, d,  $J$  = 8.0 Hz), 4.83–4.76 (1H, m), 4.64 (1H, dd,  $J$  = 10.6, 2.4 Hz), 2.88 (3H, s), 2.67–2.60 (1H, m), 2.02–1.95 (1H, m), 1.82–1.55 (5H, m);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 162.6, 146.4, 133.9, 128.8, 117.4, 114.8, 111.0, 78.1, 45.0, 34.8, 28.3, 24.7, 24.4; HRMS (ESI<sup>+</sup>): Found: 217.1340; C<sub>13</sub>H<sub>17</sub>N<sub>2</sub>O (MH<sup>+</sup>) Requires: 217.1335 (2.1 ppm error).

### 13-Methyl-13,13a-dihydro-8*H*-isoquinolino[1,2-*b*]quinazolin-8-one (**4o**)

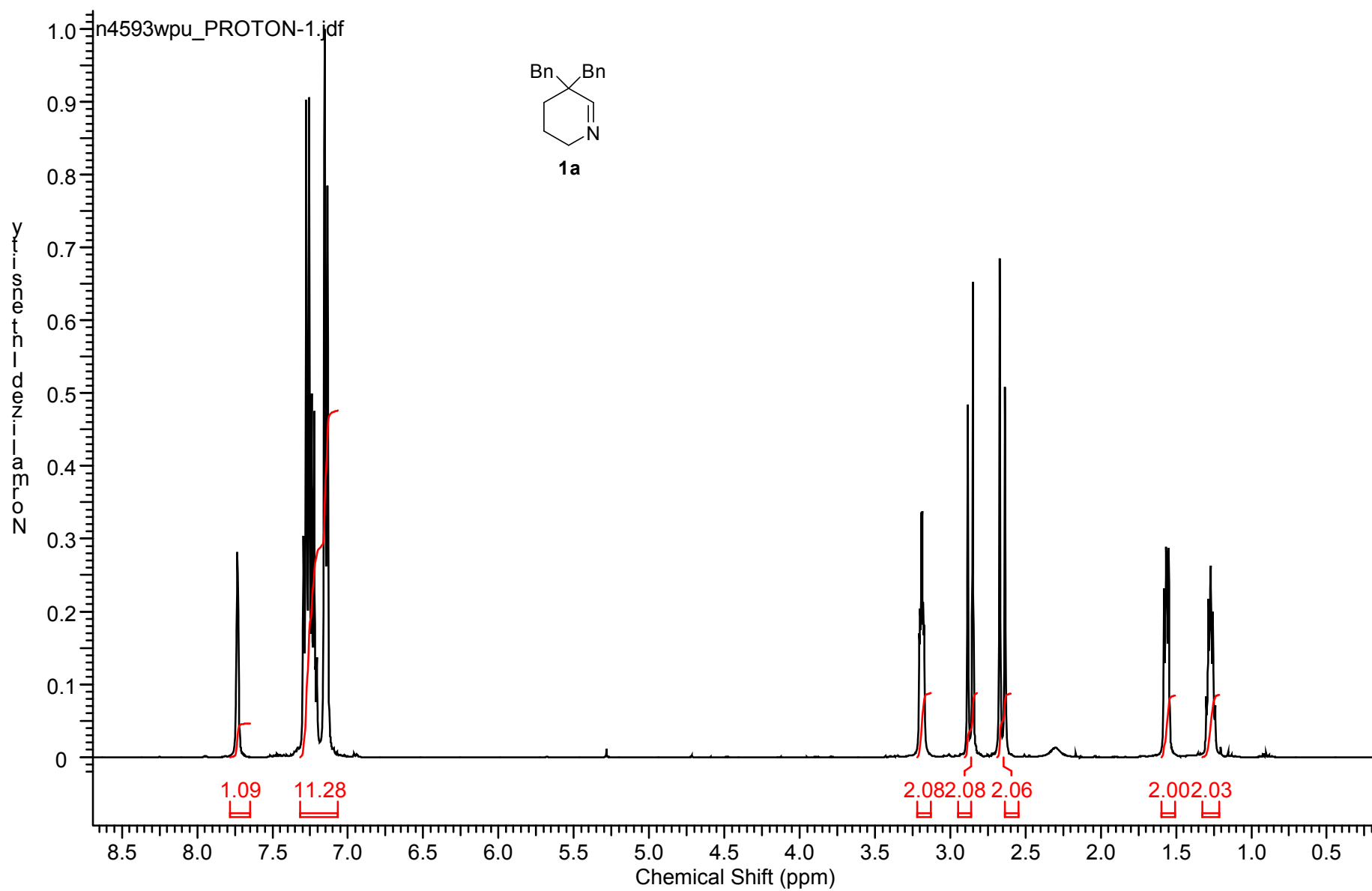


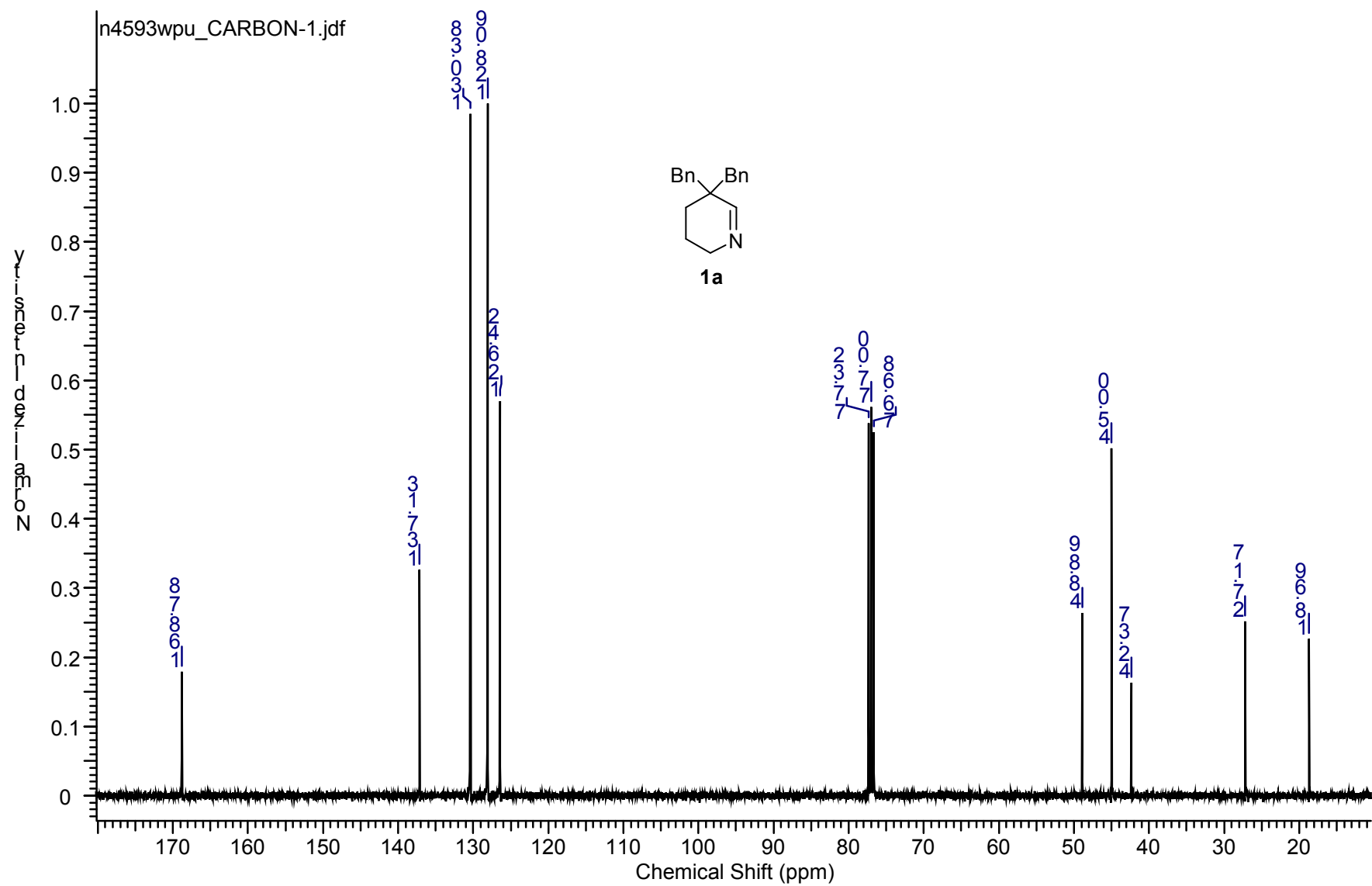
Synthesised using general CAM procedure A from isoquinoline **1g** (29.8  $\mu$ L, 0.250 mmol), acid **2h** (45.4 mg, 0.300 mmol), DIPEA (80.6  $\mu$ L, 0.463 mmol) and T3P (239 mg, 0.375 mmol) in toluene (2.5 mL) at 90 °C for 20 h. Purification by column chromatography (4:1 petrol:ethyl acetate) afforded **4o** as a colourless oil (62.0 mg, 94%).  $R_f$  0.80 (ethyl acetate);  $\nu_{\text{max}}$  (thin film)/cm<sup>-1</sup> 1641, 1618, 1581, 1432, 1395, 1362, 1304, 1238, 1154, 884;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 8.08 (1H, dd,  $J$  = 8.2, 1.5 Hz), 7.55–7.51 (1H, m), 7.44 (1H, d,  $J$  = 7.1 Hz), 7.40 (1H, d,  $J$  = 8.0 Hz), 7.30–7.18 (4H, m), 7.07–7.03 (1H, m), 6.44 (1H, s), 5.71 (1H, d,  $J$  = 8.0 Hz), 2.63 (3H, s);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 162.0, 150.5, 134.2, 131.7, 129.3, 129.2, 127.8, 127.3, 126.7, 125.7, 124.1, 123.5, 123.3, 122.8, 106.0, 72.1, 36.7; HRMS (ESI<sup>+</sup>): Found: 263.1176; C<sub>17</sub>H<sub>15</sub>N<sub>2</sub>O (MH<sup>+</sup>) Requires: 263.1179 (1.1 ppm error).

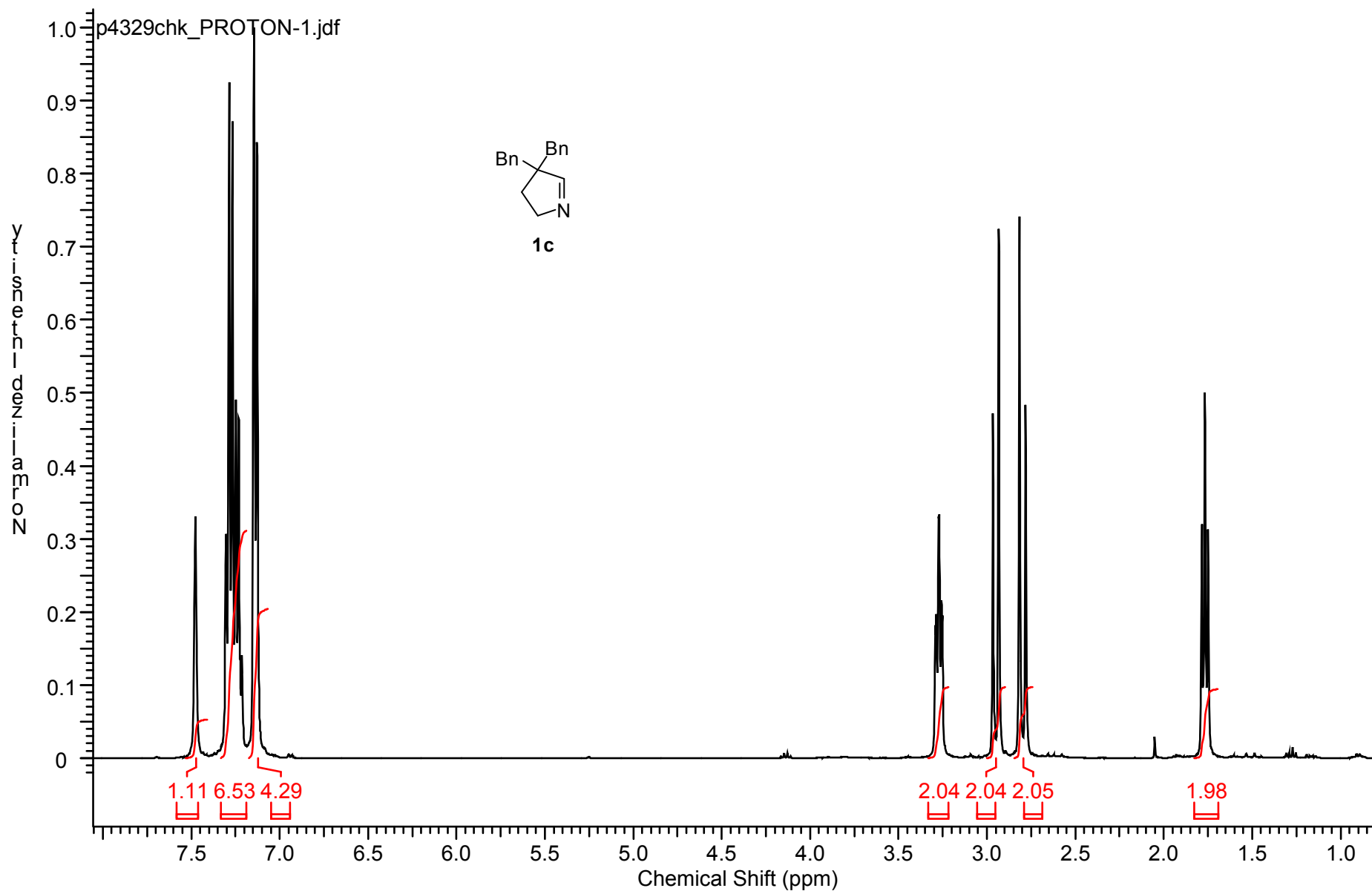
### Evodiamine (**9**)<sup>6</sup>

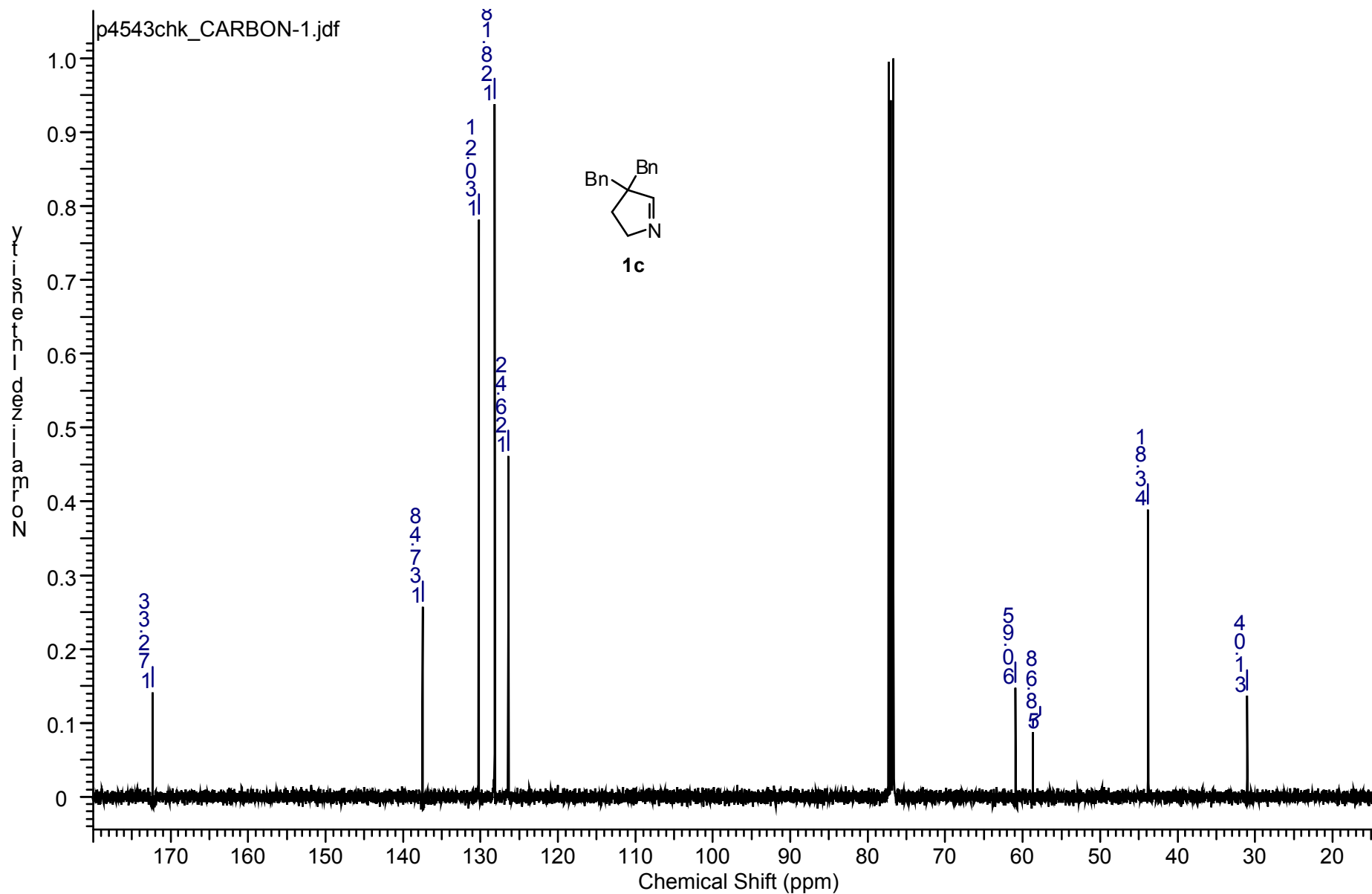


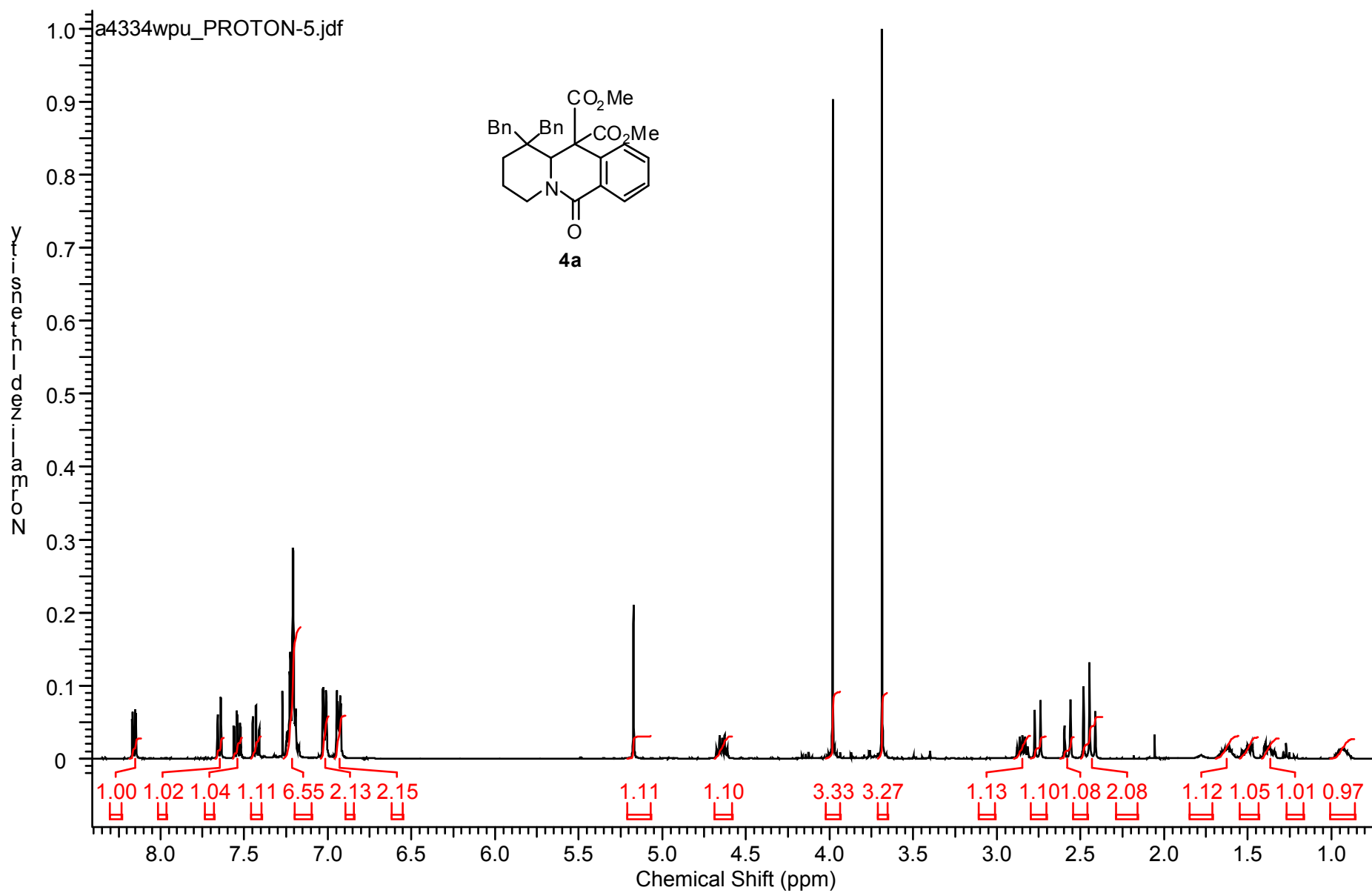
Synthesised using general CAM procedure A from  $\beta$ -carboline **1h** (34.0 mg, 0.200 mmol), acid **2h** (36.2 mg, 0.240 mmol), DIPEA (64.5  $\mu$ L, 0.370 mmol) and T3P (191 mg, 0.300 mmol) in toluene (2.0 mL) at 90 °C for 20 h. Purification by column chromatography (4:1 petrol:ethyl acetate) afforded **9** as a pale yellow solid (58.0 mg, 95%);  $R_f$  0.52 (ethyl acetate); M.p = 262–264 °C [Lit. 267–270 °C]<sup>5</sup>;  $\nu_{\text{max}}$  (thin film)/cm<sup>-1</sup> 1645;  $\delta_{\text{H}}$  (400 MHz, DMSO d-6) 11.08 (1H, s), 7.80 (1H, d,  $J$  = 7.9 Hz), 7.51–7.45 (2H, m), 7.36 (1H, d,  $J$  = 7.9 Hz), 7.12–6.94 (4H, m), 6.13 (1H, s), 4.64 (1H, dd,  $J$  = 12.8, 4.8 Hz), 3.25–3.16 (1H, m), 2.96–2.87 (1H, m), 2.88 (3H, s), 2.83–2.76 (1H, m);  $\delta_{\text{C}}$  (100 MHz, DMSO d-6) 164.3, 148.8, 136.5, 133.5, 130.6, 128.0, 126.0, 121.9, 120.3, 119.3, 118.9, 118.2, 117.5, 111.7, 111.5, 69.8, 40.8, 36.4, 19.5; HRMS (ESI<sup>+</sup>): Found: 304.1445; C<sub>19</sub>H<sub>18</sub>N<sub>3</sub>O (MH<sup>+</sup>) Requires: 304.1444 (0.1 ppm error).

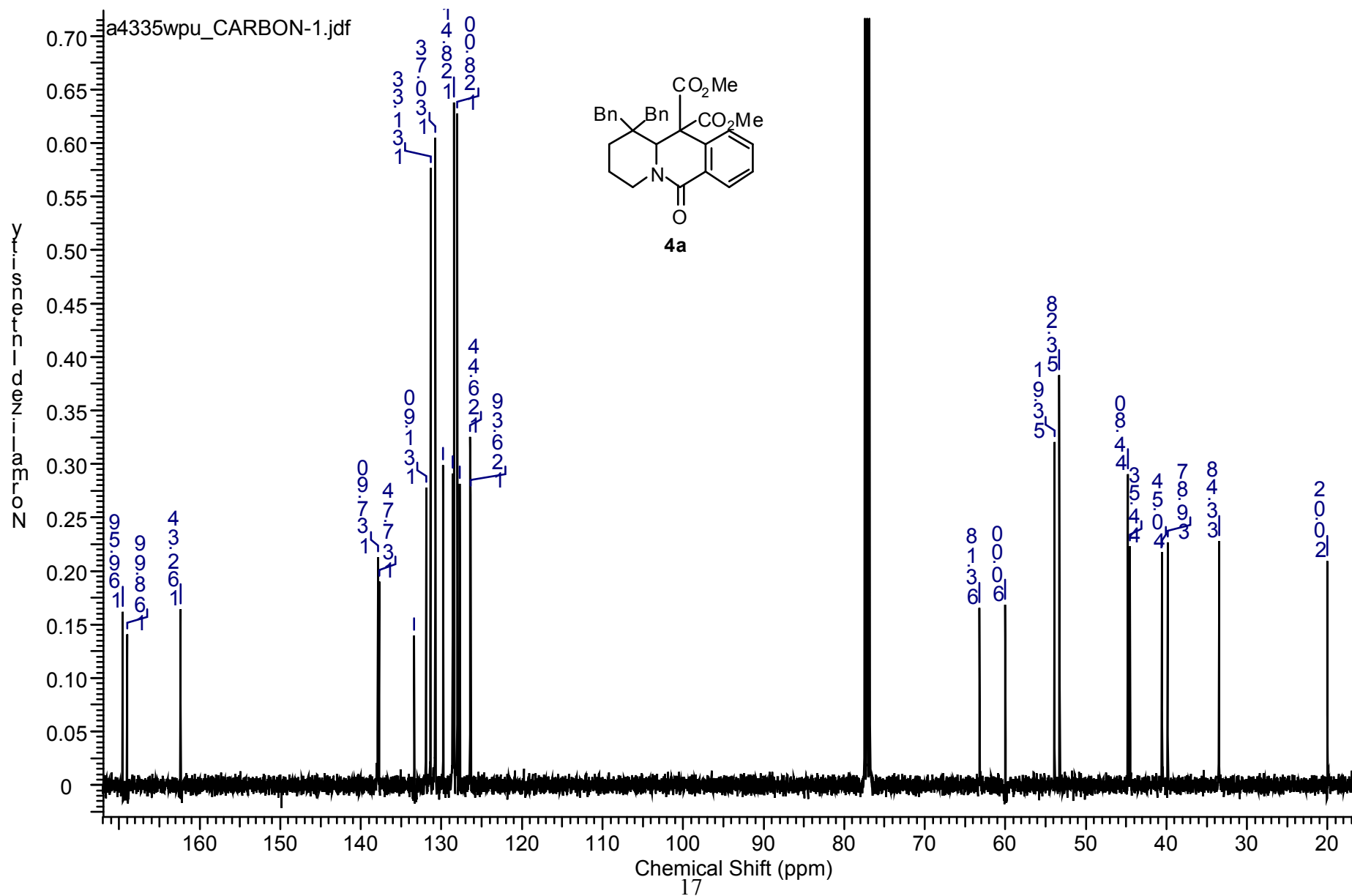


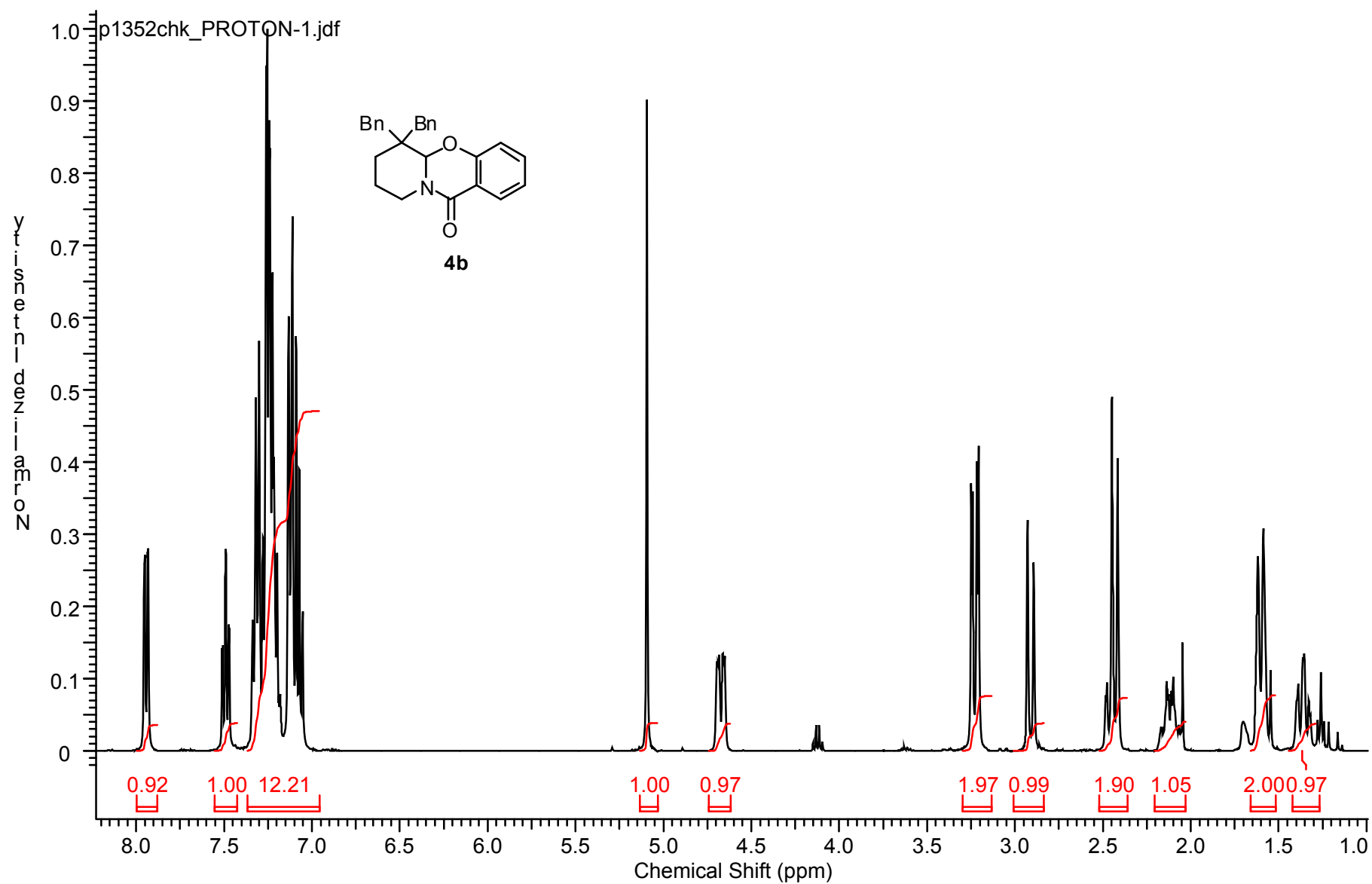


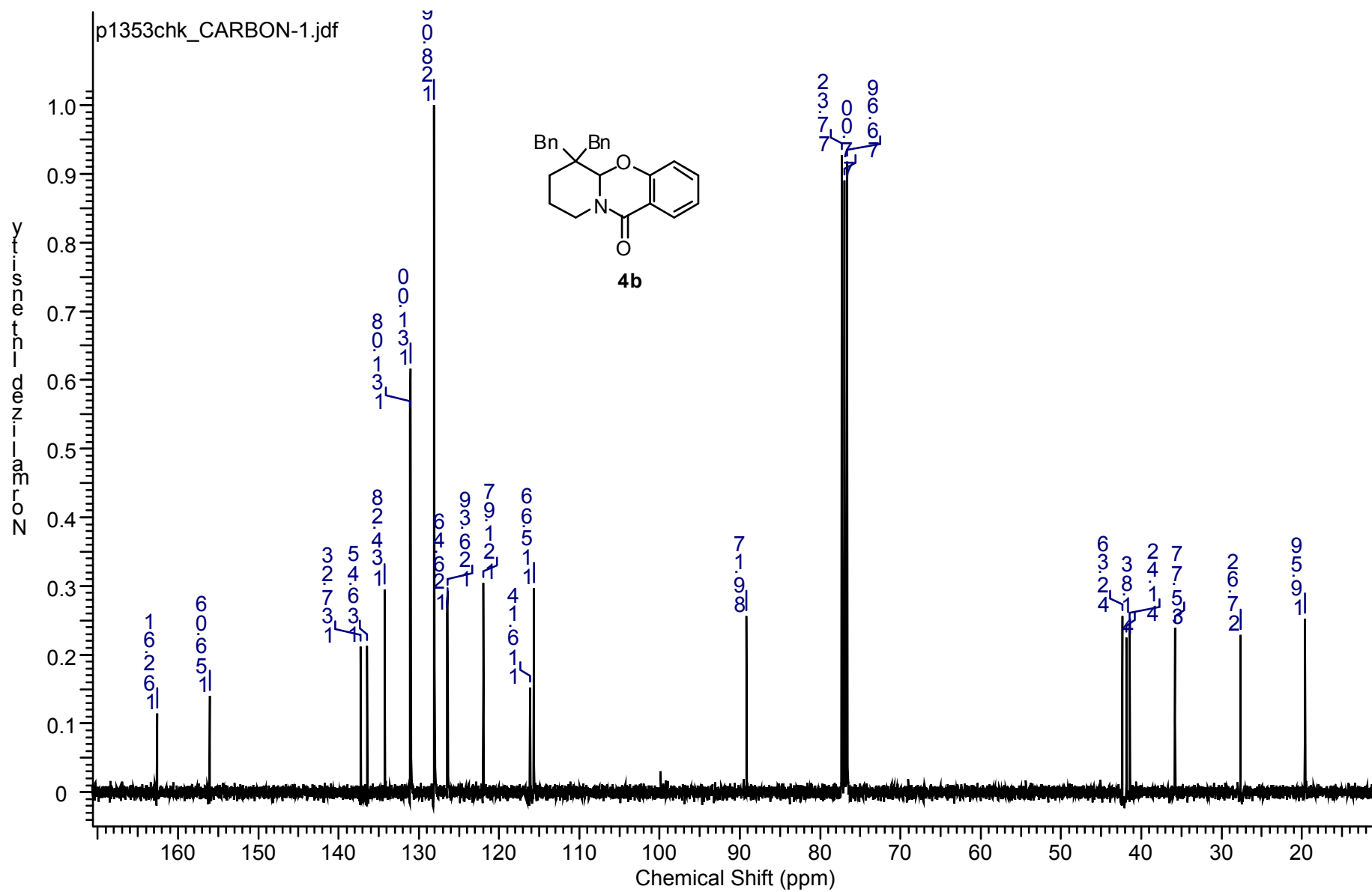


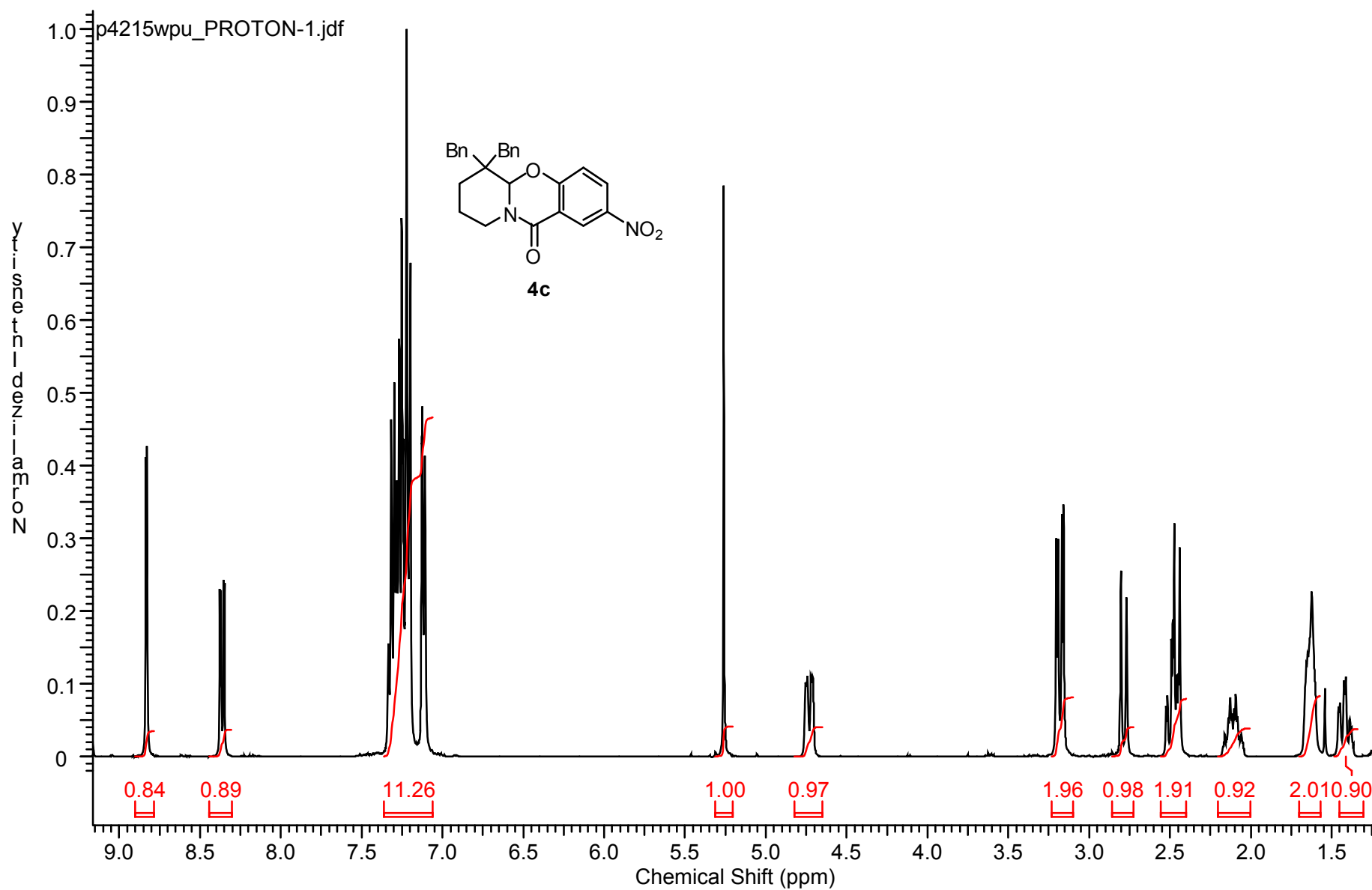


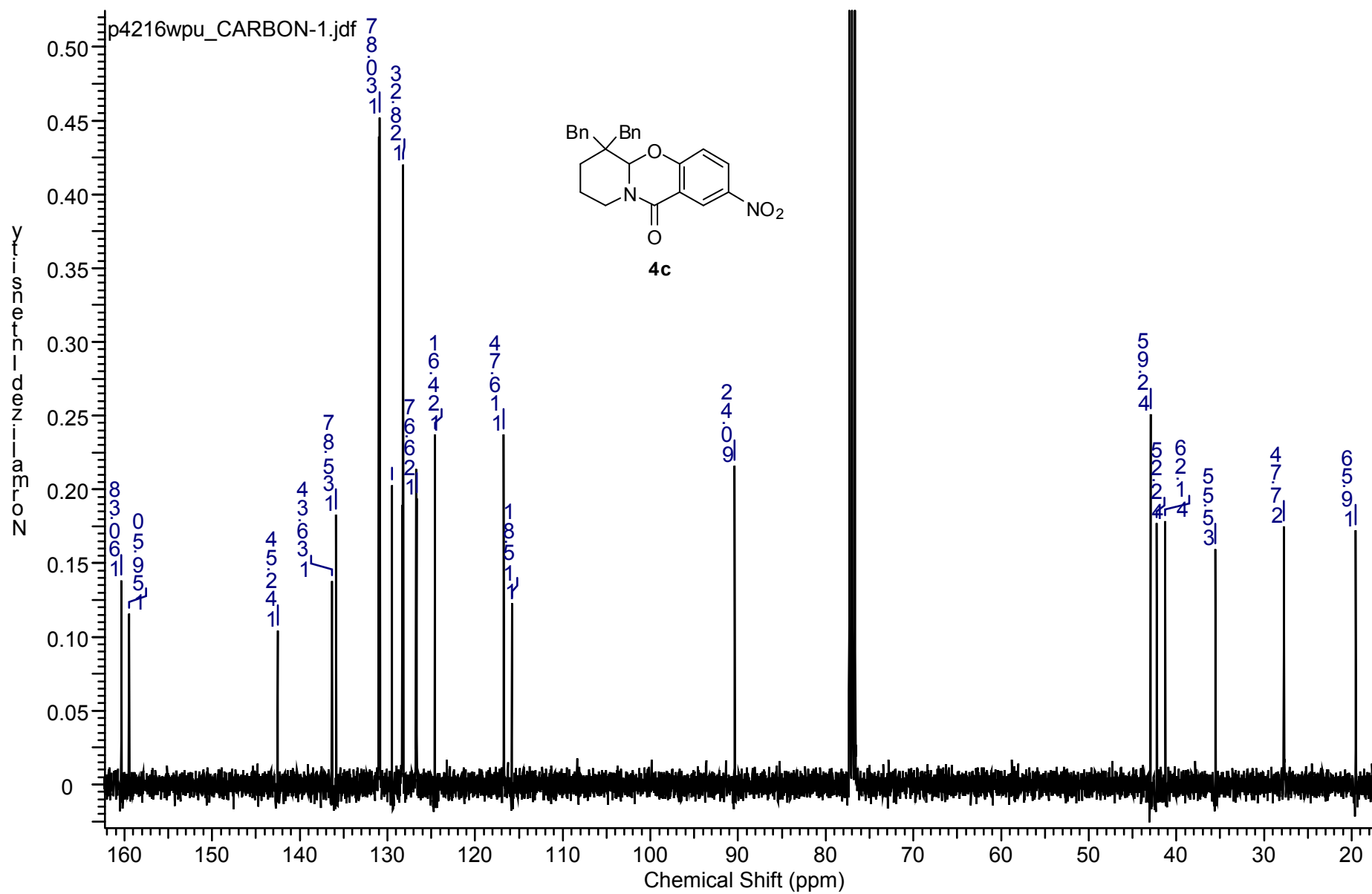


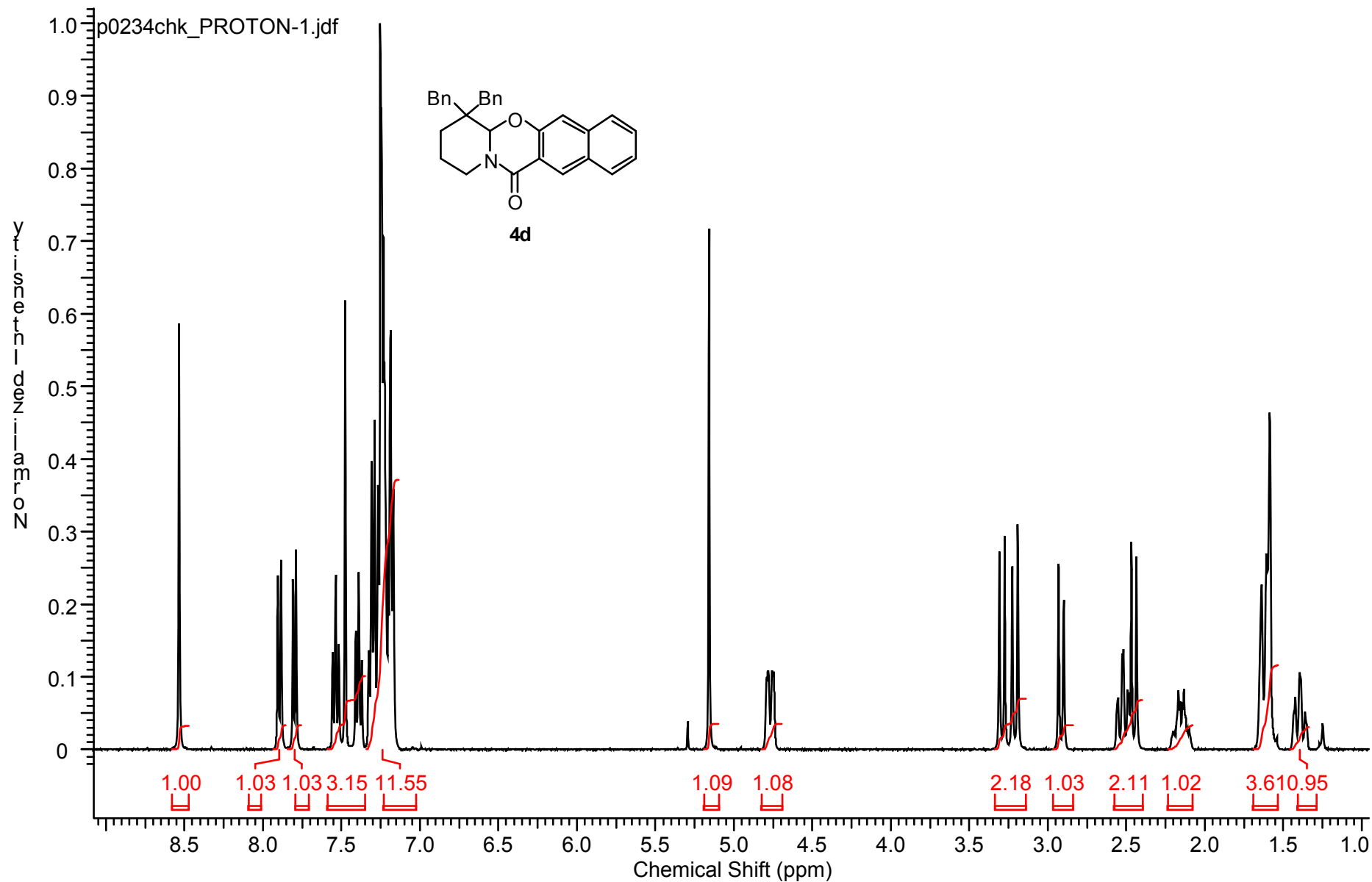


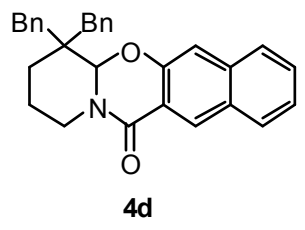
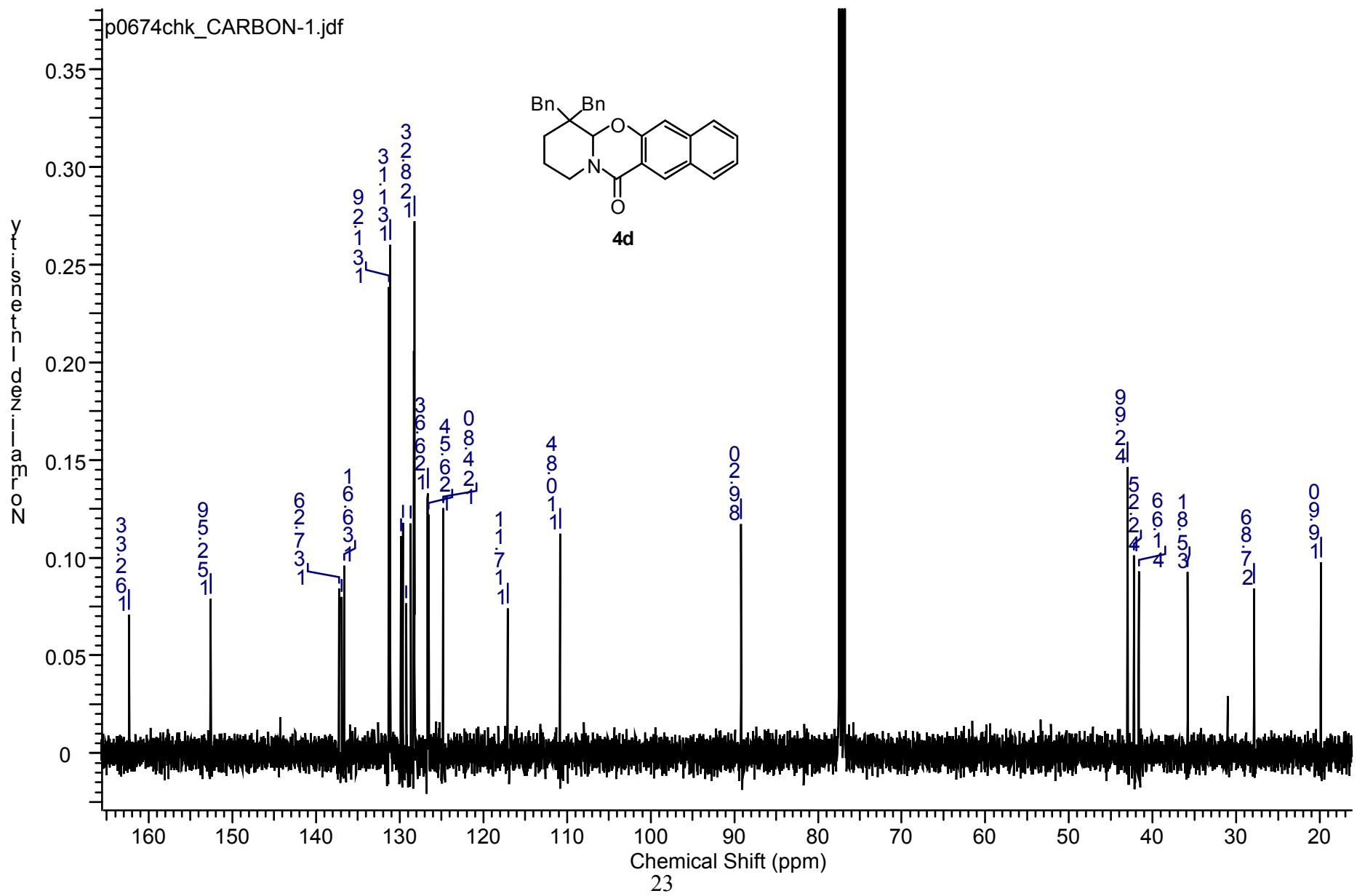


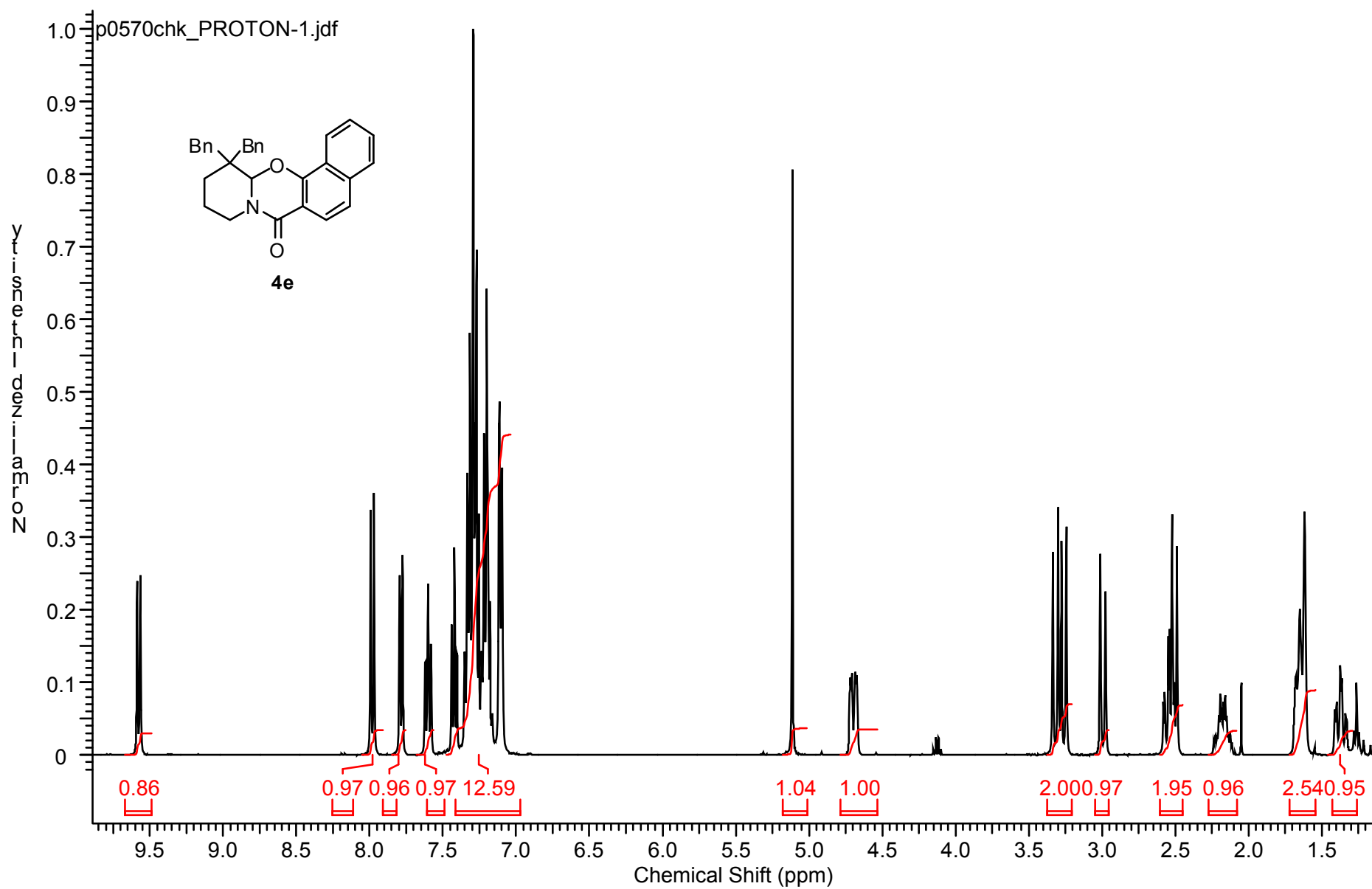


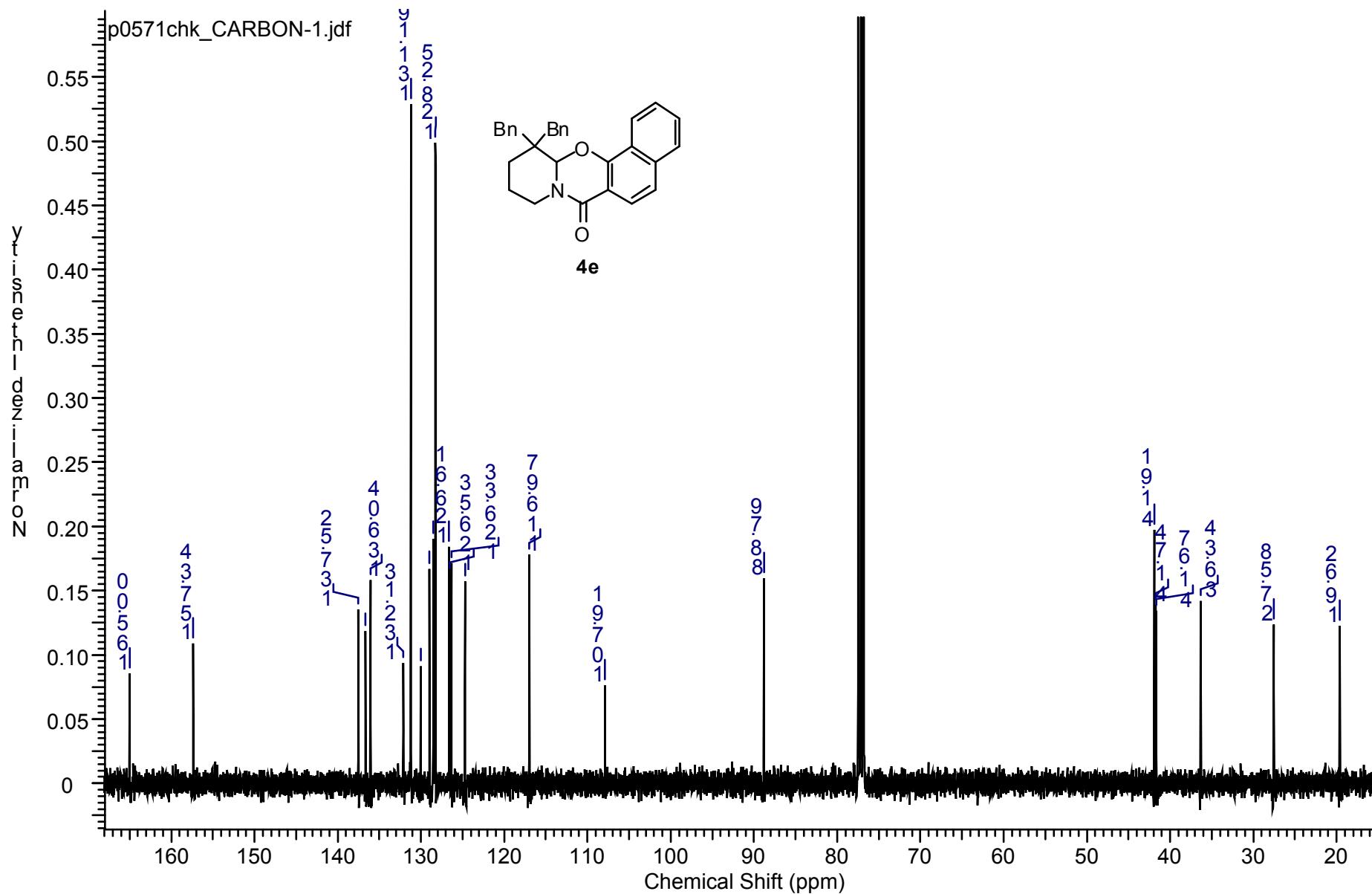


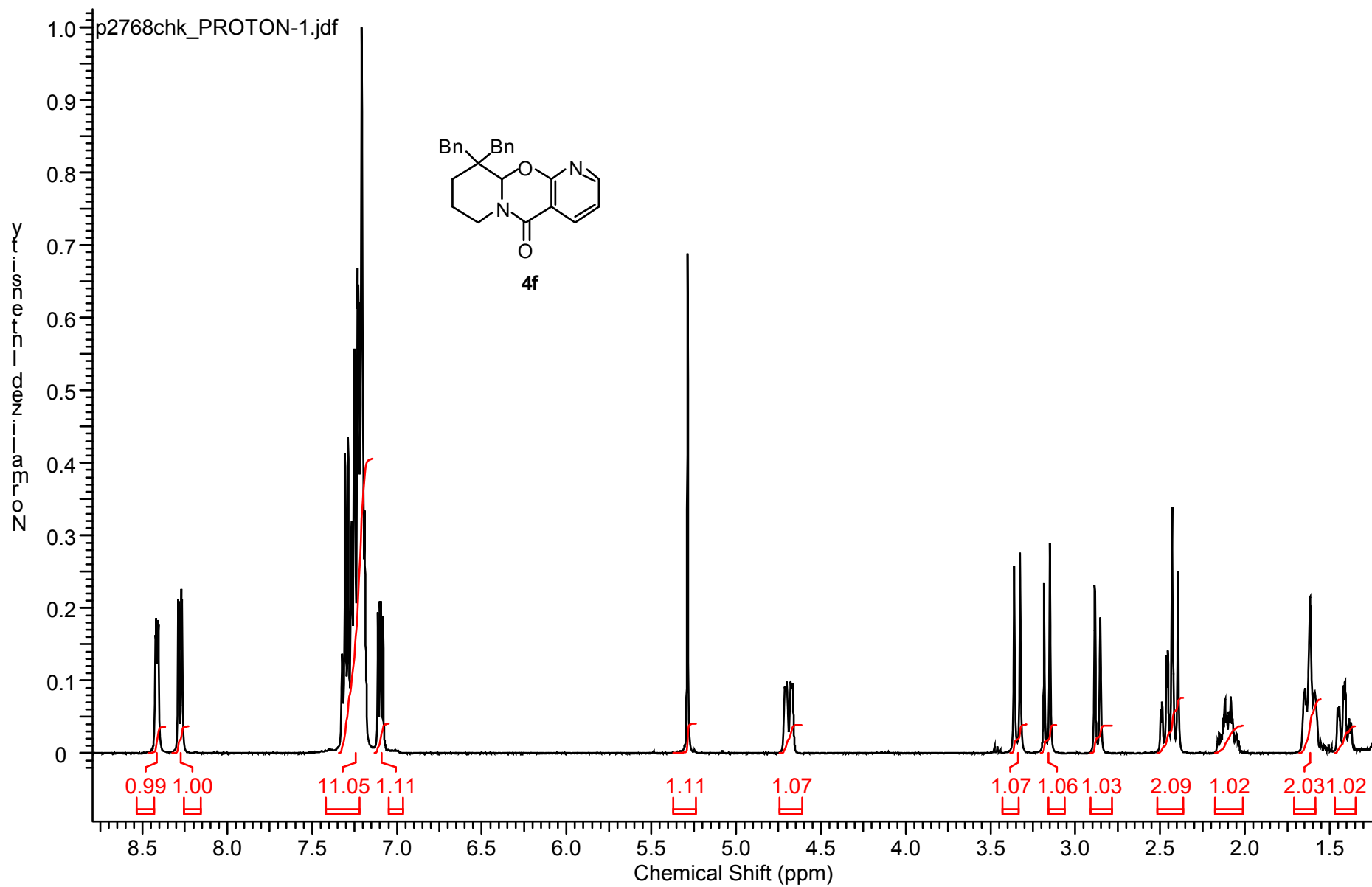


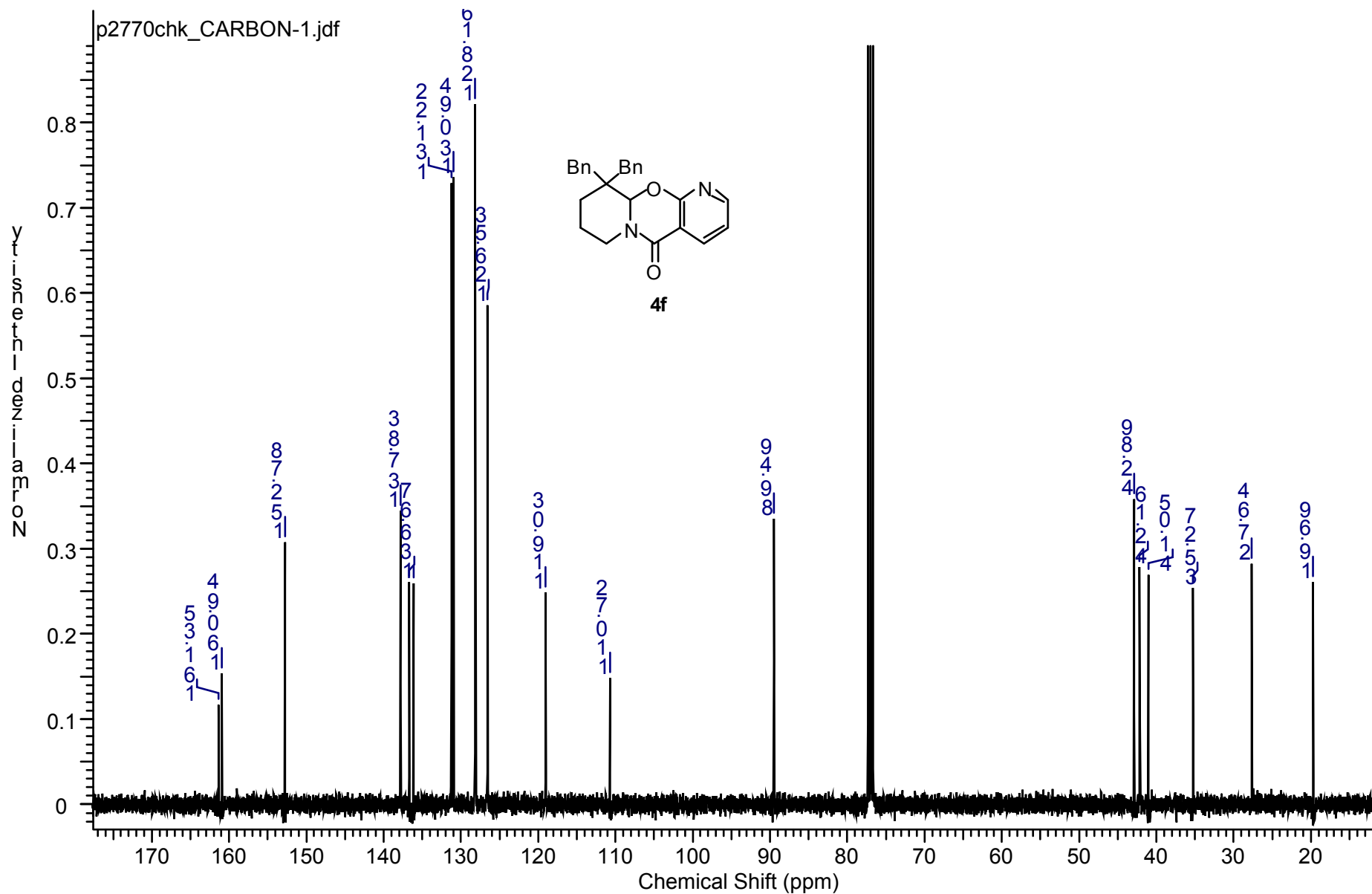


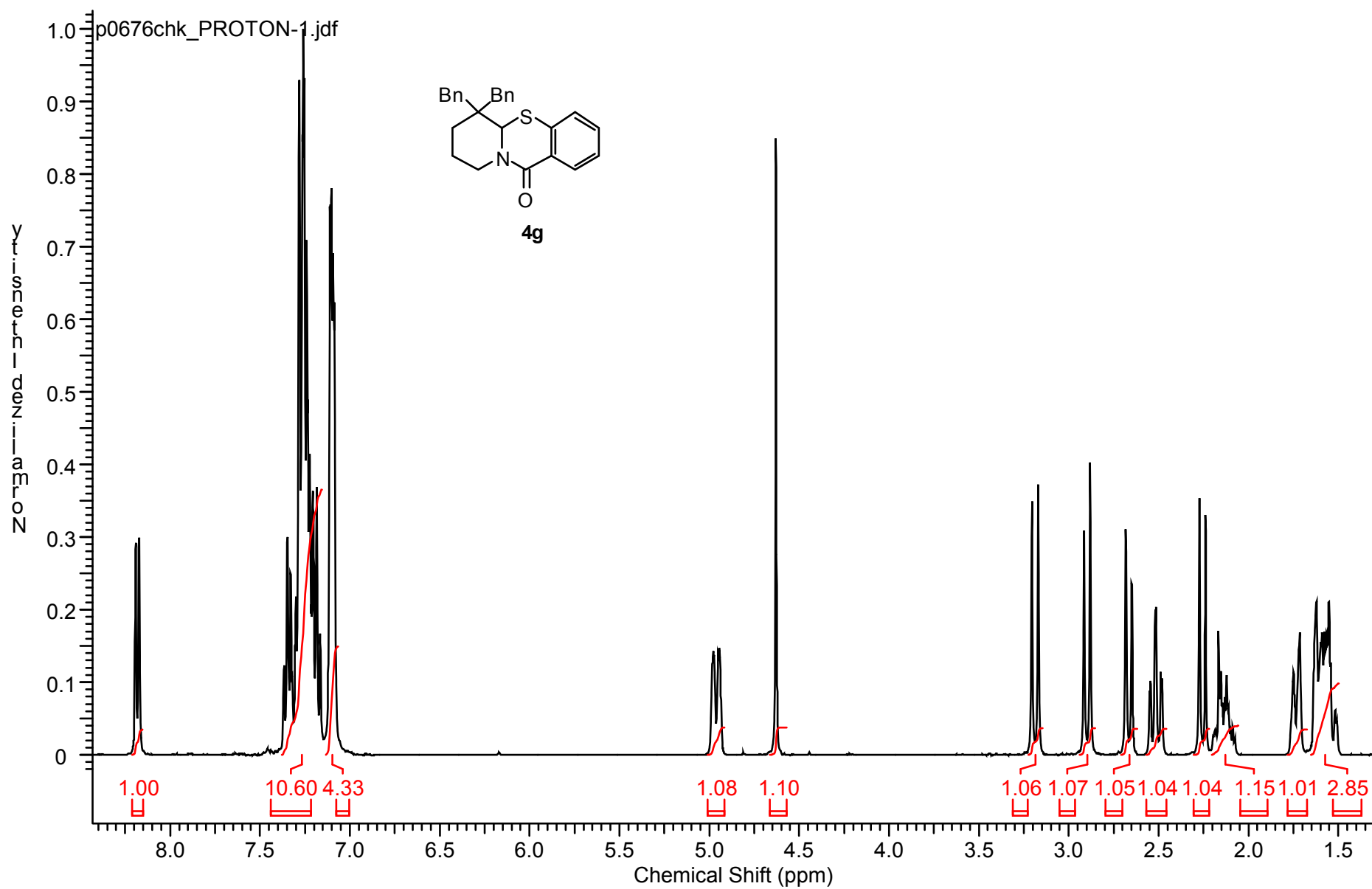


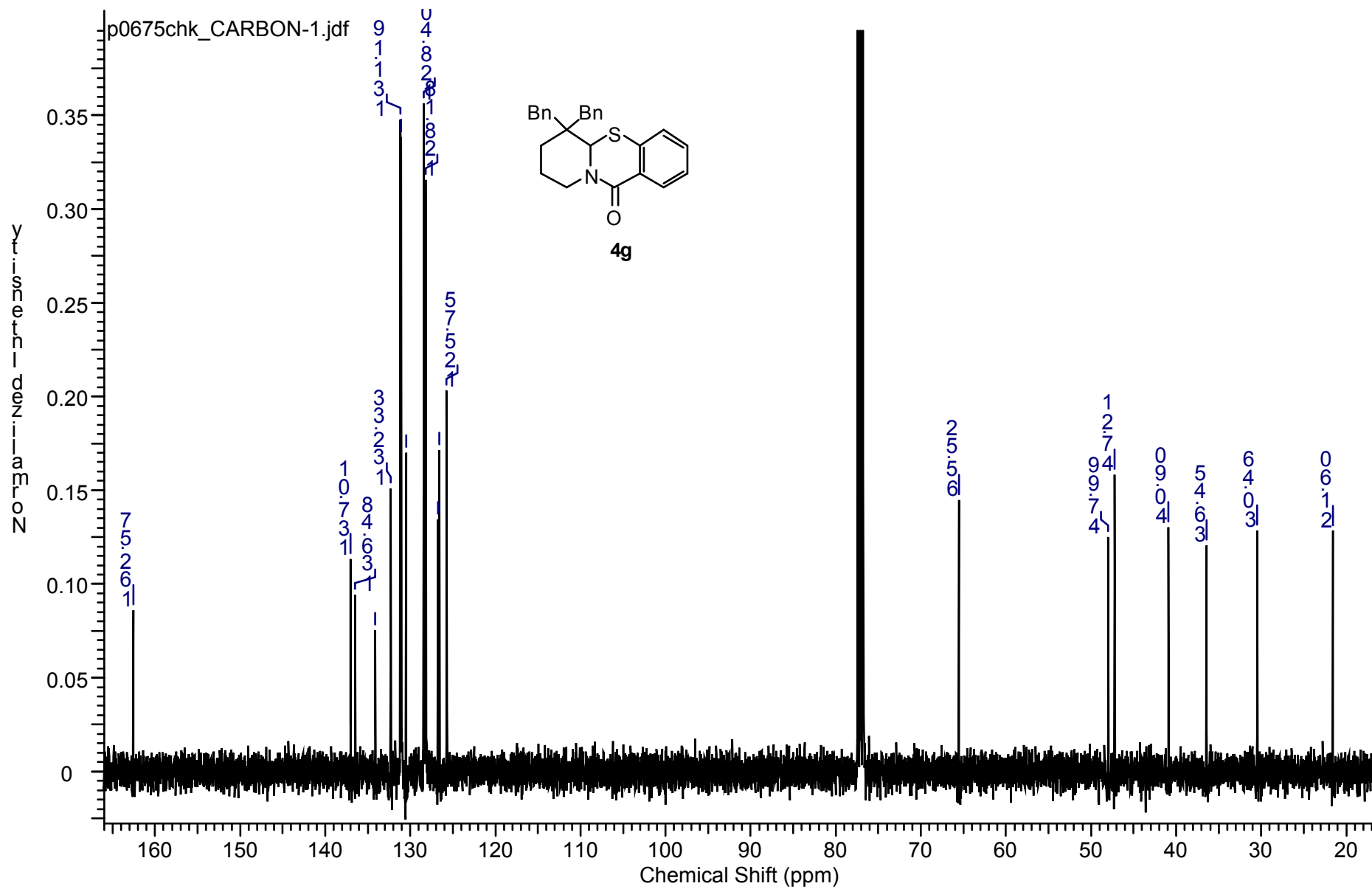


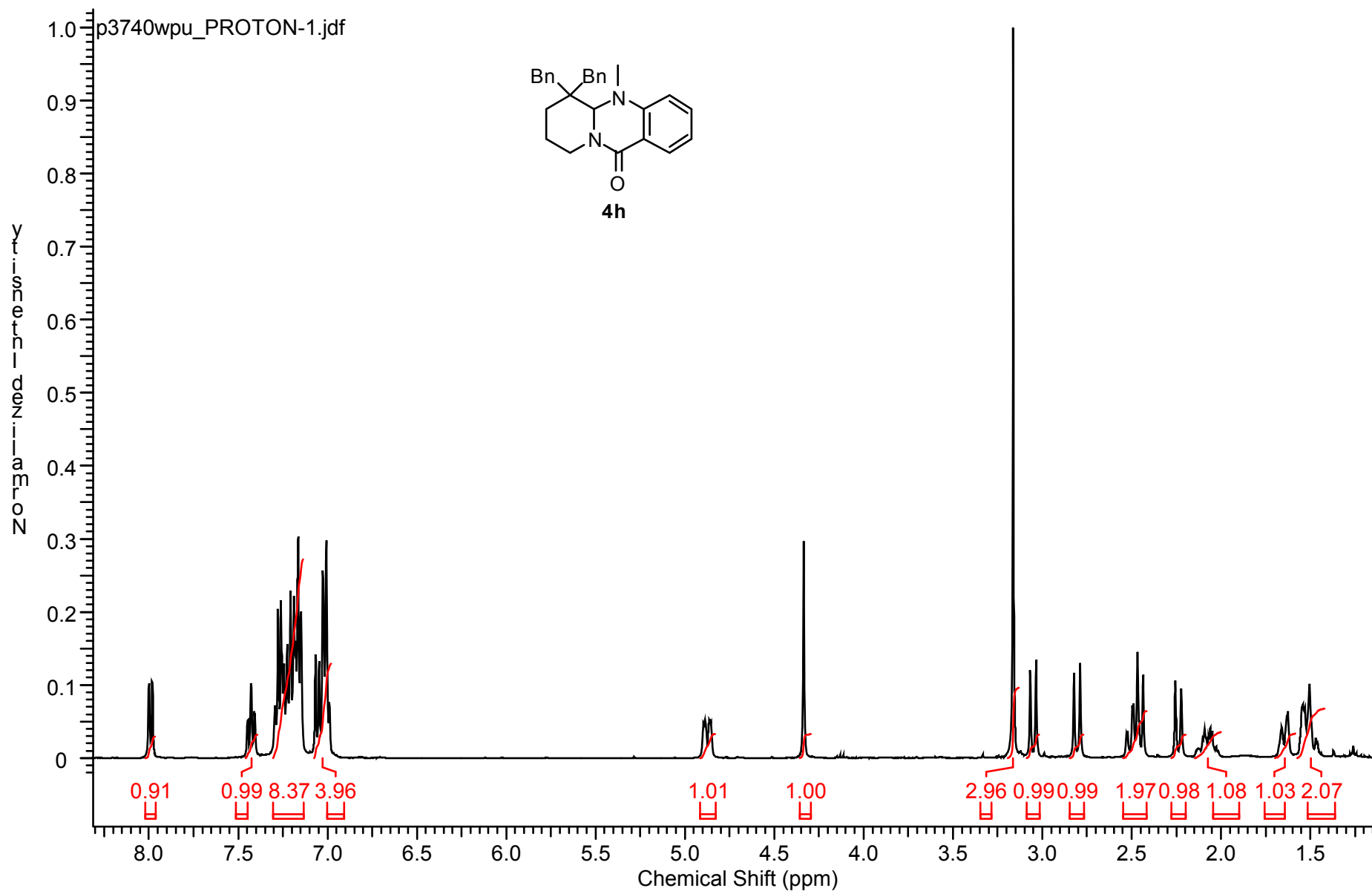


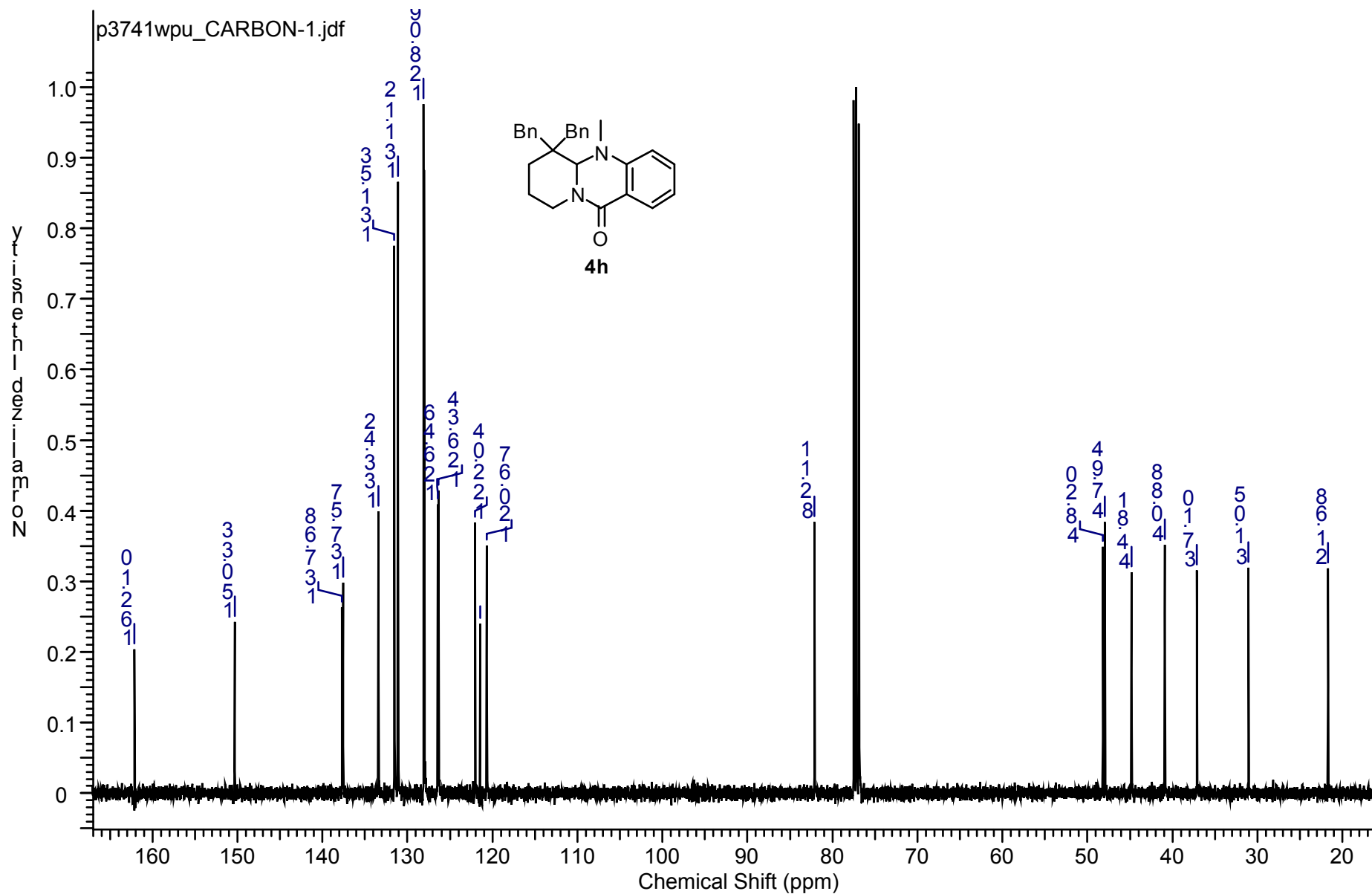


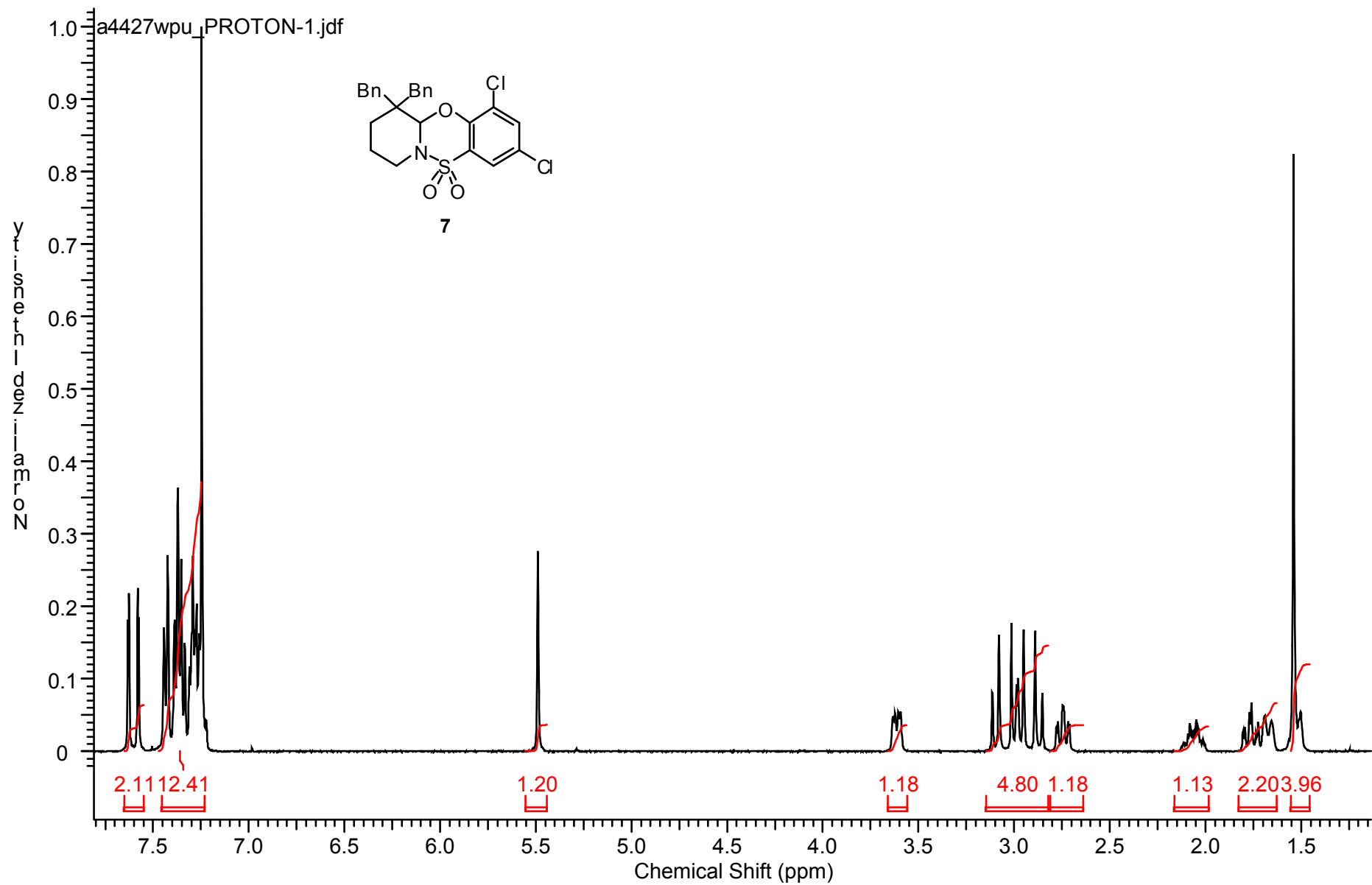


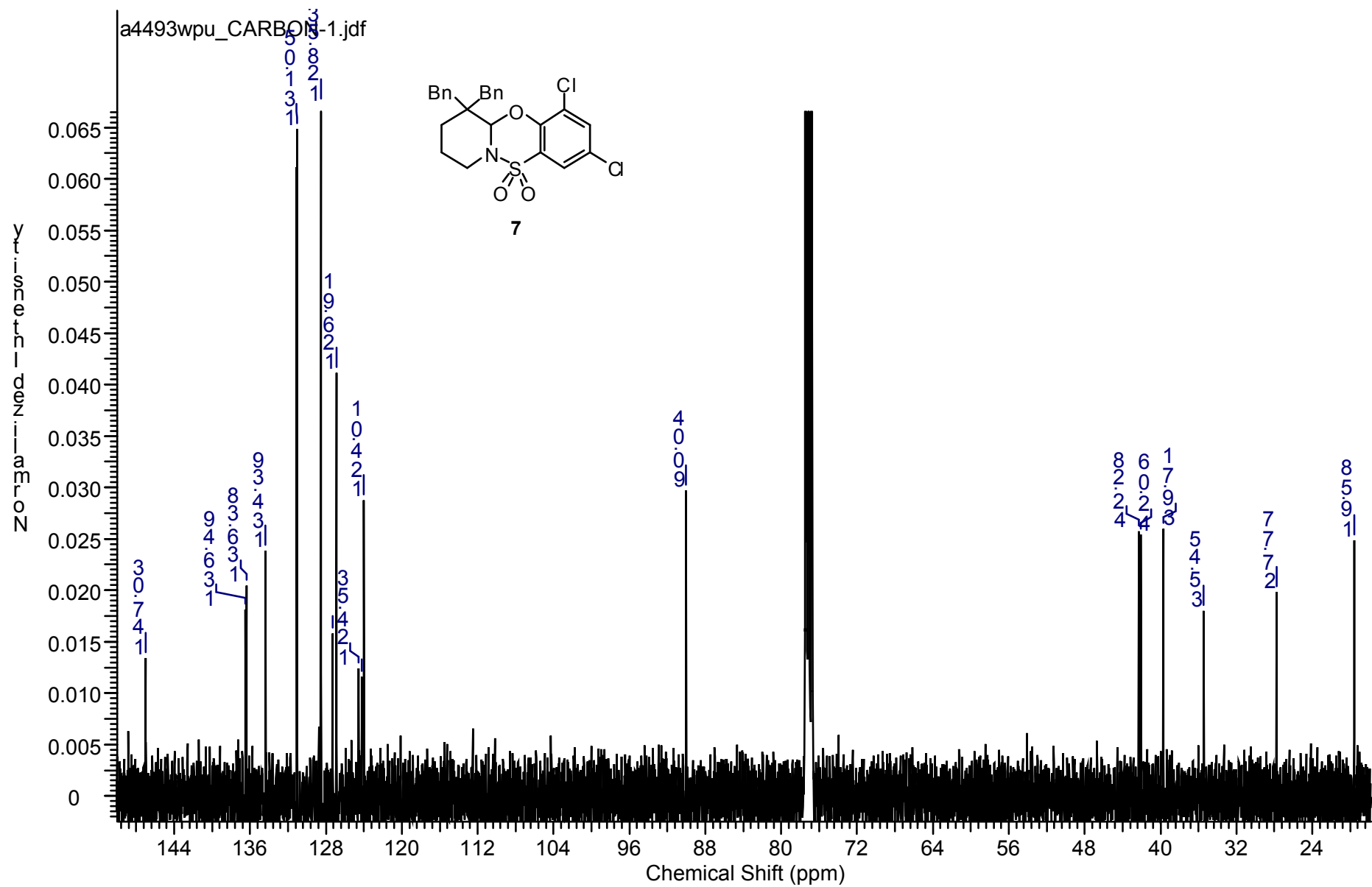


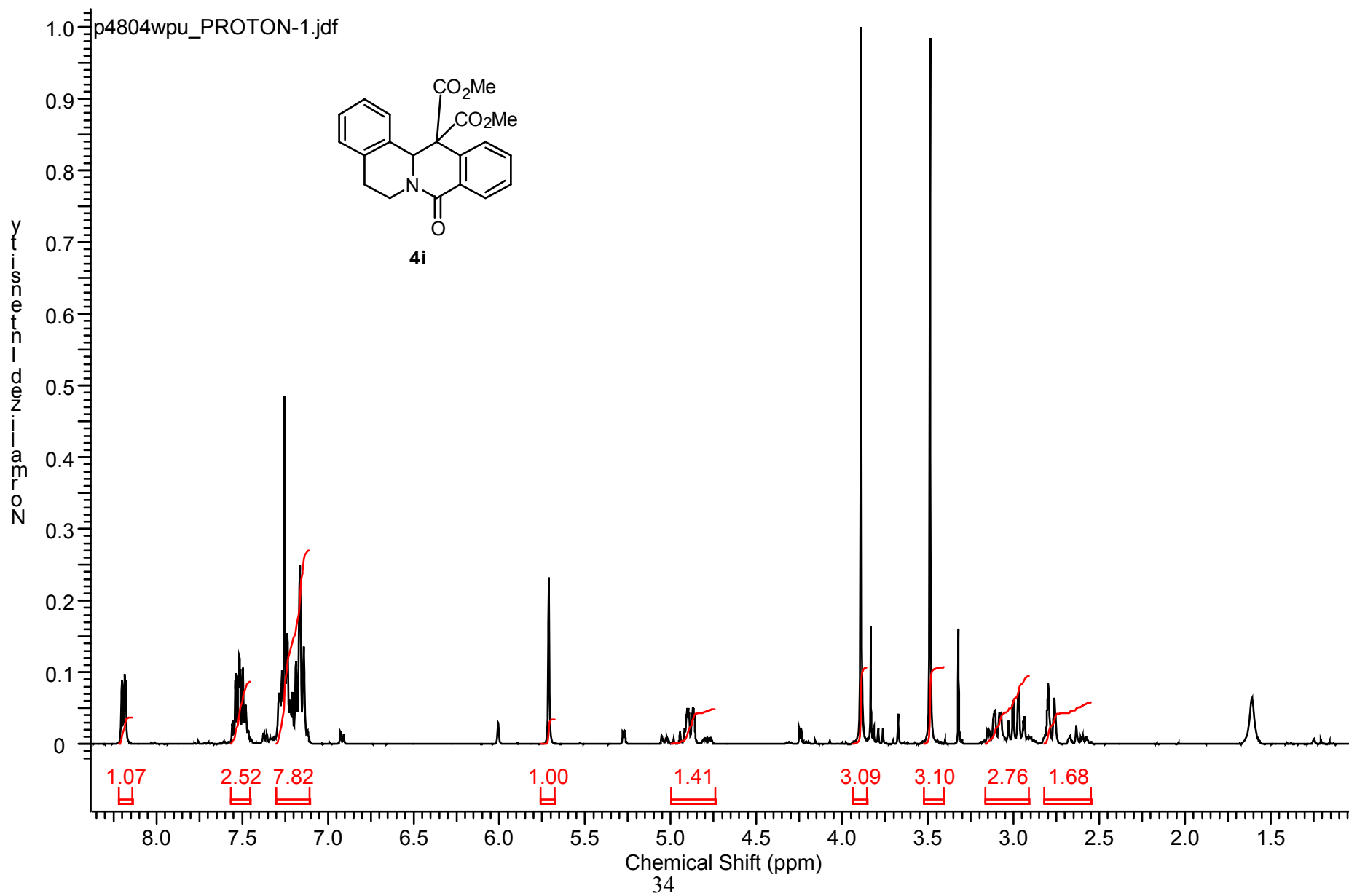


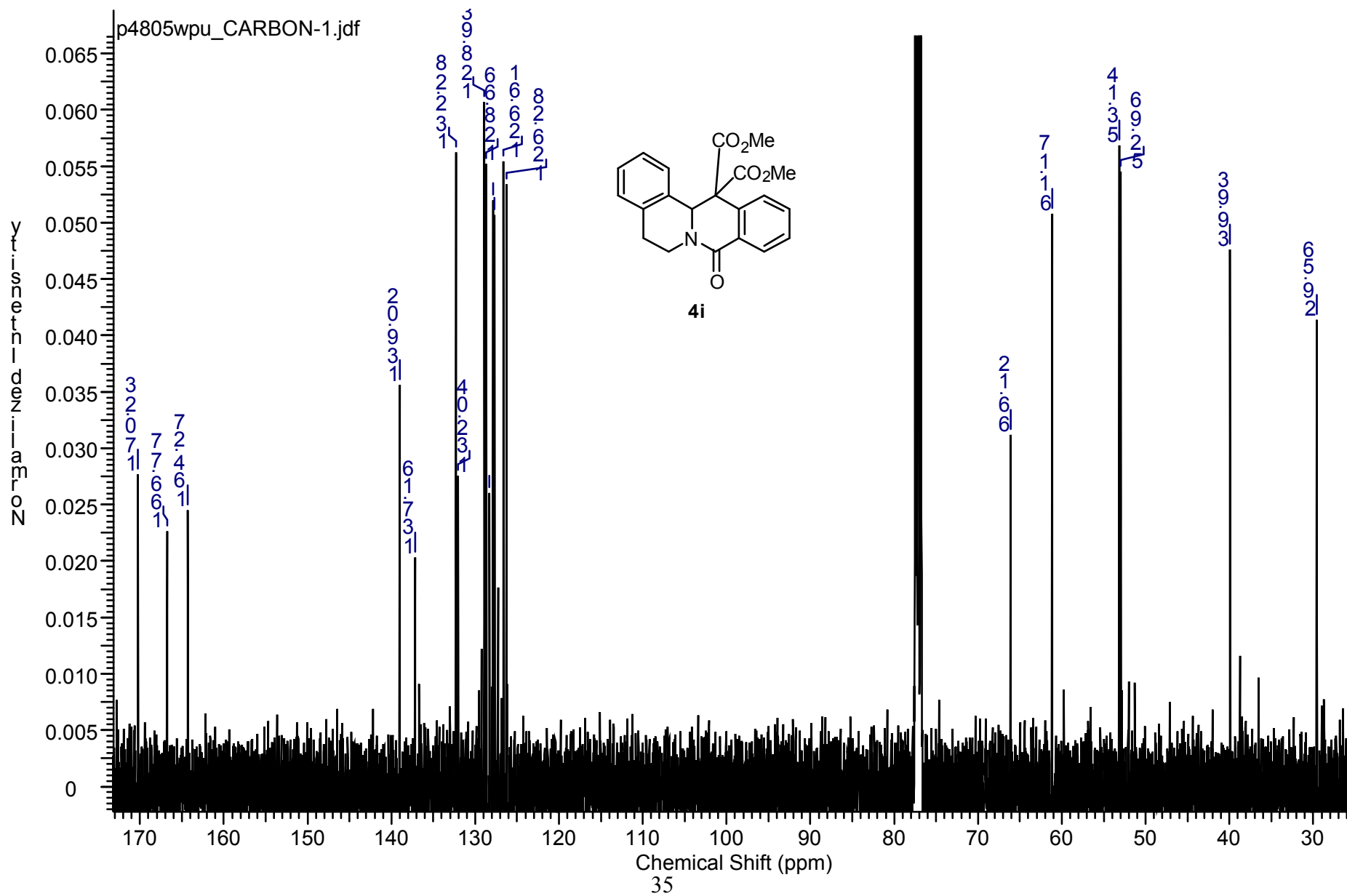


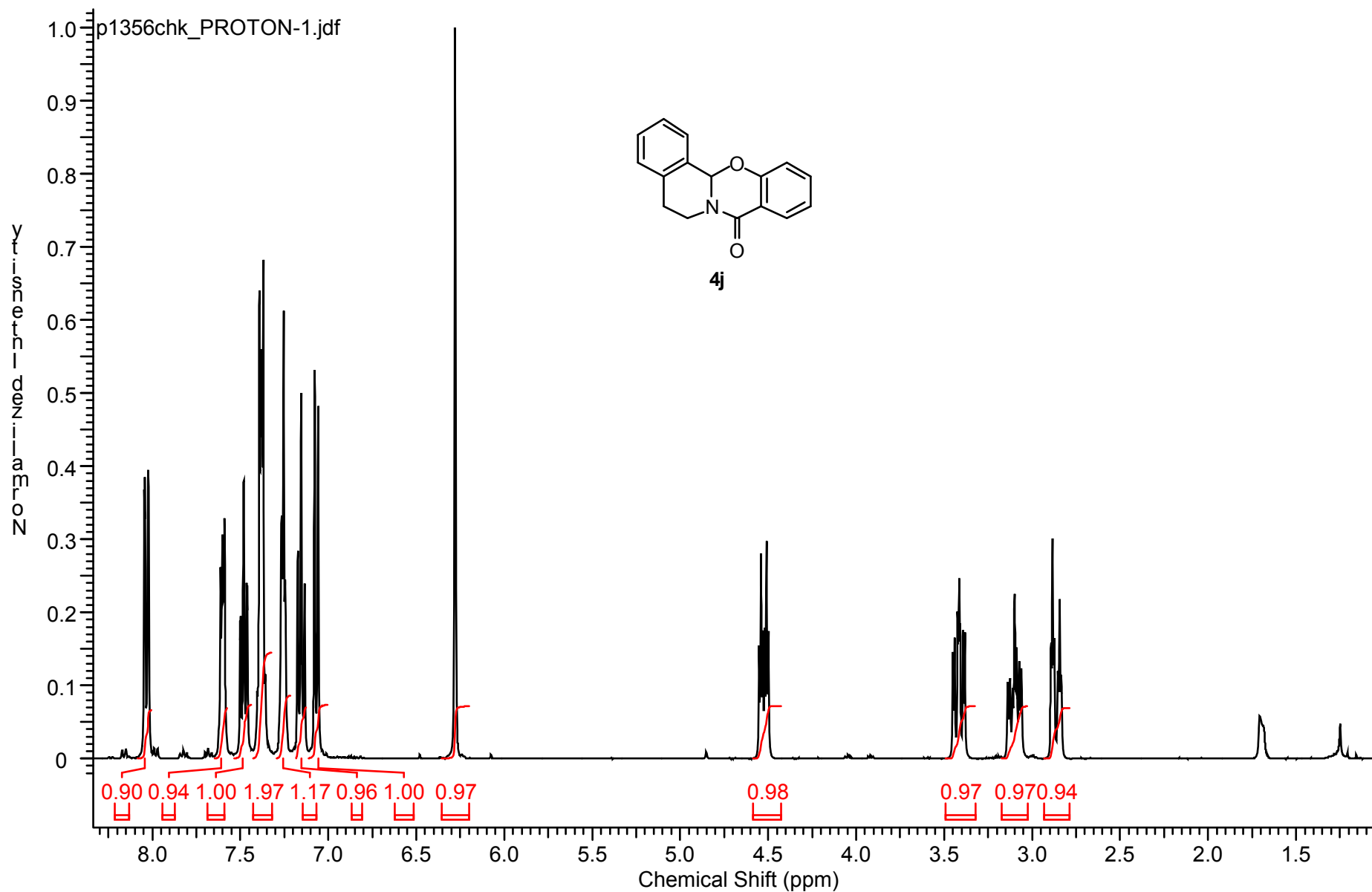


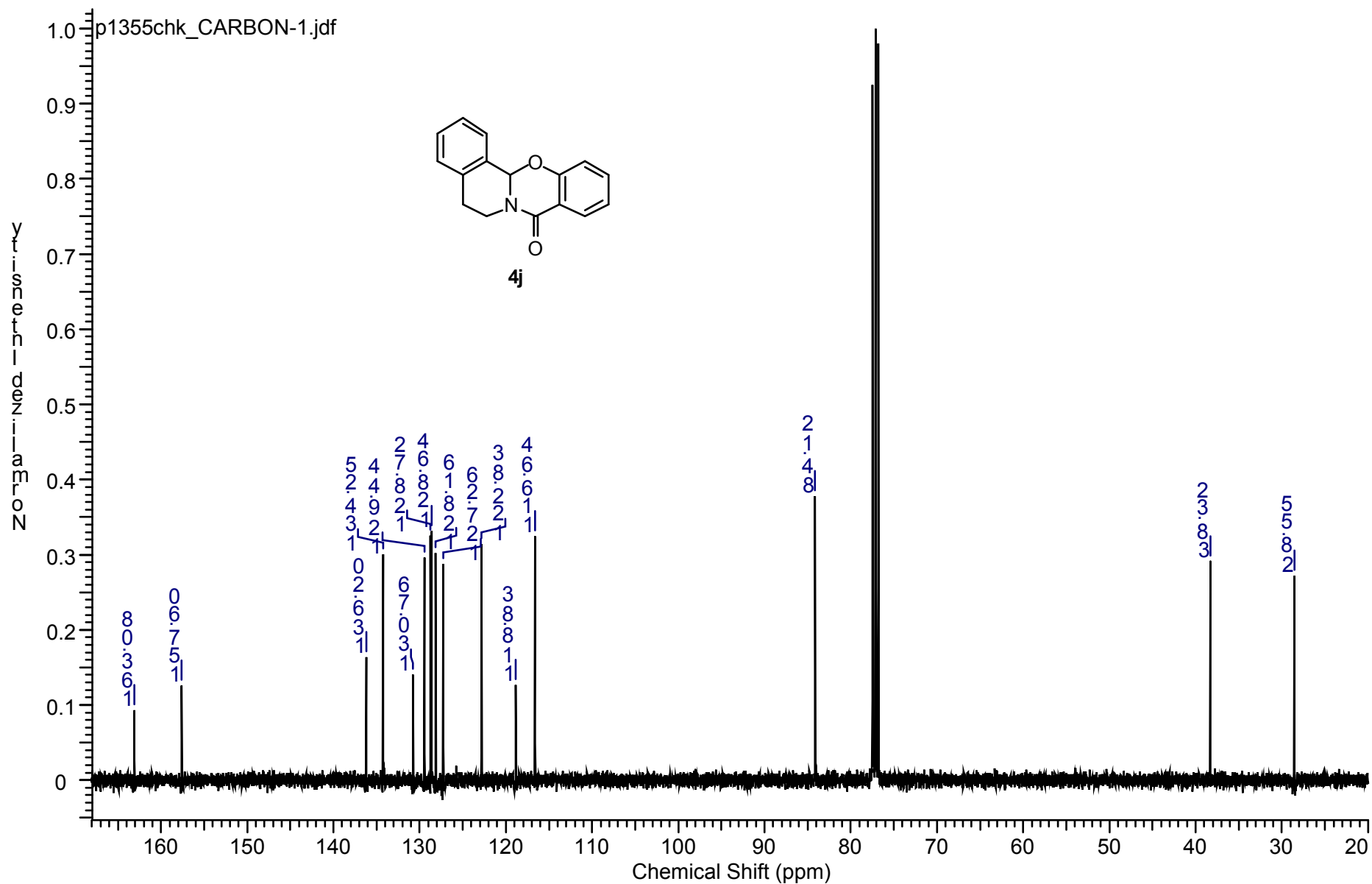


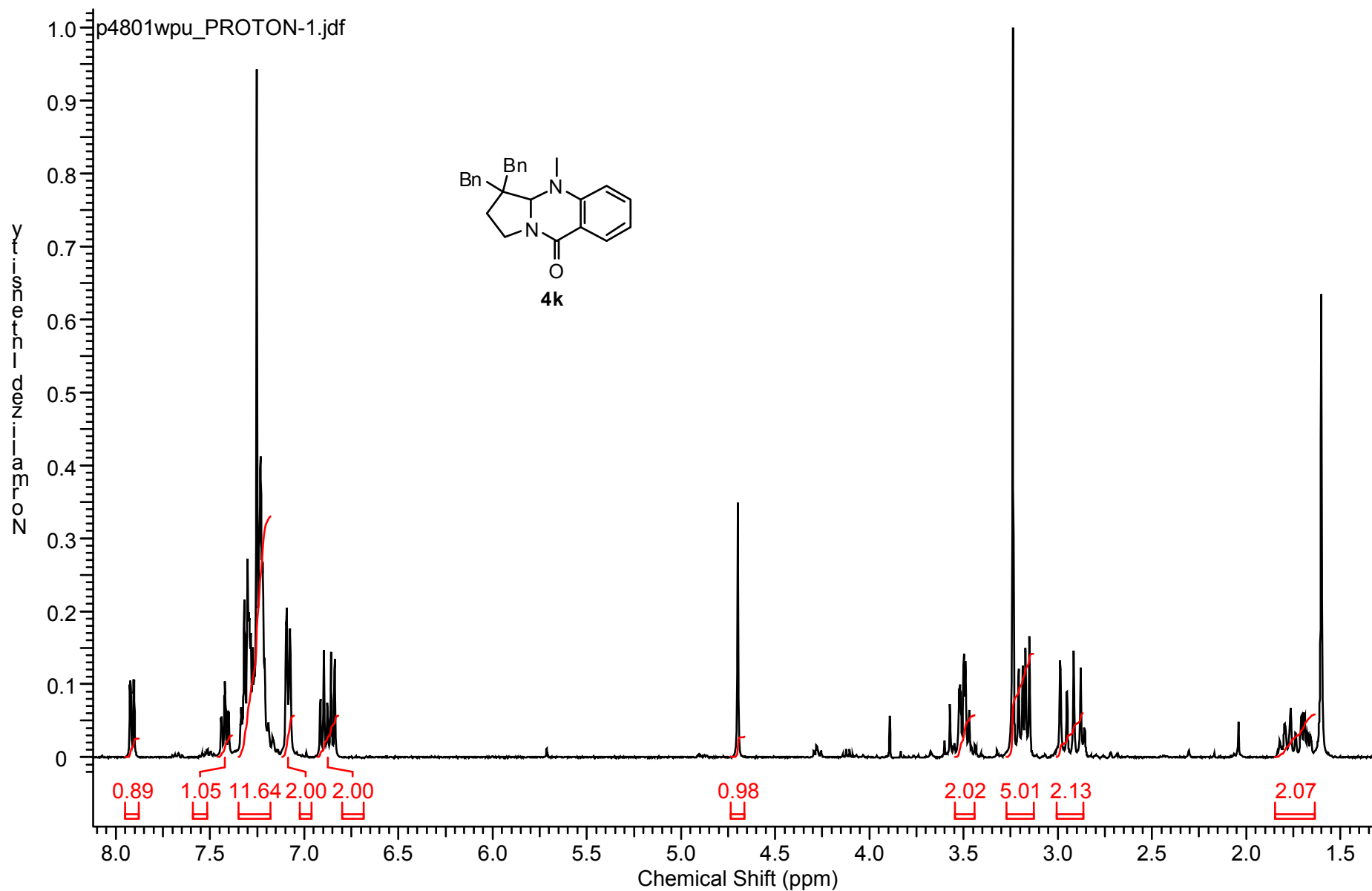


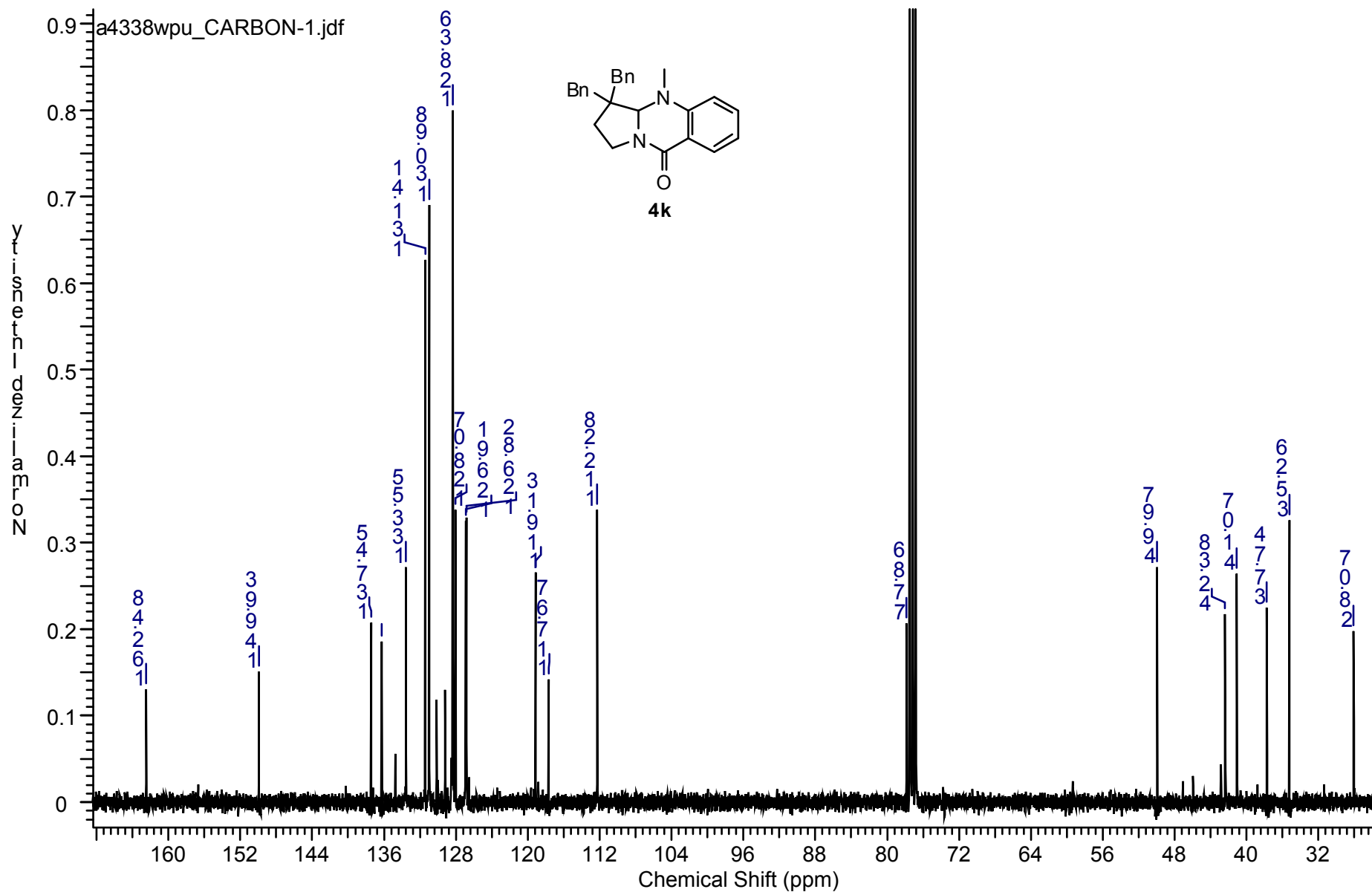


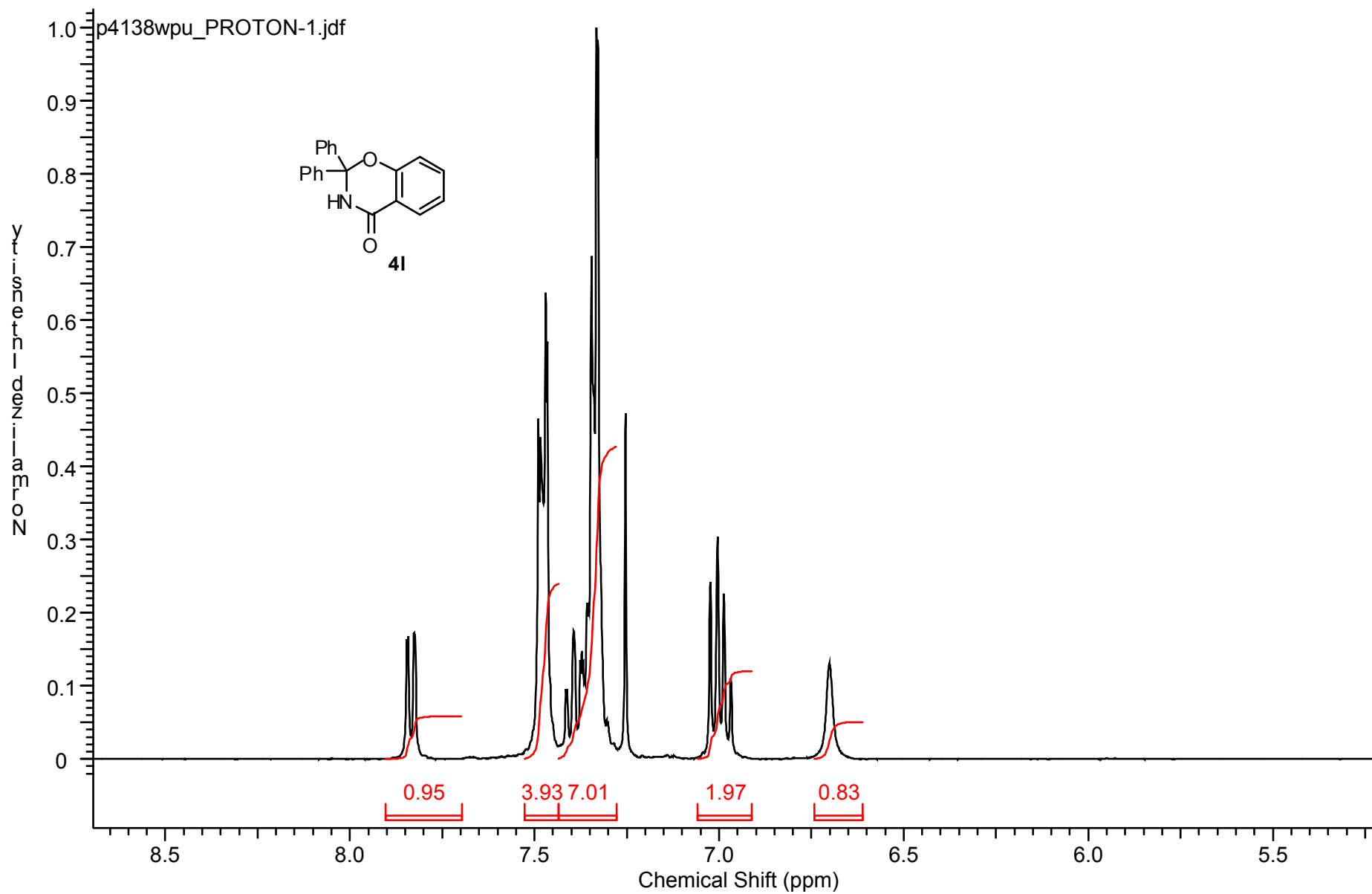


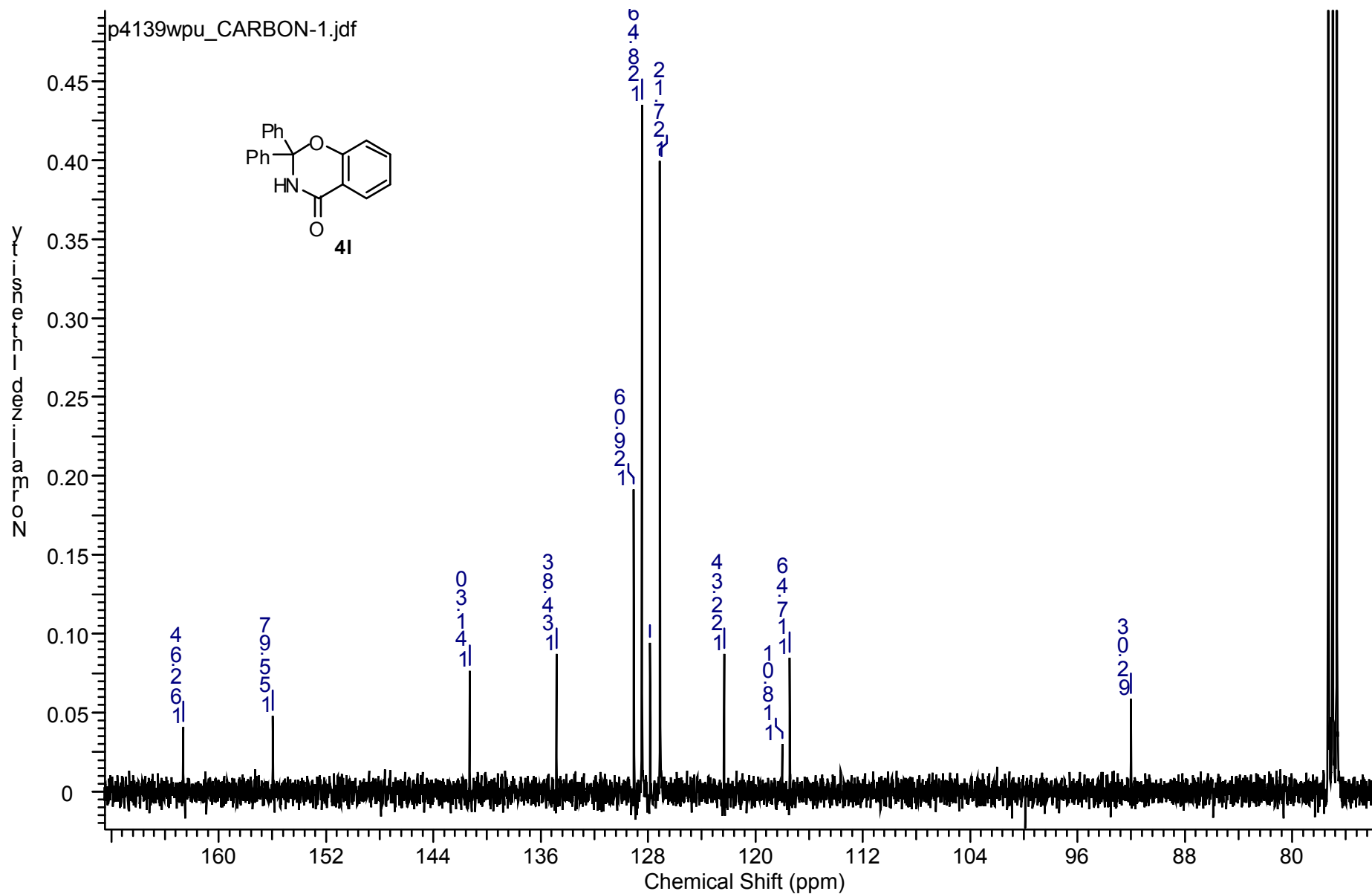


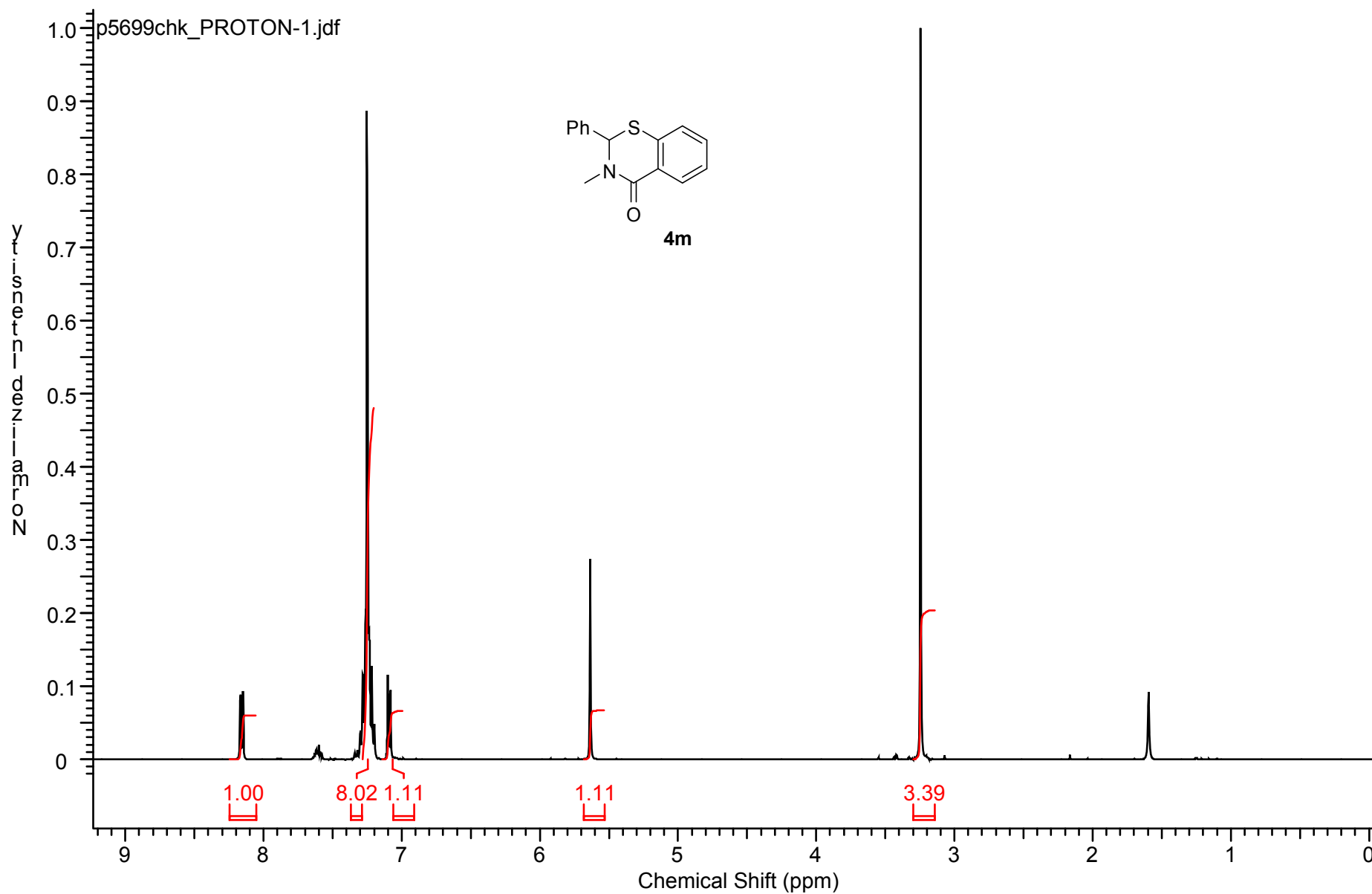


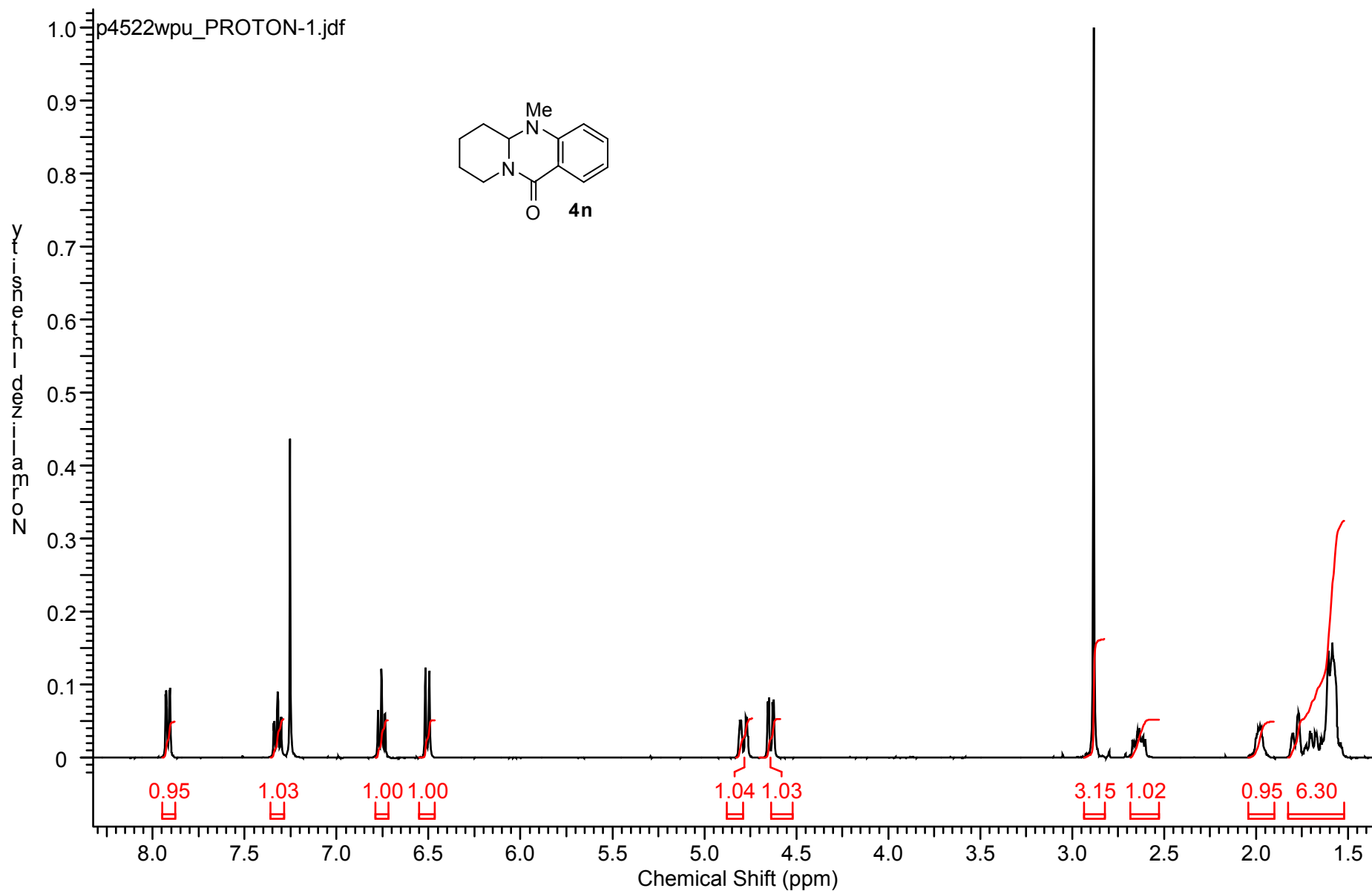


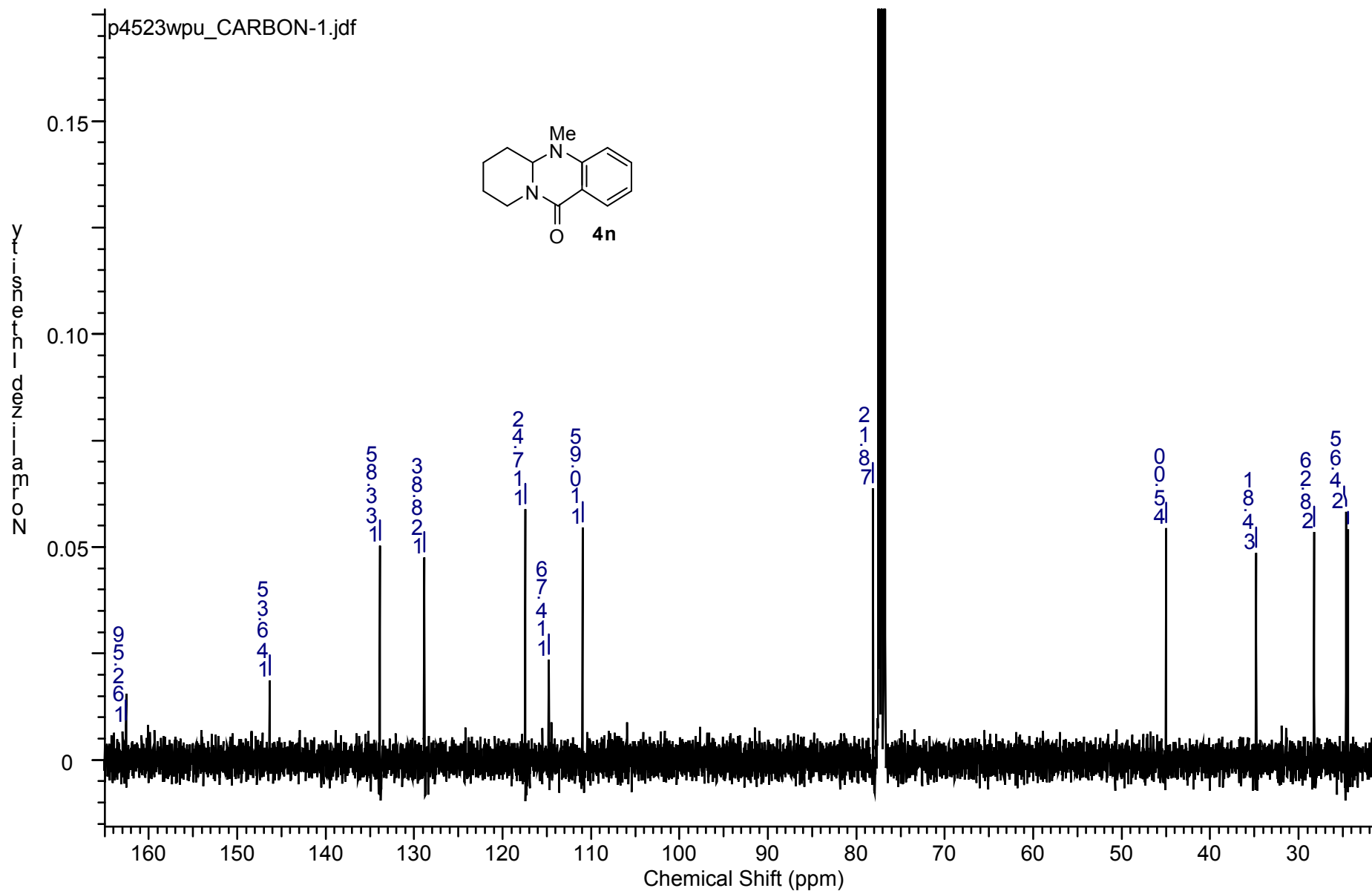


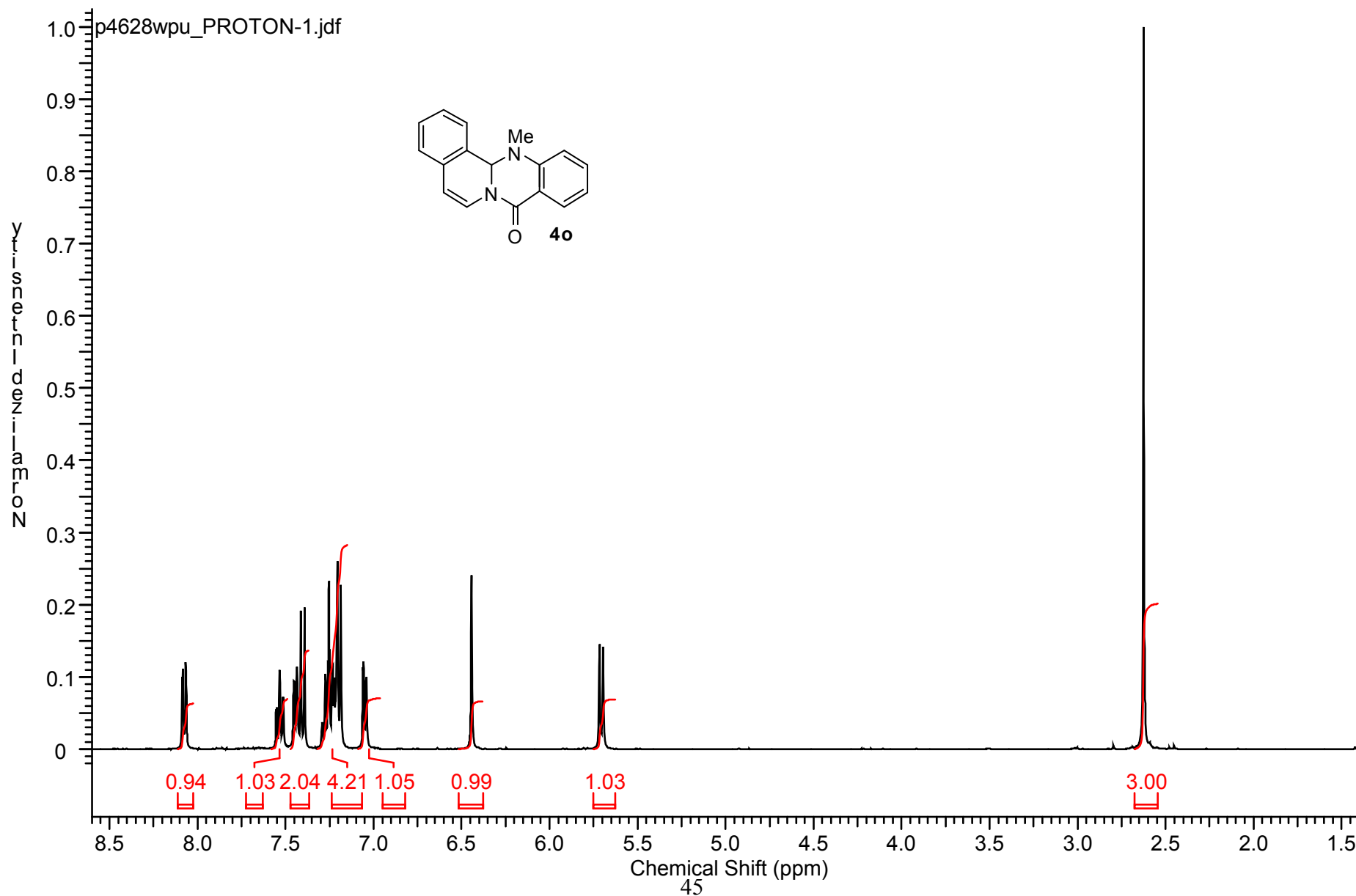


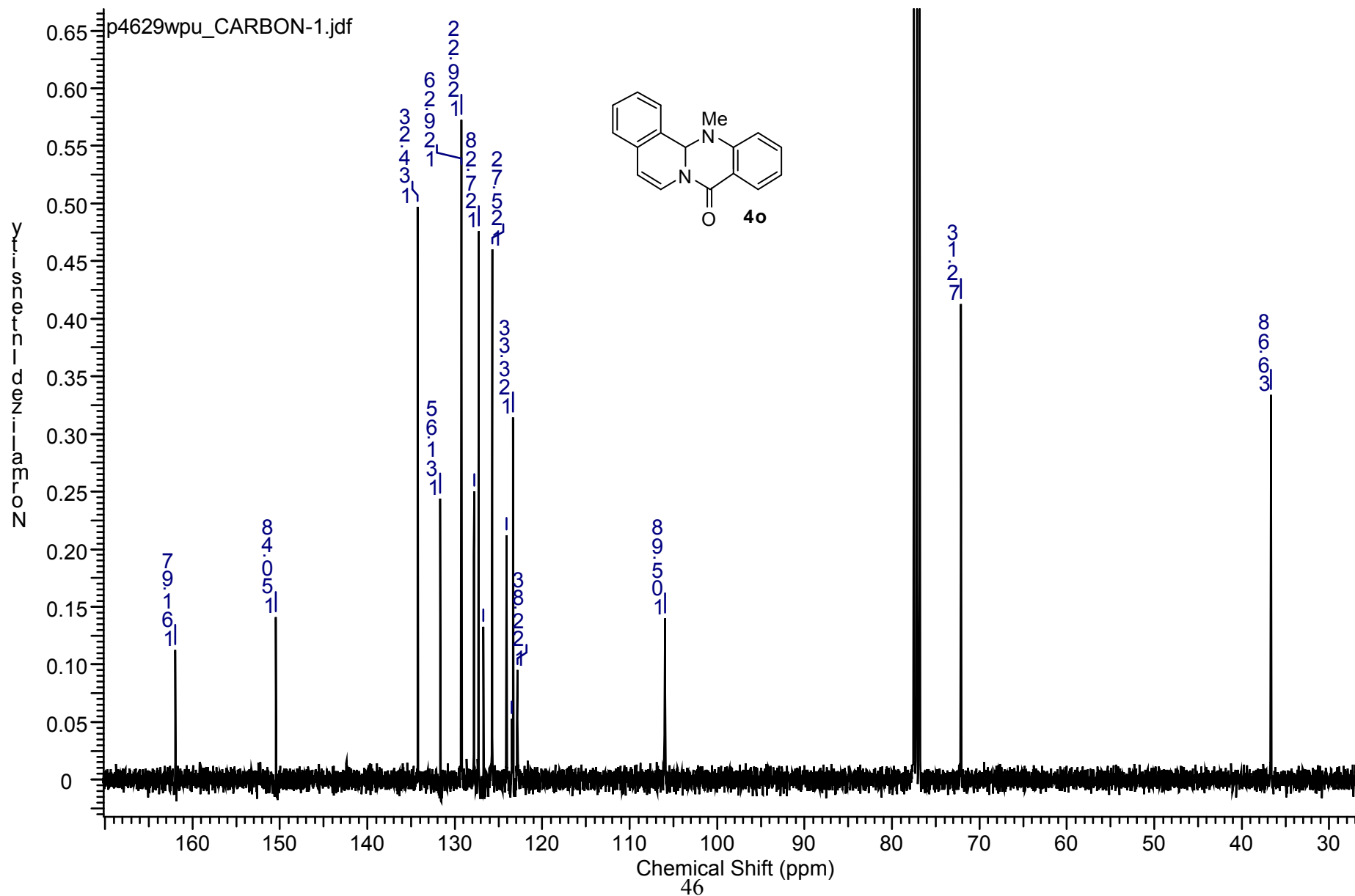


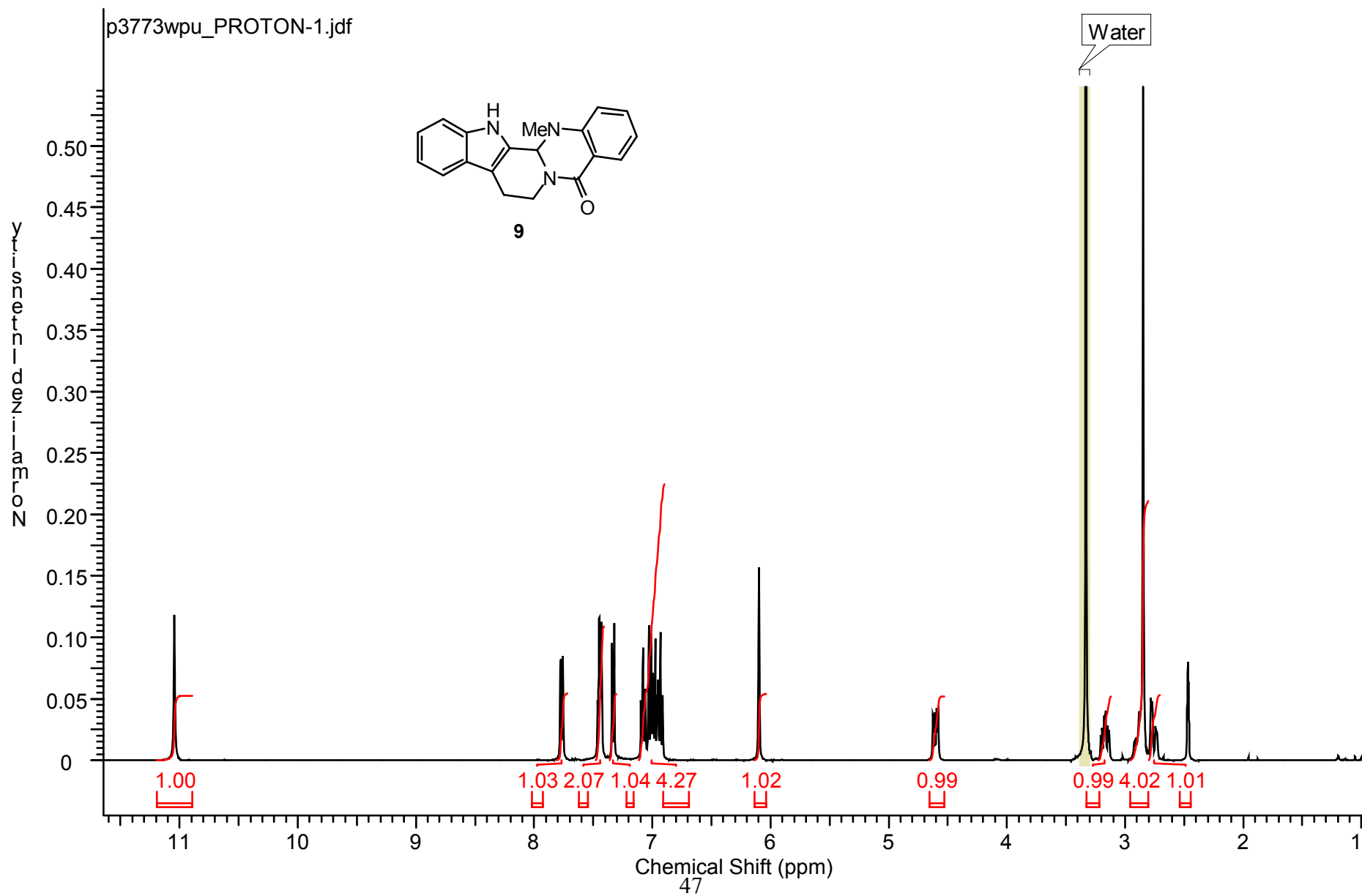


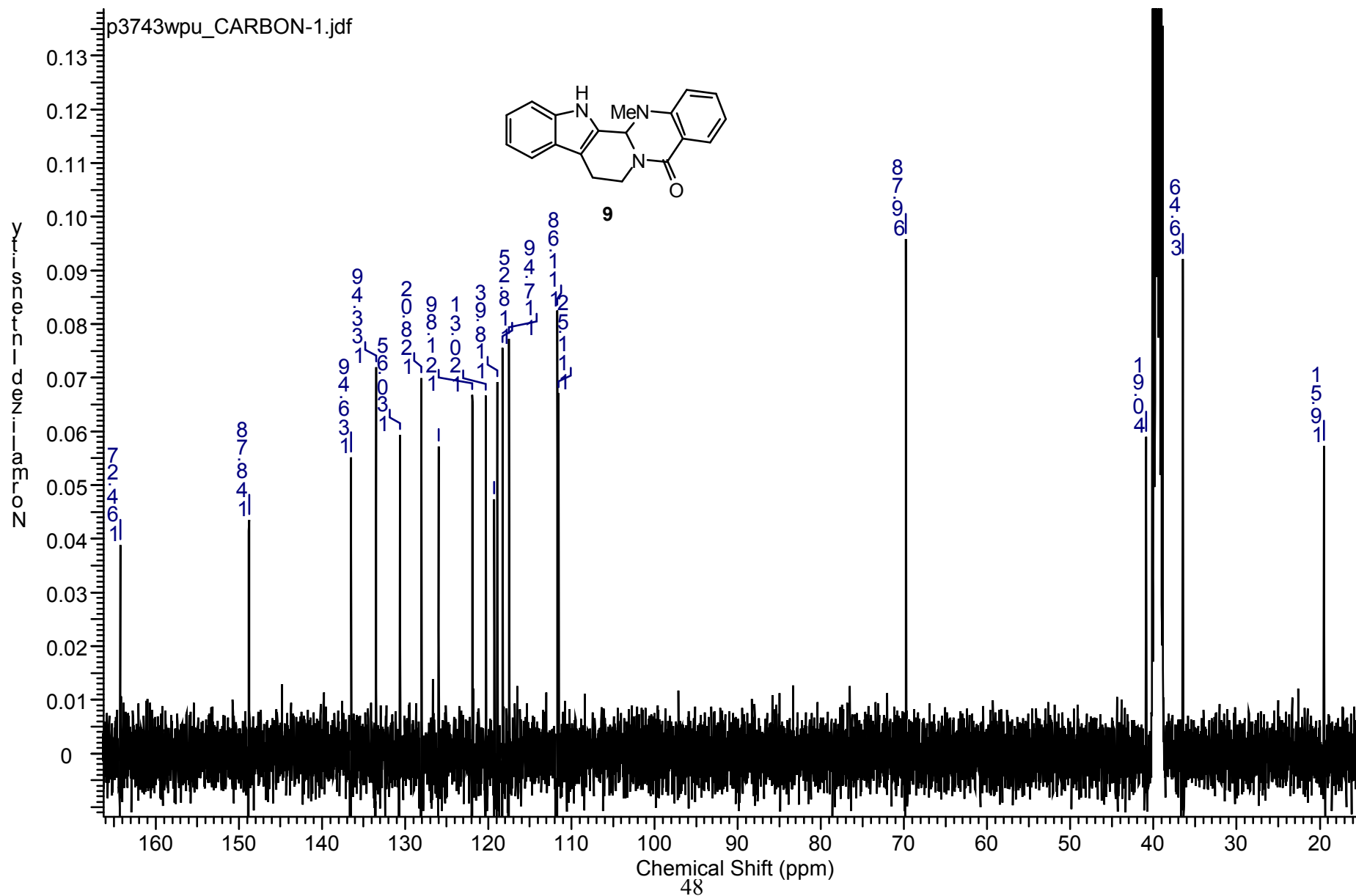








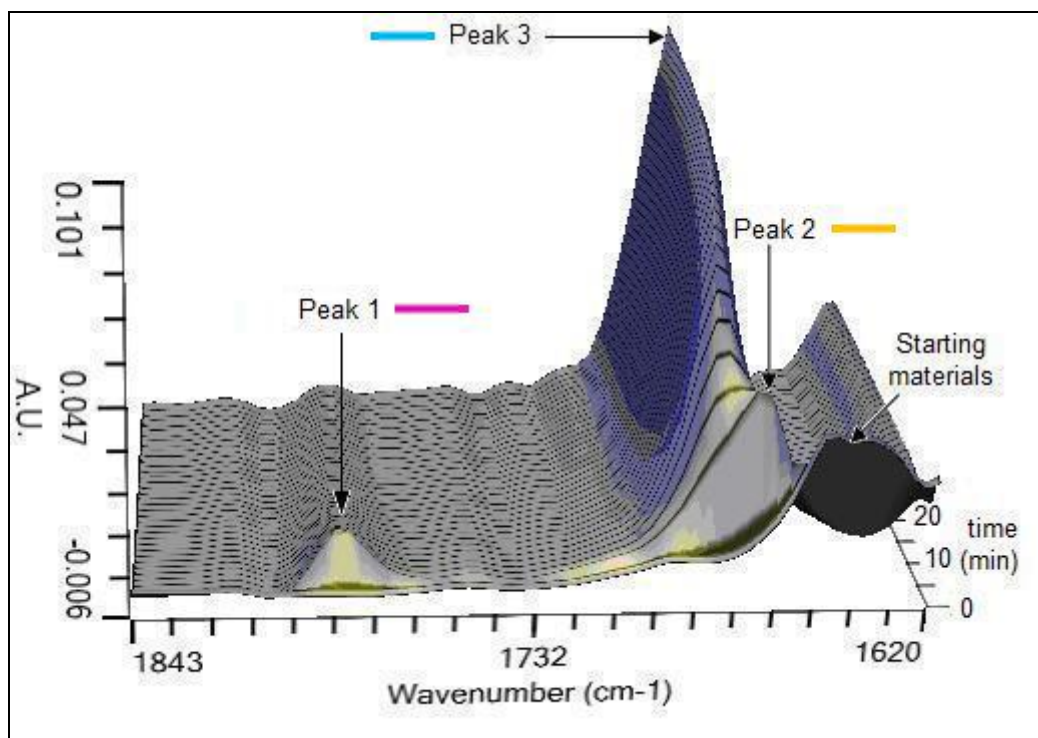




### ReactIR™ Study

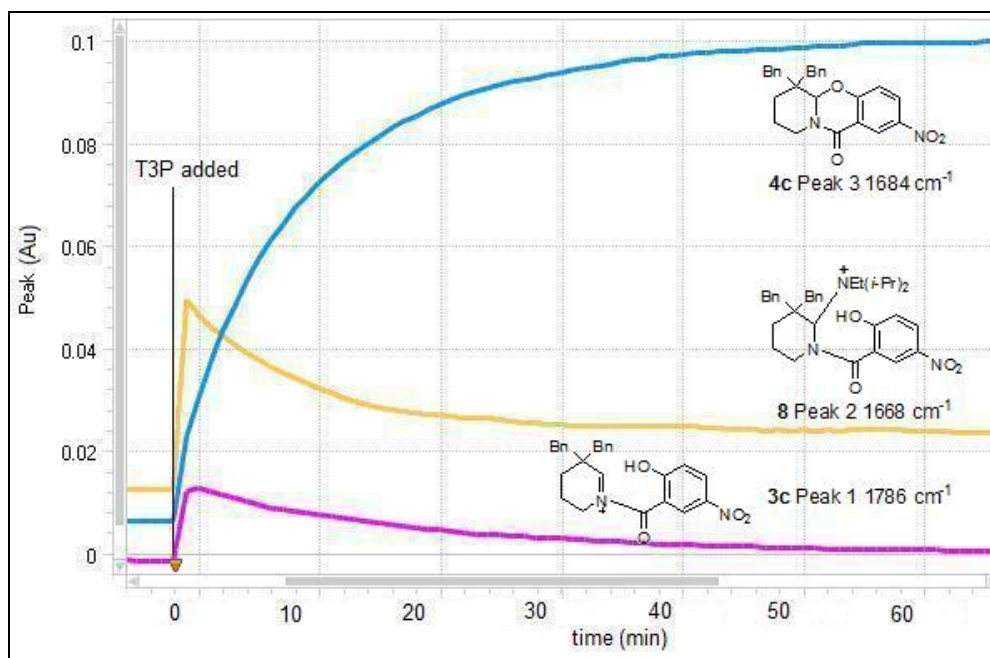
An FTIR analyser, ReactIR 4000 with a MCT detector, a KBr beam splitter and an ATR probe (DiComp) were used for all ReactIR experiments. The probe was fitted to a 50 mL glass round bottom flask containing a magnetic stirrer bar to provide agitation. A nitrogen purge was maintained on the system throughout the experiment, and a nitrogen background was used in computing the absorbance spectra. Each spectrum represents 256 co-added scans measured at a spectral resolution of 4 cm<sup>-1</sup> in the 4000–650 cm<sup>-1</sup> range with the Happ–Genzel apodisation.

To shed light on the mechanism for CAM an *in situ* ReactIR™ study was carried out using imine **1a** with 5-nitro-salicylic acid **2c**<sup>7</sup> (acid **2c** was chosen as this reaction proceeded efficiently in one hour at 50 °C, the lower temperature being more compatible with the ReactIR™ probe). The results of this study are shown in Figures S1 and S2. It should be noted that that no absorptions were observed in the region  $\nu_{\text{C=O}}$  2100–2200 cm<sup>-1</sup>, seemingly ruling out the intermediacy of a ketene (**S3**).<sup>8</sup> Also, due to severe overcrowding of the signals with wavenumbers below 1650 cm<sup>-1</sup> it was not possible to confidently derive any information from this region of the spectra, meaning that the fates of both the starting imine and acid could not be monitored (Figure S1). However, within one minute of the addition of T3P to a 50 °C solution of imine **1a**, acid **2c** and DIPEA in toluene, three new peaks were observed and monitored. An intense absorption (Peak 2 = 1668 cm<sup>-1</sup>) appeared quickly along with a much less intense peak (Peak 1 = 1786 cm<sup>-1</sup>). The intensity of Peak 2 quickly began to decrease (see Figure S2) and was accompanied by the formation of third peak (Peak 3 = 1684 cm<sup>-1</sup>) representing the carbonyl stretch of the product **4c** (confirmed with an authentic sample under the ReactIR™ conditions) which continued to increase in intensity before reaching a maximum after 1 hour. Meanwhile, Peak 1 maintained a steady low concentration, before dropping away over one hour as the reaction neared completion.



**Figure S1.** 3D Plot of atomic absorption/wavenumber/time\*

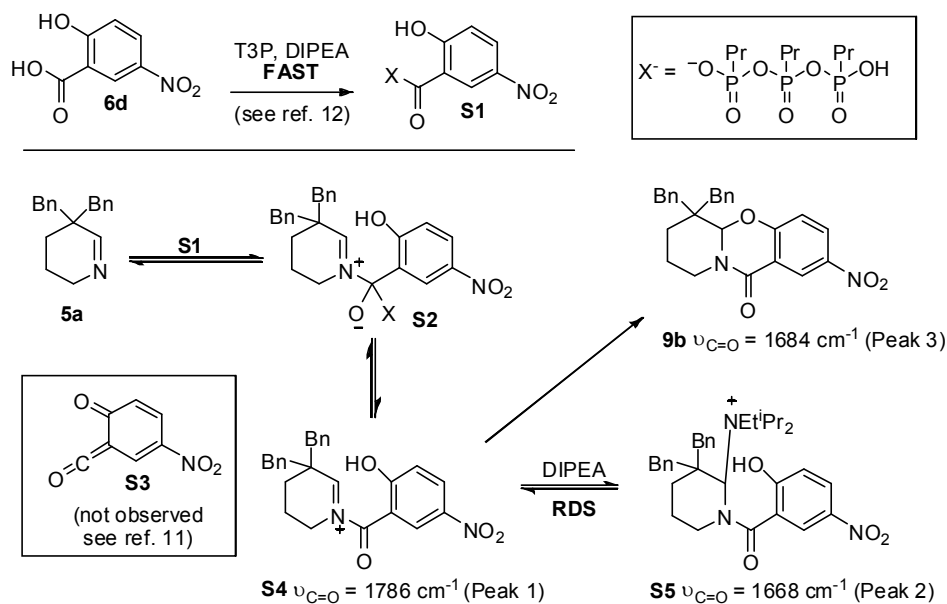
\*This plot represents the same time period to that shown in Figure S2 (*ca.* 70 min)



**Figure S2.** 2D Plot of atomic absorption/time for wavenumbers  $1668\text{ cm}^{-1}$ ,  $1684\text{ cm}^{-1}$  and  $1786\text{ cm}^{-1}$ .\*

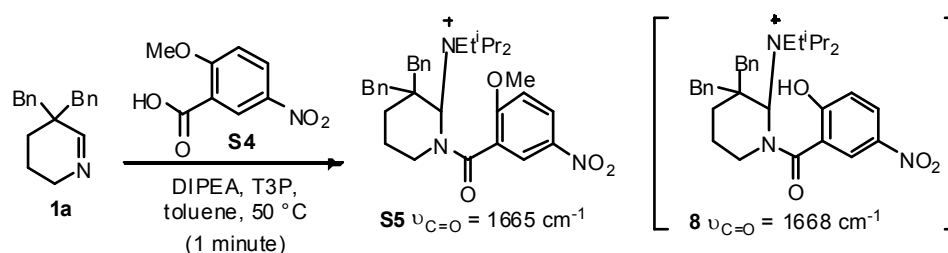
\* The absorption for Peak 2 does not appear to reach zero absorption due to peak overlap between itself and Peak 3.

These observations are consistent with a mechanism in which an intermediate (Peak 2) is formed rapidly and slowly collapses, *via* a short-lived reactive intermediate (Peak 1), to give the product (Peak 3). The following mechanism is proposed. The activation of carboxylic acid **6d** to **S1** takes place rapidly<sup>9</sup> but this intermediate is not observed in the React-IR<sup>TM</sup> as it is trapped by imine **5a** as quickly as it forms, generating the short-lived *N*-acyliminium ion **3c** (Peak 1 = 1786 cm<sup>-1</sup>).<sup>10</sup> This reactive intermediate is then primed to undergo intramolecular cyclisation to generate the final product **4c**, however, this simple mechanism does not account for the presence of Peak 2, or explain why the measured absorption of Peak 1 is so low, considering product formation requires a full hour to reach completion. It is therefore likely that prior to cyclisation the *N*-acyliminium ion **3c** is trapped by excess DIPEA in the reaction mixture, affording ammonium salt **8**.<sup>11</sup> The wavenumber of the IR absorption representing **8** (Peak 2, 1668 cm<sup>-1</sup>) is not consistent with that of an *N*-acyliminium ion carbonyl stretch, which typically appear at much higher wavenumbers,<sup>7</sup> but is reasonable for an amide carbonyl stretch. It seems likely that the formation of **8** is reversible, meaning that the extrusion of DIPEA can take place to regenerate the *N*-acyliminium ion **3c** which, over time, is removed from this equilibrium by cyclising to form the product **4c** (Peak 3 = 1684 cm<sup>-1</sup>). The mechanism proposed accounts for the persistent weak absorption of Peak 1, the relatively long reaction time and the observation of Peak 2 (Scheme 3).



**Figure S3** Proposed Mechanism for the CAM reaction of **5a** and **6d**.

Additional support for this mechanism was found via the acylation of imine **1a** with the o-anisic acid derivative **S4** in place of salicylic acid **2c** (Scheme S1). The experiment was performed in expectation that **S5** (an intermediate similar to **8**) would form, but in this case persist given that the cyclisation pathway had been negated. Thus T3P was added to a 50 °C solution of imine **1a**, acid **S4** and DIPEA in toluene and within one minute the coupling was complete and a new IR peak ( $\nu_{\text{C=O}}$  1665  $\text{cm}^{-1}$ ) had fully formed and remained unchanged for 30 minutes. No absorptions above 1700  $\text{cm}^{-1}$  were observed which ruled out the possibility of the coupled product existing as a discrete *N*-acyliminium ion. However, the wavenumber of the observed absorption closely matched (within 3  $\text{cm}^{-1}$ ) that of the initially formed intermediate **8** in the CAM reaction above (Figure S3). Thus the carbonyl stretch of ammonium salt **S5** most likely accounts for this peak and its rapid formation is in line with that observed for its phenol analogue **8**.



**Scheme S1** The formation of DIPEA adduct **S5**.

## References

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- <sup>4</sup> Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *Angew. Chem. Int. Ed.* **2003**, 42, 4077–4082.
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- <sup>6</sup> Nakasato, T.; Asada, S.; Murai, K. *J. Pharm. Soc. Jpn.* **1962**, 82, 619–626.
- <sup>7</sup> The reaction was performed using the substrate ratios and conditions of General CAM procedure A, except the temperature and reaction time were decreased (50 °C, 70 min).
- <sup>8</sup> Liu, R. C.-Y.; Luszyk, J.; McAllister, M. A.; Tidwell, T. T.; Wagner, B. D. *J. Am. Chem. Soc.* **1998**, 120, 6247–6251.
- <sup>9</sup> The rapid formation of **25a** is supported by an additional study: T3P was added to a 50 °C solution of acid **6d** and DIPEA in toluene with *in situ* IR monitoring (React IR-1, Scheme 5). The rapid formation of a new peak in the carbonyl region was observed ( $\nu_{\text{C=O}}$  1783  $\text{cm}^{-1}$ , complete within one minute), indicating that the conversion of acid **6d** to its activated form **25a** was completed within this time.
- <sup>10</sup> *N*-Acyliminium ions are rarely isolable and, as such, there is no precedent for the measurement of the IR carbonyl stretches of any compounds directly comparable to **26b**. The IR stretches of related compounds have been measured however and appear in the range 1725–1810  $\text{cm}^{-1}$ ; a) Funke, W.; Hornig, K.; Möller, M. H.; Würthwein, E-U. *Chem. Ber.* **1993**, 126, 2069–2077; b) Würthwein, E-U.; Kupfer, R.; Kaliba, C.; *Angew. Chem. Int. Ed.* **1983**, 22, 252–253; c) Jochims, J. C.; Glocker, M. O.; Hofmann, J.; Fischer, H. *Tetrahedron* **1991**, 47, 205–218.
- <sup>11</sup> For examples triamine-adducts of *N*-acyliminium ions similar to **32b** see a) Clemence, F.; Fortin, M.; Le Martret, O.; Delevallee, F.; Bois, F. S. US Patent US4816465 A1, **1989**; b) [Natural Product (–)-dysibetaine PP] IJzendoorn, D. R.; Botman, P. N. M.; Blaauw, R. H.; *Org. Lett.*, **2006**, 8, 239–242; c) Cherry, P. C.; Newall, C. E.; Watson, N. S.; *J. Chem. Soc., Chem. Commun.*, **1979**, 663–664.