

Total Synthesis of (-)-Aspergilazine A

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SUPPORTING INFORMATION

Contents

Page

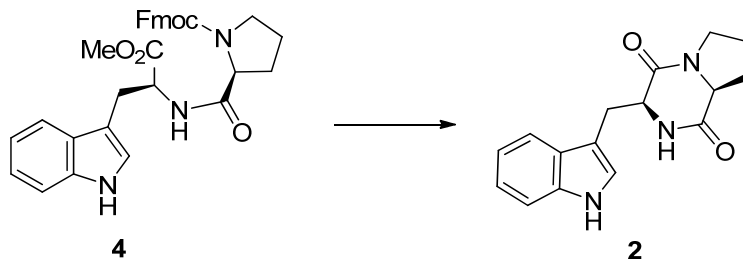
3	Experimental procedures
14	Table S1 – NMR data of natural and synthetic 1
16	References
17	¹ H NMR spectrum of 7
18	¹³ C NMR spectrum of 7
19	¹ H NMR spectrum of 3
20	¹³ C NMR spectrum of 3
21	NOESY spectrum of 3
22	¹ H NMR spectrum of 8
23	¹³ C NMR spectrum of 8
24	¹ H NMR spectrum of 9
25	¹³ C NMR spectrum of 9
26	NOESY spectrum of 9
27	¹ H NMR spectrum of <i>9-epi-9</i>
28	¹³ C NMR spectrum of <i>9-epi-9</i>
29	NOESY spectrum of <i>9-epi-9</i>
30	¹ H NMR spectrum of aspergilazine A (1)
31	¹³ C NMR spectrum of aspergilazine A (1)

Experimental

General

All reactions were carried out in oven-dried glassware under a nitrogen atmosphere unless otherwise stated. Analytical thin layer chromatography was performed using 0.2 mm Kieselgel F254 (Merck) silica plates and compounds were visualized under 365 nm ultraviolet irradiation followed by staining with either alkaline permanganate or ethanolic vanillin solution. Infrared spectra were obtained using a Perkin Elmer spectrum One Fourier Transform Infrared spectrometer as thin films between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}). Optical rotations were measured using a Perkin-Elmer 341 polarimeter at $\lambda = 598 \text{ nm}$ and are given in $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$. Melting points were recorded on an Electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded as indicated on either a Bruker DRX-400 spectrometer operating at 400 MHz for ^1H nuclei and 100 MHz for ^{13}C nuclei or on a Bruker Avance 300 spectrometer operating at 300 MHz and 75 MHz for ^1H and ^{13}C nuclei, respectively, or a Bruker Avance IIIHD-500 spectrometer operating at 500 MHz and 125 MHz for ^1H and ^{13}C nuclei, respectively. Chemical shifts are reported in parts per million (ppm) relative to the tetramethylsilane peak recorded as $\delta 0.00 \text{ ppm}$ in CDCl_3 / TMS solvent, or the residual chloroform ($\delta 7.26 \text{ ppm}$), DMSO ($\delta 2.50 \text{ ppm}$) or methanol ($\delta 3.31 \text{ ppm}$) peaks. The ^{13}C NMR values were referenced to the residual chloroform ($\delta 77.1 \text{ ppm}$), DMSO ($\delta 39.5 \text{ ppm}$) or methanol ($\delta 49.0 \text{ ppm}$) peaks. ^{13}C NMR values are reported as chemical shift δ , multiplicity and assignment. ^1H NMR shift values are reported as chemical shift δ , relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (J in Hz) and assignment. Assignments are made with the aid of DEPT 135, COSY, NOESY and HSQC experiments. High resolution mass spectra were recorded on a VG-70SE mass spectrometer at a nominal accelerating voltage of 70 eV.

Brevianamide F (2)



A solution of dipeptide **4**¹ (679 mg, 1.63 mmol) in piperidine-DMF (1:4, 17 mL) was stirred at room temperature for 2 days. The solvents were removed *in vacuo* and the crude residue purified by flash column chromatography on silica gel eluting with dichloromethane-methanol (24:1) to provide the *title compound* **2** as a colourless solid (280 mg, 0.99 mmol, 60 %)

$[\alpha]_D^{24} = -178.9$ (c = 0.43, CHCl₃) [lit.² $[\alpha]_D^{25} = -201.4$ (c = 0.43, CHCl₃)]

¹H-NMR (400 MHz, CDCl₃): $\delta_H = 8.40$ (1 H, br s, NH), 7.59 (1 H, d, $J = 8.0$, Ar-H), 7.38 (1 H, d, $J = 8.4$, Ar-H), 7.23 (1 H, td, $J = 7.5, 1.0$, Ar-H), 7.14 (1 H, td, $J = 7.5, 0.88$, Ar-H), 7.08 (1 H, d, $J = 2.1$, Ar-H), 5.78 (1 H, br s, NH), 4.37 (1 H, dd, $J = 10.8, 2.4$, CH), 4.05 (1 H, t, $J = 7.6$, CH), 3.75 (1 H, ddd, $J = 14.8, 3.6, 0.8, 0.5 \times \text{CH}_2$), 3.69 - 3.55 (2 H, m, CH₂) 2.98 (1 H, dd, $J = 15.1, 10.8, 0.5 \times \text{CH}_2$), 2.35 - 2.27 (1 H, m, $0.5 \times \text{CH}_2$), 2.04 - 1.86 (3 H, m, $1.5 \times \text{CH}_2$)

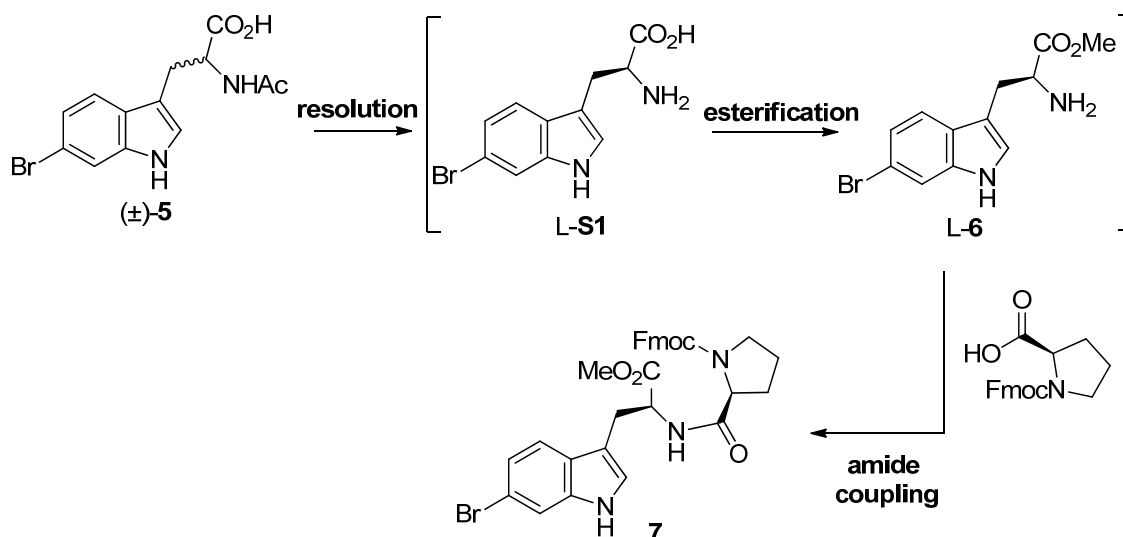
¹³C-NMR (100 MHz, CDCl₃): $\delta_C = 169.4$ (C=O), 165.6 (C=O), 136.7 (C), 126.7 (C), 123.4 (CH), 122.7 (CH), 120.0 (CH), 118.5 (CH), 111.6 (CH), 109.9 (C), 59.2 (CH), 54.6 (CH), 45.4 (CH₂), 28.3 (CH₂), 26.9 (CH₂), 22.6 (CH₂)

Mp: 168.6 – 173.2 °C (lit.² 165 – 167 °C)

ν_{max} cm⁻¹ (neat): 3263, 1669, 1643 1420, 737, 679.

Spectroscopic data consistent with literature.²

Dipeptide 7



Resolution

To a solution of racemic N^{α} -acetyl-6-bromotryptophan² (\pm)-5 (1052 mg, 3.24 mmol) in a borate buffer solution (50 mM, 40 mL) containing cobalt(II) chloride hexahydrate (1.2 mg, 0.125 mM) at pH 8 was added a solution of amino acylase (258 mg) in borate buffer (50 mM, 40 mL) with stirring. The mixture was stirred at 37 °C for 40 h and then the pH was adjusted to 3 with 2M HCl solution. The mixture was extracted by ethyl acetate (3 x 100 mL) and the combined organic layers dried (MgSO_4), filtered and the solvent evaporated *in vacuo* to give crude N -acetyl-6-bromo-D-tryptophan as a brown oil (0.569 g, 1.75 mmol). The aqueous layer was concentrated to dryness and the resulting crude solid (~1010 mg) containing 6-bromo-L-tryptophan L-S1 was used in the subsequent reaction without further purification. The enantiomeric excess of L-S1 was calculated as described on page 6.

Esterification

To a solution of the crude solid containing L-S1 obtained from the resolution (850 mg) in methanol (7.5 mL) at 0 °C was added dropwise thionyl chloride (0.48 mL, 6.6 mmol) and the reaction mixture was stirred at 80 °C for 6 h then the solvent removed *in vacuo*. The residue was taken up in water (50 mL) and the solution taken to pH 8 with Na_2CO_3 (10 % solution). The mixture was extracted with ethyl acetate (5 x 100 mL), dried (MgSO_4), filtered and the

solvent concentrated *in vacuo* to provide the methyl ester L-6 as a red oil (286 mg, 0.96 mmol) that was used in the subsequent coupling reaction without further purification.

For comparison purposes, characterisation was performed on the hydrochloride salt, a known literature compound.

$$[\alpha]_D^{22} = +18.9 \text{ (c = 1.0, MeOH)}$$

¹H-NMR (400 MHz, DMSO-*d*₆): δ_H = 11.26 (1 H, br s, NH), 8.54 (3 H, br s, NH₃⁺), 7.57 (1 H, d, *J* = 1.8, Ar-H), 7.47 (1 H, d, *J* = 8.5, Ar-H), 7.28 (1 H, d, *J* = 2.3, Ar-H), 7.15 (1 H, dd, *J* = 8.5, 1.8, Ar-H), 4.24 (1 H, m, CH), 3.66 (3 H, s, Me), 3.28 (2 H, t, *J* = 6.4, CH₂)

¹³C-NMR (100 MHz, DMSO-*d*₆): δ_C = 169.6 (C=O), 137.1 (C), 126.1 (CH), 126.0 (C), 121.5 (CH), 119.8 (CH), 114.1 (CH), 113.9 (C), 106.8 (C), 52.7 (CH₃) 52.6 (CH), 25.8 (CH₂)

¹H and ¹³C NMR data match literature values.³

Amide coupling

To a solution of L-6 (286 mg, 0.96 mmol) and Fmoc-L-proline (325 mg, 0.96 mmol) in dichloromethane-DMF (4:1, 12 mL) was added HATU (385 mg, 1.01 mmol) and *N,N'*-diisopropylethylamine (0.25 mL, 1.45 mmol). The reaction was stirred at room temperature for 8 hours and then the solvent removed *in vacuo*. The crude residue was taken up in dichloromethane (100 mL) and washed with 1M HCl solution (75 mL), saturated NaHCO₃ (75 mL), and brine (75 mL). The organic layer was dried (Na₂SO₄), filtered and the solvent concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel eluting with dichloromethane-methanol (24:1) to provide to provide the *title compound* 7 (539 mg, 0.87 mmol, 32 % over 3 steps; resolution has a maximum yield of 50%) as an orange glass.

$$[\alpha]_D^{22} = -17.4 \text{ (c = 1.0, CHCl}_3\text{)}$$

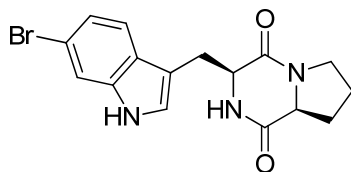
^1H NMR (400 MHz, CDCl_3): δ_{H} = 8.35 (minor conformer) + 8.07 (major conformer) (1 H, br s, NH), 7.86 – 7.69 (2 H, m, 2 x Ar-H), 7.64 – 6.78 (10.7 H, m, 10 x Ar-H + NH major conformer) 6.44 (0.3 H, br s, NH minor conformer), 4.93 – 4.80 (1 H, m, CH), 4.41 – 4.03 (4 H, m, 2 x CH + CH_2), 3.64 (major conformer) + 3.52 (minor conformer) (3 H, s, Me), 3.49 – 3.31 (2 H, m, CH_2), 3.29 – 3.16 (2 H, m, CH_2), 2.33 – 1.79 (4 H, m, 2 x CH_2)

^{13}C -NMR (125 MHz, CDCl_3): δ_{C} = 172.0 (C=O), 171.3 (C=O), 156.0 (C=O), 144.03 (C), 143.8 (C), 141.4 (C), 141.3 (C), 136.8 (C), 127.9 (2 x CH), 127.2 (CH), 127.1 (CH), 126.4 (C), 125.2 (CH), 125.1 (CH), 123.8 (CH), 122.7 (CH), 120.1 (CH), 120.0 (CH), 119.8 (CH), 115.5 (C), 114.1 (CH), 110.1 (C), 67.8 (CH_2), 60.3 (CH), 52.8 (CH), 52.4 (Me), 47.0 (CH + CH_2), 28.2 (CH_2), 27.4 (CH_2), 24.6 (CH_2)

MS [EI^+]: [MNa^+] found 638.1241. [$\text{C}_{32}\text{H}_{30}^{79}\text{BrN}_3\text{O}_5 + \text{Na}$] $^+$ requires 638.1261

m/z : 640 (MNa^+ , 100 %), 418 (97)

6-Bromobrevianamide F (**3**; Cyc-L-prolyl-6-bromo-L-tryptophan)



A solution of dipeptide **7** (539 mg, 0.87 mmol) in piperidine-DMF (1:4, 15 mL) was stirred at room temperature for 2 days. The solvents were removed *in vacuo* and the crude residue purified by flash column chromatography on silica gel eluting with dichloromethane-methanol (24:1) to provide the *title compound* **3** as a colourless solid (268 mg, 0.74 mmol, 85 %).

$[\alpha]_D^{22} = -87.3$ (c = 1.0, CHCl_3)

Mp: 198.5 – 202.9 °C

$^1\text{H-NMR}$ (400 MHz, CDCl_3): $\delta_{\text{H}} = 8.67$ (1 H, br s, NH), 7.52 (1 H, d, $J = 1.4$, Ar-H), 7.43 (1 H, d, $J = 8.4$, Ar-H), 7.22 (1 H, dd, $J = 8.5, 1.6$, Ar-H), 7.04 (1 H, d, $J = 2.0$, Ar-H), 5.84 (1 H, m, NH), 4.32 (1 H, dd, $J = 10.1, 2.8$, CH), 4.07 (1 H, t, $J = 7.4$, CH), 3.69 – 3.53 (3 H, m, 1.5 x CH_2), 2.98 (1 H, dd, $J = 15.1, 10.2, 0.5$ x CH_2), 2.33 – 2.28 (1 H, m, 0.5 x CH_2), 2.02 – 1.85 (3 H, m, 1.5 x CH_2)

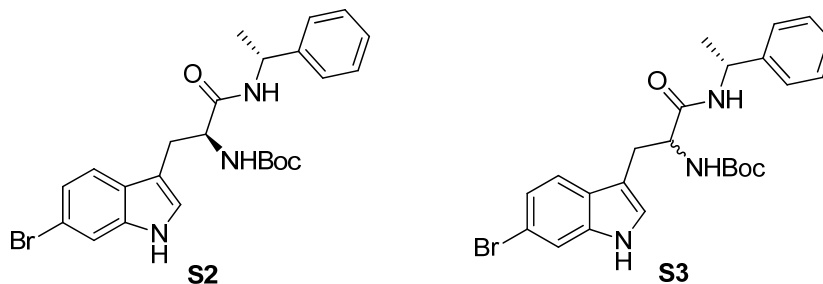
$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): $\delta_{\text{C}} = 169.4$ (C=O), 165.3 (C=O), 137.4 (C), 125.7 (C), 124.0 (CH), 123.3 (CH), 119.8 (CH), 116.3 (C), 114.5 (CH), 110.2 (C), 59.2 (CH), 54.7 (CH), 45.4 (CH_2), 28.3 (CH_2), 26.8 (CH_2), 22.6 (CH_2)

MS [EI^+]: [MNa^+] found 384.0321. [$\text{C}_{16}\text{H}_{16}^{79}\text{BrN}_3\text{O}_2 + \text{Na}^+$] requires 384.0318
 m/z : 384 (MNa^+ , 100 %), 324 (2), 210 (4)

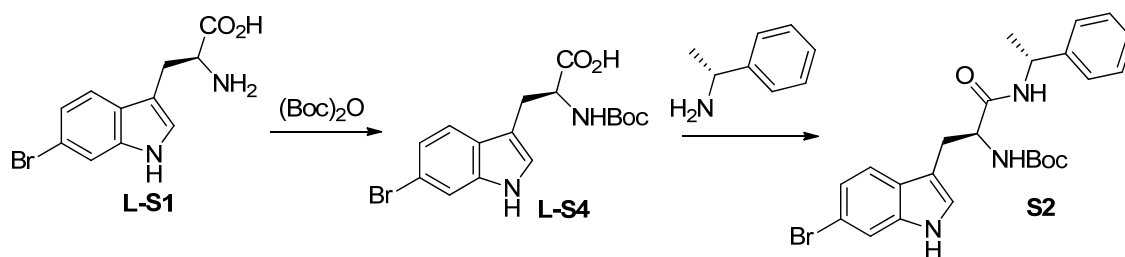
ν_{max} cm^{-1} (neat): 3364, 3202, 1671, 1643, 1438, 1423, 1300, 1274, 1120, 803, 793

The enantiomeric excess of 6-bromo-L-tryptophan L-S1

The enantiomeric excess of 6-bromo-L-tryptophan L-S1 obtained from the enzymatic resolution could not be unequivocally determined by HPLC. As a result, it was converted to its chiral amide derivative S2 and the ^1H NMR compared to that of the amide S3 prepared from a racemic sample of 6-bromotryptophan.



Synthesis of amide S2



To a solution of crude 6-bromo-L-tryptophan (L-S1) obtained from the resolution (~160 mg) in 10 % NaOH solution (1 mL) was added dioxane-water (13:1, 14 mL) followed by di-*tert*-butyl dicarbonate (171 mg, 0.78 mmol). The reaction mixture was stirred at room temperature for 17 hours, followed by heating to 80 °C for a further 2.5 hours. The solvents were removed *in vacuo* and the crude residue taken up in water (20 mL), and the pH adjusted to 3 with 2M HCl solution. The aqueous solution was extracted with ethyl acetate (5 x 20 mL), dried (Na₂SO₄), filtered and the solvent concentrated *in vacuo*. The resulting product was purified by flash column chromatography on silica gel eluting with acetic acid-methanol-dichloromethane (1:14:185) to provide N^α-Boc-6-bromo-L-tryptophan (L-S4) as a colourless glass.

¹H-NMR (400 MHz, CDCl₃): δ_H = 8.18 (1 H, br s, NH), 7.51 (1 H, s, Ar-H), 7.45 (1 H, d, *J* = 8.5, Ar-H), 7.26 (1 H, m, Ar-H), 7.20 (1 H, dd, *J* = 8.5, 1.3, Ar-H), 7.00 (1 H, br s, NH), 5.08 – 5.00 (0.5 H, m, 0.5 x CH), 4.69 – 4.59 (0.5 H, m, 0.5 x CH), 3.37 – 3.21 (2 H, m, CH₂), 1.43 (9 H, s, 3 x Me)

¹³C-NMR (100 MHz, CDCl₃): δ_C = 176.2 (C=O), 155.6 (C=O), 136.9 (C), 126.7 (C), 123.7 (CH), 122.8 (CH), 120.0 (CH), 115.6 (C), 114.2 (CH), 110.1 (C), 80.5 (C), 54.2 (CH), 28.3 (3 x Me), 27.5 (CH₂)

MS [EI⁺]: [MNa⁺] found 405.0421. [C₁₆H₁₉⁷⁹BrN₂O₄ + Na]⁺ requires 405.0420

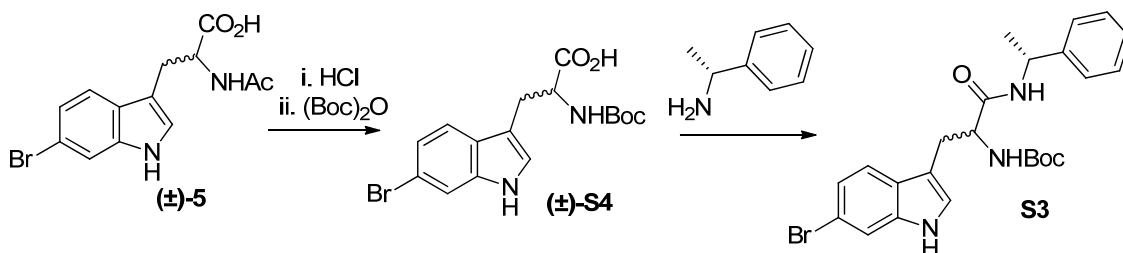
m/z: 405 (MNa⁺, 20 %), 349 (100), 305 (98)

Spectroscopic data consistent with literature.⁴

To a solution of L-S4 (10 mg, 0.026 mmol) in THF (0.7 mL) was added HATU (10 mg, 0.026 mmol), HOAt (4 mg, 0.026 mmol), *N,N'*-diisopropylethylamine (0.11 mL, 0.063 mmol) and

(*R*)-1-phenylethylamine (0.004 mL, 0.029 mmol). The reaction mixture was stirred at room temperature for 2 hours, then the solvents concentrated *in vacuo*. The crude residue was taken up in ethyl acetate (10 mL) and the resulting solution washed sequentially with 5% HCl solution (5 mL), saturated NaHCO₃ (5 mL), water (10 mL), and brine (10 mL). The organic layer was then dried (MgSO₄), filtered, and the solvent concentrated *in vacuo*. The crude product was filtered through a short plug of silica gel (dichloromethane-methanol, 49:1) to provide the amide **S2**.

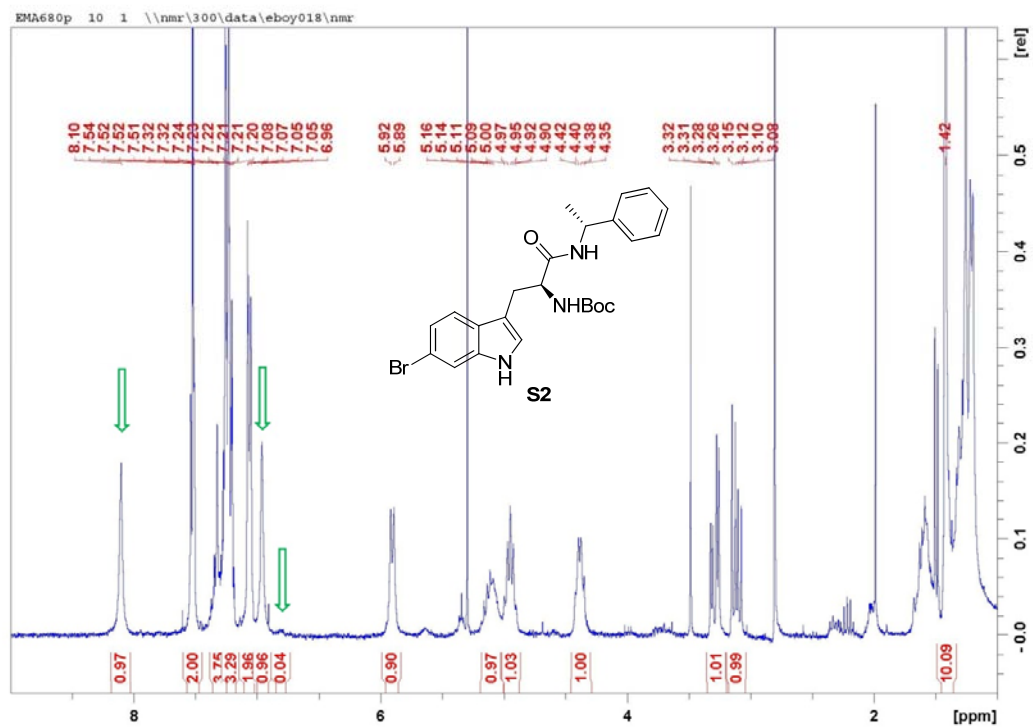
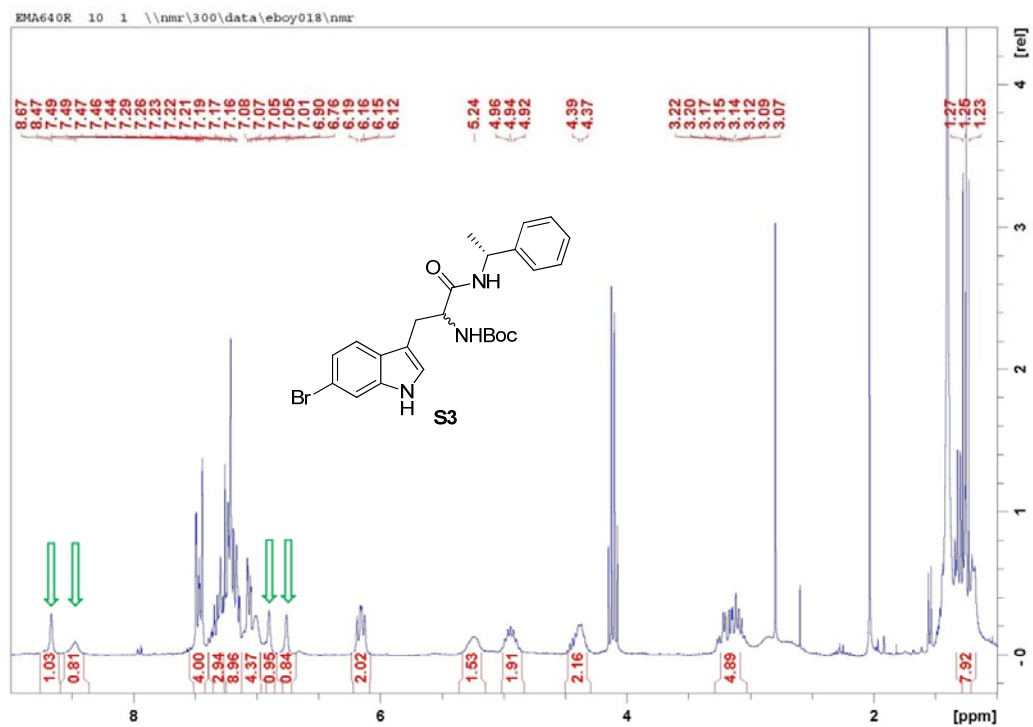
Amide **S3**



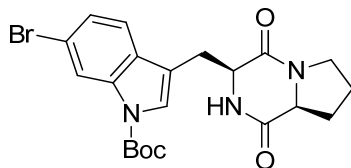
A suspension of racemic *N*^α-acetyl-6-bromotryptophan (**±**)-**5** (107 mg, 0.33 mmol) in 4 M aq. HCl (0.9 mL) was heated under reflux for 2 hours. The reaction mixture was cooled to room temperature and the solvents evaporated *in vacuo*. The crude residue was taken up in 10 % aq. NaOH (2 mL), and diluted with dioxane:water (22 mL, 13:1). Di-*tert*-butyl dicarbonate (50 mg, 0.33 mmol) was added, and the reaction mixture was stirred at room temperature for 22 hours, then the solvent removed *in vacuo*. The resulting crude (**±**)-6-bromotryptophan was taken up in water (20 mL), and the pH adjusted to 3 with 2M HCl solution. The aqueous solution was extracted with ethyl acetate (5 x 20 mL), dried (Na₂SO₄), filtered and the solvent concentrated *in vacuo*. The resulting product was purified by flash chromatography on silica gel eluting with acetic acid-methanol-dichloromethane (1:14:185) to provide *N*^α-Boc-6-bromotryptophan (**±**)-**S4** as a yellow oil.

To a solution of (**±**)-**S4** (40 mg, 0.10 mmol), HATU (40 mg, 0.10 mmol), and HOAt (14 mg, 0.10 mmol) in THF (3 mL), was added *N,N'*-diisopropylethylamine (0.044 mL, 0.25 mmol), followed by (*R*)-1-phenylethylamine (0.015 mL, 0.11 mmol). The reaction mixture was stirred at room temperature for 17 hours, then diluted with ethyl acetate (20 mL). The resulting solution was washed with 5% HCl solution (10 mL), saturated NaHCO₃ (10 mL), water (10 mL), brine (10 mL), and dried (MgSO₄), filtered, and the solvent concentrated *in vacuo* to provide the amide **S3** as a colourless glass.

^1H NMR of the amides **S2** and **S3** showed the enantiomeric excess to be 92 %



Cyc-L-prolyl-N-Boc-6-bromo-L-tryptophan (8)



To a solution of 6-bromobrevianamide F (**3**) (150 mg, 0.42 mmol) in THF (4 mL) was added di-*tert*-butyl dicarbonate (91 mg, 0.42 mmol) and DMAP (5.1 mg, 0.042 mmol). The reaction was stirred for 2.5 hours at room temperature, then the solvent evaporated *in vacuo*. The reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (6 x 15 mL). The combined organic extracts were washed with brine (40 mL), dried (Na₂SO₄), filtered and the solvent concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane-methanol (97:3) to provide the *title compound* (134 mg, 0.29 mmol, 70 %) as a cream-coloured solid.

$$[\alpha]_D^{23} = -72.0 \text{ (c = 0.53, CHCl}_3\text{)}$$

Mp: 188.4 – 189.8 °C

¹H-NMR (400 MHz, CDCl₃): δ_H = 8.38 (1 H, br s, NH), 7.46 (1 H, s, Ar-H), 7.38 (2 H, s, 2 x Ar-H), 5.74 (1 H, s, NH), 4.34 (1 H, dd, *J* = 10.8, 2.3, CH), 4.10 (1 H, t, *J* = 7.5, CH), 3.69 – 3.55 (3 H, m, 1.5 x CH₂), 2.93 – 2.86 (1 H, m, 0.5 x CH₂), 2.38 – 2.32 (1 H, m, 0.5 x CH₂), 2.09 – 1.84 (3 H, m, 1.5 x CH₂), 1.68 (9 H, s, 3 x Me)

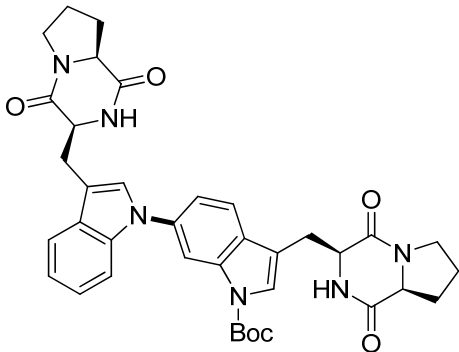
¹³C-NMR (100 MHz, CDCl₃): δ_C = 169.4 (C=O), 164.9 (C=O), 148.9 (C=O), 136.6 (C), 128.3 (C), 126.2 (CH), 124.9 (CH), 119.8 (CH), 119.0 (C), 118.9 (CH), 114.8 (C), 84.7 (C), 59.2 (CH), 54.1 (CH), 45.6 (CH₂), 28.3 (CH₂), 28.2 (3 x Me), 26.5 (CH₂), 22.7 (CH₂)

MS [EI⁺]: [MNa⁺] found 484.0842. [C₂₁H₂₄⁷⁹BrN₃O₄ + Na]⁺ requires 484.0846

m/z: 484 (MNa⁺, 14 %), 428 (100), 384 (100)

ν_{\max} cm^{-1} (neat): 3299, 2971, 1736, 1679, 1655, 1650, 1640, 1430, 1363, 1253, 1149, 1072, 814, 760

***N*-Boc Aspergilazine A (9)**



To a suspension of brevianamide F (**2**) (7 mg, 0.026 mmol) and *N*-Boc-6-bromobrevianamide F (**8**) (10 mg, 0.022 mmol) in toluene (1.5 mL) purged with nitrogen was added $\text{Pd}_2(\text{dba})_3$ (0.99 mg, 0.0011 mmol, 5 mol %), XPhos (2.1 mg, 0.0043 mmol, 20 mol %) and K_3PO_4 (4.1 mg, 0.043 mmol). The reaction mixture was stirred at 90 °C for 15 hours and then an additional portion of $\text{Pd}_2(\text{dba})_3$ (0.99 mg, 0.0011 mmol, 5 mol %) and XPhos (2.1 mg, 0.0043 mmol, 20 mol %) was added. After a further 10 hours, a third portion of $\text{Pd}_2(\text{dba})_3$ (0.99 mg, 0.0011 mmol, 5 mol %), XPhos (2.1 mg, 0.0043 mmol, 20 mol %) and K_3PO_4 (4.1 mg, 0.043 mmol) was added. The reaction mixture was stirred for a further 15 hours at 90 °C, filtered through Celite™ and concentrated to dryness. The crude mixture was purified by flash column chromatography on silica gel, initially eluting with ethyl acetate-methanol (93:7) to remove the monomeric starting materials, followed by dichloromethane-methanol (93:7) to obtain the *title compound* (11.4 mg, 0.017 mmol, 79%) as a yellow solid

$[\alpha]_D^{23} = -91.3$ ($c = 0.52$, CHCl_3)

Mp: 153.6 – 158.3 °C

$^1\text{H-NMR}$ (500 MHz, CDCl_3): $\delta_{\text{H}} = 8.34$ (1 H, br s, Ar-H), 7.65 (1 H, d, $J = 7.8$, Ar-H), 7.62 (1 H, d, $J = 3.1$, Ar-H), 7.61 (1 H, d, $J = 3.0$, Ar-H), 7.58 (1 H, br s, Ar-H), 7.39 (1 H, dd, $J = 8.4, 1.8$, Ar-H), 7.34 (1 H, s, Ar-H), 7.28 – 7.25 (1 H, m, Ar-H), 7.20 (1 H, apparent t, $J = 7.4$, Ar-H), 5.91 (1 H, br s, NH), 5.81 (1 H, br s, NH), 4.44 (2 H, td, $J = 10.9, 2.6, 2 \times \text{CH}$),

4.14 (1 H, t, $J = 7.7$, CH₂), 4.10 (1 H, t, $J = 7.8$, CH₂), 3.81 (1 H, dd, $J = 15.2, 3.5, 0.5 \times$ CH₂), 3.74 (1 H, dd, $J = 15.3, 2.9, 0.5 \times$ CH₂), 3.69 – 3.56 (4 H, m, 2 x CH₂) 3.06 (1 H, dd, $J = 15.2, 10.7, 0.5 \times$ CH₂), 2.97 (1 H, dd, $J = 15.2, 10.7, 0.5 \times$ CH₂), 2.39 – 2.31 (1 H, m, 2 x CH₂), 2.11 – 2.87 (6 H, m, 3 x CH₂), 1.67 (9 H, s, 3 x Me)

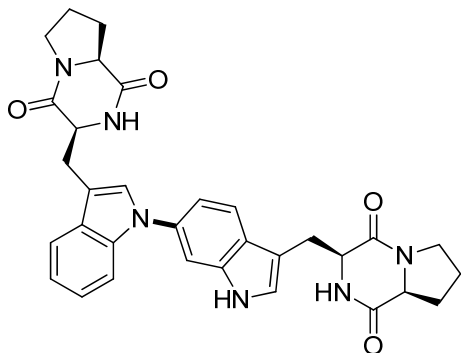
¹³C-NMR (125 MHz, CDCl₃): $\delta_C = 169.43$ (C=O), 169.40 (C=O), 165.4 (C=O), 165.0 (C=O), 149.0 (C=O), 136.8 (C), 136.7 (C), 136.3 (C), 128.2 (C), 128.0 (C), 127.4 (CH), 125.4 (CH), 123.2 (CH), 120.6 (CH), 119.7 (CH), 119.6 (CH), 118.8 (CH), 114.8 (C), 111.9 (CH), 111.0 (CH and C), 84.7 (C), 59.25 (2 x CH), 54.7 (CH), 54.1 (CH), 45.5 (CH₂), 45.4 (CH₂), 28.3 (2 x CH₂), 28.2 (3 x Me), 26.7 (CH₂), 26.6 (CH₂), 22.7 (CH₂), 22.6 (CH₂)

MS [EI⁺]: [MNa⁺] found 687.2912. [C₃₇H₄₀N₆O₆ + Na]⁺ requires 687.2902

m/z : 687 (MNa⁺, 50 %), 631 (86), 587 (100)

ν_{\max} cm⁻¹ (neat): 3460, 3249, 2921, 2851, 1731, 1660, 1492, 1456, 1445, 1388, 1368, 1253, 1154, 1107, 1088, 741

Aspergilazine A (1)



To a suspension of brevianamide F (2) (7 mg, 0.033 mmol) and 6-bromobrevianamide F (3) (10 mg, 0.028 mmol) in toluene (1.5 mL) purged with nitrogen was added Pd₂(dba)₃ (1.3 mg, 0.0014 mmol, 5 mol %), XPhos (2.6 mg, 0.0055 mmol, 20 mol %) and K₃PO₄ (10.5 mg, 0.11 mmol). The reaction mixture was stirred at 90 °C for 14 hours and then an additional portion of Pd₂(dba)₃ (1.3 mg, 0.0014 mmol, 5 mol %) and XPhos (2.6 mg, 0.0055 mmol, 20 mol %) was added. The reaction mixture was stirred for a further 9 hours at 90 °C, filtered through Celite™ and concentrated to dryness. The crude mixture was purified by flash column

chromatography on silica gel, initially eluting with ethyl acetate-methanol (93:7) to remove the monomeric starting materials, followed by dichloromethane-methanol (91:9) to obtain the *title compound* (1.4 mg, 0.0025 mmol, 9%) as a yellow solid.

$[\alpha]_D^{22} = -70.0$ (c = 0.10, CH₂Cl₂/MeOH; 1:1) [lit.⁵ $[\alpha]_D^{22} = -72.0$ (c = 0.10, CH₂Cl₂/MeOH 1:1)]

Mp: 155.4 – 157.2 °C

¹H-NMR, ¹³C-NMR See **Table S1**

ν_{\max} cm⁻¹ (neat): 3247, 2923, 2852, 1651, 1458, 1420, 1334, 1304, 1231, 1187, 1102, 1060, 807, 742

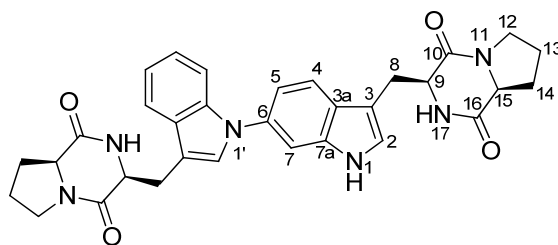
MS [EI⁺]: [MNa⁺] found 587.2373. [C₃₂H₃₂N₆O₄ + Na]⁺ requires 587.2377

m/z: 587 (MNa⁺, 100 %)

Aspergilazine A was also prepared by the deprotection of compound **9** as follows:

To a solution of *N*-Boc aspergilazine A **9** (10 mg, 0.02 mmol) in dichloromethane (1 mL) at 0 °C was added trifluoroacetic acid (0.06 mL, 0.83 mmol) and the reaction mixture was stirred at room temperature for 2 h, then partitioned between dichloromethane (2 mL) and saturated NaHCO₃ solution (2 mL). The organic layer was removed and the aqueous layer was extracted with dichloromethane (6 x 2 mL). The combined organic layers were dried (MgSO₄), filtered and the concentrated *in vacuo*. The crude product was purified by column chromatography on neutral alumina eluting with dichloromethane-methanol (49:1) to provide the *title compound* as an off-white solid (4.3 mg, 0.0077 mmol, 51 %), spectroscopic data identical to the material obtained from the *N*-arylation of **2** with **3**.

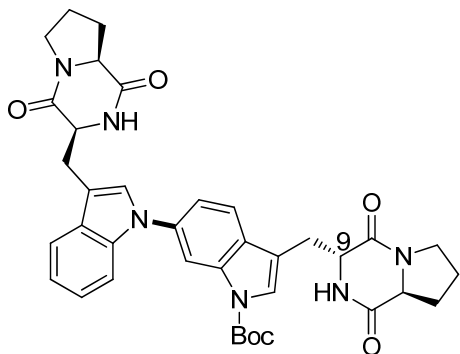
Table S1. NMR data for natural and synthetic (-)-aspergilazine A (**1**)



Pos	Natural 1 ^a δ_{H} (600 MHz, d_6 -DMSO)	Synthetic 1 δ_{H} (500 MHz, d_6 -DMSO)	Natural 1 ^b δ_{C} (150 MHz d_6 -DMSO)	Synthetic 1 δ_{C} (125 MHz d_6 -DMSO)
1	11.09 (1 H, s)	11.05 (1 H, d, $J = 1.9$)	-	-
2	7.29 (1 H, d, $J = 1.7$)	7.28 (1 H, d, $J = 2.2$)	126.3	126.2
3			110.3	110.2
4	7.48 (1 H, d, $J = 8.2$)	7.47 (1H, d, $J = 8.4$)	110.6	110.6
5	7.14 (1 H, dd, $J = 8.3, 1.9$)	7.18 - 7.13 (1 H, m)	115.8	115.7
6			129.1	129.0
7	7.45 (1 H, d, $J = 1.9$)	7.44 (1 H, d, $J = 1.9$)	107.2	107.2
	3.26 (1 H, m)	3.44 - 3.23 (1 H, m)		
8	3.16 (1 H, dd, $J = 14.9, 5.5$)	3.15 (1 H, dd, $J = 14.9, 5.7$)	26.4	26.33
9	4.41 (1H, dd, $J = 5.0, 4.9$)	4.40 (1 H, apparent t, $J = 5.1$)	55.8	55.74
10			166.0	165.9
	3.38 (1 H, m)			
12	3.26 (1 H, m)	3.44 - 3.23 (2 H, m)	45.2	45.1
13	1.65 (2 H, m)	1.74 - 1.55 (2 H, m)	22.4	22.35
	1.98 (1 H, m);	2.03 - 1.96 (1 H, m)		
14	1.37 (1 H, m)	1.46 - 1.34 (1 H, m)	28.3	28.2
15	4.07 (1H, dd, $J = 8.3, 8.3$)	4.09 (1 H, apparent t, $J = 8.4$)	59.0	58.9
16			169.7	169.6
17	8.00 (1 H, s)	7.96 (1 H, s)	-	-
1'			-	-
2'	7.47 (1 H, s)	7.46 (1 H, s)	128.9	128.8
3'			111.5	111.4
3a			126.6	126.6
3a'			133.6	133.5
4'	7.68 (1 H, br d, $J = 7.8$)	7.68 (1 H, d, $J = 7.9$)	119.9	119.9
5'	7.09 (1 H, ddd, $J = 7.4, 7.4, 0.8$)	7.10 (1 H, apparent t, $J = 7.7$)	120.3	120.2
6'	7.16 (1 H, ddd, $J = 7.7, 7.4, 1.0$)	7.18 - 7.13 (1 H, m)	122.6	122.5
7'	7.75 (1 H, br d, $J = 8.4$)	7.74 (1 H, d, $J = 8.5$)	119.9	119.9
7a			136.7	136.6
7a'			136.2	136.1
	3.38 (1 H, m)	3.44 - 3.23 (1 H, m)		
8'	3.16 (1 H, dd, $J = 14.9, 5.5$)	3.15 (1 H, dd, $J = 14.9, 5.7$)	26.3	26.27
9'	4.37 (1 H, dd, $J = 5.0, 5.0$)	4.36 (1 H, apparent t, $J = 5.0$)	55.7	55.66
10'			165.9	165.9
	3.38 (1 H, m)			
12'	3.26 (1 H, m)	3.44 - 3.23 (2 H, m)	45.2	45.1
13'	1.65 (2 H, m)	1.74 - 1.55 (2 H, m)	22.4	22.32
	1.98 (1 H, m)	2.03 - 1.96 (1 H, m)		
14'	1.37 (1 H, m)	1.46 - 1.34 (1 H, m)	28.3	28.2
15'	4.07 (1 H, dd, $J = 8.3, 8.3$)	4.09 (1 H, apparent t, $J = 8.4$)	59.0	58.9
16'			169.6	169.5
17'	7.89 (1 H, s)	7.85 (1 H, s)	-	-

Table 1 in the manuscript details certain catalytic systems that formed epimeric *N*-arylated products. From ^1H NMR of the crude reaction mixture, we were confident *9-epi-9*, *9'-epi-9* and *9,9'-di-epi-9* were all formed, but only *9-epi-9* could be obtained in sufficient quantity and purity to be completely characterised:

9-epi-N-Boc-aspergilazine A (9-epi-9)



$[\alpha]_{\text{D}}^{22} = -18.8$ ($c = 0.16$, CHCl_3)

Mp: 158.1 – 163.7

$^1\text{H-NMR}$ (500 MHz, CDCl_3): $\delta_{\text{H}} = 8.32$ (1 H, br s, Ar-H), 7.68 (1 H, d, $J = 8.4$, Ar-H), 7.64 (1 H, d, $J = 7.9$, Ar-H), 7.60 (1 H, d, $J = 8.2$, Ar-H), 7.41 (1 H, dd, $J = 8.4, 1.9$, Ar-H), 7.34 (1 H, s, Ar-H), 7.34 (1 H, s, Ar-H), 7.28 – 7.25 (1 H, m, Ar-H), 7.21 – 7.18 (1 H, m, Ar-H), 6.14 (1 H, br d, $J = 2.5$, NH), 5.89 (1 H, br s, NH), 4.45 (1 H, dd, $J = 10.8, 2.6$, CH), 4.31 – 4.28 (1 H, m, CH), 4.10 (1 H, t, $J = 7.6$, CH), 3.82 (1 H, dd, $J = 15.2, 3.4, 0.5 \times \text{CH}_2$), 3.70 – 3.65 (2 H, m, CH_2), 3.62 – 3.57 (1 H, m, $0.5 \times \text{CH}_2$), 3.51 (1 H, dd, $J = 10.5, 6.5$, CH), 3.41 – 3.36 (1 H, m, $0.5 \times \text{CH}_2$), 3.27 (2 H, d, $J = 5.8$, CH_2), 3.05 (1 H, dd, $J = 15.2, 10.7, 0.5 \times \text{CH}_2$), 2.37 – 2.25 (2 H, m, CH_2), 2.07 – 1.84 (6 H, m, $3 \times \text{CH}_2$), 1.66 (9 H, s, $3 \times \text{Me}$)

$^{13}\text{C-NMR}$ (125 MHz, CDCl_3): $\delta_{\text{C}} = 169.5$ (C=O), 168.7 (C=O), 165.5 (C=O), 165.0 (C=O), 149.2 (C=O), 136.8 (C), 136.5 (C), 128.2 (2 x C), 127.4 (CH), 126.1 (CH), 123.3 (CH), 120.6 (CH), 120.0 (CH), 119.5 (CH), 118.9 (CH), 114.4 (C), 111.6 (CH), 111.01 (CH), 110.96 (C), 84.7 (C), 59.3 (CH), 58.2 (CH), 58.0 (CH), 54.7 (CH), 45.50 (CH_2), 45.46 (CH_2), 30.5 (CH_2), 29.1 (CH_2), 28.3 (CH_2), 28.2 (3 x Me), 26.7 (CH_2), 22.7 (CH_2), 21.8 (CH_2), 1 carbon signal is not observed.

ν_{max} cm^{-1} (neat): 3230, 2925, 1731, 1652, 1492, 1444, 1367, 1255, 1154, 741

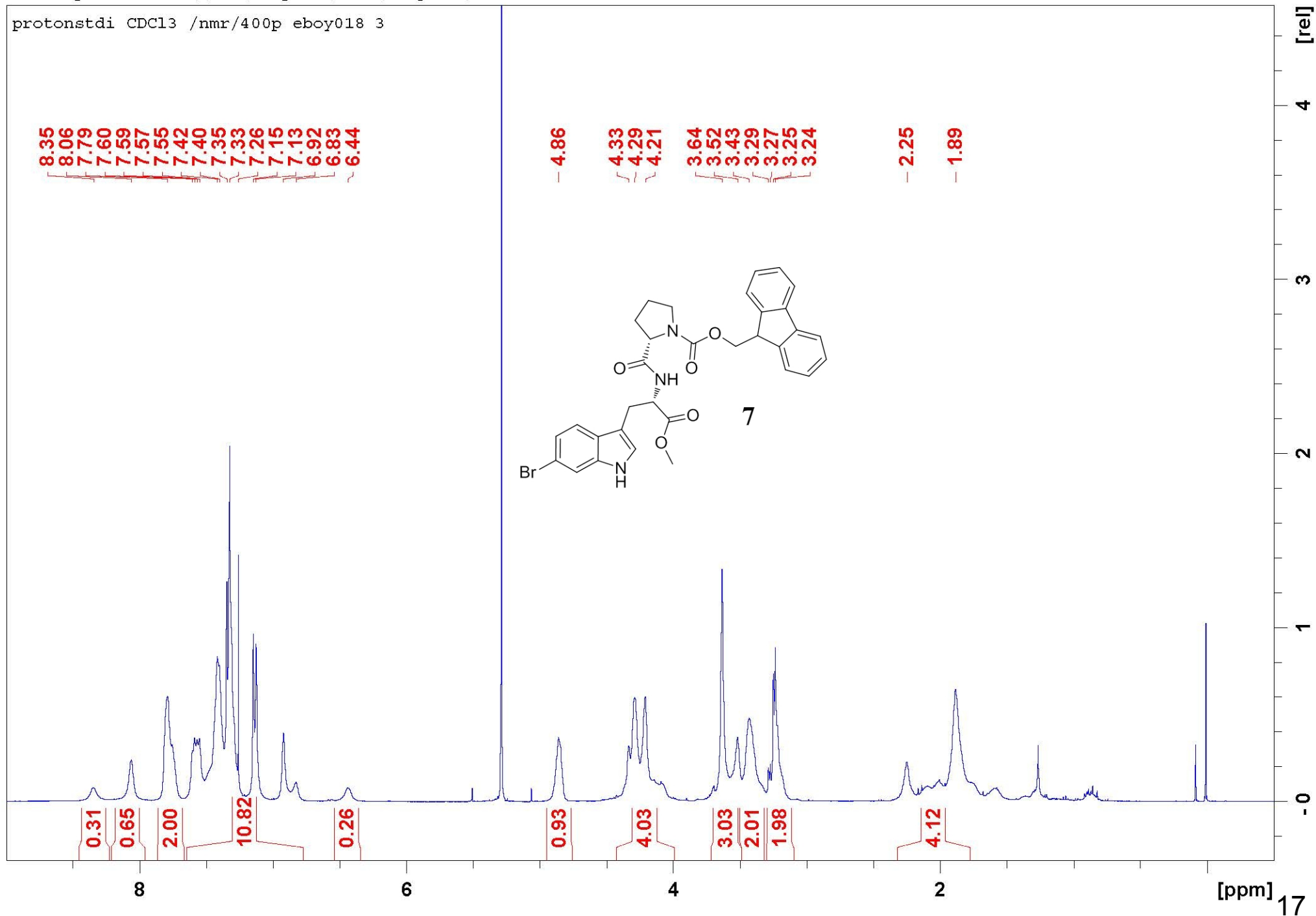
MS [EI⁺]: [M⁺] found 665.3095. [C₃₇H₄₁N₆O₆]⁺ requires 665.3082

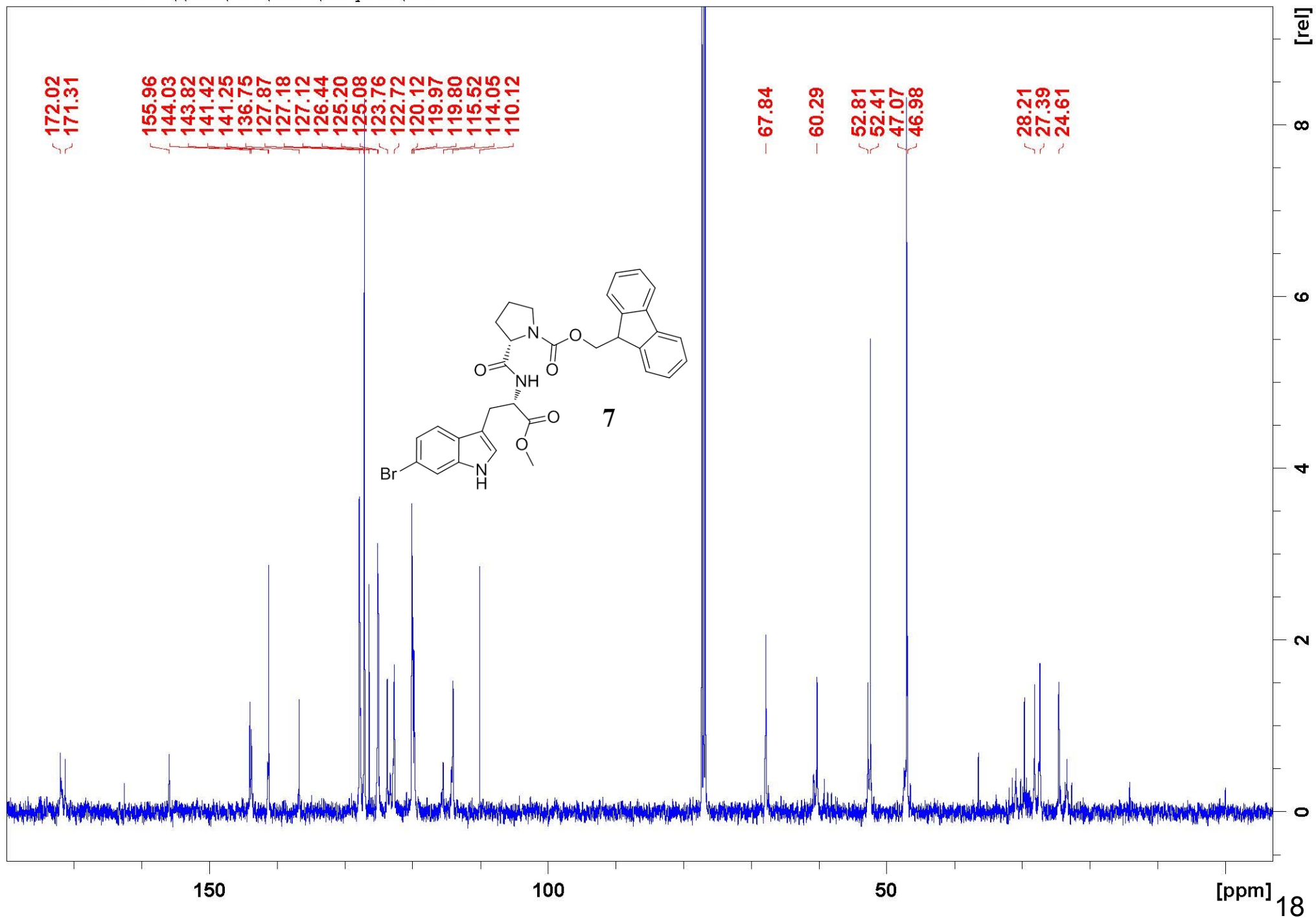
m/z: 665 (M⁺, 10 %), 609 (100), 565 (25), 455 (6), 411 (12)

References

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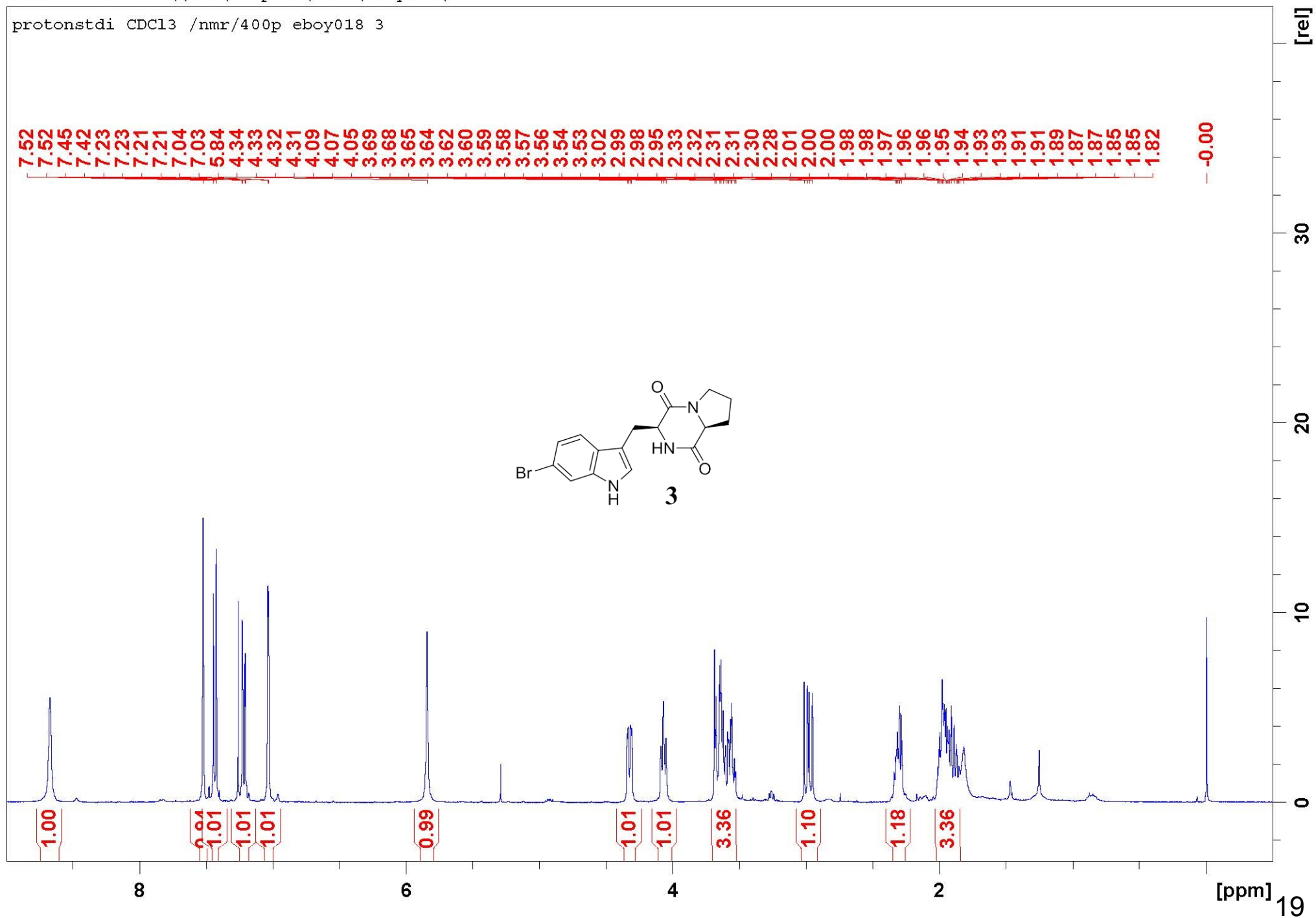
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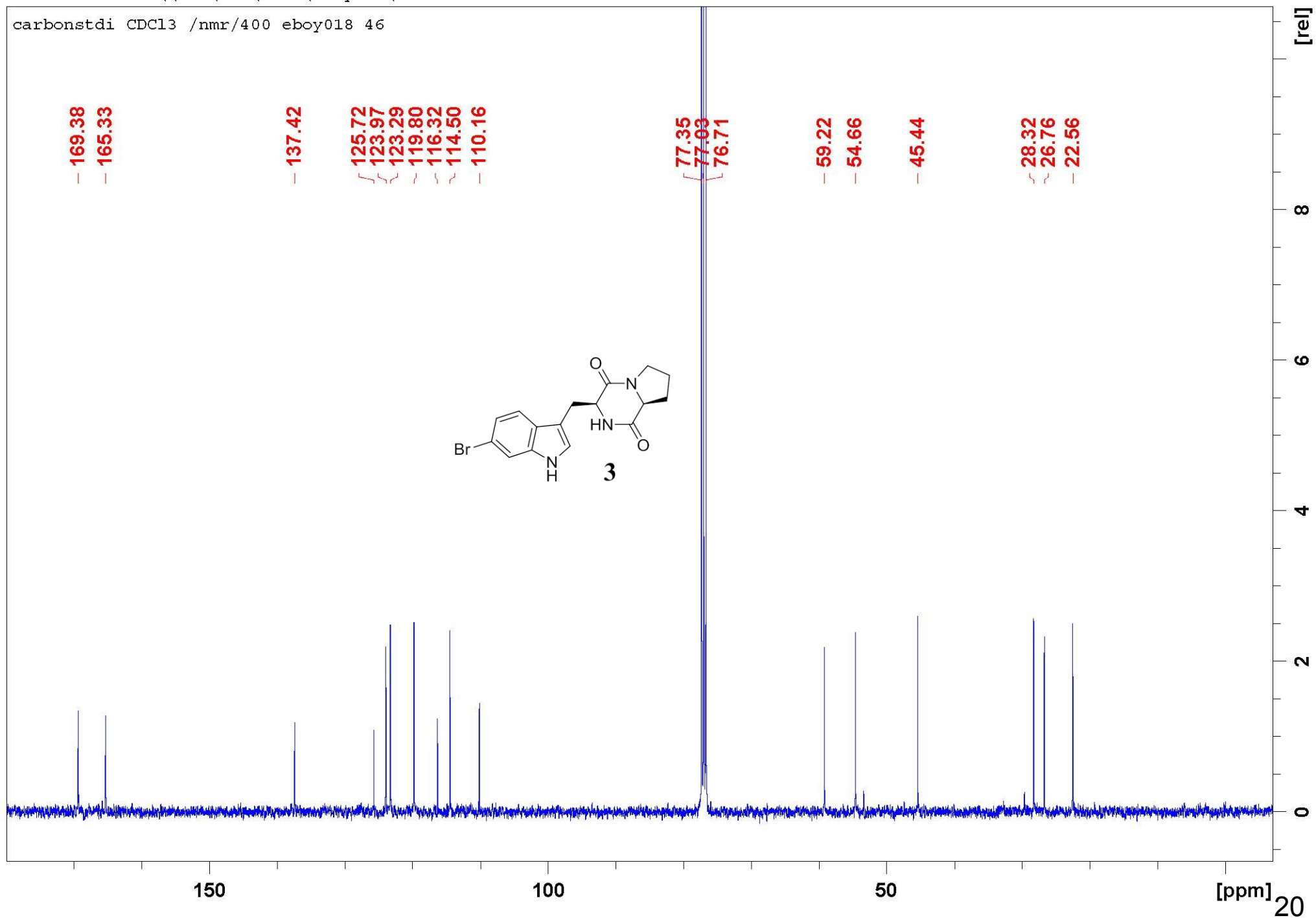
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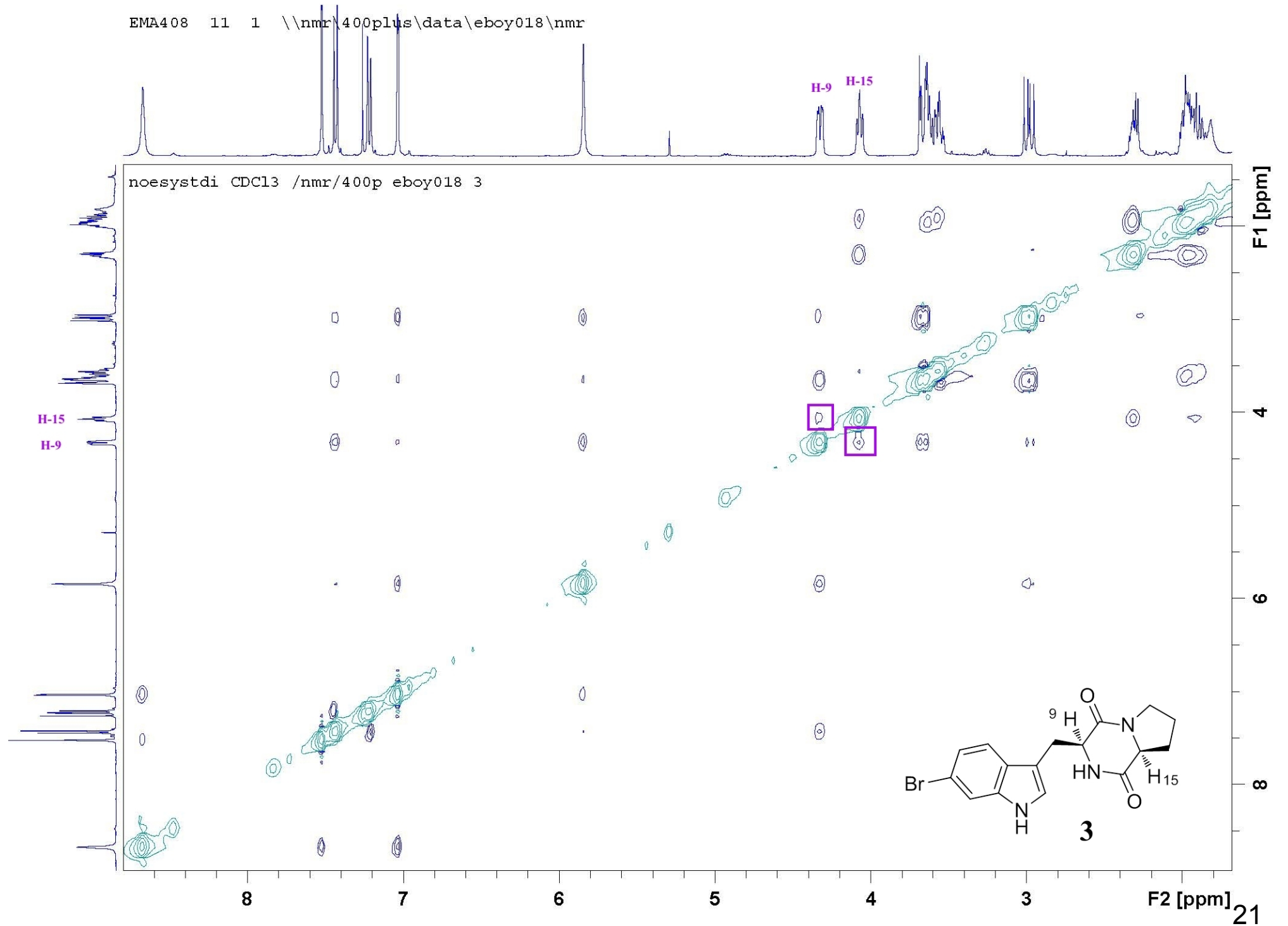
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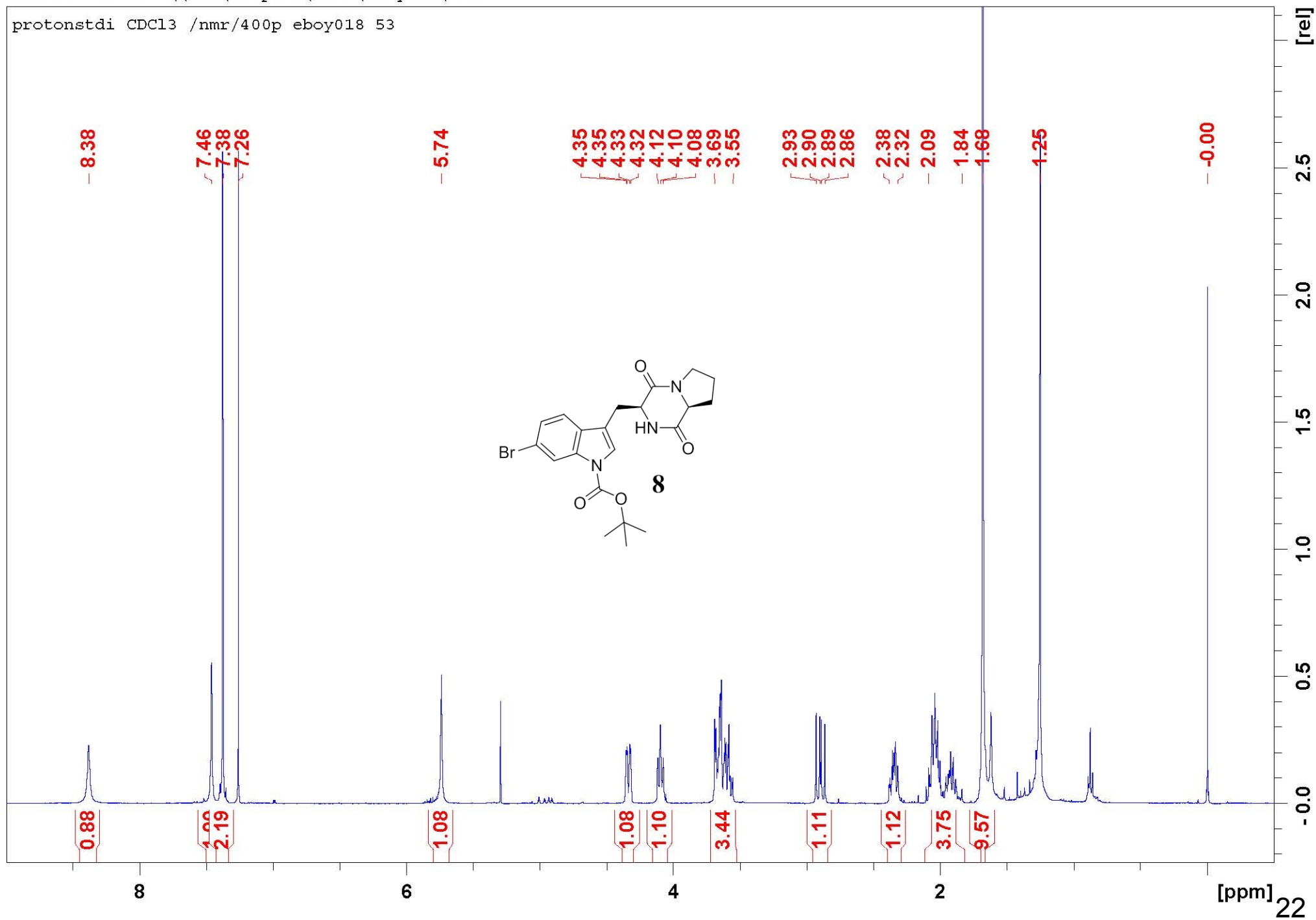


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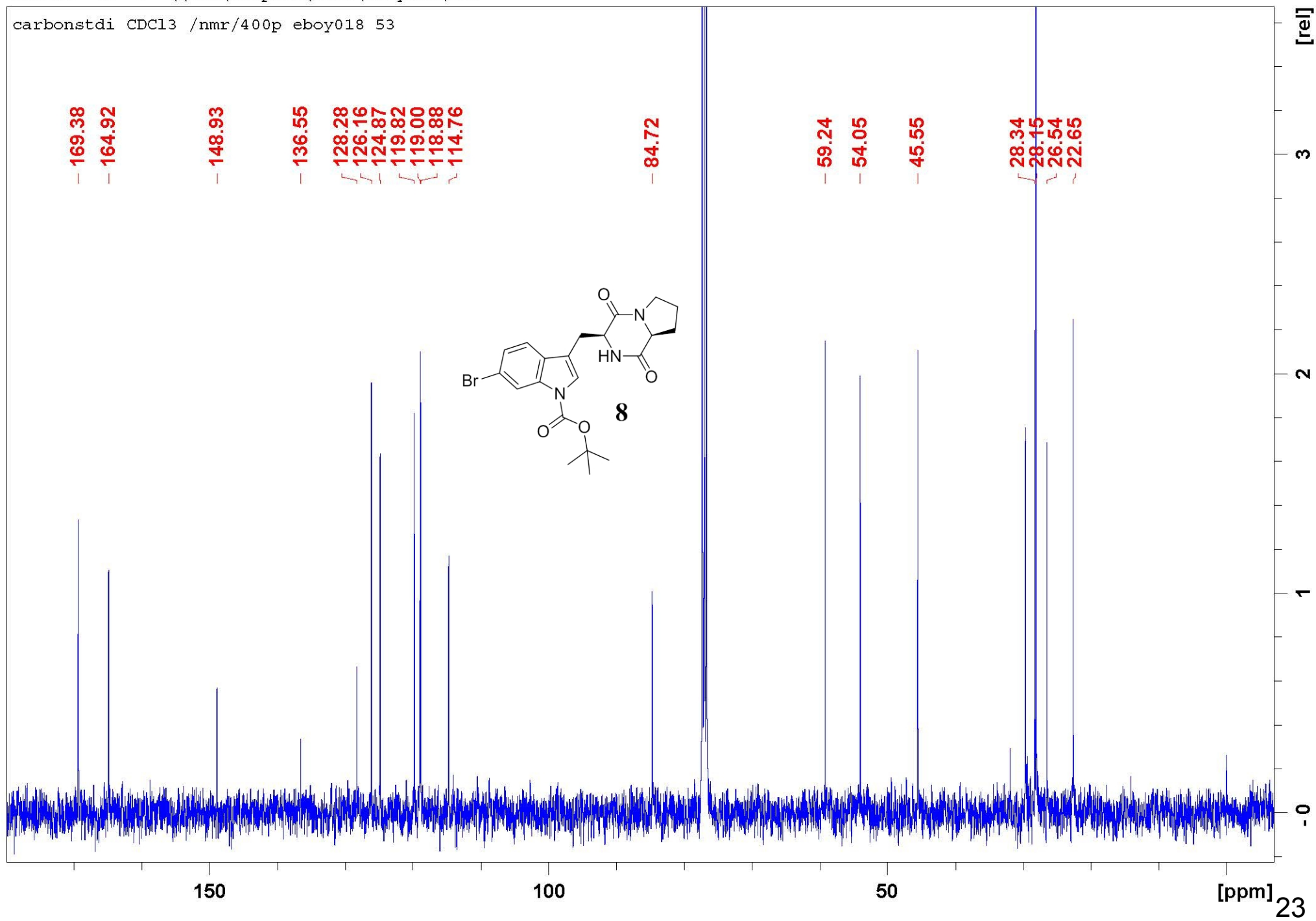


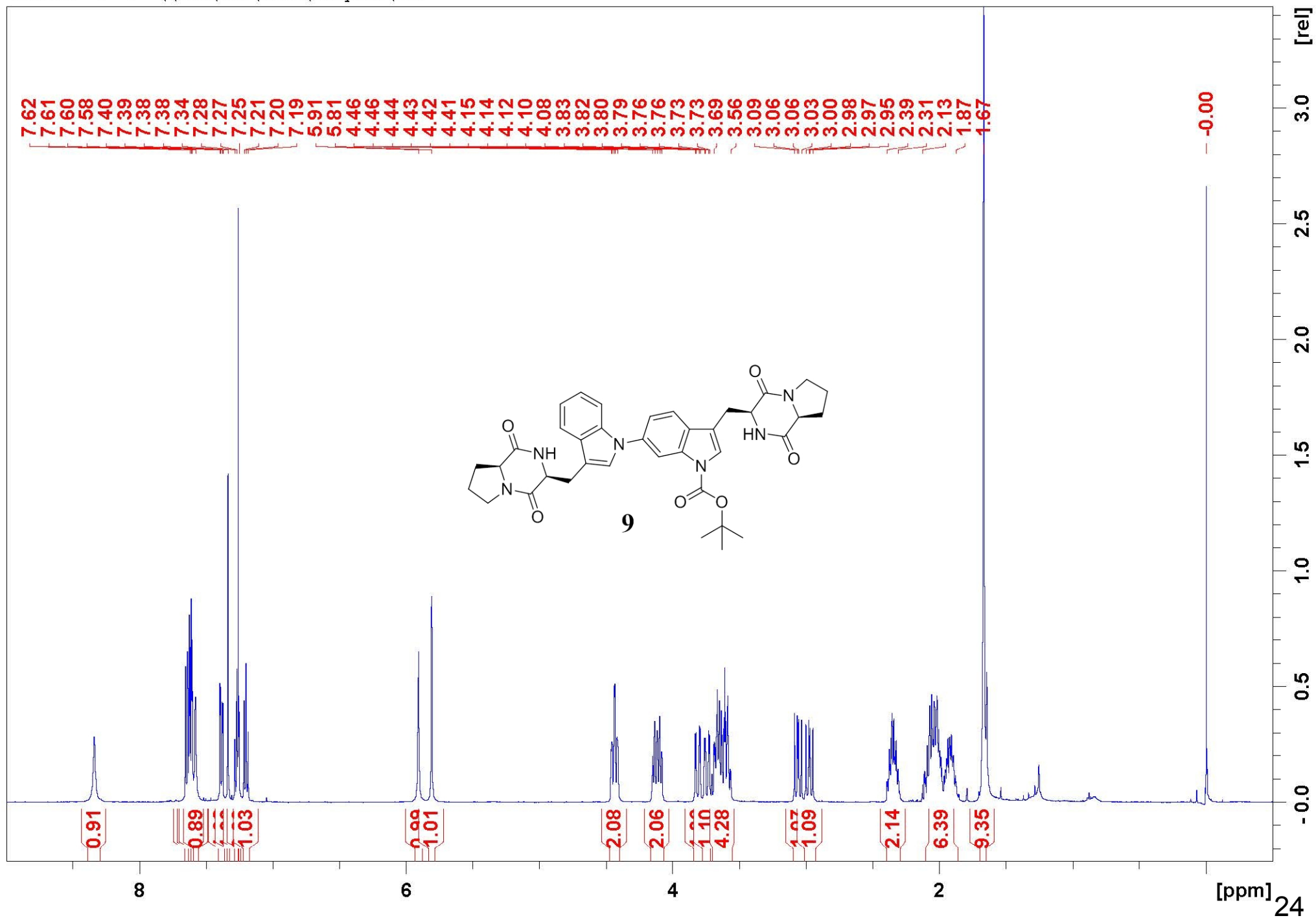
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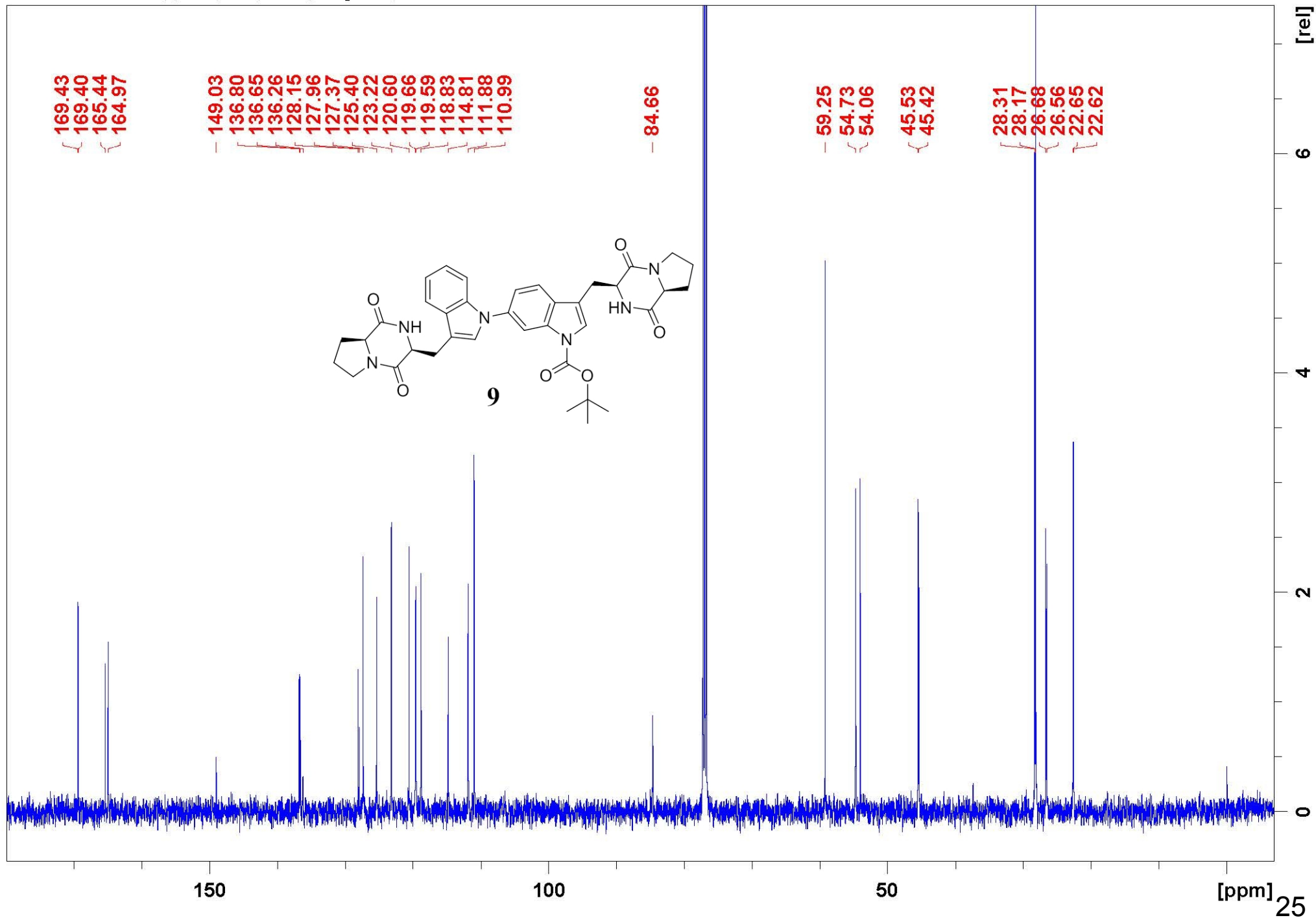


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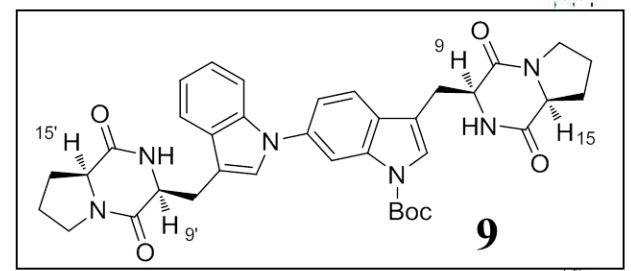
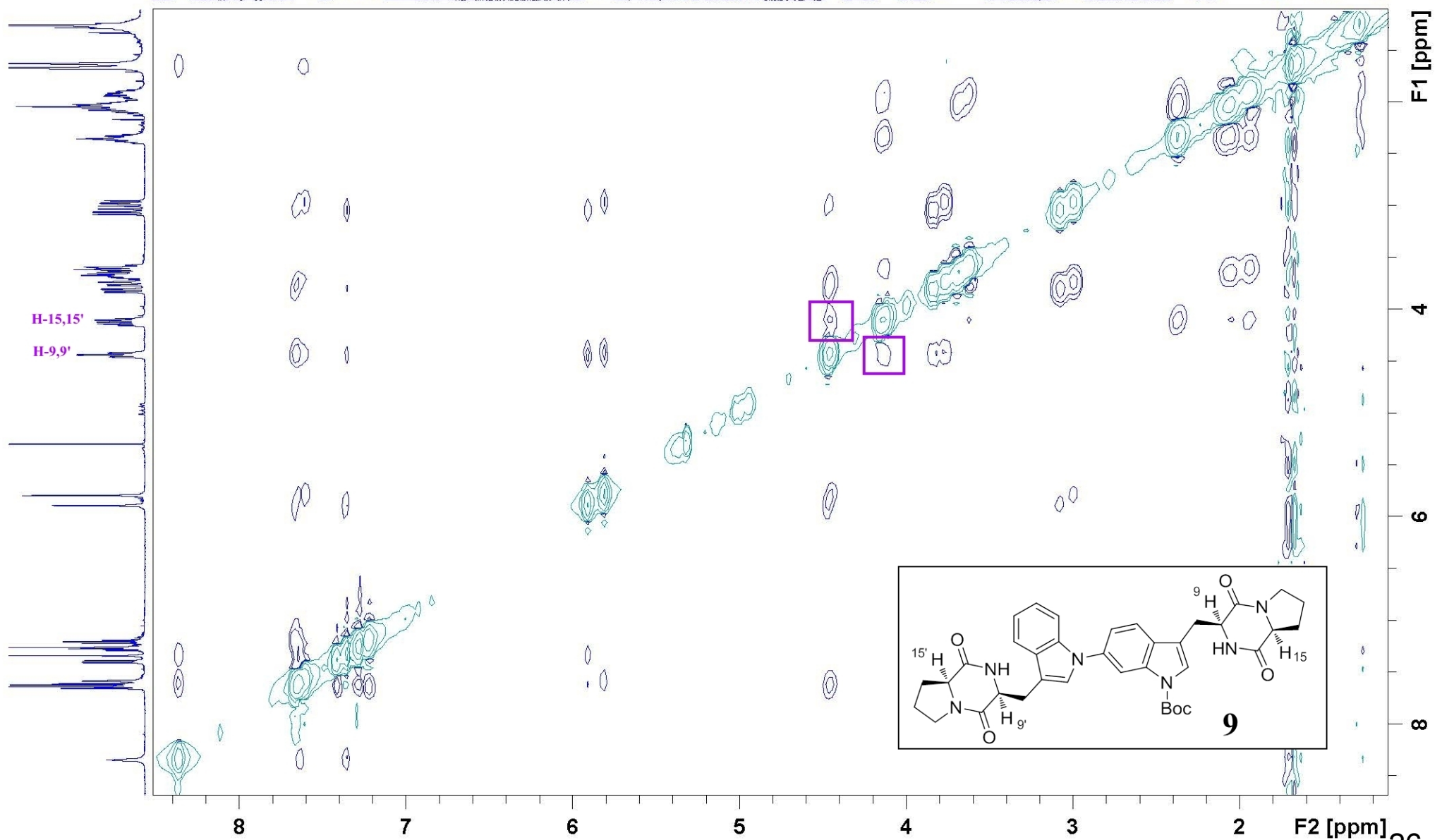




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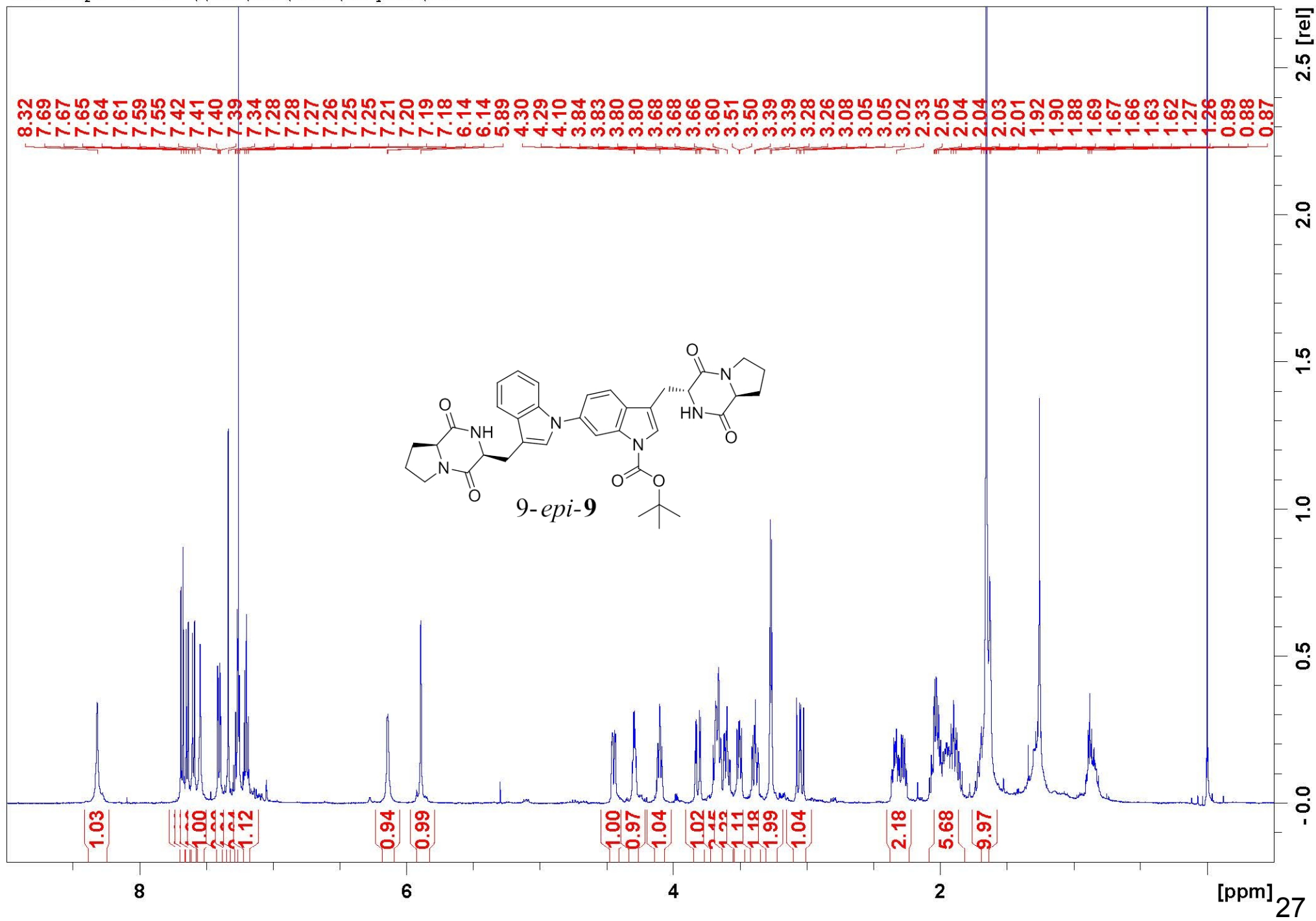
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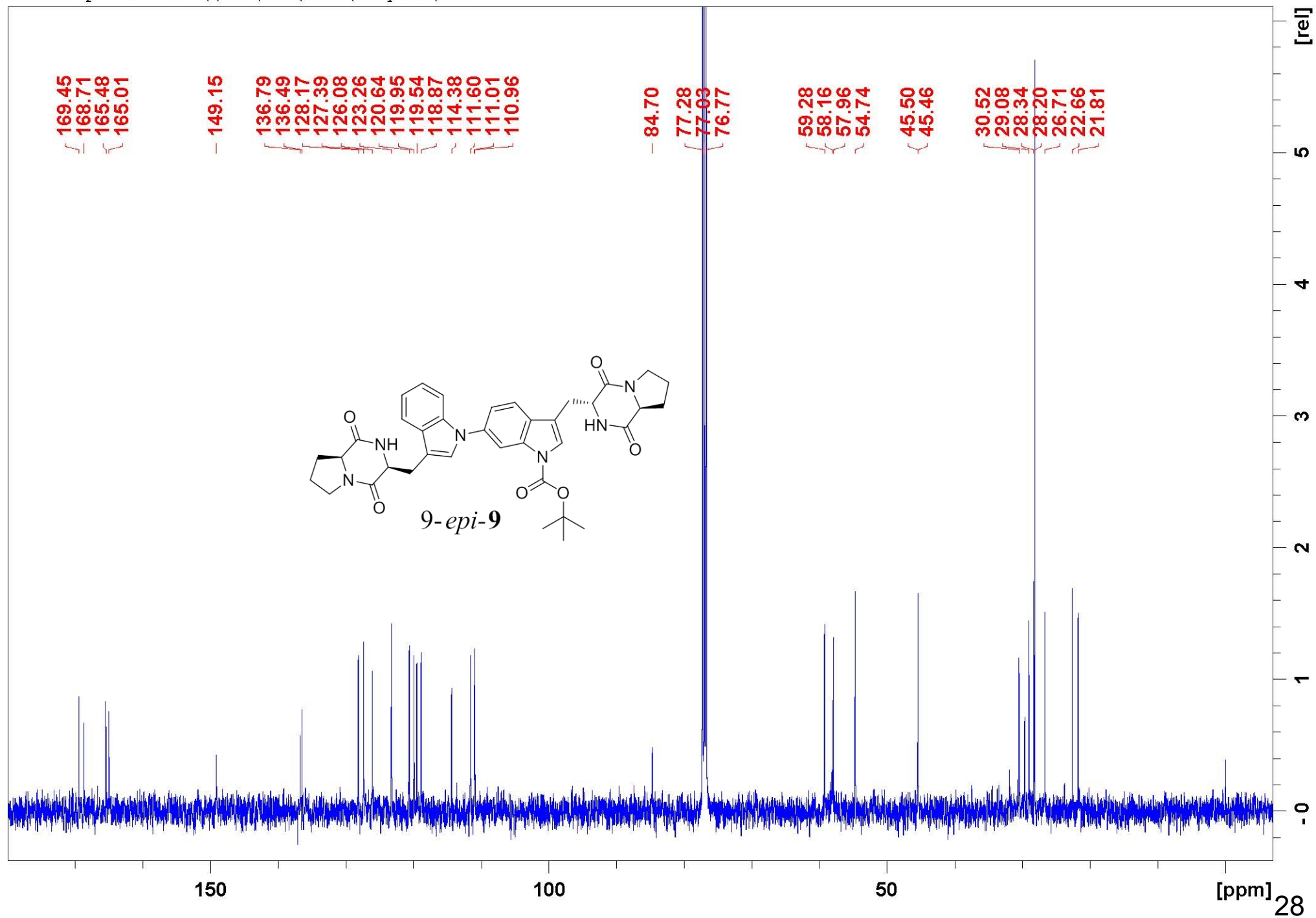
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H-9,9'



F1 [ppm] 4 6 8 26

F2 [ppm]





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