

SUPPORTING INFORMATION

Total Synthesis of Scytonemide A Employing Weinreb AM Solid-Phase Resin

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Determination of Loading Efficiency^{S1}

The Fmoc-Leu loaded Weinreb resin (100 mg, substitution = 0.44 mmol/g for synthesis of **6a**, 0.73 mmol/g for synthesis of **12a/b**) was shaken in a solution of piperidine/DMF (3 mL, 1:9 v/v) for 5 min and then repeated for 10 min. The deprotection solutions were combined and an aliquot (150 μ L) was diluted 20-fold to 3 mL. 300 μ L of this solution was then diluted 10-fold to 3 mL and placed in a quartz cuvette to measure UV absorbance of the piperidine-fulvene adduct ($\lambda = 289.8$ nm, $\epsilon_c = 6089$ M⁻¹ cm⁻¹ as recommended by Eissler et al^{S2}) for quantification of Leu loaded onto the resin.

Equation for Loading Efficiency:

$$\text{Loading} \left(\frac{\text{mmol}}{\text{g}} \right) = \frac{(\text{Abs}_{289.8} * v_{\text{cuvette}} * D)}{(\epsilon_c * l * m^{\text{resin}})}$$

where $V_{\text{cuvette}} = 3$ mL

D (dilution factor) = 200

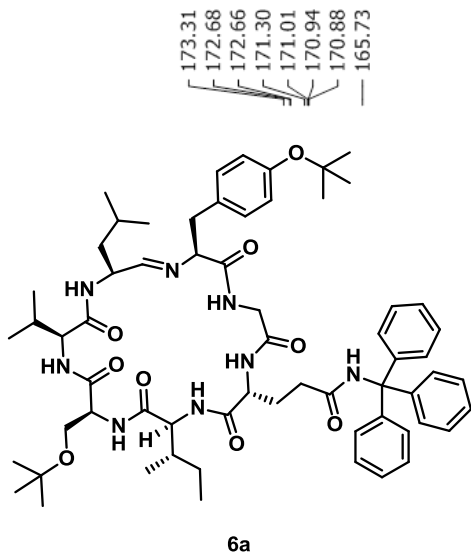
$\epsilon_c^{\text{S2}} = 6089$ mL*mmol⁻¹*cm⁻¹

l (path length) = 1 cm

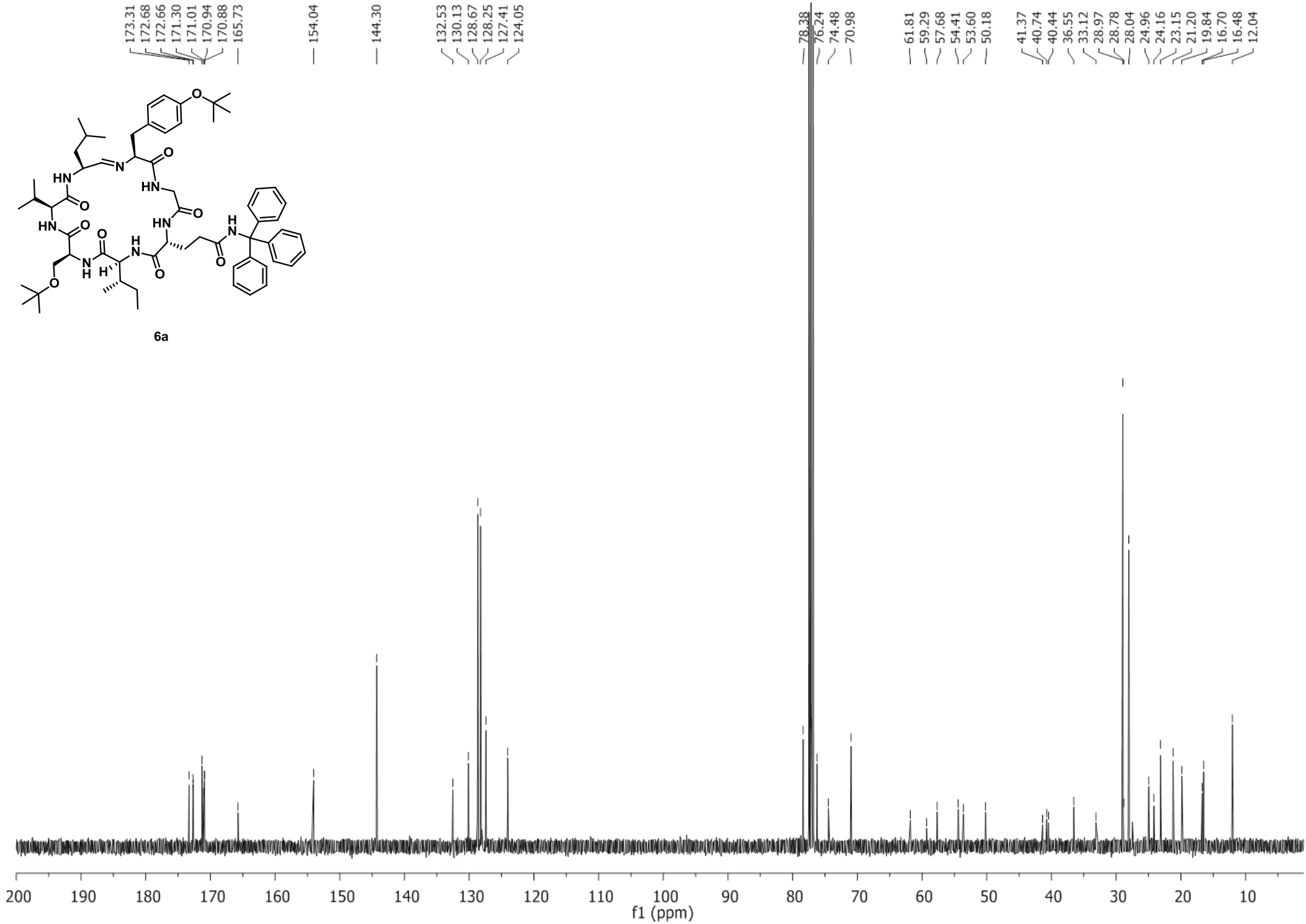
$m^{\text{resin}} = 100$ mg

Weinreb Resin, substitution = 0.44 mmol/g: Abs_{298.8} = 0.336, loading = 0.331 mmol/g

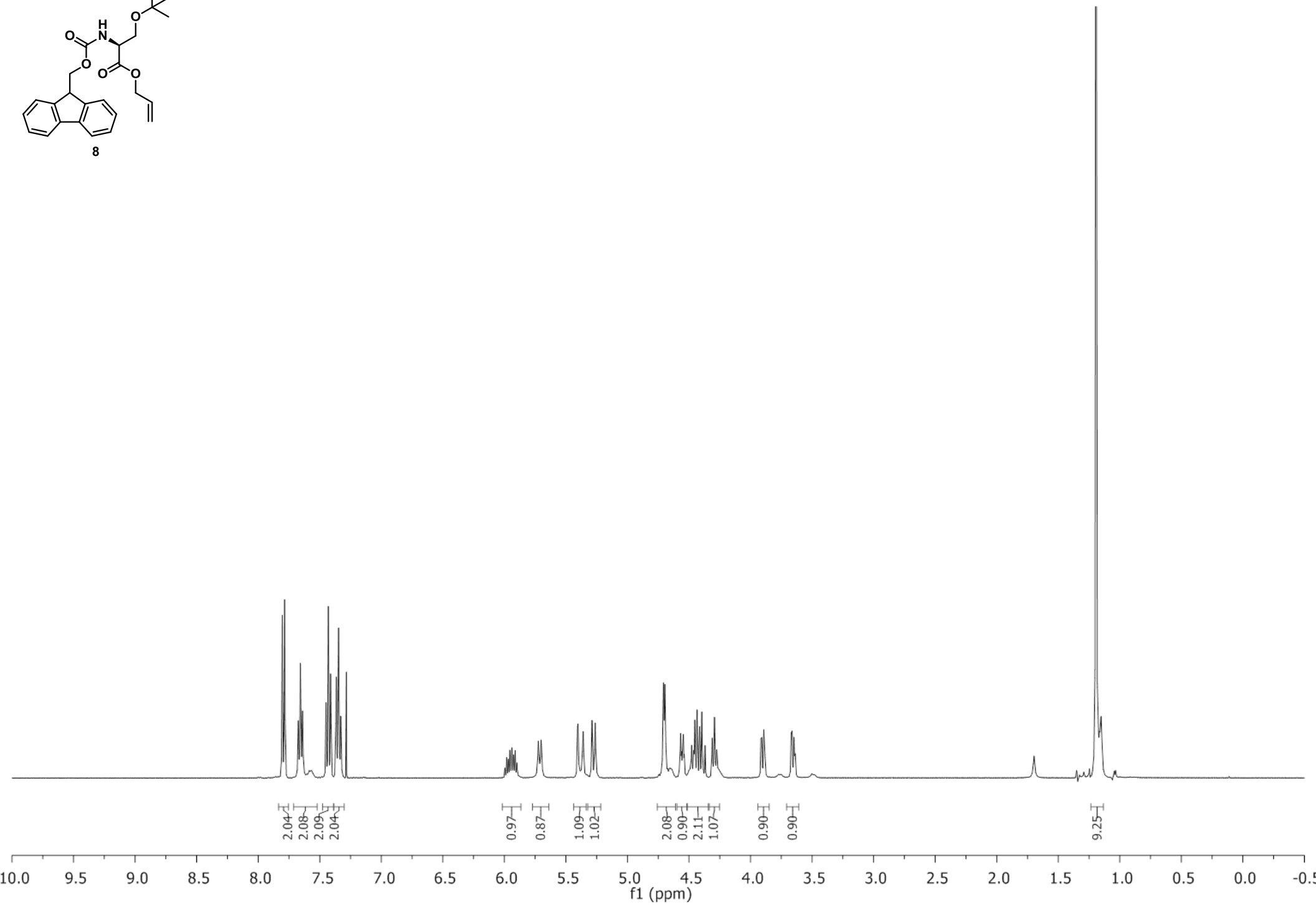
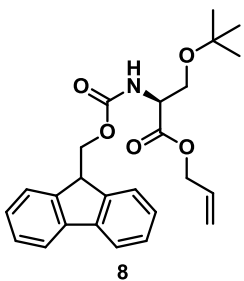
Weinreb Resin, substitution = 0.73 mmol/g: Abs_{298.8} = 0.299, loading = 0.295 mmol/g



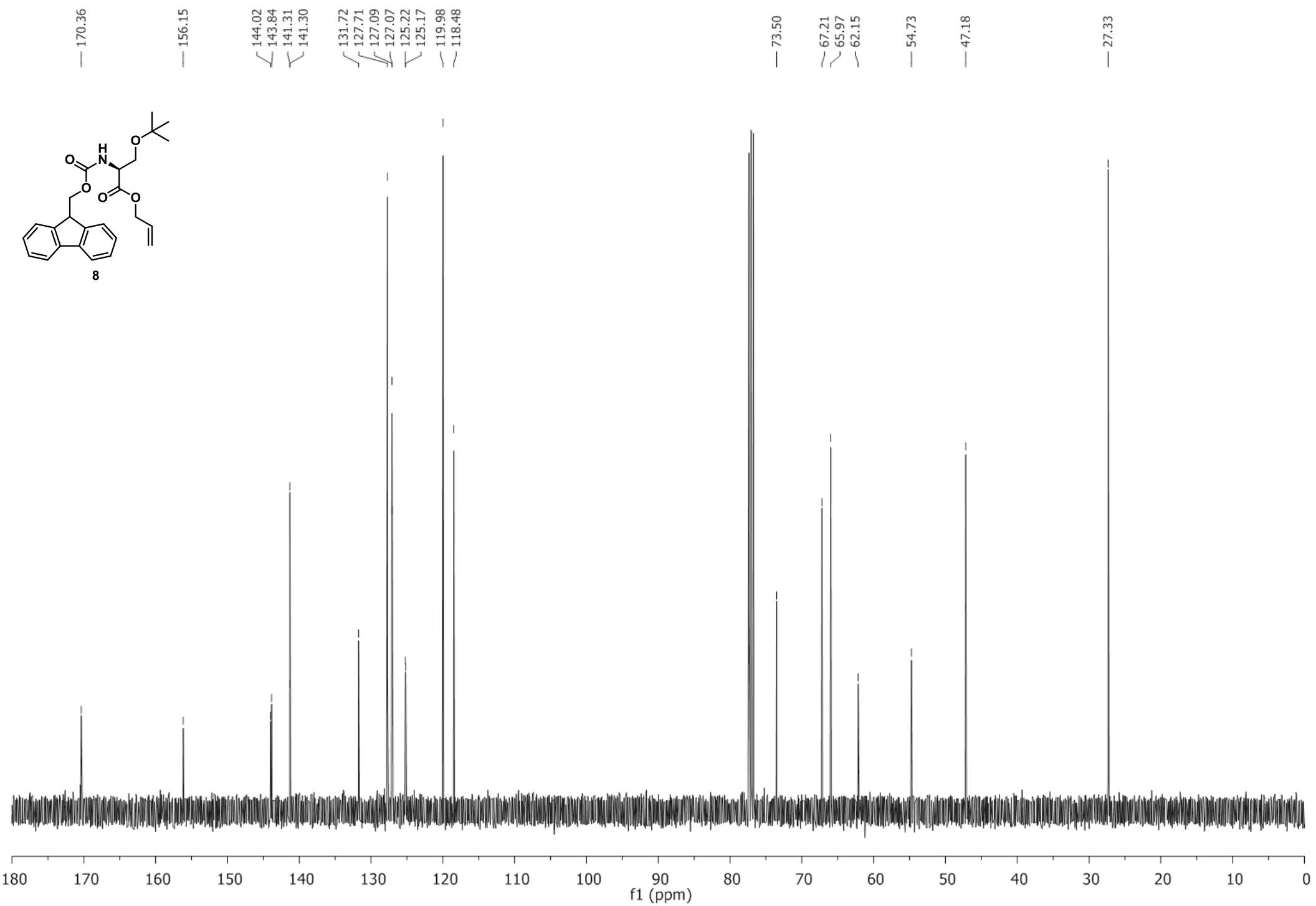
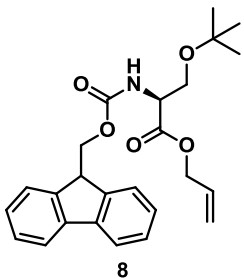
6a



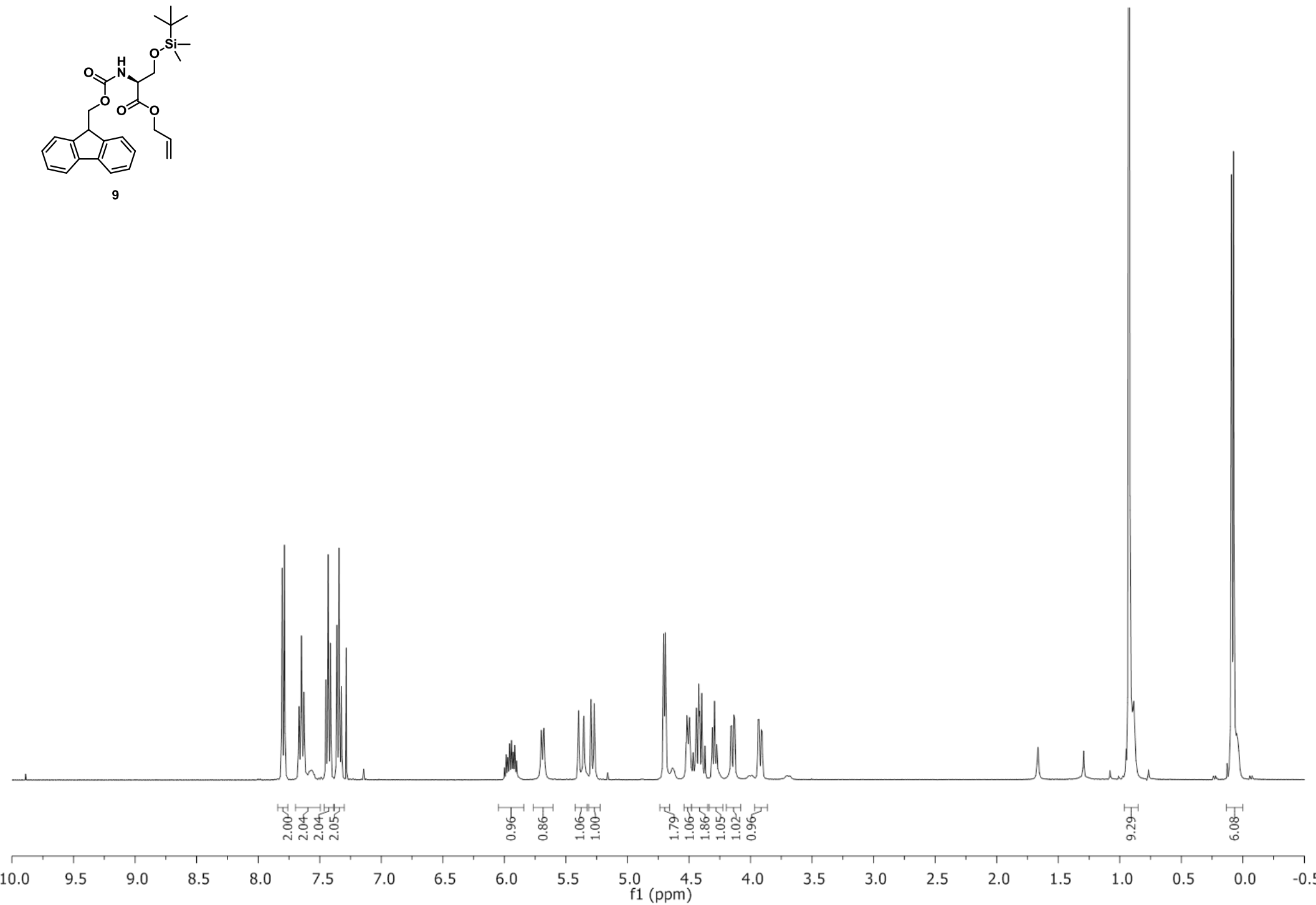
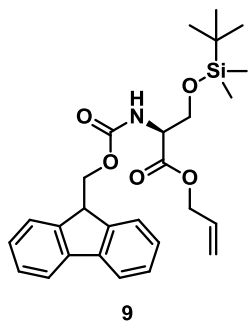
^{13}C NMR (CDCl_3 , 101 MHz) of compound **6a**.



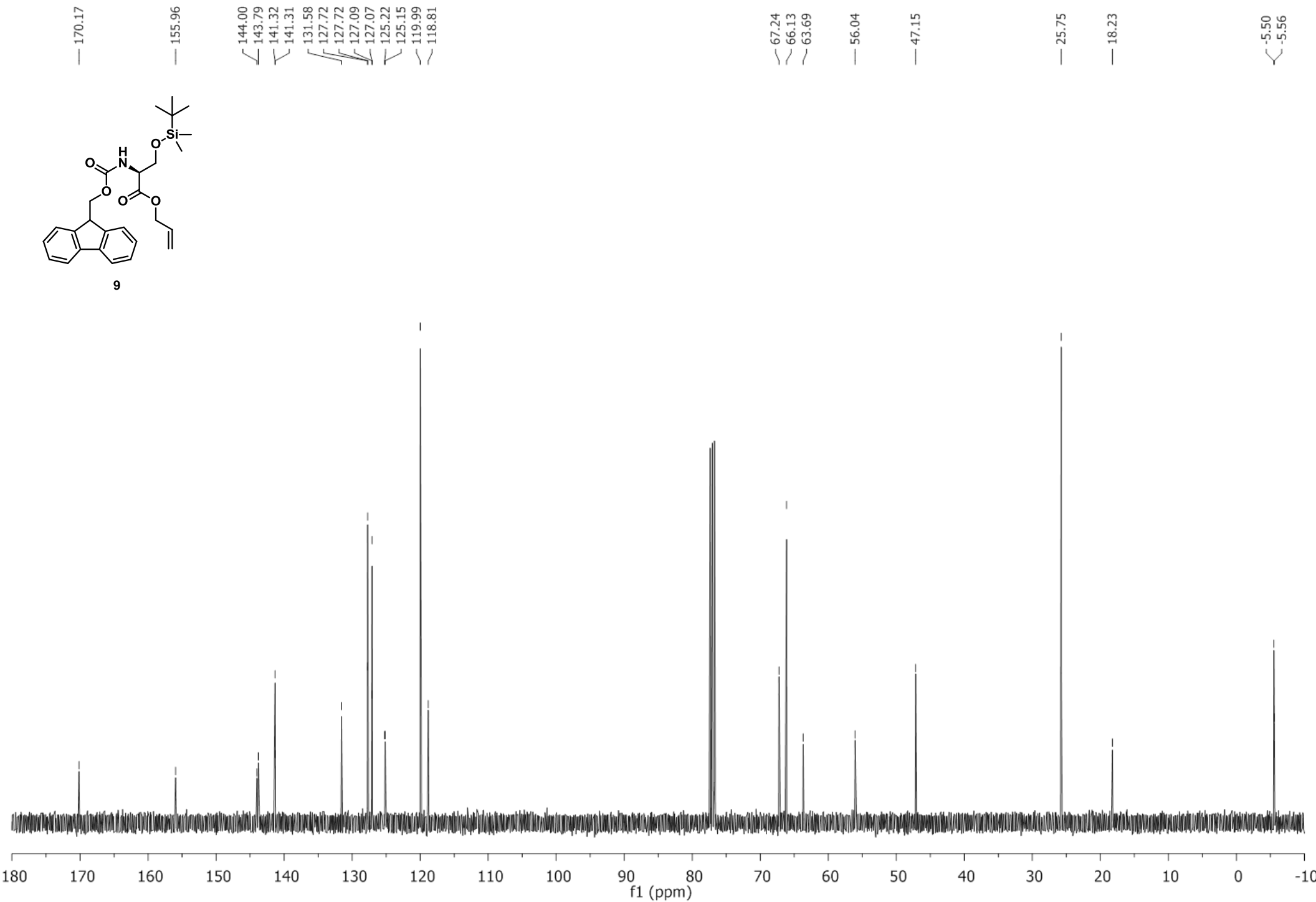
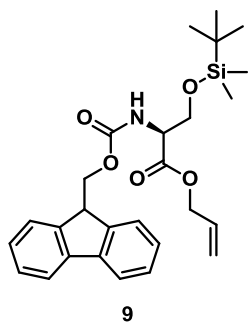
¹H NMR (CDCl₃, 400 MHz) of compound **8**.



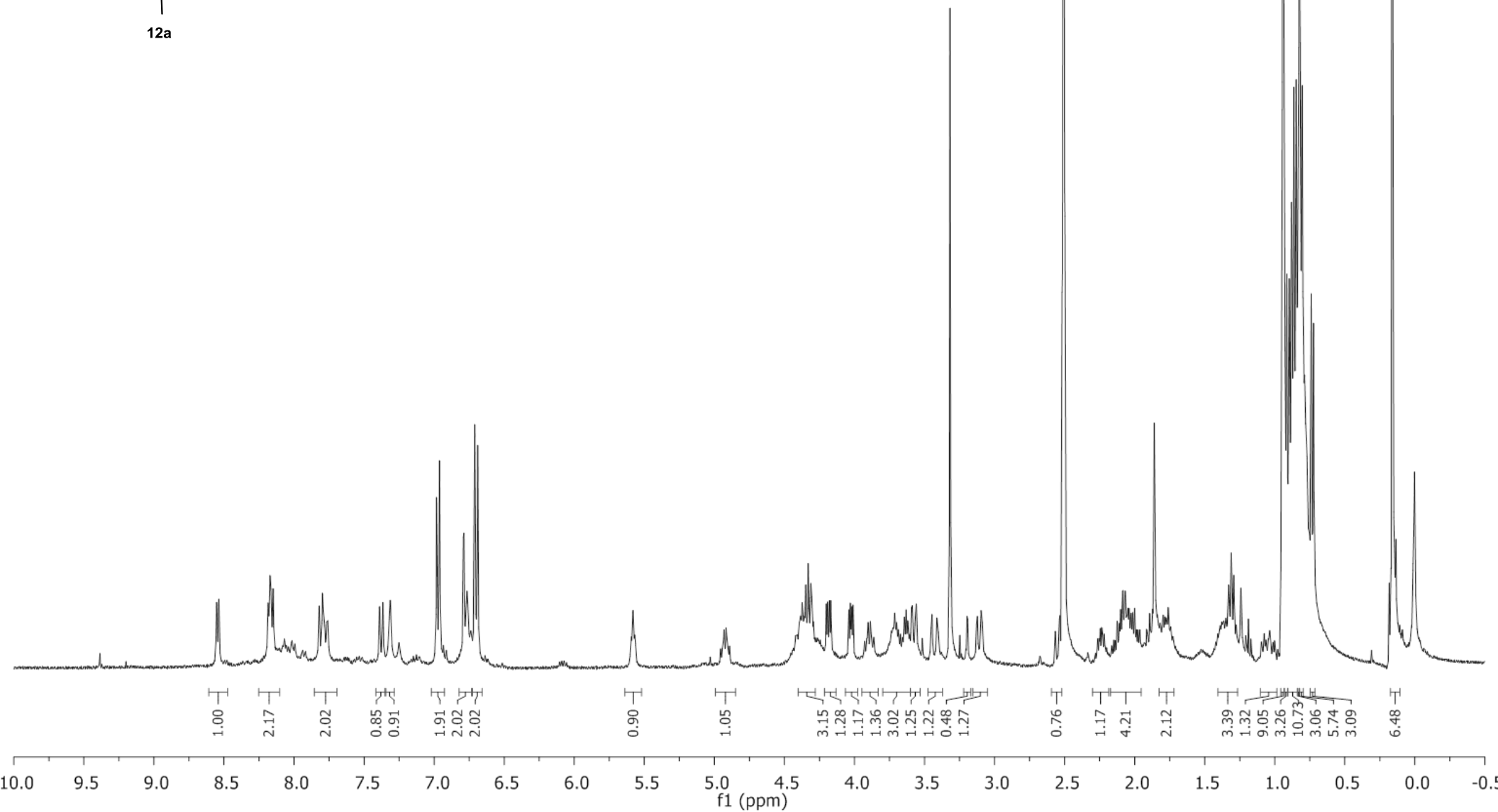
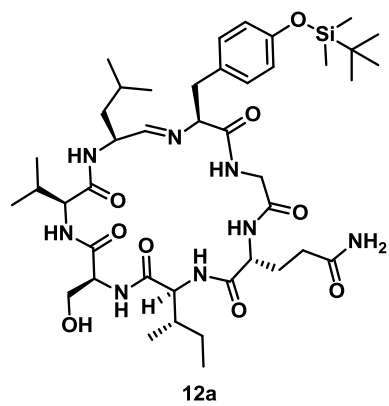
¹³C NMR (CDCl₃, 101 MHz) of compound **8**.



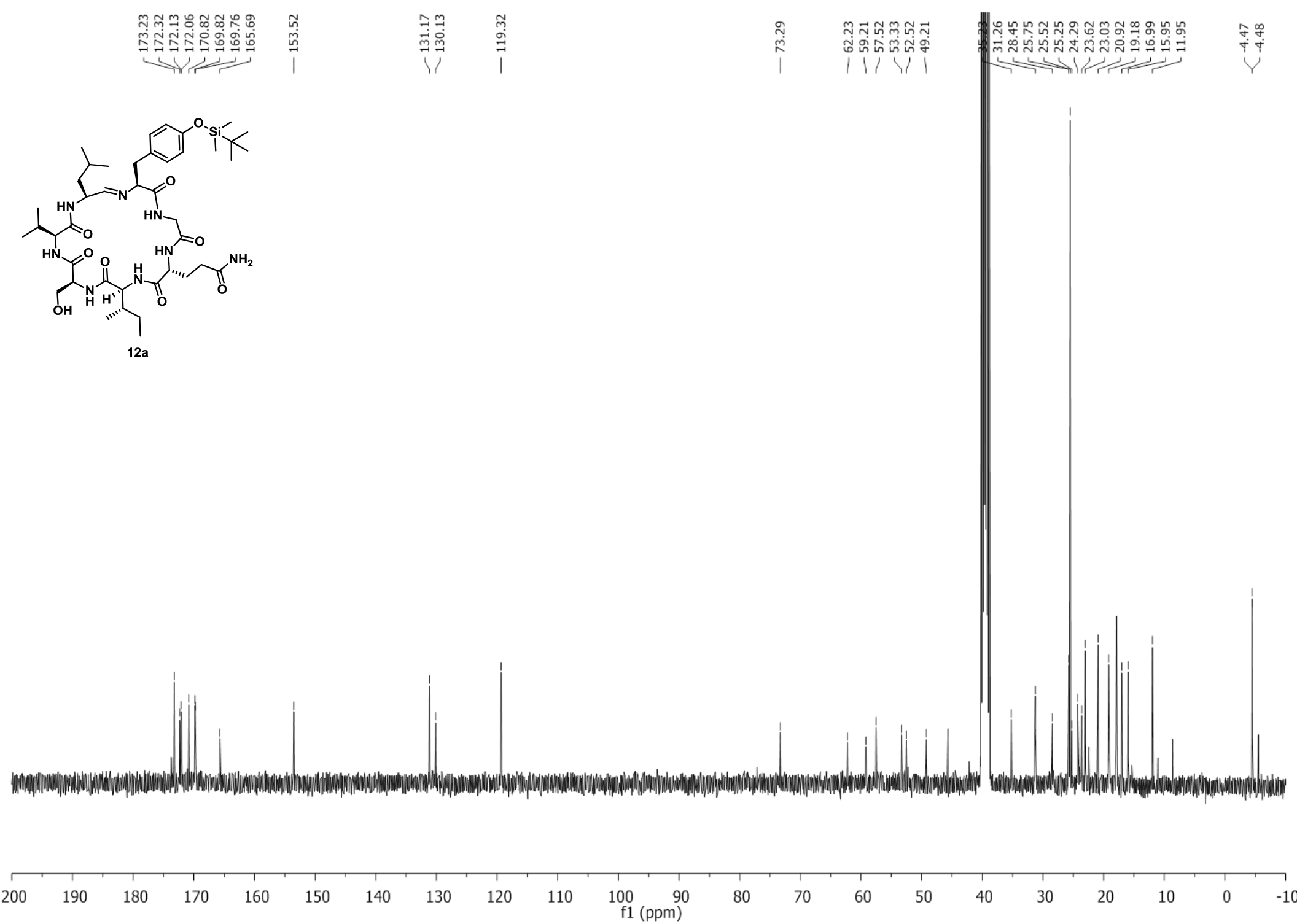
¹H NMR (CDCl₃, 400 MHz) of compound **9**.



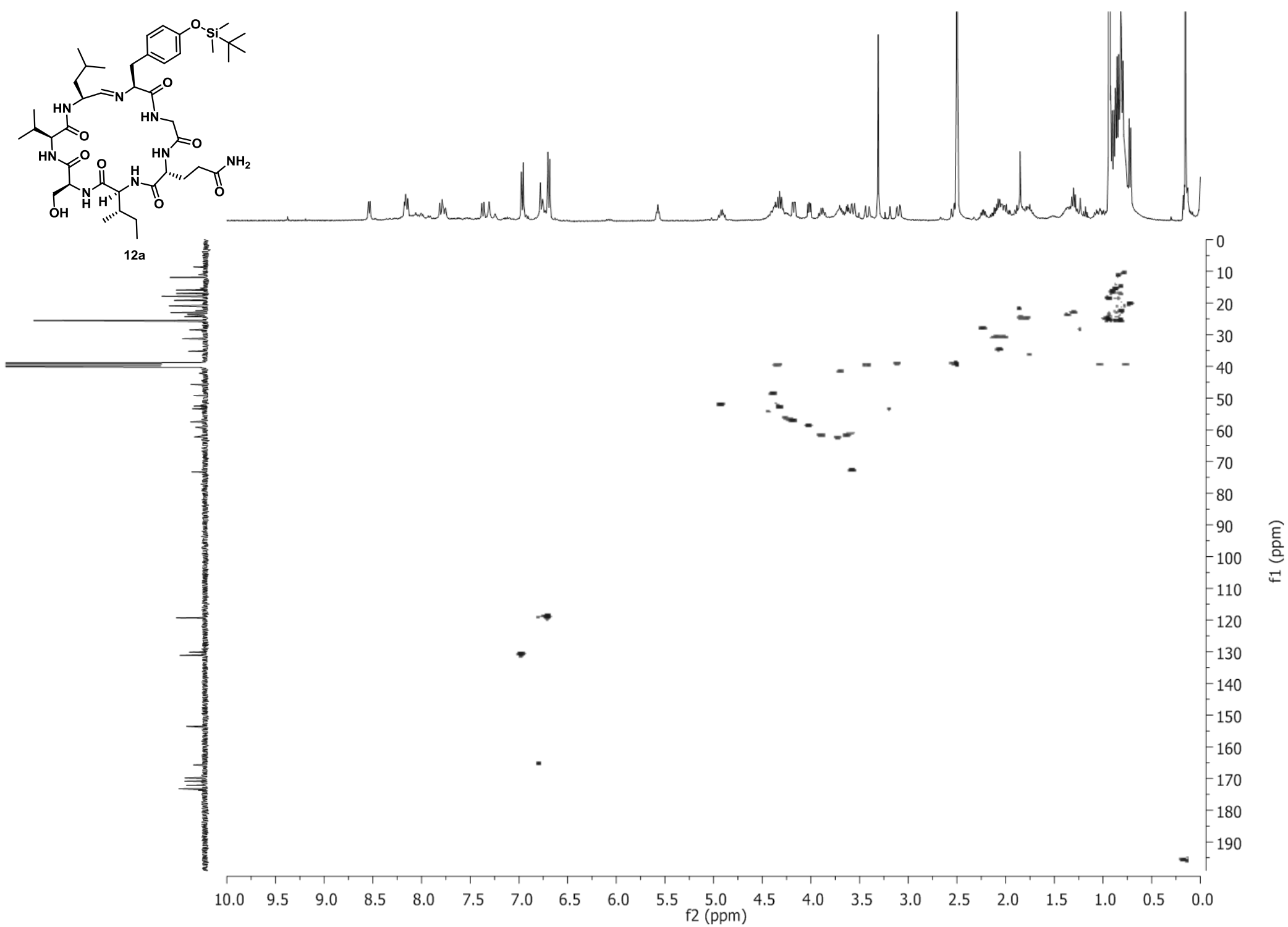
^{13}C NMR (CDCl_3 , 101 MHz) of compound **9**.



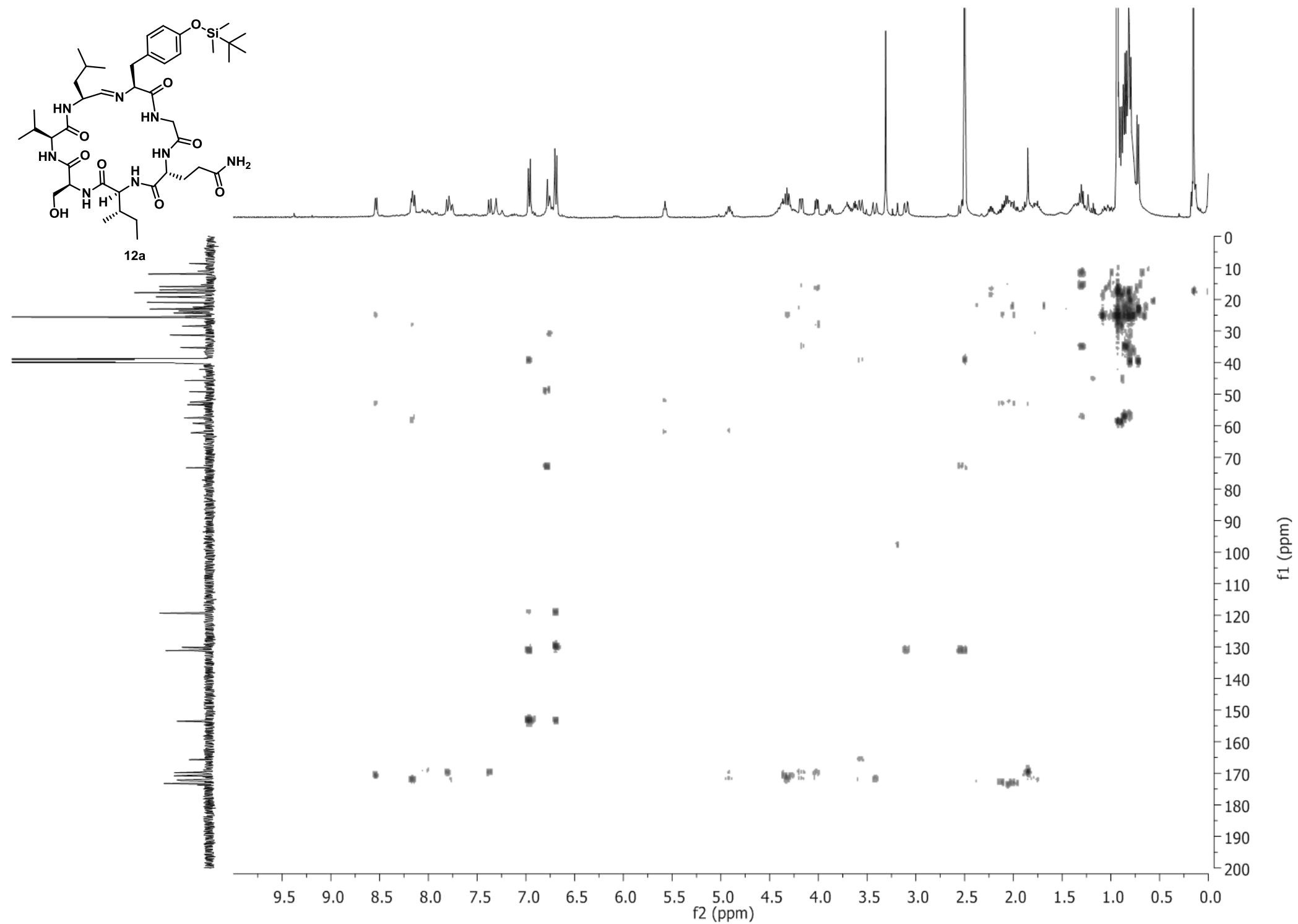
^1H NMR (d_6 -DMSO, 400 MHz) of compound **12a**.



¹³C NMR (d₆-DMSO, 101 MHz) of compound **12a**.



HSQC NMR (d_6 -DMSO, 400 MHz) of compound **12a**.



HMBC NMR (*d*₆-DMSO, 400 MHz) of compound **12a**.

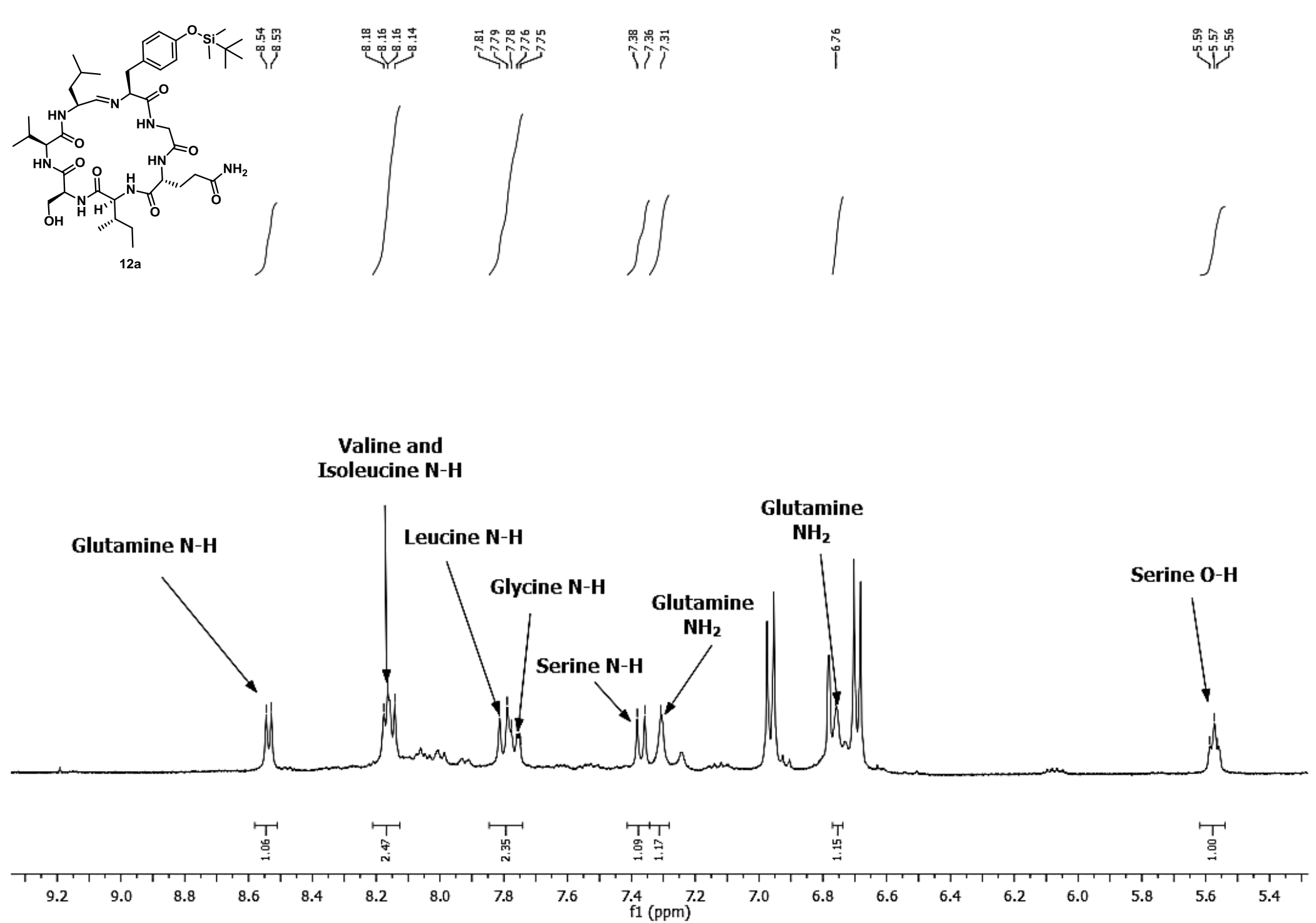


Figure S1. Assignment of -NH and -OH protons in $^1\text{H NMR}$ for **12a**.

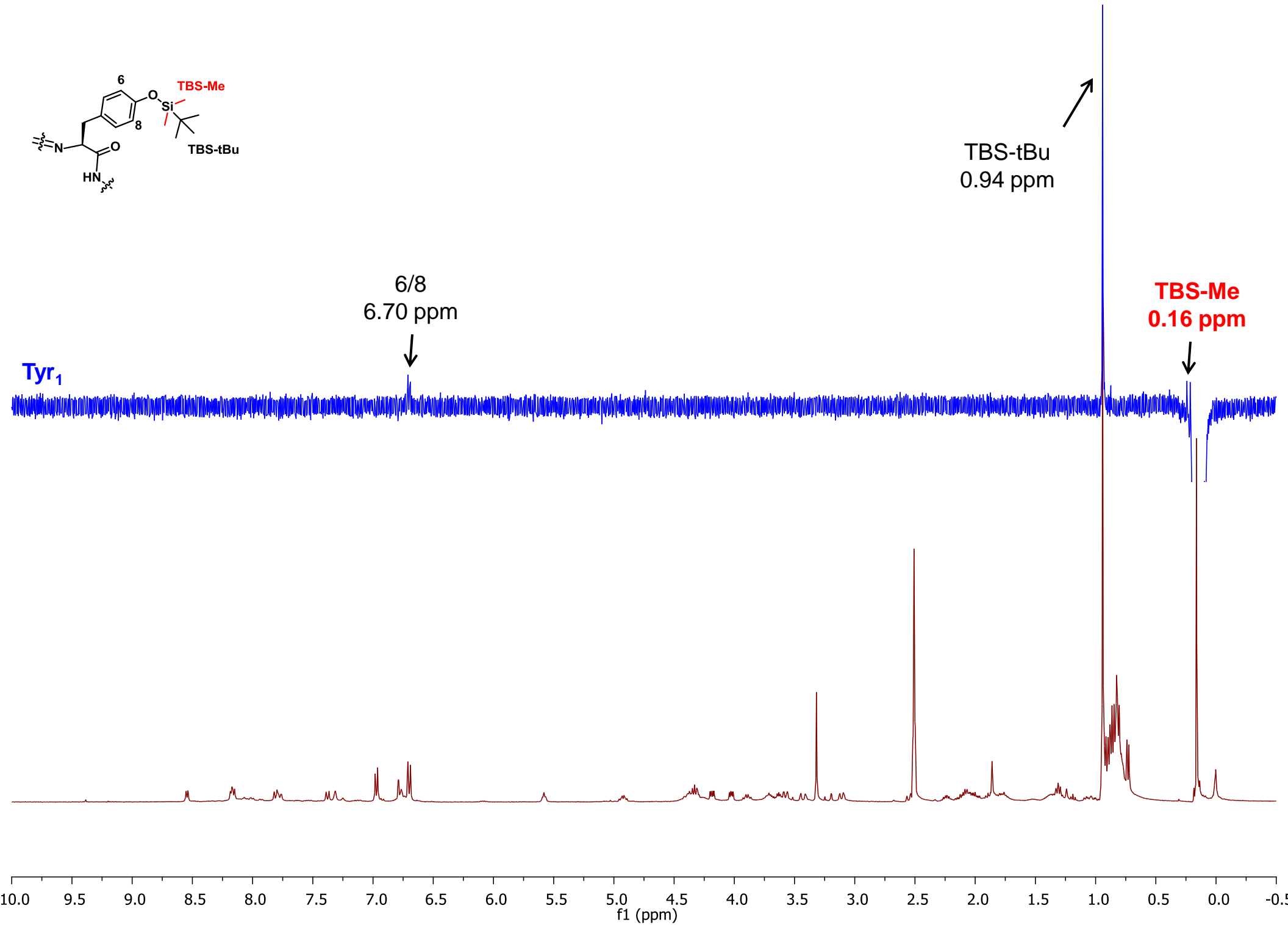


Figure S2. Selective NOESY for TBS-Me (0.16 ppm) for **12a**.

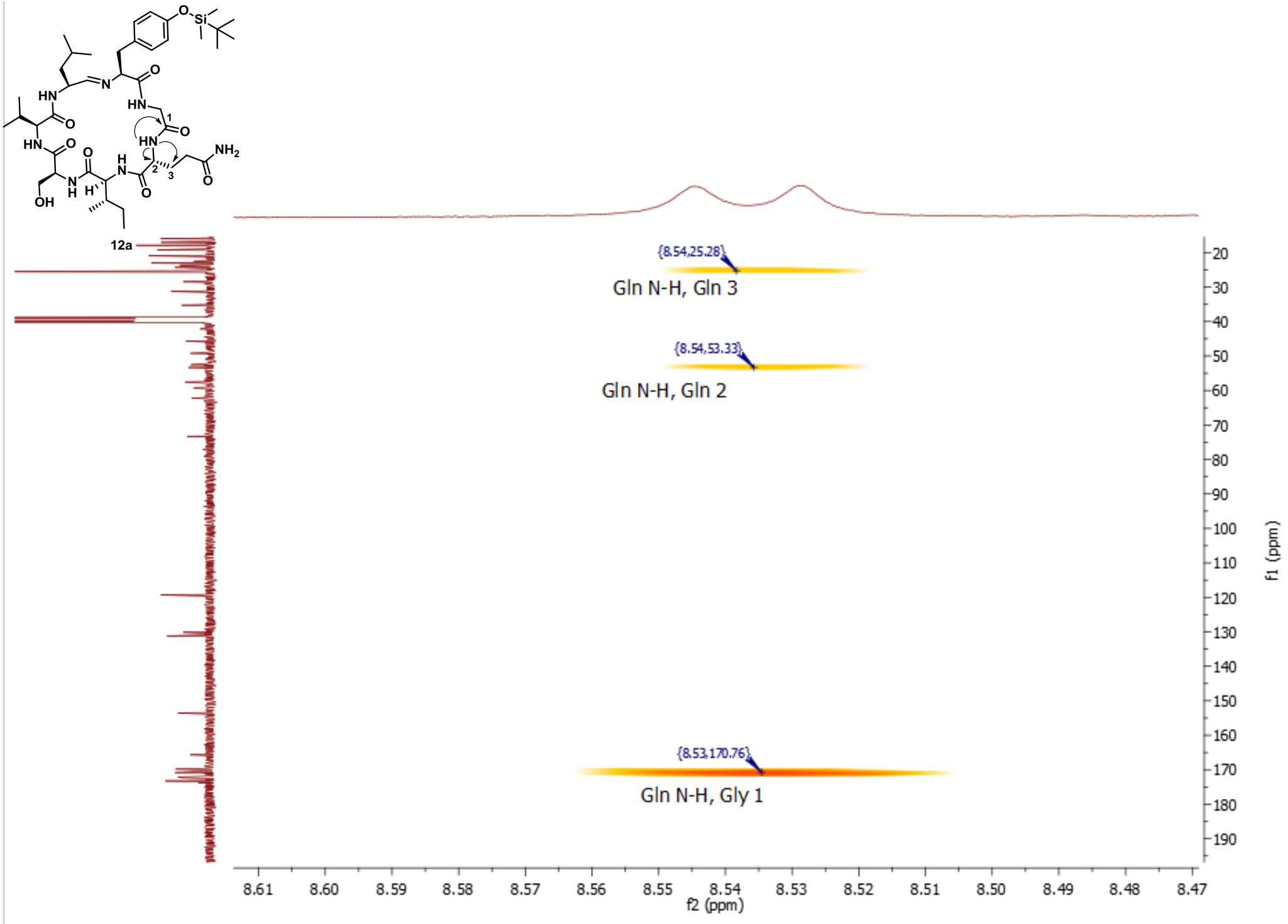


Figure S3. D-Gln₃ backbone –NH HMBC correlations for **12a**.

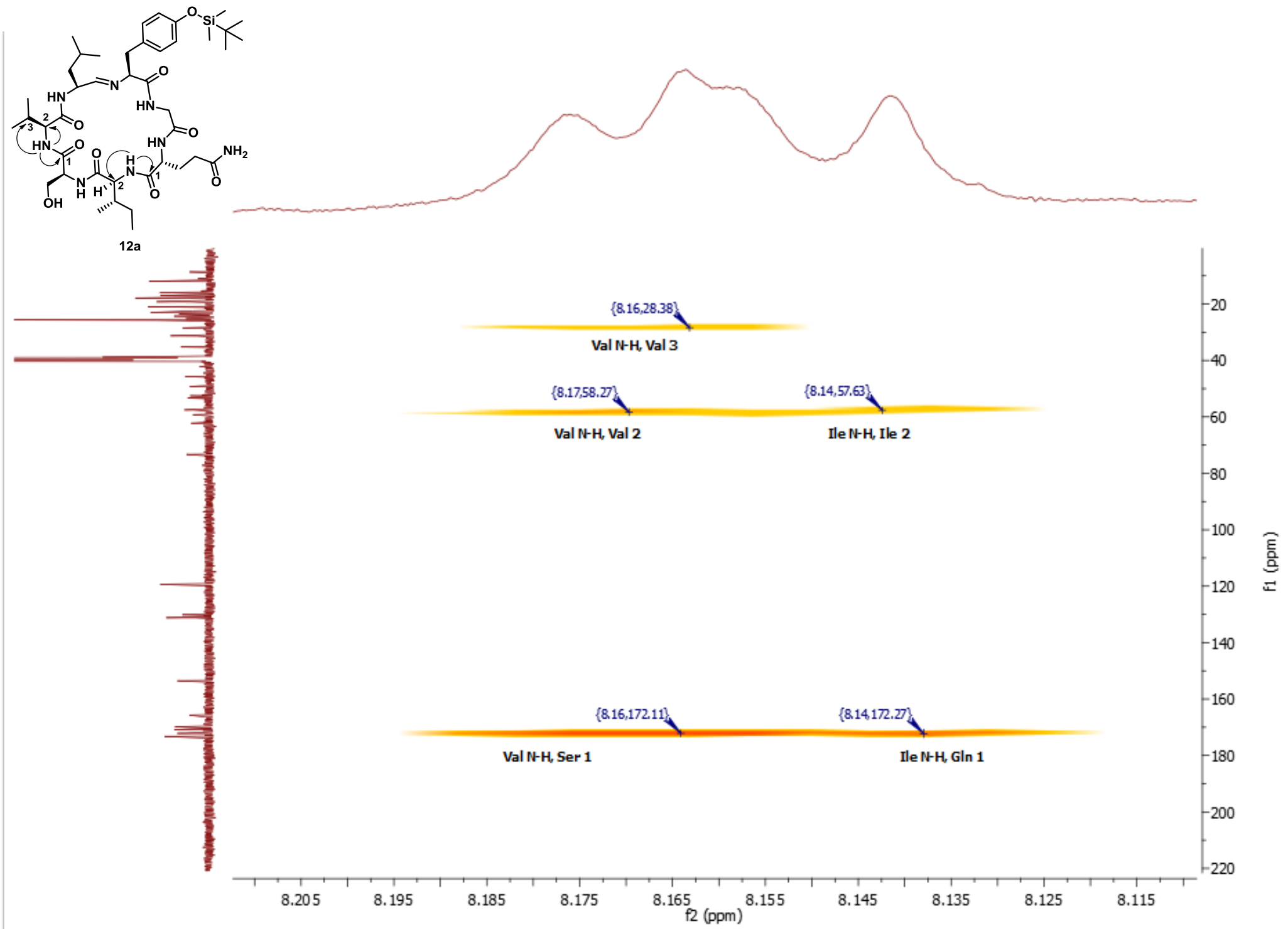


Figure S4. Val₆ and Ile₄ backbone -NH HMBC correlations for **12a**.

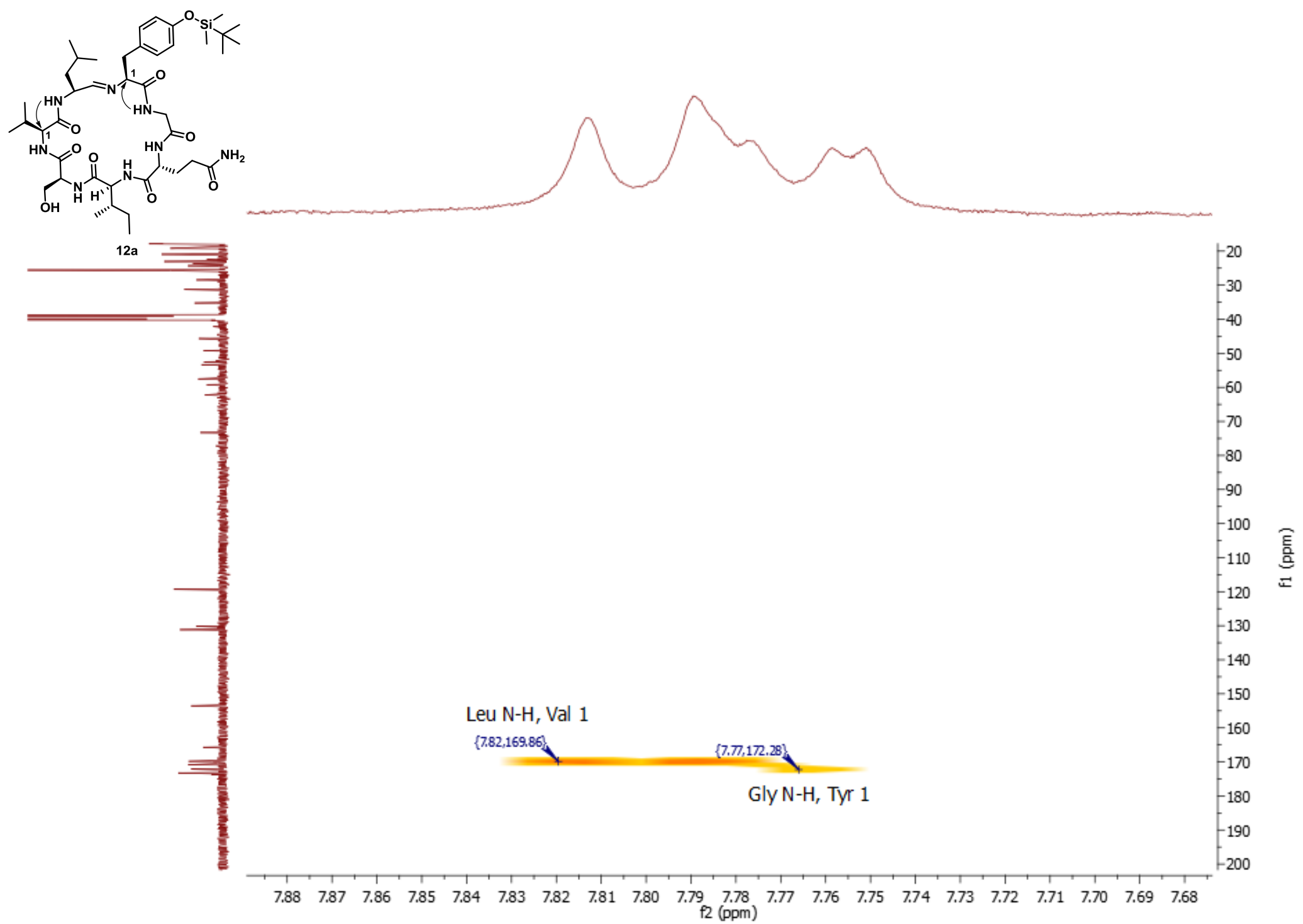


Figure S5. Leu₇ and Gly₂ backbone –NH HMBC correlations for **12a**.

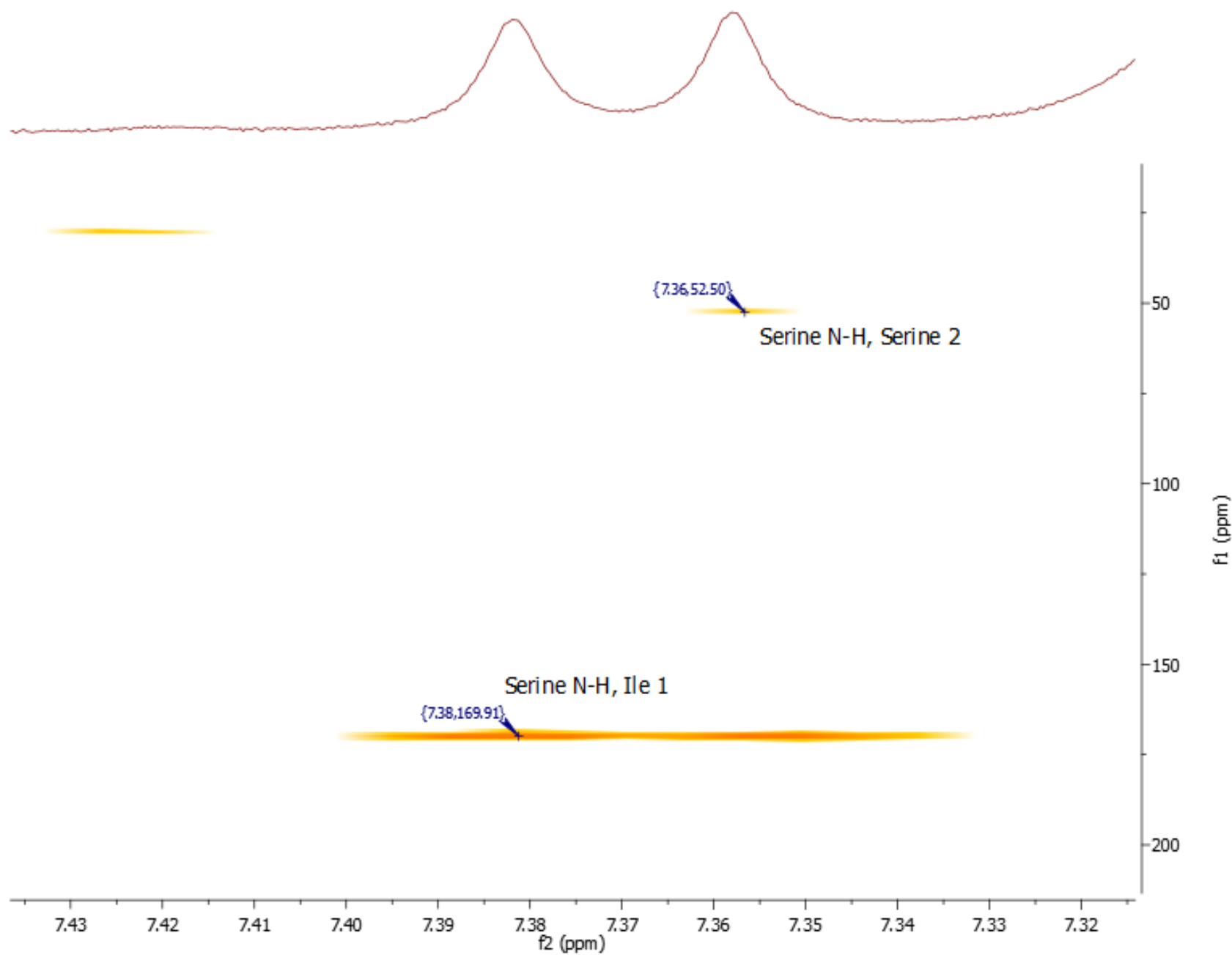
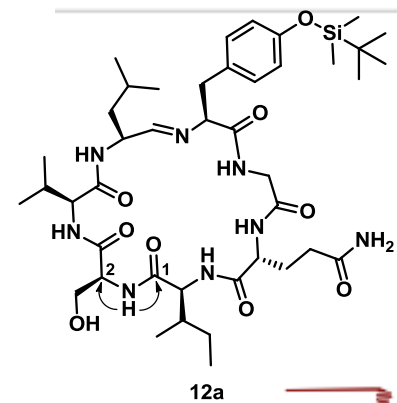


Figure S6. Ser₅ backbone $-NH$ HMBC correlations for **12a**.

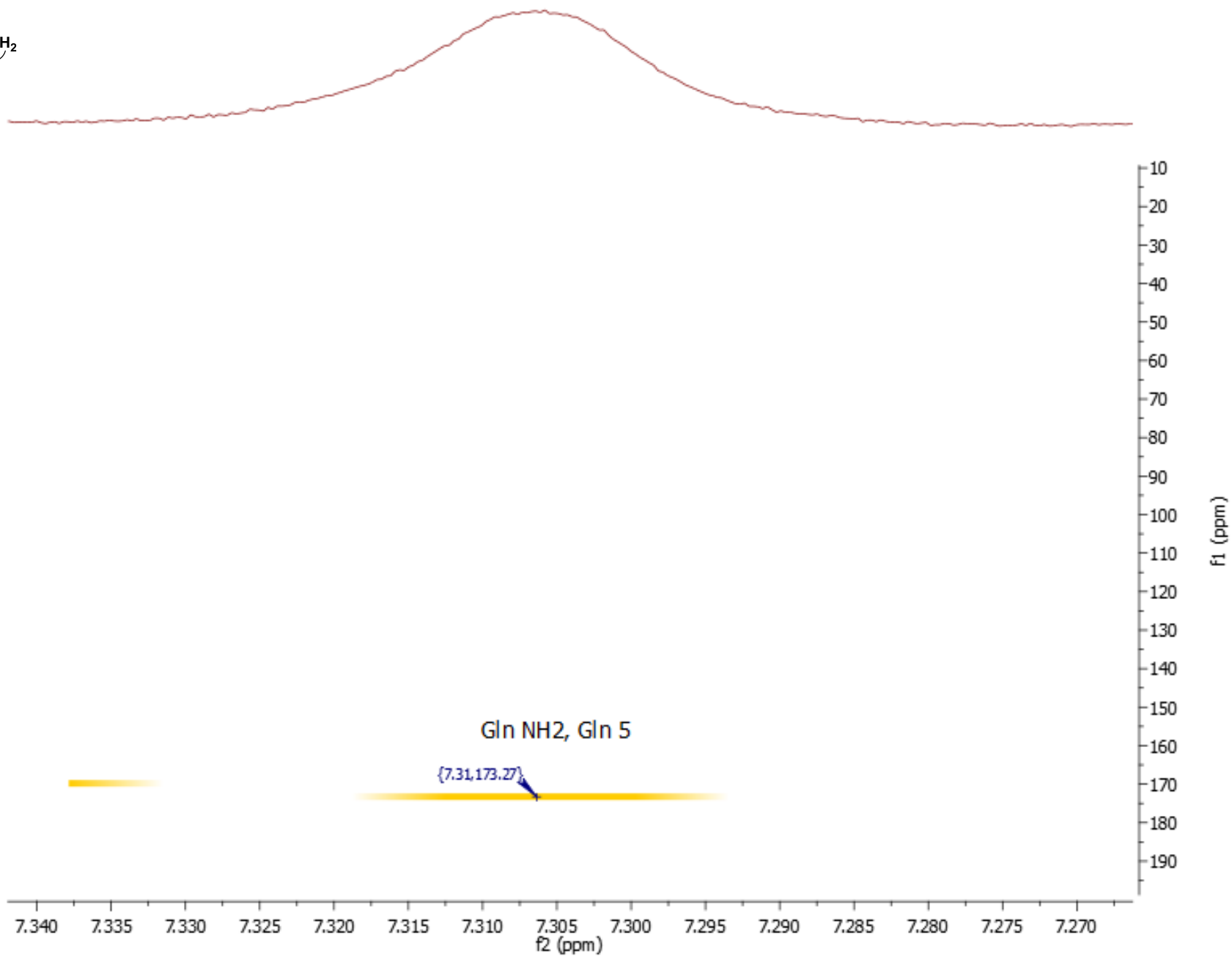
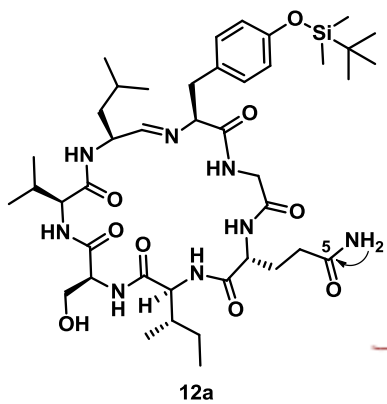


Figure S7A. D-Gln₃ side chain –NH HMBC correlations for **12a**.

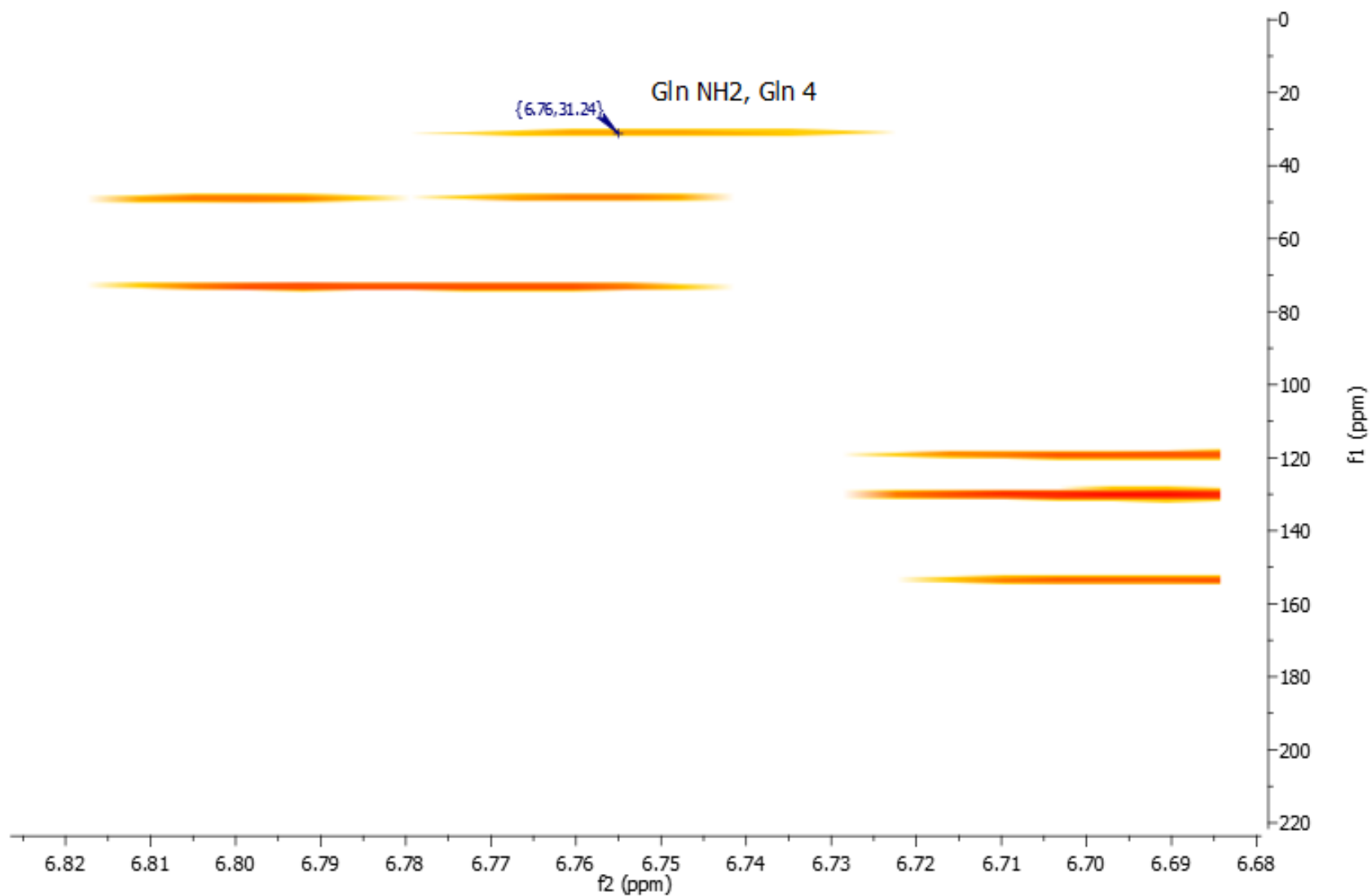
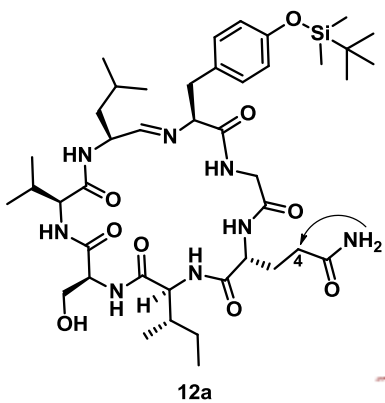


Figure S7B. D-Gln₃ side chain –NH HMBC correlations for **12a** (continued).

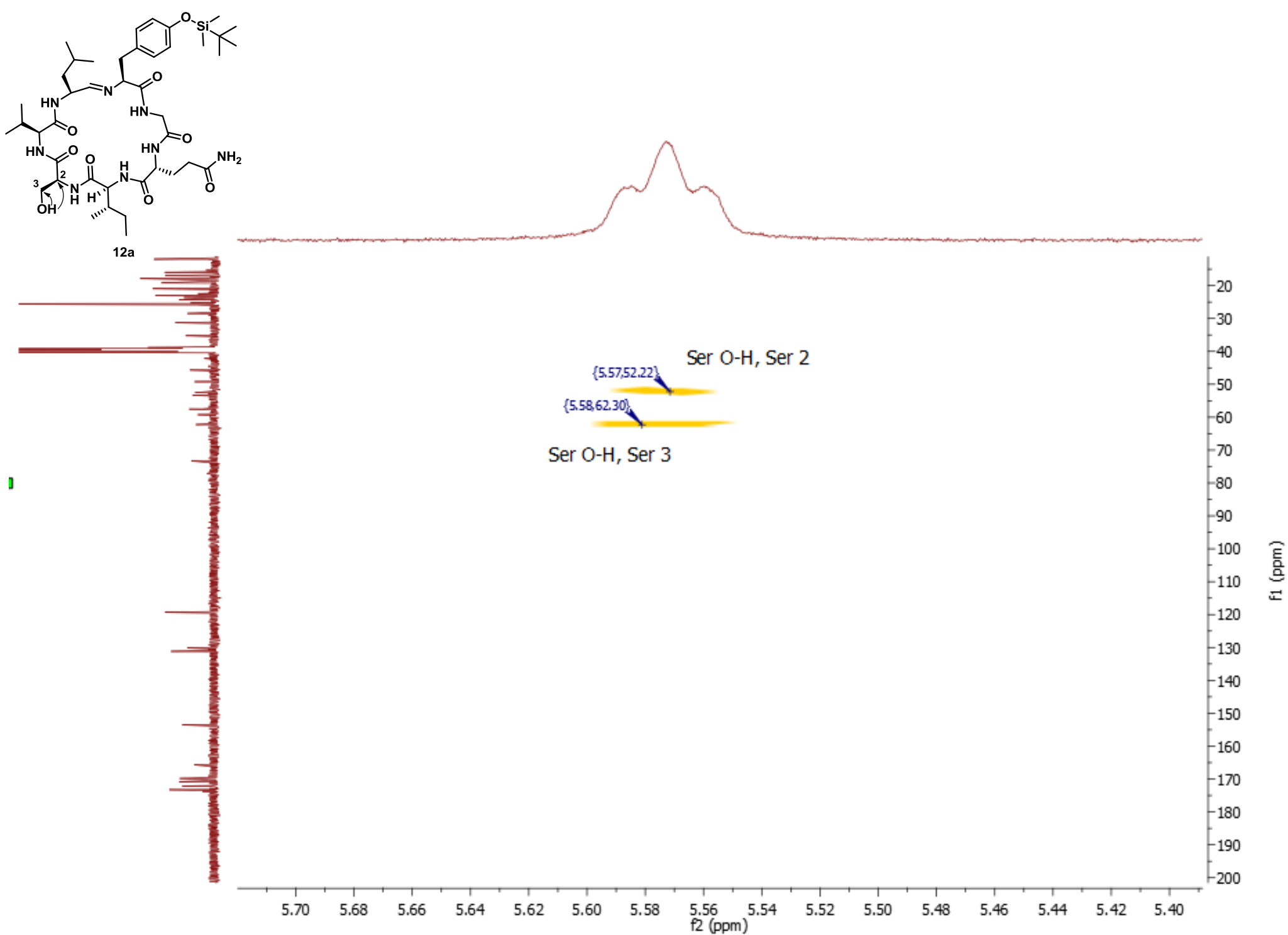
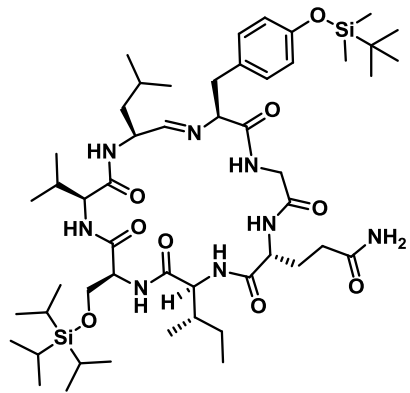
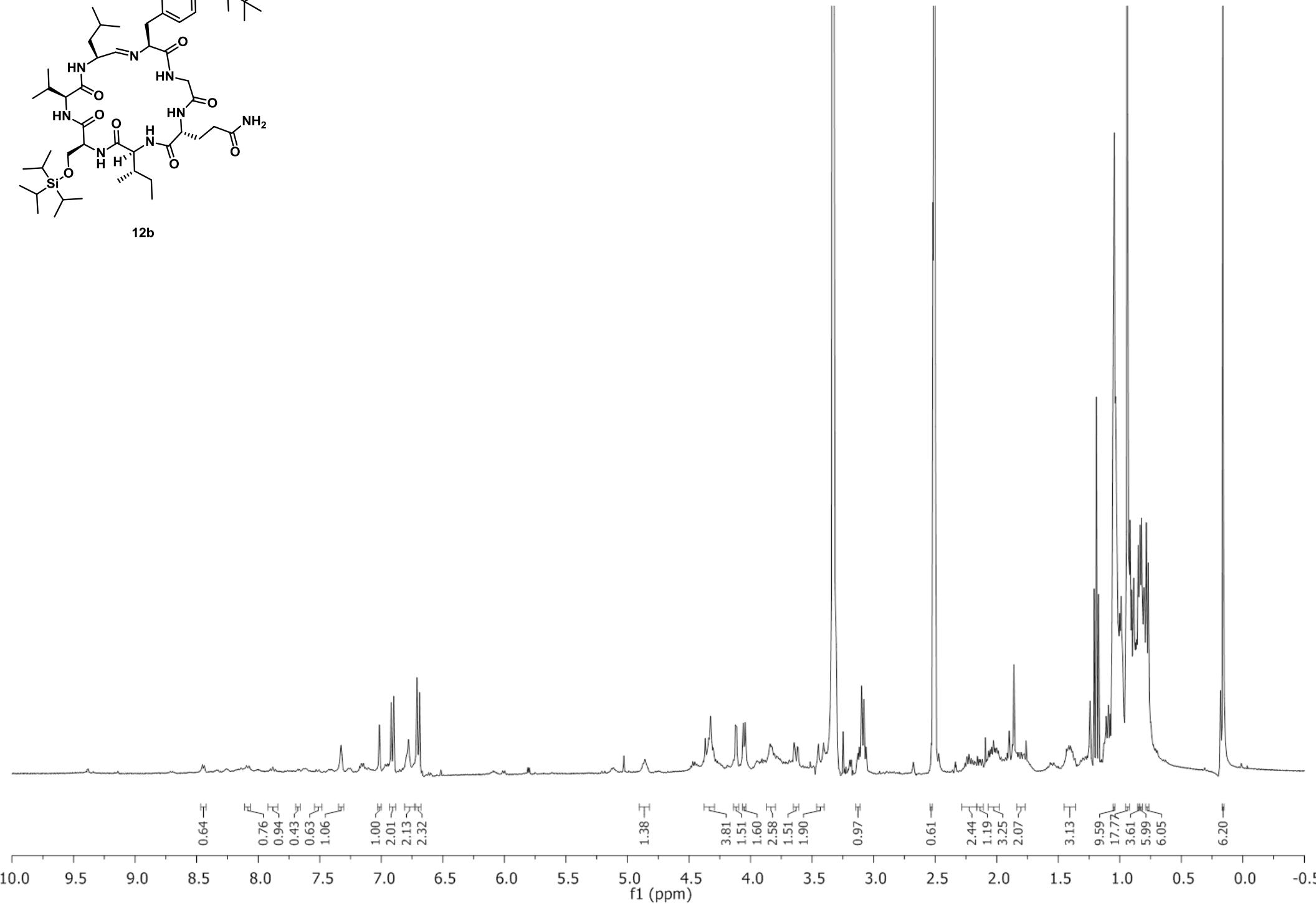


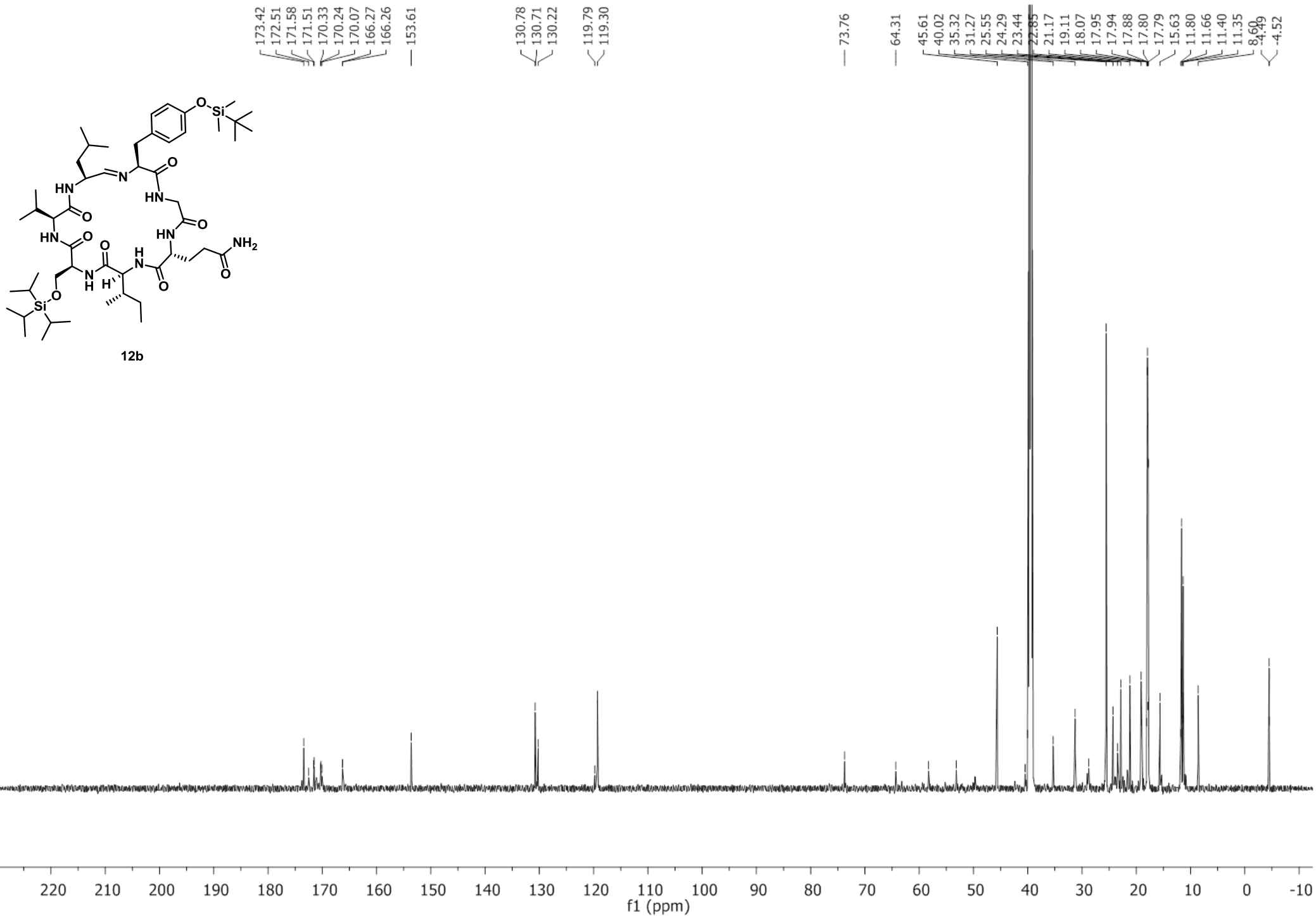
Figure S8. Ser₅ side chain -OH HMBC correlations for **12a**.



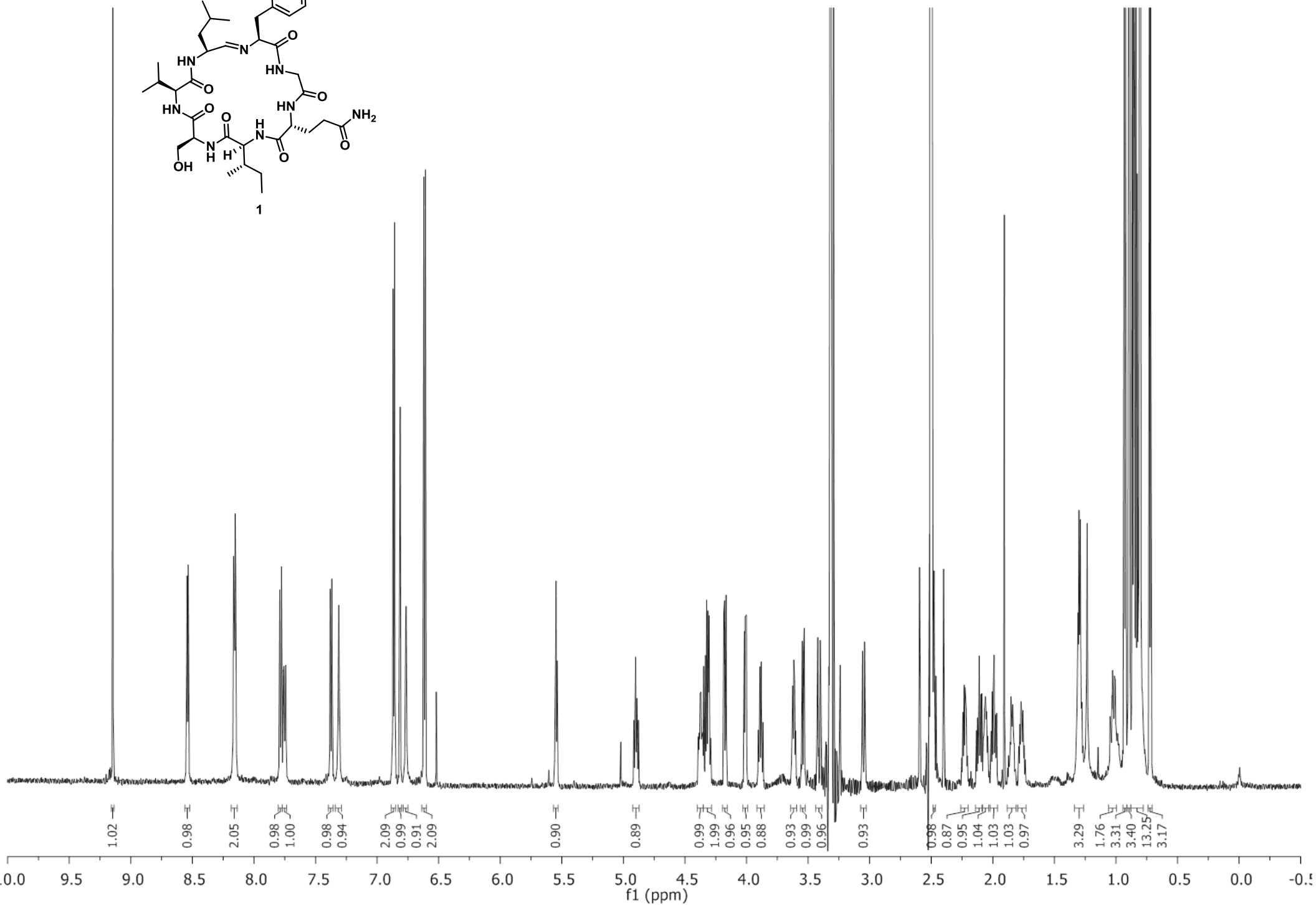
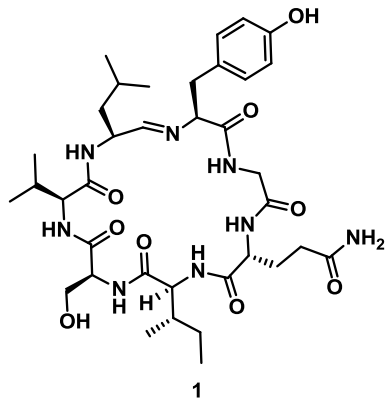
12b



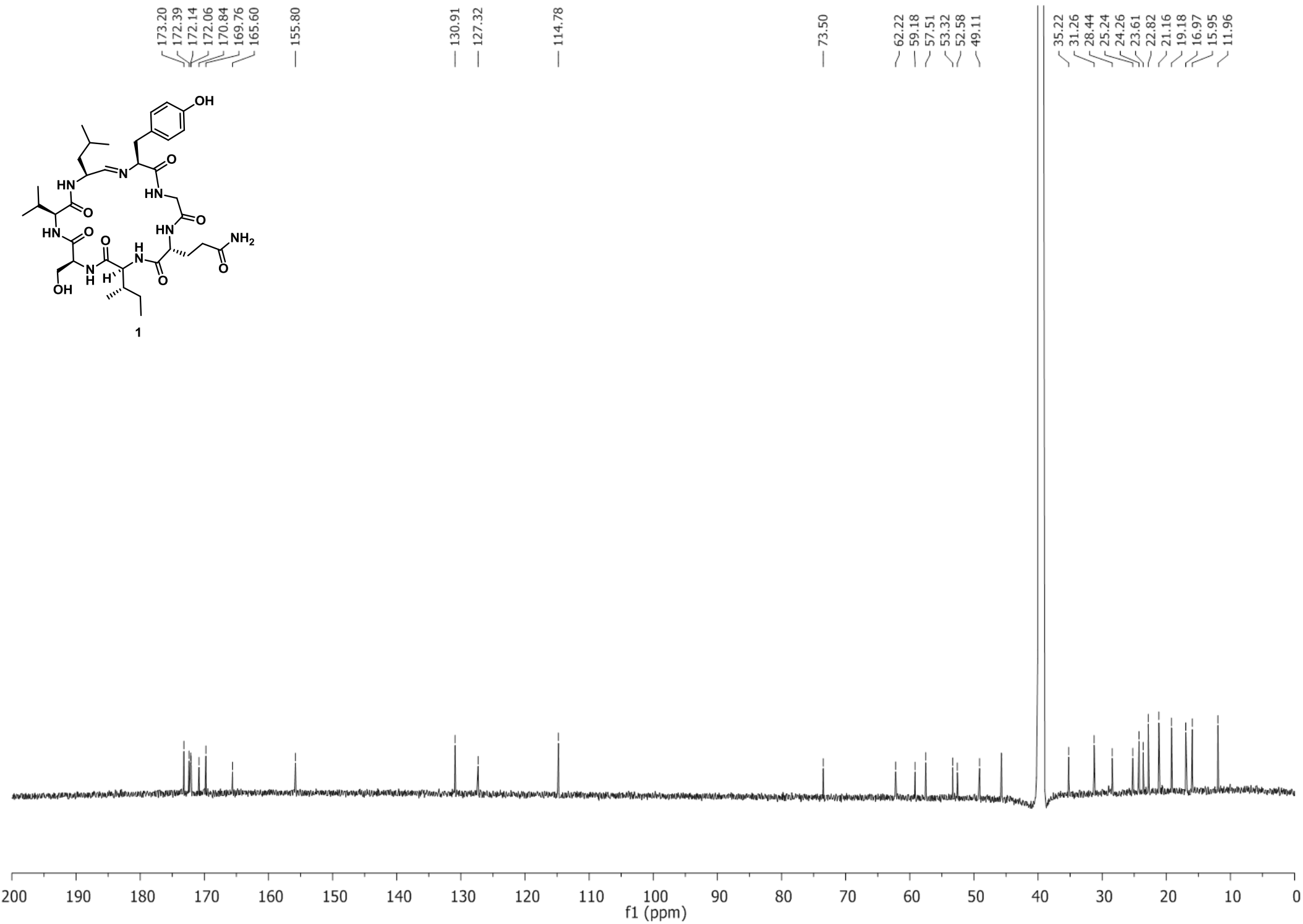
^1H NMR (d_6 -DMSO, 400 MHz) of compound **12b**.



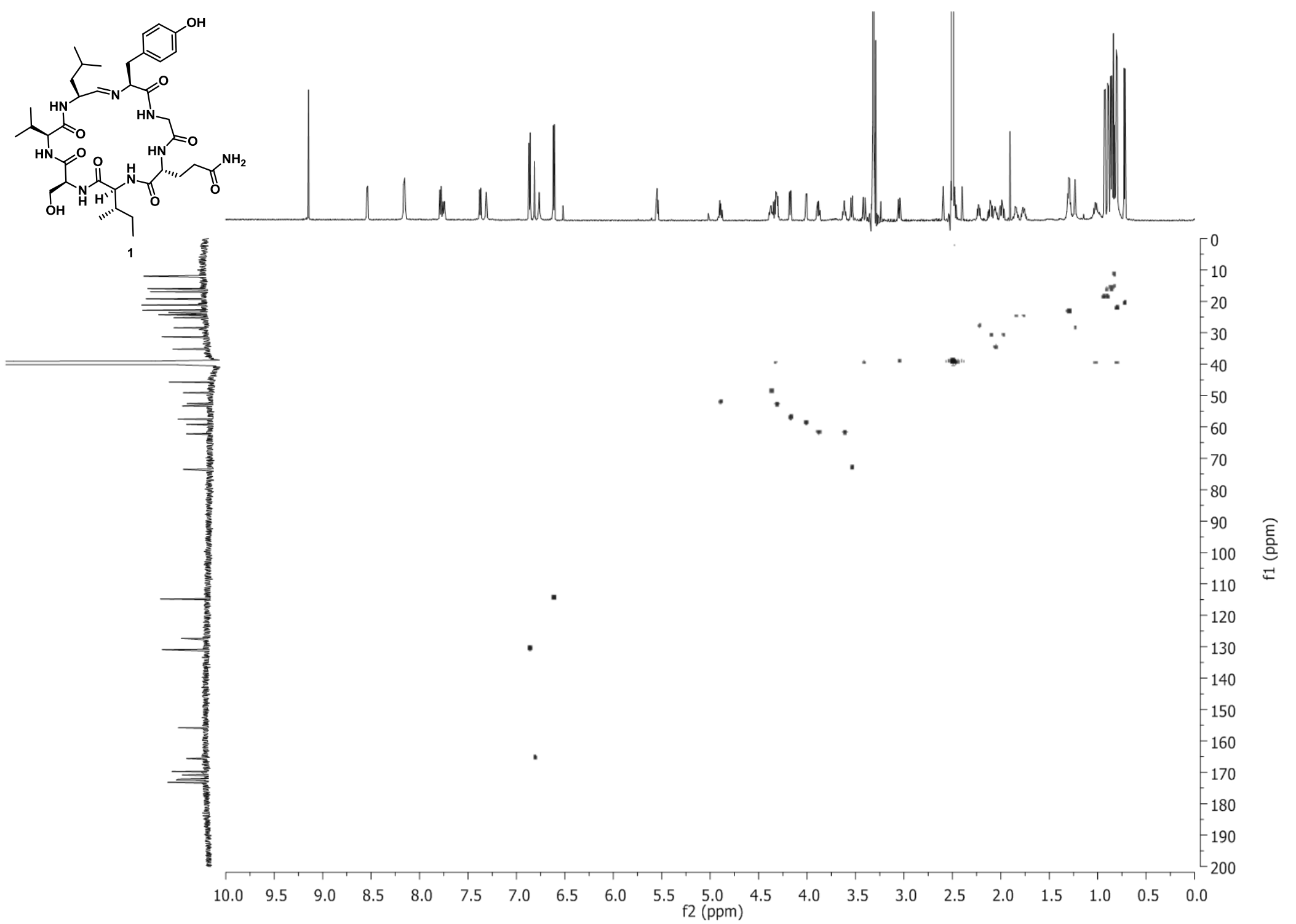
^{13}C NMR (d_6 -DMSO, 176 MHz) of compound **12b**.



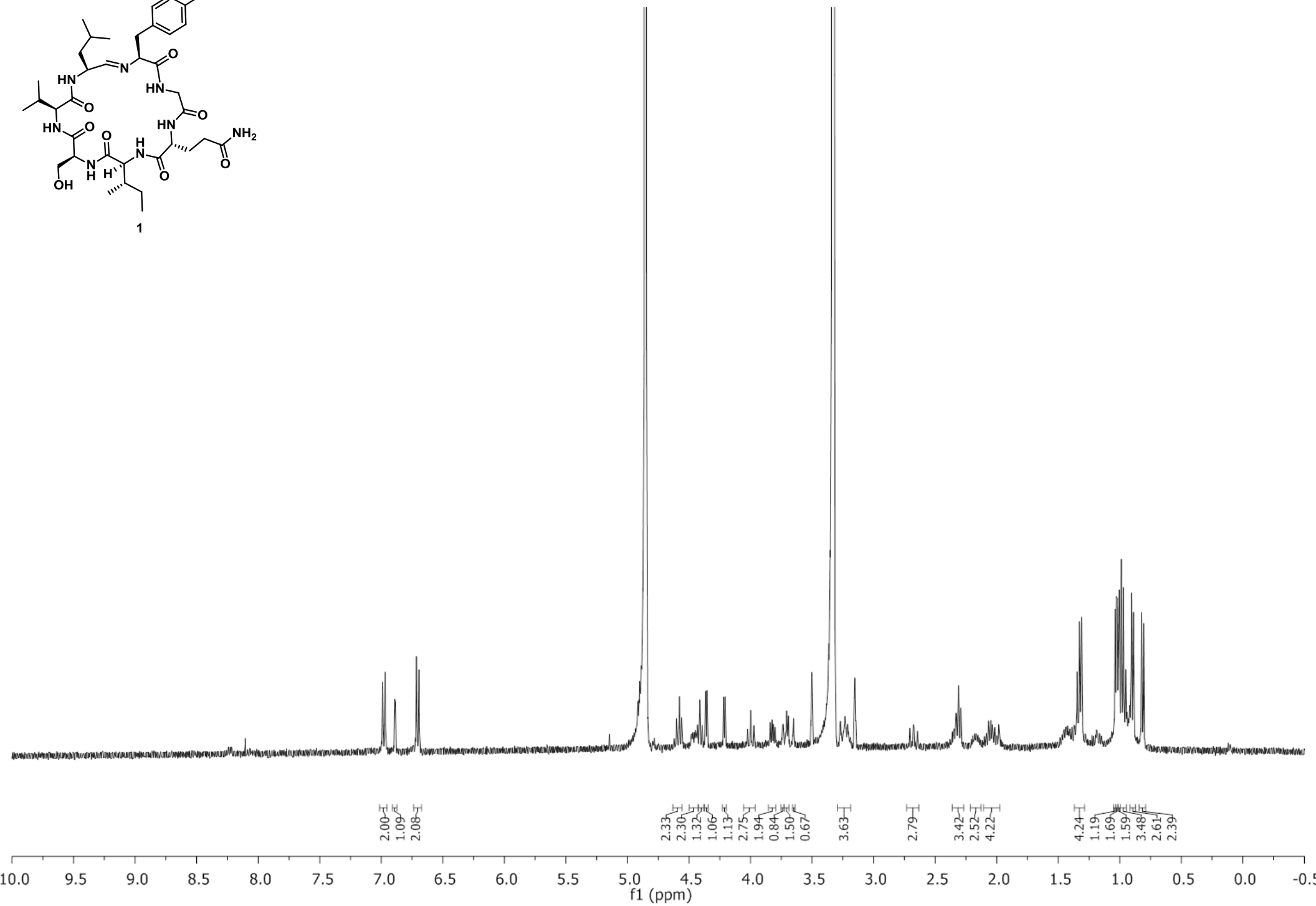
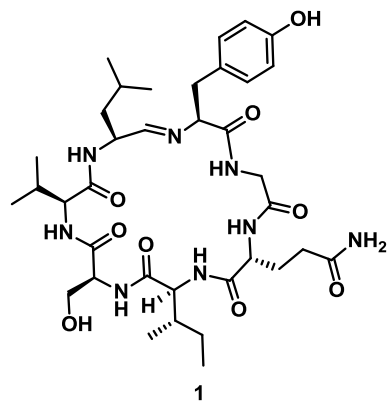
^1H NMR (d_6 -DMSO, 700 MHz) of scytonemide A (1).



^{13}C NMR (d_6 -DMSO, 176 MHz) of scytonemide A (1).

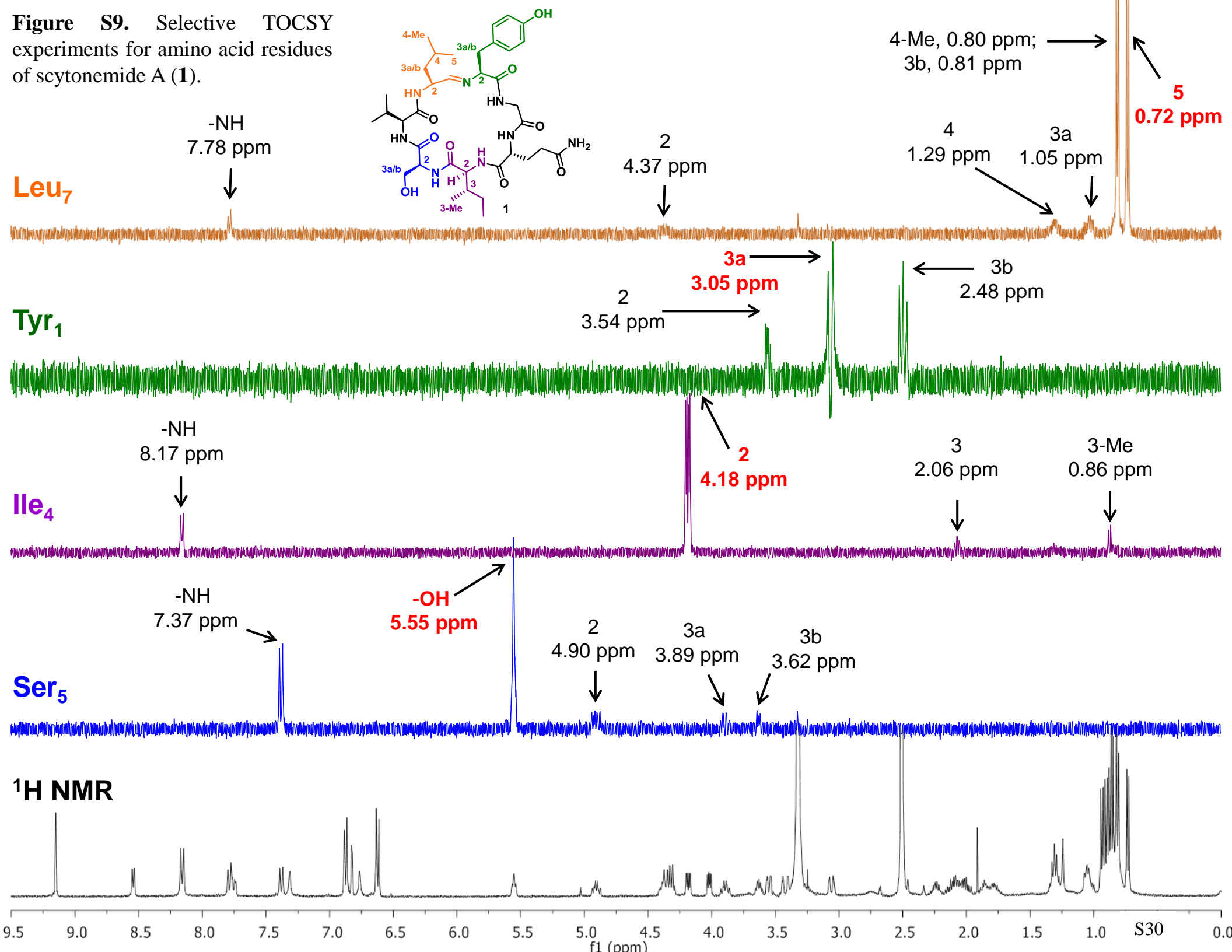


HSQC NMR (d_6 -DMSO, 700 MHz) of scytonemide A (1).



^1H NMR (methanol- d_4 , 400 MHz) of scytonemide A (1).

Figure S9. Selective TOCSY experiments for amino acid residues of scytonemide A (**1**).



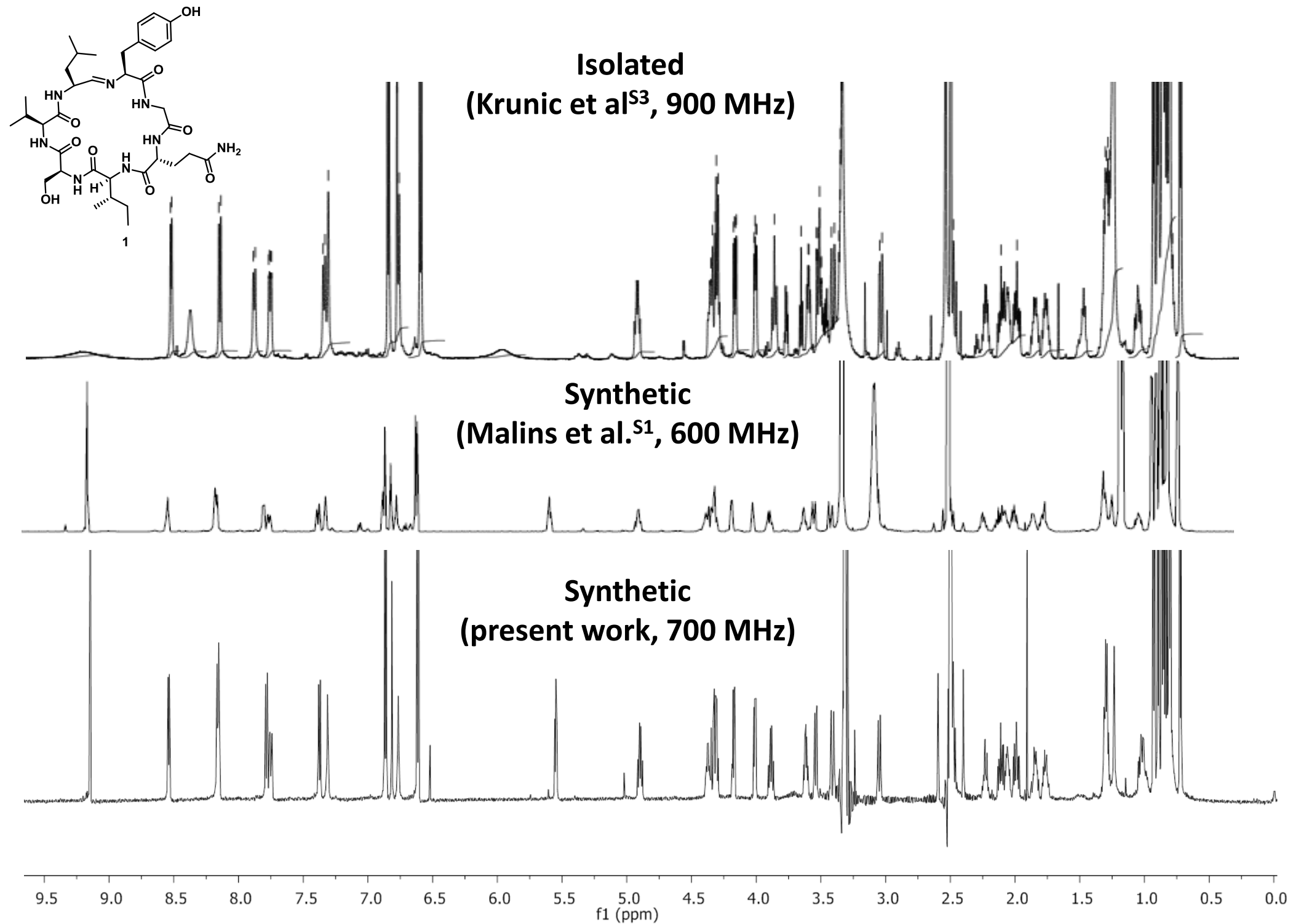


Figure S10. ¹H NMR spectra for isolated scytonemide A (**1**) (Kronic et al.^{S1} top) and synthesized **1** (Malins et al.^{S2} middle; present work, bottom).

References

(S1) Malins, L. R.; deGruyter, J. N.; Robbins, K. J.; Scola, P. M.; Eastgate, M. D.; Ghadiri, M. R.; Baran, P. S. *J. Am. Chem. Soc.* **2017**, *139*, 5233-5241.

(S2) Eissler, S.; Kley, M.; Bächle, D.; Loidl, G.; Meier, T.; Samson, D. *J. Pept. Sci.* **2017**, *23*, 757–762.

(S3) Kronic, A.; Vallat, A.; Mo, S.; Lantvit, D. D.; Swanson, S. M.; Orjala, J. *J. Nat. Prod.* **2010**, *73*, 1927–1932.