

Supplementary Materials

Synthesis of Carbohydrate Based Macrolactones and Their Applications as Receptors for Ion Recognition and Catalysis

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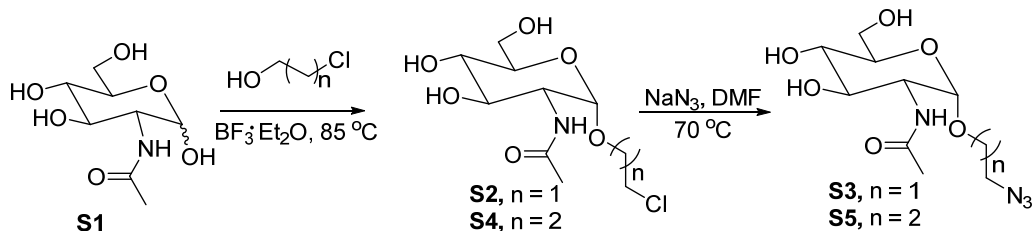
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Table of Contents

I.	Synthesis of compound S2-S5, 6c, 6e, 7c and 9.....	S2
II.	¹H and ¹³C NMR Spectra for Compounds Synthesized.....	S6
III.	2D HSQC and COSY NMR spectra.....	S53
IV.	TBAX Binding Studies.....	S80
V.	Copper Binding Studies.....	S91
VI.	Screening Macrocycles for Azide Alkyne Cycloadditions	S99
VII.	IR Spectra for Macrolactones	S111

I. Synthesis of compound S2-S5, 6c, 6e, 7c and 9



Scheme S1: Synthesis of intermediates from NAG starting material.

Synthesis of compound S2:^{1,2} *N*-acetyl-D-glucosamine **S1** (5.0 g, 22.6 mmol, 1.0 equiv) was added to a 100 mL round bottomed flask (RBF) with 2-chloroethanol (7.75 mL, 113.05 mmol, 5.0 equiv) and BF₃·Et₂O (0.71 mL, 5.65 mmol, 0.25 equiv). The reaction mixture was stirred at 85 °C for 4 h. The heating was turned off and the mixture was cooled to room temperature. The mixture was then treated with water (15 mL) and washed with DCM (20 mL x 2) to remove excess 2-chloroethanol. The aqueous layer was then collected and evaporated. The crude product was obtained as dark brown oily crude. It was then dissolved in MeOH and coated on to SiO₂ (dry loading) for purification. The crude was then purified by chromatography on silica gel using a gradient of dichloromethane (DCM) and methanol from pure DCM to up to 10% MeOH/DCM (*R_f* = 0.13 in 10% MeOH/DCM). The desired product was obtained as a white solid (4.01 g, 63%). ¹H NMR (400 MHz, D₂O + 1 drop MeOH) δ 4.91 (d, *J* = 3.6 Hz, 1H), 3.99-3.70 (m, 9H), 3.49-3.40 (m, 1H), 2.02 (s, 3H); ¹³C NMR (100 MHz, D₂O + 1 drop MeOH) δ 175.1, 97.7, 72.7, 71.5, 70.6, 68.9, 61.2, 54.3, 44.2, 22.5. LC-MS (ESI+) *m/z* calcd for C₁₀H₁₉ClNO₆ [*M* + *H*]⁺ 284.1, found 284.1.

Synthesis of compound S3:¹⁻³ Compound **S2** (4.0 g, 14.09 mmol, 1.0 equiv) was taken in DMF (8.0 mL) and NaN₃ (3.7 g, 56.39 mmol, 4.0 equiv) was added to the mixture and the reaction was heated at 85 °C for 5 h. At which point the ¹H NMR spectrum of the reaction mixture indicated the complete consumption of the starting material. The heating was then turned off and the resulted suspension was filtered, and the filtrate was collected and concentrated to afford the crude product, which was purified by flash chromatography (DCM to 10% MeOH/DCM) to obtain a white solid (3.5 g, 86%) as the desired product. Compound **S3** was synthesized in a one-pot reaction from the *N*-acetyl-D-glucosamine **S1** in 74% yield following literature procedure.³ (*R_f* = 0.25 in 10% MeOH/DCM). m.p. 120.0-122.0 °C. ¹H NMR (400 MHz, D₂O + 1 drop MeOH) δ 4.91 (d, *J* = 3.6

Hz, 1H), 3.95-3.81 (m, 3H), 3.80-3.61 (m, 4H), 3.55-3.42 (m, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, D_2O + 1 drop MeOH) δ 175.2, 97.6, 72.7, 71.5, 70.6, 67.2, 61.2, 54.2, 50.9, 22.5; LC-MS (ESI+) m/z calcd for $\text{C}_{10}\text{H}_{19}\text{N}_4\text{O}_6$ $[\text{M} + \text{H}]^+$ 291.1, found 291.1.

Synthesis of compound 6c:³ Compound **S3** (160.0 mg, 0.55 mmol, 1.0 equiv), pyridine (1.5 mL), TsCl (210.2 mg, 1.10 mmol, 2.0 equiv), 10 h. Purified by flash chromatography (DCM to 10% MeOH/DCM) to obtain a white foam (186.0 mg, 76%) as the desired product. (R_f = 0.38 in 10% MeOH/DCM). ^1H NMR (400 MHz, CDCl_3) δ 7.80 (d, J = 8.3 Hz, 2H), δ 7.34 (d, J = 8.3 Hz, 2H), 6.08 (d, J = 8.6 Hz, 1H), 4.81 (d, J = 3.8 Hz, 1H), 4.33 (dd, J = 11.0, 2.1 Hz, 1H), 4.26 (dd, J = 11.0, 5.7 Hz, 1H), 4.11-4.03 (m, 1H), 3.93-3.86 (m, 1H), 3.83-3.76 (m, 1H), 3.71-3.63 (t, J = 9.6 Hz, 1H), 3.62-3.43 (m, 3H), 3.35-3.28 (m, 1H), 2.57 (br s, 2H), 2.45 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 172.4, 145.0, 132.8, 129.9, 128.0, 97.6, 73.7, 70.9, 69.9, 69.0, 67.3, 53.4, 50.5, 23.1, 21.7. LC-MS (ESI+) m/z calcd for $\text{C}_{17}\text{H}_{25}\text{N}_4\text{O}_8\text{S}$ $[\text{M} + \text{H}]^+$ 445, found 445.

Synthesis of compound 7c:³ To a 50 mL RBF, compound **6c** (500.0 mg, 1.12 mmol, 1.0 equiv), DCM (5.0 mL), pyridine (0.45 mL, 5.62 mmol, 5.0 equiv) were added in the given order and the mixture was cooled to 0 °C. To the stirring mixture benzoyl chloride (0.32 mL, 2.81 mmol, 2.5 equiv) was added dropwise. The mixture was allowed to warm up to rt and the stirring was continued for 4 more hours. ^1H NMR spectrum indicated the completion of the reaction. Work up was performed with H_2O (25 mL) and DCM (25 mL x 3). The combined organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated to afford the crude, which was purified by column chromatography using eluent from pure DCM to 2% MeOH/DCM to give a colorless oil (572 mg, 78%) as the desired product (R_f = 0.6 in 5% MeOH/DCM). Compound **7c** was also synthesized in a one-pot reaction from compound **S3** following the literature procedure.³ ^1H NMR (400 MHz, CDCl_3) δ 7.91-7.83 (m, 4H), 7.71 (d, J = 8.3 Hz, 2H), 7.55-7.45 (m, 2H), 7.39-7.31 (m, 4H), 7.22 (d, J = 8.1 Hz, 2H), 5.91 (d, J = 9.5 Hz, 1H), 5.62 (dd, J = 10.9, 9.5 Hz, 1H), 5.36 (t, J = 9.5 Hz, 1H), 4.96 (d, J = 3.6 Hz, 1H), 4.56-4.48 (m, 1H), 4.29-4.10 (m, 3H), 4.03-3.97 (m, 1H), 3.71-3.64 (m, 1H), 3.63-3.55 (m, 1H), 3.44-3.36 (m, 1H), 2.37 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.1, 166.9, 165.1, 145.0, 133.6, 133.5, 132.4, 130.0, 129.84, 129.78, 128.7, 128.6, 128.4, 128.3, 128.0, 97.5, 71.1, 68.9, 68.6, 68.3, 67.8, 52.0, 50.4, 23.0, 21.6; LC-MS (ESI+) m/z calcd for $\text{C}_{31}\text{H}_{33}\text{N}_4\text{O}_{10}\text{S}$ $[\text{M} + \text{H}]^+$ 653.2, found 653.2.

Synthesis of compound S4:⁴ *N*-acetyl-D-glucosamine **S1** (5.0 g, 22.6 mmol, 1.0 equiv) was added to a 100 mL RBF with 3-chloro-1-propanol (7.56 mL, 90.4 mmol, 4.0 equiv) and BF₃•Et₂O (0.56 mL, 4.5 mmol, 0.2 equiv). The reaction mixture was stirred at 85 °C for 6 h. The heating was turned off and the mixture was cooled to room temperature. The mixture was then treated with water (15 mL) and washed with DCM (20 mL x 2) to remove excess 3-chloro-1-propanol. The aqueous layer was then collected and evaporated. The crude product was obtained as a dark brown oil. It was then dissolved in MeOH and loaded to SiO₂ (dry loading) for purification. The crude was then purified by chromatography on silica gel using a gradient solvent from pure DCM to up to 10% MeOH/DCM. The desired product was obtained as a white solid (4.63 g, 69%); R_f = 0.16 in 10% MeOH/DCM; m.p. 146.0-148.0 °C. ¹H NMR (400 MHz, D₂O) δ 4.85 (d, *J* = 3.6 Hz, 1H), 3.91-3.81 (m, 3H), 3.78-3.66 (m, 5H), 3.59-3.53 (m, 1H), 3.50-3.42 (m, 1H), 2.08-1.99 (m, 5H); ¹³C NMR (100 MHz, D₂O) δ 174.5, 97.0, 71.9, 71.0, 70.0, 64.6, 60.6, 53.8, 42.1, 31.4, 21.9. LC-MS (ESI+) *m/z* calcd for C₁₁H₂₁ClNO₆ [M + H]⁺, 298.2, found 298.1.

Synthesis of compound S5:^{3,4} To a solution of compound **S4** (5.0 g, 16.79 mmol, 1.0 equiv) in DMF (10.0 mL) was added NaN₃ (3.3 g, 50.38 mmol, 3.0 equiv) and the mixture was heated at 85 °C for 5.0 h. At which point the ¹H NMR spectrum of the reaction mixture indicated the complete consumption of the starting material. DMF was removed under reduced pressure to obtain the crude which was further purified by flash chromatography (DCM to 7% MeOH/DCM) to obtain a white solid (4.2 g, 82%) as the desired product (R_f = 0.25 in 10% MeOH/DCM). Compound **S5** was also synthesized in a one-pot reaction from **S1** following the literature.³ m.p. 125.0-127.0 °C. ¹H NMR (400 MHz, D₂O) δ 4.84 (d, *J* = 3.6 Hz, 1H), 3.91-3.63 (m, 6H), 3.54-3.40 (m, 4H), 2.01 (s, 3H), 1.91-1.83 (m, 2H); ¹³C NMR (100 MHz, D₂O) δ 175.0, 97.5, 72.5, 71.6, 70.6, 65.6, 61.2, 54.4, 48.8, 28.6, 22.5; LC-MS (ESI+) *m/z* calcd for C₁₁H₂₁N₄O₆ [M + H]⁺ 305.1, found 305.1.

Synthesis of compound 6e:³ To a stirring solution of compound **S5** (1.50 g, 4.91 mmol) in dry pyridine (7 mL) at 0 °C, a solution of TsCl (1.88 g, 9.82 mmol) in pyridine (2 mL) was added dropwise and the mixture was left stirring at rt for 12 h. The reaction was quenched with MeOH (2.0 mL) and the solvent was evaporated. The crude product was purified by chromatography on SiO₂ using eluent from 1% MeOH/DCM to 5% MeOH/DCM to obtain an off-white foam (1.47 g, 65%) as the desired product (R_f = 0.32 in 5% MeOH/DCM). ¹H NMR (400 MHz, CDCl₃) 7.81 (d,

$J = 8.3$ Hz, 2H), 7.36 (d, $J = 8.2$ Hz, 2H), 6.49 (d, $J = 8.8$ Hz, 1H), 4.73 (d, $J = 3.5$ Hz, 1H), 4.35-4.29 (m, 2H), 4.02 (m, 1H), 3.85-3.67 (m, 5H), 3.53-3.34 (m, 4H), 2.45 (s, 3H), 2.04 (s, 3H), 1.86 (pentet, $J = 6.2$ Hz, 2H); ^{13}C NMR (400 MHz, CDCl_3) 172.1, 145.0, 132.8, 129.9, 128.0, 97.5, 73.1, 70.4, 69.9, 69.4, 65.1, 53.5, 48.6, 28.5, 23.1, 21.6. LC-MS (ESI+) m/z calcd for $\text{C}_{18}\text{H}_{27}\text{N}_4\text{O}_8\text{S}$ $[\text{M} + \text{H}]^+$ 459, found 459.

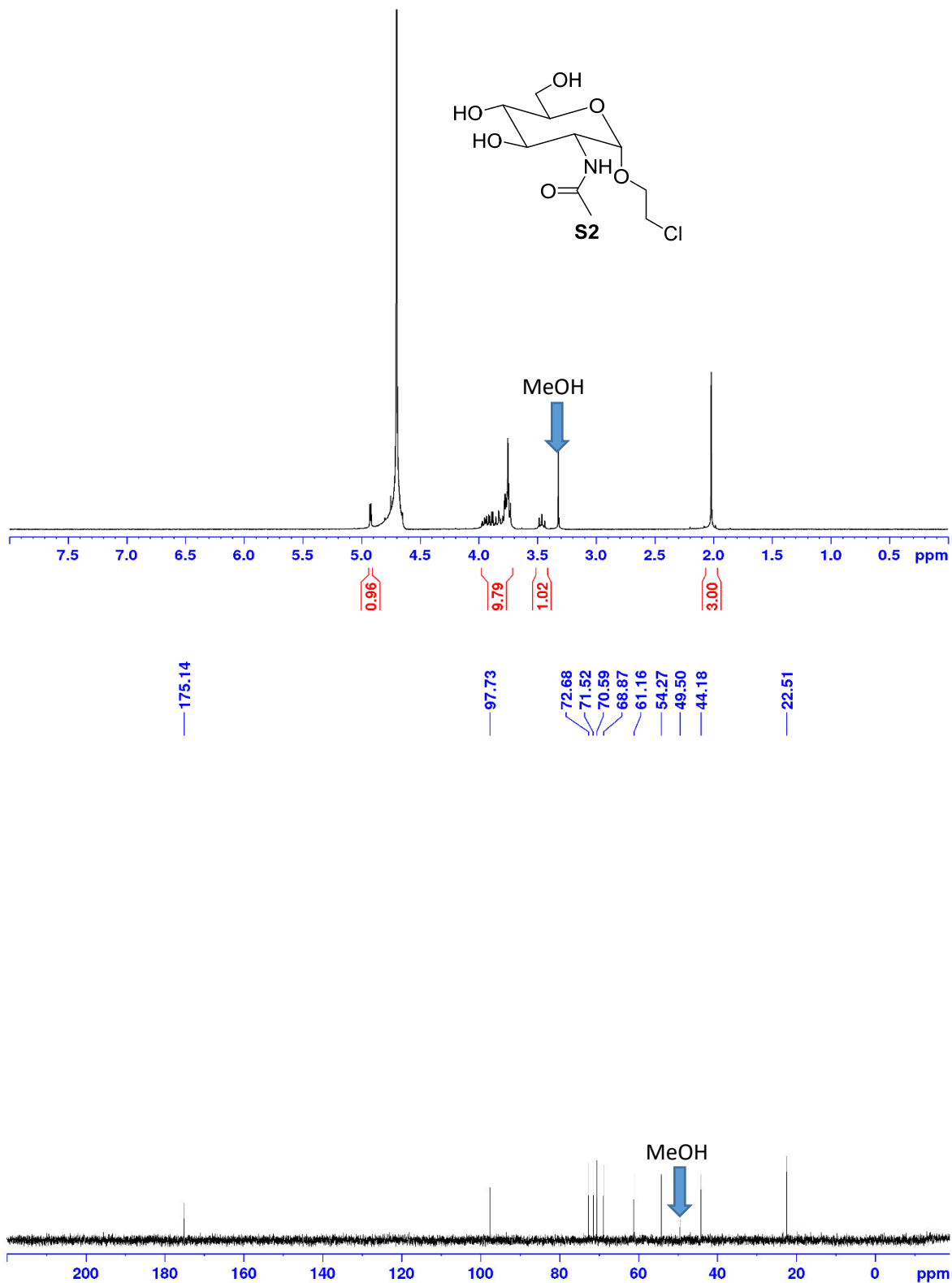
Synthesis of compound 9:³ To a 50 mL RBF, compound **6e** (1.0 g, 2.18 mmol, 1.0 equiv), DCM (8.0 mL), pyridine (0.88 mL, 10.90 mmol, 5.0 equiv) were added in the given order and the mixture was cooled to 0 °C. To the stirring mixture benzoyl chloride (0.63 mL, 5.45 mmol, 2.5 equiv) was added dropwise. The mixture was left stirring at room temperature for additional 8 hours. ^1H NMR spectrum indicated the completion of the reaction. Work up was performed with H_2O (40 mL) and DCM (50 mL x 3). The combined organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated to afford the crude, which was purified by column chromatography using eluent from DCM to 2% MeOH/DCM to give a colorless oil (1.13 g, 78%) as the desired product ($R_f = 0.65$ in 5% MeOH/DCM). Compound **9** was also synthesized using a one-pot reaction from compound **S5** directly following the literature procedure. ^1H NMR (CDCl_3 , 400 MHz) δ 7.90-7.83 (m, 4H), 7.71 (d, $J = 8.3$ Hz, 2H), 7.55-7.48 (m, 2H), 7.40-7.31 (m, 4H), 7.22 (d, $J = 8.1$ Hz, 2H), 5.89 (d, $J = 9.2$ Hz, 1H), 5.59 (dd, $J = 10.9, 9.5$ Hz, 1H), 5.35 (t, $J = 9.5$ Hz, 1H), 4.90 (d, $J = 3.6$ Hz, 1H), 4.48 (ddd, $J = 10.9, 9.2, 3.6$ Hz, 1H), 4.25-4.10 (m, 3H), 3.87 (dt, $J = 10.1, 6.0$ Hz, 1H), 3.59-3.41 (m, 3H), 2.37 (s, 3H), 2.00-1.92 (m, 2H), 1.85 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 169.9, 167.1, 165.1, 145.0, 133.53, 133.49, 132.5, 129.84, 129.78, 129.76, 128.7, 128.6, 128.43, 128.42, 128.0, 97.3, 71.4, 68.9, 68.4, 68.2, 65.6, 52.2, 48.6, 28.6, 23.1, 21.6. LC-MS (ESI+) m/z $\text{C}_{32}\text{H}_{35}\text{N}_4\text{O}_{10}\text{S}$ $[\text{M} + \text{H}]^+$ 667.2, found 667.2.

Cyclization Reactions for LM28 and DLM28

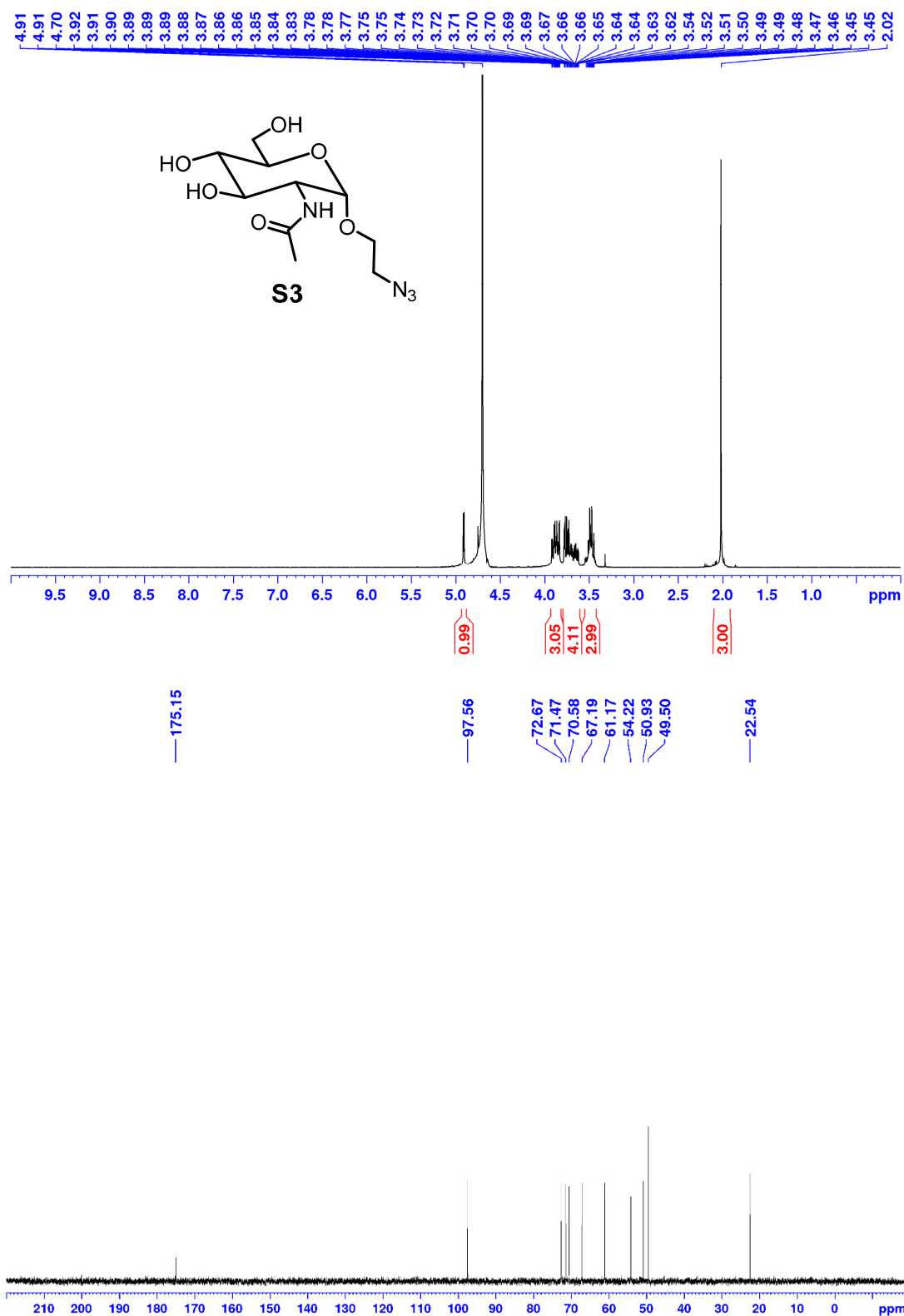
Compound **8a** macrolactonization was also carried at more concentrated conditions in an attempt to obtain more dimer. However, the formation of the monomer macrolactone is preferred.

Entry	8a (mg)	Concentration (mM)	Base 2.0 equiv	DMF (mL)	Temp (°C)	Yield %	
						Mono	Di
1	100	15.8	K_2CO_3	7.0	75	73	20
2	100	22.2	K_2CO_3	5.0	75	68	23

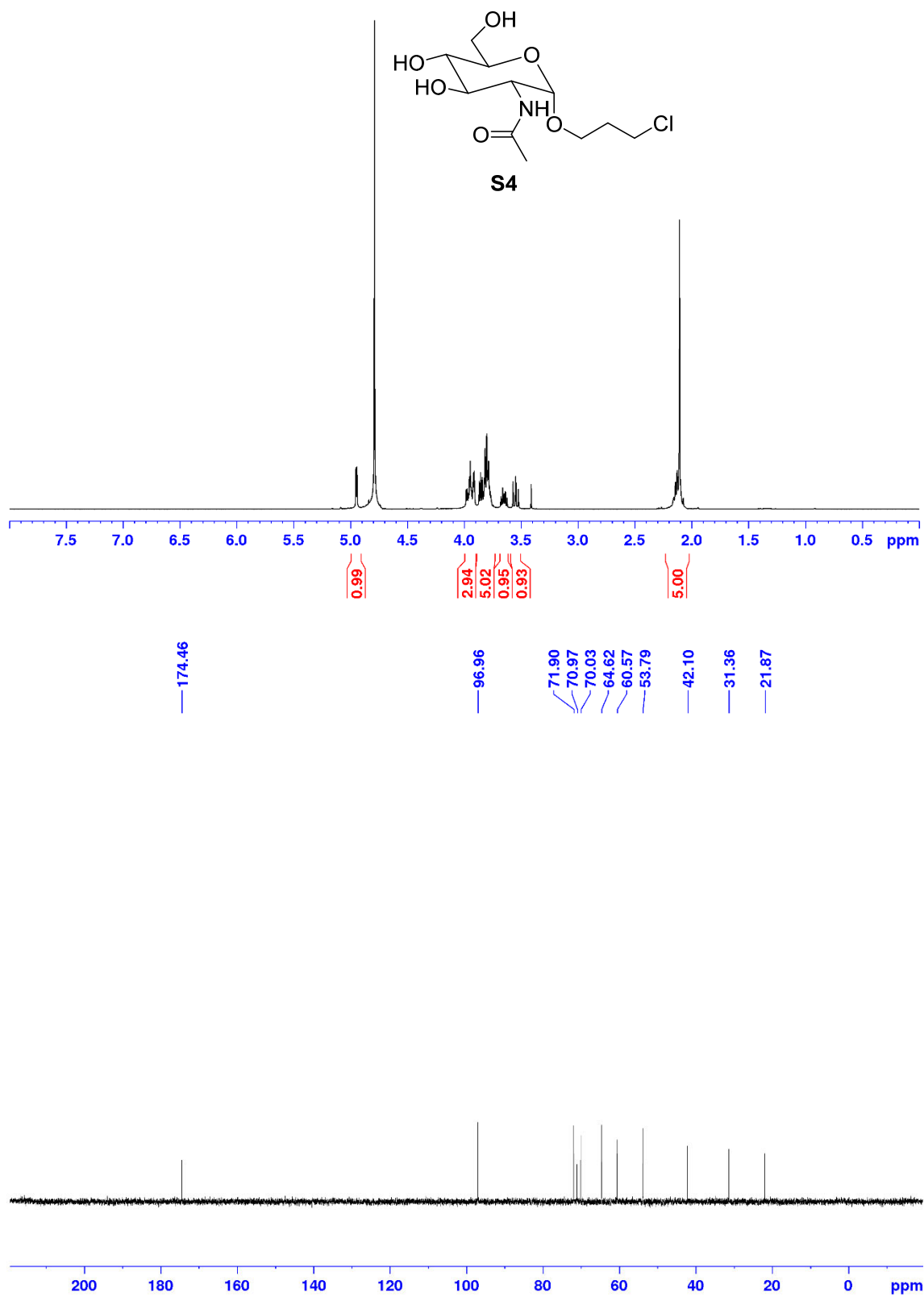
II. ^1H and ^{13}C Spectra for Compounds Synthesized (400MHz Bruker)



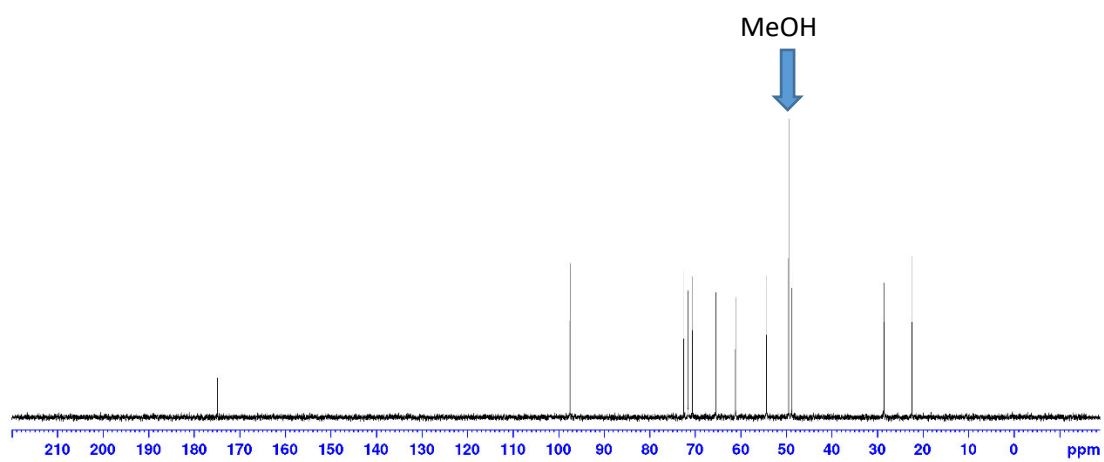
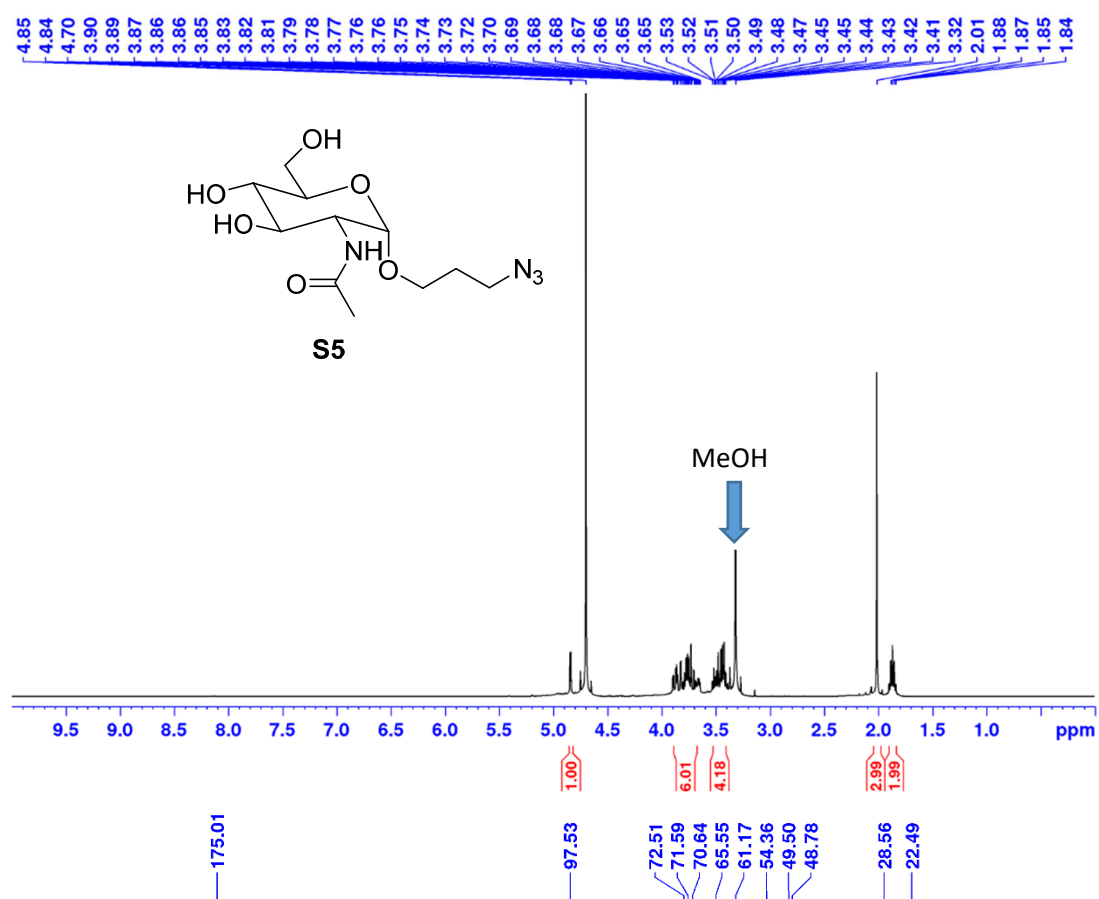
^1H NMR and ^{13}C NMR spectra of compound **S2** in D_2O and MeOH (1 drop)



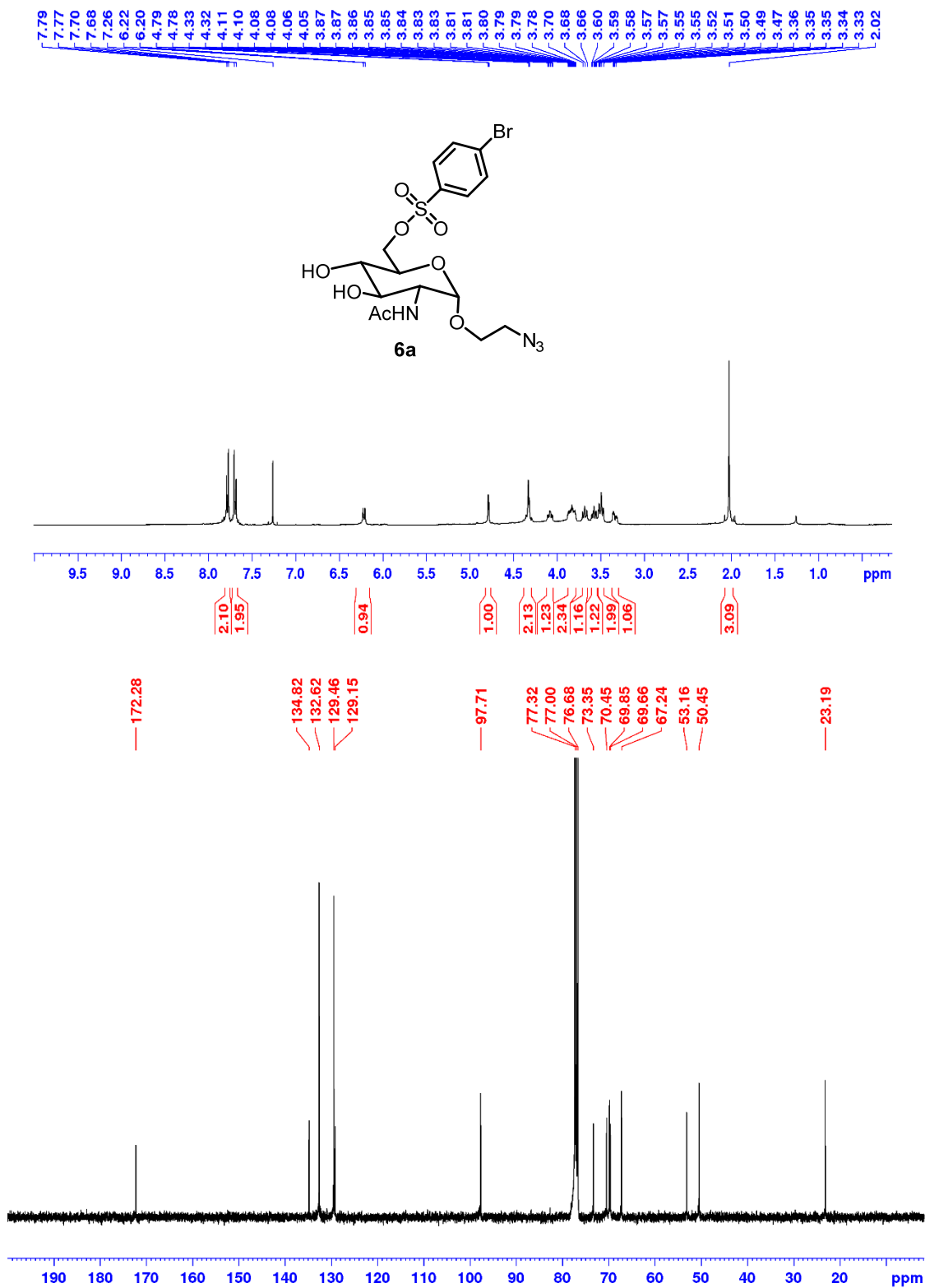
¹H NMR and ¹³C NMR spectra of compound **S3** in D₂O and MeOH (1 drop)



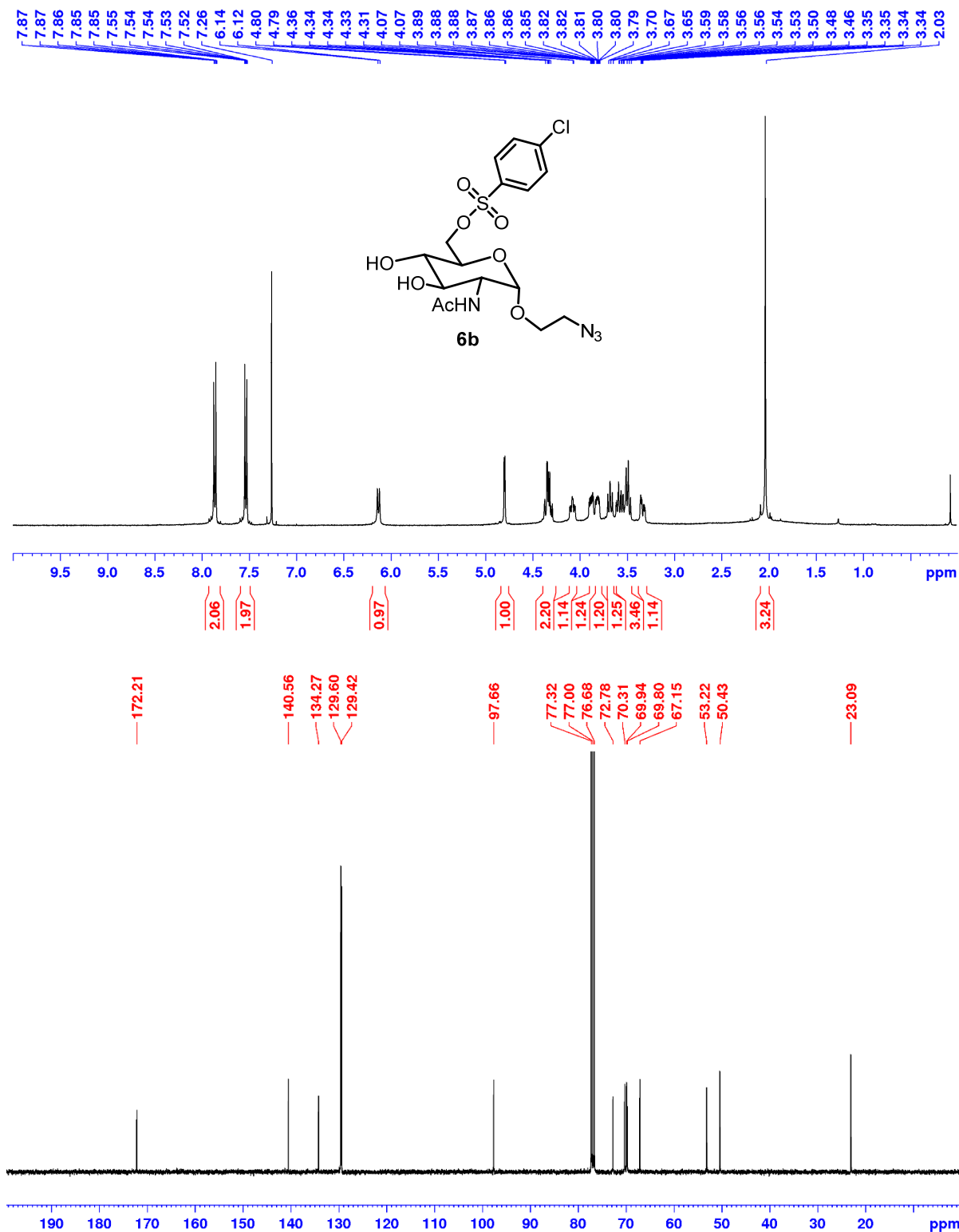
¹H NMR and ¹³C NMR spectra of compound **S4** in D₂O



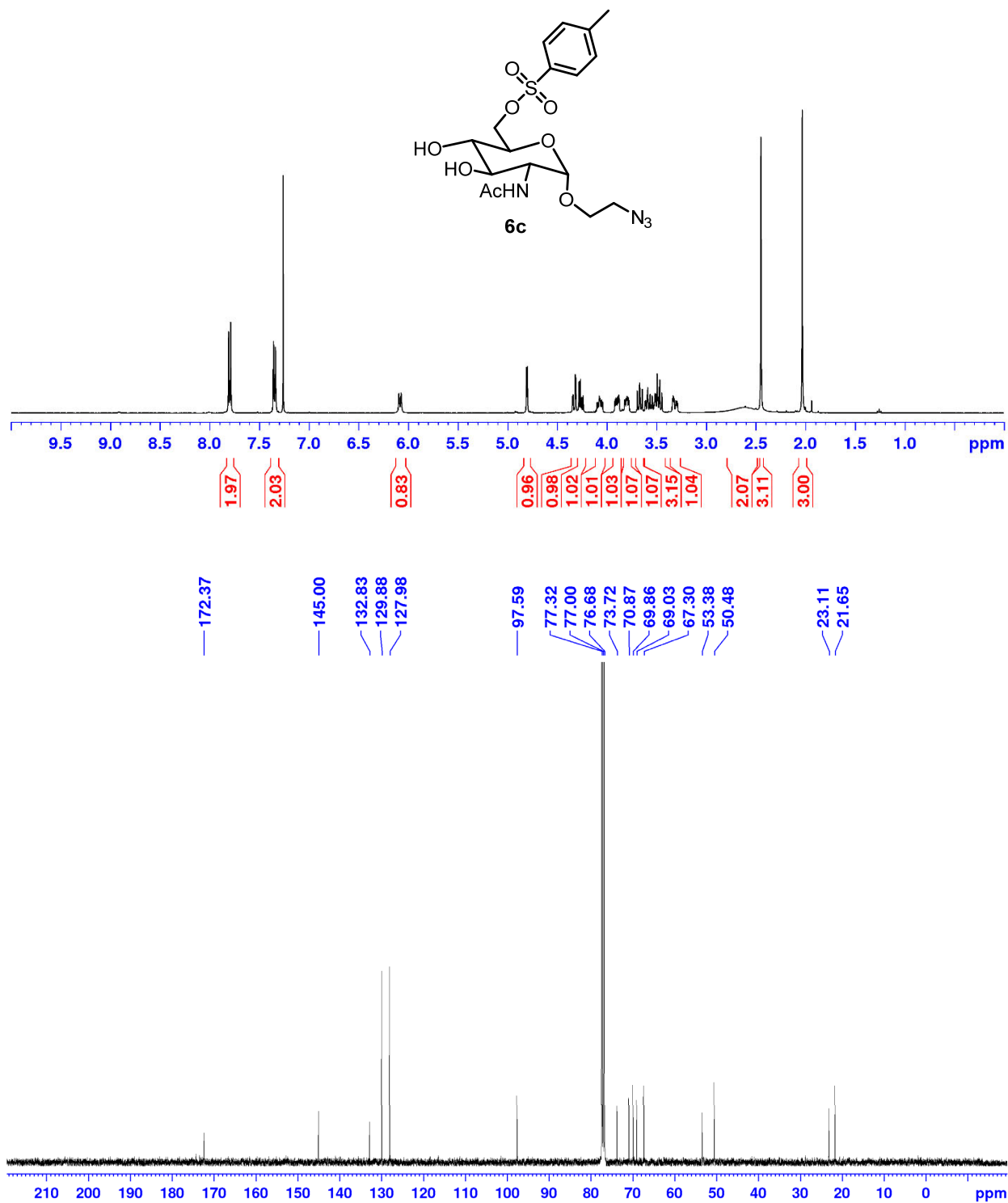
¹H NMR and ¹³C NMR spectra of compound **S5** in D₂O and MeOH (1 drop)



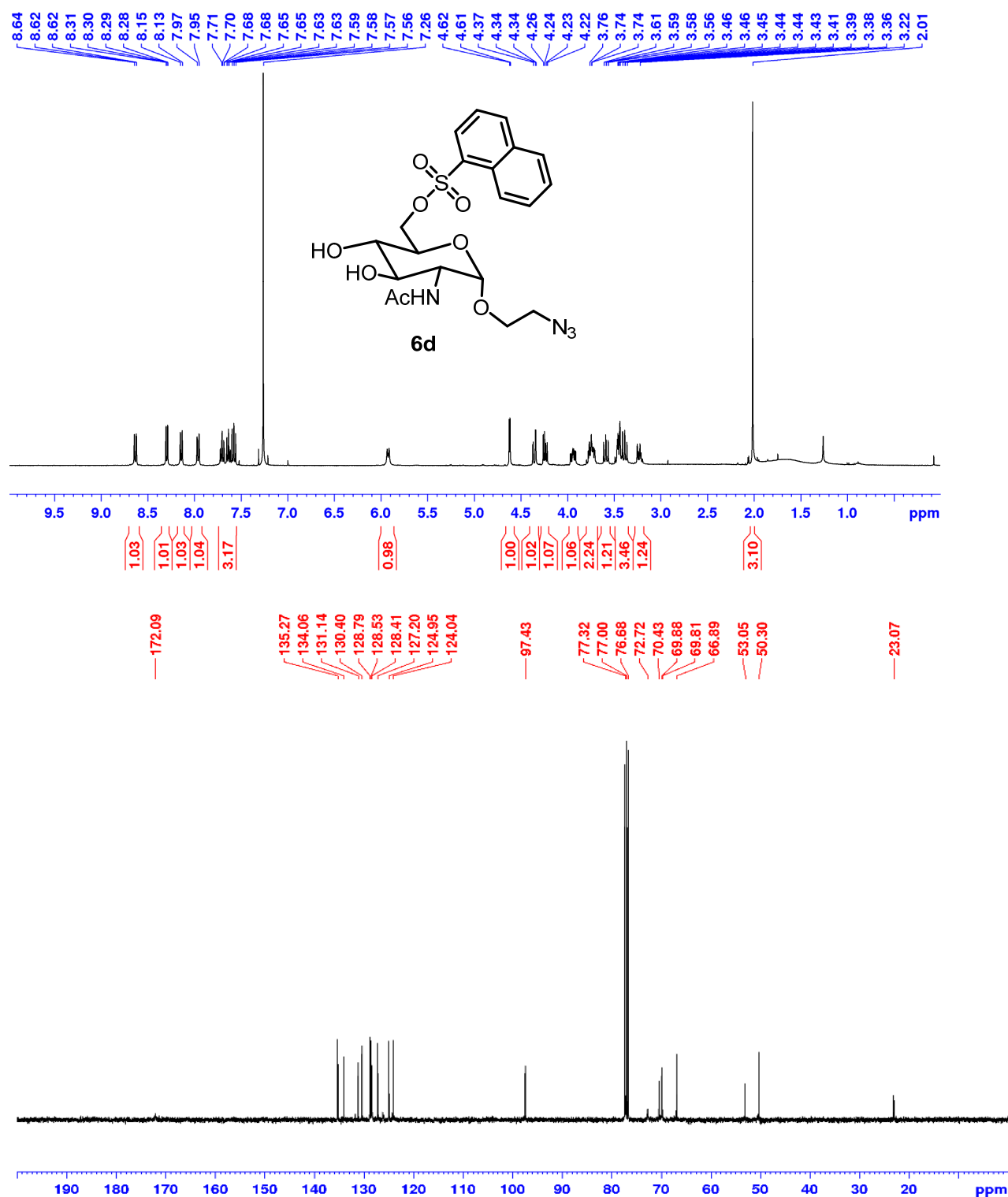
¹H NMR and ¹³C NMR spectra of compound **6a** in CDCl₃



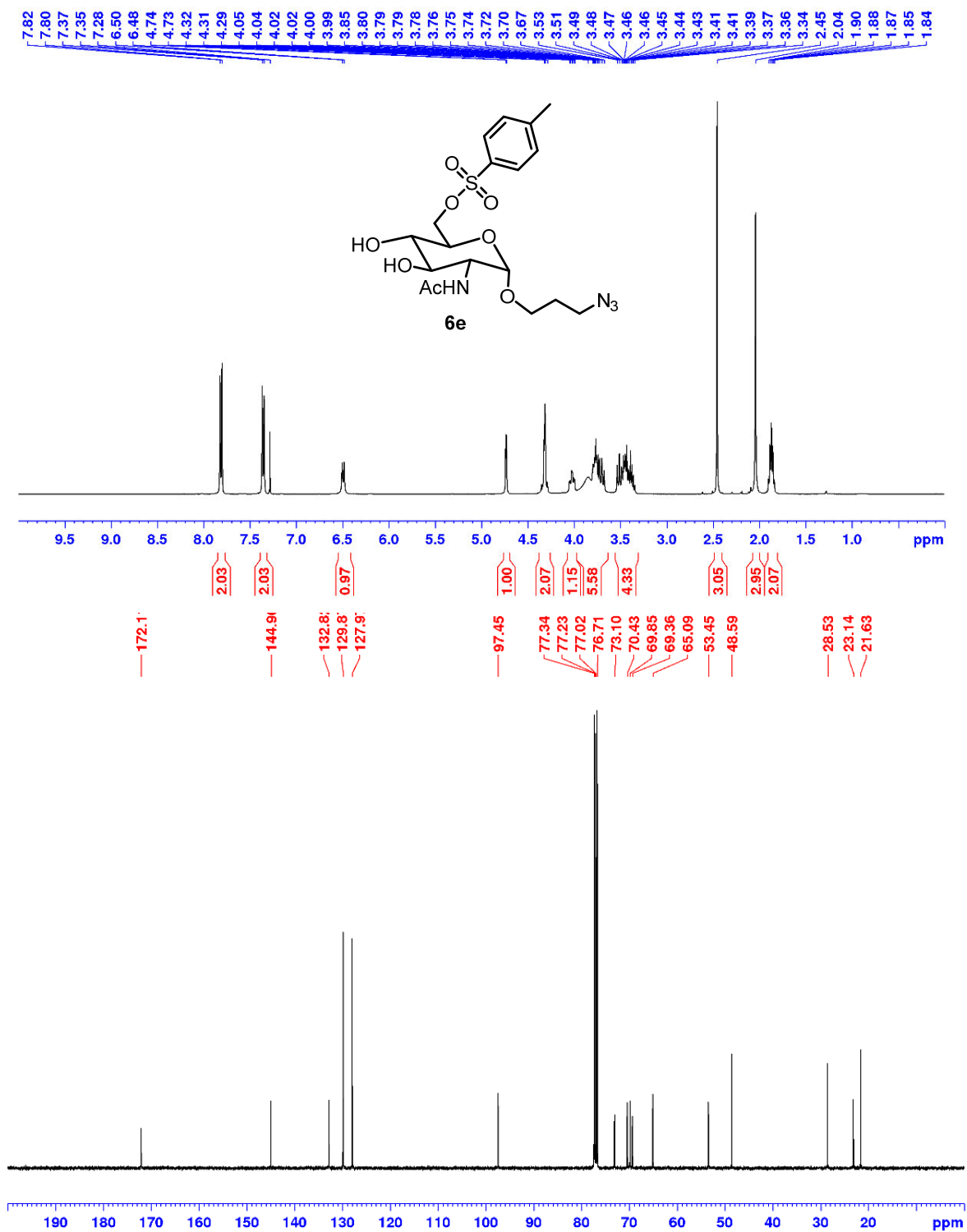
¹H NMR and ¹³C NMR spectra of compound **6b** in CDCl₃



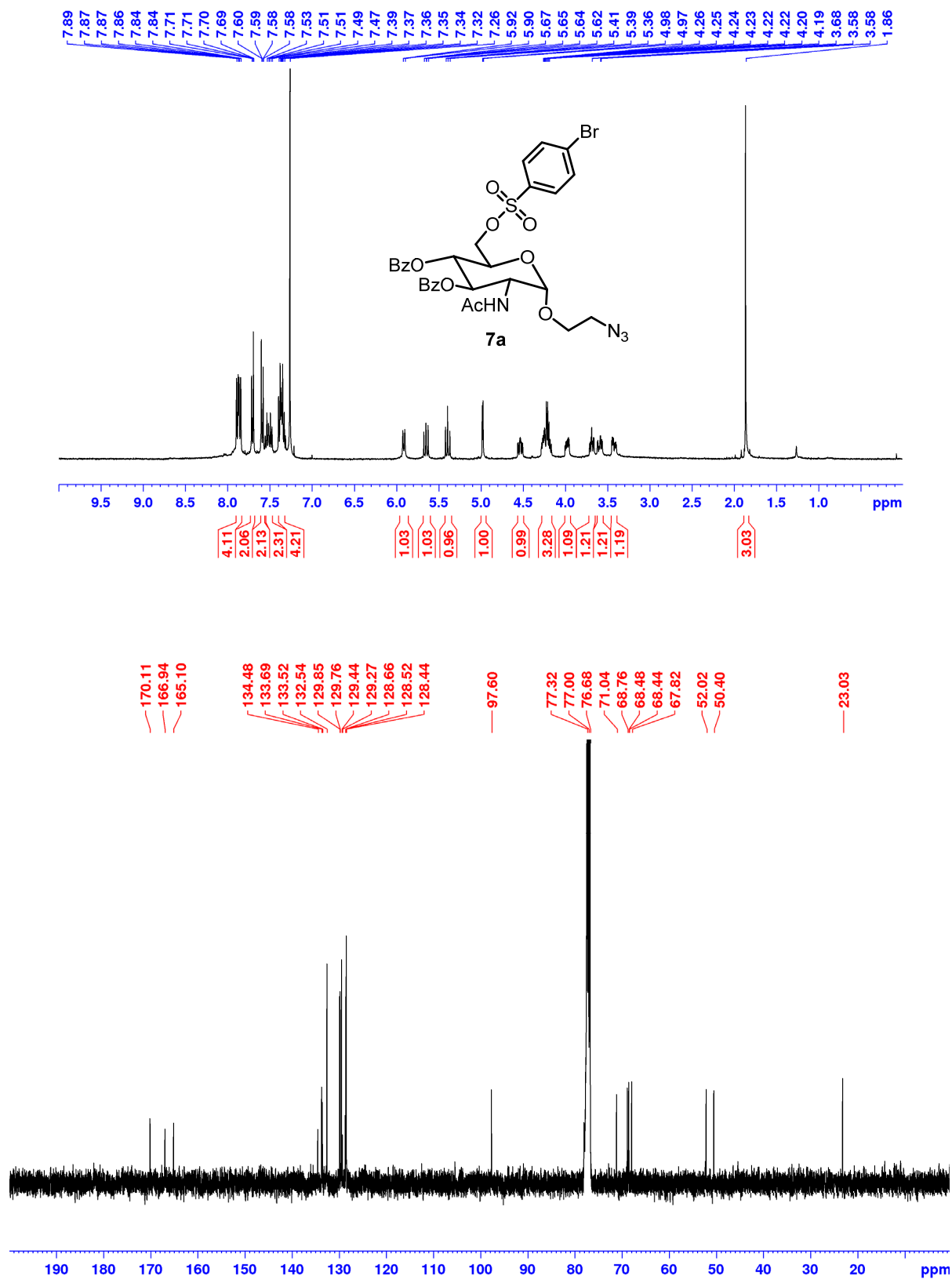
^1H NMR and ^{13}C NMR spectra of compound **6c** in CDCl_3



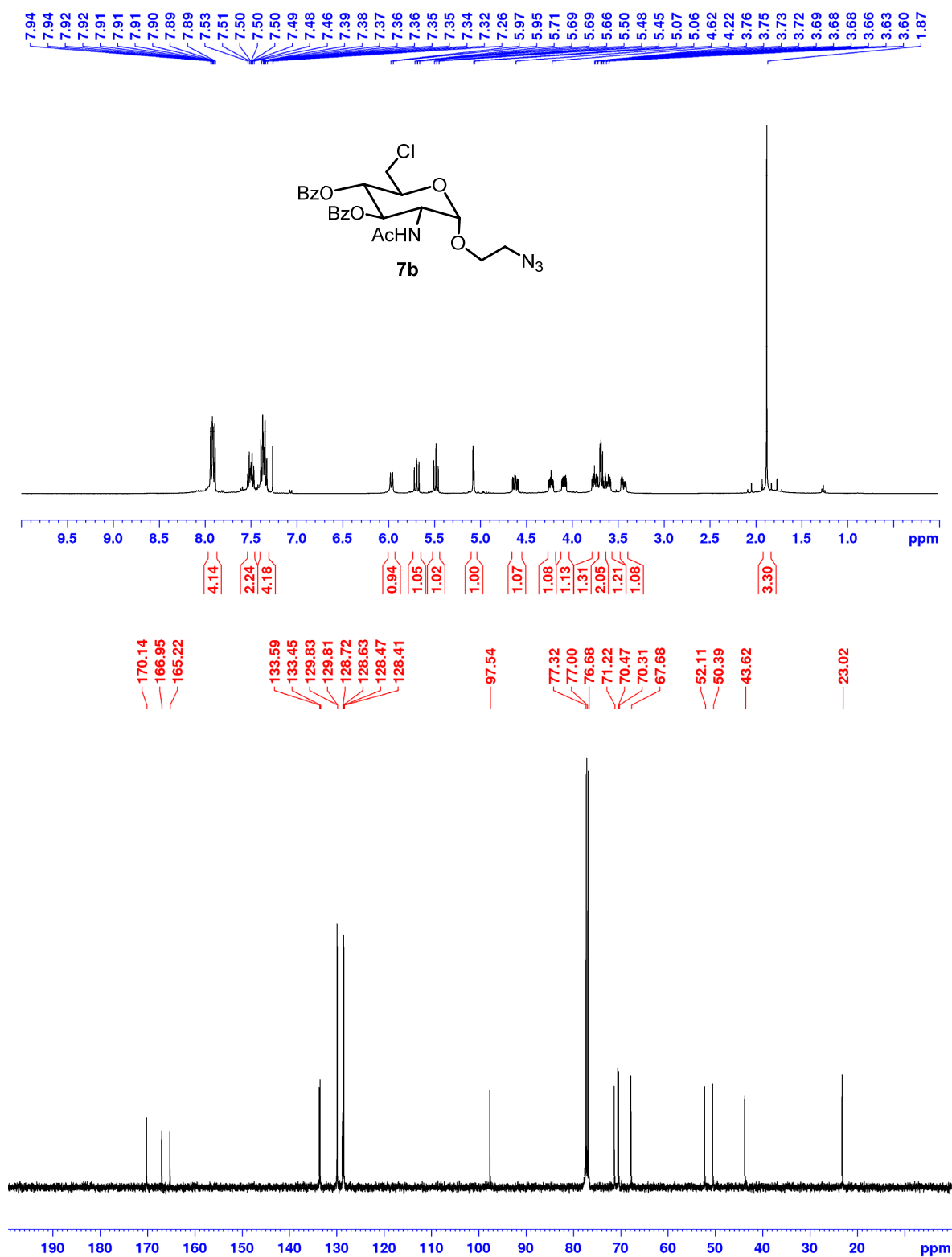
¹H NMR and ¹³C NMR spectra of compound **6d** in CDCl₃



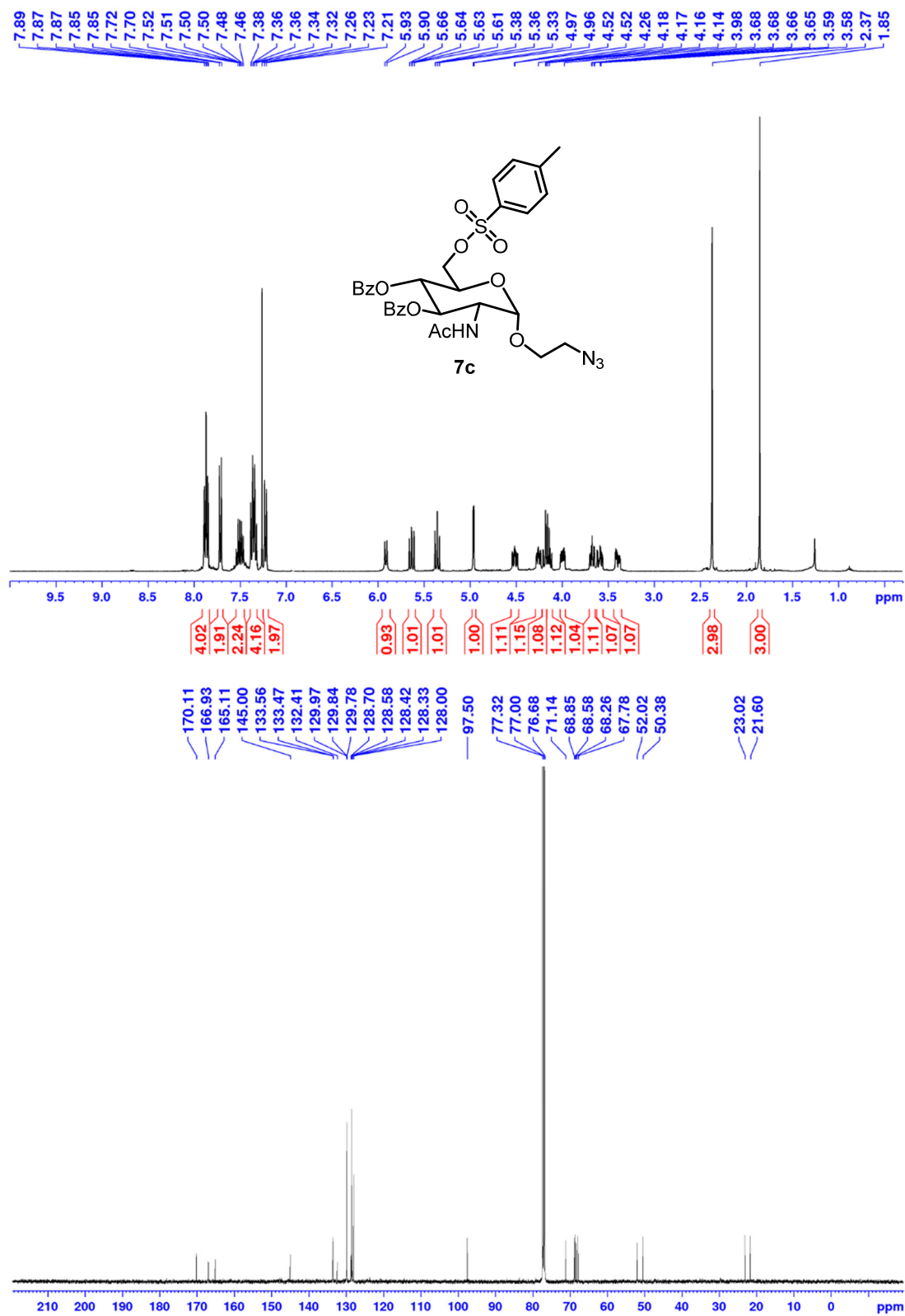
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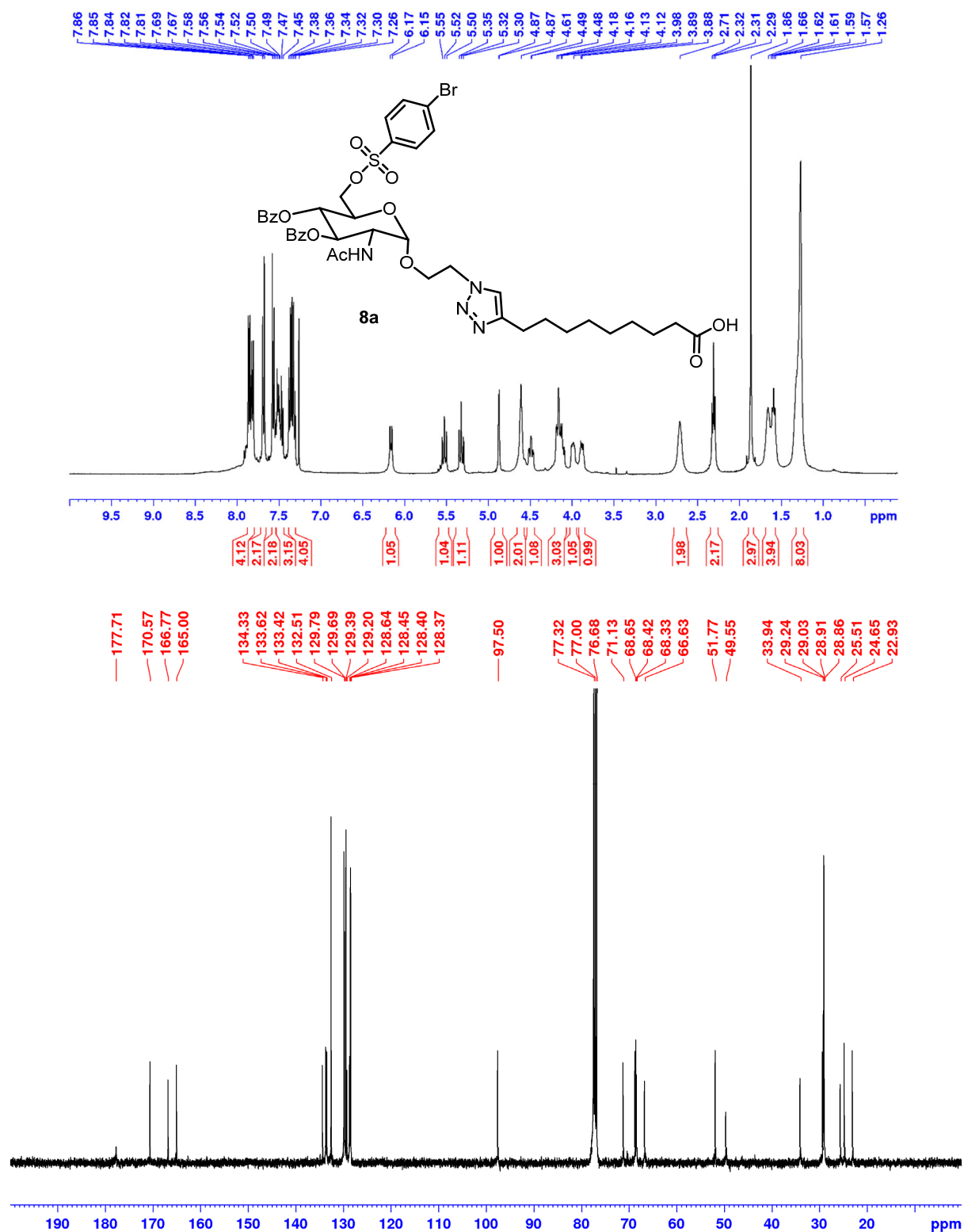
¹H NMR and ¹³C NMR spectra of compound **7a** in CDCl₃



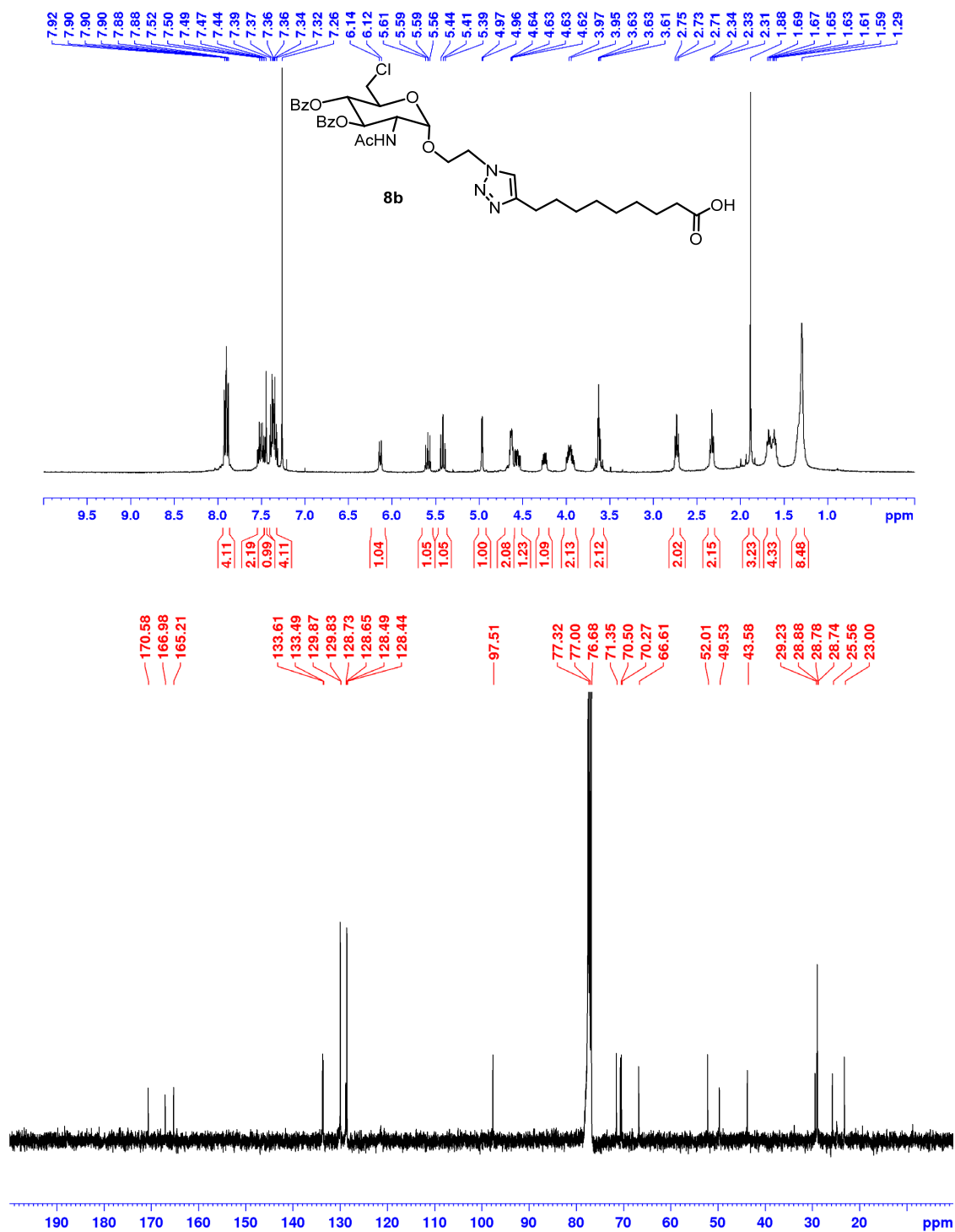
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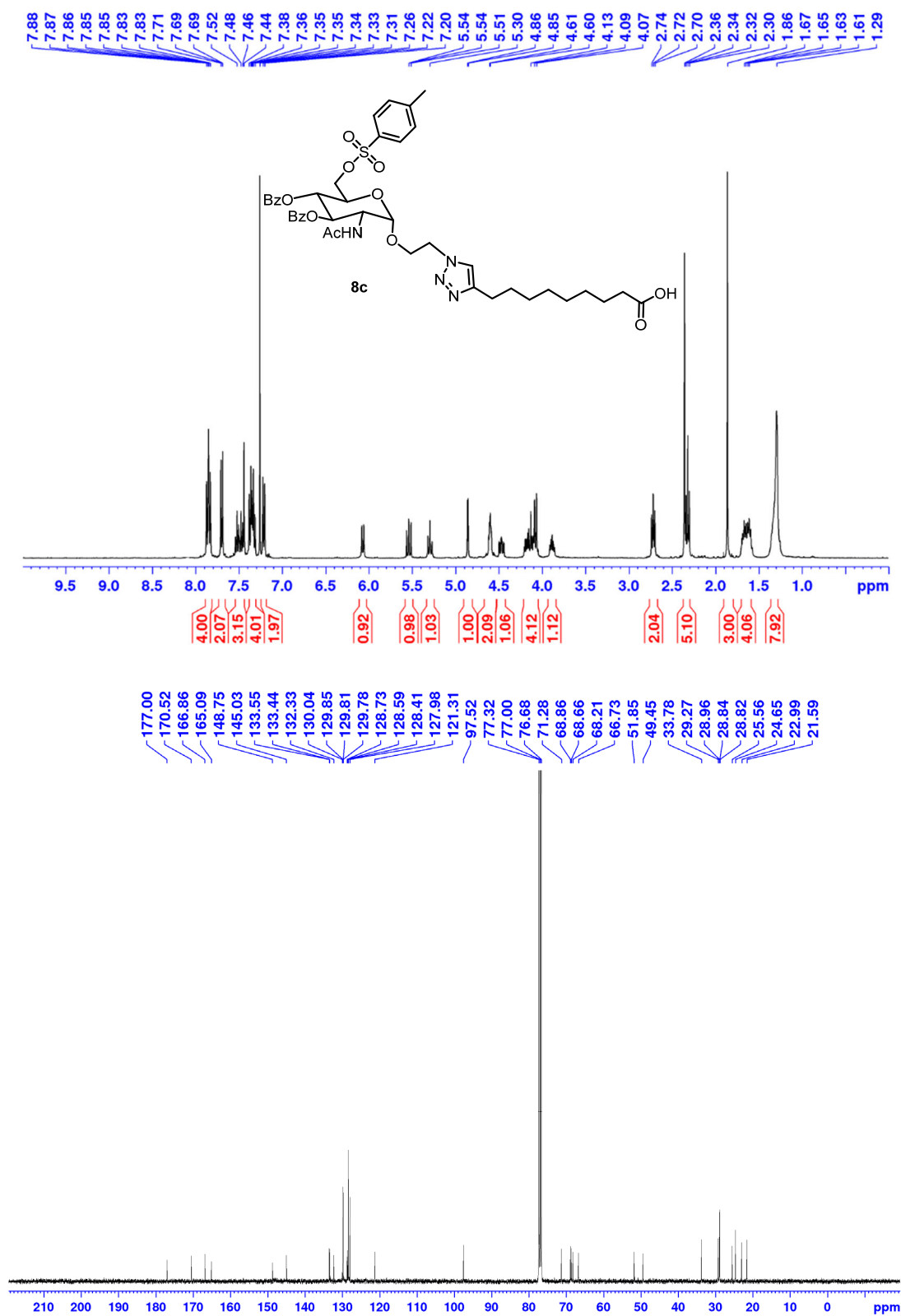
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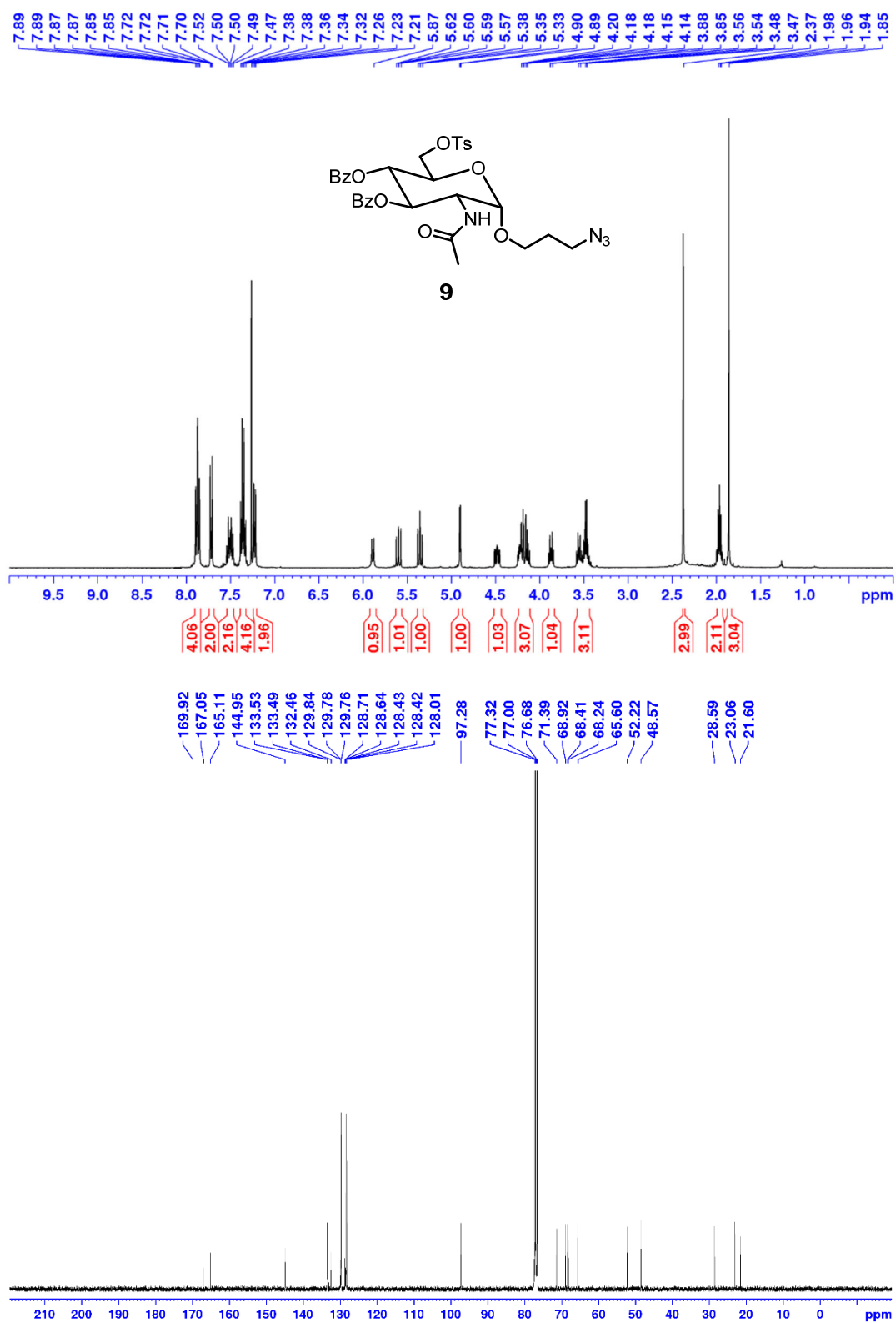
¹H NMR and ¹³C NMR spectra of compound **8a** in CDCl₃



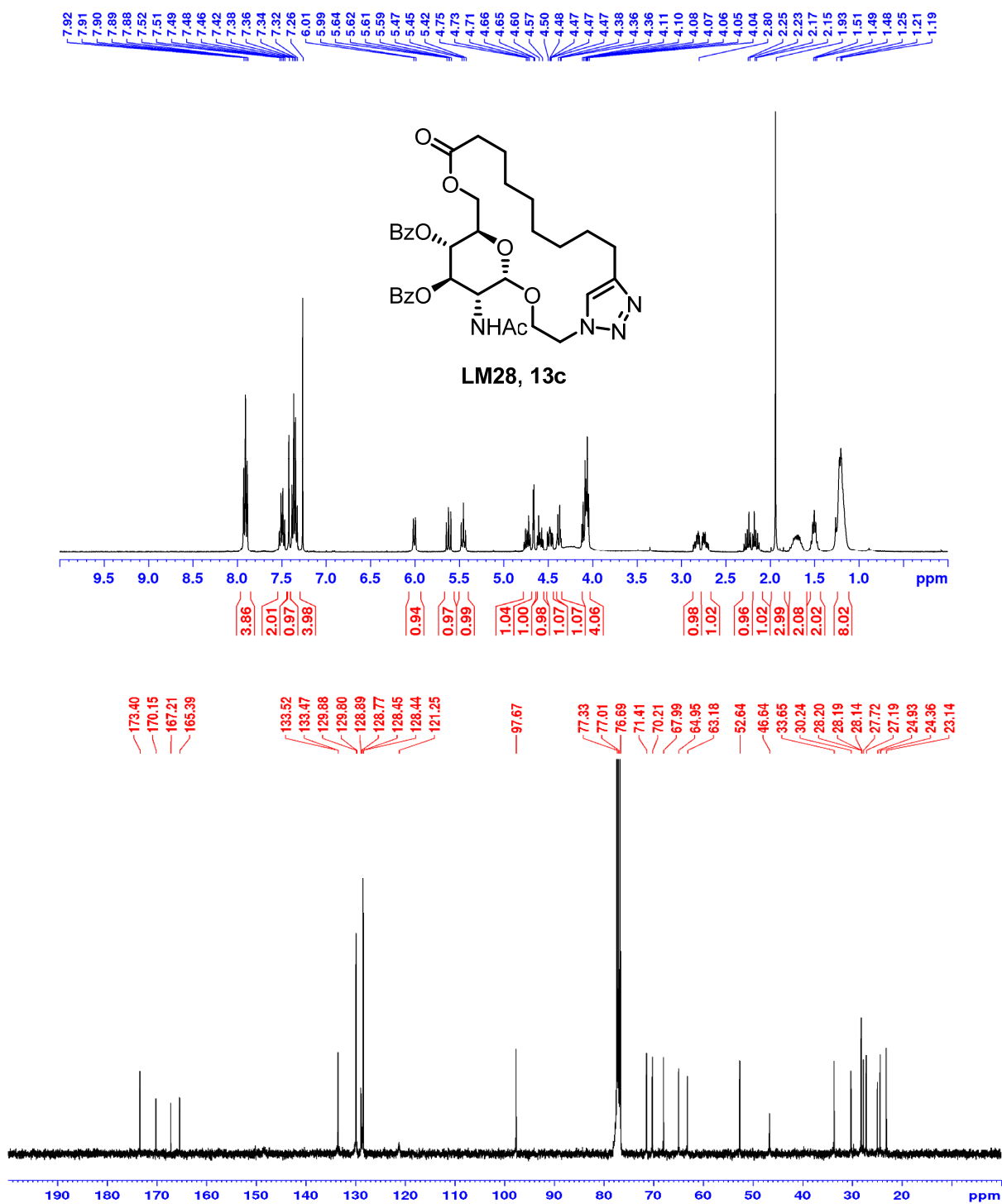
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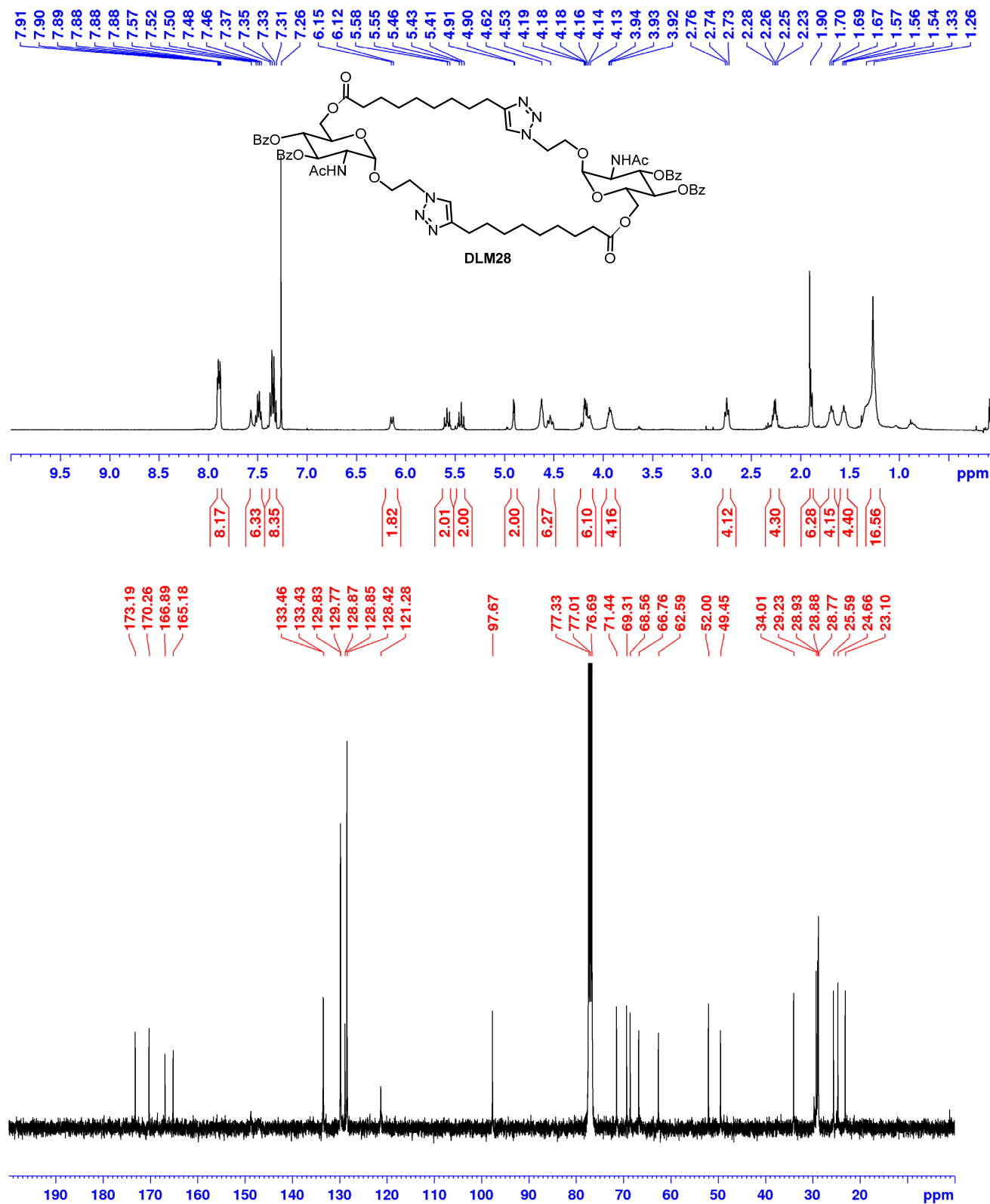
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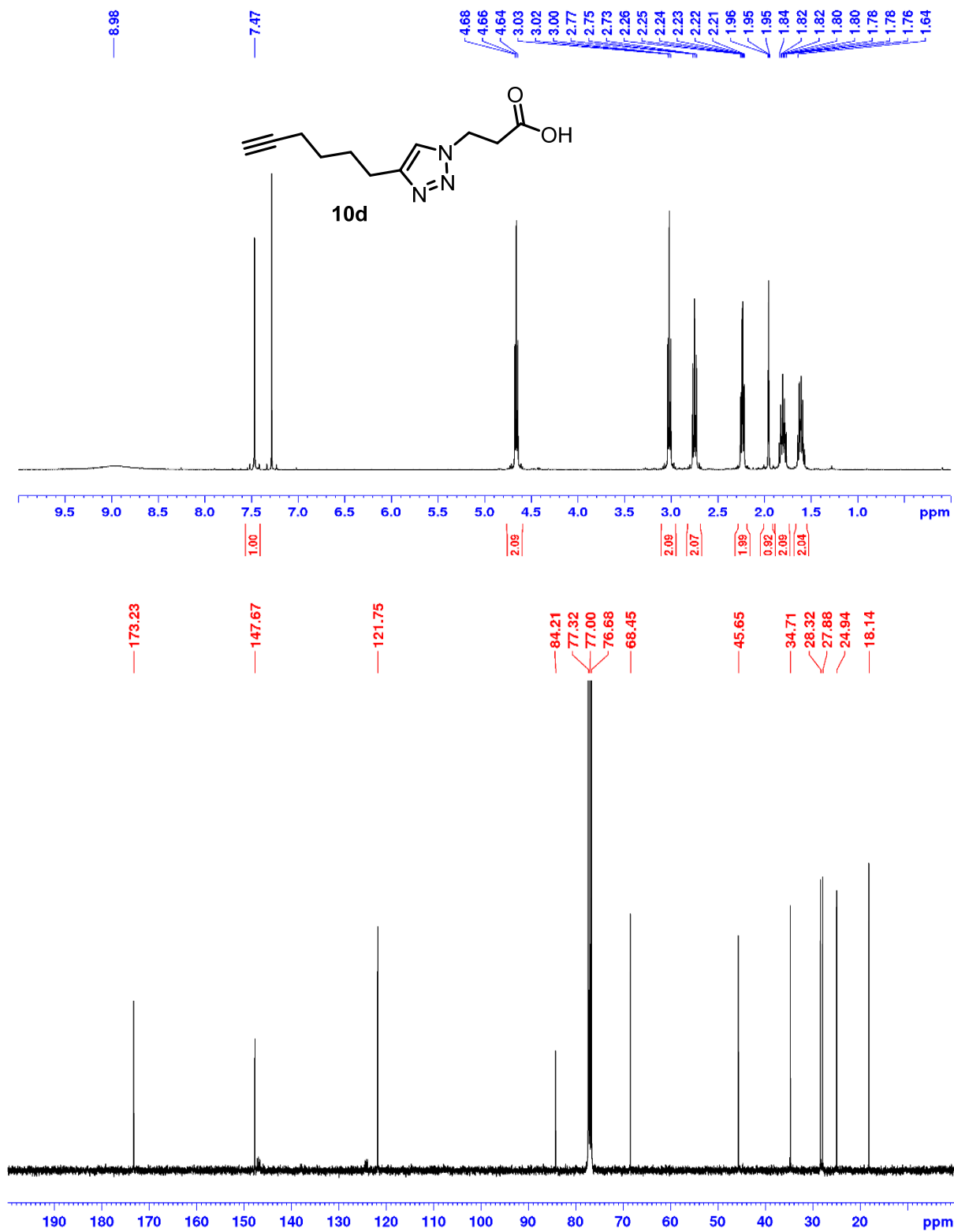
¹H NMR and ¹³C NMR spectra of compound **9** in CDCl₃



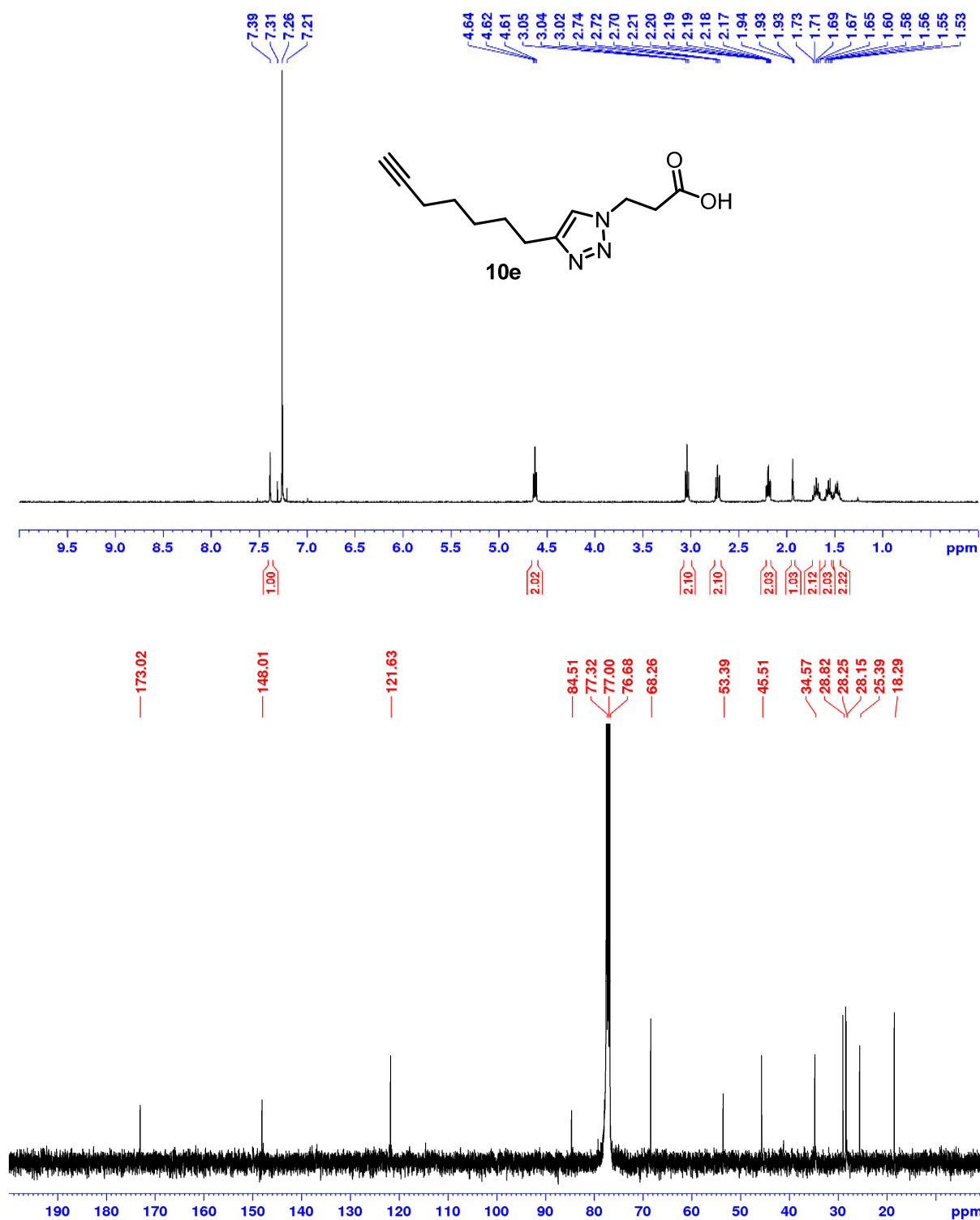
¹H NMR and ¹³C NMR spectra of compound **LM28, 13c** in CDCl₃



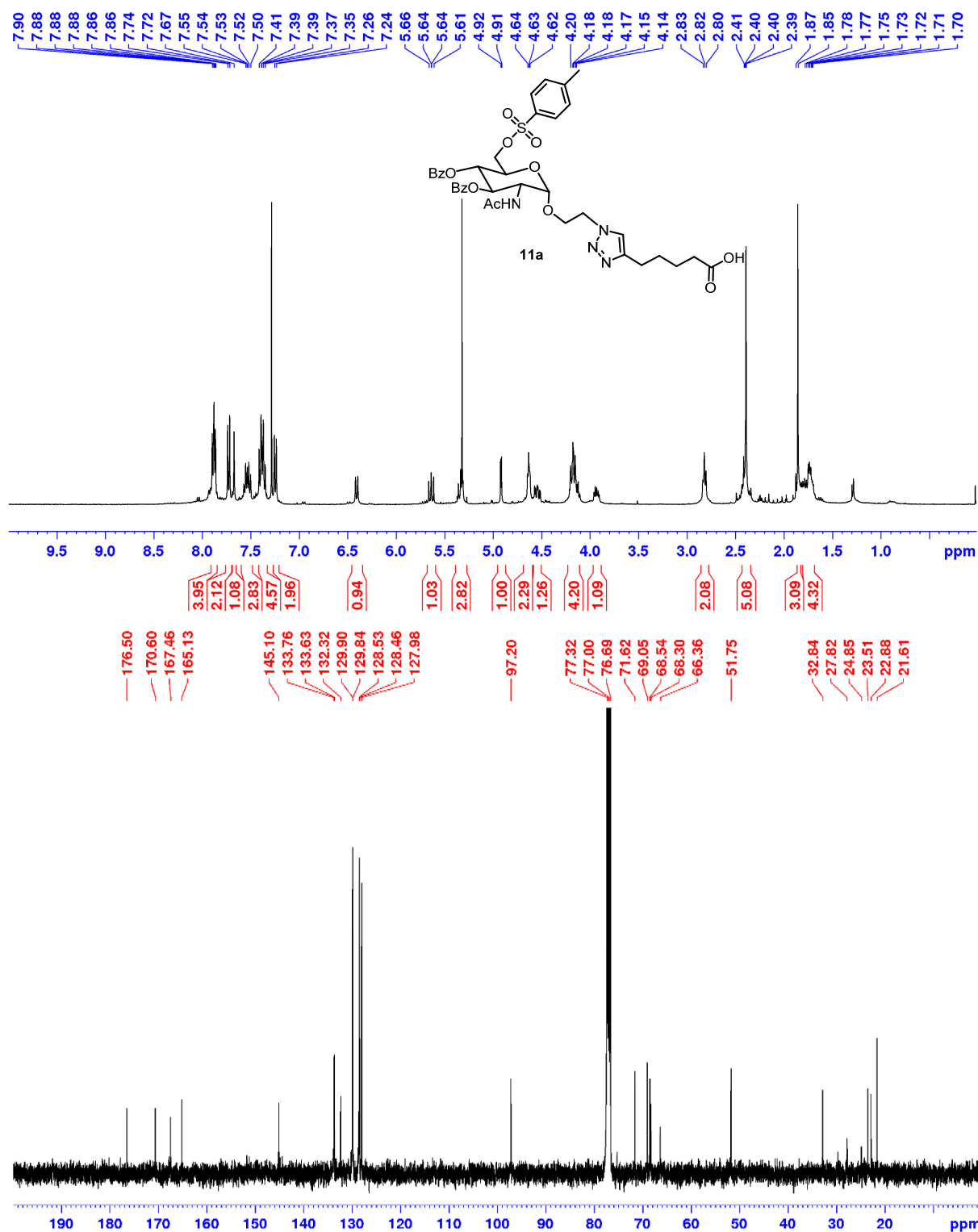
¹H NMR and ¹³C NMR spectra of compound **DLM28** in CDCl₃



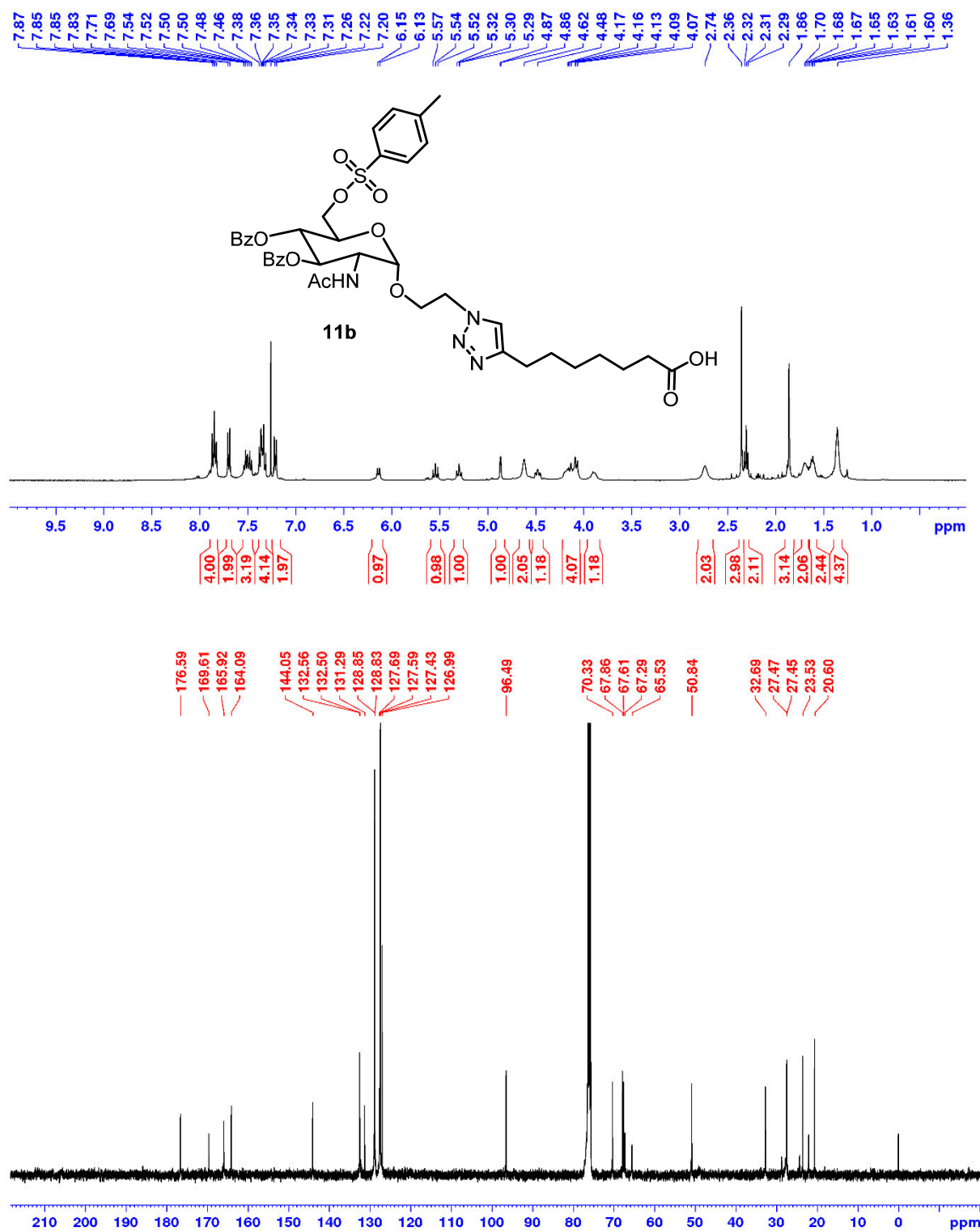
^1H NMR and ^{13}C NMR spectra of compound **10d** in CDCl₃



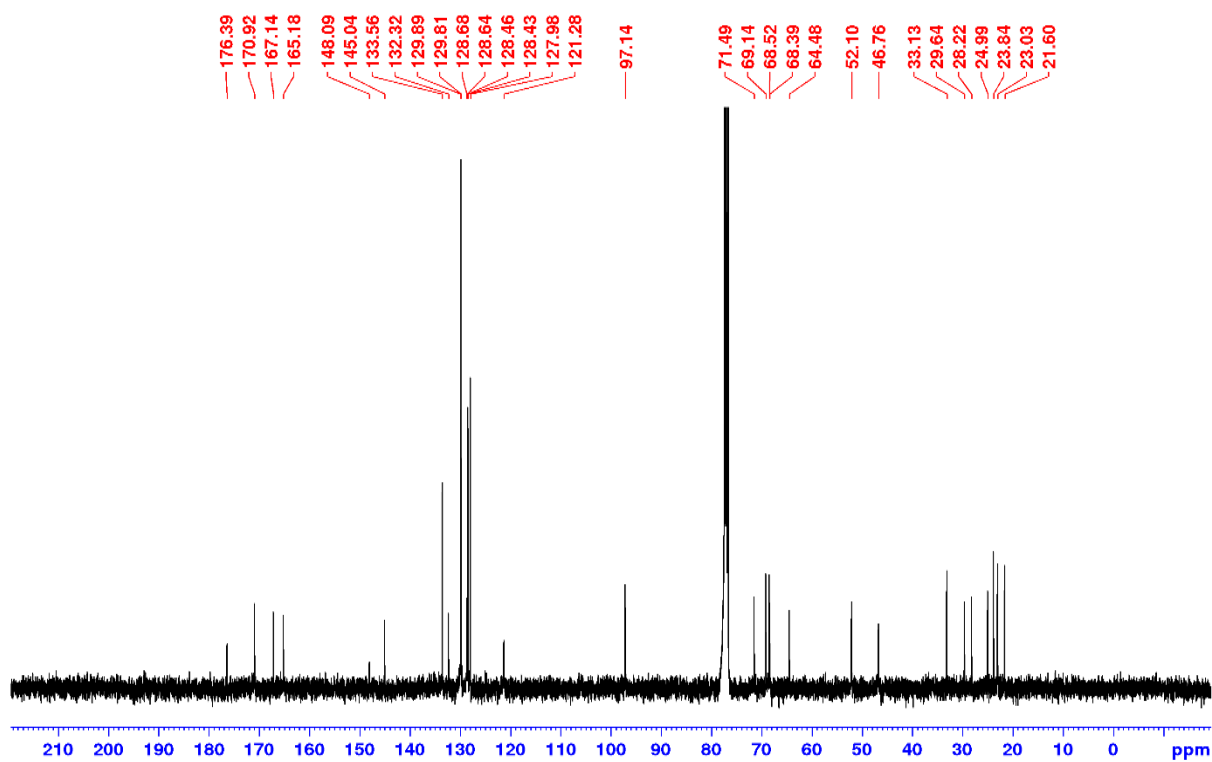
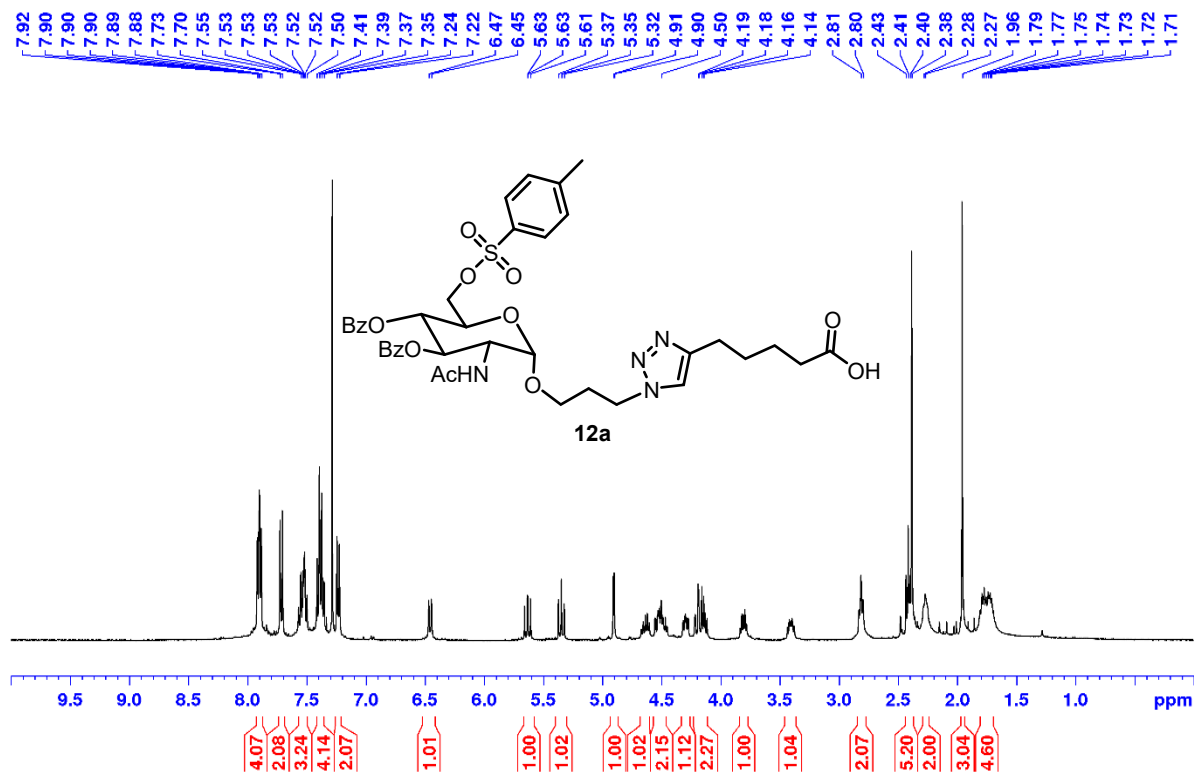
¹H NMR and ¹³C NMR spectra of compound **10e** in CDCl₃



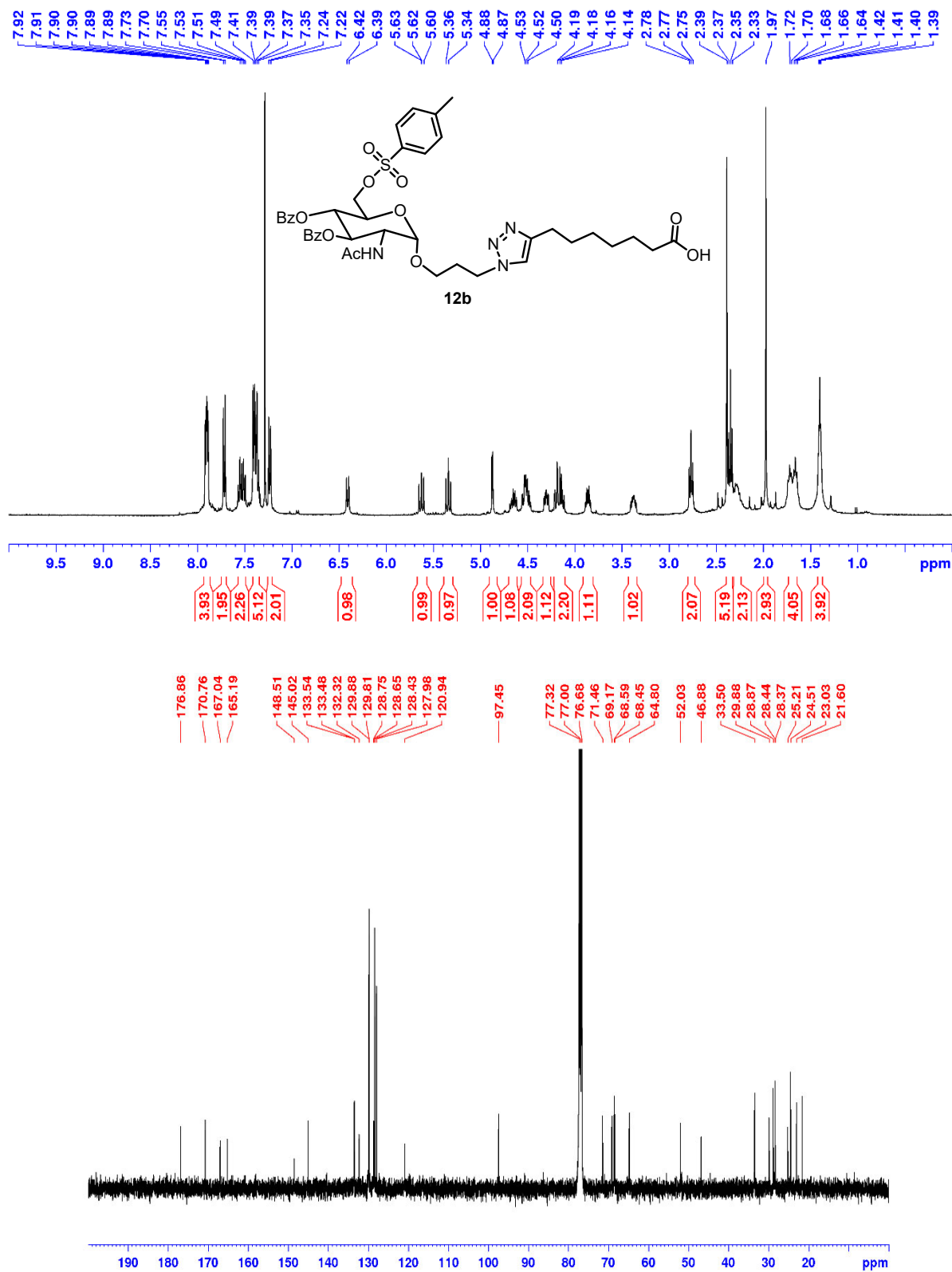
^1H NMR and ^{13}C NMR spectra of compound **11a** in CDCl_3



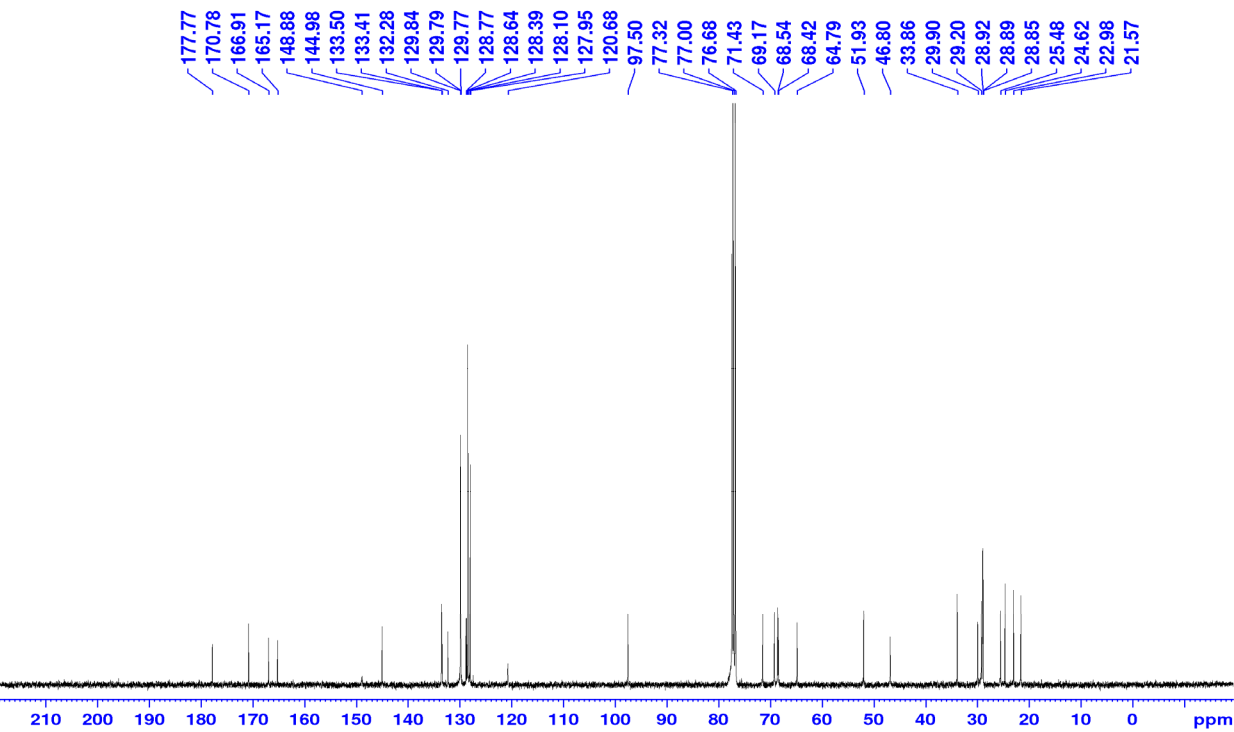
¹H NMR and ¹³C NMR spectra of compound **11b** in CDCl₃



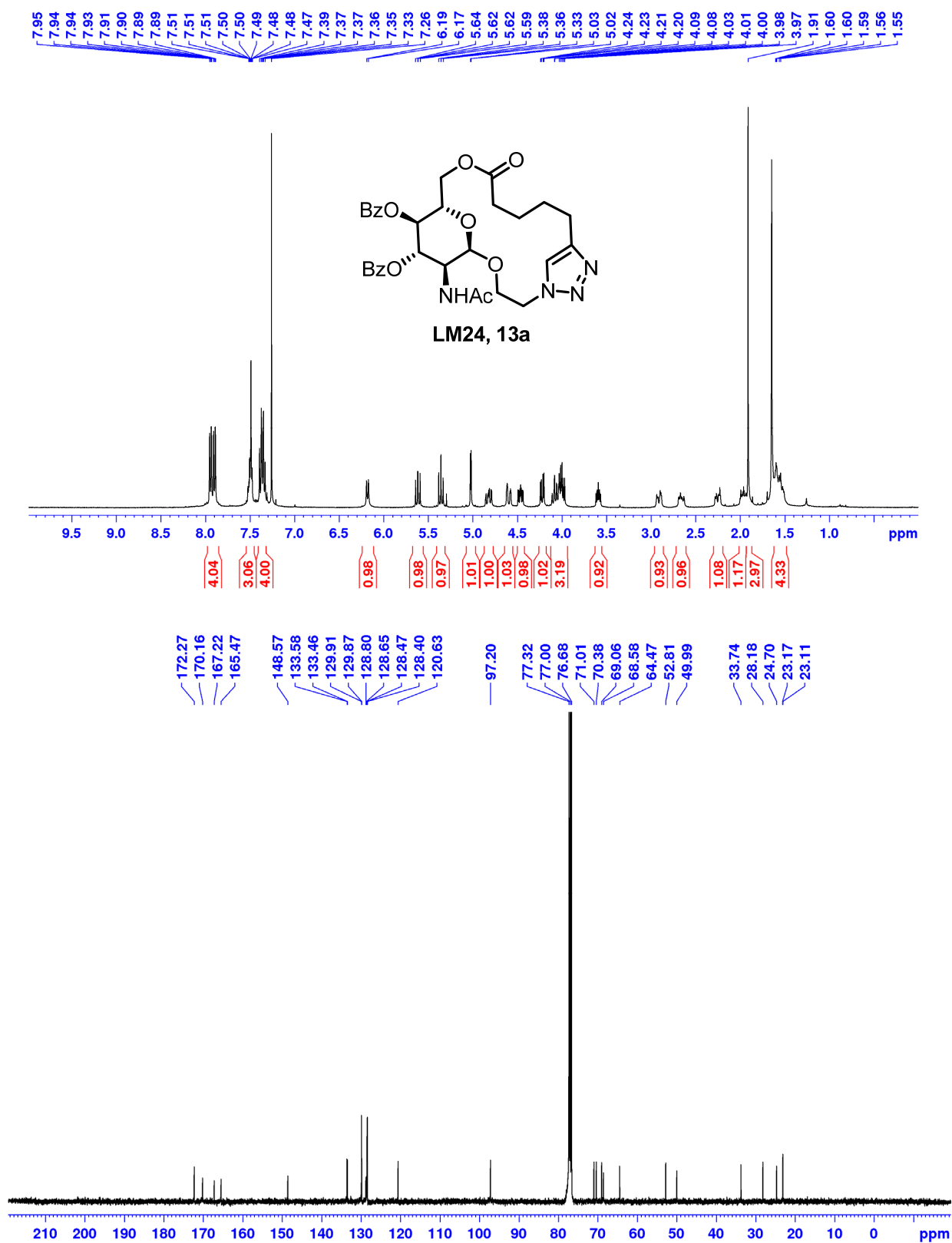
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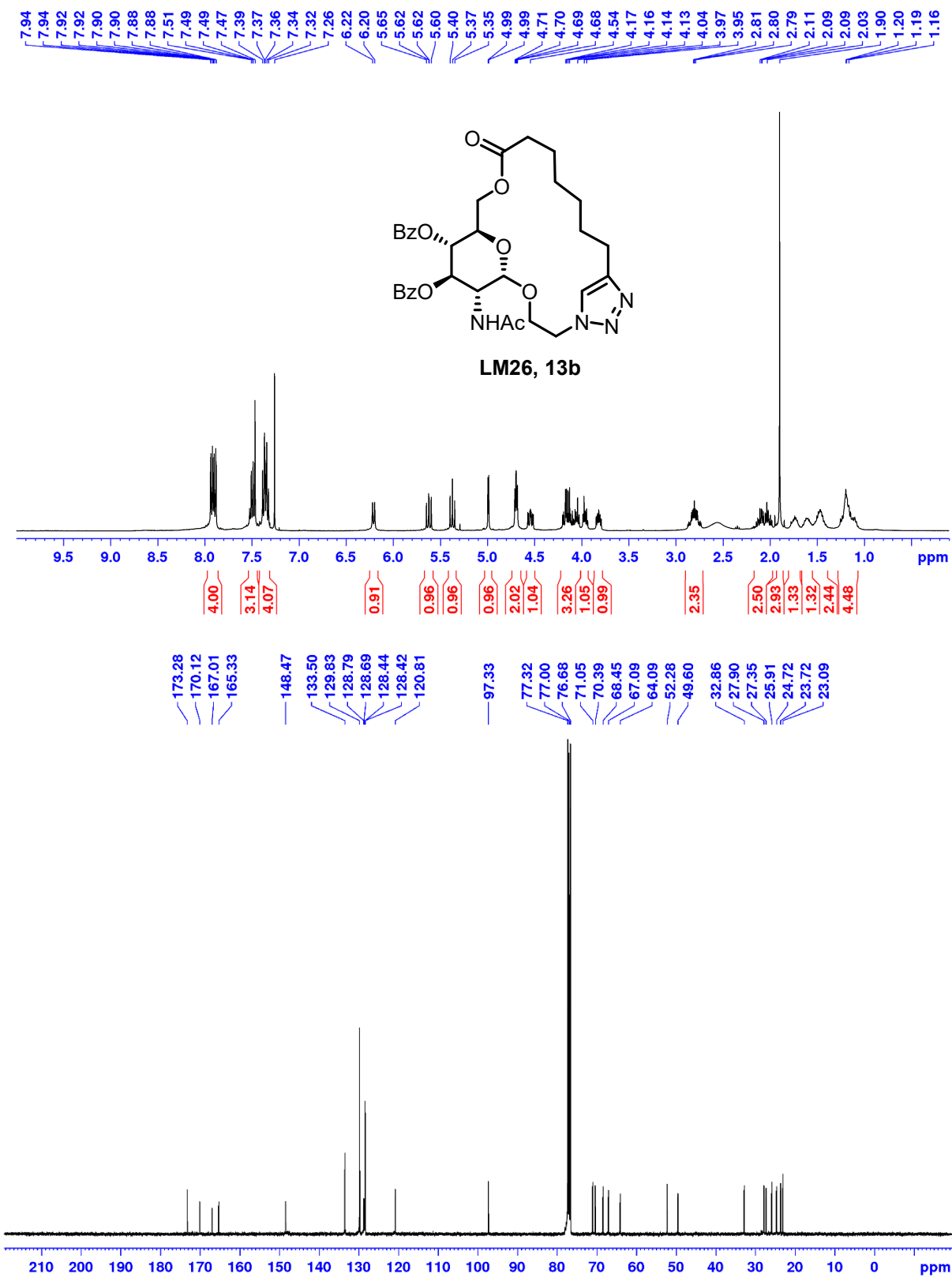


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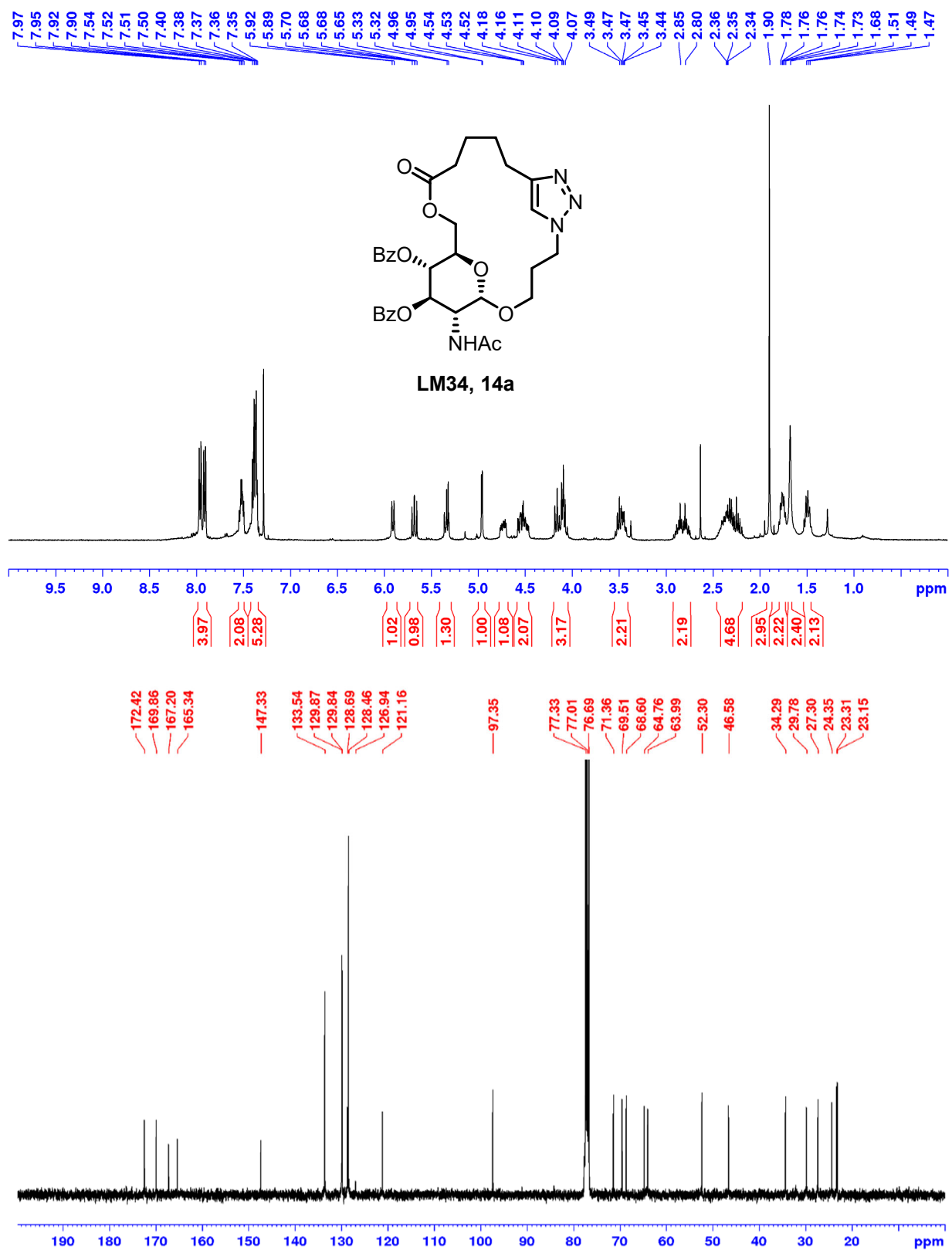


¹H NMR and ¹³C NMR spectra of compound **12c** in CDCl₃

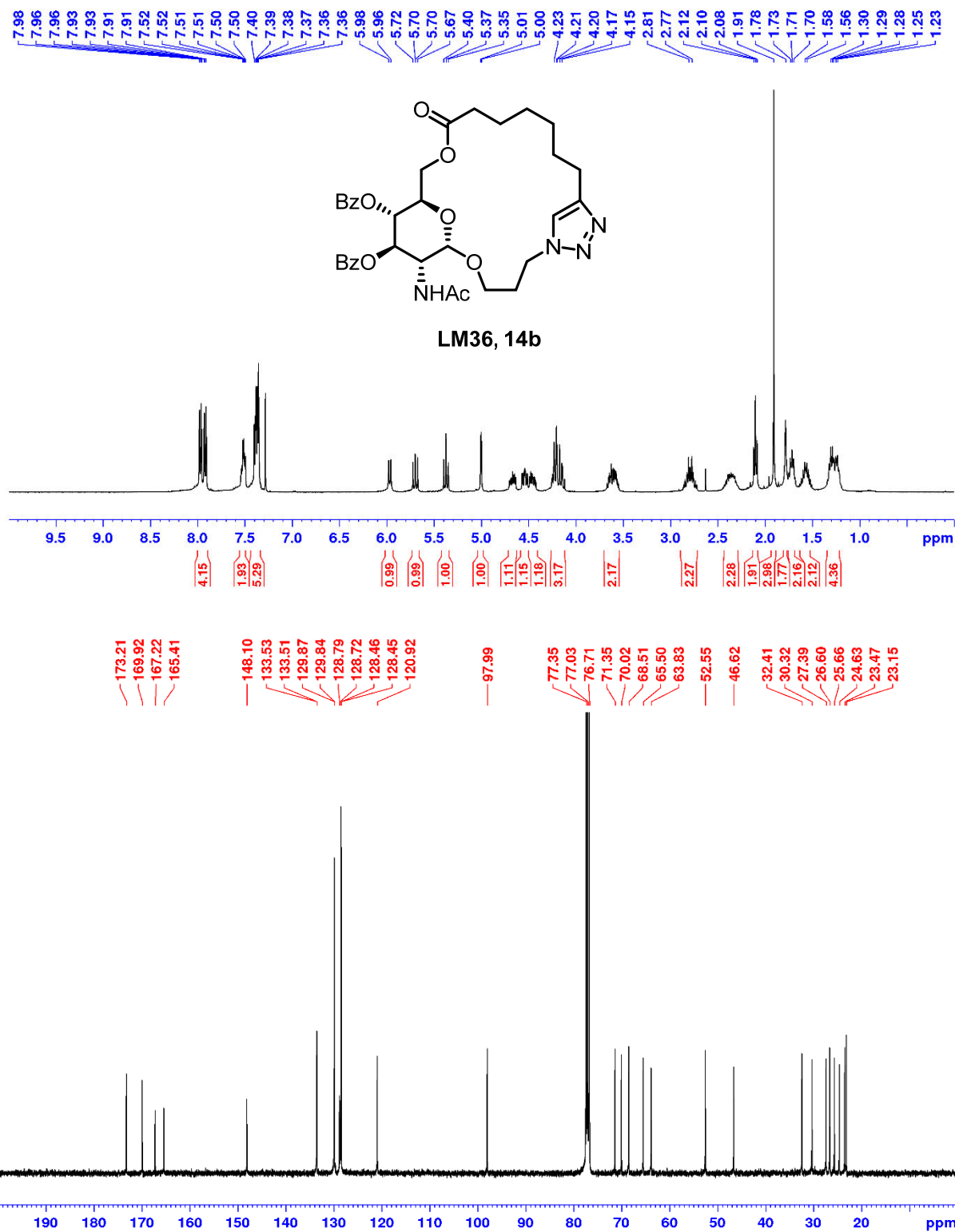




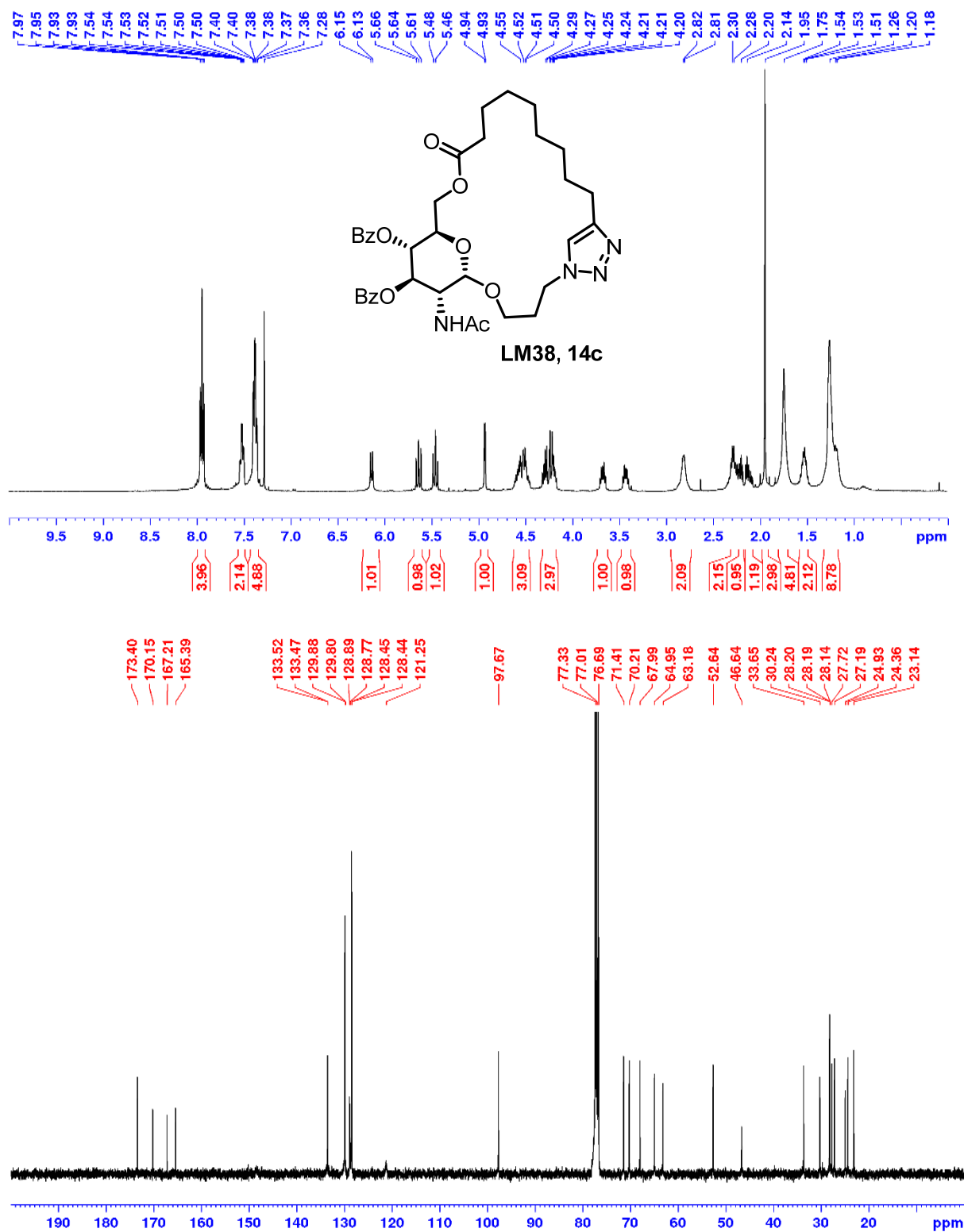
¹H NMR and ¹³C NMR spectra of compound **LM26, 13b** in CDCl₃



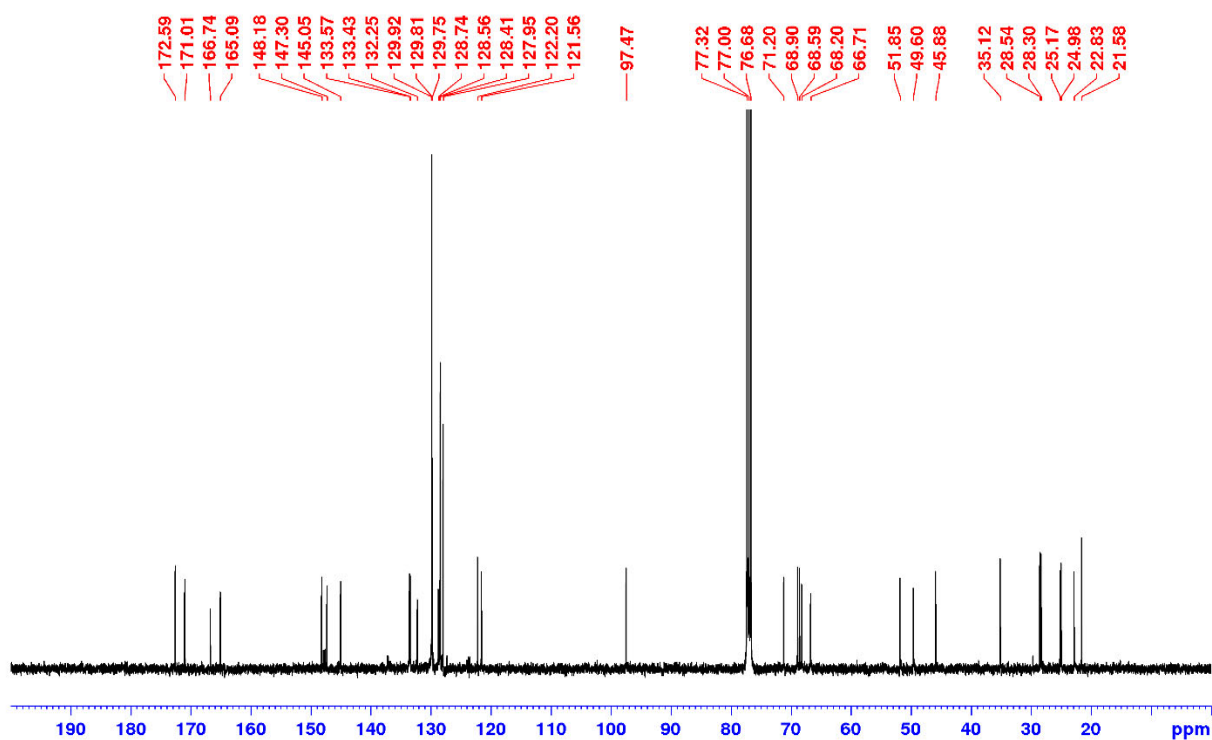
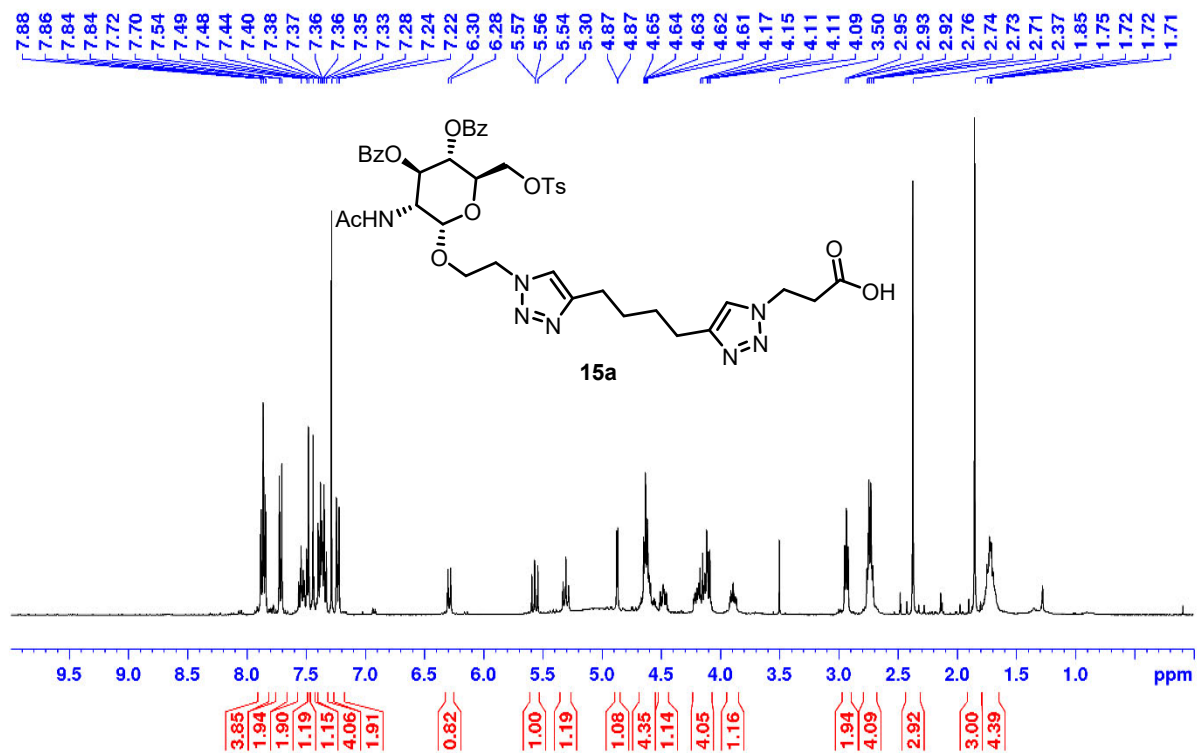
¹H NMR and ¹³C NMR spectra of compound **LM34, 14a** in CDCl₃



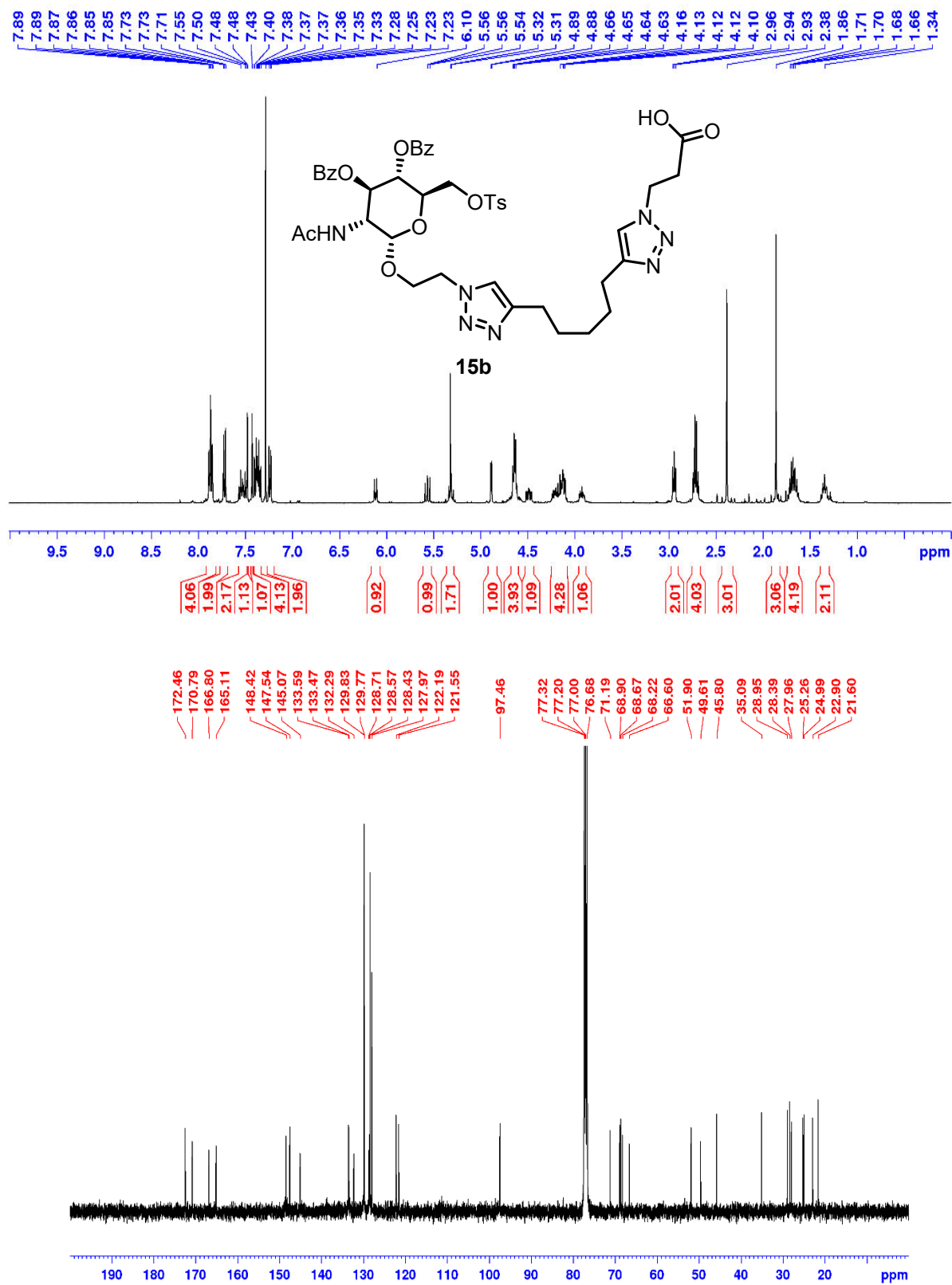
¹H NMR and ¹³C NMR spectra of compound **LM36, 14b** in CDCl₃



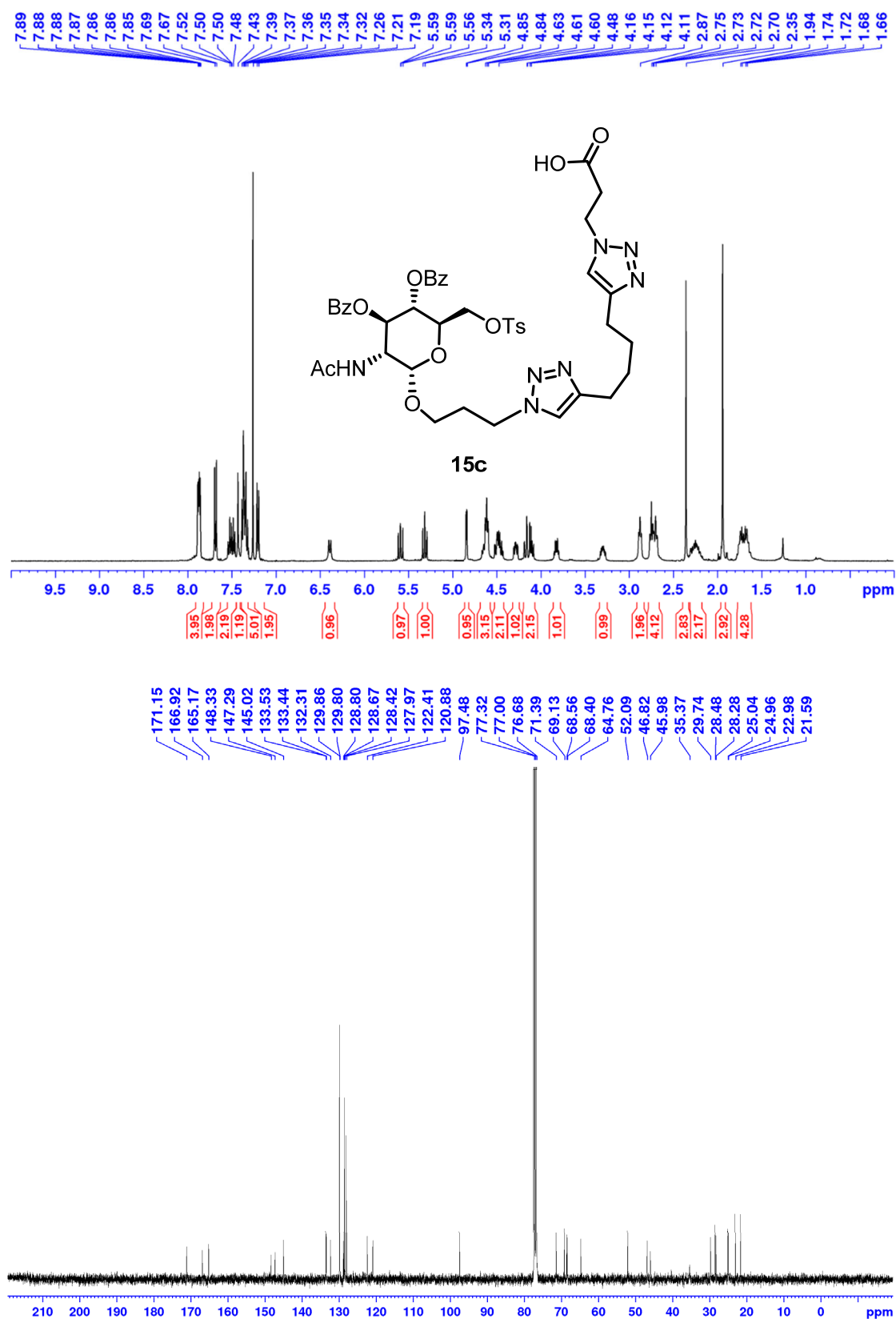
¹H NMR and ¹³C NMR spectra of compound **LM38, 14c** in CDCl₃



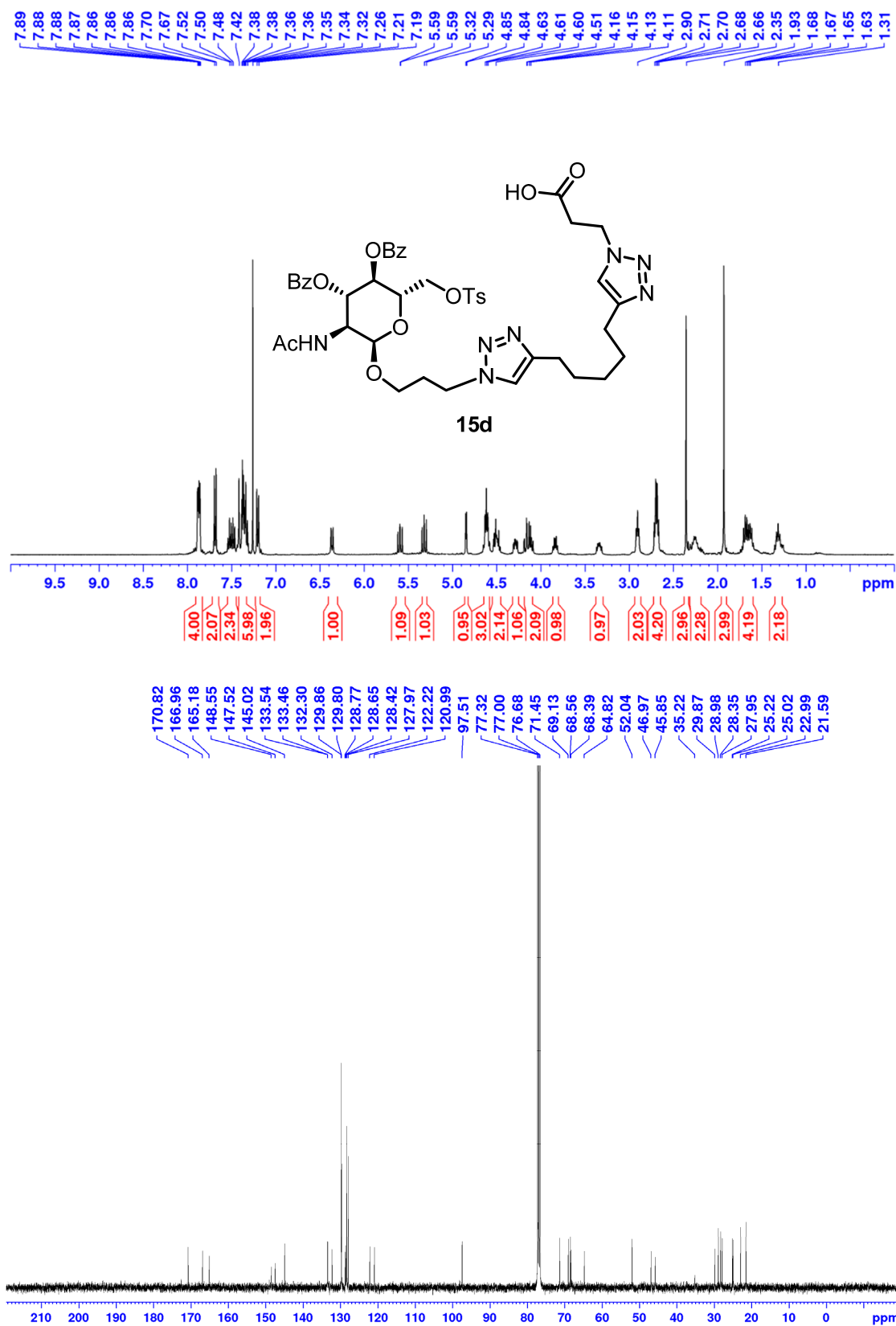
¹H NMR and ¹³C NMR spectra of compound **15a** in CDCl₃



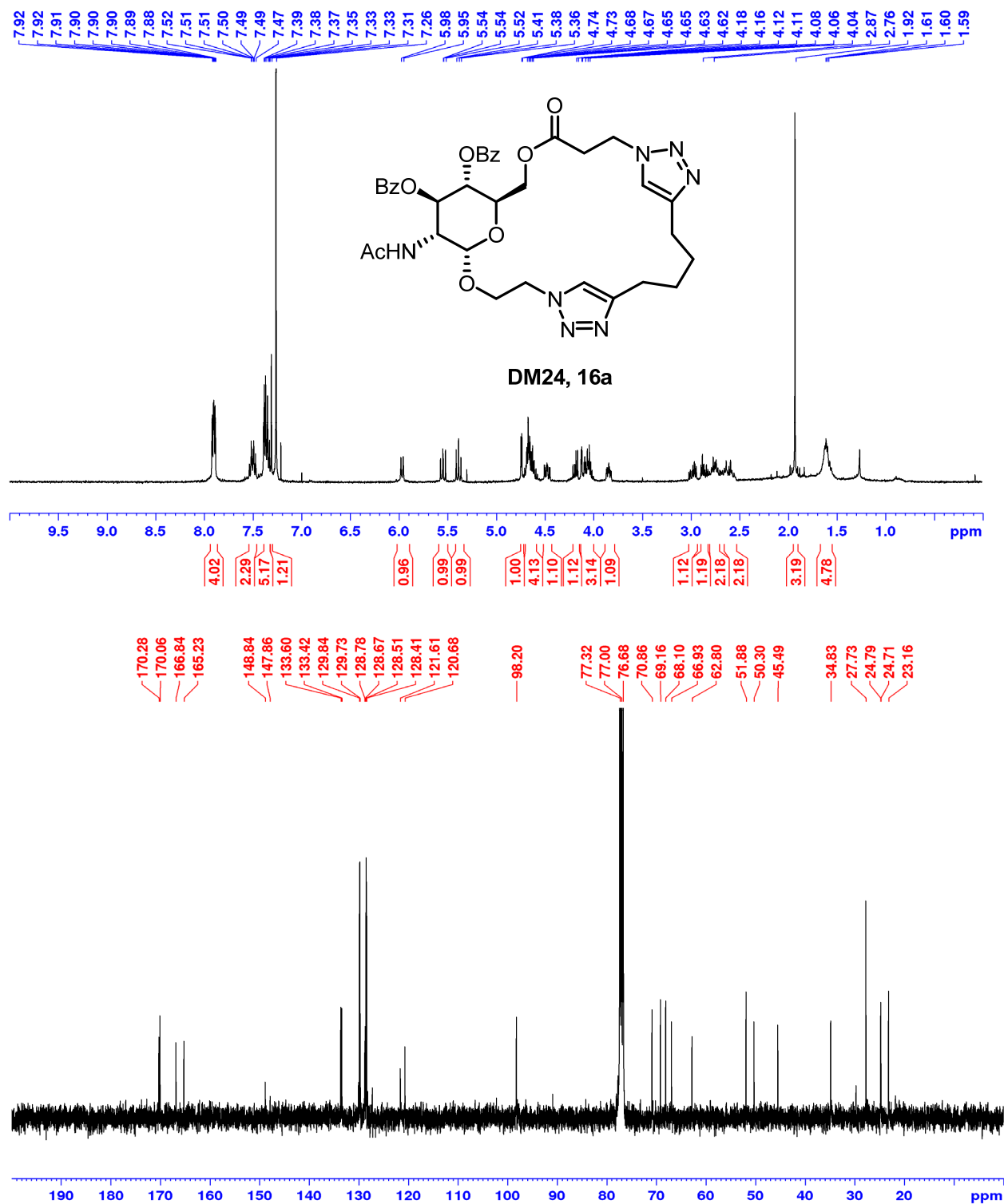
¹H NMR and ¹³C NMR spectra of compound **15b** in CDCl₃



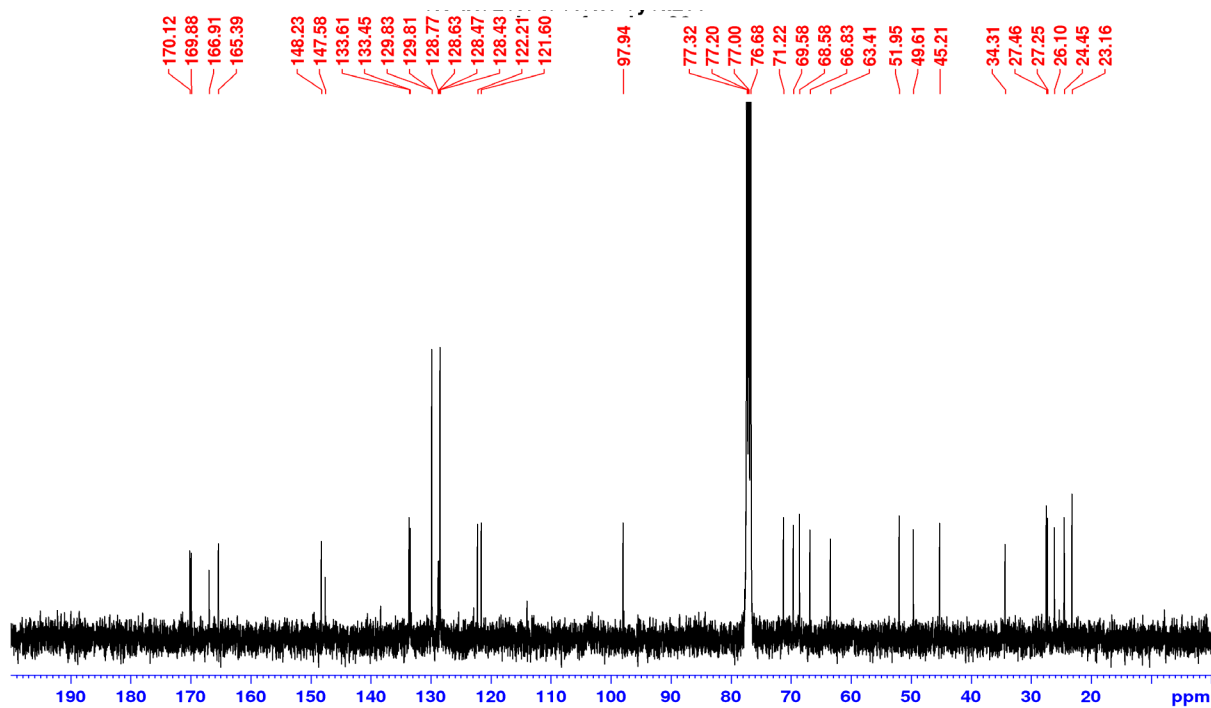
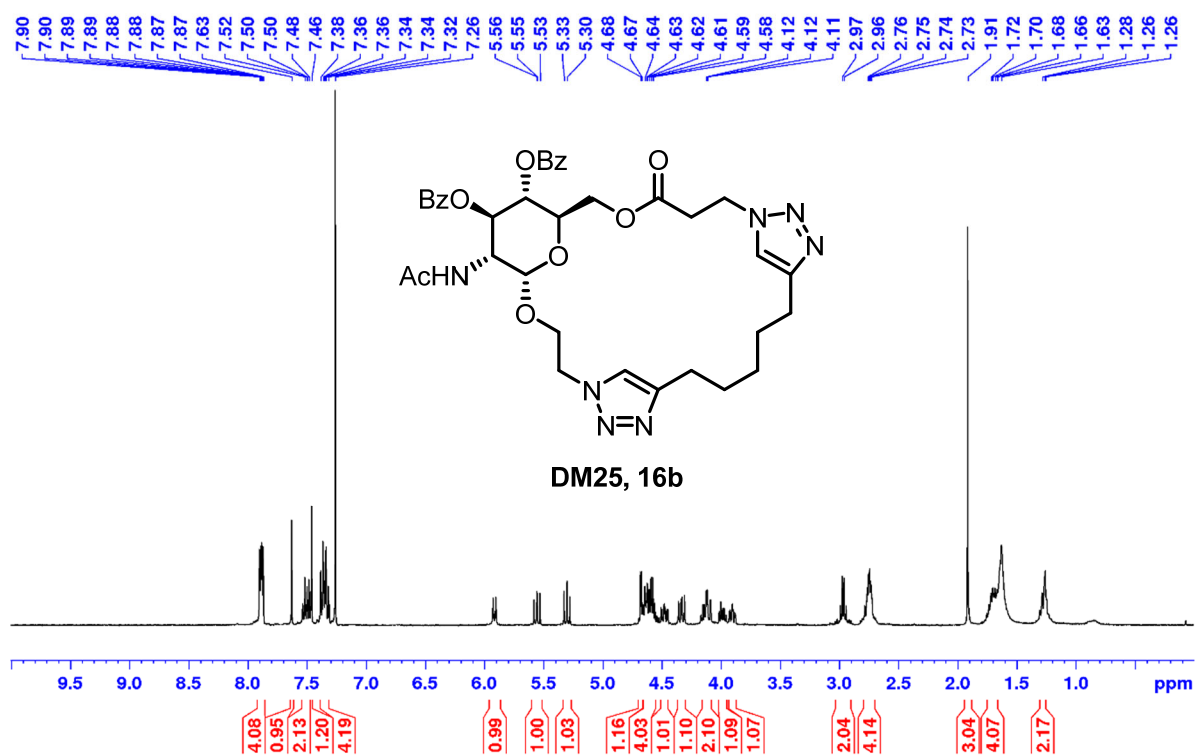
¹H NMR and ¹³C NMR spectra of compound **15c** in CDCl₃



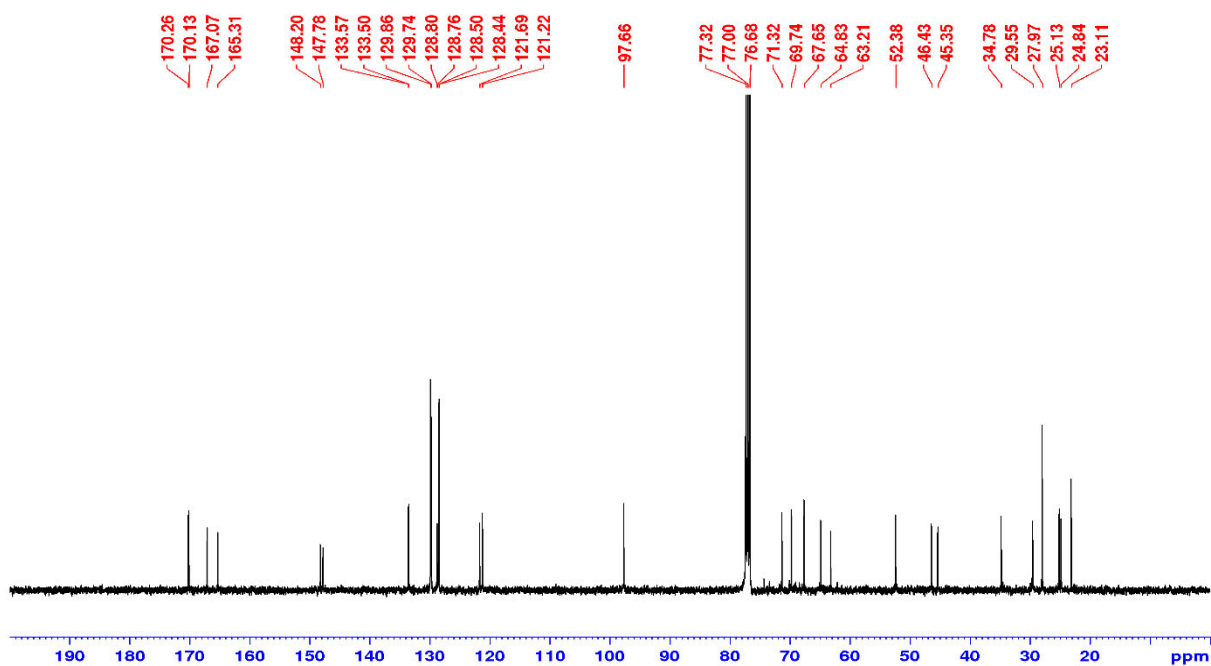
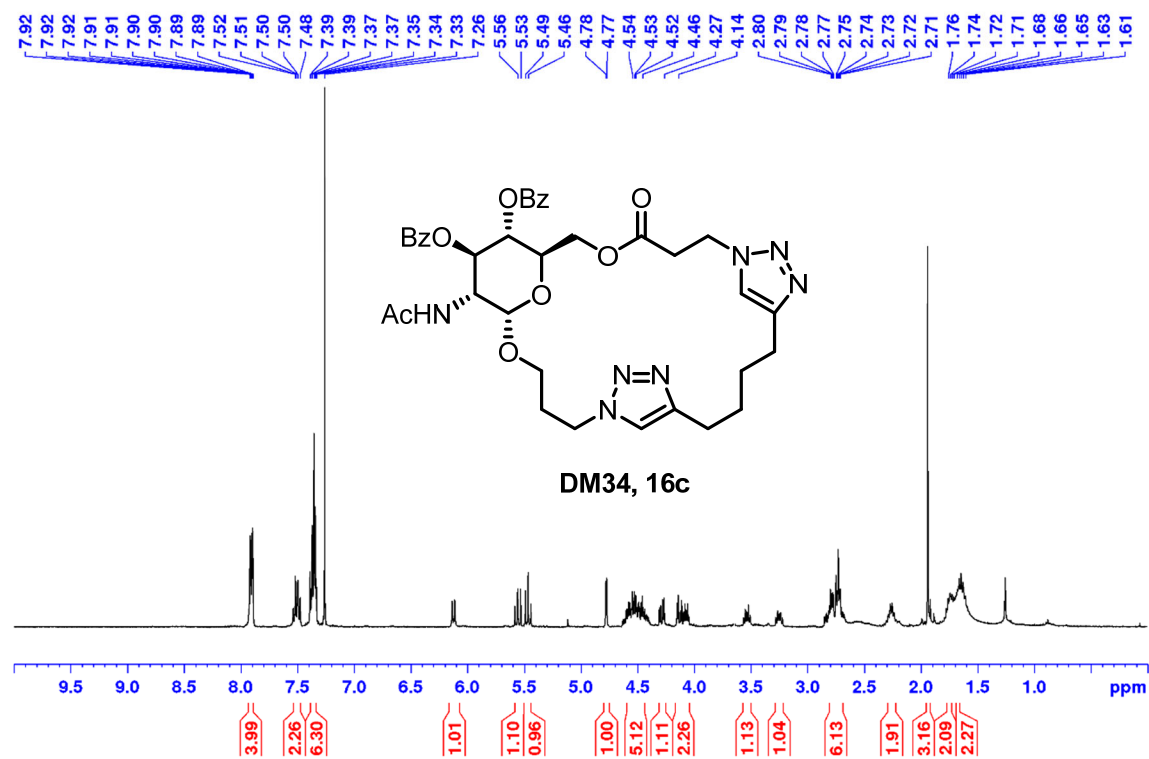
¹H NMR and ¹³C NMR spectra of compound **15d** in CDCl₃



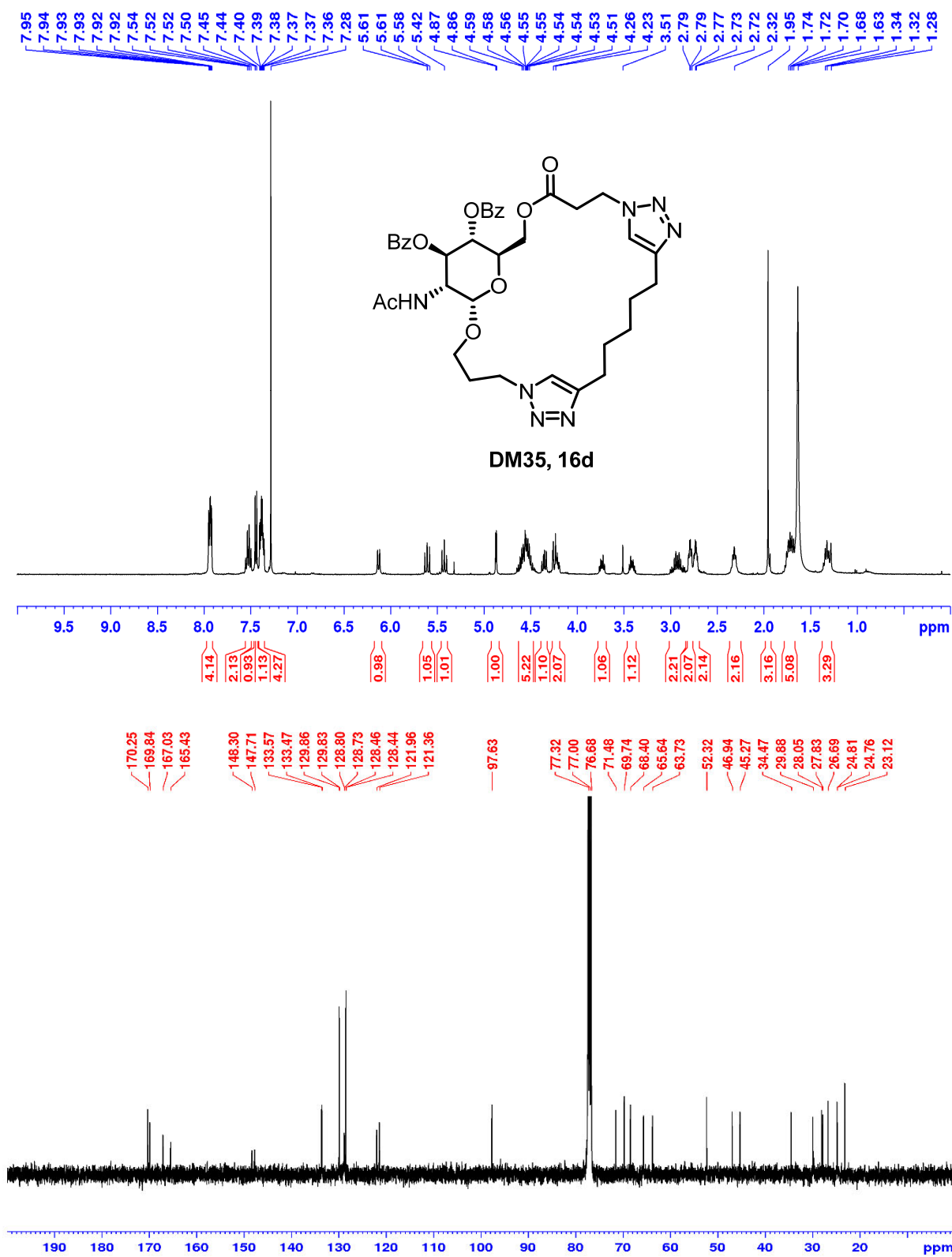
¹H NMR and ¹³C NMR spectra of compound **DM24, 16a** in CDCl₃



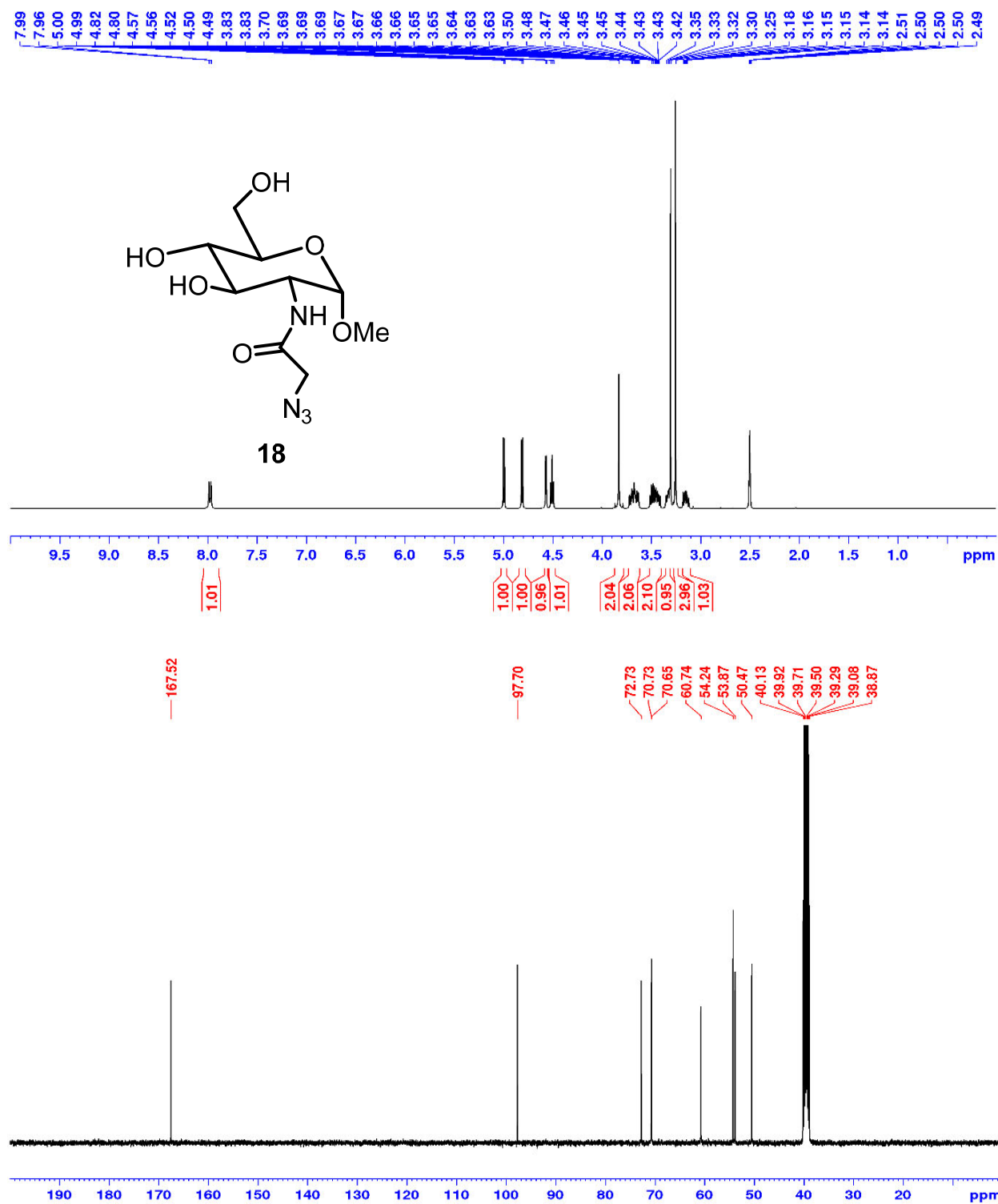
¹H NMR and ¹³C NMR spectra of compound **DM25, 16b** in CDCl₃



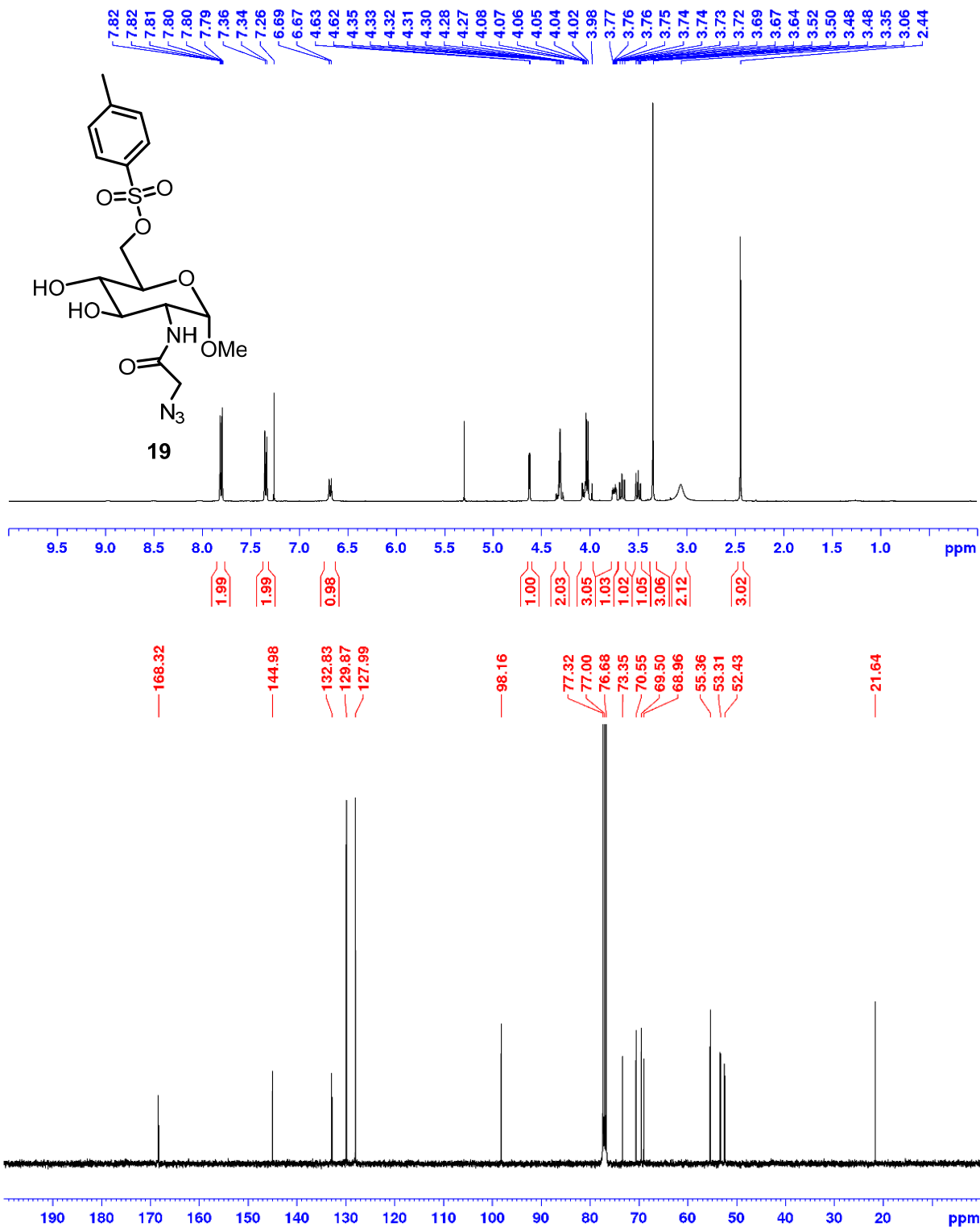
¹H NMR and ¹³C NMR spectra of compound



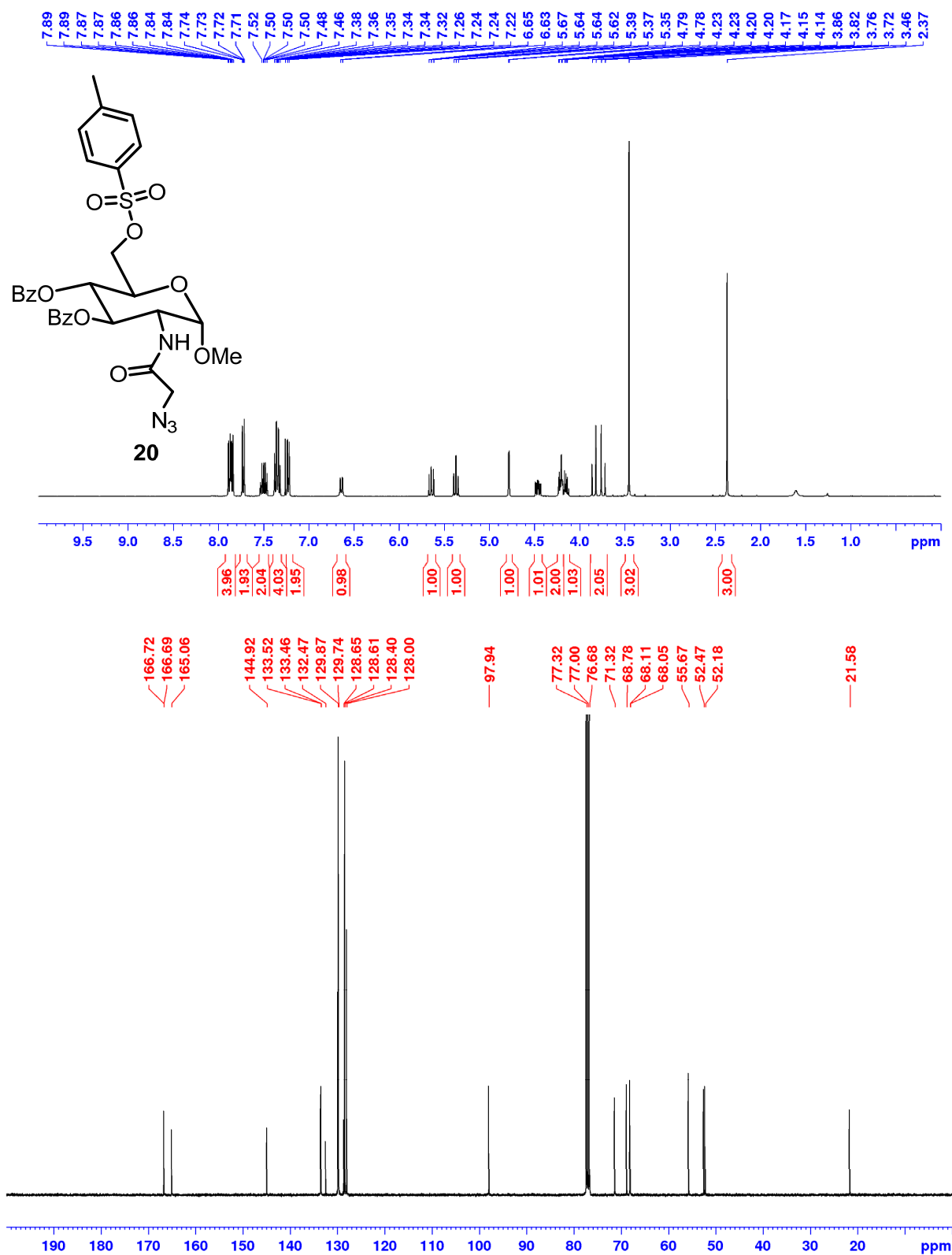
^1H NMR and ^{13}C NMR spectra of compound **DM35, 16d** in CDCl_3



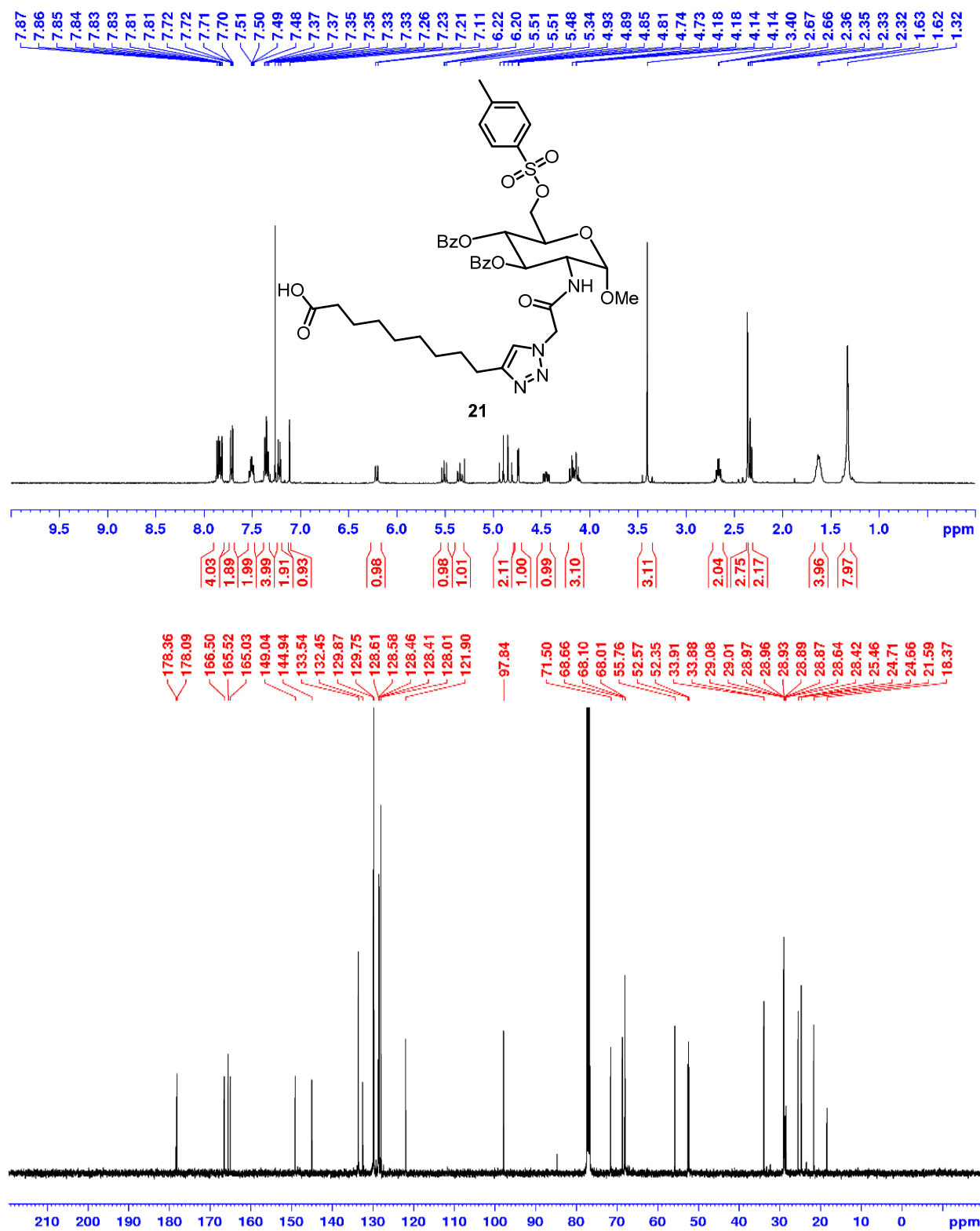
¹H NMR and ¹³C NMR spectra of compound **18** in CDCl₃



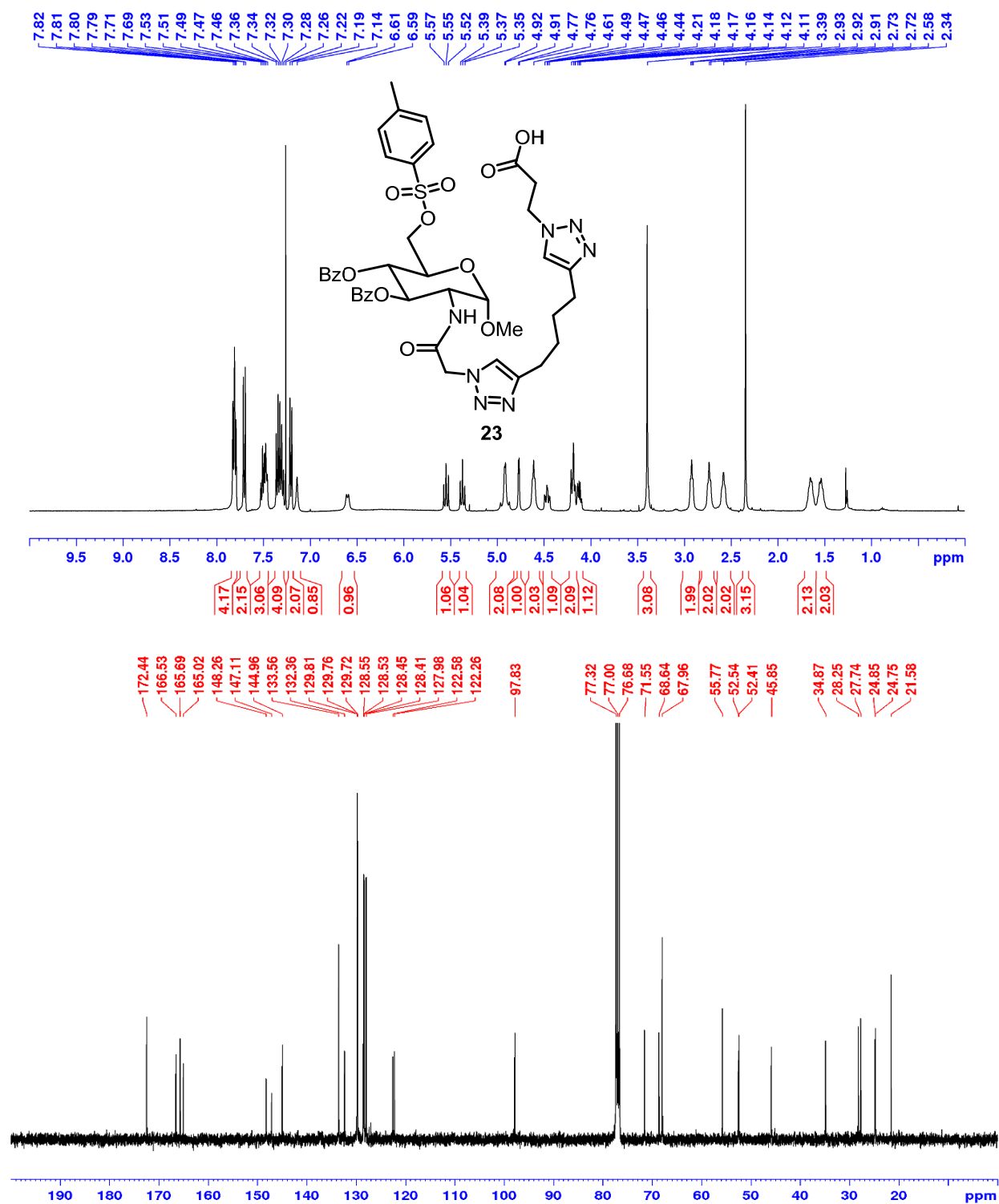
¹H NMR and ¹³C NMR spectra of compound **19** in CDCl₃



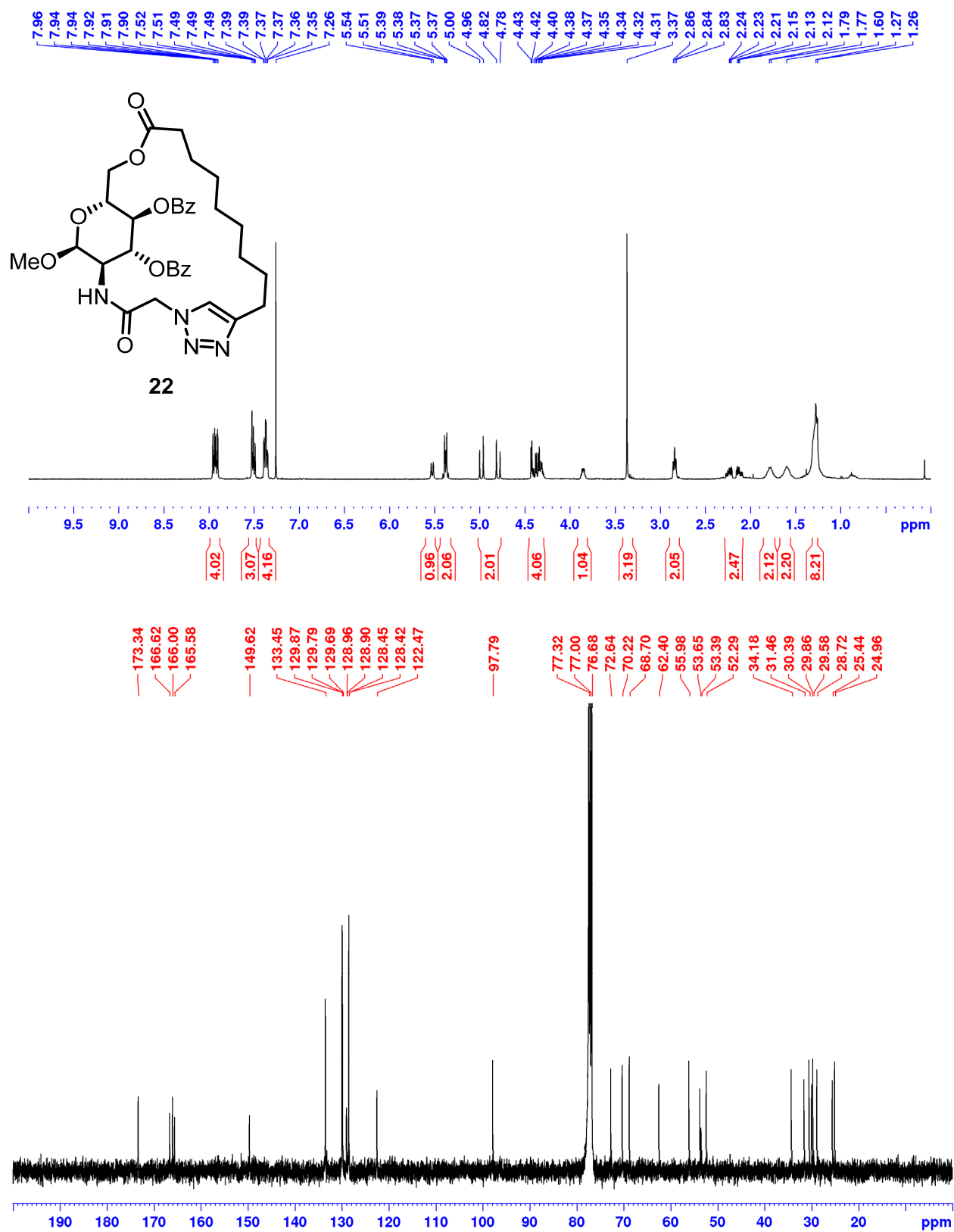
¹H NMR and ¹³C NMR spectra of compound **20** in CDCl₃



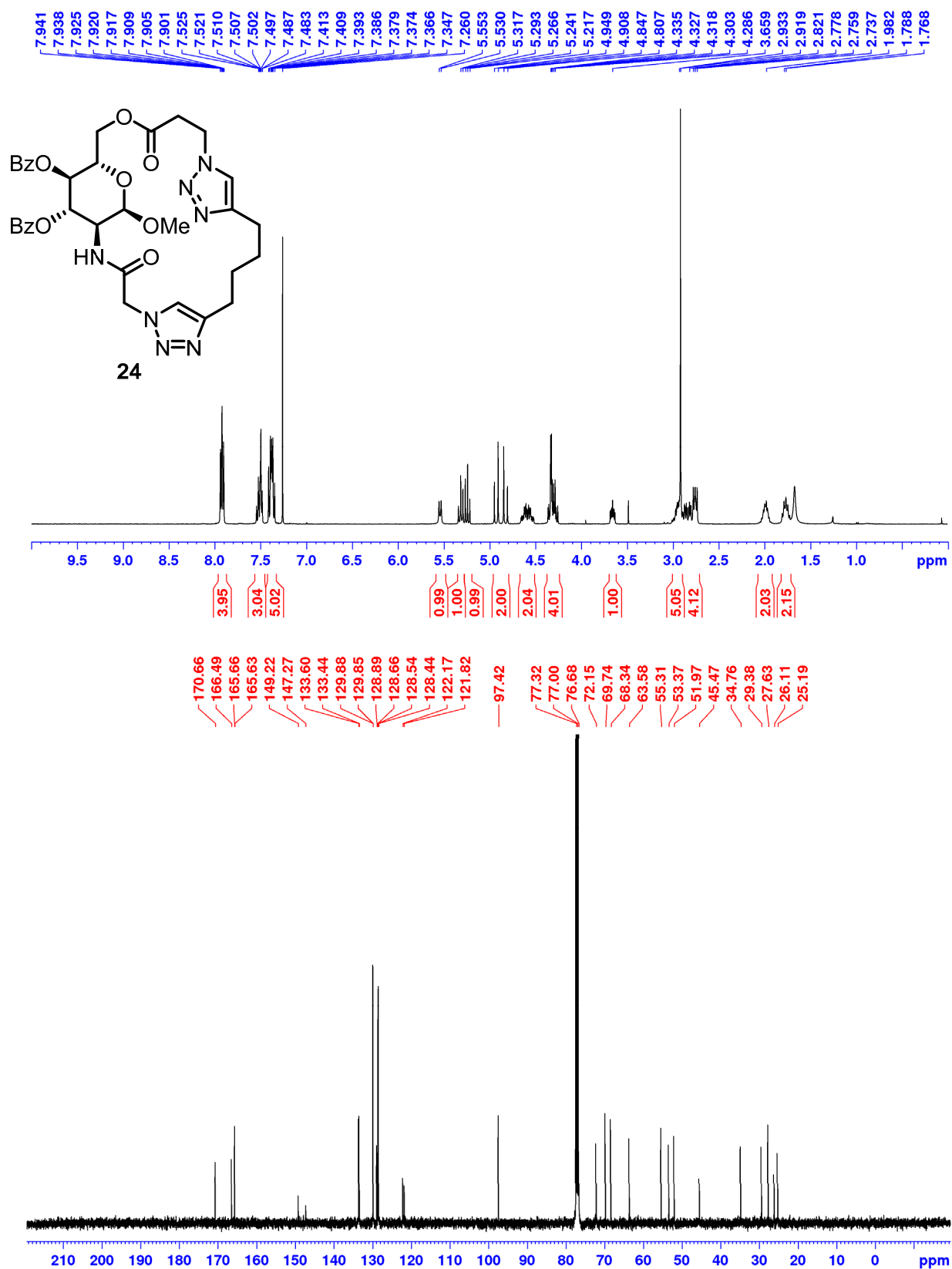
¹H NMR and ¹³C NMR spectra of compound **21** in CDCl₃



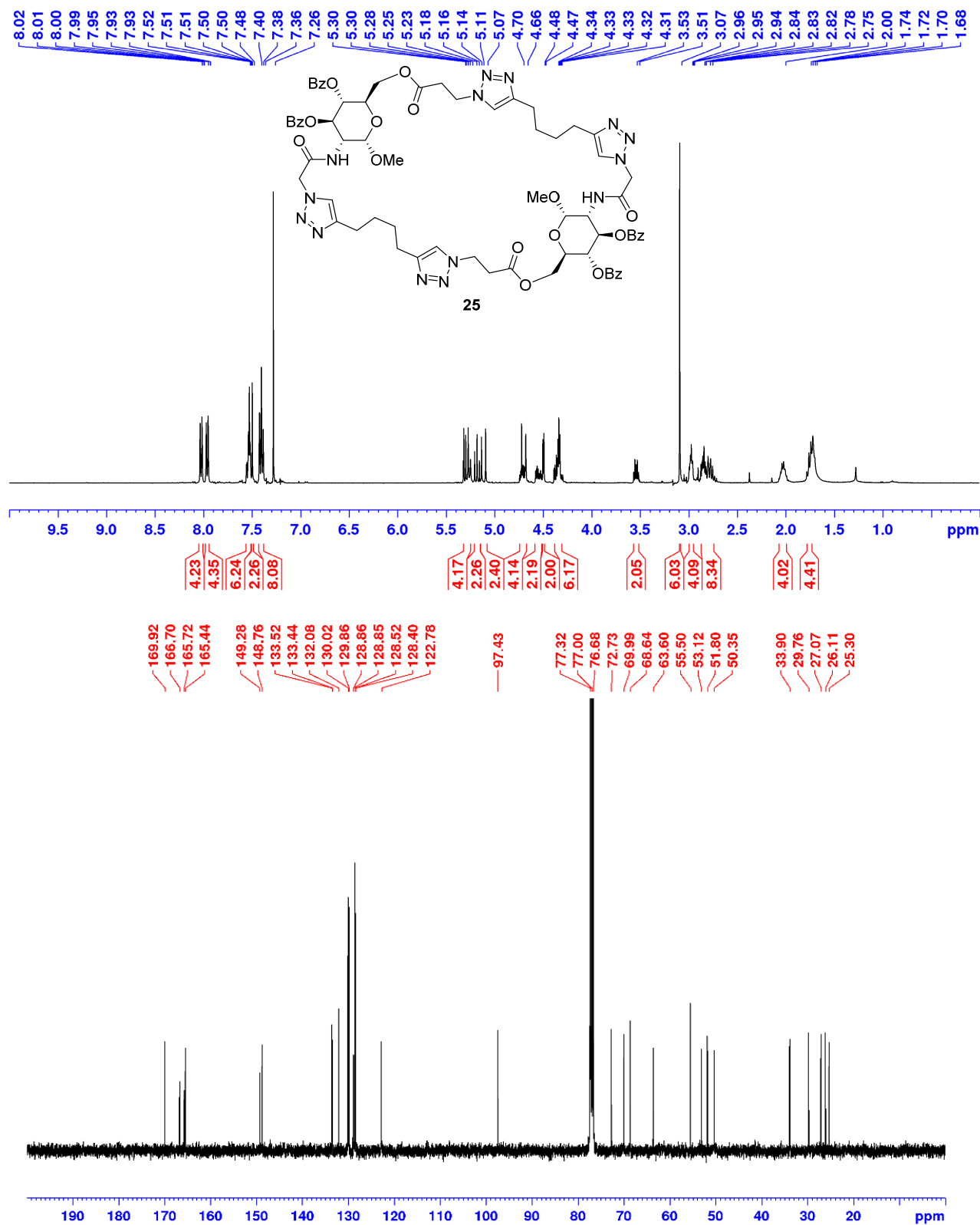
¹H NMR and ¹³C NMR spectra of compound **23** in CDCl₃



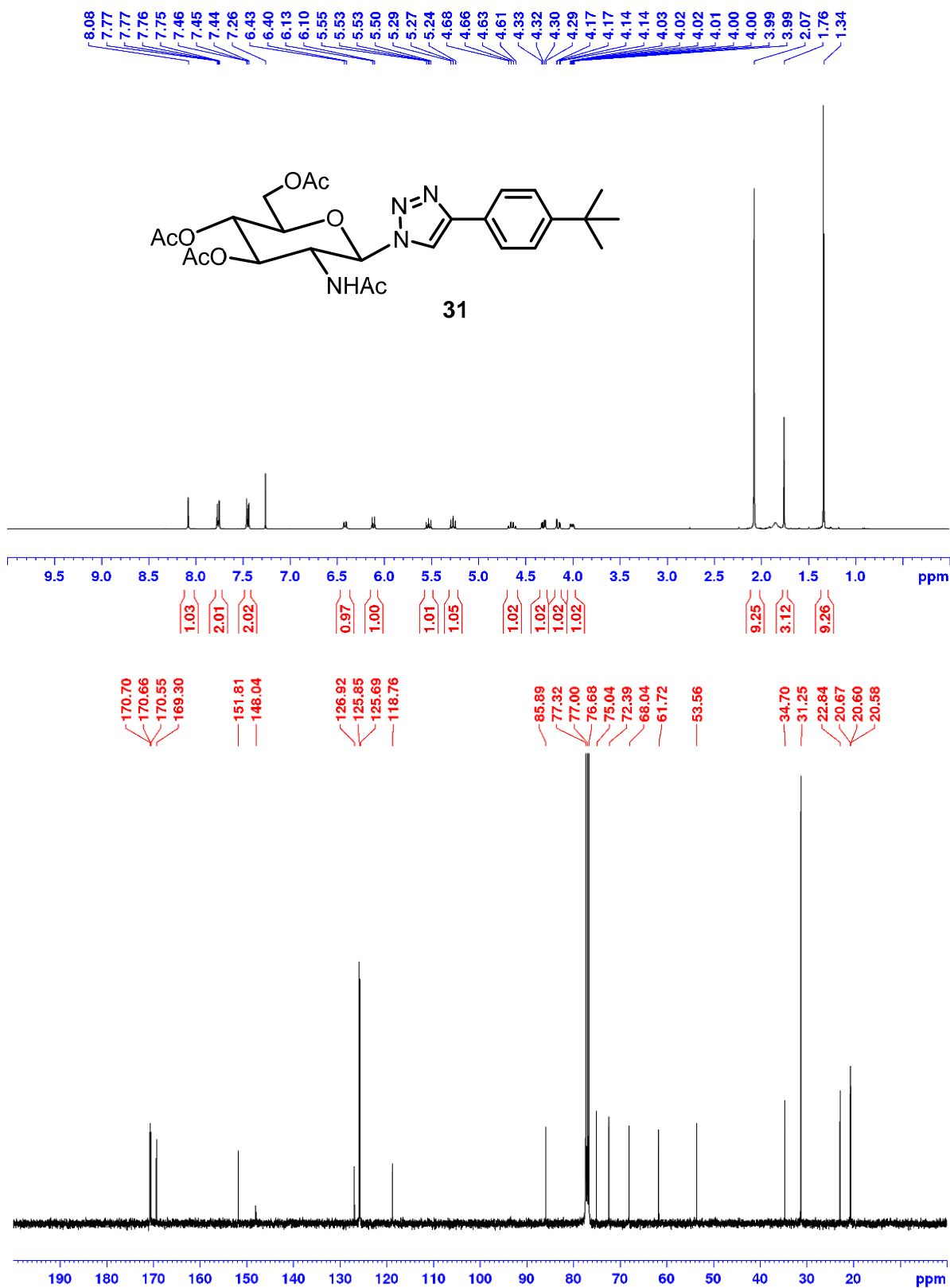
^1H NMR and ^{13}C NMR spectra of compound **22** in CDCl_3



^1H NMR and ^{13}C NMR spectra of compound **24** in CDCl_3

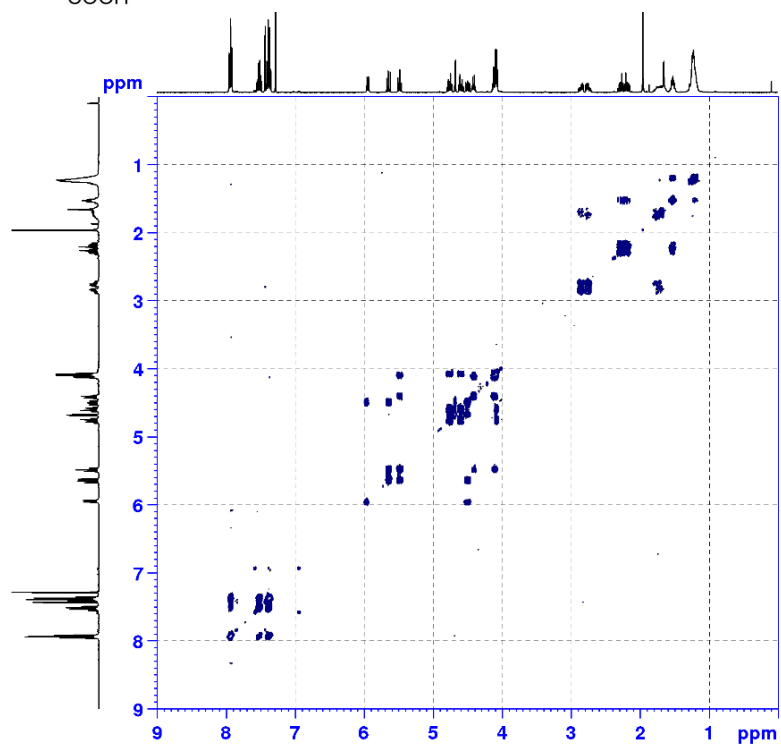
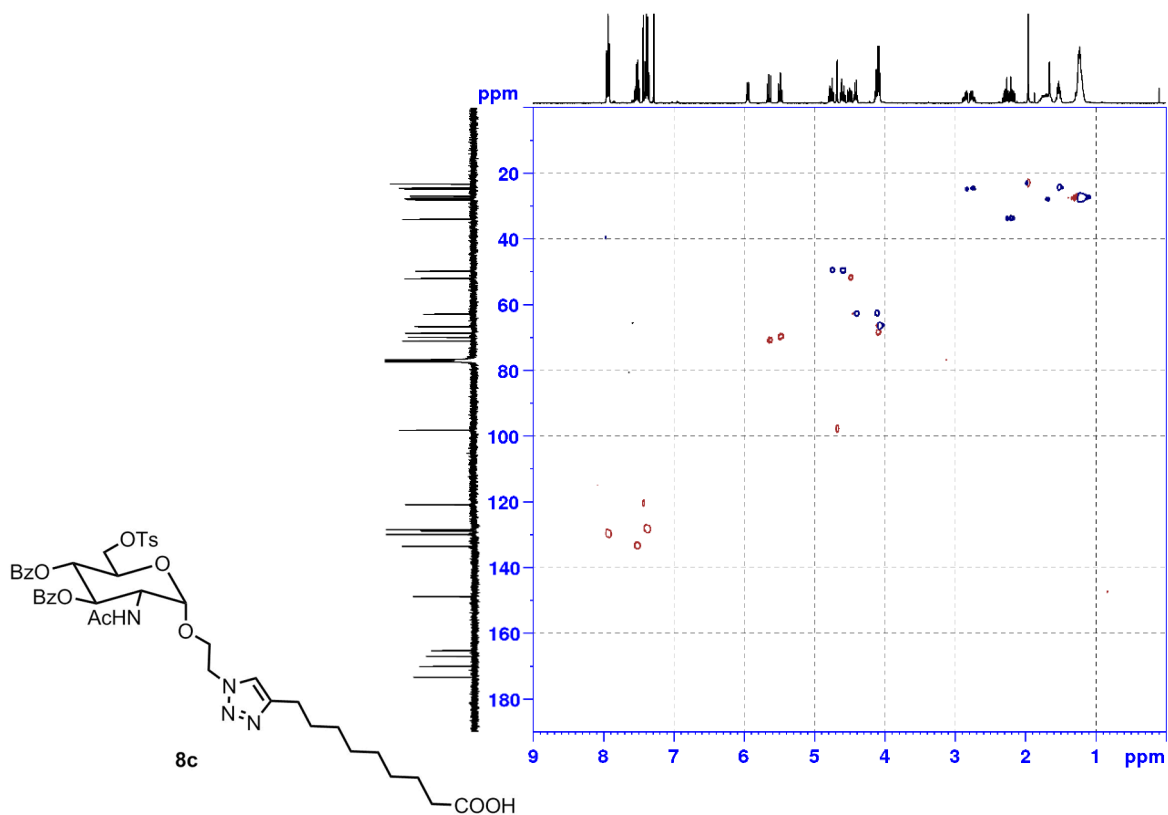


¹H NMR and ¹³C NMR spectra of compound **25** in CDCl₃

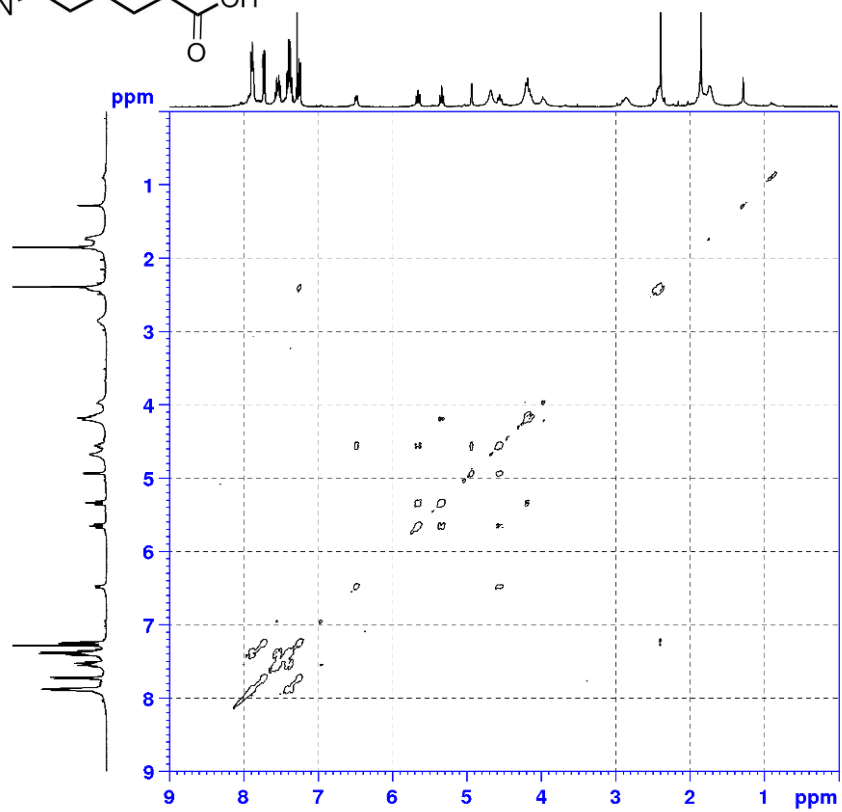
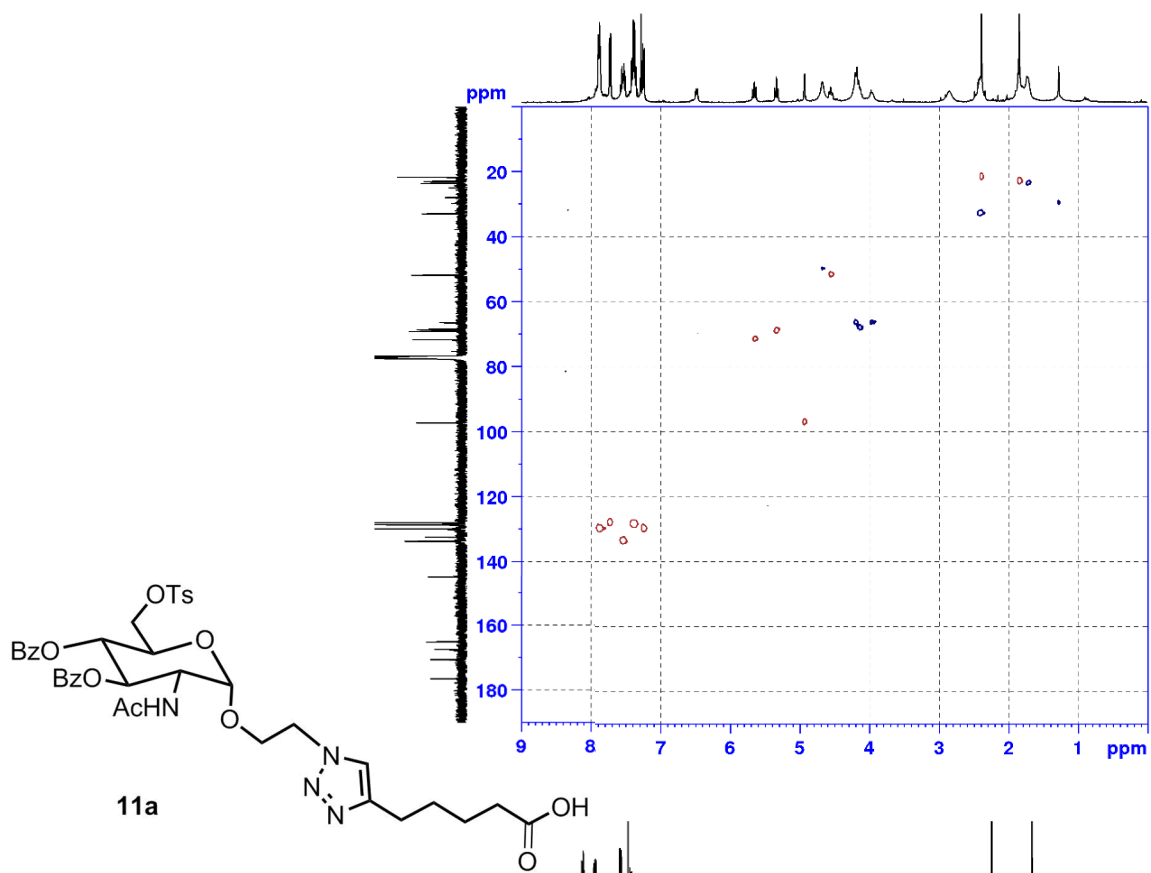


¹H NMR and ¹³C NMR spectra of compound **31** in CDCl₃

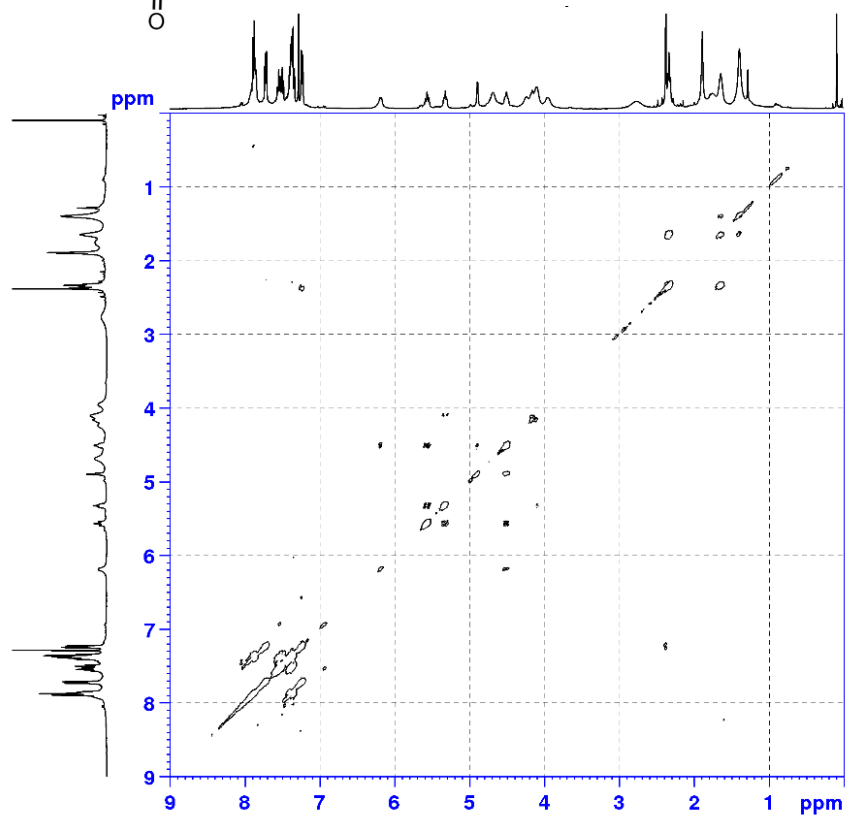
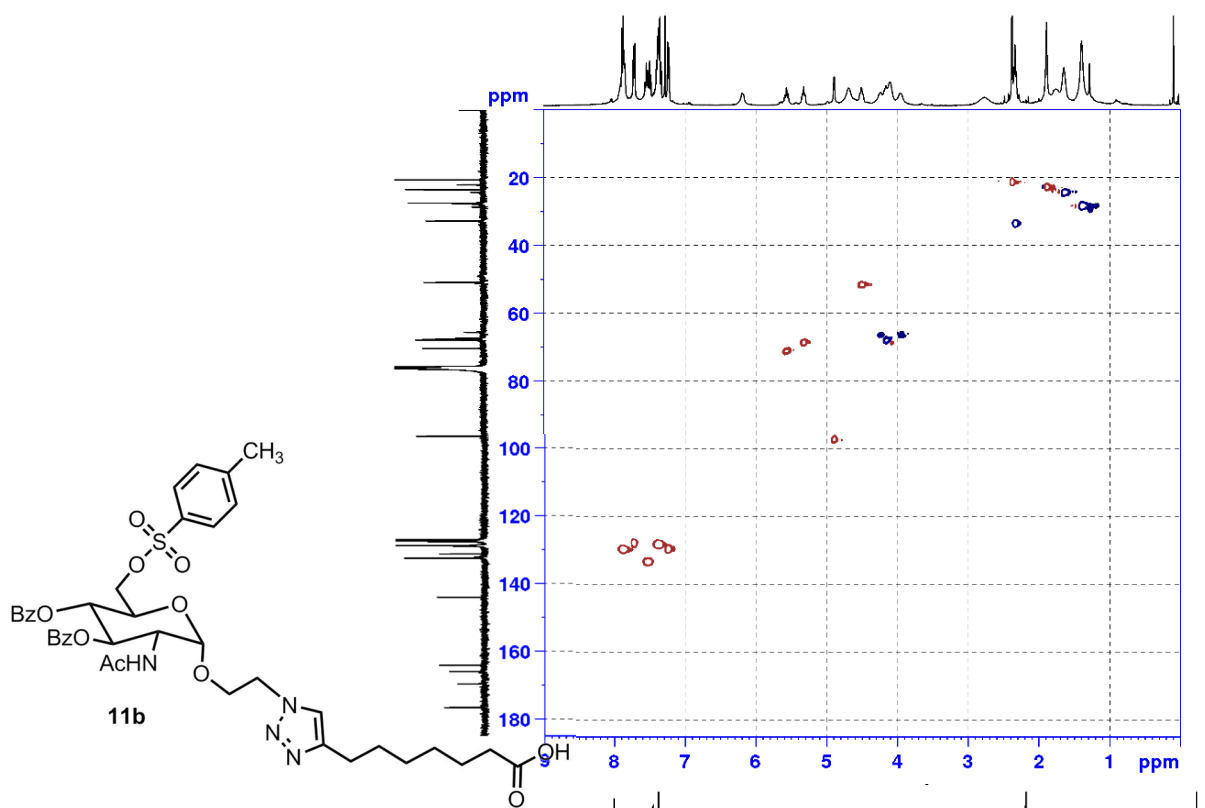
III. 2D HSQC and COSY NMR Spectra of Selected Compounds



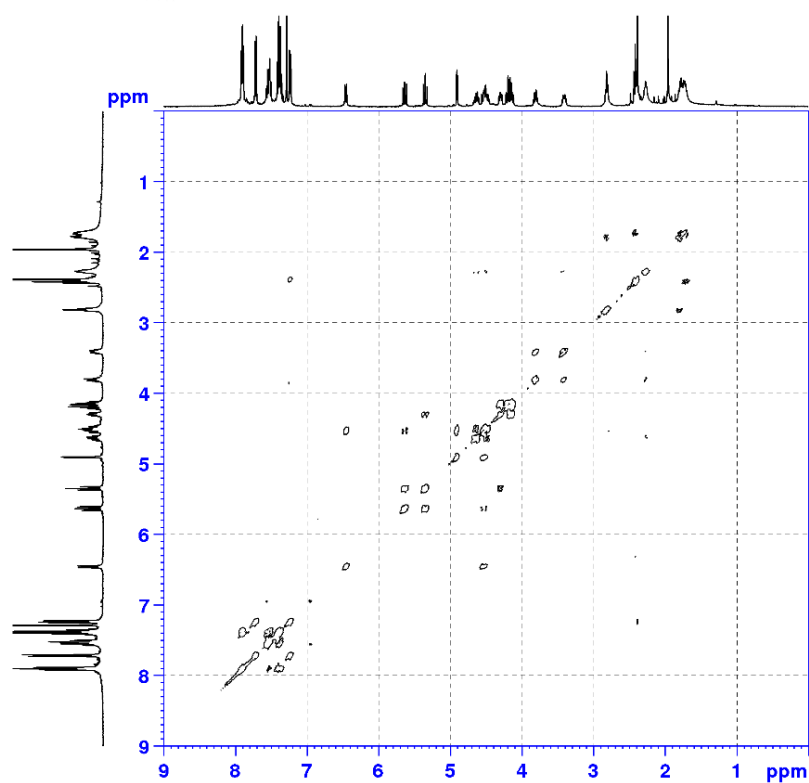
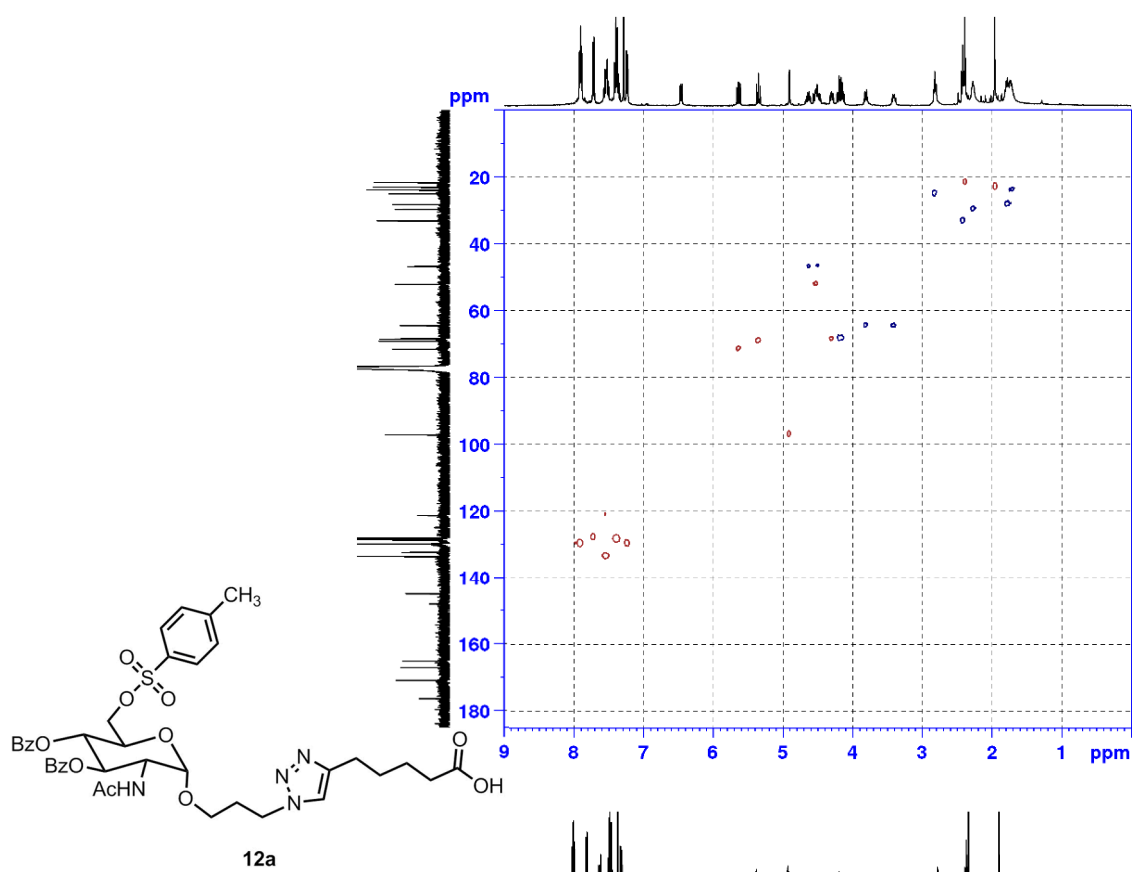
HSQC and COSY NMR spectra of compound **8c** in CDCl₃



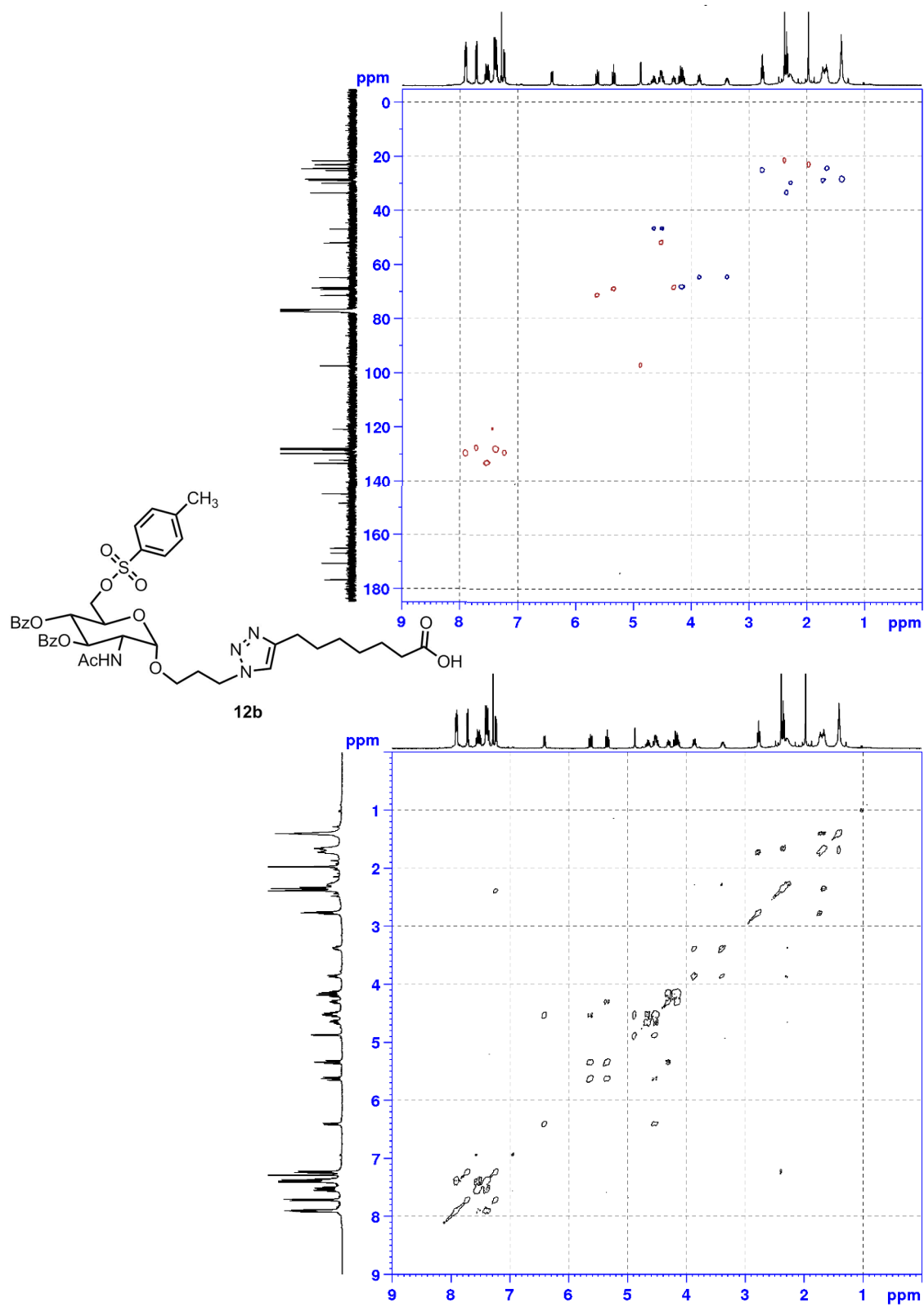
HSQC and COSY NMR spectra of compound **11a** in CDCl₃



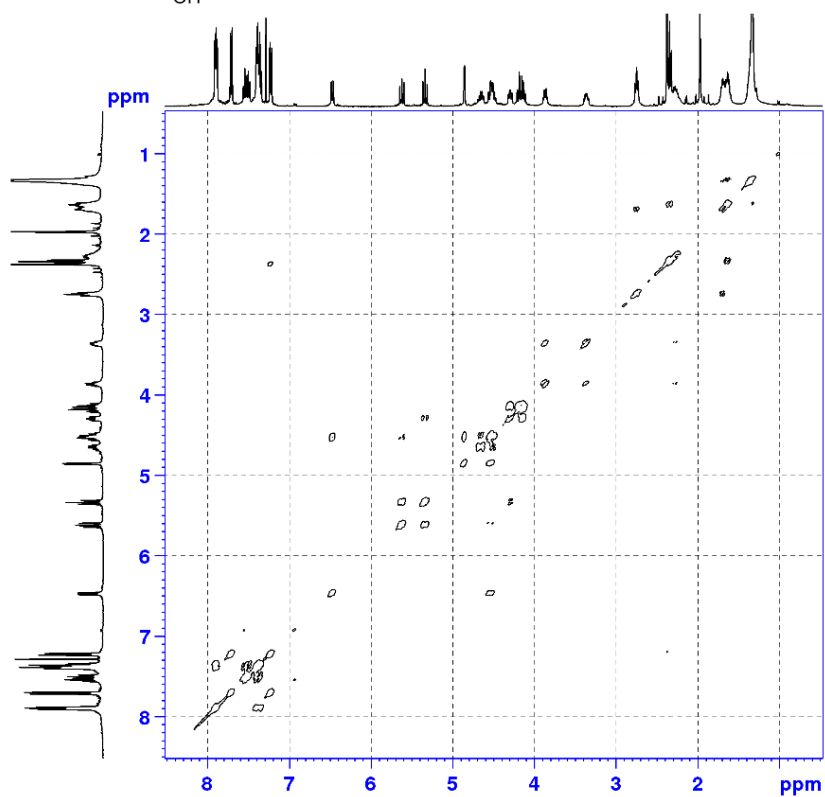
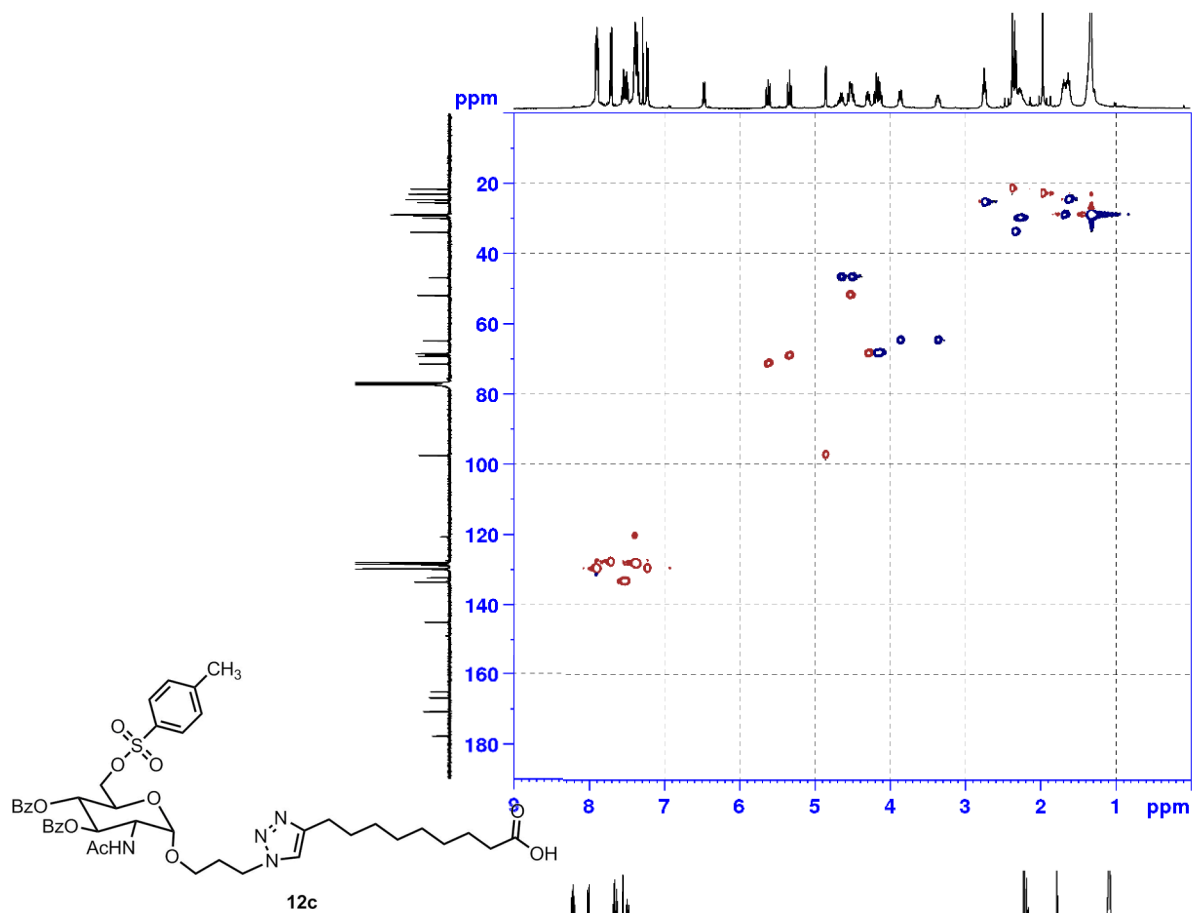
HSQC and COSY NMR spectra of compound **11b** in CDCl_3



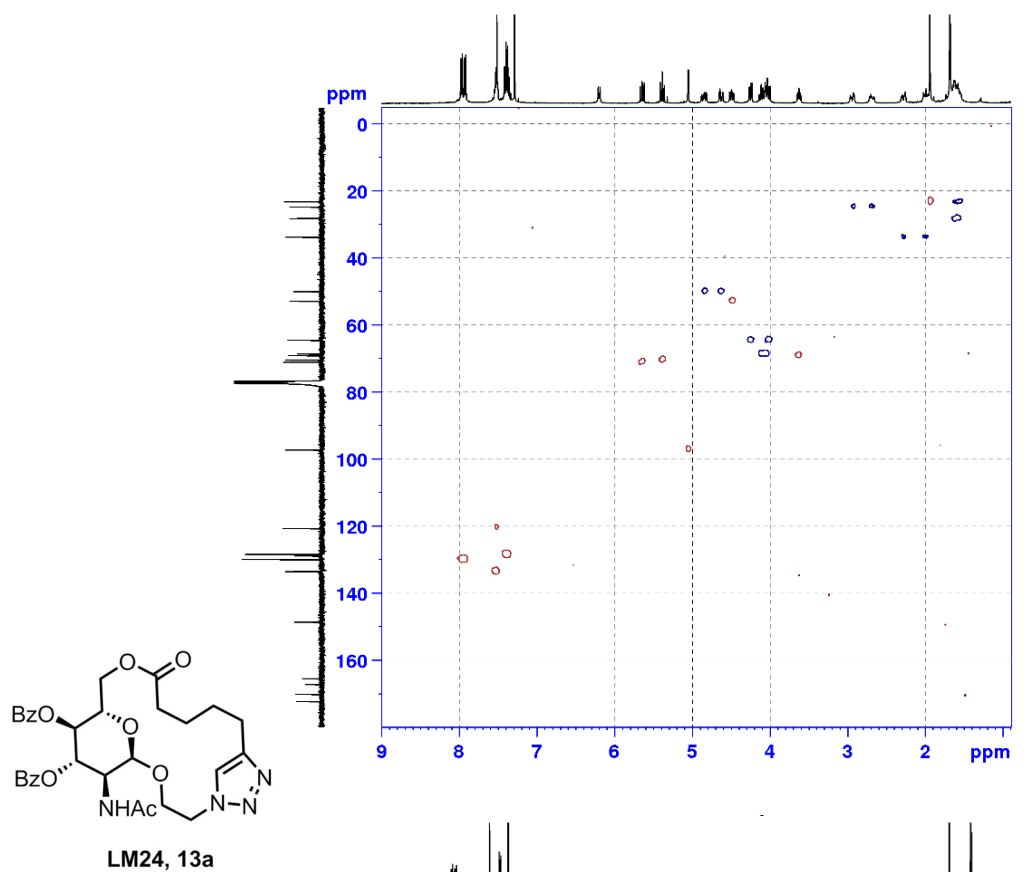
HSQC and COSY NMR spectra of compound **12a** in CDCl₃



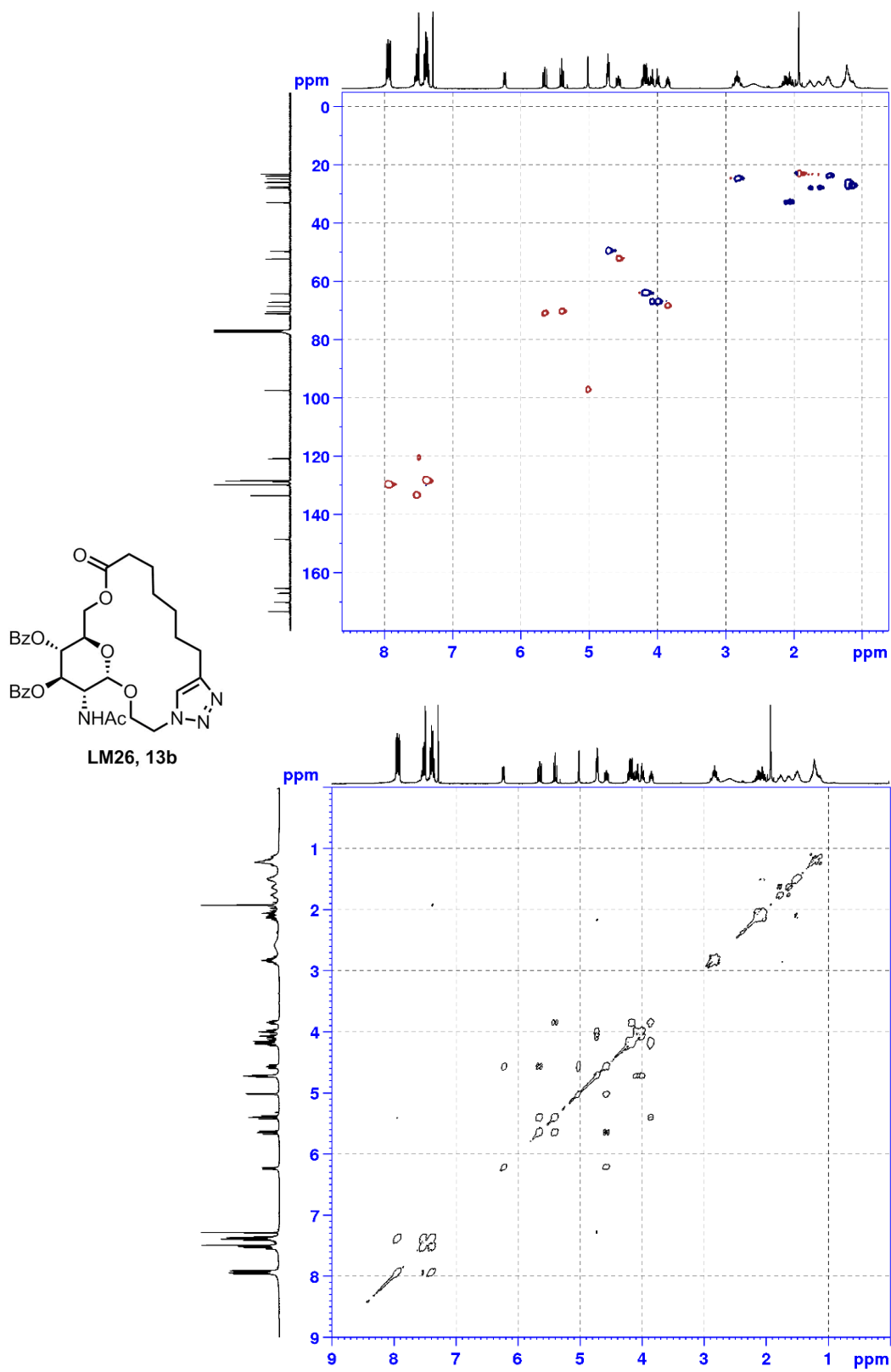
HSQC and COSY NMR spectra of compound **12b** in CDCl₃



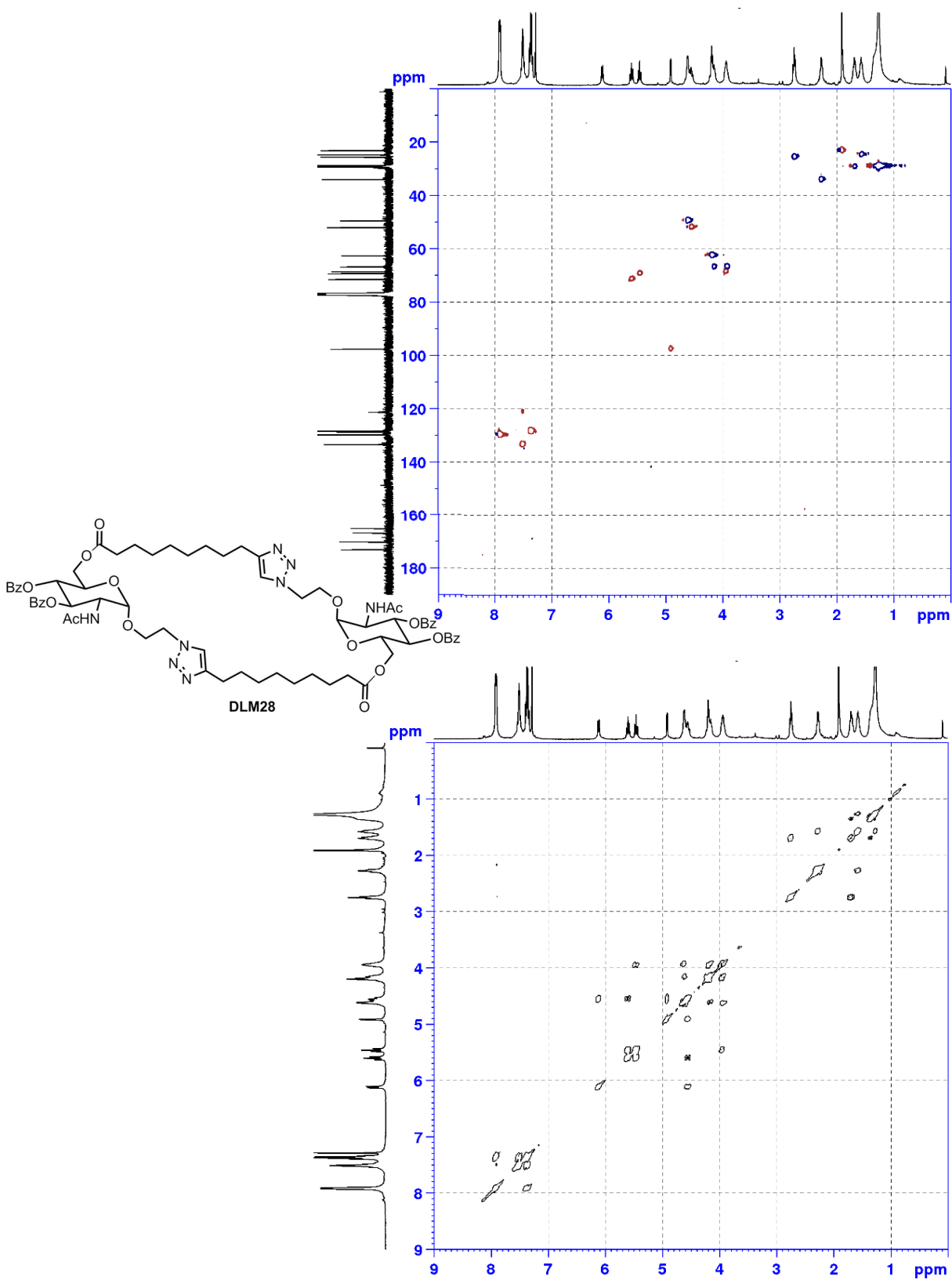
HSQC and COSY NMR spectra of compound **12c** in CDCl₃



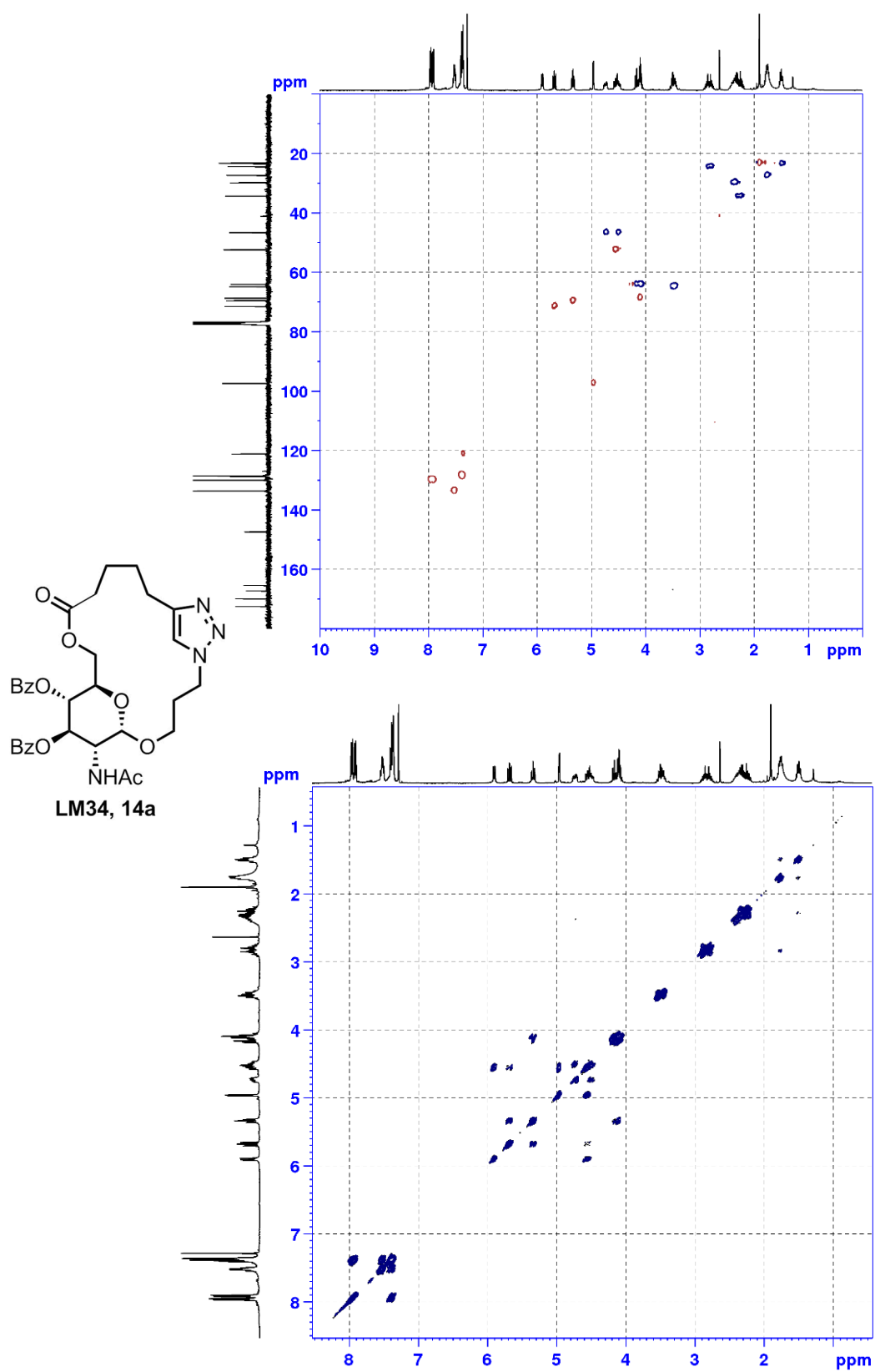
HSQC and COSY NMR spectra of compound **13a** in CDCl₃



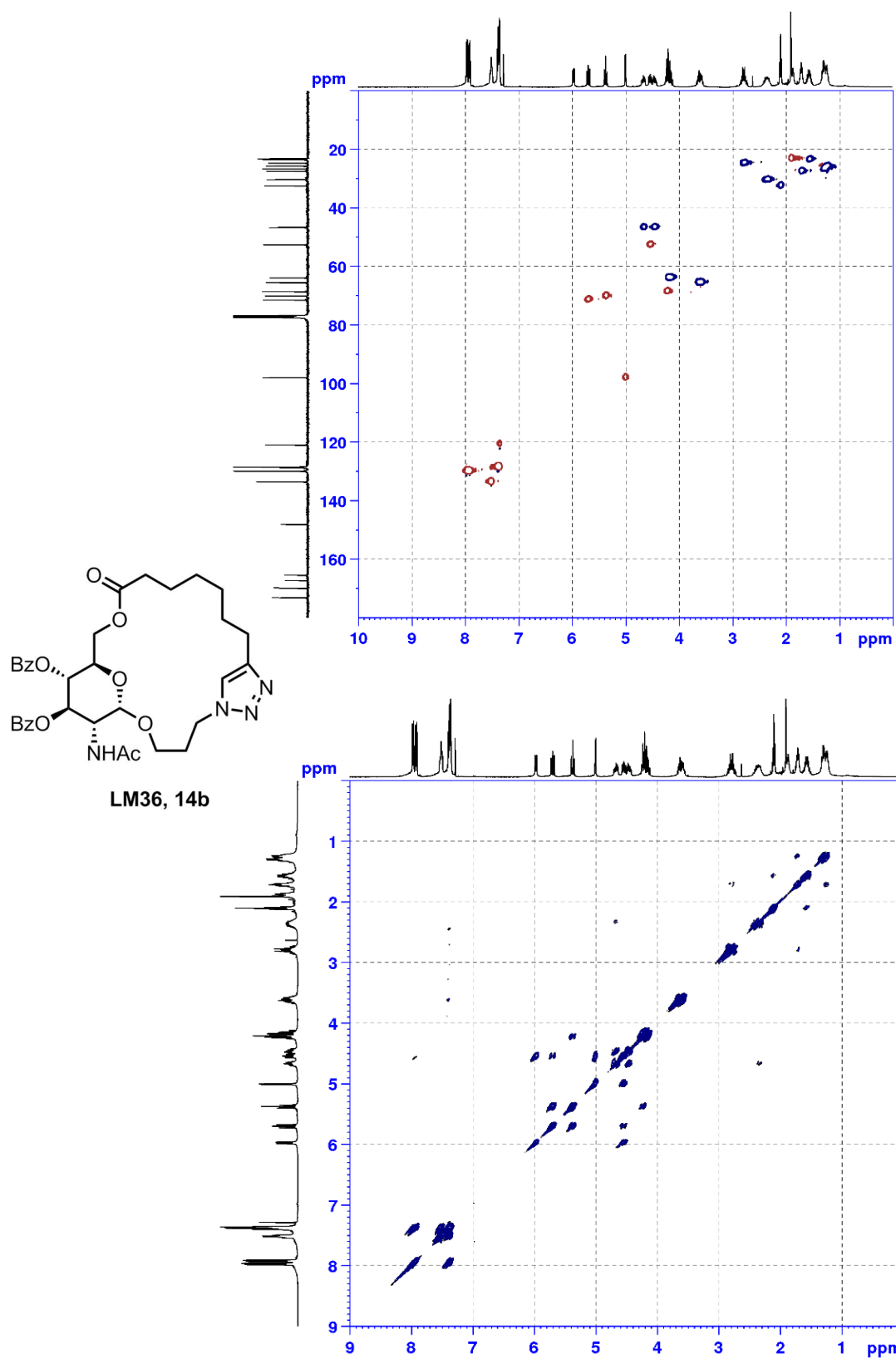
HSQC and COSY NMR spectra of compound **13b** in CDCl₃



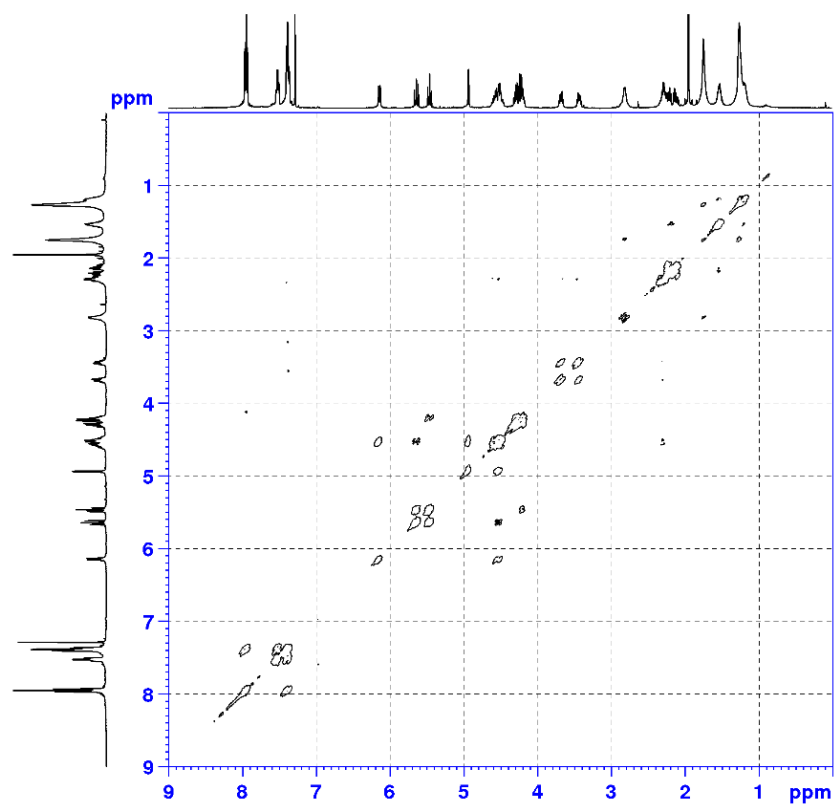
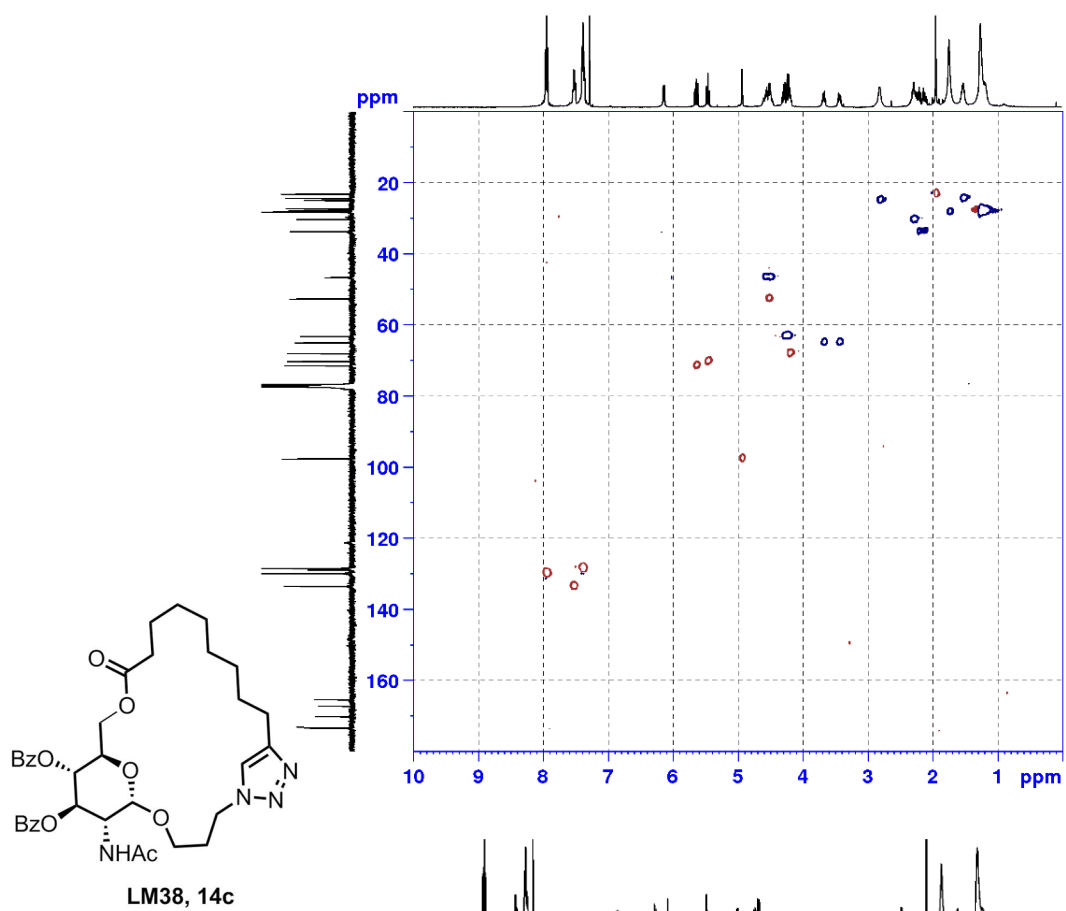
HSQC and COSY NMR spectra of compound **DLM28** in CDCl₃



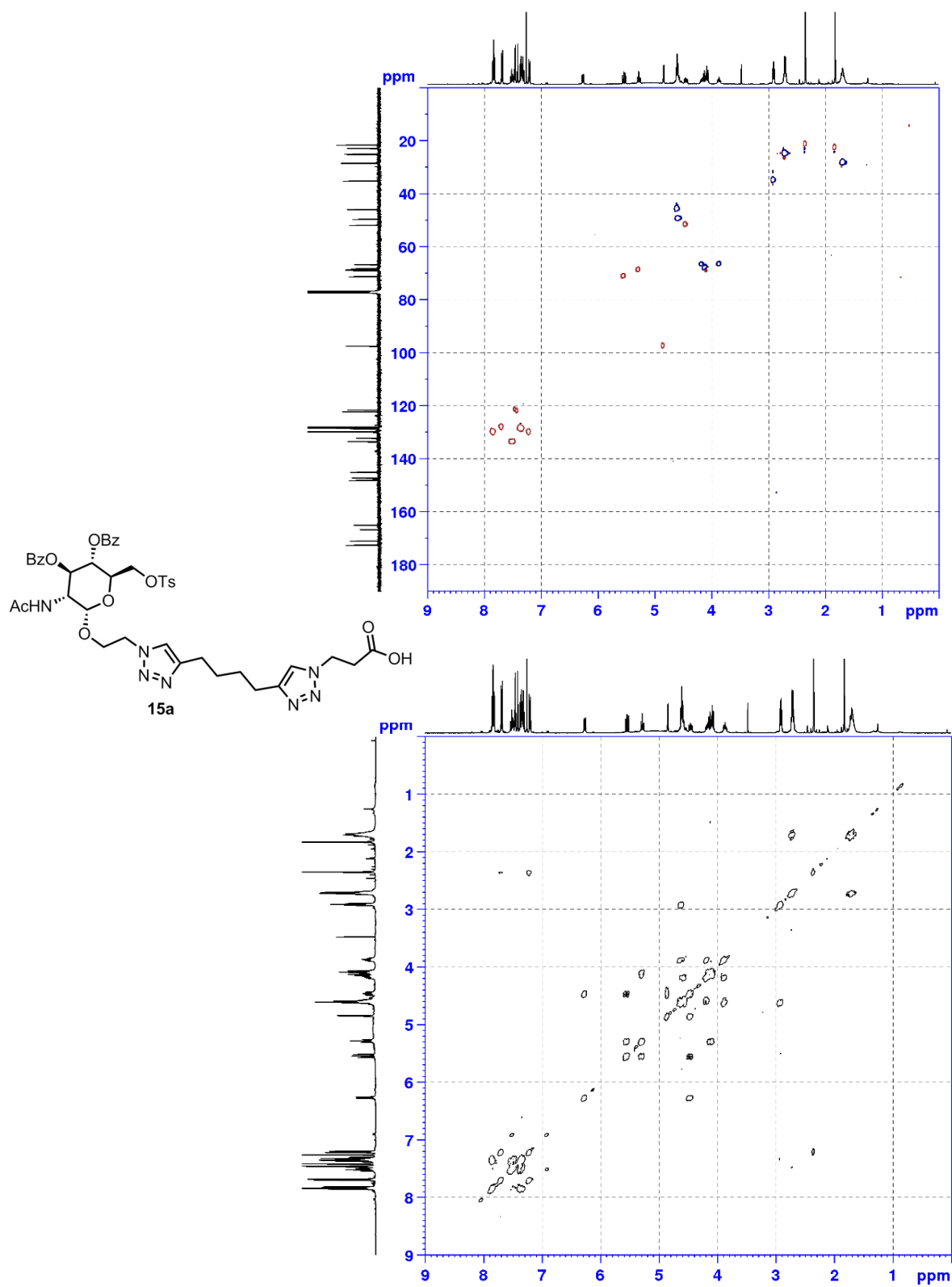
HSQC and COSY NMR spectra of compound **14a** in CDCl₃



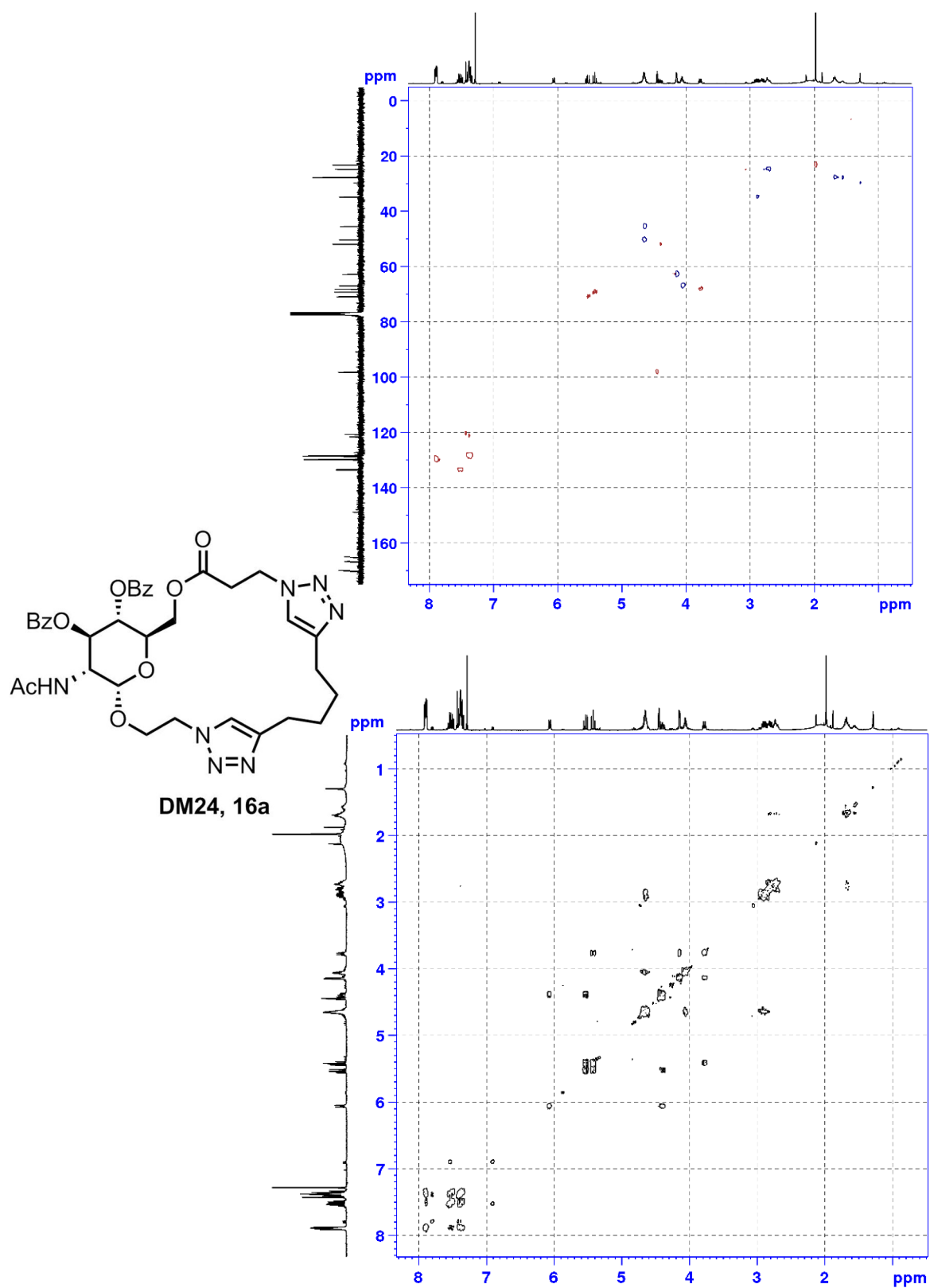
HSQC and COSY NMR spectra of compound **14b** in CDCl₃



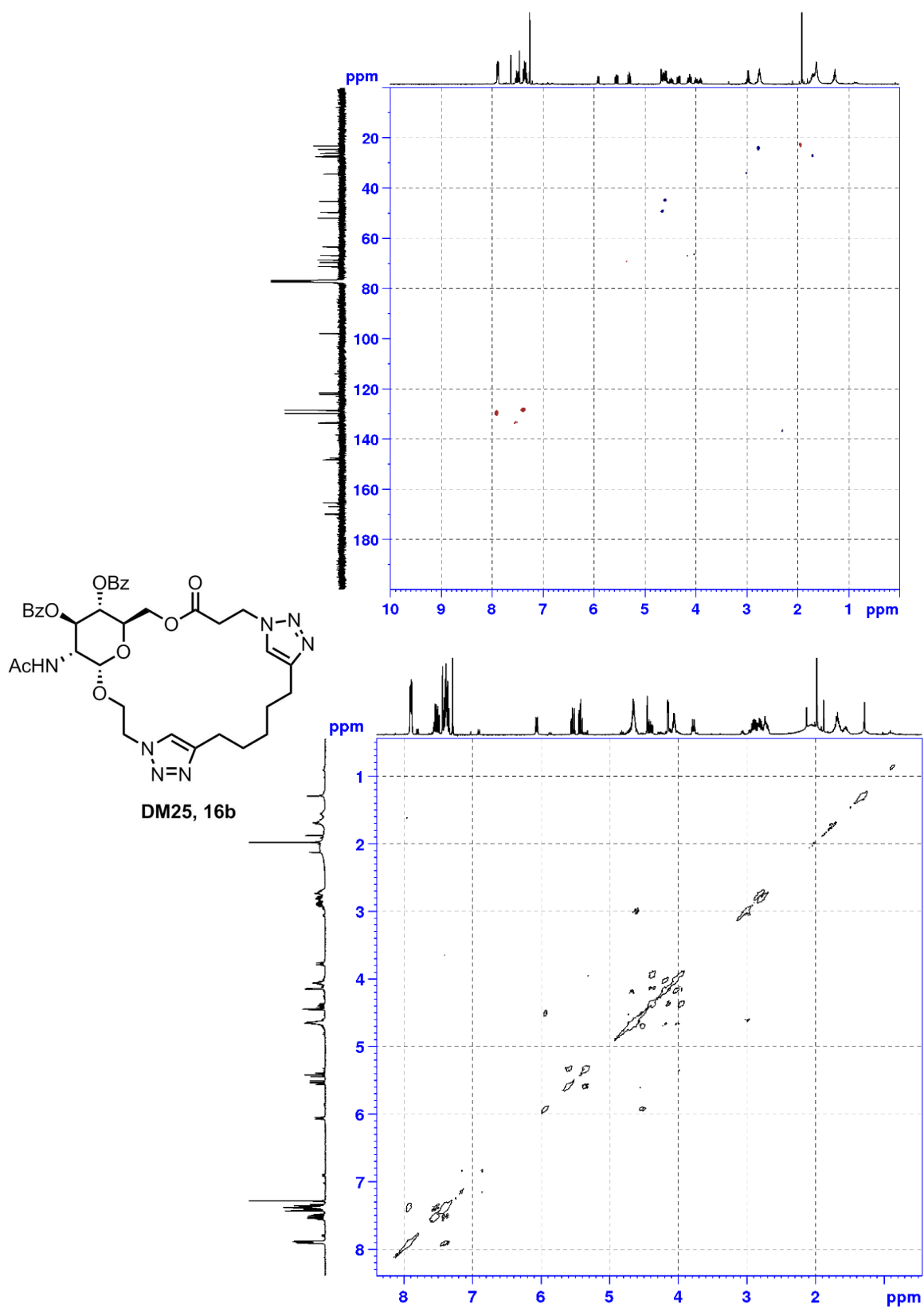
HSQC and COSY NMR spectra of compound **14c** in CDCl₃



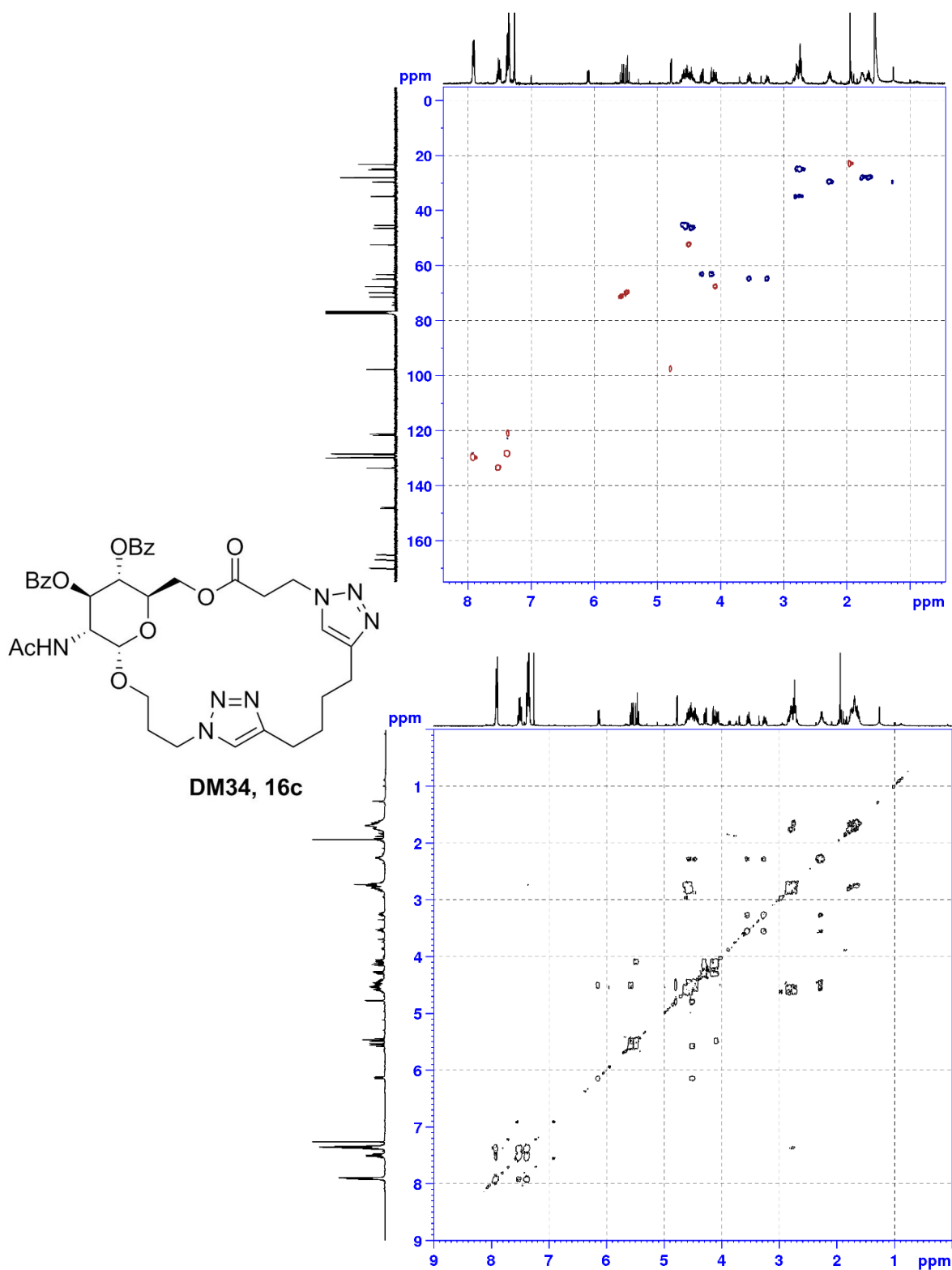
HSQC and COSY NMR spectra of compound **15a** in CDCl_3



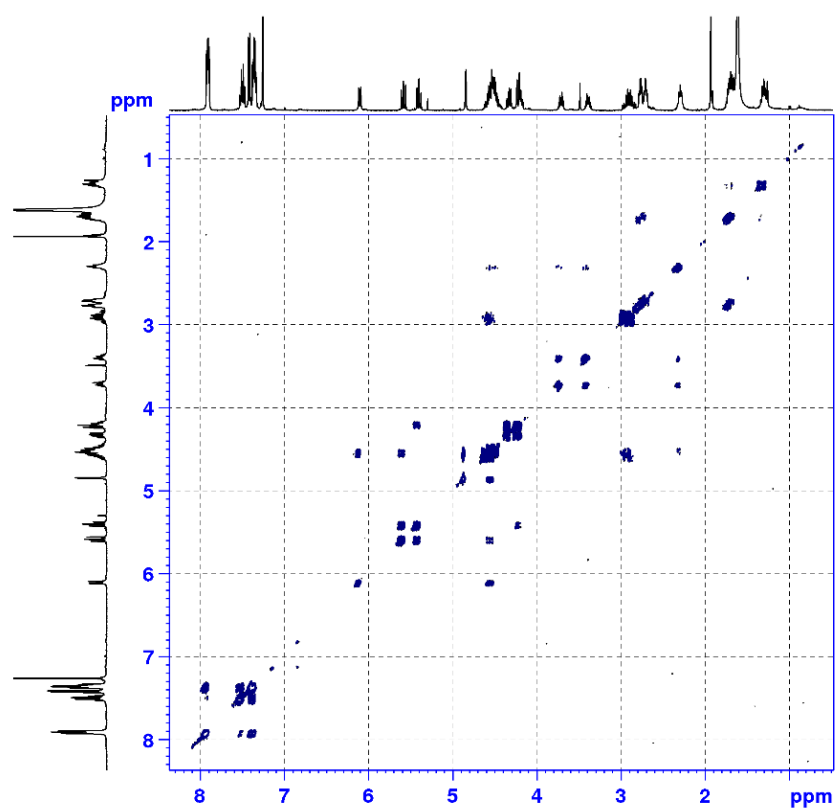
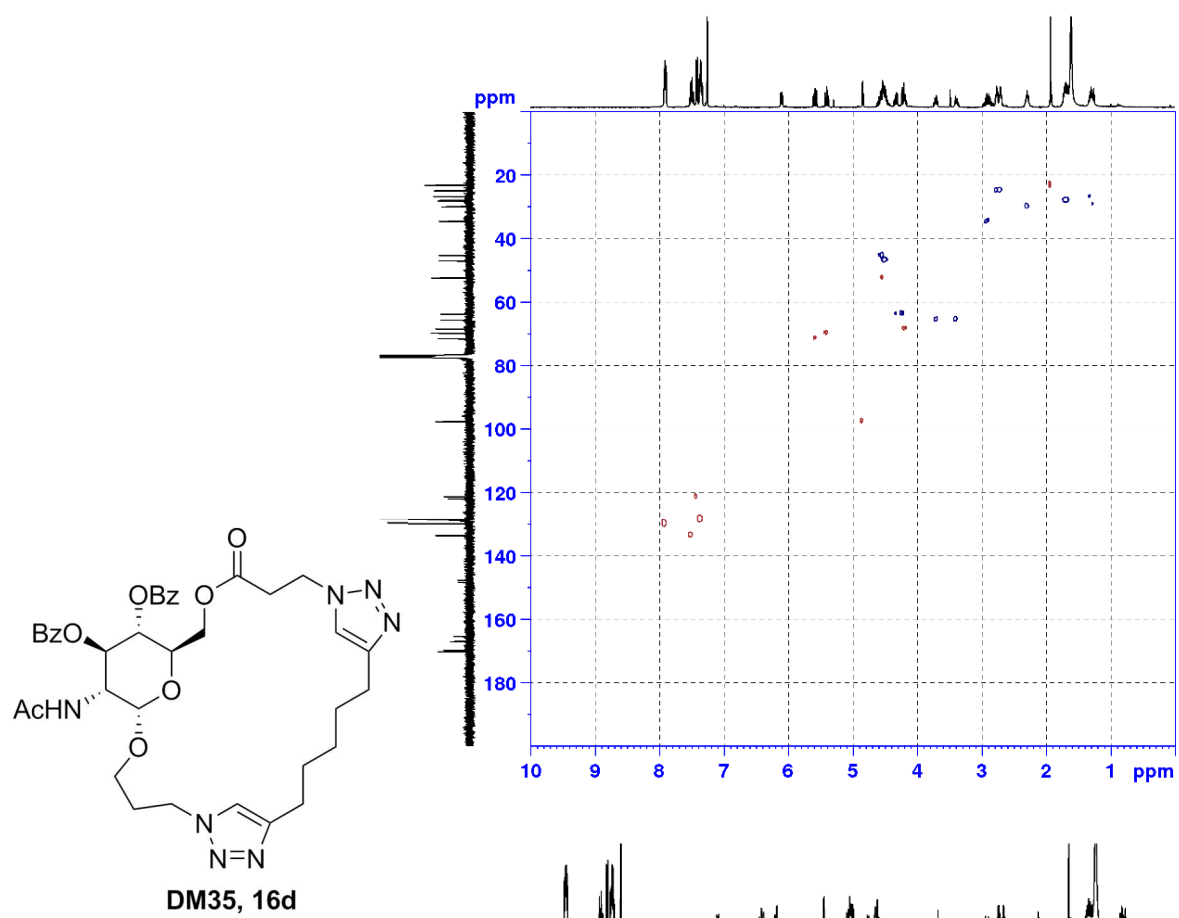
HSQC and COSY NMR spectra of compound **16a** in CDCl₃



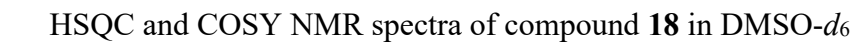
HSQC and COSY NMR spectra of compound **16b** in CDCl₃

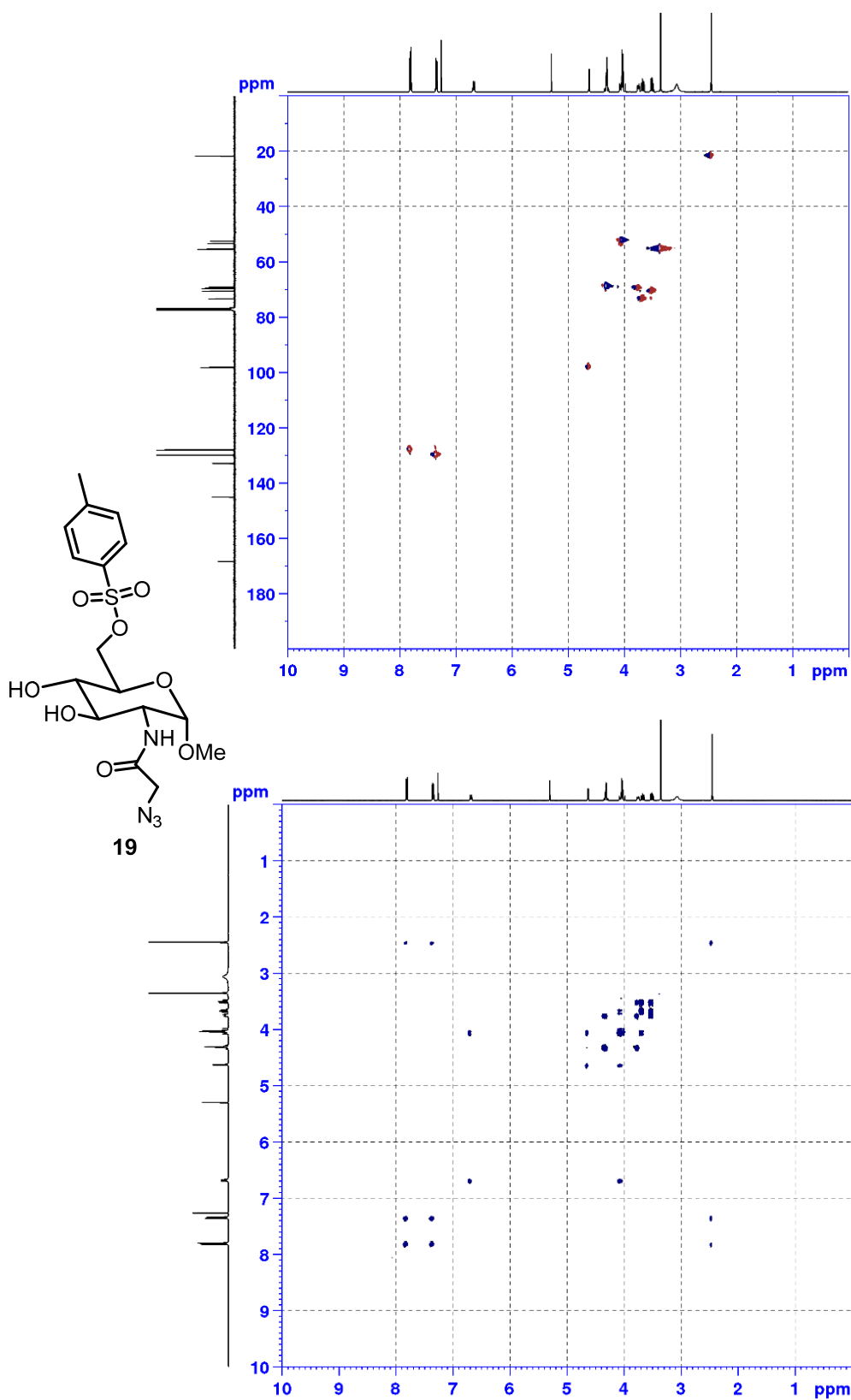


HSQC and COSY NMR spectra of compound **16c** in CDCl₃

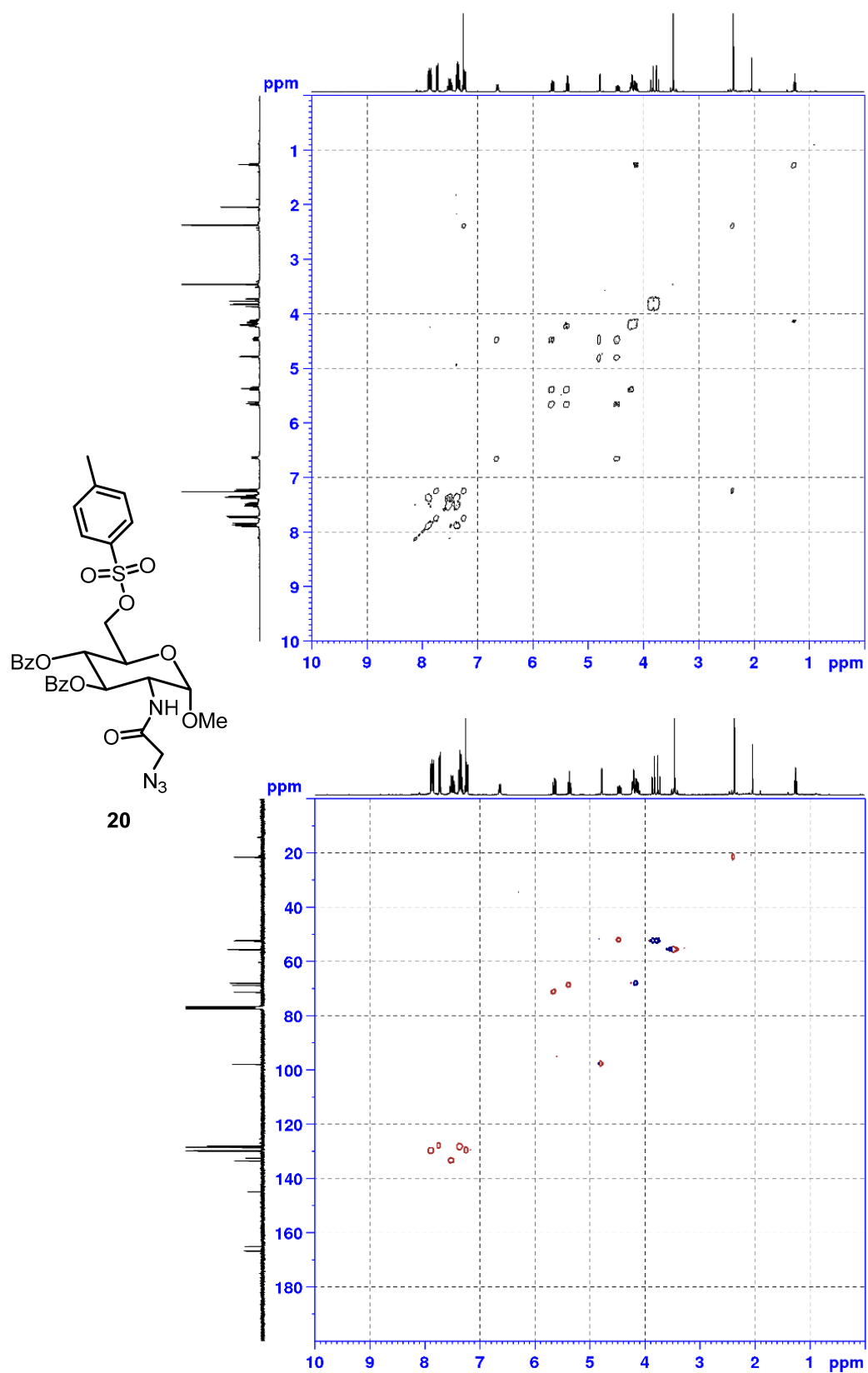


HSQC and COSY NMR spectra of compound **16d** in CDCl₃

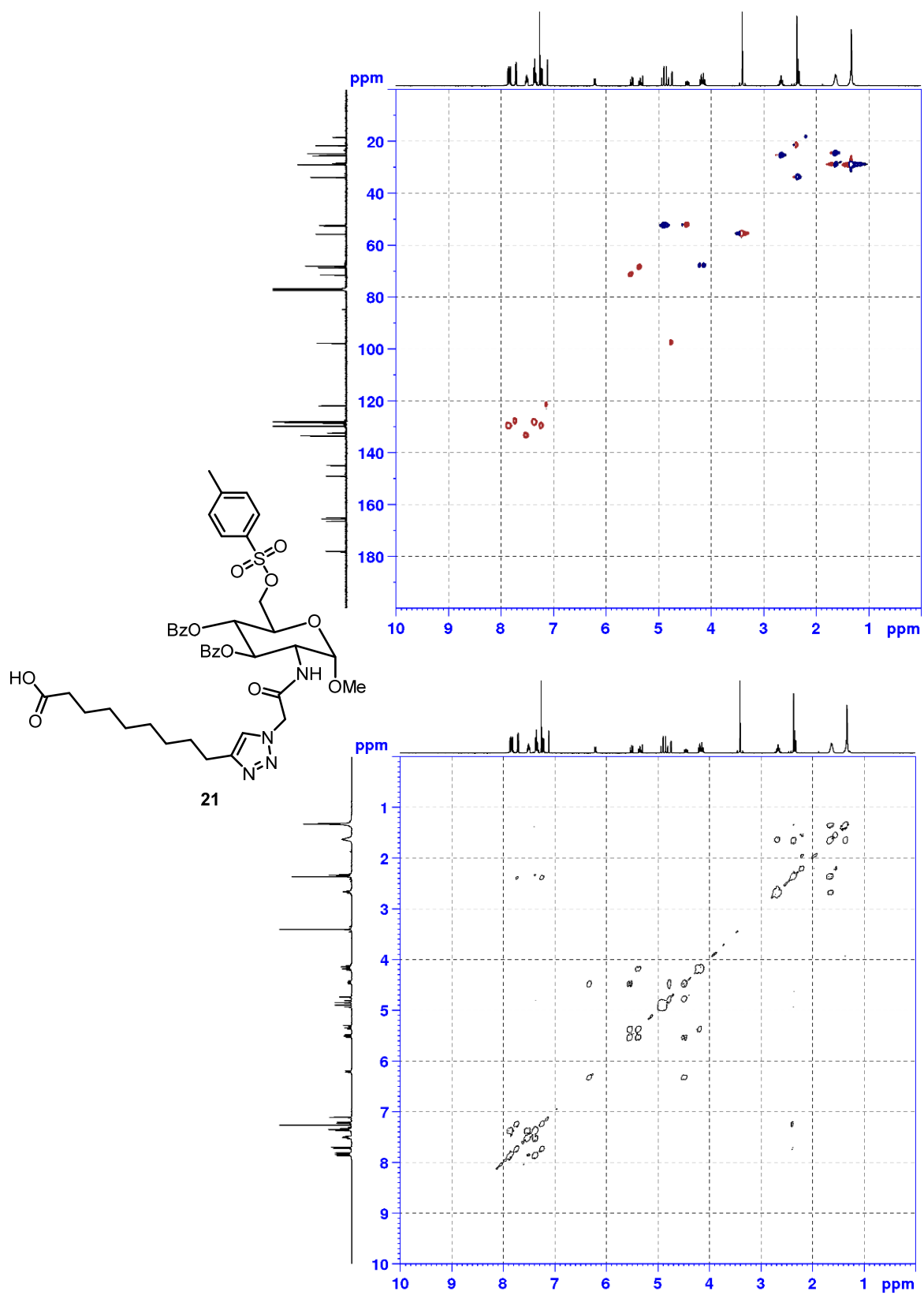




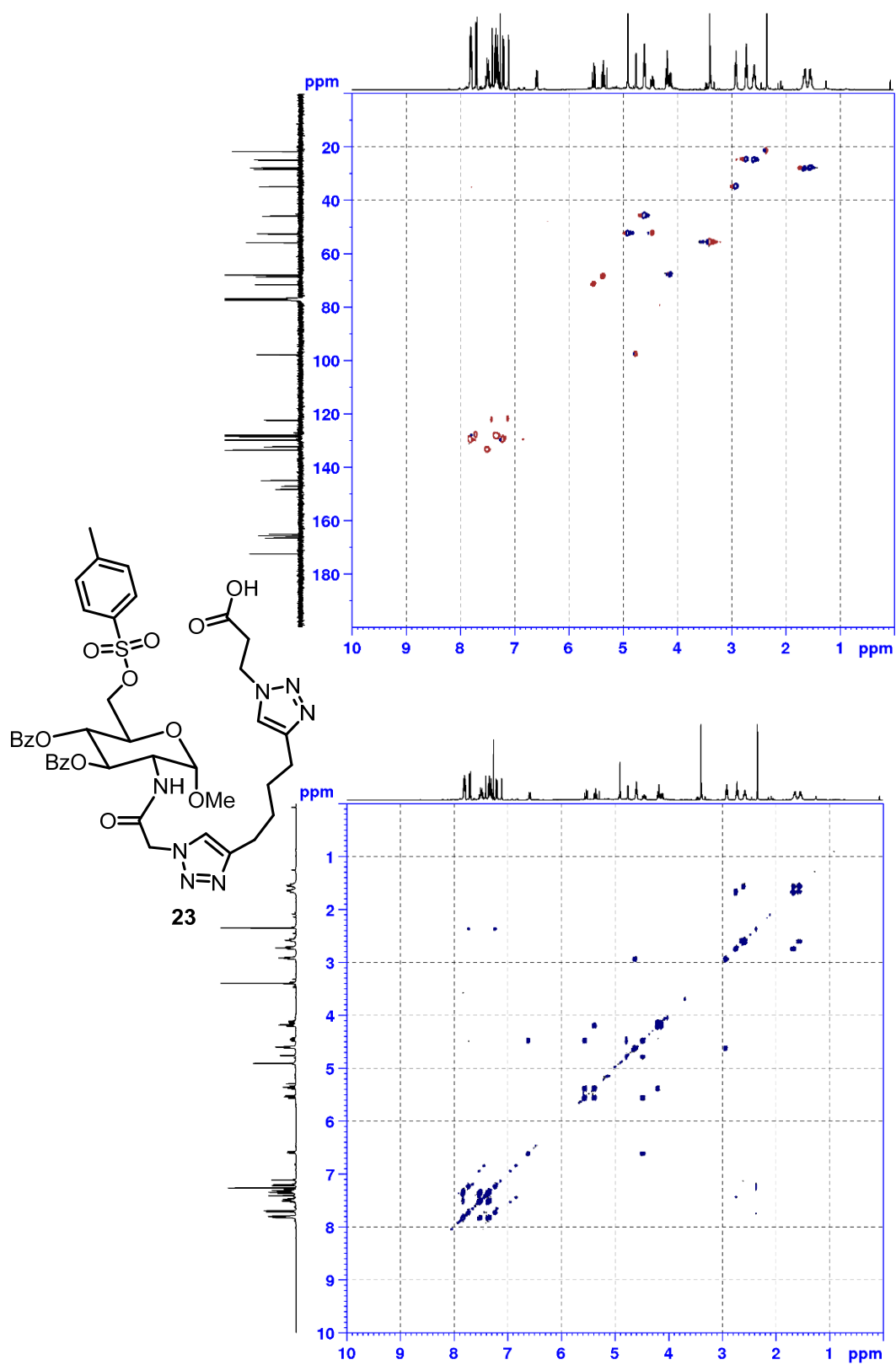
HSQC and COSY NMR spectra of compound **19** in CDCl₃



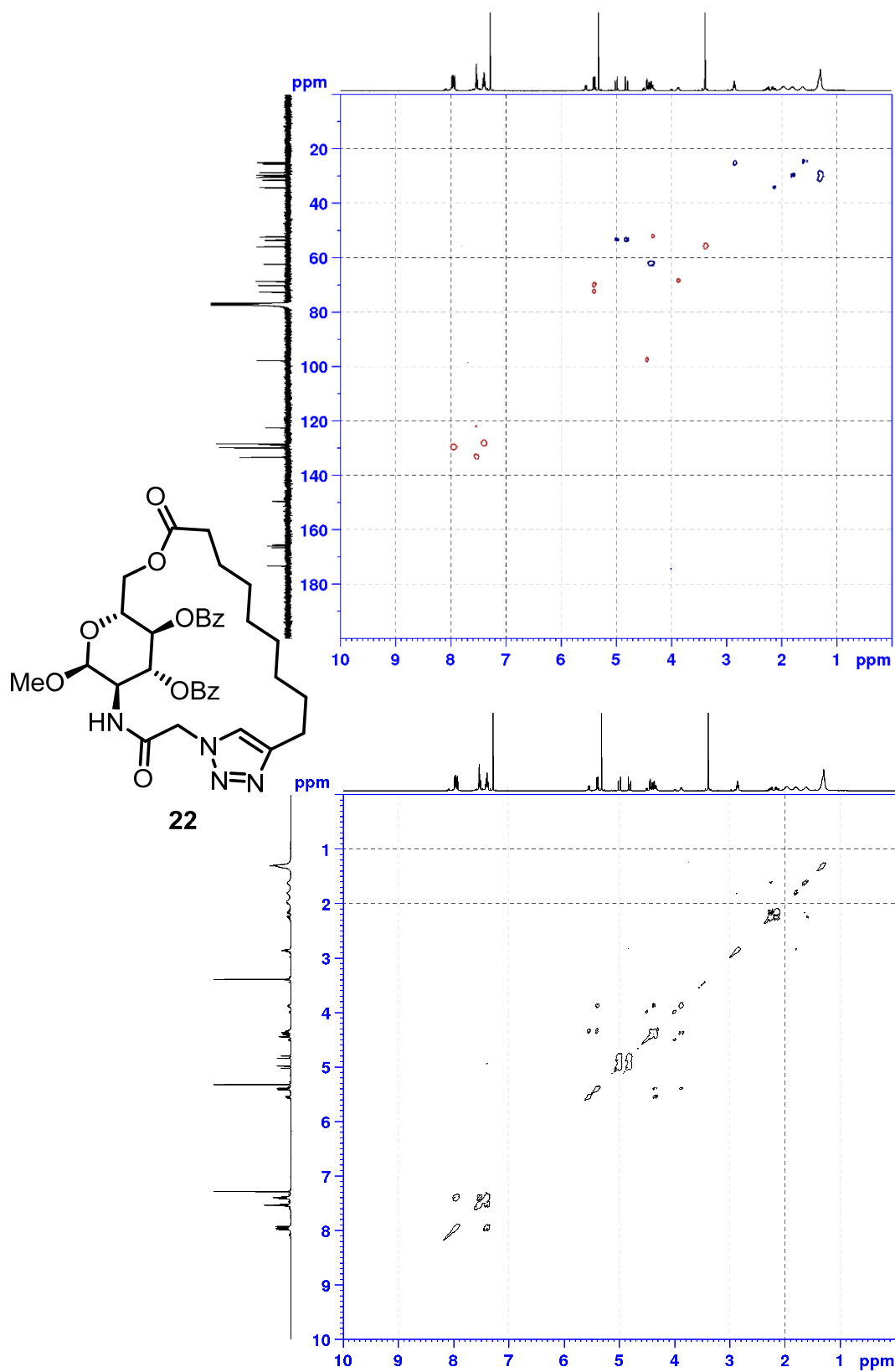
HSQC and COSY NMR spectra of compound **20** in CDCl₃



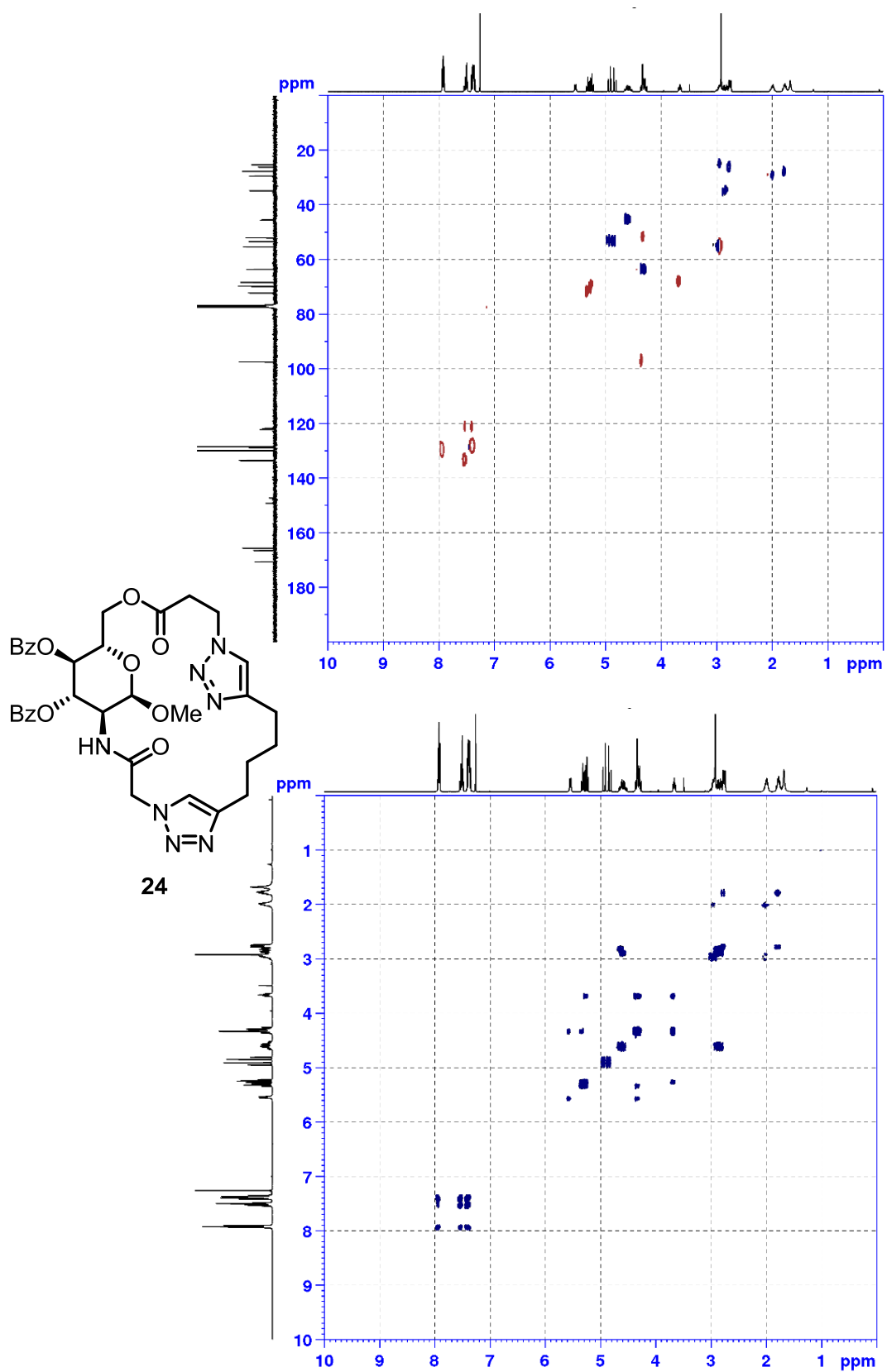
HSQC and COSY NMR spectra of compound **21** in CDCl₃



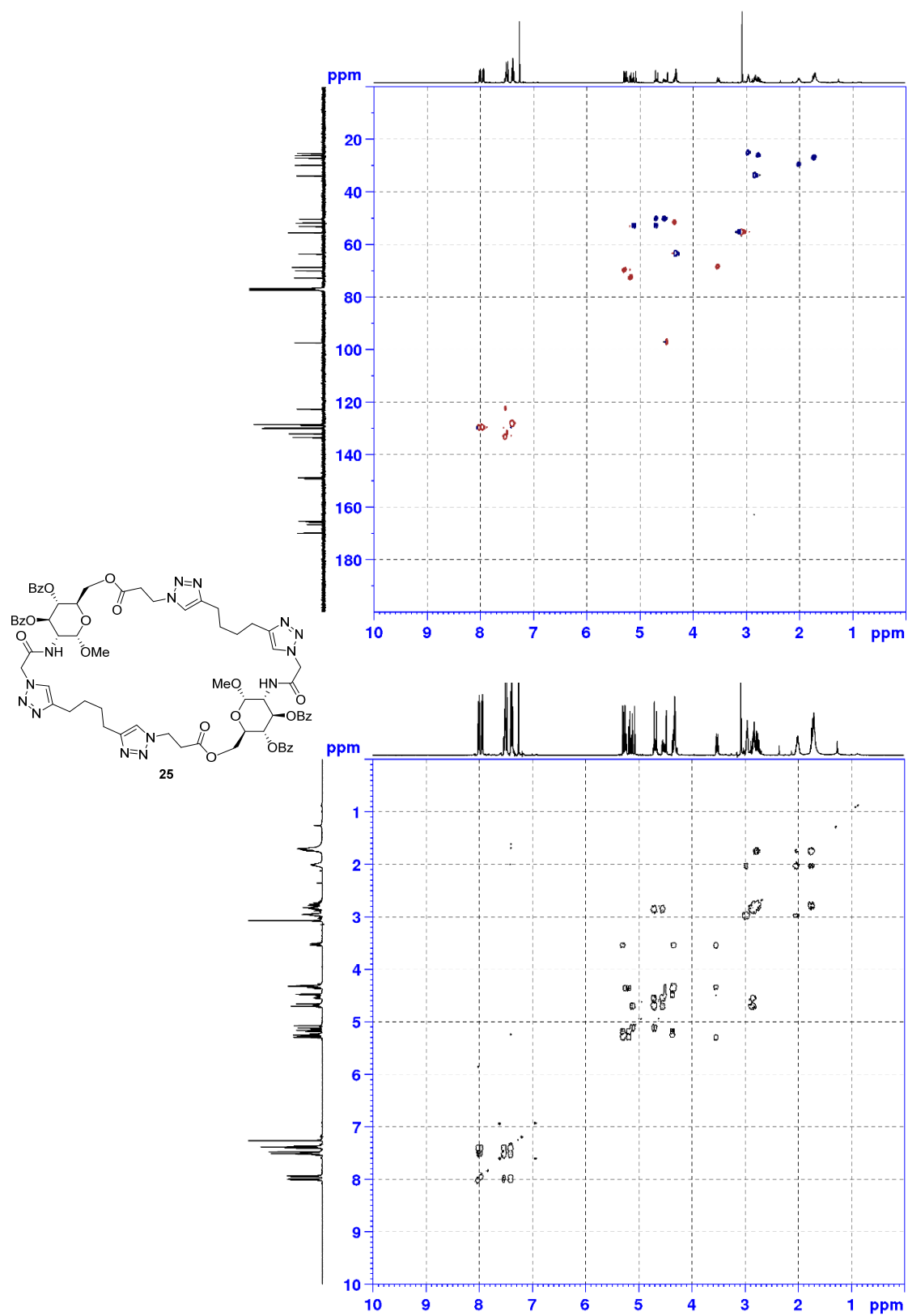
HSQC and COSY NMR spectra of compound **23** in CDCl_3



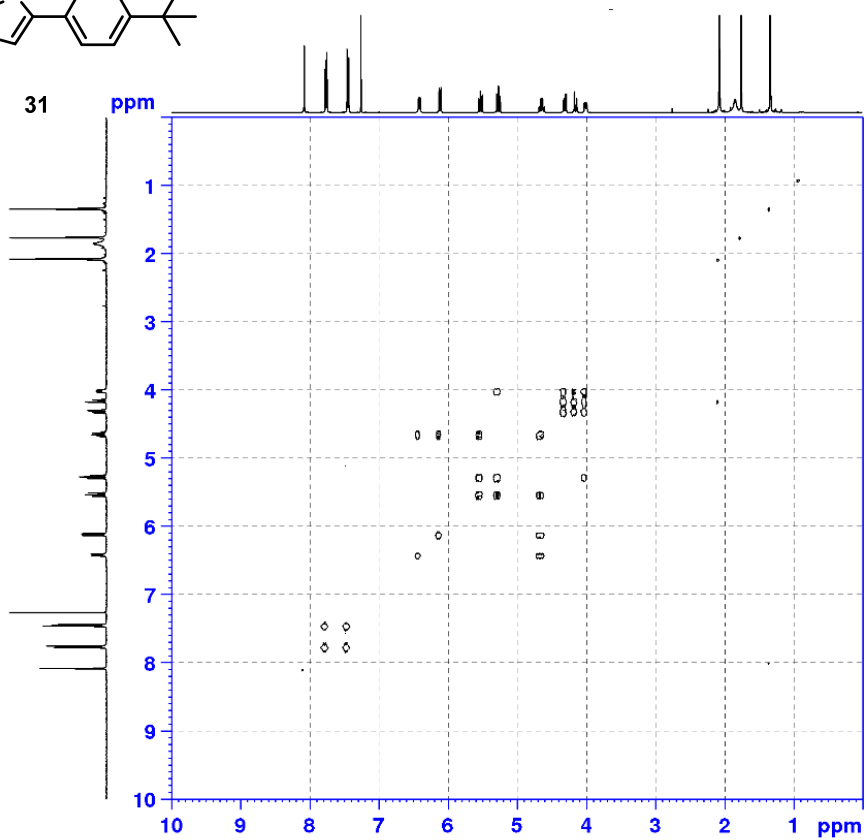
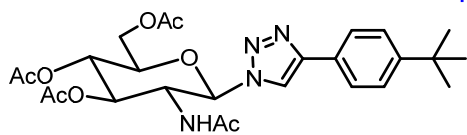
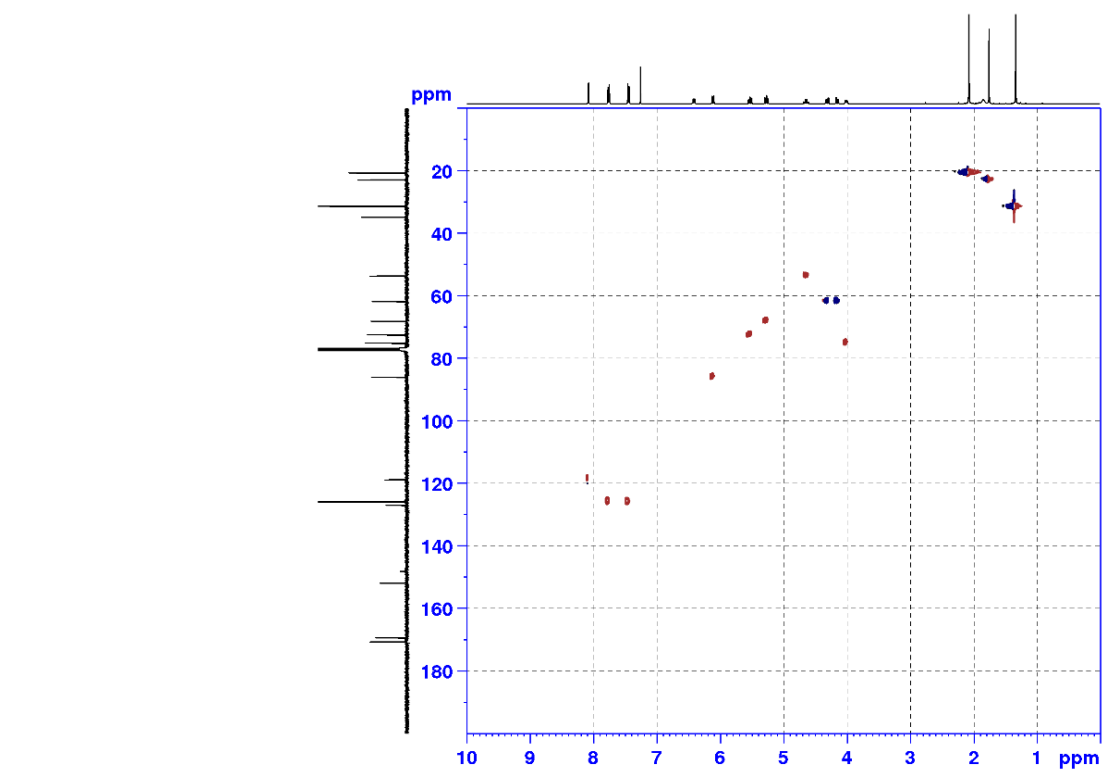
HSQC and COSY NMR spectra of compound **22** in CDCl₃



HSQC and COSY NMR spectra of compound **24** in CDCl₃



HSQC and COSY NMR spectra of compound **25** in CDCl₃



HSQC and COSY NMR spectra of compound **31** in CDCl_3

IV. Anion binding studies by ^1H NMR spectroscopy

1. **LM28** with tetrabutylammonium chloride (TBACl)

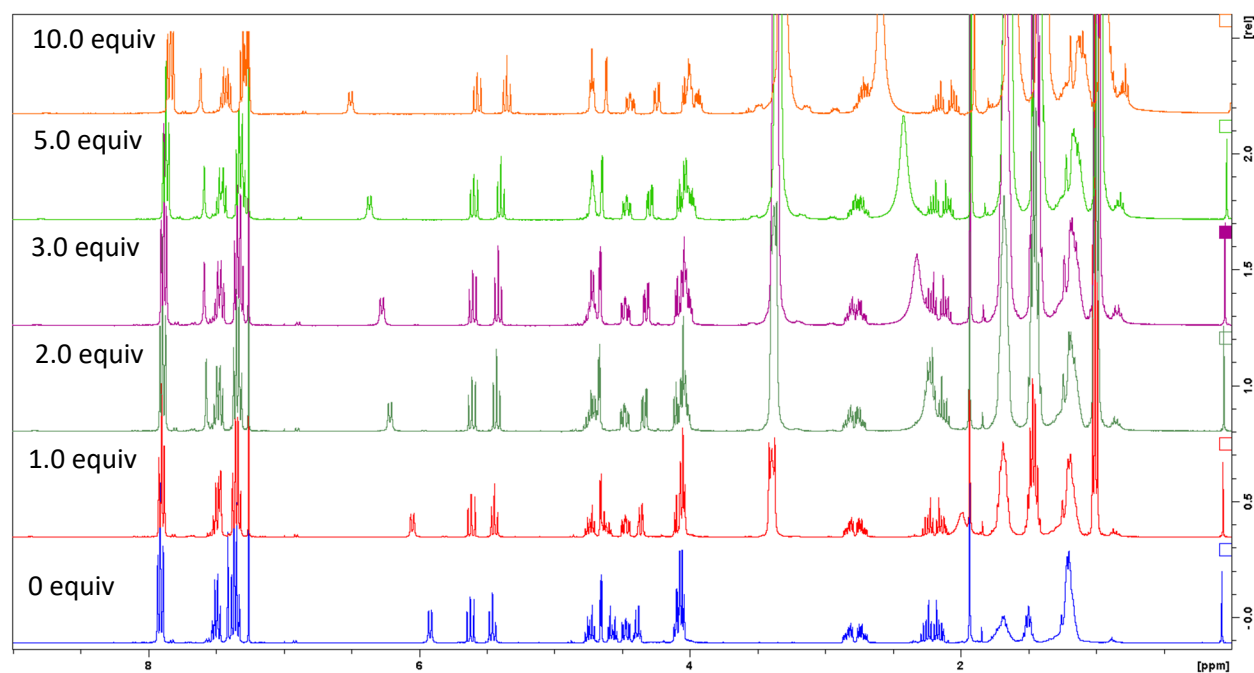


Figure S1. Stacked ^1H NMR spectra of **LM28** with different concentrations of TBACl (0-9 ppm)

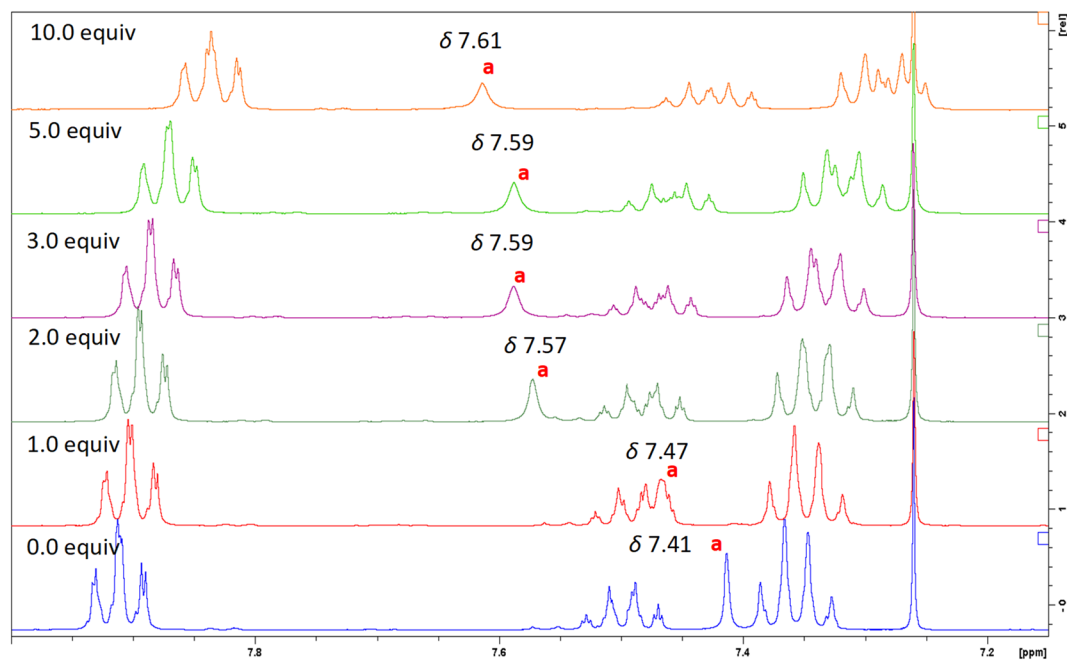


Figure S2. Stacked ^1H NMR spectra of **LM28** with different concentrations of TBACl.

2. **LM28** with tetrabutylammonium bromide (TBAB)

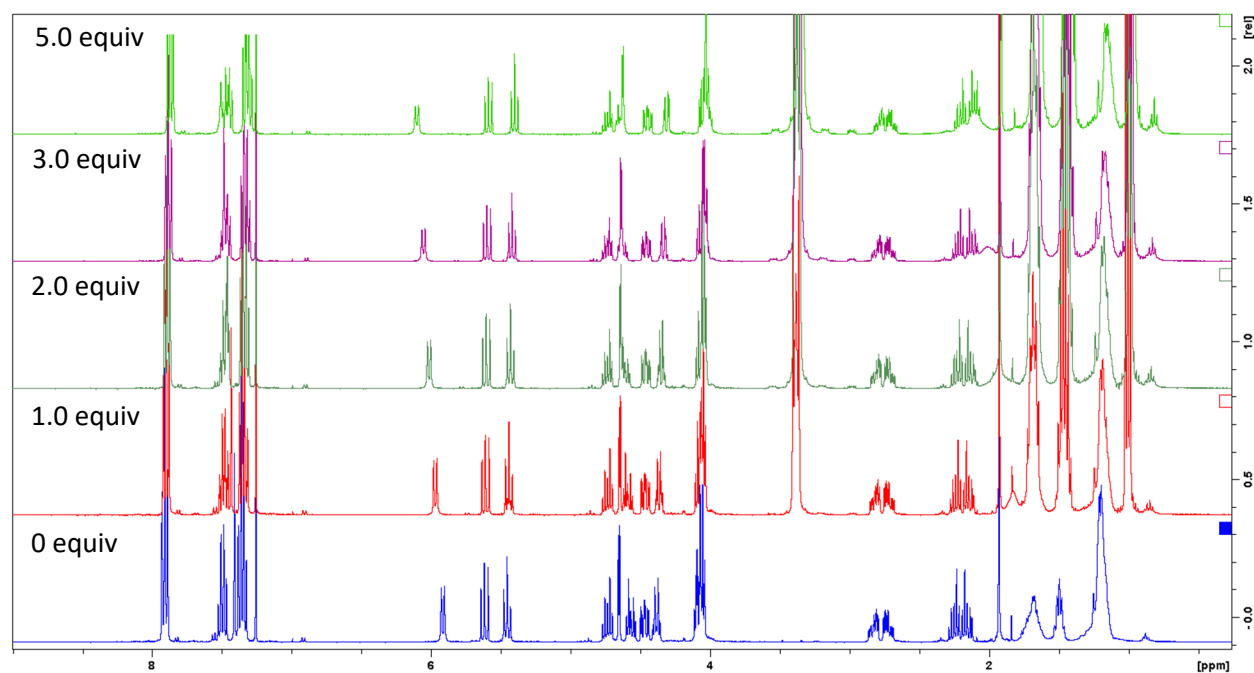


Figure S3. Stacked ^1H NMR spectra of **LM28** with different concentrations of TBAB (0-9 ppm).

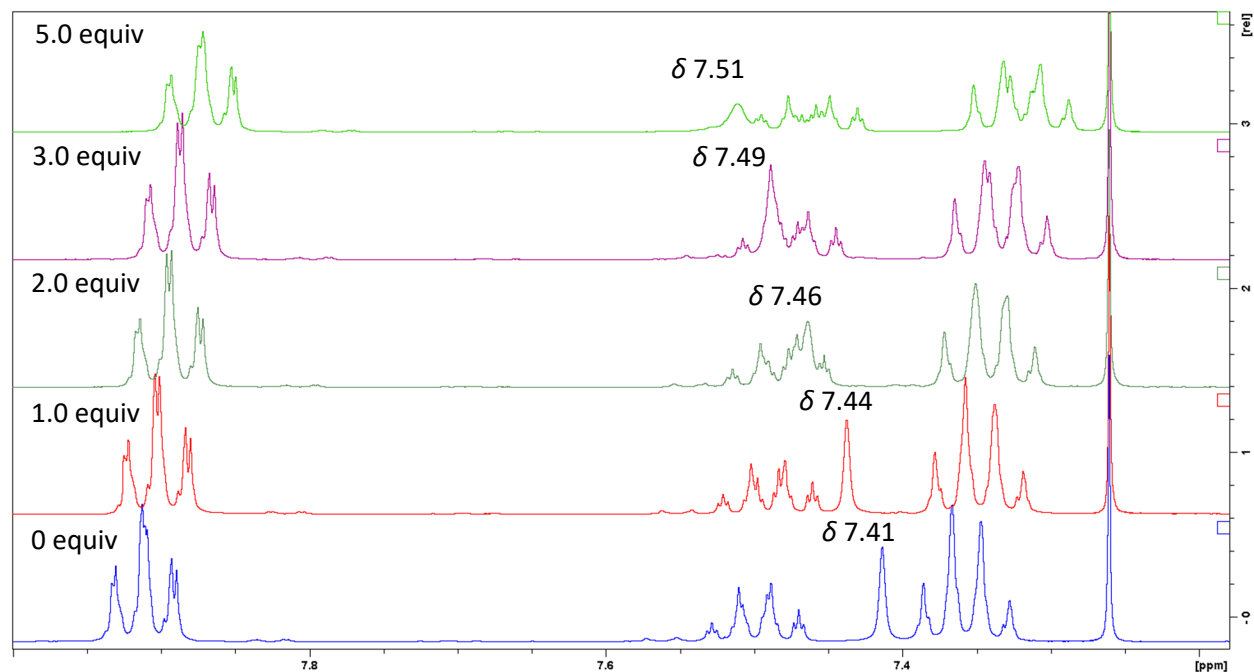


Figure S4. Stacked ^1H NMR spectra of **LM28** with different concentrations of TBAB, triazole proton labeled.

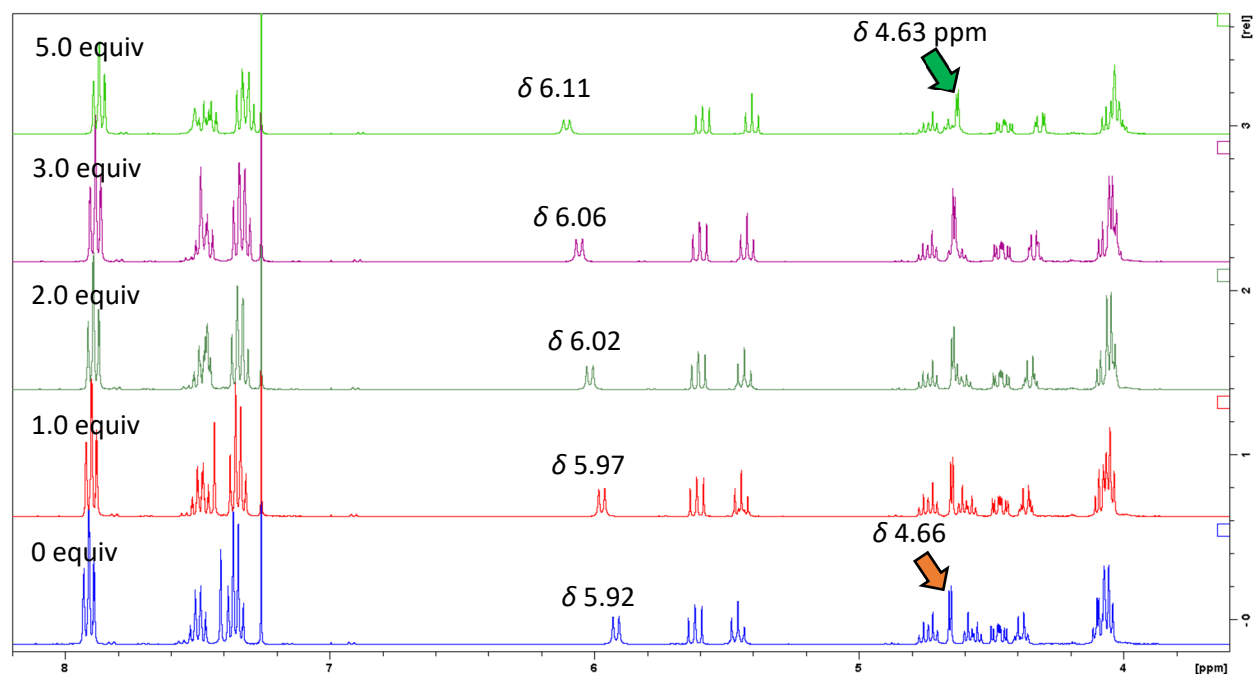


Figure S5. Stacked ^1H NMR spectra of **LM28** with different concentrations of TBAB.

3. **LM28** with tetrabutylammonium iodide (TBAI)

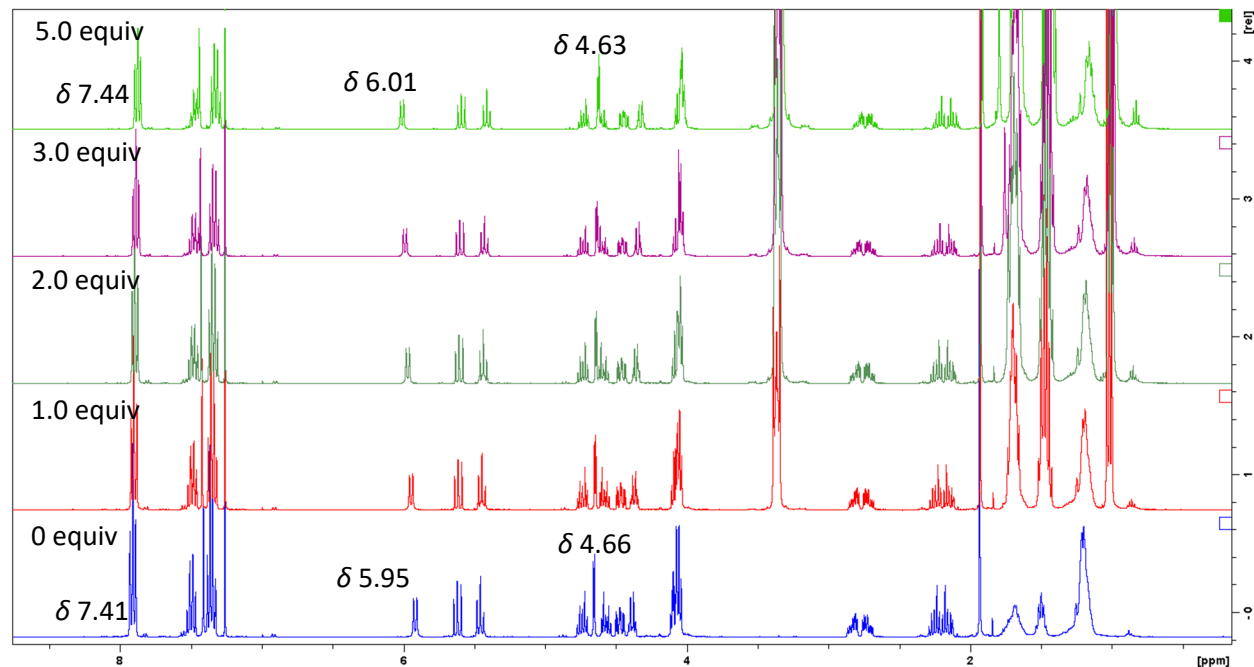


Figure S6. Stacked ^1H NMR spectra of **LM28** with different concentrations of TBAI (0-8.7 ppm).

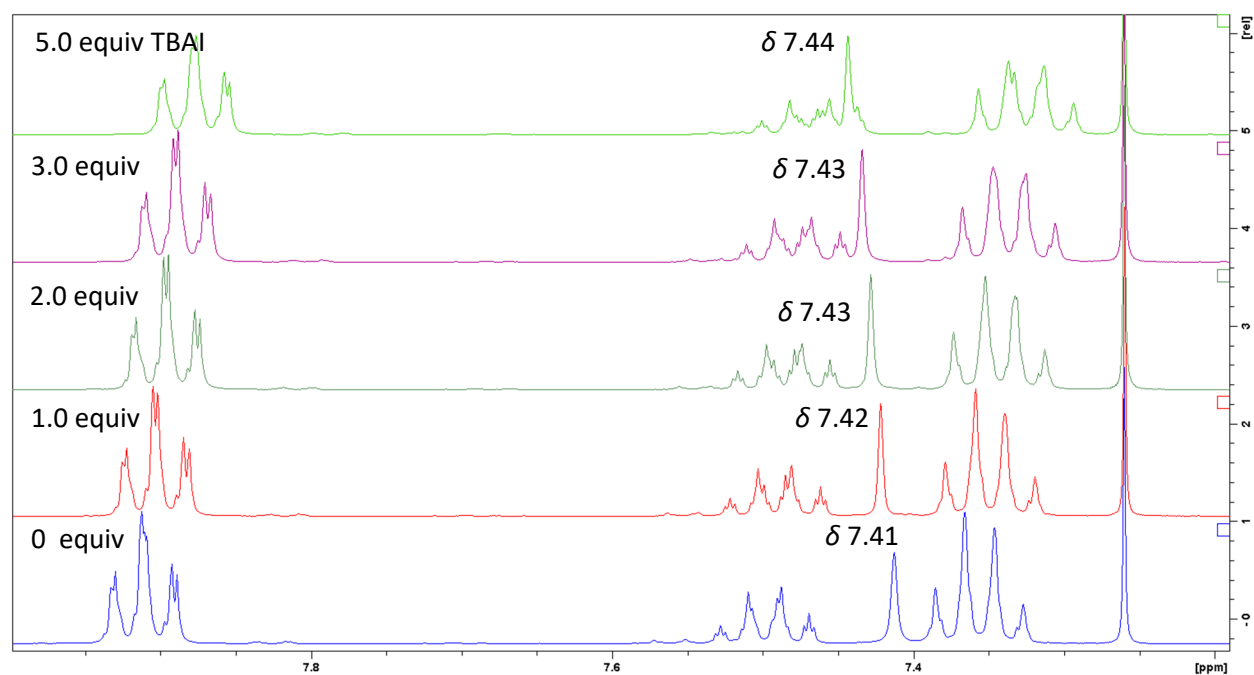


Figure S7. Stacked ^1H NMR spectra of **LM28** with different concentrations of TBAI.

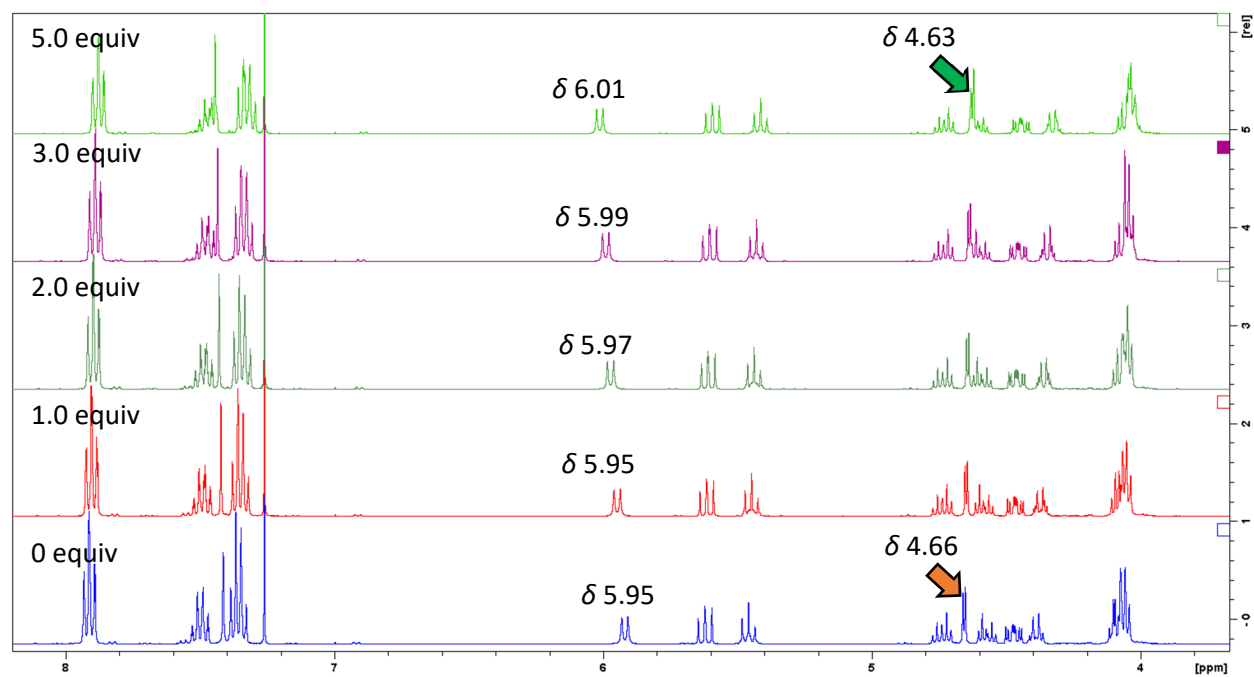


Figure S8. Stacked ^1H NMR spectra of **LM28** with different concentrations of TBAI.

4. DM35 with TBACl

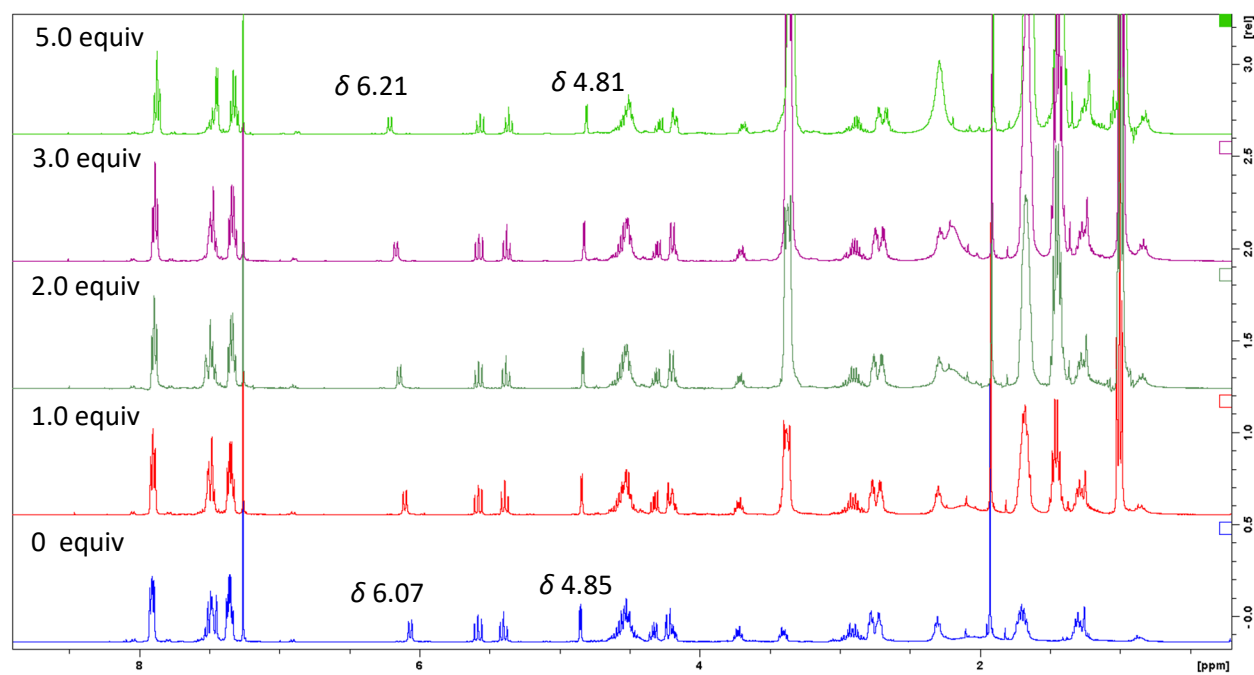


Figure S9. Stacked ^1H NMR spectra of **DM35** with different concentrations of TBACl.

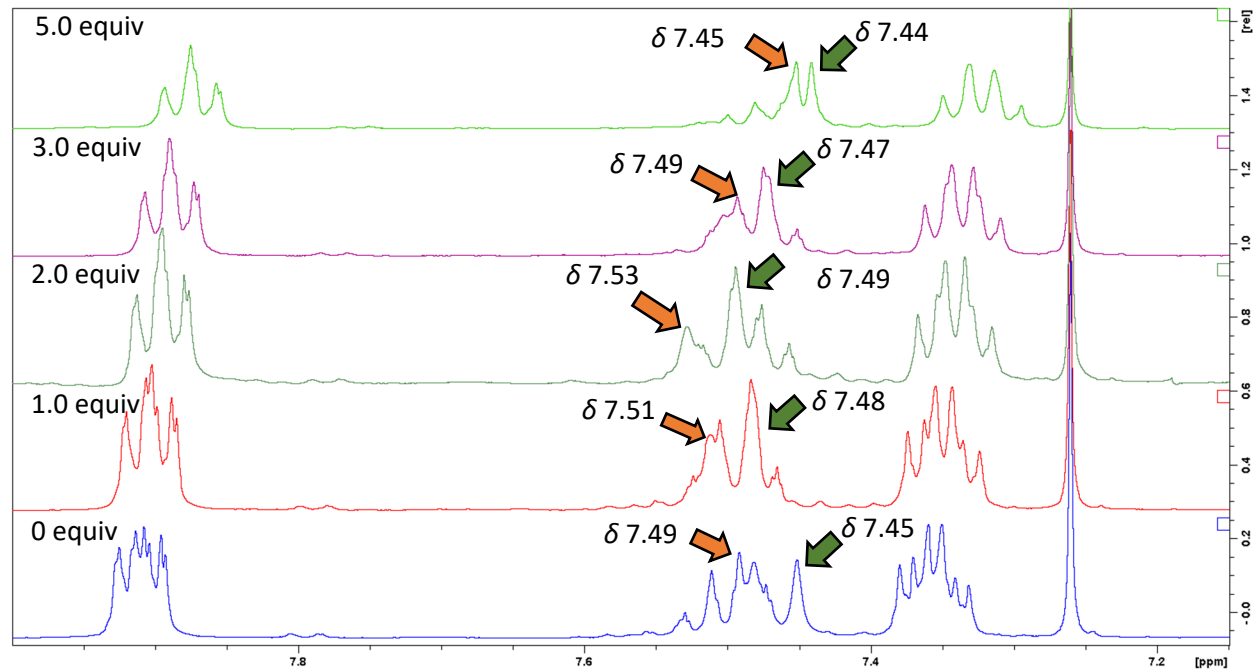


Figure S10. Stacked ^1H NMR spectra of **DM35** with different concentrations of TBACl, triazole protons labeled.

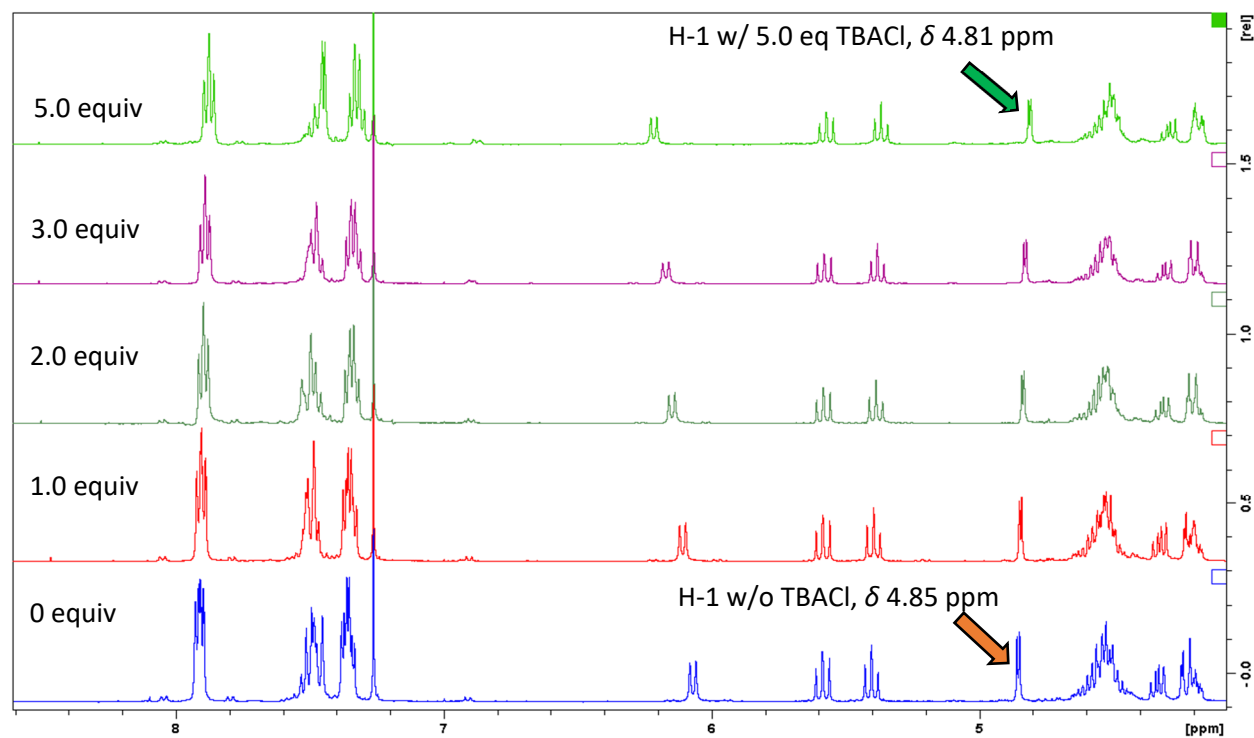


Figure S11. Stacked ^1H NMR spectra of **DM35** with different concentrations of TBACl.

5. **DM35** with TBAB

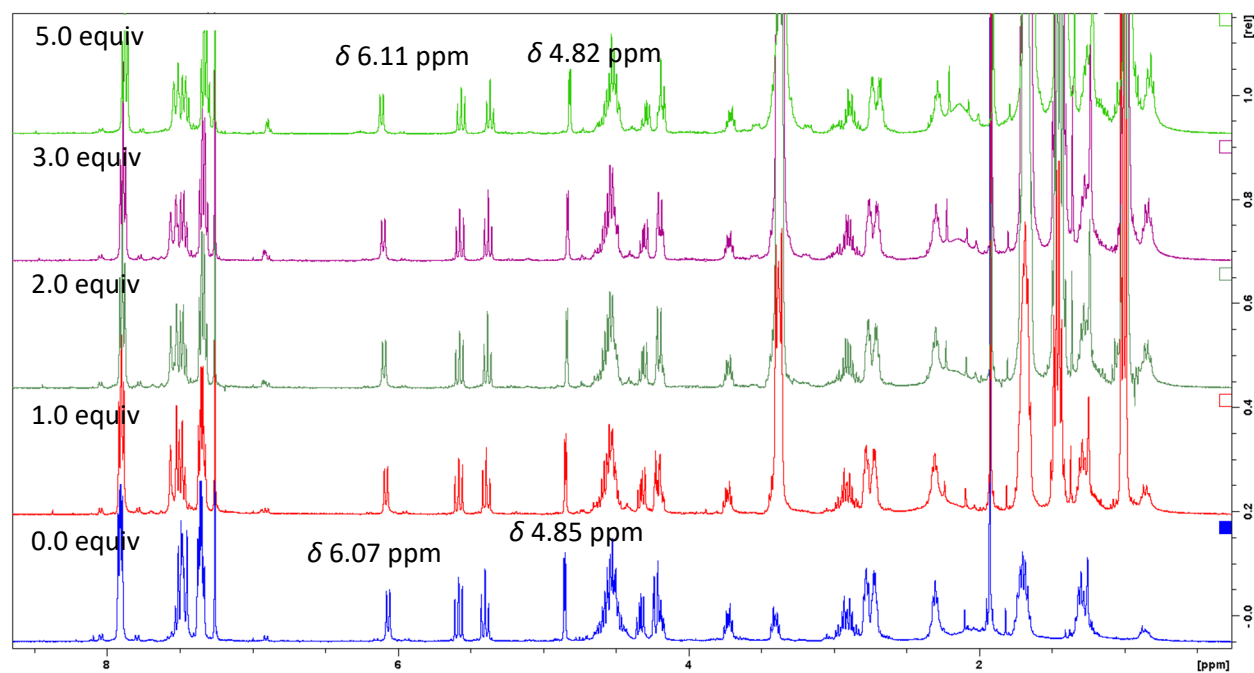


Figure S12. Stacked ^1H NMR spectra of **DM35** with different concentrations of TBAB.

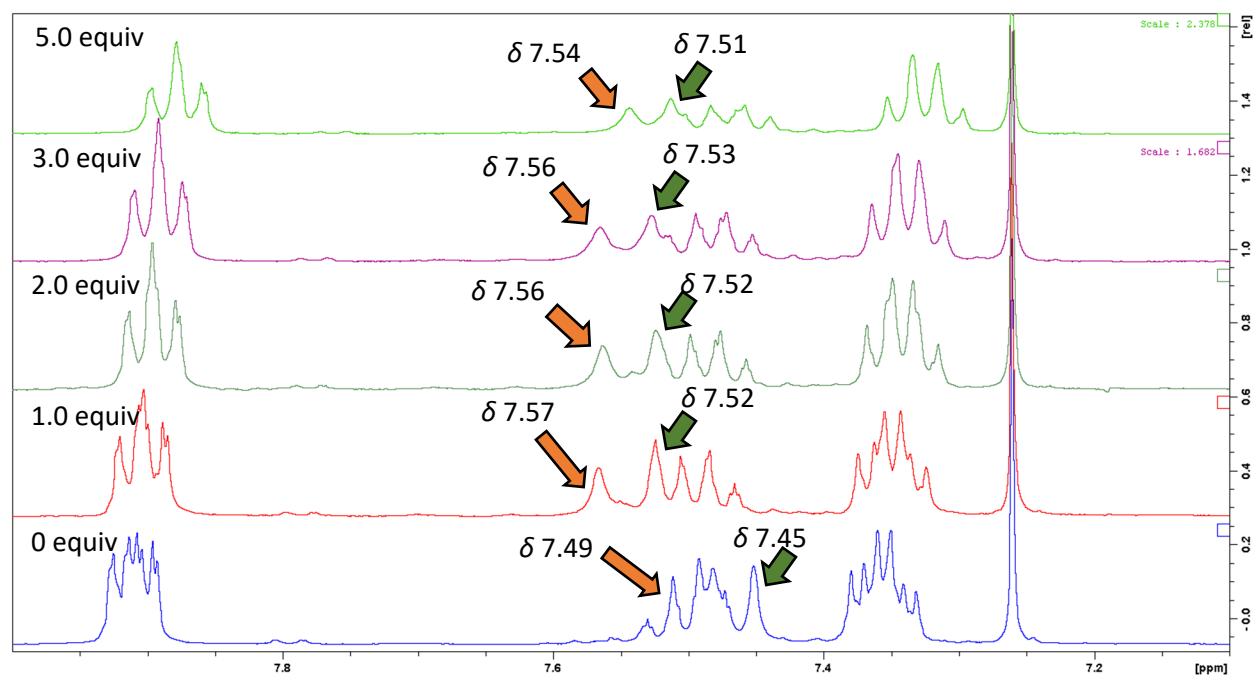


Figure S13. Stacked ^1H NMR spectra of **DM35** with different concentrations of TBAB, triazole protons marked.

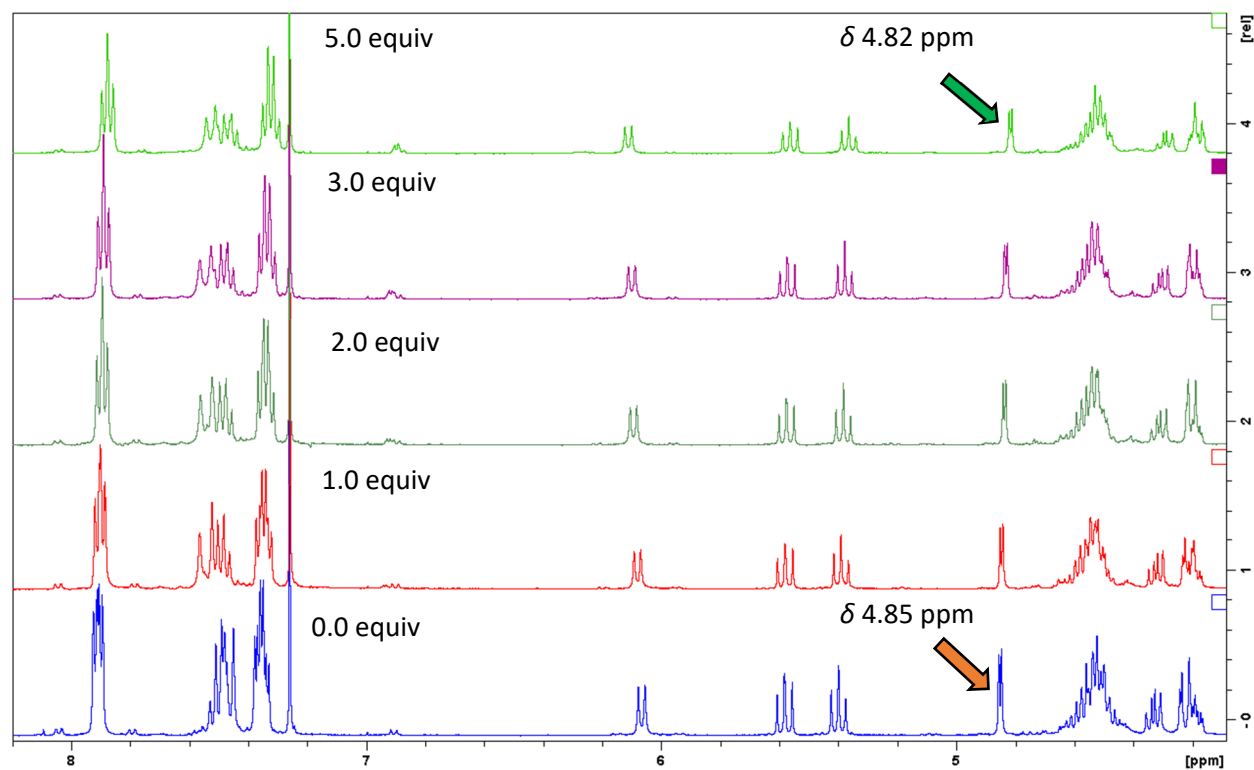


Figure S14. Stacked ^1H NMR spectra of **DM35** with different concentrations of TBAB.

6. DM35 with TBAI

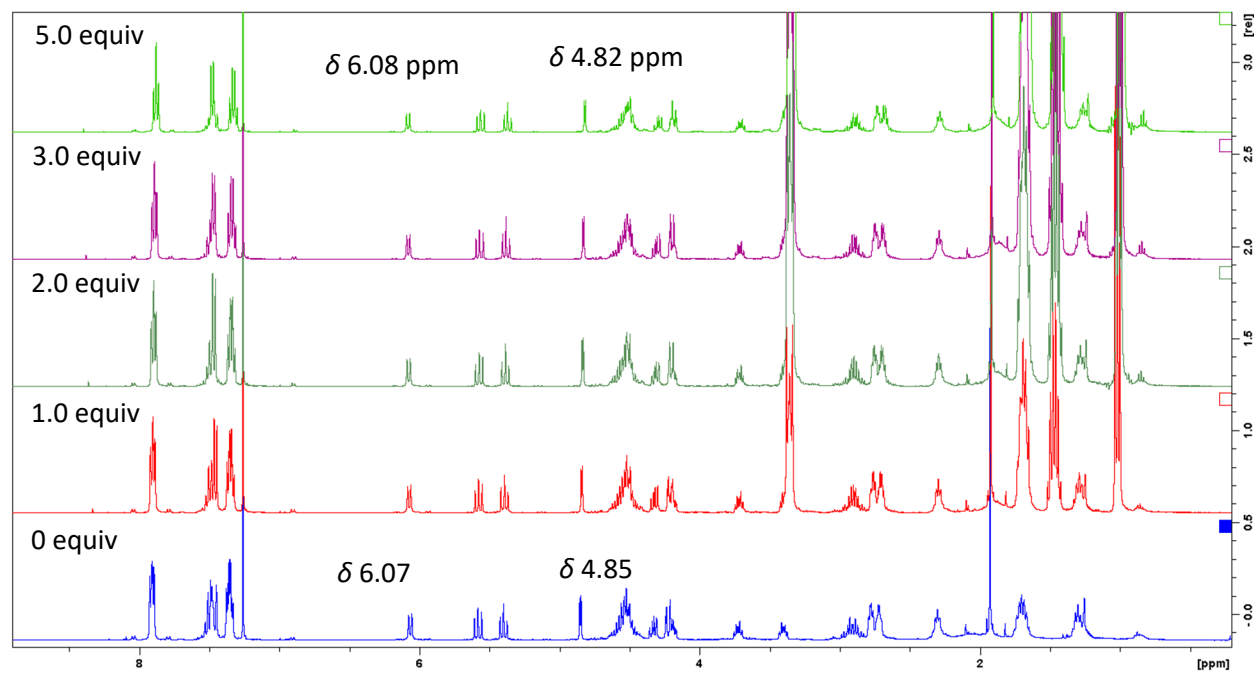


Figure S15. Stacked ^1H NMR spectra of **DM35** with different concentrations of TBAI.

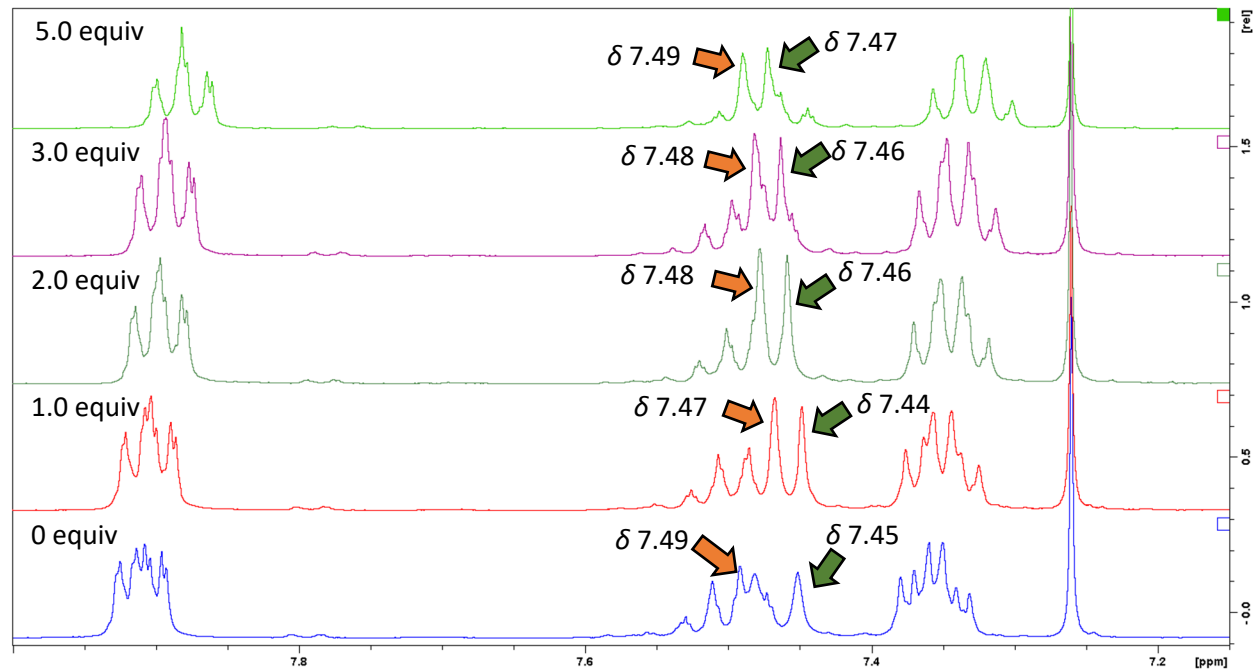


Figure S16. Stacked ^1H NMR spectra of **DM35** with different concentrations of TBAI, triazole protons labeled.

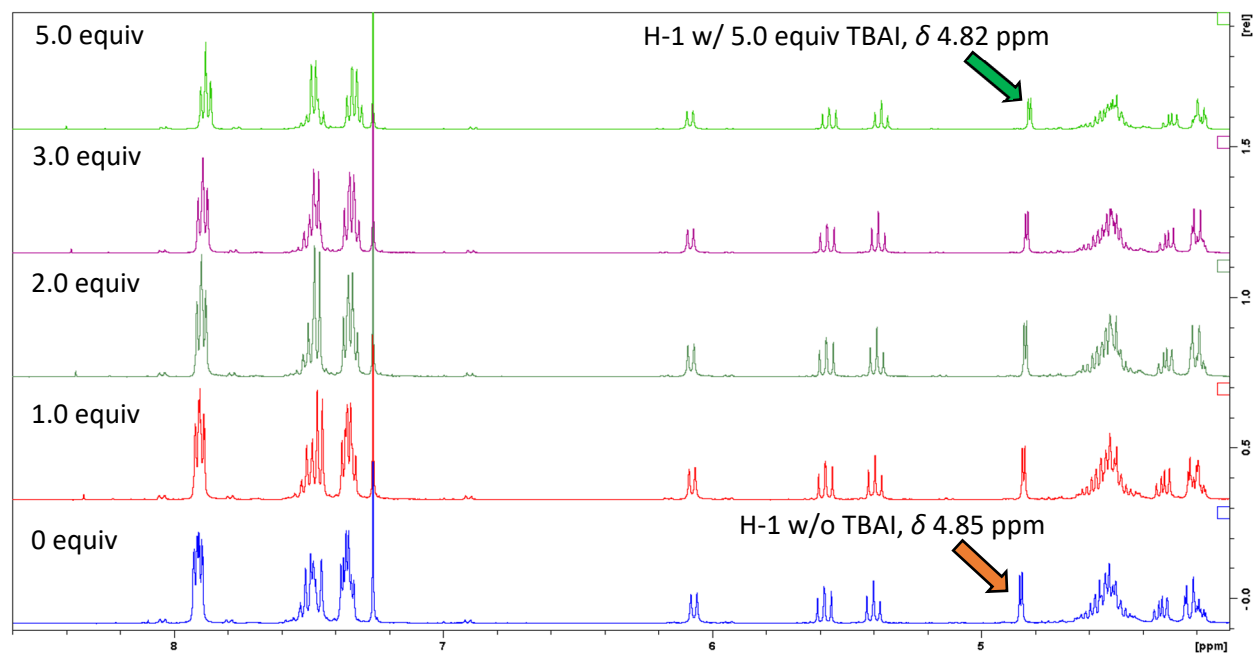


Figure S17. Overlay of ^1H NMR spectra of **DM35** with different concentrations of TBAI.

7. C2ML (compound **22**) with TBACl

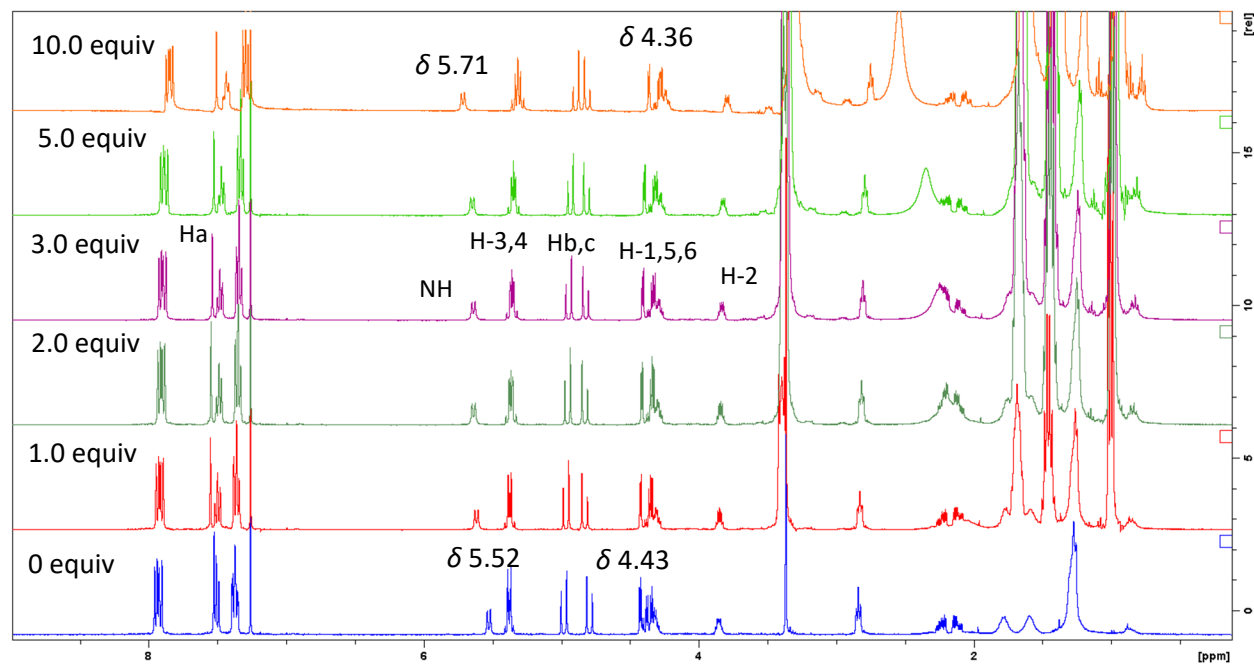


Figure S18. Stacked ^1H NMR spectra of compound **22** with TBACl (0-8.5 ppm).

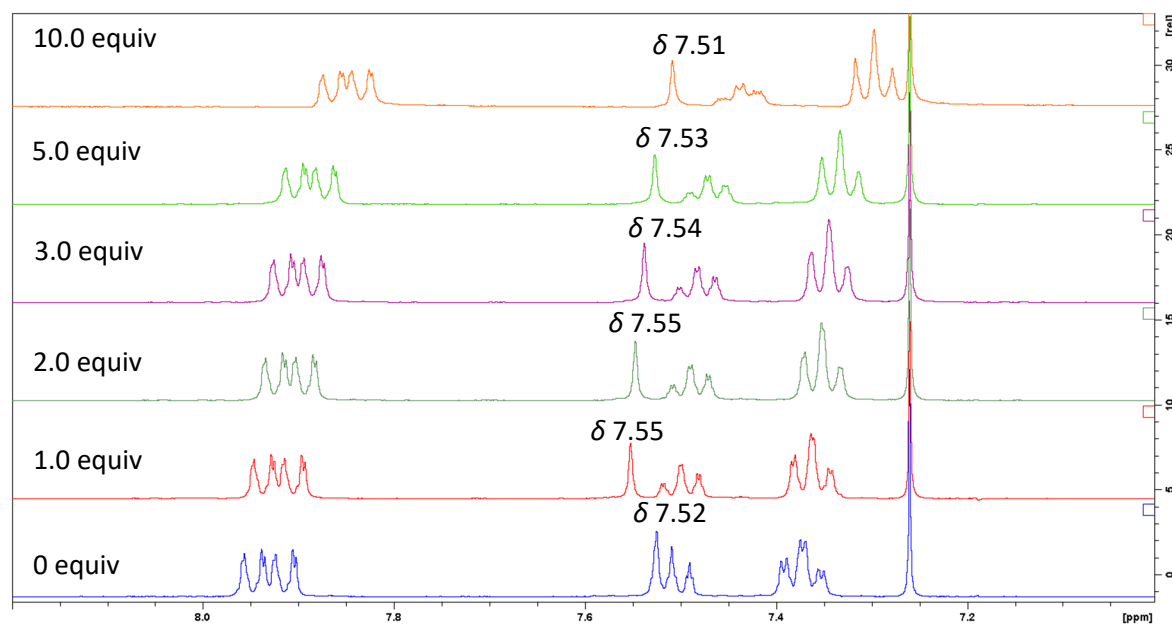


Figure S19. ^1H NMR spectra of compound **22** with TBACl, triazole signal marked.

8. C2DML (compound **24**) with TBACl

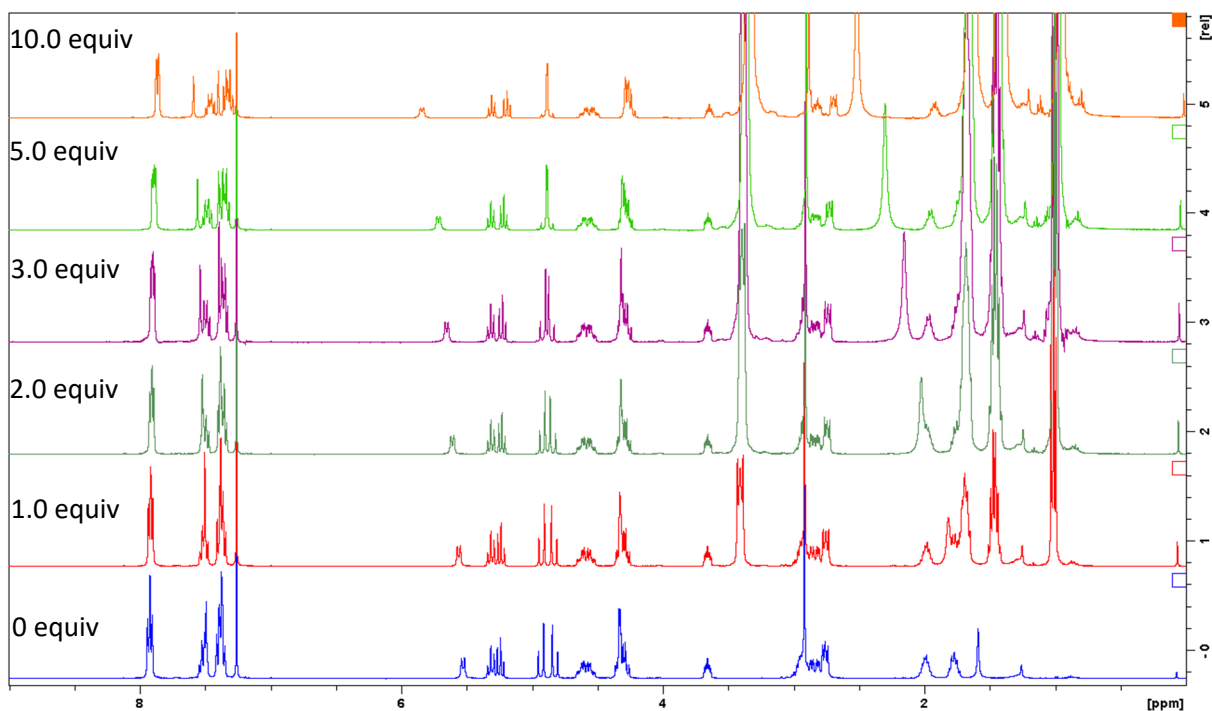


Figure S20. Stacked ^1H NMR spectra of compound **24** at different concentrations of TBACl.

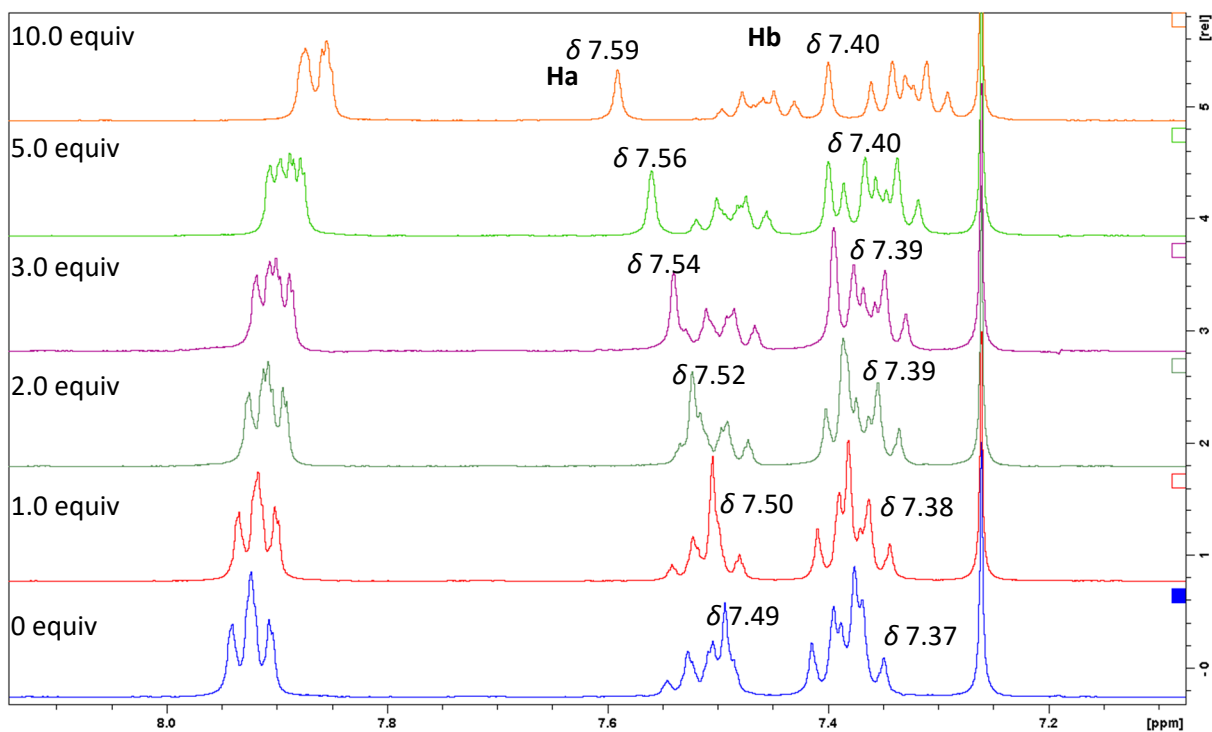


Figure S21. Stacked ^1H NMR spectra of compound **24** at different concentrations of TBACl,

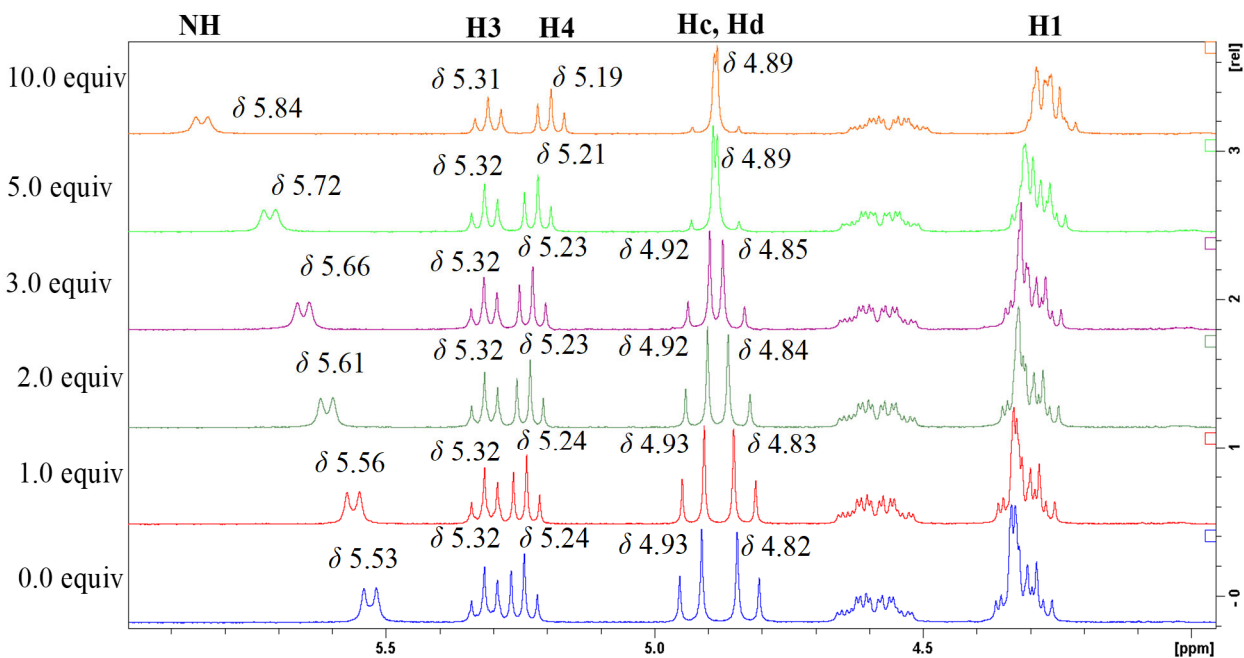


Figure S22. Stacked ^1H NMR spectra of compound **24** at different concentrations of TBACl.

V. Copper Binding Studies

DM35 with CuSO₄·5H₂O

To a 25 mL RBF, **DM35** (27.0 mg, 0.036 mmol, 1.0 equiv) was dissolved in 2.0 mL of EtOH:H₂O (v/v 1:1) and CuSO₄·5H₂O (9.23 mg, 0.036, 1.0 equiv) was added. The reaction mixture was refluxed for 3 hours to observe greenish solution. The ¹H NMR at 3.0 hour showed disappearance of triazole peaks. The reaction was stopped, and the solvent was removed under pressure to obtain light green solid.

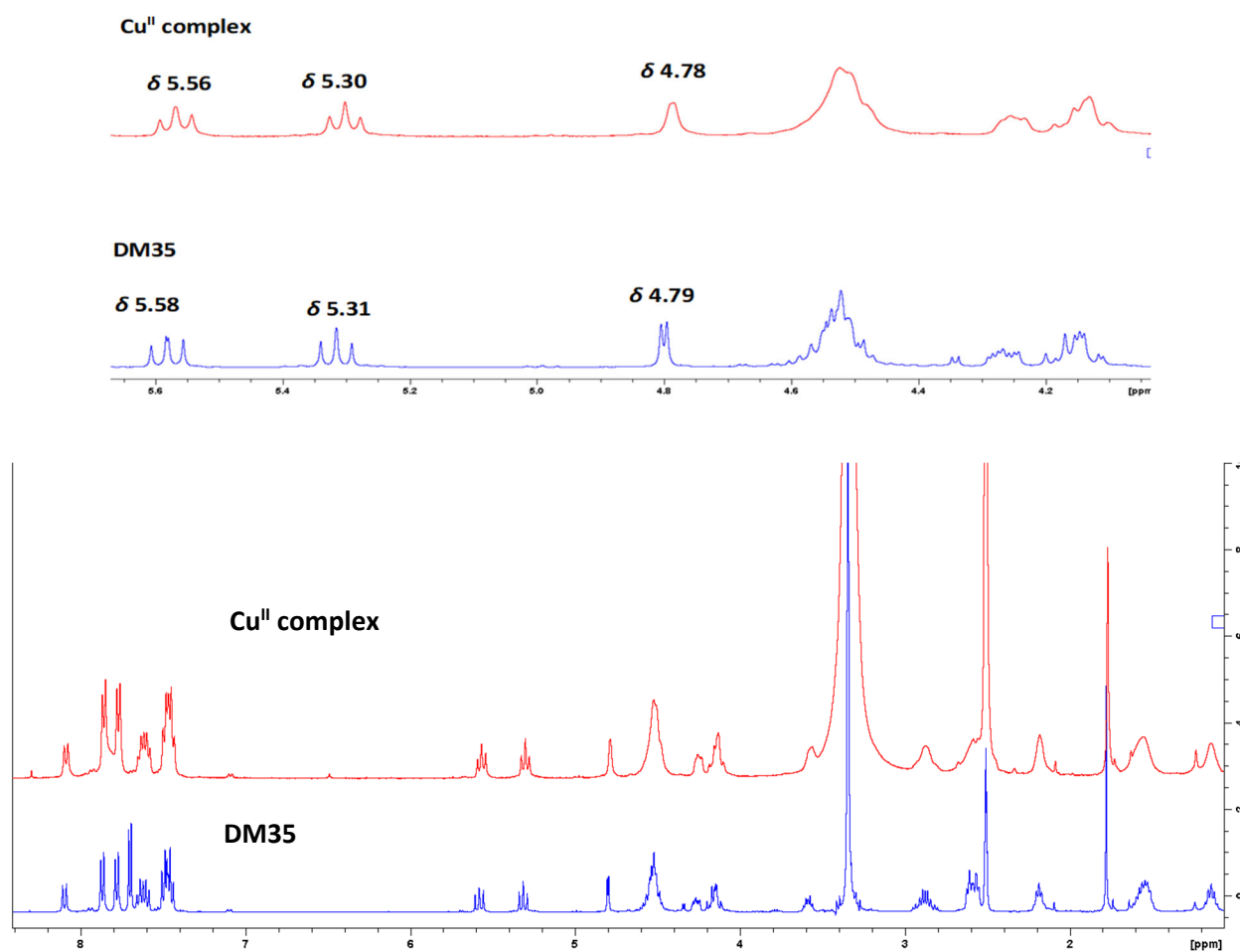


Figure S23. ¹H NMR spectra of **DM35** and its complex with CuSO₄·5H₂O in d₆-DMSO, the expanded regions are on top of the figure.

Temperature Study of DM35 Cu^{II} complex

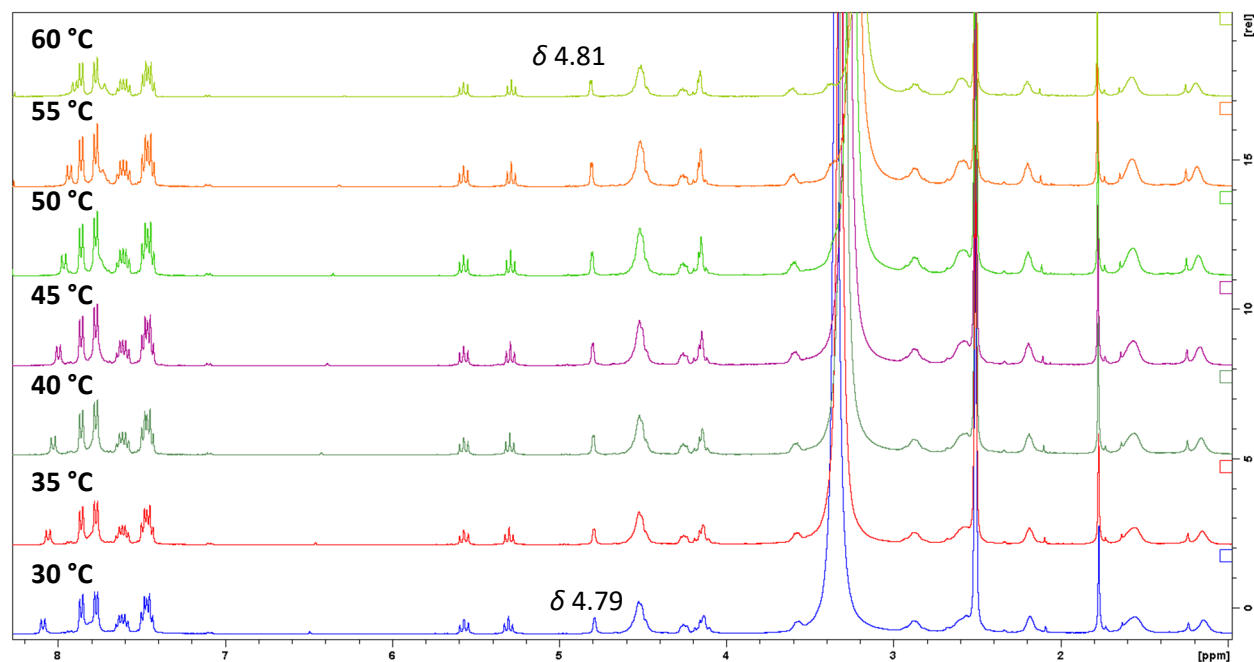


Figure S24. Stacked ¹H NMR spectra of **DM35** Cu^{II} complex with CuSO₄·5H₂O, full range.

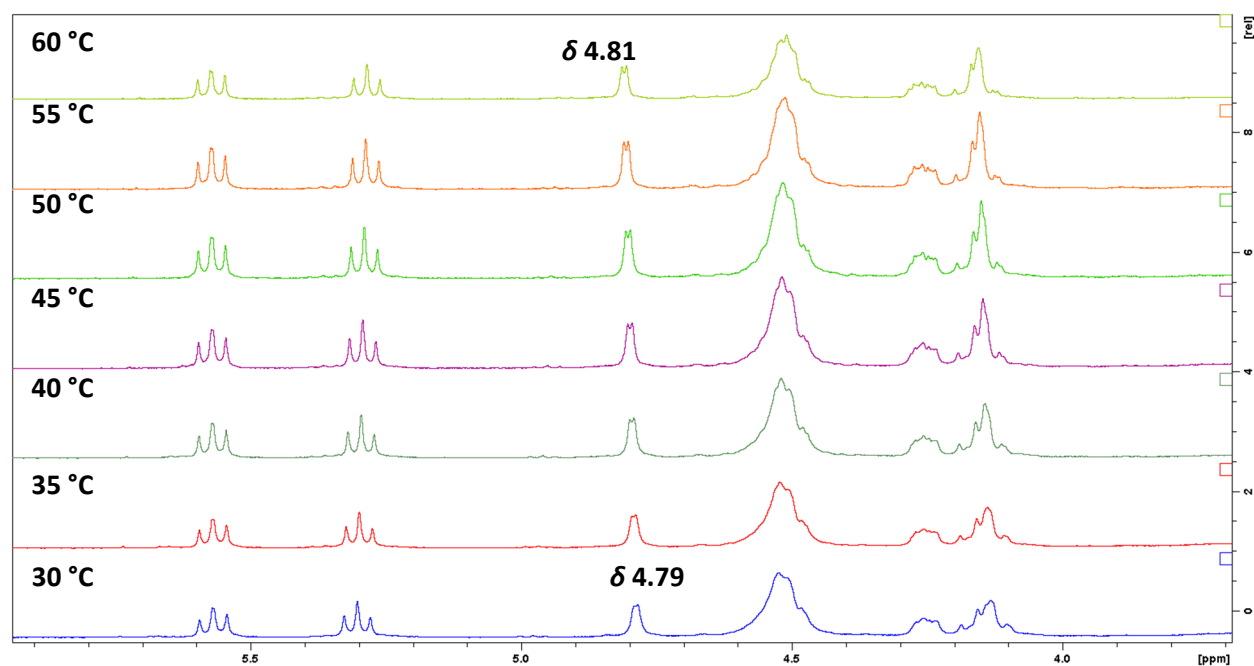


Fig S24a. ¹H NMR spectra of **DM35** Cu^{II} complex with CuSO₄·5H₂O, anomeric proton labeled.

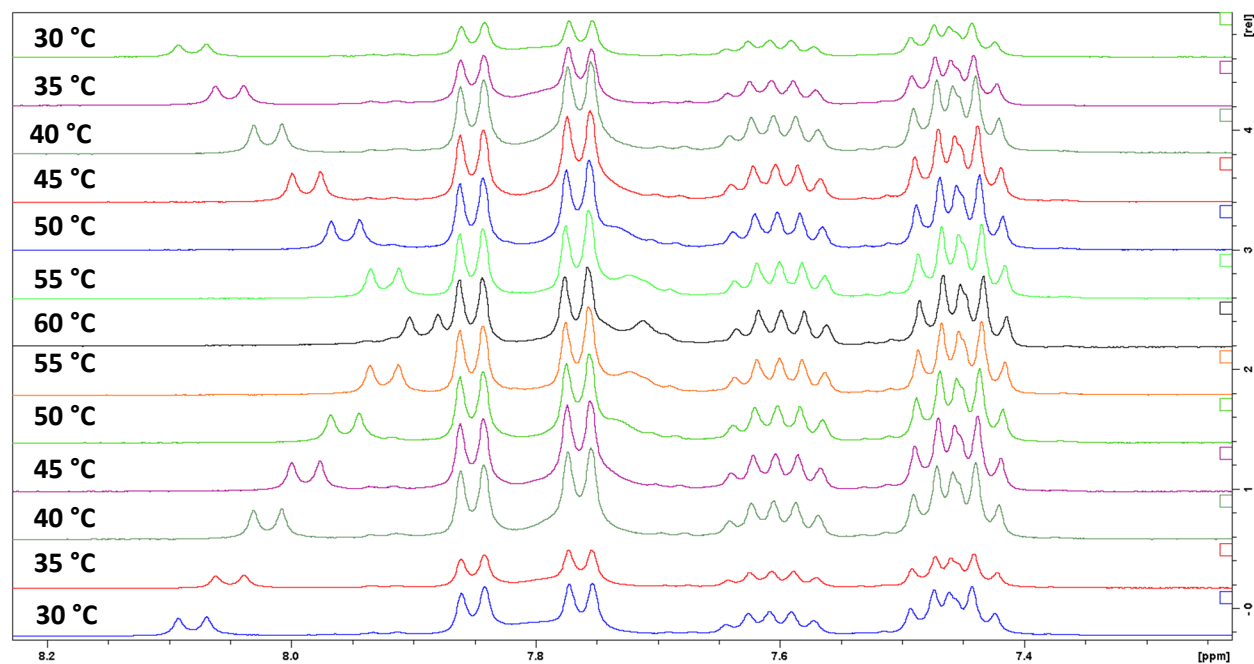


Figure S25. Stacked ^1H NMR spectra of **DM35** Cu^{II} complex with $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, increasing and decreasing the temperature.

DM35 with $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$

To a 25 mL RBF, **DM35** (12.0 mg, 0.016 mmol, 1.0 equiv) was dissolved in 1.0 mL of EtOH and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (3.28 mg, 0.016, 1.0 equiv) was added. The reaction mixture was refluxed for 2 hours to observe greenish blue solution. The ^1H NMR at 2.0 hour showed the only the broad peaks except for both triazole peaks moved downfield with broadening. The reaction was stopped, and the solvent was removed under pressure to obtain greenish solid.

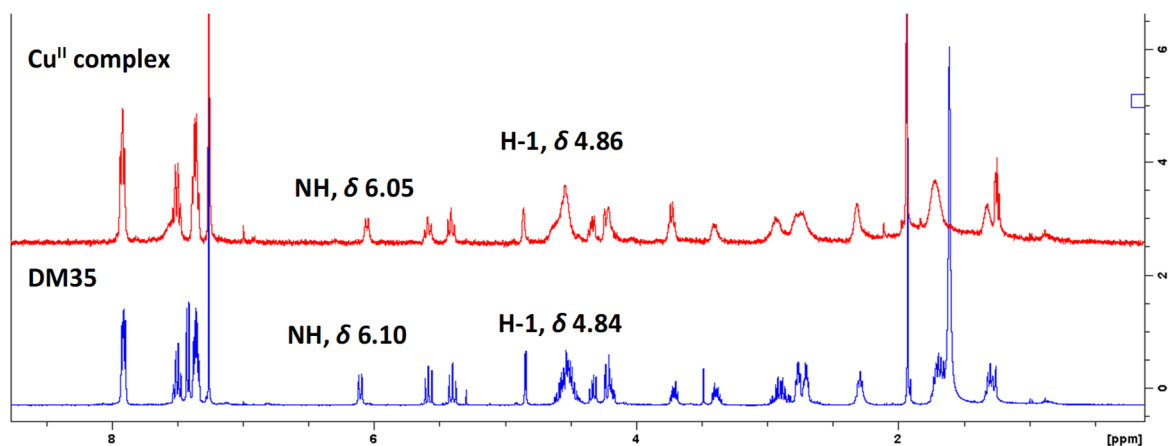


Figure S26. Stacked ^1H NMR spectra of **DM35** and its Cu^{II} complex with $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$.

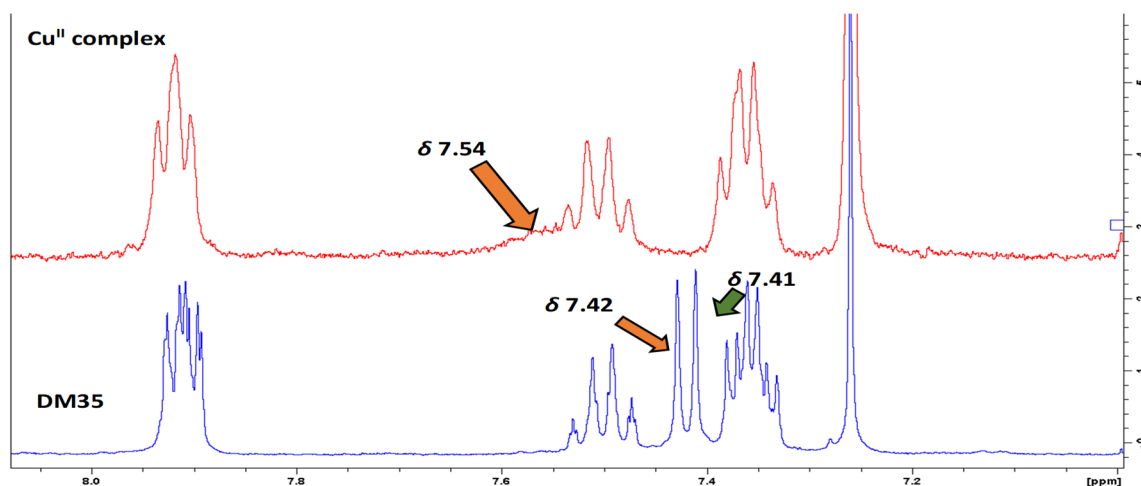


Figure S27. ^1H NMR spectra of **DM35** and its complex with $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, triazole proton.

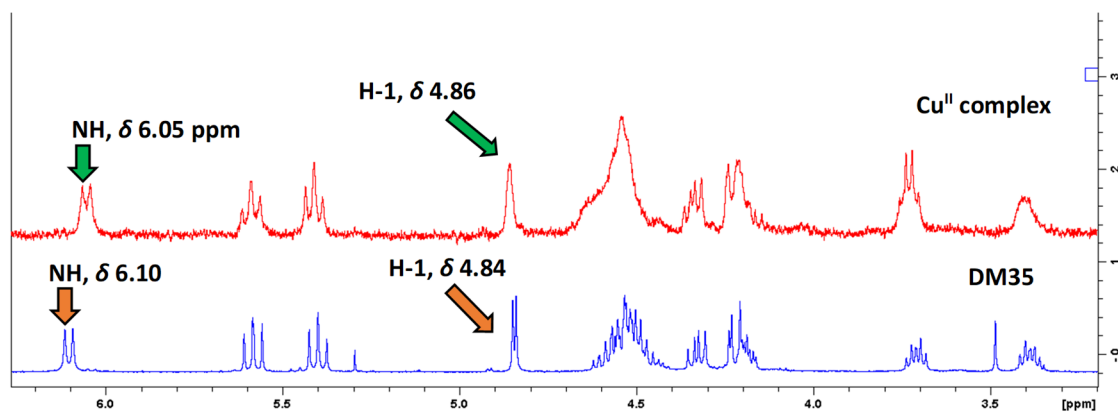


Figure S28. Stacked ^1H NMR spectra of **DM35** and its Cu^{II} complex with $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, anomeric proton.

LM28 with CuSO₄·5H₂O

To a 25 mL RBF, **LM28** (10.0 mg, 0.015 mmol, 1.0 equiv) was dissolved in 2.0 mL of EtOH:H₂O (v/v 1:1) and CuSO₄·5H₂O (3.8 mg, 0.015, 1.0 equiv) was added. The reaction mixture was refluxed for 2.0 hours to observe clear solution. The ¹H NMR at 2.0 hour showed down field shift of triazole peak. The reaction was stopped, and the solvent was removed under pressure to obtain white solid.

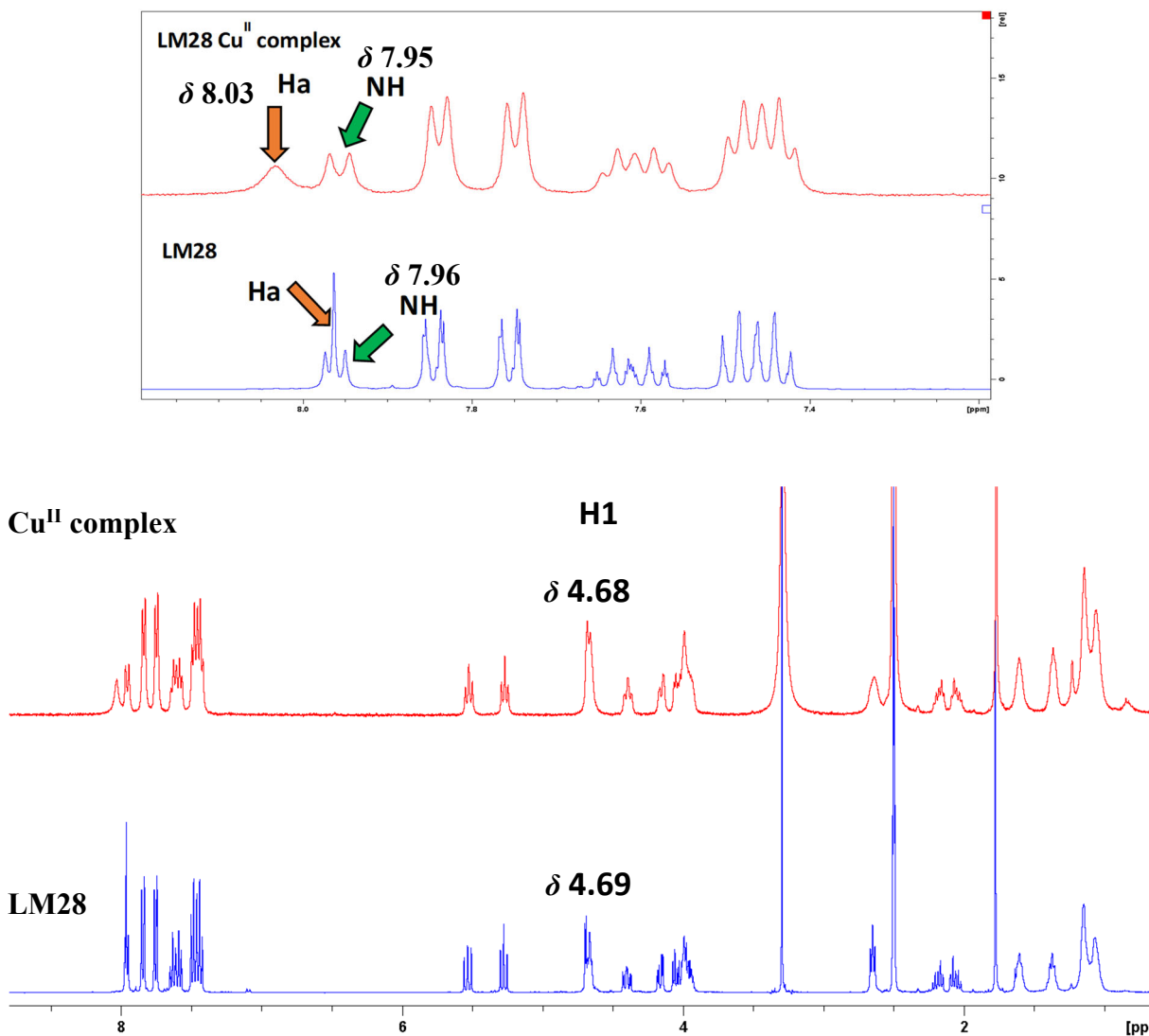


Figure S29. Stacked ¹H NMR spectra of **LM28** complex with CuSO₄·5H₂O full range, top insert shows NH and triazole proton.

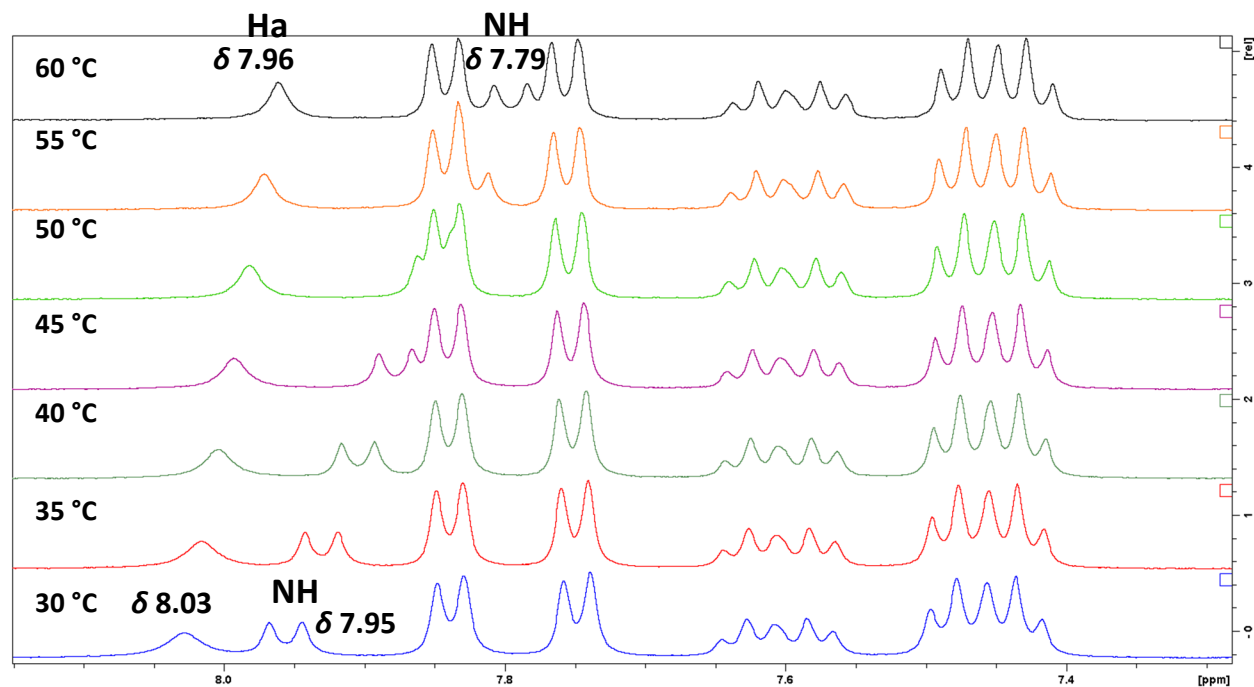


Figure S30. Stacked ^1H NMR spectra of **LM28** Cu^{II} complex with $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$.

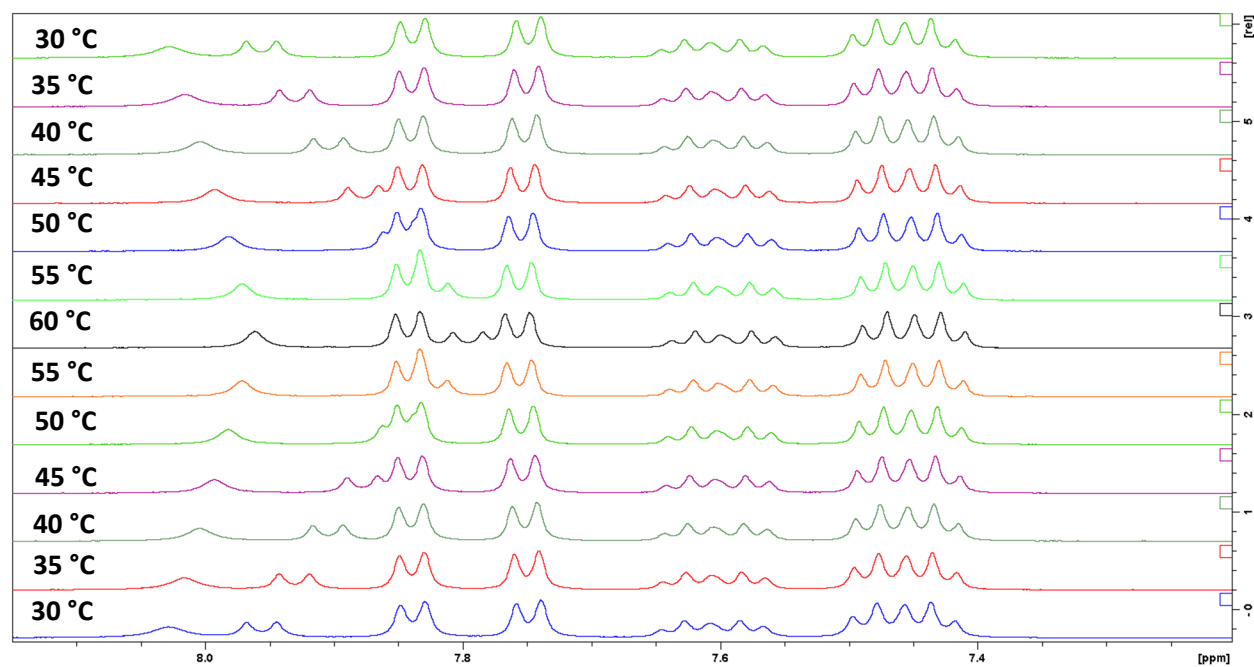


Figure S31. Stacked ^1H NMR spectra of **LM28** Cu^{II} complex with $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, anomeric proton, increasing and decreasing temperatures.

Compound **24** with $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$

Compound **24** (16.0 mg, 0.03 mmol, 1.0 equiv) was dissolved in 2.0 mL of EtOH:H₂O (v/v 1:1) and $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (5.8 mg, 0.016, 1.0 equiv) was added. The reaction mixture was refluxed for 3 hours to observe clear solution. The ¹H NMR at 3.0 hour showed disappearance of triazole peaks. Only broad peak (hump) appeared downfield due to the paramagnetism. The reaction was stopped, and the solvent was removed under pressure to obtain light green solid.

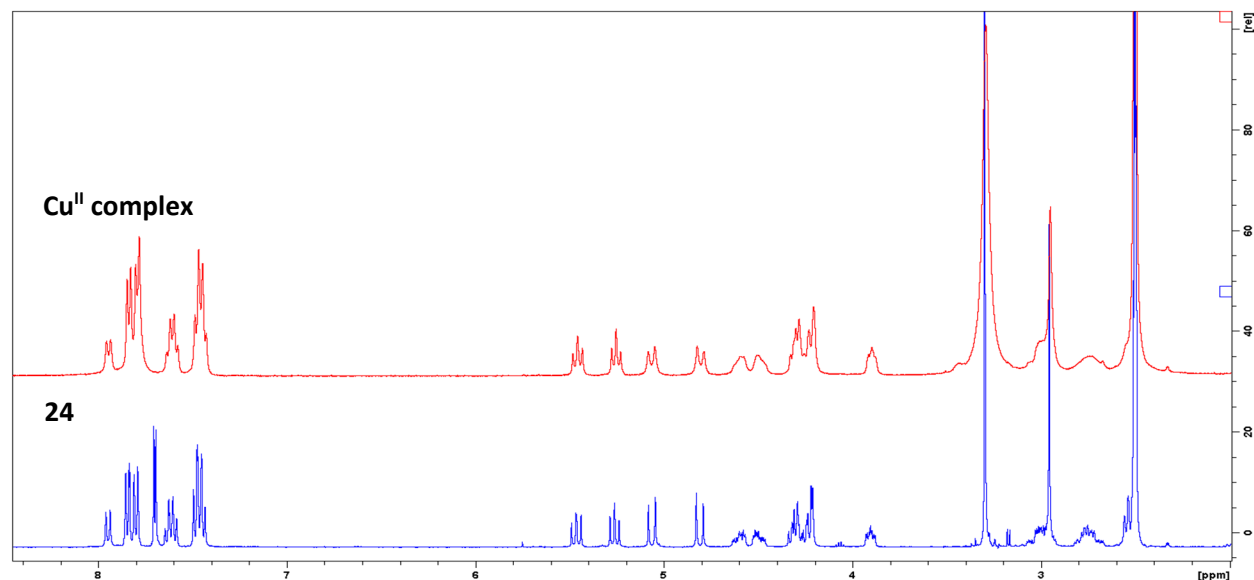


Figure S32. Overlay of ¹H NMR spectra of compound **24** and its Cu^{II} complex with $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$.

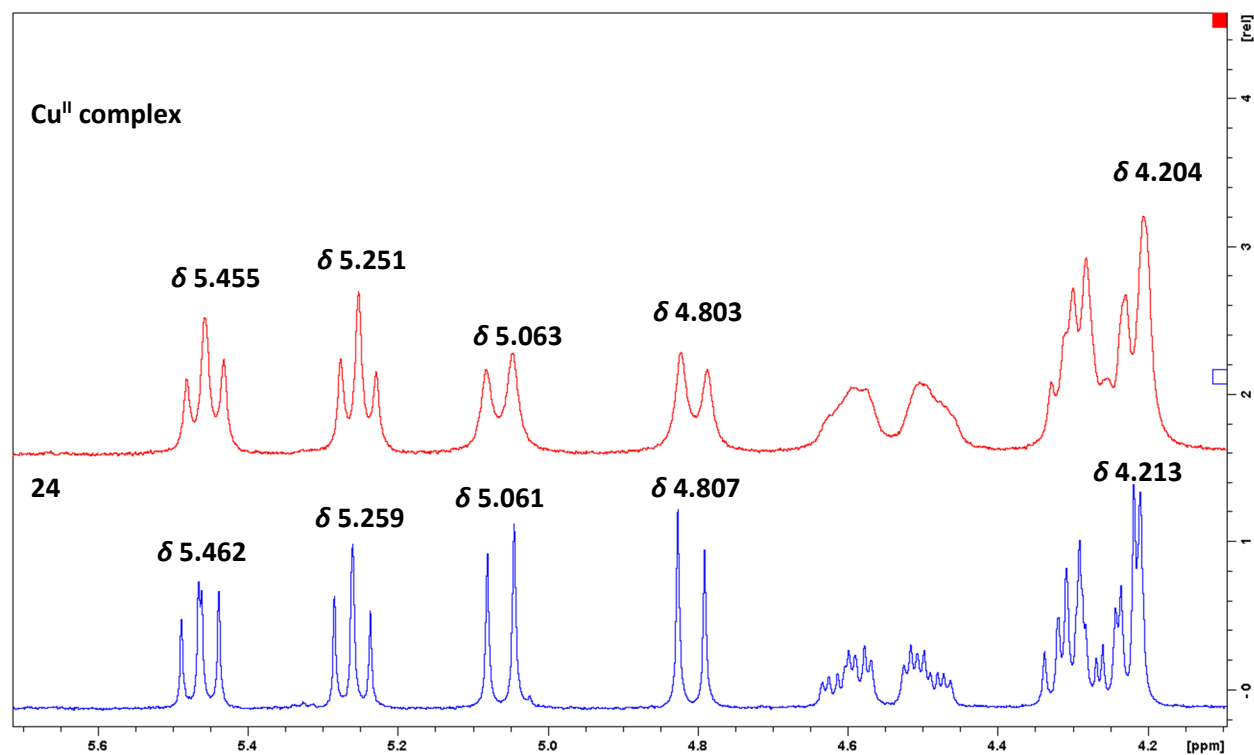


Figure S33. Stacked ¹H NMR spectra of compound **24** and its Cu^{II} complex with CuSO₄·5H₂O.

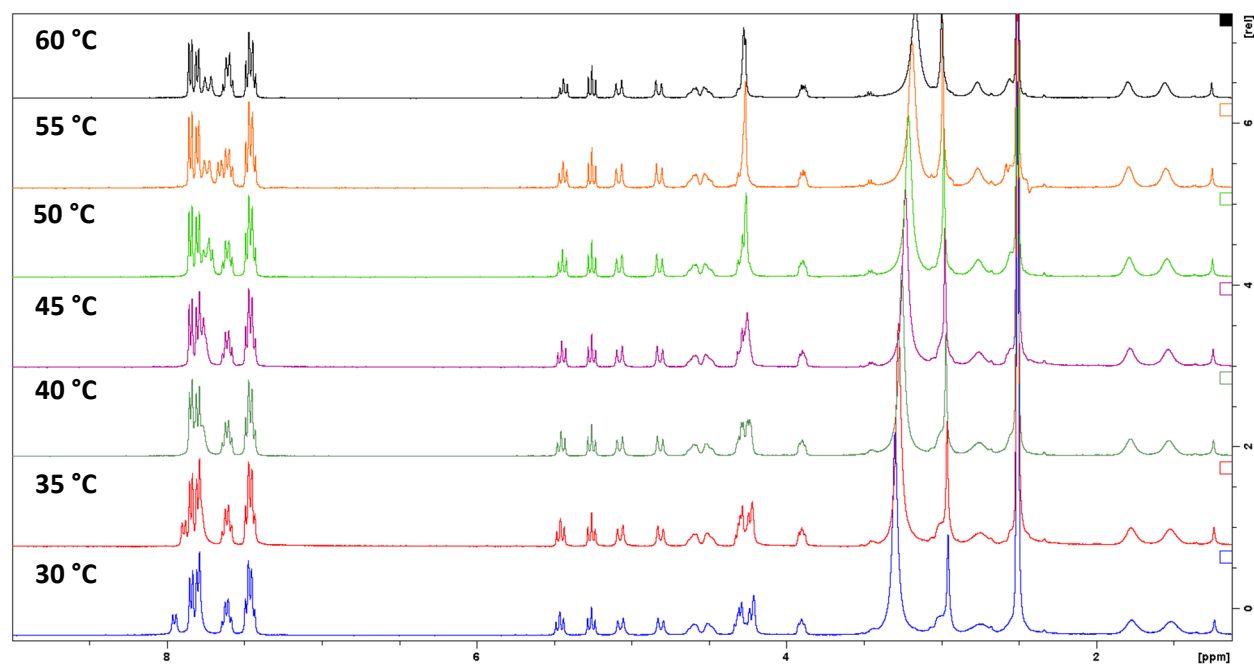


Figure S34. Stacked ¹H NMR spectra of compound **24** Cu^{II} complex with CuSO₄·5H₂O at different temperature.

VI. Screening Macrocycles for Azide Alkyne Cycloadditions

1. General method for the cycloaddition reactions of sugar azide with alkynes

The screening reactions were carried out in a Heidolph carousel 12 plus reaction station system with 20 mL glass vessels. The click test reactions were performed using the apparatus under nitrogen atmosphere at controlled temperatures using similar method as described. Control experiments without macrocycles were carried out in the same batch under the same conditions with other reactions. The reaction vessel was flushed with nitrogen, about 40.0 mg of the sugar azide **26** was added to then macrocycles were then added, followed by 1.0 mL of ethanol and the corresponding alkynes (1.2 to 1.5 equiv), followed by addition of 1.0 mL CuSO₄ aqueous solution and lastly NaAsc. The reaction vessel was capped and nitrogen balloon was used to maintain the reaction under nitrogen atmosphere. The reaction was set to stir at 1000 rpm and temperature was set at 30.0 °C. CuSO₄·5H₂O (54.0 mg) was dissolved in 10.0 mL of DI water (degassed) to prepare the stock solution for reactions of 40.0 mg of the azide for phenyl acetylene; and 27.0 mg of CuSO₄·5H₂O was dissolved in 10 mL of DI water (degassed) to make the stock solution for 1-octyne.

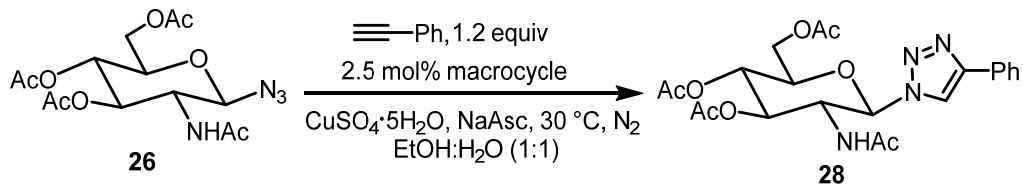
2. Tables and stacked ¹H NMR spectra of click reaction catalyst screening

2.1 Selected screening for phenylacetylene

Synthesis of compound **28**,^{5,6} general procedure for Tables 2 and S1

Sugar azide (40.0 mg, 0.107 mmol, 1.0 equiv) and Phenylacetylene (17 μ L, 0.16 mmol, 1.5 equiv) were dissolved in EtOH: H₂O (v 1:1, 2.0 mL), then CuSO₄·5H₂O (5.36 mg, 0.02 mmol, 0.2 equiv), sodium ascorbate (106 mg, 0.05 mmol, 0.5 equiv) were added to the reaction mixture. To this mixture macrocycle **DM35** (1.97, 2.5 mol%) was added. The reaction was stirred rt for 1.0 h to at which time the starting material was full converted to product, as indicated by ¹H NMR. The reaction was stopped, and solvent was removed using a rotavap, to obtain the crude, which was further purified with flash chromatography using eluent of DCM to 2% MeOH/DCM to obtain the desired product as white solid (49 mg, 96%), R_f = 0.29 in 5% MeOH/DCM. Additional screening reaction was carried out using 1.5 equivalent of phenylacetylene as shown in Table S2.

Table S1. Effect of the macrocycle on catalyzing the click chemistry using phenyl acetylene



Entry	MC code	Conversion (%) at 1 h	Conversion (%) at 2 h	Conversion (%) at 5 h	Conversion (%) at 9 h
1		-	15	21	N/A
2	LM24	38	50	57	68
3	LM26	57	61	78	85
4	LM28	57	61	67	79
5	LM34	55	66	79	93
6	LM36	56	60	77	89
7	LM38	49	49	51	51
8	DM24	51	51	54	58
9	DM25	68	84	100	
10	DM34	53	60	61	65
11	DM35	68	81	100	

Condition: Sugar azide (1.0 equiv, 40.0 mg), $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.2 equiv, 5.4 mg), phenylacetylene (1.2 equiv, 14.0 μL), EtOH/H₂O (v/v 1:1, 2.0 mL), macrocycle (2.5 mol%), NaAsc (0.4 equiv, 8.5 mg).

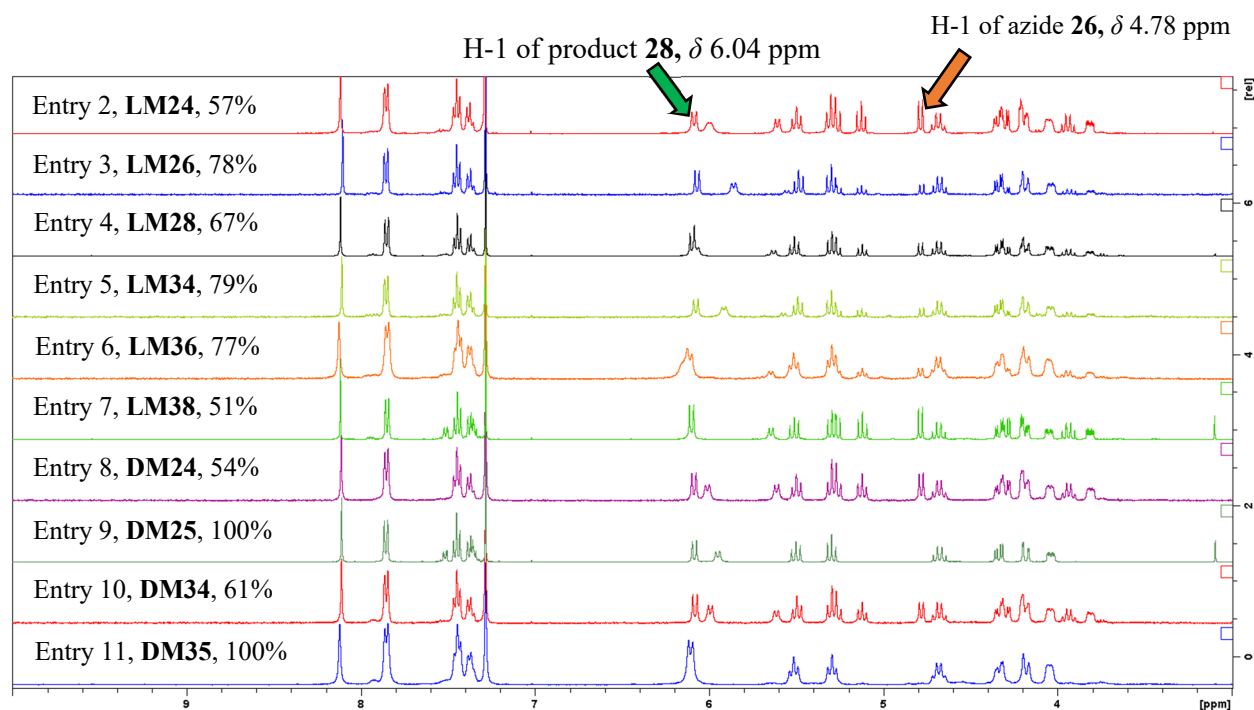


Figure S35. Overlay of ^1H NMR spectra of entries 2-11 at 5 h.

Table S2. Effect of the macrocycle on catalyzing the click chemistry using phenyl acetylene

Entry	MC code	mol% of MC	Conversion (%) at 0.5 h	Conversion (%) at 2 h	Conversion (%) at 5 h
1			18	18	21
2	LM26	5.0	51	74	100
3	LM34	5.0	42	51	94
4	LM36	5.0	27	34	87
5	DM24	2.5	43	56	70
6	DM25	2.5	46	59	100
7	DM34	2.5	46	54	68
8	DM35	2.5	35	42	100
9	22	2.5	-	10	20
10	24	2.5	-	27	56

Conditions: Sugar azide (1.0 equiv, 40.0 mg), $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.2 equiv, 5.4 mg), phenylacetylene (1.5 equiv, 17.0 μL), EtOH/ H_2O (v/v 1:1, 2.0 mL), NaAsc (0.5 equiv, 10.6 mg), 0.025 or 0.05 equivalent of the macrocycles.

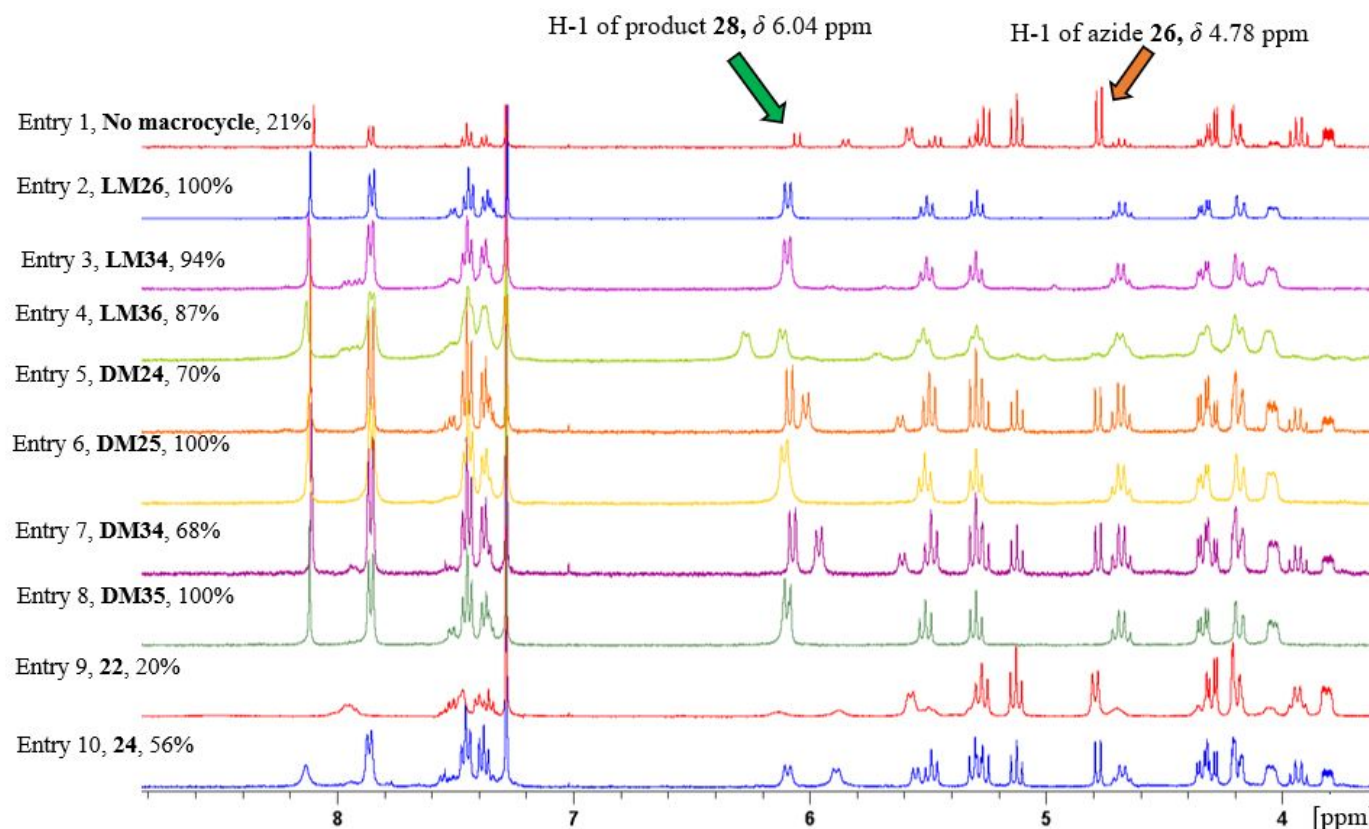


Figure S36. Overlay of ^1H NMR spectra of entries 1-10 at 5 h.

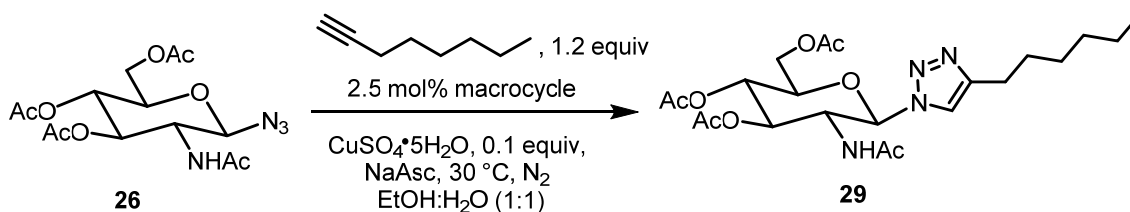
2.2 Selected screening for 1-octyne: The initial screening was done using 0.1 equiv. of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ and 2.5 mol% macrocycle, the results are shown in Table S3, stacked NMR spectra are shown in Figure S37. Further screening used 5.0 mol% for mono-triazole macrocycles and 1.5 equiv of 1-octyne and 0.3 equiv. of sodium ascorbate and the results are shown in Table S4 and Figure S38.

Synthesis of compound **29**,⁵ general procedure and one example for Table 3

Sugar azide **26** (40.0 mg, 0.107 mmol, 1.0 equiv) and 1-octyne (23.7 μL , 0.16 mmol, 1.5 equiv) were dissolved in EtOH: H_2O (v 1:1, 2.0 mL), then $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (2.7 mg, 0.01 mmol, 0.1 equiv), sodium ascorbate (6.4 mg, 0.03 mmol, 0.3 equiv) were added to the reaction mixture. To this mixture macrocycle **DM34** (1.93 mg, 2.5 mol%) was added. The reaction was stirred rt for 1.0 h to at which time the starting material was full converted to product, as indicated by ^1H NMR. The reaction was stopped, and solvent was removed using a rotavap, to obtain the crude, which was

further purified with flash chromatography using eluent of DCM to 2% MeOH/DCM to obtain the desired product as white solid (45 mg, 87%), $R_f = 0.32$ in 5% MeOH/DCM.

Table S3. Effect of the macrocycles on copper mediated click reaction of 1-octyne.



Entry	MC code	mol% of MC	Conversions (%)		
			1 h	2 h	5 h
1			-	25	28 (6 h)
2	LM24	2.5	8	9	13
3	LM26	2.5	7	9	19
4	LM28	2.5	14	16	25
5	LM34	2.5	25	25	26
6	LM36	2.5	15	16	25
7	LM38	2.5	10	16	27
8	DM24	2.5	22	27	42
9	DM25	2.5	17	24	53
10	DM34	2.5	83	93	97
11	DM35	2.5	17	26	32

Condition: Sugar azide (1.0 equiv, 40.0 mg), $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.1 equiv, 2.7 mg), 1-octyne (1.2 equiv, 19.0 μL), EtOH/H₂O (v/v 1:1, 2.0 mL), macrocycle (2.5 mol%), NaAsc (0.2 equiv, 4.3 mg)

H-1 of azide **26**, δ 4.78 ppm

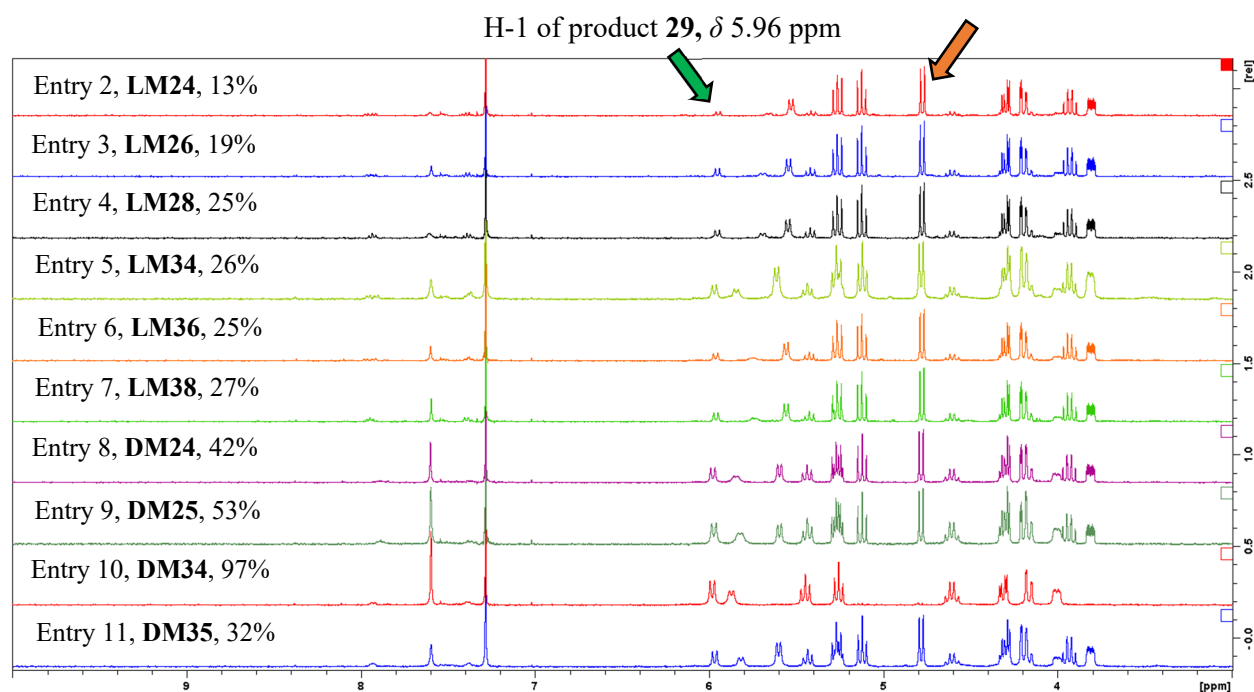


Figure S37. Overlay of ^1H NMR spectra of entries 2-11 at 5 hours.

Table S4. Effect of the macrocycle on catalyzing the click reaction of 1-octyne

Entry	MC code	mol% of MC	Conversion (%) at 1 h	Conversion (%) at 2 h	Conversion (%) at 5 h
1			11	14	20
2	LM26	5.0	8	12	25
3	LM34	5.0	16	18	28
4	LM36	5.0	12	14	23
5	DM24	2.5	27	35	46
6	DM25	2.5	12	25	57
7	DM34	2.5	100		
8	DM35	2.5	20	22	37

Condition: Sugar azide (1.0 equiv, 40.0 mg), $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.1 equiv, 2.7 mg), 1-octyne (1.5 equiv, 23.7 μL), EtOH/ H_2O (v/v 1:1, 2.0 mL), NaAsc (0.3 equiv, 6.4mg)

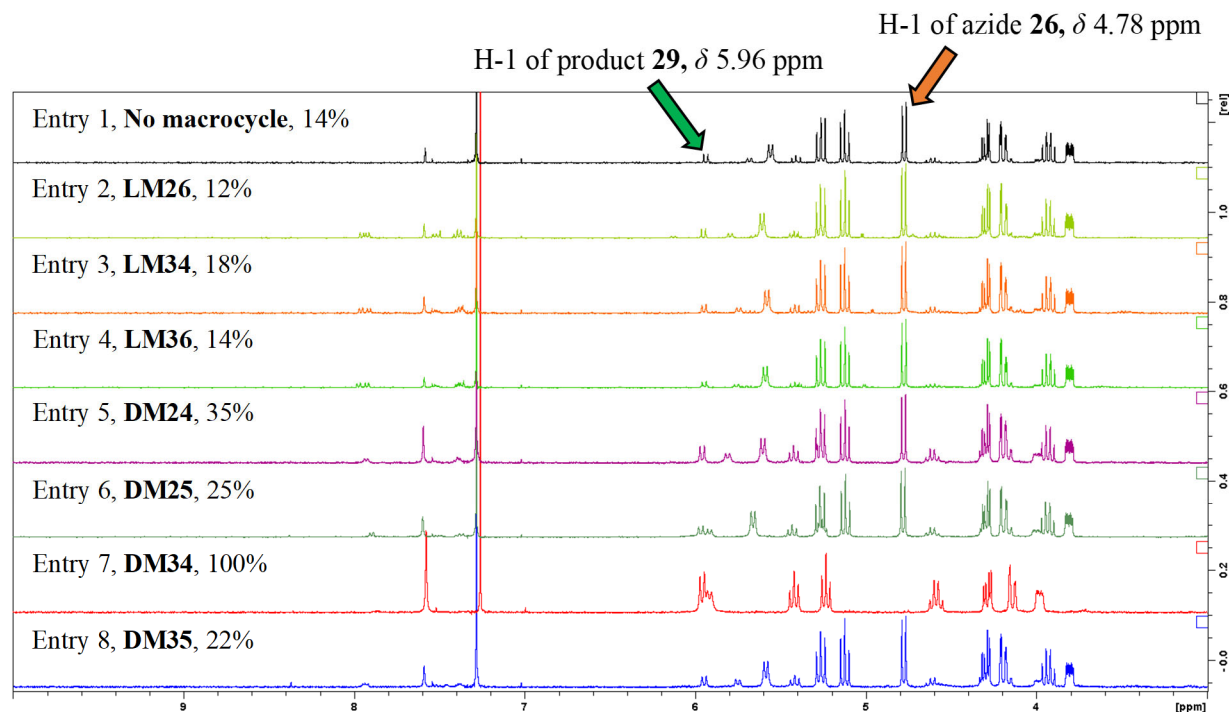
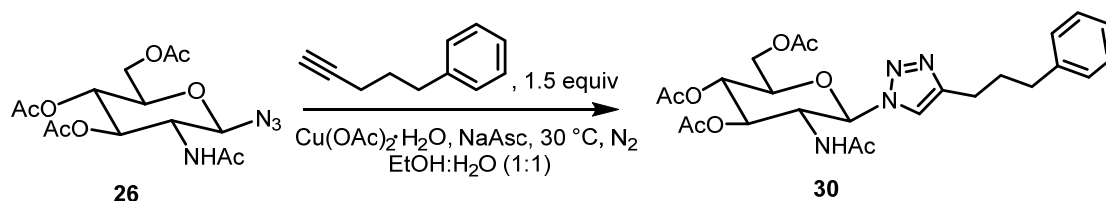


Figure S38. Overlay of ^1H NMR spectra of entries 1-5 and 8 at 2 hours and entry 7 at 1 hour.

2.3 Screening reactions for 5-phenyl-1-pentyne

Synthesis of compound **30**,⁵ general procedure and one example for Table 4

Sugar azide (40.0 mg, 0.107 mmol, 1.0 equiv) and 5-Phenyl-1-Pentyne (24.5 μL , 0.16 mmol, 1.5 equiv) were dissolved in EtOH: H_2O (v 1:1, 2.0 mL), then $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (1.34 mg, 0.005 mmol, 0.05 equiv), sodium ascorbate (2.13 mg, 0.01 mmol, 0.1 equiv) were added to the reaction mixture. To this mixture macrocycle **DM35** (1.97, 2.5 mol%) was added. The reaction was stirred rt for 1.0 h to at which time the starting material was full converted to product, as indicated by ^1H NMR. The reaction was stopped, and solvent was removed using a rotavap to obtain the crude, which was further purified with flash chromatography using eluent of DCM to 2% MeOH/DCM to afford the desired product as a white solid (48 mg, 86%), $R_f = 0.32$ in 5% MeOH/DCM.

Table S5. Screening results of 5-phenyl-1-pentyne with copper acetate

Entry	Macrocycle	Cu(OAc) ₂	Conversion (%) at 1 h	Conversion (%) at 2 h	Conversion (%) at 5h	Conversion (%) at 10 h
1	No MC	0.01	/	/	17	37
2	DM35 , 2.5%	0.01	25	/	77	99
3	No MC	0.02	/	13		
4	DM35 , 2.5%	0.02	63	100		

Condition for Table S5: **26** (1.0 equiv, 40.0 mg), Cu(OAc)₂·H₂O (0.02 equiv, 0.4 mg), 5-phenyl-1-pentyne (1.5 equiv, 24.5 μL, 23.2 mg), EtOH/H₂O (v/v 1:1, 2.0 mL), **DM35** (2.5 mol%), NaAsc (0.04 equiv, 0.9 mg). Condition for Table S6 are the same to above except CuSO₄·5H₂O (0.05 or other equiv, 1.3 mg), macrocycle (1.0-2.5 mol%), NaAsc (3 equiv. of CuSO₄).

Table S6. Screening results of 5-phenyl-1-pentyne using reduced copper sulfate

entry	Macrocycle	CuSO ₄	Conversion (%) at 1 h	Conversion (%) at 2h	Conversion (%) at 5h
1	No MC	0.01	2	5	27
2	No MC	0.05	33	51	
3	No MC	0.1	95	100	
4	2.5% of DM35	0.01	29	52	74
5	1.0 % of DM35	0.02	58	88	100 (4h)
6	2.5% of DM24	0.02	62	88	100 (4h)
7	1.0 % of DM25	0.05	77	98	
8	2.5% of DM34	0.05	100		
9	2.5% of DM35	0.05	100		

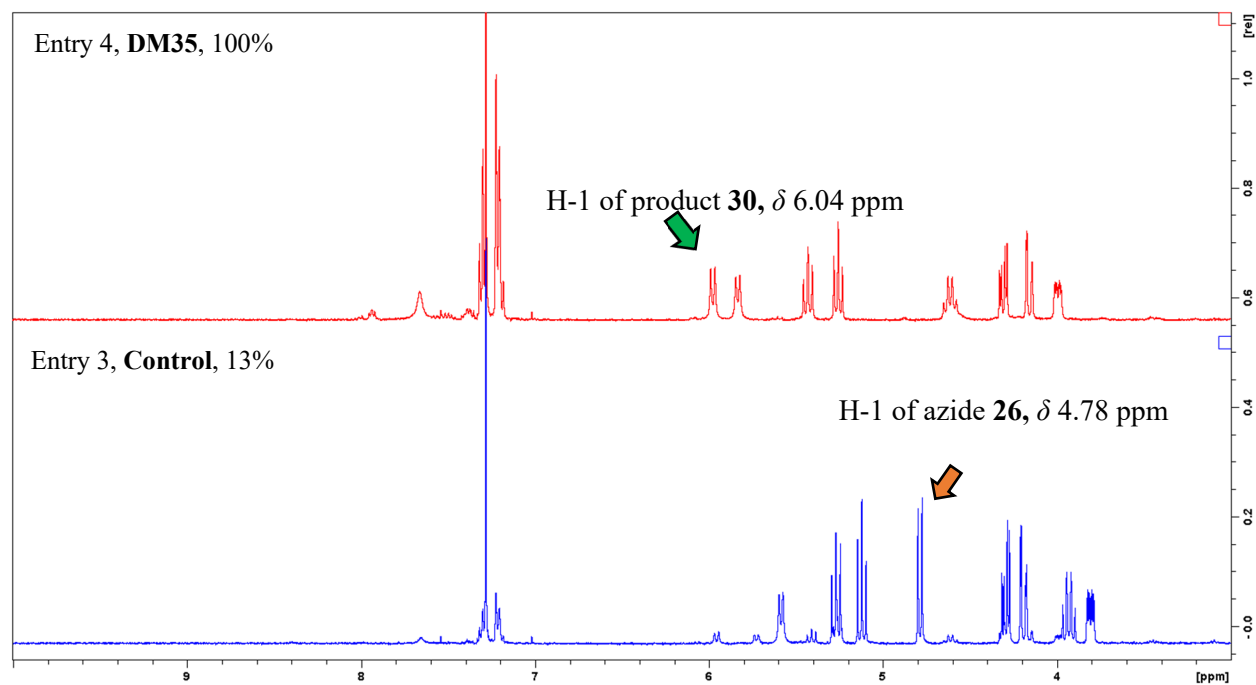


Figure S39. Overlay of ^1H NMR spectra of entries 1-2 in table S5 at 2 hours for $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$.

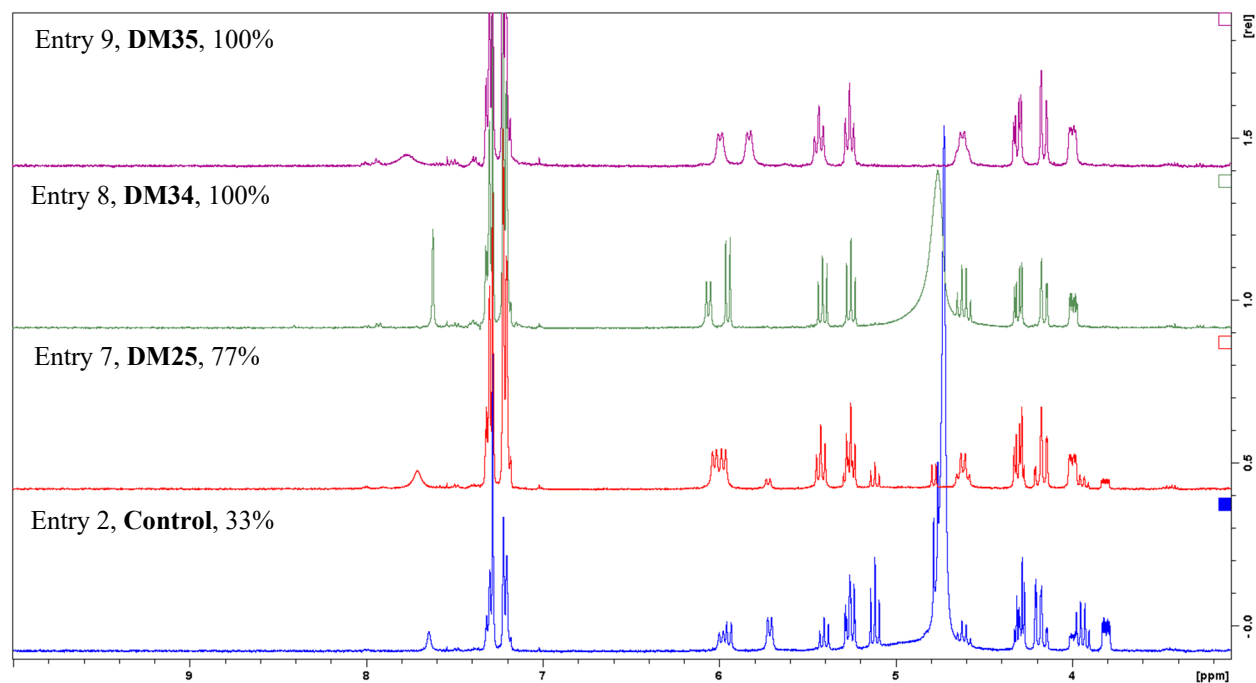
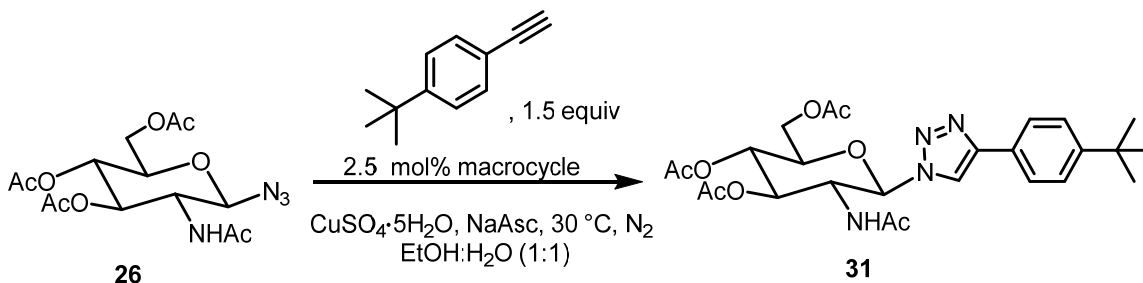


Figure S40. Overlay of ^1H NMR spectra of entries 2, 7-9 in Table S6 at 1 hour for 5% $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$

2.4 Screening reactions for 4-tert-butylphenylacetylene

Table S7. Effect of the macrocycles on copper mediated click reaction of sugar azide with 4-tert-butylphenylacetylene.



Entry		mol% of MC	Conversion (%) at 1 h	Conversion (%) at 2 h	Conversion (%) at 5 h	Conversion (%) at 20 h
1			-	4	10	27
2	DM25	2.5	26	47	80	100
3	DM34	2.5	7	15	34	70
4	DM35	2.5	19	28	45	100

Condition A: Sugar azide (1.0 equiv, 40.0 mg), $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.1 equiv, 2.7 mg), 4-tert-butylphenylacetylene (1.5 equiv, 29.0 μL), EtOH/H₂O (v/v 1:1, 2.0 mL), macrocycle (2.5 mol%), NaAsc (0.3 equiv, 6.4 mg).

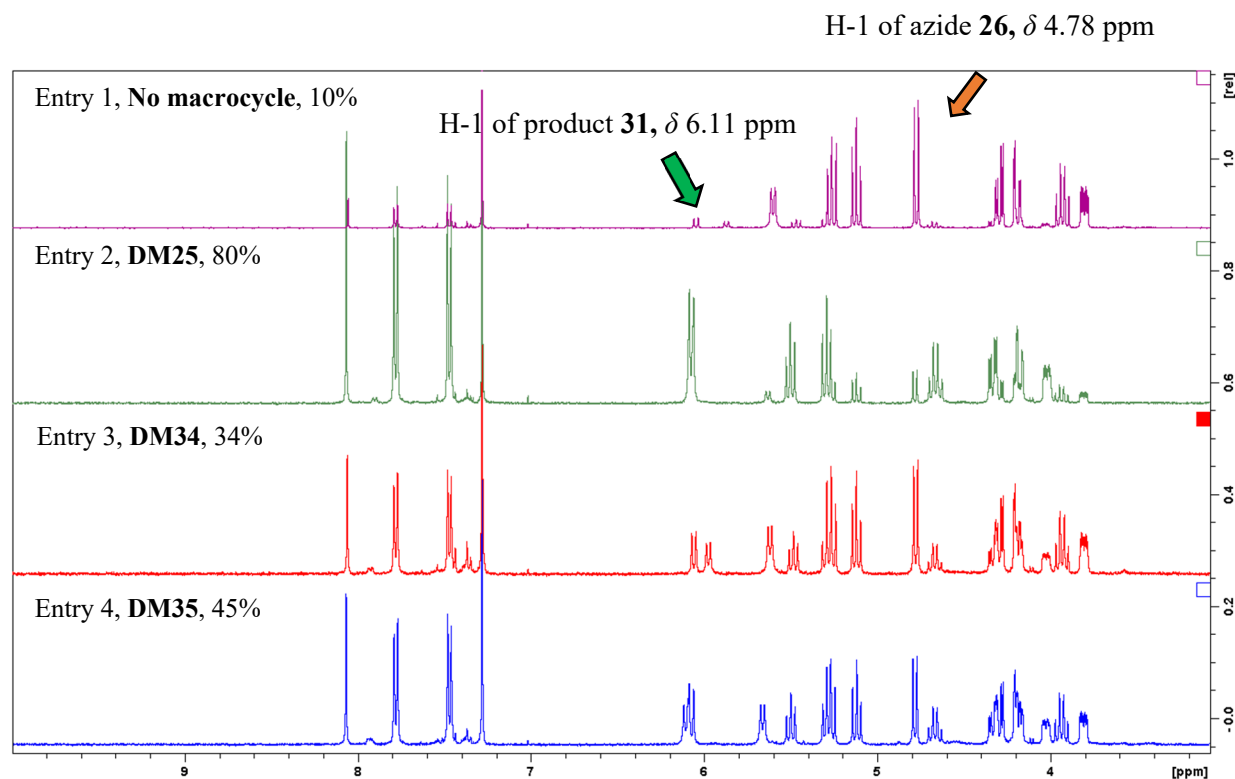


Figure S41a. Overlay of ^1H NMR spectra at 5 hours.

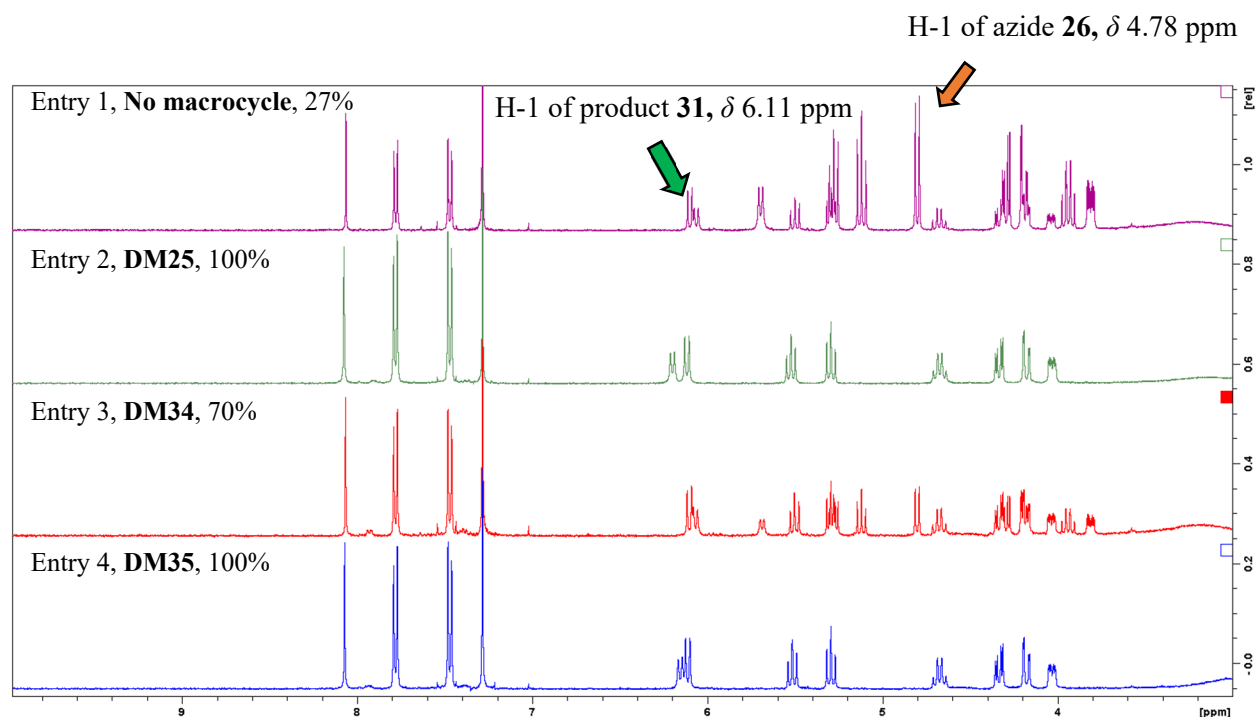


Figure S41b. Overlay of ^1H NMR spectra at 20 hours.

Table S8. Further screening reaction with p-t-butyl-phenylacetylene with increased copper amount

Entry		mol% of MC	Conversion (%) at 2 h	Conversion (%) at 5 h	Conversion (%) at 10 h
1		0	42	62	83
2	DM24	5.0	61	78	87
3	DM25	2.5	30	100	-
4	DM25	5.0	43	100	-
5	DM34	5.0	48	75	84
6	DM35	5.0	68	98	100

Condition B: Sugar azide (1.0 equiv, 40.0 mg), CuSO₄·5H₂O (0.2 equiv, 5.4 mg), 4-tert-butylphenylacetylene (1.5 equiv, 29.0 μ L), EtOH/H₂O (v/v 1:1, 2.0 mL), macrocycle (2.5 mol%), NaAsc (0.4 equiv, 8.5 mg).

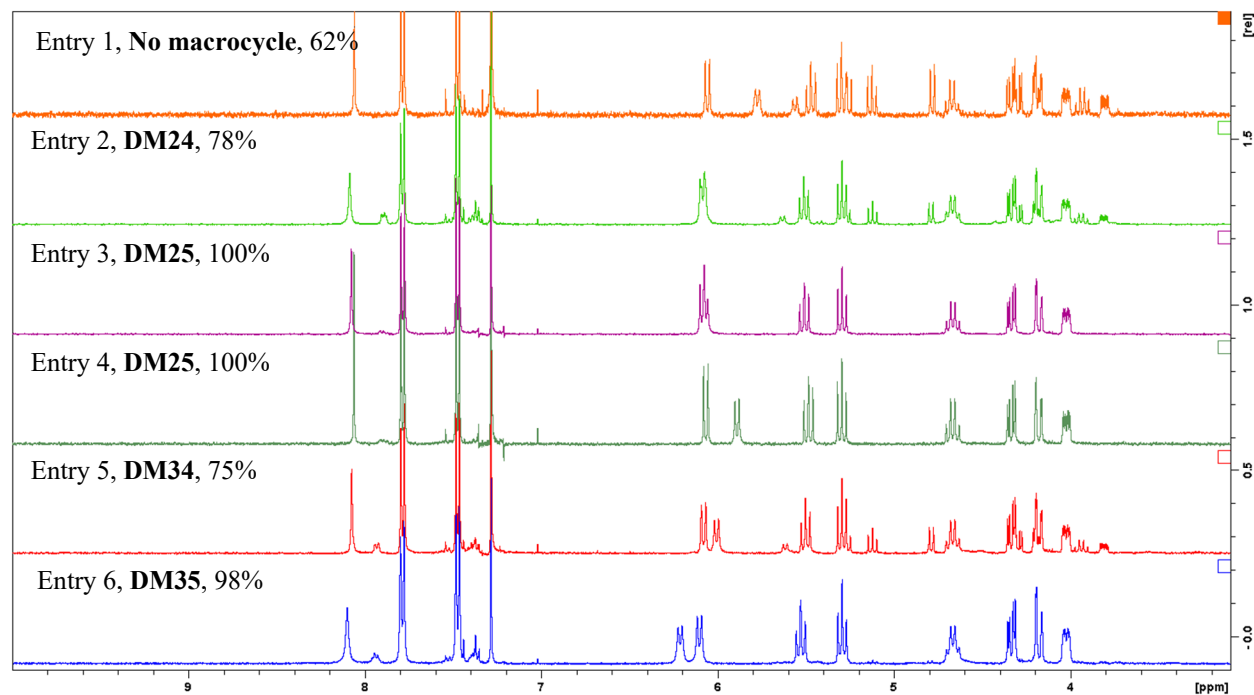
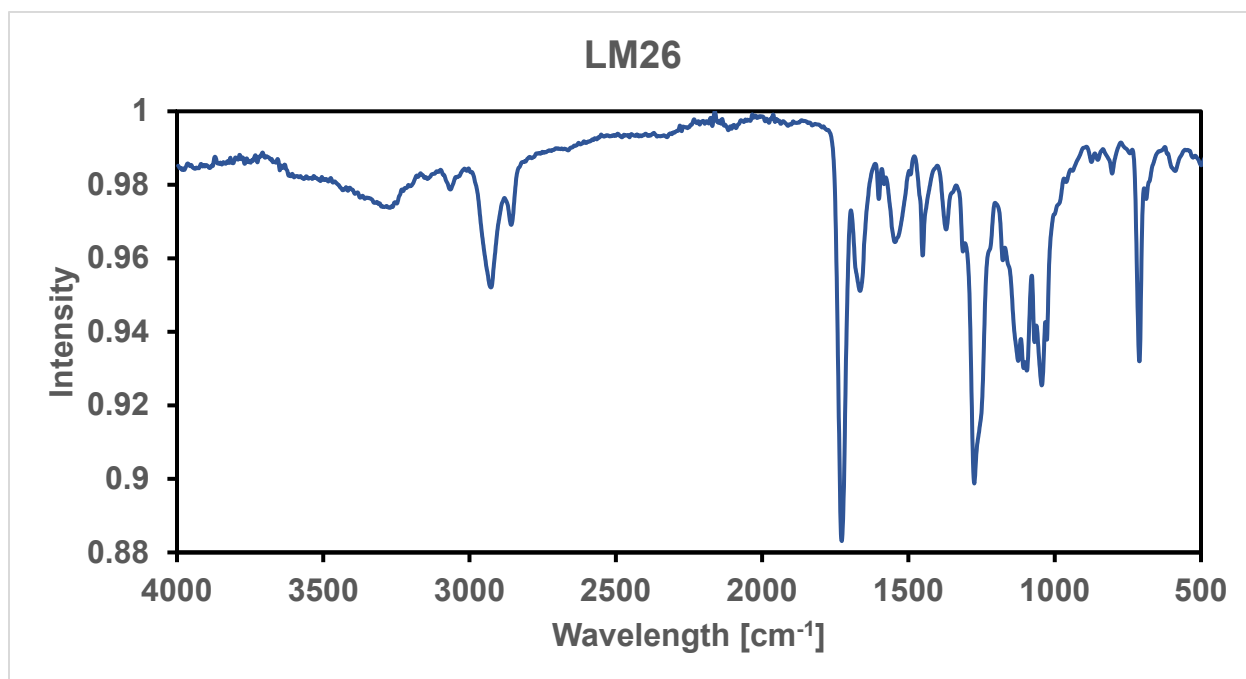
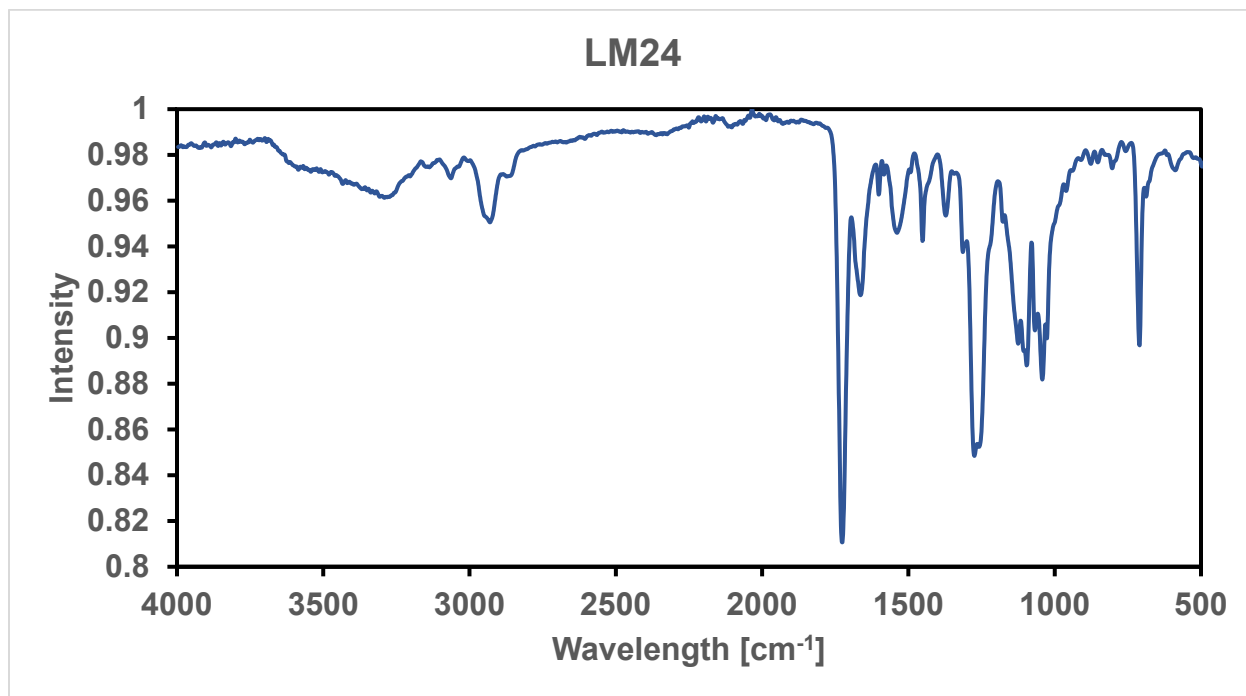
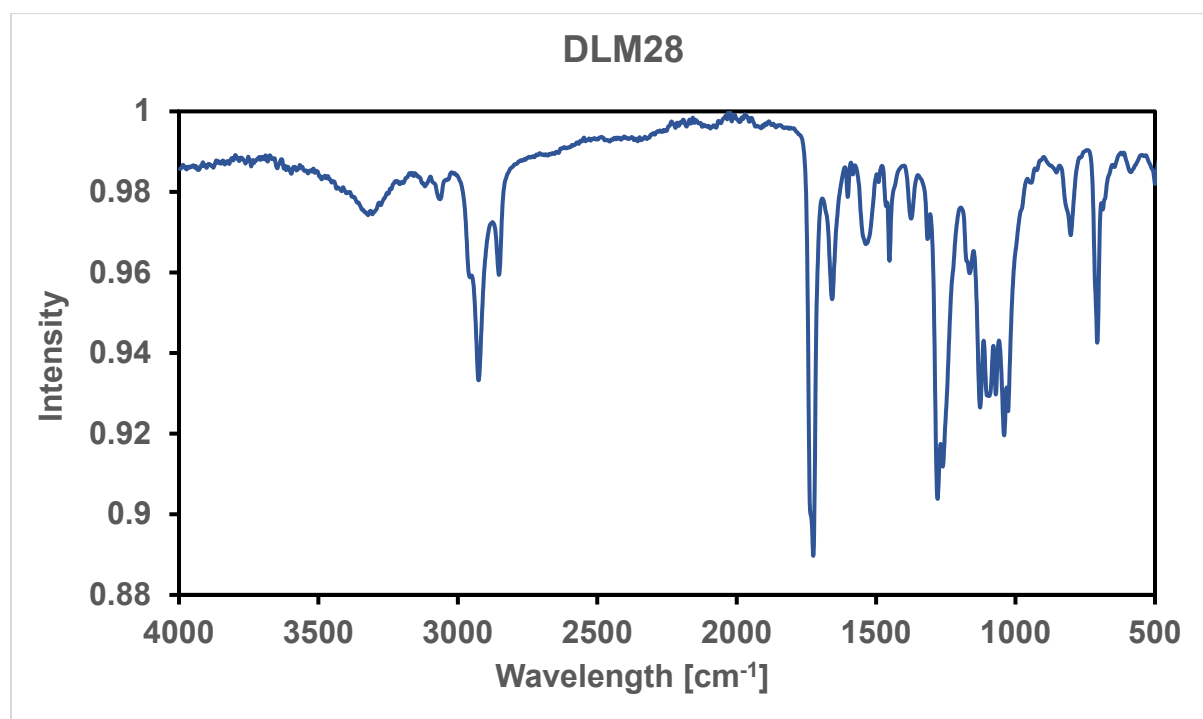
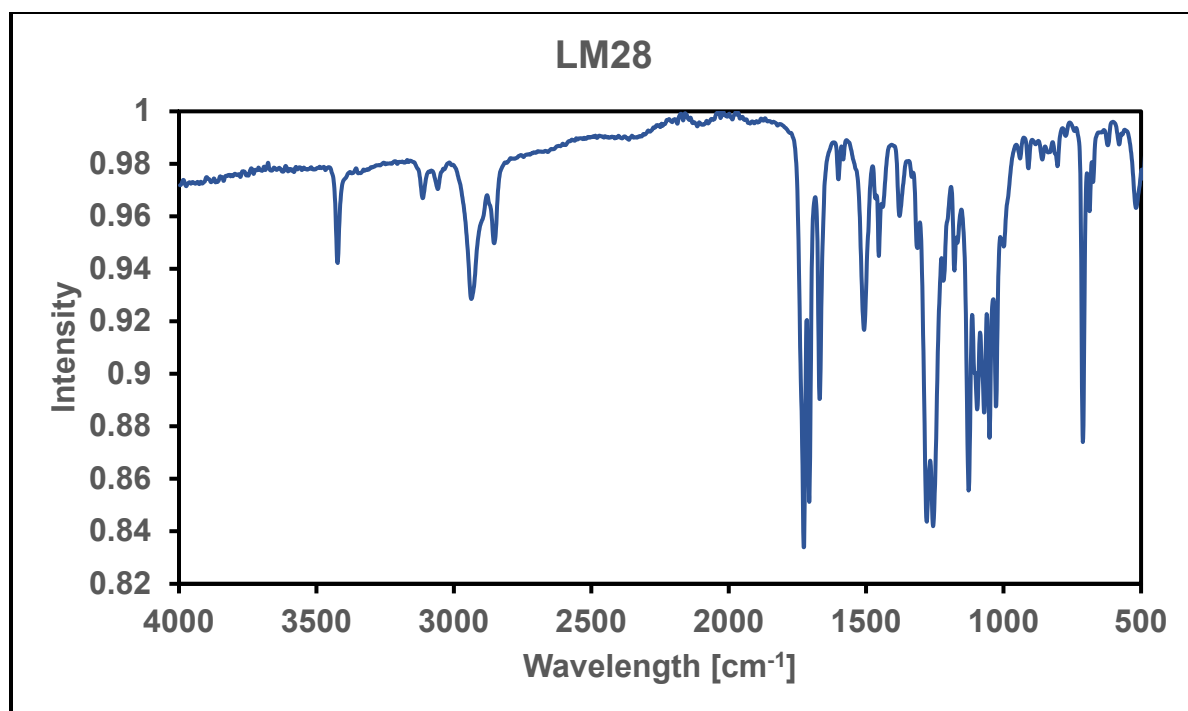


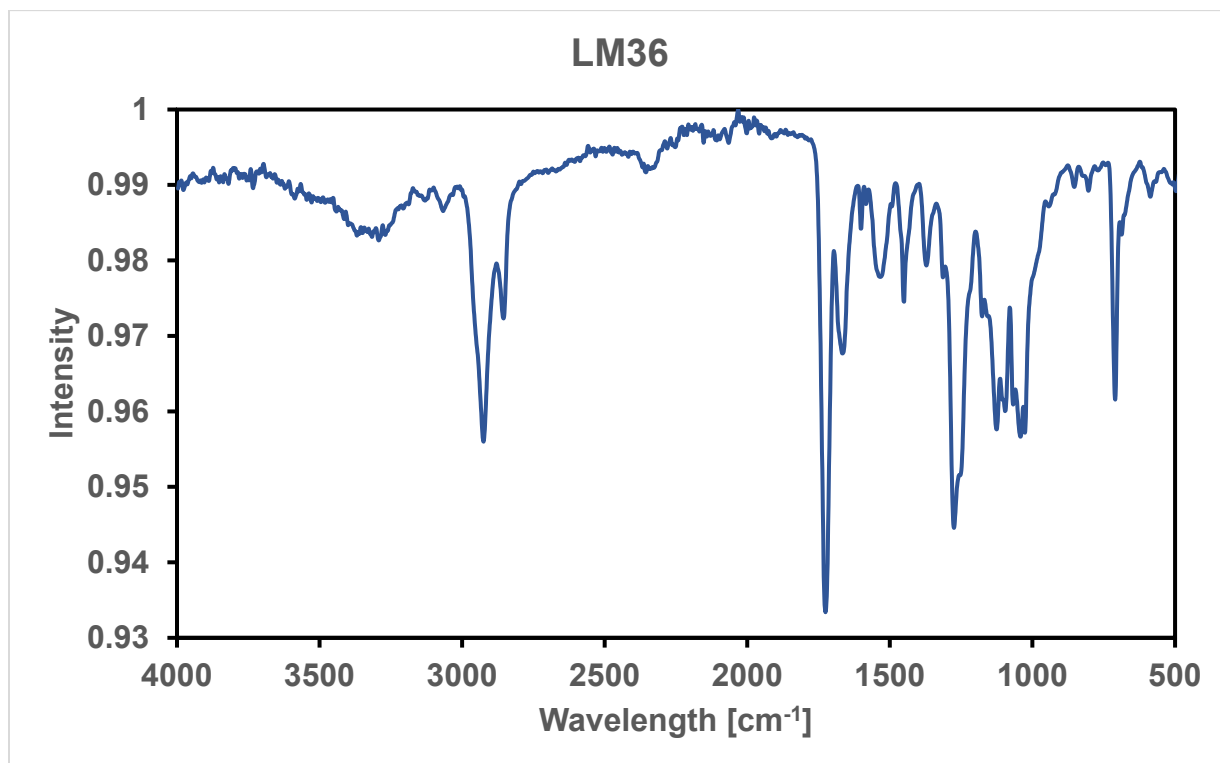
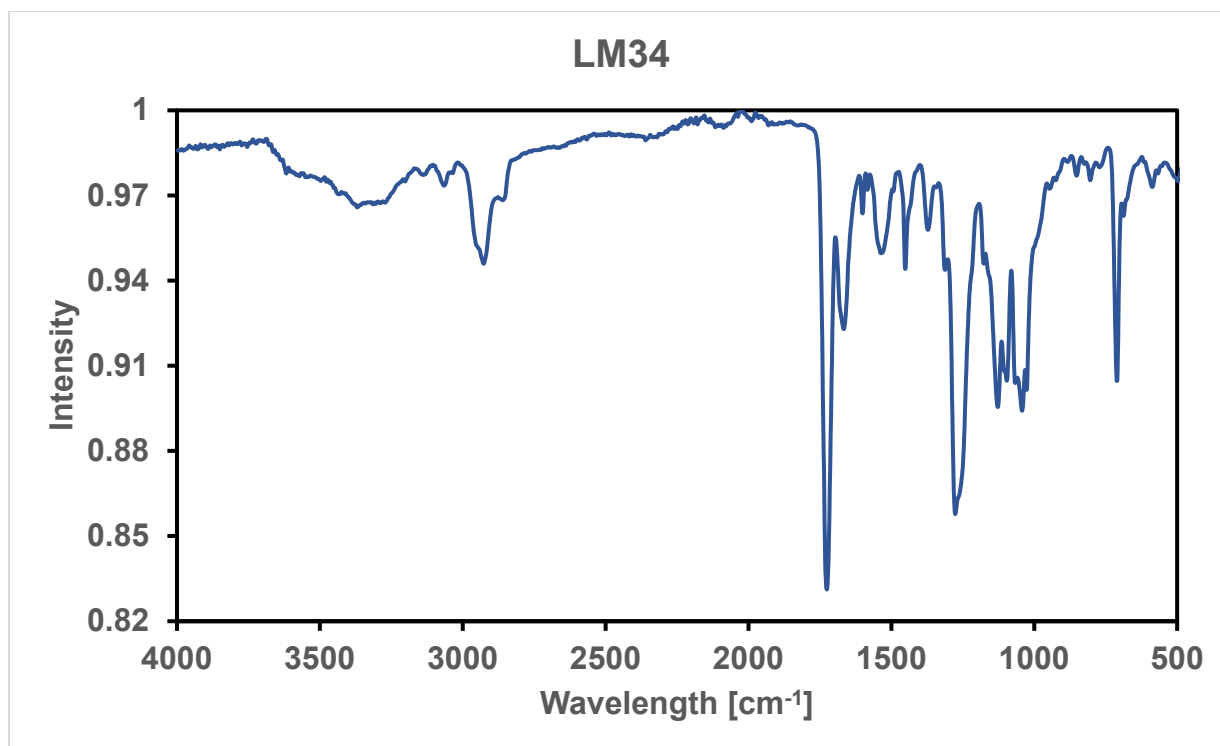
Figure S42. Overlay of ¹H NMR spectra of entries 1-6 at 5 hours.

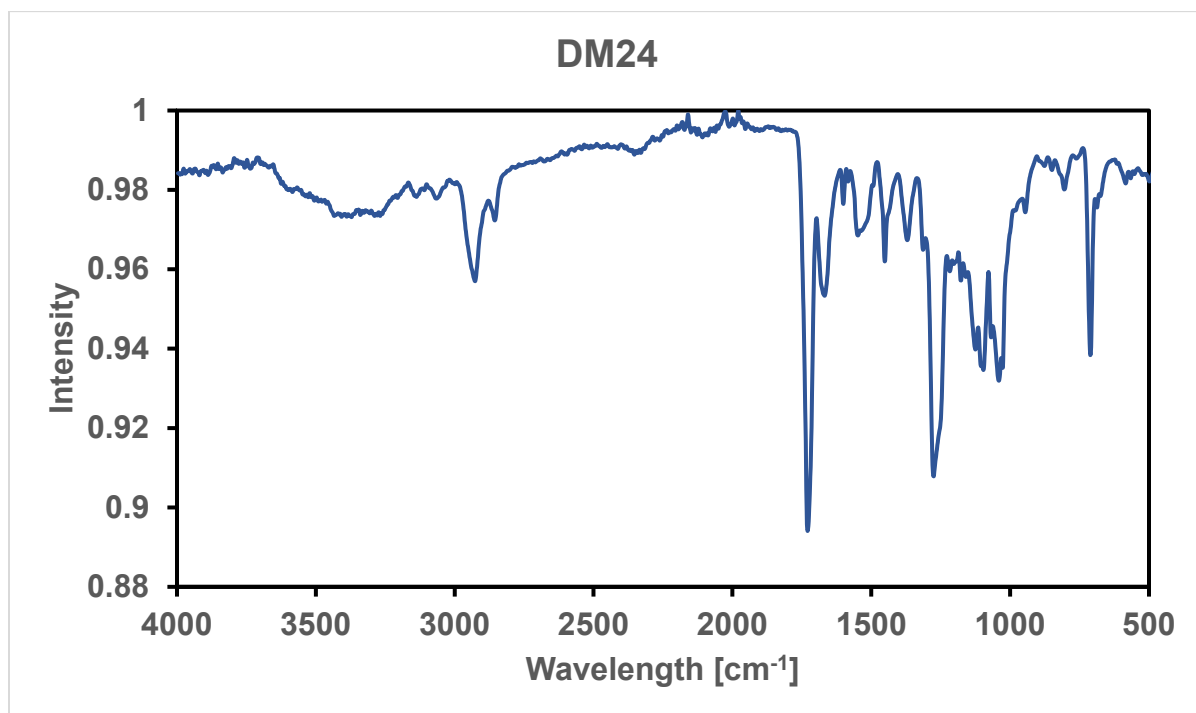
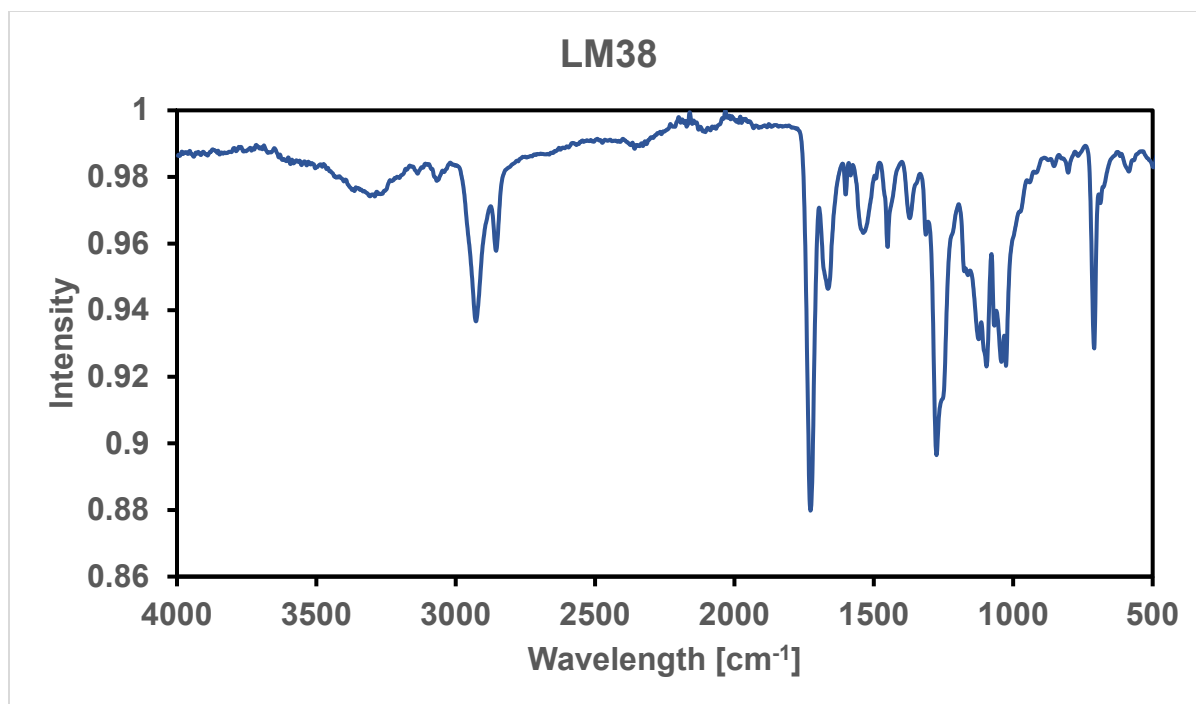
VII. IR spectra for several macrolactones:

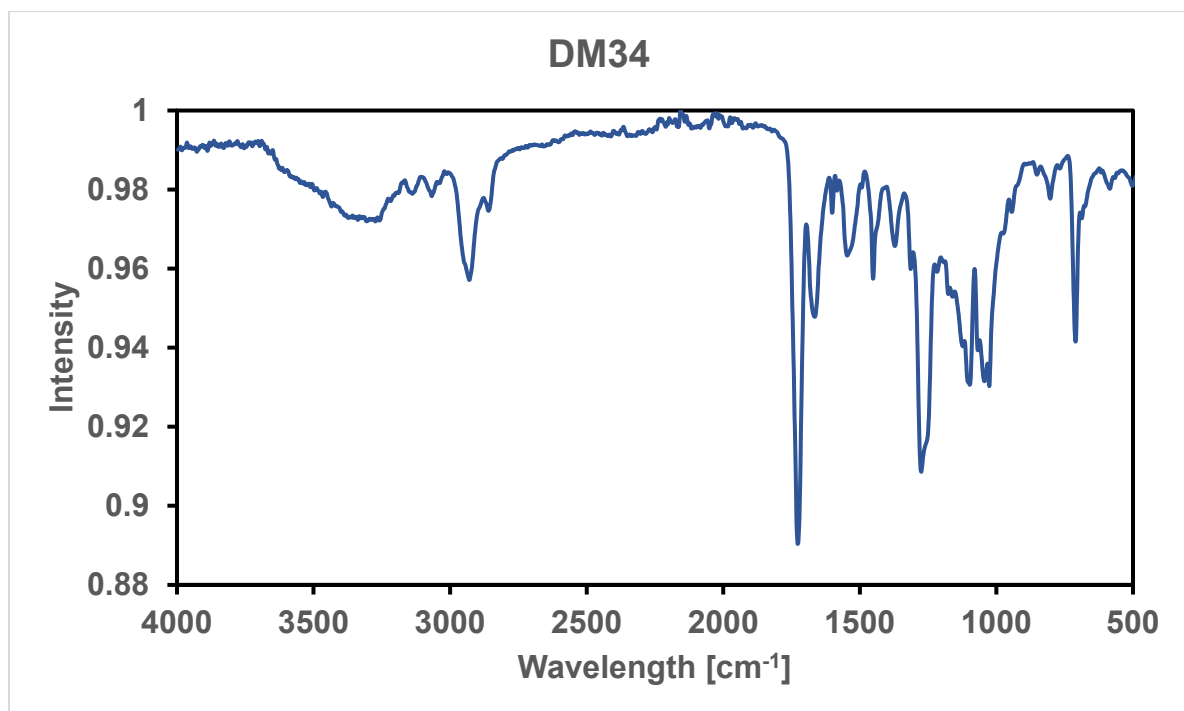
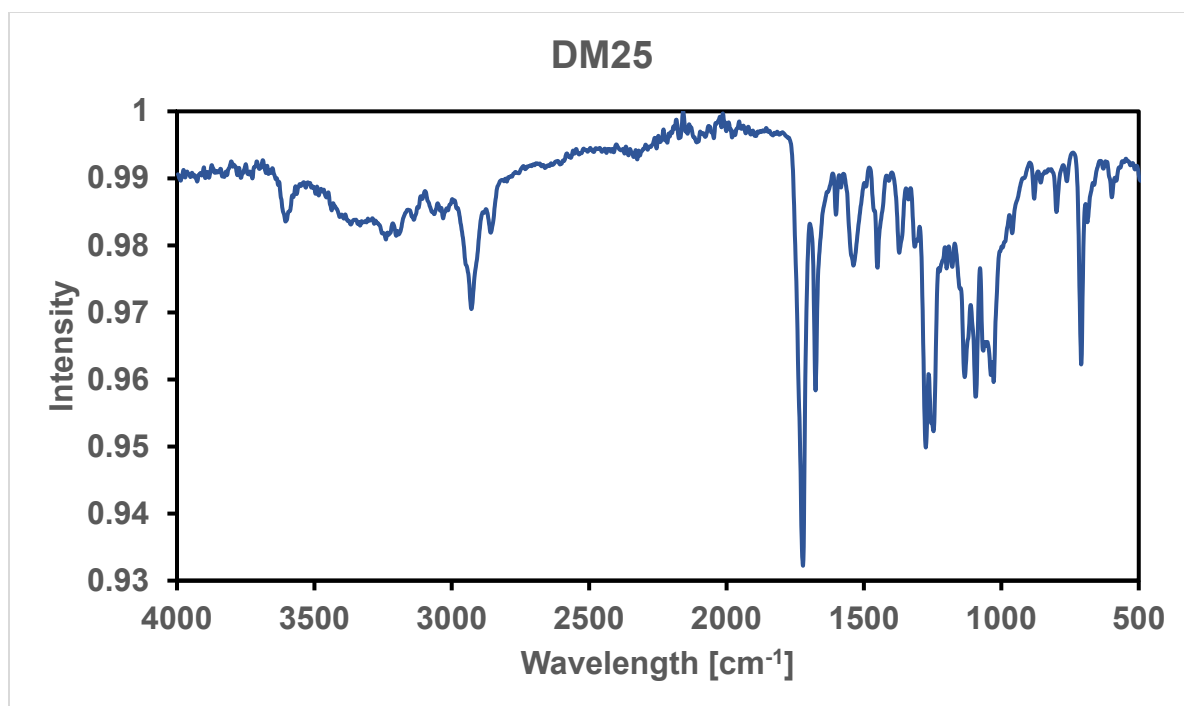
The IR spectra were obtained using a Bruker Platinum ATR (Alpha) FT-IR Spectrometer, the parameters are Resolution: 4 cm^{-1} , 64 Scans.

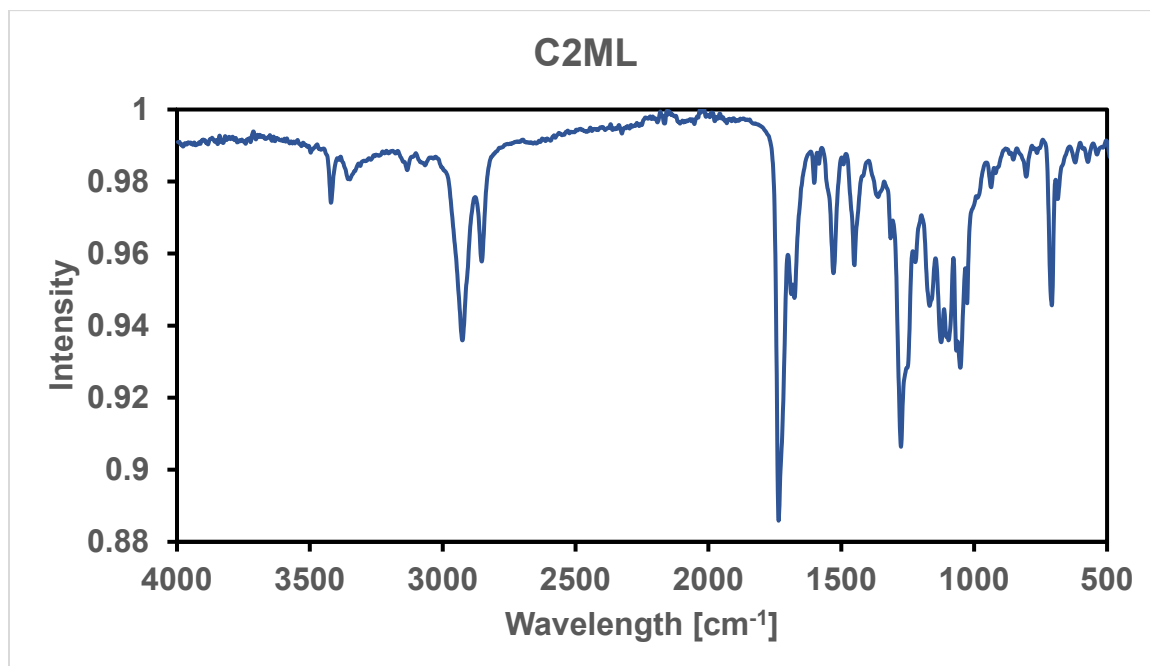
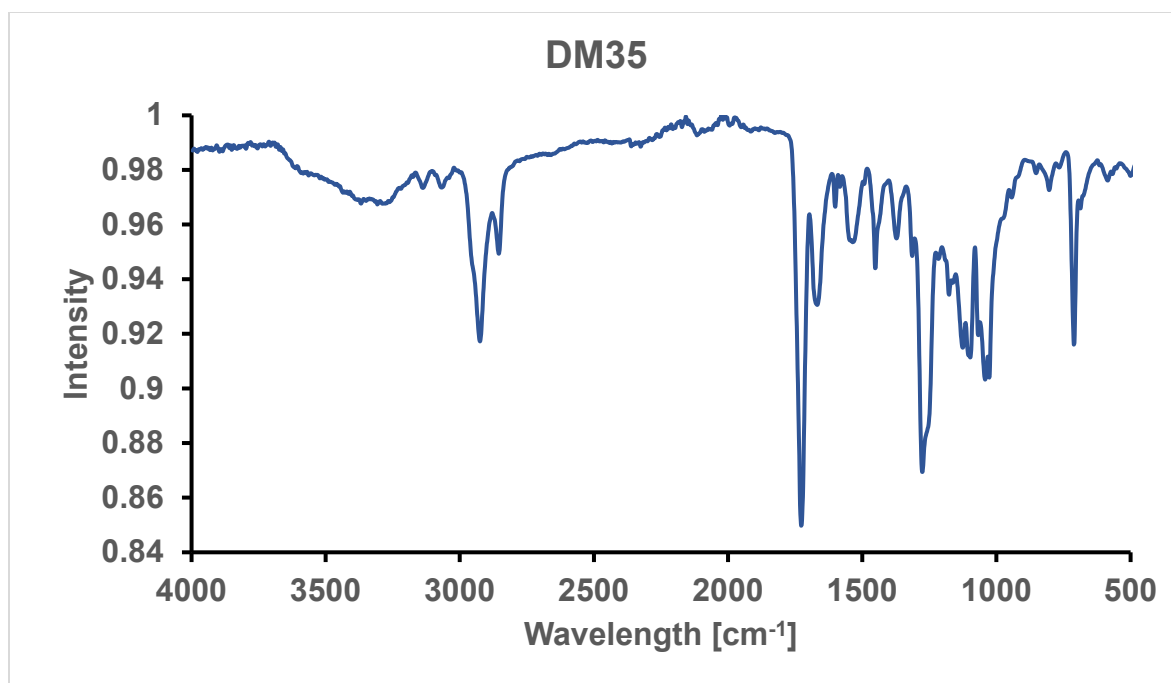


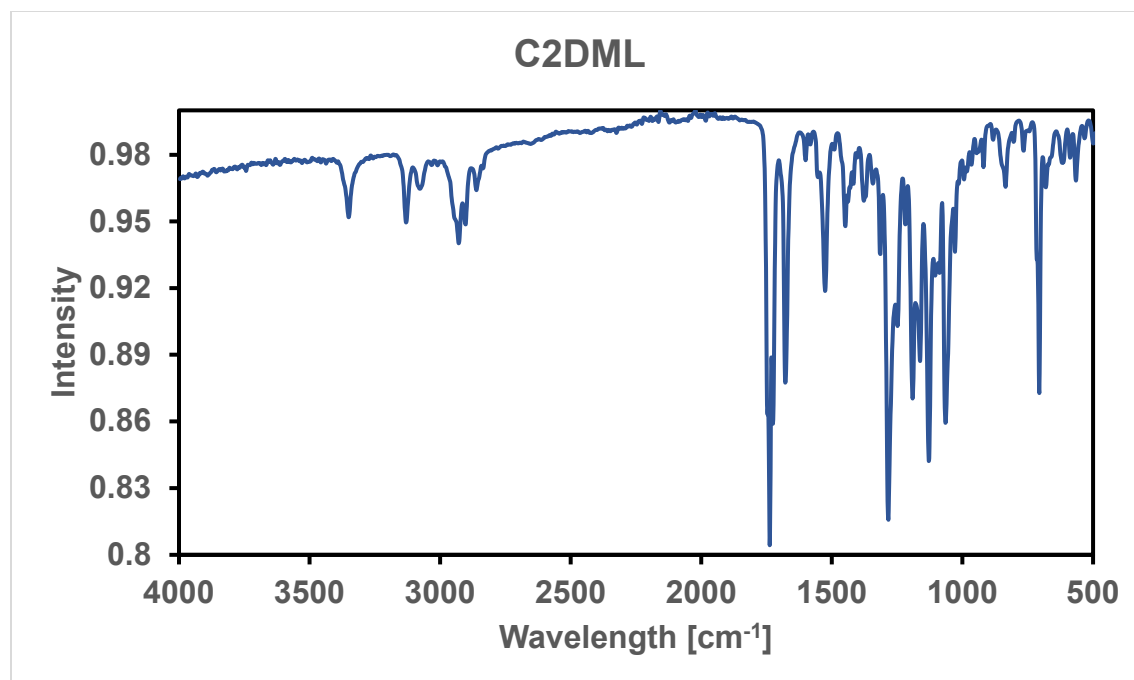












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