Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry


# Synthesis and antibacterial activity of novel neamine derivatives: preponderant role of the substituent position on the neamine core.

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## Supporting Information

**1,3,2',6'-Tetraazido-6,3',4'-tri-*O*-acetylneamine 3** [1]

To a solution of 1,3,2',6'-tetraazidoneamine (3 g, 7 mmol) in a mixture of $CH_2Cl_2$/pyridine (45 mL, 1:1 v/v) at 0°C was added $Ac_2O$ (45 mL). The reaction mixture was stirred at room temperature for 2h. It was then diluted with $CH_2Cl_2$ (50 mL) and slowly poured on an ice-cold aqueous $NaHCO_3$ saturated solution under stirring. The layers were separated, the organic layer was washed with $H_2O$ (2 x 20 mL) and concentrated under reduced pressure. The residue was taken up in EtOAc (50 mL) and washed with aqueous $NH_4Cl$ (2 x 50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), concentrated *in vacuo*, and the residue was purified by column chromatography (EtOAc/cyclohexane 15% to 20%) to afford **3** (2.5 g, 4.6 mmol, 64%) ($R_f$ 0.5 EtOAc/cyclohexane 2:3) and the tetracetylated neamine derivative (0.8 g, 1.4 mmol, 20%). ($R_f$ 0.6 EtOAc/cyclohexane 2:3). $^1$H NMR (300 MHz, $CDCl_3$) δ 5.50 (dd, *J* = 9.4, 10.5 Hz, 1H, H-3'), 5.36 (d, *J* = 3.6 Hz, 1H, H-1'), 5.06 (dd, *J* = 9.3, 10.6 Hz, 1H, H-4'), 4.94 (dd, *J* = 8.7, 9.8 Hz, 1H, H-6), 4.35 (ddd, *J* = 2.8, 4.7, 10.1 Hz, 1H, H-5'), 3.75-3.63 (m, 2H, H-5, H-2'), 3.62-3.50 (m, 2H, H-1, H-4), 3.50-3.28 (m, 4H, H-6'$_{éq}$, H-6'$_{ax}$, H-3, O<u>H</u>), 2.42 (ddd, *J* = 4.2, 4.2, 13.6 Hz, 1H, H-2$_{éq}$), 2.19 (s, 3H, $CH_3$), 2.11 (s, 3H, $CH_3$), 2.07 (s, 3H, $CH_3$), 1.62 (ddd, *J* = 13.5, 13.5, 13.5 Hz, 1H, H-2$_{ax}$); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 169.9 ($CH_3$-<u>C</u>=O), 169.7 ($CH_3$-<u>C</u>=O), 169.2 ($CH_3$-<u>C</u>=O), 98.3 (C-1'), 83.4, 74.4, 73.9, 70.8, 69.0, 68.8, 61.3 (C-$N_3$), 57.8 (C-$N_3$), 57.4 (C-$N_3$), 50.4 (C-6'), 31.5 (C-2), 20.3 ($CH_3$), 20.2 ($CH_3$), 20.1 ($CH_3$).

**3',4'-Di-*O*-acetyl-1,3,2',6'-tetraazidoneamine 4** [2]

To a solution of **3** (4 g, 7.2 mmol) in THF (80 mL) was added NaOH 0.1N (90 mL, 9 mmol). After stirring at room temperature for 1h, quantitative conversion of the starting material was observed by TLC (40% EtOAc in cyclohexane). The solution was neutralized by saturated $NH_4Cl$ aqueous solution (20 mL). The remaining solvent was removed *in vacuo* and the aqueous layer was extracted with EtOAc (3 x 50 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure to give a yellow oil which was purified by column chromatography on silica gel using 15% to 20% EtOAc in cyclohexane to obtain **4** (2.8 g, 5.4 mmol, 75%) ($R_f$ 0.4 EtOAc/cyclohexane 2:3). $^1$H NMR (300 MHz, $CDCl_3$) δ 5.51 (dd, *J* = 9.3, 10.5 Hz, 1H, H-3'), 5.36 (d, *J* = 3.6 Hz, 1H, H-1'), 5.07 (dd, *J* = 10.1, 10.1 Hz, 1H, H-4'), 4.36 (ddd, *J* = 2.7, 4.8, 10.2 Hz, 1H, H-5'), 3.79 (d, *J* = 2.6 Hz, 1H), 3.70 (dd, *J* = 3.6, 10.5 Hz, 1H, H-2'), 3.60-3.25 (m, 7H), 3.00 (s, 1H), 2.37 (ddd, *J* = 4.1, 4.1, 13.2 Hz, 1H, H-2$_{éq}$), 2.11 (s, 3H, $CH_3$), 2.07 (s, 3H, $CH_3$), 1.56 (ddd, *J* = 12.3, 12.3, 12.3 Hz, 1H, H-2$_{ax}$); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.2 (C=O), 169.8 (C=O), 98.6 (C-1'), 82.7, 76.0, 75.5, 71.0, 69.4, 69.3, 61.6 (C-$N_3$), 59.7 (C-$N_3$), 58.6 (C-$N_3$), 50.8 (C-6'), 31.8 (C-2), 20.7 ($CH_3$), 20.6 ($CH_3$); HRMS (electrospray) Calcd for $C_{16}H_{22}N_{12}O_8Na$ $[M+Na]^+$: 533.1581, found: 533.1565.

[1] W. K. C. Park, M. Auer, H. Jaksche, C-H. Wong, *J. Am. Chem. Soc.* 1996, **118**, 10150-10155.
[2] J. Li, J. Wang, P. G. Czyryca, H. Chang, T. W. Orsak, R. Evanson, C.-W. T. Chang, *Org. Lett.* 2004, **6**, 1381–1384.

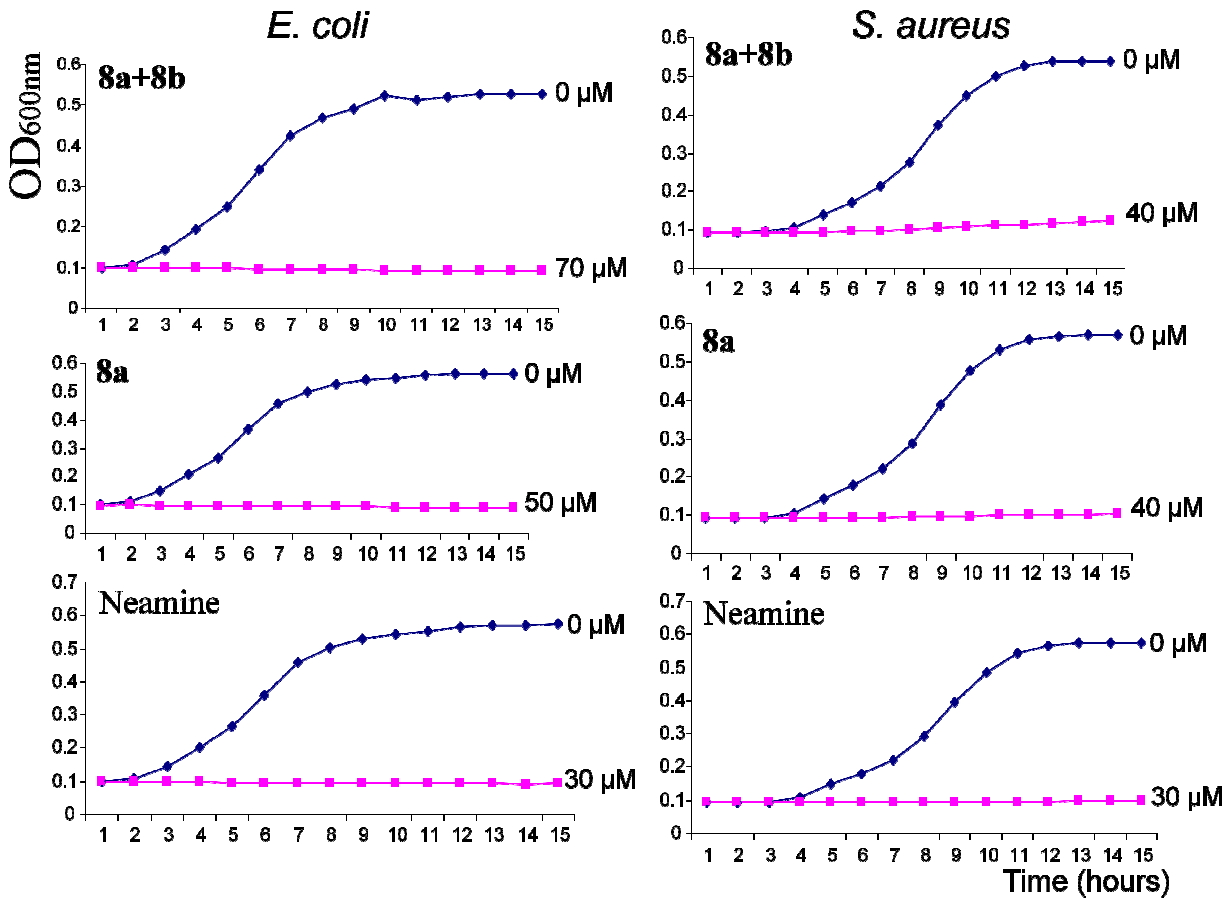
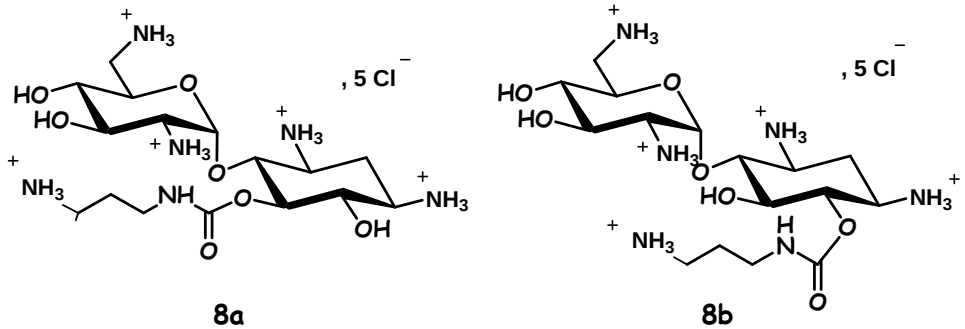
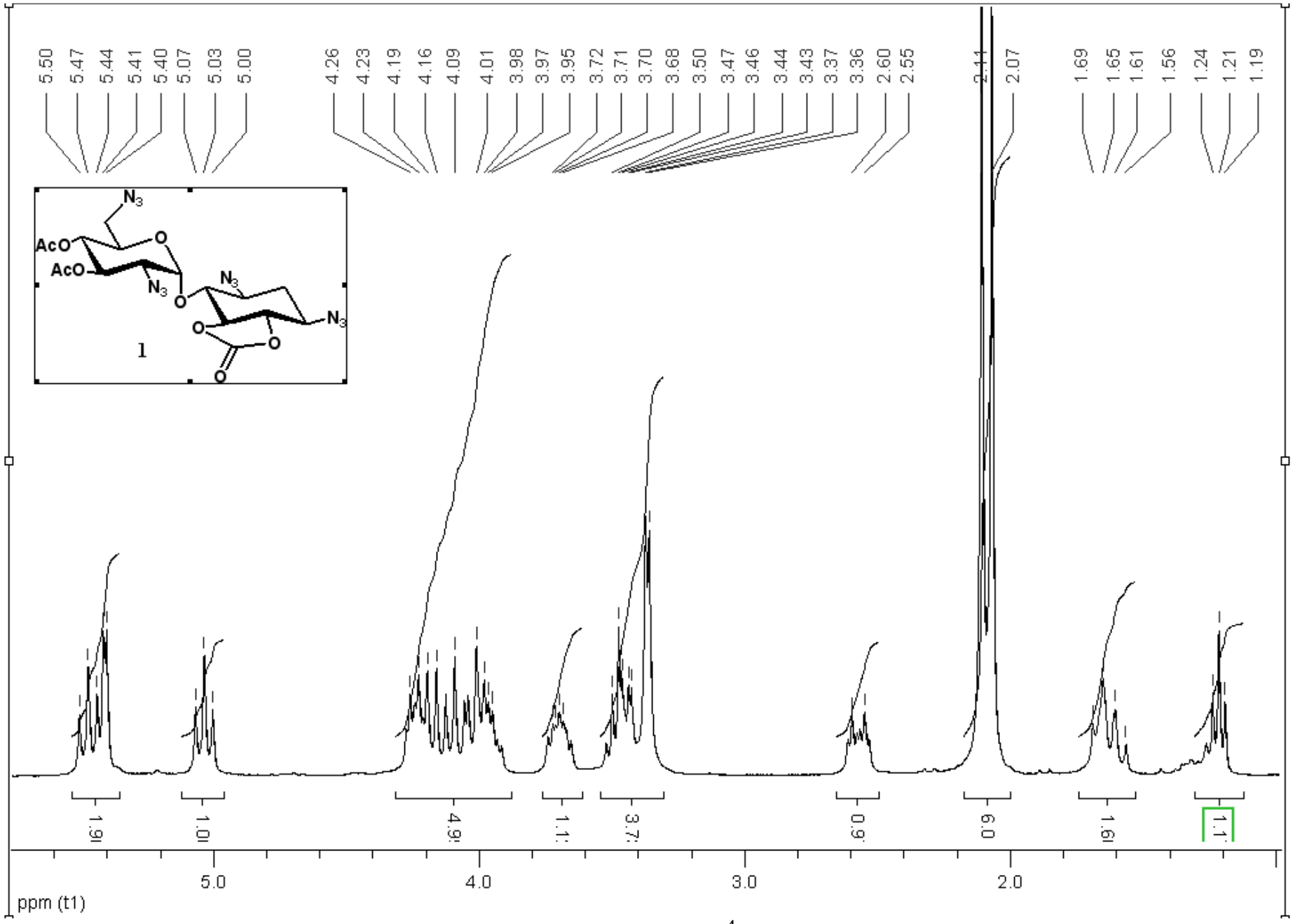


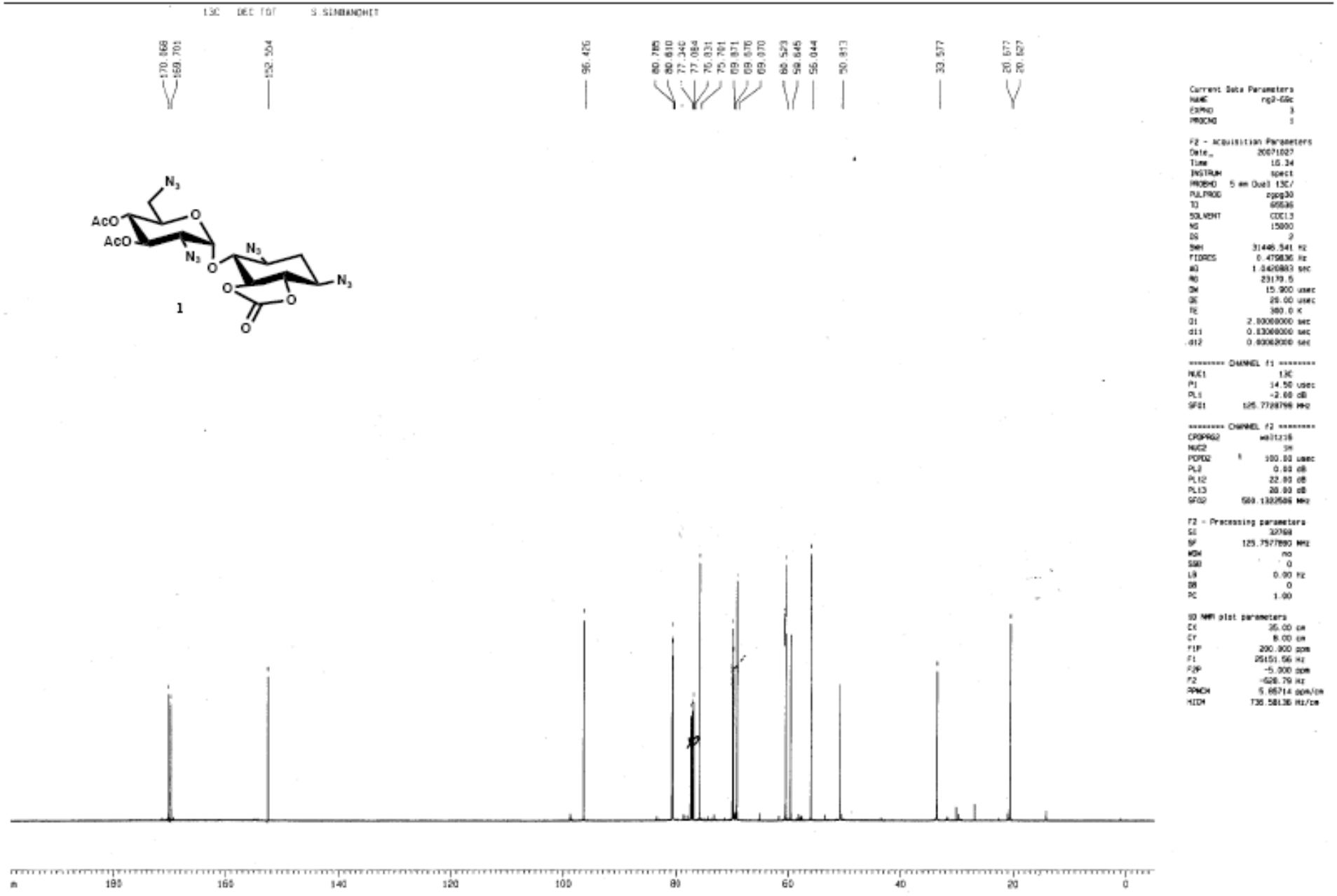

Figure 1

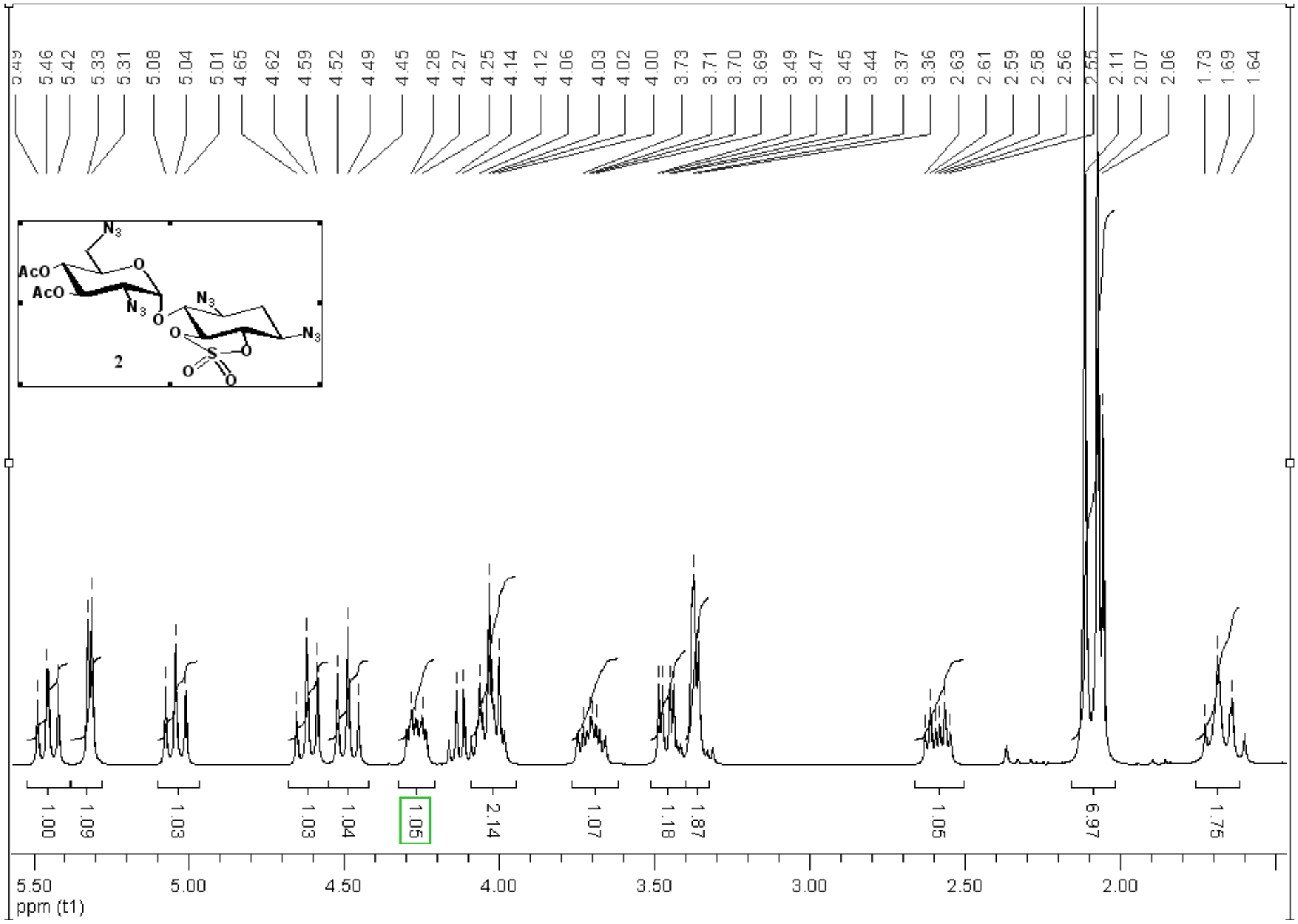
**Figure 1 legend: Growth inhibition of the aminoglycoside derivatives on *E. coli* and *S. aureus* bacteria.** Growth inhibition patterns of compounds **8a+8b** and **8a** compared to the effect of the neamine (internal control) during *E. coli* (left panels) and *S. aureus* (right panels) growths. For all the aminoside derivatives, only one concentration is indicated corresponding to the lowest that suppresses bacterial growth during a 15 hour incubation time (in red). The growth curves in the absence of the aminoglycosides are in blue.

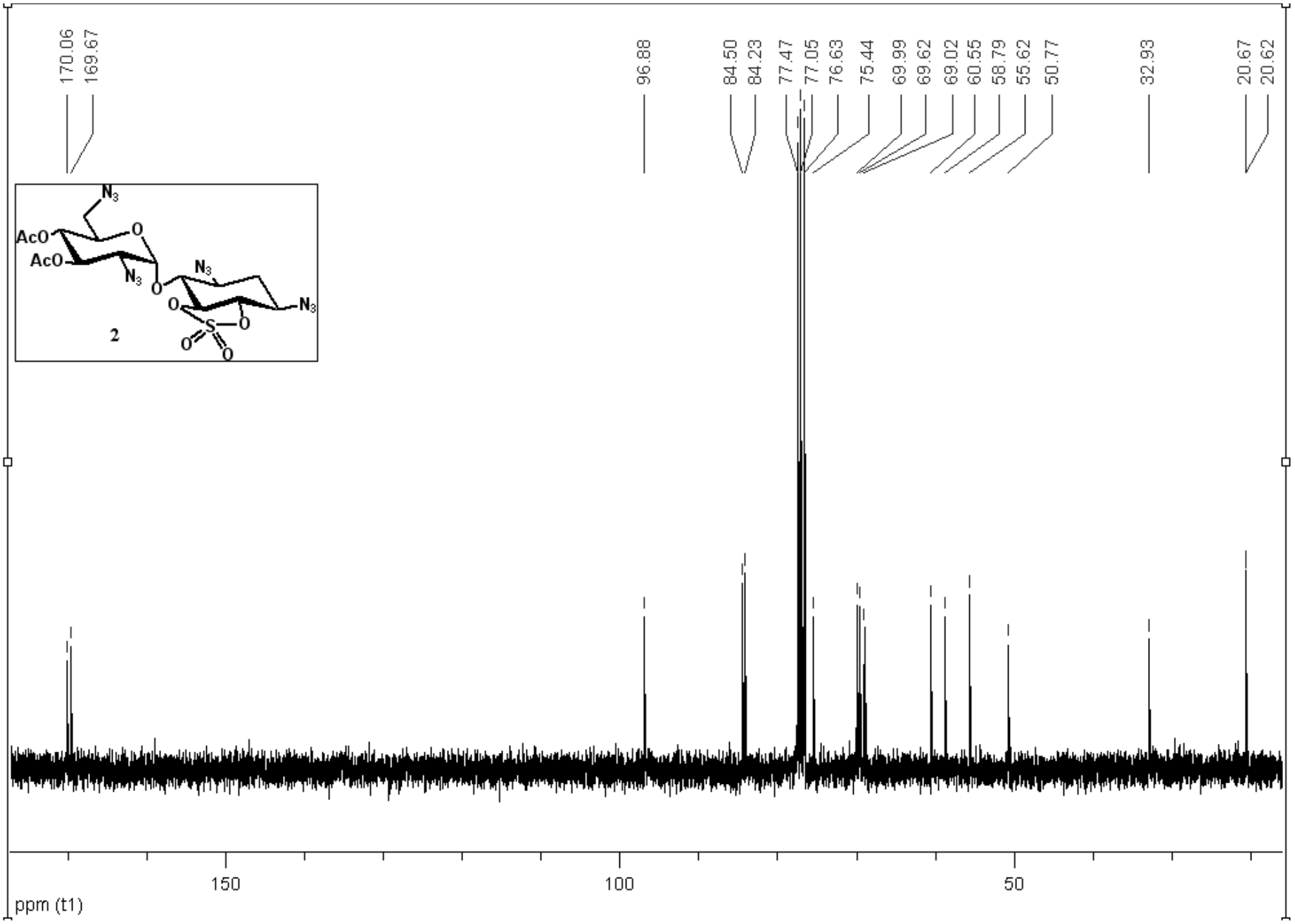


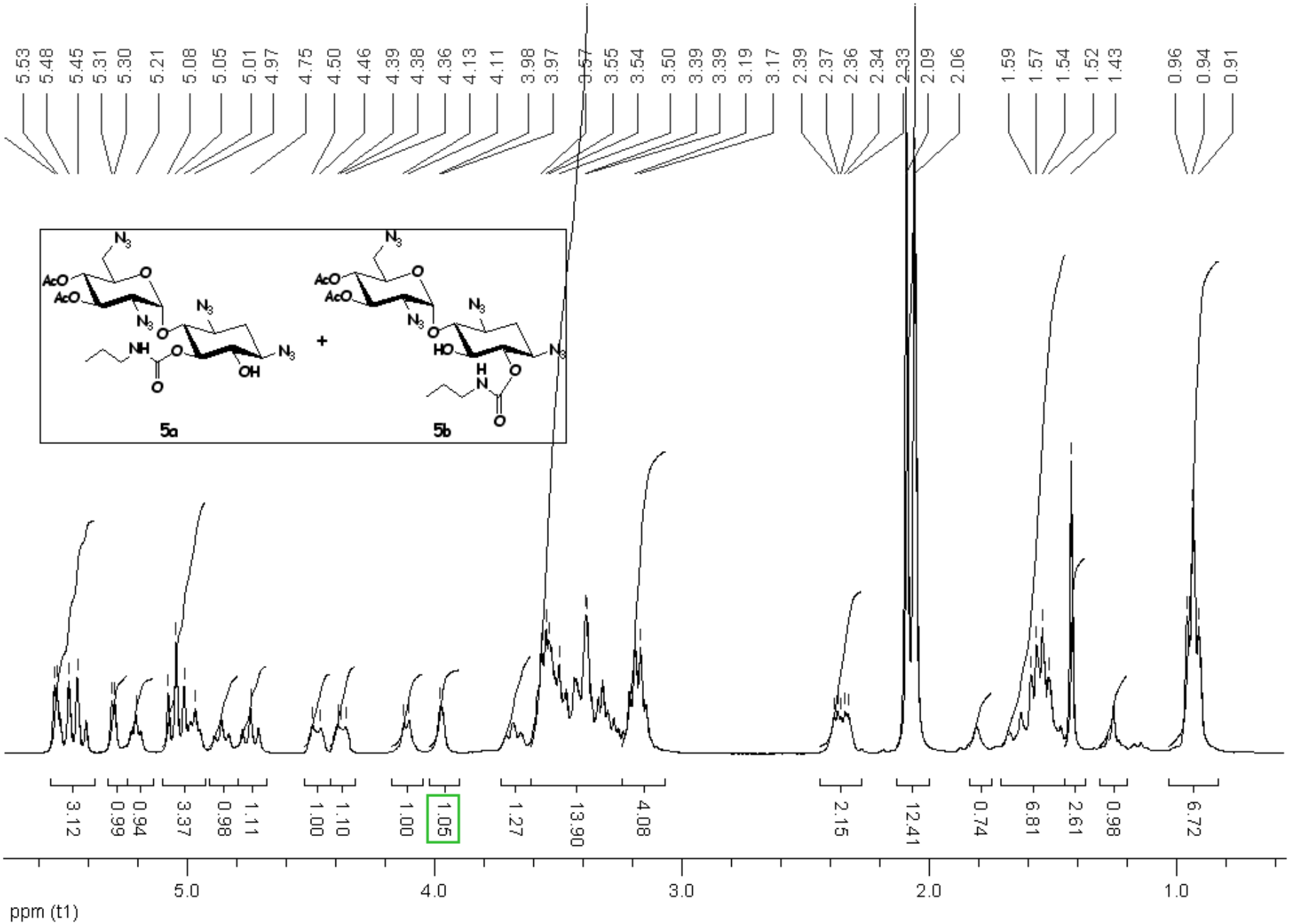
**8a** **8b**

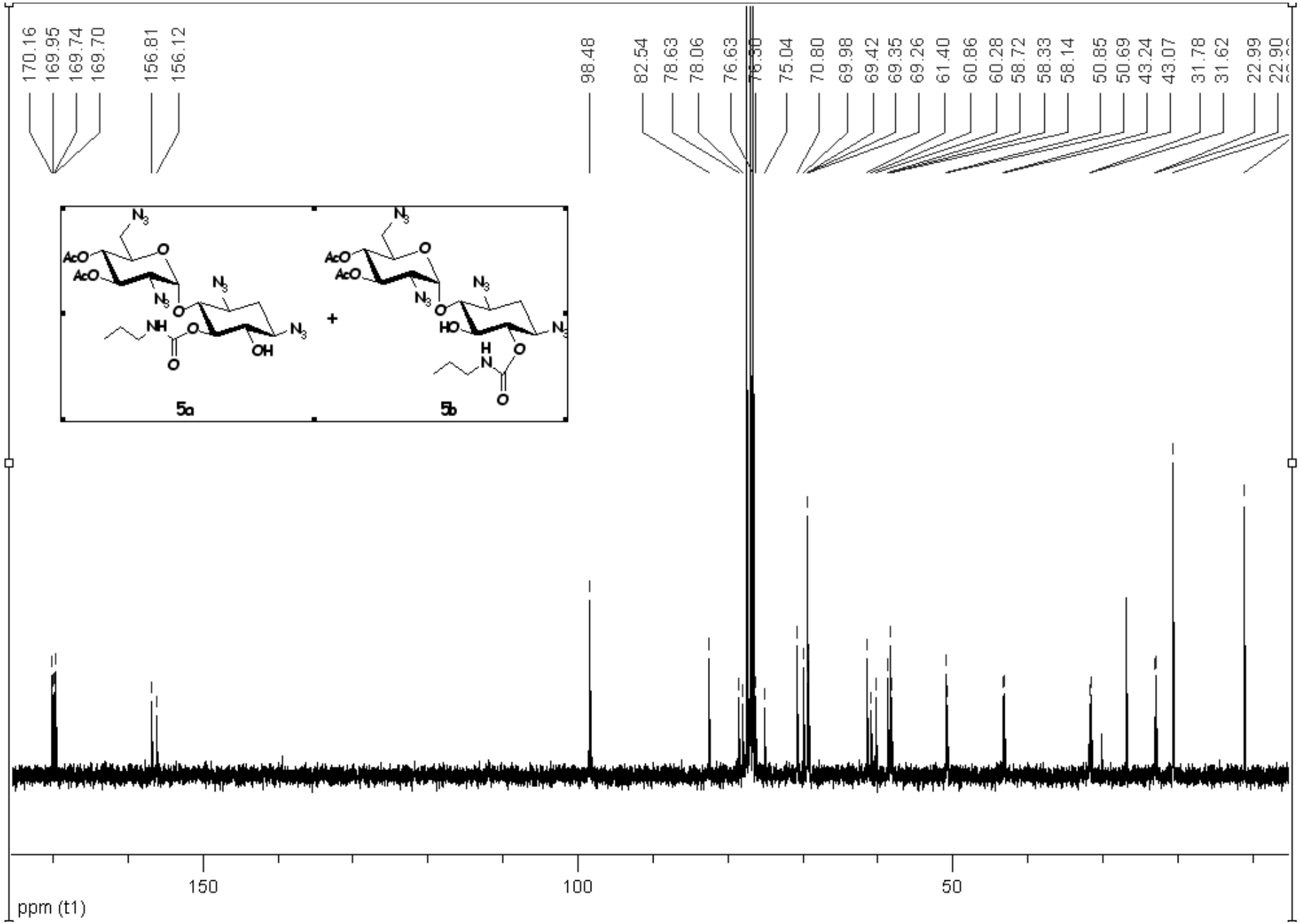


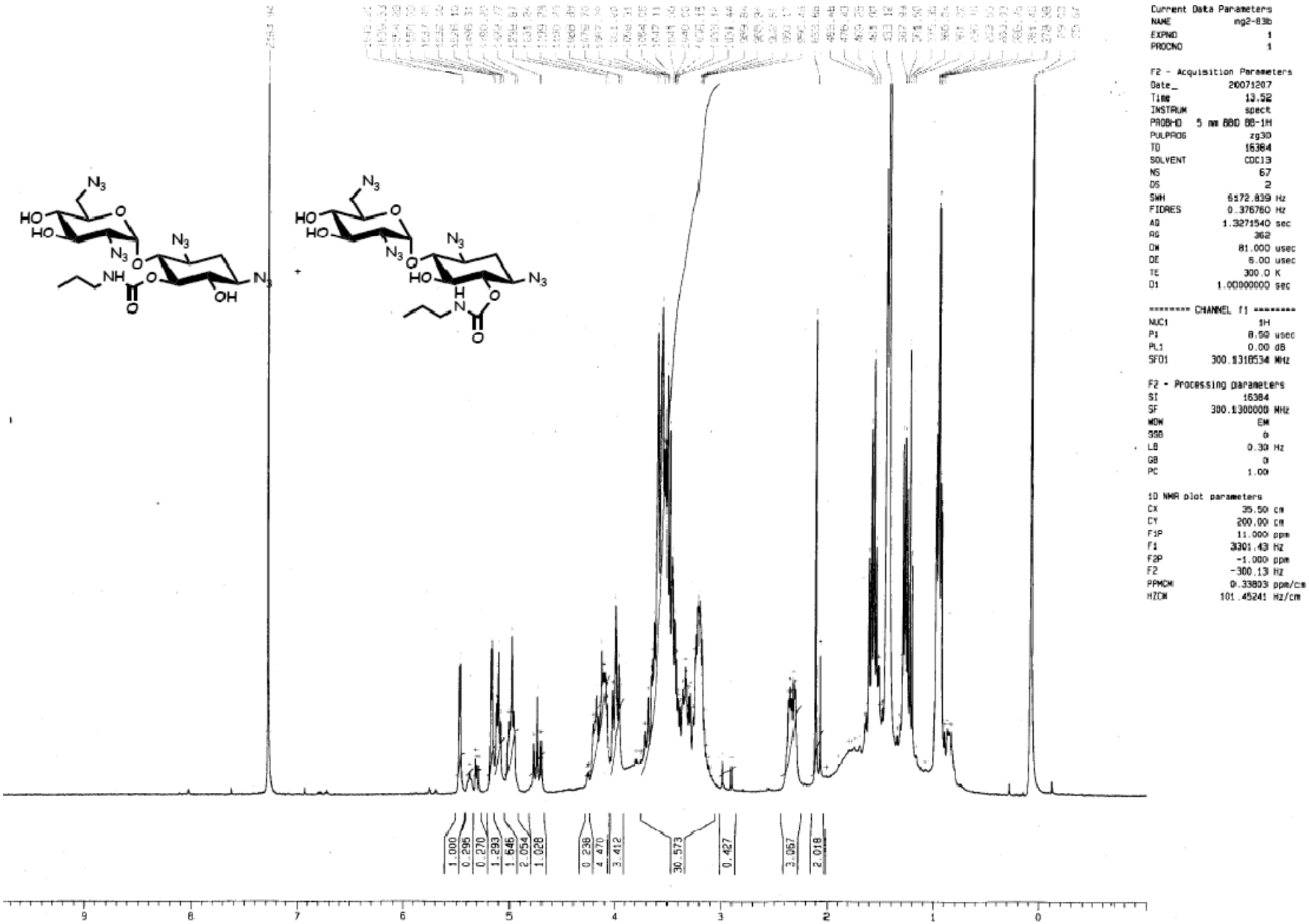


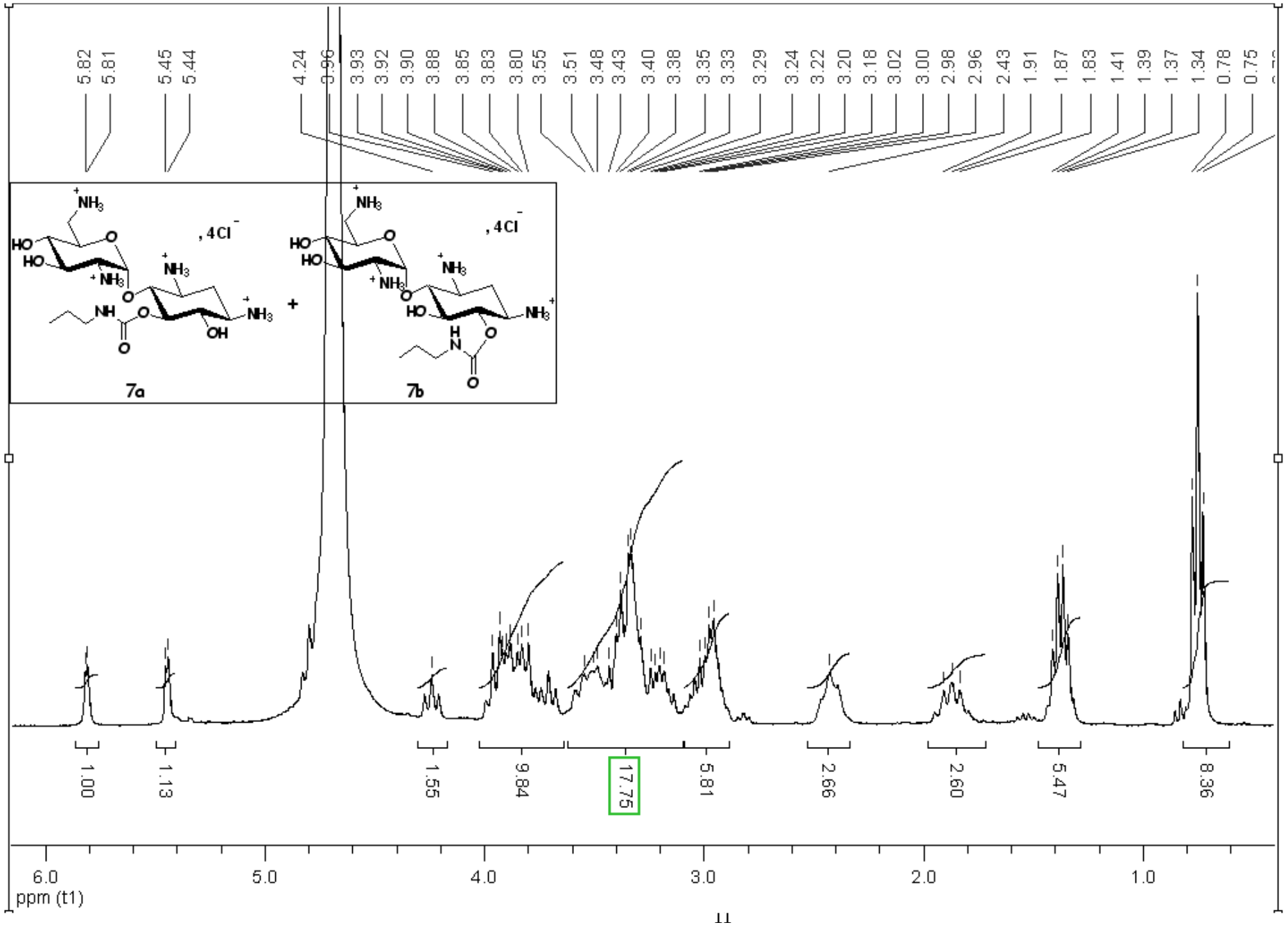


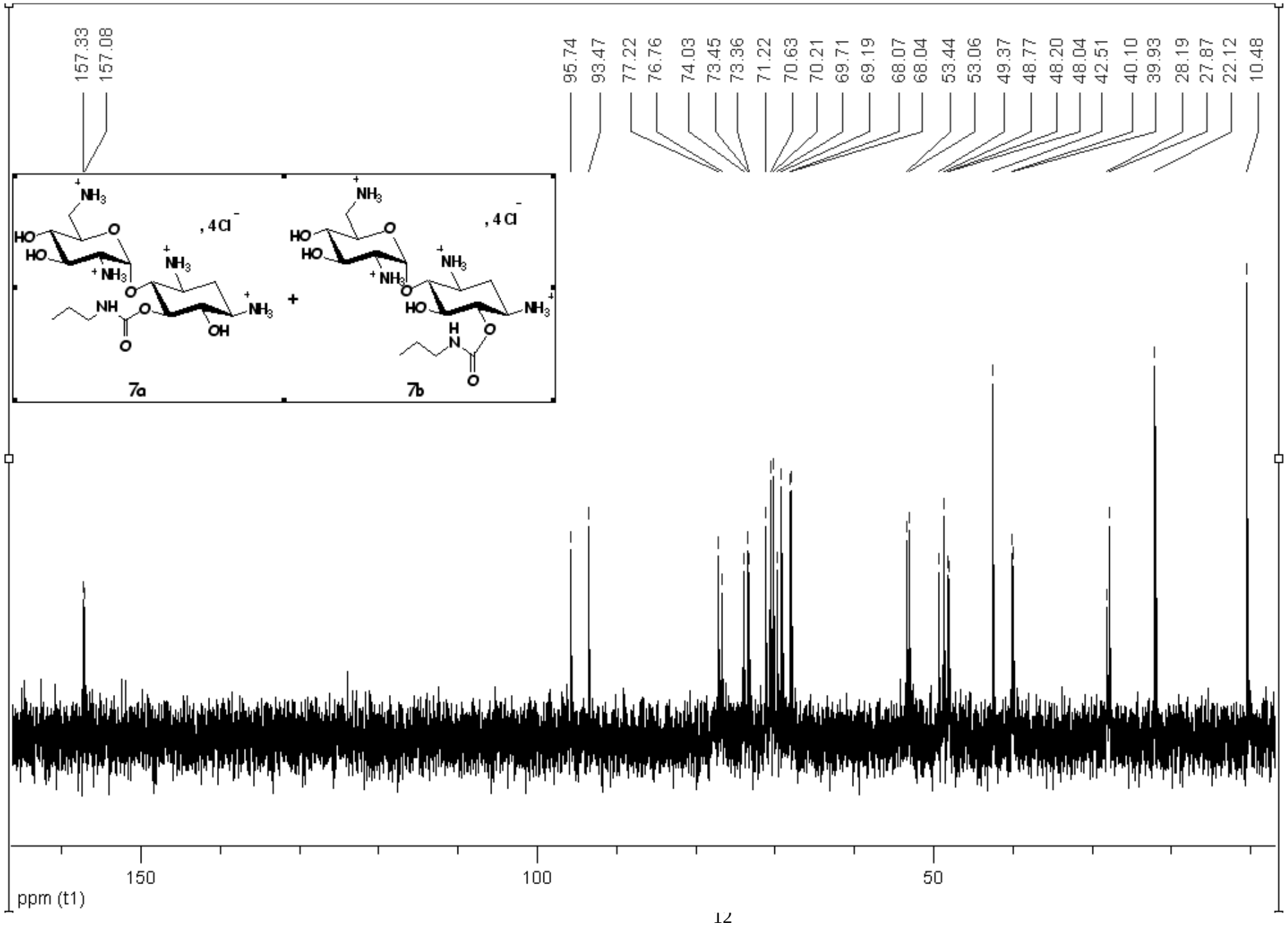


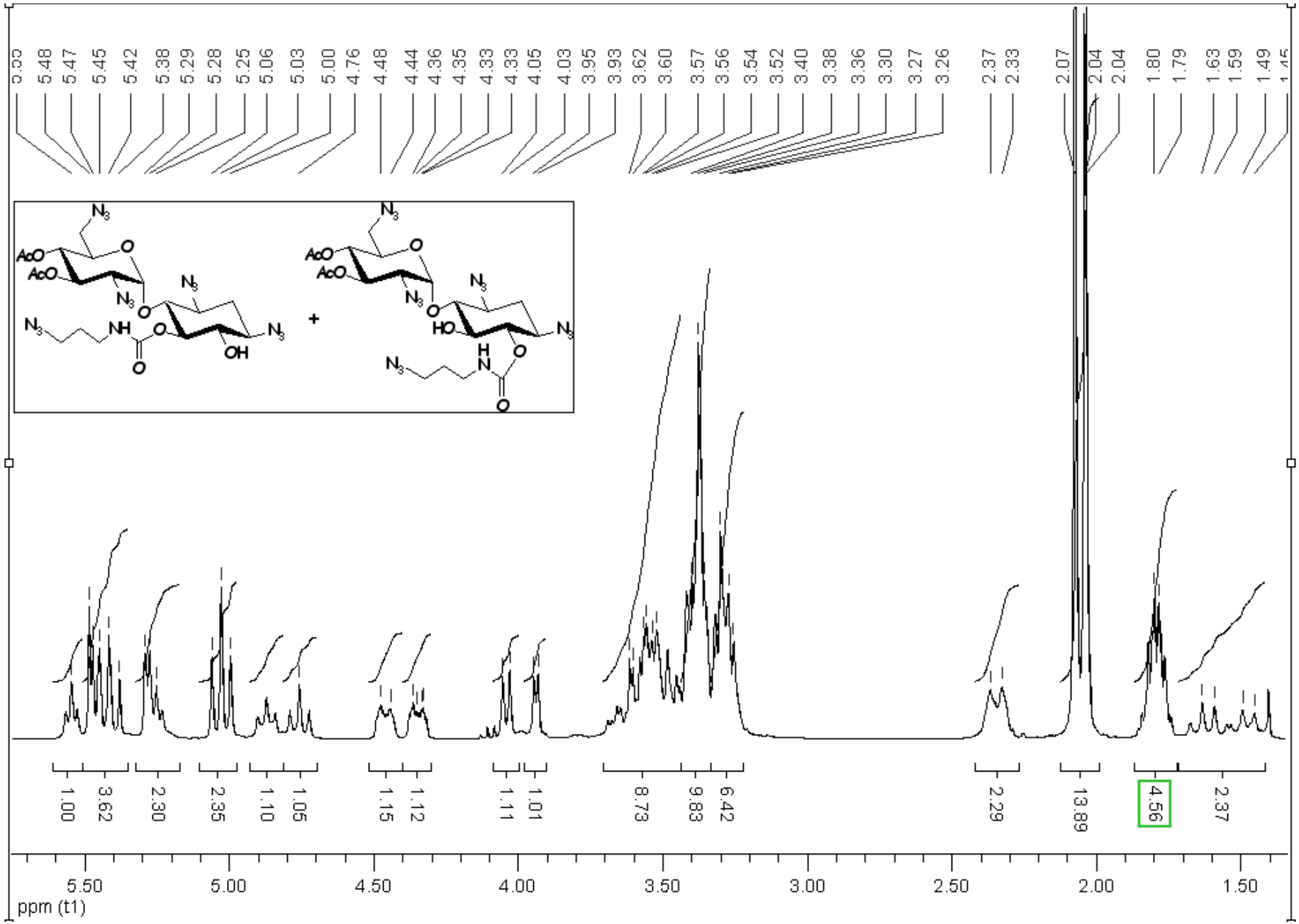


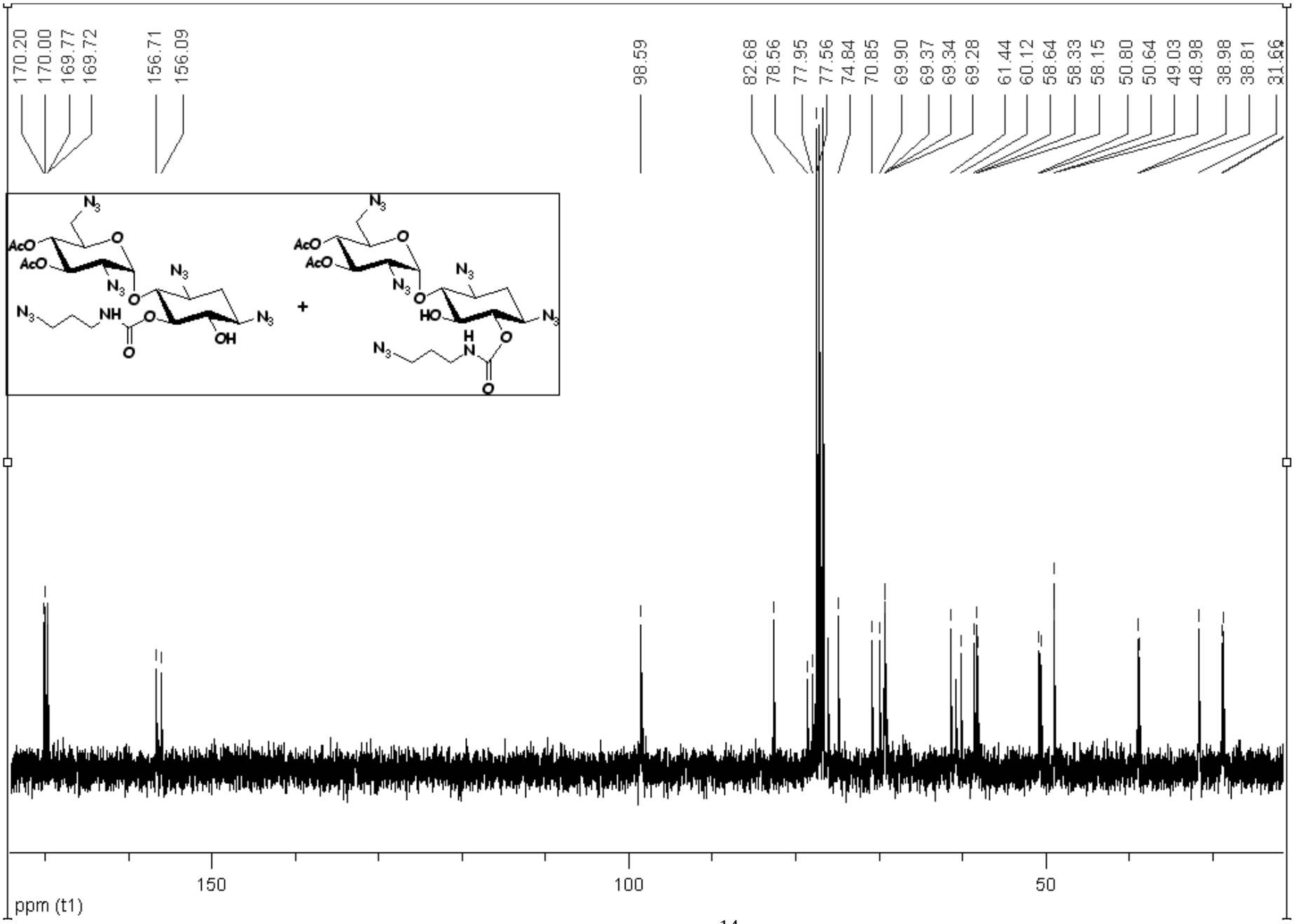


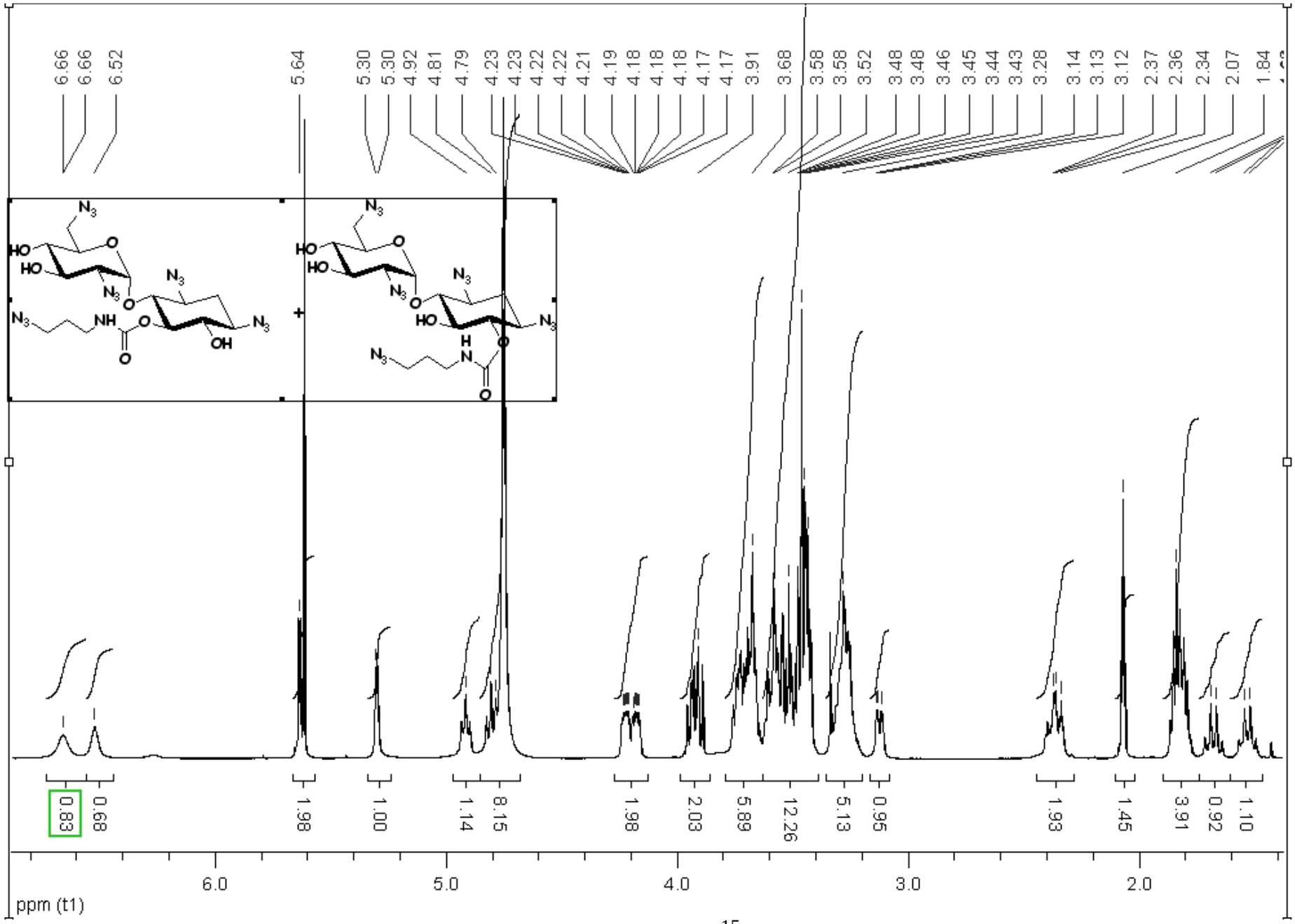


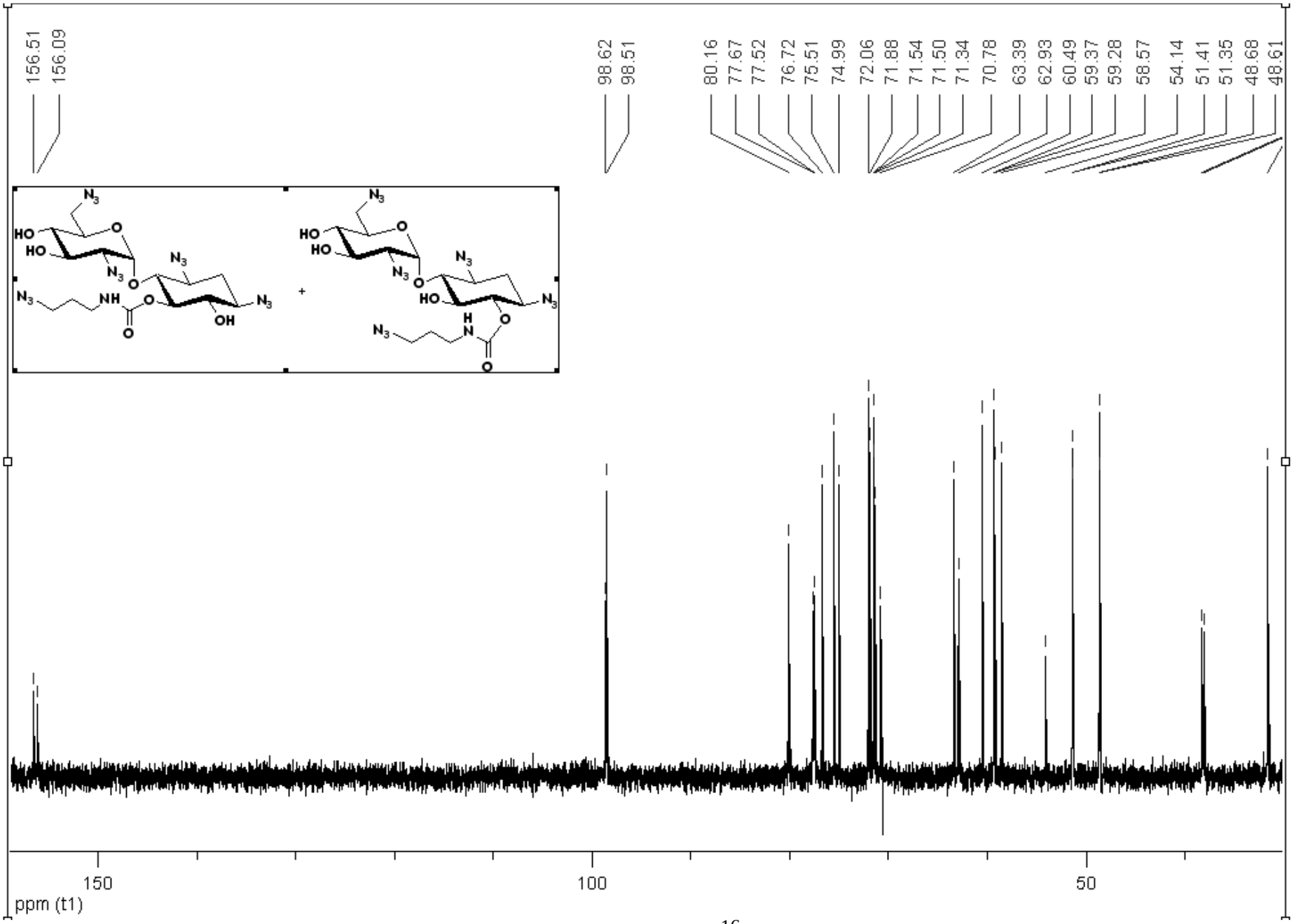


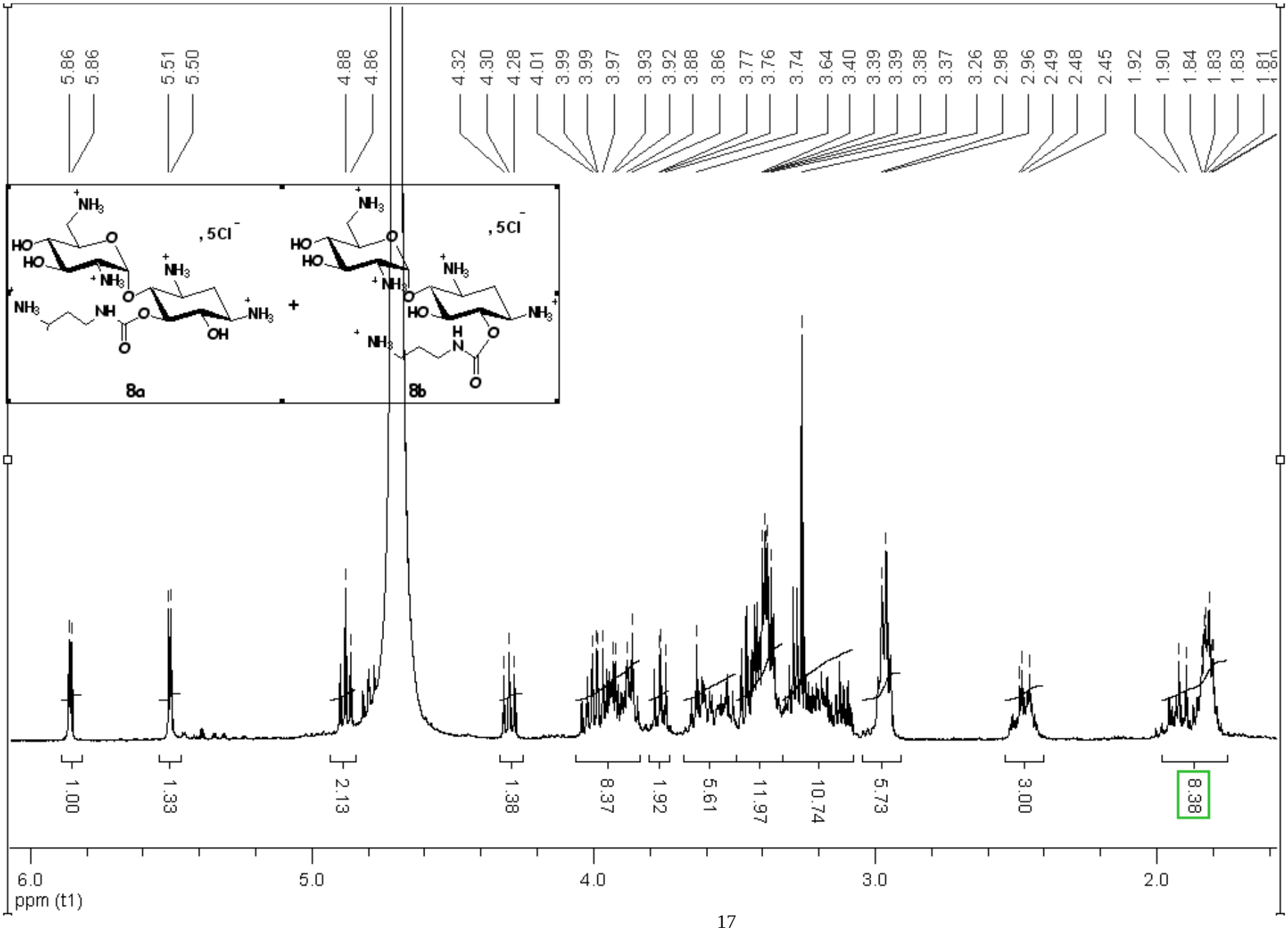


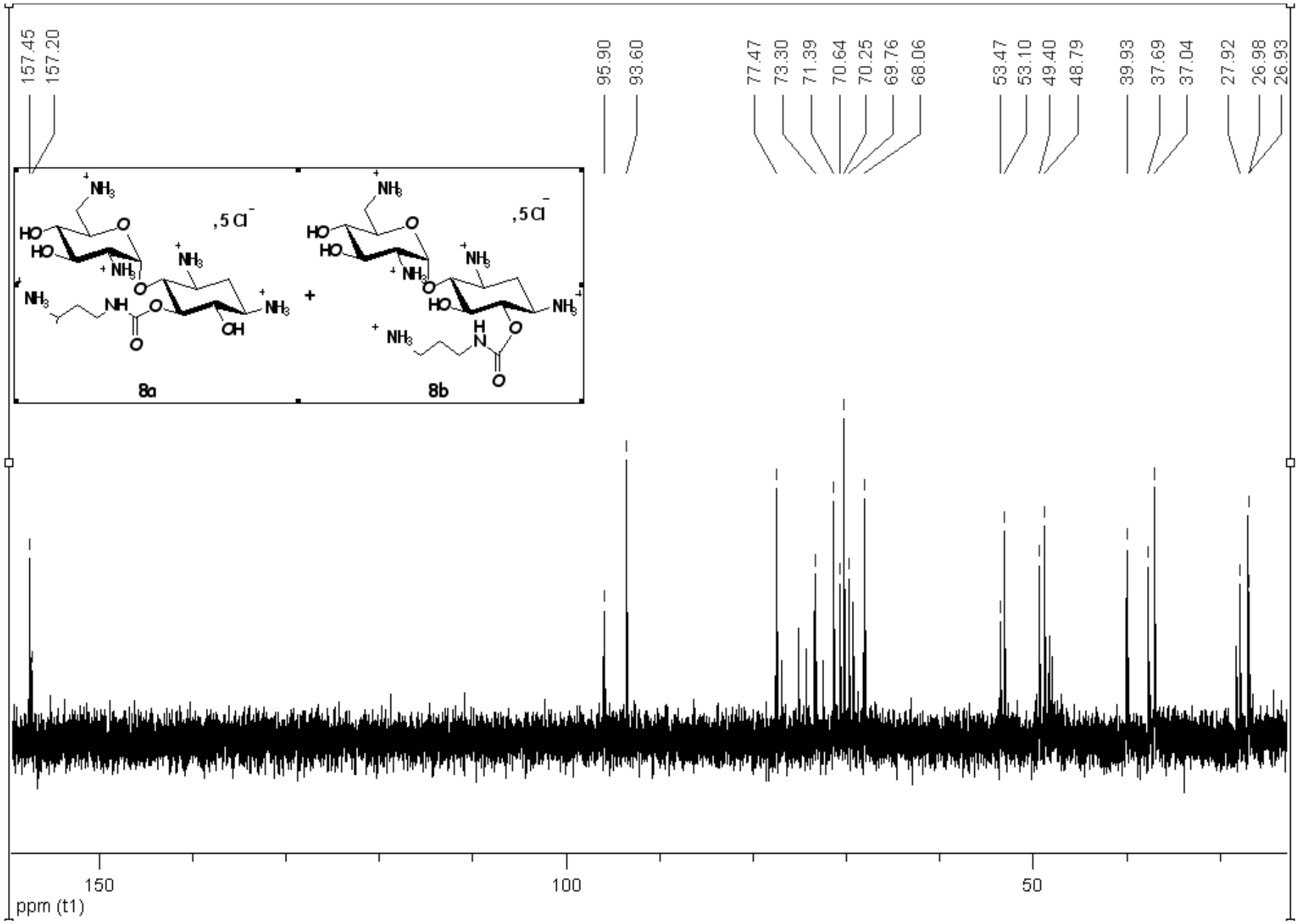


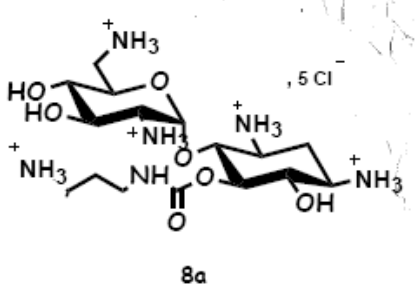













8a

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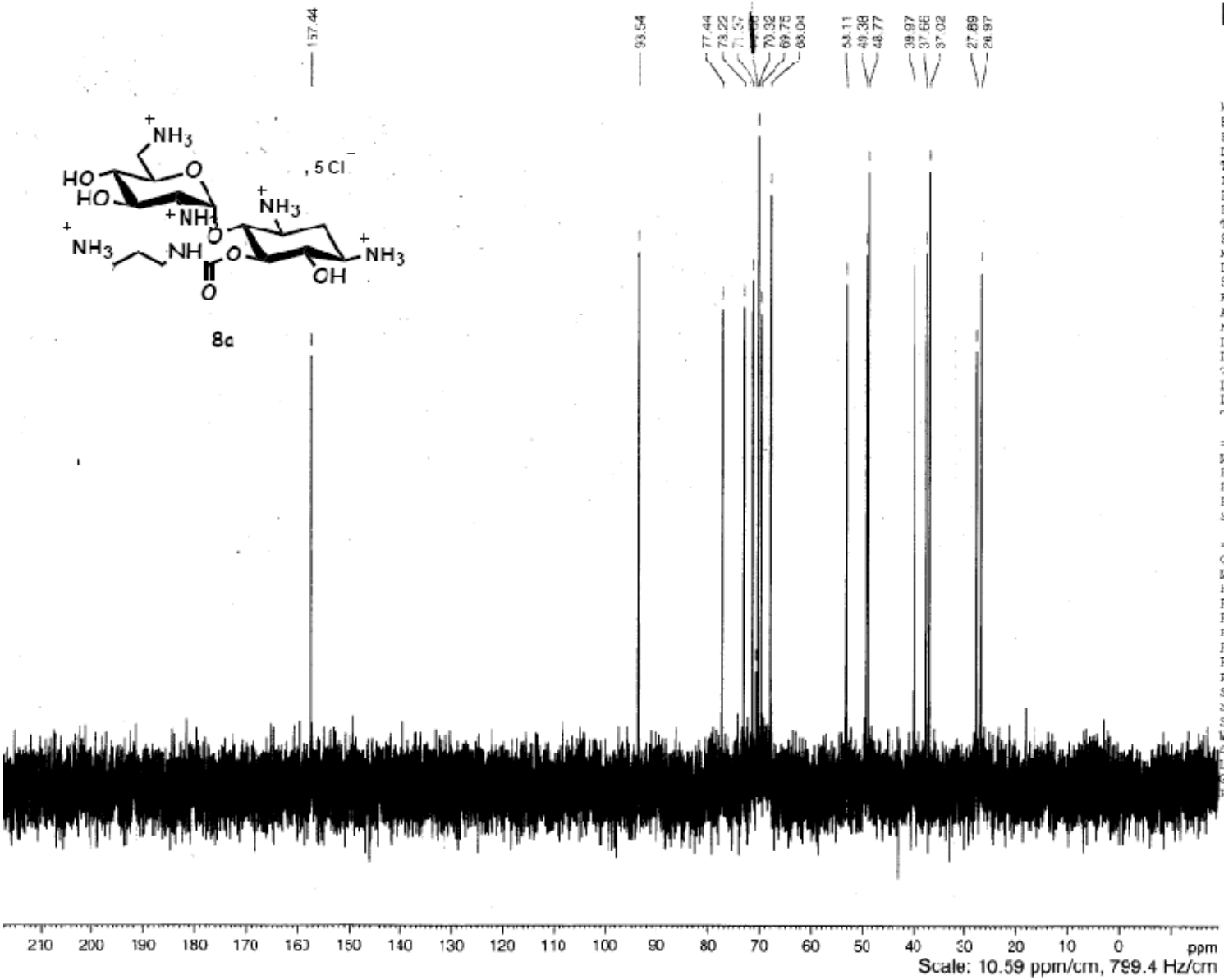


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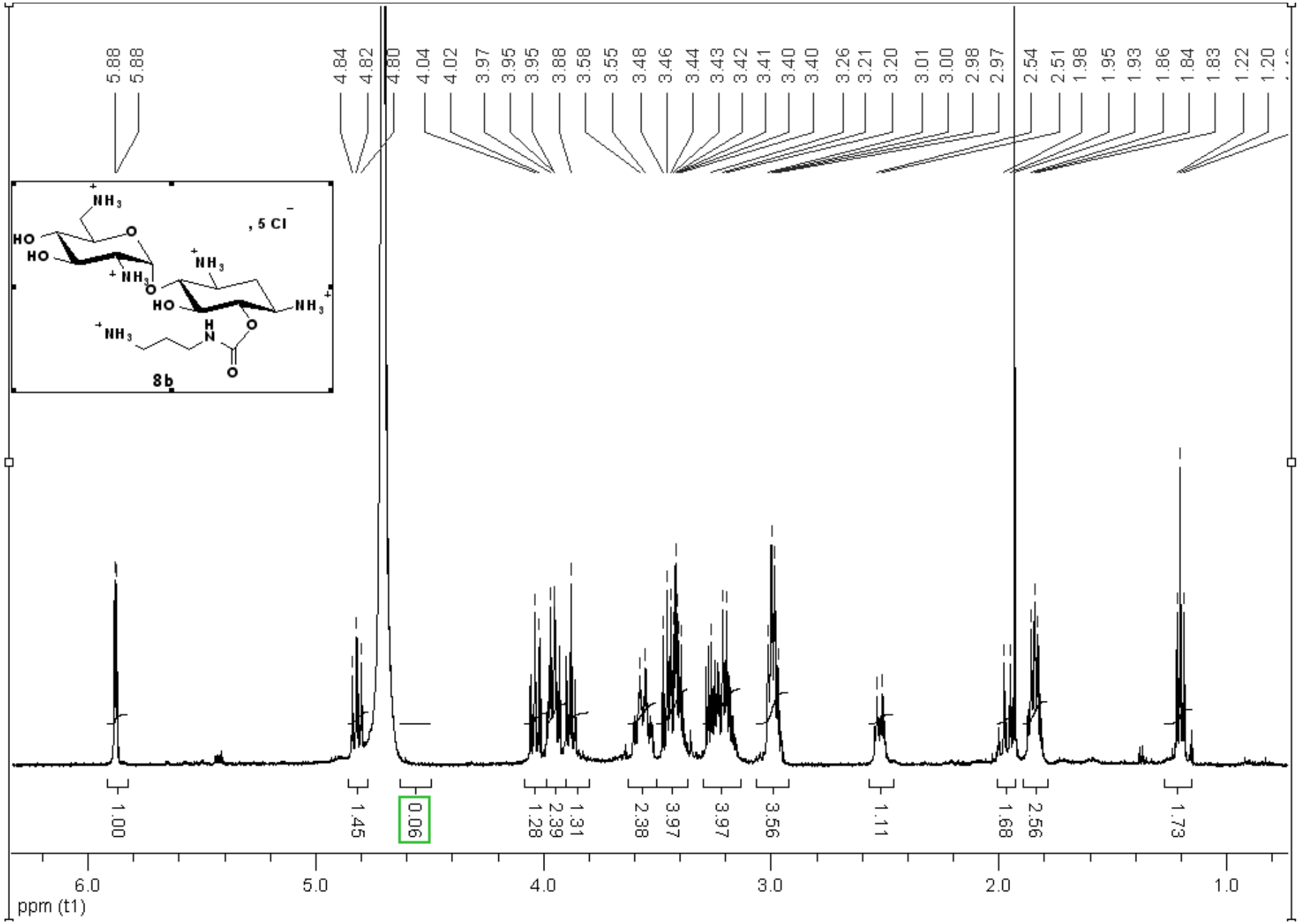

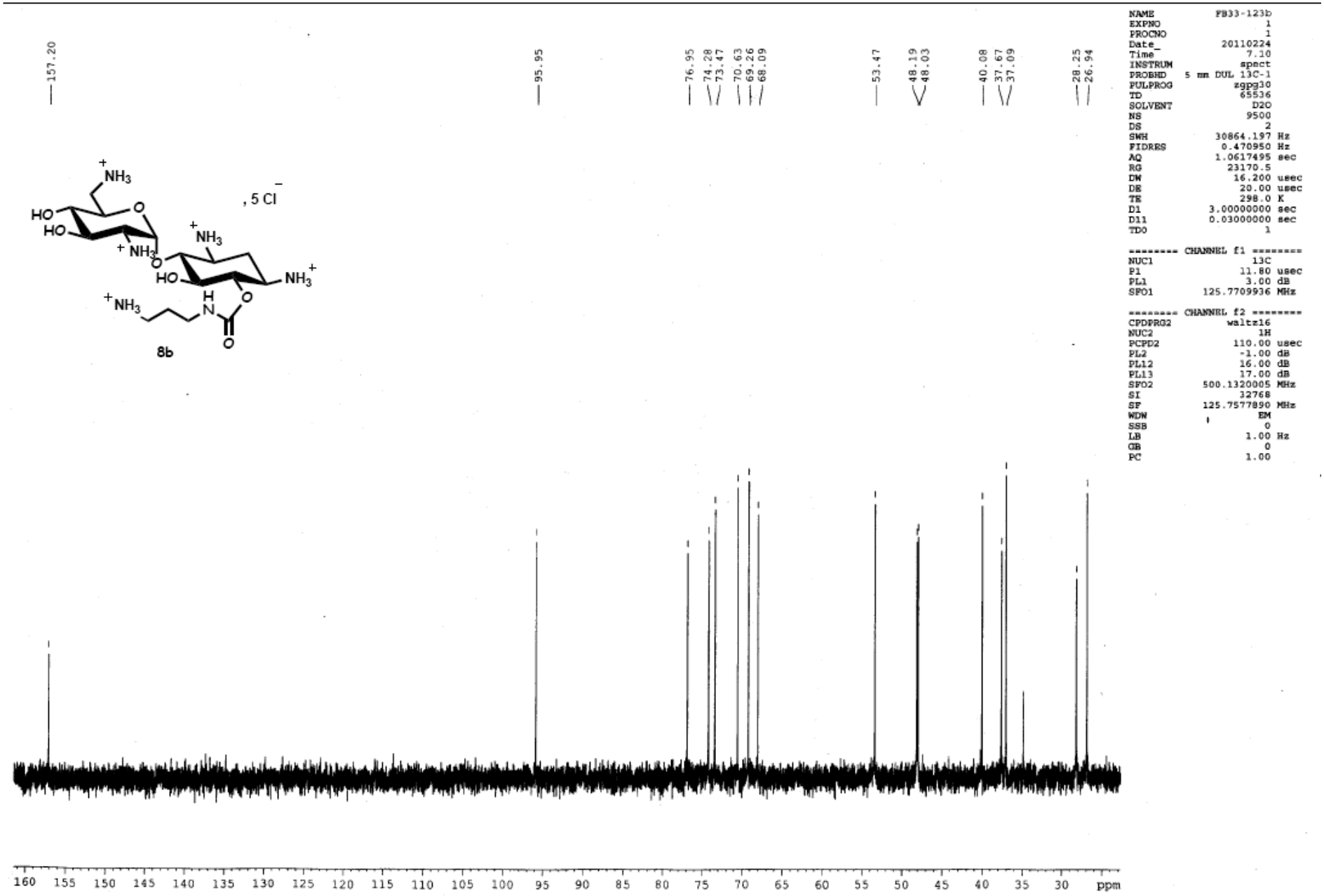

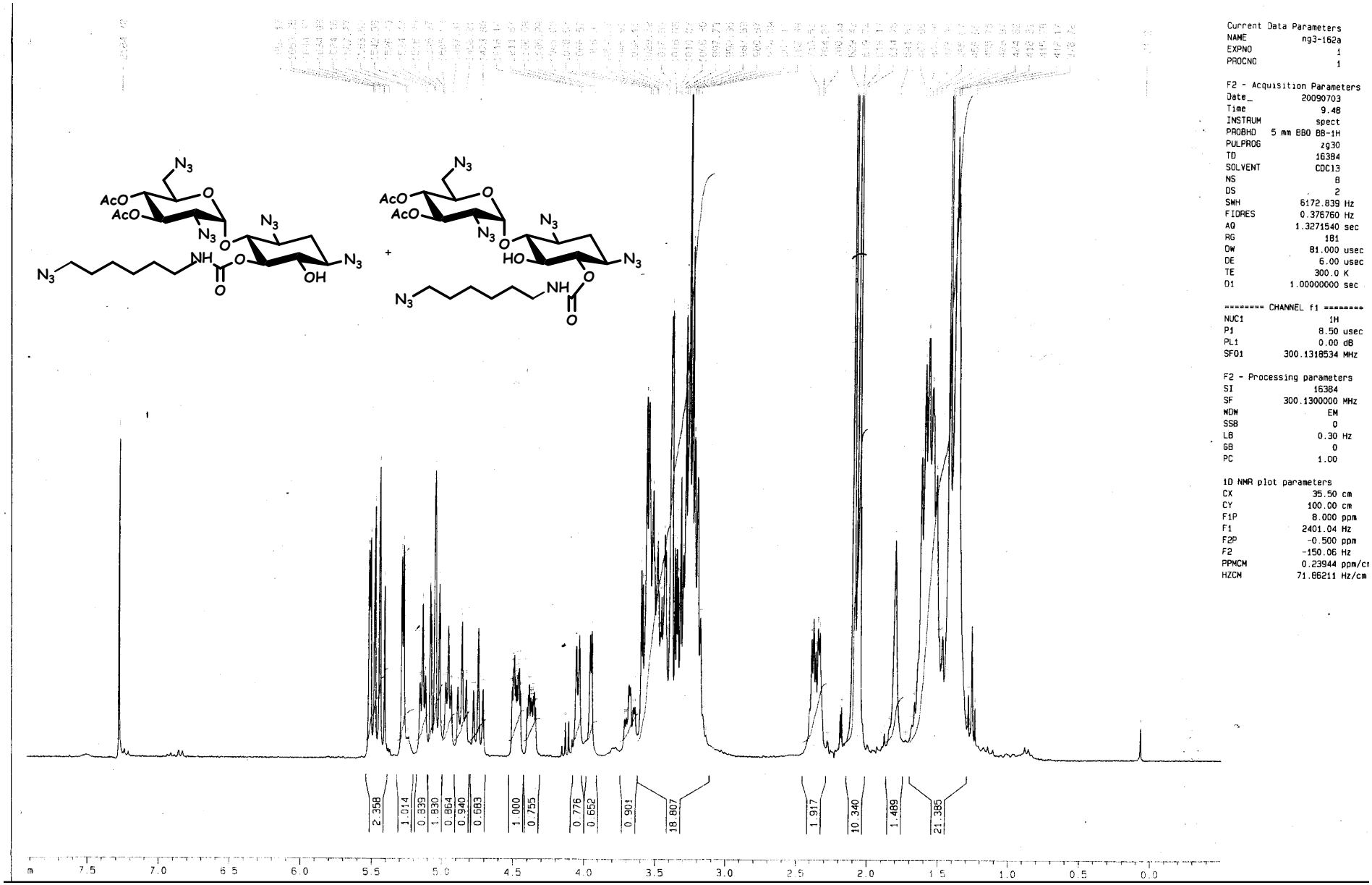

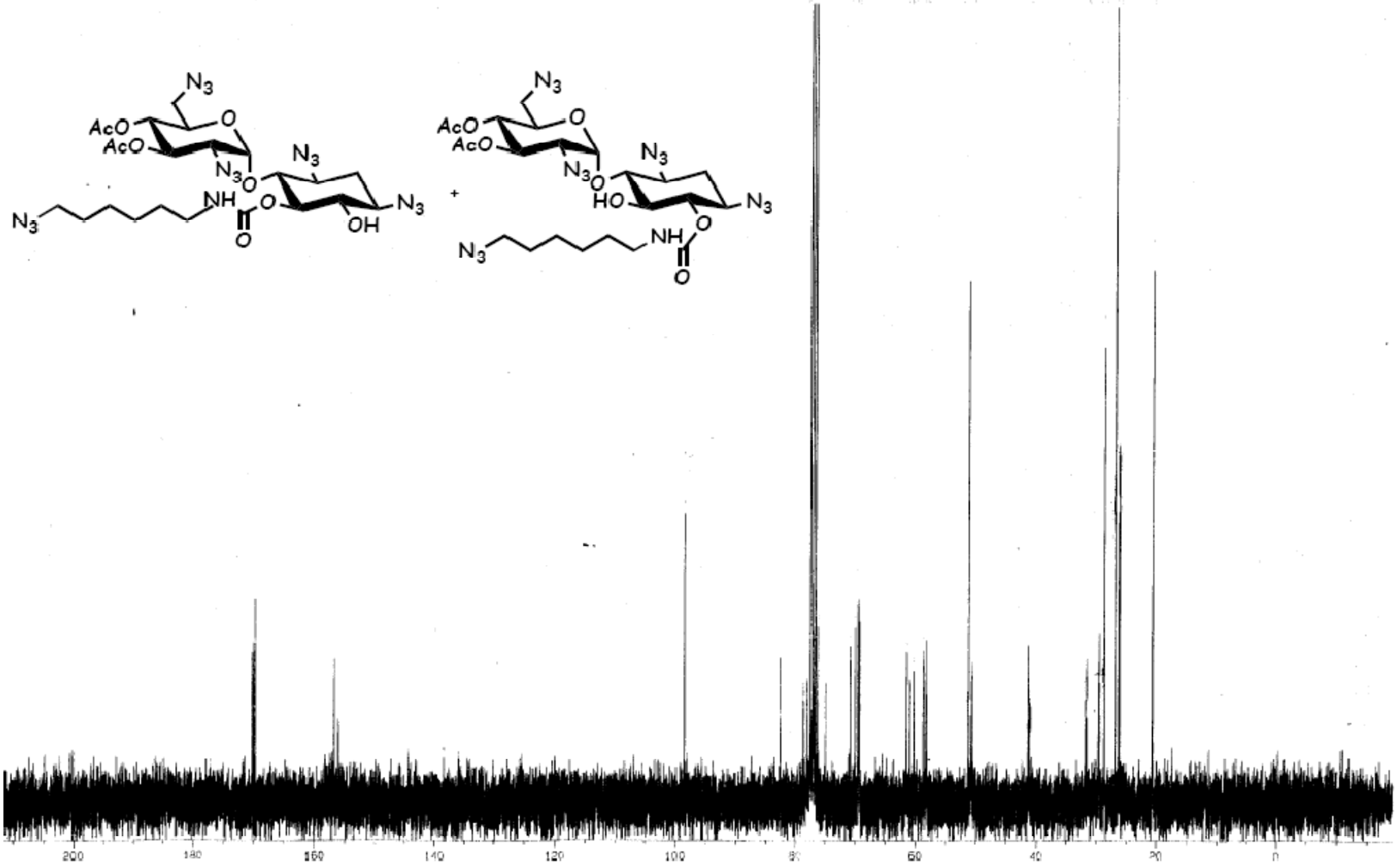


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