Imidazolium-linked azido-functionalized Guerbet glycosides: multifunctional surfactants for biofunctionalization of vesicles

- Supplementary Material -

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Physical Studies

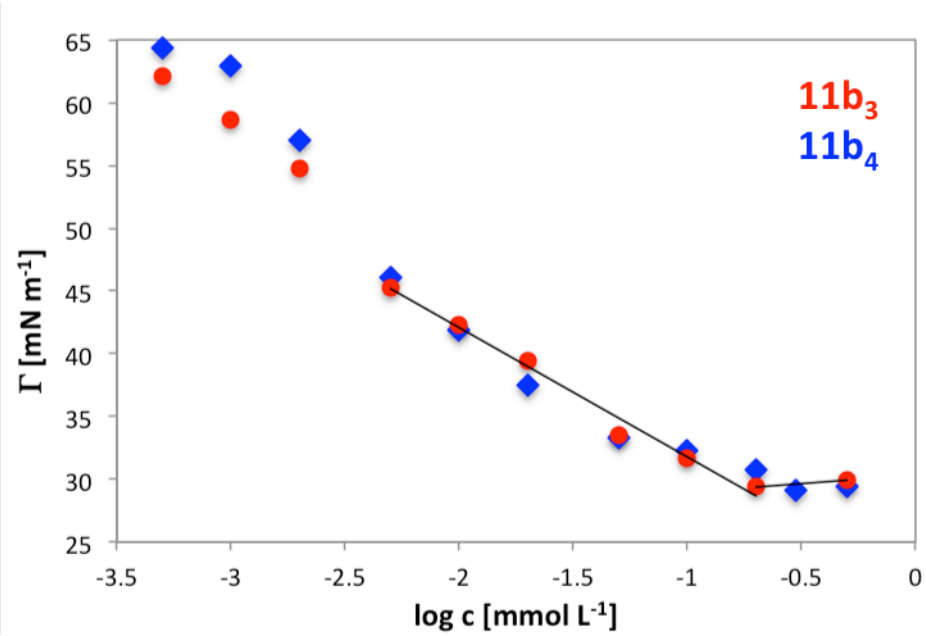

Figure S1. Surface tension behavior of **11**

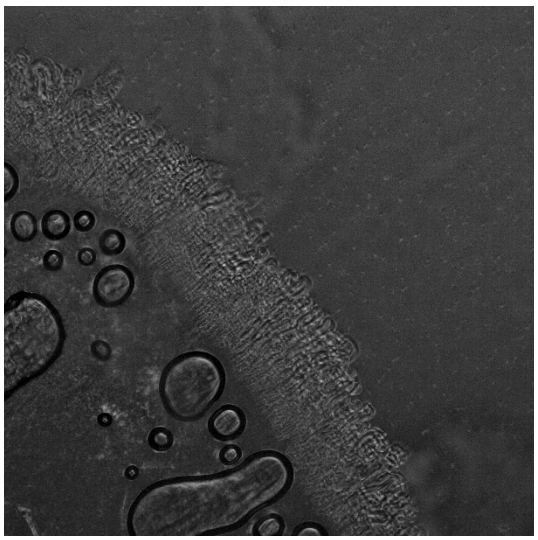

Figure S2. Contact penetration of a mixture of **12** and **11b$_3$** (10 %) with water under the optical polarizing microscope; massive formation of myelin figures indicates the lamellar phase

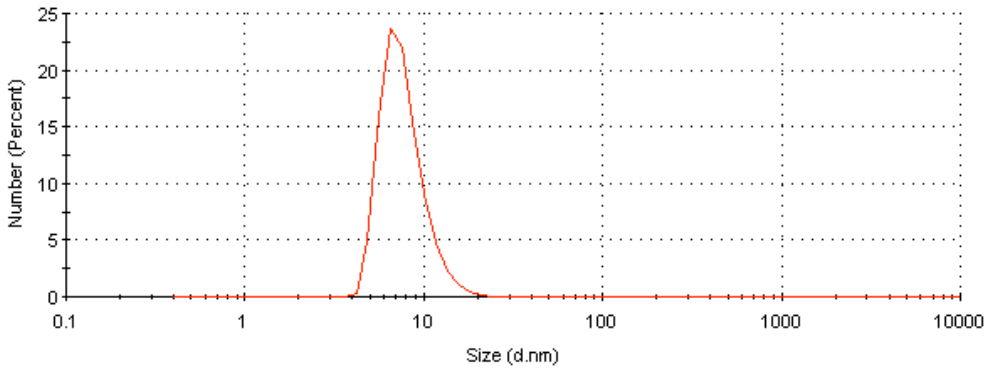

Figure S3. Vesicle size distribution for **12** with 5% **11b$_3$**

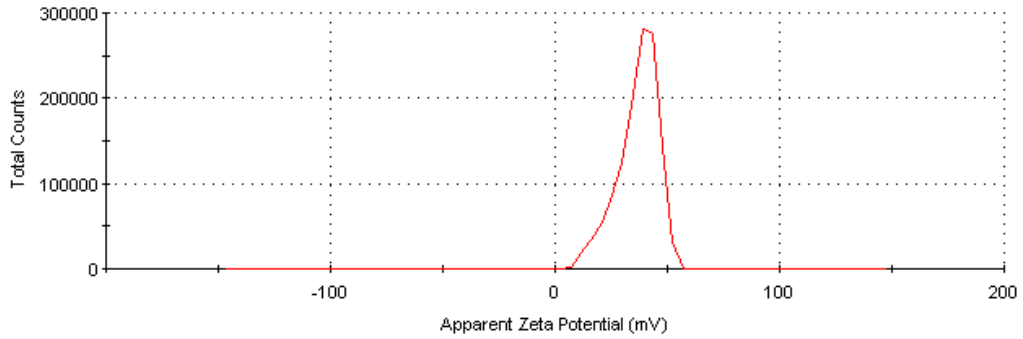

Figure S4. Zeta-potential distribution for vesicles of **12** with 5% **11b$_3$**

Experimental

Compounds containing remaining impuities

*2-Butyl-octyl 6-[1-(8-azido-3,6-dioxa-octyl)-imidazolium-3-yl]-6-deoxy-β-D-glucopyranoside bromide (**11a$_3$**).* A solution of **5a** (0.21 g, 0.39 mmol) and **9$_3$** (88 mg, 0.39 mmol) in xylene (3 mL) was heated to 130 °C. when TLC indicated the absence of starting material the solvent was evaporated to provide **10a$_3$** (0.27 g, 91%) as a yellow syrup. ^{1}H NMR analysis indicated about 25-30% remaining **5a** as impurity.

The intermediate **10a$_3$** (72 mg, 0.09 mmol) was subjected to Zemplen deacetylation in CH_3OH (5 mL) using a catalytic amount of NaOMe. After stirring at rt overnight the catalyst was removed by treatment with Amberlite IR120 (H^+) and the solvent was evaporated to furnish **11a$_3$** (54 mg, 89 %) as yellow syrup. The starting material impurities form **10a$_3$** remained.

Peracetate **10a$_3$**: $[\alpha]_D^{25}$ = -20 (c 0.38, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 10.21 (bs, imidazole), 7.48, 7.37 (2 m_c, 2 H, imidazole), 5.20 (dd~t, H-3), 4.87 (dd, H-2), 4.78-4.62 (m, 2 H, H-6), 4.67 (dd~t, H-4), 4.55 (d, H-1), 4.52 (ddd~m_c, $CH_2N_{imidazole}$-A), 4.44 (ddd~m_c, $CH_2N_{imidazole}$-B), 4.06 (ddd~bs, H-5), 3.89 (m_c, 2 H, CH_2O), 3.74-3.52 (m, 11 H, α-CH_2-A, EG-CH_2), 3.36 (t, 2 H, CH_2N_3), 3.30 (dd~m_c, α-CH_2-B), 2.22, 1.97, 1.93 (3 s, 3×3 H, Ac), 1.48 (m_c, *β*-CH), 1.20 (m_c, 16 H, bulk-CH_2), 0.84 (t, 6 H, CH_3); $^3J_{1,2}$ = 8.0, $^3J_{2,3}$ = 9.5, $^3J_{3,4}$ = 9.5, $^3J_{4,5}$ = 9.5, $^2J_6$ = 14.5 Hz. ^{13}C NMR (100 MHz, $CDCl_3$) δ= 170.50, 169.66, 169.14 (CO), 138.44 (imidazole-CHN_2), 122.74, 122.58 (imidazole), 100.93 (C-1), 73.29 / 73.26 (α), 72.03 (C-3), 71.28 (C-5), 70.95 (C-2), 70.25, 70.19, 69.84 (EG-CH_2), 68.77 (CH_2O), 68.22 (C-4), 50.55 (CH_2N_3), 49.90 ($CH_2N_{imidazole}$), 49.40 (C-6), 37.86 (β), 31.70 (ω-2), 30.95, 30.71, 30.60, 30.36, 29.55 / 29.53, 28.88, 28.73 (bulk-CH_2), 26.67 / 26.51 (γ), 22.88, 22.52 (ω-1), 21.34, 20.40, 20.35 (Ac), 13.95 (ω).

11a$_3$: IR [ATR, neat] ν/cm^{-1} 3370 (OH), 2925, 2858 (CH), 2106 (N_3). $[\alpha]_D^{25}$ = -12 (c 0.24, CH_3OH). ^{1}H NMR (400 MHz, CD_3OD): δ 9.00 (s, imidazole-CHN_2), 7.73, 7.61 (2 s, 2 H, imidazole), 4.68 (dd, H-6a), 4.48-4.43 (m, 3 H, H-6b, $CH_2N_{imidazole}$), 4.28 (d, H-1), 3.91-3.89 (m, 2 H, CH_2O), 3.71-3.64 (m, 8 H, EG-CH_2, α-CH_2-A, H-5), 3.43-3.36 (m, 4 H, CH_2N_3, α-CH_2-B, H-3), 3.17 (dd, H-2), 3.08 (dd~t, H-4), 1.60 (m_c, β–CH), 1.32 (m_c, 16 H, bulk-CH_2), 0.93 (m_c, 6H, CH_3); $^3J_{1,2}$ = 8.0, $^3J_{2,3}$ = 9.5, $^3J_{3,4}$ = 9.5, $^3J_{4,5}$ = 9.5, $^3J_{5,6a}$ = 2.0, $^3J_{6a,6b}$ = 14.5 Hz; ^{13}C NMR (100 MHz, CD_3OD): δ 138.7 (imidazole-CHN_2), 124.7, 124.1 (imidazole), 105.0 (C-1), 77.7 (C-3), 75.1 (C-2), 74.9 (C-5), 74.29 / 74.26 (α), 72.5 (C-4), 71.6 (2), 71.2 (EG-CH_2), 70.0 (CH_2O), 51.9 (C-6), 51.9 (-CH_2N_3), 51.1 ($CH_2N_{imidazole}$), 39.64 (β), 33.2, 32.4 / 32.3, 32.1 / 32.0, 30.99, 30.31 / 30.25, 28.03 / 27.96, 24.3 (bulk CH_2), 23.9 (ω-1), 14.6 (ω). HRMS (ESI): Calc. for [M-Br] $[C_{27}H_{50}N_5O_7]^+$ 556.3710, 557.3744 (30%); found 556.3727, 557.3757 (34%).

*2-Hexyl-decyl 6-[1-(5-azido-3-oxa-pentyl)-imidazolium-3yl]-6-deoxy-β-D-glucopyranoside bromide (**11b$_2$**)*. A solution of **5b** (0.12 g, 0.20 mmol) and **9$_2$** (37 mg, 0.20 mmol) in xylene (2 mL) was heated to 130 °C. when TLC indicated the absence of starting material the solvent was evaporated to provide **10b$_2$** (0.14 g, 89%) as a yellow syrup. ^{1}H NMR analysis indicated about 20-25% remaining **5b** as impurity.

The intermediate **10b$_2$** (0.12 g, 0.15 mmol) was subjected to Zemplen deacetylation in CH_3OH (5 mL) using a catalytic amount of NaOMe. After stirring at rt overnight the catalyst was removed by treatment with Amberlite IR120 (H^+) and the solvent was evaporated to furnish **11b$_2$** (90 mg, 92 %) as yellow syrup. The starting material impurities form **10b$_2$** remained.

Peracetate **10b$_2$**: $[a]_D^{25}$ = -20 (c 0.1, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ= 10.46 (s, imidazole), 7.37 (m_c, 2 H, imidazole), 5.23 (dd~t, H-3), 4.90 (dd, H-2), 4.70 (dd, H-6A), 4.70 (dd~t, H-4), 4.63-4.45 (m, 3 H, H-6B, $CH_2N_{imidazole}$), 4.56 (d, H-1), 4.05 (ddd, H-5), 3.96 (m_c, 2 H, CH_2O), 3.77-3.69 (m, 3 H, EG-CH_2, α-CH_2-A), 3.40 (t, 2 H, CH_2N_3), 3.33 (dd, α-CH_2-B), 2.27, 2.01, 1.97 (3 s, 3×3 H, Ac), 1.52 (m_c, *β*-CH), 1.24 (m_c, 24 H, bulk-CH_2), 0.87 (t, 6 H, CH_3); $^3J_{1,2}$ = 8.0, $^3J_{2,3}$ = 9.5, $^3J_{3,4}$ = 9.5, $^3J_{4,5}$ = 10.0, $^3J_{5,6A}$ = 4.0, $^3J_{5,6B}$ = 4.5, $^2J_6$ = 14.0, $^3J_{\alpha B,\beta}$ = 6.0, $^2J_\alpha$ = 9.5 Hz. ^{13}C NMR (100 MHz, $CDCl_3$) δ= 170.6, 169.8, 169.2 (CO), 138.5 (imidazole-CHN_2), 122.9, 122.6 (imidazole), 101.1 (C-1), 73.5 / 73.4 (α), 72.2 (C-3), 71.4 (C-5), 71.0 (C-2), 70.2 (EG-CH_2), 68.9 (CH_2O), 68.4 (C-4), 50.5 (CH_2N_3), 50.2 ($CH_2N_{imidazole}$), 49.6 (C-6), 38.0 (β), 31.9 (ω-2), 31.0, 30.8, 30.02 / 30.00, 29.67 / 29.65, 29.59, 29.3 (bulk-CH_2), 26.84 / 26.77 / 26.68 / 26.63 (γ), 22.6 (ω-1), 21.4, 20.52, 20.48 (Ac), 14.1 (ω).

11b$_2$: $[\propto]_D^{25}$ = -13(c 0.12, CH_3OH). IR [ATR, neat] ν/cm^{-1} 3365 (OH), 2955, 2924, 2855 (CH), 2108 (N_3). ^{1}H-NMR (400 MHz, CD_3OD) δ= 8.55 (bs, <1 H, imidazole), 7.70, 7.60 (2 d, 2 H, imidazole), 4.63 (dd~bd, H-6A), 4.46 (t, 2 H, $CH_2N_{imidazole}$), 4.41 (dd, H-6B), 4.24 (d, H-1), 3.89 (t, 2 H, CH_2O), 3.74-3.64 (m, 3 H, CH_2N_3, α-CH_2-A), 3.61 (ddd, H-5), 3.38 (dd~t, H-3), 3.37 (dd, β-CH_2-B), 3.15 (dd, H-2), 3.06 (dd~t, H-4), 1.59 (m_c, *β*-CH), 1.30 (m_c, 24 H, bulk-CH_2), 0.90 (t, 6 H, CH_3); $^3J_{1,2}$ = 8.0, $^3J_{2,3}$ = 9.0, $^3J_{3,4}$ = 9.0, $^3J_{4,5}$ = 9.5, $^3J_{5,6A}$ = 2.5, $^3J_{5,6B}$ = 7.0, $^2J_6$ = 14.5, $^3J_{\alpha,\beta}$ = 2.0, $^2J_\alpha$ = 14.5, $^3J_{CH2N,CH2O}$ = 4.5 Hz. ^{13}C NMR (100 MHz, CD_3OD) δ= 125.0, 123.9 (imidazole), 105.0 (C-1), 77.8 (C-3), 75.1 (C-2), 74.9 (C-5), 74.3 (α), 72.5 (C-4), 71.4 (EG-CH_2), 69.8 (CH_2O), 51.9 (CH_2N_3), 51.8 (C-6), 51.1 ($CH_2N_{imidazole}$), 39.7 (β), 33.2 (ω-2), 32.36 / 32.34, 32.30 / 32.28, 31.3, 31.0, 30.88 / 30.87, 30.6 (bulk-CH_2), 28.03 / 28.01 / 27.97 / 27.96 (γ), 23.9 (ω-1), 14.6 (ω). HRMS (ESI): Calc. for [M-Br] $[C_{29}H_{54}N_5O_6]^+$ 568.4074; found 568.4056.

Micelle conjugation and reference compound

*2-Butyl-octyl 6-{1-[11-(4-hydroxymethyl-1H-1,2,3-triazole-1-yl)-3,6,9-trioxa-undecyl]-imidazolium-3-yl}-6-deoxy-β-D-glucopyranoside bromide (**14**).* ^{1}H NMR (400 MHz, CD_3OD): δ 8.95 (s, imidazole-CHN_2), 7.97 (s, triazole), 7.68, 7.56 (2s, 2 H, imidazole), 4.67 (m_c, 3 H, CH_2OH, H-6A), 4.59 (t, 2 H, $CH_2N_{trizole}$), 4.40 (m_c, 3 H, $CH_2N_{imidazole}$, H-6B), 4.25 (d, H-1), 3.93-3.90 (m, >2 H, CH_2O), 3.66-3.53 (m, >12 H, EG-CH_2, H-5, α-CH_2-A), 3.40-3.35 (m, 2 H, H-3, α-CH_2-B), 3.13 (dd, H-2), 3.04 (dd~t, H-4), 1.55-1.48 (m, *β*-CH), 1.29 (m_c, >14 H, bulk-CH_2), 0.93 (m_c, 6 H, CH_3). HRMS (ESI): Calc. for [M-Br] $[C_{32}H_{58}N_5O_9]^+$ 656.4231, 657.4269 (35%); found 565.4231, 657.4257 (32%).

*1,8-Diazido-3,6-dioxa-octane (**15**).* A solution of 1,2-bis-(2-chloroethoxy)-ethane (3.0 mL, 19 mmol) in DMF (50 mL) was treated with NaN_3 (3.7 g, 57 mmol) and the reaction was heated to 80 °C overnight. The solvent was evaporated at reduced pressure and the residue extracted with CH_2Cl_2 to furnish **15** as colourless liquid (3.7 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68-3.65 (m, 8 H, OCH_2), 3.37 (t, 4 H, CH_2N_3). ^{13}C NMR (100MHz, $CDCl_3$): δ 70.8, 70.2 (-OCH_2), 50.8 (CH_2N_3).

*1,8-Bis-(4-hydroxymethyl-1,2,3-triazole-1-yl)-3,6-dioxa-octane (**16**)*. A solution of **15** (0.50 g, 2.5 mmol) and propargyl alcohol (0.36 mL, 6.2 mmol) in CH_3OH (20 mL) was treated with $Cu(OAc)_2$ (70 mg, 0.4 mmol) and sodium ascorbate (0.22 g, 1.1 mmol) under ice-bath cooling. After 30 min the reaction was alowed to warm to rt and stirred overnight. Methanol was evaporated at reduced pressure and the residue was distributed between butanol and water. The organic layer was dried over $MgSO_4$ and concentrated to furnish crude triazole **16** as yellow liquid (0.58 g, 74%). NMR-analysis revealed that the product contained minor contents of the solvent (^{n}BuOH). ^{1}H NMR (400 MHz, CD_3OD): δ 7.93 (s, 2 H, triazole), 4.68 (s, 4 H, CH_2OH), 4.55 (t, 4 H, $CH_2N_{triazole}$), 3.83 (t, 4 H, CH_2O), 3.56 (m, 4 H, EG-CH_2). ^{13}C NMR (100 MHz, CD_3OD): 149.1 (triazole-C), 124.9 (triazole-CH), 71.4 (EG-CH_2), 70.5 (CH_2O), 56.6 (CH_2OH), 51.5 (CH_2N). HRMS (ESI): Calc. for [M+Na] $[C_{12}H_{20}N_6O_4Na]^+$ 335.1431, 336.1478 (13%); found 335.1431, 336.1457 (14%).

NMR Spectra:

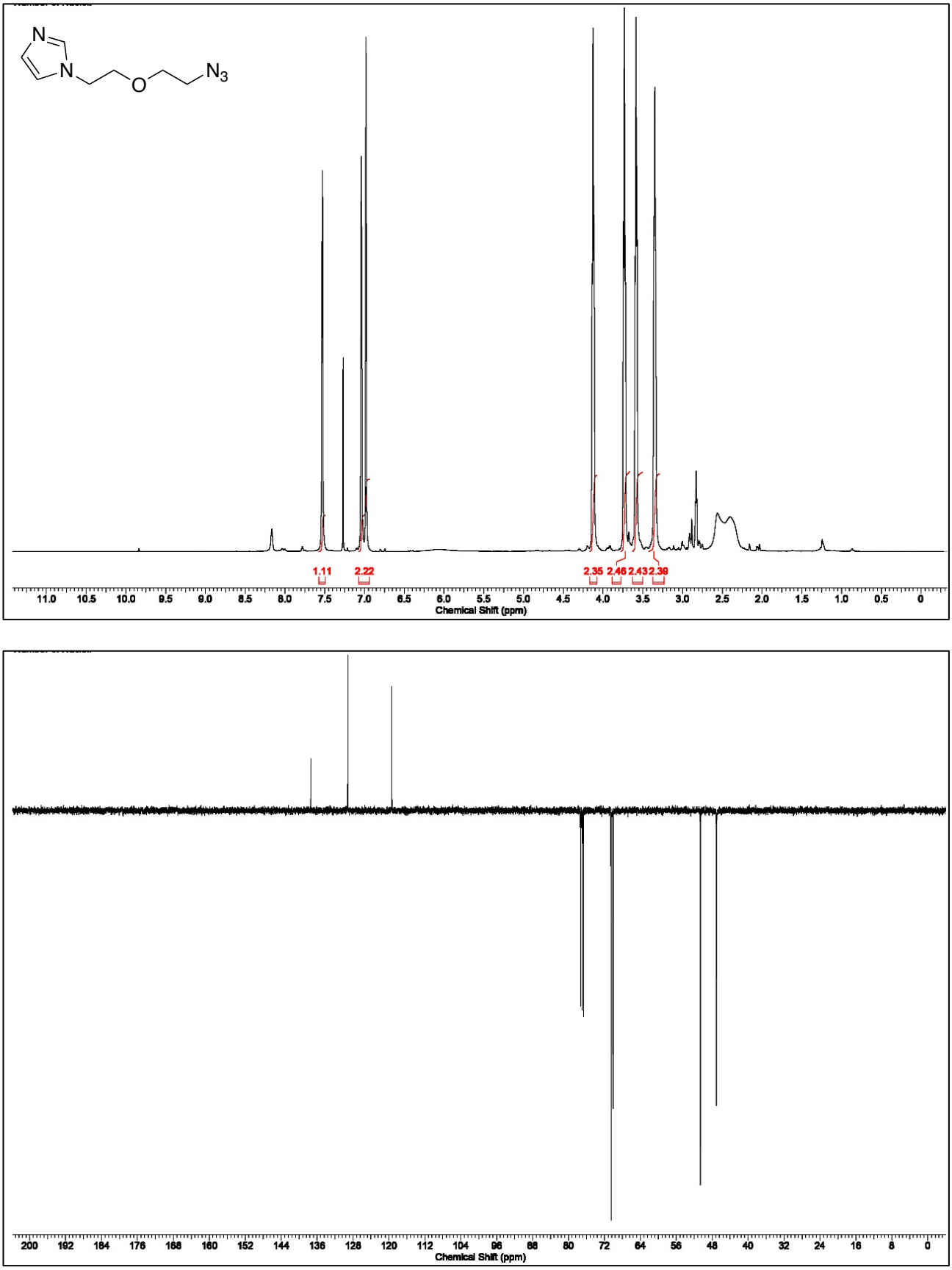

Figure S5. ^{1}H & APT-^{13}C NMR spectra of $\mathbf{9_2}$

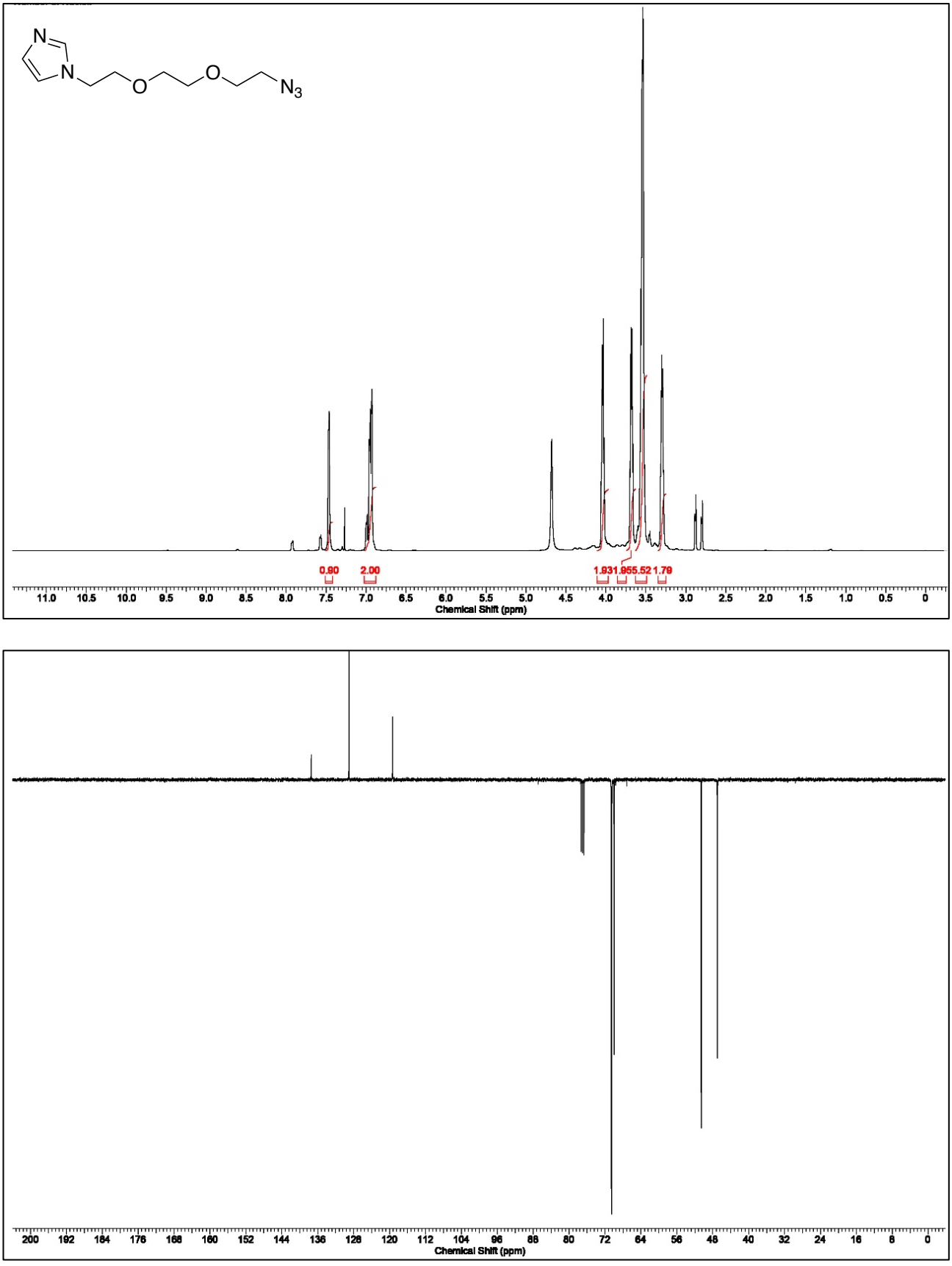

Figure S6. ^{1}H & APT-^{13}C NMR spectra of $\mathbf{9_3}$

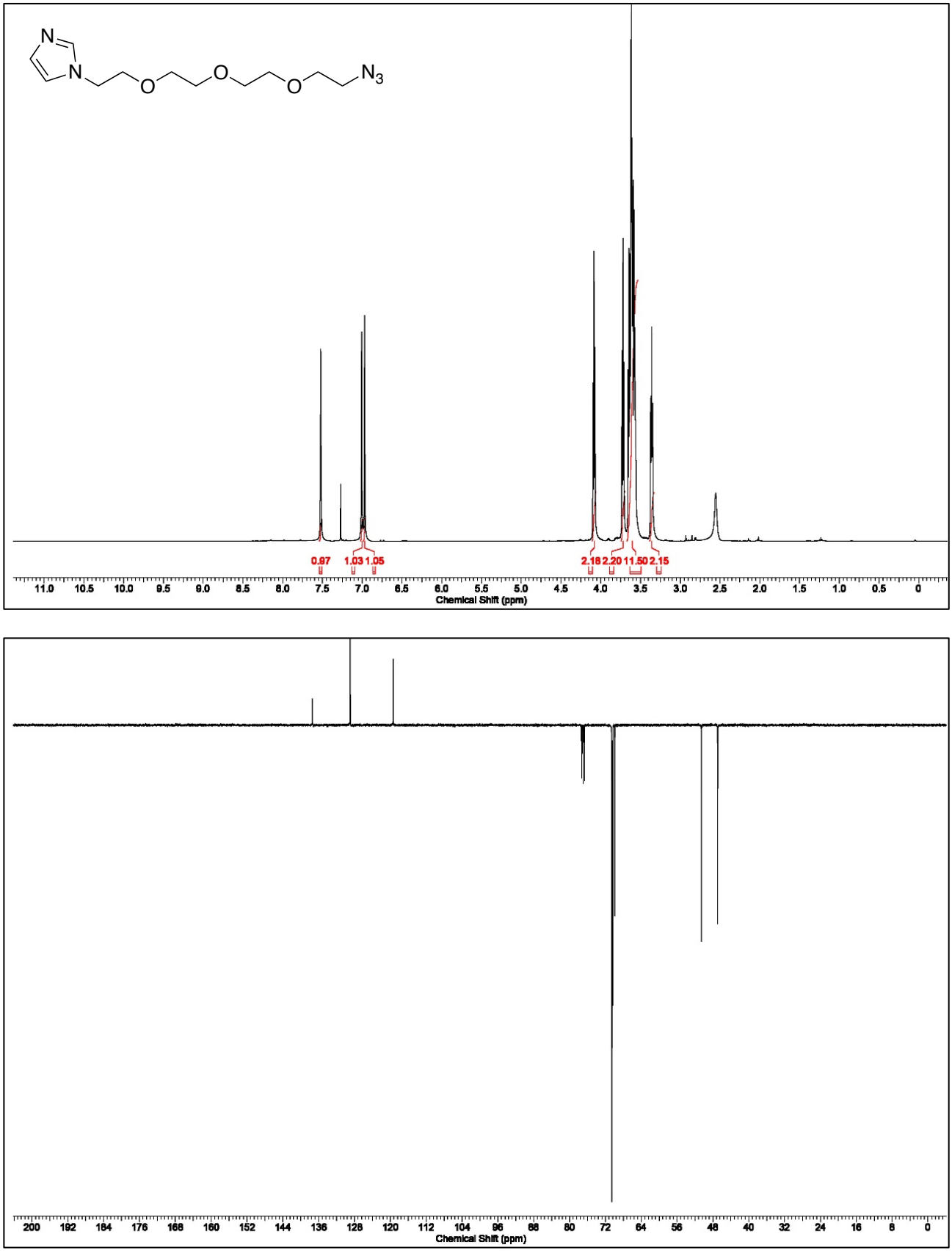

Figure S7. ^{1}H & APT-^{13}C NMR spectra of $\mathbf{9_4}$

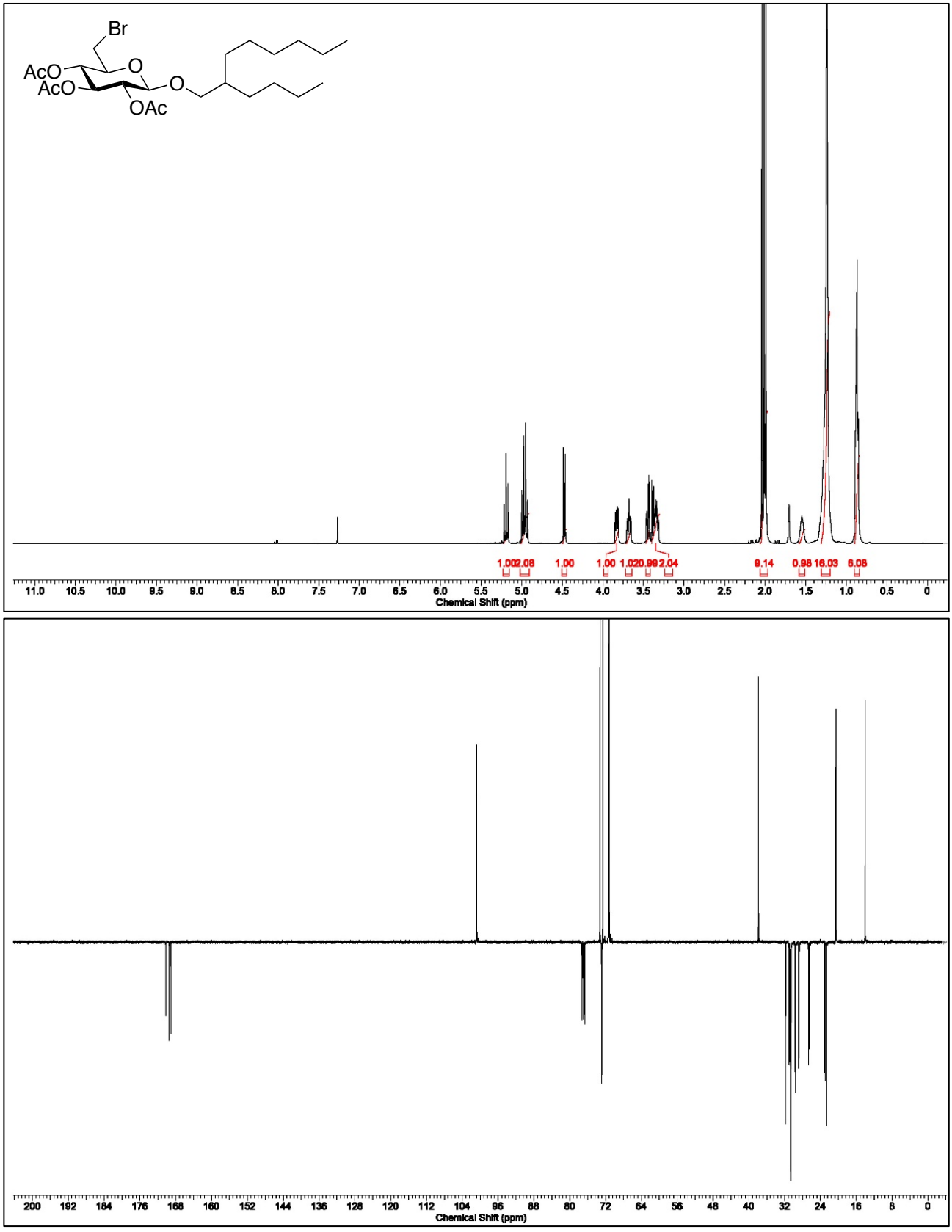

Figure S8. ^{1}H & APT-^{13}C NMR spectra of **5a**

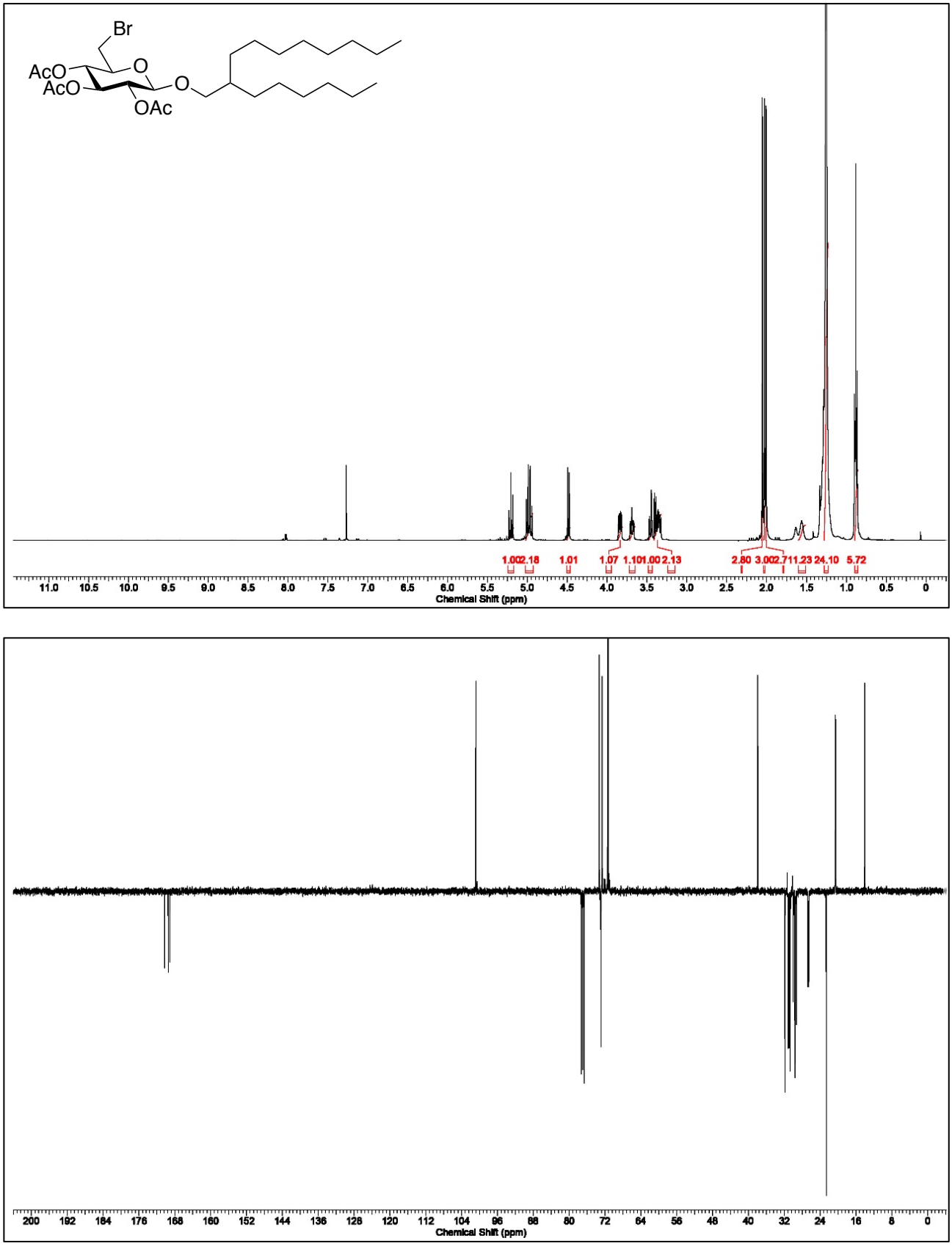

Figure S9. ^{1}H & APT-^{13}C NMR spectra of **5b**

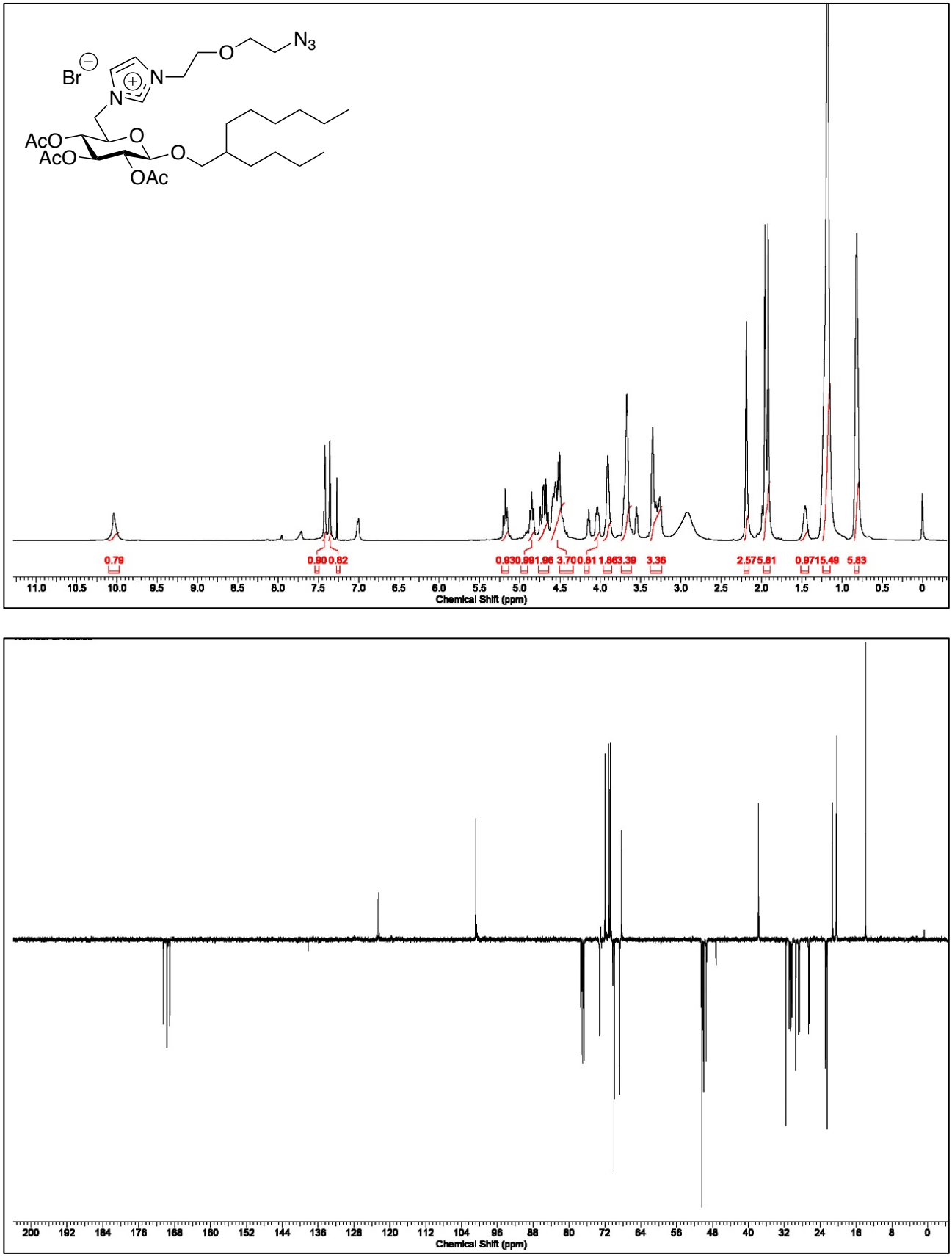

Figure S10. ^{1}H & APT-^{13}C NMR spectra of **10a$_2$**

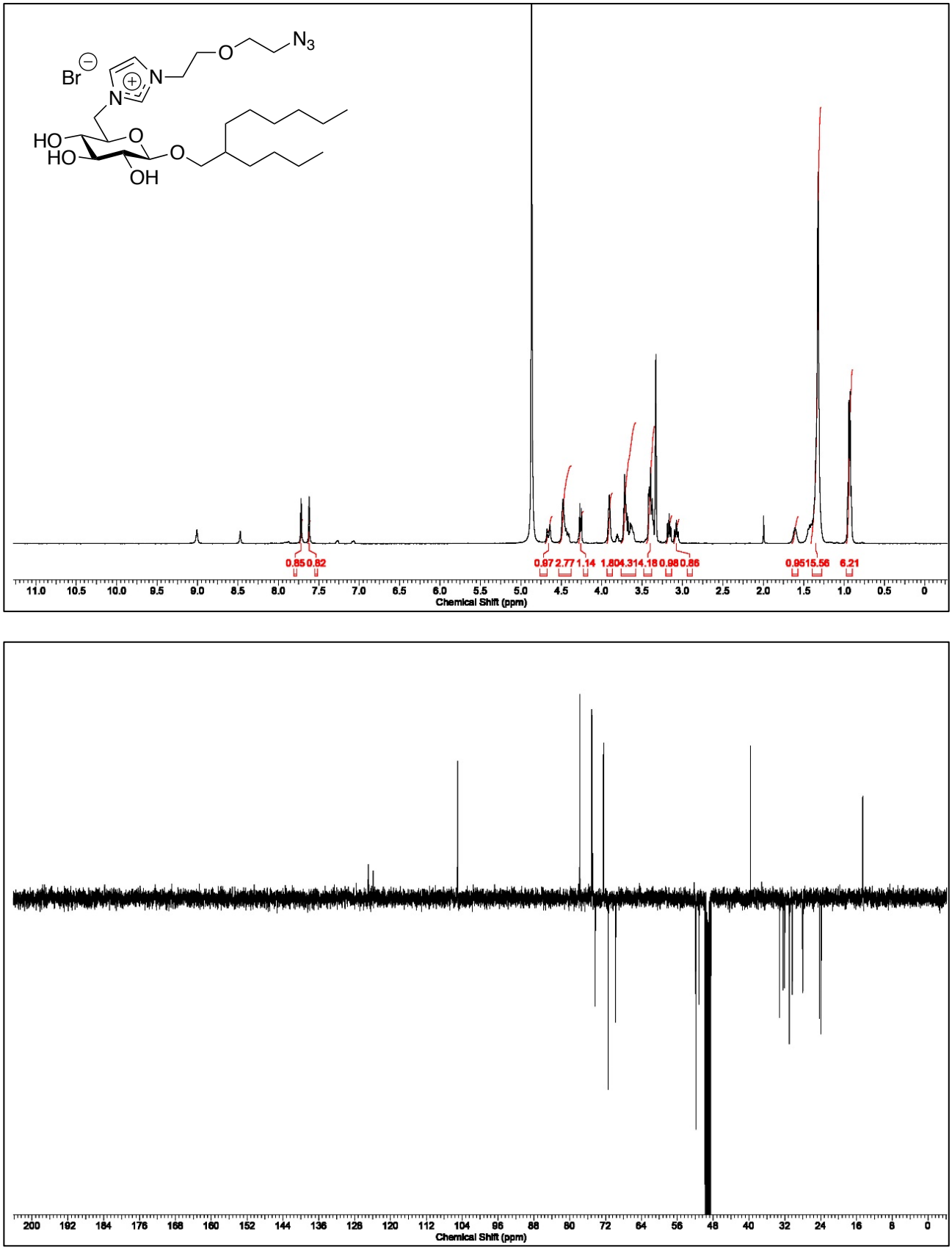

Figure S11. ^{1}H & APT-^{13}C NMR spectra of **11a$_2$**

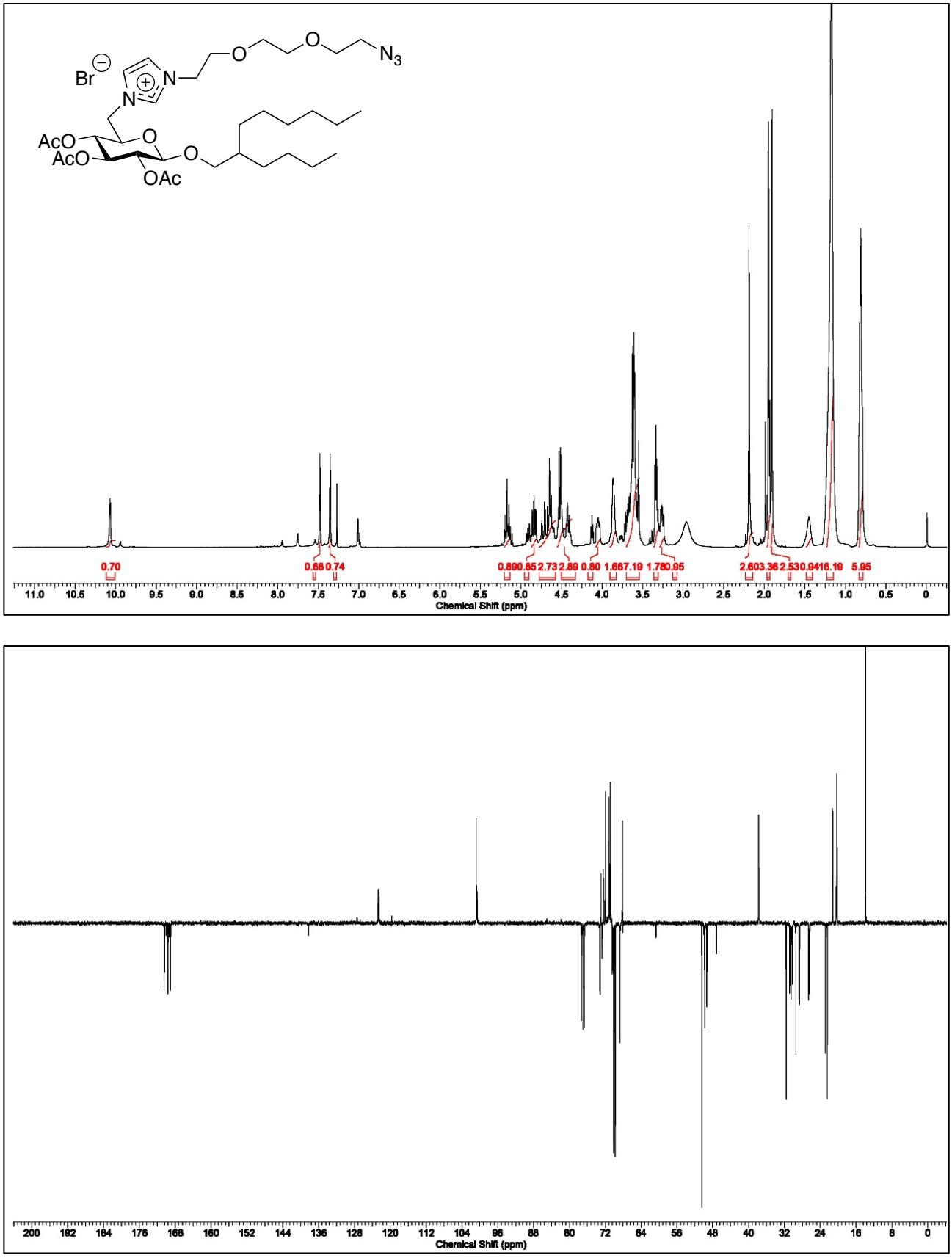

Figure S12. ^{1}H & APT-^{13}C NMR spectra of **10a$_3$**

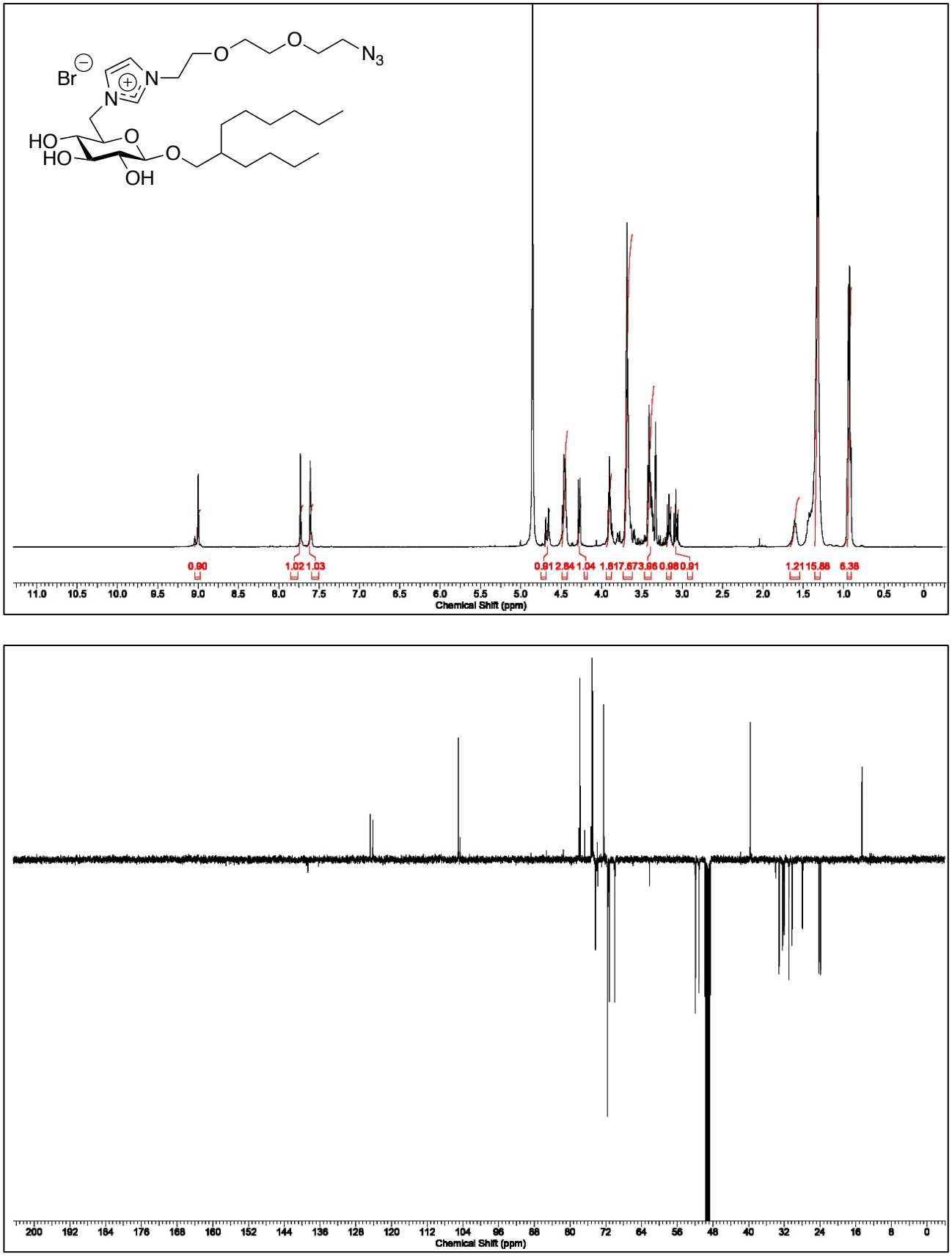

Figure S13. ^{1}H & APT-^{13}C NMR spectra of **11a$_3$**

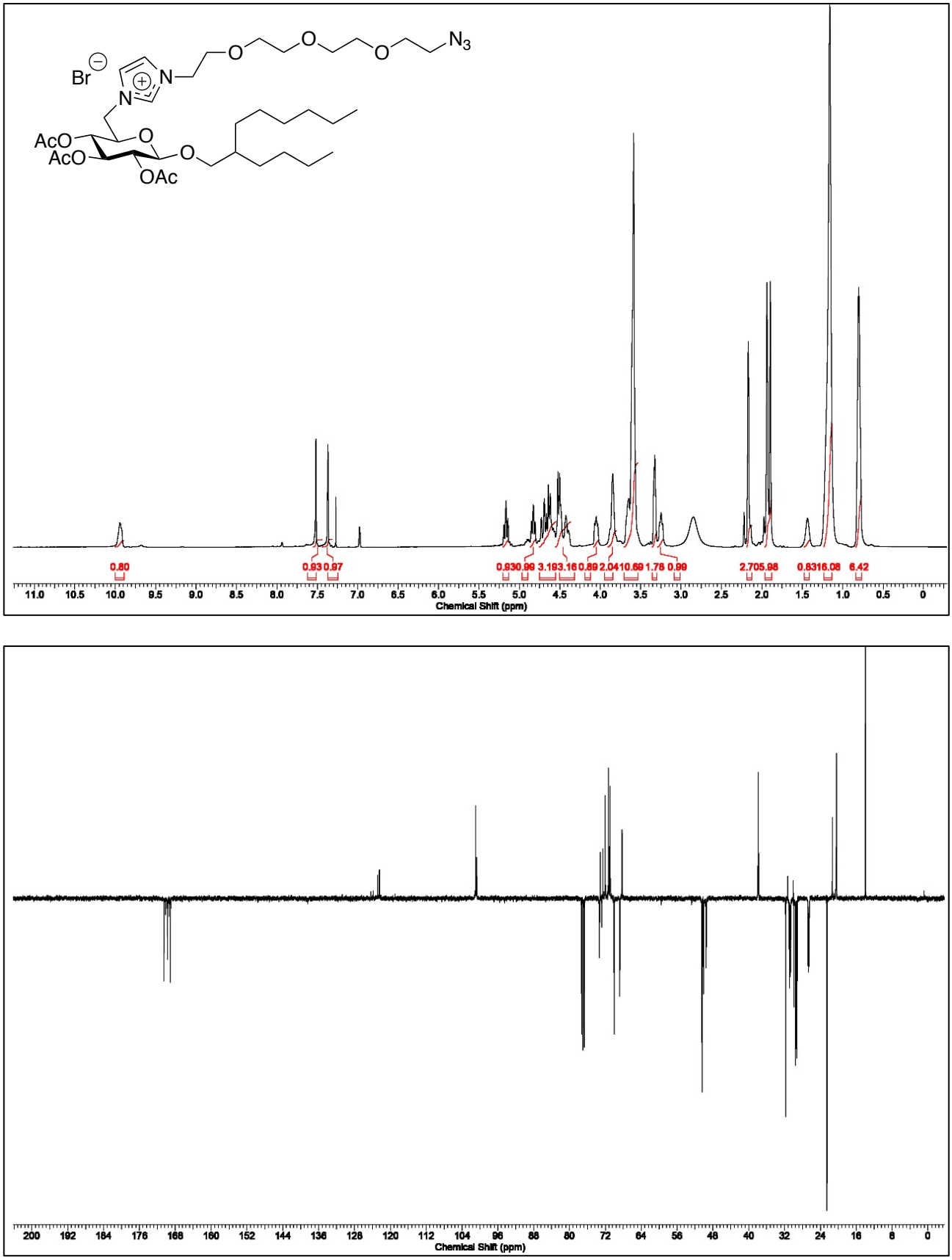

Figure S14. ^{1}H & APT-^{13}C NMR spectra of **10a$_4$**

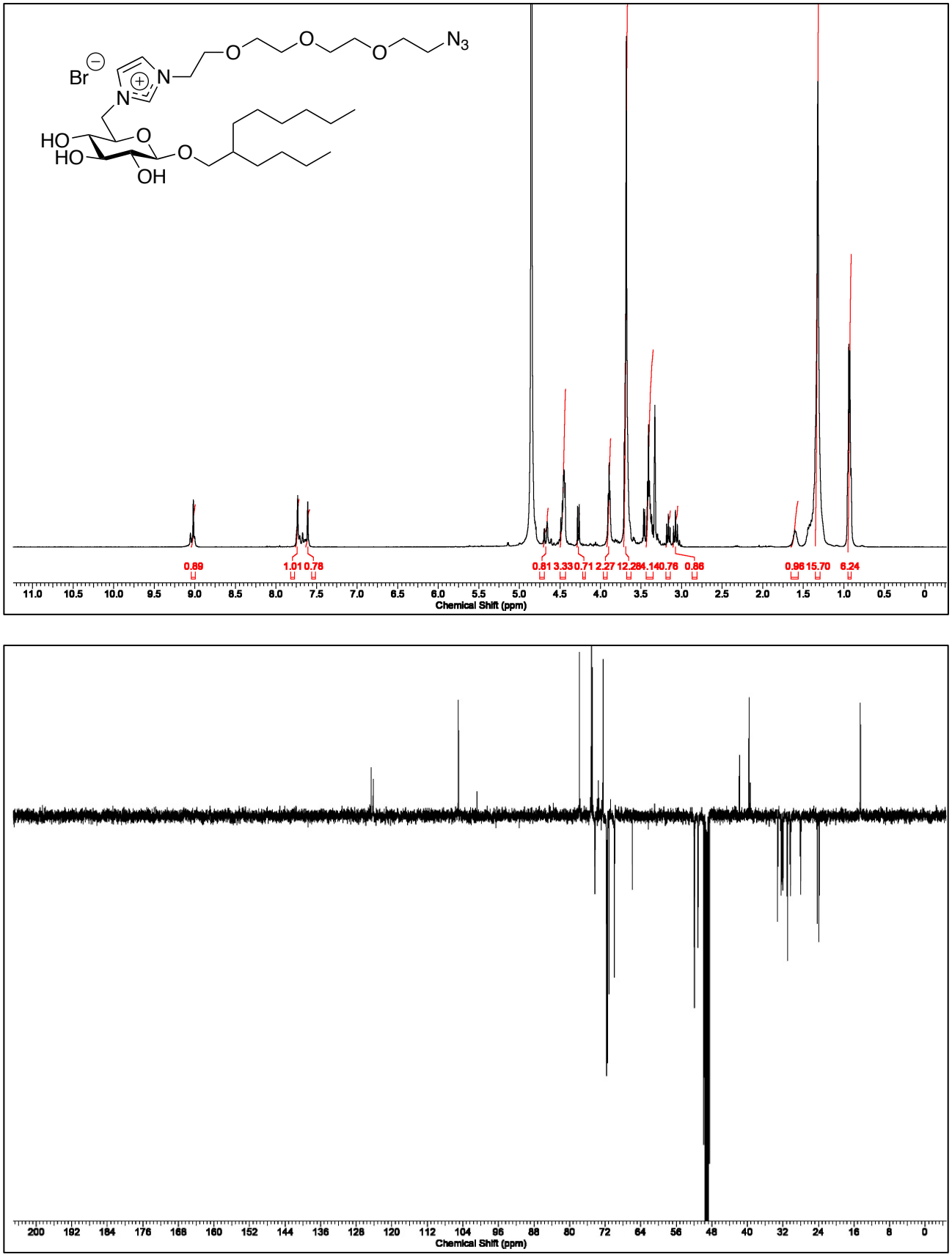

Figure S15. ^{1}H & APT-^{13}C NMR spectra of **11a$_4$**

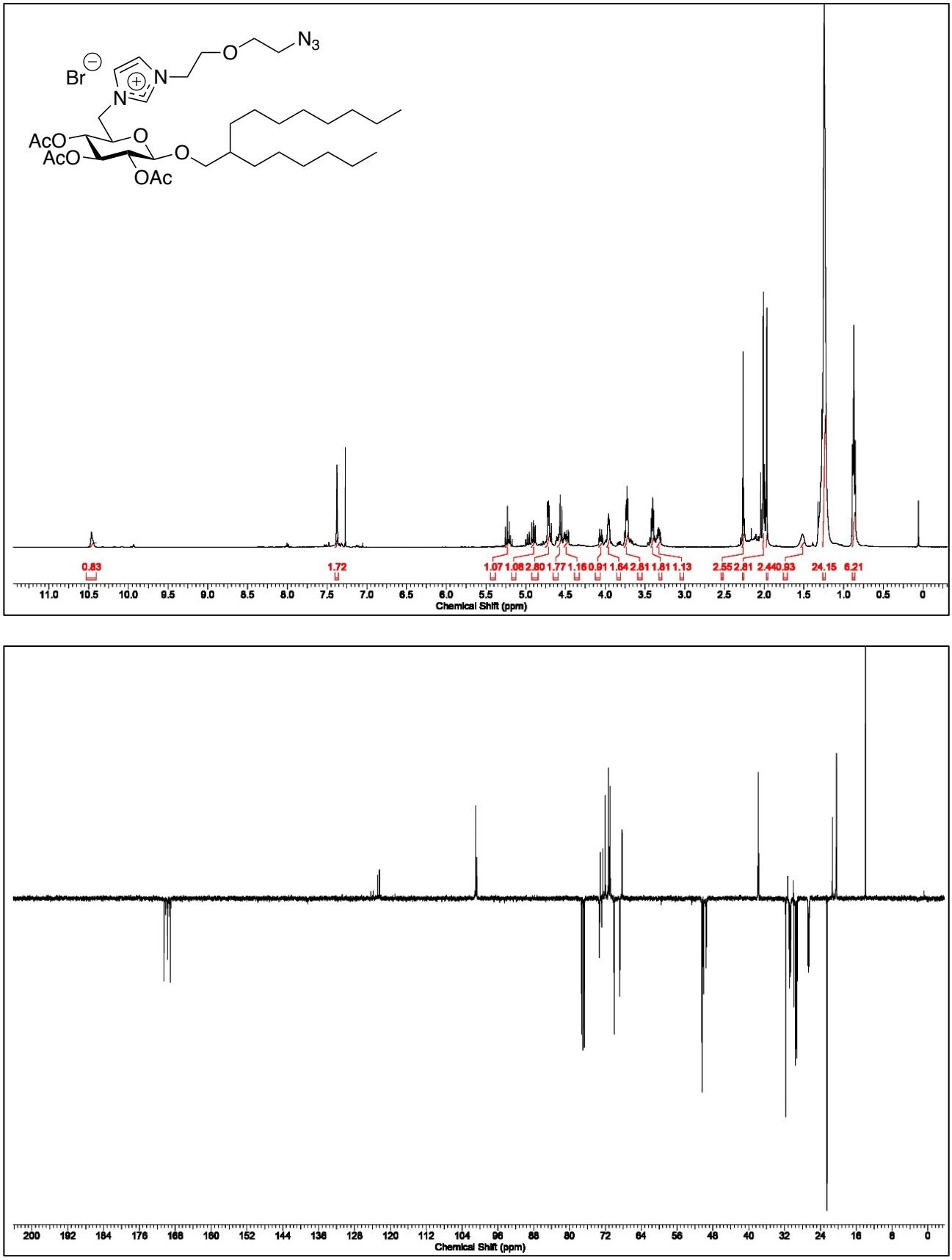

Figure S16. ^{1}H & APT-^{13}C NMR spectra of **10b$_2$**

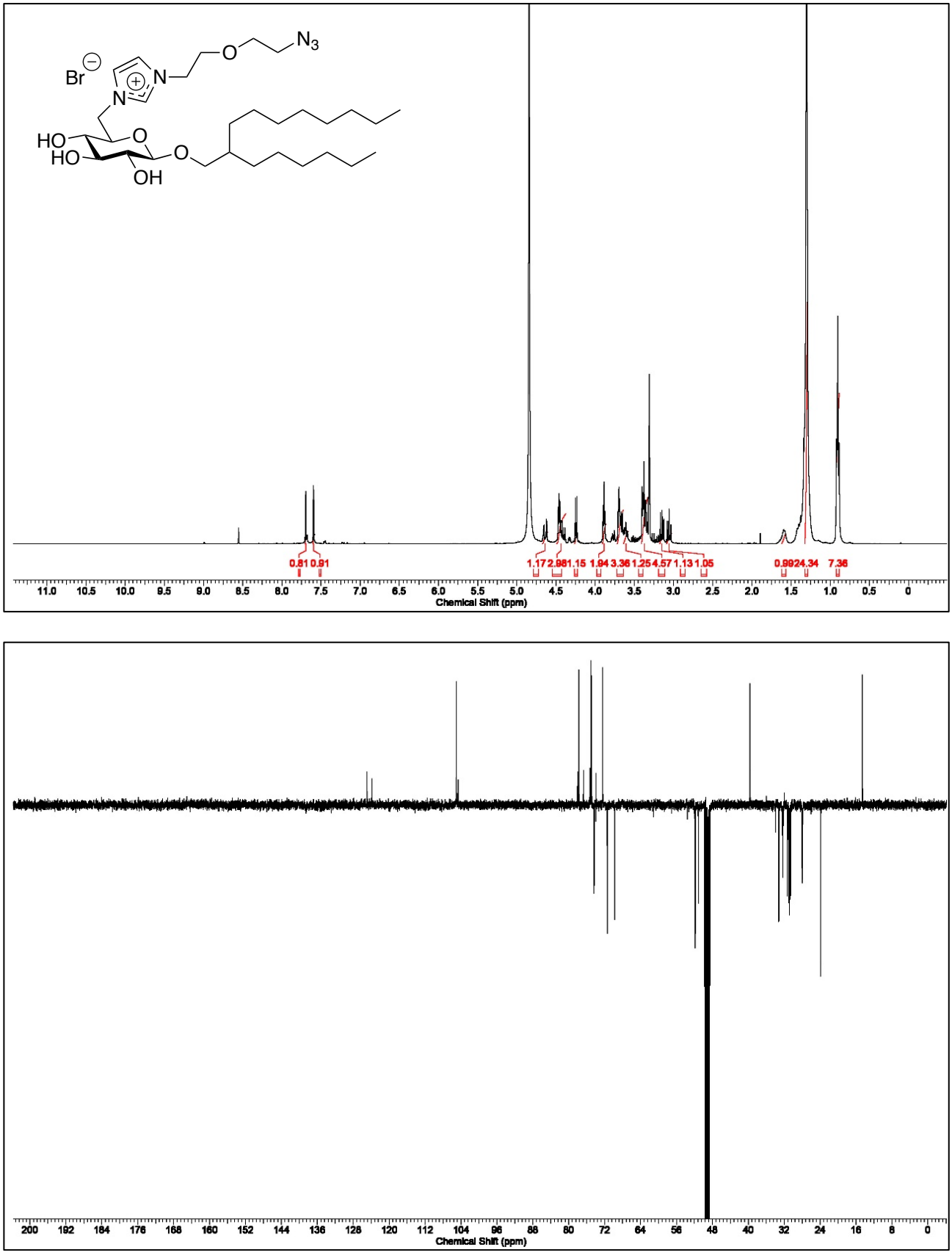

Figure S17. ^{1}H & APT-^{13}C NMR spectra of **11b$_2$**

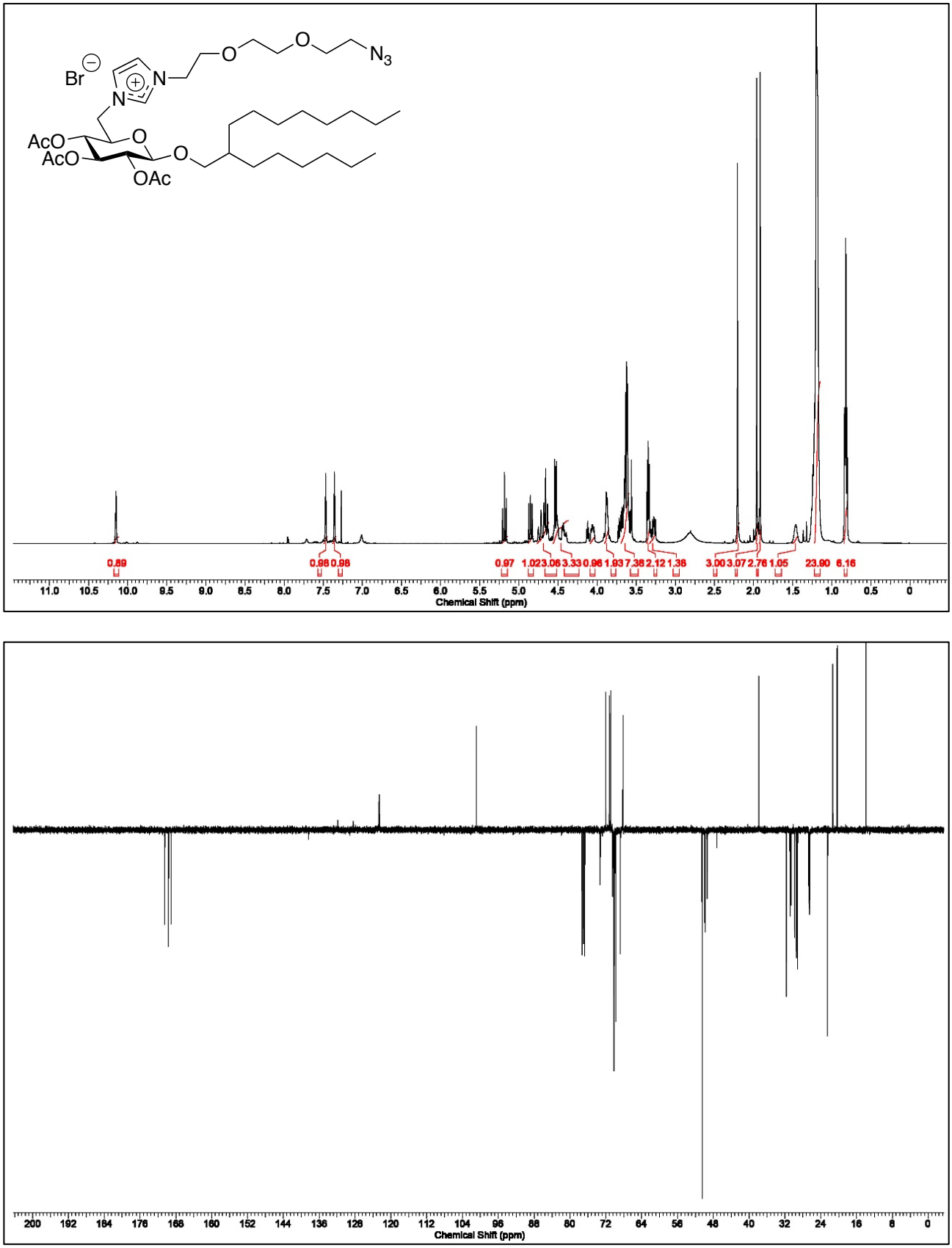

Figure S18. ^{1}H & APT-^{13}C NMR spectra of **10b$_3$**

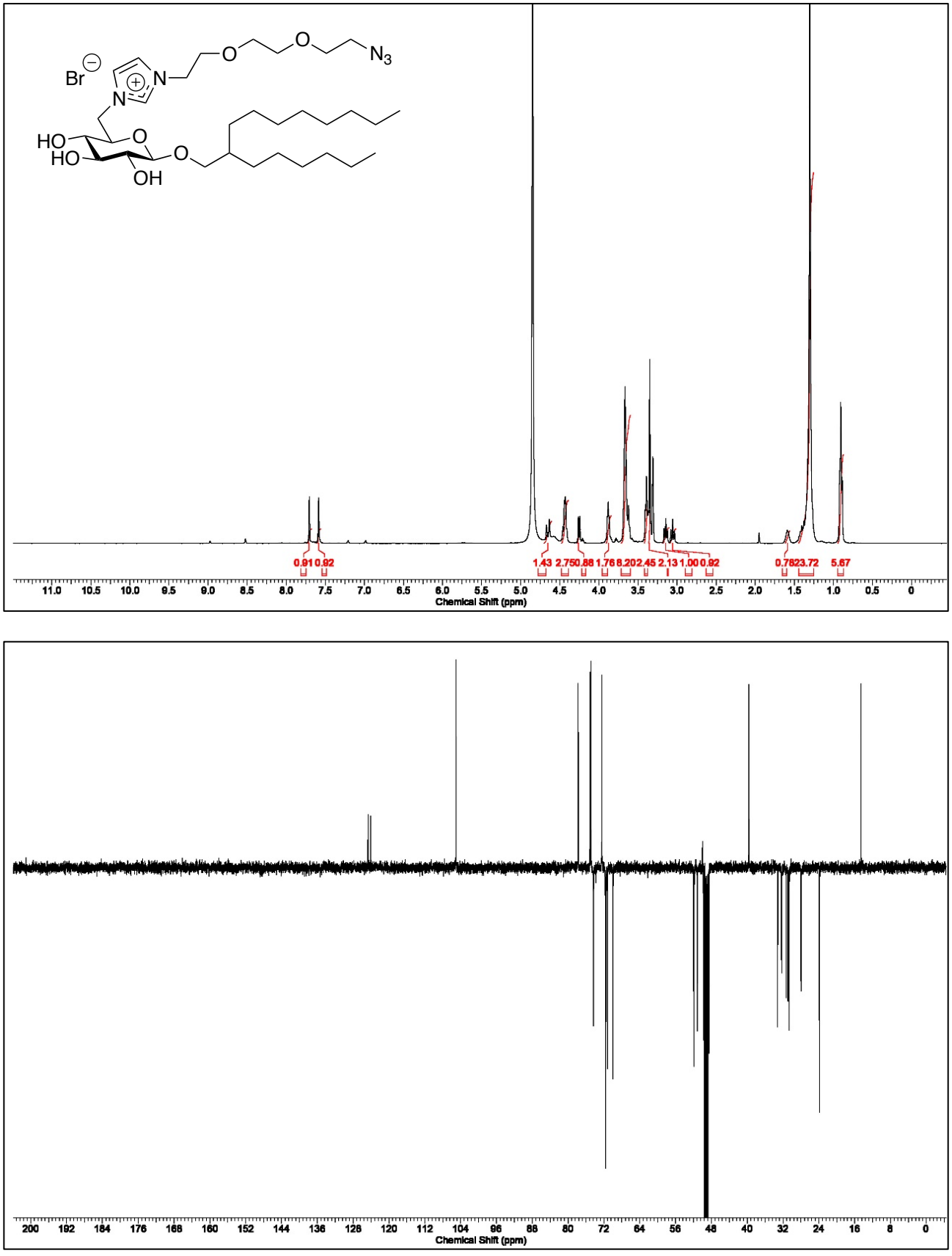

Figure S19. ^{1}H & APT-^{13}C NMR spectra of **11b$_3$**

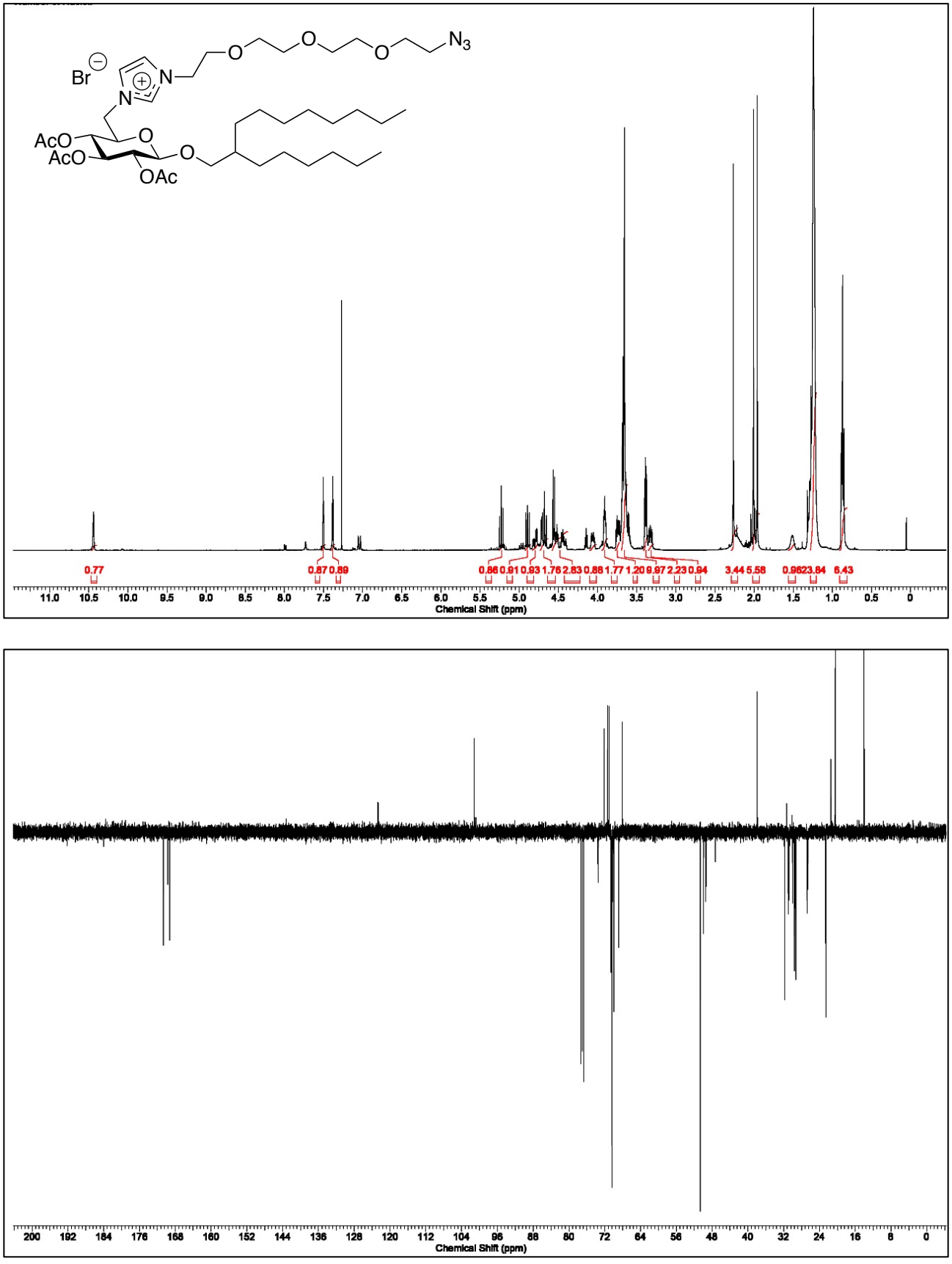

Figure S20. ^{1}H & APT-^{13}C NMR spectra of **10b$_4$**

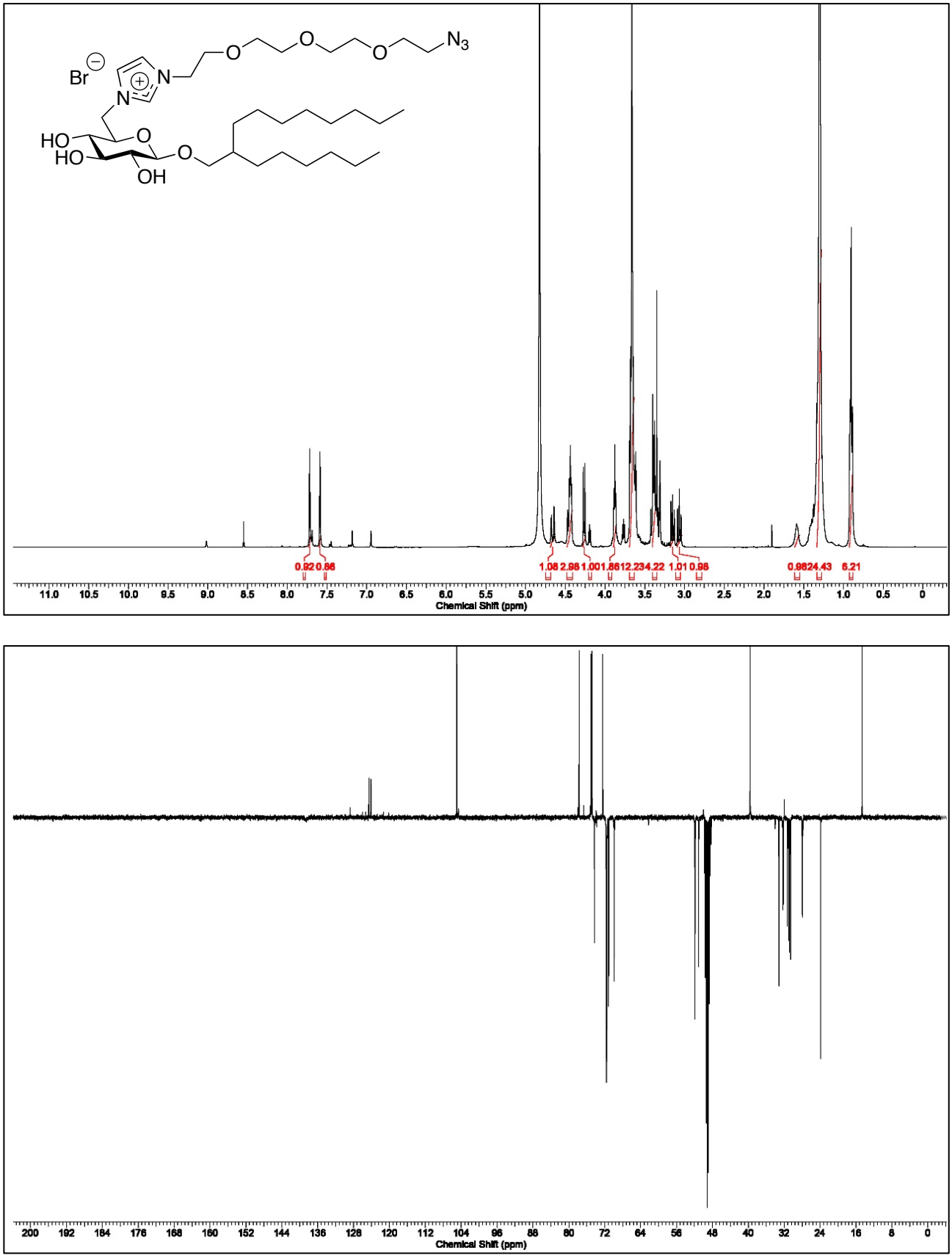

Figure S21. ^{1}H & APT-^{13}C NMR spectra of **11b$_4$**

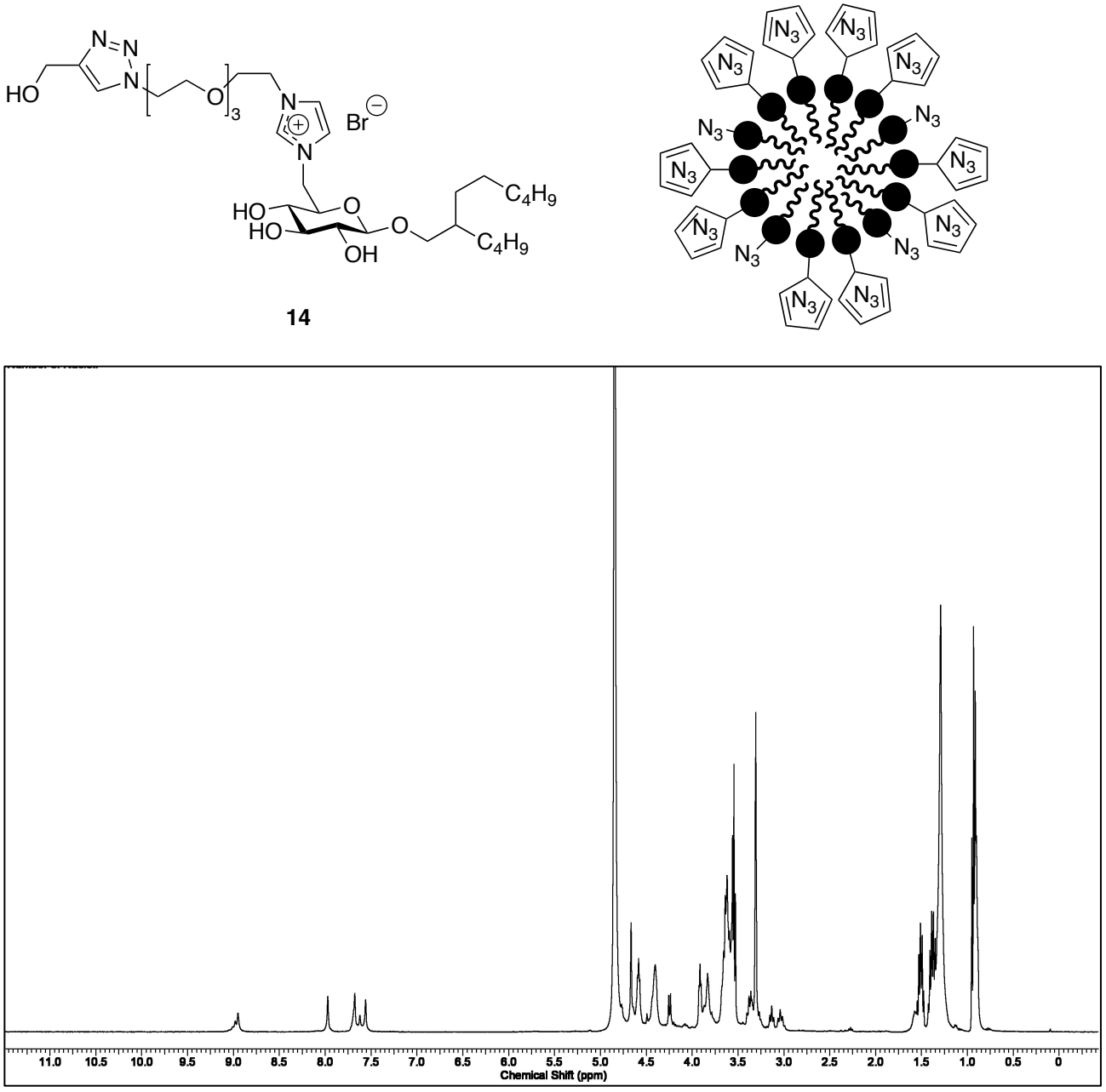

Figure 22. ^{1}H NMR spectra of **14** obtained by CLICK-coupling in micellar phase

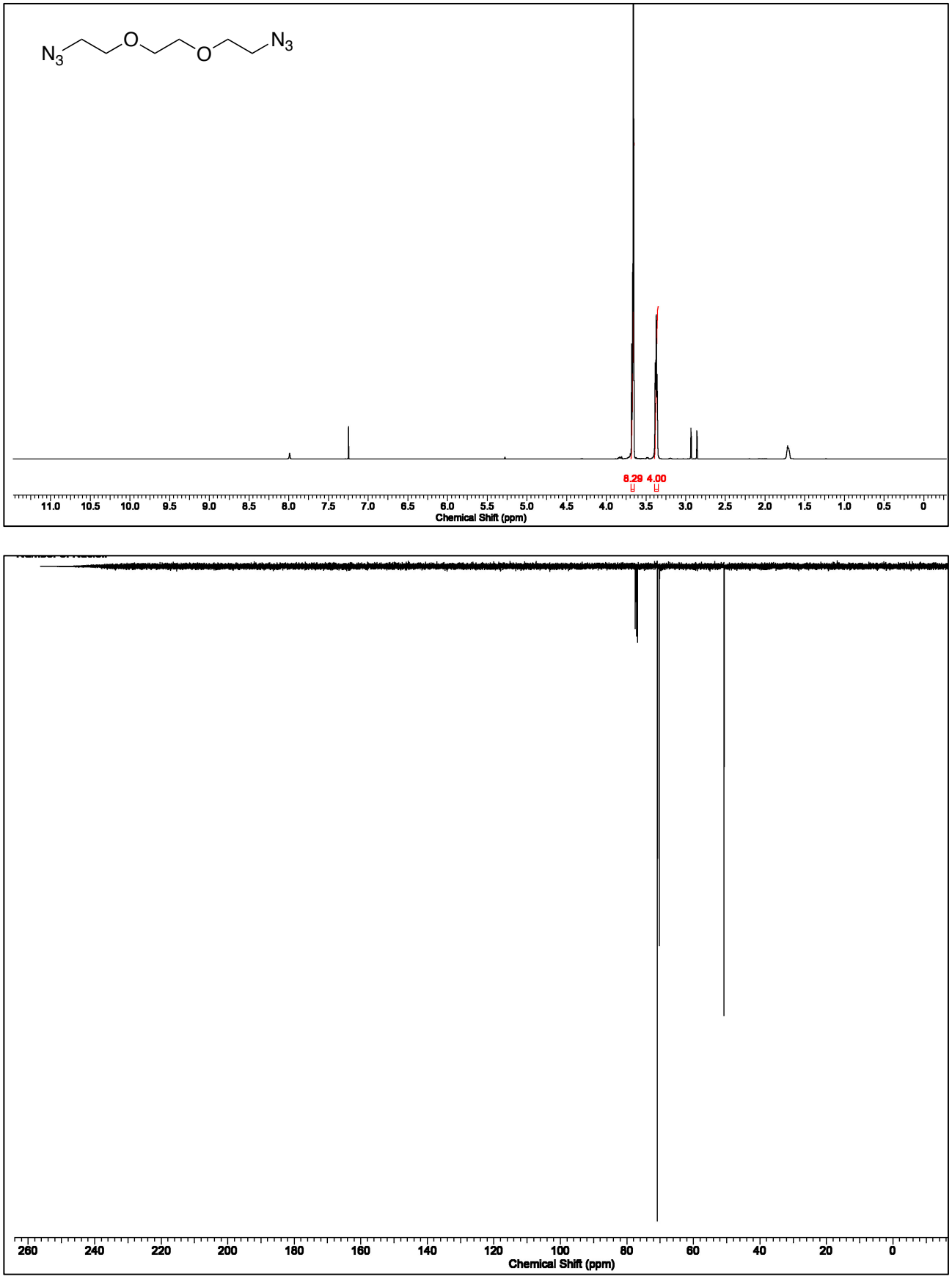

Figure S23. ^{1}H & APT-^{13}C NMR spectra of **15**

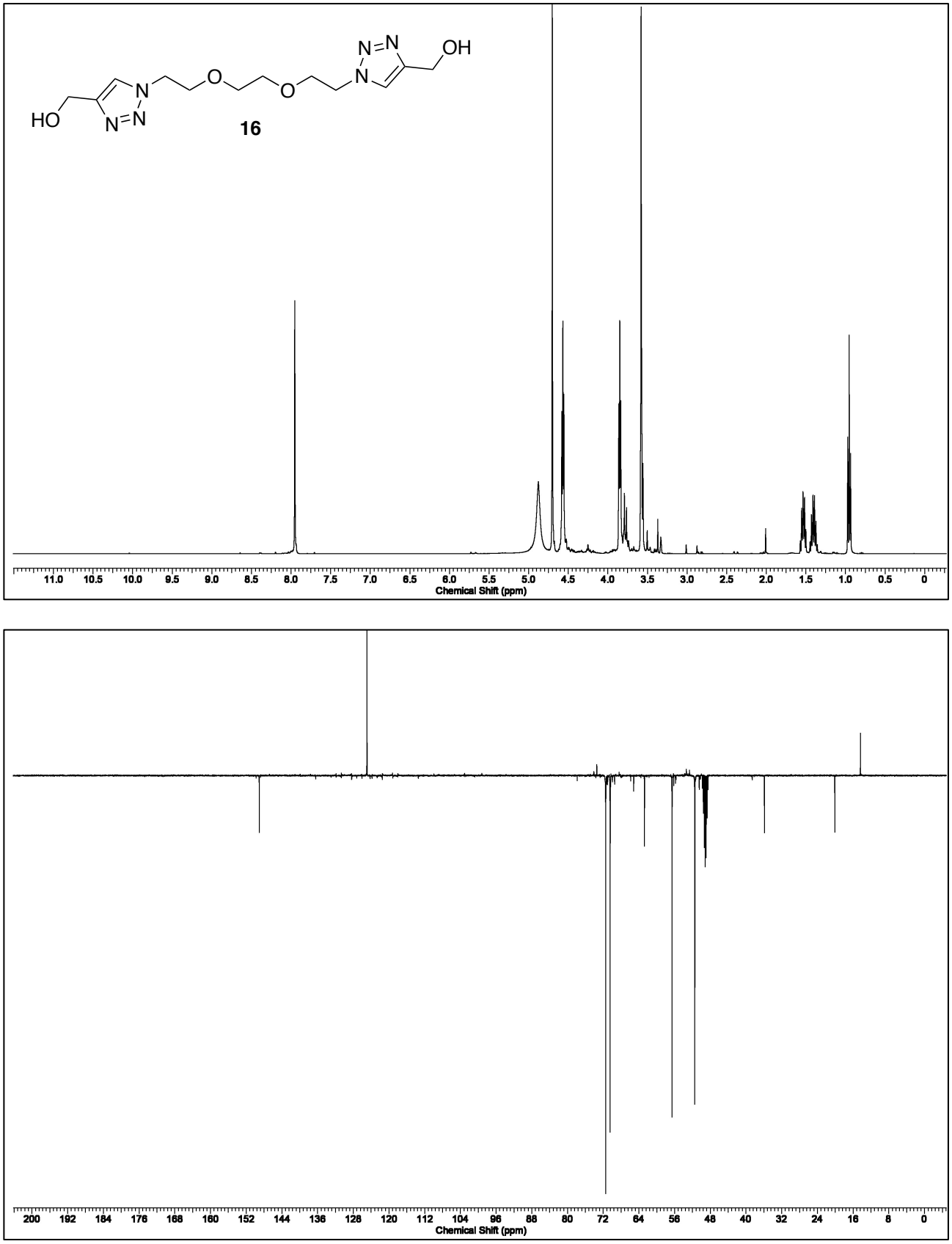

Figure S24. ^{1}H & APT-^{13}C NMR spectra of **16**