Supporting Information

for

Synthesis and solvodynamic diameter measurements of closely related mannodendrimers for the study of multivalent carbohydrate–protein interactions

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Experimental procedures, characterization data, NMR, IR and mass spectra and NMR diffusion experiments

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Experimental procedures and data

All reactions in organic medium were performed in standard oven-dried glassware under an inert atmosphere of nitrogen using freshly distilled solvents. CH₂Cl² was distilled from CaH₂ and DMF from ninhydrin, and kept over molecular sieves. Solvents and reagents were deoxygenated when necessary by purging with nitrogen. Water used for lyophilization of final dendrimers was nanopure grade, purified through Barnstead NANOPure II Filter with Barnstead MegOhm-CM Sybron meter. All reagents were used as supplied without prior purification unless otherwise stated, and obtained from Sigma–Aldrich Chemical Co. Ltd. Reactions were monitored by analytical thin layer chromatography using silica gel 60 F254 precoated plates (E. Merck) and compounds were visualized by 254 nm light, a mixture of iodine/silica gel and/or mixture of ceric ammonium molybdate solution (100 mL H₂SO₄, 900 mL H₂O, 25 g (NH₄)₆Mo₇O₂₄H₂O, 10 g Ce(SO₄)₂) and subsequent development by gentle warming with a heat-gun. Purifications were performed by flash column chromatography using silica gel from Silicycle (60 Å, 40–63 µm) with the indicated eluent.

NMR, IR spectroscopies and MS spectrometry

¹H NMR and ¹³C NMR spectra were recorded at 300 or 600 MHz and 75 or 150 MHz, respectively, on a Bruker spectrometer (300 MHz) and Varian spectrometer (600 MHz). All NMR spectra were measured at 25 °C in indicated deuterated solvents. Proton and carbon chemical shifts (δ) are reported in ppm and coupling constants (J) are reported in Hertz (Hz). The resonance multiplicity in the ¹H NMR spectra are described as “s” (singlet), “d” (doublet), “t” (triplet), and “m” (multiplet) and broad resonances are indicated by “br”. Residual protic solvent of CDCl₃ (¹H, δ 7.27 ppm; ¹³C, δ 77.0 ppm (central resonance of the triplet)), D₂O (¹H, δ 4.79 ppm and 30.89 ppm for CH₃ of acetone for ¹³C spectra of de-O-acetylated compounds), MeOD (¹H, δ 3.31 ppm and ¹³C, δ 49.0 ppm. 2D Homonuclear correlation ¹H-¹H COSY together with 2D heteronuclear correlation ¹H-¹³C HSQC experiments were used to confirm NMR peak assignments. Fourier transform infrared (FTIR) spectra were obtained with Thermo-scientific, Nicolet model 6700 equipped with ATR. The absorptions are given in wavenumbers (cm⁻¹). The intensity of the bands is described as s (strong), m (medium) or w (weak). Melting points were measured on an Electrothermal MEL-TEMP apparatus and are uncorrected.

Accurate mass measurements (HRMS) were performed on a LC–MSD-ToF instrument from Agilent Technologies in positive electrospray (ES) mode. Low-resolution mass spectra were performed on the same apparatus or on a LCQ Advantage ion trap instrument from Thermo Fisher Scientific in positive electrospray mode (Mass Spectrometry Laboratory (Université de Montréal), or Plateforme analytique pour molécules organiques (Université du Québec à Montréal), Québec, Canada). Either protonated molecular ions [M + H]⁺ or adducts [M + nX]⁺ (X = Na, K, NH₄) were used for empirical formula confirmation.
General procedures

**Procedure A:** multiple CuAAC couplings on polypropargylated cores

To a solution of polypropargylated core (1.00 equiv) and complementary azido synthon (1.25 equiv/propargyl) in a THF/H$_2$O mixture (1:1) were added sodium ascorbate (0.30 equiv/propargyl) and CuSO$_4$·5H$_2$O (0.30 equiv/propargyl). The reaction mixture was stirred at 50 °C for 3 h then at room temperature for an additional 16 h period. EtOAc (10 mL) was added and the resulting solution was poured in a separatory funnel containing 25 mL of EtOAc and 30 mL of a saturated aqueous solution of NH$_4$Cl. Organics were washed with (2 × 25 mL) of saturated NH$_4$Cl aq, water (2 × 20 mL) and brine (10 mL). The organic phase was then dried over MgSO$_4$ and concentrated under reduced pressure. Column chromatography on silica (DCM/MeOH 100:0 to 90:10) afforded the desired glycocluster.

**Procedure B:** Zemplén de-O-acetylation procedure for insoluble derivatives

The acetylated compound was dissolved in anhydrous MeOH and a solution of sodium methoxide (1 M in MeOH, 5 µL every 20 minutes until precipitation) was added. An additional 100 µL was then injected and the heterogeneous reaction mixture was stirred at room temperature for 24 h. The solvent was then removed with a Pasteur pipette and a mixture of anhydrous MeOH/DCM (4:1, 5 mL) was added to the residual white foam. A vigorous agitation was maintained for an additional 15 min period. After removal of the solvents with a Pasteur pipette, the residue was dissolved in H$_2$O (3 mL), and the pH was adjusted to 6–7 with addition of ion-exchange resin (Amberlite IR 120 H$^+$). After filtration, the solvent was removed under vacuum with rotary evaporator, lyophilized to yield the fully deprotected glycocluster.

**Synthesis of peracetylated trivalent derivative (4):** Derivative 4 was synthesized according to Procedure A with tripropargylated core 2 (15.4 mg, 47.9 µmol, 1.00 equiv), mannoside 3 (75.0 mg, 180 µmol, 3.75 equiv), sodium ascorbate (8.5 mg, 43 µmol, 0.90 equiv) and CuSO$_4$·5H$_2$O (10.8 mg, 43.1 µmol, 0.90 equiv) in a THF/H$_2$O mixture (4 mL, 1:1). Column chromatography on silica (DCM/MeOH 98:2 to 94:6) afforded the desired compound 4 (42.0 mg, 26.8 µmol, 56%) as a white solid. $R_f$ = 0.16 (94:6 DCM/MeOH); m.p. = 103-106°C (not corrected). $^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) 8.21 (m, 6H, CH$_{ar}$ + NH), 7.74 (s, 3H, CH$_{triazole}$), 5.23–5.17 (m, 9H, H$_2$, H$_3$, H$_4$), 4.81 (s, 3H, H$_1$), 4.67–4.60 (m, 12H, HNC$_{H_2}$C$_{triazole}$ + N$_{triazole}$CH$_2$), 4.21–3.89 (m, 12H, OCH$_2$ + H$_6$), 3.62–3.60 (m, 3H, H$_5$), 2.11, 2.08, 2.01, 1.96 (4s, 36H, COC$_{H_3}$). $^{13}$C($^1$H) NMR (75 MHz, CDCl$_3$) δ (ppm) 170.7, 170.1, 170.0, 169.7 (COCH$_3$), 165.9 (CONH), 145.0 (C$_{triazole}$), 134.6 (C$_{arom}$), 128.5 (CH$_{arom}$), 123.4 (CH$_{triazole}$), 97.3 (C$_1$), 69.2 (C$_2$), 68.9 (C$_3$), 68.8 (C$_5$), 66.1 (C$_6$), 65.7 (C$_4$), 62.2 (OCH$_2$), 49.7 (CH$_2$N$_{triazole}$), 35.5 (HNCH$_2$C$_{triazole}$), 20.8, 20.7, 20.6, 20.6 (COCH$_3$). HRMS ("TOF-HRMS") m/z: calculated for C$_{66}$H$_{84}$N$_{12}$O$_{33}$ [M+H]$^+$: 1573.5337, found: 1573.5327 ($\Delta = -0.88$ ppm); [M+Na]$^+$: 1595.5156, found: 1595.5151 ($\Delta = -0.29$ ppm).
Synthesis of trivalent derivative (5): A solution of sodium methoxide (1 M in MeOH, 50 μL) was added to a solution of acetylated precursor 4 (30.0 mg, 19.1 μmol) in MeOH (2.5 mL). The reaction mixture was stirred at room temperature for 24 h. The pH was adjusted to 6–7 with addition of ion-exchange resin (Amberlite IR 120 H⁺). After filtration, the solvent was removed under vacuum with rotary evaporator and the residue was lyophilized to furnish desired de-O-acetylated compound 5 (19.0 mg, 17.9 μmol, 94%) as a white solid.

$^1$H NMR (300 MHz, D$_2$O) δ (ppm) 8.27 (s, 3H, $CH_ {ar}$), 8.01 (s, 3H, $CH_{triazole}$), 4.74 (m, 3H, $H_1$), 4.63–4.59 (m, 12H, HNCH$_2$C$_{triazole}$+ N$_{triazole}$CH$_2$), 4.05–4.01 (m, 3H, CHHCH$_2$N), 3.88–3.79 (m, 6H, 6H, CHHCH$_2$N + $H_2$), 3.63–3.47 (m, 12H, $H_6$ + $H_4$ + $H_3$), 2.90–2.86 (m, 3H, $H_6$). $^{13}$C[$^1$H] NMR (75 MHz, D$_2$O) δ (ppm) 168.4 (CONH), 144.6 ($C_{triazole}$), 134.5 ($C_{arom}$), 129.3 ($CH_{arom}$), 124.7 ($CH_{triazole}$), 99.5 ($C_1$), 72.8 ($C_3$), 70.5 ($C_3$), 69.9 ($C_2$), 66.4 ($C_4$), 65.5 (OCH$_2$), 60.7 ($C_6$), 50.1 (CH$_2$N$_{triazole}$), 35.1 (HNCH$_2$C$_{triazole}$). HRMS (“TOF-HRMS”) m/z: calculated for C$_{42}$H$_{66}$N$_{12}$O$_{21}$ [M+Na]$^+$: 1091.3888, found: 1091.3888 ($\Delta = -0.11$ ppm).

Synthesis of peracetylated trivalent derivative (8): To a solution of triazido core 6 (50.0 mg, 109 μmol, 1.00 equiv) and mannoside 7 (158 mg, 409 μmol, 3.75 equiv) in a THF/H$_2$O mixture (6 mL, 1:1) were added sodium ascorbate (19.4 mg, 98.1 μmol, 0.90 equiv) and CuSO$_4$·5H$_2$O (24.5 mg, 98.1 μmol, 0.90 equiv). The reaction mixture was stirred at 50 °C for 3 h then at room temperature for an additional 16 h period. EtOAc (10 mL) was added and the resulting solution was poured in a separatory funnel containing 35 mL of EtOAc and 30 mL of a saturated aqueous solution of NH$_4$Cl. Organics were washed with (2 × 25 mL) of saturated NH$_4$Cl$_{aq}$, water (2 × 20 mL) and brine (10 mL). The organic phase was then dried over MgSO$_4$ and concentrated under reduced pressure. Column chromatography on silica (DCM/MeOH 98:2 to 94:6) afforded the desired compound 8 (138 mg, 86.0 μmol, 79%) as a viscous oil.

R$_f$ = 0.34 (95:5 DCM/MeOH). $^1$H NMR (600 MHz, CDC$_3$) δ (ppm) 8.27 (s, 3H, $CH_ {ar}$), 7.79 (s, 3H, $CH_{triazole}$), 7.72 (t, $J = 5.3$ Hz, 3H, $NH$), 5.29–5.19 (m, 9H, $H_2$, $H_3$, $H_4$), 4.92 ($s_{app}$, 3H, $H_1$), 4.77–4.62 (2×d, $J =$ 12.4 Hz, 6H, OCH$_2$), 4.54 (t, $J = 6.4$ Hz, 6H, N$_{triazole}$CH$_2$), 4.28 (dd, $J =$ 12.4 Hz, $J =$ 5.4 Hz, 3H, $H_6$), 4.11–4.03 (m, 6H, $H_5$ + $H_6a$), 3.55 (m, 6H, NHCH$_2$), 2.28 (m, 6H, CH$_2$CH$_2$CH$_2$), 2.12, 2.10, 2.02, 1.96 (4s, 36H, COCH$_3$). $^{13}$C[$^1$H] NMR (150 MHz, CDC$_3$) δ (ppm) 170.8, 170.1, 170.0, 169.7 (COCH$_3$), 166.1 (CONH), 143.5 ($C_{triazole}$), 134.9 ($C_{arom}$), 128.5 ($CH_{arom}$), 123.9 ($CH_{triazole}$), 96.7 ($C_1$), 69.3 ($C_2$), 69.0 ($C_3$), 68.7 ($C_3$), 65.9 ($C_6$), 62.3 ($C_4$), 60.7 (OCH$_2$), 48.3 ($CH_2N_{triazole}$), 37.5 (NHCH$_2$), 29.9 (CH$_2$CH$_2$CH$_2$), 20.9, 20.8, 20.7, 20.7 (COCH$_3$). MS (“TOF-MS”) m/z: calculated for C$_{69}$H$_{90}$N$_{12}$O$_{33}$ [M+H]$^+$: 1615.6, found: 1615.6.
Synthesis of trivalent derivative (9): Derivative 9 was synthesized according to Procedure B with compound 8 (120.0 mg, 74.3 μmol) previously dissolved in anhydrous MeOH (4 mL). Deprotected hexamer 9 was obtained as a white solid (78.0 mg, 70.6 μmol) in a 95% yield.

\(^1\)H NMR (300 MHz, D\(_2\)O) δ (ppm) 8.03 (s, 3H, CH\(_{ar}\)), 8.00 (s, 3H, CH\(_{triazole}\)), 4.85 (m, 3H, H1), 4.68–4.49 (m, 12H, OCH\(_2\)C\(_{triazole}\)+ N\(_{triazole}\)CH\(_2\)), 3.80–3.55 (m, 18H, H2 + H6 + H4 + H3 + H5), 3.40 (m, 6H, OCNHCH\(_2\)), 2.24 (m, 6H, CH\(_2\)CH\(_2\)CH\(_2\)), \(^{13}\)C\[^{1}\]H NMR (75 MHz, CDCl\(_3\)) δ (ppm) 168.6 (CONH), 144.2 (C\(_{triazole}\)), 135.0 (C\(_{arom}\)), 129.3 (C\(_{arom}\)), 125.8 (CH\(_{triazole}\)), 100.0 (C1), 73.6 (C3), 71.1 (C3), 70.6 (C2), 67.3 (C4), 61.5 (C6), 60.7 (OCH2), 49.1 (CH\(_2\)N\(_{triazole}\)), 38.1 (OCHNCH\(_2\)), 29.3 (CH\(_2\)CH\(_2\)CH\(_2\)). HRMS ("TOF-HRMS") m/z: calculated for C\(_{45}\)H\(_{64}\)N\(_{13}\)O\(_{21}\) [M+H]\(^+\): 1111.4538, found: 1111.4533 (Δ = −0.52 ppm); [M+Na]\(^+\): 1133.4358, found: 1133.4347 (Δ = −0.93 ppm).

Synthesis of peracetylated nonavalent derivative (11): Derivative 11 was synthesized according to Procedure A with nonapropargylated core 10 (20.0 mg, 23.2 μmol, 1.00 equiv), mannoside 3 (108.9 mg, 261.0 μmol, 11.25 equiv), sodium ascorbate (12.4 mg, 62.7 μmol, 2.70 equiv), and CuSO\(_4\)·5H\(_2\)O (15.7 mg, 62.7 μmol, 2.70 equiv) in a THF/H\(_2\)O mixture (3 mL, 1:1). Column chromatography on silica (DCM/MeOH 98:2 to 94:6) afforded the desired compound 11 (88.0 mg, 19.1 μmol, 83%) as a colorless oil.

R\(_f\) = 0.19 (95:5 DCM/MeOH). \(^1\)H NMR (300 MHz, CDCl\(_3\)) δ (ppm) 8.18 (br s, 3H, CH\(_{ar}\)), 7.77 (s, 9H, CH\(_{triazole}\)), 7.17 (m, 3H, NH), 5.28–5.15 (m, 27H, H2, H3, H4), 4.80 (br s, 9H, H1), 4.64–4.53 (m, 36H, OCH\(_2\)C\(_{triazole}\) + N\(_{triazole}\)CH\(_2\)), 4.20–3.98 (m, 27H, OCH\(_2\)CH\(_2\) + H6), 3.90–3.85 (m, 27H, H6 + NH\(_2\)CH\(_2\)O), 3.59 (m, 9H, H3), 2.09, 2.05, 2.01, 1.96 (4s, 108H, COCH3).\(^{13}\)C\[^{1}\]H NMR (75 MHz, CDCl\(_3\)) δ (ppm) 170.6, 169.9, 169.6, 169.7 (COCH3), 166.3 (CONH), 144.8 (C\(_{triazole}\)), 135.5 (C\(_{arom}\)), 128.5 (CH\(_{arom}\)), 124.0 (CH\(_{triazole}\)), 97.3 (C1), 69.0 (C2), 68.8 (C3), 68.7 (C4), 68.4 (NH\(_2\)CH\(_2\)O), 66.1 (C6), 65.5 (C4), 64.4 (OCH2C\(_{triazole}\)), 62.2 (OCH2CH\(_2\)), 60.5 (C4), 49.5 (CH\(_2\)N\(_{triazole}\)), 20.8, 20.7, 20.6, 20.6 (COCH3). HRMS ("ESI-MS") m/z: calculated for C\(_{192}H_{258}N_{30}O_{102}\) [M+2H]\(^{2+}\): 2308.8035, found: 2308.7995 (Δ = −1.73 ppm).

Synthesis of de-O-acetylated nonavalent derivative (12): A solution of sodium methoxide (1 M in MeOH, 150 μL) was added to a solution of acetylated precursor 11 (70.0 mg, 15.2 μmol) in MeOH (2.5 mL). The reaction mixture was stirred at room temperature for 24 h. The pH was adjusted to 7 with addition of ion-exchange resin (Amberlite IR 120 H\(^+\)). After filtration, the solvent was removed under vacuum with rotary evaporator and the residue was lyophilized to furnish desired de-O-acetylated compound 12 (47.0 mg, 15.2 μmol, 99%) as a white solid.

\(^1\)H NMR (300 MHz, D\(_2\)O) δ (ppm) 8.02 (m, 12H, CH\(_{ar}\) + CH\(_{triazole}\)), 4.74 (m, 9H, H1), 4.62–4.56 (m, 36H, OCH\(_2\)C\(_{triazole}\) + N\(_{triazole}\)CH\(_2\)), 4.05–4.01 (m, 9H, OCHHCH\(_2\)N), 3.89–3.78 (m, 36H, OCHHCH\(_2\)N + H2 + NH\(_2\)CH\(_2\)O), 3.71–3.53 (m, 36H, H6 + H4 + H3), 3.02 (m, 9H, H5). \(^{13}\)C\[^{1}\]H NMR (75 MHz, D\(_2\)O) δ (ppm)
169.0 (CONH), 144.7 (C\textsubscript{triazole}), 135.8 (C\textsubscript{arom}), 129.7 (CH\textsubscript{arom}), 126.1 (CH\textsubscript{triazole}), 100.2 (C\textsubscript{1}), 73.4 (C\textsubscript{2}), 71.1 (C\textsubscript{3}), 70.5 (C\textsubscript{4}), 67.9 (NHC\textsubscript{q}CH\textsubscript{2}O), 67.0 (C\textsubscript{5}), 66.1 (OCH\textsubscript{2}CH\textsubscript{2}N), 64.2 (OCH\textsubscript{2}C\textsubscript{triazole}), 61.4 (C\textsubscript{q}), 61.3 (C\textsubscript{6}), 50.7 (CH\textsubscript{2}N\textsubscript{triazole}). HRMS (*TOF-HRMS) m/z: calculated for C\textsubscript{120}H\textsubscript{186}N\textsubscript{30}O\textsubscript{66} [M+2H]\textsuperscript{2+}: 1552.6132, found: 1552.6119 (\Delta = -0.08 ppm).

**Synthesis of nonapropargylated derivative (14):** To a solution of phloroglucinol (13, 10.0 mg, 79.3 \textmu mol, 1.00 equiv) in anhydrous DMF (3 mL) was added under nitrogen anhydrous K\textsubscript{2}CO\textsubscript{3} (previously heated at 250 °C under vacuum, 39.5 mg, 285 \textmu mol, 3.60 equiv). After 10 min of vigorous stirring, tripropargylated synthon\textsuperscript{14} (93.0 mg, 285 \textmu mol, 3.60 equiv) was added into the solution under inert atmosphere and the reaction mixture was allowed to stir at 65 °C for 39 h. In the end, the dark-brown heterogeneous reaction was poured in 30 mL of EtOAc and organics were washed with a saturated aqueous solution of NH\textsubscript{4}Cl (2 \times 30 mL) then water (2 \times 20 mL) and brine (10 mL). The organic phase was then dried over MgSO\textsubscript{4} and concentrated under reduced pressure. Column chromatography on silica (EtOAc/hexane 40:60 to 50:50) afforded the desired compound 15 (32.0 mg, 33.8 \textmu mol, 43%) as a colorless oil.

\[ R_f = 0.27 \quad \text{(1:1 EtOAc/Hexane).} \]

\[ \text{\textsuperscript{1}H NMR (300 MHz, CDCl}_3\textsuperscript{3}) \delta \quad \text{ppm) 6.85 (s, 3H, NH), 6.17 (s, 3H, CH\textsubscript{ar}), 4.36 (s, 6H, OCH\textsubscript{2}CONH), 4.16 (m, 18H, OCH\textsubscript{2}C\textsubscript{triazole}), 3.87 (br s, 18H, HNC\textsubscript{q}CH\textsubscript{2}O), 2.48 (m, 9H, OCH\textsubscript{2}C\textsubscript{triazole}).} \]

\[ \text{\textsuperscript{13}C\{\textsuperscript{1}H\} NMR (75 MHz, CDCl}_3\textsuperscript{3}) \delta \quad \text{ppm) 167.3 (CONH), 159.0 (C\textsubscript{ar}OCH\textsubscript{2}), 95.8 (CH\textsubscript{ar}), 79.4 (OCH\textsubscript{2}C\textsubscript{triazole}), 74.9 (OCH\textsubscript{2}C\textsubscript{triazole}), 68.3 (HNC\textsubscript{q}CH\textsubscript{2}O), 67.5 (OCH\textsubscript{2}CONH), 59.2 (C\textsubscript{q}), 58.6 (OCH\textsubscript{2}C\textsubscript{triazole}).} \]

HRMS (*TOF-HRMS) m/z: calculated for C\textsubscript{31}H\textsubscript{57}N\textsubscript{3}O\textsubscript{15} [M+H]\textsuperscript{+}: 952.3862, found: 952.3843 (\Delta = -2.10 ppm); [M+Na]\textsuperscript{+}: 974.3682, found: 974.3662 (\Delta = -2.05 ppm).

**Synthesis of peracetylated derivative (16):** 16 was synthesized according to Procedure A with nonapropargylated core 15 (20.0 mg, 21.0 \textmu mol, 1.00 equiv), mannoside 3 (98.6 mg, 236.0 \textmu mol, 11.25 equiv), sodium ascorbate (11.2 mg, 56.7 \textmu mol, 2.70 equiv), and CuSO\textsubscript{4}+5H\textsubscript{2}O (14.2 mg, 56.7 \textmu mol, 2.70 equiv) in a THF/H\textsubscript{2}O mixture (3 mL, 1:1). Column chromatography on silica (DCM/MeOH 98:2 to 94:6) afforded the desired compound 16 (86.0 mg, 18.3 \textmu mol, 87%) as a colorless oil.

\[ R_f = 0.24 \quad \text{(93:7 DCM/MeOH).} \]

\[ \text{\textsuperscript{1}H NMR (300 MHz, CDCl}_3\textsuperscript{3}) \delta \quad \text{ppm) 7.70 (br s, 9H, CH\textsubscript{triazole}), 7.05 (br s, 3H, NH), 6.22 (br s, 3H, CH\textsubscript{ar}), 5.26–5.17 (m, 27H, H\textsubscript{2}, H\textsubscript{3}, H\textsubscript{4}), 4.79 (br s, 9H, H\textsubscript{1}), 4.60 (br s, 36H, OCH\textsubscript{2}C\textsubscript{triazole} + N\textsubscript{triazole}CH\textsubscript{2}H), 4.18 (br s, 6H, OCH\textsubscript{2}CONH), 4.16–3.91 (m, 27H, OCH\textsubscript{2}CH\textsubscript{2} + H\textsubscript{6a}), 3.90–3.84 (m, 27H, H\textsubscript{6b} + NHC\textsubscript{q}CH\textsubscript{2}O), 3.60 (m, 9H, H\textsubscript{5}), 2.11, 2.07, 2.02, 1.96 (4s, 108H, COCH\textsubscript{2}).} \]

\[ \text{\textsuperscript{13}C\{\textsuperscript{1}H\} NMR (75 MHz, CDCl}_3\textsuperscript{3}) \delta \quad \text{ppm) 170.5, 169.8, 169.8, 169.5, (COCH\textsubscript{2}), 167.5 (CONH), 158.9 (C\textsubscript{ar}OCH\textsubscript{2}), 144.6 (C\textsubscript{triazole}), 123.9 (CH\textsubscript{triazole}), 97.3 (C\textsubscript{1}), 95.4 (CH\textsubscript{ar}), 69.0 (C\textsubscript{2}), 68.8 (C\textsubscript{3}), 68.7 (C\textsubscript{5}), 68.5 (NHC\textsubscript{q}CH\textsubscript{2}O), 67.2 (OCH\textsubscript{2}CONH), 66.1 (C\textsubscript{6}), 65.5 (C\textsubscript{4}), 64.3 (OCH\textsubscript{2}C\textsubscript{triazole}), 62.0 (OCH\textsubscript{2}CH\textsubscript{2}), 59.6 (C\textsubscript{q}), 49.5 (CH\textsubscript{2}N\textsubscript{triazole}).} \]
20.7, 20.6, 20.6, 20.6 (COCH₃). HRMS ("TOF-HRMS") m/z: calculated for C₁₉₂H₂₆₄N₃₀O₁₀₅ [M+3H]³⁺: 1569.5486, found: 1569.5458 (Δ = -1.82 ppm); [M+2H]²⁺: 2353.8193, found: 2353.8088 (Δ = -4.48 ppm).

Synthesis of de-O-acetylated nonavalent derivative (17): Derivative 17 was synthesized according to Procedure B with compound 16 (45.0 mg, 9.56 μmol) previously dissolved in anhydrous MeOH (3 mL). Deprotected nonamer 17 was obtained as a white solid (27.0 mg, 8.45 μmol) in a 90% yield. ¹H NMR (300 MHz, D₂O) δ (ppm) 7.97 (m, 9H, CH₃-triazole), 6.15 (s, 3H, CH₃), 4.77 (s, 9H, H₁), 4.61−4.46 (m, 42H, OCH₂C-triazole + N₃-triazoleCH₂ + OCH₂CONH)), 4.06−4.01 (m, 9H, OCHHCH₂N), 3.90−3.56 (m, 72H, CHHCH₂N + H₂ + NHC₃CH₂O + H₆ + H₄ + H₃), 3.06 (m, 9H, H₅). ¹³C(¹H) NMR (75 MHz, CDCl₃) δ (ppm) 264.0 (C-6a), 165.6 (C₂), 145.0 (C₃), 123.7 (C₅), 97.4 (C₁), 69.1 (C₂), 68.9 (C₃), 68.8 (C₅), 68.4 (NHC₃CH₂O), 66.2 (C₆), 65.6 (C₄), 64.6 (OCH₂C-triazole), 62.1 (OCH₂CH₃), 60.2 (C₈), 49.6 (CH₂N₃-triazole), 29.7 (CH₂Br), 20.8, 20.7, 20.6, 20.6 (COCH₃).IR (cm⁻¹) 2956, 2937, 2361, 2337, 1751, 1734, 1540, 1370, 1218, 1045, 759. HRMS ("TOF-HRMS") m/z: calculated for C₁₂₃H₁₉₂N₃₀O₆₉ [M+3H]³⁺: 1065.4219, found: 1065.4221 (Δ = 0.23 ppm).

Synthesis of bromoacylated dendron (18): 18 was synthesized according to Procedure A with tripropargylated synthon 14 (140.0 mg, 393.0 μmol, 1.00 equiv), mannoside 3 (616 mg, 1.48 mmol, 3.75 equiv), sodium ascorbate (70.0 mg, 354 μmol, 0.90 equiv), and CuSO₄·5H₂O (88.4 mg, 354 μmol, 0.90 equiv) in a THF/H₂O mixture (6 mL, 1:1). Column chromatography on silica (DCM/MeOH 99:1 to 96:4) afforded the desired compound 18 (594 mg, 369.4 μmol, 94%) as a white solid. Rf = 0.47 (94:6 DCM/MeOH). m.p. = 68-72°C (not corrected). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.68 (br s, 3H, CH₃-triazole), 6.89 (br s, 1H, NH), 5.24−5.18 (m, 9H, H₂, H₃, H₄), 4.80 (d, J = 1.3 Hz, 1H, H₁), 4.61−4.58 (br s, 12H, OCH₂C-triazole + N₃-triazoleCH₂), 4.17−4.00 (m, 11H, OCH₂CH₂ + H₆a + BrCH₂CONH), 3.94−3.78 (m, 9H, H₉b + NHC₃CH₂O), 3.60 (m, 3H, H₅), 2.12, 2.08, 2.03, 1.98 (4s, 36H, COC₃). IR (cm⁻¹) 2956, 2937, 2361, 2337, 1751, 1734, 1540, 1370, 1218, 1045, 759. HRMS ("TOF-HRMS") m/z: calculated for C₁₂₅H₁₉₃BrN₁₀O₃⁰ [M+2H]²⁺: 804.2358, found: 804.2356 (Δ = 0.84 ppm); [M+H]⁺: 1607.4642, found: 1607.4620 (Δ = -1.36 ppm); [M+Na]⁺: 1629.4462, found: 1629.4448 (Δ = -0.84 ppm).
containing 20 mL of EtOAc and 30 mL of a saturated aqueous solution of NH₄Cl. Organics were washed with (2 × 30 mL) of saturated NH₄Claq, water (2 × 30 mL) and brine (20 mL). The organic phase was then dried over MgSO₄ and concentrated under reduced pressure to furnish the desired compound 19 (110 mg, 69.9 μmol, 93%) as a white solid.

\[ R_f = 0.47 \ (94:6 \text{ DCM}/\text{MeOH}). \text{ m.p.} = 62-65^\circ \text{C (not corrected).} \]

**1H NMR (300 MHz, CDCl₃)** δ (ppm) 7.68 (br s, 3H, CH₃triazole), 6.69 (br s, 1H, NH), 5.27−5.18 (m, 9H, H₂, H₃, H₄), 4.80 (d, J = 1.3 Hz, 1H, H₁), 4.61−4.58 (br s, 12H, OCH₂C=triazole + N=triazoleCH₂), 4.23−4.00 (m, 11H, OCH₂CH₂ + H₆a + N₃CH₂CONH), 3.90−3.81 (m, 9H, H₆b + NH₂qCH₂O), 3.60 (m, 3H, H₃), 2.12, 2.08, 2.03, 1.98 (4s, 36H, COCH₃).

**HRMS (TOF-HRMS) m/z:** calculated for C₂₁₅H₂₂₁N₃O₁₄: 1592.5551 found: 1592.5543 (Δ = -0.08 ppm); [M+H]^+: 1570.5551, found: 1570.5543 (Δ = -0.01 ppm); [M+Na]^+: 1592.5371, found: 1592.5366 (Δ = -0.01 ppm).

**Synthesis of peracetylated nonavalent derivative (20):** Derivative 20 was synthesized according to **Procedure A** with tripropargylated core 2 (3.9 mg, 12.1 μmol, 1.00 equiv), trimannosylated dendron 19 (75.0 mg, 47.8 μmol, 3.90 equiv), sodium ascorbate (6.5 mg, 33 μmol, 2.70 equiv), and CuSO₄·5H₂O (8.2 mg, 33 μmol, 0.90 equiv) in a THF/H₂O mixture (4 mL, 1:1). Column chromatography on silica (DCM/MeOH 98:2 to 90:10) afforded the desired compound 20 (52.0 mg, 10.2 μmol, 84%) as a colorless oil.

\[ R_f = 0.25 \ (92:8 \text{ DCM}/\text{MeOH}). \]

**1H NMR (300 MHz, CDCl₃)** δ (ppm) 8.37 (m, 3H, CH₃⁻), 8.00 (br s, 3H, NH), 7.78 (s, 3H, CH₃⁻triazole), 7.69 (s, 9H, CH₃⁻ext-triazole), 6.94 (br s, 3H, NH₃⁻int), 5.24−5.17 (m, 27H, H₅, H₆, H₇), 4.98 (br s, 6H, N₃⁻triazoleCH₂CONH), 4.80 (s, 9H, H₁), 4.64−4.52 (m, 42H, OCH₂C=triazole + N=triazoleCH₂ + NHCH₂C=triazole), 4.19−3.87 (m, 54H, OCH₂ + H₆ + NH₂qCH₂O), 3.63−3.62 (m, 9H, H₃), 2.11, 2.08, 2.01, 1.96 (4s, 108H, COCH₃).

**13C [1H] NMR (75 MHz, CDCl₃)** δ (ppm) 170.5, 170.0, 169.9, 169.5 (COCH₃), 165.8 (CONH), 165.1 (CONH), 144.8 (C⁻ext-triazole), 144.7 (C⁻int-triazole), 134.7 (C⁻arom), 128.7 (CH⁻arom), 124.1 (CH⁻int-triazole), 123.4 (CH⁻ext-triazole), 97.4 (C₁), 69.0 (C₂), 68.9 (C₃), 68.7 (C₃), 68.3 (NH₂qCH₂O), 66.1 (C₆), 65.5 (C₄), 64.5 (OCH₂C=triazole), 62.1 (OCH₂), 60.3 (C₉), 52.4 (N=triazoleCH₂CONH), 49.5 (CH₂⁻N=triazole), 35.5 (HNCH₂C=triazole), 20.8, 20.7, 20.6, 20.6 (COCH₃). **HRMS (TOF-HRMS) m/z:** calculated for C₂₀₇H₂₇₃N₃O₁₄5 [M+2H]^2+: 2515.8847, found: 2515.8845 (Δ = -0.08 ppm); [M+3H]^3+: 1677.5922, found: 1677.5936 (Δ = 0.79 ppm).

**Synthesis of de-O-acetylated nonavalent derivative (21):** Derivative 21 was synthesized according to **Procedure B** with 20 (40.0 mg, 7.95 μmol) previously dissolved in anhydrous MeOH (3 mL). After
filtration, the solvent was removed under vacuum with rotary evaporator and the residue was lyophilized to furnish desired de-O-acetylated nonamer 21 as a white solid (28.0 mg, 7.95 μmol) in a 99% yield.

**1H NMR (600 MHz, D$_2$O)** δ (ppm) 8.27 (m, 3H, CH$_{ar}$), 7.96 (m, 12H, CH$_{triazole}$), 5.15 (br s, 6H, N$_{triazole}$CH$_2$CONH), 4.72 (s, 9H, H$_t$), 4.66 (s, 6H OCNHCH$_2$C$_{triazole}$), 4.57–4.51 (m, 36H, OCH$_2$C$_{triazole}$ + N$_{triazole}$CH$_2$), 4.06–4.01 (m, 9H, OCHHCH$_2$N), 3.83–3.80 (m, 18H, OCHHCH$_2$N + H$_t$), 3.69–3.54 (m, 54H, NHC$_q$CH$_2$O + H$_t$ + H$_4$ + H$_3$), 3.01 (m, 9H, H$_t$). 13C{1H} NMR (150 MHz, D$_2$O) δ (ppm) 168.4 (CONH), 167.6 (CONH), 145.2 (C$_{ext-triazole}$), 144.5 (C$_{int-triazole}$), 135.0 (C$_{arom}$), 129.8 (CH$_{arom}$), 126.1 (CH$_{int-triazole}$), 126.0 (CH$_{ext-triazole}$), 100.2 (C$_t$), 73.4 (C$_3$), 71.1 (C$_3$), 70.6 (C$_2$), 67.8 (NHC$_q$CH$_2$O), 67.0 (OCH$_2$CH$_2$N$_{triazole}$), 66.1 (C$_4$), 64.1 (OCH$_2$C$_{triazole}$), 61.3 (C$_6$), 60.9 (C$_q$), 52.4 (N$_{triazole}$CH$_2$CONH), 50.7 (CH$_2$N$_{triazole}$), 35.7 (OCHNCH$_2$C$_{triazole}$). HRMS (ESI-HRMS) m/z: calculated for C$_{135}$H$_{204}$N$_{42}$O$_{89}$ [M+3H]$^{3+}$: 1173.4655, found: 1173.4671 (Δ = 1.44 ppm); [M+3Na]$^{3+}$: 1195.4474, found: 1195.4490 (Δ = 1.31 ppm).

**Synthesis of peracetylated 27-mer derivative (22):** Derivative 22 was synthesized according to Procedure A with nonapropargylated core 10 (4.6 mg, 5.38 μmol, 1.00 equiv), trimannosylated dendron 19 (95.0 mg, 60.5 μmol, 11.25 equiv), sodium ascorbate (2.9 mg, 15 μmol, 2.70 equiv), and CuSO$_4$·5H$_2$O (3.6 mg, 15 μmol, 0.90 equiv) in a THF/H$_2$O mixture (3 mL, 1:1). Column chromatography on silica (DCM/MeOH 98:2 to 90:10) afforded the desired compound 22 (50.0 mg, 3.33 μmol, 63%) as a yellowish oil.

R$_f$ = 0.72 (90:10 DCM/MeOH). **1H NMR (600 MHz, CDCl$_3$)** δ (ppm) 8.27 (m, 3H, CH$_{ar}$), 7.79 (s, 9H, CH$_{int-triazole}$), 7.75 (s, 27H, CH$_{ext-triazole}$), 7.34–7.31 (m, 12H, NH$_2$), 5.23–5.18 (m, 81H, H$_t$, H$_3$, H$_4$), 5.05 (br s, 18H, N$_{triazole}$CH$_2$CONH), 4.81 (s, 27H, H$_t$), 4.62–4.53 (m, 126H, OCH$_2$C$_{triazole}$ + N$_{triazole}$CH$_2$), 4.20–3.64 (m, 207H, OCH$_2$ + H$_t$ + NHC$_q$CH$_2$O + H$_3$), 2.11, 2.08, 2.01, 1.96 (4s, 324H, COCH$_3$). 13C{1H} NMR (150 MHz, CDCl$_3$) δ (ppm) 170.6, 170.5, 170.0, 169.9, 169.9, 169.7, 169.5 (CONH), 144.9 + 144.8 (C$_{ext-triazole}$), 144.5 (C$_{int-triazole}$), 135.6 (C$_{arom}$), 128.6 (CH$_{arom}$), 124.9 (CH$_{int-triazole}$), 124.0 (CH$_{ext-triazole}$), 97.5 (C$_t$), 69.1 (C$_2$), 69.0 (C$_3$), 68.7 (C$_4$), 68.4 (NHC$_q$CH$_2$O), 66.2 (C$_6$), 65.6 (C$_4$), 64.5 (OCH$_2$C$_{triazole}$), 62.1 (OCH$_3$), 60.4 (C$_q$), 52.4 (N$_{triazole}$CH$_2$CONH), 49.5 (CH$_2$N$_{triazole}$), 20.8, 20.8, 20.7, 20.7 (COCH$_3$). MS (TOF-MS) m/z: calculated for C$_{643}$H$_{834}$N$_{120}$O$_{318}$ [M+H]$^+$: 14995.8, found: 14995.9.

**Synthesis of de-O-acetylated 27-mer derivative (23):** Derivative 23 was synthesized according to Procedure B with 22 (30.0 mg, 2.00 μmol) previously dissolved in anhydrous MeOH (3 mL). After filtration, the solvent was removed under vacuum with rotary evaporator and the residue was lyophilized to yield the fully deprotected 27-mer 23 as a white solid (17.0 mg, 1.63 μmol) in a 82% yield.

**1H NMR (600 MHz, D$_2$O)** δ (ppm) 8.06 (m, 3H, CH$_{ar}$), 7.97 (s, 27H, CH$_{ext-triazole}$), 7.96 (s, 9H, CH$_{int-triazole}$), 5.14 (br s, 18H, N$_{triazole}$CH$_2$CONH), 4.75 (s, 27H, H$_t$), 4.59–4.51 (m, 126H, OCH$_2$C$_{triazole}$ + N$_{triazole}$CH$_2$), 4.05–4.03 (m, 27H, OCHHCH$_2$N), 3.83–3.80 (m, 72H, OCHHCH$_2$N + H$_t$ + NHC$_q$CH$_2$O$_{2m}$), 3.71–3.57 (m,
162H, NHC$_q$CH$_2$O$_{ext}$ + H$_6$ + H$_4$ + H$_3$), 3.01 (m, 27H, H$_3$). $^{13}$C($^1$H) NMR (150 MHz, D$_2$O) δ (ppm) 168.8 (CONH$_{int}$), 167.5 (CONH$_{ext}$), 144.7 (C$_{ext}$-triazole), 144.6 (C$_{int}$-triazole), 135.7 (C$_{arom}$), 129.7 (CH$_{arom}$), 127.0 (CH$_{int}$-triazole), 126.1 (CH$_{ext}$-triazole), 100.2 (C$_1$), 73.5 (C$_3$), 71.1 (C$_3$), 70.6 (C$_2$), 68.2 (NHC$_q$CH$_2$O), 68.0 (NHC$_q$CH$_2$O), 67.0 (OCH$_2$CH$_2$N$_{triazole}$), 66.1 (C$_4$), 64.2 (OCH$_2$C$_{triazole}$), 61.3 (C$_6$), 60.9 (C$_q$), 52.9 (N$_{triazole}$-CH$_2$CONH), 50.7 (CH$_2$N$_{triazole}$), 35.7 (OCHNCH$_2$C$_{triazole}$). HRMS (+TOF-HRMS) m/z: calculated for C$_{399}$H$_{204}$N$_{120}$O$_{210}$ [M+7H]$^{7+}$: 1494.6002, found: 1494.5951 (Δ = −3.43 ppm).
NMR, IR, and mass spectra

Figure S1: $^1$H NMR spectrum of compound 4 (CDCl$_3$, 300 MHz).

Figure S2: $^{13}$C NMR spectrum of compound 4 (CDCl$_3$, 75 MHz).
**Figure S3**: HRMS analysis (\(^{+}\)TOF) for compound 4.

**Figure S4**: \(^{1}\)H NMR spectrum of compound 5 (D\(_2\)O, 300 MHz).
Figure S5: $^{13}$C NMR spectrum of compound 5 (D$_2$O, 75 MHz).
Figure S6: HRMS analysis (+TOF) for compound 5.
Figure S7: $^1$H NMR spectrum of compound 8 (CDCl$_3$, 600 MHz).

Figure S8: $^{13}$C NMR spectrum of compound 8 (CDCl$_3$, 150 MHz).
Figure S9: MS analysis (TOF) for compound 8.
Figure S10: $^1$H NMR spectrum of compound 9 (D$_2$O, 300 MHz).

Figure S11: $^{13}$C NMR spectrum of compound 9 (D$_2$O, 75 MHz).
Figure S12: HRMS analysis (*TOF) for compound 9.
**Figure S13:** $^1$H NMR spectrum of compound 11 (CDCl$_3$, 300 MHz).

**Figure S14:** COSY spectrum of compound 11 (CDCl$_3$).
Figure S15: $^{13}$C NMR spectrum of compound 11 (CDCl$_3$, 75 MHz).

Figure S16: DEPT 135 spectrum for compound 11.
Figure S17: HSQC spectrum for compound 11.
Figure S18: HRMS spectrum (+ESI) for compound 11.
**Figure S19:** $^1$H NMR spectrum of compound 12 (D$_2$O, 300 MHz).

**Figure S20:** COSY spectrum for compound 12.
Figure S21: $^{13}$C NMR spectrum of compound 12 (D$_2$O, 75 MHz).

Figure S22: HSQC spectrum for compound 12.
Figure S23: HRMS spectrum ("TOF") for compound 12.
Figure S24: $^1$H NMR spectrum of compound 15 (CDCl$_3$, 300 MHz).

Figure S25: $^{13}$C NMR spectrum of compound 15 (CDCl$_3$, 75 MHz).
Figure S26: HRMS (+TOF) spectra and report for compound 15.
Figure S27: $^1$H NMR spectrum of compound 16 (CDCl$_3$, 300 MHz).

Figure S28: $^{13}$C NMR spectrum of compound 16 (CDCl$_3$, 75 MHz).
Figure S29: HRMS (*TOF (up) and *ESI (bottom)) and reports for compound 16.
Figure S30: $^1$H NMR spectrum of compound 17 (D$_2$O, 300 MHz).

Figure S31: $^{13}$C NMR spectrum of compound 17 (D$_2$O, 75 MHz).
Figure S32: HRMS (*TOF) spectrum for compound 17.
Figure S33: $^1$H NMR spectrum of compound 18 (CDCl$_3$, 300 MHz).

Figure S34: $^{13}$C NMR spectrum of compound 18 (CDCl$_3$, 75 MHz).
Figure S35: IR spectrum of compound 18.
Figure S36: HRMS (+TOF) spectrum and report for compound 18.

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Figure S37: $^1$H NMR spectrum of compound 19 (CDCl$_3$, 300 MHz).

Figure S38: COSY spectrum of compound 19.
Figure S39: $^{13}$C NMR spectrum of compound 19 (CDCl$_3$, 75 MHz).

Figure S40: IR spectrum of compound 19.
Figure S41: HRMS (*TOF) trace and report for compound 19.
Figure S42: $^1$H NMR spectrum of compound 20 (CDCl$_3$, 600 MHz).

Figure S43: COSY spectrum of compound 20.
Figure S44: $^{13}$C NMR spectrum of compound 20 (CDCl₃, 150 MHz).
Figure S45: HRMS (ESI) spectrum and report for compound 20.

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Figure S46: $^1$H NMR spectrum of compound 21 (D$_2$O, 600 MHz).

Figure S47: COSY spectrum (zoom) of compound 21.
Figure S48: $^{13}$C NMR spectrum of compound 21 (D$_2$O, 150 MHz).
Figure S49: HRMS ("ESI") spectrum of compound 21.
Figure S50: $^1$H NMR spectrum of compound 22 (CDCl$_3$, 600 MHz).

Figure S51: COSY spectrum of compound 22.
Figure S52: $^{13}$C NMR spectrum of compound 22 (CDCl$_3$, 150 MHz).

Figure S53: MS (*TOF) spectrum of compound 22.
Figure S54: $^1$H NMR spectrum of compound 23 (D$_2$O, 600 MHz).

Figure S55: COSY spectrum of compound 23.
Figure S56: $^{13}$C NMR spectrum of compound 23 (D$_2$O, 150 MHz).

Figure S57: HRMS (+TOF) spectrum of compound 23 (+ zoom).
NMR diffusion experiments

The measurement of the diffusion rate ($D$) allows calculating the solvodynamic diameter of a molecule.\(^1\)

The dendrimers are considered as spherical molecular objects, and characterized by an apparent diffusion coefficient $D$. The application of the Stokes-Einstein equation gives an estimate of the diameter of the molecule.

Stokes–Einstein equation:

$$D = \frac{K_B T}{6\pi \eta r_s}$$

$D$: Diffusion rate (m\(^2\)·s\(^{-1}\)); $K_B$: Boltzmann’s constant ($k_B = 1.38 \times 10^{-23}$ m\(^2\)·kg·s\(^{-2}\)·K\(^{-1}\)$); $T$: Temperature (K) ($T = 298.15$ K); $\eta$: solvent viscosity in Pa·s; $r_s$: Solvodynamic radius of the species.