Electronic Supplementary Information

Spatially Well-Defined Carbohydrate Nanoplatforms: Synthesis, Characterization and Lectin Interaction study

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Table of contents

General methods and materials	1
Experimental Procedures	1
uartz Crystal Microbalance Experiments	7
NMR Spectra of new compounds	9
IB spectra of new compounds	
References	28

General methods and materials

All chemicals were purchased from commercial suppliers and used as received. The reactions using air or moisture sensitive compounds were carried out with oven-dried glassware under an atmosphere of N₂ or Ar. Anhydrous solvents were passed through alumina columns in a Glass Contour solvent dispensing system and used directly when retrieved or were obtained using manual distillation over CaH₂ (CH₂Cl₂, NEt₃, pyridine) or sodium (THF). Solvents used during workup, extraction and flash column chromatography were analytical grade and used as supplied or technical grade and distilled prior to use. Reactions were monitored by thin-layer chromatography (TLC) using pre-coated Merck silica gel 60-F254 alumina plates (0.25 mm). Visualization was performed using ultraviolet light followed by staining in a molybdate-sufuric acid solution or potassium permanganate. Flash chromatography was carried out using Merck silica gel 60 (particle size 0.040–0.063 mm). Yields refer to chromatographically and spectroscopically homogeneous materials. ATR-IR spectroscopy (cm⁻¹) was performed on either a Perkin-Elmer Spectrum One Spectrophotometer or a Thermo Scientific Nicolet iS10 spectrophotometer. UV/Vis spectra (Imax in nm) were recorded on a Hitachi U-3000 spectrophotometer. Melting points were determined on an Electrothermal 9100 instrument in open capillary tubes and are uncorrected. Mass spectrometry was performed at the Institute of Chemistry at University of Tartu (Estonia), at the Interdisciplinary Mass Spectrometry center at University of Mons (Belgium), or at the Mass Spectrometry Laboratory at the University of Liege (Belgium). NMR spectra (¹H and ¹³C) were collected with either a Bruker Avance DMX 500 MHz, Bruker Ascend 400, Jeol JNM-EX-400 or a Jeol JNM-EX-500 spectrometer. Chemical shifts are reported as δ -values (ppm) relative to tetramethylsilane with residual undeuterated NMR solvent as internal standard. All coupling contanst (J) are given in hertz (Hz).

Experimental Procedures

Starting material synthesis

Compound **1** was synthesized according to literature procedure¹ and used directly in the synthesis of the Borromeates. The synthesis of compound **2** is depicted in scheme S1 and was started from commercially available chelidamic acid. The synthesis of the azido functionalized mannoside **6** is depicted in scheme S2 and is based on slightly modified literature procedures. The synthesis of disaccharide **3** is depicted in scheme S3 and starts from commercially available epichlorohydrin. All new and modified procedures have been described below.



Diethyl 4-hydroxypyridine-2,6-dicarboxylate (S1). Chelidamic acid (74.6 mmol, 15.0 g, 1.0 eq.) was dissolved in absolute ethanol (150 mL) and thionyl chloride (447.4 mmol, 33 mL, 6.0 eq.) was added

dropwise at 0°C. The solution was stirred at r.t. for 18 h after which the mixture was refluxed for 2 h. The mixture was concentrated *in vacuo*, cooled to 0°C and distilled water (120 mL) was added. To this mixture was added absolute ethanol (30 mL) and Na₂CO₃ (30 mL of a saturated solution in water). The formed precipitate was filtered off and dried under vacuum to afford the product (17.0 g, 71.0 mmol, 95%) as a white solid. The obtained analytical data was in agreement with previous reports.² mp: 119-121°C; ¹H NMR (400 MHz, CDCl₃, 25°C) δ = 7.37 (s, 2H), 4.48 (q, 4H, *J* = 8.0 Hz), 1.48 (t, 6H, *J* = 4.0 Hz); ¹³C NMR (100 MHz, CDCl₃, 25°C) δ = 166.8, 147.9, 119.9, 62.7, 14.3; HRMS (ESI⁺-MS, m/z) calc. for C₁₁H₁₃NO₅Na⁺ [M+Na]⁺: 262.0686, found: 262.0682, δ = 1.5 ppm.

Diethyl 4-(prop-2-yn-1-yloxy)pyridine-2,6-dicarboxylate (S2). A solution of alcohol **S1** (12.5 mmol, 3.0 g) and K₂CO₃ (25.1 mmol, 3.5 g, 2.0 eq.) in acetone (100 mL) under argon was stirred for 1 h at r.t. After 1 h propargyl bromide (50.2 mmol, 5.6 mL of a 80 wt% solution in toluene, 4.0 eq.) was added and the reaction mixture was refluxed for 15 h. The mixture was diluted with CH_2CI_2 (150 mL) and the obtained organic layer was washed with water (200 mL). The organic layer was dried over MgSO₄, filtrated and concentrated *in vacuo* to give the product (3.5 g, quantitative) as a yellow precipitate. ¹H NMR (400 MHz, CDCI₃, 25°C) δ = 7.87 (s, 2H), 4.86 (d, 2H, *J* = 2.4 Hz), 4.48 (q, 4H, *J* = 8.0 Hz), 2.62 (t, 1H, *J* = 2.4 Hz), 1.28 (t, 6H, *J* = 4.0 Hz); ¹³C NMR (100 MHz, CDCI₃, 25°C) δ = 165.6, 164.7, 150.4, 114.7, 77.6, 76.4, 62.6, 56.5, 14.3; HRMS (ESI⁺-MS, m/z) calc. for C₁₄H₁₆NO₅⁺ [M+H]⁺: 278.1023, found: 278.1023, δ = 0.2 ppm; **IR:** see attached spectrum.

4-(prop-2-yn-1-yloxy)pyridine-2,6-diyl)dimethanol (S3). Diester **S2** (10.8 mmol, 3.0 g) was dissolved in absolute ethanol (200 mL) and sodium borohydride (54.1 mmol, 2.4 g, 5.0 eq.) was added carefully to this solution. The resulting mixture was stirred under argon for 24 h, after which water (200 mL) was slowly added. The product was extracted with EtOAc (3 x 150 mL) and the combined organic layers were dried over MgSO₄, filtrated and concentrated *in vacuo* to afford the product (1.515 g, 7.8 mmol, 73%) as an orange powder. **mp:** 127-130°C; ¹**H NMR** (400 MHz, MeOD, 25°C) δ = 7.05 (s, 2H), 4.86 (d, 2H, *J* = 2.3 Hz), 4.63 (s, 4H), 3.05 (t, 1H, *J* = 2.4 Hz); ¹³**C NMR** (100 MHz, MeOD, 25°C) δ = 167.5, 163.8, 106.7, 78.6, 77.8, 65.2, 56.6; **HRMS:** (ESI⁺-MS, m/z) calcd for C₁₀H₁₂NO₃⁺ [M+H]⁺: 194.0812, found: 194.0811, δ = 0.6 ppm; **IR:** see attached spectrum.

4-(prop-2-yn-1-yloxy)pyridine-2,6-dicarbaldehyde (2). Oxalyl chloride (4.0 mmol, 0.34 mL, 2.2 eq.) was dissolved in dry CH₂Cl₂ (20 mL) and cooled to -78°C. To this solution DMSO (8.0 mmol, 0.57 mL, 4.4 eq.) in CH₂Cl₂ (5 mL) was added dropwise, after which the solution was stirred for 5 minutes. To this, diol **S3** (1.8 mmol, 0.35 g, 1.0 eq.) as solution in CH₂Cl₂:DMSO (3:1 ratio, 20 mL) was added dropwise, followed by addition of Et₃N (18.1 mmol, 2.5 mL, 10.0 eq.). The mixture was allowed to warm to r.t. and diluted with H₂O (50 mL). The obtained mixture was extracted with CH₂Cl₂ (3 x 50 mL) and the combined organic layers were dried over MgSO₄, filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (1% MeOH in CH₂Cl₂) to afford the product (0.26 g, 1.4 mmol, 76%) as a yellow solid. **mp:** 106-108°C; ¹**H NMR** (400 MHz, CDCl₃, 25°C): δ = 10.08 (s, 2H), 7.69 (s, 2H), 4.87 (d, 2H, *J* = 2.4 Hz), 2.62 (t, 1H, *J* = 2.4 Hz); ¹³**C NMR** (100 MHz, CDCl₃, 25°C) δ = 192.3, 165.7, 154.9, 111.9, 77.9, 76.2, 56.6; **HRMS:** (ESI⁺-MS, m/z) calc. for C₁₀H₇NO₃⁺[M+H]⁺: 190.1764, found: 190.0564; **IR:** see attached spectrum.





(2R,3S,4S,5R,6R)-6-(acetoxymethyl)tetrahydro-2H-pyran-2,3,4,5-tetrayl tetraacetate (S4) DMAP (11.1 mmol, 1.4 g, 0.1 eq) was added slowly to a solution of D-Mannose (111.0 mmol, 20.0 g, 1.0 eq.) and Ac₂O (833.6 mmol, 78.6 mL, 7.5 eq.) in dry pyridine (110 mL). The reaction mixture was stirred overnight at r.t. under an atmosphere of Ar, after which it was diluted with EtOAc (150 mL), washed with HCl (5x 50 mL of a 1M solution in H₂O), NH₄Cl (50 mL of a saturated solution) and brine (50 mL). The organic layer was dried over MgSO₄, filtrated and concentrated *in vacuo* to afford the product (43.0 g, 110.2 mmol, quantitative) as a sticky colorless oil. The analytical data was in agreement with previous reports.³ [a]_D (CH₂Cl₂, c = 1, 20°C) = +53.5°; ¹H NMR (400 MHz, CDCl₃, 25°C) δ = 6.06 (d, 1H, *J* = 1.8 Hz), 5.33 (m, 2H), 5.23 (d, 1H, *J* = 2.3 Hz), 4.24 (m, 1H), 4.09-4.05 (m, 2H), 2.15 (s, 3H), 2.15 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 1.98 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 170.7, 170.1, 169.8, 169.6, 168.0, 90.6, 70.6, 68.8, 69.7, 68.4, 65.5, 62.1, 20.9, 20.9, 20.8, 20.7, 20.7.

2-(2-azidoethoxy)ethan-1-ol (S5) 2-(2-chloroethoxy)ethan-1-ol (94.7 mmol, 10.0 mL) was dissolved in H₂O (60 mL) and sodium azide (236.8 mmol, 15.4 g, 2.5 eq) was added. The reaction mixture was stirred at 80°C under an atmosphere of argon for 16 h, after which it was poured into sodium hydroxide (100 mL of a 5 w/v % solution in H₂O) and extracted with diethyl ether (3 x 100 mL). The organic layer was dried over MgSO₄, filtrated and concentrated *in vacuo* to afford the product (12.4 g, 94.6 mmol, 99%) as a colorless oil. The analytical data was in agreement previous reports.⁴ ¹**H NMR** (400 MHz, CDCl₃, 25°C) δ = 3.76 (t, 2H, *J* = 4.0 Hz), 3.70 (t, 2H, *J* = 4.4 Hz), 3.61 (t, 2H, *J* = 4.8 Hz), 3.41 (t, 2H, *J* = 4.8 Hz), 2.01 (s, 1H); ¹³**C NMR** (100 MHz, CDCl₃, 25°C) δ = 72.5, 70.2, 61.9, 50.8.

(2R,3R,4S,5S,6S)-2-(acetoxymethyl)-6-(2-(2-azidoethoxy)ethoxy)tetrahydro-2H-pyran-3,4,5-triyl

triacetate (S6) A solution of S4 (10.3 mmol, 4.0 g, 1.0 eq.) and S5 (20.5 mmol, 2.7 g, 2.0 eq.) in dry acetonitrile (50 mL) under an atmosphere of argon was cooled to 0°C. To this mixture was added dropwise boron trifluoride diethyl etherate (20.5 mmol, 2.5 mL, 2.0 eq) and trimethylsilyl trifluoromethanesulfonate (2.05 mmol, 0.38 mL, 0.2 eq.). The reaction mixture was allowed to warm to r.t. and then stirred overnight. The reaction was quenched by addition of NaHCO₃ (50 mL of a saturated solution), after which the product was extracted using diethyl ether (50 mL). The organic layer was washed with NaHCO₃ (2 x 50 mL of a saturated solution), H₂O (50 mL) and brine (50 mL). The organic layer was dried over MgSO₄, filtrated and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc 7:3) to afford the desired product (4.0 g, 8.6 mmol, 84%) as a yellow oil. The analytical data was in complete agreement with previous reports.⁵ [α]_D (CHCl₃, c = 1, 20°C) = +36.6°; ¹H NMR (400 MHz, CDCl₃, 25°C) $\delta = 5.36$ (dd, 1H, J = 3.4 Hz, J = 9.8 Hz), 5.29 (t, 1H, J = 10.1 Hz), 5.28 (dd, 1H, J = 1.8Hz, J = 3.4 Hz), 4.88 (d, 1H, J = 1.8 Hz), 4.29 (dd, 1H, J = 5.0 Hz, J = 7.3 Hz), 4.11 (dd, 1H, J = 2.5 Hz, J = 7.3 Hz), 4.09 (m, 1H), 3.84-3.82 (m, 1H), 3.77-3.62 (m, 1H), 3.69 (m, 4H), 3.39 (t, 2H, J = 4.8 Hz), 2.17 (s, 3H), 2.16 (s, 3H), 2.11 (s, 3H), 2.04 (s, 3H); ¹³C NMR (100 MHz, CDCl₃, 25°C): δ = 171.5, 170.9, 170.1, 169.9, 97.9, 70.4, 70.2, 69.7, 69.2, 68.5, 67.4, 66.2, 62.6, 50.9, 21.0, 20.9, 20.8; HRMS: (ESI+-MS, m/z) calc. for C₁₈H₂₇N₃NaO₁₁⁺ [M+Na]⁺: 484.1538, found: 484.1539.

(2S,3S,4S,5S,6R)-2-(2-(2-azidoethoxy)ethoxy)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (6) A solution of **S6** (2.17 mmol, 1.0 g, 1.0 eq.) in dry methanol (20 mL) was placed under an argon atmosphere. To this was added sodium methanolate (8.67 mmol, 0.47 g, 4.0 eq.) at r.t. and the mixture was stirred. After 2 hours the reaction mixture was concentrated under reduced pressure until a volume of 10 mL and passed through a short column of dowex 50WX8-200 (H⁺ form). The resin was washed with a mixture of H₂O/MeOH 99:1 (50 mL). The obtained fractions were concentrated under reduced pressure to afford the desired product (0.65 g, 2.2 mmol, quantitative) as a yellow oil. The analytical data was in agreement with previous reports.⁵ [α]_D (MeOH, c = 1, 20°C) = +38.5°; ¹H NMR (400 MHz, D₂O, 25°C) δ =4.1 (s, 1H), 3.79 (dd, 1H, *J* = 1.6 Hz, *J* = 1.8 Hz), 3.81-3.72 (m, 2H), 3.68-3.61 (m, 3H), 3.73-3.67 (m, 2H), 3.40 (t, 2H, *J* = 5.0 Hz); ¹³C NMR (100 MHz, D₂O, 25°C) δ = 99.9, 72.6, 70.5, 70.0, 66.7, 69.4, 69.3, 66.3, 60.9, 50.1; HRMS: (ESI⁺-MS, m/z) calc. for C₁₀H₁₉N₃KO₇ [M+K]⁺: 332.0855, found: 332.0863.



Scheme S3 Synthesis disaccharide building block 3.

1,3-bis(prop-2-yn-1-yloxy)propan-2-ol (S7). Propargyl alcohol (159.8 mmol, 9.0 g, 9.3 mL, 2.5 eq.), TBAB (3.2 mmol, 1.0 g, 0.05 eq.) and cyclohexane (25 mL) were added to a solution of NaOH (18M, 35.5 mL, 10.0 eq.) under argon. After 10 minutes, epichlorohydrin (63.9 mmol, 5.9 g, 1.0 eq.) was added and the reaction mixture was heated to 65°C under vigorous stirring. After 6 h the reaction mixture was diluted with water

(50 mL) and extracted with Et₂O (4 x 20 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (cyclohexane/EtOAc, 8:2) to afford the product (6.1 g, 36.0 mmol, 56%) as colorless oil. Analytical data was in agreement with previous reports.⁶ ¹**H NMR** (400 MHz, CDCl₃, 25°C): δ = 4.20 (d, 4H, *J* = 2.8 Hz), 4.02 (m, 1H), 3.66-3.55 (m, 4H), 2.45 (t, 2H, *J* = 2.4 Hz); ¹³**C NMR** (100 MHz, CDCl₃, 25°C): δ = 79.4, 74.9, 71.0, 69.2, 58.6; **MS** ESI+: [M+H]⁺ 169.1, [M+Na]⁺ 191.1; **HRMS:** (ESI⁺-MS, m/z) calcd for C₉H₁₃O₃⁺ [M+H]⁺: 169.0859, found: 169.0860, δ = 0.2 ppm.

1,3-bis(prop-2-yn-1-yloxy)propan-2-yl 4-methylbenzenesulfonate (S8). A solution of **S7** (53.6 mmol, 9.0 g, 1.0 eq.) and p-toluenesulfonyl chloride (66.9 mmol, 12.8 g, 1.25 eq.) in freshly distilled pyridine (45 mL) was stirred at r.t. for 16 h after which it was concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂ and washed with water and Na₂CO₃ (saturated solution). The organic layer was dried over MgSO₄, filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography (cyclohexane:ethyl acetate, 9:1) to give the product (14.5 g, 45.0 mmol, 84%) as a yellow powder. ¹**H NMR** (400 MHz, CDCl₃, 25°C): $\delta =$ 7.81 (d 2H, *J* = 8.0 Hz), 7.31 (d, 2H, *J* = 8.0 Hz), 4.72 (dt, 1H, *J* = 4.8 Hz, *J* = 9.6 Hz), 4.05 (d, 4H, *J* = 2.4 Hz), 3.69 (m, 4H), 2.44 (s, 3H), 2.41 (t, 2H, *J* = 2.4 Hz); ¹³**C NMR** (100 MHz, CDCl₃, 25°C): $\delta =$ 144.8, 133.9, 129.7, 128.2, 79.1, 79.0, 75.1, 68.3, 58.7, 21.8; **MS** ESI+: [M+H]⁺ 323.1, [M+Na]⁺ 345.1, M+K]⁺ 361.1; **IR:** see attached spectrum.

Peracetylated bismannose tosylate (S9) Bisalkyne **S8** (0.31 mmol, 100 mg, 1.0 eq.) and mannoside **S6** (0.64 mmol, 315 mg, 2.2 eq.) were dissolved in 1,4-dioxane (0.4 mL). To this was added a mixture of CuSO₄ (0.09 mmol, 15 mg, 0.3 eq.) and NaAsc (0.19 mmol, 35 mg, 0.6 eq) in H₂O (0.2 mL). The reaction mixture was heated in the microwave at 80°C for 1 h. The resulting mixture was concentrated *in vacuo* and redispersed in dichloromethane. Filtration and purification of the crude filtrate by flash chromatography on silica gel (EtOAc/MeOH, 95:5) provided the desired product (330 mg, 0.27 mmol, 85%) as a white powder. **[α]**_D (CHCl₃, c = 1, 20°C) = +26.0°; ¹H NMR (400 MHz, CDCl₃, 25°C) δ = 7.76 (d, 2H, *J* = 8.0 Hz), 7.68 (s, 2H), 7.28 (d, 2H, *J* = 8.0 Hz), 5.33-5.25 (m, 6H), 4.86 (s, 2H), 4.70 (t, 1H, *J* = 4.8 Hz), 4.56 (br.s, 8H), 4.26 (dd, 2H, *J* = 5.3 Hz, *J* = 12.1 Hz), 4.10 (dd, 2H, *J* = 2.1 Hz, *J* = 12.1 Hz), 3.99 (m, 2H), 3.89 (t, 4H, *J* = 4.8 Hz), 3.78 (m, 2H), 3.66-3.60 (br.s, 10H), 2.42 (s, 3H), 2.16 (s, 6H), 2.09 (s, 6H), 2.05 (s, 6H), 2.00 (s, 6H); ¹³C NMR (100 MHz, CDCl₃, 25°C): δ = 170.3, 169.8, 169.6, 169.4, 144.4, 133.6, 123.7, 129.4, 127.6, 97.3, 79.11, 69.7, 69.1, 68.7, 68.2, 66.9, 65.8, 64.3, 62.2, 50.2, 21.4, 20.6, 20.5, 20.4, 20.4; MS ESI+: [M+H]⁺ 1245.4, [M+Na]⁺ 1267.4, [M+K]⁺ 1283.4. HRMS: (ESI⁺-MS, m/z) calc. for C₅₂H₇₂N₆O₂₇SNa⁺ [M+Na]⁺: 1267.4064, found: 1267.4009.

Peracetylated bismannose azide (S10) Tosylate **S9** (0.22 mmol, 270 mg, 1.0 eq.) was dissolved in dry DMF (0.8 mL) and NaN₃ (1.74 mmol, 113 mg, 8.0 eq.) was added. The reaction mixture was stirred at 80°C for 16 h under an atmosphere of argon. The mixture was cooled down to r.t. and poured into H₂O (20 mL), NH₄Cl (25 mL of a saturated solution) was added and the product was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (EtOAc/MeOH, 95:5) providing **S10** (185 mg, 0.17 mmol, 76%) as a white powder. **[α]**_D (CHCl₃, c = 1, 20°C) = +40.8°; ¹H **NMR** (400 MHz, CDCl₃, 25°C) δ = 7.66 (s, 2H), 5.24 (dd, 2H, *J* = 3.2 Hz, *J* = 9.9 Hz), 5.20 (d, 2H, *J* = 9.4 Hz), 5.18 (m, 2H), 4.78 (d, 2H, *J* = 1.6 Hz), 4.59 (s, 4H), 4.45 (t, 4H, *J* = 4.8 Hz), 4.19 (dd, 2H, *J* = 5.3 Hz, *J* = 12.1 Hz, 2H), 4.03 (dd, 2H, *J* = 2.3 Hz, *J* = 12.4 Hz), 3.92 (m, 2H), 3.82 (t, 4H, *J* = 5.0 Hz), 3.77-3.65 (m, 3H), 3.60-3.50 (m, 10H), 2.09 (s, 6H) 2.02 (s, 6H), 1.98 (s, 6H), 1.93 (s, 6H). ¹³C **NMR** (100 MHz, CDCl₃, 25°C): δ = 170.5, 170.0, 169.9, 169.7, 144.5, 123.7, 97.6, 70.0, 69.8, 69.5, 69.4, 68.9, 68.5, 67.1, 66.0, 64.5, 62.4, 60.4, 50.2, 20.9, 20.8, 20.7, 20.7; **MS** ESI+: [M+H]⁺ 1116.4, [M+Na]⁺ 1138.4, [M+K]⁺ 1154.4; **HRMS:** (ESI⁺-MS, m/z) calc. for C₄₅H₆₅N₉O₂₄Na⁺ [M+Na]⁺: 1138.4040, found: 1138.4003. **IR:** see attached spectrum.

Bismannose azide (3) To a solution of **S10** (0.90 mmol, 1.0 g, 1.0 eq.) in dry methanol (8.5 mL) under an argon atmosphere was added sodium methanolate (1.8 mmol, 97 mg, 2.0 eq.) at r.t. and the mixture was stirred during 3 h. The reaction mixture was concentrated *in* vacuo and passed through a short column of dowex 50WX8-200 (H⁺ form). The resin was washed with a mixture of H₂O/MeOH 1:1 (150 mL). The obtained fractions were concentrated *in vacuo* to afford the desired product (555 mg, 0.71 mmol, 79%) as a white powder. **[a]**_D (CHCl₃, c = 1, 20°C) = +36.0°; ¹H **NMR** (400 MHz, D₂O, 25°C) δ = 8.08 (s, 2H), 4.78 (d, 2H, *J* = 1.6 Hz), 4.69 (d, 4H *J* = 3.0 Hz), 4.63 (t, 4H, *J* = 4.8 Hz), 3.98 (t, 4H, *J* = 5.3 Hz), 3.88-3.52 (m, 26H); ¹³C **NMR** (100 MHz, D₂O, 25°C): δ = 143.8, 125.4, 99.8, 72.8, 70.6, 70.0, 66.8, 69.5, 69.2, 68.8, 66.3, 63.4, 60.9, 60.1, 50.1; **MS** ESI+: [M+H]⁺ 780.3, [M+Na]⁺ 802.3, [M+K]⁺ 818.3; **HRMS:** (ESI⁺-MS, m/z) calc. for $C_{29}H_{49}N_9O_{16}Na^+$ [M+Na]⁺: 802.3195, found: 802.3174; **IR:** see attached spectrum.

Carbohydrate nanoplatform synthesis

The synthesis of hexaalkyne Borromeate $BR \cdot (R^1)_6$ starting from building block 1 and 2 is depicted in scheme S4. $BR \cdot (R^2)_6$ was obtained by CuAAC of the formed hexaalkyne $BR \cdot (R^1)_6$ with 3 using solid supported copper catalyst Cu@A-21 as depicted in scheme S5. The solid supported copper catalyst Cu@A-21 was made according to literature procedure.⁷ The cage $C \cdot (R^3)_{12}$ was prepared according to literature procedure.⁸ The obtained cage was functionalized by amidation with acid chloride 5 to obtain dodecaalkyne $C \cdot (R^4)_{12}$. This dodecaalkyne was grafted with carbohydrates by CuAAC with azido functionalized mannoside 6 to obtain $C \cdot (R^5)_{12}$, as depicted in scheme S6. Both malonate 7 and with this starting material functionalized fullerene $F \cdot (R^6)_{12}$ were synthesized according to literature procedure.⁹ Similarly, this protected dodecaalkyne was grafted with carbohydrates by CuAAC with azido functionalized mannoside 6 to obtain $F \cdot (R^7)_{12}$, as depicted in scheme S7. Acid chloride 5 was synthesized according to slightly modified literature procedures¹⁰ and was used to synthesize monovalent reference 8, as shown in scheme S8.



Scheme S4 Synthesis of hexaalkyne Borromeate BR-(R1)6.

Hexaalkyne Borromeate (BR·(R¹)₆). Freshly deprotected **1** (0.15 mmol, 128.2 mg, 1.0 eq.) was dissolved in *i*-PrOH (10 mL) and **2** (0.15 mmol, 28.4 mg, 1.0 eq.) and Zn(OAc)₂·2H₂O (0.15 mmol, 28.1 mg, 1.0 eq.) were added to this solution. The reaction mixture was heated to 65 °C for 48 h, producing a pale yellow precipitate, which was filtered off and washed with *i*-PrOH (3 x 10 mL) and Et₂O (3 × 10 mL). The crude product was purified by reprecipitation from methanol (2 mL) into which Et₂O was added slowly to yield the product, (120 mg, 0.14 mmol, 95%) as a brown powder. ¹H NMR (400 MHz, MeOD, 25°C) $\delta_{\rm H}$ = 8.82 (s, 12H), 7.98 (s, 12H), 7.91 (s, 12H), 6.72 (dd, 48H, *J* = 8.4 Hz, *J* = 12.4 Hz,), 6.51 (d, 12H, *J* = 4.4 Hz,), 5.18 (s, 12H), 4.83 (s, 24H), 3.28 (t, 6H, *J* = 2.0 Hz); ¹³C NMR (400 MHz, MeOD, 25°C) $\delta_{\rm c}$ = 171.3, 169.8, 162.0, 153.3, 151.7, 149.8, 135.0, 131.2, 122.3, 117.2, 116.1, 113.6, 112.6, 79.6, 77.2, 63.1, 58.7; ¹⁹F NMR (376 MHz, CD₃OD, 25°C): δ = 76.6; MS TOF-ESI MS *m/z*: [M - 3CF₃CO₂]³⁺ 1573.2 (calc. 1573.0), [M - 4CF₃CO₂]⁴⁺ 1151.4 (calc. 1151.5), [M - 5CF₃CO₂]⁵⁺ 898.7 (calc. 898.6), [M - 6CF₃CO₂]⁶⁺ 730.1 (calc. 730.0). HRMS: (ESI⁻-MS, m/z) calc. for C₂₂₈H₁₄₈N₃₀O₄₂F₃₆Zn₆ [M-2H]²⁻ 2527.7754, found: 2528.1289; IR: see attached spectrum.



Scheme S5 Synthesis of dodecamannoside Borromeate BR·(R²)₆.

Dodecamannoside Borromeate (BR·(R²)₆). Hexaalkyne borromeate **BR·(R¹)₆** (19.8 μmol, 100 mg, 1.0 equivalent) and bismannoside **6** (138 μmol, 107.9 mg, 7 .0 eq.) were dissolved in dry DMSO (1.5 mL). To this solution was added Cu@A-21 (50 w/w %, 50 mg) and the reaction mixture was stirred in the dark under an atmosphere of argon at r.t. for 72h. The catalyst was removed by filtration and the product was precipitated by addition of acetone (10 mL). The collected solids were washed with acetone (2 x 10 mL) and *i*-PrOH (2 x 10 mL) and dried under high vacuum to afford the product (155 mg, 15.9 μmol, 81%) as a light brown powder. ¹H NMR (400 MHz, DMSO-*d*₆, 25°C) δ = 8.86 (br. s, 12 H), 8.36 (br. s, 6H), 8.01-7.97 (br. S, 18H), 6.65-6.40 (br. s, 60H), 5.50 (br. s, 12H), 5.04-4.48 (m, 96H), 3.89-3.25 (m, 198H); ¹³C NMR (100 MHz, DMSO-*d*₆, 25°C) δ = 170.3, 168.0, 161.0, 151.7, 150.4, 149.5, 148.3, 143.8, 141.0, 134.0, 130.2, 125.6, 125.1, 121.2, 116.5, 111.9, 110.7, 100.2, 74.0, 71.2, 70.6, 69.7, 69.1, 69.1, 67.2, 66.1, 64.0, 63.9, 61.5, 60.8, 50.0; ¹⁹F NMR (376 MHz, DMSO-*d*₆, 25°C): δ = 73.2; MS ESI+: [M-4TFA]⁴⁺ 2320.9, [M-5TFA]⁵⁺ 1833.7, [M-6TFA]⁶⁺ 1509.4, [M-7TFA]⁷⁺ 1277.5; HRMS: (ESI⁺-MS, m/z) calc. for C₃₉₀H₄₄₃N₈₄O₁₂₆F₁₈Zn₆ [M-6TFA]⁶⁺: 1509.6046, found: 1509.4488; **IR(ATR):** 3356.3 (O-H), 1688.2 (C=N), 1596.8 (C=C triazole).



 $C'(R^3)_{12}$ $R^3 = H$

Scheme S6 Synthesis dodecamannoside cage $C \cdot (R^5)_{12}$.

Dodecaalkyne Cage (C·(R⁴)₁₂) To a solution of dodeca-amine **C·(R³)**₁₂ (0.26 mmol, 210 mg, 1.0 eq.) in CH₂Cl₂ (15 mL) was added NEt₃ (5.68 mmol, 574 mg, 22.0 eq.). To this was added dropwise a solution of acid chloride **5** (4.74 mmol, 922 mg, 18.0 eq.) in CH₂Cl₂ (20 mL). The mixture was stirred overnight under an atmosphere of nitrogen, after which it was quenched with NaOH (50 mL of a 1M solution in H₂O). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 30 mL). The combined organic layers were washed with H₂O (30 mL), dried over MgSO₄, filtrated and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (EtOAc/CH₂Cl₂, 1:4 \rightarrow 2.5% MeOH in CH₂Cl₂) to afford the product (513 mg, 0.19 mmol, 74%) as a white crystalline powder. ¹H NMR (500 MHz, CDCl₃, 25°C) δ = 7.41 (br. m, 24H), 6.99 (br. m, 36H), 4.80 (br. s, 24H), 4.67 (br. s, 24H), 3.59 (br. s, 24H), 2.51 (s, 12H); ¹³C NMR (100 MHz, CDCl₃, 25°C) δ = 172.5, 158.7, 138.4, 128.9, 128.8, 125.7, 115.1, 78.1, 76.1, 55.9, 52.0, 38.9; HRMS: (NSI-FTMS, m/z) calc. for C₁₆₈H₁₄₅N₁₂O₂₄ [M+H]⁺: 2714.0495, found: 2714.0504; **IR:** see attached spectrum.

Dodecamannoside Cage (C·(R⁵)₁₂) The dodecaalkyne cage **C·(R⁴)**₁₂ (7.4 μmol, 20 mg, 1.0 eq.) and the azido functionalized mannose **6** (96 μmol, 28 mg, 12.5 eq.) were dissolved in a vial in DMSO-*d6* (0.2 mL). To this mixture was added CuSO₄·5H₂O (20 μmol, 5 mg, 2.7 eq.) and NaAsc (50 μmol, 10 mg, 6.8 eq.). The vial was capped and the mixture was stirred overnight at r.t. in the dark. The product was precipitated by addition of MeOH (3 mL) and collected by centrifugation, washed with MeOH (2 mL) and redissolved in a minimal amount of H₂O. Purification by size exclusion chromatography on Sephadex G25 (H₂O) afforded crude product. Addition of QuadrasilTM MP (70 mg) to the collected fractions followed by filtration and lyophilization afforded the desired product (23 mg, 3.6 μmol, 49%) as white foam. ¹H NMR (500 MHz, DMSO-*d*6, 25°C) δ = 8.18 (br. s, 12H), 7.35 (br. s, 24H), 7.10 (br. s, 36H), 5.15 (br. s, 24H), 4.73 (dd, 24H, *J* = 15.3 Hz, *J* = 4.8 Hz), 4.60 (br. s, 12H), 4.57 (d, 12H, *J* = 5.9 Hz), 4.53 (br. s, 24H), 4.46 (t, 12H, *J* = 5.8 Hz), 3.81 (br. s, 24H), 3.66-3.63 (m, 24H), 3.57-3.54 (m, 24H), 3.44-3.38 (m, 48H), 3.30 (br. s, 72H); ¹³C NMR (125 MHz, DMSO-*d*6, 25°C) δ = 169.9, 158.8, 142.4, 137.9, 128.8, 128.3, 128.0, 125.2, 114.6, 99.8, 73.9, 72.0, 70.9, 70.2, 69.2, 68.5, 66.9, 65.5, 61.2, 61.0, 60.0, 49.4; HRMS: (NSI-FTMS, m/z) calc. for C₂₈₈H₃₇₃N₄₈O₁₀₈ [M+H]⁺: 6231.517097, found: 6231.5439; **IR**: see attached spectrum.



Scheme S7 Synthesis dodecamannoside fullerene F-(R7)12

Dodecamannoside Fullerene (F·(R⁷)₁₂). TMS-protected polyalkyne **F·(R⁶)**₁₂ (16.7 μ mol, 50 mg, 1.0 eq.) was dissolved in THF (0.3 mL) and azido-functionalized mannose **6** (217 μ mol, 63 mg, 13.0 eq.) as solution in DMSO (0.5 mL) was added. To this mixture was added TBAF (250 μ mol, 0.25 mL of a 1M solution in THF,

15.0 eq.) and a solution of CuSO₄ (1.7 μmol, 0.3 mg, 0.1 eq.) and NaAsc (5 μmol, 1.0 mg, 0.3 eq.) in H₂O (0.2 mL). The reaction mixture was stirred under an atmosphere of argon at room temperature for 72 h. The product was precipitated by addition of acetone (15 mL), and the obtained solids were washed with acetone (3 x 5 mL). Purification of the crude product was done by addition of QuadraSil[™] Mercaptopropyl (20 mg, copper scavenging), followed by size exclusion chromatography on Sephadex G25. Lyophilization of the obtained fraction gave provided the desired product (46 mg, 8.2 μmol, 49%) as glassy orange-brown solid. ¹**H NMR** (400 MHz, DMSO, 25°C) δ = 7.80 (s, 12H), 4.74-4.26 (m, 96H), 3.78-3.28 (m, 156H) 2.65 (br. s., 24H), 1.96 (br. s, 24H); ¹³**C NMR** (100 MHz, DMSO, 25°C) δ = 162.8, 145.6, 145.1, 140.8, 122.3, 99.9, 74.0, 72.1, 71.0, 70.3, 69.2, 68.8, 67.0, 65.6, 61.3, 60.1, 49.2, 45.6, 27.8, 21.3; **MS** TOF-ESI MS m/*z*: [M+3H] ⁺³ 1878.6, [M+3Na] ⁺³ 1903.6, [M+3K] ⁺³ 1919.6; **IR**: see attached spectrum.



Scheme S8 Synthesis monovalent reference 8

N,*N*-diethyl-4-(prop-2-yn-1-yloxy)benzamide (S11) To a solution of acid chloride 5 (5.0 mmol, 973 mg, 1.0 eq.) in CH_2CI_2 (20 mL) was added diethylamine (12.5 mmol, 914 mg, 2.5 eq.). The mixture was stirred at r.t. for 3 days after which the reaction was quenched by addition of NaOH (10 mL of a 5 w/v % solution in H₂O). The product was extracted with CH_2CI_2 (3 x 20 mL) and the combined organic layers were washed with H_2O (25 mL) and Brine (25 mL). The organic layer was dried over MgSO₄, filtrated and concentrated *in vacuo*. The crude product was purified by flash chromatogrpahy on silica gel (2.5% MeOH in CH_2CI_2) to afford the product (1.0 g, 4.4 mmol, 87%) as clear light yellow oil.

¹H NMR (500MHz, CDCl₃, 25°C) δ =7.33 (d, 2H, *J* =8.7 Hz), 6.96 (d, 2H, *J* = 8.7 Hz), 4.69 (d, 2H, *J* = 2.4 Hz), 3.47 (br. s, 2H), 3.30 (br. s, 2H), 2.52 (t, 1H, *J* = 2.4 Hz), 1.15 (br. s, 6H); ¹³C NMR (125 MHz, CDCl₃, 25°C) δ = 171.1, 158.2, 130.5, 128.2, 114.7, 78.3, 75.9, 55.9, 43.4, 39.4, 14.2, 13.2; HRMS: (NSI-FTMS, m/z) calc. for $C_{28}H_{34}N_2O_4$ [2M+Na]⁺: 485.2416, found: 485.2398; **IR**: see attached spectrum.

N,N-diethyl-4-((1-(2-(2-(((2S,3S,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-

yl)oxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)benzamide (8) The azido functionalized carbohydrate **6** (80 μmol, 24 mg, 1.0 eq.) and alkyne **S11** (110 μmol, 26 mg, 1.38 eq.) were dissolved in DMSO-*d6* (0.2 mL) in a vial. To this mixture was added DIPEA (20 μmol, 2.3 mg, 0.25 eq.), CuBr·DMS complex (9.1 μmol, 1.9 mg, 0.11 eq.) and glacial AcOH (20 μmol, 1.1 mg, 0.25 eq.). The vial was capped and stirred at r.t. in the dark for 21 h. The mixture was diluted with CH_2Cl_2 (10 mL) and applied on a short patch of silica gel. Elution (10% MeOH in CH_2Cl_2) afforded the product (30.4 mg, 58 μmol, 72%) as a white sticky foam. ¹H NMR (400 MHz, dmso-*d6*, 25°C) δ = 8.20 (s, 1H), 7.30 (d, 2H, *J* = 8.7 Hz), 7.08 (d, 2H, *J* = 8.7 Hz), 5.18 (s, 2H), 4.79 (d, 1H, *J* = 4.9 Hz), 4.74 (d, 1H, *J* = 2.8 Hz), 4.62-4.60 (m, 2H), 4.55 (t, 2H, *J* = 5.1 Hz), 4.48 (t, 1H, *J* = 5.8 Hz), 3.82 (t, 2H, *J* = 5.1 Hz), 3.68-3.50 (m, 6H), 3.48-3.34 (m, 6H), 3.32-3.17 (m, 4H); ¹³C NMR (400 MHz, dmso-*d6*, 25°C) δ = 169.8, 158.6, 142.3, 129.7, 128.0, 125.1, 114.4, 99.9, 74.0, 71.0, 70.3, 69.3, 68.7, 67.0, 65.5, 61.3, 61.1, 49.5, 40.4, 13.4; HRMS: (NSI-FTMS, m/z) calc. for $C_{24}H_{37}N_4O_9$ [M+H]⁺: 525.2560, found: 525.2555; **IR**: see attached spectrum.

Quartz Crystal Microbalance Experiments

All QCM experiments were run on an Attana Cell 200TM biosensor starting with a LNB-carboxyl sensor chip in both channels A and B with the flow rate set to 10 µL/min. Functionalization of the chip surface was performed with 1X HBS-T (10 mM HEPES, 150 mM NaCl and 0.005% Tween) as running buffer. Manual injection of a freshly prepared EDC/sulfo-NHS solution (1:1 mixture) over both channels for 5 minutes was followed by manual injection concanavalin A (50 µg/mL solution in 10 mM pH 4 acetate buffer) over channel A only for 5 minutes. Deactivation of the remainder of the activated surface was performed by manual injection of Ethanolamine·HCI (1M) for 5 minutes on both channel A and B to give concanavalin A functionalized channel A and negative control channel B. For both intervals these experiments were run, a fresh con A functionalized sensor chip was prepared, one set of sensor chips (channel A+B) for determining the binding kinetics for **BR·(R²)₆** and **F·(R⁷)₁₂** and one set for determining the binding kinetics for **C·(R⁵)₁₂** (figure S1). In both cases single injection of the con A stock solution resulted in a satisfactory functionalization of the sensor chips' surface with a response of approximately 50 Hz.



Fig. S1 ConA immobilization for binding kinetics measurements. BR (R²)₆ and F (R⁷)₁₂. (left); C (R⁵)₁₂ and control 8 (right).

Binding experiments. For the binding experiments the running buffer was changed to a 1X PBS buffer with added Ca²⁺ (0.9 mM CaCl₂) and Mg²⁺ (0.49 mM MgCl₂) adjusted to pH 7.4 using 1N HCl. The flow rate was adjusted as well to a rate of 25µL/min. The samples were prepared by dissolving the compound in the running buffer. A dilution series was prepared with a two-fold dilution factor giving final concentrations ranging from 200 to 1.56 µg/mL. The different concentrations of sample were injected in duplicate in random order with a volume of 35 µL (84 second injections). All sample injections were followed by a regeneration of the surface with glycine (10 mM glycine pH 2.5, 12.5 µL injection over 30 seconds). For every three sample injection a new blank injection (running buffer) was recorded. Regeneration of $BR \cdot (R^2)_6$ proved to be highly efficient restoring the surface completely after glycine injection (figure S3). Surface regeneration after injection of C·(R⁵)₁₂ was proven unnecessary as the weaker binding of the carbohydrate nanoplatform to the surface was sufficient to regenerate the surface. Glycine regeneration was nevertheless still performed to ensure experimental consistency. However, dodecasaccharide F.(R⁷)₁₂ showed a lot of non-specific binding to the surface and the surface could not be fully regenerated with the glycine injections. As all data is corrected for non-specific binding using the unfunctionalized control channel B the data obtained for $\mathbf{F} \cdot (\mathbf{R}^7)_{12}$ could still be used to obtain the desired information on binding kinetics. As a result of this non-specific binding on the functionalized chip surface a lower response was obtained for later injections at the same concentration.



Fig. S2 Regeneration of QCM sensors after injections of BR·(R²)₆ (left), C·(R⁵)₁₂ (middle), F·(R⁷)₁₂ (right).

Determination of kinetics. The obtained sensograms for the functionalized channel were corrected for non-specific binding by substraction of the response obtained in the control channel. In addition, a blank injection was substracted as well to correct for background noise. The sensograms showing no spikes after correction were selected to ensure better fitting of the binding models. The data was imported in Tracedrawer and the data set was cut after a dissociation time of 350 seconds for **BR**·(**R**²)₆ and **F**·(**R**⁷)₁₂ and for 500 seconds for **C**·(**R**⁵)₁₂ (as almost full dissociation was achieved at this point). For these data sets the amount of data points were reduced by four-fold and the concentration changes were imported. Fitting of a 1:2 binding model using a local Bmax with no correction for mass transfer effects gave the best fit and provided us the binding kinetics that gave us the possibility to differentiate between the monovalent and multivalent binding event. The sensograms obtained for the monovalent control **8** showed saturation binding on the functionalized chip surfaces. The low molecular weight of the material resulted in a low frequency shift response of the QCM, therefore the data was not sufficient to be fitted to a binding model in tracedrawer. Instead the dissociation constant was determined by extracting this value from the saturation binding isotherm.

NMR Spectra of new compounds

S2















¹H NMR:





¹H NMR:

S9



S10



¹H NMR:





¹H NMR:

3



 $\mathsf{BR} \cdot (\mathsf{R}^1)_{6}$





 $BR \cdot (R^2)_6$









¹⁹F NMR



C·(R⁴)₁₂:



¹H NMR:



C·(R⁵)₁₂:







F·(R⁷)₁₂















IR spectra of new compounds

S2











BR·(R¹)₆



BR∙(R²)₆















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