Supporting Information for Peptoids and polyamines going sweet: Modular synthesis of glycosylated peptoids and polyamines using click chemistry

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Methods and NMR spectra

General methods

All chemicals were obtained from commercial suppliers (Merck, Sigma-Aldrich, Fluka, Acros, ACR, Alfa Aesar, KMF), the azidosugars, 1-azido-1-deoxy-β-D-glucopyranoside and 1-azido-1-deoxy-β-D-lactopyranoside as well as AZT were purchased from Sigma Aldrich. The solvents were anhydrous and of reagent grade. Merrifield resin was purchased from Polymer Laboratories (PL-CMS resin,
0.97 mmol/g, 1% crosslink, 75–150 µm mesh). 2-Chlorotrityl chloride resin was purchased from Agilent (PL-Cl-Trt-Cl resin, 2.06 mmol/g, 1% crosslink, 150–300 µm mesh). Rink amide resin was purchased from Novabiochem (0.64 mmol/g, 1% crosslink, 100–200 µm mesh). All solid-phase reactions were typically carried out in glass frits under argon atmosphere and, if not mentioned otherwise, at ambient temperature. All solution-phase reactions were carried out in flasks with magnetic stirring. Reactions under inert gas were carried out in flasks equipped with septa under argon (supplied by using a standard manifold with vacuum and argon lines).

NMR spectra were recorded at 25 °C by using Bruker AM 400 (400 (1H) and 100 MHz (13C)), Bruker DP300 (300 (1H) and 75 MHz (13C)), and DP400 (400 (1H) and 100 MHz (13C)) spectrometers. Due to rotamers, NMR spectra of peptoids were not recorded. All spectra are referenced to tetramethylsilane as the internal standard (δ = 0 ppm) by using the signals of the residual protons of CHCl₃ (7.26 ppm (1H) or 77.0 ppm (13C)) in CDCl₃, or CHD₂OD (3.31 ppm (1H) or 49.1 ppm (13C)) in CD₃OD. Multiplicities of signals are described as follows: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants (J) are given in hertz (Hz). Multiplicities in the 13C NMR spectra were determined by DEPT (distortionless enhancement by polarization transfer) measurements. Mass spectra (ESI) were obtained by using an Agilent 6230 TOF LC/MS. QToF electrospray-ionisation (ESI) MS was performed with a Micromass QToF2 spectrometer. MALDI-TOF mass spectra were obtained by using either a Bruker Biflex IV spectrometer with a pulsed ultraviolet nitrogen laser, 200 µJ at 337 nm and a time-of-flight mass analyzer with a 125 cm linear flight path, or a Micromass TOFSpecE spectrometer in reflectron mode. 2,5-Dihydroxybenzoic acid and α-cyano-4-hydroxy cinnamic acid were used as the matrix. HPLC was performed on a Jasco HPLC system, with a C18 column (30 x 190 mm). Flow rate: 15 mL/min; solvent A: 0.1% TFA in water; solvent B: 0.1%
TFA in MeCN. Analytical TLC was performed on MERCK ready-to-use plates with silica gel 60 (F254). Column chromatography: MERCK silica gel 60, 0.04–0.063 mm. The analytical data of resin-bound substrates were taken from the unpurified free product after test cleavage from the resin.

**General procedures for solid-phase synthesis**

**General washing procedure for resin.** Procedure A: the resin was washed three times each with 10% H₂O in THF, THF/Et₂O and Et₂O. Procedure B: the resin was washed three times each with DMF, 0.1 M EDTA solution in H₂O, 10% H₂O in THF, THF/Et₂O and Et₂O. In the steps with two solvents they were used alternatingly. Per 1 g of the resin, 50 mL solvent was used.

**Nosyl (Ns) deprotection.** For cleavage of the Ns protecting group the resin was swelled in DMF for 15 min. Then, 20.0 equiv of β-mercaptoethanol and 20.0 equiv of DBU were added. After agitation overnight the reaction mixture was removed and the resin was washed according to procedure A.

**Cleavage from the resin.** The product was cleaved from the resin by adding 1% TFA in CH₂Cl₂. Meanwhile the color of the resin turned to red. After 5–10 min the product was washed off with CH₂Cl₂ and MeOH, followed by evaporation of the solvent in high vacuum.

**Synthesis of azidosugars 1–3:** To a solution of d-mannosamine/ d-glucosamine/ d-galactosamine hydrochloride (1.00 g; 4.64 mmol) in methanol (50 mL), sodium methanolate (30% w/w NaOMe in MeOH, 1.66 mL, 4.64 mmol, 1.00 equiv) was added and the mixture was stirred at room temperature for 30 min until complete dissolution. NEt₃ (0.47 g; 4.64 mmol, 1.00 equiv) and chloroacetic anhydride (871 mg; 5.10 mmol, 1.10 equiv) were added to the solution, and stirred at room
temperature overnight. The solvent was evaporated and the crude product was used in subsequent reaction without further purification. Comment: *If necessary, sodium bicarbonate was added to neutralize the solution.*

To a solution of *N*-chloroacetylmannosamine/ *N*-chloroacetylglucosamine/ *N*-chloroacetylgalactosamine in MeOH/H₂O (10:1, (20 mL /2 mL)) sodium azide NaN₃ (1.06 g; 16.24 mmol, 3.50 equiv) was added. The mixture was stirred for 5 h at 65 °C. Subsequently, the reaction mixture was concentrated and dried in vacuo. The residue was then suspended in pyridine (20 mL) and acetic anhydride (20 mL) was added to the solution. The reaction was stirred at room temperature overnight. After concentration in vacuo, the residue was dissolved in EtOAc (50 mL) and washed with 1N HCl, NaHCO₃ and brine (each 50 mL) (*CAUTION: extraction with sodium bicarbonate causes gas formation and excess pressure in the separating funnel*). After drying over MgSO₄ the crude product was purified by column chromatography (cyclohexane/ethyl acetate 1:1) to afford the desired product (mixture of α/β anomers) as a white-yellowish oil that solidified upon lyophilization. The yield for all azides is about 55% overall yield.

**1,3,4,6-Tetra-O-acetyl-N-azidoacetyl-D-glucosamine (1);** mixture of anomers: α/β : 65/35; ¹H NMR (400 MHz, CDCl₃): δ = 6.49 (d, 1H, J = 9.3 Hz, NH-β), 6.43 (d, 1H, J = 9.3 Hz, NH-α), 6.19 (d, 1H, J = 3.7 Hz, H-1α) 5.80 (d, 1H, J = 8.7 Hz, H-1β), 5.32–5.18 (m, 3H), 5.13 (t, 1H, J = 9.6 Hz, J = 9.6 Hz), 4.44 (ddd, 1H, J = 3.7 Hz, J = 8.9 Hz, J = 10.8 Hz ), 4.29–4.17 (m, 3H), 4.14 (d, 1H, J = 2.2 Hz), 4.10 (d, 1H, J = 2.2 Hz), 3.93 (s, 2H), 3.91 (s, 2H), 3.83 (ddd, 1H, J = 2.3 Hz, J = 4.6 Hz, J = 9.8 Hz), 2.20 (s, 3H), 2.11 (s, J = 9.6 Hz), 2.09 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.04 (s, 3H). ¹³C NMR (100.6 MHz, CDCl₃): δ = 171.5, 170.8, 170.6, 170.6, 169.3, 169.2, 169.1, 168.7, 168.0, 166.8, 92.2 (C-1β), 90.2 (C-1α), 72.9, 72.1, 70.3, 69.8, 67.7, 67.4, 61.6,
61.5, 53.2, 52.6, 52.4, 51.2, 20.9, 20.8, 20.7, 20.6, 20.6, 20.5; MS (ESI), [M + Na][sup+]

C<sub>16</sub>H<sub>22</sub>N<sub>4</sub>NaO<sub>10</sub>: calcd. 453.1234; found 453.1471.

1,3,4,6-Tetra-O-acetyl-N-azidoacetyl-D-galactosamine (2); mixture of anomers: α/β: 65/35; ¹H NMR (400 MHz, CDCl₃): δ = 6.39 (d, 1H, J = 9.4 Hz, NH-β), 6.29 (d, 1H, J = 9.1 Hz, NH-α), 6.23 (d, 1H, J = 3.5 Hz, H-1α), 5.79 (d, 1H, J = 8.8 Hz, H-1β), 5.45 (d, 1H, J = 2.0 Hz), 5.39 (d, 1H, J = 3.2 Hz), 5.26 (ddd, 1H, J = 3.2 Hz, J = 11.5 Hz, J = 23.1 Hz), 4.74–4.69 (m, 1H), 4.67 (d, 1H, J = 3.6 Hz), 4.38 (td, 1H, J = 9.2 Hz, J = 11.2 Hz), 3.95 (s, 2H), 3.92 (s, 2H), 2.18 (s, 3H), 2.16 (s, 3H), 2.12 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 170.9, 170.8, 170.4, 170.4, 170.3, 170.1, 169.9, 169.3, 169.0, 168.8, 167.2, 166.9, 166.9, 93.8, 92.6, 90.9, 73.9, 71.8, 70.2, 69.9, 68.7, 67.6, 66.6, 66.6, 62.1, 61.2, 56.2, 52.6, 52.5, 49.9, 47.0, 21.0, 20.9, 20.8, 20.8, 20.7, 20.6, 20.6; MS (ESI), [M + Na][sup+]

C<sub>16</sub>H<sub>22</sub>N<sub>4</sub>NaO<sub>10</sub>: calcd. 453.1234; found 453.1451.

1,3,4,6-Tetra-O-acetyl-N-azidoacetyl-D-mannosamine (3); mixture of anomers: α/β: 54/46; ¹H NMR (400 MHz, CDCl₃): δ (ppm) = 6.67 (d, 1H, J = 9.0 Hz); 6.63 (d, 1H, J = 9.3 Hz); 6.03 (d, 1H, J = 1.8 Hz); 5.88 (d, 1H, J = 1.6 Hz); 5.33 (dd, 1H, J = 10.2 Hz, J = 4.3 Hz); 5.21 (t, 1H, J = 10.0 Hz); 5.15 (t, 1H, J = 9.8 Hz); 5.05 (dd, 1H, J = 9.9 Hz, J = 3.9 Hz); 4.72 (ddd, 1H, J = 9.0 Hz, J = 3.8 Hz, J = 1.6 Hz); 4.61 (ddd, 1H, J = 9.3 Hz, J = 4.2 Hz, J = 1.9 Hz); 4.27–4.19 (m, 2H); 4.16–3.99 (m, 7H); 3.81 (ddd, 1H, J = 9.6 Hz, J = 4.6 Hz, J = 2.5 Hz); 2.17 (s, 3H); 2.10 (s, 3H); 2.10 (s, 6H); 2.05 (s, 6H); 1.99 (s, 3H); 1.99 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) = 170.5; 170.1; 170.1; 169.6; 168.3; 168.1; 167.4; 166.8; 91.3; 90.3; 73.4; 71.4; 70.3; 68.8; 65.1; 65.0; 61.8; 61.7; 52.6; 52.4; 49.7; 49.3; 20.8; 20.7; 20.6; 20.6; MS (ESI), [M + Na][sup+]

C<sub>16</sub>H<sub>22</sub>N<sub>4</sub>NaO<sub>10</sub>: calcd. 453.1234; found 453.1481.

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Sperminyl-$N$-[($N',N''$-trinosyl)-$N''$-pent-4-ynyl]$p$-hydroxytrityl resin 9. To a suspension of 2.43 g (1.00 equiv) resin 8 and 2.09 mL (12.0 equiv) of 2,4,6-collidine in 15 mL CH$_2$Cl$_2$ was added 1.80 g (6.00 equiv) of 2-nitrobenzenesulfonylchloride. The resin was agitated for 16 h, then washed according to procedure A and dried under reduced pressure. After drying, 1.94 g (1.00 equiv) resin and 1.45 g (15.0 equiv) K$_2$CO$_3$ were suspended together in 20 mL DMF. Then, 1.0 mL (10.0 equiv) of 5-chloropent-1-ynie was added and the mixture was agitated at 60 °C for 16 h. After cooling down, the solvent was removed and the resin was washed following procedure A until all K$_2$CO$_3$ was removed. An orange resin was obtained after drying under reduced pressure. NMR data and MS were obtained after cleavage from the resin according to the general procedures for solid-phase synthesis.

$^1$H NMR (400 MHz, [D$_4$]-MeOH): $\delta$ (ppm) = 1.53 (m, 4 H, CH$_2$); 1.71 (m, 3H, CH$_2$); 1.96 (m, 4H, CH$_2$); 2.15 (m, 2H, CH$_2$); 3.05 (m, 4H, CH$_2$); 3.32–3.49 (m, 10H, CH$_2$); 7.72–7.89 (m, 9H, CH$_{ar}$); 7.97–8.10 (m, 3H, CH$_{ar}$); MS (MALDI) m/z: 824.15 [M + H]$^+$. 

Sperminyl-$N$-($N''$-1-$\beta$-D-glucopyranosyl-4-propyl-1H-1,2,3-triazole) 13. A suspension of 200 mg (1.00 equiv) resin 9 in 2 mL DMF reacted with 12.3 mg (0.500 equiv) CuSO$_4$·5H$_2$O in 1 mL DMF, 97.72 mg (5.00 equiv) sodium ascorbate in 0.5 mL aqua dest. and 40.08 mg (2.00 equiv) 1-azido-1-deoxy-$\beta$-D-glucopyranosid or 71.75 mg (2.00 equiv). After agitating for 2 d the reaction mixture was removed and the resin was washed according to procedure B. After deprotection of the nosyl group and washing of the resin according to procedure A the products were cleaved from the resin according to general procedures.

$^1$H NMR (400 MHz, [D4]-MeOH): $\delta$ (ppm) = 1.71–1.81 (m, 6H, CH$_2$); 2.01–2.15 (m, 6H, CH$_2$); 3.05–3.15 (m, 14H, CH$_2$); 3.35 (m, 2H, CH); 3.45–3.60 (m, 1H, CH); 3.72 (dd, 1H, CH$_2$, $J_1$ = 12.15 Hz, $J_2$ = 5.22 Hz); 3.88 (m, 1H, CH$_2$); 5.58 (d, 1H, CH, $J =$
9.19 Hz); 8.02 (s, 1H, CHar, (Triazole-H)); $^{13}$C NMR (100 MHz, [D4]-MeOH): δ (ppm) = 24.17; 24.90; 25.33; 27.46; 29.94; 33.72; 37.80; 39.33; 45.83; 62.26; 70.84; 73.96; 78.35; 81.00; 89.70, 122.78, 147.36; MS (ESI) m/z: 474.34 [M + H]$^+$; HRMS (EI, C$_{21}$H$_{44}$O$_5$N$_7$): calc. 474.3404; found 474.3401.

**Sperminyl-N-(N\textsuperscript{''}-1-β-D-lactopyranosyl-4-propyl-1H-1,2,3-triazole) 14.** A suspension of 200 mg (1.00 equiv) resin 9 in 2 mL DMF reacted with 12.3 mg (0.500 equiv) CuSO$_4$·5H$_2$O in 1 mL DMF, 97.72 mg (5.00 equiv) sodium ascorbate in 0.5 mL aqua dest. and 71.75 mg (2.00 equiv) 1-azido-1-deoxy-β-D-lactopyranoside. After agitating for 2 d the reaction mixture was removed and the resin was washed according to procedure B. After deprotection of the nosyl group and washing of the resin according to procedure A the products were cleaved from the resin according to general procedures.

$^1$H NMR (400 MHz, [D$_3$]-MeOH): δ (ppm) = 1.69–1.81 (m, 6H, CH$_2$); 2.01–2.15 (m, 6H, CH$_2$); 3.04–3.16 (m, 14H, CH$_2$); 3.33–3.36 (m, 2H, CH); 3.50–3.65 (m, 5H, CH$_2$+CH); 3.72–3.90 (m, 5H, CH$_2$+CH); 4.00 (m, 1H, CH); 4.43 (d, 1H, CH, J = 7.55 Hz); 5.63 (d, 1H, CH, J = 9.32 Hz); 8.03 (s, 1H, CHar, (triazole-H)); $^{13}$C NMR (100 MHz, [D$_4$]-MeOH): δ (ppm) = 24.18; 24.91; 25.33; 27.46; 29.95; 33.72; 37.81; 39.34; 45.83; 61.65; 62.71; 70.47; 72.68; 73.85; 74.94; 76.96; 77.30; 79.66; 79.94; 89.41, 105.27; 123.04; 147.26; MS (ESI) m/z: 636.40 [M + H]$^+$; HRMS (EI, C$_{27}$H$_{54}$O$_{10}$N$_7$): calc. 636.3932; found 636.3935.

**Sperminyl-N-(N\textsuperscript{''}-1-2',3'-deoxythymidine-4-propyl-1H-1,2,3-triazole) 15.** 402.5 mg (1.00 equiv) of resin 9 was suspended in 2 mL DMF. Then, 25.2 mg (0.500 equiv) CuSO$_4$·5H$_2$O in 1 mL DMF and 201.9 mg (5.00 equiv) sodium ascorbate in 0.5 mL distilled water were added, followed by 100 mg (1.86 equiv) AZT.
The suspension was agitated for 2.5 d, then the reaction mixture was removed from the resin. After that, the orange resin was washed according to procedure B, deprotected from the Nosyl group and dried under vacuum.

$^1$H NMR (400 MHz, [D$_4$]-MeOH): δ (ppm) = 1.71 (m, 2H, CH$_2$); 1.81 (m, 4 H, CH$_2$); 1.90 (d, 3 H, CH$_3$, J = 1.14 Hz); 2.10 (m, 6H, CH$_2$); 2.13 (m, 2H, CH$_2$); 2.85 (m, 2H, CH$_2$); 3.03–3.15 (m, 12H, CH$_2$); 3.77 (dd, 1H, CH$_2$, J$_1$ = 12.18 Hz, J$_2$ = 3.22 Hz); 3.89 (dd, 1H, CH$_2$, J$_1$ = 12.13 Hz, J$_2$ = 3.03 Hz); 4.35 (m, 1H, CH); 5.39 (dt, 1H, CH, J$_1$ = 8.67 Hz, J$_2$ = 4.93 Hz); 6.49 (t, 1H, CH, J = 6.57 Hz); 7.90 (d, 1H, CH$_{ar}$, J = 1.01 Hz); 7.94 (s, 1H, CH$_{ar}$, (triazole-H)); MS (ESI) m/z: 536.36 [M + H]$^+$. 

**Synthesis of 20**

In a vial 0.180 mmol of alkyne resin 16 was swelled in 6 mL abs. THF. 0.360 mmol of azidosugar 1, 0.360 mmol of copper(I) iodide and 9.00 mmol DIPEA were added. The vial was sealed and shaken for 16 h at room temperature. Afterwards, the solvent was removed and the resin was washed with THF, saturated aqueous sodium ascorbate solution, water, THF/MeOH/THF/MeOH/THF, MeOH/CH$_2$Cl$_2$/MeOH/CH$_2$Cl$_2$/MeOH, and three times with CH$_2$Cl$_2$. The resin was dried in vacuo. After cleavage from the resin with 5% TFA in dichloromethane, the product was obtained.

MS (MALDI-TOF): m/z = 838.9 [M + H]$^+$.

**Synthesis of hexaalkyne 27 on 2-chloro tritylchloride resin**

For the synthesis, 50 mg (0.103 mmol, 1.00 equiv) of 2-chlorotrityl chloride resin and washed in a fritted plastic syringe (Multisyntech) with 1 mL of dichloromethane, followed by swelling in 1 mL of dichloromethane for 5 min. The first submonomer was added by reacting 77.2 mg of bromoacetic acid (0.555 mmol, 5.40 equiv) and 99 µL of DIPEA (71.8 mg, 0.555 mmol, 5.00 equiv) in 1 mL of dichloromethane on a shaker
platform for 40 min at room temperature, followed by washing with dichloromethane (three times with 2 mL) and DMF (three times with 2 mL). The bromoacetylated resin was incubated with 1 mL of 47.0 mg propargylamine (0.855 mmol, 8.30 equiv) in 1 mL DMF on a shaker platform at room temperature, followed by washing with DMF (three times with 3 mL). The displacement reaction times were 30 min for propargylamine. The following bromoacetylations were carried out by reacting the resin with 143 mg bromoacetic acid (1.03 mmol, 10.0 equiv) and 160 µL DIC (130 mg, 1.03 mmol, 10.0 equiv) in 1 mL DMF for 30 min. Coupling steps were continued until the desired peptoid length was achieved. After the last displacement step, the resin was washed with DMF/dichloromethane/DMF (two times with 3 mL for each solvent).

For the coupling of rhodamine B, the resin was incubated for 18 h with a solution of 144 mg rhodamine B (0.309 mmol, 3.00 equiv), 40.5 mg HOBt (0.309 mmol, 3.00 equiv) and 76.4 µL DIC (61.9 mg, 0.309 mmol, 3.00 equiv) in 2 mL DMF on a shaker platform. After the reaction the resin was washed with DMF and dichloromethane until the washing solution was colorless.

Mass spectrum (MALDI): calc.: 1013.46 g/mol, found: 1013.3 [M]+.

Cu-catalyzed alkyne azide cycloaddition on resin 27 and cleavage from the resin

For the reaction with the sugar, the resin 27 was swollen in THF, and 70 mg Cu(CH$_3$CN)$_4$PF$_6$ (0.188 mmol, 1.83 equiv) was directly weighed into the plastic syringe containing the resin. In 2 mL dry THF, 310 mg of Ac$_4$GalNAz (2, 0.721 mmol, 7.00 equiv) and 100 µL 2,6-lutidine (92.0 mg, 0.859 mmol, 8.34 equiv) were dissolved and added to the resin. The resin was shaken for 18 h at rt.
After the reaction, the resin was washed with saturated aqueous sodium ascorbate solution, water, THF and dichloromethane (three times 2 mL each).

The peptoid was cleaved from the resin using 3 mL 33% HFIP in dichloromethane (v/v) at room temperature for 30 min. After collecting the cleavage solution, the resin was washed with 3 mL dichloromethane twice. The elution and washing solutions were combined. The solvent was evaporated under a stream of argon gas. After cleavage, HPLC purification and lyophilization, 70 mg (0.019 mmol, 19% yield) of a purple solid (28) were obtained.

Mass spectrum (MALDI, Matrix: DHB): calc.: 3594 g/mol, found: 3593 [M]+; Analytical HPLC (5−95% Acetonitrile +0.1% TFA in 30 min, t<sub>Ret</sub> = 15.9 min, Detection at 218 nm), Purity: 92%.
NMR spectra:

$^1$H NMR of compound 9 (after cleavage from resin):

$^{13}$C NMR of compound 9 (after cleavage from resin)
H NMR of compound 13:
$^{13}$C NMR of compound 13:
$^1$H NMR of compound 14:

$^{13}$C NMR of compound 14
2D- NMR of compound 14
Compound 15:
Compound 21, 24 and 28:
