Supporting Information File

for

Synthesis of multivalent carbohydrate mimetics with aminopolyol end groups and their evaluation as L-selectin inhibitors

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General information, experimental procedures and analytical data as well as copies of NMR spectra of all compounds

Experimental procedures

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General information

Reactions were generally performed under inert atmosphere (argon) in flame-dried flasks. Solvents and reagents were added by syringe. Solvents were dried using standard procedures and were purified with a MB SPS-800-dry solvent system. Triethylamine was distilled from CaH$_2$ and stored over KOH under argon atmosphere.

Commercially available reagents were used as received without further purification unless otherwise stated. Products were purified by flash chromatography on silica gel (230–400 mesh, Merck or MACHERY-NAGEL) or by ion exchange resin (DOWEX$^{\circledR}$ 50WX8-200 Sigma-Aldrich). DOWEX$^{\circledR}$ Na$^+$ was freshly prepared by washing DOWEX$^{\circledR}$ with a saturated solution of NaCl. Unless otherwise stated, yields refer to analytically pure samples. TLC-analyses were performed on silica gel coated aluminium plates purchased from Merck. Products were detected by UV-activity and by using staining reagents (cerium/molybdenum reagent, KMnO$_4$ and ninhydrine).

NMR spectra were recorded on BRUKER (AV 500, AV 700) and JEOL (ECP 500) instruments. Chemical shifts ($\delta$) are listed in parts per million (ppm) and are reported relative to solvent residual signals: CDCl$_3$ ($^1$H: $\delta = 7.26$ ppm, $^{13}$C: $\delta = 77.2$ ppm), CD$_3$OD ($^1$H: $\delta = 3.31$ ppm, $^{13}$C: $\delta = 49.0$ ppm), DMSO-$d_6$ ($^1$H: $\delta = 2.50$ ppm, $^{13}$C: $\delta = 116.6$ ppm), DMF-$d_7$ ($^1$H: $\delta = 2.75$ ppm, $^{13}$C: $\delta = 29.8$ ppm) or D$_2$O ($^1$H: $\delta = 4.79$ ppm). Integrals are in accordance with assignments; coupling constants ($J$) are given in Hz. All $^{13}$C NMR spectra are proton decoupled. Multiplicity is indicated as follows: s (singlet), bs (broad singlet), d (doublet), bd (broad doublet), t (triplet), q (quartet), quint. (quintet), dd (doublet of doublet), dt (doublet of triplet), td (triplet of doublet), m (multiplet), m$_c$ (centered multiplet). For detailed peak assignments 2D spectra were measured (COSY and HMQC). IR spectra were measured with a Jasco spectrometer (FT/IR-4100 with DLATGS Detector). HRMS analyses were performed with Agilent 6210 (ESI–TOF, 10 μL/min, 1.0 bar, 4 kV) and Varian/Agilent Ionspec QFT-7 (ESI–
FTICR, 4 μL/min, 1.0 bar, 4 kV) instruments. Elemental analyses were carried out with instruments from PerkinElmer (CHN-Analyzer 2400) and from Elementar (Vario, Vario EL, Vario EL III). Melting points were measured with a Reichert apparatus (Thermovar) and are uncorrected.

**General procedures and analytical data**

**Amide bond by Schotten–Baumann reaction (GP-1):** Under argon atmosphere, the amine (1.0 equiv) was dissolved in CH₂Cl₂ (8 mL/mmol) and the solution was cooled to 0 °C. After addition of Et₃N (2.0 equiv) and the corresponding acid chloride (1.2 equiv) the reaction mixture was stirred from 0 °C to rt during the indicated time. H₂O was added to the mixture and the aqueous phase was extracted with CH₂Cl₂ (3×). The combined organic phases were dried with Na₂SO₄ and the solvents removed in vacuo. The crude product was purified by flash column chromatography.

**Amide bond by coupling (GP-2):** Under argon atmosphere, the amine (1.0 equiv), the corresponding carboxylic acid (1.0 equiv) and HATU (1.0 equiv) were dissolved in DMF (8 mL/mmol). After addition of Et₃N (4.5 equiv), the reaction mixture was stirred at rt during the indicated time. After removing the solvents in vacuo, the crude product was purified by flash column chromatography.

**TBS deprotection with HF·pyridine (GP-3):** To a stirred solution of starting material (1 equiv) in THF (9 mL/mmol) at 0 °C, HF·pyridine (ca. 65–70% HF, 8 equiv) was added under argon atmosphere. After warming up to rt, the reaction mixture was stirred during the indicated time. H₂O was added to the mixture and the aqueous layer was extracted with CH₂Cl₂ (3×). The combined organic phases were dried with
Na$_2$SO$_4$ and the solvents were removed in vacuo. The crude product was purified by flash column chromatography.

**TBS deprotection by solvolysis (GP-4):** To a stirred solution of starting material (1.0 equiv) in 2-propanol (3 mL/mmol), AcCl (0.6 equiv) was added at 0 °C. The reaction mixture was stirred at rt for the indicated time. All volatiles were removed in vacuo affording the desired product without further purification.

**Polysulfation (GP-5):** The polyol (1.0 equiv) was dissolved in DMF-$d_7$ (0.6–1.0 mL). The solution was cooled to 0 °C and SO$_3$·DMF (3.0 equiv per OH) was added. The reaction mixture was stirred at rt for the indicated time. The reaction conversion was followed by $^1$H NMR spectroscopy (700 MHz). When indicated, additional SO$_3$·DMF (1.0–3.0 equiv for each OH group) was added and the reaction mixture was stirred at rt for the additional given time until full conversion was observed. The obtained sulfated intermediates were directly converted into the corresponding sodium salts according to **Method A** or **Method B**.

**Method A:** The reaction mixture was cooled to 0 °C and an aq. 1 M solution of NaOH was added dropwise until pH 10–12 was reached. The solvents were removed in vacuo and the crude product was purified by dialysis in H$_2$O.

**Method B:** The reaction solution was cooled to 0 °C and an aq. 0.5 M solution of NaOH was added dropwise until pH 7–9 was reached. The reaction mixture was filtrated through an ion exchange DOWEX$^\text{®}$ Na$^+$ column. The solvents were removed in vacuo and the crude product was purified by dialysis in H$_2$O.
The final products were filtrated through a syringe filter (diam. 25 mm; pore size 0.2 μm; PTFE membrane) when indicated.

**Surface plasmon resonance (SPR) assay:** Experiments were performed on a BIACORE X instrument (GE Healthcare, Freiburg, Germany) at 25 °C using a sensor chip (sensor chip SA, GE Healthcare).

The running buffer during the assay consisted of 20 mM HEPES pH 7.4, with 150 mM NaCl and 1 mM CaCl₂.

**Assay protocol:** Selectins (L-, P- or E-) Fc chimeras (R&D Systems GmbH, Wiesbaden-Nordenstadt, Germany) were coupled to Protein A gold particles (AuNP) (diam. 15 nm, Biotrend Chemikalien GmbH, Cologne, Germany) and led over a sensor chip surface with two flow cells (Fc1 and Fc2). On Fc2 was immobilized the selectin ligand composed of sulfated tyrosine and tetrasaccharide sialyl-Le⁰ presented in a multivalent fashion on a polyacrylamide backbone (sTyr/sLe⁰-PAA). On Fc1 (reference lane) was immobilized N-acetyllactosamine (LacNac-PAA) as background control. The signal from Fc1 was automatically subtracted from Fc2 during each measurement.

To evaluate selectin binding of potential inhibitors, before loading over the sensor chip, each sample was incubated with inhibitor (protein A gold particles coated with the respective selectin) for 18 min at rt at the desired final inhibitor concentrations.

The samples (35 μL) were injected over the reference lane and over the sTyr/SLe⁰-PAA lane at a flow rate of 20 μL/min. Each cycle consisted of aprox. 1 min waiting period for monitoring baseline stability, a 105 s period of association phase and 180 s
dissociation phase. Regeneration of the surface was done by injecting 4 M MgCl$_2$ at a flow rate of 100 μL/min for 60 s.

Measurements without inhibitor served as 100% binding references and were performed before and after each assay series to control baseline deviations. Each concentration was measured in duplicates.

**Data evaluation:** Reference lane data were subtracted from sTyr/sLe$^x$-PAA lane data. Responses of the sample injections were extracted between report points set at the start of the injection (0 s) and at the end of the dissociation phase (285 s). Each point represents the mean value of 2 measurements.

The mean value of the first and last 100% values were plotted against total number of data points. A linear regression between both points was set and using the resulting formula, 100% values were calculated for each data point. To obtain the relative binding value all mean results were divided by the respective 100% value. The relative binding was plotted against the corresponding inhibitor concentration and the IC$_{50}$ was determined manually.
To a solution of aminopyran 1 (100 mg, 487 µmol) in dry DMF (5 mL), DMAP (6 mg, 49 µmol) and Et$_3$N (0.54 mL, 3.90 mmol) were added under argon atmosphere. After cooling to 0 ºC, TBSOTf (901 mg, 0.78 mL, 3.41 mmol) was added dropwise and the reaction mixture was stirred for 1 h at 0 ºC until it reached rt. After stirring for 5 d at this temperature, a sat. aq. NaHCO$_3$ solution (15 mL) was added to the reaction mixture followed by extraction with EtOAc (3 × 40 mL). The combined organic phases were dried with Na$_2$SO$_4$ and the solvent was removed in vacuo. The crude product was purified by flash column chromatography (silica gel, hexanes 100%, hexanes/EtOAc 10:1, 9:1) affording TBS protected aminopyran 3 (268 mg, 97%) as a yellow oil.

$\left[\alpha\right]_D^{22} +0.72$ (c = 1.95, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 0.040, 0.047, 0.053, 0.055, 0.069, 0.080 (6 s, 3 H each, CH$_3$), 0.87, 0.88, 0.89 (3 s, 9 H each, tBu), 1.16, 1.44 (2 s, 3 H each, CH$_3$), 1.66 (dt, $J \approx$ 3.4, 7.7 Hz, 1 H, 5-H), 2.75 (m, 1 H, 3-H), 3.65 – 3.66 (m, 2 H, 2-CH$_2$), 3.71, 3.77 (AB part of ABX system, $J_{AX}$ = 7.5 Hz, $J_{BX}$ = 7.9 Hz, $J_{AB}$ = 10.2 Hz, 1 H each, 5-CH$_2$), 4.01 – 4.04 (m, 2 H, 4-H, 2-H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = -5.5, -5.3, -5.2, -5.1, -4.7, -4.6 (6 q, SiCH$_3$), 18.1, 18.2, 18.3 [3 s, SiC(CH$_3$)$_3$], 25.9, 26.0, 26.1 [3 q, SiC(CH$_3$)$_3$], 27.4, 27.6 (2 q, CH$_3$), 49.1 (d, C-5), 52.7 (d, C-3), 62.7 (t, 2-CH$_2$), 62.9 (t, 5-CH$_2$), 68.5 (d, C-2), 72.9 (d, C-4), 74.1
(s, C-6) ppm; IR (ATR): $\tilde{\nu}$ = 3390 (N-H), 2955-2860 (C-H), 1255, 1070 (C-O) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd. for C$_{27}$H$_{62}$NO$_4$Si$_3$ [M + H]$^+$: 548.3981; found: 548.4013.

**TBS protected amine 16**

2-Amino-1,3-diol (2, 8.02 g, 88.0 mmol) and DMAP (50 mg, 0.40 mmol) were dissolved in CH$_2$Cl$_2$ (100 mL) under argon. The reaction mixture was stirred at rt and Et$_3$N (48 mL, 344 mmol) was added. In a second flask tert-butyldimethylsilyl chloride (34.0 g, 225 mmol) was dissolved in CH$_2$Cl$_2$ (50 mL). The solution was added to the reaction mixture and stirred at rt overnight. H$_2$O (100 mL) was added to the mixture and the aqueous phase extracted with CH$_2$Cl$_2$ (3 x 150 mL). The combined organic phases were dried with Na$_2$SO$_4$ and solvents removed in vacuo. The crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc, 2:1) affording 16 (27.0 g, 96%) as a colorless liquid.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 0.04 (s, 12 H, CH$_3$), 0.88 (s, 18 H, tBu), 2.85 (quint., $J \approx$ 5.5 Hz, 1 H, 1-H), 3.50, 3.59 (AB part of ABX system, $J_{AB}$ = 9.8 Hz, $J_{AX}$ = 5.2 Hz, $J_{BX}$ = 5.7 Hz, 2 H each, 2-H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = -5.3, -3.4 (2 q, SiCH$_3$), 18.4 [s, SiC(CH$_3$)$_3$], 26.0 [q, SiC(CH$_3$)$_3$], 54.5 (d, C-1), 64.9 (t, C-2) ppm; IR (ATR): $\tilde{\nu}$ = 3370 (N-H), 1250 (C-O) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd. for C$_{15}$H$_{36}$NO$_2$Si$_2$ [M + H]$^+$: 320.2436; found: 320.2447.
According to **GP-1**, protected aminopyran 3 (208 mg, 0.38 mmol) was dissolved in CH$_2$Cl$_2$ (2.9 mL) and the solution was cooled to 0 °C under argon atmosphere. After addition of Et$_3$N (0.1 mL, 0.59 mmol) and hexanoyl chloride (61 mg, 64 μL, 0.45 mmol) the reaction mixture was stirred at 0 °C for 2.5 h, and at rt overnight. H$_2$O (5 mL) was then added to the reaction mixture and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic phases were dried with Na$_2$SO$_4$ and the solvents removed in vacuo. The crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc, 6:1) affording 4 (227 mg, 93%) as a pale yellow oil.

[α]$_D^{22}$ = +1.20 (c = 1.51, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$): δ = 0.015, 0.018, 0.028, 0.033, 0.101, 0.174 (6 s, 3 H each, CH$_3$), 0.87– 0.90 (m, 30 H, tBu, CH$_3$), 1.18 (s, 3 H, CH$_3$), 1.27 – 1.34 (m, 4 H, CH$_2$), 1.49 (s, 3 H, CH$_3$), 1.59 – 1.66 (m, 3 H, 5-H, CH$_2$), 2.03– 2.18 (m, 2 H, CH$_2$), 3.44 (dd, $J$ = 7.2, 10.2 Hz, 1 H, 5-CH$_2$), 4.15 – 4.17 (m, 1 H, 2-H), 4.24 (m, 1 H, 3-H), 5.80 (d, $J$ = 7.5 Hz, 1 H, NH) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ = -4.7, -5.01, -5.02, -5.15, -5.26, -5.27 (6 q, SiCH$_3$), 14.1 (q, CH$_3$), 18.0, 18.8, 18.4 [3 s, SiC(CH$_3$)$_3$], 22.6 (t, CH$_2$), 25.4 (t, CH$_2$), 25.9, 25.96, 26.0 [3 q, SiC(CH$_3$)$_3$], 27.3, 28.3 (2 q, CH$_3$), 31.7 (t, CH$_2$), 37.1 (t, CH$_2$), 49.5 (d, C-5), 50.2 (d, C-3), 62.8 (t, 5-CH$_2$), 63.5 (t, 2-CH$_2$), 67.2 (d, C-2), 68.9 (d, C-4), 74.2 (s, C-6), 172.5 (s, C=O) ppm; IR (ATR): $\tilde{\nu}$ = 2960 (N-H), 2930-2860 (C-H), 1680 (C=O), 1250 (C-O), 1070 (C-O-C)
cm⁻¹; HRMS (ESI-TOF): m/z calcd. for C₃₃H₇₂NO₅Si₃ [M + H]⁺: 646.4713; found: 646.4705; C₃₃H₇₁NNaO₅Si₃ [M + Na]⁺: 668.4532; found: 668.4528; Elemental Analysis calcd. (%) for C₃₃H₇₁NO₅Si₃ (646.2): C 61.34, H 11.07, N 2.17; found: C 61.15, H 11.07, N 1.99.

(2S,3R,4S,5S)-4-Hydroxy-2,5-bis(hydroxymethyl)-6,6-dimethyltetrahydro-2H-pyran-3-hexanamide (5)

According to GP-3, to a stirred solution of 4 (83 mg, 0.13 mmol) in THF (1 mL) at 0 °C, HF-pyridine (1.1 mL, 1.1 mmol) was added. After warming up to rt, the reaction mixture was stirred for 24 h. H₂O (5 mL) was added and the aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phases were dried with Na₂SO₄ and the solvents were removed in vacuo. The crude product was purified by flash column chromatography (silica gel, CH₂Cl₂/MeOH, 95:5) affording 5 (49 mg, quant.) as a colorless solid.

m.p. 108 – 110 ºC; [α]D²² = +42.7 (c = 1.49, MeOH); ¹H NMR (500 MHz, CD₂Cl₂): δ = 0.90 (t, J = 6.9 Hz, 3 H, CH₃), 1.06, 1.28 (2 s, 3 H each, CH₃), 1.30 – 1.36 (m, 2 H, CH₂), 1.57 – 1.65 (m, 4 H, CH₂), 1.84 – 1.89 (m, 1 H, 5-H), 2.20 – 2.25 (m, 2 H, CH₂), 3.53 – 3.60 (m, 1 H, 2-CH₂), 3.67 – 3.72 (m, 1 H, 5-CH₂), 3.75 (B part of ABX system, JAB = 11.0, Hz, JBX = 8.0 Hz, 1 H, 5-CH₂), 3.80 (m, 1 H, 4-H), 3.81 – 3.86 (m, 2 H, 2-H, 2-CH₂), 3.95 – 3.98 (m, 1 H, 3-H), 7.98 (s, 1 H, NH) ppm; ¹³C NMR (125 MHz CD₂Cl₂): δ = 14.6 (q, CH₃), 24.3 (q, CH₃), 26.0 (t, CH₂), 26.8 (q, CH₃), 27.3 (t, CH₂), 32.2 (t, CH₂), 37.4 (t, CH₂), 48.9 (d, C-5), 55.2 (d, C-3), 63.6 (t, 5-CH₂), 63.7 (t, 2-
CH₂), 71.5 (d, C-2), 74.0 (d, C-4), 76.0 (s, C-6), 129.0 (s, C=O) ppm; IR (ATR): ν = 3450 (N-H), 3310 (O-H), 2960-2860 (C-H), 1620 (C=O), 1230 (C-O), 1080 (C-O-C) cm⁻¹; HRMS (ESI-TOF): m/z calcd. for C₁₅H₂₉NNaO₅ [M + Na]⁺: 326.1938; found: 326.1966; Elemental analysis calcd. (%) C 59.38, H 9.63, N 4.62; found: C 59.15, H 9.63, N 4.38.

Divalent amide 10

According to GP-1, protected aminopyran 3 (200 mg, 0.36 mmol) was dissolved in CH₂Cl₂ (3.2 mL) and the solution was cooled to 0 °C. After addition of Et₃N (0.1 mL, 0.73 mmol) and terephthaloyl chloride (7, 45 mg, 0.22 mmol) the reaction mixture was stirred at 0 °C for 1 h and at rt for 20 h. H₂O (5 mL) was added and the aqueous layer was extracted with CH₂Cl₂ (3 × 10mL). The combined organic layers were dried with Na₂SO₄ and the solvents were removed in vacuo. The crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc, 6:1) affording 10 (223 mg, quant.) as colorless solid.

Melting range: 105 – 110 °C; [α]D²² = +33.8 (c = 0.73, CHCl₃); ¹H NMR (500 MHz, CDCl₃): δ = -0.20, -0.10 (2 s, 6 H each, CH₃), -0.01 (s, 12 H, CH₃), 0.14, 0.24 (2 s, 6 H each, CH₃), 0.75, 0.83, 0.92 (3 s, 18 H each, tBu), 1.21, 1.54 (2 s, 6 H each, CH₃), 1.69 (bt, J ≈ 7.6 Hz, 2 H, 5-H), 3.50 (dd, J = 8.6, 10.1 Hz, 2 H, 5-CH₂), 3.72 (d, J = 5.5 Hz, 4 H, 2-CH₂), 3.79 (dd, J = 7.1, 10.1 Hz, 2 H, 5-CH₂), 3.92 – 3.96 (m, 2 H, 3-H), 4.26 (dt, J = 2.1, 5.5 Hz, 2 H, 2-H), 4.52 – 4.55 (m, 2 H, 4-H), 6.82 (d, J = 6.8 Hz,
2 H, NH), 7.78 (s, 4 H, Ar) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = -5.45, -5.41, -5.28, -5.25, -4.93, -4.65 (6 q, SiCH$_3$), 18.0, 18.1, 18.5 [3 s, SiC(CH$_3$)$_3$], 25.88, 25.91, 25.95 [3 q, SiC(CH$_3$)$_3$], 27.3, 28.2 (2 q, CH$_3$), 49.0 (d, C-5), 51.7 (d, C-3), 62.4 (t, 5-CH$_2$), 64.0 (t, 2-CH$_2$), 66.5 (d, C-2), 67.9 (d, C-4), 74.3 (s, C-6), 127.2 (d, Ar), 137.4 (s, Ar), 166.1 (s, C=O) ppm; IR (ATR): $\tilde{\nu}$ = 3380 (N-H), 2860 (C-H), 1670 (C=O), 1525 (C=C), 1250 (C-O), 1075 (C-O-C) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd. for C$_{62}$H$_{124}$N$_2$NaO$_{10}$Si$_6$ [M + Na$^+$]: 1248.7786; found: 1248.7760; Elemental analysis calcd. (%) C 60.73, H 10.19, N 2.28; found: C 60.85, H 10.24, N 2.36.

Divalent amide 13

According to GP-3, to a stirred solution of 10 (116 mg, 0.095 mmol) in THF (0.7 mL) at 0 °C, HF-pyridine (0.15 mL, 0.15 mmol) was added. After warming up to rt, the reaction mixture was stirred for 22 h. MeOH was added to the mixture and the solvents were removed in vacuo. The crude product was purified by flash column chromatography (silica gel, CH$_2$Cl$_2$/MeOH, 9:1) affording 13 (52 mg, quant.) as a slightly pink solid.

m.p. 210 °C; $[\alpha]_{D}^{22}$ = +45.2 (c = 0.43, MeOH); $^1$H NMR (700 MHz, CD$_3$OD): $\delta$ = 1.33, 1.46 (2 s, 6 H each, CH$_3$), 1.78 (m, 2 H, 5-H), 3.51, 3.56 (AB part of ABX system, $J_{AB}$ = 11.6 Hz, $J_{AX}$ = 4.8 Hz, $J_{BX}$ = 6.9 Hz, 2 H each, 2-CH$_2$), 3.67 (dd, $J$ = 4.2, 11.1 Hz, 2 H, 5-CH$_2$), 3.96 – 3.99 (m, 4 H, 5-CH$_2$, 4-H), 4.18 – 4.21 (m, 4 H, 3-H, 2-H), 7.91 (s, 4 H, Ar) ppm; $^{13}$C NMR (175 MHz, CD$_3$OD): $\delta$ = 26.3, 27.7 (2 q, CH$_3$), 48.8 (d, C-5), 51.7 (d, C-3), 62.4 (t, 5-CH$_2$), 64.0 (t, 2-CH$_2$), 66.5 (d, C-2), 67.9 (d, C-4), 74.3 (s, C-6), 127.2 (d, Ar), 137.4 (s, Ar), 166.1 (s, C=O) ppm; IR (ATR): $\tilde{\nu}$ = 3380 (N-H), 2860 (C-H), 1670 (C=O), 1525 (C=C), 1250 (C-O), 1075 (C-O-C) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd. for C$_{62}$H$_{124}$N$_2$NaO$_{10}$Si$_6$ [M + Na$^+$]: 1248.7786; found: 1248.7760; Elemental analysis calcd. (%) C 60.73, H 10.19, N 2.28; found: C 60.85, H 10.24, N 2.36.
54.2 (d, C-3), 63.2 (t, 2-CH$_2$), 63.3 (t, 5-CH$_2$), 70.9 (d, C-2), 74.0 (d, C-4), 75.9 (s, C-6), 128.6 (d, Ar), 138.4 (s, Ar), 169.5 (s, C=O) ppm; IR (ATR): $\tilde{\nu}$ = 3290 (O-H, N-H), 2980-2910 (C-H), 1725 (C=O), 1440 (C=C), 1250 (C-O), 1070 (C-O-C) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd. for C$_{26}$H$_{40}$N$_2$NaO$_{10}$ [M +Na$^+$]: 563.2575; found: 563.2581.

**Divalent amide 11**

According to **GP-1**, protected aminopyran 3 (200 mg, 0.36 mmol) was dissolved in CH$_2$Cl$_2$ (3.2 mL) and the solution was cooled to 0 °C. After addition of Et$_3$N (0.1 mL, 0.73 mmol) and sebacoyl chloride (8, 46.7 μL, 0.219 mmol) the reaction mixture was stirred at 0 °C for 1 h and at rt for 20 h. Water (5 mL) was added and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were dried with Na$_2$SO$_4$ and the solvents were removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc, 6:1) affording 11 (132 mg, 58%) as colorless oil.

[$\alpha$]$^D_{22}$ = +32.0 (c = 0.95, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$): δ = 0.009, 0.013, 0.022, 0.028, 0.10, 0.17 (6 s, 6 H each, CH$_3$), 0.87 (s, 36 H, tBu), 0.89 (s, 18 H, tBu), 1.18 (s, 6 H, CH$_3$), 1.28 (bs, 8 H, CH$_2$), 1.48 (s, 6 H, CH$_3$), 1.57 – 1.62 (m, 6 H, CH$_2$, 5-H), 2.04 – 2.16 (m, 4 H, CH$_2$), 3.43 (dd, $J$ = 7.4, 10.2 Hz, 2 H, 5-CH$_2$), 3.59 (d, $J$ = 5.9 Hz, 4 H, 2-CH$_2$), 3.70 – 3.77 (m, 4 H, 5-CH$_2$, 3-H), 4.15 (dt, $J$ = 2.1, 5.9 Hz, 2 H, 2-H), 4.22 – 4.25 (m, 2 H, 4-H), 5.80 (d, $J$ = 7.8 Hz, 2 H, NH) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ = -5.32, -5.32, -5.31, -5.21, -5.06, -4.77 (6 q, SiCH$_3$), 17.9, 18.2, 18.3 [3 s,
SiC(CH$_3$)$_3$, 25.7 (t, CH$_2$), 25.87, 25.90, 25.97 [3 q, SiC(CH$_3$)$_3$], 27.3, 28.2 (2 q, CH$_3$), 29.4, 29.6 (2 t, CH$_2$), 37.0 (t, CH$_2$), 49.4 (d, C-5), 50.2 (d, C-3), 62.7 (t, 5-CH$_2$), 63.5 (t, 2-CH$_2$), 67.1 (d, C-2), 68.8 (d, C-4), 74.2 (s, C-6), 172.4 (s, C=O) ppm; IR (ATR): $\tilde{\nu}$ = 3275 (N-H), 2970-2855 (C-H), 1640 (C=O), 1230 (C-O), 1070 (C-O-C) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd. for C$_{64}$H$_{136}$N$_2$NaO$_{10}$Si$_6$ [M + Na]$^+$: 1283.8703; found: 1283.8759.

**Divalent amide 14**

![Divalent amide 14](image)

According to GP-3, to a stirred solution of 11 (68 mg, 0.054 mmol) in THF (0.4 mL) at 0 °C, HF·pyridine (89.6 μL, 0.089 mmol) was added. After warming up to rt, the reaction mixture was stirred for 24 h. MeOH was added to the reaction mixture and the solvents were removed in vacuo. The crude product was purified by flash column chromatography (silica gel, CH$_2$Cl$_2$/MeOH 9:1 to 4:1) affording 14 (25 mg, 80%) as a colorless solid.

m.p. 215 – 217 °C; $[\alpha]_D^{22} = +54.9$ (c = 1.24, MeOH); $^1$H NMR (500 MHz, CD$_3$OD): $\delta =$ 1.23 (s, 6 H, CH$_3$), 1.34 (s, 8 H, CH$_2$), 1.39 (s, 6 H, CH$_3$), 1.61 – 1.63 (m, 4 H, CH$_2$), 1.78 (td, $J \approx$ 5.5, 7.8 Hz, 2 H, 5-H), 2.23 (t, $J = 7.2$ Hz, 4 H, CH$_2$), 3.46 (d, $J = 6.1$ Hz, 4 H, 2-CH$_2$), 3.65 (dd, $J = 5.4$, 11.2 Hz, 2 H, 5-CH$_2$), 3.77 (dd, $J = 7.8$, 5.2 Hz, 2 H, 4-H), 3.83 (dd, $J = 5.7$, 11.2 Hz, 2 H, 5-CH$_2$), 3.91 – 3.94 (m, 2 H, 3-H), 4.05 (dt, $J =$ 3.9, 6.1 Hz, 2 H, 2-H) ppm; $^{13}$C NMR (125 MHz, CD$_3$OD): $\delta =$ 25.4 (q, CH$_3$), 26.9 (t, CH$_2$), 27.3 (q, CH$_3$), 30.0, 30.2, 37.1 (3 t, CH$_2$), 49.5 (d, C-5), 55.1 (d, C-3), 62.9 (t, 5-CH$_2$), 63.0 (t, 2-CH$_2$), 71.1 (d, C-2), 73.6 (d, C-4), 76.0 (s, C-6), 128.8 (s)* ppm;
*Signal could not be attributed. C=O singlet could not be detected; IR (ATR): \( \tilde{\nu} = \)
3320 (O-H, N-H), 2970-2890 (C-H), 1675 (C=O), 1245 (C-O), 1070 (C-O-C) cm\(^{-1}\); HRMS (ESI-TOF): m/z calcd. for C\(_{28}H_{52}N_{2}O_{10}\) [M + Na]: 601.3671; found: 601.3642.

**Divalent amide 12**

![Chemical structure of 12]

According to GP-1, protected aminopyran 3 (103 mg, 0.19 mmol) was dissolved in CH\(_2\)Cl\(_2\) (2 mL) and the solution was cooled to 0 °C. After addition of Et\(_3\)N (0.1 mL, 0.73 mmol) and acid chloride 9 (26 mg, 0.08 mmol) the reaction mixture was stirred at 0 °C for 1 h and at rt for 24 h. H\(_2\)O (5 mL) was added and the aqueous phase was extracted with CH\(_2\)Cl\(_2\) (3 × 10 mL). The combined organic phases were dried with Na\(_2\)SO\(_4\) and the solvents removed in vacuo. The crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc, 6:1) affording 12 (114 mg, quant.) as a pink solid.

Melting range: 170 – 175 °C; \([\alpha]_{D}^{22} = +40.2\) (c = 1.13, CHCl\(_3\)); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta =\) -0.16, -0.08, 0.02, 0.07, 0.16, 0.26 (6 s, 6 H each, CH\(_3\)), 0.76, 0.85, 0.93 (3 s, 18 H each, tBu), 1.22, 1.25 (2 s, 6 H each, CH\(_3\)), 1.66 – 1.69 (m, 2 H, 5-H), 3.53 (dd, \(J = 8.6, 10.1\) Hz, 2 H, 5-CH\(_2\)), 3.74, 3.76 (AB part of ABX system, \(J_{AB} = 10.9\) Hz, \(J_{AX} = 5.1\) Hz, \(J_{BX} = 5.9\) Hz, 2 H each, 2-CH\(_2\)), 3.81 (dd, \(J = 7.1, 10.1\) Hz, 2 H, 5-CH\(_2\)), 3.96 – 3.99 (m, 2 H, 3-H), 4.28 (dt, \(J \approx 2.0, 5.5\) Hz, 2 H, 2-H), 4.54 (t, \(J = 2.3\) Hz, 2 H, 4-H), 6.84 (d, \(J = 7.0\) Hz, 2 H, NH), 7.91 (d, \(J = 8.5\) Hz, 4 H, Ar), 7.98 (d, \(J = 8.5\) Hz, 4 H, Ar) ppm; \(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta =\) -5.45, -5.43, -5.25, -5.22, -4.93, -4.65 (6
q, SiCH₃), 18.0, 18.2, 18.5 [3 s, SiC(CH₃)₃], 25.89, 25.94, 25.96 [3 q, SiC(CH₃)₃],
27.3, 28.2 (2 q, CH₃), 49.0 (d, C-5), 51.6 (d, C-3), 62.5 (t, 5-CH₂), 64.0 (t, 2-CH₂),
66.7 (d, C-2), 67.9 (d, C-4), 74.3 (s, C-6), 123.2, 128.1 (2 d, Ar), 137.1, 154.1 (2 s, Ar), 166.1 (s, C=O) ppm; IR (ATR): \( \nu = 3310 \text{ (N-H), 2960-2850 (C-H), 1735 (C=O),} \)
1470 (C=C), 1250 (C-O), 1060 (C-O-C) cm⁻¹; HRMS (ESI-TOF): m/z calcd. for
C₆₈H₁₂₈N₄NaO₁₀Si₆ [M+Na]⁺: 1351.8133; found: 1351.8136.

Divalent amide 15

According to GP-3, to a stirred solution of 12 (44 mg, 0.033 mmol) in THF (0.3 mL) at
0 °C, HF-pyridine (40 μL, 0.397 mmol) was added. After warming up to rt, the
reaction mixture was stirred for 24 h. MeOH was added to the mixture and the
solvents were removed in vacuo. The crude product was purified by flash column
chromatography (silica gel, CH₂Cl₂/MeOH, 95:5) affording 15 (27 mg, quant.) as an
orange solid.

m.p. 249 ºC; \([\alpha]_{D}^{22} = +71.8 \text{ (c = 0.66, MeOH);} \)¹H NMR (700 MHz, CD₃OD): \( \delta = 1.34, \)
1.47 (2 s, 6 H each, CH₃), 1.79 (m, 2 H, 5-H), 3.54, 3.59 (AB part of ABX system, \( J_{AB} \)
= 11.7 Hz, \( J_{AX} = 4.4 \text{ Hz, } J_{BX} = 6.7 \text{ Hz, 2 H each, 2-CH₂}, \) 3.70 (dd, \( J = 4.1, 11.2 \text{ Hz, 2} \)
H, 5-CH₂), 3.97 – 4.02 (m, 4 H, 5-CH₂, 4-H), 4.18 – 4.23 (m, 4 H, 2-H, 3-H), 8.01 (d, \( J = 8.6 \text{ Hz, 4 H, Ar}, \) 8.04 (d, \( J = 8.6 \text{ Hz, 4 H, Ar} \) ppm; \(^{13}\)C NMR (175 MHz, CD₃OD): \( \delta = 26.3, 27.7 \text{ (2 q, CH₃), 48.8 (d, C-5), 54.2 (d, C-3), 63.2 (t, 2-CH₂), 63.3 (t, 5-CH₂),} \)
70.9 (d, C-2), 74.1 (d, C-4), 75.9 (s, C-6), 124.0, 129.7 (2 d, Ar), 138.1, 155.6 (2 s, Ar), 169.5 (s, C=O) ppm; IR (ATR): \( \nu = 3320 \text{ (O-H, N-H), 2960-2855 (C-H), 1730} \)
(C=O), 1440 (C=C), 1250 (C-O), 1060 (C-O-C) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd. for C$_{32}$H$_{44}$N$_{4}$NaO$_{10}$ [M + Na]$^+$: 667.2944; found: 667.2943; Elemental analysis calcd. (%) C$_{32}$H$_{44}$N$_{4}$O$_{10}$ (644.7) + 6 H$_2$O: C 51.05, H 7.50, N 7.44; found: C 51.06, H 6.08, N 7.11.

**Divalent amide 18**

According to GP-1, protected serinol 16 (200 mg, 0.626 mmol) was dissolved in CH$_2$Cl$_2$ (5.4 mL) and the solution was cooled to 0 °C. After addition of Et$_3$N (0.17 mL, 1.25 mmol) and terephthaloyl chloride (7, 76 mg, 0.38 mmol) the reaction mixture was stirred at 0 °C for 1 h and at rt for 17 h. H$_2$O (10 mL) was added to the reaction mixture and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 20 mL). The combined organic layers were dried with Na$_2$SO$_4$ and the solvents removed in vacuo. The crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc, 5:1) affording 18 (201 mg, 83%) as colorless solid.

m.p. 142 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 0.07, 0.09 (2 s, 12 H each, CH$_3$), 0.91 (s, 36 H, tBu), 3.65 (dd, $J$ = 6.4, 9.6 Hz, 4 H, 2-H), 3.87 (dd, $J$ = 3.5, 9.6 Hz, 4 H, 2-H), 4.13 – 4.19 (m, 2 H, 1-H), 6.58 (d, $J$ = 8.3 Hz, 2 H, NH), 7.80 (s, 4 H, Ar) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = -5.33, -5.25 (2 q, SiCH$_3$), 18.4 [s, SiC(CH$_3$)$_3$], 26.0 [q, SiC(CH$_3$)$_3$], 52.1 (d, C-1), 60.5 (t, C-2), 127.3 (d, Ar), 137.4 (s, Ar), 166.0 (s, C=O) ppm; IR (ATR): $\tilde{\nu}$ = 3275 (N-H), 2880 (C-H), 1630 (C=O), 1545 (C=C), 1255 (C-O) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd. for C$_{38}$H$_{76}$N$_2$NaO$_6$Si$_4$ [M + Na]$^+$: 791.4673; found:
According to GP-4, to a stirred suspension of 18 (200 mg, 0.260 mmol) in 2-propanol (0.9 mL), AcCl (10 μL, 0.16 mmol) was added at 0 °C. The reaction mixture was stirred at rt for 1.5 h. All volatiles were removed in vacuo affording 21 (73 mg, 90%) as a colorless solid.

Melting range: 178 – 182 °C; $^1$H NMR (500 MHz, DMSO-d$_6$): $\delta = 3.47 – 3.57$ (m, 8 H, 2-H), 3.93 – 4.02 (m, 2 H, 1-H), 4.68 (t, $J = 5.7$ Hz, 4 H, OH), 7.93 (s, 4 H, Ar), 8.09 (d, $J = 8.1$ Hz, 1 H, NH) ppm; $^{13}$C NMR (125 MHz, DMSO-d$_6$): $\delta = 54.0$ (d, C-1), 60.4 (t, C-2), 127.2 (d, Ar), 136.8 (s, Ar), 165.6 (s, C=O) ppm; IR (ATR): $\tilde{\nu} = 3290$-3230 (O-H, N-H), 2970-2840 (C-H), 1630 (C=O), 1555 (C=C), 1230 (C=O) cm$^{-1}$; HRMS (ESI-TOF): m/z cald. for C$_{14}$H$_{20}$N$_2$NaO$_6$ [M + Na]$^+$: 335.1214; found: 335.1216; Elemental analysis calcd. (%) C$_{14}$H$_{20}$N$_2$O$_6$ (312.3): C 53.84, H 6.45, N 8.97; found: C 53.81, H 6.59, N 8.99.
Divalent amide 19

According to GP-1, protected serinol 16 (200 mg, 0.626 mmol) was dissolved in CH$_2$Cl$_2$ (5.4 mL) and the solution was cooled to 0 °C. After addition of Et$_3$N (0.17 mL, 1.25 mmol) and sebacoyl chloride (8, 90 mg, 0.38 mmol) the reaction mixture was stirred at 0 °C for 1 h and at rt for 18 h. H$_2$O (10 mL) was added to the reaction mixture and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 20 mL). The combined organic layers were dried with Na$_2$SO$_4$ and the solvents removed in vacuo. The crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc, 5:1) affording 19 (190 mg, 75%) as colorless solid.

m.p. 75 °C; $^1$H NMR (500 MHz, CDCl$_3$): δ = 0.05, 0.06 (2 s, 12 H each, CH$_3$), 0.89 (s, 36 H, tBu), 1.29 (bs, 8 H, CH$_2$), 1.58 – 1.61 (m, 4 H, CH$_2$), 2.12 – 2.17 (m, 4 H, CH$_2$), 3.52 (dd, J = 6.4, 9.6 Hz, 4 H, 2-H), 3.73 (dd, J = 3.6, 9.6 Hz, 4 H, 2-H), 3.92 – 3.98 (m, 2 H, 1-H), 5.73 (d, J = 8.2 Hz, 2 H, NH) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ = -5.4, -5.3 (q, SiCH$_3$), 18.3 [s, SiC(CH$_3$)$_3$], 25.8 (t, CH$_2$), 25.9 [q, SiC(CH$_3$)$_3$], 29.2, 29.3, 37.0 (3 t, CH$_2$), 51.4 (d, C-1), 60.6 (t, C-2), 172.6 (s, C=O) ppm; IR (ATR): $\tilde{\nu}$ = 3290 (N-H), 2955-2855 (C-H), 1640 (C=O), 1250 (C-O) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd. for C$_{40}$H$_{88}$N$_2$NaO$_6$Si$_4$ [M + Na]$^+$: 827.5606; found: 827.5625; Elemental analysis calcd. (%) C$_{40}$H$_{88}$N$_2$O$_6$Si$_4$ (805.5) + 1 H$_2$O: C 58.34, H 11.02, N 3.40; found: C 58.37, H 9.73, N 3.22.
Divalent amide 22

According to GP-4, to a stirred solution of 19 (200 mg, 0.248 mmol) in isopropanol (0.9 mL), AcCl (10.6 μL, 0.160 mmol) was added at 0 °C. The reaction mixture was stirred at rt for 2.5 h. All volatiles were removed in vacuo affording 22 (88 mg, quant.) as a colorless solid.

m.p. 170 − 171 °C; 1H NMR (500 MHz, DMSO-d₆): δ = 1.20 − 1.25 (m, 8 H, CH₂), 1.43 − 1.50 (m, 4 H, CH₂), 2.06 (t, J = 7.5 Hz, 4 H, CH₂), 3.37 (bd, J = 5.7 Hz, 8 H, 2-H), 3.62 − 3.73 (m, 2 H, 1-H), 4.57 (bs, 4 H, OH), 7.43 (d, J = 8.1 Hz, 2 H, NH) ppm; 13C NMR (125 MHz, DMSO-d₆): δ = 25.3, 28.6, 28.7, 35.4 (4 t, CH₂), 52.7 (d, C-1), 60.2 (t, C-2), 172.1 (s, C=O) ppm; IR (ATR): ν = 3300 (O-H, N-H), 2920-2850 (C-H), 1640 (C=O), 1255 (C-O) cm⁻¹; HRMS (ESI-TOF): m/z calcd. for C₁₆H₃₆N₂NaO₆ [M + Na]⁺: 371.2153; found: 371.2154; Elemental analysis calcd. (%) C₁₆H₃₆N₂O₆ (348.4): C 55.15, H 9.26, N 8.04; found: C 55.01, H 9.31, N 7.88.

Divalent amide 20

According to GP-1, protected serinol 16 (2.00 g, 6.26 mmol) was dissolved in CH₂Cl₂ (54 mL) and the solution was cooled to 0 °C. After addition of Et₃N (1.75 mL, 12.5 mmol) and adipoyl chloride (17, 687 mg, 3.75 mmol) the reaction mixture was stirred at 0 °C for 1 h and at rt for 17 h. H₂O (100 mL) was added to the reaction and the
aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 200 mL). The combined organic layers were dried with Na$_2$SO$_4$ and the solvents removed in vacuo. The crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc, 5:1) affording 20 (1.45 g, 62%) as colorless solid.

m.p. 101 °C; $^1$H NMR (500 MHz, CDCl$_3$): δ = 0.04, 0.05 (2 s, 12 H each, CH$_3$), 0.88 (s, 36 H, tBu), 1.61 – 1.68 (m, 4 H, CH$_2$), 2.16 – 2.19 (m, 4 H, CH$_2$), 3.52 (dd, J = 6.4, 9.6 Hz, 4 H, 2-H), 3.72 (dd, J = 3.7, 9.6 Hz, 4 H, 2-H), 3.94 (m, 2 H, 1-H), 5.77 (d, J = 8.5 Hz, 2 H, NH) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$): δ = -5.35, -5.27 (2 q, SiCH$_3$), 18.4 [s, SiC(CH$_3$)$_3$], 25.3 (t, CH$_2$), 26.0 [q, SiC(CH$_3$)$_3$], 36.5 (t, CH$_2$), 51.6 (d, C-1), 60.6 (t, C-2), 172.2 (s, C=O) ppm; IR (ATR): ν = 3295 (N-H), 2960-2855 (C-H), 1710 (C=O), 1250 (C-O) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd. for C$_{36}$H$_{80}$N$_2$NaO$_6$Si$_4$ [M + Na]$^+$: 771.4986; found: 771.4960; Elemental analysis calcd. (%) C$_{36}$H$_{80}$N$_2$O$_6$Si$_4$ (749.4): C 57.70, H 10.76, N 3.74; found: C 57.88, H 10.63, N 3.71.

**Divalent amide 23**

![Divalent amide 23](image)

According to GP-4, to a stirred solution of 20 (200 mg, 0.267 mmol) in 2-propanol (0.9 mL), AcCl (11.4 μL, 0.160 mmol) was added at 0 °C. The reaction mixture was stirred at rt for 1 h and 40 min. All volatiles were removed in vacuo affording 23 (76 mg, 97%) as a colorless solid.

m.p. 174 – 175 °C; $^1$H NMR (500 MHz, DMSO-d$_6$): δ = 1.42 – 1.47 (m, 4 H, CH$_2$), 2.07 (t, J = 6.6 Hz, 4 H, CH$_2$), 3.38 (d, J = 5.7 Hz, 8 H, 2-H), 3.65 – 3.72 (m, 2 H, 1-H), 4.27 (bs, 4 H, OH), 7.45 (d, J = 8.1 Hz, 2 H, NH) ppm; $^{13}$C NMR (125 MHz, DMSO-d$_6$): δ = 25.0, 35.2 (2 t, CH$_2$), 52.8 (d, C-1), 60.2 (t, C-2), 172.0 (s, C=O) ppm;
IR (ATR): $\tilde{\nu} = 3295$ (O-H, N-H), 2965-2855 (C-H), 1635 (C=O), 1260 (C-O) cm$^{-1}$;


Divalent amide 25

According to GP-2, aminopyran 1 (50 mg, 0.24 mmol), succinic acid 24 (11 mg, 0.97 mmol) and HATU (93 mg, 0.24 mmol) were dissolved in DMF (2.0 mL). After addition of Et$_3$N (0.4 mL, 2.8 mmol), the reaction mixture was stirred at rt under argon atmosphere. After 24 h the solvent was removed in vacuo. The crude product was purified by flash column chromatography on silica gel (DCM/MeOH 9:1 to 4:1) affording 25 (35 mg, 73%) as a colorless solid.

Melting range: 185 – 201 °C; $\left[\alpha\right]_{D}^{22} = +47.2$ (c = 1.40, MeOH); $^1$H NMR (500 MHz, CD$_3$OD): $\delta$ = 1.21, 1.40 (2 s, 6 H each, CH$_3$), 1.77 – 1.81 (m, 2 H, 5-H), 2.54 (bs, 4 H, CH$_2$), 3.48 (d, $J = 6.1$ Hz, 4 H, 2-CH$_2$), 3.66 (dd, $J = 5.5$, 11.2 Hz, 2 H, 5-CH$_2$), 3.79 – 3.83 (m, 4 H, 5-CH$_2$, 4-H), 3.92 (dd, $J = 3.9$, 5.2 Hz, 2 H, 3-H), 4.06 (dt, $J = 3.9$, 6.1 Hz, 2 H, 2-H) ppm; $^{13}$C NMR (125 MHz, CD$_3$OD): $\delta$ = 25.5, 27.3 (2 q, CH$_3$), 32.1 (t, CH$_2$), 49.4 (d, C-5), 55.2 (d, C-3), 62.7 (t, 2-CH$_2$), 62.8 (t, 5-CH$_2$), 71.0 (d, C-2), 73.1 (d, C-4), 76.0 (s, C-6), 175.2 (C=O) ppm; IR (ATR): $\tilde{\nu} = 3410$-3260 (O-H, N-H), 2970-2890 (C-H), 1640 (C-O), 1075 (C-O-C) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd. for $\text{C}_{22}\text{H}_{40}\text{N}_{2}\text{NaO}_{10}$ [M + Na]$^+$: 515.2575; found: 515.2599.
Trivalent amide 27

According to GP-2, aminopyran 1 (50 mg, 0.24 mmol), acid 26 (27 mg, 61 μmol) and HATU (93 mg, 0.24 mmol) were dissolved in DMF (2.0 mL). After addition of Et₃N (0.6 mL, 4.4 mmol), the reaction mixture was stirred at rt for 24 h. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (silica gel, CH₂Cl₂/MeOH 6:1 to 4:1) affording 27 (49 mg, 80%) as a colorless solid.

m.p. 245 °C; [α]₂²₂ = +150.5 (c = 0.74, MeOH); ¹H NMR (700 MHz, CD₃OD): δ = 1.34, 1.47 (2 s, 9 H each, CH₃), 1.80 (td, J = 4.8, 10.0 Hz, 3 H, 5-H), 3.56, 3.61 (AB part of ABX system, J₅₋₆ = 11.7 Hz, J₆₋₇ = 4.6 Hz, J₅₋₇ = 6.6 Hz, 3 H each, 2-CH₂), 3.71, 4.00 (2 dd, J = 4.8, 11.1 Hz, 3 H each, 5-CH₂), 4.02 – 4.05 (m, 3 H, 4-H), 4.20 – 4.25 (m, 6 H, 2-H, 3-H), 7.76 (d, J = 8.3 Hz, 6 H, Ar), 7.82 (s, 3 H, Ar), 7.94 (d, J = 8.3 Hz, 6 H, Ar) ppm; ¹³C NMR (175 MHz, CD₃OD): δ = 26.3, 27.7 (2 q, CH₃), 49.9 (d, C-5), 54.2 (d, C-2), 63.2 (t, 2-CH₂), 63.3 (t, 5-CH₂), 70.9 (d, C-3), 74.1 (d, C-4), 75.9 (s, C-6), 126.6, 128.4, 129.2 (3 d, Ar), 134.6, 142.8, 145.0 (3 s, Ar), 170.1 (s, C=O) ppm; IR (ATR): v = 3320 (O-H, N-H), 2970-2920 (C-H), 1630 (C=O), 1440 (C=C), 1230 (C-O),
1085 (C-O-C) cm⁻¹; HRMS (ESI-TOF): m/z calcd. for C₅₄H₆₉N₃NaO₁₅ [M + Na]⁺: 1022.4615; found: 1022.4612.

**Trivalent amide 29**

According to GP-2, aminopyran 3 (87 mg, 159 µmol), 3,3',3''-nitrilotripropanoic acid 28 (9 mg, 39 µmol) and HATU (60 mg, 159 µmol) were dissolved in DMF (2.8 mL). After addition of Et₃N (0.1 mL, 0.7 mmol), the reaction mixture was stirred at rt for 24 h. Saturated NaHCO₃ solution (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with saturated NaCl solution, dried with Na₂SO₄ and the solvent was removed in vacuo. The crude product was purified by flash column chromatography (silica gel, hexanes, hexanes/EtOAc 10:1 to 6:1) affording 29 (60 mg, 83%) as a colorless oil.

\[ \alpha \] D 22 = +10.8 (c = 2.56, CHCl₃); ¹H NMR (700 MHz, CDCl₃): δ = 0.01 – 0.03 (m, 36 H, CH₃), 0.09 (s, 9 H, CH₃), 0.16 (s, 9 H, CH₃), 0.85 – 0.88 (m, 54 H, t-Bu), 0.89 (s, 27 H, t-Bu), 1.17, 1.47 (2 s, 9 H each, CH₃), 1.61 (m, 3 H, 5-H), 2.32 (t, J = 7.4 Hz, 6 H, CH₂CO), 2.73 (td, J = 7.4, 14.1 Hz, 3 H, NCH₂), 2.82 (td, J = 7.4, 14.1 Hz, 3 H, NCH₂), 3.45 (dd, J = 8.0, 10.2 Hz, 3 H, 5-CH₂), 3.52, 3.57 (AB part of ABX system, JAB = 10.5 Hz, JAB = JBX = 6.1 Hz, 3 H each, 2-CH₂), 3.70 – 3.76 (m, 6 H, 5-CH₂, 3-H), 4.16 (dt, J = 1.7, 6.1 Hz, 3 H, 2-H), 4.22 (m, 3 H, 4-H), 6.30 (d, J = 8.5 Hz, 3 H, NH)
ppm; $^{13}$C NMR (175 MHz, CDCl$_3$): $\delta = -5.14, -5.11, -5.09, -5.00, -4.97, -4.65$ (6 q, CH$_3$), 18.0, 18.2, 18.3 [3 s, SiC(CH$_3$)$_3$], 25.9, 26.0, 26.0 [3 q, SiC(CH$_3$)$_3$], 27.4, 28.0 (2 q, CH$_3$), 33.3 (t, CH$_2$CO), 49.0 (t, NCH$_2$), 49.5 (d, C-5), 50.2 (d, C-3), 62.6 (t, 5-CH$_2$), 63.3 (t, 2-CH$_2$), 67.7 (d, C-2), 68.7 (d, C-4), 74.3 (s, C-6), 171.0 (s, C=O) ppm.

IR (ATR): $\tilde{\nu}$ = 3440 (N-H), 2960-2855 (C-H), 1660, 1505 (C=O), 1245 (C -O-C) cm$^{-1}$;

HRMS (ESI-TOF): m/z calcd. for C$_{90}$H$_{193}$N$_4$O$_{15}$Si$_9$ [M + H]$^+$: 1822.2387; found: 1822.2400; calcd. for C$_{90}$H$_{192}$N$_4$NaO$_{15}$Si$_9$ [M + Na]$^+$: 1844.2206; found: 1844.2203;

Elemental analysis calcd. (%) C$_{90}$H$_{192}$N$_4$O$_{15}$Si$_9$ (1823.3): C 59.29, H 10.61, N 3.07; found: C 59.74, H 10.49, N 2.97.

Sulfated divalent amide 31

According to **GP-5**, polyol 13 (15 mg, 0.028 mmol), SO$_3$·DMF (97%, 77 mg, 0.50 mmol) and DMF-$d_7$ (0.6 mL) were stirred overnight. According to **method A**, 1 M NaOH was added dropwise until pH 10 was reached. The solvents were removed in vacuo and the crude product was purified twice by dialysis (tube width: 10–16 mm, molecular weight cut off: 100–500 Da) affording 31 (19 mg, 60%) as a colorless solid. m.p. 275 °C (decomposition); $[\alpha]^{22}_D = +33.7$ (c = 0.08, H$_2$O); $^1$H NMR (700 MHz, D$_2$O):

$\delta = 1.36, 1.52$ (2 s, 6 H each, CH$_3$), 2.53 (td, $J = 7.6, 14.3$ Hz, 2 H, 5-H), 4.09, 4.19 (AB part of ABX system, $J_{AB} = 10.9$ Hz, $J_{AX} = 4.3$ Hz, $J_{BX} = 7.5$ Hz, 2 H each, 2-CH$_2$), 4.25, 4.32 (AB part of ABX system, $J_{AB} = 10.5$ Hz, $J_{AX} = 6.3$ Hz, $J_{BX} = 7.9$ Hz, 2 H...
each, 5-CH$_2$), 4.53 – 4.57 (m, 2 H, 3-H), 4.57 – 4.62 (m, 2 H, 2-H), 4.69 – 4.76 (m, 2 H, 4-H), 7.88 (s, 4 H, Ar) ppm; $^{13}$C NMR (175 MHz, D$_2$O): $\delta = 24.8, 26.4$ (2 q, CH$_3$), 44.2 (d, C-5), 52.3 (d, C-2), 67.3 (t, 2-CH$_2$), 67.6 (t, 5-CH$_2$), 67.7 (d, C-3), 76.2 (d, C-4), 76.6 (s, C-6), 128.7 (d, Ar) ppm; signals for C=O and Ar singlet could not be detected; IR (ATR): $\tilde{\nu} = 3480$ (N-H), 2985 (C-H), 1535 (C=C), 1635 (C=O), 1255 (C-O), 1130 (SO$_3$Na$^+$) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd. for C$_{26}$H$_{34}$N$_2$Na$_7$O$_{28}$S$_6$ [M + Na]$^+$: 1174.8906; found: 1174.8819.

**Sulfated divalent amide 32**

![Sulfated divalent amide 32](image)

According to **GP-5**, polyol 21 (20 mg, 0.064 mmol), SO$_3$·DMF (118 mg, 0.770 mmol) and DMF-$d_7$ (0.6 mL) were stirred overnight. After $^1$H NMR control, the reaction mixture was stirred for 4 d and each day a new portion of SO$_3$·DMF (118 mg) was added. According to **method A**, 1 M NaOH was added dropwise until pH 12 was reached. The solvents were removed in vacuo and the crude product was purified by dialysis (tube width: 10–16 mm, molecular weight cut off: 100–500 Da) affording 32 (32 mg, 69%) as a colorless solid.

m.p. 215 – 217 °C (decomposition); $^1$H NMR (500 MHz, D$_2$O): $\delta = 4.20, 4.23$ (AB part of ABX system, $J_{AB} = 9.7$ Hz, $J_{AX} = 4.1$ Hz, $J_{BX} = 5.0$ Hz, 4 H each, 2-H), 4.58 – 4.63 (m, 2 H, 1-H), 7.81 (s, 4 H, Ar) ppm; $^{13}$C NMR (125 MHz, D$_2$O): $\delta = 49.0$ (d, C-1), 66.7 (t, C-2), 127.9 (d, Ar), 136.9 (s, Ar), 170.6 (s, C=O) ppm; IR (ATR): $\tilde{\nu} = 3375$ (N-H), 2985 (C-H), 1535 (C=C), 1645 (C=O), 1290 (C=O), 1130 (SO$_3$Na$^+$) cm$^{-1}$; HRMS (ESI-TOF): m/z calcd. for C$_{14}$H$_{16}$N$_2$Na$_5$O$_{18}$S$_4$ [M + Na]$^+$: 742.8758; found: 742.8763
Sulfated divalent amide 33

According to **GP-5**, polyol 22 (20 mg, 0.057 mmol), SO₃∙DMF (106 mg, 0.689 mmol) and DMF--d₇ (0.6 mL) were stirred overnight. According to **method A**, 1 M NaOH was added dropwise until pH 12 was reached. The solvents were removed in vacuo and the crude product was purified by dialysis (tube width: 10–16 mm, molecular weight cut off: 100–500 Da) affording 33 (34 mg, 79%) as a colorless solid.

Melting range: 200 – 205 °C (decomposition); ¹H NMR (500 MHz, D₂O): δ = 1.36 (bs, 8 H, CH₂), 1.61 – 1.69 (m, 4 H, CH₂), 2.34 (t, J = 7.4 Hz, 4 H, CH₂), 4.17, 4.20 (AB part of ABX system, JₐB = 9.0 Hz, JₐX = 3.6 Hz, JₐX = 4.3 Hz, 4 H each, 2-H), 4.47 (m, 2 H, 1-H) ppm; ¹³C NMR (125 MHz, D₂O): δ = 25.6, 28.4, 28.5, 36.1 (4 t, CH₂), 48.2 (d, C-1), 66.9 (t, C-2), 177.8 (s, C=O) ppm; IR (ATR): ν = 3385 (N-H), 2980 (C-H), 1640 (C=O), 1255 (C-O), 1130 (SO₃Na⁺) cm⁻¹ HRMS (ESI-TOF): m/z calcd. for C₁₆H₂₈N₃Na₅O₁₈S₄ [M + Na]⁺: 778.9703; found: 778.9682.
Sulfated trivalent amide 34

According to GP-5, polyol 27 (32 mg, 0.032 mmol), SO$_3$·DMF (97%, 136 mg, 0.864 mmol) and DMF-$d_7$ (0.7 mL) were stirred overnight. After $^1$H NMR control, the reaction mixture was stirred for 2 d and each day a new portion of SO$_3$·DMF (136 mg) was added. According to method B, NaOH 0.5 M was added dropwise until pH 9 was reached. The reaction mixture was filtrated through an ion exchange DOWEX$^\text{®}$ Na$^+$ column. The solvents were removed in vacuo and the crude product was purified by dialysis (tube width: 10–16 mm, molecular weight cut off: 500–1000 Da). The final product was filtrated through a syringe filter affording 34 (51 mg, 84%) as a colorless solid.

m.p. 260 °C (decomposition); $[\alpha]_D^{22} = +23.4$ (c = 0.5, H$_2$O); $^1$H NMR (700 MHz, D$_2$O): δ = 1.41, 1.55 (2 s, 9 H each, CH$_3$), 2.56 (m, 3 H, 5-H), 4.14 (A part of ABX system, $J_{AB} = 10.2$ Hz, $J_{AX} = 7.8$ Hz, 3 H, 2-CH$_2$), 4.23 – 4.26 (m, 3 H, 2-CH$_2$), 4.27 – 4.30 (m, 3 H, 5-CH$_2$), 4.36 – 4.38 (m, 3 H, 5-CH$_2$), 4.61 (m, 3 H, 2-H), 4.62 – 4.66 (m, 3 H, 3-H), 8.00 (s, 12 H, Ar), 8.17 (s, 3 H, Ar) ppm; the signal of 4-H could not be detected (overlapping with D$_2$O peak ≈ 4.77 ppm); $^{13}$C NMR (175 MHz, D$_2$O): δ = 24.2, 26.0 (2
q, CH₃), 43.9 (d, C-5), 52.0 (d, C-2), 67.1 (t, 5-CH₂), 67.4 (t, 2-CH₂), 67.5 (d, C-3),
76.3 (d, C-4), 76.4 (s, C-6), 125.8, 127.4, 128.2 (3 d, Ar), 132.9, 141.3, 143.7 (3 s, Ar), 171.0 (s, C=O) ppm; IR (ATR): ̇ν = 3460 (N-H), 2960 (C-H), 1535 (C=C), 1635
(C=O), 1220 (C-O), 1130 (SO₃Na⁺) cm⁻¹; HRMS (ESI-TOF): m/z cald. for
$^1$H NMR (500 MHz, CDCl$_3$):

$^{13}$C NMR (125 MHz, CDCl$_3$):
$^1$H NMR (700 MHz, CD$_3$OD):

13

$^{13}$C NMR (175 MHz, CD$_3$OD):

13
$^1$H NMR (500 MHz, CDCl$_3$):

$^{13}$C NMR (125 MHz, CDCl$_3$):
$^1$H NMR (500 MHz, CDCl$_3$):

$^{13}$C NMR (125 MHz, CDCl$_3$):
$^1$H NMR (500 MHz, CDCl$_3$):

$^{13}$C NMR (125 MHz, CDCl$_3$):
$^1$H NMR (500 MHz, DMSO-$d_6$):

\[
\begin{align*}
\text{HO} & \quad \text{NH} & \quad \text{O} \\
\text{HO} & \quad \text{O} & \quad \text{HN} & \quad \text{OH} \\
\end{align*}
\]

$^{13}$C NMR (125 MHz, DMSO-$d_6$):

\[
\begin{align*}
\text{HO} & \quad \text{NH} & \quad \text{O} \\
\text{HO} & \quad \text{O} & \quad \text{HN} & \quad \text{OH} \\
\end{align*}
\]
$^1$H NMR (500 MHz, CDCl$_3$):

$^{13}$C NMR (125 MHz, CDCl$_3$):
$^1$H NMR (500 MHz, CDCl$_3$):

$^{13}$C NMR (125 MHz, CDCl$_3$):
$^1$H NMR (700 MHz, CDCl$_3$):

$^{13}$C NMR (175 MHz, CDCl$_3$):
$^1$H NMR (700 MHz, D$_2$O):

$^{13}$C NMR (175 MHz, D$_2$O):
\(^1\)H NMR (500 MHz, D\(_2\)O):

\[ \text{Diagram of } ^1\text{H NMR} \]

\(^{13}\)C NMR (125 MHz, D\(_2\)O):

\[ \text{Diagram of } ^{13}\text{C NMR} \]
$^1$H NMR (500 MHz, D$_2$O):

$^{13}$C NMR (125 MHz, D$_2$O):
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**Dose Response Curve**

- **L-Selectin [binding in % of control]**
- **[nM]**

![Dose Response Curve Diagram](image)
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![Dose Response Curve](image)