Crown Ethers as Building Blocks for Carbohydrate Receptors

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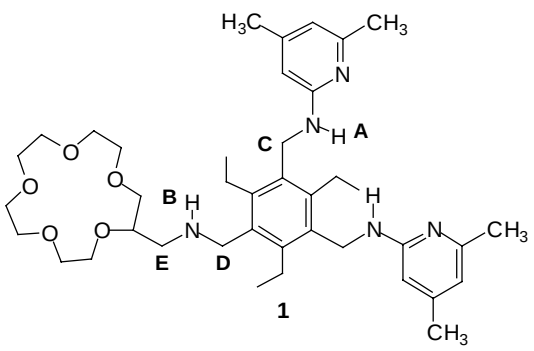
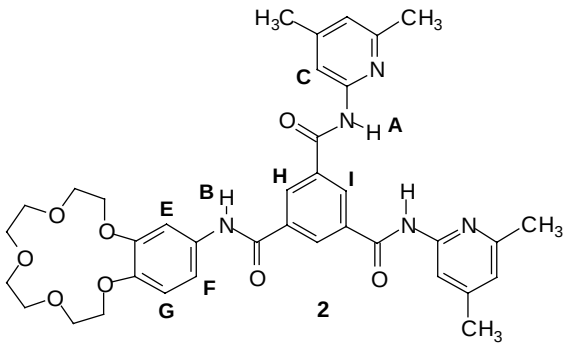


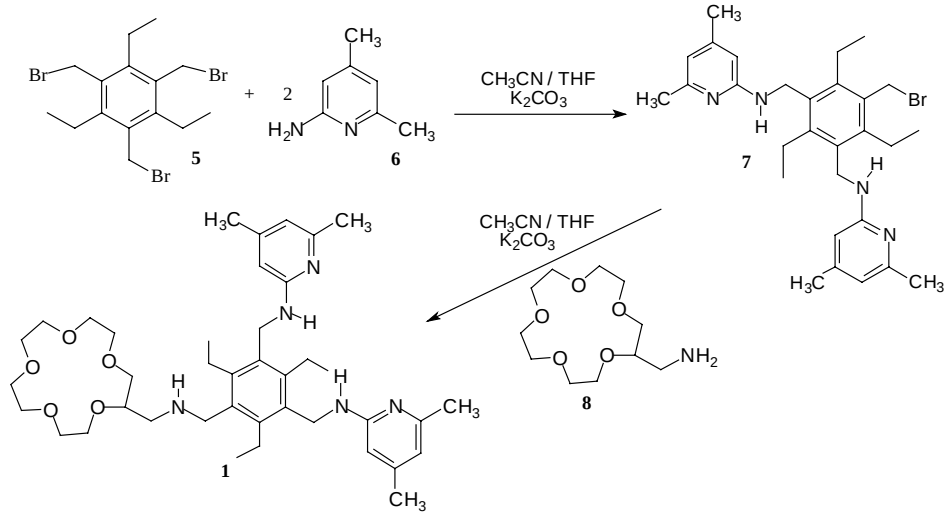


1 Syntheses of the receptors 1 and 2.

1.1 Synthesis of the receptor 1.

The synthesis of **1** started from 1,3,5-tris(bromomethyl)-2,4,6-trimethyl-benzene (**5**), which was converted into the compound **7** *via* reaction with two equivalents of 2-amino-4,6-dimethyl-pyridine (**6**), followed by the reaction with one equivalent of 2-aminomethyl-15-crown-5 (**8**), as shown in Scheme S1.

SCHEME S1



Compound 7. To a mixture of 1,3,5-tris(bromomethyl)-2,4,6-trimethyl-benzene (3.00 g, 6.80 mmol) and K_2CO_3 (1.88 g, 13.60 mmol) in CH_3CN/THF (1:1 v/v; 40 mL) was added dropwise a CH_3CN (10 mL) solution of 2-amino-4,6-dimethyl-pyridine (1.66 g, 13.60 mmol).The mixture was stirred at room temperature for 72 h. After filtration and evaporation of solvents, the crude product was purified by column chromatography (ethyl acetate/toluene, 1:3 v/v). Yield 30 %. M.p. 77-78 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.22 (t, 3H, *J* = 7.5 Hz), 1.29 (t, 6H, *J* = 7.5 Hz), 2.24 (s, 6H), 2.36 (s, 6 H), 2.73 (q, 2H, *J* = 7.5 Hz), 2.85 (q, 4H, *J* = 7.5 Hz), 4.23 (t, 2H, *J* = 4.2 Hz), 4.37 (d, 4H, *J* = 4.2 Hz), 4.62 (s, 2 H), 6.10 (s, 2 H), 6.35 (s, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 16.4, 16.7, 21.1, 22.8, 23.0, 24.1, 29.6, 40.5, 103.6, 113.9, 131.9, 133.4, 143.8, 144.9, 148.9, 156.5, 158.0. HR-MS calcd for $C_{29}H_{39}BrN_4$ 5232.2353; found: 522.2360. R_f = 0.31 (ethyl acetate/toluene, 1:3 v/v).

Receptor 1. To a mixture of compound **7** (262.5 mg, 0.50 mmol) and K_2CO_3 (69.3 mg, 0.50 mmol) in CH_3CN/THF (1:1 v/v; 20 mL) was added dropwise a CH_3CN (10 mL) solution of 2-aminomethyl-15-crown-5 (125 mg, 0.50 mmol).The mixture was stirred at room temperature for 48 h. After filtration and evaporation of solvents, the crude product was purified by column chromatography (chloroform/methanol 7:1 v/v). Yield 62 %. M.p. 57-58 °C. ^{1}H-NMR (500 MHz, $CDCl_3$, [**1**] = 0.9 mM) δ = 1.23 (t, 9H, *J* = 7.6 Hz), 2.23 (s, 6 H), 2.35 (s, 6 H), 2.77 (m, 7 H), 3.70 (m, 23 H), 4.25 (br. s, 2 H) 4.36 (d, 4H, *J* = 4.0 Hz), 6.08 (s, 2 H), 6.33 (s, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 16.8, 16.9, 21.1, 22.8, 24.1, 40.6, 47.8, 52.1, 70.1, 70.4, 70.5, 70.6, 70.8, 70.9, 71.0, 72.9, 78.7, 103.5, 113.8, 132.7, 142.9, 143.2, 148.8, 156.5, 158.2, 162.7. HR-MS calcd for $C_{40}H_{61}N_5O_5$ 691.4667; found: 691.4671. R_f = 0.10 (chloroform/methanol, 7:1 v/v).

1.2 Synthesis of the receptor 2.

To a solution of benzene-1,3,5-tricarbonyl chloride (187.4 mg, 0.70 mmol) in dry CH_2Cl_2 (10 ml) was added a CH_2Cl_2 (10 mL) solution of 4'-aminobenzo-15-crown-5 (200 mg, 0.70 mmol) and triethylamine (0.1 mL). The reaction mixture was stirred at room temperature for 45 min and then a CH_2Cl_2 (10 mL) solution of 2-amino-4,6-dimethylpyridine (172.5 mg, 1.41 mmol) was added. The mixture was stirred at room temperature for 72 h. The organic phase was washed three times with water (3 x 10 mL), dried, and the solvent was evaporated. The crude product was was purified by column chromatography (chloroform/methanol 7:1 v/v). Yield 41 %. M.p. 200 °C (decomp.). ^{1}H-NMR (500 MHz, $CDCl_3$; [**2**] = 0.9 mM) δ = 2.38 (s, 6H), 2.45 (s, 6H), 3.77 (br.s, 8H), 3.92 (m, 4H), 4.16 (m, 2H), 4.21 (m, 2H), 6.82 (s, 2H), 6.90 (d, 1H, *J* = 8.5 Hz), 7.10 (dd, 1H, *J* = 8.5/2.2 Hz), 7.47 (d, 1H, *J* = 2.2 Hz), 7.99 (s, 1H), 8.02 (s, 2H), 8.63 (s, 2H), 8.65 (s, 1H), 8.67 (s, 2H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 21.3, 23.7, 68.7, 69.4, 69.5, 69.6, 70.4, 70.5, 70.9, 107.3, 112.0, 113.1, 114.6, 121.0, 128.9, 129.1, 131.9, 135.4, 136.2, 149.2, 150.3, 150.4, 156.6, 163.6, 163.9. HR-MS calcd for $C_{37}H_{41}N_5O_8$ 683.2950; found: 683.2958. R_f = 0.66 (chloroform/methanol 7:1 v/v).

2. ^{1}H NMR titration of **1** with β-glucopyranoside **3a** (chemical shifts of the CH_3 and the pyridine CH protons).

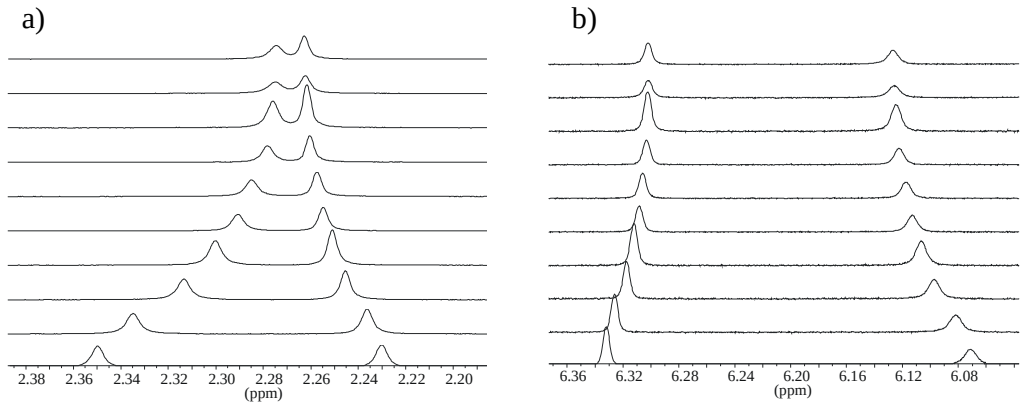


FIGURE S1. Partial ^{1}H NMR spectra (500 MHz, $CDCl_3$, 25 °C) of **1** after addition of (from bottom to top) 0, 0.27, 0.55, 0.83, 1.11, 1.38, 2.08, 2.77, 3.47 and 4.16 equiv of **3a** ([**1**] = 0.87 mM). (a) Chemical shifts of the CH_3 resonances. (b) Chemical shifts of the pyridine CH resonances.

3. ^{1}H NMR titration of **1** with α-glucopyranoside **4a** (chemical shifts of the CH_3 and the pyridine CH protons).

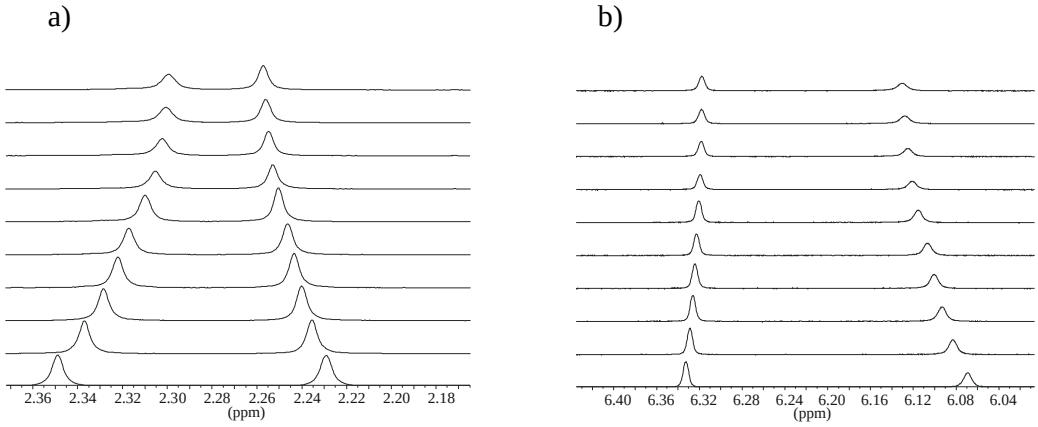


FIGURE S2. Partial ^{1}H NMR spectra (500 MHz, $CDCl_3$, 25 °C) of **1** after addition of (from bottom to top) 0, 0.44, 0.88, 1.33, 1.77, 2.66, 3.55, 4.44, 5.33 and 6.22 equiv of **4a** ([**1**] = 0.85 mM). (a) Chemical shifts of the CH_3 resonances. (b) Chemical shifts of the pyridine CH resonances.

4. ^{1}H NMR titration of **1** with β- and α-glucopyranoside, **3a** and **4a** (typical titration curves).

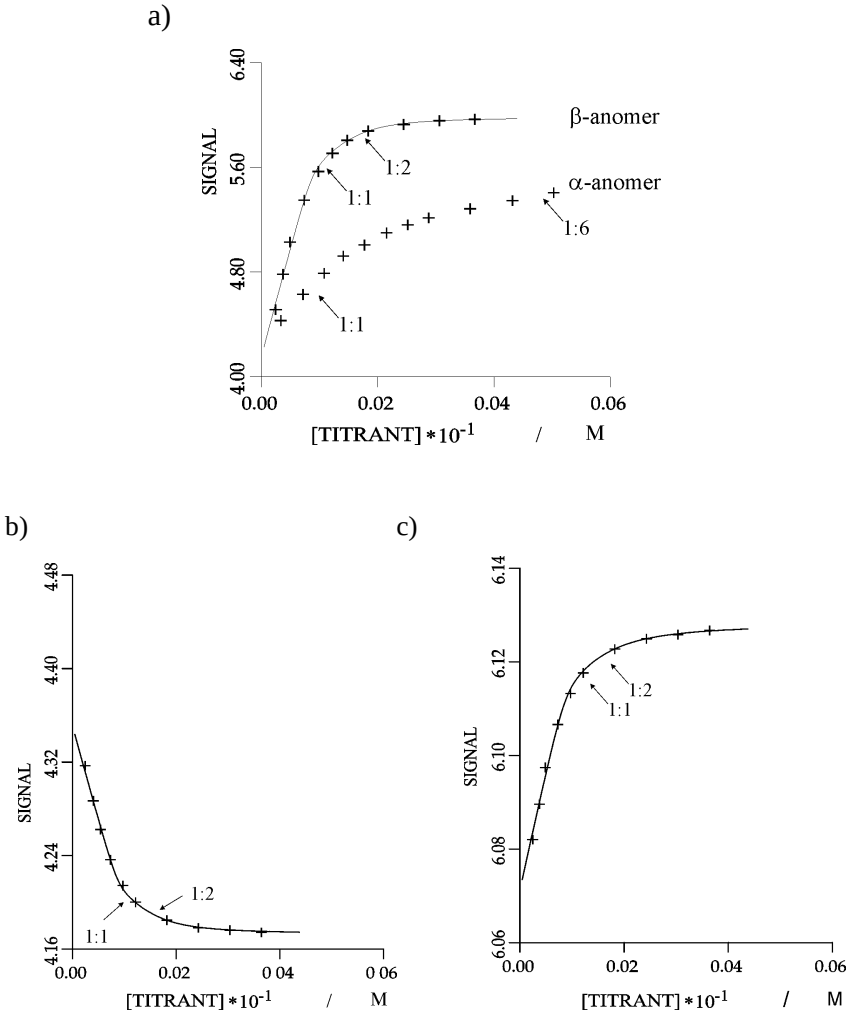


FIGURE S3. Plot of the downfield chemical shifts of the NH^{A}, resonances of **1** as a function of added β- and α-glucopyranoside, **3a** and **4a** (a) ([**1**] = 0.87 mM; Equiv of **3a** = 0.00-3.47; Equiv of **4a** = 0.00-6.22). Plot of the observed upfield chemical shifts of the $CH_2{}^{C}$ (b) and downfield chemical shifts of the pyr-CH resonances (c) of **1** as a function of added β-glucopyranoside **3a** ([**1**] = 0.87 mM; Equiv of **3a** = 0.00-4.18). The [receptor]:[sugar] ratio is marked.

5. Extraction of β- and α-methyl-glucopyranoside (**3b** and **4b**) from the solid state into a $CDCl_3$-solution of receptor **1.**

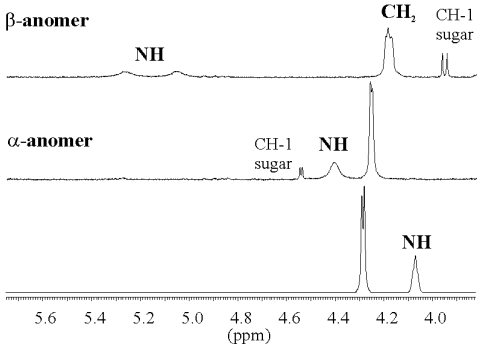


FIGURE S4. ^{1}H NMR spectra showing the NH and the CH_2 protons of receptor **1** before and after the extraction of solid methyl-α-glucopyranoside **4b** or methyl-β-glucopyranoside **3b** by a $CDCl_3$-solution of receptor **1** (0.9 mM).

6 ^{1}H NMR Titration of receptor **2** with α-glucopyranoside **4a** (chemical shifts of the CH_3 and CH resonances, protons C, E, H, and I).

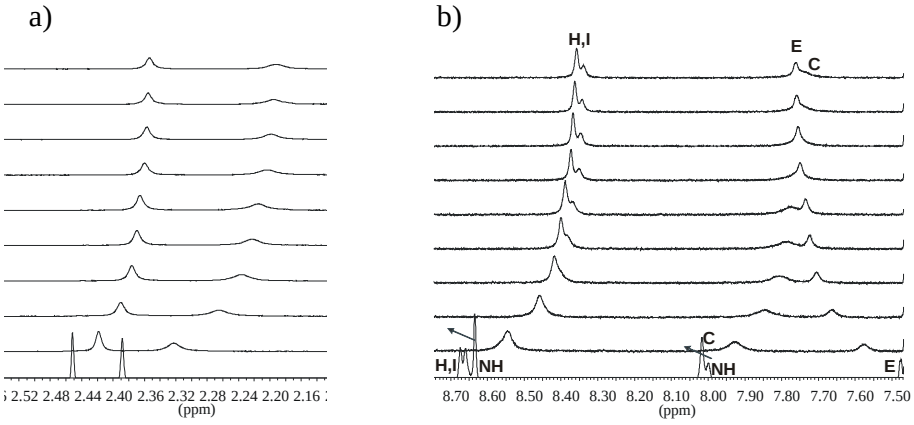


FIGURE S5. Partial ^{1}H NMR spectra (500 MHz, $CDCl_3$, 25 °C) of **2** after addition of (from bottom to top) 0, 0.20, 0.40, 0.60, 0.80, 1.00, 1.50, 2.00, 2.50 and 3.01 equiv of **4a** ([**1**] = 0.87 mM). (a) Chemical shifts of the CH_3 resonances. (b) Chemical shifts of the CH resonances, protons C, E, H, and I.

7. ^{1}H NMR titration of **2** with α-glucopyranoside **4a** in $CDCl_3$ (typical titration curve and a representative mole ratio plot).

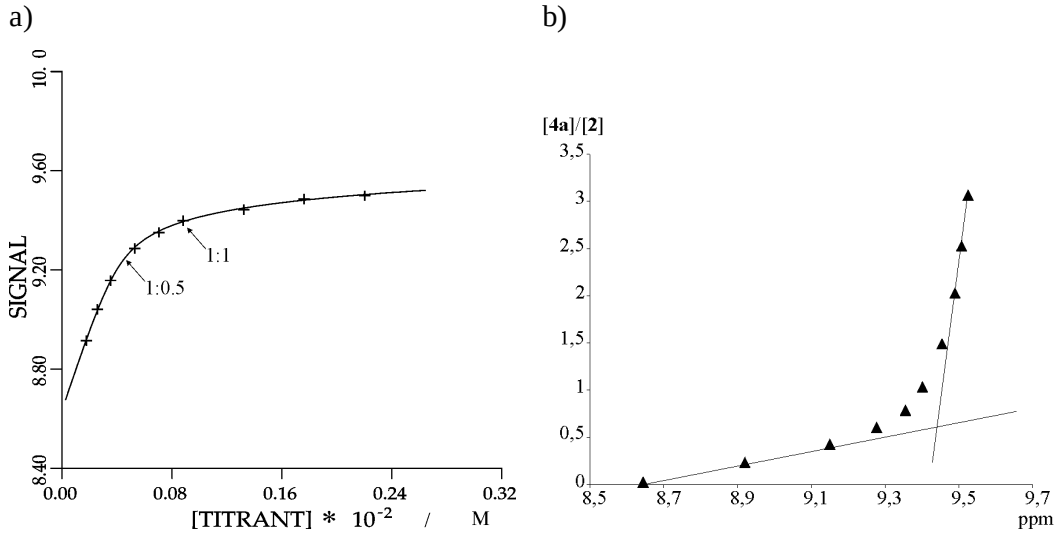


FIGURE S6. (a) Plot of the observed (**x**) and calculated (—) downfield chemical shifts of the NH^A resonances of **2** as a function of added α-glucopyranoside **4a**; [**2**] = 0.88 mM; Equiv of **4a** = 0, 0.20, 0.30, 0.40, 0.60, 0.80, 1.00, 1.50, 2.00, 2.50. The [receptor]:[sugar] ratio is marked. (b) Mole ratio plot (analysis of the shifts of the NH^A of **2**).