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PAPER

8-Hydroxyquinoline as a building block for artificial receptors: binding preferences in the recognition of glycopyranosides†

Monika Mazik* and Christoph Geffert

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8-Hydroxyquinoline-based receptors **1–3**, containing a trisubstituted triethylbenzene core, were prepared and their binding properties towards glycosides were evaluated. ^{1}H NMR and fluorescence titrations as well as binding studies in two-phase systems, such as dissolution of solid carbohydrates in apolar media and phase transfer of sugars from aqueous into organic solvents, revealed β- *vs.* α-anomer binding preferences in the recognition of glycosides. Compared to the previously described three-armed aminopyridine-based receptor, compounds **1** and **2** showed significantly increased affinity to β-galactoside. Receptor **2**, incorporating two 8-hydroxyquinoline units, was shown to be the most effective receptor for β-galactoside. Compound **3**, bearing one 8-hydroxyquinoline group, was found to be a highly effective receptor for β-glucoside and shown to be a more powerful receptor than the quinoline-based compound **4**, indicating an important role of the quinoline hydroxy group in the complex formation.

Introduction

Artificial carbohydrate receptors using noncovalent interactions for sugar binding[1–3] provide valuable model systems to study the underlying principles of carbohydrate-based molecular recognition processes and may serve as a basis for the development of saccharide sensors or new therapeutics.[4] Although effective receptor systems have been developed, the exact prediction of the binding preferences of the artificial receptors is still further away and it is hoped that systematic studies towards effective recognition motifs for carbohydrates will contribute significantly to the solution of this problem. Our previous studies showed that acyclic receptors,[5] such as compounds containing a trisubstituted trialkylbenzene core, represent particularly interesting objects for such systematic studies. Depending on the nature of the recognition units (see Fig. 1) and connecting bridges used as the building blocks, a variety of receptors with different binding properties could be obtained.

The aim of the present study was to evaluate the potential of 8-hydroxyquinoline-based receptors in the complexation of carbohydrates. The 8-hydroxyquinoline unit has been extensively used for the construction of metal ion ligands.[6] In the area of sugar recognition by receptors employing noncovalent interactions the potential of this unit has not been evaluated.[7] As first representatives of this group we have prepared compounds **1–3** (see Fig. 2), containing one to three 8-hydroxyquinoline units. The recognition properties of these compounds towards monosaccharides **5–8** were compared with those of the previously studied receptors. In addition, the properties of the 8-hydroxyquinoline-based receptor **3** were compared with those of the quinoline-based compound **4**.

Results and discussion

Synthesis of the receptors

The synthesis of compounds **1–4** started from 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene (**9**) and is summarised in Scheme 1. The reaction of **9** with potassium phthalimide gave 1,3,5-tris(phthalimidomethyl)-2,4,6-triethylbenzene (**10**),[8] which was converted into 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene (**11**). Compound **11** was allowed to react with 8-hydroxyquinoline-2-carbaldehyde (**12**) to give the imine **13**, which was subsequently reduced with sodium borohydride to yield the product **1**. 1,3-Bis(bromomethyl)-5-[(4,6-dimethylpyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene (**15**) and 1-bromomethyl-3,5-bis[(4,6-dimethylpyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene (**16**) were prepared *via* a reaction of **9** with 2-amino-4,6-dimethylpyridine (**14**); the separation of **15** and **16** was carried out by column chromatography.[5g] The reaction of **15** with potassium phthalimide gave 1,3-bis(phthalimidomethyl)-5-[(4,6-dimethylpyridin-2-yl)-aminomethyl]-2,4,6-triethylbenzene (**17**),[5c] which was converted into 1,3-bis(aminomethyl)-5-[(4,6-dimethylpyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene (**18**). The condensation of **18** with 8-hydroxyquinoline-2-carbaldehyde (**12**), followed by

Institut für Organische Chemie der Technischen Universität Braunschweig, Hagenring 30, 38106, Braunschweig, Germany. E-mail: m.mazik@tu-bs.de; Fax: +49 531 391 8185; Tel: +49 531 391 5266

† Electronic supplementary information (ESI) available: Descriptions of the ^{1}H NMR and fluorescence titration experiments (Tables S1–S5), changes in chemical shift observed for selected signals during ^{1}H NMR titrations (Table S6), and example of a fluorescence titration (Figure S1). See DOI: 10.1039/c0ob00960a

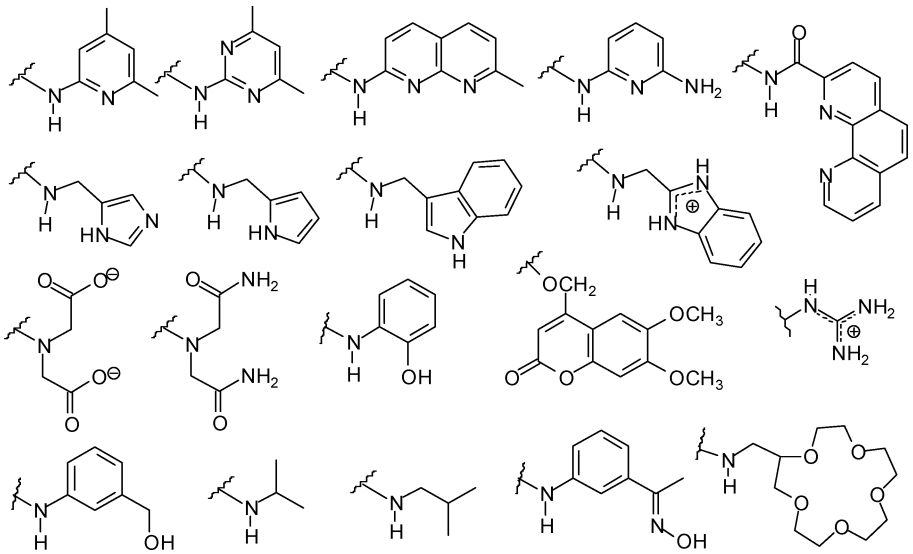


Fig. 1 Examples of recognition units that have been used for the construction of acyclic carbohydrate receptors.[5]

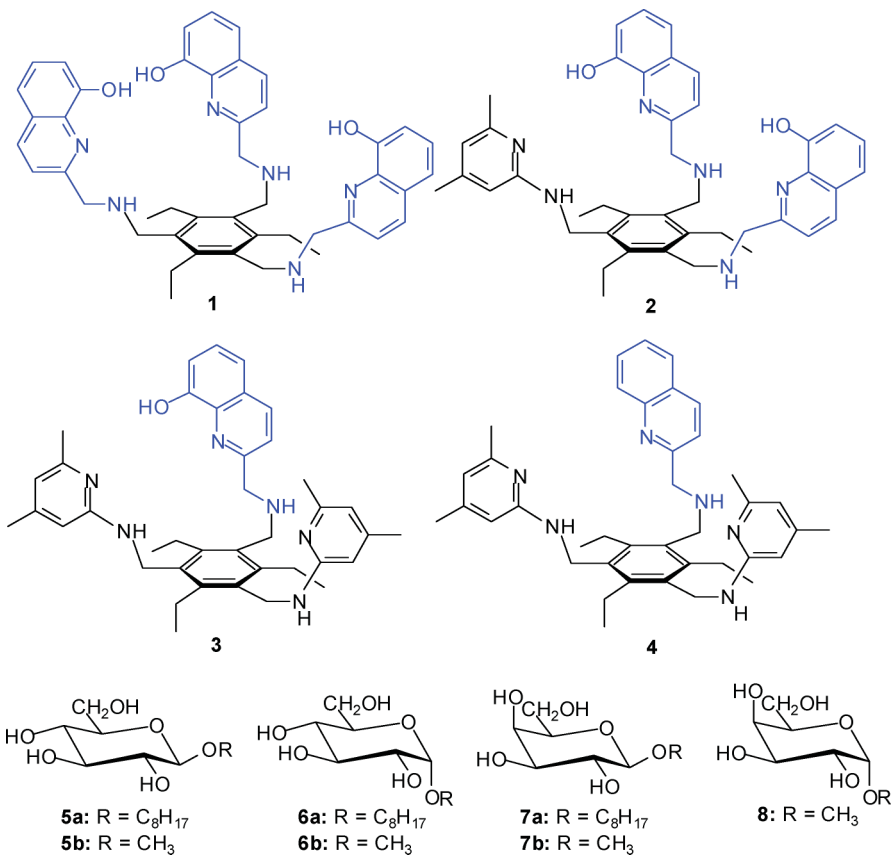
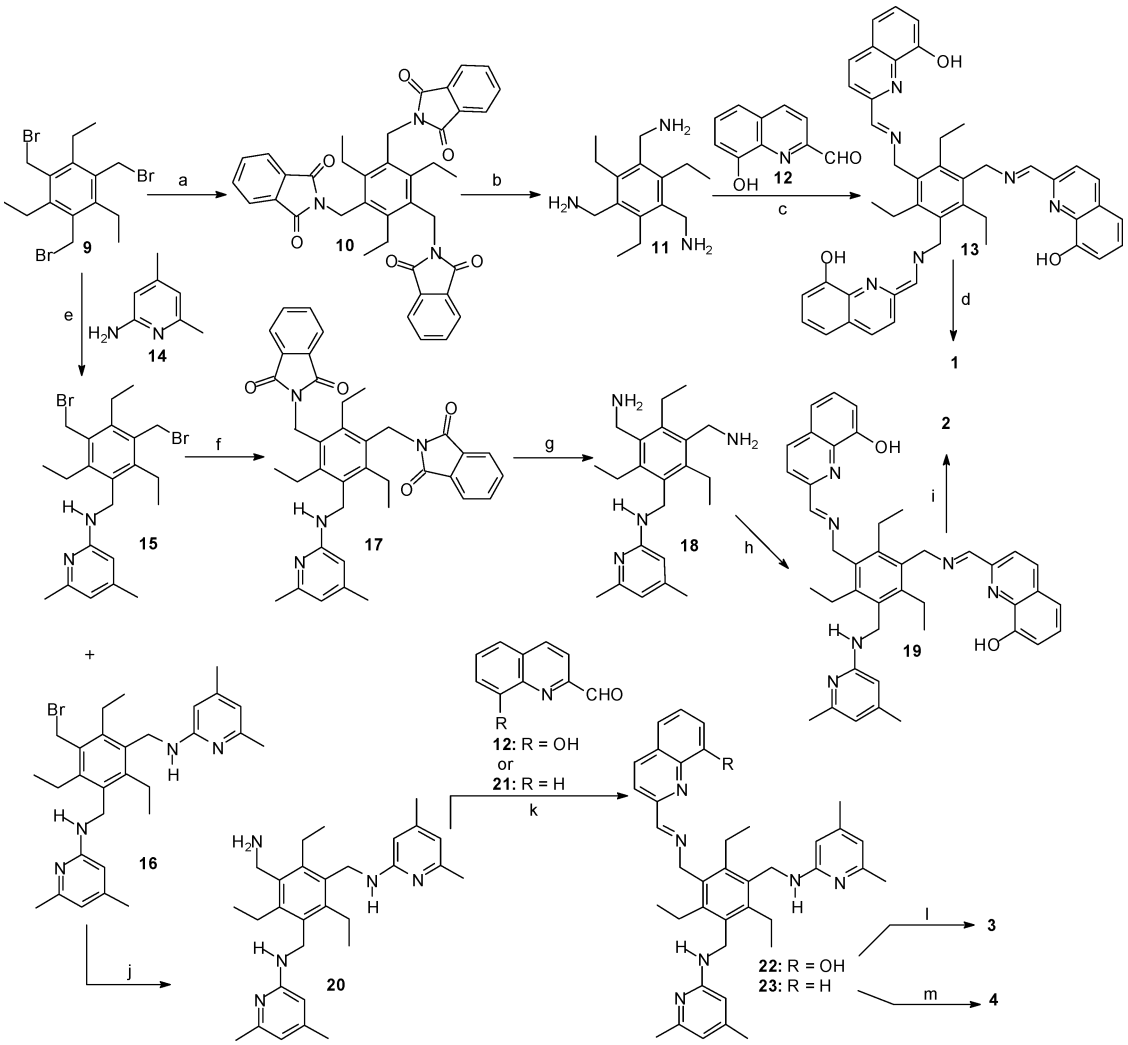


Fig. 2 Structures of receptors and sugars investigated in this study.

reduction of the corresponding imine **19**, yielded the product **2**. Treatment of **16** with aqueous ammonia gave 1-aminomethyl-3,5-bis[(4,6-dimethylpyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene (**20**), which was the base for the synthesis of compounds **3** and **4**.

Binding studies in two-phase systems: liquid–solid and liquid–liquid extractions

Extractions of methyl pyranosides, such as β-glucoside **5b**, α-glucoside **6b**, β-galactoside **7b** and α-galactoside **8**, from the



Scheme 1 *Reaction conditions*: (a) potassium phthalimide, dimethyl sulfoxide, 100 °C, 8 h (90%);[8] (b) hydrazine hydrate, ethanol/toluene, reflux, 20 h, KOH (93%);[8] (c) 3 equiv. of **12**, CH_2Cl_2, reflux, 48 h; (d) $NaBH_4$, CH_3OH, 0 °C to room temperature (45% of **1**); (e) 2 equiv. of 2-amino-4,6-dimethylpyridine, CH_3CN/THF, K_2CO_3, room temperature, 3 d (20% of **15**, 30% of **16**);[5g] (f) potassium phthalimide, dimethyl sulfoxide, 95 °C, 8 h, (57%);[5c] (g) hydrazine hydrate, ethanol/toluene, reflux, 20 h, KOH (43%);[5c] (h) 2 equiv. of **12**, CH_2Cl_2, reflux, 24 h; (i) $NaBH_4$, CH_3OH, 0 °C to room temperature (46% of **2**); (j) NH_3/H_2O (25% solution), 12 h (72%);[5g] (k) 1 equiv. of 8-hydroxyquinoline-2-carbaldehyde (**12**) or quinoline-2-carbaldehyde (**21**), CH_2Cl_2, reflux, 16 h in the case of **12** and 8 h in the case of **21**; (l, m) $NaBH_4$, CH_3OH, 0 °C to r. t. (44% of **3**, 49% of **4**).

Table 1 Solubilization of sugars in $CDCl_3$ by receptors **1–4** (1 mM solutions)

Sugar	Sugar/**1**[a]	Sugar/**2**[a]	Sugar/**3**[a]	Sugar/**4**[a]
β-D-glucoside **5b**	0.65	0.87	0.98	0.65
α-D-glucoside **6b**	0.18	0.30	0.31	0.18
β-D-galactoside **7b**	0.73	0.92	0.45	0.30
α-D-galactoside **8**	0.25	0.35	0.27	0.29

[a] Molar ratios sugar/receptor occurring in solution (the ^{1}H NMR signals of the corresponding sugar were integrated with respect to the receptor's signals to provide the sugar–receptor ratio; control experiments were performed in the absence of the receptor).

solid state into a $CDCl_3$ solution[9] of the corresponding receptor (1 mM) provided evidence for stronger complexation of the β-anomers **5b** and **7b** (see Table 1). In the case of receptors **1** and **2**, bearing three and two 8-hydroxyquinoline moieties, respectively, the extractability decreased in the sequence β-galactoside **7b** > β-glucoside **5b** > α-galactoside **8** > α-glucoside **6b** (see Table 1; control experiments were performed in the absence of the receptor). The preference of **1** and **2** for β- over α-glucoside (**5b** *vs.* **6b**) as well as for β-galactoside over β-glucoside (**7b** *vs.* **5b**) indicated by liquid–solid extractions was further confirmed by ^{1}H NMR spectroscopic titrations (see below). Compared to the previously studied symmetrical aminopyridine-based receptor,[5q] the extraction experiments indicated a significantly higher affinity of **1** and **2** towards β-galactoside. In the case of receptor **3**, containing one 8-hydroxyquinoline unit and two aminopyridine[10] moieties, the extractability decreased in the sequence β-glucoside **5b** > β-galactoside **7b** > α-glucoside **6b** > α-galactoside **8**. Compared to the quinoline-based compound **4**, the extraction experiments indicated a higher affinity of the 8-hydroxyquinoline-based receptor **3** to the substrates **5b**, **6b**, and **7b**.

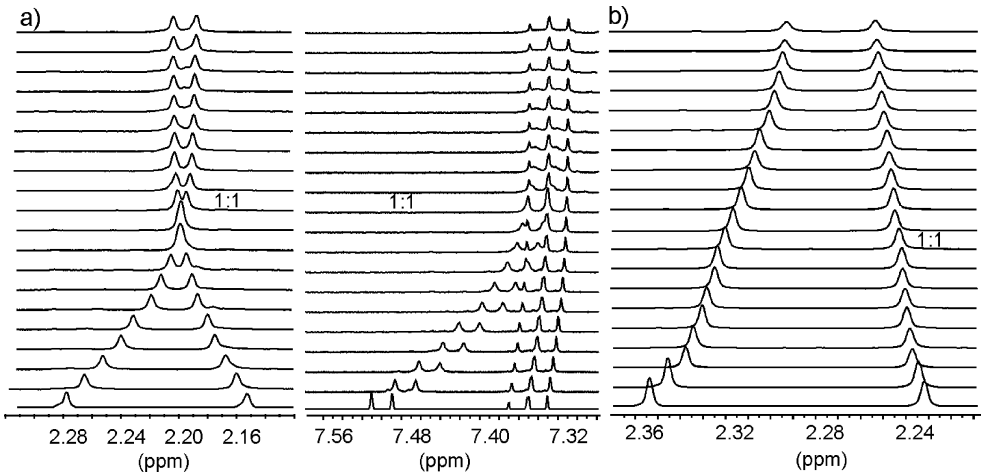


Fig. 3 (a) Partial ^{1}H NMR spectra (400 MHz; $CDCl_3$) of receptor **2** before (bottom) and after the addition of β-galactoside **7a**; shown are chemical shifts of the pyridine CH_3 and quinoline CH resonances of **2**. [**2**] = 0.88 mM, equiv. of **7a**: 0.00–3.90. (b) Chemical shifts of the pyridine CH_3 resonances of the previously described symmetrical aminopyridine-based receptor[5q] (1,3,5-tris[(4,6-dimethylpyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene, 0.90 mM) after the addition of 0.00–5.20 equiv. of β-galactoside **7a** (500 MHz; $CDCl_3$).

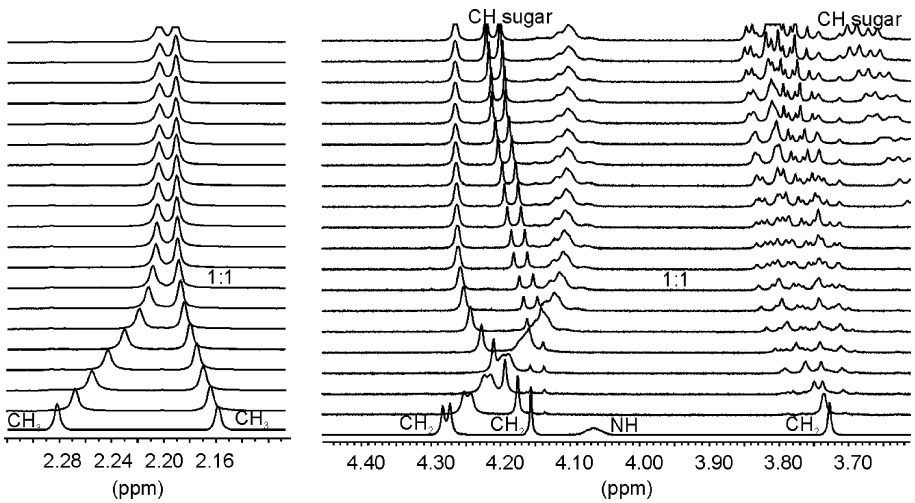


Fig. 4 Partial ^{1}H NMR spectra (400 MHz; $CDCl_3$) of receptor **3** before (bottom) and after the addition of β-glucoside **5a**; shown are chemical shifts of the pyridine CH_3 and N-CH_2 resonances of **3**; [**3**] = 1.00 mM, equiv. of **5a**: 0.00–3.44.

Studies of the extraction of methyl β-D-glucoside (**5b**) and methyl β-D-galactoside (**7b**) from aqueous solution into chloroform (using the procedure described by Davis *et al.*, see refs 11a,b; see also ref. 5c) revealed that compound **2** (1 mM chloroform solution) is capable to extract 0.15 equiv of β-glucoside **5b** and 0.25 equiv of β-galactoside **7b** from 1 M aqueous solutions (control experiments were performed in the absence of the receptor). In the case of compound **3**, about 0.19 equiv of β-glucoside **5b** could be extracted from the aqueous solution.

Binding studies in homogeneous media

The interactions of the receptors and carbohydrates were investigated by ^{1}H NMR and fluorescence spectroscopic titrations in organic media ($CDCl_3$, DMSO-d_6/$CDCl_3$ mixtures or $CHCl_3$). The ^{1}H NMR titration experiments with octyl β-glucoside **5a**, α-glucoside **6a** and β-galactoside **7a** were carried out by adding increasing amounts of the sugar to a solution of the corresponding receptor (see Supporting Information). In addition, inverse titrations were performed in which the concentration of the sugar was held constant and that of the receptor was varied. The complexation between the receptors **1–4** and monosaccharides was evidenced by several changes in the NMR spectra; examples are given in Fig. 3a and 4 as well as in Table S6 (see Supporting Information). The ^{1}H NMR titration data were analyzed using the Hostest 5.6[12] and EQNMR[13] program; the binding constants are summarised in Table 1. In all cases, the curve fitting of the titration data suggested the existence of 1 : 1 and 2 : 1 receptor–sugar complexes in $CDCl_3$ solutions, with stronger association constant for 1 : 1 binding and a weaker association constant for 2 : 1 receptor–sugar complex; this model was further supported by the mole ratio plots[14] (see Fig. 5).

The interactions of **1–3** with β-glucoside **5a** were shown to be more effective than those with the α anomer **6a**. In comparison to the previously described three-armed aminopyridine-based receptor,[5q] compounds **1** and **2** showed significantly increased

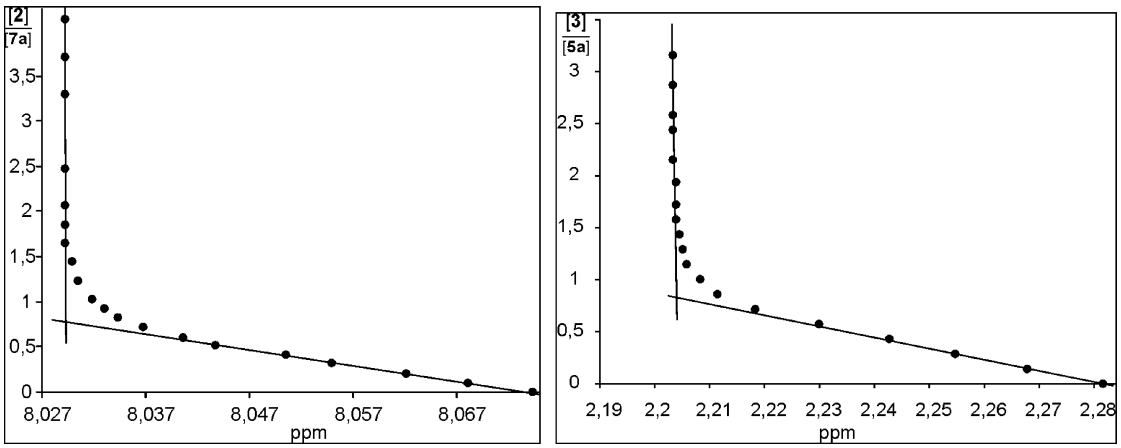


Fig. 5 Mole ratio plots: (a) Titration of receptor **2** with β-galactoside **7a** (analysis of the complexation-induced shift of the quinoline CH of **2**). (b) Titration of receptor **3** with β-glucoside **5a**(analysis of the complexation-induced shift of the pyridine CH_3 of **3**). [**2**] = 0.88 mM, equiv. of **7a**: 0.00–4.10; [**3**] = 1.00 mM, equiv. of **5a**: 0.00–3.40.

binding affinity toward β-galactoside **7a**. The differences in the complexation ability of the receptors **1**/**2** and the previously described receptor are clearly visible by the comparison of the chemical shifts of the receptor signals after the addition of β-galactoside **7a**, as illustrated in Fig. 3a and 3b for the pyridine CH_3 signals. It is noteworthy that the strong enhancement of the binding affinity of **1** and **2** towards β-galactoside was achieved through a relatively simple variation of the receptor structure. The presence of three (as in **1**) or two (as in **2**) 8-hydroxyquinoline units seems to be favourable for the recognition of β-galactoside. It should be also noted that the previously described imidazole/aminopyridine- and indole/aminopyridione-based receptors, bearing two 4(5)-substituted imidazole or 3-substituted indole units,[5b] were also found to display significantly higher binding affinity for β-galactoside than the symmetrical aminopyridine-based receptor (In contrast to **1–3** and the indole/imidazole-based[5b] receptors, the previously described phenanthroline/aminopyridine-based receptors[5c,e] were shown to display a high binding affinity towards α-galactoside as well as a strong α- *versus* β anomer binding preference). The binding affinity of **1–3** towards β-galactoside decrease in the sequence **2** > **1** > **3**. Compound **3**, bearing one hydroxyquinoline and two aminopyridine units, was found to be similar in affinity to β-galactoside as the three-armed aminopyridine-based receptor. In the case of β-glucoside **5a** the situation is reversed; the binding affinity of **1–3** towards **5a** decrease in the sequence **3** > **2** > **1**. Compound **3** was shown to be the most effective receptor for this monosaccharide. Interestingly, compound **3** was also shown to be a more powerful receptor for β-glucoside that the quinoline-based compound **4**. These results indicate an important contribution of the quinoline hydroxy group to the complex formation with β-glucoside.

In the case of **2**·**5a**, **2**·**7a** and **3**·**5a** the binding constants in $CDCl_3$ were too large to be accurately determined by the NMR spectroscopic method (for a review discussing the limitations of the NMR method, see ref. 15). To compare the binding capability of the receptors **2** and **3**, additional ^{1}H NMR titrations in a more polar solvent (DMSO-d_6/$CDCl_3$ mixture) were carried out. As expected, the affinity of **2** and **3** significantly decreased as solvent polarity increased;[16] the binding constants are given in Table 2

Table 2 Association constants[a,b] for receptors **1–4** and carbohydrates **5a**, **6a** and **7a**

Host–guest complex	Solvent	K_{11} [M^{-1}]	K_{21} [M^{-1}][c]	$\beta_{21} = K_{11}K_{21}$
1·**5a**	$CDCl_3$	19500	1380	2.69×10^7
1·**6a**	$CDCl_3$	3300	270	8.91×10^5
1·**7a**	$CDCl_3$	24700	1320	3.26×10^7
2·**5a**	$CDCl_3$	69500	1060	7.37×10^7
	5% DMSO-d_6/$CDCl_3$	4300	300	1.29×10^6
2·**6a**	$CDCl_3$	6810	100	6.81×10^5
2·**7a**	$CDCl_3$	148700	1580	2.34×10^8
	5% DMSO-d_6/$CDCl_3$	8600	770	6.62×10^6
3·**5a**	$CDCl_3$	160200	860	1.37×10^8
	5% DMSO-d_6/$CDCl_3$	8300	520	4.32×10^6
3·**6a**	$CDCl_3$	4150	430	1.78×10^6
3·**7a**	$CDCl_3$	6130	340	2.08×10^6
4·**5a**	$CDCl_3$	20700	190	3.93×10^6
4·**7a**	$CDCl_3$	4830	220	1.06×10^6

[a] Average K_a values from multiple titrations (the high values of the binding constants for **2**·**5a**, **2**·**7a**, and **3**·**5a** determined on the base of the ^{1}H NMR spectroscopic titrations in $CDCl_3$ were confirmed by fluorescence titrations in $CHCl_3$). [b] Errors in K_a are less than 20%. [c] K_{21} corresponds to 2 : 1 receptor–sugar association constant.

and show a preference of **2** for β-galactoside over β-glucoside (as already indicated by the ^{1}H NMR titrations in $CDCl_3$).

Inverse titrations provided further information about the interactions, which contribute to the stabilization of the receptor–carbohydrate complexes. During the titration of β-glucoside **5a** or β-galactoside **7a** with the receptor **1–3** in $CDCl_3$ the signals due to the OH protons of the sugar shifted downfield with strong broadening and became almost indistinguishable from the base line after the addition of only 0.1 equiv of the receptor, whereas the CH signals of **5a**/**7a** moved upfield. The spectral changes indicate the participation of the OH groups of **5a**/**7a** in the formation of intermolecular hydrogen bonds and the involvement of the sugar CHs in CH···π interactions[17] with the aromatic rings of the receptor.[18,19]

The formation of complexes was also detected by means of fluorescence spectroscopy (in the case of **2**·**5a**, **2**·**7a**, **3**·**5a**, and **4**·**5a**). The fluorescence titration experiments were carried out by

adding increasing amounts of the sugar to a $CHCl_3$ solution of the receptor (for examples, see Table S4 and S5 in the Supporting Information). On addition of the sugar the fluorescence emission was enhanced, as shown in the Supporting Information (see Figure S1). Analysis of the titration data by curve fitting (Hyperquad 2006 program[20]) yielded binding constants, which are in good agreement with the values obtained through ^{1}H-NMR titrations.

Among the tested compounds, compound **3** was shown to be the most powerful receptor for β-glucoside, whereas **2** was found to be the most effective receptor for β-galactoside.

Conclusion

Compounds **1–3**, bearing one to three 8-hydroxyquinoline-based recognition units, were established as powerful carbohydrate receptors and shown to display interesting binding preferences.[21] ^{1}H NMR and fluorescence titrations as well as binding studies in two-phase systems, such as dissolution of solid carbohydrates in apolar media and phase transfer of sugars from aqueous into organic solvents, revealed β- *vs.* α-anomer binding preferences in the recognition of glycosides. Compound **3** has been established as a highly effective receptor for β-glucoside **5**. In comparison to **3**, receptors **1** and **2** showed significantly increased affinity to β-galactoside **7**, but decreased affinity to β-glucoside **5**. It should be noted that compounds **1** and **2**, containing three and two 8-hydroxyquinoline units, respectively, were shown to be more powerful carbohydrate receptors for β-galactoside than the previously described symmetrical aminopyridine-based receptor. In particular, compound **2** has been established as a highly effective receptors for β-galactoside. It has been shown that both hydrogen bonding and interactions of the carbohydrate CH units with the aromatic rings of the receptors contribute to the stabilization of the receptor–carbohydrate complexes. The binding affinity of **1–3** towards β-galactoside **7a** and β-glucoside **5a** decreases in the sequence **2** > **1** > **3** and **3** > **2** > **1**, respectively. Compound **3**, containing the 8-hydroxyquinoline moiety, was shown to be a more effective carbohydrate receptor than the quinoline-based compound **4**, indicating an important role of the quinoline hydroxy group in the complex formation.

Experimental section

Analytical TLC was carried out on silica gel 60 F_{254} plates employing chloroform/methanol mixtures as the mobile phase. Melting points are uncorrected. Sugars **5–8** are commercially available. The binding studies are described in Supporting Information.

1,3,5-Tris-[(8-hydroxyquinolin-2-yl-methyl)aminomethyl]-2,4,6-triethylbenzene (1)

1,3,5-Tris(aminomethyl)-2,4,6-triethylbenzene (**11**) (0.11 g, 0.44 mmol) dissolved in 5 mL CH_2Cl_2 was added to a solution of 8-hydroxyquinoline-2-carbaldehyde (**12**) (0.25 g, 1.44 mmol) in CH_2Cl_2 (15 mL) and the resulting mixture was allowed to reflux for 48 h. Afterward, dry methanol (10 mL) was added, the mixture was cooled to 0 °C and $NaBH_4$ (0.20 g, 5.29 mmol) was slowly added. The reaction mixture was stirred for 2 h, the solvents were removed through rotary evaporation, and water (50 mL) was added. The mixture was stirred for 4 h and extracted with $CHCl_3$ (3 × 15 mL). The organic phase was further washed with water (3 × 30 mL), dried over $MgSO_4$, and the solvent was removed through rotary evaporation. The crude product was purified *via* column chromatography [$CHCl_3$/CH_3OH (incl. 1% 7 M NH_3 in CH_3OH), 7 : 1]. Yield 45%. M.p. 69–70 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.08 (t, J = 7.6 Hz, 9 H), 2.81 (q, J = 7.6 Hz, 6 H), 3.75 (s, 6 H), 4.21 (s, 6 H), 7.17 (dd, J = 7.5/1.1 Hz, 3 H), 7.31 (dd, J = 8.5/1.2, 3 H), 7.42 (m, 3 H), 7.55 (d, J = 8.5 Hz, 3 H); 8.13 (d, J = 8.5 Hz, 3 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 16.76, 22.72, 47.33, 56.19, 110.13, 117.7, 121.48, 127.13, 127.49, 133.98, 136.51, 137.49, 142.54, 151.95, 158.46 ppm. HR-MS (ESI) calcd for $C_{45}H_{49}N_6O_3$: 721.38606 $[M + H]^+$; found: 721.38619. R_f 0.20 [chloroform/methanol (incl. 1% NH_3), 3 : 1]. Anal. calcd for $C_{45}H_{48}N_6O_3$: C, 74.97; H, 6.71; N, 11.66; found: C, 74.89; H, 6.84; N, 11.55%.

1,3-Bis-[(8-hydroxyquinolin-2-yl-methyl)aminomethyl]-5-[(4,6-dimethyl-pyridin-2-yl)-aminomethyl]-2,4,6-triethylbenzene (2)

1,3-Bis(aminomethyl)-5-[(4,6-dimethylpyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene (**18**) (0.15 g, 0.42 mmol) dissolved in 5 mL CH_2Cl_2 was added to a solution of 8-hydroxyquinoline-2-carbaldehyde (**12**) (0.22 g, 1.27 mmol) in CH_2Cl_2 (15 mL) and the resulting mixture was refluxed for 24 h. Then, dry methanol (10 mL) was added, the solution was cooled to 0 °C and $NaBH_4$ (0.16 g, 4.24 mmol) was slowly added. The reaction mixture was stirred for 2 h, the solvent was removed by rotary evaporation and 30 mL water were added. The mixture was stirred for 4 h and extracted with $CHCl_3$. The organic phase was further washed with water (3 × 30 mL), dried over $MgSO_4$ and the solvents were removed. The crude product was purified *via* column chromatography [$CHCl_3$/CH_3OH (incl. 1% 7 M NH_3 in CH_3OH), 7 : 1]. Yield 46%. M.p. 80–81 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, J = 7.5 Hz, 3 H), 1.14 (t, J = 7.5 Hz, 6 H), 2.22 (s, 6 H), 2.35 (s, 6 H), 2.76 (q, J = 7.5 Hz, 4 H), 2.84 (q, J = 7.5 Hz, 2 H), 3.78 (s, 4 H), 4.17 (s, 1 H), 4.22 (s, 4 H), 4.33 (d, J = 4.1 Hz, 2 H), 6.05 (s, 1 H), 6.33 (s, 1 H), 7.16 (dd, J = 7.5/1.2 Hz, 2 H), 7.32 (dd, J = 8.2/1.2 Hz, 2 H), 7.42 (m, 2 H), 7.56 (d, J = 8.4 Hz, 2 H), 8.13 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 16.80, 21.09, 22.76, 24.22, 40.61, 47.34, 56.27, 103.44, 110.09, 113.73, 117.72, 121.51, 127.15, 127.49, 132.66, 134.30, 136.54, 137.49, 142.77, 142.91, 148.62, 151.90, 156.62, 158.25, 158.56 ppm. HR-MS (ESI) calcd for $C_{42}H_{49}N_6O_2$: 669.39115 $[M + H]^+$; found: 669.39140. R_f 0.38 [chloroform/methanol (incl. 1% NH_3), 7 : 1]. Anal. calcd for $C_{42}H_{48}N_6O_2$: C, 75.42; H, 7.23; N, 12.56; found: C, 75.29; H, 8.01; N, 12.70%.

General procedure for the synthesis of compounds 3 and 4

To a solution of 8-hydroxyquinoline-2-carbaldehyde (**12**) or quinoline-2-carbaldehyde (**21**) (0.38 mmol) in CH_2Cl_2 (10 mL) was added 1-aminomethyl-3,5-bis[(4,6-dimethylpyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene (**20**) (0.30 mmol) dissolved in 5 mL CH_2Cl_2. The reaction mixture was allowed to reflux for 16 h in the case of **12** and for 8 h in the case of **21**. Afterward, dry methanol (5 mL) was added, the solution was cooled to 0 °C and solid $NaBH_4$ (1.64 mmol) was added in portions. The reaction mixture was stirred for 1 h, the solvents were removed by rotary evaporation and water (30 mL) was added. The mixture

was stirred for 2 h and extracted with $CHCl_3$. The organic phase was washed with water (3 × 30 mL), dried over $MgSO_4$, and the solvent was removed. The crude product was purified *via* column chromatography [$CHCl_3$/CH_3OH (incl. 1% 7 M NH_3 in CH_3OH), 7 : 1 or 20 : 1 v/v].

1-[(8-Hydroxyquinolin-2-yl-methyl)aminomethyl]-3,5-bis[(4,6-dimethylpyridin-2-yl)-aminomethyl]-2,4,6-triethylbenzene (3)

Yield 44%. M.p. 84–85 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.17 (t, J = 7.5 Hz, 6 H), 1.20 (t, J = 7.5 Hz, 3 H), 2.23 (s, 6 H), 2.35 (s, 6 H), 2.71 (q, J = 7.5 Hz, 2 H), 2.78 (q, J = 7.5 Hz, 4 H), 3.79 (s, 2 H), 4.15 (s, 2 H), 4.22 (s, 2 H), 4.35 (d, J = 4.2 Hz, 4 H), 6.07 (s, 2 H), 6.33 (s, 2 H), 7.16 (dd, J = 7.5/1.3 Hz, 1 H), 7.32 (dd, J = 8.3/1.2 Hz, 1 H), 7.41 (m, 1 H), 7.57 (d, J = 8.4 Hz, 1 H), 8.14 (d, J = 8.5 Hz, 1 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 16.81, 21.09, 22.82, 24.22, 40.62, 47.25, 56.25, 103.45, 110.10, 113.81, 117.73, 121.51, 127.16, 127.48, 132.91, 134.49, 136.56, 137.48, 143.05, 143.22, 148.69, 151.87, 156.72, 158.25, 158.49 ppm. HR-MS (ESI) calcd for $C_{39}H_{49}N_6O$: 617.39623 $[M + H]^+$; found: 617.39611. R_f 0.50 [chloroform/methanol (incl. 1% NH_3), 7 : 1]. Anal. calcd for $C_{39}H_{48}N_6O$: C, 75.94; H, 7.84; N, 13.62; found: C, 75.80; H, 7.96; N, 13.67%.

1-[(Quinolin-2-yl-methyl)aminomethyl]-3,5-bis[(4,6-dimethylpyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene (4)

Yield 49%. M.p. 70–71 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.16 (t, J = 7.5 Hz, 6 H), 1.21 (t, J = 7.5 Hz, 3 H), 2.23 (s, 6 H), 2.35 (s, 6 H), 2.72 (q, J = 7.5 Hz, 2 H), 2.84 (q, J = 7.5 Hz, 4 H), 3.81 (s, 2 H), 4.17 (s, 2 H), 4.23 (s, 2 H), 4.36 (d, J = 4.2 Hz, 4 H), 6.07 (s, 2 H), 6.33 (s, 2 H), 7.51 (m, 1H), 7.54 (d, J = 8.2 Hz), 7.70 (m, 1 H), 7.81 (dd, J = 8.2/1.2 Hz, 1 H), 8.08 (d, J = 8.4 Hz, 1 H), 8.14 (d, J = 8.3 Hz, 1 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 16.83, 21.09, 22.77, 24.19, 40.66, 47.29, 56.53, 103.50, 113.76, 120.68, 126.04, 127.32, 127.56, 129.03, 129.44, 132.85, 134.74, 136.38, 142.96, 143.36, 147.74, 148.71, 156.68, 158.28, 160.43 ppm. HR-MS (ESI) calcd for $C_{39}H_{49}N_6$: 601.40132 $[M + H]^+$; found: 601.40143. R_f 0.30 [chloroform/methanol (incl. 1% NH_3), 7 : 1]. Anal. calcd for $C_{39}H_{48}N_6$: C, 77.96; H, 8.05; N, 13.98; found: C, 77.85; H, 8.13; N, 14.02.

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