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# 8-Hydroxyquinoline as a building block for artificial receptors: binding preferences in the recognition of glycopyranosides<sup>†</sup>

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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. <sup>1</sup>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  $\beta$ - *vs.*  $\alpha$ -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  $\beta$ -galactoside. Receptor 2, incorporating two 8-hydroxyquinoline units, was shown to be the most effective receptor for  $\beta$ -galactoside. Compound 3, bearing one 8-hydroxyquinoline group, was found to be a highly effective receptor for  $\beta$ -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<sup>1-3</sup> 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.<sup>4</sup> 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,<sup>5</sup> 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.<sup>6</sup> In the area of sugar recognition by receptors employing noncovalent interactions the potential of this unit has not been evaluated.<sup>7</sup> 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 5-8were 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 1,3,5tris(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.<sup>5g</sup> 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-2yl)aminomethyl]-2,4,6-triethylbenzene (18). The condensation of 18 with 8-hydroxyquinoline-2-carbaldehyde (12), followed by

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<sup>&</sup>lt;sup>†</sup> Electronic supplementary information (ESI) available: Descriptions of the <sup>1</sup>H NMR and fluorescence titration experiments (Tables S1–S5), changes in chemical shift observed for selected signals during <sup>1</sup>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.<sup>5</sup>



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  $\beta$ -glucoside **5b**,  $\alpha$ -glucoside **6b**,  $\beta$ -galactoside **7b** and  $\alpha$ -galactoside **8**, from the



Scheme 1 *Reaction conditions*: (a) potassium phthalimide, dimethyl sulfoxide, 100 °C, 8 h (90%);<sup>8</sup> (b) hydrazine hydrate, ethanol/toluene, reflux, 20 h, KOH (93%);<sup>8</sup> (c) 3 equiv. of 12, CH<sub>2</sub>Cl<sub>2</sub>, reflux, 48 h; (d) NaBH<sub>4</sub>, CH<sub>3</sub>OH, 0 °C to room temperature (45% of 1); (e) 2 equiv. of 2-amino-4,6-dimethylpyridine, CH<sub>3</sub>CN/THF, K<sub>2</sub>CO<sub>3</sub>, room temperature, 3 d (20% of 15, 30% of 16);<sup>5g</sup> (f) potassium phthalimide, dimethyl sulfoxide, 95 °C, 8 h, (57%);<sup>5c</sup> (g) hydrazine hydrate, ethanol/toluene, reflux, 20 h, KOH (43%);<sup>5c</sup> (h) 2 equiv. of 12, CH<sub>2</sub>Cl<sub>2</sub>, reflux, 24 h; (i) NaBH<sub>4</sub>, CH<sub>3</sub>OH, 0 °C to room temperature (46% of 2); (j) NH<sub>3</sub>/H<sub>2</sub>O (25% solution), 12 h (72%);<sup>5g</sup> (k) 1 equiv. of 8-hydroxyquinoline-2-carbaldehyde (12) or quinoline-2-carbaldehyde (21), CH<sub>2</sub>Cl<sub>2</sub>, reflux, 16 h in the case of 12 and 8 h in the case of 21; (l, m) NaBH<sub>4</sub>, CH<sub>3</sub>OH, 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/1ª	Sugar/2 <sup>a</sup>	Sugar/3 <sup>a</sup>	Sugar/4 <sup>a</sup>
β-D-glucoside <b>5b</b>	0.65	0.87	0.98	0.65
α-D-glucoside <b>6b</b>	0.18	0.30	0.31	0.18
$\beta$ -D-galactoside <b>7b</b>	0.73	0.92	0.45	0.30
α-D-galactoside <b>8</b>	0.25	0.35	0.27	0.29

<sup>*a*</sup> Molar ratios sugar/receptor occurring in solution (the <sup>1</sup>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<sub>3</sub> solution<sup>9</sup> of the corresponding receptor (1 mM) provided evidence for stronger complexation of the  $\beta$ -anomers **5b** and **7b** (see Table 1). In the case of receptors **1** and **2**, bearing three and two 8-hydroxyquinoline moieties, respectively,

 $\beta$ -glucoside **5b** >  $\alpha$ -galactoside **8** >  $\alpha$ -glucoside **6b** (see Table 1; control experiments were performed in the absence of the receptor). The preference of 1 and 2 for  $\beta$ - over  $\alpha$ -glucoside (5b vs. 6b) as well as for  $\beta$ -galactoside over  $\beta$ -glucoside (7b vs. 5b) indicated by liquid-solid extractions was further confirmed by <sup>1</sup>H NMR spectroscopic titrations (see below). Compared to the previously studied symmetrical aminopyridine-based receptor,<sup>5q</sup> the extraction experiments indicated a significantly higher affinity of 1 and 2 towards  $\beta$ -galactoside. In the case of receptor 3, containing one 8-hydroxyquinoline unit and two aminopyridine<sup>10</sup> moieties, the extractability decreased in the sequence  $\beta$ -glucoside **5b** >  $\beta$ -galactoside **7b** >  $\alpha$ -glucoside **6b** >  $\alpha$ -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.

the extractability decreased in the sequence  $\beta$ -galactoside 7b >



Fig. 3 (a) Partial <sup>1</sup>H NMR spectra (400 MHz; CDCl<sub>3</sub>) of receptor 2 before (bottom) and after the addition of  $\beta$ -galactoside 7a; shown are chemical shifts of the pyridine CH<sub>3</sub> and quinoline CH resonances of 2. [2] = 0.88 mM, equiv. of 7a: 0.00–3.90. (b) Chemical shifts of the pyridine CH<sub>3</sub> resonances of the previously described symmetrical aminopyridine-based receptor<sup>5q</sup> (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  $\beta$ -galactoside 7a (500 MHz; CDCl<sub>3</sub>).



**Fig. 4** Partial <sup>1</sup>H NMR spectra (400 MHz; CDCl<sub>3</sub>) of receptor 3 before (bottom) and after the addition of  $\beta$ -glucoside **5a**; shown are chemical shifts of the pyridine CH<sub>3</sub> and N-CH<sub>2</sub> resonances of **3**; **[3]** = 1.00 mM, equiv. of **5a**: 0.00–3.44.

Studies of the extraction of methyl  $\beta$ -D-glucoside (**5b**) and methyl  $\beta$ -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  $\beta$ -glucoside **5b** and 0.25 equiv of  $\beta$ -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  $\beta$ -glucoside **5b** could be extracted from the aqueous solution.

#### Binding studies in homogeneous media

The interactions of the receptors and carbohydrates were investigated by <sup>1</sup>H NMR and fluorescence spectroscopic titrations in organic media (CDCl<sub>3</sub>, DMSO-d<sub>6</sub>/CDCl<sub>3</sub> mixtures or CHCl<sub>3</sub>). The <sup>1</sup>H NMR titration experiments with octyl  $\beta$ -glucoside **5a**,  $\alpha$ -glucoside **6a** and  $\beta$ -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 <sup>1</sup>H NMR titration data were analyzed using the Hostest 5.6<sup>12</sup> and EQNMR<sup>13</sup> 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<sub>3</sub> 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<sup>14</sup> (see Fig. 5).

The interactions of 1–3 with  $\beta$ -glucoside 5a were shown to be more effective than those with the  $\alpha$  anomer 6a. In comparison to the previously described three-armed aminopyridine-based receptor,<sup>5q</sup> compounds 1 and 2 showed significantly increased



Fig. 5 Mole ratio plots: (a) Titration of receptor 2 with  $\beta$ -galactoside 7a (analysis of the complexation-induced shift of the quinoline CH of 2). (b) Titration of receptor 3 with  $\beta$ -glucoside 5a(analysis of the complexation-induced shift of the pyridine CH<sub>3</sub> 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  $\beta$ -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  $\beta$ galactoside 7a, as illustrated in Fig. 3a and 3b for the pyridine CH<sub>3</sub> signals. It is noteworthy that the strong enhancement of the binding affinity of 1 and 2 towards  $\beta$ -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  $\beta$ -galactoside. It should be also noted that the previously described imidazole/aminopyridineand indole/aminopyridione-based receptors, bearing two 4(5)substituted imidazole or 3-substituted indole units,<sup>5b</sup> were also found to display significantly higher binding affinity for  $\beta$ galactoside than the symmetrical aminopyridine-based receptor (In contrast to 1-3 and the indole/imidazole-based<sup>5b</sup> receptors, the previously described phenanthroline/aminopyridine-based receptors<sup>5c,e</sup> were shown to display a high binding affinity towards  $\alpha$ -galactoside as well as a strong  $\alpha$ - versus  $\beta$  anomer binding preference). The binding affinity of 1-3 towards  $\beta$ -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  $\beta$ -galactoside as the three-armed aminopyridine-based receptor. In the case of  $\beta$ -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  $\beta$ -glucoside that the quinoline-based compound 4. These results indicate an important contribution of the quinoline hydroxy group to the complex formation with  $\beta$ -glucoside.

In the case of **2.5a**, **2.7a** and **3.5a** the binding constants in CDCl<sub>3</sub> 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 <sup>1</sup>H NMR titrations in a more polar solvent (DMSO-d<sub>6</sub>/CDCl<sub>3</sub> mixture) were carried out. As expected, the affinity of **2** and **3** significantly decreased as solvent polarity increased;<sup>16</sup> the binding constants are given in Table 2

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

Host-guest complex	Solvent	<i>К</i> <sub>11</sub> [м <sup>-1</sup> ]	$K_{21}  [\mathrm{M}^{-1}]^c$	$\beta_{21} = K_{11}K_{21}$
1.5a	CDCl <sub>3</sub>	19500	1380	$2.69 \times 10^{7}$
1.6a	CDCl <sub>3</sub>	3300	270	$8.91 \times 10^{5}$
1.7a	CDCl <sub>3</sub>	24700	1320	$3.26 \times 10^{7}$
2.5a	CDCl <sub>3</sub>	69500	1060	$7.37 \times 10^{7}$
	5% DMSO-d <sub>6</sub> /CDCl <sub>3</sub>	4300	300	$1.29 \times 10^{6}$
2.6a	CDCl <sub>3</sub>	6810	100	$6.81 \times 10^{5}$
2.7a	CDCl <sub>3</sub>	148700	1580	$2.34 \times 10^{8}$
	5% DMSO-d <sub>6</sub> /CDCl <sub>3</sub>	8600	770	$6.62 \times 10^{6}$
3·5a	CDCl <sub>3</sub>	160200	860	$1.37 \times 10^{8}$
	5% DMSO-d <sub>6</sub> /CDCl <sub>3</sub>	8300	520	$4.32 \times 10^{6}$
3.6a	CDCl <sub>3</sub>	4150	430	$1.78 \times 10^{6}$
3·7a	CDCl <sub>3</sub>	6130	340	$2.08 \times 10^{6}$
4·5a	CDCl <sub>3</sub>	20700	190	$3.93 \times 10^{6}$
4·7a	CDCl <sub>3</sub>	4830	220	$1.06  imes 10^6$

<sup>*a*</sup> 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 <sup>1</sup>H NMR spectroscopic titrations in CDCl<sub>3</sub> were confirmed by fluorescence titrations in CHCl<sub>3</sub>). <sup>*b*</sup> Errors in  $K_a$  are less than 20%. <sup>*c*</sup>  $K_{21}$  corresponds to 2:1 receptor–sugar association constant.

and show a preference of **2** for  $\beta$ -galactoside over  $\beta$ -glucoside (as already indicated by the <sup>1</sup>H NMR titrations in CDCl<sub>3</sub>).

Inverse titrations provided further information about the interactions, which contribute to the stabilization of the receptorcarbohydrate complexes. During the titration of  $\beta$ -glucoside **5a** or  $\beta$ -galactoside **7a** with the receptor **1–3** in CDCl<sub>3</sub> 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… $\pi$  interactions<sup>17</sup> with the aromatic rings of the receptor.<sup>18,19</sup>

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<sub>3</sub> 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<sup>20</sup>) yielded binding constants, which are in good agreement with the values obtained through <sup>1</sup>H-NMR titrations.

Among the tested compounds, compound 3 was shown to be the most powerful receptor for  $\beta$ -glucoside, whereas 2 was found to be the most effective receptor for  $\beta$ -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.<sup>21</sup> <sup>1</sup>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  $\beta$ - vs.  $\alpha$ -anomer binding preferences in the recognition of glycosides. Compound 3 has been established as a highly effective receptor for  $\beta$ -glucoside 5. In comparison to 3, receptors 1 and 2 showed significantly increased affinity to  $\beta$ -galactoside 7, but decreased affinity to  $\beta$ -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  $\beta$ -galactoside than the previously described symmetrical aminopyridine-based receptor. In particular, compound 2 has been established as a highly effective receptors for  $\beta$ -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  $\beta$ -galactoside 7a and  $\beta$ -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<sub>2</sub>Cl<sub>2</sub> was added to a solution of 8-hydroxyquinoline-2-carbaldehyde (12) (0.25 g, 1.44 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>4</sub> (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<sub>3</sub> (3 × 15 mL). The organic phase was further washed with water (3 × 30 mL), dried over MgSO<sub>4</sub>, and the solvent was removed through rotary evaporation. The crude product was purified *via* column chromatography [CHCl<sub>3</sub>/CH<sub>3</sub>OH (incl. 1% 7 M NH<sub>3</sub> in CH<sub>3</sub>OH), 7:1]. Yield 45%. M.p. 69–70 °C. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 1.08$  (t, J = 7.6 Hz, 9 H), 2.81 (q, J = 7.6Hz, 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 = 8.5Hz, 3 H); 8.13 (d, J = 8.5 Hz, 3 H) ppm. <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 16.76$ , 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<sub>45</sub>H<sub>40</sub>N<sub>6</sub>O<sub>3</sub>: 721.38606 [M + H]<sup>+</sup>; found: 721.38619. *R*<sub>f</sub> 0.20 [chloroform/methanol (incl. 1% NH<sub>3</sub>), 3:1]. Anal. calcd for C<sub>45</sub>H<sub>48</sub>N<sub>6</sub>O<sub>3</sub>: 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<sub>2</sub>Cl<sub>2</sub> was added to a solution of 8-hydroxyquinoline-2carbaldehyde (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<sub>4</sub> (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<sub>3</sub>. The organic phase was further washed with water (3  $\times$  30 mL), dried over MgSO<sub>4</sub> and the solvents were removed. The crude product was purified via column chromatography [CHCl<sub>3</sub>/CH<sub>3</sub>OH (incl. 1% 7 M NH<sub>3</sub> in CH<sub>3</sub>OH), 7:1]. Yield 46%. M.p. 80–81 °C. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 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 = 8.2/1.2Hz, 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. <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 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]<sup>+</sup>; found: 669.39140.  $R_f$ 0.38 [chloroform/methanol (incl. 1% NH<sub>3</sub>), 7:1]. Anal. calcd for C<sub>42</sub>H<sub>48</sub>N<sub>6</sub>O<sub>2</sub>: 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<sub>4</sub> (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<sub>3</sub>. The organic phase was washed with water ( $3 \times 30$  mL), dried over MgSO<sub>4</sub>, and the solvent was removed. The crude product was purified *via* column chromatography [CHCl<sub>3</sub>/CH<sub>3</sub>OH (incl. 1% 7 M NH<sub>3</sub> in CH<sub>3</sub>OH), 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. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 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. <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 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<sub>39</sub>H<sub>49</sub>N<sub>6</sub>O: 617.39623 [M + H]<sup>+</sup>; found: 617.39611. *R*<sub>f</sub> 0.50 [chloroform/methanol (incl. 1% NH<sub>3</sub>), 7 : 1]. Anal. calcd for C<sub>39</sub>H<sub>48</sub>N<sub>6</sub>O: 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[(4,6dimethylpyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene (4)

Yield 49%. M.p. 70–71 °C. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 1.16$  (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. <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>):  $\delta = 16.83$ , 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<sub>39</sub>H<sub>49</sub>N<sub>6</sub>: 601.40132 [M + H]<sup>+</sup>; found: 601.40143. *R*<sub>f</sub> 0.30 [chloroform/methanol (incl. 1% NH<sub>3</sub>), 7:1]. Anal. calcd for C<sub>39</sub>H<sub>48</sub>N<sub>6</sub>: C, 77.96; H, 8.05; N, 13.98; found: C, 77.85; H, 8.13; N, 14.02.

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