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Carbohydrate Receptors Combining Both a Macrocyclic Building Block and Flexible Side Arms as Recognition Units: Design, Syntheses, and Binding Studies

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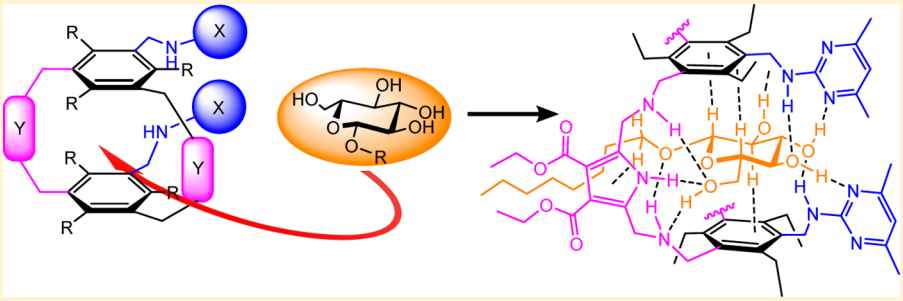
Supporting Information



ABSTRACT: Carbohydrate receptors combining a macrocyclic building block and two flexible side arms were designed on the base of the analysis of the binding motifs found in the crystal structures of the complexes formed between artificial receptors and monosaccharides, reported previously by our group. Binding studies in two-phase systems, such as extractions of sugars from water into organic phase, as well as in homogeneous organic media, using ^{1}H NMR and fluorescence spectroscopic titrations, confirmed the suitability of the designed compounds to act as highly effective and selective carbohydrate receptors. Depending on the nature of the bridges and side arms used as the building blocks, various receptors with different binding properties could be developed. The obtained results confirmed the validity of the receptor design and revealed that crystalline receptor−sugar complexes are particularly a valuable basis for the design of new effective receptor systems.

INTRODUCTION

As a part of our program aimed at the development of selective and effective carbohydrate receptors[1−3] we have recently designed and reported receptor systems of types I and II shown in Figure 1.[4] The macrocyclic compounds **1**−**5** and the acyclic molecules **6**−**9**, consisting of two central triethylbenzene units, were prepared as first representatives of the two groups. The design of the new macrocyclic and acyclic carbohydrate receptors was inspired by the binding motifs found in the crystal structures of the complexes formed between benzene-based acyclic receptors, bearing three recognition units (see Figure 2), and monosaccharides, which we have reported some time ago.[5] In particular, the formation of 2:1 receptor−sugar complexes as in the case of compound **10** (see Figure 3a/b) and participation of the central benzene ring of **10** in CH···π interactions with the CH-groups of β-glucoside[5] has inspired us to design the new receptor architecture (see Figure 3c). The macrocyclic compounds of type I, bearing two flexible side arms, were expected to have particularly favorable binding capabilities toward carbohydrates and to form 1:1 complexes with monosaccharides, especially with β-glucosides, through participation in the formation of hydrogen bonds and CH−π interactions.[6] Due to the formation of 1:1 complexes, instead of 2:1 receptor−sugar complexes as in the case of **10**, the new compounds were expected to be more effective carbohydrate receptors than the previously studied molecules. Initial binding studies with the prepared compounds, containing benzene-, pyridine-, and pyrimidine-based subunits (see Figure 1), and selected monosaccharides have confirmed the expected favorable binding capabilities of the new compounds. Recently, we have pointed out that "the binding efficiency of the macrocyclic and acyclic receptors can be further influenced by introducing other groups, such as imidazole, indole, pyrrole, pyridinium, quinolinium, and imidazolium units".[4] We now report such structural modifications, including among other things the incorporation of pyrrole groups as Y units (compounds **11**−**13**). Besides the pyrrole-based macrocycles bearing aminopyrimidine (compounds **11** and **13**) or aminopyridine groups (compound **12**) as flexible side arms (X units), compounds **14**−**16** were also prepared (see Figure 4). These compounds contain benzene-, hydroxybenzene- or pyridine-based bridges (Y units) and aminopyrimidine or 8-hydroxyquinoline groups as flexible side arms (X units). The binding properties of the newly prepared compounds **11**−**16** as well as of compounds **3**−**5**, the syntheses of which we have recently reported,[4] were analyzed and compared with those of **1** and **2**, which were found to be powerful receptors for monosaccharides, especially for β-glucosides.[4] A summary of

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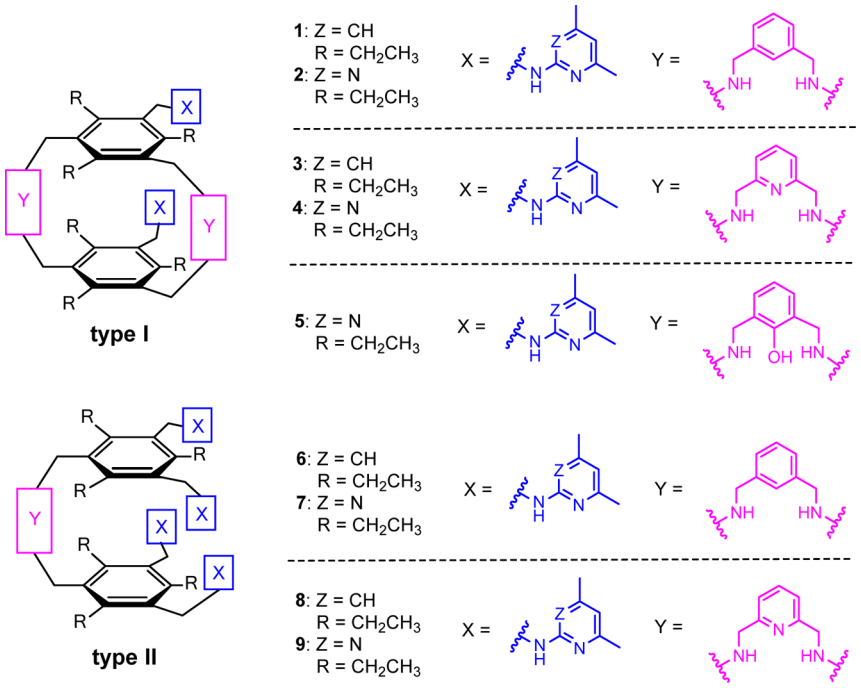

Figure 1. Structures of the previously described macrocyclic compounds **1**–**5**, containing two flexible side arms as recognition units, and the acyclic derivatives **6**–**9** (receptor systems of type I and II).[4]

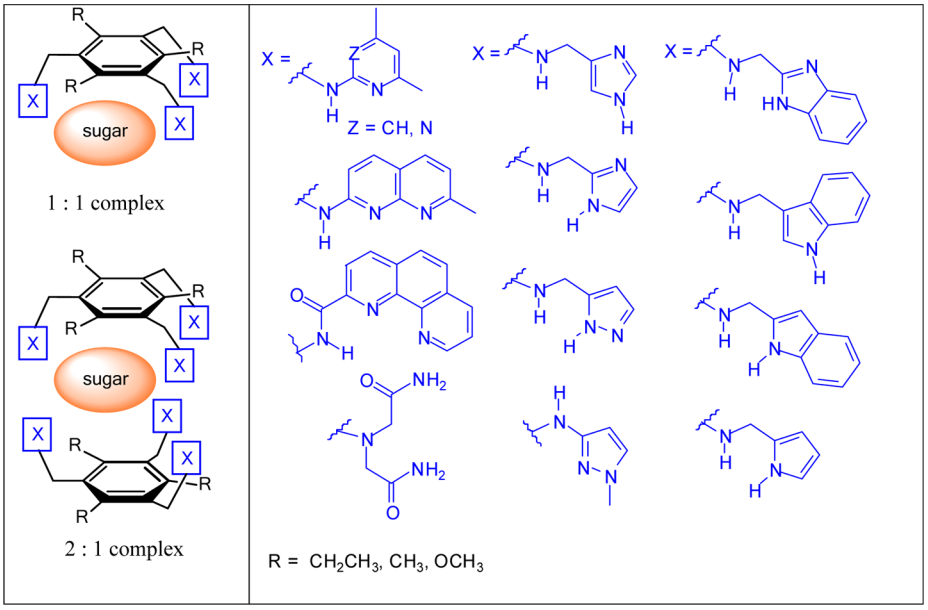

Figure 2. Examples of the previously described benzene-based acyclic receptors, consisting of three recognition groups, and schematic representation of their 1:1 and 2:1 complexes with a sugar molecule.[1,2,5]

the combinations of X and Y units, analyzed in this work, is shown in Table S1 (Supporting Information).

It should be noted that a range of macrocyclic systems have been designed and used for the recognition of carbohydrates;[7] particularly interesting designs and detailed analyses of the binding properties of macrocyclic receptors (synthetic lectins) have been reported by Davis et al.[8] The particular property of the present design, inspired by the results of our crystallographic studies (see Figure 3), is the combination of a macrocyclic building block and flexible side arms as recognition units.[4]

RESULTS AND DISCUSSION

Synthesis. Compounds **11**–**14** are accessible from 1,3-bis(aminomethyl)-5-[(4,6-dimethylpyrimidin-2-yl)aminomethyl]-2,4,6-triethylbenzene (**21**) or 1,3-bis(aminomethyl)-5-[(4,6-dimethylpyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene (**22**) and the corresponding carbaldehydes, such as pyrrole-2,5-dicarbaldehyde (**25**),[9] diethyl 2,5-diformyl-1*H*-pyrrole-3,4-dicarboxylate (**28**),[10] or 2-hydroxyisophthalaldehyde (**29**) (the aldehydes **25** and **28** were prepared on the base of compounds **23**/**24** and **26**/**27**, respectively, as shown in Scheme 1). Compounds **21** and **22** can

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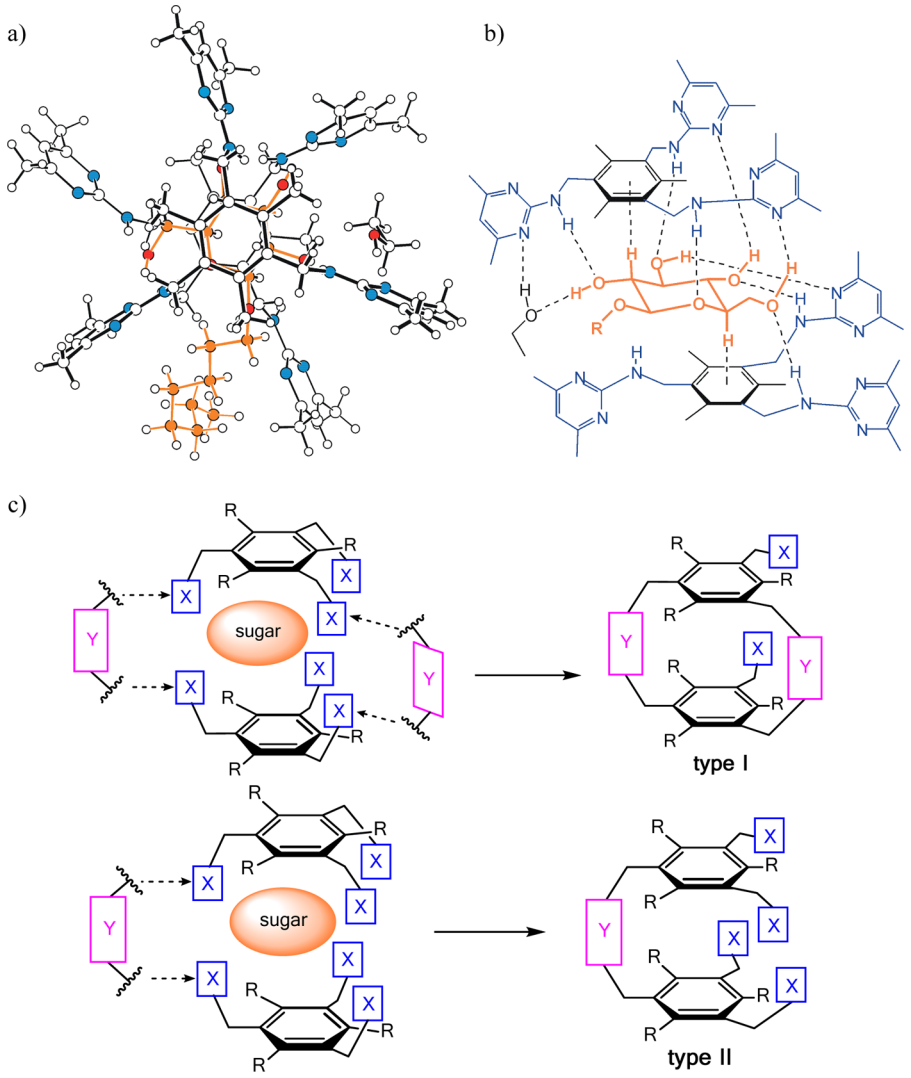

Figure 3. (a) Crystal structure of the 2:1 complex between pyrimidine-based receptor **10** (X = aminopyrimidine, R = CH_3) and octyl β-D-glucopyranoside.[5] (b) Schematic representation of the binding motifs observed in the crystal structure of the 2:1 complex between **10** and octyl β-D-glucopyranoside.[5] (c) Design of the receptors of type I and II (see also ref 4).

be obtained in two steps from the corresponding bromo derivatives **17** and **18**,[2c,4] respectively (via compounds **19** and **20**, see Scheme 1). The basis for the synthesis of compounds **15** and **16** was the diamine **33**, which was prepared from 1,3,5-tris-(aminomethyl)-2,4,6-triethylbenzene (**31**)[11] and 8-hydroxyquinoline-2-carbaldehyde (**32**). The reaction of **33** with isophthalaldehyde (**34**) or pyridine-2,6-dicarbaldehyde (**35**) provided the corresponding imines (compounds **15a** and **16a**), which were reduced without further purification with sodium borohydride to give the products **15** and **16** (see Scheme 2).

Binding Studies. The binding properties of compounds **11**–**16** and of the previously prepared **3**–**5** were analyzed on the basis of ^{1}H NMR and/or fluorescence spectroscopic titrations in organic media. In addition, binding studies in two-phase systems, such as phase transfer of sugars from aqueous into organic solvents, were carried out in the case of the pyrrole-based macrocycles **11** and **13**. The results of the extractions of methyl glycosides from aqueous solution into nonpolar solvent (liquid–liquid extractions) were compared with those obtained for compounds **1** and **2**,[4] consisting of benzene-based bridges. As mentioned by Davis et al., the extractions of substrates from water into nonpolar solvents "allow straightforward comparisons between receptors under conditions which mimic, to some extent, the cytosol-membrane interface in biology".[12]

Studies of the extraction of methyl glycosides, such as β-glucoside **36**, β-galactoside **37**, α-glucoside **38**, and α-galactoside **39**, from aqueous solution into chloroform (see Table 2) revealed a binding preference for β-glucoside, i.e., for a substrate with all-equatorial substitution pattern (similar to the receptors reported by Davis et al.[8]). Compared to **1** and **2**, compounds **11** and **13** showed increased affinity to the tested carbohydrates, but similar binding preferences; the extractability decreased in the sequence β-glucoside **36** > β-galactoside **37** > α-glucoside **38** > α-galactoside **39.** Among the tested compounds, compound **11** was found to be the most powerful receptor for β-glucoside **36**. Compared to **13**, the polarization of the pyrrole N–H bond of **11** (due to the presence of the ester groups in the pyrrole units) may be responsible for a better binding ability of **11**. It should, however, be noted that compound **13** seems to be a better receptor for β-galactoside **37** than **11** (see Table 1).

Compound **11** was further tested against D-glucose. The extractions performed with **11** (1 mM $CDCl_3$ solutions) showed that about 0.5 equiv of D-glucose (0.46–0.51 equiv in three experiments) could be extracted from 1 M aqueous solution.

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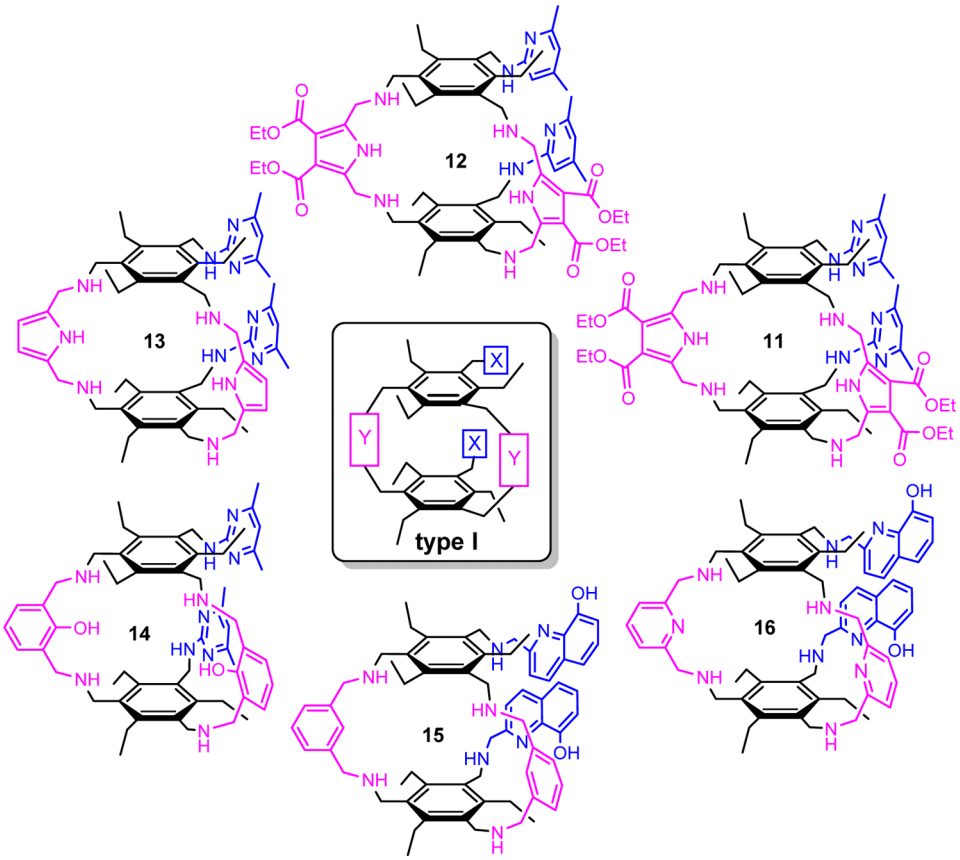

Figure 4. Structures of the macrocyclic compounds **11**−**16** bearing two flexible side arms.

It should be noted that similar extractability was observed for an interesting tricyclic carbohydrate receptor reported by Davis et al.[12]

The interactions of **11**−**16** and **3**−**5** with octyl β-D-glucopyranoside (**40**) were investigated by ^{1}H NMR spectroscopic titrations in which the concentration of the corresponding receptor was held constant and that of the sugar was varied. In addition, inverse titrations were performed, in which the concentration of β-glucopyranoside **40** was held constant. The ^{1}H NMR titration data were analyzed using the WinEQNMR 2 program;[13] the binding constants are summarized in Table 2.

In the case of compounds **11** and **13**, bearing pyrrole-based bridges[14] and aminopyrimidine groups as flexible side arms, the sequential additions of β-glucoside **40** caused progressively replacement of the receptor signals by a new set of signals, as shown in Figures 5 and S1 (see the Supporting Information). Such spectral changes, observed both in $CDCl_3$ and in DMSO-d_6/$CDCl_3$ mixtures, are consistent with complex formation in which exchange between bound and unbound forms is slow on the NMR time-scale. The estimation of the binding constants directly from the relative ratios of the free and bound receptor provided indication of very strong 1:1 binding (K_{11} > 100000 M^{-1} for both **11**·**40** and **13**·**40**); however, errors were significant and accurate binding constants could not be determined from the performed ^{1}H NMR titrations experiments.[15]

The spectra of the pyrrole-based compound **12**, bearing aminopyridine groups as flexible side arms, showed upon addition of **40** both the appearance of a new set of signals and significant movements of the receptor signals, as shown in Figure 6. This result implies complex formation with both slow and fast equilibration on the NMR time-scale. Such simultaneous presence of slow- and fast-exchanging complexes prevented quantitative calculation of the binding constants on the base of the titration data.

The binding properties of compounds **11** and **12**, containing pyrrole-based bridges, as well as of the previously reported **1** and **2**, bearing benzene-based bridges,[4] were further analyzed by fluorescence titrations in $CHCl_3$ and DMSO/$CHCl_3$ mixtures (the properties of the pyrrole-based derivative **13** could not be analyzed by the fluorescence method). The titration experiments were carried out by adding increasing amounts of the sugar to a solution of the corresponding receptor (according to the protocol described in ref 2b and in the Supporting Information). The titration data were analyzed using the ReactLab Equilibria program;[16] in all cases, the changes in the fluorescence output fitted well to a 1:1 binding model (due to lower sugar concentrations used in the case of the fluorescence measurements, the formation of additional weaker 1:2 receptor−sugar complexes, as indicated by NMR titrations, has not been detected). The addition of **40** to a solution of **11** in $CHCl_3$, for example, caused increase in the fluorescence output (saturation occurred after the addition of 1 equiv of **40**), as shown in Figure 7a, and the analysis of the titration data gave K_{11} = 393550 M^{-1} (see Table 2 and Figure S7 in Supporting Information). Thus, the fluorescence method confirmed the very strong binding indicated by the NMR titrations. As expected, the addition of 10% DMSO[17] (see Figure 7b) caused a significant decrease in binding affinity, but the binding was still strong (K_{11} = 72276 M^{-1}). According to the results of the fluorescence titrations obtained for **1**, **2**, **11**, and **12**, the binding affinity toward β-glucoside **40** decreases in the following sequence: **11** (pyrrole/pyrimidine) > **12** (pyrrole/pyridine) > **2** (benzene/pyrimidine) > **1** (benzene/pyridine-based

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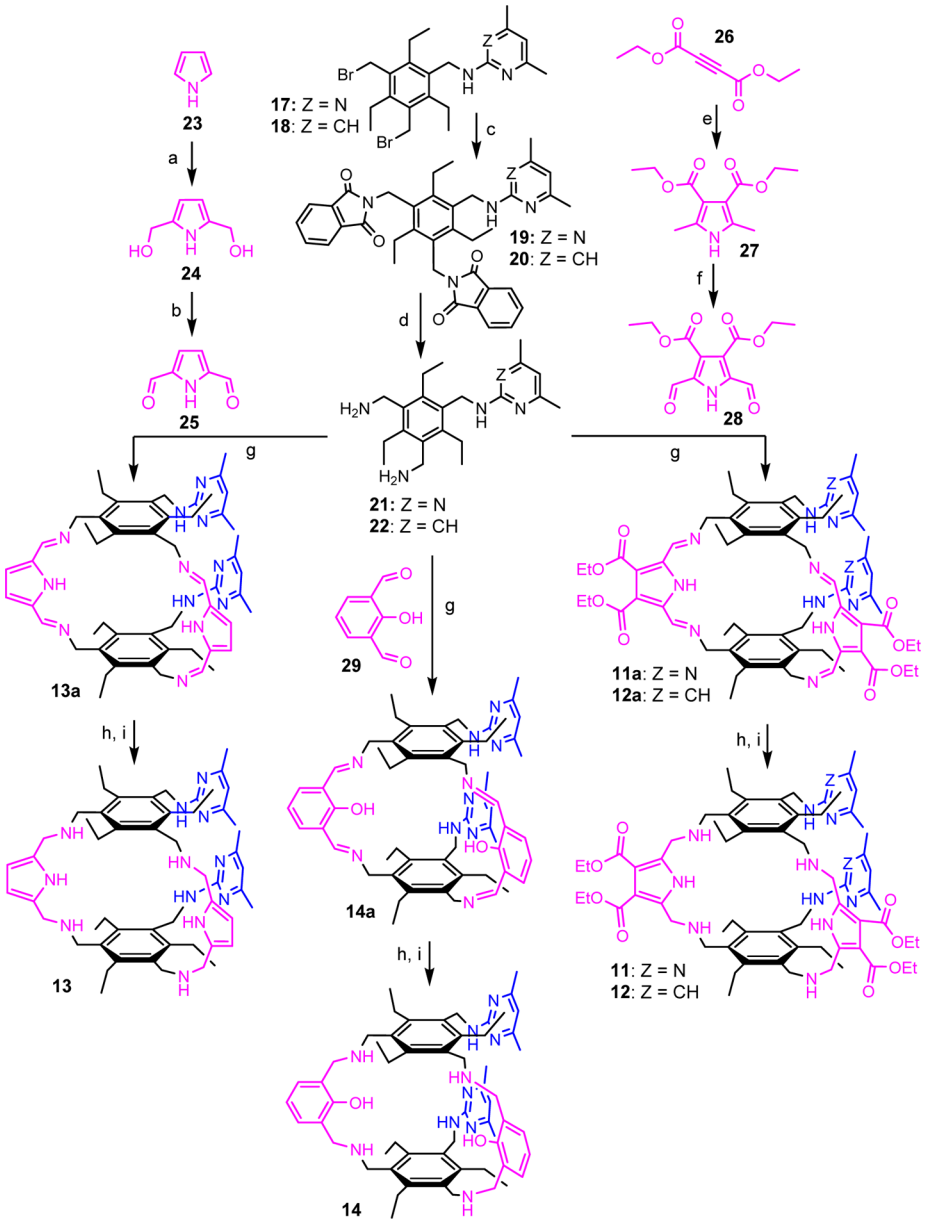
Scheme 1. Synthesis of Compounds 11−14[a]



[a]Key: (a) CH_2O, K_2CO_3; (b) activated MnO_2;[9] (c) potassium phthalimide, DMSO; (d) N_2H_4, EtOH/toluene; (e) *N*-acetyl-D,L-alanine (**30**), Ac_2O; (f) CAN (cerium ammonium nitrate), H_2O/MeCN;[10] (g) EtOH, AcOH (catalytic amount); (h) $NaBH_4$, MeOH; (i) H_2O.

Y/X combination) (see Table 2). Given the higher basicity of aminopyridine compared to aminopyrimidine, higher affinities of pyridine-based receptors might be expected; however, the presence of two nitrogens in the pyrimidine ring ensures the effective formation of the favorable hydrogen bonding motifs shown in Figure 8c (in contrast to the less favorable binding motifs shown in Figure 8b).

Compounds **3**−**5** and **14** consisting of aminopyridine or aminopyrimidine groups as flexible side arms[18] and pyridine- (**3** and **4**) or hydroxybenzene-based bridges (**5** and **14**) were shown to be less effective receptors for **40** than their analogues consisting of pyrrole- (**11**−**13**) and benzene-based bridges (**1** and **2**). In particular, a drastic reduction of the binding affinity was observed for compounds **5** and **14**, consisting of hydroxybenzene units. It should be noted that due to the possible formation of intramolecular hydrogen bonds[19] shown in Figure 9, a decrease in affinity of **3**−**5** and **14** was expected, but such a drastic drop in binding capacity as in the case of **5** and **14** has not been predicted.

Furthermore, the replacement of the aminopyridine or aminopyrimidine groups by 8-hydroxyquinoline-based side arms also results in a reduction of the binding affinity, as observed in the case of compound **15** (analogue of **1** and **2**) and **16** (analogue of **3** and **4**). The possible participation of the quinoline units of **15** and **16** in the formation of intramolecular hydrogen bonds, as illustrated in Figure 10a, can be responsible for such binding behavior.

The binding properties of compounds **3**−**5** and **14**−**16** were analyzed on the base of ^{1}H NMR titrations in $CDCl_3$. In all cases, the addition of **40** caused movements of receptor signals (for examples, see Figure 11 and Figure S3, Supporting Information), which implies binding with fast−medium

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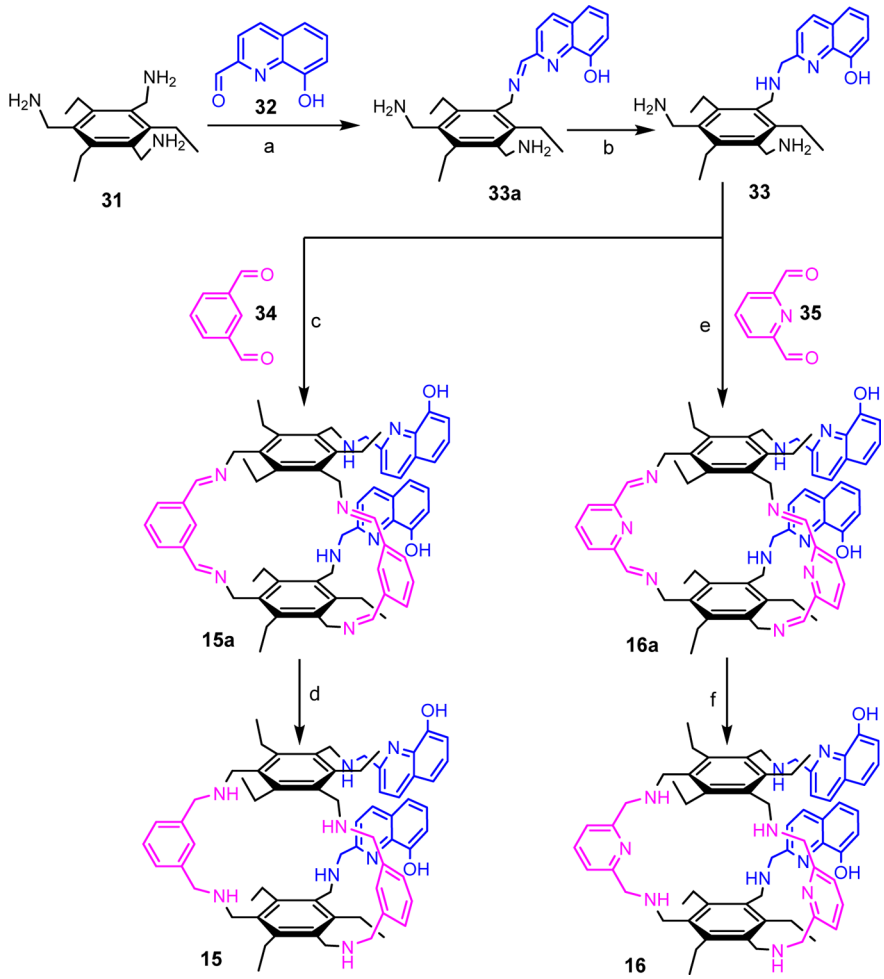
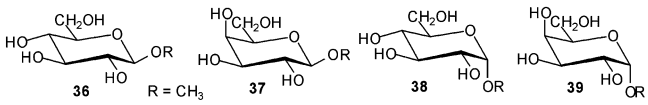
Scheme 2. Synthesis of Compounds 15 and 16[a]



[a]Key: (a) 8-hydroxyquinoline-2-carbaldehyde (**32**), CH_2Cl_2; (b) $NaBH_4$, MeOH; (c) isophthalaldehyde (**34**), CH_2Cl_2, molecular sieves 4 Å; (d) MeOH, $NaBH_4$; then H_2O; (e) pyridine-2,6-dicarbaldehyde (**35**), CH_2Cl_2, molecular sieves 4 Å; (f) MeOH, $NaBH_4$; then H_2O.

Table 1. Extractability of Methyl Glycosides 36−39 from Aqueous Solution (1 M) into $CDCl_3$ by Compounds 1, 2, 11, and 13 (1 mM $CDCl_3$ Solutions)[a,b]



receptor	β-glucoside 36	β-galactoside 37	α-glucoside 38	α-galactoside 39
11	0.81	0.50	0.45	0.38
13	0.74	0.58	0.38	0.22
2[b]	0.50	0.40	n.d.[c]	0.09
1[b]	0.40	0.36	0.15	0.06

[a]Values in molar equivalents with respect to receptor; 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). [b]Results for **1** and **2** from ref 4. [c]Not determined.

exchange on the NMR time scale. The motions of the receptor signals gave the best fit to a mixed 1:1 and 1:2 receptor−sugar binding model (for examples, see Figures S4−S6, Supporting Information) and were analyzed to give the binding constants listed in Table 2.

The binding studies revealed that for the different combinations of the X and Y units, the affinity of the tested compounds increases in the order shown in Table 3.

Selected Molecular Modeling and ROESY Studies. Among the tested compounds, compounds **11** and **13**, bearing pyrrole and pyrimidine groups, were found to be particularly powerful receptors for β-glucosides **36** and **40** (as shown by studies in two-phase systems and in homogeneous media). Molecular modeling calculations indicated the formation of the expected CH−π interactions and hydrogen bonds in the complexes **11**·**36**, **11**·**40**, **13**·**36**, and **13**·**40**, as shown in Figures 12 and 14 and Figures S8 and S9 (see also Figures S27 and S28, Supporting Information). Structural aspects of binding were also detailed analyzed by NMR spectroscopy. ROESY studies confirm the geometry of binding and give detailed structures for the complexes **11**·**40** (see Figure 13) and **13**·**40** (see Figure S10, Supporting Information).

The binding motifs shown in Figures 12 and 14 show remarkable similarity to the motifs found in the crystal structures of the complexes formed between artificial receptors and β-glucosides (see, for example, the complex **10**·**40**,[4] Figure 3a/b) as well as to the motifs observed in the crystal structures of protein−carbohydrate complexes.[20] As in the crystalline complexes, all OH groups and the ring oxygen atom of the bound sugar are involved in the formation of hydrogen bonds,

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Table 2. Association Constants[a,b] for Compounds 11−16 and 1−5 and β-Glucopyranoside 40

receptor	solvent	method[e]	K_{11} [M^{-1}], K_{12}[c] [M^{-1}], β^{d} [M^{-2}]
11	$CDCl_3$	NMR	indication of very strong binding, see[f]
	$CHCl_3$	fluorescence	393550 (K_{11})
	10% DMSO/$CHCl_3$	fluorescence	72276 (K_{11})
12	$CDCl_3$	NMR	indication of very strong binding[g]
	$CHCl_3$	fluorescence	278821 (K_{11})
13	$CDCl_3$	NMR	indication of very strong binding[f,h]
14	$CDCl_3$	NMR	5984 (K_{11}), 475 (K_{12}), 2.84×10^6 (β)
5	$CDCl_3$	NMR	3300 (K_{11}), 578 (K_{12}), 1.91×10^6 (β)
15	$CDCl_3$	NMR	69662 (K_{11}), 404 (K_{12}), 2.81×10^7 (β)
16	$CDCl_3$	NMR	38097 (K_{11}), 2223 (K_{12}), 8.46×10^7 (β)
4	$CDCl_3$	NMR	44200 (K_{11}), 3340 (K_{12}), 1.47×10^8 (β)
3	$CDCl_3$	NMR	40060 (K_{11}), 1780 (K_{12}), 7.13×10^7 (β)
2	$CHCl_3$	fluorescence	253512 (K_{11})
	5% DMSO/$CHCl_3$	fluorescence	113000 (K_{11})
	10% DMSO/$CHCl_3$	fluorescence	23496 (K_{11})
1	$CHCl_3$	fluorescence	210870 (K_{11})

[a]Average K_a values from multiple titrations. [b]Errors were estimated at ⩽10%. [c]K_{12} corresponds to 1:2 receptor−sugar association constant titrations. [d]Cumulative binding constant. [e]Fluorescence or ^{1}H NMR spectroscopic titrations. [f]Complex formation with slow equilibration on the NMR time-scale (NMR titrations in which the concentration of receptor remains constant and that of sugar varied); binding constants evaluated from the relative ratios of the free and bound receptor provided indication of very strong 1:1 binding (K_{11} > 100000 M^{-1}), however, errors were significant and accurate binding constants could not be determined. [g]Complex formation with both slow and fast equilibration on the NMR time-scale prevented quantitative calculation of the binding constants. [h]Analysis of the complexation-induced chemical shifts of the sugar signals observed during the titrations of β-glucoside **40** with **13** (inverse titrations) gave a very good fit to a mixed 1:1 and 1:2 receptor−sugar binding model [292000 (K_{11}), 4170 (K_{12}), 1.22×10^9 (β)].

including cooperative hydrogen bonds (such as NH → OH → N). Furthermore, the CHs of the sugar molecule participate in the formation of the CH···π interactions with the two central benzene rings of the receptor molecule. Both sides of the pyranose ring are involved in CH···π interactions (as in the complexes of sugar binding proteins where often one or two aromatic residues stack on the sugar ring), so that the sugar is fully encapsulated in the receptor cavity. In the case of the pyrrole units substituted with ester groups, the studies indicated interactions of the octyl chain of **40** with the pyrrole rings of **11**, as shown in Figure 12. Comparison of Figure 12a (complex **11**·**40**) or Figure 14a (complex **13**·**40**) with Figure 3a (crystalline complex **10**·**40**) clearly shows the similarity of the binding modes and reflects the usefulness of the receptor design illustrated in Figure 3c.

CONCLUSION

In summary, we have presented here the design, syntheses, and binding properties of compounds combining a macrocyclic building block and flexible side arms as recognition units for carbohydrates (compounds of type I). The design of such receptor architecture was inspired by the binding motifs observed in the crystal structures of complexes formed between artificial receptors and monosaccharides, reported by our group some times ago. The obtained results confirmed the validity of the receptor design illustrated in Figure 3c and revealed that crystalline receptor−sugar complexes are particularly valuable basis for the design of new effective receptor systems (as shown already in ref 4). The expected favorable binding capabilities of the new compounds were confirmed by studies in two-phase systems, such as liquid−liquid extractions of glycosides **36**−**39** and D-glucose from water into organic phase, and by studies in homogeneous media, including ^{1}H NMR and fluorescence spectroscopic titrations with β-glucoside **40**. The studies performed with compounds **11**−**13** revealed a binding preference[21] for sugars with all-equatorial substitution pattern (**36** and **40**) and the formation of very strong 1:1 complexes with β-glucoside **40** (K_{11} > 100000 M^{-1} in $CDCl_3$; see Table 2). ^{1}H NMR titrations indicated that besides the strong 1:1 complexes, considerable weaker 1:2 receptor−sugar complexes exist in the

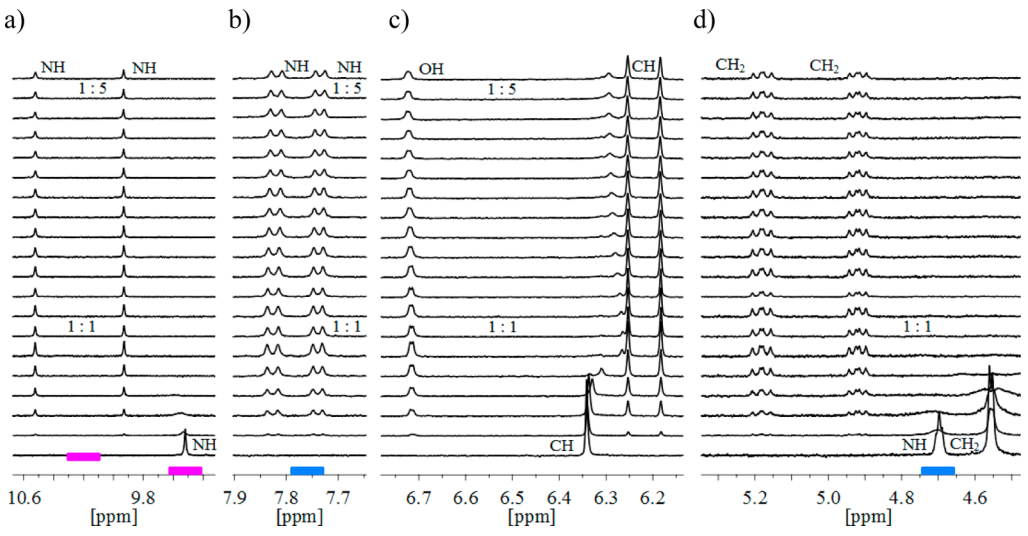

Figure 5. Partial ^{1}H NMR spectra ($CDCl_3$, 500 MHz) of compound **11** after the addition of 0.00−5.35 equiv of octyl β-glycoside **40**; [**11**] = 1.00 mM. Shown are the (a) NH(A), (b) NH(B), (c) CH(C), (d) NH (B), and CH_2(D) signals of **11** [for labeling see Figure 13; in (c) shown is also OH-3 signal of **40**]. Color code: NH(A), magenta; NH(B), blue.

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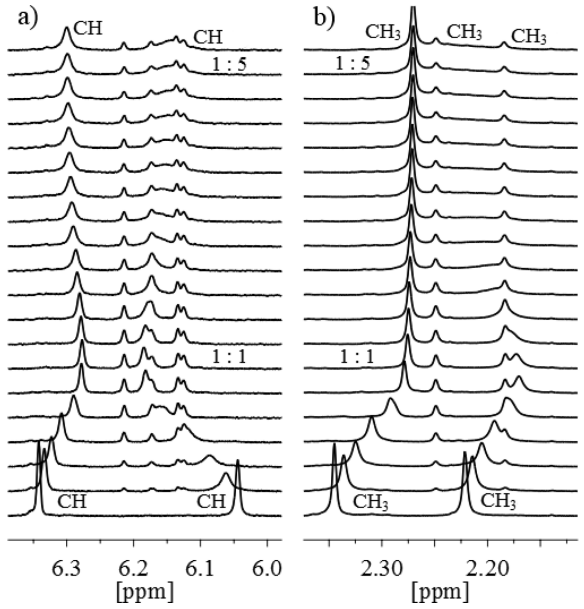

Figure 6. Partial ^{1}H NMR ($CDCl_3$, 500 MHz) spectra of receptor **12** after the addition of 0.00−5.33 equiv of β-glucoside **40**; [**12**] = 0.99 mM.

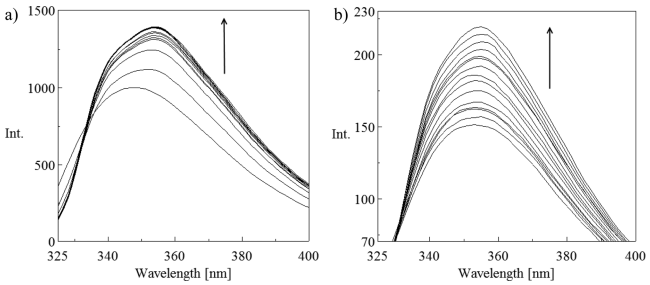

Figure 7. Fluorescence titration of receptor **11** with β-glucoside **40** in (a) $CHCl_3$ and (b) 10% DMSO/$CHCl_3$. Excitation wavelength 296 nm. (a) [**11**] = 0.10 mmol, equiv of **40**: 0.00−3.43 (saturation occurred after the addition of 1 equiv of **40**); (b) [**11**] = 0.12 mmol, equiv of **40**: 0.00−3.22.

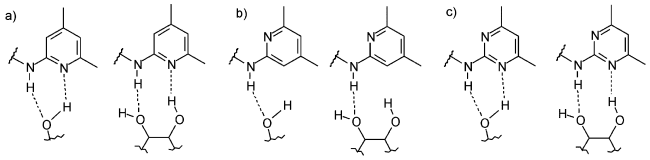

Figure 8. Examples of hydrogen bonding motifs formed by aminopyridine (a, b) and aminopyrimidine group (c) with carbohydrates.

solution under the used titration conditions. Because of the lower sugar concentrations used in the case of the fluorescence titrations, the formation of complexes of higher stoichiometry has not been detected. The three-dimensional structures of the receptor−sugar complexes were examined on the basis of ROESY and molecular modeling studies, which provided a structural understanding of the factors influencing the complex stability.

Compared to the previously tested receptors **1** and **2**, bearing benzene-based bridges and aminopyridine or aminopyrimidine groups as flexible side arms, the pyrrole-based analogues **11**−**13** were shown to be more effective in the recognition of β-glucoside. Compounds bearing pyrimidine groups seem to be more effective than those with pyridine-based side arms. The binding affinity decreases in the sequence **11** > **13** > **12** > **2** > **1** > **4** > **3** > **15** > **16** >**14** > **5** (for relative comparison of the binding capacity of **1**−**16**, see Table 3).

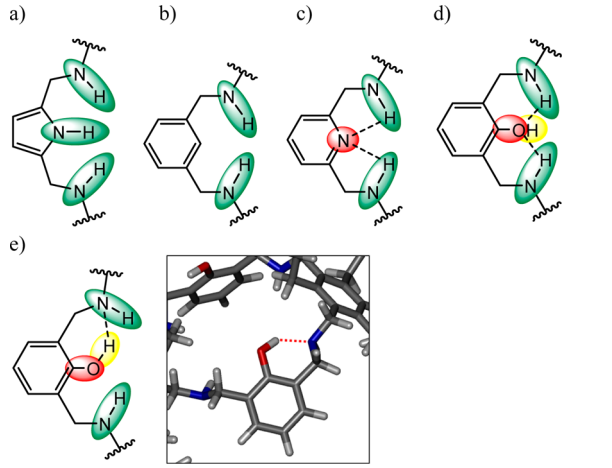

Figure 9. Pyrrole- (a), benzene- (b), pyridine- (c), and hydroxybenzene-based (d, e) bridges used for the construction of compounds **1**−**16** with marked intramolecular hydrogen bonds (d, e) indicated by molecular modeling calculations (MacroModel V.8.5, OPLS AA force field, MCMM, 50000 steps).

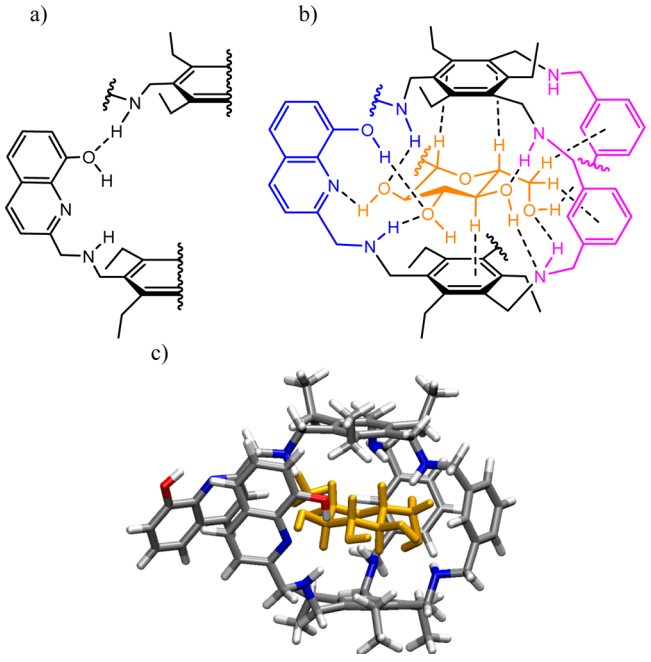

Figure 10. (a) Example of an intramolecular hydrogen bond in the case of compound **15**. (b) Schematic representation of the binding motifs indicated by molecular modeling for the 1:1 complex between **15** and β-glucoside **40**. (c) Energy-minimized structure of the 1:1 complex **15**·**36** [MacroModel V.8.5, OPLS AA force field, MCMM, 50000 steps. Color code: receptor N, blue; receptor C, gray; the sugar molecule is highlighted in orange].

The considerably lower affinity of compounds **3**−**5** and **14**, consisting of pyridine- or hydroxybenzene-based bridges, in comparison to the benzene- and pyrrole-based analogues, are probably a consequence of the participation of the bridge units of **3**−**5** and **14** in intramolecular hydrogen bonds, as illustrated in Figure 9. Furthermore, the participation of the side arms in intramolecular noncovalent interactions, as in the case of compounds **15** and **16**, incorporating 8-hydroxyquinoline-based side arms,

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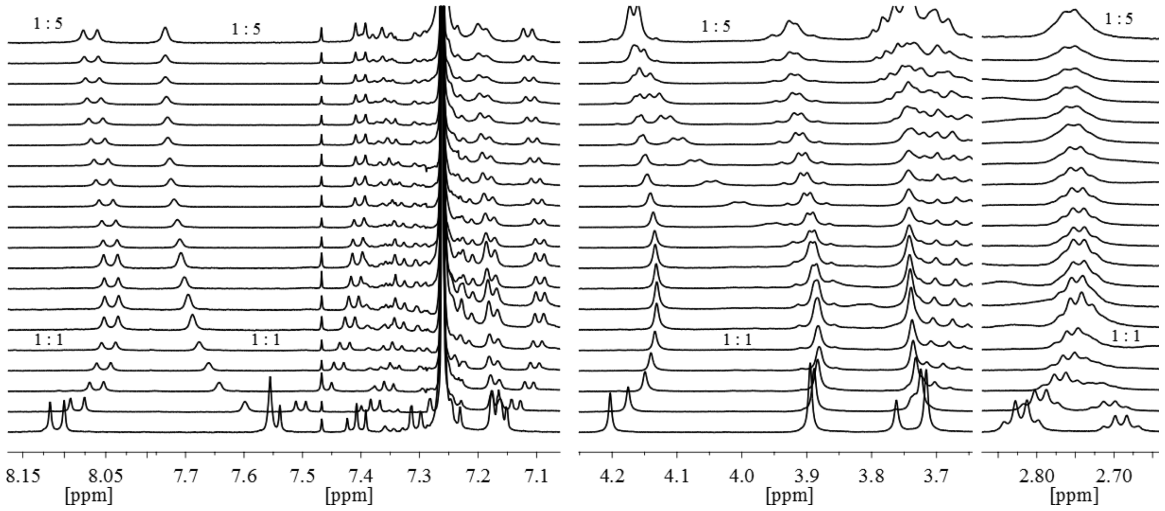
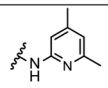
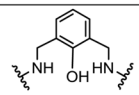
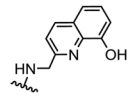
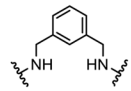
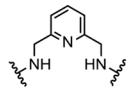
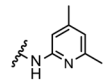
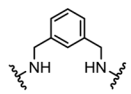
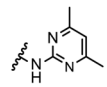
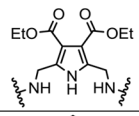
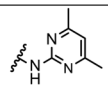
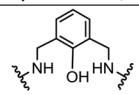
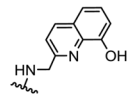
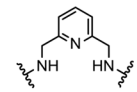
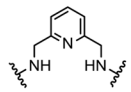
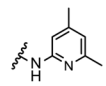
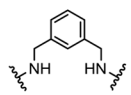
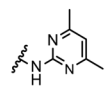
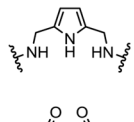
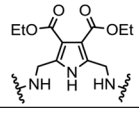


Figure 11. Partial ^{1}H NMR spectra ($CDCl_3$, 500 MHz) of compound **15** after the addition of 0.00−5.02 equiv of *β*-glycoside **40**; [**15**] = 1.01 mM. Shown are following signals of **15** (from left to right): the *CH* (quinoline), $-CH_2NHCH_2-$ (quinoline-based side arms), $-CH_2NHCH_2-$ (benzene-based bridges), and $-CH_2CH_3$.

Table 3. Relative Comparison of the Binding Capacity of Compounds 1−16.

Receptor	X	Y		Receptor	X	Y
5			increase in binding affinity	**15**		
3	"			**1**		"
1	"			**2**		"
12	"					
14			increase in binding affinity	**16**		
4	"			**3**		"
2	"			**4**		"
13	"					
11	"					

result in a reduction of the binding affinity (in comparison to their analogues bearing aminopyridine and aminopyrimidine groups). As revealed by complexation studies with **1**−**16**, it is possible to tune the binding properties of the receptor through the incorporation of different X and Y units and by placing substituents in these subunits.

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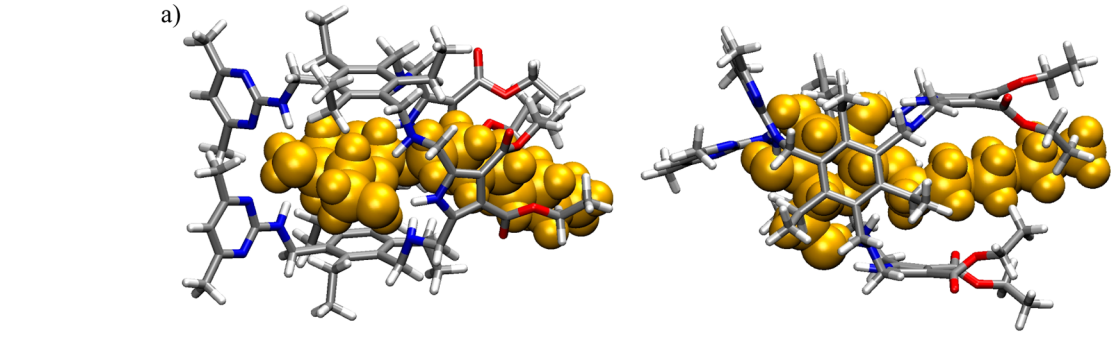
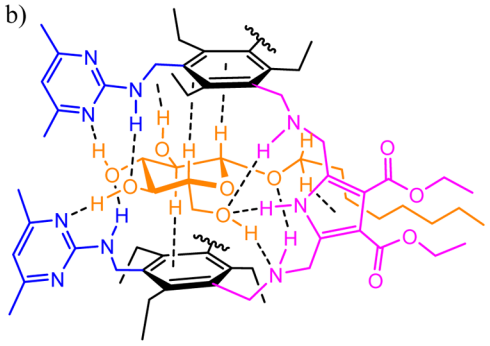


b)



CH-π interactions (sugar···receptor)	Hydrogen bonds (examples) (sugar···receptor)
1-CH···benzene ring	3-HO···HN (aminopyrimidine)
2-CH···benzene ring	3-OH···N (pyrimidine)
5-CH···benzene ring	4-HO···HN (aminopyrimidine)
octyl-CH···pyrrole ring	4-OH···N (pyrimidine)
(2.4 – 2.8 Å)	2-HO···HN (pyrrole), not shown in the Figure 12b
	2-OH···NH, not shown in the Figure 12b
	octyl-O···HN (pyrrole-based bridge)
	(1.7 – 1.9 Å)

Figure 12. (a) Energy-minimized structure of the 1:1 complex formed between receptor **11** and octyl *β*-glucoside **40**; two views of the complex **11**·**40** (MacroModel V.8.5, OPLS 2001 force field, MCMM, 50000 steps). Color code: receptor N, blue; receptor C, gray; the sugar molecule is highlighted in orange. (b) Schematic representation of the binding motifs indicated by molecular modeling and confirmed by NMR spectroscopy for **11**·**40**.

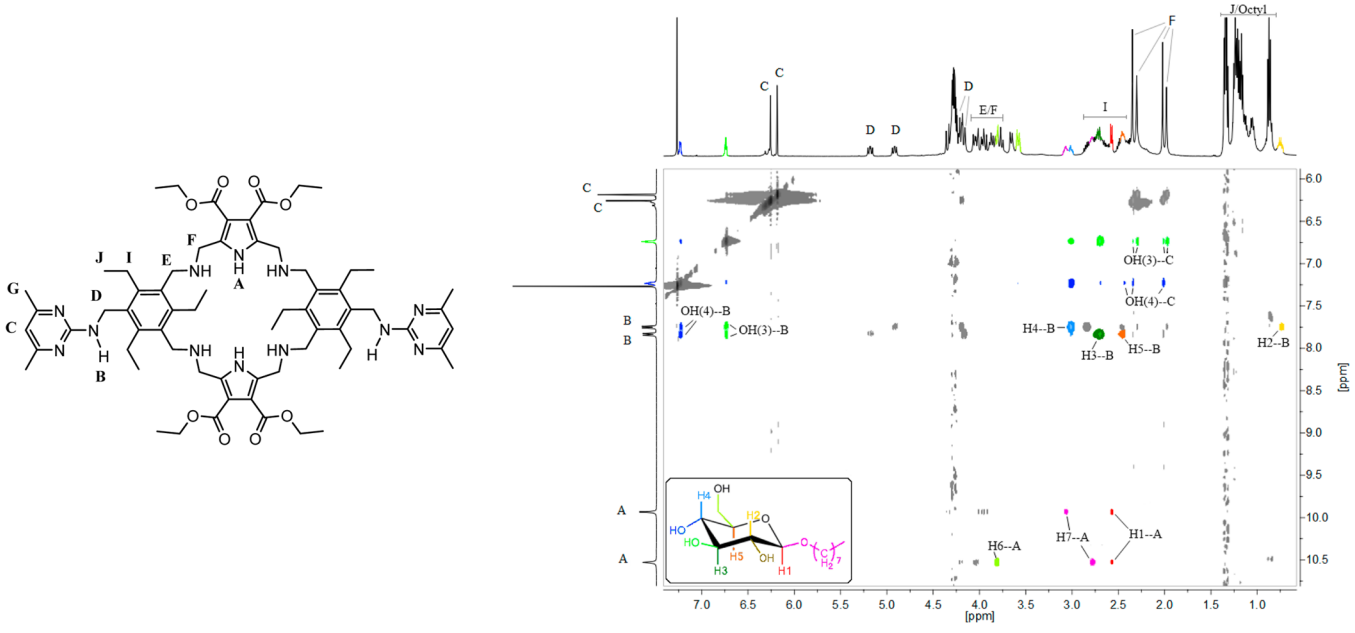


Figure 13. Partial ROESY spectrum of receptor **11** (1 mM) and *β*-glucoside **40** (1 mM) showing intermolecular connections between carbohydrate and receptor (mixing time = 165 ms). The important carbohydrate signals and crosspeaks are highlighted according to the shown molecules.

The properties of compounds of type I are very promising, and their structures provide a basis for further developments. It should be noted that the possibilities of the structure variation of compounds of type I are enormous; some further combinations of X and Y units are shown in Figure 15. In addition, the receptor subunits can have the same of different nature; for example, different X units can be incorporated into the receptor structure (units X1 and X2). The syntheses of new representatives of receptors of type I are the subject of current work.

EXPERIMENTAL SECTION

Analytical TLC was carried out on silica gel 60 F_{254} plates; column chromatography was performed on silica gel. Melting points are uncorrected. Bruker solarix 15T FT-ICR-MS-ESI was used for the HRMS measurements. The syntheses of compounds **21** and **22** are described in refs 2c and 4, whereas the syntheses of **25**, **28**, and **29** are given in refs 9, 10, and 22, respectively. Compounds **32**, **34**, and **35** are commercially available. Descriptions of binding studies in two-phase systems and ^{1}H NMR titrations are given in ref 4 and in the Supporting

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Information, whereas the description of fluorescence titrations is given in ref 2b.

General Procedure for the Synthesis of Compounds 11−14. To a solution of **21** or **22** (0.75 mmol) in dry EtOH/MeOH (50:1 v/v) (10 mL) were added the corresponding aldehyde (**25**, **28**, or **29**; 0.75 mmol) and one drop of acetic acid, and the resulting mixture was stirred for 10 h at 70 °C (in the case of **11**), for 4 or 7 h at 40 °C (in the case of **12** and **13**, respectively), or for 12 h at 60 °C (in the case of **14**). After the mixture was cooled to room temperature, the precipitate (imine **11a**, **12a**, **13a** or **14a**) was filtered, washed with small amounts of EtOH, and dissolved in dry MeOH (10 mL). To this solution was slowly added $NaBH_4$ (about 10 equiv), and the mixture was stirred at room temperature for 3 h. After the solvent was evaporated, the residue was suspended in a mixture of $H_2O/CHCl_3$ (3:1 v/v) and the suspension stirred again for another 3 h. Afterward, the suspension was extracted with $CHCl_3$, and the combined organic layers (100 mL) were washed with H_2O (50 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue dried in vacuum and purified by column chromatography.

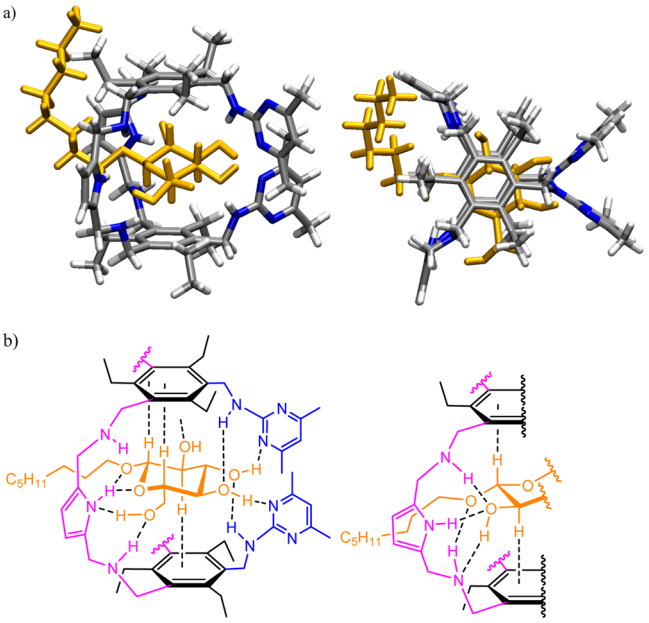

Figure 14. (a) Energy-minimized structure of the 1:1 complex formed between receptor **13** and octyl β-glucoside **40**; two views of the complex **13**·**40** (MacroModel V.8.5, OPLS 2001 force field, MCMM, 50000 steps). Color code: receptor N, blue; receptor C, gray; the sugar molecule is highlighted in orange. (b) Schematic representation of the binding motifs indicated by molecular modeling (interactions with the second pyrrole-based bridge of **13** are shown right) and confirmed by NMR spectroscopy for **13**·**40**.

*Compound **11***. Yield: 49% (0.18 mmol, 216 mg). Mp: 135−140 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.4 Hz, 18H), 1.35 (t, J = 7.1 Hz, 12H), 2.30 (s, 12H), 2.69 (q, J = 7.3 Hz, 8H), 3.04 (q, J = 7.4 Hz, 4H), 3.73 (s, 8H), 4.13 (s, 8H), 4.31 (q, J = 7.1 Hz, 8H), 4.56 (d, J = 4.2 Hz, 4H), 4.72 (t, J = 4.1 Hz, 2H), 6.34 (s, 2H), 9.54 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.4, 16.2, 16.9, 22.5, 23.0, 23.9, 39.9, 46.2, 47.8, 60.2, 109.9, 112.3, 132.8, 134.0, 135.0, 142.5, 143.5, 161.8, 165.2, 167.5. HR-MS (ESI): calcd for $C_{66}H_{93}N_{12}O_8$ 1181.72338 $[M + H]^+$, found 1181.72342.

*Compound **12***. Yield: 83% (0.31 mmol, 366 mg). Mp: 152−153 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.4 Hz, 18H), 1.35 (t, J = 7.1 Hz, 12H), 2.22 (s, 6H), 2.34 (s, 6H), 2.68 (q, J = 7.2 Hz, 8H), 3.03 (q, J = 7.3 Hz, 4H), 3.73 (s, 8H), 4.13 (s, 8H), 4.31 (q, J = 7.1 Hz, 8H), 4.35 (d, J = 4.0 Hz, 4H), 6.05 (s, 2H), 6.34 (s, 2H), 9.54 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.3, 16.2, 17.0, 21.0, 22.5, 22.9, 24.2, 40.6, 46.3, 47.9, 60.1, 103.5, 112.4, 113.9, 132.9, 134.1, 134.9, 142.5, 143.5, 148.7, 156.7, 158.2, 165.9. HR-MS (ESI): calcd for $C_{68}H_{95}N_{10}O_8$ 1179.73288 $[M + H]^+$, found 1179.73287.

*Compound **13***. Yield: 85% (0.32 mmol, 285 mg). Mp: 143−145 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.19 (t, J = 7.4 Hz, 12H), 1.23 (t, J = 7.4 Hz, 6H), 2.30 (s, 12H), 2.71 (q, J = 7.3 Hz, 8H), 2.97 (q, J = 7.2 Hz, 4H), 3.72 (s, 8H), 3.91 (s, 8H), 4.54 (d, J = 4.2 Hz, 4H), 4.70 (t, J = 4.3 Hz, 2H), 5.94 (d, J = 2.5 Hz, 4H), 6.33 (s, 2H), 8.87 (s, 2H). ^{13}C NMR = (125 MHz, $CDCl_3$): δ 16.2, 16.9, 22.2, 22.9, 23.9, 39.9, 47.3, 47.7, 105.4, 109.7, 129.9, 132.4, 134.4, 142.2, 143.6, 161.9, 167.4. HR-MS (ESI): calcd for $C_{54}H_{77}N_{12}$ 893.63886 $[M + H]^+$, found 893.63890.

*Compound **14***. The product was obtained as a light yellowish solid by column chromatography [$CHCl_3$/ MeOH (10:1 v/v) + 1% NH_3 in MeOH). Yield: 36% (0.14 mmol, 127 mg). Mp: 144−145 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.12 (t, J = 7.4 Hz, 6H), 1.22 (t, J = 7.4 Hz, 12H), 2.27 (s, 12H), 2.66 (q, J = 7.3 Hz, 4H), 2.76 (q, J = 7.3 Hz, 8H), 3.75 (s, 8H), 3.97 (s, 8H), 4.53 (d, J = 4.3 Hz, 4H), 4.70 (t, J = 4.0 Hz, 2H), 6.30 (s, 2H), 6.75 (t, J = 7.5 Hz, 2H), 7.05 (d, J = 7.5 Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.7, 16.8, 22.5, 22.8, 23.9, 39.8, 47.3, 52.3, 109.7, 118.7, 124.5, 128.8, 132.8, 133.6, 142.5, 142.9, 156.6, 161.8,

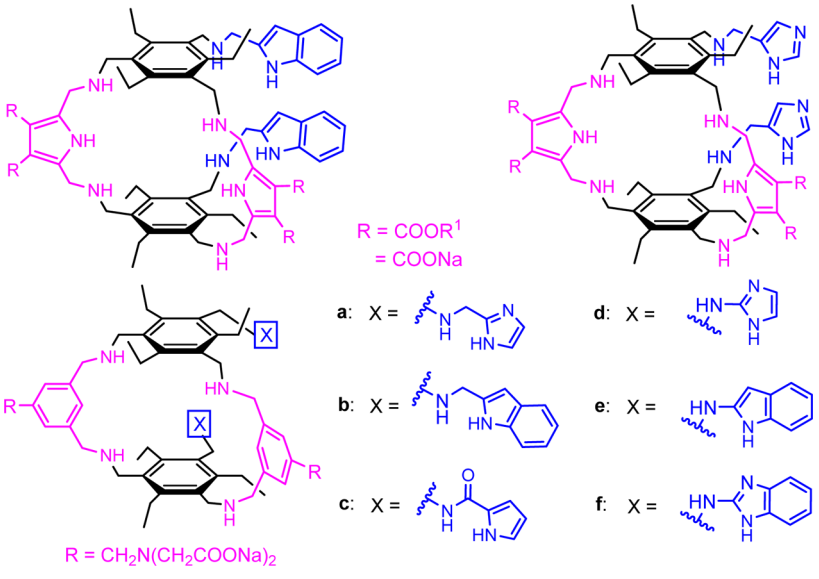

Figure 15. Further examples of receptors of type I and examples of X units, which can be used for their construction.

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167.4. HR-MS (ESI): calcd for $C_{58}H_{79}N_{10}O_2$ 947.63819 $[M + H]^+$, found 947.63904.

General Procedure for the Synthesis of Compounds 15 and 16. A mixture of **33** (200 mg, 0.50 mmol), aldehyde **34** or **35** (0.50 or 0.55 mmol), and molecular sieves (4 Å) in dichloromethane was stirred for 72 h at 40 °C. The molecular sieves were removed, MeOH and $NaBH_4$ (about 5.9 mmol) were added, and the reaction mixture was stirred for another 3 h. Afterward, the solvent was evaporated, the residue was suspended in water (20 mL), and the resulting mixture was stirred again for another 3 h. The suspension was extracted with $CHCl_3$, and the combined organic layers (60 mL) were washed with water (30 mL) and dried over $MgSO_4$. Then the solvent was evaporated, and the residue was dried in vacuum and purified by column chromatography [$CHCl_3$/ MeOH (5:1 v/v) + 1% 7 M NH_3 in MeOH).

Compound ***15***. Yield: 42% (0.11 mmol, 108 mg). Mp: 106−109 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.09 (t, J = 7.5 Hz, 6H), 1.16 (t, J = 7.5 Hz, 12H), 2.67 (q, J = 7.4 Hz, 4H), 2.82 (q, J = 7.4 Hz, 8H), 3.72 (s, 8H), 3.76 (s, 4H), 3.88 (s, 8H), 4.19 (s, 4H), 4.27 (s, 2H), 7.15 (dd, J = 1.1/7.5 Hz, 2H), 7.17 (dd, J = 1.0/7.6 Hz, 4H), 7.24 (m, 2H), 7.29 (dd, J = 1.1/8.3 Hz, 2H), 7.40 (dd, J = 8.2/7.5 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 7.52 (s, 2H), 8.09 (d, J = 8.5 Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.7, 16.9, 22.5, 22.8, 47.3, 47.4, 55.0, 56.1, 110.2, 117.7, 121.4, 126.9, 127.1, 127.5, 127.9, 133.7, 134.2, 137.5, 140.5, 142.0, 142.5, 152.0, 158.4. HR-MS (ESI): calcd for $C_{66}H_{81}N_8O_2$: 1017.64770 $[M + H]^+$, found 1017.64780. R_f = 0.27 [$CHCl_3$/MeOH (7:1) + 1% 7 M NH_3 in MeOH].

Compound ***16***. The product was obtained as a white solid. Yield: 22% (0.06 mmol, 57 mg). Mp: 109−111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.09 (t, J = 7.3 Hz, 6H), 1.16 (t, J = 7.4 Hz, 12H), 2.75 (m, 4H), 2.87 (m, 8H), 3.70 (s, 8H), 3.76 (s, 4H), 4.00 (s, 8H), 4.18 (s, 4H), 7.13 (d, J = 7.9 Hz, 4H), 7.15 (dd, J = 1.3/7.8 Hz, 2H), 7.29 (dd, J = 1.2/8.3 Hz, 2H), 7.40 (m, 2H), 7.54 (d, J = 8.4 Hz,2H), 7.59 (t, J = 7.6 Hz, 2H), 8.09 (d, J = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6, 16.7, 17.3, 22.6, 47.1, 47.4, 55.7, 56.3, 110.1, 117.7, 120.6, 121.2, 121.4, 127.0, 127.5, 134.1, 136.4, 136.7, 137.5, 141.6, 142.6, 152.0, 158.7, 159.1. HR-MS (ESI) calcd for $C_{64}H_{79}N_{10}O_2$: 1019.63819 $[M + H]^+$, found 1019.63816. R_f = 0.15 [$CHCl_3$/ MeOH, 5/1 + 1% 7 M NH_3 in MeOH).

Compound ***33***. A mixture of 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene (**31**) (200 mg, 0.8 mmol) dissolved in 10 mL of dichloromethane, 8-hydroxychinoline-2-carbaldehyde (**32**) (152 mg, 0.88 mmol), and molecular sieves (4 Å) was refluxed for 24 h. After the mixture was cooled to room temperature, the molecular sieves were removed, MeOH (10 mL) and $NaBH_4$ (81 mg, 2.2 mmol) were added, and the resulting mixture was stirred for 3 h. Afterward, the solvent was removed under reduced pressure, the resulting solid suspended in water, and the suspension stirred at room temperature. Then, $CHCl_3$ (5 mL) was added, the organic phase was separated, and the water phase extracted three more times with $CHCl_3$. Combined organic layers were washed with water (15 mL) and dried over $MgSO_4$. The solvent was evaporated and the crude product purified by column chromatography [$CHCl_3$/ MeOH (7:1) + 1% 7 M NH_3 in MeOH]. Yield: 46% (0.37 mmol, 150 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (m, 9H), 2.83 (m, 6H), 3.78 (s, 2H), 3.86 (s, 4H), 4.23 (s, 2H), 7.17 (dd, J = 1.3/7.5 Hz, 1H), 7.32 (dd, J = 1.3/8.3 Hz, 1H), 7.42 (dd, J = 8.3/7.5 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 8.13 (d, J = 8.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.8, 22.6, 39.6, 47.3, 56.2, 110.2, 117.7, 121.4, 127.1, 127.5, 136.5, 136.6, 137.5, 140.4, 151.9, 158.3. HR-MS (ESI): calcd for $C_{25}H_{35}N_4O$: 407.28053 $[M + H]^+$, found 407.28059. R_f = 0.25 [$CHCl_3$/ MeOH (7:1 v/v) + 1% 7 M NH_3 in MeOH].

■ ASSOCIATED CONTENT

Supporting Information

Description of the binding studies. Examples of fitting curves for ^{1}H NMR and fluorescence titrations. Examples of energy-minimized structures of the complexes **11**·**36** and **13**·**36**. ROESY studies for **13**·**40**. Copies of the ^{1}H and ^{13}C NMR spectra of **11**−**16** and **33**. Exemplary energies of the complexes **11**·**40**, **12**·**40**, **13**·**40**, and **15**·**36** (molecular modeling). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to the memory of Professor Dr. Dr. h.c. Reiner Sustmann.

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