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# Artificial Receptors Inspired by Crystal Structures of Complexes Formed between Acyclic Receptors and Monosaccharides: Design, Syntheses, and Binding Properties

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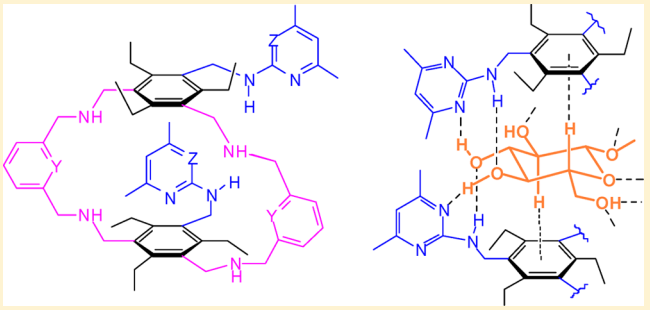
Supporting Information

**ABSTRACT:** The binding motifs found in the crystal structures of complexes formed between artificial receptors and monosaccharides, reported previously by our group, have inspired us to design new macrocyclic and acyclic receptors, which were expected to form strong 1:1 complexes with monosaccharides, in particular with $\beta$-glucosides, through participation in the formation of CH-$\pi$ interactions and hydrogen bonds with the sugar substrate. As first representatives of these compounds we have prepared the macrocycles **8**−**12** and the acyclic molecules **13**−**16**, incorporating two central triethylbenzene units. The new compounds had been designed to bind monosaccharides via interactions of both central benzene rings with the sugar CH groups. Initial binding studies have confirmed the expected favorable binding capabilities of the macrocyclic compounds and indicated interesting binding properties of the acyclic analogues.



## INTRODUCTION

A large number of X-ray crystal structures of carbohydrate-binding proteins bound to various sugar substrates have been described in the literature;[1] however, the crystalline complexes between artificial receptors and sugars are largely unexplored.[2] In this context, the crystal structures of the complexes formed between acyclic receptors and monosaccharides, reported previously by our group,[3] provide valuable model systems to study the basic molecular features of carbohydrate recognition (see Figure 1). The binding motifs found in the crystal structures of the complexes between the aminopyridine-based receptor **1** and methyl $\beta$-glucopyranoside **3a** and also between the pyrimidine-based receptor **2** and octyl $\beta$-glucopyranoside **3b** (see Figure 1b) show remarkable similarity to the motifs observed in the crystal structures of protein−carbohydrate complexes.[1b] All OH groups and the ring oxygen atom of the bound sugar **3a** or **3b** are involved in the formation of hydrogen bonds, including cooperative and bidentate hydrogen bonds; most of the hydrogen bonds exhibit nearly optimal geometry. The typical hydrogen bonding scheme involving sugar OH groups is NH→OH→N, where NH is the amine group and N the pyridine or pyrimidine nitrogen atom of the receptor **1** or **2**. In addition, the CHs of the sugar molecule participate in the formation of the CH···$\pi$ interactions with the central benzene ring of the receptor molecule. For example, in the case of the 2:1 receptor−sugar complex **2**·**3b**, both sides of the pyranose ring are involved in CH···$\pi$ interactions; the 2-CH of **3b** interacts with the benzene ring of one receptor molecule, whereas the 5-CH interacts with the central benzene ring of the other receptor, as shown in Figure 1b. It should be noted that in the complexes of sugar binding proteins often one or two aromatic residues stack on the sugar ring.[1] The most common hydrogen bonding scheme involving sugar OHs in natural complexes (such as complex of galactose-binding protein (GBP) with D-glucose) is $(NH)_n$→OH→O═C, where NH is a hydrogen bond donor group and O═C is a carbonyl or carboxylate acceptor.[1b]

The binding motifs found in the crystal structures[4] of the complexes **1**·**3a** and **2**·**3b**,[3] in particular the participation of the central benzene ring in CH···$\pi$ interactions with the sugar CH-groups, have inspired us to design new macrocyclic and acyclic carbohydrate receptors of types I and II (see Figure 2a). As first representatives of the two groups we have prepared the macrocyclic compounds **8**−**12** and the acyclic molecules **13**−**16** (see Figure 2b), consisting of two central triethylbenzene units. The macrocyclic compounds of type I were expected to have particularly favorable binding capabilities toward carbohydrates and to form 1:1 complexes with monosaccharides, especially with $\beta$-glucosides, through participation in the formation of hydrogen bonds and CH-$\pi$ interactions.[4] Both triethylbenzene units of the prepared compounds were anticipated to participate in CH-$\pi$ interactions with the sugar CH groups. As a result of the formation of 1:1 complexes, instead of 2:1 receptor−sugar complexes as in the case of receptor **2** (both in the solid state and in solution[3]), the new compounds were expected to be more effective carbohydrate receptors than the previously studied molecules. Examples of binding interactions, indicated by molecular modeling for complexes

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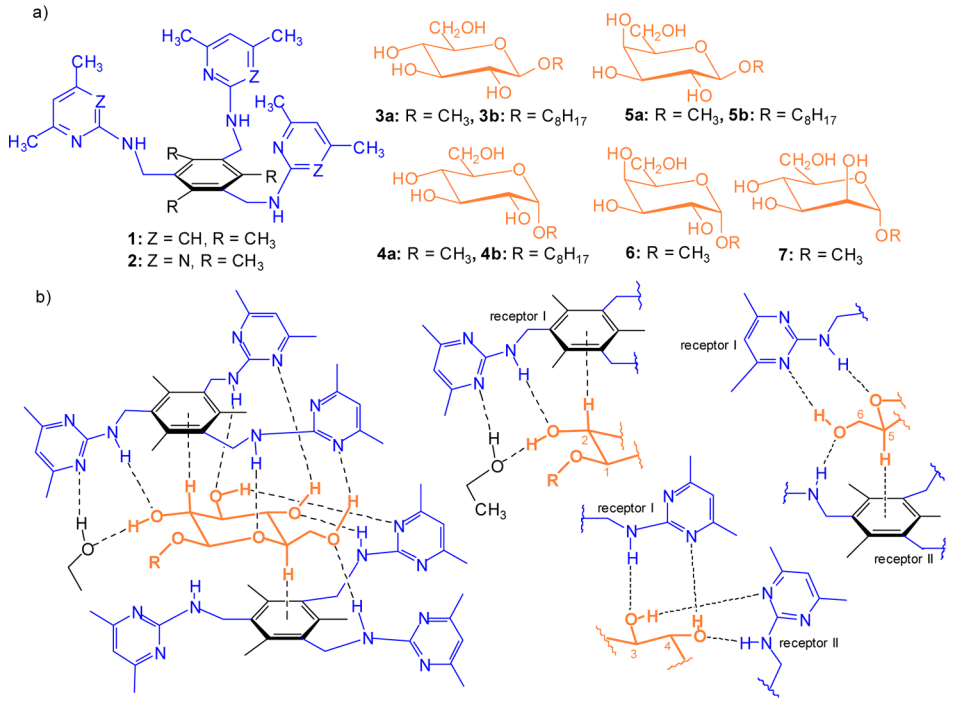


**Figure 1.** (a) Structures of the previously described pyridine- and pyrimidine-based receptors **1** and **2** as well as sugars used for the binding studies. (b) Schematic representation of the binding motifs observed in the crystal structure of the 2:1 complex between pyrimidine-based receptor **2** and octyl $\beta$-D-glucopyranoside (**3b**).[3]

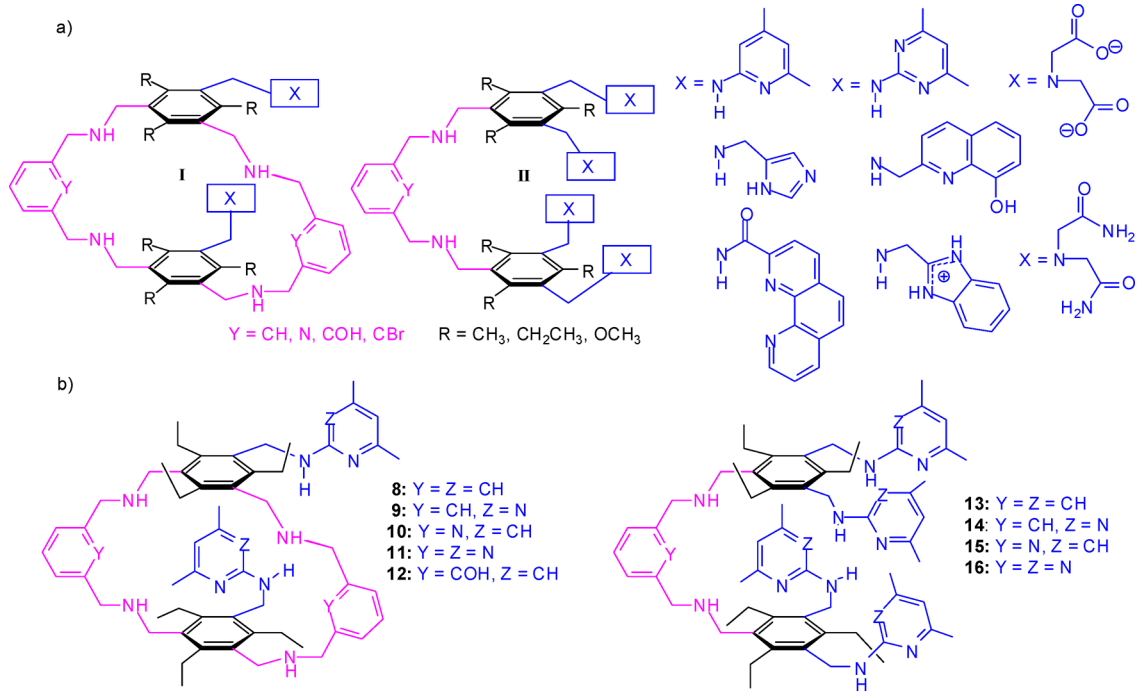


**Figure 2.** (a) Structures of the receptors of types I and II. (b) Structures of the prepared macrocyclic compounds **8**–**12** (receptors of type I) and acyclic derivatives **13**–**16** (type II).

with $\beta$-glucosides, are shown in Figure 3a and b for the complex **9**·**3a**. First binding studies with selected monosaccharides (see below, Tables 1 and 2) have confirmed the expected favorable binding capabilities of the macrocyclic compounds and indicated interesting binding properties of the acyclic analogues.

It should be noted that a number of our previous studies with artificial receptors showed the important role of CH-$\pi$ interactions in the stabilization of receptor–sugar complexes not only in the crystalline state[3] but also in solutions.[6] Particularly interesting results showing the importance of CH-$\pi$ interactions in the molecular recognition of carbohydrates by artificial receptors have been reported in excellent works of Davis et al.[7]


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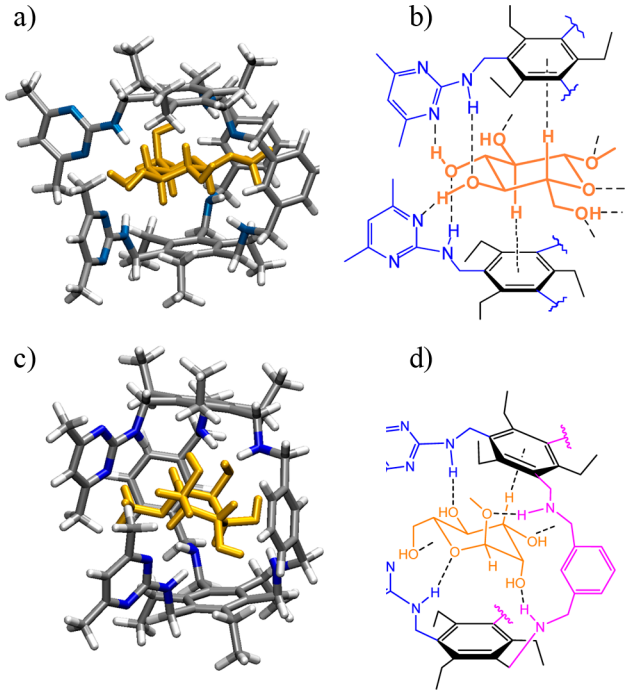


**Figure 3.** Energy-minimized structure of the 1:1 complex formed between receptor **9** and $\alpha$-glucoside **3a** (a) and between **9** and $\alpha$-mannoside **7** (c) [MacroModel V.8.5, OPLS 2001 force field, MCMM, 50000 steps. Color code: receptor N, blue; receptor C, gray; the sugar molecule is highlighted in orange]. (b, d) Examples of binding motifs indicated by molecular modeling for the 1:1 complexes **9·3a** and **9·7**.

## RESULTS AND DISCUSSION

The syntheses of the macrocycles **8**–**12** and the acyclic compounds **13**–**16** are summarized in Schemes 1 and 2, respectively. The basis for the syntheses of compounds **8**–**16** was 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene (**17**), which could be easily obtained[8] from commercially available 1,3,5-triethylbenzene. The reaction of **17** with 2-amino-4,6-dimethylpyridine (**18a**) gave the mono- and disubstituted products **19a** and **28a**, respectively. In the case of the syntheses of **19b** and **28b**, the lower reactivity of 2-amino-4,6-dimethylpyrimidine (**18b**) could be compensated by raising the reaction temperature from room temperature to 55 °C; by doing so the yields of **19b** and **28b** were doubled (a further increase of temperature showed no additional formation of the desired products). Exchange of the solvent from $CH_3CN$/THF to DMF and the base from $K_2CO_3$ to NaOH led almost exclusively to the entirely substituted 1,3,5-tris[(4,6-dimethyl-pyrimidin-2-yl)-aminomethyl]-2,4,6-triethylbenzene.

The conversion of **19a** to the corresponding bis-amine **21a** was carried out via Gabriel synthesis. Compared to the synthesis of **21a** previously reported by our group, compound **21b** could be obtained in better yield of 60% by improving the workup. In contrast to **21a/b** compounds **29a/b** could be easily synthesized in a one-step reaction by stirring **28a/b** in a 7 N solution of ammonia in methanol. The resulting raw products were purified by column chromatography with a methanol/chloroform mixture as a mobile phase to yield **29a** in 78% and **29b** in 87%. Condensation of the corresponding carbaldehyde, such as isophtalaldehyde (**22a**), pyridine-2,6-dicarbaldehyde (**22b**), and 2-hydroxyisophtalaldehyde (**22c**) in dry ethanol, provided the insoluble imines (to increase the yield molecular sieves and a catalytic amount of acetic acid were used). In the case of the cyclic receptors **8**–**12** precipitation of the imines **23**–**27** could be observed almost immediately. For the acyclic receptors **13**–**16** the reaction time had to be doubled to obtain the desired imines **30**–**33**. The imines were filtered off and reduced without further purification with sodium borohydride.

The binding properties of compounds **8**–**12** were first evaluated in two-phase systems through extractions of methyl pyranosides from the solid state into a 1 mM $CDCl_3$ solution of the corresponding macrocyclic compound. Monosaccharides such as $\beta$-glucoside **3a**, $\alpha$-glucoside **4a**, $\beta$-galactoside **5a**, $\alpha$-galactoside **6** and $\alpha$-mannoside **7** were selected as substrates for these experiments. The liquid–solid extractions indicated the expected favorable interactions between the binding partners and provided evidence for stronger complexation of the $\beta$-anomers

**Table 2. Examples of Association Constants[a,b] for Receptors 8/9 and Sugars 3b, 4b, and 5b**

| receptor–sugar complex | solvent[c] | $K_{11}$ [$M^{-1}$] | $K_{12}$[d] [$M^{-1}$] | $\beta_{12} = K_{11}K_{12}$ [$M^{-2}$] |
|---|---|---|---|---|
| **8·3b** | $CDCl_3$ | >100000[e] | *e* | |
| | 5% DMSO-$d_6$/$CDCl_3$ | 16900 | 260 | $4.39 \times 10^6$ |
| **8·4b** | $CDCl_3$ | 11000 | 210 | $2.31 \times 10^6$ |
| **8·5b** | $CDCl_3$ | 12000 | 930 | $1.11 \times 10^7$ |
| **9·3b** | $CDCl_3$ | >100000[e] | *e* | |
| | 5% DMSO-$d_6$/$CDCl_3$ | >100000[e] | *e* | |
| | 10% DMSO-$d_6$/$CDCl_3$ | 22540 | 180 | $4.06 \times 10^6$ |
| **9·4b** | $CDCl_3$ | 13000 | 280 | $3.64 \times 10^6$ |
| **9·5b** | $CDCl_3$ | 16500 | 1100 | $1.81 \times 10^7$ |
| **13·3b** | $CDCl_3$ | 64400 | 1160 | |
| **14·3b** | $CDCl_3$ | >100000[e] | *e* | |

[a]Average $K_a$ values from multiple titrations. [b]Errors in $K_a$ are less than 10%. [c]$CDCl_3$ was stored over activated molecular sieves and deacidified with $Al_2O_3$. [d]$K_{12}$ corresponds to 1:2 receptor–sugar association constant. [e]Calculation program indicated "mixed" 1:1 and 1:2 receptor–sugar binding model with $K_{11}$ > 100000 $M^{-1}$; the binding constants were too large to be accurately determined by the NMR method.

**Table 1. Solubilization of Sugars in $CDCl_3$ by Receptors 8–12 (1 mM Solutions)[a]**

| receptor | $\beta$-glucoside **3a** | $\beta$-galactoside **5a** | $\alpha$-glucoside **4a** | $\alpha$-galactoside **6** | $\alpha$-mannoside **7** |
|---|---|---|---|---|---|
| **8** | 1.12 | 1.10 | 0.46 | 0.50 | 0.14 |
| **9** | 1.40 | 1.25 | 0.41 | 0.82 | 0.23 |
| **10** | 1.23 | 1.15 | 0.44 | 0.44 | 0.18 |
| **11** | 1.28 | 1.05 | 0.36 | 0.62 | 0.15 |
| **12** | 0.43 | 0.48 | 0.19 | 0.25 | 0.14 |

[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.


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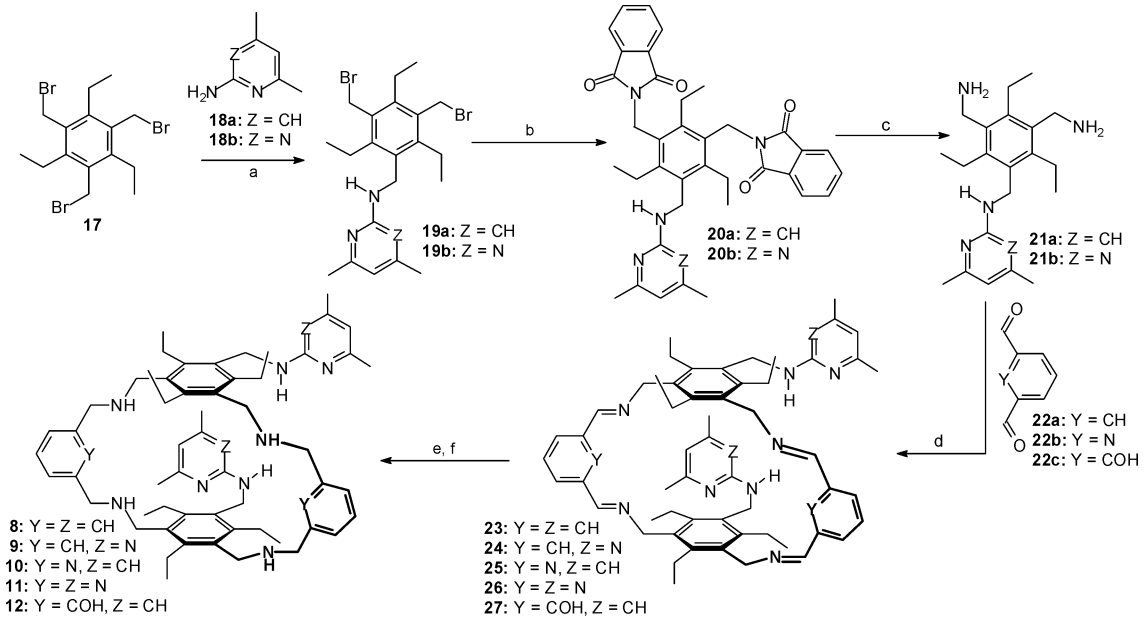
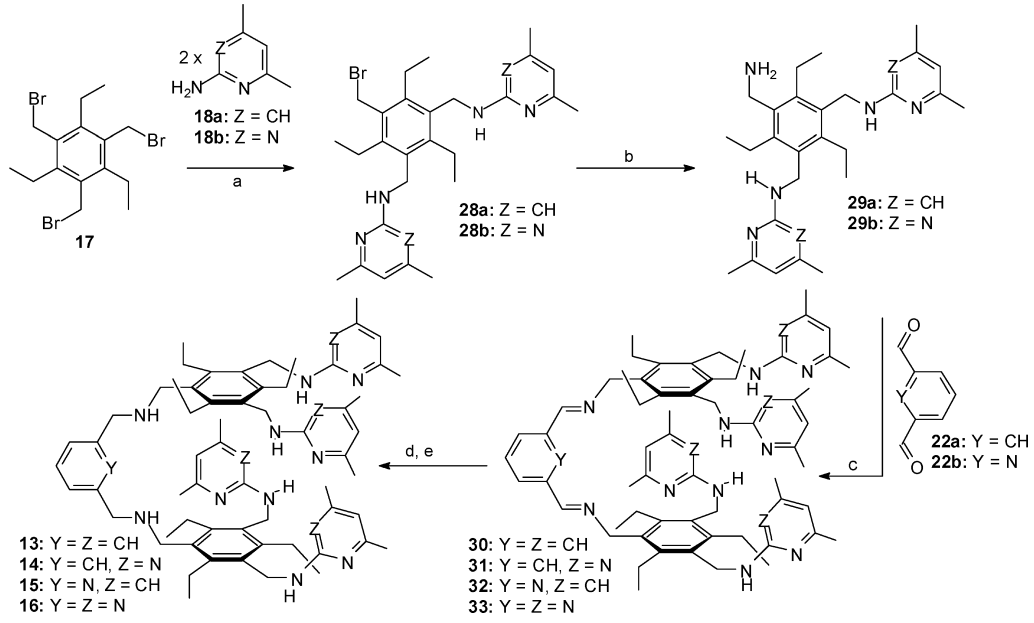
**Scheme 1. Synthesis of Compounds 8−12**[a]




[a]Reagents and conditions: (a) $CH_3CN$/THF, $K_2CO_3$; (b) potassium phthalimide, DMSO; (c) $N_2H_4$, EtOH/toluene; (d) EtOH, AcOH (catalytic amount); (e) $NaBH_4$, MeOH; (f) $H_2O$.

**Scheme 2. Synthesis of Compounds 13−16**[a]




[a]Reagents and conditions: (a) $CH_3CN$/THF, $K_2CO_3$; (b) $NH_3$/MeOH (c) EtOH, AcOH (catalytic amount); (d) $NaBH_4$, MeOH; (f) $H_2O$.

**3a** and **5a** (see Table 1). The preference of **8** and **9** for $\beta$- versus $\alpha$-glucoside indicated by liquid−solid extractions (see also Figure 4) was further confirmed by $^1$H NMR spectroscopic titrations (see below), which showed a particularly high affinity of **8** and **9** for $\beta$-glucoside. Among the tested monosaccharides, $\alpha$-mannoside **7** was the least extracted substrate (see Table 1). Weaker binding of **7** in comparison to **3** was also indicated by molecular modeling calculations, as shown in Figure 3c and d for the complex **9**·**7**. According to the calculations, the binding mode of $\alpha$-mannoside **7** is quite different from that of $\beta$-glucoside **3a**. For example, in contrast to the binding of **3a** by **9**, the pyrimidine nitrogens of **9** do not participate in the formation of hydrogen bonds with the hydroxy groups of **7** (for comparison, see Figure 3b and d).

It should be also noted that in the case of compounds **8**−**11** more than the stoichiometric amount of $\beta$-glucoside **3a** and/or $\beta$-galactoside **5a** was extracted from the solid, suggesting the occurrence of complexes of stoichiometry higher than 1:1.

The properties of macrocycles **8** and **9** were also analyzed through extraction of methyl glycosides from aqueous solution into nonpolar solvent (liquid−liquid extractions), using the procedure described by Davis et al.[9] Studies of the extraction of $\beta$-glucoside **3a**, $\beta$-galactoside **5a**, $\alpha$-glucoside **4a**, and $\alpha$-galactoside **6** from aqueous solution into chloroform revealed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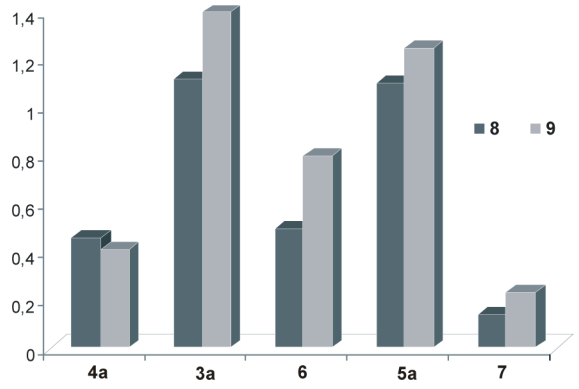


**Figure 4.** Solubilization of sugars **3a**, **4a**, **5a**, **6**, and **7** in $CDCl_3$ by macrocyclic compounds **8** and **9** (1 mM $CDCl_3$ solutions).

that compound **9** (1 mM chloroform solution) is able to extract about 0.50 equiv of $\beta$-glucoside **3a**, 0.4 equiv of $\beta$-galactoside **5a**, and 0.09 equiv $\alpha$-galactoside **6** from 1 M aqueous solutions, whereas **8** is able to extract about 0.40 equiv of **3a**, 0.36 equiv of **5a**, 0.15 equiv of **4a**, and 0.06 equiv of **6** (control experiments were performed in the absence of the corresponding receptor).

As mentioned above, the binding properties of **8** and **9** toward selected monosaccharides were further studied by $^1$H NMR spectroscopic titrations. The interactions of the both compounds with carbohydrates were investigated in $CDCl_3$ and DMSO-$d_6$/$CDCl_3$ mixtures (5:95 and 10:90 v/v) by adding increasing amounts of the carbohydrate to a solution of **8** or **9** as well as by inverse titrations, in which the concentration of sugar was held constant and that of the corresponding receptor was varied. Octyl glycosides such as $\beta$-glucoside **3b**, $\alpha$-glucoside **4b**, and $\beta$-galactoside **5b** were selected as substrates for the initial titration experiments. The $^1$H NMR titration data (for examples, see Figure 5 and Figures S1–S5 in Supporting Information) were analyzed using the EQNMR program;[10] the binding constants are summarized in Table 1.

In the case of $\beta$-glucoside **3b** the interactions with both receptors **8** and **9** in $CDCl_3$ were too strong to be accurately analyzed by the NMR method; the analysis of the titration data indicated the formation of very strong 1:1 receptor–sugar complexes ($K_{11}$ > 100000 $M^{-1}$; see Table 1). After the addition of 5% DMSO-$d_6$ the binding constants for **9**·**3b** were still too strong to be determined by the NMR method ($K_{11}$ > 100000 $M^{-1}$; see Table 2), whereas those for **8**·**3b** were determined to be 16900 ($K_{11}$) and 260 $M^{-1}$ ($K_{12}$), indicating weaker interactions of $\beta$-glucoside **3b** with **8** compared to those with the receptor **9**. Studies performed with $\beta$-glucoside **3b** and compound **9** in 10% DMSO-$d_6$ in $CDCl_3$ revealed $K_{11}$ = 22540 $M^{-1}$ and $K_{12}$ = 180 $M^{-1}$. The observed complexation-induced shifts of the receptor or sugar signals, depending on the titration conditions, revealed that both hydrogen bonds and CH-$\pi$ interactions contribute to the stabilization of the receptor-sugar complex (for examples of spectral changes observed during the titrations, see Figures S1–S8 and Table S1 in Supporting Information).

The spectral changes observed during the titrations of **9** with **3b** in methanol/chloroform mixture (5% $CD_3OD$ in $CDCl_3$; see Table 7 in Supporting Information) were less substantial than those observed during the titrations in dimethyl sulfoxide-containing chloroform solutions. The curve fitting of the titration data obtained in the presence of 5% $CD_3OD$ indicated the formation of weak complexes with 1:1 receptor–sugar stoichiometry ($K_{11} \approx 300$ $M^{-1}$). As expected, the interactions between **9** and **3b** in a more polar solvent such as $CD_3OD$/$CDCl_3$ mixture are weaker than those observed in $CDCl_3$ and in DMSO-$d_6$/$CDCl_3$ mixtures, but it should be noted that the decrease of the binding constant is particularly drastic.

Detailed analyses of the different interactions contributing to complex stability for compounds **8**/**9** and other prepared compounds are the subject of current work. Binding constants obtained for $\beta$-glucoside **3b** and the compounds **8**/**9** in $CDCl_3$ were significantly higher than those determined for $\alpha$-glucoside **4b** and $\beta$-galactoside **5b** (see Table 1). Thus, as in the case of the receptor systems reported by Davis et al.,[7] the compounds **8** and **9** show preference for $\beta$-glucoside, i.e., for a substrate with an all-equatorial substitution pattern. As in the case of the macrocycles **8** and **9**, the acyclic aminopyrimidine-based compound **14** was shown to be a more effective receptor for $\beta$-glucoside **3b** ($K_{11}$ > 100000 $M^{-1}$; see Table 2) than the aminopyridine-based analogue **13**. The binding studies revealed that 1:1 complexes predominate in the solution; however, the presence of weaker 1:2

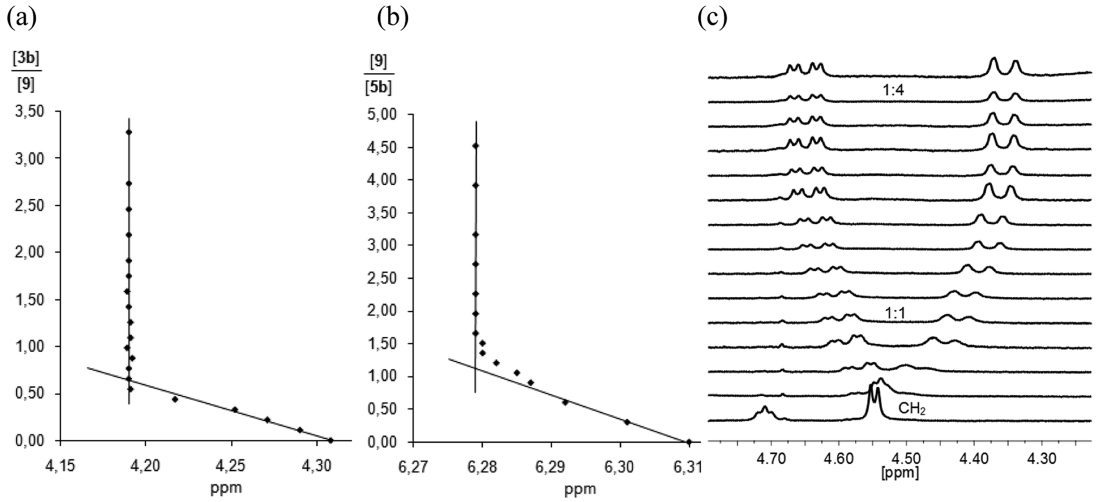


**Figure 5.** (a, b) Mole ratio plots: (a) titration of $\beta$-glucoside **3b** with receptor **9** (analysis of the complexation-induced shift of the CH signal of **3b**; inverse titration) and (b) titration of receptor **9** with $\beta$-galactoside **5b** in $CDCl_3$ (analysis of the complexation-induced shift of the pyrimidine CH signal of **9**). (c) Partial $^1$H NMR spectra (400 MHz) of receptor **9** ([**9**] = 1.01 mM) after addition of 0.00–4.52 equiv of **5b** in $CDCl_3$.


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receptor−sugar complexes were also detected in the $CDCl_3$ or $CDCl_3$/DMSO-$d_6$ mixture.

## CONCLUSION

We have presented here the successful synthesis of nine representatives of new carbohydrate receptors of types I and II shown in Figure 2 (compounds **8**−**16**). The design of these macrocyclic and acyclic compounds was inspired by the binding motifs, especially CH-$\pi$ interactions, observed in the crystal structures of complexes formed between artificial receptors and monosaccharides (complexes **1**·**3a** and **2**·**3b**), reported previously by our group.[3] In contrast to the 2:1 receptor−sugar binding, which was observed in the case of receptor **2** in the solid state and in solution, the new compounds were expected to form strong 1:1 complexes with monosaccharides, especially with $\beta$-glucosides. Preliminary binding studies, including $^1$H NMR spectroscopic titrations and binding studies in two-phase systems, have confirmed the expected favorable binding capabilities of the macrocyclic compounds and indicated promising binding properties of the acyclic analogues.

In the case of the macrocyclic compounds **8** and **9**, the $^1$H NMR titrations revealed effective recognition of neutral carbohydrates, $\beta$- versus $\alpha$-anomer binding preferences in the recognition of glycosides, high binding preference for $\beta$-glucoside, i.e., for a substrate with an all-equatorial substitution pattern ($K_{11}$ > 100000 $M^{-1}$ in $CDCl_3$), and considerably increased binding affinity toward the tested carbohydrates in comparison with the previously described acyclic aminopyridine-based receptor with triethylbenzene-derived core.[11] Complexation-induced upfield shifts of the sugar CH resonances, observed upon addition of **8** or **9** to the $\beta$-glucoside **3b** ("inverse" titrations), clearly indicated the interactions of the CH groups of **3b** with the aromatic residues of the corresponding receptor. Liquid−liquid extractions demonstrated the ability of **8** and **9** to extract monosaccharides from water into nonpolar solvent.

Macrocycle **9** and the acyclic compound **14**, containing aminopyrimidine groups, were shown to be more effective carbohydrate receptors than the aminopyridine-based analogues **8** and **13**, respectively.

The binding properties of compounds **8**−**16** will be analyzed in more detail by $^1$H NMR and fluorescence spectroscopy as well as isothermal titration calorimetry (ITC) in competitive and noncompetitive organic media; it is hoped that suitable derivatives will allow also complexation in aqueous media. X-ray crystallographic investigations are also carried out in our laboratory. Efforts to examine the three-dimensional structures of the receptor−sugar complexes and toward the development of a more complete structural understanding of the factors influencing the complex stability are currently underway.

The binding efficiency of the macrocyclic and acyclic receptors can be further influenced by introducing of other groups, such as imidazole, indole, pyrrole, pyridinium, quinolinium, and imidazolium units as well as other groups, which are shown in Figure 2. The properties of the triethylbenzene-based receptors will be compared with those of the trimethylbenzene- and trimethoxybenzene-based systems. The syntheses of these compounds, including water-soluble analogues, which are expected to perform effective carbohydrate recognition in aqueous solutions, are the subject of current work.

## EXPERIMENTAL SECTION

Analytical TLC was carried out on silica gel 60 $F_{254}$ plates; column chromatography was carried out on silica gel. Melting points are uncorrected. The mass analyzer used for the HRMS measurements was Finnigan MAT 95 XLT (Orbitrap). The syntheses of compounds **19a**, **20a**, and **21a** are described in ref 5m, whereas the syntheses of **28a** and **29a** are given in ref 5l. Compounds **22a** and **22b** are commercial available and the synthesis of **22c** is described in ref 12. For examples of other triethylbenzene-based macrocyclic receptors, see ref 13.

**General Procedure for the Synthesis of Macrocyclic Compounds 8−12.** To a solution of **21a** or **21b** (0.65 mmol) in dry EtOH/MeOH (50:1 v/v) (10 mL) were added the corresponding aldehyde (**22a**, **22b**, or **22c**, 0.65 mmol) and one drop of acetic acid, and the mixture was heated to 70 °C for 12 h. After the mixture was cooled to room temperature, the precipitate was filtered and washed with small amounts of EtOH. The precipitate was solved in dry MeOH (10 mL), $NaBH_4$ (7.28 mmol) was slowly added, and the mixture stirred at room temperature for 3 h. Afterward the solvent was evaporated, the residue was suspended in a mixture of $H_2O$/$CHCl_3$ (3:1 v/v), and the resulting mixture was allowed to stir for 3 h. The suspension was extracted with $CHCl_3$; all combined organic layers (100 mL) were washed with $H_2O$ (50 mL), dried over $MgSO_4$, and evaporated; and the residue was purified by column chromatography ($CHCl_3$/MeOH, 7:1).

**Compound 8.** Yield: 55% (160 mg). Mp: 138−139 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.13 (t, $J$ = 7.4 Hz, 6H), 1.14 (t, $J$ = 7.3 Hz, 12H), 2.21 (s, 6H), 2.34 (s, 6H), 2.71 (q, $J$ = 7.3 Hz, 8H), 2.78 (q, $J$ = 7.3 Hz, 8H), 3.74 (s, 8H), 3.91 (s, 8H), 4.19 (s, 2H), 4.35 (d, $J$ = 4.0 Hz, 4H), 6.08 (s, 2H), 6.32 (s, 2H), 7.17 (t, $J$ = 1.5 Hz, 2H), 7.19 (d, $J$ = 1.3 Hz, 4H), 7.56 (s, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 16.7, 16.9, 22.9, 24.0, 29.7, 40.6, 47.4, 54.9, 103.7, 113.6, 127.2, 128.1, 132.4, 134.4, 142.5, 143.1, 146.1, 158.0. HR-MS (ESI): calcd for $C_{60}H_{81}N_8$ 913.65787 $[M + H]^+$; found 913.65780. $R_f$ = 0.10 ($CHCl_3$/MeOH, 7:1 v/v).

**Compound 9.** Yield: 67% (200 mg). Mp: 142−143 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 1.12 (t, $J$ = 7.4 Hz, 6H), 1.24 (t, $J$ = 7.4 Hz, 3H), 2.29 (s, 12H), 2.69 (q, $J$ = 7.2 Hz, 4H), 2.79 (q, $J$ = 7.4 Hz, 2H), 3.74 (s, 8H), 3.90 (s, 8H), 4.55 (d, $J$ = 4.3 Hz, 4H), 4.73 (t, $J$ = 4.3 Hz, 2H), 6.32 (s, 2H), 7.22 (m, 6H), 7.55 (s, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 167.4, 161.8, 142.9, 142.5, 140.5, 134.4, 132.3, 128.0, 127.0, 127.0, 109.6, 54.9, 47.4, 39.9, 23.9, 22.8, 22.4, 16.8, 16.8. HR-MS (ESI): calcd for $C_{58}H_{79}N_{10}$ 915.64836 $[M + H]^+$; found 915.64840. $R_f$ = 0.67 ($CHCl_3$/MeOH + 1% $NH_3$, 10:1 v/v).

**Compound 10.** Yield: 30% (85 mg). Mp: 180 °C (decomposition). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 1.14 (t, $J$ = 7.3 Hz, 6H), 1.23 (t, $J$ = 7.46 Hz, 12H), 2.19 (s, 6H), 2.35 (s, 6H), 2.83 (q, $J$ = 7.3 Hz, 8H), 2.93 (q, $J$ = 7.3 Hz, 4H), 3.74 (s, 8H),), 4.02 (s, 8H), 4.37 (d, $J$ = 3.4 Hz, 4H), 5.99 (s, 2H), 6.29 (s, 2H), 7.14 (d, $J$ = 7.65 Hz, 4H), 7.60 (t, $J$ = 7.6 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 15.6, 16.3, 20.0, 21.6, 23.1, 39.5, 46.0, 54.7, 102.8, 112.4, 120.0, 131.8, 133.3, 135.7, 141.0, 141.8, 157.2, 158.0. HR-MS (ESI): calcd for $C_{58}H_{79}N_{10}$ 915.64836 $[M + H]^+$; found 915.64839. $R_f$ = 0.41 [$CHCl_3$/MeOH (incl 1% $NH_3$), 7:1 v/v].

**Compound 11.** Yield: 52% (200 mg). Mp: 156−157 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.21 (m, 18H), 2.28 (s, 12H), 2.84 (q, $J$ = 7.5 Hz, 8H), 2.90 (q, $J$ = 7.4 Hz, 4H), 3.74 (s, 8H), 4.01 (s, 8H), 4.55 (d, $J$ = 4.05 Hz, 4H), 4.78 (s, 2H), 6.29 (s, 2H), 7.14 (d, $J$ = 7.6 Hz, 4H), 7.59 (t, $J$ = 7.6 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 16.5, 22.7, 23.9, 39.9, 47.0, 55.7, 109.5, 121.0, 132.7, 134.3, 136.7, 142.0, 142.9, 159.0, 161.8, 167.3. HR-MS (ESI): calcd for $C_{56}H_{77}N_{12}$ 917.63886 $[M + H]^+$; found 917.63910. $R_f$ = 0.10 ($CHCl_3$/MeOH, 7:1 v/v).

**Compound 12.** Yield: 43% (130 mg). Mp: 151−152 °C; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 1.12 (t, $J$ = 7.2 Hz, 6H), 1.22 (t, $J$ = 7.4 Hz, 12H), 2.17 (s, 6H), 2.34 (s, 6H), 2.63 (q, $J$ = 7.3 Hz, 8H), 2.74 (q, $J$ = 7.3 Hz, 4H), 3.75 (s, 8H), 3.97 (s, 8H), 4.06 (s, 2H), 4.35 (d, $J$ = 3.7 Hz, 4H), 5.97 (s, 2H), 6.29 (s, 2H), 6.76 (t, $J$ = 7.5 Hz, 2H), 7.06 (d, $J$ = 7.5 Hz, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 16.8, 21.0, 22.5, 22.8, 24.2, 40.0, 47.3, 52.2, 104.0, 113.6, 118.7, 124.5, 128.8, 133.0, 133.6, 142.4, 142.9, 148.4, 156.6, 158.2. HR-MS (ESI): calcd for $C_{60}H_{81}N_8O_2$ 945.64770 $[M + H]^+$; found 945.64795. $R_f$ = 0.35 [$CHCl_3$/MeOH (incl. 1% $NH_3$) 10:1 v/v].


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**General Procedure for the Synthesis of the Acyclic Compounds 13−16.** In a 25 mL flask were dissolved the corresponding amine (compound **29a** or **29b**, 2 equiv) and the aldehyde (compound **22a** or **22b**, 1 equiv) in dry EtOH. One drop of acetic acid and molecular sieves (3 Å) were added, and the mixture was stirred at 70 °C for 24 h. Afterward the mixture was cooled to room temperature, the resulting precipitate was filtered off and washed with small amounts of EtOH. The solid imine was dissolved in dry MeOH/$CHCl_3$ (20:1 v/v), $NaBH_4$ (12 equiv) was slowly added, and the mixture was stirred for 3 h at room temperature. After addition of $H_2O$, the resulting suspension was extracted with $CHCl_3$, all combined organic layers (50 mL) were washed with $H_2O$ (50 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Pure product was obtained as light yellowish or white solid.

**Compound 13.** Yield: 56% (40 mg). Mp: 100−101 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.18 (m, 18H), 2.22 (s, 12H), 2.34 (s, 12H), 3.70 (s, 4H), 3.92 (s, 4H), 4.14 (s, 4H), 4.33 (d, $J$ = 4.0 Hz, 8H), 6.06 (s, 12H), 6.33 (s, 12H), 7.29 (m, 3H), 7.40 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 16.8, 21.0, 22.7, 22.8, 24.2, 40.5, 46.9, 54.7, 103.4, 113.7, 126.8, 128.1, 128.3, 132.7, 134.7, 140.3, 142.8, 143.1, 148.6, 156.6, 158.2. HR-MS (ESI): calcd for $C_{66}H_{89}N_{10}$ 1021.72662 $[M + H]^+$; found 1021.72678.

**Compound 14.** Yield: 17% (53 mg). Mp: 111−112 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.18 (m, 18H), 2.29 (s, 24H), 2.73 (m, 12H), 3.70 (s, 4H), 3.92 (s, 4H), 4.54 (d, $J$ = 4.3 Hz, 8H), 4.73 (t, $J$ = 4.2 Hz, 4H), 6.32 (s, 4H), 7.30 (m, 3H), 7.38 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 16.6, 16.7, 22.7, 22.8, 23.9, 39.9, 47.0, 54.7, 109.7, 126.7, 128.1, 128.3, 132.7, 134.7, 140.3, 142.9, 143.2, 161.8, 167.4; HR-MS (ESI): calcd for $C_{62}H_{85}N_{14}$ 1025.70761 $[M + H]^+$; found 1025.70690.

**Compound 15.** Yield: 36% (83 mg). Mp: 118−19 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.17 (t, $J$ = 7.4 Hz, 12H), 1.20 (t, $J$ = 7.4 Hz, 6H), 2.22 (s, 12H), 2.34 (s, 12H), 2.70 (q, $J$ = 7.4 Hz, 4H), 2.78 (q, $J$ = 7.4 Hz, 8H), 3.74 (s, 4H), 4.04 (s, 4H), 4.34 (d, $J$ = 4.1 Hz, 4H), 6.06 (s, 4H), 6.32 (s, 4H), 7.29 (d, $J$ = 7.7 Hz, 1H), 7.64 (t, $J$ = 7.7 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 16.8, 21.0, 22.7, 22.8, 24.2, 40.6, 47.2, 56.0, 103.4, 113.7, 120.5, 132.8, 134.7, 136.8, 142.9, 143.2, 148.6, 156.6, 158.2, 159.5. HR-MS (ESI): calcd for $C_{65}H_{88}N_{11}$ 1022.72187 $[M + H]^+$; found 1022.72230.

**Compound 16.** Yield: 27% (40 mg). Mp: 110−111 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 1.17 (t, $J$ = 7.5 Hz, 12H), 1.20 (t, $J$ = 7.5 Hz, 6H), 2.29 (s, 24H), 2.72 (q, $J$ = 7.5 Hz, 4H), 2.78 (q, $J$ = 7.5 Hz, 8H), 3,74 (s, 4H), 4.05 (s, 4H), 4.55 (d, $J$ = 4.3 Hz, 8H), 4.75 (t, $J$ = 4.3 Hz, 4H), 6.33 (s, 4H), 7.30 (d, $J$ = 7.7 Hz, 2H), 7.65 (t, $J$ = 7.6 Hz, 1H). $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 16.6, 16.7, 22.7, 22.9, 23.9, 39.9, 47.1, 56.0, 109.7, 120.4, 132.7, 134.6, 136.8, 142.9, 143.2, 159.5, 161.8. HR-MS (ESI): calcd for $C_{61}H_{84}N_{15}$ 1026.70286 $[M + H]^+$; found 1026.70360.

**1,3-Bis(bromomethyl)-5[(4,6-dimethylpyrimidin-2-yl)-aminomehtyl]-2,4,6-triethyl-benzene (19b) and 1-(Bromomethyl)-3,5-bis[(4,6-dimethylpyrimidin-2-yl)aminomethyl]-2,4,6-triethylbenzene (28b).** A suspension of 2-amino-4,6-dimethylpyrimidine (5.00 g, 40.68 mmol), 1,3,5-tris(bromomethyl)-2,4,6-trimethyl-benzene (6.00 g, 13.56 mmol), and $K_2CO_3$ (5.76 g, 40.68 mmol) in $CH_3CN$/THF (1:2 v/v; 150 mL) was stirred at 50 °C for 72 h. After cooling to room temperature, filtration, and evaporation of solvents, the crude product was purified by column chromatography (EtOAc/toluene, 1:3 v/v).

**Compound 19b.** Yield 20% (1.29 g). Mp: 70−71 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.27 (t, $J$ = 7.6 Hz, 6H), 1.35 (t, $J$ = 7.6, 3H), 2.31 (s, 6H), 2.85 (q, $J$ = 7.6 Hz, 4H), 2.95 (q, $J$ = 7.6 Hz, 2H), 4.57 (d, $J$ = 3.7 Hz, 2H), 4.59 (s, 4H), 4.77 (s, 1H), 6.36 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 167.5, 161.7, 145.0, 143.9, 133.8, 132.3, 109.9, 39.7, 29.1, 24.0, 23.9, 16.2. MS (EI; 70 eV): $m/z$ (%): 483 (2) $[M^+]$, 402 (15), 322 (100), 296 (55), 187 (35), 171 (46), 136 (37), 124 (45), 81 (25). Anal. Calcd for $C_{21}H_{29}Br_2N_3$: C, 52.19; H, 6.05; N, 8.69. Found: C, 52.09; H, 6.07; N, 8.72. $R_f$ = 0.60 (EtOAc/toluene, 1:3 v/v).

**Compound 28b.** Yield: 7% (480 mg). Mp: 79−80 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.21 (t, $J$ = 7.5 Hz, 3H), 1.28 (t, $J$ = 7.5 Hz, 6H), 2.30 (s, 12H), 2.74 (q, $J$ = 7.5 Hz, 2H), 2.68 (q, $J$ = 7.5 Hz, 4H), 4.57 (d, $J$ = 4.3 Hz, 4H), 4.61 (s, 2H), 4.82 (br.s, 2H), 6.35 (s, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 16.2, 16.5, 22.7, 23.9, 29.6, 39.7, 109.8, 131.8, 133.3, 143.7, 144.9, 161.6, 167.5. HR-MS (ESI): calcd for $C_{27}H_{38}N_6Br$ 527.23192 $[M + H]^+$; found 527.23169. $R_f$ = 0.38 (EtOAc/toluene, 1:3 v/v).

**1,3-Bis(phthalimidomethyl)-5-[(4,6-dimethylpyrimidin-2-yl)-aminomethyl]-2,4,6-triethyl-benzene (20b).** A mixture of compound **19b** (2.00 g, 4.15 mmol) and potassium phthalimide (2.30 g, 12.44 mmol) in dry DMSO (50 mL) was heated to 95 °C for 8 h. After the mixture was cooled to room temperature, $H_2O$ (150 mL) was added, and the formed precipitate was filtered and washed with $H_2O$ (200 mL). Then the precipitate was suspended in $H_2O$ (100 mL), and the suspension was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were washed with $H_2O$ (50 mL), dried over $MgSO_4$, and evaporated, and the residue was purified by column chromatography (toluene/EtOAc, 3:1 v/v). Yield: 63% (1.60 g). Mp: 120−121 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.00 (t, $J$ = 7.5 Hz, 3H), 1.09 (t, $J$ = 7.5 Hz, 6H), 2.27 (s, 6H), 2.87 (q, $J$ = 7.5 Hz, 4H), 3.18 (q, $J$ = 7.5 Hz, 2H), 4.58 (d, $J$ = 4.0 Hz, 2H), 4.80 (t, $J$ = 4.0 Hz, 1H), 4.95 (s, 4H), 6.30 (s, 1H), 7.69 (m, 4H), 7.80 (m, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 168.2, 167.4, 161.8, 145.4, 144.6, 133.9, 132.8, 132.0, 129.5, 123.2, 109.6, 39.8, 37.4, 23.9, 23.3, 23.4, 16.1, 15.7. MS (EI; 70 eV): $m/z$ (%): 615 (15) $[M]^+$, 586 (100), 455 (20), 332 (39), 160 (62). Anal. Calcd for $C_{37}H_{37}N_5O_4$: C, 72.17; H, 6.06; N, 11.37. Found: C, 72.10; H, 6.08; N, 11.41. $R_f$ = 0.23 (toluene/EtOAc, 3:1 v/v).

**1,3-Bis(aminomethyl)-5-[(4,6-dimethylpyrimidin-2-yl)-aminomethyl]-2,4,6-triethyl-benzene (21b).** Compound **20b** (1.45 g, 2.36 mmol) was dissolved in a mixture of dry EtOH/toluene (2:1 (v/v)) and refluxed with hydrazine hydrate (0.31 mL, 10.00 mmol) for 20 h. Afterward the solvent was evaporated, the precipitate was suspended in a solution of 40% aq KOH (100 mL), and the suspension was extracted with $CHCl_3$ (100 mL). The extraction was repeated three times, and the combined organic extracts were washed with $H_2O$, dried over $MgSO_4$ and filtered. Yield: 60% (503 mg). Mp: 59−60 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.25 (m, 9H), 2.30 (s, 6H), 2.77 (q, $J$ = 7.5 Hz, 4H), 2.84 (q, $J$ = 7.4 Hz, 2H), 3.88 (s, 4H), 4.56 (d, $J$ = 4.4 Hz, 2H), 4.76 (s, 1H), 6.34 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 167.5, 161.8, 141.5, 141.1, 137.5, 132.9, 109.8, 39.9, 39.7, 23.9, 22.7, 22.6, 16.8. MS (EI; 70 eV): $m/z$ (%): 355 (15) $[M]^+$, 338 (75), 309 (100), 295 (36), 232 (18), 187 (19), 124 (92). Anal. Calcd for $C_{21}H_{33}N_5$ C, 70.95; H, 9.36; N, 19.70. Found: C, 71.00; H, 9.37; N, 19.63. $R_f$ = 0.11 ($CHCl_3$/MeOH, 5:1 v/v).

**1-Aminomethyl-3,5-bis[(4,6-dimethylpyrimidin-2-yl)-aminomethyl]-2,4,6-triethyl-benzene (29b).** In a 50-mL three-necked flask with a dropping funnel, a solution of 1-(brommethyl)-3,5-bis-[(4,6-dimethylpyrimidin-2-yl)aminomehtyl]-2,4,6-triethylbenzene (**28b**) (211 mg, 0.46 mmol) in methanol was slowly dropped into a solution of 2 N ammonia in methanol. The mixture was stirred at room temperature for 48 h, the solvent was removed under reduced pressure, and the residue was purified by column chromatography ($CHCl_3$/MeOH, 5:1 v/v). Yield: 87% (184 mg). Mp: 206−207 °C. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 1.17 (t, $J$ = 7.5 Hz, 6H), 1.22 (t, $J$ = 7.5 Hz, 3H), 2.27 (s, 12H), 2.71 (q, $J$ = 7.5 Hz, 2H), 2.77 (q, $J$ = 7.5 Hz, 4H), 4.24 (s, 2H), 4.52 (s, 4H), 5.18 (s, 2H), 6.33 (s, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 16.4, 16.5, 23.5, 23.7, 37.1, 39.8, 109.9, 127.9, 133.0, 144.1, 145.6, 161.4, 167.6. HR-MS (ESI): calcd for $C_{27}H_{40}N_7$ 462.33397 $[M + H]^+$; found 462.33410. $R_f$ = 0.33 ($CHCl_3$/MeOH, 5:1 v/v).

## ■ ASSOCIATED CONTENT

### Supporting Information

Description of the binding studies; examples of $^1$H NMR titrations; representative mole ratio plots; representative EQNMR plots; change in chemical shift observed during $^1$H NMR titrations; copies of the $^1$H and $^{13}$C NMR spectra of **8−16**, **19b**, **20b**, **21b**, **28b**, and **29b**. 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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## ■ REFERENCES

(1) For examples, see: (a) Lis, H.; Sharon, N. *Lectins*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2003. (b) Quiocho, F. A. *Pure. Appl. Chem.* **1989**, *61*, 1293−1306. (c) Weiss, W. I.; Drickamer, K. *Annu. Rev. Biochem.* **1996**, *65*, 441−473. (d) Gabius, H.-J. *The Sugar Code−Fundamentals of Glycoscience*; Wiley-Blackwell: New York, 2009.

(2) (a) Mazik, M. *Chem. Soc. Rev.* **2009**, *38*, 935−956. (b) Mazik, M. *RSC Adv.* **2012**, *2*, 2630−2642.

(3) Mazik, M.; Cavga, H.; Jones, P. G. *J. Am. Chem. Soc.* **2005**, *127*, 9045−9052.

(4) It should be noted that the identification of weak noncovalent interactions by crystals structures is known to be difficult; see, for example, the controversies about F as hydrogen bond acceptor: (a) Dunitz, J. D. *ChemBioChem* **2004**, *5*, 614−621. (b) Schneider, H.-J. *Chem. Sci.* **2012**, *3*, 1381.

(5) (a) For a recent discussion on the importance of carbohydrate-aromatic interactions, see: Asensio, J. L.; Arda, A.; Caňada, F. J.; Jiménez-Barbero, J. *Acc. Chem. Res.* **2013**, *46*, 946−954. (b) For a recent discussion on the importance of aromatic rings in chemical and biological recognition, see: Salonen, L. M.; Ellermann, M.; Diederich, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 4808−4812. (c) For a discussion on CH-$\pi$ interactions, see: Nishio, M. *Phys. Chem. Chem. Phys.* **2011**, *13*, 13873−13900.

(6) (a) Geffert, C.; Mazik, M. *J. Org. Chem.* **2013**, *78*, 292−300. (b) Sonnenberg, C.; Hartmann, A.; Mazik, M. *Nat. Prod. Commun.* **2012**, *7*, 321−326. (c) Mazik, M.; Geffert, C. *Org. Biomol. Chem.* **2011**, *9*, 2319−2326. (d) Mazik, M.; Sonnenberg, C. *J. Org. Chem.* **2010**, *75*, 6416−6423. (e) Mazik, M.; Hartmann, A. *Beilstein J. Org. Chem.* **2010**, *6*, 9. (f) Mazik, M.; Hartmann, A. *J. Org. Chem.* **2008**, *73*, 7444−7450. (g) Mazik, M.; Buthe, A. C. *Org. Biomol. Chem.* **2008**, *6*, 1558−1568. (h) Mazik, M.; Kuschel, M. *Eur. J. Org. Chem.* **2008**, 1517−1526. (i) Mazik, M.; Cavga, H. *J. Org. Chem.* **2006**, *71*, 2957−2963. (j) Mazik, M.; Kuschel, M.; Sicking, W. *Org. Lett.* **2006**, *8*, 855−858. (k) Mazik, M.; Kuschel, M. *Chem.—Eur. J.* **2008**, *14*, 2405−2419. (l) Mazik, M.; Hartmann, A.; Jones, P. G. *Chem.—Eur. J.* **2009**, *15*, 9147−9159.

(7) (a) Ke, C.; Destecroix, H.; Crump, M. P.; Davis, A. P. *Nat. Chem.* **2012**, *4*, 718−723. (b) Barwell, N. P.; Davis, A. P. *J. Org. Chem.* **2011**, *76*, 6548−6557. For reviews, see: (c) Walker, D. B.; Joshi, G.; Davis, A. P. *Cell. Mol. Life Sci.* **2009**, *66*, 3177−3191. (d) Davis, A. P. *Org. Biomol. Chem.* **2009**, *7*, 3629−3638. (e) Davis, A. P.; James, T. D. In *Functional Synthetic Receptors*; Schrader, T., Hamilton, A. D., Eds.; Wiley-VCH: Weinheim, Germany, 2005; pp 45−109.

(8) Wallace, K. J.; Hanes, R.; Anslyn, E.; Morey, J.; Kilway, K. V.; Siegel, J. *Synthesis* **2005**, *12*, 2080−2083.

(9) (a) Velasco, T.; Lecollinet, G.; Ryan, T.; Davis, A. P. *Org. Biomol. Chem.* **2004**, *2*, 645−647. (b) Ladomenou, K.; Bonar-Law, R. P. *Chem. Commun.* **2002**, 2108−2109.

(10) Hynes, M. J. *J. Chem. Soc., Dalton Trans.* **1993**, 311−312.

(11) Mazik, M.; Radunz, W.; Boese, R. *J. Org. Chem.* **2004**, *69*, 7448−7462.

(12) Zondervan, C.; van den Beuken, E. K.; Kooijman, H.; Spekband, A.; Feringa, B. L. *Tetrahedron Lett.* **1997**, *38* (17), 3111−3114.

(13) (a) Francesconi, O.; Gentili, M.; Roelens, S. *J. Org. Chem.* **2012**, *77*, 7548−7554. (b) Kitamura, M.; Shabbir, S. H.; Anslyn, E. V. *J. Org. Chem.* **2009**, *74*, 4479−4489.