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Trimethoxybenzene- and trimethylbenzene-based compounds bearing imidazole, indole and pyrrole groups as recognition units: synthesis and evaluation of the binding properties towards carbohydrates†

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The aim of the study was to evaluate the potential of trimethoxybenzene- and trimethylbenzene-based compounds bearing imidazole or indole groups as recognition sites in the complexation of carbohydrates. Representatives of these compounds were prepared and their binding properties toward selected carbohydrates evaluated. The results of the binding studies were compared with those obtained for the prepared pyrrole bearing analogues and for the previously described triethylbenzene-based receptors.

Introduction

The imidazole ring of His and the indole ring of Trp are often used by carbohydrate-binding proteins to bind the sugar substrate by hydrogen bonding and CH–π interactions,[1] as shown in Fig. 1 for galactose binding by human galectin-1 and for a complex of Galβ3GalNac with *Amaranthus caudatus* agglutinin. The participation of these electron-rich heterocycles in biorecognition of carbohydrates has inspired us to design artificial carbohydrate receptors[2] consisting of imidazole- and indole-based recognition units; the first representatives of these receptor molecules were reported by our group some years ago.[3] Compounds **1–3**, **6** and **7**, including both 4(5)-substituted imidazole or 3-substituted indole units as the entities used in nature and 2-aminopyridine group as a heterocyclic analogue of the asparagine/glutamine primary amide side chain, were established to be powerful carbohydrate receptors with interesting binding preferences, and were shown to be able to recognize carbohydrates by multiple interactions, including hydrogen bonding and CH–π interactions. The binding properties of **1–3** were compared with those of compounds **4** and **5**, containing pyrrole units and 1-substituted imidazole group, respectively. The 1,3,5-substituted 2,4,6-triethylbenzene scaffold, which was shown to be a valuable building block for carbohydrate receptors[4,5] and other artificial receptor molecules,[6] was used for the construction of both the aminopyridine bearing compounds **1–7** and the symmetrical imidazole-based derivatives **8–10**. The heterocyclic groups of **1–10** were connected to the central benzene ring *via* $-CH_2NH-$, $-CH_2NHCH_2-$ or $-CONHCH_2-$ linkers. In addition to the analysis of the binding properties of the indole and imidazole containing compounds, the properties of the benzimidazole-based derivative **11** were also reported by our group in a previous work.[7]

It is well known that hexaethylbenzene and hexasubstituted benzene derivatives possessing substituents nearly isosteric to ethyl groups adopt a preferred conformation with full up-down alternation of the side-arms, as shown in Fig. 3.[8] In this arrangement the three CH_2X groups of **I** are oriented toward the same face of the central benzene ring, whereas the ethyl groups point in the opposite direction. The 1,3,5 *versus* 2,4,6 facial differentiation of the side-arms of **I** has been exploited for the design of artificial receptors with preorganized binding groups,[6] including the acyclic carbohydrate receptors mentioned above. The 1,3,5-substituted 2,4,6-triethylbenzene scaffold has been found to improve the binding affinities of artificial receptors compared to analogues, which are based on the trimethylbenzene core **II**.[9] By studying experimental data from the literature and the Cambridge Structural Database, Hof and Wang concluded that "the steric gearing offered by the ethyl groups confers some energetic advantage over the methyl groups, but the size of this advantage can be small and is dependent on the groups involved".[10]

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†Electronic supplementary information (ESI) available: Representative EQNMR plots (Fig. S1–S11). Representative mole ratio plots (Fig. S12–S18). ^{1}H NMR titrations of compounds **14a**, **14b**, **16a** and **16b** with β-glucoside **27a** or β-galactoside **29a** (Fig. S19–S27). Copies of the ^{1}H and ^{13}C NMR spectra of **12a–16a** and **12b–16b** (Fig. S28–S48). CCDC 938511. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob41540f

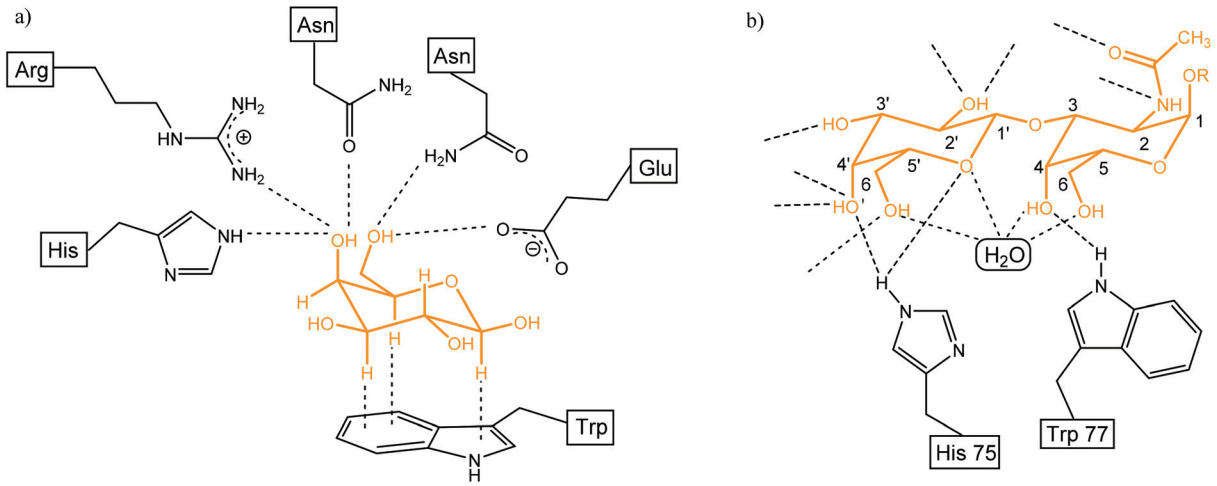


Fig. 1 Examples of noncovalent interactions in the complex of (a) human galectin-1 with galactose[1e,f] and (b) *Amaranthus caudatus* agglutinin with Galβ3GalNAc.[1a]

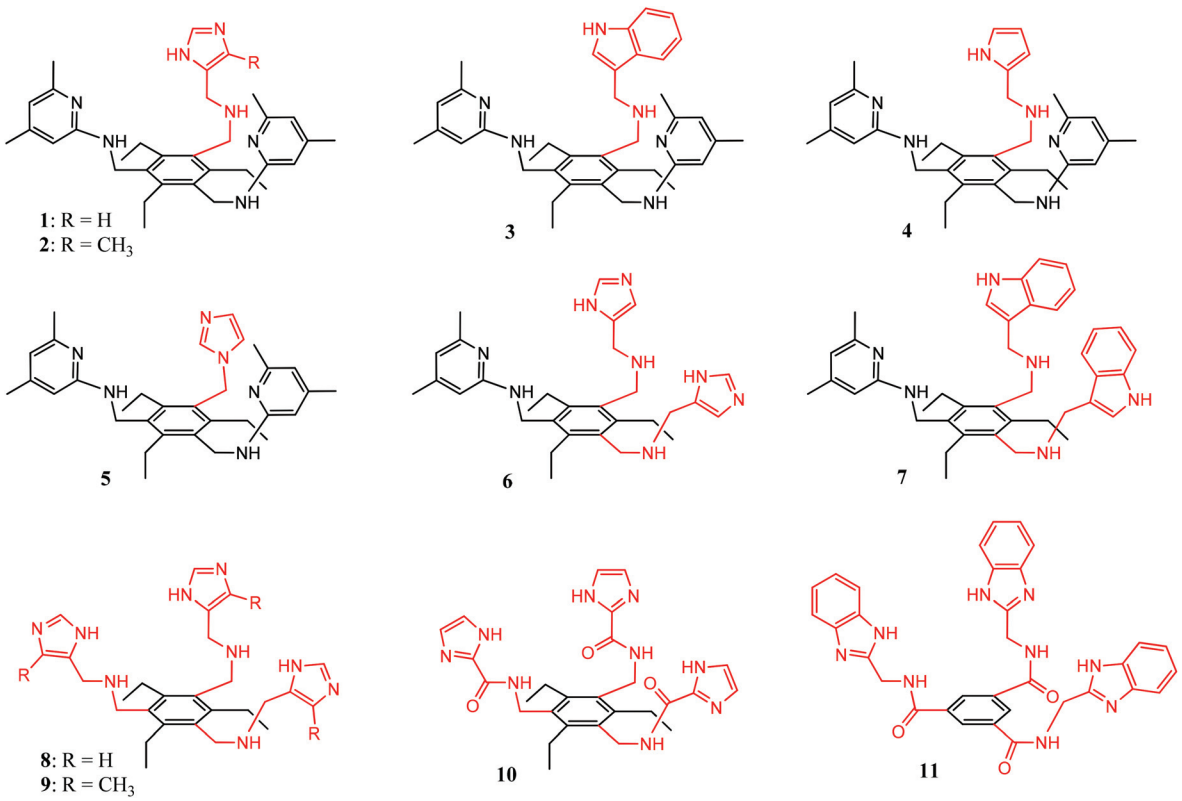


Fig. 2 Structures of the previously described imidazole-, indole- and benzimidazole-based receptors **1–11**.

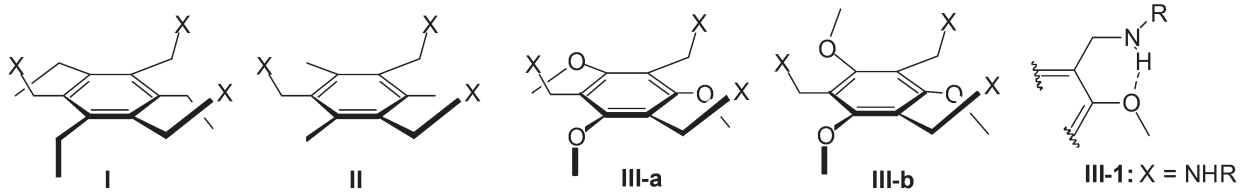


Fig. 3 Triethylbenzene- (**I**), trimethylbenzene- (**II**) and trimethoxybenzene-based (**III**) systems (only selected conformations are shown).

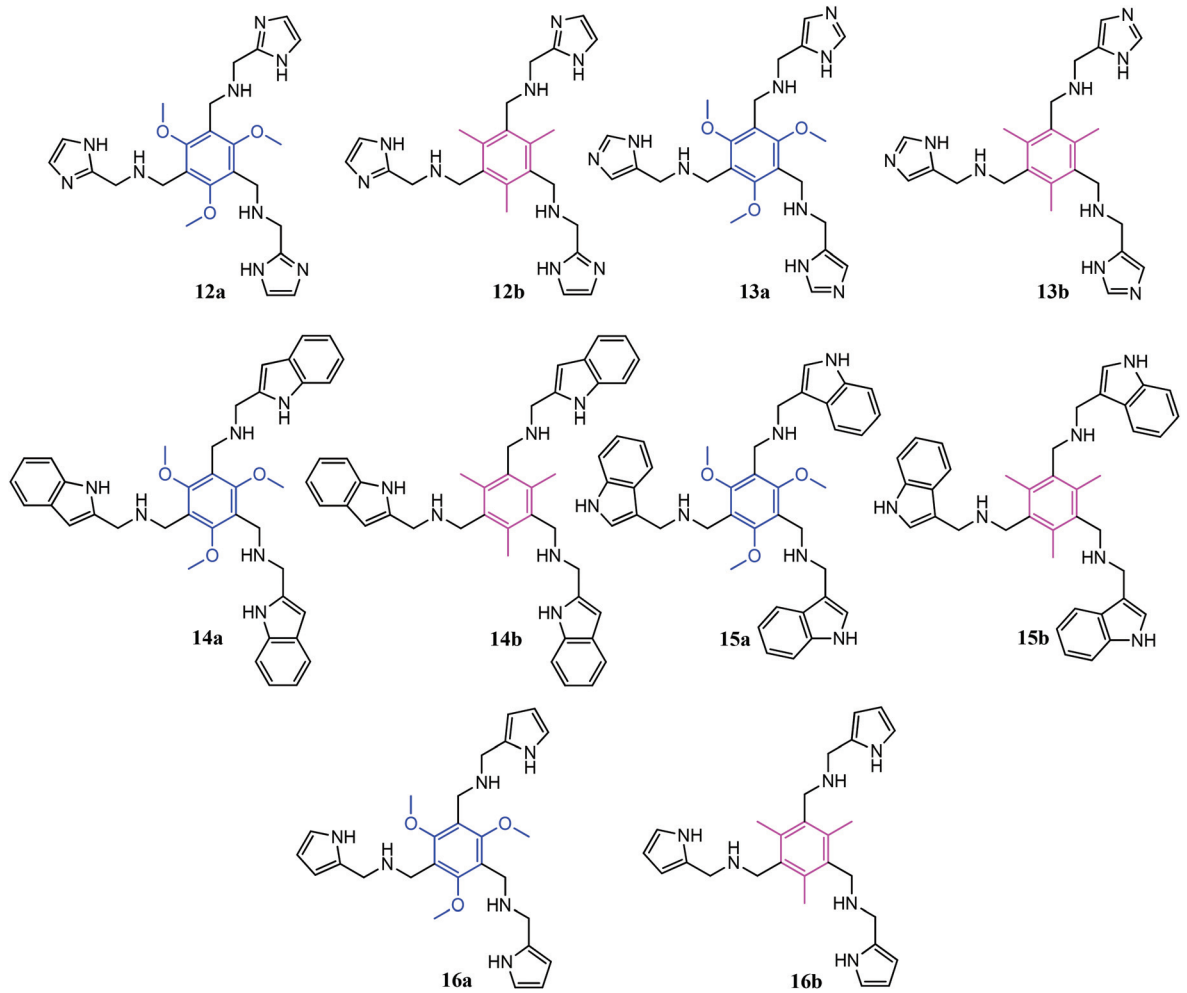


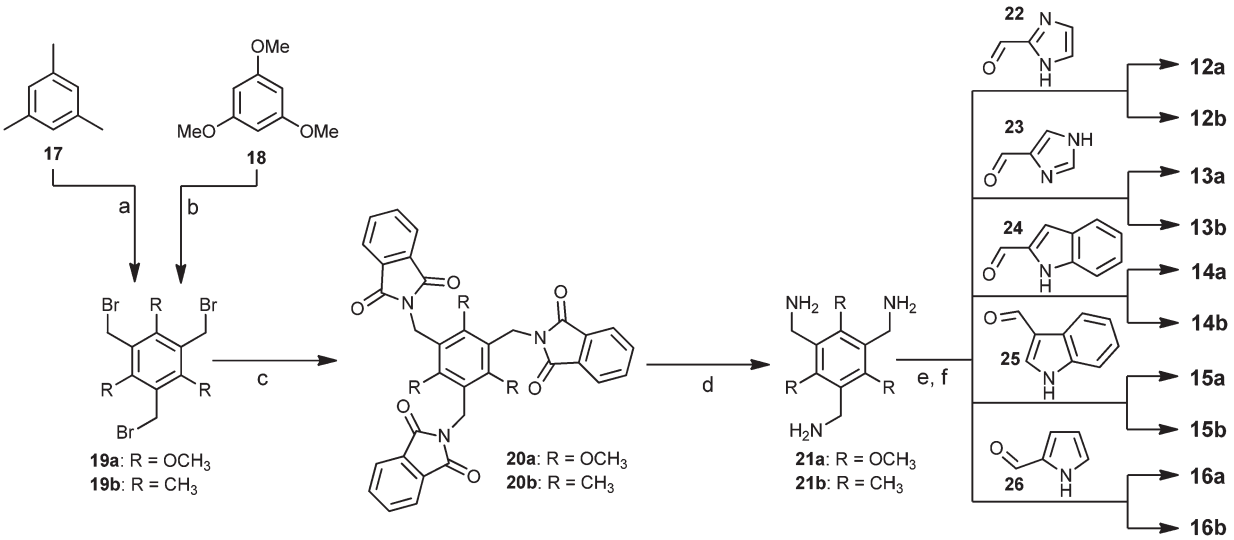
Fig. 4 Structures of the prepared trimethoxybenzene-based compounds **12a–16a** and the trimethylbenzene-based analogues **12b–16b**.

The trimethoxybenzene-based scaffold **III** represents a further platform for receptor systems and we were interested to see how this scaffold affects binding properties of carbohydrate receptors. As mentioned by Biali *et al.*,[11] for derivatives of **III** a lower relative stability of the all-alternated up-down arrangement (**III-a**) over nonalternated ones, such as **III-b**, (as compared to hexaethylbenzene) could be expected since conformation **III-a** should be destabilized by the presence of the three OMe dipoles oriented in a nearly parallel fashion. This effect may influence unfavourably the binding capabilities of the trimethoxybenzene-based receptors in comparison to those of the triethylbenzene-based systems. Compared to **I** and **II**, the methoxy groups of **III** provide additional hydrogen bonding sites for substrate complexation; however, the possible formation of intramolecular hydrogen bonds in the case of some derivatives of **III**, such as **III-1** (see Fig. 3), may be responsible for weaker intermolecular interactions with the substrate molecule. The central benzene ring is expected to participate in CH–π interactions with sugar CHs and it should be noted that the methoxy groups may significantly influence the contribution of the CH–π interactions to the overall binding.

The aim of the present study was to evaluate the potential of both trimethoxybenzene- and trimethylbenzene-based compounds bearing imidazole or indole groups (compounds **12a–15a** and **12b–15b**) in the complexation of carbohydrates and to compare their properties with those of the previously described triethylbenzene-based receptors. The properties of the indole and imidazole bearing compounds (in particular the properties of compounds **14a** and **14b** containing 2-substituted indole units) were further compared with those of the pyrrole-based analogues **16a** and **16b** (Fig. 4).

Results and discussion

The basis for the syntheses of compounds **12a/b–16a/b** was 1,3,5-tris(aminomethyl)-2,4,6-trimethoxybenzene (**21a**) or 1,3,5-tris(aminomethyl)-2,4,6-trimethylbenzene (**21b**); the synthetic routes for **12a/b–16a/b** are shown in Scheme 1. The synthesis of the tris-amines **21a** and **21b** started from commercially available 1,3,5-trimethoxybenzene (**18**) and 1,3,5-trimethylbenzene (**17**), respectively, which were converted into the corresponding tris-bromomethyl derivatives **19a** and **19b**



Scheme 1 Reaction conditions: (a) 33% HBr in CH_3COOH, $(CH_2O)_n$, 100 °C, 24 h (88%); (b) 33% HBr in CH_3COOH, $(CH_2O)_n$, 70 °C, 3 h (27%); (c) potassium phthalimide, dimethyl sulfoxide, 100 °C, 8 h (46% of **20a**, 97% of **20b**); (d) hydrazine hydrate, ethanol–toluene, reflux, 20 h, KOH (83% of **21a**, 58% of **21b**); (e) 6 equiv. of 2-imidazole-carbaldehyde (**22**), 4(5)-imidazole-carbaldehyde (**23**), 2-indole-carbaldehyde (**24**), 3-indole-carbaldehyde (**25**) or 2-pyrrole-carbaldehyde (**26**), CH_3OH, r.t., 3–7 days; (f) 7.5 equiv. of $NaBH_4$, r.t., 24 h (63% of **12a**, 89% of **12b**, 70% of **13a**, 92% of **13b**, 83% of **14a**, 54% of **14b**, 42% of **15a**, 29% of **15b**, 53% of **16a**, 68% of **16b**).

by a reaction with paraformaldehyde and hydrobromic acid. Compound **19b** could be isolated in a good yield of 88%, whereas **19a** was obtained in a yield of only 27%. By variation of the reaction conditions no better yield of **19a** could be achieved; higher temperatures, longer reaction times or addition of the catalyst $ZnBr_2$ only led to increased polymer formation (see also ref. 12). Conversion of **19a**/**19b** to tris-amines **21a**/**21b** was accomplished *via* Gabriel synthesis involving the preparation of compounds **20a** and **20b** in 46% and 97% yield, respectively. The condensation of the tris-amines **21a** and **21b** with the corresponding carbaldehyde, such as 2-imidazole-carbaldehyde (**22**), 4(5)-imidazole-carbaldehyde (**23**), 2-indole-carbaldehyde (**24**), 3-indole-carbaldehyde (**25**) or 2-pyrrole-carbaldehyde (**26**), provided the corresponding imines, which were soluble in the reaction mixture and were further reduced with sodium borohydride to give the products **12a/b–16a/b** (isolation of the imines was not necessary). All products were purified by column chromatography on silica gel using a chloroform–methanol mixture as an eluant and could be isolated in 29%–92% yield (see Scheme 1).

Crystallization of the tripodal receptor **12b** from $CHCl_3$ yields an inclusion compound with one host molecule, one chloroform molecule and six water molecules in the asymmetric part of the unit cell, two of the latter being disordered over two positions. A perspective view of the molecular structure is displayed in Fig. 5. As is evident from Fig. 5 and 6, the water molecules primarily contribute to the crystal stabilization. Although the positions of their hydrogens could not be obtained from the difference electron-density map, the O···O and O···N distances of 2.729(2)–2.836(2) and 2.734(2)–2.884(2) Å, respectively, indicate the presence of a close network of O–H···O and O–H···N hydrogen bonds. The included chloroform molecule was found to be highly disordered and could not be satisfactorily modelled. Thus the PLATON SQUEEZE routine was used on the raw data to create a modified data set that removed the scattering contribution of the disordered molecule (Fig. 5b). This procedure reveals that the chloroform molecules occupy lattice voids of 181.4 $Å^3$ per unit cell which represents 11.2% of the total cell volume. It should be noted that the conformation adopted in the crystal by **12b** does not correspond to the concave conformation indicated by molecular modeling for complexes with glycopyranosides; the three amino nitrogen atoms (N1, N4 and N7) point to the same face of the receptor (see Fig. 5), but the rest of the arms open out leaving an open cavity. Noncovalent interactions of **12b** with chloroform and water molecules as well as packing forces may be responsible for the nearly open conformation in the crystal.

To compare the binding properties of the new compounds with those of the previously published receptors, three representative monosaccharides, such as octyl β-D-glucoside (**27a**), octyl β-D-galactoside (**29a**), and octyl α-D-galactoside (**30a**), were selected as substrates for the binding studies in homogeneous media (^{1}H NMR spectroscopic titrations). Methyl pyranosides, such as β-glucoside **27b**, α-glucoside **28** and β-galactoside **29b** (Fig. 7), were employed for the binding studies in two-phase systems.

Similar to the previously described triethylbenzene-based compounds **8–10**, incorporating three imidazole groups, the symmetrical trimethoxybenzene- and trimethylbenzene-based compounds **12a/b–13a/b**, consisting of 2- or 4(5)-substituted imidazole groups, were almost insoluble in $CDCl_3$, but could be solubilized in this solvent in the presence of β-glucoside **27a**. Such solubility behavior indicates favorable interactions between the binding partners. The extraction of compounds

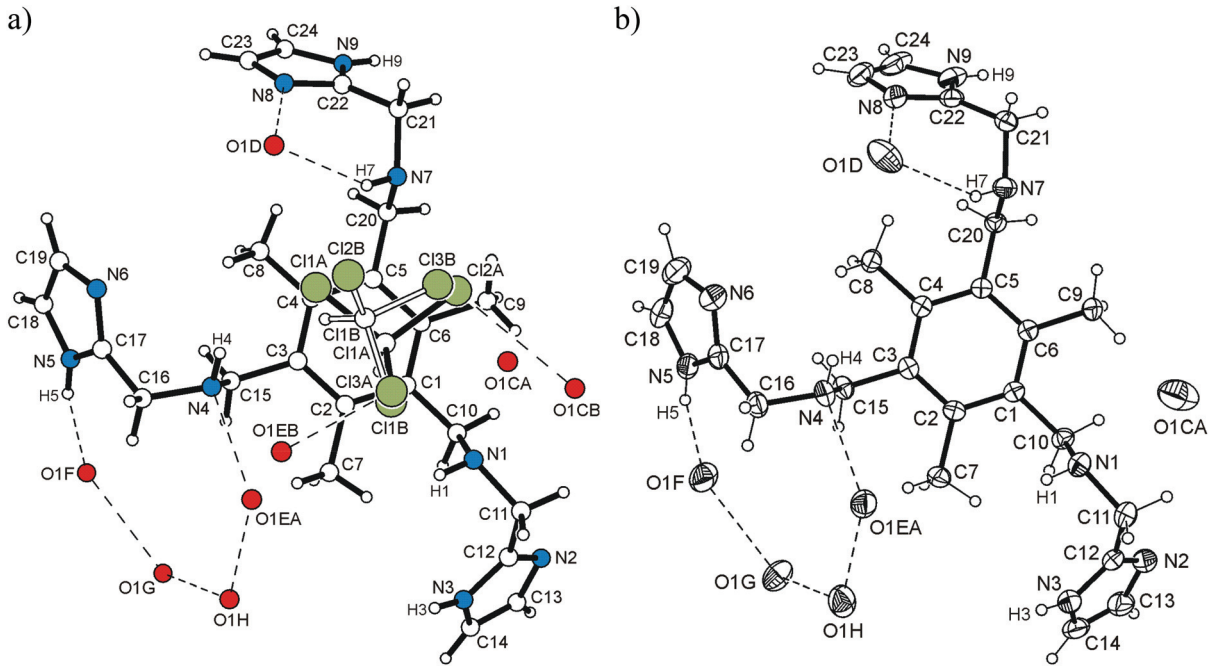


Fig. 5 (a) Molecular structure of **12b** in the crystal; $CHCl_3$ and H_2O molecules are included in the crystal. (b) ORTEP diagram of the molecular structure of **12b**; thermal ellipsoids are drawn at the 50% probability level; broken lines represent hydrogen bond interactions (the PLATON SQUEEZE routine was used).

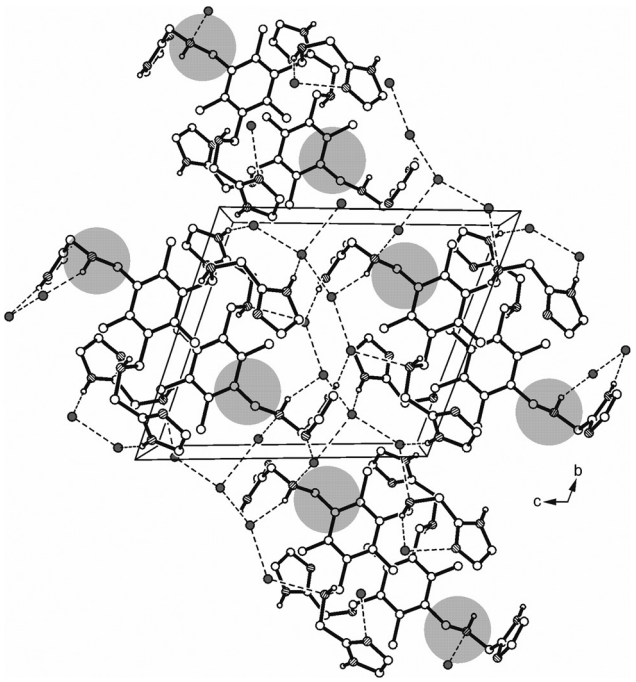


Fig. 6 Packing excerpt of **12b** viewed down the crystallographic *a*-axis. Shaded areas represent positions occupied by the disordered chloroform molecules. Oxygens are displayed as dark grey, and nitrogen atoms as hatched circles. Hydrogen bond interactions are marked by broken lines.

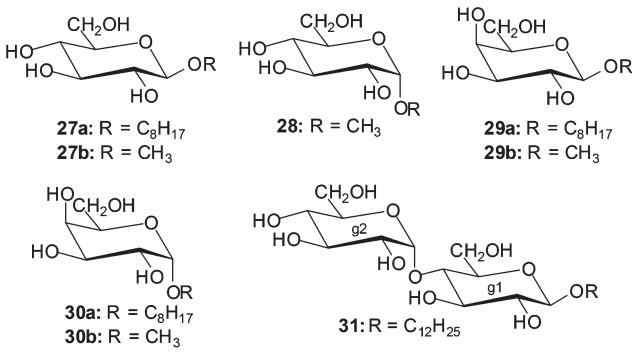


Fig. 7 Structures of sugars investigated in this study.

12a/b–13a from the solid state into a 1 mM solution of β-glucoside **27a** indicated that **12b**, consisting of the trimethylbenzene core and 2-imidazolyl groups, displays a significantly higher affinity to β-glucoside than the trimethoxybenzene-based compounds **12a** and **13a** (the solubilization of **12b** was about 6 times more effective than that of **12a**). The extractability decreased in the sequence **12b** > **12a** > **13a** (control experiments were performed in the absence of β-glucoside **27a**); thus, of the two trimethoxybenzene-based compounds, compound **12a**, bearing 2-imidazolyl groups, was found to be more effective than **13a**, consisting of 4(5)-substituted imidazole groups. These results suggest that 2-substituted imidazole groups are particularly suitable building blocks for carbohydrate receptors.

Compounds **14a**/**14b**, **15a** and **16a**/**16b**, incorporating indole groups substituted in 2- or 3-position or 2-substituted pyrrole groups, were shown to be soluble in $CDCl_3$ and their binding properties could be investigated in this solvent by ^{1}H NMR spectroscopic titrations. The ^{1}H NMR titration experiments with β-glucoside **27a**, β-galactoside **29a**, and α-galactoside **30a** were carried out by adding increasing amounts of the

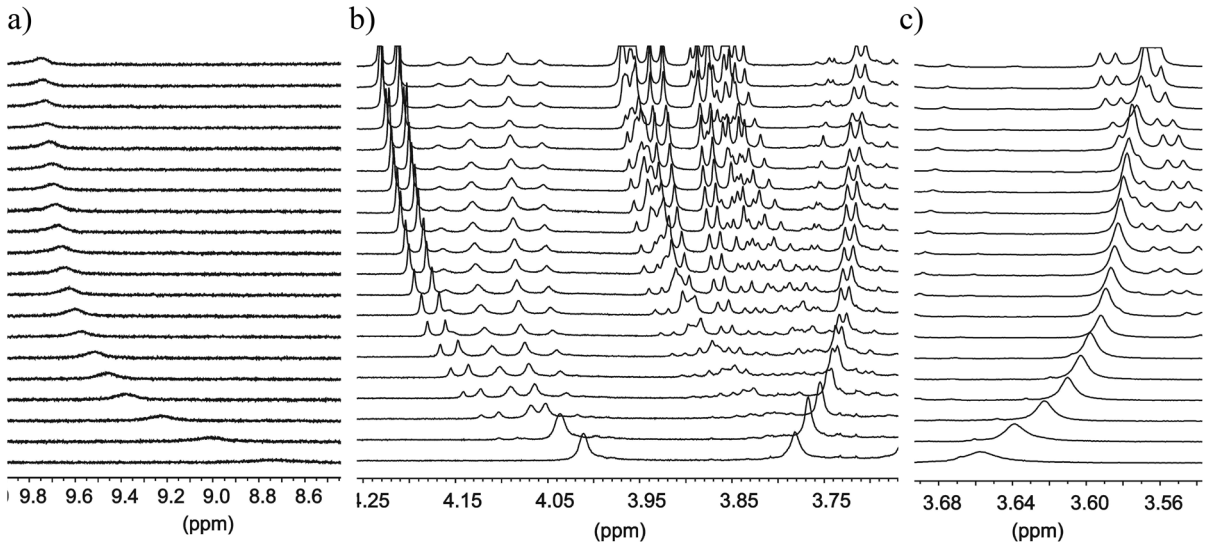


Fig. 8 (a) Partial ^{1}H NMR spectra (400 MHz) of receptor **14a** ([**14a**] = 0.99 mM) after the addition of 0.00–4.00 equiv. of β-galactoside **29a** in $CDCl_3$. Chemical shifts of the indole NH (a), CH_2 (b) and CH_3 (c) signals of **14a** are shown.

sugar to a solution of the corresponding receptor. The complexation between **14a**/**14b**, **15a** and **16a**/**16b** and monosaccharides was evidenced by several changes in the NMR spectra; examples are given in Fig. 8 and Fig. S19–S27 in the ESI.† The titration data were analyzed using the EQNMR[13] program; the binding constants are summarised in Table 1. With only one exception, namely **14a·29a**, the movements of the receptor signals gave very good fits to a 1 : 1 binding model (for examples, see Fig. S1–S11 in ESI†). In the case of **14a·29a**, the curve fitting of the titration data suggested the existence of 1 : 1 and 2 : 1 receptor–sugar complexes in the $CDCl_3$ solution (see Fig. S5†); this model was further supported by the mole ratio plot[14] (for examples of mole ratio plots, see Fig. S12–S18†). The binding constant for the 1 : 1 binding was determined to be significantly higher than that for the 2 : 1 receptor–sugar complex.

Table 1 Association constants[a,b] for receptors **14a**/**14b**, **15a** and **16a**/**16b** and carbohydrates **28a**, **29a**, **30a** and **31**[a,b]

Host–guest complex	K_{11} [M^{-1}] K_{21} [M^{-1}][c], $\beta_{21} = K_{11}K_{21}$
14a·27a	1440
14a·29a	5690 (K_{11}), 510 (K_{21}), 2.90×10^6 (β_{21})
14a·30a	1210
14b·27a	5950
15a·27a	650
16a·27a	3500
16a·29a	8390
16a·30a	1200
16b·27a	6760
16b·29a	8430
16b·31	2800 (K_{11}), 82 370 (K_{21}), 2.31×10^8 (β_{21})

[a] Average K_a values from multiple titrations in $CDCl_3$. [b] Errors in K_a are less than 5%. [c] K_{21} corresponds to a 2 : 1 receptor–sugar association constant.

The interactions of the trimethylbenzene-based compounds **14b** and **16b** with β-glucoside **27a** were shown to be more effective than those with the trimethoxybenzene-based analogues **14a** and **16a**. The binding affinity of **14a**/**14b**, **15a** and **16a**/**16b** towards **27a** decreased in the sequence **16b** > **14b** > **16a** > **14a** > **15a**. Among the tested compounds, compound **16b**, bearing three pyrrole units, was shown to be the most effective receptor for this monosaccharide (for examples of effective triethylbenzene-based receptors bearing pyrrole groups, see ref. 15).

In comparison to the tested triethylbenzene-based imidazole and indole bearing receptors[3] and the previously described symmetrical aminopyridine-based receptor,[4b] the trimethoxybenzene-based compounds **14a** and **16a** showed a significantly decreased binding affinity towards β-glucoside **27a**; the binding affinity of the three receptor types decreased in the sequence triethyl→trimethyl→trimethoxy-based compounds (for an analysis of the abilities of 1,3,5-triethylbenzene and 1,3,5-trimethylbenzene-based scaffolds to preorganize the binding elements of supramolecular hosts and to improve the binding of targets, see ref. 10).

The ^{1}H NMR titration experiments indicated furthermore a higher binding affinity of **14a** and **16a** for β-galactoside **29a** than for β-glucoside **27a**. The binding affinity of **14a** and **16a** towards the tested octyl glycosides decreased in the sequence β-galactoside **29a** > β-glucoside **27a** > α-galactoside **30a**.

The interactions of β-glucoside **27** with **14a**, consisting of 2-substituted indole groups, were shown to be more effective than those with the analogue **15a**, bearing indole groups substituted in the 3-position (see Tables 1 and 2).

A lower affinity of β-glucoside **27a** to compound **14a** in comparison to the trimethylbenzene-based analogue **14b** was also indicated by liquid–solid extractions (see Table 2). Extraction of methyl pyranosides from the solid state into a $CDCl_3$

Table 2 Solubilization of sugars in $CDCl_3$ by receptors **14a**, **14b**, and **15a** (1 mM solutions)[a]

Receptor	β-Glucoside **27b**	β-Galactoside **29b**	α-Glucoside **30b**
14a	0.45	0.61	0.35
14b	0.58	0.47	0.24
15a	0.24	[b]	0.20

[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). [b] Not determined.

solution of the corresponding receptor (1 mM solution) indicated furthermore a preference of **14a** and **14b** for β-glucoside **27b** *versus* α-glucoside **28** as well as a preference of **14a** for β-galactoside **29b** *versus* β-glucoside **27b**. The β-galactoside *versus* β-glucoside preference of **14a** was also shown by ^{1}H NMR spectroscopic titrations of **14a** with the octyl glycosides **27a** and **29a** (see above).

In the case of the trimethoxybenzene-based compounds **12a–16a**, molecular modeling calculations indicated the formation of intramolecular NH···O hydrogen bonds between the amine NHs and the methoxy groups, as shown in Fig. 9a/b for compound **14a** (the participation of the indole NH in intramolecular NH···π interactions was also indicated by molecular modelling calculations, see Fig. 9b). The participation of the amine NH in an intramolecular hydrogen bond was further indicated by NMR spectroscopy (see, for example, Fig. S48† showing partial ^{1}H NMR spectra of compound **14a** and of the trimethylbenzene-based analogue **14b**). Thus, the lower affinity of the trimethoxybenzene-based compounds towards β-glucoside **27** in comparison to the trimethylbenzene-based analogues may be a consequence of the participation of the important recognition sites of **12a–16a** in intramolecular hydrogen bonds.[16]

According to molecular modeling calculations, the complexes between **12a/b–16a/b** and glycosides are stabilized by both hydrogen bonds and CH···π interactions[17–19] (for examples, see Fig. 9c/d). The sugar OH groups are involved in the formation of cooperative hydrogen bonds, which result from the simultaneous participation of a sugar OH group as the donor and acceptor of hydrogen bonds; the central benzene ring of the corresponding receptor stacks on the sugar ring.

In the case of **16b**, the binding properties of this compound were also tested against a disaccharide, such as dodecyl

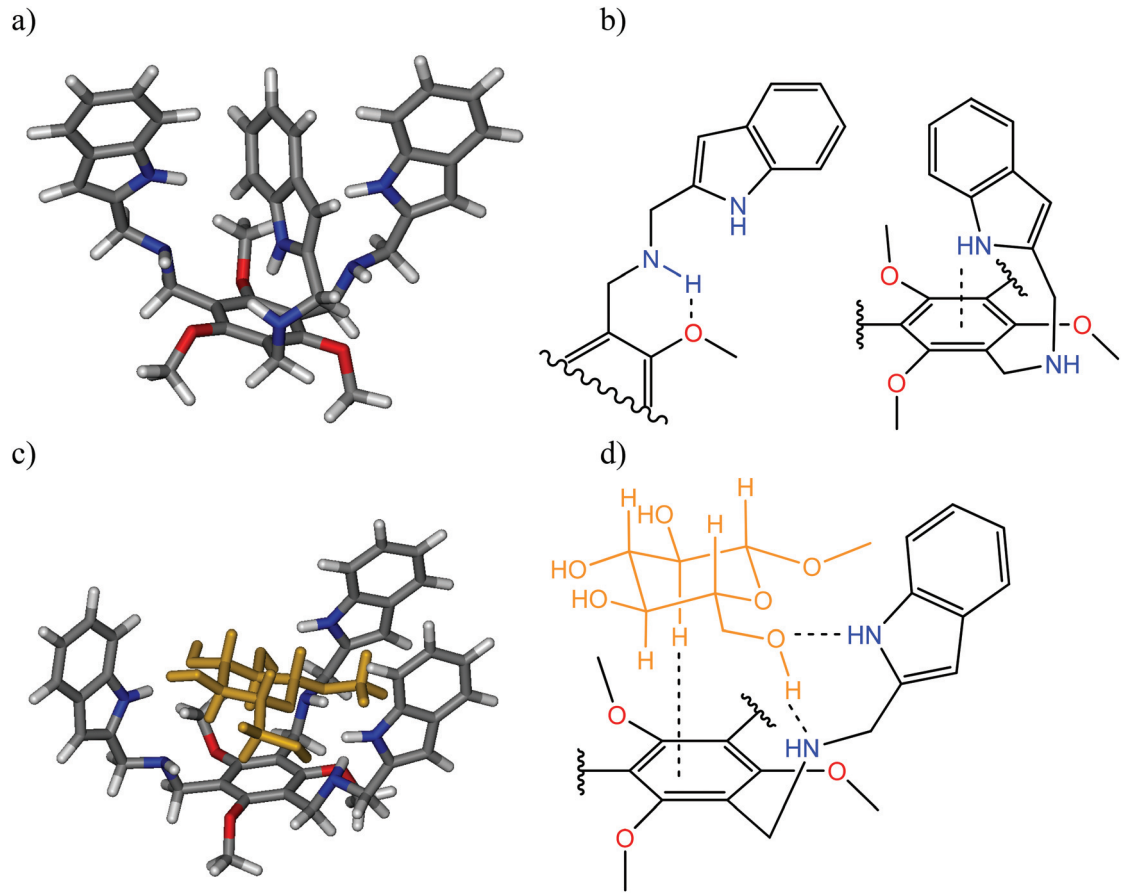


Fig. 9 (a) Energy-minimized structure of **14a** (MacroModel V.9.8, OPLS_2001 force field, MCMM, 50 000 steps). (b) Examples of intramolecular interactions in **14a**. (c) Energy-minimized structure of the 1 : 1 complex formed between **14a** and β-glucopyranoside **27b**. (d) Examples of intermolecular interactions in the **14a**·**27b** complex. Color code: receptor N, blue; receptor C, grey; receptor O, red; the sugar molecule is highlighted in orange.

β-maltoside **31**. In contrast to the relatively weak binding of monosaccharides, the binding of β-maltoside **31** by compound **16b** was shown to be strong (see also ref. 20). Although β-maltoside **31** is poorly soluble in $CDCl_3$, it could be solubilized in this solvent in the presence of **16b** and the interactions between the binding partners could be investigated by ^1H NMR titrations (the receptor in $CDCl_3$ was titrated with a solution of β-maltoside dissolved in the same receptor solution by following the titration protocol described in ref. 20*a*). The addition of only 0.5 equiv. of **31** led to practically complete complexation of the receptor **31** in $CDCl_3$, indicating the formation of 2 : 1 receptor–disaccharide complexes under the titration conditions. The binding constants in $CDCl_3$ were determined to be 2800 $[M^{-1}]$ (K_{11}) and 82 370 $[M^{-1}]$ (K_{21}) ($\beta_{21} = 2.31 \times 10^8\ M^{-2}$).

Molecular modeling calculations indicated that in the 2 : 1 receptor–sugar complex the disaccharide **31** is fully encapsulated in the cavity between the two receptor molecules, as shown in Fig. 10 (it should be noted that the dodecyl-chain projects to the exterior). According to the calculations, the complex is stabilized by several hydrogen bonds, including cooperative hydrogen bonds, CH–π and OH–π interactions as well as a number of van der Waals contacts[21] (for examples of noncovalent interactions, see Table 3).

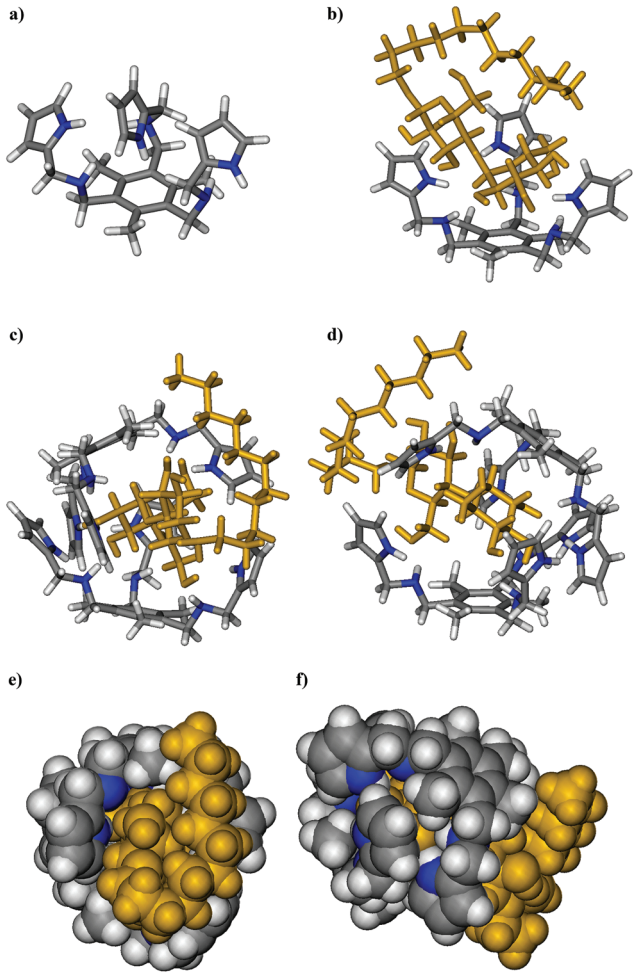


Fig. 10 Energy-minimized structures of (a) compound **16b**, (b) the 1 : 1 complex formed between **16b** and dodecyl β-maltoside **31** as well as (c–f) the 2 : 1 receptor–maltoside complex (four different representations). MacroModel V.9.8, OPLS_2001 force field, MCMM, 50 000 steps. Color code: receptor N, blue; receptor C, grey; the sugar molecule is highlighted in orange.

Table 3 Examples of noncovalent interactions indicated by molecular modeling calculations[a] for the complex formed between receptor **16b** and disaccharide **31**

Receptor–substrate complex	Noncovalent interactions[b,c]
16b·31 2 : 1 receptor–sugar complex[b]	(I) Pyrrole–NH···OH-3 (g1) (II) Amine–NH···OH-6 (g1)
	(I) Pyrrole–NH···OH-2 (g2); (I) amine–NH···OH-2 (g2): (II) pyrrole ring···HO-2 (g2) (I) Pyrrole–NH···OH-3 (g2); (II) amine–N···HO-3 (g2) (II) Amine–NH···OH-4 (g2); (II) pyrrole–N···HO-4 (g2) (I) Amine–NH···HO-6 (g2) (I) Amine–NH···O-ring (g2) (I) Central benzene ring···HC-2 (g2); (I) Pyrrole ring···HC-1, HC-3 and HC-5 (g1)

[a] MacroModel V.9.8, OPLS_2001 force field, MCMM, 50 000 steps. [b] I and II: two receptors in the 2 : 1 receptor–sugar complex; [c] g1 and g2: the glucose units of **31** (for labeling see Fig. 7).

Conclusion

Ten representatives of trimethoxybenzene- (**12a–16a**) and trimethylbenzene-based compounds (**12b–16b**), bearing imidazole, indole and pyrrole groups as recognition units, were prepared and their binding properties towards selected carbohydrates evaluated. The design of the previously described receptors consisting of imidazole or indole recognition units (see Fig. 2) as well as the new tripodal compounds **12a/b–15a/b** was inspired by the crystal structures of protein–carbohydrate complexes (see Fig. 1). We were furthermore interested to see how the trimethoxybenzene and trimethylbenzene scaffolds affect binding properties of carbohydrate receptors. Compounds **16a/b**, containing 2-substituted pyrrole groups, were prepared as analogues of compounds **14a/b**, bearing 2-substituted indole units. ^1H NMR titrations as well as binding studies in two-phase systems, such as dissolution of solid carbohydrates in apolar media, which were carried out with **14a**, **14b**, **15a** and **16a**, revealed β- *vs.* α-anomer binding preferences in the recognition of glycosides. The binding studies showed furthermore a preference of compounds **14a** and **16a** for β-galactoside **29** *versus* β-glucoside **27**.

Compounds **12a/b–13a/b**, consisting of 2- or 4(5)-substituted imidazole groups, were almost insoluble in $CDCl_3$, but could be solubilized in this solvent in the presence of β-glucoside **27a**, indicating favorable interactions between the binding partners. The solubilization experiments suggested that 2-substituted imidazole groups are particularly suitable building blocks for carbohydrate receptors.

Compared to the previously described triethylbenzene-based receptors, the tested trimethoxybenzene- and trimethylbenzene-based compounds were shown to be less effective in the recognition of β-glucoside **27**; the binding affinity for β-glucoside decreased in the sequence triethylbenzene→trimethylbenzene→trimethoxybenzene-based compounds. It should be however noted that some compounds showed an interesting preference[22] for β-galactoside *versus* β-glucoside (for examples of receptors showing increased binding affinity toward β-galactoside, see ref. 3*b*). The lower affinity of the trimethoxybenzene-based compounds towards β-glucoside **27** in comparison to the triethylbenzene- and trimethylbenzene-based analogues may be a consequence of the participation of the amine NHs of **12a–16a** in intramolecular hydrogen bonds as well as a result of a lower degree of preorganisation of the trimethoxybenzene scaffold (see above).

The binding properties of compounds **12a/b–16a/b** towards various carbohydrates are now analysed in more detail in competitive and noncompetitive[23] media. Efforts to examine the three-dimensional structures of the receptor–sugar complexes are currently underway.

Experimental section

Analytical TLC was carried out on silica gel 60 F_{254} plates employing chloroform–methanol mixtures as the mobile phase, and column chromatography was carried out on silica gel. Melting points are uncorrected. Sugars **27–31**, 2-imidazole-carbaldehyde (**22**), 4(5)-imidazole-carbaldehyde (**23**), 2-indole-carbaldehyde (**24**), 3-indole-carbaldehyde (**25**) and 2-pyrrole-carbaldehyde (**26**) are commercially available.

General procedure for the synthesis of compounds 12a–16a

To a solution of the corresponding carbaldehyde (compounds **22–26**) in methanol (12 mL) was added 1,3,5-tris(aminomethyl)-2,4,6-trimethoxybenzene (**21a**) (0.21–0.39 mmol) dissolved in methanol (10 mL) and the reaction mixture was stirred for 6 days at room temperature. Then $NaBH_4$ (1.56–3.01 mmol) was added in portions and the reaction mixture was stirred for 24 h at room temperature. The solvent was removed, water was added to the residue and the mixture was stirred additionally for 24 h. The suspension was extracted with chloroform (3 × 20 mL). The combined organic extracts were washed with water, dried over $MgSO_4$, and the solvent was removed (or product was present in the water phase). The crude product was purified *via* column chromatography [$CHCl_3$–CH_3OH (incl. 1% 7 M NH_3 in CH_3OH), 7 : 1 to 2 : 1 v/v].

1,3,5-Tris[(2-imidazolyl-methyl)aminomethyl]-2,4,6-trimethoxybenzene (12a). Yield: 63%. M.p. 124 °C. ^{1}H-NMR (400 MHz, MeOD-d_4, ~25 mM): δ = 7.07 (s, 6H), 3.91 (s, 6H), 3.83 (s, 6H), 3.68 (s, 9H) ppm. ^{13}C-NMR (100 MHz, MeOD-d_4): δ = 160.48, 146.80, 123.13, 122.81, 63.11, 45.95, 42.85 ppm. HR-MS (ESI) calcd for $C_{24}H_{34}N_9O_3$: 496.27846 $[M + H]^+$; found: 496.27837. R_f 0.06 [$CHCl_3$–CH_3OH, 7 : 1].

1,3,5-Tris[(4-imidazolyl-methyl)aminomethyl]-2,4,6-trimethoxybenzene (13a). Yield: 70%. M.p. 95 °C. ^{1}H-NMR (400 MHz, $CDCl_3$ + MeOD-d_4, ~25 mM): δ = 7.55 (s, 3H), 6.93 (s, 3H), 3.75 (s, 6H), 3.72 (s, 6H), 3.68 (s, 9H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$ + MeOD-d_4): δ = 162.38, 139.01, 126.75, 65.95, 45.81, 45.79 ppm. HR-MS (ESI) calcd for $C_{24}H_{34}N_9O_3$: 496.27846 $[M + H]^+$; found: 496.27839. R_f 0.42 [$CHCl_3$–CH_3OH, 2 : 1].

1,3,5-Tris[(2-indolyl-methyl)aminomethyl]-2,4,6-trimethoxybenzene (14a). Yield: 83%. M.p. 104 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, ~25 mM): δ = 9.18 (br. s, 3H), 7.54 (d, J = 7.7 Hz, 3H), 7.31 (d, J = 8.0 Hz, 3H), 7.13 (ddd, J = 8.1/7.2/1.3 Hz, 3H), 7.06 (ddd, J = 7.9/7.3/1.0 Hz, 3H), 6.37 (s, 3H), 3.96 (s, 6H), 3.73 (s, 6H), 3.56 (s, 9H), 2.96 (br. S, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 158.66, 136.55, 136.23, 128.34, 122.92, 121.53, 120.10, 119.55, 110.86, 100.97, 62.60, 46.34, 42.02 ppm. HR-MS (ESI) calcd for $C_{39}H_{43}N_6O_3$: 643.33966 $[M + H]^+$; found: 643.33958. R_f 0.43 [$CHCl_3$–CH_3OH, 2 : 1].

1,3,5-Tris[(3-indolyl-methyl)aminomethyl]-2,4,6-trimethoxybenzene (15a). Yield: 42%. M.p. 105 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, ~25 mM): δ = 8.23 (br. s, 3H), 7.60 (d, J = 7.9 Hz, 3H), 7.26 (dt, J = 8.1/0.8 Hz, 3H), 7.12 (ddd, J = 8.1/7.2/1.1 Hz, 3H), 7.03 (ddd, J = 7.9/7.1/1.0 Hz, 3H), 6.97 (d, J = 2.3 Hz, 3H), 3.96 (s, 6H), 3.83 (s, 6H), 3.63 (s, 9H), 1.91 (br. S, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 158.28, 136.37, 127.14, 123.66, 122.69, 121.86, 119.32, 118.92, 115.01, 111.05, 62.26, 44.60, 42.99 ppm. HR-MS (ESI) calcd for $C_{39}H_{43}N_6O_3$: 643.33966 $[M + H]^+$; found: 643.33957. R_f 0.45 [$CHCl_3$–CH_3OH (incl. 1% 7 M NH_3 in CH_3OH), 2 : 1].

1,3,5-Tris[(2-pyrrolyl-methyl)aminomethyl]-2,4,6-trimethoxybenzene (16a). Yield: 53%. M.p. 64 °C. ^{1}H-NMR (600 MHz, $CDCl_3$, ~25 mM): δ = 8.78 (br. s, 3H), 6.67–6.65 (m, 3H), 6.12–6.11 (m, 3H), 6.05–6.03 (m, 3H), 3.78 (s, 6H), 3.75 (s, 6H), 3.69 (s, 9H), 2.03 (br. s, 3H) ppm. ^{13}C-NMR (150 MHz, $CDCl_3$): δ = 158.30, 130.53, 123.58, 116.99, 108.02, 106.24, 62.35, 46.17, 42.45 ppm. HR-MS (ESI) calcd for $C_{27}H_{37}N_6O_3$: 493.29271 $[M + H]^+$; found: 493.29261. R_f 0.08 [$CHCl_3$–CH_3OH, 5 : 1].

General procedure for the synthesis of compounds 12b–16b

To a solution of the corresponding carbaldehyde (compounds **22–26**) (2.89 mmol) in methanol (10 mL) was added 1,3,5-tris-(aminomethyl)-2,4,6-trimethylbenzene (**21b**)[24] (0.48 mmol) dissolved in methanol (10 mL). The reaction mixture was stirred for 7 days at room temperature. Afterwards $NaBH_4$ (3.62 mmol) was added in portions and the reaction mixture was stirred for 24 h at room temperature. The solvent was removed, water was added to the residue and the mixture was stirred additionally for 24 h. The suspension was extracted with chloroform (3 × 10 mL). The combined organic extracts were washed with water and dried over $MgSO_4$, and the solvent was removed (or the product was present in water phase). The crude product was purified *via* column chromatography [$CHCl_3$–CH_3OH (incl. 1% 7 M NH_3 in CH_3OH), 10 : 1 to/or 2 : 1 v/v].

1,3,5-Tris[(2-imidazolyl-methyl)aminomethyl]-2,4,6-trimethylbenzene (12b). Yield: 89%. M.p. 104 °C. ^{1}H-NMR

(400 MHz, MeOD-d_4, ~30 mM): δ = 7.00 (s, 6H), 3.87 (s, 6H), 3.66 (s, 6H), 2.19 (s, 9H) ppm. ^{13}C-NMR (100 MHz, MeOD-d_4): δ = 148.23, 136.88, 135.34, 122.75, 48.31, 47.07, 15.69 ppm. HR-MS (ESI) calcd for $C_{24}H_{33}N_9Na$: 470.27566 $[M + Na]^+$; found: 470.27559. R_f 0.11 [$CHCl_3$–CH_3OH (incl. 1% 7 M NH_3 in CH_3OH), 2 : 1].

1,3,5-Tris[(4-imidazolyl-methyl)aminomethyl]-2,4,6-trimethylbenzene (13b). Yield: 92%. M.p. (dec.) 160 °C. ^{1}H-NMR (400 MHz, MeOD-d_4, ~30 mM): δ = 7.64 (d, J = 1.2 Hz, 3H), 7.03 (d, J = 1.0 Hz, 3H), 3.80 (s, 6H), 3.71 (s, 6H), 2.22 (s, 9H) ppm. ^{13}C-NMR (100 MHz, MeOD-d_4): δ = 136.98, 136.81, 136.41, 135.56, 118.93, 48.02, 46.35, 15.78 ppm. HR-MS (ESI) calcd for $C_{24}H_{34}N_9$: 448.29372 $[M + H]^+$; found: 448.29365. R_f 0.03 [$CHCl_3$–CH_3OH (incl. 1% 7 M NH_3 in CH_3OH), 2 : 1].

1,3,5-Tris[(2-indolyl-methyl)aminomethyl]-2,4,6-trimethylbenzene (14b). Yield: 54%. M.p. 99 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, ~25 mM): δ = 8.58 (br. s, 3H), 7.54 (dd, J = 7.3/0.5 Hz, 3H), 7.26 (d, J = 7.3 Hz, 3H), 7.13 (ddd, J = 8.1/7.3/1.4 Hz, 3H), 7.07 (ddd, J = 8.1/7.1/1.1 Hz, 3H), 6.36 (d, J = 1.0 Hz, 3H), 4.00 (s, 6H), 3.77 (s, 6H), 2.31 (s, 9H), 1.70 (br. s, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 137.38, 135.98, 135.50, 134.75, 128.43, 121.48, 120.12, 119.63, 110.71, 100.42, 48.10, 47.25, 15.62 ppm. HR-MS (ESI) calcd for $C_{39}H_{43}N_6$: 595.35492 $[M + H]^+$; found: 595.35495. R_f 0.09 [$CHCl_3$–CH_3OH, 7 : 1].

1,3,5-Tris[(3-indolyl-methyl)aminomethyl]-2,4,6-trimethylbenzene (15b). Yield: 29%. M.p. 129 °C. ^{1}H-NMR (300 MHz, $CDCl_3$, ~25 mM): δ = 8.37 (br. s, 3H), 7.60 (d, J = 7.6 Hz, 3H), 7.16 (d, J = 7.9 Hz, 3H), 7.13–7.08 (m, 3H), 7.07–7.02 (m, 3H), 6.86 (s, 3H), 3.99 (s, 6H), 3.76 (s, 6H), 2.23 (s, 9H), 1.33 (br. s, 3H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 136.30, 135.30, 134.96, 127.08, 122.60, 121.85, 119.32, 118.81, 114.76, 111.13, 48.28, 45.14, 15.39 ppm. HR-MS (ESI) calcd for $C_{39}H_{43}N_6$: 595.35492 $[M + H]^+$; found: 595.35492. R_f 0.40 [$CHCl_3$–CH_3OH (incl. 1% 7 M NH_3 in CH_3OH), 1 : 1].

1,3,5-Tris[(2-pyrrolyl-methyl)aminomethyl]-2,4,6-trimethylbenzene (16b). Yield: 68%. M.p. 122 °C. ^{1}H-NMR (400 MHz, $CDCl_3$, ~30 mM): δ = 8.63 (br. s, 3H), 6.67–6.65 (m, 3H), 6.12 (dd, J = 5.9/2.7 Hz, 3H), 6.06–6.04 (m, 3H), 3.86 (s, 6H), 3.75 (s, 6H), 2.31 (s, 9H), 1.34 (br. s, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 135.22, 134.93, 130.56, 117.07, 108.00, 106.09, 48.04, 46.94, 15.43 ppm. HR-MS (ESI) calcd for $C_{27}H_{37}N_6$: 445.30797 $[M + H]^+$; found: 445.30768. R_f 0.03 [$CHCl_3$–CH_3OH, 2 : 1].

1,3,5-Tris(aminomethyl)-2,4,6-trimethoxybenzene (21a). 1,3,5-Tris(phthalimidomethyl)-2,4,6-trimethoxybenzene (**20a**)[25] (189 mg, 0.3 mmol) was dissolved in a mixture of dry ethanol–toluene (15 mL, 2 : 1 v/v) and heated at reflux with hydrazine hydrate (0.1 mL, 2.1 mmol) for 20 h. Afterwards the mixture was cooled to room temperature, an aqueous solution of KOH (40%, 3 mL) was added and the mixture was extracted with $CHCl_3$ (4 × 10 mL). The combined organic layer was washed with brine (20 mL) and water (20 mL), dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. Drying under vacuum afforded the desired compound **21a** as a yellow solid. Yield: 83%; M.p. (dec): 140 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 3.79 (s, 9H), 3.70 (s, 6H) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 156.91, 125.75, 62.34, 35.19 ppm; MS (EI): m/z = 255 [M^+], 239, 225, 223, 209, 207, 195, 165.

Crystallographic data for 12b

$C_{24}H_{33}N_9{\cdot}CHCl_3{\cdot}6H_2O$, M_r = 675.06, triclinic, space group $P\bar{1}$, a = 11.5740(3), b = 12.0274(3), c = 13.1839(6) Å, α = 104.872(1), β = 101.801(2), γ = 107.204(1)°, T = 100 K, Z = 2, μ = 0.337 mm^{-1}, $R_F(R_{wF})$ = 0.0657(0.1852) for 6752 observed independent reflections. The intensity data were collected at 100 K on a Kappa APEX2 diffractometer (Bruker AXS) with MoK_α radiation (λ = 0.71073 Å) using ω- and ϕ-scans. Reflections were corrected for background, Lorentz and polarization effects. Preliminary structure models were derived by application of direct methods (SHELXL-97) and were refined by full-matrix least-squares calculation based on F^2 values for all unique reflections (SHELXS-97). Empirical absorption correction based on multi-scans was applied by using the SADABS program. All non-hydrogen atoms were refined anisotropically. With the exception of the amino hydrogens H(1), H(4) and H(7) all other hydrogen atoms were included in the models in calculated positions and were refined as constrained to bonding atoms. The PLATON SQUEEZE routine was used on the raw data to create a modified data set that removed the scattering contribution of the disordered chloroform molecule. Deposit number: CCDC 938511.

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