RSC Advances

Cite this: *RSC Advances*, 2012, **2**, 2630–2642

www.rsc.org/advances

REVIEW

Recent developments in the molecular recognition of carbohydrates by artificial receptors

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Received 19th November 2011, Accepted 21st November 2011
DOI: 10.1039/c2ra01138g

Despite the key role that carbohydrates play in a wide range of biological processes, the molecular details of carbohydrate-mediated recognition events are not fully understood. In this context, artificial receptors using noncovalent interactions for sugar binding provide useful model systems to study the basic principles of carbohydrate-based molecular recognition processes. The studies in this area are also strongly motivated by the belief that carbohydrate-binding agents could be used for the detection and treatment of diseases. This review covers representative examples of carbohydrate receptors operating through noncovalent interactions, with a focus on developments in receptor systems over the last two years.

1. Introduction

The development of new receptors for carbohydrate recognition continues to be a fascinating and important area of research. Interest derives from the enormous importance of carbohydrate-mediated recognition processes in biology,[1] and the need for new therapeutics (*e.g.* anti-infective agents) and carbohydrate sensors, which can be developed on the base of carbohydrate-binding agents. Two main strategies have been employed for the design of synthetic carbohydrate receptors. One strategy involves the exploitation of non-natural bonding interactions and relies on the reversible formation of covalent bonds from diol units and boronic acids.[2] The second strategy exploits noncovalent interactions for sugar binding and aims at the development of biomimetic receptors.[3] The design of biomimetic receptors can be directed towards either a better understanding of recognition phenomena in nature, or towards potential applications in medicine, analytical chemistry and other areas.

It should be noted that both effective and selective recognition of carbohydrates by receptors operating through noncovalent interactions is still a challenging goal of artificial receptor chemistry. In particular, the recognition of carbohydrates in aqueous media, in which solvent molecules compete significantly for binding sites of the receptor, remains a challenge. Mimicking the binding motifs observed in the crystal structures of protein–carbohydrate complexes[4] (for examples, see Fig. 1) was shown to be very useful for the development of artificial carbohydrate receptors. Although very interesting receptor systems have been developed, the exact prediction of the binding preferences of the artificial receptors is still far away and it is hoped that systematic studies in this area will contribute significantly to the solution of this problem.

This review covers examples of artificial receptors using noncovalent interactions for sugar binding, with a focus on representative developments in receptor systems over the last two years; earlier examples are described in several reviews, which are cited in ref. 3.

2. Binding studies in organic media

Several receptor types based on a macrocyclic and acyclic scaffold have been designed for the binding studies in non-polar and polar organic solvents, although solvent competition usually makes recognition in polar solvents much less effective.[5] Particularly, many representatives of hydrogen bonding receptors have been prepared and studied. The receptor molecules

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Monika Mazik received her PhD degree in chemistry from the Silesian Technical University at Gliwice, and did post-doctoral work with Prof. Reiner Sustmann at the University of Essen, Germany. After post-doctoral research, she worked on her habilitation (1998–2000) at the University of Essen. In 2002 she became Professor at the Technical University of Braunschweig, Germany, and since 2011 she has been Professor at the Technical University of Freiberg. Her research interests involve the design and synthesis of receptors for molecular recognition of biorelevant molecules, self-assembly of organic compounds, synthesis of heterocycles, as well as molecular modeling calculations.

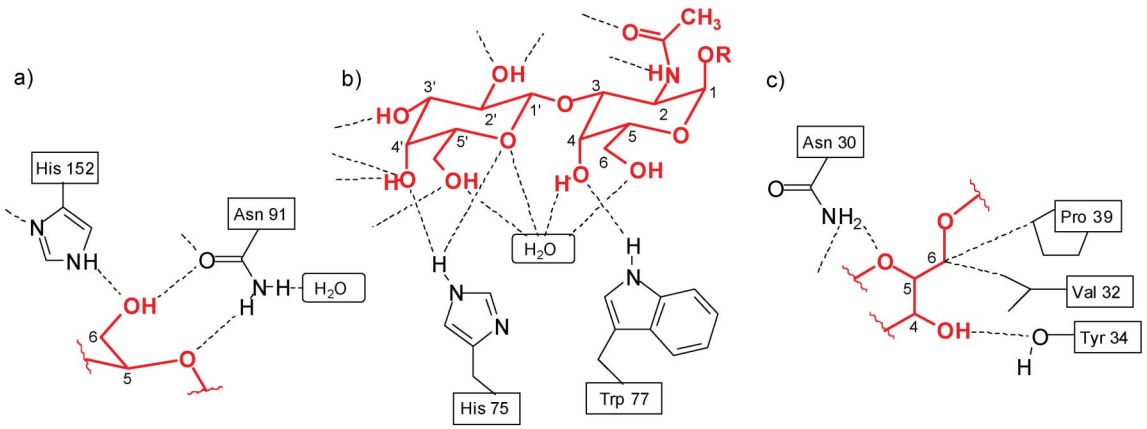


Fig. 1 Examples of hydrogen bonds in the complexes of galactose-binding protein with D-glucose (a)[4c] and *Amaranthus caudatus* agglutinin with Galβ3GalNAc (b).[4a] Examples of hydrogen bonds and van der Waals contacts in the complex of *Galanthus nivalis* agglutinin with Manα3(Manα6)Man (c).[4a,4f]

have been constructed on the base of both neutral and ionic recognition groups, to form neutral and ionic hydrogen bonds with the sugar substrates. Long-chain alkyl glycosides have usually been investigated as substrates for artificial receptors in homogeneous organic media, whereas sugar derivatives, which are insoluble in non-polar media, have been used for recognition studies in two-phase systems. Such studies involve dissolution of solid carbohydrates in non-polar solvents[6] or extraction of carbohydrates from aqueous into non-polar media.[7] It should also be noted that oligosaccharides have received far less attention in artificial receptor chemistry than monosaccharides.

2.1. Molecular recognition of monosaccharides

An azacrown-attached *meta*-ethynylpyridine polymer **1** was investigated for its carbohydrate recognition and the additive effect of triethylene tetramine–trifluoroacetic acid (TETA–TFA) by Abe, Inouye *et al.* in 2009.[8] When octyl β-D- (**2a**) and L-glucopyranosides (**3a**) were added to a CH_2Cl_2 solution of **1**, a mirror-image pair of induced circular dichroism (ICD) bands was observed, indicating that **1** formed chiral helical complexes with the guests. These ICDs were significantly enhanced by the addition of oligoammonium cations. The authors concluded that the ICD enhancements arise from the formation of a pseudopolyrotaxane structure between the azacrown and the oligoammonium moieties, which stabilize the chiral helical complexes by cross-linking the side chains. The binding constants were further enhanced by the addition of trifluoroacetic acid; the binding constants for β-glucoside **2** were found to be 800 and 1500 M^{-1} in the absence and presence of TFA, respectively (in the absence of both TETA and TFA the binding constant amounted to 100 M^{-1}).

The synthesis and binding properties of eight porphyrin-based receptors containing urea, carbamate or amide groups were described in 2010 by Hong *et al.*[9] The interactions of these receptors with three octyl glycosides, such as β-D-glucoside (**2a**) , α-D-glucoside (**4a**), and β-D-galactoside (**5a**), were investigated by ^{1}H NMR and UV-Vis titrations, as well as induced circular dichroism (ICD). In chloroform the binding constants ranged from 10^2 to 10^5 M^{-1}; the best results were obtained with a urea-appended zinc porphyrin incorporating four benzyl groups. The binding affinity of this receptor decreased in the sequence β-galactoside **5a** > β-glucoside **2a** > α-glucoside **4a**. In a more competitive medium, such as $CDCl_3$–CD_3OD (10 : 1, v/v), a significant drop in binding constants was observed ($K_{11} \sim 10^2$ M^{-1}). The authors concluded that in the case of the urea-appended porphyrins, the urea NHs act as strong hydrogen bonding donors for sugar hydroxyl oxygens and the porphyrin plane is used for mimicking the CH–π interactions[10–12] with sugar CHs.

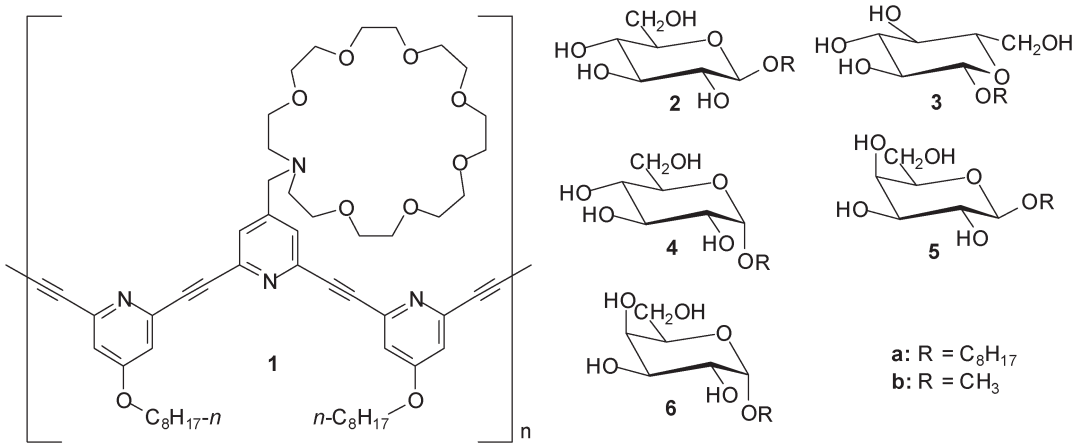


Table 1 Examples of association constants[a,b,c] for receptors **8**, **13** and **18** and sugars **2a**, **2b**, **4a**, **4b** and **5a**

Receptor–sugar complex	Solvent	K_{11} [M^{-1}]	K_{21}[h] or K_{12}[i] [M^{-1}]	$\beta_{21} = K_{11}K_{21}$ or $\beta_{12} = K_{11}K_{12}$ [M^{-2}]
8•2a	$CDCl_3$	69 500	1060; [h]	7.37×10^7
	5% DMSO-d_6–$CDCl_3$	4300	300; [h]	1.29×10^6
8•4a	$CDCl_3$	6810	100; [h]	6.81×10^5
8•5a	$CDCl_3$	148 700	1580; [h]	2.34×10^8
	5% DMSO-d_6–$CDCl_3$	8600	770; [h]	6.62×10^6
13•2a	$CDCl_3$[c]	$>10^5$	[j]	
	H_2O-containing $CDCl_3$[d]	$>10^5$	[j]	
	5% DMSO-d_6–$CDCl_3$[e]	78 400	1200; [h]	9.40×10^7
13•2b	10% DMSO-d_6–$CDCl_3$[f]	11 950	340; [h]	4.06×10^6
13•4a	$CDCl_3$[c]	$>10^5$	[j]	
	H_2O-containing $CDCl_3$[d]	$>10^5$	[j]	
	5% DMSO-d_6–$CDCl_3$[e]	$>10^5$	[j]	
13•4b	10% DMSO-d_6–$CDCl_3$[f]	110 340	2470; [h]	2.72×10^8
	20% DMSO-d_6–$CDCl_3$[g]	24 070	650; [h]	1.56×10^7
13•5a	$CDCl_3$	13 360	800; [h]	1.06×10^7
18•2a	$CDCl_3$	28 800	530; [h]	1.52×10^7
	5% DMSO-d_6–$CDCl_3$[e]	2550	190; [i]	4.85×10^5
18•4a	$CDCl_3$	4360	210 ; [i]	9.15×10^5
18•5a	$CDCl_3$	44 540	1680; [h]	7.48×10^7
	5% DMSO-d_6–$CDCl_3$[e]	3830	300; [i]	1.15×10^6

[a] Average K_a values from multiple titrations. [b] Errors in K_a are less than 20%. [c] $CDCl_3$ was stored over activated molecular sieves and deacidified with Al_2O_3. [d] 0.02–0.04% H_2O. [e] DMSO-d_6–$CDCl_3$, 5 : 95 v/v. [f] DMSO-d_6–$CDCl_3$, 10 : 90 v/v. [g] DMSO-d_6–$CDCl_3$, 20 : 80 v/v. [h] K_{21} corresponds to 2 : 1 receptor–sugar association constant. [i] K_{12} corresponds to 1 : 2 receptor–sugar association constant. [j] Hostest program indicated "mixed" 1 : 1 and 2 : 1 receptor–sugar binding model with $K_{11} > 10^5$ and $K_{21} \sim 10^4$; however, the binding constants were too large to be accurately determined by the NMR method.[16,17]

Our group has continued the studies on acyclic receptors,[6g,6h,13–15] such as compounds containing a trisubstituted trialkylbenzene core, which were shown to be particularly interesting objects for systematic studies. Depending on the nature of the recognition units and connecting bridges used as building blocks, a variety of receptors with different binding preferences and affinities could be obtained.

In comparison to the previously described symmetrical, three-armed aminopyridine-based receptor **7**,[6f] which was shown to exhibit high affinity and preference for β-glucoside **2**, 8-hydroxyquinoline-based receptors **8** and **9**[13] showed significantly increased binding affinity toward β-galactoside **5** (K_{11} = 148 700 and K_{21} = 1580 M^{-1} for **8•5a**[16,17] compared to K_{11} = 3070 and K_{12} = 470 M^{-1} for **7•5a** in $CDCl_3$). It is noteworthy that the enhancement of the binding affinity of **8/9** towards **5** was achieved through a relatively simple variation of the receptor structure.

It should also be noted that the imidazole/aminopyridine- and indole/aminopyridine-based receptors **10** and **11**[6g] were also found to display significantly higher binding affinity for β-galactoside **5** than the symmetrical aminopyridine-based receptor **7**[6f]. The design of receptors **10** and **11**, including both 4(5)-substituted imidazole or 3-substituted indole units as the entities used in nature, and a 2-aminopyridine group as a heterocyclic analogue of the asparagine/glutamine primary amide side chain, was inspired by hydrogen bonding motifs shown in Fig. 1a,b. Both hydrogen-bonding and interactions of the sugar CHs with the phenyl rings of the receptors, as characterized by ^{1}H NMR spectroscopy and X-ray analysis, were shown to contribute to the stabilisation of the receptor–sugar complexes. Such interactions were also suggested by molecular modelling calculations, as shown for **10•5b** in Fig. 2.

In contrast to 8-hydroxyquinoline-based receptors **8/9**[13] and to the indole/imidazole-based receptors **10/11**,[6g] the phenanthroline/aminopyridine-based receptors[6h,14a] **12** and **13** were shown to display a high binding affinity towards α-glucoside **4** and α-galactoside **6** ($K_{11} > 10^5$ M^{-1} in $CDCl_3$; for examples, see Table 1) as well as a strong α- *vs.* β anomer binding preference. In comparison to the symmetrical receptor **7**, dramatic changes of the binding affinity and selectivity were observed after the replacement of one or two pyridine-based recognition units by phenanthroline-based units; the values of the association constants K_{11} ranged from 1310 M^{-1} for **7•4a** to $K_{11} > 10^5$ M^{-1} for **12•4a** and **13•4a** in $CDCl_3$. According to molecular modelling calculations, the 1 : 1 complexes between receptor **12/13** and α-glucopyranoside **4** were shown to be stabilized by several hydrogen bonds as well as interactions of sugar CHs with the aromatic groups of the receptor molecule (see Fig. 3).

The binding studies in DMSO-d_6–$CDCl_3$ mixtures showed that affinities of **13** for the tested glycosides decrease as solvent polarity increases (see Table 1); however, the determined binding constants were significantly higher than those determined for **12** (for example, K_{11} = 110 340 M^{-1} and K_{21} = 2470 M^{-1} for **13•4b**, in comparison with K_{11} = 10 500 M^{-1} and K_{21} = 840 M^{-1} for **12•4a** in 10% DMSO-d_6 in $CDCl_3$). The binding strength towards the examined glycosides was shown to decrease in the sequence α-glucoside **4** > β-glucoside **2** ~ α-galactoside **6** > β-galactoside **5**.

Extractions of sugars **2b**, **4b**, **5b**, **6b**, and **14**–**17** from the solid state into a $CDCl_3$ solution of receptor **13** provided further evidence for strong complexation of α-glycosides, in agreement with the results obtained in homogenous solutions by ^{1}H NMR titrations.[6h] The extractability decreased in the sequence α-glucoside **4b** > β-glucoside **2b** ~ α-galactoside **6** > fucose **14** > β-galactoside **5b** ~ *N*-acetyl-galactosamine **16** > α-mannoside **15** > *N*-acetyl-glucosamine **17**. The α- *vs.* β-anomer binding preference of **13** in the recognition of glucosides indicated by ^{1}H NMR titrations, was also confirmed by the extractions of methyl α-D-glucoside (**4b**) and methyl β-D-glucoside (**2b**) from water into

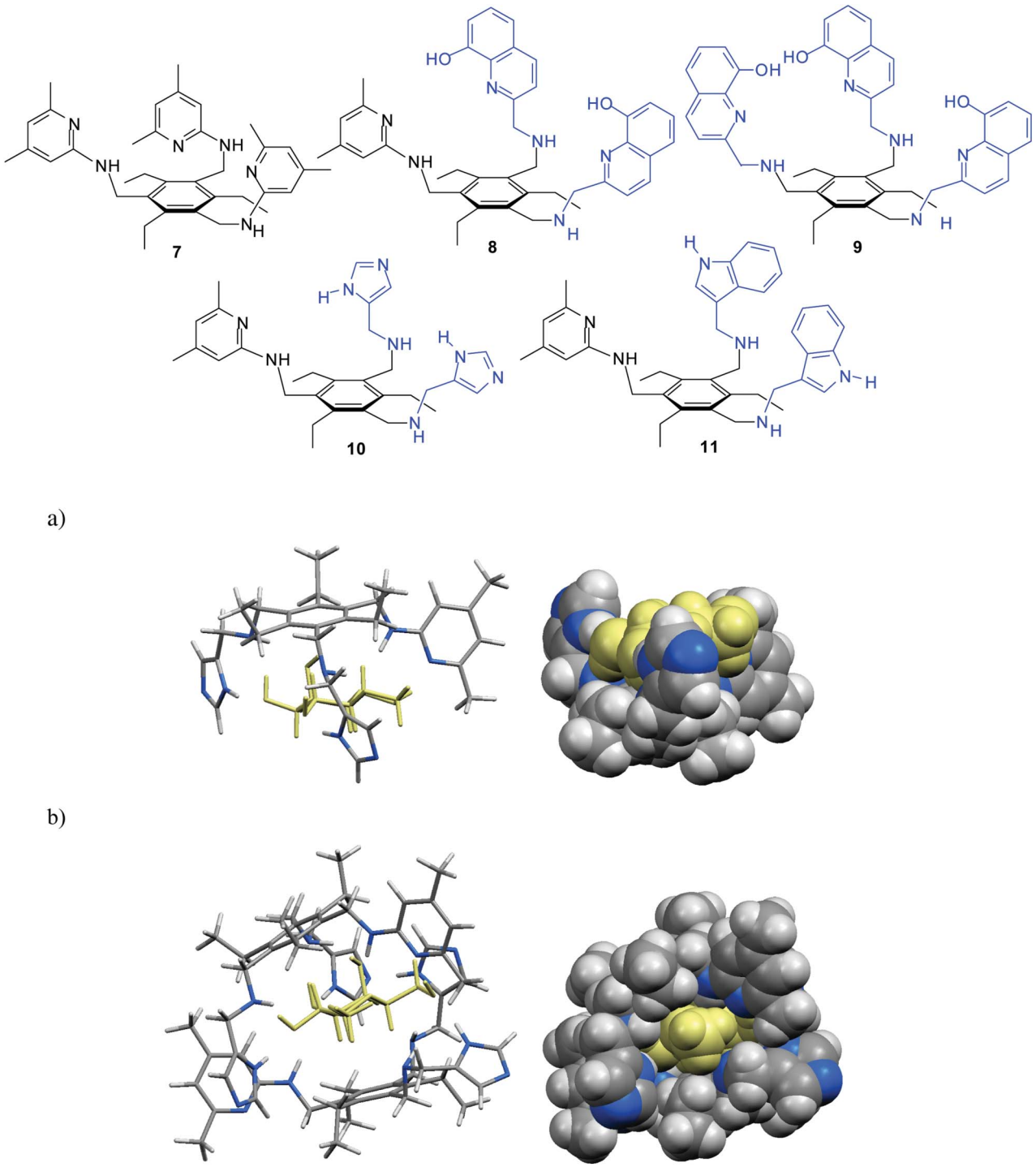


Fig. 2 Energy-minimized structure of the 1 : 1 (a) and 2 : 1 complex (b) formed between imidazole/aminopyridine-based receptor **10** and *β*-galactoside **5b** (different representations). MacroModel V.8.5, OPLS-AA force field, MCMM, 50 000 steps. Color code: receptor C, grey; receptor N, blue; sugar molecule, yellow.[6g]

chloroform. Compound **13** (1 mM chloroform solution) showed notable selectivity for α-glucoside, extracting 0.4 equiv. of α-glucoside **4b**, but only about 0.15 equiv. of *β*-glucoside **2b**, from 1 M aqueous solution of the corresponding sugar. Furthermore, compound **13** showed notable α- *vs.* *β*-anomer selectivity in the recognition of galactosides; the receptor was able to extract about 0.3 equiv. of α-galactoside **6** from water into chloroform solution. It should be noted that the observed preference for α- over the *β*-glycosides differs from those observed for other receptor systems, which usually showed higher affinity for the *β*-anomers.[18,19]

It is also noteworthy that interesting hydrogen-bonded complexes with water molecules have been revealed by the X-ray analysis of the phenanthroline-based receptors.[6h,14] In the

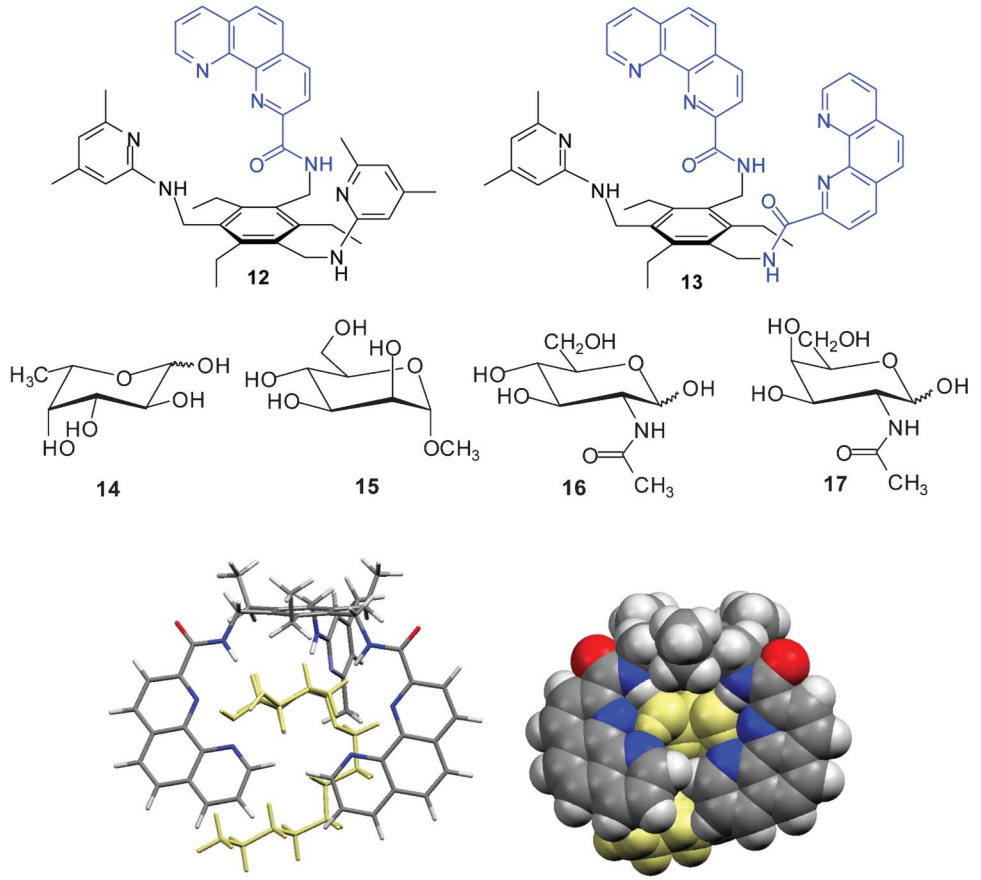


Fig. 3 Energy-minimized structure of the 1 : 1 complex formed between receptor **13** and octyl α-D-glucopyranoside (**4a**) (MacroModel V.8.5, OPLS-AA force field, MCMM, 50 000 steps). Color code: receptor C, grey; O, red; N, blue; the sugar molecule is highlighted in yellow.[6h]

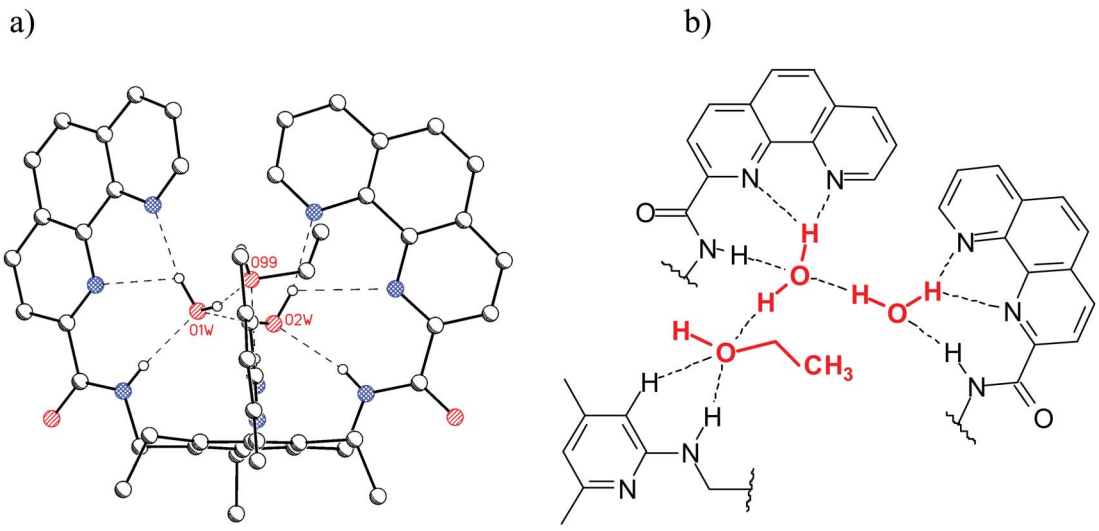


Fig. 4 (a) Crystal structure of **13** (C–Hs are omitted for clarity); two hydrogen-bonded water molecules and one ethanol molecule are present in the binding pocket of **13**. (b) Schematic representation of the binding motifs in the binding pocket of **13**.[6h]

case of compound **12**, X-ray crystallographic investigations revealed the presence of three water molecules in the binding pocket of the receptor (the **12**·3H_2O aggregate is stabilized by NH···O, OH···N, and OH···O hydrogen bonds), whereas in the case of **13** the presence of two water molecules and one ethanol was observed (see Fig. 4).

Binding motifs observed in the crystal structures of protein–carbohydrate complexes, in particular the participation of the primary amide group of asparagine and the isopropyl group of valine (see Fig. 1c) in the formation of hydrogen bonds and van der Waals contacts, respectively, has also inspired the design of artificial receptor **18**,[15] which was expected to be able to

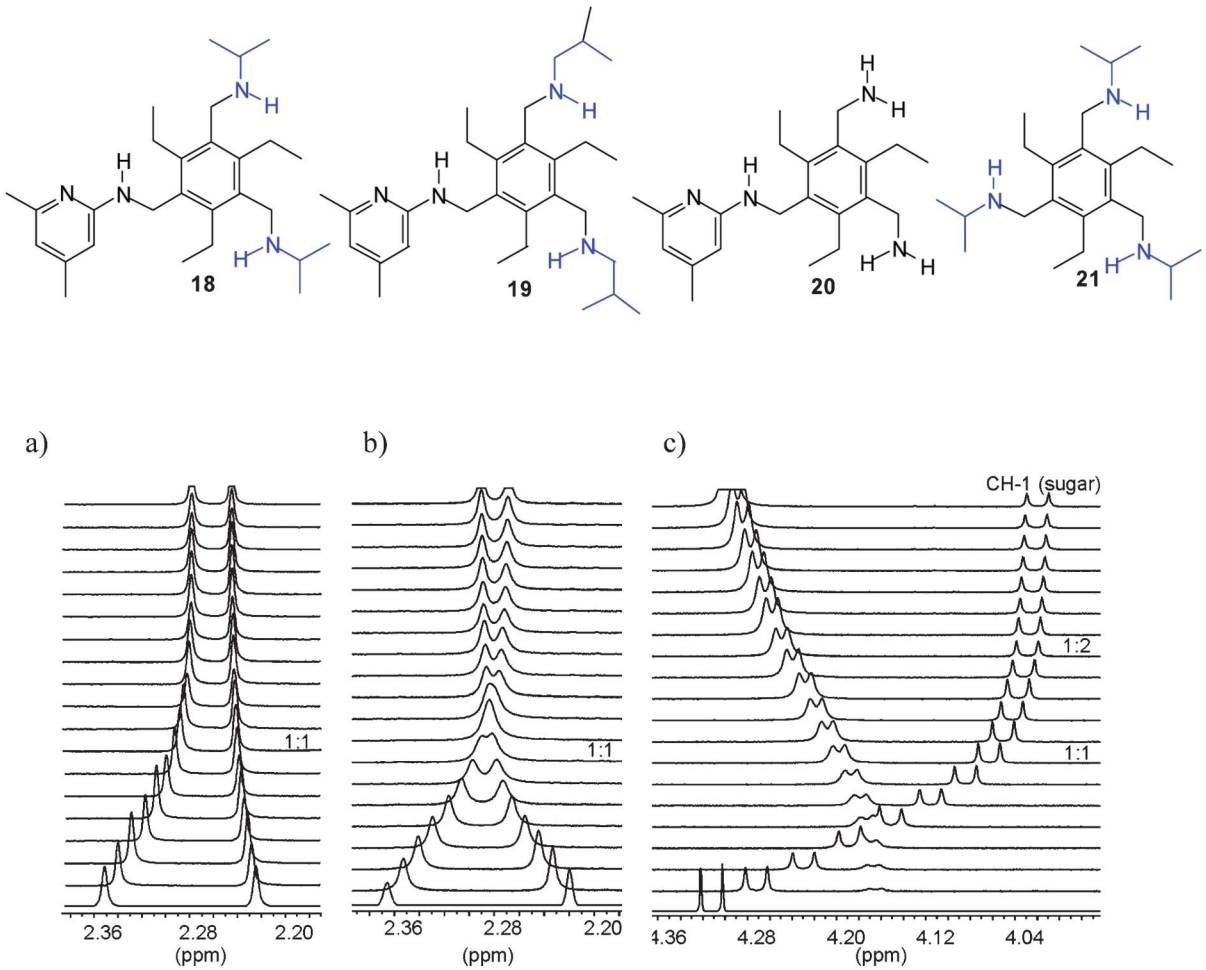


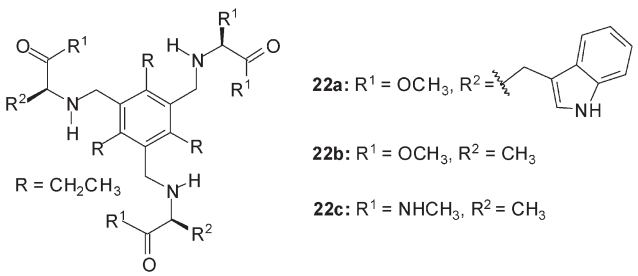
Fig. 5 (a,b) Partial ^{1}H NMR spectra (400 MHz; $CDCl_3$) of receptor **18** before (bottom) and after the addition of β-glucoside **2a** (a) and β-galactoside **5a** (b); [**18**] = 0.97 mM, equiv. of **2a** or **5a**: 0.00–4.80. Shown are pyridine CH_3 resonances of **18**. (c) Partial ^{1}H NMR spectra of sugar **2a** before (bottom) and after the addition of receptor **18** (inverse titration); [**2a**] = 0.78 mM, equiv. of **18**: 0.00–4.99.[15]

recognise a sugar molecule through a combination of NH···O and OH···N hydrogen bonds, CH–π interactions[10–12] and van der Waals contacts. Instead of the primary amide group shown in Fig. 1c, the 2-aminopyridine unit was used, which can be regarded as a heterocyclic analogue of the asparagine/glutamine primary amide side chain and was shown to be an effective recognition group for carbohydrates. The binding properties of **18** towards selected monosaccharides were compared with those of compounds **19**–**21**.

^{1}H NMR spectroscopic titrations (for examples, see Fig. 5) and binding studies in two-phase systems, such as dissolution of solid carbohydrates in apolar media, revealed effective recognition of neutral carbohydrates by **18**, β- *vs.* α-anomer binding preferences in the recognition of glycosides and significantly increased binding affinity towards β-galactoside **5** in comparison with the previously described symmetrical receptor **7**[6f] and other acyclic receptors.[20] Although 1 : 1 complexes predominated in the solution, the presence of 1 : 2 or 2 : 1 receptor–sugar complexes, depending on the titration conditions, were also detected.

Compound **18**, containing isopropylamino groups, was shown to be a more effective carbohydrate receptor than the isobutylamino-based compound **19**. Liquid–liquid extractions demonstrated its ability to extract monosaccharides from water into chloroform; such ability is interesting, considering that the receptor possesses a very simple, acyclic structure. Compared to the previously described receptor **7**, incorporating three aminopyridine-based recognition units,[6f] receptor **18** showed significantly increased affinity to β-galactoside **5** (about 10 times higher affinity), but decreased affinity towards β-glucoside **2** (about 2 times lower). The affinities of **20** for the tested monosaccharides were shown to be considerably lower than those of **18** and **19**. Tighter binding of monosaccharides by **18**/**19** compared to **20** has been attributed to van der Waals contacts between the monosaccharide substrate and the isopropyl/isobutyl groups, that are absent in **20**. The replacement of the aminopyridine group in **18** and **19** by an isopropylamino or isobutylamino unit resulted in a fall in the binding constants. The affinity of the symmetrical isopropylamino-based receptor **21** towards the selected β-glycosides was shown to be similar to that of **20**. Compared to the symmetrical aminopyridine-based receptor **7**, compound **21**, possessing only three NH groups as hydrogen bonding sites, showed a significantly decreased affinity (about 10 times lower) to β-glucoside **2a**, but a similar affinity towards β-galactoside **5a**. Considering the simple structure of **21**, the binding affinity towards β-galactoside is noteworthy.

Evaluation of amino acids as chiral ligands for the enantiodifferentiation of carbohydrates was reported by Riguera, Fernandez-Megia *et al.* in 2010.[21] The interactions of receptors of type **22** with octyl β-D-glucoside (**2a**) and octyl β-L-glucoside (**3a**) were studied by ^{1}H NMR spectroscopy in $CDCl_3$. ^{1}H NMR titrations, which were performed at constant concentration of the corresponding sugar, revealed severe overlapping of carbohydrate and receptor resonances. The authors proved 1D TOCSY (Total Correlation Spectroscopy) NMR experiments to be a useful filtering strategy widening the scope of NMR titrations to systems where overlapping hampers the direct analysis of the carbohydrate resonances. The best fit of the titration data was obtained when a mixed 1 : 1 and 2 : 1 binding model (receptor to sugar ratio) was used for the calculation of the binding constants (EQNMR software[16c]). The tested receptors showed only moderate affinity in $CDCl_3$; the binding constants K_{11} and K_{21} were in the range of 58–465 M^{-1} and 51–142 M^{-1}, respectively. Whereas **22a** was not able to discriminate between the enantiomers **2a** and **3a**, receptors **22b** and **22c** showed a slightly preference for the β-L-glucoside **3a**.



22a: $R^1 = OCH_3$, R^2 =

22b: $R^1 = OCH_3$, $R^2 = CH_3$

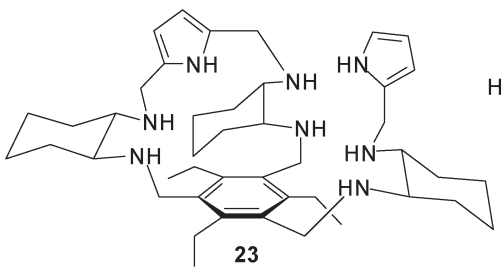
22c: $R^1 = NHCH_3$, $R^2 = CH_3$

Roelens, Jiménes-Barbero *et al.* described effective recognition of mannosides by receptor **23**, which was developed by combining a chiral diamino building block with pyrrolic hydrogen-bonding units on the triethylbenzene scaffold.[22] Receptor **23** was prepared in both enantiomerically pure forms, the *R,R,R,R,R,R* enantiomer [(*R*)-**23**] and the *S,S,S,S,S,S* enantiomer [(*S*)-**23**]. Interestingly, (*S*)-**23** displayed a clear preference for octyl β-D-mannoside (**24**) over the corresponding α-anomer **25** [K_{11} = 10 000 M^{-1} and K_{12} = 1096 M^{-1} for (*S*)-**23•24** compared to K_{11} = 3090 M^{-1} and K_{21} = 223 M^{-1} for (*S*)-**23•25**; the titration results indicated different binding models for the two systems]. Furthermore, (*S*)-**23** showed stronger binding of β-mannoside **24** than (*R*)-**23** in a polar medium like acetonitrile [K_{11} = 758 M^{-1} and K_{21} = 26 M^{-1} for (*R*)-**23•24**]. It should be noted that **23** did not show any enantiodiscrimination in binding to octyl α-mannoside **25**. The structural features of the receptor–mannoside complexes were investigated in solution and in the solid state by a combined X-ray, NMR spectroscopy, and molecular modelling approach.[22b]

2.2. Molecular recognition of disaccharides: di- *vs.* monosaccharide binding preferences

Although some receptors show interesting oligo- *vs.* monosaccharides preferences, the selective recognition of oligosaccharides by receptors using noncovalent interactions is still rare; some examples published until 2008 are given in ref. 23.

In 2009, dimesitylmethane-derived receptors **26/27**, incorporating four heterocyclic recognition groups capable of serving as hydrogen bonding sites, were designed to recognize disaccharides.[24] It has been



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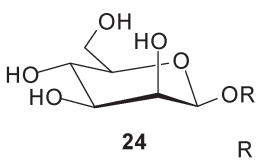

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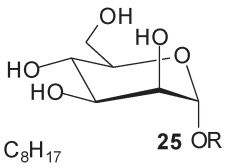
R = C_8H_{17}



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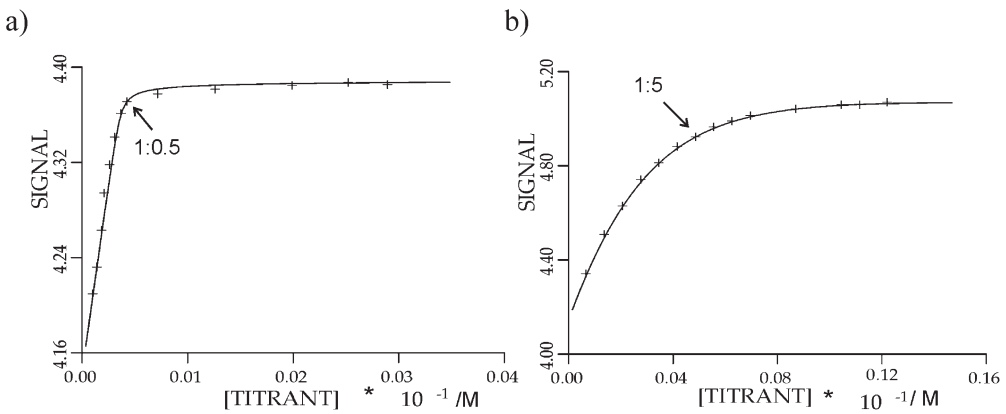
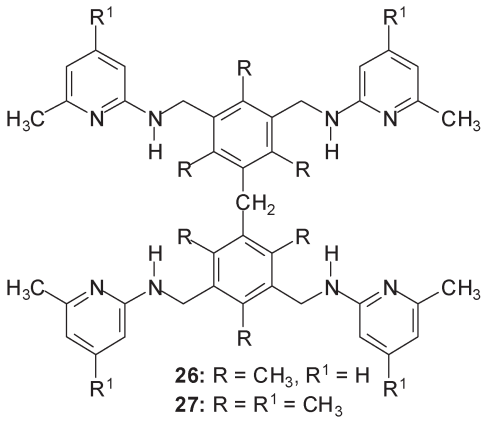
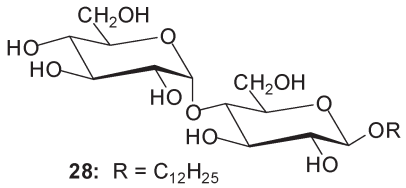
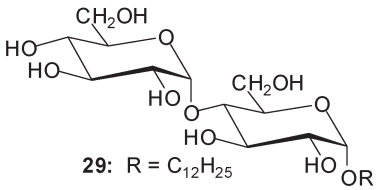
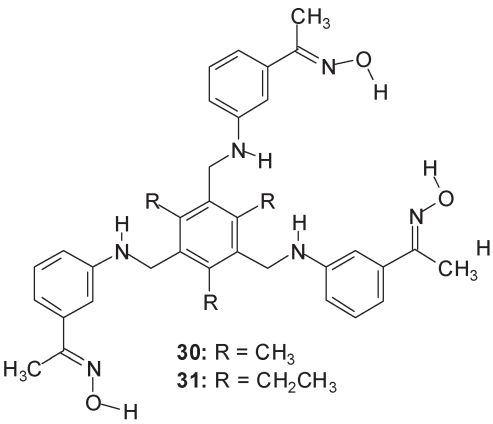


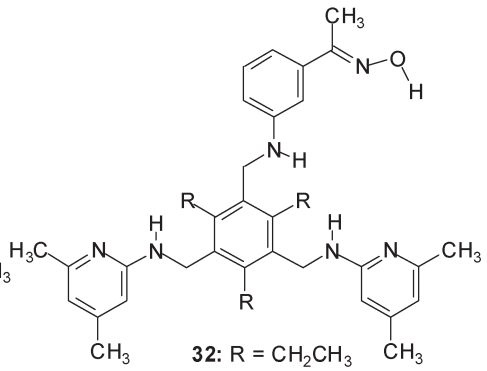
Fig. 6 Plot of the observed (×) and calculated (–) chemical shifts of the NH resonances of **27** (1.02 mM) as a function of added β-maltoside **28** (a) or β-glucopyranoside **2a** (b) The [receptor]:[sugar] ratio is marked.[24]

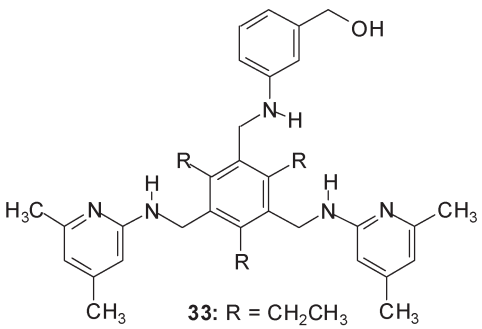


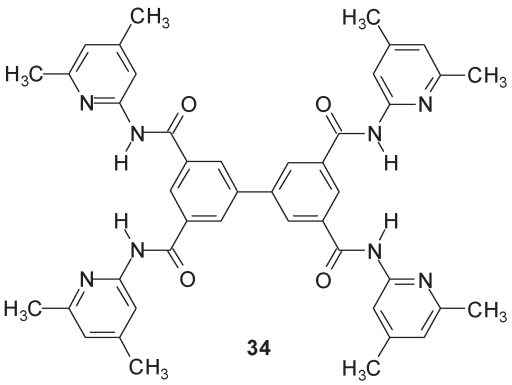




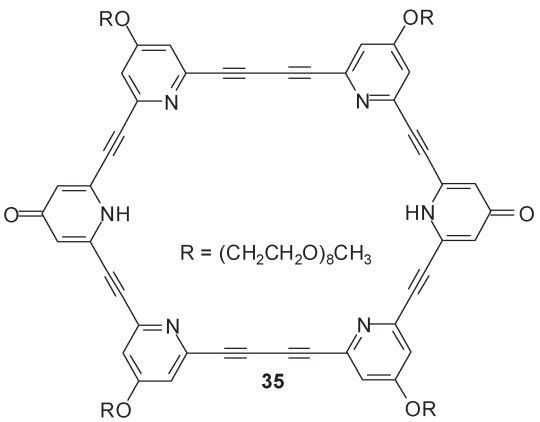


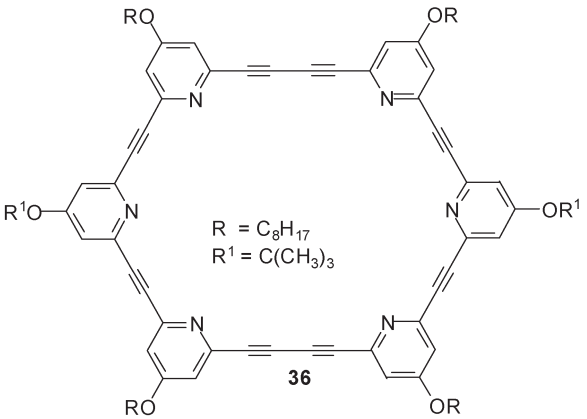






shown by ^{1}H NMR and fluorescence spectroscopic titrations (for examples, see Fig. 6 and 7) that compounds **26/27** display high binding affinities towards α- and β-maltoside, **28** and **29**, as well as strong di- *vs.* monosaccharide preferences in organic media (similar to the previously described receptors **30**–**34**;[25] examples of association constants are given in Table 2).





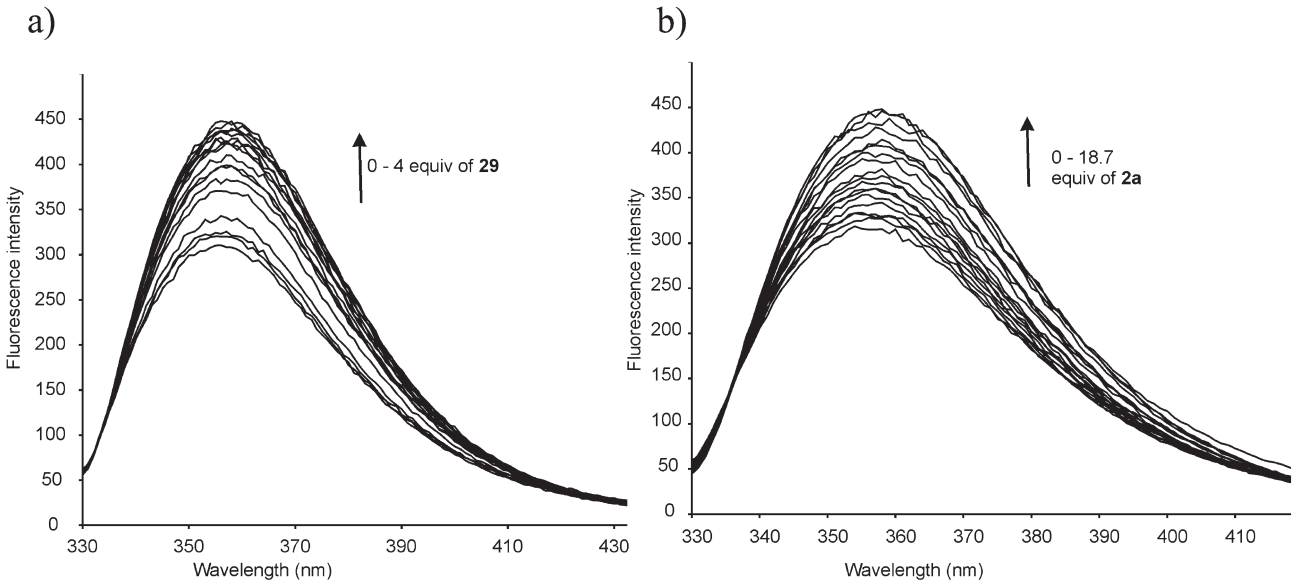


Fig. 7 Fluorescence titration of receptor **26** with α-maltoside **29** (a) and β-glucopyranoside **2a** (b) in $CHCl_3$; [**26**] = 8.51 × 10^{-5} and 9.57 × 10^{-5} M; Equiv. of **29** = 0.00–4.03; Equiv. of **2a** = 0.00–18.69. Excitation wavelength 324 nm. Fluorescence intensity increased with increasing sugar concentration.[24]

Table 2 Examples of association constants[a,b] for receptors **26**, **30** and **34** and sugars **2b**, **28** and **29**

Receptor–sugar complex	Solvent	K_{11} [M^{-1}]	K_{21}[c] or K_{12}[d] [M^{-1}]	β_{21} or β_{12}[e] [M^{-2}]	Method[f]
26•28	$CDCl_3$		>100 000 (K_{21})[g]		NMR
	$CHCl_3$		5.76 × 10^7 (K_{21})		fluorescence
	1% DMSO–$CHCl_3$	14 600			fluorescence
26•29	$CHCl_3$		1.61 × 10^7 (K_{21})		fluorescence
	1% DMSO–$CHCl_3$	10 300			fluorescence
26•2b	$CDCl_3$	260	630 (K_{12})	1.63 × 10^5	NMR
	$CHCl_3$	350	840 (K_{12})	2.94 × 10^5	fluorescence
30•28	$CDCl_3$	100 500			NMR
	$CHCl_3$	98 900			fluorescence
30•2b	$CDCl_3$	170	1730 (K_{12})	2.94 × 10^5	NMR
34•28	$CDCl_3$		>100 000 (K_{21})[g]		NMR
34•2b	$CDCl_3$	8800	300 (K_{12})	2.64 × 10^6	NMR

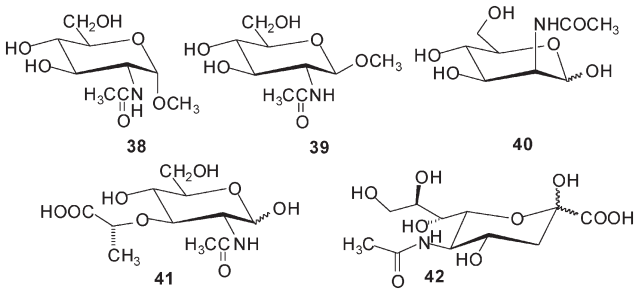
[a] Average K_a values from multiple titrations. [b] Errors in K_a are less than 20%. [c] K_{21} corresponds to 2 : 1 receptor–sugar association constant. [d] K_{12} corresponds to 1 : 2 receptor–sugar association constant. [e] $\beta_{21} = K_{11}K_{21}$, $\beta_{12} = K_{11}K_{12}$. [f] ^{1}H NMR spectroscopic titrations ($CDCl_3$ and DMSO-d_6–$CDCl_3$, 1 : 99 v/v) or fluorescence titrations ($CHCl_3$ and DMSO/$CHCl_3$, 1 : 99 v/v). [g] The best fit of the titration data was obtained with the "pure" 2 : 1 receptor-substrate binding model.[16]

The curve fitting of all titration data suggested the existence of very strong 2 : 1 receptor–disaccharide complexes in chloroform solutions (K_{21} > 10^5 M^{-1}, see Table 2).[24] The addition of dimethyl sulfoxide caused both the change of the binding model and a substantial drop in the binding affinity. The curve fitting of the titration data obtained in the presence of DMSO indicated the formation of complexes with 1 : 1 receptor–disaccharide stoichiometry with K_{11} of 10^4 M^{-1} (see Table 2). As expected, relatively low binding constants were obtained upon titrating compounds **26**/**27** with β-glucopyranoside **2a**. The binding studies indicated the formation of complexes with 1 : 1 and 1 : 2 receptor–monosaccharide stoichiometry with K_{11} and K_{12} of 10^2 M^{-1} in chloroform (see Table 2). Both ^{1}H NMR and fluorescence titrations clearly showed that the receptor–monosaccharide complexes are much less stable than those formed with the disaccharides **28**/**29**. Receptors **26**/**27** are thus representatives of a series of acyclic carbohydrate-binding receptors displaying an interesting di- *vs.* monosaccharide preference. The acyclic architecture is notably easy to prepare and especially suitable for systematic variations.

In 2011, Abe, Inouye *et al.* reported the synthesis of a D_{2h}-symmetrical diacetylenic macrocycle having pyridine–pyridone–pyridine modules (compound **35**).[26] The binding properties of the macrocyclic receptor towards carbohydrates were studied by CD and UV-vis titration experiments in CH_2Cl_2 and CH_3CN. As substrates for these studies, four monosaccharides, octyl β-D-glucopyranoside (**2a**), octyl β-D-galactopyranoside (**5a**), octyl β-D-mannopyranoside (**24**) and octyl β-D-fructopyranoside were used, and one disaccharide, dodecyl β-D-maltopyranoside (**28**).

In CH_2Cl_2, macrocycle **35** showed a much greater affinity for β-maltoside **28** (K_{11} = 1.4 × 10^6 M^{-1}) than for the tested monosaccharides (K_{11} values were estimated to be in the range of 10^3 M^{-1} for **2a** and **5a**, and 10^4 M^{-1} for **24**). The authors

pointed out that the pyridine N–H and pyridine N atoms act as hydrogen bond donors (D) and acceptors (A), respectively, so that alkyl glycosides can be recognized within the cavity of **35**. The binding of *β*-maltoside **28** was less effective in a more polar solvent like acetonitrile (K_{11} was estimated to be 1.8×10^3 M^{-1} for **35•28**); no association was detected with saccharides in a water solution by CD analyses. The efficiency of the pyridone rings was shown by the comparison with all-pyridine macrocycle **36**; the $(A–D–A)_2$-type macrocycle **35** was shown to be more powerful carbohydrate receptor than the $(A–A–A)_2$-type compound **36**.



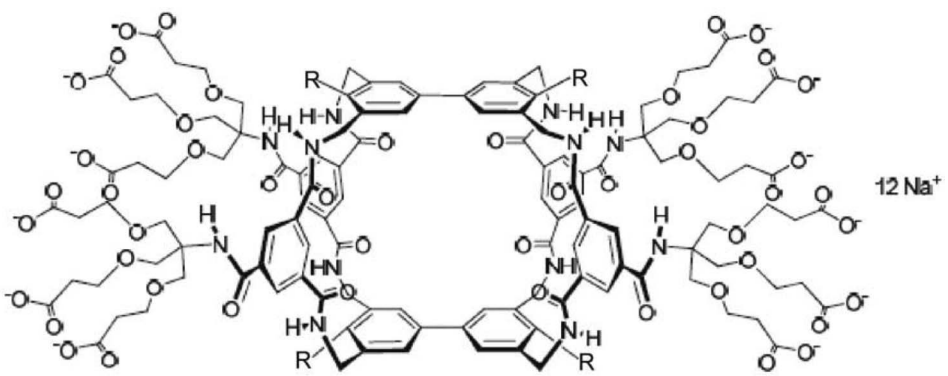
3. Binding studies in aqueous media

Davis and coworkers have continued their successful studies on macrocyclic receptors, which were inspired by carbohydrate-binding proteins, and were designed to provide both apolar and polar contacts to a saccharide molecule.[27,28] The studies focused on binding the *β*-glucosyl family of saccharides, characterized by ''all-equatorial'' arrays of polar functional groups. Compound **37a** was shown to be a selective receptor for O-linked *β*-*N*-acetyl-D-glucosaminyl units.[27] The binding of **37a** to *N*-acetylamino carbohydrates, such as methyl glycosides of GlcNAc (**38** and **39**), *N*-acetyl-D-galactosamine (**17**), *N*-acetyl-D-mannosamine (**40**), *N*–acetylmuramic acid (**41**), and *N*–acetylneuraminic acid (**42**), was studied in D_2O by using ^1H NMR titrations. In some cases the results were checked using isothermal titration calorimetry (ITC) and induced circular dichroism (ICD). The results of the binding studies with *N*-acetylamino carbohydrates were compared with those obtained for 15 other carbohydrates (among other things, methyl *β*-D-glucoside, methyl *α*-D-glucoside, D-cellobiose, D-maltose, and L-fucose). Particularly interesting results were obtained with GlcNAc*β*-OMe **39**. Receptor **37a** showed a remarkable preference for **39** (K_{11} = 630 M^{-1}) *versus* other tested carbohydrates, including the *α* anomer **38** (K_{11} = 24 M^{-1}) and *N*-acetylgalactosamine (**17**) (K_{11} = 2 M^{-1}). Both GlcNAc*α*-OMe (**38**) and methyl *β*-D-glucoside (**2b**) (K_{11} = 28 M^{-1}) were bound with affinities that are more than 20 times lower than that of **39**.

The binding studies with **37b** showed that the incorporation of the methoxy groups produces a general increase in affinities (K_{11} was determined to be 730 M^{-1} for GlcNAc*β*-OMe **39**, 70 M^{-1} for *β*-glucoside **2b**, and 35 M^{-1} for D-glucose).[28] The only exception was *N*-acetyl-D-glucosamine (GlcNAc **16**; K_{11} = 41 M^{-1}), for which a small decrease in affinities was observed between compound **37a** and **37b**. Binding to glucose was enhanced by a factor of about 4.

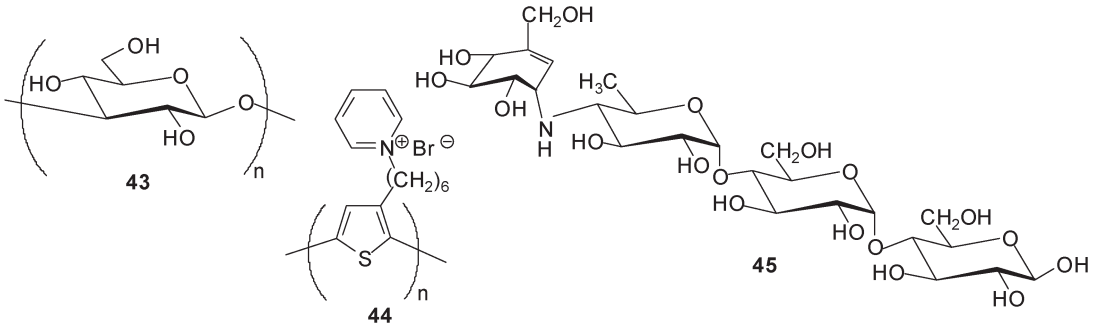
The replacement of the methoxy substituents by ethoxy or propoxy groups (compounds **37c** and **37d**) produced a further increase in affinities for such substrates as D-glucose, methyl *β*-D-glucoside (**2b**) and D-cellobiose, as well as for the closely related all-equatorial substrates 2-deoxy-D-glucose and D-xylose. By contrast, binding to GlcNAc (**16**) and GlcNAc*β*-OMe (**39**) was substantially decreased. Finally, the presence of butoxy substituents (**37e**) caused a drop in binding constants for most substrates.

As mentioned by the authors, particularly interesting results were obtained with **37d**. In contrast to **37a**, macrotricycle **37d** was shown to be a more promising receptor for *β*-glucosyl units, and for glucose itself.[28] In comparison to the 4,4′-unsubstituted receptor **37a**, it bound glucose more strongly (by a factor of *ca.* 6) and considerably more selective (K_{11} = 60 M^{-1} for **37d** and D-glucose). Receptor **37d** showed glucose–glactose selectivity of 20 : 1 and glucose–GlcNAc selectivity of 9 : 1, whereas the corresponding values for **37a** were 4.5 : 1 and 1 : 6, respectively. It should be noted that receptor **37d** was shown to be more glucose selective than the readily available lectins used for this



37a: R = H, **37b:** R = OCH_3; **37c:** R = OCH_2CH_3; **37d:** R = $OCH_2CH_2CH_3$

37e: R = O $CH_2CH_2CH_2CH_3$



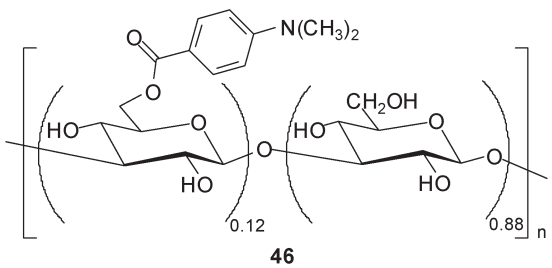
substrate, such as concanavalin A, *Lens culinaris* agglutinin and *Pisum sativum* agglutinin.

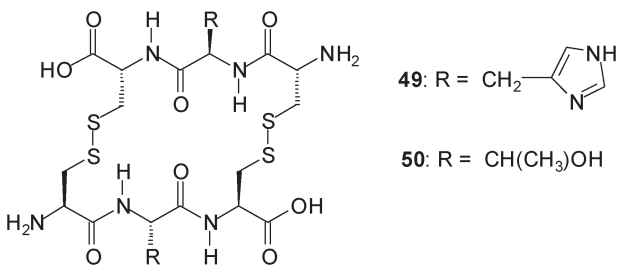
Fukuhara and Inoue tested the combined use of curdlan (**43**), a linear glucan composed of (1–3)-linked *β*-D-glucose units, and 2,5-poly[3-(1-pyridinium)hexylthiophene] (**44**) in saccharide sensing.[29] The studies showed that an *in situ* hybrid complex of curdlan with the water-soluble polythiophene was able to act as a saccharide chemosensor in aqueous media, enabling the discrimination of tetrasaccharide acarbose (**45**) at 1 μM from 24 mono-, di-, tri-, tetra-, and pentasaccharides. The properties of the curdlan-polythiophene system were examined by UV-vis and CD spectroscopies.

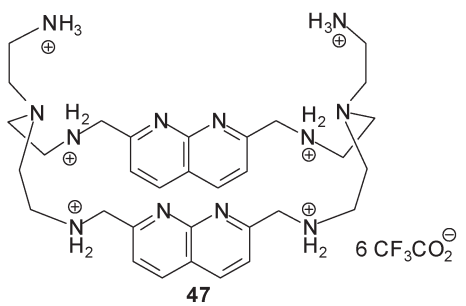
In addition, Fukuhara and Inoue[30] reported oligosaccharide sensing with chromophore-modified curdlan, 6-*O*-[4-(dimethylamino)benzoyl]curdlan, in aqueous media. The degree of substitution of the modified curdlan used for the complexation studies was determined as 0.12 (see structure **46**). The authors investigated the ability of **46** for sensing a variety of saccharides in DMSO–H_2O mixture (1 : 9 v/v) by using circular dichroism (CD) spectroscopy. Interestingly, **46** displayed a preference for tetrasaccharides and was shown to be able to discriminate the tetrasaccharide acarbose at a concentration of $\geqslant$30 mM from 24 mono-, di-, tri- and tetrasaccharides. As mentioned by the authors, the sensing strategy used utilizes the glucan as a recognition device and the appended chromophore as a reporter.

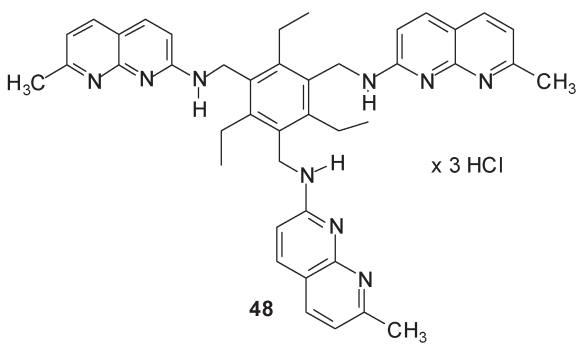
The binding abilities of 1,8-naphthyridine-based macrocyclic receptor **47** against 14 neutral (such as D-galactose, D-glucose, 2-deoxy- and 3-deoxy-D-glucose) and anionic carbohydrates (*N*-acetylneuraminic acid, muramic acid, D-glucose-1-phosphate and D-glucose-6-phosphate) were tested by Mensah and Cudic.[31] The binding affinities were examined by UV/vis and fluorescence titrations in cacodylate buffer at pH 6.5. Among the monosaccharide substrates receptor **47** showed the strongest binding affinity for *N*-acetylneuraminic acid (**42**); the binding constant K_{11} determined on the base of the UV/vis and fluorescence method was found to be $\sim$1200 M^{-1} and $\sim$3000 M^{-1}, respectively. Earlier studies from our group showed that acyclic 1,8-naphthyridine-based receptor **48** was able to recognize *N*-acetylneuraminic acid (**42**) with K_{11} = 3880 M^{-1} and K_{12} = 10930 M^{-1} in a D_2O–DMSO-d_6 (1 : 9, v/v) mixture.[32,33]

Ravoo and coworkers described a dynamic combinatorial approach to the identification of biomimetic carbohydrate receptors.[34] They explored a dynamic combinatorial library (DCL) of cyclic peptides to select receptors that are assembled from tripeptides under thermodynamic equilibrium. To create DCLs from a set of tripeptides under physiological conditions they used the reversible disulfide exchange. In a DCL composed of three tripeptides, for example, an interaction between the cyclic dimer HisHis (**49**) and *N*-acetylneuraminic acid (**42**) was identified, whereas in a DCL of six tripeptides, a selective 1 : 1 interaction of the cyclic dimmer TyrTyr (**50**) with trehalose was found.









4. Conclusion

Recent studies have shown that the area of sugar recognition by receptors operating through noncovalent interactions continues to grow. Strong binding of sugars could be achieved in organic media with both acyclic and macrocyclic receptors. Many of these receptors were inspired by carbohydrate-binding proteins, and were designed to provide both apolar and polar contacts to a sugar molecule. In some cases, studies in two-phase systems, such as dissolution of solid carbohydrates in apolar media and phase transfer of sugars from aqueous into organic solvents, revealed effective recognition of neutral carbohydrates and interesting binding preferences. Most of the binding studies involved the complexation of monosaccharides and, although some receptors showed interesting di- *vs.* monosaccharides preference, the selective recognition of oligosaccharides by receptors using noncovalent interactions is rare. While many interesting systems have been reported and encouraging results generated, the exact prediction of the binding preferences[35] of the receptors still represents an unsolved problem. Systems which operate in water, in which the solvent molecules compete significantly for binding sites of the receptor, are still very rare and their affinities are mostly low; however, very promising results have been reported. Particular powerful carbohydrate receptors, which can be seen as ''synthetic lectins'', have been described by Davis and coworkers.

It is without doubt that molecular recognition of carbohydrates remains a fascinating area of future research, and it seems to be realistic that studies with well-designed synthetic receptors will significantly contribute to the solution of some unsolved problems. It is hoped that artificial carbohydrate receptors will help to enhance the knowledge on molecular details of carbohydrate-mediated recognition events and will provide a base for the development of systems with interesting applications in medicine and other areas.

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