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Purine unit as a building block of artificial receptors designed for the recognition of carbohydrates

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Abstract: 1,3,5-Substituted 2,4,6-triethylbenzene derivatives bearing pyridine/pyrimidine and purine units were synthesized and their potential to function as carbohydrate receptors was evaluated. Compounds consisting of 2-chloro-9*H*(7*H*)-purin-6-yl unit have the ability to act both as carbohydrate-binding agents and as a basis for further functionalisation through the nucleophilic displacement of the chlorine atom. Microwave-assisted reactions and/or the application of sealed tubes allowed the preparation of derivatives with a varying substituent pattern on the purine ring. The relatively drastic reaction conditions required for the successful functionalisation reflect the unfavorable influence of the bulky C6-substituent on the nucleophilic substitution at purine C2. Initial binding studies towards carbohydrates showed that the properties of this type of purine-bearing compounds can be fine-tuned by the variation of the C2-substituent of the purine ring and represents a valuable basis for the identification of new structure-activity relationships. Such findings are of high importance for further developments in the area of molecular recognition of carbohydrates by artificial receptors.

Introduction

Carbohydrates play a key role in a wide range of biological processes[1,2] and the detailed understanding of the principles of their recognition by carbohydrate-binding proteins is of particular interest for researchers. Crystallographic studies revealed that hydrogen bonds, CH···π interactions and numerous van der Waals contacts are involved in selective carbohydrate recognition by proteins.[2] The structural features of protein-carbohydrate interactions have

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inspired the design of artificial carbohydrate-binding agents (carbohydrate receptors).[3,4] The representatives of such artificial receptors are regarded not only as model systems, which should help us to enhance the knowledge on molecular details of carbohydrate-mediated recognition processes, but also as compounds with potential valuable biological activities, including antibacterial, antiviral and anticancer activities.

Within the scope of our studies in the area of sugar recognition by artificial receptors operating by noncovalent interactions, we have developed both acyclic[5-8] and macrocyclic systems[9] (for examples, see Figure 1) showing different interesting binding efficiencies and selectivities towards carbohydrates in dependency of the type of the aromatic platform, the nature of the recognition groups (units X in Figure 1) and the way of their connection (units L and Y) with the aromatic core.

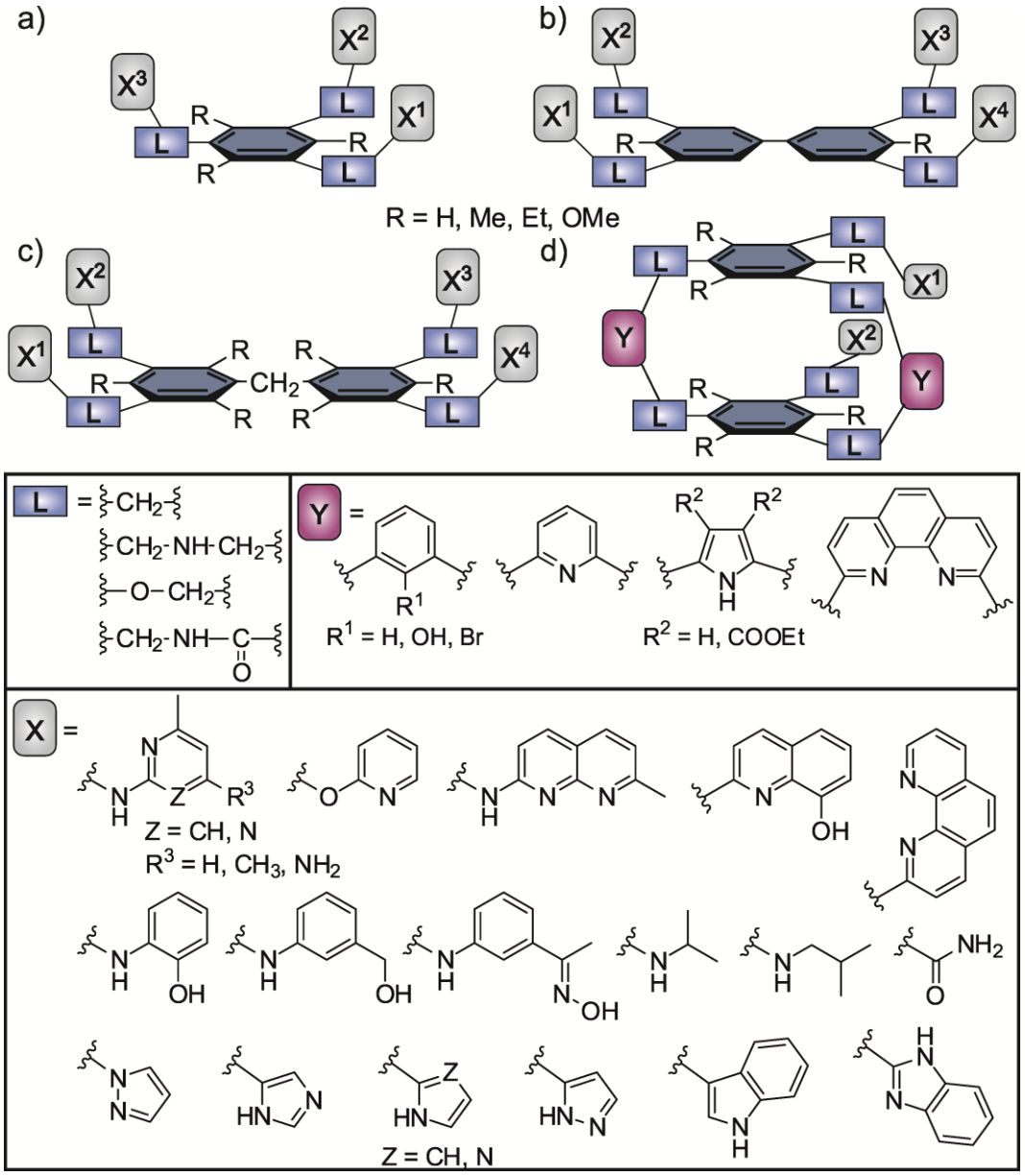

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Figure 1. Examples of acyclic[5-8] (a-c) and macrocyclic[9] (d) carbohydrate receptors reported by our group (X = recognition groups, L / Y = linker / bridge units).

Systematic binding studies revealed that compounds bearing different types of recognition groups (units X^{1-4}, Figure 1a-c) are often more selective carbohydrate receptors than those that consist of identical recognition units. Such a combination of different types of recognition groups has been for example realised in the case of compounds bearing both 2-aminopyrimidine/-pyridine units and pyrrole-, imidazole-, indole-, pyrazole-, quinoline-, pyridinium-, phenanthroline- or isopropylamino-based recognition groups.

It is also worth noting that we have succeeded in obtaining single crystals of the receptor-carbohydrate complexes suitable for X-ray structure analyses, which revealed the involvement of hydrogen bonding (for examples, see Figure 2a), CH···π interactions and van der Waals contacts in the stabilization of these complexes,[5h] as in the case of protein-carbohydrate complexes.

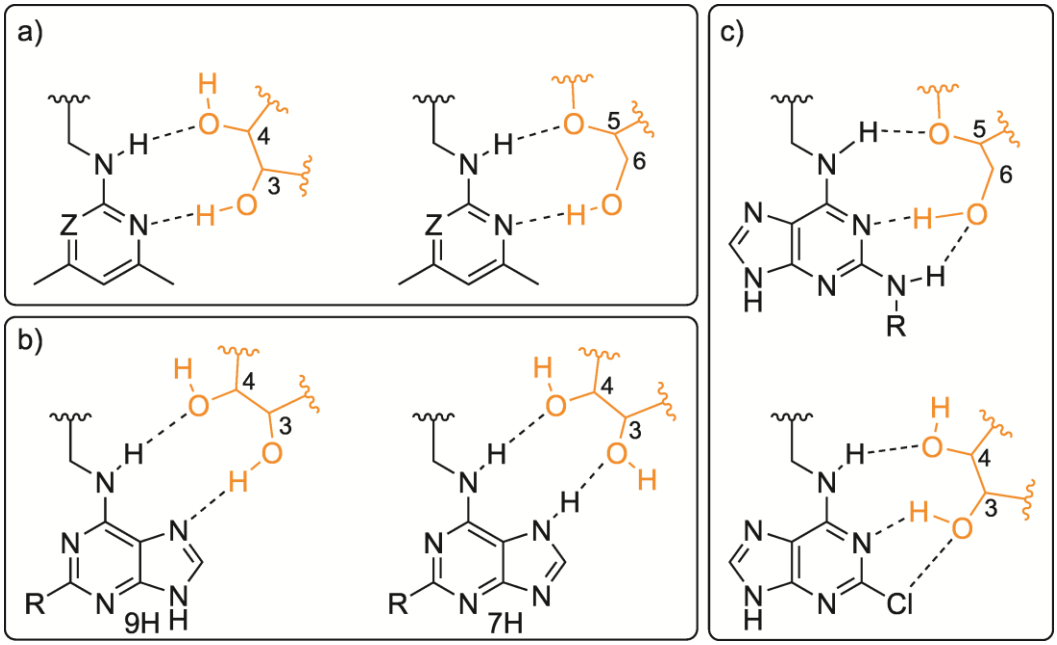

Figure 2. (a) Examples of hydrogen bonds observed in the complexes of glycosides with artificial receptors bearing 2-aminopyridine- (Z = CH) and 2-aminopyrimidine-based recognition groups (Z = N; see, for example ref. 5h); (b,c) Examples of hydrogen bonds which can be formed between purine units and carbohydrates (in the case of the 2-chloro-substituted purine unit, the formation of the C-Cl···O halogen bond could also be expected).

Our studies showed the enormous potential of the designed acyclic and macrocyclic receptor architectures for versatile structural modifications, which enable the identification of interesting

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structure-activity relationships. The aim of this study was the synthesis of new 1,3,5-substituted 2,4,6-triethylbenzene derivatives[10,11] bearing beside the above mentioned 2-aminopyridine/-pyrimidine units, which can be regarded as heterocyclic analogues of the asparagine/glutamine primary amide side chain,[12] also purine unit(s), having the ability to participate in the formation of hydrogen bonds (see Figure 2b and 2c) with the carbohydrate substrate. We were interested to see how the incorporation of the purine-based recognition group(s) influences the binding properties of this type of compounds (see structures **1**-**4**, Figure 3). In addition, the integration of the 2-chloro substituted purine unit (as in **2**-**4**) offers the opportunity for further functionalisation of the triethylbenzene-based compounds (see Figure 3). First tests in this direction have been carried out using compounds **2** and **3** for reactions with selected amines, such as cyclohexylamine, benzylamine, 2-picolylamine, 3-picolylamine and tryptamine, to obtain the compounds **5**-**9**.

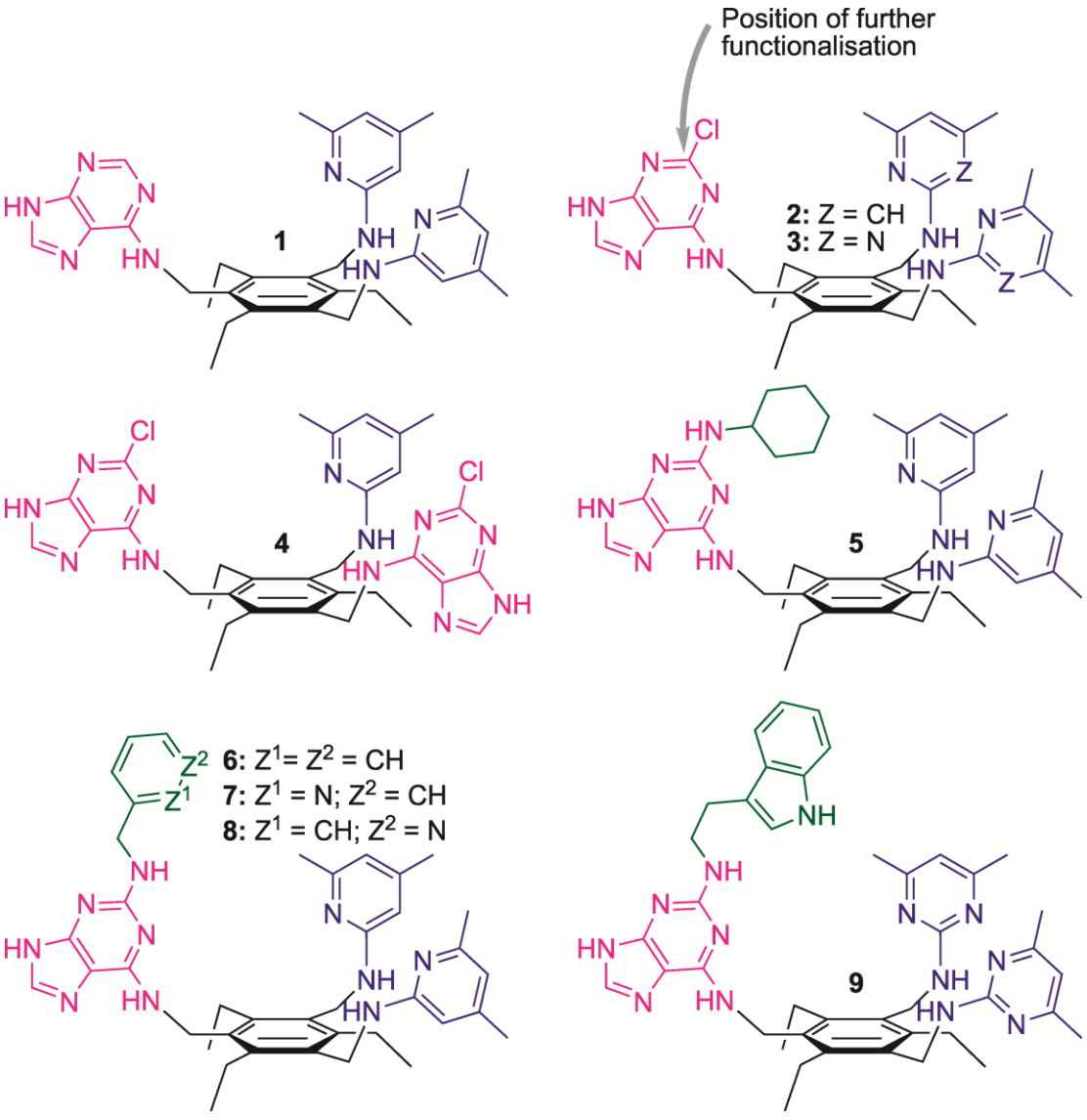

Figure 3. Structures of the target compounds **1**-**9** considered in this study.

The purine skeleton represents a highly important natural building block and has found also broad applications in medicinal chemistry.[13,14] In addition, various organic derivatives consisting of a purine subunit have been used as basis for the formation of different supramolecular assemblies, liquid crystals and other supramolecular systems.[15-17]

Results and discussion

Synthesis of the target compounds 1-9.

Compounds **1** and **2** were prepared by the reaction of 1-aminomethyl-3,5-bis[(4,6-dimethylpyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene (**10**) with 6-chloropurine and 2,6-dichloropurine, respectively, whereas the reaction of 1-aminomethyl-3,5-bis[(4,6-dimethylpyrimidin-2-yl)aminomethyl]-2,4,6-triethylbenzene (**11**, the pyrimidine analoque of **10**) with 2,6-dichloropurine provided the derivative **3** (see Scheme 1). The basis for the synthesis of compound **4**, bearing two 2-chloropurine groups, was 1,3-bis(aminomethyl)-5-[(4,6-dimethylpyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene (**12**), as shown in Scheme 1.

The preparation of compounds **10**-**12** was carried out according to the procedure reported by us previously[6b,6g] and is summarized in Scheme 2. This procedure comprises the synthesis of compounds **15a/16a** and **15b/16b** bearing bromomethyl group(s) by a reaction of 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene (**14**) with 2-amino-4,6-dimethylpyridine (Z = CH, see Scheme 2) and 2-amino-4,6-dimethylpyrimidine (Z = N), respectively. Treatment of **16a** and **16b** with a solution of ammonia in methanol allows their facile convertion into the corresponding aminomethyl derivatives **10** and **11**, respectively, whereas the Gabriel synthesis was used for the conversion of **15a** into the educt **12** possessing two aminomethyl groups.

The reaction of **10** with 6-chloropurine (synthesis of **1**; see Scheme 1) was accomplished through conventional heating (110 °C, up to 16 hours), whereas the reactions of **10**, **11** and **12** with 2,6-dichloropurine (syntheses of **2-4**) were performed using conventional (80 - 110 °C, up to 24 hours) and/or microwave heating (80 °C, approx. 1 hour). The higher reactivity in the 6-position of the 2,6-dichloropurine[18] allows the sequential replacement of the chlorine atoms and the synthesis of compounds bearing 2-chloropurine unit(s), as in the case of **2-4**. Compounds **1**-**4** were prepared with yields in the range of 25 % to 81 % (see Scheme 1). The main advantage of the microwave procedure over the conventional method was the much shorter reaction time (approx. 1 hour *vs* 24 hours).

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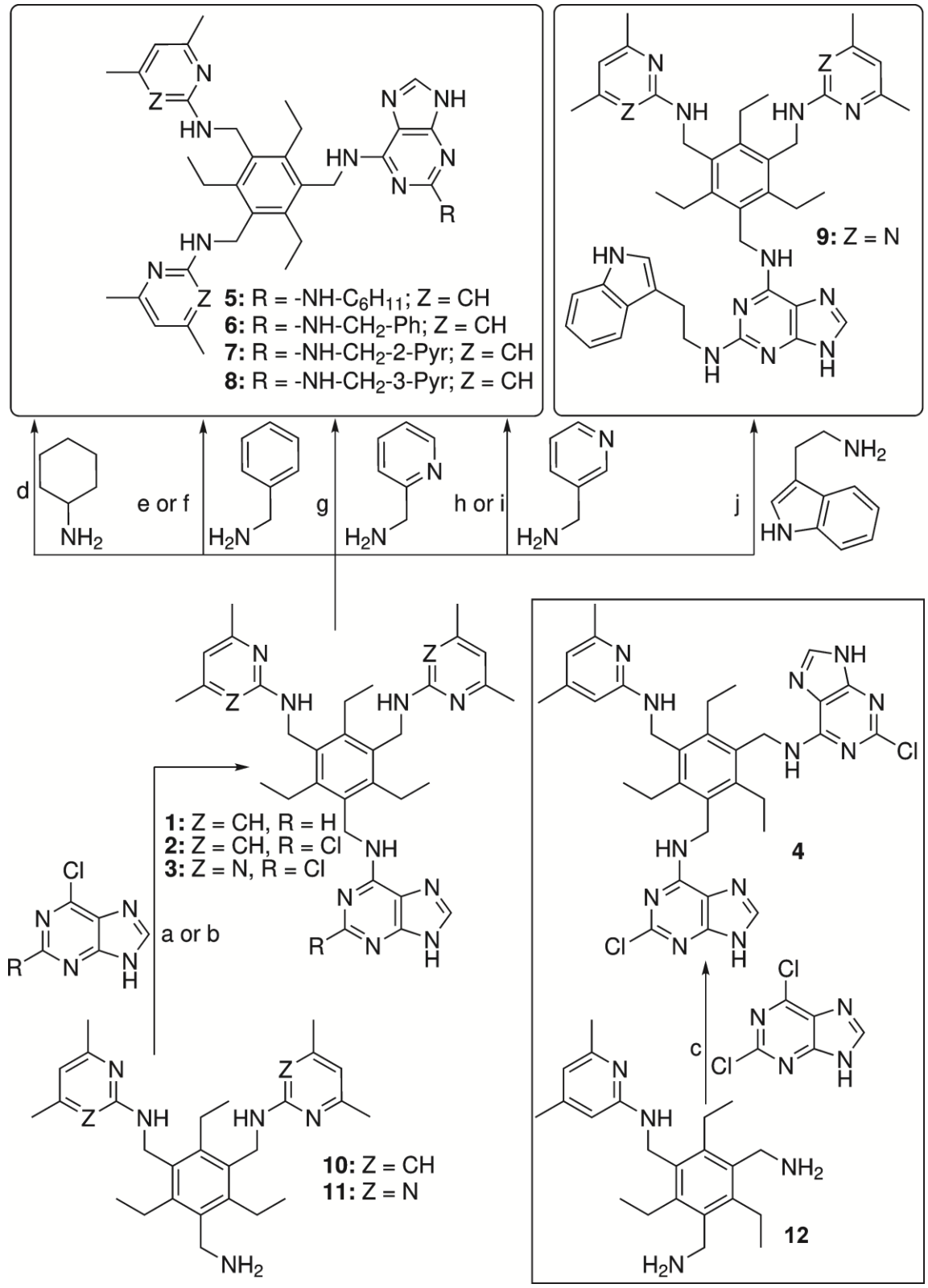
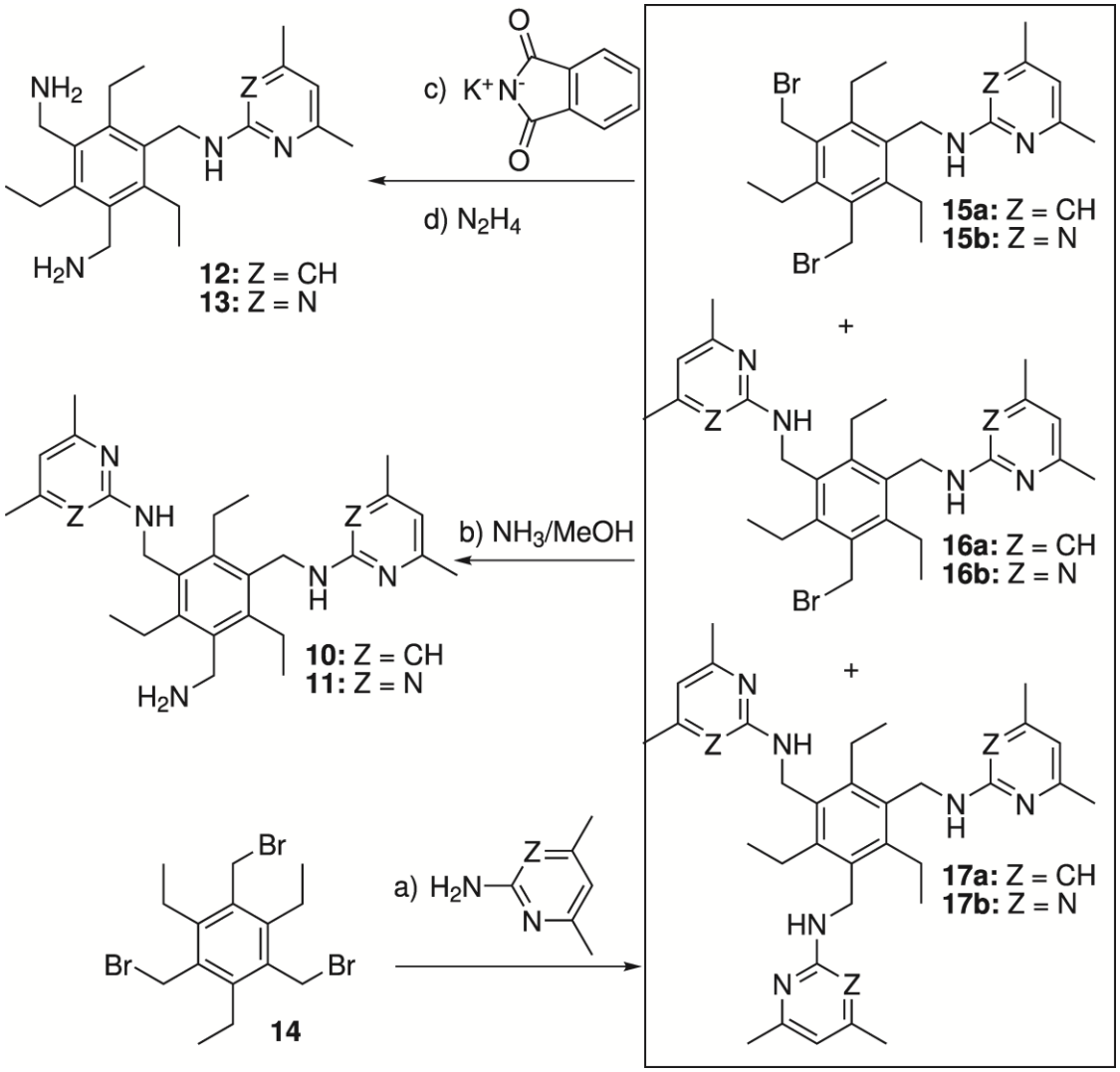


Scheme 1. Reaction conditions: (a) 6-Chloropurine or 2,6-dichloropurine, DIPEA, *n*-butanol, 80-110 °C, 16-24 h (45 % of **1**, 78 % of **2**); (b) 2,6-Dichloropurine, DIPEA, *n*-butanol, microwave irradation, 80 °C, 1-1.25 h (81 % of **2**, 75 % of **3**); (c) 2,6-dichloropurine, DIPEA, *n*-butanol, 110 °C, 24 h (25 % of **4**); (d) Cyclohexylamine, *n*-butanol, sealed tube, 140 °C, 7 d (44 % of **5**); (e) Benzylamine, *n*-butanol, sealed tube, 140 °C, 7 d (45 % of **6**); (f) Benzylamine, *n*-

butanol, microwave irradiation (180 W), 170 °C, 8 h (79 % of **6**); (g) 2-Picolylamine, *n*-butanol, sealed tube, 140 °C, 7 d (34 % of **7**); (h) 3-Picolylamine, *n*-butanol, sealed tube, 125 °C, 6 d (25 % of **8**); (i) 3-Picolylamine, *n*-butanol, microwave irradiation (200 W), 160 °C, 4 h (47 % of **8**); (j) Tryptamine, *n*-butanol, microwave irradiation (160 W), 170 °C, 6 h (42 % of **9**).



Scheme 2. Reaction conditions: (a) 2-Amino-4,6-dimethylpyridine or -pyrimidine, K_2CO_3, THF/acetonitrile, room temperature (in the case of the pyridine derivative) or 50 °C (in the case of the pyrimidine analogue), 3 d (25 % of **15a**, 28 % of **15b**, 20 % of **16a**, 16 % of **16b**); (b) NH_3 (7 N) in MeOH, room temperature, 2 d (69 % of **10**, 38 % of **11**); (c) Potassium phthalimide, DMSO, 12 h, 95 °C; (d) $N_2H_4 \cdot H_2O$, EtOH/toluene, 20 h, 90 °C (37 % of **12**).

After the replacement of the chlorine atom in the 6-position of the 2,6-dichloropurine by a nitrogen nucleophile, the subsequent nucleophilic displacement in the 2-position requires more drastic reaction conditions. Such nucleophilic displacement has often been explored,[19-21] but not in the presence of as bulky group as that attached to the 6-position of the purine ring of

compounds **2** and **3.** The steric effect of such bulky group unfavourably affects the nucleophilic substitution at purine C2.

The functionalisation of compounds **2** and **3** in the 2-position of the purine ring has been tested by us with five selected amines, such as cyclohexylamine, benzylamine, 2-picolylamine, 3-picolylamine and tryptamine (Scheme 1). The reactions were performed in *n*-butanol and *N*,*N*-diisopropylethylamine (DIPEA) was used as a base. By carrying out the reaction of **2** with cyclohexylamine, benzylamine 2-picolylamine and 3-picolylamine in a sealed tube at 125-140 °C, compounds **5**, **6**, **7** and **8** could be obtained with 44 %, 45 %, 34 % and 25 % yield, respectively, but a long reaction time of several days was necessary. Through the use of microwave heating the reaction time could be shortened from several days to 4-8 hours and the yields increased significantly. The yield of **6** could be improved from 45 % to 79 % and that of **8** from 25 % to 47 %. The microwave-assisted reaction of compound **3** with tryptamine allowed the preparation of **9** with 42 % yield after 6 hours. Although the reaction time could be considerably shortened, the required time is much longer than typically known[22] for microwave-assisted reactions. This fact clearly reflects the reactivity problems at the C2-position and can be traced back to steric effects caused by the large C6-substituent.

Exemplary binding studies towards selected carbohydrates.

^{1}H NMR spectroscopic titrations of compounds **1** and **2** with selected glycosides (see Table 1, Figure 4 and Supporting Information) revealed that these two compounds display similar binding efficiency as the previously investigated symmetrical triethylbenzene-based compound bearing three aminopyridine groups[5k] (see structure **17a** in Scheme 2).

The binding preference for β-glucoside versus β-galactoside observed in the homogenous phase was also confirmed by binding studies in two-phase systems. The extractions of methyl glycosides from the solid state into a $CDCl_3$ solution of the corresponding receptor (1 mM solutions) showed that the extractability decreases in the sequence β-glucoside > β-galactoside ≈ α-glucoside (see Table 2).

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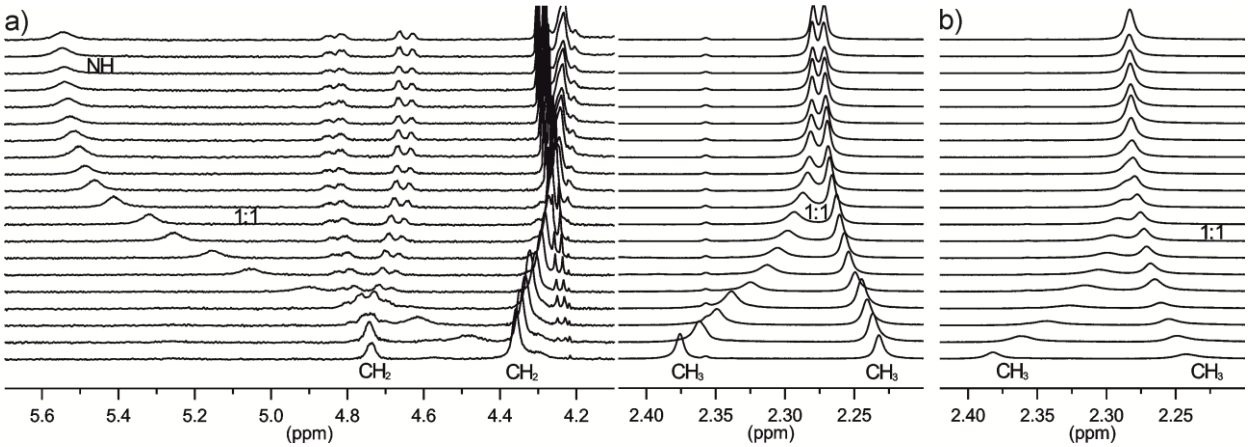

Figure 4. Partial ^{1}H NMR spectra (500 MHz, $CDCl_3$) of compound **2** ([**2**] = 1.01 mM) after addition of (a) 0.00-4.56 equiv of octyl β-D-glucoside and (b) 0.00-5.49 equiv of octyl β-D-galactoside. Shown are the chemical shifts of the CH_2NH and pyr-CH_3 signals of **2**.

Table 1. Association constants[a,b] for the complexation of octyl β-D-glucoside (βglc**)** and octyl β-D-galactoside (βgal) with compounds **1**, **2** and **5-8** (results of ^{1}H NMR spectroscopic titrations, $CDCl_3$, 20 °C).

Receptor/substrate	K_{11} / K_{21}[c] [M^{-1}]	$\beta_{21} = K_{11} \times K_{21}$ [M^{-2}]
1 / βglc[d]	39300 / 680	2.67 x 10^7
2 / βglc	34700 / 930	3.23 x 10^7
5 / βglc	29900 / 350	1.05 x 10^7
6 / βglc	42700 / 290	1.24 x 10^7
7 / βglc	58200 / 290	1.69 x 10^7
8 / βglc	33200 / 140	4.65 x 10^6
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2 / βgal	9800 / 170	1.66 x 10^6
5 / βgal	7000	
6 / βgal	4500	

[a]Average K_a values from multiple titrations evaluated on the basis of different programs (WinEQNMR,[23] HypNMR[24] and SupraFit[25]). [b]Errors were estimated at < 6 %. [c]K_{21} corresponds to 2:1 receptor−sugar association constant. [d]For the previously investigated symmetrical analogue **17a** the K_a values were found to be 48630 M^{-1} (K_{11}) and 1320 M^{-1} (K_{12}) (for details see ref. 5k).

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Table 2. Solubilization of methyl glycosides in $CDCl_3$ by compounds **1** and **2** (1 mM solutions).

Receptor	Molar ratios sugar/receptor occurring in solution[a]		
	β-D-Glucoside	β-D-Galactoside	α-D-Glucoside
1	0.82	0.34	0.40
2	0.70	0.45	0.45

[a]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.

Thus, the replacement of one pyridine-2-yl group by 9*H*(7*H)*-purin-6-yl or 2-chloro-9*H*(7*H*)-purin-6-yl unit does not significantly affect the binding properties of the purine-bearing analogues under the chosen titration and extraction conditions (see Table 1 and 2). However, initial binding studies with compounds **5**-**9** confirmed our expectations that the binding properties of this type of purine-bearing compounds can be fine-tuned by the variation of the C2-substituent of the purine ring. For example, just such a small structural change as the replacement of pyridine-2-yl (compound **7**) by pyridine-3-yl unit (compound **8**) is responsible for a decrease in the binding capacity. Due to the purine tautomerism both the 9*H*- and 7*H*-tautomer can participate in the binding process (see Figure 2b); however, the 9*H*-tautomer represents the major form in the case of the examinated compounds. Through systematic structural modifications of this type of architecture numerous compounds can be prepared, which represent a valuable basis for studying the structure-activity relationships. Currently we are synthesizing analogues of compounds **6**-**9** to study in detail the interactions between the α- and/or β-face of the carbohydrate and the aromatic group(s) of the receptor molecule. The structural modifications involve the variation of the aromatic group and the connecting bridge (subunit Y, see Figure 5). In this connection it should be mentioned that the studies on aromatic-sugar interactions[26] are of high current research interest.

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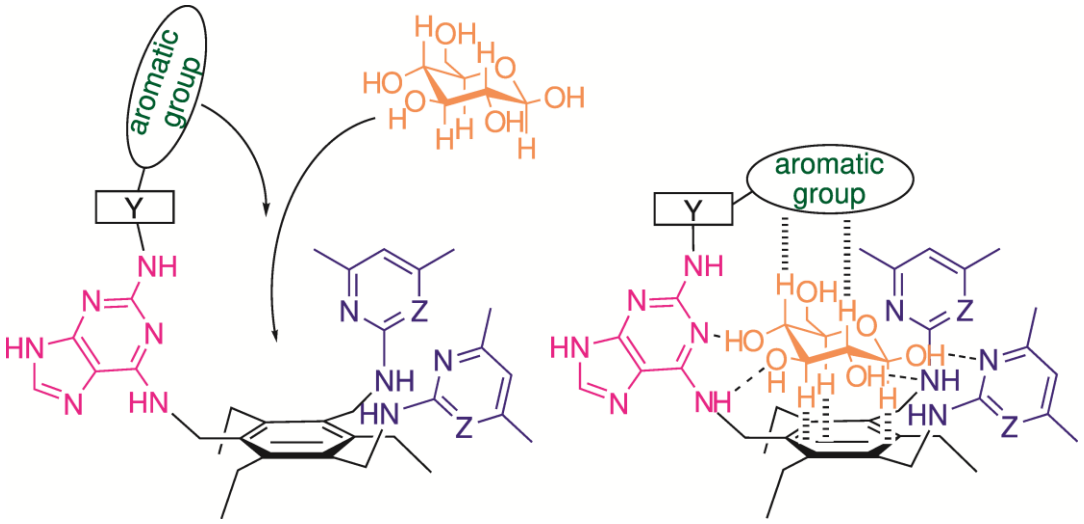

Figure 5. Schematic illustration of the binding mode of carbohydrates by purine-bearing receptors, which are accessible by structural modifications of the basic chemical structure described in this work.

Conclusion

New representatives of the class of 1,3,5-substituted 2,4,6-triethylbenzenes bearing beside 2-aminopyridine/-pyrimidine unit(s) also purine-based recognition group(s) were prepared and their ability to act as carbohydrate receptors was tested on the basis of ^{1}H NMR spectroscopic titrations and extraction experiments. Compounds **1**-**4**, consisting of 9*H*(7*H*)-purin-6-yl or 2-chloro-9*H*(7*H*)-purin-6-yl group(s), were prepared via reaction of 6-chloropurine or 2,6-dichloropurine with the corresponding amino derivative, such as 1-aminomethyl-3,5-bis[(4,6-dimethylpyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene (**10**), 1-aminomethyl-3,5-bis[(4,6-dimethylpyrimidin-2-yl)aminomethyl]-2,4,6-triethylbenzene (**11**) and 1,3-bis(aminomethyl)-5-[(4,6-dimethylpyrimidin-2-yl)aminomethyl]-2,4,6-triethylbenzene (**12**).

Further functionalisation of the 2-chloropurine-bearing compounds **2** and **3** allowed the preparation of derivatives **5**-**9** with a varying substituent pattern on the purine ring. The reactions of **2** and **3** with selected amines, such as cyclohexylamine, benzylamine, 2-picolylamine, 3-picolylamine and tryptamine, were performed using sealed tubes and/or microwave heating. The unfavourable influence of the large C6-substituent has clearly been reflected by the relatively drastic reaction conditions required for the nucleophilic displacement of the chlorine atom in the C2-position of the purine ring and the successful synthesis of compounds **5**-**9**.

Initial studies on carbohydrate-binding by compounds **5**-**8** confirmed our expectations and showed that the properties of this type of purine-bearing compounds can be fine-tuned by the variation of the C2-substituent. The results with compounds **1**, **2** and **5**-**8** confirmed also our

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previous observations that in the case of 1,3,5-substituted 2,4,6-triethylbenzenes the combination of two 2-aminopyridine/pyrimidine units with another recognition group seems to be a particularly suitable architecture for the recognition of β-glucoside, but represents a less effective receptor architecture for β-galactoside. In contrast, the combination of one 2-aminopyrimidine/pyridine unit with two other recognition groups, such as isopropylamino-, imidazole-, indole- or 8-hydroxyquinoline-based recognition group, was previously shown to provide particularly powerful receptors for β-galactoside.

The type of purine-bearing compounds studied here represents a valuable basis for systematic structural modifications and provides through this the possibility of identification of new structure-activity relationships, which are of high importance for the development of artificial receptors with predictable binding properties. It should be noted that the exact prediction of the binding strength and selectivity of artificial carbohydrate receptors has not yet been realised and represents the basis of intensive research activities.

Experimental Section

Analytical TLC was performed on commercial Merck plates coated with silica gel 60 F_{254} and the silica gel used for flash chromatography was Merck Kieselgel 60. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance III 500, Bruker Nanobay 400 or Jeol Resonance ECZ500R NMR spectrometer using Me_4Si as internal standard (strong broadening of some NMR peaks of the purine-bearing compounds in $CDCl_3$ results in missing splitting; see Supporting Information). Mass spectra were recorded on Bruker amaZon SL and JEOLAccuTOF 4G LC-Plus mass spectrometer as well as on Bruker solariX 15T (HRMS measurements).

The titration experiments were carried out by addition of increasing amounts of the tested carbohydrate to a solution of the corresponding receptor. In addition, inverse titrations were performed in which the concentration of the sugar was held constant and that of the receptor was varied (see Supporting Information). The titration data were analyzed by non-linear regression analysis, using the programs WinEQNMR,[23] HypNMR[24] and SupraFit,[25] and the complex stoichiometry was analysed on the basis of the mole ratio method[27] (see Supporting Information).

Preparation of compounds 1-4 using conventional heating and/or microwave irradiation

1-[(Purine-6-yl)-aminomethyl]-3,5-bis-[(4,6-dimethyl-pyridin-2-yl)-aminomethyl]-2,4,6-triethylbenzene (1). ***Procedure A (conventional heating).*** A mixture of 6-chloropurine (0.03 g, 0.196 mmol), 1-aminomethyl-3,5-bis-[(4,6-dimethylpyridin-2-yl)aminomethyl]-2,4,6-triethyl-benzene (**9**) (0.10 g, 0.22 mmol) and *N*,*N*-diisopropylethylamine (DIPEA) (0.06 mL, 0.37 mmol) in *n*-butanol (15 ml) was stirred for 16 h at 110 °C. Afterwards, the solvent was removed by rotary evaporation, the residue washed with water and the crude product was purified via column chromatography [$CHCl_3$/CH_3OH incl. 1% 7 M NH_3 in CH_3OH, 15:1]. Yield 45 %. M.p. 99 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.15 (m, 6 H), 1.24 (t, *J* = 6.8 Hz, 3 H), 2.27 (s, 6 H), 2.41 (s, 6 H), 2.58 (m, 4 H), 2.77 (m, 2 H), 4.28 (br s, 2 H), 4.34 (s, 4 H), 4.74 (s, 2 H), 5.22 (br s, 1 H), 6.26 (s, 2 H), 6.36 (s, 2 H), 8.30 (s, 1 H), 8.50 (s, 1 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 16.5, 16.8, 18.1, 2.4, 22.9, 23.1, 39.2, 40.8, 104.1, 113.8, 130.5, 131.9, 132.3, 143.9, 144.2, 145.5, 149.5, 151.3, 152.8, 152.9, 154.5 ppm. HRMS (ESI): calcd for $C_{34}H_{44}N_9$: 578.37142 $[M+H]^+$ and for $C_{34}H_{45}N_9$: 289.68935 $[M+2H]^{2+}$; found: 578.37147 $[M+H]^+$, 289.68937 $[M+2H]^{2+}$. R_f = 0.25 [$CHCl_3$/CH_3OH (15:1, v/v) incl. 1% 7 M NH_3 in CH_3OH].

1-[(2-Chloro-9*H*-purine-6-yl)-aminomethyl]-3,5-bis-[(4,6-dimethyl-pyridin-2-yl)-aminomethyl]-2,4,6-triethylbenzene (2). ***Procedure A (conventional heating).*** A mixture of 2,6-dichloropurine (0.28 g, 1.5 mmol), 1-(aminomethyl)-3,5-bis-[(4,6-dimethylpyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene (**9**) (0.60 g, 1.31 mmol) and DIPEA (0.34 mL, 2.0 mmol) in *n*-butanol (20 ml) was stirred for 24 h at 80 °C. Then, the solvent was removed by rotary evaporation, the residue washed with water and the crude product was purified via column chromatography [$CHCl_3$/IPA incl. 2% 7 N NH_3 in CH_3OH]. Yield 78 % (0.63 g, 1.03 mmol).

Procedure B (microwave conditions). 2,6-Dichloropurine (0.25 g, 1.31 mmol) and compound **9** (0.60 g, 1.31 mmol) dissolved in *n*-butanol (20 ml) and DIPEA (0.24 mL, 1.41 mmol) were placed in a microwave vessel. After purging with argon and closing of the microwave vessel, the microwave irradiation (70 W) was applied for 1 h at 80 °C. Afterwards, the solvent was removed by rotary evaporation, the residue washed with water and the crude product was purified via column chromatography [$CHCl_3$/IPA incl. 2% 7 N NH_3 in CH_3OH]. Yield 81 % (0.65 g, 1.06 mmol). M.p. 131 °C. ^{1}H-NMR (500 MHz, $CDCl_3$/CD_3OD 5:1): δ = 1.27 (t, *J* = 7.4 Hz, 9 H), 2.28 (s, 6 H), 2.36 (s, 6 H), 2.79 (q, *J* = 7.6 Hz, 2 H), 2.80 (q, *J* = 7.5 Hz, 4 H), 4.39 (s, 4 H), 4.80 (s, 2 H), 6.25 (s, 2 H), 6.39 (s, 2 H), 7.88 (s, 1 H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 16.4, 16.9, 21.2, 22.8, 23.0, 24.0, 39,2, 40.7, 103.8, 114.0, 118.0, 131.2, 132.9, 138.2, 138.6, 143.8, 143.9, 149.2, 150.8, 154.3, 154.5, 156.4, 158.3 ppm. HRMS (ESI): calcd for $C_{34}H_{43}ClN_9$:

612.332447 $[M+H]^+$; found: 612.332451. R_f = 0.10 [$CHCl_3$/CH_3OH incl. 1% NH_3 (7N) in CH_3OH, 10:1 v/v].

1-[(2-Chloro-9*H*-purine-6-yl)-aminomethyl]-3,5-bis-[(4,6-dimethyl-pyrimidin-2-yl)-amino-methyl]-2,4,6-triethylbenzene (3). ***Procedure B (microwave conditions).*** 2,6-Dichloropurine (0.15 g, 0.81 mmol) and 1-(aminomethyl)-3,5-bis-[(4,6-dimethylpyrimidin-2-yl)aminomethyl]-2,4,6-triethylbenzene (**10**) (0.34 g, 0.73 mmol) dissolved in *n*-butanol (10 ml) and DIPEA (0.19 mL, 1.10 mmol) were placed in a microwave vessel. After purging with argon and closing of the vessel, the microwave irradiation (75 W) was applied for 75 min at 80 °C. Afterwards, the solvent was removed by rotary evaporation, the residue washed with water and the crude product was purified via column chromatography [ethylacetate/ethanol incl. 2% 7 N NH_3 in CH_3OH, 10:1]. Yield 75 % (0.34 g, 0.55 mmol). M.p. 158 °C. ^{1}H-NMR (500 MHz, $CDCl_3$/CD_3OD 5:1): δ = 1.26 (t, *J* = 7.5 Hz, 9 H), 2.33 (s, 12 H), 2.81 (q, *J* = 7.3 Hz, 6 H), 4.61 (s, 4 H), 4.80 (s, 2 H), 6.40 (s, 2 H), 7.85 (s, 1 H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 16.5, 16.6, 23.0, 23.0, 23.9, 39.5, 39.8, 109.8, 118.2, 131.2, 133.1, 138.5, 143.9, 144.3, 150.5, 154.2, 154.6, 161.8, 167.6 ppm. HRMS (ESI): calcd for $C_{32}H_{41}ClN_{11}$: 614.322945 $[M+H]^+$; found: 614.322947. R_f = 0.25 [ethylacetate/ethanol incl. 2% 7 N NH_3 in CH_3OH, 10:1].

1,3-bis-[(2-Chloro-9*H*-purine-6-yl)-aminomethyl]-5-[(4,6-dimethyl-pyridin-2-yl)-amino-methyl]-2,4,6-triethylbenzene (**4**). ***Procedure A (conventional heating).*** A mixture of 2,6-dichloropurine (0.05 g, 0.28 mmol), 1,3-bis-(aminomethyl)-5-[(4,6-dimethylpyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene (**11**) (0.05 g, 0.14 mmol) and DIPEA (0.08 mL, 0.43 mmol) in *n*-butanol (10 mL) was stirred for 24 h at 110 °C. Afterwards, the solvent was removed by rotary evaporation, the residue washed with water and the crude product was purified via column chromatography [$CHCl_3$/CH_3OH incl. 1% 7 M NH_3 in CH_3OH, 10:1]. Yield 25 %. M.p. > 200 °C. ^{1}H-NMR (400 MHz, $CDCl_3$/CD_3OD 7:1): δ = 1.26 (t, *J* = 7.4 Hz, 9 H), 2.26 (s 2 H), 2.34 (s, 3 H), 2.81 (m, 6 H), 4.38 (s, 2 H), 4.81 (s, 4 H), 6.18 (s, 1 H), 6.36 (s, 1 H), 7.82 (br s, 2 H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$/CD_3OD 7:1): δ = 16.48, 16.66, 21.23, 23.21, 23.33, 39.43, 40.85, 104.38, 110.44, 114.29, 131.82, 133.20, 144.34, 144.54, 147.27, 149.23, 154.63, 156.32, 158.34, 161.80 ppm. HRMS (ESI): calcd for $C_{32}H_{36}Cl_2N_{12}$: 659.26412 $[M+H]^+$; found: 659.26397. R_f = 0.10 [$CHCl_3$/CH_3OH incl. 1% NH_3 7N in CH_3OH, 10:1].

Preparation of compounds 5-8 using sealed tubes and/or microwave irradiation

General procedures. ***Procedure C (sealed tube).*** 1-[(2-Chloro-9*H*-purine-6-yl)-aminomethyl]-3,5-bis-[(4,6-dimethylpyridin-2-yl)-aminomethyl]-2,4,6-triethylbenzene (**2**) and the

corresponding amine in *n*-butanol (5 mL) were placed in a sealed tube. After purging with argon and closing of the tube, the reaction mixture was stirred at 130 °C for 7 d. Then, the solvent was removed by rotary evaporation, the residue washed with water and the crude product was purified via column chromatography or by means of preparative HPLC (for details, see below).

Procedure D (microwave conditions). 1-[(2-chloro-9*H*-purine-6-yl)-aminomethyl]-3,5-bis-[(4,6-dimethyl-pyridin-2-yl)-aminomethyl]-2,4,6-triethylbenzene (**2**) or 1-[(2-chloro-9*H*-purine-6-yl)-aminomethyl]-3,5-bis-[(4,6-dimethyl-pyrimidin-2-yl)-amino-methyl]-2,4,6-triethylbenzene (**3**) and the corresponding amine were dissolved in *n*-butanol (3 mL) in a microwave vessel. After purging with argon and closing of the vessel, the microwave irradiation was applied for several hours at 160 - 170 °C (for details, see below). Afterwards, the solvent was removed by rotary evaporation, the residue washed with water and the crude product was purified via column chromatography (for details, see below).

1-{[2-(Cyclohexylamino)-9*H*-purin-6-yl]aminomethyl}-3,5-bis[4,6-dimethylpyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene (5). ***Procedure C.*** Compound **5** was prepared from **2** (0.091 g, 0.14 mmol) and cyclohexylamine (0.17 mL, 1.5 mmol). Purification was performed by means of preparative HPLC (Nucleodur 100-5 NH_2 Macherey-Nagel, Isocratic $CHCl_3$/ethanol 93:7, t_R = 8.2 min). Yield 44 % (0.045 g, 0.065 mmol). M.p. 132 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.01 - 1.32 (m, 12 H), 1.60 (m, 1 H), 1.71 (m, 2 H), 1.83 (m, 2 H), 2.23 (s, 6 H), 2.36 (s, 6 H), 2.55 (q, *J* = 7.1 Hz, 4 H), 2.76 (q, *J* = 7.2 Hz, 2 H), 4.33 (s, 4 H), 4.53 (br s, 2 H), 4.70 (s, 2 H), 4.79 (br s, 1 H), 6.17 (s, 2 H), 6.35 (s, 2 H), 6.74 (s, 1 H), 7.65 (s, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 16.5, 16.8, 21.2, 22.8, 23.0, 24.1, 25.1, 25.7, 36.7, 39.3, 40.6, 50.5, 103.9, 114.0, 117.9, 131.3, 133.1, 138.9, 143.8, 144.0, 149.0, 151.2, 154.3, 154.5, 156.5, 158.3. HRMS (ESI): calcd for $C_{40}H_{55}N_{10}$: 675.460568 $[M+H]^+$; found: 675.460567. R_f = 0.83 [$CHCl_3$/IPA (incl. 1% NH_3 (7N) in CH_3OH), 3:1].

1-[(2-Benzylamino-9H-purin-6-yl)aminomethyl]-3,5-bis-[(4,6-dimethylpyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene (6). ***Procedure C.*** Compound **6** was prepared from **2** (0.090 g, 0.146 mmol) and benzylamine (0.155 g, 1.46 mmol). Purification was performed by means of preparative HPLC (Nucleodur 100-5 NH_2 Macherey-Nagel, Isocratic $CHCl_3$/IPA 91:9, t_R = 10.5 min). Yield 45 % (0.045 g, 0.066 mmol).

Procedure D. Compound **6** was prepared from **2** (0.107 g, 0.175 mmol) and benzylamine (0.37 g, 3.49 mmol). Microwave irradiation (180 W) was applied for 8 h at 170 °C. Purification was performed by column chromatography [$CHCl_3$/IPA incl. 2 % NH_3 7N in CH_3OH, 7:1]. Yield 79 % (0.094 g, 0.138 mmol). R_f = 0.44 [$CHCl_3$/IPA incl. 2 % 7 N NH_3 in CH_3OH, 7:1]. M.p. 117

°C. ^{1}H-NMR (500 MHz, $CDCl_3/CD_3OD$ 5:1): δ 1.22 (t, *J* = 7.6 Hz, 6 H), 1.25 (t, *J* = 7.3 Hz, 3 H), 2.25 (s, 6 H), 2.34 (s, 6 H), 2.78 (m, 6 H), 4.38 (s, 4 H), 4.68 (s, 2 H), 4.73 (br s, 2 H), 6.19 (s, 2 H), 6.36 (s, 2 H), 7.24 (t, *J* = 7.3 Hz, 1 H), 7.32 (t, *J* = 7.6 Hz, 2 H), 7.40 (d, *J* = 7.4 Hz, 2 H), 7.54 (s, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 16.5, 16.8, 21.2, 22.7, 22.9, 24.1, 38.4, 40.6, 45.8, 103.59, 113.7, 126.9, 128.5, 132.2, 132.8, 134.8, 143.6, 148.9, 151.4, 154.3, 156.6, 158.5, 159.8. HRMS (ESI): calcd for $C_{41}H_{51}N_{10}$: 683.429268 $[M+H]^+$; found: 683.429271.

1-{{2-[(Pyridin-2-yl)methylamino]-9*H*-purin-6-yl}aminomethyl}-3,5-bis-[(4,6-dimethyl-pyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene (7). ***Procedure C.*** Compound **7** was prepared from **2** (0.08 g, 0.13 mmol) and 2-picolylamine (0.16 mL, 1.57 mmol). Purification was performed by column chromatography [$CHCl_3$/IPA incl. 2 % NH_3 7 N in CH_3OH, 5:4]. Yield 34 % (0.03 g, 0.044 mmol). R_f = 0.57 [$CHCl_3$/IPA incl. 2 % 7 N NH_3 in MeOH, 5:4]. M.p. 155 °C. ^{1}H-NMR (500 MHz, $CDCl_3/CD_3OD$ 5:1): δ = 1.20 (t, *J* = 7.4 Hz, 6 H), 1.25 (t, *J* = 7.5 Hz, 3 H), 2.26 (s, 6 H), 2.35 (s, 6 H), 2.75 (q, *J* = 7.3 Hz, 4 H), 2.77 (q, J = 7.5 Hz, 2 H), 4.36 (s, 4 H), 4.66 (s, 2 H), 4.80 (s, 2 H), 6.20 (s, 2 H), 6.36 (s, 2 H), 7.22 (m, 1 H), 7.38 (m, 1 H), 7.46 (d, *J* = 7.9 Hz, 1 H), 7.57 (s, 1 H), 7.69 (td, *J* = 7.7/1.7 Hz, 1 H), 8.49 (m, 1 H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3/CD_3OD$): δ = 16.6, 16.8, 21.3, 23.1, 23.5, 24.9, 38.7, 40.8, 47.1, 104.2, 110.1, 114.1, 121.8, 122.3, 132.4, 132.8, 135.6, 137.3, 144.0, 144.0, 148.7, 149.9, 149.9, 154.1, 156.0, 158.3, 159.61, 159.7 ppm. HRMS (ESI): calcd for $C_{41}H_{51}N_{10}$: 684.424517 $[M+H]^+$; found 684.424518.

1-{{2-[(Pyridin-3-yl)methylamino]-9*H*-purin-6-yl}aminomethyl}-3,5-bis-[(4,6-dimethyl-pyridin-2-yl)aminomethyl]-2,4,6-triethylbenzene (8). ***Procedure C.*** Compound **8** was prepared from **2** (0.080 mg, 0.13 mmol) and 3-picolylamine (0.070 mL, 0.68 mmol). The crude product was purified by column chromatography [$CHCl_3$/IPA incl. 1 % NH_3 7N in CH_3OH, 5:1]. Yield 25 % (0.024 g, 0.036 mmol).

Procedure D. Compound **8** was prepared from **2** (0.08 g, 0.13 mmol) and 3-picolylamine (0.13 mL, 1.28 mmol). Microwave irradiation (200 W) was applied for 4 h at 160 °C. Purification was performed by column chromatography [$CHCl_3$/IPA incl. 2 % NH_3 7N in CH_3OH, 5:1]. Yield 47 % (0.042 g, 0.061 mmol). R_f = 0.47 [$CHCl_3$/IPA incl. 2 % NH_3 7 N in CH_3OH, 5:1]. M.p. 151 °C. ^{1}H-NMR (500 MHz, $CDCl_3/CD_3OD$ 5:1): δ = 1.22 (t, J = 7.5 Hz, 6 H), 1.25 (t, *J* = 7.5 Hz, 3 H), 2.25 (s, 6 H), 2.34 (s, 6 H), 2.77 (q, *J* = 7.0 Hz, 6 H), 4.01 (s, 1 H), 4.37 (s, 4 H), 4.69 (brs, 4 H), 4.72 (s, 2 H), 6.19 (s, 2 H), 6.36 (s, 2 H), 7.33 (dd, *J* = 7.7 Hz / 5.0 Hz, 1 H), 7.55 (s, 1 H), 7.85 (d, *J* = 7.7 Hz, 1 H), 8.40 (dd, *J* = 4.8 Hz / 1.4 Hz, 1 H), 8.60 (d, *J* = 1.4 Hz, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 16.4, 16.8, 21.2, 22.6, 22.8, 24.0, 38.3, 40.7, 43.3, 103.4, 113.6,

113.7, 123.2, 132.1, 132.5, 134.9, 135.3, 135.7, 143.3, 143.5, 148.2, 149.1, 149.3, 151.6, 154.2, 156.6, 158.6, 159.7. HRMS (ESI): calcd for $C_{41}H_{51}N_{10}$: 684.424517 $[M+H]^+$; found: 684.424519.

1-{{2-[(Indol-3-yl)ethylamino]-9*H*-purin-6-yl}aminomethyl}-3,5-bis-[(4,6-dimethyl-pyrimidin-2-yl)aminomethyl]-2,4,6-triethylbenzene (9). ***Procedure D.*** Compound **9** was prepared from **3** (0.10 g, 0.16 mmol) and tryptamine (0.26 g, 1.36 mmol). Microwave irradiation (160 W) was applied for 6 h at 170 °C. Purification was performed by column chromatography [$CHCl_3$/IPA incl. 2 % NH_3 7N in CH_3OH, 2:1]. Yield 42 % (0.05 g, 0.07 mmol). Mp 165 °C. ^{1}H-NMR (500 MHz, $CDCl_3/CD_3OD$ 5:1): δ = 1.24 (t, *J* = 7.4 Hz, 6 H), 1.26 (t, *J* = 8.4 Hz, 3 H), 2.32 (s, 12 H), 2.80 (q, *J* = 7.4 Hz, 2 H), 2.82 (q, *J* = 7.3 Hz, 4 H), 3.14 (t, *J* = 6.8 Hz, 2 H), 3.79 (t, *J* = 6.4 Hz, 2 H), 3.95 (br s, 1 H), 4.60 (s, 4 H), 4.78 (s, 2 H), 6.39 (s, 2 H), 6.94 (s, 1 H), 7.06 (m, 1 H), 7.12 (s, 1 H), 7.15 (m, 1 H), 7.39 (d, *J* = 8.1 Hz, 1 H), 7.53 (br s, 1 H), 7.66 (d, *J* = 7.8 Hz, 1 H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ 16.5, 16.6, 22.8, 23.0, 23.9, 25.4, 38.4, 39.9, 42.3, 43.3, 109.7, 111.2, 113.6, 115.1, 118.82, 119.2, 121.9, 122.0, 127.5, 132.3, 132.7, 134.4, 136.4, 143.7, 143.7, 151.9, 154.9, 159.9, 162.0, 167.6 ppm. HRMS (ESI): calcd for $C_{41}H_{51}N_{10}$: 738.446315 $[M+H]^+$; found: 738.446317.

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Supporting Information Available. Description of the ^{1}H NMR titrations (Tables S1 and S2). Representative mole ratio plots (Figures S1a-d). Copies of the ^{1}H and ^{13}C NMR spectra of compounds **1-9** in $CDCl_3/CD_3OD$ and $CDCl_3$ (Figures S2 – S25).

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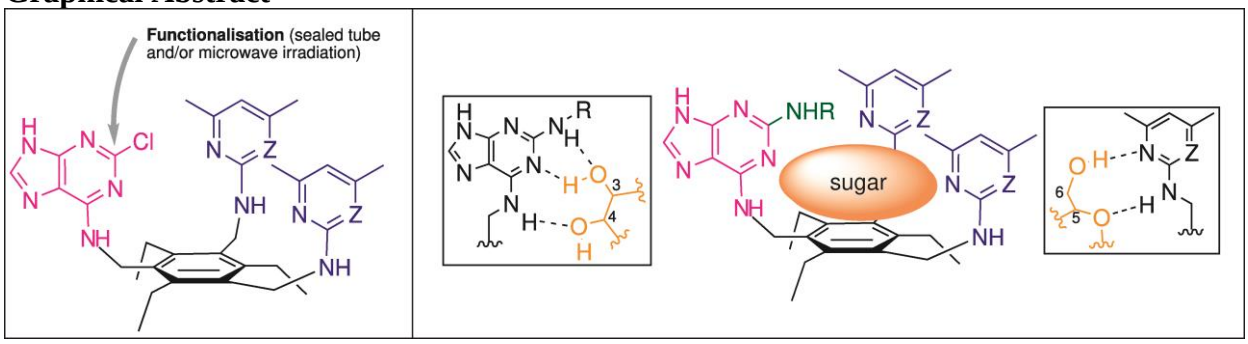
Graphical Abstract



Key Topics: Artificial Carbohydrate Receptors, Molecular Recognition

Short Text: Representatives of 1,3,5-substituted 2,4,6-triethylbenzenes consisting of 2-chloro-purin-6-yl group(s) have the ability to act both as carbohydrate-binding agents and as a basis for the preparation of derivatives with a varying substituent pattern on the purine ring.