Tetrahedron 70 (2014) 8758–8767

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of compounds based on a dimesitylmethane scaffold and representative binding studies showing di- vs monosaccharide preference

Niklas Koch, Jan-Ruven Rosien, Monika Mazik *

Institut für Organische Chemie, Technische Universität Bergakademie Freiberg, Leipziger Strasse 29, 09599 Freiberg, Germany

ARTICLE INFO

Article history:
Received 20 May 2014
Received in revised form 31 August 2014
Accepted 5 September 2014
Available online 16 September 2014

Keywords:
Dimesitylmethane
Molecular recognition
Receptors
Supramolecular chemistry
Saccharides

ABSTRACT

Dimesitylmethane-based compounds **9**–**17**, incorporating four groups capable of serving as hydrogen bonding sites, such as pyrazole, pyrimidine, imidazole, indole and aminoalkyl groups, were prepared and their ability to complex selected carbohydrates tested. The tetrasubstituted dimesitylmethane scaffold provides a cavity of a correct shape and size for disaccharide encapsulation and its aromatic units are able to participate in CH-π interactions with the sugar substrate. First binding studies confirmed the expected di- vs monosaccharide binding preference of this type of compounds and their tendency to form strong complexes with maltoside.

1. Introduction

The design of artificial carbohydrate receptors remains an important area of current research.[1] The molecular structure of such receptors is often inspired by the type of the recognition groups, which are used by the carbohydrate binding proteins for the formation of noncovalent interactions with the sugar substrate.[2] Most of the described artificial receptor molecules have been designed and used for the recognition of monosaccharides,[1] whereas the binding studies with oligosaccharides have received less attention.[3,4]

Our previous studies showed that compounds **1**–**8**, which are based on a dimesitylmethane, biphenyl, trimethyl- and triethylbenzene scaffold (see Fig. 1), are able to recognize both mono- and disaccharides, with a strong preference for the disaccharides.[4]

Among the receptors **1**–**8**, the dimesitylmethane-based compounds **1** and **2**,[4d] incorporating four 2-aminopyridine units[5] capable of serving as hydrogen bonding sites, were tested against α- and β-maltoside and shown to form very strong complexes with these disaccharides. The tetrasubstituted dimesitylmethane scaffold provides a cavity of a correct shape and size for disaccharide encapsulation and its aromatic units are able to participate in CH-π interactions[6,7] with the sugar substrate. We were interested to see if further representatives of this class of compounds display similar binding properties.

In this paper we describe the synthesis of nine new dimesitylmethane-based derivatives, containing such heterocyclic groups as pyrazole (compounds **9** and **10**), pyrimidine (compound **11**), imidazole (compounds **12** and **13** with 2- and 4(5)-substituted imidazole groups,[8] respectively) and indole (compounds **14** and **15** with 2- and 3-substituted indole groups, respectively), which are attached to the dimesitylmethane-spacer via $-CONHCH_2-$, $-NHCH_2-$ and $-CH_2NHCH_2-$ linker units. The heterocyclic recognition groups have been previously used by our group for the construction of effective carbohydrate receptors based on a substituted benzene scaffold.[9] In addition, the synthesis of compounds **16** and **17**, incorporating isopropylamino and isobutylamino groups, which were previously identified as valuable recognition groups for carbohydrates,[10] are also described in this work (Fig. 2).

2. Results and discussion

2.1. Synthesis of compounds 9–17

The synthetic routes for **9**–**17** are shown in Scheme 1. Four bromomethyl groups were appended to dimesithylmethane (**18**) over two steps leading to 3,3′,5,5′-tetrabromomethyl-2,2′,4,4′,6,6′-

* Corresponding author. E-mail addresses: monika.mazik@chemie.tu-freiberg.de, m.mazik@tu-bs.de (M. Mazik).

http://dx.doi.org/10.1016/j.tet.2014.09.016
0040-4020/

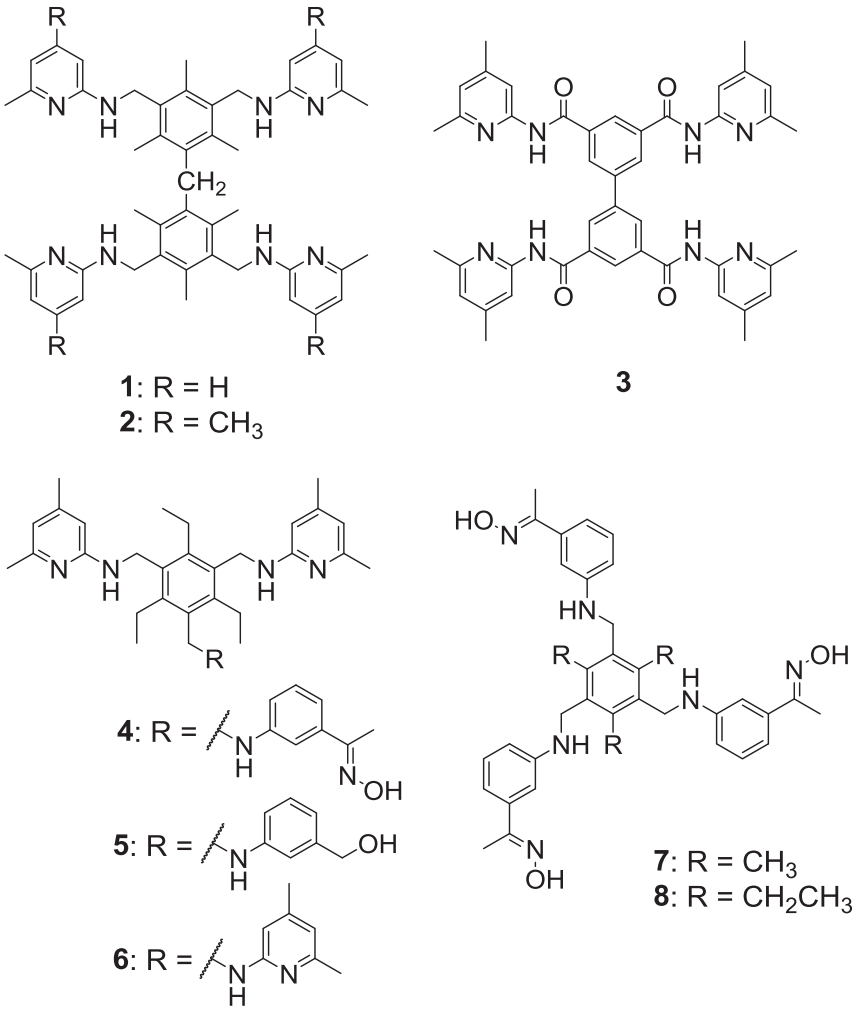

Fig. 1. Structures of the previously studied receptors **1**–**8**.[4]

hexamethyldiphenylmethane (**20**).[11,4d] The reaction of **20** with 3-amino-1-methylpyrazole (**23**), 2-amino-4,6-dimethylpyrimidine (**24**), isopropylamine (**25**) or isobutylamine (**26**) provided the products **10**, **11**, **16** and **17**, respectively. The reaction of **20** with potassium phthalimide gave compound **21**, which was converted into the dimesitylmethane derivative **22**, containing four aminomethyl groups, by treatment with hydrazine hydrate. Compound **22** was the base for the synthesis of dimesitylmethane-based derivatives **9** and **12**–**15**. The condensation of **22** with 2-imidazole-carbaldehyde (**28**), 2-indole-carbaldehyde (**29**), 4(5)-imidazole-carbaldehyde (**30**) or 3-indole-carbaldehyde (**31**) provided the corresponding imines, which were further reduced with sodium borohydride to give the products **12**–**15** (two imines, **12a** and **14**a, could be isolated from the reaction mixture, see Experimental Section). Compound **9**, bearing pyrazole-based recognition groups, was prepared by a reaction of **22** with 5-methyl-1*H*-pyr azole-3-carboxylic acid (**27**).

2.2. Representative binding studies

To explore the expected di- vs monosaccharide binding preference[12] of the new compounds and to compare their binding properties with those of the previously published receptors, the dodecyl β-D-maltoside (**32**) and octyl β-D-glucopyranoside (**33**) were selected as substrates for first binding studies. The interactions between the binding partners were investigated by ^{1}H NMR spectroscopy in organic media ($CDCl_3$, DMSO-d_6/$CDCl_3$ or CD_3OD/$CDCl_3$ mixture). The ^{1}H NMR titration data were analysed using the WinEQNMR2 program,[13] the stoichiometry of the receptor-sugar complexes was determined by mole ratio plots[14] and by the curve-fitting analysis of the titration data.

Dodecyl β-D-maltoside (**32**) is almost unsoluble in $CDCl_3$, but could be solubilized in this solvent in the presence of the soluble compounds **10**, **11** and **14**, bearing pyrazole, pyrimidine and 2-substituted indole groups as heterocyclic recognition units, respectively (compounds **12**, **13** and **15** bearing imidazole or 3-substituted indole groups are not soluble in $CDCl_3$; the binding properties of **12** were analysed in DMSO-d_6/$CDCl_3$ or CD_3OD/$CDCl_3$ mixture, see Table 1). Such solubility behaviour of the disaccharide **32** indicates favourable interactions between the binding partners in $CDCl_3$ and was also observed in the presence of the previously described compounds **1**–**8**, which were established as powerful receptors for maltosides.[4] It should be noted that **32** shows the best solubility in $CDCl_3$ in the presence of the aminopyrazole-based compound **10**, indicating particular favourable interactions between **10** and **32**. In contrast to the aminopyrazole-based compound **10**, compounds **34** and **35**, bearing pyrazol-1-yl groups, show only a very poor dissolution capacity for the tested disaccharide and therefore no titration experiments could be performed. As expected, the presence of unsuitable linked heterocyclic recognition units drastically reduces the capability of dimesitylmethane-based compounds to act as disaccharide receptors (Fig. 3).