Check for updates

EurJOC

European Journal of Organic Chemistry

Chemistry Europe

European Chemical Societies Publishing

Accepted Article

Title: Compounds combining a macrocyclic building block and flexible side-arms as carbohydrate receptors: syntheses and structure-binding activity relationship studies

Authors: Felix Amrhein and Monika Mazik

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202100758

Link to VoR: https://doi.org/10.1002/ejoc.202100758

WILEY-VCH

10.1002/ejoc.202100758

Compounds combining a macrocyclic building block and flexible side-arms as carbohydrate receptors: syntheses and structure-binding activity relationship studies

Felix Amrhein and Monika Mazik*[a]

Dedicated to the memory of Prof. Dr. Klaus Hafner

Dr. Felix Amrhein, Prof. Dr. Monika Mazik

[a]Institut für Organische Chemie, Technische Universität Bergakademie Freiberg, Leipziger Strasse 29, 09599 Freiberg, Germany; Tel.: 03731392389; Fax: 03731393170

e-mail: monika.mazik@chemie.tu-freiberg.de; https://tu-freiberg.de/fakultaet2/orgch

Abstract: A series of new representatives of compounds combining a macrocyclic building block and flexible side-arms were prepared and their ability to act as carbohydrate receptors evaluated. The target compounds were obtained via multi-step syntheses, which included the preparation of numerous precursors as well as the isolation of a large number of by-products. The structure-binding activity relationship studies comprise in particular the variation of the side-arms in order to demonstrate the importance of the presence of a hydrogen bond donor in these units for the effective complexation of carbohydrates. Based on the findings of our previous studies, the variation of the bridge units is limited to benzene- and pyrrole-based moieties, whereby the use of the last-mentioned bridge type was expected to produce more effective systems. This assumption was confirmed by ^{1}H NMR titrations and isothermal titration calorimetry.

1 Introduction

In the course of our studies on the molecular recognition of carbohydrates by artificial receptors operating through noncovalent interactions, we have developed a whole range of receptor molecules, including both acyclic compounds[1-4] and macrocyclic ones with flexible side-arms.[5-7] First representatives of the macrocyclic systems (compounds **1**-**11**; see Figure 1 and Supporting Information) have been reported by us in 2013[5] and 2015.[6] This was followed by a further

Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/ejoc.202100758

structural optimization including the replacement of the heterocyclic units in the two side-arms by hydroxy groups (compounds **12-14**).[7] Receptors **12-14** impressively demonstrated that even a structurally very simple recognition unit, such as the hydroxymethyl group, enables effective complexation of the carbohydrate substrate. The incorporation of the hydroxy groups into the receptor structure was inspired by the participation of the side chains of serine and threonine in the natural recognition[8] of carbohydrates, as shown in Figure 2. The OH group is available to act both as a hydrogen bond donor and as an acceptor and can thus participate in the formation of cooperative hydrogen bonds. These studies repeatedly showed that mimicking the natural binding motifs represents a valuable strategy for the development of effective carbohydrate receptors.

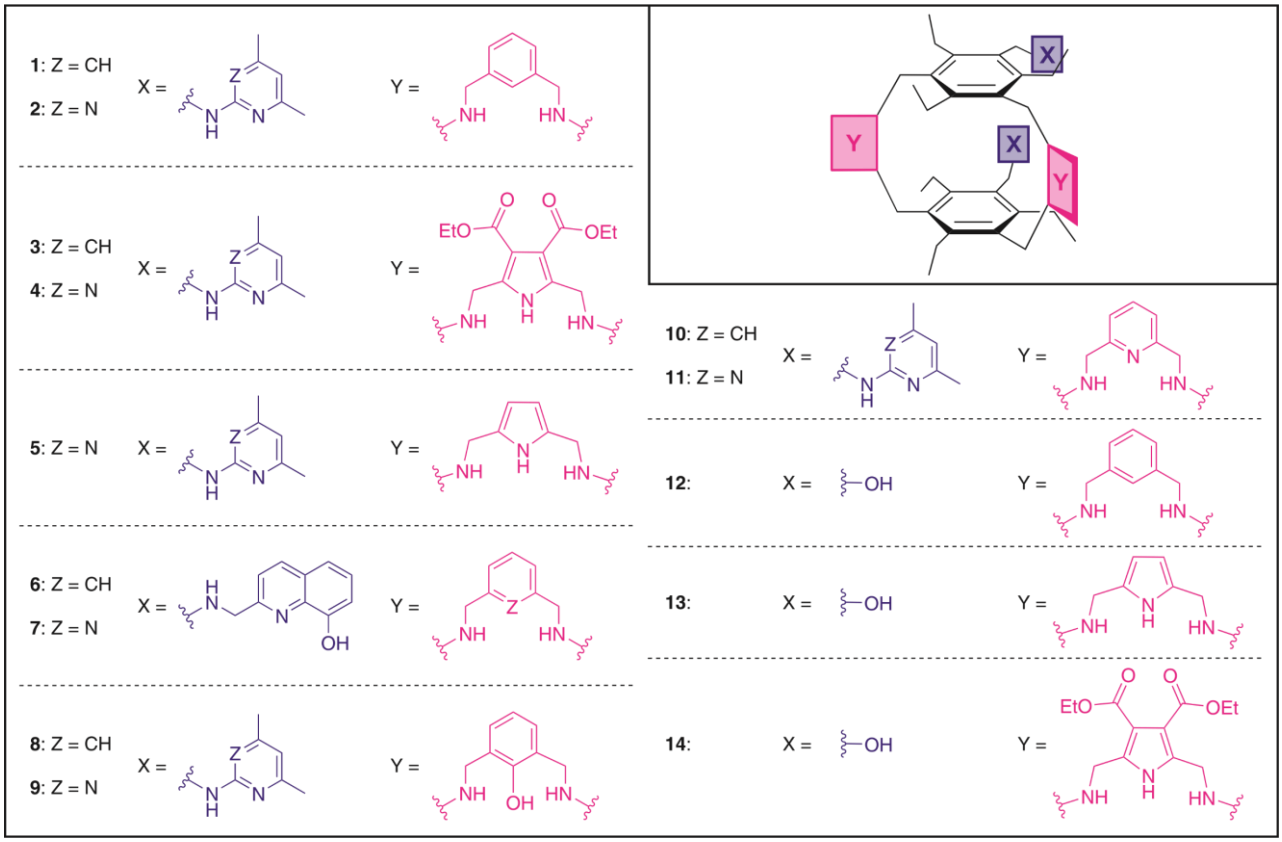


Figure 1. Structures of the macrocyclic compounds **1**−**14** with two flexible side-arms acting as recognition units, reported by us previously. [5-7]

Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/ejoc.202100758

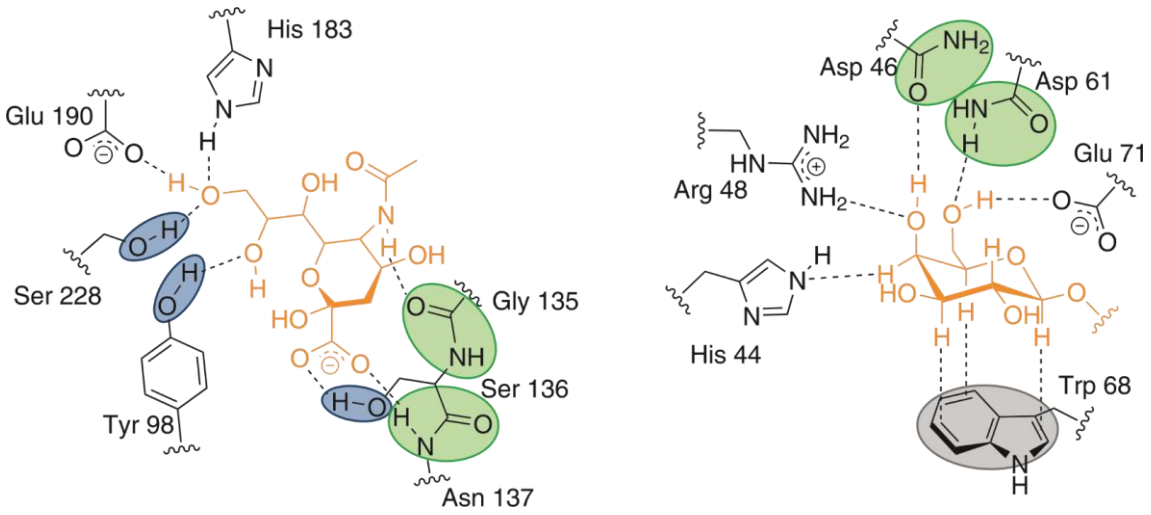


Figure 2. Examples of hydrogen bonds and CH···π interactions in the complex of influenza hemagglutinin with *N*-acetylneuraminic acid (left)[8a] and galectin-1 with *N*-acetyllactosamine (right).[8b]

Furthermore, it should be emphasized that the design of the compounds consisting of a macrocyclic building block and flexible side-arms was inspired by the results of our crystallographic studies, including the analysis of the binding motifs in a 2:1 receptor-sugar complex (see Figure 3a), reported by us some time ago[9] (for recent reports on crystalline complexes formed between acyclic receptors and α-/β-D-glucosides, see ref.[10a,b]).

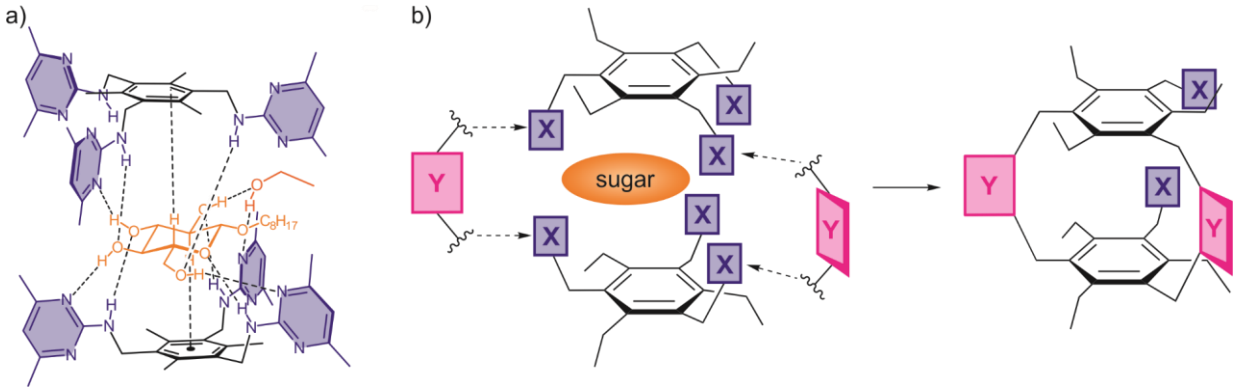


Figure 3. (a) Crystal structure of a 2:1 receptor-carbohydrate complex[9] that served as a source of inspiration for the (b) design of carbohydrate receptors combining both a macrocyclic building block and flexible side-arms (Y = bridge units, CH_2X = side-arms).[5-7]

Due to the combination of a macrocyclic backbone with flexible side-arms, this type of compounds exhibits particularly interesting binding properties toward carbohydrates and is able to form predictable 1:1 receptor-sugar complexes, especially with all-equatorial substituted

This article is protected by copyright. All rights reserved.

Accepted Manuscript

10.1002/ejoc.202100758

sugars, such as β-glucopyranoside.[5-7] The carbohydrate is sandwiched between two benzene rings and participates in the formation of both hydrogen bonding and CH···π interactions with the receptor molecule.

In this work we describe further structural modifications of this type of compounds, particularly involving the variation of the side-arms, as shown in Figure 4 (selection criteria for the corresponding subunits are given below).

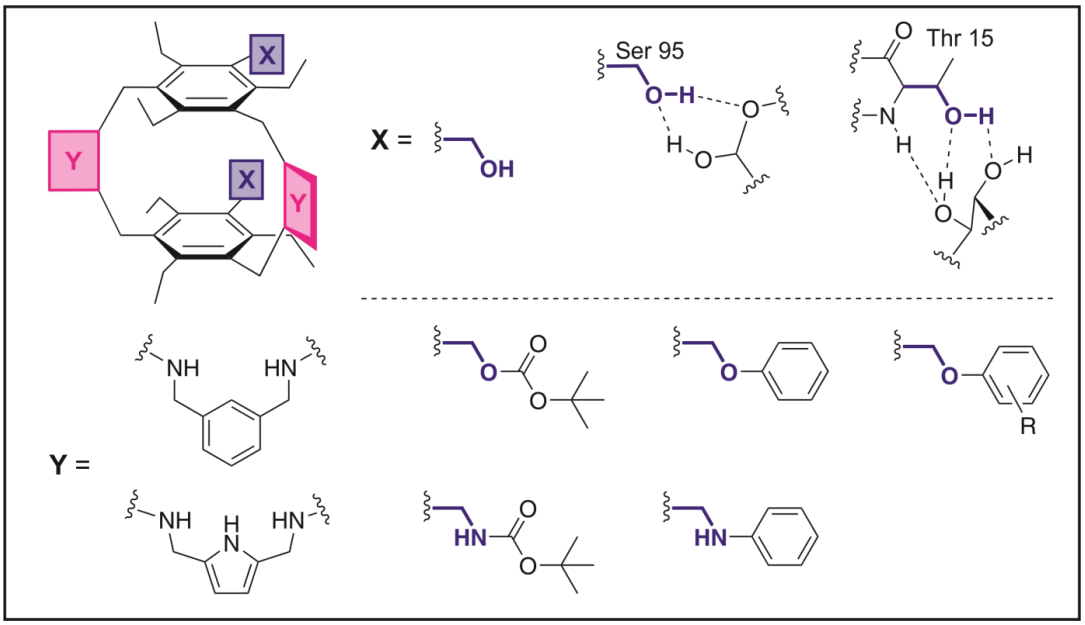


Figure 4. Building blocks [side-arms (X) and bridge units (Y)] used for the construction of the target compounds considered in this work (replacement of the two CH_2OH side-arms by CH_2OR or CH_2NHR units); the OH group's ability[8k,8l] to participate in cooperative hydrogen bonds is also illustrated in this figure.

It should be mentioned that artificial carbohydrate receptors represent valuable model systems to study the basic principles of molecular recognition of carbohydrates[11-13] and are also regarded as a potential basis for the development of new therapeutics.[14]

2 Results and discussion

2.1 Structures of the target compounds (selection criteria)

To demonstrate the importance of the presence of a hydrogen bond donor in the side-arms for the effective complexation of carbohydrates, structural variations were carried out in which the CH_2OH groups (acting as side-arms in compounds **12** and **13**) were replaced by CH_2OR units (Figure 4). The significance of the hydrogen bond donor should further to be visualised by

This article is protected by copyright. All rights reserved.

Accepted Manuscript

10.1002/ejoc.202100758

comparing the complexation properties of the compounds bearing CH_2OR groups with those of the analogues compounds having CH_2NHR units as side-arms, which were expected to be more powerful carbohydrate receptors. In this context, the residue R should not contain any donor site for the formation of classical hydrogen bonds and should be relatively easy to incorporate into the receptor structure. In addition, a sterically demanding residue R should confirm the thesis that, despite the steric hindrance emanating from this residue, the neighbouring hydrogen bond donor site (e.g. NH in CH_2NHR) can exert a favourable influence on the complexation properties of the target compounds. This was done by applying the *tert*-butyloxycarbonyl moiety (Boc group) as a bulky group, which is synthetically easy to incorporate. Furthermore, unsubstituted and methoxy-substituted (*o*-, *m*- and *p*-substituted) phenyl groups were taken into account as residue R for incorporation into the CH_2NHR and CH_2OR side-arms.

Based on the findings of our previous studies, the variation of the bridge units only includes the use of the benzene- and pyrrole-based moieties, whereby the use of the last-mentioned bridge type was expected to produce more effective systems. The combination of the building blocks, which are given in Figure 4, provided the structures of the target compounds **15-24** shown in Figures 5 and 6.

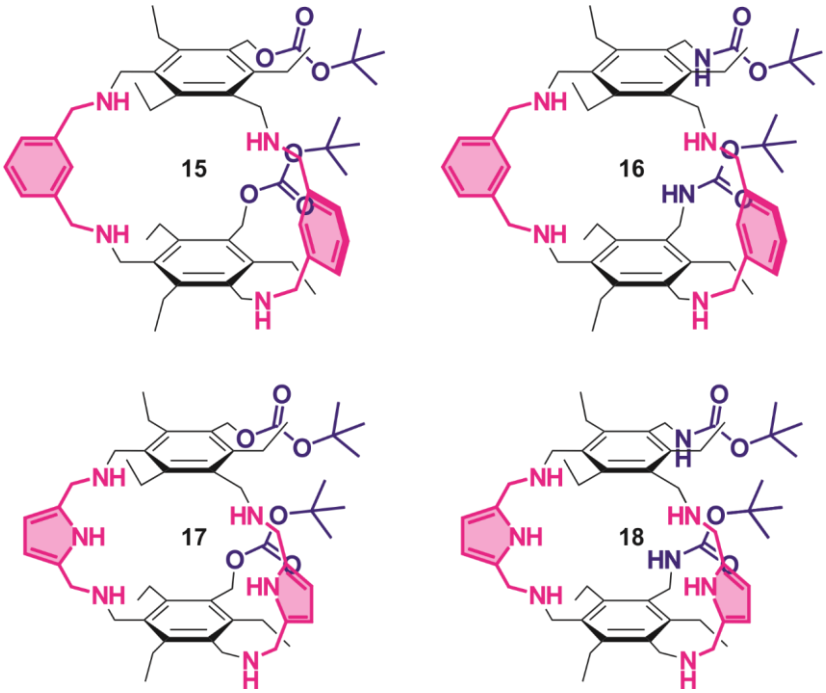


Figure 5. Structures of the macrocyclic compounds **15-18** with CH_2OBoc and CH_2NHBoc units as side-arms.

This article is protected by copyright. All rights reserved.

Accepted Manuscript

10.1002/ejoc.202100758

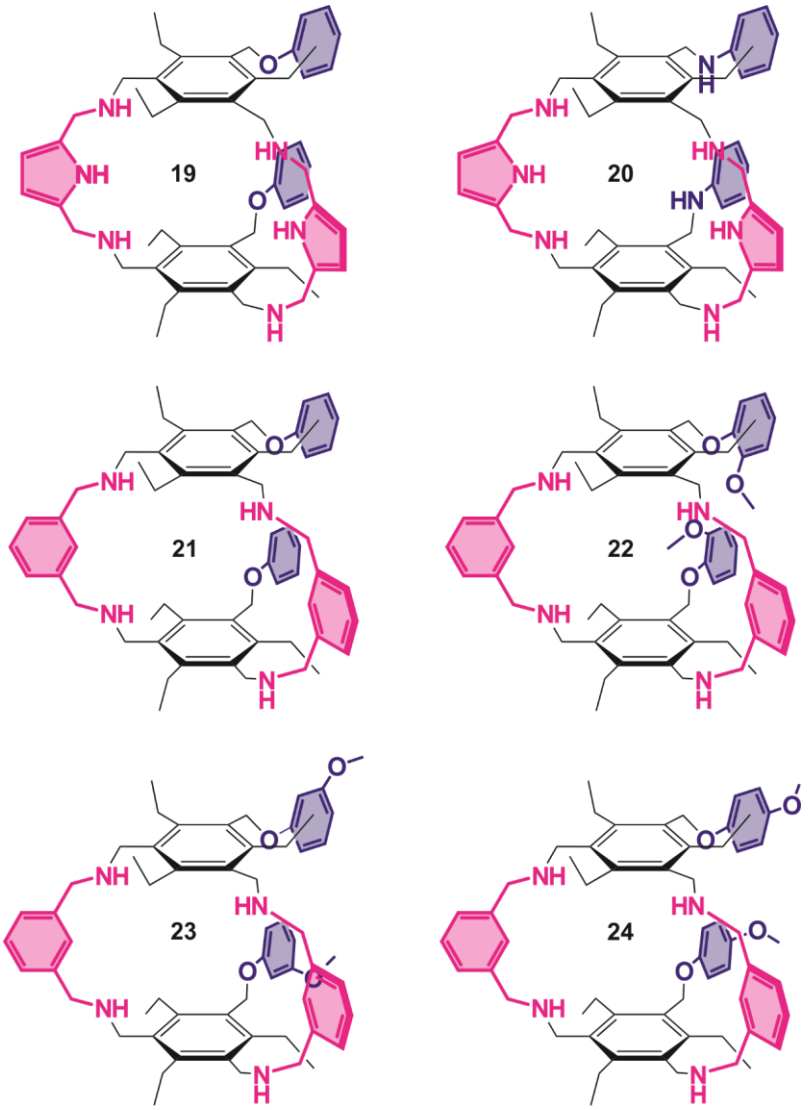


Figure 6. Structures of the macrocyclic compounds **19–24** with two flexible side-arms bearing unsubstituted and methoxy-substituted phenyl groups.

2.2 Syntheses of the target compounds 15-18.

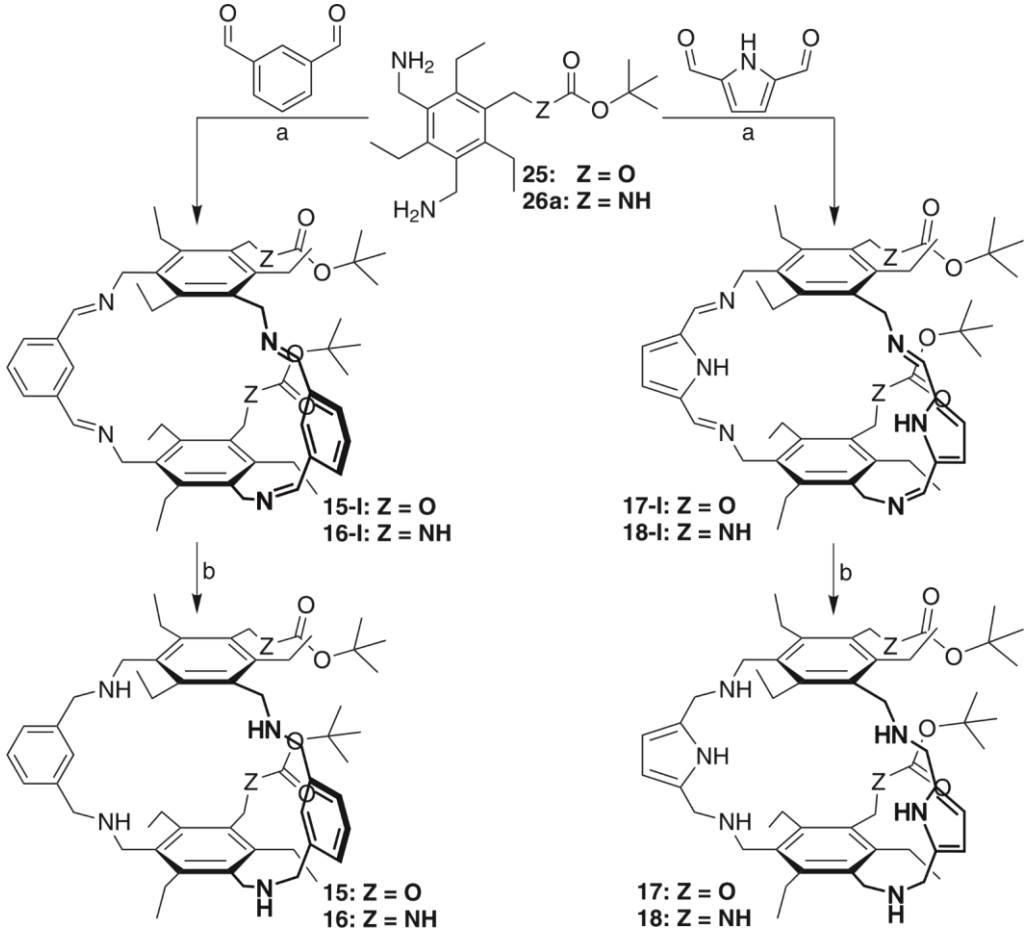
The syntheses of the macrocyclic compounds **15-18** were performed on the basis of the reaction of the bis(aminomethyl)benzene derivatives **25** and **26a**, bearing a *tert*-butoxycarbonyloxymethyl and *tert*-butoxycarbonylaminomethyl moiety as a side-arm, respectively, with the corresponding bisaldehyde, such as isophthalaldehyde and 1*H*-pyrrole-2,5-dicarboxaldehyde (see Scheme 1). The macrocyclization reactions were carried out in dry ethanol in the presence of a catalytic amount of acetic acid at 45-50 °C and provided the compounds **15-I** to **18-I**, having four imine functionalities, with 70 to 93 % yield (see Scheme 1). The best yield was achieved in the case of the benzene-bridged derivative **15-I** (see Scheme 1). Crystallization of **18-I** from methanol provided crystals suitable for X-ray analysis.[15] The

This article is protected by copyright. All rights reserved.

Accepted Manuscript

10.1002/ejoc.202100758

compound was found to crystallize as a methanol solvate of the space group $P2_1/c$ with the asymmetric part of the unit cell containing one half of the macrocyle and one solvent molecule (1:2 host-guest complex).



Scheme 1. Syntheses of compounds **15–18**. Reaction conditions: (a) dry EtOH, catalytic amount of acetic acid; 93 % of **15-I**, 80 % of **16-I**, 70 % of **17-I**, 81 % of **18-I**; (b) 1. $NaBH_4$, $MeOH/CH_2Cl_2$, 2. $CHCl_3/H_2O$; 89 % of **15**, 100 % of **16**, 97 % of **17**, 98 % of **18**.

The imines **15-I** to **18-I** were reduced to the target compounds **15–18** using sodium borohydride. While the reduction of **16-I** was successful in pure methanol, the addition of dry dichloromethane was necessary in the case of **15-I**. This was subsequently established as the standard procedure. After the final hydrolysis and extraction, the target compounds were obtained in 89-100 % yield. The yield of the macrocyclisation over two stages was between 68 % (**17**) and 83 % (**15**).

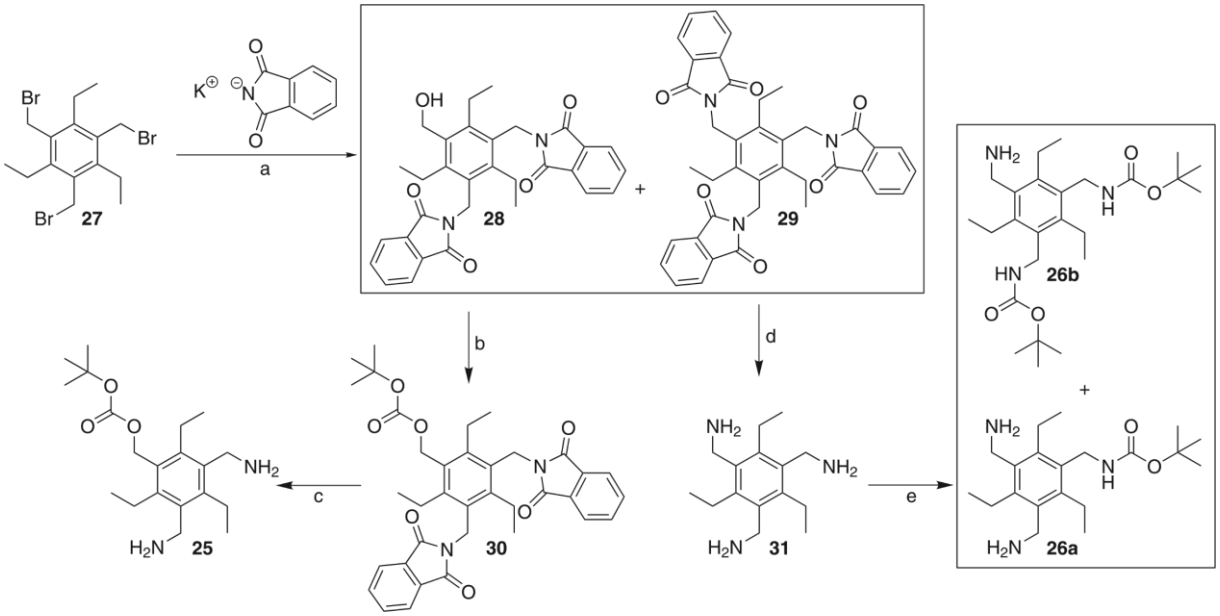
The syntheses of the precursors **25** and **26a**, used for the macrocyclization reactions, started with 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene (**27**), which was treated with potassium phthalimide in water-containing DMSO to obtain the compounds **28**[7] and **29**, as shown in

This article is protected by copyright. All rights reserved.

Accepted Manuscript

10.1002/ejoc.202100758

Scheme 2. Depending on the water content of the solvent, different products can be obtained. In an anhydrous environment, in addition to the compound **29**, mainly the aldehyde **32** (see Scheme 3) is formed by Kornblum oxidation.[16] When the water content is between 2.5 % and 15 %, compound **28**, containing one hydroxymethyl and two phthalimidomethyl groups, is formed in 39-43 % yield. At high water contents, the bis(hydroxymethyl)benzene derivative **33** (see Scheme 3) is also obtained in an appreciable amount (~ 10 %).

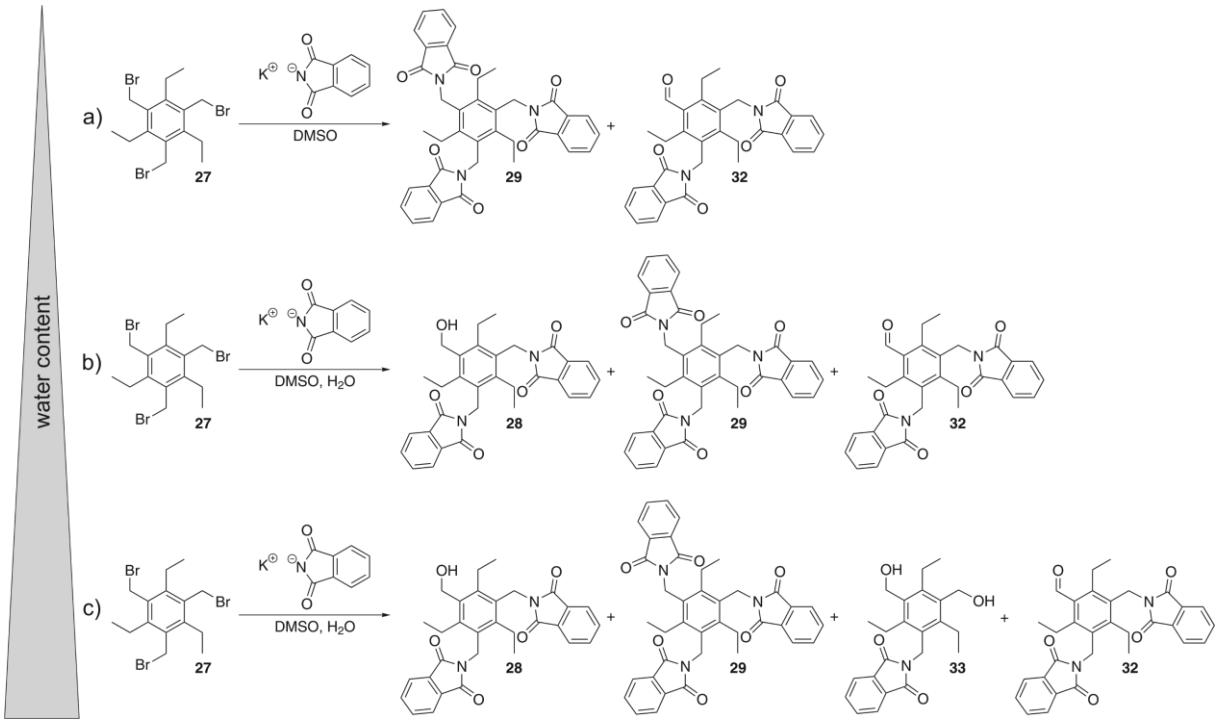


Scheme 2. Syntheses of compounds **25–26a**. Reaction conditions: (a) DMSO/H_2O, 43 % of **28**, 40 % of **29**[7]; (b) di-*tert*-butyl dicarbonate, zinc acetate dihydrate, CH_2Cl_2, 51 % of **30**; (c, d) hydrazine hydrate, toluene/EtOH, 86 % of **25**, 97 % of **31**; (e) di-*tert*-butyl dicarbonate, $CHCl_3$, 41 % of **26a**.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/ejoc.202100758



Scheme 3. Products of the reaction of 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene (**27**) with potassium phthalimide, formed in dependence of the water content of DMSO [in the case of (c), compound **32** was isolated in traces).

The conversion of compounds **28** and **29** to the corresponding amino derivatives **25** and **26a** was performed in two different ways. The derivative **28** was converted by the procedure described for benzyl alcohol by Bartoli *et al.*,[17] which includes the use of di-*tert*-butyl dicarbonate in dichloromethane under Lewis acid catalysis of zinc acetate (see Scheme 2). The obtained Boc-protected derivative **30** was further converted into **25** by the treatment with hydrazine hydrate in a mixture of toluene and ethanol (86 % yield).

The synthesis of **26a**, which is also shown in Scheme 2, includes the conversion of compound **29** into 1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene (**31**) by treatment with hydrazine hydrate (97 % yield) and the subsequent reaction of **31** with di-*tert*-butyl dicarbonate in chloroform. The latter reaction is based on the findings of Anslyn *et al.*[18] and was optimized to obtain the best yield of the product containing only one Boc-protected amino group. To increase the yield of **26a**, the amount of di-*tert*-butyl dicarbonate was reduced from 1.10 (21 % yield)[18a] and 0.78 (18 % yield)[18b] equivalents to 0.60 equivalents. Furthermore, the concentration of the di-*tert*-butyl dicarbonate solution was decreased, and the addition time of this solution was increased from 2[18a] to 9 hours. Especially the lowering of the concentration of the di-*tert*-butyl dicarbonate solution from 0.26 mol/L to 0.09 mol/L is likely to play an important role in

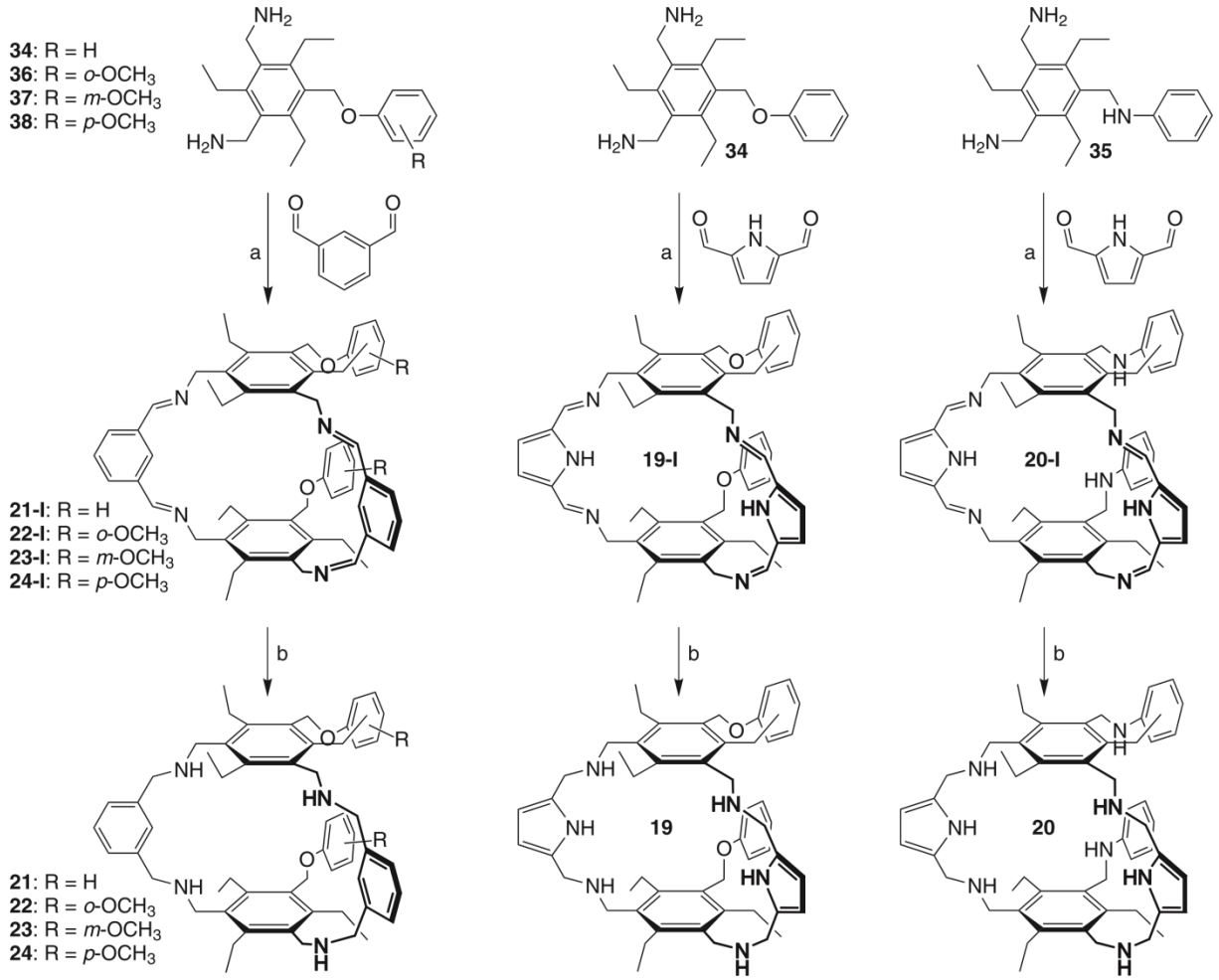
This article is protected by copyright. All rights reserved.

Accepted Manuscript

suppressing the multiple substitutions. Through this reaction optimization the yield of compound **26a** was almost doubled from 21 %[18a] to 41 %.

2.3 Syntheses of the macrocyclic compounds 19-24.

The target macrocycles **19-24**, consisting of two side-arms each bearing a phenyl group, were prepared through the reduction of the macrocyclic precursors **19-I** to **24-I** possessing four imine functionalities. The syntheses of the last mentioned compounds are based on the macrocyclization reactions of the educts **34-38**, containing two aminomethyl groups, with isophthalaldehyde and 1*H*-pyrrole-2,5-dicarbaldehyde (see Scheme 4).



Scheme 4. Syntheses of compounds **19**–**21**. Reaction conditions: (a) dry EtOH, catalytic amount of acetic acid, 56 % of **19-I**, 58 % of **20-I**, 84 % of **21-I**, 73 % of **22-I**, 66 % of **23-I**, 70 % of **24-I**; (b) 1. $NaBH_4$, $MeOH/CH_2Cl_2$, 2. $CHCl_3/H_2O$, 100 % of **19**, 93 % of **20**, 100 % of **21**, 94 % of **22**, 97 % of **23**, 100 % of **24**.

This article is protected by copyright. All rights reserved.

Accepted Manuscript

10.1002/ejoc.202100758

The reactions were carried out in dry ethanol in the presence of catalytic amounts of acetic acid and depend on the same factors as observed in the case of the macrocycles **15**-**18** with Boc-containing side-arms. The phenylene-bridged imines **21**-**I** to **24**-**I** were obtained in acceptable to very good yields of 66-84 %, whereas the yields of the pyrrole-bridged imines **19**-**I** and **20**-**I** were lower with 56 % and 58 %, respectively. The reduction of **19**-**I** to **24**-**I** with sodium borohydride in a methanol/dichloromethane mixture provided the target molecules **19**-**24** in 93 % to 100 % yield.

The starting point of the synthesis routes to the above mentioned compounds **34**–**38** was again 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene (**27**) (see Schemes 5 and 7). Two strategies were applied, which are described below.

The first strategy involves the monosubstitution of **27** with a phenoxy group, followed by the conversion of the prepared compounds **39a**-**42a** into the corresponding bis(phthalimidomethyl)benzene derivative **43a**-**46a** (see Scheme 5), and finally their hydrazinolysis to the corresponding amino derivatives **34** and **36**-**38**.

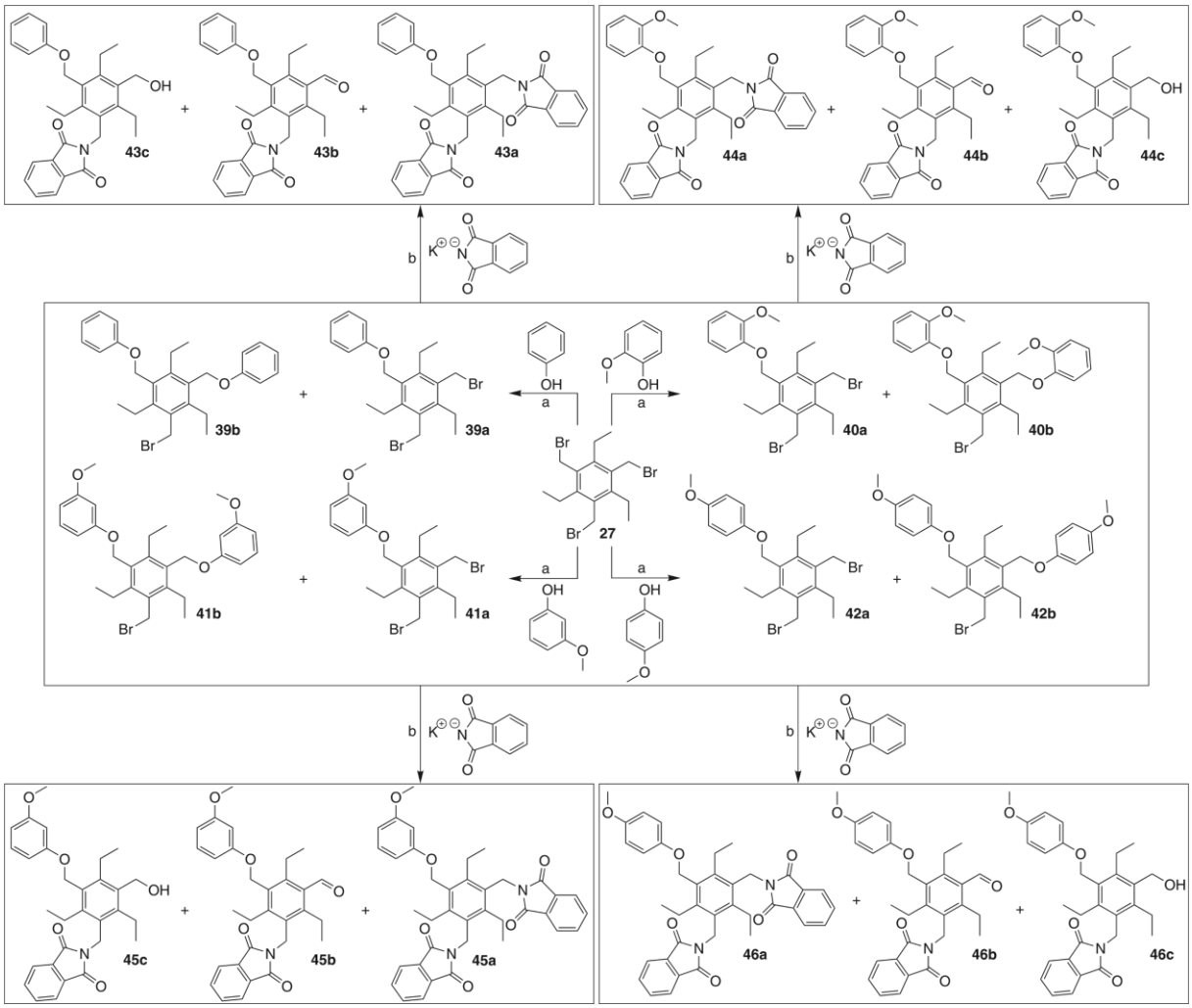
The second strategy first provides compound **48** through the reaction of **27** with potassium phthalimide (see Scheme 7), followed by the incorporation of a phenoxy or phenylamino group to produce compounds **43a**-**46a** and **49**, the hydrazinolysis of which is the basis for the preparation of the desired compounds **34**-**38**.

In the case of the first strategy shown in Scheme 5, the phenol derivative dissolved in acetonitrile was deprotonated by potassium carbonate and then reacted with **27** (the progress of the reactions was monitored by thin layer chromatography). After the chromatographic separation of the di- (**39b**-**42b**) and trisubstituted derivatives (**39c**-**41c**), the desired monosubstituted compounds **39a**-**42a** were obtained with 40-52 % yield. Optimization of the reaction conditions for the formation of the monosubstituted derivatives was performed in detail for compound **39a** and is described in Supporting Information. The knowledge gained from this was transferred to the syntheses of **40a**-**42a**.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/ejoc.202100758



Scheme 5. Syntheses of compounds **39a**-**42a** and **43a**–**46a**. Reaction conditions: (a) K_2CO_3, acetonitrile/THF, 40 % of **39a**, 8 % of **39b**, 42 % of **40a**, 11 % of **40b**, 50 % of **41a**, 22 % of **41b**, 52 % of **42a**, 30 % of **42b**; (b) DMSO, 47 % of **43a**, 57 % of **44a**, 59 % of **45a**, 32 % of **46a** (experimental data for the by-products **39b**-**46b** and **43c**-**46c** are given in Experimental Section).

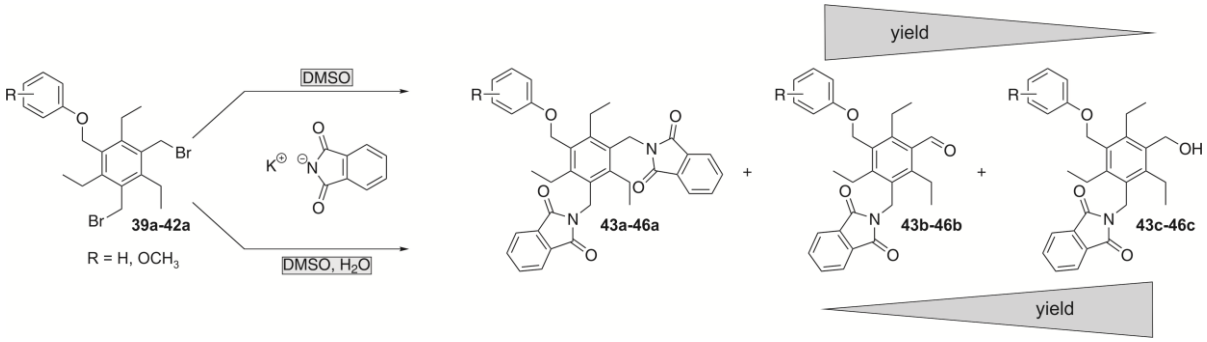
The aforementioned reaction of **39a**-**42a** with potassium phthalimide provided the derivatives **43a**–**46a** with yields in the range of only 32 to 59 %. This is due to the Kornblum oxidation that occurs during this process, which causes the formation of the by-products **43b**-**46b** containing an aldehyde group (see Scheme 5). These have an almost identical retention behaviour as the compounds **43a**–**46a** and are difficult to separate by column chromatography. The problematic separation and the resulting mixed fractions lead to further reduction of the yields of the desired products. To develop a method for a better isolation of the target compound **43a**–**46a**, water-containing DMSO (0.5 –1.0 % water) was used as an alternative (see Scheme 6). This procedure also results in yield losses, but the formation of by-products containing a hydroxymethyl group

Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/ejoc.202100758

instead of an aldehyde functionality (compounds **43c**-**46c**) enables easier chromatographic separation of the raw mixture, due to the much lower retention factor of these compounds. All by-products (compounds **43b**-**46b** and **43c**-**46c**) were isolated and are described in Experimental Section.



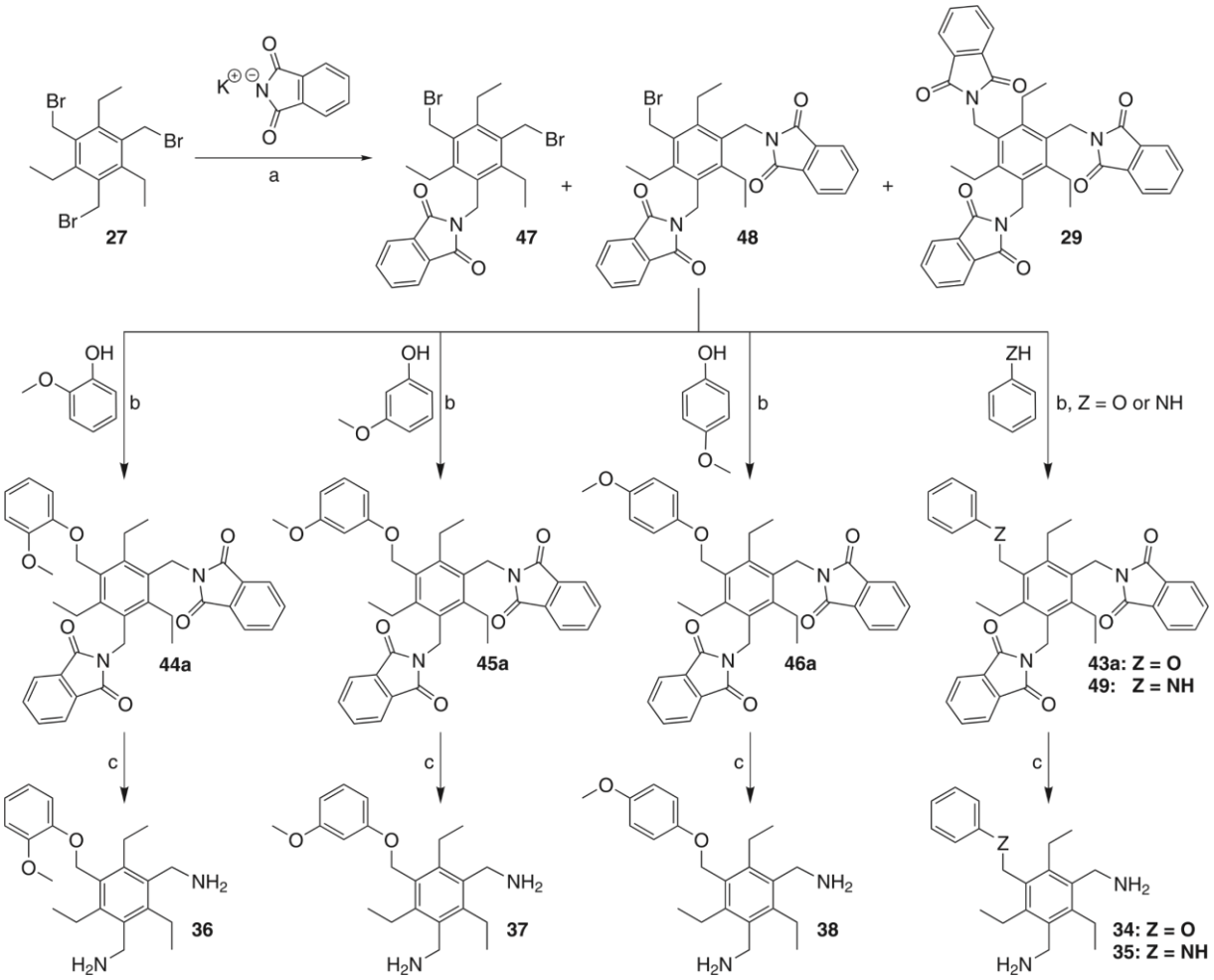
Scheme 6. Synthesis of bis(phthalimidomethyl)benzene derivatives **43a**–**46a** on the basis of the reactions of **39a**-**42a** with potassium phthalimide in DMSO and water-containing DMSO (influence of the presence of water on the product formation).

To further improve the yields of the derivatives **43a**–**46a**, containing two phthalimidomethyl moieties, an alternative synthetic route was developed (above-named as the second strategy, see Scheme 7), which includes the preparation of the precursor **48** having a good linkage possibility due to the presence of the bromomethyl functionality. This synthetic route also makes the compound **49** accessible, which is the basis for the synthesis of the bis(aminomethyl)-substituted derivative **35** and therefore of the target macrocycle **20** (see Scheme 4).

Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/ejoc.202100758



Scheme 7. Syntheses of compounds **34 – 38**. Reaction conditions: (a) 1,4-dioxane/DMF, 19 % of **47**, 49 % of **48**, 15 % of **29**, (b) K_2CO_3, acetonitrile/toluene, 65 % of **43a**, 67 % of **44a**, 63 % of **45a**, 65 % of **46a**, 87 % of **49**; (c) hydrazine hydrate, toluene/EtOH, 87 % of **34**, 83 % of **35**, 90 % of **36**, 89 % of **37**, 87 % of **38**.

The syntheses started again with 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene (**27**), which was reacted with two equivalents of potassium phthalimide in a 1,4-dioxane/DMF mixture. The desired disubstituted derivative **48** was separated from the mono- and trisubstituted triethylbenzenes (**47** and **29**, respectively) by column chromatography. Compounds **43a**-**46a** and **49** were then readily accessible by reacting the precursor **48** with the corresponding phenol derivative or aniline in acetonitrile/toluene in the presence of potassium carbonate. The compounds **43a-46a** were synthesized with 63 - 67 % yield and the compound **49** was obtained in a very good yield of 87 %. It should be noted, that the directly reaction of **27** with aniline would lead to an inseparable mixture of compounds with various substitution patterns, whereas the use of the reactant **48** only yields the desired product **49**. In summary, the second strategy

Accepted Manuscript

This article is protected by copyright. All rights reserved.

(Scheme 7) is to be preferred, since only two instead of 14 by-products are synthesized on the preparation of compounds **43a**-**46a**. Furthermore, the chromatographic separation in both stages (starting from **27**) is easy to realize.

Compound **49** could also be obtained under the reaction conditions described by Sing *et al,*.[19] which involve the heating of urea and choline chloride under an argon atmosphere to form a deep eutectic solvent, which serves as reaction matrix for the two reactants. After extraction and column chromatography, the product was obtained with a yield of 65 %. Due to the more difficult handling, the aforementioned "classical" synthesis is recommended.

The prepared bis(phthalimidomethyl)-substituted triethylbenzenes **44a**- **46a** and **49** could finally be converted into the corresponding amino derivatives **34-38** in very good yields of 83 % – 90 % via reaction with hydrazine hydrate.

2.4 Binding properties of compounds 15–24.

The ability of the macrocyclic compounds **15-24** to act as carbohydrate receptors was evaluated on the basis of ^{1}H NMR titrations and isothermal titration calorimetry (ITC).

Taking into account the findings of our previous studies, which have shown the particular suitability of this type of compounds for complexing all-equatorial substituted sugars, octyl β-D-glucopyranoside (**βGlc**) was selected as a test substrate for the binding studies.

2.4.1 ^{1}H NMR spectroscopic titrations.

The ^{1}H NMR titrations were performed either at a constant concentration of the receptor or at a constant concentration of the substrate ("inverse" titrations). The titration data were evaluated on the basis of WinEQNMR,[20] HypNMR[21] and SupraFit programs,[22] and the complex stoichiometry was analyzed by using the mole ratio method[23] (for examples, see Supporting Information); the determined association constants are summarized in Table 1.

The formation of complexes showing slow exchange on the NMR time scale and the coexistence of fast and slow exchanging complexes prevented the use of the NMR method for the determination of the binding constants in some cases; the binding properties were then only analyzed on the basis of the isothermal titration calorimetry.

This article is protected by copyright. All rights reserved.

Accepted Manuscript

10.1002/ejoc.202100758

Table 1. Association constants[a,b] for the complexation of octyl β-D-glucoside (**βGlc**) with compounds **15-24**.

Compound	Aromat in the bridge unit Y / Side-arm X	K_{11} [M^{-1}]	Method
15	benzene / CH_2**O**Boc	360	NMR
16	benzene / CH_2**NH**Boc	4810	NMR
		4990	ITC[e]
17	pyrrole / CH_2**O**Boc	3400	NMR
18[c]	pyrrole / CH_2**NH**Boc	79000	ITC[e]
13[c]	pyrrole / CH_2OH	195000	ITC[f]
19[d]	pyrrole / CH_2**O**Ph	12000	ITC[e]
20	pyrrole / CH_2**NH**Ph	36000	NMR, ITC[e]
21	benzene / CH_2**O**Ph	550	NMR
22	benzene / CH_2**O**(*o*-OCH_3)C_6H_4	640	NMR
23	benzene / CH_2**O**(*m*-OCH_3)C_6H_4	590	NMR
24	benzene / CH_2**O**(*p*-OCH_3)C_6H_4	540	NMR

[a]In $CDCl_3$, 20°C or 22°C (NMR), 25°C (ITC); [b]Errors are ≤ 8 %; [c]Slow exchanging complex; [d]Fast and slow exchanging complex; [e]For further details, see Table 2; [f]Ref.[7]

The results of the binding studies of compounds **15-24** towards octyl β-D-glucoside (**βGlc**) are summarized in points (a) - (e).

(a) As expected, compounds with flexible side-arms bearing a hydrogen bond donor group were found to be more powerful receptors than the analogs lacking such donor groups. This is clearly visible by comparing the binding properties of compounds **15** and **17**, containing two CH_2**O**Boc moieties, with those of the analogs **16** and **18**, having CH_2**NH**Boc groups as side-arms. Depending on the type of the bridging unit Y (benzene- or pyrrole-based bridge), the value of the complexation constant increased by a factor of 14 (**15** to **16**) and 23 (**17** to **18**), due to the presence of the amino functionality in the side-arms (see Table 1 and Figures 7 and 9). The same tendency, but less pronounced, is shown by comparing the binding constants determined for compounds **19** and **20**, containing CH_2**O**Ph and CH_2**NH**Ph groups as side-arms, respectively. In this case, the incorporation of the amino functionality leads to an increase in the binding strength by a factor of 3 (see Table 1 and Figures 8 and 9).

Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/ejoc.202100758

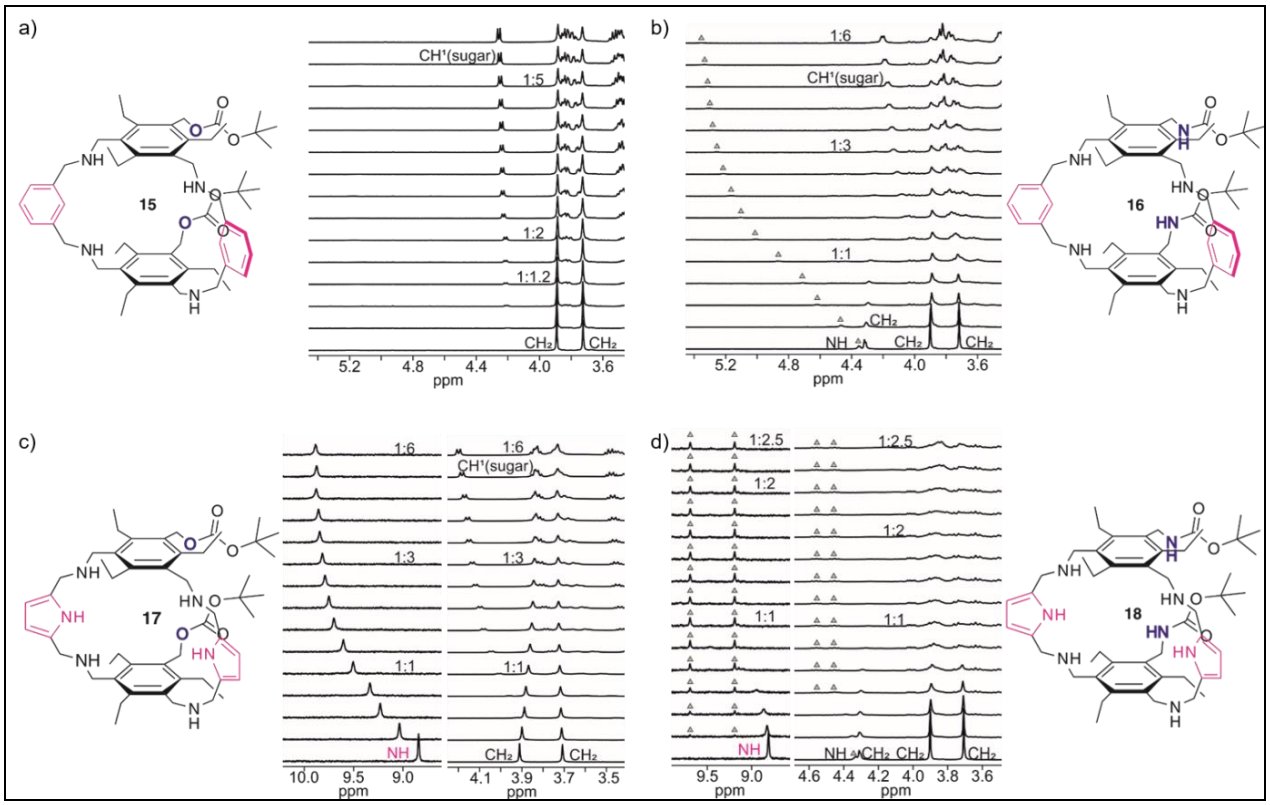


Figure 7. Partial ^{1}H NMR spectra (500 MHz, $CDCl_3$, 295 K) of compound **15** (a), **16** (b), **17** (c) and **18** (d) after the addition of octyl β-D-glucoside (**βGlc**). (a) 0.00-6.26 equiv of **βGlc**, [**15**] = 1.00 mM; (b) 0.00-6.07 equiv of **βGlc**, [**16**] = 1.01 mM; (c) 0.00-6.00 equiv of **βGlc**, [**17**] = 1.00 mM; (d) 0.00-2.54 equiv of **βGlc**, [**18**] = 1.00 mM. Shown are the chemical shifts of the C*H*$_2$NHC*H*$_2$ signals of **15**-**18**, the C*H*$_2$N*H*Boc signals (NH marked by triangles) of **16**/**18** and the pyrrole NH signals of **17**/**18** (marked by triangles in the case of **18**).

Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/ejoc.202100758

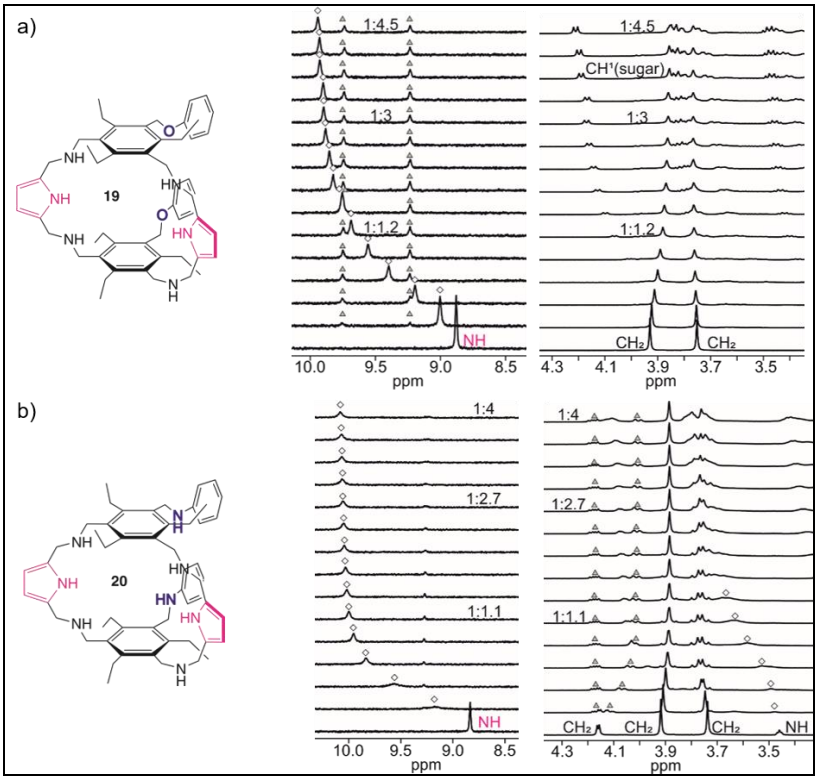


Figure 8. Partial ^{1}H NMR spectra (500 MHz, $CDCl_3$, 293 K) of compound **19** (a) and **20** (b) after the addition of octyl β-D-glucoside (**βGlc**). (a) 0.00-4.50 equiv of **βGlc**, [**19**] = 1.00 mM; (b) 0.00-4.01 equiv of **βGlc**, [**20**] = 1.00 mM. Shown are the chemical shifts of the pyrrole NH (marked by triangles and/or rhombs) and C*H*$_2$NHC*H*$_2$ signals of **19** and **20** as well as the C*H*$_2$N*H*Ph signals of **20** (CH_2 marked by triangles, NH marked by rhombs).

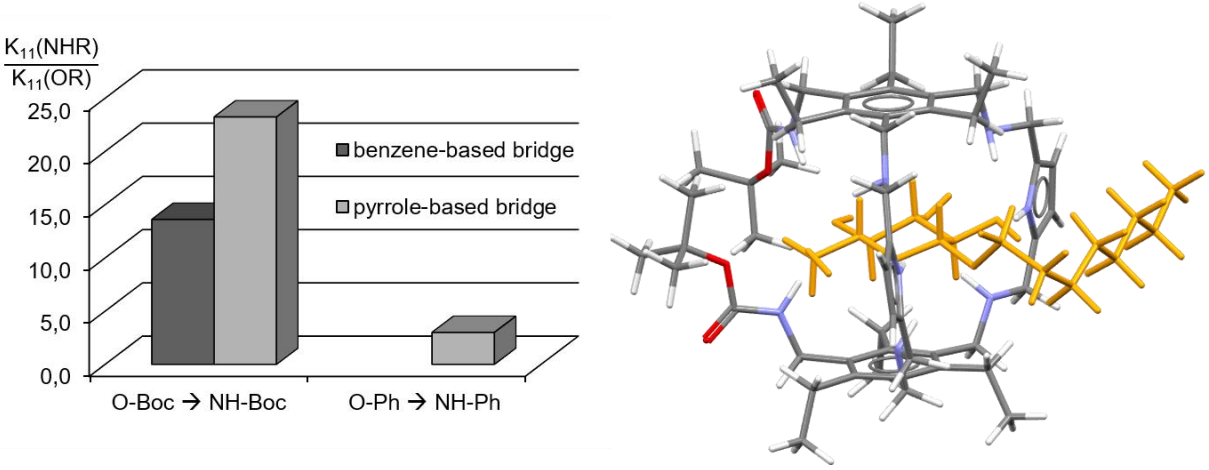


Figure 9. (Left) Bar graph illustrating the higher binding affinity of compounds containing CH_2**NH**R groups as side-arms (compounds **16**, **18** and **20**) in comparison to their analogues with CH_2**O**R groups (**15**, **17** and **19**) towards octyl β-D-glucoside (**βGlc**) (increase of the binding constants K_{11} given as a factor). (Right) Energy-minimized structure of the 1:1 complex of compound **18** and octyl β-D-glucopyranoside (**18•βGlc**; the glucoside ring is located in the

This article is protected by copyright. All rights reserved.

Accepted Manuscript

cavity of the receptor molecule). MacroModel V.9.8, OPLS_2001 force field, MCMM, 50000 steps; Color code: receptor N, blue; receptor C, grey; receptor O, red; sugar molecule, orange.

(b) The binding properties of the pyrrole-bridged compound **18**, bearing two CH_2**NH**Boc groups, support the thesis that even in the presence of a sterically demanding residue, the adjacent hydrogen bond donor can significantly contribute to effective complexation (K_{11} = 79000 M^{-1} *versus* 3400 M^{-1} for the analogue **17** lacking the donor site; see Figure 7). Compound **16** with benzene-based bridges and two side-arms containing the NH functionality also shows this in direct comparison to the donor-free analogue **15** (K_{11} = 4900 M^{-1} *versus* 360 M^{-1}), as shown in Figure 7. This confirms that the presence of hydrogen bond donating groups in the side-arms is of great importance for the development of effective receptors belonging to the class of compounds, which consist of a macrocyclic building block and two flexible side-arms.

(c) The present study confirmed our previous findings regarding the influence of the type of bridge unit on the binding properties and showed that the incorporation of pyrrole-containing bridges leads to more effective receptors than in the case of the use of benzene-based bridge units (for examples of other macrocyclic carbohydrate receptors bearing pyrrole-based bridges, see ref.[24]).

A significantly improved binding affinity could be observed between compounds **15** and **17** (factor 9) and **16** and **18** (factor 16). The 22-fold increase in binding strength between **21** and **19** is similar to that observed previously for the analogues **12** and **13**, bearing hydroxymethyl groups as side-arms (about 24-fold weaker binding of **βGlc** by **12** in comparison to **13**).

In general, it can be stated that the pyrrole-based bridging units lead to a significantly more effective carbohydrate recognition, as illustrated also by bar graph in Figure S109. However, if the units, which function as side-arms, are not capable of effective interactions with the substrate, pyrrole-bridged derivatives also represent weak systems. Thus, the nature of the side-arms has a strong influence on the binding properties of the potential receptor (see Figure S108).

(d) The combination of phenoxymethyl units, acting as side-arms, with benzene-based bridges provides compounds displaying very weak binding affinity towards β-glucopyranoside (compounds **21**-**24**). As mentioned above, the presence of a hydrogen bond donating functionality in the side-arms (as in **20**) and/or the use of pyrrole-based bridge units (as in **20** and **19**) causes a significant increase in the binding affinity. In the case of compounds **19**-**24** the

This article is protected by copyright. All rights reserved.

Accepted Manuscript

receptor efficiency decreases in the sequence: pyrrole / CH_2NHPh (**20**) > pyrrole / CH_2OPh (**19**) >> benzene /CH_2OPh (**21**) (specified is: aromatic ring in the bridge unit / side-arm).

Energy-minimalized structure of the complex **21•βGlc** in comparison with the structures of the more stable complexes **19•βGlc** and **20•βGlc** are shown in Figure S110 in Supporting Information.

Pyrrole-bridged compound **19**, containing CH_2OPh units as side-arms, is about 19- to 22-fold more effective than the phenylene-bridged analogues **21**-**24** (without and with methoxy substituent in the phenyl ring of the CH_2OPh units). Beside the unfavourable structural properties of the side-arms, the formation of intramolecular interactions seems to be further responsible for the weak binding properties of compounds **21-24**, as indicated by molecular modeling calculations (for example, see Figure 10) and determined by ROESY experiments (for examples, see Figures S111 and S112).

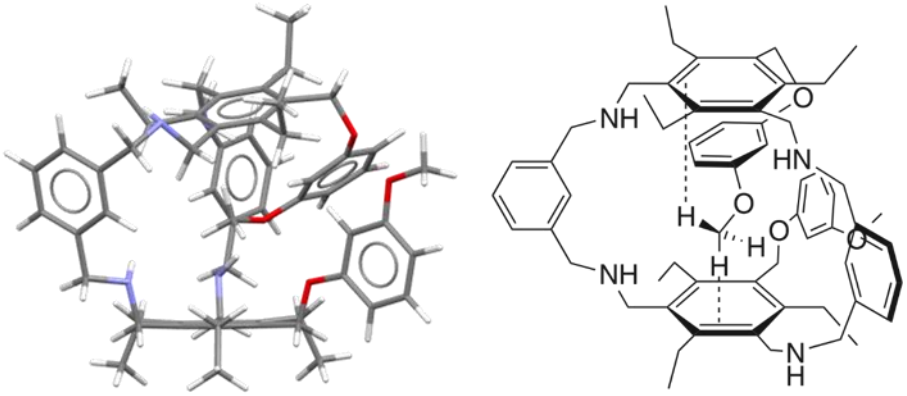


Figure 10. (Left) Energy-minimized structure of compound **23** indicating the formation of intramolecular interactions. MacroModel V.9.8, OPLS_2001 force field, MCMM, 50000 steps; Color code: receptor N, blue; receptor C, grey; receptor O, red. (Right) Schematic illustration of the intramolecular interactions.

(e) According to the design principle, which is illustrated in Figure 3, the receptor molecules form 1:1 complexes with the tested carbohydrate. As in the case of the previously investigated compounds of this type (see Figure 1), the complexation-induced chemical shifts observed during the titrations performed with compounds **15-20** show that the receptor-sugar complexes are stabilized by both hydrogen bonds (see Figures 7, 8 and 11) and CH···π[25] interactions. The involvement of the sugar CH's in CH···π interactions with the central benzene rings of the receptor is for example indicated by the upfield shift of the CH peaks observed during the titrations of **βGlc** with the corresponding receptor molecule (for an example, see Figure S105).

This article is protected by copyright. All rights reserved.

Accepted Manuscript

10.1002/ejoc.202100758

The most effective receptor **18**, equipped with pyrrole-based bridging units and CH_2**NH**Boc groups as side-arms, shows a slow exchange on the NMR time scale when using the octyl β-D-glucopyranoside as substrate (see Figures 7d and 11), which can be explained by a special positioning of the carbohydrate in the receptor cavity, as illustrated by the schematic representation of the receptor-sugar complex in Figure 11 (for excerpts from the ROESY spectrum of **18•βGlc** in $CDCl_3$, see Figure S113 in the Supporting Information). While slow exchange can be observed for compound **18**, the analogue **17**, bearing two CH_2**O**Boc groups as side-arms, forms complexes that show fast exchange on the NMR time scale (see Figure 11). Furthermore, fast and slow exchanging complexes also coexist, as in the case of compound **19** (see Figure 8a; for excerpts from the ROESY spectrum of **19•βGlc**. see Figure S114).

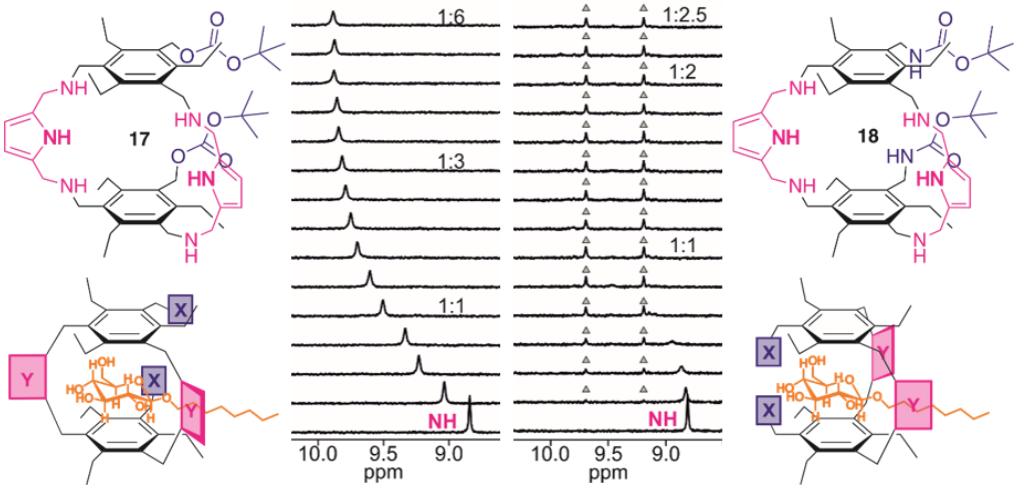


Figure 11. Partial ^{1}H NMR spectra (500 MHz, $CDCl_3$, 295 K) of compounds **17** and **18** after the addition of octyl β-D-glucoside (**βGlc**). [**17**] = 1.00 mM, 0.00-6.00 equiv of **βGlc**; [**18**] = 1.00 mM, 0.00-2.54 equiv of **βGlc**. Shown are the chemical shifts of the pyrrole NH (marked by triangles in the case of **18**) and the schematic illustration of the receptor-sugar complexes showing different positioning of the β-D-glucopyranoside in the receptor cavity.

It is also worth noting that a different positioning of the β-D-glucopyranoside in the receptor cavity was observed in two crystalline complexes, which were recognized in a crystal structure of an acyclic receptor.[10a] In each of the two 1:1 receptor-sugar complexes the hydroxy groups of the sugar interact in a different way with the binding site of the receptor molecule belonging to the class of compounds consisting of a 1,3,5-trisubstituded 2,4,6-triethylbenzene scaffold.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/ejoc.202100758

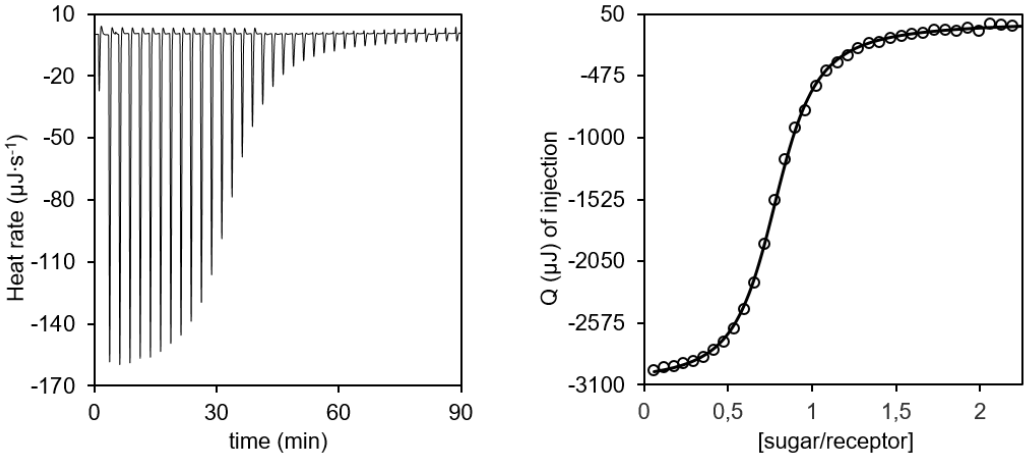
2.4.2 Microcalorimetric titrations.

The microcalorimetric titrations were carried out by adding increasing amounts of the sugar to a solution of the corresponding receptor (compounds **16** and **18**-**20**; see Table 2 and Figure 12). The binding constants were determined from three independent microcalorimetric titrations and in all cases the best fit of the titration data was obtained with the 1:1 receptor-sugar binding model (data were evaluated on the basis of NanoAnalyze and SupraFit programms).

Table 2. Results of microcalorimetric titrations of compounds **16** and **18-20** with octyl β-D-glucopyranoside.[a-c]

Compound	lg K_{11} (K_{11} [M^{-1}])	ΔG [kJ/mol]	ΔH [kJ/mol]	$T\Delta S$ [kJ/mol]	ΔS [J/mol K]
16	3.70 ± 0.05 (4990 ± 570)	-21.1 ± 0.6	-64.0 ± 4.6	-42.9	-144
18	4.90 ± 0.03 (79000 ± 5500)	-27.9 ± 0.5	-75.9 ± 2.3	-48.0	-161
19	4.08 ± 0.05 (12000 ± 1380)	-23.3 ± 0.5	-43.0 ± 1.5	-19.7	-66
20	4.55 ± 0.01 (36000 ± 800)	-26.0 ± 0.1	-65.9 ± 0.3	-39.9	-134

[a] In dry $CDCl_3$ at 25 °C.[b]Used concentrations: [**16**] = 0.5 mM, [**βGlc**] = 16.8 mM; [**18**] = 0.5 mM, [**βGlc**] = 7.2 mM; [**19**] = 0.5 mM, [**βGlc**] = 10.8 mM; [**20**] = 0.4 mM, [**βGlc**] = 5.7 mM. [c]The errors listed are the standard deviations for a minimum of three replicated ITC titrations.



This article is protected by copyright. All rights reserved.

Accepted Manuscript

Figure 12. ITC thermogram (left) and titration curve-fitting (right) for the titration of **18** with **βGlc** in dry $CDCl_3$ (the heat of dilution has been subtracted). Titration mode: addition of β-glucoside ($c_{syringe}$ = 7.23 mM) into **18** (c_{cell} = 0.52 mM) at 298 K in 35 steps.

The experiments showed that the enthalpic driving force of all the investigated binding processes is partially compensated by negative entropy (ΔS); the enthalpy (ΔH) is more negative than the free energy of binding (ΔG) (as reported also for protein-carbohydrate complexes[26]). As already indicated by the results of the NMR titrations, compound **18** was found to be a much more effective receptor for **βGlc**.

Consideration of the results of all binding experiments (NMR and microcalorimetric titrations) revealed that by replacing the CH_2OBoc by CH_2NHBoc units a gain in binding free energy between -6 kJ/mol and -8 kJ/mol is observed. By changing the flexible side-arms from CH_2OPh to CH_2NHPh units this energetic gain was about -3 kJ/mol. The incorporation of pyrrole- instead of benzene-based bridges increases the binding free energy by about 6-7 kJ/mol.

At this point it should also be mentioned that a comprehensive discussion of the experimental binding energies in supramolecular complexes, including receptor-sugar complexes, can be found in an excellent review of F. Biedermann and H.-J. Schneider[27] (see also ref.[28]).

3 Conclusion

To perform further structure-activity relationship studies with compounds consisting of a macrocyclic building block and flexible side-arms, new representatives of this class of compounds were prepared (compounds **15-24**) and their binding properties toward a selected sugar evaluated. The target compounds were obtained via multi-step syntheses, which included the preparation of numerous precursors as well as the isolation of a large number of by-products. The reduction of the macrocyclic precursors **15-I** to **24-I** possessing imine functionalites was not performed in situ, but all of them were isolated in good to excellent yields of 70 –93 %. Beside the 21 acyclic precursors (compounds **25, 26a**, **28-31**, **34-38**, **39a-46a** and **48**), 19 by-products were isolated and characterized (compounds **26b**, **26c**, **32**, **33**, **39b-46b, 39c, 41c, 43c-46c** and **47**).

Extensive ^1H NMR and microcalorimetric titrations showed that under the experimental conditions used, the macrocyclic compounds with a hydrogen bond donor site in each of the flexible side-arms have a higher efficiency in carbohydrate complexation than the corresponding analogues lacking such donor site. Even in the presence of a sterically demanding residue, the

This article is protected by copyright. All rights reserved.

Accepted Manuscript

10.1002/ejoc.202100758

adjacent hydrogen bond donor can contribute to effective complexation of the carbohydrate substrate. By using of pyrrole-containing bridges more powerful receptors have been generated than in the case of the use of benzene-based bridges; however, if the units acting as side-arms do not possess the capability for effective interactions with the substrate, pyrrole-bridged derivatives also represent weak systems. The present study confirmed the results of our previous investigations and showed again that the structural properties of both the side-arms (units X) and bridge units (Y) strongly influence the binding strength. It should be however noted that the side-arms are essential for strong complexation.

It should also be emphasized that within the compounds **12-24** the structurally very simple recognition unit, such as the hydroxymethyl group, enables the most effective complexation if acting as a side-arm, as revealed by the comparison of the properties of the previously investigated compounds **12-14** with those of **15-24** (see Figure 13).

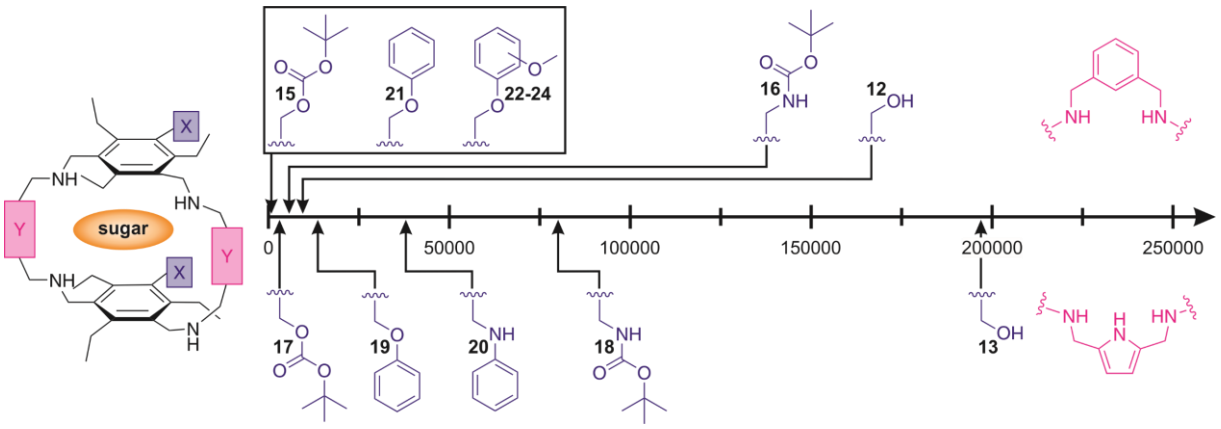


Figure 13. Comparison of the binding strength of compounds **12**, **13** and **15- 24** towards octyl β-D-glucopyranoside (K_{11} values [M^{-1}]).

The new representatives once again show the importance of the design strategy of artificial receptors that we reported some years ago,[9] which comprises the adaptation of the binding mode found in the crystal structure of a 2:1 receptor-carbohydrate complex, in which the all-equatorial substituted substrate is sandwiched between the aromatic units of two identical receptor molecules. This finding formed the basis for the development of the macrocyclic receptor system by linking two triethylbenzene-based building blocks via bridging units.

In summary, compounds that display a combination of a macrocyclic backbone and flexible side arms are valuable objects for conducting systematic studies on the molecular recognition of carbohydrates. Our previous[5-7] and current extensive studies on structure-binding activity

This article is protected by copyright. All rights reserved.

Accepted Manuscript

relationships using macrocyclic compounds possessing two flexible side-arms provide a large number of findings that make a valuable contribution to the understanding of molecular recognition processes and provide new impulses for further development in this field of research.

4 Experimental Section

Analytical TLC was carried out on silica gel 60 F_{254} plates; column chromatography was carried out on silica gel. Isophthalaldehyde is commercially available and 1*H*-pyrrole-2,5-dicarboxaldehyde was synthesized according to the procedure reported by Sudhakar *et al.*[29] The precursors **26a**,[18a,b] **27**[30] and **31**[30] are literature-known compounds. The NMR and mass spectra as well as the melting point of compound **26a** match the data published by Anslyn *et al.* [7a,b]

Reaction optimization for compound **39a** (by-products: **39b** and **39c**[31]) is given in Supporting Information and the experimental data for the by-products **32**, **33**, **39b-46b**, **41c** and **43c-46c** are given below. The NMR and mass spectra as well as the melting point of the by-product **26b** match the data published by Anslyn *et al.*[18a,b] The NMR data of compounds **26c** and **39c** match the data reported by Davis *et al.*[18d] and by Kim *et al.*,[31] respectively.

Binding studies (^{1}H NMR and microcalorimetric titrations) were carried out according to the procedures described by us previously (see for example ref.'s [5-7]). Octyl β-D-glycoside is commercially available.

General procedure for the synthesis of the macrocyclic compounds 15-I–24-I and 15–24.

To a solution of the triethylbenzene derivative **25**, **26a** or **34-38** in dry ethanol the corresponding aldehyde (isophthalaldehyde or 1*H*-pyrrole-2,5-dicarboxaldehyde) and one drop of acetic acid were added and the resulting mixture was stirred (for details, see below). The formed macrocyclic compound was separated by centrifugation, washed with small amounts of ethanol and dried under vacuum. All imines except **19-I** and **20-I** were obtained as white solids; **19-I** was obtained as white-yellow and **20-I** as yellow solid.

The corresponding imine was suspended in dry methanol (in the case of **16-I**) or a mixture of methanol and dichloromethane. To this suspension sodium borohydride (10 equiv.) was slowly added and the mixture was stirred at room temperature (for details, see below). Then the solvent was removed under vacuum, the residue was suspended in a mixture of water/chloroform [10 mL, 9:1 (*v/v*)] and the suspension stirred again for another 12 h. The mixture was extracted with

This article is protected by copyright. All rights reserved.

Accepted Manuscript

chloroform and the combined organic phases were washed with water and dried over magnesium sulfate. The solvent was evaporated and the residue dried under vacuum. All products except **19** and **20** were obtained as white solids; **19** was obtained as pale yellow and **20** as yellow solid.

Compound 15-I was prepared from **25** (108 mg, 0.33 mmol) and isophthalaldehyde (44 mg, 0.33 mmol) in ethanol (4 mL); the reaction mixture was stirred at 45 °C for 4 h. Yield 93 % (128 mg, 0.14 mmol); m.p. 205 – 207 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.19 (m, 18H), 1.49 (s, 18H), 2.40 (s, 4H), 2.61 (s, 8H), 5.01 (s, 8H), 5.20 (s, 4H), 7.48 (t, *J* = 10 Hz, 2H), 7.49 (br s, 2H), 7.92 (s, 4H), 8.02 (d, *J* = 7.6 Hz, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.7, 16.0, 23.2, 23.5, 27.8, 55.4, 63.4, 82.2, 128.7, 128.9, 129.8, 130.5, 131.8, 136.7, 144.8, 145.3, 153.6, 159.0 ppm; HRMS (ESI): *m/z* calcd for $C_{56}H_{72}N_4O_6$+H^+: 897.55246 $[M+H]^+$, found: 897.55360. $C_{56}H_{72}N_4O_6$+ H^+: 897.55246 $[M+H]^+$, found: 897.55360.

Compound 15 was prepared from **15-I** (114 mg, 0.13 mmol) and sodium borohydride (50 mg, 1.32 mmol) in methanol/dichloromethane [5 mL, 4:1 (*v/v*)]; the mixture was stirred at room temperature for 4 h. Yield 89 % (102 mg, 0.11 mmol); m.p. 155 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.09 (t, *J* = 7.4 Hz, 6H), 1.22 (t, *J* = 7.5 Hz, 12H), 1.48 (s, 18H), 2.68 (q, *J* = 7.4 Hz, 4H), 2.82 (q, *J* = 7.5 Hz, 8H), 3.73 (s, 8H), 3.89 (s, 8H), 5.19 (s, 4H), 7.15 – 7.19 (m, 4H), 7.24 – 7.27 (m, 2H), 7.53 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.7, 22.6, 22.8, 27.8, 47.3, 54.9, 63.4, 81.9, 127.0, 127.1, 128.0, 129.0, 134.4, 140.5, 143.4, 144.4, 153.8 ppm; HRMS (ESI): *m/z* calcd for $C_{56}H_{80}N_4O_6$+H^+: 905.61506 $[M+H]^+$, found: 905.61486.

Compound 16-I was prepared from **26a** (245 mg, 0.70 mmol) and isophthalaldehyde (94 mg, 0.70 mmol) in ethanol (2 mL); the mixture was stirred at 50 °C for 8.25 h. Yield 80 % (252 mg, 0.28 mmol); m.p. 225 °C (decomp.); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.18 (t, *J* = 7.4 Hz, 6H), 1.20 (t, *J* = 7.5 Hz, 12H), 1.43 (s, 18H), 2.51 (s, 4H), 2.60 (d, *J* = 7.4 Hz, 8H), 4.35 (d, *J* = 4.4 Hz, 4H), 4.47 (s, 2H), 4.97 (s, 8H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.72 (s, 2H), 7.92 (d, *J* = 7.8 Hz, 4H), 8.07 (s, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.6, 16.1, 23.1, 23.3, 28.4, 38.9, 56.1, 79.4, 128.7, 128.9, 129.6, 132.2, 132.3, 136.6, 143.7, 144.2, 155.4, 159.7 ppm; HRMS (ESI): *m/z* calcd for $C_{56}H_{74}N_6O_4$+H^+: 895.58443 $[M+H]^+$, found: 895.58453.

Compound 16 was prepared from **16-I** (220 mg, 0.24 mmol) and sodium borohydride (205 mg, 5.42 mmol) in methanol (10 mL); the mixture was stirred at room temperature for 3.5 h. Yield 100 % (221 mg, 0.24 mmol); m.p. 150 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.10 (t, *J* = 7.5 Hz, 6H), 1.23 (t, *J* = 7.5 Hz, 12H), 1.43 (s, 18H), 2.68 (q, *J* = 7.5 Hz, 4H), 2.76 (q, *J* = 7.5 Hz, 8H), 3.72 (s, 8H), 3.90 (s, 8H), 4.32 (d, *J* = 4 Hz, 4H), 4.37 (t, *J* = 4 Hz, 2H), 7.17 – 7.19 (m, 4H), 7.25 – 7.28 (m, 2H), 7.54 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.85, 16.88, 22.6,

This article is protected by copyright. All rights reserved.

Accepted Manuscript

22.9, 28.5, 38.9, 47.4, 55.0, 79.3, 126.9, 127.2, 128.1, 131.7, 134.6, 140.5, 142.5, 143.2, 155.6 ppm; HRMS (ESI): *m/z* calcd for $C_{56}H_{82}N_6O_4$+H^+: 903.64703 $[M+H]^+$, found: 903.64661.

Compound 17-I was prepared from **25** (270 mg, 0.77 mmol) and 1*H*-pyrrole-2,5-dicarboxaldehyde (95 mg, 0.77 mmol) in ethanol (8 mL); the mixture was stirred at 50 °C for 1.5 h. Yield 70 % (237 mg, 0.27 mmol); m.p. 180 °C (decomp. 190 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.14 (t, *J* = 7.5 Hz, 12H), 1.19 (t, *J* = 7.5 Hz, 6H), 1.44 (s, 18H), 2.64 (q, *J* = 7.5 Hz, 8H), 3.03 (q, *J* = 7.5 Hz, 4H), 4.75 (br. s, 8H), 5.14 (s, 4H), 6.52 (s, 4H), 8.17 (s, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.0, 16.1, 22.5, 22.6, 27.7, 57.6, 63.1, 81.9, 113.9, 129.2, 132.9, 133.0, 143.8, 145.2, 151.2, 153.7 ppm; HRMS (ESI): *m/z* calcd for $C_{52}H_{70}N_6O_6$+H^+: 875.54296 $[M+H]^+$, found: 875.54276.

Compound 17 was prepared from **17-I** (208 mg, 0.24 mmol) and sodium borohydride (90 mg, 2.38 mmol) in methanol/dichloromethane [10 mL, 1:1 (*v/v*)]; the mixture was stirred at room temperature for 16 h. Yield 97 % (204 mg, 0.23 mmol); m.p. 152 – 155 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.14 (t, *J* = 7.5 Hz, 6H), 1.20 (t, *J* = 7.5 Hz, 12H), 1.47 (s, 18H), 2.72 (q, *J* = 7.5 Hz, 8H), 2.96 (q, *J* = 7.5 Hz, 4H), 3.70 (s, 8H), 3.89 (s, 8H), 5.16 (s, 4H), 5.93 (d, *J* = 2.6 Hz, 4H), 8.94 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.1, 16.8, 22.2, 22.9, 27.8, 47.1, 47.6, 63.2, 82.0, 105.2, 128.9, 129.8, 134.3, 143.0, 145.1, 153.7 ppm; HRMS (ESI): *m/z* calcd for $C_{52}H_{78}N_6O_6$+H^+: 883.60556 $[M+H]^+$, found: 883.60690.

Compound 18-I was prepared from **26a** (172 mg, 0.50 mmol) and 1*H*-pyrrole-2,5-dicarboxaldehyde (61 mg, 0.50 mmol) in ethanol (6 mL); the mixture was stirred at 45 °C for 5 h. Yield 81 % (173 mg, 0.20 mmol); m.p. 260 °C (decomp.); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 7.5 Hz, 6H), 1.21 (t, *J* = 7.5 Hz, 12H), 1.38 (s, 18H), 2.57 (q, *J* = 7.5 Hz, 8H), 3.05 – 3.08 (m, 4H), 4.26 (d, *J* = 4.2 Hz, 4H), 4.36 (s, 2H), 4.72 (br. s, 8H), 6.51 (s, 4H), 8.22 (s, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.0, 16.2, 22.43, 22.45, 28.3, 38.7, 57.9, 79.2, 114.1, 131.5, 132.8, 133.4, 142.7, 144.1, 151.1, 155.5 ppm; HRMS (ESI): *m/z* calcd for $C_{52}H_{72}N_8O_4$+H^+: 873.57493 $[M+H]^+$, found: 873.57663.

Compound 18 was prepared from **18-I** (168 mg, 0.19 mmol) and sodium borohydride (84 mg, 2.22 mmol) in methanol/dichloromethane [6 mL, 2:1 (*v/v*)]; the mixture was stirred at room temperature for 4.5 h. Yield 98 % (166 mg, 0.19 mmol); m.p. 165 °C (decomp. 175 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.15 (t, *J* = 7.5 Hz, 6H), 1.21 (t, *J* = 7.4 Hz, 12H), 1.42 (s, 18H), 2.66 (q, *J* = 7.4 Hz, 8H), 2.90 (q, *J* = 7.5 Hz, 4H), 3.71 (s, 8H), 3.88 (s, 8H), 4.29 (d, *J* = 4.4 Hz, 4H), 4.35 (s, 2H), 5.94 (d, *J* = 2.6 Hz, 4H), 9.01 (br. s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$):

Accepted Manuscript

This article is protected by copyright. All rights reserved.

δ = 16.1, 16.9, 22.1, 22.8, 28.4, 38.8, 47.2, 47.6, 79.3, 105.3, 129.7, 131.6, 134.5, 142.0, 143.7, 155.4 ppm; HRMS (ESI): *m/z* calcd for $C_{52}H_{80}N_8O_4$+H^+: 881.63753 $[M+H]^+$, found: 881.63562.

Compound 19-I was prepared from **34** (109 mg, 0.33 mmol) and 1*H*-pyrrole-2,5-dicarboxaldehyde (41 mg, 0.34 mmol) in ethanol (7 mL); the mixture was stirred at 55 °C for 2.5 h. Yield 56 % (76 mg, 0.09 mmol); m.p. 260 °C (decomp.); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.18 (t, *J* = 7.5 Hz, 12H), 1.26 (t, *J* = 7.5 Hz, 6H), 2.68 (q, *J* = 7.5 Hz, 8H), 3.11 (q, *J* = 7.5 Hz, 4H), 4.79 (s, 8H), 5.00 (s, 4H), 6.50 (s, 4H), 6.95 – 6.99 (m, 2H), 7.00 – 7.02 (m, 4H), 7.29 – 7.33 (m, 4H), 8.24 (s, 4H), 9.59 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.1, 16.3, 22.6, 22.7, 58.0, 64.1, 113.7, 114.6, 120.8, 129.6, 130.5, 132.9, 133.6, 143.6, 145.1, 151.0, 159.1 ppm; HRMS (ESI): *m/z* calcd for $C_{54}H_{62}N_6O_2$+H^+: 827.50070 $[M+H]^+$, found: 827.50112.

Compound 19 was prepared from **19-I** (75 mg, 0.09 mmol) and sodium borohydride (34 mg, 0.90 mmol) in methanol/dichloromethane [8 mL, 1:1 (*v/v*)]; the mixture was stirred at room temperature for 3.5 h. Yield 100 % (78 mg, 0.09 mmol); m.p. 130 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.19 – 1.25 (m, 18H), 2.74 (q, *J* = 7.5 Hz, 8H), 3.03 (q, *J* = 7.5 Hz, 4H), 3.75 (s, 8H), 3.93 (s, 8H), 5.00 (s, 4H), 5.95 (d, *J* = 2.6 Hz, 4H), 6.98 – 7.00 (m, 2H), 7.01 – 7.03 (m, 4H), 7.32 – 7.35 (m, 4H), 8.89 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.2, 17.0, 22.3, 23.0, 47.4, 47.8, 64.2, 105.2, 114.6, 120.9, 129.6, 129.9, 130.4, 134.7, 143.0, 145.0, 159.1 ppm; HRMS (ESI): *m/z* calcd for $C_{54}H_{70}N_6O_2$+H^+: 835.56330 $[M+H]^+$, found: 835.56346.

Compound 20-I was prepared from **35** (153 mg, 0.47 mmol) and 1*H*-pyrrole-2,5-dicarboxaldehyde (58 mg, 0.47 mmol) in ethanol (7 mL); the mixture was stirred at 60 °C for 5 h. Yield 58 % (110 mg, 0.13 mmol); m.p. 265 °C (decomp.); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.5 Hz, 12H), 1.28 (t, *J* = 7.5 Hz, 6H), 2.63 (d, *J* = 5.9 Hz, 8H), 3.11 (q, *J* = 7.5 Hz, 4H), 3.56 (s, 2 H), 4.16 (d, *J* = 2.2 Hz, 4H), 4.77 (br. s, 8H), 6.50 (s, 4H), 6.62 (d, *J* = 7.8 Hz, 4H), 6.71 (t, *J* = 7.3 Hz, 2H), 7.19 (t, *J* = 7.9 Hz, 4H), 8.27 (s, 4H), 9.54 (br. s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.1, 16.5, 22.4, 22.6, 42.0, 58.2, 112.24, 114.1, 117.0, 129.3, 132.6, 132.9, 133.6, 143.0, 143.9, 148.3, 151.1 ppm; HRMS (ESI): *m/z* calcd for $C_{54}H_{64}N_8$+H^+: 825.53267 $[M+H]^+$, found: 825.53297.

Compound 20 was prepared from **20-I** (99 mg, 0.12 mmol) and sodium borohydride (45 mg, 1.20 mmol) in methanol/dichloromethane [8 mL, 1:1 (*v/v*)]; the mixture was stirred at room temperature for 16.5 h. Yield 93 % (93 mg, 0.11 mmol); m.p. 184 °C (decomp.); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 – 1.26 (m, 18H), 2.71 (q, *J* = 7.4 Hz, 8H), 2.98 (q, *J* = 7.5 Hz, 4H), 3.46 (t, *J* = 4.3 Hz, 2H), 3.75 (s, 8H), 3.92 (s, 8H), 4.17 (d, *J* = 4.1 Hz, 4H), 5.95 (d, *J* = 2.6 Hz, 4H), 6.64 – 6.66 (m, 4H), 6.73 – 6.76 (m, 2H), 7.22 – 7.25 (m, 4H), 8.89 (s, 2H) ppm; ^{13}C NMR (125

This article is protected by copyright. All rights reserved.

Accepted Manuscript

MHz, $CDCl_3$): δ = 16.3, 17.2, 22.2, 23.0, 42.1, 47.4, 47.9, 105.4, 112.4, 117.3, 129.4, 129.9, 132.6, 134.7, 142.3, 143.8, 148.3 ppm; HRMS (ESI): *m/z* calcd for $C_{54}H_{72}N_8$+H^+: 833.59527 $[M+H]^+$, found: 833.59576.

Compound 21-I was prepared from **34** (101 mg, 0.31 mmol) and isophthalaldehyde (42 mg, 0.31 mmol) in ethanol (6 mL); the mixture was stirred at 50 °C for 1.5 h. Yield 84 % (111 mg, 0.13 mmol); m.p. 230 °C (decomp.). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.19 – 1.23 (m, 18H), 2.45 (s, 4H), 2.68 (s, 8H), 5.03 (s, 8H), 5.08 (s, 4H), 6.97 – 7.00 (m, 2H), 7.01 – 7.04 (m, 4H), 7.31 – 7.34 (m, 4H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.59 (br. s, 2H), 7.95 – 7.97 (m, 4H), 8.00 (s, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.7, 16.1, 23.2, 23.4, 55.8, 64.5, 114.8, 121.0, 128.9, 129.0, 129.5, 129.8, 131.2, 132.0, 136.7, 144.6, 144.9, 158.8, 159.4 ppm; HRMS (ESI): *m/z* calcd for $C_{58}H_{64}N_4O_2$+H^+: 849.51020 $[M+H]^+$, found: 849.51058.

Compound 21 was prepared from **21-I** (98 mg, 0.12 mmol) and sodium borohydride (44 mg, 1.15 mmol) in methanol/dichloromethane [6 mL, 1:1 (*v/v*)]; the mixture was stirred at room temperature for 4 h. Yield 100 % (0.99 mg, 0.12 mmol); m.p. 207 – 210 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.14 (t, *J* = 7.5 Hz, 6H), 1.24 (t, *J* = 7.5 Hz, 12H), 2.74 (q, *J* = 7.5 Hz, 4H), 2.82 (q, *J* = 7.5 Hz, 8H), 3.77 (s, 8H), 3.91 (s, 8H), 5.01 (s, 4H), 6.97 – 7.00 (m, 2H), 7.01 – 7.03 (m, 4H), 7.17 – 7.19 (m, 4H), 7.24 – 7.27 (m, 2H), 7.31 – 7.34 (m, 4H), 7.57 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.7, 16.8, 22.6, 22.8, 47.4, 55.0, 64.3, 114.6, 120.7, 127.00, 127.05, 128.0, 129.5, 130.3, 134.5, 140.6, 143.3, 144.2, 159.1 ppm; HRMS (ESI): *m/z* calcd for $C_{58}H_{72}N_4O_2$+H^+: 857.57280 $[M+H]^+$, found: 857.57275.

Compound 22-I was prepared from **36** (181 mg, 0.51 mmol) and isophthalaldehyde (68 mg, 0.51 mmol) in ethanol (7 mL); the mixture was stirred at 45 °C for 3 h. Yield 73 % (169 mg, 0.19 mmol); m.p. 200 – 202 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.18 (t, *J* = 7.6 Hz, 6H), 1.22 (t, *J* = 7.5 Hz, 12H), 2.37 (s, 4H), 2.71 (s, 8H), 3.77 (s, 6H), 5.05 (s, 8H), 5.08 (s, 4 H), 6.88 – 6.97 (m, 6H), 7.05 – 7.06 (m, 2H), 7.43 (s, 2H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.90 (s, 4H), 8.02 (d, *J* = 7.5 Hz, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.8, 16.1, 23.2, 23.4, 55.4, 55.7, 66.5, 112.1, 115.8, 120.8, 122.2, 128.4, 129.0, 131.3, 131.6, 136.7, 144.8, 145.0, 148.4, 150.6, 158.9 ppm; HRMS (ESI): *m/z* calcd for $C_{60}H_{68}N_4O_4$+H^+: 909.53133 $[M+H]^+$, found: 909.53230.

Compound 22 was prepared from **22-I** (65 mg, 0.07 mmol) and sodium borohydride (27 mg, 0.71 mmol) in methanol/dichloromethane [6 mL, 1:1 (*v/v*)]; the mixture was stirred at room temperature for 14 h. Yield 94 % (61 mg, 0.07 mmol); m.p. 125 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.12 (t, *J* = 7.5 Hz, 6H), 1.25 (t, *J* = 7.5 Hz, 12H), 2.74 (q, *J* = 7.4 Hz, 4H), 2.86 (q, *J* = 7.5 Hz, 8H), 3.76 (s, 8H), 3.79 (s, 6H), 3.91 (s, 8H), 5.03 (s, 4H), 6.90 – 6.93 (m, 2H), 6.93 –

This article is protected by copyright. All rights reserved.

Accepted Manuscript

6.95 (m, 2H), 6.96 – 6.99 (m, 2H), 7.10 – 7.12 (m, 2H), 7.17 – 7.19 (m, 4H), 7.24 – 7.27 (m, 2H), 7.58 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.92, 16.96, 22.7, 23.0, 47.5, 55.1, 55.9, 66.0, 112.2, 114.7, 120.9, 121.7, 127.1, 128.1, 130.6, 134.5, 140.7, 143.6, 144.2, 148.9, 150.4 ppm; HRMS (ESI): *m/z* calcd for $C_{60}H_{76}N_4O_4$+H^+: 917.59393 $[M+H]^+$, found: 917.59598.

Compound 23-I was prepared from **37** (152 mg, 0.43 mmol) and isophthalaldehyde (57 mg, 0.43 mmol) in ethanol (6 mL); the mixture was stirred at 45 °C for 2.75 h. Yield 66 % (128 mg, 0.14 mmol); m.p. 235 °C (decomp.); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.12 – 1.18 (m, 18H), 2.57 – 2.60 (m, 4H), 2.70 (q, *J* = 7.5 Hz, 8H), 3.70 (s, 6H), 4.90 (s, 4H), 4.96 (s, 8H), 6.46 – 6.53 (m, 4H), 6.55 – 6.57 (m, 2H), 7.13 – 7.15 (m, 2H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.52 (s, 2H), 7.88 (d, *J* = 7.7 Hz, 4H), 7.93 (s, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.8, 16.2, 23.3, 23.5, 55.3, 55.9, 64.7, 101.3, 106.4, 107.0, 129.0, 129.1, 130.0, 131.1, 132.1, 136.8, 144.7, 145.0, 159.5, 160.2, 160.9 ppm; HRMS (ESI): *m/z* calcd for $C_{60}H_{68}N_4O_4$+H^+: 909.53133 $[M+H]^+$, found: 909.53097.

Compound 23 was prepared from **23-I** (120 mg, 0.13 mmol) and sodium borohydride (52 mg, 1.39 mmol) methanol/dichloromethane [6 mL, 2:1 (*v/v*)]; the mixture was stirred at room temperature for 16 h. Yield 97 % (116 mg, 0.13 mmol); m.p. 137-140 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.13 (t, *J* = 7.5 Hz, 6H), 1.24 (t, *J* = 7.5 Hz, 12H), 2.74 (q, *J* = 7.5 Hz, 4H), 2.82 (q, *J* = 7.5 Hz, 8H), 3.77 (s, 8H), 3.80 (s, 6H), 3.90 (s, 4H), 3.91 (s, 8H), 5.00 (s, 4H), 6.54 – 6.58 (m, 4H), 6.62 – 6.65 (m, 2H), 7.17 – 7.19 (m, 4H), 7.23 (t, *J* = 8.2 Hz, 2H), 7.24 – 7.28 (m, 2H), 7.57 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.8, 16.9, 22.7, 22.9, 47.5, 55.0, 55.4, 64.4, 101.2, 106.3, 106.8, 127.1, 127.2, 128.1, 130.0, 130.3, 134.6, 140.6, 143.4, 144.3, 160.4, 160.9 ppm; HRMS (ESI): *m/z* calcd for $C_{60}H_{76}N_4O_4$+H^+: 917.59393 $[M+H]^+$, found: 917.59340.

Compound 24-I was prepared from **38** (85 mg, 0.24 mmol) and isophthalaldehyde (32 mg, 0.24 mmol) in ethanol (5 mL); the mixture was stirred at 50 °C for 2.5 h. Yield 70 % (75 mg, 0.08 mmol); m.p. 260 °C (decomp.); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.19 – 1.23 (m, 18H), 2.44 (s, 4 H), 2.68 (s, 8H), 3.79 (s, 6H), 5.02 (s, 4H), 5.03 (s, 8H), 6.87 – 6.90 (m, 4H), 6.97 – 7.00 (m, 4H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.58 (s, 2H), 7.96 (d, *J* = 7.7 Hz, 4H), 8.00 (s, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.8, 16.2, 23.3, 23.5, 55.8, 65.5, 114.8, 115.8, 129.1, 130.1, 131.5, 132.0, 136.8, 144.4, 144.7, 145.0, 153.2, 154.1, 159.4 ppm; HRMS (ESI): *m/z* calcd for $C_{60}H_{68}N_4O_4$+H^+: 909.53133 $[M+H]^+$, found: 909.53138.

Compound 24 was prepared from **24-I** (65 mg, 0.07 mmol) and sodium borohydride (27 mg, 0.72 mmol) in methanol/dichloromethane [8 mL, 1:1 (*v/v*)]; the mixture was stirred at room temperature for 7.5 h. Yield 100 % (66 mg, 0.07 mmol); m.p. 113 °C; ^{1}H NMR (500 MHz,

This article is protected by copyright. All rights reserved.

Accepted Manuscript

$CDCl_3$): δ = 1.13 (t, *J* = 7.4 Hz, 6H), 1.25 (t, *J* = 7.5 Hz, 12H), 2.73 (q, *J* = 7.4 Hz, 4H), 2.83 (q, *J* = 7.5 Hz, 8H), 3.77 (s, 8H), 3.79 (s, 6H), 3.91 (s, 8H), 4.96 (s, 4H), 6.84 – 6.89 (m, 4H), 6.94 – 6.97 (m, 4H), 7.17 – 7.19 (m, 4H), 7.25 – 7.27 (m, 2H), 7.57 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.8, 16.9, 22.7, 22.9, 47.5, 55.1, 55.9, 65.0, 114.8, 115.5, 127.0, 127.1, 128.1, 130.6, 134.6, 140.7, 143.3, 144.2, 153.4, 153.9 ppm; HRMS (ESI): *m/z* calcd for $C_{60}H_{76}N_4O_4+H^+$: 917.59393 $[M+H]^+$, found: 917.59392.

Synthesis of the compounds 26a and 30.

1,3-Bis(phthalimidomethyl)-5-(*tert*-butoxycarbonyloxymethyl)-2,4,6-triethylbenzene (30). 1-Hydroxymethyl-3,5-bis(phthalimidomethyl)-2,4,6-triethylbenzene (**28**; 918 mg, 1.80 mmol) was dissolved in dichloromethane (30 mL). After addition of di-*tert*-butyl dicarbonate (450 mg, 2.06 mmol, 1.1 equiv.) and zinc acetate dihydrate (40 mg, 0.18 mmol, 0.1 equiv.), the reaction mixture was heated to 40 °C and stirred for 19 h. Then the mixture was filtered off, the solvent removed under vacuum and the crude product purified by column chromatography [toluene/ethyl acetate, 5:1 (*v/v*)]. Compound **30** was obtained as a white solid.

Yield 51 % (558 mg, 0.91 mmol); R_f = 0.26 [toluene/ethyl acetate, 5:1 (*v/v*)]; m.p. 170 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.5 Hz, 3H), 1.07 (t, *J* = 7.5 Hz, 6H), 1.47 (s, 9H), 2.89 (q, *J* = 7.5 Hz, 4H), 3.22 (q, *J* = 7.5 Hz, 2H), 4.95 (s, 4H), 5.21 (s, 2H), 7.68 – 7.71 (m, 4H), 7.79 – 7.82 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.93, 15.95, 23.0, 23.5, 27.7, 37.3, 63.2, 82.0, 123.2, 129.57, 129.59, 131.9, 133.9, 145.5, 146.9, 153.7, 168.2 ppm; MS (ESI): *m/z* calcd for $C_{36}H_{38}N_2O_7+Na^+$: 633.26 $[M+Na]^+$, found 633.29; elemental analysis calcd (%) for $C_{36}H_{38}N_2O_7$: C 70.80 %, H 6.27 %, N 4.59 %; found C 70.47 %, H 6.24 %, N 4.57 %.

1-{[(1,1-Dimethylethoxy)carbonyl]aminomethyl}-3,5-bis(aminomethyl)-2,4,6-triethylbenzene (26a).[18b] 1,3,5-Tris(aminomethyl)-2,4,6-triethylbenzene (**31**; 1860 mg, 6.90 mmol) was dissolved in chloroform (80 mL) and a solution of di-*tert*-butyl dicarbonate (898 mg, 4.47 mmol, 0.6 equiv.) in chloroform (45 mL) was added dropwise. The reaction mixture was stirred over night at room temperature. Afterwards the solvent was removed under vacuum and the crude product purified by column chromatography [chloroform/methanol 8:1 (*v/v*) + 1-5 vol.-% 7N ammonia in methanol]. Compound **26a** was obtained as a white solid.

Yield 41 % (978 mg, 2.80 mmol); R_f = 0.15 [chloroform/methanol 8:1 (*v/v*) + 1 vol.-% 7N NH_3 in methanol]; m.p. 133-135 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 – 1.23 (m, 9H), 1.45 (s, 9H), 2.77 (q, *J* = 7.5 Hz, 4H), 2.83 (q, *J* = 7.5 Hz, 2H), 3.88 (s, 4H), 4.34 (d, *J* = 4.3 Hz, 2H), 4.45 (br s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.7, 16.9, 22.8, 28.5, 38.9, 39.5, 79.4,

This article is protected by copyright. All rights reserved.

Accepted Manuscript

132.2, 137.2, 141.6, 141.8, 155.6 ppm; MS (ESI): *m/z* calcd for $C_{20}H_{35}N_3O_2$+H^+: 350.28 $[M+H]^+$, found 350.16.

General procedure for the synthesis of compounds 39a, 40a, 41a and 42a

1,3,5-Tris(bromomethyl)-2,4,6-triethylbenzene (**27**) dissolved in tetrahydrofuran/acetonitrile [40 mL, 3:1 (*v*/*v*)] was added to a mixture of the corresponding hydroxybenzene derivative and an equimolar amount of anhydrous potassium carbonate in acetonitrile (20 mL). The reaction mixture was stirred under reflux for 4 h. After filtration and removing of the solvents under vacuum, the corresponding crude product was purified by column chromatography. All products and the by-products (**39b**, **39c**, **40b**, **41b, 41c** and **42b**) were obtained as white solids.

1,3-Bis(bromomethyl)-5-(phenoxymethyl)-2,4,6-triethylbenzene (39a). Compound **39a** was prepared from **27** (1.00 g, 2.27 mmol) and phenol (0.22 g, 2.27 mmol). Yield 40 % (0.41 g, 0.91 mmol); R_f = 0.39 [toluene/hexane, 1:4 (*v/v*)]; m.p. 130 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.6 Hz, 6H), 1.36 (t, *J* = 7.6 Hz, 3H), 2.88 (q, *J* = 7.6 Hz, 4H), 2.98 (q, *J* = 7.6 Hz, 2H), 4.63 (s, 4H), 5.01 (s, 2H), 7.00 – 7.05 (m, 3H), 7.33 – 7.37 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.6, 16.0, 22.7, 22.9, 28.9, 63.8, 114.5, 121.1, 129.6, 131.8, 132.3, 144.9, 145.7, 158.7 ppm; MS (ESI): *m/z* calcd for $C_{21}H_{26}Br_2O$+NH_4^+: 472.07 $[M+NH_4]^+$, found 472.31; elemental analysis calcd (%) for $C_{21}H_{26}Br_2O$: C 55.53 %, H 5.77 %; found C 55.61 %, H 5.60 %.

1,3-Bis(bromomethyl)-5-(2-methoxyphenoxymethyl)-2,4,6-triethylbenzene (40a).

Compound **40a** was prepared from **27** (1.83 g, 4.15 mmol) and guaiacol (0.52 g, 4.16 mmol). Yield 42 % (0.85 g, 1.76 mmol); R_f = 0.41 [toluene/hexane, 2:1 (*v/v*)]; m.p. 133 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.6 Hz, 6H), 1.35 (t, *J* = 7.5 Hz, 3H), 2.92 (q, *J* = 7.6 Hz, 4H), 2.96 (q, *J* = 7.5 Hz, 2H), 3.84 (s, 3H), 4.63 (s, 4H), 5.04 (s, 2H), 6.93 – 7.03 (m, 3H), 7.11 (dd, *J* = 7.7/1.7 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.7, 16.0, 22.7, 22.9, 29.1, 55.7, 65.6, 112.0, 114.9, 120.8, 122.0, 131.9, 132.1, 144.8, 146.0, 148.4, 150.3 ppm; MS (ESI): *m/z* calcd for $C_{22}H_{28}Br_2O_2$+NH_4^+: 502.08 $[M+NH_4]^+$, found 502.32; elemental analysis calcd (%) for $C_{22}H_{28}Br_2O_2$: C 54.56 %, H 5.83 %; found C 54.46 %; H 5.76 %.

1,3-Bis(bromomethyl)-5-(3-methoxyphenoxymethyl)-2,4,6-triethylbenzene (41a).

Compound **41a** was prepared from **27** (1.75 g, 3.97 mmol) and 3-methoxyphenol (0.49 g, 3.97 mmol). Yield 50 % (0.96 g, 1.98 mmol); R_f = 0.46 [toluene/hexane, 2:1 (*v/v*)]; m.p. 145 – 147 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.28 (t, J = 7.6 Hz, 6H), 1.36 (t, *J* = 7.6 Hz, 3H), 2.87 (q, *J*

This article is protected by copyright. All rights reserved.

Accepted Manuscript

= 7.6 Hz, 4H), 2.98 (q, *J* = 7.6 Hz, 2H), 3.81 (s, 3H), 4.62 (s, 4H), 5.00 (s, 2H), 6.56 – 6.58 (m, 2H), 6.63 – 6.65 (m, 1H), 7.25 (t, *J* = 8.6 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.6, 16.0, 22.7, 22.8, 28.9, 55.4, 63.9, 101.1, 106.5, 106.6, 130.0, 131.7, 132.3, 144.9, 145.7, 160.0, 160.9 ppm; MS (APCI): *m/z* calcd for $C_{22}H_{28}Br_2O_2$+H^+: 485.05 $[M+H]^+$, found 485.08; elemental analysis calcd (%) for $C_{22}H_{28}Br_2O_2$: C 54.56 %, H 5.83 %; found C 54.87 %, H 5.92 %.

1,3-Bis(bromomethyl)-5-(4-methoxyphenoxymethyl)-2,4,6-triethylbenzene (42a).

Compound **42a** was prepared from **27** (0.50 g, 1.13 mmol) and 4-methoxyphenol (0.30 g, 2.38 mmol). Yield 52 % (0.29 g, 0.59 mmol); R_f = 0.18 [toluene/hexane, 2:1 (*v/v*)]; m.p. 129 – 131 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.6 Hz, 6H), 1.35 (t, *J* = 7.6 Hz, 3H), 2.88 (q, *J* = 7.6 Hz, 4H), 2.97 (q, *J* = 7.6 Hz, 2H), 3.79 (s, 3H), 4.62 (s, 4H), 4.96 (s, 2 H), 6.88 – 6.90 (m, 2H), 6.95 – 6.98 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.8, 16.1, 22.8, 23.0, 29.1, 55.9, 64.6, 114.8, 115.5, 132.1, 132.3, 144.9, 145.8, 153.0, 154.2 ppm; HRMS (ESI): *m/z* calcd for $C_{22}H_{28}Br_2O_2$+Na^+: 507.03292 $[M+Na]^+$, found 507.03543.

General procedure for the synthesis of compounds 43a-46a.

The corresponding triethylbenzene derivative **39a**, **40a**, **41a** or **42a** and potassium phthalimide were dissolved in dimethyl sulfoxide (25-50 mL). The reaction mixture was stirred for 10 h at 100 °C. After cooling down to room temperature, the reaction mixture was poured onto water (50-100 mL) and the resulting precipitate was filtered off and washed with water to fully remove dimethyl sulfoxide. Then the solid was suspended in water and extracted with chloroform (4 × 30 mL). The combined organic phases were dried over magnesium sulfate, the solvent was removed under vacuum and the corresponding crude product was purified by column chromatography. All products were obtained as white solids.

1,3-Bis(phthalimidomethyl)-5-phenoxymethyl-2,4,6-triethylbenzene (43a). Compound **43a** was prepared from **39a** (618 mg, 1.36 mmol) and potassium phthalimide (680 mg, 3.37 mmol). Yield 47 % (376 mg, 0.64 mmol); R_f = 0.37 [toluene/ethyl acetate, 11:1 (*v/v*)]; m.p. 130 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.01 (t, *J* = 7.5 Hz, 3H), 1.07 (t, *J* = 7.5 Hz, 6H), 2.89 (q, *J* = 7.5 Hz, 4H), 3.24 (q, *J* = 7.5 Hz, 2H), 4.97 (s, 4H), 5.02 (s, 2H), 6.95 – 6.96 (m, 1H), 6.98 – 7.01 (m, 2H), 7.29 – 7.32 (m, 2H), 7.67 – 7.70 (m, 4H), 7.78 – 7.82 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.0, 16.1, 23.1, 23.7, 37.5, 64.2, 114.6, 120.9, 123.3, 129.5, 129.7, 131.0, 132.0, 134.0, 145.4, 146.6, 159.0, 168.3 ppmHRMS (ESI): *m/z* calcd for $C_{37}H_{34}N_2O_5$+Na^+:

This article is protected by copyright. All rights reserved.

Accepted Manuscript

609.23599 $[M+Na]^+$, found: 609.23665; elemental analysis calcd (%) for $C_{37}H_{34}N_2O_5$: C 75.75 %, H 5.84 %, N 4.77 %; found C 75.47 %, H 5.88 %, N 4.78 %.

1,3-Bis(phthalimidomethyl)-5-(2-methoxyphenoxymethyl)-2,4,6-triethylbenzene (44a). Compound **44a** was prepared from **40a** (904 mg, 1.87 mmol) and potassium phthalimide (1038 mg, 5.60 mmol). Yield 57 % (651 mg, 1.06 mmol); R_f = 0.46 [toluene/ethyl acetate, 5:1 (*v/v*)]; m.p. 193 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.01 (t, *J* = 7.6 Hz, 3H), 1.10 (t, *J* = 7.5 Hz, 6H), 2.96 (q, *J* = 7.5 Hz, 4H), 3.26 (q, *J* = 7.6 Hz, 2H), 3.80 (s, 3H), 4.98 (s, 4H), 5.06 (s, 2H), 6.89 – 6.98 (m, 3H), 7.07 – 7.09 (m, 1H), 7.67 – 7.70 (m, 4H), 7.79 – 7.83 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.9, 16.0, 23.1, 23.5, 37.4, 55.8, 66.1, 112.2, 115.3, 120.8, 121.8, 123.2, 129.5, 131.1, 132.0, 133.9, 145.7, 146.5, 148.6, 150.5, 168.2 ppm; HRMS (ESI): *m/z* calcd for $C_{38}H_{36}N_2O_6$+Na^+: 639.24656 $[M+Na]^+$, found: 639.24747; elemental analysis calcd (%) for $C_{38}H_{36}N_2O_6$: C 74.01 %, H 5.88 %, N 4.54 %; found C 73.86 %, H 5.84 %, N 4.58 %.

1,3-Bis(phthalimidomethyl)-5-(3-methoxyphenoxymethyl)-2,4,6-triethylbenzene (45a). Compound **45a** was prepared from **41a** (912 mg, 1.88 mmol) and potassium phthalimide (1046 mg, 5.65 mmol). Yield 59 % (681 mg, 1.10 mmol); R_f = 0.51 [toluene/ethyl acetate, 5:1 (*v/v*)]; m.p. 205 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.01 (t, *J* = 7.6 Hz, 3H), 1.08 (t, *J* = 7.5 Hz, 6H), 2.89 (q, *J* = 7.5 Hz, 4H), 3.24 (q, *J* = 7.6 Hz, 2H), 3.78 (s, 3H), 4.98 (s, 4H), 5.01 (s, 2H), 6.52 – 6.56 (m, 2H), 6.61 – 6.63 (m, 1H), 7.21 (t, *J* = 8.2 Hz, 1H), 7.67 – 7.71 (m, 4H), 7.79 – 7.83 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.0, 16.1, 23.1, 23.6, 37.5, 55.3, 65.9, 101.2, 106.4, 106.7, 123.3, 129.7, 129.9, 130.9, 132.1, 134.0, 145.4, 146.6, 160.3, 160.9, 168.3 ppm; HRMS (ESI): *m/z* calcd for $C_{38}H_{36}N_2O_6$+H^+: 639.24656 $[M+H]^+$, found: 639.24705.

1,3-Bis(phthalimidomethyl)-5-(4-methoxyphenoxymethyl)-2,4,6-triethylbenzene (46a). Compound **46a** was prepared from **42a** (370 mg, 0.76 mmol) and potassium phthalimide (354 mg, 1.91 mmol). Yield 32 % (148 mg, 0.24 mmol); R_f = 0.36 [toluene/ethyl acetate, 11:1 (*v/v*)]; m.p. 191 – 193 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.00 (t, *J* = 7.6 Hz, 3H), 1.07 (t, *J* = 7.5 Hz, 6H), 2.89 (q, *J* = 7.5 Hz, 4H), 3.23 (q, *J* = 7.6 Hz, 2H), 3.76 (s, 3H), 4.96 (s, 2H), 4.97 (s, 4H), 6.83 – 6.86 (m, 2H), 6.91 – 6.95 (m, 2H), 7.66 – 7.70 (m, 4H). 7.78 – 7.82 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.0, 16.1, 23.1, 23.7, 37.5, 55.8, 64.9, 114.7, 115.5, 123.3, 129.7, 131.2, 132.0, 134.0, 145.4, 146.5, 153.2, 153.9, 168.3 ppm; MS (ESI): *m/z* calcd for $C_{38}H_{36}N_2O_6$+Na^+: 639.25 $[M+Na]^+$, found 639.40; elemental analysis calcd (%) for $C_{38}H_{36}N_2O_6$: C 74.01 %, H 5.88 %, N 4.54 %; found C 73.77 %, H 5.88 %, N 4.47 %.

Synthesis of compounds 43a-46a and 49 via precursor 48.

This article is protected by copyright. All rights reserved.

Accepted Manuscript

1,3-Bis(phthalimidomethyl)-5-phenylaminomethyl-2,4,6-triethylbenzene (49). Under argon atmosphere 1-bromomethyl-3,5-bis(phthalimidomethyl)-2,4,6-triethylbenzene (**48**)[32] (500 mg, 0.87 mmol) dissolved in acetonitrile/toluene [60 mL, 1:5 (*v/v*)] was added dropwise to a mixture of aniline (244 mg, 239 µL, 2.62 mmol, 3 equiv.) and anhydrous potassium carbonate (180 mg, 1.31 mmol, 1.5 equiv.) in acetonitrile (40 mL). The reaction mixture was stirred at 45 °C for 5 d. After filtration, removing of the solvents and drying under vacuum, the product was obtained as a yellow solid (87 %). R_f = 0.51 [toluene/ethyl acetate, 5:1 (*v/v*)]; m.p. 230 – 232 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.03 (t, *J* = 7.6 Hz, 3H), 1.12 (t, *J* = 7.5 Hz, 6H), 2.85 (q, *J* = 7.5 Hz, 4H), 3.23 (q, *J* = 7.6 Hz, 2H), 3.60 (s, 1H), 4.19 (s, 2H), 4.97 (s, 4H), 6.63 – 6.65 (m, H), 6.70 (tt, *J* = 7.3/1.1 Hz, 1H), 7.18 – 7.21 (m, 2H), 7.68 – 7.72 (m, 4H), 7.80 – 7.83 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.0, 16.2, 23.0, 23.6, 37.5, 42.0, 112.3, 117.1, 123.4, 129.3, 129.7, 132.0, 133.0, 134.1, 144.7, 145.8, 148.2, 168.4 ppm; MS (ESI): *m/z* calcd for $C_{37}H_{35}N_3O_4$+H^+: 586.27 $[M+H]^+$, found 586.40; elemental analysis calcd (%) for $C_{37}H_{35}N_3O_4$: C 75.88 %, H 6.02 %, N 7.17 %; found C 75.90 %, H 6.32 %, N 6.98 %.

Compounds 43a-46a. The synthetic procedure was analogous to that described for compound **49**.

1,3-Bis(phthalimidomethyl)-5-phenoxymethyl-2,4,6-triethylbenzene (43a).

Compound **43a** was prepared from **48** (500 mg, 0.87 mmol) and phenol (152 mg, 1.62 mmol). Yield 65 % (332 mg, 0.57 mmol).

1,3-Bis(phthalimidomethyl)-5-(2-methoxyphenoxymethyl)-2,4,6-triethylbenzene (44a).

Compound **44a** was prepared from **48** (500 mg, 0.87 mmol) and guaiacol (201 mg, 1.62 mmol). Yield 67 % (360 mg, 0.58 mmol).

1,3-Bis(phthalimidomethyl)-5-(3-methoxyphenoxymethyl)-2,4,6-triethylbenzene (45a).

Compound **45a** was prepared from **48** (503 mg, 0.88 mmol) and 3-methoxyphenol (212 mg, 1.71 mmol). Yield 63 % (339 mg, 0.55 mmol).

1,3-Bis(phthalimidomethyl)-5-(4-methoxyphenoxymethyl)-2,4,6-triethylbenzene (46a).

Compound **46a** was prepared from **48** (500 mg, 0.87 mmol) and 4-methoxyphenol (201 mg, 1.62 mmol). Yield 65 % (350 mg, 0.57 mmol).

General procedure for the synthesis of compounds 25 and 34-38.

A solution of the corresponding triethylbenzene derivative **30, 43a- 46a** or **49** in toluene/ethanol [30 mL, 2:1 (*v/v*)] was refluxed with hydrazine hydrate (64%) for 16 h. After cooling down to

This article is protected by copyright. All rights reserved.

Accepted Manuscript

room temperature, the reaction mixture containing a precipitate was stirred and a solution of 40% aq. KOH was added until the solid was completely dissolved. Then the organic phase was separated, dried over magnesium sulfate and the solvent was removed under vacuum. All products except **35** were obtained as a white solid; **35** was obtained as pale brown solid.

1,3-Bis(aminomethyl)-5-(*tert*-butoxycarbonyloxymethyl)-2,4,6-triethylbenzene (25). Compound **25** was prepared from **30** (545 mg, 0.89 mmol) and hydrazine hydrate (180 µL, 3.59 mmol). Yield 86 % (267 mg, 0.76 mmol); m.p. 87-90 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.6 Hz, 6H), 1.21 (t, *J* = 7.5 Hz, 3H), 1.48 (s, 9H), 2.79 (q, J = 7.6 Hz, 4H), 2.82 (q, *J* = 7.5 Hz, 2H), 3.86 (s, 4H), 5.19 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.6, 16.7, 22.7, 27.8, 39.5, 63.2, 82.1, 129.4, 137.3, 142.5, 142.6, 153.7 ppm; HRMS (ESI): *m/z* calcd for $C_{20}H_{34}N_2O_3$+H^+: 351.26422 $[M+H]^+$, found: 351.26411.

1,3-Bis(aminomethyl)-5-phenoxymethyl-2,4,6-triethylbenzene (34). Compound **34** was prepared from **43a** (581 mg, 0.94 mmol) and hydrazine hydrate (175 µL, 3.50 mmol). Yield 87 % (291 mg, 0.82 mmol); m.p. 109 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.5 Hz, 6H), 1.26 (t, *J* = 7.5 Hz, 3H), 2.82 (q, *J* = 7.5 Hz, 4H), 2.88 (q, *J* = 7.5 Hz, 2H), 3.91 (s, 4H), 5.03 (s, 2H), 6.99-7.02 (m, 1H), 7.03-7.06 (m, 2H), 7.32 – 7.36 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.7, 16.8, 22.6, 22.7, 39.7, 64.1, 114.5, 120.9, 129.5, 130.8, 137.5, 142.45, 142.46, 159.0 ppm; HRMS (ESI): *m/z* calcd for $C_{21}H_{30}N_2O$+H^+: 327.24309 $[M+H]^+$, found: 327.24337.

1,3-Bis(aminomethyl)-5-phenylaminomethyl-2,4,6-triethylbenzene (35). Compound **35** was prepared from **49** (357 mg, 0.61 mmol) and hydrazine hydrate (118 µL, 2.44 mmol). Yield 83 % (171 mg, 0.52 mmol); m.p. 173 – 176 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.22 – 1.28 (m, 9H), 2.79 (q, *J* = 7.5 Hz, 4H), 2.87 (q, *J* = 7.5 Hz, 2H), 3.54 (t, *J* = 4.4 Hz, 1H), 3.90 (s, 4H), 4.19 (d, *J* = 4.4 Hz, 2H), 6.66 – 6.69 (m, 2H), 6.73 – 6.76 (m, 1H), 7.22-7.28 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.9, 17.0, 22.7, 39.7, 42.1, 112.4, 117.3, 129.4, 133.1, 137.6, 141.5, 141.7, 148.3 ppm; HRMS (ESI): *m/z* calcd for $C_{21}H_{30}N_3$+H^+: 326.25907 $[M+H]^+$, found: 326.25773.

1,3-Bis(aminomethyl)-5-(2-methoxyphenoxymethyl)-2,4,6-triethylbenzene (36). Compound **36** was prepared from **44a** (324 mg, 0.53 mmol) and hydrazine hydrate (103 µL, 2.10 mmol). Yield 90 % (169 mg, 0.47 mmol); m.p. 97 – 100 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.5 Hz, 3H), 1.25 (t, *J* = 7.6 Hz, 6H), 2.86 (q, *J* = 7.5 Hz, 2H), 2.87 (q, *J* = 7.6 Hz, 4H), 3.83 (s, 3H), 3.90 (s, 4H), 5.04 (s, 2H), 6.93 – 7.02 (m, 3H), 7.12 – 7.14 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.7, 16.8, 22.7, 39.7, 55.8, 66.0, 112.1, 115.0, 120.8, 121.8, 131.0, 137.4,

This article is protected by copyright. All rights reserved.

Accepted Manuscript

142.2, 142.6, 148.7, 150.4 ppm; HRMS (ESI): *m/z* calcd for $C_{22}H_{32}N_2O_2$+H^+: 357.25366 $[M+H]^+$, found: 357.25431.

1,3-Bis(aminomethyl)-5-(3-methoxyphenoxymethyl)-2,4,6-triethylbenzene (37). Compound **37** was prepared from **45a** (217 mg, 0.35 mmol) and hydrazine hydrate (75 µL, 1.33 mmol). Yield 89 % (111 mg, 0.31 mmol); m.p. 215 °C (decomp.); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.6 Hz, 6H), 1.25 (t, *J* = 7.5 Hz, 3H), 2.80 (q, *J* = 7.6 Hz, 4H), 2.86 (q, *J* = 7.5 Hz, 2H), 3.79 (s, 3H), 3.89 (s, 4H), 5.01 (s, 2H), 6.54 – 6.60 (m, 2H), 6.64 – 6.66 (m, 1H), 7.23 (t, *J* = 8.3 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.85, 16.89, 22.7, 22.8, 39.7, 55.4, 64.3, 101.2, 106.4, 106.8, 130.1, 130.8, 137.5, 142.5, 142.6, 160.3, 160.9 ppm; HRMS (ESI): *m/z* calcd for $C_{22}H_{32}N_2O_2$+ H^+: 357.25366 $[M+H]^+$, found: 357.25378.

1,3-Bis(aminomethyl)-5-(4-methoxyphenoxymethyl)-2,4,6-triethylbenzene (38). Compound **38** was prepared from **46a** (80 mg, 0.13 mmol) and hydrazine hydrate (23 µL, 0.47 mmol). Yield 87 % (40 mg, 0.11 mmol); m.p. 200 °C (decomp.); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.6 Hz, 6H), 1.25 (t, *J* = 7.6 Hz, 3H), 2.82 (q, *J* = 7.6 Hz, 4H), 2.87 (q, *J* = 7.6 Hz, 2H), 3.80 (s, 3H), 3.91 (s, 4H), 4.97 (s, 2H), 6.87 – 6.91 (m, 2H), 6.95 – 7.00 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.71, 15.75, 21.6, 21.7, 38.6, 54.7, 63.8, 113.7, 114.4, 130.0, 136.4, 141.3, 141.4, 152.2, 152.9 ppm; HRMS (ESI): *m/z* calcd for $C_{22}H_{32}N_2O_2$+H^+: 357.25366 $[M+H]^+$, found: 357.25410.

Experimental data for the by-products 32, 33, 39b-46b, 41c and 43c-46c.

3,5-Bis(phthalimidomethyl)-2,4,6-triethylbenzaldehyde (32). R_f = 0.53 [toluene/ethyl acetate, 5:1 (*v*/*v*)]; m.p. 172 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.01 (t, *J* = 7.6 Hz, 3H), 1.10 (t, *J* = 7.5 Hz, 6H), 3.01 (q, *J* = 7.5 Hz, 4H), 3.20 (q, *J* = 7.6 Hz, 2H), 4.96 (s, 4H), 7.69 – 7.72 (m, 4H), 7.79 – 7.83 (m, 4H), 10.58 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.6, 16.3, 22.5, 23.8, 36.6, 123.2, 130.2, 131.8, 133.4, 134.1, 145.6, 149.9, 168.1, 195.9 ppm; HRMS (ESI): *m/z* calcd for $C_{31}H_{28}N_2O_5$+ Na^+: 531.18904 $[M+Na]^+$, found 531.18818.

1,3-Bis(hydroxymethyl)-5-phthalimidomethyl-2,4,6-triethylbenzene (33). R_f = 0.04 [toluene/ethyl acetate, 5:1 (*v*/*v*)]; m.p. 176 – 180 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.12 (t, *J* = 7.5 Hz, 6H), 1.25 (t, *J* = 7.5 Hz, 3H), 2.93 (q, *J* = 7.5 Hz, 2H), 3.01 (q, *J* = 7.5 Hz, 4H), 4.76 (d, *J* = 4.7 Hz, 4H), 4.94 (s, 2H), 7.68 – 7.72 (m, 2H), 7.77 – 7.80 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$/CD_3OD 5:1 *v*/*v*): δ = 16.3, 16.8, 22.6, 23.0, 37.5, 58.3, 123.4, 129.2, 131.9, 134.5, 134.6, 144.4, 144.8, 168.8 ppm; HRMS (ESI): *m/z* calcd for $C_{23}H_{27}NO_4$+Na^+: 404.18323 $[M+Na]^+$, found 404.18224.

This article is protected by copyright. All rights reserved.

Accepted Manuscript

1,3-Bis(phenoxymethyl)-5-(bromomethyl)-2,4,6-triethylbenzene (39b). Yield 8 % (0.09 g, 0.18 mmol); R_f = 0.19 [toluene/hexane, 1:4 (*v/v*)]; m.p. 167 – 168 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.6 Hz, 3H), 1.30 (t, *J* = 7.6 Hz, 6H), 2.81 (q, *J* = 7.6 Hz, 2H), 2.91 (q, *J* = 7.6 Hz, 4H), 4.67 (s, 2H), 5.05 (s, 4H), 6.99 – 7.05 (m, 6H), 7.33 – 7.36 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.1, 16.3, 22.90 23.0, 29.3, 63.9, 114.5, 121.0, 129.5, 131.4, 131.9, 145.6, 146.4, 158.8 ppm; MS (APCI): *m/z* calcd for $C_{27}H_{31}BrO_2$ +NH_4^+: 486.18 $[M+NH_4]^+$, found 486.20.

1,3-Bis(2-methoxyphenoxymethyl)-5-(bromomethyl)-2,4,6-triethylbenzene (40b). Yield 11 % (0.25 g, 0.46 mmol); R_f = 0.08 [toluene/hexane, 2:1 (*v/v*)]; m.p. 138 – 140 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.6 Hz, 3H), 1.31 (t, *J* = 7.6 Hz, 6H), 2.90 (q, *J* = 7.6 Hz, 2H), 2.95 (q, *J* = 7.6 Hz, 4H), 3.82 (s, 6H), 4.67 (s, 2H), 5.06 (s, 4H), 6.91 – 7.01 (m, 6H), 7.11 (dd, *J* = 7.6/1.8 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.3, 16.5, 23.0, 23.2, 29.8, 55.9, 65.7, 112.2, 114.7, 120.9, 121.9, 131.5,131.6, 145.9, 147.1, 148.7, 150.4 ppm; HRMS (ESI): *m/z* calcd for $C_{29}H_{35}BrO_4$+Na^+: 551.15952 $[M+Na]^+$, found 551.16023.

1,3-Bis(3-methoxyphenoxymethyl)-5-(bromomethyl)-2,4,6-triethylbenzene (41b). Yield 22 % (0.46 g, 0.87 mmol); R_f = 0.23 [toluene/hexane, 2:1 (*v/v*)]; m.p. 118 – 121 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.6 Hz, 3H), 1.30 (t, *J* = 7.6 Hz, 6H), 2.80 (q, *J* = 7.6 Hz, 2H), 2.91 (q, *J* = 7.6 Hz, 4H), 3.81 (s, 6H), 4.67 (s, 2H), 5.03 (s, 4H), 6.56 – 6.59 (m, 4H), 6.63 – 6.66 (m, 2H), 7.24 (t, *J* = 8.1 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.1, 16.3, 22.8, 22.9, 29.3, 55.3, 64.0, 101.1, 106.4, 106.6, 130.0, 131.3, 131.9, 145.6, 146.4, 160.1, 160.9 ppm; HRMS (ESI): *m/z* calcd for $C_{29}H_{35}BrO_4$+Na^+: 551.15952 $[M+Na]^+$, found 551.16172.

1,3,5-Tris(3-methoxyphenoxymethyl)-2,4,6-triethylbenzene (41c). Yield 2 % (0.05 g, 0.08 mmol); m.p. 116 – 118 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.5 Hz, 9H), 2.83 (q, *J* = 7.5 Hz, 6H), 3.81 (s, 9H), 5.06 (s, 6 H), 6.55 – 6.66 (m, 6H), 6.65 (dd, *J* = 8.2/2.3 Hz, 3H), 7.23 (d, *J* = 8.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.4, 22.9, 55.3, 64.1, 101.1, 106.4, 106.7, 129.9, 131.0, 146.2, 160.2, 160.9 ppm; MS (ESI): *m/z* calcd for $C_{36}H_{42}O_6$+Na^+: 593.29 $[M+Na]^+$, found 593.32.

1,3-Bis(4-methoxyphenoxymethyl)-5-(bromomethyl)-2,4,6-triethylbenzene (42b). Yield 30 % (0.18 g, 0.34 mmol); R_f = 0.05 [toluene/hexane, 1:2 (*v/v*)]; m.p. 153 – 155 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.5 Hz, 3H), 1.30 (t, *J* = 7.6 Hz, 6H), 2.81 (q, *J* = 7.5 Hz, 2H), 2.91 (q, *J* = 7.6 Hz, 4H), 3.80 (s, 6H), 4.67 (s, 2H), 4.99 (s, 4H), 6.88 – 6.90 (m, 4H), 6.96 – 6.98 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.1, 16.4, 22.8, 22.9, 29.4, 55.7, 64.5, 114.7, 115.3, 131.6, 131.8, 145.4, 146.2, 153.0, 154.0 ppm; MS (ESI): *m/z* calcd for

This article is protected by copyright. All rights reserved.

Accepted Manuscript

$C_{29}H_{35}BrO_4$+ NH_4^+: 546.20 $[M+NH_4]^+$, found 546.36; elemental analysis calcd (%) for $C_{29}H_{35}BrO_4$: C 66.03 %, H 6.69 %; found C 65.98 %; H 6.60 %.

3-Phenoxymethyl-5-phthalimidomethyl-2,4,6-triethylbenzdehyde (43b). R_f = 0.43 [toluene/ethyl acetate, 11:1 (*v/v*)]; m.p. 78 – 82 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.11 – 1.15 (m, 6H), 1.24 (t, *J* = 7.5 Hz, 3H), 2.90 (q, *J* = 7.5 Hz, 2H), 3.00 (q, *J* = 7.6 Hz, 2H), 3.11 (q, *J* = 7.5 Hz, 2H), 4.99 (s, 2H), 5.06 (s, 2H), 7.00 – 7.01 (m, 1H), 7.02 – 7.04 (m, 2H), 7.33 – 7.36 (m, 2H), 7.71 – 7.72 (m, 2H), 7.81 – 7.82 (m, 2H), 10.62 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.0, 16.5, 16.7, 22.5, 22.7, 23.6, 36.6, 63.3, 114.7, 121.2, 123.4, 129.7, 130.4, 131.6, 131.9, 133.4, 134.3, 146.2, 146.8, 149.9, 158.8, 168.3, 195.8 ppm; MS (ESI): *m/z* calcd for $C_{29}H_{29}NO_4$+Na^+: 478.20 $[M+Na]^+$, found 478.20.

1-Hydroxymethyl-3-phenoxymethyl-5-phthalimidomethyl-2,4,6-triethylbenzene (43c). R_f = 0.15 [toluene/ethyl acetate, 11:1 (*v/v*)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.08 (t, *J* = 7.5 Hz, 3H), 1.13 (t, *J* = 7.5 Hz, 3H), 1.24 (t, *J* = 7.5 Hz, 3H), 2.87 (q, *J* = 7.5 Hz, 2H), 2.94 (q, *J* = 7.6 Hz, 2H), 3.07 (q, *J* = 7.5 Hz, 2H), 4.78 (s, 2H), 4.96 (s, 2H), 5.04 (s, 2H), 6.97 – 6.99 (m, 1H), 7.00 – 7.02 (m, 2H), 7.30 – 7.34 (m, 2H), 7.66 – 7.69 (m, 2H), 7.75 – 7.77 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.2, 16.6, 16.8, 22.9, 23.1, 37.4, 59.1, 64.2, 114.6, 121.0, 123.3, 129.6, 129.9, 131.0, 132.0, 134.2, 134.9, 144.9, 145.6, 145.7, 159.0, 168.3 ppm; HRMS (ESI): *m/z* calcd for $C_{29}H_{31}NO_4$+Na^+: 480.21453 $[M+Na]^+$, found: 480.21536.

3-(2-Methoxyphenoxymethyl)-5-phthalimidomethyl-2,4,6-triethylbenzaldehyde (44b). R_f = 0.50 [toluene/ethyl acetate, 5:1 (*v/v*)]; m.p. 136 – 139 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.11 – 1.15 (m, 6H), 1.25 (t, *J* = 7.5 Hz, 3H), 2.97 (q, *J* = 7.5 Hz, 2H), 3.03 (q, *J* = 7.6 Hz, 2H), 3.12 (q, *J* = 7.5 Hz, 2H), 3.82 (s, 3H), 4.98 (s, 2H), 5.07 (s, 2H), 6.91 – 7.02 (m, 3H), 7.09 – 7.11 (m, 1H), 7.69 – 7.72 (m, 2H), 7.79 – 7.82 (m, 2H), 10.62 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.9, 16.4, 16.7, 22.4, 22.7, 23.5, 36.5, 55.8, 65.1, 112.2, 115.4, 120.9, 122.2, 123.2, 130.2, 131.7, 131.9, 133.2, 134.1, 146.4, 146.7, 148.4, 150.0, 150.5, 168.1, 195.8 ppm; MS (ESI): *m/z* calcd for $C_{30}H_{31}NO_5$+Na^+: 508.21 $[M+Na]^+$, found 508.19.

1-Hydroxymethyl-3-(3-methoxyphenoxymethyl)-5-phthalimidomethyl-2,4,6-triethylbenzene (44c). R_f = 0.13 [toluene/ethyl acetate, 5:1 (*v/v*)]; m.p. 110 – 112 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.10 (t, *J* = 7.5 Hz, 3H), 1.12 (t, *J* = 7.5 Hz, 3H), 1.25 (t, *J* = 7.5 Hz, 3H), 2.93 (q, *J* = 7.5 Hz, 2H), 2.97 (q, *J* = 7.5 Hz, 2H), 3.08 (q, *J* = 7.5 Hz, 2H), 3.78 (s, 3H), 4.76 (s, 2H), 4.95 (s, 2H), 5.06 (s, 2H), 6.89 – 6.99 (m, 3H), 7.09 – 7.11 (m, 1H), 7.65 – 7.67 (m, 2 H), 7.73 – 7.76 (m, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.1, 16.5, 16.7, 22.9, 23.0,

This article is protected by copyright. All rights reserved.

Accepted Manuscript

37.3, 55.8, 59.1, 66.0, 112.2, 115.1, 120.9, 121.9, 123.2, 129.6, 131.2, 131.9, 134.0, 134.8, 145.1, 145.6 145.7, 148.6, 150.5, 168.3 ppm; HRMS (ESI): *m/z* calcd for $C_{30}H_{33}NO_5$+Na^+: 510.22509 $[M+Na]^+$, found: 510.22696.

3-(3-Methoxyphenoxymethyl)-5-phthalimidomethyl-2,4,6-triethylbenzaldehyde (45b). R_f = 0.57 [toluene/ethyl acetate, 5:1 (*v/v*)]; m.p. 130 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.10 – 1.14 (m, 6H), 1.23 (t, *J* = 7.5 Hz, 3H), 2.89 (q, *J* = 7.5 Hz, 2H), 2.99 (q, *J* = 7.6 Hz, 2H), 3.10 (q, *J* = 7.5 Hz, 2H), 3.80 (s, 3H), 4.98 (s, 2H), 5.03 (s, 2H), 6.56 – 6.58 (m, 2H), 6.62 – 6.64 (m, 1H), 7.22 – 7.25 (m, 1H), 7.70 – 7.73 (m, 2H), 7.79 – 7.82 (m, 2H), 10.62 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.9, 16.4, 16.6, 22.4, 22.6, 23.5, 36.5, 55.3, 63.2, 101.1, 106.6, 106.7, 123.3, 130.0, 130.3, 131.4, 131.8, 133.3, 134.2, 146.1, 146.7, 149.8, 160.0, 160.9, 168.1, 195.6 ppm; HRMS (ESI): *m/z* calcd for $C_{30}H_{31}NO_5$+Na^+: 508.20944 $[M+Na]^+$, found: 508.20951.

1-Hydroxymethyl-3-(3-methoxyphenoxymethyl)-5-phthalimidomethyl-2,4,6-triethylbenzene (45c). R_f = 0.16 [toluene/ethyl acetate, 5:1 (*v/v*)]; m.p. 154 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.08 (t, *J* = 7.6 Hz, 3H), 1.14 (t, *J* = 7.5 Hz, 3H), 1.24 (t, *J* = 7.6 Hz, 3H), 2.87 (q, *J* = 7.5 Hz, 2H), 2.94 (q, *J* = 7.6 Hz, 2H), 3.07 (q, *J* = 7.6 Hz, 2H), 3.79 (s, 3H), 4.78 (s, 2H), 4.97 (s, 2H), 5.02 (s, 2H), 6.54 – 6.58 (m, 2H), 6.62 – 6.65 (m, 1H), 7.23 (t, *J* = 8.2 Hz, 1H), 7.69 – 7.71 (m, 2H), 7.79 – 7.81 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.1, 16.4, 16.7, 22.8, 23.0, 23.1, 37.3, 55.3, 59.1, 64.2, 101.1, 106.4, 106.7, 123.2, 129.8, 129.9, 130.9, 131.9, 134.0, 134.8, 144.8, 145.6, 145.7, 160.2, 160.8, 168.2 ppm; HRMS (ESI): *m/z* calcd for $C_{30}H_{33}NO_5$+ Na^+: 510.22509 $[M+Na]^+$, found: 510.22616.

3-(4-Methoxyphenoxymethyl)-5-phthalimidomethyl-2,4,6-triethylbenzaldehyde (46b). R_f = 0.45 [toluene/ethyl acetate, 11:1 (*v/v*)]; m.p. 113 – 115 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.11 – 1.14 (m, 6H), 1.24 (t, *J* = 7.6 Hz, 3H), 2.91 (q, *J* = 7.4 Hz, 2H), 3.00 (q, *J* = 7.7 Hz, 2H), 3.10 (q, *J* = 7.5 Hz, 2H), 3.79 (s, 3H), 4.98 (s, 2H), 5.00 (s, 2H), 6.86 – 6.89 (m, 2H), 6.94 – 6.98 (m, 2H), 7.69 – 7.73 (m, 2H), 7.79 – 7.83 (m, 2H), 10.62 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.0, 16.5, 16.8, 22.5, 22.7, 23.6, 36.6, 55.9, 64.0, 114.9, 115.6, 123.4, 130.4, 131.8, 132.0, 133.4, 134.3, 146.1, 146.7, 149.9, 153.0, 154.3, 168.2, 195.8 ppm; HRMS (ESI): *m/z* calcd for $C_{30}H_{31}NO_5$+Na^+: 508.20944 $[M+Na]^+$, found: 508.20929.

1-Hydroxymethyl-3-(4-methoxyphenoxymethyl)-5-phthalimidomethyl-2,4,6-triethylbenzene (46c). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.08 (t, *J* = 7.5 Hz, 3H), 1.13 (t, *J* = 7.5Hz, 3H), 1.23 (t, *J* = 7.5 Hz, 3H), 2.87 (q, *J* = 7.5 Hz, 2H), 2.94 (q, *J* = 7.5 Hz, 2H), 3.06 (q, *J* = 7.5 Hz, 2H), 3.77 (s, 3H), 4.77 (d, *J* = 4.5 Hz, 2H), 4.96 (s, 2H), 4.98 (s, 2H), 6.85 – 6.88 (m,

This article is protected by copyright. All rights reserved.

Accepted Manuscript

2H), 6.93 – 6.97 (m, 2H), 7.66 – 7.70 (m, 2H), 7.75 – 7.79 (m, 2H) ppm; MS (ESI): *m/z* calcd for $C_{30}H_{33}NO_5$+ Na^+: 510.23 $[M+Na]^+$, found 510.22.

Supporting Information Available. Structures of the macrocyclic compounds bearing two flexible side-arms reported by us previously. Structures of the by-products considered in the Supporting Information. Optimization of the reaction conditions for the formation of compound **39a** (by-products **39b** and **39c**). ^{1}H and ^{13}C NMR spectra of compounds **15-I–18-I** and **15–18** (Figures S1-S15). ^{1}H and ^{13}C NMR spectra of compounds **19-I–24-I** and **19–24** (Figures S16-S39). ^{1}H and ^{13}C NMR spectra of compounds **25**, **26**, **30**, **32 – 46**, **49** (Figures S40-S103). ^{1}H NMR and ITC binding studies (further examples, Figures S104-S107). Schematic illustrations of the binding strength of compounds **15-21** in comparison with that of the previously investigated compounds **12** and **13** (Figures S108 and S109). Examples of molecular modelling calculations (Figure S110). Excerpts from the ROESY spectra of the tested compounds and from the spectra of the receptor-sugar complexes (examples; Figures S111-S114).

Keywords: Molecular Recognition / Receptors / Receptor-Sugar-Complexes / Hydrogen bond donor and acceptor / CH-pi Interactions / Structure-activity relationships

References and footnotes

[1] For examples of 1,3,5-substituted 2,4,6-triethylbenzene derivatives bearing pyridine-, pyrimidine-, purine-, phenanthroline-, naphthyridine-, quinoline-, pyridinium-, quinolinium-, alkyl(cycloalkyl)amino- or oxime-based recognition groups, see: a) M. Stapf, W. Seichter, M. Mazik, *Eur. J. Org. Chem.* **2020**, 4900-4915; b) S. Kaiser, C. Geffert, M. Mazik, *Eur. J. Org. Chem.* **2019**, 7555-7562; c) C. Geffert, M. Kuschel, M. Mazik, *J. Org. Chem.* **2013**, *78*, 292-300; d) M. Mazik, C. Geffert, *Org. Biomol. Chem.* **2011**, *9*, 2319-2326; e) M. Mazik, C. Sonnenberg, *J. Org. Chem.* **2010**, *75*, 6416-6423; f) M. Mazik, A. Hartmann, P. G. Jones, *Chem. Eur. J.* **2009**, *15*, 9147-9159; g) M. Mazik, A. Hartmann, *J. Org. Chem.* **2008**, *73*, 7444-7450; h) M. Mazik, H. Cavga, *Eur. J. Org. Chem.* **2007**, 3633-3638; i) M. Mazik, H. Cavga, *J. Org. Chem.* **2006**, *71*, 2957-2963; j) M. Mazik, A. C. Buthe, *J. Org. Chem.* **2007**, *72*, 8319-8326; k) M. Mazik, A. C. Buthe, *Org. Biomol. Chem.* **2008**, *6*, 1558-1568; l) M. Mazik, W. Radunz, R. Boese, *J. Org. Chem.* **2004**, *69*, 7448-7462.

[2] For examples of acyclic receptors with a triethyl-, trimethyl- or trimethoxybenzene core, including imidazole-, benzimidazole-, indole-, pyrrole-, pyrazole- or pyrimidine-based

This article is protected by copyright. All rights reserved.

Accepted Manuscript

recognition groups, see: a) M. Mazik, M. Kuschel, *Chem. Eur. J.* **2008**, *14*, 2405-2419; b) M. Mazik, S. Hartmann, *Beilstein J. Org. Chem.* **2010**, *6*, No. 9; c) C. Sonnenberg, A. Hartmann, M. Mazik, *Nat. Prod. Commun.* **2012**, *7*, 321-326; d) M. Mazik, H. Cavga, *J. Org. Chem.* **2007**, *72*, 831-838; e) J.-R. Rosien, W. Seichter, M. Mazik, *Org. Biomol. Chem.* **2013**, *11*, 6569-6579; f) J. Lippe, W. Seichter, M. Mazik, *Org. Biomol. Chem.* **2015**, *13*, 11622; g) N. Koch, M. Mazik, *Synthesis* **2016**, *48*, 2757-2767.

[3] For further acyclic receptor molecules composed of a central benzene ring, see: a) M. Mazik, M. Kuschel, W. Sicking, *Org. Lett.* **2006**, *8*, 855-858; b) M. Mazik, W. Sicking, *Tetrahedron Lett.* **2004**, *45*, 3117-3121; c) M. Mazik, W. Sicking, *Chem. Eur. J.* **2001**, *7*, 664-670; d) M. Mazik, H. Bandmann, W. Sicking, *Angew. Chem. Int. Ed.* **2000**, *39*, 551-554; *Angew. Chem.* **2000**, *112*, 562-565; e) M. Mazik, W. Radunz, *Org. Lett.* **2002**, *4*, 4579-4582.

[4] For examples of acyclic carbohydrate receptors consisting of a biphenyl-, diphenylmethane- or dimesitylmethane-based scaffold, see: a) M. Mazik, A. König, *J. Org. Chem.* **2006**, *71*, 7854-7857; b) M. Mazik, A. C. Buthe, *Org. Biomol. Chem.* **2009**, *7*, 2063-2071; c) N. Koch, J.-R. Rosien, M. Mazik, *Tetrahedron* **2014**, *70*, 8758-8767.

[5] J. Lippe; M. Mazik, *J. Org. Chem.* **2013**, *78*, 9013−9020.

[6] J. Lippe, M. Mazik, *J. Org. Chem.* **2015**, *80*, 1427−1439.

[7] F. Amrhein, J. Lippe, M. Mazik, *Org. Biomol. Chem.*, **2016**, *14*, 10648–10659.

[8] a) S. J. Watowich, J. J. Skehel, D. C. Wiley, *Structure* **1994**, *2*, 719–731; b) D.-I. Liao, G. Kapadia, H. Ahmed, G. R. Vasta, O. Herzberg, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 1428–1432; c) H. Lis, N. Sharon, *Lectins;* Kluwer Academic Publishers: Dordrecht, The Netherlands, 2003; d) H. Lis, N. Sharon, *Chem. Rev.*, **1998**, *98*, 637-674; e) W. I. Weiss, K. Drickamer, *Annu. Rev. Biochem.*, **1996**, *65*, 441-473; f) F. A. Quiocho, *Pure. Appl. Chem.*, **1989**, *61*, 1293-1306; g) F. A. Quiocho, D. K. Wilson, *Nature*, **1989**, *340*, 404-407; h) R. U. Lemieux, *Acc. Chem. Res.*, **1996**, *29*, 373–380; i) M. Chandravanshi, P. Gogoi, S. P. Kanaujia, *FEBS J.*, **2020**, *287*, 1576–1597; j) H. J. Gabius, *The Sugar Code – Fundamentals of Glycoscience*, Wiley-Blackwell, **2009**, pp. 233-315; k) H.-J. Gabius, S. André, J. Jiménez-Barbero, A. Romero, D. Solis, *Trends Biochem Sci.*, **2011**, *36*, 298-313; l) N. K. Sauter, G. D. Glick, R. L. Crowther, S. J. Park, M. B. Eisen, J. J. Skehel, J. R. Knowles, D. C. Wiley, *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 324–328; m) T. K. Dam, S. Oscarson, C. F. Brewer, *J. Biol. Chem.* **1998**, *273*, 12082–12088.

[9] M. Mazik, H. Cavga, P. G. Jones, *J. Am. Chem. Soc.* **2005**, *127*, 9045-9052.

[10] a) L. Köhler, W. Seichter, M. Mazik, *Eur. J. Org. Chem.* **2020**, 7023-7034; b) L. Köhler, W. Seichter, C. Hübler, M. Mazik, *RSC Adv.* **2021**, *11*, 22221-22229.

This article is protected by copyright. All rights reserved.

Accepted Manuscript

[11] For reviews on carbohydrate recognition with artificial receptors using noncovalent interactions, see: a) A. P. Davis, T. D. James, In *Functional Synthetic Receptors;* (Eds.: T. Schrader, A. D. Hamilton), Wiley-VCH, Weinheim, **2005**, p 45-109; b) D. B. Walker, G. Joshi, A. P. Davis, *Cell. Mol. Life Sci*. **2009**, *66*, 3177-3191; c) M. Mazik, *Chem. Soc. Rev.* **2009**, *38*, 935-956; d) S. Jin, Y. Cheng, S. Reid, M. Li, B. Wang, *Med. Res. Rev.* **2010**, *30*, 171-257; e) A. P. Davis, *Org. Biomol. Chem*. **2009**, *7*, 3629-3638; f) S. Kubik, *Angew. Chem. Int. Ed.* **2009**, *48*, 1722-1725; *Angew. Chem.* **2009**, *121*, 1750-1753; g) M. Mazik, *ChemBioChem.* **2008**, *9*, 1015-1017; h) M. Mazik, *RSC Adv.* **2012**, *2*, 2630-2642; i) T. K. Lindhorst, S. Kubik, S. *Supramolecular Approaches to the Study of Glycobiology*, in *Supramolecular Chemistry: from Molecules to Nanomaterials*, (Eds.: J. W. Steed, P. A. Gale), John Wiley & Sons Ltd., Chichester, UK, **2012**, pp 1685-1712; j) C. E. Miron, A. Petitjean, *ChemBioChem.* **2015**, *16*, 365-379; j) A. P. Davis, *Chem. Soc. Rev.* **2020**, *49*, 2531-2545.

[12] For recent examples of binding studies with artificial carbohydrate receptors operating via noncovalent interactions, see refs. 1a,b and: a) Y. Ohishi, K. Masuda, K. Kudo, H. Abe, M. Inouye, *Chem. Eur. J.*, **2021**, *27*, 785-793; b) P. Mateus, N. Chandramouli, C. D. Mackereth, B. Kauffmann, Y. Ferrand, I. Huc, *Angew. Chem. Int. Ed.*, **2020**, *59*, 5797–5805; *Angew. Chem.*, **2020**, *132*, 5846–5854; c) M. F. Bravo, K. Palanichamy, M. A. Shlain, F. Schiro, Y. Naeem, M. Marianski, A.B. Braunschweig, *Chem. Eur. J.*, **2020**, *26*, 11782-11795; d) R. A. Tromans, T. S. Carter, L. Chabanne, M. P. Crump, H. Li, J. V. Matlock, M. G. Orchard, A. P. Davis, *Nat. Chem.*, **2019**, *11*, 52-56; e) P. Stewart, C. M. Renney, T. J. Mooibroek, S. Ferheen, A. P. Davis, *Chem. Commun.*, **2018**, *54*, 8649-8652; f) P. Mateus, B. Wicher, Y. Ferrand, I. Huc, *Chem. Commun.*, **2018**, *54*, 5078-5081; g) S. Saha, B. Kauffmann, Y. Ferrand, I. Huc, *Angew. Chem. Int. Ed.*, **2018**, *57*, 13542-13546; h) O. Francesconi, M. Martinucci, L. Badii, C. Nativi, S. A. Roelens, *Chem. Eur. J.*, **2018**, *24*, 6828-6836; i) K. Palanichamy, M. F. Bravo, M. A. Shlain, F. Schiro, Y. Naeem, M. Marianski, A. B. Braunschweig, *Chem. Eur. J.*, **2018**, *24*, 13971-13982.

[13] For further examples of binding studies with receptors operating via noncovalent interactions, see: a) P. Rios, T. J. Mooibroek, T. S. Carter, C. Williams, M. R. Wilson, M. P. Crump, A.P. Davis, *Chem. Sci.*, **2017**, *8*, 4056-4061; b) Y. Ohishi, H.Abe, M. Inouye, *Eur. J. Org. Chem.*, **2017**, 6975-6979; c) T. J. Mooibroek, J. M.Casas-Solvas, R. L. Harniman, C. M. Renney, T. S. Carter, M. P. Crump, A. P. Davis, *Nature Chem.*, **2016**, *8*, 69-74; d) N. Chandramouli, Y. Ferrand, G. Lautrette, B. Kauffmann, C. D. Mackereth, M. Laguerre, D. Dubreuil, I. Huc, *Nature Chem.*, **2015**, 7, 334-341; e) M. Rauschenberg, S. Bandaru, M. P. Waller, B. J. Ravoo, *Chem. Eur. J.*, **2014**, *20*, 2770-2782; f) O. Francesconi, M. Gentili, C.

This article is protected by copyright. All rights reserved.

Accepted Manuscript

Nativi, A. Ardá, F. J. Cañada, J. Jiménez-Barbero, S. Roelens, *Chem. Eur. J.* **2014,** *20*, 6081-6091; g) Y. Jang, R. Natarajan, Y. H. Ko, K. Kim, *Angew. Chem., Int. Ed.*, **2014**, *53*, 1003-1007; *Angew. Chem.* **2014**, *53*, 1003-1007.

[14] a) N. Sharon, H. Lis, *Sci. Am.* **1993**, *268(1)*, 74-81; b) N. Sharon, H. Lis, *Science* **1989**, *246*, 227-234; c) N. Sharon, *Nature Struct. Biol.* **1994**, *1*, 843-845; d) M. Mazik Aminonaphthydrine Derivatives. EP 2 139 889 B1, **2008**; e) M. Mazik; Balzarini, J. Anti-infective agents. EP 2 139 463 B1, **2008**.

[15] F. Amrhein, A. Schwarzer, M. Mazik, *Acta Cryst. E77*, **2021**, 233-236.

[16] (a) N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand, W. M. Weaver, *J. Am. Chem. Soc.* **1957**, *79*, 6562; (b) N. Kornblum, W. J. Jones, G. J. Anderson, *J. Am. Chem. Soc.* **1959**, *81*, 4113-4114.

[17] G. Bartoli, M. Bosco, A. Carlone, R. Dalpozzo, M. Locatelli, P. Melchiorre, P. Palazzi, L. Sambri, *Synlett* **2006**, *13*, 2104–2108.

[18] a) M. D. Best, E. V. Anslyn, *Chem. Eur. J.*, **2003**, *9*, 51–57; b) S. L. Wiskur, J. J. Lavigne, A. Metzger, S. L. Tobey, V. Lynch, E. V. Anslyn, *Chem. Eur. J.*, **2004**, *10*, 3792–3804; c) L. A. Cabell, M. D. Best, J. J. Lavigne, S. E. Schneider, D. M., Perreault, M.-K. Monahan, E. V. Anslyn, *J. Chem. Soc., Perkin Trans. 2*, **2001**, *3*, 315–323; For NMR data of **26c**, see: d) A. Davis, R. Tromans, M. R. Wilson, M. G. Orchard, A. M. Chapman, M. R. Tomsett, J. V. Matlock, Macrocyclic Compounds. WO 2018/167503, **2018**.

[19] B. Singh, H. Lobo, G. Shankarling, *Catal. Lett.* **2011**, *141*, 178-182.

[20] M. J. Hynes, *J. Chem. Soc., Dalton Trans.* **1993**, 311-312.

[21] a) C. Frassineti, S. Ghelli, P. Gans, A. Sabatini, M. S. Moruzzi, A. Vacca, *Anal. Biochem.* **1995**, *231*, 374-382; b) C. Frassineti, L. Alderighi, P. Gans, A. Sabatini, A. Vacca, S. Ghelli, *Anal. Bioanal. Chem.* **2003**, *376*, 1041-1052.

[22] Program SupraFit: https://github.com/conradhuebler/SupraFit; C. Hübler, Institut für Organische Chemie, TU Freiberg, DOI 10.5281/zenodo.3364569.

[23] For a description of the mole ratio method, see: a) H.-J. Schneider, A. Yatsimirsky, *Principles and Methods in Supramolecular Chemistry*; John Wiley & Sons, Chichester, **2000**, p 148; b) H. Tsukube, H. Furuta, A. Odani, Y. Takeda, Y. Kudo, Y. Inoue, H. Liu, K. Sakamoto, K. Kimura, in *Comprehensive Supramolecular Chemistry* (Eds.: J.-L. Atwood, J. E. D. Davis, D. D. MacNicol, F. Vögtle), Vol. 8, Pergamon: Oxford, **1996**; p 425.

[24] For examples of other macrocyclic carbohydrate receptors bearing pyrrole-based bridges, see ref. 13f and: (a) G. Joshi, A. P. Davis,. *Org. Biomol. Chem.* **2012**, *10*, 5760-5763; (b) O.

This article is protected by copyright. All rights reserved.

Accepted Manuscript

Francesconi, A. Ienco, G. Moneti, C. Nativi, S. Roelens, *Angew. Chem. Int. Ed.* **2006**, *45*, 6693-6696.

[25] For discussions on the importance of carbohydrate-arene interactions, see: a) J. Houser, S. Kozmon, D. Mishra, Z. Hammerová, M. Wimmerová, J. Koća, *Chem. Eur. J.* **2020**, *26*, 10769–10780; b) J. L. Asensio, A. Ardá, F. J. Caňada, J. Jiménez-Barbero, *Acc. Chem. Res.*, **2013**, *46*, 946-954; c) S. Tsuzuki, T. Uchimaru, M. Mikami, *J. Phys. Chem. B*, **2009**, *113*, 5617-5621; d) G. Terraneo, D. Potenza, A. Canales, J. Jiménez-Barbero, K. K. Baldridge, A. A. Bernardi, *J. Am. Chem. Soc.*, **2007**, *129*, 2890-2900; e) M. I. Chávez, C. Andreu, P. Vidal, N. Aboitiz, F. Freire, P. Groves, J. L. Asensio, G. Asensio, M. Muraki, F. J. Caňada, J. Jiménez-Barbero, *Chem. Eur. J.*, **2005**, *11*, 7060-7074; f) J. Screen, E. C. Stanca-Kaposta, D. P. Gamblin, B. Liu, N. A. Macleod, L. C. Snoek, B. G. Davis, J. P. Simons, *Angew. Chem. Int. Ed.*, **2007**, *46***,** 3644-3648; g) S. H. Kiehna, Z. R. Laughrey, M. L. Waters, *Chem. Commun.*, **2007**, 4026-4028.

[26] E. J. Toone, *Curr. Opin. Struct. Biol.* **1994**, *4*, 719-728.

[27] F. Biedermann, H.-J. Schneider, *Chem. Rev.*, **2016**, ***116***, 5216-5300.

[28] For reviews on supramolecular complexations, see: a) H.-J. Schneider, P. Agrawal, A. K. Yatsimirsky, *Chem. Soc. Rev.*, **2013**, *42*, 6777-6800; b) H.-J. Schneider, *Angew. Chem. Int. Ed.* **2009**, *48*, 3924-3977; *Angew. Chem.* **2009**, *121*, 3982-4036.

[29] G. Sudhakar, V. D. Kadam, S. Bayya, G. Pranitha, B. Jagadeesh, *Org. lett.* **2011**, *13*, 5452-5455.

[30] K. J. Wallace, R. Hanes, E. Anslyn, J. Morey, K. V. Kilway, J. Siegel, *Synthesis* **2005**, *12*, 2080-2083.

[31] H.-S. Kim, D.-H. Kim, K. S. Kim, H.-J. Choi, J. H. Shim, I. S. Jeong, G. S. Cha, H. Nam, *J. Inclusion Phenom. Macrocyclic Chem.* **2003**, *46*, 201-205.

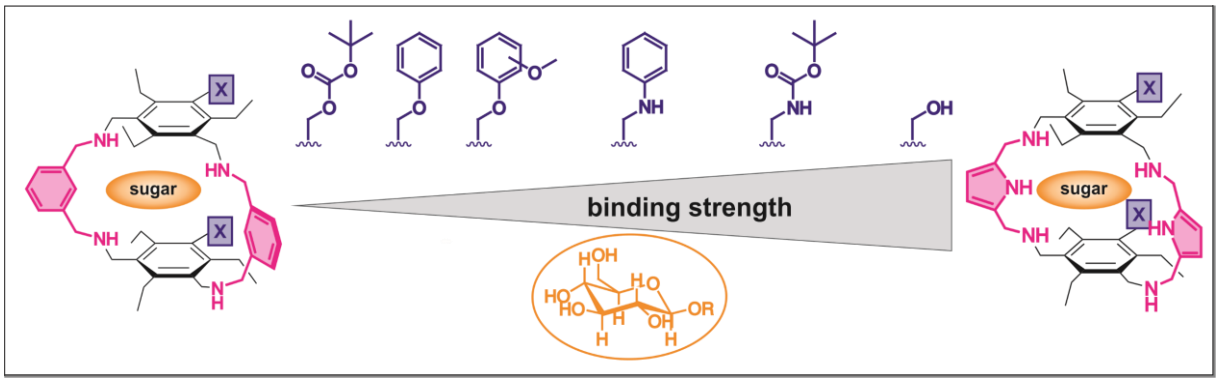
[32] M. Stapf, B. Leibiger, A. Schwarzer, M. Mazik, *Acta Cryst. E77*, **2021**, https://doi.org/10.1107/S205698902100788X.

Graphical Abstract

This article is protected by copyright. All rights reserved.

Accepted Manuscript

10.1002/ejoc.202100758



Key Topics: Artificial Carbohydrate Receptors, Molecular Recognition of Carbohydrates

Short Text: Structure-binding activity relationship studies with compounds consisting of a macrocyclic building block and flexible side-arms revealed the essential role of the side-arms in achieving strong complexation of all-equatorial substituted sugars, such as β-D-glucopyranoside.

Accepted Manuscript

This article is protected by copyright. All rights reserved.