Synthesis of Macrocyclic, Triazine-Based Receptor Molecules

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The synthesis of triazine-based macrocyclic scaffolds is presented. The strategy employed allows for the facile functionalization of the macrocyclic molecules and combinatorial construction of putative receptor molecules. It is shown that the functional groups on the macrocyclic molecules, the size of the rings and the nature of the diamines linking the triazines can all be varied. In addition to the description of the stepwise synthesis of these compounds, it is shown that macrocycles based on triazine and xylenediamine are able to bind pyranosides and cyanuric acid.

Introduction

Supramolecular receptor chemistry has progressed considerably over the last few decades.[1] Beginning with the complexation of simple ligands such as inorganic and small organic ions,[2] increasingly more elaborate structures have been designed in order selectively to recognize more complex ligands.[3] A further challenge has become the design of molecules that are able to interact selectively with biologically interesting compounds such as oligopeptides,[4] proteins[5] and carbohydrates.[6] However, the design of synthetic receptors for such molecules is a difficult task. Given the enormous diversity of potential biological targets in nature, the preferred receptor molecule would have a structure and functionality that might be modified easily in a way that would complement its target. The archetypal answer to this multiple recognition problem, antibodies, consist of a polypeptide scaffold that forms the foundation for a hypervariable region able to recognize its target antigen with high affinity and selectivity.[7] Inspired by nature, it is our opinion that macrocyclic molecules with a well defined structure could be employed for such a purpose, especially when utilized as scaffolds in a combinatorial synthesis, rapidly affording a variety of potential receptor molecules. Indeed, some success with such an approach has already been reported in the literature.[8] However, whilst many macrocyclic molecules have been synthesized to date,[9] their synthesis is in most cases difficult and/or relatively inflexible towards functionalization.[10] A stepwise approach which allows for a combinatorial synthesis seems to be an attractive proposition. Here we report a synthetic route to functionalizable macrocycles based on building blocks comprising a triazine ring and a diamine linker. Triazine was chosen as a constituent of the ring molecules in view of our interest in the moiety and previous success in using it as part of an affinity ligand.[11] Furthermore, triazine-based compounds have been shown to perform well as recognition elements, providing both hydrogen bond donor and acceptor sites[12] for the recognition of biological targets. Again, this feature is exemplified in nature, in which many protein-carbohydrate complexes are stabilized by the formation of numerous hydrogen bonds with the hydroxyl groups present.[13] Moreover, the melamine moieties were expected to exhibit affinity for sugars in a similar fashion to 2-aminopyridines, which have already been shown to act as recognition motifs in receptor molecules associating with carbohydrates.[14]

We adopted a stepwise approach for the synthesis of the proposed triazine-based macrocycles. The somewhat laborious nature of such an approach is greatly compensated for by the high level of control it is possible to achieve over the size and functionality of the target ring molecules. It has already been shown by us that macrocycles containing three piperazine-triazine moieties can easily be prepared in such a way.[15] We now report a further elaboration on this approach, showing that it is possible to vary not only the functionality on the triazine rings, but also the size of the macrocycles, simply by increasing the number of steps used in preparing the macrocycle precursors. Furthermore, we replaced piperazine as the linker between the triazine rings by xylenediamine. The resulting structures display numerous potential hydrogen bond donor and acceptor sites, and produce compounds with potential affinity for compounds, such as carbohydrates, that possess complementary functionality. Finally, to gain insight into the properties of the triazine-xylenediamine macrocycles, the binding of cyanuric acid and some pyranosides was investigated in order to demonstrate their ability to form complexes by hydrogen bond formation.

Results and Discussion

Synthesis of Triazine Macrocycles

The piperazine-triazine trimeric macrocycles were synthesized as outlined in Scheme 1 and reported earlier.[15] In

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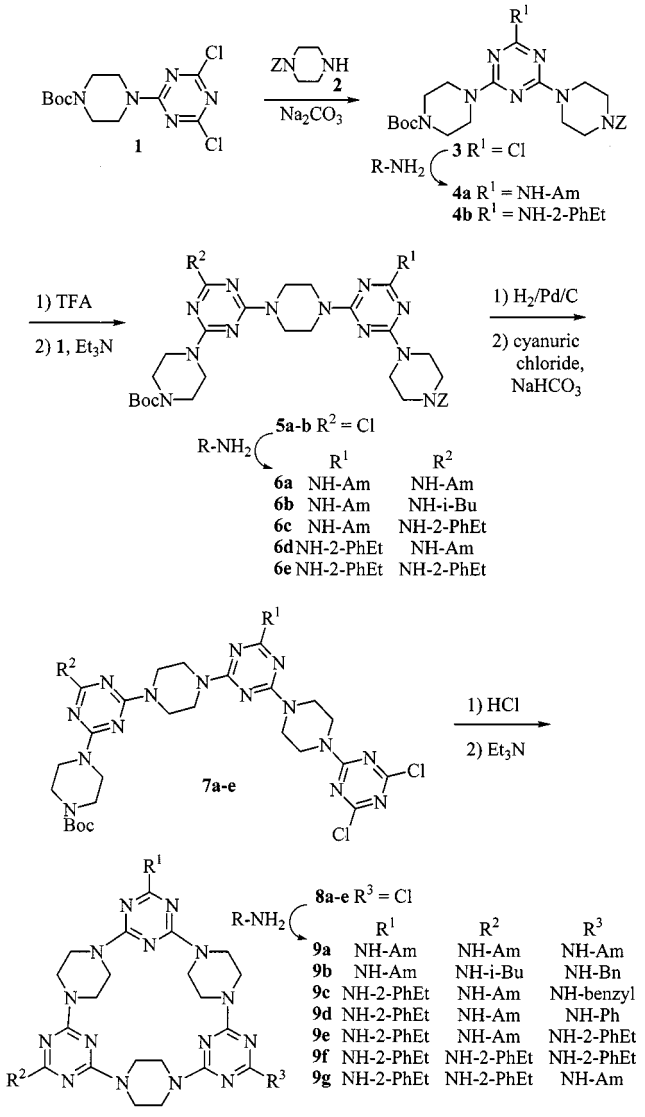
brief, the synthesis commenced by elongation of compounds **4**, using building block **1**. After functionalization of the newly introduced triazine ring, deprotection and treatment with cyanuric chloride, linear precursors to the trimeric macrocycles were generated. At this stage the linear dichlorides **7** were converted into their corresponding macrocycles **8a**−**e** by sequential removal of the Boc group using HCl and cyclization under basic conditions. All cyclizations proceeded quickly, with yields of 40−73%.[16] The synthesis was concluded by substitution of the remaining chlorine atom, using an excess of amine, to afford macrocycles **9a**−**g**. It has been shown that a variety of macrocycles can be prepared in a rapid and facile manner, with each differently functionalized at the triazines by changing the amines used during the synthesis. However, as a consequence of the symmetry of the macrocycles, diversity might be reduced since compounds **8c** and **8d**, as well as **9e** and **9g**, were found to be identical despite being prepared from different starting materials. Furthermore, variable temperature NMR experiments showed that the macrocyclic tristriazines are conformationally mobile and are probably able to invert at room temperature.

An example of the preparation of larger macrocycles is shown in Scheme 2, and is demonstrated with compound **6b** as the starting point. To obtain a macrocycle containing four triazine units, precursor **12** was prepared by an additional round of elongation and functionalization. From this precursor **12**, the corresponding macrocycle was prepared in 23% yield by sequential treatment with acid and base. Mass spectrometry confirmed the formation of macrocycle **13**. The low yield was due to competitive formation of a dimer (31%) containing eight triazine rings. It is likely that compound **12** is significantly strained and thus that its formation is hampered. The multiplet for the ethylene bridges of the piperazines in the ^{1}H NMR spectrum is indicative of high rotational barriers, producing a more rigid molecule.[17] In contrast, the much larger dimer shows a broad singlet for the same protons as evidence of more flexibility in the macrocycle. Finally, the remaining chlorine atom was substituted, using an excess of 2-phenylethylamine, to give **14** in 74% yield.

Scheme 3 shows that even larger macrocycles can be prepared by deprotection, elongation, cyclization, and functionalization of compound **11**. Both macrocycle **16**, possessing five differently functionalized triazine rings, and macrocycle **18** (Scheme 4), possessing six triazine rings, were obtained in good overall yields. The ease of formation of the latter macrocycle from its oligomeric precursor was surprising considering the size of the ring that is formed (42 atoms). Although longer oligomers were prepared, no attempt was made to synthesize even larger macrocycles, since the concept of synthesizing macrocycles of various sizes based on triazine moieties substituted with different functionalities has been established in this work.

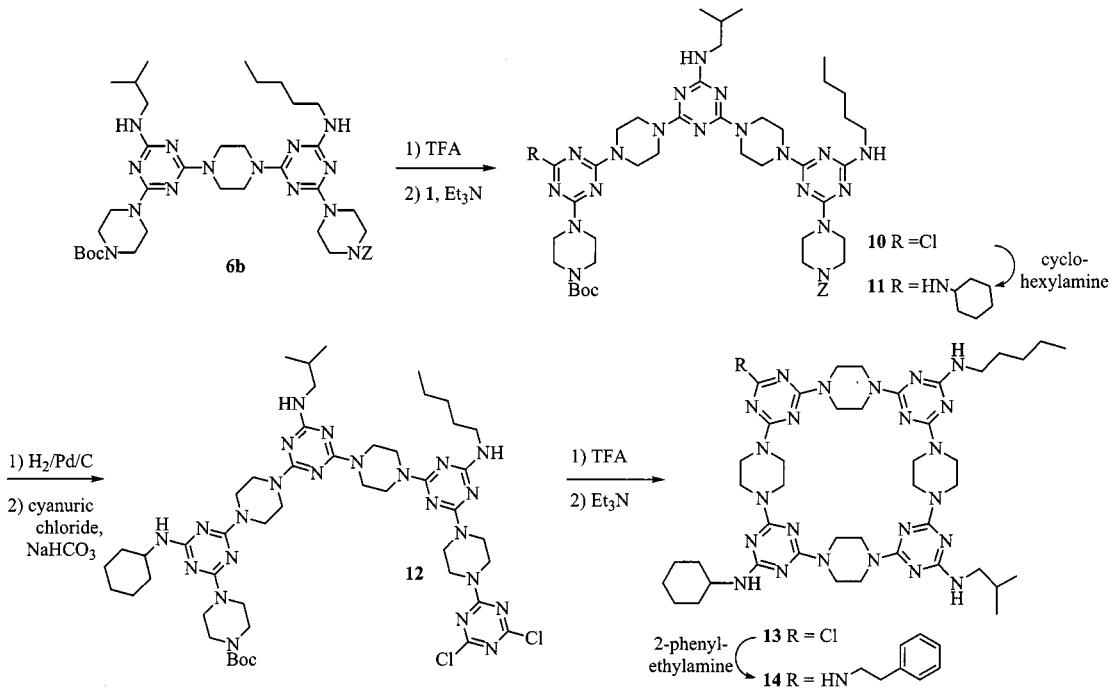
To explore our generic strategy further, it was decided to investigate whether other diamines could be used to link the triazine moieties. Xylenediamine was chosen to demonstrate proof-of-concept. In addition, the resulting macrocycles, comprising a great number of hydrogen bond donors and acceptors, were expected to possess interesting binding properties, since analogous, but linear, compounds of this kind have been shown to have affinity for barbiturates.[18]



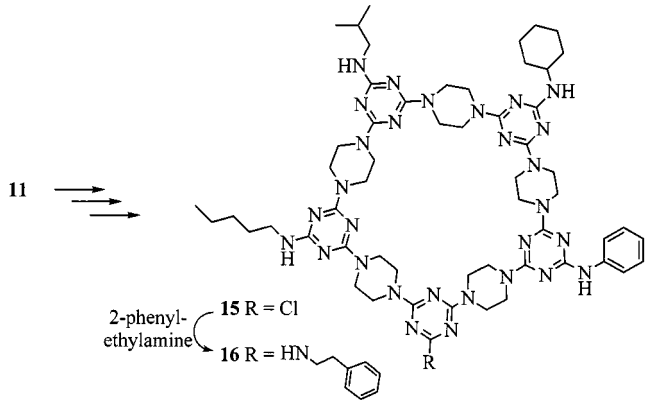
Scheme 1. Synthesis of piperazine-spaced cyclotristriazine macrocycles

For the preparation of such xylenediamine-triazine macrocycles, a new building block **20** was required. This was easily prepared from monoprotected xylenediamine **19** and cyanuric chloride, in 85% yield, as illustrated in Scheme 5. After introduction of orthogonally protected linker **21** (96% yield), the remaining chlorine in triazine **22** was substituted using an excess of amylamine to afford triazine **23** in 98% yield. Compound **23** can be regarded as a starting point for the preparation of xylene-triazine oligomers.

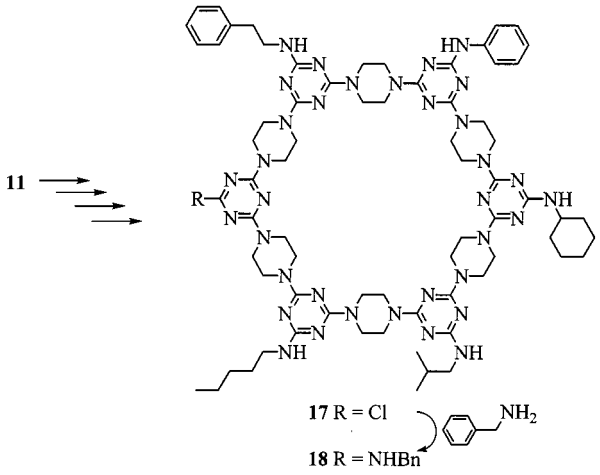
Monotriazine **23** was elongated by subsequent treatment with TFA and building block **20** to give bistriazine **24** in 83% yield. Refluxing this compound with an excess of either amylamine or isobutylamine afforded oligomers **25a** and **25b**, both in 97% yield. In order to obtain precursors to macrocycles containing three triazine moieties, the Z



Scheme 2. Synthesis of a cyclotetratriazine macrocycle containing piperazine spacers

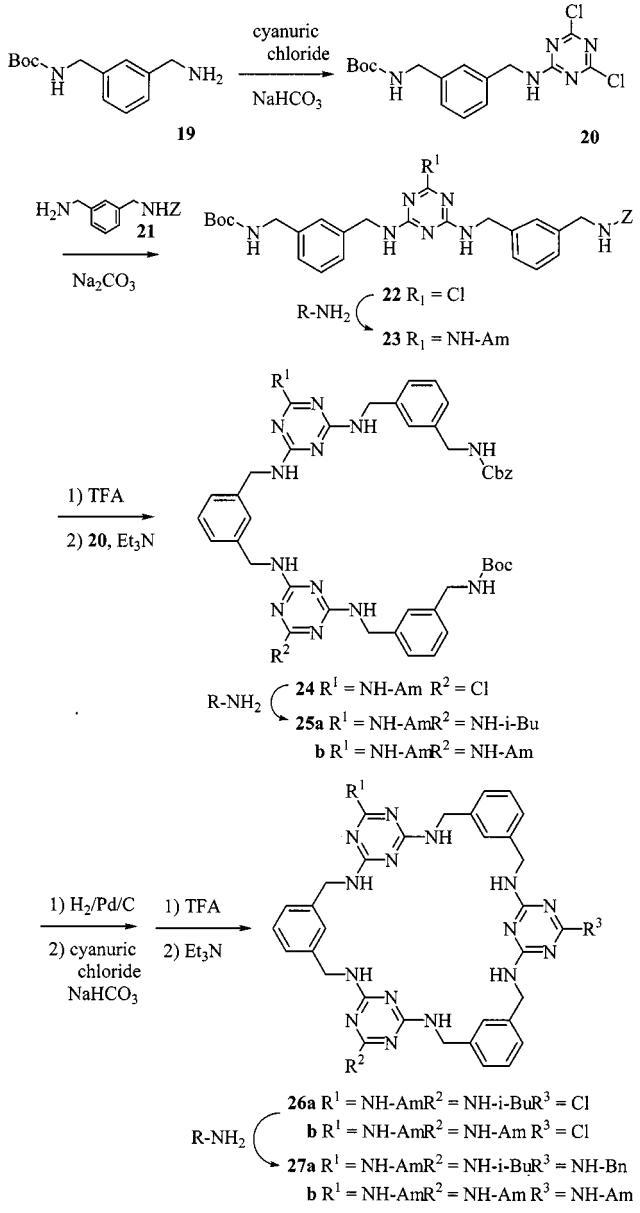


Scheme 3. Synthesis of a cyclopenta(triazine-piperazine) macrocycle



Scheme 4. Synthesis of xylenediamine-spaced cyclotristriazine macrocycles

group was removed from compounds **25**, and the resulting free amine was subsequently used in a reaction with cyanuric chloride. The crude dichlorotriazines obtained were used directly for cyclization to afford macrocycles **26a** and **26b**. Unfortunately, this final cyclization did not proceed as smoothly as in the case of piperazine-linked triazines, as evidenced by the poor yields of 36% and 34%, respectively, for the cyclizations affording rings **26a** and **26b**. The lower yields are probably the result of the presence of rotamers, not all of which allow for cyclization. Another factor reducing the overall yield was the side effects experienced on removal of the Z group. The multiple benzylamine elements present in compounds **25** may cause them and their products to be labile under the hydrogenolytic conditions required for deprotection. Nevertheless, the obtained macrocycles were further functionalized by refluxing in the presence either of amylamine or of benzylamine to afford **27a** and **27b** in 71% and 72% yields, respectively. The symmetric nature of **27b** is nicely reflected in its NMR spectrum, which shows only one set of signals for the three amyl groups present. Furthermore, the macrocycles possess considerable conformational freedom. This results in interconverting (on the NMR timescale) rotamers, as is evidenced by the broad signals for all hydrogens, which sharpen upon heating from 25 to 50 °C. To date, we have not attempted to prepare larger macrocycles using xylenediamine as a linker. Nevertheless, the macrocycles containing three triazine-xylenediamine units displayed interesting binding properties as will be discussed below.



Scheme 5. Synthesis of a piperazine-spaced macrocycle possessing six differently functionalized triazine rings

Binding Properties of Tris(xylenediamine-triazine) Macrocycles

Upon inspection of a three dimensional model of compounds **27**, it was anticipated that they should be able to bind both to cyanuric acid (or its derivatives) and to saccharides. Firstly, cyanuric acid was considered, since the work of Mathias et al.,[18b] and more recently that of Lipkowski et al.,[18a] had shown that structures based on triazine-xylenediamine elements display high affinities for barbiturates. Secondly, saccharides were considered potential ligands because of the abundance of convergent hydrogen bond donor and acceptor groups in compounds **27**. Furthermore, it was interesting to examine the influence of the cyclic nature of our triazine-xylenediamine compounds **27** in terms of their abilities to bind these ligands.

Since compounds **27** possess one more triazine-xylene unit than those reported by Mathias et al.[18b] and are cyclic in nature, it was anticipated that they should be able completely to encircle one molecule of cyanuric acid **28**. Molecular modelling on these compounds confirmed these expectations; as Figure 1 shows, the cyclic molecule **27** ($R^1 = R^2 = R^3 = NH_2$) is able to bind cyanuric acid with nine hydrogen bonds.

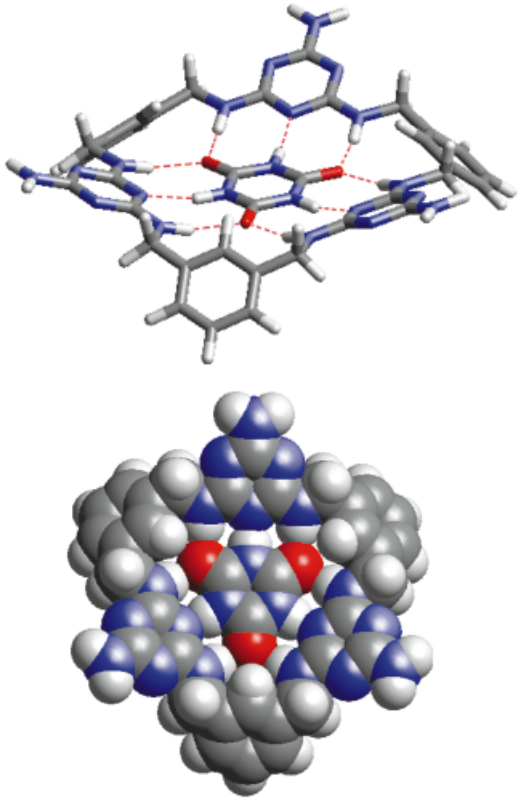


Figure 1. A stick- and a CPK-model of an energy-minimized complex between cyanuric acid **28** and macrocycle **27** with $R^1 = R^2 = R^3 = NH_2$[32]

To corroborate this expectation, compound **27b** was titrated with 0.1 to 2 equivalents of cyanuric acid. Receptors **27** were able to dissolve at least one equivalent of cyanuric acid in $CDCl_3$; cyanuric acid was otherwise poorly soluble in that solvent. Figure 2 (a) shows that addition of cyanuric acid generates new signals in the NMR spectrum; these were assigned to the newly formed complex. The equilibrium established between the free and the bound state has to be a slow one, on the NMR timescale, as both the free and bound state were visible.[19] A binding constant of $2.5 \cdot 10^4\ M^{-1}$ ($\Delta G = -25$ kJ/mol) was calculated from the binding isotherm depicted in Figure 2 (b), by nonlinear regression. The curve is consistent with the postulated 1:1 stoichiometry.

Remarkably, the addition of cyanuric acid to **27a** resulted in a second spot on TLC ($R_f = 0.85$; 10% methanol in dichloromethane), moving faster than pure **27a** ($R_f = 0.25$). The spot for uncomplexed **27a** completely disappeared after equilibration of the receptor with excess cyanuric acid, pro-

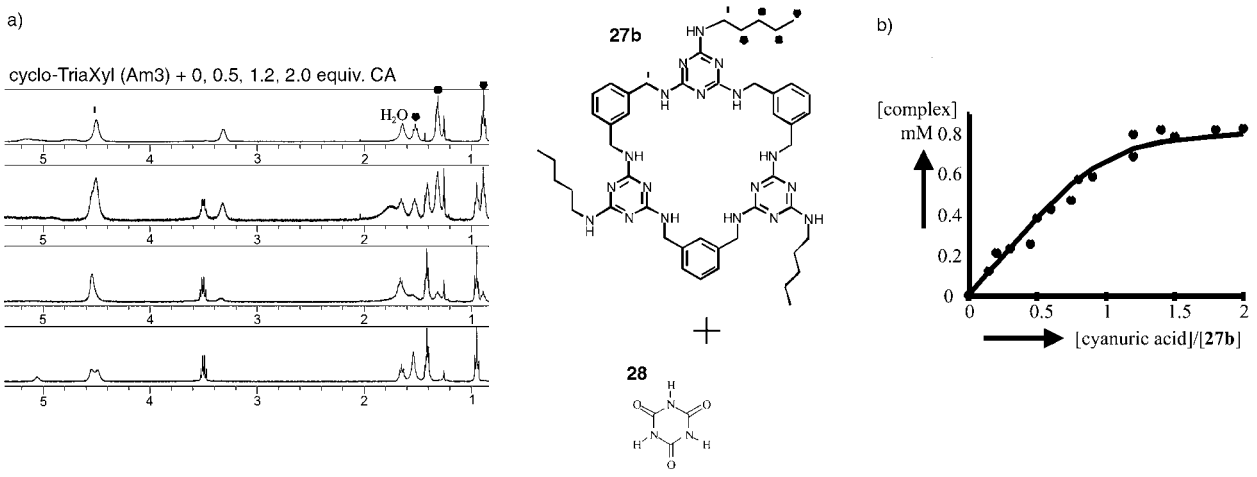


Figure 2. Titration of **27b** with cyanuric acid. a) NMR spectra after addition of 0 (top), 0.5, 1.2, and 2.0 (bottom) equivalents of cyanuric acid; b) the corresponding binding isotherm

viding evidence for the stability of the complex and the slow kinetics of the equilibrium. Although the affinity is quite respectable, it was somewhat lower than anticipated[20] when compared with the binding constants of the linear analogues for barbiturates as described by Lipkowski et al.[18a] For one of their assemblies, which was able to form no more than six hydrogen bonds, in contrast with our presumed nine, an association constant of $7.6 \cdot 10^4$ M^{-1} was reported. A closer look at our system, however, reveals that the angles of the formed hydrogen bonds are not optimal, due to the fact that cyanuric acid is bound slightly out of the plane of the macrocycle, thereby reducing their strength. Furthermore, it was surprising to see that even the NMR signals of the terminal methyls of the amyl groups are shifted in the bound state, despite the fact that they appear to be far removed from the site at which cyanuric acid binds. This could be caused either by a large conformational change or by an intermolecular reorganization of the receptor molecule, breaking intramolecular or intermolecular hydrogen bonds. Either eventuality would cause the methyl groups to undergo a change in environment, and probably be reflected in a relatively large shift of their NMR resonances. The energy lost in such a process would of course, further reduce the affinity, as would a considerable amount of entropy lost in the process of complex formation. This conclusion was reached following observation of a transition from the mainly broad signals in the NMR spectrum of **27b** to the sharp ones seen after addition of cyanuric acid, suggesting a rigidification of the receptor molecule. Additional experiments will be needed to establish the exact nature of the processes involved. To test the selectivity of **27b** towards cyanuric acid, attempts were made to bind analogues such as thymine, uracil and 5-bromouracil. However, none of these potential ligands could be solubilized into $CDCl_3$ since they lacked affinity for the macrocycle.

The circular presentation of hydrogen bond donors and acceptors in the macrocycles enticed us to examine octyl glycosides as another group of putative binding ligands. Preliminary molecular modelling studies suggested that the size of the ring is such that it could provide for hydrogen bond donors and acceptors complementary to those of pyranosides, as shown in Figure 3.

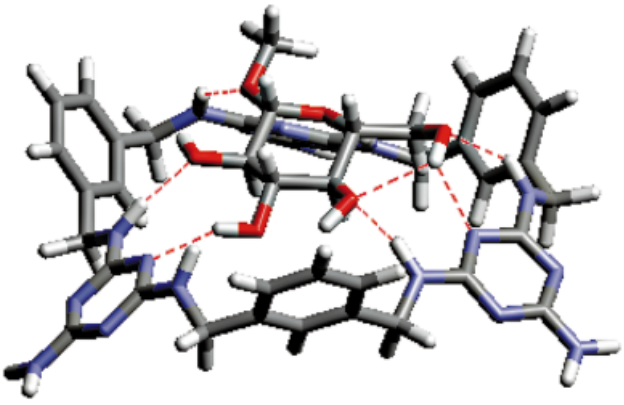


Figure 3. Energy minimized 3D model of a possible binding mode of β-glucopyranoside **30** to receptor **27b**. For clarity, the side chains of the receptor and the alkyl chain of the sugar have been replaced by NH_2 moieties and a methyl group, respectively

Both compounds **27a** and **27b** were titrated with 1-*O*-*n*-octyl-α-D-glucopyranoside **29**, 1-*O*-*n*-octyl-β-D-glucopyranoside **30** and 1-*O*-*n*-octyl-β-D-galactopyranoside **31** (Figure 4). In these experiments, complexation-induced shifts of the anomeric protons were observed on increasing the number of equivalents of receptor molecule from 0.1 to 8.[21] Figure 5 (a) shows the results for compound **27b** (the curves were similar for receptor **27a**). In all cases, an upfield complexation-induced shift was observed for the anomeric pro-

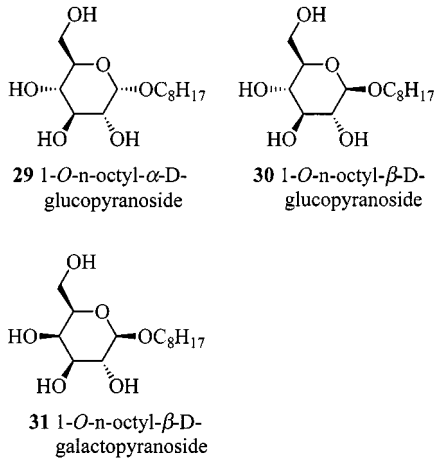


Figure 4. Glycosides used in NMR titration experiments

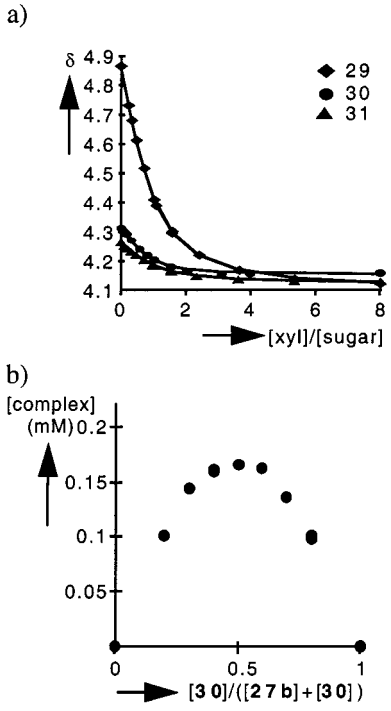


Figure 5. a) Complexation-induced shift for the anomeric proton of octyl-glycosides **29**, **30** and **31** upon addition of macrocycle **27b**; b) the corresponding Job plot for the association of **27b** and **30**

ton of the glycosides and all the binding isotherms matched well with the formation of 1:1 complexes. This was confirmed for all combinations by Job plots, which had their maximum at a mol fraction of 0.5, as illustrated in Figure 5 (b) for octyl-β-glucopyranoside **30** and macrocycle **27b**. Assuming 1:1 stoichiometry for these complexes, binding constants of $2.5-7.6\cdot10^3$ M^{-1} ($\Delta G = -19.4$ to -22.1 kJ/mol) were calculated using nonlinear regression, as summarized in Table 1. These affinity constants compare quite favourably with those reported to date for similar compounds in the literature.[6]

Neither receptor displayed a high degree of selectivity towards the different saccharides, which differed in stereochemistry only at C^1 and C^4. The low selectivity is probably due to the fairly flexible nature of the macrocycles, allowing them to adapt to the various ligands. Nevertheless, macrocycles **27** showed similar selectivities, both favouring octyl-β-glucopyranoside **30**. Interestingly, the magnitude of the observed upfield shift did not correlate with the calculated association constants. On binding to the triazine macrocycles, the anomeric proton of α-glucopyranoside **29** will be directed towards the shielding zone of one of the aromatic rings. Assuming a similar mode of binding for β-glycosides **30** and **31**, the anomeric proton would be directed away from this zone and would not produce the same degree of shielding after complexation. This is in agreement with the binding mode presented in Figure 3. Van't Hoff analysis for the complex between receptor **27b** and β-glucopyranoside **30** afforded $\Delta H = -34.5\pm0.5$ kJ/mol and $\Delta S = -43\pm2$ J/mol·K for the changes in enthalpy and entropy respectively.[22] Thus, the process is enthalpy driven, and from the relatively small entropy change, it can be concluded that there is still a substantial amount of (rotational) freedom after complex formation. This conclusion is in accordance with the observation that the signals in the ^{1}H NMR spectrum of the receptor remain broad after complexation. It is possible that not one, but a whole ensemble of binding modes is present, collectively resulting in the observed affinity. The results suggest that cyanuric acid and the glycosides utilize the same binding site. Indeed, it was found that cyanuric acid, possessing the higher affinity, was able to displace any bound glycoside in receptors **27**.

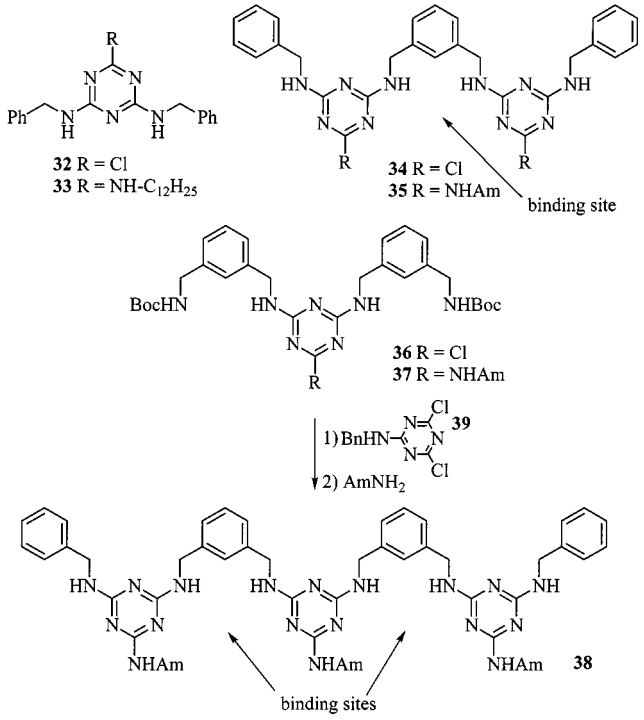
Table 1. Association constants between receptors **27** and three octyl glycosides in $CDCl_3$

Receptor	Saccharide	K (M^{-1})[a]	ΔG (kJ/mol)
27a	α-Glucopyranoside **29**	$2.5\cdot10^3$	−19.4
27a	β-Glucopyranoside **30**	$4.2\cdot10^3$	−20.6
27a	β-Galactopyranoside **31**	$2.5\cdot10^3$	−19.4
27b	α-Glucopyranoside **29**	$3.9\cdot10^3$	−20.5
27b	β-Glucopyranoside **30**	$7.6\cdot10^3$	−22.1
27b	β-Galactopyranoside **31**	$3.4\cdot10^3$	−20.1

[a] At 298 K; estimated error is 10−15%.

In order to examine the significance of the cyclic nature of the receptor molecules on the binding properties, linear compound **38** was prepared for comparison. Oligomer **38** is the linear analogue of macrocycle **27b** and can be synthesized in four steps from Boc-xylenediamine. The stepwise approach was the synthetic method of choice, as shown in Scheme 6. However, the number of steps necessary could be reduced by taking advantage of the symmetry in **38**. Additionally, the shorter derivatives **35** and **33**, containing only two and one triazine ring, respectively, were prepared. Monotriazine **33** was obtained in two steps from cyanuric chloride and bistriazine **35** in two steps from xylenediamine.

Surprisingly, when β-glucopyranoside **30** was titrated with tristriazine **38**, it was found that two saccharides were bound by the linear compound. The observed association curve could be described by assuming two cooperative



Scheme 6. Oligotriazines consisting of one, two, and three triazines

binding sites with the stepwise affinity constants of $2.0 \cdot 10^3$ M^{-1} (K_{11}) and $9.1 \cdot 10^2$ M^{-1} (K_{12}). This stoichiometry was confirmed by examination of the corresponding Job plot, which displayed its maximum at a mol fraction of approximately 0.66. It thus appears that on conversion of linear **38** to cyclic **27b**, one binding site is lost. Nevertheless, binding affinity is increased when these recognition sites are combined into one, as is obvious from the threefold increase in affinity for β-glucopyranoside. From these results, it was expected that the shorter **35** would bind only one sugar molecule. Indeed, titration of β-glucopyranoside **30** with bistriazine **35** afforded a binding curve consistent with a 1:1 stoichiometry and an association constant of $2.3 \cdot 10^3$ M^{-1} ($\Delta G = -19.1$ kJ/mol). This suggests that a pyranoside molecule is sandwiched between two triazine rings in the positions indicated in Scheme 5. This assumption was substantiated by the fact that **33**, a single triazine unit, has an affinity constant for β-glucopyranoside no larger than 50 M^{-1}. In the cyclic receptors **27**, the conformation is restrained to such an extent that there is no space for two glycosides and the two binding sites are combined into one.

Conclusion

In this paper we have presented the synthesis of macrocycles containing triazine moieties linked by diamines. The stepwise approach we adopted resulted in a very flexible strategy with several distinct advantages. Firstly, each triazine unit in the ring can be functionalized separately. The use of generic building blocks removed the need for extensive monomer synthesis. The functionalization of each triazine ring took place in a step following the elongation of the intermediate oligomers, using the required amine. It is evident that this strategy may easily be combined with a combinatorial approach, rapidly producing a large number of macrocycles. Secondly, the synthesis is adaptable to many sizes of macrocycle. The size can be varied by changing the number of elongation and functionalization steps leading to the precursors of the final macrocycles. We have demonstrated that it is possible to incorporate up to six differently functionalized triazine rings. To date, there is no evidence that larger rings could not be prepared in a similar fashion. Thirdly, we have also shown that the diamines linking the triazine rings can be varied. In this paper, we illustrate this by the incorporation of xylenediamine as a linker. Currently, we are investigating the use of other diamines such as ethylenediamine and diamines derived from amino acids. Altogether, an enormous variety of possible macrocycles can be synthesized in a combinatorial fashion by varying the substituents, the size of the macrocycles and the linkers. Finally, we have demonstrated that the triazine-xylenediamine macrocycles exhibit very promising binding properties towards cyanuric acid and glycosides. Their association behaviour is predominantly determined by the presence of many hydrogen bond donor and acceptor sites. As the triazine-xylenediamine macrocycles are quite flexible they are able to adopt a conformation which allows positioning of its binding sites complementary to those of the presented ligand.

Experimental Section

General: Cyanuric chloride was recrystallized from petroleum ether 80−100. DIPEA was successively distilled from ninhydrin and KOH. All other chemicals were used as received from commercial suppliers. Reactions were carried out at ambient temperature unless stated otherwise. − TLC analysis was performed on Macherey−Nagel polyester pre-coated silica gel (250 μm, 5−17 μm) plates. Spots were viewed with the aid of UV light, ninhydrin (0.3 g in 100 mL HOAc/*n*BuOH 3:97 v/v) or Cl_2-TDM.[23] − Solvents were evaporated under reduced pressure at 40 °C. − Column chromatography was performed on Merck Kieselgel 60 (40−63 μm) and flash column chromatography on Merck Kieselgel 60H (5−40 μm, applying 1 bar pressure). Sephadex LH-20 from Pharmacia was used for gel permeation chromatography. − ^1H and ^{13}C NMR spectra were recorded with a Jeol Lambda 400 spectrometer [399.65 MHz for ^1H, chemical shift values are given in ppm relative to TMS; 100.4 MHz for ^{13}C, chemical shift values are given in ppm relative to $CDCl_3$ ($\delta = 77.0$) or [D_6]DMSO ($\delta = 39.5$)]. The temperature was 298 K (±0.5 K) for all experiments unless stated otherwise. − Electron Spray Mass Spectrometry (ESI), Fast Atom Bombardment (FAB), and Liquid secondary Ion Mass Spectrometry (LSIMS) were carried out on a Bruker Bio-Apex II FT-ICR, Micromass Q-TOF or MSI Concept. − For the synthesis of compounds **6c**, **6d**, **6e**, **7c**, **7d**, **7e**, **8c**, **8e**, **9c**, **9d**, **9f**, **15**, and **17** the reader is referred to the electronic supporting information.

1-Boc-piperazine:[24] A solution of Boc_2O (4.37 g, 20.0 mmol) in DCM (50 mL) was added over a period of three hours to a solution of piperazine (3.44 g, 39.9 mmol) in DCM (100 mL). The mixture was allowed to stir for 22 hours before the solvent was evaporated.

Water (100 mL) was added to the residue and the insoluble product was removed by filtration. The aqueous solution was extracted with DCM (three portions of 100 mL) and the combined organic layers were evaporated to afford Boc-piperazine (3.08 g, 83%). Analytical data were identical to those reported in the literature.[24b]

Monosubstituted Triazine 1: A fine slurry of cyanuric chloride was prepared by adding a solution of cyanuric chloride (1.11 g, 6.00 mmol) in acetone (24 mL) to well stirred ice-water (36 mL).[25] A solution of Boc-piperazine (1.12 g, 6.00 mmol) in acetone (10 mL) and one of $NaHCO_3$ (504 mg, 6.00 mmol) in water (10 mL) were then added. After stirring the mixture for 2 hours at 0 °C, the solid was filtered off, washed with water and dried in vacuo over P_2O_5 to afford (1.93 g, 96%) of product. R_f = 0.63 (EtOAc/hexanes 1:1). − ^{1}H NMR ($CDCl_3$): δ = 1.44 [s, 9 H, $C(CH_3)_3$], 3.47 (t, 4 H, CH_2NAr), 3.82 (2, 4 H, CH_2NBoc). − ^{13}C NMR ($CDCl_3$): δ = 28.3 [$C(CH_3)_3$], 43.2 (broad, CH_2NBoc), 43.9 (CH_2NAr), 80.6 [$C(CH_3)_3$], 154.3 (C=O), 164.1, 170.4 (C-triazine). − HRMS (ESI) calcd. for $C_{12}H_{17}Cl_2N_5NaO_2$ $(M + Na)^+$: 356.0657, found *m/z*: 356.0685. − $C_{12}H_{17}Cl_2N_5O_2$ (334.2): calcd. C 43.13, H 5.13 N 20.96; found C 43.64, H 5.24 N 20.57.

1-Boc-4-Z-piperazine: A solution of benzylchloroformate (433 μL, 3.03 mmol) in DCM (10 mL) was added at 0 °C to a solution of Boc-piperazine (559 mg, 3.00 mmol) and Et_3N (460 μL, 3.30 mmol) in DCM (20 mL). The mixture was stirred at room temperature for 30 minutes and the solution was then concentrated in vacuo. The residue was dissolved in EtOAc and the resulting solution was washed with $KHSO_4$ (1 M, twice), 5% $NaHCO_3$ and brine, and dried with Na_2SO_4. Evaporation of the solvent yielded 957 mg of title compound (100%). R_f = 0.55 (EtOAc/hexanes 1:1). − ^{1}H NMR ($CDCl_3$): δ = 1.35 [s, 9 H, $C(CH_3)_3$], 3.30, 3.36 (bs and t, 8 H, CH_2CH_2), 5.03 (s, 2 H, OCH_2), 7.24 (m, 5 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 28.2 [$C(CH_3)_3$], 43.5 (broad, CH_2CH_2), 67.2 (OCH_2), 80.0 [$C(CH_3)_3$], 127.8, 128.0, 128.4, 136.4 (C^{Ar}), 154.5, 155.0 (C=O).

1-Z-piperazine 2: TFA (10 mL) was added at 0 °C to a solution of 1-Boc-4-Z-piperazine (4.14 g, 12.9 mmol) in DCM (30 mL). The mixture was stirred for 30 minutes at room temperature and then concentrated in vacuo. NaOH (1 M, 150 mL) was added to the residue and the aqueous layer was extracted with DCM (150 mL and subsequently 100 mL) and the combined organic layers were dried with $MgSO_4$ and evaporated to afford 1-Z-piperazine (2.85 g, 100%). − ^{1}H NMR ($CDCl_3$): δ = 2.10 (s, 1 H, NH), 2.71 (br. s, 4 H, CH_2NH), 3.38 (t, 4 H, CH_2CH_2N), 5.03 (s, 2 H, OCH_2), 7.24 (m, 5 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 44.6, 45.6 (broad, CH_2CH_2), 66.9 (OCH_2), 127.7, 127.8, 128.3, 136.5 (C^{Ar}), 155.1 (C=O).

Disubstituted Triazine 3: Na_2CO_3 (583 mg, 5.50 mmol) and a suspension of monosubstituted triazine **1** (1.67 g, 5.00 mmol) in acetone (10 mL) were added to a solution of Z-piperazine (1.21 g, 5.50 mmol) in water (30 mL).[25] After stirring at 65 °C for 5 hours, the white solid was filtered off and washed with water. Drying in vacuo over P_2O_5 overnight yielded 2.51 g of product (97%). R_f = 0.25 (1% MeOH in DCM). − ^{1}H NMR ($CDCl_3$): δ = 1.45 [s, 9 H, $C(CH_3)_3$], 3.43, 3.52, 3.76 (three br. s, 16 H, CH_2CH_2), 5.14 (s, 2 H, OCH_2), 7.33 (m, 5 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 28.3 [$C(CH_3)_3$], 43.2 (broad m, CH_2CH_2), 67.3 (OCH_2), 80.2 [$C(CH_3)_3$], 127.9, 128.1, 128.5, 136.4 (C^{Ar}), 154.5, 155.1 (C=O), 164.38, 164.43, 169.6 (C-triazine). − HRMS (FAB) calcd. for $C_{24}H_{33}ClN_7O_4$ $[M + H]^+$: 518.2283, found *m/z*: 518.2291. − $C_{24}H_{32}ClN_7O_4$ (518.0): calcd. C 55.65, H 6.23, N 18.93; found C 56.05, H 6.26, N 18.50.

Trisubstituted Triazine 4a:[26] A solution of disubstituted triazine **3** (1.04 g, 2.00 mmol) and amylamine (1159 μL, 10.0 mmol) in THF (20 mL) was refluxed for 6 hours, after which the solvent was evaporated. The residue was dissolved in EtOAc and the resulting solution was washed with $KHSO_4$ (1 M, twice), water, 5% $NaHCO_3$ and brine, and dried with $MgSO_4$. Evaporation of the solvent afforded 1.13 g of trisubstituted triazine **4a** (99%). R_f = 0.08 (1% MeOH in DCM). − ^{1}H NMR ($CDCl_3$): δ = 0.92 (t, 3 H, CH_2CH_3), 1.28 (m, 4 H, $CH_2CH_2CH_3$), 1.45 [s, 9 H, $C(CH_3)_3$], 1.56 (m, 2 H, $NHCH_2CH_2$), 3.36 (q, 2 H, $NHCH_2CH_2$), 3.45, 3.54 (two br. s, 8 H, $CH_2NC(O)$], 3.76 (br. s, 8 H, CH_2NAr), 5.18 (s, 2 H, OCH_2), 5.32 (br. s, 1 H, NH), 7.38 (m, 5 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 22.3 (CH_2CH_3), 28.4 [$C(CH_3)_3$], 29.1, 29.5 ($CH_2CH_2CH_2CH_3$), 40.6 ($NHCH_2$), 42.8, 43.7 (broad, CH_2CH_2), 67.2 (OCH_2), 79.8 [$C(CH_3)_3$], 127.9, 128.0, 128.5, 136.6 (C^{Ar}), 154.8, 155.3 (C=O), 165.2, 166.3 (C-triazine). − HRMS (ESI) calcd. for $C_{29}H_{45}N_8O_4$ $[M + H]^+$: 569.35582 found *m/z*: 569.3562.

Trisubstituted Triazine 4b: Title compound **4b** was prepared from disubstituted **3** (1.55 g, 3.00 mmol) and 2-phenylethylamine (1.88 mL, 15.0 mmol) according to the procedure described for **4a**, but refluxing for 24 hours. R_f = 0.44 (EtOAc/hexanes 1:1). − ^{1}H NMR ($CDCl_3$): δ = 1.50 [s, 9 H, $C(CH_3)_3$], 2.88 (t, 2 H, CH_2Ph), 3.46, 3.54 (two br. s, 8 H, $CH_2NC(O)$], 3.64 (q, 2 H, CH_2CH_2Ph), 3.76 (br. s, 8 H, CH_2NAr), 4.85 (t, 1 H, $NHCH_2$), 5.18 (s, 2 H, OCH_2), 7.20−7.40 (m, 10 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 28.4 [$C(CH_3)_3$], 36.0 (CH_2Ph), 42.1 ($NHCH_2CH_2Ph$), 42.8, 42.9, 43.7 (NCH_2CH_2N), 67.2 (OCH_2), 79.9 [$C(CH_3)_3$], 126.3, 127.9, 128.0, 128.48, 128.52, 128.7, 136.6, 139.3 (C^{Ar}), 154.8, 155.3 (C=O), 165.3, 166.2 (C-triazine). − HRMS (ESI) calcd. for $C_{32}H_{42}N_8O_4$ $[M + H]^+$: 603.3407 found *m/z*: 603.3409

Bistriazine 5a: TFA (2 mL) was added to a solution of triazine **4a** (989 mg, 1.74 mmol) in DCM (6 mL), and the mixture was stirred for 30 minutes before it was evaporated. The residue was coevaporated three times with THF. The residue was redissolved in THF (30 mL), and Et_3N (485 μL, 3.48 mmol) and monosubstituted **1** (581 mg, 1.74 mmol) were added. The mixture was stirred for 2 hours at 40 °C and kept basic by addition of Et_3N. The volatiles were removed in vacuo. The residue was taken up in EtOAc and the resulting solution was washed with $KHSO_4$ (1 M, twice), water, 5% $NaHCO_3$ and brine, and dried with $MgSO_4$. Evaporation of the solvent and column chromatography (eluent: EtOAc/hexanes 1:2) afforded 1.33 g of product (100%). R_f = 0.51 (EtOAc/hexanes 1:1). − ^{1}H NMR ($CDCl_3$): δ = 0.87 (t, 3 H, CH_2CH_3), 1.31 (m, 4 H, $CH_2CH_2CH_3$), 1.46 [s, 9 H, $C(CH_3)_3$], 1.52 (m, 2 H, $NHCH_2CH_2$), 3.32 (q, 2 H, $NHCH_2CH_2$), 3.44, 3.50 (two br. s, 8 H, $CH_2NC(O)$], 3.75 (br. s, 16 H, CH_2NAr), 4.77 (br. s, 1 H, NH), 5.04 (s, 2 H, OCH_2), 7.34 (m, 10 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 22.4 (CH_2CH_3), 28.3 [$C(CH_3)_3$], 29.1, 29.5 ($CH_2CH_2CH_2CH_3$), 40.6 ($NHCH_2CH_2$), 42.8, 43.2, 43.3, 43.7 (broad, CH_2CH_2), 67.2 (OCH_2), 80.2 [$C(CH_3)_3$], 127.9, 128.0, 128.5, 136.6 (C^{Ar}), 154.6, 155.3 (C=O), 164.4, 165.2, 166.2, 169.7 (C-triazine). − HRMS (ESI) calcd. for $C_{36}H_{53}ClN_{13}O_4$ $[M + H]^+$: 766.4032 found *m/z*: 766.4028. − $C_{36}H_{52}ClN_{13}O_4$ (766.3): calcd. C 56.42, H 6.84, N 23.76; found C 56.31, H 6.89, N 23.64.

Bistriazine 5b: Bistriazine **5b** was prepared from triazine **4b** (1.62 g, 2.69 mmol) according to the procedure described for **5a**. Column chromatography (first column: eluent: EtOAc/hexanes 1:2, second: eluent: 1.9% MeOH in DCM) afforded 1.67 g of product (78%). R_f = 0.48 (EtOAc/hexanes 1:1). − ^{1}H NMR ($CDCl_3$): δ = 1.50 [s, 9 H, $C(CH_3)_3$], 2.88 (t, 2 H, CH_2Ph), 3.48, 3.54 (two br. s, 8 H, $CH_2NC(O)$], 3.63 (q, 2 H, CH_2CH_2Ph), 3.80 (br. s, 16 H, CH_2NAr), 4.84 (t, 1 H, $NHCH_2$), 5.18 (s, 2 H, OCH_2), 7.22−7.39

(m, 10 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 28.4 [C(CH_3)$_3$], 36.1 (CH_2Ph), 42.1 (CH_2CH_2Ph), 42.7, 42.9, 43.3, 43.4, 43.8 (NCH_2CH_2N), 67.3 (OCH_2), 80.2 [$C(CH_3)_3$], 126.4, 127.9, 128.1, 128.5, 128.6, 128.8, 136.6, 139.3 (C^{Ar}), 154.7, 155.3 (C=O), 164.5, 165.3, 166.3, 169.7 (C-triazine). − HRMS (ESI) calcd. for $C_{39}H_{51}ClN_{13}O_4$ [M + H]$^+$: 800.3875 found *m*/*z*: 800.3845.

Bistriazine 6a: A solution of bistriazine **5a** (0.51 g, 0.67 mmol) and amylamine (386 μL, 3.33 mmol) in THF (10 mL) was refluxed overnight. The solvent was removed in vacuo and the residue was redissolved in EtOAc. The resulting solution was washed with $KHSO_4$ (1 M, twice), water (twice), 5% $NaHCO_3$ and brine. Drying with $MgSO_4$ and evaporation of the solvent afforded 509 mg of product (93%). R_f = 0.52 (EtOAc/hexanes 1:1). − ^{1}H NMR ($CDCl_3$): δ = 0.90 (t, 6 H, CH_2CH_3), 1.34 (m, 8 H, $CH_2CH_2CH_2CH_3$), 1.49 [s, 9 H, C(CH_3)$_3$], 1.55 (m, 4 H, $NHCH_2CH_2$), 3.36 (q, 2 H, $NHCH_2CH_2$), 3.44, 3.53 (two br. s, 8 H, $CH_2NC(O)$], 3.78 (br. s, 16 H, CH_2NAr), 4.80 (br. s, 2 H, N*H*CH_2), 5.17 (s, 2 H, OCH_2), 7.37 (m, 5 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 22.4 (CH_2CH_3), 28.4 [C(CH_3)$_3$], 29.1, 29.5 ($CH_2CH_2CH_2CH_3$), 40.6 (NHCH_2CH_2), 42.8, 42.9, 43.0, 43.7 (NCH_2CH_2N), 67.2 (OCH_2), 79.8 [$C(CH_3)_3$], 127.9, 128.0, 128.5, 136.6 (C^{Ar}), 154.8, 155.3 (C=O), 165.3, 166.3 (C-triazine). − HRMS (ESI) calcd. for $C_{41}H_{65}N_{14}O_4$ [M + H]$^+$: 817.5313 found *m*/*z*: 817.5322

Bistriazine 6b: Bistriazine **6b** was prepared from bistriazine **5a** (1.16 g, 1.51 mmol) and isobutylamine (665 μL, 6.69 mmol) according to the procedure described for **6a**, to afford 1.13 g of product (93%). R_f = 0.52 (EtOAc/hexanes 1:1). − ^{1}H NMR ($CDCl_3$): δ = 0.90 (t, 3 H, CH_2CH_3), 0.94 [d, 6 H, CH(CH_3)$_2$], 1.34 (m, 4 H, $CH_2CH_2CH_3$), 1.48 [s, 9 H, C(CH_3)$_3$], 1.55 (m, 2 H, $NHCH_2CH_2$), 1.83 [m, 1 H, C*H*(CH_3)$_2$], 3.20 (t, 2 H, $NHCH_2CH$), 3.35 (q, 2 H, $NHCH_2CH_2$), 3.44, 3.52 (two br. s, 8 H, $CH_2NC(O)$], 3.77 (br. s, 16 H, CH_2NAr), 4.75 (t, 1 H, N*H*CH_2CH_2), 4.81 (t, 1 H, N*H*CH_2CH), 5.16 (s, 2 H, OCH_2), 7.34 (m, 5 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 20.3 [CH(CH_3)$_2$], 22.4 (CH_2CH_3), 28.4 [C(CH_3)$_3$], 28.8 [*C*H(CH_3)$_2$], 29.1, 29.6 ($CH_2CH_2CH_2CH_3$), 40.7 (NHCH_2CH_2), 42.85, 42.94, 43.0, 43.8 (broad, NCH_2CH_2N), 48.3 (NHCH_2CH), 67.2 (OCH_2), 79.8 [$C(CH_3)_3$], 127.9, 128.1, 128.5, 136.6 (C^{Ar}), 154.8, 155.3 (C=O), 165.3, 166.4, 166.6 (C-triazine). − HRMS (ESI) calcd. for $C_{40}H_{63}N_{14}O_4$ [M + H]$^+$: 803.5151 found *m*/*z*: 803.5149. − $C_{40}H_{62}N_{14}O_4$: calcd. C 59.83, H 7.78, N 24.42; found C 59.31, H 7.62, N 24.26.

Precursor 7a: Pd/C (10 %, 350 mg) was added to a solution of compound **6a** (0.51 g, 0.62 mmol) in THF/EtOH (4:3, 25 mL) and the resulting solution was stirred under a hydrogen atmosphere overnight. The catalyst was filtered off and the filtrate evaporated. The residue was dissolved in acetone (3 mL) and the resulting solution was added to a freshly prepared suspension of cyanuric chloride (111 mg, 0.60 mmol), precipitated from acetone (5 mL) in water (5 mL). After this, $NaHCO_3$ (50 mg, 0.60 mmol) was added. After stirring for two hours at 0 °C, the aqueous suspension was extracted with DCM (twice) and the combined organic layers were dried with $MgSO_4$ and evaporated. Column chromatography (eluent: 2% MeOH in DCM) yielded 280 mg of product (54%). R_f = 0.56 (EtOAc/hexanes 1:1). − ^{1}H NMR ($CDCl_3$): δ = 0.91 (t, 6 H, CH_2CH_3), 1.36 (m, 8 H, $CH_2CH_2CH_2CH_3$), 1.49 [s, 9 H, C(CH_3)$_3$], 1.56 (m, 4 H, $NHCH_2CH_2$), 3.37 (q, 4 H, $NHCH_2CH_2$), 3.45, [br. s, 4 H, $CH_2NC(O)$], 3.70−3.90 (broad m, 20 H, CH_2NAr), 4.76, 4.80 (two t, 2 H, N*H*CH_2). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 22.4 (CH_2CH_3), 28.4 [C(CH_{33}), 29.1, 29.5 ($CH_2CH_2CH_2CH_3$), 40.66, 40.69 (NHCH_2CH_2), 42.6, 42.92, 42.97, 43.03, 44.1 (NCH_2CH_2N), 79.9 [$C(CH_3)_3$], 154.8 (C=O), 164.1, 165.3, 166.4, 170.4 (C-triazine). − HRMS (ESI) calcd. for $C_{36}H_{58}Cl_2N_{17}O_2$ [M + H]$^+$: 830.4336 found *m*/*z*: 830.4294.

Precursor 7b: Bistriazine **7b** was prepared from bistriazine **6b** (1.10 g, 1.37 mmol) according to the procedure described for **7a** to afford 595 mg of product (61%). R_f = 0.46 (EtOAc/hexanes 1:1). − ^{1}H NMR ($CDCl_3$): δ = 0.92 (t, 3 H, CH_2CH_3), 0.95 [d, 6 H, CH(CH_3)$_2$], 1.36 (m, 4 H, $CH_2CH_2CH_3$), 1.49 [s, 9 H, C(CH_3)$_3$], 1.57 (m, 2 H, $NHCH_2CH_2$), 1.85 [m, 1 H, C*H*(CH_3)$_2$], 3.21 (t, 2 H, CH_2CH), 3.37 (q, 2 H, $NHCH_2CH_2$), 3.45 [br. s, 4 H, $CH_2NC(O)$], 3.70−3.95 (two broad m, 20 H, CH_2NAr), 4.82 (br. s, 2 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 13.9 (CH_2CH_3), 20.2 [CH(CH_3)$_2$], 22.3 (CH_2CH_3), 28.3 [C(CH_3)$_3$], 28.7 [*C*H(CH_3)$_2$], 29.0, 29.4 ($CH_2CH_2CH_2CH_3$), 40.6 (NHCH_2CH_2), 42.5, 42.9, 44.0, (NCH_2CH_2N), 48.2 (NHCH_2CH), 79.7 [$C(CH_3)_3$], 154.7 (C=O), 164.0, 165.2, 166.2, 166.4, 170.2 (C-triazine). − HRMS (ESI) calcd. for $C_{35}H_{56}Cl_2N_{17}O_2$ [M + H]$^+$: 816.4180 found *m*/*z*: 816.4184.

Cyclotristriazine 8a: A solution of dichloride **7a** (0.20 g, 0.24 mmol) in aq. HCl (4 M, 25 mL) in dioxane was stirred for two hours. The volatiles were removed in vacuo and the residue was coevaporated twice with THF. The intermediate was dried in vacuo in a desiccator over KOH for one hour. The intermediate was then dissolved in DMF (75 mL), and a solution of Et_3N (0.47 mL, 3.4 mmol) in DMF (50 mL) was added dropwise at 45 °C to the resulting solution. After continuing stirring for 30 minutes at this temperature, the solvent was removed in vacuo. The residue was dissolved in DCM and the resulting solution was washed with 1 M HCl and water, and dried with $MgSO_4$. Column chromatography (eluent: 2.5% MeOH in DCM) afforded 115 mg of macrocycle **8a** (69%). An analytically pure sample was obtained by gel permeation chromatography (DCM/MeOH 2:1). R_f = 0.24 (3% MeOH in DCM). − ^{1}H NMR ($CDCl_3$): δ = 0.91 (t, 6 H, CH_2CH_3), 1.36 (m, 8 H, $CH_2CH_2CH_2CH_3$), 1.57 (m, 4 H, $NHCH_2CH_2$), 3.38 (q, 4 H, $NHCH_2CH_2$), 3.82, 3.85 (two br. s, 24 H, CH_2NAr), 4.83 (t, 2 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 22.4 (CH_2CH_3), 29.1, 29.5 ($CH_2CH_2CH_2CH_3$), 40.7 (NHCH_2CH_2), 42.6, 42.8, 43.0, 43. 3, 43.5 (NCH_2CH_2N), 164.4, 165.1, 166.4, 169.8 (C-triazine). − HRMS (ESI) calcd. for $C_{31}H_{48}ClN_{17}$ [M + H]$^+$: 694.4045 found *m*/*z*: 694.4077.

Cyclotristriazine 8b: Macrocycle **8b** was prepared from precursor **7b** (0.17 g, 0.21 mmol) according to the procedure described for **7a**. Column chromatography (eluent: 3% MeOH in DCM) afforded 63% of the title compound. R_f = 0.52 (3% MeOH in DCM). − ^{1}H NMR ($CDCl_3$): δ = 0.91 (t, 3 H, CH_2CH_3), 0.95 [d, 6 H, CH(CH_3)$_2$], 1.36 (m, 4 H, $CH_2CH_2CH_3$), 1.57 (m, 2 H, $NHCH_2CH_2$), 1.86 [m, 1 H, C*H*(CH_3)$_2$], 3.22 (t, 2 H, CH_2CH), 3.38 (q, 2 H, $NHCH_2CH_2$), 3.82, 3.85 (two br. s, 24 H, CH_2NAr), 4.88, 4.92 (two br. s, 2 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 20.3 [CH(CH_3)$_2$], 22.4 (CH_2CH_3), 28.7 [*C*H(CH_3)$_2$], 29.1, 29.5 ($CH_2CH_2CH_2CH_3$), 40.6 (NHCH_2CH_2), 42.5, 42.8, 42.9, 43.3, 43.4 (NCH_2CH_2N), 48.3 (NHCH_2CH), 164.3, 165.0, 166.3, 166.5, 169.7 (C-triazine). − HRMS (ESI) calcd. for $C_{30}H_{47}ClN_{17}$ [M + H]$^+$: 680.3883 found *m*/*z*: 680.3851.

Cyclotristriazine 8d: Macrocycle **8d** was prepared from precursor **7d** (0.11 g, 0.13 mmol) according to the procedure described for **8c** to afford 68 mg (73%) of the title compound. However, DIPEA was used instead of Et_3N. The product was identical to macrocycle **8c**.

Cyclotristriazine 9a: A solution of macrocycle **8a** (0.12 g, 0.17 mmol) and amylamine (192 μL, 1.66 mmol) in THF (5 mL) was refluxed for 36 hours. The solvent was evaporated and the residue taken up in DCM. The resulting solution was washed with HCl (1 M, twice), dried with $MgSO_4$ and evaporated. Column chro-

matography (eluent: first 5% MeOH in DCM then 10% MeOH in DCM) afforded 112 mg of macrocycle **9a** (90%). R_f = 0.24 (3% MeOH in DCM). − ^{1}H NMR ($CDCl_3$): δ = 0.91 (t, 9 H, CH_2CH_3), 1.35 (m, 12 H, $CH_2CH_2CH_3$), 1.54 (m, 6 H, $NHCH_2CH_2$), 3.38 (q, 6 H, $NHCH_2CH_2$), 3.83 (br. s, 24 H, CH_2NAr), 4.84 (t, 3 H, $NHCH_2$). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 22.4 (CH_2CH_3), 29.1, 29.6 ($CH_2CH_2CH_2CH_3$), 40.7 ($NHCH_2CH_2$), 43.0 (NCH_2CH_2N), 165.2, 166.4 (C-triazine). − HRMS (ESI) calcd. for $C_{36}H_{61}N_{18}$ $[M + H]^+$: 745.5276 found *m/z*: 745.5327.

Cyclotristriazine 9b: A solution of macrocycle **8b** (0.13 g, 0.19 mmol) and benzylamine (204 μL, 1.87 mmol) in THF (4 mL) was refluxed for 36 hours. The solvent was evaporated and the residue taken up in DCM. The resulting solution was washed with 1 M HCl, water (three times) and 5% $NaHCO_3$, dried with $MgSO_4$, and evaporated. Column chromatography (eluent: 4% MeOH in DCM) afforded 110 mg of macrocycle **9b** (78%). R_f = 0.30 (4% MeOH in DCM). − ^{1}H NMR ($CDCl_3$): δ = 0.91 (t, 3 H, CH_2CH_3), 0.96 [d, 6 H, $CH(CH_3)_2$], 1.36 (m, 4 H, $CH_2CH_2CH_3$), 1.57 (m, 2 H, $NHCH_2CH_2$), 1.85 [m, 1 H, $CH(CH_3)_2$], 3.23 (t, 2 H, CH_2CH), 3.38 (q, 2 H, $NHCH_2CH_2$), 3.84 (br. s, 24 H, CH_2NAr), 4.62 (d, 2 H, CH_2Ph), 4.76, 4.83, 5.10 (three br. s, 3 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 20.3 [$CH(CH_3)_2$], 22.4 (CH_2CH_3), 28.7 [$CH(CH_3)_2$], 29.1, 29.5 ($CH_2CH_2CH_2CH_3$), 40.6 ($NHCH_2CH_2$), 42.9 (NCH_2CH_2N), 44.8 (CH_2Ph), 48.3 ($NHCH_2CH$), 127.0, 127.6, 128.4, 139.7 (C^{Ar}), 165.1, 166.43, 166.5 (C-triazine). − HRMS (ESI) calcd. for $C_{37}H_{55}N_{18}$ $[M + H]^+$: 751.4852 found *m/z*: 751.4873.

Cyclotristriazine 9e: A solution of macrocycle **8c** (32 mg, 44 μmol) and 2-phenylethylamine (55 μL, 0.44 mmol) in THF (2.5 mL) was refluxed overnight. The solvent was removed in vacuo and flash column chromatography (eluent: 2.5% MeOH in DCM) yielded 25 mg of product (70%). R_f = 0.23 (2.5% MeOH in DCM). − ^{1}H NMR ($CDCl_3$): δ = 0.92 (t, 3 H, CH_2CH_3), 1.35 (m, 4 H, $CH_2CH_2CH_3$), 1.56 (m, 2 H, $NHCH_2CH_2CH_2$), 2.89 (t, 4 H, CH_2Ph), 3.38 (q, 2 H, $NHCH_2CH_2CH_2$), 3.65 (q, 4 H, CH_2CH_2Ph), 3.84 (broad m, 24 H, CH_2NAr), 4.82 (t, 1 H, $NHCH_2CH_2CH_2$), 4.88 (t, 2 H, $NHCH_2CH_2Ph$), 7.22−7.34 (m, 5 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 22.4 (CH_2CH_3), 29.1, 29.6 ($CH_2CH_2CH_2CH_3$), 36.2 (CH_2Ph), 40.7 ($NHCH_2CH_2CH_2$), 42.2 (CH_2CH_2Ph), 43.0, (NCH_2CH_2N), 126.3, 128.5, 128.8, 139.5 (C^{Ar}), 165.2, 166.36, 166.45 (C-triazine). − HRMS (ESI) calcd. for $C_{42}H_{57}N_{18}$ $[M + H]^+$: 813.5014, found *m/z*: 813.5049.

Cyclotristriazine 9g: A solution of macrocycle **8e** (28 mg, 37 μmol) and 2-phenylethylamine (43 μL, 0.37 mmol) in THF (2.5 mL) was refluxed overnight. The solvent was evaporated and flash column chromatography (eluent: 3% MeOH in DCM) yielded 22 mg of product (73%). The analytical data of the product were identical to those of macrocycle **9e**.

Tristriazine 10: Tristriazine **10** was prepared from bistriazine **6b** (0.40 g, 0.50 mmol) according to the procedure described for **5a**. Column chromatography (eluent: EtOAc/hexanes 2:3) afforded 465 mg of product (93%). R_f = 0.45 (EtOAc/hexanes 1:1). − ^{1}H NMR ($CDCl_3$): δ = 0.91 (t, 3 H, CH_2CH_3), 0.95 [d, 6 H, $CH(CH_3)_2$], 1.36 (m, 4 H, $CH_2CH_2CH_3$), 1.50 [s, 9 H, $C(CH)_3$], 1.54 (m, 2 H, $NHCH_2CH_2$), 1.85 [m, 1 H, $CH(CH_3)_2$], 3.21 (t, 2 H, CH_2CH), 3.36 (q, 2 H, $NHCH_2CH_2$), 3.48, 3.54 [br. s, 8 H, $CH_2NC(O)$], 3.79 (broad m, 24 H, CH_2NAr), 4.78 (t, 1 H, $NHCH_2CH_2$), 4.87 (t, 1 H, $NHCH_2CH$), 5.18 (s, 2 H, OCH_2Ar), 7.38 (m, 5 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 20.3 [$CH(CH_3)_2$], 22.4 (CH_2CH_3), 28.4 [$C(CH_3)_3$], 28.8 [$CH(CH_3)_2$], 29.1, 29.6 ($CH_2CH_2CH_2CH_3$), 40.7 ($NHCH_2CH_2$), 42.7, 42.8, 43.0, 43.3, 43.4, 43.8, (broad, NCH_2CH_2N), 48.3 ($NHCH_2CH$), 67.3 (OCH_2Ar), 80.2 [$C(CH_3)_3$], 127.9, 128.1, 128.5, 136.6 (C^{Ar}), 154.7, 155.4 (C=O), 164.48, 164.52, 165.3, 166.4, 166.6, 169.7 (C-triazine). − HRMS (ESI) calcd. for $C_{47}H_{71}ClN_{19}O_4$ $[M + H]^+$: 1000.5625 found *m/z*: 1000.5649. − $C_{47}H_{70}ClN_{19}O_4$ (1000.6): calcd. C 56.41, H 7.05, N 26.60; found C 56.60, H 7.11, N 26.18.

Tristriazine 11: A solution of tristriazine **10** (0.42 g, 0.42 mmol) and cyclohexylamine (239 μL, 2.09 mmol) in THF (5 mL) was refluxed for 20 hours. The solvent was removed in vacuo and the residue was redissolved in EtOAc. The resulting solution was washed with water (acidified to pH 2 with 1 M HCl), water (twice), 5% $NaHCO_3$ and brine, dried with $MgSO_4$, and evaporated, affording 413 mg of product (92%). R_f = 0.40 (EtOAc/hexanes 1:1). − ^{1}H NMR ($CDCl_3$): δ = 0.90 (t, 3 H, CH_2CH_3), 0.94 [d, 6 H, $CH(CH_3)_2$], 1.16−2.01 (m, 10 H, CH_2-cyclohexyl), 1.34 (m, 4 H, $CH_2CH_2CH_3$), 1.48 [s, 9 H, $C(CH)_3$], 1.54 (m, 2 H, $NHCH_2CH_2$), 1.86 [m, 1 H, $CH(CH_3)_2$], 3.21 (t, 2 H, $NHCH_2CH$), 3.36 (q, 2 H, $NHCH_2CH_2$), 3.44, 3.52 [br. s, 8 H, $CH_2NC(O)$], 3.78 (br. s, 25 H, CH_2NAr, CH-cyclohexyl), 4.68 (d, 1 H, NH-cyclohexyl), 4.75 (t, 1 H, $NHCH_2CH_2$), 4.82 (t, 1 H, $NHCH_2CH$), 5.17 (s, 2 H, OCH_2Ar), 7.35 (m, 5 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 20.3 [$CH(CH_3)_2$], 22.4 (CH_2CH_3), 25.0, 25.8 (C^3, C^4-cyclohexyl), 28.4 [$C(CH_3)_3$], 28.8 [$CH(CH_3)_2$], 29.1, 29.6 ($CH_2CH_2CH_2CH_3$), 33.3 (C^2-cyclohexyl), 40.7 ($NHCH_2CH_2$), 42.9, 43.0, 43.8, (broad, NCH_2CH_2N), 48.3 ($NHCH_2CH$), 49.2 (C^1-cyclohexyl), 67.2 (OCH_2Ar), 79.8 [$C(CH_3)_3$], 127.9, 128.1, 128.5, 136.6 (C^{Ar}), 154.8, 155.3 (C=O), 165.3, 165.6, 166.4, 166.6 (broad, C-triazine). − HRMS (ESI) calcd. for $C_{53}H_{82}N_{20}NaO_4$ $(M + Na)^+$: 1085.6726, found *m/z*: 1085.6744. − $C_{53}H_{82}N_{20}O_4$: calcd. C 59.23, H 7.41, N 27.63: calcd. C 59.86, H 7.77, N 26.34; found C 59.86, H 7.70, N 26.18.

Precursor 12: Pd/C (200 mg, 10%) was added to a solution of compound **11** (0.35 g, 0.33 mmol) in THF/EtOH (1:1, 20 mL) and the resulting solution was stirred under a hydrogen atmosphere overnight. The catalyst was filtered off and the filtrate evaporated. The residue was dissolved in acetone (2 mL) and the resulting solution was added to a freshly prepared suspension of cyanuric chloride (61 mg, 0.33 mmol), precipitated from acetone (4 mL) in water (6 mL), after which $NaHCO_3$ (28 mg, 0.33 mmol) was added. After stirring for two hours at 0 °C, the aqueous suspension was extracted with DCM (three times) and the combined organic layers were dried with $MgSO_4$ and evaporated. Column chromatography (eluent: EtOAc/hexanes 1:2) yielded 227 mg of the title compound (68%). R_f = 0.52 (EtOAc/hexanes 1:1). − ^{1}H NMR ($CDCl_3$): δ = 0.92 (t, 3 H, CH_2CH_3), 0.94 [d, 6 H, $CH(CH_3)_2$], 1.15−2.05 (m, 10 H, CH_2-cyclohexyl), 1.33 (m, 4 H, $CH_2CH_2CH_3$), 1.47 [s, 9 H, $C(CH)_3$], 1.55 (m, 2 H, $NHCH_2CH_2$), 1.83 [m, 1 H, $CH(CH_3)_2$], 3.21 (t, 2 H, CH_2CH), 3.36 (q, 2 H, $NHCH_2CH_2$), 3.44 [br. s, 4 H, $CH_2NC(O)$], 3.79, 3.89 (two br. s, 25 H, CH_2NAr, CH-cyclohexyl), 4.75, 4.95 (two br. s, 3 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 20.3 [$CH(CH_3)_2$], 22.4 (CH_2CH_3), 24.9, 25.7 (C^3, C^4-cyclohexyl), 28.4 [$C(CH_3)_3$], 28.7 [$CH(CH_3)_2$], 29.1, 29.5 ($CH_2CH_2CH_2CH_3$), 33.2 (C^2-cyclohexyl), 40.7 ($NHCH_2CH_2$), 42.5, 43.0, 44.0 (NCH_2CH_2N), 48.2 ($NHCH_2CH$), 49.1 (C^1-cyclohexyl), 79.8 [$C(CH_3)_3$], 154.8 (C=O), 164.0, 165.2, 166.3, 170.3 (C-triazine). − HRMS (ESI) calcd. for $C_{48}H_{76}Cl_2N_{23}O_2$ $[M + H]^+$: 1076.5924 found *m/z*: 1076.5945.

Cylcotetratriazine 13: A solution of dichloride **12** (0.10 g, 94 μmol) in HCl (4 M, 10 mL) in dioxane was stirred for four hours. The

volatiles were removed in vacuo and the residue was coevaporated twice with THF. The intermediate was dried in vacuo in a desiccator over KOH overnight. Subsequently, the intermediate was dissolved in DMF (45 mL) and a solution of Et_3N (0.13 mL, 0.94 mmol) in DMF (5 mL) was added dropwise at 45 °C to the resulting solution. After continuing stirring for 30 minutes at this temperature, the solvent was removed in vacuo. The residue was dissolved in DCM and the resulting solution was washed with water (twice) and brine and dried with $MgSO_4$. Column chromatography (eluent: 3% MeOH in DCM) afforded a mixture of the title compound and its corresponding dimer. These were separated by gel permeation chromatography (eluent: DCM/MeOH 2:1) to afford 20 mg of macrocycle **13** (23%). R_f = 0.20 (3% MeOH in DCM). − ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, 3 H, CH_2CH_3), 0.91 [d, 6 H, $CH(CH_3)_2$], 1.17 (m, 2 H, H^{2a}-cyclohexyl), 1.32 (m, 6 H, $CH_2CH_2CH_3$, H^{3a}-cyclohexyl), 1.53 (m, 2 H, $NHCH_2CH_2$), 1.59 (m, 2 H, H^4-cyclohexyl), 1.73 (m, 2 H, H^{3b}-cyclohexyl), 1.81 [m, 1 H, $CH(CH_3)_2$], 1.97 (broad d, 2 H, H^{2b}-cyclohexyl), 3.18 (br. s, 2 H, CH_2CH), 3.33 (q, 2 H, $NHCH_2CH_2$), 3.50−4.00 (m, 33 H, CH_2NAr, H^1-cyclohexyl), 4.68 (d, 1 H, NH-cyclohexyl), 4.75 (t, 1 H, $NHCH_2CH_2$), 4.79 (br. s, 1 H, $NHCH_2CH$). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 20.3 [$CH(CH_3)_2$], 22.4 (CH_2CH_3), 24.9, 25.8 (C^3, C^4-cyclohexyl), 28.7 [$CH(CH_3)_2$], 29.1, 29.5 ($CH_2CH_2CH_2CH_3$), 33.2 (C^2-cyclohexyl), 40.7 ($NHCH_2CH_2$), 42.7, 43.17, 43.23, 43.5 (NCH_2CH_2N), 48.2 ($NHCH_2CH$), 49.2 (C^1-cyclohexyl), 165.5, 165.7, 166.4, 166.47, 166.52, 166.6, 166.7, 169.7 (C-triazine). − HRMS (LSIMS) calcd. for $C_{43}H_{67}ClN_{23}$ [M + H]$^+$: 940.5633 found *m*/*z*: 940.5723. Additionally, 27 mg dimer was isolated (31%): R_f = 0.17 (3% MeOH in DCM). − ^{1}H NMR ($CDCl_3$): δ = 0.90 (t, 3 H, CH_2CH_3), 0.94 [d, 6 H, $CH(CH_3)_2$], 1.19 (m, 2 H, H^{2a}-cyclohexyl), 1.34 (m, 6 H, $CH_2CH_2CH_3$, H^{3a}-cyclohexyl), 1.55 (m, 2 H, $NHCH_2CH_2$), 1.63 (br. s, 2 H, H^4-cyclohexyl), 1.73 (m, 2 H, H^{3b}-cyclohexyl), 1.83 [m, 1 H, $CH(CH_3)_2$], 2.00 (broad d, 2 H, H^{2b}-cyclohexyl), 3.20 (t, 2 H, CH_2CH), 3.35 (q, 2 H, $NHCH_2CH_2$), 3.78 (br. s, 33 H, CH_2NAr, H^1-cyclohexyl), 4.70 (d, 1 H, NH-cyclohexyl), 4.77 (br. s, 1 H, $NHCH_2CH$), 4.82 (br. s, 1 H, $NHCH_2CH_2$). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 20.3 [$CH(CH_3)_2$], 22.4 (CH_2CH_3), 25.0, 25.8 (C^3, C^4-cyclohexyl), 28.8 [$CH(CH_3)_2$], 29.2, 29.6 ($CH_2CH_2CH_2CH_3$), 33.3 (C^2-cyclohexyl), 40.7 ($NHCH_2CH_2$), 42.6, 43.1 (NCH_2CH_2N), 48.3 ($NHCH_2CH$), 49.2 (C^1-cyclohexyl), 164.7, 165.5, 165.7, 166.4, 166.6, 169.6 (C-triazine). − HRMS (LSIMS) calcd. for $C_{86}H_{133}Cl_2N_{46}$ [M + H]$^+$: 1880.1193 found *m*/*z*: 1880.1048.

Cyclotetratriazine 14: A solution of macrocycle **13** (5.0 mg, 5.3 μmol) and 2-phenylethylamine (20 μL, 0.16 mmol) in THF (1.5 mL) was refluxed for 24 hours. The solvent was evaporated and the residue taken up in DCM. The resulting solution was washed with 1 M HCl, water (twice), 5% $NaHCO_3$ and brine, dried with $MgSO_4$, and evaporated. Column chromatography (eluent: 3% MeOH in DCM) afforded 4.0 mg of macrocycle **14** (74%). R_f = 0.46 (5% MeOH in DCM). − ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, 3 H, CH_2CH_3), 0.91 [d, 6 H, $CH(CH_3)_2$], 1.16 (m, 2 H, H^{2a}-cyclohexyl), 1.31 (m, 6 H, $CH_2CH_2CH_3$, H^{3a}-cyclohexyl), 1.52 (m, 2 H, $NHCH_2CH_2$), 1.61 (m, 2 H, H^4-cyclohexyl), 1.71 (m, 2 H, H^{3b}-cyclohexyl), 1.81 [m, 1 H, $CH(CH_3)_2$], 1.97 (broad d, 2 H, H^{2b}-cyclohexyl), 2.85 (t, 2 H, CH_2Ph), 3.18 (br. s, 2 H, CH_2CH), 3.33 (q, 2 H, $NHCH_2CH_2CH_2$), 3.50−3.95 (br. s, 35 H, CH_2NAr, H^1-cyclohexyl, CH_2CH_2Ph), 4.67 (d, 1 H, NH-cyclohexyl), 4.74 (t, 1 H, $NHCH_2CH_2CH_2$), 4.80 (q, 2 H, $NHCH_2CH$, $NHCH_2CH_2Ph$), 7.19−7.32 (m, 5 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 20.3 [$CH(CH_3)_2$], 22.4 (CH_2CH_3), 25.0, 25.8 (C^3, C^4-cyclohexyl), 28.7 [$CH(CH_3)_2$], 29.1, 29.5 ($CH_2CH_2CH_2CH_3$), 33.2 (C^2-cyclohexyl), 36.1 (CH_2Ph), 40.7 ($NHCH_2CH_2CH_2$), 42.2 (CH_2CH_2Ph), 43.2, 43.5 (NCH_2CH_2N), 48.3 ($NHCH_2CH$), 49.2 (C^1-cyclohexyl), 126.3, 128.5, 128.8, 139.5 (C^{Ar}), 165.8, 166. 5, 166.8 (C-triazine). − HRMS (ESI) calcd. for $C_{51}H_{76}N_{24}$ [M + H]$^+$: 1025.6763 found *m*/*z*: 1025.6696.

Cyclopentatriazine 16: A solution of cyclopentatriazine **15** (35 mg, 29 μmol) and 2-phenylethylamine (55 μL, 0.44 mmol) in THF (2 mL) was refluxed for 6 hours. The solvent was removed in vacuo and the residue was redissolved in EtOAc. The resulting solution was washed with water (acidified to pH 4 with 1 M HCl), water, 5% $NaHCO_3$ and brine, dried with $MgSO_4$, and evaporated. Gel permeation chromatography (eluent: DCM/MeOH 2:1) afforded 30 mg of product (80%). R_f = 0.52 (4% MeOH in DCM). − ^{1}H NMR ($CDCl_3$): δ = 0.90 (t, 3 H, CH_2CH_3), 0.94 [d, 6 H, $CH(CH_3)_2$], 1.19 (m, 2 H, H^{2a}-cyclohexyl), 1.34 (m, 6 H, $CH_2CH_2CH_3$, H^{3a}-cyclohexyl), 1.55 (m, 2 H, $NHCH_2CH_2$), 1.62 (broad d, 2 H, H^4-cyclohexyl), 1.73 (m, 2 H, H^{3b}-cyclohexyl), 1.84 [m, 1 H, $CH(CH_3)_2$], 2.00 (broad d, 2 H, H^{2b}-cyclohexyl), 2.88 (t, 2 H, CH_2Ph), 3.21 (t, 2 H, $NHCH_2CH$), 3.36 (q, 2 H, $NHCH_2CH_2CH_2$), 3.64 (q, 2 H, CH_2CH_2Ph), 3.81, 3.84 (two broad s, 41 H, CH_2NAr, H^1-cyclohexyl), 4.74 (d, 1 H, NH-cyclohexyl), 4.82 (t, 1 H, $NHCH_2CH_2CH_2$), 4.88 (q, 2 H, $NHCH_2CH$, $NHCH_2CH_2Ph$), 6.86 (s, 1 H, NHPh), 7.01 (t, 1 H, ArH), 7.22−7.31 (m, 7 H, ArH), 7.56 (d, 2 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 20.3 [$CH(CH_3)_2$], 22.4 (CH_2CH_3), 25.0, 25.8 (C^3, C^4-cyclohexyl), 28.7 [$CH(CH_3)_2$], 29.1, 29.5 ($CH_2CH_2CH_2CH_3$), 33.3 (C^2-cyclohexyl), 36.1 (CH_2Ph), 40.7 ($NHCH_2CH_2CH_2$), 42.1 (CH_2CH_2Ph), 43.2 (NCH_2CH_2N), 48.3 ($NHCH_2CH$), 49.1 (C^1-cyclohexyl), 119.7, 122.3, 126.3, 128.5, 128.7, 128.8, 139.4, 139.5 (C^{Ar}), 164.7, 165.39, 165.42, 165.5, 165.8, 166.6, 166.7, 166.8 (C-triazine). − HRMS (LSIMS) calcd. for $C_{64}H_{91}N_{30}$ [M + H]$^+$: 1279.8043, found *m*/*z*: 1279.8091.

Cyclohexatriazine 18: A solution of cyclohexatriazine **17** (74 mg, 50 μmol) and benzylamine (82 μL, 0.75 mmol) in THF (3 mL) was refluxed for 36 hours and stirred at room temperature overnight. The solvent was removed in vacuo and the residue was redissolved in DCM. The resulting solution was washed with water (acidified with 0.6 mL 1 M HCl), water (three times), dried with $MgSO_4$ and evaporated. Column chromatography (eluent: 3.5% MeOH in DCM) followed by gel permeation chromatography (eluent: DCM/MeOH 2:1) afforded 57 mg of product (74%). R_f = 0.37 (4% MeOH in DCM). − ^{1}H NMR ($CDCl_3$, 30 °C): δ = 0.91 (t, 3 H, CH_2CH_3), 0.96 [d, 6 H, $CH(CH_3)_2$], 1.22 (m, 2 H, H^{2a}-cyclohexyl), 1.35 (m, 6 H, $CH_2CH_2CH_3$, H^{3a}-cyclohexyl), 1.55 (m, 2 H, $NHCH_2CH_2CH_2$), 1.65 (m, 2 H, H^4-cyclohexyl), 1.75 (m, 2 H, H^{3b}-cyclohexyl), 1.85 [m, 1 H, $CH(CH_3)_2$], 2.03 (broad d, 2 H, H^{2b}-cyclohexyl), 2.90 (t, 2 H, CH_2Ph), 3.23 (t, 2 H, $NHCH_2CH$), 3.39 (q, 2 H, $NHCH_2CH_2CH_2$), 3.66 (q, 2 H, CH_2CH_2Ph), 3.79, 3.83, 3.86 (broad m, 49 H, CH_2NAr, H^1-cyclohexyl), 4.61 (d, 2 H, NCH_2Ph), 4.69 (d, 1 H, NH-cyclohexyl), 4.74 (t, 1 H, $NHCH_2CH_2CH_2$), 4.82 (t, 2 H, $NHCH_2CH$, $NHCH_2CH_2Ph$), 5.09 (t, 1 H, $NHCH_2Ph$), 6.71 (s, 1 H, NHPh), 7.02 (t, 1 H, ArH), 7.23−7.34 (m, 12 H, ArH), 7.57 (d, 2 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 20.3 [$CH(CH_3)_2$], 22.4 (CH_2CH_3), 24.9, 25.8 (C^3, C^4-cyclohexyl), 28.8 [$CH(CH_3)_2$], 29.1, 29.6 ($CH_2CH_2CH_2CH_3$), 33.2 (C^2-cyclohexyl), 36.2 (CH_2Ph), 40.7 ($NHCH_2CH_2CH_2$), 42.2 (CH_2CH_2Ph), 43.0, 43.3 (NCH_2CH_2N), 44.8 (NCH_2Ph), 48.3 ($NHCH_2CH$), 49.1 (C^1-cyclohexyl), 119.7, 122.3, 126.3, 127.0, 127.6, 128.4, 128.5, 128.7, 128.8, 139.4, 139.5, 139.7 (C^{Ar}), 164.5, 165.2, 165.6, 166.36 166.42, 166.6 (C-triazine). − HRMS (ESI) calcd. for $C_{78}H_{107}N_{36}$ [M + H]$^+$: 1547.9474, found *m*/*z*: 1547.9496.

Boc-Xylenediamine 19: The title compound was synthesized according to Callahan et al.[27] The product was purified further by column chromatography (eluent: 30% MeOH in DCM). Xylenediamine (11 mL) and Boc_2O (2.18 g, 10.0 mmol) afforded 1.69 g (72%) of title compound.

Monosubstituted Triazine 20: The title compound was prepared from amine **19** (1.59 g, 6.73 mmol) according to the procedure described for **1** (the reaction time was 3 hours, however), to afford 2.20 g of triazine **20** (85%). R_f = 0.57 (EtOAc/hexanes 1:1). − ^{1}H NMR ($CDCl_3$): δ = 1.45 [s, 9 H, $C(CH_3)_3$], 4.30 (d, 2 H, CH_2NHBoc), 4.65 (s, 2 H, CH_2NHAr), 4.91 (br. s, 1 H, NHBoc), 6.62 (br. s, 1 H, NHAr), 7.19−7.34 (m, 4 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 28.4 [$C(CH_3)_3$], 44.4, 45.3 (CH_2N), 79.7 [$C(CH_3)_3$], 126.6, 127.1, 129.2, 136.6, 139.8 (C^{Ar}), 155.9 (C=O), 165.8, 170.0, 171.1 (C-triazine). − HRMS (ESI) calcd. for $C_{16}H_{19}Cl_2N_5NaO_2$ $(M + Na)^+$: 406.0813, found *m/z*: 406.0818. − $C_{16}H_{19}Cl_2N_5O_2$ (384.3): calcd. C 50.01, H 4.98, N 18.23; found C 50.14, H 4.97, N 17.86.

α-Boc-ω-Z-Xylenediamine: The title compound was prepared from amine **20** (1.57 g, 6.64 mmol) according to the procedure described for 1-Boc-4-Z-piperazine to give 2.14 g product (87%). R_f = 0.47 (EtOAc/hexanes 1:1). − ^{1}H NMR ($CDCl_3$): δ = 1.46 [s, 9 H, $C(CH_3)_3$], 4.28, 4.37 (two s, 4 H, CH_2NH), 4.86 (br. s, 2 H, NH), 5.13 (s, 2 H, OCH_2), 7.17−7.36 (m, 9 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 28.4 [$C(CH_3)_3$], 44.5, 45.0 (CH_2N), 79.5 [$C(CH_3)_3$], 126.4, 126.6, 128.1, 128.5, 128.9, 136.4, 138.8, 139.4 (C^{Ar}), 155.8, 156.4 (C=O).

Z-Xylenediamine 21: The title compound was prepared from α-Boc-ω-Z-xylenediamine (1.98 g, 5.34 mmol) according to the procedure described for **2** to yield 1.36 g product (94%). R_f = 0.18 (10% MeOH and 1% Et_3N in DCM). − ^{1}H NMR ($CDCl_3$): δ = 1.48 (s, 2 H, NH_2), 3.83 (s, 2 H, CH_2NH_2), 4.36 (d, 2 H, CH_2NHBoc), 5.13 (s, 2 H, OCH_2), 5.25 (br. s, 1 H, NHZ), 7.14−7.36 (m, 9 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 45.0, 46.2 (CH_2N), 66.8 (OCH_2), 125.9, 126.1, 126.2, 128.1, 128.5, 128.8, 136.5, 138.7, 143.7 (C^{Ar}), 156.4 (C=O).

Disubstituted Triazine 22: Na_2CO_3 (316 mg, 2.99 mmol) and a solution of monosubstituted triazine **20** (1.04 g, 2.71 mmol) in acetone (7 mL) were added to a solution of Z-xylenediamine **21** (807 mg, 2.99 mmol) in water/acetone (1:1, 20 mL). After stirring at 65 °C for 5 hours, the suspension was cooled to room temperature and the white solid filtered off and washed with water. Drying in vacuo over P_2O_5 overnight yielded 1.60 g of product (96%). R_f = 0.64 (10% MeOH in DCM). − ^{1}H NMR ([D_6]DSMO; 100 °C): δ = 1.38 (s, 2 H, $C(CH_3)_3$], 4.11, 4.20 (two d, 4 H, CH_2NHC(O)], 4.44 (d, 4 H, CH_2NHAr), 5.05 (s, 2 H, OCH_2), 7.10−7.33 (m, 13 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 27.7 [$C(CH_3)_3$], 43.3, 43.4, 43.7 (CH_2N), 64.9 (OCH_2), 77.3 [$C(CH_3)_3$], 125.0, 125.1, 125.2, 125.3, 125.4, 125.6, 127.0, 127.1, 127.5, 127.6, 127.7, 136.8, 138.6, 138.7, 139.2, 139.7 (C^{Ar}), 155.1, 155.7 (C=O) 165.3 (C-triazine). − HRMS (ESI) calcd. for $C_{32}H_{36}ClN_7NaO_4$ $(M + Na)^+$: 640.2415, found *m/z*: 640.2446. − $C_{32}H_{36}ClN_7O_4$ (618.1): calcd. C 62.18, H 5.87, N 15.86; found C 62.02, H 5.82, N 15.63.

Trisubstituted Triazine 23: Trisubstituted triazine **23** was prepared from triazine **22** (1.00 g, 1.62 mmol) according to the procedure described for **4a** to afford 1.06 g of the title compound (98%). R_f = 0.66 (10% MeOH in DCM). − ^{1}H NMR ($CDCl_3$): δ = 0.87 (t, 3 H, CH_2CH_3), 1.28 (m, 4 H, $CH_2CH_2CH_3$), 1.44 [s, 9 H, $C(CH_3)_3$], 1.48 (m, 2 H, $NHCH_2CH_2$), 3.28 (br. s, 2 H, $NHCH_2CH_2$), 4.23, 4.29 (two br. s, 4 H, CH_2NC(O)], 4.48 (br. s, 4 H, CH_2NAr), 5.10 (s, 2 H, OCH_2), 7.14−7.34 (m, 13 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 22.4 (CH_2CH_3), 28.4 [$C(CH_3)_3$], 29.1, 29.5 ($CH_2CH_2CH_2CH_3$), 40.6 ($NHCH_2$), 44.5, 44.6, 45.0 (CH_2N), 66.8 (OCH_2), 79.4 [$C(CH_3)_3$], 126.3, 126.6, 128.1, 128.5, 128.7, 128.8, 136.5, 138.6, 139.1, 139.9 (C^{Ar}), 155.9, 156.4 (C=O), 166.1 (C-triazine). − HRMS (ESI) calcd. for $C_{37}H_{49}N_8O_4$ $[M + H]^+$: 669.3877, found *m/z*: 669.3855. − $C_{37}H_{48}N_8O_4$ (668.8): calcd. C 66.44, H 7.23, N 16.75; found C 66.49, H 7.21, N 16.70.

Bistriazine 24: Bistriazine **24** was prepared from tetratriazine **23** (1.03 g, 1.54 mmol) and monosubstituted triazine **20** (563 mg, 1.54 mmol) according to the procedure described for **5a** (the reaction time was extended to 4 hours, however). Column chromatography (eluent: 4% MeOH in DCM) afforded 1.17 g of product (83%). R_f = 0.50 (10% MeOH in DCM). − ^{1}H NMR ([D_6]DMSO, 100 °C): δ = 0.85 (t, 3 H, CH_2CH_3), 1.27 (m, 4 H, $CH_2CH_2CH_3$), 1.38 [s, 9 H, $C(CH_3)_3$], 1.47 (m, 2 H, $NHCH_2CH_2$), 3.19 (q, 2 H, $NHCH_2CH_2$), 4.10, 4.19 (two d, 4 H, CH_2NC(O)], 4.43 (m, 8 H, CH_2NAr), 5.04 (s, 2 H, OCH_2), 6.04, 6.50, 6.81, 7.85 (four br. s, 7 H, NH), 7.11−7.32 (m, 17 H, ArH, NH). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 22.4 (CH_2CH_3), 28.4 [$C(CH_3)_3$], 29.1, 29.4 ($CH_2CH_2CH_2CH_3$), 40.6 ($NHCH_2$), 44.4, 44.7, 45.0 (CH_2N), 66.8 (OCH_2), 79.5 [$C(CH_3)_3$], 126.2, 126.4, 126.7, 128.1, 128.5, 128.7, 128.8, 136.5, 138.1, 138.3, 138.4, 138.6, 139.4, 140.0 (C^{Ar}), 155.9, 156.4 (C=O), 165.4, 165.7, 166.0, 168.3, 169.3 (C-triazine). − HRMS (ESI) calcd. for $C_{48}H_{59}ClN_{13}O_4$ $[M + H]^+$: 916.4501, found *m/z*: 916.4511. − $C_{48}H_{58}ClN_{13}O_4$ (916.5): calcd. C 62.90, H 6.38, N 19.87; found C 62.69, H 6.34, N 19.73.

Bistriazine 25a: Bistriazine **25a** was prepared from bistriazine **24** (0.50 g, 0.52 mmol) and isobutylamine (414 μL, 4.17 mmol) according to the procedure described for **6a** to afford 500 mg of the title compound (97%). R_f = 0.47 (10% MeOH in DCM). − ^{1}H NMR ([D6]DMSO, 80 °C): δ = 0.82 [d, 6 H, $CH(CH_3)_2$], 0.84 (t, 3 H, CH_2CH_3), 1.26 (m, 4 H, $CH_2CH_2CH_3$), 1.37 [s, 9 H, $C(CH_3)_3$], 1.45 (m, 2 H, $NHCH_2CH_2$), 1.78 [m, 1 H, $CH(CH_3)_2$], 3.02 (t, 2 H, $NHCH_2CH$)], 3.17 (q, 2 H, $NHCH_2CH_2$), 4.09, 4.18 (two d, 4 H, CH_2NC(O)], 4.40 (t, 8 H, CH_2NAr), 5.04 (s, 2 H, OCH_2), 6.1−7.5 (broad, 8 H, NH), 7.08−7.22 (m, 17 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 20.2 [$CH(CH_3)_2$], 22.4 (CH_2CH_3), 28.4 [$C(CH_3)_3$], 29.1, 29.5 ($CH_2CH_2CH_2CH_3$), 40.6 ($NHCH_2$), 44.5, 45.0 (CH_2N), 48.2 (CH_2CH), 66.7 (OCH_2), 79.4 [$C(CH_3)_3$], 126.3, 126.6, 128.1, 128.5, 128.69, 128.74, 136.5, 138.6, 139.1, 139.6 (C^{Ar}), 155.9, 156.4 (C=O), 166.0 (C-triazine). − HRMS (LSIMS) calcd. for $C_{52}H_{69}N_{14}O_4$ $[M + H]^+$: 953.5626, found *m/z*: 953.5637. − $C_{52}H_{68}N_{14}O_4 \cdot 0.5\ H_2O$ (962.2): calcd. C 64.91, H 7.22, N 20.38; found C 64.93, H 7.17, N 20.17.

Bistriazine 25b: Bistriazine **25b** was prepared from bistriazine **24** (0.54 g, 0.59 mmol) and amylamine (543 μL, 4.69 mmol) according to the procedure described for **6a** to afford 550 mg of the title compound (97%). R_f = 0.53 (10% MeOH in DCM). − ^{1}H NMR ([D_6]DMSO, 80 °C): δ = 0.85 (t, 6 H, CH_2CH_3), 1.26 (m, 8 H, $CH_2CH_2CH_3$), 1.37 [s, 9 H, $C(CH_3)_3$], 1.46 (m, 4 H, $NHCH_2CH_2$), 3.18 (q, 4 H, $NHCH_2CH_2$), 4.09, 4.18 (two d, 4 H, CH_2NC(O)], 4.40 (t, 8 H, CH_2NAr), 5.04 (s, 2 H, OCH_2), 6.1−7.5 (broad, 8 H, NH), 7.08−7.32 (m, 17 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 22.4 (CH_2CH_3), 28.4 [$C(CH_3)_3$], 29.1, 29.5 ($CH_2CH_2CH_2CH_3$), 40.6 ($NHCH_2$), 44.5, 45.0 (CH_2N), 66.8 (OCH_2), 79.4 [$C(CH_3)_3$], 126.3, 126.6, 128.1, 128.5, 128.69, 128.75, 136.5, 138.6, 139.1, 139.9 (C^{Ar}), 155.9, 156.4 (C=O), 166.0 (C-triazine). − HRMS (ESI) calcd. for $C_{53}H_{71}N_{14}O_4$ $[M + H]^+$: 967.5783, found *m/z*: 967.5748. − $C_{53}H_{70}N_{14}O_4$ (967.2): calcd. C 65.81, H 7.29, N 20.27; found C 65.56, H 7.37, N 20.03.CBO

Precursor to Cyclotristriazine 26a: Pd/C (10%, 250 mg) was added to a solution of Z-compound **25a** (0.24 g, 0.25 mmol) in THF/

EtOH (1:1, 14 mL) and the resulting solution was stirred under a hydrogen atmosphere overnight. After the addition of another 250 mg of Pd/C and stirring for 8 hours, the catalyst was filtered off and the filtrate evaporated. The residue was dissolved in acetone (2 mL) and the resulting solution was added to a freshly prepared suspension of cyanuric chloride (44 mg, 0.24 mmol), precipitated from acetone (2 mL) in water (4 mL), after which $NaHCO_3$ (21 mg, 0.25 mmol) was added. After stirring for 30 minutes at 0 °C, the aqueous suspension was extracted with DCM and the organic layer was dried with $MgSO_4$ and evaporated. Flash column chromatography (eluent: 5% MeOH in DCM) yielded 106 mg of product (44%). The crude product was used directly to prepare macrocycle **26a**. R_f = 0.20 (5% MeOH in DCM). − ^{1}H NMR ($CDCl_3$): δ = 0.85 [broad m, 9 H, $CH(CH_3)_2$, CH_2CH_3], 1.25 (broad m, 4 H, $CH_2CH_2CH_3$), 1.42 [br. s, 11 H, $C(CH)_3$, $NHCH_2CH_2$], 1.73 [m, 1 H, $CH(CH_3)_2$], 3.10, 3.23 (two br. s, 4 H, $NHCH_2CH$, $NHCH_2CH_2$), 4.20 [br. s, 4 H, $CH_2NC(O)$], 4.40 (broad m, 8 H, CH_2NAr), 5.28 (s, 2 H, OCH_2), 7.06 (broad m, 12 H, ArH). − ^{13}C NMR ($CDCl_3$) peaks of the predominant rotamer: δ = 13.9 (CH_2CH_3), 20.2 [$CH(CH_3)_2$], 22.3 (CH_2CH_3), 28.3 [$C(CH_3)_3$], 29.0, 29.4 ($CH_2CH_2CH_2CH_3$), 40.5 ($NHCH_2$), 44.5, 45.0 (CH_2N), 48.1 (CH_2CH), 79.3 [$C(CH_3)_3$], 126.2, 126.5, 128.3, 128.4, 128.6, 128.8, 136.4, 137.9, 139.1, 139.6 (C^{Ar}), 155.9 (C=O), 165.5, 165.8, 169.6, 170.8 (C-triazine). − HRMS (ESI) calcd. for $C_{47}H_{62}Cl_2N_{17}O_2$ [M + H]$^+$: 966.4649, found 966.4686.

Precursor to Cyclotristriazine 26b: Pd/C (10%, 350 mg) was added to a solution of Z-compound **15b** (0.26 g, 0.27 mmol) in THF/EtOH (1:1, 14 mL). After stirring the solution under a hydrogen atmosphere overnight, the catalyst was filtered off and the filtrate evaporated. The residue was dissolved in acetone/THF (1:1, 2 mL) and the resulting solution was added to a freshly prepared suspension of cyanuric chloride (47 mg, 0.26 mmol), precipitated from acetone (2 mL) in water (4 mL), after which $NaHCO_3$ (23 mg, 0.27 mmol) was added. After stirring for 30 minutes at 0 °C, water was added, the aqueous suspension was extracted with DCM and the combined organic layers were dried with $MgSO_4$ and evaporated. Flash column chromatography (eluent: 5% MeOH in DCM) yielded 127 mg of product (48%). The crude product was used directly to prepare macrocycle **26b**. R_f = 0.15 (5% MeOH in DCM). − ^{1}H NMR ($CDCl_3$): δ = 0.85 (t, 6 H, CH_2CH_3), 1.25 (broad m, 8 H, $CH_2CH_2CH_3$), 1.43 (br. s, 13 H, $C(CH)_3$, $NHCH_2CH_2$), 3.24 (br. s, 4 H, $NHCH_2CH_2$), 4.10−4.55 (broad m, 12 H, $CH_2NC(O)$, CH_2NAr), 5.28 (s, 2 H, OCH_2), 7.06 (broad m, 12 H, ArH). − ^{13}C NMR ($CDCl_3$) peaks of the predominant rotamer: δ = 14.0 (CH_2CH_3), 22.4 (CH_2CH_3), 28.4 [$C(CH_3)_3$], 29.0, 29.4 ($CH_2CH_2CH_2CH_3$), 40.6 ($NHCH_2$), 44.5, 45.0 (CH_2N), 79.3 [$C(CH_3)_3$], 126.2, 126.5, 128.4, 128.6, 128.8, 136.5, 139.1, 139.6 (C^{Ar}), 155.9 (C=O), 165.5, 165.8, 169.6, 170.8 (C-triazine). − HRMS (ESI) calcd. for $C_{48}H_{64}Cl_2N_{17}O_2$ [M + H]$^+$: 980.4806; found *m*/*z*: 980.4869.

Cyclotristriazine 26a: A solution of its precursor (55 mg, 57 μmol) in HCl in dioxane (4 M, 5 mL) was stirred for six hours. The volatiles were removed in vacuo and the residue was coevaporated with THF twice. The intermediate was dried in vacuo in a desiccator over KOH overnight. Subsequently, the intermediate was dissolved in DMF (25 mL) and a solution of DIPEA (79 μL, 0.57 mmol) in DMF (5 mL) was added dropwise at 45 °C to the resulting solution. Another aliquot of DIPEA (79 μL) was added and stirring was continued for 45 minutes at 45 °C, after which the solvent was removed in vacuo. Flash column chromatography (eluent: 6% MeOH in DCM) afforded 17 mg of macrocycle **8a** (36%). The product was used without further purification to prepare macrocycle **27a**. R_f = 0.25 (6% MeOH in DCM). − ^{1}H NMR ($CDCl_3$ + [D_6]MeOD): δ = 0.88 [broad m, 9 H, $CH(CH_3)_2$, CH_2CH_3], 1.29 (br. s, 4 H, $CH_2CH_2CH_3$), 1.49 (br. s, 2 H, $NHCH_2CH_2$), 1.77 (broad m, 1 H, $CH(CH_3)_2$], 3.09, 3.25 (two br. s, 4 H, $NHCH_2CH$, $NHCH_2CH_2$), 4.40 (broad m, 12 H, CH_2NAr), 7.11 (broad m, 12 H, ArH). − ^{13}C NMR ($CDCl_3$ + [D_6]MeOD): δ = 14.0 (CH_2CH_3), 20.2 [$CH(CH_3)_2$], 22.4 (CH_2CH_3), 28.5 [$C(CH_3)_3$], 29.1, 29.4 ($CH_2CH_2CH_2CH_3$), 40.6, 40.7 ($NHCH_2CH_2$), 44.4, 44.6 (CH_2N), 48.1 ($NHCH_2CH$), 125.8, 126.5, 128.5, 128.7, 138.1, 138.4, 139.9 (C^{Ar}), 155.9 (C=O), 165.6, 165.8, 168.2, 169.2 (C-triazine). − HRMS (ESI) calcd. for $C_{42}H_{52}ClN_{17}$ [M + H]$^+$: 830.4359, found 830.4302.

Cyclotristriazine 26b: Cyclotristriazine **26b** was prepared from 125 mg of its precursor (127 μmol) according to the procedure described for **26a**. Flash column chromatography (eluent: 4.5% MeOH in DCM) afforded 37 mg of macrocycle **26b** (34%). The product was used without further purification to prepare macrocycle **27b**. R_f = 0.11 (5% MeOH in DCM). − ^{1}H NMR ($CDCl_3$): δ = 0.85 (t, 6 H, CH_2CH_3), 1.26 (br. s, 8 H, $CH_2CH_2CH_3$), 1.45 (br. s, 4 H, $NHCH_2CH_2$), 3.26 (br. s, 4 H, $NHCH_2CH_2$), 4.39 (br. s, 12 H, $CH_2NC(O)$, CH_2NAr), 7.13 (broad m, 12 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 22.4 (CH_2CH_3), 29.1, 29.5 ($CH_2CH_2CH_2CH_3$), 40.6 ($NHCH_2$), 44.6 (CH_2N), 79.3 [$C(CH_3)_3$], 126.5, 128.5, 128.7, 138.1, 138.4, 139.8, 140.0 (C^{Ar}), 166.0, 168.3 (C-triazine). − HRMS (ESI) calcd. for $C_{43}H_{54}ClN_{17}$ [M + H]$^+$: 844.4509; found *m*/*z*: 844.4542.

Cyclotristriazine 27a: A solution of cyclotristriazine **26a** (17 mg, 20 μmol) and benzylamine (22 μL, 0.20 mmol) in THF (3 mL) was refluxed overnight. The solvent was removed in vacuo and the residue was purified by column chromatography (eluent: 10% MeOH in DCM) followed by gel permeation chromatography (eluent: DCM/MeOH 2:1) to yield 13 mg of product (71%). R_f = 0.26 (10% MeOH in DCM). − ^{1}H NMR ($CDCl_3$): δ = 0.86 (t, 9 H, $CH(CH_3)_2$, CH_2CH_3), 1.27 (br. s, 4 H, $CH_2CH_2CH_3$), 1.46 (br. s, 2 H, $NHCH_2CH_2$), 1.74 [br. s, 1 H, $CH(CH_3)_2$], 3.10, 3.26 (two br. s, 4 H, $NHCH_2CH$, $NHCH_2CH_2$), 4.41 (broad m, 12 H, CH_2NAr), 4.96 (br. s, 2 H, CH_2Ph), 6.95−7.30 (broad m, 17 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 20.2 [$CH(CH_3)_2$], 22.4 (CH_2CH_3), 28.5 [$C(CH_3)_3$], 29.1, 29.4 ($CH_2CH_2CH_2CH_3$), 40.6 ($NHCH_2CH_2$), 44.4 (CH_2N, CH_2Ph), 48.1 ($NHCH_2CH$), 126.0, 126.6, 126.9, 127.4, 128.4, 139.7 (C^{Ar}), 166.0 (C-triazine). − HRMS (ESI) calcd. for $C_{49}H_{61}N_{18}$ [M + H]$^+$: 901.5327, found 901.5374.

Cyclotristriazine 27b: A solution of cyclotristriazine **26b** (33 mg, 39 μmol) and amylamine (43 μL, 0.39 mmol) in THF (2 mL) was refluxed for 20 hours. The solvent was removed in vacuo and the residue was purified by flash column chromatography (eluent: 7% MeOH in DCM) to afford 25 mg of product (72%). R_f = 0.22 (7% MeOH in DCM). − ^{1}H NMR ($CDCl_3$, 50 °C): δ = 0.88 (t, 9 H, CH_2CH_3), 1.30 (m, 12 H, $CH_2CH_2CH_3$), 1.51 (m, 6 H, $NHCH_2CH_2$), 3.30 (q, 6 H, $NHCH_2CH_2$), 4.48 (d, 12 H, CH_2NAr), 4.75 (br. s, 3 H, $NHCH_2CH_2$), 5.15 (br. s, 6 H, $NHCH_2Ar$), 7.10−7.25 (m, 12 H, ArH). − ^{1}H NMR ($CDCl_3$, 2.0 equivalents cyanuric acid): δ = 0.95 (t, 9 H, CH_2CH_3), 1.41 (m, 12 H, $CH_2CH_2CH_3$), 1.65 (m, 6 H, $NHCH_2CH_2$), 3.50 (q, 6 H, $NHCH_2CH_2$), 4.49, 4.55 (two br. s, 12 H, CH_2NAr), 5.06 (br. s, 3 H, $NHCH_2CH_2$), 7.23 (m, 12 H, ArH), 7.45−7.65 (broad m, 6 H, $NHCH_2Ar$). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 22.4 (CH_2CH_3), 29.1, 29.5 ($CH_2CH_2CH_2CH_3$), 40.6 ($NHCH_2$), 44.5 (CH_2N), 126.0, 126.7, 128.5, 139.7 (C^{Ar}), 166.0 (C-triazine). − HRMS (ESI) calcd. for $C_{48}H_{67}N_{18}$ [M + H]$^+$: 895.5791; found *m*/*z*: 895.5864.

***N,N′*-Dibenzyl-6-chloro-[1,3,5]triazine-2,4-diamine (32):** A fine slurry of cyanuric chloride was prepared by adding a solution of cyanuric chloride (1.11 g, 6.00 mmol) in acetone (24 mL) to well stirred ice-water (36 mL).[25] A solution of benzylamine (1.31 mL, 12.0 mmol) and $NaHCO_3$ (1.01 g, 12.0 mmol) in water (10 mL) was then added. After stirring the mixture for one hour at 0 °C, the temperature was raised to 50 °C and stirring was continued for two hours. The solid was filtered off, washed with water, and dried in vacuo over P_2O_5 to afford 1.66 g (85%) of title compound. − ^{1}H NMR ([D$_6$]DMSO, 120 °C): δ = 4.46 (d, 4 H, CH_2), 7.23 (m, 10 H, ArH), 7.81 (br. s, 2 H, NH). − ^{13}C NMR ([D$_6$]DMSO): δ = 43.3, 43.4, 43.6 (CH_2), 126.7, 127.1, 127.2, 127.3, 128.2, 128.3, 139.1, 139.3 (C^{Ar}), 165.4, 167.8, 168.5 (C-triazine). − MS (ESI) calcd. for $C_{17}H_{17}ClN_5$ [M + H]$^+$: 326.12, found 326.20.

***N,N′*-Dibenzyl-*N′′*-dodecyl-[1,3,5]triazine-2,4,6-triamine (33):** A solution of disubstituted triazine **32** (325 mg, 1.0 mmol) and dodecylamine (0.93 g, 5.0 mmol) in THF (10 mL) was refluxed overnight. The solvent was removed in vacuo and the residue was purified by column chromatography (eluent: 10% MeOH in DCM) to afford 465 mg of product (98%). R_f = 0.73 (10% MeOH in DCM). − ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, 3 H, CH_3), 1.25 [br. s, 18 H, $(CH_2)_9$], 1.51 (m, 2 H, $NHCH_2CH_2$), 3.32 (br. s, 2 H, $NHCH_2CH_2$), 4.47 (br. s, 4 H, CH_2Ph), 7.25 (m, 10 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 14.1 (CH_3), 22.7 (CH_3CH_2), 26.9 (CH_2CH_2N), 29.3, 29.4, 29.6, 29.7, 29.9 (CH_2), 31.9 ($CH_3CH_2CH_2$), 40.7 (CH_2CH_2N), 44.7 (CH_2Ph), 127.1, 127.5, 128.5, 139.5 (C^{Ar}), 166.3 (C-triazine). − MS (ESI) calcd. for $C_{29}H_{43}N_6$ [M + H]$^+$: 475.4, found 475.4.

Bistriazine 35: DIPEA (0.37 mL, 2.1 mmol) and monosubstituted triazine **39** (0.51 g, 2.0 mmol) were added to a solution of xylenediamine (0.13 mL, 1.0 mmol) in THF (15 mL). After stirring for six hours at 45 °C, amylamine (0.58 mL, 5.0 mmol) was added and the mixture was refluxed overnight. The volatiles were removed in vacuo and the residue was redissolved in EtOAc. The resulting solution was washed with 1 M HCl (twice), water (twice), 5% $NaHCO_3$ and brine, dried with $MgSO_4$, and evaporated. Flash column chromatography (eluent: 5% MeOH in DCM) yielded 50 mg (7%) of the pure title compound (in addition, 320 mg material of a lower purity was obtained). R_f = 0.23 (5% MeOH in DCM). − ^{1}H NMR ($CDCl_3$, 50 °C): δ = 0.86 (t, 6 H, CH_3), 1.27 (m, 8 H, $CH_2CH_2CH_3$), 1.47 (m, 4 H, $NHCH_2CH_2$), 3.27 (q, 4 H, $NHCH_2CH_2$), 4.45 (d, 4 H, CH_2Ar), 4.51 (d, 4 H, CH_2Ph), 4.93 (br. s, 2 H, $NHCH_2CH_2$), 5.42 (br. s, 2 H, $NHCH_2Ph$), 5.61 (br. s, 2 H, $NHCH_2Ar$), 7.12−7.26 (m, 14 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 13.9 (CH_3), 22.4 (CH_2CH_3), 29.1, 29.5 ($NHCH_2CH_2CH_2$), 40.7 ($NHCH_2CH_2$), 44.6 (CH_2Ar, CH_2Ph), 126.3, 126.8, 127.0, 127.5, 128.4, 128.6, 139.7, 139.8 (C^{Ar}), 166.3 (C-triazine). − MS (ESI) calcd. for $C_{38}H_{51}N_{12}$ [M + H]$^+$:675.4360, found 675.4370.

Disubstituted Triazine 36: Na_2CO_3 (326 mg, 3.42 mmol) and a solution of monosubstituted triazine **20** (1.18 g, 3.08 mmol) in acetone (8 mL) were added to a solution of Boc-xylenediamine (808 mg, 3.42 mmol) in water/acetone (1:1, 20 mL). After stirring at 65 °C for 4 hours, the suspension was cooled to room temperature and the white solid filtered off and washed with water. Drying in vacuo over P_2O_5 overnight yielded 1.66 g of product (92%). R_f = 0.38 (EtOAc/hexanes 1:1). − ^{1}H NMR ([D$_6$]DMSO; 100 °C): δ = 1.38 [s, 18 H, $C(CH_3)_3$], 4.11 [d, 4 H, $CH_2NHC(O)$], 4.44 (d, 4 H, CH_2NHAr), 7.10−7.22 (m, 8 H, ArH). − ^{13}C NMR ([D$_6$]DMSO): δ = 28.3 [$C(CH_3)_3$], 43.2, 43.3, 43.6 (CH_2N), 77.7 [$C(CH_3)_3$], 125.3, 125.4, 125.5, 125.8, 128.1, 139.0, 139.2, 139.4, 140.1, 140.2 (C^{Ar}), 155.7 (C=O) 165.35, 165.38, 165.44, 165.7, 165.8, 168.3 (C-triazine). − HRMS (ESI) calcd. for $C_{29}H_{38}ClN_7NaO_4$ (M + Na)$^+$: 606.2571, found 606.2592. − $C_{29}H_{38}ClN_7O_4$ (584.1): calcd. C 59.63, H 6.56, N 16.79; found C 59.29, H 6.40, N 16.53.

Trisubstituted Triazine 37: A mixture of disubstituted triazine **36** (1.17 g, 2.00 mmol) and amylamine (1.16 mL, 10.0 mmol) in THF (20 mL) was refluxed overnight, during which the suspension dissolved. The solvent was evaporated, the residue was dissolved in EtOAc and the resulting solution was washed with 1 M $KHSO_4$ (twice), water, 5% $NaHCO_3$ and brine, and dried with $MgSO_4$. Evaporation of the solvent afforded 1.18 g of trisubstituted triazine (93%). R_f = 0.56 (10% MeOH in DCM). − ^{1}H NMR ([D$_6$]DMSO; 70 °C): δ = 0.85 (t, 3 H, CH_2CH_3), 1.24 (m, 4 H, $CH_2CH_2CH_3$), 1.37 [s, 18 H, $C(CH_3)_3$], 1.46 (m, 2 H, $NHCH_2CH_2$), 3.17 (q, 2 H, $NHCH_2CH_2$), 4.09 [d, 4 H, $CH_2NHC(O)$], 4.41 (d, 4 H, CH_2NAr), 7.06−7.21 (m, 8 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 13.9 (CH_2CH_3), 21.9 (CH_2CH_3), 28.2 [$C(CH_3)_3$], 28.6, 29.0 ($CH_2CH_2CH_2CH_3$), 42.9, 43.4 (CH_2N), 77.6 [$C(CH_3)_3$], 124.9, 125.1, 125.3, 125.7, 127.8, 139.9, 140.9 (C^{Ar}), 155.7 (C=O), 165.72, 165.79 (C-triazine). − HRMS (ESI) calcd. for $C_{34}H_{51}N_8O_4$ [M + H]$^+$: 635.4033, found 635.4039. − $C_{34}H_{50}N_8O_4$ (634.8): calcd. C 64.33, H 7.94, N 17.65; found C 63.86, H 7.88, N 17.52.

Tristriazine 38: TFA (1 mL) was added to a solution of triazine **37** (0.19 g, 0.30 mmol) in DCM (3 mL). The mixture was stirred for 45 minutes before being evaporated, coevaporated three times with THF and dried in vacuo. The residue was redissolved in 10 mL THF, the pH of the resulting solution set to 8 using Et_3N, and monosubstituted triazine **39** (0.15 g, 0.58 mmol) was added. The mixture was stirred for 2.5 hours at 45 °C and kept basic by the addition of Et_3N, after which the volatiles were removed in vacuo. The residue was taken up in EtOAc and the resulting solution was washed with 1 M $KHSO_4$ (twice), water (twice) and 5% $NaHCO_3$. The resulting foamy mixture was extracted four times with DCM. The combined organic layers were dried with $MgSO_4$ and evaporated to give 200 mg (79%) of the crude intermediate dichloro compound. R_f = 0.61 (10% MeOH in DCM). A solution of this intermediate and amylamine (0.28 mL, 2.4 mmol) in THF (5 mL) was refluxed overnight, after which the volatiles were removed in vacuo. The residue was dissolved in EtOAc, and the resulting solution washed with 1 M HCl, water (twice), 5% $NaHCO_3$ and brine, and dried with $MgSO_4$. Flash column chromatography (eluent: 6% MeOH in DCM) afforded 171 mg of product (59% overall yield). R_f = 0.51 (10% MeOH in DCM). − ^{1}H NMR ($CDCl_3$, 50 °C): δ = 0.86 (m, 9 H, CH_2CH_3), 1.29 (m, 12 H, $CH_2CH_2CH_3$), 1.49 (m, 6 H, $NHCH_2CH_2$), 3.29 (broad d, 6 H, $NHCH_2CH_2$), 4.49, 4.53 (two d, 12 H, CH_2NAr), 7.15−7.27 (m, 18 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_2CH_3), 22.4 (CH_2CH_3), 29.1, 29.5 ($CH_2CH_2CH_2CH_3$), 40.6 (CH_2CH_2NH), 44.5 ($ArCH_2NH$), 126.3, 127.0, 127.5, 128.4, 128.5, 139.7 (C^{Ar}), 166.1 (C-triazine). − HRMS (ESI) calcd. for $C_{54}H_{73}N_{18}$ [M + H]$^+$: 973.6266, found 973.6268.

Benzyl(4,6-dichloro-[1,3,5]triazin-2-yl)amine (39): Monosubstituted triazine **43** was prepared from benzylamine (0.66 mL, 6.0 mmol) according to the procedure described for **1** to afford 1.24 g (81%) of title compound. R_f = 0.65 (EtOAc/hexanes 1:1). − ^{1}H NMR ($CDCl_3$): δ = 4.61 (d, 2 H, CH_2), 6.73 (br. s, 1 H, NH), 7.26 (m, 5 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 45.3 (CH_2), 127.7, 128.1, 128.9, 136.3 (C^{ar}), 165.8, 169.9, 171.1 (C-triazine).

Binding Experiments: For all binding studies a freshly opened bottle of $CDCl_3$ (GOSS Scientific Instruments Ltd, UK) was used. For the cyanuric acid titration, the receptor concentration was kept constant at 1.0 mM, while varying the concentration of cyanuric acid from 0 to 2.0 mM. After the addition of the appropriate[28] amount of cyanuric acid, each sample was sonicated for three

hours. For the glycoside titrations the receptor concentration was kept constant at 0.83 mM (**27a** with **29** and **31**, **27b** with **29**−**31**), 0.89 mM (**27a** with **30**), 5.0 mM (**33** with **30**) and 2.0 mM (**35** and **38** with **30**), while varying the concentration from 0 to 6.6 mM (**27a** and **27b** with **29**−**31**), 0 to 40 mM (**33** with **30**), 0 to 33 mM (**35** with **30**) and 0 to 30 mM (**38** with **30**). For all glycoside titrations, the corresponding Job plot[29] was also acquired. All Job plots confirmed a 1:1 stoichiometry, except for **38** with **30**, in which a 1:2 stoichiometry was found. With these stoichiometries, the titration data were evaluated using a nonlinear least squares fitting procedure to afford the association constants involved.[30] Self-association of the sugars was negligible at concentrations below 1 mM, but was nevertheless not taken into account for **33**, **35** and **38** even though slightly higher concentrations were used in these cases. A van't Hoff plot was acquired for **27b** and **30**, by performing a variable temperature (298−321 K) single-point analysis of the complex,[31] afforded the corresponding thermodynamic parameters. A straight plot was obtained by correcting for the drift of the resonance of the fully complexed glucoside. For this purpose a sample containing 8 equivalents of glucoside was taken as a reference.

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