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Synthesis of new calix[4]arenes containing nucleoside bases

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Abstract—A family of novel calix[4]arene derivatives containing nucleoside bases were designed and synthesized. Coupling reaction between *para* mono- or bis-amino calix[4]arenes **5**, **6** or **7** and thymin-1-ylacetic acid in the presence of DCC afforded mono- or bis-thymine-substituted calix[4]arenes **8**, **9** or **10** in over 70% yield. Owing to the low solubility of adenine-N^9-ylacetic acid in DMF and DMSO and the weak nucleophilicity of aminocalix[4]arene derivatives, alternatively, the substitution reaction of bromoacetylated aminocalix[4]arenes derivatives **11**, **12**, **13** with adenine in the presence of sodium hydride was carried out to synthesize mono- or bis-adenine-substituted calix[4]arenes. Two kinds of isomers **15** and **16** or **17** and **18** were obtained due to the non-regiospecific alkylation of adenine, and their structures have been confirmed by ^{13}C NMR and ^{1}H NMR spectra.

1. Introduction

During the past 30 years, supramolecular science has been developed tremendously.[1,2] Hydrogen bonds, the most important non-covalent bond type in biochemistry, play a crucial role in the formation of biological macromolecules such as globular proteins, the DNA double helix and in the mechanism of enzyme–substrate recognition.[3] Especially, complementary nucleoside base pairs with hydrogen bonds are the basis of the storage and decoding of genetic information. According to the complementarity and cooperativity of hydrogen bonds, chemists have developed lots of new artificial recognition systems for molecules or bio-molecules and constructed novel self-organized supermolecules or macromolecules by non-covalent synthesis.[4] Artificial receptors and self-assembly systems based on nucleoside base pairs have also been reported because they could provide chemical and biological insight into fundamental base-pairing processes and also offer a means of constructing complex, but well-defined synthetic arrays.[5]

Calix[*n*]arenes are one of the most extensively studied synthetic receptors due to their ease of synthesis, convenience of functionalization, controllable conformations and versatile complexation properties.[6] Calix[4]arenes have successfully been used as versatile building blocks for the construction of highly sophisticated molecules in fields such as molecular recognition and self-assembly. At present, using hydrogen bonds, considerable effort in the recognition and assembly of calix[4]arenes has focused on the complementary combination of cyanuric acid-melamine,[7] pyridine–carboxylic acid[8] and ureas.[9] Reinhoudt et al. have also reported a calixarene derivative containing an α-pyridone moiety at the upper rim, and then investigated the aggregation and the complexation properties with urea guests.[10] However, there are very few reports studying the synthesis, recognition and assembly of nucleotide based on calixarene.[11]

We are interested in the construction of calix[4]arene-based receptors functionalized with a nucleoside base pendant tail and recently reported, in letter form, the synthesis and self-assembly properties of calix[4]arene receptors containing a mono-nucleoside base.[12] In this paper, we present full details of the synthesis of a family of the mono- and bis-nucleoside base derived calix[4]arene receptors.

2. Results and discussion

Calix[4]arene can be selectively functionalized at the upper rim with different numbers of pendant tails. Various methods have been developed for the complete and partial substitution of calix[4]arenes both at the upper and at the lower rim in order to introduce the desired functional groups in appropriate arrangements or to obtain the preorganized conformation. According to the primary concept, calix[4]-arene fixed in the cone conformation possesses the calix shape of the cavity, which is fit for binding organic molecules within its cavity. To fix the cone conformation of calixarene could be achieved by means of intramolecular hydrogen bonds or tetra-*O*-alkylation at the lower rim using the group bigger than ethyl.[13] In order to prevent hydrogen bonds between the phenol groups and nucleoside bases, the

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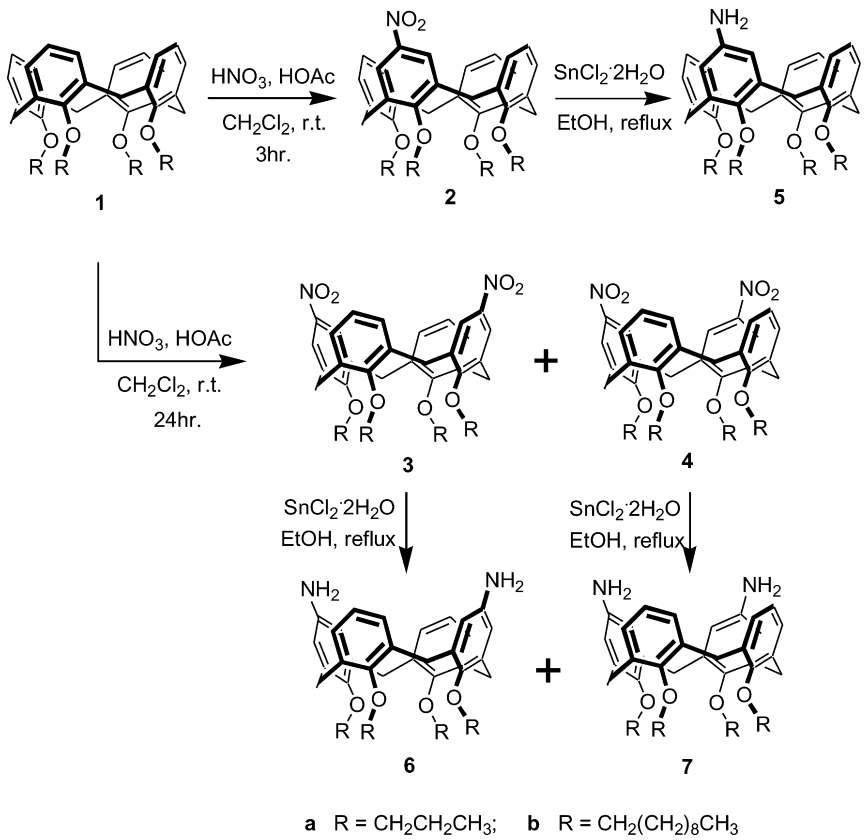


Scheme 1.

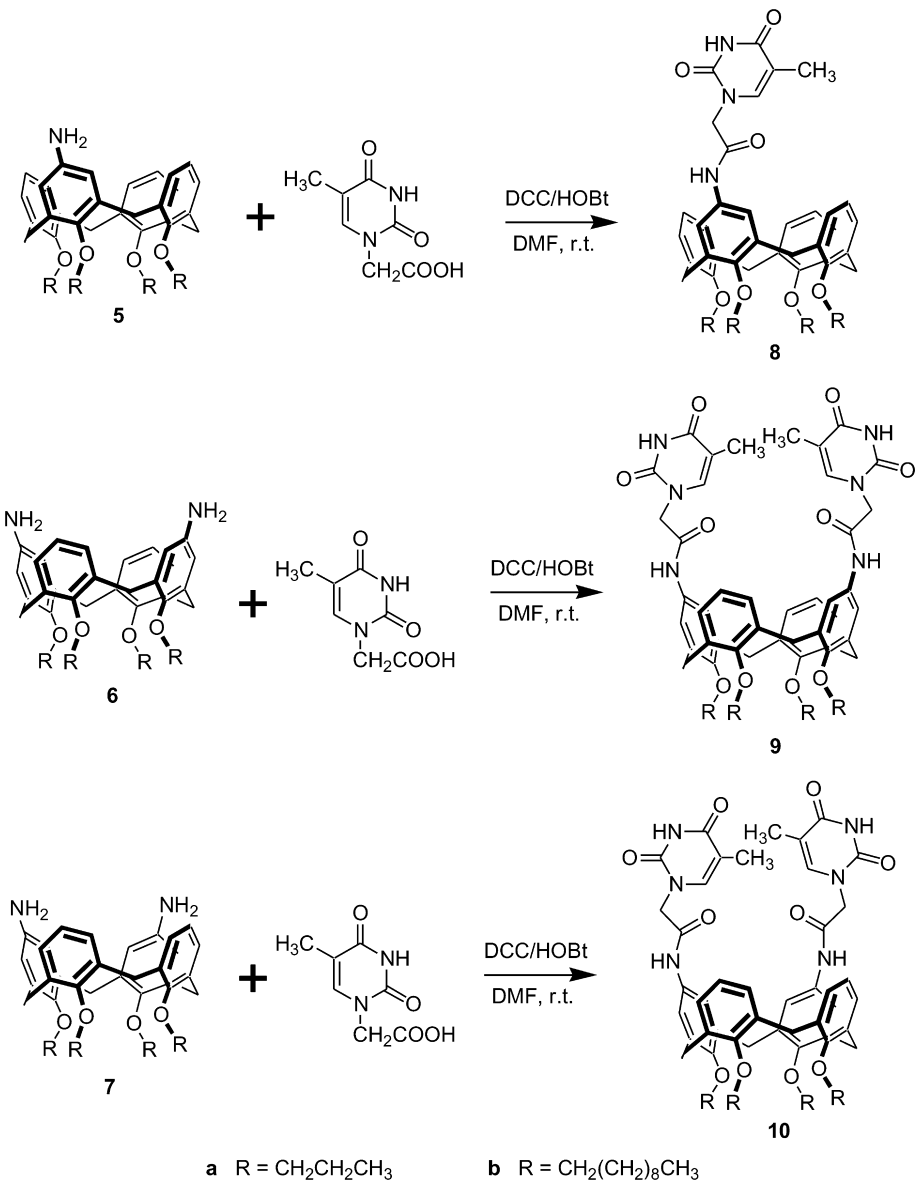
latter approach was used in our system. Moreover, the introduction of four alkyl groups can improve the solubility of the calix[4]arene derivatives and thus facilitates the study. In this work, adenine and thymine have been introduced to define positions on the rigid calix[4]arene scaffold.

Among many suitable reactions leading to the insertion of appendages, nitration attracted our attention due to the accessibility to one or two appendages properly arranged within a molecule from the same precursor **1** that promises the shortest way to the proposed type of receptors.[14] As shown in Scheme 1, 5-nitrocalix[4]arene (**2**), 5,17-dinitro-calix[4]arene (**3**) and 5,11-dinitro-calix[4]arene (**4**) were obtained by nitration of tetra-alkoxycalix[4]arene (**1**) with 65% nitric acid in dichloromethane. Mono-nitrated calix[4]-arene **2** could be detected by TLC after 30 min and produced at first in 25–30% yield after about 3 h. When the reaction continued to 24 h, 1,3-*distal* dinitrated product **3** was then obtained in about 30% yield, and 1,2-*proximal* dinitrated calix[4]arene **4** was the byproduct and could be isolated simultaneously in about 9% yield. Compounds **3** and **4** could be differentiated by their ^{1}H NMR spectra. According to the symmetry of their structures, the protons of the methylene groups between the phenol moieties of **3** appear as a pair of doublets, and those of **4** appear as three pairs of doublets. Reductive derivatives **5**, **6** and **7** were obtained using tin dichloride in boiling ethanol in almost quantitative yield.

Coupling reaction between **5**, **6** or **7** and thymin-1-ylacetic acid in the presence of DCC afforded mono- or bis-thymine-substituted calix[4]arenes receptor **8**, **9** or **10** in over 70% yield (Scheme 2). Spectroscopic data and elemental analysis are in agreement with the structure of the products. In their ^{1}H NMR spectra a $\Delta\delta$ separation >1 ppm between the *exo* and *endo* geminal protons and in their ^{13}C NMR spectra resonances for the pertinent carbon atoms close to 31 ppm for the $ArCH_2Ar$ groups indicate that all products adopt the cone conformation.[6d] On the basis of symmetry considerations, in their ^{1}H NMR spectra, the protons for $ArCH_2Ar$ of **9** and **10** show one and three AX systems, respectively. In **9**, the protons of two aromatic rings with substituents appear as a singlet. In contrast, in **10**, they appear as two doublets.

The same synthetic strategy did not apply to their corresponding adenine analogs because of the sparing solubility of adenine-N^9-ylacetic acid in DMF and DMSO and the weak nucleophilicity of the aminocalix[4]arene derivatives. Alternatively, the substitution reaction of bromoacetylated aminocalix[4]arene derivatives **11**, **12**, **13** with adenine in the presence of sodium hydride were carried out (Scheme 3). However, the alkylation of adenine is non-regiospecific although the product of 9-substitution is often dominant (Chart 1).[15]

The position of substitution on the adenine ring can be determined by examination of the ^{1}H NMR spectra of the two isomers since, in general, the signals for the H-8 proton in the N^9 isomer is shifted upfield relative to the corresponding H-8 signal for the N^7 isomer. This analysis

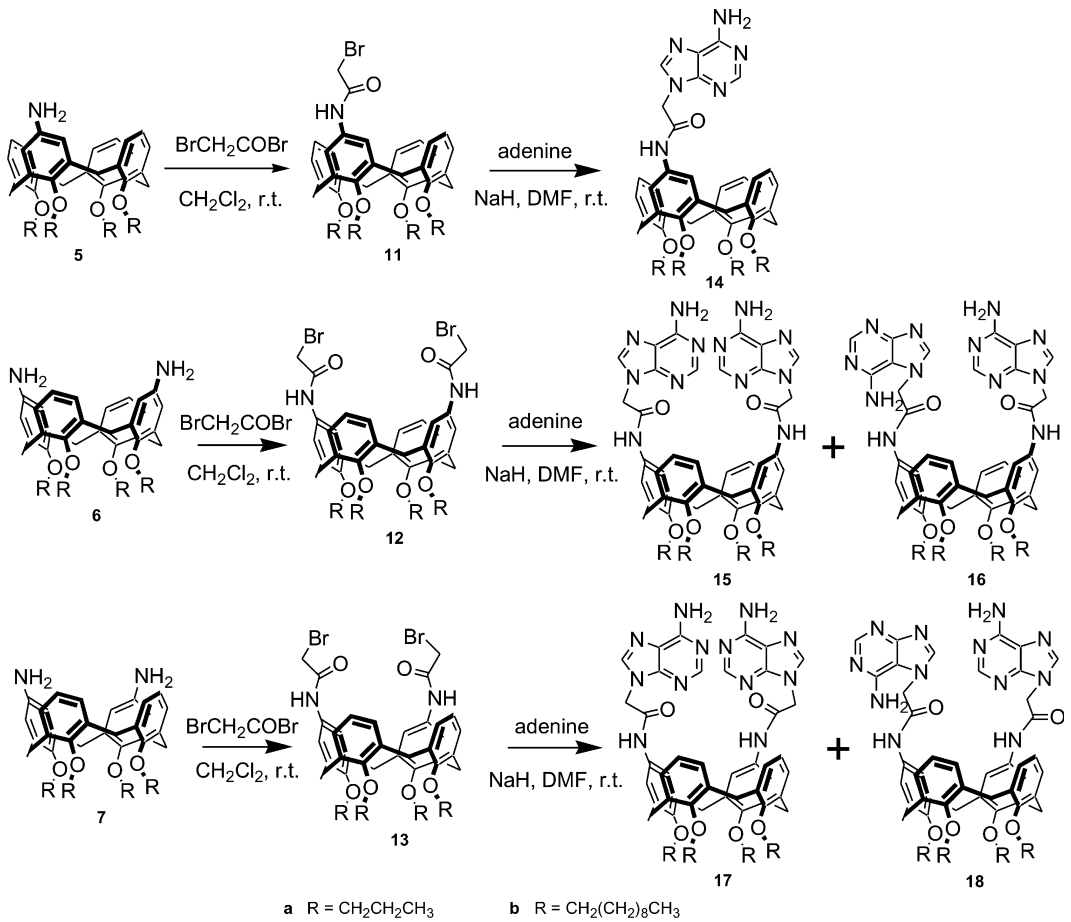


Scheme 2.

requires that both N^7 and N^9 isomers are in hand.[16] In the absence of one of the isomers, the assignment cannot be unambiguously made by these means but the question can be solved by the comparison of the ^{13}C NMR spectrum measured of our products, with those reported by Chenon et al. for 7-methyladenine and 9-methyladenine.[17] In the reaction between **11** and adenine, very little of the undesired regioisomer was produced, and column chromatography readily provided the desired compound **14** free of any other regioisomers. However, in the alkylation reaction between adenine and **12** or **13**, each gave two isomers in 25 and 15% yield respectively.

The ^{13}C NMR spectra of the major products show that the two adenine subunits are equivalent (N^9 isomer). However, the two adenine subunits in the minor products are not equivalent, and there are two sets of values which are respectively consistent with their values for 7-methyladenine and 9-methyladenine (Table 1). The ^1H NMR spectra of **15a** and **16a** in $CDCl_3/CD_3OD$ (95:5, v/v) further confirm their structure. For example, there are four singlets (8.31, 8.18, 8.10, 7.99 ppm) for adenine C–H of **16a** and their integration is 1:1:1:1 (Fig. 1), which show that there are two different adenine residues (8.31, 8.10 ppm for N^7 isomer and 8.18, 7.99 ppm for N^9 isomer). However, two singlets (8.18, 7.95 ppm) for adenine C–H of **15a**, whose integration is 2:2, demonstrate that both of the two adenines are N^9 isomers because the signals for the two H-8 proton (8.18 ppm) in **15a** is shifted upfield relative to the corresponding H-8 signal (8.31 ppm) for the N^7 adenine residue in **16a**.

The aggregation behavior of these nucleoside base derived calix[4]arene receptors was observed by ^1H NMR. Mononucleoside base derived calix[4]arenes **8** or **14** tend to undergo aggregation through intermolecular hydrogen bonding in solution, which could be confirmed by the chemical shift of the protons in the nucleoside base which



Scheme 3.

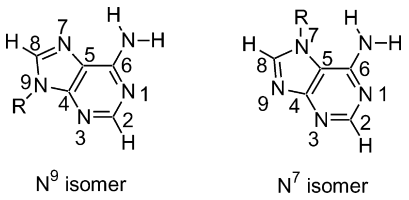


Chart 1.

depended upon the concentration in $CDCl_3$. Intermolecular hydrogen bond formation was further confirmed by the variable-temperature ^1H NMR spectrum. A downfield shift of 0.75–0.60 or of 0.16 ppm was observed corresponding to the thymine imido-H of **8** and the adenine amino-H of **14** respectively when the temperature decreased from 326 to 300 K (Fig. 2). There is also distinct solvent dependence of the signal of the thymine imido-H and the amino protons of adenine. For example, the change of the solvent from $CDCl_3$ to DMSO[D_6] resulted in the shift of the imido-H peak of **8a** from 8.15 to 11.26 ppm or of the amino-H peak of **14a** from 5.92 to 7.17 ppm. Except for the observation of the peak shifts of thymine imido-H and of adenine amino-H mentioned above, the proton signals of the rest of the molecule remained almost constant under the conditions employed.

However, the ^1H NMR spectra of bis-nucleoside base

Table 1. Comparative ^{13}C NMR assignments for 7- and 9-methyladenine and compounds **15**–**18**

Compounds	C-2		C-4		C-5		C-6		C-8	
	N^7 isomer	N^9 isomer	N^7 isomer	N^9 isomer	N^7 isomer	N^9 isomer	N^7 isomer	N^9 isomer	N^7 isomer	N^9 isomer
7-Methyl-adenine	152.4		159.8		111.7		151.9		145.9	
9-Methyl-adenine		152.9		149.9		118.7		155.9		141.4
15a		152.7		150.0		118.5		155.7		142.4
16a	152.5	153.0	160.0	150.1	112.2	118.6	152.0	155.8	147.1	142.2
15b		152.5		149.3		118.7		155.8		141.7
16b	152.4	153.2	158.7	149.1	112.5	118.2	152.2	156.6	146.2	141.7
17a		152.5		149.8		118.3		156.2		142.0
18a	152.2	152.5	159.6	149.8	111.8	118.3	151.7	156.2	146.8	141.9
17b		152.8		150.2		118.8		156.3		142.1
18b	152.3	153.5	159.6	149.7	112.4	118.3	152.3	156.3	146.8	141.5

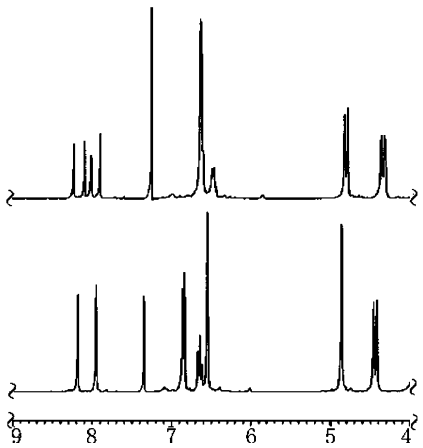


Figure 1. The partial ^{1}H NMR spectra of **16a** (top) and **15a** (bottom). Spectra were recorded in $CD_3OD/CDCl_3$ (5:95, v/v) on a 300 MHz spectrometer.

derived calix[4]arenes were quite different from those for the mono-nucleoside base derived calix[4]arenes. For instance, the sharp and well-resolved signals of **8b** in $CDCl_3$ are replaced by broadened, nondescript spectra of **9b** or **10b**. Due to conformational isomers and intermolecular aggregation, broadened, nondescript spectra of **9**, **10**, **15**, **16**, **17** and **18** in $CDCl_3$, as well as in [D_6]benzene or [D_4]dichlorobenzene were detected. This was transformed to a well-defined spectrum in [D_6]DMSO, which will destroy the aggregation between the nucleoside bases.

3. Conclusions

We have synthesized a family of novel calix[4]arene derivatives containing nucleoside bases. Coupling reaction between *para* mono- or bis-amino calix[4]arenes and thymin-1-ylacetic acid in the presence of DCC could afford mono- or bis-thymine-substituted calix[4]arenes in over 70% yield. Owing to the low solubility of adenine-N^9-yl-acetic acid in DMF and DMSO and the weak nucleophilicity of aminocalix[4]arene derivatives, alternatively, the substitution reaction of bromoacetylated aminocalix[4]arenes derivatives with adenine in the presence of sodium hydride was carried out to synthesize mono- or bis-adenine-substituted calix[4]arenes. Two kinds of isomers (N^7 and N^9 isomers of adenine) were obtained due to the non-regiospecific alkylation of adenine, and their structures have been confirmed by ^{13}C NMR and ^{1}H NMR spectra.

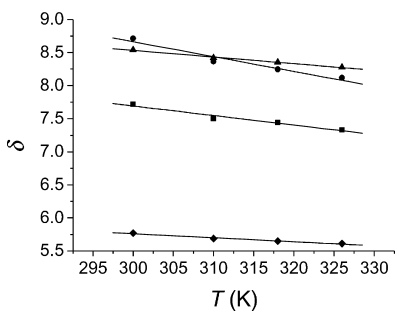


Figure 2. The temperature dependence of the chemical shift of protons involved in hydrogen bonds of **8b** or **14b** (● **8b**-CONHAr; ■ **8b**-T-NH; ▲ **14b**-CONH; ◆ **14b**-A-NH_2; [**8b**], [**14b**]=10 mM in $CDCl_3$).

4. Experimental

4.1. General methods

All reagents and solvents employed are commercially available and were used without further purification unless otherwise stated. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker DMX 300 MHz spectrometer, unless otherwise indicated. Matrix-assisted laser desorption ionization time-of-fight (MALDI-TOF) mass spectra were recorded on a Bruker BIFLEX III spectrometer using CCA (2-cyano-4′-hydroxycinnamic acid) as matrix. High-resolution mass spectra were recorded on a Bruker APEX II spectrometer. Microanalytical samples were dried for at least 10 days at 140°C under reduced pressure, and the analyses were carried out by the Analytical Laboratory of the Institute. 25,26,27,28-Tetrapropoxy-calix[4]arene (**1a**)[13] and 25,26,27,28-tetradecyloxycalix-[4]arene (**1b**)[18] was prepared according to literature procedures.

4.2. General procedure for nitration of calix[4]arene 1

To a solution of **1** (1.7 mmol) in a mixture of CH_2Cl_2 (100 ml) and acetic acid (4 ml) was added 65% nitric acid (1 ml, 25 mmol, 15 equiv.). The reaction mixture was stirred at room temperature until the black–purple color discharged (about 3 h) and subsequently the reaction was stopped by the addition of water (100 ml), and the product mixture was extracted with CH_2Cl_2 (3×25 ml). The organic layer was washed with saturated sodium bicarbonate solution (3×25 ml) and water (3×25 ml), dried over $MgSO_4$ and concentrated. The reaction mixture consisted mainly of mononitrocalix[4]arene **2** (20–30%) and traces of 5,17-dinitrocalix[4]arene **3** and 5,11-dinitrocalix[4]arene **4**. The same reaction with **1** for 24 h afforded **3** and **4** in 20–30% and 7–10% yields, respectively. Purification of the yellow residue by silica gel column chromatography eluting with a mixture of petroleum ether (60–90°C) and dichloromethane with successive increases of dichloromethane afforded the corresponding products as white solids. **2a**, **3a** and **4a** have been previously reported.[14]

4.2.1. 25,26,27,28-Tetra-decyloxy-5-nitrocalix[4]arene (2b). Yield: 25.6%. Mp 62–63°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91–0.95 (m, 12H; $(CH_2)_7CH_3$), 1.31–1.57 (m, 56H; $(CH_2)_7CH_3$), 1.89–1.94 (m, 8H; OCH_2CH_2), 3.21 (AB-d, ^2J=12.5 Hz, 2H; $ArCH_2Ar$), 3.25 (AB-d, ^2J=11.9 Hz, 2H; $ArCH_2Ar$), 3.80 (t, ^3J=6.3 Hz, 2H; OCH_2CH_2), 3.90 (t, ^3J=6.3 Hz, 2H; OCH_2CH_2), 3.96 (t, ^3J=6.3 Hz, 2H; OCH_2CH_2), 4.04 (t, ^3J=6.3 Hz, 2H; OCH_2CH_2), 4.47 (AB-d, ^2J=13.2 Hz, 2H; $ArCH_2Ar$), 4.52 (AB-d, ^2J=13.2 Hz, 2H; $ArCH_2Ar$), 6.27 (s, 3H, ArH), 6.88 (t, ^3J=7.2 Hz, 2H; ArH), 6.98 (d, ^3J=7.2 Hz, 4H; ArH), 7.16 (s, 2H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.0, 22.7, 26.1, 26.4, 26.5, 29.4, 29.7, 29.8, 30.0, 30.2, 30.3, 30.4, 30.9, 31.0, 31.9, 75.1, 75.4, 121.6, 122.3, 123.1, 127.6, 128.4, 129.3, 133.8, 134.9, 135.8, 136.6, 142.4, 155.7, 157.1, 161.3; FTIR (KBr): ν=1512, 1345 cm^{-1} (NO_2); MS

(MALDI-TOF, positive): *m/z*: 1052.85 $[M+Na]^+$. Elemental analysis calcd (%) for $C_{68}H_{103}NO_6$ (1030.51): C 79.25, H 10.08, N 1.36. Found C 80.90, H 10.93, N 0.98.[19]

4.2.2. 25,26,27,28-Tetra-decyloxy-5,17-dinitrocalix[4]-arene (3b). Yield: 24.5%. Mp 137–138°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.91 (t, ^3J=6.6 Hz, 12H; $(CH_2)_7CH_3$), 1.28–1.38 (m, 56H; $(CH_2)_7CH_3$), 1.87–1.92 (m, 8H; OCH_2CH_2), 3.27 (AB-d, ^2J=13.8 Hz, 4H; $ArCH_2Ar$), 3.92 (t, ^3J=7.8 Hz, 4H; OCH_2CH_2), 3.96 (t, ^3J=7.2 Hz, 4H; OCH_2CH_2), 4.48 (AB-d, ^2J=13.8 Hz, 4H; $ArCH_2Ar$), 6.76 (s, 6H; ArH), 7.44 (s, 4H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.1, 22.7, 26.2, 29.4, 29.8, 29.8, 29.9, 30.0, 30.2, 30.4, 31.0, 32.0, 75.4, 75.8, 123.0, 123.4, 128.9, 134.2, 136.3, 142.4, 156.3, 161.9; FTIR (KBr): ν=1521, 1357 cm^{-1}(NO_2); MS (MALDI-TOF, positive): *m/z*: 1097.96 $[M+Na]^+$, 1113.93 $[M+K]^+$. Elemental analysis calcd (%) for $C_{68}H_{102}N_2O_8$ (1075.52): C 75.93, H 9.56, N, 2.61. Found C 76.42, H 9.53, N 2.30.

4.2.3. 25,26,27,28-Tetra-decyloxy-5,11-ditrocalix[4]-arene (4b). Yield: 8.6%. Mp 67–69°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.93–1.05 (m, 12H; $(CH_2)_7CH_3$), 1.30–1.38 (m, 56H; $(CH_2)_7CH_3$), 1.95–2.05 (m, 8H; OCH_2CH_2), 3.20–3.35 (m, 4H; $ArCH_2Ar$), 3.90–4.10 (m, 8H; OCH_2CH_2), 4.50–4.60 (m, 4H; $ArCH_2Ar$), 6.55–6.62 (m, 6H; ArH), 7.45–7.52 (m, 4H; ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.0, 22.6, 22.6, 26.2, 26.3, 29.3, 29.4, 29.5, 29.7, 29.8, 29.9, 30.3, 30.8, 30.8, 30.9, 31.5, 31.9, 75.2, 75.6, 122.1, 123.0, 124.0, 127.9, 128.8, 133.5, 135.2, 136.9, 142.3, 142.3, 156.3, 162.0; FTIR (KBr): ν=1519, 1343 cm^{-1} (NO_2); MS (MALDI-TOF, positive): *m/z*: 1097.77 $[M+Na]^+$, 1113.76 $[M+K]^+$. Elemental analysis calcd (%) for $C_{68}H_{102}N_2O_8$ (1075.52): C 75.93, H 9.56, N, 2.61. Found C 76.04, H 10.02, N 2.23.

4.3. General procedure for the reduction of 2, 3 and 4

A suspension of the appropriate nitrocalix[4]arene and $SnCl_2{\cdot}2H_2O$ (5 equiv. per nitro group) in EtOH (25 ml) was refluxed until no starting material was detected by TLC. After cooling to room temperature, the mixture was poured into crushed ice and the pH was adjusted to 9–10 with 1 M KOH solution. After extraction with CH_2Cl_2 the combined organic layers were washed with brine (25 ml) and dried over Na_2SO_4. Aminocalix[4]arenes were obtained after concentrating and drying in vacuo and used without further purification. **5a**, **6a** and **7a** have been reported.[20]

4.3.1. 5-Amino-25,26,27,28-tetra-decyloxycalix[4]arene (5b). Yield: 92.5%. Mp 85–86°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (t, ^3J=6.75 Hz, 12H; $(CH_2)_7CH_3$), 1.20–1.40 (m, 56H; $(CH_2)_7CH_3$), 1.80–1.89 (m, 8H; OCH_2CH_2), 3.02 (AB-d, ^2J=13.2 Hz, 2H; $ArCH_2Ar$), 3.14 (AB-d, ^2J=13.2 Hz, 2H; $ArCH_2Ar$), 3.38 (t, ^3J=6.6 Hz, 2H; OCH_2CH_2), 3.77 (t, ^3J=7.5 Hz, 2H; OCH_2CH_2), 3.82–3.89 (m, 4H; OCH_2CH_2), 4.36 (AB-d, ^2J=13.2 Hz, 2H; $ArCH_2Ar$), 4.44 (AB-d, ^2J=13.2 Hz, 2H; $ArCH_2Ar$), 5.94 (s, 2H; ArH), 6.48–6.65 (m, 9H; ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.1, 22.7, 26.2, 26.4, 26.4, 29.3, 29.5, 29.6, 29.6, 29.8, 30.0, 30.3, 30.3, 31.0, 31.9, 32.0, 71.0, 75.1, 75.2, 115.4, 121.5, 121.8, 127.9, 128.0, 128.1, 135.2, 135.2, 135.6, 135.6, 140.2, 149.8, 156.7, 156.7; FTIR (KBr): ν=3448, 3359 cm^{-1} (NH_2); MS (MALDI-TOF, positive): *m/z*: 999.46 $[M]^+$, 1022.44 $[M+Na]^+$. Elemental analysis calcd (%) for $C_{68}H_{105}NO_4$ (1000.53): C 81.62, H 10.58, N 1.40. Found C 81.58, H 11.01, N 0.94.

4.3.2. 5,17-Diamino-25,26,27,28-tetra-decyloxycalix[4]-arene (6b). Yield: 93.8%. Mp 118–120°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (t, ^3J=6.6 Hz, 12H; $(CH_2)_7CH_3$), 1.26–1.34 (m, 56H; $(CH_2)_7CH_3$), 1.86–1.88 (m, 8H; OCH_2CH_2), 3.03 (AB-d, ^2J=13.5 Hz, 4H; $ArCH_2Ar$), 3.78 (t, ^3J=6.9 Hz, 4H; OCH_2CH_2), 3.86 (t, ^3J=6.9 Hz, 4H; OCH_2CH_2), 4.37 (AB-d, ^2J=13.5 Hz, 4H; $ArCH_2Ar$), 5.94 (s, 4H; ArH), 6.60 (t, ^3J=7.2 Hz, 2H; ArH), 6.71 (d, ^3J=7.2 Hz, 4H; ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.2, 22.8, 26.3, 26.5, 29.5, 29.8, 29.8, 30.0, 30.3, 30.3, 31.1, 32.0, 75.1, 75.2, 115.8, 121.7, 128.1, 135.4, 135.5, 140.3, 149.9, 156.9; FTIR (KBr): ν=3445, 3364 cm^{-1} (NH_2); MS (MALDI-TOF, positive): *m/z*: 1014.83 $[M]^+$, 1037.82 $[M+Na]^+$. High-resolution MS (ESI-FTMS, positive) for $C_{68}H_{107}N_2O_4$ (1015.8225): *m/z*: 1015.8243 $[M+H]^+$.

4.3.3. 5,11-Diamino-25,26,27,28-tetra-decyloxycalix[4]-arene (7b). Yield: 91.4%. Mp 88–90°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.91–0.99 (m, 12H; $(CH_2)_7CH_3$), 1.25–1.50 (m, 56H; $(CH_2)_7CH_3$), 1.93–1.98 (m, 8H; OCH_2CH_2), 3.00 (AB-d, ^2J=13.2 Hz, 1H; $ArCH_2Ar$), 3.12 (AB-d, ^2J=13.3 Hz, 2H; $ArCH_2Ar$), 3.24 (AB-d, ^2J=13.4 Hz, 1H; $ArCH_2Ar$), 3.85 (t, ^3J=7.5 Hz, 4H; OCH_2CH_2), 3.94 (t, ^3J=7.2 Hz, 4H; OCH_2CH_2), 4.38 (AB-d, ^2J=13.1 Hz, 1H; $ArCH_2Ar$), 4.46 (AB-d, ^2J=13.2 Hz, 2H; $ArCH_2Ar$), 4.54 (AB-d, ^2J=13.3 Hz, 1H; $ArCH_2Ar$), 6.09 (s, 2H; ArH), 6.13 (s, 2H; ArH), 6.64–6.75 (m, 6H; ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.1, 22.7, 26.3, 26.4, 29.3, 29.4, 29.7, 29.8, 30.0, 30.2, 30.3, 31.0, 31.9, 75.0, 75.1, 115.3, 115.3, 121.4, 127.9, 128.0, 135.2, 135.6, 135.6, 140.1, 140.1, 149.8, 156.7; FTIR (KBr): ν=3442, 3356 cm^{-1} (NH_2); MS (MALDI-TOF, positive): *m/z*: 1014.76 $[M]^+$. Elemental analysis calcd (%) for $C_{68}H_{106}N_2O_4$ (1015.55): C 80.42, H 10.52, N 2.76; found C 80.67, H 11.00, N 2.41.

4.4. General procedure for bromoacetylation of 5, 6 and 7

Bromoacetyl bromide (0.11 mmol) in 10 ml CH_2Cl_2 was added dropwise over a period of 40 min to a mixture of 0.10 mmol of **5** (0.05 mmol for **6** and **7**) and 0.11 mmol of triethylamine in CH_2Cl_2 (20 ml) at room temperature. The reaction mixture was stirred for 2 h. Water (50 ml) was then added, and the aqueous layer was extracted with 100 ml of CH_2Cl_2. The combined CH_2Cl_2 layer was dried over $NaSO_4$ and concentrated to dryness on a rotary evaporator. The residue was purified by column chromatography (eluent: EtOAc/petroleum ether (60–90°C)) as a white solid. **11a**, **12a** and **13a** were similar to the compounds of chloroacetylaminocalix[4]arene[21] and used for the next procedure without characterization.

4.4.1. 5-Bromoacetylamino-25,26,27,28-tetra-decyloxycalix[4]-arene (11b). Yield: 68.9%. Mp 148–150°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (t, ^3J=6.5 Hz, 12H; $(CH_2)_7CH_3$), 1.25–1.50 (m, 56H; $(CH_2)_7CH_3$), 1.80–1.90

(m, 8H; OCH_2CH_2), 3.12–3.16 (m, 4H; $ArCH_2Ar$), 3.81–3.88 (m, 8H; OCH_2CH_2), 3.93 (s, 2H; $COCH_2$), 4.41–4.46 (m, 4H; $ArCH_2Ar$), 6.48–6.51 (m, 3H; ArH), 6.55 (s, 2H; ArH), 6.65 (t, ^3J=6.3 Hz, 2H; ArH), 6.72 (d, ^3J=6.3 Hz, 4H; ArH), 7.65 (s, 1H; NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.2, 22.7, 26.3, 26.4, 29.5, 29.8, 30.0, 30.3, 30.4, 31.0, 32.0, 75.2, 75.2, 120.6, 121.4, 122.0, 127.9, 128.3, 128.4, 130.3, 134.9, 135.1, 135.6, 135.7, 154.1, 156.5, 156.9, 162.9; FTIR (KBr): ν=3297, 3260 (NH), 1655 cm^{-1} (CONH); MS (MALDI-TOF, positive): *m/z*: 1142.48 $[M+Na]^+$, 1158.44 $[M+K]^+$. Elemental analysis calcd (%) for $C_{70}H_{106}BrNO_5$ (1121.46): C 74.96, H 9.53, N 1.25. Found C 74.67, H 9.62, N 0.80.

4.4.2. 5,17-Bis(bromoacetylamino)-25,26,27,28-tetradecyloxy-calix[4]arene (12b). Yield: 59.4%. Mp 158–159°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.83–0.90 (m, 12H; $(CH_2)_7CH_3$), 1.20–1.45 (m, 56H; $(CH_2)_7CH_3$), 1.86–1.95 (m, 8H; OCH_2CH_2), 3.14 (AB-d, ^2J=13.2 Hz, 4H; $ArCH_2Ar$), 3.80 (t, ^3J=6.9 Hz, 4H; OCH_2CH_2), 3.90 (t, ^3J=6.9 Hz, 4H; OCH_2CH_2), 3.98 (s, 4H; $COCH_2$), 4.42 (AB-d, ^2J=13.2 Hz, 4H; $ArCH_2Ar$), 6.60–6.70 (m, 6H; ArH), 6.73 (s, 4H; ArH), 8.20 (br, 2H; NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.1, 22.7, 26.3, 26.3, 29.1, 29.4, 29.8, 29.9, 30.0, 30.2, 31.0, 31.9, 75.2, 75.4, 121.3, 122.3, 128.4, 130.0, 134.8, 135.5, 154.3, 156.5, 164.0; FTIR (KBr): ν=3365, 3324 (NH), 1665 cm^{-1} (CONH); MS (MALDI-TOF, positive): *m/z*: 1277.86 $[M+Na]^+$, 1293.81 $[M+K]^+$. Elemental analysis calcd (%) for $C_{72}H_{108}Br_2N_2O_6$ (1257.42): C 68.77, H 8.66, N 2.23. Found C 69.17, H 8.99, N 1.71.

4.4.3. 5,11-Bis(bromoacetylamino)-25,26,27,28-tetradecyloxy-calix[4]arene (13b). Yield: 67.8%. Mp 97–99°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (t, ^3J=6.6 Hz, 12H; $(CH_2)_7CH_3$), 1.25–1.35 (m, 56H; $(CH_2)_7CH_3$), 1.83–1.89 (m, 8H; OCH_2CH_2), 3.10–3.16 (m, 4H; $ArCH_2Ar$), 3.79–3.86 (m, 8H; OCH_2CH_2), 3.96 (s, 4H; $COCH_2$), 4.39–4.44 (m, 4H; $ArCH_2Ar$), 6.59–6.63 (m, 6H; ArH), 6.65 (s, 2H; ArH), 6.73 (s, 2H; ArH), 7.41 (br, 2H; NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.5, 23.1, 26.7, 29.8, 29.9, 30.2, 30.3, 30.6, 30.7, 31.3, 31.4, 32.3, 75.6, 75.6, 120.9, 121.2, 122.0, 128.4, 128.6, 130.9, 135.2, 135.7, 135.9, 136.5, 154.6, 157.1, 163.2; FTIR (KBr): ν=3302, 3202 (NH), 1659 cm^{-1} (CONH); MS (MALDI-TOF, positive): *m/z*: 1277.62 $[M+Na]^+$, 1293.59 $[M+K]^+$. Elemental analysis calcd (%) for $C_{72}H_{108}Br_2N_2O_6$ (1257.42): C 68.77, H 8.66, N 2.23. Found C 68.97, H 8.89, N 1.82.

4.5. General procedure for the condensation reaction of thymin-1-ylacetic acid with 5, 6 or 7

Thymin-1-ylacetic acid (0.11 mmol), HOBt (0.11 mmol) and DCC (0.11 mmol) were dissolved in DMF (20 ml) and stirred for 30 min at room temperature. To the mixture was added 0.10 mmol of monoamino-calix[4]arene **5** (0.05 mmol of bisamino-calix[4]arene **6** and **7**) and stirred for another 24 h. The reaction mixture was filtered and DMF was removed under reduced pressure. The purified product was obtained by column chromatography (eluent: $CHCl_3$/CH_3OH).

4.5.1. Compound 8a. Yield: 84.8%. Mp 222–224°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.85–1.01 (m, 12H; CH_2CH_3), 1.83–1.94 (m, 11H; CH_2CH_3, T-CH_3), 3.12 (AB-d, ^2J=13.2 Hz, 2H; $ArCH_2Ar$), 3.16 (AB-d, ^2J=13.2 Hz, 2H; $ArCH_2Ar$), 3.76–3.88 (m, 8H; OCH_2), 4.43 (AB-d, ^2J=13.2 Hz, 2H; $ArCH_2Ar$), 4.47 (AB-d, ^2J=13.2 Hz, 2H; $ArCH_2Ar$), 4.45 (s, 2H; $COCH_2$), 6.50 (s, 6H; ArH), 6.58 (t, ^3J=7.3 Hz, 1H; ArH), 6.67 (d, ^3J=7.3 Hz, 2H; ArH), 6.87 (s, 2H; ArH), 7.23 (s, 1H; T-H), 8.34 (br, 1H; CONH), 9.77 (br, 1H; T-NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=10.2, 10.3, 12.3, 23.1, 23.2, 29.7, 31.0, 51.6, 76.6, 76.7, 111.2, 120.2, 121.5, 122.0, 128.0, 128.2, 128.2, 131.0, 134.4, 134.9, 135.4, 135.9, 141.0, 151.3, 154.0, 156.3, 156.8, 164.0, 164.3; FTIR (KBr): ν=3302 (NH), 1680 cm^{-1} (CONH); MS (MALDI-TOF, positive): *m/z*: 773.39 $[M]^+$, 796.38 $[M+Na]^+$, 812.36 $[M+K]^+$. Elemental analysis calcd (%) for $C_{47}H_{55}N_3O_7$ (773.93): C 72.94, H 7.16, N 5.43. Found C 72.99, H 7.18, N 5.20.

4.5.2. Compound 8b. Yield: 78.1%. Mp 168–170°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (t, ^3J=6.4 Hz, 12H; $(CH_2)_9CH_3$), 1.25–1.40 (m, 56H; $(CH_2)_7CH_3$), 1.85–1.93 (m, 8H; OCH_2CH_2), 1.92 (s, 3H; T-CH_3), 3.07 (AB-d, ^2J=13.2 Hz, 2H; $ArCH_2Ar$), 3.12 (AB-d, ^2J=13.2 Hz, 2H; $ArCH_2Ar$), 3.79–3.91 (m, 8H; OCH_2), 4.36 (s, 2H; $COCH_2$), 4.37 (AB-d, ^2J=13.2 Hz, 2H; $ArCH_2Ar$), 4.42 (AB-d, ^2J=13.2 Hz, 2H; $ArCH_2Ar$), 6.45–6.52 (m, 6H; ArH), 6.58 (t, ^3J=6.0 Hz, 1H; ArH), 6.65 (d, ^3J=6.0 Hz, 2H; ArH), 6.86 (s, 2H; ArH), 7.20 (s, 1H; T-H), 8.52 (br, 1H; CONH), 10.0 (br, 1H; T-NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=12.3, 14.1, 22.7, 26.3, 26.4, 29.4, 29.6, 29.8, 29.9, 30.0, 30.2, 30.2, 30.3, 30.3, 31.0, 31.9, 51.4, 75.1, 75.2, 111.1, 120.2, 121.6, 122.0, 128.0, 128.1, 128.2, 131.1, 134.4, 134.8, 135.5, 135.9, 141.2, 151.4, 154.0, 156.3, 156.8, 164.1, 164.6; FTIR (KBr): ν=3441 (NH), 1681 cm^{-1} (CONH); MS (MALDI-TOF, positive): *m/z*: 1188.6 $[M+Na]^+$, 1204.6 $[M+K]^+$. Elemental analysis calcd (%) for $C_{75}H_{111}N_3O_7$ (1166.66): C 77.21, H 9.59, N 3.60. Found C 77.36, H 9.82, N 3.30.

4.5.3. Compound 9a. Yield: 86.4%. Mp > 300°C; ^{1}H NMR (300 MHz, DMSO[D_6]): δ=0.93 (t, ^3J=7.5 Hz, 6H; $CH_2CH_2CH_3$), 1.00 (t, ^3J=7.2 Hz, 6H; $CH_2CH_2CH_3$), 1.77 (s, 6H; T-CH_3), 1.85–1.91 (m, 8H; OCH_2CH_2), 3.11 (AB-d, ^2J=12.9 Hz, 4H; $ArCH_2Ar$), 3.71 (t, ^3J=6.9 Hz, 4H; OCH_2), 3.83 (t, ^3J=7.8 Hz, 4H; OCH_2), 4.33 (d, ^3J=12.9 Hz, 4H; $ArCH_2Ar$), 4.43 (s, 4H; CH_2CO), 6.46 (s, 6H; ArH), 7.09 (s, 4H; ArH), 7.47 (s, 2H; T-H), 9.93 (s, 2H; CONH), 11.35 (s, 2H; T-NH); ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ=10.5, 10.8, 12.4, 23.1, 23.3, 30.8, 50.2, 76.8, 76.9, 108.4, 119.9, 122.4, 128.0, 132.8, 134.0, 135.6, 143.0, 151.5, 152.9, 155.9, 164.8, 165.4; FTIR (KBr): ν=3462 (NH), 1692 cm^{-1} (CONH); MS (MALDI-TOF, positive): *m/z*: 954.43 $[M]^+$, 977.43 $[M+Na]^+$, 993.40 $[M+K]^+$. Elemental analysis calcd (%) for $C_{54}H_{62}N_6O_{10}$ (955.09): C 67.90, H 6.54, N 8.80. Found C 67.87, H 6.46, N 8.53.

4.5.4. Compound 9b. Yield: 77.9%. Mp 280–282°C; ^{1}H NMR (300 MHz, [D_6]DMSO): δ=0.83–0.85 (m, 12H; $(CH_2)_7CH_3$), 1.26–1.48 (m, 56H; $(CH_2)_7CH_3$), 1.77 (s, 6H; T-CH_3), 1.87–1.89 (m, 8H; OCH_2CH_2), 3.09 (AB-d, ^2J=12.6 Hz, 4H; $ArCH_2Ar$), 3.73 (t, ^3J=5.31 Hz, 4H;

OCH_2), 3.87 (t, ^3J=4.89 Hz, 4H; OCH_2), 4.31 (AB-d, ^2J=12.6 Hz, 4H; $ArCH_2Ar$), 4.43 (s, 4H; CH_2CO), 6.42 (s, 6H; ArH), 7.09 (s, 4H; ArH), 7.46 (s, 2H; T-H), 9.94 (s, 2H; CONH), 11.32 (s, 2H; T-NH); ^{13}C NMR (75.5 MHz, [D_6]DMSO/$CDCl_3$=2:1, v/v): δ=12.1, 14.0, 22.4, 26.2, 29.2, 29.6, 29.8, 30.1, 30.5, 30.7, 31.5, 31.7, 50.0, 75.0, 75.3, 108.4, 119.8, 122.3, 128.1, 132.5, 134.5, 134.8, 142.5, 151.3, 152.5, 156.1, 164.7, 165.1; FTIR (KBr): ν=3292 (NH), 1694 cm^{-1} (CONH); MS (MALDI-TOF, positive): *m/z*: 1369.72 $[M+Na]^+$, 1385.73 $[M+K]^+$. Elemental analysis calcd (%) for $C_{82}H_{118}N_6O_{10}$ (1347.81): C 73.07, H 8.82, N 6.24; found C 73.28, H 8.99, N 6.07.

4.5.5. Compound 10a. Yield: 82.3%. Mp 244–246°C; ^{1}H NMR (300 MHz, [D_6]DMSO): δ=0.91–0.97 (m, 12H; $CH_2CH_2CH_3$), 1.75 (s, 6H; T-CH_3), 1.81–1.88 (m, 8H; $CH_2CH_2CH_3$), 3.00–3.17 (m, 4H; $ArCH_2Ar$), 3.71–3.79 (m, 8H; OCH_2), 4.30–4.37 (m, 4H; $ArCH_2Ar$), 4.37 (s, 4H; CH_2CO), 6.54–6.60 (m, 6H; ArH), 6.76 (d, ^4J=1.71 Hz, 2H; ArH), 6.92 (d, ^4J=1.71 Hz, 2H; ArH), 7.45 (s, 2H; T-H), 9.81 (s, 2H; CONH), 11.28 (s, 2H; T-NH); ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ=10.1, 11.8, 22.6, 22.7, 30.2, 30.4, 30.4, 30.6, 49.7, 76.1, 76.1, 107.8, 118.6, 119.2, 121.7, 127.7, 128.0, 132.4, 132.5, 134.2, 134.5, 134.6, 142.5, 151.0, 152.1, 156.0, 164.4, 164.6; FTIR (KBr): ν=3464 (NH), 1686 cm^{-1} (CONH); MS (MALDI-TOF, positive): *m/z*: 954.50 $[M]^+$, 977.48 $[M+Na]^+$. Elemental analysis calcd (%) for $C_{54}H_{62}N_6O_{10}$ (955.09): C 67.90, H 6.54, N 8.80. Found C 67.55, H 6.71, N 8.46.

4.5.6. Compound 10b. Yield: 72.1%. Mp 268–270°C; ^{1}H NMR (300 MHz, [D_6]DMSO): δ=0.75–0.79 (m, 12H; $(CH_2)_7CH_3$), 1.17–1.25 (m, 56H; $(CH_2)_7CH_3$), 1.73 (s, 6H; T-CH_3), 1.74–1.85 (m, 8H; OCH_2CH_2), 2.90–3.05 (m, 4H; $ArCH_2Ar$), 3.68–3.80 (m, 8H; OCH_2), 4.20–4.35 (m, 4H; $ArCH_2Ar$), 4.38 (s, 4H; CH_2CO), 6.48 (s, 6H; ArH), 6.77 (s, 2H; ArH), 6.93 (s, 2H; ArH), 7.38 (s, 2H; T-H), 9.79 (s, 2H; CONH), 11.28 (s, 2H; T-NH); ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ=12.3, 13.9, 22.7, 26.7, 29.6, 30.0, 30.3, 30.9, 31.1, 31.2, 31.8, 32.0, 50.1, 75.2, 75.4, 108.3, 119.2, 119.7, 122.0, 128.3, 128.5, 133.2, 134.5, 134.6, 134.7, 135.0, 142.9, 151.5, 152.4, 156.3, 164.8, 165.2; FTIR (KBr): ν=3291 (NH), 1686 cm^{-1} (CONH); MS (MALDI-TOF, positive): *m/z*: 1369.74 $[M+Na]^+$, 1385.73 $[M+K]^+$. Elemental analysis calcd (%) for $C_{82}H_{118}N_6O_{10}$ (1347.81): C 73.07, H 8.82, N 6.24. Found C 72.78, H 9.04, N 6.24.

4.6. General procedure for reaction of adenine and 11, 12 or 13

To a mixture of adenine (0.15 mmol) and NaH (0.12 mmol, 60%) in DMF (20 ml), which was stirred at room temperature for 2 h, was added 0.10 mmol of compound **11** (0.05 mmol for **12** and **13**) in CH_2Cl_2 for 30 min. The reaction mixture was stirred for 24 h at room temperature and the solvent was removed under reduced pressure. The residue was purified by column chromatography with simultaneous monitoring by TLC (eluent: $CHCl_3/CH_3OH/NH_4OH$=120:10:1) to afford **14**, **15**, **16**, **17**, **18** as white solids.

4.6.1. Compound 14a. Yield: 47.2%. Mp 276–278°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.91–1.02 (m, 12H; CH_2CH_3), 1.82–1.95 (m, 8H; CH_2CH_3), 3.09 (AB-d, ^2J=13.2 Hz, 2H; $ArCH_2Ar$), 3.11 (AB-d, ^2J=13.2 Hz, 2H; $ArCH_2Ar$), 3.72–3.86 (m, 8H; OCH_2), 4.39 (AB-d, ^2J=13.2 Hz, 2H; $ArCH_2Ar$), 4.41 (AB-d, ^2J=13.2 Hz, 2H; $ArCH_2Ar$), 4.84 (s, 2H; $COCH_2$), 6.09 (t, ^3J=7.47 Hz, 1H; ArH), 6.18 (s, 2H; A-NH_2), 6.33 (d, ^3J=7.47 Hz, 2H; ArH), 6.54 (s, 2H; ArH), 6.61–7.02 (m, 6H; ArH), 7.91 (s, 1H; A-C_2–H), 8.33 (s, 1H; A-C_8–H), 8.79 (s, 1H; CONH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=10.2, 10.4, 23.1, 23.3, 30.9, 31.0, 48.6, 76.6, 77.0, 119.3, 120.0, 121.2, 121.9, 127.8, 128.3, 128.4, 131.0, 134.7, 135.1, 135.5, 135.6, 141.0, 149.8, 153.0, 153.6, 155.8, 156.3, 156.9, 163.3; FTIR (KBr): ν=3420, 3390 (NH_2, NH), 1655 cm^{-1} (CONH); MS (MALDI-TOF, positive): *m/z*: 783.66 $[M+H]^+$, 805.61 $[M+Na]^+$. Elemental analysis calcd (%) for $C_{47}H_{54}N_6O_5$ (782.95): C 72.10, H 6.95, N 10.74. Found C 71.85, H 7.33, N 10.52.

4.6.2. Compound 14b. Yield: 41.3%. Mp 188–190°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.87 (t, ^3J=6.4 Hz, 12H; $(CH_2)_9CH_3$), 1.20–1.35 (m, 56H; $(CH_2)_7CH_3$), 1.80–1.90 (m, 8H; OCH_2CH_2), 3.07 (AB-d, ^2J=13.5 Hz, 2H; $ArCH_2Ar$), 3.09 (AB-d, ^2J=13.5 Hz, 2H; $ArCH_2Ar$), 3.73–3.80 (m, 4H; OCH_2), 3.86 (t, ^3J=7.4 Hz, 4H; OCH_2), 4.37 (AB-d, ^2J=13.5 Hz, 2H; $ArCH_2Ar$), 4.39 (AB-d, ^2J=13.5 Hz, 2H; $ArCH_2Ar$), 4.83 (s, 2H; CH_2CO), 6.07 (t, ^3J=7.3 Hz, 1H; ArH), 6.25 (br, 2H; A-NH_2), 6.31 (d, ^3J=7.3 Hz, 2H; Ar-H), 6.52 (s, 2H; ArH), 6.60–6.72 (m, 6H; ArH), 7.90 (s, 1H; A-C_2–H), 8.32 (s, 1H; A-C_8–H), 8.75 (s, 1H; CONH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.1, 22.7, 26.3, 26.4, 29.5, 29.8, 30.0, 30.0, 30.3, 30.4, 30.9, 31.0, 32.0, 48.5, 75.1, 77.2, 119.3, 120.0, 121.2, 121.9, 127.8, 128.3, 128.4, 131.0, 134.7, 135.2, 135.5, 135.6, 141.1, 149.7, 152.8, 153.6, 155.7, 156.3, 156.9, 163.2; FTIR (KBr): ν=3428 (NH), 1642 cm^{-1} (CONH); MS (MALDI-TOF, positive): *m/z*: 1175.84 $[M+H]^+$, 1197.80 $[M+Na]^+$. Elemental analysis calcd (%) for $C_{75}H_{110}N_6O_5$ (1175.68): C 76.62, H 9.43, N 7.15. Found C 76.34, H 9.42, N 6.90.

4.6.3. Compound 15a. Yield: 27.4%. Mp 220–222°C; ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$=90/10 v/v): δ=0.92 (t, ^3J=7.5 Hz, 6H; $CH_2CH_2CH_3$), 1.04 (t, ^3J=7.2 Hz, 6H; $CH_2CH_2CH_3$), 1.82–1.98 (m, 8H; $CH_2CH_2CH_3$), 3.14 (AB-d, ^2J=13.5 Hz, 4H; $ArCH_2Ar$), 3.72 (t, ^3J=6.9 Hz, 4H; OCH_2), 3.94 (t, ^3J=8.1 Hz, 4H; OCH_2), 4.44 (AB-d, ^2J=13.5 Hz, 4H; $ArCH_2Ar$), 4.86 (s, 4H; CH_2CO), 6.55 (s, 4H; ArH), 6.64 (t, ^3J=7.5 Hz, 2H; ArH), 6.85 (d, ^3J=7.5 Hz, 4H; ArH), 7.95 (s, 2H; A-C_2–H), 8.18 (s, 2H; A-C_8–H), 9.48 (s, 2H; CONH); ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ=10.3, 10.6, 22.9, 23.1, 30.6, 45.7, 76.6, 76.7, 118.5, 119.9, 122.2, 127.8, 132.7, 133.8, 135.5, 142.2, 150.0, 152.7, 152.9, 155.7, 156.1, 164.8; FTIR (KBr): ν=3324 (NH_2, NH), 1630 cm^{-1} (CONH); MS (MALDI-TOF, positive): *m/z*: 973.43 $[M+H]^+$, 995.41 $[M+Na]^+$, 1011.42 $[M+K]^+$. Elemental analysis calcd (%) for $C_{54}H_{60}N_{12}O_6{\cdot}H_2O$ (991.14): C 65.43, H 6.31, N 16.96. Found C 65.44, H 6.28, N 16.75.

4.6.4. Compound 15b. Yield: 24.3%. Mp 232–234°C; ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$=95/5 v/v): δ=0.82–0.85 (m, 12H; $(CH_2)_7CH_3$), 1.20–1.45 (m, 56H; $(CH_2)_7CH_3$), 1.79–1.89 (m, 8H; OCH_2CH_2), 3.09 (AB-d, ^2J=13.2 Hz, 4H; $ArCH_2Ar$), 3.66 (t, ^3J=6.9 Hz, 4H; OCH_2), 3.97 (t,

^3J=7.2 Hz, 4H; OCH_2), 4.38 (AB-d, ^2J=13.2 Hz, 4H; $ArCH_2Ar$), 4.79 (s, 4H; CH_2CO), 6.42 (s, 4H; ArH), 6.62 (t, ^3J=7.2 Hz, 2H; ArH), 6.87 (d, ^3J=7.2 Hz, 4H; ArH), 7.81 (s, 2H; A-C_2–H), 8.12 (s, 2H; A-C_8–H), 9.41 (s, 2H; CONH); ^{13}C NMR (75.5 MHz, $CDCl_3$/CD_3OD=95/5 v/v): δ=14.1, 22.8, 26.2, 26.6, 29.5, 29.5, 29.7, 29.8, 29.9, 30.2, 30.5, 31.1, 32.0, 46.2, 75.2, 75.5, 118.7, 120.5, 122.0, 128.7, 130.9, 134.5, 136.1, 141.7, 149.3, 152.5, 153.2, 155.8, 157.4, 163.6; FTIR (KBr): ν=3322 (NH_2, NH), 1642 cm^{-1} (CONH); MS (MALDI-TOF, positive): *m/z*: 1365.45 $[M+H]^+$, 1387.43 $[M+Na]^+$. Elemental analysis calcd (%) for $C_{82}H_{116}N_{12}O_6$ (1365.85): C 72.10, H 8.56, N 12.31. Found C 71.79, H 8.74, N 12.13.

4.6.5. Compound 16a. Yield: 16.7%. Mp 254–256°C; ^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD=50:50 v/v): δ=0.85–1.01 (m, 12H; $CH_2CH_2CH_3$), 1.82–1.92 (m, 8H; $CH_2CH_2CH_3$), 3.08 (AB-d, ^2J=13.2 Hz, 4H; $ArCH_2Ar$), 3.69 (t, ^3J=6.9 Hz, 4H; OCH_2), 3.86 (t, ^3J=8.1 Hz, 4H; OCH_2), 4.38 (AB-d, ^2J=13.2 Hz, 4H; $ArCH_2Ar$), 4.81 (s, 2H; CH_2CO), 4.86 (s, 2H; CH_2CO), 6.53–6.80 (m, 10H; ArH), 7.92 (s, 1H; A-C_2–H), 8.04 (s, 1H; A-C_2–H), 8.10 (s, 1H; A-C_8–H), 8.23 (s, 1H; A-C_8–H); ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ=10.4, 10.7, 23.0, 23.2, 30.4, 32.2, 45.8, 49.7, 76.8, 76.8, 112.2, 118.6, 119.9, 122.4, 128.0, 132.8, 132.9, 134.0, 135.6, 142.2, 147.1, 150.1, 152.0, 152.5, 152.8, 152.9, 153.0, 155.8, 156.2, 156.3, 160.0, 161.7, 165.0, 165.3; FTIR (KBr): ν=3324 (NH_2, NH), 1638 cm^{-1} (CONH); MS (MALDI-TOF, positive): *m/z*: 973.23 $[M+H]^+$, 995.18 $[M+Na]^+$, 1011.14 $[M+K]^+$. Elemental analysis calcd (%) for $C_{54}H_{60}N_{12}O_6{\cdot}H_2O$ (991.14): C 65.43, H 6.31, N 16.96. Found C 65.31, H 6.29, N 16.81.

4.6.6. Compound 16b. Yield: 13.5%. Mp 236–238°C; ^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD=90/10 v/v): δ=0.75–0.80 (m, 12H; $(CH_2)_7CH_3$), 1.02–1.50 (m, 56H; $(CH_2)_7CH_3$), 1.70–1.90 (m, 8H; OCH_2CH_2), 3.02 (AB-d, ^2J=13.2 Hz, 4H; $ArCH_2Ar$), 3.65–3.88 (m, 8H; OCH_2), 4.32 (AB-d, ^2J=13.2 Hz, 4H; $ArCH_2Ar$), 4.80 (s, 2H; CH_2CO), 4.90 (s, 2H; CH_2CO), 6.49–6.75 (m, 10H; ArH), 7.87 (s, 1H; A-C_2–H), 7.99 (s, 1H; A-C_2–H), 8.06 (s, 1H; A-C_8–H), 8.12 (s, 1H; A-C_8–H); ^{13}C NMR (75.5 MHz, $CDCl_3$/CD_3OD=90/10 v/v): δ=14.0, 22.6, 26.2, 26.4, 29.3, 29.4, 29.6, 29.7, 29.8, 30.0, 30.3, 30.9, 31.9, 46.0, 50.2, 75.1, 75.2, 112.5, 118.2, 120.2, 120.6, 122.0, 128.4, 130.5, 131.0, 134.7, 134.9, 135.4, 141.7, 146.2, 149.1, 152.2, 152.4, 153.2, 153.6, 155.5, 156.6, 156.8, 158.7, 163.9, 164.7; FTIR (KBr): ν=3343 (NH_2, NH), 1612 cm^{-1} (CONH); MS (MALDI-TOF, positive): *m/z*: 1365.78 $[M+H]^+$, 1387.69 $[M+Na]^+$, 1403.70 $[M+K]^+$. Elemental analysis calcd (%) for $C_{82}H_{116}N_{12}O_6{\cdot}H_2O$: (1383.86): C 71.16, H 8.59, N 12.15. Found C 71.18, H 8.62, N 12.14.

4.6.7. Compound 17a. Yield: 24.7%. Mp 224–225°C; ^{1}H NMR (300 MHz, [D_6]DMSO): δ=0.89–1.00 (m, 12H; $CH_2CH_2CH_3$), 1.75–1.88 (m, 8H; $CH_2CH_2CH_3$), 3.04–3.20 (m, 4H; $ArCH_2Ar$), 3.69–3.77 (m, 8H; OCH_2), 4.22–4.36 (m, 4H; $ArCH_2Ar$), 4.93 (s, 4H; CH_2CO), 6.49 (s, 6H; ArH), 6.76 (d, ^4J=2.1 Hz, 2H; ArH), 6.89 (d, ^4J=2.1 Hz, 2H; ArH), 7.20 (br, 4H; A-NH_2), 8.07 (s, 4H; A-C–H), 10.00 (s, 2H; CONH); ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ=10.3, 10.4, 22.8, 22.9, 30.4, 30.5, 30.6, 45.5, 76.3, 76.4, 118.3, 119.0, 119.4, 121.9, 127.9, 128.2, 132.6, 134.4, 134.5, 134.7, 134.9, 142.0, 149.8, 152.4, 152.5, 156.0, 156.2, 164.4; FTIR (KBr): ν=3324 (NH_2, NH), 1630 cm^{-1} (CONH); MS (MALDI-TOF, positive): *m/z*: 973.22 $[M+H]^+$, 995.20 $[M+Na]^+$, 1011.19 $[M+K]^+$. Elemental analysis calcd (%) for $C_{54}H_{60}N_{12}O_6{\cdot}H_2O$ (991.14): C 65.43, H 6.31, N 16.96. Found C 65.41, H 6.25, N 16.94.

4.6.8. Compound 17b. Yield: 21.8%. Mp 206–208°C; ^{1}H NMR (300 MHz, [D_6]DMSO): δ=0.78–0.80 (m, 12H; $(CH_2)_7CH_3$), 1.20–1.30 (m, 56H; $(CH_2)_7CH_3$), 1.81–1.83 (m, 8H; OCH_2CH_2), 2.94~3.08 (m, 4H; $ArCH_2Ar$), 3.72–3.76 (m, 8H; OCH_2), 4.27–4.31 (m, 4H; $ArCH_2Ar$), 4.91 (s, 4H; CH_2CO), 6.50 (s, 6H; ArH), 6.76 (s, 2H; ArH), 6.88 (s, 2H; ArH), 7.08 (br, 4H; A-NH_2), 8.00 (s, 2H; A-C_2–H), 8.06 (s, 2H; A-C_8–H), 9.94 (s, 2H, CONH); ^{13}C NMR (75.5 MHz, [D_6]DMSO/$CDCl_3$=1:1 v/v): δ=14.3, 22.7, 26.5, 29.4, 29.8, 30.0, 30.1, 30.3, 30.4, 31.9, 45.9, 75.2, 75.2, 118.8, 119.3, 119.4, 122.1, 128.2, 128.4, 132.8, 134.7, 134.9, 135.1, 135.2, 142.1, 150.2, 152.8, 156.2, 156.3, 156.5, 164.5; FTIR (KBr): ν=3338 (NH_2, NH), 1640 cm^{-1} (CONH); MS (MALDI-TOF, positive): *m/z*: 1365.67 $[M+H]^+$, 1387.66 $[M+Na]^+$, 1403.62 $[M+K]^+$. Elemental analysis calcd (%) for $C_{82}H_{116}N_{12}O_6{\cdot}H_2O$: (1383.86): C 71.16, H 8.59, N 12.15. Found C 71.24, H 8.69, N 12.07.

4.6.9. Compound 18a. Yield: 13.5%. Mp 246–247°C; ^{1}H NMR (300 MHz, [D_6]DMSO): δ=0.92–1.01 (m, 12H; $CH_2CH_2CH_3$), 1.80–1.89 (m, 8H; $CH_2CH_2CH_3$), 3.03–3.18 (m, 4H; $ArCH_2Ar$), 3.72–3.79 (m, 8H; OCH_2), 4.29–4.37 (m, 4H; $ArCH_2Ar$), 4.96 (s, 2H; CH_2CO), 5.16 (s, 2H; CH_2CO), 6.54–6.60 (m, 6H; ArH), 6.80 (d, ^4J=2.2 Hz, 1H; ArH), 6.84 (d, ^4J=2.2 Hz, 1H; ArH), 6.86 (s, 2H; A-NH_2), 6.91 (d, ^4J=3.1 Hz, 1H; ArH), 6.92 (d, ^4J=2.2 Hz, 1H; ArH), 7.26 (s, 4H, A-NH_2), 8.09 (s, 1H; A-C_2–H), 8.10 (s, 1H; A-C_2–H), 8.20 (s, 1H; A-C_8–H); 8.25 (s, 1H; A-C_8–H), 9.95 (s, 1H; CONH), 10.05 (s, 1H; CONH); ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ=10.3, 22.7, 22.8, 30.3, 30.5, 30.7, 45.5, 49.3, 76.3, 76.4, 111.8, 118.3, 119.0, 119.1, 119.3, 121.9, 127.9, 128.2, 132.3, 132.6, 134.3, 134.5, 134.7, 134.9, 141.9, 146.8, 149.8, 151.7, 152.2, 152.4, 152.5, 156.0, 156.2, 159.6, 164.4, 164.8; FTIR (KBr): ν=3379, 3347 (NH_2, NH), 1610 cm^{-1} (CONH); MS (MALDI-TOF, positive): *m/z*: 973.40 $[M+H]^+$, 995.34 $[M+Na]^+$, 1011.32 $[M+K]^+$. High-resolution MS (P-SIMS-Gly) for $C_{54}H_{61}N_{12}O_6$ (973.4831): *m/z*: 973.4815 $[M+H]^+$. Elemental analysis calcd (%) for $C_{54}H_{60}N_{12}O_6{\cdot}H_2O$ (991.14): C 65.43, H 6.31, N 16.96. Found C 65.44, H 6.29, N 16.65.

4.6.10. Compound 18b. Yield:11.8%. Mp 248–249°C; ^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD=1:1 v/v): δ=0.84–0.90 (m, 12H; $(CH_2)_7CH_3$), 1.25–1.40 (m, 56H; $(CH_2)_7CH_3$), 1.80–1.89 (m, 8H; OCH_2CH_2), 3.05–3.16 (m, 4H; $ArCH_2Ar$), 3.77–3.96 (m, 8H; OCH_2), 4.31–4.39 (m, 4H; $ArCH_2Ar$), 4.90 (s, 2H; CH_2CO), 4.96 (s, 2H; CH_2CO), 6.44–6.80 (m, 10H; ArH), 7.40 (br, 4H; A-NH_2), 8.05 (s, 1H; A-C_2–H), 8.16 (s, 1H; A-C_2–H); 8.20 (s, 1H; A-C_8–H), 8.35 (s, 1H; A-C_8–H); ^{13}C NMR (75.5 MHz, $CDCl_3$/CD_3OD=1:1 v/v): δ=13.7, 22.4, 26.1, 29.2, 29.5, 29.7, 30.0, 30.7, 31.7, 46.1, 50.3, 75.0, 75.1, 112.4, 118.3, 119.9, 120.1, 120.3, 121.3, 127.7, 128.0, 130.5, 131.0, 134.5, 134.8, 135.1, 135.6, 141.5, 146.8, 149.7, 152.3, 152.3, 153.5, 153.9, 155.4, 156.3, 159.6, 163.8, 164.4; FTIR

(KBr): ν=3332, 3194 (NH_2, NH), 1641 cm^{-1} (CONH); MS (MALDI-TOF, positive): *m/z*: 1365.27 $[M+H]^+$, 1387.23 $[M+Na]^+$, 1403.20 $[M+K]^+$. Elemental analysis calcd (%) for $C_{82}H_{116}N_{12}O_6 \cdot H_2O$: (1383.86): 71.16, H 8.59, N 12.15. Found C 71.35, H 8.74, N 11.96.

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