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Reaction of Bromoacetyl and Sulfhydryl Groups: Efficient Synthesis of Aromatic Oligoamides Consisting of Benzene-1,3,5-tricarboxamide Units

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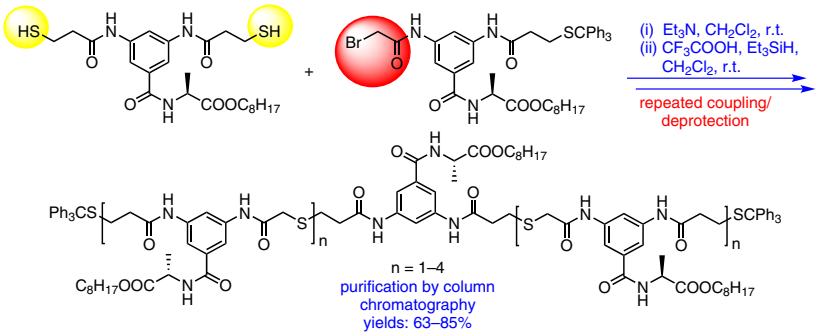

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Abstract A series of aromatic oligoamides consisting of benzene-1,3,5-tricarboxamide (BTA) residues linked by thioether bonds were designed and synthesized based on the highly efficient and specific reaction between sulfhydryl and bromoacetyl groups. Initial assessment of the folding of these oligoamides with circular dichroism (CD) spectroscopy showed that these oligoamides could fold into a helical conformation.

Key words benzene-1,3,5-tricarboxamides, bromoacetyl group, sulfhydryl group, oligoamides, circular dichroism, folded conformation

In the past decade, much attention has been paid to the synthesis and application of various benzene-1,3,5-tricarboxamide (BTA) molecules owing to their simple structure, ready synthetic accessibility, and their now well-understood self-assembling behavior.[1] These versatile building blocks have been frequently employed in the development of various materials such as liquid crystals, organogels, and hydrogels.[2] The three *meta*-distributed amide groups of BTA and its homologues can engage in triple intermolecular H-bonding interaction under proper conditions, leading to hydrogen-bonded columnar structures.[3] However, controlling the stacking of disclike molecules based solely on noncovalent forces such as H-bonding and π–π stacking is quite challenging, and rarely results in well-defined columns.[4] An effective strategy for curbing the growth of otherwise extended stacks is to resort to the assistance of additional covalent forces that act by reinforcing the stacking of disclike units and also controlling the alignment of such units. Another benefit of introducing covalent forces is that the presence of covalent linkages allows the adoption of stepwise introduction of disclike residues, leading to discrete oligomers that otherwise would not be possible to form in self-assembling systems.[5] Oligoamides consisting of BTA units have an additional feature in that the high propensity of such units to stack via the assistance of triple H-bonded networks can be explored to result in the folding of the corresponding oligomers, leading to defined secondary structures. Thus far, only a small number of oligomers based on covalently linked BTA units are known. For instance, Nuckolls and co-workers designed and explored a series of oligomers by connecting adjacent BTA units using short linkers.[6] In a different approach, Gong and co-workers synthesized and studied a series of oligomers by attaching (grafting) BTA units to oligoamine linkers.[7] These previous example demonstrated the effectiveness of controlling and defining the stacking of disclike aromatic units by combining covalent and noncovalent interactions. However, the further development and expansion of this effective approach call for new coupling methods that allow the highly efficient covalent assembly of BTA and other disclike units into oligomers of desired lengths.

We report herein the rapid and efficient synthesis of linear oligoamides **1** composed of BTA. The objective here is to connect disclike units by forming thioether linkers based on the highly efficient and highly specific reaction between bromoacetyl and sulfhydryl groups. Oligoamides **1** (Figure 1) were obtained in overall yields ranging from 63–85%. Circular dichroism (CD) spectroscopy indicated that these oligoamides folded into chiral conformations that are most likely to be helical.

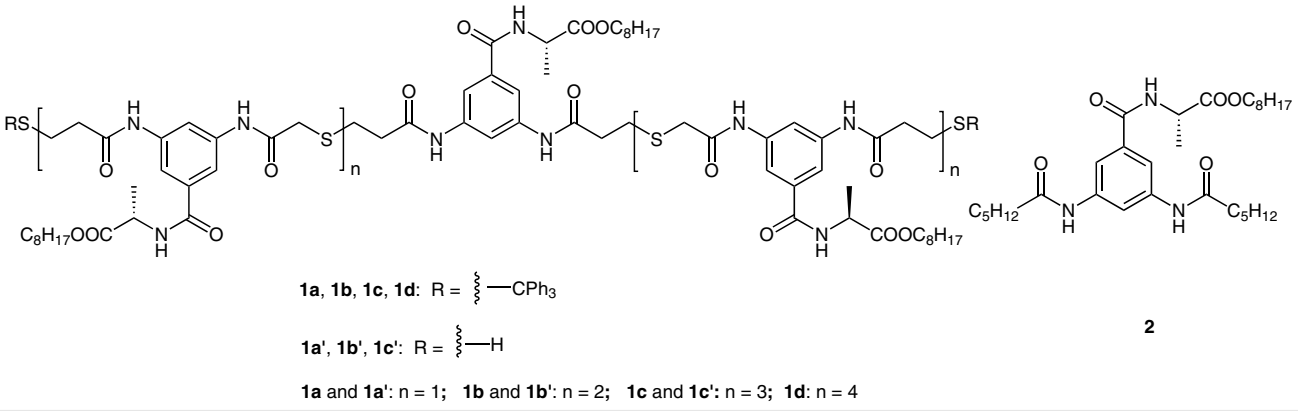
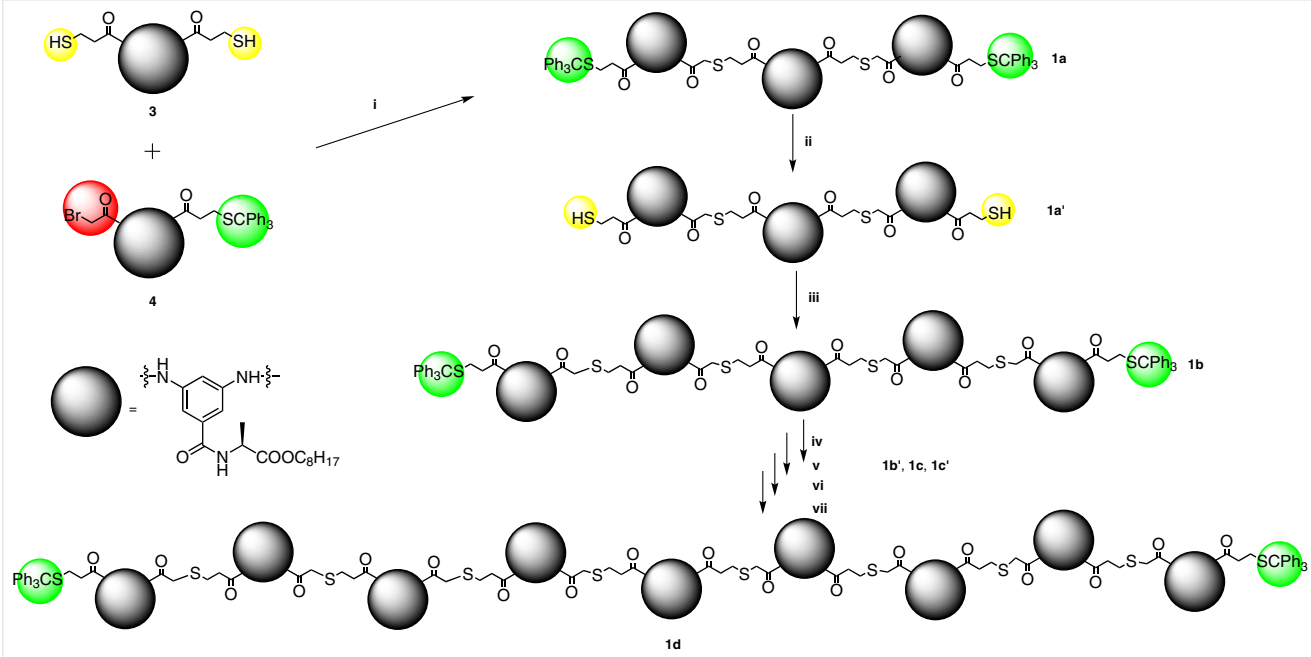


Figure 1 Structure of oligoamides **1** and compound **2**

Our approach to target oligoamides **1** was planned such that it would take advantage of the highly efficient reaction between bromoacetyl and sulfhydryl groups in order to couple BTA monomers. Each of the coupling steps can be performed under moderately basic conditions, free of additional coupling reagents and without further modification on the reactants.[8] Scheme 1 shows the synthesis route of oligomers **1a–d**. Compounds **3** bearing two sulfhydryl groups and **4** having one bromoacetyl group and one trityl-protected sulfhydryl group, prepared through straightforward amide chemistry, were the designed BTA units used for constructing oligoamides **1**.

Coupling of the designed BTA units was first probed by treating dithiol **3** with compound **4** which would lead to trimer **1a**. Specifically, dithiol **3** was let to react with an excess amount of **4** in CH_2Cl_2 the presence of triethylamine (Et_3N) at room temperature for eight hours. After removing CH_2Cl_2 and other volatile components, the solid residue left was subjected to flash column chromatography (silica gel, 3% MeOH in CH_2Cl_2) to give purified trimer **1a** in 70% yield.

To probe the preparation of longer oligomers, trimer **1a**, bearing two trityl-protected sulfhydryl groups at its ends, was treated with trifluoroacetic acid (TFA) to give dithiol **1a′**. Using the same reaction conditions for preparing **1a**, dithiol **1a′** was reacted with compound **4**. Pentamer **1b** was obtained in 85% yield after being purified with flash column chromatography.



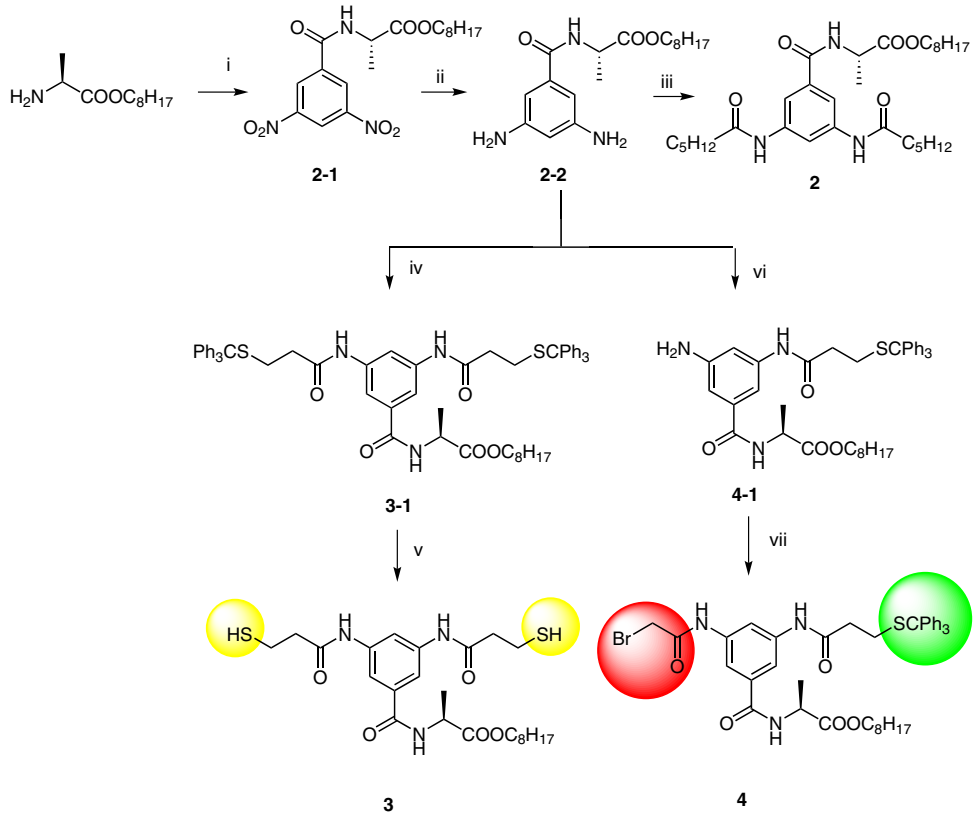
Scheme 1 Synthetic route of oligomers **1**. *Reagents and conditions*: (i), (iii), (v), and (vii): **4** (2.4 equiv), Et_3N, CH_2Cl_2, r.t. 8 h; (ii), (iv), and (vi): TFA, Et_3SiH, CH_2Cl_2, r.t., 1 h.

The similar high yields observed for the formation of trimer **1a** and pentamer **1b** demonstrates that the efficiency of the coupling reaction is not compromised as the length of the oligoamides product extended. Such a judgement is confirmed by the synthesis of heptamer **1c** and the much longer nonamer **1d**. Briefly, repeating the above deprotection and coupling steps led to **1c** and **1d** in 63% and 77%, respectively.

It was observed that removing the trityl groups of **1a**–**c** with TFA, which led to the corresponding dithiol oligomers **1a′**–**c′**, proceeded quantitatively. Oligomers **1a′**–**c′** were then reacted with compound **4** to give pure **1b**–**d**. The final yields of **1a**–**d** are not optimized but are comparable given that these oligomers were subjected to extensive column chromatography (silica gel, with 3% MeOH in CH_2Cl_2 as the eluent).

The successful preparation of oligoamides **1a**–**d** demonstrates that our approach, which is based on the reaction between sulfhydryl and bromoacetyl groups for coupling disclike units as exemplified by the BTA monomers, presents a new, efficient method for the coupling of designed structural units under coupling and deprotection conditions that involve simple treatment by washing with acid and base. The similarly high yields for **1a**–**d** suggests that our method is generally applicable for the efficient synthesis of thioether-linked oligomers of different lengths.

A synthetic route for the preparation of compounds **2**–**4** is depicted in Scheme 2. Compounds **2**–**4** were prepared starting from 3,5-dinitrobenzoic acid which owned 1,3,5-substituted benzene structure. Treating (*S*)-octyl 2-aminopropanoate[7] with 3,5-dinitrobenzoic acid chloride leaded to **2-1** which was then converted into diamine **2-2** based on a reduction reaction. Compound **2** was subsequently obtained by one-step acylation of **2-2** with 55% yield. Compound **3-1** and amine **4-1** were obtained from **2-2** in 62% and 50% yield, respectively, by controlling the ratios of 3-(tritylthio)propanoic acid and **2-2** with the condensation agent HATU. Especially mentioned, this synthetic method for **4-1** was quite facile, by which the typical amino protection and deprotection reactions could be excluded and **3-1**, main side product in this reaction, could also be used. Dithiol **3** formed almost quantitatively by removing the trityl group of **3-1** with excess TFA/Et_3SiH.[9] As dithiol compounds are easily oxidized by air, **3** was directly used for the



Scheme 2 Synthetic route for the preparation of compounds **2**–**4**. *Reagents and conditions*: (i) 3,5-dinitrobenzoic acid, $(COCl)_2$, Et_3N, CH_2Cl_2, 82%; (ii) H_2, 10% Pd/C, CH_2Cl_2, 98%; (iii) hexanoic acid, *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI), hydroxybenzotriazole (HOBT), *N*,*N*-diisopropylethylamine (DIPEA), CH_2Cl_2, 55%; (iv) 3-(tritylthio)propanoic acid (2.4 equiv), 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate) (HATU), 1-hydroxy-7-azabenzotriazole (HOAT), 4-dimethylaminopyridine (DMAP), DIPEA, CH_2Cl_2, 65%; (v) TFA, Et_3SiH, CH_2Cl_2, 98%; (vi) 3-(tritylthio)propanoic acid (1.2 equiv), HATU, HOAT, DMAP, DIPEA, CH_2Cl_2, 50%; (vii) $BrCH_2COBr$, Et_3N, CH_2Cl_2, 66%.

next reaction step after flash column chromatography, which could decrease the purification difficulty and increase the reaction yield. Compound **4** was produced in 66% yield by treating **4-1** with bromoacetyl bromide.

Oligoamides **1** bear side chains with a chiral moiety derived from L-alanine, which could serve to bias the handedness of the well-known H-bonded helical columns, which, in this case are also covalently tethered, formed by BTA units. The potential chiral conformations could be revealed with circular dichroism (CD) spectroscopy. Chiral compound **2**, corresponding to a single BTA unit of **1**, was also examined with CD as a control.

Thus, the potential handedness of oligoamides **1** was investigated with CD spectroscopy in $CHCl_3$.[10] Notable CD signals in the range of 260–400nm were detected for **1b**–**d**, while no CD signal could be detected for **2** in the range of 260–400nm (Figure 2 and Supporting Information S1), suggesting the transfer of chirality from the UV-silent side chains to the oligoamide backbone. As shown in Figure 2 (a), CD maxima at λ = 277 nm and 319 nm were observed in the spectrum of **1b**. The CD spectra of **1c** and **1d** shared similar shapes, with signals at around λ = 280 nm (λ = 279 nm for **1c** and λ = 275 nm for **1d**) and 319 nm (Figure 2, b and c). In the range from 20–100 μM, the CD spectra of **1b**–**d** showed growth in the intensity of CD signals with increasing concentration. These observations indicated that **1b**–**d** adopted similar chiral conformations with a biased handedness, which may be owing to chirality transfer from the chiral side chains to the stacked aromatic rings derived by the well-known triple H-bonding interaction between BTA motifs. However, only weak CD signals could be recorded for **1a** from 20–100 μM in $CHCl_3$, which is likely due to the insufficient stability of the biased handedness structure of this short oligomer.

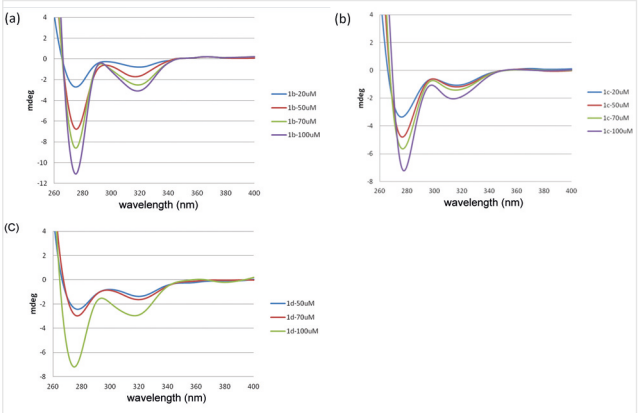


Figure 2 Concentration-dependent CD spectra of oligomers **1** and compound **2**: (a) **1b**, (b) **1c**, and (c) **1d** recorded in $CHCl_3$ at r.t.

In summary, a series of oligoamides consisting of different numbers of BTA units connected via thioether linkers have been prepared based on the highly efficient reaction between sulfhydryl and bromoacetyl groups.[11] The unoptimized yields of oligoamides **1a**–**d**, after being subjected to purification with column chromatography, were quite satisfactory ranging from 63–85%. The coupling–deprotection strategy described here is straightforward and should be of value to the preparation of more oligomers or polymers consisting of a variety of basic units. Preliminary CD experimental study showed that the backbone of the oligoamides indeed adopted folded conformations that are most likely helical, as revealed by the introduced chiral side chains that bias the handedness of the folded molecules. Future studies will focus on the folded (secondary) structures of these oligomers.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560510.

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(11) **Selected Spectroscopic Data**

Compound 2-1

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87–0.94 (m, 6 H), 1.30–1.41 (m, 8 H), 1.57–1.66 (m, 4 H), 4.08–4.22 (m, 2 H), 4.82–4.87 (m, 1 H), 7.37 (d, *J* = 6.99 Hz, 1 H), 8.96 (m, 2 H), 9.16 (m, 1 H) ppm.

Compound **2**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90–0.92 (m, 11 H), 1.25–1.40 (m, 16 H), 1.53 (d, *J* = 7.5 Hz, 3 H), 1.65–1.72 (m, 6 H), 2.35 (t, *J* = 7.5 Hz, 4 H), 3.99–4.17 (m, 2 H), 4.67–4.75 (m, 1 H), 7.11 (d, *J* = 7.2 Hz, 1 H), 7.69 (s, 2 H), 7.78 (s, 2 H), 8.00 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 14.0,18.0, 22.4, 22.9, 23.7, 23.8, 25.2, 28.9, 30.3, 30.4, 31.4, 37.5, 38.8, 38.8, 49.0, 68.0, 113.8, 114.0, 135.0, 139.0, 167.0, 172.2, 173.3 ppm. ESI-HRMS: *m/z* calcd for $C_{30}H_{49}N_3O_5Na$ [M + Na]$^+$: 554.3570; found: 554.3583.

Compound 3-1

Compound **3-1** was prepared by controlling the molar ratios of 3-(trithylthio)propanoic acid and diamine **2-2** as 2.4 in 65% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.80–0.84 (m, 6 H), 1.21–1.30 (m, 8 H), 1.39 (d, *J* = 7.26 Hz, 3 H), 1.52 (m, 1 H), 2.37–2.50 (m, 8 H), 3.91–4.02 (m, 2 H), 4.43 (t, *J* = 7.08 Hz, 1 H), 7.06–7.34 (m, 30 H), 7.68 (d, *J* = 0.99 Hz, 2 H), 8.10 (s, 1 H), 8.75 (d, *J* = 6.78 Hz, 1 H), 10.10 (s, 2 H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 10.8, 10.9, 13.9, 16.6, 22.4, 23.1, 23.2, 27.3, 28.3, 29.7, 29.8, 35.1,38.2, 48.5, 66.1, 66.3, 112.7, 113.4, 126.7, 128.0, 129.1, 135.4, 139.2, 144.4, 166.7, 169.3, 172.7 ppm. ESI-HRMS: *m/z* calcd for $C_{62}H_{65}N_3O_5S_2Na$ [M + Na]$^+$: 1018.4263; found: 1018.4263.

Compound 4-1

Compound **4-1** was prepared by controlling the molar ratios of 3-(trithylthio)propanoic acid and diamine **2-2** as 1.2 in 50% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.78–0.83 (m, 6 H), 1.20–1.26 (m, 8 H), 1.33 (d, *J* = 7.26 Hz, 3 H), 1.50 (m, 1 H), 2.29–2.35 (m, 4 H), 3.85–4.02 (m, 2 H), 4.34 (t, *J* = 7.08 Hz, 1 H), 5.25 (s, 2 H), 6.65 (s, 1 H), 7.00 (s, 1 H), 7.05 (s, 1 H), 7.23–7.32 (m, 15 H), 8.50 (d, *J* = 6.54 Hz, 1 H), 9.74 (s, 1 H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 10.8, 13.9, 16.7, 22.4, 23.1, 27.5, 28.4, 29.8, 30.4, 35.1, 38.2, 48.4, 66.2, 106.7, 107.4, 108.3, 126.7, 128.0, 129.1, 135.5, 139.5, 144.38, 144.47. 148.9, 167.4, 168.9, 172.8 ppm. ESI-HRMS: *m/z* calcd for $C_{40}H_{47}N_3O_4SNa$ [M + Na]$^+$: 688.3185; found: 688.3179.

Compound 4

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.80–0.84 (m, 6 H), 1.21–1.30 (m, 8 H), 1.38 (d, *J* = 7.26 Hz, 3 H), 1.50–1.52 (m, 1 H), 2.34–2.42 (m, 4 H), 3.92–4.04 (m, 4 H), 4.41 (m, 1 H), 7.23–7.37 (m, 15 H), 7.68 (s, 2 H), 8.09 (s, 1 H), 8.79 (d, *J* = 6.90 Hz, 1 H), 10.13 (s, 1 H), 10.54 (s, 1 H) ppm. ^{13}C NMR (75MHz, DMSO-d_6): δ = 10.8, 13.9, 16.6, 22.4, 23.1, 27.3, 28.3, 29.8, 38.2, 40.1, 48.5, 66.1, 66.3, 112.9, 113.5, 130.0, 126.7, 128.0, 129.1, 135.5, 138.7, 144.4, 164.8, 166.5, 169.3, 172.6 ppm. ESI-HRMS: *m/z* calcd for $C_{42}H_{48}BrN_3O_5SNa$ [M + Na]$^+$: 808.2396; found: 808.2374.

Oligoamide 1a

Light yellow powder (540 mg) in 70% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.80–0.84 (m, 18 H), 1.21–1.30 (m, 24 H), 1.38 (d, *J* = 7.17 Hz, 9 H), 1.50–1.52 (m, 3 H), 2.35–2.42 (m, 8 H), 2.69–

2.71 (m, 4 H), 2.92–2.94 (m, 4 H), 3.38 (s, 4 H), 3.92–4.01 (m, 6 H), 4.39–4.44 (m, 3 H), 7.24–7.33 (m, 30 H), 7.68–7.70 (m, 6 H), 8.11–8.13 (m, 3 H), 8.75–8.77 (m, 3 H), 10.10 (s, 2 H), 10.16 (s, 2 H), 10.26 (s, 2 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 10.9, 13.9, 16.7, 22.4, 23.2, 27.4, 27.7, 28.3,29.8, 29.9, 35.1, 36.3, 38.3, 48.6, 66.2, 66.3, 112.7, 113.4, 126.8, 128.0, 129.1, 135.5, 139.3, 144.4, 166.7, 168.2, 169.3, 169.6, 172.7 ppm. ESI-HRMS: *m/z* calcd for $C_{108}H_{130}N_9O_{15}S_4Na$ [M + Na]$^+$: 1943.8467; found: 1943.8134.

Oligoamide 1b

Using **1a′** as starting material, light yellow powder (502 mg) in 85% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.79–0.84 (m, 30 H), 1.21–1.30 (m, 40 H), 1.37 (d, *J* = 7.41 Hz, 15 H), 1.52 (m, 5 H), 2.34–2.39 (m, 8 H), 2.66–2.70 (m, 8 H), 2.91–2.93 (m, 8 H), 3.34 (s, 8 H), 3.99–4.01 (m, 10 H), 4.41–4.43 (m, 5 H), 7.22–7.34 (m, 30 H), 7.67–7.70 (m, 10 H), 8.10–8.13 (m, 5 H), 8.73–8.75 (m, 5 H), 10.08–10.25 (m, 10 H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 10.8, 10.9, 13.9, 16.7, 22.4, 23.2, 27.6, 28.3, 29.8, 29.9, 36.2, 38.3, 48.5, 66.2, 66.3, 112.7, 113.4, 113.6, 126.7, 128.0, 129.1, 135.5, 139.2, 139.3, 144.4, 166.7, 168,2, 169.3, 169.6, 169.7, 172.7 ppm. ESI-HRMS: *m/z* calcd for $C_{154}H_{196}N_{15}O_{25}S_6Na_2$ [M + 2Na – H]$^+$: 2893.2646; found: 2893.2623.

Oligoamide 1c

Using **1b′** as starting material, light yellow powder (301 mg) in 63% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.80–0.84 (m, 42 H), 1.12–1.30 (m, 56 H), 1.38 (d, *J* = 7.20 Hz, 21 H), 1.51 (m, 7 H), 2.34–2.40 (m, 8 H), 2.66–2.71 (m, 12 H), 2.91–2.96 (m, 12 H), 3.35 (s, 12 H), 3.92–4.01 (m, 14 H), 4.39–4.41 (m, 7 H), 7.22–7.36 (m, 30 H), 7.67–7.70 (m, 14 H), 8.10–8.13 (m, 7 H), 8.75–8.78 (m, 7 H), 10.09–10.26 (m, 14 H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 10.8, 10.9, 13.9, 16.7, 22.4, 23.2, 23.3, 27.3, 27.6, 28.4, 29.8, 29.9, 35.1, 35.4, 36.2, 38.2, 38.3, 48.6, 66.2, 66.3, 112.7, 113.4, 113.6, 126.8, 128.1, 129.1, 135.5, 139.2, 139.3, 144.4, 166.8, 168,3, 169.3, 169.6, 169.7, 172.7 ppm. ESI-HRMS: *m/z* calcd for $C_{200}H_{262}N_{21}O_{35}S_8KNa$ [M + Na + K – H]$^+$: *m/z* 3835.6668; found: 3835.6474.

Oligoamide 1d

Using **1c′** as starting material, light yellow powder (43 mg) in 77% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.80–0.84 (m, 54 H), 1.12–1.30 (m, 72 H), 1.38 (d, *J* = 7.23 Hz, 27 H), 1.50–1.52 (m, 9 H), 2.34–2.40 (m, 8 H), 2.66–2.71 (m, 16 H), 2.92–2.96 (m, 16 H), 3.35 (s, 16 H), 3.92–4.01 (m, 18 H), 4.39–4.44 (m, 9 H), 7.24–7.37 (m, 30 H), 7.67–7.71 (m, 18 H), 8.10–8.13 (m, 9 H), 8.75–8.78 (m, 9 H), 10.1–10.3 (m, 18 H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 11.2, 11.3, 14.3, 17.1, 22.8, 23.6, 23.7, 27.7, 28.1, 28.7, 28.8, 30.2, 30.3, 35.6, 35.8, 36.7, 38.6, 38.7, 49.0, 66.6, 66.8, 113.2, 113.8, 114.1, 127.2, 128.5, 129.5, 135.9, 139.6, 139.7, 144.9, 167.2, 168.6, 169.7, 170.1, 173.1 ppm. ESI-HRMS: *m/z* calcd for $C_{247}H_{329}Cl_2N_{27}O_{45}S_{10}$ [M + CH_2Cl_2 – 2H]$^{2-}$: 2392.555; found: 2392.8.

Representative Procedure for the Preparation of Oligoamide 1a

The solution of compound **4** (802 mg, 1.02 mmol) dissolved in CH_2Cl_2 (10 mL) was added dropwise to the ice-cold mixture of compound **3** (209 mg, 0.409 mmol) and Et_3N(0.14 mL, 1.02 mmol) in CH_2Cl_2 (20 mL). The mixture was allowed to warm to r.t. and kept at this temperature overnight. The resulting mixture was washed with 1 M HCl solution (30 mL), brine (30 mL), and then dried over anhydrous Na_2SO_4. After filtration and concentration the crude product was purified by column chromatography (3 vol% MeOH in CH_2Cl_2, R_f = 0.1) to afford pure compound **1a**.

Oligoamides **1b**–**d** could be prepared using the same method described as **1a**.

Representative Procedure for the Preparation of Oligoamide 1a′

The solution of TFA (0.31 mL, 4.16 mmol) in CH_2Cl_2 (10 mL) was added dropwise to the ice-cold mixture of compound **1a** (400 mg, 0.208 mmol) and triethylsilane (0.33 mL, 2.08 mmol) in CH_2Cl_2 (20 mL) over 15 min. The mixture was allowed to warm to r.t. and kept at this temperature for 1 h. After concentration, the crude mixture was purified by flash column chromatography (5% v/v MeOH in CH_2Cl_2, R_f = 0.2) to give compound **1a′**.

Oligoamides **1b′** and **1c′** could be prepared using the same method described as **1a′**.

Oligoamide 1a′

White solid; yield: 293 mg (98%).

Oligoamide 1b′

White solid; yield: 289 mg (97%).

Oligoamide 1c′

White solid; yield: 38 mg (97%).